2019 年度　博士学位論文

ビタミン D およびアンドロゲン核内受容体の新規機能制御剤の創製研究

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第 1 章　序論

1.1　核内受容体[1)]

1.1.1　概要[1s,2,3)]

様々なシグナル伝達物質と結合するタンパク質を、特に受容体タンパク、あるいは単に受容体と呼ぶ。受容体に結合するシグナル伝達物質はリガンドと呼ばれ、リガンドが受容体に結合すると、受容体は構造変化を起こし、一連の反応を開始させる。

受容体は存在場所により、細胞膜受容体あるいは核内（細胞内）受容体に分類される。核内受容体は、核受容体（細胞核内に存在）あるいは、細胞質受容体（細胞質に存在）に大別され、いずれも細胞膜を通過可能な、脂溶性の小分子をリガンドとする（Fig.1-1）。内因性リガンドとしては、ステロイドホルモン、ビタミン A やビタミン D などの脂溶性ビタミン、甲状腺ホルモンなどが知られている。リガンドが結合した、リガンド-受容体複合体は、核内に移行し、DNA 上の特異的な結合部位（response element）に結合する。

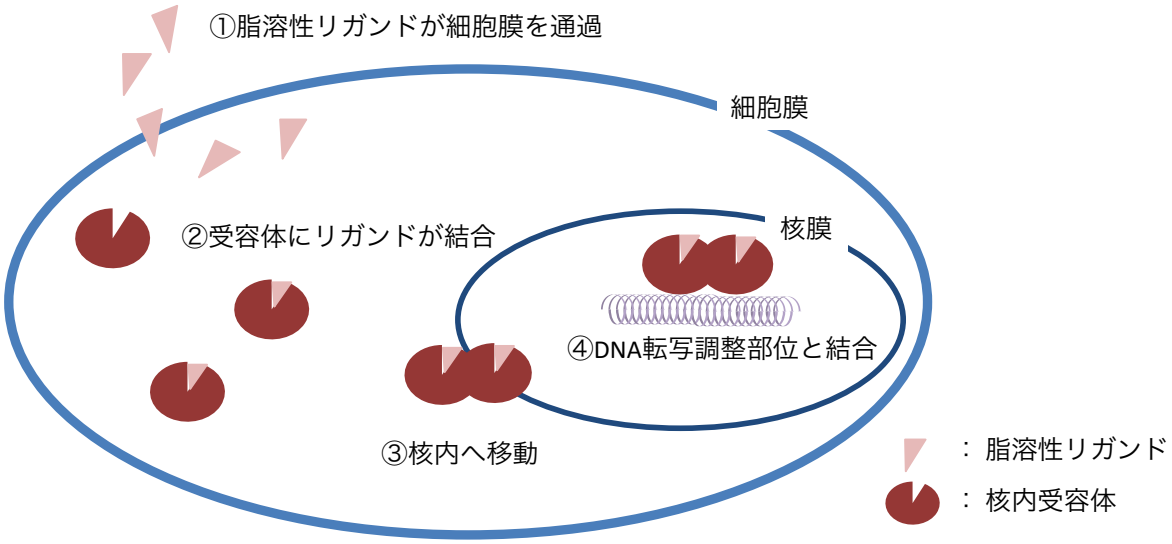


Fig.1-1 核内受容体の機能発現の模式図

核内受容体は、リガンド未結合では転写促進能をもたないが、アゴニストの結合により転写促進能を獲得し、発生、恒常性、代謝など、生命維持の根幹に係わる遺伝子転写を制御している。また、多くの核内受容体とそのリガンドが病気の発症や治療とも深く関係していることが示されており、内因性リガンドの同定及び合成リガンド（アゴニストやアンタゴニストなど）の創製など、多くの医薬化

学研究者の興味の対象となっている[4)]。

1.1.2 核内受容体の種類[2,3a,5)]

核内受容体は一つの遺伝子から分子進化した遺伝子スーパーファミリーを形成している。1980 年代にグルココルチコイド受容体 (GR)[6)]、エストロゲン受容体(ER)[7)] がクローニングされ、その後ビタミン D 受容体(VDR)[8)]、甲状腺ホルモン受容体(TR)[9)]、レチノイン酸受容体(RAR)[10)]など多くの受容体のクローニングが相次いだ。また、これらの受容体をプローブにスクリーニングが行われ、リガンド不明の受容体（オーファン受容体）も配列相同性からクローニングされた。このように種々の生理活性物質に対する核内受容体が同定され、そのアミノ酸配列が明らかになるに至り、これらの受容体が一つの遺伝子ファミリーを形成することがわかってきた。ヒトゲノム解析の結果から、ヒトでは 48 遺伝子にコードされることがわかっている[11)]。

分子系統樹に基づく分類、機能に基づく分類、リガンドに基づく分類などがされているが、分子系統樹に基づく分類と、それぞれの受容体のリガンドを Table1-1 に、もととなった分子系統樹を Fig.1-2 にまとめた。

サブファミリー	グループ	統一命名法	サブタイプと略称	リガンド
甲状腺ホルモン型	甲状腺ホルモン受容体	NR1A1	TRα	甲状腺ホルモン
		NR1A2	TRβ	
	レチノイン酸受容体	NR1B1	RARα	ビタミンA関連化合物
		NR1B2	RARβ	
		NR1B3	RARγ	
	ペルオキシソーム増殖因子活性化受容体	NR1C1	PPARα	脂肪酸、プロスタグランジン
		NR1C2	PPARβ / δ	
		NR1C3	PPARγ	
	Rev-ErbA	NR1D1	Rev-ErbAa	ヘム
		NR1D2	Rev-ErbAb	
	RAR関連オーファン受容体	NR1F1	RORα	コレステロール、ATRA
		NR1F2	RORβ	
		NR1F3	RORγ , RORC	
	肝X受容体型	NR1H3	LXRα	oxysteroids
		NR1H2	LXRβ	
		NR1H4	FXR	
	ビタミンD受容体型	NR1I1	VDR	ビタミンD
		NR1I2	PXR	生体異物
		NR1I3	CAR	アンドロスタン
レチノイドX受容体型	肝細胞核因子4	NR2A1	HNF4 α	脂肪酸
		NR2A2	HNF4 γ	
	レチノイドX受容体	NR2B1	RXRα	レチノイド
		NR2B2	RXRβ	
		NR2B3	RXRγ	
	Testicular receptor	NR2C1	TR2	
		NR2C2	TR4	
	TLX/PNR	NR2E1	TLX	
		NR2E3	PNR	
	COUP/EAR	NR2F1	COUP-TFI	
		NR2F2	COUP-TFII	
		NR2F6	EAR-2, COUP-TFIII	
エストロゲン受容体型	エストロゲン受容体	NR3A1	ERα	エストロゲン
		NR3A2	ERβ	
	エストロゲン関連受容体	NR3B1	ERRα	
		NR3B2	ERRβ	
		NR3B3	ERRγ	
	3-ケトステロイド受容体	NR3C1	GR	コルチゾール
		NR3C2	MR	アルドステロン
		NR3C3	PR	プロゲステロン
		NR3C4	AR	テストステロン
神経成長因子IB 型	NGFIB/NURR1/NOR1	NR4A1	NGFIB	
		NR4A2	NURR1	
		NR4A3	NOR1	
ステロイド産生因子型	SF1/LRH1	NR5A1	SF1	ホスファチジルイノシトール
		NR5A2	LRH1	
胚細胞核因子型	GCNF	NR6A1	GCNF	
その他	DAX/SHP	NR0B1	DAX1	
		NR0B2	SHP	

Table 1-1　核内受容体の分子系統樹に基づく分類 [3,12,13)]

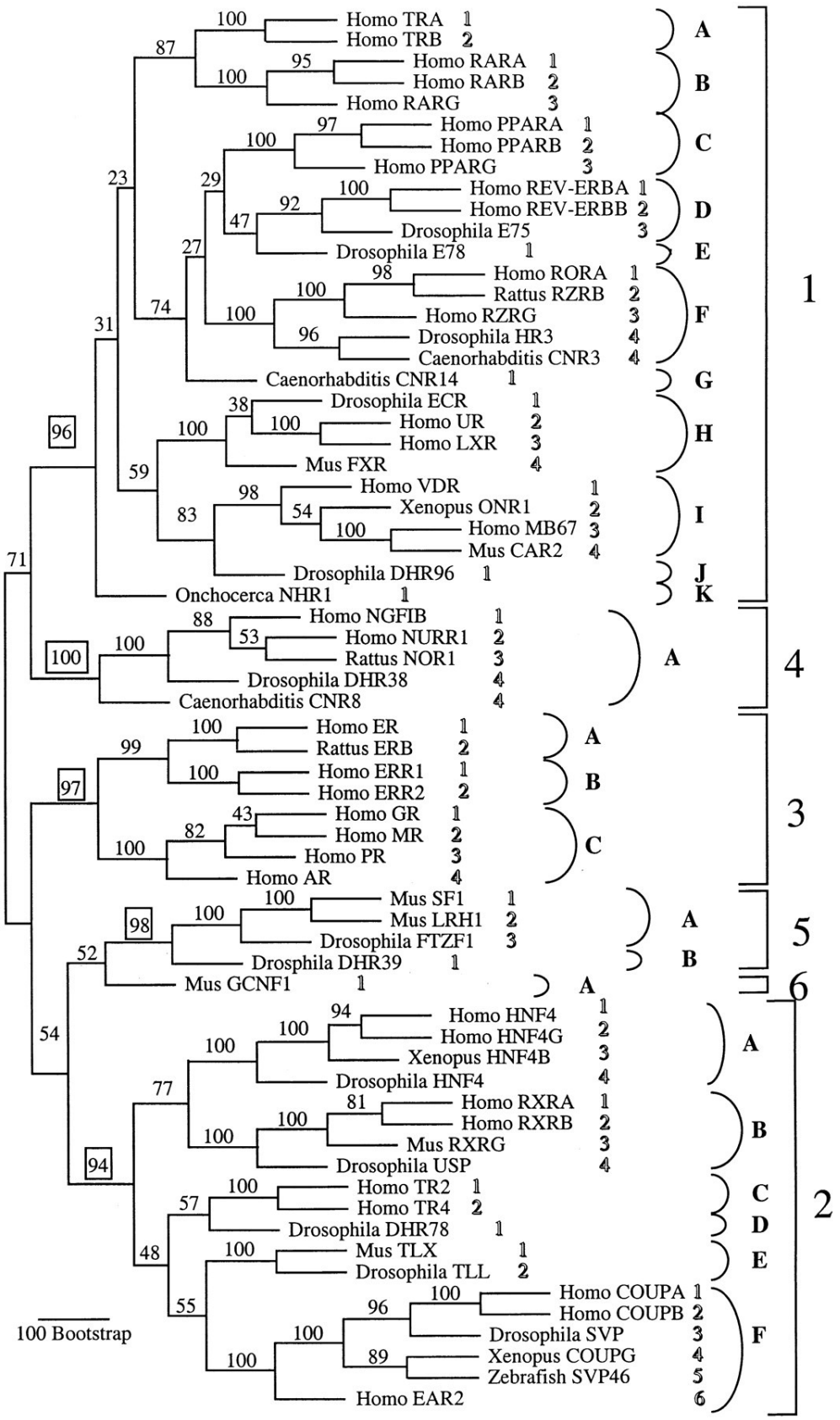


Fig. 1-2 核内受容体の分子系統樹（文献 3）より引用）

1.1.3　核内受容体の構造 [2a,14)]

核内受容体は、リガンド依存的に標的遺伝子の転写を制御する転写因子であり、遺伝子がスーパーファミリーを形成することから、受容体の構造を共通の領域構造に分割できる。それぞれ機能の異なる A-F の６つのドメインから構成される。(Fig.1-3)

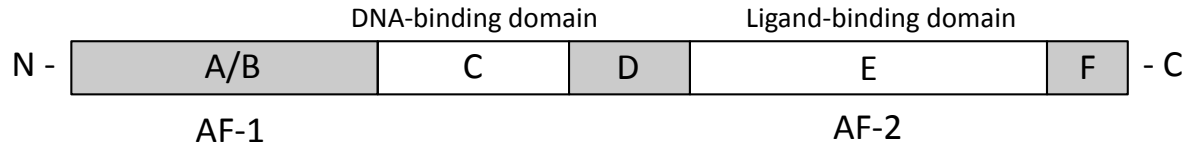


Fig. 1-3　核内受容体のドメイン構造

核内受容体のもっとも重要な機能である転写活性化機能は、N 末端側の A/B 領域及び C 末端側の E 領域の２か所に存在する。E 領域はリガンド結合領域であり、リガンド依存的な転写活性化機能を有する転写促進領域２（AF-2）が存在する。A/B 領域に存在する転写促進領域１（AF-1）はリガンド非依存的な恒常的転写促進機能を有するものの、リガンドが結合していない状態では AF-2 により抑制されており、リガンドの結合により AF-2 だけでなく AF-１の機能も誘導されることになる。AF-1、AF-2 の活性は細胞種によって異なり、同じ細胞であっても細胞の状態により異なることが知られている [1b)]。

C 領域は DNA 結合領域であり、２つの高度に保存された亜鉛フィンガー構造を有し、これが DNA の配列を認識することができる [14)]。

E 領域（リガンド結合領域）は、ホモあるいはヘテロ二量体を形成する部位でもあり、多くの親水性残基と１２個のαヘリックスから構成され、詳細は後項で述べるが、ヘリックス１２の立体構造が転写活性に重要であるとされている。

D 領域は、ヒンジ領域であると考えられている。F 領域は核内受容体によっては存在しないものもあり、その機能について十分な知見は得られていない。

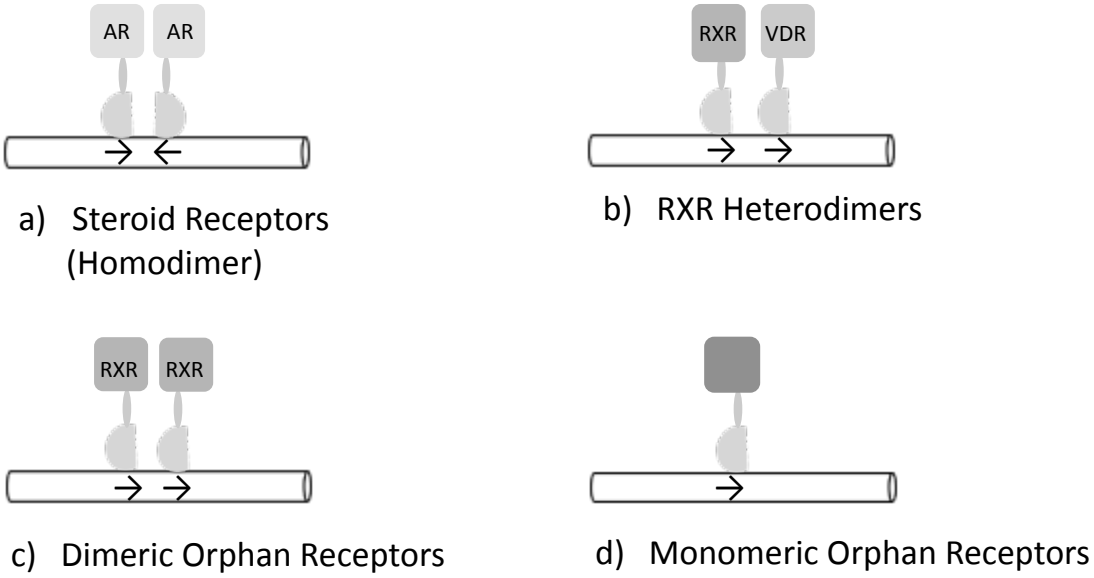


Fig. 1-4　DNA 結合様式による核内受容体の分類 [2a)]

Fig. 1-4 は、核内受容体を、DNA 結合様式によって４つに大別したものである。ステロイドホルモン受容体群（例：アンドロゲン受容体（AR））はホモ２量体として二重鎖の一方を読んだ場合ともう一方を逆向きに読んだ配列順序が同じになる回文配列上に並んだ 2 つのホルモン応答エレメント(HRE)に結合する(Fig.1-4 (a))。ビタミン A/D・甲状腺ホルモン受容体群（例：ビタミン D 受容体（VDR））はレチノイド X 受容体（RXR）とヘテロ 2 量体を形成して同方向に並んだ２つの HRE に結合する(Fig.1-4 (b))。一方、リガンド未知のオーファン受容体は、2 量体もしくは 1 量体として DNA に結合する(Fig.1-4 (c),(d)) [13)]。

1.1.4　核内受容体の立体構造と活性化機構

1980 年代になって、様々な核内受容体のリガンド結合領域（LBD）の X 線構造解析が行われ、その構造が明らかになってきた [15)]。Fig.1-5 は文献 2b)より引用したレチノイド X 受容体の LBD の X 線結晶構造解析である。Fig.1-5 (a)はリガンドの結合していないアポ型であるが、LBD が 12 のαヘリックス（H1 – H12）と逆並行に配置された短いβターン(s1、s2)からなることが示されている。Fig.1-5 (a)で示した全体的な折りたたみ構造は、核内受容体 LBD に共通する構造である。Fig.1-5 (b)(c)はリガンドが結合した LBD の概略図で、(b）はアゴニストが結合したホロ型であり、(c)はアンタゴニストが結合したものである。

アポ型とホロ型の模式図を比較した場合、最も大きな構造変化が見られるのは、C 末端側のヘリックス 12（H12）である。赤で示した H12 は AF-2 を含む活性化ドメインコアであるが、アポ型の場合、LBD の外側に伸びており、ホロ型の LBD ではリガンド結合ポケット（LBP）を閉じるように折

りたたまれている。一方、アンタゴニストが結合した受容体（Fig.1-5 (c)）では、H12 が LBP 付近に折り畳まれているものの、その折りたたみ構造が Fig.1-5 (b)と異なっており、この構造の違いが、アゴニスト／アンタゴニスト活性の違いに反映していると考えられている。H12 の構造変化は他の核内受容体 LBD にも共通して見られ、この変化が核内受容体の活性化に重要な役割を果たすと考えられる。

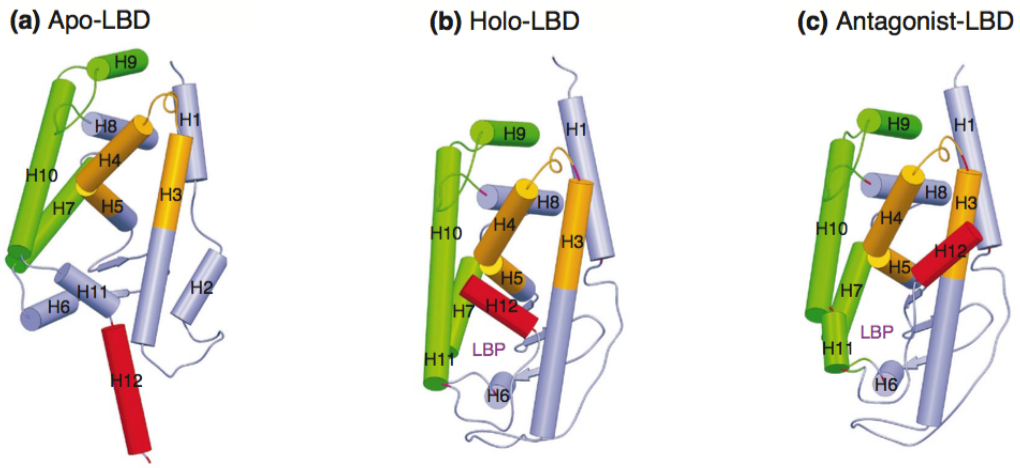


Fig.1-5　レチノイド X 受容体の LBD の X 線結晶構造解析 [2b)]

核内受容体は、アゴニストが未結合の状態では転写を制御する転写共役制御因子（コリプレッサー）が結合しており、リガンドが結合することでコリプレッサーが解離し、代わりに転写共役活性化因子（コアクチベーター）が結合することが報告されている [16)]。

これまでの研究から核内受容体のリガンド結合領域とコアクチベータの結合部位は LxxLL モチーフ(x は任意のアミノ酸)と呼ばれる領域であり [17)]、核内受容体のコリプレッサーやコアクチベーターとの接触部位は　E 領域の AF-2 AD core と呼ばれる 1 つのαヘリックスであることが知られている。この結合部位である AF-2 AD core は H12 であり、このことから H12 が活性化に重要な役割を果たすことが説明可能である。(Fig.1-6)

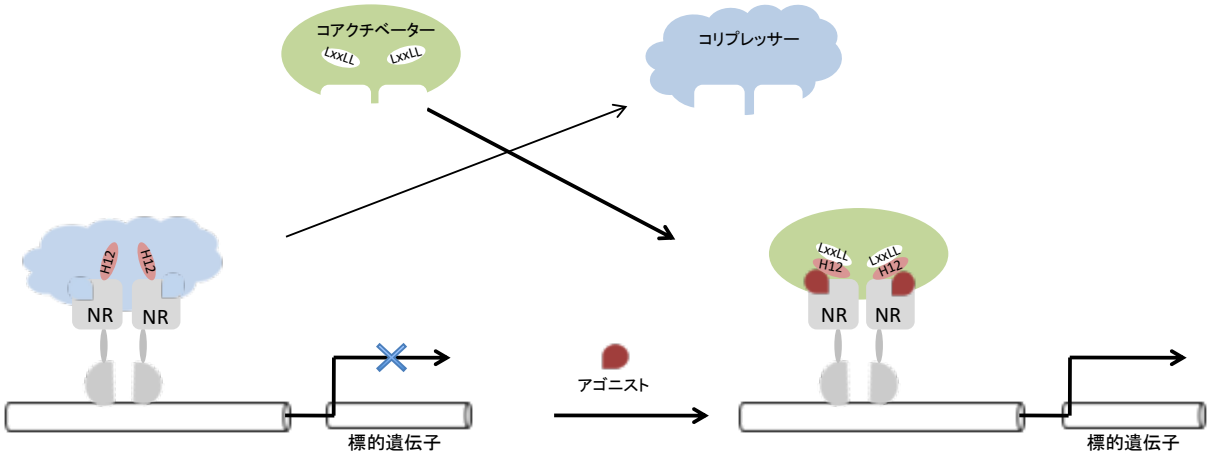


Fig.1-6　リガンド依存的な転写共役因子群の解離と会合

近年、これまでリガンド未結合であるアポ型 LBD の構造解析が行われてこなかった受容体であるビタミン D 受容体のアポ型の構造が解明され、新たなリガンド結合メカニズムも提唱されている。解明した構造・相互作用機構の、核内受容体全般への適用も期待されている [18]。

1.1.5　核内受容体リガンドの臨床応用と問題点

1.1.1 項で述べたように、核内受容体は、発生、恒常性、代謝など生命維持の根幹にかかわる遺伝子転写を制御しており、受容体とそのリガンドの多くが、病気の発症や治療と深く関わっている。Table 1-2 は核内受容体に関連する疾患の例である。例えば、アンドロゲン受容体は前立腺癌、エストロゲン受容体は乳癌治療に深く関与しており、受容体リガンドが治療薬として用いられている。しかし、核内受容体の働きは多様であり、副作用や薬剤抵抗が生じるなど、問題も発生しており解決が望まれている。

核内受容体	関連する疾患例
アンドロゲン受容体	前立腺癌
エストロゲン受容体	乳癌、子宮癌、骨粗鬆症
グルココルチコイド受容体	炎症性疾患
甲状腺ホルモン受容体	橋本病
ビタミン A 受容体	急性前骨髄球性白血病
ビタミン D 受容体	骨粗鬆症、乾癬

Table 1-2　核内受容体に関連する疾患の例

1.2　本研究の目的

本研究では、核内受容体の活性化機構をもとに、これを制御することで臨床応用における様々な問題解決に寄与できるのではないかと考え、核内受容体のうち、ビタミン D 受容体及びアンドロゲン受容体に焦点を合わせ、これらの受容体に活性を示す新規化合物を創製することを目的とした。

ビタミン D 受容体(VDR)についての詳細は第２章で述べるが、医薬品としての応用例はそれほど多くない。VDR リガンドとして報告されている化合物も、天然リガンド VD_3 の誘導体が多く、ほとんどがセコステロイド骨格を持つ化合物である。構造多様性に乏しいだけでなく、セコステロイド骨格は合成が煩雑で、安定性に問題があるため、ビタミン D の更なる医薬展開のためには新たな構造を有する非セコステロイド型 VDR リガンドの創製が望まれている。また、VDR の機能の一つに細胞分化誘導があり、VDR アゴニストは癌治療への応用も期待されている。VDR の主な機能としてカルシウム代謝調節があり、VDR リガンドを医薬品として応用するためには、分化誘導とカルシウム代謝の機能を分離した作用分離型のアゴニストが必要と考えられている。

本研究では、非セコステロイド骨格を持つ VDR アゴニストの創製を行い、細胞分化誘導活性を評価する。天然とは異なる骨格をもつリガンドの構造活性相関や受容体結合様式を明らかにすることができれば、新たなリガンドの創製が可能になると考えられ、さらに機能分離型アゴニストの創製につながる可能性もあると考えている。

アンドロゲン受容体は、アンタゴニストが前立腺癌治療薬として重要な位置を占めることから、多くのリガンドが創製され、ステロイド性のもの、非ステロイド性のものがともに臨床応用されている。しかし、長期的には、治療を継続していても癌の抑制が効かなくなる去勢抵抗性前立腺癌（CRPC）という状態になるため、CRPC に対して有効な AR アンタゴニストの開発が望まれている。

そこで、本研究では第 3 章で述べる核内受容体機能制御仮説に基づき、変異型 AR にも強力な効果を発揮するアンタゴニストの創製を行うこととした。

以上、本研究では、核内受容体の活性発現機構をもとに、ビタミン D 受容体及びアンドロゲン受容体の新たな機能制御剤を創製し、その活性を評価することを目的とする。

第２章　リトコール酸を基盤としたビタミン D 受容体リガンドの創製

2.1　背景

2.1.1 ビタミン D[19)]

ビタミン D は脂溶性ビタミンの一種であり、1919 年に抗くる病因子として発見された。1931 年にエルゴステロール溶液の紫外線照射反応物中より結晶が単離されたが、後にこの結晶は混合物であることが判明し、この混合物をビタミン D_1、エルゴカルシフェロールをビタミン D_2 と命名した。現在ではビタミン D_2〜D_7 の６種類が知られているが、その中で高い生物効力値を示すものとして実用に供されているのはビタミン D_2 及びビタミン D_3（VD_3）と命名されたコレカルシフェロールの２種類のみである（Fig. 2-1）。いずれも、ステロイド骨格の B 環に相当する部位が開環したセコステロイド骨格をベースに 17 位に側鎖のある構造をしている。

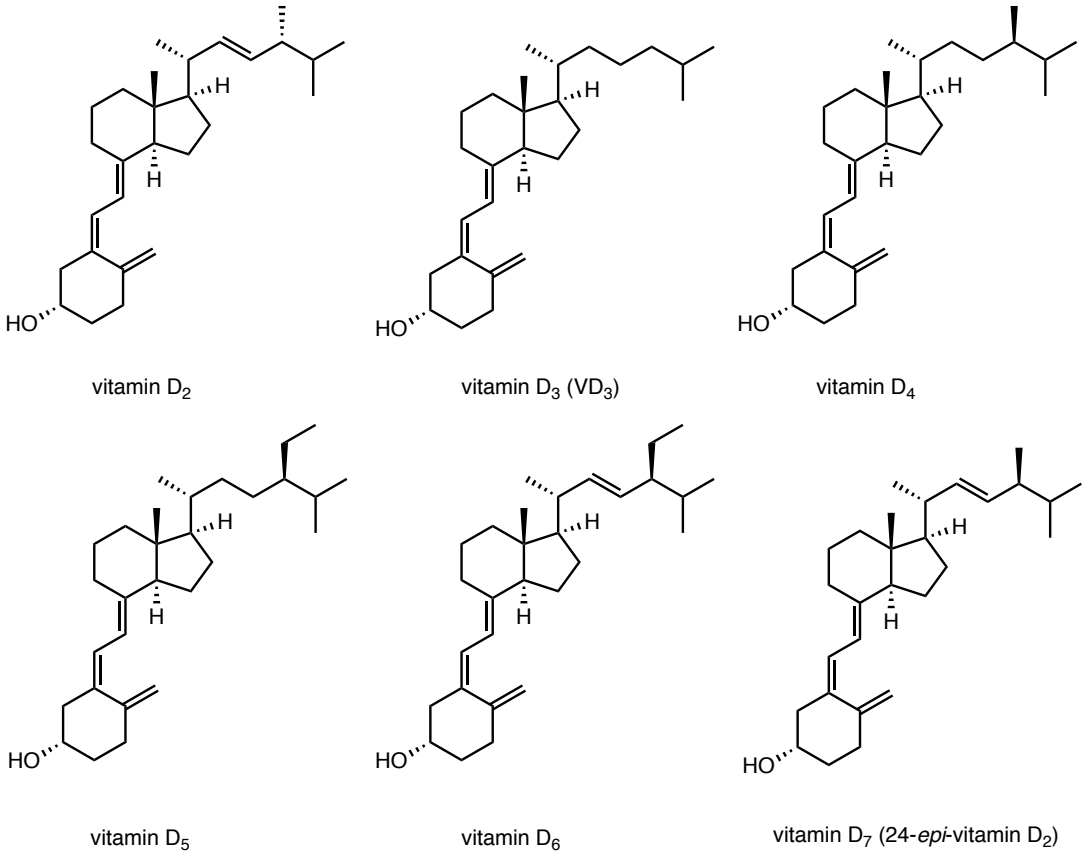


Fig. 2-1 ビタミン D 天然誘導体の構造

ビタミン D は、他のビタミンと異なり、体内でも合成が可能である。VD_3は、皮膚において紫外線の作用により 7-デヒドロコレステロールより生成する。体内で生成した、あるいは、経口的に摂取した VD_3 は、肝臓で水酸化され、$25(OH)D_3$ となり、さらに腎臓で活性型ビタミン D_3 と呼ばれる $1\alpha,25(OH)_2D_3$へと変換される [20]（Fig. 2-2）。

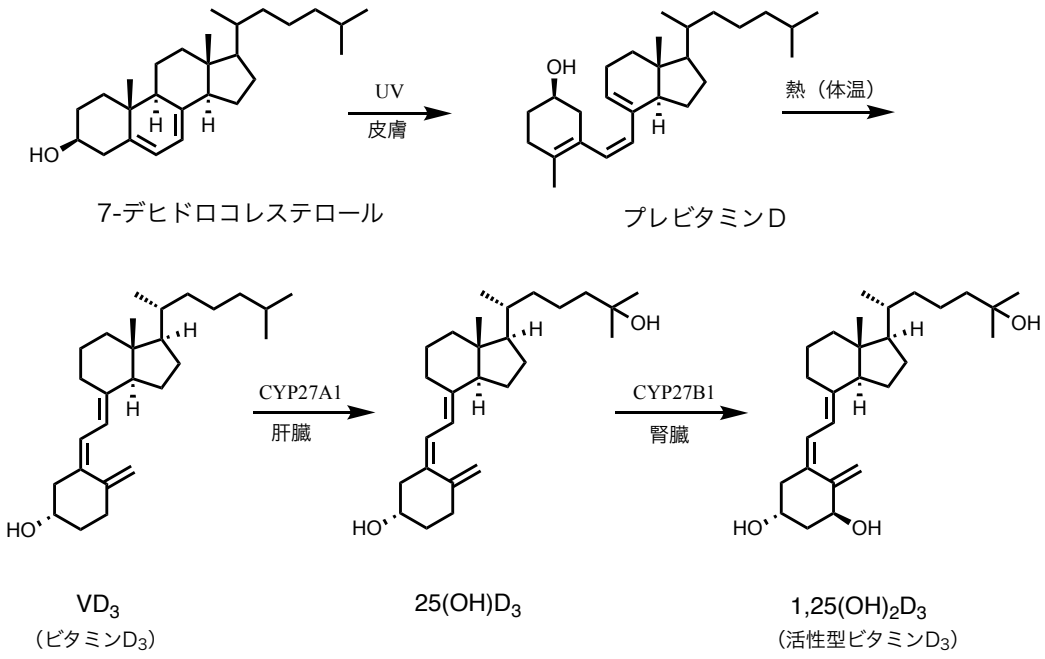


Fig. 2-2　体内における活性型ビタミン D_3 の生成

ビタミンDの生理作用としてこれまでに明らかにされていることは、VDR を介して小腸からのカルシウムとリンの吸収を促進し、骨の形成と成長を促進することである。また副甲状腺ホルモンとの協調作用により骨塩の溶出を促進することによって、血清カルシウム及びリン濃度を高め、生体のカルシウムとリンの恒常性の維持に寄与している。活性型ビタミン D_3 は骨芽細胞を介して骨吸収を司る破骨細胞の形成と分化を促進する。また、表皮細胞、造血細胞など種々の細胞の増殖と分化に関与している。[21]

2.1.2 ビタミン D 受容体（VDR）及び VDR リガンド

ビタミン D 受容体（vitamin D receptor、VDR）はビタミン D をリガンドとする核内受容体である。腸管や腎臓などの標的細胞に存在し、ビタミン D と複合体を形成し、この複合体はレチノイド X 受容体（RXR）とヘテロ二量体を形成して DNA のホルモン応答エレメント(HRE)に結合する [1a]。VDR は腸管や腎臓だけでなく、胃、皮膚、膵臓、下垂体、脳、肝臓、甲状腺、副腎、食道、肺上皮など多

くの組織の細胞に発現している[22]。

これまでにビタミン代謝異常症、皮膚疾患、骨疾患や癌の治療を目的に数多くのビタミン D 誘導体が合成されてきたが、副作用として高カルシウム血症を引き起こすため[23-25]、カルシウム作用を分離した作用分離型の誘導体の開発が進められてきた。臨床応用されているリガンドを Fig.2-3 に[26]、それ以外の代表的なリガンドを Fig. 2-4 に[27-29]に示す。AH-1[27a]と MART-10[27b]はいずれも VDR アゴニストであるが、AH-1 は優れた骨形成作用が認められ、MART-10 は高いがん細胞増殖抑制効果を示す。VDR リガンドの報告は、ほとんどがアゴニストであり、アンタゴニストは TEI-9647[28]、DLAM[29]など非常に限られた報告しか見当たらない。また、現在日本で医薬品として使用されている VDR リガンドはすべてセコステロイド骨格をもつ VDR アゴニストである（Fig. 2-3）。

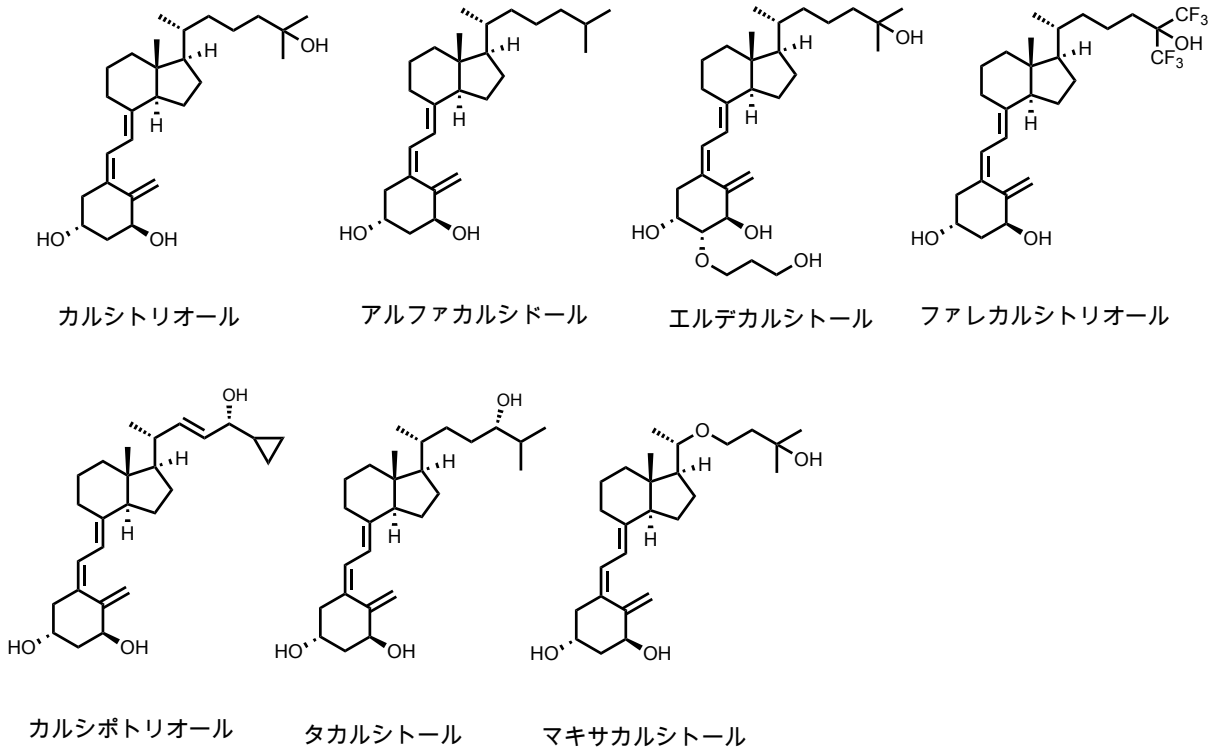


Fig. 2-3　臨床応用されている VDR アゴニストの構造

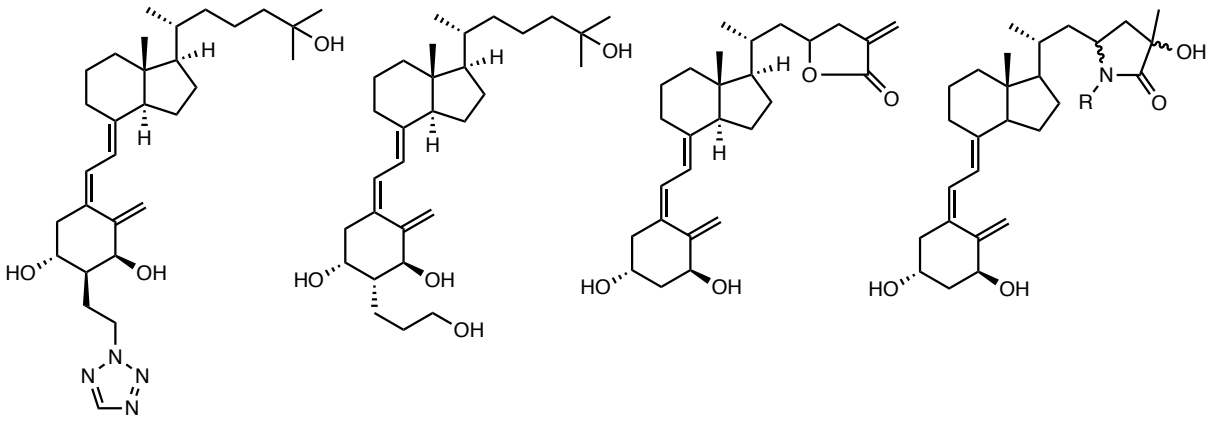


Fig. 2-4　代表的な VDR リガンドの構造

VDR リガンドとして知られている化合物はセコステロイド骨格を保持したものがほとんどである。セコステロイド構造は高活性誘導体創製の骨格として有用であるものの、合成が煩雑である、化学的に安定性に乏しいものが多く扱いにくいなどの欠点が有り、それがビタミン D の医薬応用を狭めているとも考えられ、非セコステロイド型 VDR リガンドの開発が望まれている。しかし、高活性な非ステロイド型の VDR リガンドの報告例は、米国リガンド社が開発したジフェニルペンタン誘導体 [30]、所属研究室と東京医科歯科大学とで開発したカルボラン [31]およびビシクロオクタン誘導体 [32]など、数例に限られている（Fig. 2-5）。

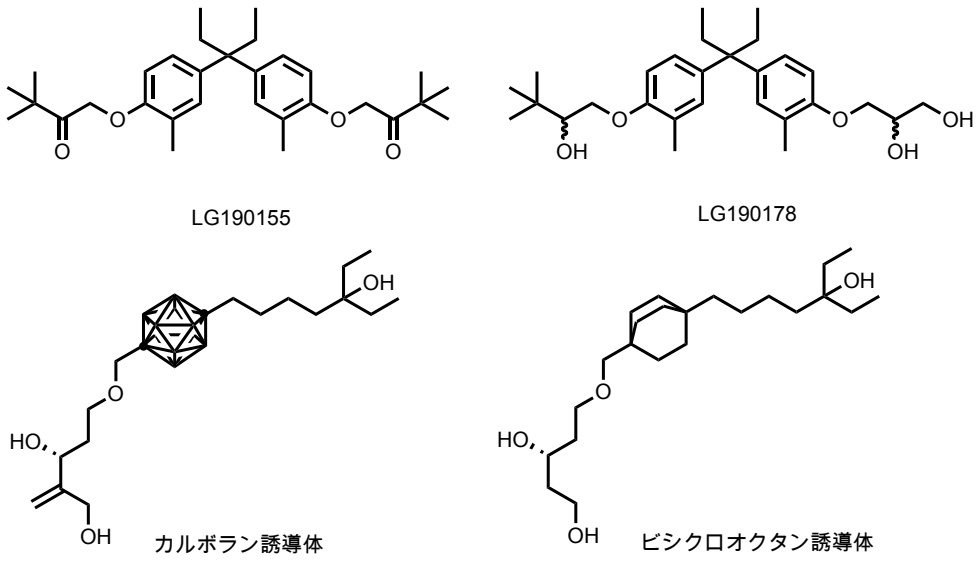


Fig. 2-5　非セコステロイド型 VDR アゴニストの構造

2.1.3　リトコール酸

2002 年に槇島らにより二次胆汁酸であるリトコール酸（LCA）と 3-keto-LCA（**2-1**） (Fig. 2-6) が弱いながらも VDR アゴニスト活性を持つ第二の内因性 VDR リガンドとして同定され [33]、その後の研究で LCA の 3 位をエステル化した LCA acetate（**2-2**）が LCA よりも活性が高いことが報告された [34]。生体内で LCA と結合した VDR の機能は明確にされていないが、小腸細胞内で生理的濃度以上に蓄積された LCA が VDR に結合し、CYP3A を誘導することで有毒な LCA の代謝・解毒を促し、大腸がんなどの発症を予防しているのではないかとも考えられている [35,36]。また、LCA 誘導体は高カルシウム血症を引き起こさずに VDR を活性化するとの報告もあり [37]、作用分離型誘導体の開発への期待も持たれる。

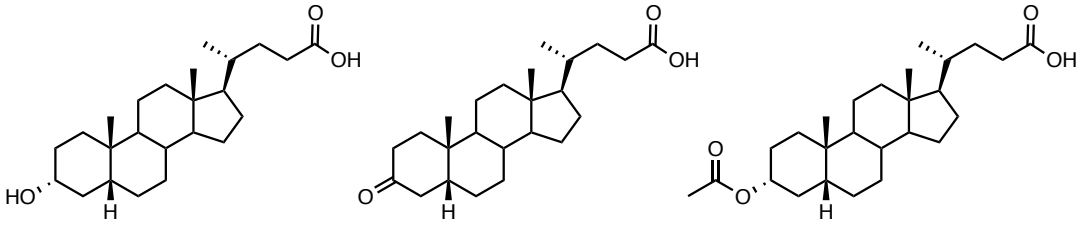


Fig. 2-6 リトコール酸及び誘導体

VDR が内在性リガンドである活性型ビタミン D_3 と全く異なる構造の LCA を認識する機構を明らかにすることは、LCA をリード化合物とした新たな VDR リガンドの創製に有用である。ラットの VDR リガンド結合領域（Rat VDR-LBD）と LCA 誘導体の結晶構造解析が行われ、LCA 及び 3-keto-LCA（**2-1**）が内在性リガンドである 1α,25$(OH)_2D_3$ と同じポケットに結合することが判明した。Fig.2-7(a)は、LCA acetate（**2-2**）と Rat VDR-LBD の結晶構造を示したもので、(b)は **2-2**（黄緑色）と 1α,25$(OH)_2D_3$（紫色）を重ねて示したものである（文献 38）より引用、一部改）。結晶構造解析の結果から化合物 **2-2** も LCA や 3-keto-LCA(**2-1**)と同様に 1α,25$(OH)_2D_3$ と同じポケットに結合しており、化合物 **2-2** の側鎖のカルボキシ基は Tyr143（N 末端から数えて 143 番目のアミノ酸であるチロシン、以後同様に略称で記す）および Ser274 と水素結合を形成していること、Ser233 および Arg270 と水を介して水素結合を形成していることがわかる。これらの残基は 1α,25$(OH)_2D_3$ の 3 位および 1 位のヒドロキシ基と水素結合を形成している残基である。また、化合物 **2-2** の 3 位のカルボニル酸素は 1α,25$(OH)_2D_3$ の 25 位のヒロドキシ基の酸素と同じく His301 と水素結合を形成していることも判明している。これらのことから LCA の A 環部は天然ホルモンである 1α,25$(OH)_2D_3$ の

側鎖部に対応すると考えられ、A 環部３位のヒロドキシ基を修飾することで生理活性が上昇したことは LCA をリード化合物とした構造展開を考える上で重要な知見である。

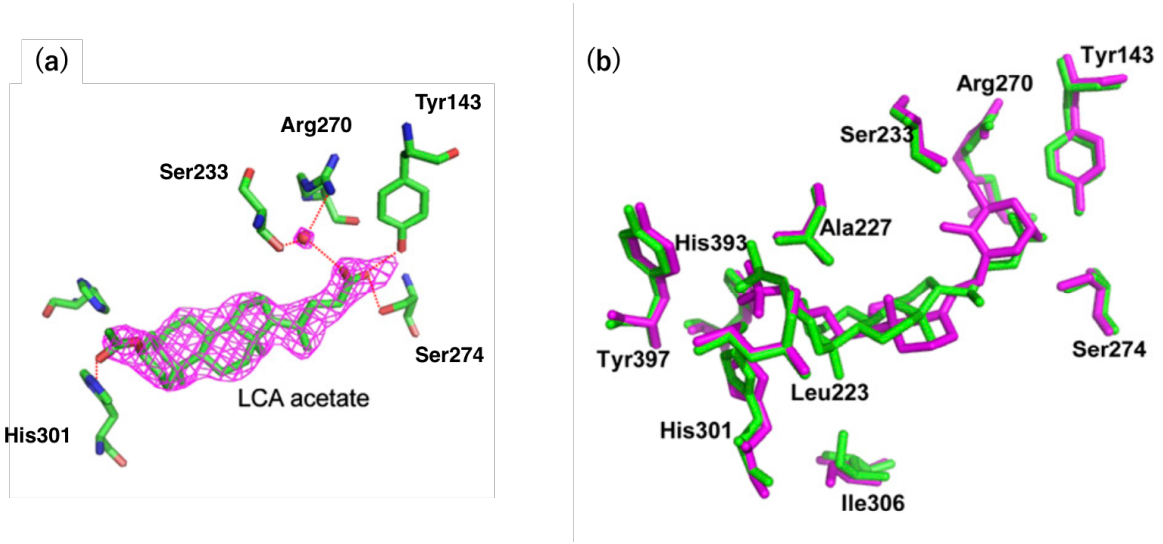
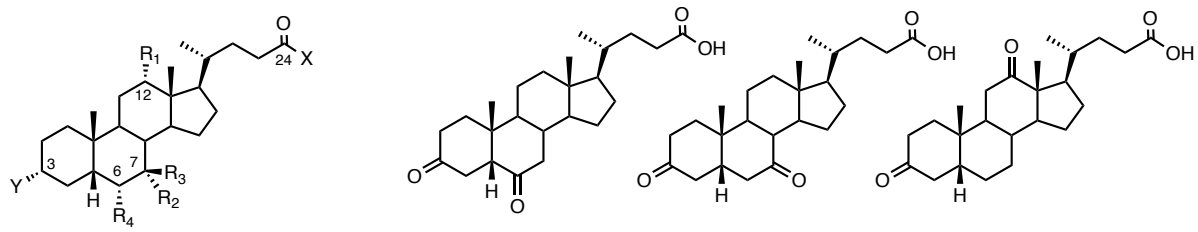


Fig. 2-7 Rat VDR-LBD と LCA 誘導体(**2-2**)及び活性型ビタミン D_3 との複合体の X 線構造解析 [38)]

本研究は、以上の先行研究を踏まえ、内在性リガンドである活性型ビタミン D_3 と全く異なる構造の LCA をリード化合物とし、より高活性な新規誘導体を創製することを目的として行った。

2.2 化合物のデザイン

リトコール酸をはじめとする胆汁酸類の VDR リガンドの構造活性相関については複数の報告があり、現在までに判明していることは以下の通りである [33,34)]。なお、各化合物の構造は Fig. 2-6 及び Fig. 2-8 に示した。



2-3 ～**2-13**　　**2-14**　　**2-15**　　**2-16**

2-3～**2-9 :**　R_1, R_2, R_3, R_4 = H

2-3 Propionate : X=OH, Y=O-COC_3H_7
2-4 Formate : X=OH, Y=O-COH
2-5 Methyl ester : X=OCH_3, Y=OH
2-6 Ethyl ester : X=OC_2H_5, Y=OH
2-7 Benzyl ester : X=OC_4H_9, Y=OH
2-8 Tauro- : X=$NH(CH_2)_2SO_3H$, Y=OH
2-9 Glyco- : X=$NHCH_2COOH$, Y=OH

2-10～**2-13 :** X = OH, Y = OH

2-10 Chenodeoxycholic acid : R_1, R_3, R_4 = H, R_2 = OH
2-11 Deoxycholic acid : R_2, R_3, R_4 = H, R_1 = OH
2-12 Ursodeoxycholic acid : R_1, R_2, R_4 = H, R_3 = OH
2-13 Hyodeoxycholic acid : R_1, R_2, R_3 = H, R_4 = OH

Fig. 2-8 胆汁酸類及びリトコール酸誘導体の構造

まず、リトコール酸ステロイド骨格の３位の置換基(Y)については、α-ヒドロキシ基（LCA）及びケト体（化合物 **2-1**）(Fig. 2-6）はアゴニスト活性があり、**2-1** の方が強い活性を示すと報告されている。また、３位のヒドロキシ基をエステル体にすることで活性が強くなり、**2-4**＜**2-2**＜**2-3** の順に強い活性を示す。一方で、側鎖については、側鎖を延長すると活性が下がり、アルコール体は活性がないという報告がある。また、側鎖のエステル体（**2-5**～**2-7**)、及び胆汁酸コンジュゲート（**2-8**, **2-9**）は活性が弱いと報告されている。さらに、３位以外のところが酸化された胆汁酸誘導体（**2-10**～**2-16**）には活性が無いと報告されている。

これらの構造活性相関の研究から、側鎖構造あるいは A 環部３位を構造修飾することにより、VDR アゴニスト活性の上昇が期待できる。そこで、本研究においては、Series 1 として、LCA の３位の酸素官能基を窒素官能基とした誘導体を合成することとした。具体的には、３位にアミノ基（**2-18**)、アセトアミド基（**2-19**)、スルホンアミド基（**2-20**）を持つ化合物を設計した（Fig. 2-9)。LCA アセテート **2-2** の結晶構造では、３位ヒドロキシ基が His301 とだけ水素結合しており、1α,25$(OH)_2D_3$ の 25 位のヒロドキシ基が His301 と His393 の２つのヒスチジンと水素結合していることから、より効果的な水素結合が形成されることにより、活性が向上すると考えた。

次に、Series ２として、側鎖を修飾した化合物の合成を計画した。側鎖部分においても、結晶構造解析により、LCA アセテート **2-2** のカルボキシ基は Ser233 および Arg270 は水を介した水素結合をしている。そこで、新たな水素結合性官能基を導入することで、より強固な水素結合が形成され、結合親和性が向上すると考えた。具体的には、LCA の３位をアセチル化した **2-2** をリード化合物として、側鎖α位もしくはβ位を修飾した化合物を計画した（Fig. 2-9)。化合物の合成は 2.3 節、活性評価は 2.4 節で述べる。

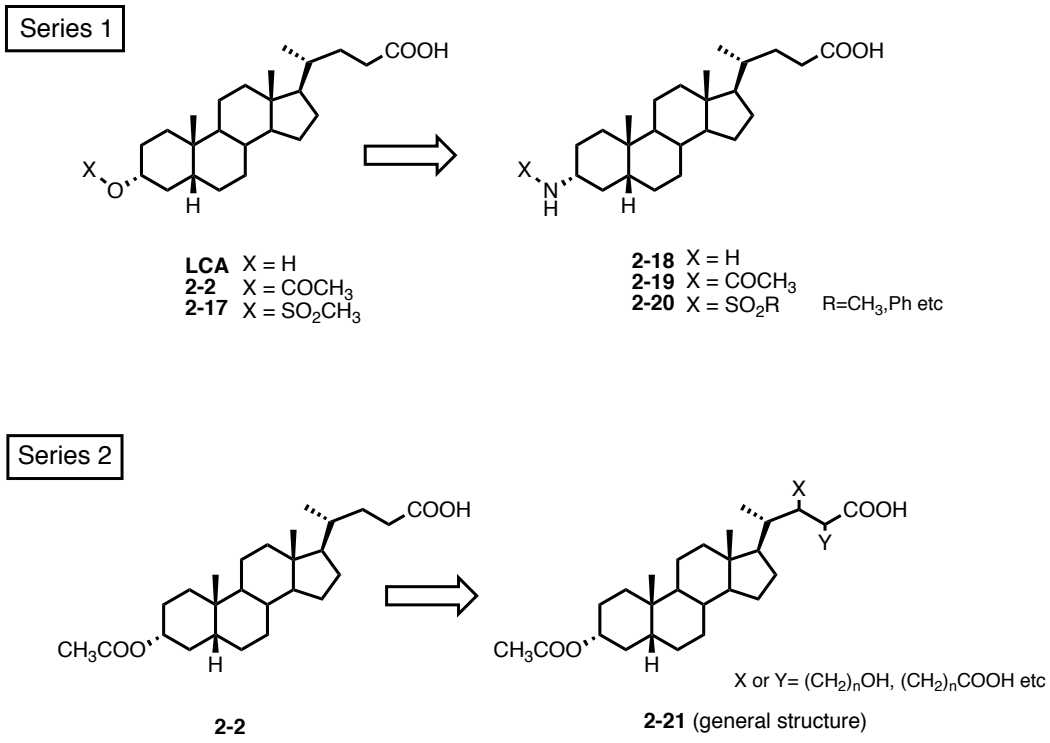
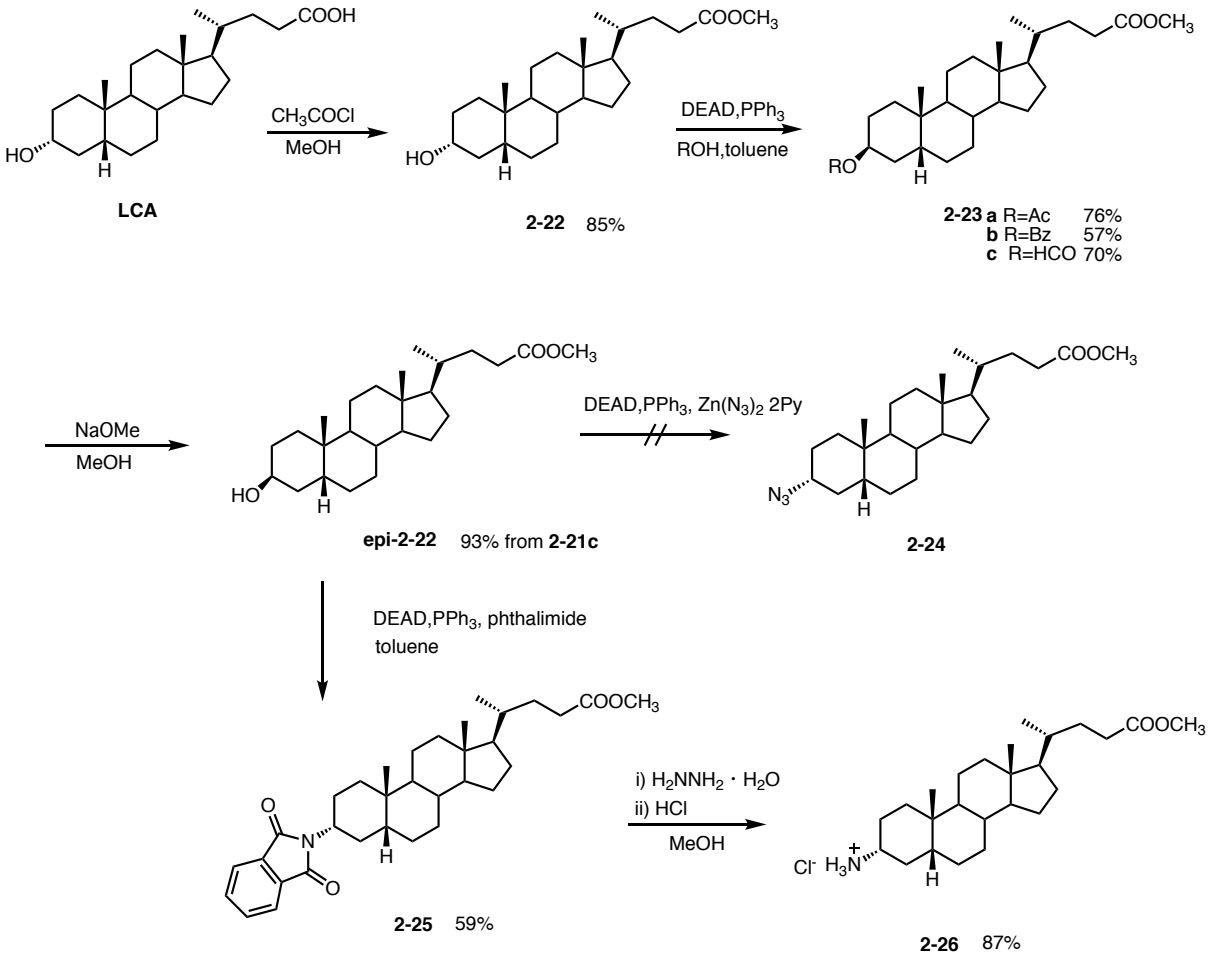


Fig. 2-9　合成目標化合物

2.3　化合物の合成

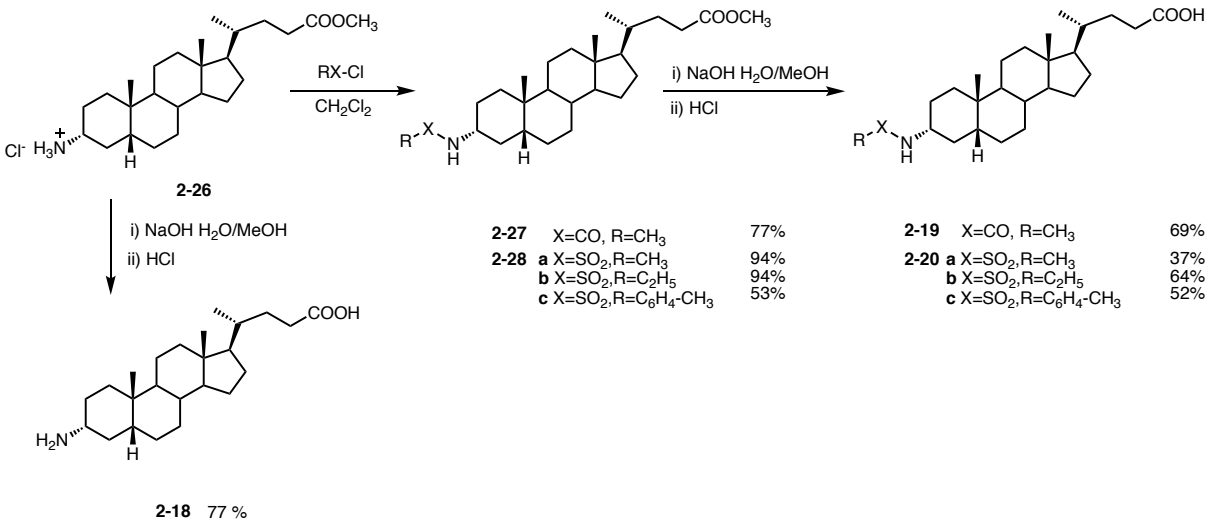
2.3.1　3 位に窒素原子を導入した化合物の合成 [39)]

LCA のカルボキシ基をメチルエステルにして保護した後に光延反応を行い、得られた **2-23a, 2-23b** から **epi-2-22** への変換のため加水分解反応を行ったが室温ではほとんど進行しなかった [40)]。そこで、光延反応により **2-23c** を合成し、加水分解反応を行ったところ、室温で速やかに反応が進行したため、**2-23c** を経て **epi-2-22** を合成することにした。続いてアジド化により **2-24** を合成しようと試みたが反応が進行しなかったため、フタロイル化を行い **2-25** を得た。続くイミド結合の開裂反応は室温ではほとんど進行しないがメタノール中で還流したところ速やかに反応が進行した。反応終了後、アルミナのカラムを用いた精製を試みたが、不純物が溶出し精製が困難であったので、塩酸を加え、塩酸塩 **2-26** として単離した。LCA からの収率は 5 工程で 27%であった（Scheme 2-1）。



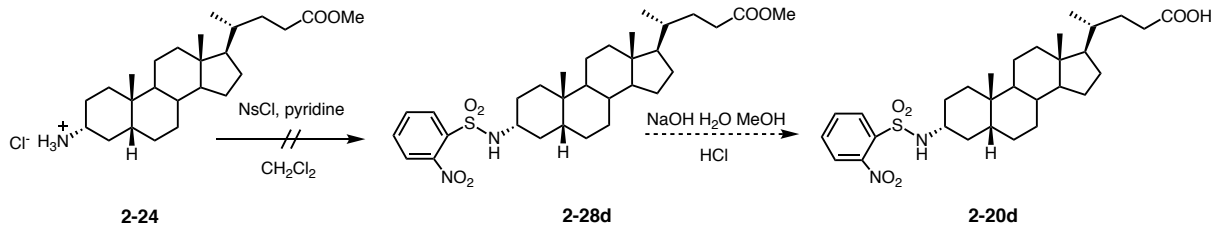
Scheme 2-1　化合物 **2-26** の合成

2-26 から **2-27** 及び **2-28**(**a-c**)を合成し、それぞれ側鎖のエステル保護を外し、カルボン酸 **2-19** 及び **2-20(a-c)**とした。また、同じく **2-26** の側鎖のエステル保護を外し、アミノ酸**2-18** を得た(Scheme 2-2)。



