PPARα/γデュアルアゴニストの創薬研究

柴田, 憲宏

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緒論

1. 2 型糖尿病とその薬剤

2015 年、約 500 万人が糖尿病を原因として死亡した [1)]。その数は、HIV/AIDS で死亡した 150 万人を、さらに結核で死亡した 150 万人，マラリアで死亡した 60 万人をはるかに上回る。国際糖尿病連合 (IDF) の発表によると、現在約 4 億 1500 万人の成人 (20—79 歳) がその疾患に苦しんでおり、そして 2040 年には約 6 億 4200 万人に達すると予想され (**Figure 1**)[1)]、成人の 10 人に 1 人が罹患するとされている。

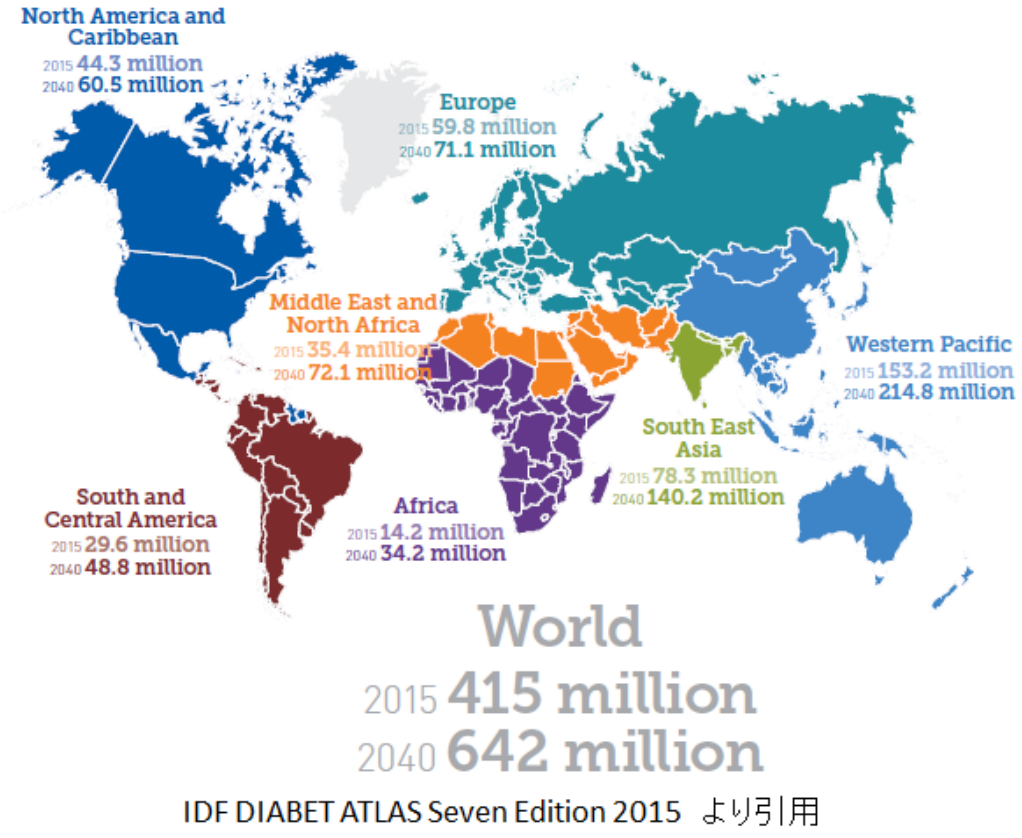


Figure 1. Diabetes: A global emergency[1)]

特に経済発展の著しい中国やインドにおける糖尿病患者数は、それぞれ 1 億 960 万人、6920 万人と抜きん出ており、今後さらにそれらの国々が患者数の増加を牽引していくといっても過言ではない。また有病率という観点では、アメリカにおいて全人口の 12.8%、日本でも 7.6%と高い水準を示しており、世界的増加の一途をたどる糖尿病患者の予防や治療に対する我々製薬メーカーの果たすべき使命は大きい。

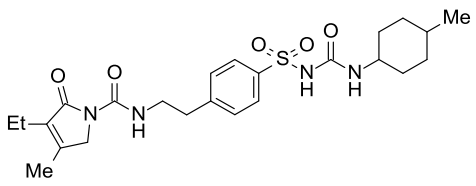
糖尿病患者のうち 90%以上は 2 型である[2)]。その 2 型糖尿病は、インスリン分泌不全によるものとインスリン抵抗性によるものの 2 つに大別される。インスリン分泌不全に関しては、民族性などの遺伝的要因によるところが大きい一方、インスリン抵抗性は、民族性や家族歴、加齢などの遺伝的要因に加え、過度の肥満や運動不足、栄養の偏りなどの環境的要因に影響される。その結果、内臓脂肪が蓄積され、骨格筋でのインスリンの情報伝達系を抑制する TNF-α をはじめとするアディポサイトカインが肥大化した脂肪細胞から分泌されるとともに、インスリン抵抗性を解除するアディポネクチンの分泌が低下することによるものとされている[3)]。インスリン抵抗性は、糖尿病の発症および糖尿病合併症、特に大血管障害の発症や進展に寄与するとされ[4)]、さらに最近では癌リスクの上昇に関係していることが明らかになってきている[5)]。さらに高血糖状態が続くと、神経障害や網膜症、腎症、壊疽が高い確立で発症することが知られている。つまりインスリン抵抗性が亢進した 2 型糖尿病の予防や治療は、QOL の維持にますます重要になってきている。

これまで以下に示す多様な 2 型糖尿病治療薬が開発されてきている (**Figure 2**)。

【インスリン分泌促進作用】

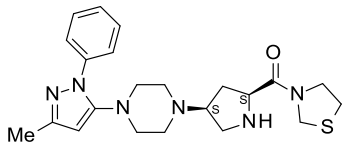
◆ **スルホニル尿素受容体結合薬(SU 薬):**インスリン分泌を増加させる作用を有する。

Glimepiride



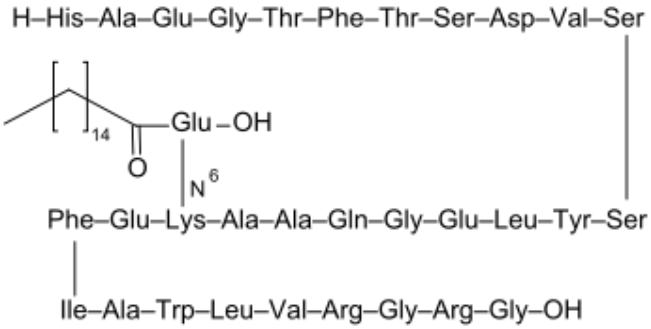
◆ **DPP4 阻害薬:**インスリン分泌作用やグルカゴン濃度低下作用をもつインクレチンホルモンの分解を抑制する。

Teneligliptin



◆ **GLP-1 受容体作動薬:**インクレチンホルモンを活性化する

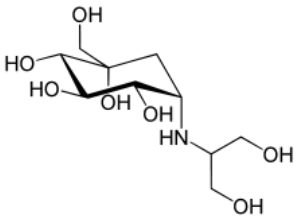
Liraglutide



【糖吸収抑制作用】

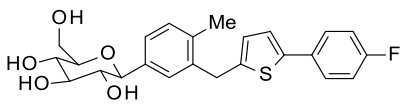
◆ **α－グルコシダーゼ阻害薬:**炭水化物の分解や吸収を遅らせ食後高血糖を抑制する。

Voglibose



◆ **SGLT2 阻害薬:**腎臓での糖の再吸収を抑制する。

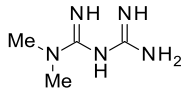
Canagliflozin



【インスリン抵抗性改善作用】

◆ **グリセロールリン酸脱水素酵素阻害薬（ビグアノイド薬）:** インスリン抵抗性を改善する。

Metformin



◆ **ペルオキシゾーム増殖剤応答性受容体 (PPAR) γ 作動薬:** インスリン抵抗性を改善する。

Pioglitazone　　Rosiglitazone

Figure 2. 多様な 2 型糖尿病薬

著者は、それらの中で特にインスリン抵抗性、高血糖および脂質代謝障害による各種合併症の発症や進展に対する抑制薬である PPARγ 活性化を作用機作とするインスリン抵抗性改善薬に注目した。

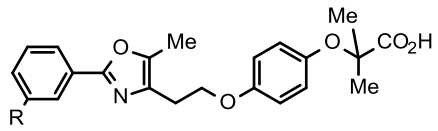
PPAR は、リガンド応答性核内受容体型の転写因子であり、α、δ、γ と 3 つのサブタイプが知られている。その中で PPARγ は、白色脂肪組織で脂肪生成やグルコース恒常性の中心的な役割を担っている。PPARγ が活性化されると、脂肪細胞が分化促進され、アディポサイトカインを出す大型脂肪細胞が減少し、アディポネクチンや TNF-α、レプチンなどの生理活性物質のバランスを整えられることによってインスリン抵抗性が解除されるとされている [6,7]。これまでにこの PPARγ を標的とした薬剤として Pioglitazone や Rosiglitazone 等が見出されており、顕著な血糖低下作用を示すことが臨床結果により明らかとなっている。しかし、主薬理作用の PPARγ 活性化にともなって体重増加や浮腫などの副作用が高い頻度で発生することが顕在化してきており、現有の PPARγ 選択的アゴニストは必ずしも満足できる薬剤というわけではない [8]。

一方、そのサブタイプである PPARα は主に肝臓に発現しており、脂肪酸の取り込みや酸化、リ

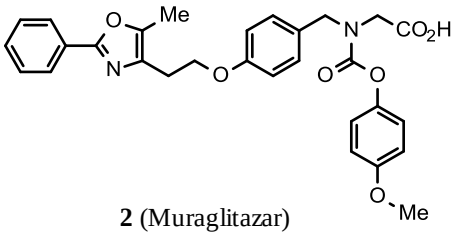
ポタンパク代謝の主調節因子であり、脂質恒常性を維持する重要な機能を果たしている。PPARα の活性化は、抗高脂血症薬であるフィブレート系薬剤のこれまでの研究によって明らかにされており、血中トリグリセリドの低下や LDL コレステロールの減少、HDL コレステロールの増加、さらに心血管転帰の改善を示す。さらにその薬剤をげっ歯類に投与すると食事の影響なく体重減少作用を示すことも報告されている[9]。それ故に PPARα 活性化を付与することは、PPARγ 活性化によって引き起こされる体重増加などの副作用を抑制するとともに脂質パラメーターの改善が期待される[10]。

2. 研究成果の概略

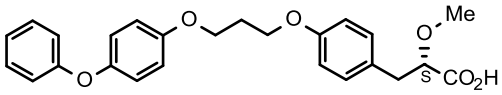
著者は、PPARγ アゴニストに PPARα 作用を付加することで PPARγ アゴニストが有する副作用を抑え、加えて脂質パラメーターの改善が期待できるという新たなコンセプトのもと創薬研究を開始した。PPARα/γ デュアルアゴニストの研究は既に世界中で行われており、その特徴的な構造は、カルボン酸を有する酸性部分と脂溶性の高い部分を比較的単純なリンカーで結ぶように構成されている。これまでに報告されている代表的な PPARα/γ デュアルアゴニストには、Eli Lilly 社から報告されている compound **1** (a, b)[11] をはじめ、Bristol-Myers Squibb 社の Muraglitazar (**2**)[12]、AstraZeneca 社の Tesaglitazar (**3**)[13]、Eli Lilly 社の Naveglitazar (**4**)[14]、Novo Nordisk 社の Ragaglitazar (**5**)[15]、杏林製薬の KRP-297 (**6**)[16] などがある (**Figure 3**)。



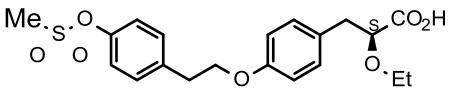
1a: R = H (Ely Lilly)
1b: R = Br (Ely Lilly)
1a; α: EC_{50} = 0.7 μM, γ: EC_{50} = 2.1 μM [11]



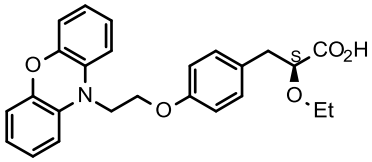
2 (Muraglitazar)
α: EC_{50} = 0.3 μM, γ: EC_{50} = 0.1 μM [12]



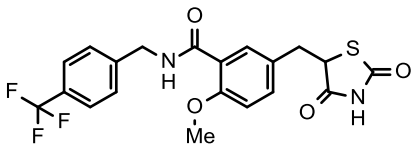
4 (Naveglitazar)
α: EC_{50} = 2.8 μM, γ: EC_{50} = 0.4 μM [14]



3 (Tesaglitazar)
α: EC_{50} = 1.2 μM, γ: EC_{50} = 1.3 μM [13]



5 (Ragaglitazar)
α: EC_{50} = 3.2 μM, γ: EC_{50} = 0.6 μM [15]



6 (KRP-297)
α: EC_{50} = 0.8 μM, γ: EC_{50} = 1.0 μM [16]

Figure 2. 他社 PPARα/γ デュアルアゴニスト

これらの化合物は、酸性部分と脂溶性部分にはバラエティーに富んだ構造を配しているが、リンカーにあたる部分には、エーテル構造あるいはアミド構造しかこれまで展開されてきていなかった。一方、リンカー部分にアミノ基を配した化合物は、PPARα アゴニスト[17] や PPARδ アゴニスト[18] では知られていたが、デュアルアゴニストではこれまで知られていなかった。

これまでに報告されている酸性 PPARα/γ デュアルアゴニストは、十分な血糖低下作用を示さない上に PPARγ 活性化由来の体重増加を抑制できていないことが確認された。

その原因として、

① 不十分な *in vivo* 薬効は、高い脂溶性と酸性構造が原因であり、薬効を示す有効血中濃度まで十分に血中濃度を上げられていない等薬物動態に問題がある。

② 体重増加作用は、PPARα 活性化作用の弱さに問題がある。

著者は、上記 2 つの問題を解決することによって PPARγ アゴニストが有する副作用を抑え、加えて脂質パラメーターの改善が期待できる PPARα/γ デュアルアゴニストを獲得することを図った。まず副作用を回避するためには PPARγ よりも PPARα に強力に作用する薬剤が好ましいと考え、PPARα に優位に効果を示す Eli Lilly 社の compound **1a** をリード化合物とし創薬研究をスタートした。*in vivo* 活性向上に向けた戦略は、物理化学的や薬物動態学的に不利だと考えられた高脂溶性や酸性度を減弱させるべく、リンカー部にアミノ基を配した化合物の展開を軸とし、望むべく化合物を獲得することとした(**Figure 4**)。

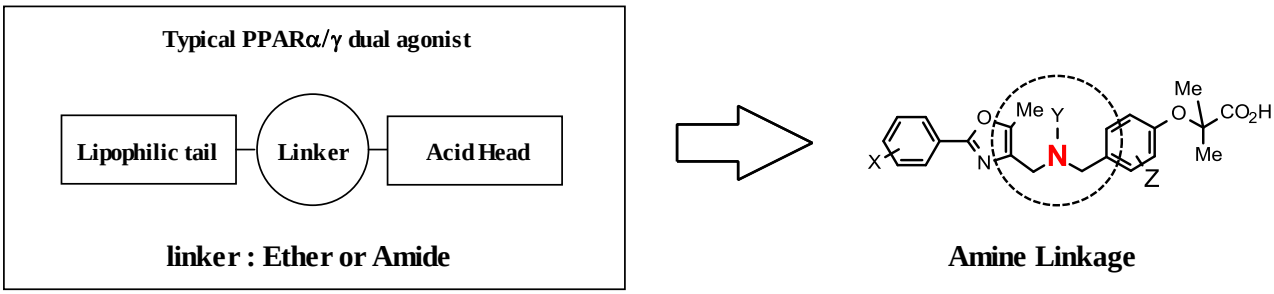


Figure 4. Drug design for novel PPARα/γ dual agonists by incorporating amine linkage

以下、得られた研究成果の概略を **Figure 5** に記した。

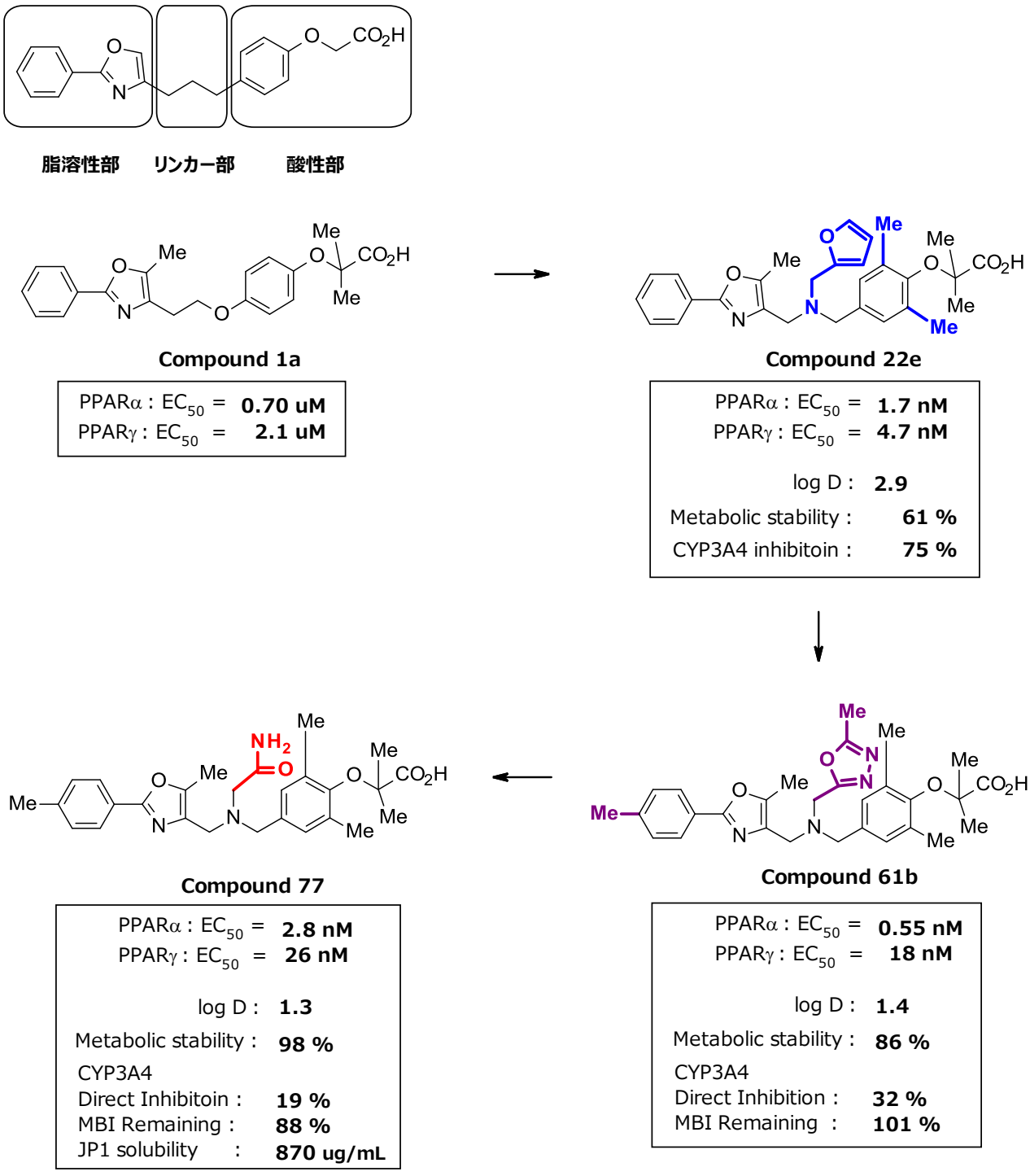


Figure 5

様々な誘導体展開から、トリアリールアミン型構造が PPARα 活性に大きく寄与することを見出し、また酸性部ベンゼン環上へのジメチル基の導入が PPARα 活性を維持しつつ PPARγ の活性向上に効果的である構造活性相関を構築した。その結果、著者は *in vitro* において PPARα 優位に活

性を示す化合物 **22e** を獲得した。この化合物は *in vivo* 試験においてその強力な PPARα 活性により PPARγ 活性の副作用を抑制しつつ優れた血糖低下作用と脂質低下作用を示した (第 1 章)。

ところが、化合物 **22e** は、生体内代謝酵素であるシトクロム P450 3A4（CYP3A4）を強く阻害することが明らかとなり、併用する薬剤の血中コントロールを困難にし重篤な副作用を引き起こす危険性を有していることが判明した。様々なパラメーターを用いてその原因を調査した結果、その阻害作用は脂溶性の高さに関係していることが判明し、CYP3A4 阻害作用と脂溶性の相関図から著者の化合物の脂溶性は LogD 値が 2 以下であることが望ましいと考えられた。さらに、代謝された化合物が、代謝酵素に共有結合を形成し、代謝酵素阻害作用（MBI）を示す起因構造の可能性を有するフラン環を他の低脂溶性複素環へと変換することで薬物間相互作用のリスク低減を図った。その結果、1,3,4－オキサジアゾール環がフラン環に代わる構造であることを見出し、CYP3A4 の直接阻害作用や MBI リスクを低減させることに成功した低脂溶性化合物 **61b** を獲得した (第 2 章)。

ところが、化合物 **61b** に代表されるオキサジアゾール誘導体の溶液安定性を測定したところ、胃内酸性を想定した日本薬局方第 1 液において 1,3,4－オキサジアゾール環が経時的に分解していくことが確認された。そのためオキサジアゾール環に代わる新規側鎖の探索を実施したところ、アミド基に変換可能であることを見出した。アミド基上の置換基変換では、無置換のアミド化合物が活性と選択性、物性に最もバランスの取れた側鎖であることを見出した。

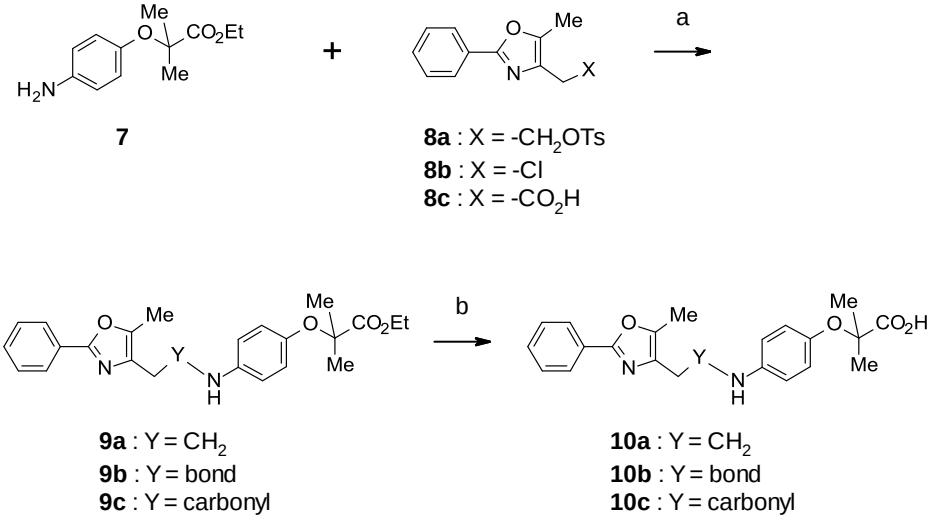
著者は、PPARα/γ デュアルアゴニストの合成研究の集大成として、PPARα 優位に活性を示し、また物性にも優れた化合物 **77** を獲得した。この化合物は、病態モデル動物を用いた *in vivo* 試験において副作用を抑制しつつ強い血糖低下作用と脂質低下作用を示した。さらに先行の PPARα/γ デュアルアゴニストと比較試験を行った結果、PPARα 活性の弱い他社化合物は PPARγ による血糖低下作用を示すものの体重増加を抑えることができなかった一方、著者の化合物 **77** は全ての要件を満たす化合物であった。 (第 3 章)

本論

第 1 章　リンカー部に窒素原子を導入した化合物の合成と構造活性相関

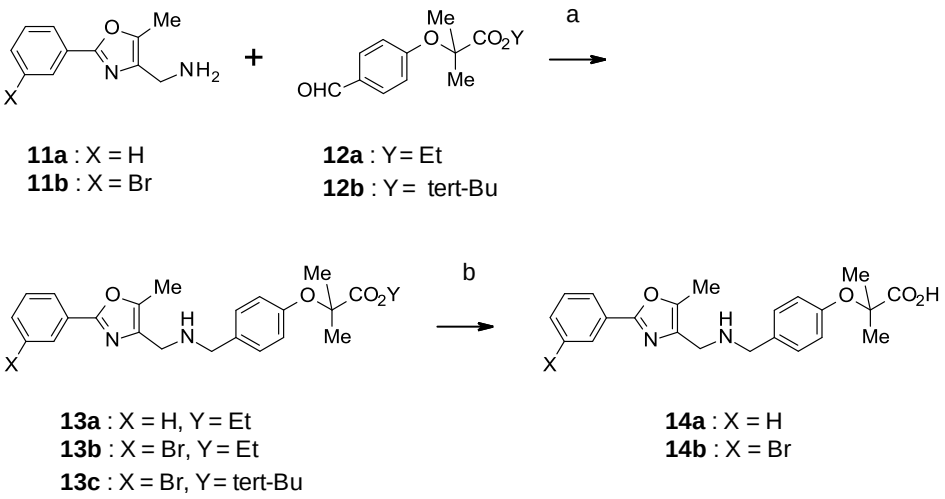
第 1 節　リンカー部に窒素原子を導入した化合物の合成

2 級アミン化合物の **10a** や **10b**、またアミド化合物 **10c** の合成法を **Scheme 1** に示した。**10a** や **10b** は、対応するトシル体 **8a**[19] やクロル体 **8b** とアニリン **7**[20] を DMF 溶媒中炭酸セシウムを用いて反応させた後、水酸化ナトリウム水溶液にてエチルエステル基を加水分解することにより合成した。**10c** はカルボン酸体 **8c** と **7** を EDCI と HOBt を用いて縮合しアルカリ加水分解することによって合成した。



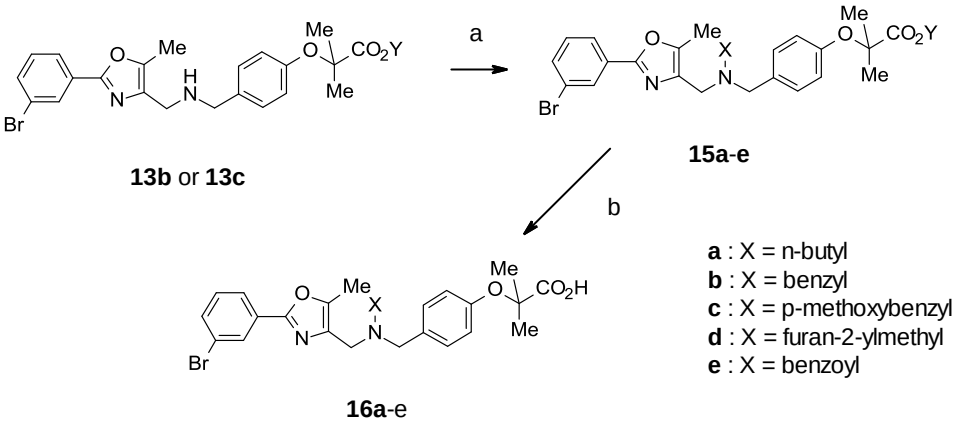
Scheme 1. Reagents and conditions: (a) Cs_2CO_3, DMF, 60ºC, **9a**: 43%, **9b**: 60% or EDCl, HOBt, DMF, rt, **9c**: 6%; (b) NaOH, MeOH, rt, **10a**: 49%, **10b**: 64%, **10c**: 58%.

次にリンカー部分の窒素原子を α 位から β 位に移動させた化合物 **14a** と **14b** を合成した (**Scheme 2**)。1 級アミン **11**[21] とホルミル体 **12**[22] を $NaBH(OAc)_3$ を用いて還元的アミノ化に付した後、加水分解することによって目的物 **14** へと導いた。



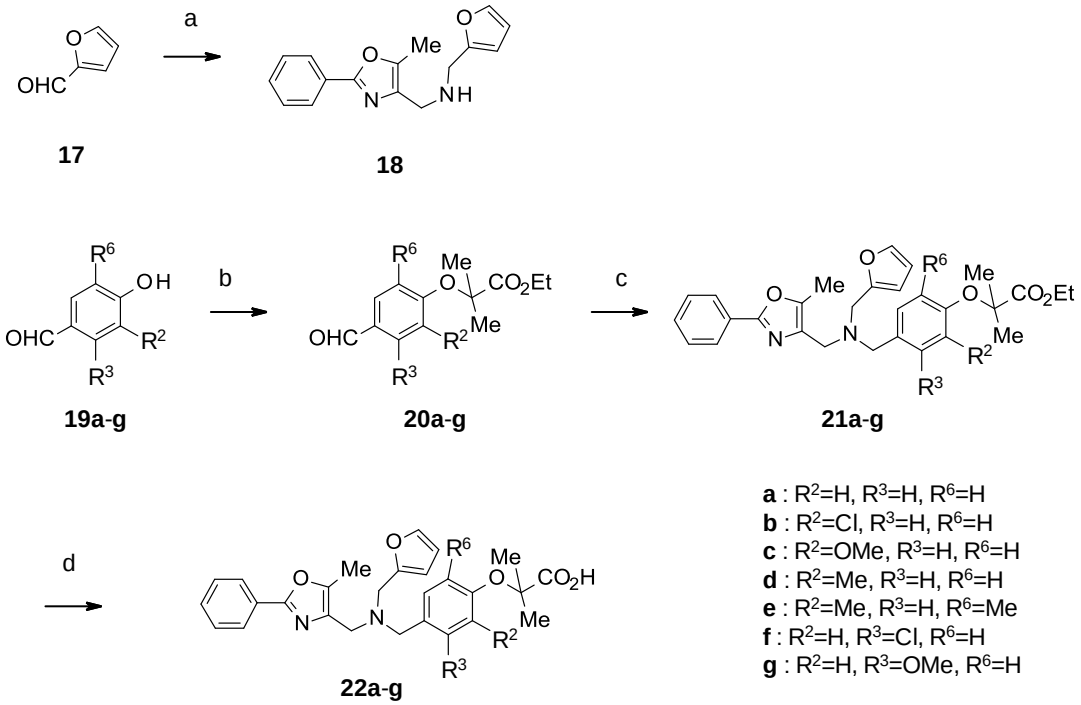
Scheme 2. Reagents and conditions: (a) $NaBH(OAc)_3$, TEA, DCM, rt, **13a**: 43%, **13b**: 55%, **13c**: 71%; (b) NaOH, MeOH, reflux, **14a**: 67%; NaOH, MeOH, rt, **14b**: 54%.

窒素原子上に置換基を導入した 3 級アミン化合物 **16a—d** は、Scheme 2 で得られた 2 級アミン中間体 **13** に対し対応する市販のアルデヒドを還元的アミノ化で導入し **15a—d** へと導いた後、加水分解することによって合成した。アミド体 **16e** は安息香酸を EDCI と HOBt の縮合剤を用いて反応させた後、脱保護することにより導いた**(Scheme 3)**。



Scheme 3. Reagents and conditions: (a) RCHO, $NaBH(OAc)_3$, DCM, rt, **15a**: 91%, **15b**: quant., **15c**: 75%, **15d**: 52% or Benzoic acid, EDCI, HOBt, DCM, rt, **15e**: 85%; (b) NaOH, MeOH, rt, **16a**: 49%, **16c**: 49% or TFA, DCM, rt, **16b**: 76%, **16d**: quant., **16e**: 34%.

酸性部ベンゼン環の構造活性相関を把握するためにベンゼン環上に様々な置換基を配した **22a—g** の合成法を **Scheme 4** に示した。市販のフルフラール **(17)** とアミン中間体 **11a** を用いてエタノール中加熱還流することによりイミンを形成し、冷却後 $NaBH_4$ を加え還元することによりモノ置換化合物である2級アミン中間体 **18** を合成した。ベンゼン環上の置換基展開については、2位や3位、6位に様々な置換基を有する市販の 4-ヒドロキシベンズアルデヒド **19a—g** と 2-ブロモ-2-メチルプロピオン酸エチルエステルを DMF 中炭酸セシウムを用いて反応させて得られた **20a—g** を、先に合成した **18** と $NaBH(OAc)_3$ により還元的アミノ化反応を行った後、アルカリ加水分解することにより目的とする **22a—g** を合成した。

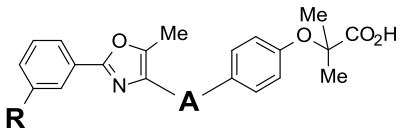


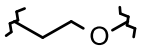
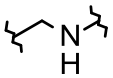
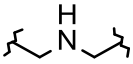
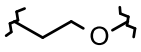
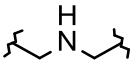
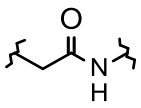
Scheme 4. Reagents and conditions: (a) (1) **11a**, EtOH, reflux; (2) $NaBH_4$, 0°C－rt, 86%; (b) Ethyl 2-bromo-2-methylpropanoate, Cs_2CO_3, DMF, 80°C, **20a**: 65%, **20b**: 71%, **20c**: 72%, **20d**: 54%, **20e**: 71%, **20f**: 37%, **20g**: 48%; (c) **18**, $NaBH(OAc)_3$, DCM, rt, **21a**: 58%, **21b**: 89%, **21c**: 87%, **21d**: 62%, **21e**: 87%, **21f**: 87%, **21g**: 87%; (d) NaOH, MeOH, rt, **22a**: 73%, **22b**: 91%, **22c**: 86%, **22d**: 86%, **22e**: 95%, **22f**: 84%, **22g**: 70%.

