博士論文

スクアレン合成酵素阻害薬の合成研究

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略号表

本論文に用いた略語および略記号は以下の通りである。

Ac	acetyl
AcOH	acetic acid
*sec*BuLi	*sec*-butyllithium
*t*Bu	*tert*-Butyl
bid	bis in die (一日 2 回)
Chol	cholesterol
CSI	Cholesterol Synthesis Inhibitory activity in rat hepatic cell
DEAD	diethyl azodicarboxylate
DMAP	*N,N*-dimethyl-4-aminopyridine
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDC or WSCI	*N*-[3-(Dimethylamino)propyl]-*N*'-ethylcarbodiimide
Et_3N	triethylamine
EtOH	ethanol
AcOEt	ethyl acetate
HDL	high density lipoprotein
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA
HOBt	1-hydroxybenzotriazole
IC_{50}	50% inhibitory concentration
i.p.	intraperitoneal
K_2CO_3	Potassium carbonate
LDL	low density lipoprotein
Me	methyl
Ms	methanesulfonyl
$NaBH_4$	sodium borohydride
NaH	sodium hydride
Pd-C	palladium on carbon
PDB	Protein Data Bank (蛋白質構造データバンク)
Ph_3P	triphenylphosphine
Ph_3PO	triphenylphosphine oxide
quant.	quantitative yield
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
SSI	rat Squalene Synthase Inhibitory activity

TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf_2O	trifluoromethanesulfonic anhydride
TC	total cholesterol
TG	triglyceride
THF	tetrahydrofuran

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序論

第一章　　スクアレン合成酵素とその阻害剤

近年、欧米型の食生活の広まりと人口の高齢化により、動脈硬化や冠動脈疾患そして脳卒中などの血管疾患が世界中で増加している。本邦における死因の 3 割は、脳および心臓の血管で起こる循環器疾患である。その循環器疾患の三大危険因子として、高血圧・糖尿病・脂質異常症（高脂血症）が知られている。脂質異常症とは、高 LDL コレステロール血症、高トリグリセリド血症、低 HDL コレステロール血症であり、何れも動脈硬化を進展させる独立した危険因子である。これら脂質異常症の治療薬には、ニコチン酸製剤、フィブラート系製剤、陰イオン交換樹脂、プロブコール、HMG-CoA 還元酵素阻害剤（スタチン）、コレステロールトランスポーター阻害剤などの薬剤が使用されている（**Figure 1**）。

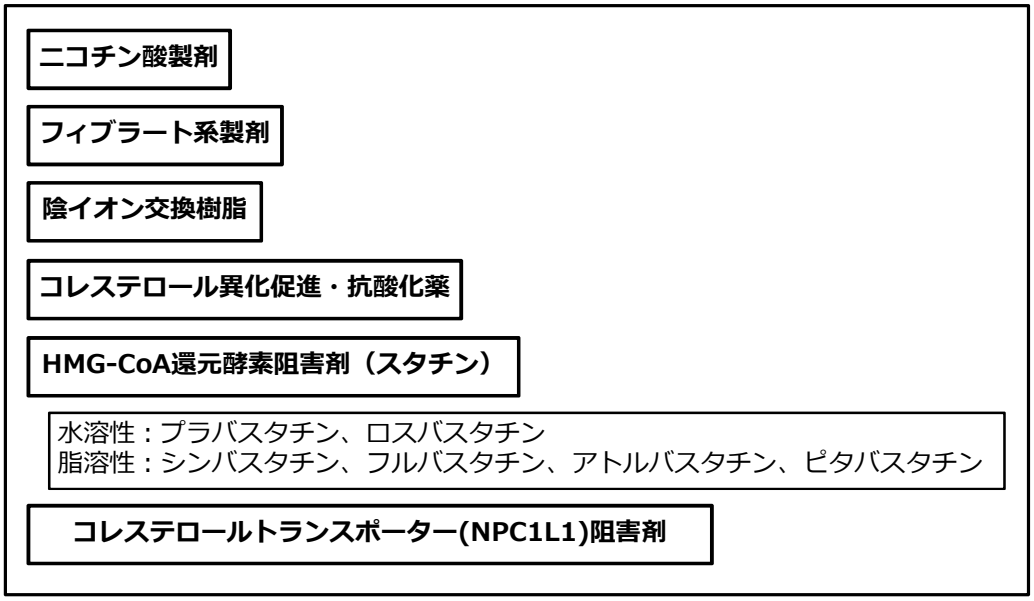
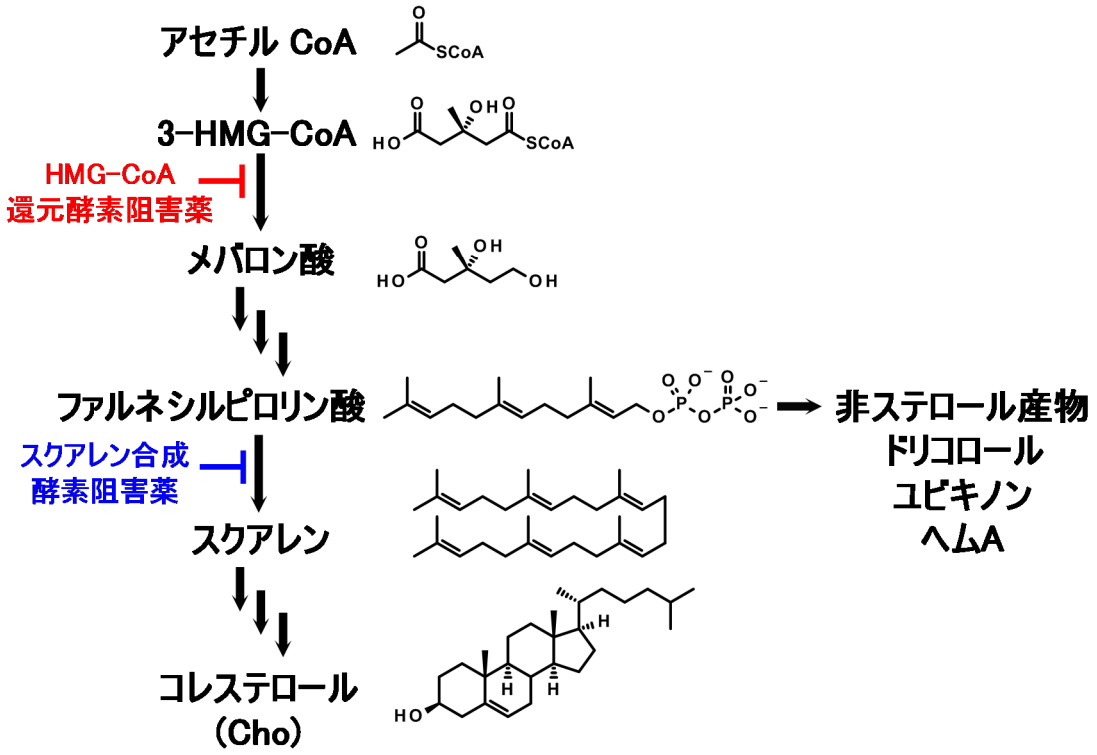


Figure 1. Medicines for dyslipidemia

遺伝的要因で高 LDL コレステロール血症を有する家族性高脂血症患者から得られた知見から、高脂血症の治療には血液中の LDL コレステロールの量を正常値まで低下させることが有効と考えられている。また生体内のコレステロールの大半は、食物からの

摂取ではなく肝臓で自ら生合成されるため、食事療法や運動療法に加えて、薬剤による治療が有効である。

特に、冠動脈疾患に対する HMG-CoA 還元酵素阻害剤（スタチン）のリスク低減効果は、数多くの大規模臨床試験により証明されている[1-3]。しかしスタチンには、筋障害や筋肉痛、倦怠感、極稀に横紋筋融解症[4-6]などの副作用のリスクが報告されている。これらの副作用は、HMG-CoA 還元酵素阻害剤が、ゲラニルゲラニルピロリン酸やユビキノン（コエンザイム Q）等の非ステロールイソプレノイド産物の生合成をも阻害することに因る。そのような生体に必須な成分の生合成を阻害しないためには、コレステロールの生合成経路においてファルネシルピロリン酸よりも下流に位置する酵素を標的とすることが好ましい。**Scheme 1** にコレステロールの生合成経路を示す。



Scheme 1. Sites of inhibition of cholesterol biosynthesis

スクアレン合成酵素は、2 分子のファルネシルピロリン酸からスクアレンを合成する酵素であり、この酵素の阻害によりコレステロールの生合成が抑えられることに加え、原料であるファルネシルピロリン酸を増加させることでスタチン投与により減少する非ステロール産物を逆に増加させ、横紋筋融解症などのリスクを低減し、さらにはトリ

グリセリドの低下作用をも期待できる魅力的な創薬標的である[7-10]。1992 年に Merck と Glaxo から同時に、このスクアレン合成酵素を阻害する天然物ファミリーが報告された。それぞれ zaragozic acid[11-12]（Merck）、squalestatin (Glaxo)と呼ばれたこの天然物ファミリーの発見により、スクアレン合成酵素阻害剤の研究は大きく進展した。著者らのグループにおいても、zaragozic acid をもとに合成展開を実施し、独自の酒石酸母核を有するスクアレン合成酵素阻害剤の獲得に成功していた[13]（**Figure 2**）。しかしこの誘導体 **1** は、高いスクアレン合成酵素阻害活性を有していたにもかかわらず、その非常に高い蛋白結合率のため、*in vivo* 試験における薬効は不十分なものであった。著者は、この高い蛋白結合率を回避して高い薬効を示す化合物を獲得することが出来れば、非ステロール中間産物の生合成を阻害せず HMG-CoA 還元酵素阻害剤を上回る高い安全性を有する脂質低下薬を得られると考え、新規スクアレン合成酵素阻害剤の探索研究を開始した。

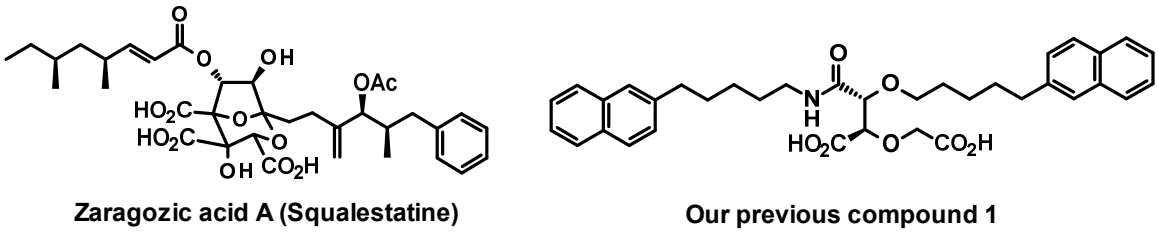


Figure 2. Zaragozic acid A and our previous compound

著者らが本研究を開始した時点で既に、Abbott、エーザイ、山之内製薬（現アステラス製薬）、Bayer、武田薬品工業など複数のグループから、スクアレン合成酵素の阻害剤が報告されていた。Zaragozic acid を模した阻害剤[14-15]や、スクアレン合成酵素の基質であるファルネシルピロリン酸に類似した化合物[16-17]、ファルネシルピロリン酸からスクアレンへの反応中間体であるカルボカチオンを模した二級アミンやキヌクリジン型の阻害剤[18-20]、そして武田化合物に代表される 7 員環構造を有する阻害剤[21-22]などである。その中で、武田薬品工業の **TAK-475** は最も開発が進み臨床第三相試験が開始されていたが、後に開発は中断された。このように、現在までに上市されたスクアレン合成酵素阻害薬は存在せず、著者らはファーストインクラスの治療薬を目指した研究を展開してきた。

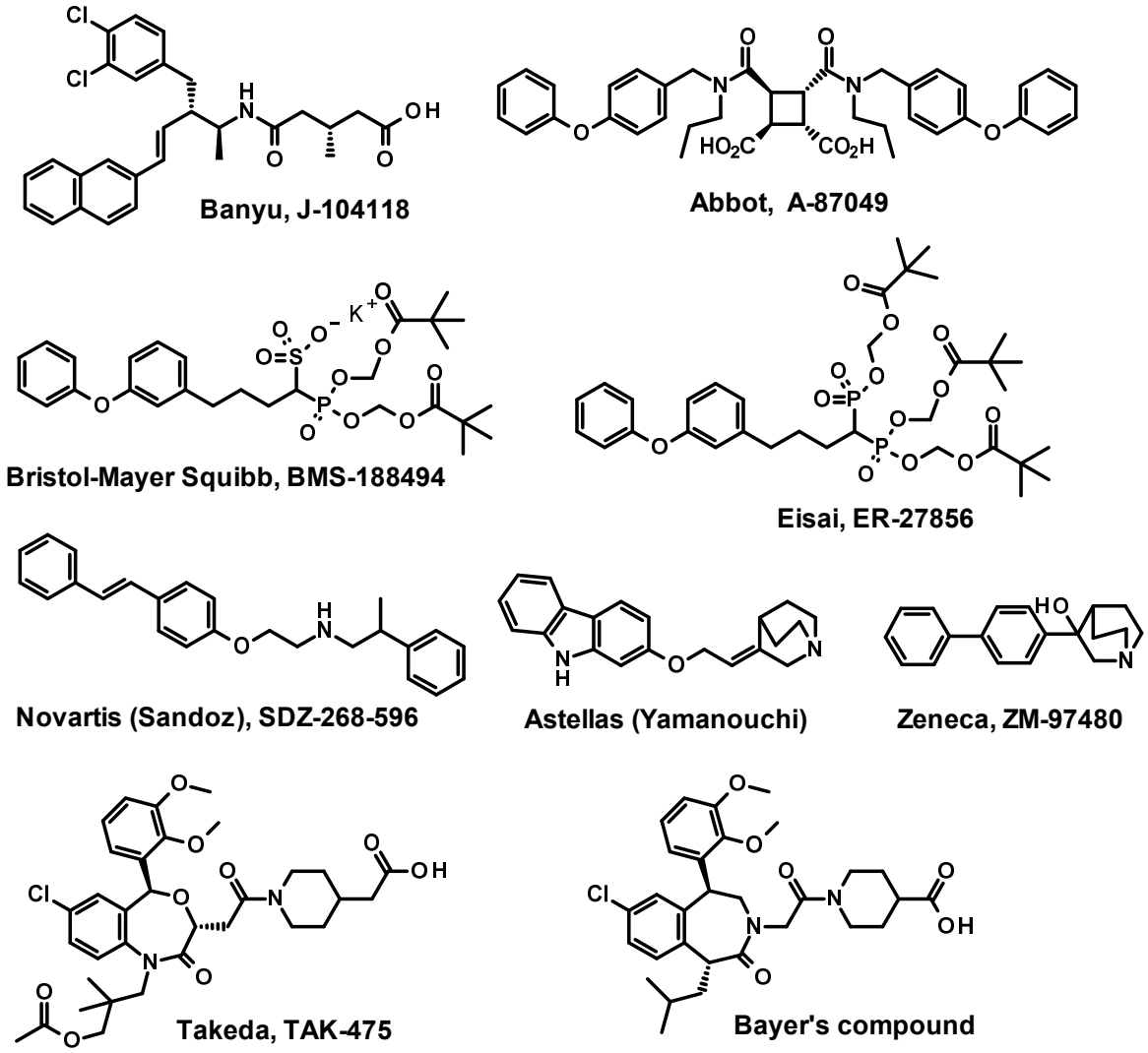
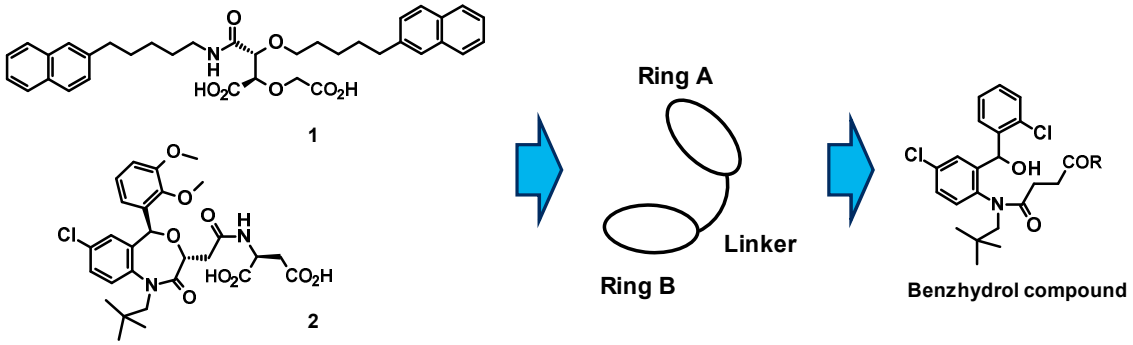


Figure 3. Compounds reported as squalene synthase inhibitors.

第二章　　研究成果の概要

著者らの研究グループでは既に、非常に強いスクアレン合成酵素阻害活性を有する化合物 **1**[13]を報告している。しかしこの化合物は、非常に高い蛋白結合率を有しており、現実的な投与量において十分な薬効を示すことが出来なかった。そこで著者は、更に脂溶性の低い阻害剤の獲得を目指し、新たな母核のデザインを行った。既報阻害剤 **1** および武田特許化合物 **2**[23]とスクアレン合成酵素との複合体X線結晶構造解析の結果 [24]を基に、両阻害剤の二つの芳香環が互いに非常に良く重なり合うことに着目し、二つの芳香環をアルキル鎖で短く繋いだアミノベンズヒドロール誘導体を設計・合成した。検討

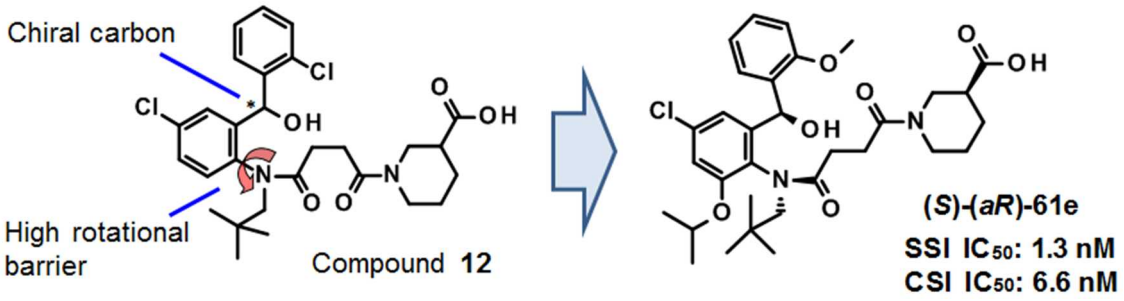
の結果、側鎖の末端構造の変換により、強いスクアレン合成酵素阻害（SSI）活性[25]を有する誘導体の合成に成功した。



Scheme 2. Design of the novel squalene synthase inhibitor

次に著者は、その活性体の立体構造の解明を行った。ラセミ体の化合物 **12** とスクアレン合成酵素との複合体X線結晶構造解析を実施したところ、(*S*)-ヒドロキシ-(*aR*)-アトロープ体のみが確認され、これが最も阻害活性の強い異性体であることが判明した。また非常に興味深いことに、この活性異性体はベンズヒドロール部分の水酸基と側鎖末端側のアミドカルボニル基との間で分子内水素結合を形成し、11 員環構造を形成してスクアレン合成酵素を阻害していることが明らかとなった（第一章）。

得られたベンズヒドロール型誘導体は、アミド結合の窒素原子と芳香環を繋ぐ C-N 結合での高い立体障害による回転異性体(アトロープ異性体)の混合物であり、溶液状態で容易に異性化することが問題であった。そこで著者は、このアトロープ異性化の回避を試みた。検討の結果、回転軸近傍であるアニリンのオルト位にアルコキシ基等を導入して回転障害を高め、両異性体を固定化して分離する事に成功した。更に、両アトロープ異性体の酵素阻害活性を各々評価したところ、主生成物として得られるアトロープ異性体がより強い活性を有することが判明した。更に、これら固定化された誘導体は、肝細胞で強いコレステロール合成阻害（CSI）活性[25]を示した。その中から著者は、複数種の *in vivo* モデルでの経口連投試験において血中脂質低下作用を示す、**(*S*)-(*aR*)-61e** を獲得することに成功した（第二章）。



Scheme 3. Fixation of the atrop isomerization

以下、本研究の内容について、各章にて詳細に記述する。

本論

第一章 2-アミノベンズヒドロールをテンプレートにした高活性スクアレン合成酵素阻害剤の発見

第一項　研究背景

既に著者らの研究グループでは、化合物 **1** に代表されるスクアレン合成酵素阻害剤を報告している[13]。それら阻害剤は、1 nM 以下の IC_{50} 値を示す非常に強力なスクアレン合成酵素阻害活性（SSI 活性）を有していた。しかし、これら一連の阻害剤は、強い *in vitro* 活性を有していたが、*in vivo* 試験において実用的な投与量で十分な薬効を示すには至らなかった。この結果は、これら化合物の非常に高い蛋白結合率が原因であると考えられた。この高い蛋白結合率は、これら阻害剤が、非常に脂溶性が高い平面構造であるナフタレン環を、その両端にそれぞれ有していることに由来すると考えられた。これら阻害剤はその高い蛋白結合率のため、生体内におけるフリー体の濃度が非常に低く、スクアレン合成酵素を実際に阻害できる分子の総量が少ないため、*in vivo* 試験においてコレステロールの生合成経路を十分に抑えることが出来なかったものと推察される。以上の理由から、より低い蛋白結合率を有し *in vivo* 試験において充分な薬効を示す新たな化合物の獲得が求められていた。我々の研究グループにおいて既に、この化合物 **1**[13]と武田薬品工業の特許化合物 **2**[23]のそれぞれについて、スクアレン合成酵素の水溶性部位との X 線結晶構造解析が行われ、その相互作用形式が明らかにされている（**Figure 4**）[24]。その解析結果から、化合物 **1** および **2** の有する二つの芳香環はそれぞれ非常に良く重なり合っており、分子内で互いに直行した配置を取っていた。そしてスクアレン合成酵素の活性中心にある二つの脂溶性ポケットに対して同様に相互作用をしていることが確認されていた（**Figure 5a**, **b**）。

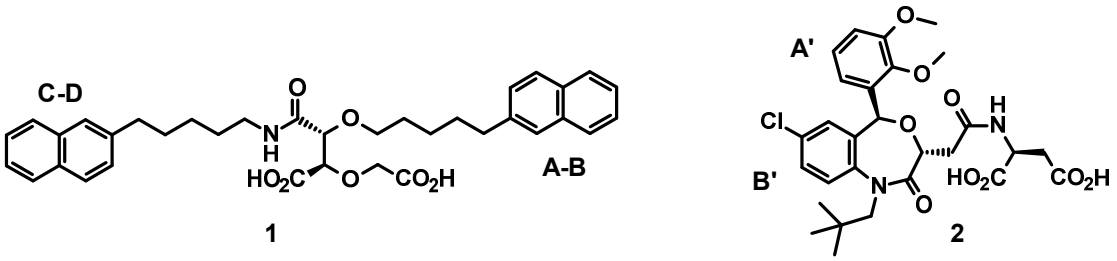


Figure 4. Structure of compound **1** and **2**.

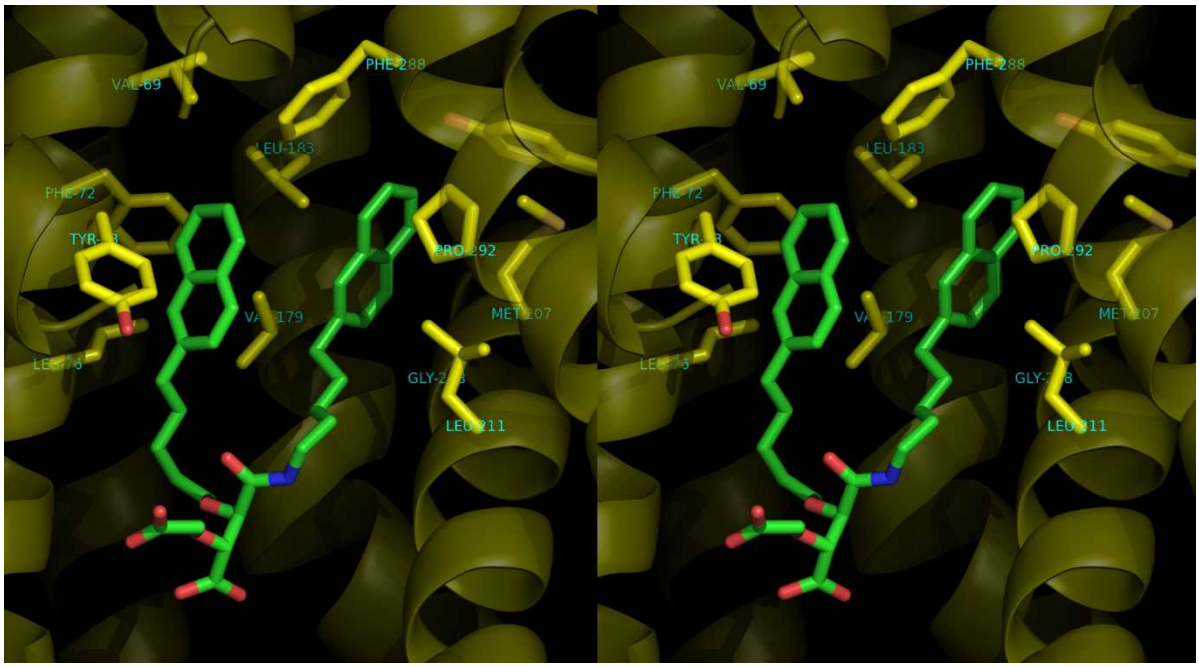


Figure 5a. Crystal structure of compound **1** bound in two lipophilic pockets of squalene synthase (PDB code: **3Q30**).

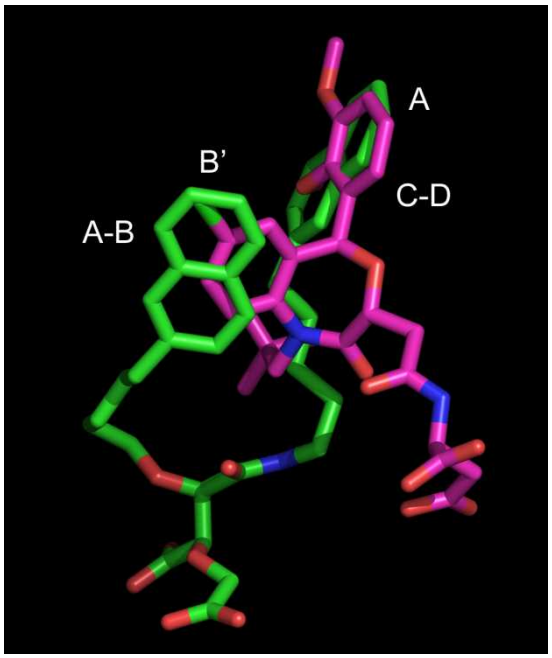
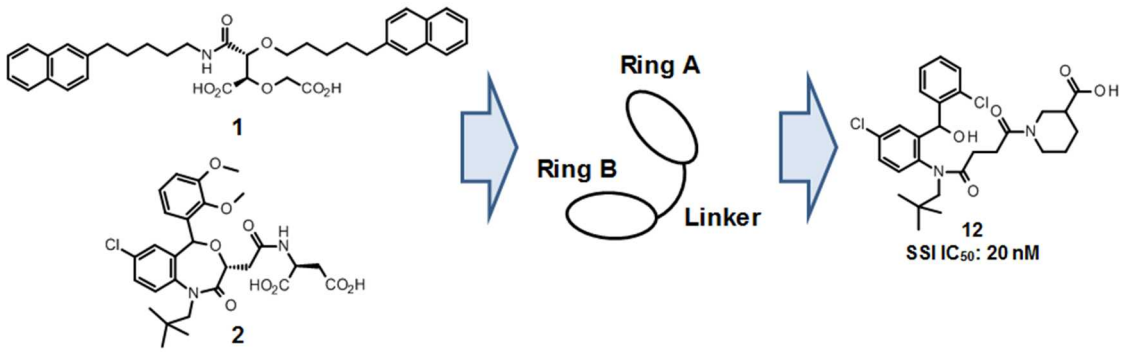


Figure 5b. X-ray crystal structure of compound **1** (green carbons, PDB code: **3Q30**) overlaid with the bound crystal structure of **2** (magenta carbons, PDB code: **3Q2Z**) (protein not shown).

化合物 **1** の A-B 環と化合物 **2** の B’ 環は、スクアレン合成酵素の Phe 54、Val 69、Phe 72、Tyr 73、Leu 76、Val 179、Leu 183 そして Phe 288 の側鎖からなる脂溶性ポケットに囲まれており、化合物 **1** の C-D 環と化合物 **2** の A’ 環は、同様に Val 179、Leu 183、Met 207、Gly 208、Leu 211、Tyr 276、Phe 288 そして Pro292 からなる脂溶性ポケットに囲まれている。何れの脂溶性ポケットも、それぞれ一分子のファルネシルピロリン酸が相互作用すると考えられる部位であり、まさにスクアレン合成酵素の活性中心といえる部位である。

これら二つの脂溶性ポケットは、スクアレン合成酵素を阻害するうえで重要な標的部位であると考えられる。新たな阻害剤をデザインするに際して、これら二つの芳香環部分を直接繋ぐことが合理的と考えられた。そこで著者は、より分子量が小さく効果の高いスクアレン合成酵素阻害剤を得るため、二つの芳香環をフレキシブルに繋いだ直鎖型のテンプレートをデザインし合成を行った。その際、化合物 **1** が非常に高い脂溶性を有していたため充分な薬効を示さなかったことを考慮し、より脂溶性の低い阻害剤を設計した。芳香環部位にナフタレン環に代わってベンゼン環を選択し、更に親水性を増すために水酸基を有するベンズヒドロール誘導体をデザインした。

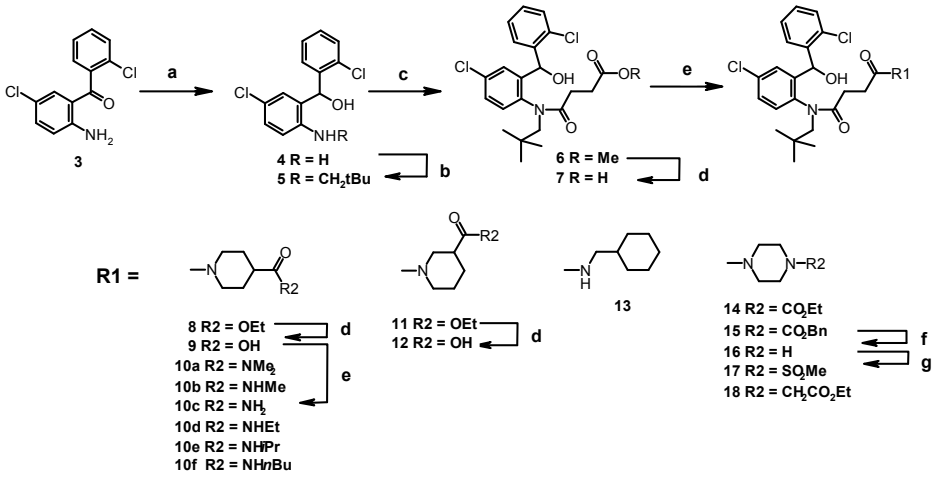


Scheme 4. Design of novel benzhydrol template

この章では、2-アミノベンズヒドロール構造を有する新規テンプレートの発見と、そのスクアレン合成酵素阻害剤としての構造活性相関の詳細について述べる。

第二項　直鎖型化合物の合成

一連の新規直鎖型スクアレン合成酵素阻害剤は、Scheme 5 に示したようにベンゾフェノンから合成を行った。市販のアミノベンゾフェノン **3** を水素化ホウ素ナトリウムで還元し、2-アミノベンズヒドロール **4** を得た。続く還元的アミノアルキル化によりネオペンチルアミン **5** を良好な収率で得た後、メチルコハク酸クロリドを反応させアミド **6** を合成した。このアミド **6** を加水分解することで、求めていたカルボン酸 **7** を合成した。コハク酸ジアミド **8** は、カルボン酸 **7** とイソニペコチン酸エステルを *N*-[3-(ジメチルアミノ)プロピル]-*N'*-エチルカルボジイミド（EDC）を用いて縮合することで合成した。その後エステルを加水分解し、EDC を用いて各種アミンと縮合を行い、一連のイソニペコチン酸アミド **10a-f** を得た。ニペコチン酸誘導体 **11** と **12** は、ニペコチン酸エチルを用いて同様の手法で合成を行った。

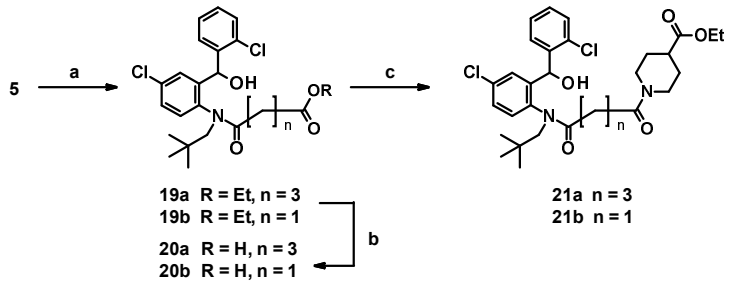


Scheme 5. Synthesis of open form compounds **8-18**. Reagents and conditions: (a) $NaBH_4$, MeOH, 0°C – rt (quant.); (b) *t*BuCHO, $NaBH_4$, AcOH, 0°C – rt (81%); (c) methyl 4-chloro-4-oxobutanoate, $NaHCO_3$, CH_2Cl_2, 0°C – rt (61%); (d) K_2CO_3, MeOH – H_2O, rt (**9** 88%, **12** 68%); (e) amine, EDC, HOBt, CH_2Cl_2, rt (**8** 76%, **10a** 57%, **10b** 61%, **10c** 34%, **10d** 42%, **10e** 38%, **10f** 45%, **11** 85%, **13** 65%, **14** quant., **15** 69%, **18** 71%); (f) H_2, Pd-C, MeOH, rt (quant.); (g) MsCl, Et_3N, CH_2Cl_2, 0°C – rt (62%).

ピペラジン誘導体 **14-18** は、カルボン酸 **7** より誘導した。カルボン酸 **7** と 4-ベンジルオキシカルボニルピペラジンとの縮合で得られたベンジルカーバメート **15** を、10% パラジウム炭素で接触水素還元することによりアミン **16** へと変換し、続くメタンスル

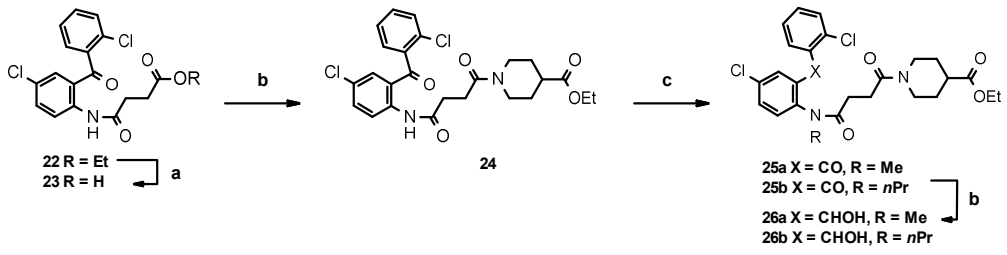
ホニル化により化合物 **17** を合成した。酢酸ユニットを導入した化合物 **18** は、カルボン酸 **7** と 4-（エトキシカルボニルメチル）ピペラジンとの縮合で得た。

異なる炭素数のメチレン鎖を有する化合物の合成を **Scheme 6** に示す。ネオペンチルアミン **5** をマロニルクロリド及びグルタル酸クロリドと反応させることにより、アミド **19a**, **b** をそれぞれ合成した。続く加水分解とイソニペコチン酸エチルエステルとの縮合により **21a**, **b** を得た。



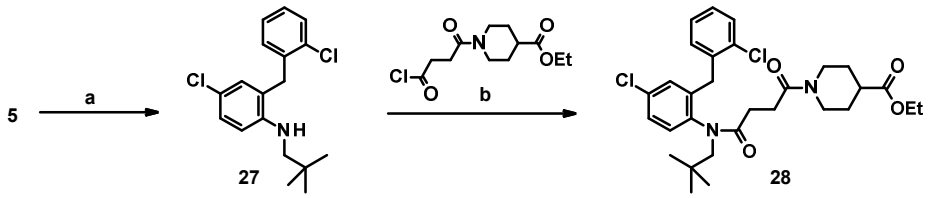
Scheme 6. Synthesis of various length compounds. Reagents and conditions: (a) acid chloride, $NaHCO_3$, CH_2Cl_2, 0°C – rt (quant.); (b) Na_2CO_3, MeOH – H_2O, rt (quant.); (c) ethyl isonipecotate, EDC, HOBt, CH_2Cl_2, rt (**21a** 86%, **21b** 78%).

N-メチルおよび*N*-プロピル誘導体**26a** と **26b** は、**Scheme 7** に示したように合成した。化合物 **22** の加水分解と、それに続く縮合反応によりイソニペコチン酸エステル **24** を調製した。続いて水素化ナトリウムとヨウ化アルキルを用いた **24** の *N*-アルキル化により化合物 **25a**, **b** を合成した。最後に $NaBH_4$ を用いたベンゾフェノンの還元により、ベンズヒドロール **26a**, **b** を得た。



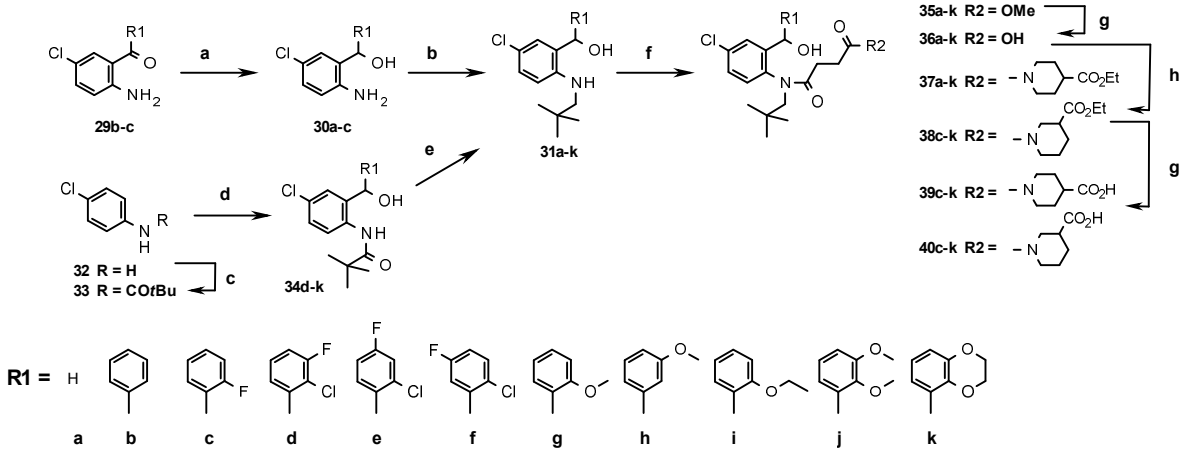
Scheme 7. Synthesis of smaller alkyl compounds. Reagents and conditions: (a) K_2CO_3, MeOH – H_2O, 60°C (67%); (b) amine, EDC, HOBt, CH_2Cl_2, rt (95%); (c) alkyl iodide, NaH, DMF, 0°C (**25a** 95%, **25b** 68%); (d) $NaBH_4$, EtOH, 0°C (**26a** 83%, **26b** 79%).

水酸基を持たないメチレン型化合物 **28** は、ベンズヒドロール **5** より合成した。鍵となる脱ヒドロキシ反応は、トリフェニルホスフィンオキシドと無水トリフルオロメタンスルホン酸、$NaBH_4$ を用いた条件[26]により 87%の収率で進行した。得られたアミン **27** に酸クロリドを反応させることで化合物 **28** を合成した（**Scheme 8**）。



Scheme 8. Synthesis of non-hydroxyl compound. Reagents and conditions: (a) Ph_3PO, Tf_2O, $NaBH_4$, CH_2Cl_2, 0°C – rt (87%); (b) acid chloride, $NaHCO_3$, CH_2Cl_2, 0°C – rt (32%).

上部のベンゼン環を変換した化合物群は、アミノベンズヒドロール **31a-k** を経由して合成した（**Scheme 9**）。先ず、市販のベンゾフェノン **29b**, **c** あるいはベンジルアルコール **30a** よりアミノベンズヒドロール **31a-c** を合成した。また、対応するベンゾフェノンが市販されていない 2-アミノベンズヒドロール誘導体 **31d-k** は、ピバル酸アミド **33** に対し 2 当量のアルキルリチウムによるオルトリチエーションを行い、各種アルデヒドを反応させ、続くアミド部分の還元により合成した。



Scheme 9. Synthesis of various upper ring compounds. Reagents and conditions: (a) $NaBH_4$, MeOH, 0°C (**30b** 91%, **30c** 88%); (b) *t*BuCHO, $NaBH_4$, AcOH, 0°C – rt (**31a** 73%, **31b** 45%, **31c** 62%); (c) pivaloyl chloride, DMAP, Et_3N, CH_2Cl_2, 0°C – rt (91%); (d) *sec*BuLi, THF then aldehyde -78°C – rt (**34d** 46%, **34g** 76%, **34h** quant., **34i** quant., **34j** 46%, **34k** 77%); (e) Red-Al, THF, rt (**31d** 47%, **31e** 14%, **31f** 87%, **31g** 49%, **31h** quant., **31i** quant. , **31j** 77%, **31k** 78%); (f) methyl 4-chloro-4-oxobutanoate, $NaHCO_3$, CH_2Cl_2, rt (**35a** 85%, **35b** 85%, **35c** 87%, **35d** 55%, **35e** 60%, **35f** 67%, **35g** 79%, **35h** 86%, **35i** 91%, **35j** 96%, **35k** 89%); (g) K_2CO_3, MeOH – H_2O, 50°C (**36a** 98%, **36b** quant., **36c** quant., **36d** 86%, **36e** 86%, **36f** 97%, **36g** 93%, **36h** quant., **36i** quant., **36j** quant., **36k** 88%, **39c** quant., **39d** 87%, **39e** 83%, **39f** 64%, **39g** 92%, **39h** quant, **39i** quant, **39j** 91%, **39k** 87%, **40c** 96%, **40d** 92%, **40e** 83%, **40f** 80%, **40g** 90%, **40h** quant, **40i** quant, **40j** 89%, **40k** quant.); (h) amine, EDC, HOBt, CH_2Cl_2, rt (**37a** 81%, **37b** 53%, **37c** 78%, **37d** 58%, **37e** 76%, **37f** 71%, **37g** 91%, **37h** 98%, **37i** 99%, **37j** 62%, **37k** 57%, **38c** 93%, **38d** 80%, **38e** 63%, **38f** 73%, **38g** 69%, **38h** 95%, **38i** 93%, **38j** 51%, **38k** 84%).

第三項　ベンズヒドロール誘導体の評価結果と考察

新規化合物の生物活性を **Table 1** に示す。最初に合成を行った 2-アミノベンズヒドロール誘導体であるエステル **6** とカルボン酸 **7** のスクアレン合成酵素阻害（SSI）活性を測定したところ、それぞれの IC_{50} 値は 1.7 μM と 6.5 μM であり、武田薬品工業の特許記載化合物 **2**（IC_{50} = 11 nM）に比べ、非常に弱い活性を示すに留まった。これは、酵素と脂溶性相互作用をする二つの芳香環の相対的な位置関係が変化したためと考えられた。

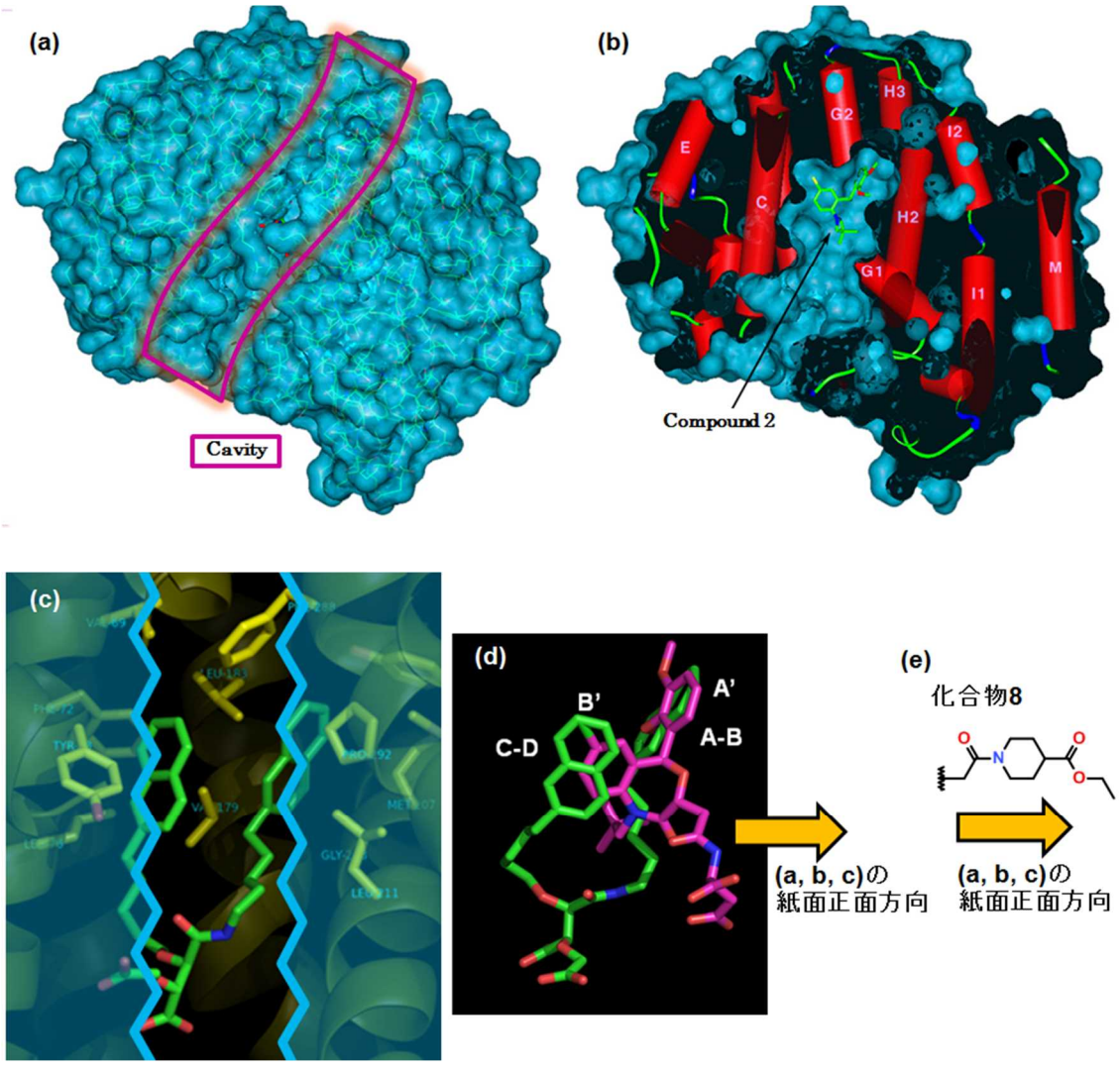


Figure 6. a) Crystal structure of compound **2** bound in squalene synthase (the cavity was highlighted, PDB code: **3Q2Z**), **b**) Half-cut structure, **c**) Crystal structure of compound **1** and squalene synthase (PDB code: **3Q30**), **d**) The side view of compound **1** overlaide with compound **2** (protein not shown), **e**) The side chain of compound **8** .

新たな活性向上策を見出すため、先に示したX線構造解析の結果を再検討した（**Figure 6**）[24]。スクアレン合成酵素の活性中心は蛋白の非常に深い部分にあり、溶媒側から伸びる深い溝の奥に、基質であるファルネシルピロリン酸2分子が相互作用するポケットが並んで存在している。基質や阻害剤は、ページ下側に方向にある活性部位の入り口から近づくと考えられる（**Figure 6a, b**）。そして、活性中心の紙面の正面側は、両側からせり出した蛋白の側鎖により半分隠された状態となっている（**Figure 6c**）。化合物 **2** のX線構造解析の結果から、化合物 **6**, **7** の側鎖部分も同様に、この活性部位に沿った蛋白の溝を通して溶媒側つまり紙面の正面側へ向いていると推察される（**Figure 6d**）。そこで活性の向上を目指し、この溝状のポケットの壁面部分との新たな相互作用を期待して、カルボン酸部分への環状の置換基の導入を試みた（**Figure 6e**）。イソニペコチン酸エステルを導入した化合物 **8** をデザインしたところ、前駆体であるカルボン酸 **7** に比べSSI活性が劇的に向上することが明らかとなった（IC_{50} = 0.85 nM）。4,1-ベンズオキサゼピン型化合物に匹敵するポテンシャルを有する、スクアレン合成酵素阻害剤の新規テンプレートを見出すことに成功した。

詳細な構造活性相関（SAR）を把握するため、全ての化合物についてラット肝ミクロソーム由来のスクアレン合成酵素阻害（SSI）活性を測定し、高活性を示した化合物についてラット初代培養肝細胞を用いたコレステロール合成阻害（CSI）活性を測定した[25]。SSI活性は、化合物の酵素を阻害するポテンシャルを向上させるための指標とした。一方の CSI 活性は、SSI 活性に比べ化合物の肝細胞内部への移行性についても加味した評価が可能であることから、効果的なコレステロール低下薬を取得する上でより重視すべき要素であり、動物モデルでの肝臓コレステロール合成阻害活性を推定する指標とした。従って研究の初期段階においては、SSI 活性と CSI 活性の両方を向上させることに焦点を当てて合成展開を行った。

興味深いことに、イソニペコチン酸 **9** の SSI 活性は、そのエステル体 **8** に比べて劇的に低下したが、それとは対照的に、ニペコチン酸 **12** とそのエステル体 **11** は逆の関係を示し、カルボン酸体 **12** の方が高い SSI 活性を示した。SSI 活性に関しては、エステルのような脂溶性の置換基はピペリジン環上の4位が好ましく、カルボン酸のような親水性の置換基は、ピペリジン環上の3位が好ましいと推察された。

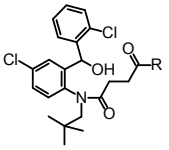
意外なことに、カルボン酸 **9** の SSI 活性はエステル体 **8** の 150 分の 1 であるにもかかわらず、その CSI 活性はエステル **8** よりも 7 倍強い値を示した。CSI/SSI の活性比

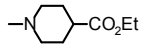
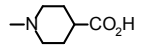
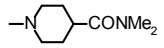
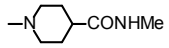
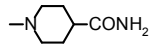
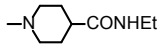
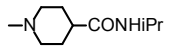
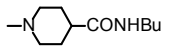
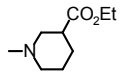
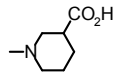
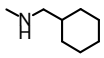
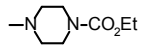
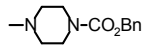
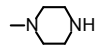
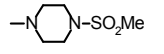
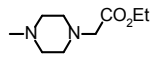
に関しては、化合物 **9** や **12** のようなカルボン酸を有する化合物が、その他の誘導体よりも良好な数値を示すことが明らかとなった。

この結果は、化合物 **9** および **12** のカルボン酸部分が、肝細胞表面に存在する有機アニオントランスポーターに認識され、肝細胞内部に効率的に輸送されていることが原因であると推測された。非常に脂溶性の高い化合物 **13** も良好な CSI/SSI 比を示しているが、それは化合物の高い細胞膜透過性によるものと考えられた。しかしながら、トランスポーターの関与を検証するためには、新たな評価系の構築を含めた更なる研究が必要とされ、更に踏み込むことは出来なかった。

引き続きイソニペコチン酸部分の修飾を行った結果、全ての化合物において中程度以上の SSI 活性が確認された。イソニペコチン酸の一置換アミド（**10b, d, e, f**）では、無置換および二置換アミド（**10a, c**）に比べて 10 倍高い活性が見られた。これらの結果は、一置換アミドの有する窒素原子上の水素原子が、活性向上に有効であることを示している。また、このアミドに置換するアルキル基の大きさは、SSI 活性に大きな影響を与えていないことが分かった。最初に行った X 線構造解析の結果から、嵩高い長い置換基は溶媒側に露出しており、酵素との相互作用には影響を与えないが、無置換アミド体 **10c** で活性が減弱していることから、小さなメチル基であっても脂溶性基の置換基の存在が高活性に繋がることが明らかになった。

Table 1. Evaluation of squalene synthase inhibitory (SSI) activity and cholesterol synthesis inhibitory (CSI) activity (Part 1)



Compound	R	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)	CSI/SSI ratio
6	OMe	1700	-	-
7	OH	6500	-	-
8		0.85	1700	200
9		130	250	1.9
10a		97	-	-
10b		1.3	900	692
10c		280	-	-
10d		2.4	-	-
10e		3.7	1600	432
10f		1.6	2000	1250
11*		410	-	-
12*		20	270	13.5
13		220	2600	11.8
14		2.3	-	-
15		1.1	-	-
16		2100	-	-
17		260	-	-
18		7.9	1400	177

SSI: Squalene Synthase Inhibitory activity. CSI: Cholesterol Synthesis Inhibitory activity in rat liver cell. "*: diastereomixture, -: not tested".

