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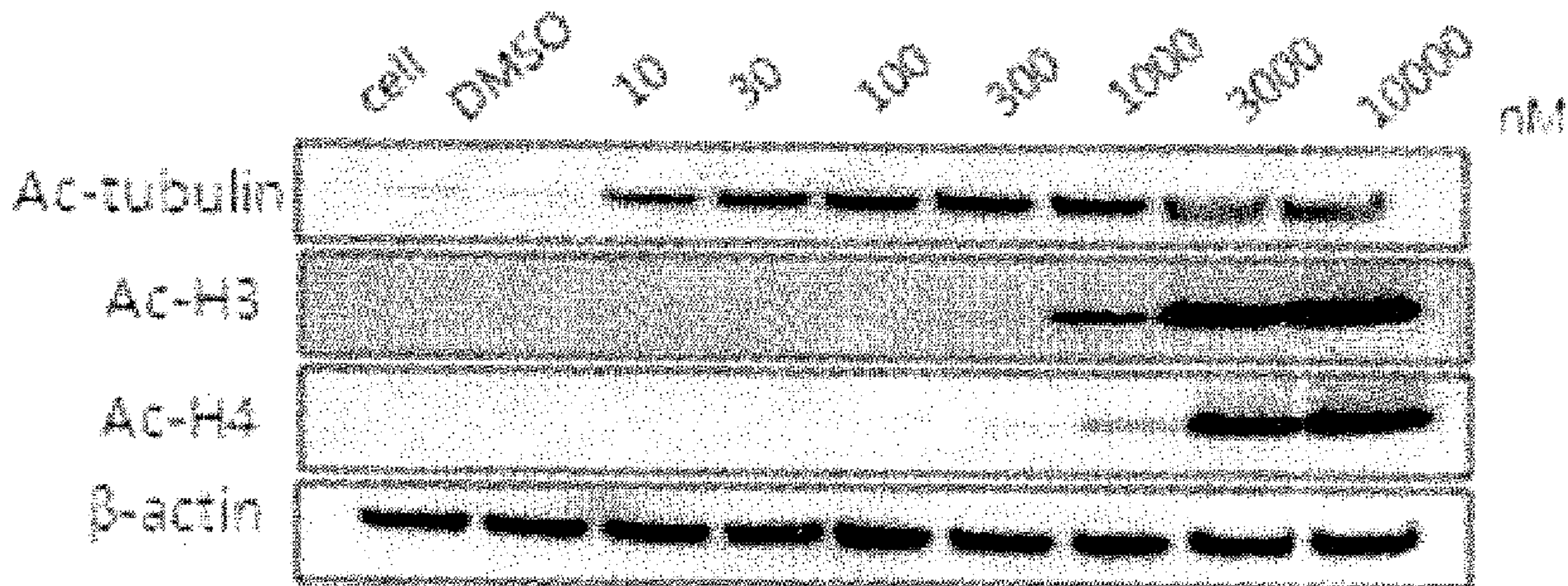
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(72) **Inventeurs/Inventors:**
LEE, CHANGSIK, KR;
YANG, HYUN-MO, KR;
CHOI, HOJIN, KR;
KIM, DOHOON, KR;
KIM, SOYOUNG, KR;
HA, NINA, KR;
...

(73) **Propriétaire/Owner:**
CHONG KUN DANG PHARMACEUTICAL CORP., KR

(74) **Agent:** CASSAN MACLEAN

(54) **Titre : NOUVEAUX COMPOSES POUR INHIBITEURS SELECTIFS D'HISTONE DESACETYLASES ET COMPOSITION PHARMACEUTIQUE LES COMPRENANT**
(54) **Title: NOVEL COMPOUNDS FOR SELECTIVE HISTONE DEACETYLASE INHIBITORS, AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME**



(57) **Abrégé/Abstract:**

The present invention relates to novel urea derivatives and, more particularly, to novel urea derivatives with histone deacetylase (HDAC) inhibitory activity, isomers thereof, pharmaceutically acceptable salts thereof, their use for the preparation of a medicaments comprising the same, a pharmaceutical composition comprising the same, a treatment method using the composition, and a method for preparing novel urea derivatives. The novel urea derivatives as selective histone deacetylase (HDAC) inhibitors are effective for the treatment of histone deacetylase-mediated diseases such as malignant tumors, inflammatory diseases, rheumatoid arthritis, neurodegeneration, etc.

(72) **Inventeurs(suite)/Inventors(continued):** LIM, HYOJIN, KR; KO, EUNHEE, KR; YOON, SEONGAE, KR;
BAE, DAEKWON, KR

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(74) Agent: AHN, So-Young; Dr. Ahn International Patent Law Office, 4th Fl., 344, Seocho-daero, Seocho-gu, Seoul 137-881 (KR).

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(71) Applicant: CHONG KUN DANG PHARMACEUTICAL CORP. [KR/KR]; 8, Chungjeong-ro, Seodaemun-gu, Seoul 120-756 (KR).

(72) Inventors: LEE, Changsik; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). YANG, Hyun-Mo; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). CHOI, Hojin; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). KIM, Dohoon; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). KIM, Soyoung; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). HA, Nina; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). LIM, Hyojin; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). KO, Eunhee; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 446-916 (KR). YOON, Seongae; 315-20, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do

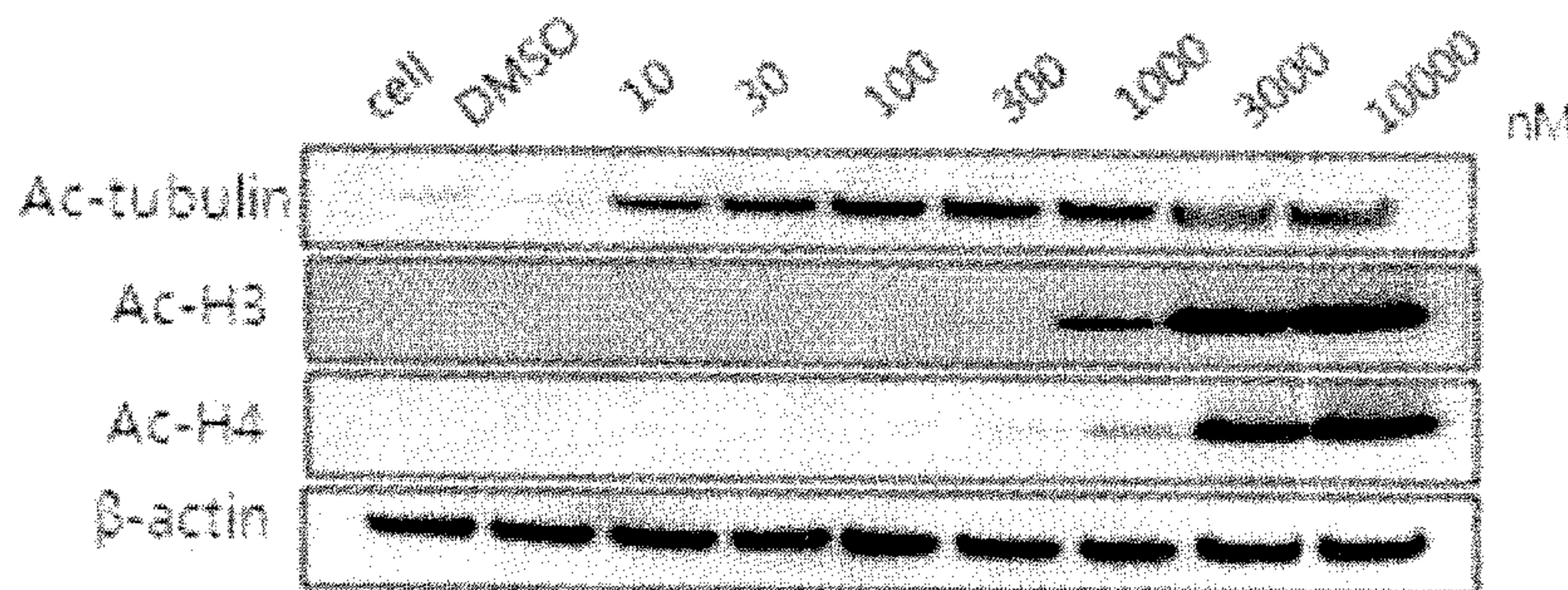
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(54) Title: NOVEL COMPOUNDS FOR SELECTIVE HISTONE DEACETYLASE INHIBITORS, AND PHARMACEUTICAL COMPOSITION COMPRISING THE SAME