第 2 節　リンカー部に窒素原子を導入した化合物の *in vitro* 評価

2 級アミンやアミド化合物の *in vitro* 評価を **Table 1** に示した。化合物 **10a** は、他社が多用したエーテルリンカー化合物 **1a** に比べ活性は弱いが、著者が望んだ PPARα 優位な活性を示した。類似した傾向が 1 炭素短い **10b** や *β* 位に窒素原子を移動した **14a** でも観察された。さらに脂溶性部ベンゼン環に脂溶性の高いブロム基を導入した化合物では、PPARα と PPARγ 共に活性が向上する結果を得た。一方、アミドリンカー化合物の **10c** では活性が消失し、アミンリンカー化合物の展開を強く押す結果となった。窒素原子の位置としては、*α* 位へ導入した **10a** では α/γ の選択性が低下傾向にあった一方、*β* 位に導入した **14a** および **14b** では高い選択性が保持されることが確認され、特に **14b** においては 10 倍以上の選択性を示したことから、以下の誘導体展開は *β* 位に窒素原子を導入したベンジルアミン型化合物に注力することとした。

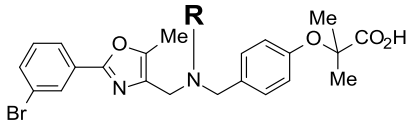
Table 1. *In vitro* trans activation activities of various linkage compounds

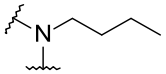
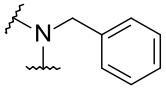
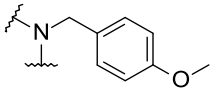
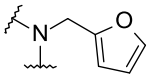
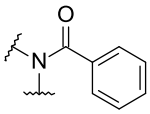


Compd	R	A	PPARα EC_{50} (nM)	PPARγ EC_{50} (nM)
1a	H		500	>25000
10a	H		5200	16000
10b	H		7200	8800
14a	H		10000	>25000
1b	Br		81	800
14b	Br		670	7700
14c	H		>25000	>25000

次に窒素原子上の置換基効果について検証した **(Table 2)**。脂溶性部を 3-ブロモフェニル構造とした化合物においてより効果が明確に確認されたので、著者は、構造活性相関の取得のためにはこの化合物をリードとすることが望ましいと考え、脂溶性部分をこの構造に固定し、誘導体展開を進めた。その結果、窒素原子上にアルキル側鎖を導入するといずれの化合物においても活性が向上する結果を得た。しかし *n*-butyl 基を導入した **16a** では選択性の低下が確認された。一方、**16c** や **16d** に代表されるアリールメチル基を導入した化合物では、高い選択性を維持しつつ PPARα/γ 共に活性を向上させることが判明した。特にフラニルメチル基を導入した **16d** においては非常に強い PPARα 活性を示すことを見出し、著者は、PPARγ 活性を消失することなく PPARα 活性を向上させるためにはトリアリールメチル構造が重要であると推察し、以後、この骨格に焦点を当て研究を進めた。

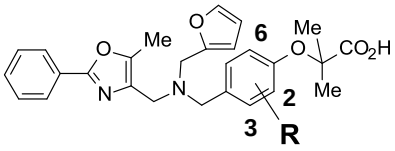
Table 2. *In vitro* trans activation activities of compounds **16a—e**



Compd	R	PPARα EC_{50} (nM)	PPARγ EC_{50} (nM)
16a		500	1300
16b		56	2200
16c		26	700
16d		8.1	310
16e		> 25000	> 25000

次に酸性部ベンゼン環上の置換基効果について検証した **(Table 3)**。一般的に、脂溶性の高い化合物は、複数のターゲットに対しての親和性が増加する可能性が高く、また受容体との相互作用が非特異的な相互作用を示す可能性があると言われている。その非特異的な活性による高活性化効果を避けるために、脂溶性部フェニルオキサゾール環上は、脂溶性の低い無置換フェニル基で検討を行った。酸性部ベンゼン環 2 位に置換基を導入した **22b—e** の化合物は、無置換化合物の **22a** や 3 位に置換した **22f** あるいは **22g** に比べ、PPARα と PPARγ 共に活性を向上させることが明らかとなった。特にその置換基効果は PPARγ に対して顕著であった。さらに 2 位と 6 位の両オルト位にメチル基を導入した **22e** では、活性が飛躍的に向上する結果を得た。この化合物の活性は、研究初期にリード化合物とした Eli Lilly 社の compound **1a** に比べ、PPARα で約 300 倍, PPARγ では 5000 倍以上向上する結果を得た。PPARγ との複合体 X 線結晶解析の結果、今回高活性化に寄与したジメチル基は、脂溶性リッチな空間を占有することによる疎水性相互作用とスレオニンのベンゼン環およびフェニルアラニンのベンゼン環との CH-π 相互作用によって高活性化を導いたことが示唆された。

Table 3. *In vitro* trans activation activities of compounds **22a—g**



Compd	R on Phenyl-ring	PPARα EC_{50} (nM)	PPARγ EC_{50} (nM)
22a	H	13	670
22b	2-Cl	5.1	71
22c	2-OCH_3	9.0	180
22d	2-CH_3	3.9	42
22e	2,6-CH_3	1.7	4.7
22f	3-Cl	36	890
22g	3-OCH_3	32	330

第 3 節　リンカー部に窒素原子を導入した化合物の *in vivo* 評価

PPARα に選択性を示しつつ両サブタイプに対し強い活性を示す **22e** を用いて、インスリン抵抗性や高トリグリセリド血症を発症させた 2 型糖尿病モデルの *db/db* マウスを使用した *in vivo* 試験を実施した。化合物 **22e** は、14 日間の 1 日 1 回連続経口投与において、10mg/kg の投与量で顕著な血糖低下作用とトリグリセリド低下作用を示した(**Figure 6** and **Table 4**)。PPARγ 選択的アゴニストである Rosiglitazone の 10mg/kg 投与では、54%の血糖低下作用を示し、また Eli Lilly 社化合物 **1a** (30mg/kg) は 25%の低下作用を示した。一方で著者の化合物 **22e** は、Rosiglitazone と同じ投与量で 74%の血糖低下作用を示した。また **22e** は、その投与量でトリグリセリドを 88%低下させる結果を得た。PPARγ 活性化による血糖低下作用を示すこの用量において、PPARα 活性が強いこの化合物 **22e** は、PPARγ 活性化による副作用である体重増加を抑制する結果を得た。

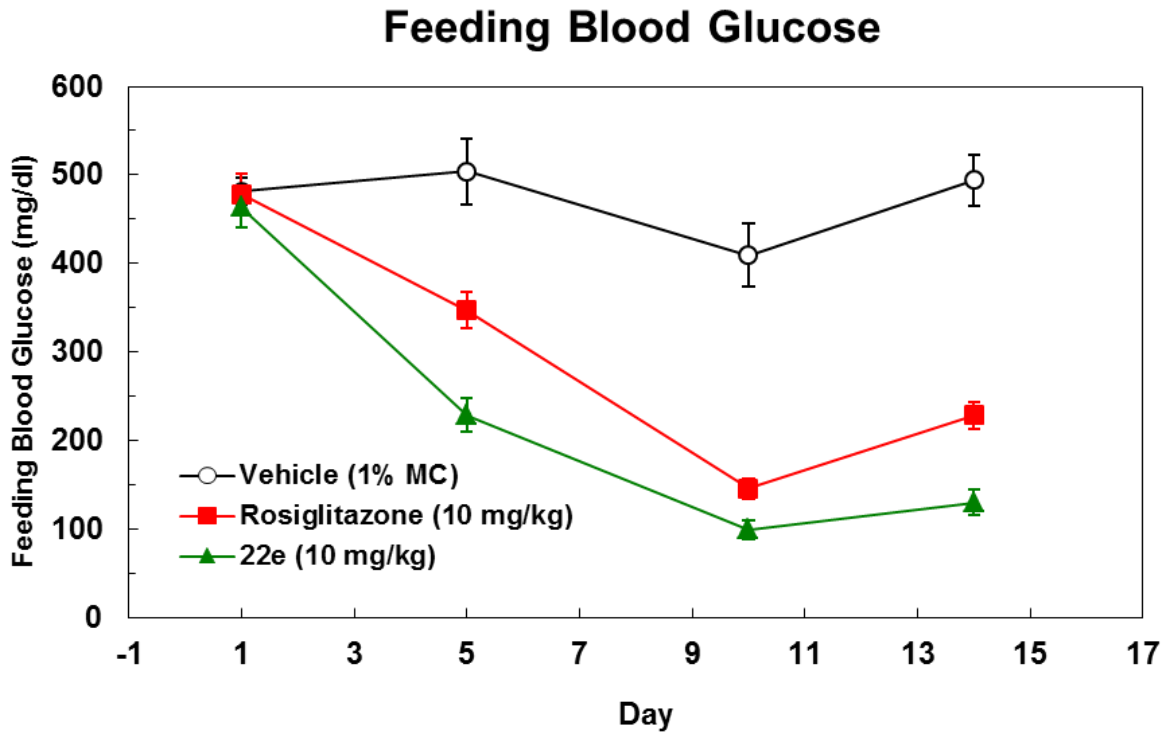


Figure 6. Plasma glucose decrease test in *db/db* mice. Plasma glucose decrease test was conducted with 14 days of treatment.

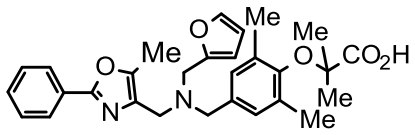
Table 4. Parameters *in vivo* study for compound **22e** on *db/db* mice

Exp.	Compds	Dose (mg/kg)	Plasma Glucose[a] (mg/dl)	change (%)	Plasma Triglyceride[a] (mg/dl)	change (%)	BW change (%)
1	vehicle		494 ± 106		165 ± 116		
	22e	10	130 ± 51	-74[b]	20 ± 12	- 88[b]	- 7.6
	Rosiglitazone	10	228 ± 50	-54[b]	69 ± 24	- 58[b]	+ 10.1[c]
2	vehicle		487 ± 57		152 ± 41		
	1a	30	365 ± 13	-25[c]	67 ± 23	- 56[d]	+ 8.4[b]

[a] Mean ± SD (n = 6). [b] $p < 0.001$, [c] $p < 0.01$, [d] $p < 0.05$ vs. vehicle control (t-test).

第 2 章　CYP 阻害作用減弱に導く化合物の合成と構造活性相関

体重増加を示さずに強い血糖低下作用と脂質プロファイル改善作用を示した化合物 **22e** であったが、生体内代謝酵素である CYP3A4 を強力に阻害することが明らかとなった **(Figure 4)**。



Compound 22e

PPARα : EC_{50} =	**1.7 nM**
PPARγ : EC_{50} =	**4.7 nM**
log D :	**2.9**[a)]
Metabolic stability :	**61 %**[b)]
CYP3A4 inhibitoin :	**75 %**[c)]

Figure 7. Profile of compound **22e**

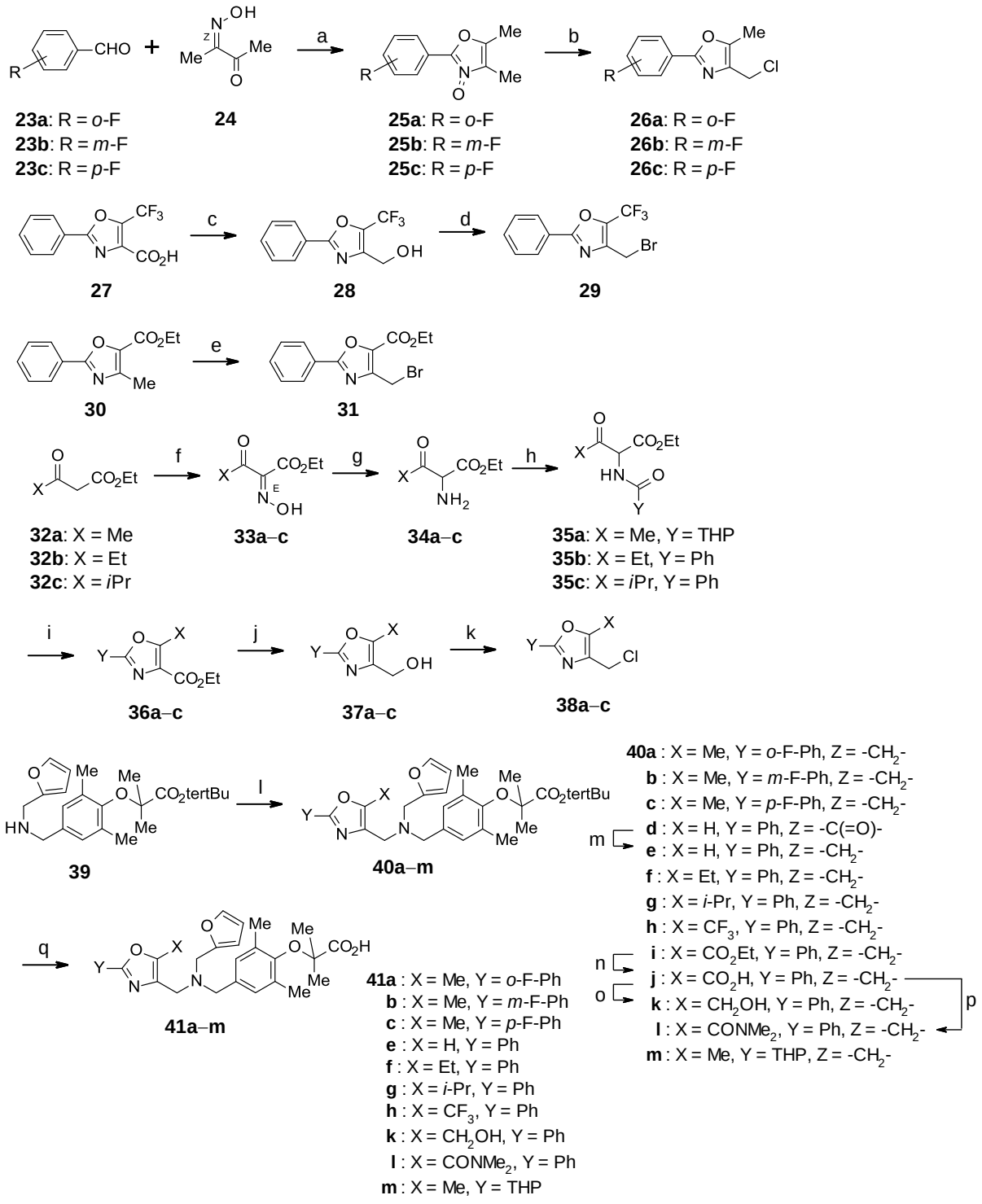
a) Value at pH 7.4. *b*) % remaining value using human microsomes. *c*) % inhibition value at 10 μM concentration of compound **22e**.

CYP は、薬物の代謝において重要な役割を担っており、それが薬物自身によって、あるいは薬物の代謝物によって阻害されるようなことがあると、薬物自身または併用する薬物の代謝過程に影響を及ぼし、血中コントロールを困難にする薬物間相互作用（DDI）を惹起する危険性がある [23)]。DDI が原因で、薬物の臨床開発が中止され、また一旦承認されていたとしても市場から撤退することもある。それゆえに、DDI リスクを早期に評価し見極めることは、臨床研究を円滑に進行させるために非常に重要である。特にメタボリックシンドロームに位置づけられる 2 型糖尿病患者は、様々な疾患を併発し、他の薬物を併用していることが多いことから DDI リスクの危険性が高い。

著者は、構造変換による物理化学的性質の変化が導く化合物の CYP3A4 阻害作用への影響に焦点をあて、CYP3A4 の直接阻害や代謝物による阻害（MBI）リスクの低減を志向した誘導体展開について報告する。

第 1 節　CYP 阻害作用減弱に導く化合物の合成

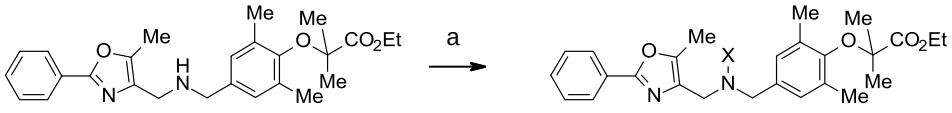
まず脂溶性部分の置換基効果を確認するために **41a—m** をデザインし合成した **(Scheme 5)**。ジアセチル モノオキシム **24** と対応するアルデヒド **23a—c** と反応させた後、得られた *N*-オキシド体をオキシ塩化リンで処理することによりクロル体 **26a—c** を合成した。化合物 **29** は、Borane-THF 錯体を用いて化合物 **27**[24] のカルボン酸を還元しアルコール体 **28** へと導いた後、臭素化することにより合成した。**30**[25] のメチル基に対し、NBS/AIBN を用いてラジカル的臭素化反応を行い **31** を得た。**38a—c** の合成は、Soukup らの方法を参考に合成した [26]。詳細には、まず *β*-ケトエステル **32a—c** のニトロソ化によってオキシムを形成させ、それを塩酸酸性条件下パラジウム炭素を用いて水素化分解を導き、1 級アミンの **34a—c** を合成した。対応する市販の酸クロライドを用いて **34a—c** のアシル化反応を実施した後、脱水剤としてオキシ塩化リンを用ることでオキサゾール環 **36a—c** を構築した。その後、水素化ホウ素リチウムを用いて **36a—c** のエステル基を還元し、得られた水酸基をチオニルクロライドでクロル化することによって **38a—c** へと導いた。2 級アミン **39** は、上記合成した脂溶性部と DMF 中 EDCI/HOBt あるいは DMF 中 K_2CO_3 を用いて縮合した後、エステル基を加水分解することによって目的とする **41a—m** を合成した。



Scheme 5. Reagents and conditions: (a) 4M HCl in EtOAc, rt, **25a**: 81%, **25b**: 85%, **25c**: 47%; (b) $POCl_3$, $CHCl_3$, rt, **26a**: 79%, **26b**: 14%, **26c**: 42%; (c) 1M BH_3-THF solution, THF, rt, 87%; (d) NBS, PPh_3, DCM, rt, 92%; (e) NBS, AIBN, CCl_4, reflux, 45%; (f) $NaNO_2$, AcOH, rt; (g) 10% Pd/C, 1N HCl-EtOH solution, rt; (h) Corresponding acid chloride reagent, TEA, DCM, rt, **35a**: 48% (3 steps), **35b**: 78% (3 steps), **35c**: 67% (3 steps); (i) $POCl_3$, reflux, **36a**: 63%, **36b**: 88%, **36c**: 90%;

(j) $LiBH_4$, THF, reflux; (k) $SOCl_2$, $CHCl_3$, rt, **38a**: 18% (2 steps), **38b**: 86% (2 steps), **38c**: 89% (2 steps); (l) Corresponding lipophilic tail moieties, EDCI, HOBt, DMF, rt or K_2CO_3, DMF, 40°C, 22%－91%; (m) 1M BH_3-THF solution, THF, 50°C, 50%; (n) 1N NaOH aq. THF, 50°C; (o) (1) *iso*-butyl chloroformate, NMM, THF, -40°C; (2) $NaBH_4$, rt, 65% (2 steps); (p) Dimethylamine, WSCl, HOBt, DMF, rt, 94%; (q) 4M HCl in Dioxane, DCM, rt, 37%－89%.

フラン環以外のアリール基については、2 級アミン **42** と対応するアルデヒドを用いた還元的アミノ化反応、引き続く加水分解によって **43a—c** へと導いた (**Scheme 6**)。



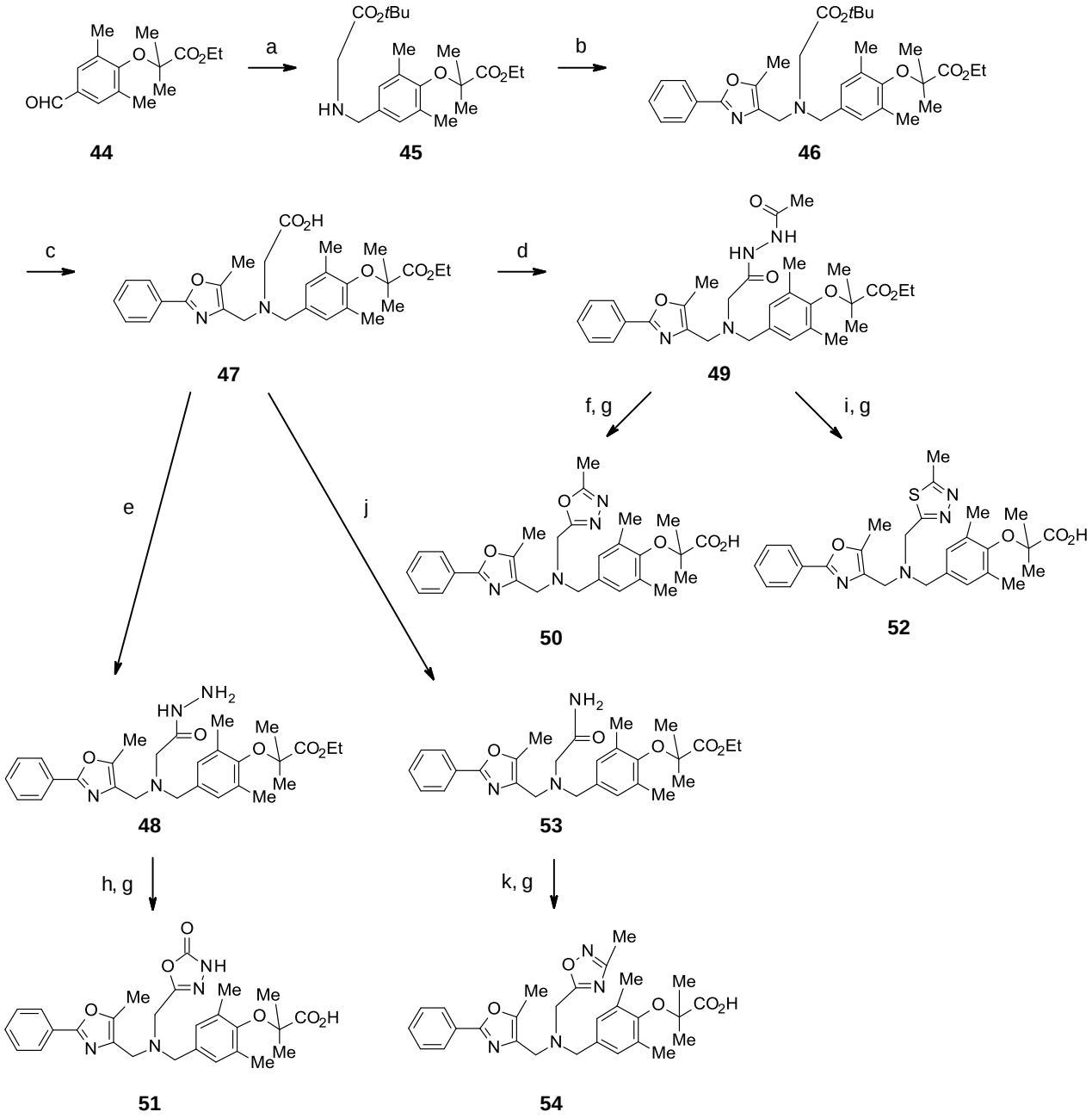
42

43a: X = oxazol-2-ylmethyl
b: X = thiazol-2-ylmethyl
c: X = *N*-methylimidazol-2-ylmethyl

Scheme 6. Reagents and conditions: (a) (1) Corresponding commercially available aldehyde reagents, $NaBH(OAc)_3$, DCM, rt; (2) NaOH, MeOH, rt, **43a**: 56%, **43b**: 32%, **43c**: 44%.

鍵中間体 **47** を経由したヘテロ環の合成を **Scheme 7** に示した。アルデヒド **44** とグリシン *tert*-ブチルエステルを硫酸マグネシウム存在下 THF 中加熱還流することでイミンを形成させ、引き続き水素化ホウ素ナトリウムを用いて還元することで、2 級アミン **45** を合成した。DMF 中炭酸カリウム存在下 **45** に脂溶性部分として 4-(クロロメチル)-5-メチル-2-フェニル-1,3-オキサゾールを反応させ、酸加水分解により共通鍵中間体となるモノエステル体 **47** を合成した。**47** に対しアセトヒドラジドを DMF 中 EDCI/HOBt を縮合剤として用いたアミド化反応を実施することにより、**49** を合成した。穏和な脱水剤である PPh_3/C_2Cl_6 を用いて **49** を 1,3,4-オキサジアゾール環へと環化し、その後加水分解することにより **50** へと導いた。また **49** を THF 中 Lawesson's reagent と反応させることでチアゾール環を構築し、引き続く加水分解により **52** を合成した。中間体 **47** は、Boc 保護されたヒドラジンをアミド化後、Boc 基の脱保護により **48** へと導いた。**48** の環化をトリホスゲンを用いて実施し、引き

続く加水分解によりオキサジアゾロン化合物 **51** へと導いた。さらに中間体 **47** は、塩化アンモニウムを用いてカルボキサミド体 **53** へと導いた。**53** と*N,N*-ジメチルアセトアミド ジメチル アセタールを縮合しアシルアミジン中間体へと導いた後、ヒドロキシルアミンを作用させ 1,2,4-オキサジアゾール環を構築し、加水分解することで **54** を良好な収率で合成した。



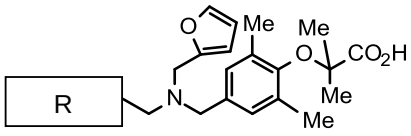
Scheme 7. Reagents and conditions: (a) (1) *tert*-butylglycinate, $MgSO_4$, THF, reflux; (2) $NaBH_4$, MeOH, rt, 95%; (b) 4-(Chloromethyl)-5-methyl-2-phenyl-1,3-oxazole, K_2CO_3, MeCN, reflux, 81%; (c) 4M HCl-dioxane solution, DCM, 0°C, 82%; (d) Acetohydrazide, EDCI, HOBt, DMF, rt; (e) (1)

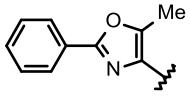
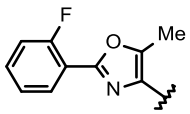
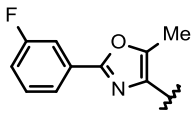
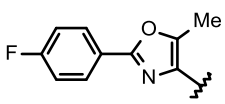
Hydrazinecarboxylic acid tert-butyl ester, EDCI, HOBt, DMF, rt; (2) TFA, DCM, rt; (f) PPh_3, C_2Cl_6, TEA, DCM, rt; (g) NaOH, MeOH, reflux, **50**: 70% (3 steps), **51**: 84%, **52**: 56%, **54**: 71%; (h) Triphosgene, 1,4-dioxane, 60°C, 84% (2 steps); (i) Lawesson's reagent, THF, reflux, 88% (2 steps); (j) NH_4Cl, EDCI, HOBt, DMF, rt; (k) (1) *N*,*N*-dimethylacetamide dimethyl acetal, 120°C; (2) Hydroxylamine (50% aqueous solution), acetic acid (70% aqueous solution), rt, 88% (2 steps).

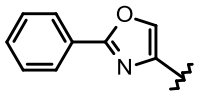
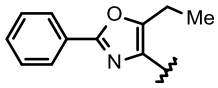
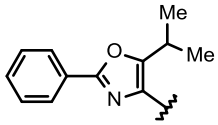
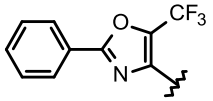
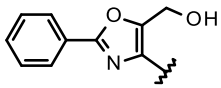
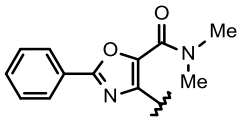
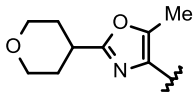
第 2 節　CYP 阻害作用減弱に導く化合物の *in vitro* 評価

これまでに、脂溶性の高い化合物は CYP3A4 の直接阻害作用を示す傾向にあることが報告されている[27]。著者のフラン誘導体においても脂溶性とCYP3A4阻害に関連性があるか確認するために、脂溶性に着目して誘導体展開を実施した (**Table 5**)。その結果、低脂溶性化合物である **41k**, **41l**, **41m** において明らかな減弱効果を確認することができた。さらに Y 軸に CYP3A4 阻害率と X 軸に pH7.4 における脂溶性の指標である LogD 値をプロットした結果、CYP 阻害率と脂溶性に明確な相関が確認され、今後の誘導体展開において LogD 値を 2 以下に抑えることが望ましいことが想定された (**Figure 8**)。

Table 5. *In vitro* activity and physicochemical properties of compound **1** and **20a－m**.



Compd	R	PPARα EC_{50} (nM)	PPARγ EC_{50} (nM)	Log D[a)]	CYP3A4 Direct Inhibition[b)] (%)	MBI Remaining[c)] (%)
22e		1.7	4.7	2.9	75	91
41a		2.6	1.2	2.7	53	63
41b		1.5	0.39	3.1	53	60
41c		0.81	0.51	3.2	65	65

41e		8.1	18	2.5	37	78
41f		0.85	0.38	3.4	81	NT[d)]
41g		4.6	8.8	4.1	77	NT
41h		2.8	1.6	4.4	71	NT
41k		5.5	11	1.7	24	NT
41l		14	210	1.7	43	77
41m		8.5	1.5	1.0	< 10	NT

a) Log D values were determined from the partition coefficient for 1-octanol/phosphate buffer saline (PBS) at pH 7.4. *b*) CYP3A4 direct inhibition values were shown in % inhibition at 10 μM concentration of the compounds for 60 min incubation. *c*) MBI values were shown in % remaining at 100 μM concentration of the compounds reacted with CYP3A4 probe substrates after 30 min preincubation in human liver microsomes. *d*) Not tested.

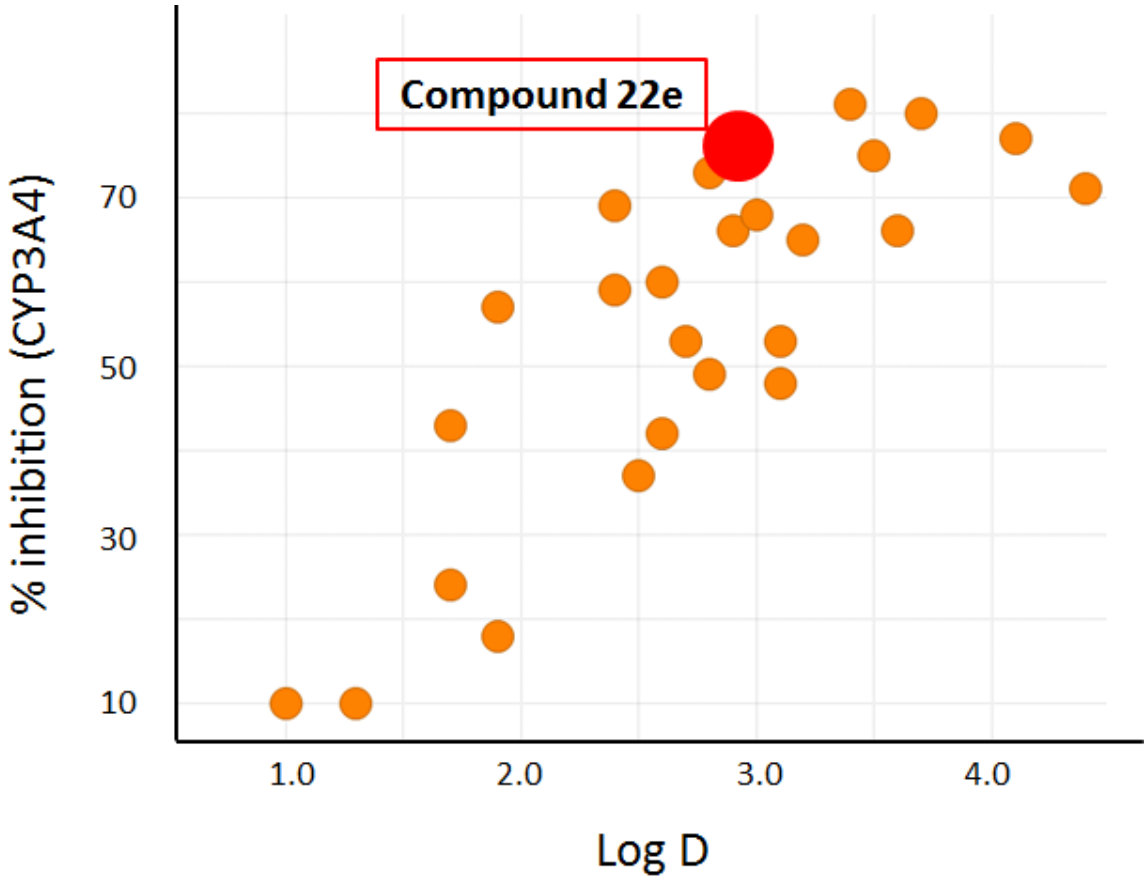
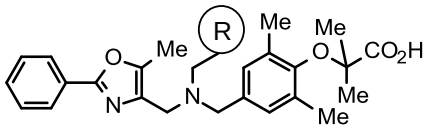


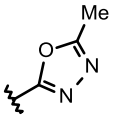
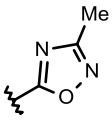
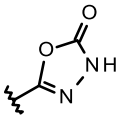
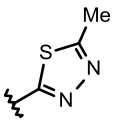
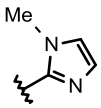
Figure 8. A diagram showing the relationship between % inhibition of CYP3A4 and Log D values at pH 7.4 of furan derivatives.

さらに、化合物自身による直接阻害ではなく、ヒト肝ミクロソーム存在下にて生成する代謝物による酵素阻害作用（MBI）において、酵素活性の残存率が 80%以下の場合 MBI 陽性と判断する自社基準を用いた結果、**Table 5** に示した多くのフラン誘導体は、CYP3A4 に対して MBI を示した。

そこで著者は、これまでの研究 [28] において MBI の原因構造になりうると推定されているフラン環を他のヘテロ環へ変換する試みを行った **(Table 6)**。その結果、変換した全てのヘテロ環化合物において MBI 陰性を示し、MBI にはフラン環が関与していたことが明らかとなった。

Table 6. *In vitro* activities and physicochemical properties of derivatives with novel hetero-rings.



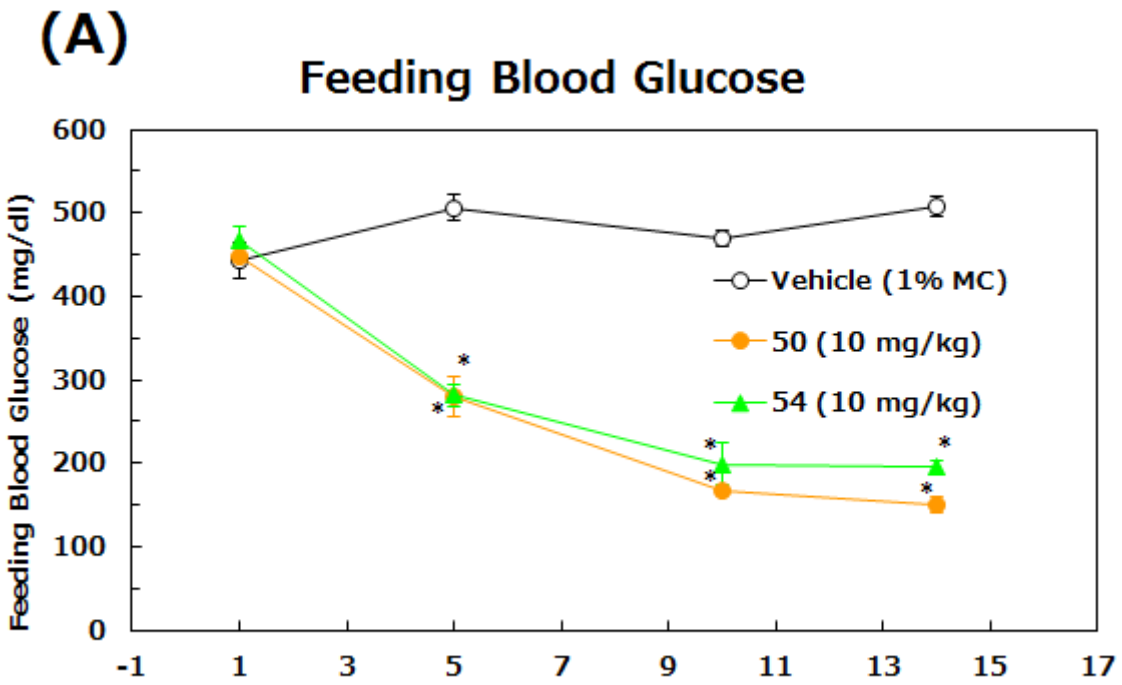
Compd	R	PPARα EC_{50} (nM)	PPARγ EC_{50} (nM)	Log D[a)]	CYP3A4 Direct Inhibition[b)] (%)	CYP3A4 MBI Remaining[c)] (%)
43a		1.6	5.5	1.8	22	88
50		2.9	33	1.1	28	110
54		2.7	6.9	1.8	25	83
51		17	93	0.9	15	124
43b		2.4	8.8	2.6	42	93
52		1.9	4.2	1.6	NT[d)]	84
43c		110	110	NT	NT	NT

a) Log D values were determined from the partition coefficient for 1-octanol/phosphate buffer saline (PBS) at pH 7.4. *b*) CYP3A4 direct inhibition values were shown in % inhibition at 10 μM concentration of the compounds for 60 min incubation. *C*) MBI values were shown in % remaining at 100 μM concentration of the compounds reacted with CYP3A4 probe substrates after 30 min preincubation in human liver microsomes. *d*) Not tested.