ピペラジンカーバメート **14**, **15** とスルホンアミド **17** は、高い SSI 活性を示した。一方、無置換のピペラジン **16** は非常に低活性であった。当初この位置に塩基性部位があることは、酵素との相性が悪いと考えられた。しかし、塩基性アミンを有するエトキシカルボニルメチルピペラジン **18** が高い SSI 活性を保持していたことから、脂溶性基を先に伸ばした場合には、塩基性部分による活性の低下を解消できる可能性があることが推察された。

イソニペコチン酸エステル **8** の酵素阻害に必須な部分構造を特定するため、次のような変換を試みた。

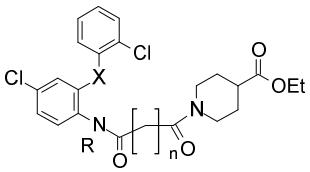
（１）側鎖部分にある二つのアミド結合間のメチレン鎖の長さの調整。

（２）大きな脂溶性基であるネオペンチル基の、より小さなアルキル基への置換。

（３）ベンズヒドロール部分の水酸基の除去。

以上の検討を順に行った。その評価結果を **Table 2** に示す。

Table 2. Evaluation of squalene synthase inhibitory (SSI) activity and cholesterol synthesis inhibitory (CSI) activity (Part 2)



Compound	X	R	n	SSI (IC_{50}, nM)
8	**CHOH**	**CH_2*t*Bu**	**2**	**8.5**
21a	**CHOH**	**CH_2*t*Bu**	**3**	**>6000**
21b	**CHOH**	**CH_2*t*Bu**	**1**	**>600**
26a	**CHOH**	**Me**	**2**	**21000**
26b	**CHOH**	***n*Pr**	**2**	**600**
28	**CH_2**	**CH_2*t*Bu**	**2**	**650**

側鎖を三炭素鎖に伸ばしたグルタル酸アミド体 **21a** と、一炭素へと短くしたマロン酸アミド体 **21b** は、元々のコハク酸アミド **8** に比べて非常に弱い SSI 活性を示すだけであった。また、ネオペンチル基に換えてより小さなメチル基やプロピル基を有する **26a, b** も、非常に弱い SSI 活性しか示さなかった。更に、水酸基を除いた化合物 **28** においても、同様に弱い活性が観察された。これらの結果から、二つのアミドをメチレン鎖二つで繋いだコハク酸アミド側鎖と立体的に嵩高いアルキル部分そしてベンズヒドロール部分の水酸基が、このテンプレートの活性を示すコンホメーションを適切に保持するために必須であることが明らかとなった。

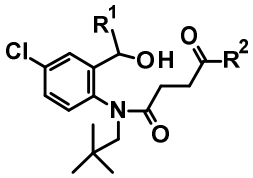
続いて、上部ベンゼン環の置換基効果を確認するため、一連の化合物群を合成し評価した（**Table 3**）。側鎖の末端部分については、エステル体で最も SSI 活性の強かったイソニペコチン酸エステル **37a-k** およびそのカルボン酸 **39c-k**、カルボン酸で最も活性が強く SSI/CSI 比が良好であったニペコチン酸 **40c-k** とそのエステル体 **38c-k** について合成した。

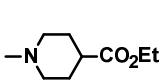
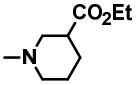
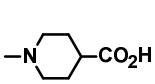
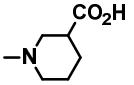
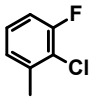
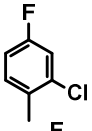
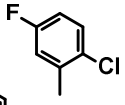
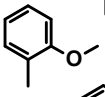
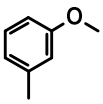
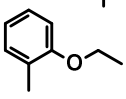
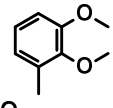
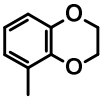
合成した一連の誘導体において、これまでと同様にイソニペコチン酸エステル体 **37** が最も強い SSI 活性を持つことが確認された。また、上部にベンゼン環を持たないイソニペコチン酸エステル **37a** は殆ど活性を示さず、ベンゼン環上に置換基を持たない **37b** は非常に弱い活性を示すに留まった。

一方、2-フルオロベンゼンのイソニペコチン酸エステル **37c** は、最も強い SSI 活性を示した。しかし、その他の 2-フルオロベンゼン誘導体 **38-40c** は、2-クロロベンゼン誘導体よりも低い SSI 活性であった。このことは、2-フルオロベンゼン誘導体の持つ阻害活性のポテンシャルは基本的に低いが、酵素との親和性の高いイソニペコチン酸エステル体 **37c** のみで高い活性が保たれていたと考えられる。

既に高い活性を有することが判っている 2-クロロベンゼン誘導体を基本として、更にもう一つの置換基としてフルオロ基を導入した誘導体 **d**, **e**, **f** を合成した。その結果、2-クロロ-3-フルオロベンゼン誘導体 **d** は 2-クロロベンゼン誘導体よりも高い SSI 活性を示すことが明らかとなった。しかし、2-クロロ-4-フルオロベンゼン誘導体 **e** では阻害活性が大きく低下し、2-クロロ-5-フルオロベンゼン誘導体 **f** は全く阻害活性を示さなかった。これらの結果は、上部ベンゼン環の 4 位と 5 位への置換基の導入は、スクアレン合

Table 3. Evaluation of squalene synthase inhibitory (SSI) activity and cholesterol synthesis inhibitory (CSI) activity (Part 3)



Compound		37a-k	38c-k	39c-k		40c-k	
	R^2 / R^1						
		SSI (nM)	SSI (nM)	SSI (nM)	CSI (nM)	SSI (nM)	CSI (nM)
		0.85	410	130	250	20	270
a	H	>6000	-	-	-	-	-
b		770	-	-	-	-	-
c		0.45	>600	1700	>10000	290	200
d		7.2	28	17	920	8.4	1300
e		2	>600	>600	-	190	-
f		>600	>600	>600	-	>600	-
g		1.1	2.6	1.7	600	1.3	84
h		210	>600	>600	-	>600	-
i		410	>600	>600	-	>600	-
j		1.1	1.3	2.8	1600	2.0	1500
k		10	13	7	230	6.8	170

SSI: Squalene Synthase Inhibitory activity. CSI: Cholesterol Synthesis Inhibitory activity in rat liver cell. "*: diastereomixture, -, not tested".

成酵素の脂溶性ポケットとの相互作用に適さないことを示している。また、3-メトキシベンゼン誘導体 **h** は殆ど活性を示さず、ベンゼン環 3 位の置換基だけでは高い活性が得られないことが明らかとなった。

更に、2-メトキシ誘導体、2,3-ジメトキシベンゼン誘導体および 1,4-ベンズジオキサン誘導体（**g**, **j**, **k**）は、何れも強い SSI 活性を示した。特に、2-メトキシベンゼン誘導体 **g** と 1,4-ベンズジオキサン誘導体 **k** は、共に良好な CSI 活性を有していた。この CSI 活性の向上は、メトキシ基による化合物全体の脂溶性の低減によるものと考えられた。

しかし、2,3-ジメトキシベンゼン誘導体 **j** は強い SSI 活性を示したが、それと比較してその CSI 活性はかなり減弱した。その原因として、1,4-ベンゾジオキサンと比べて二つのメトキシ基が自由に回転できる 2,3-ジメトキシベンゼンの場合、化合物の側鎖部分の位置に影響を与えているため、あるいは肝細胞のトランスポーターによる認識に影響を与えているためと考えられた[27, 28]。

上述のように今回得られたデータから上部ベンゼン環の構造活性相関を明らかにすることが出来た。先ず化合物 **37a**, **b** の結果から、この新規テンプレートにおいて上部ベンゼン環がスクアレン合成酵素の阻害に重要であることが明らかになった。そして、上部ベンゼン環上の置換基の存在、特にその 2 位置換基が活性発現に必須であることが判明した。更に、強い SSI 活性と良好な CSI 活性を有する 2-メトキシベンゼン誘導体 **g** と 1,4-ベンズジオキサン誘導体 **k** を獲得することに成功した。

こうして新たにデザインしたベンズヒドロール誘導体において、強い SSI 活性および良好な CSI 活性を有する化合物を合成することに成功した。しかし化合物 **12** に代表される殆どのベンズヒドロール誘導体は、アトロープ異性体[29, 30]の混合物であった。この一組の回転異性体は、アニリド部分の窒素原子と芳香環部分とを結ぶ C-N 結合を中心とした高い回転障害により生じていた。これは、このアミド結合の窒素原子上に、嵩高いネオペンチル基とオルト位が置換した嵩高い芳香環が置換していることに起因していた。更にこれら全ての誘導体は、ベンズヒドロール部分に不斉炭素を有しており、アトロープ異性と合わせて 4 つの異性体の混合物として存在していた。それら異性体の中で、どの異性体が最も活性が高い異性体であるのかを明らかにする必要があった。

次に、最も阻害活性の高い異性体を明らかにするため、ソーキング法を用いスクアレン合成酵素の単結晶と異性体の混合物である **12** から複合体結晶を作製しX線結晶構造解析を行った。その結果、唯一(*S*)-ヒドロキシ-(*aS*)-アトロープ異性体のみがスクアレン合成酵素の活性中心である脂溶性ポケットに深く嵌っている複合体像が解析された。阻害活性のより低い他の異性体を退けてこの異性体のみが複合体結晶を与えたことから、この異性体が最も阻害活性が強い異性体であると推察された （**Figure 7**）。この異性体が最も高活性であることは、後に合成した光学活性な類縁体の SSI 活性と、そのスクアレン合成酵素との複合体X線構造解析の結果から確認された[31]。

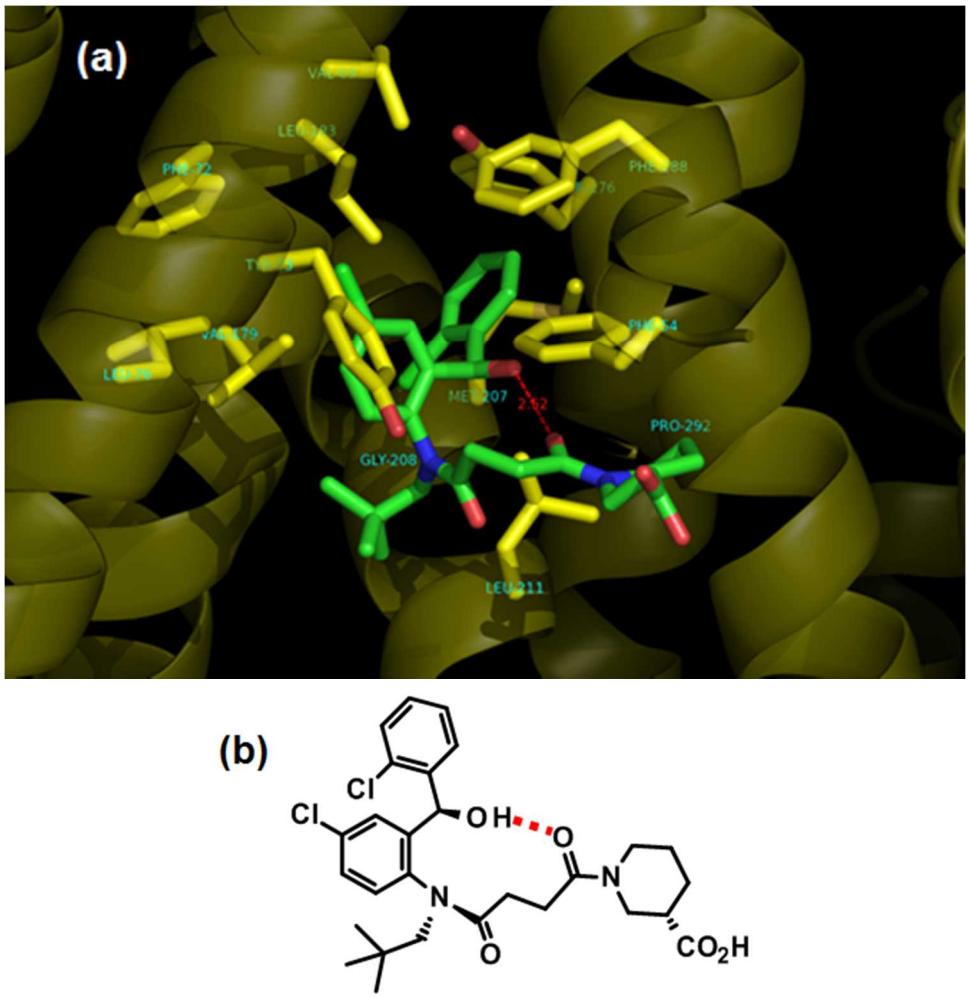


Figure 7. a) Crystal structure of compound **12** bound in squalene synthase. The intramolecular hydrogen bond between the proton of the hydroxyl group and the oxygen atom of side chain amide is highlighted (PDB code: **3ASX**), **b**) Structure of the detected isomer of compound **12**.

更に非常に興味深いことに、化合物 **12** の水酸基のプロトンと側鎖の末端側のアミド基の酸素原子との間で分子内水素結合が形成され、ユニークな 11 員環構造を形成して酵素を阻害していることが判明した。この結果から、側鎖の末端にニペコチン酸部分やイソニペコチン酸部分を導入した際に SSI 活性が大きく向上した理由が明らかとなった。即ち、これら環状アミンを側鎖末端側にアミド結合で導入したことにより、それまでのエステル体**6**やコハク酸**7**と比べて側鎖末端側のカルボニル基の双極子モーメントが増し、その結果として強い分子内水素結合が形成され、化合物のコンホメーションが固定化されて SSI 活性が大きく向上したと考えられる。

第四項　第一章小括

新たに著者がデザインした 2-アミノベンズヒドロール母核は、スクアレン合成酵素阻害薬として高い資質を有することが明らかになった。見出された化合物 **8** は、4,1-ベンズオキサゼピン誘導体に匹敵する強い阻害活性を有し、研究の新たな出発点となった。続いて実施したこの新テンプレートの構造活性相関の取得を目指した研究において、カルボン酸を有する化合物がラット肝細胞において高い CSI 活性を有することを明らかにした。特に、2-メトキシベンゼン誘導体と 1,4-ベンズジオキサン誘導体は、強力な SSI 活性と CSI 活性を有していた。

また、スクアレン合成酵素とラセミ体のアトロープ混合物である化合物 **12** との共結晶を用いた X 線結晶構造解析により、化合物 **12** の(*S*)-ヒドロキシ-(*aS*)-アトロープ異性体のみが合成酵素の活性中心である脂溶性ポケットに埋っており、更にその異性体が、水酸基と側鎖のアミド結合との間で分子内水素結合を形成し、11 員環構造をしたユニークな活性コンホメーションを取っていることを明らかにした。

この新しいテンプレートについて、更なる構造の最適化と生物活性の評価を引き続き実施することとした。

第二章　　アトロープ異性の固定化に成功したアルコキシアミノベンズヒドロール誘導体の発見

第一項　研究背景

脂質異常症の新規治療薬を見出す目的で、著者は経口活性を有するベンズヒドロール型のスクアレン合成酵素阻害剤の獲得を目指した研究を行って来た。第一章においては、化合物 **12** に代表されるベンズヒドロール誘導体のデザインと合成、その高いスクアレン合成酵素阻害活性について報告した。これらの化合物は、不斉炭素に結合した水酸基をベンズヒドロール部分に有し、更には容易に異性化してしまうアトロープ異性体の混合物であった。即ち化合物 **12** は、8 つの立体異性体の混合物であり、臨床候補化合物に相応しい資質を持ち合わせてはいなかった（**Figure 8**）。このアトロープ異性体のペアは、アミド部分の窒素原子と芳香環部分とを結ぶ C-N 結合を中心とした高い回転障害により生じ、アミドの窒素原子上に、嵩高いネオペンチル基とオルト位が置換した芳香環が置換していることがその原因であると考えられた。更に、単離したアトロープ異性体は溶液状態において容易に異性化し、化合物に特有と考えられる一定の異性体比を取るアトロープ異性体の混合物となることが判明していた。

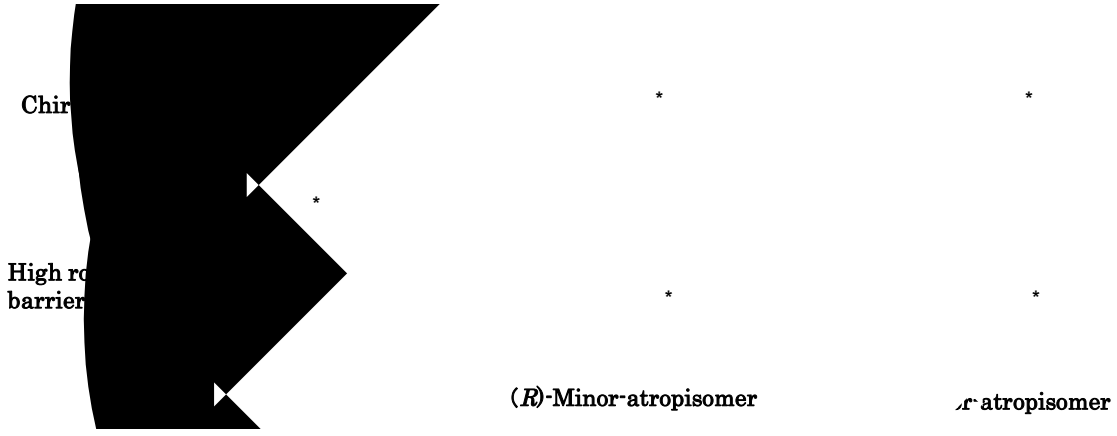


Figure 8. Compound **12** consists of four stereo isomers

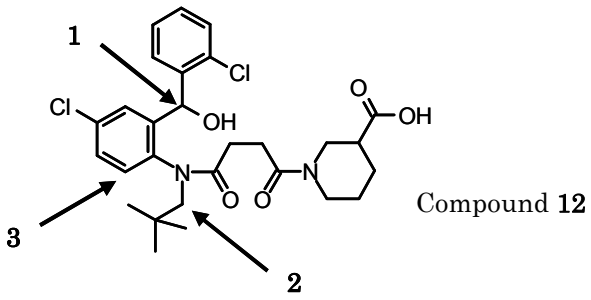
研究を進捗させるためには、このアトロープ異性化の問題を解決して光学活性体の合成･評価を行い、臨床試験に耐え得る候補化合物を見出す必要があった。そこで先ず、これら異性体の中で最も強い活性を有する異性体を単離することに注力した。

第一章で述べた様に、スクアレン合成酵素と化合物 **12** との共結晶の X 線結晶構造解析の結果から、唯一 (*S*)-ヒドロキシ-(*aS*)-アトロープ異性体のみが、分子内水素結合を介した 11 員環構造を取って酵素の活性部位と相互作用している様子が確認された。明らかにこの異性体が、4 種類全ての異性体の中で、最も活性の高い異性体であると推測された。

この最も活性の高い異性体の獲得を実現するため、著者は二つのアプローチを取った。一つ目は、キラルカラムを用いた高速液体クロマトグラフィーによるベンズヒドロール部分の光学異性体の分割の検討。もう一つは、新しい置換基を導入して C-N 結合の回転障壁を更に高めてアトロープ異性化を固定し、各々の異性体を単離する試みである。

著者は先ず、C-N 結合の周辺に立体的に嵩高い置換基を導入して回転障壁を更に高くする方法について、検討を実施した。このベンズヒドロール型化合物の C-N 結合周辺には、新たに置換基の導入が可能性な位置は三ヶ所考えられた（**Figure 9**）。

（1） 水酸基が置換している不斉炭素。
（2） ネオペンチルアルキル基のメチレン部位。
（3） 芳香環のオルト位。



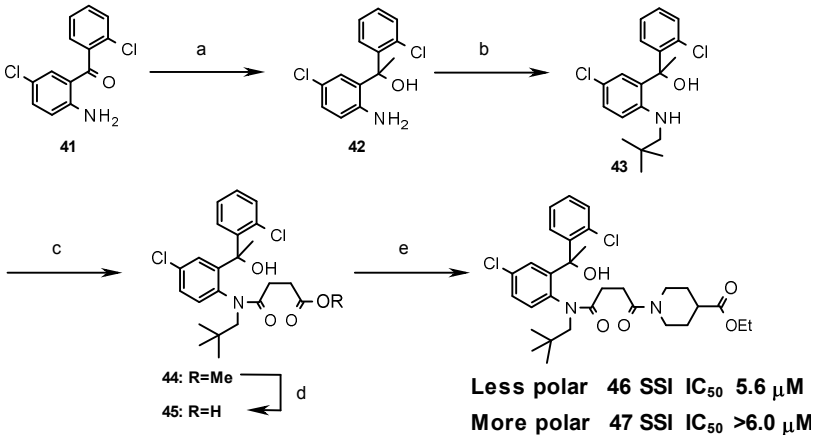
Compound **12**

Figure 9. Three possible positions near the C-N bond to attach new substitute: (1) alcohol attached chiral carbon; (2) methylene carbon of neopentyl alkyl part; (3) ortho-position of aryl ring.

第二章では、このアトロープ異性の固定化の試みと、動物モデルでの経口連投試験において血中脂質低下作用を示した高活性な新規アルコキシアミノベンズヒドロール誘導体の獲得について、その詳細を述べる。

第二項　アトロープ異性を固定化した化合物の合成

立体障害を更に高めることによりアトロープ異性化を固定しようと考え、先ずはベンズヒドロール部分を三級アルコールへと変換した化合物の合成を試みた。三級アルコール誘導体は、ベンゾフェノン **41** から **Scheme 10** に示した方法で合成した。市販の **41** をメチルマグネシウムブロミドと反応させ、三級アルコール **42** を得た。引き続く還元的アミノアルキル化とメチルコハク酸クロリドによるアシル化により、アミド **44** へ導き、その加水分解により対応するカルボン酸 **45** を得た。これにイソニペコチン酸エステル部分を縮合することにより、アトロープ異性体の混合物を合成した。引き続くカラムクロマトグラフィーによる精製工程において、アトロープ異性体のペアである化合物 **46** と **47** をそれぞれ単一の異性体として得ることに成功した。得られた両異性体は、重クロロホルム溶液中で長時間保管しても異性化することはなく、アトロープ異性の固定化にも成功していることが ^{1}H-NMR によって確認された。



Scheme 10. Synthesis of *tert*-alcohol compounds. Reagents and conditions: (a) 3eq. MeMgBr, THF, -78°C – rt, 20 h (26%); (b) *t*BuCHO, $NaBH_4$, AcOH, 0°C , 10 min (31%); (c) methyl 4-chloro-4-oxobutanoate, $NaHCO_3$, CH_2Cl_2, rt, 42 h (76%); (d) K_2CO_3, MeOH – H_2O, 50°C, 1 h (78%); (e) ethyl isonipecotate, EDC, HOBt, CH_2Cl_2, rt, 17 h (**46** 17%, **47** 59%).

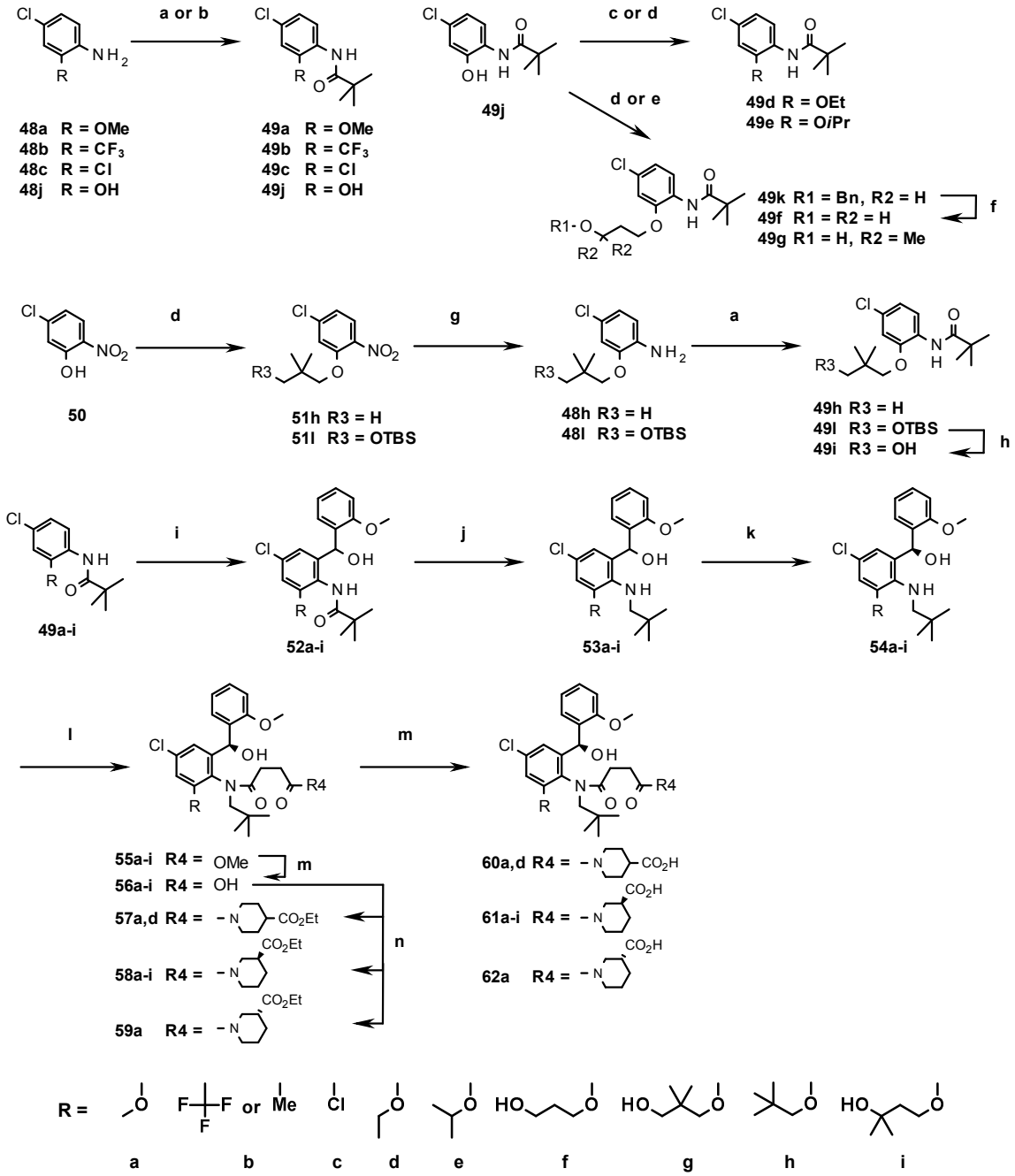
続いて、ネオペンチル基のメチレン部分へのメチル基の導入を試みた。しかし、ネオペンチル部分の大きな嵩高さのため、目的とする化合物を合成出来なかった。

最後に、芳香環のオルト位への置換基の導入を検討した。**Scheme 11** にその一般的合成法を示す。アニリン **48a-c, j** をピバル酸クロリドと反応させてアミド **49a-c, j** を得た。アミドのエトキシ体 **49d** とイソプロピルオキシ体 **49e**、3-ヒドロキシプロピルオキシ体 **49f, g** は、フェノール **49j** とアルキルハライドまたはアルコールから合成した。非常に嵩高いアルコキシ側鎖を有する 2,2-ジメチル-3-ヒドロキシプロピルオキシ体とネオペンチルオキシ体の中間体 **49h, i** は、立体障害のためピバル酸アミド **49j** からの合成が不可能であったため、2-ニトロフェノール **50** から誘導した。

一連のピバル酸アミド **49a-i** と 2-メトキシベンズアルデヒドとのジアニオンまたはトリアニオン中間体を経たカップリング反応により、ベンズヒドロール **52a-j** を得た。続く水素化ビス(2-メトキシエトキシ)アルミニウムナトリウム（Red-Al）還元によりアミン **53a-i** を合成した。その際、トリフルオロメチルアミド **52b** は、メチルアミン **53b** へと還元された。

更に、メトキシ誘導体 **a** についてベンズヒドロール部分の両光学異性体の合成を行った。他のアルコキシ誘導体も、このアミノアルコール中間体において光学活性なカラムを用いた高速液体クロマトグラフィーにより光学分割を実施した。より保持時間の短い異性体を **isomer A**、より保持時間の長い異性体を **isomer B** と決めた。オルトクロロ体 **53c** については、この段階での光学分離が困難であったため、後にジアミド体 **58c** に導いた段階で分割を行った。モノアミド **55a-i** は、キラルなアミノベンズヒドロールとコハク酸モノクロライドを反応させて合成した。このコハク酸部分を導入した後、major および minor それぞれのアトロープ異性体が ^{1}H-NMR によって確認された。続く塩基による加水分解と環状アミンとの縮合反応により、ジアミドエステル **57a, d**、**58a-i**、**59a** を得た。エステル部分の加水分解により、最終体であるカルボン酸 **60a, d**、**61a-i**、**62a** を良好な収率で合成することが出来た。またこれら誘導体において、期待していた通りアトロープ異性は固定化されており、重クロロホルム溶液中で数日間放置した場合でもアトロープ異性化は確認されなかった。

そしてエトキシ体 **d** において、major および minor の両アトロープ異性体を単離し、それぞれを最終体であるカルボン酸へと導くことに成功した。また多くの化合物において、通常の精製手段により最終体であるカルボン酸体を、純粋な major アトロープ異性体として得ることに成功した。



Scheme 11. Synthesis of various upper ring compounds. Reagents and conditions: (a) pivaloyl chloride, Et_3N, DMAP, CH_2Cl_2, 0°C – rt, 2 h (**49a** 98%, **49b** 37%, **49c** 78%, **49h** 66%, **49l** 94%); (b) pivaloyl chloride, $NaHCO_3$, CH_2Cl_2, rt, 1.5 h (**49d** 95%); (c) RI, K_2CO_3, DMF, rt, 19 h (**49d** 95%); (d) ROH, DEAD, PPh_3, THF, 0°C – rt , 2 h (**49e** 93%, **49k** 87%) or rt – 60°C, 2 h (**51h** 83%, **51l** 97%); (e) ROMs, K_2CO_3, DMF, rt, 60°C, 6 h (**49g** 99%); (f) Pd-C, H_2, AcOEt, rt, 7 h (87%); (g) Raney-Ni, H_2, EtOH, rt (**48h** 87%, **48l** 97%); (h)TBAF, THF, rt (96%); (i) *sec*BuLi, THF then 2-methoxybenzaldehyde,

-78°C – rt (**52a** 88%, **52b** 25%, **52c** 47%, **52d** 66%, **52e** 40%, **52f** 43%, **52g** 80%, **52h** 47%, **52i** 88%); (j) Red-Al, THF, rt (**53a** 89%, **53b** 66%, **53c** 64%, **53d** 84%, **53e** 37%, **53f** quant., **53g** 92%, **53h** 50%, **53i** 77%); (k) HPLC separation by using CHIRALCEL OD (2-PrOH – *n*-hexane); (l) methyl 4-chloro-4-oxobutanoate, $NaHCO_3$, CH_2Cl_2, rt ((*S*)-**55a** 93%, (*R*)-**55a** 98%, **55b** 88%, **55c** 49%, **55d** quant., **55e** 99%, **55f** quant., **55g** 98%, **55h** quant., **55i** 99%); (m) K_2CO_3, MeOH – H_2O, 50°C ((*S*)-**56a** quant., (*R*)-**56a** quant., **56b** 92%, **56c** 96%, **56d** 99%, **56e** 93%, **56f** 99%, **56g** 97%, **56h** 87%, **56i** 97%, (*S*)-(*aR*)-**60a** 68%, (*R*)-(*aS*)-**60a** 99%, (*S*)-(*aR*)-**60d** 80%, (*S*)-(*aS*)-**60d** 36%, (*S*)-(*aR*)-**61a** 97%, (*R*)-(*aS*)-**61a** 93%, **61b** 78%, **61c** 48%, (*S*)-(*aR*)-**61d** 87%, (*S*)-(*aS*)-**61d** 93%, **61e** 99%, **61f** 86%, **61g** 89%, **61h** 90%, **61i** 86%, (*S*)-(*aR*)-**62a** 92%, (*R*)-(*aS*)-**62a** 89%); (n) amine, EDC, HOBt, CH_2Cl_2, rt ((*S*)-**57a** 56%, (*R*)-**57a** 56%, (*S*)-(*aR*)-**57d** 87%, (*S*)-(*aS*)-**57d** 7%, (*S*)-(*aR*)- **58a** 74%, (*R*)-(*aS*)- **58a** 19%, **58b** 72%, **58c** 88%, (*S*)-(*aR*)-**58d** 74%, (*S*)-(*aS*)-**58d** 7%, **58e** 68%, **58f** 88%, **58g** 81%, **58h** 92%, **58i** 87%, (*S*)-**59a** 76%, (*R*)-**59a** 31%).

第三項　アトロープ異性を固定化した化合物の評価結果と考察

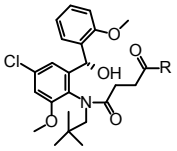
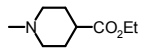
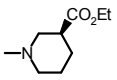
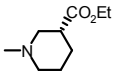
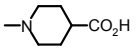
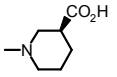
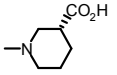
C-N 結合の回転障壁を高めてアトロープ異性を固定化するため、この C-N 結合近傍に新たな置換基の導入を行った。先ず初めに、ベンズヒドロール部分の不斉炭素へのメチル基の導入を試みた。合成した三級アルコール体はラセミ体であったが、アトロープ異性の固定化と両アトロープ異性体の分離に成功した。両アトロープ異性体のうち、より低極性な片方の異性体（化合物 **46**）だけが SSI 活性を示したが、その活性は IC_{50} = 5600 nM であり、化合物 **12**（IC_{50} = 0.85 nM）に比べて大きく低下していた。原因として三級アルコール体は、分子内水素結合を介したユニークな 11 員環型の活性コンホメーションを形成出来なかったと考えられる。第一章で述べた X 線結晶構造の結果から、この 11 員環構造はスクアレン合成酵素を阻害する上で非常に重要であることが明らかになっている。

続くネオペンチル基のメチレン部分への置換基の導入によるアトロープ異性の固定化は、ネオペンチル部分の大きな嵩高さのため目的とする化合物を合成出来ず、断念せざるを得なかった。

最後に残された部位である芳香環のオルト位に置換基を導入した化合物群は、その嵩高くなった回転障害により、アトロープ異性が固定化されていることが明らかとなった。更に、不斉炭素を有するベンズヒドロール部分のより高活性な異性体を明らかにするため、メトキシ基がアニリンのオルト位に置換した誘導体 **a** について、そのベンズヒドロール部分の両光学異性体の活性を測定した。

Table 4 に示した様に、キラルカラムでより長い保持時間を有するアミノアルコール **54a-isomer B** より合成した最終体 **57-62a-isomer B** が、より保持時間の短いアミノアルコール **54a-isomer A** から得られた誘導体 **57-62a-isomer A** よりも強い阻害活性を示した。スクアレン合成酵素と化合物 **12** との複合体の X 線結晶構造解析の結果から、より高活性な異性体 **isomer B** は(*S*)-配座の水酸基を有する異性体であると推定された。

Table 4. Evaluation of squalene synthase inhibitory (SSI) activity and cholesterol synthesis inhibitory (CSI) activity of major atropisomer of ortho-methoxy derivatives **57-62a**

		Isomer A from shorter retention time aminoalcohol		Isomer B from longer retention time aminoalcohol	
					
	R	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)
57a		**72**	**-**	**1.3**	**-**
58a		**95**	**-**	**3.4**	**-**
59a		**90**	**-**	**2.5**	**-**
60a		**65**	**880**	**1.6**	**25**
61a*		**55**	**690**	**1.5**	**8.6**
62a		**50**	**830**	**1.6**	**15**

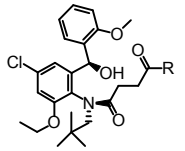
SSI: Squalene Synthase Inhibitory activity. CSI: Cholesterol Synthesis Inhibitory activity in rat hepatic cell. "-, not tested".

*: Only major atropisomer.

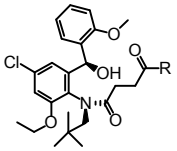
続いて、major および minor それぞれのアトロープ異性体について、その酵素阻害活性の評価を試みた。オルト位にエトキシ基が置換した化合物**(*S*)-57**, **58**, **60**, **61d** について、光学活性なアミノアルコール**(*S*)-54** から得られた中間体より major および minor の両アトロープ異性体をそれぞれ分離し、各々から最終体を得ることに成功した。それぞれの SSI 活性を測定して比較した結果、主成分として得られる major アトロープ異性体**(*S*)-*major*-57**, **58**, **60**, **61d** が、対応する minor アトロープ異性体**(*S*)-*minor*-57**, **58**, **60**, **61d** に比べて、強い SSI 活性を示すことが明らかとなった（**Table 5**）。X 線結晶構造解析の結果より、この major アトロープ異性体は(*S*)-ヒドロキシ-(*aR*)-アトロープ

異性体であると推察された。また、このアトロープ異性体がより高活性であることは、後に得られた光学活性な類縁体の SSI 活性と、そのスクアレン合成酵素との複合体 X 線構造解析から得られる知見と合致した[31]。

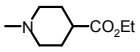
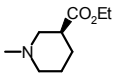
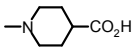
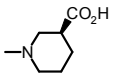
Table 5. Evaluation of SSI and CSI activity of major and minor atropisomers of ortho-ethoxy derivatives **57**, **58**, **60**, **61d**



(*S*)-hydroxyl-*major*-atropisomer



(*S*)-hydroxyl-*minor*-atropisomer

	R	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)
57d		**3.4**	**-**	**32**	**-**
58d		**4.5**	**-**	**>600**	**-**
60d		**4.5**	**150**	**40**	**-**
61d		**2.9**	**77**	**300**	**>300**

SSI: Squalene Synthase Inhibitory activity.　CSI: Cholesterol Synthesis Inhibitory activity in rat hepatic cell. "-, not tested".

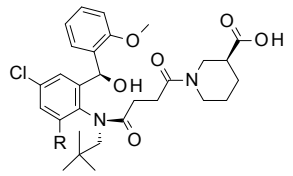
更に、オルト位にメトキシ基およびエトキシ基が置換したこれらアルコキシ誘導体において、(*S*)-ニペコチン酸型化合物 **61a**, **d** が最も強い CSI 活性を示すことが明らかとなった。この側鎖末端部分の違いによる大きな CSI 活性の差異は、カルボン酸部分の構造に依存していると推察され、肝細胞表面の有機アニオントランスポーターによるカルボン酸部分の認識と、それに続く阻害剤の選択的な取り込みの差に因ると考察した。

続いて、ベンゼン環オルト位の置換基を最適化した。メチル基、クロロ基、各種アルコキシ基、極性相互作用や物性改善を期待したヒドロキシプロピルオキシ基を置換した化合物群を合成し、その活性を評価した。その結果、それら全ての誘導体においてアト

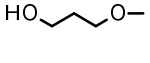
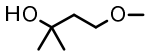
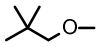
ロープ異性を固定化出来ることが判明した。**Table 6** に見られるように、メトキシ基とイソプロピルオキシ基が置換した誘導体**(*S*)-(*aR*)-61a**, **e** において、特に強い SSI および CSI 活性が確認された。加えて 3-ヒドロキシプロピルオキシ体**(*S*)-61f** において、SSI および CSI 活性を低下させることなく、酸性条件での水溶性が向上していることが明らかとなった。

3-ヒドロキシプロピルオキシ誘導体において期待すべき結果が得られたことから、次に Caco-2 細胞を用いた膜透過性の評価を行った。β-ブロッカーのアテノロールと各化合物の膜透過性の比を取り、透過性がアテノロールの何倍であるかを算出した。その結果、メチルおよびアルコキシ誘導体 **61a**, **b**, **d**, **e** は何れも高い膜透過性を示したが、3-ヒドロキシプロピルオキシ体 **61f** の膜透過性は 2.6 と低かった。そこで膜透過性の向上を狙い、水酸基の近傍にジェミナルジメチル基を導入した化合物を合成した。得られたジェミナルジメチル誘導体**(*S*)-61g**, **i** は強い阻害活性を保持していたが、その膜透過性は他のアルコキシ誘導体と比較して高いものではなかった。メチル基二つ分の脂溶性の付加では、膜透過性に対する末端水酸基の悪影響を改善するには不充分であると推察される。

Table 6. Evaluation of SSI and CSI activity, solubility, and cell permeability of (*S*)-hydroxyl-(*aR*)-atropisomers **61a-i**



(*S*)-hydroxyl-(*aR*)-atropisomer

	R	SSI (IC_{50}, nM)	CSI (IC_{50}, nM)	Solubility (pH 1.2 / 6.8)	Caco-2 cell permeability ratio
61a	**MeO**	**1.5**	**8.6**	**<3 / 980**	**24**
61b	**Me**	**11**	**310**	**<3 / >1100**	**30**
61c	**Cl**	**9.7**	**270**	**- / -**	**-**
61d	**EtO**	**2.9**	**77**	**<3 / 1000**	**>30**
61e	***i*PrO**	**1.3**	**6.6**	**<3 / 97**	**>30**
61f#		**2.5**	**8.4**	**92 / 440**	**2.6**
61g#		**3.8**	**18**	**37 / 280**	**3.6**
61h		**2.4**	**19**	**<3 / 110**	**>30**
61i#		**3.7**	**35**	**12 / 210**	**18.1**

SSI: Squalene Synthase Inhibitory activity. CSI: Cholesterol Synthesis Inhibitory activity in rat hepatic cell. "-, not tested". Solubility: μg/ml in pH 1.2 and 6.8 buffer. Caco-2 cell permeability ratio: atenolol = 1. #: Containing small amount of minor atropisomer.

実験動物での薬理試験に先立ち、経口投与で有効なスクアレン合成酵素阻害剤としての資質を評価するため、動物への経口投与後の阻害剤の体内動態、特に標的臓器である肝臓への選択性の測定を行った。高い細胞膜透過性を有するネオペンチルオキシ体**(*S*)-(*aR*)-61h** を選抜し、血中脂質低下試験を行う最初の動物種であるハムスターを用いた薬物動態試験を実施した。

その結果、**(*S*)-(*aR*)-61h** は投与 4 時間後で血中濃度の 50 倍以上の高い肝臓選択性を示すことが明らかとなり、スクアレン合成酵素阻害剤として好ましい薬物動態を有していることが確認された（**Table 7**）。

Table 7. PK profile of **(*S*)-(*aR*)-61h** in hamster.

Time after administration (h)	Plasma conc. (ng / mL)	Liver conc. (ng / g of liver)	Kp (liver / plasma)
4	486	24,867	54.5
7	244	19,707	79.8

100 mg/kg/5mL p.o. Fed. hamster.

続いて、ハムスターを用いた経口連投血中脂質低下試験を実施した。この試験は、肝臓におけるコレステロール生合成を化合物の連続投与により継続して阻害することで、コレステロールなど脂質の運搬を担う LDL の肝臓への取り込みを促進し、血中脂質の低下を狙った試験である。ハムスターにおいては、血中総コレステロール量（TC）と血中トリグリセリド量（TG）がその指標となる。

強い CSI 活性と高い細胞膜透過性を有しているイソプロピルオキシ体およびネオペンチルオキシ体**(*S*)-(*aR*)-61e, h** を選抜し、ハムスター経口連投血中脂質低下試験を実施した（**Figure 10**）。一日二回の 100 mg/kg 経口投与を二週間継続した結果、両化合物 **(*S*)-(*aR*)-61e, h** は有意に血中総コレステロール量（**61e** で-32%、**61h** で-24%）と血中トリグリセリド量（**61e** で-35%、**61h** で-44%）を低下させた。一方、HMG-CoA 還元酵素阻害薬であるアトルバスタチンは、有意に総コレステロール量を低下させたが TG に対しては影響を示さなかった。これは著者らの高用量ハムスター血中脂質低下試験に限定した結果であるが、スクアレン合成酵素阻害剤の HMG-CoA 還元酵素阻害剤に対する優位性を示した一例といえる。

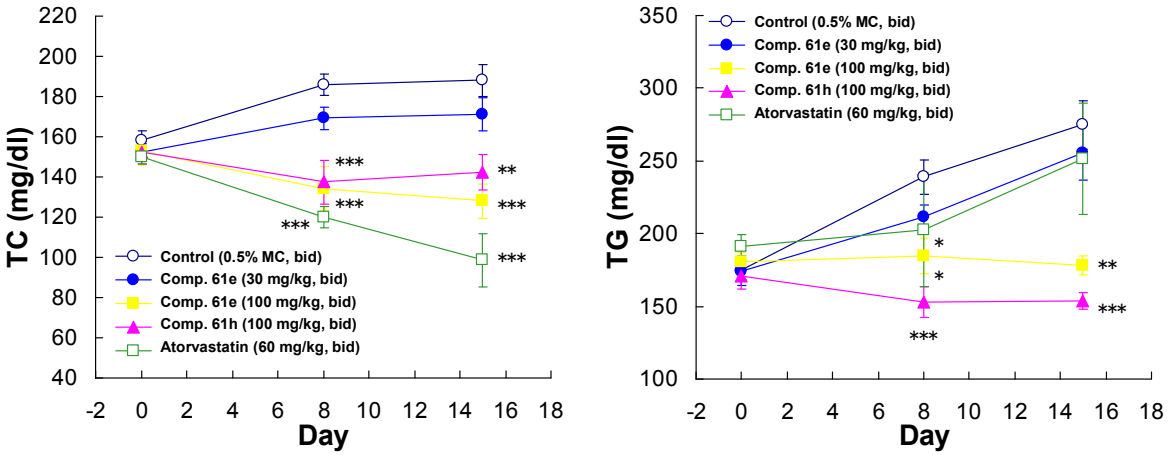


Figure 10. Evaluation of plasma lipid lowering effects of **(*S*)-(*aR*)-61e**, **h** and atorvastatin in hamster orally repeated doses for 14 days

TC: total cholesterol. TG: triglyceride. Values are means ±S.E.M. (n = 8). * P<0.05, ** P<0.01, *** P<0.001 vs. control values.

次に、非げっ歯類であるマーモセットにおける経口連投血中脂質低下試験を実施した。マーモセットにおいては、血中総コレステロール量（TC）と血中トリグリセリド量（TG）の他に、HDL コレステロールと non-HDL コレステロールを測定することで、より臨床に近い血中脂質の変化が観察可能となる。この試験により、HDL コレステロールを低下させず non-HDL コレステロールと TG を低下させる、脂質低下薬として好ましい薬効プロファイルを有する化合物であるかを評価する。

アルコキシ誘導体の代表としてイソプロピルオキシ体**(*S*)-(*aR*)-61e** を選抜し、マーモセット連投血中脂質低下試験を実施した（**Figure 11**）。その結果、100 mg/kg/day での 5 日間連投試験において、イソプロピルオキシ体**(*S*)-(*aR*)-61e** は統計的に有意な non-HDL コレステロール低下作用（コントロール比で-34%）を示した。更に投与初期値からの変化率においては、non-HDL コレステロールと TG の両方を有意に低下させていた。また HDL コレステロールは減少させず、逆に僅かながら増加させた。

著者は、ベンズヒドロール母核の問題点であったアトロープ異性の問題を解決し、複数の動物種における経口連続投与試験において明確な血中脂質低下作用を示す、アルコキシベンズヒドロール型のスクアレン合成酵素阻害剤**(*S*)-(*aR*)-61e** を見出すことに成功した。

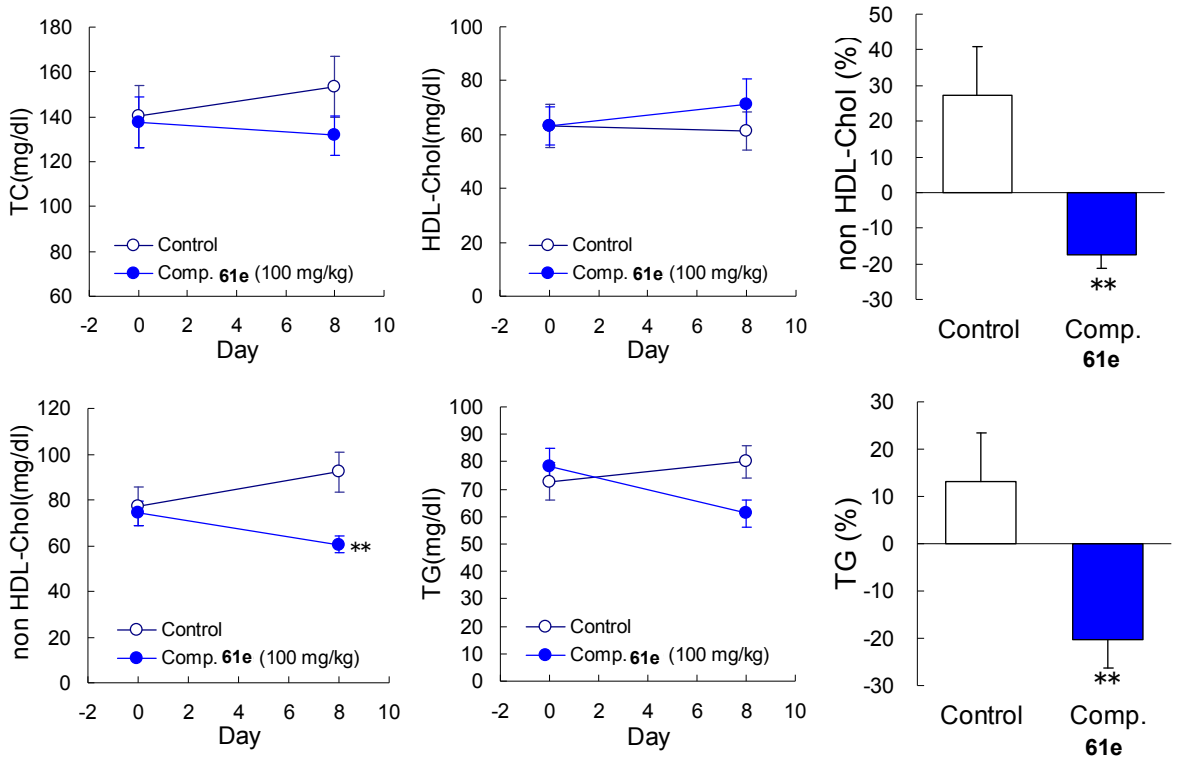


Figure 11. Evaluation of plasma lipid lowering effects of **(*S*)-(*aR*)-61e** in marmoset 100 mg/kg/day orally repeated doses for 7 days; change values (for total cholesterol, HDL cholesterol, non-HDL cholesterol, and triglyceride; line graph) and percent changes from initial values (for non-HDL cholesterol and triglyceride; bar graph). Values are means ±S.E.M. (n = 6). **: P<0.001 vs. control values.