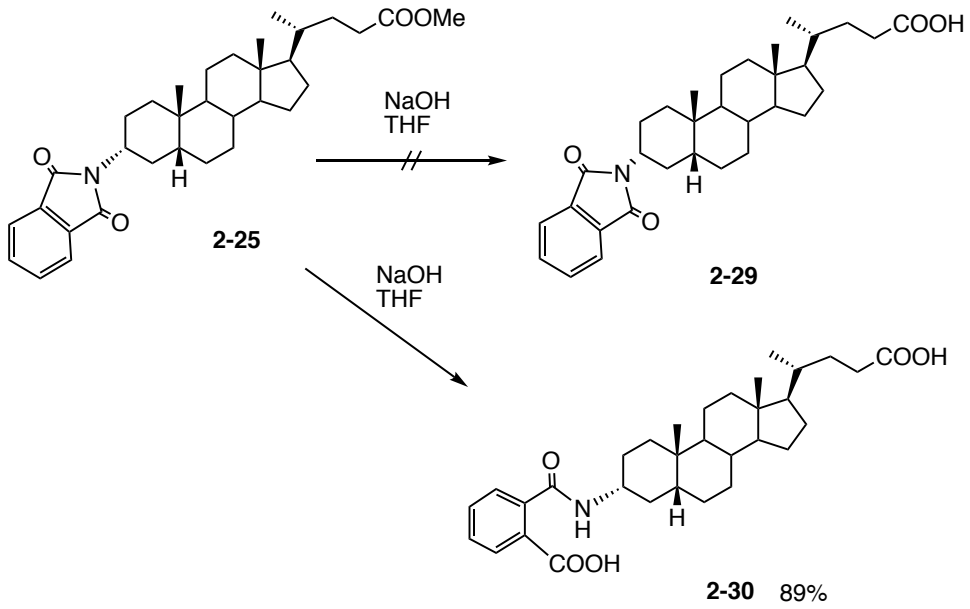
Scheme 2-2 化合物 **2-18**、**2-19** 及び **2-20**(**a-c**)の合成

また、化合物 **2-20d** の合成の原料となる **2-28d** の合成も試みたが、副生成物が多く **2-28d** を得ることができなかった。(Scheme 2-3)



Scheme 2-3 化合物 **2-28d** の合成の試み

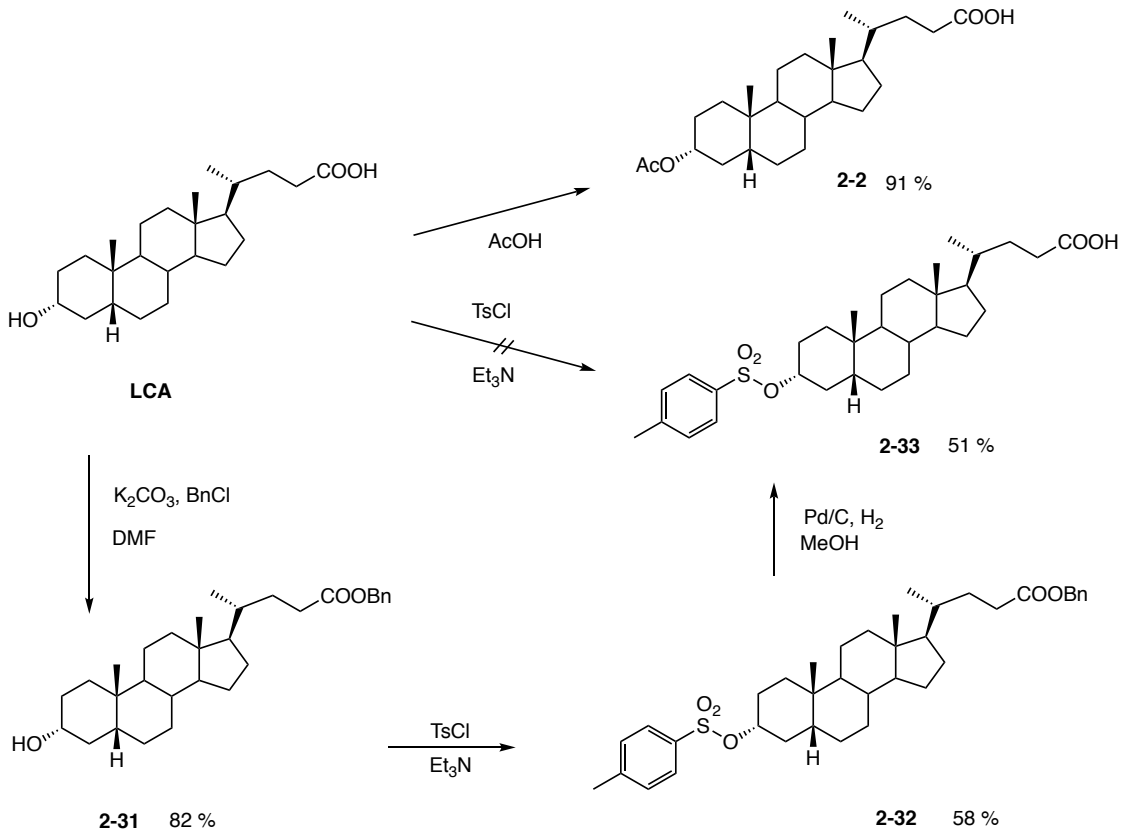
続いて化合物 **2-29** についても活性評価を行いたいと考え、**2-25** の側鎖のメチルエステルを外す反応を行ったが、**2-29** は得られず **2-30** が得られたため、**2-29** を得る試みは断念した(Scheme 2-4)。



Scheme 2-4 化合物 **2-23** の加水分解

2.3.2　メチルエステル及びスルホン酸エステルの合成

次にリトコール酸のエステル体 **2-2** 及び **2-33** を得ることを目標に反応を行った。アセテート **2-2** は **LCA** から直接合成することができたが、スルホン酸エステル **2-33** は直接得ることができなかったため、側鎖のカルボキシ基を保護してからトシル化した後にカルボキシ基の保護を外す方法で合成した (Scheme 2-5)。

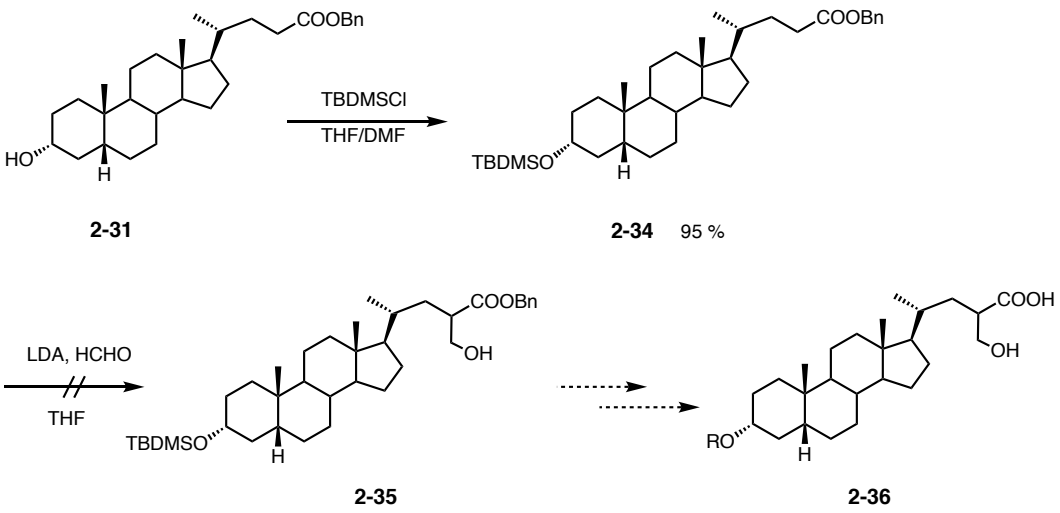


Scheme 2-5 化合物 **2-2** 及び **2-33** の合成

2.3.3 リトコール酸の側鎖を修飾した化合物の合成

側鎖α位を修飾した化合物群 **2-36** を得るため、Scheme 2-6 に従い **2-35** の合成を試みた。

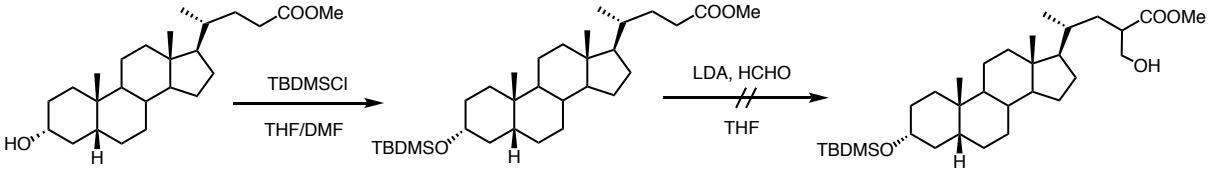
まず、リトコール酸のベンジルエステル体 **2-31** の３位のヒドロキシ基を *t*-ブチルジメチルシリル(TBDMS)基で保護し **2-34** とした。続いて、**2-35** を得るため、-78℃でリチウムジイソプロピルアミド（LDA）に **2-34** を加え、一定時間攪拌後に、ガス状のホルムアルデヒドよりも取り扱いの容易なパラホルムアルデヒドを加えたが、複数の微量の副生成物と原料の混合物が回収され **2-35** は得られなかった。反応が進行するよう、反応温度を-15℃まであげたが、**2-35** は得られなかった。反応温度や攪拌時間、試薬を加える順序などを変更して詳細に検討したが、反応は進行しなかった。さらに、パラホルムアルデヒドの代わりにトリオキサンを用いる、ガス状のホルムアルデヒドを加える、などを検討したが、いずれも反応が十分に進行せず、**2-35** を得ることができなかった。



2-31 **2-34** 95 % **2-35** **2-36**

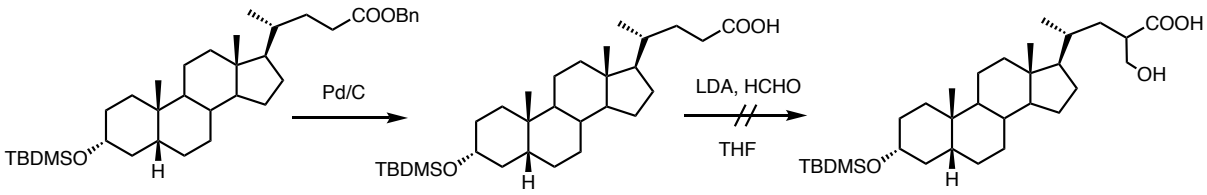
Scheme 2-6　化合物 **2-35** の合成の試み

そこで、側鎖の保護をベンジルエステルではなくメチルエステルにした化合物 **2-37** を合成し、同様の条件で反応を行ったが、**2-38** は得られなかった（Scheme 2-7）。カルボン酸 **2-37** に二当量の LDA を加える方法でも反応を行ったが、反応は進行しなかった(Scheme 2-8)。以上の検討を行ったが、目的とする化合物（**2-35**、**2-38** または **2-40**）を得ることができなかったため、化合物群 **2-36** を得る試みは中断することにした。



2-22 **2-37** 77% **2-38**

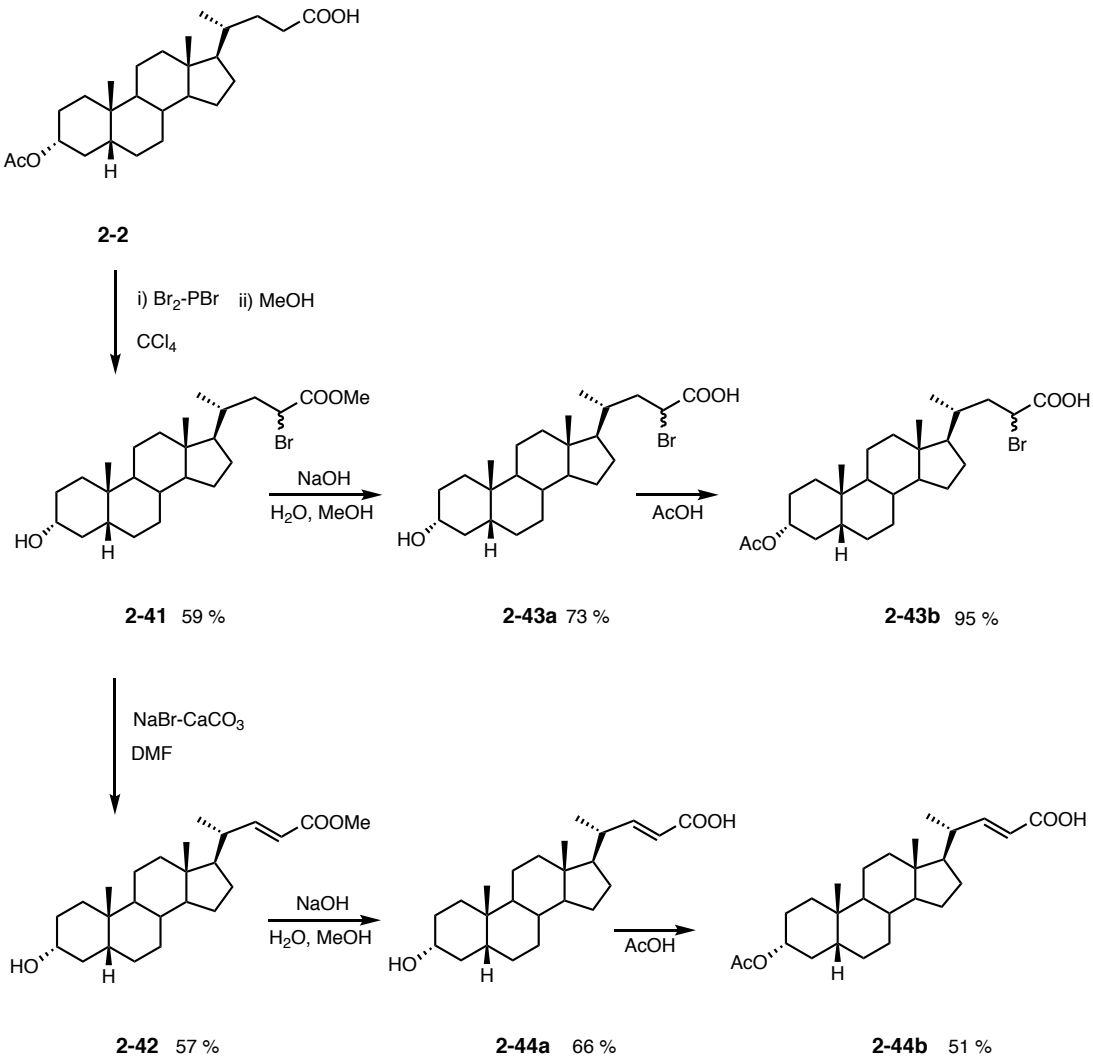
Scheme 2-7　化合物 **2-38** の合成の試み



2-34 **2-39** 39% **2-40**

Scheme 2-8　化合物 **2-40** の合成の試み

次に側鎖α位をブロモ化した化合物 **2-43a,b** 及び側鎖に二重結合をもつ化合物 **2-44a,b** の合成を行った。Scheme 2-9 に従い **2-2** のα位のブロモ化を行い、**2-41** を得た。**2-41** の脱離反応では原料 **2-41** と生成物 **2-42** の分離が非常に困難であるため、原料が完全に消失するよう DMF 還流で反応を行い、原料消失後に目的物 **2-42** を単離した。得られた **2-42** のエステルを加水分解し、**2-44a** とした。得られた **2-44a** は酢酸中で一晩還流した後再結晶により精製し、**2-44b** を得た。ブロモ体 **2-41** も同様に側鎖エステルの加水分解及び３位ヒドロキシ基のアセチル化を行い、**2-43a** 及び **2-43b** を得た。

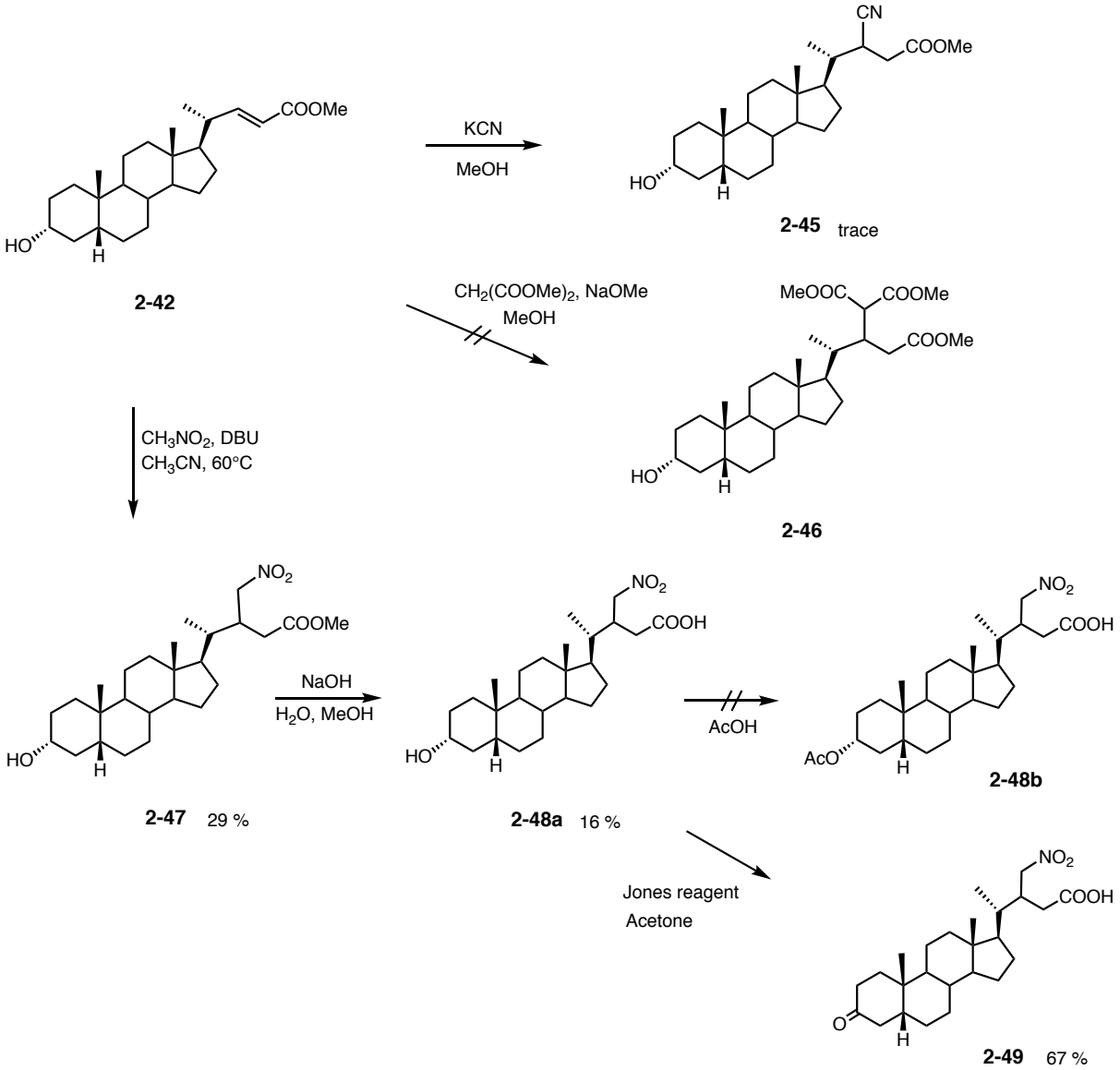


Scheme 2-9　化合物 **2-43**、**2-44** の合成

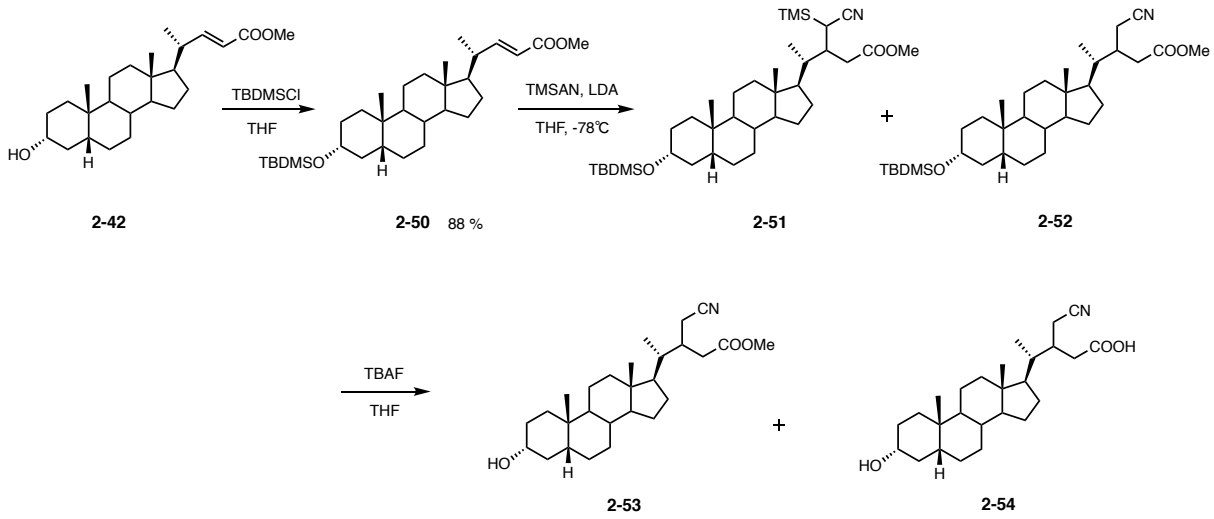
続いて得られた **2-42** を用いてマイケル付加反応を行った。はじめに、シアン化カリウムを加えてシアノ化を行った。原料は消失しなかったが反応を停止し、酢酸エチルで抽出を行ったところ、一部が酢酸エチルで抽出されたので精製を行った。得られたのはわずかに 0.6 mg であったが、^{1}H NMR で

確認したところ、**2-45** が得られた可能性が高いと思われた。ただ、量が少ないことと十分に精製できなかったため、構造の確認はできなかった。また、マロン酸ジメチルと塩基（水酸化カリウム[41] またはナトリウムメトキシド[42]）を加えて反応を行ったが、目的物 **2-46** は得られなかった。

次に、**2-42** にニトロメタンを加えてニトロメチル化を行った。60 ℃で７時間撹拌しても原料は消失しなかったが、さらに温度を上げても変化が見られないため反応を停止した。後処理後、カラムで精製を行ったところ、ほぼ一方のジアステレオマーである **4-47** を得た。得られた **4-47** は側鎖のエステルを加水分解し、**2-48a** を得た。**2-48a** を酢酸中で加熱もしくは無水酢酸を用いてアセチル化を試みた[43]が **2-48b** は得られなかったので、ジョーンズ酸化により、**2-48b** と同様の活性が期待できる３-keto 体 **2-49** を合成した。(Scheme 2-10)



Scheme 2-10　化合物 **2-42** のマイケル付加反応



Scheme 2-11　化合物 **2-42** のシアノメチル化

2-42 のヒドロキシ基を TBDMS 基で保護した後、トリメチルシリルアセトニトリル（TMSAN）を加えたところ、**2-51** が生成した [44]。**2-51** はシリカゲルカラムでの精製中に一部が分解して **2-52** となった（計算上の収率：15%）。**2-51** と **2-52** の混合物をフッ化テトラブチルアンモニウム(TBAF)により脱保護したところ、**2-53** と **2-54** の混合物が得られた。(Scheme 2-11)

2.4　合成した化合物の VDR 活性

2.4.1　3 位を修飾した化合物 [39]

合成した化合物 **2-2**、**2-18**、**2-19** 及び **2-20(a-c)**のビタミン D 活性を調べるため、HL-60 細胞(Human promyelocytic leukemia cells)を用いた分化誘導試験を行った [45]。HL-60 細胞は、白血病細胞株でありビタミン D 依存的に分化する。VDR に対するアゴニスト活性が高ければ、より多くの細胞が分化するものでビタミン D 誘導体創製におけるファーストスクリーニングによく用いられる方法である [30b,46,47]。分化率の測定は、単球及び顆粒球への分化指標である NBT 陽性の細胞数の測定により行った。比較のために用いた化合物 **2-17** は我々の研究グループで以前合成したものを用いた。結果を Fig. 2-10 に示す。本実験系では、LCA は 10 μM 以下の濃度は活性を示さず（データ不掲載）、アセテート **2-2** は 10 μM で分化誘導活性を示す。比較として検討した酸素官能基を持つ誘導体の中では、メタンスルホン酸エステル **2-17** が最も活性が強く、1 μM 以上で活性を示した。３位に窒素官能基として、アミノ基、アミド基を有する化合物には活性が見られなかった。一方、スルホンアミド **2-20a** は 10 μM で

活性を示した。スルホンアミド **2-20a**、**2-20b** 及び **2-20c** の比較では、置換基 R がかさ高くなるにつれ活性が低下する傾向が認められた。

今回合成した化合物の中で最も高い活性を示した化合物 **2-20a** は、天然リガンドである活性型 VD_3 に比べれば、VDR リガンドとして十分な活性とは言えないが、LCA よりは高い活性を有している。酸素官能基を有する化合物の中で最も高い活性を示した化合物 **2-17** の３位置換基であるメシレートは化学的に反応性が高い。一方で、化合物 **2-20a** が持つスルホンアミド基はより安定な置換基であり、さらなる構造最適化を行うことで、より高い活性を持つ非セコステロイド型 VDR リガンドになり得ると考えている。

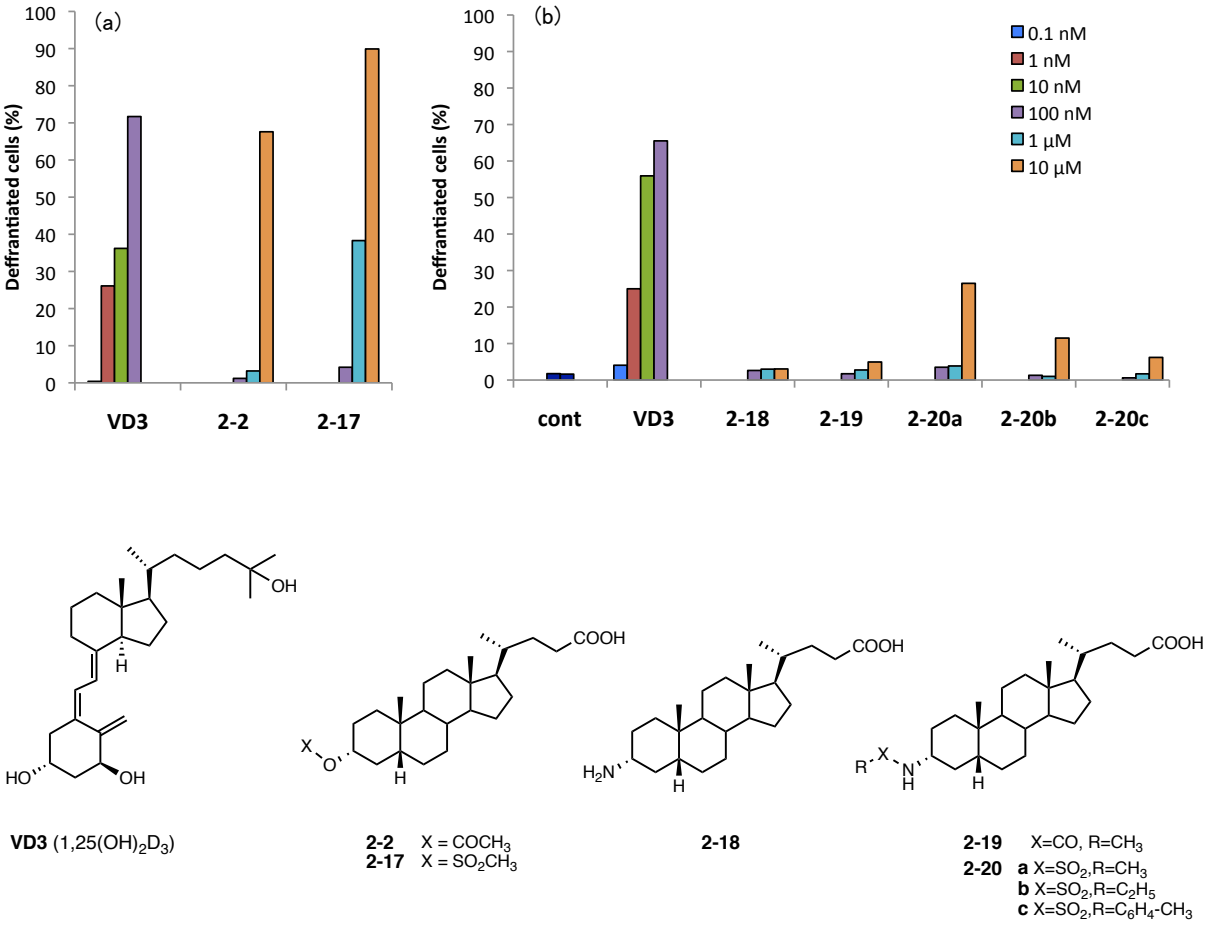


Fig. 2-10 HL-60 細胞を用いた分化誘導試験 (1)

2.4.2　側鎖を修飾した化合物

次に側鎖を修飾した化合物の VDR に対するアゴニスト活性を調べるため、HL-60 細胞を用いた分化誘導試験を行った。結果を Fig. 2-11 及び Fig. 2-12 に示す。

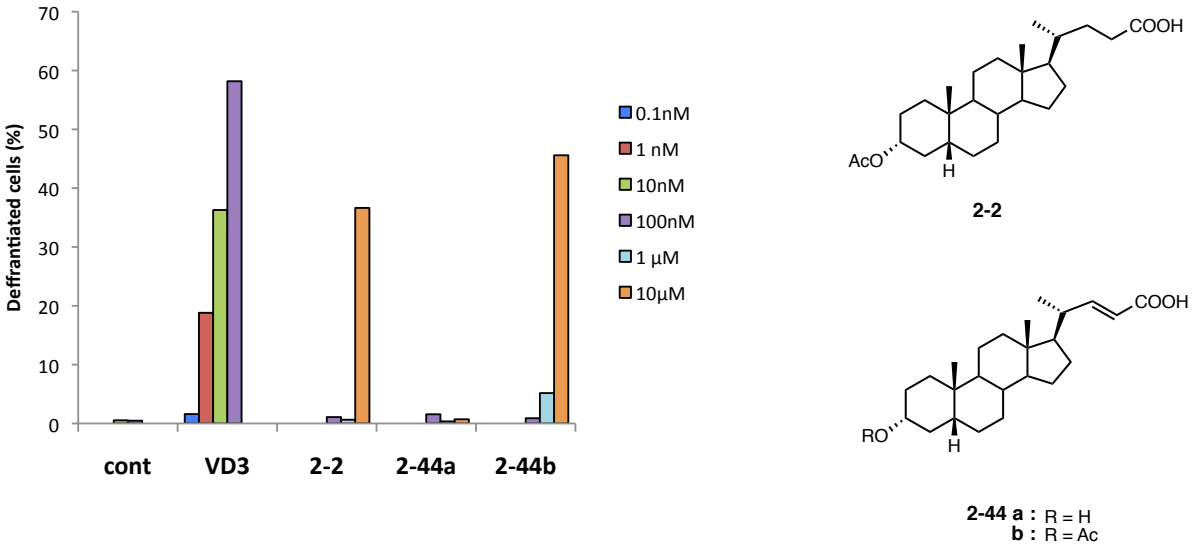


Fig. 2-11　HL-60 細胞を用いた分化誘導試験 (2)

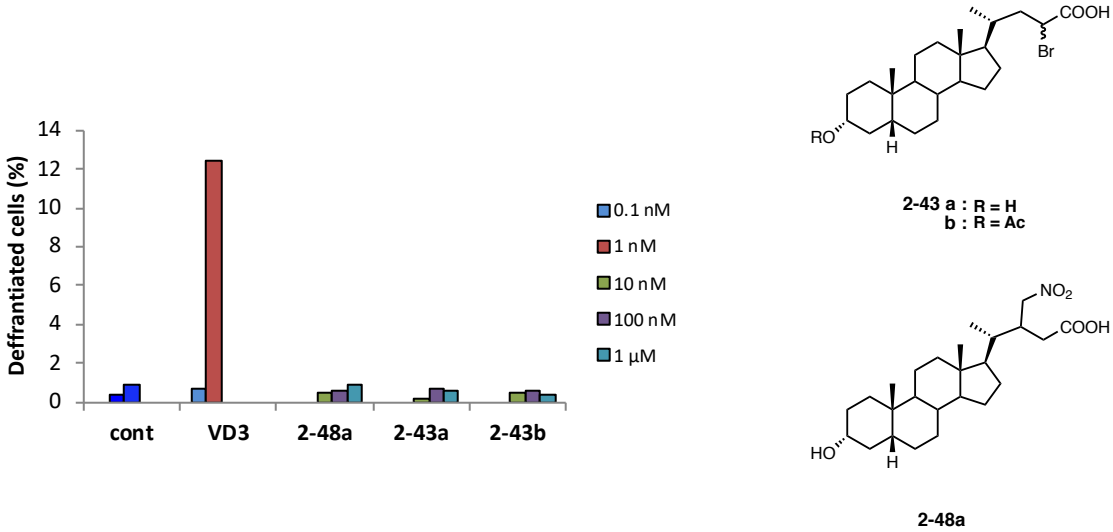


Fig. 2-12　HL-60 細胞を用いた分化誘導試験 (3)

化合物 **2-2** と **2-44b** の活性にほとんど差がみられないことから、側鎖の二重結合の有無は活性にほとんど影響しないと考えられた。また、化合物 **2-43a**、**2-43b** 及び **2-48a** も顕著なアゴニスト活性を示さず、側鎖α位の臭素及び側鎖β位のニトロメチル基には活性を増加させる効果はないと考えられた。

2.5　小括

本研究は、VDR に弱いアゴニスト活性を有する LCA をリードとして、新規非セコステロイド型の VDR リガンドの開発を目的に行った。

本研究では、LCA の３位を修飾した化合物としてアミン（**2-18**）、アセトアミド（**2-19**）スルホンアミド（**2-20**）及び側鎖を修飾した化合物として臭素置換した化合物（**2-43**）、ニトロメチル化した化

合物（**2-48**）や側鎖に二重結合を持つ化合物（**2-44**）を合成し、HL-60 細胞を用いた分化誘導試験を行った。その結果から、LCA の３位については アミノ官能基よりも酸素官能基の方がビタミン D 活性が高い傾向が認められた。含窒素誘導体の中では、アミドよりもスルホンアミドの方が活性が高く、いずれの場合も、大きな置換基の導入は活性を低下させることが確認できた。

また、側鎖の修飾については、側鎖α位を臭素置換した化合物及び側鎖β位をニトロメチル化した化合物は顕著な活性を示さず、二重結合の有無は活性に影響しないことが明らかとなったが、合成できた化合物が限られ、十分な知見を得ることができなかった。

今回、合成した化合物の中では、スルホンアミド体 **2-20a** が最も強い活性を示し、リード化合物である LCA よりも強い活性を有していた。スルホンアミド体 **2-20a** は対応する酸素官能基であるスルホンエステル基をもつ化合物 **2-17** よりも活性は低かったが、スルホンアミド基はスルホンエステル基よりも化学的に安定であり、さらなる構造最適化を行うことで、より高い活性を持つ非セコステロイド型 VDR リガンドになり得ると考えている。

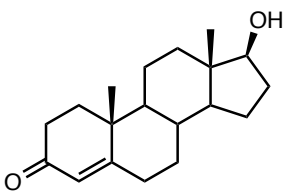
第３章　カルボランを疎水性骨格とする新規 AR アンタゴニストの創製

3.1　背景

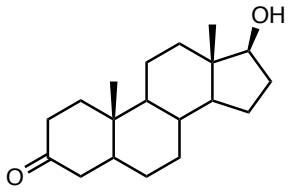
3.1.1　アンドロゲン受容体 (AR)及びアンドロゲン

アンドロゲン受容体は核内受容体スーパーファミリーの一員であり、AR 遺伝子にコードされた約 110kDa の受容体である。AR 遺伝子は、1981 年にヒト X 染色体から同定され [48]1998 年には、クローニングされた [49]。ヒト体内では、主に前立腺、骨格筋、肝臓、中枢神経などに発現している [50]。前立腺癌には過剰に発現しており、乳がん組織にも発現が認められる。

アンドロゲン受容体の内因性リガンドは、テストステロンやジヒドロテストステロンに代表される男性ホルモンである（Fig. 3-1)。テストステロンは最も重要な男性ホルモンであり、主に生殖腺や副腎においてコレステロールから生合成される。テストステロンは分泌後、5α-還元酵素の働きにより活性の高い 5α-ジヒドロテストステロン(DHT)に変換される。5α-還元酵素欠如症の男児が性分化疾患を呈することから、DHT は特に男性において重要であるとされている [51]。



テストステロン(TS)



デヒドロテストステロン(DHT)

Fig. 3-1　アンドロゲン受容体の内因性リガンド

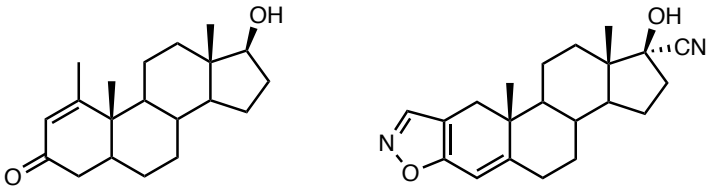
アンドロゲン作用の大部分は AR を介して発揮されており、アンドロゲンは、男性生殖のみならず女性生殖にも重要な役割を果たす。さらに、生殖にとどまらず、多様な生理作用を示すことも知られている。AR はプロゲステロン受容体と構造が似ており、高容量のプロゲステロンは AR を阻害する [52]。

3.1.2　AR アゴニスト

AR アゴニストはアンドロゲン受容体作動薬として、テストステロン、メテノロンおよびダナゾールなどが使われており、いずれもステロイド骨格を持つ(Fig. 3-2)。テストステロンは天然のリガンドであり、エステル体が男性性腺機能不全や造精機能障害、再生不良性貧血、骨髄線維症、腎性貧血など

の治療薬として使用されている。メテノロンはアンドロスタンの誘導体であり、弱いアンドロゲン作用をもつタンパク同化ステロイドであり、エステル体が、再生不良性貧血や低身長などの治療に用いられている。ダナゾールは、婦人科領域で低エストロゲン状態を作り上げるときによく使われ、性腺刺激ホルモンであるゴナドトロピンの分泌を抑制するものである。

テストステロンの長期使用は前立腺肥大や前立腺癌を引き起こすリスクがあること、ステロイド骨格を維持した誘導体は長期使用で肝臓毒性を示すことが多いことから、ステロイド骨格を持たない AR アゴニストも開発されてきたが、報告は限られており [53]日本における臨床応用例は見当たらず、今後の発展が期待される。



メテノロン　　ダナゾール

Fig. 3-2 アンドロゲン受容体作動薬

3.1.3　AR アンタゴニスト

AR アンタゴニストは主にアンドロゲン受容体拮抗薬として前立腺癌治療に用いられている [54]。AR の転写活性化は前立腺癌の発症と進展に深く関与していると考えられており、治療目的で様々な AR アンタゴニストが開発され、ステロイド骨格をもつステロイド性およびステロイド骨格ではない骨格を持つ非ステロイド性のものがともに臨床応用されている。(Fig. 3-3)

シプロテロン酢酸エステルやクロルマジノン酢酸エステルはステロイド骨格をもつアンタゴニストである。クロルマジノン酢酸エステルは、前立腺癌の治療アンドロゲンのはらたきを抑える効果以外に LH 分泌を阻害し、アンドロゲンの分泌を抑える働きもあることが知られている。

フルタミド [55]、ヌルタミド及びビカルタミド [56]は、ステロイド骨格をもたない第一世代の抗アンドロゲン薬である。前立腺癌にこれらの薬剤を用いたホルモン療法は前立腺局所だけでなく全身に対して癌の抑制が可能であり、局所進行癌または転移性の癌(PSA が高く、微小な転移が強く疑われる場合も含む)に対し最もよい適応がある。ホルモン療法は継続して行う必要があるが、継続により薬剤が効かなくなることがあり、このような状態を去勢抵抗性前立腺癌（CRPC）と呼び、問題となっている [57,58]。2014 年から、CRPC に対して有効な AR アンタゴニスト製剤としてエンザルタミド、アパルタミドおよびダロルタミドの承認申請が続いた [59]。これらはすべて非ステロイド性の抗アンドロゲン剤である。

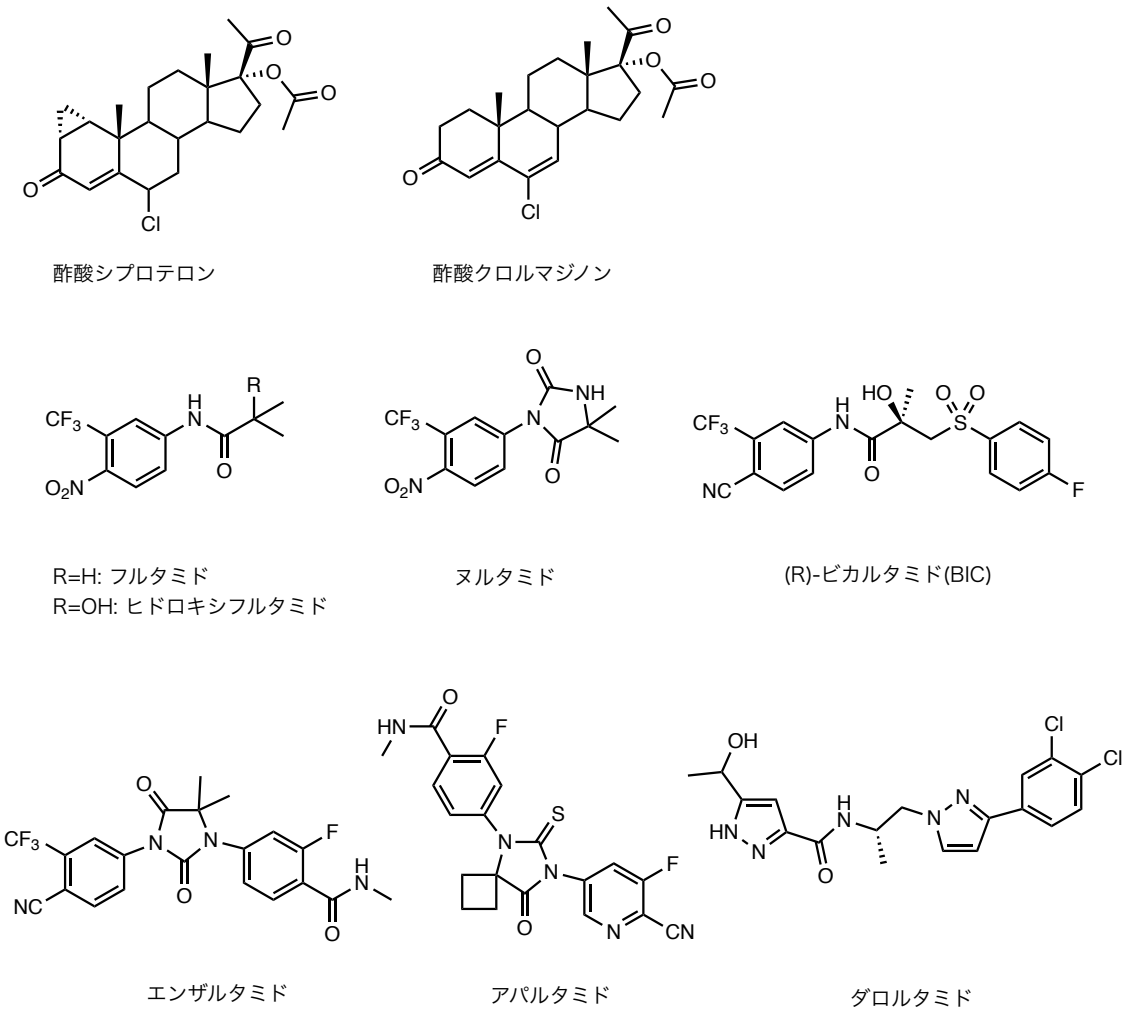


Fig. 3-3　臨床応用されている AR アンタゴニスト

前立腺癌は、国立がんセンターによると 2014 年における罹患数が男性の４位であり、治療薬の開発が強く望まれている。これまでに、AR アンタゴニスト活性が認められた天然物及び合成化合物の一例を Fig. 3-4 に示す。フタルイミド誘導体である DMIP は 1970 年代に報告されており [60]橋本らはその誘導体である　R–FPTH や ISOP-4 に顕著な AR アンタゴニスト活性及び VDR 活性を見出した [61]。

甲状腺ホルモンの一種である TRIAC や非ステロイド性抗炎症薬であるフルフェナム酸が、AR 活性を示すことも報告されている [62]。ぶどうの皮などに含まれる抗酸化物質レスベラトロールは　AR の転写を阻害すると報告がある [63]。天然物であるクルクミンの幾つかの誘導体には、変異 AR に対するアゴニスト活性が認められている [64,65]。

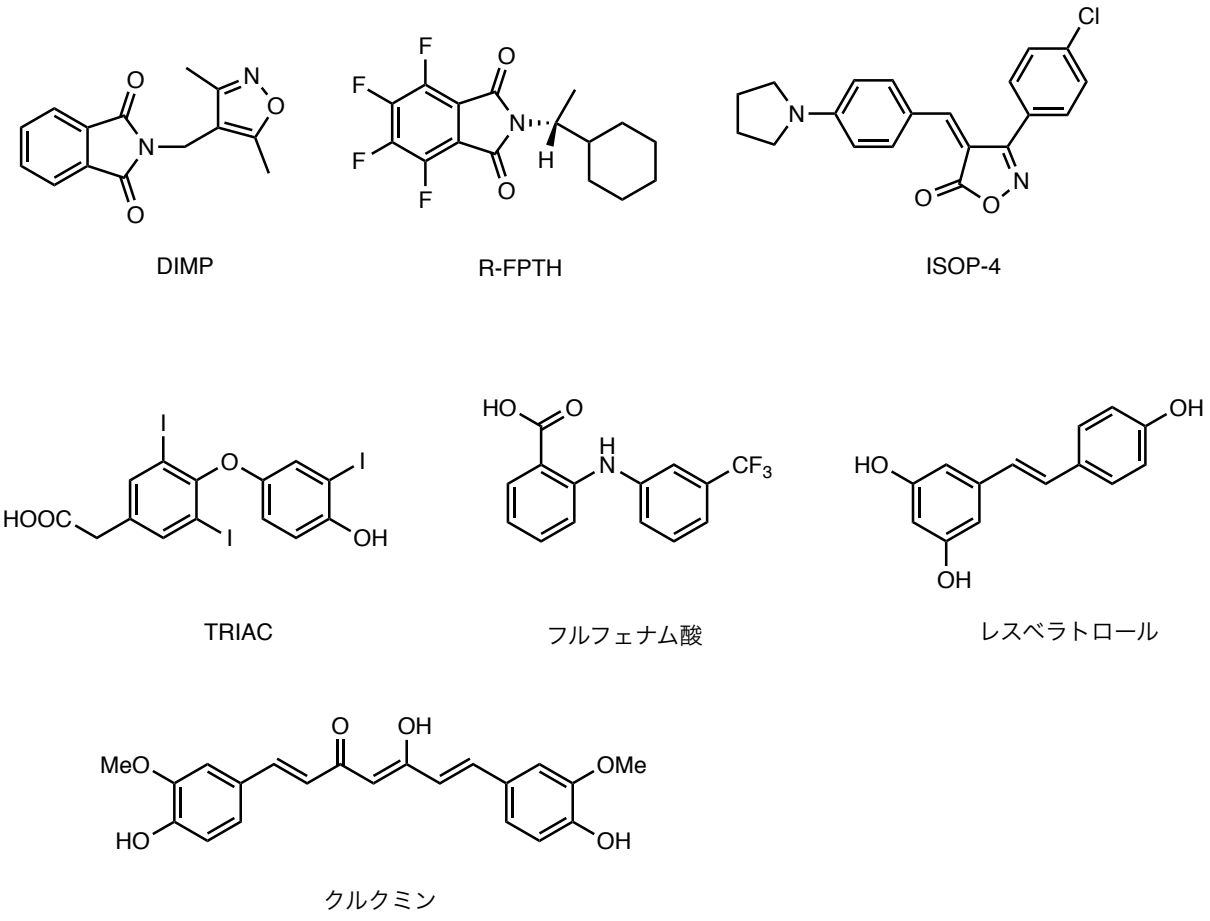


Fig. 3-4　AR アンタゴニスト活性が認められた天然物及び合成化合物

3.1.4　変異 AR と核内受容体機能制御仮説

前項で述べたように、第一世代の AR アンタゴニストは、治療継続によって、その効果が認められなくなるばかりか、逆に癌の増殖を促進することもある。前立腺癌が治療中に内分泌療法に抵抗性を示すようになる原因として、アンドロゲン受容体の変異が考えられている[66-68]。変異の多くは LBD に認められ[69]、これまでに１００種類以上同定されている[70]。Table 3-1 は変異 AR の例を示したものである。このような変異 AR は恒常的活性化能を有することがあり、また、変異 AR では AR アンタゴニストがアゴニストとして機能することもある。

変異	効果	細胞株	文献
L701H	副腎皮質ホルモンがアゴニストとして働く		71
V715M	低濃度 DHT による転写		72
R726L	エストラジオールがアゴニストとして働く		73
W741C	ビカルタミドがアゴニストとして働く		74
W741L	ビカルタミドがアゴニストとして働く		75
V757A	リガンド結合能が低下する		76
H874Y	リガンド結合能が低下する	22Rv1	77
T877A	様々なリガンドがアゴニストとして働く	LNCaP	78
T877S	エストラジオールとプロゲステロンがアゴニストとして働く		77

Table 3-1　変異 AR の例

このような AR アンタゴニストの機能転換について、橋本、棚谷は以下のような核内受容体機能制御に関する仮説を提唱している[79]。(Fig. 3-5)

1.1.4 項で述べたように、核内受容体の活性発現には LBD のヘリックス 12（H12）の立体構造の転換が重要な役割を果たしていると考えられている。正常な受容体の場合、アポ型では H12 の蓋が開いた不活性な構造をしているのに対し、アゴニストが結合（ホロ型）するとふたが閉じた活性化構造へと変化するが、既存のアンタゴニストが結合した場合は H12 の折りたたみ構造がホロ型と異なる立体構造となり、活性化されない。このようなアンタゴニストは正常でない H12 の折り畳み構造を誘起することから、ミスフォールディング誘導型アンタゴニストと呼ばれる。しかし、変異受容体の場合は、リガンドが結合していないにもかかわらず H12 がホロ型に近い立体構造を持つことにより活性を示したり、ミスフォールディング誘導型アンタゴニストが結合しても、その構造が大きく変化しないため、活性化構造は維持されることがある。そこで、このような不完全な阻害ではなく、H12 の折りたたみ構造自体を阻止するようなアンタゴニストであれば、変異受容体にも有効であると考えられる。このようなアンタゴニストは折りたたみ阻害型アンタゴニストと呼ばれている。

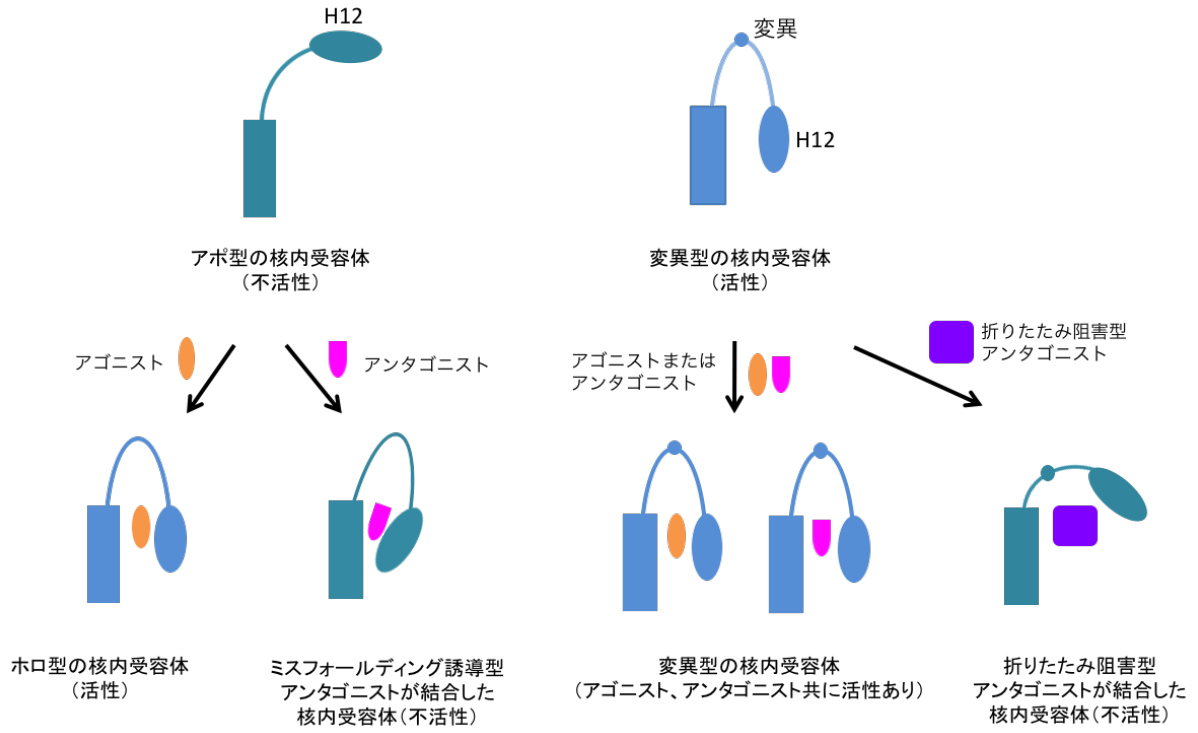


Fig. 3-5　正常および変異核内受容体のリガンド結合による機能発現の模式図 [79)]

3.1.5　カルボラン

所属研究室の共同研究者である藤井らは、疎水性のホウ素クラスターであるカルボランを種々の核内受容体のリガンドの骨格構造として用いた化合物を合成してきた [80-83)] 。

カルボランは、２つの炭素原子を有する正十二面体型ホウ素クラスターで、化学的・熱的安定性が高い。炭化水素に匹敵する高い疎水性を有し、２つの炭素原子の位置により、オルト・メタ・パラの３種の異性体が存在する [84,85)] （Fig. 3-6）。

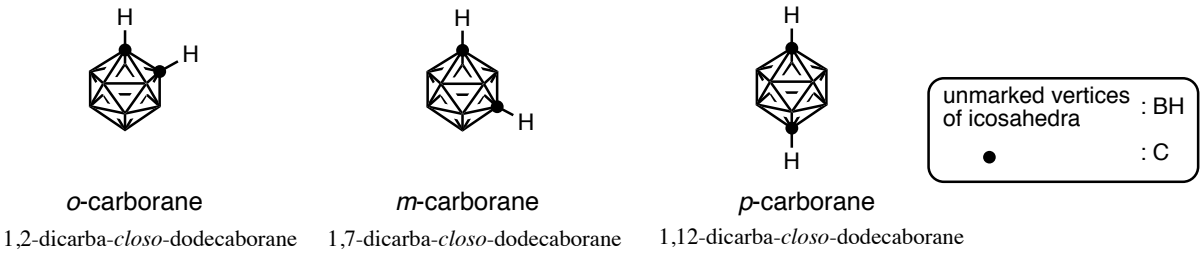


Fig. 3-6 カルボランの異性体の構造

カルボランは、その骨格の空間的占有がステロイド骨格における CD 環に類似することから、ステロイドホルモンやビタミン D の CD 環をカルボランに置き換えた化合物が合成され、高いアゴニストまたはアンタゴニスト活性を示す化合物が見出されている。Fig. 3-7 は、ビタミン D 受容体タンパク質とカルボランを疎水性骨格として有する合成リガンドの共結晶の X 線結晶構造である。

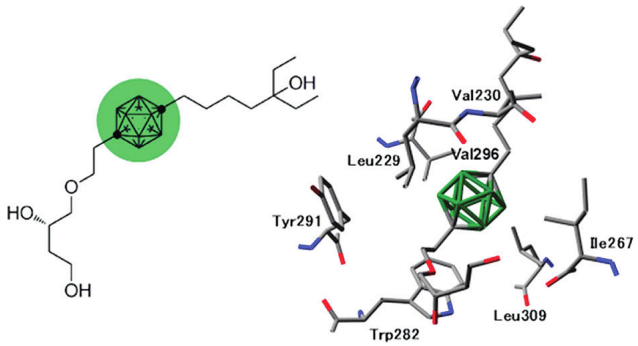
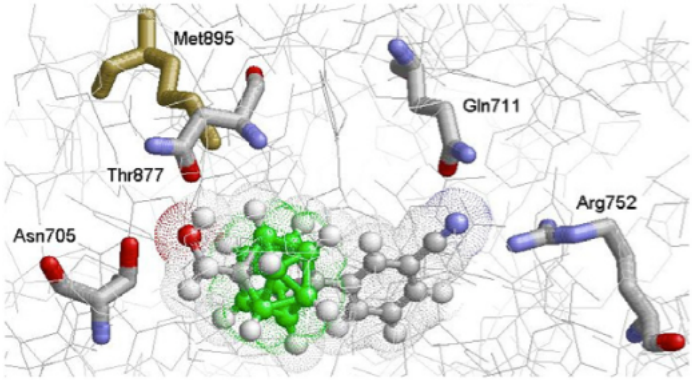
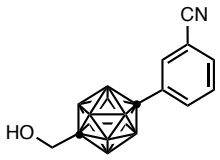


Fig. 3-7　ビタミン D 受容体タンパク質とカルボラン含有リガンド複合体の結晶構造 [57)]

カルボランを骨格構造として用いる新しい非ステロイド型ＡＲアンタゴニストも報告されており、例えばシアノフェニルカルボラン誘導体 BA341[86-88)]は、野生型ＡＲに対してヒドロキシフルタミドやビカルタミドと同等以上の高いアンタゴニスト活性を示す。Fig3-4 は　BA341 と AR のドッキングシミュレーションであるが [89)]、フェニルカルボラン骨格がステロイド誘導体と同じようにリガンド結合空間に結合し、N705 側鎖のカルボニル基と T877 側鎖のヒドロキシル基が BA341 のヒドロキシル基と相互作用すると推測されている。





BA341

Fig.3-8 BA341 と hAR LBD のドッキングモデル [89)]

一方で、現在の前立腺癌治療における問題の一つに薬剤耐性があげられており、この主要な原因は

AR の変異であると考えられている。野生型 AR に対しては高いアンタゴニスト活性を示す BA341 も、T877A 変異 AR を有する前立腺癌細胞 LNCaP[90]に対してはアゴニスト活性を示した。これに対し共同研究者の山田らは、BA341 をリードとして、変異 AR に対してもアンタゴニスト活性を持つ新規 AR アンタゴニストの創製を行い、カルボランーアニリド構造を有する化合物 **3-1**(Fig. 3-9)が LNCaP 細胞に対してもアンタゴニスト活性を示すことを見いだした [91] 。これは、**3-1** の嵩高いアニリド構造が AR の機能発現に必要なヘリックス１２の折りたたみを阻害するためである、と説明できる。また、さらなる構造展開により、ベンズイミダゾールなどアミド構造をアゾール構造に縮環させた化合物 **3-2** が顕著なアンタゴニスト活性を示すことも判明している。そこで、本研究では、先行研究をもとに、シアノフェニル-パラ-カルボランにもう一つ芳香環が直結したジアリルカルボラン構造が変異ＡＲに対するアンタゴニストのファーマコフォアとして有効であると考え、種々のジアリルカルボラン誘導体類 **3-3** の合成を計画した。本章では、これらのジアリルカルボラン誘導体類 **3-3** の合成及び生物活性について述べる。

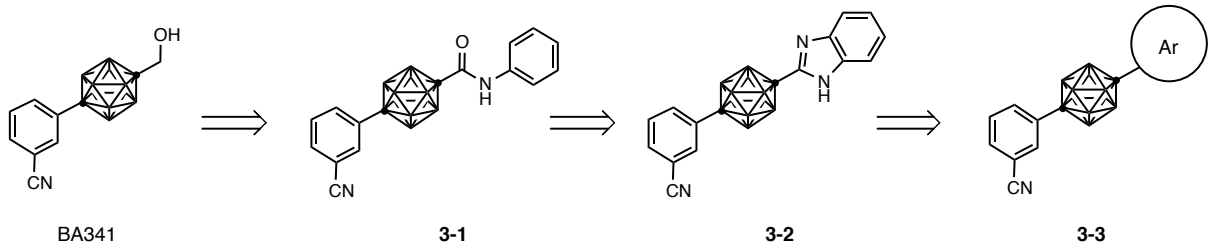
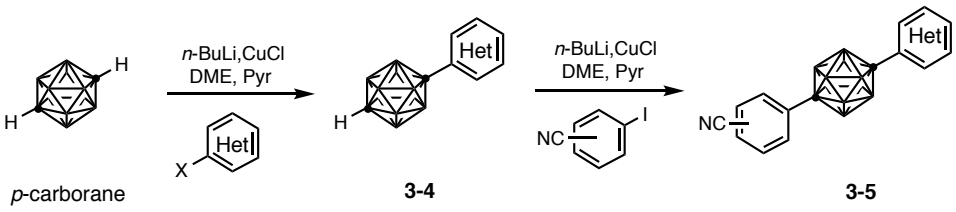


Fig. 3-9　リード化合物 **3-1** の構造展開：ジアリルカルボラン誘導体の分子設計

3.2　化合物のデザイン

Fig. 3-9 の一般式 **3-3** において、カルボランに結合する芳香環としては、種々の単環および複環の芳香環、複素環を導入することを計画した。芳香環をカルボランに導入する方法としては銅を用いた Ullmann 型のカップリング反応 [92]を用いるが(Scheme 3-1)、シアノ基が同反応の条件に耐えないため、シアノフェニル基を後で導入し、*m*-シアノ体、*p*-シアノ体の両方の活性を評価することとした。合成目標化合物の構造は Fig. 3-10 に示した。