第 3 節　CYP 阻害作用減弱に導く化合物の *in vivo* 評価

Table 6 に示した複素環化合物の中で 1,3,4-オキサジアゾール構造を有する **50** は、PPARγ (EC_{50} = 33 nM) よりも PPARα (EC_{50} = 2.9 nM) により強力にアゴニスト活性を示し、著者の目指す化合物プロファイルを示した。つまり強力な PPARα 活性により PPARγ の活性化による副作用、例えば体重増加を抑制できる可能性が示唆された。

そこで著者は、化合物 **50** に構造が類似しつつも PPARγ に強力に作用する (EC_{50} = 6.9 nM) 化合物 **54** をカウンターパートに設定し、化合物 **50** と **54** の *in vivo* プロファイルの確認試験を *db/db* マウスを用いて実施した。その結果を **Figure 9** と **Table 7** に示した。両化合物とも同等の血糖低下作用を示した一方で、副作用の発現に大きな差が生じた。つまり著者の仮説どおりに PPARα により優位に活性を示す化合物 **50** の方が副作用である体重増加をより抑制する結果を得ることが出来た (dosed orally at 10 mg/kg in *db/db* mice [six per group] for 14 days)。



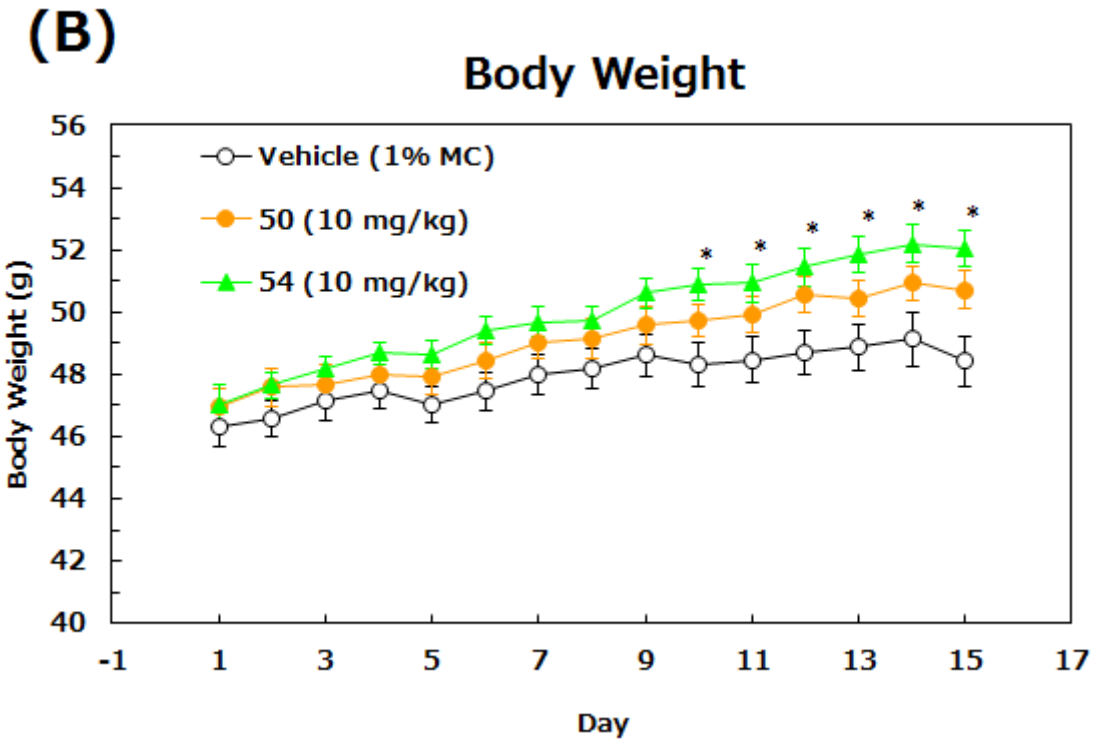


Figure 9. Plasma glucose decrease test in *db/db* mice. Blood glucose change (A) and body weight change (B) were conducted with 14 days of treatment.

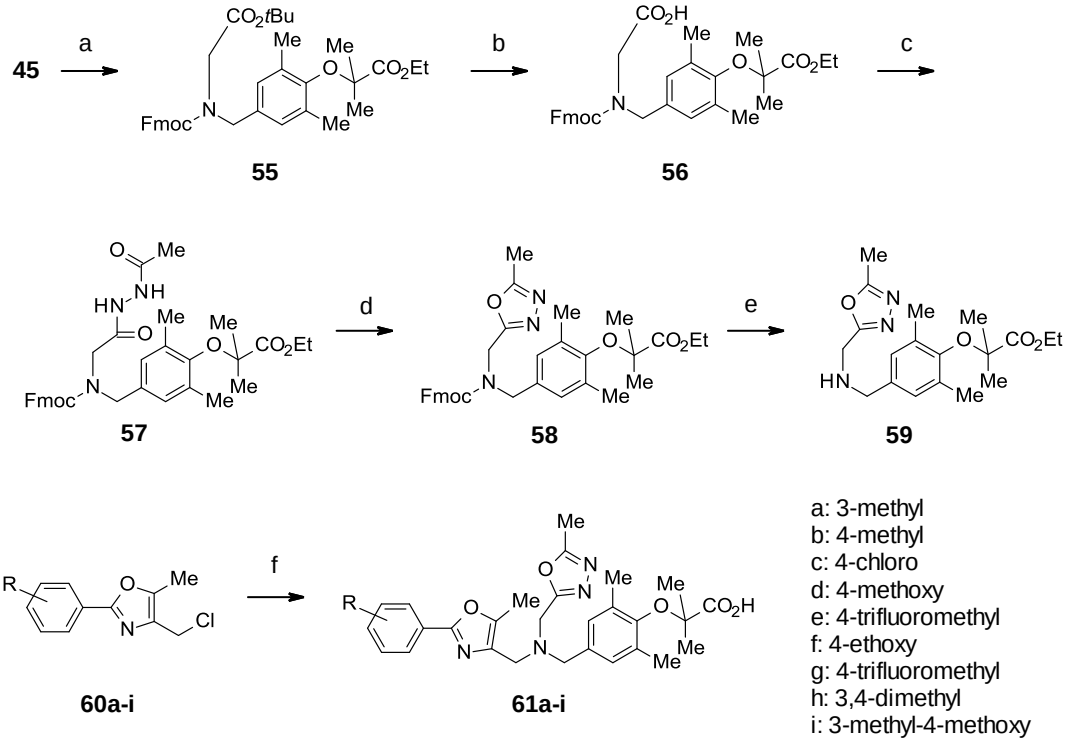
Table 7. Parameters of *in vivo* study with **50** and **54** in *db/db* mice

Exp.	Compds	Dose (mg/kg)	Plasma Glucose[a)] (mg/dl)	Change (%)	Plasma Triglyceride[a)] (mg/dl)	Change (%)	BW change (%)
1	vehicle		404 ± 28		227 ± 154		
	50	10	151 ± 39	− 63[b)]	79 ± 15	− 65[b)]	+ 4.8
	54	10	195 ± 32	− 52[b)]	76 ± 16	− 67[b)]	+ 7.6[d)]
	Rosiglitazone	10	174 ± 50	− 57[b)]	90 ± 38	− 60[b)]	+ 11.2[c)]

a) Mean ± standard deviation (n = 6). *b*) $P < 0.001$. *c*) $P < 0.01$. *d*) $P < 0.05$. versus vehicle control (*t*-test).

第 4 節　オキサジアゾール化合物の最適化研究

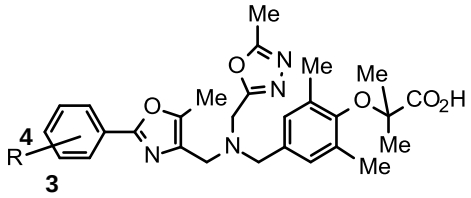
化合物 **50** が好ましい効果を示したので、著者はこの化合物を基に更なる最適化研究を実施した。脂溶性部ベンゼン環上に様々な置換基を導入した化合物 **61a—f** の合成を **Scheme 8** に示した。**45** の Fmoc 保護、引き続き酸性条件での加水分解によりモノカルボン酸体 **56** を合成した。化合物 **50** と同様に 1, 3, 4-オキサジアゾール環を構築し **58** を獲得した。ジエチルアミンを用いて Fmoc 基を脱保護し **59** へと導いた後、Scheme 5 のクロライド **26** と同様に合成した **60a—f** を作用させ、最後に加水分解することにより目的とする **61a—f** を合成した。



Scheme 8. Reagents and conditions: (a) 9-Fluorenylmethylsuccinimidyl carbonate, MeCN, rt, 94%; (b) TFA, DCM, rt; (c) Acetohydrazide, EDCI, HOBt, MeCN, rt; 67% (2 steps); (d) PPh_3, C_2Cl_6, TEA, DCM, rt, 94%; (e) DBU, THF, 0^{o}C, 82%; (f) (1) **59**, Cs_2CO_3, DMF, KI, 60°C; (2) NaOH, MeOH, reflux, 24%－61%.

第 5 節　オキサジアゾール誘導体の *in vitro* 評価

Table 8. *In vitro* activity and physicochemical data of compounds **61** substituted at 3- and/or 4-position of the phenyloxazole ring.



Compd	R	PPARα EC_{50} (nM)	PPARγ EC_{50} (nM)	Log D[a)]	CYP3A4 Direct Inhibition[b)] (%)	CYP3A4 MBI Remaining[c)] (%)
61a	3-CH_3	0.51	2.7	1.6	47	91
61b	4-CH_3	0.55	18	1.4	32	101
61c	4-Cl	1.2	26	1.6	32	99
61d	4-OCH_3	0.56	22	1.1	25	104
61e	4-OCF_3	0.47	0.54	2.2	69	NT[d)]
61f	4-OC_2H_5	0.67	3.6	1.5	61	88
61g	4-CF_3	0.47	12	1.9	74	98
61h	3,4-CH_3	0.19	1.8	1.8	53	89
61i	3-CH_3-4-OCH_3	0.15	0.69	1.7	57	NT

a) Log D values were determined from the partition coefficient for 1-octanol/phosphate buffer saline (PBS) at pH 7.4. *b*) Direct CYP3A4 inhibition values were shown in % inhibition at 10 μM concentration of the compounds for 60 min incubation. *c*) MBI values were shown in % remaining at 100 μM concentration of the compounds reacted with CYP3A4 probe substrates after 30 min preincubation in human liver microsomes. *d*) Not tested.

Table 8 に示した 1,3,4-オキサジアゾール誘導体はいずれも非常に強い PPARα 活性を示した。脂溶性部ベンゼン環上の 3 位にメチル基を導入した **61a** は、4 位にメチル基を導入した **61b** に比べ PPARγ 活性が強い結果となった。同様の結果が **61h** や **61i** にも観察され、3 位への置換基導入が PPARγ 活性を向上させる傾向を見出した。また 4 位でもトリフルオロメトキシ基 (**61e**) やエトキシ基 (**61i**) のように嵩高い置換基を導入すると PPARγ 活性が強まり、選択性が低下する結果を得た。

物理化学的性質の観点からは、フラン環を 1,3,4-オキサジアゾール環に変換することによって低脂溶性化を可能にした。1,3,4-オキサジアゾール誘導体もフラン誘導体と同様に LogD が高い (**61e**: logD = 2.2, **61g**: logD = 1.9) と強い CYP3A4 阻害活性を示すのに対して、脂溶性が低下した化合物に関しては CYP3A4 阻害活性を減弱化できる、フラン誘導体と同様の結果を得た。さらに今回のオキサジアゾール誘導体に関しては、脂溶性の高低に関わらず MBI に陰性の結果を得たことから、フラン誘導体の MBI 作用はフラン環が原因であったことが示唆された。

第 6 節　オキサジアゾール誘導体の *in vivo* 評価

すぐれた物理化学的プロファイルと強力なアゴニスト活性を有する1,3,4-オキサジアゾール誘導体の *in vivo* 研究を実施した {3 mg/kg QD for 14 days in *db/db* mice (six per group)}。PPARα 優位に活性を示す全ての化合物において、際立った体重増加を引き起こすことなく血中グルコースや血中トリグリセリドを顕著に低下させる結果を得た (**Table 9**)。

Table 9. Parameters of *in vivo* study with 1,3,4-oxadiazole derivatives in *db/db* mice.

Exp.	Compds	Dose (mg/kg)	Plasma Glucose[a)] (mg/dl)	Change (%)	Plasma Triglyceride[a)] (mg/dl)	Change (%)	BW change (%)
1	vehicle		404 ± 28		258 ± 104		
	61b	3	134 ± 35	− 67[b)]	60 ± 14	− 77[b)]	− 1.7
	61c	3	159 ± 41	− 61[b)]	76 ± 21	− 71[b)]	− 1.1
	Rosiglitazone	10	203 ± 42	− 50[b)]	92 ± 26	− 64[b)]	+ 10.2[c)]
2	vehicle		564 ± 45		198 ± 217		
	61a	3	263 ± 31	− 53[b)]	61 ± 17	− 69[b)]	+ 1.2
	61d	3	220 ± 57	− 61[b)]	68 ± 24	− 66[b)]	+ 0.6
3	vehicle		552 ± 29		239 ± 232		
	61f	3	195 ± 48	− 65[b)]	65 ± 18	− 73[b)]	+ 2.1
	61h	3	135 ± 49	− 76[b)]	68 ± 12	− 71[b)]	− 2.1
4	vehicle		548 ± 51		209 ± 91		
	61g	3	162 ± 23	− 70[b)]	59 ± 17	− 72[b)]	− 2.6

a) Mean ± standard deviation (n = 6). *b*) $p < 0.001$. *c*) $p < 0.01$ versus vehicle control (*t*-test).

DDI リスクを有する CYP3A4 の直接あるいは代謝的阻害を回避した 1,3,4-オキサジアゾール化合物 **61b** だったが、これらオキサジアゾール誘導体は化学的に不安定であるという新たな問題が浮上した。まず何が原因かを突き止めるにあたって、日本薬局方 1 液 (pH 1.2; JP1)、日本薬局方 2 液 (pH 6.8; JP2)、Britton-Robinson バッファー (pH 4.0) を用いて化合物の化学的安定性を調査した。その結果、胃液を想定した強酸性の JP1 において、1,3,4-オキサジアゾール環が経時的に分解することが明らかとなった (**Figure 10**)。

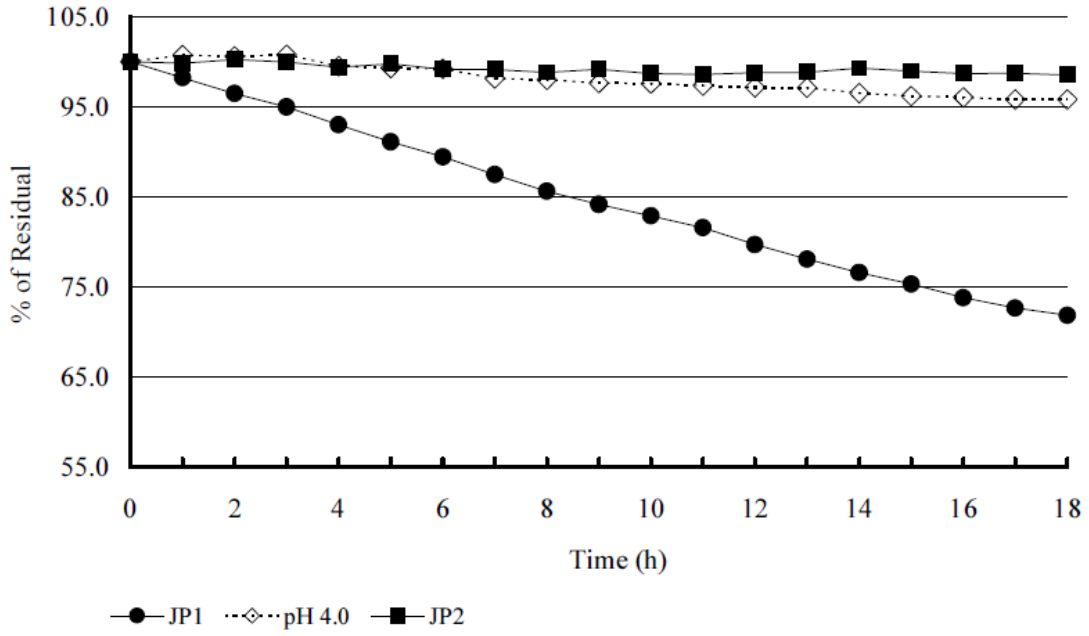
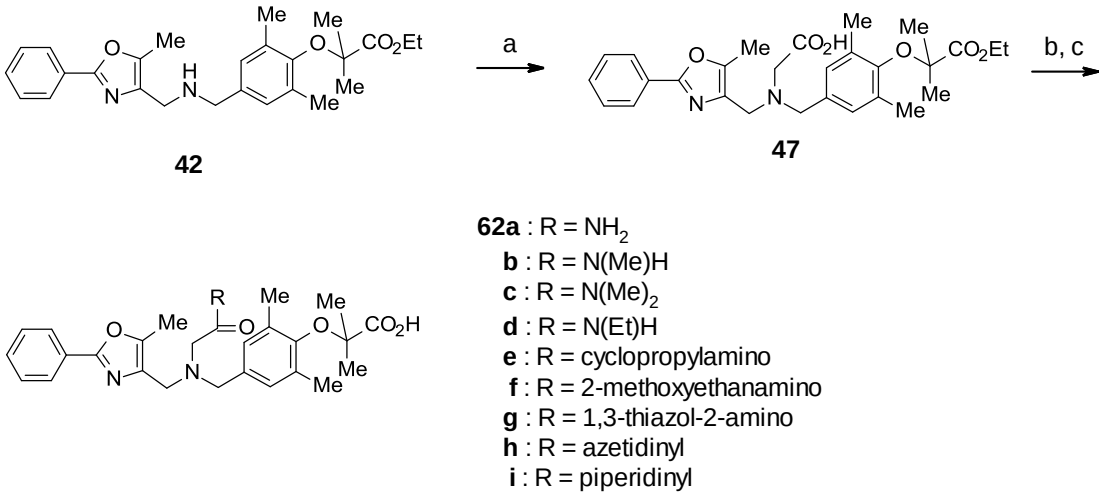


Figure 10. Time Course of Residual Compound Contents in Various Aqueous Solutions at 37ºC.

経口投与剤を目指した医薬品研究の中で、この酸に対する不安定性は問題であるため、早急な解決が求められた。そこで著者は、1,3,4-オキサジアゾール環を化学的に安定な他の側鎖への変換の可能性を追求し研究を始めた。

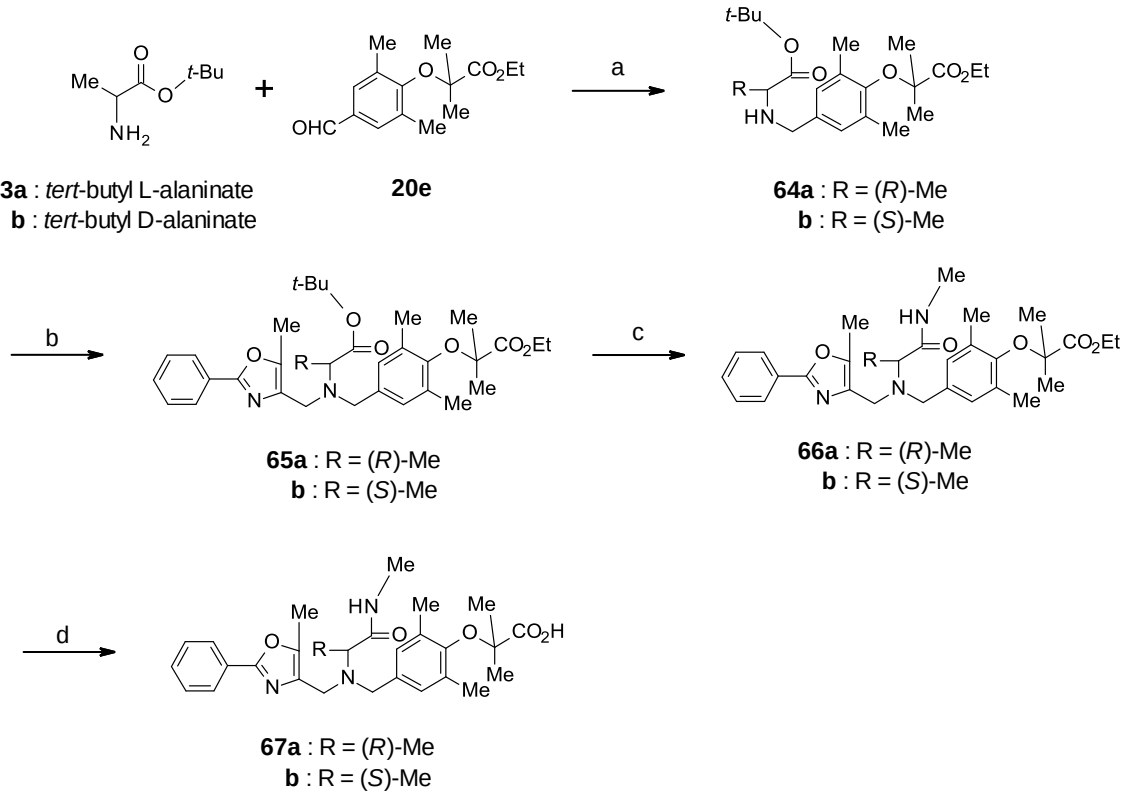
第 1 節　化学的安定性を向上した化合物の合成

はじめに、オキサジアゾール基の変換としてアミド基の可能性について検討するために化合物 **62a-i** を合成した (**Scheme 9**)。メタノール中 $NaBH(OAc)_3$ を用いたグリオキシル酸と 2 級アミン **42** の還元的アルキル化は共通鍵中間体となるカルボン酸体 **47** を与えた。DMF 中 EDCI と HOBt を用いた **47** と対応するアミンとのアミド化反応の後、エステル基を加水分解することにより目的とする **62a-i** へと導いた。



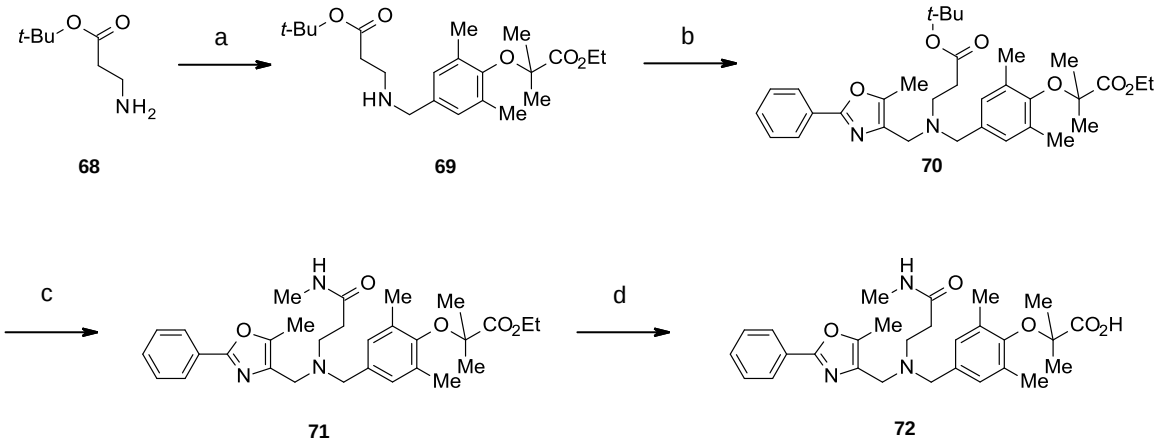
Scheme 9. Reagents and conditions: (a) Glyoxylic acid, $NaBH(OAc)_3$, MeOH, rt, 91%; (b) Corresponding commercially available amino reagents, EDCI, HOBt, DMF, rt; (c) NaOH, MeOH, 50°C, **62a**: 59% (2 steps), **62b**: 66% (2 steps), **62c**: 52% (2 steps), **62d**: 36% (2 steps), **62e**: 52% (2 steps), **62f**: 43% (2 steps), **62g**: 59% (2 steps), **62h**: 30% (2 steps), **62i**: 61% (2 steps).

α 位にメチル基を導入したアラニン誘導体の合成を **Scheme 10** に示した。アルデヒド **20e** とアラニン *tert*-ブチルエステルをエタノール中加熱還流することによりイミンを形成させ、$NaBH_4$ 処理することによって 2 級アミン **64** (a, b) へと導いた。メタノール中 $NaBH(OAc)_3$ を用いて市販されているアルデヒドを 2 級アミンに還元的に導入し、3 級アミン体 **65** (a, b) を得た。酸加水分解後、EDCI/HOBt 条件においてメチルアミンを導入し誘導した **66** (a, b) のエステル基をアルカリ加水分解することにより **67a** と **67b** を合成した。



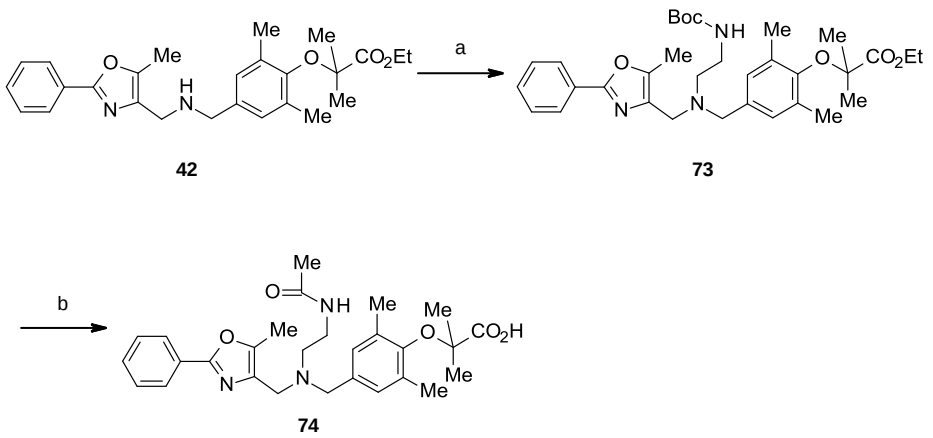
Scheme 10. Reagents and conditions: (a) (1) THF, reflux; (2) $NaBH_4$, MeOH, rt, **64a**: 93%, **64b**: 80%; (b) 5-methyl-2-phenyl-1,3-oxazole-4-carbaldehyde, $NaBH(OAc)_3$, MeOH, rt, **65a**: 58%, **65b**: 73%; (c) (1) 4M HCl in dioxane, DCM, rt; (2) methylamine, NMM, EDCI, HOBt, DMF, rt, **66a**: 78%, **66b**: 27%; (d) NaOH, MeOH, reflux, **67a**: 67%, **67b**: 33%.

一炭素増炭した化合物 **72** の合成を **Scheme 11** に示した。アルデヒド体 **20e** と市販の 3-アミノプロピオン酸 *tert*-ブチルエステル **72** の共存下で加熱還流を行いイミンを形成させた後に $NaBH_4$ 処理することにより 2 級アミン体 **68** へと導いた。アセトニトリル中炭酸カリウム存在下 **69** と 4-(クロロメチル)-5-メチル-2-フェニル-1,3-オキサゾールを反応させることにより **70** を与えた。**70** の *tert*-ブチルエステルを酸加水分解に付した後、メチルアミンとアミド化することにより **71** へと導いた。最後にエチルエステル基をアルカリ加水分解することにより **72** を合成した。



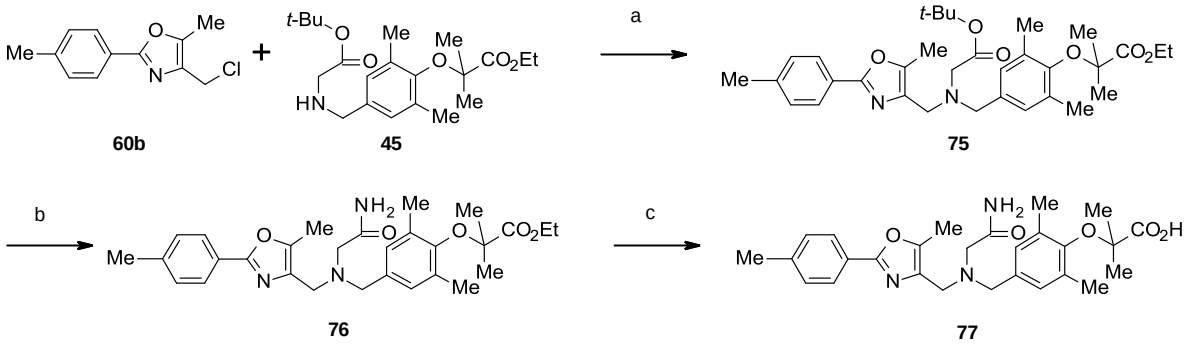
Scheme 11. Reagents and conditions: (a) (1) **20e**, THF, reflux; (2) $NaBH_4$, MeOH, 0°C; (b) 4-(chloromethyl)-5-methyl-2-phenyl-1,3-oxazole, K_2CO_3, MeCN, 70°C, 87% (2 steps); (c) (1) 4M HCl in dioxane, DCM, rt; (2) methylamine, TEA, EDCI, HOBt, DMF, rt, 96%; (d) NaOH, MeOH, reflux, 80%.

リバースアミド化合物 **74** の合成を **Scheme 12** に示した。ジクロロメタン中 $NaBH(OAc)_3$ 存在下 2 級アミン **42** と *N*-Boc-2-アミノアセトアルデヒドを反応させることにより **73** を得た。**73** の Boc 基を TFA を用いて脱保護後、アセチル化を経てエチルエステル基を加水分解することにより **74** を合成した。



Scheme 12. Reagents and conditions: (a) *N*-Boc-2-aminoacetaldehyde, $NaBH(OAc)_3$, DCM, rt, 71%; (b) (1) TFA, DCM, rt; (2) AcCl, TEA, rt; (3) NaOH, MeOH, rt, 31% (2 steps).

化合物 **77** の合成を **Scheme 13** に示した。この化合物はクロル体 **60b** と 2 級アミン **45** を用いて化合物 **72** と同様に合成した。

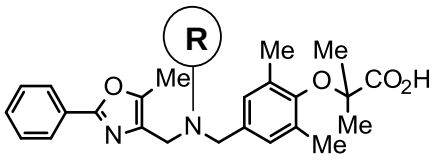


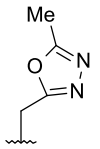
Scheme 13. Reagents and conditions: (a) K_2CO_3, MeCN, reflux, 98%; (b) (1) TFA, DCM, rt; (2) NH_4Cl, TEA, EDCI, HOBt, DMF, rt, 89%; (c) NaOH, MeOH, reflux, 46%.

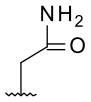
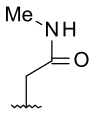
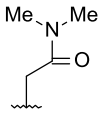
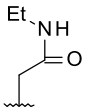
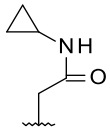
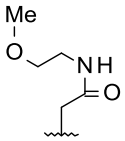
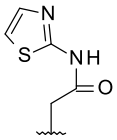
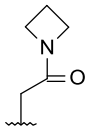
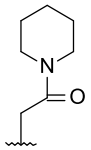
第 2 節　化学的安定性を向上した化合物の *in vitro* 評価

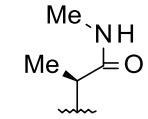
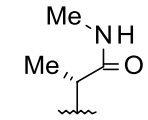
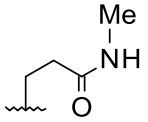
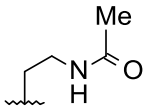
アミド誘導体の *in vitro* 評価を **Table 10** に示した。これまで著者は、化合物 **50** のような無置換フェニルオキサゾール誘導体の構造活性相関を多く構築してきており、また高脂溶性による偽陽性の結果を生じさせないためにも、今回のアミド誘導体の構造活性相関の構築にあたり、まず脂溶性の低い無置換フェニルオキサゾール構造に固定した。無置換アミド基あるいは短鎖アルキルアミド基を有する **62a—c** は許容可能なアゴニスト活性を示した。しかしながら嵩高いアミド基を有する化合物 **62d—g** は低活性しか示さなかった。さらにこれらの中で、メトキシエチルアミド体 **62f** やチアゾリルアミド体 **62g** は PPARα への選択性が低下する結果を得た。環状アミンを導入したアミド化合物 **62h** や **62i** もまた活性が大きく低下した。また α 位にメチル基を導入した **67a** や **67b**、一炭素増炭した **72**、リバースアミドとした **74** もまた活性が減弱する結果となった。以上の結果より、低級アルキルあるいは無置換のアミド体であればオキサジアゾール環の代替基として可能であることを見出した。

Table 10. *In Vitro* Activity and Physicochemical Properties of Compound **1** and Amide compounds.



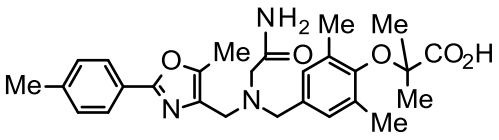
Compd.	R	PPARα EC_{50} (nM)	PPARγ EC_{50} (nM)	Log D[a)]	CYP3A4 Direct Inhibition[b)] (%)	MBI Remaining[c)] (%)	Solubility[e)] JP1 (μg/mL)
50		2.9	33	1.1	28	110	Decomposed

62a		41	92	0.8	< 10	98	> 740
62b		25	53	0.9	26	89	> 760
62c		24	110	1.1	16	122	> 720
62d		27	230	1.8	21	NT[d)]	> 640
62e		15	280	1.4	39	NT	> 890
62f		340	470	1.0	19	NT	> 920
62g		250	67	2.1	75	NT	810
62h		150	220	1.1	51	NT	> 690
62i		60	340	2.2	37	NT	> 810

67a		1500	2100	1.5	22	NT	> 700
67b		620	1400	1.6	22	86	> 780
72		180	1500	0.8	41	NT	> 860
74		290	1100	1.0	27	NT	> 570

a) The log D values were determined from the partition coefficient for 1-octanol/phosphate buffer saline (PBS) at pH 7.4. *b*) The CYP3A4 direct inhibition values were shown in % inhibition at a 10 μM concentration of the compounds for 60 min incubation. *c*) The MBI values were shown in % remaining at 100 μM concentration of the compounds reacted with CYP3A4 probe substrates after 30 min preincubation in human liver microsomes. *d*) Not tested. *e*) Water solubility was measured at JP1. **50** was decomposed. Amide derivatives were all stable under the acidic condition.