第四項　第二章小括

強い活性を有し経口投与で有効なスクアレン合成酵素阻害剤の獲得を目指した研究において、多くのアミノベンズヒドロール誘導体の探索を行った。そして、アミノベンズヒドロール母核の問題点であったアトロープ異性を、アニリンのオルト位にアルコキシ基を導入して立体障害を高めて固定化することに成功した。その結果、高い活性を有する単一異性体の阻害剤の取得が可能となった。更なるアルコキシ部分の変換を行った結果、ハムスターおよびマーモセットでの経口連投試験において、有意な血中脂質低下作用を示すイソプロピルオキシ体**(*S*)-(*aR*)-61e** の獲得に成功した。

結論

これまで述べてきたように、著者はコレステロール生合成経路におけるステロイド合成と非ステロイド分子の合成との分岐点の下流に位置する最初の酵素であるスクアレン合成酵素を阻害することで、非ステロール中間産物の合成を阻害せず、筋障害等を引き起こさない安全な脂質低下薬を得ることが出来ると考え、新規スクアレン合成酵素阻害薬の創製を目指し本研究に着手し、以下に示す成果を得た。

1. 新たにデザインした 2-アミノベンズヒドロール母核が、スクアレン合成酵素阻害薬として高い資質を有することを明らかにした。見出された化合物 **8** は、4,1-ベンズオキサゼピン誘導体に匹敵する強い阻害活性を有し、研究の新たな出発点となった。続いて実施したこの新テンプレートの構造活性相関の取得を目指した研究において、カルボン酸を有する化合物がラット肝細胞において高い CSI 活性を有することを見出した。特に、2-メトキシベンゼン誘導体と 1,4-ベンズジオキサン誘導体は、強力な SSI 活性と CSI 活性を有していた。また、この新しいテンプレートを有するラセミ体のアトロープ混合物である化合物 **12** とスクアレン合成酵素との共結晶を用いた X 線結晶構造解析により、化合物 **12** の(*S*)-ヒドロキシ-(*aS*)-アトロープ異性体のみが酵素の活性中心である脂溶性ポケットに埋っており、更にその異性体が、水酸基と側鎖末端側アミドのカルボニル基との間で分子内水素結合を形成し、11 員環構造をしたユニークな活性コンホメーションを取っていることを明らかにした。

2. 強い活性を有し経口投与で有効な薬効を示すスクアレン合成酵素阻害剤の獲得を目指し、多くのアミノベンズヒドロール誘導体の探索を行った。そして、アミノベンズヒドロール母核の問題点であったアトロープ異性を、アニリンのオルト位にアルコキシ基等を導入して立体障害を高めることで固定化することに成功した。その結果、高い活性を有する単一異性体の阻害剤を取得した。このアルコキシ部分の変換を行った結果、ハムスターおよびマーモセットでの経口連投試験において有意な血中脂質低下作用を示す、イソプロピルオキシ体**(*S*)-(*aR*)-61e** の獲得に成功した。

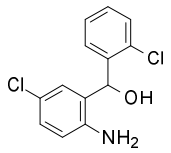
本研究の過程で見出された多くの新しい知見は、今後の新たなスクアレン合成酵素阻害薬の探索研究に資する有用な情報であると期待される。

実験の部

第一章　　Chemistry

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded on JEOL JNM-EX400 spectrometers, and chemical shifts are given in ppm from tetramethylsilane as an internal standard. Spin-spin couplings were depicted by using standard abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad). Parenthetical peak derives from minor atropisomer. FAB mass spectra were recorded on a JEOL JMS-HX110 spectrometer. HR-FAB mass spectra were recorded on a JEOL JMS-700. ESI mass spectra were recorded on SCIEX API-150EX and Agilent Technologies Agilent 1100 series LC/MS. Optical rotations were recorded on a Autopol V plus. Column chromatography was performed with Merck silica gel 60 (particle size 0.060-0.200 or 0.040-0.063). Flash column chromatography was performed with YAMAZEN cartridge series or Ultra Pack series. Thin-layer chromatography (TLC) was performed on Merck pre-coated TLC glass sheets with silica gel 60F254 or Whatman Partisil PLK5F with Silica gel 150Å.

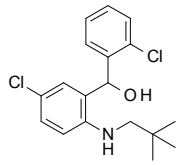
[2-amino-5-chlorophenyl](2-chlorophenyl)methanol (4).



{4-chloro-2-[(2-chlorophenyl)carbonyl]phenyl}amine (30.0 g, 113 mmol) was dissolved in MeOH (400 ml). Sodium borohydride (8.53 g, 225 mmol) was added to the solution at 0°C. The reaction mixture was stirred at 0°C for 2 h. To the reaction mixture, sat NH_4Claq was added. The mixture was concentrated in reduced pressure. The concentrate was diluted with AcOEt. The organic material was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Then, the residue was washed with diethyl ether and hexane to give compound **4** (30.2 g, 113 mmol, quant.) as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ 2.57 (1H, br s), 4.07 (2H, br s), 6.16 (1H, s), 6.64 (1H, d, *J* = 8.5 Hz), 6.89 (1H, d, *J* = 2.5 Hz), 7.07 (1H, dd, *J* = 8.3, 2.5 Hz), 7.28-7.34 (2H, m), 7.39-7.42 (1H, m), 7.46-7.49 (1H, m).

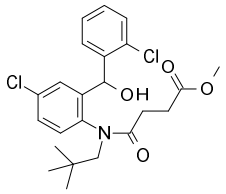
[5-chloro-2-(2,2-dimethylpropylamino)phenyl](2-chlorophenyl)methanol (5).



Compound **4** (5.00 g, 18.7 mmol) was dissolved in 1,2-dichloroethane. Pivalaldehyde (2.43 mL, 22.4 mmol) was added to the solution at rt. To the cloudy solution, sodium tri(acetoxy)borohydride (4.74 g, 22.4 mmol) was added at 0°C. The reaction mixture was stirred for 30 min. at 0°C. Sat. $NaHCO_3$aq was added to the solution, the organic material was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 10) to give compound **5** (5.12 g ,15.1 mmol, 81%) as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ 1.04 (9H, s), 4.06 (1H, br s), 4.53 (1H, br s), 6.31 (1H, s), 6.55 (1 H, s), 6.59 (1 H, d, *J* = 8.5 Hz), 6.99 (1 H, dd, *J* = 2.4, 0.7 Hz), 7.25-7.28 (1, m), 7.38-7.44 (1H, m).

Methyl 4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl) amino]-4-oxobutanoate (6).



An ice-cooled solution of {5-chloro-2-[(2,2-dimethylpropyl)amino]phenyl} (2-chlorophenyl)methanol (0.50 g, 1.5 mmol) in CH_2Cl_2 (50 ml) was added ethyl 4-chloro-4-oxobutanoate (0.23 g, 1.7 mmol) and $NaHCO_3$ (0.37 g, 4.4 mmol). After being stirred for 2 h at room temperature, the reaction was quenched with water. The organic material was extracted with CH_2Cl_2. The extract was washed with

brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 2 – 1 : 1) to give compound **6** (0.41 g ,0.90 mmol, 61%) as a colorless powder.

^{1}H-NMR ($CDCl_3$) δ 0.87 (0.88) (9H, s), 2.23-2.39 (3H, m), 2.80-2.90 (1H, m), 3.02 (2.98) (1H, d, *J* = 13.8 Hz), 3.66 (3.57)(3H, s), 4.44 (4.50) (1H, d, 13.8 Hz), 4.56-4.57 (1H, m), 6.13 (6.33) (1H, br s), 7.03 (1H, br s), 7.21-7.37 (5H, m), 7.73-7.78 (1H, m).

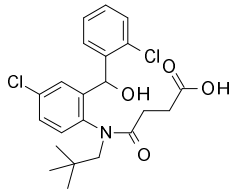
IR (ATR) cm^{-1} 3359, 2950, 1745, 1650, 1432, 1168, 1027, 752, 420.

Mp 130-132 °C.

MS (FAB) *m/z* 452 $(M + H)^+$.

Anal. Calcd. for $C_{23}H_{27}NO_4Cl_2$: C, 61.07; H, 6.02; N, 3.10; Cl, 15.67. Found: C, 61.09; H, 6.04; N, 3.00; Cl, 15.78.

4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)-amino]-4-oxobutanoic acid (7).



Compound **6** (0.20 g, 0.44 mmol) was suspended in a mixture of MeOH (10 ml) and water (5 ml), and K_2CO_3 was added at room temperature, followed by stirring for 12 h at same temperature. The solvent was removed under reduced pressure and was adding 1N hydrochloric acid and CH_2Cl_2. The organics were extracted with CH_2Cl_2 (3 times). The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Then, the residue was washed with diethyl ether and hexane to give compound **7** (0.19 g, 0.44 mmol, quant.) as a colorless powder.

^{1}H-NMR (DMSO-d_6) δ 0.76 (0.84) (9H, s), 1.06-1.27 (1H, m), 1.71-2.48 (3H, m), 2.54 (3.03) (1H, d, *J* = 13.7 Hz), 4.20 (4.40) (1H, d, *J* = 13.7 Hz), 5.89 (6.09) (1H, br s), 6.27 (1H, br), 7.07 (1H, d, *J* = 2.4 Hz), 7.28-7.61 (6H, m).

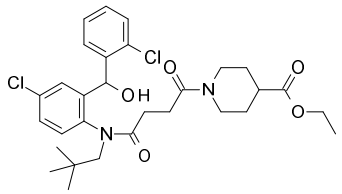
IR (ATR) cm^{-1} 2954, 1710, 1641, 1477, 1396, 1168, 1027, 750.

Mp 78-80 °C.

MS (ESI) *m/z* 438 $(M + H)^+$.

Anal. Calcd. for $C_{23}H_{27}NO_4Cl_2 \cdot 0.25H_2O$: C, 59.67; H, 5.80; N, 3.16; Cl, 16.01. Found: C, 59.36; H, 5.96; N, 2.96; Cl, 16.30.

Ethyl 1-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (8).



To a solution of Compound **7** (0.16 g, 0.37 mmol) and isonipecotic acid ethyl ester (0.086 ml, 0.56 mmol) in CH_2Cl_2 was added WSCI·HCl (0.11 g) and HOBt (0.085 g), and then the mixture was stirred at room temperature for 18 h. The reaction mixture was diluted with water and the organics were extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, then concentrated in vacuo, and then the residue was purified with silica gel column chromatography (0-5% MeOH – CH_2Cl_2 as eluent) to give compound **8** (0.16 g, 0.28 mmol, 76 %) as a colorless powder.

^{1}H-NMR ($CDCl_3$) δ 0.91 (9H, s), 1.24 (1.26) (3H, t, J = 7.0 Hz), 1.80-1.97 (3H, m), 2.11-2.22 (2H, m), 2.38-2.52 (2H, m), 2.68-2.89 (2H, m), 3.07-3.19 (2H, m), 3.29 (3.28) (1H, d, J = 13.9 Hz), 3.83-3.84 (1H, m), 4.12 (4.14) (2H, q, J = 7.3 Hz), 4.26-4.40 (1H, m), 4.50 (4.51) (1H, d, J = 13.7 Hz), 6.16 (1H, s), 6.40 (6.30) (1H, d, J = 5.0 Hz), 6.98 (1H. d, J = 1.2 Hz), 7.30-7.42 (5H, m), 7.92-7.95 (1H, m).

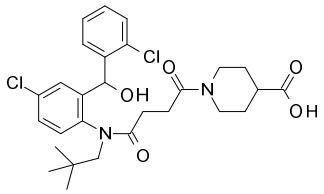
IR (ATR) cm^{-1} 3320, 2950, 1731, 1664, 1625, 1394, 1166, 1041, 746, 478.

Mp 138-140°C.

MS (ESI) *m/z* 577 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{38}N_2O_5Cl_2$: C 62.39, H 6.63, N 4.85, Cl 12.28. Found: C 62.24, H 6.63, N 4.79, Cl 12.05.

1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)-amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (9).



Compound **9** was prepared in a similar manner described for **8** in 88% yield as a colorless powder.

^{1}H-NMR (DMSO-d_6) δ 0.73 (0.81) (9H, s), 1.27-1.46 (2H, m), 1.73-1.81 (2H, m), 1.96-2.17 (1H, m), 2.29-2.69 (5H, m), 2.97-3.06 (2H, m), 4.12-4.38 (3H, m), 5.88 (6.07) (1H, br s), 6.26 (1H, br s), 7.02 (1H, s), 7.26 (1H, s), 7.34-7.60 (5H, m).

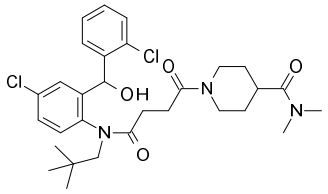
IR (ATR) cm^{-1} 2952, 1727, 1658, 1621, 1475, 1396, 1170, 1020, 744, 541, 420.

Mp 168-170 °C.

MS (ESI) *m/z* 549 $(M + H)^+$.

Anal. Calcd. for $C_{28}H_{34}N_2O_5Cl_2$: C, 61.20; H, 6.24; N, 5.10; Cl, 12.90. Found: C, 60.96; H, 6.29; N, 4.89; Cl, 12.69.

1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)-amino]-4-oxobutanoyl}-*N*,*N*-dimethylpiperidine-4-carboxamide (10a).



Compound **10a** was prepared from **9** in a similar manner described for **8** in 57% yield as a colorless powder.

^{1}H-NMR ($CDCl_3$) δ 0.91 (9H, s), 1.69-1.76 (3H, m), 2.11-2.24 (2H, m), 2.41-2.49 (1H, m), 2.66-2.75 (2H, m), 2.93 (3H, s), 3.06 (3H, s), 3.10-3.17 (3H, m), 3.29 (3.27) (1H, d, J = 13.7 Hz), (3.95) 4.50 (1H, d, J = 13.7 Hz), 4.45-4.57 (1H, m), 6.15-6.18 (1H, m), 6.42 (6.25) (1H, d, J = 5.0 Hz), 6.97-6.99 (1H, m), 7.22-7.42 (5H, m), 7.95 (7.91) (1H, d, J = 7.7 Hz).

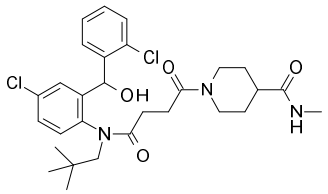
IR (ATR) cm^{-1} 3278, 2948, 1639, 1617, 1398, 1276, 1027, 750, 482.

Mp 197-199 °C.

MS (FAB) *m/z* 576 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{39}N_3O_4Cl_2 \cdot 1.5H_2O$: C 59.70, H 7.01, N 6.96, Cl 11.75. Found: C 59.96, H 6.76, N 6.84, Cl 11.84.

1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)-amino]-4-oxobutanoyl}-*N*-methylpiperidine-4-carboxamide (10b).



Compound **10b** was prepared from **9** in a similar manner described for **8** in 61% yield as a colorless powder.

^{1}H-NMR ($CDCl_3$) δ 0.90(0.91) (9H, s), 1.61-1.87 (3H, m), 2.11-2.47 (5H, m), 2.63-2.70 (1H, m), 2.81 (3H, s), 3.03-3.14 (2H, m), 3.28 (3.94) (1H, d, J = 13.7 Hz), 4.49 (4.50) (1H, d, J = 13.8 Hz), 4.11-4.57 (1H, m), 5.42 (5.58) (1H, br), 6.14-6.17 (1H, m), 6.37 (6.28) (1H, d, J = 5.1 Hz), 6.98 (6.99) (1H, s), 7.22-7.41 (5H, m), 7.91-7.95 (1H, m).

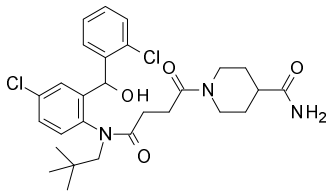
IR (ATR) cm^{-1} 3266, 2948, 1652, 1627, 1475, 1407, 1168, 1027, 833, 746, 534.

Mp 130-132 °C.

MS (FAB) *m/z* 562 $(M + H)^+$.

Anal. Calcd. for $C_{29}H_{37}N_3O_4Cl_2 \cdot 0.5H_2O$: C 60.94, H 6.70, N 7.35, Cl 12.41. Found: C 60.84, H 6.64, N 7.21, Cl 12.42.

1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)-amino]-4-oxobutanoyl}piperidine-4-carboxamide (10c).



Compound **10c** was prepared from **9** in a similar manner described for **8** in 34% yield as a colorless powder.

^{1}H-NMR ($CDCl_3$) δ 0.91 (9H, s), 1.84-1.95 (3H, m), 2.11-2.22 (2H, m), 2.35-2.48 (2H, m), 2.68-2.74 (2H, m), 3.03-3.17 (2H, m), 3.28 (3.27) (1H, d, J = 13.8 Hz), (3.94) 4.49

(1H, d, J = 13.8 Hz), 4.48-4.55 (1H, m), 5.28 (1H, br), 5.41 (5.60) (1H, br), 6.15-6.17 (1H, m), 6.34 (6.27) (1 H, d, J = 5.0 Hz), 6.98 (1H, d, J = 1.7 Hz), 7.23-7.52 (4H, m), 7.91-7.94 (1H, m).

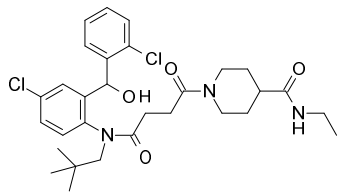
IR (ATR) cm^{-1} 3324, 2950, 1677, 1654, 1614, 1475, 1402, 1270, 1027, 763, 570.

Mp 90-92°C.

MS (ESI) *m/z* 548 $(M + H)^+$.

Anal. Calcd. for $C_{28}H_{35}N_3O_4Cl_2 \cdot 1.0H_2O$: C 59.36, H 6.58, N 7.42, Cl 12.52. Found: C 59.12, H 6.64, N 7.21, Cl 12.31.

1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)-amino]-4-oxobutanoyl}-*N*-ethylpiperidine-4-carboxamide (10d).



Compound **10d** was prepared from **9** in a similar manner described for **8** in 42% yield as a colorless powder.

^{1}H-NMR ($CDCl_3$) δ 0.91 (0.90) (9H, s), 1.12 (1.14) (3H, t, J = 7.1 Hz), 1.78-2.66 (8H, m), 2.93-3.10 (3H, m), 3.29 (2H, q, J = 7.1 Hz), 3.26-3.31 (1H, m), 3.94 (1H, br d, J = 11.7 Hz), 4.50 (4.51) (1H, d, J = 13.6 Hz), 4.45-4.53 (1H, m), 5.38 (5.50) (1H, br), 6.15-6.17 (1H, m), 6.37 (6.28) (1H, d, J = 5.0 Hz), 6.98 (1H, s), 7.23-7.42 (5H, m), 7.91-7.95 (1H, m).

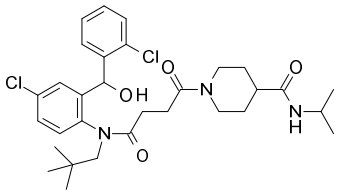
IR (ATR) cm^{-1} 3266, 2954, 1662, 1625, 1475, 1394, 1180, 1029, 744, 576, 480.

Mp 148-150 °C.

MS (FAB) *m/z* 576 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{39}N_3O_4Cl_2 \cdot 0.5H_2O$: C 61.53, H 6.89, N 7.18, Cl 12.11. Found: C 61.56, H 6.81, N 7.12, Cl 12.22.

1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)-amino]-4-oxobutanoyl}-*N*-isopropylpiperidine-4-carboxamide (10e).



Compound **10e** was prepared from **9** in a similar manner described for **8** in 38% yield as a colorless powder.

^{1}H-NMR ($CDCl_3$) δ 0.91 (9H, s), 1.12-1.16 (6H, m), 1.76-1.87 (3H, m), 2.11-2.66 (5H, m), 3.02-3.13 (3H, m), 3.28 (3.27) (1H, d, *J* = 13.8 Hz), 3.93 (1H, br d, *J* = 14.2 Hz), 4.03-4.06 (1H, m), 4.51 (4.50) (1H, d, *J* = 13.7 Hz), 4.48-4.56 (1H, m), 5.20 (5.29) (1H, br), 6.16 (1H, br), 6.37 (6.27) (1H, br), 6.98 (1H, s), 7.24-7.52 (5H, m), 7.91-7.95 (1 H, m).

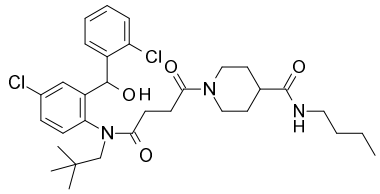
IR (ATR) cm^{-1} 3282, 2958, 1662, 1623, 1473, 1394, 1166, 1027, 744, 541, 480.

Mp 148-150 °C.

MS (ESI) *m/z* 590 $(M + H)^+$.

Anal. Calcd. for $C_{31}H_{41}N_3O_4Cl_2 \cdot 0.25H_2O$: C 62.57, H 7.03, N 7.06, Cl 11.91. Found: C 62.69, H 6.98, N 7.04, Cl 11.53.

_N_-Butyl-1-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoyl}piperidine-4-carboxamide (10f).



Compound **10f** was prepared from **9** in a similar manner described for **8** in 45% yield as a colorless powder.

^{1}H-NMR ($CDCl_3$) δ 0.91 (9H, s), 1.30-1.55 (7H, m), 1.78-1.88 (3H, m), 2.11-2.45 (4H, m), 2.64-2.70 (1H, m), 3.03-3.30 (6H, m), 3.94 (1H, br d, *J* = 13.2 Hz), 4.51 (4.50) (1H, d, *J* = 13.6 Hz), 4.48-4.51 (1H, m), 5.38 (5.51) (1H, br), 6.16 (1H, t, *J* = 4.9 Hz), 6.38 (6.28) (1H, d, *J* = 4.9 Hz), 6.98 (1H, d, *J* = 2.0 Hz), 7.22-7.42 (5H, m), 7.91-7.95 (1H, m).

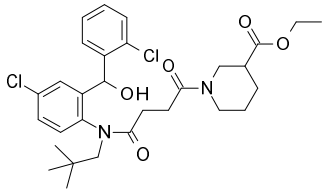
IR (ATR) cm^{-1} 3259, 2956, 1662, 1623, 1473, 1394, 1180, 1027, 744, 478, 422.

Mp 178-180 °C.

MS (ESI) *m/z* 604 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{43}N_3O_4Cl_2 \cdot 0.25H_2O$: C 63.10, H 7.20, N 6.90, Cl 11.64. Found: C 63.09, H 7.14, N 6.88, Cl 11.87.

Ethyl 1-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate (11).



Compound **11** was prepared from **7** in a similar manner described for **8** in 85% yield as a colorless amorphous.

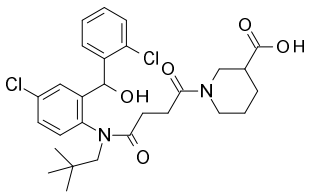
^{1}H-NMR ($CDCl_3$) δ 0.91 (0.90) (9H, s), 1.25 (1.26) (3H, t, *J* = 7.08 Hz), 1.35-2.21 (4H, m), 2.32-3.53 (6H, m), 3.73-4.19 (5H, m), 4.51 (4.50) (1H, d, *J* = 13.7 Hz), 4.48-4.75 (1H, m), 6.16-6.18 (1H, m), 6.28-6.40 (1H, m), 6.98 (1H, d, *J* = 1.95 Hz), 7.24-7.43 (5H, m), 7.91-7.96 (1H, m).

IR (ATR) cm^{-1} 3345, 2950, 1727, 1627, 1168, 1027, 750, 480.

MS (ESI) *m/z* 577 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{38}N_2O_5Cl_2$: C, 62.39; H, 6.63; N, 4.85; Cl, 12.28. Found: C, 62.02; H, 6.69; N, 4.71; Cl, 11.99.

1-{4-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)-amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (12).



Compound **12** was prepared from **11** in a similar manner described for **7** in 68% yield as a colorless powder.

^{1}H-NMR (DMSO-d_6) δ 0.69-0.86 (9H, m), 1.09-3.96 (13H, m), 4.08-4.42 (2H, m), 5.76-6.30 (2H, m), 6.98-7.73 (7H, m).

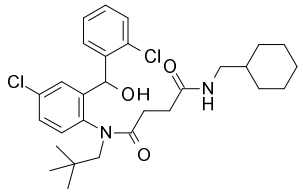
IR (ATR) cm^{-1} 3326, 2952, 1621, 1475, 1394, 1168, 1029, 748, 480, 420.

Mp 153-155 °C.

MS (ESI) *m/z* 549 $(M + H)^+$.

Anal. Calcd. for $C_{28}H_{34}N_2O_5Cl_2 \cdot 2.1H_2O$: C, 57.26; H, 6.56; N, 4.77; Cl, 12.07. Found: C, 56.99; H, 6.32; N, 4.49; Cl, 11.86.

N-{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}-N'-(cyclohexylmethyl)-N-(2,2-dimethylpropyl)succinamide (13).



Compound **13** was prepared from **7** in a similar manner described for **8** in 65% yield as a colorless amorphous.

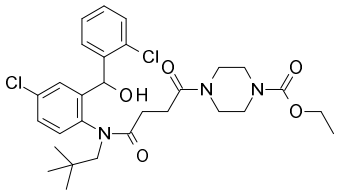
^{1}H-NMR ($CDCl_3$) δ 0.87 (9H, s), 0.88-1.68 (11H, m), 2.09-2.17 (1H, m), 2.23-2.28 (1H, m), 2.46-2.54 (1H, m), 2.63-2.77 (1H, m), 2.94-3.03 (1H, m), 3.03 (1H, d, J = 13.8 Hz), 3.14-3.21 (1H, m), 4.42 (4.52) (1H, d, J = 13.8 Hz), 5.70 (1H, m), 5.89 (1H, d, J = 5.3 Hz), 6.07 (1H, d, J = 5.3 Hz), 7.11 (1H, d, J = 2.20 Hz), 7.21-7.38 (5H, m), 7.81-7.83 (1H, m).

IR (ATR) cm^{-1} 3330, 2923, 1639, 1475, 1394, 1276, 1168, 1027, 748, 478, 422.

MS (ESI) *m/z* 533 $(M + H)^+$.

Anal. Calcd. for $C_{29}H_{38}N_2O_3Cl_2 \cdot 0.9H_2O \cdot 0.3$ether: C, 63.42; H, 7.54; N, 4.90; Cl, 12.40. Found: C, 63.77; H, 7.28; N, 4.81; Cl, 12.07.

Ethyl 4-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperazine-1-carboxylate (14).



Compound **14** was prepared from **7** in a similar manner described for **8** in quantitative yield as a colorless powder.

^{1}H-NMR ($CDCl_3$) δ 0.91 (0.89) (9H, s), 1.27 (1.21) (3H, t, *J* = 7.1 Hz), 2.13-2.49 (3H, m), 3.05-3.14 (1H, m), 3.28 (2.94) (1H, d, *J* = 13.7 Hz), 3.33-3.66 (8H, m), 4.15 (2H, q, *J* = 7.1 Hz), 4.50 (4.46) (1H, d, *J* = 13.7 Hz), 6.15-6.18 (2H, m), 6.98 (1H, dd, *J* = 2.0, 0.73 Hz), 7.21-7.43 (4H, m), 7.92 (1H, dd, *J* = 7.8, 1.5 Hz).

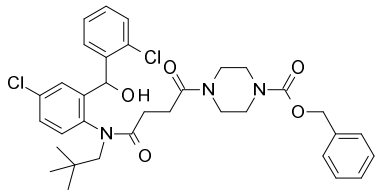
IR (ATR) cm^{-1} 3332, 2948, 1700, 1662, 1635, 1423, 1234, 1184, 1027, 750.

Mp 177-179 °C.

MS (ESI) *m/z* 578 $(M + H)^+$.

Anal. Calcd. for $C_{29}H_{37}N_3O_5Cl_2$: C 60.21, H 6.45, N 7.26, Cl 12.26. Found: C 60.07, H 6.46, N 7.30, Cl 12.18.

Benzyl 4-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoyl}piperazine-1-carboxylate (15).



Compound **15** was prepared from **7** in a similar manner described for **8** in 69% yield as a colorless powder.

^{1}H-NMR ($CDCl_3$) δ 0.91 (9H, s), 2.15-2.45 (2H, m), 3.09-3.62 (11H, m), 4.50 (1H, d, *J* = 14.9 Hz), 5.15 (2H, s), 6.15 (2H, m), 6.98 (1H, br s), 7.26-7.36 (10H, m), 7.93 (1H, m).

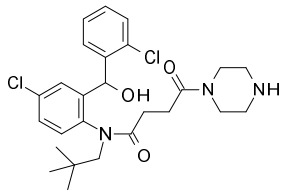
IR (ATR) cm^{-1} : 3345, 2960, 1695, 1664, 0625, 1427, 1222, 1020, 748, 696, 574.

Mp 129-132 °C.

MS (ESI) *m/z* 640 $(M + H)^+$.

Anal. Calcd. for $C_{34}H_{39}N_3O_5Cl_2$: C 63.75, H 6.14, N 6.56, Cl 11.07. Found: C 63.58, H 6.18, N 6.33, Cl 11.22.

_N_-{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}-_N_-(2,2-dimethylpropyl)-4-oxo-4-piperazin-1-ylbutanamide (16).



A suspension of **15** (0.15 g, 0.23 mmol) and 10% palladium on carbon (50% water, 30 mg) in MeOH (30 ml) was hydrogenated for 2 h. The reaction mixture was filtrated and concentrated in vacuo to give **16** (0.12 g, quant.) as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.87 (9H, s), 2.14-2.25 (2H, m), 2.54-3.98 (11H, m), 4.35-4.60 (1H, m), 5.79-6.28 (2H, m), 7.00 (1H, s), 7.24-7.37 (5H, m), 7.81 (1H, s).

IR (ATR) cm^{-1} 3338, 2952, 1637, 1392, 1247, 1024, 700, 561, 509.

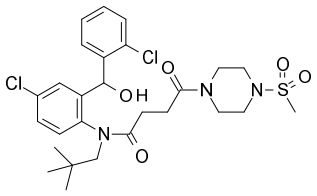
Mp 148-150°C.

MS (FAB) *m/z* 506 $(M + H)^+$.

HRMS (FAB) *m/z* 506.1951 (Calcd. for $C_{26}H_{34}O_3N_3Cl_2$: 506.1977).

Anal. Calcd. for $C_{26}H_{33}N_3O_3Cl_2 \cdot 1.5H_2O \cdot 0.25$hexane·0.20ether: C 59.65, H 7.34, N 7.37, Cl 12.44. Found: C 59.77, H 7.72, N 7.46, Cl 12.56.

_N_-{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}-_N_-(2,2-dimethylpropyl)-4-[4-(methylsulfonyl)piperazin-1-yl]-4-oxobutanamide (17).



Compound **17** was dissolved in CH_2Cl_2, followed by the addition of Et_3N (0.028 ml, 0.20 mmol) and methane sulfonyl chloride (0.013 ml, 0.16 mmol). The reaction mixture was stirred at room temperature for 18 h. The mixture was diluted with water and CH_2Cl_2. The organics were extracted with CH_2Cl_2, the extract was

washed with brine, and then dried with Na_2SO_4. The organic solvent was removed under reduced pressure and the residue was purified with silica gel column chromatography (5-7% MeOH – CH_2Cl_2) to give Compound **17** (49 mg, 0.083 mmol, 62%) as colorless powder.

^{1}H-NMR (DMSO-d_6) δ 0.76-0.86 (9H, m), 2.04-2.71 (5H, m), 2.87 (3H, s), 2.92-3.12 (4H, m), 3.37-3.54 (4H, m), 4.08-4.42 (1H, m), 5.63-6.21 (2H, m), 7.02-7.69 (7H, m).

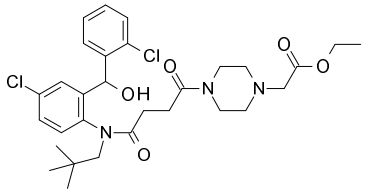
IR (ATR) cm^{-1} 3388, 2954, 1635, 1324, 1157, 958, 775, 516.

Mp 104-106 °C.

MS (FAB) *m/z* 584 $(M + H)^+$.

HRMS (FAB) *m/z* 584.1714 (Calcd. for $C_{27}H_{36}O_5N_3Cl_2S$: 584.1753).

Ethyl (4-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperazin-1-yl)acetate (18).



Compound **18** was prepared from **7** in a similar manner described for **8** in 71% yield as a colorless amorphous.

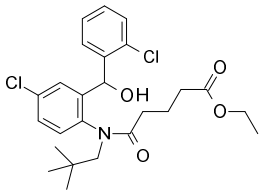
^{1}H-NMR ($CDCl_3$) δ 0.91 (9H, s), 1.27 (3H, t, *J* = 7.10 Hz), 2.11-2.22 (2H, m), 2.38-2.66 (5H, m), 3.05-3.12 (1H, m), 3.20 (2H, s), 3.27 (1H, d, *J* = 13.7 Hz), 3.48-3.72 (4H, m), 4.18 (2H, q, *J* = 7.10 Hz), 4.50 (1H, d, *J* = 13.7 Hz), 6.15 (1H, d, *J* = 5.0 Hz), 6.28 (1H, d, *J* = 5.0 Hz), 6.97 (1H, s), 7.24-7.41 (5H, m), 7.92 (1H, d, *J* = 7.6 Hz).

IR (ATR) cm^{-1} 3266, 2962, 1749, 1664, 1625, 1440, 1180, 1160, 746.

MS (ESI) *m/z* 592 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{39}N_3O_5Cl_2 \cdot 0.5H_2O$: C, 59.90; H, 6.70; N, 6.99; Cl, 11.79. Found: C, 60.04; H, 6.61; N, 6.93; Cl, 12.03.

Ethyl 5-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-5-oxopentanoate (19a).



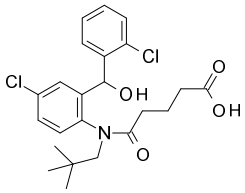
Compound **19a** was prepared from **5** in a similar manner described for **6** in quantitative yield as a colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.91 (9H, s), 1.17-1.28 (3H, m), 1.77-2.56 (6H, m), 4.00-4.16 (2H, m), 4.35 (1H, d, *J* = 13.7 Hz), 4.53 (1H, d, *J* = 13.7 Hz), 6.11 (1H, br s), 6.34 (1H, s), 7.19-7.76 (7H, m).

MS (FAB) *m/z* 480 $(M + H)^+$.

HRMS (FAB) *m/z* 480.1682 (Calcd. for $C_{29}H_{37}O_5N_2Cl_2$: 480.1708).

5-[{4-Chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)-amino]-5-oxopentanoic acid (20a).



Compound **20a** was prepared from **19a** in a similar manner described for **7** in quantitative yield as a colorless amorphous.

^{1}H-NMR (DMSO-d_6) δ 0.77-0.86 (9H, m), 0.93-3.03 (6H, m), 4.22 (1H, br d, *J* = 13.3Hz), 4.40 (1H, br d, *J* = 13.3), 5.84-6.20 (2H, m), 6.76-7.62 (7H, m), 11.97 (1H, br).

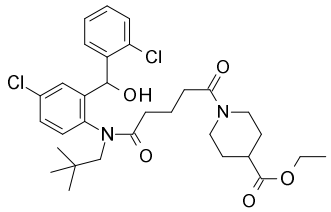
IR (ATR) cm^{-1} 2954, 1706, 1635, 1475, 1396, 1166, 1025, 754, 418.

Mp 65-67 °C.

MS (ESI) *m/z* 452 $(M + H)^+$.

Anal. Calcd. for $C_{23}H_{27}NO_4Cl_2 \cdot 0.3H_2O \cdot 0.2$ether: C 60.49, H 6.31, N 2.96, Cl 15.00. Found: C 60.83, H 6.27, N 2.80, Cl 14.71.

Ethyl 1-{5-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl)amino]-5-oxopentanoyl}piperidine-4-carboxylate (21a).



Compound **21a** was prepared from **20a** in a similar manner described for **8** in 86% yield as a colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.81-0.90 (9H, s), 1.26 (3H, t, *J* = 7.1Hz), 1.41-2.31 (8H, m), 2.48-3.21 (6H, m), 3.68-3.81 (1H, m), 4.12-4.18 (2H, m), 4.27-4.53 (2H, m), 5.84-6.33 (2 H, m), 7.17-7.74 (7 H, m).

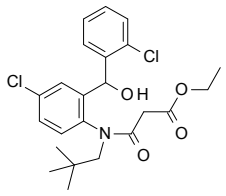
IR (ATR) cm^{-1} 2952, 1727, 1639, 1475, 1170, 1037, 755, 418.

Mp 58-60 °C.

MS (ESI) *m/z* 591$(M + H)^+$.

Anal. Calcd. for $C_{31}H_{40}N_2O_5Cl_2 \cdot 0.4H_2O \cdot 0.2$ether: C 62.25, H 7.03, N 4.57, Cl 11.56. Found: C 62.52, H 6.97, N 4.46, Cl 11.16.

Ethyl 3-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl) amino]-3-oxopropanoate (19b).

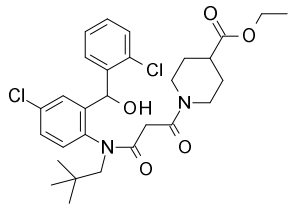


Compound **19b** was prepared from **5** in a similar manner described for **6** in 81% yield as a yellow oil.

^{1}H-NMR ($CDCl_3$) δ 0.89 and 0.94 (9H, s), 1.20-1.30 (3H, m), 2.30 and 2.70 (1H, d, *J*= 15.7 Hz), 2.83 and 4.57 (1H, d, *J* = 13.4 Hz), 3.05 and 4.46 (1H, d, *J* = 13.7 Hz), 3.18-3.27 (1H, m), 4.40-4.19 (2H, m), 6.15 and 6.32 (1H, s), (7.00-7.06) 7.20-7.39 (6H, m), 7.58-7.67 (1H, m).

MS (ESI) *m/z* 452 $(M + H)^+$.

Ethyl 1-{3-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-3-oxopropanoyl}piperidine-4-carboxylate (21b).



Compound **21b** was prepared from **19b** in a similar manner described for **20a** and **21a** in 78% yield from **19b** as a colorless amorphous.

^{1}H-NMR (DMSO-d_6) δ 0.74-0.84 (9H, m), 1.15 (3H, t, J = 7.1 Hz), 1.32-1.78 (3H, m), 2.23-3.74 (8H, m), 4.04 (2H, q, J = 7.2 Hz), 4.10-4.38 (2H, m), 5.86-6.03 (1H, m), 6.34 (1H, br), 6.98 (1H, dd, J = 11.2, 2.4 Hz), 7.30-7.53 (6H, m).

IR (ATR) cm^{-1} 3345, 2952, 1727, 1623, 1475, 1166, 1029, 748, 586, 418.

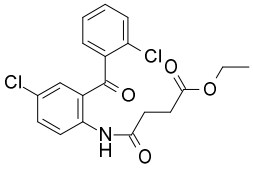
Mp 90-92 °C.

MS (FAB) *m/z* 563 $(M + H)^+$.

HRMS (FAB) *m/z* 563.2100 (Calcd. for $C_{29}H_{37}O_5N_2Cl_2$: 563.2080).

Anal. Calcd. for $C_{29}H_{37}N_2O_5Cl_2$: C 61.81, H 6.44, N 4.96, Cl 12.58. Found: C 61.45, H 6.46, N 4.85, Cl 12.54.

Ethyl 4-({4-chloro-2-[(2-chlorophenyl)carbonyl]phenyl}amino)-4-oxobutanoate (22).



Compound **22** was prepared from **3** in a similar manner described for **6** in 52% yield as a colorless amorphous.

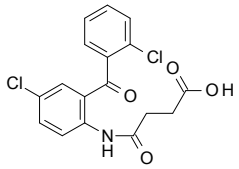
^{1}H-NMR ($CDCl_3$) δ 1.27 (3H, t, J = 7.1 Hz), 2.74-2.77 (2H, m), 2.81-2.85 (2H, m), 4.17 (2H, q, J = 7.1 Hz), 7.29-7.33 (2H, m), 7.39-7.42 (1H, m), 7.48-7.53 (3H, m), 8.78 (1H, d, J = 9.3 Hz), 11.48 (1H, br s).

IR (ATR) cm^{-1} 3291, 1735, 1698, 1637, 1577, 1425, 1398.

MS (ESI) *m/z* 396 [$(M + H)^+$, ^{37}Cl], 394 [$(M + H)^+$, ^{35}Cl].

Anal. Calcd. for $C_{19}H_{17}Cl_2NO_4$: C, 57.88; H, 4.35; Cl, 17.99; N, 3.55. Found: C, 57.84; H, 4.34; Cl, 17.97; N, 3.42.

4-({4-Chloro-2-[(2-chlorophenyl)carbonyl]phenyl}amino)-4-oxobutanoic acid (23).



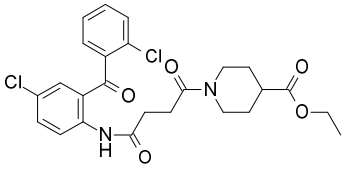
Compound **23** was prepared from **22** in a similar manner described for **7** in 67% yield as a colorless crystal.

^{1}H-NMR ($CDCl_3$) δ 2.79-2.85 (4H, m), 7.26-7.34 (2H, m), 7.39-7.43 (1H, m), 7.48-7.54 (3H, m), 8.76 (1H, d, J = 9.3 Hz), 11.50 (1H, bs).

Mp 152-155 °C.

MS (ESI) *m/z* 366 [(M + H)$^+$, ^{35}Cl].

Ethyl 1-[4-({4-chloro-2-[(2-chlorophenyl)carbonyl]phenyl}amino)-4-oxobutanoyl]-piperidine-4-carboxylate (24).



Compound **24** was prepared from **23** in a similar manner described for **8** in 95% yield as a colorless crystal.

^{1}H-NMR ($CDCl_3$) δ 1.26 (3H, t, J = 7.1 Hz), 1.59-1.78 (2H, m), 1.89-2.05 (2H, m), 2.51-2.57 (1H, m), 2.72-2.90 (5H, m), 3.14-3.21 (1H, m), 3.87-3.94 (1H, m), 4.13 (2H, q, J = 7.1 Hz), 4.37-4.43 (1H, m), 7.26-7.33 (2H, m), 7.37-7.43 (1H, m), 7.47-7.54 (3H, m), 8.78 (1H, d, J = 9.1 Hz), 11.50 (1H, bs).

IR (ATR) cm^{-1} 3300, 3200, 1727, 1702, 1641, 1598, 1577, 1504, 1432, 1398, 1375, 1315, 1240, 1162, 1101.

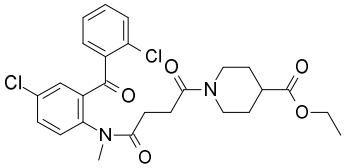
Mp 155-157 °C (AcOEt – *n*-hexane).

MS (ESI) *m/z* 507 [(M + H)$^+$, ^{37}Cl], 505 [(M + H)$^+$, ^{35}Cl].

HRMS (FAB) *m/z* 507.1316 (Calcd. for $C_{25}H_{27}Cl_2N_2O_5$: 507.1297).

Anal. Calcd. for $C_{25}H_{26}Cl_2N_2O_5$: C, 59.41; H, 5.19; Cl, 14.03; N, 5.54. Found: C, 59.41; H, 5.13; Cl, 13.87; N, 5.61.

Ethyl 1-{4-[{4-chloro-2-[(2-chlorophenyl)carbonyl]phenyl}(methyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (25a).

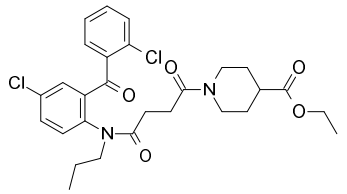


To the solution of compound **24** (0.52 g, 1.03 mmol) in *N*,*N*-dimethylformamide (10 ml) was added sodium hydride (60%net, 45 mg, 1.13 mmol) at 0°C, and stirred for 10 min. Then, the reaction mixture was added diazomethane (0.79 ml, 0.73 g, 5.15 mmol) and stirred for 50 min at the same temperature. The reaction mixture was diluted with AcOEt and organics were washed with brine. The extract was dried over Na_2SO_4 and then concentrated in vacuo, and the residue was purified with silica gel column chromatography (0-5% MeOH – CH_2Cl_2) to give Compound **25a** (0.51 g, 0.98 mmol, 95 %) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ 1.25 (3H, t, *J* = 7.1 Hz), 1.55-1.74 (2H, m), 1.86-1.97 (2H, m), 2.16-2.25 (1H, m), 2.34-2.62 (3H, m), 2.76-2.90 (2H, m), 2.99 (3.28) (3H, s), 3.82-3.90 (1H, m), 4.14 (2H, q, *J* = 7.1 Hz), 4.31-4.40 (1H, m), 7.40-7.59 (7H, m).

MS (ESI) *m/z* 521 [(M + H)$^+$, ^{37}Cl], 519 [(M + H)$^+$, ^{35}Cl].

Ethyl 1-{4-[{4-chloro-2-[(2-chlorophenyl)carbonyl]phenyl}(propyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (25b).



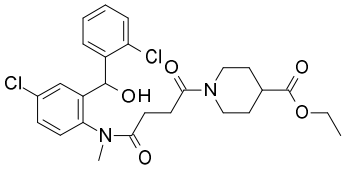
Compound **25b** was prepared from **24** in a similar manner described for **25a** in 68% yield as a pale yellow amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.83 (0.89) (3H, t, *J* = 7.6 Hz), 1.25 (3H, t, *J* = 7.1 Hz), 1.40-1.77 (4H, m), 1.86-1.97 (2H, m), 2.14-2.25 (1H, m), 2.36-2.54 (3H, m), 2.76-2.91 (3H, m), 3.06-3.15 (1H, m), 3.86-3.91 (1H, m), 3.95-4.02 (1H, m), 4.13 (2H, q, *J* = 7.1 Hz), 4.29-4.37 (1H, m), 7.27-7.47 (6H, m), 7.54 (7.55) (1H, d, *J* = 8.3 Hz).

MS (ESI) *m/z* 549 [(M + H)$^+$, ^{37}Cl], 547 [(M + H)$^+$, ^{35}Cl].

HRMS (FAB) *m/z* 547.1789 (Calcd. for $C_{28}H_{33}Cl_2N_2O_5$: 547.1767).

Ethyl 1-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(methyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (26a).



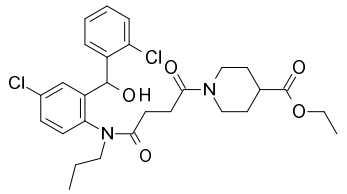
Compound **26a** was prepared from **25a** in a similar manner described for **4** in 83% yield as a colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 1.22-1.27 (3H, m), 1.50-1.72 (2H, m), 1.82-2.04 (3H, m), 2.20-2.25 (1H, m), 2.48-2.67 (2H, m), 2.80-2.96 (1H, m), 3.08-3.22 (2H, m), 3.37 (3.38) (3H, s), 3.82-3.89 (1H, m), 4.10-4.17 (2H, m), 4.26-4.40 (1H, m), 6.25-6.28 (1H, m), 6.56 (0.45H, d, *J* = 5.6 Hz, exchangeable with D_2O), 6.66 (0.55H, d, *J* = 5.9 Hz, exchangeable with D_2O), 6.94 (1H, d, *J* = 2.5 Hz), 7.05-7.08 (1H, m), 7.26-7.32 (3H, m), 7.39-7.43 (1H, m), 7.98-8.01 (1H, m).

MS (ESI) *m/z* 523 [(M + H)$^+$, ^{37}Cl], 521 [(M + H)$^+$, ^{35}Cl].

HRMS (FAB) *m/z* 521.1636 (Calcd. for $C_{26}H_{31}Cl_2N_2O_5$: 521.1610).

Ethyl 1-{4-[{4-chloro-2-[(2-chlorophenyl)(hydroxy)methyl]phenyl}(propyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (26b).



Compound **26b** was prepared from **25b** in a similar manner described for **4** in 79% yield as a colorless amorphous.

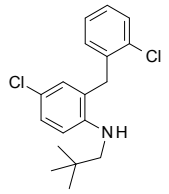
^{1}H-NMR ($CDCl_3$) δ 0.88 (3H, t, *J* = 7.3 Hz), 1.20-1.28 (4H, m), 1.40-1.75 (3H, m), 1.82-2.03 (5H, m), 2.44-2.55 (2H, m), 2.73-2.90 (1H, m), 3.05-3.29 (2.4H, m), 3.81-3.89 (0.6H, m), 4.11-4.41 (2H, m), 6.23-6.26 (1H, m), 6.51 (0.4H, d, *J* = 5.6 Hz),

6.59 (0.6H, d, J = 2.4 Hz), 7.01-7.04 (1H, m), 7.26-7.35 (3H, m), 7.39-7.43 (1H, m), 7.77-8.00 (1H, m).

MS (ESI) *m/z* 551 [(M + H)$^+$, ^{37}Cl], 549 [(M + H)$^+$, ^{35}Cl].

HRMS (FAB) *m/z* 549.1901 (Calcd. for $C_{28}H_{35}Cl_2N_2O_5$: 549.1923).

4-Chloro-2-(2-chlorobenzyl)-*N*-(2,2-dimethylpropyl)aniline (27).

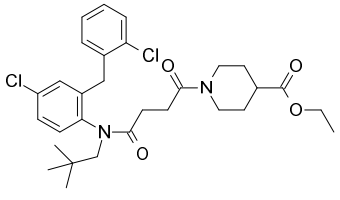


A solution of triphenylphosphineoxide (329 mg, 1.18 mmol) in CH_2Cl_2 (5.0 ml) was cooled to 0ºC, added trifulic anhydride (109 μl, 0.65 mmol), and stirred for 1h. At the same temperature, the mixture was added [5-chloro-2-(2,2-dimethylpropyl-amino)phenyl](2-chlorophenyl)methanol (200 mg, 0.591 mmol) and stirred for 2h. Then, the reaction mixture was added sodium borohydride (89.5 mg, 2.36 mmol) and allowed to warm to room temperature for 2 h. The solution was removed under reduced pressure, the residue was extracted with AcOEt, and then saturated NH_4Claq. The organic layer was washed with brine and dried over Na_2SO_4. The solution was concentrated in vacuo and the residue was purified by column chromatography (AcOEt : *n*-hexane = 0 : 1 – 1 : 0) to give the title compound (166 mg, 87%).

^{1}H-NMR ($CDCl_3$) δ 0.81 (9H, s), 2.77 (2 H, s), 3.34 (1 H, br s), 3.94 (2 H, s), 6.55 (1 H, d, J = 8.8 Hz), 6.97-7.03 (2 H, m), 7.10-7.18 (3 H, m), 7.38-7.42 (1 H, m).

MS (ESI) *m/z* 322 (M + H)$^+$.

Ethyl 1-(4-{[4-chloro-2-(2-chlorobenzyl)phenyl](2,2-dimethylpropyl)amino}-4-oxo-butanoyl)piperidine-4-carboxylate (28).



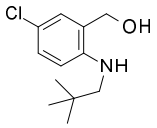
A solution of 1-(3-Carboxypropionyl)piperidine-4-carboxylic acid ethyl ester (100 mg, 0.384 mmol) in CH_2Cl_2 (3.0 ml) was added *N,N*-dimethylformamide (50 μl) and cooled to -15°C. The mixture was added oxalyl chloride (40.2 μl, 0.471 mmol) and stirred for 1h. The solution was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (3.0 ml) and added [4-chloro-2-(2-chlorobenzyl)phenyl](2,2-dimethylpropyl) amine (82.5 mg, 0.256 mmol) at 0°C, 4-dimethylaminopyridine (47.0 mg, 0.384 mmol) and diisopropylethylamine (66.9 μl, 0.384 mmol). The reaction mixture was stirred for 12 h and treated with H_2O. The organic layer was washed with brine and dried over Na_2SO_4. The solution was concentrated in vacuo and the residue was purified by column chromatography (AcOEt : *n*-hexane = 0 : 1 – 1 : 0) to give the title compound (45.3 mg, 32%).

^{1}H-NMR ($CDCl_3$) δ 0.92 (9 H, s), 1.25 (3 H, t, *J* = 7.2 Hz), 1.53-1.75 (2 H, m), 1.85-1.95 (2 H, m), 1.95-2.13 (1 H, m), 2.40-2.82 (6 H, m), 3.05-3.13 (1 H, m), 3.79-3.89 (1 H, m), 3.95-4.06 (2 H, m), 4.14 (2 H, q, *J* = 7.2 Hz), 4.32-4.40 (2 H, m), 6.87-6.92 (1 H, m), 7.15-7.27 (3 H, m), 7.36-7.45 (1 H, m).

MS (ESI) *m/z* 561 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{38}Cl_2N_2O_4$: C, 64.17; H, 6.82; N, 4.99. Found: C, 64.10; H, 7.25; N, 4.63.

{5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}methanol (31a).



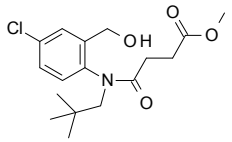
Compound **31a** was prepared from **30a** in a similar manner described for **5** in 73% yield as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ 1.02 (9H, s), 2.88 (2H, s), 4.64 (2H, d, *J* = 3.2 Hz), 4.85 (1H, br s), 6.58 (1H, d, *J* = 8.5 Hz), 7.02 (1H, d, *J* = 2.4 Hz), 7.14 (1H, dd, *J* = 8.5, 2.4 Hz).

IR (ATR) cm^{-1} 3568, 2954, 1604, 1581, 1508, 1475, 1200, 1001, 872, 802.

MS (ESI) *m/z* 228 [$(M + H)^+$, ^{35}Cl], 230 [$(M + H)^+$, ^{37}Cl].

Methyl 4-{[4-chloro-2-(hydroxymethyl)phenyl](2,2-dimethylpropyl)amino}-4-oxo-butanoate (35a).



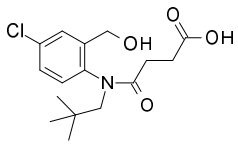
Compound **35a** was prepared from **31a** in a similar manner described for **6** in 85% yield as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ 0.89 (9H, s), 2.09-2.42 and 2.80-2.90 (4H, m), 2.68 (4.26) (1H, d, *J* = 13.4 Hz), 3.14-3.20 (1H, m), 3.66 (3H, s), 4.49 (4.51) (1H, d, *J* = 12.9 Hz), 4.67 (4.68) (1H, d, *J* = 12.9 Hz), 7.21 (1H, d, *J* = 8.3 Hz), 7.29 (1H, dd, *J* = 8.1, 2.2 Hz), 7.66 (1H, d, *J* = 2.2 Hz).

IR (ATR) cm^{-1} 3450, 2952, 1736, 1645, 1479, 1406, 1365, 1236, 1169, 1045, 847.