Scheme 3-1　Ullmann 型カップリング反応によるジアリルカルボラン誘導体の合成計画

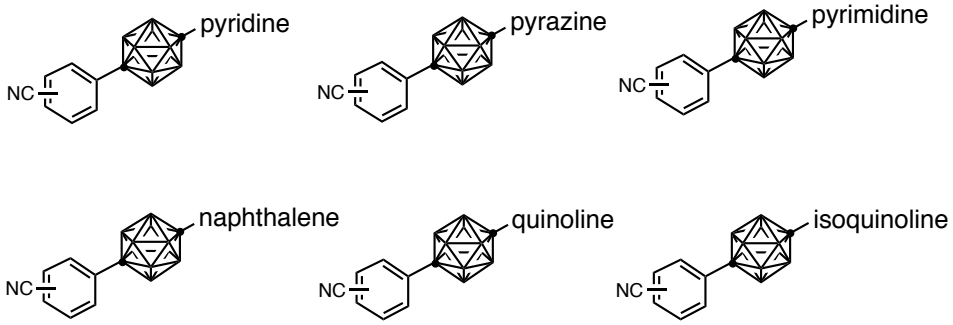
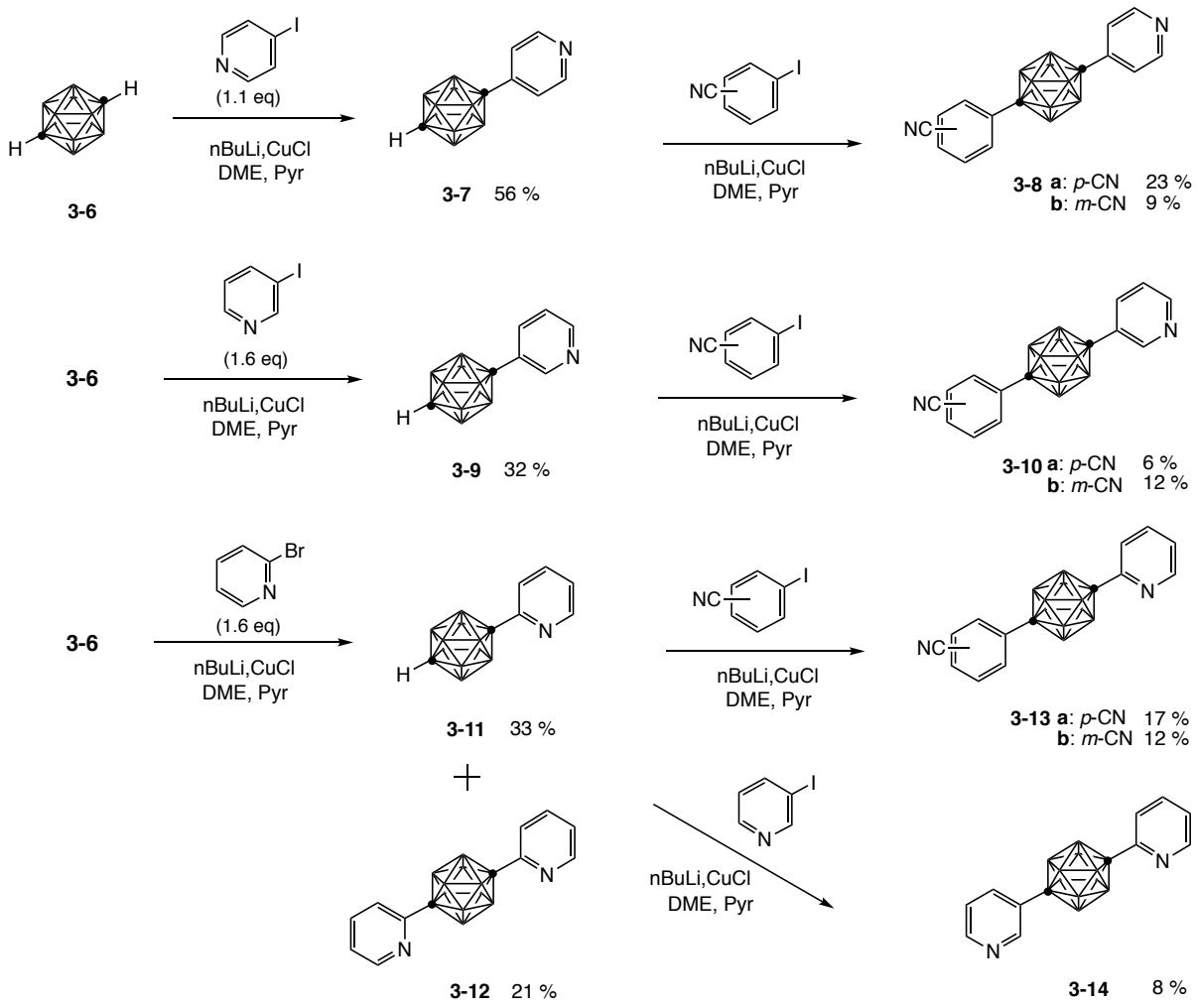


Fig. 3-10　合成目標化合物

3.3　化合物の合成

3.3.1　ピリジン環を導入した化合物の合成

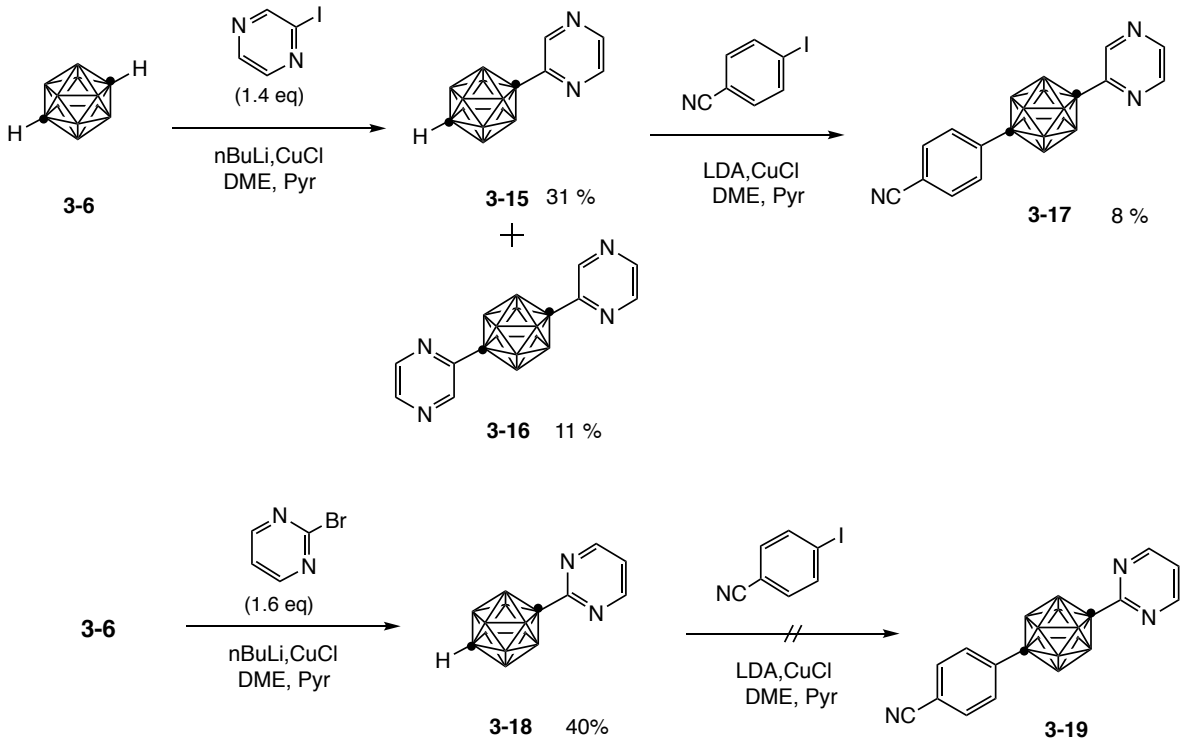
ピリジン環を *p*-カルボランに導入した化合物群は、*p*-カルボランを原料として Scheme 3-2 に従って Ullmann 型のカップリング反応により合成を行い、**3-8a**、**3-8b**、**3-10a**、**3-10b**、**3-13a**、**3-13b** 及び **3-14** を得た。また、合成の過程で *p*-カルボランの両側にピリジン環が導入された **3-12** が副生成物として得られた。



Scheme 3-2　ピリジン環を有する化合物群の合成

3.3.2　ピラジン環及びピリミジン環を導入した化合物の合成

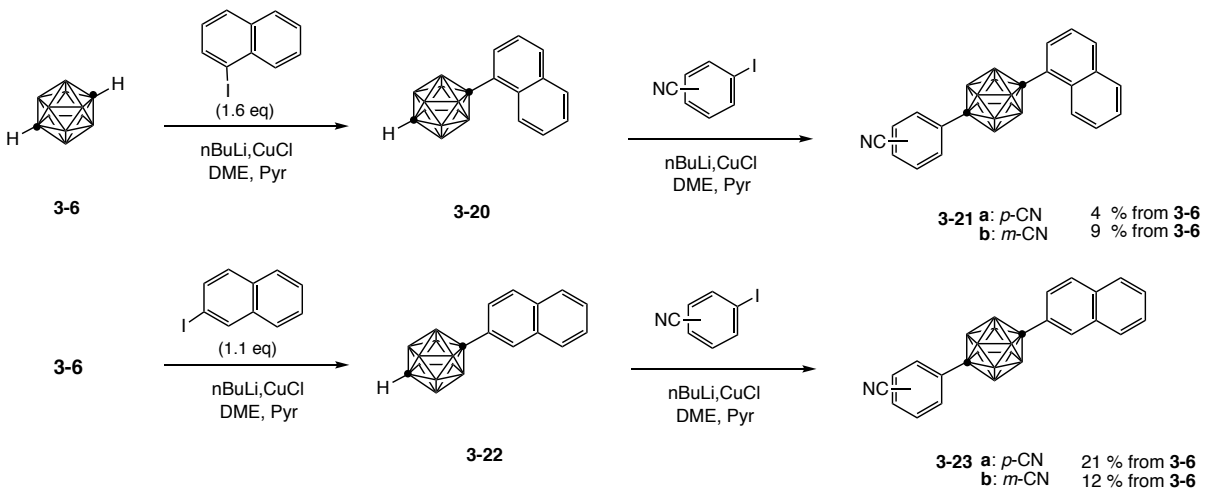
ピラジン環、ピリミジン環を *p*-カルボランに導入した **3-15** 及び **3-18** は Scheme 3-2 と同じ条件で Ullmann 型カップリング反応を行うと、原料が分解してしまい、反応が進行しなかった。そこで、**3-15** を原料にブチルリチウムの代わりに LDA を用いて低温（-18 ℃）で反応を行ったところ、**3-17** を得ることができた。しかし **3-18** を原料に用いて同じ条件で反応を行っても、**3-19** を得ることはできなかった。また、合成の過程で *p*-カルボランの両側にピラジン環が導入された **3-16** も得られた(Scheme 3-3)。



Scheme 3-3　ピラジン環を有する化合物の合成

3.3.3　ナフタレン環を導入した化合物の合成

p-カルボランに 1 –ヨードナフタレンを導入した **3-20** は試薬として用いた 1-ヨードナフタレンとの分離が困難であったため、1-ヨードナフタレンを含んだまま、次の反応に用いた。得られた **3-21a** 及び **3-21b** は 1-ヨードナフタレンとは分離可能であったが、試薬として用いた *m*-ヨードベンゾニトリルもしくは *p*-ヨードベンゾニトリルとの分離が困難であったため、リサイクル GPC を用いて精製した。シリカゲルカラムで粗精製した後にリサイクル GPC を用いたところ、目的物 **3-21a** または **3-21b** と試薬であるヨードベンゾニトリルが分離したため、**3-21a** 及び **3-21b** を分取し、それぞれ単体として得ることができた。2–ヨードナフタレンを試薬として用いた場合も同様に、生成物 **3-22** と試薬である 2-ヨードナフタレンの分離が困難であったため、**3-22** は試薬を含んだまま次の反応に用い、**3-23a** 及び **3-23b** はリサイクル GPC を用いて精製することで、それぞれ単体として得ることができた。(Scheme 3-4)



Scheme 3-4 ナフタレン環を有する化合物の合成

3.3.4　キノリン環及びイソキノリン環を導入した化合物の合成

p-カルボランにイソキノリン環を導入した **3-24** を合成し、ブチルリチウムを用いて **3-26b** を得る反応を行った。得られた化合物の ^{1}H NMR を Fig. 3-11 に示す。低磁場領域にキノリン環及びベンゼン環のプロトンのピークが観測されるが、積分値より、9H であると帰属された。もし得られた化合物が **3-26b** であれば 10H であるため、1H 不足していた。また、高磁場領域に特徴的なピークが観測され、これらは n-ブチル基に帰属できる。従って、得られた化合物は、**3-26b** ではなく、いずれかの位置に n-ブチル基が置換した化合物であると考えた。置換位置を決定するため、二次元 NMR の測定を行い、n-ブチル基の置換位置がキノリン環の 4 位である **3-25** と決定した。

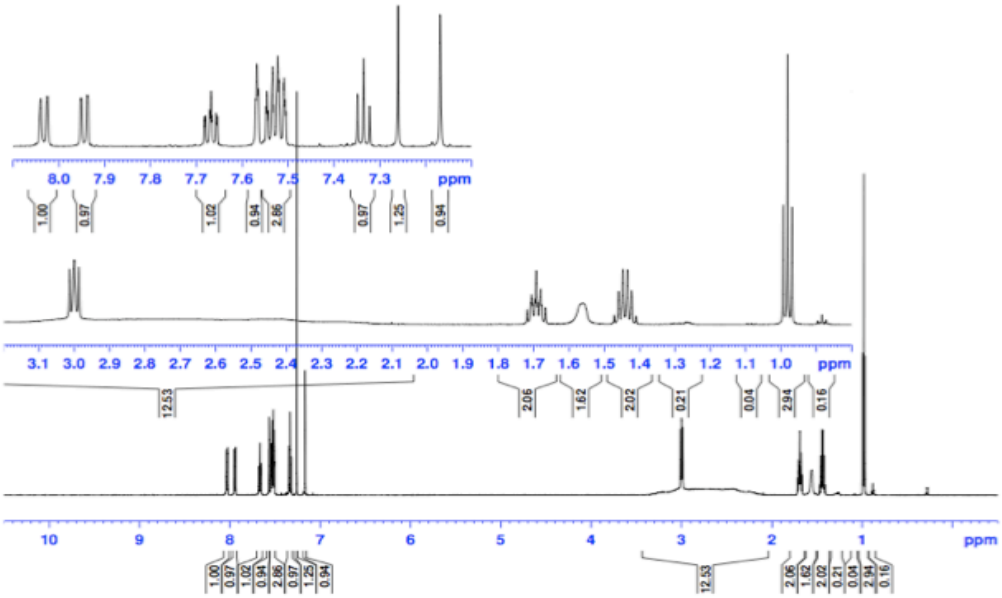
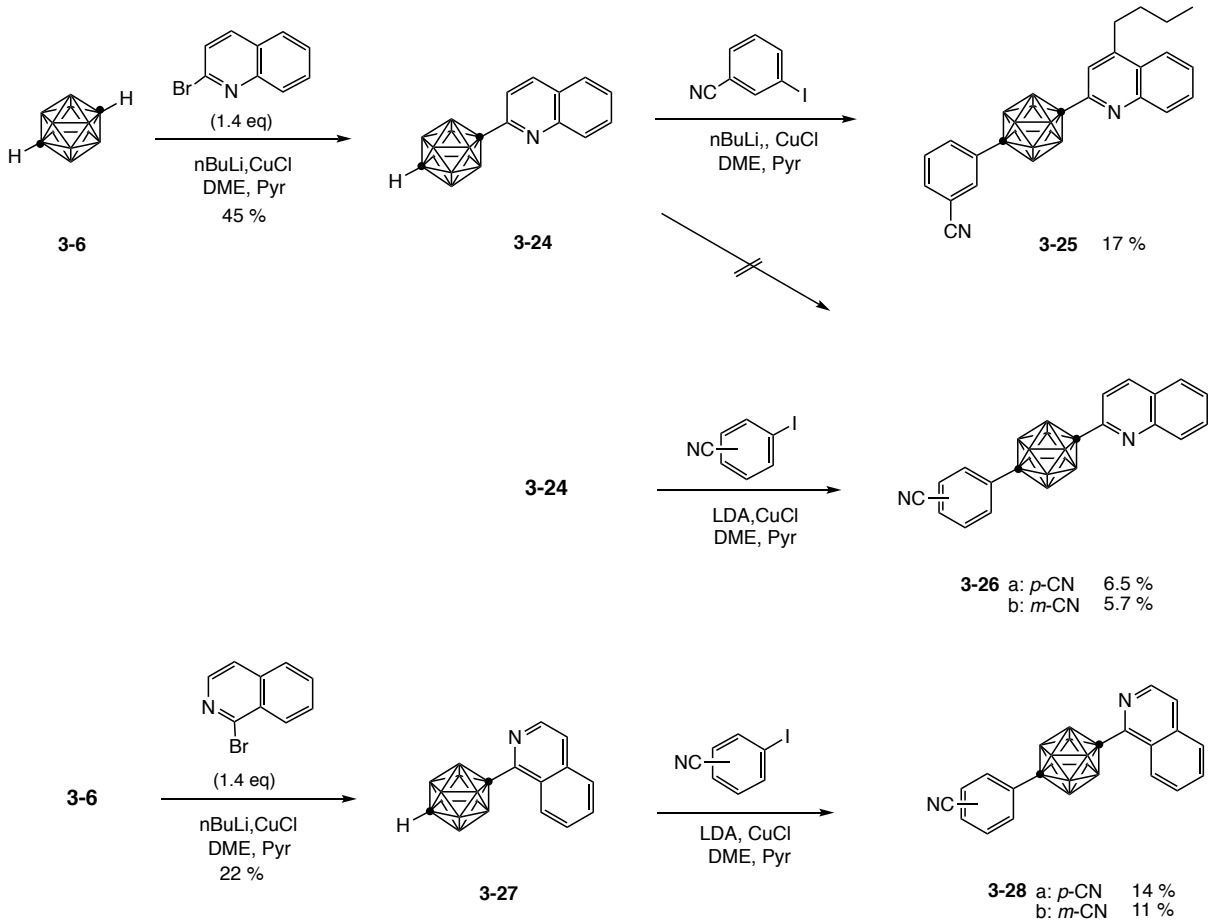


Fig. 3-11　化合物 **3-25** の ^{1}H NMR スペクトル

ブチルリチウムの代わりに LDA を用いて反応を行ったところ、**3-26a** 及び **3-26a** を得ることができた。同様に、キノリン環を導入した化合物 **3-27** を原料として LDA を用いて反応を行い、**3-28a** 及び **3-28b** を得た。いずれの化合物もカラムで粗精製後、再結晶により精製した(Scheme 3–5)。



Scheme 3-5　イソキノリン環及びキノリン環を有する化合物の合成

3.4　合成した化合物の AR 活性

3.4.1　単環性芳香環を導入したジアリルカルボラン誘導体の AR 活性

合成した化合物のアンドロゲン受容体活性の確認は、アンドロゲン依存的に増殖する SC-3 細胞および、LNCaP 細胞を用いた細胞増殖試験により行った[93]。今回用いた SC-3 細胞はマウスの乳癌細胞であり、野生型 AR を持っている。一方、LNCaP 細胞は、T877A 変異 AR を有するヒト前立腺癌細胞である。アゴニスト活性は、合成した化合物を単独で細胞に加えて培養し、細胞数が濃度依存的に増加するかどうかを調べる試験で確認した。細胞数は検出試薬 Cell Counting Kit-8 を用いて吸光度の測定によりカウントした。アンタゴニスト活性は、細胞に合成した化合物及び内因性のアンドロゲン受容体(AR)アゴニストであるジヒドロテストステロン(DHT)を加えて培養し、DHT による細胞数の増加を合成化合物が抑えることができるかどうかを調べる試験により確認した。

単環を有するカルボラン誘導体 **3-8a**、**3-8b**、**3-10a**、**3-10b**、**3-12**、**3-13a**、**3-13b**、**3-14** 及び **3-16**

の計 9 種類の化合物について、SC-3 細胞を用いた単独での活性評価（アゴニスト活性試験）の結果を Fig. 3-13 に、LNCaP 細胞を用いた単独での活性評価の結果を Fig. 3-14 に、SC-3 細胞を用いた 1nM DHT 共存の活性評価（アンタゴニスト活性試験）の結果を Fig. 3-15 に、LNCaP 細胞を用いたアンタゴニスト活性試験の結果を Fig. 3-16 に示す。アッセイに使用した化合物の構造は Fig. 3-17 に示した。

活性試験に用いた化合物は、いずれもアゴニスト活性はなく、**3-10b** 及び **3-13a** に野生型 AR に対する弱いアンタゴニスト活性が認められたものの(Fig. 3-9)変異型 AR に対してはアンタゴニスト活性は認められなかった(Fig. 3-16)。以上の活性試験の結果から、ピリジン環では AR の機能発現に必要なヘリックス 12 の折りたたみを阻害する程度が弱く、よりかさ高い複環の導入が必要であると考えられる。

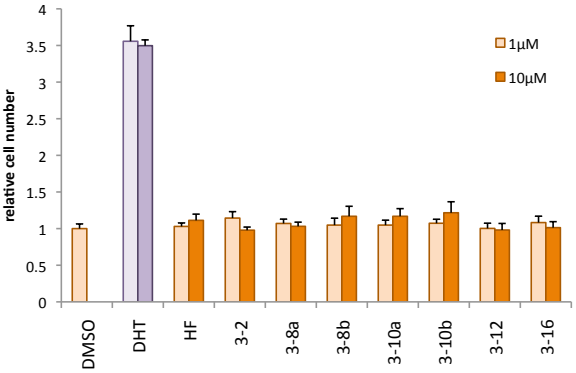


Fig. 3-13　活性評価（SC-3 細胞、化合物単独）

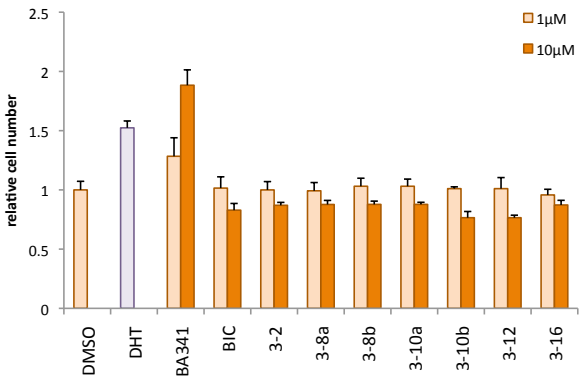


Fig. 3-14 活性評価（LNCaP 細胞、化合物単独）

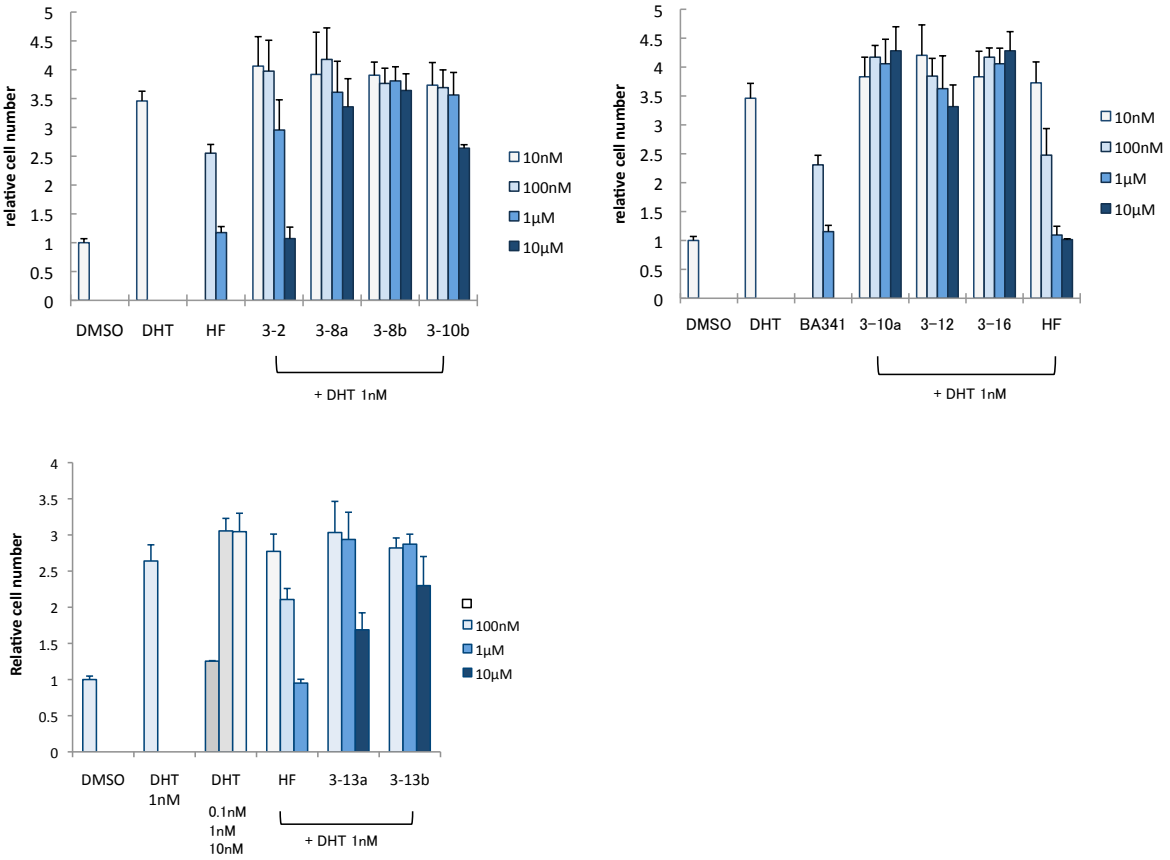


Fig. 3-15　活性評価 1 (SC-3 細胞、DHT 1nM 共存下)

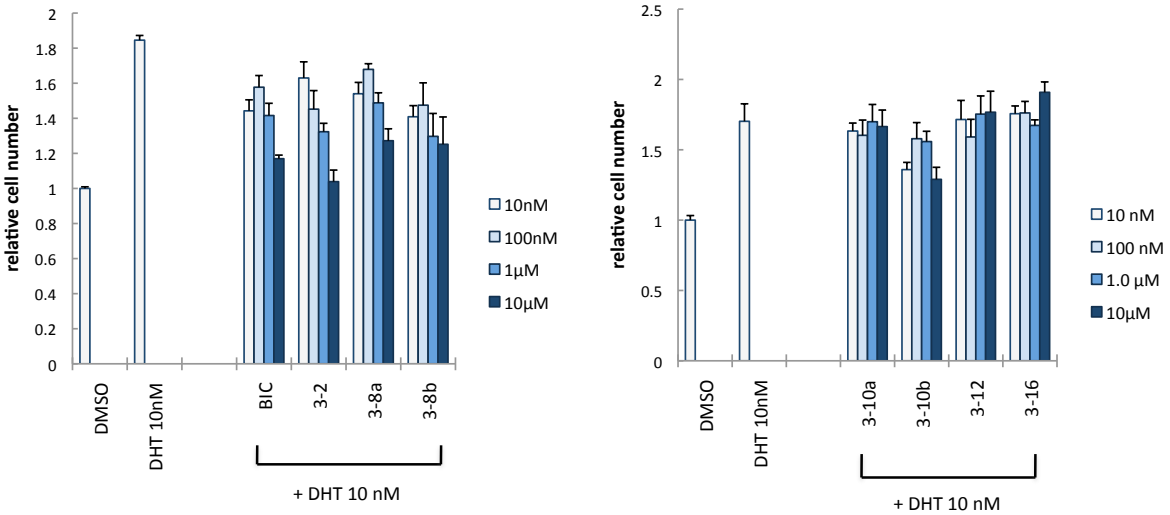


Fig. 3-16　活性評価 2（LNCaP 細胞、DHT 1nM 共存下）

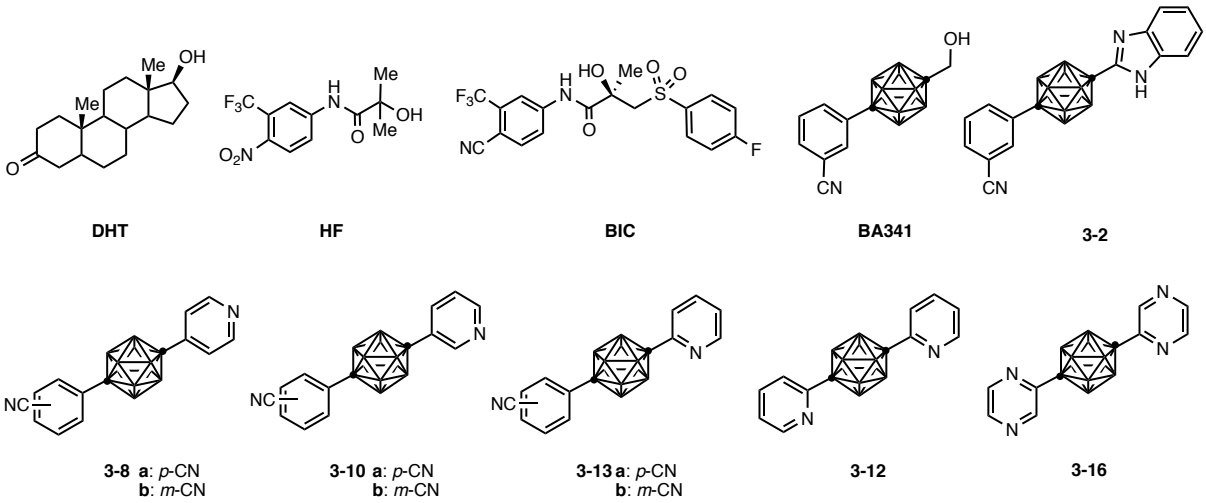


Fig. 3-17　Fig. 3-13～3-16 のアッセイに用いた化合物の構造

3.4.2　多環式芳香環を導入したジアリルカルボラン誘導体の AR 活性

多環式芳香環を有する化合物 **3-21a**、**3-21b**、**3-23a**、**3-23b**、**3-25**、**3-26a**、**3-26b**、**3-28a** 及び **3-28b** の SC-３細胞用いた活性評価を行った。結果を Fig. 3-18 及び Fig. 3-19 に、用いた化合物の構造を Fig. 3-20 に示す。強い活性を示す化合物は無かったが、**3-21a**、**3-21b**、**3-28a** 及び **3-28b** は単独で行った活性評価(Fig.3-18)の結果から弱いアゴニスト活性を示し、**3-21b** 及び **3-28b** は DHT 共存下で行った活性評価(Fig.3-19)から弱いアンタゴニスト活性を示すことがわかった。以上のことから、ナフタレンやイソキノリンの１位でカルボランに結合したジアリルカルボラン誘導体類は、弱いながらも AR アゴニストまたはアンタゴニスト活性を生じると推定した。

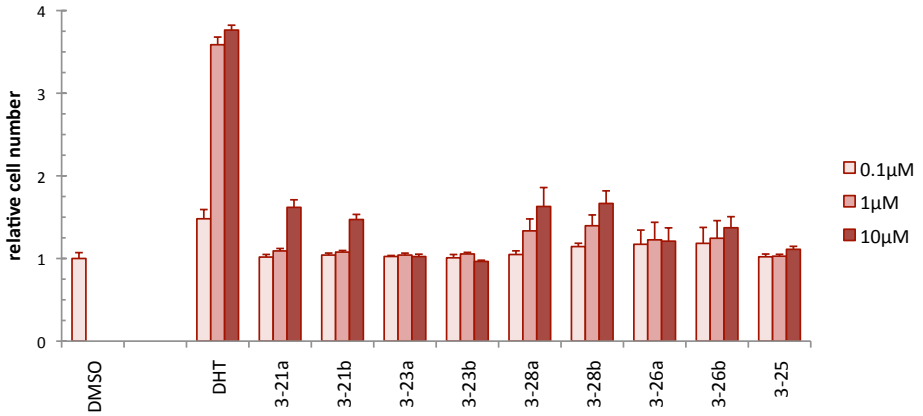


Fig. 3-18　活性評価（SC-３細胞、化合物単独）

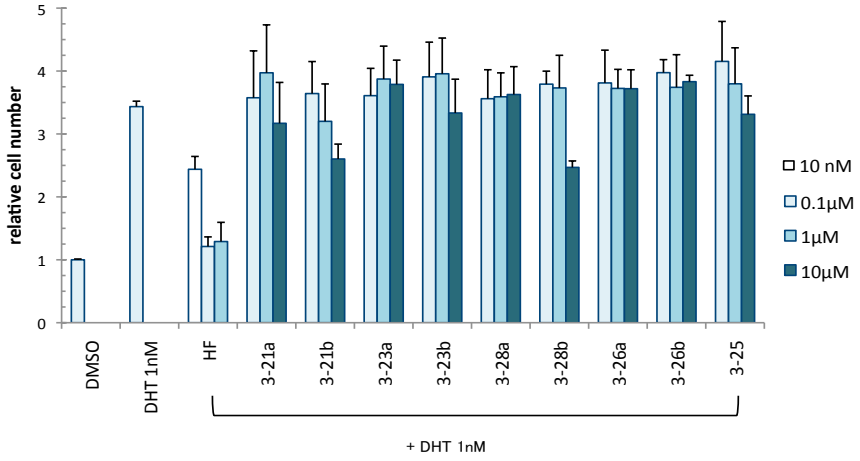


Fig. 3-19　活性評価（SC-３細胞、DHT 1nM 共存下）

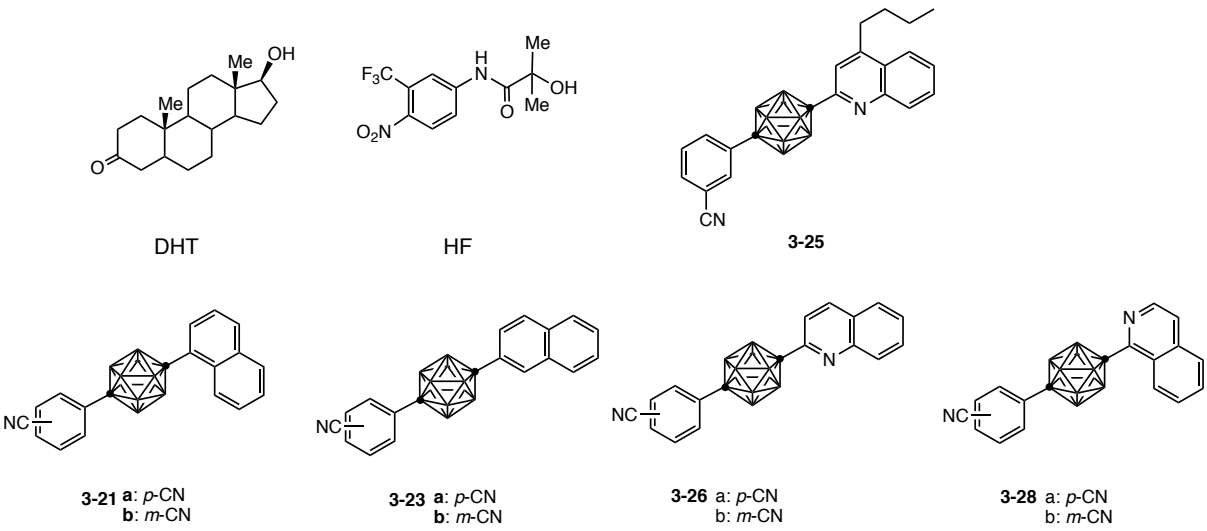


Fig. 3-20　Fig. 3-18、3-19 のアッセイに用いた化合物の構造

3.5　小括

本章ではカルボランを疎水性骨格とする AR アンタゴニストとしてジアリルカルボラン誘導体類を合成し、その生物活性を評価した。合成には Ulmann 型のカップリング反応を用い、反応条件を工夫することで合成に成功した。合成した化合物は野生型 AR を有する SC−３細胞及び変異 AR を有する LNCaP 細胞を用いて単独及び DTH 共存での生物活性を調べ、アゴニスト活性及びアンタゴニスト活性を評価した。

今回合成した化合物には AR に対し、活性を示すものが存在したが、いずれも IC_{50} は 10 μM 以上で

あり、高い活性を示す化合物は得られなかった。しかし、活性は決して高くはないものの、**3-21b**、**3-28b**など、アゴニスト活性とアンタゴニスト活性の両方を示す、興味深い化合物を得ることができた。このような性質を持つ化合物は、医薬品としての応用だけでなく、核内受容体の機能解明に利用できる可能性がある。

第 4 章：フェノキシフェノール骨格を有する AR アンタゴニストの構造展開 [94)]

4.1　背景

クルクミンは、ウコンなどに含まれるポリフェノールであり、3.1.3 項で紹介したようにアンドロゲン受容体（AR）にアンタゴニスト活性を示すことが知られている [64,65)]。所属研究室では、東京医科歯科大学との共同研究により、クルクミンの構造要素を基盤として創製したフェノキシフェノール誘導体である **4-1a** 及び **4-1b**（Fig.4-1）が、アンドロゲン依存的に増殖する SC-3 細胞や変異 AR を有する LNCaP 細胞に対して高い抗アンドロゲン活性を示し、**4-1b** よりも **4-1a** のほうが活性が高いことを報告した [95)]。化合物 **4-1a** 及び **4-1b** は、いずれも hAR（ヒトアンドロゲン受容体）に対して高い結合親和性を有し、AR を介して作用を発揮すると考えられるが、一方で化合物 **4-1a** 及び **4-1b** は、アンドロゲン非依存的な細胞増殖も抑制することから、AR アンタゴニスト作用とは異なる作用を有することも示唆されている。

本章では、第 3 章に引き続き AR をターゲットに、より高い抗腫瘍活性を有する化合物の創製や、他の作用を分離した AR アンタゴニストの創製を目的として、化合物 **4-1a** をリード化合物としたフェノキシフェノール骨格を有する AR アンタゴニストの合成及び生物活性について検討した。

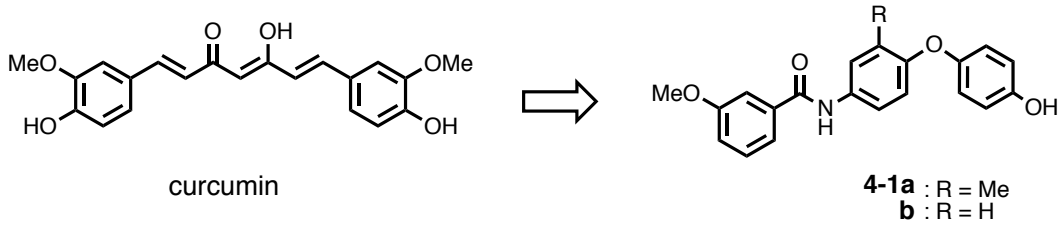


Fig. 4-1 クルクミンをもとに創製された AR アンタゴニスト **4-1a,b** の構造

4.2　分子設計

AR リガンド結合領域（AR-LBD）と化合物 **4-1a** のドッキングシミュレーション（Fig.4-2）では、フェノール性ヒドロキシ基がステロイド 17 位側に相当し、アミドが本来安定な trans 型ではなく cis 型コンフォメーションをとる可能性も示唆されている [96)]。

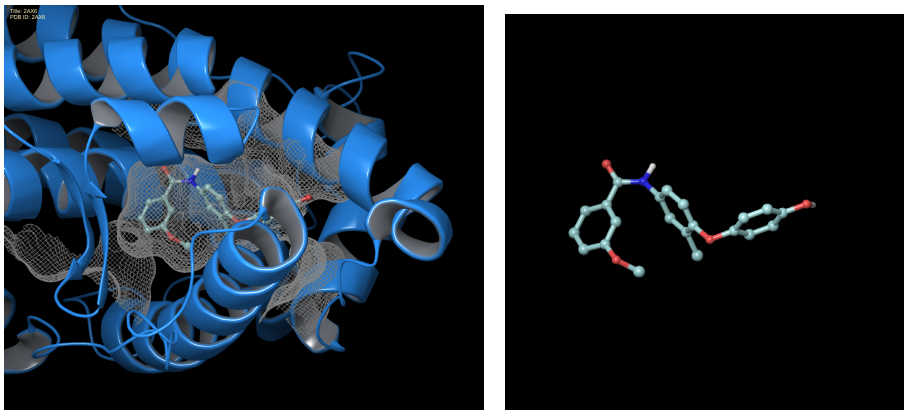


Fig. 4-2 AR-LBD と化合物 **4-1a** のドッキングシミュレーション [96)]

フェノール性ヒドロキシ基とアミド構造との距離および位置関係やアミド結合のコンフォメーションが活性に重要であることが予想されることから、center ring(B 環)の置換位置異性体や、*N*アルキルアミド誘導体、スルホンアミド誘導体を合成、その生物活性を検討した。なお、本章で合成及び生物活性を論じるフェノキシフェノール誘導体類の有する 3 つの芳香環については、それぞれを A 環、B 環及び C 環と称した（Fig. 4-3）。なお、先行研究において化合物 **4-1a** は **4-1b** に比べて活性が強いことが見出されているが、基本的な活性が同様にみられることから、B 環部のメチル基の有無を含めて新規化合物をデザインした。

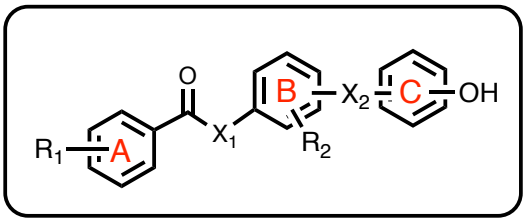


Fig. 4-3　本研究で合成したフェノキシフェノール誘導体の一般式と各環の名称

分子設計は Fig. 4-4 の(a)～(c)に示した。Fig. 4-4(a)は A 環、B 環、C 環の置換位置の異なる構造異性体の分子設計である。化合物 **4-1a** は B 環部が 1,4-置換構造であるが、この構造の違いによる活性相関を検討するため、B 環部が 1,3-置換構造をもつ化合物群を設計した。A 環については、オルト置換、メタ置換及びパラ置換を合成することとした。C 環のヒドロキシ基は、**4-1a** と同じパラ置換体に加え、メタ置換体も合成することとした。

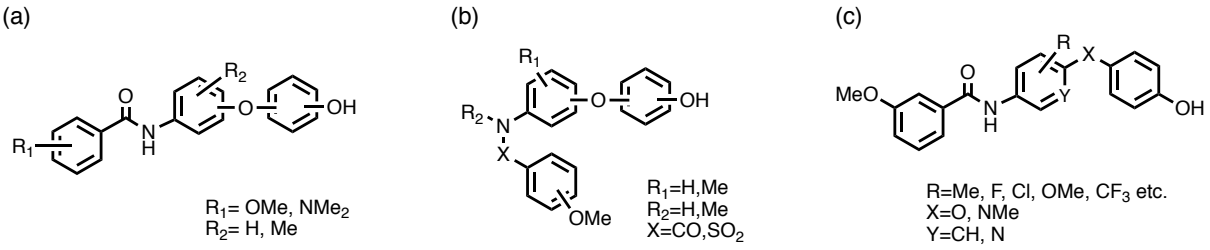


Fig. 4-4 本研究で分子設計した化合物の構造

Fig.4-4(b)は A 環と B 環のリンカー部のアミド結合を変換した化合物の設計である。本研究のリード化合物である化合物 **4-1a** と AR-LBD のドッキングシミュレーション (Fig.4-2) から A 環と B 環のリンカー部であるアミド結合が本来安定なトランス型ではなく、シス型コンフォメーションを取る可能性が示唆されている。所属研究室では、芳香族アミドの立体化学に関する基礎研究を行っており、ベンズアニリド等の芳香族二級アミド結合は、*N*-メチル化することで、トランス型からシス型コンフォメーションに変化することがわかっている [97]。ドッキングシミュレーションの結果が正しいならば、リンカー部の構造をメチルアミドにすることでシス型コンフォメーションが安定構造となり、高い活性を示す化合物が得られることを期待した。

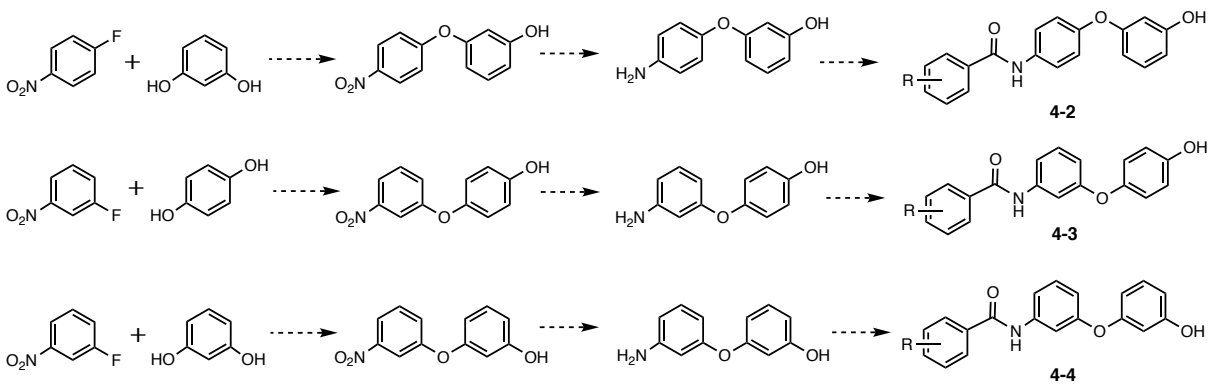
また、アミド結合ではなく、スルホンアミド結合をリンカーとすることで、立体構造が変化すると考えられ、立体構造と活性との関連性を明らかとする目的で、リンカーをスルホンアミドとした化合物の合成も行うこととした。スルホンアミド型の化合物も、NH 型、N-メチル型の両方を合成した。

Fig. 4-4(c)は B 環置換基を変換した化合物の分子設計である。化合物 **4-1a** は B 環部にメチル基を有するが、メチル基を導入することで化合物 **4-1b** よりも活性が増強している [95]。そこで、B 環置換基の構造活性相関の検討のため、メチル基以外の様々な置換基を導入した化合物を合成する。なお、この検討は、B 環部の置換構造などを最適化してから行う。

4.3 化合物の合成

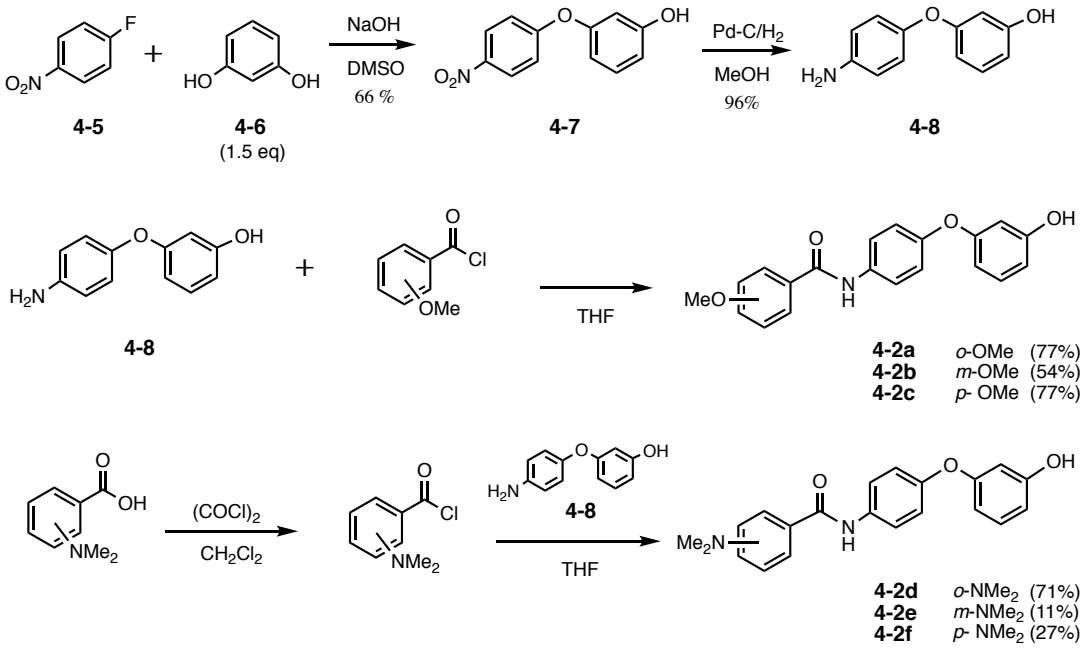
4.3.1 B 環の位置異性体の合成 (シリーズ(a))

まず始めに B 環の骨格構造の異性体の構造活性相関を検討するため、**4-2**、**4-3** 及び **4-4** に示すような構造をもつ化合物群を以下のスキームで合成することを計画した(Scheme 4-1)。



Scheme 4-1　化合物群 **4-2**、**4-3** 及び **4-4** の合成計画

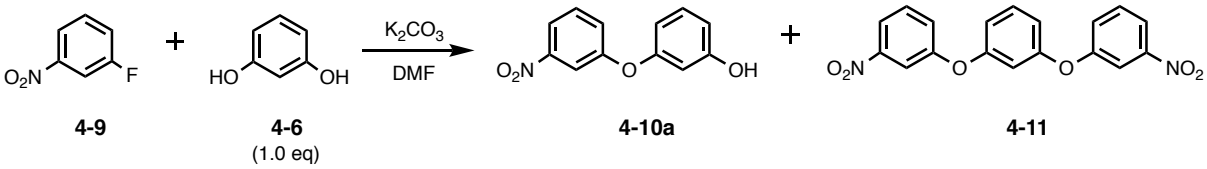
化合物群 **4-2** は以下の Scheme 4-2 に従って合成した。**4-5** と **4-6** を原料に用いた S_NAr 反応は、粘性が高くなるためメカニカルスターラーを用いて行った [98]。得られた **4-7** のニトロ基を接触還元し、アミン **4-8** を得た。得られた **4-8** を用いて **4-2a**～**4-2f** を合成した。



Scheme 4-2 化合物 **4-2a**～**4-2f** の合成

続いて化合物群 **4-3** 及び **4-4** の合成を行った。化合物群 **4-3** の合成原料となる **4-10a** の合成を Scheme 4-2 の **4-7** の合成と同様に、レゾルシノール **4-6** に 3-フルオロニトロベンゼン **4-7** を加えて DMSO 中加熱して得ようとしたが **4-10a** は得られなかった。これは、*m*-ニトロフルオロベンゼンが芳

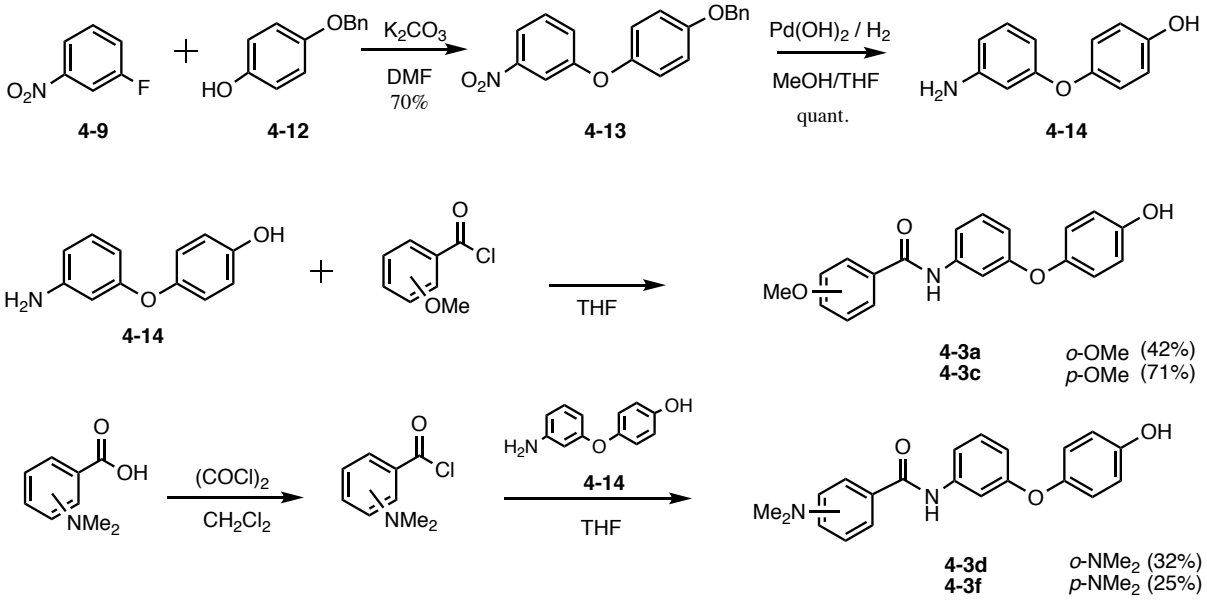
香族求核置換反応に不利な配向性であるためと考え、文献 99）を参考に K_2CO_3 と DMF を用いて 150 ℃に加熱し 24 時間反応を行ったところ、目的物 **4-10a** を得ることはできたが、収率が低く、副生成物として bis 体 **4-11** が生成した (Scheme 4-3)。そこで、化合物群 **4-3** 及び **4-4** の合成は、ヒドロキノン、レゾルシノールの一方のヒドロキシ基が保護された、*p*- または *m*-ベンジルオキシフェノールを原料として反応を行うことにした。



4-9 **4-6** (1.0 eq) **4-10a** **4-11**

Scheme 4-3 化合物 **4-10a** の合成

C 環のヒドロキシ基が *p*-置換である化合物群 **4-3** の合成のため、*p*-オキシベンジルフェノール **4-12** と 3-フルオロニトロベンゼン **4-9** を用いた反応を行ったところ、化合物群 **4-3** の合成原料となる **4-13** を 70%の収率で得ることができた。化合物 **4-7**(Scheme 4-2)の接触還元反応において、パラジウム炭素を用いたところ反応の進行が遅かったため、**4-13** の接触還元には水酸化パラジウムカーボンを用いた。得られた **4-14** は不安定であったため、精製せず、そのままアミド化を行い **4-3a**、**4-3c**、**4-3d** 及び **4-3f** を得た(Scheme 4-4)。



4-14 **4-12** **4-13** **4-14**

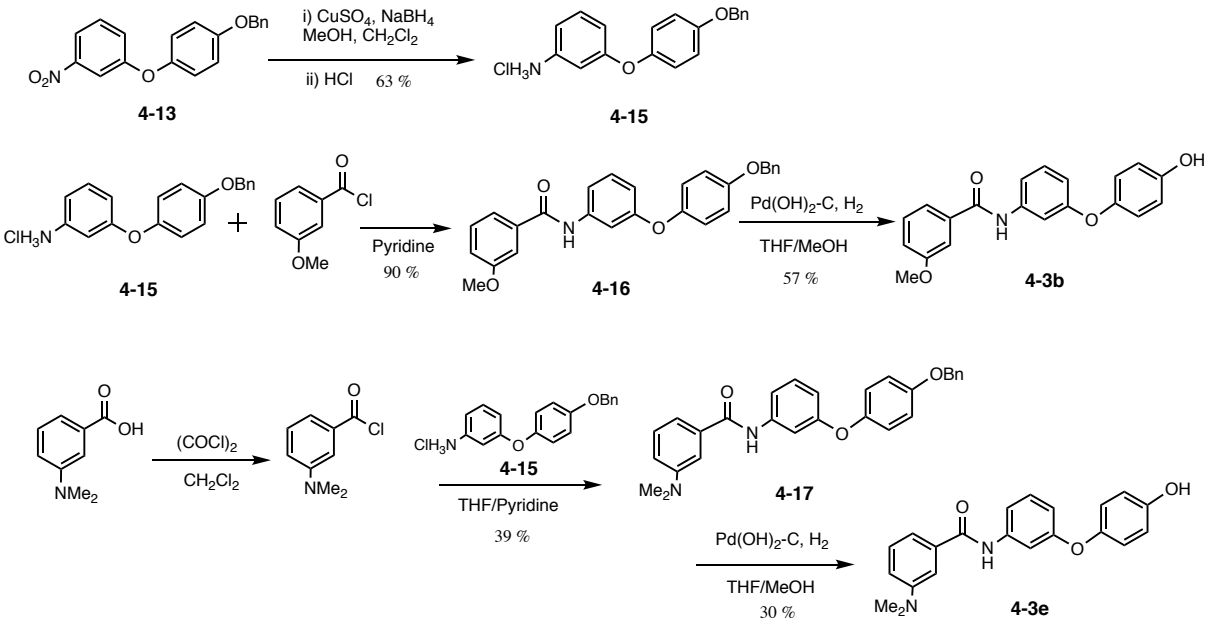
4-14

4-3a *o*-OMe (42%)
4-3c *p*-OMe (71%)

4-3d *o*-NMe_2 (32%)
4-3f *p*-NMe_2 (25%)

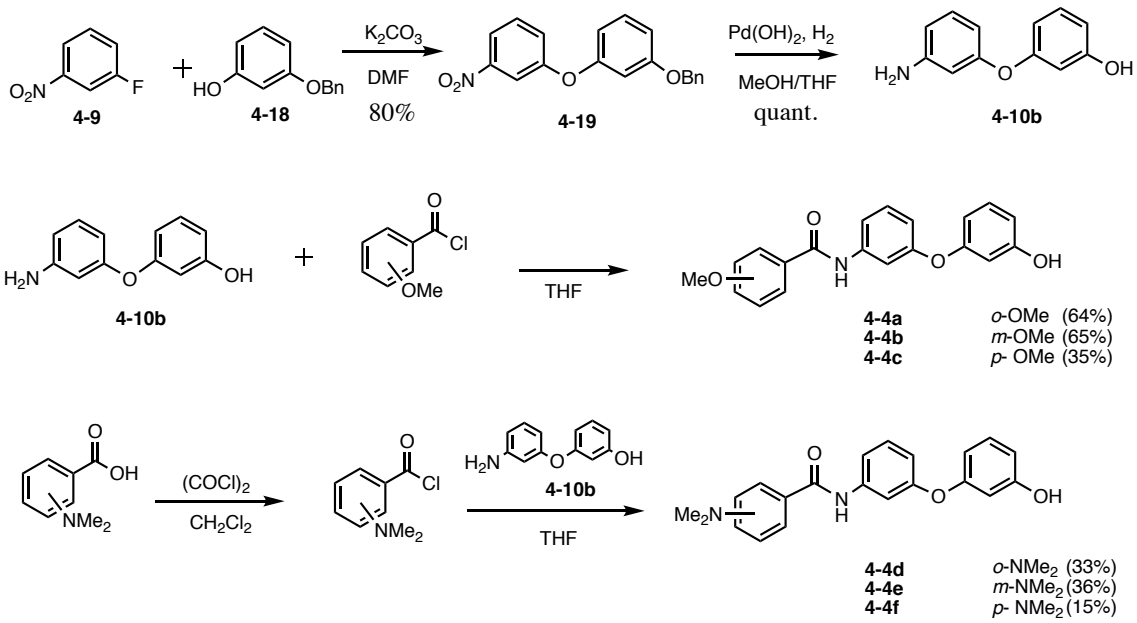
Scheme 4-4 化合物 **4-3a**, **3c**, **3d** 及び **3f** の合成

Scheme 4-4 で示した **4-14** を経る方法で合成を行うと、**4-14** のアミノ基とフェノール性ヒドロキシ基の双方が反応するため収率があまり良くない(25～71 %)のではないかと考え、収率の向上をめざして合成経路を Scheme 4-5 のように変更した。Scheme 4-5 に従い **4-13** のベンジル保護基を残したままニトロ基をアミノ基へ還元して **4-15** とし、A 環を導入した後に、ベンジル保護基を外して **4-3b** 及び **4-3e** を得た。このように経路を変更することで、ヒドロキシ基を保護した状態で A 環を導入する反応を行うことができるため、収率が向上するのではないかと期待したが、それぞれの収率は、57 % 及び 30 %であり、**4-14** を経る方法と比べて収率の向上は見られなかった。



Scheme 4-5 化合物 **4-3b** 及び **4-3e** の合成

Scheme 4-4 及び Scheme 4-5 の結果から、化合物群 **4-4** の合成は、Scheme 4-4 と同様の方法で行うことにした。*m*-オキシベンジルフェノール **4-18** と 3-フルオロニトロベンゼン **4-9** の反応は収率よく進行し、**4-19** が得られた。得られた **4-19** を還元し、**4-10b** を得た。**4-10b** は精製せず、そのままアミド化により A 環を導入し、化合物群 **4-4(a-f)**を得た(Scheme 4-6)。



Scheme 4-6　化合物群 **4-4** の合成

次に、B 環の骨格構造が 1,3-置換の化合物における B 環メチル基の位置異性体について検討するため、以下の Fig.4-5 に示す化合物 **4-20**～**4-24** の合成を計画した。

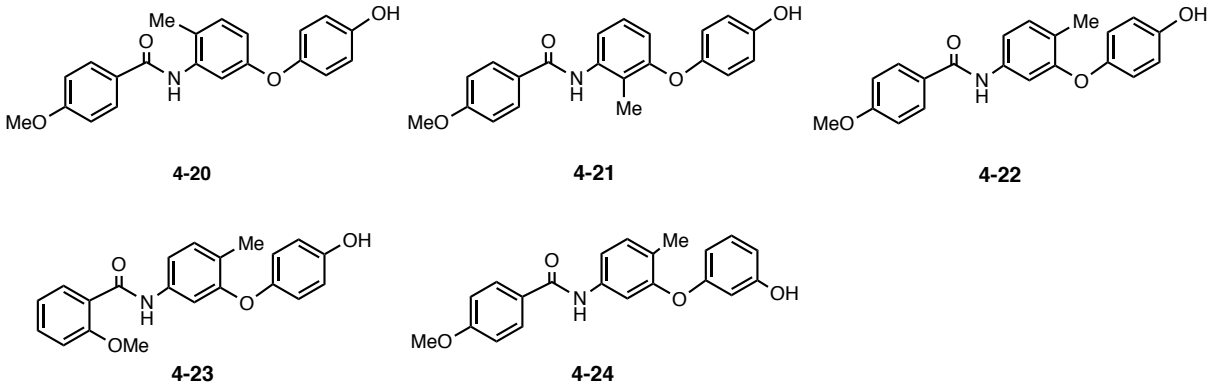
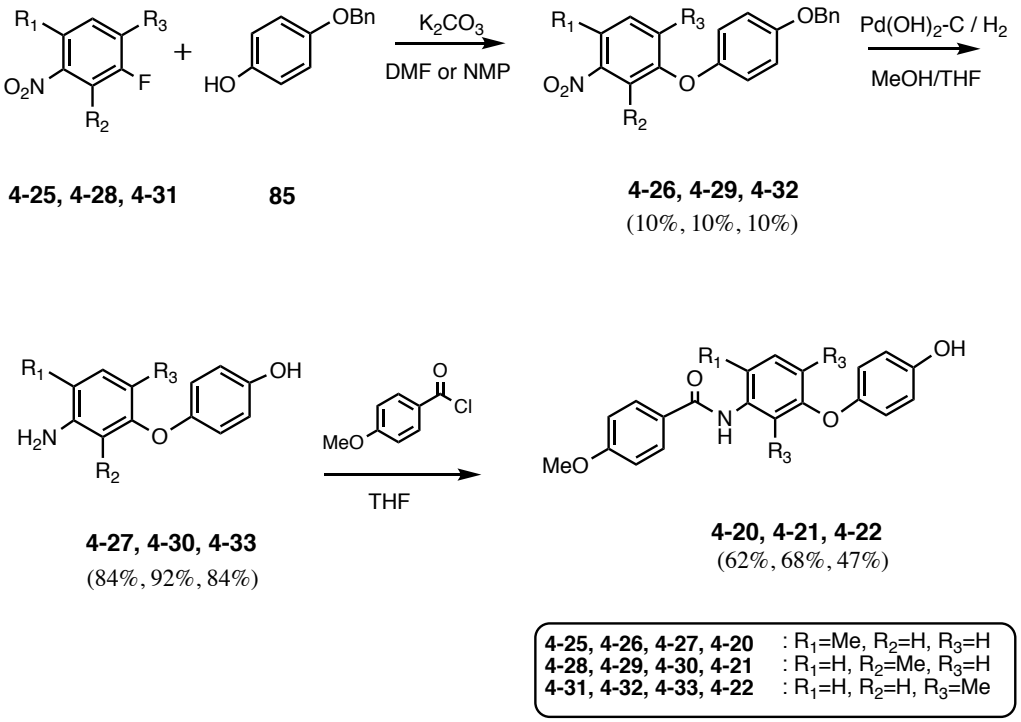