今回獲得した化合物の中で、特に脂溶性が低い化合物 **62a** のさらなる最適化を実施した。これまで行ってきた研究の中で、脂溶性部ベンゼン環上 4 位にメチル基を導入すると、PPARα 優位に両サブタイプを高活性化可能である知見を得てきた。そこで著者は、その構造活性相関の知見を基に化合物 **77** を合成した。その結果、**77** は PPARα (EC_{50} = 2.8 nM) に強い活性を示し、またそれは PPARγ (EC_{50} = 26 nM) に比べ優位性が高く、PPARγ 活性化による副作用を十分に抑えられる選択性であると示唆された。また **77** は、低脂溶性と高代謝安定性を示し、さらに CYP 阻害作用を回避するなど物理化学的、薬物動態学的プロファイルに優れた化合物であった (**Figure 11**)。



Compound 77

PPARα : EC_{50} =	**2.8 nM**
PPARγ : EC_{50} =	**26 nM**
log D :	**1.3**[a)]
Metabolic stability :	**98 %**[b)]
CYP3A4 Direct Inhibitoin :	**19 %**[c)]
MBI Remaining :	**88 %**[d)]
JP1 solubility :	**870 ug/mL**

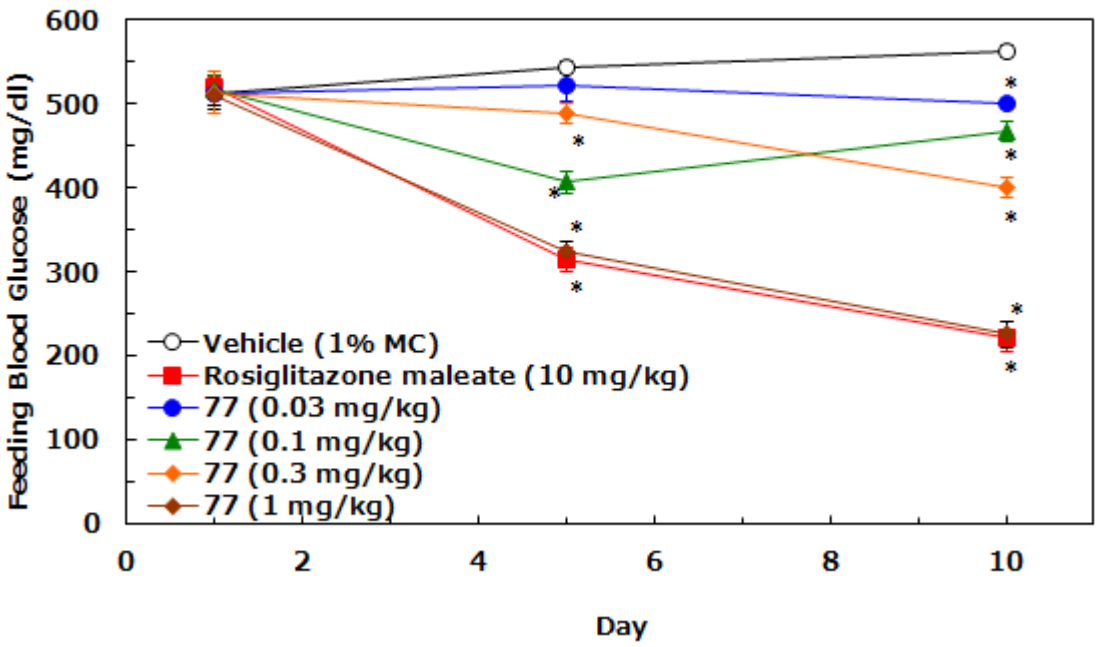
Figure 11. Profile of Compound **77**

a) The value at pH 7.4. *b*) The % remaining value using human microsomes. *c*) The % inhibition value at a 10 μM concentration of compound **77**. *d*) The % remaining value at a 100 μM concentration of compound **77** reacted with CYP3A4 probe substrates after 30 min preincubation in human liver microsomes.

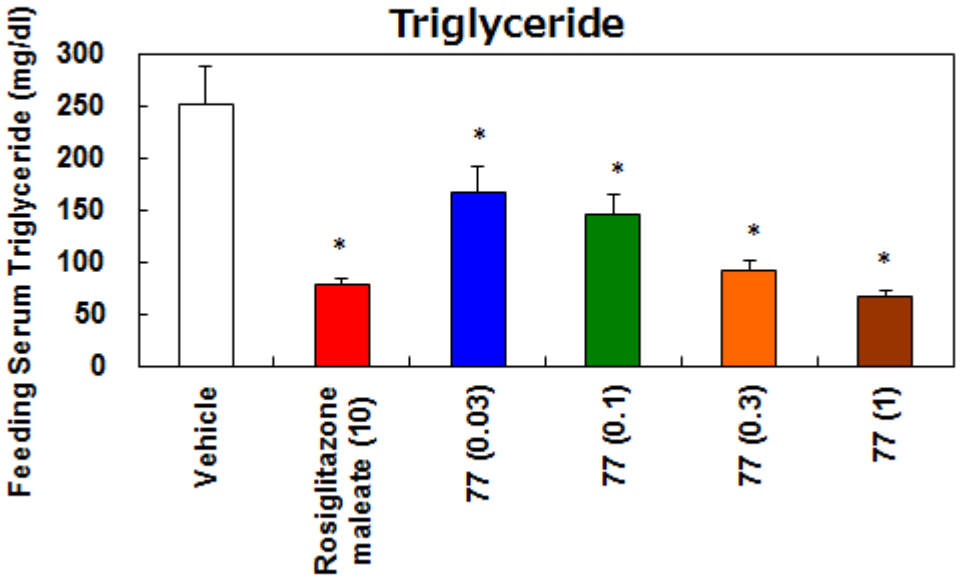
第 3 節　化学的安定性を向上した化合物の *in vivo* 評価

選択的な PPARγ 活性化薬である Rosiglitazone を対照薬とし、**77** の *in vivo* 試験を 2 型糖尿病モデルである *db/db* マウスを用いて実施した。両薬剤とも 1 日 1 回経口投与の 10 日間連続投与で結果を算出した。Rosiglitazone は顕著な血糖低下作用と脂質低下作用を示したけれども、体重増加という副作用を導いた。一方、化合物 **77** は用量依存的に薬効を示し、Rosiglitazone の 1/10 量にあたる 1mg/kg において体重増加を併発せずにすぐれた血糖低下作用と脂質低下作用を示した(**Figure 12** and **Table 11**)。PPARα 活性, PPARγ 活性共に化合物 **61b** より減弱した化合物 **77** ではあったが、物理化学的、薬物動態学的プロファイルの改善により化合物 **61b** と同等以上の *in vivo* 薬効が示されたと推察された。

(A)


Feeding Blood Glucose
Feeding Blood Glucose (mg/dl)
600
500
400
300
200
100
0
0
2
4
6
8
10
Day
Vehicle (1% MC)
Rosiglitazone maleate (10 mg/kg)
77 (0.03 mg/kg)
77 (0.1 mg/kg)
77 (0.3 mg/kg)
77 (1 mg/kg)

(B)


Triglyceride
Feeding Serum Triglyceride (mg/dl)
300
250
200
150
100
50
0
Vehicle
Rosiglitazone maleate (10)
77 (0.03)
77 (0.1)
77 (0.3)
77 (1)

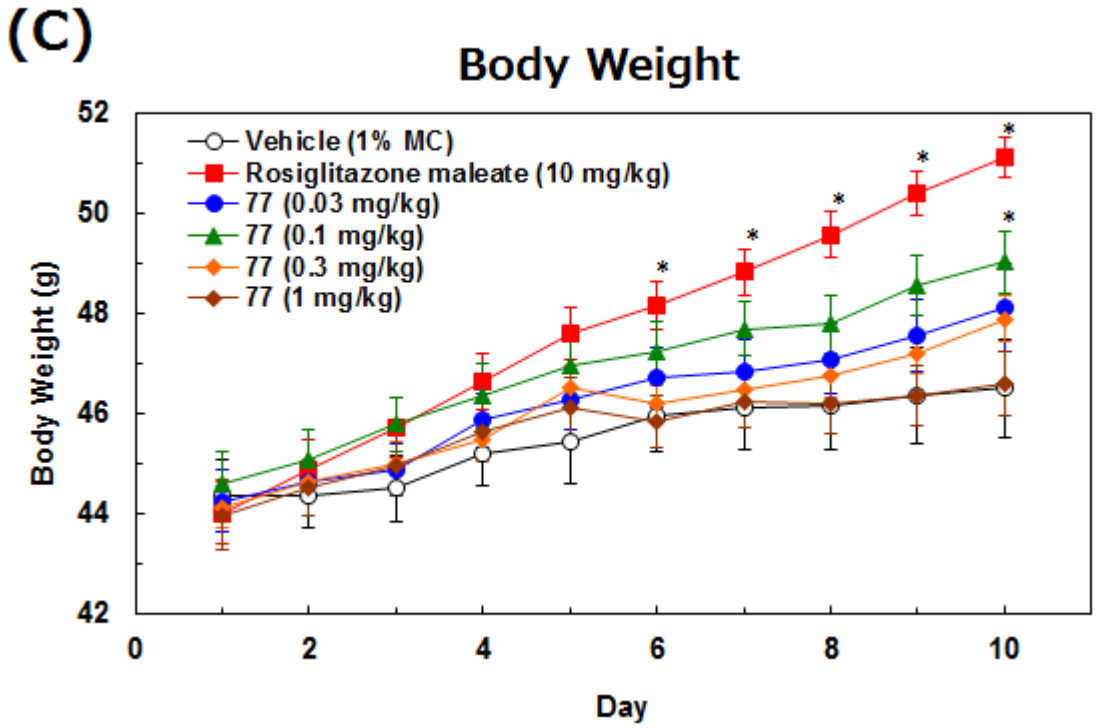


Figure 12. Plasma Glucose Decrease Test in *db/db* Mice. Blood glucose change (A), triglyceride change (B) and body weight change (C) were conducted with 10 days of treatment.

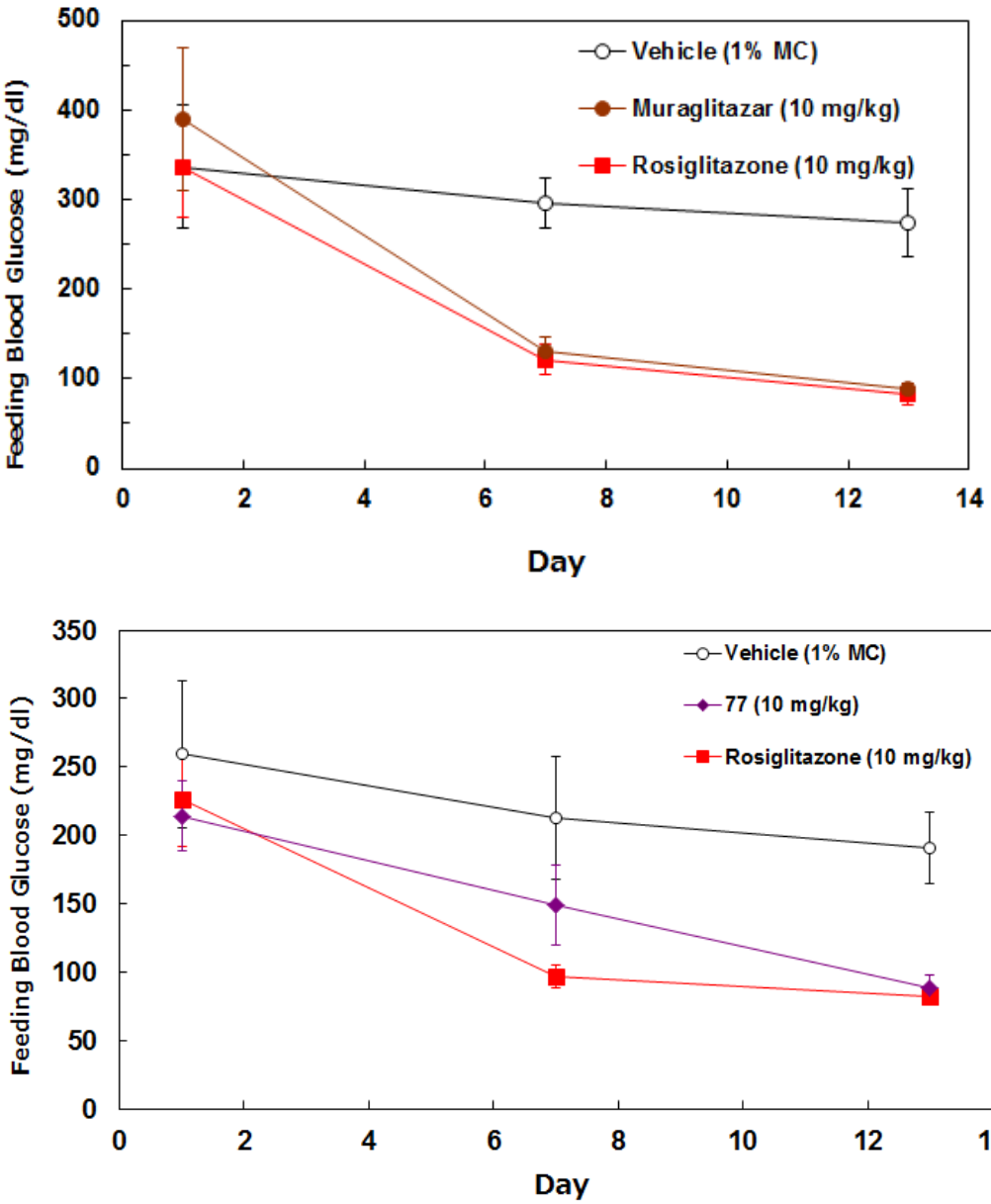
Table 11. Parameters of *In Vivo* Study with **77** on *db/db* Mice

Exp.	Compd.	Dose (mg/kg)	Plasma Glucose[a)] (mg/dl)	Change (%)	Plasma Triglyceride[a)] (mg/dl)	Change (%)	BW Change (%)
	Vehicle		563 ± 7.6		251 ± 36		
1	**77**	1	227 ± 15	− 40[b)]	67 ± 5.4	− 73[b)]	± 0.0
	Rosiglitazone	10	223 ± 17	− 40[b)]	77 ± 6.2	− 69[b)]	+ 9.9[b)]

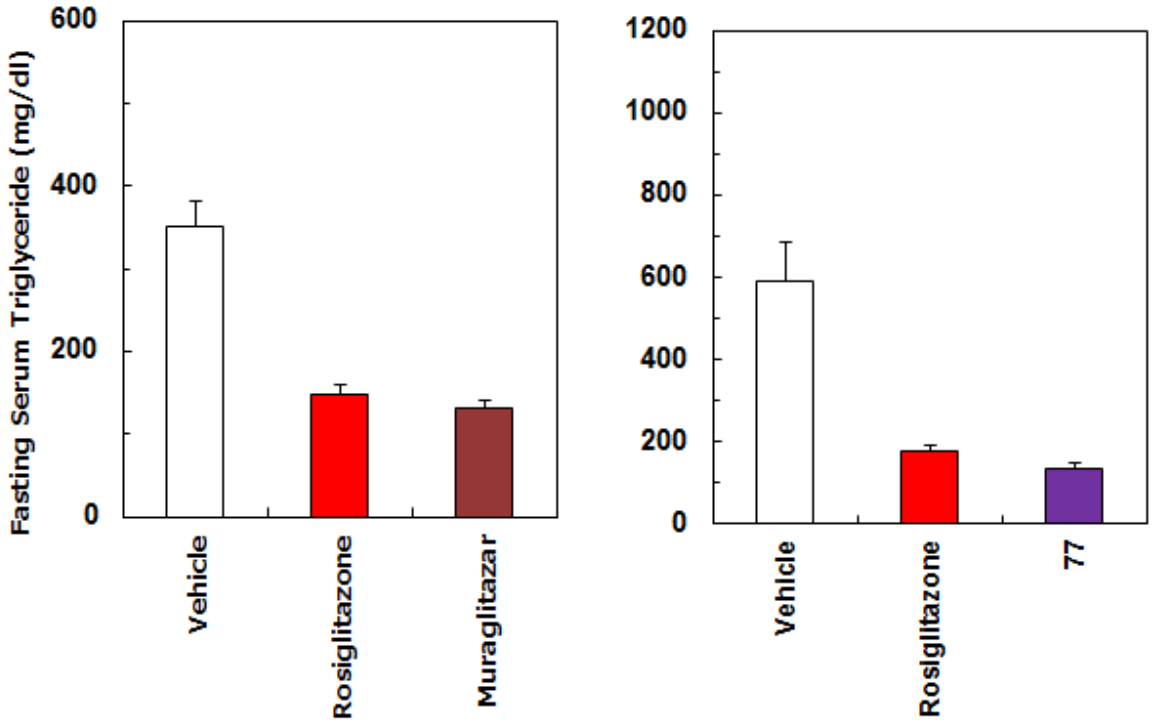
a) Mean ± standard deviation (n = 6). *b*) $P < 0.001$ versus vehicle control (*t*-test).

さらに今回初めて先行PPARα/γデュアルアゴニストである Muraglitazar (α: EC_{50} = 0.3 μM, γ: EC_{50} = 0.1 μM)[12] との比較試験を肥満や高血糖、高インスリン血症を発症した2型糖尿病もであるであるZucker Fatty ratsを用いて実施した (**Figure 13** and **Table 12**)。化合物**77**, Muraglitazarともに顕著な血糖低下作用とトリグリセリド減少作用を示した。しかし、よりPPARαに優位に活性を示す化合物**77**の方が、Muraglitazarよりも体重増加を抑制させることに成功し、著者の仮説がここに証明される結果となった (dosed orally at 10 mg/kg in Zucker Fatty Rat [six per group] for 13 days)。

(A) Feeding Blood Glucose



(B) Triglyceride



(C) Body Weight

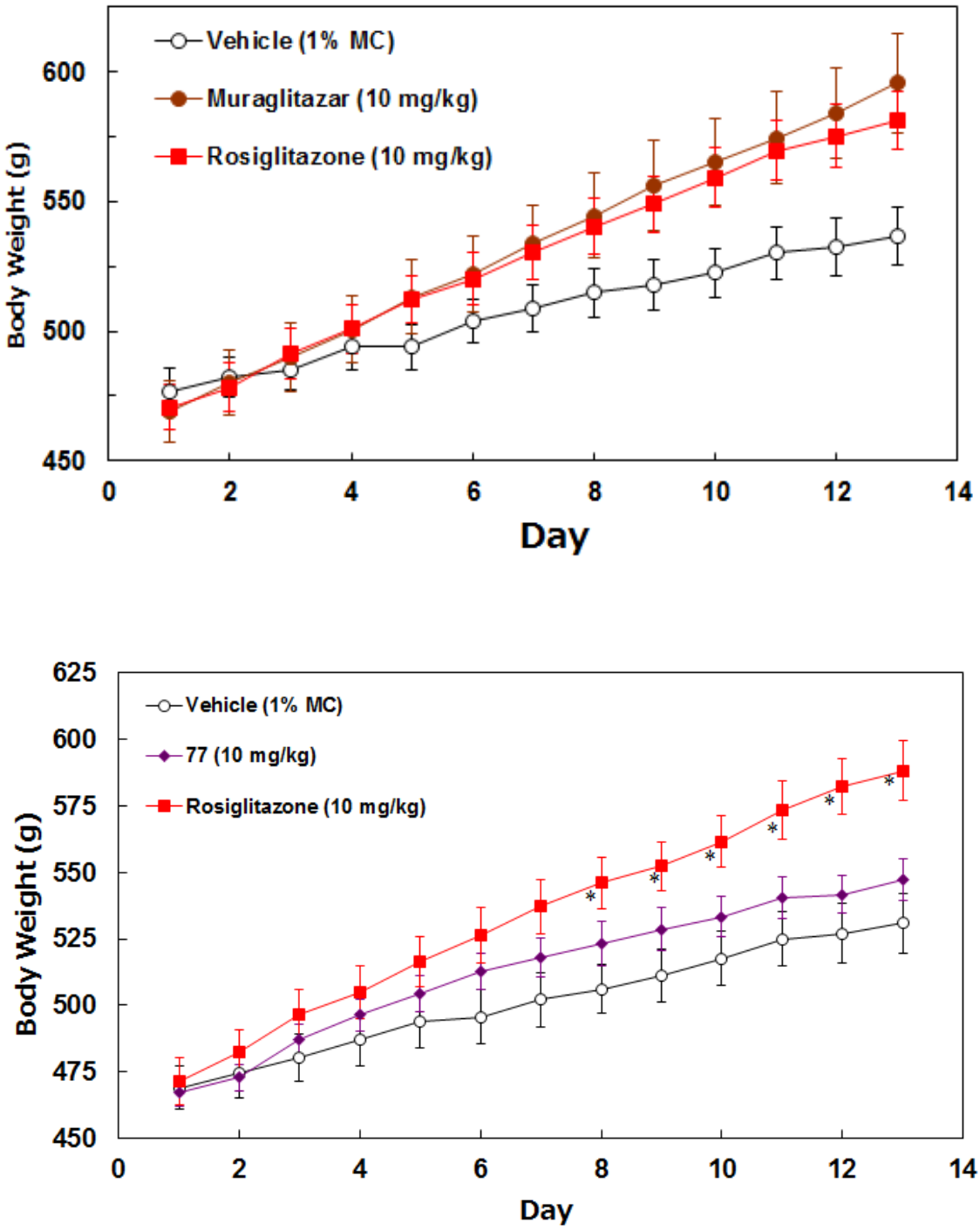


Figure 13. Plasma Glucose Decrease Test in Zucker Fatty Rat. Blood glucose change (A), triglyceride change (B) and body weight change (C) were conducted with 13 days of treatment.

Table 12. Parameters of *In Vivo* Study with **22** on *Zucker Fatty Rat*

Exp.	Compds	Dose (mg/kg)	Plasma Glucose[a)] (mg/dl)	Change (%)	Plasma Triglyceride[a)] (mg/dl)	Change (%)	BW Change (%)
	Vehicle		191 ± 26		591 ± 97		
1	**77**	10	88 ± 9.5	− 53[b)]	133 ± 13	− 77	+ 2.3
	Rosiglitazone	10	82 ± 5.2	− 57[b)]	175 ± 18	− 70	+ 11[c)]
	Vehicle		274 ± 39		350 ± 32		
2	Muraglitazar	10	89 ± 5.8	− 68[b)]	132 ± 6.8	− 62[b)]	+ 9.7
	Rosiglitazone	10	83 ± 11	− 70[b)]	147 ± 11	− 58[b)]	+ 8.7

a) Mean ± standard deviation (n = 6). *b*) $P < 0.01$. versus vehicle control (*t*-test).

結論

著者らは、PPARγアゴニストにPPARα作用を付加することで、PPARγアゴニストが有する副作用を抑え、加えて脂質パラメーターの改善が期待できるというコンセプトのもと創薬研究を行った。特に、先行 PPARα/γ デュアルアゴニストが副作用を回避できていない点に着目し、PPARα 優位にアゴニスト活性を示す化合物獲得を鍵とし、誘導体展開を進めた。その際、Eli Lilly 社 Compound 1 を基本骨格として、部分構造の変換および置換基導入といった合成研究を実施した。さらに先行薬剤の高い脂溶性と酸性構造による貧弱な PK プロファイルを改善すべく、リンカー部にアミノ基を配した化合物の展開を軸とし構造活性相関の構築を実施した。本研究において、以下に示すような成果および本骨格を有する新規 PPARα/γ デュアルアゴニストの創製につながるいくつかの有用な知見を得た。

1. 既存のエーテル結合やアミド結合から脱し、リンカー部をアミノ結合に変換した化合物は、アゴニスト活性を示すことを見出した。特にトリアリールアミン構造が PPARα/γ 共に活性発現に重要であることを見出し、特にフラニルメチル基を導入した **16d** において非常に強い PPARα 活性を示す有用な知見が得られた。
2. 酸性部ベンゼン環 2 位への置換基導入は活性向上へと導き、特にその置換基効果は PPARγ に対して顕著であることが判明した。さらに 2 位と 6 位の両オルト位にメチル基を導入した **22e** では PPARγ 活性がさらに飛躍的に向上し、無置換化合物 **22a** に比べ 100 倍以上向上する結果を得た。*In vivo* 試験において、強力な PPARα 作用を有する **22e** は、PPARγ 選択的アゴニストとは対照的に体重増加を引き起こすことなく、顕著な血糖低下作用とトリグリセリド低下作用を示すことが確認され、その強力な PPARα 活性の効果が副作用回避に重要であるという著者の仮説を肯定する有用な知見が得られた。
3. **22e** 等のフラン誘導体は、直接その薬剤によって、あるいはその代謝物においても強く CYP3A4 を阻害することが明らかとなり、薬物間相互作用のリスクを有していることが判明し

た。その直接阻害作用は脂溶性の高さと相関していることが判明し、さらに MBI を誘導する構造はフラン環であることを見出した。

4. 薬物間相互作用のリスク低減を図るためにフラン環に代わる新たな側鎖の検討を行った結果、低脂溶性の 1,3,4－オキサジアゾール環を導入した誘導体によって CYP3A4 の直接阻害や MBI を低減させる知見が得られた。
5. 1,3,4－オキサジアゾール誘導体は、PPARα 優位に強力なアゴニスト活性を示すことを見出した。類似した構造を有する 1,2,4－オキサジアゾール化合物 **54** は、PPARα に対する選択性が低く、この化合物をカウンターパートとし、**50** の *in vivo* 試験を実施したところ、両化合物とも同等の血糖低下作用を示す一方で、副作用の発現に大きな差が生じた。つまり著者の仮説どおりに PPARα 優位に活性を示す化合物 **50** において、副作用である体重増加をより抑制する結果が得られた。
6. 脂溶性部ベンゼン環 4 位にへの置換基導入は PPARα 優位にアゴニスト作用を示しつつ、PPARα/γ ともに高活性化可能であった一方で、3 位への置換基導入は、PPARγ 優位にアゴニスト活性を向上させ、選択性が低下する構造活性相関を構築した。
7. CYP3A4 の直接あるいは代謝的阻害を回避した 1,3,4-オキサジアゾール誘導体は、強酸性下において化学的に不安定であるという結果が得られた。経口投与剤を目指し代替側鎖の研究を実施した結果、低級アルキルあるいは無置換のアミド体であれば置換可能であることを見出した。
8. 脂溶性部ベンゼン環 4 位にメチル基を導入した化合物 **77** は、PPARα (EC_{50} = 2.8 nM) に強い活性を示し、それは PPARγ (EC_{50} = 26 nM) に比べ約 10 倍の優位性を示すものであった。また **77** は、低脂溶性と高代謝安定性を示し、さらに CYP 阻害作用を回避する等、優れた物理化学的、薬物動態学的プロファイルを示すことが判明した。
9. *db/db* マウスを用いて *in vivo* 試験を実施した結果、対照薬の Rosiglitazone の 1/10 量において顕著な血糖低下作用と脂質低下作用を示し、それはまた副作用である体重増加を抑制することが判明した。さらに先行 PPARα/γ デュアルアゴニストである Muraglitazar との比

較試験を Zucker Fatty rats を用いて実施した結果、両薬剤とも顕著な血糖低下作用とトリグリセリド減少作用を示した。しかし PPARα 優位にアゴニスト活性を示す化合物 **77** のみ体重増加を抑制させることに成功し、著者の仮説がここに証明され、人々の健康文化に貢献可能な化合物を獲得することに成功した。

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実験の部

第 1 章　Chemistry

General.

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. ^{1}H-NMR spectra were determined on a JEOL JNM-EX400 spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Significant ^{1}H-NMR data are tabulated in the following order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), and coupling constant(s) in hertz. Electron spray ionization condition (ESI) mass spectra were recorded on an Agilent 1100 and SCIEX API-150EX spectrometer. Fast atom bombardment ionization condition (FAB) mass spectra were recorded on a JEOL JMSHX110 spectrometer. Electron impact ionization condition (EI) mass spectra were recorded on a JEOL JMS-AX505W. Column chromatography was performed with Merck silica gel 60 (particle size 0.060—0.200 or 0.040—0.063 mm). Flash column chromatography was performed with Biotage FLASH Si packed columns. Thin layer chromatography (TLC) was performed on Merck pre-coated TLC glass sheets with silica gel 60 F_{254}, and compound visualization was effected with a 5% solution of phosphomolybdic acid in ethanol, UV lamp, iodine, or Wako ninhydrin spray. Elemental analysis was performed using a PerkinElmer CHNS/O 2400II or a Yokokawa Analysis IC7000RS, and analytical results were within ± 0.4% of the theoretical values unless otherwise noted.

Ethyl 2-methyl-2-(4-{[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethyl]amino}phenoxy)propanoate (9a)

To a solution of ethyl 2-(4-aminophenoxy)-2-methylpropanoate (**7**) (0.20 g, 0.89 mmol) in DMF (1.5 mL), 2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethyl 4-methylbenzenesulfonate (**8a**) (0.30 g, 0.85 mmol), cesium carbonate (0.36 g, 1.1 mmol) and potassium iodide (71 mg, 0.43 mmol)were added and stirred at 60°C for 20 h. After the reaction mixture was diluted with EtOAc, the organic layer was washed with water, saturated sodium bicarbonate aqueous solution and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (Hexane/Acetone = 6/1, v/v) to provide **9a** as a pale yellow oil (0.15 g, 43%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, J = 7.1 Hz), 1.50 (6H, s), 2.25 (3H, s), 2.77 (2H, t, J = 6.3 Hz), 3.41 (2H, t, J = 6.3 Hz), 4.23 (2H, q, J = 7.1 Hz), 6.52 (2H, d, J = 8.8 Hz), 6.77 (2H, d, J = 8.8 Hz), 7.41−7.43 (3H, m), 7.97−7.99 (2H, m).

MS (ESI) m/z: 409 $(M+H)^+$.

2-Methyl-2-(4-{[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethyl]amino}phenoxy)propanoic acid (10a)

To a solution of **9a** (0.15 g, 0.37 mmol) in methanol (5.0 mL), NaOH (1M aqueous solution, 0.50 mL) was added and stirred at room temperature for 13 h. After HCl (1M aqueous solution, 0.50 mL) was added to the reaction mixture, the solvent was removed *in vacuo*. After EtOAc was added to the residue, the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. Recrystallization from Chloroform-Hexane-Diethyl ether produced **10a** as a colorless solid (68 mg, 49%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.36 (6H, s), 2.26 (3H, s), 2.67 (2H, t, J = 6.8 Hz), 3.23 (2H, t, J = 6.8 Hz), 5.29−5.33 (1H, br-s), 6.48 (2H, d, J = 8.8 Hz), 6.68 (2H, d, J = 8.8 Hz), 7.45−7.51 (3H,

m), 7.90 (2H, d, *J* = 6.1 Hz), 12.6−12.7 (1H, br-s).

MS (ESI) *m/z*: 381 $(M+H)^+$.

Anal. Calcd. for $C_{22}H_{24}N_2O_4 \cdot 0.75H_2O$: C, 67.07; H, 6.52; N, 7.11. Found: C, 66.63; H, 6.05; N, 6.99.

Ethyl 2-methyl-2-(4-{[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}phenoxy)propanoate (9b)

To a solution of ethyl 2-(4-aminophenoxy)-2-methylpropanoate (**7**) (0.30 g, 1.4 mmol) in DMF (3.0 mL), 4-(chloromethyl)-5-methyl-2-phenyl-1,3-oxazole (**8b**) (0.28 g, 1.4 mmol), cesium carbonate (0.36 g, 1.1 mmol) and potassium iodide (0.22 mg, 1.4 mmol) were added and stirred at 60°C for 17 h. After the reaction mixture was diluted with EtOAc, the mixture was washed with water, saturated sodium bicarbonate aqueous solution and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (Hexane/Acetone = 4/1, v/v) to provide **9b** as a pale red oil (0.32 g, 60%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, t, *J* = 6.8 Hz), 1.52 (6H, s), 2.38 (3H, s), 4.14 (2H, s), 4.23 (2H, q, *J* = 7.1 Hz), 6.59 (2H, d, *J* = 8.8 Hz), 6.79 (2H, d, *J* = 8.8 Hz), 7.41−7.44 (3H, m), 7.98−8.01 (2H, m).

MS (ESI) *m/z*: 395 $(M+H)^+$.

2-Methyl-2-(4-{[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}phenoxy)propanoic acid (10b)

To a solution of **9b** (50 mg, 0.13 mmol) in tetrahydrofuran (THF) (3.0 mL), NaOH (1M aqueous solution, 0.38 mL) and NaOH (5M aqueous solution, 76 μL) were added and stirred at room temperature for 6 d. After HCl (1M aqueous solution, 0.76 mL) was added to the reaction mixture, the solvent was removed *in vacuo*. After EtOAc was added to the residue, the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. Recrystallization from

Dichloromethane-Hexane produced **10b** as a colorless solid (31 mg, 64%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.38 (6H, s), 2.38 (3H, s), 4.07 (2H, s), 6.55 (2H, d, J = 8.8 Hz), 6.69 (2H, d, J = 8.8 Hz), 7.49–7.51 (3H, m), 7.90–7.91 (2H, m).

MS (ESI) *m/z*: 365 $(M-H)^-$.

Anal. Calcd. for $C_{21}H_{22}N_2O_4 \cdot 1.5H_2O$: C, 64.11; H, 6.40; N, 7.12. Found: C, 64.33; H, 5.75; N, 6.83.

Ethyl 2-methyl-2-(4-{[(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetyl]amino}phenoxy)propanoate (9c)

To a solution of ethyl 2-(4-aminophenoxy)-2-methylpropanoate (**7**) (0.20 g, 0.89 mmol) in DMF (3.0 mL), (5-methyl-2-phenyl-1,3-oxazol-4-yl)acetic acid (**8c**) (0.22 g, 0.97 mmol), EDCI (0.26 g, 1.4 mmol) and HOBt (0.21 g, 1.4 mmol) were added and stirred at room temperature for 2 h. After EtOAc was added to the residue, the organic layer was washed with water, 10% citric acid aqueous solution, saturated sodium bicarbonate aqueous solution and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by preparative TLC plates (Hexane/EtOAc = 1/1, v/v) to provide **9c** as a pale yellow oil (25 mg, 6%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.25 (3H, t, J = 7.1 Hz), 1.55 (6H, s), 2.39 (3H, s), 3.58 (2H, s), 4.21 (2H, q, J = 7.1 Hz), 6.82 (2H, d, J = 9.0 Hz), 7.40 (2H, d, J = 8.8 Hz), 7.46–7.49 (3H, m), 8.00–8.03 (2H, m), 9.07 (1H, s).

MS (ESI) *m/z*: 423 $(M+H)^+$.

2-Methyl-2-(4-{[(5-methyl-2-phenyl-1,3-oxazol-4-yl)acetyl]amino}phenoxy)propanoic acid (10c)

To a solution of **9c** (90 mg, 0.21 mmol) in methanol (5.0 mL), NaOH (1M aqueous solution, 0.64 mL) was added and stirred at room temperature for 19 h. After HCl (1M aqueous solution, 0.64 mL) was added to the reaction mixture, the solvent was removed *in vacuo*. After EtOAc was added to the residue, the mixture was washed with 10% citric acid aqueous solution and brine, dried over

Na_2SO_4 and concentrated. Recrystallization from Chloroform-Hexane-Diethyl ether produced **10c** as a pale brown solid (49 mg, 58%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.44 (6H, s), 2.37 (3H, s), 3.55 (2H, s), 6.78 (2H, d, J = 9.0 Hz), 7.45–7.49 (5H, m), 7.88 (2H, d, J = 6.1 Hz), 10.0 (1H, br-s).

MS (ESI) *m/z*: 393 $(M-H)^-$.

Anal. Calcd. for $C_{22}H_{22}N_2O_5 \cdot 0.33H_2O$: C, 66.00; H, 5.70; N, 7.00. Found: C, 65.78; H, 5.67; N, 6.77.