MS (ESI) *m/z* 342 [(M + H)$^+$, ^{35}Cl], 364 [(M + Na)$^+$, ^{35}Cl].

4-{[4-Chloro-2-(hydroxymethyl)phenyl](2,2-dimethylpropyl)amino}-4-oxobutanoic acid (36a).



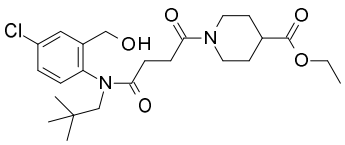
Compound **36a** was prepared from **35a** in a similar manner described for **7** in 98% yield as a colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.90 (9H, s), 2.15-2.45 and 2.77-2.90 (4H, m), 2.68 (1H, d, *J* = 13.5 Hz), 4.29 (1H, d, *J* = 13.5 Hz), 4.50 (1H, d, *J* = 13.5 Hz), 4.65 (1H, d, *J* = 13.5 Hz), 7.20 (1H, d, *J* = 8.5 Hz), 7.30 (1H, dd, *J* = 8.5, 2.4 Hz), 7.64 (1H, d, *J* = 2.4 Hz).

IR (ATR) cm^{-1} 3423, 2954, 1712, 1639, 1477, 1394, 1246, 1171, 1093, 1043, 829.

MS (ESI) *m/z* 328 (M + H)$^+$.

1-(4-{[4-Chloro-2-(hydroxymethyl)phenyl](2,2-dimethylpropyl)amino}-4-oxo-butanoyl)piperidine-4-carboxylate (37a).



Compound **37a** was prepared from **36a** in a similar manner described for **8** in 81% yield as a colorless amorphous.

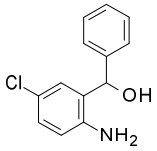
^{1}H-NMR ($CDCl_3$) δ 0.89 (9H, s), 1.24 (1.26) (3H, t, *J* = 7.1 Hz), 1.70-2.05 (5H, m), 2.06-2.21 (1H, m), 2.29-2.54 (2H, m), 2.60 (2.63) (1H, d, *J* = 13.4 Hz), 2.70-2.85 (1H, m), 2.92-3.19 (2H, m), 3.78-3.87 (1H, m), 4.13 (4.14) (2H, q, *J* = 7.1 Hz), 4.18-4.40 (2H, m), 4.30 (1H, d, *J* = 13.6 Hz), 4.67 (1H, d, *J* = 13.6 Hz), 4.75-4.94 (1H, m), 7.10-7.31 (2H, m), 7.65 (1H, s).

IR (ATR) cm^{-1} 3440, 2952, 1728, 1630, 1477, 1392, 1273, 1173, 1039.

MS (ESI) *m/z* 467 [$(M + H)^+$, ^{35}Cl], 469 [$(M + H)^+$, ^{37}Cl].

Anal. Calcd. for $C_{24}H_{35}ClN_2O_5 \cdot 0.2H_2O$: C, 61.25; H, 7.58; Cl, 7.53; N, 5.95. Found: C, 61.06; H, 7.56; Cl, 7.76; N, 5.65.

(2-Amino-5-chlorophenyl)(phenyl)methanol (30b).



Compound **30b** was prepared from **29b** in a similar manner described for **4** in 91% yield as a colorless crystal.

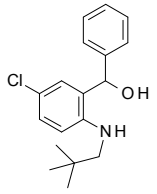
^{1}H-NMR ($CDCl_3$) δ 3.94 (1H, br s), 5.81 (1H, s), 6.59 (1H, dd, *J* = 8.8, 1.0 Hz), 7.02-7.09 (2H, m), 7.27-7.41 (5H, m).

IR (ATR) cm^{-1} 3213, 1603, 1485, 1448, 1417, 1257, 1200, 1028, 906, 854, 823, 686.

MS (ESI) *m/z* 234 [$(M + H)^+$, ^{35}Cl], 236 [$(M + H)^+$, ^{37}Cl].

Anal. Calcd. for $C_{13}H_{12}ClNO \cdot 0.05H_2O$: C, 66.56; H, 5.20; Cl, 15.11; N, 5.97. Found: C, 66.58; H, 5.15; Cl, 15.03; N, 5.90.

{5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}(phenyl)methanol (31b).



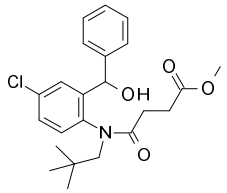
Compound **31b** was prepared from **30b** in a similar manner described for **5** in 45% yield as a pale yellow syrup.

^{1}H-NMR ($CDCl_3$) δ 0.81 (9H, s), 2.45 (1H, br s), 2.72 and 2.73 (2H, both s), 4.34 (1H, br s), 5.78 (1H, br s), 6.55 (1H, d, J = 8.8 Hz), 7.08 (1H, d, J = 2.4 Hz), 7.14 (1H, dd, J = 8.6, 2.4 Hz), 7.25-7.40 (5H, m).

IR (ATR) cm^{-1} 3409, 2954, 1600, 1579, 1508, 1475, 1252, 1170, 1018, 804, 700.

MS (ESI) *m/z* 304 [(M + H)$^+$, ^{35}Cl], 306 [(M + H)$^+$, ^{37}Cl].

Methyl 4-[{4-chloro-2-[hydroxy(phenyl)methyl]phenyl}(2,2-dimethylpropyl)amino] -4-oxobutanoate (35b).



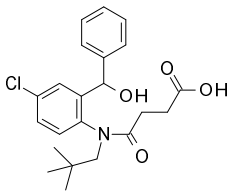
Compound **35b** was prepared from **31b** in a similar manner described for **6** in 85% yield as a colorless syrup.

^{1}H-NMR ($CDCl_3$) δ (0.70-0.82 and 1.73-1.82) 2.07-2.19 and 2.23-2.44 and 2.94-3.04 (4H, m), 0.90 (0.92) (9H, s), 2.55 (2.86) (1H, d, J = 13.3 Hz), 3.58 (3.69) (3H, s), 4.45 (4.48) (1H, d, J = 13.3 Hz), 4.71 (4.72) (1H, br s), 5.81 (5.88) (1H, s), 7.22-7.43 (7H, m), 7.93 (1H, d, J = 2.2 Hz).

IR (ATR) cm^{-1} 3423, 2952, 1736, 1664, 1475, 1238, 1167, 1024, 835, 700, 501.

MS (ESI) *m/z* 418 [(M + H)$^+$, ^{35}Cl], 420 [(M + H)$^+$, ^{37}Cl].

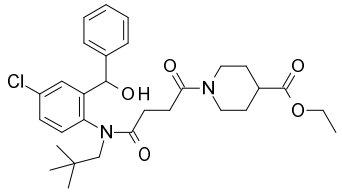
4-[{4-Chloro-2-[hydroxy(phenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxo-butanoic acid (36b).



Compound **36b** was prepared from **35b** in a similar manner described for **7** in quantitative yield as a colorless amorphous.

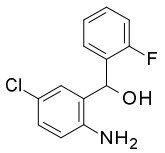
^{1}H-NMR ($CDCl_3$) δ 0.87 (0.92) (9H, s), 1.80-1.89 and 2.00-2.24 and 2.33-2.47 and 2.91-2.99 (4H, m), 2.48 (2.90) (1H, d, *J* = 13.4 Hz), 4.39 (4.49) (1H, d, *J* = 13.4 Hz), 5.79 (5.84) (1H, s), 7.15-7.43 (7H, m), 8.00 (1H, d, *J* = 2.7 Hz).
MS (ESI) *m/z* 404 [(M + H)$^+$, ^{35}Cl], 406 [(M + H)$^+$, ^{37}Cl].

Ethyl 1-{4-[{4-chloro-2-[hydroxy(phenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37b).



Compound **37b** was prepared from **36b** in a similar manner described for **8** in 53% yield as a colorless amorphous.
^{1}H-NMR ($CDCl_3$) δ 0.92 (9H, s), 1.24 (1.25) (3H, t, *J* = 7.1 Hz), 1.47-1.73 (2H, m), 1.75-1.99 (2H, m), 2.00-2.09 (1H, m), 2.14-2.23 (1H, m), 2.36-2.55 (2H, m), 2.66 (1H, d, *J* = 13.7 Hz), 2.70-2.89 (1H, m), 3.05-3.19 (2H, m), 3.79-3.89 (1H, m), 4.12 (4.14) (2H, q, *J* = 7.1 Hz), 4.23-4.40 (1H, m), 4.50 (4.52) (1H, d, *J* = 13.7 Hz), 5.89-5.95 (1H, m), 6.08-6.19 (1H, m), 7.18-7.43 (8H, m).
IR (ATR) cm^{-1} 3388, 2952, 1728, 1626, 1475, 1392, 1274, 1169, 1038, 700.
MS (ESI) *m/z* 543 [(M + H)$^+$, ^{35}Cl], 445 [(M + H)$^+$, ^{37}Cl].
Anal. Calcd. for $C_{30}H_{39}ClN_2O_5$: C, 66.35; H, 7.24; N, 5.16; Cl, 6.53. Found: C, 66.41; H, 7.25; N, 4.96; Cl, 6.83.

(2-Amino-5-chlorophenyl)(2-fluorophenyl)methanol (30c).



Compound **30c** was prepared from **29c** in a similar manner described for **4** in 88% yield as a colorless crystal.

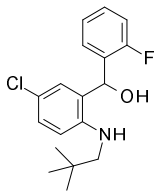
^{1}H-NMR ($CDCl_3$) δ 4.10 (1H, br s), 6.10 (1H, s), 6.62 (1H, d, *J* = 8.5 Hz), 7.00 (1H, s), 7.04-7.13 (2H, m), 7.19 (1H, dd, *J* = 7.6 Hz), 7.22-7.27 (1H, m), 7,29-7.37 (1H, m), 7.43 (1H, dd, *J* = 7.6 Hz).

IR (ATR) cm^{-1} 3307, 1618, 1585, 1483, 1454, 1279, 1217, 1026, 802, 748.

MS (ESI) *m/z* 252 [$(M + H)^+$, ^{35}Cl], 254 [$(M + H)^+$, ^{37}Cl].

Anal. Calcd. for $C_{13}H_{11}ClFNO$: C, 61.32; H, 4.43; Cl, 14.04; F, 7.52; N, 5.55. Found: C, 61.69; H, 4.38; Cl, 13.96; F, 7.43; N, 5.47.

{5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}(2-fluorophenyl)methanol (31c).

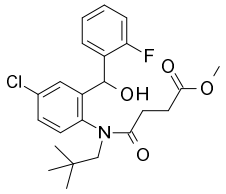


Compound **31c** was prepared from **30c** in a similar manner described for **5** in 62% yield as a pale yellow syrup.

^{1}H-NMR ($CDCl_3$) δ 0.94 (9H, s), 2.49 (1H, br s), 2.82 (2H, s), 4.59 (1H, br s), 6.07 (1H, s), 6.59 (1H, d, *J* = 8.8 Hz), 7.00 (1H, d, *J* = 2.2 Hz), 7.05-7.18 (4H, m), 7.28-7.35 (1H, m), 7.38 (1H, ddd, *J* = 7.6, 7.6, 1.7 Hz).

MS (ESI) *m/z* 322 [$(M + H)^+$, ^{35}Cl], 324 [$(M + H)^+$, ^{37}Cl].

Methyl 4-[{4-chloro-2-[(2-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoate (35c).



Compound **35c** was prepared from **31c** in a similar manner described for **6** in 87% yield as a colorless syrup.

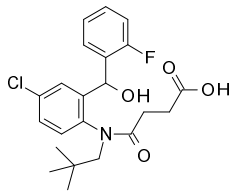
^{1}H-NMR ($CDCl_3$) δ 0.91 (0.93) (9H, s), (1.18-1.27 and 1.93-2.03) 2.14-2.49 and 2.95-3.04 (4H, m), 2.95 (2.97) (1H, d, *J* = 13.7 Hz), 3.58 (3.61) (3H, s), 4.51 (4.52) (1H,

d, J = 13.7 Hz), 5.05-5.09 (1H, m), 6.08-6.18 (1H, m), 6.99-7.06 (2H, m), 7.13-7.17 (1H, m), 7.22-7.39 (3H, m), 7.69-7.78 (1H, m).

IR (ATR) cm^{-1} 2954, 1736, 1579, 1508, 1367, 1230, 1144, 985, 806, 756, 696.

MS (ESI) *m/z* 436 $[(M + H)^+, {}^{35}Cl]$, 438 $[(M + H)^+, {}^{37}Cl]$.

4-[{4-Chloro-2-[(2-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)-amino]-4-oxobutanoic acid (36c).

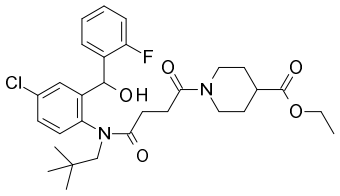


Compound **36c** was prepared from **35c** in a similar manner described for **7** in quantitative yield as a light green amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.91 (0.92) (9H, s), (1.25-1.35 and 1.95-2.10) 2.20-2.50 and 2.85-2.95 (4H, m), 2.87 (2.98) (1H, d, J = 13.6 Hz), 4.47 (4.53) (1H, d, J = 13.6 Hz), 6.06 (6.17) (1H, s), 6.96-7.07 (1H, m), 7.09-7.17 (1H, m), 7.20-7.39 (4H, m), 7.70-7.77 (1H, m).

MS (ESI) *m/z* 422 $(M + H)^+$.

Ethyl 1-{4-[{4-chloro-2-[(2-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37c).



Compound **37c** was prepared from **36c** in a similar manner described for **8** in 78% yield as a colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ (0.90) 0.93 (9H, s), 1.24 (1.25) (3H, t, J = 6.8 Hz), 1.48-1.72 (2H, m), 1.80-1.99 (2H, m), 2.04-2.21 (2H, m), 2.34-2.55 (2H, m), 2.74-2.90 (1H, m), 3.03-3.20 (3H, m), 3.79-3.88 (1H, m), 4.12 (4.14) (2H, q, J = 6.8 Hz), 4.21-4.41 (1H,

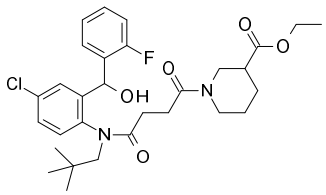
m), 4.53 (4.56) (1H, d, J = 13.7 Hz), 6.09-6.16 (1H, m), (6.54) 6.55 (1H, d, J = 5.1 Hz), 6.95-7.03 (1H, m), 7.10-7.14 (1H, m), 7.19-7.34 (4H, m), 7.90-7.97 (1H, m).

IR (ATR) cm^{-1} 3322, 2952, 1728, 1662, 1624, 1477, 1392, 1167, 1038, 756.

MS (ESI) *m/z* 562 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{38}ClFN_2O_5 \cdot 0.1CH_2Cl_2 \cdot 0.2H_2O$: C, 63.07; H, 6.79; N, 4.89; Cl, 7.42; F, 3.31. Found: C, 63.24; H, 6.74; N, 4.70; Cl, 7.15; F, 3.33.

Ethyl 1-{4-[{4-chloro-2-[(2-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate (38c).



Compound **38c** was prepared from **36c** in a similar manner described for **8** in 93% yield as a colorless amorphous.

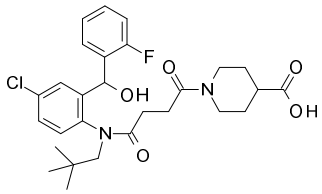
^{1}H-NMR ($CDCl_3$) δ 0.94 (9H, s), 1.19-1.29 (3H, m), 1.30-1.88 (2H, m), 1.90-2.22 (2H, m), 2.26-2.52 (2H, m), 2.57-2.74 (1H, m), 2.86-3.28 (3H, m), 3.47-4.02 (2H, m), 4.06-4.19 (2H, m), 4.34-4.57 (2H, m), 6.13 (1H, s), 6.48-6.60 (8H, m), 6.96-7.03 (1H, m), 7.06-7.15 (1H, m), 7.19-7.34 (4H, m), 7.92-7.99 (1H, m).

IR (ATR) cm^{-1} 3321, 2951, 1728, 1662, 1624, 1475, 1248, 1169, 1030, 756.

MS (ESI) *m/z* 561 $[(M + H)^+, {}^{35}Cl]$, 563 $[(M + H)^+, {}^{37}Cl]$.

Anal. Calcd. for $C_{30}H_{38}ClFN_2O_5 \cdot 0.1H_2O$: C, 64.01; H, 6.84; N, 4.98; Cl, 6.30; F, 3.38. Found: C, 64.10; H, 6.68; N, 4.83; Cl, 6.40; F, 3.40.

1-{4-[{4-Chloro-2-[(2-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (39c).



Compound **39c** was prepared from **37c** in a similar manner described for **9** in quantitative yield as a light green amorphous.

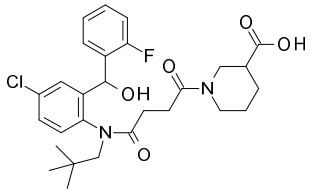
^{1}H-NMR ($CDCl_3$) δ 0.90 (0.94) (9H, s), 1.24-1.76 (3H, m), 1.77-2.04 (2H, m), 2.05-2.22 (1H, m), 2.28-47 (1H, m), 2.49-2.65 (1H, m), 2.70-2.97 (1H, m), 2.98-3.23 (2H, m), 3.68-3.88 (1H, m), 4.24-4.39 (1H, m), 4.43-4.57 (1H, m), 6.13 (6.19) (1H, br s), 6.95-7.06 (1H, m), 7.08-7.18 (1H, m), 7.22-7.45 (7.61-7.67 and 7.90-7.97) (5H, m).

IR (ATR) cm^{-1} 3346, 2952, 1728, 1620, 1477, 1396, 1169, 1030, 756.

MS (ESI) *m/z* 533 [$(M + H)^+$, ^{35}Cl], 535 [$(M + H)^+$, ^{37}Cl].

Anal. Calcd. for $C_{28}H_{34}ClFN_2O_5 \cdot 1.0H_2O$: C, 61.03; H, 6.58; N, 5.08. Found: C, 60.86; H, 6.28; N, 4.85.

1-{4-[{4-Chloro-2-[(2-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)-amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (40c).



Compound **40c** was prepared from **38c** in a similar manner described for **9** in 96% yield as a light green amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.90 (0.93) (9H, s), 1.19-1.47 (1H, m), 1.50-1.88 (2H, m), 1.98-2.22 (2H, m), 2.25-3.22 (7H, m), 3.40-4.07 (2H, m), 4.40-4.58 (2H, m), 6.00-6.21 (2H, m), 6.90-7.04 (1H, m), 7.06-7.46 (4H, m), 7.53-7.67 (1H, m), 7.84-7.97 (1H, m).

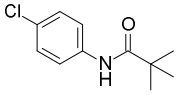
IR (ATR) cm^{-1} 3500-3200, 2952, 1728, 1620, 1477, 1396, 1169, 756.

MS (ESI) *m/z* 531 [$(M + H)^+$, ^{35}Cl], 533 [$(M + H)^+$, ^{37}Cl].

HRMS (FAB) *m/z* 533.2195 (Calcd. for $C_{28}H_{35}ClFN_2O_5$ 533.2219).

Anal. Calcd. for $C_{28}H_{34}ClFN_2O_5 \cdot 0.2CH_2Cl_2 \cdot 0.3H_2O$: C, 60.98; H, 6.35; N, 5.04. Found: C, 61.09; H, 5.96; N, 4.85.

***N*-(4-Chlorophenyl)-2,2-dimethylpropanamide (33).**



To a solution of 4-chloroaniline (**32**, 2.592 g, 20.32 mmol) in CH_2Cl_2 (40 ml) was added 4-(dimethylamino)pyridine (273 mg, 2.23 mmol), triethylamine (3.11 ml, 22.3 mmol), and pivaloyl chloride (2.63 ml, 251.3 mmol) at 0°C. The mixture was stirred at room temperature for 1h. After water was added, the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was recrystallized from n-hexane and CH_2Cl_2 to afford the title compound (**33**, 3.912 g, 18.48 mmol, 91%) as a colorless crystal.

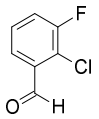
^{1}H-NMR ($CDCl_3$) δ 1.31 (9H, s), 7.26-7.30 (2H, m), 7.45-7.52 (2H, m).

IR (ATR) cm^{-1} 3294, 2966, 1655, 1593, 1523, 1491, 1396, 1309, 1244, 1173, 827.

MS (ESI) *m/z* 212 $(M + H)^+$.

Anal. Calcd. for $C_{11}H_{14}ClNO$: C, 62.41; H, 6.67; Cl, 16.75; N, 6.62. Found: C, 62.37; H, 6.71; Cl, 16.59; N, 6.55.

2-Chloro-3-fluorobenzaldehyde.

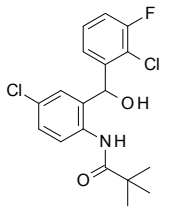


To a solution of 2-Chloro-3-fluoro-benzoic acid (1.00 g, 5.73 mmol) in THF (40 ml) was added borane-tetrahydrofuran complex (1.0 M solution, 20.1 ml, 20.1 mmol) at 0°C. The mixture was stirred under reflux overnight and then cooled with crushed ice. After 1N HClaq and AcOEt were added to the reaction mixture, the two layer ware separated. The organic layer was dried over Na_2SO_4 and concentrated in vacuo, and then alcohol residue was obtained. Separately, to the solution of oxalyl chloride (737 μl, 8.60 mmol) in CH_2Cl_2 (50 ml) was dropped dimethylsulfoxide (1.22 ml, 17.2 mmol) at -78°C. The mixture was stirred for 5 min at the same temperature. Then, the residue described above was added with CH_2Cl_2 (15 ml) to the reaction mixture at -78°C. The solution was stirred for 1 h at -40°C, and then triethylamine (3.97 ml, 28.7 mmol) was added. The mixture was stirred and warmed to room temperature. After 0.5N HClaq was added, the two layers were separated. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced

pressure, and the residue was chromatographed (AcOEt : *n*-hexane = 1 : 50) to give the title compound (500 mg, 55%).

^{1}H-NMR ($CDCl_3$) δ 7.35-7.43 (2H, m), 7.72-7.78 (1H, m), 10.47 (1H, s).

N-{4-Chloro-2-[(2-chloro-3-fluorophenyl)hydroxymethyl]phenyl}-2,2-dimethyl-propionamide (34d).

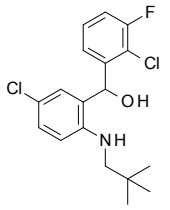


N-Pivaloyl-4-chloroaniline (**33**, 595 mg, 2.81 mmol) was dissolved in THF (50 ml), and the solution was added s*ec*-butyl lithium *c*-hexane, *n*-hexane solution (0.99 M, 5.96 ml, 6.18 mmol) at -78°C, and then stirred at 0°C for 2 h. The mixture was added 2-chloro-3-fluoro-benzaldehyde (490 mg, 3.09 mmol) at the same temperature for 30 min. The reaction mixture was poured saturated with NH_4Claq and AcOEt. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (AcOEt : *n*-hexane = 1 : 9) to give the title compound (676 mg, 65%) as light yellow oil.

^{1}H-NMR ($CDCl_3$) δ 1.27 (9H, s), 3.85 (1H, d, *J* = 3.5 Hz), 4.81 (1H, br s), 6.95 (1H, d, *J* = 3.5 Hz), 7.08-7.17 (1H, m), 7.28-7.32 (3H, m), 7.72 (1H, d, *J* = 8.8 Hz), 8.39 (1H, br s).

MS (FAB) *m/z* 370 $(M + H)^+$.

[5-Chloro-2-(2,2-dimethylpropylamino)phenyl]-(2-chloro-3-fluorophenyl)methanol (31d).

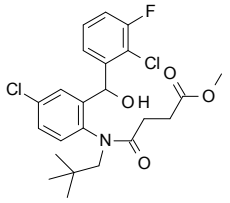


A solution of *N*-{4-Chloro-2-[(2-chloro-3-fluorophenyl)hydroxymethyl]phenyl}-2,2-dimethylpropionamide (**34d**, 670 mg, 1.81 mmol) was dissolved in THF (30 ml). To the solution was dropwised a toluene solution of sodium bis(2-methoxyethoxy) aluminum hydride (35%, 3.37 ml, 10.9 mmol) at 0°C. The mixture was stirred for 2h at room temperature. The reaction mixture was added saturated (+)-tartaric acid sodium potassium solution and stirred for 5 min. The mixture was added AcOEt and separated with a funnel. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (AcOEt : *n*-hexane = 1 : 20) to give the title compound (300 mg, 47%) as light yellow oil.

^{1}H-NMR ($CDCl_3$) δ 0.94 (9H, s), 2.85 (2H, s), 6.14 (1H, s), 6.62 (1H, d, *J* = 8.8 Hz), 6.88 (1H, d, *J* = 2.4 Hz), 7.10-7.18 (2H, m), 7.24-7.30 (2H, m).

MS (FAB) *m/z* 357 $(M + H)^+$.

Methyl 4-[{4-chloro-2-[(2-chloro-3-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35d).



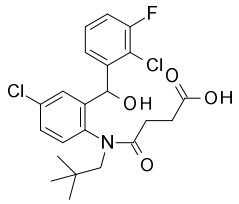
Compound **35d** was prepared from **31d** in a similar manner described for **6** in 55% yield as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ 0.90 (0.94) (9H, s), 2.18-2.27 (1H, m), 2.23-2.47 (2H, m), 2.87-2.96 (1H, m), 3.07 (1H, d, *J* = 16.3 Hz), 3.66 (3.69) (3H, s), 4.49 (1H, d, *J* = 16.3 Hz), 6.14 (1H, s), 7.00-7.06 (1H, m), 7.14-7.21 (1H, m), 7.27-7.32 (1H, m), 7.23-7.39 (2H, m), 7.63 (1H, d, *J* = 7.8 Hz).

IR (ATR) cm^{-1} 3411, 2956, 2869, 1743, 1648, 1577, 1469, 1434, 1409, 1351, 1263, 1232, 1164, 1114, 1068, 1043, 998, 948, 904, 873, 846, 809.

MS (FAB) *m/z* 470 $(M + H)^+$.

4-[{4-Chloro-2-[(2-chloro-3-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (36d).



Compound **36d** was prepared from **35d** in a similar manner described for **7** in 86% yield as a colorless amorphous.

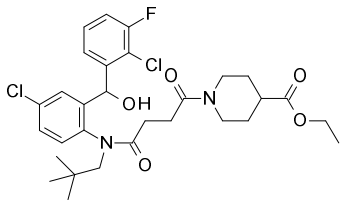
^{1}H-NMR ($CDCl_3$) δ 0.89 (0.90) (9H, s), (1.56-1.58 and 2.05-2.10) 2.24-2.48 and 2.78-2.86 (4H, m), 2.96 (3.08) (1H, d, J = 13.4 Hz), 4.45 (4.50) (1H, d, J = 13.4 Hz), 6.05 (6.29) (1H, s), 6.92 (1H, d, J = 2.2 Hz), 7.09-7.17 (1H, m), 7.24-7.32 (4H, m), 7.50-7.59 (1H, m).

IR (ATR) cm^{-1} 2956, 2869, 1708, 1637, 1579, 1467, 1442, 1396, 1365, 1322, 1263, 1168, 1114, 1101, 1043, 968, 946, 902, 875, 833, 808.

MS (FAB) *m/z* 456 $(M+H)^+$.

Anal. Calcd. for $C_{22}H_{24}Cl_2FNO_4 \cdot 0.4CHCl_3$: C, 53.81; H, 4.83; N, 2.75. Found: C, 53.90; H, 4.99; N, 2.65.

Ethyl 1-{4-[{4-chloro-2-[(2-chloro-3-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37d).



Compound **37d** was prepared from **36d** in a similar manner described for **8** in 58% yield as a colorless amorphous.

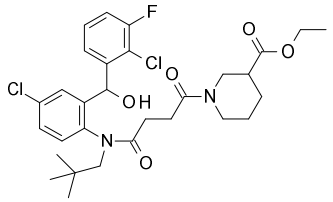
^{1}H-NMR ($CDCl_3$) δ (0.89) 0.91 (9H, s), 1.24 (1.26) (3H, t, J = 7.1 Hz), 1.75-2.00 and 2.05-2.20 (3H, m), 2.41-2.56 (2H, m), (2.69-2.91) 3.00-3.21 (3H, m), 3.12 (1H, d, J = 13.5 Hz), 3.67-3.82 (1H, m), 4.10-4.18 (3H, m), 4.22-4.50 (1H, m), 4.52 (4.53) (1H, d, J = 13.5 Hz), 6.13-6.16 (1H, m), 6.45-6.71 (6.51-6.54) (1H, m), 6.96 (1H, s), 7.14-7.20 and 7.33-7.40 (3H, m), 7.73-7.80 (1H, m).

IR (ATR) cm^{-1} 3318, 2954, 2865, 1727, 1625, 1577, 1467, 1442, 1392, 1365, 1313, 1263, 1168, 1097, 1039, 987, 970, 946, 902, 875, 833, 808.

MS (FAB) *m/z* 595 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{37}Cl_2FN_2O_5 \cdot 0.5H_2O$: C, 59.60; H, 6.34; N, 4.63. Found: C, 59.26; H, 6.20; N, 4.46.

Ethyl 1-{4-[{4-chloro-2-[(2-chloro-3-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate (38d).



Compound **38d** was prepared from **36d** in a similar manner described for **8** in 80% yield as a colorless amorphous.

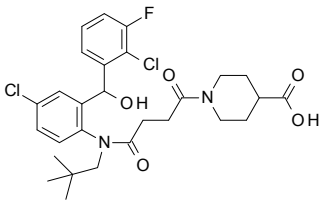
^{1}H-NMR ($CDCl_3$) δ (0.91) 0.92 (9H, s), 1.23 (1.24) (3H, t, *J* = 7.3 Hz), (1.65-1.73) 1.90-2.14 (4H, m), 2.20-2.52 and 2.55-2.70 (3H, m), (2.79-2.88) 2.93-3.18 (2H, m), 3.19-3.28 (3.49-3.56) (1H, m), 3.70-3.86 (3.92-3.99) (4.35-4.44) (4.70-4.73) (2H, m), 4.07-4.19 (2H, m), 4.52 (1H, d, *J* = 13.7 Hz), 6.16 (6.32) (1H, d, *J* = 4.1 Hz), 6.93-7.00 (1H, m), 7.14-7.19 (2H, m), 7.28-7.41 (2H, m), 7.72-7.78 (1H, m).

IR (ATR) cm^{-1} 3332, 2950, 2865, 1727, 1625, 1579, 1467, 1442, 1392, 1365, 1309, 1261, 1170, 1114, 1068, 1031, 1006, 946, 900, 875, 856, 833, 808.

MS (FAB) *m/z* 595 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{37}Cl_2FN_2O_5 \cdot 0.5H_2O$: C, 59.60; H, 6.34; N, 4.63. Found: C, 59.26; H, 6.19; N, 4.46.

1-{4-[{4-Chloro-2-[(2-chloro-3-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (39d).



Compound **39d** was prepared from **37d** in a similar manner described for **9** in 87% yield as a colorless amorphous.

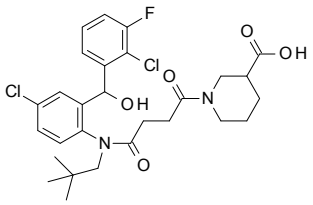
^{1}H-NMR ($CDCl_3$) δ (0.89) 0.91 (9H, s), 1.36-1.74 (3H, m), 1.75-2.27 (3H, m), 2.28-2.62 (3H, m), 2.68-3.28 (3H, m), 3.71-3.87 (1H, m), 4.20-4.52 (2H, m), 6.14 (1H, s), (6.31) 6.94 (1H, d, J = 8.6 Hz), 7.00-7.46 (4H, m), (7.53-7.58) 7.67-7.77 (1H, m).

IR (ATR) cm^{-1} 2954, 2865, 1727, 1623, 1467, 1444, 1396, 1365, 1263, 1170, 1105, 1031, 948, 929, 902, 875, 833, 808.

MS (FAB) *m/z* 567 $(M + H)^+$.

Anal. Calcd. for $C_{28}H_{33}Cl_2FN_2O_5$: C, 59.26; H, 5.86; N, 4.94. Found: C, 59.49; H, 6.10; N, 4.58.

1-{4-[{4-Chloro-2-[(2-chloro-3-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (40d).



Compound **40d** was prepared from **38d** in a similar manner described for **9** in 92% yield as a colorless amorphous.

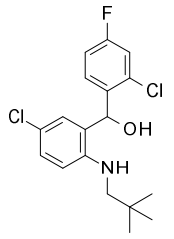
^{1}H-NMR ($CDCl_3$) δ (0.88) 0.90 (9H, s), 1.46-1.87 (2H, m), 1.88-2.25 (3H, m), 2.30-2.70 (1H, m), 2.77-3.22 (3H, m), (3.40-3.49) 3.55-4.15 (4.29-4.44) (4.57-4.64) (4H, m), 4.45-4.56 (1H, m), 6.10-6.14 (6.23-6.31) (1H, m), 6.97 (1H, s), 7.01-7.41 (7.42-7.60) (4H, m), 7.62-7.73 (1H, m).

IR (ATR) cm^{-1} 2950, 2867, 1727, 1619, 1579, 1467, 142, 1396, 1365, 1261, 1170, 1116, 1043, 1008, 977, 948, 900, 873, 856, 833, 808.

MS (FAB) *m/z* 567 $(M + H)^+$.

Anal. Calcd. for $C_{28}H_{33}Cl_2FN_2O_5$: C, 59.26; H, 5.86; N, 4.94. Found: C, 59.04; H, 5.98; N, 4.63.

{5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}(2-chloro-4-fluorophenyl)methanol (31e).

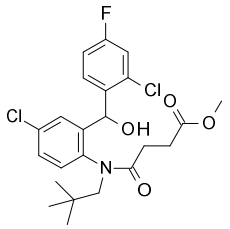


Compound **31e** was prepared from **33** in a similar manner described for **31d** in 14% yield in 2 steps as a pale yellow amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.93 (9H, s), 2.84 (2H, s), 6.11 (1H, s), 6.61 (1H, d, J = 8.8 Hz), 6.95 (1H, d, J = 2.4 Hz), 6.96-7.05 (1H, m), 7.13-7.18 (2H, m), 7.38-7.42 (1H, m).

MS (FAB) *m/z* 356 $(M + H)^+$.

Methyl 4-[{4-chloro-2-[(2-chloro-4-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35e).



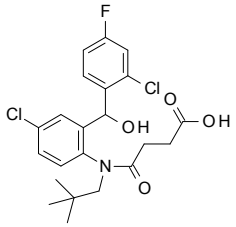
Compound **35e** was prepared from **31e** in a similar manner described for **6** in 60% yield as a colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.89 (0.90) (9H, s), 2.18-2.25 (1H, m), 2.32-2.49 (2H, m), 2.88-2.98 (1H, m), 3.02 (1H, d, J = 13.7 Hz), (3.60) 3.68 (3H, s), 4.48 (1H, d, J = 13.7 Hz), 4.80 (1H, d, J = 5.8 Hz), 6.10 (6.30) (1H, d, J = 5.8 Hz), 7.02 (1H, d, J = 2.0 Hz), 7.08-7.16 (2H, m), 7.28-7.37 (2H, m), (7.68-7.70) 7.78-7.83 (1H, m).

IR (ATR) cm^{-1} 3392, 2960, 1739, 1646, 1600, 1481, 1434, 1411, 1396, 1351, 1288, 1226, 1164, 1112, 1054, 1031, 998, 962, 937, 912, 863, 835, 804.

MS (FAB) *m/z* 470 $(M + H)^+$.

4-[{4-Chloro-2-[(2-chloro-4-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoic acid (36e).



Compound **36e** was prepared from **35e** in a similar manner described for **7** in 86% yield as a colorless amorphous.

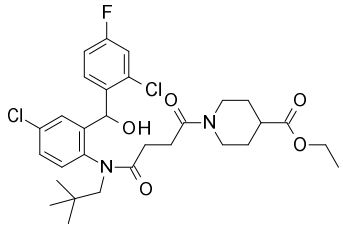
^{1}H-NMR ($CDCl_3$) δ 0.88 (0.90) (9H, s), (1.38-1.46) (2.01-2.09) 2.21-2.49 (2.77-2.86) (4H, m), 2.89 (3.03) (1H, d, *J* = 13.7 Hz), 4.43 (4.51) (1H, d, *J* = 13.7 Hz), 6.02 (6.28) (1H, s), 6.93-7.14 and 7.27-7.36 (5H, m), 7.62-7.68 (1H, m).

IR (ATR) cm^{-1} 2954, 1710, 1639, 1600, 1477, 1394, 1326, 1259, 1226, 1166, 1114, 1052, 1029, 981, 912, 860, 833.

MS (FAB) *m/z* 456 $(M + H)^+$.

Anal. Calcd. for $C_{22}H_{24}Cl_2FNO_4 \cdot 0.5H_2O$: C, 56.78; H, 5.41; N, 3.01. Found: C, 56.56; H, 5.25; N, 3.07.

Ethyl 1-{4-[{4-chloro-2-[(2-chloro-4-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37e).



Compound **37e** was prepared from **36e** in a similar manner described for **8** in 76% yield as a colorless amorphous.

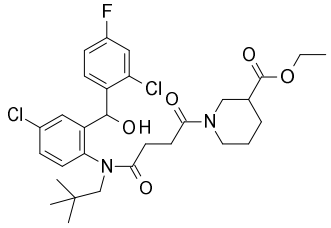
^{1}H-NMR ($CDCl_3$) δ (0.89) 0.90 (9H, s), 1.23 (1.26) (3H, t, *J* = 7.1 Hz), (1.28-1.39) 1.49-1.71 (1H, m), 1.78-1.98 (2H, m), 2.06-2.66 (4H, m), 2.69-2.90 (1H, m), 2.94-3.21 (3.63-3.85) (3H, m), 4.05-4.13 (2H, m), 4.18-4.51 (2H, m), 6.06-6.09 (6.28-6.30) (6.37-6.40) (6.42-6.48) (1H, m), 6.95 (1H, d, *J* = 2.0 Hz), 7.08-7.12 (2H, m), 7.17-7.39 (2H, m), (7.66-7.68) 7.84-7.91 (1H, m).

IR (ATR) cm^{-1} 2952, 2867, 1727, 1627, 1475, 1448, 1392, 1365, 1313, 1272, 1220, 1168, 1112, 1033, 946, 912, 858, 833, 804, 752.

MS (FAB) *m/z* 595 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{37}Cl_2FN_2O_5 \cdot 0.5H_2O$: C, 59.60; H, 6.34; N, 4.63. Found: C, 59.44; H, 6.18; N, 4.58.

Ethyl 1-{4-[{4-chloro-2-[(2-chloro-4-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate (38e).



Compound **38e** was prepared from **36e** in a similar manner described for **8** in 63% yield as a colorless amorphous.

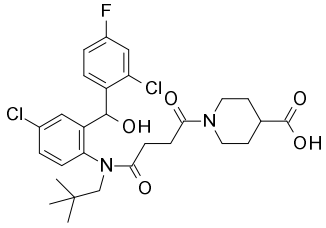
^{1}H-NMR ($CDCl_3$) δ (0.89) 0.90 (9H, s), 1.23 (1.25) (3H, t, J = 7.1 Hz), (1.30-1.46) 1.50-1.85 (3H, m), 1.90-2.26 (3H, m), 2.27-3.15 (5H, m), 3.16-3.26 (3.46-3.52) (1H, m), 3.62-3.87 (3.94-4.00) (4.32-4.40) (4.69-4.73) (2H, m), (4.43)4.48 (1H, d, J = 13.7 Hz), 6.07-6.12 (6.28-6.31) (6.35-6.40) (6.43-6.47) (1H, m), 6.95 (1H, s), 7.05-7.12 (2H, m), 7.19-7.46 (2H, m), (7.63-7.71) 7.83-7.93 (1H, m).

IR (ATR) cm^{-1} 2950, 2865, 1727, 1627, 1475, 1442, 1392, 1309, 1280, 1255, 1220, 1174, 1114, 1031, 912, 856, 833, 804, 754.

MS (FAB) *m/z* 595 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{37}Cl_2FN_2O_5 \cdot 0.5H_2O$: C, 59.60; H, 6.34; N, 4.63. Found: C, 59.44; H, 6.18; N, 4.58.

1-{4-[{4-Chloro-2-[(2-chloro-4-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (39e).



Compound **39e** was prepared from **37e** in a similar manner described for **9** in 83% yield as a colorless amorphous.

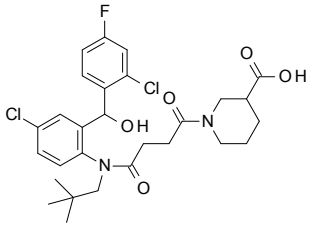
^{1}H-NMR ($CDCl_3$) δ (0.89) 0.90 (9H, s), (1.20-1.38) 1.50-1.72 (2H, m), 1.75-2.02 (3H, m), 2.05-2.60 (3H, m), 2.70-2.92 (1H, m), 2.96-3.37 (3H, m), 3.67-3.88 (1H, m), 4.21-4.56 (2H, m), 6.10 (6.29) (1H, s), 6.94 (1H, d, J = 7.2 Hz), 7.03-7.16 (2H, m), 7.20-7.34 (7.37-7.43) (2H, m), (7.62-7.67) 7.82-7.93 (1H, m).

IR (ATR) cm^{-1} 2956, 2867, 1724, 1621, 1602, 1477, 1396, 1365, 1265, 1222, 1168, 1112, 1029, 912, 858, 833, 804, 750.

MS (FAB) *m/z* 567 $(M + H)^+$.

Anal. Calcd. for $C_{28}H_{33}Cl_2FN_2O_5 \cdot 0.5H_2O$: C, 55.01; H, 5.33; N, 4.42. Found: C, 55.35; H, 5.58; N, 4.39.

1-{4-[{4-Chloro-2-[(2-chloro-4-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (40e).



Compound **40e** was prepared from **38e** in a similar manner described for **9** in 83% yield as a colorless amorphous.

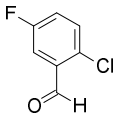
^{1}H-NMR ($CDCl_3$) δ 0.89 (9H, s), 1.18-1.90 (5H, m), 1.91-2.69 (4H, m), 2.80-3.22 (3.36-3.55) (3H, m), 3.69-3.92 (3.96-4.09) (1H, m), 4.30-4.69 (2H, m), 6.00-6.12 (6.20-6.3) (1H, m), 6.83-7.48 (5H, m), (7.56-7.70) 7.80-7.95 (1H, m).

IR (ATR) cm^{-1} 2952, 2867, 1725, 1623, 1602, 1475, 1396, 1365, 1286, 1255, 1222, 1174, 1114, 1052, 1031, 912, 858, 833.

MS (FAB) *m/z* 567 $(M + H)^+$.

Anal. Calcd. for $C_{28}H_{33}Cl_2FN_2O_5 \cdot 0.4CHCl_3$: C, 55.79; H, 5.43; N, 4.52. Found: C, 55.59; H, 5.58; N, 4.29.

2-Chloro-5-fluorobenzaldehyde.

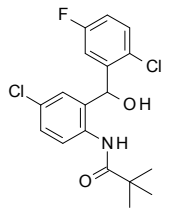


The solution of 2-Chloro-5-fluoro-benzoic acid (4.00 g, 23.0 mmol) in THE (200 ml) was added triethylamine (4.14 ml, 29.9 mmol). At -30°C, the mixture was added ethyl chloroformate (2.62 ml, 27.8 mmol) and stirred for 10 min. The solution was added sodium borohydride (2.60 g, 68.9 mmol) and stirred for 5 min. The mixture was added H_2O (10 ml) and stirred for 20 min at room temperature. The solution was concentrated in vacuo and the residue was added $CHCl_3$ and 1N HClaq. The organic layer was washed with 1N NaOHaq and dried over Na_2SO_4. The solution was removed in reduced pressure. The residue was washed with *n*-hexane to give alcohol as a colorless solid. To the CH_2Cl_2 suspension of dimethylsulfoxide (2.43 ml, 34.2 mmol) was added a solution of oxalyl chloride (1.47 ml, 17.1 mmol) in 50 ml of dry CH_2Cl_2 at -78°C, and the resulting mixture was stirred for 20 min. CH_2Cl_2 (15 ml) solution of the alcohol was added to the reaction mixture at -78°C. The mixture was allowed to warm to -40 °C for 1 h. The mixture was added triethylamine (7.89 ml, 57.0 mmol), allowed to warm to room temperature, and was treated with 0.1N HClaq. The organic layer was washed with saturated Na_2CO_3aq, dried over Na2SO4, and concentrated in vacuo to give the title compound (1.33 g, 37%) as a colorless solid after trituration with *n*-hexane.

^{1}H-NMR ($CDCl_3$) δ 7.22-7.28 (1H, m), 7.41-7.47 (1H, m), 7.58-7.64 (1H, m), 10.42 (1H, d, J = 3.2 Hz).

MS (EI) *m/z* 158 M^+.

N-{4-Chloro-2-[(2-chloro-5-fluorophenyl)(hydroxy)methyl]phenyl}-2,2-dimethyl-propanamide (34f).

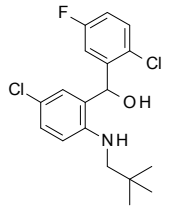


Compound **34f** was prepared from **33** in a similar manner described for **34d** in 46% yield as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ 1.30 (9H, s), 3.90 (1H, d, *J* = 3.5 Hz), 5.99 (1H, d, *J* = 3.5 Hz), 6.93 (1H, br s), 6.98-7.04 (1H, m), 7.27-7.36 (3H, m), 7.63 (1H, d, *J* = 8.8 Hz), 8.21 (1H, br s).

MS (FAB) *m/z* 371 $(M + H)^+$.

{5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}(2-chloro-5-fluorophenyl)methanol (31f).

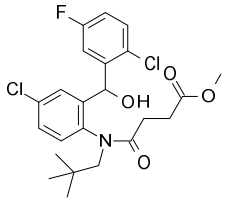


Compound **31f** was prepared from **34f** in a similar manner described for **31d** in 87% yield as a pale yellow syrup.

^{1}H-NMR ($CDCl_3$) δ 0.95 (9H, s), 2.85 (2H, s), 6.09 (1H, s), 6.63 (1H, d, *J* = 8.8 Hz), 6.90 (1H, d, *J* = 2.4 Hz), 6.98-7.07 (1H, m), 7.14-7.21 (2H, m), 7.37 (1H, dd, *J* = 5.1, 8.8 Hz).

MS (FAB) *m/z* 357 $(M + H)^+$.

Methyl 4-[{4-chloro-2-[(2-chloro-5-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35f).

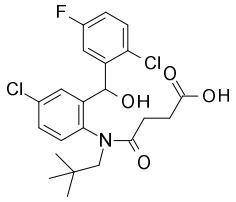


Compound **35f** was prepared from **31f** in a similar manner described for **6** in 67% yield as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ 0.90 (0.92) (9H, s), 2.17-2.24 (1H, m), 2.33-2.45 (2H, m), 2.88-2.98 (1H, m), 3.16 (1H, d, *J* = 13.7 Hz), (3.61) 3.69 (3H, s), 4.50 (1H, d, *J* = 13.7 Hz), 4.97 (1H, d, *J* = 5.4 Hz), 6.07 (6.30) (1H, d, *J* = 5.4 Hz), 6.94 (1H, d, *J* = 2.0 Hz), 6.97-7.03 (1H, m), 7.27-7.35 (3H, m), 7.60-7.64 (1H, m).

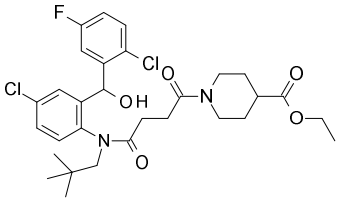
IR (ATR) cm^{-1} 3338, 3266, 2950, 1729, 1625, 1587, 1465, 1434, 1396, 1357, 1290, 1263, 1199, 1170, 1114, 1064, 1031, 998, 943, 904, 873, 819.
MS (FAB) *m/z* 470 $(M + H)^+$.

4-[{4-Chloro-2-[(2-chloro-5-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (36f).



Compound **36f** was prepared from **35f** in a similar manner described for **7** in 97% yield as a colorless amorphous.
^{1}H-NMR ($CDCl_3$) δ 0.90 (0.91) (9H, s), (1.50-1.58) (2.08-2.15) 2.22-2.49 (2.78-2.88) (4H, m), 3.04 (3.07) (1H, d, *J* = 13.7 Hz), 4.48 (4.53) (1H, d, *J* = 13.7 Hz), 6.01 (6.25) (1H, s), 6.88 (1H, d, *J* = 2.2 Hz), 6.94-7.07 (7.08-7.14) (2H, m), 7.20-7.33 (2H, m), 7.48-7.51 (7.58-7.60) (1H, m).
IR (ATR) cm^{-1} 2954, 1710, 1637, 1587, 1469, 1396, 1324, 1261, 1170, 1112, 1052, 1027, 966, 941, 902, 885, 813.
MS (FAB) *m/z* 456 $(M + H)^+$.
Anal. Calcd. for $C_{22}H_{24}Cl_2FNO_4 \cdot 0.3CHCl_3$: C, 54.75; H, 4.94; N, 2.83. Found: C, 54.58; H, 5.02; N, 2.91.

Ethyl 1-{4-[{4-chloro-2-[(2-chloro-5-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37f).



Compound **37f** was prepared from **36f** in a similar manner described for **8** in 71% yield as a colorless amorphous.

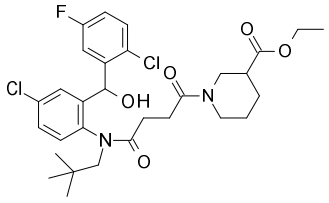
^{1}H-NMR ($CDCl_3$) δ (0.89) 0.92 (9H, s), 1.24 (1.26) (3H, t, *J* = 7.1 Hz), (1.48-1.74) 1.78-1.99 (3H, m), 2.07-2.23 (2H, m), 2.33-2.54 (2H, m), (2.55-2.65) 2.71-2.96 (2H, m), 3.00-3.19 (2H, m), 3.33 (1H, d, *J* = 13.4 Hz), 3.72-3.87 (1H, m), 4.07-4.16 (2H, m), 4.18-4.43 (1H, m), 4.52 (4.54) (1H, d, *J* = 13.4 Hz), 6.04-6.09 (6.22-6.26) (1H, m), (6.55) 6.62 (1H, d, *J* = 5.2 Hz), 6.90 (1H, s), 6.92-7.11 (1H, m), (7.05-7.17) 7.20-7.32 (7.40-7.52) (2H, m), 7.69-7.75 (1H, m).

IR (ATR) cm^{-1} 3330, 2952, 2863, 1727, 1625, 1467, 1392, 1365, 1313, 1261, 1170, 1112, 1035, 946, 902, 875, 813.

MS (FAB) *m/z* 595 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{37}Cl_2FN_2O_5$: C, 60.37; H, 6.27; N, 4.71. Found: C, 60.50; H, 6.26; N, 4.70.

Ethyl 1-{4-[{4-chloro-2-[(2-chloro-5-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate (38f).



Compound **38f** was prepared from **36f** in a similar manner described for **8** in 73% yield as a colorless amorphous.

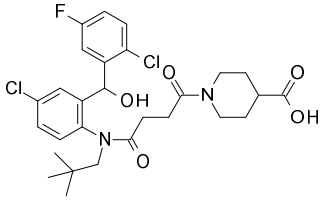
^{1}H-NMR ($CDCl_3$) δ (0.89) 0.92 (9H, s), 1.18-1.28 (3H, m), (1.30-1.45) 1.47-1.86 (3H, m), 1.96-2.23 (3H, m), 2.28-2.51 (2.55-2.72) (2H, m), 2.83-3.24 (2H, m), 3.27-3.36 (3.46-3.53) (1H, m), 3.68-3.87 (3.94-4.02) (4.33-4.46) (4.68-4.73) (2H, m), 4.48-4.54 (2H, m), 6.04-6.12 (6.24-6.29) (1H, m), 6.54-6.65 (1H, m), 6.90 (1H, s), 6.92-7.02 (1H, m), (7.03-7.14) 7.18-7.30 (7.36-7.57) (2H, m), 7.69-7.77 (1H, m).

IR (ATR) cm^{-1} 3320, 2950, 2865, 1727, 1625, 1467, 1392, 1365, 1309, 1278, 1249, 1172, 1112, 1029, 960, 902, 813.

MS (FAB) *m/z* 595 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{37}Cl_2FN_2O_5$: C, 60.50; H, 6.26; N, 4.70. Found: C, 60.48; H, 6.33; N, 4.64.

1-{4-[{4-Chloro-2-[(2-chloro-5-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (39f).



Compound **39f** was prepared from **37f** in a similar manner described for **9** in 64% yield as a colorless amorphous.