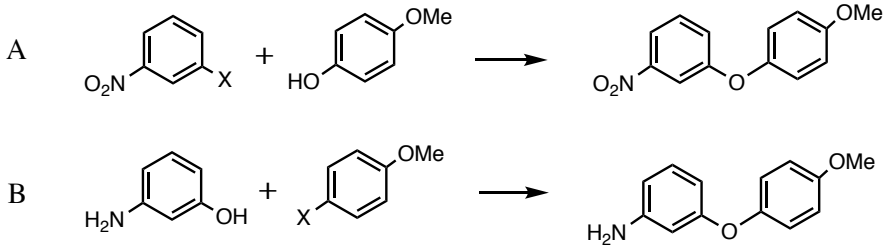
Fig. 4-5　合成目標化合物 **4-20**～**4-24** の構造

4-20、**4-21** 及び **4-22** の合成は以下の Scheme 4-7 に従って行った。**4-26** 及び **4-29** の合成は前節で述べた化合物 **4-13**、**4-19** と同様に、DMF を溶媒に用いて加熱還流下で反応を行ったが副生成物が多く低収率であった。そこで **4-32** の合成では DMF の代わりに N-メチルピロリドン(NMP)を溶媒に用いたが、収率の改善はみられなかった。得られた **4-26**、**4-29** 及び **4-32** は少量であったが、そのまま反応を進めて **4-20**、**4-21** 及び **4-22** を得た。



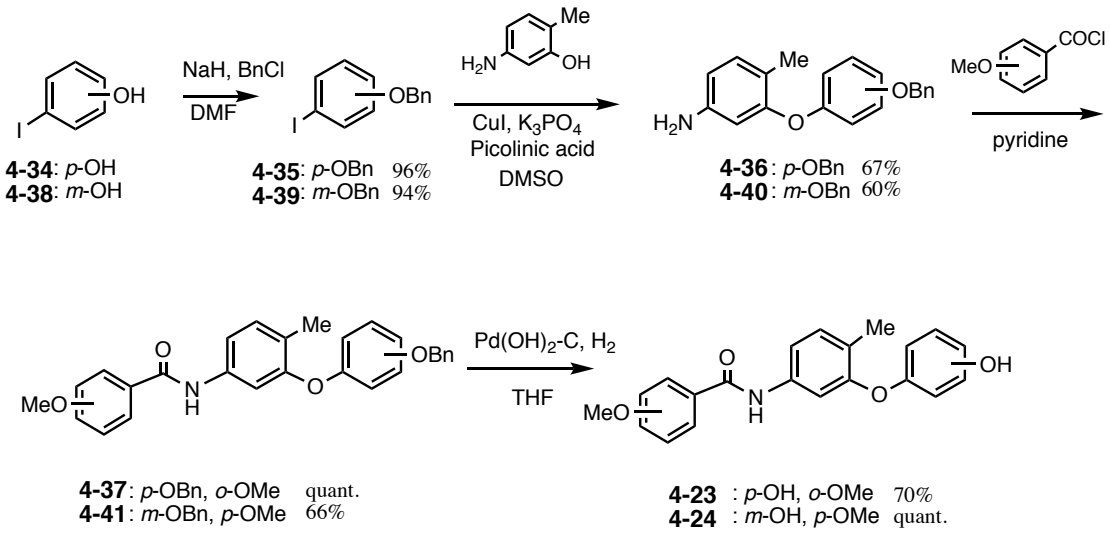
Scheme 4-7　化合物 **4-20**～**4-22** の合成

すでに述べたように **4-20**～**4-22** の合成(Scheme 4-7)では、B 環と C 環の結合反応の収率が低く、*m*-フルオロベンゼンにメチル基の置換したニトロフルオロトルエン類とベンジルオキシフェノールの反応は困難であることが予想された。そこで、Scheme 4-8 の A で示す方法で行っていた B 環と C 環の結合反応を B の方法に変更することを考えた[100]。



Scheme 4-8　B 環と C 環のカップリング方法

4-36 及び **4-40** の合成を Scheme 4-8 の B の方法で行ったところ、反応は問題なく進行したので、そのまま合成をすすめて **4-23** 及び **4-24** を得た（Scheme 4-9）



Scheme 4-9　化合物 **4-23** 及び **4-24** の合成

4.3.2　メチルアミド誘導体、スルホンアミド誘導体の合成 (シリーズ(b))

本項では A 環と B 環のリンカー構造の最適化を検討するため、リンカー部の構造をメチルアミドにした化合物の合成を行った。また、リンカー部の構造をスルホンアミドにした化合物も合わせて合成し、スルホンアミド型の化合物は、NH 型、N-メチル型の両方を合成した。(Fig.4-6)

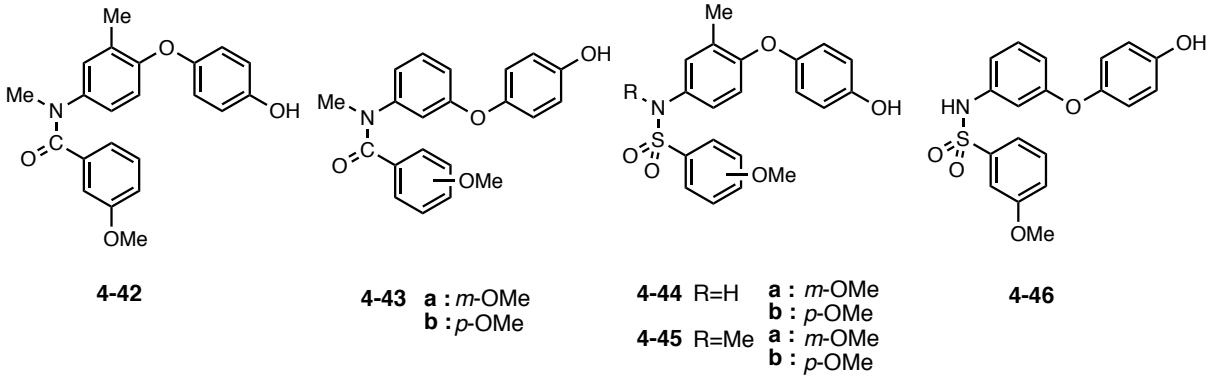
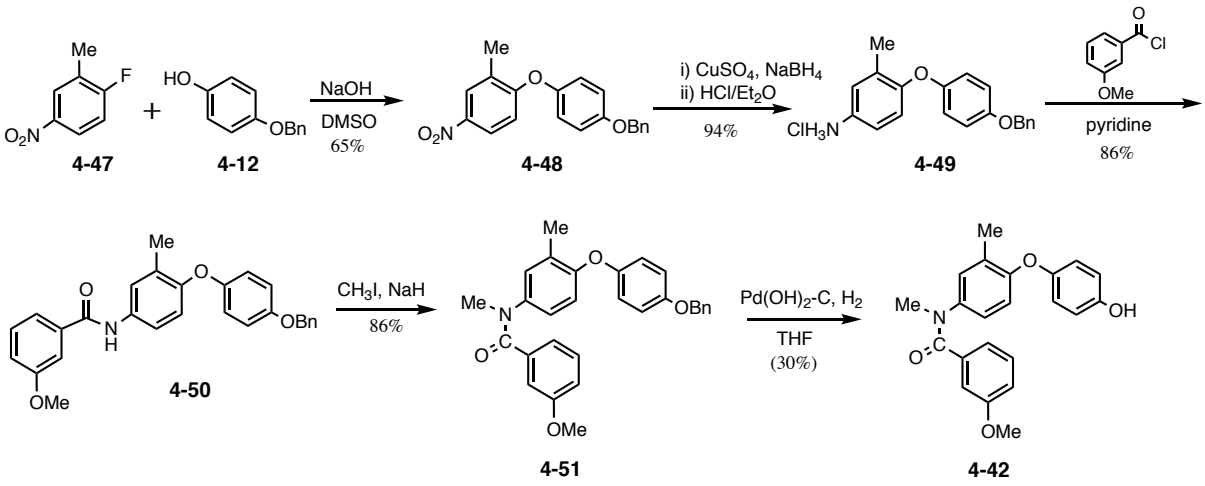


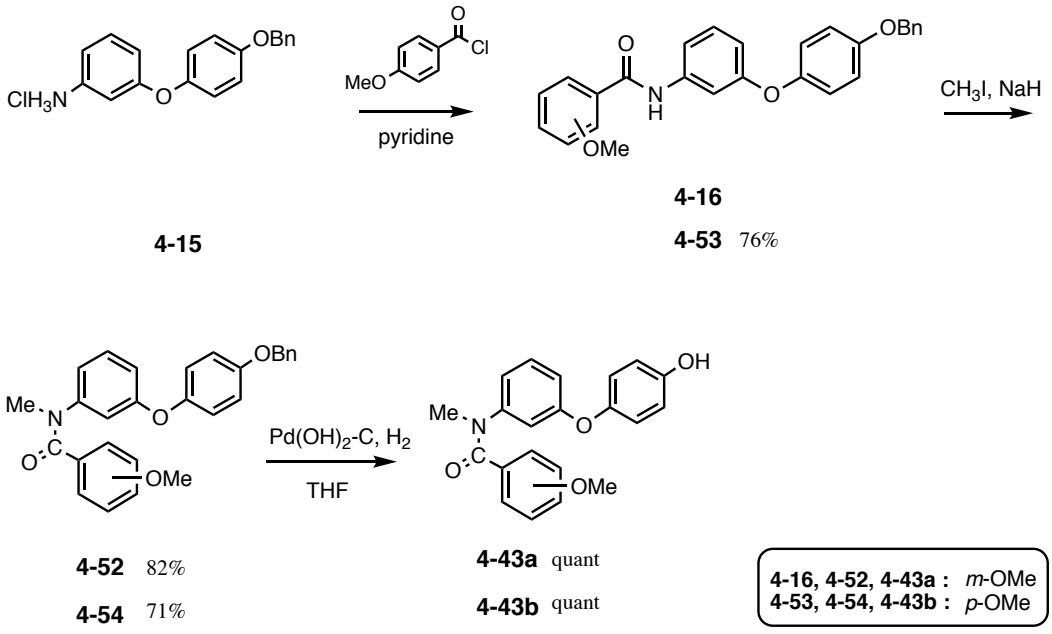
Fig. 4-6　合成目標化合物 **4-42**～**4-46**

化合物 **4-1a** の *N*-メチル誘導体である化合物 **4-40** は、C 環ヒドロキシ基のベンジル保護基を残したまま A 環を結合し、アミド結合をメチル化してから最後に保護基を除去する方法で合成を行い、収率よく得ることができた(Scheme 4-10)。



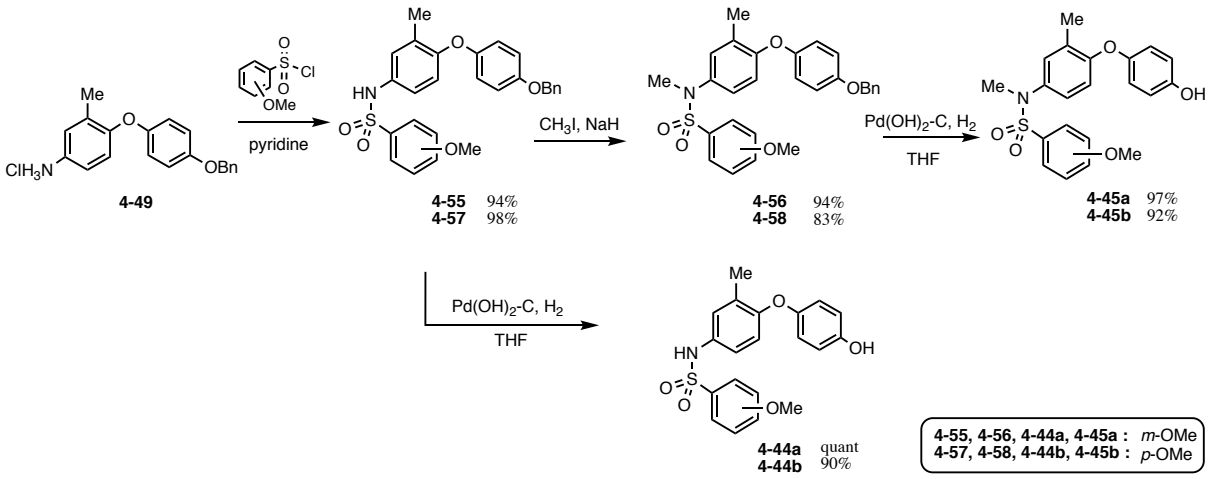
Scheme 4-10　化合物 **4-42** の合成

B 環の骨格構造が 1,3-置換型のメチルアミド誘導体（**4-43a**、**44b**）については、**4-43a** は **4-15** から、**4-43b** は **4-16** を用いて合成を行い、収率良く得ることができた(Scheme 4-11)。

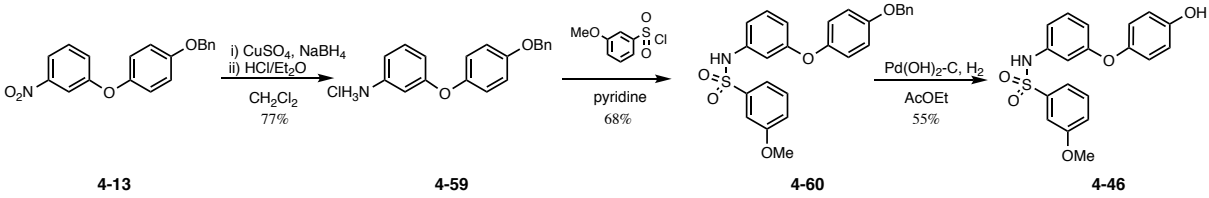


Scheme 4-11 化合物 **4-43a** 及び **44b** の合成

スルホンアミド誘導体類（**4-44**～**4-46**）は、Scheme 4-10 で合成した **4-49** とメトキシベンゼンスルホニルクロリドを用いて合成を行った(Scheme 4-12)。また、化合物 **4-13** を用い、B 環の骨格構造が 1,3-型のスルホンアミド誘導体 **4-46** も合成した(Scheme 4-13)。これらの化合物はいずれも結晶性が悪く、**4-44**、**4-45** は結晶を得ることが出来なかった。



Scheme 4-12 化合物 **4-44(a**, **b)**及び **4-45(a**, **b)**の合成



Scheme 4-13 化合物 **4-46** の合成

4.3.3 B 環上に種々の置換基をもつ化合物の合成 (シリーズ(c))

B 環置換基の構造活性相関を検討するため、化合物 **4-1a** と同じ骨格を有し、B 環置換基の種類及び置換位置の異なる誘導体類の合成を計画した。B 環メチル基置換体の場合、無置換(**4-1b**)、一置換(**4-1a**)、二置換では、一置換体である **4-1a** が最も活性が高いことが先行研究により明らかにされている [95]。そこで、本研究においても置換数の違いによる構造活性相関を検討するため、種々の一置換体に加えて、二置換体の合成も計画した。合成目標化合物の構造は Fig.4-7 に示した。

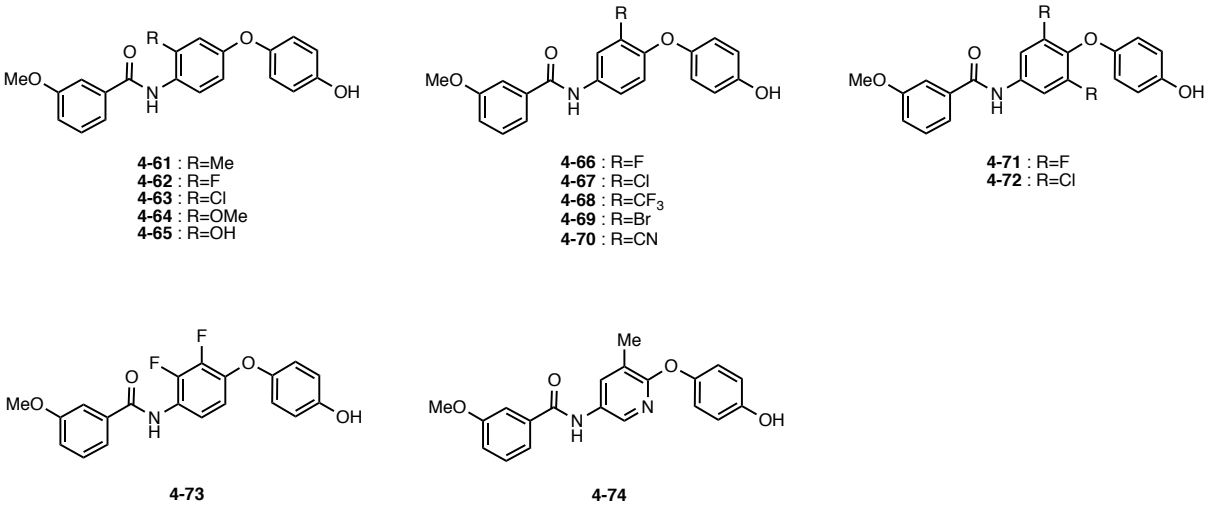
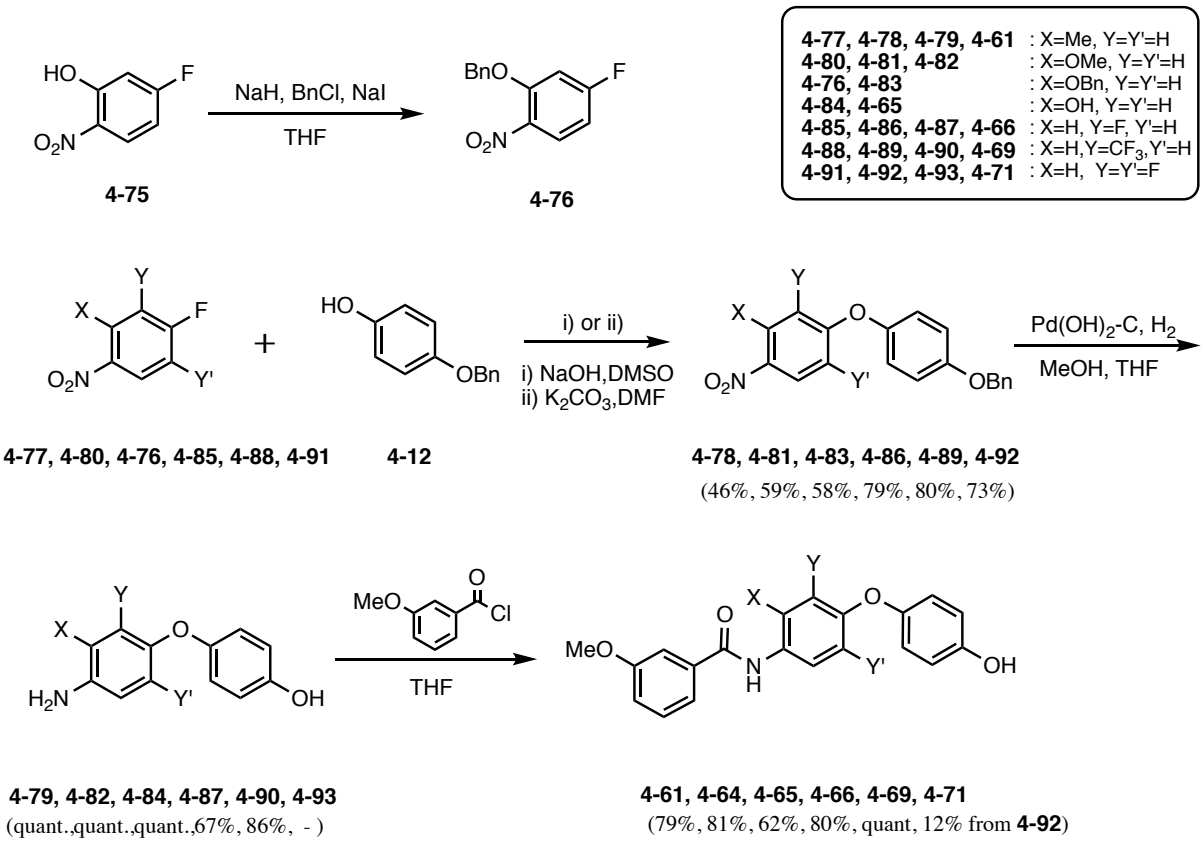


Fig. 4-7　合成目標化合物 **4-51**～**4-74** の構造

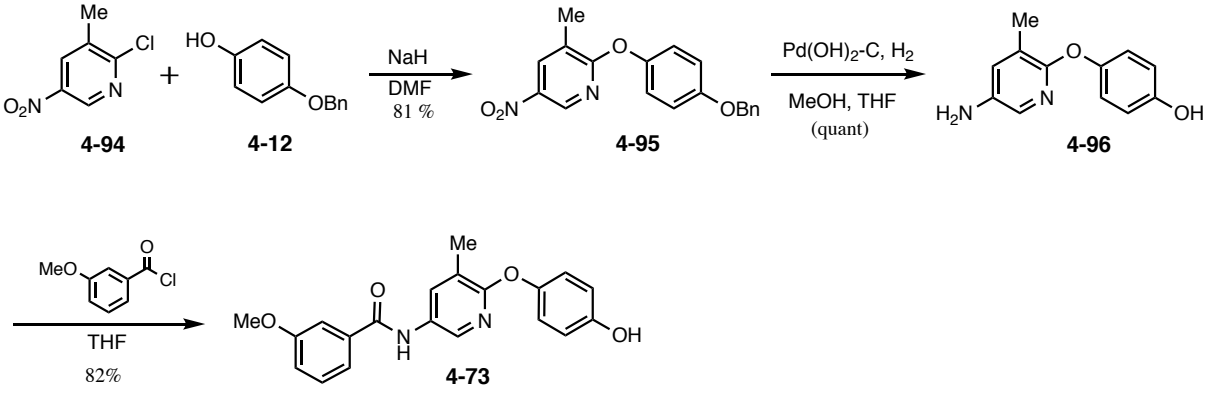
原料に *p*-ニトロフルオロベンゼン類（**4-77**, **80**, **76**, **85**, **88** 及び **91**）を用い、塩基を加えて *p*-ベンジルオキシフェノール(**4-12**)と S_NAr 反応を行った。原料 **4-76** は入手できなかったため、**4-75** のヒドロキシ基をベンジル化して用いた。塩基には水酸化ナトリウムまたは炭酸カリウムを用いた。

続いて水酸化パラジウムカーボンを触媒として接触水素化反応を行い、ニトロ基のアミノ基への還元とベンジル保護基の脱離を同時に行った。得られた生成物は不安定で精製中に酸化されやすく、シリカゲルに吸着するため、シリカゲルカラムや再結晶などの精製は行なわず、NMR により構造を確認後すぐに m–塩化アニソイルを加えてアミド化を行い、目的化合物を得た。なお、化合物 **4-92** の接触水素化反応では構造不明の副生成物が生じ単離出来なかったため、副生成物と **4-93** の混合物のままアミド化反応を行った後に精製して **4-71** を得た。(Scheme 4-14)



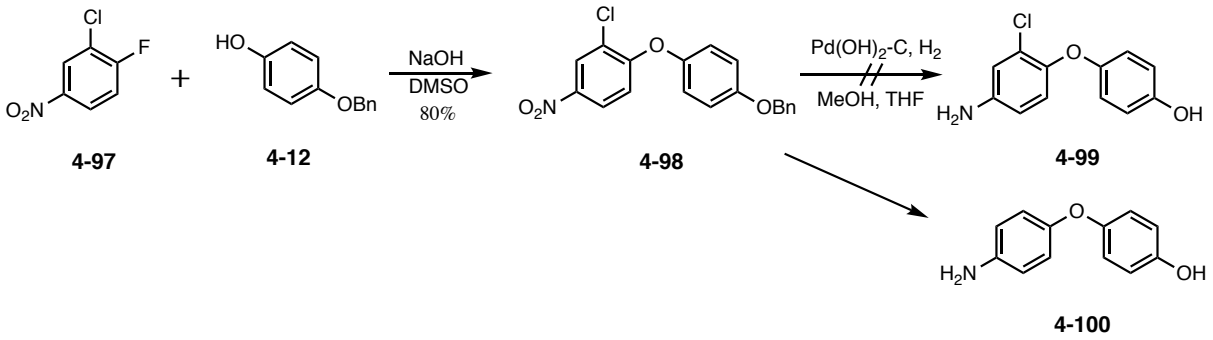
Scheme 4-14　化合物 **4-61,4-64,4-65, 4-66, 4-69** 及び **4-71** の合成

また、**4-73** の合成を行うため、原料として 2 –クロロ-3-メチル-5-ニトロピリジン(**4-94**)を用いて Scheme 4-14 と同様の条件で S_NAr 反応を行ったが低収率であった。そこで、塩基を NaH に変更し、室温で反応を行ったところ収率が 81%に改善した [101]。得られた **4-95** を用いて接触還元及びアミド化を行い、**4-73** を得た。(Scheme 4-15)



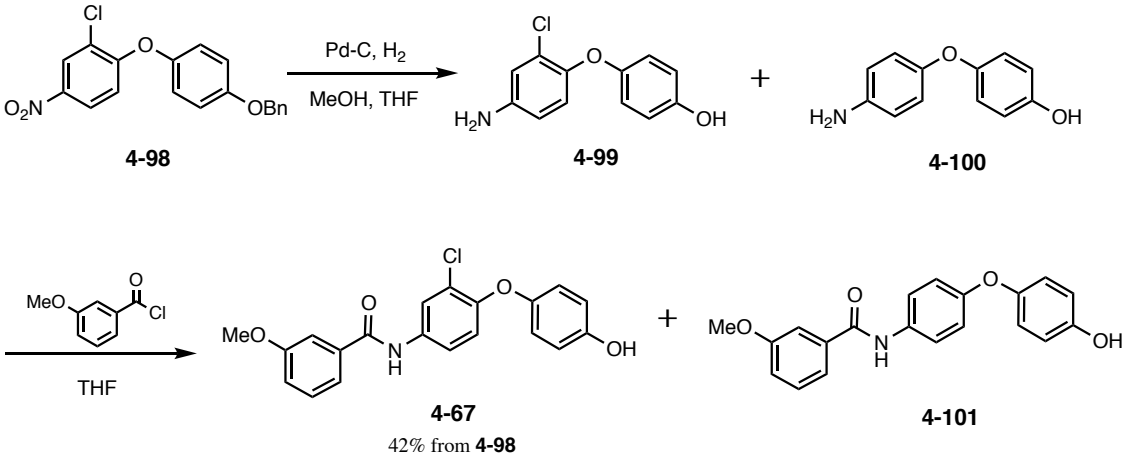
Scheme 4-15 化合物 **4-73** の合成

塩素置換基をもつ **4-97** の合成のために Scheme 4-15 と同じ条件で S_NAr 反応を行った後に接触還元反応を行ったが、目的物 **4-99** は得られなかった。生成物はカラムで分離できず精製することが出来なかったが、**4-100** を含む複数の生成物が生じたものと考えた(Scheme 4-16)。



Scheme 4-16 化合物 **4-98** の合成及び還元

そこで、接触水素化反応の触媒をパラジウム炭素に変えてニトロ基の還元速度を速め、ハロゲンの還元が進む前に反応を停止し、混合物のままアミド化反応を行って A 環を導入してから単離する方法に変更して **4-67** を得た。(Scheme 4-17)

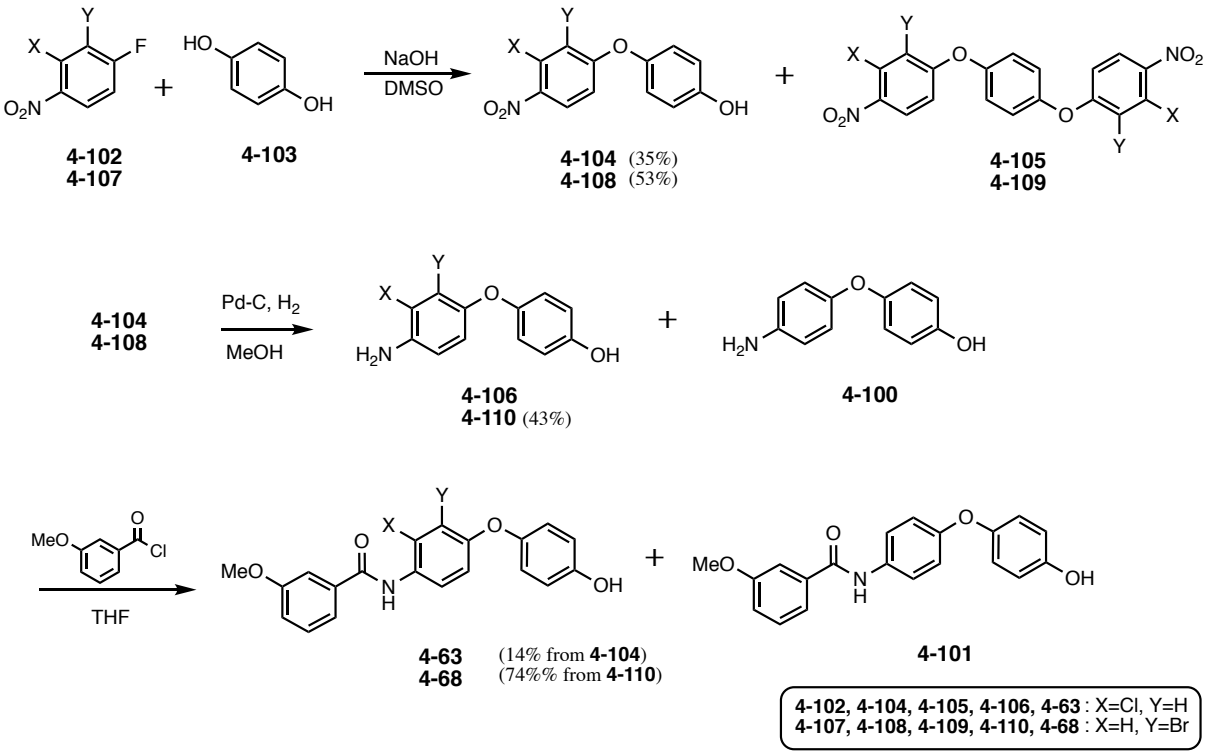


Scheme 4-17　化合物 **4-67** の合成

続いて塩素の置換位置の異なる **4-63** 及び臭素置換基をもつ **4-68** の合成を行った。接触水素化反応は、ニトロ基の還元は速やかに進行する一方、ベンジル保護基の脱離には時間を要する。Scheme 4-17 の方法は、ハロゲンの還元が進む前に反応を停止するため、原料が残った状態で反応を停止することになり、得られる生成物が複雑になる。そこで、ベンジル保護基を有しない **4-102** のニトロ基の還元

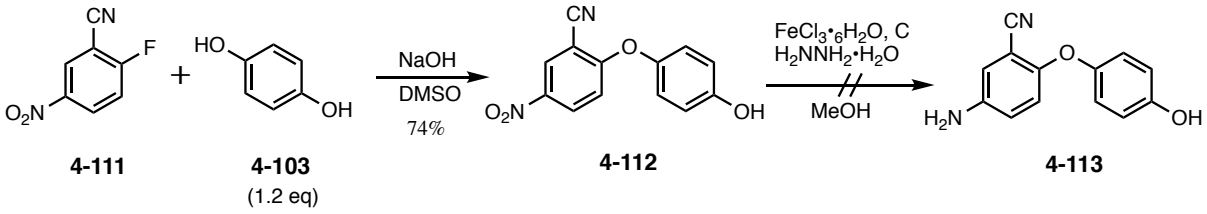
を行うことにより、目的物の収率があがると考えた。

4-104 を得るため S_NAr 反応の原料の *p*–ベンジルオキシフェノールをヒドロキノン(**4-103**)に変えて反応を行ったところ、目的物 **4-104** 以外に副生成物 **4-105** が生じたが、カラムでの精製が可能であった。得られた **4-104** を接触還元したところ、短時間の反応でも原料は残らなかったが、**4-106** 以外に **4-100** と思われる生成物が生じた。この段階では分離精製が出来ないため、混合物のままアミド化反応により A 環を導入後に精製して目的物の **4-63** を得た。同様の方法で **4-68** も合成した。(Scheme 4-18)



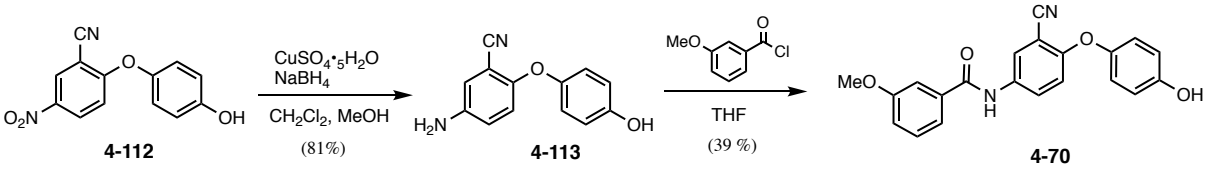
Scheme 4-18 化合物 **4-63** 及び **4-68** の合成

シアノ基をもつ **4-70** を得るために **4-113** の合成を試みた。文献 102)を参考に塩化鉄、活性炭及びヒドラジンを用いて **4-112** のニトロ基の還元を行ったが、反応は進行しなかった(Scheme 4-19)。



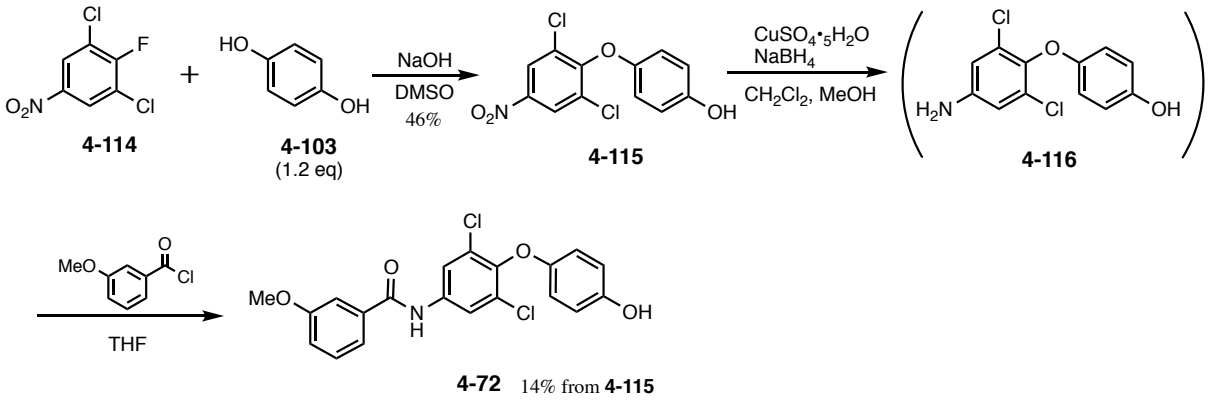
Scheme 4-19　化合物 **4-112** の還元反応

そこで、還元条件を変え、水素化ホウ素ナトリウム及び硫酸銅を用いて行ったところ **4-113** が得られたので、アミド化反応を行い **4-70** を合成した。シリカゲルカラムでは副生成物が取り除けなかったので、逆相系のフラッシュクロマトグラフィーを用いて精製を行ったところ、**4-70** を単離することができた(Scheme 4-20)。



Scheme 4-20　化合物 **4-70** の合成

二つの塩素置換基を有する **4-72** の合成も、**4-70** の合成と同様の方法で行った。還元反応において構造不明の副生成物が生じたが、混合物のままアミド化反応を行った後に **4-72** を単離した。(Scheme 4-21)

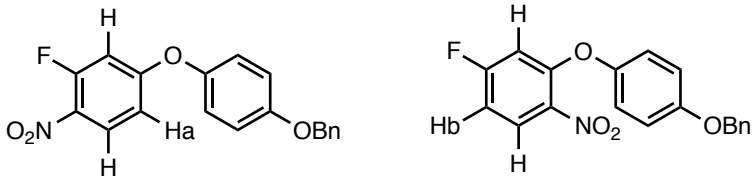


Scheme 4-21　化合物 **4-72** の合成

4-62 の合成を行うため、**4-66** の合成と同様に、水酸化ナトリウムを塩基として用いて S_NAr 反応を行ったところ、**4-119** は痕跡量しか得られず、**4-118** と思われる化合物が約 30%の収率で得られた。そこで、塩基と溶媒及び反応温度を変更して反応を行ったところ、**4-119** と **4-120** の混合物が得られた。これらの化合物はカラムによる精製で完全に分離することが出来なかったが、一方の異性体の割合が高く、ほぼ単一化合物からなるフラクション（Fr. A 及び Fr. B）を少量ずつ得ることが出来た。

Fr. A 及び Fr. B の ^{1}H NMR 測定を行ったところ、**4-119** の Ha または **4-120** の Hb (Fig.4-8)に帰属されるピークが観測され、それぞれのピークのカップリング定数(J 値)は 9.6,2.7,1.4Hz および 9.3, 6.9, 2.7Hz であった。Ha、Hb ともにプロトンとオルト及びメタカップリングするが、**4-119** の Ha はフッ素とパラカップリング、**4-120** の Hb はオルトカップリングすると考えられる。先ほど示した J

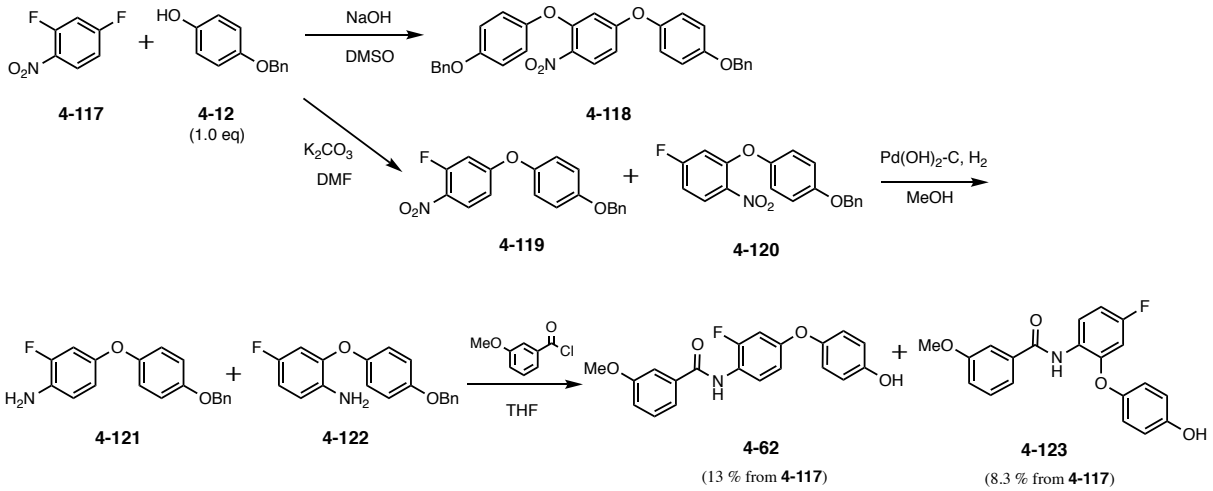
値のうちフッ素とのカップリングに由来する J 値は 1.4H 及び 6.9Hz であり、この値からそれぞれがフッ素とのパラカップリング、オルトカップリングに由来すると考えて構造を **4-119** 及び **4-120** と帰属し、Fr. A 及び Fr. B の各フラクションに含まれている化合物を同定した。



4-119 **4-120**

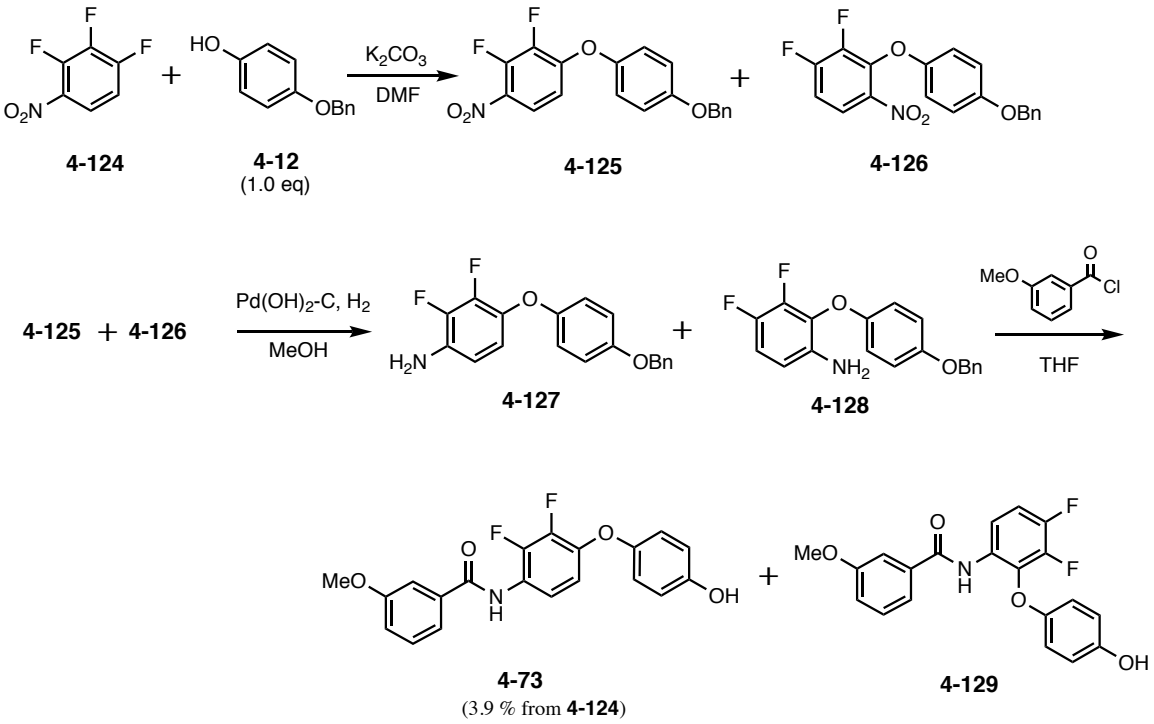
Fig. 4-8 化合物 **4-119** 及び **4-120** の構造

化合物 **4-119** と **4-120** は分離が困難であり、大部分が混合物として得られた。そこで混合物のまま還元アミノ化及びアミド化による A 環の導入を行い、最後にカラムによる精製を行って **4-62** 及び **4-123** をそれぞれ単離した(Scheme 4-22)。それぞれの構造は、原料に用いた **4-119** 及び **4-120** の比率を参考に、NMR により同定した。



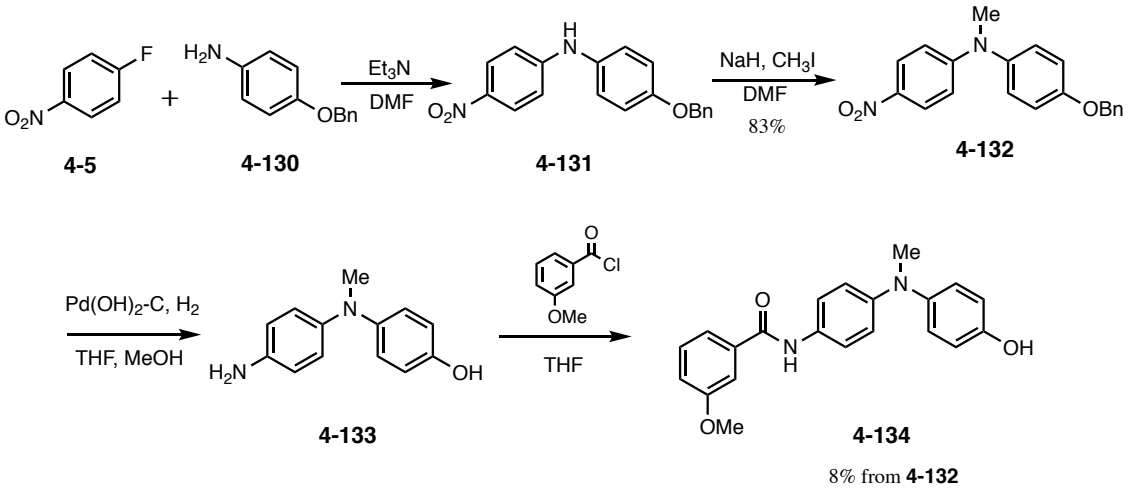
Scheme 4-22　化合物 **4-62** の合成

4-73 も同様に、**4-125** と **4-126** の分離が困難であったので、混合物のまま反応を行い、**4-73** を得た。**4-129** は痕跡量であったため、単離生成は行わなかった。(Scheme 4-23)



Scheme 4-23 化合物 **4-73** の合成

これまでに合成した化合物はすべて B 環と C 環の結合部がエーテル結合であったが、この結合部を *N*-メチルアミノ基に置き換えた化合物 **4-134** も以下の Scheme 4-24 に従い合成した [103]。



Scheme 4-24 化合物 **4-134** の合成

4.4　合成した化合物の構造活性相関

4.4.1　野生型 AR に対するアゴニスト活性

合成した化合物 **4-2**～**4-4**、**4-20**～**4-24**、**4-41**～**4-45**、**4-61**～**4-65**、**4-123** 及び **4-134** の野生型 AR に対するアゴニスト活性を評価するために、第 3 章でも用いた SC–3 細胞を用いて同様の方法で活性試験を行った。結果を Fig.4-9 から Fig.4-13 に示す。

まず、化合物 **4-2**～**4-4**、**4-20**～**4-24**（シリーズ(a)）及び **4-41**～**4-45**（シリーズ(b)）について活性試験を行った結果 (Fig.4-9～4-12) から、シリーズ(a)及び(b)で合成し活性試験を行った化合物には、単独で細胞増殖を促進するアゴニスト活性をもつものはなく、10μM では細胞増殖を抑制する傾向が認められた。また、4.3.3 項で合成した **4-61**～**4-65**、**4-123** 及び **4-134**（シリーズ(c)）についても単独で細胞増殖を促進するアゴニスト活性をもつものはなく、高濃度で細胞増殖を抑制する傾向が認められた（Fig. 4-13)。なかでも、**4-66**、**4-67**、**4-69** 及び **4-71** のような B 環の 2 位に置換基をもつ化合物にその傾向が強く認められた。

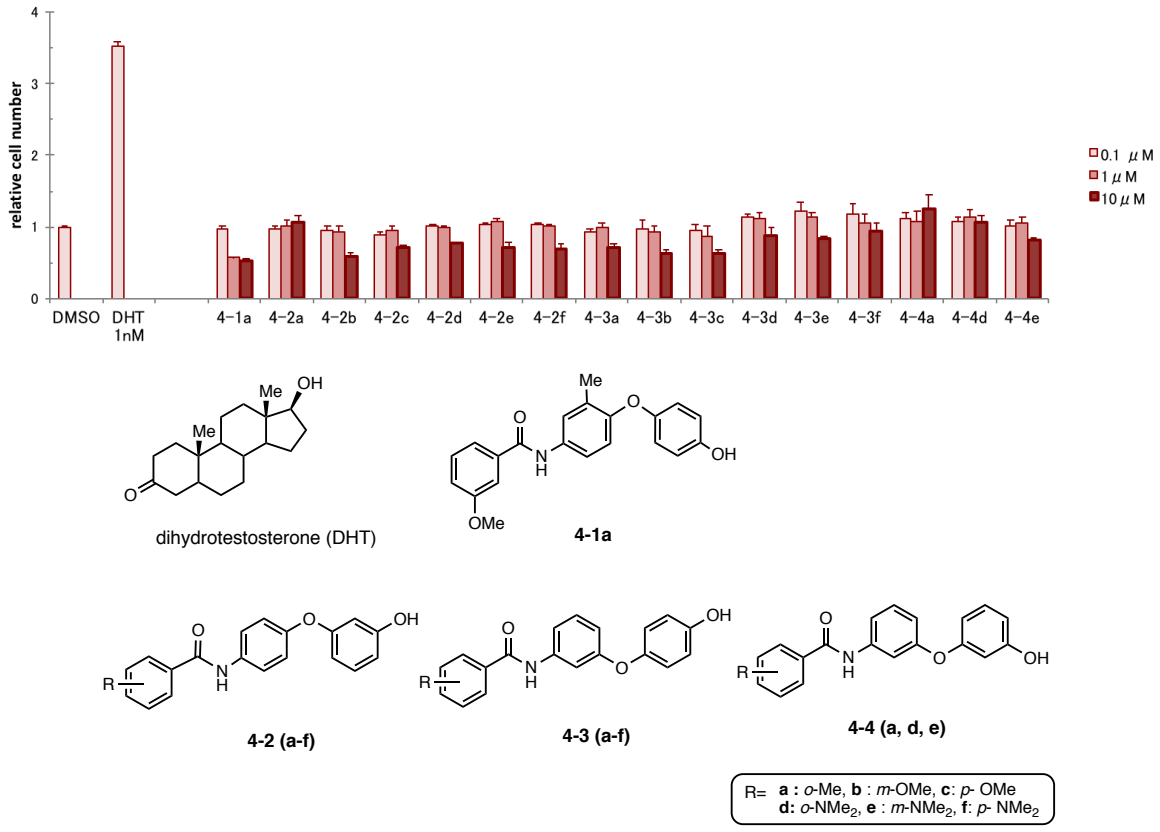


Fig. 4-9 化合物 **4-2**～**4-4** の AR 活性評価　（SC-3 細胞、化合物単独）

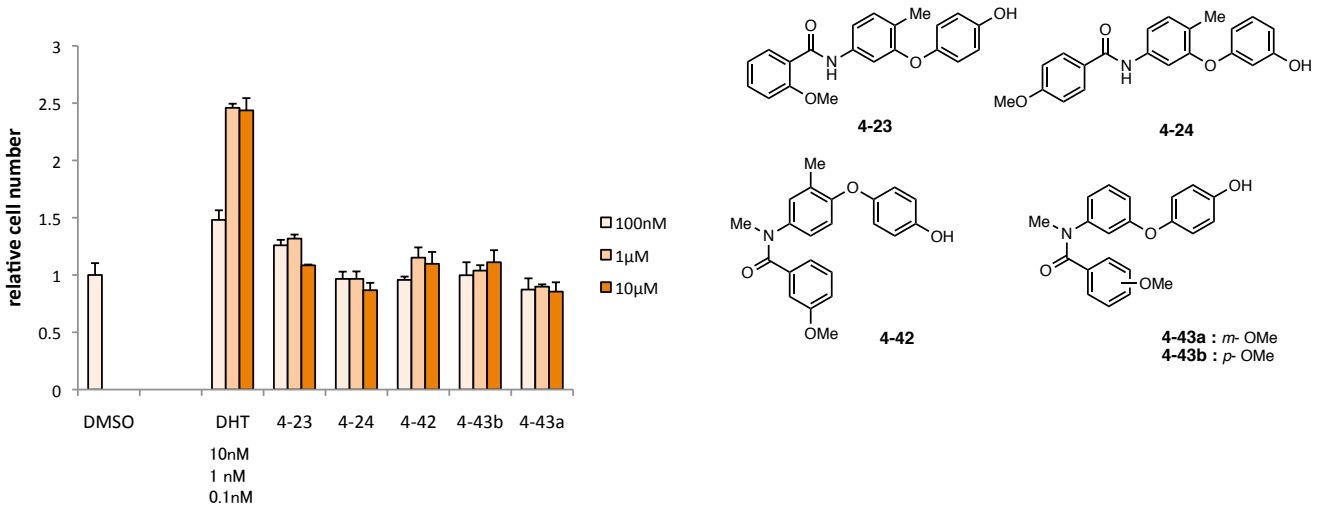


Fig. 4-10　化合物 **4-23**, **4-24**, **4-42** 及び **4-43** の AR 活性評価　（SC-3 細胞、化合物単独）

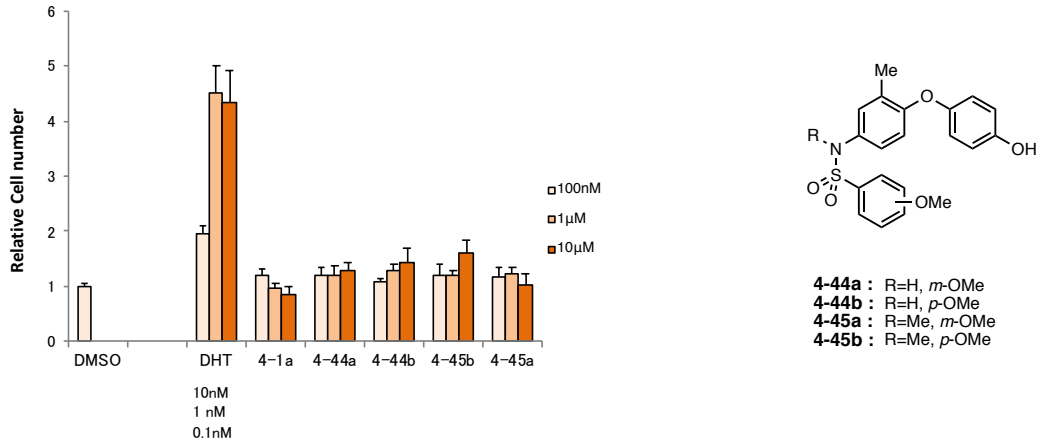


Fig. 4-11　化合物 **4-44** 及び **4-45** の AR 活性評価　（SC-3 細胞、化合物単独）

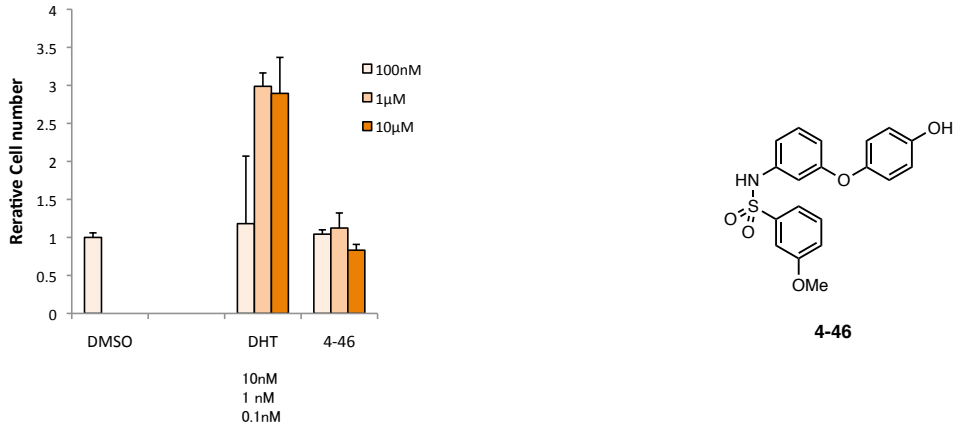
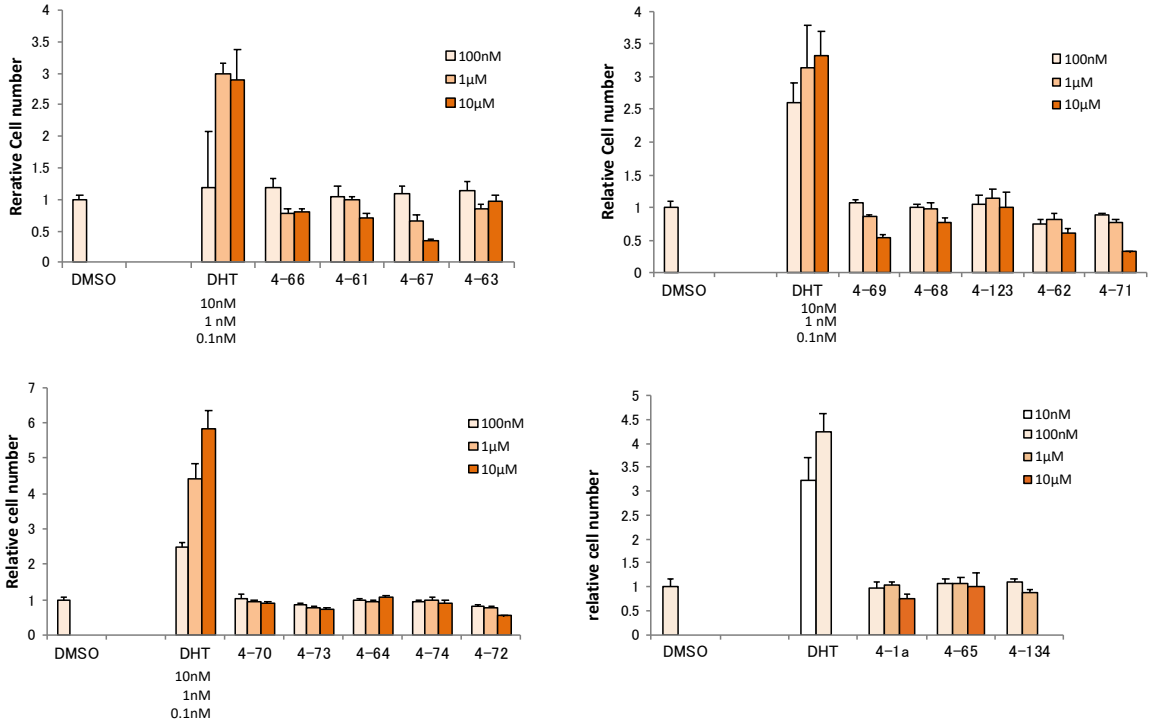


Fig. 4-12　化合物 **4-46** の AR 活性評価　（SC-3 細胞、化合物単独）



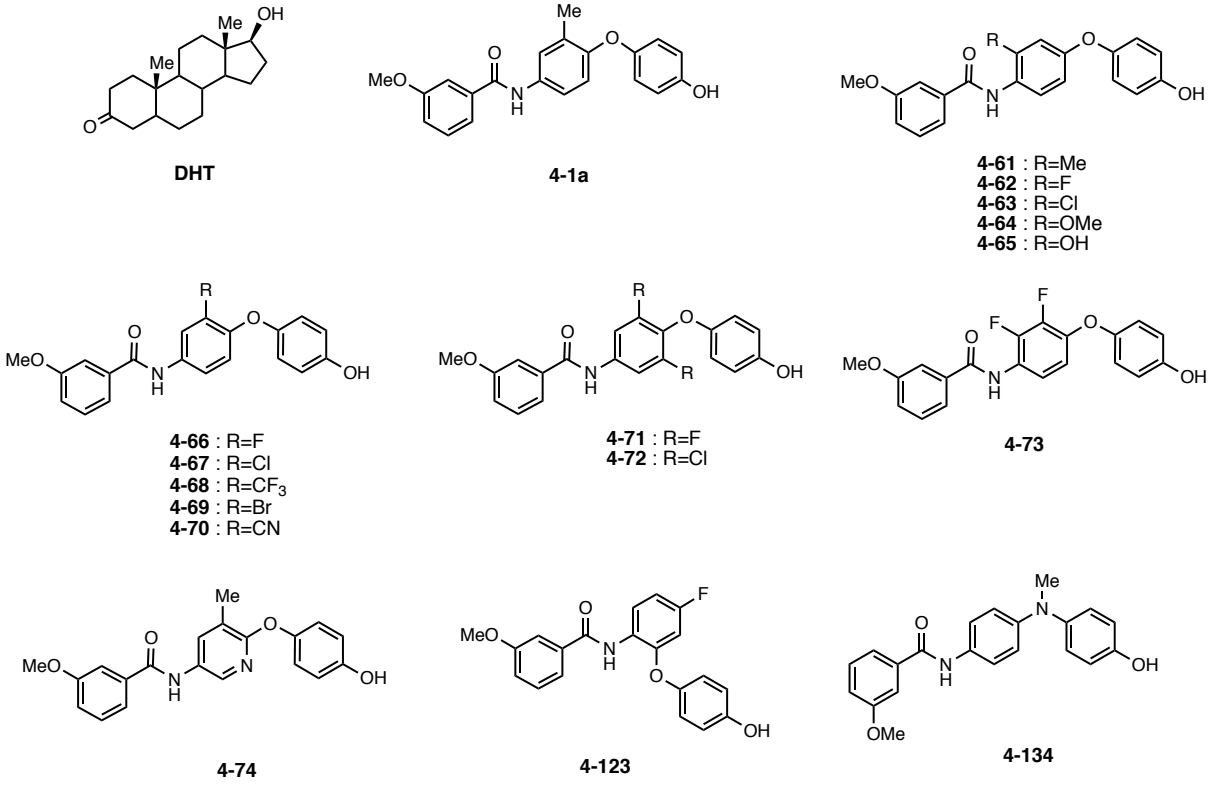


Fig. 4-13　化合物 **4-61**～**4-74**, **4-123** 及び **4-134** の AR 活性評価　（SC-3 細胞、化合物単独)

4.4.2　野生型 AR に対するアンタゴニスト活性

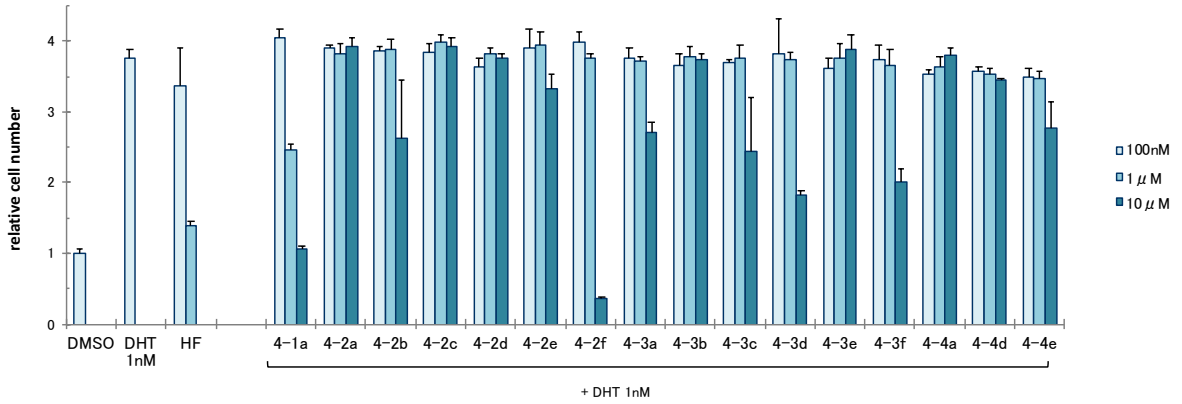
続いて SC–３細胞を用いて DHT(1nM)共存の条件で活性評価（アンタゴニスト活性試験）を行った。結果を Fig. 4-14～Fig. 4-19 に示す。 また活性試験の結果からそれぞれの化合物の IC_{50} をもとめ、Table 4-1 にまとめた。