(57) Abstract: The present invention relates to novel urea derivatives and, more particularly, to novel urea derivatives with histone deacetylase (HDAC) inhibitory activity, isomers thereof, pharmaceutically acceptable salts thereof, their use for the preparation of a medicaments comprising the same, a pharmaceutical composition comprising the same, a treatment method using the composition, and a method for preparing novel urea derivatives. The novel urea derivatives as selective histone deacetylase (HDAC) inhibitors are effective for the treatment of histone deacetylase-mediated diseases such as malignant tumors, inflammatory diseases, rheumatoid arthritis, neurodegeneration, etc.



WO 2014/178606 A1

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JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

【DESCRIPTION】**【Invention Title】**

**NOVEL COMPOUNDS FOR SELECTIVE HISTONE DEACETYLASE
INHIBITORS, AND PHARMACEUTICAL COMPOSITION COMPRISING THE
SAME**

5

【Technical Field】

The present invention relates to novel compounds
having histone deacetylase (HDAC) inhibitory activity,
10 optical isomers thereof, pharmaceutically acceptable salts
thereof, their use for the preparation of medicaments for
the treatment of HDAC-mediated diseases, a pharmaceutical
composition comprising the same, a treatment method using
the composition, and a preparation method thereof.

15

【Background Art】

The cellular transcriptional regulation is a complex
biological process. One of the basic principles is the
post-translation modification of histone proteins H2A/B, H3
20 and H4 that form the octameric histone core complex. The
complex N-terminal modifications at lysine residues by
acetylation or methylation and at serine residues by
phosphorylation constitute part of the so-called "histone
code" (Stahl & Ellis, Nature 403, 41-45, 2000).

25

In a simple model, acetylation of positively charged

lysine residues decreases affinity to negatively charged DNA, thus transcription factors may be easily entered.

Histone acetylation and deacetylation is catalysed by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively. The HDAC is associated with transcriptional repressor complexes, switching chromatin to a transcriptionally inactive, silent structure (Marks et al. Nature Cancer Rev 1, 189-202, 2001). The opposite holds true for certain HATs which are associated with transcriptional activator complexes. Three different classes of HDACs, located in the nucleus, have been described so far, namely, class I (HDAC 1-3, 8; Mr=42-55 kDa) sensitive towards inhibition Trichostatin A (TSA), class II (HDAC 4-7, 9, 10; Mr=120-130 kDa) sensitive to TSA, and class III (Sir2) which are quite distinct by their NAD⁺ dependency and TSA insensitivity.

Inhibitors of histone deacetylases (HDACs) constitute a new class of anticancer drugs with differentiation and apoptosis activity. By targeting histone deacetylases (HDACs), the HDAC inhibitors affect histone (protein) acetylation and chromatin structure, inducing a complex transcriptional reprogramming, exemplified by reactivation of tumor suppressor genes and repression of oncogenes. In addition to generating acetylation of N-terminal lysine residue in core histone protein, there are non-histone

targets important for cancer cell biology, including heat-shock-protein (HSP90), tubulin or p53 tumor suppressor protein. Therefore, the HDAC inhibitors can be used for the treatment of cancers as well as inherited metabolic diseases, autoimmune diseases, etc., since the efficacy in animal models for inflammatory diseases, rheumatoid arthritis, and neurodegeneration has been shown.

Examples of histone deacetylase-mediated diseases include cell proliferative diseases including malignant tumors such as cancers, etc., autosomal dominant diseases such as Huntington's diseases, etc., inherited metabolic diseases such as cystic fibrosis, hepatic fibrosis, kidney fibrosis, pulmonary fibrosis, skin fibrosis, etc, autoimmune diseases such as rheumatoid arthritis, etc., acute and chronic neurological diseases such as diabetes, stroke, etc., hypertrophy such as cardiac hypertrophy, etc., hemorrhagic heart failure, amyotrophic lateral sclerosis, glaucoma, ocular diseases (associated with angiogenesis), Alzheimer's disease, etc.

HDAC inhibitors known up to now can be classified into four categories according to their structures: 1) short chain fatty acids (butyric acid, valproic acid); 2) hydroxamic acids (trichostatin A, SAHA, LBH-589); 3) cyclic peptides (desipeptide); and 4) benzamide (MS-275, MGCD-0103) (International Journal of Oncology 33, 637-646, 2008).

These many HDAC inhibitors (SAHA, LBH-589, MS-275, etc.) .
effectively induce growth inhibition, differentiation, and
apoptosis of various transformed cells in culture medium as
well as in animal models (Marks, P.A et. al., Curr Opin
5 Oncol. 2001. 13. 477-483), and some HDAC inhibitors such as
SAHA, LBH-589, MS-275, etc. are clinically evaluated for the
treatment of various cancers (Johnstone, R. W Nat. Rev. Drug
Discov. 2002 1. 287-299). Typical examples of HDAC
inhibitor compounds that are currently known include
10 hydroxamate compounds, such as SAHA (U.S. Patent No. 771,760,
Zolinza, Vorinostat), PXD101 (WO 02/30879, Belinostat), LBH-
589 (WO 02/22577, Panobinostat), and benzamide compounds
such as MS-275 (EP8799) and MGCD0103 (WO 04/69823). Among
these compounds, SAHA was approved on October 2006 and has
15 been used for the treatment of CTCL (cutaneous T-cell
lymphoma). Diseases for which medicine is efficacious have
been additionally expanded, but it is known that there are
drawbacks in terms of effectiveness and side effects (Cancer
Res 2006, 66, 5781-5789).

20 That is, although many HDAC inhibitors have been
reported to date, most of the HDAC inhibitors have drawbacks
in terms of efficacy and side effects. Therefore, in order
to overcome these drawbacks, there is a continuous need to
develop an effective HDAC inhibitor with high selectivity
25 and less side effects (Mol Cancer Res, 5, 981, 2007).

【Disclosure】**【Technical Problem】**

An object of the present invention is to provide novel compounds, optical isomers thereof, or pharmaceutical salts thereof.
5

Another object of the present invention is to provide a pharmaceutical composition comprising novel compounds with highly selective histone deacetylase (HDAC) inhibitory activity, optical isomers thereof, or pharmaceutical salts thereof.
10

Still another object of the present invention is to provide a preparation method thereof.