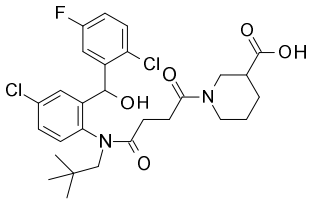
^{1}H-NMR ($CDCl_3$) δ 0.92 (9H, s), 1.50-1.75 (2H, m), 1.77-2.04 (3H, m), 2.07-2.29 (2H, m), 2.30-2.70 (2H, m), 2.72-3.40 (3H, m), 3.71-3.90 (1H, m), 4.18-4.58 (2H, m), 5.99-6.27 (1H, m), 6.46-7.09 (3H, m), 7.11-7.54 (2H, m), 7.60-7.83 (1H, m).

IR (ATR) cm^{-1} 2950, 2865, 1725, 1619, 1587, 1469, 1407, 1365, 1265, 1170, 1112, 1029, 964, 929, 902, 875, 813.

MS (FAB) *m/z* 567 $(M + H)^+$.

Anal. Calcd. for $C_{28}H_{33}Cl_2FN_2O_5 \cdot 0.3CHCl_3$: C, 56.60; H, 5.53; N, 4.62. Found: C, 56.85; H, 5.72; N, 4.57.

1-{4-[{4-Chloro-2-[(2-chloro-5-fluorophenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (40f).



Compound **40f** was prepared from **38f** in a similar manner described for **9** in 80% yield as a colorless amorphous.

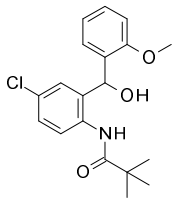
^{1}H-NMR ($CDCl_3$) δ 0.91 (9H, s), 1.18-1.90 (5H, m), 1.91-3.55 (7H, m), 3.71-4.07 (1H, m), 4.34-4.70 (2H, m), 6.01-6.16 (6.19-6.28) (1H, m), 6.85-7.10 (2H, m), 7.13-7.54 (3H, m), 7.63-7.79 (1H, m).

IR (ATR) cm^{-1} 2952, 2865, 1725, 1619, 1587, 1469, 1409, 1365, 1249, 1172, 1112, 1052, 1029, 960, 902, 875, 813.

MS (FAB) *m/z* 567 $(M + H)^+$.

Anal. Calcd. for $C_{28}H_{33}Cl_2FN_2O_5 \cdot 0.4CHCl_3$: C, 55.79; H, 5.43; N, 4.52. Found: C, 55.41; H, 5.57; N, 4.43.

N-{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]phenyl}-2,2-dimethylpropanamide (34g).



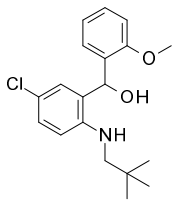
Compound **34g** was prepared from **33** in a similar manner described for **34d** in 76% yield as a colorless crystal.

^{1}H-NMR ($CDCl_3$) δ 1.13 (9H, s), 3.93 (3H, s), 4.10 (1H, d, J = 4.4 Hz), 5.99 (1H, d, J = 4.6 Hz), 6.82-6.93 (2H, m), 6.96-7.00 (2H, m), 7.28-7.35 (2H, m), 8.20 (1H, d, J = 8.8 Hz), 9.20 (1H, br).

IR (ATR) cm^{-1} 3313, 2958, 1645, 1510, 1394, 1254, 1039, 818, 746, 654.

MS (ESI) *m/z* 348 $(M + H)^+$.

{5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}(2-methoxyphenyl)methanol (31g).



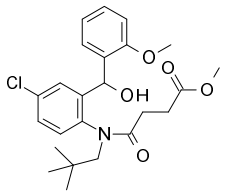
Compound **31g** was prepared from **34g** in a similar manner described for **31d** in 49% yield as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ 0.92 (9H, s), 2.83 (2H, s), 3.27 (1H, br s), 3.89 (3H, s), 4.86 (1H, br s), 5.99 (1H, s), 6.58 (1H, d, J = 8.5 Hz), 6.91-7.00 (3H, m), 7.09-7.15 (2H, m), 7.28-7.34 (1H, m).

IR (ATR) cm^{-1} 3421, 2954, 1601, 1508, 1464, 1240, 1026, 752.

MS (ESI) *m/z* 334 $(M + H)^+$.

Methyl 4-[{4-chloro-2-[hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35g).



Compound **35g** was prepared from **31g** in a similar manner described for **6** in 79% yield as a colorless solid.

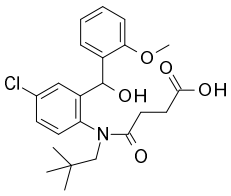
^{1}H-NMR ($CDCl_3$) δ (0.91) 0.93 (9H, s), (0.95-1.10) (1.76-1.88) 2.15-2.47 (3H, m), (2.64-2.70) 2.78-2.94 (1H, m), (2.95) 3.05 (1H, d, J = 13.4 Hz), (3.58) 3.68 (3H, s), 3.73 (3.82) (3H, s), 4.41-4.47 (1H, m), 4.60 (1H, d, *J* = 5.1 Hz), 6.09 (6.23) (1H, d, *J* = 5.1 Hz), 6.84-6.91 (2H, m), 7.05-7.11 (2H, m), 7.16-7.18 (1H, m), 7.21-7.35 (1H, m), 7.65-7.69 (7.82-7.85) (1H, m).

IR (ATR) cm^{-1} 3373, 2949, 1738, 1635, 1242, 1167, 1038, 748.

MS (ESI) *m/z* 448 $(M + H)^+$.

Anal. Calcd. for $C_{24}H_{30}ClNO_5$: C, 64.35; H, 6.75; Cl, 7.91; N, 3.13. Found: C, 64.27; H, 6.76; Cl, 8.02; N, 3.13.

4-[{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl) amino]-4-oxobutanoic acid (36g).



Compound **36g** was prepared from **35g** in a similar manner described for **7** in 93% yield as a colorless amorphous.

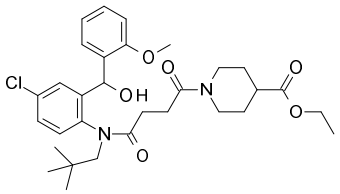
^{1}H-NMR (DMSO-d_6) δ 0.85 (9H, s), (0.90-1.05) (1.73-1.86) 2.07-2.40 (4H, m), 2.81 (3.01) (1H, d, *J* = 14.0 Hz), 3.65 (3.66) (3H, s), 4.27 (4.34) (1H, d, *J* = 13.5 Hz), 5.75 (5.81) (1H, s), 5.85 (6.06) (1H, d, *J* = 4.9 Hz), 6.86-7.08 (3H, m), 7.17-7.61 (4H, m).

IR (ATR) cm^{-1} 3421, 2964, 1734, 1643, 1475, 1394, 1246, 1169, 1028, 756.

MS (ESI) *m/z* 434 $(M + H)^+$.

Anal. Calcd. for $C_{23}H_{28}ClNO_5 \cdot 0.1CH_2Cl_2$: C, 62.71; H, 6.42; Cl, 9.62; N, 3.17. Found: C, 63.03; H, 6.44; Cl, 9.37; N, 3.12.

Ethyl 1-{4-[{4-chloro-2-[hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37g).



Compound **37g** was prepared from **36g** in a similar manner described for **8** in 91% yield as a colorless amorphous.

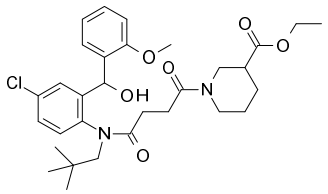
^{1}H-NMR ($CDCl_3$) δ (0.91) 0.97 (9H, s), 1.14-1.28 (4H, m), 1.55-1.71 (1H, m), 1.74-1.98 (2H, m), 2.02-2.23 (2H, m), 2.34-2.53 (2H, m), 2.66-2.90 (2H, m), 2.96-3.19 (2H, m), 3.21-3.34 (1H, m), 3.69 (3H, s), 3.73-3.89 (1H, m), 4.12 (2H, q, J = 7.0 Hz), 4.19-4.55 (2H, m), 6.04-6.41 (1H, m), 6.85 (1H, d, J = 8.3 Hz), 7.03-7.13 (2H, m), 7.15-7.34 (2H, m), 7.79-7.92 (1H, m).

IR (ATR) cm^{-1} 3309, 2964, 1730, 1660, 1624, 1444, 1394, 1240, 1176, 1028, 750.

MS (ESI) *m/z* 573 $(M + H)^+$.

Anal. Calcd. for $C_{31}H_{41}ClN_2O_6$: C, 64.97; H, 7.21; Cl, 6.19; N, 4.89. Found: C, 64.71; H, 7.22; Cl, 6.59; N, 4.90.

Ethyl 1-{4-[{4-chloro-2-[hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate (38g)



Compound **38g** was prepared from **36g** in a similar manner described for **8** in 69% yield as a colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.97 (9H, s), 1.14-1.39 (4H, m), 1.55-1.84 (2H, m), 1.89-2.88 (6H, m), 2.94-3.35 (3H, m), 3.40-3.90 (2H, m), 3.69 (3H, s), 3.94-4.19 (2H, m), 4.33-4.58

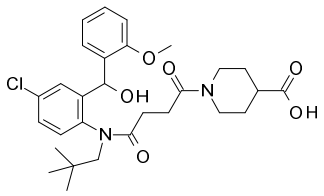
(2H, m), 6.05-6.41 (2H, m), 6.85 (1H, d, J = 8.8 Hz), 7.02-7.13 (2H, m), 7.17-7.35 (3H, m), 7.80-7.94 (1H, m).

IR (ATR) cm^{-1} 3354, 2954, 1732, 1664, 1628, 1473, 1406, 1242, 1163, 1030, 752.

MS (ESI) *m/z* 573 $(M + H)^+$.

Anal. Calcd. for $C_{31}H_{41}ClN_2O_6$: C, 64.97; H, 7.21; Cl, 6.19; N, 4.89. Found: C, 64.93; H, 7.26; Cl, 6.37; N, 4.87.

1-{4-[{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl) amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (39g).



Compound **39g** was prepared from **37g** in a similar manner described for **9** in 92% yield as a colorless amorphous.

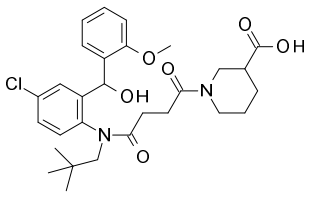
^{1}H-NMR (DMSO-d_6) δ (0.85) 0.86 (5H, s), 0.88-1.04 (1H, m), 1.20-1.55 (2H, m), 1.69-1.89 (2H, m), 2.03-2.20 (1H, m), 2.26-2.76 (4H, m), 2.84-3.14 (2H, m), 3.53-3.86 (1H, m), (3.66) 3.67 (3H, s), 4.05-4.20 (1H, m), 4.29 (4.34) (1H, d, *J* = 13.7 Hz), 5.79-6.09 (2H, m), 6.86-7.10 (2H, m), 7.17-7.27 (1H, m), 7.29-7.43 (2H, m), 7.49-7.60 (2H, m).

IR (ATR) cm^{-1} 2952, 1726, 1620, 1483, 1396, 1284, 1242, 1171, 1030, 750.

MS (ESI) *m/z* 545 $(M + H)^+$.

Anal. Calcd. for $C_{29}H_{37}ClN_2O_6$: C, 63.90; H, 6.84; Cl, 6.50; N, 5.14. Found: C, 63.84; H, 6.91; Cl, 6.63; N, 5.03.

1-{4-[{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl) amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (40g)



Compound **40g** was prepared from **38g** in a similar manner described for **9** in 90% yield as a colorless amorphous.

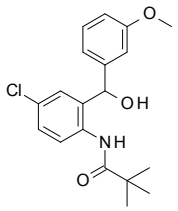
^{1}H-NMR (DMSO-d_6) δ (0.85) 0.86 (7H, s), 0.94-1.34 (1H, m), 1.45-1.72 (2H, m), 1.83-2.24 (3H, m), 2.26-2.71 (3H, m), 2.84-3.09 (2H, m), 3.15-3.88 (2H, m), 3.67 (3H, s), 4.24-4.42 (2H, m), 5.80-6.09 (2H, m), 6.86-7.10 (2H, m), 7.17-7.28 (1H, m), 7.29-7.42 (2H, m), 7.47-7.60 (2H, m).

IR (ATR) cm^{-1} 2951, 1728, 1622, 1475, 1396, 1240, 1167, 1115, 1030, 756.

MS (ESI) *m/z* 545 $(M + H)^+$.

Anal. Calcd. for $C_{29}H_{37}ClN_2O_6$: C, 63.90; H, 6.84; Cl, 6.50; N, 5.14. Found: C, 64.03; H, 7.09; Cl, 6.49; N, 4.90.

N-{4-Chloro-2-[hydroxy(3-methoxyphenyl)methyl]phenyl}-2,2-dimethylpropanamide (34h).

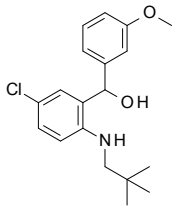


Compound **34h** was prepared from **33** in a similar manner described for **34d** in quantitative yield.

^{1}H-NMR ($CDCl_3$) δ 1.09 (9 H, s), 3.35-3.38 (1 H, m), 3.76 (3 H, s), 5.79 (1 H, br s), 6.80-6.94 (1 H, m), 7.08 (1 H, d, J = 2.5 Hz), 7.22-7.30 (2 H, m), 8.11 (1 H, d, J = 8.8 Hz), 8.72 (1 H, br s).

MS (ESI) *m/z* 348 $(M + H)^+$.

{5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}(3-methoxyphenyl)methanol (31h)

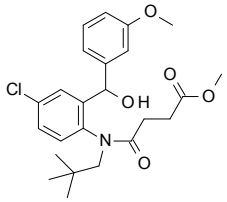


Compound **31h** was prepared from **34h** in a similar manner described for **31d** in quantitative yield.

^{1}H-NMR ($CDCl_3$) δ 0.83 (9 H, s), 2.58 (1 H, br s), 2.73 (2 H, s), 3.78 (3 H, s), 4.37 (1 H, br s), 5.72 (1 H, s), 6.55 (1 H, d, *J* = 8.6 Hz), 6.82-6.85 (1 H, m), 6.82-6.85 (1 H, m), 7.06 (1 H, d, *J* = 2.5 Hz), 7.06 (1 H, d, *J* = 2.5 Hz), 7.13 (1 H, dd, *J* = 8.6, 2.7 Hz,), 7.24-7.28 (1 H, m).

MS (ESI) *m/z* 334 $(M + H)^+$.

Methyl 4-[{4-chloro-2-[hydroxy(3-methoxyphenyl)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoate (35h).



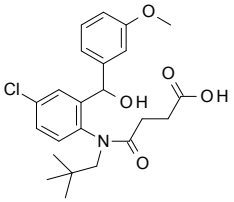
Compound **35h** was prepared from **31h** in a similar manner described for **6** in 86% yield.

^{1}H-NMR ($CDCl_3$) δ (0.90) 0.91 (9H, s), (1.81-1.91) 2.09-2.22 and 2.23-2.44 (2.63-2.78) (2.93-3.05) (4H, m), 2.60 (2.86) (1H, d, *J* = 13.5 Hz), 3.59 (3.69) (3H, s), (3.78) 3.82 (3H, s), (4.47) 4.49 (1H, d, *J* = 13.5 Hz), (4.66-4.75), 5.76-5.88 (1H, m), 6.77-6.90 (6.92-6.97) (7.03-7.06) (2H, m), 7.32-7.19 (4H, m), (7.40)7.89 (1H, d, *J* = 2.0 Hz).

MS (ESI) *m/z* 448 $(M + H)^+$.

Anal. Calcd. for $C_{24}H_{30}ClNO_5 \cdot 0.25H_2O$: C, 63.71; H, 6.79; N, 3.09. Found: C, 63.83; H, 6.77; N, 2.66.

4-[{4-Chloro-2-[hydroxy(3-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)-amino]-4-oxobutanoic acid (36h).



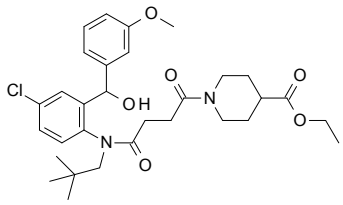
Compound **36h** was prepared from **35h** in a similar manner described for **7** in quantitative yield.

^{1}H-NMR ($CDCl_3$) δ (0.88) 0.91 (9H, s), 2.06 (1H, d, *J* = 12.5 Hz), (1.88-1.98) 2.08-2.25 (2H, m), 2.30-2.45 (2.63-2.76) (2H, m), (2.51) 2.90 (1H, d, *J* = 13.5 Hz), 3.76 (3H, s), (3.80) 3.82 (3H, s), (4.39) 4.48 (1H, d, *J* = 13.5 Hz), 4.67 (1H, s), (5.78) 5.74 (1H, s), 6.75-6.87 (3H, m), 6.91-6.98 (1H, m), 7.32-7.17 (2H, m), (7.39) 7.90 (1H, d, *J* = 2.5 Hz).

MS (ESI) *m/z* 434 $(M + H)^+$.

Anal. Calcd. for $C_{23}H_{28}ClNO_5$: C, 63.66; H, 6.50; N, 3.23. Found: C, 63.47; H, 6.70; N, 2.76.

Ethyl 1-{4-[{4-chloro-2-[hydroxy(3-methoxyphenyl)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37h).



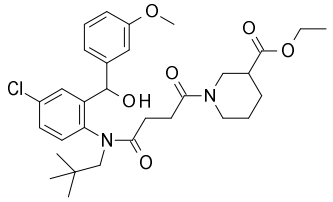
Compound **37h** was prepared from **36h** in a similar manner described for **8** in 98% yield.

^{1}H-NMR ($CDCl_3$) δ (0.89), 0.93 (9H, s), (1.21-1.29) 1.48-1.62 (2H, m), 1.77-2.10 (3H, m), 2.13-2.28 (1H, m), 2.36-2.60 (2H, m), 2.69 (1H, d, *J* = 13.0 Hz), (2.95-3.21) 2.72-2.91 (2H, m), (3.78) 3.82 (3H, s), 4.08-4.19 (2H, m), 4.22-4.47 (1H, m), 4.51 (4.53) (1H, d, *J* = 13.5 Hz), 5.80-5.93 (1H, m), 6.12 (1H, d, *J* = 5.6 Hz), 6.17 (1H, d, *J* = 5.1 Hz), 6.75-6.92 (2H, m), 7.07-7.11 (1H, m), 7.17-7.38 (7.83-7.74) (3H, m).

MS (ESI) *m/z* 573 $(M + H)^+$.

Anal. Calcd. for $C_{31}H_{41}ClN_2O_6$: C, 64.97; H, 7.21; N, 4.89. Found: C, 64.78; H, 7.26; N, 4.83.

Ethyl 1-{4-[{4-chloro-2-[hydroxy(3-methoxyphenyl)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate (38h).



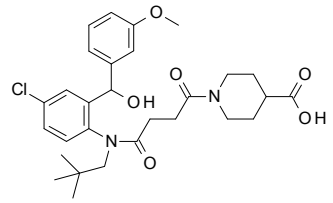
Compound **38h** was prepared from **36h** in a similar manner described for **8** in 95% yield.

^{1}H-NMR ($CDCl_3$) δ (0.89) 0.93 (9H, s), 1.20-1.31 (1H, m), 1.32-1.88 (3H, m), 1.92-2.12 (3H, m), 2.13-2.52 (2H, m), 2.54-2.86 (2H, m), 2.89-3.29 (3.47-3.56) (2H, m), (3.77) 3.82 (3H, s), 4.06-4.20 (2H, m), (4.64-4.72) 4.29-4.60 (2H, m), 5.80-5.92 (1H, m), 6.08-6.21 (1H, m), 6.75-6.91 (3H, m), 7.06-7.12 (1H, m), 7.19-7.30 (2H, m), 7.31-7.40 (7.81-7.72) (1H, m).

MS (ESI) *m/z* 573 $(M + H)^+$.

Anal. Calcd. for $C_{31}H_{41}ClN_2O_6$: C, 64.97; H, 7.21; N, 4.89. Found: C, 64.75; H, 7.25; N, 4.71.

1-{4-[{4-Chloro-2-[hydroxy(3-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl) amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (39h).



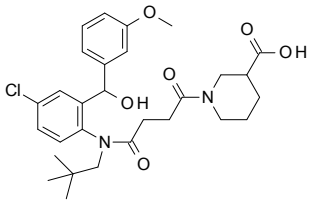
Compound **39h** was prepared from **37h** in a similar manner described for **9** in quantitative yield.

^{1}H-NMR ($CDCl_3$) δ (0.89) 0.92 (9H, s), (1.07-1.17) 1.48-1.74 (2H, m), 1.77-2.11 (3H, m), 2.14-2.30 (1H, m), 2.37-2.61 (2H, m), 2.65-2.90 (2H, m), 2.97-3.21 (2H, m), (3.77) 3.82 (3H, s), 4.23-4.40 (2H, m), (4.51) 4.53 (1H, d, J = 13.2 Hz), 5.83 (1H, s), 5.90 (1H, d, J = 4.2 Hz), 6.75-6.91 (3H, m), 7.06-7.10 (1H, m), 7.18-7.30 (2H, m), 7.32-7.39 (7.81-7.77) (1H, m).

MS (ESI) *m/z* 545 $(M + H)^+$.

Anal. Calcd. for $C_{29}H_{37}ClN_2O_6$: C, 63.90; H, 6.84; N, 5.14. Found: C, 63.64; H, 7.16; N, 4.79.

1-{4-[{4-Chloro-2-[hydroxy(3-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl) amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (40h).



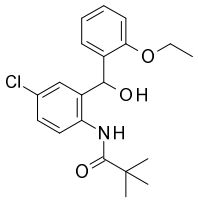
Compound **40h** was prepared from **38h** in a similar manner described for **9** in quantitative yield.

^{1}H-NMR ($CDCl_3$) δ 0.89 (0.93) (9H, s), 1.02-1.58 (2H, m), 1.60-1.90 (1H, m), 1.96-2.59 (5H, m), 2.62-2.91 (1H, m), 2.93-3.27 (2H, m), 3.30-3.94 (1H, m), (3.78) 3.82 (3H, s), 4.31-4.55 (2H, m), 5.78-5.92 (1H, m), 6.75-6.92 (3H, m), 7.04-7.10 (1H, m), 7.17-7.31 (7.70-7.82) (2H, m), 7.32-7.41 (1H, m).

MS (ESI) *m/z* 545 $(M + H)^+$.

Anal. Calcd. for $C_{29}H_{37}ClN_2O_6$: C, 63.90; H, 6.84; N, 5.14. Found: C, 64.03; H, 7.15; N, 4.87.

***N*-{4-Chloro-2-[(2-ethoxyphenyl)(hydroxy)methyl]phenyl}-2,2-dimethylpropanamide (34i).**

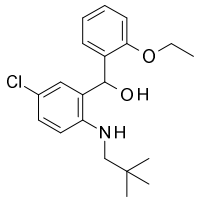


Compound **34i** was prepared from **33** in a similar manner described for **34d** in quantitative yield.

^{1}H-NMR ($CDCl_3$) δ 1.10 (9 H, s), 1.44 (3 H, d, J = 7.2 Hz), 4.05-4.25 (2 H, m), 4.29 (1 H, d, J = 4.4 Hz), 5.99 (1 H, d, J = 3.7 Hz), 6.80-6.93 (1 H, m), 6.96 (1 H, d, J = 8.1 Hz), 7.01 (1 H, d, J = 2.5 Hz), 7.23-7.33 (2 H, m), 8.20 (1 H, d, J = 8.8 Hz), 9.19 (1 H, br s).

MS (ESI) *m/z* 362 $(M + H)^+$.

{5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}(2-ethoxyphenyl)methanol (31i).

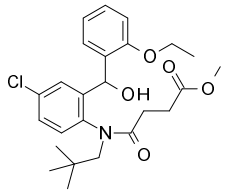


Compound **31i** was prepared from **34i** in a similar manner described for **31d** in quantitative yield.

^{1}H-NMR ($CDCl_3$) δ 0.91 (9 H, s), 1.40 (3 H, t, *J* = 6.9 Hz), 2.82 (2 H, s), 3.37 (1 H, br s), 4.06-4.16 (2 H, m), 4.78 (1 H, s), 5.98 (1 H, s), 6.57 (1 H, d, *J* = 8.6 Hz), 6.85-6.96 (2 H, m), 6.99 (1 H, d, *J* = 2.7 Hz,), 7.09-7.14 (1 H, m), 7.23-7.30 (1 H, m).

MS (ESI) *m/z* 348 $(M + H)^+$.

Methyl 4-[{4-chloro-2-[(2-ethoxyphenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoate (35i).



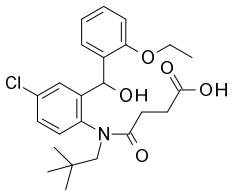
Compound **35i** was prepared from **34i** in a similar manner described for **6** in 91% yield.

^{1}H-NMR ($CDCl_3$) δ 0.89 (9H, s), 0.90 (10H, s), 1.29 (3H, t, *J* = 7.4 Hz), 1.47 (10H, t, *J* = 7.1 Hz), (0.72-0.83) 1.66-1.76 (1H, m), (2.08-2.18) 2.23-2.34 and 2.36-2.52 (2.73-2.83) (3H, m), 2.80 (2.89) (1H, d, *J* = 13.7 Hz), 2.93 (4.15) (1H, d, *J* = 5.4 Hz), (3.57) 3.68 (3H, s), 3.99-4.17 (2H, m), 4.37 (4.45) (1H, d, *J* = 13.5 Hz), (6.11) 6.19 (1H, d, *J* = 5.1 Hz), 6.81-6.91 (2H, m), 6.98-7.04 (1H, m), 7.17-7.33 (7.45-7.51) (7.96-7.94) (4H, m).

MS (ESI) *m/z* 462 $(M + H)^+$.

Anal. Calcd. for $C_{25}H_{32}ClNO_5$: C, 65.00; H, 6.98; N, 3.03. Found: C, 64.65; H, 7.05; N, 2.84.

4-[{4-Chloro-2-[(2-ethoxyphenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl) amino]-4-oxobutanoic acid (36i).



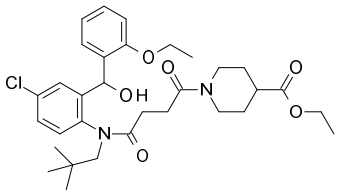
Compound **35i** was prepared from **34i** in a similar manner described for **7** in quantitative yield.

^{1}H-NMR ($CDCl_3$) δ 0.88 (0.92) (9H, s), 1.30 (1.48) (3H, t, *J* = 7.1 Hz), (1.76-1.86) 1.95-2.14 (1H, m), 2.31-2.47 (2H, m), 2.51-2.60 (2.62-2.72) (2H, m), 2.74 (2.92) (1H, d, *J* = 13.7 Hz), 3.97-4.14 (2H, m), 4.36 (4.48) (1H, d, *J* = 13.7 Hz), 6.06 (6.23) (1H, s), 6.83-6.92 (2H, m), 6.97-7.03 (2H, m), 7.13-7.40 (8.03-7.99) (4H, m).

MS (ESI) *m/z* 448 $(M + H)^+$.

Anal. Calcd. for $C_{24}H_{30}ClNO_5 \cdot 0.25H_2O$: C, 63.71; H, 6.79; N, 3.09. Found: C, 63.78; H, 6.73; N, 2.96.

Ethyl 1-{4-[{4-chloro-2-[(2-ethoxyphenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37i).



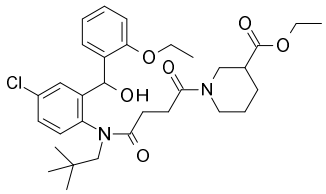
Compound **37i** was prepared from **36i** in a similar manner described for **8** in 99% yield.

^{1}H-NMR ($CDCl_3$) δ (0.94) 0.94 (9H, s), 1.17-1.28 (6H, m), (1.44-1.72) 1.76-1.99 (3H, m), 2.10-2.29 (2H, m), 2.37-2.54 (2H, m), 2.72-2.92 (1H, m), 2.95-3.19 (3H, m), 3.78-3.89 (1H, m), 4.02-4.18 (4H, m), 4.22-4.32 (1H, m), 4.36-4.45 (1H, m), 4.48 (1H, d, *J* = 13.7 Hz), (5.89) 6.08 (1H, d, *J* = 5.1 Hz), 6.12-6.18 (1H, m), 6.86 (1H, d, *J* = 8.3 Hz), 6.98-7.09 (1H, m), 7.12-7.16 (1H, m), 7.19-7.31 (7.92-7.73) (4H, m).

MS (ESI) *m/z* 587 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{43}ClN_2O_6$: C, 65.46; H, 7.38; N, 4.77. Found: C, 65.37; H, 7.47; N, 4.66.

Ethyl 1-{4-[{4-chloro-2-[(2-ethoxyphenyl)(hydroxy)methyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate (38i).



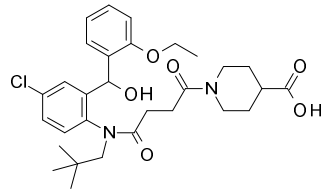
Compound **38i** was prepared from **36i** in a similar manner described for **8** in 93% yield.

^{1}H-NMR ($CDCl_3$) δ (0.90) 0.94 (9H, s), 1.17-1.31 (6H, m), 1.33-1.86 (3H, m), 1.93-2.53 (4H, m), 2.55-2.93 (2H, m), 2.95-3.29 (3H, m), (3.47) 3.49 (1H, d, *J* = 13.5 Hz), 3.56-3.90 (1H, m), 4.02-4.21 (4H, m), 4.32-4.60 (4.70-4.78) (1H, m), 4.47 (4.49) (1H, d, *J* = 13.5 Hz), (5.92) 6.01 (1H, d, *J* = 5.1 Hz), (6.09) 6.12-6.20 (1H, m), 6.81-6.89 (1H, m), 6.97-7.09 (1H, m), 7.11-7.40 (4H, m), 7.74-7.83 (7.92-7.89) (1H, m).

MS (ESI) *m/z* 587 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{43}ClN_2O_6$: C, 65.46; H, 7.38; N, 4.77. Found: C, 65.33; H, 7.48; N, 4.55.

1-{4-[{4-Chloro-2-[(2-ethoxyphenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl) amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (39i).



Compound **39i** was prepared from **37i** in a similar manner described for **9** in quantitative yield.

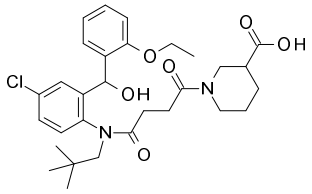
^{1}H-NMR ($CDCl_3$) δ (0.90) 0.94 (9H, s), 1.20 (1.47) (3H, t, *J* = 7.1 Hz), 1.51-1.72 (2H, m), 1.76-2.02 (3H, m), 2.13-2.31 (2H, m), 2.36-2.59 (2H, m), 2.68-2.85 (1H, m), 2.89 (3.13) (1H, d, *J* = 13.5 Hz), 2.94-3.11 (3.63-3.73) (1H, m), 3.78-3.90 (1H, m), 4.23-4.43

(1H, m), (3.42-3.48) 4.00-4.12 (2H, m), 4.48 (4.49) (1H, d, J = 13.5 Hz), 6.16 (1H, d, J = 7.4 Hz), 6.80-6.89 (2H, m), 6.98-7.09 (1H, m), 7.11-7.39 (3H, m), 7.74-7.80 (7.92-7.88) (1H, m).

MS (ESI) *m/z* 559 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{39}ClN_2O_6$: C, 64.45; H, 7.03; N, 5.01. Found: C, 64.49; H, 7.17; N, 4.80.

1-{4-[{4-Chloro-2-[(2-ethoxyphenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl) amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (40i).



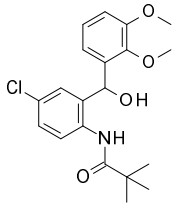
Compound **40i** was prepared from **38i** in a similar manner described for **9** in quantitative yield.

^{1}H-NMR ($CDCl_3$) δ (0.90) 0.92 (9H, s), 1.16-1.25 (1.42-1.49) (3H, m), 1.57-1.87 (2H, m), 1.96-2.13 (1H, m), 2.14-2.32 (1H, m), 2.32-2.58 (2H, m), 2.61-3.27 (4H, m), 3.39-3.67 (1H, m), 3.69-3.92 (1H, m), 3.96-4.12 (2H, m), 4.32-4.56 (4.61-4.69) (1H, m), 6.09-6.19 (1H, m), 6.79-6.89 (2H, m), 6.97-7.08 (1H, m), 7.10-7.42 (3H, m), 7.67-7.81 (7.93-7.87) (1H, m).

MS (ESI) *m/z* 559 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{39}ClN_2O_6$: C, 64.45; H, 7.03; N, 5.01. Found: C, 64.48; H, 7.41; N, 4.68.

***N*-{4-Chloro-2-[2,3-dimethoxyphenyl(hydroxy)methyl]phenyl}-2,2-dimethylpropanamide (34j).**



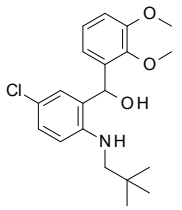
Compound **34j** was prepared from **33** in a similar manner described for **34d** in 46% yield as a pale yellow crystal.

^{1}H-NMR ($CDCl_3$) δ 1.13 (9H, s), 3.89 (3H, s), 3.90 (3H, s), 4.23 (1H, d, *J* = 4.4 Hz), 5.98 (1H, d, *J* = 4.4 Hz), 6.50 (1H, dd, *J* = 7.5, 1.2 Hz), 6.93-7.01 (3H, m), 7.31 (1H, dd, *J* = 8.8, 2.5 Hz), 8.17 (1H, d, *J* = 8.8 Hz), 9.19 (1H, br s).

MS (ESI) *m/z* 378 $(M + H)^+$.

Anal. Calcd. for $C_{20}H_{24}ClNO_4$: C, 63.57; H, 6.40; Cl, 9.38; N, 3.71. Found: C, 63.50; H, 6.49; Cl, 9.33; N, 3.60.

[5-Chloro-2-(2,2-dimethylpropylamino)phenyl](2,3-dimethoxyphenyl)methanol (31j).



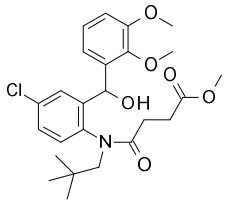
Compound **31j** was prepared from **34j** in a similar manner described for **31d** in 77% yield.

^{1}H-NMR ($CDCl_3$) δ 0.92 (9H, s), 2.83 (2H, s), 3.83 (3H, s), 3.88 (3H, s), 5.99 (1H, s), 6.57 (1H, d, *J* = 8.5 Hz), 6.80 (1H, dd, *J* = 7.8, 1.5 Hz), 6.90 (1H, dd, *J* = 8.3, 1.5 Hz), 6.99 (1H, d, *J* = 2.4 Hz), 7.03 (1H, dd, *J* = 8.1, 7.8 Hz), 7.10 (1H, dd, *J* = 8.5, 2.4 Hz).

Mp 118-119 °C (AcOEt – *n*-hexane).

MS (ESI) *m/z* 362 $(M + H)^+$.

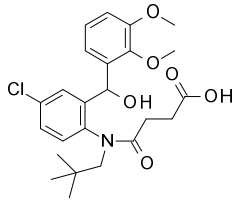
Methyl 4-[{4-chloro-2-[(2,3-dimethoxyphenyl)(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (35j).



Compound **35j** was prepared from **31j** in a similar manner described for **6** in 96% yield.

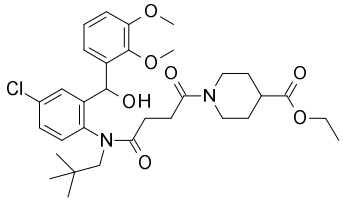
^{1}H-NMR ($CDCl_3$) δ 0.91 (0.94) (9H, s), (1.25-1.35) (1.85-1.95) 2.10-2.25 (3 H, m), 2.82-2.93 (1H, m), 2.97 (3.08) (1H, d, *J* = 13.7 Hz), 3.59 (3.60) (3H, s), 3.68 (3.78) (3H, s), 3.83 (3.88) (3H, s), 4.46 (4.47) (1H, d, *J* = 13.7 Hz), 4.64 (1H, d, *J* = 5.1 Hz), 6.04 (6.09) (1H, d, *J* = 5.1 Hz), 6.73-7.74 (6H, m).
MS (ESI) *m/z* 478 $(M + H)^+$.

N-{4-Chloro-2-[(2,3-dimethoxyphenyl)hydroxymethyl]phenyl}-N-(2,2-dimethylpropyl)succinamic acid (36j).



Compound **36j** was prepared from **35j** in a similar manner described for **7** in quantitative yield.
^{1}H-NMR ($CDCl_3$) δ (0.91) 0.92 (9H, s), 1.18-1.39 (3.44-3.52) (1H, m), (1.91-2.01) 2.19-2.34 (2H, m), 2.38-2.53 (2.73-2.84) (2H, m), (2.96) 2.98 (1H, d, *J* = 13.9 Hz), 3.62 (3.78) (3H, s), (3.83) 3.87 (3H, s), (4.43) 4.47 (1H, d, *J* = 24.7 Hz), (6.05) 6.08 (1H, s), 6.70-7.23 (7.83-7.79) (6H, m).
MS (ESI) *m/z* 464 $(M + H)^+$.

Ethyl 1-{3-[{4-Chloro-2-[(2,3-dimethoxyphenyl)hydroxymethyl]phenyl}-(2,2-dimethylpropyl)carbamoyl]propionyl}piperidine-4-carboxylate (37j).



Compound **37j** was prepared from **36j** in a similar manner described for **8** in 62% yield.
^{1}H-NMR ($CDCl_3$) δ 0.94 (9H, s), 1.21-1.25 (3H, m), 1.47-1.97 (4H, m), 2.09-2.22 (2H, m), 2.37-2.51 (2H, m), 2.73-2.92 (1H, m), 3.02-3.18 (2H, m), 3.28 (3.29) (1H, d, *J* = 13.7 Hz), 3.56 (3.57) (3H, s), 3.79-3.86 (1H, m), 3.87 (3H, s), 4.10-4.16 (2H, m),

4.22-4.28 (4.37-4.43) (1H, m), 4.51 (4.53) (1H, d, J = 13.7 Hz), 6.11 (6.12) (1H, d, J = 5.1 Hz), 6.28 (6.39) (1H, d, J = 5.1 Hz), 6.91-6.94 (1H, m), 7.09-7.24 (4H, m), 7.48-7.52 (1H, m).

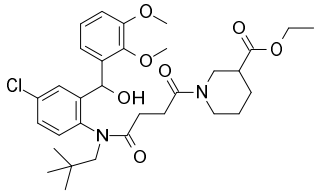
IR (ATR) cm^{-1} 3316 (br), 3000-2850 (br), 1733, 1662, 1625, 1477, 1442, 1394, 1317.

Mp 152-153°C (AcOEt – *n*-hexane).

MS (ESI) *m/z* 606, 604 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{43}ClN_2O_7$: C, 63.72; H, 7.19; Cl, 5.88; N, 4.64. Found: C, 63.55; H, 7.26; Cl, 5.96; N, 4.51.

Ethyl 1-{3-[{4-Chloro-2-[(2,3-dimethoxyphenyl)hydroxymethyl]phenyl}-(2,2-dimethylpropyl)carbamoyl]propionyl}piperidine-3-carboxylate (38j).



Compound **38j** was prepared from **36j** in a similar manner described for **8** in 51% yield.

^{1}H-NMR ($CDCl_3$) δ 0.97 (9H, s), 1.2-1.33 (3H, m), 1.5-3.8 (13H, m), 3.56 (3.57) (3H, s), 3.87 (3H, s), 4.0-4.8 (4H, m), 6.12-6.13 (1H, m), 6.27-6.30, 6,35-6.39 (1H, m), 6.91 (6.93) (1H, s), 7.08-7.09 (1H, m), 7.15-7.25 (3H, m), 7.48-7.51 (1H, m).

IR (ATR) cm^{-1} 3345, 3000-2800 (br), 1731, 1654, 1625, 1475, 1438, 1411, 1367, 1303, 1274.

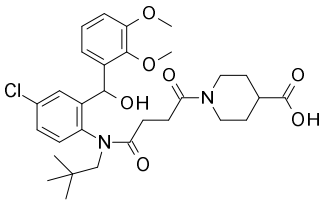
Mp 127-129 °C (AcOEt – *n*-hexane).

MS (ESI) *m/z* 606, 604 $(M + H)^+$.

HRMS (FAB) *m/z* 603.2834 (Calcd. for $C_{32}H_{44}ClN_2O_7$: 603.2837).

Anal. Calcd. for $C_{32}H_{43}ClN_2O_7 \cdot 0.33C_6H_{14}$: C, 64.63; H, 7.60; Cl, 5.61; N, 4.43. Found: C, 64.46; H, 7.70; Cl, 5.64; N, 4.26.

1-{3-[{4-Chloro-2-[(2,3-dimethoxyphenyl)hydroxymethyl]phenyl}-(2,2-dimethyl-propyl)carbamoyl]propionyl}piperidine-4-carboxylic acid (39j).



Compound **39j** was prepared from **37j** in a similar manner described for **9** in 91% yield as a colorless amorphous.

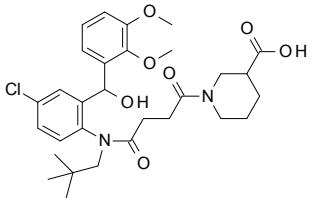
^{1}H-NMR ($CDCl_3$) δ 0.90 (0.97) (9H, s), 1.3-3.3 (13H, m), 3.562 (3.76) (3H, s), 3.83 (3.87) (3H, s), 4.25-4.6 (2H, m), 6.06 (6.12) (1H, s), 6.7-7.7 (6H, m).

IR (ATR) cm^{-1} 2952 (br), 1727, 1625, 1477, 1270.

MS (ESI) *m/z* 578, 576 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{39}ClN_2O_7 \cdot 0.3H_2O$: C, 62.07; H, 6.88; Cl, 6.11; N, 4.83. Found: C, 62.06; H, 6.87; Cl, 6.10; N, 4.64.

1-{3-[{4-Chloro-2-[(2,3-dimethoxyphenyl)hydroxymethyl]phenyl}-(2,2-dimethyl-propyl)carbamoyl]propionyl}piperidine-3-carboxylic acid (40j).



Compound **40j** was prepared from **40j** in a similar manner described for **9** in 89% yield.

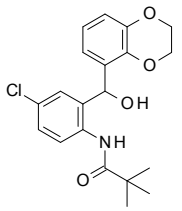
^{1}H-NMR ($CDCl_3$) δ 0.90, 0.91, 0.95, 0.96 (total 9H, s each), 1.3-4.9 (20H, m), 4.3-4.7 (1H, m), 6.04-6.14 (1H, m), 6.7-7.7 (6H, m).

IR (ATR) cm^{-1} 3050-2850 (br), 1727, 1623, 1477, 1272.

MS (ESI) *m/z* 578, 576 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{39}ClN_2O_7 \cdot 0.3H_2O$: C, 62.07; H, 6.88; Cl, 6.11; N, 4.83. Found: C, 62.12; H, 6.87; Cl, 6.03; N, 4.65.

***N*-{4-Chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl}-2,2-dimethylpropanamide (34k).**

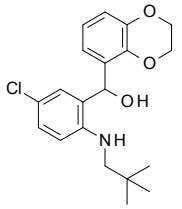


Compound **34k** was prepared from **33** in a similar manner described for **34d** in 77% yield as a pale yellow amorphous.

^{1}H-NMR ($CDCl_3$) δ 1.16 (9H, s), 3.82 (1H, br s), 4.25-4.40 (4H, m), 5.97 (1H, s), 6.48-6.53 (1H, m), 6.78-6.82 (1H, m), 6.88-6.90 (1H, m), 6.97 (1H, s), 7.28-7.33 (1H, m), 8.17 (1H, d, J = 8.8 Hz), 9.15 (1H, br s).

MS (CI) *m/z* 375 M^+.

{5-Chloro-2-[(2,2-dimethylpropyl)amino]phenyl}(2,3-dihydro-1,4-benzodioxin-5-yl) methanol (31k).

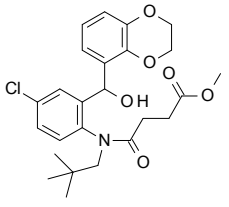


Compound **31k** was prepared from **34k** in a similar manner described for **31d** in 78% yield as a colorless syrup.

^{1}H-NMR ($CDCl_3$) δ 0.95 (9H, s), 2.84 (2H, s), 4.27-4.36 (4H, m), 5.95 (1H, s), 6.59 (1H, d, J = 8.5 Hz), 6.70-6.78 (1H, m), 6.80-6.89 (2H, m), 6.93 (1H, d, J = 2.4 Hz), 7.10-7.14 (1H, m).

MS (CI) *m/z* 361 M^+.

Methyl 4-[{4-chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl} (2,2-dimethylpropyl)amino]-4-oxobutanoate (35k).



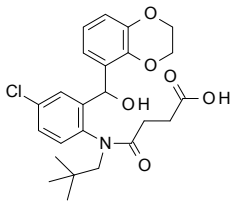
Compound **35k** was prepared from **31k** in a similar manner described for **6** in 89% yield as a colorless solid.

^{1}H-NMR ($CDCl_3$) δ 0.89 (0.90) (9H, s), (1.80-1.88) 2.15-2.28 and 2.31-2.45 (2.82-2.90) (4H, m), 2.90 (2.99) (1H, d, *J* = 13.7 Hz), (3.59) 3.67 (3H, s), (4.08-4.15) 4.17-4.29 (4.29-4.38) (4H, m), 4.42 (4.44) (1H, d, *J* = 13.7 Hz), 4.50-4.53 (1H, m), 6.05 (6.23) (1H, d, *J* = 4.9 Hz), (6.63-6.69) 6.70-6.77 (1H, m), 6.83-6.92 (1H, m), 7.18-7.23 (2H, m), 7.87 (1H, s).

IR (ATR) cm^{-1} 3409, 2952, 2875, 1735, 1644, 1600, 1473, 1407, 1363, 1324, 1280, 1241, 1193, 1166, 1087, 1039, 993, 956, 921, 889, 817.

MS (FAB) *m/z* 476 $(M+H)^+$.

4-[{4-Chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid (36k).



Compound **36k** was prepared from **35k** in a similar manner described for **7** in 88% yield as a colorless amorphous.

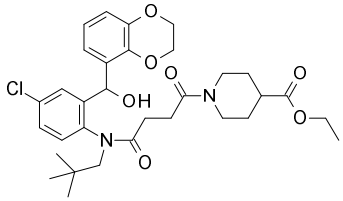
^{1}H-NMR ($CDCl_3$) δ (0.87) 0.91 (9H, s), (1.05-1.14) (1.87-1.96) 2.12-2.52 (2.76-2.83) (4H, m), 2.86 (2.94) (1H, d, *J* = 13.7 Hz), 4.10-4.33 (4H, m), (4.36) 4.47 (1H, d, *J* = 13.7 Hz), (6.00) 6.24 (1H, s), (6.61-6.64) 6.72-6.79 (1H, m), 6.82-6.90 (6.97-7.01) (1H, m), 7.15-7.33 (3H, m), 7.89 (1H, d, *J* = 2.4 Hz).

IR (ATR) cm^{-1} 2950, 2875, 1710, 1637, 1602, 1473, 1396, 1280, 1257, 1193, 1168, 1087, 1051, 956, 921, 889, 817.

MS (FAB) *m/z* 462 $(M+H)^+$.

Anal. Calcd. for $C_{23}H_{27}ClNO_5 \cdot 0.3CHCl_3$: C, 58.93; H, 5.69; N, 2.79. Found: C, 59.38; H, 5.87; N, 2.83.

Ethyl 1-{4-[{4-chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (37k).



Compound **37k** was prepared from **36k** in a similar manner described for **8** in 57% yield as a colorless amorphous.

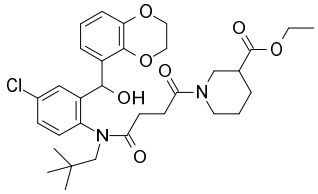
^{1}H-NMR ($CDCl_3$) δ (0.90) 0.93 (9H, s), 1.23 (1.25) (3H, t, *J* = 7.1 Hz), (1.59-1.80) 1.80-1.97 (3H, m), 2.07-2.32 (1H, m), 2.35-2.52 (3H, m), 2.68-3.30 (3H, m), 3.66-3.87 (1H, m), 4.02-4.52 (8H, m), 6.05-6.10 (1H, m), 6.18-6.21 (6.30-3.33)(1H, m), (6.61-6.66) 6.70-6.76 (1H, m), (6.82-6.84) 6.88-6.97 (1H, m), 7.12-7.42 (3H, m), 7.79-7.82 (7.97-8.00) (1H, m).

IR (ATR) cm^{-1} 3340, 2950, 2873, 1727, 1625, 1473, 1392, 1363, 1313, 1280, 1259, 1170, 1089, 1039, 958, 921, 887, 817.

MS (FAB) *m/z* 601 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{41}ClN_2O_7$: C, 63.94; H, 6.87; N, 4.66. Found: C, 63.61; H, 6.86; N, 4.93.

Ethyl 1-{4-[{4-chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate (38k).



Compound **38k** was prepared from **36k** in a similar manner described for **8** in 84% yield as a colorless amorphous.

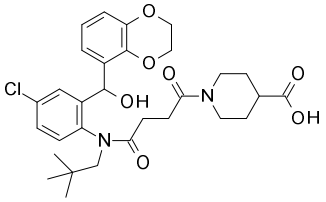
^{1}H-NMR ($CDCl_3$) δ (0.90) 0.93 (9H, s), 1.12-1.28 (3H, m), (1.32-1.45) 1.55-1.90 (3H, m), 1.92-2.52 (4H, m), 2.54-3.30 (3H, m), (3.42-3.52) 3.60-3.89 (1H, m), 4.10-4.37 (7H, m), 4.40-4.59 (4.68-4.4.74) (1H, m), 6.03-6.10 (1H, m), 6.16-6.34 (1H, m), 6.61-6.77 (1H, m), 6.78-6.977 (1H, m), 7.09-7.46 (7.78-7.82) (4H, m).

IR (ATR) cm^{-1} 3322, 2948, 2867, 1727, 1625, 1473, 1392, 1363, 1311, 1280, 1257, 1174, 1114, 1087, 1051, 956, 921, 887, 817.

MS (FAB) *m/z* 601 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{41}ClN_2O_7$: C, 63.94; H, 6.87; N, 4.66. Found: C, 63.60; H, 6.91; N, 4.76.

1-{4-[{4-Chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid (39k).



Compound **39k** was prepared from **37k** in a similar manner described for **9** in 87% yield as a colorless amorphous.

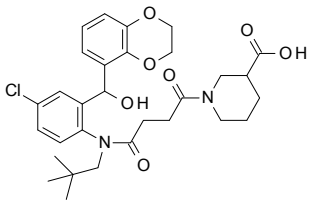
^{1}H-NMR ($CDCl_3$) δ 0.90 (0.93) (9H, s), 1.39-2.00 (4H, m), 2.06-2.59 (4H, m), 2.65-3.41 (4H, m), 3.62-3.89 (1H, m), 3.96-4.52 (6H, m), 6.10 (6.22) (1H, s), 6.53-6.78 (1H, m), 6.79-6.99 (1H, m), 7.00-7.43 (3H, m), 7.76-7.83 (1H, m).

IR (ATR) cm^{-1} 2950, 2933, 2869, 1725, 1621, 1473, 1396, 1365, 1311, 1280, 1259, 1170, 1087, 1031, 956, 921, 889, 815.

MS (FAB) *m/z* 573 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{37}ClN_2O_7 \cdot 0.4CHCl_3$: C, 59.13; H, 6.03; N, 4.48. Found: C, 59.48; H, 6.27; N, 4.50.

1-{4-[{4-Chloro-2-[2,3-dihydro-1,4-benzodioxin-5-yl(hydroxy)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid (40k).



Compound **40k** was prepared from **38k** in a similar manner described for **9** in quantitative yield as a colorless amorphous.

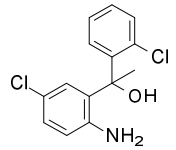
^{1}H-NMR ($CDCl_3$) δ 0.90 (0.98) (9H, s), 1.18-1.92 (4H, m), 1.95-2.69 (4H, m), 2.71-3.34 (3H, m), 3.36-3.89 (2H, m), 3.90-4.62 (6H, m), 6.07 (6.20) (1H, s), 6.60-6.98 (2H, m), 6.99-7.43 (3H, m), 7.72-7.83 (1H, m).

IR (ATR) cm^{-1} 2948, 2867, 1725, 1619, 1473, 1396, 1363, 1280, 1255, 1170, 1116, 1087, 1051, 1008, 956, 921, 889, 815.

MS (FAB) *m/z* 573 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{37}ClN_2O_7 \cdot 0.6CHCl_3$: C, 57.48; H, 5.81; N, 4.30. Found: C, 57.80; H, 6.10; N, 4.35.