General procedure for ethyl or tert-butyl 2-methyl-2-[4-({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]propanoate (13a−c)

To a solution of 1-(5-methyl-2-phenyl-1,3-oxazol-4-yl)methanamine (**11a** or **11b**) and ethyl or tert-butyl 2-(4-formylphenoxy)-2-methylpropanoate (**12a** or **12b**) in dichloromethane (DCM), sodium triacethoxyborohydride ($NaBH(OAc)_3$) was added and stirred at room temperature for 24 h. After the solvent was removed *in vacuo*, the residue was dissolved in EtOAc, washed with saturated sodium bicarbonate aqueous solution and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Chloroform/Methanol as eluent) to provide **13a−c**.

Ethyl 2-methyl-2-[4-({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]propanoate (**13a**).

This compound was obtained as a pale yellow oil in 43% yield by using **11a** (2.4 mmol), **12a** (2.4 mmol), $NaBH(OAc)_3$ (3.6 mmol) and DCM (20 mL).

MS (ESI) *m/z*: 409 $(M+H)^+$.

Ethyl 2-{4-[({[2-(3-bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}amino)methyl]phenoxy}-2-methylpropanoate (**13b**).

This compound was obtained as a pale yellow oil in 55% yield by using **11b** (0.28 mmol), **12a** (0.28 mmol), $NaBH(OAc)_3$ (0.36 mmol) and DCM (2.0 mL).

^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J = 6.9 Hz), 1.58 (6H, s), 2.32 (3H, s), 3.66 (2H, s), 3.75 (2H, s), 4.23 (3H, q, J = 6.9 Hz), 6.81 (2H, d, J = 8.6 Hz), 7.21 (2H, d, J = 8.6 Hz), 7.30 (1H, dd, J = 8.6, 6.9 Hz), 7.52−7.54 (1H, m), 7.90-7.92 (1H, m), 8.15-8.16 (1H, m).

MS (ESI) *m/z*: 489 $(M+H)^+$.

tert-Butyl 2-{4-[({[2-(3-bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}amino)methyl]phenoxy}-2-methylpropanoate (**13c**).

This compound was obtained as a pale yellow oil in 71% yield by using **11b** (7.5 mmol), **12b** (7.5 mmol), $NaBH(OAc)_3$ (9.8 mmol) and DCM (30 mL).

^{1}H-NMR ($CDCl_3$) δ: 1.44 (9H, s), 1.55 (6H, s), 2.32 (3H, s), 3.66 (2H, s), 3.73 (1H, s), 3.75 (2H, s), 6.82 (2H, d, J = 8.5 Hz), 7.21 (2H, d, J = 8.5 Hz), 7.28−7.32 (1H, m), 7.51−7.54 (1H, m), 7.90−7.93 (1H, m), 8.15−8.16 (1H, m).

MS (ESI) *m/z*: 517 $(M+H)^+$.

2-Methyl-2-[4-({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy] propanoic acid (14a)

To a mixture of **13a** (0.20 g, 0.48 mmol) in methanol (3.0 mL), NaOH (1M aqueous solution, 1.0 mL) was added and stirred under reflux conditions for 21 h. After HCl (1M aqueous solution, 1.0 mL) was added to the reaction mixture, the solvent was removed *in vacuo* until reduced by half. Insoluble material was collected by filtration, washed with water and dried. After the resulting solid was dissolved in methanol (3.0 mL) and treated with NaOH (1M aqueous solution, 0.48 mL), the solvent was removed *in vacuo* and the residue was dried to provide **14a** sodium salts as a colorless

solid (0.17 g, 67%).

^{1}H-NMR (CD_3OD) δ: 1.48−1.50 (6H, m), 2.32−2.33 (3H, m), 3.61 (2H, d, J = 3.2 Hz), 3.70 (2H, d, J = 3.2 Hz), 6.87−6.90 (2H, m), 7.16−7.19 (2H, m), 7.45−7.48 (3H, m), 7.98−7.96 (2H, m).

MS (ESI) m/z: 381 $(M+H)^+$.

Anal. Calcd. for $C_{22}H_{24}N_2O_4 \cdot Na \cdot 2H_2O \cdot 2.5MeOH$: C, 48.79; H, 4.65; N, 5.17. Found: C, 48.67; H, 4.28; N, 4.97.

2-{4-[({[2-(3-Bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}amino)methyl]phenoxy}-2-methylpropanoic acid (14b)

To a mixture of **13b** (74 mg, 0.15 mmol) in methanol (2.0 mL), NaOH (1M aqueous solution, 0.30 mL) was added and stirred at room temperature for 15 h. After HCl (1M aqueous solution, 0.30 mL) was added to the reaction mixture, the solvent was removed *in vacuo* until reduced by half. Insoluble material was collected by filtration, washed with water and dried. After the resulting solid was treated with HCl (4M dioxane solution), the solvent was removed *in vacuo* and the residue was dried to provide **14b** HCl salts as a colorless solid (37 mg, 54%).

^{1}H-NMR (DMSO-d_6) δ: 1.52 (6H, s), 2.43 (3H, s), 4.10 (2H, s), 4.15 (2H, s), 6.85 (2H, d, J = 8.8 Hz), 7.43 (2H, d, J = 8.6 Hz), 7.52 (1H, t, J = 8.6 Hz), 7.74−7.76 (1H, m), 7.96−7.94 (1H, m), 8.09 (1H, t, J = 1.7 Hz).

MS (ESI) m/z: 460 $(M+H)^+$.

Anal. Calcd. for $C_{22}H_{23}BrN_2O_4 \cdot HCl \cdot 0.5H_2O$: C, 52.35; H, 4.99; N, 5.55; Br, 15.83; Cl, 7.02. Found: C, 52.06; H, 4.59; N, 5.83; Br, 16.94; Cl, 7.12.

General procedure for ethyl or tert-butyl 2-(4-{[{[2-(3-bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(alkyl)amino]methyl}phenoxy)-2-methylpropanoate (15a−d)

To a mixture of **13** (b or c) and corresponding aldehyde in dichloromethane, $NaBH(OAc)_3$ was added and stirred at room temperature. After the solvent was removed *in vacuo*, the residue was

dissolved in EtOAc, washed with saturated sodium bicarbonate aqueous solution and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc as eluent) to provide **15a**−**d**.

Ethyl 2-(4-{[{[2-(3-bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(butyl)amino]methyl} phenoxy)-2-methylpropanoate (**15a**).

This compound was obtained as a pale yellow oil in 91% yield by using **13b** (0.21 mmol), *n*-butylaldehyde (0.27 mmol), $NaBH(OAc)_3$ (0.31 mmol) and DCM (5.0 mL).

^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, J = 7.2 Hz), 1.25 (3H, t, J = 7.2 Hz), 1.27−1.31 (2H, m), 1.48−1.54 (2H, m), 1.57 (6H, s), 2.30 (3H, s), 2.48 (2H, t, J = 7.4 Hz), 3.49 (2H, s), 3.54 (2H, s), 4.23 (2H, q, J = 7.2 Hz), 6.79 (2H, d, J = 8.6 Hz), 7.21 (2H, d, J = 8.6 Hz), 7.28−7.31 (1H, m), 7.50−7.53 (1H, m), 7.90−7.92 (1H, m), 8.14−8.15 (1H, m).

MS (ESI) *m/z*: 543 $(M+H)^+$.

tert-Butyl 2-{4-[(benzyl{[2-(3-bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}amino)methyl] phenoxy}-2-methylpropanoate (**15b**).

This compound was obtained as a colorless oil in quantitative yield by using **13c** (0.58 mmol), benzaldehyde (0.70 mmol), $NaBH(OAc)_3$ (0.87 mmol) and DCM (10 mL).

^{1}H-NMR ($CDCl_3$) δ: 1.43 (9H, s), 1.55 (6H, s), 2.23 (3H, s), 3.51 (2H, s), 3.58 (2H, s), 3.64 (2H, s), 6.81−6.84 (2H, m), 7.23−7.33 (6H, m), 7.37−7.40 (2H, m), 7.50−7.53 (1H, m), 7.90−7.93 (1H, m), 8.14 (1H, t, J = 1.6 Hz).

MS (ESI) *m/z*: 607 $(M+H)^+$.

Ethyl 2-(4-{[{[2-(3-bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(4-methoxybenzyl)amino] methyl}phenoxy)-2-methylpropanoate (**15c**).

This compound was obtained as a colorless oil in 75% by using **13b** (0.19 mmol),

p-methoxybenzaldehyde (0.29 mmol), $NaBH(OAc)_3$ (0.29 mmol) and DCM (25 mL).

^{1}H-NMR ($CDCl_3$) δ: 1.43 (18H, s), 1.55 (12H, s), 2.21 (3H, s), 3.48 (2H, s), 3.55 (4H, s), 6.81 (4H, d, J = 8.6 Hz), 7.23 (4H, d, J = 8.6 Hz), 7.29 (1H, t, J = 7.8 Hz), 7.50−7.53 (1H, m), 7.89−7.92 (1H, m), 8.14−8.13 (1H, m).

MS (ESI) *m/z*: 609 $(M+H)^+$.

tert-Butyl 2-(4-{[{[2-(3-bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino]methyl}phenoxy)-2-methylpropanoate (**15d**).

This compound was obtained as a colorless oil in 52% by using **13c** (0.058 mmol), furan-2-carbaldehyde (0.078 mmol), $NaBH(OAc)_3$ (0.087 mmol) and DCM (5.0 mL).

^{1}H-NMR ($CDCl_3$) δ: 1.43 (9H, s), 1.52 (6H, s), 2.29 (3H, s), 3.55 (2H, s), 3.58 (2H, s), 3.72 (2H, s), 6.24 (1H, d, J = 3.2 Hz), 6.33−6.35 (1H, m), 6.82 (2H, d, J = 8.6 Hz), 7.23−7.40 (4H, m), 7.50−7.53 (1H, m), 7.92−7.94 (1H, m), 8.16 (1H, t, J = 1.7 Hz).

MS (ESI) *m/z*: 597 $(M+H)^+$.

***tert*-Butyl 2-{4-[(benzoyl{[2-(3-bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}amino)methyl]phenoxy}-2-methylpropanoate (15e)**

To a solution of **13c** (75 mg, 0.15 mmol) in DMF (2.0 mL), benzoic acid (27 mg, 0.22 mmol), EDCI (56 mg, 0.29 mmol) and HOBt (45 mg, 0.29 mmol) were added and stirred at room temperature for 21 h. After EtOAc was added to the residue, the organic layer was washed with water, 10% citric acid aqueous solution, saturated sodium bicarbonate aqueous solution and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by preparative TLC plates (Hexane/EtOAc = 5/2, v/v) to provide **15e** as a colorless oil (77 mg, 85%).

^{1}H-NMR ($CDCl_3$) δ: 1.19 (6H, s), 1.45 (9H, s), 1.99−2.39 (3H, m), 4.50−4.76 (4H, m), 6.84 (2H, d, J = 8.8 Hz), 7.05−7.23 (2H, m), 7.30−7.69 (6H, m), 7.94 (1H, t, J = 5.2 Hz), 8.08−8.11 (1H, m), 8.15 (1H, t, J = 1.2 Hz).

MS *m/z*: 621 $(M+H)^+$.

General procedure for 2-(4-{[{[2-(3-bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(alkyl) amino]methyl}phenoxy)-2-methylpropanoic acid (16a, 16c)

To a mixture of **15** (a or c) in methanol, NaOH (1M aqueous solution) was added and stirred at room temperature. After HCl (1M aqueous solution) was added to the reaction mixture, the solvent was removed *in vacuo*. After EtOAc was added to the residue, the organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by preparative TLC plates (Chloroform/Methanol, v/v) and then recrystallized from Acetone-Hexane to provide provide **16** (a, c).

2-(4-{[{[2-(3-Bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(butyl)amino]methyl}phenoxy)-2-methylpropanoic acid (**16a**)

This compound was obtained as a pale yellow solid in 49% by using **15a** (0.15 mmol), NaOH (1M aqueous solution, 0.15 mmol) and methanol (2.0 mL).

^{1}H-NMR (DMSO-d_6) δ: 0.79−0.87 (3H, m), 1.22−1.29 (4H, m), 1.49 (6H, s), 2.33 (3H, s), 3.29−3.34 (4H, m), 3.44−3.52 (2H, m), 6.79 (2H, s), 7.22 (2H, s), 7.49 (1H, br s), 7.70 (1H, br s), 7.92 (1H, d, J = 7.4 Hz), 8.03 (1H, br s).

MS (ESI) *m/z*: 517 $(M+H)^+$.

Anal. Calcd. for $C_{26}H_{31}BrN_2O_4 \cdot 0.3H_2O$: C, 58.54; H, 6.05; N, 5.25; Br, 14.98. Found: C, 59.03; H, 6.01; N, 5.15; Br, 14.59

2-(4-{[{[2-(3-Bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(4-methoxybenzyl)amino]methyl} phenoxy)-2-methylpropanoic acid (**16c**)

This compound was obtained as a pale yellow solid in 49% by using **15c** (0.14 mmol), NaOH (1M aqueous solution, 1.0 mmol) and methanol (10 mL).

^{1}H-NMR (DMSO-d_6) δ: 1.47 (6H, s), 2.24 (3H, s), 3.44 (2H, s), 3.51 (2H, s), 3.53 (2H, s), 3.72 (3H, s), 6.79 (2H, d, J = 8.8 Hz), 6.89 (2H, d, J = 8.8 Hz), 7.24−7.30 (4H, m), 7.48 (1H, t, J = 7.8 Hz), 7.68−7.70 (1H, m), 7.92 (1H, d, J = 7.8 Hz), 8.03 (1H, s).

MS (ESI) m/z: 579 $(M+H)^+$.

Anal. Calcd. for $C_{30}H_{31}BrN_2O_5$: C, 62.18; H, 5.39; N, 4.83. Found: C, 61.88; H, 5.50; N, 4.78.

General procedure for 2-(4-{[{[2-(3-bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(alkyl) amino]methyl}phenoxy)-2-methylpropanoic acid (16b, 16d, 16e)

To a solution of **15** (b, d, e) in DCM, trifluoroacetic acid (TFA) was added and stirred at room temperature. After the solvent was removed *in vacuo*, EtOAc was added to the residue and the organic layer was washed with dilute sodium bicarbonate aqueous solution and brine, dried over Na_2SO_4 and concentrated. After the residue was diluted with dioxane, HCl (4M dioxane solution) or NaOH (1M aqueous solution) was added and concentrated to provide **16** (b, d, e).

2-{4-[(Benzyl{[2-(3-bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}amino)methyl]phenoxy}-2-methylpropanoic acid (**16b**).

This compound was obtained as HCl salt form of a pale yellow solid in 76% by using **15b** (0.060 mmol), TFA (1.0 mL), dichloromethane (1.0 mL).

^{1}H-NMR (DMSO-d_6) δ: 1.51 (6H, s), 2.25 (3H, s), 3.18−3.39 (4H, m), 4.28−4.48 (2H, m), 6.85 (2H, s), 7.56−7.44 (8H, m), 7.75 (1H, s), 7.96 (1H, s), 8.10 (1H, s).

MS (ESI) m/z: 551 $(M+H)^+$.

Anal. Calcd. for $C_{29}H_{29}BrN_2O_4$·HCl: C, 59.45; H, 5.16; N, 4.78. Found: C, 58.99; H, 5.28; N, 4.50.

2-(4-{[{[2-(3-Bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino]methyl} phenoxy)-2-methylpropanoic acid (**16d**).

This compound was obtained as HCl salt form of a colorless solid in quantitative yield by using **15d**

(0.027 mmol), TFA (0.50 mL), dichloromethane (1.0 mL).

^{1}H-NMR (DMSO-d_6) δ: 1.51 (6H, s), 2.33 (3H, s), 4.11−4.40 (6H, m), 6.57 (1H, s), 6.83−6.86 (3H, m), 7.53−7.45 (3H, m), 7.74 (1H, d, J = 7.6 Hz), 7.82 (1H, s), 7.96 (1H, d, J = 7.6 Hz), 8.09 (1H, s).

MS (ESI) *m/z*: 541 $(M+H)^+$.

Anal. Calcd. for $C_{27}H_{27}BrN_2O_5 \cdot HCl$: C, 56.31; H, 4.90; N, 4.86. Found: C, 56.00; H, 4.95; N, 4.76.

2-{4-[(Benzoyl{[2-(3-bromophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}amino)methyl]phenoxy}-2-methylpropanoic acid (**16e**).

This compound was obtained as sodium salt form of a pale yellow solid in 34% by using **15e** (0.60 mmol), TFA (1.0 mL), dichloromethane (5.0 mL).

^{1}H-NMR (DMSO-d_6) δ: 1.32 (9H, s), 2.04−2.31 (3H, m), 4.15−4.54 (4H, m), 6.76 (2H, d, J = 8.8 Hz), 6.95−7.08 (1H, m), 7.51−7.43 (6H, m), 7.60 (1H, s), 7.70 (1H, d, J = 7.6 Hz), 7.94 (1H, d, J = 8.1 Hz), 8.03 (1H, s).

MS (ESI) *m/z*: 565 $(M+H)^+$.

Anal. Calcd. for $C_{29}H_{26}BrN_2O_5 \cdot Na$: C, 59.50; H, 4.48; N, 4.79. Found: C, 59.12; H, 4.67; N, 4.60.

1-(Furan-2-yl)-*N*-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]methanamine (18)

To a solution of **11a** (27 g, 0.14 mol) in ethanol (0.50 L), furan-2-carbaldehyde (**17**) (14 g, 0.14 mol) was added and stirred under reflux conditions for 1 h. After the reaction mixture was cooled in an ice bath, sodium borohydride (10 g, 2.6 mol) was added at the same temperature and then stirred at room temperature for 12 h. After the solvent was removed *in vacuo*, the residue was dissolved in EtOAc, washed with water, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (EtOAc) to provide **18** (32 g, 86%).

^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s), 3.69 (2H, s), 3.82 (2H, s), 6.20−6.22 (1H, m), 6.31−6.33 (1H, m), 7.36−7.45 (4H, m), 7.98−8.01 (2H, m).

MS (ESI) *m/z*: 269 $(M+H)^+$.

General procedure for ethyl 2-(4-formylphenoxy)-2-methylpropanoate (20a−g)

To a mixture of **19**, ethyl 2-bromo-2-methylpropanoate and DMF, cesium carbonate was added and stirred at 80°C. After the reaction mixture was diluted with EtOAc, the mixture was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (Hexane/EtOAc as eluent) to provide **20a**−**g**.

Ethyl 2-(4-formylphenoxy)-2-methylpropanoate (**20a**).

This compound was obtained as a colorless oil in 65% yield by using **19a** (25 mmol), ethyl 2-bromo-2-methylpropanoate (64 mmol), cesium carbonate (98 mmol) and DMF (30 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21 (3H, t, J = 7.6 Hz), 1.67 (6H, s), 4.23 (2H, q, J = 7.6 Hz), 6.89 (2H, d, J = 8.8 Hz), 7.78 (2H, d, J = 8.8 Hz), 9.88 (1H, s).

MS (ESI) *m/z*: 277 $(M+CH_3CN)^+$.

Ethyl 2-(2-chloro-4-formylphenoxy)-2-methylpropanoate (**20b**)

This compound was obtained as a colorless oil in 71% yield by using **19b** (32 mmol), ethyl 2-bromo-2-methylpropanoate (69 mmol), cesium carbonate (98 mmol) and DMF (20 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21 (3H, t, J = 7.6 Hz), 1.67 (6H, s), 4.23 (2H, q, J = 7.6 Hz), 6.70−6.80 (1H, m), 6.89 (1H, s), 7.90−7.92 (1H, m), 10.40 (1H, s).

MS (ESI) *m/z*: 311 $(M+CH_3CN)^+$.

2-(4-Formyl-2-methoxyphenoxy)-2-methylpropanoate (**20c**).

This compound was obtained as a colorless solid in 72% yield by using **19c** (33 mmol), ethyl 2-bromo-2-methylpropanoate (51 mmol), cesium carbonate (50 mmol) and DMF (20 mL).

^{1}H NMR(400MHz, $CDCl_3$) δ: 1.23 (3H, t, J = 7.1 Hz), 1.66 (6H, s), 3.90 (3H, s), 4.24 (2H, q, J = 7.1 Hz), 6.85 (1H, d, J = 8.3 Hz), 7.35 (1H, dd, J = 1.9, 8.3 Hz), 7.42 (1H, d, J = 1.9 Hz), 9.85 (1H, s).

Ethyl 2-(4-formyl-2-methylphenoxy)-2-methylpropanoate (**20d**).

This compound was obtained as a colorless oil in 54% yield by using **19d** (37 mmol), ethyl 2-bromo-2-methylpropanoate (77 mmol), cesium carbonate (46 mmol) and DMF (30 mL).

MS (ESI) *m/z*: 251 $(M+H)^+$.

Ethyl 2-(4-formyl-2,6-dimethylphenoxy)-2-methylpropanoate (**20e**): This compound was obtained as a colorless solid in 71% yield by using **19e** (33 mmol), ethyl 2-bromo-2-methylpropanoate (50 mmol), cesium carbonate (46 mmol) and DMF (20 mL).

^{1}H NMR(400MHz; $CDCl_3$) δ: 1.35(3H, t, J = 7.2Hz), 1.50(6H, s), 2.31(6H, s), 4.30(2H, q, J = 7.2Hz), 7.52 (2H, s), 9.85(1H, s).

Ethyl 2-(3-chloro-4-formylphenoxy)-2-methylpropanoate (**20f**).

This compound was obtained as a colorless oil in 37% yield by using **19f** (32 mmol), ethyl 2-bromo-2-methylpropanoate (64 mmol), cesium carbonate (28 mmol) and DMF (20 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21 (3H, t, J = 7.6 Hz), 1.70 (6H, s), 4.23 (2H, q, J = 7.6 Hz), 6.70−6.80 (1H, m), 6.89 (1H, s), 7.90−7.92 (1H, m), 10.40 (1H, s).

Ethyl 2-(4-formyl-3-methoxyphenoxy)-2-methylpropanoate (**20g**).

This compound was obtained as a colorless oil in 48% yield by using **19g** (33 mmol), ethyl 2-bromo-2-methylpropanoate (64 mmol), cesium carbonate (98 mmol) and DMF (30 mL).

MS (ESI) *m/z*: 267 $(M+H)^+$.

General procedure for ethyl 2-[4-({(furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoate (21a−g)

To a solution of **18** in dichloromethane, **20a−g** and $NaBH(OAc)_3$ was added and stirred at room temperature. After the reaction mixture was diluted with EtOAc, the organic layer was washed with water, saturated sodium bicarbonate aqueous solution and brine, dried over Na_2SO_4 and

concentrated. The residue was purified by column chromatography on silica gel (Hexane/EtOAc as eluent) to provide **21a**−**g**.

2-[4-({(Furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoate (**21a**).

This compound was obtained as a pale yellow oil in 58% yield by using **18** (0.56 mmol), **20a** (0.56 mmol), $NaBH(OAc)_3$ (0.84 mmol) and dichloromethane (10 mL).

MS (ESI) *m/z*: 489 $(M+H)^+$.

Ethyl 2-[2-chloro-4-({(furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino} methyl)phenoxy]-2-methylpropanoate (**21b**).

This compound was obtained as a pale yellow oil in 89% yield by using **18** (0.50 mmol), **20b** (0.50 mmol), $NaBH(OAc)_3$ (1.0 mmol) and dichloromethane (5.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21 (3H, t, J = 7.6 Hz), 1.67 (6H, s), 2.40 (3H, s), 3.50(2H, s), 3.55(2H, s), 3.75(2H, s), 4.23 (2H, q, J = 7.6 Hz), 6.22−6.36 (2H, m), 6.89 (3H, m), 7.40−7.50 (5H, m), 8.00−8.10 (1H, m).

Ethyl 2-[4-({(furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-2-methoxyphenoxy]-2-methylpropanoate (**21c**).

This compound was obtained as a pale yellow oil in 87% yield by using **18** (0.50 mmol), **20c** (1.0 mmol), $NaBH(OAc)_3$ (1.4 mmol) and dichloromethane (5.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.30 (3H, t, J = 7.6 Hz), 1.55 (6H, s), 2.25 (3H, s), 3.50(2H, s), 3.52(2H, s), 3.75(2H, s), 3.80 (3H, s), 4.25 (2H, q, J = 7.6 Hz), 6.20 (1H, s), 6.35(1H, s), 6.80 (2H, s), 7.00 (1H, s), 7.40−7.50 (4H, m), 8.00−8.05 (2H, m).

Ethyl 2-[4-({(furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-2-methylphenoxy]-2-methylpropanoate (**21d**).

This compound was obtained as a pale yellow oil in 62% yield by using **18** (1.0 mmol), **20d** (1.0 mmol), $NaBH(OAc)_3$ (1.9 mmol) and dichloromethane (5.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.30 (3H, t, J = 7.6 Hz), 1.55 (6H, s), 2.25 (3H, s), 2.30 (3H, s), 3.50(2H, s), 3.52(2H, s), 3.75(2H, s), 4.25 (2H, q, J = 7.6 Hz), 6.20 (1H, s), 6.35(1H, s), 6.80 (2H, s), 7.00 (1H, s), 7.40−7.50 (4H, m), 8.00−8.05 (2H, m).

Ethyl 2-[4-({(furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoate (**21e**)

This compound was obtained as a pale yellow oil in 87% yield by using **18** (0.50 mmol), **20e** (0.50 mmol), $NaBH(OAc)_3$ (0.95 mmol) and dichloromethane (5.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.30 (3H, t, J = 7.6 Hz), 1.55 (6H, s), 2.25 (3H, s), 2.60 (3H, s), 3.50 (2H, s), 3.52 (2H, s), 3.75 (2H, s), 4.25 (2H, q, J = 7.6 Hz), 6.20 (1H, s), 6.35(1H, s), 6.80 (2H, s), 7.00 (1H, s), 7.40−7.50 (3H, m), 8.00−8.05 (2H, m).

Ethyl 2-[3-chloro-4-({(furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino} methyl)phenoxy]-2-methylpropanoate (**21f**)

This compound was obtained as a pale yellow oil in 87% yield by using **18** (1.0 mmol), **20f** (1.0 mmol), $NaBH(OAc)_3$ (1.9 mmol) and dichloromethane (5.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21 (3H, t, J = 7.6 Hz), 1.67 (6H, s), 2.20 (3H, s), 3.50(2H, s), 3.70(2H, s), 3.75(2H, s), 4.23 (2H, q, J = 7.6 Hz), 6.22−6.24 (2H, m), 6.75−6.90 (2H, m), 7.40−7.50 (5H, m), 8.00−8.05 (2H, m).

Ethyl 2-[4-({(furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-3-methoxyphenoxy]-2-methylpropanoate (**21g**)

This compound was obtained as a pale yellow oil in 87% yield by using **18** (1.0 mmol), **20g** (1.0 mmol), $NaBH(OAc)_3$ (1.9 mmol) and dichloromethane (5.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.21 (3H, t, *J* = 7.6 Hz), 1.62 (6H, s), 2.25 (3H, s), 3.50(2H, s), 3.60(2H, s), 3.70(2H, s), 3.75 (3H, s), 4.23 (2H, q, *J* = 7.6 Hz), 6.22−6.50 (4H, m), 7.40−7.50 (5H, m), 8.00−8.05 (2H, m).

General procedure for 2-[4-({(furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl] amino}methyl)phenoxy]-2-methylpropanoic acid (22a−g)

To a solution of **21a**−**g** in methanol and THF, NaOH (1M aqueous solution) was added and stirred at room temperature. After HCl (1M aqueous solution) was added to the reaction mixture, the solvent was removed *in vacuo*. After EtOAc was added to the residue, the mixture was washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Chloroform/Methanol as eluent) to provide **22a**−**g**.

2-[4-({(Furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoic acid (**22a**)

This compound was obtained as a colorless solid in 73% yield by using **21a** (0.33 mmol), NaOH (1M aqueous solution, 1.0 mL), methanol (1.0 mL) and THF (2.0 mL).

^{1}H-NMR ($CDCl_3$) *δ*: 1.60 (6H, s), 2.14 (3H, s), 3.12−3.62 (1H, m), 3.76 (2H, s), 4.02 (2H, s), 4.14 (2H, s), 6.37-6.38 (1H, m), 6.51 (1H, d, *J* = 2.4 Hz), 6.96 (2H, d, *J* = 8.5 Hz), 7.39−7.47 (6H, m), 8.00−8.02 (2H, m).

MS (ESI) m/z: 461 $[M+H]^+$.

Anal. Calcd. for $C_{27}H_{28}N_2O_5 \cdot 0.5H_2O$: C, 69.07; H, 6.23; N, 5.97. Found: C, 69.17; H, 6.31; N, 5.94.

2-[2-Chloro-4-({(furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl) phenoxy]-2-methylpropanoic acid (**22b**)

This compound was obtained as a pale yellow solid in 91% yield by using **21b** (0.35 mmol), NaOH (1M aqueous solution, 1.0 mL), methanol (1.0 mL) and THF (2.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.67 (6H, s), 2.40 (3H, s), 4.00 (2H, s), 4.10−4.25 (4H, m), 6.22 (1H, s), 6.89 (2H, m), 7.40−7.50 (5H, m), 7.70−7.80(1H, m), 8.00−8.10 (2H, m).

MS (ESI) *m/z*: 495 $(M+H)^+$.

Anal. Calcd. for $C_{27}H_{27}ClN_2O_5 \cdot 2H_2O \cdot 0.3CHCl_3$: C, 57.85; H, 5.57; N, 4.94. Found: C, 58.25; H, 5.52; N, 5.07.

2-[4-({(Furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-2-methoxy phenoxy]-2-methylpropanoic acid (**22c**)

This compound was obtained as a pale yellow solid in 86% yield by using **21c** (0.95 mmol), NaOH (1M aqueous solution, 2.0 mL), methanol (2.0 mL) and THF (4.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.62 (6H, s), 2.30 (3H, s), 3.50(3H, s), 3.60(2H, s), 3.70 (2H, s), 3.90 (3H, s), 6.20 (1H, s), 6.35(1H, s), 6.90 (2H, s), 7.00 (1H, s), 7.40−7.50 (4H, m), 8.00−8.05 (2H, m).

MS (ESI) *m/z*: 491$(M+H)^+$.

Anal. Calcd. for $C_{28}H_{30}N_2O_6 \cdot 1.25H_2O$: C, 65.55; H, 6.38; N, 5.46. Found: C, 65.45; H, 6.33; N, 5.45.

2-[4-({(Furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-2-methyl phenoxy]-2-methylpropanoic acid (**22d**)

This compound was obtained as a pale yellow solid in 86% yield by using **21d** (0.32 mmol), NaOH (1M aqueous solution, 1.0 mL), methanol (1.0 mL) and THF (2.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.55 (6H, s), 2.10 (3H, s), 2.20 (3H, s), 3.80 (2H, s), 4.05 (2H, s),

4.15 (2H, s), 6.35 (1H, m), 6.50 (1H, m), 7.00 (1H, m), 7.10 (1H, m), 7.30−7.50 (6H, m), 8.00−8.05 (2H, m).

MS (ESI) *m/z*: 475 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{30}N_2O_5 \cdot 0.75H_2O$: C, 68.91; H, 6.51; N, 5.74. Found: C, 68.99; H, 6.47; N, 5.66.

2-[4-({(Furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoic acid (**22e**)

This compound was obtained as a colorless solid in 95% yield by using **21e** (0.39 mmol), NaOH (1M aqueous solution, 1.0 mL), methanol (1.0 mL) and THF (2.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.55 (6H, s), 2.20 (6H, s), 2.30 (3H, s), 3.50 (2H, s), 3.52 (2H, s), 3.75 (3H, s), 6.20 (1H, s), 6.40(1H, s), 7.00 (2H, s), 7.40−7.50 (4H, m), 8.00−8.05 (2H, m).

MS (ESI) *m/z*: 489 $(M+H)^+$.

HRMS (ESI) *m/z*: $[M-H]^-$ Calcd for $C_{29}H_{32}N_2O_5$ 487.2239; Found 487.2252.

Anal. Calcd. for $C_{29}H_{32}N_2O_5 \cdot 0.5H_2O$: C, 70.00; H, 6.68; N, 5.63. Found: C, 70.06; H, 6.71; N, 5.53.

2-[3-Chloro-4-({(furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl) phenoxy]-2-methylpropanoic acid (**22f**)

This compound was obtained as a pale yellow solid in 84% yield by using **21e** (0.78 mmol), NaOH (1M aqueous solution, 2.0 mL), methanol (2.0 mL) and THF (4.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.67 (6H, s), 2.05 (3H, s), 3.70(2H, s), 4.00−4.15 (5H, m), 6.30 (1H, s), 6.50−6.53(1H, m), 6.75−6.90 (2H, m), 7.40−7.50 (5H, m), 8.00−8.05 (2H, m).

MS (ESI) *m/z*: 495 $(M+H)^+$.

Anal. Calcd. for $C_{27}H_{27}ClN_2O_5 \cdot H_2O$: C, 63.22; H, 5.70; N, 5.46. Found: C, 63.35; H, 5.74; N, 5.17.

2-[4-({(Furan-2-ylmethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-3-methoxy phenoxy]-2-methylpropanoic acid (**22g**)

This compound was obtained as a pale yellow solid in 70% yield by using **21g** (0.87 mmol), NaOH (1M aqueous solution, 2.0 mL), methanol (2.0 mL) and THF (4.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.62 (6H, s), 2.00 (3H, s), 3.50(3H, s), 3.80(2H, s), 4.00 (2H, s), 4.20 (2H, s), 6.20−6.60 (4H, m), 7.40−7.50 (6H, m), 8.00−8.05 (2H, m).

MS (ESI) *m/z*: 491 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{30}N_2O_6 \cdot 0.75H_2O$: C, 66.72; H, 6.30; N, 5.56. Found: C, 66.86; H, 6.28; N, 5.49.

General procedure for 2-[(substituted)-Fluorophenyl]-4,5-dimethyloxazole 3-oxide (25a−c)

To a solution of HCl (4M EtOAc solution, 5.0 mL) were added corresponding aldehyde (**23a−c**, 5.0 mmol) and diacetyl monooxyme (**24**, 0.51 g, 5.0 mmol) at 0°C and stirred at room temperature overnight. After the solvent was removed *in vacuo*, the residue was solidified with diethyl ether to provide **25a−c** HCl salts.

2-(2-Fluorophenyl)-4,5-dimethyloxazole 3-oxide (**25a**)

This compound was obtained as a pale yellow solid in 81% yield.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.15 (3H, s), 2.41 (3H, s), 7.41−7.49 (2H, m), 7.63 (1H, dd, J = 13.7, 6.3 Hz), 8.82−8.86 (1H, m).

MS (ESI) *m/z* 208 $(M+H)^+$.

2-(3-Fluorophenyl)-4,5-dimethyl-oxazole 3-oxide (**25b**)

This compound was obtained as a pale yellow solid in 85% yield.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.48 (3H, s), 2.50 (3H, s), 7.38−7.43 (1H, m), 7.58−7.64 (1H, m), 8.01−8.04 (1H, m), 8.18−8.20 (1H, m).

MS (ESI) *m/z*: 208 $(M+H)^+$.

2-(4-Fluorophenyl)-4,5-dimethyloxazole 3-oxide (**25c**)

This compound was obtained as a pale yellow solid in 47% yield.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.45 (3H, s), 1.57 (3H, s), 7.34−7.37 (4H, m).

MS (ESI) *m/z*: 208 $(M+H)^+$.