Yet another object of the present invention is to provide a pharmaceutical composition comprising the above compounds for the treatment of diseases associated with HDAC activity, including cancers, inflammatory diseases, autoimmune diseases, neurological or neurodegenerative diseases, etc.
15

Still yet another object of the present invention is to provide their use for the preparation of medicaments for the treatment of HDAC-mediated diseases such as cancers, inflammatory diseases, autoimmune diseases, neurological or neurodegenerative diseases, etc.
20

A further object of the present invention is to provide a method for the treatment of HDAC-mediated diseases
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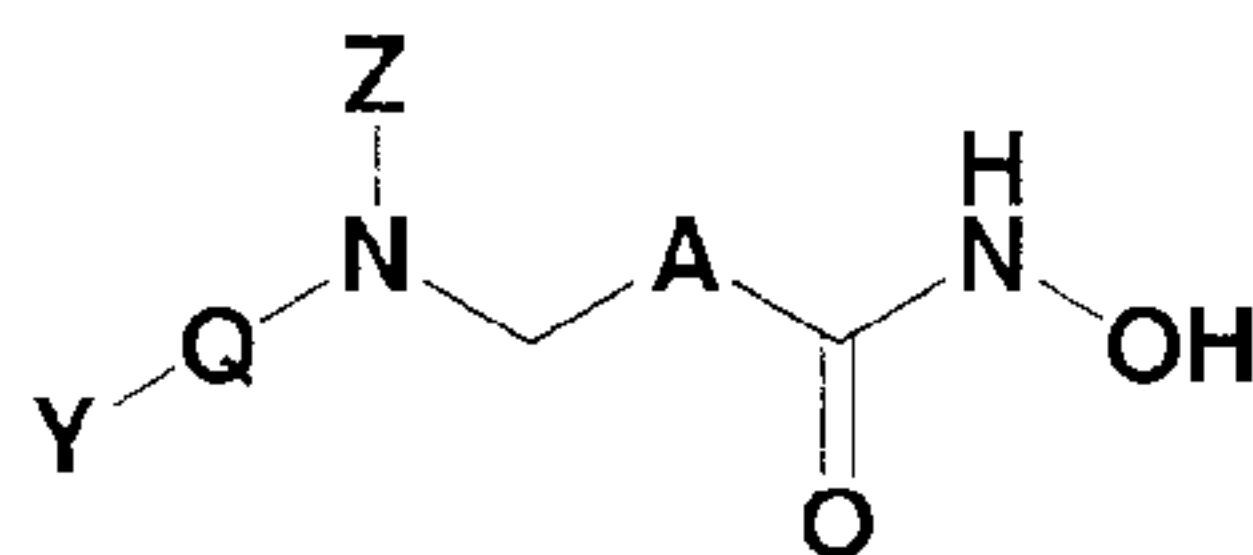
such as cancers, inflammatory diseases, autoimmune diseases,
 neurological or neurodegenerative diseases, etc., the method
 comprising administering a therapeutically effective amount
 of the pharmaceutical composition comprising the above
 5 compounds.

【Technical Solution】

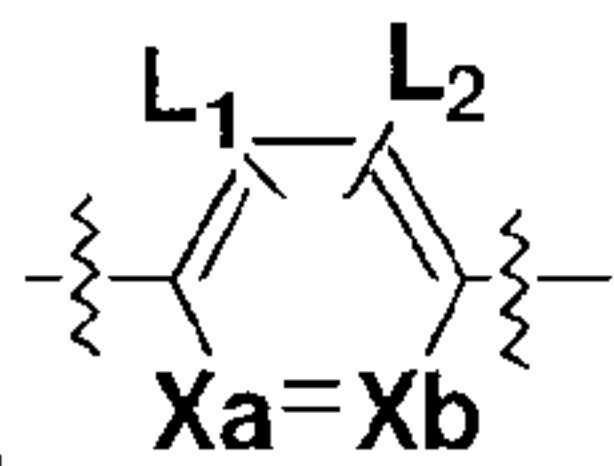
The present inventors have found novel compounds with
 histone deacetylase (HDAC) inhibitory activity and used the
 10 same for the treatment of histone deacetylase-mediated
 diseases, thus completing the present invention.

According to the above objects, the present invention
 provides a compound of the following Formula I, an optical
 isomer thereof, or a pharmaceutically acceptable salt
 15 thereof:

[Formula I]



20



wherein A is

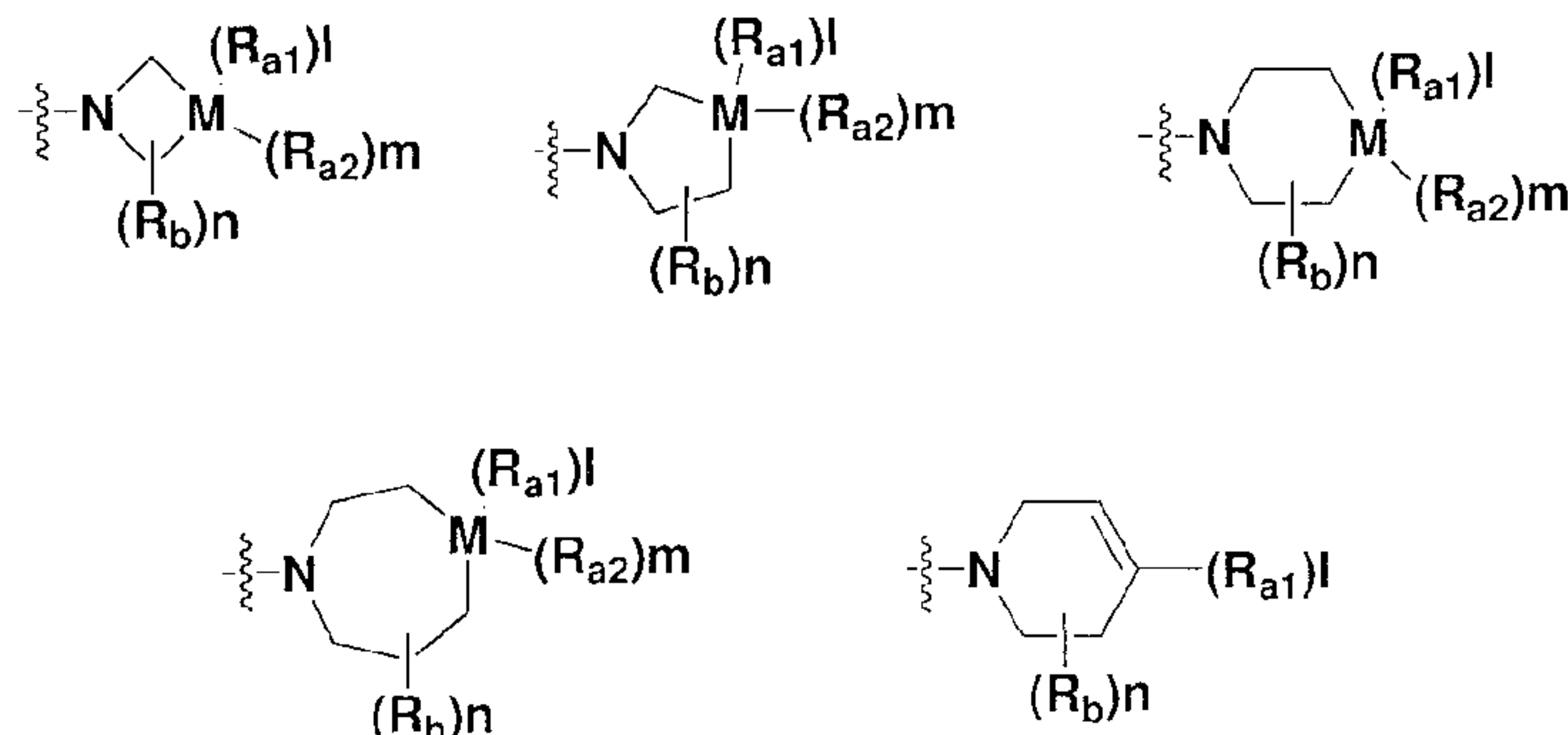
Xa and Xb are each independently C or N,