1-(2-Amino-5-chlorophenyl)-1-(2-chlorophenyl)ethanol (42)



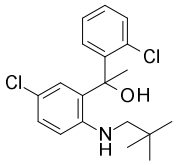
A solution of 2-amino-5-chloro-2'-chlorobenzophenone (3.00 g, 11.3 mmol) in THF (30 ml) was added methylmagnesium bromide (0.93 mol/l in THF, 13.3 ml, 12 mmol) at -78°C. The resulting mixture was gradually warmed to -40 °C, and recooled to -78°C, then methylmagnesium bromide (0.93 mol/l in THF, 26.6 ml, 24.8 mmol) was added again. The solution was allowed to reach room temperature and stirred for 19 h, then saturated ammonium chloride solution was added. The organic material was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Then, the residue was purified by a silica gel column chromatography (AcOEt : *n*-hexane = 1 : 10) to give compound **42** (0.82 g, 2.9 mmol, 26%) as a colorless syrup.

^{1}H-NMR ($CDCl_3$) δ 2.00 (3H, s), 4.05 (2H, br s), 6.55 (1H, d, *J* = 8.3 Hz), 7.03-7.08 (2H, m), 7.23-7.37 (3H, m), 7.73 (1H, dd, *J* = 7.8, 1.3 Hz).

IR (ATR) cm^{-1} 3377, 1724, 1614, 1487, 1410, 1263, 1036, 868, 816, 758.

MS (FAB) *m/z* 283 [$(M + H)^+$, $^{35}Cl^{35}Cl$], 285 [$(M + H)^+$, $Cl_{35}Cl_{37}$], 287 [$(M + H)^+$, $^{37}Cl^{37}Cl$].

1-[5-Chloro-2-(2,2-dimethylpropylamino)phenyl]-1-(2-chlorophenyl)ethanol (43)



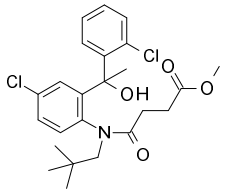
To a solution of compound **42** (760 mg, 2.69 mmol) in acetic acid (30 ml), pivalaldehyde (321 µl, 2.96 mmol) was added , then stirred for 5 min at room temperature. To the resulting mixture, sodium borohydride (132 mg, 3.50 mmol) was added at 0°C, and allowed to reach room temperature and then stirred for 24 h. The solution was removed in vacuo, and the residue was dissolved in AcOEt and H_2O. Then, the organic material was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Then, the residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 10) to give compound **43** (0.29 g, 0.82 mmol, 31%) as pale yellow syrup.

^{1}H-NMR ($CDCl_3$) δ 0.84 (9H, s), 1.97 (3H, s), 3.37 (1H, d, *J* = 14.6 Hz), 3.42 (1H, d, *J* = 14.6 Hz), 6.57 (1H, s), 6.97 (1H, d, *J* = 8.8 Hz), 7.09 (1H, dd, *J* = 8.8, 2.5 Hz), 7.11-7.34 (3H, m), 7.36-7.45 (2H, m).

IR (ATR) cm^{-1} 3390, 2962, 1597, 1491, 1431, 1367, 1284, 1203, 1039, 879, 804, 760.

MS (ESI) *m/z* 353 [(M + H)$^+$, ^{35}Cl^{35}Cl], 355 [(M + H)$^+$, ^{37}Cl^{37}Cl].

Methyl 4-[{4-chloro-2-[1-(2-chlorophenyl)-1-hydroxyethyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoate (44)



To an ice-cooled solution of compound **43** (0.21 g, 0.59 mmol) in CH_2Cl_2 (6 ml), ethyl 4-chloro-4-oxobutanoate (0.15 g, 1.77 mmol) and $NaHCO_3$ (0.15 g, 1.77 mmol) were added. After being stirred for 14 h at room temperature, To the recooled reaction mixture, ethyl 4-chloro-4-oxobutanoate (0.11 g, 0.71 mmol) and $NaHCO_3$ (0.15 g, 1.77 mmol) were added. After being stirred for 14 h at room temperature, the reaction was quenched with water. The organic material was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and then concentrated in

vacuo. The residue was purified by silica gel chromatography (AcOEt : *n*-hexane = 1 : 10) to give compound **44** (0.21 g, 0.45 mmol, 76%) as a colorless amorphous.

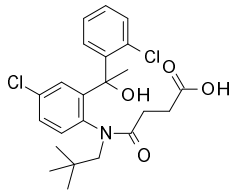
^{1}H-NMR ($CDCl_3$) δ 0.70 (0.88) (9H, s), 2.00-2.39 (2H, m), 2.41-2.71 (2H, m), (2.95) 3.56 (1H, d, J = 14.2 Hz), 4.06-4.18 (1H, m), 7.10-7.44 (5H, m), 7.61-8.02 (2H, m).

IR (ATR) cm^{-1} 3396, 2951, 1736, 1635, 1475, 1435, 1365, 1167, 1034, 756.

MS (ESI) *m/z* 466 [(M + H)$^+$, ^{35}Cl^{35}Cl], 468 [(M + H)$^+$, ^{35}Cl^{37}Cl], 470 [(M + H)$^+$, ^{37}Cl^{37}Cl].

Anal. Calcd. for $C_{24}H_{29}Cl_2N_1O_4 \cdot 0.4\ H_2O$: C, 60.87; H, 6.34; N, 2.96. Found: C, 60.99; H, 6.24; N, 2.81.

4-[{4-Chloro-2-[1-(2-chlorophenyl)-1-hydroxyethyl]phenyl}(2,2-dimethylpropyl) amino]-4-oxobutanoic acid (45)



Compound **44** (0.20 g, 0.42 mmol) was suspended in a mixture of MeOH (4 ml) and water (2 ml), and K_2CO_3 (0.18 g, 1.26 mmol) was added at room temperature, followed by stirring for 14 h at the same temperature. The solvent was removed under reduced pressure and was added to 1N hydrochloric acid (3.2 ml to pH 4) and CH_2Cl_2. The organics were extracted with CH_2Cl_2 (3 times). The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. Then, the residue was washed with diethyl ether and *n*-hexane to give compound **45** (0.15 g, 0.33 mmol, 78%) as a colorless powder.

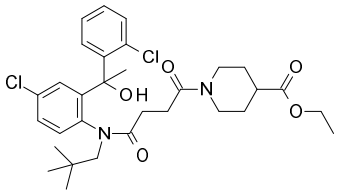
^{1}H-NMR (DMSO-d_6) δ 0.68 (0.74) (9H, s), 1.85 (3H, s), 1.89-2.68 (4H, m), 3.20-3.78 (2H, m), 6.07 (6.19) (1H, s), 7.16-7.50 (6H, m), 7.75-7.90 (1H, m).

IR (ATR) cm^{-1} 3396, 2952, 1712, 1631, 1477, 1431, 1255, 1182, 1036, 827, 750.

MS (ESI) *m/z* 452 [(M + H)$^+$, ^{35}Cl^{35}Cl], 454 [(M + H)$^+$, ^{35}Cl^{37}Cl].

Anal. Calcd. for $C_{23}H_{27}Cl_2NO_4 \cdot 0.1\ H_2O$: C, 60.82; H, 6.04; N, 3.08. Found: C, 60.84; H, 6.06; N, 3.02.

Ethyl 1-{4-[{4-chloro-2-[1-(2-chlorophenyl)-1-hydroxyethyl]phenyl}(2,2-dimethyl-propyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate (low polarity isomer 46 and high polarity isomer 47)



To a solution of Compound **45** (94 mg, 0.21 mmol) and ethyl isonipecotate (42 µl, 0.27 mmol) in CH_2Cl_2, WSCI·HCl (60 mg, 0.31 mmol) and HOBt (14 mg, 0.11 mmol) were added, and then the mixture was stirred at room temperature for 17 h. The reaction mixture was diluted with water and the organics were extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, then concentrated in vacuo, and the residue was purified with thin layer silica gel chromatography (1mm x 20 cm x 20 cm x 2, 5% MeOH – CH_2Cl_2) to give less polarity compound **46** (21.5 mg, 17%) and more polarity compound **47** (73 mg, 59%) as a colorless powder.

Low polarity isomer 46: ^{1}H-NMR ($CDCl_3$) δ 0.78-1.00(1H, m), 0.97 (9H, s), 1.21-1.30 (3H, m), 1.48-2.00 (4H, m), 2.03 (3H, s), 2.03-2.23 (2H, m), 2.28-2.55 (2H, m), 2.73-3.19 (3H, m), 3.08 (1H, d, *J* = 13.6 Hz), 3.79-3.91 (1H, m), 4.37-4.45 (1H, m), 4.10-4.18 (2H, m), 429 (1H, d, *J* = 13.6 Hz), 5.93 and 6.15 (1H, s), 7.01-7.07 (1H, m), 7.18-7.33 (4H, m), 7.36-7.42 (1H, m), 8.14-8.20 (1H, m).

IR (ATR) cm^{-1} 3315, 2927, 1730, 1651, 1620, 1473, 1281, 1171, 1034, 835, 756.

MS (ESI) *m/z* 591 [(M + H)$^+$, ^{35}Cl^{35}Cl], 593 [(M + H)$^+$, ^{35}Cl^{37}Cl].

HRMS (FAB) *m/z* 591.2407 (Calcd. for $C_{31}H_{41}Cl_2N_2O_5$ 591.2393).

Anal. Calcd. for $C_{31}H_{40}Cl_2N_2O_5$: C, 62.94; H, 6.82; N, 4.74. Found: C, 63.17; H, 6.88; N, 4.51.

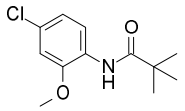
High polarity isomer 47: ^{1}H-NMR ($CDCl_3$) δ 0.66 (9H, s), 0.86-0.98 (1H, m), 1.20-1.28 (3H, m), 1.38-1.78 (1H, m), 1.83-1.98 (2H, m), 2.06 (3H, s), 2.09-2.56 (4H, m), 2.76-2.94 (2H, m), 3.06-3.17 (1H, m), 3.36-3.49 (1H, m), 3.87 (1H, *J* = 14.2 Hz), 4.09-4.18 (2H, m), 4.28-4.48 (1H, m), 4.56-4.72 (1H, m), 7.10-7.51 (6H, m), 7.74 (1H, dd, *J* = 11.5, 2.4 Hz), 7.88 (1H, d, *J* = 7.6 Hz).

IR (ATR) cm^{-1} 3300, 2947, 1734, 1660, 1624, 1475, 1277, 1182, 1038, 841, 764.

MS (ESI) *m/z* 591 [(M + H)$^+$, ^{35}Cl^{35}Cl], 593 [(M + H)$^+$, ^{35}Cl^{37}Cl].

Anal. Calcd. for $C_{31}H_{40}Cl_2N_2O_5$: C, 62.94; H, 6.82; Cl, 11.99; N, 4.74. Found: C, 63.05; H, 6.91; Cl, 11.74; N, 4.68.

N-(4-Chloro-2-methoxyphenyl)-2,2-dimethylpropanamide (49a)



Triethylamine (6.70 ml, 48.2 mmol), pivaloyl chloride (2.92 g, 24.1 mmol) and 4-dimethylaminopyridine (0.267 g, 2.19 mmol) were added to an ice-cooled solution of 4-chloro-2-methoxyaniline hydrochloride (**48a**, 4.25 g, 21.9 mmol) in CH_2Cl_2 (100 ml). After being stirred for 16 h at room temperature, the solvent was concentrated, and the residue was dissolved in AcOEt and water. The organic material was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 2 : 8 – 1 : 3) to give compound **49a** (5.22 g, 21.6 mmol, 98%) as a colorless powder.

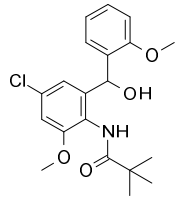
^{1}H-NMR ($CDCl_3$) δ 1.31 (9H, s), 3.89 (3H, s), 6.85 (1H, d, *J* = 2.2 Hz), 6.93 (1H, dd, *J* = 8.8, 2.2 Hz), 8.01 (1H, br), 8.34 (1H, d, *J* = 8.8 Hz).

IR (ATR) cm^{-1} 3442, 2954, 1668, 1521, 1403, 1251, 1037, 862, 796, 613, 584.

MS (ESI) *m/z* 242 (M + H)$^+$.

Anal. Calcd. for $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; N, 5.79; found: C, 59.35; H, 6.52; N, 5.81.

N-{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}-2,2-dimethyl-propanamide (52a)



Compound **49a** (2.22 g, 9.21 mmol) was dissolved in THF (100 ml). To the solution, s*ec*-butyl lithium (0.99 mol/l in *c*-hexane and *n*-hexane, 21.0 ml, 21.0 mmol) was added at -78°C, and stirred at 0°C for 15 min then at rt for 15 min. The mixture was cooled to -78°C again, and 2-methoxybenzaldehyde (1.22 ml, 10.1 mmol) was added. The reaction mixture was stirred at -50°C for 1.5 h, and poured saturated with NH_4Claq and AcOEt. The organic material was extracted with AcOEt. Combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (AcOEt : *n*-hexane = 1 : 3 – 1 : 1) to give compound **52a** (3.08 g, 88%) as colorless powder.

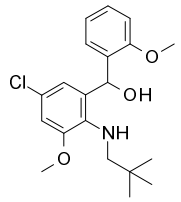
^{1}H-NMR ($CDCl_3$) δ 1.30 (9H, s), 3.68 (3H, s), 3.82 (3H, s), 4.37 (1H, d, *J* = 3.2 Hz), 5.97 (1H, s, *J* = 2.7 Hz), 6.79-6.83 (3H, m), 7.02 (1H, t, *J* = 7.6 Hz), 7.24-7.29 (1H, m), 7.56-7.58 (1H, m).

IR (ATR) cm^{-1} 3266, 1639, 1461, 1240, 1008, 761, 640.

MS (ESI) *m/z* 360 $(M - OH)^+$.

Anal. Calcd. for $C_{20}H_{24}ClNO_4$: C, 63.57; H, 6.40; N, 3.71; Cl, 9.38. Found: C, 63.20; H, 6.35; N, 3.64; Cl, 9.39.

{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-methoxyphenyl}(2-methoxyphenyl) methanol (53a)



A solution of compound **52a** (15.5 g, 40.9 mmol) was dissolved in THF (100 ml). Sodium bis(2-methoxyethoxy)aluminum hydride (60% in toluene, 62 ml) was added to the solution at 0°C. The mixture was stirred for 4h at 50°C. The reaction mixture was added to saturated (+)-tartaric acid sodium potassium solution and stirred for 5 min. The mixture was added to AcOEt and separated with a funnel. The organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography

(AcOEt : *n*-hexane = 1 : 20) to give the title compound **53a** (13.3 g, 36.5 mmol, 89%) as as colorless powder.

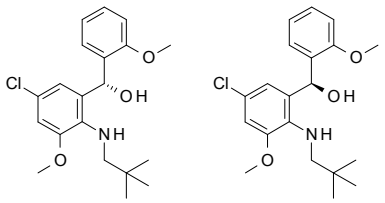
^{1}H-NMR ($CDCl_3$) δ 0.97 (9H, s), 2.69 (1H, d, *J* = 11.2 Hz), 2.76 (1H, d, *J* = 11.2 Hz), 3.83 (3H, s), 3.84 (3H, s), 4.35 (1H, br), 6.31 (1H, s), 6.59 (1H, d, *J* = 2.0 Hz), 6.76 (1H, d, *J* = 2.2 Hz), 6.91-6.99 (2H, m), 7.28-7.31 (2H, m).

IR (ATR) cm^{-1} 3353, 2942, 1602, 1587, 1459, 1236, 1024, 829, 757, 607.

MS (ESI) *m/z* 364 $(M + H)^+$.

Anal. Calcd. for $C_{20}H_{26}ClNO_3$: C, 66.01; H, 7.20; N, 3.85. Found: C, 65.72; H, 7.13; N, 3.95.

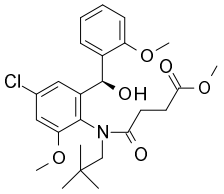
(*R*) and (*S*)-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-methoxyphenyl}(2-methoxyphenyl)methanol ((*R*)-54a and (*S*)-54a)



Compound **53a** (3.00 g, 8.24 mmol) was optically resolved by HPLC with an oprically active column (CHIRALCEL-OD, Φ20 x 250 mm) into isomer A (**(*R*)-54a**, 1.5 g) and isomer B (**(*S*)-54a**, 1.5 g).

Resolution conditions: Flow rate, 20 ml/min; Developing solvent, 25% 2-propanol – *n*-hexane; Retention time: isomer A, 4 min; isomer B, 8 min. The peaks similar to the racemate were obtained by ^{1}H-NMR ($CDCl_3$).

Methyl 4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2- dimethylpropyl)amino]-4-oxobutanoate ((*S*)-55a)



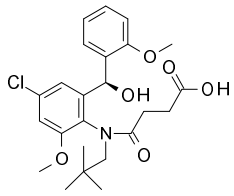
Methyl 4-chloro-4-oxobutanoate (0.203 ml, 1.65 mmol) and $NaHCO_3$ (345 mg, 4.11 mmol) were added to an ice-cooled solution of **(*S*)-54a** (500 mg, 1.37 mmol) in CH_2Cl_2

(20 ml). After being stirred for 1 h at room temperature, the reaction was quenched with water. The organic material was extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 2 – 2 : 1) to give compound **(*S*)-55a** (611 mg, 1.28 mmol, 93%) as a colorless oil.

^{1}H-NMR ($CDCl_3$) δ 0.89 (9H, s), 2.22-2.34 (2H, m), 2.52-2.65 (1H, m), 2.90-3.00 (1H, m), 3.09 (1H, d, *J* = 13.6 Hz), 3.67 (3H, s), 3.73 (3H, s), 3.86 (3H, s), 4.45 (1H, d, *J* = 13.6 Hz), 4.79 (1H, d, *J* = 5.4 Hz), 6.11 (1H, d, *J* = 5.1 Hz), 6.70 (1H, d, *J* = 2.1 Hz), 6.82 (1H, d, *J* = 2.1 Hz), 6.87 (1H, d, *J* = 7.8 Hz), 7.05-7.09 (1H, m), 7.29-7.34 (1H, m), 7.70 (1H, d, *J* = 7.6 Hz).

MS (ESI) *m/z* 460 $(M - OH)^+$.

4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-56a)



Compound **(*S*)-55a** (500 mg, 1.05 mmol) was suspended in a mixture of MeOH (10 ml) and water (5 ml), and K_2CO_3 (0.361 g, 2.62 mmol) was added at room temperature, followed by stirring for 2.5 h at 60°C. The solvent was removed under reduced pressure, and was added 1N citric acid solution and AcOEt. The organics were extracted with AcOEt (3 times). The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was washed with diethyl ether and *n*-hexane to give compound **(*S*)-56a** (486 mg, 1.05 mmol, quant.) as a colorless amorphous.

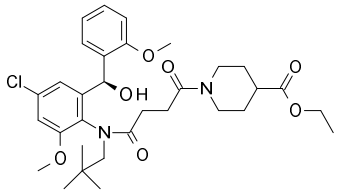
^{1}H-NMR ($CDCl_3$) δ 0.84 (0.88) (9H, s), 2.28-2.86 (4H, m), 2.89 (1H, d, *J* = 13.6 Hz), 3.75 (3.82) (3H, s), 3.87 (3.83) (3H, s), 4.39 (1H, d, *J* = 13.6 Hz), 6.06 (6.31) (1H, s), 6.77 (1H, d, *J* = 2.2 Hz), 6.85-6.89 (2H, m), 7.02 (1H, t, *J* = 7.4 Hz), 7.30-7.34 (1H, m), 7.45-7.47 (1H, m).

IR (ATR) cm^{-1} 3409, 2952, 1712, 1637, 1394, 1240, 1025, 754.

MS (ESI) *m/z* 446 $(M - OH)^+$.

Anal. Calcd. for $C_{24}H_{309}NO_6Cl \cdot 1.0H_2O$: C, 59.81; H, 6.69; N, 2.91. Found: C, 59.78; H, 6.58; N, 2.66.

Ethyl 1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate ((*S*)-57a)



To a solution of compound **(*S*)-56a** (100 mg, 0.216 mmol) and isonipecotic acid ethyl ester (42.0 mg, 0.270 mmol) in CH_2Cl_2 (5 ml), WSCI·HCl (52.0 mg, 0.270 mmol) and HOBt (41.0 mg, 0.270 mmol) were added, and then the mixture was stirred at room temperature for 2.5 h. The reaction mixture was diluted with water and the organics were extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, then concentrated in vacuo, The residue was purified with silica gel column chromatography (AcOEt : *n*-hexane = 1 : 2 – 1 : 1) to give compound **(*S*)-57a** (72.2 mg, 0.120 mmol, 56 %) as a colorless amorphous.

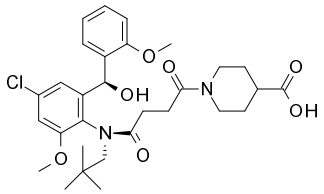
^{1}H-NMR ($CDCl_3$) δ 0.93 (9H, s), 1.24 (3H, t, *J* = 7.1 Hz), 1.53-1.92 (4H, m), 2.05-2.20 (2H, m), 2.46-2.85 (3H, m), 3.07-3.14 (2H, m), 3.30 (1H, d, *J* = 13.4 Hz), 3.70 (3H, s), 3.85 (3H, s), 3.81-3.85 (1H, m), 4.12 (2H, q, *J* = 7.1 Hz), 4.38-4.41 (1H, m), 4.50 (1H, d, *J* = 13.4 Hz), 6.14-6.16 (1H, m), 6.35-6.42 (1H, m), 6.63 (1H, d, *J* = 2.1 Hz), 6.78 (1H, d, *J* = 2.1 Hz), 6.85 (1H, d, *J* = 8.5 Hz), 7.08-7.11 (1H, m), 7.28-7.33 (1H, m), 7.87-7.90 (1H, m).

IR (ATR) cm^{-1} 3369, 2950, 1727, 1660, 1623, 1241, 1174, 1031, 754, 576.

MS (ESI) *m/z* 603 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{43}N_2O_7Cl$: C, 63.72; H, 7.19; N, 4.64. Found: C, 63.42; H, 7.26; N, 4.64.

(*aR*)-1-{4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid ((*S*)-(*aR*)-60a).



Compound **(*S*)-60a** was prepared from **(*S*)-57a** in a similar manner described for **(*S*)-56a**. Then, the obtained amorphous was washed with diethyl ether and *n*-hexane to give compound **(*S*)-(*aR*)-60a** in 68% yield as a colorless powder.

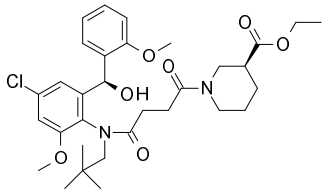
^{1}H-NMR (CD_3OD) δ 0.87 (9H, m), 1.28-1.97 (6H, m), 2.31-3.26 (5H, m), 3.03 (1H, d, *J* = 13.6 Hz), 3.74 (3H, s), 3.89 (3H, s), 3.89-3.93 (1H, m), 4.26-4.27 (1H, m), 4.34 (1H, d, *J* = 13.6 Hz), 6.02 (1H, s), 6.62 (1H, d, *J* = 2.2 Hz), 6.98 (1H, d, *J* = 8.3 Hz), 7.03-7.07 (2H, m), 7.32-7.36 (1H, m), 7.56-7.59 (1H, m).

IR (ATR) cm^{-1} 3407, 2950, 1718, 1614, 1282, 1025, 750, 578.

MS (ESI) *m/z* 575 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{39}N_2O_7Cl \cdot 0.33H_2O$: C, 62.01; H, 6.88; N, 4.82. Found: C, 62.09; H, 6.88; N, 4.77.

Ethyl (3*S*)-1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-58a)

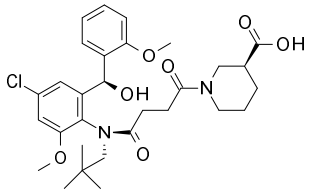


Compound **(*S*)-58a** was prepared from **(*S*)-56a** in a similar manner described for **(*S*)-57a** in 74% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.93 (9H, s), 1.20-1.28 (3H, m), 1.61-1.69 (4H, m), 2.11-3.32 (10H, m), 3.70 (3H, s), 3.84 (3H, s), 4.08-4.16 (2H, m), 4.48-4.56 (1H, m), 6.15 (1H, t, *J* = 5.2 Hz), 6.35 (1H, d, *J* = 5.1 Hz), 6.63 (1H, t, *J* = 2.5 Hz), 6.78 (1H, t, *J* = 2.5 Hz), 6.85

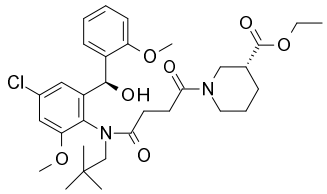
(1H, d, J = 8.1 Hz), 7.09 (1H, t, J = 7.6 Hz), 7.28-7.33 (1H, m), 7.88 (1H, t, J = 5.6 Hz).
^{13}C-NMR ($CDCl_3$) δ 14.26, 24.32, 24.72, 27.40 (27.44), 28.00 (27.57), 28.08, 34.43, 41.04 (42.36), 44.04, 45.88, 47.24, 54.90, 55.49, 60.66 (60.95), 64.85 (64.90), 110.14, 111.03 (110.99), 120.73, 120.93, 127.89, 128.32, 129.54 (129.48), 130.28 (130.25), 134.65, 145.30 (145.23), 155.77, 156.32, 171.13 (170.98), 172.86, 173.50 (173.39).
IR (ATR) cm^{-1} 3330, 2942, 1727, 1660, 1625, 1461, 1241, 1178, 1029, 754, 576.
MS (ESI) *m/z* 603 $(M + H)^+$.
Anal. Calcd. for $C_{32}H_{43}N_2O_7Cl \cdot 0.33H_2O$: C, 63.10; H, 7.22; N, 4.60. Found: C, 63.27; H, 7.25; N, 4.46.

(*aR*)-(3*S*)-1-{4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-61a)



Compound **(*S*)-(*aR*)-61a** was prepared from **(*S*)-58a** in a similar manner described for **(*S*)-(*aR*)-60a** in 97% yield as colorless powder.
^{1}H-NMR (DMSO-d_6) δ 0.81 (9H, s), 1.26-1.42 (1H, m), 1.48-1.69 (2H, m), 1.88-1.98 (1H, m), 2.11-2.48 (4H, m), 2.51-2.70 (1H, m), 2.81-3.00 (1H, s), 2.93 (1H, d, J = 13.3 Hz), 3.23-3.31 (2H, m), 3.67 (3H, s), 3.70-3.83 (1H, m), 3.85 (3H, s), 4.28 (1H, d, J = 13.3 Hz), 5.83-5.84 (1H, m), 5.92 (1H, m), 6.44 (1H, s), 6.99 (1H, d, J = 8.3 Hz), 7.05 (1H, t, J = 7.3 Hz), 7.11 (1H, d, J = 2.2 Hz), 7.29-7.34 (1H, m), 7.57 (1H, d, J = 7.3 Hz), 12.38 (1H, s).
IR (ATR) cm^{-1} 2948, 1727, 1621, 1587, 1461, 1407, 1241, 1178, 1029, 754, 576, 489.
MS (ESI) *m/z* 575 $(M + H)^+$.
Anal. Calcd. for $C_{30}H_{39}N_2O_7Cl$: C, 62.65; H, 6.84; N, 4.87. Found: C, 62.37; H, 7.06; N, 4.62.

Ethyl (3*R*)-1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-59a)



Compound **(*S*)-59a** was prepared from **(*S*)-56a** in a similar manner described for **(*S*)-57a** in 76% yield as colorless amorphous.

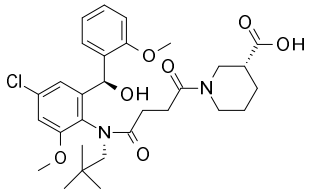
^{1}H-NMR ($CDCl_3$) δ 0.93 (9H, s), 1.21-1.27 (3H, m), 1.76-2.33 (8H, m), 2.54-2.67 (1H, m), 3.01-3.19 (2H, m), 3.22-3.32 (1H, m), 3.46-3.51 (1H, m), 3.70 (3H, s), 3.70-3.82 (1H, m), 3.85 (3H, s), 4.07-4.15 (2H, m), 4.48-4.53 (1H, m), 6.15 (1H, d, J = 5.4 Hz), 6.43 (6.39, 1H, d, J = 5.2 Hz), 6.62-6.64 (1H, m), 6.78-6.79 (1H, m), 6.85 (1H, d, J = 8.5 Hz), 7.07-7.12 (1H, m), 7.28-7.32 (1H, m), 7.89 (1H, d, J = 7.6 Hz).

IR (ATR) cm^{-1} 3353, 2924, 1727, 1658, 1625, 1461, 1241, 1176, 1029, 755, 576, 489.

MS (ESI) *m/z* 603 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{43}N_2O_7Cl$: C, 63.72; H, 7.19; N, 4.64. Found: C, 63.58; H, 7.35; N, 4.39.

(*aR*)-(3*R*)-1-{4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-62a)



Compound **(*S*)-(*aR*)-62a** was prepared from **(*S*)-59a** in a similar manner described for **(*S*)-(*aR*)-60a** in 92% yield as colorless powder.

^{1}H-NMR (CD_3OD) δ 0.87 (9H, s), 1.28 (1H, m), 1.49-1.52 (1H, m), 1.63 (1H, m), 1.77-1.80 (1H, m), 1.98 (2H, m), 2.33-2.59 (3H, m), 2.71-2.83 (2H, m), 2.99-3.05 (1H, m), 3.47 (1H, m), 3.74 (3H, s), 3.89 (3H, s), 3.77-3.85 (1H, m), 4.34 (1H, d, J = 13.7

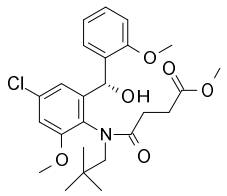
Hz), 6.02 (1H, s), 6.63 (1H, d, *J* = 6.3, 2.2 Hz), 6.98-7.06 (3H, m), 7.31-7.36 (1H, m), 7.55-7.58 (1H, m).

IR (ATR) cm^{-1} 2944, 1727, 1621, 1461, 1409, 1286, 1241, 1178, 1029, 754, 576, 489.

MS (ESI) *m/z* 575 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{39}N_2O_7Cl \cdot 0.33H_2O$: C, 62.01; H, 6.88; N, 4.82. Found: C, 62.20; H, 7.05; N, 4.59.

Methyl 4-[{4-chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*R*)-55a)



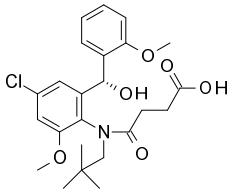
Compound **(*R*)-55a** was prepared in a similar manner described for **(*S*)-55a** in 98% yield as colorless oil.

^{1}H-NMR ($CDCl_3$) δ 0.890 (9H, s), 2.23-2.34 (2H, m), 2.52-3.00 (2H, m), 3.09 (1H, d, *J* = 13.7 Hz), 3.67 (3H, s), 3.73 (3H, s), 3.86 (3H, s), 4.45 (1H, d, *J* = 13.7 Hz), 4.78 (1H, d, *J* = 5.4 Hz), 6.11 (1H, d, *J* = 4.9 Hz), 6.71 (1H, d, *J* = 2.2 Hz), 6.82 (1H, d, *J* = 2.2 Hz), 6.87 (1H, d, *J* = 8.1 Hz), 7.06-7.09 (1H, m), 7.30-7.34 (1H, m), 7.71 (1H, d, *J* = 7.6 Hz).

IR (ATR) cm^{-1} 3419, 2944, 1731, 1644, 1324, 1282, 1031, 757, 499.

MS (ESI) *m/z* 460 $(M - OH)^+$.

4-[{4-Chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*R*)-56a)



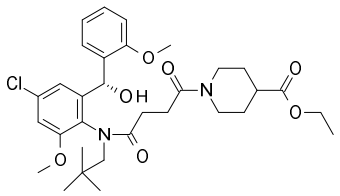
Compound **(*R*)-56a** was prepared in a similar manner described for **(*S*)-56a** in quantitative yield as colorless amorphous.

^{1}H-NMR (DMSO-d_6) δ 0.80 (9H, s), 2.16-2.42 (4H, m), 2.83 (1H, d, *J* = 13.4 Hz), 3.68 (3H, s), 3.86 (3H, s), 4.26 (1H, d, *J* = 13.4 Hz), 5.82 (1H, s), 6.49 (1H, d, *J* = 2.4 Hz), 6.99-7.06 (3H, m), 7.13 (1H, d, *J* = 2.4 Hz), 7.30-7.35 (1H, m), 7.50 (1H, dd, *J* = 7.4, 1.6 Hz).

IR (ATR) cm^{-1} 3380, 2946, 1737, 1643, 1286, 1247, 1174, 1025, 863, 757, 574.

MS (ESI) *m/z* 446 $(M - OH)^+$.

Ethyl 1-{4-[{4-chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate ((*R*)-57a)



Compound **(*R*)-57a** was prepared from **(*R*)-56a** in a similar manner described for **(*S*)-57a** in 56% yield as colorless amorphous.

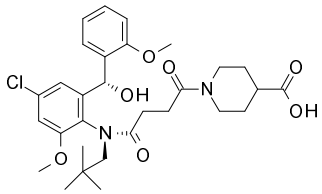
^{1}H-NMR ($CDCl_3$) δ 0.927 (9H, s), 1.24 (3 H, t, *J* = 7.3 Hz), 1.48-1.96 (4H, m), 2.04-2.21 (2H, m), 2.46-2.51 (1H, m), 2.54-2.62 (1H, m), 2.73-2.88 (1H, m), 3.06-3.17 (2H, m), 3.30 (1H, d, *J* = 13.5 Hz), 3.70 (3H, s), 3.85 (3H, s), 3.81-3.85 (1H, m), 4.12 (2H, q, *J* = 7.3 Hz), 4.24-4.40 (1H, m), 4.51 (1H, d, *J* = 13.5 Hz), 6.14-6.16 (1H, m), 6.34-6.42 (1H, m), 6.63 (1H, d, *J* = 2.3 Hz), 6.78-6.79 (1H, m), 6.85 (1H, d, *J* = 8.3 Hz), 7.08-7.11 (1H, m), 7.29-7.32 (1H, m), 7.87-7.90 (1H, m).

IR (ATR) cm^{-1} 3343, 2950, 1727, 1660, 1623, 1241, 1176, 1031, 755, 576.

MS (ESI) *m/z* 603 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{43}N_2O_7Cl \cdot 0.33H_2O$: C, 63.10; H, 7.22; N, 4.60. Found: C, 63.23; H, 7.01; N, 4.74.

(*aS*)-1-{4-[{4-Chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid ((*R*)-(*aS*)-60a)



Compound **(*R*)-(*aS*)-60a** was prepared from **(*R*)-57a** in a similar manner described for **(*S*)-(*aR*)-60a** in 99% yield as colorless amorphous.

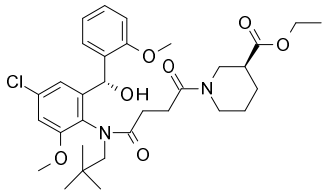
^{1}H-NMR ($CDCl_3$) δ 0.926 (9H, s), 1.48-1.99 (4H, m), 2.12-2.22 (2H, m), 2.49-2.61 (2H, m), 2.74-2.81 (1H, m), 3.04-3.22 (2H, m), 3.31 (1H, t, *J* = 14.2 Hz), 3.70 (3H, s), 3.85 (3H, s), 3.80-3.85 (1H, m), 4.32-4.41 (1H, m), 4.51 (1H, d, *J* = 14.2 Hz), 6.16 (1H, d, *J* = 3.2 Hz), 6.61-6.62 (1H, m), 6.78 (1H, d, *J* = 2.3 Hz), 6.84-6.86 (1H, m), 7.08-7.11 (1 H, m), 7.29-7.32 (1H, m), 7.84-7.88 (1H, m).

IR (ATR) cm^{-1} 3340, 2950, 1727, 1623, 1461, 1176, 1027, 754, 491.

MS (ESI) *m/z* 575 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{39}N_2O_7Cl$: C, 62.65; H, 6.84; N, 4.87. Found: C, 62.37; H, 7.13; N, 4.57.

Ethyl (3*S*)-1-{4-[{4-chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*R*)-58a)



Compound **(*R*)-58a** was prepared from **(*R*)-56a** in a similar manner described for **(*S*)-57a** in 19% yield as colorless amorphous.

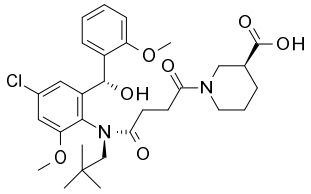
^{1}H-NMR ($CDCl_3$) δ (0.89) 0.90 (9H, s), 1.17-1.24 (3H, m), 1.42-1.53 (1H, m), 1.68-1.80 (1H, m), 1.85-2.44 (7H, m), 2.91-3.15 (2H, m), 3.41-3.48 (2H, m), (3.67) 3.67 (3H, s), 3.81 (3H, s), 4.03-4.14 (2H, m), 4.41-4.51 (1H, m), 4.68-4.77 (1H, m), 6.09-6.13 (1H, m), 6.35-6.43 (1H, m), 6.59 (6.60) (1H, d, *J* = 2.3 Hz), 6.73-6.77 (1H, m), 6.79-6.85 (1H, m), 7.02-7.10 (1H, m), 7.25-7.32 (1H, m), 7.89-7.82 (1H, m).

IR (ATR) cm^{-1} 3349, 2942, 1727, 1658, 1623, 1461, 1241, 1176, 1029, 755, 576.

MS (ESI) *m/z* 603 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{43}N_2O_7Cl \cdot 0.33H_2O$: C, 63.10; H, 7.22; N, 4.60. Found: C, 63.11; H, 7.04; N, 4.73.

(*aS*)-(3*S*)-1-{4-[{4-Chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*R*)-(*aS*)-61a)



Compound **(*R*)-(*aS*)-61a** was prepared from **(*R*)-58a** in a similar manner described for **(*S*)-(*aR*)-60a** in 93% yield as colorless amorphous.

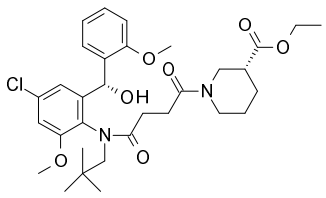
^{1}H-NMR ($CDCl_3$) δ (0.87) 0.90 (9H, s), 1.18-1.41 (1H, m), 1.43-1.83 (2H, m), 1.95-2.27 (4H, m), (2.29-2.44) 2.48-2.71 (2.77-2.97) (2H, m), 3.00-3.16 (2H, m), (3.18) 3.27 (1H, d, *J* = 13.7 Hz), 3.37-3.47 (3.85-3.93),(1H, m), (3.67) 3.69 (3H, s), 3.82 (3H, s), 4.39-4.51 (4.54-4.61) (1H, m), 6.10 (1H, s), (6.59) 6.61 (1H, d, *J* = 2.0 Hz), 6.73-6.77 (1H, m), 6.79-6.85 (1H, m), 7.03-7.09 (1H, m), 7.25-7.30 (1H, m), 7.87-7.77 (1H, m).

IR (ATR) cm^{-1} 3347, 2950, 1727, 1621, 1461, 1241, 1178, 1029, 754, 576, 491.

MS (ESI) *m/z* 575 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{39}N_2O_7Cl \cdot 0.33H_2O$: C, 62.01; H, 6.88; N, 4.82. Found: C, 62.06; H, 7.07; N, 4.55.

Ethyl (3*R*)-1-{4-[{4-chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*R*)-59a)



Compound **(*R*)-59a** was prepared from **(*R*)-56a** in a similar manner described for **(*S*)-57a** in 31% yield as colorless amorphous.

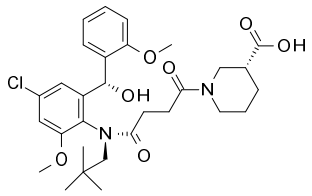
^{1}H-NMR ($CDCl_3$) δ 0.931 (0.925) (9H, s), 1.25 (1.22) (3H, t, *J* = 7.3 Hz), 1.62-2.20 (5H, m), 2.29-2.85 (4.42-4.75) (2H, m), 2.99-3.22 and 3.46-3.50 and 3.74-3.81 and 3.89-4.04 (2H, m), 3.30 (3.28) (1H, d, *J* = 13.5 Hz), 3.70 (3H, s), 3.85 (3H, s), 4.14 (4.09) (2H, q, *J* = 7.3 Hz), 4.51 (4.50) (1H, d, *J* = 13.5 Hz), 6.14-6.17 (1H, m), 6.34-6.42 (1H, m), 6.62-6.64 (1H, m), 6.78-6.79 (1H, m), 6.85 (1H, d, *J* = 8.2 Hz), 7.08-7.11 (1H, m), 7.30 (1H, d, *J* = 7.8 Hz), 7.87-7.89 (1H, m).

IR (ATR) cm^{-1} 3382, 2950, 1720, 1639, 1284, 1180, 1031, 856, 754, 572, 422.

MS (ESI) *m/z* 603 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{43}N_2O_7Cl$: C, 63.72; H, 7.19; N, 4.64. Found: C, 63.60; H, 6.99; N, 4.68.

(*aS*)-(3*R*)-1-{4-[{4-Chloro-2-[(*R*)-hydroxy(2-methoxyphenyl)methyl]-6-methoxyphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*R*)-(*aS*)-62a)



Compound **(*R*)-(*aS*)-62a** was prepared from **(*R*)-59a** in a similar manner described for **(*S*)-(*aR*)-60a** in 89% yield as colorless amorphous.

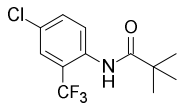
^{1}H-NMR ($CDCl_3$) δ (0.88) 0.89 (9H, s), 1.18-1.42 (1H, m), 1.57-1.85 (2.07-2.22) (3H, m), 2.34-2.47 (1H, m), 2.48-2.69 (2H, m), 2.78-2.98 (1H, m), 3.00-3.30 (4H, m), 3.44-3.53 (1H, m), 3.67 (3.68) (3H, s), 3.71-3.90 (1H, m), (3.80) 3.81 (3H, s), 4.39-4.51 (2H, m), 6.11 (1H, d, *J* = 7.0 Hz), (6.59) 6.61 (1H, d, *J* = 2.3 Hz), 6.74-6.77 (1H, m), 6.79-6.85 (1H, m), 7.05 (1H, t, *J* = 7.8 Hz), 7.24-7.30 (1H, m), 7.86-7.77 (1H, m).

IR (ATR) cm^{-1} 3355, 2950, 1727, 1623, 1241, 1178, 1029, 754, 576, 489.

MS (ESI) *m/z* 575 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{39}N_2O_7Cl \cdot 0.33H_2O$: C, 62.01; H, 6.88; N, 4.82. Found: C, 62.15; H, 7.03; N, 4.57.

***N*-[4-Chloro-2-(trifluoromethyl)phenyl]-2,2-dimethylpropanamide (49b)**



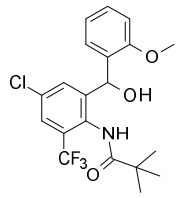
Compound **49b** was prepared in a similar manner described for **49a** in 37% yield as colorless crystal.

^{1}H-NMR ($CDCl_3$) δ 1.32 (9H, s), 7.51 (1H, dd, J = 8.9, 2.3 Hz), 7.58 (1H, d, J = 2.3 Hz), 7.75 (1H, br), 8.24 (1H, d, J = 8.8 Hz).

IR (ATR) cm^{-1} 3288, 2974, 1645, 1496, 1304, 1138, 1053, 816, 607.

MS (ESI) *m/z* 280 $(M + H)^+$.

***N*-{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-6-(trifluoromethyl)phenyl}-2,2-dimethylpropanamide (52b)**



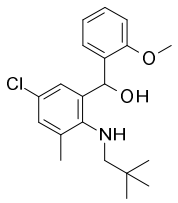
Compound **52b** was prepared in a similar manner described for **52a** in 25% yield as colorless crystal.

^{1}H-NMR ($CDCl_3$) δ 1.32 (9H, s), 3.67 (3H, s), 4.05 (1H, d, J = 3.2 Hz), 5.98 (1H, d, J = 2.9 Hz), 6.82 (1H, d, J = 8.1 Hz), 7.03-7.08 (1H, m), 7.27-7.33 (1H, m), 7.44 (1H, d, J = 2.2 Hz), 7.57-7.62 (1H, m), 7.56 (1H, d, J = 2.4 Hz).

IR (ATR) cm^{-1} 3284, 2952, 1655, 1510, 1468, 1311, 1242, 1161, 1128, 881, 760.

MS (ESI) *m/z* 398 $(M + H)^+$.

{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-methylphenyl}(2-methoxyphenyl) methanol (53b)

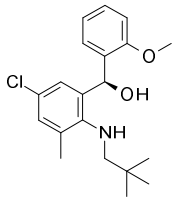


Compound **53b** was prepared in a similar manner described for **53a** in 66% yield as colorless crystal.

^{1}H-NMR ($CDCl_3$) δ 0.98 (9H, s), 2.29 (3H, s), 2.61 (1H, d, J = 11.2 Hz), 2.65 (1H, d, J = 11.2 Hz), 3.84 (3H, s), 6.20 (1H, s), 6.86-7.02 (3H, m), 7.07 (1H, d, J = 2.4 Hz), 7.18-7.36 (2H, m).

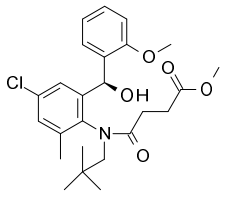
MS (ESI) *m/z* 348 $(M + H)^+$.

(*S*)-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-methylphenyl}(2-methoxyphenyl) methanol (54b)



Compound **(*S*)-54b** was separated in a similar manner described for **(*S*)-54a** by using HPLC with a CHIRALCEL OD as colorless crystal.

Methyl 4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methylphenyl} (2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-55b)



Compound **(*S*)-55b** was prepared in a similar manner described for **(*S*)-55a** in 88% yield as colorless amorphous.

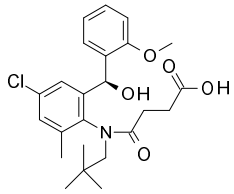
^{1}H-NMR ($CDCl_3$) δ 0.87 (0.95) (9H, s), 1.92-2.02 and 2.11-2.21 (1H, m), 2.24-2.37 (1H, m), 2.40-2.50 (1H, m), 2.45 (3H, s), 2.51-2.62 (2.71-2.74) (1H, m), 2.75-2.89 (1H, m),

3.06 (3.36) (1H, d, *J* = 13.7 Hz), (3.56) 3.68 (3H, s), 3.77 (3.86) (3H, s), (3.91) 4.12 (1H, q, *J* = 7.2 Hz), 4.31 (1H, d, *J* = 13.7 Hz), 4.42 (1H, d, *J* = 4.9 Hz), 6.06 (6.39) (1H, d, *J* = 5.4 Hz), 6.83-6.94 (1H, m), 6.99-7.09 (2H, m), 7.20 (1H, d, *J* = 2.4 Hz), 7.28-7.35 (1H, m), 7.51-7.56 (7.74-7.71) (1H, m).

IR (ATR) cm^{-1} 3410, 2952, 1736, 1647, 1437, 1238, 1167, 1030, 754.

MS (FAB) *m/z* 462 $(M + H)^+$. MS (ESI) *m/z* 460 $(M - H)^-$.

4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methylphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-56b)

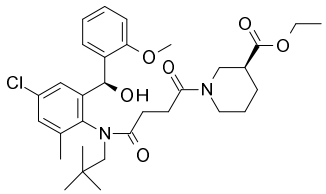


Compound **(*S*)-56b** was prepared in a similar manner described for **(*S*)-56a** in 92% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.84 (9H, s), 2.15-2.35 (2H, m), 2.43 (3H, s), 2.47-2.64 (2H, m), 2.72-2.84 (1H, m), 2.92 (1H, d, *J* = 13.4 Hz), 3.79 (3H, s), 4.26 (1H, d, *J* = 13.7 Hz), 6.03 (1H, s), 6.91 (1H, d, *J* = 7.8 Hz), 6.97-7.04 (1H, m), 7.11 (1H, d, *J* = 2.4 Hz), 7.23 (1H, d, *J* = 2.4 Hz), 7.30-7.26 (1H, m), 7.34 (2H, d, *J* = 7.8 Hz).

MS (ESI) *m/z* 430 $(M - OH)^+$. MS (ESI) *m/z* 446 $(M - H)^-$.

Ethyl (3*S*)-1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methylphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-58b)



Compound **(*S*)-58b** was prepared from **(*S*)-56b** in a similar manner described for **(*S*)-57a** in 72% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.93 and 0.94 (9H, s), 1.20-1.31 (5H, m), 1.59-1.84 (2H, m), 2.00-2.13 (2H, m), 2.16-2.38 (2H, m), 2.43 (3H, d, *J* = 2.4 Hz), 2.44-2.74 (2H, m),

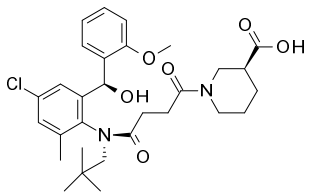
2.83-3.16 (2H, m), 3.18-3.36 (2H, m), 3.71 (3H, s), 4.06-4.20 (2H, m), 4.35-4.55 (2H, m), 6.07-6.13 (1H, m), 6.86 (1H, d, J = 7.8 Hz), 6.92-6.97 (1H, m), 7.07 (1H, t, J = 7.4 Hz), 7.17-7.12 (1H, m), 7.34-7.28 (1H, m), 7.80 (1H, t, J = 7.4 Hz).

IR (ATR) cm^{-1} 3325, 2952, 1728, 1658, 1624, 1458, 1240, 1178, 1032, 754.

MS (ESI) *m/z* 587 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{43}ClN_2O_6$: C, 65.46; H, 7.38; N, 4.77. Found: C, 65.53; H, 7.69; N, 4.50.

(*aR*)-(3*S*)-1-{4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-methylphenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-61b)



Compound **(*S*)-(*aR*)-61b** was prepared from **(*S*)-58b** in a similar manner described for **(*S*)-(*aR*)-60a** in 78% yield as colorless amorphous.

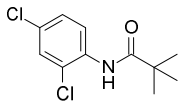
^{1}H-NMR ($CDCl_3$) δ 0.91 and 0.92 (9H, s), 1.21-1.33 (2H, m), 1.59-1.87 (2H, m), 1.95-2.32 (3H, m), 2.42 and 2.43 (3H, s), 2.45-2.67 (2H, m), 2.91-3.16 (2H, m), 3.20-3.29 (1H, m), 3.39-3.54 (1H, m), 3.71 snd 3.72 (3H, s), 3.73-4.06 (1H, m), 4.35-4.52 (1H, m), 6.08 (1H, d, J = 5.1 Hz), 6.82-6.90 (1H, m), 6.95-7.01 (1H, m), 7.06 (1H, t, J = 7.4 Hz), 7.13-7.17 (1H, m), 7.27-7.35 (1H, m), 7.78-7.70 (1H, m).

IR (ATR) cm^{-1} 2952, 1728, 1622, 1460, 1240, 1180, 1032, 754.

MS (ESI) *m/z* 559 $(M + H)^+$.

Anal. Calcd. for $C_{30}H_{39}ClN_2O_6$: C, 64.45; H, 7.03; N, 5.01. Found: C, 64.32; H, 7.33; N, 4.71.

***N*-(2,4-Dichlorophenyl)-2,2-dimethylpropanamide (49c)**

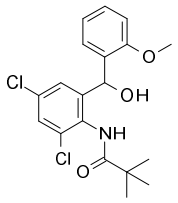


Compound **49c** was prepared in a similar manner described for **49a** in 78% yield as colorless oil.

^{1}H-NMR ($CDCl_3$) δ 1.34 (9 H, s), 7.23-7.26 (1 H, m), 7.38 (1 H, d, J = 2.4 Hz), 7.95 (1 H, br), 8.38 (1 H, d, J = 9.0 Hz).

MS (ESI) *m/z* 246 $(M + H)^+$.

N-{2,4-Dichloro-6-[hydroxy(2-methoxyphenyl)methyl]phenyl}-2,2-dimethyl-propanamide (52c)



Compound **52c** was prepared in a similar manner described for **52a** in 47% yield as colorless amorphous.

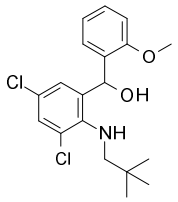
^{1}H-NMR ($CDCl_3$) δ 1.28 (9H, s), 3.75 (3H, s), 5.97 (1H, d, J = 3.7 Hz), 6.86 (1H, d, J = 8.1 Hz), 6.98-7.02 (1H, m), 7.13 (1H, d, J = 2.4 Hz), 7.27-7.32 (1H, m), 7.37 (1H, d, J = 2.2 Hz), 7.38-7.41 (1H, m), 7.51 (1H, br s).