General procedure for 4-(chloromethyl)-2-[(substituted)-fluorophenyl]-5-methyl-1,3-oxazole (26a–c)

To a solution of **25a−c** in MeCN (40 ml) was added phosphoryl chloride at 0°C and stirred at room temperature, overnight. After the solvent was removed *in vacuo*, the resulting solid was collected by filtration and washed with water to provide **26a−c**.

4-(Chloromethyl)-2-(2-fluorophenyl)-5-methyl-1,3-oxazole (**26a**)

This compound was obtained as a colorless solid in 79 % yield by using **25a** (4.0 mmol), MeCN (40 mL) and phosphoryl chloride (8.0 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.45 (3H, s), 4.58 (2H, s), 7.16−7.27 (2H, m), 7.39−7.45 (1H, m), 7.98−8.03 (1H, m).

MS (ESI) *m/z*: 226 $(M+H)^+$.

4-(Chloromethyl)-2-(3-fluorophenyl)-5-methyl-1,3-oxazole (**26b**)

This compound was obtained as a colorless solid in 14 % yield by using **25b** (3.0 mmol), MeCN (5.0 mL) and phosphoryl chloride (3.0 mmol): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.43 (3H, s), 4.54 (2H, s), 7.09−7.15 (1H, m), 7.38−7.43 (1H, m), 7.67−7.71 (1H, m), 7.77−7.80 (1H, m). MS (ESI) *m/z*: 226 $(M+H)^+$.

4-(Chloromethyl)-2-(4-fluorophenyl)-5-methyl-1,3-oxazole (**26c**)

this compound was obtained as a colorless solid in 42 % yield by using **25c** (2.3 mmol), MeCN (20 mL) and phosphoryl chloride (4.7 mmol).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.42 (3H, s), 4.54 (2H, s), 7.10−7.15 (2H, m), 7.98−8.02 (2H, m).

MS (ESI) *m/z*: 226 $(M+H)^+$.

[2-Phenyl-5-(trifluoromethyl)-1,3-oxazol-4-yl]methanol (28)

To a solution of **27** (0.48 g, 1.9 mmol) in THF (30 mL), BH_3-THF complex (1 M THF solution, 9.4 mL) was added and stirred at room temperature for 3 hours. After the solvent was removed *in vacuo*, the residue was dissolved in CH_2Cl_2, washed with water, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc = 3/1, v/v) to provide **28** as a colorless solid (0.40 g, 87%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 2.17 (1H, br s), 4.76−4.77 (2H, m), 7.47−7.56 (3H, m), 8.07−8.10 (2H, m).

MS (ESI) *m/z*: 244 $(M+H)^+$.

4-(Bromomethyl)-2-phenyl-5-(trifluoromethyl)-1,3-oxazole (29)

To a solution of **28** (0.19 g, 0.76 mmol) in CH_2Cl_2 (20 mL) were added triphenylphosphine (0.40 g, 1.5 mmol) and *N*-bromosuccinimide (0.36 g, 1.5 mmol), and stirred at room temperature for 3 hours. Water was added to the reaction mixture and extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc = 4/1, v/v) to provide **29** as a colorless solid (214 mg, 92%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.48 (2H, s), 7.47−7.57 (3H, m), 8.07−8.10 (2H, m).

MS (ESI) *m/z*: 306 $(M+H)^+$.

Ethyl 4-(bromomethyl)-2-phenyl-1,3-oxazole-5-carboxylate (31)

To a solution of **30** (0.97 g, 4.2 mmol) in CCl_4 (20 mL) were added *N*-bromosuccinimide (0.75 g, 4.2 mmol) and 2,2'-azobis(isobutyronitrile) (0.14 g, 0.84 mmol), and stirred under a reflux condition overnight. After precipitates were filtered out, the filtrate was concentrated and then the crude product was purified by column chromatography on silica gel (Hexane/EtOAc = 93/7 then 9/1 as eluent, v/v) to provide **31** as a colorless solid (766 mg, 45%).

^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J = 7.3 Hz), 4.46 (2H, q, J = 7.3 Hz), 4.73 (2H, s), 7.47−7.53 (3H,

m), 8.14−8.15 (2H, m).

General procedure for 2-(substituted)amino-3-oxo-(alkanoic) acid ethyl ester (35a−c)

After **32−c** was added to acetic acid, a solution of sodium nitrite in water was added dropwise to this at 0°C. After the reaction mixture was stirred at room temperature overnight, saturated $NaHCO_3$ aqueous solution was added to the reaction mixture, extracted with EtOAc, dried over Na_2SO_4 and concentrated to afford **33a−c**. After **33a−c** was dissolved in HCl (1M ethanol solution), 10% palladium on carbon was added and then the reaction mixture was stirred under hydrogen atmosphere at room temperature overnight. Palladium on carbon was filtered out and then the filtrate was concentrated to provide **34a−c** HCl salts. To a solution of **34a−c** in CH_2Cl_2 were added triethylamine and a corresponding acid chloride. The mixture was stirred at room temperature for 2 hours. Water was added to the reaction mixture, extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel to provide **35a−c**.

2-[(Tetrahydropyran-4-ylcarbonyl)amino]-3-oxo-butyric acid ethyl ester (**35a**)

This compound was obtained as a pale yellow solid in 48% yield by using **32a** (20 mmol), acetic acid (20 mL), sodium nitrite (30 mmol) and 10% palladium on carbon (0.40 g), followed by **34a** (10 mmol), TEA (30 mmol), tetrahydropyran-4-carbonyl chloride (12 mmol) and CH_2Cl_2 (0.10 L).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32 (3H, t, J = 7.1 Hz), 1.77−1.84 (4H, m), 2.41 (3H, s), 2.44−2.52 (1H, m), 3.40−3.47 (2H, m), 3.99−4.04 (2H, m), 4.24−4.32 (2H, m), 5.23 (1H, d, J = 6.6 Hz), 6.65 (1H, d, J = 5.1 Hz).

MS (ESI) m/z: 258 $(M+H)^+$.

2-Benzoylamino-3-oxo-pentanoic acid ethyl ester (**35b**)

This compound was obtained as a colorless oil in 78% yield by using **32b** (8.7 mmol), acetic acid

(10 mL), sodium nitrite (13 mmol), 10% palladium on carbon (0.20 g), TEA (17 mmol), benzoyl chloride (8.7 mmol) and CH_2Cl_2 (50 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.15 (3H, t, J = 7.1 Hz), 1.32 (3H, t, J = 7.1 Hz), 2.75−2.91 (2H, m), 4.30 (2H, q, J = 7.1 Hz), 5.44 (1H, d, J = 6.6 Hz), 7.33−7.56 (4H, m), 7.84−7.86 (2H, m).

MS (ESI) *m/z*: 264 $(M+H)^+$.

2-Benzoylamino-4-methyl-3-oxo-pentanoic acid ethyl ester (**35c**)

This compound was obtained as a pale yellow solid in 67% yield by using **32c** (32 mmol), acetic acid (40 mL), sodium nitrite (47 mmol) and 10% palladium on carbon (0.50 g), followed by **34c** (11 mmol), TEA (21 mmol), benzoyl chloride (16 mmol) and CH_2Cl_2 (0.10 L).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.16 (3H, d, J = 6.8 Hz), 1.26 (3H, d, J = 6.8 Hz), 1.32 (3H, t, J = 7.1 Hz), 3.16 (1H, hept., J = 6.8 Hz), 4.26−4.34 (2H, m), 5.60 (1H, d, J = 6.5 Hz), 7.31 (1H, br d, J = 6.5 Hz), 7.44−7.56 (3H, m), 7.83−7.87 (2H, m).

MS (ESI) *m/z*: 278 $(M+H)^+$.

General procedure for Ethyl 5-(substituted)-2-(substituted)-1,3-oxazole-4-carboxylate (36a−c)

To a solution of **35a−c** in chloroform (0−5 mL) was added phosphoryl chloride and stirred under reflux conditions for 1 hour. The reaction mixture was dropped into an ice-cold saturated $NaHCO_3$ aqueous solution and then the mixture was stirred for 2 hours. Organics was extracted with chloroform, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc) to provide **36a−c**.

Ethyl 5-methyl-2-(tetrahydro-2H-pyran-4yl)-1,3-oxazole-4-carboxylate (**36a**)

This compound was obtained as a pale yellow oil in 63% yield by using **35a** (2.2 mmol), $CHCl_3$ (10 mL) and phosphoryl chloride (5.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.32 (3H, t, J = 6.7 Hz), 1.97 (4H, br s), 2.61 (3H, s), 3.08 (1H, br s),

3.47−3.55 (2H, m), 4.00−4.06 (2H, m), 4.39 (2H, d, *J* = 6.7 Hz).

MS (ESI) *m/z*: 240 $(M+H)^+$.

Ethyl 5-ethyl-2-phenyl-1,3-oxazole-4-carboxylate (**36b**)

This compound was obtained as a colorless solid in 88% yield by using **35b** (6.7 mmol), and phosphoryl chloride (11 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 1.35 (3H, t, *J* = 7.6 Hz), 1.42 (3H, t, *J* = 7.1 Hz), 3.14 (2H, t, *J* = 7.6 Hz), 4.43 (2H, t, *J* = 7.1 Hz), 7.45−7.47 (3H, m), 8.07−8.10 (2H, m).

MS (ESI) *m/z*: 246 $(M+H)^+$.

Ethyl 5-(propan-2-yl)-2-phenyl-1,3-oxazole-4-carboxylate (**36c**)

This compound was obtained as a pale yellow solid in 90% yield by using **35c** (9.3 mmol), and phosphoryl chloride (16 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 1.37 (6H, d, *J* = 7.0 Hz), 1.43 (3H, t, *J* = 7.1 Hz), 3.85 (1H, hept., *J* = 7.0 Hz), 4.43 (2H, q, *J* = 7.1 Hz), 7.44−7.48 (3H, m), 8.06−8.10 (2H, m).

MS (ESI) *m/z*: 260 $(M+H)^+$.

General procedure for 4-Chloromethyl-5-(substituted)-2-(substituted)-1,3-oxazole (38a−c)

To a solution of **36a−c** in THF was added lithium borohydride and stirred under a reflux condition for 1 hour. After the solvent was removed *in vacuo*, water was added to the residue, extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (chloroform/methanol) to provide **37a−c**. To a solution of **37a−c** in chloroform was added thionyl chloride and stirred at room temperature for 2 hours. After the solvent was removed *in vacuo*, the crude product was purified by column chromatography on silica gel (hexane/EtOAc) to provide **38a−c**.

4-(Chloromethyl)-5-methyl-2-(tetrahydro-2*H*-pyran-4-yl)-1,3-oxazole (**38a**)

This compound was obtained as a pale yellow solid in 18% yield by using **36a** (3.3 mmol), lithium borohydride (10 mmol), THF (50 mL), thionyl chloride (10 mmol) and chloroform (15 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.86−1.99 (4H, m), 2.32 (3H, s), 2.95−3.03 (1H, m), 3.47−3.54 (2H, m), 3.99−4.04 (2H, m), 4.47 (2H, s).

MS (ESI) *m/z*: 216 $(M+H)^+$.

4-(Chloromethyl)-5-ethyl-2-phenyl-1,3-oxazole (**38b**)

This compound was obtained as a yellow oil in 86% yield by using **36b** (5.7 mmol), lithium borohydride (8.6 mmol), THF (70 mL), thionyl chloride (15 mmol) and chloroform (30 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ:1.33 (3H, t, J = 7.6 Hz), 2.79 (2H, q, J = 7.6 Hz), 4.57 (2H, s), 7.42−7.45 (3H, m), 8.00−8.04 (2H, m).

MS (ESI) *m/z*: 222 $(M+H)^+$.

4-(Chloromethyl)-5-(propan-2-yl)-2-phenyl-1,3-oxazole (**38c**)

This compound was obtained as a yellow oil in 89% yield by using **36c** (8.3 mmol), lithium borohydride (12 mmol) and THF (0.10 L), followed by **37c** (3.0 mmol), thionyl chloride (9.0 mmol) and chloroform (20 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.37 (6H, d, J = 7.1 Hz), 3.19 (1H, q, J = 7.1 Hz), 4.59 (2H, s), 7.42−7.47 (3H, m), 8.00−8.04 (2H, m).

General procedure for 2-[4-({[2-(Substituted)-5-(substituted)oxazol-4-ylmethyl]furan-2-yl methylamino}methyl)-2,6-dimethylphenoxy]-2-methylpropionic acid *tert*-butyl ester (40a−c, f−i and m)

To a solution of **26a−c**, **29**, **31** or **38a−c** with **39** in DMF was added potassium carbonate and stirred at 40°C for 1−3 days. Water was added to the reaction mixture and extracted with EtOAc. The

organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc) to provide **40**.

tert-Butyl 2-(4-{[{[2-(2-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino] methyl}-2,6-dimethylphenoxy)-2-methylpropanoate (**40a**).

This compound was obtained as a pale yellow solid in 81% yield by using **26a** (1.0 mmol), **39** (1.0 mmol), potassium carbonate (1.2 mmol) and DMF (10 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ:1.41 (6H, s), 1.51 (9H, s), 2.21 (6H, s), 2.29 (3H, s), 3.54 (2H, s), 3.57 (2H, s), 3.76 (2H, s), 6.26−6.28 (1H, m), 6.33−6.35 (1H, m), 6.98 (2H, s), 7.14−7.26 (2H, m), 7.37−7.40 (2H, m), 8.00−8.04 (1H, m).

MS (EI) *m/z*: 562 M^+.

tert-Butyl 2-(4-{[{[2-(3-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino] methyl}-2,6-dimethylphenoxy)-2-methylpropanoate (**40b**)

This compound was obtained as a colorless solid in 34% yield by using **26b** (0.34 mmol), **39** (0.90 mmol), potassium carbonate (0.38 mmol) and DMF (5.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.41 (6H, s), 1.51 (9H, s), 2.21 (6H, s), 2.26 (3H, s), 3.54 (4H, s), 3.77 (2H, s), 6.25−6.27 (1H, m), 6.35 (1H, br s), 6.97 (2H, s), 7.06−7.13 (1H, m), 7.37−7.44 (2H, m), 7.68−7.72 (1H, m), 7.80 (1H, d, J = 7.4 Hz).

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

tert-Butyl 2-(4-{[{[2-(4-fluorophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino] methyl}-2,6-dimethylphenoxy)-2-methylpropanoate (**40c**).

This compound was obtained as a colorless solid in 86% yield by using **26c** (0.91 mmol), **39** (0.91 mmol), potassium carbonate (1.0 mmol) and DMF (10 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.41 (6H, s), 1.51 (9H, s), 2.21 (6H, s), 2.25 (3H, s), 3.53 (4H, s),

3.77 (2H, s), 6.25−6.26 (1H, m), 6.33−6.35 (1H, m), 6.97 (2H, s), 7.08−7.15 (2H, m), 7.40−7.41 (1H, m), 7.98−8.02 (2H, m).

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

tert-Butyl 2-[4-({[(2-phenyl-5-ethyl-1,3-oxazol-4-yl)methyl](furan-2-ylmethyl)amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoate (**40f**)

This compound was obtained as a colorless solid in 22% yield by using **38b** (1.1 mmol), **39** (1.1 mmol), potassium carbonate (1.2 mmol) and DMF (10 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.23 (3H, t, J = 7.6 Hz), 1.41 (6H, s), 1.51 (9H, s), 2.21 (6H, s), 2.64 (2H, q, J = 7.6 Hz), 3.53 (2H, s), 3.56 (2H, s), 3.76 (2H, s), 6.26 (1H, d, J = 2.9 Hz), 6.34 (1H, dd, J = 2.9, 1.7 Hz), 6.98 (2H, s), 7.39−7.46 (4H, m), 8.01−8.04 (2H, m).

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

tert-Butyl 2-(4-{[{[2-phenyl-5-(propan-2-yl)-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoate (**40g**)

This compound was obtained as a colorless solid in 57% yield by using **38c** (0.90 mmol), **39** (0.90 mmol), potassium carbonate (1.4 mmol) and DMF (10 mL).

^{1}H-NMR (DMSO-D_6) δ: 1.20 (6H, d, J = 6.8 Hz), 1.33 (9H, s), 2.13 (6H, s), 2.97−3.03 (1H, m), 3.46 (2H, s), 3.49 (2H, s), 3.69 (2H, s), 6.37 (1H, d, J = 3.2 Hz), 6.43−6.44 (1H, m), 6.97 (2H, s), 7.48−7.54 (3H, m), 7.62−7.63 (1H, m), 7.92−7.96 (2H, m).

tert-Butyl 2-(4-{[{[2-phenyl-5-(trifluoromethyl)-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoate (**40h**)

This compound was obtained as a colorless solid in 87% yield by using **29** (0.69 mmol), **39** (0.69 mmol), potassium carbonate (0.76 mmol) and DMF (5.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.40 (6H, s), 1.51 (9H, s), 2.20 (6H, s), 3.59 (2H, s), 3.75 (2H, s),

3.82 (2H, s), 6.27 (1H, d, *J* = 3.2 Hz), 6.33−6.35 (1H, m), 6.98 (2H, s),7.40−7.41 (1H, m), 7.47−7.52 (3H, m), 8.09−8.12 (2H, m).

MS (ESI) *m/z*: 599 $(M+H)^+$.

Ethyl 4-{[{4-[(1-tert-butoxy-2-methyl-1-oxopropan-2yl)oxy]-3,5-dimethylbenzyl}(furan-2-yl methyl)amino]methyl}-2-phenyl-1,3-oxazole-5-carboxylate (**40i**)

This compound was obtained as a pale yellow oil in 91% yield by using **31** (1.9 mmol), **39** (1.8 mmol), potassium carbonate (1.9 mmol) and DMF (10 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 1.35 (3H, t, *J* = 7.1 Hz), 1.40 (6H, s), 1.50 (9H, s), 2.20 (6H, s), 3.65 (2H, s), 3.84 (2H, s), 4.03 (2H, s), 4.34 (2H, q, *J* = 7.1 Hz), 6.24−6.36 (2H, m), 7.00 (2H, s), 7.40 (1H, br s), 7.48−7.53 (3H, m), 8.18−8.21 (2H, m).

tert-Butyl 2-(4-{[{[2-(tetrahydro-2*H*-pyran-4-yl)-5-methyl-1,3-oxazol-4-yl]methyl}(furan-2-yl methyl)amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoate (**40m**)

This compound was obtained as a colorless solid in 77% yield by using **38a** (0.59 mmol), **39** (0.59 mmol), potassium carbonate (0.88 mmol) and DMF (10 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 1.42 (6H, s), 1.51 (9H, s), 1.89−1.97 (4H, m), 2.14−2.23 (9H, m), 2.94−2.99 (1H, m), 3.42−3.54 (6H, m), 3.70 (2H, s), 3.98−4.04 (2H, m), 6.20−6.23 (1H, m), 6.32 (1H, br s), 6.96 (2H, s), 7.38 (1H, br s).

MS (ESI) *m/z*: 553 $(M+H)^+$.

tert-Butyl 2-[4-({(furan-2-ylmethyl)[(2-phenyl-1,3-oxazol-4-yl)carbonyl]amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoate (40d)

To a solution of methyl 2-phenyl-1,3-oxazole-4carboxylate (0.21 g, 1.0 mmol) in THF (7.0 mL) and water (2.0 mL) was added lithium hydroxide (49 mg, 2.0 mmol) and stirred at room temperature overnight. HCl (1M aqueous solution, 1.0 mmol) was added to the reaction mixture and then stirred

at room temperature. After the solvent was removed *in vacuo*, DMF (10 mL), **39** (0.38 g, 1.0 mmol), EDCI (0.39 g, 2.0 mmol) and HOBt (69 mg, 0.51 mmol) were added to the residue and stirred at room temperature for 2 days. After the solvent was removed *in vacuo*, water was added to the residue and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc = 3/1, v/v) to provide **40d** as a colorless solid (0.23 g, 41%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ:1.43 (6H, s), 1.51 (9H, s), 2.22 (6H, s), 4.61, 4.64 (2H, each s), 5.11, 5.14 (2H, each s), 6.27−6.32 (2H, m), 6.94 (2H, s), 7.36−7.49 (4H, m), 7.95−8.07 (2H, m), 8.26−8.33 (1H, m).

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

***tert*-Butyl 2-[4-({[(2-phenyl -1,3-oxazol-4-yl)methyl](furan-2-ylmethyl)amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoate (40e)**

To a solution of **40d** (0.23 g, 0.42 mmol) in THF (20 mL) was added BH_3-THF complex (1 M THF solution, 4.2 mL) and stirred at 50°C overnight. After the solvent was removed *in vacuo*, EtOH (8.0 mL), water (2.0 mL) and TEA (2.0 mL) were added to the residue and stirred under a reflux condition for 2 hours. After the solvent was removed *in vacuo*, water was added to the residue, extracted with DCM, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc = 2/1, v/v) to provide **40e** as a colorless solid (0.11 g, 50%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.42 (6H, s), 1.51 (9H, s), 2.23 (6H, s), 3.58 (2H, s), 3.69 (2H, s), 3.75 (2H, s), 6.24 (1H, d, J = 3.1 Hz), 6.34 (1H, dd, J = 3.1, 2.0 Hz), 7.00 (2H, s), 7.41−7.47 (4H, m), 7.63 (1H, s), 8.04−8.06 (2H, m).

MS (ESI) *m/z*: 531 $(M+H)^+$.

***tert*-Butyl 2-(4-{[{[2-phenyl -5-(hydroxymethyl)-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl) amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoate (40k)**

To a mixture of **40i** (0.85 g, 1.4 mmol), THF (15 mL) and water (3.0 mL) was added NaOH (1M aqueous solution, 3.1 mL) and stirred at 50°C for 1.5 hours and then stirred at room temperature for 3 days. After HCl (1M aqueous solution, 3.1 mL) was added to the reaction mixture, the solvent was removed *in vacuo*. After CH_2Cl_2 was added to the residue, precipitates were filtered out and the filtrate was concentrated. After the residue was dissolved in THF (20 mL), *N*-methylmorpholine (0.19 mL, 1.7 mmol) and isobutyl chloroformate (0.22 mL, 1.7 mmol) were added to the reaction solution at -40°C and stirred at the same temperature for 15 minutes. After precipitates were filtered out, sodium borohydride (79 mg, 2.1 mmol) was added to the filtrate and stirred at room temperature for 1 hour. After the solvent was removed *in vacuo*, water was added to the residue, extracted with CH_2Cl_2, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc = 3/1, v/v) to provide **40k** as a pale yellow solid (0.59 g, 65%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.42 (6H, s), 1.51 (9H, s), 2.22 (6H, s), 3.56 (2H, br s), 3.70 (4H, br s), 4.69 (2H, s), 6.28−6.36 (2H, m), 6.94 (2H, br s), 7.40−7.48 (4H, m), 7.95−8.01 (2H, m).

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

***tert*-Butyl 2-(4-{[{[2-phenyl -5-(dimethylcarbamoyl)-1,3-oxazol-4-yl]methyl}(furan-2-yl methyl)amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoate (40l)**

To a mixture of **40i** (0.68 g, 1.1 mmol), THF (20 mL) and water (5.0 mL) was added NaOH (1M aqueous solution, 3.4 mL) and stirred at 50°C for 4 hours. After DMF (20 mL), dimethylamine HCl salts (0.14 g, 1.7 mmol), EDCI (0.43 g, 2.3 mmol) and HOBt (76 mg, 0.57 mmol) were added to the reaction mixture at room temperature and the mixture was stirred overnight. After the solvent was removed *in vacuo*, water was added to the residue, extracted with EtOAc, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel

(Hexane/EtOAc = 1/1, v/v) to provide **40l** as a pale yellow solid (0.64 g, 94%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.40 (6H, s), 1.51 (9H, s), 2.21 (6H, s), 3.10 (3H, s), 3.16 (3H, s), 3.61 (2H, s), 3.79 (2H, s), 3.93 (2H, s), 6.25 (1H, s), 6.32 (1H, s), 7.00 (2H, s), 7.38−7.51 (4H, m), 8.09−8.10 (2H, m).

MS (ESI) *m/z*: 602 $(M+H)^+$.

General procedure for 2-[4-({[2-(Substituted)-5-(substituted)oxazol-4-ylmethyl]furan-2-yl methylamino}methyl)-2,6-dimethylphenoxy]-2-methylpropionic acid (41a−m)

To a solution of **40** in CH_2Cl_2 was added HCl (4M dioxane solution) and stirred at room temperature overnight. After the solvent was removed *in vacuo*, the residue was purified by preparative thin-layer chromatography (dichloromethane/MeOH) to provide **41a−m**.

2-(4-{[{[2-(2-Fluorophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoic acid (**41a**)

This compound was obtained as a pale yellow solid in 89% yield by using **40a** (0.79 mmol), CH_2Cl_2 (3.0 mL) and HCl (4M dioxane solution, 6.0 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.33 (6H, s), 2.14 (6H, s), 2.25 (3H, s), 3.48 (2H, s), 3.50 (2H, s), 3.69 (2H, s), 6.37 (1H, d, J = 3.2 Hz), 6.43 (1H, d, J = 3.2, 1.7 Hz), 6.97 (2H, s), 7.33−7.40 (2H, m), 7.51−7.57 (1H, m), 7.62−7.63 (1H, m), 7.96−8.00 (1H, m).

MS (ESI) *m/z* : 507$(M+H)^+$.

Anal. Calcd. for $C_{29}H_{31}FN_2O_5 \cdot 0.3H_2O \cdot 0.25$dioxane: C, 67.48; H, 6.34; F,3.56; N, 5.25. Found: C, 67.51; H, 6.22; F, 3.51; N, 5.42.

2-(4-{[{[2-(3-Fluorophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoic acid (**41b**)

This compound was obtained as a colorless solid in 73% yield by using **40b** (0.12 mmol), CH_2Cl_2

(3.0 mL) and HCl (4M dioxane solution, 3.0 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.26 (6H, s), 2.06 (6H, s), 2.17 (3H, s), 3.40 (2H, s), 3.42 (2H, s), 3.62 (2H, s), 6.29 (1H, d, J = 3.2 Hz), 6.35−6.37 (1H, m), 6.89 (2H, s), 7.24−7.30 (1H, m), 7.47−7.60 (3H, m), 7.70 (1H, d, J = 6.8 Hz), 12.75 (1H, br s).

MS (ESI) *m/z*: 507$(M+H)^+$.

Anal. Calcd. for $C_{29}H_{31}FN_2O_5 \cdot 0.3H_2O$: C, 68.03; H, 6.22; F, 3.71; N, 5.47. Found: C, 67.98; H, 6.14; F, 3.82; N, 5.39.

2-(4-{[{[2-(4-Fluorophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoic acid (**41c**)

This compound was obtained as a colorless solid in 47% yield by using **40c** (0.87 mmol), CH_2Cl_2 (5.0 mL) and HCl (4M dioxane solution, 5.0 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.32 (6H, s), 2.13 (6H, s), 2.23 (3H, s), 3.45 (2H, s), 3.49 (2H, s), 3.69 (2H, s), 6.36 (1H, d, J = 2.9 Hz), 6.43 (1H, dd, J = 2.9, 1.8 Hz), 6.95 (2H, s), 7.33−7.37 (2H, m), 7.62 (1H, d, J = 1.8 Hz), 7.95−7.99 (2H, m), 12.81 (1H, br s).

MS (ESI) *m/z*: 507 $(M+H)^+$.

Anal. Calcd. for $C_{29}H_{31}FN_2O_5 \cdot 0.3H_2O \cdot 0.15$dioxane: C, 67.93; H, 6.28; F,3.63; N, 5.35. Found: C, 67.77; H, 6.25; F, 3.63; N, 5.29.

2-[4-({[(2-Phenyl -1,3-oxazol-4-yl)methyl](furan-2-ylmethyl)amino}methyl)-2,6-dimethyl phenoxy]-2-methylpropanoic acid (**41e**)

This compound was obtained as a colorless solid in 67% yield by using **40e** (0.21 mmol), CH_2Cl_2 (5.0 mL) and HCl (4M dioxane solution, 10 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.31 (6H, s), 2.18 (6H, s), 3.51 (2H, s), 3.56 (2H, s), 3.65 (2H, s), 6.37 (1H, d, J = 2.9 Hz), 6.43 (1H, dd, J = 2.9, 2.0 Hz), 6.98 (2H, s), 7.52−7.56 (3H, m), 7.63 (1H, dd, J = 1.7, 0.7 Hz), 7.97−8.00 (2H, m), 8.08 (1H, s).

MS (ESI) *m/z*: 475 $(M+H)^+$.

2-[4-({[(2-Phenyl-5-ethyl-1,3-oxazol-4-yl)methyl](furan-2-ylmethyl)amino}methyl)-2,6-dimethyl phenoxy]-2-methylpropanoic acid (**41f**)

This compound was obtained as a colorless solid in 50% yield by using **40f** (0.25 mmol), CH_2Cl_2 (5.0 mL) and HCl (4M dioxane solution, 5.0 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.16 (3H, t, J = 7.5 Hz), 1.32 (6H, s), 2.14 (6H, s), 2.60 (2H, q, J = 7.5 Hz), 3.46 (2H, s), 3.49 (2H, s), 3.69 (2H, s), 6.36 (1H, d, J = 3.2 Hz), 6.43 (1H, dd, J = 3.2, 2.0 Hz), 6.96 (2H, s), 7.46−7.54 (3H, m), 7.62−7.63 (1H, m), 7.93−7.95 (2H, m).

MS (ESI) *m/z*: 503 $(M+H)^+$.

Anal. Calcd. for $C_{30}H_{34}N_2O_5 \cdot 0.3H_2O$: C, 70.93; H, 6.86; N, 5.51. Found: C, 70.89; H, 6.86; N, 5.42.

2-(4-{[{[2-Phenyl-5-(propan-2-yl)-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoic acid (**41g**)

This compound was obtained as a colorless solid in 37% yield by using **40g** (0.50 mmol), CH_2Cl_2 (5.0 mL) and HCl (4M dioxane solution, 5.0 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.20 (6H, d, J = 6.8 Hz), 1.33 (6H, s), 2.13 (6H, s), 2.97−3.03 (1H, m), 3.46 (2H, s), 3.49 (2H, s), 3.69 (2H, s), 6.36−6.38 (1H, m), 6.42−6.44 (1H, m), 6.97 (2H, s), 7.46−7.55 (3H, m), 7.62−7.63 (1H, m), 7.92−7.96 (2H, m), 12.80 (1H, br s).

MS (FAB) *m/z*: 517$(M+H)^+$.

Anal. Calcd. for $C_{31}H_{36}N_2O_5 \cdot 0.3H_2O$: C, 71.32; H, 7.07; N, 5.37. Found: C, 71.35; H, 7.00; N, 5.17.

2-(4-{[{[2-Phenyl-5-(trifluoromethyl)-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoic acid (**41h**)

This compound was obtained as a pale yellow solid in 82% yield by using **40h** (0.60 mmol), CH_2Cl_2 (5.0 mL) and HCl (4M dioxane solution, 5.0 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.29 (6H, s), 2.09 (6H, s), 3.55 (2H, s), 3.67 (2H, s), 3.78 (2H, s), 6.37 (1H, d, J = 3.2 Hz), 6.43 (1H, dd, J = 3.2, 2.0 Hz), 6.94 (2H, s), 7.57−7.66 (4H, m), 8.03−8.05 (2H, m).

MS (ESI) m/z: 543 $(M+H)^+$.

Anal. Calcd. for $C_{29}H_{29}N_2O_5 \cdot 0.4H_2O$: C, 63.36; H, 5.46; N, 5.10; F, 10.37. Found: C, 63.28; H, 5.39; N, 5.16; F, 10.46.

2-(4-{[{[2-Phenyl -5-(hydroxymethyl)-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoic acid (**41k**)

This compound was obtained as a colorless solid in 77% yield by using **40k** (0.31 mmol) CH_2Cl_2 (10 mL) and HCl (4M dioxane solution, 10 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.33 (6H, s), 2.14 (6H, s), 3.50 (2H, s), 3.53 (2H, s), 3.70 (2H, s), 4.43 (2H, s), 5.33 (1H, br s), 6.37 (1H, d, J = 3.2 Hz), 6.43 (1H, dd, J = 3.2, 1.9 Hz), 6.98 (2H, s), 7.51−7.56 (3H, m), 7.63 (1H, dd, J = 1.9, 0.7 Hz), 7.96−7.99 (2H, m).

MS (ESI) m/z: 505 $(M+H)^+$.

Anal. Calcd. for $C_{29}H_{32}N_2O_6 \cdot 0.3H_2O$: C, 68.30; H, 6.44; N, 5.49. Found: C, 68.26; H, 6.38; N, 5.38.

2-(4-{[{[2-Phenyl -5-(dimethylcarbamoyl)-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino] methyl}-2,6-dimethylphenoxy)-2-methylpropanoic acid (**41l**)

This compound was obtained as a colorless solid in 77% yield by using **40l** (0.27 mmol) CH_2Cl_2 (3.0 mL) and HCl (4M dioxane solution, 6.0 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.32 (6H, s), 2.13 (6H, s), 2.98 (3H, br s), 3.11 (3H, br s), 3.53 (2H, s), 3.70 (2H, s), 3.75 (2H, s), 6.33 (1H, d, J = 3.1 Hz), 6.41 (1H, dd, J = 3.1, 2.0 Hz), 6.95 (2H, s), 7.56−7.61 (4H, m), 8.03−8.06 (2H, m), 12.79 (1H, br s).

MS (FAB) m/z: 546 $(M+H)^+$.

Anal. Calcd. for $C_{31}H_{35}N_3O_6 \cdot 0.6H_2O$: C, 66.91; H, 6.56; N, 7.55. Found: C, 66.88; H, 6.48; N, 7.45.

2-(4-{[{[2-(Tetrahydro-2*H*-pyran-4-yl)-5-methyl-1,3-oxazol-4-yl]methyl}(furan-2-ylmethyl)amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoic acid (**41m**)

This compound was obtained as a colorless solid in 75% yield by using **40m** (0.46 mmol) CH_2Cl_2 (5.0 mL) and HCl (4M dioxane solution, 5.0 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.34 (6H, s), 1.62−1.75 (2H, m), 1.84−1.91 (2H, m), 2.12 (3H, s), 2.14 (6H, s), 2.97−3.02 (1H, m), 3.30−3.47 (5H, m), 3.56−3.64 (3H, m), 3.84−3.89 (2H, m), 6.31−6.33 (1H, m), 6.40−6.42 (1H, m), 6.94 (2H, s), 7.61 (1H, s), 12.80 (1H, br s).

MS(FAB) *m/z*: 497 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{36}N_2O_6 \cdot 0.5H_2O$: C, 66.52; H, 7.38; N, 5.54. Found: C, 66.47; H, 7.40; N, 5.26.

General procedure for 2-[2,6-dimethyl-4-({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl][(1,3-azol)-2-ylmethyl]amino}methyl)phenoxy]-2-methylpropanoic acid (43a−c)

To a solution of **42** in CH_2Cl_2 were added a corresponding aldehyde and sodium triacethoxyborohydride and stirred at room temperature overnight. The reaction mixture was diluted with EtOAc, washed with water, saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (Hexane/EtOAc) to provide tertiary amine compounds. To a solution of the prepared compound in methanol was added NaOH (2M aqueous solution) and stirred at room temperature overnight. The reaction mixture was quenched by HCl (1M aqueous solution). After methanol was removed *in vacuo*, the organics were extracted with EtOAc and then the organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/methanol) to provide the free form of **43a−c**. **43a** and **43b** were hydrochlorinated with HCl (4M dioxane solution), concentrated and recrystallized from (Hexane/EtOAc) to afford **43a** and **43b** HCl salts, respectively.