L₁ and L₂ are each independently hydrogen, -F, -Cl, -Br,

-I, -CH₃, or -C₁₋₃ straight or branched chain alkyl,

Q is C(=O), S(=O)₂, S(=O), or C(=NH),

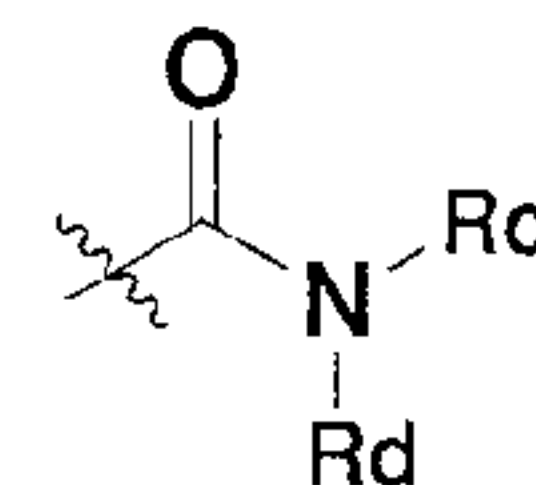
Y is selected from the group consisting of:



5 M is C, O, N, S(=O)₂, or S,

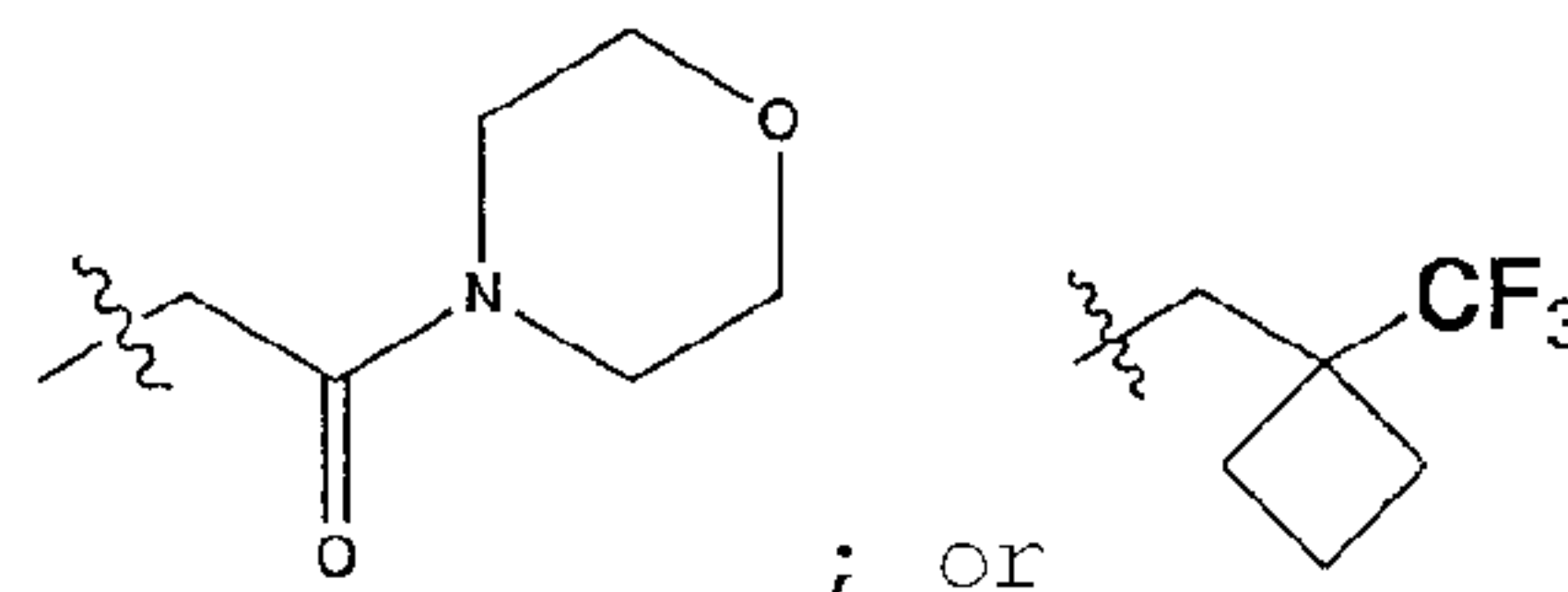
l and m are each independently an integer of 0 or 1,
 R_{a1} and R_{a2} are each independently hydrogen; hydroxy; -C₁₋₄
 straight or branched chain alkyl, unsubstituted or
 substituted with one or more F, Cl, Br or I; -C₁₋₄ straight or
 10 branched chain alcohol; benzhydryl; -C₁₋₄ straight or branched
 chain alkyl substituted with a saturated or unsaturated 5- to
 7-membered heterocyclic compound comprising 1 to 3
 heteroatoms selected from N, O, and S as a ring member
 (wherein the heterocyclic compound may be unsubstituted or at
 15 least one hydrogen may be optionally substituted with OH,
 OCH₃, CH₃, CH₂CH₃, F, Cl, Br, or I); a saturated or
 unsaturated 5- to 7-membered heterocyclic compound comprising
 1 to 3 heteroatoms selected from N, O, and S as a ring member
 (wherein the heterocyclic compound may be unsubstituted or at
 20 least one hydrogen may be optionally substituted with OH,

OCH₃, CH₃, CH₂CH₃, F, Cl, Br, or I); phenyl, unsubstituted or substituted with one or more F, Cl, Br, I, C₁₋₄ alkoxy, C₁₋₂ alkyl, or hydroxy; benzyl, unsubstituted or substituted with one or more F, Cl, Br, I, C₁₋₄ alkoxy, C₁₋₂ alkyl, or hydroxy;
 5 -S((=O)₂)CH₃; -F; -Cl; -Br; -I; -C₁₋₆ straight or branched chain alkoxy; -C₂₋₆ alkyl alkoxy; -C(=O)R_x, wherein R_x is



straight or branched C₁₋₃ alkyl or C₃₋₁₀ cycloalkyl;

wherein R_c and R_d are each independently hydrogen, C₁₋₃



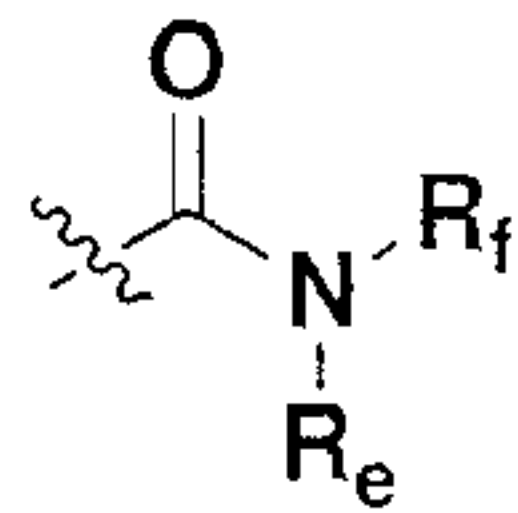
straight or branched chain alkyl;