IR (ATR) cm^{-1} 3289, 2962, 1668, 1484, 1465, 1230, 1016, 869, 755, 489.

MS (ESI) *m/z* 365 $(M - OH)^+$.

Anal. Calcd. for $C_{19}H_{21}Cl_2NO_3 \cdot 0.3Et_2O$: C, 59.98; H, 5.98; N, 3.46. Found: C, 60.37; H, 5.72; N, 3.77.

{3,5-Dichloro-2-[(2,2-dimethylpropyl)amino]phenyl}(2-methoxyphenyl)methanol (53c)



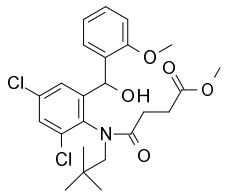
Compound **53c** was prepared in a similar manner described for **53a** in 64% yield as pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ 0.98 (9H, s), 2.76 (2H, s), 3.84 (3H, s), 4.32 (1H, br), 6.29 (1H, s), 6.29-7.00 (3H, m), 7.23-7.34 (3H, m).

IR (ATR) cm^{-1} 3380, 2952, 1459, 1240, 1027, 858, 752, 568.

MS (ESI) *m/z* 350 $(M - OH)^+$.

Methyl 4-[{2,4-dichloro-6-[hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate (55c)



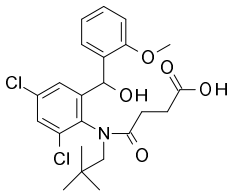
Compound **55c** was prepared in a similar manner described for **55a** in 49% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.96 (9H, s), 2.32-2.61 (3H, m), 2.96-3.04 (1H, m), 3.19 (1H, d, *J* = 13.7 Hz), 3.68 (3H, s), 3.74 (3H, s), 4.43 (1H, d, *J* = 13.7 Hz), 4.99 (1H, d, *J* = 5.6 Hz), 6.10 (1H, d, *J* = 5.4 Hz), 6.89 (1H, d, *J* = 8.3 Hz), 7.05-7.10 (2H, m), 7.32-7.36 (1H, m), 7.40 (1H, d, *J* = 2.4 Hz), 7.70 (1H, dd, *J* = 8.0, 1.3 Hz).

MS (ESI) *m/z* 464 $(M - OH)^+$.

Anal. Calcd. for $C_{24}H_{29}Cl_2NO_5$: C, 59.76; H, 6.06; N, 2.90. Found: C, 60.07; H, 6.08; N, 2.77.

4-[{2,4-Dichloro-6-[hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl) amino]-4-oxobutanoic acid (56c)



Compound **56c** was prepared in a similar manner described for **56a** in 96% yield as colorless amorphous.

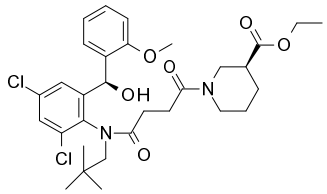
^{1}H-NMR ($CDCl_3$) δ 0.915 (9H, s), 2.43-2.55 (3H, m), 2.95-2.99 (1H, m), 2.99 (1H, d, *J* = 13.6 Hz), 3.76 (3H, s), 4.37 (1H, d, *J* = 13.6 Hz), 6.06 (1H, s), 6.90 (1H, d, *J* = 8.5

Hz), 7.02-7.06 (1H, m), 7.11 (1H, d, J = 2.2 Hz), 7.33-7.37 (1H, m), 7.43 (1H, d, J = 2.4 Hz), 7.49 (1H, d, J = 7.3 Hz).

MS (ESI) *m/z* 450 $(M - OH)^+$.

Anal. Calcd. for $C_{23}H_{27}Cl_2NO_5$: C, 58.98; H, 5.81; N, 2.99. Found: C, 59.02; H, 5.90; N, 3.20.

Ethyl (3*S*)-1-{4-[{2,4-dichloro-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-58c)



Compound **58c** was prepared in a similar manner described for **(*S*)-57a** in 88% yield as colorless amorphous. Then, the enantiomers were separated by HPLC with an oprically active column (CHIRALCEL-OD, Φ20 x 250 mm) into isomer A (**(*R*)-58c**) and isomer B (**(*S*)-58c**).

Resolution conditions: Flow rate, 7 ml/min; Developing solvent, 10% 2-propanol – *n*-hexane; Retention time: isomer A, 21 min; isomer B, 26 min.

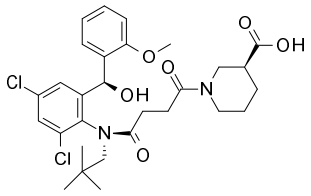
(*S*)-58c: ^{1}H-NMR ($CDCl_3$) δ 1.00 (9H, s), 1.19-1.29 (3H, m), 1.63-1.79 (3H, m), 2.07-2.66 (5H, m), 2.86-3.39 (4H, m), 3.71 (3H, s), 3.71-3.79 (1H, m), 4.01-4.19 (2H, m), 4.38-4.50 (2H, m), 6.12-6.14 (1H, m), 6.57-6.59 (1H, m), 6.87 (1H, d, J = 8.1 Hz), 6.97 (1H, t, J = 2.7 Hz), 7.08-7.20 (1H, m), 7.30-7.36 (2H, m), 7.86-7.88 (1H, m).

IR (ATR) cm^{-1} 3345, 2952, 1727, 1670, 1556, 1448, 1238, 1180, 1029, 754, 578.

MS (ESI) *m/z* 607 $(M + H)^+$.

(*R*)-58c: the peak similar to the enantiomer was obtained.

(*aR*)-(3*S*)-1-{4-[{2,4-Dichloro-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-61c)



Compound **(*S*)-(*aR*)-61c** was prepared from **(*S*)-58c** in a similar manner described for **(*S*)-(*aR*)-60a** in 48% yield as colorless powder (minor atropisomer **(*S*)-(*aS*)-61c** was separated in 12% yield.)

(*S*)-(*aR*)-61c: ^{1}H-NMR ($CDCl_3$) δ 0.97 (0.91) (H, s), 1.12-2.55 (9H, m), 3.00-3.51 (4H, m), 3.70 (3.68) (3H, s), 3.72-3.87 (1H, m), 4.43 (4.34) (1H, d, J = 13.7 Hz), 5.59 (1H, br), 6.10 (1H, s), 6.84-6.87 (1H, m), 6.93-7.11 (2H, m), 7.22-7.39 (2H, m), 7.85 (7.64) (1H, d, J = 7.45 Hz).

IR (ATR) cm^{-1} 3316, 2950, 1619, 1448, 1390, 1238, 1184, 1031, 754, 514.

MS (ESI) *m/z* 579 $(M + H)^+$.

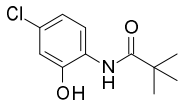
Anal. Calcd. for $C_{29}H_{36}N_2O_6Cl_2 \cdot 1.5H_2O$: C, 57.43; H, 6.48; N, 4.62. Found: C, 57.29; H, 6.21; N, 4.46.

(*S*)-(*aS*)-61c: ^{1}H-NMR ($CDCl_3$) δ 0.93 (0.92) (9H, s), 1.26-1.35 (1H, m), 1.58-2.04 (4H, m), 2.17-2.57 (3H, m), 2.70-3.48 (5H, m), 3.65 (3.72) (3H, s), 3.55-3.84 (1H, m), 4.21-4.44 (1H, m), 6.06-6.26 (1H, m), 6.79-6.92 (2H, m), 7.16-7.70 (4H, m).

MS (ESI) *m/z* 579 $(M + H)^+$.

Anal. Calcd. for $C_{29}H_{36}N_2O_6Cl_2 \cdot 1.5H_2O$: C, 57.43; H, 6.48; N, 4.62. Found: C, 57.04; H, 6.40; N, 4.22.

N-(4-Chloro-2-hydroxyphenyl)-2,2-dimethylpropanamide (49j)



2-Amino-4-chlorophenol (25.32 g, 176.4 mmol) was dissolved in CH_2Cl_2 (1500 ml). To the solution at 0 °C, and $NaHCO_3$ (44.45 g, 529.1 mmol) and pivaloyl chloride (23.89 ml, 194.0 mmol) were added. The mixture was gradually wormed to room temperature for 1.5 h. 1N HClaq (360 ml) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was

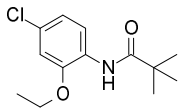
washed with brine, and dried over Na_2SO_4. The solvent was removed in a reduced presser, and the residue was recrystallized with diethyl ether and *n*-hexane to give compound **49j** (29.30 g, 128.7 mmol, 73%) as pale purple crystal.

^{1}H-NMR ($CDCl_3$) δ 1.35 (9H, s), 6.83 (1H, dd, *J* = 8.5, 2.4 Hz), 6.90 (1H, d, *J* = 8.5 Hz), 7.02 (1H, d, *J* = 2.4 Hz), 7.53 (1H, br), 9.07 (1H, s).

IR (ATR) cm^{-1} 3425, 2958, 1641, 1583, 1537, 1514, 1410, 1371, 1265, 1205, 935, 841.

MS (ESI) *m/z* 228 [(M + H)$^+$, ^{35}Cl], 230 [(M + H)$^+$, ^{37}Cl].

N-(4-Chloro-2-ethoxyphenyl)-2,2-dimethylpropanamide (49d)



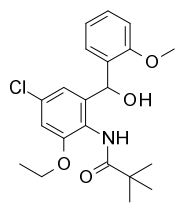
Compound **49j** (303 mg, 1.33 mmol) was dissolved in DMF (10 ml). K_2CO_3 (139 mg, 1.00 mmol) and iodoethane (160 μl, 2.00 mmol) were added to the solution, and the mixture was stirred at room temperature for 19h. The reaction mixture was concentrated in vacuo, and the residue was dissolved in AcOEt (20 ml), 1N HClaq (2 ml) and H_2O (15 ml). The layers were separated, and the organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (AcOEt : *n*-hexane = 1 : 8) to give compound **49d** (325 mg, 1.27 mmol, 95%) as pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ 1.31 (9H, s), 1.47 (3H, t, *J* = 7.1 Hz), 4.08 (2H, q, *J* = 7.1 Hz), 6.84 (1H, d, *J* = 2.2 Hz), 6.92 (1H, dd, *J* = 8.5, 2.2 Hz), 8.10 (1H, br s), 8.33 (1H, d, *J* = 8.5 Hz).

IR (ATR) cm^{-1} 3440, 2974, 1674, 1601, 1514, 1389, 1255, 1124, 1038, 943, 820, 586.

MS (ESI) *m/z* 256 [(M + H)$^+$, ^{35}Cl], 258 [(M + H)$^+$, ^{37}Cl].

N-{4-Chloro-2-ethoxy-6-[hydroxy(2-methoxyphenyl)methyl]phenyl}-2,2-dimethyl-propanamide (52d)



Compound **52d** was prepared in a similar manner described for **52a** in 66% yield as colorless crystal.

^{1}H-NMR ($CDCl_3$) δ 1.31 (9H, s), 1.41 (3H, t, *J* = 7.1 Hz), 4.01 (2H, q, *J* = 7.1), 4.44 (1H, d, *J* = 3.5 Hz), 5.98 (1H, d, *J* = 3.5 Hz), 6.77 (1H, d, *J* = 2.2 Hz), 6.79 (1H, d, *J* = 2.2 Hz), 6.80 (1H, dd, *J* = 8.4, 1.0 Hz), 7.01 (1H, td, *J* = 7.5, 1.0 Hz), 7.21-7.29 (1H, m), 7.57 (1H, dd, *J* = 7.5, 1.0 Hz).

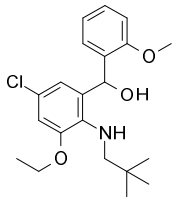
IR (ATR) cm^{-1} 3429, 3248, 2974, 1660, 1585, 1493, 1389, 1292, 1228, 1043, 758.

MS (ESI) *m/z* 374 [(M + H)$^+$, ^{35}Cl], 376 [(M + H)$^+$, ^{37}Cl].

MS (ESI) *m/z* 390 [(M - H)$^-$, ^{35}Cl], 392 [(M - H)$^-$, ^{37}Cl].

Anal. Calcd. for $C_{21}H_{26}ClNO_4 \cdot 0.5H_2O$: C, 62.92; H, 6.79; N, 3.49. Found: C, 63.15; H, 6.69; N, 3.58.

{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-ethoxyphenyl}(2-methoxyphenyl) methanol (53d)



Compound **53d** was prepared in a similar manner described for **53a** in 84% yield as colorless crystal.

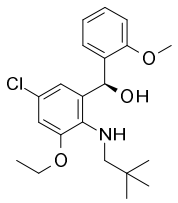
^{1}H-NMR ($CDCl_3$) δ 0.98 (9H, s), 1.44 (3H, t, *J* = 7.0 Hz), 2.67 (1H, d, *J* = 11.2 Hz), 2.78 (1H, d, *J* = 11.2 Hz), 3.84 (3H, s), 4.02 (2H, q, *J* = 7.0 Hz), 6.36 (1H, s), 6.55 (1H, d, *J* = 2.2 Hz), 6.74 (1H, d, *J* = 2.2 Hz), 6.92 (1H, d, *J* = 7.5 Hz), 6.98 (1H, td, *J* = 7.3, 1.0 Hz), 7.30 (1H, td, *J* = 7.8, 1.7 Hz), 7.32 (1H, dd, *J* = 7.3, 1.7 Hz).

IR (ATR) cm^{-1} 3246, 2945, 1591, 1462, 1390, 1292, 1236, 1188, 1039, 903, 822, 752.

MS (ESI) *m/z* 378 [(M + H)$^+$, ^{35}Cl], 380 [(M + H)$^+$, ^{37}Cl].

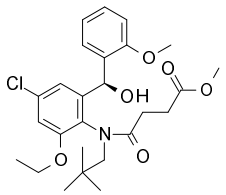
Anal. Calcd. for $C_{21}H_{28}ClNO_3$: C, 66.74; H, 7.47; N, 3.71. Found: C, 67.07; H, 7.54; N, 3.59.

(*S*)-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-ethoxyphenyl}(2-methoxyphenyl) methanol (54d)



Compound **(*S*)-54d** was separated in a similar manner described for **(*S*)-54a** using by HPLC with a CHIRALCEL OD as colorless crystal.

Methyl 4-[{4-chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-55d)



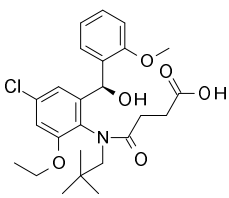
Compound **(*S*)-55d** was prepared in a similar manner described for **(*S*)-55a** in quantitative yield as colorless oil.

^{1}H-NMR ($CDCl_3$) δ (0.89) 0.91 (9H, s), 1.48 (3H, t, *J* = 7.0 Hz), (1.16-1.29 and 1.72-1.83 and 2.12-2.25) 2.24-2.36 and 2.53-2.64 and 2.87-3.02 (4H, m), (2.90) 3.09 (1H, d, *J* = 13.5 Hz), (3.56) 3.67 (3H, s), 3.73 (3.82) (3H, s), 3.94-4.14 (2H, m), (4.39) 4.44 (1H, d, J = 13.5 Hz), 4.78 (1H, d, *J* = 5.4 Hz), 6.10 (6.26) (1H, d, *J* = 5.4 Hz), 6.70 (1H, d, *J* = 2.2 Hz), 6.81 (1H, d, *J* = 2.2 Hz), 6.82-7.18 (2H, m), 7.19-7.29 (1H, m), (7.45-7.54) 7.70 (1H, d, *J* = 7.6 Hz).

IR (ATR) cm^{-1} 3411, 2951, 1736, 1645, 1579, 1466, 1392, 1286, 1238, 1161, 1030, 754.

MS (ESI) *m/z* 474 [(M - OH)$^+$, ^{35}Cl], 476 [(M - OH)$^+$, ^{37}Cl], 492 [(M + H)$^+$, ^{35}Cl], 494 [(M + H)$^+$, ^{37}Cl], 514 [(M + Na)$^+$, ^{35}Cl], 516 [(M + Na)$^+$, ^{37}Cl].

4-[{4-Chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-56d)



Compound **(*S*)-56d** was prepared in a similar manner described for **(*S*)-56a** in 99% yield as colorless amorphous.

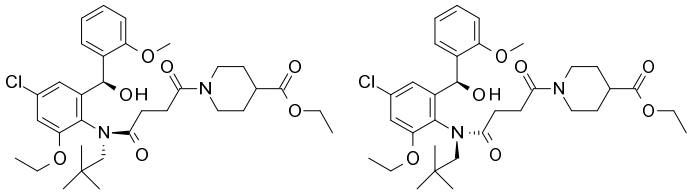
^{1}H-NMR ($CDCl_3$) δ 0.88 (0.90) (9H, s), (1.41) 1.47 (3H, t, *J* = 7.0), (1.10-1.17 and 1.92-2.11) 2.30-2.65 and 2.77-2.96 (4H, m), 2.89 (1H, d, *J* = 13.7 Hz), 3.76 (3.83) (3H, s), 3.98-4.17 (2H, m), 4.38 (1H, d, *J* = 13.7 Hz), 5.30 (1H, s), 6.05 (6.31) (1H, s), 6.76 (1H, d, *J* = 2.2 Hz), 6.84 (1H, d, *J* = 2.2 Hz), 7.70-7.87 (1H, m), 6.99-7.08 (1H, m), 7.20-7.38 (1H, m), 7.43-7.50 (7.55-7.60) (1H, m).

IR (ATR) cm^{-1} 3415, 2952, 1712, 1639, 1466, 1392, 1289, 1240, 1174, 1028, 754.

MS (ESI) *m/z* 460 [(M - OH)$^+$, ^{35}Cl], 462 [(M - OH)$^+$, ^{37}Cl], 478 [(M + H)$^+$, ^{35}Cl], 480 [(M + H)$^+$, ^{37}Cl].

MS (ESI) *m/z* : 476 [(M - H)$^-$, ^{35}Cl], 478 [(M -H)$^-$, ^{37}Cl].

(*aR*) and (*aS*)-Ethyl 1-{4-[{4-chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl) methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylate ((*S*)-(*aR*)-57d, (*S*)-(*aS*)-57d)



Compound **(*S*)-(*aR*)-57d** and **(*S*)-(*aS*)-57d** were prepared from **(*S*)-56d** in a similar manner described for **(*S*)-57a**. Purification using preparative TLC (1mm x 20 cm x 20 cm, MeOH : CH_2Cl_2 = 1 : 15) gave **(*S*)-(*aR*)-57d** (87%) and **(*S*)-(*aS*)-57d** (7%) as colorless amorphous.

(*S*)-(*aR*)-57d: ^{1}H-NMR ($CDCl_3$) δ 0.95 (9H, s), 1.21-1.33 (6H, m), 1.46 (3H, t, *J* = 7.1 Hz), 1.57-1.73 (1H, m), 1.75-1.98 (2H, m), 2.08-2.26 (2H, m), 2.42-2.66 (2H, m), 2.71-2.92 (1H, m), 3.04-3.19 (2H, m), 3.30 (1H, dd, *J* = 13.7, 2.9 Hz), 3.70 (3H, s), 3.78-3.90 (1H, m), 3.96-4.17 (4H, m), 4.50 (1H, dd, *J* = 13.4, 6.3 Hz), 6.10-6.16 (1H, m), 6.62 (1H, d, *J* = 2.0 Hz), 6.77 (1H, d, *J* = 2.2 Hz), 6.85 (1H, d, *J* = 7.8 Hz), 7.09 (1H, t, *J* = 7.4 Hz), 7.27-7.33 (1H, m), 7.91-7.85 (1H, m).

IR (ATR) cm^{-1} 3348, 2952, 1728, 1660, 1624, 1466, 1392, 1242, 1174, 1034, 754.

MS (ESI) *m/z* 617 [(M + H)$^+$, ^{35}Cl], 619[(M + H)$^+$, ^{37}Cl].

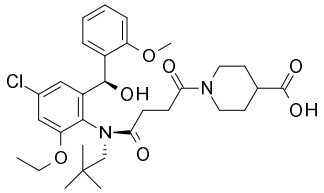
Anal. Calcd. for $C_{33}H_{45}ClN_2O_7 \cdot 0.25H_2O$: C, 63.76; H, 7.38; N, 4.51. Found: C, 63.74; H, 7.44; N, 4.24.

(*S*)-(*aS*)-57d: ^{1}H-NMR ($CDCl_3$) δ 0.89 (9H, s), 1.22-1.30 (3H, m), 1.38-1.46 (3H, m), 1.49-1.77 (2H, m), 1.81-1.90 (2H, m), 2.12-2.25 (1H, m), 2.29-2.52 (2H, m), 2.61-2.85 (2H, m), 2.86-3.00 (2H, m), 3.62-3.74 (1H, m), 3.84 (3H, s), 3.96-4.19 (4H, m), 4.22-4.32 (1H, m), 4.39 (1H, d, *J* = 13.4 Hz), 6.21 (1H, s), 6.82-6.88 (3H, m), 6.98-7.05 (1H, m), 7.15-7.25 (1H, m), 7.41 (1H, dd, *J* = 10.3, 2.0 Hz).

IR (ATR) cm^{-1} 3381, 2951, 1635, 1466, 1392, 1242, 1180, 1036, 754.

Anal. Calcd. for $C_{33}H_{45}ClN_2O_7$: C, 64.22; H, 7.35; N, 4.54. Found: C, 64.16; H, 7.47; N, 4.38.

(*aR*)-1-{4-[{4-Chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid ((*S*)-(*aR*)-60d)



Compound **(*S*)-(*aR*)-60d** was prepared from **(*S*)-(*aR*)-57d** in a similar manner described for **(*S*)-(*aR*)-60a** in 80% yield as colorless amorphous.

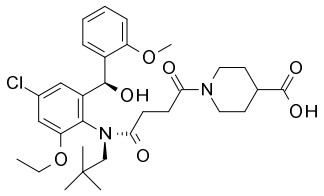
^{1}H-NMR ($CDCl_3$) δ 0.95 (9H, s), 1.47 (3H, t, *J* = 7.0 Hz), 1.51-1.73 (4H, m), 1.80-2.03 (2H, m), 2.09-2.27 (2H, m), 2.49-2.67 (2H, m), 2.74-2.88 (1H, m), 3.03-3.22 (2H, m), 3.32 (1H, dd, *J* = 13.5, 7.0 Hz), 3.71 (3H, d, *J* = 2.2 Hz), 3.80-3.91 (1H, m), 3.96-4.15 (2H, m), 4.51 (1H, dd, *J* = 13.5, 9.2 Hz), 6.14 (1H, s), 6.61 (1H, d, *J* = 2.2 Hz), 6.76-6.79 (1H, m), 6.82-6.88 (1H, m), 7.05-7.13 (1H, m), 7.28-7.33 (1H, m), 7.90-7.84 (1H, m).

IR (ATR) cm^{-1} 2952, 1736, 1658, 1620, 1466, 1392, 1288, 1242, 1028, 754.

MS (ESI) *m/z* 571 [(M - OH)$^+$, ^{35}Cl], 589[(M + H)$^+$, ^{35}Cl].

Anal. Calcd. for $C_{31}H_{41}ClN_2O_7 \cdot 0.25H_2O$: C, 62.72; H, 7.05; N, 4.72. Found: C, 62.61; H, 7.08; N, 4.55.

(*aS*)-1-{4-[{4-Chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-4-carboxylic acid ((*S*)-(*aS*)-60d)



Compound **(*S*)-(*aS*)-60d** was prepared from **(*S*)-(*aS*)-57d** in a similar manner described for **(*S*)-(*aR*)-60a** in 36% yield as colorless amorphous.

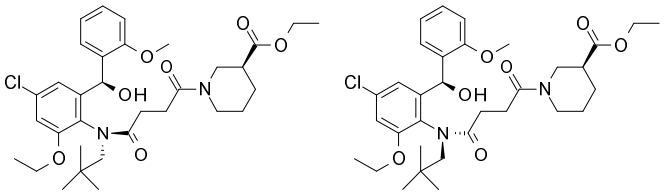
^{1}H-NMR ($CDCl_3$) δ 0.92 (9H, s), 0.96 (3H, s), 1.27-1.31 (1H, m), 1.40-1.50 (4H, m), 1.72-1.94 (2H, m), 2.15-2.28 (2H, m), 2.30-2.46 (2H, m), 2.48-2.68 (4H, m), 2.72-2.87 (1H, m), 2.89-3.03 (1H, m), 3.78 (3H, s), 3.84-3.89 (2H, m), 6.20-6.29 (1H, m), 6.32-6.41 (1H, m), 6.83-6.92 (1H, m), 7.03-7.10 (1H, m), 7.25-7.28 (1H, m), 7.32-7.36 (1H, m), 7.42-7.52 (1H, m), 7.75-7.67 (1H, m).

IR (ATR) cm^{-1} 2951, 1726, 1624, 1466, 1392, 1286, 1242, 1182, 1030, 754.

MS (ESI) *m/z* 589 [$(M + H)^+$, ^{35}Cl], 591[$(M + H)^+$, ^{37}Cl].

Anal. Calcd. for $C_{31}H_{41}ClN_2O_7 \cdot 0.25H_2O$: C, 62.72; H, 7.05; N, 4.72. Found: C, 62.79; H, 7.15; N, 4.48.

(*aR*) and (*aS*)-Ethyl (3*S*)-1-{4-[{4-chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl) methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-(*aR*)-58d, (*S*)-(*aS*)-58d)



Compound **(*S*)-(*aR*)-58d** (74%) and **(*S*)-(*aS*)-58d** (7%) were prepared from **(*S*)-56d** in a similar manner described for **(*S*)-(*aR*)-57d** as colorless amorphous.

(*S*)-(*aR*)-58d: ^{1}H-NMR ($CDCl_3$) δ 0.94 and 0.95 (9H, s), 1.22 and 1.26 (3H, t, J = 7.1 Hz), 1.28-1.82 (2H, m), 1.46 (3H, t, J = 7.0 Hz), 2.00-2.36 (3.5H, m), 2.42-2.44 (2H, m), 2.77-2.87 (0.5H, m), 2.96-3.22 (2H, m), 3.26-3.33 (2H, m), 3.70 (3H, s), 3.72-3.84 (1H, m), 3.96-4.19 (5H, m), 4.42-4.58 (2H, m), 6.11-6.17 (1H, m), 6.36 (1H, d, J = 4.9

Hz), 6.60-6.63 (1H, m), 6.76-6.78 (1H, m), 6.83-6.87 (1H, m), 7.07-7.12 (1H, m), 7.28-7.33 (1H, m), 7.86-7.91 (1H, m).

IR (ATR) cm^{-1} 3330, 2945, 1660, 1626, 1466, 1392, 1288, 1242, 1178, 1113, 1030, 754.

MS (ESI) *m/z* 617 [$(M + H)^+$, ^{35}Cl], 619[$(M + H)^+$, ^{37}Cl].

Anal. Calcd. for $C_{33}H_{45}ClN_2O_7$: C, 64.22; H, 7.35; N, 4.54. Found: C, 64.28; H, 7.49; N, 4.35.

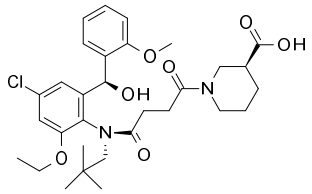
(*S*)-(*aS*)-19d: ^{1}H-NMR ($CDCl_3$) δ 0.89 (9H, s), 1.18-1.28 (3H, m), 1.28-1.51 (3H, m), 1.43 (3H, t, *J* = 7.1 Hz), 1.60-1.82 (3H, m), 1.97-2.09 (1H, m), 2.13-2.26 (1H, m), 2.27-2.48 (2H, m), 2.64-2.94 (3H, m), 3.15 (1H, dd, *J* = 13.7, 10.0 Hz), 3.54-3.79 (1H, m), 3.83 (3H, s), 3.84 (3H, s), 3.96-4.20 (4H, m), 4.39 (1H, dd, *J* = 13.4, 4.2 Hz), 4.47-4.57 (1H, m), 6.19-6.25 (1H, m), 6.79-6.90 (3H, m), 6.98-7.07 (1H, m), 7.15-7.25 (1H, m), 7.43-7.37 (1H, m).

IR (ATR) cm^{-1} 3317, 2935, 1728, 1660, 1626, 1475, 1529, 1219, 1176, 1032, 1003, 760.

MS (ESI) *m/z* 617 [$(M + H)^+$, ^{35}Cl], 619[$(M + H)^+$, ^{37}Cl].

Anal. Calcd. for $C_{33}H_{45}ClN_2O_7$: C, 64.22; H, 7.35; N, 4.54. Found: C, 64.11; H, 7.42; N, 4.44.

(*aR*)-(3*S*)-1-{4-[{4-Chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-61d)



Compound **(*S*)-(*aR*)-61d** was prepared from **(*S*)-(*aR*)-58d** in a similar manner described for **(*S*)-(*aR*)-60a** in 87% yield as colorless amorphous.

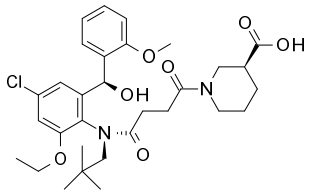
^{1}H-NMR ($CDCl_3$) δ 0.93 (9H, s), 1.22-1.31 (1H, m), 1.43-1.49 (3H, m), 1.59-1.84 (2H, m), 1.94-2.66 (7H, m), 2.86-3.52 (3H, m), 3.70 (3H, s), 3.71-3.90 (1H, m), 3.94-4.14 (3H, m), 4.43-4.53 (2H, m), 6.13 (1H, d, *J* = 6.1 Hz), 6.64 (1H, d, *J* = 2.2 Hz), 6.75-6.79 (1H, m), 6.81-6.88 (1H, m), 7.05-7.12 (1H, m), 7.27-7.34 (1H, m), 7.87-7.81 (1H, m).

IR (ATR) cm^{-1} 2951, 1728, 1622, 1466, 1392, 1286, 1241, 1180, 1030, 754.

MS (ESI) *m/z* 589 $[(M + H)^+, {}^{35}Cl]$, 591$[(M + H)^+, {}^{37}Cl]$.

Anal. Calcd. for $C_{31}H_{41}ClN_2O_7$: C, 63.20; H, 7.01; N, 4.76. Found: C, 62.91; H, 7.20; N, 4.58.

(*aS*)-(3*S*)-1-{4-[{4-Chloro-2-ethoxy-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aS*)-61d).



Compound **(*S*)-(*aS*)-61d** was prepared from **(*S*)-(*aS*)-58d** in a similar manner described for **(*S*)-(*aR*)-60a** in 93% yield as colorless amorphous.

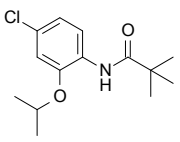
^{1}H-NMR ($CDCl_3$) δ 0.89 (9H, s), 1.35-1.46 (4H, m), 1.59-1.89 (3H, m), 1.98-2.12 (1H, m), 2.14-2.27 (1H, m), 2.29-2.49 (2H, m), 2.71-3.02 (3H, m), 3.09-3.28 (1H, m), 3.44-3.63 (1H, m), 3.83 (3H, s), 3.96-4.13 (2H, m), 4.30-4.44 (1H, m), 6.21 (1H, s), 6.81-6.90 (3H, m), 6.98-7.08 (1H, m), 7.24-7.16 (1H, m), 7.41 (1H, d, J = 2.0 Hz).

IR (ATR) cm^{-1} 2954, 1724, 1618, 1464, 1392, 1286, 1242, 1111, 1039, 754.

MS (ESI) *m/z* 589 $[(M + H)^+, {}^{35}Cl]$, 591$[(M + H)^+, {}^{37}Cl]$.

Anal. Calcd. for $C_{31}H_{41}ClN_2O_7$: C, 63.20; H, 7.01; N, 4.76. Found: C, 63.09; H, 7.16; N, 4.63.

***N*-[4-Chloro-2-(propan-2-yloxy)phenyl]-2,2-dimethylpropanamide (49e)**



To a stirred solution of **49j** (4.01 g, 17.6 mmol) in tetrahydrofuran (200 mL) at 0 °C, 2-propanol (2.02 ml, 26.4 mmol) and triphenylphosphine (6.92 g, 26.4 mmol) was added, followed by a drop in diethyl azodicarboxylate (40% in toluene, 11.5 g, 26.4 mmol). After 2 h, a saturated aqueous solution of ammonium chloride was added

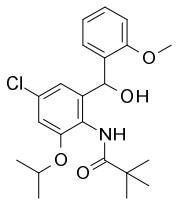
and the mixture was extracted with AcOEt. The extract was washed with brine, dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 10) to give compound **49e** (4.40 g, 16.3 mmol, 93%) as a pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ 1.31 (9H, s), 1.39 (6H, d, *J* = 6.1 Hz), 4.52-4.59 (1H, m), 6.86 (1H, d, *J* = 2.2 Hz), 6.92 (1H, dd, *J* = 8.8, 2.2 Hz), 8.13 (1H, s), 8.36 (1H, dd, *J* = 13.4, 8.8 Hz).

IR (ATR) cm^{-1} 3428, 2976, 1684, 1595, 1508, 1479, 1408, 1246, 1119, 962, 819, 586.

MS (ESI) *m/z* 270 [$(M + H)^+$, ^{35}Cl], 272 [$(M + H)^+$, ^{37}Cl].

N-{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-6-(propan-2-yloxy)phenyl}-2,2-dimethylpropanamide (52e)



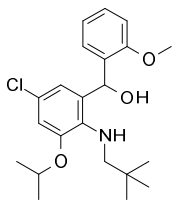
Compound **52e** was prepared in a similar manner described for **52a** in 40% yield as colorless crystal.

^{1}H-NMR ($CDCl_3$) δ 1.31 (9H, s), 1.34 (6H, dd, *J* = 23.4, 11.7 Hz), 4.49-4.52 (2H, m), 5.97 (1H, d, *J* = 3.4 Hz), 6.78 (1H, s), 6.81 (1H, d, *J* = 7.3 Hz), 7.01-7.04 (1H, m), 7.23-7.26 (3H, m), 7.60-7.62 (1H, m).

IR (ATR) cm^{-1} 3523, 2972, 1670, 1585, 1491, 1319, 1111, 1047, 1014, 831, 754.

MS (ESI) *m/z* 404 $(M - H)^-$.

{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-(propan-2-yloxy)phenyl}(2-methoxyphenyl)methanol (53e)



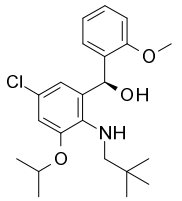
Compound **53e** was prepared in a similar manner described for **53a** in 37% yield as colorless oil.

^{1}H-NMR ($CDCl_3$) δ 0.99 (9H, s), 1.35 (6H, dd, *J* = 5.5, 2.7 Hz), 2.63 (1H, d, *J* = 11.0 Hz), 2.76 (1H, d, *J* = 11.0 Hz), 3.83 (3H, s), 4.48-4.57 (1H, m), 6.33 (1H, s), 6.48 (1H, d, *J* = 2.2 Hz), 6.75 (1H, d, *J* = 2.2 Hz), 6.92 (1H, d, *J* = 8.3 Hz), 6.98 (1H, t, *J* = 7.4 Hz), 7.29 (1H, td, *J* = 15.3, 7.6 Hz), 7.35 (1H, dd, *J* = 7.4, 1.6 Hz).

IR (ATR) cm^{-1} 2952, 1587, 1464, 1240, 1113, 1028, 752.

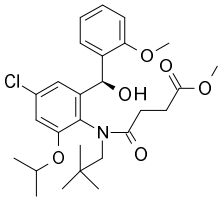
MS (ESI) *m/z* 392 $(M + H)^+$.

(*S*)-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-(propan-2-yloxy)phenyl}(2-methoxyphenyl)methanol (54e)



Compound **(*S*)-54e** was separated in a similar manner described for **(*S*)-54a** using HPLC with a CHIRALCEL OD as colorless crystal.

Methyl 4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(propan-2-yloxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-55e)



Compound **(*S*)-55e** was prepared in a similar manner described for **(*S*)-55a** in 99% yield as colorless amorphous.

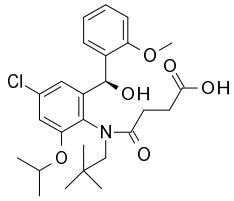
^{1}H-NMR ($CDCl_3$) δ (0.90) 0.91 (9H, s), 1.37-1.44 (6H, m), 2.16-2.38 (2H, m), 2.51-2.66 (1H, m), 2.88-3.00 (1H, m), 3.05 (1H, d, *J* = 13.7 Hz), (3.56) 3.67 (3H, s), 3.74 (3H, s), 3.83 (1H, s), 4.42 (1H, d, *J* = 13.2 Hz), 4.55-4.66 (1H, m), 4.70 (1H, d, *J* = 5.1 Hz), 6.09 (6.24-6.28) (1H, d , *J* = 5.4 Hz (and m)), 6.69 (1H, d, *J* = 2.2 Hz), 6.79 and 6.82

(1H, d, J = 2.5 Hz), 6.84-6.93 (1H, m), 7.03-7.09 (1H, m), 7.20-7.25 (1H, m), 7.29-7.35 (1H, m), 7.41-7.44 (1H, m), 7.65-7.70 (1H, m).

IR (ATR) cm^{-1} 3410, 2951, 1736, 1645, 1466, 1284, 1238, 1163, 1113, 1020, 754.

MS (ESI) *m/z* 488 $(M - OH)^+$, 506 $(M + H)^+$.

4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(propan-2-yloxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-56e)



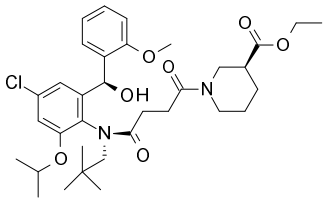
Compound **(*S*)-56e** was prepared in a similar manner described for **(*S*)-56a** in 93% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ (0.87) 0.92 (9H, s), 1.27-1.66 (2H, m), 1.36-1.43 (6H, m), 2.31-2.62 (3H, m), 2.72-2.83 (1H, m), 2.86 (1H, d, J = 13.5 Hz), 3.78 (3.84) (3H, s), 4.36 (1H, d, J = 13.5 Hz), 4.54-4.67 (1H, m), 6.04 (1H, s), 6.75 (1H, d, J = 2.2 Hz), 6.83 (1H, d, J = 2.7 Hz), 6.90 (1H, d, J = 7.2 Hz), 6.99-7.05 (1H, m), 7.29-7.36 (1H, m), 7.39-7.45 (7.55-7.50) (1H, m).

IR (ATR) cm^{-1} 2949, 1712, 1637, 1581, 1464, 1389, 1284, 1240, 1174, 1113, 1022, 754.

MS (ESI) *m/z* 492 $(M + H)^+$. MS (ESI) *m/z* 490 $(M - H)^-$.

(*aR*)-Ethyl (3*S*)-1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(propan-2-yloxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-(*aR*)-58e)



Compound **(*S*)-(*aR*)-58e** was prepared from **(*S*)-56e** in a similar manner described for **(*S*)-(*aR*)-57d** in 68% yield as colorless amorphous.

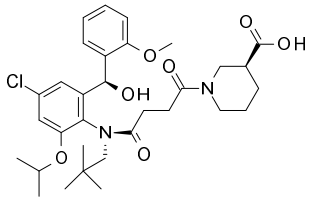
^{1}H-NMR ($CDCl_3$) δ 0.95 and 0.96 (9H, s), 1.19-1.33 (2H, m), 1.26 (3H, t, *J* = 7.3 Hz), 1.36-1.42 (6H, m), 1.57-1.81 (2H, m), 2.01-2.36 (4H, m), 2.42-2.67 (2H, m), 2.83 (0.5H, dd, *J* = 13.1, 10.6 Hz), 2.96-3.22 (2H, m), 3.29 (1H, dd, *J* = 13.4, 7.3 Hz), 3.71 (3H, s), 3.73-3.82 (0.5H, m), 4.01-4.19 (2H, m), 4.42-4.64 (3H, m), 6.13 (1H, t, *J* = 5.1 Hz), 6.34 (1H, d, *J* = 5.1 Hz), 6.59 (1H, t, *J* = 2.3 Hz), 6.72-6.76 (1H, m), 6.85 (1H, d, *J* = 7.8 Hz), 7.09 (1H, t, *J* = 7.6 Hz), 7.27-7.33 (1H, m), 7.91-7.83 (1H, m).

IR (ATR) cm^{-1} 3350, 2941, 1728, 1660, 1626, 1464, 1286, 1242, 1178, 1115, 1018, 754.

MS (ESI) *m/z* 613 $(M - OH)^+$, 631 $(M + H)^+$.

Anal. Calcd. for $C_{34}H_{47}ClN_2O_7$: C, 64.70; H, 7.51; N, 4.44. Found: C, 64.78; H, 7.69; N, 4.22.

(*aR*)-(3*S*)-1-{4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(propan-2-yloxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-61e)



Compound **(*S*)-(*aR*)-61e** was prepared from **(*S*)-(*aR*)-58e** in a similar manner described for **(*S*)-(*aR*)-60d** in 99% yield as colorless amorphous.

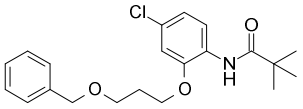
^{1}H-NMR ($CDCl_3$) δ 0.94 and 0.95 (9H, s), 1.36-1.43 (6H, m), 1.58-1.82 (2H, m), 1.96-2.43 (3H, m), 2.51-2.67 (2H, m), 2.73-2.88 (1H, m), 2.94-3.37 (3H, m), 3.70 and 3.71 (3H, s), 3.74-3.86 (1H, m), 3.93 (0.5H, dd, *J* = 13.4, 3.2 Hz), 4.11-4.23 (0.5H, m), 4.42-4.51 (1H, m), 4.53-4.64 (2H, m), 6.12 (1H, d, *J* = 7.8 Hz), 6.60 (1H, d, *J* = 2.5 Hz), 6.73-6.76 (1H, m), 6.84 (1H, t, *J* = 7.8 Hz), 7.03-7.11 (1H, m), 7.25-7.33 (1H, m), 7.87-7.79 (1H, m).

IR (ATR) cm^{-1} 2947, 1728, 1624, 1464, 1410, 1284, 1242, 1180, 1115, 1009, 754.

MS (ESI) *m/z* 585 $(M - OH)^+$, 603 $(M + H)^+$.

Anal. Calcd. for $C_{32}H_{43}ClN_2O_7$: C, 63.72; H, 7.19; N, 4.64. Found: C, 63.79; H, 7.51; N, 4.43.

N-{2-[3-(Benzyloxy)propoxy]-4-chlorophenyl}-2,2-dimethylpropanamide (49k)



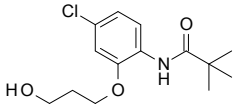
Compound **49k** was prepared from **49j** in a similar manner described for **49e** in 89% yield as pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ 1.25 (9H, s), 2.10-2.17 (2H, m), 3.62-3.67 (2H, m), 4.13-4.18 (2H, m), 4.53 (2H, s), 6.86 (1H, d, J = 2.2 Hz), 6.93 (1H, dd, J = 8.8, 2.2 Hz), 7.27-7.34 (5H, m), 7.99 (1H, br), 8.33 (1H, d, J = 8.8 Hz).

IR (ATR) cm^{-1} 3444, 2958, 2868, 1684, 1567, 1512, 1412, 1248, 1117, 922, 812, 735.

MS (ESI) *m/z* 376 $(M + H)^+$.

N-[4-Chloro-2-(3-hydroxypropoxy)phenyl]-2,2-dimethylpropanamide (49f)



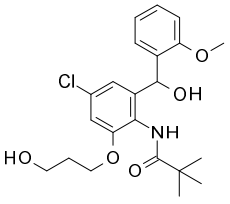
A solution of **49k** (4.76 g, 12.7 mmol) and 10% palladium on carbon (50% water, 650 mg) in AcOEt (120 ml) was hydrogenated for 7 h. The reaction mixture was filtrated and concentrated in vacuo to give **49f** (3.16 g, 11.1 mmol, 87%) as colorless crystal.

^{1}H-NMR ($CDCl_3$) δ 1.31 (9H, s), 2.07-2.14 (2H, m), 3.88 (2H, q, J = 5.6 Hz), 4.16-4.20 (2H, m), 6.88 (1H, d, J = 2.2 Hz), 6.94 (1H, dd, J = 8.6, 2.2 Hz), 8.05 (1H, br s), 8.32 (1H, d, J = 8.6 Hz).

IR (ATR) cm^{-1} 3431, 3342, 2964, 1658, 1601, 1514, 1392, 1255, 1061, 1020, 839, 588.

MS (ESI) *m/z* 286 $(M + H)^+$.

N-{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxypropoxy)phenyl}-2,2-dimethylpropanamide (52f)



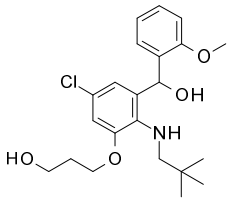
Compound **52f** was prepared from **49f** in a similar manner described for **52a**, using 3.5eq *sec*-butyl lithium, in 43% yield as colorless needle crystal.

^{1}H-NMR ($CDCl_3$) δ 1.18 (9H, s), 1.97-2.04 (2H, m), 2.63 (1H, t, J = 6.2 Hz), 3.78-3.83 (2H, m), 3.82 (3H, s), 4.07-4.09 (1H, m), 4.16 (2H, t, J = 5.9 Hz), 5.96-5.99 (1H, m), 6.81 (1H, d, J = 2.2 Hz), 6.87-7.01 (3H, m), 7.18-7.24 (1H, m), 7.27-7.33 (1H, m), 7.77 (1H, br s).

IR (ATR) cm^{-1} 3367, 2960, 1653, 1587, 1489, 1234, 1034, 833, 756.

MS (ESI) *m/z* 404 [(M - OH)$^+$, ^{35}Cl], 406 [(M - OH)$^+$, ^{37}Cl].

3-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-[hydroxy(2-methoxyphenyl)methyl] phenoxy}propan-1-ol (53f)



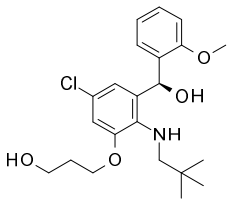
Compound **53f** was prepared in a similar manner described for **53a** in quantitative yield as colorless oil.

^{1}H-NMR ($CDCl_3$) δ 0.97 (9H, s), 2.04-2.11 (2H, m), 2.69 (1H, d, J = 11.3 Hz), 2.77 (1H, d, J = 11.0 Hz), 3.82-3.90 (2H, m), 3.84 (3H, s), 4.07-4.17 (2H, m), 6.29 (1H, s), 6.59 (1H, d, J = 2.2 Hz), 6.80 (1H, d, J = 2.5 Hz), 6.90-7.01 (2H, m), 7.27-7.39 (2H, m).

IR (ATR) cm^{-1} 3338, 2951, 1587, 1462, 1240, 1028, 889, 831, 752.

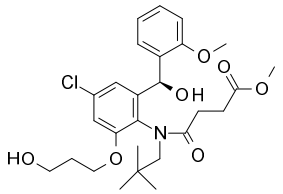
MS (ESI) *m/z* 408 (M + H)$^+$.

3-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-[(*S*)-hydroxy(2-methoxyphenyl)methyl] phenoxy}propan-1-ol ((*S*)-54f)



Compound **(*S*)-54f** was separated in a similar manner described for **(*S*)-54a** using by HPLC with a CHIRALCEL OD as colorless needle crystal.

Methyl 4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxypropoxy) phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-55f)



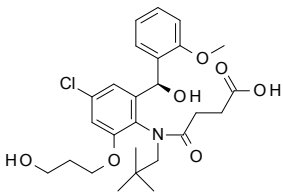
Compound **(*S*)-55f** was prepared in a similar manner described for **(*S*)-55a** in quantitative yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.87 (0.89) (9H, s), 1.83 (1H, t, *J* = 4.8 Hz), 2.01-2.23 (2H, m), 2.24-2.45 (2H, m), 2.48-2.65 (2H, m), 2.75-2.86 (1H, m), 2.99 (1H, d, *J* = 13.7 Hz), (3.60) 3.68 (3H, s), 3.76 (3.82) (3H, s), 3.80-3.93 (2H, m), 4.04-4.14 (1H, m), 4.15-4.24 (1H, m), 4.34-4.42 (2H, m), 6.08 (6.29) (1H, d, *J* = 4.9 Hz), 6.78 (1H, d, *J* = 2.2 Hz), 6.84-6.94 (2H, m), 6.99-7.11 (1H, m), 7.29-7.35 (1H, m), (7.47-7.51) 7.60-7.55 (1H, m).

IR (ATR) cm^{-1} 3423, 2952, 1736, 1643, 1579, 1464, 1286, 1238, 1165, 1026, 754.

MS (ESI) *m/z* 504 $(M - OH)^+$, 522 $(M + H)^+$.

4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxypropoxy)phenyl} (2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-56f)



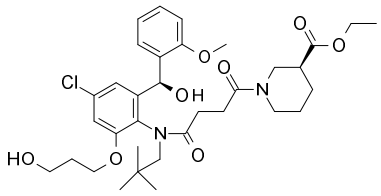
Compound **(*S*)-56f** was prepared in a similar manner described for **(*S*)-55a** in 99% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.84 (0.89) (9H, s), 1.98-2.23 (2H, m), 2.38-2.70 (4H, m), 2.85 (2.96) (1H, d, *J* = 13.7 Hz), 3.74-3.90 (3H, m), 3.78 (3.83) (3H, s), 4.04-4.24 (2H, m), 4.32 (1H, d, *J* = 13.7 Hz), 4.36 (1H, d, *J* = 13.2 Hz), 6.03 (6.31) (1H, s), 6.84 (1H, dd, *J* = 13.4, 3.6 Hz), 6.87-6.94 (2H, m), 6.99-7.05 (7.05-7.09) (1H, m), 7.29-7.37 (1H, m), 7.39 (7.55) (1H, dd, *J* = 7.6, 1.5 Hz).

IR (ATR) cm^{-1} 3381, 2951, 1712, 1637, 1464, 1392, 1286, 1240, 1174, 1026, 754.

MS (ESI) *m/z* 490 $(M - OH)^+$, 508 $(M + H)^+$. MS (ESI) *m/z* 506 $(M - H)^+$.

Ethyl (3*S*)-1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxypropoxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-58f)



Compound **(*S*)-58f** was prepared from **(*S*)-56f** in a similar manner described for **(*S*)-57a** in 88% yield as colorless amorphous.

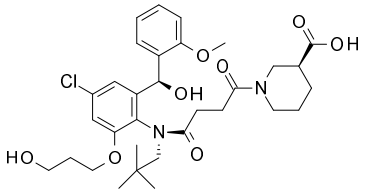
^{1}H-NMR ($CDCl_3$) δ 0.91 and 0.93 (9H, s), 1.19-1.33 (5H, m), 1.57-1.82 (2H, m), 1.87-1.94 (1H, m), 1.97-2.15 (3H, m), 2.17-2.41 (2H, m), 2.42-2.61 (1H, m), 2.63-2.88 (1H, m), 2.90-3.09 (1H, m), 3.14-3.28 (1H, m), 3.72 and 3.73 (3H, s), 3.74-3.88 (3H, m), 3.96-4.23 (4H, m), 4.30-4.59 (2H, m), 5.80 (0.5H, d, J = 5.1 Hz), 5.96 (0.5H, d, J = 5.1 Hz), 6.12 (1H, t, J = 5.5 Hz), 6.68 (1H, dd, J = 12.4, 2.3 Hz), 6.82-6.90 (2H, m), 7.02-7.11 (1H, m), 7.28-7.35 (1H, m), 7.83-7.72 (1H, m).

IR (ATR) cm^{-1} 3365, 2951, 1728, 1624, 1464, 1286, 1242, 1180, 1026, 754.

MS (ESI) *m/z* 629 $(M - OH)^+$, 647 $(M + H)^+$.

Anal. Calcd. for $C_{34}H_{47}ClN_2O_8 \cdot 0.25H_2O$: C, 63.15; H, 7.49; N, 4.21. Found: C, 63.23; H, 7.74; N, 4.15.

(*aR*)-(3*S*)-1-{4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxypropoxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-61f)



Compound **(*S*)-61f** was prepared from **(*S*)-58f** in a similar manner described for **(*S*)-60a** in 86% yield containing small amount of minor atropisomer as colorless amorphous.

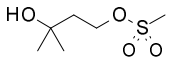
^{1}H-NMR ($CDCl_3$) δ 0.89 and 0.91 (9H, s), 1.22-1.47 (2H, m), 1.55-1.85 (2H, m), 1.92-2.15 (3H, m), 2.22-2.61 (4H, m), 2.90-3.19 (3H, m), 3.43-3.54 (1H, m), 3.72 and 3.74 (3H, s), 3.77-3.95 (4H, m), 4.01-4.12 (1H, m), 4.14-4.25 (1H, m), 4.36-4.48 (1H, m), 6.10 (1H, d, J = 9.8 Hz), 6.71 (1H, d, J = 2.2 Hz), 6.82-6.90 (2H, m), 7.02-7.11 (1H, m), 7.27-7.35 (1H, m), 7.74-7.64 (1H, m).