2-[2,6-Dimethyl-4-({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl](1,3-oxazol-2-ylmethyl)amino} methyl)phenoxy]-2-methylpropanoic acid (**43a**)

This compound was obtained as HCl salt form of a colorless solid in 56% yield.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.33 (6H, s), 2.14 (6H, s), 2.32 (3H, s), 4.11−4.35 (6H, m), 7.14 (2H, s), 7.30 (1H, m), 7.51-7.55 (3H, m), 7.93−7.95 (2H, m), 8.19 (1H, m).

MS (ESI) *m/z*: 490 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{31}N_3O_5$·HCl: C, 63.93; H, 6.13; N, 7.99. Found: C, 63.63; H, 6.42; N, 7.58.

2-[2,6-Dimethyl-4-({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl](1,3-thiazol-2-ylmethyl)amino} methyl)phenoxy]-2-methylpropanoic acid (**43b**)

This compound was obtained as HCl salt form of a colorless solid in 32% yield.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.41 (6H, s), 2.22 (6H, s), 2.25 (3H, s), 3.64 (2H, s), 3.65 (2H, s), 4.09 (2H, s), 7.04 (2H, s), 7.28 (1H, d, J = 3.2 Hz), 7.39−7.45 (3H, m), 7.69 (1H, d, J = 3.2 Hz), 7.98−8.01 (2H, m).

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

Anal. Calcd. for $C_{28}H_{31}N_3O_4S$ 1.25HCl·0.75H_2O: C, 59.55; H, 6.02; N, 7.45; S, 5.67; Cl, 7.84. Found: C, 59.67; H, 5.92; N, 6.99; S, 5.45; Cl, 8.14.

2-[2,6-Dimethyl-4-({[(1-methyl-1*H*-imidazol-2yl)methyl] [(5-methyl-2-phenyl-1,3-oxazol-4-yl) methyl]amino}methyl)phenoxy]-2-methylpropanoic acid (**43c**)

This compound was obtained as a colorless solid in 44% yield.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.32 (6H, s), 2.12 (6H, s), 2.22 (3H, s), 3.47 (2H, s), 3.48 (2H, s), 3.51 (3H, s), 3.68 (2H, s), 6.76 (1H, d, J = 1.2 Hz), 6.91 (2H, s), 7.03 (1H, d, J = 1.2 Hz), 7.48−7.54 (3H, m), 7.92−7.94 (2H, m).

MS (ESI) *m/z*: 503 $(M+H)^+$.

Anal. Calcd. for $C_{29}H_{34}N_4O_4$·0.25H_2O: C, 68.69; H, 6.86; N, 11.05. Found: C, 68.49; H, 6.93; N,

10.76.

Ethyl 2-(4-{[(2-*tert*-butoxy-2-oxoethyl)amino]methyl}-2,6-dimethylphenoxy)-2-methyl propanoate (45)

To a solution of **44** (16 g, 60 mmol) in THF (0.30 L) were added *tert*-butylglycinate (9.0 mL, 96 mmol) and $MgSO_4$ (50 g), and then the mixture was stirred under a reflux condition for 4 hours. After the insoluble matter was filtered through Celite, the filtrate was concentrated. After the residue was dissolved with methanol (0.10 L), sodium borohydride (2.3 g, 60 mmol) was added at 0°C and then the reaction mixture was stirred at room temperature for 4 hours. The solvent was removed *in vacuo* and the residue was diluted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 99/1 then 19/1 as eluent) to give compound **45** (22 g, 95%) as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.1 Hz), 1.46 (6H, s), 1.48 (9H, s), 2.18 (6H, s), 3.30 (2H, s), 3.65 (2H, s), 4.29 (2H, q, J = 7.1 Hz), 6.93 (2H, s).

MS (ESI) *m/z*: 380 $(M+H)^+$.

Ethyl 2-[4-({(2-*tert*-butoxy-2-oxoethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino} methyl)-2,6-dimethylphenoxy]-2-methylpropanoate (46)

To a solution of 4-(chloromethyl)-5-methyl-2-phenyl-1,3-oxazole (1.9 g, 9.0 mmol) and **45** (3.9 g, 10 mmol) in MeCN (30 mL) was added K_2CO_3 (2.5 g, 18 mmol). The reaction mixture was stirred under a reflux condition for 24 hours. After cooling the mixture to an ambient temperature, the solvent was removed *in vacuo*. The residue was diluted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 9/1 then 2/1 as eluent) to provide compound **46** (4.0 g, 81%) as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.1 Hz), 1.45 (6H, s), 1.48 (9H, s), 2.17 (6H, s), 2.30 (3H, s), 3.30 (2H, s), 3.71 (2H, s), 3.75 (2H, s), 4.28 (2H, q, J = 7.1 Hz), 6.99 (2H, s), 7.38−7.46 (3H, m), 8.00−8.02 (2H, m).

MS (ESI) *m/z*: 551 $(M+H)^+$.

_N_-{4-[(1-Ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3,5-dimethylbenzyl}-_N_-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]glycine (47)

To a solution of **46** (4.0 g, 7.3 mmol) in CH_2Cl_2 was added HCl (4M dioxane solution, 30 mL) at 0°C and stirred at room temperature for 14 hours. After the solvent was removed *in vacuo*, the residue was solidified with *n*-hexane to provide compound **47** HCl salt (3.2 g, 82%) as a pale yellow solid.

MS *m/z*: 495 $(M+H)^+$.

Ethyl 2-[4-({[2-(2-acetylhydrazinyl)-2-oxoethyl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl] amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoate (49)

To a solution of **47** (0.40 g, 0.86 mmol) in DMF (3.0 mL) were added acetohydrazide (77 mg, 1.0 mmol), EDCI (0.25 g, 1.3 mmol) and HOBt (0.20 g, 1.3 mmol). The reaction mixture was stirred at room temperature for 20 hours. The mixture was diluted with EtOAc, washed with water, 10% citric acid aqueous solution, saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, filtered and concentrated to give **49** (0.50 g) as a pale yellow oil. This compound was used for the next reaction without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.1 Hz), 1.45 (6H, s), 2.02 (3H, s), 2.18 (6H, s), 2.23 (3H, s), 3.40 (2H, s), 3.60 (2H, s), 3.65 (2H, s), 4.28 (2H, q, J = 7.1 Hz), 6.98 (2H, s), 7.42−7.45 (3H, m), 8.00−8.02 (2H, m), 8.62 (1H, br s), 10.12 (1H, br s).

MS (ESI) *m/z*: 551 $(M+H)^+$.

2-[2,6-Dimethyl-4-({[(5-methyl-1,3,4-oxadiazol-2-yl)methyl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoic acid (50)

To a solution of triphenylphosphine (0.68 g, 2.6 mmol) in CH_2Cl_2 (15 ml) were added hexachloroethane (0.51 g, 2.2 mmol) and triethylamine (0.72 mL, 5.1 mmol). After the reaction mixture was stirred at room temperature for 10 minutes, a solution of **28** (0.50 g, 1.0 mmol) in CH_2Cl_2 (5.0 mL) was added and stirred at the same temperature overnight. Saturated $NaHCO_3$ aqueous solution was added to the reaction mixture and stirred at an ambient temperature for 1 hour. The organics was extracted with CH_2Cl_2 and washed with brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 4/1 then 1/2 as eluent) to provide ethyl 2-[2,6-dimethyl-4-({[(5-methyl-1,3,4-oxadiazol-2-yl)methyl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoate as a yellow oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.1 Hz), 1.45 (6H, s), 2.18 (6H, s), 2.27 (3H, s), 2.51 (3H, s), 3.67 (4H, br-s), 3.99 (2H, s), 4.28 (2H, q, J = 7.1 Hz), 6.98 (2H, s), 7.40−7.45 (3H, m), 8.00−8.02 (2H, m). MS *m/z*: 533 $(M+H)^+$. To a solution of the prepared ester compound in MeOH (10 ml) was added NaOH (1N aqueous solution, 3.0 ml) at room temperature and stirred under a reflux condition for 1 hour. After cooling the mixture to an ambient temperature, the reaction mixture was quenched by the addition of HCl (1N aqueous solution, 3.0 mL). The solvent was removed *in vacuo* and the residue was diluted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 19/1 then 9/1 as eluent). HCl (4M dioxane solution) was added to the obtained the free form and then the solvent was removed *in vacuo* to give **50** HCl salt as a colorless solid (315 mg, 70%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.33 (6H, s), 2.13 (6H, s), 2.29 (3H, s), 2.46 (3H, s), 3.66−4.26 (6H, m), 7.05 (2H, s), 7.50−7.52 (3H, m), 7.91−7.93 (2H, m).

MS (ESI) *m/z*: 505 $(M+H)^+$.

HRMS (ESI) *m/z*: $[M-H]^-$ Calcd for $C_{28}H_{31}N_4O_5$ 503.2300; Found 503.2280.

Anal. Calcd. for $C_{28}H_{32}N_4O_5 \cdot HCl \cdot 0.75H_2O$: C, 60.64; H, 6.27; N, 10.10; Cl, 6.39. Found: C, 61.04; H, 6.47; N, 9.69; Cl, 6.22.

Ethyl 2-[4-({(2-amino-2-oxoethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoate (53)

To a solution of **47** (0.40 g, 0.86 mmol) in DMF (3.0 mL) were added ammonium chloride (55 mg, 1.0 mmol), EDCI (0.25 g, 1.3 mmol) and HOBt (0.20 g, 1.3 mmol), and then the reaction mixture was stirred at room temperature for 14 hours. The mixture was diluted with EtOAc, washed with water, 10% citric acid aqueous solution, saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, filtered and concentrated to give compound **53** (0.53 g) as a pale yellow oil. This compound was used for the next reaction without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.1 Hz), 1.45 (6H, s), 2.17 (6H, s), 2.25 (3H, s), 3.24 (2H, s), 3.54 (2H, s), 3.60 (2H, s), 4.28 (2H, q, J = 7.1 Hz), 6.91 (2H, s), 7.44−7.45 (3H, m), 7.98−8.02 (2H, m).

MS *m/z*: 494 $(M+H)^+$.

2-[2,6-dimethyl-4-({[(3-methyl-1,2,4-oxadiazol-5-yl)methyl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoic acid (54)

To a solution of **53** (0.81 mmol) was added (1,1-dimethoxyethyl)-dimethylamine (5.0 mL) a nd stirred at 120°C for 2 hours. After the solvent was removed *in vacuo*, hydroxylamine (5 0% aqueous solution, 70 μL, 0.52 mmol) and acetic acid (70% aqueous solution, 6.0 mL) were added to the residue and then stirred at room temperature for 5 days. The mixture wa s diluted with EtOAc, washed with water, saturated $NaHCO_3$ aqueous solution and brine, dr ied over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatogr aphy on silica gel (*n*-hexane/AcOEt = 9/1 then 3/1 as eluent) to provide ethyl 2-[2,6-dimeth

yl-4-({[(3-methyl-1,2,4-oxadiazol-5-yl)methyl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino} methyl)phenoxy]-2-methylpropanoate as a colorless oil (0.38 g, 88%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.1 Hz), 1.45 (6H, s), 2.18 (6H, s), 2.27 (3H, s), 2.41 (3H, s), 3.67 (2H, s), 3.70 (2H, s), 4.04 (2H, s), 4.28 (2H, q, J = 7.1 Hz), 7.00 (2H, s), 7.40−7.46 (3H, m), 7.99−8.01 (2H, m). MS (ESI) *m/z*: 533 $(M+H)^+$. To a solution of the prepared ester (0.38 g, 0.70 mmol) in methanol (10 mL) was added NaOH (1M aqueous solution, 3.0 mL) at room temperature and stirred under a reflux condition overnight. After cooling the mixture to ambient temperature, the reaction mixture was quenched by the addition of HCl (1M aqueous solution, 3.0 mL). The solvent was removed *in vacuo* and the residue was diluted with EtOAc. The organic layer was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/MeOH = 19/1 then 9/1 as eluent). HCl (4M dioxane solution) was added to the obtained free form and the solvent was removed *in vacuo* to give **54** HCl salt as a colorless solid (0.27 g, 71%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.32 (6H, s), 2.13 (6H, s), 2.27 (3H, s), 2.31 (3H, s), 3.81 (4H, br-s), 4.15 (2H, br-s), 7.01 (2H, s), 7.49−7.53 (3H, m), 7.90−7.92 (2H, m).

MS (ESI) *m/z*: 505 $(M+H)^+$.

HRMS (ESI) *m/z*: $[M-H]^-$ Calcd for $C_{28}H_{31}N_4O_5$ 503.2300; Found 503.2301.

Anal. Calcd. for $C_{28}H_{32}N_4O_5 \cdot HCl \cdot 0.25H_2O$: C, 61.65; H, 6.19; N, 10.27. Found: C, 62.02; H, 6.53; N, 9.87.

Ethyl 2-[4-({(2-hydrazinyl-2-oxoethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino} methyl)-2,6-dimethylphenoxy]-2-methylpropanoate (48)

To a solution of **47** (1.0 g, 2.0 mmol) in DMF (3.0 mL) were added hydrazine carboxylic acid *tert*-butyl ester (0.40 g, 3.0 mmol), EDCI (0.78 g, 4.0 mmol) and HOBt (0.62 g, 4.0 mmol) and then stirred at room temperature for overnight. The mixture was diluted with EtOAc, washed with water,

10% citric acid aqueous solution, saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, filtered and concentrated. To a solution of the residue in CH_2Cl_2 (5.0 mL) was added TFA (5.0 mL) and stirred at room temperature for 14 hours. The mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, filtered and concentrated to give **48** (1.1 g) as a pale yellow oil. This compound was used for the next reaction without further purification.

MS (ESI) *m/z*: 509 $(M+H)^+$.

2-[2,6-Dimethyl-4-({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl][5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-ylmethyl]amino}methyl)phenoxy]-2-methylpropionic acid (51)

To a solution of **48** (0.20 g, 0.39 mmol) in dioxane (5.0 mL) was added triphosgene (0.47 g, 1.6 mmol) and stirred at 60ºC for 4 hours. After the solvent was removed *in vacuo*, water was added to the residue, extracted with EtOAc, washed with saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc = 3/1 then 1/2 as eluent) to provide ethyl 2-[2,6-dimethyl-4-({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl][5-oxo-4,5-dihydro-1,3,4-oxadiazol-2-ylmethyl]amino}methyl)phenoxy]-2-methylpropanoate as a colorless oil (0.18 g, 84%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.1 Hz), 1.57 (6H, s), 2.18 (6H, s), 2.28 (3H, s), 3.65 (2H, s), 3.67 (2H, s), 3.73 (2H, s), 4.28 (2H, q, J = 7.1 Hz), 6.97 (2H, s), 7.40−7.46 (3H, m), 7.99−8.01 (2H, m), 8.54 (1H, s). MS (ESI) *m/z*: 535 $(M+H)^+$. The prepared ethyl ester form was hydrolyzed in a similar manner with **43** to afford **51** as a colorless solid (0.10 g, 62%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.32 (6H, s), 2.12 (6H, s), 2.26 (3H, s), 3.57 (2H, s), 3.59 (2H, s), 3.62 (2H, s), 6.95 (2H, s), 7.46−7.53 (3H, m), 7.90−7.92 (2H, m).

MS (ESI) *m/z*: 505 $(M-H)^-$.

Anal. Calcd. for $C_{27}H_{30}N_4O_6 \cdot 0.25H_2O$: C, 63.46; H, 6.02; N, 10.96. Found: C, 63.44; H, 6.11; N,

10.73.

2-[2,6-Dimethyl-4-({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl][(5-methyl-1,3,4-thiadiazol-2-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoic acid (52)

To a solution of **49** (0.50 g, 0.90 mmol) in THF (50 mL) was added Lawesson's reagent (0.73 g, 1.8 mmol) and stirred under a reflux condition for 30 minutes. After the solvent was removed *in vacuo*, the residue was purified by column chromatography on silica gel (CH_2Cl_2/methanol = 19/1, v/v) to provide ethyl 2-[2,6-dimethyl-4-({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl][(5-methyl-1,3,4-thiadiazol-2-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoate as a pale green solid (0.44 g, 88%): ^{1}H-NMR (400 MHz, $CDCl_3$) δ:1.35 (3H, t, J = 7.2 Hz), 1.46 (6H, s), 2.20 (6H, s), 2.24 (3H, s), 2.74 (3H, s), 3.61 (2H, s), 3.63 (2H, s), 4.13 (2H, s), 4.29 (2H, q, J = 7.2 Hz), 6.99 (2H, s), 7.40-7.47 (3H, m), 7.98−8.01 (2H, m). The prepared ethyl ester form was hydrolyzed in a similar manner with **43** to afford **52** as a colorless solid (0.24 g, 56%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ:1.34 (6H, s), 2.16 (6H, s), 2.24 (3H, s), 2.68 (3H, s), 3.58 (2H, s), 3.59 (2H, s), 4.08 (2H, s), 7.01 (2H, s), 7.50−7.55 (3H, m), 7.92−7.96 (2H, m).

MS (FAB) *m/z*: 521 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{32}N_4O_4S$·0.1dioxane·0.8H_2O: C, 62.72; H, 6.38, N, 10.30; S, 5.90. Found: C, 62.84; H, 6.24, N, 10.02; S, 5.87.

Ethyl 2-[4-({(2-*tert*-butoxy—2-oxoethyl)[(9*H*-fluoren-9-ylmethoxy)carbonyl]amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoate (55)

To a solution of **45** (3.5 g, 9.2 mmol) in MeCN (30 mL) was added 9-fluorenylmethylsuccinimidyl carbonate (3.7 g, 11 mmol) at 0°C and stirred at room temperature for 4 hours. After the solvent was removed *in vacuo*, water was added to the residue, extracted with EtOAc, washed with saturated $NaHCO_3$ aqueous solution, 10% citric acid aqueous solution and brine, dried over Na_2SO_4 and

concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc = 9/1 then 3/1 as eluent) to provide **55** as a pale yellow solid (5.2 g, 94%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.34-1.38 (3H, m), 1.44 (9H, d, J = 5.9 Hz), 1.47 (6H, d, J = 2.5 Hz), 2.18 (6H, d, J = 2.7 Hz), 3.81 (2H, d, J = 23.0 Hz), 4.26−4.30 (3H, m), 4.44−4.49 (4H, m), 6.77 (1H, s), 6.85 (1H, s), 7.25−7.29 (2H, m), 7.36−7.41 (2H, m), 7.53 (1H, d, J = 7.4 Hz), 7.60 (1H, d, J = 7.4 Hz), 7.74 (1H, d, J = 11.8 Hz), 7.76 (1H, d, J = 11.8 Hz).

MS (ESI) *m/z*: 602 $(M+H)^+$.

_N_-{4-[(1-Ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3,5-dimethylbenzyl}-_N_-[(9_H_-fluoren-9-yl methoxy)carbonyl]glycine (56)

To a solution of **55** (5.2 g, 8.7 mmol) in CH_2Cl_2 (60 ml) was added TFA (20 ml) at 0°C and stirred at room temperature overnight. The mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography on silica gel ($CHCl_3$/methanol = 19/1 then 9/1 as eluent) to provide **56** as a pale yellow oil (5.7 g).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.33−1.38 (3H, m), 1.46 (6H, d, J = 5.9 Hz), 2.17 (6H, s), 3.88 (2H, d, J = 81.3 Hz), 4.25−4.32 (3H, m), 4.44 (2H, s), 4.52−4.55 (2H, m), 6.75 (1H, s), 6.82 (1H, s), 7.23−7.31 (2H, m), 7.38 (2H, t, J = 7.4 Hz), 7.53−7.56 (2H, m), 7.74 (2H, d, J = 7.4 Hz).

MS (ESI) *m/z*: 568 $(M+Na)^+$.

Ethyl 2-[4-({[2-(2-acetylhydrazinyl)-2-oxoethyl][(9_H_-fluoren-9-ylmethoxy)carbonyl]amino} methyl)-2,6-dimethylphenoxy]-2-methylpropanoate (57)

56 was amidated in a similar manner with **49** to afford **57** as colorless solid (1.1 g, 67%).

MS (ESI) *m/z*: 602 $(M+H)^+$.

Ethyl 2-[4-({[(9*H*-fluoren-9-ylmethoxy)carbonyl][(5-methyl-1,3,4-oxadiazol-2-yl)methyl] amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoate (58)

To a solution of triphenylphosphine (1.5 g, 5.9 mmol) in CH_2Cl_2 (30 ml) were added hexachloroethane (1.2 g, 4.9 mmol), triethylamine (1.6 mL, 12 mmol) and **57** (1.1 g, 1.8 mmol). After the mixture was stirred at room temperature overnight, the reaction mixture was diluted with EtOAc. The organic layer was washed with water, 10% citric acid aqueous solution, saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc = 3/1 then 1/3 as eluent) to provide **58** as a pale yellow oil (1.0 g, 94%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.36 (3H, t, J = 7.1 Hz), 1.46 (6H, s), 2.16 (6H, s), 2.47 (3H, d, J = 10.5 Hz), 4.26−4.31 (3H, m), 4.39−4.44 (3H, m), 4.55−4.59 (3H, m), 6.79−6.85 (2H, m), 7.36−7.40 (2H, m), 7.46−7.49 (1H, m), 7.53−7.57 (3H, m), 7.65−7.70 (1H, m), 7.73−7.75 (2H, m).

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

Ethyl 2-[2,6-dimethyl-4-({[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoate (59)

To a solution of **58** (1.0 g, 1.8 mmol) in THF (50 mL) was added DBU (2% THF solution, 42 mL, 5.5 mmol) at 0^{o}C and stirred at the same temperature for 2 hours. The reaction mixture was diluted with EtOAc, washed with saturated $NaHCO_3$ aqueous solution and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/methanol = 99/1 then 9/1 as eluent) to provide **59** as a yellow oil (0.54 g, 82%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.1 Hz), 1.46 (7H, s), 2.19 (6H, s), 2.53 (3H, s), 3.73 (2H, s), 3.98 (2H, s), 4.29 (2H, q, J = 7.1 Hz), 6.92 (2H, s).

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

General procedure for the preparation of compound (61a−i)

To a solution of **59** in MeCN were added **60**, Cs_2CO_3 and KI and then the mixture was stirred at 75°C overnight. The reaction mixture was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel (Hexane/EtOAc). To a solution of the prepared tertiary amine compounds in methanol was added NaOH (1M aqueous solution) at room temperature and stirred under a reflux condition. After the reaction mixture was quenched by HCl (1M aqueous solution), the solvent was removed *in vacuo*. The residue was diluted with EtOAc, washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography on silica gel ($CHCl_3$/methanol) to provide **61a−i**. **61a**, **61d** and **61e** was hydrochlorinated with HCl (4M dioxane solution), concentrated and recrystallized from (Hexane/EtOAc) to afford **61a** HCl salt, **61d** HCl salt and **61e** HCl salt.

2-{2,6-Dimethyl-4-[({[5-methyl-2-(3-methylphenyl)-1,3-oxazol-4-yl]methyl}[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino)methyl]phenoxy}-2-methylpropanoic acid (**61a**)

This compound was obtained as the HCl salt form of a colorless solid in 25% yield by using **59** (0.42 mmol), **60a** (0.42 mmol), Cs_2CO_3 (0.62 mmol), KI (0.12 mmol) and MeCN (5.0 mL), followed by NaOH (2.0 mmol), MeOH (5.0 mL) and HCl (4M dioxane solution, 2.0 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.33 (6H, s), 2.14 (6H, s), 2.25 (3H, s), 2.36 (3H, s), 2.45 (3H, s), 3.57 (2H, s), 3.61 (2H, s), 3.91 (2H, s), 6.96 (2H, s), 7.32 (2H, d, J = 8.1 Hz), 7.81 (2H, d, J = 8.1 Hz).

MS (ESI) *m/z*: 519 $(M+H)^+$.

Anal. Calcd. for $C_{29}H_{34}N_4O_5 \cdot HCl \cdot 0.5H_2O$: C, 61.75; H, 6.43; N, 9.93. Found: C, 61.47; H, 6.43; N, 9.65.

2-{2,6-Dimethyl-4-[({[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]methyl}[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino)methyl]phenoxy}-2-methylpropanoic acid (**61b**)

This compound was obtained as a colorless solid in 39% yield by using **59** (0.41 mmol), **60b** (0.41 mmol), Cs_2CO_3 (0.61 mmol), KI (0.12 mmol) and MeCN (5.0 mL), followed by NaOH (2.0 mmol) and MeOH (10 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.33 (6H, s), 2.14 (6H, s), 2.25 (3H, s), 2.36 (3H, s), 2.45 (3H, s), 3.57 (2H, s), 3.61 (2H, s), 3.91 (2H, s), 6.96 (2H, s), 7.32 (2H, d, J = 8.1 Hz), 7.81 (2H, d, J = 8.1 Hz).

MS (ESI) *m/z*: 519 $(M+H)^+$.

HRMS (ESI) *m/z*: $[M-H]^-$ Calcd for $C_{29}H_{33}N_4O_5$ 517.2456; Found 517.2431.

Anal. Calcd. for $C_{29}H_{34}N_4O_5 \cdot 0.6H_2O$: C, 65.79; H, 6.70; N, 10.58. Found: C, 66.10; H, 6.75; N, 10.30.

2-{4-[({[2-(4-Chlorophenyl)-5-methyl-1,3-oxazol-4-yl]methyl}[(5-methyl-1,3,4-oxadiazol-2-yl) methyl]amino)methyl]-2,6-dimethylphenoxy}-2-methylpropanoic acid (**61c**)

This compound was obtained as a colorless solid in 43% yield by using **59** (0.41 mmol), **60c** (0.41 mmol), Cs_2CO_3 (0.61 mmol), KI (0.12 mmol) and MeCN (5.0 mL), followed by NaOH (2.0 mmol) and MeOH (10 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.33 (6H, s), 2.13 (6H, s), 2.26 (3H, s), 2.46 (3H, s), 3.59 (2H, s), 3.61 (2H, s), 3.91 (2H, s), 6.96 (2H, s), 7.58 (2H, d, J = 8.6 Hz), 7.92 (2H, d, J = 8.6 Hz).

MS (ESI) *m/z*: 540 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{31}ClN_4O_5 \cdot 0.75H_2O$: C, 60.87; H, 5.93; N, 10.14. Found: C, 61.36; H, 5.92; N, 9.64.

2-{4-[({[2-(4-Methoxyphenyl)-5-methyl-1,3-oxazol-4-yl]methyl}[(5-methyl-1,3,4-oxadiazol-2-yl) methyl]amino)methyl]-2,6-dimethylphenoxy}-2-methylpropanoic acid (**61d**)

This compound was obtained as the HCl salt form of a colorless solid in 24% yield by using **59** (0.42 mmol), **60d** (0.42 mmol), Cs_2CO_3 (0.62 mmol), KI (0.12 mmol) and MeCN (5.0 mL), followed by NaOH (2.0 mmol), MeOH (10 mL) and HCl (4M dioxane solution, 2.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.52 (6H, s), 2.25 (6H, s), 2.46 (3H, s), 2.58 (3H, s), 3.87 (3H, s), 4.31 (2H, s), 4.46 (2H, s), 4.56 (2H, s), 6.96 (2H, d, J = 8.8 Hz), 7.45 (2H, s), 7.88 (2H, d, J = 8.8 Hz).

MS (ESI) *m/z*: 535 $(M+H)^+$.

Anal. Calcd. for $C_{29}H_{34}N_4O_6 \cdot HCl \cdot 0.5H_2O$: C, 60.05; H, 6.26; N, 9.66. Found: C, 60.31; H, 6.30; N, 9.46.

2-[2,6-Dimethyl-4-({[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]({5-methyl-2-[4-(trifluoromethoxy) phenyl]-1,3-oxazol-4-yl}methyl)amino}methyl)phenoxy]-2-methylpropanoic acid (**61e**)

This compound was obtained as HCl salt form of a colorless solid in 58% yield by using **59** (0.28 mmol), **60e** (0.28 mmol), Cs_2CO_3 (0.41 mmol), KI (0.080 mmol) and MeCN (10 mL), followed by NaOH (2.0 mmol), MeOH (10 mL) and HCl (4M dioxane solution, 2.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.52 (6H, s), 2.25 (6H, s), 2.46 (3H, s), 2.59 (3H, s), 4.19 (2H, s), 4.32−4.35 (4H, m), 7.29 (2H, d, J = 8.8 Hz), 7.36 (2H, s), 7.98 (2H, d, J = 8.8 Hz).

MS (ESI) *m/z*: 589 $(M+H)^+$.

Anal. Calcd. for $C_{29}H_{31}F_3N_4O_6 \cdot HCl \cdot 0.25H_2O$: C, 55.33; H, 5.20; N, 8.90. Found: C, 55.31; H, 5.22; N, 8.65.

2-{4-[({[2-(4-Ethoxyphenyl)-5-methyl-1,3-oxazol-4-yl]methyl}[(5-methyl-1,3,4-oxadiazol-2-yl) methyl]amino)methyl]-2,6-dimethylphenoxy}-2-methylpropanoic acid (**61f**)

This compound was obtained as a colorless solid in 46% yield by using **59** (0.28 mmol),**60f** (0.28

mmol), Cs_2CO_3 (0.41 mmol), KI (0.080 mmol) and MeCN (10 mL), followed by NaOH (2.0 mmol) and MeOH (10 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.44 (3H, t, J = 7.0 Hz), 1.50 (6H, s), 2.22 (6H, s), 2.28 (3H, s), 2.52 (3H, s), 3.67 (2H, s), 3.69 (2H, s), 3.98 (2H, s), 4.08 (2H, q, J = 7.0 Hz), 6.93 (2H, d, J = 8.8 Hz), 7.04 (2H, s), 7.92 (2H, d, J = 8.8 Hz).

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

Anal. Calcd. for $C_{30}H_{36}N_4O_6 \cdot 0.75H_2O$: C, 64.10; H, 6.72; N, 9.97. Found: C, 64.33; H, 6.64; N, 9.81.

2-[2,6-Dimethyl-4-({[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]({5-methyl-2-[4-(trifluoromethyl) phenyl]-1,3-oxazol-4-yl}methyl)amino}methyl)phenoxy]-2-methylpropanoic acid (**61g**)

This compound was obtained as a colorless solid in 51% yield by using **59** (0.28 mmol), **60g** (0.28 mmol), Cs_2CO_3 (0.41 mmol), KI (0.080 mmol) and MeCN (10 mL), followed by NaOH (2.0 mmol) and MeOH (10 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.51 (6H, s), 2.23 (6H, s), 2.33 (3H, s), 2.53 (3H, s), 3.70−3.71 (4H, m), 3.98 (2H, s), 7.04 (2H, s), 7.70 (2H, d, J = 8.1 Hz), 8.12 (2H, d, J = 8.1 Hz).

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

Anal. Calcd. for $C_{29}H_{31}F_3N_4O_5 \cdot 0.5H_2O$: C, 59.89; H, 5.55; N, 9.63. Found: C, 59.95; H, 5.48; N, 9.49.

2-{4-[({[2-(3,4-Dimethylphenyl)-5-methyl-1,3-oxazol-4-yl]methyl}[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino)methyl]-2,6-dimethylphenoxy}-2-methylpropanoic acid (**61h**)

This compound was obtained as a colorless solid in 61% yield by using **59** (0.28 mmol), **60h** (0.28 mmol), Cs_2CO_3 (0.41 mmol), KI (0.080 mmol) and MeCN (10 mL), followed by NaOH (2.0 mmol) and MeOH (10 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.50 (6H, s), 2.22 (6H, s), 2.29 (3H, s), 2.30 (3H, s), 2.32 (3H, s),

2.52 (3H, s), 3.68−3.69 (4H, m), 3.98 (2H, s), 7.03 (2H, s), 7.19 (1H, d, *J* = 7.8 Hz), 7.72 (1H, d, *J* = 7.8 Hz), 7.80 (1H, s).

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

Anal. Calcd. for $C_{30}H_{36}N_4O_5 \cdot 0.5H_2O$: C, 66.52; H, 6.89; N, 10.34. Found: C, 66.91; H, 6.92; N, 10.13.

2-{4-[({[2-(4-Methoxy-3-methylphenyl)-5-methyl-1,3-oxazol-4-yl]methyl}[(5-methyl-1,3,4-oxadiazol-2-yl)methyl]amino)methyl]-2,6-dimethylphenoxy}-2-methylpropanoic acid (**61i**)

This compound was obtained as a colorless solid in 50% yield by using **59** (0.28 mmol), **60i** (0.28 mmol), Cs_2CO_3 (0.41 mmol), KI (0.080 mmol) and MeCN (10 mL), followed by NaOH (2.0 mmol) and MeOH (10 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.50 (6H, s), 2.22 (6H, s), 2.26 (3H, s), 2.28 (3H, s), 2.52 (3H, s), 3.67 (2H, s), 3.68 (2H, s), 3.88 (3H, s), 3.98 (2H, s), 6.86 (1H, d, *J* = 9.1 Hz), 7.04 (2H, s), 7.80−7.81 (2H, m).

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

Anal. Calcd. for $C_{30}H_{36}N_4O_6 \cdot 0.5H_2O$: C, 64.62; H, 6.69; N, 10.05. Found: C, 64.87; H, 6.75; N, 9.81.

2*N*-{4-[(1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3,5-dimethylbenzyl}-*N*-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]glycine (47)

To a solution of ethyl 2-[2,6-dimethyl-4-({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoate (**42**) (3.0 g, 6.9 mmol) in methanol (30 mL), glyoxylic acid monohydrate (0.84 g, 8.9 mmol) and sodium triacethoxyborohydride (2.3 g, 10 mmol) were added. The mixture was stirred at room temperature overnight. After the solvent was removed *in vacuo*, the residue was dissolved in ethyl acetate (EtOAc), washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Chloroform/Methanol = 19/1 as eluent, v/v) to provide **3** as a colorless solid (3.1 g, 91%).

MS (ESI) *m/z*: 495 $(M+H)^+$.

General procedure for 2-{4-[({2-[(subsituted)-amino]-2-oxoethyl}[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino)methyl]-2,6-dimethylphenoxy}-2-methylpropanoic acid (62a−i)

To a solution of **47** in DMF or acetonitrile (MeCN), commercially available amines, EDCI and HOBt were added. The mixture was stirred at room temperature overnight. After the solvent was removed *in vacuo*, the residue was dissolved in EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc as eluent) to provide **62a−i** ethyl ester form. To a mixture of **62a−i** ethyl ester form and methanol was added NaOH (1M aqueous solution) and stirred at 50°C overnight. After HCl (1M aqueous solution) was added to the reaction mixture, the solvent was removed *in vacuo*. After EtOAc was added to the residue, the mixture was washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Chloroform/Methanol). The residue was triturated with EtOAc-Hexane or freeze-dried from

1,4-dioxane to provide **62a**−**i.**

2-[4-({(2-Amino-2-oxoethyl)[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoic acid (**62a**)

This compound was obtained as a colorless solid in 59% yield by using **47** (0.28 mmol), NH_4Cl (0.42 mmol), *N*-methylmorpholine (NMM) (0.42 mmol), EDCI (0.42 mmol), HOBt (0.42 mmol), MeCN (2.0 mL) and NaOH (4.5 eq.).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.32 (6H, s), 2.13 (6H, s), 2.24 (3H, s), 3.07 (2H, s), 3.53 (2H, s), 3.57 (2H, s), 7.15 (1H, br s), 7.31 (1H, br s), 7.49−7.53 (3H, m), 7.91−7.94 (2H, m).