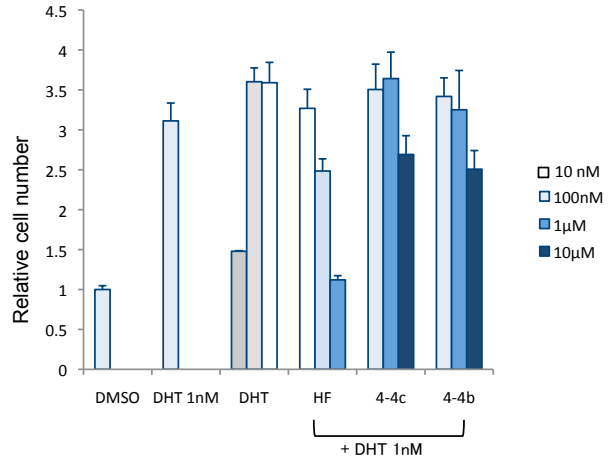
はじめにシリーズ(a)の化合物を用いて活性試験を行った（Fig. 4-14, 15）。B 環の骨格構造が化合物 **4-1a** と同じく 1,4-置換で、C 環の置換基が化合物 **4-1a** とは異なり *m*-ヒドロキシ基を持つ化合物群 **4-2** では、主に A 環が *m*-置換体の化合物に弱い活性が認められる傾向があった。しかし、いずれの化合物も化合物 **4-1a** に比べて活性は弱く、C 環は *m*-ヒドロキシ基よりも *p*-ヒドロキシ基がよいと考えた。

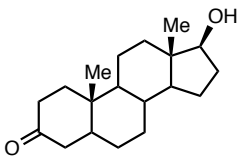
B 環が 1,3-置換型の化合物群(**4-3** 及び **4-4**)は、C 環が *p*-ヒドロキシ基の化合物群 **4-3** の場合は A 環が *o*-置換体及び *p*-置換体の化合物に弱いアンタゴニスト活性が認められ、C 環が *m*-ヒドロキシ基の化合物群の中では、A 環が *m*-置換体及び一部の *p*-置換体の化合物に活性が認められた。しかし、強い活性を示す化合物はなく、B 環の骨格構造は 1,4-置換体が適していると考えられる。

B 環が 1,3-置換型の化合物群(**4-3** 及び **4-4**)はいずれも低い活性を示したが、B 環が 1,4-置換型の化合物は化合物 **4-1a** と **4-1b** の活性の比較から B 環上のメチル基が活性に影響を及ぼしていると報告されており [95]、B 環上にメチル基を置換することで、同様に高い活性を持つ化合物を得られる可能性があると考えた。

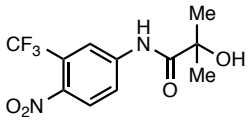
化合物群 **4-3** の活性試験の結果から、A 環は *p*-メトキシ置換体を優先し、化合物 **4-20**～**4-24** を合成し活性試験を行ったが、いずれの化合物も低活性であり(Fig.4-15)、B 環の 1,4-置換型の骨格構造がアンタゴニスト活性を発現するのに重要であると結論した。



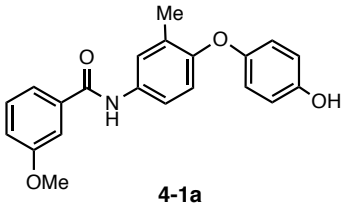




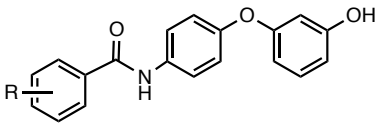
dihydrotestosterone (DHT)



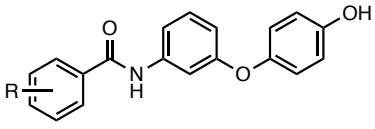
hydroxyflutamide (HF)



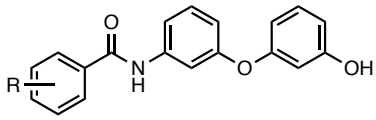
4-1a



4-2 (a-f)



4-3 (a-f)



4-4 (a-e)

R= **a :** *o*-Me, **b** : *m*-OMe, **c**: *p*- OMe
d: *o*-NMe_2, **e** : *m*-NMe_2, **f**: *p*- NMe_2

Fig. 4-14 化合物 **4-2**～**4-4** の AR 活性評価　（SC-3 細胞、1nM DHT 共存下）

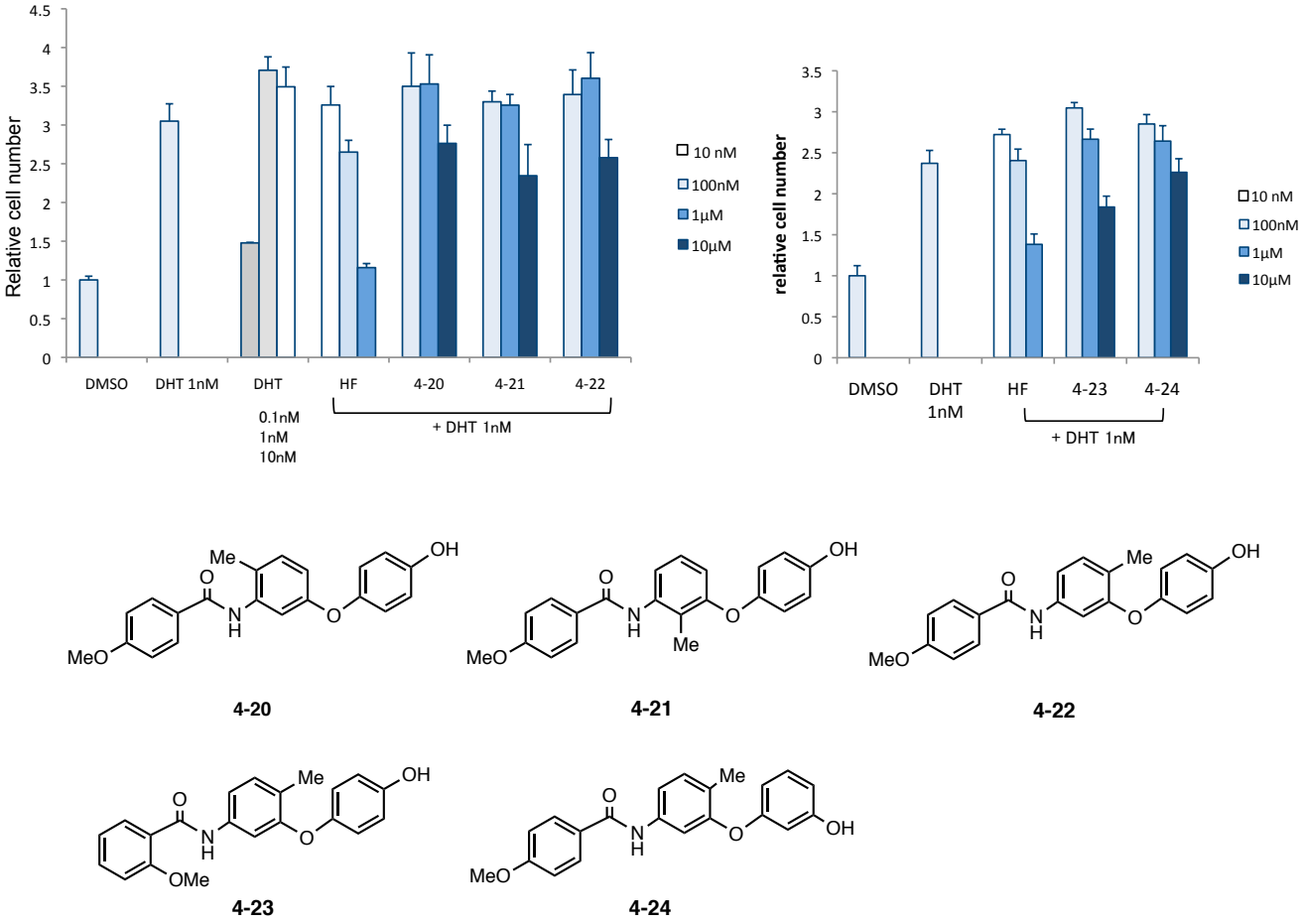


Fig. 4-15　化合物 **4-23,4-24,4-42** 及び **4-43** の AR 活性評価（SC-3 細胞、1nM DHT 共存下)

次に、シリーズ(b)の化合物 **4-42**～**4-46** を用いてアンタゴニスト活性試験を行い、A 環と B 環のリンカー構造による構造活性相関を検討した。**4-1a** を *N*-メチル化した **4-42** は *N*-メチル化することで、活性に有利なシス型コンフォメーションをとり、高い活性を示すことを期待して合成したが、高濃度でわずかに細胞増殖を抑制するのみであった。また、B 環の骨格構造が 1,3-置換体のなかでやや高い活性を示した **4-3c** 及び **4-3c** の A 環メトキシ基の位置異性体である **4-3b** の *N*-メチル化誘導体 **4-43b** 及び **4-43a** は全く活性を示さず、*N*-メチル化は活性を低下させることが示された（Fig. 4-16)。ドッキングシミュレーションの結果(Fig. 4-2)では、N-H の周りには空間的余裕が少なく、メチル化体が許容されない可能性があるのではないかと考えている。

さらに、リンカー構造をスルホンアミドとした化合物 **4-44a**、**4-44b** 及び **4-46** は高い活性を示さなかった。なお、スルホンアミドにおいても *N*-メチル化体 **4-45b** はほとんど活性を示さず、アミド結合同様、*N*-メチル化により活性が低下することが示唆された。**4-45a** については、高濃度で細胞毒性が認められた(Fig. 4-17、18)。

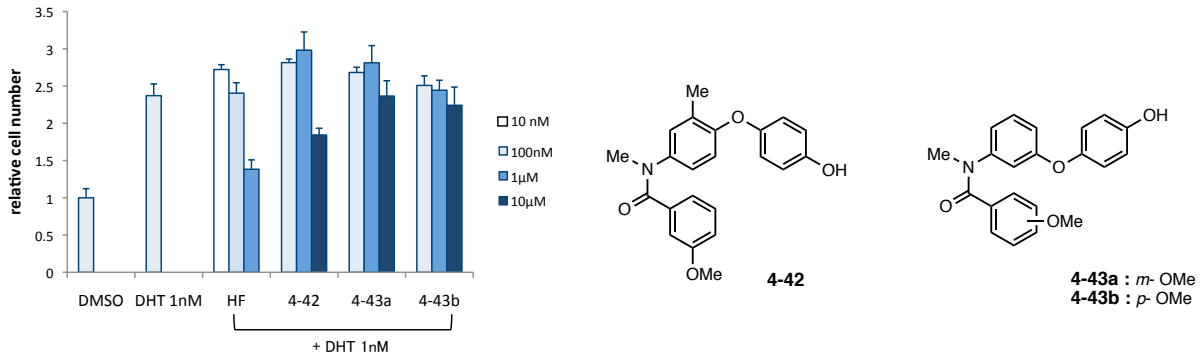


Fig. 4-16　化合物 **4-42** 及び **4-43** の AR 活性評価（SC-3 細胞、1nM DHT 共存下)

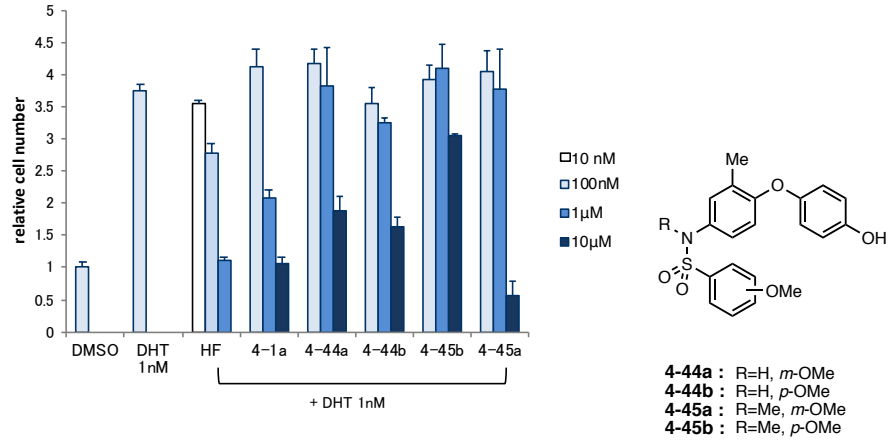


Fig. 4-17　化合物 **4-44** 及び **4-45** の AR 活性評価（SC-3 細胞、1nM DHT 共存下)

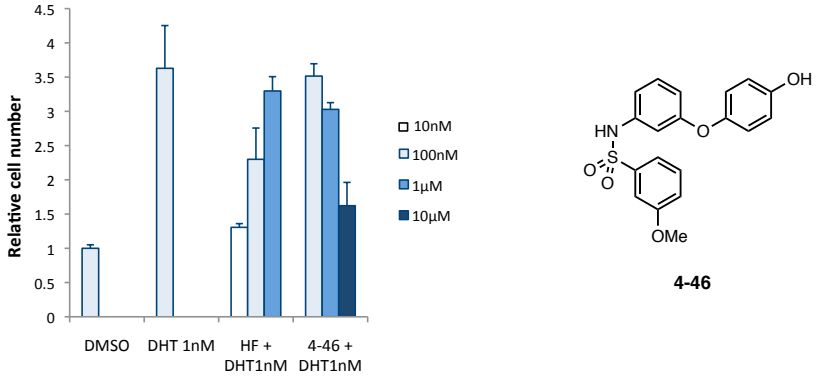


Fig. 4-18　化合物 **4-46** の AR 活性評価（SC-3 細胞、1nM DHT 共存下）

シリーズ(a)及び(b)の活性試験の結果から B 環の骨格構造は 1,4-置換型であることアンタゴニスト活性発現に重要であり、A 環と B 環のリンカー構造はアミドが最適で *N*-メチル化すると活性が低下すると結論した。

なお、ここにはデータは示していないが、スルホンアミド体は AR アンタゴニスト活性は低いものの、同じ核内受容体ファミリーに属するプロゲステロン受容体(PR)に対しては活性が高い傾向が認められたため、PR アンタゴニスト創製への展開が期待できる [104]。

最後にシリーズ(c)の化合物の DHT(1nM)共存の条件で活性評価（アンタゴニスト活性試験）を行った（Fig. 4-19, Table 4-1）。**4-1a** の B 環２位のメチル基をフッ素、塩素に置換した化合物 **4-66** 及び **4-67** は **4-1a** と同等の活性が認められた。しかし、臭素、トリフルオロメチル、ニトリルに置換した化合物 **4-68**、**4-69** 及び **4-70** は低活性であり、B 環がピリジン環の化合物 **4-74** は活性が認められなかった。

これらの置換基の大きさを表す代表的なパラメーターである立体因子(Taft)Es は、H を基準として、メチル基 -1.24、トリフルオロメチル基 -2.40、フッ素 -0.46、塩素 -0.97、臭素 -1.16 である [105]。トリフルオロメチル基はメチル基と比べて空間的サイズが大きいこと、ハロゲン置換化合物において、空間的サイズの大きい臭素置換体に活性が認められなかったことから、B 環の置換基は空間的なサイズが活性に大きな影響を及ぼしていると考えられるが、Es 値の近いメチル基と臭素の活性が大きく異なることから、電子的な効果などの影響も大きいと思われる。

また、置換位置の異なる化合物 **4-61**～**4-65**（B 環３位に置換基を有する化合物）についても検討したが、３位にフッ素を有する **4-62** を除き活性がほとんど認められなかった。

以上の結果から、B 環２位にサイズの小さい置換基（Me、F、Cl）を有する化合物が高い活性を示すと結論した。

続いて行った塩素の二置換体（**4-72**）、及びフッ素の二置換体２種類(**4-71** 及び **4-73**)の活性試験の結果、**4-1a** やフッ素一置換体(**4-66**)と比べても高い活性が認められた。B 環の置換基がメチル基の化合物は、二置換体の活性が一置換体に比べて低いことが報告されているが [95]、フッ素置換体、塩素置換体では、複数の置換基を有する化合物の方が強いアンタゴニスト活性を持つことが示された。

なお、B 環に置換基を持たない化合物 **4-134** は比較的高い活性を有していることから、B 環と C 環のリンカーは窒素でも活性は維持され、さらにリンカー窒素へのメチル置換は、活性発現に B 環３位の置換基と類似した効果を発揮する可能性があると考えている。

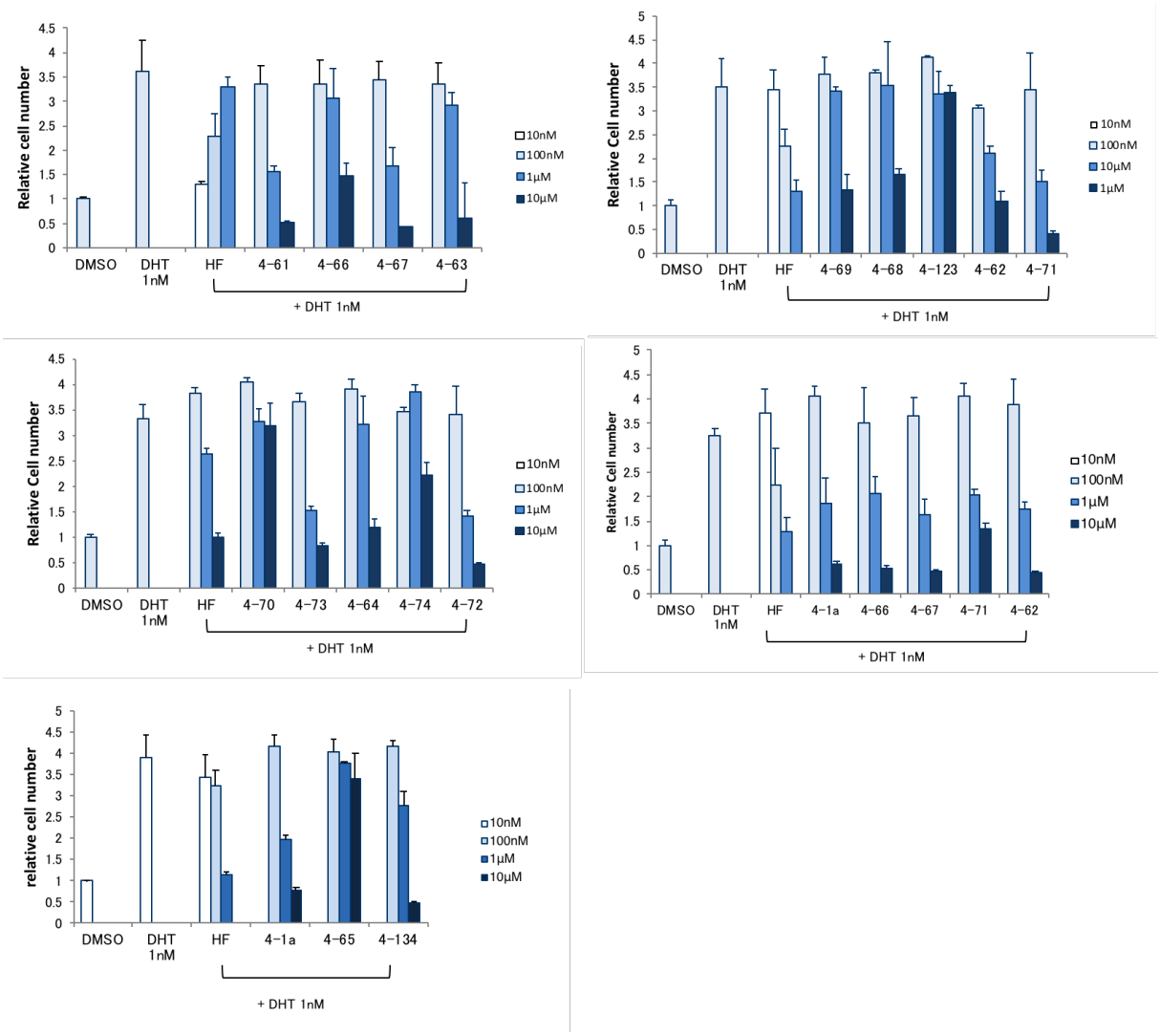


Fig. 4-19 化合物 **4-61**～**4-74**, **4-123** 及び **4-134** の AR 活性評価（SC-3 細胞、1nM DHT 共存下）

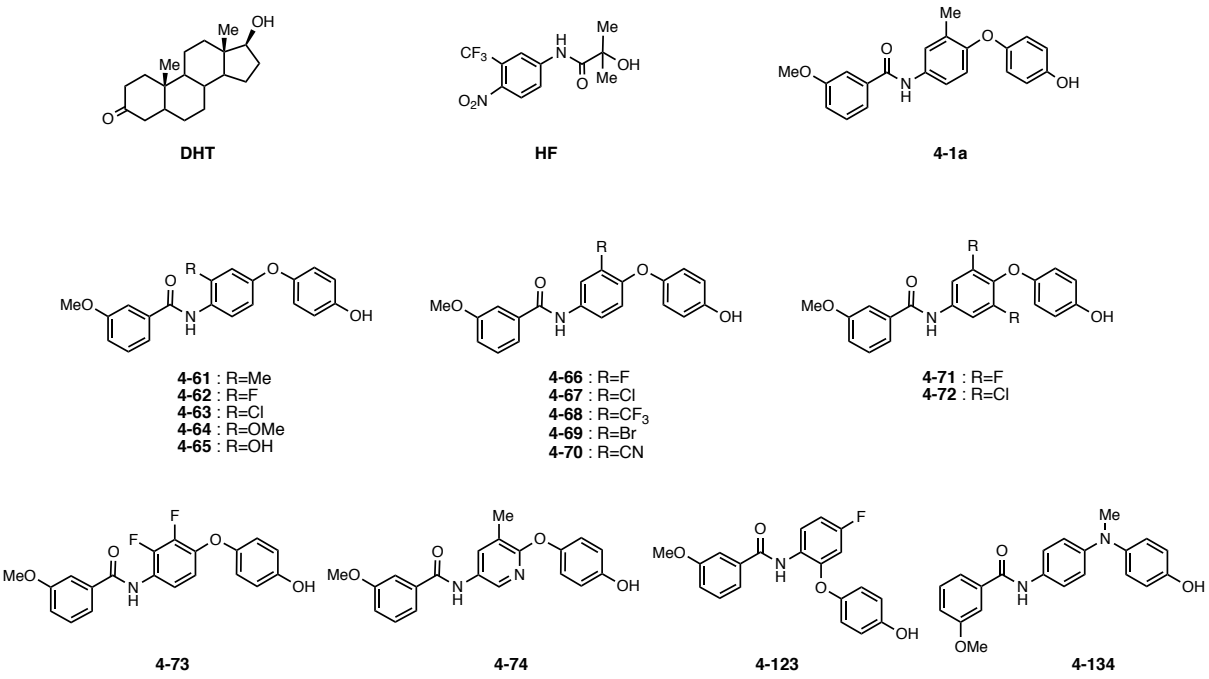


Fig. 4-20　Fig. 4-19 のアッセイに用いた化合物の構造

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
4-1a[95]	0.75	**4-42**	7.6
4-1b[95]	2.0	**4-43a**	Inactive
4-2a	Inactive	**4-43b**	Inactive
4-2b	> 10	**4-44a**	5.6
4-2c	Inactive	**4-44b**	3.5
4-2d	Inactive	**4-45a**	cytotoxicity
4-2e	Inactive	**4-45b**	> 10
4-2f	3.2	**4-46**	3.2
4-3a	> 10	**4-61**	3.0
4-3b	Inactive	**4-62**	0.65
4-3c	> 10	**4-63**	1.7
4-3d	6.3	**4-64**	3.4
4-3e	inactive	**4-65**	Inactive
4-3f	7.4	**4-66**	0.40
4-4a	inactive	**4-67**	0.48
4-4b	> 10	**4-68**	5.7
4-4c	> 10	**4-69**	4.3
4-4d	inactive	**4-70**	Inactive
4-4e	> 10	**4-71**	0.51
4-20	> 10	**4-72**	0.48
4-21	> 10	**4-73**	0.53
4-22	> 10	**4-123**	Inactive
4-23	5.3	**4-134**	1.4

Table 4-1 合成した化合物のアンタゴニスト活性

4.4.3 変異 AR に対する活性

4.4.2 項で AR に対して高いアンタゴニスト活性が認められた化合物 **4-62**、**4-66**、**4-67**、**4-71**、**4-72** 及び **4-73** について、いずれもヒト前立腺癌細胞である LNCaP 細胞[90]、22Rv1 細胞[106]及び PC–3 細胞[107]を用いた活性試験を行った。LNCaP 細胞は、3 章でも活性試験に用いた T877A 変異 AR を有するヒト前立腺癌細胞で、22Rv1 細胞は H874Y 変異 AR を有するヒト前立腺癌細胞である。LNCaP

細胞および 22Rv1 細胞がアンドロゲン依存性であるのに対し、PC-3 細胞はアンドロゲン非依存的な細胞増殖活性を持つことが知られている。ビカルタミド（BIC）は LNCaP 細胞の増殖を抑制するが、22Rv1 及び PC-3 細胞の増殖は増殖を抑制しないと報告されている。

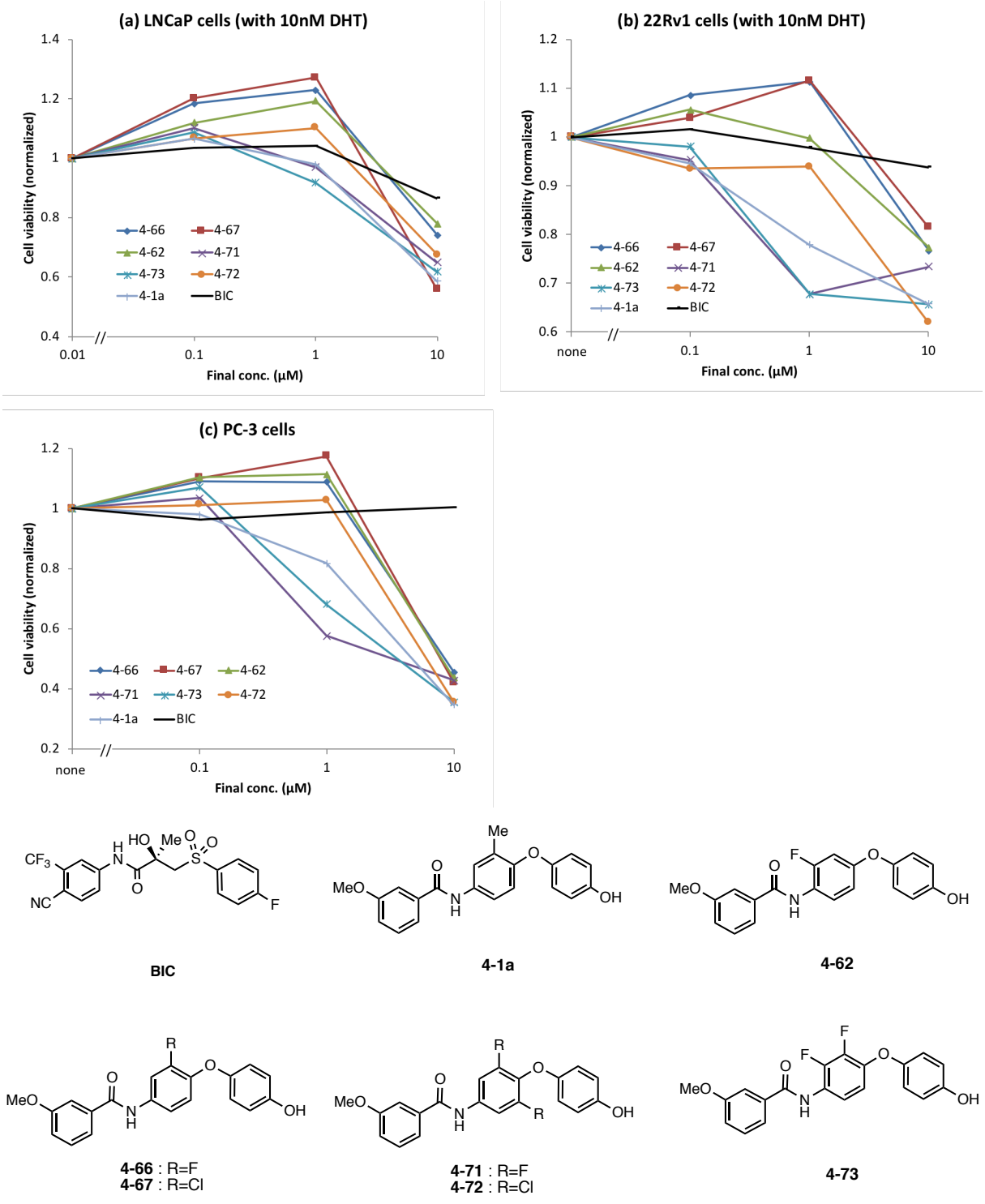


Fig. 4-21　変異 AR を有する細胞を用いた生物活性試験

今回活性試験に用いた６種類の化合物はいずれも３種類すべての細胞で容量依存的に増殖を抑制した。特にフッ素二置換体である **4-71** と **4-73** は本研究のリード化合物である **4-1a** よりも 22Rv1 細胞及び PC-3 細胞の増殖を強く抑制した(Fig. 4-21)。

活性試験の結果は、これらの化合物が、AR アンタゴニストとしての働き以外にも、何らかのメカニズムで細胞増殖を抑制していることを示唆していており、その機能の解明につながるものである。

4.5　小括

本章では、クルクミンの構造要素を基盤として創製したフェノキシフェノール骨格を有する化合物類を合成し、生物活性評価を行った。

合成した化合物類は A 環、B 環、及び C 環の３つの芳香環を有するが、それぞれの置換基と置換位置、環同士のリンカー構造などを変化させた化合物類を系統的に合成し、その生物活性評価を行うことで、構造の最適化に成功した。

本研究の中で、野生型 AR を有する細胞のみならず、変異細胞を用いた生物活性試験においても、本研究のリードとした化合物 **4-1a** と同等もしくはより強い増殖抑制活性を示す化合物（**4-71**、**4-73**）を見いだした。既存の非ステロイド型のアンタゴニストである BIC は、変異 AR を有する LNCaP 細胞の増殖を抑制するが、22Rv1 及び PC-3 の増殖は抑制しないことが知られている。今回得られた化合物 **4-71** 及び **4-73** は、これらの変異細胞の増殖も強く抑制した。PC-3 細胞はアンドロゲン非依存的な細胞増殖活性を持つことから、**4-71** 及び **4-73** は AR を介さない細胞増殖抑制活性も有すると推定される。

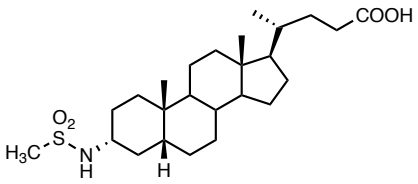
本研究の成果及び増殖抑制機能の詳細についての検討が、将来的に前立腺癌の治療薬の開発に役立つものと考える。

第５章　総括

以上、本研究では、核内受容体のうち、ビタミン D 受容体（VDR）及びアンドロゲン受容体（AR）に焦点を合わせ、これらの受容体の機能を制御する新規化合物を創製した。

第２章では、リトコール酸（LCA）を基盤としたビタミン D 受容体のリガンドの創製のため、LCA の３位及び側鎖を修飾した化合物を合成し、その生物活性をビタミン D 依存的に分化する白血病細胞株である HL-60 細胞を用いた分化誘導試験により評価した。

３位修飾化合物については、酸素官能基を窒素官能基に代替する試みとして３位にアミノ基（**2-18**）、アセトアミド基（**2-19**）、スルホンアミド基（**2-20**）を持つ化合物の合成を行った。その結果、窒素官能基を有する化合物は対応する酸素官能基を有する化合物よりも活性が低いことがわかった。窒素官能基を有する化合物の中では、スルホンアミド体 **2-20a**（Fig. 5-1）が最も強い活性を示し、リード化合物であるリトコール酸よりも強い活性を有していた。スルホンアミド体 **2-20a** は対応する酸素官能基であるスルホンエステル基をもつ化合物 **2-17** よりも活性は低かったが、スルホンアミド基はスルホンエステル基よりも化学的に安定であり、さらなる構造最適化を行うことで、より高い活性を持つ非セコステロイド型 VDR リガンドになり得ると考えている。



2-20a

Fig. 5-1 化合物 **2-20a** の構造

第３章では疎水性のホウ素クラスターであるカルボランを疎水性骨格とする新規アンドロゲン受容体アンタゴニストの創製を行った。カルボランの疎水性領域の空間的占有がステロイド骨格における CD 環に類似することから、CD 環をカルボランに置き換えた化合物が合成され、VDR や AR に対して活性を示す化合物が見出されている。本研究では、先行研究をもとに、種々のジアリルカルボラン誘導体類の合成を行い、アンドロゲン依存的に増殖する乳がん細胞 SC-3 および、変異 AR を有する前立腺癌細胞 LNCaP を用いた細胞増殖試験を行った。

今回合成した化合物はいずれも IC_{50} が 10μM 以上であり、高い活性を示す化合物は得られなかった。しかし、活性は決して高くはないものの、**3-21b**、**3-28b**（Fig. 5-2）など、アゴニスト活性とアンタゴニスト活性の両方を示す興味深い化合物を得ることができた。このような性質を持つ化合物は、核内受容体の機能解明に利用できる可能性があり、化合物の構造と受容体との結合様式、結合能、生物

活性との関係等の更なる解明につながる。

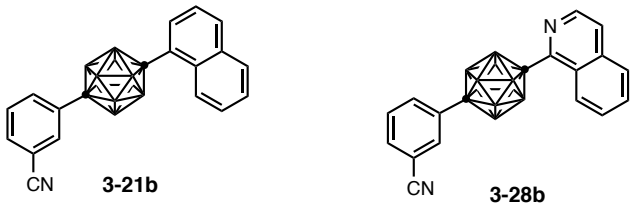


Fig. 5-2　化合物 **3-21b** 及び **3-28b** の構造

第４章では、フェノキシフェノール骨格を有する新規アンドロゲン受容体アンタゴニストの創製を行った。クルクミンの構造要素を基盤として創製されたフェノキシフェノール誘導体に高い活性を示す化合物 **4-1a** があるという先行研究をもとに、様々な置換位置異性体、*N*アルキルアミド誘導体、スルホンアミド誘導体を系統的に合成し、生物活性を検討した。生物活性の検討は、第３章でも用いた SC-3 細胞や LNCaP 細胞以外に前立腺癌細胞である 22Rv1 細胞及び PC-3 細胞も用いて細胞増殖試験を行った。

本研究で合成した化合物では、中央の環である B 環にフッ素や塩素が置換した化合物に、野生型 AR を有する SC-3 細胞に対して高い活性が認められた。なかでも **4-71** 及び **4-73**（Fig. 5-3）は、野生型 AR を有する細胞のみならず、変異 AR を有する細胞を用いた生物活性試験においても強い増殖抑制活性を示した。既存の非ステロイド型のアンタゴニストであるビカルタミドは、変異 AR を有する LNCaP 細胞の増殖を抑制するが、他の変異 AR を有する細胞 22Rv1 の増殖は抑制しないことが知られている。今回得られた化合物 **4-71** 及び **4-73** は、これらの変異 AR を有する細胞の増殖も強く抑制したことから、これらの変異により薬剤耐性となった前立腺がんにも有効と考えられる。一方で、化合物 **4-71** 及び **4-73** は AR 非依存的な細胞 PC-3 に対しても細胞増殖抑制活性を持つことから、**4-71** 及び **4-73** は AR を介さない細胞増殖抑制活性も有すると思われる。

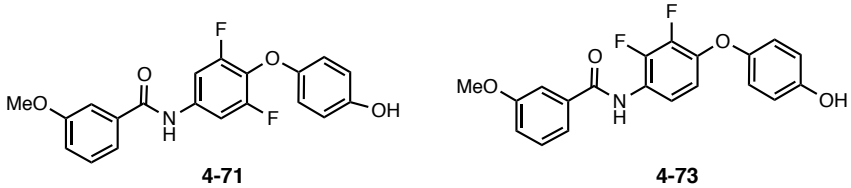


Fig. 5-3 化合物 **4-71** 及び **4-73** の構造

以上、本研究では、ビタミン D 受容体及アンドロゲン受容体の機能制御剤を設計、合成した。その

結果、新規構造を有する VDR アゴニストや AR アンタゴニストを見いだすとともに、構造活性相関に関する知見を得た。特に、AR アンタゴニストである化合物 **4-71** 及び **4-73** は臨床で問題となっている去勢抵抗性前立腺癌（CRPC）の原因の一つとされる変異 AR に対してもアンタゴニストとして働くことから、更なる構造展開や、より詳細な解析をすることで、臨床応用可能な化合物へと展開できると考えている。

第６章　実験項

Chemistry

All reagents were purchased from Sigma-Aldrich Chemical Co., Tokyo Kasei Kogyo Co., Wako Pure Chemical Industries, or Kanto Kagaku Co., Inc. Silica gel for column chromatography was purchased from Kanto Kagaku Co., Inc. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECA 600, or Bruker 600 spectrometer or JEOL JNM-AL 400. Mass spectral data was obtained on a Bruker Daltonics microTOF-2focus, Thermo Scientific Q-Exactive or Waters Q-TOF Premier in the positive ion detection mode. Melting points were determined on a RFS-30 melting point apparatus (Round Science).

Synthesis of Methyl 3α-hydroxycholanate **(2-22):** To a solution of lithocholic acid (**LCA**, 497 mg, 1.32 mmol) in methanol (5 ml) was added acetyl chloride (50 µl) and stirred for 4 hours at room temperature. The reaction mixture was added water and filtered. The precipitation was dissolved to ethanol and evaporated in vacuo. The residue was recrystallized with hexane to yield 438 mg (1.12 mmol, 85 %) of compound **2-22**. ^{1}H-NMR (600MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.62-3.59 (m, 1H), 2.35 (ddd, *J* = 15.4, 10.4, 5.0 Hz, 1H), 2.21 (ddd, *J* = 15.4, 9.9, 6.6 Hz, 1H), 1.97-0.93 (m), 0.91 (s, 3H), 0.90 (d, *J* = 6.5 Hz, 3H), 0.64 (s, 3H).

Synthesis of Methyl 3β-acetoxycholanate **(2-23a**): To a solution of lithocholic acid methyl ester (**2-22**, 55 mg 0.15 mmol) in toluene (1ml) was added triphenylphosphine (51 mg, 0.20 mmol) acetic acid (10 ml, 0.17 mmol) and DEAD (2.2 M solution in toluene, 70 µl, 0.15 mmol). And this solution was stirred at 0°C for 1hour then room temperature for 20 hours. The reaction mixture was quenched with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (5 g, 25 % ethyl acetate-hexane) to yield 46 mg (0.11 mmol, 76 %) of acetate **2-23a**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.06 (m, 1H), 3.66 (s, 3H), 2.34 (m, 1H), 2.21 (m, 1H), 2.05 (s, 3H), 1.97-1.75 (m, 5H), 1.65-0.99 (m), 0.96 (s, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.65 (s, 3H).

Synthesis of Methyl 3β-benzyloxycholanate **(2-23b**): To a solution of lithocholic acid methyl ester (**2-22**, 51 mg 0.13 mmol) in toluene (1ml) was added triphenylphosphine (41 mg, 0.16 mmol) benzoic acid (20 mg, 0.15 mmol) in toluene (1 ml) and DEAD (2.2 M solution in toluene, 70 µl, 0.15 mmol). And this solution was stirred at 0°C for 1hour then room temperature for 26 hours. The reaction mixture was quenched with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (6 g, 25 % ethyl acetate-hexane) to yield 33 mg (0.067 mmol, 57 %) of benzoate **2-33b**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.05 (d, 2H, *J*=8.1 Hz), 7.55 (t, *J* = 7.1 Hz, 1H), 7.45 (t, *J* = 7.1 Hz, 2H), 5.34 (s, 1H), 3.67 (s, 3H), 2.36 (ddd, *J* = 15.0, 9.9, 5.0 Hz, 1H), 2.22 (ddd, *J* = 15.4, 9.9, 6.6 Hz, 1H), 2.10-1.55 (m), 1.48-1.03 (m), 1.02 (s, 3H), 0.92 (d, *J* = 6.1 Hz, 3H), 0.68

(s, 3H).

Synthesis of Methyl 3β-formlyoxycholanate **(2-23c**): To a solution of lithocholic acid methyl ester (**2-22**, 50 mg 0.13 mmol) in toluene (1ml) was added triphenylphosphine (79 mg, 0.30 mmol) formic acid (12 µl, 0.3 mmol) and DEAD (2.2 M solution in toluene, 140 µl, 0.30 mmol). And this solution was stirred at 0℃ for 1hour then room temperature for 17 hours. The reaction mixture was quenched with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (5 g, 10 % ethyl acetate-hexane) to yield 37 mg (0.090 mmol, 70 %) of farmate **2-23c**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H), 5.22 (bs, 1H), 3.66 (s, 3H), 2.34 (ddd, *J*=15.2, 10.0, 5.2 Hz, 1H), 2.21 (ddd, *J* = 16.8, 10.4, 6.8 Hz, 1H), 1.97-0.93 (m), 0.96 (s, 3H), 0.91(d, *J*=6.4Hz, 3H), 0.65 (s, 3H).

Synthesis of Methyl 3β-hydroxyoxycholanate (isolithocholic acid methyl ester, ***epi*-2-22**)**:** To a solution of formate (**2-23c**, 699 mg, 1.67 mmol) in methanol (150 ml) was added sodium methoxide (155 mg) and stirred for 2 hours at room temperature. The reaction mixture was added 2M HCl and filtered. The precipitation was washed with water and dissolved to ethanol, ethyl acetate and evaporated in vacuo. The residue was chromatographed on silica gel (15 g, 20-50 % ethyl acetate-hexane) to yield 606 mg (1.55 mmol, 93 %) of product ***epi*-2-22**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.10 (bs, 1H), 3.66 (s, 3H), 2.35 (ddd, *J* = 14.8, 9.9, 4.9 Hz, 1H), 2.21 (ddd, *J* = 15.9, 9.9, 6.6 Hz, 1H), 1.97-0.93 (m), 0.95 (s, 3H), 0.91(d, *J*=6.1Hz, 3H), 0.64 (s, 3H).

Synthesis of Compound **2-25:** To a solution of isolithocholic acid methyl ester (***epi*-2-22**, 281 mg, 0.72 mmol) in toluene (4 ml) was added triphenylphosphine (379 mg, 1.4 mmol), phthalimide (231 mg, 1.6 mmol) and DEAD (2.2 M dolution in toluene, 620 µl, 1.4 mmol). And this solution was stirred at room temperature for 2.5 hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (24 g, 5-10 % ethyl acetate-hexane) to yield 218 mg (0.42 mmol, 59 %) of desired product **2-25**. ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.80 (dd, *J*=5.4, 2.9 Hz), 7.69 (dd, *J*=5.6, 3.2 Hz, 1H), 4.10-4.25 (m, 1H), 3.67 (s, 3H), 2.73 (q, *J*=12.7Hz, 1H), 2.30-2.40 (m, 2H), 2.22 (ddd, *J*=16.1, 9.8, 7.0 Hz, 1H), 1.97-0.93 (m), 0.97 (s, 3H), 0.92 (d, *J*=6.3Hz, 3H), 0.66 (s, 3H).

Synthesis of Methyl 3α-aminocholanate **2-26:** To a solution of phthalimide (**2-25**, 520 mg 1.00 mmol) in methanol (25 ml) was added hydrazine monohydrate (250 µl, 5.0 mmol) and stirred under reflux for 5.5 hours. The reaction mixture was quenched with brine and extracted with dichloromethane. The organic layer was washed with aqueous sodium hydrogen carbonate, dried with sodium sulfate, and evaporated in vacuo. The

residue was resolved with diethyl ether, added with 1M HCl and filterd. 372.1 mg of desired product **2-26** (0.873 mmol, 87.3%) was obtained. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 3H), 3.66 (s, 3H), 3.18 (brs, 1H), 2.36 (ddd, 1H, *J* = 15.1, 10.3, 4.8 Hz), 2.21 (ddd, 1H, *J* = 15.1, 10.3, 6.8 Hz), 2.0-0.9 (m), 0.91 (s, 3H), 0.90 (d, 3H, *J* = 6.2 Hz), 0.63 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 174.77, 55.07, 55.77, 51.95, 51.47, 42.66, 42.22, 40.30, 39.80, 35.80, 35.35, 35.10, 34.56, 31.63, 31.09, 30.97, 28.13, 26.79, 26.25, 24.20, 23.39, 20.85, 18.27, 12.01.

Synthesis of Compound **2-28a:** To a solution of methyl 3α-aminocholanate chloride (**2-26**, 69.0 mg, 0.16 mmol) in dichloromethane (1.5 ml) was added pyridine (500 µl), methanesulfonyl chloride (300 µl). This solution was stirred at 0°C for 1 hour then at room temperature for 17 hours. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (4 g, 20-40 % ethyl acetate-hexane) to yield 58.2 mg (0.124 mmol, 76.8 %) of desired product **2-28a**. The residue was recrystallized with ethyl acetate. Colorless prisms (ethyl acetate); mp 155 °C; ^{1}H-NMR(600 MHz, $CDCl_3$) δ 4.14-4.12 (m, 1H), 3.66 (s, 3H), 3.35-3.28 (m, 1H), 2.35 (ddd, *J*=15.1, 9.6, 4.8 Hz, 1H), 2.22 (ddd, *J*=15.8, 9.6, 6.2 Hz, 1H), 1.96 (bdt, *J*= 13.8, 2.7, 1H), 1.9-0.98 (m), 0.93 (s, 3H), 0.91 (d, *J*=6.9Hz, 3H), 0.64 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 174.76, 56.48, 55.96, 54.12, 51.49, 42.72, 42.57, 42.25, 40.51, 40.09, 35.86, 35.74, 35.35, 35.07, 34.40, 31.04, 30.98, 29.35, 28.16, 26.92, 26.31, 24.15, 23.45, 20.80, 18.26, 12.03.

Synthesis of Compound **2-28b:** To a solution of methyl 3α-aminocholanate chloride (**2-26**, 76.5 mg, 0.18 mmol) in dichlorometane (1.5 ml) was added triethylamine (80 ml), ethanesulfonyl chloride (37.5 ml). And this solution was stirred at 0°C for 1.5 hours then added triethylamine (50 ml), ethanesulfonyl chloride (18.5 ml), and stirred at 0 °C for 1 hour then room temperature for 1 hour. The reaction mixture was quenched with aqueous sodium bicarbonate and extracted with dichlorometane. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (4 g, 17-30 % ethyl acetate-hexane) to yield 81 mg (94%) of **2-28b**. Colorless prisms (hexane/ethyl acetate); mp 137-138 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 3.98 (d, *J* = 3.98, 1H), 3.67 (s, 3H), 3.32-3.24 (m, 1H), 3.04 (q, *J* = 7.56, 2H), 2.35 (ddd, *J* = 15.8, 10.3, 5.5 Hz, 1H), 2.22 (ddd, *J* = 16.5, 10.3, 6.8 Hz, 1H), 2.0-1.0 (m), 1.37 (t, *J* = 6.9, 3H), 0.93 (s, 3H), 0.91 (d, *J* = 6.8Hz, 3H), 0.64 (s,3H).

Synthesis of Compound **2-28c:** To a solution of methyl 3α-aminocholanate chloride (**2-26**, 70.6 mg, 0.17 mmol) in dichlorometane (2 ml) was added triethylamine (92 ml, 0.58 mmol), p-toluenesulfonyl chloride (72.5 mg, 0.38 mmol). And this solution was stirred at 0°C for 3 hours then room temperature for 15.5 hours. The reaction mixture was quenched with aqueous sodium bicarbonate and extracted with dichlorometane. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was

chromatographed on silica gel (4 g, 12.5-25 % ethyl acetate-hexane) to yield 84.6 mg (94%) of **2-28c**. Colorless prisms (hexane/ethyl acetate); mp 103-105 °C. ^{1}H-NMR (600 MHz, CD_3OD) δ 7.89 (s, 1H), 7.72 (d, *J*= 8.28, 2H), 7.35 (d, *J*= 7.56, 2H), 3.63 (s, 3H), 3.02-2.95 (m, 1H), 2.42 (s, 3H), 2.35 (ddd, *J*=15.1, 9.6, 5.5 Hz, 1H), 2.22 (ddd, *J*=16.5, 9.6, 6.8 Hz, 1H), 2.0-0.9 (m), 0.88 (s, 3H), 0.91(d, *J*=6.2 Hz, 3H), 0.65 (s, 3H).

Synthesis of Compound **2-20a:** To a solution of compound **2-28a** (23.6 mg, 0.050 mmol) in methanol (21 ml) was added 2M NaOH aq (7 ml). And this solution was stirred at room temperature for 2 hours. The reaction mixture was quenched with 2M HCl aq and extracted with dichloromethane. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was recrystallized with ethyl acetate to yield 8.4 mg (0.0185 mmol, 36.7 %) of compound **2-20a**. Colorless prisms (chloroform); mp 160-161.5 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.14-4.12 (m, 1H), 3.35-3.28 (m, 1H), 2.35 (ddd, *J* = 15.1, 9.6, 4.8 Hz, 1H), 2.22 (ddd, *J*=15.8, 9.6, 6.2 Hz, 1H), 1.96 (bdt, *J*= 13.8, 2.7 Hz, 1H), 1.9-0.98 (m), 0.93 (s, 3H), 0.91(d, *J*=6.9 Hz, 3H), 0.64 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 178.51, 56.51,55.99, 54.09, 42.75, 42.58, 42.25, 40.52, 40.11, 35.88, 35.75, 35.34, 35.06, 34.40, 30.75, 30.71, 29.36, 28.17, 26.93, 26.32, 24.17, 23.46, 20.81, 18.25, 12.04.

Synthesis of Compound **2-20b:** To a solution of compound **2-28b** (40.0 mg, 0.083 mmol) in methanol (12 ml) was added 2M NaOH aq (4 ml) and this solution was stirred at 0°C for 0.5 hour. This solution was added methanol (12ml), 0.5N NaOH aq (8 ml) and 6.25 M NaOH aq (3.5 ml) and then stirred at room temperature for 4 hours. The reaction mixture was quenched with 2M HCl aq and extracted with dichlorometane. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was recrystallized with ethyl acetate to yield 24 mg of compound **2-20b** (0.051 mmol, 62%). Colorless prisms (hexane/ethyl acetate); mp 158 °C. ^{1}H-NMR(600 MHz, $CDCl_3$) δ 4.3 (bs, 1H), 3.35-3.2 (m, 1H), 3.04 (q, *J*= 6.8, 2H), 2.41 (ddd, *J*=15.8, 10.3, 5.5 Hz, 1H), 2.26 (ddd, *J* = 16.5, 10.3, 6.8 Hz, 1H), 1.9-0.98 (m), 0.93 (s, 3H), 0.93 (d, *J* = 6.9Hz, 3H), 0.65 (s, 3H).

Synthesis of Compound **2-20c:** To a solution of compound **2-28c** (46.6 mg, 0.085 mmol) in methanol (21 ml) was added 2M NaOH aq (7 ml). This solution was stirred at 0°C for 0.5 hour and then stirred at room temperature for 1 hour. The reaction mixture was quenched with 2M HCl aq and extracted with dichlorometane. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was recrystallized with acetonitrile to yield 24 mg (0.044 mmol, 52 %) of compund **2-20c**. Colorless prisms; mp 182 °C. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J*= 8.22, 2H), 7.30 (d, *J*= 8.22, 2H), 4.5-4.6 (m, 1H), 3.15-3.05 (m, 1H), 2.43 (s, 3H), 2.40 (ddd, *J*=15.8, 10.3, 4.8 Hz, 1H), 2.26 (ddd, *J*=15.8, 9.7, 6.2 Hz, 1H), 2.0-0.9 (m), 0.87 (s,3H), 0.91(d, *J*=6.8Hz, 3H), 0.62 (s, 3H).

Synthesis of Compound **2-27:** To a solution of methyl 3α-aminocholanate chloride (**2-26**, 68.5 mg, 0.16 mmol) in dichloromethane (1.5 ml) was added pyridine (500 ml), acetic anhydride (200 ml). And this solution was stirred at 0°C for 1 hour then room temperature for 22.5 hours. The reaction mixture was quenched with water and extracted with dichloromethane. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was recrystallized with ethyl acetate to yield 36.3 mg (0.084 mmol, 53 %) of compound **2-27**. Colorless prisms (ethyl acetate); mp 208 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 5.29 (bd, *J*=7.6, 1H), 3.66 (s, 3H), 3.81-3.74 (m, 1H), 2.35 (ddd, *J* =15.8, 10.3, 5.5 Hz, 1H), 2.22 (ddd, *J* = 15.1, 9.6, 6.2 Hz, 1H), 1.95 (s, 3H), 1.9-1.0 (m), 0.93 (s, 3H), 0.91(d, *J* = 6.2Hz, 3H), 0.64 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 174.78, 169.12, 56.66, 56.06, 51.49, 49.44, 42.75, 42.30, 40.58, 40.22, 35.78, 35.38, 34.55, 33.70, 31.08, 31.01, 28.20, 27.98, 26.97, 26.41, 24.18, 23.64, 23.53, 20.81, 18.27, 12.04.

Synthesis of Compound **2-19:** To a solution of compound **2-27** (18.6 mg, 0.045 mmol) in methanol (12 ml) was added 2M NaOH aq (4 ml). And this solution was stirred at room temperature for 3.5 hours. The reaction mixture was quenched with 2M HCl aq and extracted with dichloromethane. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was recrystallized with ethyl acetate to yield 12.9 mg (69.3 %) of compound **2-19**. Colorless prisms (methanol); mp 268 °C; ^{1}H-NMR (600 MHz, CD_3OD) δ 7.9 (m), 4.61 (brs), 3.6-3.7 (m), 2.32 (ddd, *J* = 15.8, 10.3, 6.5 Hz, 1H), 2.19 (ddd, *J* = 16.5, 9.6, 6.9 Hz, 1H), 2.02 (bdt, *J* = 12.4, 2.7 Hz, 1H), 1.95-1.0 (m), 0.96 (s, 3H), 0.94 (d, *J* = 6.9Hz, 3H), 0.69 (s, 3H).

Compound **2-18**: To a solution of compound **2-26** (39.8 mg, 0.093 mmol) in methanol (3 ml) was added 2M NaOH aq (1 ml). And this solution was stirred at 0°C for 1 hour then room temperature for 8 hours. The reaction mixture was quenched with 2M HCl aq and filterd. The precipittion was resolved with methanol and evaporated in vacuo. 27.1 mg of desired product **2-18** (0.072 mmol, 77.3%) was obtained. ^{1}H-NMR (600 MHz, CD_3OD) δ 3.04-3.1 (m, 1H), 2.18 (ddd, *J* = 13.7, 10.3, 4.8 Hz, 1H), 1.99-2.05 (m, 2H), 1.02-1.98 (m), 0.97 (s, 3H), 0.92 (d, *J* = 6.2Hz, 3H), 0.67 (s, 3H).

Synthesis of Compound **2-30:** To a solution of compound **2-25** (55.3 mg, 0.106 mmol) in methanol (5 ml) and THF (10mL) was added 2M NaOH aq (5 ml). And this solution was stirred at 0 °C for 2 hours. The reaction mixture was quenched with 2M HCl aq and extracted with dichloromethane. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo and yield 49.3 mg (0.094 mmol, 89 %) of compound **2-30**.; ^{1}H-NMR (600 MHz, CD_3OD) δ 7.94 (d, *J*= 7.6 Hz, 1H), 7.58 (t, *J*= 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 1H), 7.39 (d, *J*= 7.6 Hz, 1H), 3.84 (brt, *J* = 11.6 Hz, 1H), 2.31 (ddd, *J* = 15.1, 9.6, 4.8 Hz, 1H), 2.18 (ddd, *J* = 15.8, 8.9, 6.8 Hz, 1H), 1.0-2.0 (m), 0.98 (s, 3H), 0.93 (d, *J* = 6.2 Hz, 3H), 0.69 (s, 3H).

Synthesis of **benzyl 3α-hydroxycholanate (2-31):** To a solution of lithocholic acid in DMF (5 ml) was added potassium carbonate (420 mg), benzyl chloride (480 µl). And this solution was stirred at 40°C for 3 hours, at room temperature for 19 hours and at 60 °C for 3 hours, the reaction mixture was quenched with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was recrystallized with ethyl acetate to yield 525 mg (1.13 mmol, 82 %) of compound **2-31**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.4-7.3 (m, 5H), 5.12 (d, *J* = 12.4 Hz, 1H), 5.10 (d, *J* = 12.4 Hz, 1H), 3.65-3.55 (m, 1H), 2.40 (ddd, *J* = 15.1, 9.7, 4.8 Hz, 1H), 2.27 (ddd, *J* = 15.8, 9.6, 6.2 Hz, 1H), 1.9-0.98 (m), 0.92 (s, 3H), 0.91(d, *J* = 6.2Hz, 3H), 0.62 (s, 3H).

Synthesis of Compound **2-32:** To a solution of **2-31** (104 mg, 0.22 mmol) in dichlorometane (2 ml) was added triethylamine (156 µl), *p*-toluenesulfonyl chloride (127.7 mg, 0.67 mmol). And this solution was stirred at room temperatur for 16.5 hours then under reflux for 7.5 hours. The reaction mixture was quenched with aqueous sodium bicarbonate and extracted with dichlorometane. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (8 g, 10.5-25 % ethyl acetate-hexane) to yield 81 mg (58 %) of **2-32;** ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.28 Hz, 2H), 7.4-7.3 (m, 5H), 7.33 (d, *J*= 8.22 Hz, 2H), 5.12 (d, *J*=12.4 Hz, 1H), 5.10 (d, *J*=12.4 Hz, 1H), 4.14-4.12 (m, 1H), 3.66 (s, 3H), 3.35-3.28 (m, 1H), 2.40 (ddd, *J*=15.1, 10.3, 4.8 Hz, 1H), 2.27 (ddd, *J*=15.8, 8.9, 6.2 Hz, 1H), 2.45 (s, 3H), 2.0-1.0 (m), 0.88 (s, 3H), 0.89 (d, *J*=6.9Hz, 3H), 0.60 (s, 3H).

Synthesis of Compound **2-33:** A mixture of **2-32** (23.9 mg, 0.038 mmol) and 10% palladium on carbon (18.4 mg) in ethyl acetate (10 ml) and methanol (6 ml) was stirred under a hydrogen atmosphere for 4 h. The reaction mixture was filtered over Celite, and the filtrate was evaporated. The residue was resolved in ethyl acetate and filtered. The filtrate was evaporated in vacuo and yield of compound **2-33** (10.4 mg, 51%); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 4.45 (sep, *J* = 4.8 Hz, 1H), 2.45 (s, 3H), 2.37 (brs, 1H), 2.23 (brs, 1H), 2.0-1.0 (m), 0.91(d, *J* = 6.2 Hz, 3H), 0.88 (s, 3H), 0.62 (s, 3H).

Synthesis of Compound **2-34:** To a solution of **2-31** (296 mg, 0.64 mmol) in THF (2 ml) was added TBDMS-Cl (200 mg, 1.3 mmol), 4-dimethylaminopyridine (179 mg, 1.5 mmol) and DMF (1ml). And this solution was stirred at room temperature for 24.5 hours. The reaction mixture was quenched with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (8 g, 2-33 % ethyl acetate-hexane) to yield 350 mg (0.60 mmol, 95 %) of **2-34.** ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.4-7.3 (m, 5H), 5.12 (d, *J* = 12.4, 1H), 5.10 (d, *J* = 12.4, 1H), 3.61-3.54 (m, 1H), 2.40 (ddd, *J* = 15.8, 10.3, 5.5 Hz, 1H), 2.27 (ddd, *J* = 15.8, 9.6, 6.8 Hz, 1H), 1.9-1.0 (m), 0.89 (s, 9H), 0.61 (s, 3H), 0.06 (s, 6H).

Synthesis of Compound **2-37:** To a solution of **2-22** (310 mg, 0.80 mmol) in THF (2 ml) was added TBDMS-Cl (252 mg, 1.7 mmol), 4-dimethylaminopyridine (223 mg, 1.8 mmol) and DMF (1ml). And this solution was stirred at room temperatur for 17 hours. The reaction mixture was quenched with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, dried with sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (10 g, 2-11 % ethyl acetate-hexane) to yield 309 mg (0.61 mmol, 77 %) of**.** ^{1}H-NMR (600 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.61-3.54 (m, 1H), 2.35 (ddd, *J*=15.1, 10.3, 4.8 Hz, 1H), 2.21 (ddd, *J*=16.4, 9.6, 6.2 Hz, 1H), 1.9-1.0 (m), 0.90 (s), 0.89 (s), 0.63 (s, 3H), 0.06 (s, 6H).

Synthesis of Compound **2-39:** A mixture of **2-34** (171.6 mg, 0.295 mmol) and 10% palladium on carbon (25 mg) in ethyl acetate (10 ml) and methanol (10 ml) was stirred under a hydrogen atmosphere for 3 h. The reaction mixture was filtered over Celite, and the filtrate was evaporated. The residue was purified by recrystallization from methanol/ethyl acetate to give **2-39** (56.7 mg, 39 %). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 3.54-3.60 (m, 1H), 2.3-2.4 (brs, 1H), 2.15-2.25 (brs, 1H), 1.9-1.0 (m), 0.63 (s, 3H), 0.056 (s, 6H).

Synthesis of Compound **2-41:** Bromine (790 mg) is added slowly at room temperature to a mechanically stirred mixture of **2-2** (2.01g), carbon tetrachloride (11 ml) and phosphorus tribromide (1.34 g) in a ml. flask fitted with a reflux condensenser topped by drying tube containing anhydrous calcium sulfate. After 30 minutes, additional bromine (2.38 g) in carbon tetrachloride (3 ml) is added and the mixture is refluxed for 19 hours. The dark red soluton is cooled to room temparature and methanol (20 ml) is added dropwise. Esterification is completed by for refluxing the mixture for 1 hour. The mixture is then cooled to room thmperature, diluted with methylene chloride (20 ml).The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated in vacuo. The residual gum was purified by column chromatography on silica gel (88 g, 0-10 % ethyl acetate - methylene chloride) to give compound **2-41** as an orange solid (1.34 g, 59 %). ^{1}H-NMR(600 MHz, $CDCl_3$) (Major : Minor = 1.3 : 1) (Major) δ 4.31(dd, *J*=11.6, 4.1 Hz, 1H), 3.76 (s, 3H), 3.64-3.58 (m, 1H), 2.39 (td, *J*=11.7, 2.8 Hz, 1H), 1.91 (dt, *J*=12.4, 3.4 Hz, 1H), 1.88-1.0 (m), 0.95 (t, *J*=3.1 Hz, 1H), 0.92(d, *J*=6.2 Hz, 3H), 0.89 (s, 3H), 0.59 (s, 3H). (Minor) δ 4.29 (dd, *J*=11.0, 3.4 Hz, 1H), 3.76 (s, 3H), 3.64-3.58 (m, 1H), 2.15 (ddd, *J*=14.5, 11.7, 2.8 Hz, 1H), 1.95 (dt, *J*=12.4, 3.5 Hz, 1H), 1.88-1.0 (m), 0.97 (t, *J*=3.1 Hz, 1H), 0.90 (d, *J*=5.5 Hz, 3H), 0.90 (s, 3H), 0.66 (s, 3H).