; or ,

10 (wherein the structure of heterocyclic compound in R_{a1} and R_{a2} mentioned as alkyl substituted with heterocyclic compound or heterocyclic compound is preferably pyridine, morpholine or tetrahydropyran)

n is an integer of 0, 1, or 2,

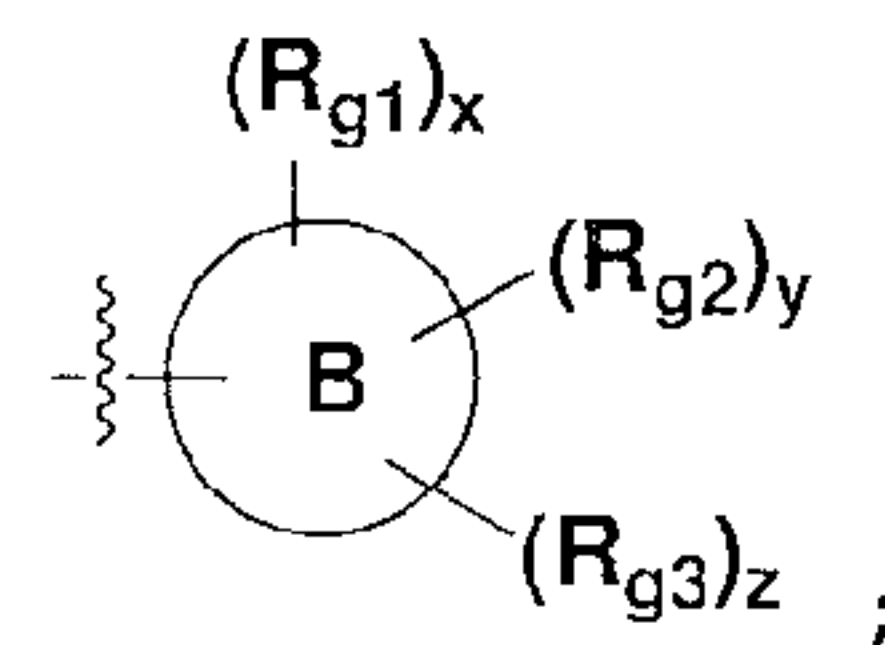
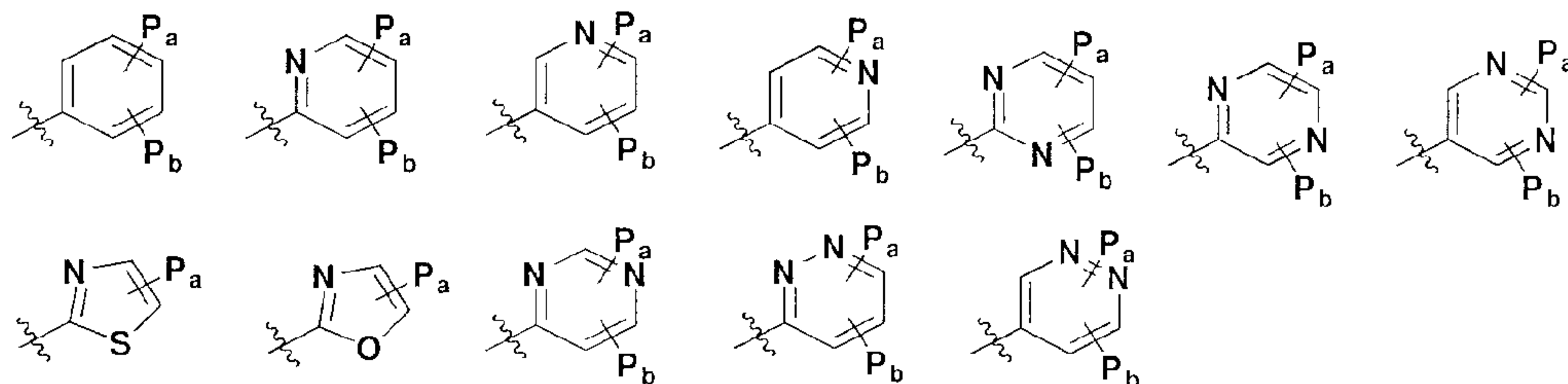
15 R_b is hydrogen; hydroxy; -C₁₋₆ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br, or I; -C(=O)CH₃; -C₁₋₄ straight or branched chain alcohol; -C₁₋₆ straight or branched chain alkoxy; -C₂₋₆ straight or branched chain alkyl alkoxy; -CF₃; -F; -Cl; -Br;



-I; or $\text{N}(\text{R}_e)(\text{R}_f)\text{C}(=\text{O})\text{Z}$, Wherein R_e and R_f are each independently hydrogen or $-\text{C}_{1-3}$ straight or branched chain alkyl, and

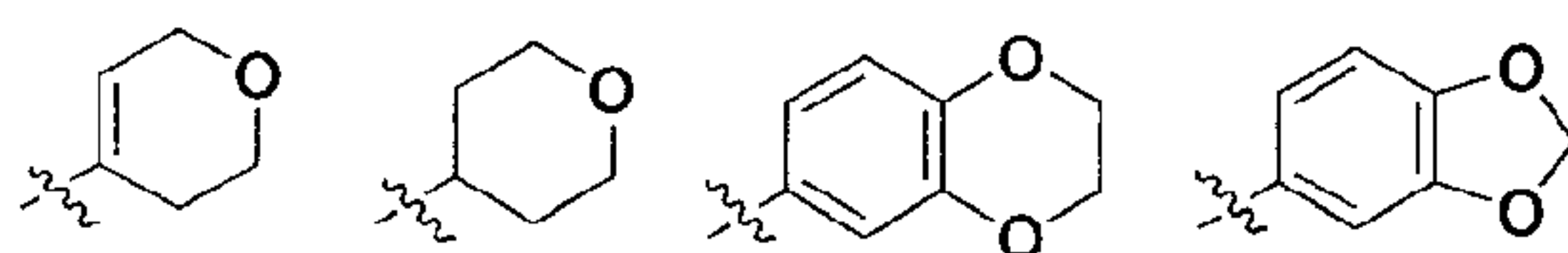
Z is phenyl; or a saturated or unsaturated 5- to 7-membered heterocycle comprising 1 to 3 heteroatoms selected from N, O, and S as a ring member, wherein the phenyl or heterocycle of Z may be unsubstituted or substituted with at least one hydroxy; $-\text{C}_{1-4}$ straight or branched chain alkyl, unsubstituted or having one or more substituents; $-\text{CF}_3$, unsubstituted or having one or more substituents; $-\text{CN}$, unsubstituted or having one or more substituents; $-\text{C}_{1-6}$ straight or branched chain alkoxy, unsubstituted or having one or more substituents; $-\text{C}_{2-6}$ straight or branched chain alkyl alkoxy, unsubstituted or having one or more substituents; $-\text{C}_{1-3}$ alcohol, unsubstituted or having one or more substituents; phenyl, unsubstituted or having one or more substituents; heterocycle, unsubstituted or having one or more substituents; or halogen unsubstituted or having one or more substituents.