IR (ATR) cm^{-1} 3377, 2945, 1720, 1631, 1464, 1284, 1246, 1182, 1030, 752.

MS (ESI) *m/z* 601 $(M - OH)^+$, 619 $(M + H)^{+\cdot}$ MS (ESI) *m/z* 617 $(M - H)^-$.

Anal. Calcd. for $C_{32}H_{43}ClN_2O_8 \cdot 0.75H_2O$: C, 60.75; H, 7.09; N, 4.43. Found: C, 60.44; H, 6.72; N, 4.41.

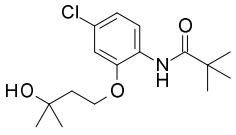
3-Hydroxy-3-methylbutyl methanesulfonate



3-Methyl-1,3-butandiol (3.83 g, 36.8 mmol) was dissolved in CH_2Cl_2 (150 ml). Triethylamine (6.66 ml, 47.8 mmol) and methanesulfonyl chloride (3.13 ml, 40.5 mmol) were added to the ice-cooled solution, and stirred for 7.5h at room temperature. Water (100 ml) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. Then, combined organic layer was washed with brine, and dried over Na_2SO_4. The solvent was removed in a reduced presser to give title compound (4.79 g, 26.3 mmol, 72%) as colorless oil.

^{1}H-NMR ($CDCl_3$) δ 1.30 (6H, s), 1.96 (2H, t, J = 6.8 Hz), 3.02 (3H, s), 4.42 (2H, t, J = 6.8 Hz).

N-[4-Chloro-2-(3-hydroxy-3-methylbutoxy)phenyl]-2,2-dimethylpropanamide (49g)

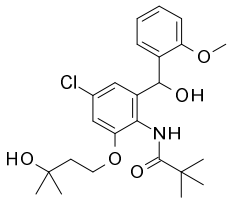


Compound **49j** (4.60 g, 20.2 mmol) was dissolved in DMF (50 ml). To the solution, 3-hydroxy-3-methylbutyl methanesulfonate (4.79 g, 26.3 mmol) and sodium

carbonate (8.38 g, 60.7 mmol) were added, and stirred at 60 °C for 6h. The solvent was removed in vacuo, and the residue was diluted in AcOEt (100 ml) and water (80 ml). The layers were separated, and the aqueous layer was extracted with AcOEt. Combined organic layer was washed with brine, and dried over Na_2SO_4. The solvent was removed in a reduced presser, and the residue was purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 4 – 1 : 3) to give compound **49g** (5.73 g, 18.3 mmol, 90%) as colorless oil.

^{1}H-NMR ($CDCl_3$) δ 1.30 (9H, s), 1.35 (6H, s), 2.03 (2H, t, *J* = 6.6 Hz), 4.21 (2H, t, *J* = 6.6 Hz), 6.89 (1H, d, *J* = 2.2 Hz), 6.94 (1H, dd, *J* = 8.7, 2.2 Hz), 8.04 (1H, s), 8.34 (1H, d, *J* = 8.7 Hz).

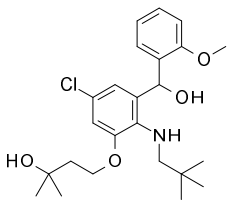
N-{4-Chloro-2-[hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxy-3-methylbutoxy) phenyl}-2,2-dimethylpropanamide (52g)



Compound **52g** was prepared from **49g** in a similar manner described for **52f** in 80% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 1.23 (9H, s), 1.30 (3H, s), 1.31 (3H, s), 1.98 (2H, td, *J* = 6.3, 1.9 Hz), 2.32 (1H, s), 3.76 (3H, s), 4.15-4.22 (3H, m), 5.97 (1H, d, *J* = 3.4 Hz), 6.81 (1H, d, *J* = 2.2 Hz), 6.86 (1H, d, *J* = 8.3 Hz), 6.88 (1H, d, *J* = 2.2 Hz), 6.98 (1H, td, *J* = 7.5, 1.1 Hz), 7.25-7.30 (1H, m), 7.36 (1H, dd, *J* = 7.5, 1.1 Hz), 7.55 (1H, s).

4-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-[hydroxy(2-methoxyphenyl)methyl] phenoxy}-2-methylbutan-2-ol (53g)



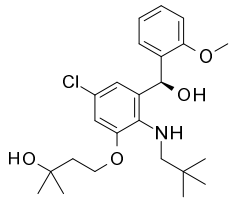
Compound **53g** was prepared in a similar manner described for **53a** in 92% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.97 (9H, s), 1.33 (6H, s), 2.02 (2H, t, *J* = 6.6 Hz), 2.69 (1H, d, *J* = 11.3 Hz), 2.76 (1H, d, *J* = 11.3 Hz), 3.84 (3H, s), 4.11-4.20 (2H, m), 4.96 (1H, br), 6.30 (1H, s), 6.58 (1H, d, *J* = 2.2 Hz), 6.81 (1H, d, *J* = 2.2 Hz), 6.92 (1H, dd, *J* = 8.6, 1.0 Hz), 6.98 (1H, td, *J* = 7.6, 1.0 Hz), 7.28-7.33 (2H, m).

IR (ATR) cm^{-1} 3329, 3234, 2956, 1587, 1460, 1240, 1186, 1147, 1016, 833, 756.

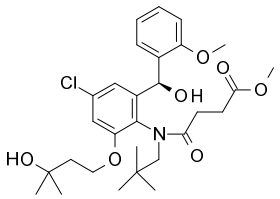
MS (ESI) *m/z* 436 $(M + H)^+$.

4-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-[(*S*)-hydroxy(2-methoxyphenyl)methyl] phenoxy}-2-methylbutan-2-ol ((*S*)-54g)



Compound **(*S*)-54g** was separated in a similar manner described for **(*S*)-54a** by using HPLC with a CHIRALCEL OD as colorless crystal.

Methyl 4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxy-3-methylbutoxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-55g)



Compound **(*S*)-55g** was prepared in a similar manner described for **(*S*)-55a** in 98% yield as colorless amorphous.

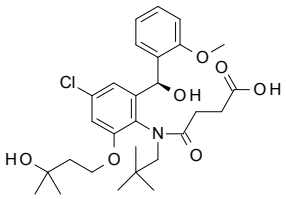
^{1}H-NMR ($CDCl_3$) δ (0.89) 0.89 (9H, s), (1.27) 1.32 (3H, s), (1.31) 1.34 (3H, s), 1.99-2.14 (2H, m), 2.18-2.39 (2H, m), 2.50-2.68 (1H, m), 2.84-2.97 (1H, m), 3.06 (1H, d, *J* = 13.7 Hz), (3.58) 3.67 (3H, s), 3.74 (3.82) (3H, s), 4.08-4.27 (2H, m), (4.32) 4.41 (1H, d, *J* = 13.5 Hz), 4.68 (1H, d, *J* = 5.1 Hz), 6.09 (6.26) (1H, d, *J* = 5.1 Hz), 6.73 (1H,

d, *J* = 2.2 Hz), 6.83-6.98 (3H, m), 7.03-7.10 (1H, m), 7.32 (1H, td, *J* = 7.8, 1.6 Hz), 7.69-7.64 (1H, m).

IR (ATR) cm^{-1} 3423, 2952, 1720, 1643, 1466, 1286, 1238, 1169, 1026, 754.

MS (ESI) *m/z* 550 $(M + H)^+$.

4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxy-3-methylbutoxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-56g)



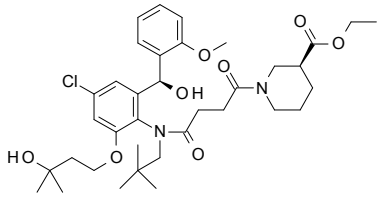
Compound **(*S*)-56g** was prepared in a similar manner described for **(*S*)-56a** in 97% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.85 (0.89) (9H, s), (1.27) 1.31 (3H, s), (1.28) 1.33 (3H, s), 1.84-2.18 (2H, m), 2.31-2.41 (1H, m), 2.42-2.59 (2H, m), 2.68-2.79 (1H, m), 2.88 (2.96) (1H, d, *J* = 13.7 Hz), 3.76 (3.82) (3H, s), 4.07-4.26 (2H, m), 4.34 (4.36) (1H, d, *J* = 13.5 Hz), 6.04 (6.30) (1H, s), (6.63) 6.78 (1H, d, *J* = 2.2 Hz), 6.85-6.94 (2H, m), 6.99-7.07 (1H, m), 7.32 (1H, td, *J* = 7.8, 1.6 Hz), 7.44 (7.56-7.52) (1H, dd, *J* = 7.6, 1.5 Hz).

IR (ATR) cm^{-1} 3390, 1712, 1639, 1466, 1392, 1286, 1240, 1171, 1026, 754.

MS (ESI) *m/z* 536 $(M + H)^+$.

Ethyl (3*S*)-1-{4-[{4-chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxy-3-methylbutoxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-58g)



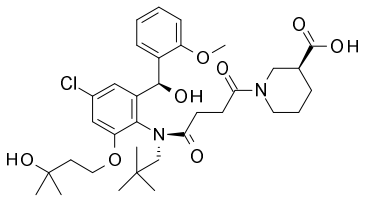
Compound **(*S*)-58g** was prepared from **(*S*)-56g** in a similar manner described for **(*S*)-57a** in 81% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ (0.88 and 0.89) 0.93 and 0.94 (9H, s), (1.22) 1.26 (3H, t, *J* = 7.4 Hz), 1.32 (3H, s), 1.33 (3H, s), 1.36-1.50 (1H, m), 1.58-1.80 (2H, m), 2.00-2.11 (3H, m), 2.12-2.27 (2H, m), 2.27-2.37 (1H, m), 2.43-2.52 (1H, m), 2.52-2.64 (1H, m), 2.68-2.87 (1H, m), 2.92-3.32 (3H, m), 3.71 (3H, s), (3.73-3.85) 3.99-4.26 (5H, m), 4.39-4.58 (2H, m), 6.13 (1H, t, *J* = 5.4 Hz), 6.23 (1H, dd, *J* = 16.9, 5.1 Hz), 6.62-6.66 (1H, m), 6.82-6.88 (6.90-6.94) (2H, m), (6.99-7.05) 7.05-7.12 (1H, m), 7.30 (1H, td, *J* = 7.7, 1.6 Hz), (7.39-7.43) 7.88-7.81 (1H, m).

MS (FAB) *m/z* 675 $(M + H)^+$.

Anal. Calcd. for $C_{36}H_{51}ClN_2O_8 \cdot 0.5H_2O \cdot 0.25$*n*-hexane: C, 63.81; H, 7.93; N, 3.97. Found: C, 64.01; H, 7.99; N, 3.70.

(*aR*)-(3*S*)-1-{4-[{4-Chloro-2-[(*S*)-hydroxy(2-methoxyphenyl)methyl]-6-(3-hydroxy-3-methylbutoxy)phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-61g)



Compound **(*S*)-(*aR*)-61g** was prepared from **(*S*)-58g** in a similar manner described for **(*S*)-60a** in 89% yield containing small amount of minor atropisomer as colorless amorphous.

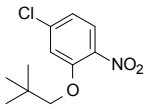
^{1}H-NMR ($CDCl_3$) δ 0.91 (9H, s), 1.30 and 1.31 (3H, s), 1.32 and 1.33 (3H, s), 1.55-1.84 (2H, m), 1.92-2.15 (4H, m), 2.16-2.32 (2H, m), 2.40-2.63 (4H, m), 2.89-3.02 (1H, m), 3.03-3.25 (3H, m), 3.61-3.69 (0.5H, m), 3.71 (3H, s), 3.87-3.98 (0.5H, m), 4.05-4.30 (3H, m), 4.44 (1H, d, *J* = 13.5 Hz), 6.10 (1H, d, *J* = 2.9 Hz), 6.66 (1H, dd, *J* = 6.1, 2.2 Hz), 6.82-6.90 (2H, m), 7.04-7.11 (1H, m), 7.27-7.33 (1H, m), 7.82-7.72 (1H, m).

IR (ATR) cm^{-1} 3371, 2954, 1712, 1635, 1464, 1408, 1244, 1182, 1028, 752.

MS (FAB) *m/z* 647 $(M + H)^+$.

Anal. Calcd. for $C_{34}H_{47}ClN_2O_8 \cdot 0.25H_2O$: C, 62.66; H, 7.35; N, 4.30. Found: C, 62.49; H, 7.37; N, 4.14.

4-Chloro-2-(2,2-dimethylpropoxy)-1-nitrobenzene (51h)



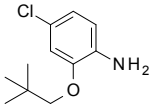
Compound **51h** was prepared from **50** in a similar manner described for **49e** in 83% yield as brown crystal.

^{1}H-NMR ($CDCl_3$) δ 1.08 (9H, s), 3.72 (2H, s), 6.98 (1H, dd, *J* = 8.6, 2.0 Hz), 7.04 (1H, d, *J* = 2.0 Hz), 7.84 (1H, d, *J* = 8.8 Hz).

IR (ATR) cm^{-1} 3113, 2952, 1604, 1568, 1512, 1471, 1398, 1335, 1250, 1003, 908, 748.

MS (FAB) *m/z* 244 [(M + H)$^+$, ^{35}Cl], 246 [(M + H)$^+$, ^{37}Cl].

4-Chloro-2-(2,2-dimethylpropoxy)aniline (48h)



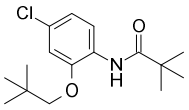
A solution of **51h** (4.76 g, 12.7 mmol) and Raney nickel catalyst (600 mg) in AcOEt (120 ml) was hydrogenated for 7 h. The reaction mixture was filtrated and concentrated in vacuo to give **48h** (3.16 g, 11.1 mmol, 87%) as colorless crystal.

^{1}H-NMR ($CDCl_3$) δ 1.06 (9H, d, *J* = 1.2 Hz), 3.61 (2H, d, *J* = 1.0 Hz), 3.76 (2H, br), 6.62 (1H, dd, *J* = 8.8, 1.2 Hz), 6.71-6.76 (2H, m).

IR (ATR) cm^{-1} 3431, 3342, 2964, 1658, 1601, 1514, 1392, 1255, 1061, 1020, 839, 588.

MS (ESI) *m/z* 286 (M + H)$^+$.

***N*-[4-Chloro-2-(2,2-dimethylpropoxy)phenyl]-2,2-dimethylpropanamide (49h)**

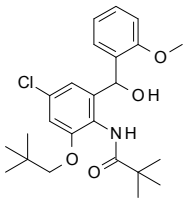


Compound **49h** was prepared from **48h** in a similar manner described for **49a** in 66% yield as pale yellow needle crystal.

^{1}H-NMR ($CDCl_3$) δ 1.06 (9H, d, *J* = 1.2 Hz), 3.61 (2H, d, *J* = 1.0 Hz), 3.76 (2H, br s), 6.62 (1H, dd, *J* = 8.8, 1.2 Hz), 6.71-6.76 (2H, m).

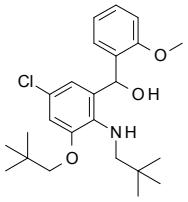
IR (ATR) cm^{-1} 3448, 2956, 1693, 1595, 1516, 1475, 1396, 1207, 1018, 924, 806, 579.
MS (ESI) *m/z* 298 $(M + H)^+$.

N-{4-Chloro-2-(2,2-dimethylpropoxy)-6-[hydroxy(2-methoxyphenyl)methyl]phenyl} -2,2-dimethylpropanamide (52h)



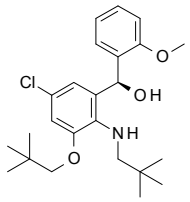
Compound **52h** was prepared from **49h** in a similar manner described for **52a** in 47% yield as colorless amorphous.
^{1}H-NMR ($CDCl_3$) δ 1.05 (9H, s), 1.30 (9H, s), 3.60 (2H, dd, *J* = 15.4, 8.6 Hz), 3.71 (3H, s), 4.41 (1H, d, *J* = 3.2 Hz), 5.96-5.99 (1H, m), 6.79 (1H, dd, *J* = 4.2, 2.0 Hz), 6.83 (1H, d, *J* = 7.6 Hz), 7.02 (1H, td, *J* = 7.6, 0.7 Hz), 7.23-7.29 (1H, m), 7.32 (1H, s), 7.55 (1H, dd, *J* = 7.6, 1.0 Hz).
IR (ATR) cm^{-1} 3371, 2956, 1647, 1591, 1490, 1421, 1240, 1072, 1014, 895, 758.
MS (ESI) *m/z* 416 $(M - OH)^+$. MS (ESI) *m/z* 432 $(M - H)^-$.

{5-Chloro-3-(2,2-dimethylpropoxy)-2-[(2,2-dimethylpropyl)amino]phenyl} (2-methoxyphenyl)methanol (53h)



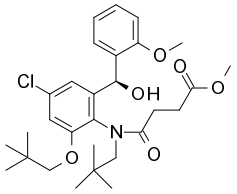
Compound **53h** was prepared in a similar manner described for **53a** in 50% yield as colorless powder.
^{1}H-NMR ($CDCl_3$) δ 1.00 (9H, s), 1.07 (9H, s), 2.76 (2H, s), 3.55-3.73 (2H, m), 3.83 (3H, s), 5.35 (1H, bs), 6.35 (1H, s), 6.49 (1H, d, *J* = 2.2 Hz), 6.75 (1H, d, *J* = 2.2 Hz), 6.93 (1H, d, *J* = 8.1 Hz), 6.96-7.04 (1H, m), 7.23-7.36 (2H, m).
IR (ATR) cm^{-1} 3361, 2954, 1591, 1464, 1236, 1186, 1045, 889, 752.
MS (ESI) *m/z* 420 $(M + H)^+$.

(*S*)-{5-Chloro-3-(2,2-dimethylpropoxy)-2-[(2,2-dimethylpropyl)amino]phenyl}(2-methoxyphenyl)methanol (54h)



Compound **(*S*)-54h** was separated in a similar manner described for **(*S*)-54a** using HPLC with a CHIRALCEL OD as colorless crystal.

Methyl 4-[{4-chloro-2-(2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-55h)

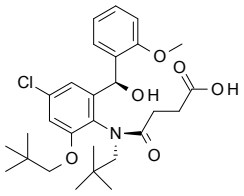


Compound **(*S*)-55h** was prepared in a similar manner described for **(*S*)-55a** in quantitative yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.92 (9H, s), 1.08 (9H, s), 2.21-2.37 (2H, m), 2.55-2.65 (1H, m), 2.87-2.97 (1H, m), 3.10 (1H, d, *J* = 13.5 Hz), 3.57 (1H, d, *J* = 8.6 Hz), 3.67 (3H, d, *J* = 1.0 Hz), 3.75-3.75 (1H, m), 3.75 (3H, d, *J* = 0.7 Hz), 4.36 (1H, d, *J* = 13.7 Hz), 4.64 (1H, d, *J* = 5.1 Hz), 5.30 (1H, d, *J* = 1.2 Hz), 6.09 (1H, d, *J* = 5.1 Hz), 6.75-6.77 (1H, m), 6.86-6.94 (2H, m), 7.06 (1H, t, *J* = 7.5 Hz), 7.32 (1H, t, *J* = 7.6 Hz), 7.65 (1H, d, *J* = 7.4 Hz).

IR (ATR) cm^{-1} 3415, 2952, 1736, 1647, 1577, 1464, 1286, 1238, 1171, 1026, 754.

(*aR*)-4-[{4-Chloro-2-(2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-(*aR*)-56h)



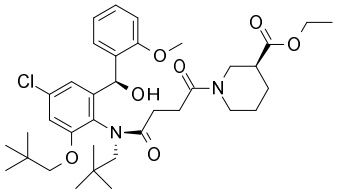
Compound **(*S*)-(*aR*)-56h** was prepared in a similar manner described for **(*S*)-56a** in 87% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.88 (9H, s), 1.07 (9H, s), 2.28-2.47 (2H, m), 2.55-2.66 (1H, m), 2.73-2.83 (1H, m), 2.93 (1H, d, *J* = 13.5 Hz), 3.57 (1H, d, *J* = 8.6 Hz), 3.76 (1H, d, *J* = 7.8 Hz), 3.77 (3H, s), 4.29 (1H, d, *J* = 13.5 Hz), 6.05 (1H, s), 6.81 (1H, d, *J* = 2.2 Hz), 6.87-6.93 (2H, m), 7.05-6.98 (1H, m), 7.35-7.29 (1H, m), 7.40 (1H, dd, *J* = 7.5, 1.3 Hz).

IR (ATR) cm^{-1} 2954, 1712, 1641, 1464, 1402, 1286, 1240, 1186, 1055, 1026, 754.

MS (ESI) *m/z* 502 (M - OH)$^+$, 520 [(M + H)$^+$, 542 [(M + Na)$^+$.

(*aR*)-Ethyl (3*S*)-1-{4-[{4-chloro-2-(2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylate ((*S*)-(*aR*)-58h)



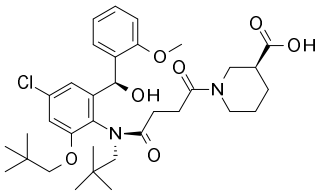
Compound **(*S*)-(*aR*)-58h** was prepared from **(*S*)-(*aR*)-56h** in a similar manner described for **(*S*)-57a** in 92% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.96 and 0.97 (9H, s), 1.08 (9H, s), 1.22 and 1.26 (3H, t, *J* = 7.4 Hz), 1.28-1.41 (2H, m), 1.58-1.84 (2H, m), 1.99-2.37 (3H, m), 2.43-2.69 (2H, m), 2.79-3.25 (2H, m), 3.32 (1H, dd, *J* = 13.4, 4.5 Hz), 3.55 (1H, d, *J* = 8.8 Hz), 3.70 (3H, s), 3.75 (2H, d, *J* = 8.8 Hz), 3.98-4.05 (1H, m), 4.06-4.19 (4H, m), 4.45 (1H, dd, *J* = 13.5, 3.7 Hz), 4.49-4.58 (0H, m), 6.09-6.16 (6.22-6.30) (1H, m), 6.26 (1H, dd, *J* = 13.5, 5.4 Hz), 6.66 (1H, d, *J* = 2.2 Hz), 6.82-6.89 (2H, m), 7.08 (1H, t, *J* = 7.5 Hz), 7.33-7.27 (1H, m), 7.86 (1H, d, *J* = 7.4 Hz).

IR (ATR) cm^{-1} 3354, 2954, 1728, 1662, 1630, 1464, 1288, 1244, 1180, 1026, 756.

MS (FAB) *m/z* 659 $(M + H)^+$, 681 $(M + Na)^+$.

(*aR*)-(3*S*)-1-{4-[{4-Chloro-2-(2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl) methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl}piperidine-3-carboxylic acid ((*S*)-(*aR*)-61h)



Compound **(*S*)-(*aR*)-61h** was prepared from **(*S*)-(*aR*)-58h** in a similar manner described for **(*S*)-60a** in 90% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.95 and 0.96 (9H, s), 1.08 (9H, s), 1.22-1.44 (2H, m), 1.59-1.82 (2H, m), 1.96-2.28 (3H, m), 2.36-2.67 (2H, m), 2.84-3.20 (3H, m), 3.27 (1H, dd, *J* = 13.5, 4.0 Hz), 3.33-3.44 (0.5H, m), 3.56 (1H, dd, *J* = 8.5, 1.7 Hz), 3.70 and 3.71 (3H, s), 3.75 (1H, d, *J* = 8.5 Hz), 3.86-3.95 (0.5H, m), 4.06-4.15 (0.5H, m), 4.43 (1H, dd, J = 13.5, 10.1 Hz), 4.47-4.55 (0.5H, m), 6.11 (1H, d, *J* = 5.1 Hz), 6.67-6.71 (1H, m), 6.82-6.88 (2H, m), 7.03-7.11 (1H, m), 7.34-7.27 (1H, m), 7.80 (1H, d, *J* = 7.8 Hz).

IR (ATR) cm^{-1} 2954, 1728, 1624, 1464, 1402, 1244, 1026, 754.

MS (FAB) *m/z* 631 $(M + H)^+$, 653 $(M + Na)^+$.

Anal. Calcd. for $C_{34}H_{47}ClN_2O_7 \cdot 0.5H_2O$: C, 63.79; H, 7.56; N, 4.38. Found: C, 63.97; H, 7.23; N, 4.29.

3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,2-dimethylpropan-1-ol

2,2-Dimethyl-1,3-propandiol (1.60 g, 15.4 mmol) was dissolved in CH_2Cl_2 (150 ml). To the ice-cooled solution, imidazole (2.55 g, 16.9 mmol) and *tert*-butyldimethylsilyl chloride (1.36 g, 20.0 mmol) were added, and stirred at room temperature for 1h. Water (40 ml) was added, and the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4. The solvent was removed in a reduced presser, and the residue was

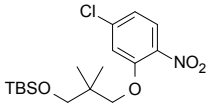
purified by silica gel column chromatography (AcOEt : *n*-hexane = 1 : 9) to give title compound (2.57 g, 11.8 mmol, 77%) as colorless oil.

^{1}H-NMR ($CDCl_3$) δ 0.07 (6H, s), 0.89 (6H, s), 0.90 (9H, s), 2.85 (1H, t, *J* = 5.9 Hz), 3.46-3.48 (4H, m).

IR (ATR) cm^{-1} 3415, 2954, 2858, 1471, 1252, 1093, 1045, 833, 773.

MS (ESI) *m/z* 219 $(M + H)^+$.

tert-Butyl [3-(5-chloro-2-nitrophenoxy)-2,2-dimethylpropoxy]dimethylsilane (51l)



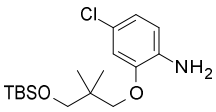
Compound **51l** was prepared from **50** in a similar manner described for **49e** in 97% yield as colorless oil.

^{1}H-NMR ($CDCl_3$) δ 0.02 (6H, s), 0.87 (9H, s), 1.02 (6H, s), 3.48 (2H, s), 3.85 (2H, s), 6.99 (1H, dd, *J* = 8.8, 2.0 Hz), 7.09 (1H, d, *J* = 2.0 Hz), 7.86 (1H, d, *J* = 8.6 Hz).

IR (ATR) cm^{-1} 2954 1604, 1522, 1342, 1259, 1093, 1022, 835, 773.

MS (FAB) *m/z* 374 $(M + H)^+$.

2-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,2-dimethylpropoxy)-4-chloroaniline (48l)



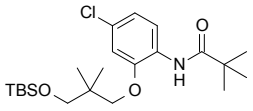
Compound **48l** was prepared from **51l** in a similar manner described for **48h** in 99% yield as pale yellow oil.

^{1}H-NMR ($CDCl_3$) δ 0.01 (6H, s), 0.88 (9H, s), 1.00 (6H, s), 3.45 (2H, s), 3.72 (2H, s), 3.75 (2H, br), 6.61 (1H, d, *J* = 7.8 Hz), 6.74 (1H, dd, *J* = 7.8, 2.2 Hz), 6.77 (1H, d, *J* = 2.2 Hz).

IR (ATR) cm^{-1} 2954, 2856, 1614, 1504, 1462, 1223, 1092, 833, 773.

MS (ESI) *m/z* 344 $(M + H)^+$.

N-[2-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2,2-dimethylpropoxy)-4-chlorophenyl]-2,2-dimethylpropanamide (49l)



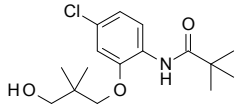
Compound **49l** was prepared from **48l** in a similar manner described for **49a** in 94% yield as pale red oil.

^{1}H-NMR ($CDCl_3$) δ 0.01 (6H, s), 0.87 (9H, s), 1.02 (6H, s), 1.32 (9H, s), 3.46 (2H, s), 3.78 (2H, s), 6.85 (1H, d, *J* = 2.2 Hz), 6.92 (1H, dd, *J* = 8.8, 2.2 Hz), 8.07 (1H, s), 8.35 (1H, d, *J* = 8.5 Hz).

IR (ATR) cm^{-1} 2956, 1687, 1597, 1512, 1396, 1248, 1093, 833, 773.

MS (ESI) *m/z* 428 $(M + H)^+$.

N-[4-Chloro-2-(3-hydroxy-2,2-dimethylpropoxy)phenyl]-2,2-dimethylpropanamide (49i)



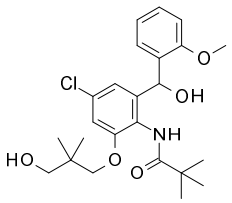
Tetrabutylanmonium fluoride (1.00 mol/l in THF, 6.46 ml, 6.46 mmol) was added to ice-cooled THF (45 ml) solution of compound **49l** (2.30 g, 5.38 mmol), the mixture was stirred and gradually warmed to room temperature for 2h. The solution was removed in vacuo, the residue was diluted with water and AcOEt, and the layers were separated. The aqueous layer was extracted with AcOEt, and the combined organic layer was washed with brine, dried over Na_2SO_4. The solvent was removed in a reduced presser to give compound **49i** (1.63 g, 5.1 mmol, 96%) as colorless oil.

^{1}H-NMR ($CDCl_3$) δ 1.08 (6H, s), 1.32 (9H, s), 3.52-3.58 (2H, m), 3.83 (2H, s), 6.88 (1H, d, *J* = 2.2 Hz), 6.94 (1H, dd, *J* = 8.6, 2.2 Hz), 8.04 (1H, s), 8.32 (1H, d, *J* = 8.8 Hz).

IR (ATR) cm^{-1} 3481, 2960, 1660, 1593, 1523, 1402, 1032, 926, 798, 613.

MS (ESI) *m/z* 314 $(M + H)^+$.

N-{4-Chloro-2-(3-hydroxy-2,2-dimethylpropoxy)-6-[hydroxy(2-methoxyphenyl) methyl] phenyl}-2,2-dimethylpropanamide (52i)



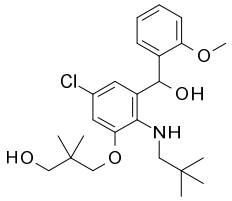
Compound **52i** was prepared in a similar manner described for **52f** in 88% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.97 (3H, s), 0.99 (3H, s), 1.15 (9H, s), 3.03 (1H, t, *J* = 6.9 Hz), 3.37 (1H, dd, *J* = 11.0, 6.6 Hz), 3.46 (1H, dd, *J* = 11.0, 6.6 Hz), 3.74 (1H, d, *J* = 8.3 Hz), 3.82 (1H, d, *J* = 8.3 Hz), 3.86 (3H, s), 4.05 (1H, d, *J* = 3.9 Hz), 5.97 (1H, d, *J* = 3.9 Hz), 6.79 (1H, d, *J* = 2.0 Hz), 6.90-6.97 (3H, m), 7.09 (1H, d, *J* = 7.6 Hz), 7.26-7.32 (1H, m), 7.95 (1H, s).

IR (ATR) cm^{-1} 3467, 3309, 2958, 1628, 158, 1518, 1466, 1240, 1011, 1061, 897, 761.

MS (ESI) *m/z* 432 $(M - OH)^+$.

3-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-[hydroxy(2-methoxyphenyl)methyl] phenoxy}-2,2-dimethylpropan-1-ol (53i)



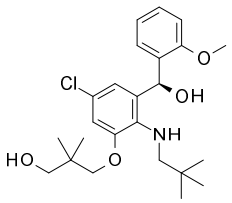
Compound **53i** was prepared in a similar manner described for **53a** in 77% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.99 (9H, s), 1.06 (3H, s), 1.06 (3H, s), 2.73-2.83 (2H, m), 3.53-3.58 (2H, m), 3.73 (3H, s), 3.84-3.84 (2H, m), 6.31 (1H, s), 6.55 (1H, d, *J* = 2.2 Hz), 6.81 (1H, d, *J* = 2.2 Hz), 6.93 (1H, dd, *J* = 8.6, 1.0 Hz), 6.95-7.01 (1H, m), 7.26-7.38 (2H, m).

IR (ATR) cm^{-1} 3485, 2949, 1585, 1460, 1396, 1248, 1026, 823, 750.

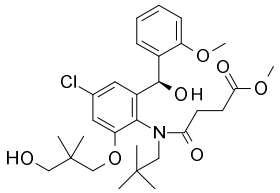
MS (ESI) *m/z* 436 $(M + H)^+$.

3-{5-Chloro-2-[(2,2-dimethylpropyl)amino]-3-[(*S*)-hydroxy(2-methoxyphenyl)methyl] phenoxy}-2,2-dimethylpropan-1-ol ((*S*)-54i)



Compound **(*S*)-54i** was separated in a similar manner described for **(*S*)-54a** using by HPLC with a CHIRALCEL OD as pale yellow crystal.

Methyl 4-[{4-chloro-2-(3-hydroxy-2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoate ((*S*)-55i)



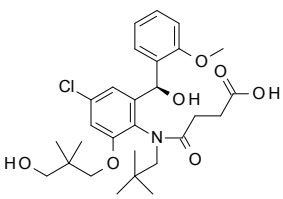
Compound **(*S*)-55i** was prepared in a similar manner described for **(*S*)-55a** in 99% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.88 and 0.94 (9H, s), (0.98) 1.05 (3H, s), (1.00) 1.06 (3H, s), (1.58-1.68) 2.20 (1H, t, *J* = 4.8 Hz), (2.04-2.15) 2.35-2.47 (2H, m), 2.48-2.59 (1H, m), (2.62-2.65) 2.66-2.77 (1H, m), 3.02 (3.19) (1H, d, *J* = 13.4 Hz), (3.29) 3.46 (1H, dd, *J* = 10.4, 4.3 Hz), (3.58-3.71) 3.79-3.86 (2H, m), 3.68 (3H, s), 3.78 (3H, s), (3.90) 4.17 (1H, d, *J* = 4.6 Hz), (4.06) 4.26 (1H, d, *J* = 13.4 Hz), 6.07 (6.37) (1H, d, *J* = 4.6 Hz), 6.83 (1H, d, *J* = 2.0 Hz), 6.85-6.94 (2H, m), 6.97 (1H, d, *J* = 2.2 Hz), 6.98 (1H, d, *J* = 2.0 Hz), 6.99-7.09 (1H, m), 7.29-7.36 (1H, m), 7.65 (7.50) (1H, d, *J* = 6.8 Hz).

IR (ATR) cm^{-1} 3425, 2952, 1720, 1645, 1464, 1238, 1169, 1026, 889, 754.

MS (ESI) *m/z* 550 $(M + H)^+$.

4-[{4-Chloro-2-(3-hydroxy-2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl) methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoic acid ((*S*)-56i)



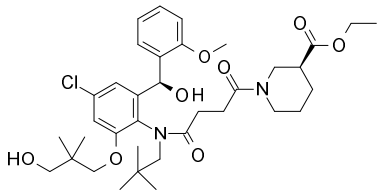
Compound **(*S*)-56i** was prepared in a similar manner described for **(*S*)-56a** in 97% yield as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.85 (9H, s), (0.94 and 0.98) 1.03 (6H, s), (1.11-1.28 and 1.71-1.81 and 1.97-2.07 and 2.18-2.29) 2.43-2.63 (4H, m), 2.94 (3.17) (1H, d, *J* = 13.7 Hz), (3.30) 3.41 (1H, d, *J* = 10.3 Hz), (3.55) 3.64 (1H, d, *J* = 10.8 Hz), 3.67-3.76 (1H, m), 3.77 (3H, s), 3.79 (3H, s), 3.81-3.87 (2H, m), (4.13) 4.18 (1H, d, *J* = 13.7 Hz), 6.04 (6.38) (1H, s), (6.65) 6.86 (1H, d, *J* = 2.7 Hz), 6.88-6.93 (1H, m), 6.96-7.09 (2H, m), 7.36-7.30 (7.59-7.49) (2H, m).

IR (ATR) cm^{-1} 3415, 2954, 1712, 1464, 1392, 1240, 1174, 1026, 754.

MS (ESI) *m/z* 518 $(M - OH)^+$.

Ethyl (3*S*)-1-{4-[{4-chloro-2-(3-hydroxy-2,2-dimethylpropoxy)-6-[(*S*)-hydroxy-(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl} piperidine-3-carboxylate ((*S*)-58i)



Compound **(*S*)-58i** was prepared from **(*S*)-56i** in a similar manner described for **(*S*)-57a** in 87% yield as colorless amorphous.

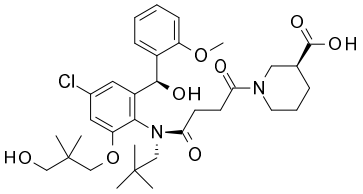
^{1}H-NMR ($CDCl_3$) δ (0.91) 0.94 (9H, s), (1.03) 1.06 (6H, s), (1.23) 1.26 (3H, t, *J* = 6.9 Hz), 1.34-1.45 (1H, m), 1.48-1.82 (2H, m), 1.99-2.11 (1H, m), 2.21-2.60 (2H, m), 2.66-2.87 (1H, m), 2.89-3.07 (1H, m), 3.09-3.32 (2H, m), 3.42-3.53 (2H, m), 3.56-3.66 (2H, m), 3.73 (3H, s), 3.74 (3H, s), 3.76-3.89 (3H, m), 3.90-4.04 (1H, m), 4.05-4.20 (2H, m), 4.23-4.49 (4.50-4.60) (2H, m), (5.65) 6.10 (1H, d, *J* = 4.7 Hz), 6.73 (1H, dd, *J* = 17.0, 2.3 Hz), 6.87 (2H, d, *J* = 8.6 Hz), 6.90-6.94 (1H, m), (6.96-7.01) 7.02-7.10 (1H, m), 7.28-7.34 (1H, m), (7.46-7.53) 7.76-7.64 (1H, m).

IR (ATR) cm^{-1} 3388, 2952, 1728, 1626, 1462, 1242, 1180, 1028, 754.

MS (FAB) *m/z* 675 $(M + H)^+$.

Anal. Calcd. for $C_{36}H_{51}ClN_2O_8$: C, 64.03; H, 7.61; N, 4.15. Found: C, 63.91; H, 7.86; N, 3.89.

(*aR*)-(3*S*)-1-{4-[{4-Chloro-2-(3-hydroxy-2,2-dimethylpropoxy)-6-[(*S*)-hydroxy(2-methoxyphenyl)methyl]phenyl}(2,2-dimethylpropyl)amino]-4-oxobutanoyl} piperidine-3- carboxylic acid ((*S*)-61i)



Compound **(*S*)-61i** was prepared from **(*S*)-58i** in a similar manner described for **(*S*)-(*aR*)-60a** in 86% yield containing small amount of minor atropisomer as colorless amorphous.

^{1}H-NMR ($CDCl_3$) δ 0.90 (9H, s), 1.05 (6H, s), 1.24-1.48 (1H, m), 1.52-1.84 (3H, m), 1.90-2.11 (1H, m), 2.26-2.40 (1H, m), 2.43-2.62 (3H, m), 2.82-3.01 (1H, m), 3.03-3.24 (2H, m), 3.29-3.52 (2H, m), 3.58-3.73 (2H, m), 3.74 and 3.74 (3H, s), 3.77-3.86 (2H, m), 3.87-3.94 (1H, m), 4.27-4.47 (1H, m), 6.08 (1H, d, J = 13.7 Hz), 6.74 (1H, dd, J = 10.8, 2.2 Hz), 6.83-6.91 (1H, m), 6.92-6.96 (1H, m), 7.10-6.97 (1H, m), 7.35-7.27 (1H, m), 7.67-7.58 (1H, m).

IR (ATR) cm^{-1} 3280, 2945, 1712, 1637, 1464, 1242, 1182, 1051, 1022, 750.

Anal. Calcd. for $C_{34}H_{47}ClN_2O_8 \cdot 0.5H_2O$: C, 62.23; H, 7.37; N, 4.27. Found: C, 62.00; H, 6.94; N, 4.22.

第二章　Biological evaluation method

第一項　Animals

Male Syrian hamsters (6 weeks) were purchased from Charles River (Kingston, NY). They were fed a commercial chow diet (F2; Funabashi Farm, Funabashi, Japan) and allowed access to water ad libitum. Male and female common marmosets (305–410 g) were purchased from Clea Japan (Tokyo, Japan), and fed a commercial chow diet (CMS-1M; Clea Japan) and allowed access to water ad libitum. All animal experiments were carried out according to the Daiichi Sankyo Animal Care Guidelines.

第二項　Biological evaluation procedure of squalene synthase inhibitory activity

SSI IC_{50} values were measured using by slightly modified Shechter's method. And CSI IC_{50} values were measured as described below.

第三項　Biological evaluation procedure of inhibitory effects on cholesterol synthesis in rat hepatic cells

Preparation of rat primary hepatocytes

Shechter's method[25] was slightly modified. This study consisted of three experiments, and the effects of inhibitors at each concentration were evaluated in triplicate. One animal was used to prepare the hepatocytes for each experiment. Under anesthesia by thiopental sodium (0.1 g/kg, i.p.), a plastic catheter was introduced through the portal vein. The rat liver was perfused with Ca^{2+}, Mg^{2+} free Hanks' balanced salts solution (pH 7.2) containing 2% albumin, 0.5 mM EGTA, 10 mM HEPES, and 41.7 mM $NaHCO_3$ at 37°C for 10 min at 19 - 21 mL/min; and then with Ca^{2+}, Mg^{2+} free Hanks' balanced salts solution (pH 7.5) containing 0.05% collagenase, 4 mM $CaCl_2$, 10 mM HEPES, and 41.7 mM $NaHCO_3$ for another 15 minutes. Liver cells were dispersed in DMEM supplemented with 100 U/mL penicillin and 100 μg/ml streptomycin by dissection and gentle pipetting. After filtration through a 70 μm nylon mesh filter (Cell Strainer, BD Falcon), hepatocytes were obtained by repeated centrifugation (3 times) at 600 rpm (centrifuge; 5930,

swinging bucket rotor: RS-3011M) for 1 minute at 4°C. After the last centrifugation, the medium was changed to DMEM supplemented with 10% LPDS, 100 U/ml penicillin, and 100 µg/ml streptomycin. Then, viability was determined by staining with trypan blue. Hepatocytes with over 80% viability were cultured in 6-well cell culture plates (10^6 cells/well).

Measurement of cholesterol biosynthetic activity of rat hepatocytes

The following day, the medium was replaced with media supplemented with 5% LPDS, 25 mM HEPES, and inhibitors (final concentrations: 0, 1, 3, 10, 30, 100, 300, 1000, and 3000 nM). After incubation for 1 hour at 37°C, 10 µl of [^{14}C] mevalonolactone (5 µCi/ml) was added into the media, and the incubation was continued for another 1 hour. The cells were washed with D-PBS (3 times) and dissolved in 1 ml of 0.1 M NaOH. Ten micro liters of the cell lysates were transferred to a 96-well plate to determine the protein concentration in duplicate. Eight hundred microliters of the remains were saponified for 1 hour at 75°C by adding 2 mL of ethanol and 0.5 mL of 50 (w/v)% KOH. After the addition of 50 or 100 µl of [^{3}H] cholesterol (0.45 µCi/ml) as an internal standard, the nonsaponifiable lipids were extracted with 4.5 mL of petroleum ether. The water layer was frozen in dry ice and ethanol, and the upper layer was transferred to another tube. The extracts in the tubes were dried under N_2 gas at 40°C. The residue was dissolved in 50 µl of dichloromethane - methanol (2 : 1) solution including 10 mg/ml cholesterol, applied onto TLC plastic sheets (Silica gel 60), and developed with a solvent (toluene - ethyl acetate, 3 : 1). The radio activities incorporated into the cholesterol fractions in Aquasol-2 were counted with a liquid scintillation counter.

The protein concentration was determined using a BCA Protein Assay Kit.

The radioactivities incorporated into the cholesterol fractions were corrected from the formula as follows:

Radioactivities incorporated (dpm/µg protein) = Radioactivities of [^{14}C] cholesterol (dpm) × 50,000 (dpm) / radioactivities of [^{3}H] cholesterol (dpm) / protein content (µg)

Referring to the mean radioactivity of the cells in the three wells treated with 0 nM of inhibitors, inhibition (%) of cholesterol synthesis at each concentration was calculated by the following equation:

Inhibition (%) = (1 – arithmetic mean radioactivity incorporated of three wells at each concentration / arithmetic mean radioactivity incorporated of three wells at 0 nM) × 100

第四項　Rat single-dose *in vivo* hepatic cholesterol synthesis inhibitory activity

A rat single-dose liver-cholesterol synthesis inhibitory effect was measured as described below.

To each the compounds was added a necessary amount of a 0.5% methyl cellulose solution immediately before use. Then, an equivalent molar amount of sodium hydroxide or sodium hydrogen carbonate was added to dissolve or suspend it in the resulting solution. 6-week-old Wistar male rats were orally administered each of the compounds (1 or 3 mg/kg, n = 4-6), while only a 0.5% methyl cellulose solution was administered to the control group. 1,4 or 7 h later, physiological saline of mevalonic acid (5 μCi / 5 ml/kg) labeled with a radioisotope ^{14}C was intraperitoneally administered. The rats were sacrificed 1 hour later. To 1 g of the liver obtained from the rats was added 5 ml of a 15% KOH ethanol solution and the resulting mixture was left to stand for 15 hours. After heating at 75°C for 2 hours, the reaction mixture was extracted with 5 ml of water and 10 ml of petroleum ether. The petroleum ether layer was collected, evaporated to dryness and then dissolved in 50 μl of a $CHCl_3$: acetone = 2 : 1 solution. The cholesterol band was separated by silica gel thin layer chromatography (Art.5748, toluene : ethyl acetate = 3 : 1) and cut out. It was placed into a vial container, followed by the addition of 10 ml of Aquasol-2 (product of Packard BioScience Company). The radioactivity was measured using a liquid scintillation counter. A ratio of the radioactivity relative to that of a control group was determined and liver-cholesterol synthesis inhibitory activity (%) was calculated.

第五項　Plasma lipid lowering studies in hamsters

Before the experiment, blood samples were collected under nonfasted conditions. Plasma total cholesterol and triglyceride were measured enzymatically (Cholesterol E test Wako, Triglyceride E test Wako; Wako Pure Chemical Industries, Osaka, Japan). Hamsters were divided into five groups matched for body weight, plasma total cholesterol and triglyceride (n = 8). These five groups were assigned to receive vehicle (0.5% methylcellulose solution) or compounds **61e**, **h** (30, 100 mg/kg). Compounds were suspended in 0.5% methylcellulose solution by Teflon homogenizer, and vehicle and compounds suspension were administered orally at 10 mL/kg twice a day (9AM and 4PM) for 14 days. The following morning after the seventh and the final administrations, blood samples were collected and plasma parameters were measured.

第六項　Plasma lipid lowering studies in common marmosets

Male and female common marmosets (305 - 410 g) were purchased from Clea Japan (Tokyo, Japan), fed a commercial chow diet (CMS-1M; Clea Japan) and allowed access to water ad libitum. All animal experiments were carried out according to the Daiichi Sankyo Animal Care Guidelines. Before the experiment, blood samples were collected under nonfasted conditions. Plasma total cholesterol and triglyceride were measured as described above. High-density lipoprotein (HDL) was separated by precipitation reagents (Wako Pure Chemical Industries), and then the cholesterol was measured enzymatically. Non HDL-cholesterol was calculated by subtracting HDL-cholesterol from total cholesterol. Common marmosets were divided into two groups (control vs prepared compound, 30 mg/kg, n = 8); groups were matched for body weight, plasma total cholesterol, triglyceride, HDL cholesterol and non-HDL cholesterol. Drugs were suspended in 0.5% methylcellulose solution and administered orally at 5 ml/kg once a day (9-10AM) for 7 days. The next morning after the final administration of drugs, blood samples were collected under nonfasted conditions and plasma parameters were measured.

主論文目録

本学位論文内容は、下記の発表論文による。

1) Ichikawa, Masanori; Yokomizo, Aki; Itoh, Masao; Usui, Hiroyuki; Shimizu, Hironari; Suzuki, Makoto; Terayama, Koji; Kanda, Akira; Sugita, Kazuyuki.
Discovery of a new 2-aminobenzhydrol template for highly potent squalene synthase inhibitors.
Bioorganic & Medicinal Chemistry **2011**, *19* (6), 1930-1949.

2) Ichikawa, Masanori; Yokomizo, Aki; Itoh, Masao; Haginoya, Noriyasu; Sugita, Kazuyuki; Usui, Hiroyuki; Terayama, Koji; Kanda, Akira.
Discovery of atrop fixed alkoxy-aminobenzhydrol derivatives: Novel, highly potent and orally efficacious squalene synthase inhibitors.
Bioorganic & Medicinal Chemistry **2011**, *19* (17), 5207-5224.

関連発表

1) 第 28 回メディシナルケミストリーシンポジウム 2010 東京
2P-62 アミノベンズヒドロール構造をもつ新規スクアレン合成酵素阻害薬の合成研究
市川 正則、横溝 亜紀、伊藤 雅夫、杉田 和幸、碓井 博幸、清水 洋成、鈴木 誠、寺山 浩司、神田 明

2) 242nd ACS National Meeting & Exposition, Denver, CO, United States, 2011.
MEDI-345 Discovery of atrop fixed alkoxy-aminobenzhydrol derivatives: Novel, highly potent and orally efficacious squalene synthase inhibitors
Ichikawa, Masanori; Yokomizo, Aki; Itoh, Masao; Haginoya, Noriyasu; Sugita, Kazuyuki; Usui, Hiroyuki; Terayama, Koji; Kanda, Akira.

3) 242nd ACS National Meeting & Exposition, Denver, CO, United States, 2011.
MEDI-346 Discovery of novel tricyclic compounds as squalene synthase inhibitors
Ichikawa, Masanori; Ohtsuka, Masami; Ohki, Hitoshi; Haginoya, Noriyasu; Itoh, Masao; Usui, Hiroyuki; Terayama, Koji; Kanda, Akira.

4) 第 30 回メディシナルケミストリーシンポジウム 2012 東京
2P-06　新規三環性スクアレン合成酵素阻害薬の合成研究
市川 正則、大塚 雅己、大木 仁、萩野谷 憲康、伊藤 雅夫、杉田 和幸、鈴木 誠、寺山 浩司、神田 明、碓井 博幸

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6) Ichikawa, Masanori; Ohtsuka, Masami; Ohki, Hitoshi; Ota, Masahiro; Haginoya, Noriyasu; Itoh, Masao; Shibata, Yoshihiro; Ishigai, Yutaka; Terayama, Koji; Kanda, Akira; Sugita, Kazuyuki.
Discovery of DF-461, a Potent Squalene Synthase Inhibitor

ACS Medicinal Chemistry Letters **2013**, *4* (19), 932-936.

7) 第 31 回メディシナルケミストリーシンポジウム 2013 広島

1P-38　スクアレン合成酵素阻害薬 DF-461 の創製

市川 正則、大塚 雅己、大木 仁、太田 雅浩、萩野谷 憲康、伊藤 雅夫、柴田 憲宏、杉田 和幸、石貝 裕、寺山 浩司、神田 明、碓井 博幸

（平成 25 年度日本薬学会メディシナルケミストリーシンポジウム優秀発表賞 受賞）

8) 市川 正則、大塚 雅己、杉田 和幸

スクアレン合成酵素阻害薬 DF-461 の創製

MEDCHEM NEWS **2014**, *24* (3), 37-43.

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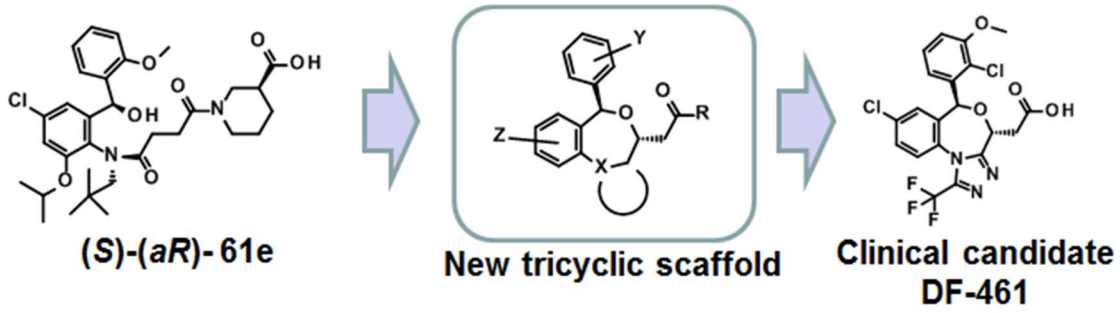
付記

尚著者らの研究グループでは、本研究で得られた多くの知見をもとに鋭意研究を重ねることで、より強力な *in vivo* 活性を有する新規三環性化合物の発見[31]、それに続く開発候補品 **DF-461** の獲得へと繋がる大きな成果を上げることに成功している[32]。



Scheme 12. Design of the novel tricyclic template and our clinical candidate **DF-461**

本研究をもとに生み出されたスクアレン合成酵素阻害薬 **DF-461** が、開発候補品として更なる高次評価を経た後、脂質異常症治療薬として、臨床の現場に貢献できる日が来ることを願ってやまない。

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