Synthesis of Compound **2-42**: With mechanical stirring, a mixture of Bromide **2-41** (0.073 mmol, 34 mg), sodium bromide (0.22 mmol, 25 mg) and calcium carbonate (24 mg) in dimethylformamide (1 ml) is heated to 130 °C in an atmosphere of nitrogen for 2 hours. The resulting dark solution is cooled to room temperature, inorganic solution material is filtered off and the solution diluted with water and extracted three times with methylene

chloride. The combined methylene chloride extracts are then washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (25 %) and yields **2-42** as a colorless solid (16 mg, 57 %). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.84 (dd, *J*=15.8, 8.9 Hz, 1H), 5.73 (d, J=15.1 Hz, 1H), 3.72 (s, 3H), 3.63 (sep, J=5.3 Hz, 1H), 2.2-2.3 (m, 1H), 1.15-1.90 (m), 1.08 (d, *J* = 6.8 Hz, 3H), 0.98 (td, *J* = 13.7 Hz, 3.5, 1H), 0.92 (s, 3H), 0.68 (s, 3H).

Synthesis of Compound **2-44a:** To a solution of compound **2-42** (73.3 mg, 0.19 mmol) in methanol (3 ml) was added 2M NaOH aq (1 ml) and this solution was stirred at room temperature for 1.5 hours. This solution was added 2M NaOH aq (2 ml) and then stirred at room temperature for 17.5 hours and stirred at 40 ℃ for 7 hours. The reaction mixture was quenched with 1M HCl aq and extracted with ethyl acetate. The organic layer was washed with water, and brine, dried with sodium sulfate, and evaporated in vacuo. The residue was recrystallized with ethaanol to yield 46.7 mg (66 %) of compound **2-44a** as a colorless solid. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.80 (dd, *J*=15.8, 8.9 Hz, 1H), 5.71 (d, *J* = 15.1 Hz, 1H), 3.53 (tt, *J* = 11.0, 4.8 Hz, 1H), 2.27-2.33 (m, 1H), 2.01 (brd, *J* = 11.7 Hz, 1H), 1.90 (tt, *J* = 13.7, 4.8 Hz, 1H), 1.81 (dt, *J* = 14.4, 3.4 Hz, 1H), 1.1-1.7 (m), 1.10 (d, *J* = 6.9 Hz, 3H), 0.99 (td, *J* = 14.4, 3.48 Hz, 1H), 0.95 (s, 3H), 0.73 (s, 3H).

Synthesis of Compound **2-44b**: To a solution of **2-44a** (29.0 mg, 0.0775 mol) in 1.5 ml of acetic acid was stirred under reflux for 20.5 h. Water is added to complete precipitation. The product is filtered off, washed with water and dried. Recrystallization from ethyl acetate yields 16.5 mg of **2-44b** as a colorless solid (51%). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.93 (dd, *J* = 16.5, 8.9 Hz, 1H), 5.75 (d, *J* = 15.8 Hz, 1H), 4.72 (tt, *J* = 11.6, 4.8 Hz, 1H), 2.66-2.34 (m, 1H), 2.03 (s, 3H), 1.96 (brd, *J* = 11.7 Hz, 1H), 1.07- 1.9 (m), 1.09 (d, *J* = 6.2 Hz, 3H), 1.04 (td, *J* = 13.7, 3.4 Hz, 1H), 0.93 (s, 3H), 0.69 (s, 3H).

Synthesis of Compound **2-43a:** To a solution of compound **2-41** (33 mg, 0.070 mmol) in methanol (1.5 ml) was added 2M NaOH aq (0.5 ml) and this solution was stirred at room temperature for 2 hours. This solution was washed with methylene cloride, added 1M HCl aq and extracted with ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated in vacuo to yield 23 mg (73 %) of compound **2-51** as a yellow solid. ^{1}H-NMR(600 MHz, $CDCl_3$) (Major : Minor = 1.9 : 1) (Major) δ 4.30 (dd, *J*=11.7, 3.4 Hz, 1H), 3.61-3.68 (m, 1H), 2.15 (td, *J*=13.7, 2.04 Hz, 1H), 1.96 (td, *J*=12.4, 2.8 Hz, 1H), 1.0-1.9 (m), 0.92 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 3H), 0.67 (s, 3H). (Minor) δ 4.30 (dd, *J* = 11.7, 3.4 Hz, 1H), 3.61-3.68 (m, 1H), 2.15 (td, *J* = 13.7, 2.04 Hz, 1H), 1.96 (td, *J* = 12.4, 2.8 Hz, 1H), 1.0-1.9 (m), 0.92 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 3H), 0.61 (s, 3H).

Synthesis of Compound **2-43b**: To a solution of a **2-43a** (20.4 mg, 0.0448 mol) in 1.5 ml of acetic acid was stirred under reflux for 14.5 h. Water is added to complete precipitation. The product is washed with water and dried

to yields 21 mg of **2-43b** as a pale yellow solid (95 %). ^{1}H-NMR (600 MHz, $CDCl_3$) (Major : Minor = 1.6 : 1) (Major) δ 4.66-4.73 (m, 1H), 4.30 (dd, *J* =11.0, 3.5 Hz, 1H), 2.14 (td, *J*=11.7, 2.1 Hz, 1H), 2.01 (s, 3H), 1.97 (dt, *J*=12.4, 3.4 Hz, 1H), 0.92 (d, *J*=6.8 Hz, 3H), 0.91(s, 3H), 0.67 (s, 3H). (Minor) δ 4.66-4.73 (m, 1H), 4.32 (dd, *J* = 11.7, 4.1 Hz, 1H), 2.39 (td, *J* = 13.7, 2.0 Hz, 1H), 2.01 (s, 3H), 1.93 (dt, *J* = 12.4, 2.8 Hz, 1H), 0.95 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 3H), 0.61 (s, 3H).

Synthesis of Compound **2-47:** To a solution of **2-42** (145mg, 0.37 mmol) in 3ml of acetonitrile was added nitromethane (200 ul, 37 mmol) drop wise, followed by 1,8-diazabicycl[5.4.0] undec-7-ene (DBU) (280µl, 1.88 mmol). The mixture was heated at 60 °C for 6h, cooled, and diluted with ethyl acetate and washed with saturated aqueous NH_4Cl and brine. The orange layer was dried Na_2SO_4, filtered, and evaporated under reduced pressure. The resulting residue was purified by column chromatography on silica gel with n-hexane containing acetone (17 %) to yield **2-47** as a pale yellow solid (49 mg, 29 %). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.53 (dd, *J*=12.4, 5.5 Hz, 1H), 4.37 (dd, *J*=12.4, 9.7 Hz, 1H), 3.70 (s, 3H), 3.63 (sep, *J*=5.3 Hz, 1H), 2.88-2.94 (m, 1H), 2.48 (dd, *J*=15.8, 2.8 Hz, 1H), 2.05 (dd, *J*=15.8, 11.0 Hz, 1H), 0.95-1.95 (m), 0.92 (s, 3H), 0.85 (d, *J*=6.9 Hz, 3H), 0.63 (s, 3H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 172.6136, 71.7818, 56.5579, 53.1493, 52.0003, 42.7798, 41.9851, 40.3574, 40.1946, 36.6232, 36.3838, 35.8764, 35.7998, 35.2732, 34.5168, 30.5815, 30.4762, 27.7378, 27.0867, 26.3208, 23.9941, 23.3239, 20.7770, 13.1267, 12.0065.

Synthesis of Compound **2-48a:** To a solution of compound **2-47** (48.3 mg, 0.11 mmol) in ethanol (3 ml) was added 2M NaOH aq (2.5 ml) and this solution was stirred at room temperature for 1.5 hours. The reaction mixture was quenched with 2M HCl aq and extracted with ethyl acetate. The organic layer was washed with water, and brine, dried with sodium sulfate, and evaporated in vacuo. The resulting residue was purified by preparative TLC with ethyl acetate containing n-hexane (25 %) and acetic acid (1%) to yield **2-48a** as a colorless solid (12.4 mg, 16%). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.52 (dd, *J* = 12.4, 4.8 Hz, 1H), 4.36 (dd, *J* = 12.4, 10.3 Hz, 1H), 3.63 (tt, *J* = 11.0, 4.8 Hz, 1H), 2.87-2.93 (m 1H), 2.50 (dd, *J* = 16.5, 2.7 Hz, 1H), 2.09 (s, 3H), 2.04-2.10 (m, 1H), 1.0-1.92 (m), 0.95 (td, *J* = 14.4, 3.4 Hz, 1H), 0.89 (s, 3H), 0.84 (d, *J* = 6.8 Hz, 3H), 0.61 (s, 3H).

Synthesis of Compound **2-49**: To a solution of **2-48a** (5.1 mg, 0.012 mmol) in 0.5 ml of acetone was added Jones reagent drop wise at 15°C . The mixture was stirred at 15 °C for 35 minutes, and quenched with isopropyl alcohol, inorganic solution material is filtered off and the solution diluted with ethyl acetate and washed with saturated aqueous NH_4Cl and brine. The orange layer was dried over Na_2SO_4, filtered, and evaporated under reduced pressure and yield **2-49** as a colorless solid (3.5 mg, 67 %). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 4.53 (dd, *J* = 12.4, 4.9 Hz, 1H), 4.37 (dd, *J* = 12.4, 9.6 Hz, 1H), 2.87-2.94 (m, 1H), 2.66 (t, *J* = 14.4 Hz, 1H), 2.50 (dd, *J* = 16.5, 2.8 Hz, 1H), 2.30 (td, *J* = 14.5, 4.8 Hz, 1H), 2.15 (brd, *J* = 14.5 Hz, 1H), 2.08 (dd, *J* = 11.6, 5.5 Hz, 1H), 1.8- 2.05 (m),

1.01-1.65 (m), 1.00 (s, 3H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.66 (s, 3H).

Synthesis of Compound **2-50:** To a solution of **2-42** (154 mg, 0.40 mmol) in THF (2 ml) was added TBDMS-Cl (119 mg, 0.79 mmol), 4-dimethylaminopyridine (112 mg, 0.92 mmol) and DMF (1ml). And this solution was stirred at room temperature for 38.5 hours. The reaction mixture was quenched with aqueous sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with brine, dried with sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (6.3 g, 4 % ethyl acetate-hexane) to yield 178 mg (88 %) of **2-50** as a colorless solid. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 6.84 (dd, *J* = 15.8, 9.0 Hz, 1H), 5.73 (d, *J* = 15.1, 1H), 3.72 (s, 3H), 3.56-3.66 (m, 1H), 2.2-2.3 (m, 1H), 1.9-0.8 (m), 0.67 (s, 3H), 0.057 (s, 6H).

Synthesis of compound **3-7**: To a solution of p-carborane (640 mg, 4.43 mmol) in 1,2-dimethoxyethane (4 ml) was added dropwise a 1.5 M solution of n-BuLi in hexane (3.25 ml, 4.88 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 20 min at room temperature and CuCl (570 mg, 5.76 mmol) was added in one potion at 0 °C . Stirring was continued at room temperature for 1h. Pyridine (2 ml) and 4-Iodopyridine (1.0 g, 4.88 mmol) was added in one portion, and the mixture was heated 90 °C for 3h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 10 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (10 : 1) yields **3-7** as a colorless solid (2.48 mmol, 56%).

Synthesis of compound **3-8a**: To a solution of **3-7** (100 mg, 0.45 mmol) in 1,2-dimethoxyethane (0.7 ml) was added dropwise a 1.63 M solution of n-BuLi in hexane (0.42 ml, 0.68 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 20 min at room temperature and CuCl (72 mg, 0.73 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (0.2 ml) and 4-Iodobenzonitrile (155mg, 0.5 mmol) was added in one portion, and the mixture was heated 80 °C for 3h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (25 %) and recrystallization from dichloromethane-hexane yields **3-8a** as a pale brown solid (33.5mg, 23%) ^{1}H-NMR(600 MHz, $CDCl_3$) δ 8.46 (bs, 2H), 7.50 (dd, *J* = 8.94, 2.04 Hz, 2H), 7.33 (dd, *J* = 8.94, 2.04 Hz, 2H), 7.11 (d, *J* = 4.8 Hz), 2.0-3.2 (m, 10H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 149.88, 144.13, 140.53, 131.98, 127.94, 121.70, 117.90, 112.75, 82.27, 81.25.

Synthesis of compound **3-8b**: To a solution of **3-7** (96.5 mg, 0.44 mmol) in 1,2-dimethoxyethane (0.7 ml) was

added dropwise a 1.63 M solution of n-BuLi in hexane (0.42 ml, 0.68 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred for 20 min at room temperature and CuCl (72 mg, 0.73 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (0.2 ml) and 3-Iodobenzonitrile (155mg, 0.5 mmol) was added in one portion, and the mixture was heated 85 °C for 4h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (25 %) and recrystallization from dichloromethane-hexane yields **3-8b** as a pale brown solid (12.3 mg, 23%); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.44 (bs, 2H), 7.53 (dt, *J* = 7.56, 1.32 Hz, 1H), 7.50 (t, *J* = 2.1 Hz, 1H), 7.45 (dd, *J* = 8.28, 1.38 Hz, 1H), 7.32 (t, *J* = 8.22 Hz, 1H), 7.11 (d, *J* = 5.46 Hz, 2H), 2.0-3.1 (m, 10H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 149.81, 144.21, 137.36,132.12, 131.41, 130.70, 129.20, 121.76, 117.99, 112.71, 81.77, 80.92.

Synthesis of compound **3-9**: To a solution of p-carborane (502 mg, 3.48 mmol) in 1,2-dimethoxyethane (4 ml) was added dropwaise a 1.63 M solution of n-BuLi in hexane (3.4 ml, 5.5 mmol) at 0 °C under Ar atomosphere. The mixture was stirred for 10 min at room temperature and CuCl (551 mg, 5.6 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (1.2 ml) and 3-Iodopyridine (1.13 g, 5.5 mmol) was added in one portion, and the mixture was heated 80 °C for 3h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 10 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (11 %) yields **3-9** as a colorless solid (250mg, 32%). ^{1}H-NMR(600 MHz, $CDCl_3$) δ 8.44 (dd, *J*= 4.8, 1,38 Hz, 1H), 8.43 (d, *J*=2.04 Hz, 1H), 7.48 (ddd, *J*= 8.22, 2.76, 1.38 Hz, 1H), 7.10 (dd, *J*= 8.94, 4.8 Hz, 1H), 1.8-3.0 (m, 11H).

Synthesis of compound **3-10a**: To a solution of **3-9** (100.8 mg, 0.49 mmol) in 1,2-dimethoxyethane (0.5 ml) was added dropwaise a 1.63 M solution of n-BuLi in hexane (0.43 ml, 0.70 mmol) at 0 °C under N_2 atomosphere. The mixture was stirred for 20 min at room temperature and CuCl (75 mg, 0.76 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (0.2 ml) and 4-Iodobenzonitrile (160 mg, 0.69 mmol) was added in one portion, and the mixture was heated 80 °C for 5h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (20 %) and recrystallization from ethyl acetate -hexane yields **3-10a** as a colorless crystal (6.9mg, 4%); mp: 201 °C; ^{1}H-NMR(600 MHz, $CDCl_3$) δ 8.50 (brd, *J* = 4.1 Hz, 1H), 8.48 (bs, 1H), 7.49-7.54 (m, 3H), 7.36 (dd, *J* =

8.94, 2.04 Hz, 2H), 7.16 (dd, 8.3, 4.8 Hz, 1H), 2.1-3.2 (m, 10H),: Anal. Calcd. For $C_{14}B_{10}H_{18}N_2$: C, 52.15 ;H, 5.63 ; N,8.69. FOUND C, 52.07 ; H,5.38 ; N,8.67.

Synthesis of compound **3-10b**: To a solution of **3-9** (105.5 mg, 0.48 mmol) in 1,2-dimethoxyethane (0.5 ml) was added dropwaise a 1.63 M solution of n-BuLi in hexane (0.47 ml, 0.77 mmol) at 0 °C under N_2 atomosphere. The mixture was stirred for 30 min at room temperature and CuCl (75 mg, 0.76 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (0.2 ml) and 3-Iodobenzonitrile (173mg, 0.76 mmol) was added in one portion, and the mixture was heated 85 °C for 6 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (18 %) and recrystallization from ethyl acetate yields **3-10b** as a pale brown crystal (7.1 mg, 4.6%) ; ^{1}H-NMR(600 MHz, $CDCl_3$) δ 8.48 (bs, 2H), 7.52-7.56 (m, 3H), 7.48 (dd, *J*=8.3, 2.0 Hz, 1H), 7.34(t, *J* = 7.6 Hz, 1H), 7.16 (brd dd, *J*=7.6, 4.8 Hz, 1H), 2.1-3.2 (m, 10H).

Synthesis of compounds **3-11, 3-12**: To a solution of p-carborane (495 mg, 3.43 mmol) in 1,2-dimethoxyethane (3.8 ml) was added dropwise a 1.63 M solution of n-BuLi in hexane (3.5 ml, 5.8 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred for 20 min at room temperature and CuCl (553 mg, 5.6 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (1.3 ml) and 2-bromopyridine (878 mg, 5.6 mmol) was added in one portion, and the mixture was heated 85 °C for 8 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 15 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (2-20 %), yields **3-11** (252mg, 33%) and **3-12** (220mg, 21%). **3-11**: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 4.86, 2.1 Hz, 1H), 7.51 (td, *J* = 7.56, 2.04 Hz, 1H), 7.21 (d, *J* = 8.22 Hz, 1H), 7.13 (ddd, *J* = 7.56, 4.8, 1.38 Hz, 1H), 1.8-3.0 (m, 11H).; ^{13}C-NMR (600 MHz, $CDCl_3$) δ 153.634, 148.60, 136.52, 123.14, 121.02, 86.54, 60.64; **3-12**: ^{1}H-NMR(600 MHz, $CDCl_3$) δ 8.48 (d, *J* = 1.38 Hz, 2H), 7.53 (td, *J* = 7.56, 2.04 Hz, 2H), 7.24 (d, *J* = 8.28 Hz, 2H), 7.15 (dd, *J* = 7.56, 4.8 Hz, 2H), 1.8-3.0 (m, 10H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 153.54, 148.69, 136.55, 123.22, 121.17, 83.97.; Anal. Calcd. For $C_{12}B_{10}H_{18}N_2 \cdot 1/2C_6H_{14}$: C, 46.89 ; H,6.23 ; N,9.11. FOUND C, 47.18 ; H, 5.85 ; N,9.05.

Synthesis of compound **3-13a**: To a solution of **3-11** (101 mg, 0.46 mmol) in 1,2-dimethoxyethane (0.5 ml) was added dropwise a 1.63 M solution of n-BuLi in hexane (0.44 ml, 0.72 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 20 min at room temperature and CuCl (72 mg, 0.73 mmol) was added in one potion at

0 °C. Stirring was continued at room temperature for 1h. Pyridine (0.2 ml) and 4-Iodobenzonitrile (167 mg, 0.73 mmol) was added in one portion, and the mixture was heated 80 °C for 6.5 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (4.5-5 %) and yields **3-13a** as a pale brown solid (25 mg, 17%). The compound was recrystallized with ethyl acetate.; mp: 201 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 4.5, 2.0 Hz, 1H), 7.57 (td, *J* = 8.2, 2.0 Hz, 2H), 7.50 (dt, *J* =8.9, 2.0 Hz, 2H), 7.37 (dt, *J*= 8.9, 2.0 Hz, 2H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.19 (dd, *J* = 7.6, 4.8 Hz, 1H), 2.1-3.2 (m, 10H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 153.0715, 148.7437, 141.0073, 136.6317, 131.8921, 128.0048, 123.3802, 121.0727, 118.0087, 112.5128, 84.1811, 81.7778.; Anal. Calcd. For $C_{14}B_{10}H_{18}N_2$: C, 52.15 ; H,5.63 ; N,8.69. FOUND C, 51.86 ;H, 5.44 ; N,8.64.

Synthesis of compound **3-13b**: To a solution of **3-11** (101 mg, 0.46 mmol) in 1,2-dimethoxyethane (0.5 ml) was added dropwise a 1.63 M solution of n-BuLi in hexane (0.44 ml, 0.72 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 20 min at room temperature and CuCl (72 mg, 0.73 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (0.2 ml) and 3-Iodobenzonitrile (167 mg, 0.73 mmol) was added in one portion, and the mixture was heated 80 °C for 6.5 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (5 %) and yields **3-13b** as a pale brown solid (18 mg, 12%). The compound was recrystallized with methanol-chloroform.; mp: 202.3 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.44 (d, *J* = 4.8 Hz, 1H), 7.48-7.59 (m, 4H), 7.33 (t, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.19 (dd, *J*= 7.6, 4.8 Hz, 1H), 2.1-3.2 (m, 10H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 153.0715, 148.7533, 137.7806, 136.6412, 131.9400, 131.5092, 130.7815, 129.0867, 123.3802, 121.0918, 118.0949, 112.5798, 83.9896, 81.3661.; Anal. Calcd. For $C_{14}B_{10}H_{18}N_2 \cdot 1/4H_2O$: C, 51.44 ; H,5.70 ; N,8.57. FOUND C, 51.55 ;H, 5.62 ; N,8.17.

Synthesis of compound **3-14**: To a solution of **3-11** (101 mg, 0.46 mmol) in 1,2-dimethoxyethane (0.5 ml) was added dropwise a 1.63 M solution of n-BuLi in hexane (0.42 ml, 0.68 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 15 min at room temperature and CuCl (68 mg, 0.69 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (0.2 ml) and 3-Iodopyridine (157 mg, 0.77 mmol) was added in one portion, and the mixture was heated 80 °C for 6.5 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then

concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (8 %) and yields **3-14** as a colorless solid (10 mg, 8%); ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.47 (d, *J* = 2.7 Hz, 1H), 8.46 (dd, *J* = 4.8, 1.4 Hz, 1H), 8.42 (dd, *J* = 4.8, 2.1 Hz, 1H), 7.54 (td, *J* = 8.2 ,2.0 Hz, 1H), 7.51-7.54 (m, 1H), 7.25 (d, *J* = 8.3 Hz, 1H), 7.16 (ddd, *J* = 7.6, 4.8, 1.4 Hz, 1H), 7.13 (dd, *J* = 9.0, 4.8 Hz, 1H), 2.1-3.2 (m, 10H);

Synthesis of compound **3-15**: To a solution of p-carborane (504 mg, 3.49 mmol) in 1,2-dimethoxyethane (4 ml) was added dropwise a 1.57 M solution of n-BuLi in hexane (3.5 ml, 5.5 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 20 min at room temperature and CuCl (554 mg, 5.6 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (1.2 ml) and Iodopyrazine (1 g, 4.9 mmol) was added in one portion, and the mixture was heated 85 °C for 15.5 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (17 %) yields **3-15** as a colorless solid (241 mg, 31 %) and **3-16** as a colorless solid (113mg, 11%). The compound **3-16** was recrystallized with ethyl acetate. **3-15**: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.48(d, *J* = 1.38 Hz, 1H), 8.43 (d, *J* = 2.76 Hz, 1H), 8.36 (dd, *J* = 2.7, 1.38 Hz, 1H), 1.8-3.0 (m, 11H); ^{13}C-NMR (600 MHz, $CDCl_3$) δ 149.50, 144.16, 144.06, 142.95, 142.22, 82.28, 61.54. **3-16**: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 1.38 Hz, 2H), 8.47 (d, *J* = 2.04 Hz, 2H), 8.39 (t, *J* = 2.04 Hz, 2H), 2.0-3.2 (m, 10H); Anal. Calcd. For $C_{10}B_{10}H_{16}N_4 \cdot 1/2H_2O$: C, 59.44 ; H,6.01 ; N,7.11. FOUND C, 59.73 ; H, 5.78 ; N,7.28.

Synthesis of compound **3-17:** To a solution of **3-15** (99 mg, 0.44 mmol) in 1,2-dimethoxyethane (0.5 ml) was added dropwise a 1.14 M solution of LDA (0.62 ml, 0.71 mmol) at -17 °C under Ar atmosphere. The mixture was stirred for 30 min at -17 °C and CuCl (70 mg, 0.71 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (0.2 ml) and 4-Iodobenzonitrile (155mg, 0.5 mmol) was added in one portion, and the mixture was heated 80 °C for 5h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (10 %) and yields **3-17** (13 mg, 9 %).

Synthesis of compound **3-18:** To a solution of p-carborane (515 mg, 3.57 mmol) in 1,2-dimethoxyethane (3.8 ml) was added dropwise a 1.63 M solution of n-BuLi in hexane (3.5 ml, 5.7 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred for 20 min at room temperature and CuCl (565 mg, 5.7 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (1.2 ml) and 2-Bromopyrimidine (902 mg,

5.67 mmol) was added in one portion, and the mixture was heated 80 °C for 8h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off through Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (5 %-25 %) yields **3-18** as a pale brown power (312mg, 40 %). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.59 (d, *J*= 4.80 Hz, 1H), 7.17 (t, *J*= 4.86 Hz, 2H), 3.1-1.7 (m, 11H).

Synthesis of compound **3-21a**: To a solution of p-carborane (508 mg, 3.52 mmol) in 1,2-dimethoxyethane (3.8ml) was added dropwise a 1.63 M solution of n-BuLi in hexane (3.5 ml, 5.71 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred for 25 min at room temperature and CuCl (557 mg, 5.63 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (1.2 ml) and 1-iodonaphthalene (1.43g, 5.63 mmol) was added in one portion, and the mixture was heated 80 °C for 6.5 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane and recrystallization from 1-iodonaphthalene yields mixture of **3-20** and 1-iodonaphthalene as a colorless solid (225 mg). To a solution of the mixture of **3-20** and 1-iodonaphtalene (116 mg) in 1,2-dimethoxyethane (0.6 ml) was added dropwise a 1.63 M solution of n-BuLi in hexane (0.47 ml, 0.77 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred for 20 min at 0°C and CuCl (85 mg, 0.86 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (0.2 ml) and 4-Iodobenzonitrile (257 mg, 1.12 mmol) was added in one portion, and the mixture was heated 80 °C for 6.5 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (0-2%) and recrystallization from hexane, ethyl acetate and dichloromethane yields **3-21a** as a colorless crystal. (17 mg, 3.5%, 2 steps).; .mp: 220.7 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.79 (d, *J* = 8.94 Hz, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.81 (td, *J* = 7.56, 1.38 Hz, 2H), 7.77 (d, *J* = 8.28 Hz, 1H), 7.51- 7.54 (m, 3H), 7.45 (td, *J* = 6.9, 1.38 Hz, 1H), 7.41 (dt, *J* = 8.22, 2.1 Hz, 2H), 2.1-3.6 (m, 10H); ^{13}C- NMR (150MHz, $CDCl_3$) δ 140.98, 134.71, 132.06, 130.89, 130.77, 129.88, 129.46, 129.21, 128.11, 126.16, 125.56, 125.45, 124.55, 118.13, 112.70, 85.06, 83.89.; Anal. Calcd. For $C_{19}B_{10}H_{21}N$: C,61.43 ; H,5.70 ; N,3.77. FOUND C, 61.14 ;H, 5.96 ; N,3.78.; HRMS *m/z* calcd. for $C_{19}B_{10}H_{21}N$ Na (M+Na) 396.2500; found .396.2489;

Synthesis of compound **3-21b**: To a solution of p-carborane (508 mg, 3.52 mmol) in 1,2-dimethoxyethane (3.8ml) was added dropwise a 1.63 M solution of n-BuLi in hexane (3.5 ml, 5.71 mmol) at 0 °C under N_2

atmosphere. The mixture was stirred for 25 min at room temperature and CuCl (557 mg, 5.63 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (1.2 ml) and 1-iodonaphthalene (1.43g, 5.63 mmol) was added in one portion, and the mixture was heated 80 °C for 6.5 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane and recrystallization from 2-iodonaphthalene yields mixture of **3-22** and 2-iodonaphthalene as a colorless solid (225 mg). To a solution of the mixture (101mg, **3-22** and 2-iodonaphtalene) in 1,2-dimethoxyethane (0.6 ml) was added dropwise a 1.63 M solution of n-BuLi in hexane (0.47 ml, 0.77 mmol) at 0 °C under N_2 atmosphere. The mixture was stirred for 20 min at 0°C and CuCl (85 mg, 0.86 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (0.2 ml) and 3-Iodobenzonitrile (210 mg, 0.917 mmol) was added in one portion, and the mixture was heated 80 °C for 6.5 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (0-10%), recycle-GPC, and recrystallization from hexane, ethyl acetate and dichloromethane yields **3-21b** (32 mg, 9%, 2 steps); .mp: 226.5-227.0 °C; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.80 (d, *J* = 9.2 Hz, 1H), 7.76-7.83 (m, 3H), 7.51-7.59 (m, 4H), 7.46 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 2.0-3.8 (m, 10H); ^{13}C-NMR (100MHz, $CDCl_3$) δ 137.6562, 134.6051, 131.9908, 131.4749, 130.7651, 130.6472, 129.7893, 129.3382, 129.1234, 126.0477, 125.4407, 125.3460, 124.4284, 118.0975, 112.6429, 84.7546, 83.3673; Anal. Calcd. For $C_{19}B_{10}H_{21}N$: C, 61.43 ; H,5.70 ; N,3.77. FOUND C, 61.16 ;H, 5.74 ; N,3.72. : HRMS *m/z* calcd. for $C_{19}B_{10}H_{21}N$ Na (M+Na) 396.2500; found .396.2493.

Synthesis of compound **3-23a**: To a solution of p-carborane (497 mg, 3.45 mmol) in 1,2-dimethoxyethane (3.5ml) was added dropwise a 1.63 M solution of n-BuLi in hexane 3.0 ml, 4.89 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 20 min at room temperature and CuCl (510 mg, 5.15 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (1.2 ml) and 2-iodonaphthalene (1g, 3.94 mmol) was added in one portion, and the mixture was heated 80 °C for 5.5 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane yields mixture of **65** and 2-Iodonaphthalene as a colorless powder (720 mg). To a solution of the mixture of 65 and 2-Iodonaphtalene (148 mg) in 1,2-dimethoxyethane (0.5 ml) was added dropwise a 1.63 M solution of n-BuLi in hexane, (0.54 ml, 0.88 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 20

min at 0°C and CuCl (109 mg, 1.10 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (0.2 ml) and 4-Iodobenzonitrile (302 mg, 1.32 mmol) was added in one portion, and the mixture was heated 80 °C for 6h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (0-5%) recycle-GPC and recrystallization from hexane, ethyl acetate and chloroform yields yields **3-23a** as a colorless solid. (17 mg, 21%, 2 steps) ; .mp: 254-255 °C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 7.75-7.78 (m, 2H), 7.71 (d, *J* = 1.7 Hz, 1H), 7.68 (d, *J* = 7.3 Hz, 1H), 7.51 (dt, *J* = 7.2, 1.7 Hz, 2H), 7.46-7.49 (m, 2H), 7.38 (dt, *J* = 7.2, 1.6 Hz, 1H), 7.33 (dd, *J* = 7.3, 1.8 Hz, 1H), 2.1-3.3 (m, 11H) , ^{13}C-NMR (125MHz, $CDCl_3$) δ 141.0051, 132.2644, 132.8273, 132.4944, 131.9243, 128.3280, 128.0801, 127.8911, 127.3484, 126.9062, 126.7220, 126.5271, 124.6312, 118.0132, 112.5917, 84.1581, 81.0244.; Anal. Calcd. For $C_{19}B_{10}H_{21}N$: C, 61.43 ; H,5.70 ; N,3.77. FOUND C, 61.51 ;H, 5.62 ; N,3.68. : HRMS *m/z* calcd. for $C_{19}B_{10}H_{21}N$ Na (M+Na) 396.2500; found .396.2495.

Synthesis of compound **3-23b**: To a solution of p-carborane (497 mg, 3.45 mmol) in 1,2-dimethoxyethane (3.5ml) was added dropwise a 1.63 M solution of n-BuLi in hexane 3.0 ml, 4.89 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 20 min at room temperature and CuCl (510 mg, 5.15 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (1.2 ml) and 2-iodonaphthalene (1g, 3.94 mmol) was added in one portion, and the mixture was heated 80 °C for 5.5 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane yields mixture of **3-22** and 2-Iodonaphthalene as a colorless powder (720 mg). To a solution of the mixture of 65 and 2-Iodonaphtalene (153mg) in 1,2-dimethoxyethane (0.5 ml) was added dropwise a 1.63 M solution of n-BuLi in hexane, (0.55 ml, 0.57 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 20 min at 0°C and CuCl (111 mg, 1.12 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (0.2 ml) and 3-Iodobenzonitrile (257 mg, 1.12 mmol) was added in one portion, and the mixture was heated 80 °C for 7h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (0-5%) and preparative TLC yields **3-23b** as a colorless solid. (10.1 mg, 3.6%, 2 steps); mp: 213 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.75-7.79 (m, 2H), 7.71 (d, *J* = 2.1 Hz, 1H), 7.68 (d, *J* = 8.88 Hz, 1H), 7.56 (d, *J* = 1.38 Hz, 1H), 7.54 (d, *J* = 7.56, 1H), 7.50 (dd, *J* = 2.04, 6.18 Hz, 1H), 7.46-7.48 (m, 2H), 7.32-7.35 (m, 2H), 2.1-3.3 (m, 10H), ^{13}C- NMR (150MHz, $CDCl_3$) δ 137.72,

133.20, 132.78, 132.45, 131.94, 131.55, 130.83, 129.10, 128.31, 127.87, 127.33, 126.88, 126.69, 126.51, 124.62, 118.10, 112.59, 83.90, 80.54; Anal. Calcd. For $C_{19}B_{10}H_{21}N \cdot 1/10H_2O$: C, 61.14 ; H,5.72 ; N,3.75. FOUND C, 60.93 ;H, 5.43 ; N,3.59. : HRMS *m/z* calcd. for $C_{19}B_{10}H_{21}N$ Na (M+Na) 396.2500; found .396.2491.

Synthesis of compound **3-24**: To a solution of p-carborane (488 mg, 3.39 mmol) in 1,2-dimethoxyethane (3.5ml) was added dropwise a 1.63 M solution of n-BuLi in hexane 3.4 ml, 5.54 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 15 min at room temperature and CuCl (537 mg, 5.42 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (1.2 ml) and 2- bromoquinoline (1g, 4.81 mmol) was added in one portion, and the mixture was heated 80 °C for 6h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane yields **3-24** as a colorless powder (417 mg, 45 %).; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.56 Hz, 1H), 8.00 (d, *J* = 8.22 Hz, 1H), 7.73 (d, *J* = 8.22 Hz, 1H), 7.68 (ddd, *J* = 8.22, 6.84, 1.38 Hz, 1H), 7.51 (ddd, *J* = 8.22, 6.84, 1.08 Hz, 1H), 7.33 (d, *J* = 8.94 Hz, 1H), 1.7-3.2 (m, 11H).; ^{13}C- NMR (150 MHz, $CDCl_3$) δ 152.99, 146.91, 136.55, 129.92, 129.87, 127.10, 118.55, 87.15, 60.83.

Synthesis of compound **3-26a**: To a solution of **3-24** (94.8 mg, 0.35 mmol) in 1,2-dimethoxyethane (0.5 ml) was added dropwaise a 1.14 M solution of LDA (0.49 ml, 0.56 mmol) at -15 °C under Ar atomosphere. The mixture was stirred for 25 min at -15 °C and CuCl (56.1 mg, 0.57 mmol) was added in one potion at -15 °C. Stirring was continued at 0 °C for 1h and room temperature for 15 min. Pyridine (0.2 ml) and 4-Iodobenzonitrile (127.9 mg, 0.56 mmol) was added in one portion, and the mixture was heated 80 °C for 15h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 25 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat. NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (0-2%) yields **3-26a** as a pale yellow solid (8.4 mg, 6.5 %) and recovers **3-24** (49.4 mg, 52%). The compound was recrystallized with hexane-chloroform. **3-26a**; colorless prism; mp: 269-270 °C; ^{13}C- NMR(150MHz, $CDCl_3$) δ152.4543, 146.9789, 141.1591, 136.7255, 131.9107, 130.0383, 129.8977, 128.0659, 127.2868, 127.1848, 127.1678, 118.4930, 118.0301m 112.5686, 84.8069, 81.9711. Anal. Calcd. For $C_{18}B_{10}H_{20}N_2$: C, 58.04 ; H,5.41 ; N,7.52. FOUND C, 57.87 ;H, 5.53 ; N,7.42. : HRMS *m/z* calcd. for $C_{18}B_{10}H_{21}N_2$ (M+H) 375.2633; found .375.2623.

Synthesis of compound **3-26b**: To a solution of **3-24** (99.1 mg, 0.37 mmol) in 1,2-dimethoxyethane (0.5 ml) was added dropwise a 1.14 M solution of LDA (0.51 ml, 0.58 mmol) at -18 °C under Ar atmosphere. The mixture

was stirred for 20 min at -15 °C and CuCl (57.8 mg, 0.58 mmol) was added in one potion at -15 °C. Stirring was continued at 0 °C for 1h and room temperature for 15 min. Pyridine (0.2 ml) and 3-Iodobenzonitrile (133.7 mg, 0.58 mmol) was added in one portion, and the mixture was heated 80 °C for 15.5h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat. NH_4Cl and brine, dried over $MgSO_4$, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (1%) and recrystallization from hexane - chloroform yields **3-26b** as a colorless solid. (4.4 mg, 3.2 %) mp: 222°C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.034 (d, *J* = 7.9 Hz, 1H), 8.028 (d, *J* = 8.4 Hz, 1H), 7.75 (d *J* = 8.1 Hz, 1H), 7.70 (dd, *J* = 6.9, 1.4 Hz, 1H), 7.50-7.57 (m, 4H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.34 (t, *J* = 8.1 Hz, 1H), 2.1-3.5 (m,10H).; ^{13}C- NMR (150MHz, $CDCl_3$) δ 152.45, 146.98, 137.94, 136.73, 131.94, 131.55, 130.84, 130.04, 129.91, 129.10, 127.28, 127.20, 127.17, 118.51, 118.11, 112.64, 84.63, 81.57.; Anal. Calcd. For $C_{18}B_{10}H_{20}N_2 \cdot 1/4C_6H_{14}$: C, 59.44 ; H,6.01 ; N,7.11. FOUND C, 59.73 ; H, 5.78 ; N,7.28.; HRMS m/z calcd. for $C_{18}H_{21}N_2B_{10}$ 375.2633 (M+1); found 375.2619.

Synthesis of compound **3-25:** To a solution of **3-24** (96.3 mg, 0.355 mmol) in 1,2-dimethoxyethane (0.5 ml) was added dropwise a 1.63 M solution of LDA (0.35 ml, 0.57 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 20 min at -15 °C and CuCl (56 mg, 0.596 mmol) was added in one potion at 0 °C. Stirring was continued at 0 °C for 25 min and room temperature for 40 min. Pyridine (0.2 ml) and 3-Iodobenzonitrile (130 mg, 0.568 mmol) was added in one portion, and the mixture was heated 80 °C for 6h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat. NH_4Cl and brine, dried over $MgSO_4$, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (1%) and yields **3-25** as a colorless solid (26 mg, 17%). The compound was recrystallization from hexane.; mp: 132.5-133.5 °C; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.0 Hz, 1H), 7.94 (d, *J* = 7.0 Hz, 1H), 7.67 (ddd *J* = 6.9, 5.7, 1.2 Hz, 1H), 7.57 (t, *J* = 1.4 Hz, 1H), 7.50-7.55 (m, 3H), 7.34 (t, *J* = 6.5 Hz, 1H), 7.17 (s, 1H), 2.1-3.4 (m, 10H), 3.00 (t, *J* = 6.5 Hz, 2H), 1.69 (quin, *J* = 5.3 Hz, 2H), 1.44 (sext, *J* = 6.3 Hz, 2H), 0.98 (t, *J* = 6.1 Hz, 3H).; Anal. Calcd. For $C_{22}B_{10}H_{28}N_2 \cdot 1/8H_2O$: C, 61.33 ; H,6.61 ; N,6.50. FOUND C, 61.07 ;H, 6.53 ; N,6.24.; HRMS m/z calcd. for $C_{22}H_{29}N_2B_{10}$ (M+1) 431.3260; found 431.3244.

Synthesis of compound **3-27**: To a solution of p-carborane (498 mg, 3.45 mmol) in 1,2-dimethoxyethane (3.6 ml) was added dropwise a 1.63 M solution of n-BuLi in hexane 3.45 ml, 5.62 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 20 min at room temperature and CuCl (52 mg, 0.53 mmol) was added in one potion at 0 °C. Stirring was continued at room temperature for 1h. Pyridine (0.2 ml) and 1-bromoisoquinoline (1g, 4.81 mmol) was added in one portion, and the mixture was heated 80 °C for 6h. After

cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over Na_2SO_4, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (2 -10 %) and recrystallization from hexane yields **3-27** as a colorless solid (203 mg, 22 %).; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.78 (d, *J* = 8.22 Hz, 1H), 8.38 (d, *J* = 5.52 Hz, 1H), 7.75 (dd, *J* = 1.38, 8.22 Hz, 1H), 7.62 (t, *J* = 7.56 Hz, 1H), 7.58 (ddd, *J* = 1.74, 7.2, 8.94 Hz, 1H), 7.54 (d, *J* = 5.52 Hz, 1H), 1.8-3.5 (m, 11H); ^{13}C- NMR (150 MHz, $CDCl_3$) δ 150.52, 140.36, 137.70, 129.49, 127.83, 127.11, 126.78, 124.91, 122.13, 88.37, 63.29.

Synthesis of compound **3-28a**: To a solution of **3-27** (138mg, 0.51 mmol) in 1,2-dimethoxyethane (0.75 ml) was added dropwise a 1.14 M solution of LDA (0.53 ml, 0.60 mmol) at -18 °C under Ar atmosphere. The mixture was stirred for 25 min at -18 °C, CuCl (64 mg, 0.64 mmol) was added in one potion at -18 °C. Stirring was continued at -0 °C for 60 min and room temperature for 15 min. Pyridine (0.2 ml) and 4-Iodobenzonitrile (138 mg, 0.60 mmol) was added in one portion, and the mixture was heated 80 °C for 16.5 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 30 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over $MgSO_4$, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (0-4%) yields **3-28a** (19.4 mg, 13.8 %). The solid was recrystallized with n-hexane - chloroform to yield 10 mg of colorless prism. mp: 238 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.75 (d, *J* = 8.5 Hz, 2H), 8.39 (t, *J* =5.5 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.57-7.63 (m, 3H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.5 Hz, 2H), 2.0-3.6 (m, 10H); ^{13}C-NMR (150MHz, $CDCl_3$) δ 150.05, 141.07, 140.40, 137.70, 131.90, 129.61, 127.99, 127.92, 127.29, 126.47, 125.01, 122.30, 118.01, 112.58, 85.80, 84.34.; Anal. Calcd. For $C_{18}B_{10}H_{20}N_2 \cdot 1/2H_2O$: C, 56.67 ; H,5.55 ; N,7.34. FOUND C, 56.84 ;H, 5.37 ; N,7.37. : HRMS *m/z* calcd. for $C_{18}B_{10}H_{21}N_2$ (M+H) 375.2633; found .375.2622.

Synthesis of compound **3-28b:** To a solution of **3-27** (92.1 mg, 0.34 mmol) in 1,2-dimethoxyethane (0.6 ml) was added dropwise a 1.14 M solution of LDA (0.48 ml, 0.55 mmol) at -18 °C under Ar atmosphere. The mixture was stirred for 25 min at -18 °C, CuCl (64 mg, 0.64 mmol) was added in one potion at -18 °C. Stirring was continued at -0 °C for 60 min and room temperature for 15 min. Pyridine (0.2 ml) and 3-Iodobenzonitrile (124 mg, 0.54 mmol) was added in one portion, and the mixture was heated 80 °C for 17 h. After cooling, the reaction mixture was diluted with Et_2O and stirred at room temperature for 20 min. Insoluble solids were filtered off throught Celite, and the filtrate was washed with 5% $Na_2S_2O_3$, sat NH_4Cl and brine, dried over $MgSO_4$, and then concentrated. The residue was purified by column chromatography on silica gel with n-hexane containing ethyl acetate (0-2%) yields **3-28b** as a colorless solid (14.2 mg, 11.2 %). The solid was recrystallized

with n-hexane - chloroform to yield 7.8 mg of colorless prism. mp: 226.5-227.0 °C; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.75 (d, *J* = 8.6 Hz, 1H), 8.40 (d, *J* = 5.4 Hz, 1H), 7.80 (d, *J* = 7.9 Hz, 1H), 7.52-7.66 (m, 6H), 7.35 (t, *J* = 8.1 Hz, 1H), 2.1-3.6 (m, 10H); ^{13}C- NMR (150 MHz, $CDCl_3$) δ 150.06, 140.41, 137.88, 137.72, 131.97, 131.48, 130.77, 129.63, 129.10, 127.93, 127.31, 126.51, 125.04, 122.31, 118.11, 112.64, 85.60, 83.94.; Anal. Calcd. For $C_{18}B_{10}H_{20}N_2$: C, 58.04 ; H,5.41 ; N,7.52. FOUND C, 57.81 ;H, 5.31 ; N,7.44. : HRMS *m/z* calcd. for $C_{18}B_{10}H_{21}N_2$ (M+H) 375.2633; found .375.2619.

Synthesis of compound **4-7:** A 5 M aqueous solution of sodium hydroxide (12.5 ml, 62.5 mmol) was added to DMSO (35 ml) at room temperature under an Ar atmosphere. After 30 min, resorcinol (4.13 g, 37.5 mmol) was added, and the mixture was stirred at 50°C for 30 min. Then, a solution of 4-fluoronitrobenzene (3.53 g, 25.0 mmol) in DMSO (5 ml) was added slowly to the reaction mixture, and stirring was continued at 50°C for 2.5 h. The reaction mixture was poured into ice water and filtered. The aqueous layer was acidified with 2 M HCl, and extracted with ethyl acetate. The organic layer was dried with magnesium sulfate, and evaporated to give **4-7** (3.82 g, 66%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.3 Hz, 2H), 7.28 (t, *J* = 8.2 Hz, 1H), 7.04 (d, *J* = 7.1 Hz, 2H), 6.71 (ddd, *J* = 8.0, 2.3, 0.7 Hz, 1H), 6.66 (ddd, *J* = 8.2, 2.2, 0.8 Hz, 1H), 6.59 (t, *J* = 2.3 Hz, 1H), 4.96 (br, 1H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.01, 157.17, 155.99, 142.82, 130.98, 125.93, 117.40, 112.63, 112.41, 107.87.

Synthesis of compound **4-8:** A mixture of **4-7** (2.31 g, 10 mmol) and 10% palladium on carbon (234 mg) in methanol (100 ml) was stirred under a hydrogen atmosphere for 2 h. The reaction mixture was filtered over Celite, and the filtrate was evaporated. The residue was purified by silica-gel column chromatography (hexane/ethyl acetate 1:1) to afford **4-8** (1.93 g, 96 %). ^{1}H NMR (600 MHz, CD_3OD) δ 7.09 (t, *J* = 8.2 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.76 (d, *J* = 9.8 Hz, 2H), 6.46 (dt, *J* = 8.0, 1.3 Hz, 1H), 6.38 (dt, *J* = 8.7, 1.0 Hz, 1H), 6.34 (td, *J* = 0.5, 2.2 Hz, 1H), ^{13}C NMR (150 MHz, CD_3OD) δ 162.04, 160.09, 150.02, 145.31, 131.24, 122.32, 118.02, 110.42, 109.52, 105.58.

Synthesis of compound **4-2a: 4-8** (101 mg, 0.50 mmol) was added to a solution of *o*-anisoyl chloride (271 mg, 1.59 mmol) in tetrahydrofuran (15 ml). The mixture was stirred at room temperature for 30min, and poured into water, and extracted with ethyl acetate. The organic layer was washed successively with saturated sodium hydrogen carbonate, 2 M HCl, water, and brine, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 3:1 to 2:1) to afford **4-2a** (130 mg, 77%). Colorless prisms (methanol); mp 176.2°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.95 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.70 (dd, *J* = 6.6, 1.8 Hz, 2H), 7.57 (td, *J* = 8.9, 1.7 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.17 (t, *J* = 8.4 Hz, 1H), 7.14 (t, *J* = 7.2 Hz, 1H), 7.05 (dd, *J* = 6.6, 1.8 Hz, 2H), 6.45 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.57 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.45 (t, *J* = 2.1 Hz, 1H), 4.07 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 166.87, 160.54, 160.34, 159.15, 155.41, 135.47, 134.52, 132.24, 131.52, 124.43, 123.87, 122.41, 120.81, 113.38, 111.64, 110.76, 107.00, 57.03; HRMS Calcd. for $C_{20}H_{18}NO_4$ $[M+H]^+$ 336.1230; Found 336.1231.; Anal. Calcd. For $C_{20}H_{17}NO_4 \cdot 1/8H_2O$: C, 71.15; H, 5.15; N,4.15. FOUND C,

71.12; H, 5.20; N, 4.00.

Synthesis of compound **4-2b: 4-8** (101 mg, 0.50 mmol) was added to a solution of *m*-anisoyl chloride (273 mg, 1.60 mmol) in tetrahydrofuran (15 ml). The mixture was stirred at room temperature for 40min, and poured into water, and extracted with ethyl acetate. The organic layer was washed successively with saturated sodium hydrogen carbonate, 2 M HCl, water, and brine, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 2:1) to afford **4-2b** (92 mg). Colorless prisms (chloroform); mp 112.4°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.69 (d, *J* = 8.9 Hz, 2H), 7.53 (m, 2H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.17 (m, 2H), 7.04 (dt, *J* = 8.9, 2.0 Hz, 2H), 6.57 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.48 (dd, *J* = 8.2, 1.9 Hz, 1H), 6.46 (t, *J* = 7.3 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.90, 161.64, 160.48, 160.30, 155.52, 137.87, 135.56, 131.52, 130.99, 124.43, 120.98, 120.67, 119.00, 114.25, 111.65, 110.80, 107.03, 56.24; HRMS Calcd. for $C_{20}H_{18}NO_4$ $[M+H]^+$ 336.1230; Found 336.1234. ; Anal. Calcd. For $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. FOUND C, 71.36; H, 5.08; N, 4.23.

Synthesis of compound **4-2c: 4-8** (103 mg, 0.51 mmol) was added to a solution of *p*-anisoyl chloride (276 mg, 1.62 mmol) in tetrahydrofuran (15 ml). The mixture was stirred at room temperature for 40min, and poured into water, and extracted with ethyl acetate. The organic layer was washed successively with saturated sodium hydrogen carbonate, 2 M HCl, water, and brine, dried over magnesium sulfate, and evaporated. The residue was washed with dichloromethane to afford **4-2c** (132 mg). Colorless prisms (chloroform/ethyl acetate); mp 183.3°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.96 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 9.0 Hz, 2H), 7.17 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.56 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.48 (dd, *J* = 8.0, 2.2 Hz, 1H), 6.45 (t, *J* = 1.6, Hz 1H), 3.91 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.69, 164.48, 160.56, 160.31, 115.36, 135.79, 131.51, 130.81, 128.49, 124.42, 120.71, 115.16, 111.62, 110.76, 106.99, 56.30; HRMS Calcd. for $C_{20}H_{18}NO_4$ $[M+H]^+$ 336.1230; found 336.1236.; Anal. Calcd. For $C_{20}H_{17}NO_4 \cdot 1/6H_2O$: C, 71.00 ;H, 5.16 ; N,4.14. FOUND C, 71.01; H, 5.10; N, 4.08.

Synthesis of compound **4-2d:** Oxalyl chloride (125 μl, 1.46 mmol) was added to a solution of *o*-dimethylaminobenzoic acid (82 mg, 0.49 mmol) and a drop of N,N-dimethylformamide in dichloromethane at 0°C and stirred at room temperature. After 30 min, the reaction mixture was evaporated and dissolved in tetrahydrofuran (5 ml). **4-8** (100mg, 0.50 mmol) was added to this solution and stirred at room temperature. After 3 hour, the reaction was quenched with aqueous 5% potassium hydrogen sulfate and diluted with ethyl acetate. The organic layer was washed with aqueous saturated sodium hydrogen carbonate, water and brine, dried with magnesium sulfate, and evaporated. The crude product was purified by silica gel; column chromatography (chloroform /ethyl acetate 7:1) and 124 mg of **4-2d** was obtained. The compound was recrystallized with dichloromethane/*n*-hexane. Pale brown prisms (methylene chloride/hexane); mp 103.7°C; ^{1}H NMR (600 MHz, CD_3OD) δ 8.01 (d, *J* = 7.8 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.55 (t, *J* = 8.4 Hz, 1H), 7.41(d, *J* = 8.4

Hz, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.17 (t, *J* = 8.4 Hz, 1H), 7.06 (d, *J* = 8.4 Hz, 2H), 6.57 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.46 (dd, *J* = 8.4, 1.2 Hz, 1H), 6.45 (t, *J* = 2.1 Hz, 1H), 2.88 (s, 6H); ^{13}C NMR (150 MHz, CD_3OD) δ 167.66, 160.57, 160.32, 155.16, 154.02, 135.74, 133.90, 131.97, 131.54, 128.85, 125.14, 123.33, 121.52, 121.01, 111.55, 110.64, 106.87, 45.52; HRMS Calcd. for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 349.1547; found 349.1536.; Anal. Calcd. For $C_{21}H_{20}N_2O_3$: C, 72.40 ;H, 5.79 ; N,8.04. FOUND C, 72.32 ; H,5.68 ; N,7.91.

Synthesis of compound **4-2e:** Oxalyl chloride (195 µl, 2.28 mmol) was added to a solution of *m*-dimethylaminobenzoic acid (125 mg, 0.75 mmol) and a drop of N,N-dimethylformamide in dichloromethane at 0°C and stirred at room temperature. After 30 min, the reaction mixture was evaporated and dissolved in tetrahydrofuran (5 ml) and acetonitrile(3ml). **4-8** (100mg, 0.50 mmol) was added to this solution and stirred at room temperature. After 2 hours, the reaction was quenched with aqueous 5% potassium hydrogen sulfate and diluted with ethyl acetate. The organic layer was washed with aqueous saturated sodium hydrogen carbonate, water and brine, dried with magnesium sulfate, and evaporated. The crude product was purified by silica gel; column chromatography (chloroform /ethyl acetate 4/1) and 20 mg of **4-2e** was obtained. The compound was recrystallized with chloroform. Pale yellow prisms (Chloroform); mp 171.0°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.69 (d, *J* = 8.6 Hz, 2H), 7.37, (t, *J* = 9.0 Hz, 1H), 7.34 (s, 1H), 7.28 (d, *J* = 6.9 Hz, 1H), 7.17 (t, *J* = 8.2 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 9.7 Hz, 1H), 6.57 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.48 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.45 (t, *J* = 2.2 Hz, 1H), 3.05 (s, 6H); ^{13}C NMR (150 MHz, CD_3OD) δ 170.02, 160.52, 160.32, 155.38, 152.46, 137.16, 135.72, 131.54, 130.54, 124.42, 120.70, 117.43, 116.90, 113.05, 111.58, 110.71, 106.91, 41.18; HRMS Calcd. for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 349.1547; found 349.1543. Anal. Calcd. For $C_{21}H_{20}N_2O_3 \cdot 1/4H_2O$: C, 71.47 ;H, 5.86 ; N,7.94. FOUND C, 71.50 ; H,5.64 ; N,7.75.

Synthesis of compound **4-2f:** Oxalyl chloride (125 µl, 1.46 mmol) was added to a solution of *p*-dimethylaminobenzoic acid (82 mg, 0.49 mmol) and a drop of N,N-dimethylformamide in dichloromethane at 0°C and stirred at room temperature. After 30 min, the reaction mixture was evaporated and dissolved in tetrahydrofuran (5 ml). **4-8** (101mg, 0.50 mmol) was added to this solution and stirred at room temperature. After 2 hours, the reaction was quenched with aqueous 5% potassium hydrogen sulfate and diluted with ethyl acetate. The organic layer was washed with aqueous saturated sodium hydrogen carbonate, water and brine, dried with magnesium sulfate, and evaporated. The crude product was purified by silica gel; column chromatography (chloroform /ethyl acetate 4/1) and 48 mg of **4-2f** was obtained. The compound was recrystallized with chloroform. Pale yellow prisms (Chloroform); mp 163.9°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.88 (dt, *J* = 7.0, 2.0 Hz, 2H), 7.66 (dt, *J* = 6.8, 2.2 Hz, 2H), 7.16 (t, *J* = 8.4 Hz, 1H), 7.03 (dt, *J* = 7.0, 2.0 Hz, 2H), 6.82 (dt, *J* = 7.0, 2.0 Hz, 2H), 6.56 (ddd, *J*= 8.2, 2.3, 0.7 Hz, 1H), 6.48 (ddd, *J*= 8.0, 2.3, 0.7 Hz, 1H), 6.45 (t, *J* = 2.3 Hz, 1H), 3.10 (s, 6H) ; ^{13}C NMR (150 MHz, CD_3OD) δ 169.26, 160.65, 160.27, 155.09, 154.84, 136.09, 131.50, 130.45,

124.39, 122.55, 120.73, 112.52, 111.54, 110.71, 106.91, 40.53; HRMS Calcd. for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 349.1547; found 349.1547.; Anal. Calcd. For $C_{21}H_{20}N_2O_3 \cdot 1/4H_2O$: C, 71.47 ;H, 5.86 ; N,7.94. FOUND C, 71.22 ; H,5.61 ; N,7.88.

Synthesis of compound **4-13:** A mixture of *p*-(benzyloxy)phenol (220 mg, 1.10 mmol), *m*-fluoronitrobenzen (149 mg, 1.05 mmol), and potassium carbonate (173 mg, 1.25 mmol) in DMF (1.5 ml) was stirred at 150°C for 3 h, and at 80°C for 24 h. After cooling to room temperature, 1 M HCl were added to the mixture, extracted with ethyl acetate. The organic layer was dried with sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 19:1) to afford **4-13** (237 mg, 70% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (ddd, *J* = 7.8, 2.4, 0.6 Hz, 1H), 7.72 (t, *J* = 2.4 Hz, 1H), 7.43 (m, 5H), 7.35 (t, *J* = 5.4 Hz, 1H), 7.28 (ddd, *J* = 8.4, 2.4, 0.6 Hz, 1H), 7.01 (s, 4H), 5.08 (s, 2H).

Synthesis of compound **4-14:** A mixture of **4-13** (160 mg, 0.5 mmol) and palladium hydroxide on carbon (17 mg) in tetrahydrofuran (5 ml) and methanol (5 ml) was stirred under hydrogen atmosphere for 18 h. The reaction mixture was filtered over celite, and the filtrate was evaporated to afford **4-14** (106 mg, quant) as pale brown oil. ^{1}H NMR (600 MHz, CD_3OD) δ 7.05 (t, *J* = 8.4 Hz, 1H), 6.88 (dt, *J* = 9.0, 2.4 Hz, 2H), 6.80 (dt, *J* = 9.0, 2.4 Hz, 2H), 6.46 (ddd, *J* = 7.8, 1.8, 0.6 Hz, 1H), 6.53 (t, *J* = 2.4 Hz, 1H), 6.29 (ddd, *J* = 8.4, 2.4, 0.6 Hz, 1H).

Synthesis of compound **4-3a: 4-14** (89 mg, 0.44 mmol) was added to a soluion of *o*-anisoyl chloride (228 mg, 1.34 mmol) in tetrahydrofuran (15 ml). The mixture was stirred at room temperature for 30 min, and poured into water, and extracted with ethyl acetate. The organic layer was washed successively with saturated sodium hydrogen carbonate, 2 M HCl, water, and brine, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (chloroform/ethyl acetate 4:1) to afford **4-3a** (63 mg, 43%). Colorless prism (chloroform/ethyl acetate); mp 189.4°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.89 (dd, *J*= 7.7, 1.6 Hz, 1H), 7.56 (td, *J* = 7.8, 1.6 Hz, 1H), 7.48 (t, *J* = 1.0 Hz, 1H), 7.29 (m, 2H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 6.94 (dt, *J* = 8.9, 2.2 Hz, 2H), 6.84 (dt, *J* = 8.8, 2.1 Hz, 2H), 6.70 (m, 1H), 4.04 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 167.01, 161.06, 159.09, 155.34, 150.72, 141.26, 134.52, 132.17, 131.04, 124.54, 122.40, 122.34, 117.55, 115.85, 114.51, 113.38, 111.33, 57.02; HRMS Calcd. for $C_{20}H_{18}NO_4$ $[M+H]^+$ 336.1230; found 336.1226.; Anal. Calcd. For $C_{20}H_{17}NO_4 \cdot 1/4H_2O$: C, 70.68 ;H, 5.19 ; N,4.12. FOUND C, 70.80 ; H,5.06 ; N,4.06.

Synthesis of compound **4-3c: 4-14** (103 mg, 0.52 mmol) was added to a soluion of *p*-anisoyl chloride (262 mg, 1.54 mmol) in tetrahydrofuran (15 ml) and stirred at room temperature. After 1 hour, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with aqueous saturated sodium hydrogen carbonate, aqueous 2M HCl, water and brine, dried with magnesium sulfate, and evaporated. The crude product was purified by silica gel; column chromatography (n-hexane /ethyl acetate 3/2) and 122 mg of **4-3c** was obtained. The compound was recrystallized with ethyl acetate. Colorless prisms (ethyl acetate); mp

163.6°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.92 (d, *J* = 8.9 Hz, 2H), 7.40 (t, *J* = 2.2 Hz, 1H), 7.37 (ddd, *J* = 7.9, 1.7, 0.7 Hz, 1H), 7.29 (t, *J* = 8.1 Hz, 1H), 7.05 (d, *J* = 8.9 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.71 (ddd, *J* = 8.1, 2.3, 0.8 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.75, 164.50, 160.99, 155.33, 150.70, 141.68, 130.90, 130.85, 128.50, 122.39, 117.54, 116.26, 115.12, 114.46, 111.58, 56.27; HRMS Calcd. for $C_{20}H_{18}NO_4$ $[M+H]^+$ 336.1230; found 336.1224. ; Anal. Calcd. For $C_{20}H_{17}NO_4$: C, 71.63 ;H, 5.11 ; N,4.18. FOUND C, 71.53 ; H,5.10 ; N,4.11.