Preferably, Z may be selected from the group consisting of the following compounds:



wherein P_a and P_b are each independently hydrogen; hydroxy; $-C_{1-4}$ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br or I;
 5 $-F$; $-Cl$; $-Br$; $-I$; $-CF_3$; $-OCF_3$; $-CN$; $-C_{1-6}$ straight or branched alkoxy; $-C_{2-6}$ straight or branched alkyl alkoxy; $-CH_2F$; or $-C_{1-3}$ alcohol,

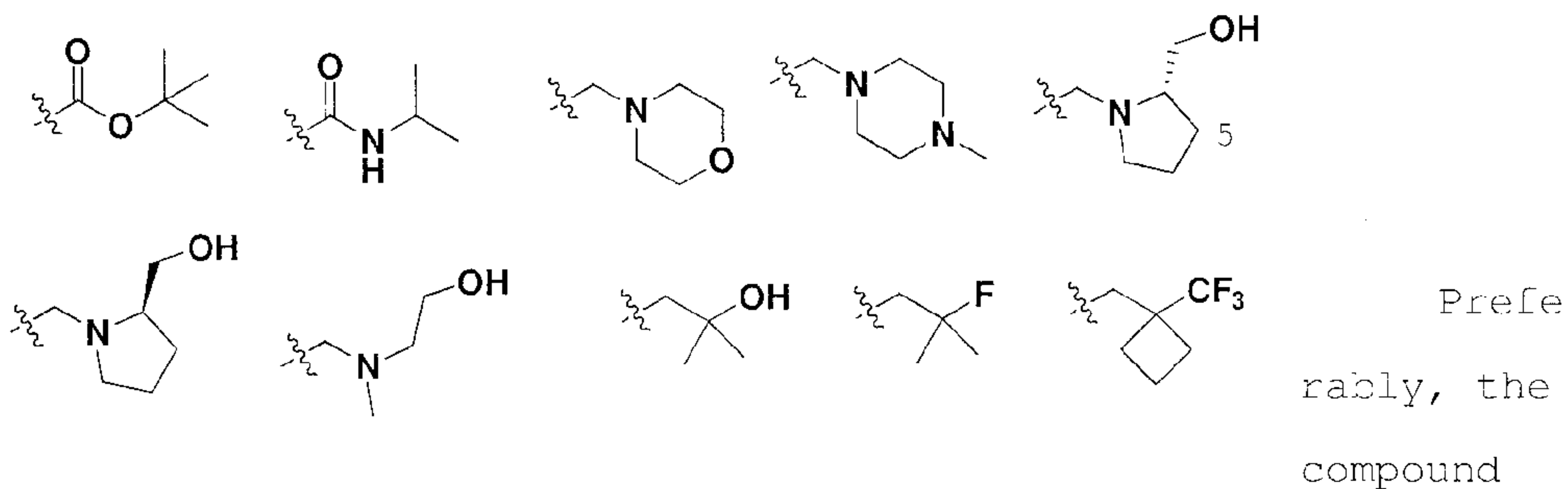
wherein $\textcircled{B}$ is selected from phenyl, pyridine, pyrimidine, thiazole, indole, indazole, piperazine, quinoline,
 10 furan, tetrahydropyridine, piperidine, or the following group:



15 x , y and z are each independently an integer of 0 or 1, and

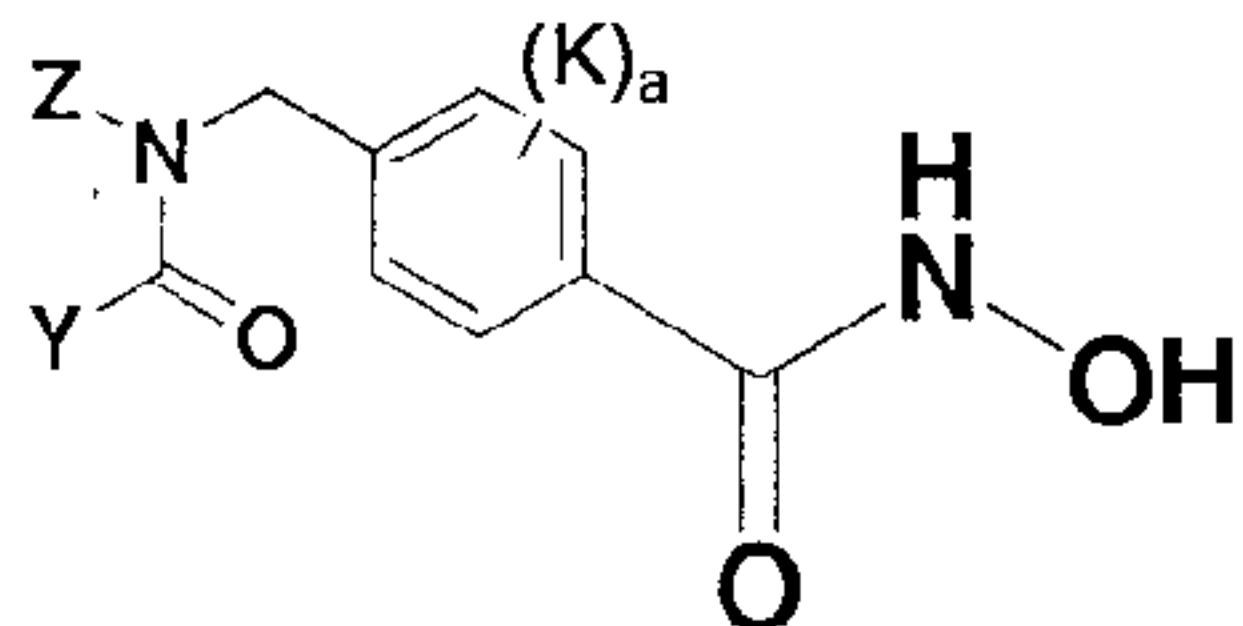
R_{g1} , R_{g2} and R_{g3} are each independently selected from hydrogen; hydroxy; $-C_{1-3}$ alkyl; $-CF_3$; $-C_{1-6}$ straight or branched chain alkoxy; $-C_{2-6}$ straight or branched chain alkyl

alkoxy; $-C(=O)CH_3$; $-C_{1-4}$ straight or branched chain alcohol; $-N(CH_3)_2$; $-F$; $-Cl$; $-Br$; $-I$; phenyl; $-S(=O)_2CH_3$; or the following group:



10 represented by the above Formula I may be a compound represented by the following Formula II:

[Formula II]