MS (ESI) *m/z*: 466 $(M+H)^+$.

Anal. Calcd. for $C_{26}H_{31}N_3O_5 \cdot 0.5H_2O \cdot 0.2EtOAc$: C, 65.40; H, 6.88; N, 8.54. Found: C, 65.22; H, 6.78; N, 8.16.

2-[2,6-Dimethyl-4-({[2-(methylamino)-2-oxoethyl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl] amino}methyl)phenoxy]-2-methylpropanoic acid (**62b**)

This compound was obtained as a colorless solid in 66% yield by using **47** (5.9 mmol), methylamine (8.9 mmol), EDCI (12 mmol), HOBt (12 mmol), DMF (10 mL) and NaOH (2.9 eq.).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.31 (6H, s), 2.12 (6H, s), 2.22 (3H, s), 2.60 (3H, d, J = 4.6 Hz), 3.09 (2H, s), 3.50 (2H, s), 3.56 (2H, s), 6.99 (2H, s), 7.48−7.53 (3H, m), 7.74−7.78 (1H, m), 7.91−7.93 (2H, m).

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

Anal. Calcd. for $C_{27}H_{33}N_3O_5$: C, 67.62; H, 6.94; N, 8.76. Found: C, 67.57; H, 7.09; N, 8.56.

2-[4-({[2-(Dimethylamino)-2-oxoethyl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl) -2,6-dimethylphenoxy]-2-methylpropanoic acid (**62c**)

This compound was obtained as HCl salts of a colorless solid in 52% yield by using **47** (4.5 mmol),

dimethylamine (6.7 mmol), EDCI (8.9 mmol), HOBt (8.9 mmol), DMF (10 mL) and NaOH (2.9 eq.), and being hydrochlorinated with HCl (4M dioxane solution).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.36 (6H, s), 2.18 (6H, s), 2.42 (3H, s), 2.84 (3H, s), 2.89 (3H, s), 4.11−4.40 (6H, m), 7.31 (2H, s), 7.54−7.59 (3H, m), 7.97−7.99 (2H, m).

MS (ESI) *m/z*: 494 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{35}N_3O_5 \cdot HCl \cdot 1.5H_2O \cdot 0.2$dioxane: C, 60.19; H, 7.12; N, 7.31. Found: C, 60.15; H, 6.74; N, 7.36.

2-[4-({[2-(Ethylamino)-2-oxoethyl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoic acid (**62d**)

This compound was obtained as HCl salts of a colorless solid in 36% yield by using **47** (0.40 mmol), ethylamine (0.81 mmol), EDCI (0.81 mmol), HOBt (0.81 mmol), DMF (2.0 mL) and NaOH (6.9 eq.), and being hydrochlorinated with HCl (4M EtOAc solution).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.99 (3H, t, J = 7.1 Hz), 1.36 (6H, s), 2.18 (6H, s), 2.41 (3H, s), 3.08 (3H, s), 3.79−3.90 (2H, m), 4.01−4.06 (2H, m), 4.24−4.39 (4H, m), 7.27 (2H, s), 7.54−7.57 (3H, m), 8.00−7.96 (2H, m).

MS (ESI) *m/z*: 494 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{35}N_3O_5 \cdot HCl \cdot H_2O \cdot 0.2$EtOAc$\cdot 0.1$Hexane: C, 61.49 H, 7.20; N, 7.32. Found: C, 61.75; H, 7.12; N, 6.97.

2-[4-({[2-(cyclopropylamino)-2-oxoethyl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoic acid (**62e**)

This compound was obtained as a colorless solid in 52% yield by using **47** (0.28 mmol), cyclopropylamine (0.42 mmol), EDCI (0.42 mmol), HOBt (0.42 mmol), DMF (2.0 mL) and NaOH (9.5 eq.).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 0.36−0.40 (2H, m), 0.59−0.63 (2H, m), 1.32 (6H, s), 2.11 (6H,

s), 2.25 (3H, s), 2.66−2.68 (1H, m), 3.06 (2H, s), 3.53 (2H, s), 3.57 (2H, s), 6.94 (2H, s), 7.50−7.55 (3H, m), 7.83 (1H, d, *J* = 4.2 Hz), 7.92−7.95 (2H, m).

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

Anal. Calcd. for $C_{29}H_{35}N_3O_5 \cdot 0.75H_2O$: C, 67.10; H, 7.09; N, 8.09. Found: C, 67.21; H, 6.69; N, 7.93.

2-{4-[({2-[(2-Methoxyethyl)amino]-2-oxoethyl}[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl] amino)methyl]-2,6-dimethylphenoxy}-2-methylpropanoic acid (**62f**)

This compound was obtained as a colorless solid in 43% yield by using **47** (0.28 mmol), 2-methoxyethylamine (0.42 mmol), EDCI (0.42 mmol), HOBt (0.42 mmol), DMF (2.0 mL) and NaOH (12 eq.).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.33 (6H, s), 2.13 (6H, s), 2.24 (3H, s), 3.11 (2H, s), 3.22 (3H, s), 3.23−3.26 (2H, m), 3.32−3.35 (2H, m), 3.52 (2H, s), 3.57 (2H, s), 6.99 (2H, s), 7.49−7.54 (3H, m), 7.85 (1H, t, *J* = 6.1 Hz), 7.94−7.96 (2H, m).

MS (ESI) *m/z*: 524 $(M+H)^+$.

Anal. Calcd. for $C_{29}H_{37}N_3O_6 \cdot 0.5H_2O$: C, 65.40; H, 7.19; N, 7.89. Found: C, 65.49; H, 6.84; N, 7.73.

2-[2,6-Dimethyl-4-({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl][2-oxo-2-(1,3-thiazol-2-ylamino) ethyl]amino}methyl)phenoxy]-2-methylpropanoic acid (**62g**)

This compound was obtained as a colorless solid in 59% yield by using **47** (0.28 mmol), 1,3-thiazol-2-amine (0.42 mmol), EDCI (0.42 mmol), HOBt (0.42 mmol), DMF (2.0 mL) and NaOH (7.8 eq.).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.32 (6H, s), 1.43−1.49 (1H, m), 1.73−1.83 (3H, m), 2.13 (6H, s), 2.25 (3H, s), 3.06−3.10 (1H, m), 3.12 (2H, s), 3.16−3.24 (1H, m), 3.53 (2H, s), 3.57 (2H, s), 3.60−3.64 (1H, m), 3.72−3.85 (2H, m), 6.99 (2H, s), 7.49-7.54 (3H, m), 7.87 (1H, t, *J* = 5.8 Hz), 7.94−7.96 (2H, m).

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

Anal. Calcd. for $C_{29}H_{32}N_4O_5S \cdot 0.75H_2O \cdot 0.1$dioxane: C, 61.84; H, 6.05; N, 9.81; S, 5.62. Found: C, 61.62; H, 5.69; N, 9.44; S, 5.51.

2-[4-({[2-(Azetidin-1-yl)-2-oxoethyl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoic acid (**62h**)

This compound was obtained as HCl salts of a colorless solid in 30% yield by using **47** (0.28 mmol), azetidine hydrochloric acid (0.47 mmol), NMM (0.85 mmol), EDCI (0.56 mmol), HOBt (0.56 mmol), DMF (5.0 mL) and NaOH (11 eq.), and being hydrochlorinated with HCl (4M dioxane solution).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.36 (6H, s), 2.16−2.21 (8H, m), 2.41 (3H, s), 3.31−3.40 (4H, m), 3.84−3.90 (2H, m), 4.03−4.07 (2H, m), 4.20−4.32 (2H, m), 7.24 (2H, s), 7.54−7.59 (3H, m), 7.97−8.00 (2H, m).

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

Anal. Calcd. for $C_{29}H_{35}N_3O_5 \cdot HCl \cdot 2H_2O \cdot 0.25$EtOAc: C, 60.04; H, 7.05; N, 7.00. Found: C, 60.08; H, 6.72; N, 6.60.

2-[2,6-Dimethyl-4-({[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl][2-oxo-2-(piperidin-1-yl)ethyl]amino}methyl)phenoxy]-2-methylpropanoic acid (**62i**)

This compound was obtained as HCl salts of a colorless solid in 61% yield by using **47** (0.40 mmol), piperidine (0.81 mmol), EDCI (0.81 mmol), HOBt (0.81 mmol), DMF (2.0 mL) and NaOH (5.6 eq.), and being hydrochlorinated with HCl (4M dioxane solution).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.56−1.33 (6H, m), 2.18 (6H, s), 2.42 (3H, s), 3.56−3.58 (4H, m), 4.17−4.42 (6H, m), 7.31 (2H, s), 7.55−7.58 (3H, m), 7.96−7.99 (2H, m).

MS (ESI) *m/z*: 534 $(M+H)^+$.

Anal. Calcd. for $C_{31}H_{39}N_3O_5 \cdot HCl \cdot 2H_2O \cdot 0.25$EtOAc: C, 61.18; H, 7.38; N, 6.69. Found: C, 61.08; H,

7.28; N, 6.35.

General procedure for *tert*-butyl *N*-{4-[(1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3,5-dimethylbenzyl}alaninate (64a, 64b)

The mixture of *tert*-butyl alaninate **63** (a or b), ethyl 2-(4-formyl-2,6-dimethylphenoxy)-2-me thylpropanoate (**20e**) and triethylamine (TEA) in tetrahydrofuran (THF) was stirred under ref lux conditions. After the insoluble matter was removed by filtration through celite, the filtra te was concentrated. After the residue was dissolved in methanol, sodium borohydride was added to the solution and the mixture was stirred at room temperature. After the solvent w as removed *in vacuo*, the residue was dissolved in EtOAc, washed with saturated sodium bicarbonate aqueous solution and brine, dried over Na_2SO_4 and concentrated to provide **7** (a or b).

tert-Butyl *N*-{4-[(1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3,5-dimethylbenzyl}-*D*-alaninate (**64a**)

This compound was obtained as a pale yellow oil in 93% yield by using *L*-Alanine *tert*-butyl ester hydrochloride (**63a**, 1.7 mmol), **20e** (1.1 mmol), TEA (1.7 mmol), THF (10 mL), sodium borohydride (1.1 mmol) and methanol (5.0 mL).

MS (ESI) *m/z*: 394 $(M+H)^+$.

tert-Butyl *N*-{4-[(1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3,5-dimethylbenzyl}-*L*-alaninate (**64b**)

This compound was obtained as a pale yellow oil in 80% yield by using *D*-Alanine *tert*-butyl ester hydrochloride (**63b**, 1.7 mmol), **20e** (1.1 mmol), TEA (1.7 mmol), THF (10 mL), sodium borohydride (1.1 mmol) and methanol (5.0 mL).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.28 (3H, d, J = 6.9 Hz), 1.35 (3H, t, J = 7.1 Hz), 1.45 (6H, s), 1.49 (9H, s), 2.18 (6H, s), 3.28−3.22 (1H, m), 3.52 (1H, d, J = 12.3 Hz), 3.66 (1H, d, J = 12.3 Hz), 4.29

(2H, q, *J* = 7.1 Hz), 6.93 (2H, s).

MS (ESI) *m/z*: 394 $(M+H)^+$.

General procedure for *tert*-butyl *N*-{4-[(1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3,5-dimethylbenzyl}alaninate (65a, 65b)

To a solution of *tert*-butyl *N*-{4-[(1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3,5-dimethylbenzyl}alaninate **64** (a or b) and 5-methyl-2-phenyl-1,3-oxazole-4-carbaldehyde in dichloromethane, sodium triacethoxyborohydride was added and stirred at room temperature overnight. After EtOAc was added to the residue, the mixture was washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc as eluent) to provide **65** (a or b).

tert-Butyl *N*-{4-[(1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3,5-dimethylbenzyl}-*N*-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]-*D*-alaninate (**65a**)

This compound was obtained as a colorless oil in 58% yield by using **64a** (0.51 mmol), 5-methyl-2-phenyl-1,3-oxazole-4-carbaldehyde (0.51 mmol), dichloromethane (3.0 mL) and sodium triacethoxyborohydride (0.76 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.31−1.36 (6H, m), 1.42 (6H, s), 1.51 (9H, s), 2.14 (6H, s), 2.26 (3H, s), 3.65−3.77 (5H, m), 4.27 (2H, q, *J* = 7.1 Hz), 6.94 (2H, s), 7.38−7.43 (3H, m), 7.96−7.99 (2H, m).

MS (ESI) *m/z*: 565 $(M+H)^+$.

tert-Butyl *N*-{4-[(1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3,5-dimethylbenzyl}-*N*-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]-*L*-alaninate (**65b**)

This compound was obtained as a colorless oil in 73% yield by using **64a** (0.51 mmol), 5-methyl-2-phenyl-1,3-oxazole-4-carbaldehyde (0.51 mmol), dichloromethane (3.0 mL) and

sodium triacethoxyborohydride (0.76 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.31−1.36 (6H, m), 1.42 (6H, s), 1.51 (9H, s), 2.14 (6H, s), 2.26 (3H, s), 3.51−3.77 (5H, m), 4.27 (2H, q, J = 7.1 Hz), 6.94 (2H, s), 7.38−7.43 (3H, m), 7.96−7.99 (2H, m).

MS (ESI) *m/z*: 565 $(M+H)^+$.

General procedure for ethyl 2-[2,6-dimethyl-4-({[1-(methylamino)-1-oxopropan-2-yl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoate (66a, 6 6b)

To a solution of **65** (a or b) in dichloromethane, HCl (4M dioxane solution) was added and stirred at room temperature overnight. After the solvent was removed *in vacuo*, the residue was dissolved in DMF. Methylamine hydrochloric acid, NMM, EDCI and HOBt was added to the reaction solution and stirred at room temperature overnight. After EtOAc was added to the residue, the mixture was washed with water, 10% citric acid aqueous solution, satd. sodium bicarbonate aqueous solution and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc as eluent) to provide **66** (a or b).

Ethyl 2-[2,6-dimethyl-4-({[(2*R*)-1-(methylamino)-1-oxopropan-2-yl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoate (**66a**)

This compound was obtained as a colorless oil in 78% yield by using **65a** (0.28 mmol), HCl (4M dioxane solution, 2.0 mL), dichloromethane (5.0 mL), DMF (5.0 mL), methyl amine hydrochloric acid (0.43 mmol), NMM (0.43 mmol), EDCI (0.43 mmol) and HOBt (0.43 mmol).

MS (ESI) *m/z*: 522 $(M+H)^+$.

Ethyl 2-[2,6-dimethyl-4-({[(2*S*)-1-(methylamino)-1-oxopropan-2-yl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoate (**66b**)

This compound was obtained as a colorless oil in 27% yield by using **65b** (0.35 mmol), HCl (4M dioxane solution, 5.0 mL), dichloromethane (5.0 mL), DMF (5.0 mL), methyl amine hydrochloric acid (0.43 mmol), NMM (0.43 mmol), EDCI (0.43 mmol) and HOBt (0.43 mmol).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.31−1.35 (6H, m), 1.42 (6H, s), 2.11 (6H, s), 2.22 (3H, s), 2.91 (3H, d, J = 4.9 Hz), 3.31−3.61 (5H, m), 4.26 (2H, q, J = 7.1 Hz), 6.84 (2H, s), 7.43−7.47 (3H, m), 7.99−8.01 (2H, m), 8.50 (1H, s).

MS (ESI) *m/z*: 522 $(M+H)^+$.

General procedure for *N*-{4-[(1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3,5-dimethylbenzyl}-*N*-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]alanine (67a, 67b)

To a mixture of **66** (a or b) in methanol, NaOH (1M aqueous solution) was added and stirred under reflux conditions. After HCl (1M aqueous solution) was added to the reaction mixture, the solvent was removed *in vacuo*. After EtOAc was added to the residue, the mixture was washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Chloroform/Methanol as eluent). The residue was hydrochlorinated with HCl (4M dioxane solution), and then concentrated. Recrystallization from EtOAc-Hexane produced **67** (a or b) HCl salts.

2-[2,6-Dimethyl-4-({[(2*R*)-1-(methylamino)-1-oxopropan-2-yl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoic acid (**67a**)

This compound was obtained as a colorless solid in 67% yield by using **66a** (0.21 mmol), methanol (5.0 mL) and NaOH (1M aqueous solution, 2.0 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.34 (6H, s), 2.14 (6H, s), 2.69 (3H, d, J = 4.2 Hz), 3.10−3.61 (4H, m), 3.97−4.41 (4H, m), 7.06−7.60 (5H, m), 7.97−7.99 (2H, m), 8.23−8.75 (1H, m).

MS (ESI) *m/z*: 494 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{35}N_3O_5 \cdot HCl \cdot 2H_2O$: C, 59.41; H, 7.12; N, 7.42. Found: C, 59.58; H, 6.91; N, 7.21.

2-[2,6-Dimethyl-4-({[(2*S*)-1-(methylamino)-1-oxopropan-2-yl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoic acid (**67b**)

This compound was obtained as a colorless solid in 33% yield by using **66b** (0.096 mmol), methanol (5.0 mL) and NaOH (1M aqueous solution, 2.0 mL).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.34 (6H, s), 2.14 (6H, s), 2.69 (6H, d, J = 4.7 Hz), 3.03-3.73 (4H, m), 3.98−4.57 (4H, m), 7.06−7.63 (5H, m), 7.96−8.00 (2H, m), 8.41−8.54 (1H, m).

MS (ESI) *m/z*: 494 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{35}N_3O_5 \cdot HCl \cdot 0.75H_2O \cdot 0.2EtOAc$: C, 62.14; H, 6.99; N, 7.55. Found: C, 62.26; H, 7.09; N, 7.22.

***tert*-Butyl *N*-{4-[(1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3,5-dimethylbenzyl}-*β*-alaninate (69)**

To a solution of **6** (0.19 g, 0.72 mmol) in THF (5.0 mL), **68** (0.16 g, 0.86 mmol) and TEA (0.12 μL, 0.86 mmol) were added and stirred under reflux condition for 3.5 h. After the solvent was removed *in vacuo*, the residue was dissolved in methanol (5.0 mL). Sodium borohydride (40 mg, 1.1 mmol) was added to the reaction solution at 0°C and stirred at the same temperature for 40 min. After water and satd. sodium bicarbonate aqueous solution were added to the reaction mixture, the organics were extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated to provide **69** (0.30 g, crude product). This compound was used at the next step without further purification.

tert-Butyl _N_-{4-[(1-ethoxy-2-methyl-1-oxopropan-2-yl)oxy]-3,5-dimethylbenzyl}-_N_-[(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]-_β_-alaninate (70)

To a solution of **69** (0.30 g, ca.0.72 mmol) and 4-(chloromethyl)-5-methyl-2-phenyl-1,3-oxazole (0.21 g, 1.0 mmol) in MeCN (6.0 mL), K_2CO_3 (0.15 g, 1.1 mmol) was added and stirred at 70°C for 2 days. After the insoluble matter was removed by filtration through celite, the filtrate was concentrated. The residue was purified by column chromatography on silica gel (Hexane/EtOAc = 46/1 then 21/4 as eluent, v/v) to provide **70** as a colorless oil (0.35 g, 87% for 2 steps).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.1 Hz), 1.42 (9H, s), 1.45 (6H, s), 2.17 (6H, s), 2.23 (3H, s), 2.47 (2H, t, J = 7.2 Hz), 2.91 (2H, t, J = 7.2 Hz), 3.47−3.56 (4H, m), 4.28 (2H, q, J = 7.1 Hz), 6.95 (2H, s), 7.36−7.45 (3H, m), 7.96−8.03 (2H, m).

MS (ESI) m/z: 565 $(M+H)^+$.

Ethyl 2-[2,6-dimethyl-4-({[3-(methylamino)-3-oxopropyl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)phenoxy]-2-methylpropanoate (71)

To a solution of **70** (0.35 g, 0.63 mmol) in dichloromethane, HCl (4M dioxane solution, 8.0 mL) was added and stirred at room temperature overnight. After the solvent was removed *in vacuo*, the residue was dissolved in DMF (6.0 mL). Methylamine hydrochloric acid (50 mg, 0.75 mmol), EDCI (0.18 g, 0.94 mmol), HOBt (84 mg, 0.63 mmol) and TEA (0.24 mL, 1.7 mmol) were added to the reaction mixture and stirred at room temperature overnight. After the reaction mixture was diluted with dichloromethane, the mixture was washed with satd. sodium bicarbonate aqueous solution, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (Dichloromethane/Methanol = 97/3 then 93/7 as eluent, v/v) to provide **71** as a pale yellow oil (0.30 g, 96%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.33−1.37 (3H, m), 1.46 (6H, s), 2.18 (6H, s), 2.24 (3H, s), 2.39−2.49 (2H, m), 2.72 (3H, d, J = 4.9 Hz), 2.74−2.83 (2H, m), 3.49 (2H, s), 3.56 (2H, s), 4.24−4.33 (2H, m), 6.90 (2H, s), 7.39−7.49 (3H, m), 7.95−8.04 (2H, m), 8.26−8.37 (1H, m).

MS (ESI) *m/z* : 522 $(M+H)^+$.

2-[2,6-Dimethyl-4-({[3-(methylamino)-3-oxopropyl][(5-methyl-2-phenyl-1,3-oxazol-4-yl) methyl]amino}methyl)phenoxy]-2-methylpropanoic acid (72)

To a solution of **71** (0.30 g, 0.58 mmol) in THF (5.0 mL), NaOH (0.5 M aqueous solution, 5.0 mL) was added and stirred under reflux condition overnight. After the reaction mixture was cooled to room temperature, HCl (1M aqueous solution, 2.5 mL) and water were added and the organics was extracted with dichloromethane. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (Dichloromethane/Methanol = 95/5 then 91/9 as eluent, v/v) to provide **72** as a colorless solid (0.24 g, 80%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.48 (6H, s), 2.20 (6H, s), 2.28 (3H, s), 2.50−2.61 (2H, m), 2.73 (3H, d, J = 4.6 Hz), 2.82−2.93 (2H, m), 3.62 (2H, s), 3.69 (2H, s), 6.96 (2H, s), 7.40−7.49 (3H, m), 7.96−8.03 (2H, m), 8.25−8.37 (1H, m).

IR (ATR) cm^{-1}: 3276, 2991, 2917, 2817, 1720, 1637, 1556, 1482, 1448, 1407, 1382, 1361, 1338, 1301, 1286, 1214, 1133, 1068, 1025.

MS (ESI) *m/z*: 494 $(M+H)^+$.

Anal. Calcd for $C_{28}H_{35}N_3O_5 \cdot 0.5H_2O$: C, 66.91; H, 7.22; N, 8.36. Found: C, 67.12; H, 7.35; N, 8.13.

Ethyl 2-{4-[({2-[(*tert*-butoxycarbonyl)amino]ethyl}[(5-methyl-2-phenyl-1,3-oxazol-4-yl) methyl]amino)methyl]-2,6-dimethylphenoxy}-2-methylpropanoate (73)

To a solution of **42** (0.43 g, 0.98 mmol) and *tert*-butyl (2-oxoethyl)carbamate (0.28 g, 1.7 mmol) in dichloromethane (10 mL), sodium triacethoxyborohydride (0.49 g, 0.84 mmol) was added and stirred at room temperature for 16 h. After the reaction mixture was diluted with EtOAc, the mixture was washed with satd. sodium bicarbonate aqueous solution and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (Hexane/EtOAc = 9/1 then 2/1 as eluent, v/v) to provide **16** as a colorless oil (0.40 g, 71%).

MS (ESI) *m/z*: 580 $(M+H)^+$.

2-[4-({[2-(Acetylamino)ethyl][(5-methyl-2-phenyl-1,3-oxazol-4-yl)methyl]amino}methyl)-2,6-dimethylphenoxy]-2-methylpropanoic acid (74)

To a solution of **73** (1.5 g, 4.1 mmol) in dichloromethane (5.0 mL), trifluoroacetic acid (2.0 mL, 26 mmol) was added at 0˚C and stirred at room temperature for 20 h. After the solvent was removed *in vacuo*, the residue was used at the next step without further purification: MS (ESI) *m/z*: 480 $(M+H)^+$. To the mixture of the above crude product (200 mg, ca. 0.35 mmol) in dichloromethane (10 mL), acetyl chloride (37 μL, 0.52 mmol) and TEA (0.19 mL, 1.4 mmol) were added at 0˚C and stirred at room temperature for 16 h. After the reaction mixture was diluted with EtOAc, the mixture was washed with satd. sodium bicarbonate aqueous solution and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (Hexane/EtOAc = 3/1 then 1/3 as eluent, v/v) to provide acetamide intermediate as a pale yellow oil: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.1 Hz), 1.46 (6H, s), 1.90 (3H, s), 2.18 (6H, s), 2.24 (3H, s), 2.69 (2H, t, J = 5.5 Hz), 3.30−3.34 (2H, m), 3.53 (2H, s), 3.58 (2H, s), 4.28 (2H, q, J = 7.1 Hz), 6.68−6.70 (1H, m), 6.93 (2H, s), 7.42−7.46 (3H, m), 8.01−7.98 (2H, m). MS (ESI) *m/z*: 522 $(M+H)^+$. To the mixture of acetamide intermediate (60 mg, 0.12 mmol) in methanol (5.0 mL), NaOH (1M aqueous solution, 2.0 mL) was added and stirred at room temperature for 2 d. HCl (1M aqueous solution, 2.5 mL) and water were added and the organics was extracted with EtOAc. The organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (Chloroform/Methanol = 9/1 as eluent, v/v) and triturated with EtOAc-Hexane to provide **17** as a colorless solid (51 mg, 31%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 1.33 (6H, s), 1.76 (3H, s), 2.13 (6H, s), 2.27 (3H, s), 2.52−2.55 (2H, m), 3.17−3.22 (2H, m), 3.49 (2H, s), 3.52 (2H, s), 6.97 (2H, s), 7.48−7.53 (3H, m), 7.68−7.71 (1H, m), 7.93−7.91 (2H, m).

MS *m/z*: 494 $(M+H)^+$.

Anal. Calcd. for $C_{28}H_{35}N_3O_5 \cdot 1.25H_2O$: C, 65.16; H, 7.32; N, 8.14. Found: C, 65.43; H, 7.35; N, 7.74.

Ethyl 2-(4-{[(2-*tert*-butoxy-2-oxoethyl){[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]methyl} amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoate (75)

To a solution of **60b** (1.0 g, 4.5 mmol) and **45** (2.0 g, 5.2 mmol) in MeCN (20 mL), K_2CO_3 (0.94 g, 6.8 mmol) was added and stirred under reflux conditions for 2 h. After the solvent was removed *in vacuo*, the residue was dissolved in EtOAc, washed with water and brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (Hexane/EtOAc = 9/1 then 3/1 as eluent, v/v) to provide **75** as a pale yellow oil (2.5 g, 98%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.2 Hz), 1.45 (6H, s), 1.47 (9H, s), 2.17 (6H, s), 2.29 (3H, s), 2.39 (3H, s), 3.30 (2H, s), 3.71 (2H, s), 3.74 (2H, s), 4.28 (2H, q, J = 7.2 Hz), 6.99 (2H, s), 7.23 (2H, d, J = 8.1 Hz), 7.89 (2H, d, J = 8.1 Hz).

MS (ESI) *m/z*: 565 $(M+H)^+$.

Ethyl 2-(4-{[(2-amino-2-oxoethyl){[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]methyl} amino]methyl}-2,6-dimethylphenoxy)-2-methylpropanoate (76)

To a solution of **75** (1.5 g, 2.7 mmol) in dichloromethane, trifluoroacetic acid (10 mL, 0.13 mol) was added at 0˚C and stirred at room temperature for 5 d. After the solvent was removed *in vacuo*, the residue (0.15 g, 0.29 mmol) was dissolved in DMF (5.0 mL), and then NH_4Cl (20 mg, 0.44 mmol), TEA (0.16 mL, 1.2 mmol), EDCI (80 mg, 0.44 mmol) and HOBt (40 mg, 0.29 mmol) were added to the reaction solution and stirred at room temperature for 20 h. After the reaction mixture was diluted with chloroform, the mixture was washed with water, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel (Chloroform/Methanol = 20/1 as eluent, v/v) to provide **76** as a colorless oil (0.13 g, 89%).

^{1}H-NMR(400 MHz, $CDCl_3$) δ: 1.35 (3H, t, J = 7.1 Hz), 1.45 (6H, s), 2.16 (6H, s), 2.24 (3H, s), 2.40

(3H, s), 3.23 (2H, s), 3.53 (2H, s), 3.60 (2H, s), 4.27 (2H, q, *J* = 7.1 Hz), 5.44 (1H, br), 6.91 (2H, s), 7.25 (2H, d, *J* = 8.2 Hz), 7.69 (1H, br), 7.87 (2H, d, *J* = 8.2 Hz).

MS (ESI) *m/z*: 508 $(M+H)^+$.

2-(4-{[(2-Amino-2-oxoethyl){[5-methyl-2-(4-methylphenyl)-1,3-oxazol-4-yl]methyl}amino] methyl}-2,6-dimethylphenoxy)-2-methylpropanoic acid (77)

To a solution of **76** (0.13 g, 0.26 mmol) in methanol (2.0 mL) and THF (5.0 mL) NaOH (1M aqueous solution, 1.3 mL) was added and stirred under reflux conditions for 15.5 h. After the reaction mixture was cooled to room temperature, water was added and the aqueous layer was washed with diethyl ether. HCl (1M aqueous solution) was added to the aqueous layer and the organics were extracted with chloroform. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by crystallization from Hexane-Diethyl ether to provide **77** as a colorless solid (56 mg, 46%).

^{1}H-NMR(400 MHz, $CDCl_3$) δ: 1.50 (6H, s), 2.20 (6H, s), 2.28 (3H, s), 2.40 (3H, s), 3.22 (2H, s), 3.57 (2H, s), 3.62 (2H, s), 5.75 (1H, br), 6.95 (2H, s), 7.26 (2H, d, *J* = 8.2 Hz), 7.75 (1H, br), 7.87 (2H, d, *J* = 8.2 Hz).

IR (ATR) cm^{-1}: 3334, 2920, 1730, 1678, 1120, 733, 700.

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

HRMS (FAB) *m/z*: $[M+H]^+$ Calcd for: $C_{27}H_{34}O_5N_3$; 480.2498; Found 480.2500.

Anal. Calcd for $C_{27}H_{33}O_5N_3 \cdot H_2O$: C, 65.17; H, 7.09; N, 8.44. Found: C, 64.92; H, 6.73; N, 8.20.

第 2 章　Biological evaluation method

PPAR transactivation assay The fusion protein (PPAR ligand binding domain - GAL4 DNA binding domain) expression plasmid (pFA-PPARγ/GAL4 or pFA-PPARα/GAL4) and the reporter plasmid (pFA-SEAP, Stratagene) were used. HEK 293T cells were grown in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum (DMEM-FBS) at 37°C in 5% CO_2. After 24 h of culture, the cells were co-transfected with pFA-PPAR/GAL and pFA-SEAP using Lipofectamine (Invitrogen) and Plus Reagents (Invitrogen) according to the manufacturer's protocol. After 5 h of transfection, the cells were treated with DMEM-FBS containing a test compound at 37°C in 5% CO_2. After 48 h of incubation, the conditioned medium was collected and the SEAP activity in it was measured using the Reporter assay kit – SEAP (TOYOBO) according to the manufacturer's protocol. Chemiluminescence was read by ARVOsx, PerkinElmer. The fold increase in chemiluminescence in the presence of a test compound compared to that in the absence of it was calculated, and then the EC_{50} value was obtained.

Animal Animal facilities, animal care, and study programs were in accordance with the in-house guideline of the Institutional Animal Care and Use Committee of Daiichi Sankyo Co, Ltd. Female *db*/*db* (C57BLKS/J-m+/+*Lepr*^{db}) mice were purchased at 10 weeks old from CREA Japan, Inc. (Tokyo, Japan) and used as a type 2 diabetic animal model. Male Zucker Fatty (Crlj:ZUC-Leprfa) rats were purchased at 6 weeks old from Charles River Laboratories Japan, Inc. (Kanagawa, Japan) and used as a type 2 diabetic animal model. All of the animals were housed six per cage and maintained on an 8 am light/8 pm dark schedule. Rodent chow and water were given ad libitum.

In Vivo *db*/*db* Mouse Studies. Mice (six per group) received a once daily oral dosing of a test compound or vehicle (0.5% methylcellulose) by oral gavage for 10 d. Blood was collected from the

tail vein immediately prior to the next dosing on Days 0, 5 and 10 for measurement of the plasma glucose and triglyceride levels.

In Vivo Zucker Fatty Rat Studies. Mice (six per group) received a once daily oral dosing of a test compound or vehicle (0.5% methylcellulose) by oral gavage for 13 d. Blood was collected from the tail vein immediately prior to the next dosing on Days 1, 7 and 13 for measurement of the plasma glucose and triglyceride levels.

Distribution Coefficient The distribution coefficients (log *D*) between 1-octanol and phosphate buffered saline (PBS) were assayed by a shaking flask method.[29] Equal amounts of PBS and 1-octanol were shaken and left for over 12 h. The upper layer (1-octanol) and lower layer (PBS) were collected individually. Each compound was dissolved in 1-octanol or PBS (200 μM). The same amount of either PBS or 1-octanol was added and the mixture was shaken vigorously for 30 min at room temperature. Then, both phases were separated and assayed using LC–MS methodologies (LC–Mass spectrometer: 1100 Series LC/MSD, Agilent; Analytical Column: X Terra® MSC18 3.5 μM, 3.0 × 30 mm, Waters; Mobile Phase: 10 mM ammonium acetate buffer (pH 4.5)/0.05% acetic acid in acetonitrile = 95/5 to 10/90 v/v). The values of log *D* were analyzed using Analyst software program (version 1.4, Applied Bio. Systems).

CYP3A4 Direct Inhibition Assay[30] P450 3A4 inhibition activities were measured with a high throughput inhibitor screening kit (Baculovirus-insect cell-expression system, SupersomesTM, and a fluorescent substrate (7-Benzyloxy-trifluoromethylcoumarin)) available from CORNING.
% inhibition was estimated by fluorescence at 10 μM of the test compounds.

MBI Assay[31, 32] Mechanism based inactivation against CYP3A4 is estimated as the percentage of the enzymatic activity (1'-hydroxylation of midazolam) remaining, after the 30-min preincubation

of the test compounds in pooled human liver microsomes.

Solubilities The solubilities were determined by HPLC analysis. Ten millimolars of compound solution in DMSO (50 μL) was freeze-dried. To the residue JP XIV 1st fluid (250 μL, pH 1.2) was added, and the mixture was stirred by pipette operation. The mixture was saved under shading over 12 h. After filtration of the mixture, the resulting filtrate was diluted 20 times by adding aqueous DMSO solution (1:1 (v/v)) to obtain the measurement sample solution. Five micromolars of compound solution in aqueous DMSO solution (1:1 (v/v)) and 100 μM of compound solution in aqueous DMSO solution (1:1 (v/v)) were prepared to create a calibration curve. The measurement sample solution, 5 μM solution and 100 μM solution were assayed using HPLC methodologies (Analytical Column: X Terra® MSC18 3.5 μM, 3.0 x 30 mm, Waters; Mobile Phase: 10 mM ammonium acetate buffer (pH 4.5)/0.05% acetic acid in acetonitrile = 95:5 to 10:90 v/v; Wave length: PDA 220– 420 nm). The solubilities were analyzed using Millenium software (Waters).

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