Synthesis of compound **4-3d:** Oxalyl chloride (125 µl, 1.46 mmol) was added to a solution of *o*-dimethylaminobenzoic acid (81 mg, 0.49 mmol) and a drop of N,N-dimethylformamide in dichloromethane at 0℃ and stirred at room temperature. After 30 min, the reaction mixture was evaporated and dissolved in tetrahydrofuran (5 ml). **4-14** (100mg, 0.50 mmol) was added to this solution and stirred at room temperature. After 1 hour, the reaction was quenched with aqueous 5% potassium hydrogen sulfate and diluted with ethyl acetate. The organic layer was washed with aqueous saturated sodium hydrogen carbonate, water and brine, dried with magnesium sulfate, and evaporated. The crude product was washed with dichloromethane and 57mg of **4-3d** was obtained. The compound was recrystallized with methanol/ ethyl acetate. Pale brown prisms (methanol/ ethyl acetate); mp 196.4°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.96 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.54 (td, *J* = 8.6, 1.6 Hz, 1H), 7.48 (t, *J* = 2.0 Hz, 1H), 7.40 (d, *J* = 8.1 Hz, 1H), 7.31 (m, 1H), 7.24 (m, 2H), 6.95 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.69 (dd, *J* = 8.2, 2.2 Hz, 1H), 2.85 (s, 6H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.56, 159.33, 154.43, 151.62, 148.22, 141.14, 131.98, 130.34, 128.02, 121.99, 121.60, 119.20, 116.75, 113.87, 112.27, 108.67, 44.30; HRMS Calcd. for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 349.1547; found 349.1544. ; Anal. Calcd. For $C_{21}H_{20}N_2O_3$・1/8H_2O: C, 71.93 ;H, 5.82 ; N,7.99. FOUND C, 71.94 ; H,5.69 ; N,7.96.

Synthesis of compound **4-3f:** Oxalyl chloride (125 µl, 1.46 mmol) was added to a solution of *p*-dimethylaminobenzoic acid (82 mg, 0.49 mmol) and a drop of N,N-dimethylformamide in dichloromethane at 0℃ and stirred at room temperature. After 30 min, the reaction mixture was evaporated and dissolved in tetrahydrofuran (5 ml). **4-14** (101mg, 0.50 mmol) was added to this solution and stirred at room temperature. After 1 hour, the reaction was quenched with aqueous 5% potassium hydrogen sulfate and diluted with ethyl acetate. The organic layer was washed with aqueous saturated sodium hydrogen carbonate, water and brine, dried with magnesium sulfate, and evaporated. The crude product was purified by silica gel; column chromatography (n-hexane /ethyl acetate 3/2) and 44 mg of **4-3f** was obtained. The compound was recrystallized with ethyl acetate. Pale yellow prisms (ethyl acetate); mp 205.8°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.87 (d, *J* = 8.9 Hz, 2H), 7.43 (t, *J* = 2.2 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.2 Hz, 1H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 9.0 Hz, 2H), 6.71 (dd, *J* = 8.1, 2.0 Hz, 1H), 3.10 (s, 6H); ^{13}C NMR (150 MHz, CD_3OD) δ 169.29, 160.93, 155.27, 154.86, 150.78, 141.97, 130.83, 130.50, 122.55, 122.35, 117.53, 116.26,

114.17, 112.47, 111.60, 40.50; HRMS Calcd. for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 349.1547; found 349.1544. ; Anal. Calcd. For $C_{21}H_{20}N_2O_3$: C, 72.40 ;H, 5.79 ; N,8.04. FOUND C, 72.34 ; H,6.03 ; N,8.03.

Synthesis of compound **4-15:** A solution of copper (II) sulfate·$5H_2O$ (267 mg, 1.07 mmol) in methanol (4 ml) was added to a solution of sodium borohydride (111 mg, 2.94 mmol) and **4-13** (165 mg, 0.5 mmol) in methylene chloride (5 ml), and the mixture was stirred at 0°C for 3 h and at room temperature for 2 h. The mixture was poured into water, and extracted with methylene chloride. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was dissolved in meyhylene chloride, and 1 M hydrochloric acid in ether was added to it. The resulting precipitate was collected to afford **4-15** (108 mg, 63 %). Pale yellow powder; ^{1}H NMR (600 MHz, CD_3OD) δ 7.43 (d, 2*J* = 7.6 Hz, 2H), 7.36 (t, *J* = 6.9 Hz, 2H), 7.29 (t, *J* = 6.9 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.12 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.01 (dt, *J* = 9.6, 2.8 Hz, 2H), 6.90 (dt, *J* = 8.9, 2.0 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 1H), 5.06 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 158.08, 156.78, 151.44, 138.65, 131.96, 129.52, 128.92, 128.58, 126.62, 126.08, 122.65, 121.20, 119.00, 117.32, 71.50, 16.31.

Synthesis of compound **4-16:** *m*-Anisoyl chloride (161 mg, 0.18 mmol) was added to a solution of **4-15** (103 mg, 0.49 mmol) in pyridine (5 ml). The mixture was stirred at room temperature for 45 min, then poured into water, and extracted with ethyl acetate. The organic layer was successively washed with saturated sodium hydrogen carbonate, 2 M hydrochloric acid, water and brine, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 2:1) to give **4-16** (122 mg, 90%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (br, 1H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.33-7.41 (m, 7H), 7.29 (t, *J* = 8.3 Hz, 1H), 7.01 (ddd, *J* = 7.6, 2.8, 1.4 Hz, 1H), 7.01 (dt, *J* = 8.9, 2.7 Hz, 2H), 6.97 (dt, *J* = 9.6, 2.7 Hz, 2H), 6.75 (ddd, *J* = 8.3, 2.0, 1.4 Hz, 1H), 5.05 (s, 2H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.44, 160.01, 159.15, 155.29, 149.99, 139.13, 136.97, 136.33, 130.06, 129.80, 128.60, 128.00, 127.53, 121.01, 118.58, 118.12, 115.9597, 114.08, 113.73, 112.46, 109.35, 70.52, 55.50.

Synthesis of compound **4-3b:** A mixture of **4-16** (74 mg, 0.17 mmol) and palladium hydroxide on carbon (5 mg) in tetrahydrofuran (5 ml) and methanol (2 ml) was stirred at 45°C under a hydrogen atmosphere for 41 h. The reaction mixture was filtered over Celite, and the filtrate was evaporated. The residue was purified by silica gel column chromatography (hexane /ethyl acetate 3:2), followed by recrystallization from chloroform/ethyl acetate to give **4-3b** (33 mg, 57 %). Colorless prisms (chloroform/ethyl acetate); mp 144.6°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.50 (t, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 2.1 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 2.5 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.30 (t, *J* = 8.2 Hz, 1H), 7.16 (ddd, *J* = 8.0, 2.2, 0.5 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 6.72 (dd, *J* = 8.1, 1.7 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR(150 MHz, CD_3OD) δ 169.01, 161.64, 161.00, 155.35, 150.67, 141.49, 137.90, 130.97, 130.94, 122.40, 121.03, 119.12, 117.55, 116.30, 114.66, 114.21, 111.63, 56.25; HRMS Calcd. for $C_{20}H_{18}NO_4$ $[M+H]^+$ 336.1230; found 336.1226.; Anal. Calcd. For $C_{20}H_{17}NO_4$・1/8H_2O: C, 71.15 ;H, 5.15 ; N,4.15. FOUND C, 71.17 ; H,5.08 ; N,4.16.

Synthesis of compound **4-17:** Oxalyl chloride (385 µl, 4.5 mmol) was added to a solution of *m*-dimethylaminobenzoic acid (246 mg, 1.5 mmol) and a drop of N,N-dimethylformamide in dichloromethane at 0°C and stirred at room temperature. After 30 min, the reaction mixture was evaporated and dissolved in tetrahydrofuran (10 ml). **4-15** (119 mg, 0.36 mmol) was added to 5ml of this solution and stirred at room temperature. After 3 hours, the reaction was quenched with aqueous sodium hydrogen carbonate and diluted with ethyl acetate. The organic layer was washed with aqueous saturated sodium hydrogen carbonate, water and brine, dried with magnesium sulfate, and evaporated. The crude product was purified by silica gel; column chromatography (chloroform /ethyl acetate 2:1) and 62 mg of **4-17** was obtained. ^{1}H-NMR (400MHz,$CDCl_3$) δ 8.01 (brs, 1H), 7.50 (d, *J* = 7.3, 2H), 7.46 (t, J= 6.9, 2H), 7.29-7.42 (m, 5H), 7.10 (d, *J* = 7.8, 1H), 7.06 (d, *J* = 9.1, 2H), 7.01 (d, *J* = 9.2, 2H), 6.91 (dd, *J* = 8.2, 2.3, 1H), 6.80 (ddd, *J* = 8.2, 2.3, 0.9, 1H), 5.09 (s, 2H), 3.03 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4438, 158.9736, 155.2028, 150.5659, 150.1843, 139.4615, 137.0253, 135.7641, 129.8798, 129.2537, 128.5207, 127.9056, 127.4463, 120.8229, 115.9845, 115.8544, 115.7609, 114.2574, 113.5696, 111.5507, 109.6184, 109.4583, 70.5447, 40.5113.

Synthesis of compound **4-3e: 4-17** (62 mg, 0.14 mmol) was dissoled in tetrahydrofuran (6ml) and methanol (2 ml). Palladium Hydroxide on carbon (10 mg) was suspended in the solution and stirred at 45°C under hydrogen atmosphere. After 47 h, the reaction mixture was filtered through Celite and evaporated. The crude product was purified by silica gel column chromatography (n-hexane /ethyl acetate 3/2) and recrystallized with ethyl acetate-chloroform. 15 mg of **4-3e** (0.043 mmol, 30 %) was obtained. Colorless prisms; mp 167.2°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.43 (t, J = 1.8 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.30 (t, J = 8.2 Hz, 1H), 7.28 (s, 1H), 7.22 (d, J = 7.6 Hz, 1H), 6.98 (ddd, J = 8.2, 2.6, 0.5 Hz, 1H), 6.94 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 6.72 (ddd, J = 7.4, 2.6, 1.6 Hz, 1H), 3.03 (s, 6H); ^{13}C NMR (150 MHz, CD_3OD) δ 170.17, 161.00, 155.37, 152.55, 150.56, 141.62, 137.14, 130.92, 130.48, 122.46, 117.51, 117.32, 116.70, 116.21, 114.46, 112.90, 111.49, 41.06; HRMS Calcd. for $C_{21}H_{21}N_2O_3$ $[M+H]^+$ 349.1547; found 349.1544.; Anal. Calcd. For $C_{21}H_{20}N_2O_3$・1/8H_2O: C, 71.93 ;H, 5.82 ; N,7.99. FOUND C, 71.72 ; H,5.72 ; N,7.88.

Synthesis of compound **4-19:** *O*-Monobenzylresorcinol (220 mg, 1.10 mmol) was added to a solution of *m*-fluoronitrobenzene (149 mg, 1.05 mmol) and potassium carbonate (173 mg, 1.25 mmol) in DMF (1.5 ml) under an argon atmosphere, and the mixture was stirred at 150°C for 3 h and at 80°C for 24 h. It was allowed to cool to room temperature, then poured into 1 M HCl, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 19:1) to afford **4-19** (273 mg, 80%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.94 (ddd, *J* = 8.4, 2.4, 0.6 Hz, 1H), 7.81 (t, *J* = 2.4 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.36 (m, 7H), 6.84 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.67 (m, 2H), 5.06 (s, 2H).

Synthesis of compound **4-4a:** A mixture of **4-19** (166 mg, 0.5 mmol) and palladium hydroxide on carbon (20 mg) in THF (5 ml) and methanol (5 ml) was stirred under a hydrogen atmosphere for 14 h. The reaction mixture was filtered over Celite, and evaporated to give **4-10b** (107 mg, quant), which was used for the next reaction without further purification. **4-10b** (115 mg, 0.57 mmol) was added to a solution of *o*-anisoyl chloride (295 mg, 1.73 mmol) in tetrahydrofuran (15 ml), and the mixture was stirred at room temperature for 30 min, then poured into water, and extracted with ethyl acetate. The organic layer was washed successively with saturated sodium hydrogen carbonate, 2 M hydrochloric acid, water and brine, dried over magnesium sulfate, and evaporated. The residue was washed with dichloromethane to give **4-4a** (122 mg, 71%), which was purified by recrystallization from chloroform. Pale brown prisms (chloroform); mp 166.0°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.90 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.56 (m, 2H), 7.37 (m, 2H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.18 (t, *J* = 8.1 Hz, 1H), 6.80 (ddd, *J* = 7.9, 3.3, 1.0 Hz, 1H), 6.59 (ddd, *J* = 8.3, 2.2, 0.7 Hz, 1H), 6.52 (dd, *J* = 8.2, 1.7 Hz, 1H), 6.48 (t, *J* = 2.3 Hz, 1H), 4.04 (s, 3H) ; ^{13}C NMR (150 MHz, CD_3OD) δ 167.10, 160.36, 160.01, 159.35, 159.04, 141.42, 134.56, 132.12, 131.57, 131.19, 124.50, 122.34, 116.72, 116.04, 113.27, 112.76, 111.85, 111.14, 107.35, 56.95; HRMS; Calcd. for $C_{20}H_{18}NO_4$ $[M+H]^+$ 336.1230; found 336.1228.; Anal. Calcd. For C20H17NO4・1/6H2O: C, 71.00 ;H, 5.16 ; N,4.14. FOUND C, 70.72 ; H,5.09 ; N,4.14.

Synthesis of compound **4-4b: 4-10b** (93 mg, 0.46 mmol) was added to a soluion of *o*-anisoyl chloride (232 mg, 1.36 mmol) in tetrahydrofuran (12 ml) and stirred at room temperature. After 40min, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with aqueous saturated sodium hydrogen carbonate, aqueous 2M HCl, water and brine, dried with magnesium sulfate, and evaporated. The crude product was purified by silica gel; column chromatography (n-hexane /ethyl acetate 6:1) and 100 mg (0.30 mmol, 65%) of **4-4b** was obtained. Pale brown prisms (chloroform); mp 129.5-130.5°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.40 (m, 5H), 7.33 (m, 1H), 7.13 (m, 2H), 6.77 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.54 (dd, *J* = 8.3, 2.7 Hz, 1H), 6.48 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.44 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.72, 161.30, 160.07, 159.65, 159.03, 141.36, 137.52, 131.29, 130.81, 130.71, 120.73, 118.84, 116.83, 115.83, 113.82, 112.73, 111.58, 110.93, 107.14, 55.90; HRMS Calcd. for $C_{20}H_{18}NO_4$ $[M+H]^+$ 336.1230; found 336.1228.

Synthesis of compound **4-4c: 4-10b** (89mg, 0.44 mmol) was added to a soluion of *p*-anisoyl chloride (225 mg, 1.32 mmol) in tetrahydrofuran (12 ml) and stirred at room temperature. After 30 min, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with aqueous saturated sodium hydrogen carbonate, aqueous 2M HCl, water and brine, dried with magnesium sulfate, and evaporated. The crude product was purified by silica gel; column chromatography (n-hexane /ethyl acetate 3/1) and 52 mg (0.16 mmol, 35%) of **4-4c** was obtained. Pale brown prisms; mp 132-132.5°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.89 (dd, *J* = 6.8, 2.0 Hz, 2H), 7.45 (t, *J* = 2.0 Hz, 1H), 7.42 (d, *J*= 9.0 Hz, 1H), 7.31 (t, *J* = 8.2 Hz, 1H), 7.13 (t, *J* = 8.2 Hz, 1H), 7.01 (d, *J* = 8.9 Hz, 2H), 6.75 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.54 (dd, *J* = 8.6, 2.7 Hz, 1H), 6.48 (dd, *J* = 8.3, 2.1 Hz,

1H), 6.44 (t, *J* = 2.4 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.76, 164.51, 160.34, 159.97, 159.30, 141.84, 131.59, 131.08, 130.91, 128.36, 117.11, 115.94, 115.11, 113.01, 111.85, 111.22, 107.43, 56.27; HRMS Calcd. for $C_{20}H_{18}NO_4$ $[M+H]^+$ 336.1230; found 336.1228.

Synthesis of compound **4-4d:** Oxalyl chloride (125 µl, 1.46 mmol) was added to a solution of *o*-dimethylaminobenzoic acid (82 mg, 0.50 mmol) and a drop of N,N-dimethylformamide in dichloromethane at 0°C and stirred at room temperature. After 30 min, the reaction mixture was evaporated and dissolved in tetrahydrofuran (7 ml). **4-10b** (98 mg, 0.48 mmol) was added to this solution and stirred at room temperature. After 1.5 hour, the reaction was quenched with aqueous 5% potassium hydrogen sulfate and diluted with ethyl acetate. The organic layer was washed with aqueous saturated sodium hydrogen carbonate, water and brine, dried with magnesium sulfate, and evaporated. The crude product was purified by silica gel; column chromatography (chloroform/ethyl acetate 9:1) and 56 mg of **4-4d** was obtained. The compound was recrystallized with chloroform. Pale yellow prisms (chloroform); mp 164.8°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.97 (d, *J* = 7.2 Hz, 1H), 7.58 (s, 1H), 7.55 (t, *J* = 8.1 Hz, 1H), 7.38 (m, 3H), 7.24 (t, *J* =7.6 Hz, 1H), 7.19 (t, *J* = 8.1 Hz, 1H), 6.79 (dt, *J* = 6. 8, 2.3 Hz, 1H), 6.59 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.53 (dd, *J* = 8.2, 2.2 Hz, 1H), 6.49 (t, *J* = 2.2 Hz, 1H), 2.86 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.83, 160.38, 159.95, 159.50, 154.02, 141.64, 134.00, 131.99, 131.58, 131.32, 128.78, 125.15, 121.54, 116.33, 115.81, 112.35, 111.90, 111.20, 107.42, 45.50; HRMS Calcd. for $C_{20}H_{18}NO_4$ $[M+H]^+$ 349.1547; found 349.1544.; Anal. Calcd. For $C_{21}H_{20}N_2O_3$: C, 72.40 ;H, 5.79 ; N, 8.04. FOUND C, 72.19 ; H,5.91 ; N,8.02.

Synthesis of compound **4-4e:** Oxalyl chloride (193 µl, 2.25 mmol) was added to a solution of *m*-dimethylaminobenzoic acid (123 mg, 0.74 mmol) and a drop of N,N-dimethylformamide in dichloromethane at 0°C and stirred at room temperature. After 30 min, the reaction mixture was evaporated and dissolved in tetrahydrofuran (5 ml). **4-10b** (117mg, 0.58 mmol) was added to this solution and stirred at room temperature. After 30 min, the reaction was quenched with aqueous 5% potassium hydrogen sulfate and diluted with ethyl acetate. The organic layer was washed with aqueous saturated sodium hydrogen carbonate, water and brine, dried with magnesium sulfate, and evaporated. The crude product was purified by silica gel column chromatography (4:1 chloroform-ethyl acetate) and recrystallized with ethyl acetate. 73 mg of **4-4e** was obtained. Pale brown prisms; mp 179.3°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.51 (t, *J* = 2.3 Hz, 1H), 7.47 (ddd, *J* = 8.2, 1.7, 0.8 Hz, 1H), 7.36 (m. 2H), 7.30 (t, *J* = 1.9 Hz, 1H), 7.23 (dd, *J* = 6.9, 1.3 Hz, 1H), 7.18 (t, *J* = 8.1 Hz, 1H), 6.99 (dd, *J* = 6.9, 1.3 Hz, 1H), 7.18 (t, *J* = 8.1 Hz, 1H), 6.99 (dd, *J* = 8.0, 2.6 Hz, 1H), 6.81 (ddd, *J* = 8.2, 2.3, 0.7 Hz, 1H), 6.58 (ddd, *J* = 8.2, 2.2, 0.7 Hz, 1H), 6.53 (ddd, *J* = 8.3, 2.3, 0.7 Hz, 1H), 6.49 (t, *J*= 2.3 Hz, 1H), 3.04 (s, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.11, 160.27, 159.98, 159.27, 152.56, 141.71, 137.09, 131.54, 131.03, 130.46, 117.36, 117.27, 116.68, 116.07, 113.20, 112.93, 111.89, 111.26, 107.48, 41.04. HRMS Calcd. for $C_{21}H_{21}N_2O_3$

$[M+H]^+$ 349.1547; found 349.1542.; Anal. Calcd. For $C_{21}H_{20}N_2O_3$: C, 72.40 ;H, 5.79 ; N, 8.04. FOUND C, 72.29 ; H,5.78 ; N,7.93.

Synthesis of compound **4-4f:** Oxalyl chloride (195 µl) was added to a solution of *o*-dimethylaminobenzoic acid (125 mg, 0.76 mmol) and a drop of N,N-dimethylformamide in dichloromethane at 0°C and stirred at room temperature. After 30 min, the reaction mixture was evaporated and dissolved in tetrahydrofuran (2 ml). The solution of **4-10b** (109 mg, 0.54 mmol, THF 5ml) was added to this solution and stirred at room temperature. After 1.5 hour, the reaction was quenched with aqueous 5% potassium hydrogen sulfate and diluted with ethyl acetate. The organic layer was washed with aqueous saturated sodium hydrogen carbonate, water and brine, dried with magnesium sulfate, and evaporated. The crude product was purified by silica gel; column chromatography (1:1 hexane - ethyl acetate) and preparative TLC (7:1 chloroform-ethyl acetate) 27 mg (0.079 mmol, 15%) of **4-4f** was obtained. ^{1}H-NMR (500MHz, CD_3OD) δ 7.85 (dd, *J* = 7.5, 2.5 Hz, 2H), 7.49 (t, *J* = 1.0 Hz, 1H), 7.44 (dd, *J* = 7.0, 1.5 Hz, 1H), 7.33 (quin, *J* = 2.5 Hz, 1H), 7.18 (t, *J*= 6.5, 2H), 6.76 (d, *J*= 7.5, 2H), 6.58 (dd, *J*= 6.5, 1.5, 1H), 6.52 (dd, *J*= 7.0, 2.0 Hz, 1H), 6.49 (t, *J* = 2.0 Hz, 1H), 3.4 (s, 3H);

Synthesis of compound **4-26:** *m*-(benzyloxy)phenol (444 mg, 2.22 mmol) was added to a solution of 4-fluoro-2-nitrotoluene (315 mg, 2.03 mmol) and potassium carbonate (173 mg, 1.25 mmol) in DMF (1.5 ml) under an argon atmosphere, and the mixture was stirred at 150°C for 25 h. It was allowed to cool to room temperature, then poured into 1 M HCl, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 24:1) to afford **4-26** (70 mg, 10%). ^{1}H-NMR (600MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.4 Hz, 1H), 7.34-7.48 (m, 5H), 7.25 (d, *J* = 8.4 Hz, 1H), 7.12 (dd, *J* = 8.4, 3.0 Hz, 1H), 7.00 (s, 4H), 5.08 (s, 2H), 2.55 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 157.1530, 155.7460, 149.4721, 149.0708, 136.7315, 133.5859, 128.5856, 128.0312, 127.4637, 126.9998, 122.0880, 121.0554, 116.1582, 112.9568, 70.4724, 19.6676.

Synthesis of compound **4-20:** A mixture of **4-26** (69 mg, 0.23 mmol) and 10% palladium hydroxide on carbon (8 mg) in tetrahydrofuran (2 ml) and methanol (2 ml) was stirred under a hydrogen atmosphere for 17 h. The reaction mixture was filtered over Celite, and the filtrate was evaporated to afford 37 mg of **4-27** (0.17 mmol, 84%). **4-27** was added to a solution of *m*-anisoyl chloride (178 mg, 0.76 mmol) in tetrahydrofuran (5 ml). The mixture was stirred at room temperature for 1h, and poured into water, and extracted with ethyl acetate. The organic layer was washed successively with saturated sodium hydrogen carbonate, 1 M HCl, water, and brine, dried over magnesium sulfate, and evaporated. The residue was washed by dichloromethane to afford **4-20** (38 mg, 62%). **4-20**: Pale orange prisms (methanol); mp 189.5-190°C; ^{1}H NMR (600 MHz, acetone-d_6) δ 8.83 (s, 1H), 8.34 (s, 1H), 7.95 (d, *J* = 8.9 Hz, 1H), 7.34 (dd, *J* = 11.0, 2.1 Hz, 2H), 7.17 (d, *J* = 8.2 Hz, 1H), 7.01 (dt, *J* = 8.9, 2.0

Hz, 2H), 6.89 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.83 (dt, *J* = 8.9, 2.7 Hz, 2H), 6.67 (dd, *J* = 8.3, 2.8 Hz, 1H), 3.86 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (150 MHz, acetone-d_6) δ 165.42, 163.33, 157.84, 154.55, 150.21, 138.73, 131.80, 131.69, 130.18, 128.04, 126.32, 121.54, 116.99, 116.90, 114.90, 114.63, 114.52, 114.44, 55.80, 17.440; HRMS Calcd. for $C_{21}H_{20}NO_4$ $[M+H]^+$ 350.1387; found 350.1384.

Synthesis of compound **4-29:** *m*-(benzyloxy)phenol (446 mg, 2.23 mmol) was added to a solution of 2-fluoro-6-nitrotoluene (317 mg, 2.04 mmol) and potassium carbonate (342 mg, 2.48 mmol) in DMF (3 ml) under an argon atmosphere, and the mixture was stirred at 150°C for 23 h. It was allowed to cool to room temperature, then poured into 1 M HCl, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 24:1) to afford **4-29** (70 mg, 10%). ^{1}H-NMR (600MHz, $CDCl_3$) δ 7.56 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.32-7.46 (m, 5H), 7.21 (t, *J* = 8.4 Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 1H), 6.98 (d, *J* = 9.0 Hz, 2H), 9.92 (d, *J* = 9.0 Hz, 2H), 5.06 (s, 2H), 2.48 (s, 3H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ 157.2614, 155.3428, 151.2494, 150.0312, 136.7869, 128.6114, 128.0502, 127.4522, 126.6937, 124.1270, 121.0781, 120.1138, 118.3426, 116.1356, 70.5204, 11.9641.

Synthesis of compound **4-30:** A mixture of **4-29** (70 mg, 0.21 mmol) and 10% palladium hydroxide on carbon (8 mg) in tetrahydrofuran (2ml) and methanol (2 ml) was stirred under a hydrogen atmosphere for 19.5 h. The reaction mixture was filtered over Celite, and the filtrate was evaporated to afford **4-30** (0.17 mmol, 92%). ^{1}H-NMR (600 MHz, CD_3OD) δ 6.95 (t, *J* = 8.2 Hz, 1H), 6.73 (s, 4H), 6.63 (d, *J* = 7.6 Hz, 1H), 6.30 (d, *J* = 8.3 Hz, 1H), 2.11 (s, 3H).

Synthesis of compound **4-21: 4-30** (52 mg, 0.19 mmol) was added to a solution of *m*-anisoyl chloride (117 mg, 0.69 mmol) in tetrahydrofuran (5 ml). The mixture was stirred at room temperature for 1h, and poured into water, and extracted with ethyl acetate. The organic layer was washed successively with saturated sodium hydrogen carbonate, 1 M HCl, water, and brine, dried over magnesium sulfate, and evaporated. The residue was washed by dichloromethane to afford **4-21** (46 mg, 68%). **4-21**: Pale brown prisms (methanol); mp 203-204°C; ^{1}H NMR (600 MHz, acetone-d_6) δ 9.03 (s,1H), 8.01 (dt, *J* = 9.0, 2.1 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.13 (t, *J* = 8.3 Hz, 1H), 7.04 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.83 (s, 1H), 6.64 (d, *J* = 7.5 Hz, 1H), 3.87 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (150 MHz, acetone-d_6) δ 165.61, 163.32, 157.29, 154.16, 150.90, 139.27, 130.23, 126.87, 121.12, 120.37, 116.97, 116.88, 115.57, 114.45, 55.81, 11.23; HRMS Calcd. for $C_{21}H_{20}NO_4$ $[M+H]^+$ 350.1387; found 350.1383.

Synthesis of compound **4-32:** *P*-(benzyloxy)phenol (442 mg, 2.21 mmol) was added to a solution of 2-fluoro-4-nitrotoluene (315 mg, 2.03 mmol) and potassium carbonate (337 mg, 2.44 mmol) in NMP (2 ml) under an argon atmosphere, and the mixture was stirred at 160°C for 6 h. It was allowed to cool to room

temperature, then poured into 1 M HCl, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 25:1) to afford **4-32** (71 mg, 11%). ^{1}H-NMR (600 MHz, CD_3OD) δ 7.84 (dd, *J* = 8.2, 2.1 Hz, 1H), 7.50 (d, *J* = 2.0 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 2H), 7.42 (d, *J* = 8.2 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.04 (dt, *J* = 9.6, 2.7 Hz, 2H), 6.98 (dt, *J* = 8.9, 2.7 Hz, 2H), 5.09 (s, 2H), 2.42 (s, 3H).

Synthesis of compound **4-33:** A mixture of **4-32** (71 mg, 0.21 mmol) and 10% palladium hydroxide on carbon (10 mg) in tetrahydrofuran (2ml) and methanol (2 ml) was stirred under a hydrogen atmosphere for 18 h. The reaction mixture was filtered over Celite, and the filtrate was evaporated to afford **4-33** (38 mg, 0.18 mmol, 84 %). ^{1}H-NMR (600 MHz, CD_3OD) δ 7.12 (d, *J* = 8.3 Hz, 1H), 6.82 (q, *J* = 8.9 Hz, 4H), 6.63 (d, *J* = 6.8 Hz, 1H), 6.39 (s, 1H), 2.21 (s, 3H).

Synthesis of compound **4-22: 4-33** (38 mg, 0.18 mmol) was added to a solution of *p*-anisoyl chloride (88 mg, 0.52 mmol) in tetrahydrofuran (5 ml). The mixture was stirred at room temperature for 50min, and poured into water, and extracted with ethyl acetate. The organic layer was washed successively with saturated sodium hydrogen carbonate, 2M HCl, water, and brine, dried over magnesium sulfate, and evaporated. The residue was purified by silica gel column chromatography (chloroform /ethyl acetate 10:1) to give 29 mg of **4-22** (0.083 mmol, 47%) was obtained. **4-22**: Colorless prisms (chloroform/ethyl acetate); mp 179.0-179.5°C; ^{1}H NMR (600 MHz, acetone-d_6) δ 9.35 (br, 1H), 8.21 (br, 1H), 7.91 (d, J = 8.3 Hz, 2H), 7.54 (dt, J = 8.2, 2.8 Hz, 1H), 7.29 (t, J = 2.1 Hz, 1H), 7.19 (d, 8.3 Hz, 1H), 6.99 (dt, J = 9.0, 2.7 Hz, 2H), 6.85 (m, 4H), 3.85 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (150 MHz, acetone-d_6) δ 165.47, 163.21, 157.09, 154.19, 150.64, 139.59, 131.72, 130.09, 128.26, 123.93, 120.66, 116.99, 116.90, 115.26, 114.33, 110.14, 55.76, 15.81; HRMS Calcd. for $C_{21}H_{20}NO_4$ $[M+H]^+$ 350.1387; found 350.1383.

Synthesis of compound **4-35:** Sodium hydride (240 mg, 6.0 mmol) was washed with *n*-hexane twice. A solution of 4-iodophenol (1.1 g, 5.0 mmol) was added to suspendion of sodium hydride in dry dimethylformamide (10 ml) at room temperature and stirred. After 30 min, benzyl chloride (760 mg, 2.0 mmol) was added at room temperature. After being stirred for 21 h at room temperature, the reaction was quenched with water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and filtered. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane) and 1.49 g of **4-35** (4.79 mmol, 96%) was obtained. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.55 (dt, *J* = 8.9, 2.1 Hz, 2H), 7.37-7.42 (m, 4H), 7.33 (t, *J* = 6.9 Hz, 1H), 6.75 (dt, *J* = 8.9, 2.1 Hz, 2H), 5.03 (s, 2H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.5962, 138.2306, 136.4785, 128.6367, 128.1101, 127.4207, 117.2715, 83.0321, 70.0487.

Synthesis of compound **4-36:** Under argon atmosphere, a solution of copper(I) iodide (4.8 mg, 0.025 mmol), 2-picolinic acid (6.6 mg, 0.054 mmol), aryl iodide **4-35** (152 mg, 0.49 mmol), 5-amino-o-cresol (74 mg, 0.60 mmol) and K_3PO_4 (212 mg, 1.0 mmol) in dimethylsulfoxide (1 ml) was stirred vigorously for 24 h at 80°C. The reaction mixture was cooled to room temperature. Ethyl acetate and H_2O were added and the mixture was stirred. The organic layer was separated and the aqueous layer was extracted twice more with ethyl acetate. Combined organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated and the resulting residue was purified by silica gel; column chromatography (chloroform /ethyl acetate 3:1) and 100 mg of **4-36** (0.33 mmol, 67 %) was obtained. ^{1}H-NMR (600MHz, $CDCl_3$) δ 7.43 (d, *J* = 6.8 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 6.92 (dt, *J* = 9.0, 2.8 Hz, 2H), 6.88 (dt, *J* = 9.6, 2.8 Hz, 2H), 6.36 (dd, *J* = 8.2, 2.7 Hz, 1H), 6.15 (d, *J* = 2.1 Hz, 1H), 5.03 (s, 2H), 3.50 (brs, 2H), 2.14 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 156.3078, 154.3928, 151.1853, 145.5075, 137.0434, 131.6815, 128.5601, 127.9378, 127.4782, 119.3875, 118.6981, 115.7587, 110.0904, 105.4275, 70.5179, 15.3289.

Synthesis of compound **4-37:** *o*-anisoyl chloride (36 mg, 0.21 mmol) was added to solution of **4-36** (22 mg, 0.071 mmol) in pyridine (1.2 ml) and stirred at room temperature for 30 min. Then the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 2M HCl, water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 3:1) to give 35 mg of **4-37**(0.081 mmol) was obtained. ^{1}H-NMR (600MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.23 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.46 (td, *J* = 8.9, 2.1 Hz, 1H), 7.42-7.44 (m, 2H), 7.38 (t, *J* = 7.5, 2H), 7.30-7.34 (m, 2H), 7.25 (d, *J* = 5.5 Hz, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 5.02 (s, 2H), 3.99 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 163.02, 157.09, 155.39, 154.33, 151.40, 137.31, 137.06, 133.16, 132.43, 131.32, 128.53, 127.90, 127.48, 125.14, 121.63, 121.59, 118.76, 115.84, 115.59, 111.43, 111.21, 70.50, 56.17, 15.79.

Synthesis of compound **4-23: 4-37**(35 mg, 0.081 mmol) was dissolved in THF (2 ml). Palladium hydroxide on carbon (5 mg) was suspended in the THF and stirred under hydrogen atmosphere. After 21 h, the reaction mixture was filtered through Celite and evaporated. The crude product was recrystallized with methanol and 19.7 mg of **4-23** (0.056 mmol, 70%) was obtained. **4-23**: Colorless needles (methanol); mp 190.0-191.5°C; ^{1}H NMR (600 MHz, acetone-d_6) δ 9.81 (br, 1H), 8.19 (s, 1H), 7.98 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.51 (ddd, *J* = 8.2, 6.9, 1.4 Hz, 1H), 7.48 (d, *J* = 2.7 Hz, 1H), 7.36 (dd, *J* = 8.3, 2.1 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.08 (td, *J* = 7.6, 1.3 Hz, 1H), 6.84 (s, 4H), 4.03 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 166.65, 158.68, 157.52, 154.37, 151.23, 138.59, 134.12, 132.17, 131.74, 125.87, 124.25, 122.01, 120.60, 117.16, 116.22, 112.92, 111.51, 56.60, 15.93; HRMS Calcd. for $C_{21}H_{20}NO_4$ $[M+H]^+$ 350.1387; found 350.1385.

Synthesis of compound **4-39:** Sodium hydride (240 mg, 6.0 mmol) was washed with *n*-hexane twice. A solution of 3-iodophenol (1.1 g, 5.0 mmol) was added to suspendion of sodium hydride in dry dimethylformamide (10 ml) at room temperature and stirred. After 30 min, benzyl chloride (760 mg, 2.0 mmol) was added at room temperature. After being stirred for 21.5 h at room temperature, the reaction was quenched with water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and filtered. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane) and 1.45 g of **4-39** (4.67 mmol, 94 %) was obtained.; ^{1}H-NMR (600MHz,$CDCl_3$) δ 7.35-7.43 (m,4H), 7.33-7.35 (m, 2H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.00 (t, *J*=7.5 Hz, 1H), 6.94 (dd, *J* = 8.3, 2.1 Hz, 1H), 5.03 (s, 2H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2951, 136.3731, 130.7910, 130.0921, 128.6367, 128.1484, 127.5069, 124.0217, 114.4661, 94.3399, 70.1253.

Synthesis of compound **4-40:** Under argon atmosphere, a solution of copper(I) iodide (5.1 mg, 0.027 mmol), 2-picolinic acid (6.7 mg, 0.054 mmol), aryl iodide **4-39** (152 mg, 0.49 mmol), 5-amino-o-cresol (74 mg, 0.60 mmol) and K_3PO_4 (212 mg, 1.0 mmol) in dimethylsulfoxide (1 mL) was stirred vigorously for 24 h at 80°C. The reaction mixture was cooled to room temperature. Ethyl acetate and H_2O were added and the mixture was stirred. The organic layer was separated and the aqueous layer was extracted twice more with ethyl acetate. Combined organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated and the resulting residue was purified by silica gel; column chromatography (4:1 chloroform-ethyl acetate) and 90 mg of **4-40** (0.29 mmol, 60 %) was obtained. ;^{1}H-NMR (600MHz, $CDCl_3$) δ 7.36-7.42 (m, 4H), 7.31 (t, *J* = 6.9 Hz, 1H), 7.18 (t, *J* = 8.2 Hz, 1H), 7.00 (d, *J* = 8.3 Hz, 1H), 6.66 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.54 (t, *J* = 2.1 Hz, 1H), 6.52 (dd, *J* = 7.6, 2.1 Hz, 1H), 6.43 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.28 (d, *J* = 2.1 Hz, 1H), 5.01 (s, 2H), 2.08 (s, 3H) ; ^{13}C NMR (150 MHz, $CDCl_3$) δ 160.0228, 159.1132, 154.6705, 145.6511, 136.7657, 131.8443, 129.9963, 128.5601, 127.9761, 127.5739, 119.6939, 111.2681, 109.8510, 108.5106, 107.2371, 104.2115, 70.0296, 15.2428.

Synthesis of compound **4-41:** *p*-anisoyl chloride (70 mg, 0.41 mmol) was added to solution of **4-40** (30 mg, 0.10 mmol) in pyridine (1 ml) and stirred at room temperature for 40 min. Then the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 3:2 and chloroform/ethyl acetate 4:1) to give 34 mg of **4-41** (0.079 mmol, 80%) was obtained. ^{1}H-NMR (500 MHz, CD_3OD) δ 7.90 (dt, *J* = 8.9, 2.1 Hz, 2H), 7.43 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.33-7.41 (m, 5H), 7.27-7.30 (m, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.22 (t, *J* = 8.2 Hz, 1H), 7.02 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.71 (ddd, *J* = 8.2, 2.2, 0.48 Hz, 1H), 6.55 (t, *J* = 2.34 Hz, 1H), 6.52 (ddd, *J* = 8.0, 2.2, 0.60 Hz, 1H), 5.04 (s, 2H), 3.87 (s, 3H),

2.17 (s, 3H); ^{13}C-NMR (125MHz, CD_3OD) δ 173.8396, 169.1645, 164.9942, 162.4327, 161.2049, 156.3497, 140.0912, 139.3934, 133.2001, 132.1299, 131.3961, 130.3473, 129.6928, 129.3923, 128.9347, 127.7306, 118.8571, 115.6312, 114.8869, 111.5440, 111.1498, 106.0714, 71.8770, 56.7974, 16.6612.

Synthesis of compound **4-24:** A mixture of **4-41** (34 mg, 0.079 mmol) and 10% palladium hydroxide on carbon (5 mg) in tetrahydrofuran (2 ml) was stirred under a hydrogen atmosphere for 24 h. The reaction mixture was filtered over Celite, and the filtrate was evaporated to afford **4-24** (0.080mmol, quant.). Colorless prism; mp: 202.5-203 °C (ethyl acetate). ^{1}H-NMR (600 MHz, CD_3OD) δ 7.90 (dt, *J* = 8.9, 2.1 Hz, 2H), 7.43 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.38 (d, *J* = 2.1 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.13 (t, *J* = 8.1 Hz, 1H), 7.04 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.51 (ddd, *J* = 8.1, 2.3, 0.8 Hz, 1H), 6.42 (ddd, *J* = 8.2, 2.4, 0.9 Hz, 1H), 6.37 (t, *J* = 2.2 Hz, 1H), 3.88 (s, 3H), 2.21 (s, 3H); Anal. Calcd. For $C_{21}H_{19}NO_4$・1/4H_2O: C, 71.27; H, 5.55; N, 3.96. Found C, 71.48; H, 5.62; N, 3.94.

Synthesis of compound **4-48:** An aqueous solution of 5 M sodium hydroxide (2.0 ml, 10 mmol) was added to DMSO (8 ml) at room temperature under an Ar atmosphere. After 10 min, *o*-monobenzylhydroquinone (961 mg, 4.8 mmol) was added to it. The mixture was stirred at 50°C for 15 min, then 2-fluoro-5-nitrotoluene (620 mg, 4.0 mmol) was added, and stirring was continued at 50°C for 5.5 h, and at room temperature for 15 h. The reaction mixture was then poured into ice water and the precipitate was collected by filtration to give **122** (1.04 g, 65%). Yellow powder; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 2.1 Hz, 1H), 7.96 (dd, *J* = 8.9, 2.7 Hz, 1H), 7.36 (m, 5H), 7.02 (dt, *J* = 9.6, 2.8 Hz, 2H), 6.99 (dt, *J* = 8.9, 2.7 Hz, 2H), 6.69 (d, *J* = 8.9 Hz, 1H), 5.08 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.21, 156.04, 148.51, 142.06, 136.67, 128.65, 128.12, 127.48, 126.64, 123.14, 121.50, 116.24, 114.47.

Synthesis of compound **4-49:** A solution of copper (II) sulfate·5H_2O (502 mg, 2.0 mmol) in methanol (4 ml) was added to a solution of sodium borohydride (189 mg, 5.0 mmol) and **4-48** (234 mg, 0.70 mmol) in methylene chloride (5 ml), and the mixture was stirred at 0°C for 2.5 h. Sodium borohydride (76 mg, 2.0 mmol) was added to it, and stirring was continued at 0°C for 2 h. Sodium borohydride (76 mg, 2.0 mmol) was added, and the reaction mixture was stirred at 0°C for 1 h, then poured into water, and extracted with methylene chloride. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was dissolved in ether, and 1 M hydrochloric acid in ether was added to the solution. The resulting precipitate was collected to afford **4-49** (205 mg, 86%). Pale brown powder; ^{1}H NMR (600 MHz, CD_3OD) δ 7.43 (d, *J* = 7.6 Hz, 2H), 7.33 (m, 3H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.12 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.01 (dt, *J* = 9.6, 2.8 Hz, 2H), 6.90 (dt, *J* = 8.9, 2.0 Hz, 2H), 6.80 (d, *J* = 8.9 Hz, 1H), 5.06 (s, 2H), 2.33 (s, 3H) ; ^{13}C NMR (150 MHz, CD_3OD) δ 158.08, 156.78, 151.44, 138.65, 131.96, 129.52, 128.92, 128.58, 126.62, 126.08, 122.65, 121.20, 119.00, 117.32, 71.50, 16.31.

Synthesis of compound **4-50:** *M*-Anisoyl chloride (61 mg, 0.36 mmol) was added to a solution of **4-49** (102 mg, 0.30 mmol) in pyridine (5 ml). The mixture was stirred at room temperature for 30 min, then poured into water,

and extracted with ethyl acetate. The organic layer was washed successively with saturated sodium hydrogen carbonate, 1 M hydrochloric acid, water and brine, dried over sodium sulfate, and evaporated to give **4-50** (113 mg, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.54 (d, *J* = 2.7 Hz, 1H), 7.39 (m, 8H), 7.08 (dt, *J* = 6.9, 2.7 Hz, 1H), 6.93 (dt, *J* = 9.6, 2.7 Hz, 2H), 6.75 (dt, *J* = 9.0, 2.4 Hz, 2H), 6.56 (d, *J* = 9.0 Hz, 1H), 5.04 (s, 2H), 3.87 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.41, 159.97, 154.37, 152.25, 151.58, 137.03, 136.43, 133.14, 130.19, 129.77, 128.57, 127.96, 127.49,123.37, 119.10, 118.77, 118.55, 117.94, 115.85, 112.45, 70.56, 55.48, 16.38.

Synthesis of compound **4-51:** Sodium hydride (8.0 mg, 0.30 mmol) was washed with *n*-hexane twice. A solution of **4-50** (44 mg, 0.10 mmol) in dry DMF (0.5 ml) was added to a suspension of sodium hydride in dry DMF (0.3 ml) at 0°C, and the mixture was stirred at room temperature for 30 min. Iodomethane (43 mg, 0.30 mmol) in dry DMF (0.3 ml) was added at 0°C, and stirring was continued at room temperature for 30 min. Remaining iodomethane was removed *in vacuo*. The residue was poured into water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 2:1 to 3:2) to afford **4-51** (38 mg, 86%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.37 (m, 5H), 7.08 (t, *J* = 7.9 Hz, 1H), 6.95 (br, 1H), 6.90 (m, 3H), 6.86 (br d, *J* = 7.5 Hz, 1H), 6.80 (m, 3H), 6.75 (br d, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 9.0 Hz, 1H), 5.02 (s, 2H), 3.69 (s, 3H), 3.46 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.33, 158.85, 154.63, 154.07, 150.82, 139.72, 137.20, 136.90, 129.39, 128.68, 128.55, 127.96, 127.41, 119.21, 118.25, 115.85, 115.81, 70.50, 55.14, 38.51, 16.15.

Synthesis of compound **4-42:** A mixture of **4-51** (38 mg, 0.086 mmol) and palladium hydroxide on carbon (5 mg) in THF (2 ml) was stirred under a hydrogen atmosphere for 21 h. The reaction mixture was filtered over Celite, and the filtrate was evaporated. The crude product was recrystallized from methanol to give **4-42** (9 mg, 30%). Colorless prisms (methanol); mp 172-173°C; ^{1}H NMR (600 MHz, acetone-d_6) δ 7.12 (t, J = 7.5 Hz, 2H), 6.90 (br dd, *J* = 9.0, 2.8 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 2H), 6.85 (m, 1H), 6.80 (m, 3H), 6.74 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.60 (d, *J* = 8.9 Hz, 1H), 3.66 (s, 3H) , 3.37 (s, 3H) , 2.13 (s, 3H); ^{13}C NMR (150 MHz, acetone- d_6) δ 170.16, 159.80, 155.29, 154.27, 154.17, 150.54, 140.88, 138.99, 130.67, 130.11, 129.47, 126.74, 121.65, 120.35, 118.53, 118.53, 117.00, 115.95, 114.62, 55.45, 38.37, 16.18; HRMS Calcd. for $C_{21}H_{20}NO_4$ $[M+H]^+$ 350.1387; found 350.1384. Anal. Calcd. For $C_{22}H_{21}NO_4 \cdot 1/4H_2O$: C, 71.82; H, 5.89; N, 3.81. Found C, 71.84; H, 5.84; N, 3.81. ;

Synthesis of compound **4-52:** Sodium hydride (8.0 mg, 0.30 mmol) was washed with *n*-hexane twice. A solution of **4-16** (44 mg, 0.10 mmol) in dry DMF (0.7 ml) was added to a suspension of sodium hydride in dry DMF (0.3 ml) at 0°C, and the mixture was stirred at room temperature for 30 min. Iodomethane (47 mg, 0.33 mmol) was added at 0°C, and stirring was continued at room temperature for 40 min. Remaining iodomethane was removed *in vacuo*, then the residue was poured into water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl 2:1) to give **4-52** (37 mg, 82%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, *J*

= 6.9 Hz, 2H), 7.4 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.20 (t, *J* = 8.3 Hz, 1H), 7.06 (t, *J* = 8.2 Hz, 1H), 6.84 (m, 5H), 6.78 (m, 2H), 6.48 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.45 (t, *J* = 2.1 Hz, 1H), 5.04 (s, 2H), 3.67 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.31, 159.02, 158.62, 155.16, 149.40, 145.99, 137.02, 136.85, 130.09, 128.77, 128.59, 128.01, 127.41, 121.03, 120.47, 120.11, 116.32, 116.22, 115.98, 115.86, 113.36, 70.41, 55.14, 38.09.

Synthesis of compound **4-43a:** A mixture of **4-52** (37 mg, 0.085 mmol) and palladium hydroxide on carbon (5 mg) in tetrahydrofuran (2.5 ml) was stirred under a hydrogen atmosphere for 18.5 h. The reaction mixture was filtered over Celite, and evaporated. The crude product was recrystallized from chloroform to give **4-43a** (19 mg, 64%). Colorless prisms (chloroform); mp 160-160.5°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.21 (t, *J* = 8.3 Hz, 1H), 7.09 (dt, *J* = 7.5, 1.4 Hz, 1H), 6.84 (m, 3H), 6.78 (m, 2H), 6.72 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.59 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.42 (br, 1H), 5.16 (s, 1H), 3.69 (s, 3H), 3.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.55, 159.07, 158.84, 152.24, 149.01, 145.89, 136.94, 130.14, 128.82, 121.03, 120.80, 119.97, 116.38, 116.33, 116.15, 115.99, 113.36, 55.19, 38.19; HRMS Calcd. for $C_{21}H_{20}NO_4$ $[M+H]^+$ 350.1387; found 350.1385.

Synthesis of compound **4-53:** *P*-anisoyl chloride (30 mg, 0.18 mmol) was added to solution of **4-15** (49 mg, 0.15 mmol) in pyridine (5 ml) and stirred at room temperature. After 40 min, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 2:1) and preparative thin-layer chromatography (*n*-hexane/ethyl acetate 1:1) to give 49 mg of **4-53** (0.11 mmol, 76%) was obtained. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.01 (s, 1H), 7.77 (dt, *J* = 8.9, 2.0 Hz, 2H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.38 (td, *J* = 7.6, 2.4 Hz, 1H), 7.33-7.31 (m, 2H), 7.26 (t, *J* = 2.4 Hz, 1H), 7.22 (t, J = 9.0 Hz, 1H), 6.96 (dt, *J* = 8.9, 2.4 Hz, 2H), 6.92 (dt, *J* = 10.0, 2.4 Hz, 2H), 6.81 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.70 (ddd, *J* = 8.2, 2.8, 1.4 Hz, 1H), 5.00 (s, 2H), 3.81 (s, 3H); ^{13}C-NMR (150MHz, $CDCl_3$) δ 165.26, 162.43, 158.98, 155.15, 150.00, 139.40, 136.90, 129.91, 128.91, 128.54, 127.95, 127.48, 126.87, 120.90, 115.85, 114.23, 113.85, 113.43, 109.46, 70.42, 55.39.

Synthesis of compound **4-54:** Sodium hydride (8.0 mg, 0.30 mmol) was washed with *n*-hexane twice. A solution of **4-53** (44 mg, 0.10 mmol) in dry dimethylformamide (0.6 ml) was added to suspendion of sodium hydride in dry dimethylformamide (0.3 ml) at 0°C and stirred at room temparature. After 30 min, iodomethane (43 mg, 0.30 mmol) in dry dimethylformamide (0.2 ml) was added at 0°C. After being stirred for 30 min at room temperature, iodomethane was removed in vacuo. Then the residue was quenched with water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and filtered. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl 3:2) and 32 mg of **4-54** (0.072 mmol, 71%) was obtained. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.44-7.34

(m, 5H), 7.23 (dt, *J* = 8.9, 2.1 Hz, 2H), 7.19 (t, *J* = 9.3, 1H), 6.85 (dt, *J* = 9.7, 2.8 Hz, 2H), 6.80 (dd, *J* = 6.9, 2.1 Hz, 1H), 6.77 (dd, *J* = 8.3, 3.4 Hz, 1H), 6.69-6.66 (m, 4H), 6.48 (t, *J* = 2.1 Hz, 1H), 5.05 (s, 2H), 3.76 (s, 3H), 3.44 (s, 3H) ; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 170.18, 160.60, 158.57, 155.10, 149.53, 146.53, 136.87, 130.77, 130.07, 128.59, 128.00, 127.86, 127.38, 120.42, 120.28, 116.43, 115.86, 115.71, 112.99, 55.21, 38.30.

Synthesis of compound **4-43b: 4-54** (32 mg, 0.072 mmol) was dissolved in THF (2.5 ml). Palladium hydroxide on carbon (5 mg) was suspended in the THF and stirred under hydrogen atmosphere. After 17 h, the reaction mixture was filtered through Celite® and evaporated. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl 1:1) and recrystallized with diisopropylether, then 11 mg of **4-43b** (0.032 mmol, 45%) was obtained. Colorless needles; mp 107.5-108.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (dt, *J* = 8.9, 2.1 Hz, 2H), 7.21 (t, *J* = 8.2 Hz, 1H), 6.81 (dd, *J* = 6.9, 2.1 Hz, 1H), 6.78(ddd, *J* = 8.3, 2.7, 1.4 Hz, 1H), 6.72 (m, 4H), 6.63 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.47 (t, *J* = 2.1 Hz, 1H), 5.34 (br d, *J* = 10.3 Hz, 1H), 3.79 (s, 3H) , 3.46 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.45, 160.70, 158.80, 152.30, 149.11, 146.39, 130.79, 130.14, 127.74, 120.71, 120.15, 116.37, 116.29, 115.78, 113.08, 55.27, 38.42; HRMS Calcd. for $C_{21}H_{20}NO_4$ $[M+H]^+$ 350.1387; found 350.1383.

Synthesis of compound **4-55:** *M*-methoxybenzenesulfonyl chloride (121 mg, 0.59 mmol) was added to solution of **4-49** (170 mg, 0.50 mmol) in pyridine (5 ml) and stirred at room temperature. After 1.5 h, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate, and evaporated and 221 mg of **4-55** (0.47 mmol, 94%) was obtained. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.43 (d, *J* = 6.8 Hz, 2H), 7.39 (t, *J* = 6.9 Hz, 2H), 7.32-7.37 (m, 3H), 7.22 (brs, 1H), 7.07 (ddd, *J* = 7.6, 2.7, 1.4 Hz, 1H), 6.95 (d, *J* = 2.7 Hz, 1H), 6.91 (dt, *J* = 8.9, 2.7 Hz, 2H), 6.81 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.78 (dd, *J* = 8.2, 2.0 Hz, 1H), 6.65 (d, *J* = 9.0 Hz, 1H), 6.50 (brs, 1H), 5.03 (s, 2H), 3.77 (s, 3H), 2.19 (s, 3H); ^{13}C-NMR (150MHz, $CDCl_3$) δ 159.7068, 154.6322, 153.9524, 150.9459, 140.0594, 136.9380, 130.9251, 130.2166, 129.9868, 128.5793, 127.9952, 127.4590, 126.2718, 121.8482, 119.5407, 119.4066, 119.1960, 118.5353, 115.8927, 111.7564, 70.5370, 55.5717, 16.2290.

Synthesis of compound **4-56:** Sodium hydride (16 mg, 0.40 mmol) was washed with *n*-hexane twice. A solution of **4-55** (95 mg, 0.20 mmol) in dry dimethylformamide (0.5 ml) was added to suspendion of sodium hydride in dry dimethylformamide (1.4 ml) at 0℃ and stirred at room temparature. After 30 min, iodomethane (88 mg, 0.62 mmol) was added at 0℃. After being stirred for 40 min at room temperature, iodomethane was removed in vacuo. Then the residue was quenched with water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and filtered. After solvent was removed in vacuo, the

residue was purified by silica gel column chromatography (*n*-hexane/ethyl acetate 2:1) and 92 mg of **4-55** (0.19 mmol, 94%) was obtained.; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.13 (dd, *J* = 8.3, 2.8 Hz, 1H), 7.06 (t, *J* = 2.0 Hz, 1H), 7.02 (d, *J* = 2.1 Hz, 1H), 6.97 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.91 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.81 (dd, *J* = 8.9, 2.7 Hz, 2H), 6.69 (d, *J* = 8.2 Hz, 2H), 5.06 (s, 2H), 3.77 (s, 3H), 3.17 (s, 3H), 2.26 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 159.4675, 155.1301, 154.7663, 150.5342, 137.5125, 136.8614, 135.9710, 129.8719, 129.6516, 129.2782, 128.5218, 127.9282, 127.4016, 125.1228, 120.0386, 119.6460, 119.2534, 117.3672, 115.8640, 112.3500, 70.4509, 55.4568, 38.4233, 16.1811.

Synthesis of compound **4-45a: 4-56** (53 mg, 0.11 mmol) was dissolved in THF (3 ml). Palladium hydroxide on carbon (7 mg) was suspended in the THF and stirred under hydrogen atmosphere. After 19 h, the reaction mixture was filtered through Celite and evaporated. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl 3:2) and 42 mg of **4-45a** (0.11 mmol, 97%) was obtained. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.38 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.11 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.04 (t, *J* = 2.7 Hz, 1H), 6.98 (d, *J* = 2.7 Hz, 1H), 6.76-6.84 (m, 5H), 6.64 (d, *J* = 9.0 Hz, 1H), 5.04 (s, 1H), 3.76 (s, 3H), 3.15 (s, 3H), 2.23 (s, 3H);^{13}C-NMR (150 MHz, $CDCl_3$) δ 159.5345, 155.3599, 151.6640, 150.2661, 137.5317, 135.8465, 129.9389, 129.7187, 129.2495, 125.2281, 120.1152, 120.0194, 119.3971, 117.1566, 116.3140, 112.3500, 55.5334, 38.5190, 16.2290.

Synthesis of compound **4-44a: 4-55** (57 mg, 0.12 mmol) was dissolved in THF (3 ml). Palladium hydroxide on carbon (6 mg) was suspended in the THF and stirred under hydrogen atmosphere. After 21 h, the reaction mixture was filtered through Celite® and evaporated. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl 3:2) and 49 mg of crude product was obtained. Then, a part of this product (20 mg) was purified by preparative TLC and of **4-44a** (18 mg, 0.05 mmol) was obtained. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.6 Hz, 1H), 7.32-7.35 (m, 1H), 7.23 (t, *J* = 2.0 Hz, 1H), 7.07 (ddd, *J* = 7.5, 2.8, 1.3 Hz, 1H), 6.95 (d, *J* = 2.7 Hz, 1H), 6.76-6.79 (m, 5H), 6.64 (d, *J* = 9.0 Hz, 1H), 6.59 (brs, 1H), 5.01 (s, 2H) , 3.77 (s, 3H) , 2.18 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 159.6781, 153.9907, 151.6066, 150.4863, 139.9158, 130.8293, 129.9772, 126.1186, 121.7046, 119.5598, 119.4354, 119.3971, 118.2385, 116.2470, 111.6990, 55.5429, 16.1811.

Synthesis of compound **4-57:** *p*-methoxybenzenesulfonyl chloride, (68 mg, 0.33 mmol) was added to solution of **4-49** (94 mg, 0.28 mmol) in pyridine (5 ml) and stirred at room temperature. After 1 h, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium

sulfate, and evaporated and 128 mg of **4-57** (0.27 mmol, 98%) was obtained. **4-57**; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.68 (dt, *J* = 8.9, 2.1 Hz, 2H), 7.43 (d, *J* = 6.9 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 6.94 (d, *J* = 2.8 Hz, 1H), 6.89-6.92 (m, 4H), 6.82 (dt, *J* = 8.9, 2.7 Hz, 2H), 6.76 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.65 (d, *J* = 8.9 Hz, 1H), 6.38 (s, 1H), 5.03 (s, 2H), 3.84 (s, 3H), 2.19 (s, 3H); ^{13}C-NMR (150MHz, $CDCl_3$) δ 160.0484, 154.6035, 153.7322, 150.9842, 136.9476, 131.1740, 130.6474, 130.1878, 129.4410, 128.5793, 127.9856, 127.4590, 126.0420, 121.5897, 119.1768, 118.5353, 115.8736, 114.0831, 70.5370, 55.5717, 16.2481.

Synthesis of compound **4-58:** Sodium hydride (12 mg, 0.30 mmol) was washed with *n*-hexane twice. A solution of **4-57** (67 mg, 0.14 mmol) in dry dimethylformamide (0.3 ml) was added to suspendion of sodium hydride in dry dimethylformamide (0.5 ml) at 0°C and stirred at room temparature. After 25 min, iodomethane (88 mg, 0.62 mmol) was added at 0°C. After being stirred for 50 min at room temperature, iodomethane was removed in vacuo. Then the residue was quenched with water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and filtered. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 3:1 to 3:2) and 57 mg of **4-58** (0.12 mmol, 83%) was obtained.; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.52 (dt, *J* = 8.9, 2.1 Hz, 2H), 7.44 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 6.9 Hz, 2H), 7.33 (t, *J* = 6.9 Hz, 2H), 6.99 (d, *J* = 2.8 Hz, 1H), 6.93 (tt, *J* = 8.9, 2.7 Hz, 4H), 6.89 (dt, *J* = 8.9, 2.7 Hz, 2H), 6.76 (dd, *J* = 8.9, 2.7 Hz, 1H), 6.65 (d, *J* = 8.9 Hz, 1H), 5.04 (s, 2H), 3.86 (s, 3H), 3.12 (s, 3H), 2.23 (s, 3H) ; ^{13}C-NMR (150MHz,$CDCl_3$) δ 162.9144, 155.0535, 154.8046, 150.6300, 136.9380, 136.2391, 130.0346, 129.9580, 129.3046, 128.5889, 128.3016, 127.9952, 127.4686, 125.0845, 119.7226, 117.3768, 115.9214, 113.8054, 70.5370, 55.5621, 38.3754, 16.2673.

Synthesis of compound **4-45b: 4-58** (52 mg, 0.11 mmol) was dissolved in THF (3 ml). Palladium hydroxide on carbon (6 mg) was suspended in the THF and stirred under hydrogen atmosphere. After 17 h, the reaction mixture was filtered through Celite and evaporated. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl 3/2) and recycle-GPC, then 31 mg of **4-45b** (0.078 mmol, 74 %) was obtained. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.53 (dt, *J* = 8.9, 2.0 Hz, 2H), 6.98 (d, *J* = 2.7 Hz, 1H), 6.93 (dt, *J* = 8.9, 2.0 Hz, 2H), 6.79-6.85 (m, 4H), 6.75 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 1H), 3.87 (s, 3H), 3.12 (s, 3H), 2.22 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 162.9622, 155.3216, 151.8459, 150.0938, 135.9231, 130.0155, 129.9293, 129.1442, 128.1197, 125.1324, 120.0673, 117.0225, 116.3104, 113.8533, 55.5717, 38.4137, 16.2385.