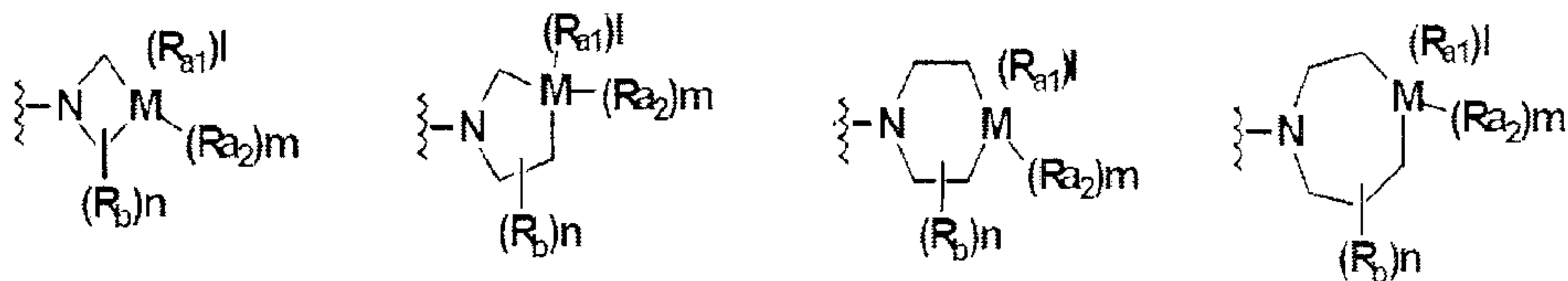
15

wherein

a is an integer of 0, 1 or 2,

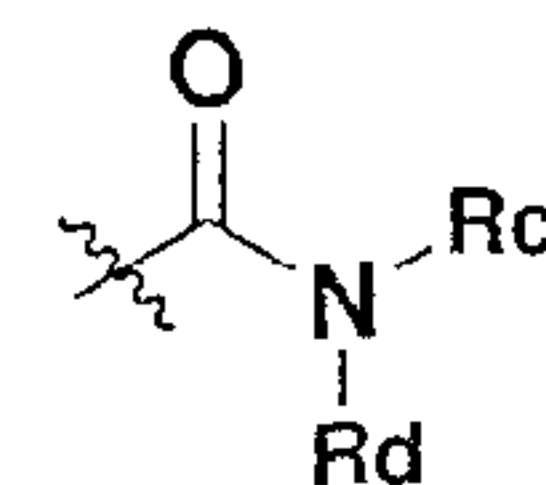
K is independently hydrogen, $-F$, $-Cl$, $-Br$ or $-I$,

Y is selected from the group consisting of:



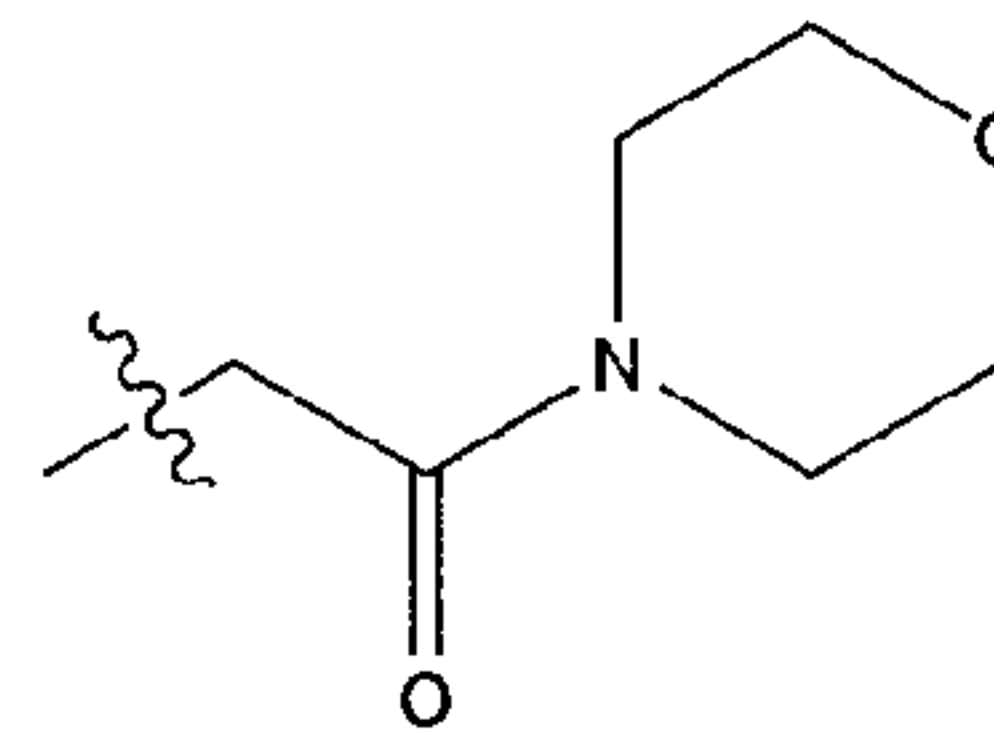
M is C, O or N,

l and m are each independently an integer of 0 or 1,
 R_{a1} and R_{a2} are each independently hydrogen; hydroxy; -C₁₋₄
 straight or branched chain alkyl, unsubstituted or
 5 substituted with one or more F, Cl, Br or I; -C₁₋₄ straight or
 branched chain alcohol; benzhydryl; -C₁₋₄ straight or branched
 chain alkyl substituted with a saturated or unsaturated 5- to
 7-membered heterocyclic compound comprising 1 to 3
 heteroatoms selected from N, O, and S as a ring member
 10 (wherein the heterocyclic compound may be unsubstituted or at
 least one hydrogen may be optionally substituted with OH,
 OCH₃, CH₃, CH₂CH₃, F, Cl, Br, or I); a saturated or
 unsaturated 5- to 7-membered heterocyclic compound comprising
 1 to 3 heteroatoms selected from N, O, and S as a ring member
 15 (wherein the heterocyclic compound may be unsubstituted or at
 least one hydrogen may be optionally substituted with OH,
 OCH₃, CH₃, CH₂CH₃, F, Cl, Br, or I); phenyl, unsubstituted or
 substituted with one or more F, Cl, Br, I, C₁₋₄ alkoxy, C₁₋₂
 alkyl, or hydroxy; benzyl, unsubstituted or substituted with
 20 one or more F, Cl, Br, I, C₁₋₄ alkoxy, C₁₋₂ alkyl, or hydroxy;
 -S((=O)₂)CH₃; -F; -Cl; -Br; -I; -C₁₋₆ straight or branched
 chain alkoxy; -C₂₋₆ alkyl alkoxy; -C(=O)R_x, wherein R_x is

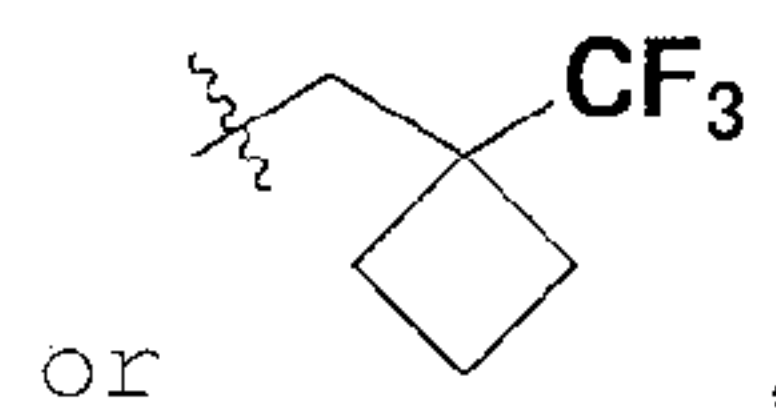


straight or branched C₁₋₃ alkyl or C₃₋₁₀ cycloalkyl;

wherein R_c and R_d are each independently hydrogen, C₁₋₃

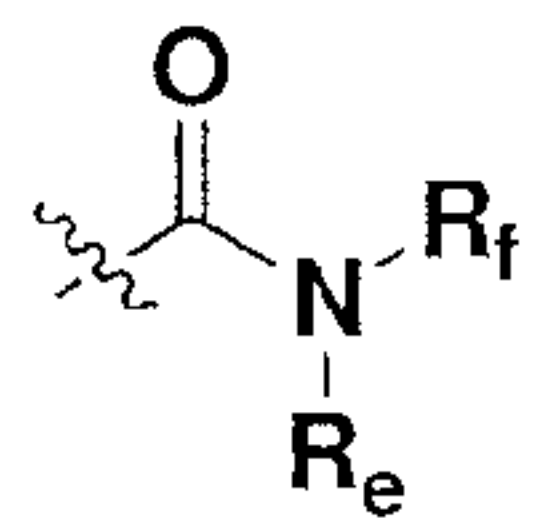


straight or branched chain alkyl;