Synthesis of compound **4-44b: 4-57** (52 mg, 0.11 mmol) was dissolved in THF (3 ml). Palladium hydroxide on carbon (9 mg) was suspended in the THF and stirred under hydrogen atmosphere. After 17 h, the reaction mixture was filtered through Celite® and evaporated. After solvent was removed in vacuo, the residue was

purified by silica gel column chromatography (eluent: *n*-hexane/ethyl 1:1) and 39 mg of **4-44b** (0.10 mmol, 90 %) was obtained. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.68 (dt, *J* = 8.9, 2.0 Hz, 2H), 6.94 (d, *J* = 2.8 Hz, 1H), 6.90 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.75-6.79 (m, 5H), 6.62 (d, *J* = 8.9 Hz, 1H), 6.59 (s, 1H), 5.09 (brs, 1H), 3.84 (s, 3H), 2.18 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 163.0484, 153.8375, 151.3002, 150.7640, 131.0783, 130.6091, 130.1017, 129.4314, 126.0803, 121.6088, 119.4545, 118.3438, 116.2470, 114.0926, 55.5812, 16.2385.

Synthesis of compound **4-59:** Sodium hydride (10 mg, 0.25 mmol) was washed with *n*-hexane twice. A solution of **4-59** (45 mg, 0.097 mmol) in dry dimethylformamide (0.7 ml) was added to suspendion of sodium hydride in dry dimethylformamide (0.3 ml) at 0°C and stirred at room temparature. After 30 min, iodomethane (51 mg, 0.36 mmol) was added at 0°C. After being stirred for 30 min at room temperature, iodomethane was removed in vacuo. Then the residue was quenched with water, and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, and filtered. After solvent was removed in vacuo, 44 mg of **4-59** (0.093 mmol, 96%) was obtained.; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 6.9 Hz, 2H), 7.41 (t, *J* = 6.9 Hz, 2H), 7.34 (t, *J* = 8.2 Hz, 2H), 7.22 (t, *J* = 8.3 Hz, 1H), 7.17 (ddd, *J* = 7.5, 2.7, 1.4 Hz, 1H), 7.09 (ddd, *J* = 8.2, 2.8, 1.4 Hz, 1H), 7.00 (dd, *J* = 2.8,1.3 Hz, 1H), 6.94 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.90 (dt, *J* = 8.9, 2.0 Hz, 2H), 6.83-6.86 (m, 2H), 6.66 (t, *J* = 2.1 Hz, 1H), 5.05 (s, 2H), 3.74 (s, 3H), 3.13 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 159.5345, 158.5866, 155.2737, 149.6438, 142.7499, 137.3689, 136.8710, 129.7474, 129.5846, 128.6080, 128.0335, 127.4782, 120.7088, 119.9716, 119.4354, 116.4480, 115.9310, 115.6150, 112.2256, 70.4987, 55.5334, 38.1073.

Synthesis of compound **4-60:** *m*-methoxybenzenesulfonyl chloride (77 mg, 0.37 mmol) was added to solution of **4-59** (102 mg, 0.31 mmol) in pyridine (4.5 ml) and stirred at room temperature. After 40 min, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 2:1 to 3:2) and 97 mg of **4-60** (0.21 mmol, 68%) was obtained. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 6.9 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.32-7.36 (m, 3H), 7.24(brs, 1H), 7.16 (t, 1H, *J* = 8.2 Hz), 7.05-7.08 (m, 1H), 6.93 (dt, *J* = 8.9, 2.7 Hz, 2H), 6.86 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.77 (dd, *J* = 7.5, 2.1 Hz, 1H), 6.69 (dd, *J* = 8.2, 1.3 Hz, 1H), 6.64 (brs, 1H), 6.62 (t, *J* = 2.1 Hz, 1H), 5.05 (s, 2H), 3.76 (s, 3H); ^{13}C-NMR (150MHz, $CDCl_3$) δ 159.7547, 159.0940, 155.2354, 149.5767, 139.7722, 137.7232, 136.8423, 130.0442, 128.5793, 127.9952, 127.4590, 120.7854, 119.7322, 119.4354, 115.8831, 115.0884, 114.2075, 111.5936, 110.2436, 70.4413, 55.5334.

Synthesis of compound **4-46: 4-60** (40 mg, 0.087 mmol) was dissolved in ethyl acetate (2.5 ml). Palladium hydroxide on carbon (7 mg) was suspended in the ethyl acetate and stirred under hydrogen atmosphere. After

17.5 h, the reaction mixture was filtered through Celite and evaporated. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl 3:2) and 17 mg of **4-46** (0.048 mmol, 55%) was obtained. The compound was recrystallized with chloroform.; mp: 107°C; ^{1}H-NMR (600 MHz, CD_3OD) δ 7.37 (t, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 7.56 Hz, 1H), 7.19 (t, *J* = 2.1 Hz, 1H), 7.11-7.14 (m, 2H), 6.71-6.77 (m, 5H), 6.60 (dd, *J* = 8.28, 3.42 Hz, 1H), 6.56 (t, *J* = 2.1 Hz, 1H), 3.77 (s, 3H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 159.7547, 159.2760, 152.1619, 149.2129, 139.7243, 137.5795, 130.2932, 130.1112, 121.1301, 119.7513, 119.4354, 116.4002, 115.1076, 114.2937, 111.6607, 110.1000, 55.5717.; Anal. Calcd. For $C_{19}H_{17}NO_4S$: C, 61.28; H, 4.62; N, 3.77. Found C, 61.28; H, 4.62; N, 3.69. ;

Synthesis of compound **4-78:** Under argon atmosphere, aqueous solution of 5M NaOH (1.0 ml, 5 mmol) was added to DMSO (3.5 ml) and stirred. After 15 min, 4-(phenylmethoxy) phenol (480 mg, 2.4 mmol) was added to the mixture and stirred at 50°C. After 20 min, 4-fluoro-2-nitrotoluene **4-77** (310 mg, 2.0 mmol) was added to the reaction and stirred at 50°C for 5 h, then cooled to room temperature. After 18.5 h, the reaction was poured into ice water and filtered. 469 mg of **4-78** (1.34 mmol, 66%) was obtained. Yellow powder. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.40 (d, *J* = 9.6 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 6.8 Hz, 1H), 7.01 (s, 4H), 6.80 (s, 1H), 6.79 (dd, *J* = 8.2, 2.7 Hz, 1H), 5.08 (s, 2H), 2.59 (s, 3H). ; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 162.3782, 156.1546, 148.1405, 143.0850, 137.0817, 136.6508, 128.6463, 128.1197, 127.4877, 127.4494, 121.7812, 119.7513, 116.1895, 114.3224, 70.4892, 21.4568.

Synthesis of compound **4-79: 4-78** (158 mg, 0.453 mmol) was dissolved in THF (4 ml) and methanol (4 ml). Palladium hydroxide on carbon (21 mg) was suspended in the solution and stirred under hydrogen atmosphere. After 15.5 h, the reaction mixture was filtered through Celite and evaporated. 115 mg of **4-79** (0.532 mmol) was obtained. Pale brown solid. ^{1}H-NMR (600 MHz, CD_3OD) δ 6.74 (dt, *J* = 8.9, 2.8 Hz, 2H), 6.67-6.71 (m, 3H), 6.64 (d, *J* = 2.8 Hz, 1H), 6.58 (dd, *J* = 8.2, 2.7 Hz, 1H). ^{13}C-NMR (125 MHz, CD_3OD) δ 153.8056, 152.5896, 151.8236, 141.7701, 125.9238, 121.6151, 120.2364, 117.9576, 117.6033, 116.8756, 17.6617.

Synthesis of compound **4-61:** *M*-Anisoyl chloride (30 mg, 0.18 mmol) was added to a solution of **4-79** (103 mg, 0.49 mmol) in THF (10 ml). The mixture was stirred at room temperature for 45 min, then poured into water, and extracted with ethyl acetate. The organic layer was washed successively with saturated sodium hydrogen carbonate, 1 M hydrochloric acid, water and brine, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 3:2) to give (132 mg, 79%). Colorless prisms (chloroform); mp 78.5-79.5°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.52 (d, *J* = 7.5 Hz, 1H), 7.50 (d, *J* = 2.6 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 8.2 Hz, 1H), 7.14 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.87 (dt, *J* = 9.2, 2.7 Hz, 2H), 6.83 (d, *J* = 2.8 Hz, 1H), 6.78 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.75 (dd, *J* = 8.3, 2.8 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ

169.24, 161.34, 158.98, 155.01, 150.45, 137.69, 136.96, 131.29, 130.75, 129.33, 122.01, 120.72, 120.04, 117.18, 116.06, 113.89, 55.89, 18.35; HRMS Calcd for $C_{21}H_{20}NO_4$ $[M+H]^+$: 350.1387. Found 350.1813. Anal. Calcd. For $C_{21}H_{19}NO_4$: C, 72.19; H, 5.48; N, 4.01; O, 18.32. Found C, 71.94; H, 5.73; N, 4.02.

Synthesis of compound **4-81:** Under argon atmosphere, *m*-(benzyloxy)phenol (667 mg, 3.33 mmol) was added to 5-fluoro-2-nitroanisole **4-80** (514 mg, 3.0 mmol), K_2CO_3 (498 mg, 3.6 mmol) and DMF (4.5 ml) and stirred at room temperature for 3 hours and 80℃ for 3 hours. After cooling to room temperature, ethyl acetate was added. The layers were separated, and the aqueous layer was extracted with additional ethyl acetate. The organic layer was dried with Na_2SO_4 and evaporated to give a crude mixture of products. The crude product was purified by silica-gel chromatography (5:1 hexane-ethyl acetate) and recrystallized with n-hexane/ethyl acetate to afford 412 mg (59% yield) of **4-81**. Columnar crystals of pale yellow. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.91 (d, *J* = 8.9 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.00 (s, 4H), 6.58 (d, *J* = 2.7Hz, 1H), 6.42 (dd, *J* = 9.6, 2.7 Hz, 1H), 5.06 (s, 2H), 3.87 (s, 3H) ; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 164.0634, 156.2504, 155.6088, 147.9299, 136.5934, 113.6539, 128.6463, 128.2920, 128.1484, 127.4973, 121.8099, 116.2087, 107.5244, 101.6359, 70.4892, 56.5196

Synthesis of compound **4-82:** Following the procedure described for the synthesis of **4-79**, compound **4-82** was prepared from **4-81** (174 mg, 0.50 mmol) and Palladium hydroxide on carbon (18 mg) in THF (4 ml) and MeOH (4 ml). A brown solid was isolated in quant (190 mg, 0.51 mmol). ; ^{1}H-NMR (600 MHz, CD_3OD) δ 6.77 (dt, *J* = 8.9, 2.8 Hz, 2H), 6.71 (dt, *J* = 8.9, 2.7 Hz, 2H) , 6.69 (d, *J* = 8.2 Hz, 1H) , 6.52 (d, *J* = 2.8 Hz, 1H) , 6.32 (dd, *J* = 8.2, 2.8 Hz, 1H) ; ^{13}C-NMR (150 MHz, CD_3OD) δ 154.0066 152.5321, 152.2640, 150.0905, 132.5591, 120.4566, 117.0384, 116.0139, 111.3031, 103.5475, 56.0470.

Synthesis of compound **4-64:** Following the procedure described for the synthesis of **4-64**, compound **4-64** was prepared from **4-82** (108 mg, 0.49 mmol), anisole chloride (100mg, 0.59 mmol) in THF (10 ml). **4-64** (144 mg, 0.40 mmol) was obtained in 81 % yield and recrystallized with *n*-hexane/ethyl acetate. **4-64**: Colorless prisms (hexane/ethyl acetate); mp 161-161.5°C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.41 (s, 1H), 9.34 (s, 1H), 7.49 (m, 3H), 7.40 (t, *J* = 7.5 Hz, 1H), 7.12 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.90 (dt, *J* = 9.0, 2.1Hz, 2H), 6.73 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.72 (d, *J* = 2.1 Hz, 1H), 6.38 (dd, *J* = 8.9, 2.7 Hz, 1H), 3.80 (s, 3H), 3.75 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 164.82, 159.22, 156.65, 153.80, 153.54, 148.02, 135.92, 129.57, 126.43, 121.19, 120.75, 119.65, 117.37, 116.22, 112.64, 107.72, 101.70, 55.79, 55.30; HRMS Calcd for $C_{21}H_{20}NO_5$ $[M+H]^+$: 366.1341. Found 366.1332. Anal. Calcd. For $C_{21}H_{19}NO_5 \cdot 1/8\ H_2O$: C, 68.03; H, 5.24; N, 3.83. Found C, 68.60; H, 5.32; N, 3.84.

Synthesis of compound **4-76:** Sodium hydride (144mg, 3.6 mmol) was washed with n-hexane twice. Benzyl

chloride(456 mg, 3.6 mmol) and 5-fluoro-2-nitrophenol phenol **4-75** was added to a suspension of NaH in dimethylformamide (4 ml) at room temperature. After 18 hours, NaI (90 mg, 0.60 mmol) was added and stirred at 60 °C. After 5 hours, the reaction was quenched with water. The reaction mixture was extracted with additional ethyl acetate. The organic layer was dried with Na_2SO_4 and evaporated to give a crude mixture of products. The crude product was purified by silica-gel chromatography (20:1 hexane-ethyl acetate) to afford 624 mg (2.5 mmol, 85%) of **4-76**.; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.9, 6.2 Hz, 1H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 6.81 (dd, *J* = 10.4, 2.8 Hz, 1H), 6.72 (ddd, *J* = 9.0, 7.6, 2.8 Hz, 1H), 5.20 (s, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 165.5762 (d, *J* = 255.65 Hz), 154.1247 (d, *J* = 11.49 Hz), 136.3157, 134.7741, 128.7899, 128.4357, 128.0766 (d, *J* = 10.05 Hz), 126.9324, 107.6105 (d, *J* = 23.12 Hz), 102.7896 (d, *J* = 27.45 Hz), 71.4275.

Synthesis of compound **4-83:** Following the procedure described for the synthesis of **4-81**, compound **4-83** was prepared from **4-12** (542 mg, 2.46 mmol), **4-76** (604 mg, 2.45 mmol) and K_2CO_3 (540 mg, 3.9 mmol) in DMF (3.5 ml). A yellow solid was isolated in 58 % yield (612 mg, 1.43 mmol).; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.9 Hz,1H), 7.29-7.46 (m, 10H), 6.99 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.58 (d, *J* = 1.7 Hz, 1H), 6.46 (dd, *J* = 9.6, 2.7 Hz, 1H), 5.12 (s, 2H), 5.08 (s, 2H) ; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 163.7665, 156.2025, 154.3737, 147.8820, 136.6412, 135.2720, 134.0848, 128.6846, 128.6654, 128.1867, 128.1484, 127.4686, 126.9803,121.7908, 116.2182, 108.0701, 103.0242, 71.0732, 70.4892.

Synthesis of compound **4-84:** Following the procedure described for the synthesis of **2-79**, compound **2-84** was prepared from **8-81** (113 mg, 0.26 mmol) and Palladium hydroxide on carbon (13 mg) in THF (3 ml) and MeOH (3 ml). A brown solid was isolated in quant (190 mg, 0.27 mmol). ^{1}H-NMR (600 MHz, CD_3OD) δ 6.76 (dt, *J* = 8.9, 2.8 Hz, 2H), 6.71 (dt, *J* =8.9, 2.0 Hz, 1H), 6.68 (d, *J* = 8.2 Hz, 1H), 6.36 (d, *J* = 2.7 Hz, 1H), 6.26 (dd, *J* = 8.2, 2.0 Hz, 1H).

Synthesis of compound **4-65:** Following the procedure described for the synthesis of **4-61**, compound **4-65** was prepared from **4-81** (58 mg, 0.27 mmol), anisole chloride (55 mg, 0.32 mmol) in THF (5 ml). **4-65** (57 mg, 0.16 mmol) was obtained in 62 % yield and recrystallized with n-hexane/ethyl acetate. **4-65**: Pale pink prisms (hexane/ethyl acetate); mp 147-148°C; ^{1}H NMR (600 MHz, acetone-d_6) δ 9.45 (br, 1H), 8.40 (br, 1H), 7.57 (m, 3H), 7.43 (t, *J* = 8.2 Hz, 1H), 7.15(dd, *J* = 7.6, 2.7 Hz, 2H), 6.91 (dt, *J* = 9.0, 2.8 Hz, 2H), 6.85 (dt, *J* = 8.9, 2.8 Hz, 2H), 6.50 (d, *J* = 2.7 Hz, 1H), 6.45 (dd, *J* = 9.0, 2.8 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.41, 161.40, 158.76, 155.02, 151.85, 150.38, 137.11, 130.83, 125.73, 122.09, 121.47, 120.47, 118.83, 117.13, 113.81, 109.25, 106.15, 55.90; HRMS Calcd for $C_{20}H_{18}NO_5$ $[M+H]^+$: 352.1185. Found 352.1182.; Anal. Calcd. For $C_{20}H_{17}NO_5 \cdot 1/16$ H_2O: C, 68.15; H, 4.90; N, 3.97. Found C, 68.03; H, 5.05; N, 3.98.

Synthesis of compound **4-86:** Under argon atmosphere, aqueous solution of 5M NaOH (1.0 ml, 5 mmol) was added to DMSO (3.0 ml) and stirred. After 10 min, 4-(phenylmethoxy) phenol (480 mg, 2.4 mmol) was added to the mixture and stirred at 50°C. After 15 min, 3,4-difluoronitrobenzene **4-85** (320 mg, 2.0 mmol) was added to the reaction and stirred at 50°C for 5 h, then cooled to room temperature. After 18 h, the reaction was poured into ice water and filtered. 541 mg of **4-85** (1.59 mmol, 79%) was obtained. Yellow powder; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.07 (dd, *J* = 10.3, 2.8 Hz, 1H), 7.95 (ddd, *J* = 9.6, 2.8, 1.4 Hz, 1H), 7.45 (d, *J* = 6.8 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.05–7.30 (m, 4H), 6.88 (t, *J* = 9.0 Hz, 1H), 5.08 (s, 2H). ^{13}C-NMR (150 MHz, $CDCl_3$) δ 156.4323, 152.3247 (d, *J* = 11.49 Hz), 151.6497 (d, *J* = 251.34 Hz), 147.7958, 142.0222, 136.5455, 128.6654, 128.1580, 127.4877, 121.2833, 120.5556, 116.7161, 116.3044, 113.0251 (d, *J* = 21.56 Hz), 70.5179.

Synthesis of compound **4-87:** A mixture of **4-86** (153 mg, 0.80 mmol) and palladium hydroxide on carbon (36 mg) in THF (4 ml) and methanol (4 ml) was stirred under a hydrogen atmosphere for 20 h, then filtered over Celite. The filtrate evaporated to give **4-87** (115 mg, 67%). Red brown solid; ^{1}H NMR (600 MHz, CD_3OD) δ 6.78 (t, *J* = 8.9 Hz, 2H), 6.70 (m, 4H), 6.53 (dd, *J* = 12.4, 2.8 Hz, 1H), 6.44 (ddd, *J* = 8.9, 2.8, 1.4 Hz, 1H); ^{13}C NMR (150 MHz, CD_3OD) δ 156.37 (d, *J* = 242.73 Hz), 153.59, 153.14, 146.86 (d, *J* = 8.63 Hz), 136.46 (d, *J* = 12.92 Hz), 123.95, 118.27, 116.80, 112.04, 104.48 (d, *J* = 21.54 Hz).

Synthesis of compound **4-66:** *m*-Anisoyl chloride (97 mg, 0.57 mmol) was added to a solution of **4-87** (104 mg, 0.47 mmol) in THF (10 ml). The mixture was stirred at room temperature for 50 min, then poured into water, and extracted with ethyl acetate. The organic layer was washed successively with saturated sodium hydrogen carbonate, 1 M hydrochloric acid, water and brine, dried over sodium sulfate, and evaporated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate 2:1 to 1:1) to give (134 mg, 80%). Colorless prisms (chloroform); mp 160-161°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.73 (dd, *J* = 13.0, 2.8 Hz, 1H), 7.49 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.47 (t, *J* = 2.1 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.36 (dt, *J* = 8.9, 1.7 Hz, 1H), 7.14 (ddd, *J* = 8.3, 2.7, 1.3 Hz, 1H), 6.95 (t, *J* = 9.0 Hz, 1H), 6.68 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.76 (dt, *J* = 8.9, 2.4 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.55, 161.33, 154.71 (d, *J* = 244.16 Hz), 154.67, 151.33, 142.94 (d, *J* = 11.49 Hz), 137.34, 136.04 (d, *J* = 10.065 Hz), 130.75, 121.52, 120.70, 120.01, 118.81, 118.12, 117.10, 113.89, 111.09 (d, *J* = 22.98 Hz), 55.91; HRMS Calcd for $C_{20}H_{17}NO_4F$ $[M+H]^+$: 354.1142. Found 354.1142. Anal. Calcd. For $C_{20}H_{16}NO_4F \cdot 1/4\ H_2O$: C, 67.13; H, 4.65; N, 3.91. Found C, 67.32; H, 4.63; N, 3.87.

Synthesis of compound **4-89:** Under argon atmosphere, *m*-(benzyloxy)phenol (484 mg, 2.42 mmol) was added to **4-88** (420 mg, 2.01 mmol), K_2CO_3 (342 mg, 2.48 mmol) and DMF (3 ml) and stirred at room temperature. After 1.5 hours, *m*-(benzyloxy)phenol (98 mg, 0.49 mmol) was added to the mixture and stirred at room temperature. After 1 hour, 1M HCl was added and filtered. The crude product was purified by silica-gel chromatography (10:1 hexane-ethyl acetate) to afford 618 mg (80% yield) of **4-89**. Yellow powder; ^{1}H-NMR (600

MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.8 Hz, 1H), 8.26 (dd, *J* = 9.7, 2.8 Hz, 1H), 7.43 (d, *J* = 6.9 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.03 (s, 4H), 6.87 (d, *J* = 8.9 Hz, 1H), 5.07 (s, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 161.7175, 156.7770, 147.2979, 141.3424, 136.4402, 128.7612, 128.6750, 128.1867, 127.4686, 123.8063(d, *J* = 4.31 Hz), 122.1786 (q, *J* = 271.46 Hz), 121.9248, 120.1678 (d, *J* = 33.03 Hz), 116.4385, 116.2948, 70.4987.

Synthesis of compound **4-90: 4-89** (191 mg, 0.49 mmol) was dissolved in THF (4 ml) and MeOH (4 ml). Palladium hydroxide on carbon (26 mg) was suspended in the solution and stirred under hydrogen atmosphere. After 16 hours, the reaction mixture was filtered through Celite and evaporated. The product **4-90** (113mg, 0.42 mmol, 86%) was obtained. **4-90**. Pale brown solid; ^{1}H-NMR (600 MHz, CD_3OD) δ 6.98 (d, *J* = 2.7 Hz, 1H), 6.70 (d, *J* = 8.9 Hz, 1H) ; ^{13}C-NMR (150 MHz, CD_3OD) δ 154.3609, 151.9863, 148.3958, 144.7095, 125.0334 (q, *J* = 270.02 Hz), 122.6828 (d, *J* = 30.17 Hz), 121.9024, 120.7151, 120.4087, 116.9809, 113.6298.

Synthesis of compound **4-69:** *m*-anisoyl chloride (85 mg, 0.50 mmol) was added to solution of **4-90** (110 mg, 0.41 mmol) in THF (10 ml) and stirred at room temperature. After 60 min, *m*-anisoyl chloride (19 mg, 0.11 mmol) was added to solution and stirred at room temperature. After 35 min, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue was washed with dichloromethane and 185 mg of **4-69** was obtained. The compound was recrystallized with n-hexane/ethyl acetate. Colorless prisms (hexane/ethyl acetate); mp 189°C; ^{1}H NMR (600 MHz, CD_3OD) δ 8.09 (d, *J* = 2.8 Hz, 2H), 7.78 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.50 (dt, *J* = 8.9, 1.4 Hz, 1H), 7.47 (dd, *J* = 2.8, 1.2 Hz, 1H), 7.41 (t, *J* = 8.2 Hz, 1H), 7.13 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.89 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 1H), 6.50 (dt, *J* = 8.9, 2.0 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.61, 161.35, 155.57, 154.43, 149.98, 137.19, 134.37, 130.77, 127.24, 124.82 (q, *J* = 270.00 Hz), 121.98, 121.24 (d, *J* = 31.59 Hz), 120.87 (d, *J* = 5.75 Hz), 119.25, 118.91, 117.37, 113.87, 55.92; HRMS Calcd for $C_{21}H_{17}NO_4F_3$ $[M+H]^+$: 404.1110. Found 404.1108. Anal. Calcd. For $C_{21}H_{16}NO_4F_3 \cdot 1/8\ H_2O$: C, 62.19; H, 4.04; N, 3.45. Found C, 62.14; H, 4.08; N, 3.45.

Synthesis of compound **4-92:** Following the procedure described for the synthesis of **4-78**, compound **4-92** was prepared from **4-91** (354 mg, 2.0 mmol), **4-12** (481 mg, 2.4 mmol) and aqueous solution of 5M NaOH (1.0 ml, 5 mmol) in DMSO (3 ml). A yellow solid was isolated in 73 % yield (520 mg, 1.5 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.91-7.95 (m, 2H), 7.42 (d, *J* = 6.8 Hz, 2H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 6.93 (s, 4H), 5.03 (s, 2H) ; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 155.3216, 155.2402 (d, *J* = 254.22 Hz), 151.0225, 143.0946, 138.6423(t, *J* = 14.36 Hz), 136.6987, 128.6176, 128.0718, 127.4686, 117.1087, 115.8161, 109.1569 (dd, *J* = 21.54, 7.19 Hz), 70.5466.

Synthesis of compound **4-71: 4-92** (160 mg, 0.45 mmol) was dissolved in THF (4 ml) and methanol (4 ml). Palladium on carbon (20 mg) was suspended in the solution and stirred under hydrogen atmosphere. After 17 h, the reaction mixture was filtered through Celite and evaporated. 135 mg of mixture include **4-93** was obtained. *m*-anisoyl chloride (107 mg, 0.63 mmol) was added to solution of mixture (include **4-93**) in THF (10 ml) and stirred at room temperature. After 1 hour, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue was washed with dichloromethane and 95.7 mg of filtrate was obtained. The filtrate (65.7 mg) was purified by by silica-gel chromatography (9:1 chloroform-ethyl acetate) and preparative thin-layer chromatography (dichloromethane/acetone 9:1) to give 13 mg of **4-71** (0.036 mmol, 12%) was obtained.Colorless prisms (chloroform); mp 169 °C; ^{1}H NMR (600 MHz, acetone-d_6) δ 7.71 (d, *J* = 10.3 Hz, 1H), 7.54 (dd, *J* = 7.6, 2.7 Hz, 1H), 7.51(t, J = 2.1 Hz, 1H), 7.43 (t, J = 7.9 Hz, 1H), 6.95 (m, 4H), 3.00 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.61, 161.36, 158.19 (d, *J* = 7.19 Hz), 156.53 (d, *J* = 5.75 Hz), 154.08, 152.75, 137.48 (t, *J* = 12.93 Hz), 137.09, 130.81, 129.44 (t, *J* = 14.37 Hz), 120.74, 119.00, 117.00 (d, *J* = 37.35 Hz), 113.96, 105.64 (d, *J* = 27.29 Hz), 55.94; HRMS Calcd for $C_{20}H_{16}NO_4F_2$ $[M+H]^+$: 372.1047. Found 372.1046. Anal. Calcd. For $C_{20}H_{15}NO_4F_2 \cdot 1/4\ H_2O$: C, 63.91; H, 4.16; N, 3.73. Found C, 63.90; H, 4.29; N, 3.81.

Synthesis of compound **4-95:** Sodium hydride (24mg, 0.63 mmol) was washed with n-hexane twice. 4-(phenylmethoxy) phenol was added to a suspension of NaH in dimethylformamide (1 ml) at 0°C. After 30 min, 2-chloro-3-methyl-5-nitropyridine (81mg, 0.47 mmol) was added and stirred at room temperature. After 30 min, the reaction was quenched with saturated aqueous ammonium chloride solution. The reaction mixture was extracted with additional ethyl acetate. The organic layer was dried with Na_2SO_4 and evaporated to give a crude mixture of products. The crude product was purified by silica-gel chromatography (19:1 to 9:1 hexane-ethyl acetate) to afford 122 mg (0.38 mmol, 81%) of **4-95**. ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.82 (d, *J* = 2.7 Hz, 1H), 8.28 (d, *J* = 2.7 Hz, 1H), 7.43 (d, *J* = 6.9 Hz, 2H), 7.35 (td, *J* = 6.2, 1.4 Hz, 2H), 7.33 (tt, *J* = 6.9, 1.4 Hz, 1H), 7.0-7.1 (m, 4H), 5.06 (s, 2H), 2.43 (s, 3H) ; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 165.5283, 156.3940, 146.4745, 141.9265, 140.0881, 136.7466, 134.1518, 128.6271, 128.0718, 127.5165, 122.5089, 122.2312, 115.6821, 70.4126, 16.0949.

Synthesis of compound **4-96:** Following the procedure described for the synthesis of **4-79**, compound **4-96** was prepared from **4-95** (56 mg, 0.17 mmol) and Palladium hydroxide on carbon (8 mg) in THF (1.5 ml) and MeOH (1.5 ml). A brown solid was obtained in quant (47 mg, 0.22 mmol). ^{1}H-NMR (600 MHz, acetone-d_6) δ 7.40 (d, *J* = 2.8 Hz, 1H), 6.99 (d, *J* = 2.7 Hz, 1H), 6.81 (dt, *J* = 8.9, 2.8 Hz, 2H), 6.76 (dt, *J* = 8.9, 2.8 Hz, 2H), 4.48 (brs, 1H), 3.06 (brs, 1H) ; ^{13}C-NMR (150 MHz, CD_3COCD_3) δ 154.7125, 153.8316, 149.8198, 141.8919, 130.8618, 127.2808,

122.6945, 121.3731, 116.2602, 16.0219.

Synthesis of compound **4-73:** Following the procedure described for the synthesis of **4-61**, compound **4-73** was prepared from **4-96** (47 mg, 0.22 mmol), anisole chloride (35 mg, 0.21 mmol) in THF (5 ml). **4-73** (48 mg, 0.14 mmol) was obtained in 82 % yield and recrystallized with *n*-hexane/ethyl acetate. Colorless prism. mp: 207-207.5 °C. ^{1}H-NMR (600 MHz, DMSO-d6) δ 10.25 (s, 1H), 9.28 (s, 1H), 8.21 (d, *J* = 2.1 Hz, 1H), 8.03 (d, *J* = 2.8 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.48 (s, 1H), 7.44 (t, *J* = 8.2 Hz, 1H), 7.16 (dd, *J* = 8.2, 2.7 Hz, 1H), 6.88 (dt, *J* = 8.9, 2.0 Hz, 2H), 6.74 (dt, *J* = 8.9, 1.7 Hz, 2H), 3.83 (s, 3H), 2.29 (s, 3H) ; ^{13}C-NMR (150 MHz, DMSO-*d6*) δ 165.1688, 159.1941, 157.9398, 153.8131, 146.4310, 136.4062, 135.7647, 132.9114, 131.1496, 129.6081, 122.0440, 120.5025, 119.7940, 117.4290, 115.6098, 112.8714, 55.3462, 15.7546.; Anal. Calcd. For $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found C, 68.46; H, 5.19; N, 7.95. ; HRMS: Calcd for $C_{20}H_{19}N_2O_4$ $[M+H]^+$: 351.1345. Found 351.1354.

Synthesis of compound **4-98:** Under argon atmosphere, aqueous solution of 5M NaOH (1.0 ml, 5 mmol) was added to DMSO (3 ml) and stirred. After 20 min, 4-(phenylmethoxy) phenol (480 mg, 2.4 mmol) was added to the mixture and stirred at 50°C. After 15 min, 3-chloro-4-fluoronitrotbenzene (351 mg, 2.0 mmol) was added to the reaction and stirred at 50°C for 5 h, then cooled to room temperature. After 18 h, the reaction was poured into ice water and filtered. 469 mg of **4-98** (1.6 mmol, 80%) was obtained. Colorless powder; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.8 Hz, 1H), 8.02 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.45 (d, *J* = 6.8 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.04 (s, 4H), 6.80 (d, *J* = 9.7 Hz, 1H), 5.09 (s, 2H).; ^{13}C-NMR (150 MHz, $CDCl_3$) δ 159.8122, 156.5472, 147.7097, 142.1659, 136.5168, 128.6559, 128.1580, 127.4782, 126.4441, 123.8781, 123.5812, 121.6663, 116.3619, 115.5959, 70.4987.

Synthesis of compound **4-67: 4-98** (141mg, 0.38 mmol) was dissolved in THF (3 ml) and methanol (3 ml). Palladium on carbon (15 mg) was suspended in the solution and stirred under hydrogen atmosphere. After 22 h, the reaction mixture was filtered through Celite and evaporated. 115 mg of residue include **4-99** was obtained. *m*-anisoyl chloride (78 mg, 0.46 mmol) was added to solution of residue (include **4-99**) in THF (6 ml) and stirred at room temperature. After 40 min, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue was washed with dichloromethane and 89mg of filtrate was obtained. The filtrate (30mg) was purified by preparative thin-layer chromatography (dichloromethane/acetone 24:1) to give 20 mg of **4-67** (0.054 mmol, 42%) was obtained and recrystallized with *n*-hexane/ethyl acetate. Colorless needles (hexane/ethyl acetate); mp: 187-188 °C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.92 (d, *J* = 2.8 Hz, 1H), 7.48 (m, 3H), 7.41

(t, *J* = 7.5 Hz, 1H), 7.13 (dd, *J* = 8.2, 2.7 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 1H), 6.82 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.77 (dt, *J* = 8.9, 2.7 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 167.22, 160.00, 153.58, 150.41, 149.43, 135.97, 134.39, 129.41, 124.24, 122.93, 120.56, 119.37, 118.88, 117.49, 115.87, 112.54, 54.58; HRMS Calcd for $C_{20}H_{17}NO_4Cl$ $[M+H]^+$: 370.0846. Found 370.0844. Anal. Calcd. For $C_{20}H_{16}NO_4Cl{\cdot}1/8\ H_2O$: C, 67.57; H, 4.40; N, 3.76. Found C, 64.62; H, 4.51; N, 3.82.

Synthesis of compound **4-104:** Under argon atmosphere, **4-102** (346 mg, 2.0 mmol) was added to **4-103** (250 mg, 2.1 mmol), 5M NaOH in DMF (4 ml) and stirred at 50 °C. After 2 hours, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue was purified by silica-gel chromatography (5:1 to 2:1 n-hexane: ethyl acetate) to afford 239 mg (0.69 mmol, 35 %) of **4-104** and 36 mg (0.085 mmol, 9%) of **4-105**. **4-104**; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.94 (d, 1H, *J*= 8.9 Hz), 6.98 (d, *J* = 2.8 Hz, 1H), 6.95 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.88 (dt, *J* = 8.9, 2.8 Hz, 2H), 6.85 (d, *J* = 2.0 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ 162.3686, 153.3013, 147.4990, 141.6201, 129.6612, 127.9856, 122.0589, 119.0428, 116.9076, 115.0214. **4-105**; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 7.99 (d,2H, *J* = 9.7 Hz), 7.15 (s, 4H), 7.08 (d, *J* = 2.0 Hz, 2H), 6.95 (dd, *J* = 8.9, 2.8 Hz, 2H).

Synthesis of compound **4-63: 4-104** (71 mg, 0.27 mmol) was dissolved in methanol (5 ml). Palladium on carbon (7 mg) was suspended in the solution and stirred under hydrogen atmosphere. After 40 min, the reaction mixture was filtered through Celite and evaporated. 61 mg of product (include **4-106**) was obtained. *M*-anisoyl chloride (55 mg, 0.32 mmol) was added to solution of crude product (**4-106**) in THF (5 ml) and stirred at room temperature. After 30 min, the reacstion was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 7:3 to 2:1) to give 37 mg of **4-63** (0.037 mmol, 14 %, 2 steps) was obtained and recrystallized with chloroform.; mp: 176-177 °C; **4-63**: Colorless prisms (chloroform); mp 176-176.5°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.54 (d, *J* = 9.2 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.50 (br, 1H), 7.42(t, *J* = 7.7 Hz, 1H), 7.15 (dd, *J* = 8.2, 2.7 Hz, 1H), 7.00 (d, *J* = 2.8 Hz, 1H), 6.92 (dt, *J* = 9.0, 2.8 Hz, 2H), 6.90 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.82 (dt, *J* = 8.9, 2.8 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 167.65, 160.04, 158.04, 154.34, 148.22, 135.36, 130.68, 129.48, 128.69, 121.059, 119.40, 117.70, 117.47, 116.06, 115.63, 112.57, 54.56; HRMS Calcd for $C_{20}H_{17}NO_4Cl$ $[M+H]^+$: 370.0846. Found 370.0844. Anal. Calcd. For $C_{20}H_{16}NO_4Cl{\cdot}1/8\ H_2O$: C, 64.57; H, 4.40; N, 3.76. Found C, 64.51; H, 4.58; N, 3.69.

Synthesis of compound **4-108:** Following the procedure described for the synthesis of **4-104**, compound **4-108**

was prepared from **4-107** (440 mg, 2.0 mmol), **4-103** (264 mg, 2.4 mmol) and aqueous solution of 5M NaOH (1.0 ml, 5 mmol) in DMSO (4.5 ml). A yellow solid was isolated in 53 % yield (330 mg, 1.1 mmol). ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.52 (d, *J* = 2.4 Hz, 2H), 8.05 (dd, *J* = 8.9, 2.8 Hz, 2H), 6.98 (d, *J* = 8.2 Hz, 2H), 6.89 (d, *J* = 8.3 Hz, 2H), 6.75 (d, *J* = 8.3 Hz, 1H), 4.85 (brs, 1H).

Synthesis of compound **4-110:** A solution of $CuSO_4 \cdot 5H_2O$ (172 mg, 0.69 mmol) in methanol (3 ml) was added to a solution of NaBH4 (65 mg, 1.72 mmol) and **4-108** (107 mg, 0.35 mmol) in dichloromethane (5 ml) and methanol (0.5 ml) and stirred at 0°C. After 2.5 hours, $NaBH_4$ (32 mg, 0.85 mmol) was added to the reaction and stirred at 0°C for 1 h, then quenched with water. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The crude product was dissolved in ethyl acetate. The organic layer was washed with water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue was washed with dichloromethane and 41 mg of **4-110** (43%) was obtained. Ocher powder. ^{1}H-NMR (600 MHz, CD_3OD) δ 6.96 (d, *J* = 2.1 Hz, 1H), 6.72(d, 1H, *J* = 8.9 Hz), 6.66-6.70 (m, 4H), 6.63 (dd, 1H, *J* = 8.9, 2.8 Hz). ^{13}C-NMR (150 MHz, CD_3OD) δ 153.7290, 152.5800, 146.7968, 146.5287, 122.8886, 120.4853, 118.9533, 116.8661, 116.5692, 116.4065.

Synthesis of compound **4-68:** *m*-anisoyl chloride (27 mg, 0.16 mmol) was added to solution of **4-110** (37 mg, 0.13 mmol) in THF (3 ml) and stirred at room temperature. After 45 min, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue was purified by silica-gel chromatography (10:1 chloroform/acetone) to afford 41 mg (74 %) of **4-68**. Colorless prisms (hexane/ethyl acetate); mp 192-193°C; ^{1}H NMR (600 MHz, CD_3OD) δ 8.07 (d, *J* = 2.2 Hz, 1H), 7.55 (dd, *J* = 8.9, 2.8 Hz, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.46 (t, *J* = 2.1 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.13 (dq, *J* = 6.9, 1.4 Hz, 1H), 6.83 (m, 3H), 6.77 (dt, *J* = 9.0, 2.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.56, 161.34, 154.96, 152.99, 150.75, 137.31, 135.91, 130.76, 127.29, 122.64, 120.86, 120.72, 119.91, 118.84, 117.22, 114.35, 113.88, 55.92; HRMS Calcd for $C_{20}H_{17}NO_4Br$ $[M+H]^+$: 414.0341. Found 414.0342. Anal. Calcd. For $C_{20}H_{16}NO_4Br$: C, 57.99; H, 3.89; N, 3.38. Found C, 57.74; H, 3.94; N, 3.24.

Synthesis of compound **4-112:** Under argon atmosphere, aqueous solution of 5M NaOH (1.0 ml, 5 mmol) was added to DMSO (3 ml) and stirred. After 15 min, hydroquinone **4-103** (264 mg, 2.40 mmol) was added to the mixture and stirred at 50°C. After 15 min, **4-111** (333 mg, 2.0 mmol) was added to the reaction and stirred at 50°C. After 2.5 h, the reaction was poured into ice water and filtered. The crude product was purified by silica-gel chromatography (2:1n-hexane:acetone) to afford **4-112** (377 mg, 74 % yield). yellow powder; ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.54 (d, 1H, *J* = 2.8 Hz), 8.28 (dd, 1H, *J* = 9.6, 2.8 Hz), 7.00 (dt, 2H, *J* = 9.0, 2.8 Hz), 6.92 (dt,

2H, *J* = 9.0, 2.8 Hz), 6.85 (d, 1H, *J* = 9.6 Hz), 5.1 (brs, 1H).

Synthesis of compound **4-113:** Following the procedure described for the synthesis of **4-110**, compound **4-113** was prepared from **4-112** (121 mg, 0.47 mmol), $NaBH_4$ (178mg,4.7mmol) and solution of $CuSO_4 \cdot 5H_2O$ (235 mg, 0.94 mmol) in methanol (3 ml) in dichloromethane (5 ml). A pale brown solid was isolated in 81% yield (86 mg, 0.38 mmol). ^{1}H-NMR (600 MHz, CD_3OD) δ 6.93 (d, *J* = 2.8 Hz, 1H), 6.88 (dd, *J* = 8.9, 2.8 Hz, 1H), 6.83 (dt, *J* = 8.9, 2.0 Hz, 2H), 6.76 (dt, *J* = 8.9, 2.8 Hz, 2H), 6.69(d, *J* = 8.9 Hz, 1H); ^{13}C-NMR (150 MHz, CD_3OD) δ 155.0407, 152.9917, 150.9140, 145.3319, 122.4098, 120.8779, 120.3225, 118.9629, 117.4214, 117.2012, 104.8880.

Synthesis of compound **4-70:** Following the procedure described for the synthesis of **4-61**, compound **4-70** was prepared from **4-113** (85 mg, 0.38 mmol), anisole chloride (76mg, 0.45 mmol) in THF (8 ml). the residue(129mg) was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 3:2 to 2:3) to give 120 mg of clude (include **4-70**). The crude (76 mg) was purified by flash chromatography and 33 mg of **4-70** (0.091 mmol, 39 %) was obtained. The compound was recrystallized with acetonitrile. : Colorless prisms (acetonitrile); mp 229-230°C; ^{1}H NMR (600 MHz, acetone-d_6) δ 9.74 (br, 1H), 8.29 (t, *J* = 3.1 Hz, 1H), 7.94 (dt, *J* = 8.9, 2.8 Hz, 1H), 7.55(dd, *J* = 6.9, 2.1 Hz, 1H), 7.41 (t, *J* = 8.2 Hz, 1H), 7.14 (ddd, *J* = 8.2, 2.8, 1.4 Hz, 1H), 7.01 (dt, *J* = 9.0, 2.1 Hz, 1H), 6.91 (dt, *J* = 9.0, 2.8 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 165.29, 159.21, 156.02, 154.67, 146.87, 135.66, 133.99, 129.67, 127.34, 124.67, 121.07, 119.84, 117.55, 116.02, 112.93, 101.50, 55.37; HRMS: Calcd for $C_{21}H_{17}N_2O_4$ [M+H]+: 361.1188. Found 361.1187. ; Anal. Calcd. For $C_{21}H_{16}N_2O_4 \cdot 1/4\ H_2O$: C, 69.13; H, 4.56; N, 7.68. Found C, 69.19; H, 4.57; N, 7.81.

Synthesis of compound **4-115:** Following the procedure described for the synthesis of **4-112**, compound **4-115** was prepared from **4-74** (349 mg, 2.0 mmol), **4-103** (264mg, 2.4 mmol) and aqueous solution of 5M NaOH (1.0 ml, 5 mmol) in DMSO (4.5 ml). A yellow solid was isolated in 46% yield (307 mg, 0.91 mmol). ^{1}H-NMR (600 MHz, acetone-d_6) δ 8.40 (s, 2H), 6.80 (dt, *J* = 9.6, 2.8 Hz, 2H), 6.76 (dt, *J* = 9.0, 2.8 Hz, 2H) ; ^{13}C-NMR (150 MHz, acetone-d_6) δ 154.3008, 154.2051, 153.8508, 150.2986, 145.6644, 131.2831, 125.7775, 116.9305.

Synthesis of compound **4-72:** A solution of $CuSO_4 \cdot 5H_2O$ (250 mg, 1.0 mmol) in methanol (5 ml) was added to a solution of NaBH4 (96 mg, 2.54 mmol) and **4-115** (150 mg, 0.50 mmol) in dichloromethane (5 ml) and stirred at 0°C. After 2.5 hours, quenched with water and the reaction mixture was filtered through Celite. The organic layer was washed with water and brine, dried with sodium sulfate, and evaporated. The crude product (104 mg, include **4-116**) was obtained. *M*-anisoyl chloride (55 mg, 0.32 mmol) was added to solution of the crude product **(4-116)** in THF (10 ml) and stirred at room temperature. After 40 min, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a

sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue (129mg) was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 3:1 to 2:1) to give 29 mg of starting matelial **4-115** (0.10 mmol, 10%), 7mg of **4-72** and 67 mg of mixture (include **4-72**). The mixture was purified by preparative TLC and 29mg of **4-72** (0.072 mmol, 14 %) was obtained. The compound was recrystallized with chloroform. **4-72**: Colorless prisms (chloroform); mp 168-169°C; ^{1}H NMR (600 MHz, acetone-d_6) δ 9.78 (br, 1H), 8.22 (br, 1H), 8.97 (d, *J* = 2.0 Hz, 2H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 2.1 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.16 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.78 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.70 (dt, *J* = 9.6, 2.8 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 168.62, 161.37, 153.73, 151.73, 145.13, 138.16, 137.02, 130.82, 122.28, 120.79, 119.07, 116.89, 116.73, 113.98, 55.95; HRMS Calcd for $C_{20}H_{16}NO_4Cl_2$ $[M+H]^+$:404.0456. Found 404.0459. Anal. Calcd. For $C_{20}H_{15}NO_4Cl_2$: C, 59.42; H, 3.74; N, 3.46. Found C, 59.17; H, 3.85; N, 3.26.

Synthesis of compound **4-119**, **4-120:** Under argon atmosphere, m-(benzyloxy)phenol (414 mg, 2.1 mmol) was added to **4-117** (327 mg, 2.1 mmol), K_2CO_3 (342 mg, 2.7 mmol) and DMF (3 ml) and stirred at room temperature. After 3.5 hours, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (eluent: *n*-hexane/ethyl acetate 15:1) to afford mixture of **4-119** and **4-120**（389mg,1.77mmol, 86%, **4-119** : **4-120** = 1:1）. **4-119**: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.06 (t, *J* = 8.9 Hz, 3H), 7.44 (d, *J* = 7.5 Hz, 2H), 7.39 (t, J=6.9, 2H), 7.34 (t, *J* = 6.9 Hz, 1H), 7.01-7.02 (m, 4H), 6.76 (ddd, J=9.6, 2.7, 1.4 Hz, 1H), 6.69 (dd, *J* = 12.4, 2.8 Hz, 1H), 5.07 (s, 2H) ; **4-120**: ^{1}H-NMR (600 MHz, $CDCl_3$) δ 8.01(dd, *J*= 8.9, 6.2 Hz), 7.43 (d, *J* = 6.9 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 6.9 Hz, 1H), 6.9-7.1 (m, 4H), 6.78 (ddd, *J* = 9.3, 6.9, 2.7 Hz), 6.55 (dd, *J* = 10.8, 2.7 Hz), 5.06 (s,2H).

Synthesis of compound **4-62:** The mixture (**4-119** and **4-120**, 59 mg) was dissolved in THF (3 ml) and methanol (3 ml). Palladium hydroxide on carbon (9 mg) was suspended in the solution and stirred under hydrogen atmosphere. After 17.5 h, the reaction mixture was filtered through Celite and evaporated. The mixture of **4-121** and **4-122** (35 mg) was obtained. Following the procedure described for the synthesis of **4-61**, compound **4-62** was prepared from mixture (**4-121** and **4-122**, 35 mg), anisole chloride (44 mg, 0.26 mmol) in THF (5 ml). The crude product was washed with dichloromethane and purified by silica gel column chromatography (*n*-hexane/ethyl acetate 2:1) to afford **4-62** (12.5 mg, 0.035 mmol, 13 % from **4-117**) and **4-123** (8.3 mg, 0.024 mmol, 8 % from **4-117**). **4-62**: Pale brown prisms (hexane/ethyl acetate); mp: 156-157°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.51 (d, *J* = 2.7 Hz, 1H), 7.50 (s, 1H), 7.48 (d, *J* = 2.8 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 6.91 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.81 (dt, *J* = 8.9, 2.4 Hz, 2H), 6.73 (m, 2H) 3.86 (s, 3H); ^{13}C NMR (150 MHz, CD_3OD) δ 169.06, 161.29,

159.59 (d, *J* = 10.05 Hz), 159.06, 157.42, 155.50, 149.61, 136.57, 130.83, 129.03, 122.42, 120.83, 120.52 (d, *J* = 12.93 Hz), 119.07, 117.40, 113.90, 113.51, 105.84 (d, *J* = 22.98 Hz), 55.95; HRMS Calcd for $C_{20}H_{17}NO_4F$ $[M+H]^+$: 354.1142. Found 354.1141. Anal. Calcd. For $C_{20}H_{16}NO_4F \cdot 1/8\ H_2O$: C, 64.30; H, 4.11; N, 3.75. Found C, 64.11; H, 4.23; N, 3.73. **4-123**: Colorless prisms (hexane/ethyl acetate); mp: 146-147°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.77 (dd, *J* = 8.9, 6.2 Hz, 1H), 7.42 (d, *J* = 8.3 Hz, 1H), 7.35-7.40 (m, 2H), 7.10 (ddd, *J* = 8.2, 2.3, 1.4 Hz, 1H), 6.93 (d, *J* = 6.9 Hz, 2H), 6.84 (td, J = 8.9, 3.4 Hz, 1H), 6.79 (dt, J = 6.2, 2.0 Hz, 2H), 6.53 (dd, J = 10.3, 2.8 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (150 MHz, CD_3OD) δ 168.81, 162.93, 161.31, 155.66, 154.15, 149.45, 137.03, 130.76, 128.14, 125.29, 121.83, 120.61, 119.00, 117.36, 113.70, 109.82 (d, *J* = 22.98 Hz), 105.52 (s, *J* = 27.29 Hz), 55.88.

Synthesis of compound **4-73:** Under argon atmosphere, *m*-(benzyloxy)phenol (602 mg, 3.0 mmol) was added to **4-124** (533 mg, 3.0 mmol), K_2CO_3 (499 mg, 3.6 mmol) and DMF (5 ml) and stirred at room temperature. After 3 hours, the reaction was poured into ice water and filtered. The crude product was purified by silica-gel chromatography (5:1 n-hexane:acetone) to afford **4-125** as a mixture (84 mg).The mixture (include **4-125**, 59 mg) was dissolved in THF (3 ml) and methanol (3 ml). Palladium hydroxide on carbon (9 mg) was suspended in the solution and stirred under hydrogen atmosphere. After 17.5 h, the reaction mixture was filtered through Celite and evaporated. The mixture of **4-127** (35 mg) was obtained. Following the procedure described for the synthesis of **4-61**, compound **4-73** was prepared from mixture of **4-127** (35 mg), anisole chloride (44mg, 0.26 mmol) in THF (5 ml). The crude product was washed with dichloromethane and purified by preparative TLC to afford **4-73** (30 mg, 0.082 mmol, 3.9 % from **4-124**). The compound was recrystallized with n-hexane/ethyl acetate. **4-124**: Pale brown prisms (hexane/ethyl acetate); mp 141-141.5°C; ^{1}H NMR (600 MHz, CD_3OD) δ 7.52 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.49 (t, *J* = 2.1 Hz, 1H), 7.42 (t, *J* = 8.2 Hz, 1H), 7.28 (td, *J* = 8.9, 2.1 Hz, 1H), 7.15 (dd, *J* = 8.2, 2.7 Hz, 1H), 6.91 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.79 (dt, *J* = 8.9, 3.1 Hz, 2H), 6.73 (td, *J* = 8.9, 2.8 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (150 MHz, acetone-d_6) δ 166.25 (d, *J* = 10.05 Hz), 160.70, 155.11, 146.00 (dt, *J* = 247.04, 10.82 Hz), 144.99, 143.29 (dd, *J* = 245.58, 12.93 Hz), 136.39, 130.45, 123.20 (t, *J* = 10.07 Hz), 120.87 (d, *J* = 15.80 Hz), 120.69, 120.53, 118.63, 117.08 (d, *J* = 12.92 Hz), 114.26, 113.58, 55.72; HRMS Calcd for $C_{20}H_{16}NO_4F_2$ $[M+H]^+$: 372.1047. Found 372.1058. Anal. Calcd. For $C_{20}H_{16}NO_4F \cdot 1/8\ H_2O$: C, 64.30; H, 4.11; N, 3.75. Found C, 64.11; H, 4.23; N, 3.73.

Synthesis of compound **4-131:** Under argon atmosphere, **4-5** (676 mg, 4.8 mmoll) was added to **4-130** (801 mg, 4.0 mmol), triethylamine (489 mg) and dry DMF (5 ml) and stirred at 85 °C. After 87 hours, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (n-hexane/ethyl acetate 4:1 to 2:1) to give 296 mg (0.92 mmol, 23%) of **4-131**. ^{1}H NMR (600

MHz, $CDCl_3$) δ 8.07 (dt, *J* = 9.6, 2.0 Hz, 2H), 7.43 (d, *J* = 6.8 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.13 (brd, *J* = 8.9 Hz, 2H), 6.99 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.75 (d, *J* = 8.9 Hz, 2H), 5.07 (s, 2H).

Synthesis of compound **4-132:** Sodium hydride (60 mg, 1.5 mmol) was washed with *n*-hexane twice. A solution of **4-131** (162 mg, 0.51 mmol) in dry DMF (2 ml) was added to a suspension of sodium hydride in dry DMF (3 ml) at 0°C, and the mixture was stirred at room temperature for 30 min. Iodomethane (212 mg, 1.5 mmol) in dry DMF (1 ml) was added at 0°C, and stirring was continued at room temperature for 30 min. Remaining iodomethane was removed in vacuo. The residue was poured into water and filtered to afford 140 mg of **4-132** (0.42 mmil, 83 %). Yellow powder. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.03 (dt, *J* = 8.9, 2.1 Hz, 2H), 7.44 (d, *J* = 6.9 Hz, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.34 (t, *J* = 6.9 Hz, 1H), 7.12 (dt, *J* = 8.9, 2.0 Hz, 2H), 7.03 (dt, *J* = 8.9, 2.0 Hz, 2H), 6.58 (dt, *J* = 7.6, 2.1 Hz, 2H), 5.08 (s, 2H), 3.34 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 157.50, 154.18, 139.36, 137.82, 136.58, 128.68, 128.23, 128.17, 127.50, 125.82, 116.30, 111.86, 70.32, 40.67.

Synthesis of compound **4-134: 4-132** (99 mg, 0.30 mmol) was dissolved in THF (1.5 ml) and methanol (1.5 ml). Palladium hydroxide on carbon (13 mg) was suspended in the solution and stirred under hydrogen atmosphere. After 18 h, the reaction mixture was filtered through Celite and evaporated. 76 mg of residue include **4-133** was obtained. *M*-anisoyl chloride (50 mg, 0.29 mmol) was added to solution of residue (76mg, include **4-132**) in THF (5 ml) and stirred at room temperature. After 40 min, the reaction was quenched with water and diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of a sodium hydrogen carbonate, aqueous solution of 1M HCl, water and brine, dried with sodium sulfate and filtered. After solvent was removed in vacuo, the residue was purified by silica gel column chromatography (hexane/ethyl acetate 3:1 to 3:1) to give **4-132** (8 mg, 8% from **4-132**). Pale brown columnar (ethyl acetate); mp 167.5-168°C; ^{1}H NMR (600 MHz, acetone-d_6) δ 7.60 (d, *J* = 9.0 Hz, 2H), 7.53 (d, *J* = 8.9 Hz, 2H), 7.50 (t, *J* = 7.9 Hz, 1H), 7.08 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.98 (dt, *J* = 8.9, 2.0 Hz, 2H), 6.83 (dt, *J* = 8.9, 2.1 Hz, 2H), 6.74 (dt, *J* = 8.9, 2.0 Hz, 2H), 3.84 (s, 3H), 3.20 (s, 3H). ^{13}C NMR (150 MHz, acetone-d_6) δ 165.47, 160.65, 154.97, 147.60, 142.33, 137.94, 131.45, 130.22, 126.83, 122.21, 122.11, 120.21, 117.82, 116.90, 116.54, 113.39, 55.67, 40.95.

HL-60 Cell Differentiation Assay

HL-60 cells were cultured in RPMI-1640 medium supplemented with 5% FBS and penicillin G and streptomycin at 37 °C under 5% CO_2 in air. The cells were diluted to 8.0×10^4 cell/mL with RPMI-1640 (5% FBS), and ethanol solution of a test compound was added to give 10^{-9} to 10^{-6} M final concentration. Control cells were treated with the same volume of ethanol alone. 1α,25$(OH)_2D_3$ was always assayed at the same time as a positive control. The cells were incubated at 37 °C under 5% CO_2 in air for 4 days. The percentage of differentiated cells was determined by nitro-blue tetrazolium (NBT) reduction assay. Cells were incubated at 37 °C for 20 min in RPMI-1640 (5% FBS) and an equal volume of phosphate-buffered saline (PBS) containing

NBT (0.2%) and 12-*O*-tetradecanoylphorbol 13-acetate (TPA; 200 ng/mL). The percentage of cells containing blue-black formazan was determined in a minimum of 200 cells.

SC-3 Growth Inhibition Assay

SC-3 cells were cultured in MEMα (Wako Co.) supplemented with 2% FBS (fetal bovine serum) and 1 nM DHT at 37°C in an incubator under an atmosphere of 5% CO_2 in humidified air. All experiments were performed in triplicate or more. Cells were trypsinized and diluted to 20,000 cells/mL with MEMα supplemented with 2% charcoal-stripped FBS. This cell suspension was seeded in 96-well plates at a volume of 100 µL/well and the plates were incubated for 24 h. Then, 10 µL of medium was removed from each well, and replaced with 10 µL of drug solution supplemented with serial dilutions of test compound or DMSO as a dilution control in the presence of 1 nM DHT. The plates were incubated at 37°C under 5% CO_2 in air for 3 days, and the cell number was determined using a Cell Counting Kit-8 (Dojindo). A 10 µL aliquot of WST-8 [2-2(methoxy-4-nitrophenyl)-3-(4-nitrophenyl)- 5-(2,4-disulfophenyl)-*2H*-tetrazolium, monosodium salt] was added to each well, then the cells were incubated for 2 h, and the absorbance at 450 nm was measured with a microplate reader. This parameter is proportional to the number of living cells in the culture. Initially we tested the activity of compounds at the concentration of 10 µM, and if the inhibition exceeded 50% at the concentration of 10 µM, the IC_{50} value was determined in the concentration range of 0.01 to 10 µM. IC_{50} (Table 4-1) is the concentration of test compound that reduces DHT-induced cell growth to 50% of the control.

LNCaP cell proliferation assay

The human prostate adenocarcinoma cell line LNCaP was routinely cultivated in RPMI-1640 supplemented with 10% FBS at 37°C in an incubator under an atmosphere of 5% CO_2 in humidified air. All experiments were performed in triplicate or more. Cells were trypsinized and diluted to 20,000 cells/mL with RPMI-1640 supplemented with 10% charcoal-stripped FBS. This cell suspension was seeded in 96-well plates at a volume of 100 µL/well and the plates were incubated at 24 h. Then, 10 µL of medium was removed from each well, and replaced with 10 µL of the drug solution supplemented with serial dilutions of the test compounds or DMSO as a dilution control in the presence or absence of 10 nM DHT. The final concentrations of compounds were 10 nM to 10 µM. Cells were incubated for 6 days, and half of the medium was removed and replaced once after 3 days with medium containing test compound or DMSO as a dilution control in the presence or absence of 10 nM DHT. At the end of the incubation, proliferation was evaluated by adding 10 µM WST-8 to microcultures and incubating the cells for 2 h. The absorbance at 450 nm was measured. This parameter is proportional to the number of living cells in the culture.

22Rv1 growth inhibition assay

The human prostate cancer cell line 22Rv1 was routinely cultivated in RPMI-1640 supplemented with 10% FBS at 37 °C in an incubator under an atmosphere of 5% CO_2 in humidified air. All experiments were performed in triplicate or more. Cells were trypsinized and diluted to 20,000 cells/mL with RPMI-1640 supplemented with 10% charcoal-stripped FBS. This cell suspension was seeded in 96-well plates at a volume of 100 µL/well and

the plates were incubated at 24 h. Then, 10 µL of mediumf was removed from each well, and replaced with 10 µL of drug solution supplemented with serial dilutions of test compound or DMSO as a dilution control in the presence of 1 nM DHT in triplicate microcultures. After incubation for 3 days, cell proliferation was evaluated by adding 10 µM WST-8 to microcultures and incubating the cells for 2 h. The absorbance at 450 nm was measured. This parameter is proportional to the number of living cells in the culture.

PC-3 growth inhibition assay

The human prostate cancer cell line PC-3 was routinely cultivated in RPMI-1640 medium supplemented with 10% FBS at 37°C in an incubator under an atmosphere of 5% CO_2 in humidified air. Cells were trypsinized and diluted to 20,000 cells/mL with RPMI-1640 supplemented with 10% charcoal-stripped FBS. This cell suspension was seeded in 96-well plates at a volume of 100 µL/well and incubated at 24 h. Then, 10 µL of medium was removed from each well, and replaced with 10 µL of drug solution supplemented with serial dilutions of test compound or DMSO as a dilution control in the presence of 1 nM DHT. Cells were incubated for 3 days, and at the end of the incubation time, proliferation was evaluated by adding 10 µM WST-8 to the microcultures and incubating the cells for 2 h. The absorbance at 450 nm was measured. This parameter is proportional to the number of living cells in the culture.

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