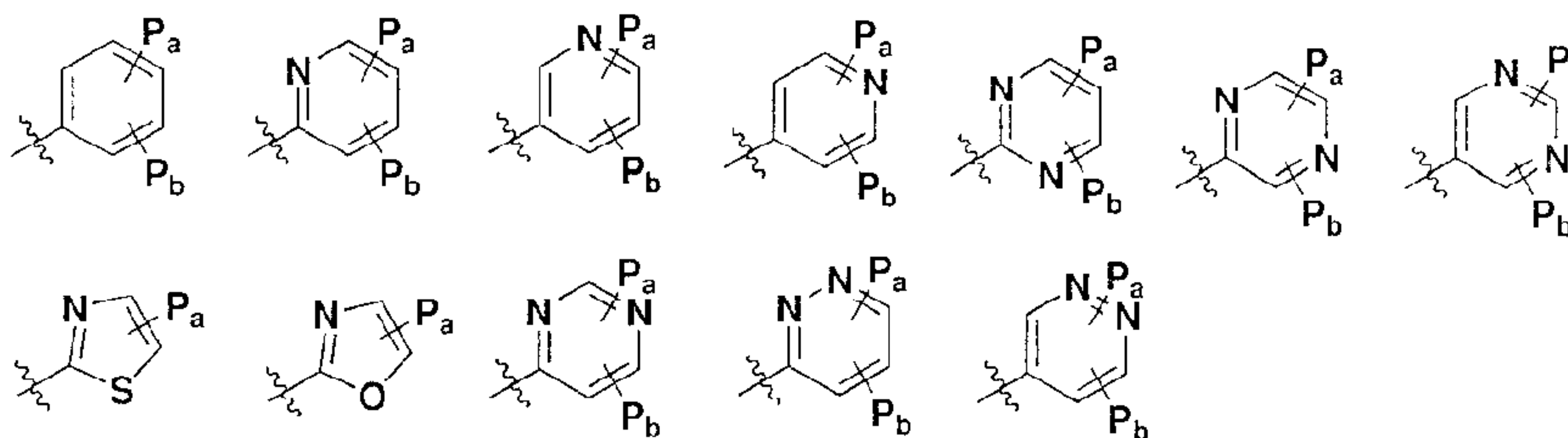
n is an integer of 0, 1, or 2,

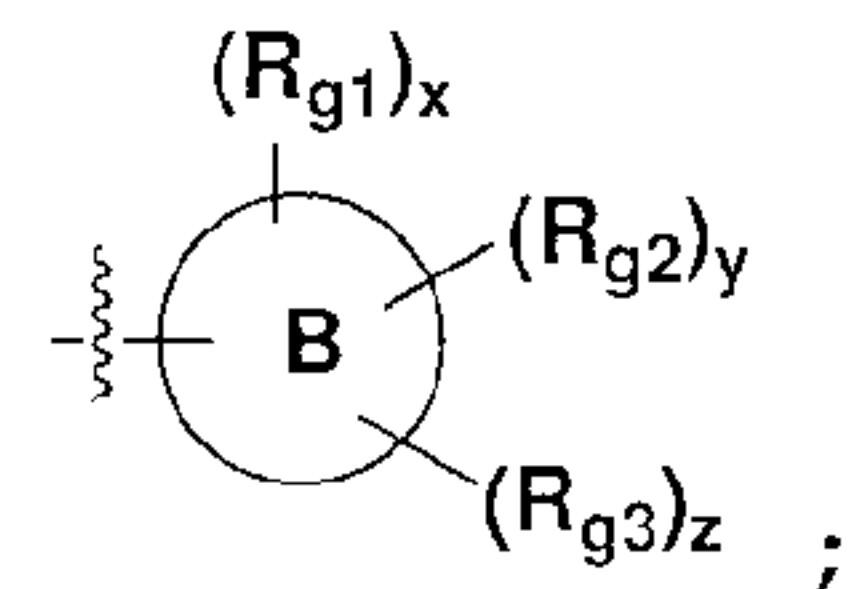
R_b is hydrogen; hydroxy; -C₁₋₆ straight or branched
 5 chain alkyl, unsubstituted or substituted with one or more F,
 Cl, Br, or I; -C(=O)CH₃; -C₁₋₄ straight or branched chain
 alcohol; -C₁₋₆ straight or branched chain alkoxy; -C₂₋₆
 straight or branched chain alkyl alkoxy; -CF₃; -F; -Cl; -Br;



-I; or , whrerin R_e and R_f are each independently
 10 hydrogen or -C₁₋₃ straight or branched chain alkyl, and

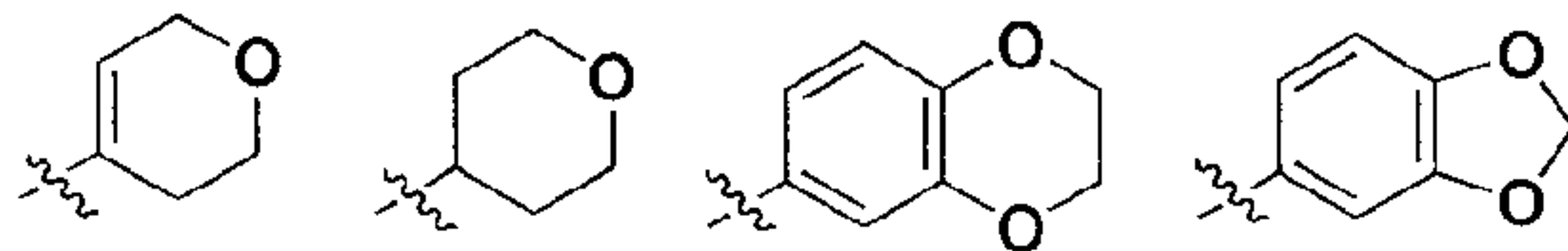
Z is selected from the group consisting of the following
 compounds:





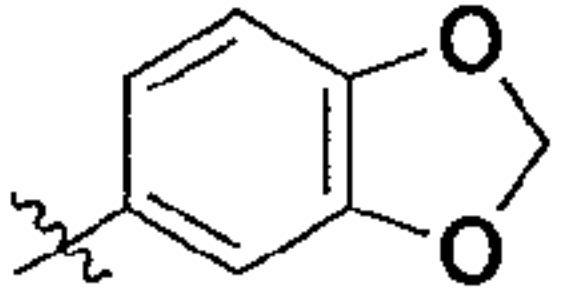
wherein P_a and P_b are each independently
hydrogen; hydroxy; $-C_{1-4}$ straight or branched chain alkyl,
unsubstituted or substituted with one or more F, Cl, Br or I;
 $-F$; $-Cl$; $-Br$; $-I$; $-CF_3$; $-OCF_3$; $-CN$; $-C_{1-6}$ straight or branched
5 alkoxy; $-C_{2-6}$ straight or branched alkyl alkoxy; $-CH_2F$; or $-C_{1-3}$
alcohol,

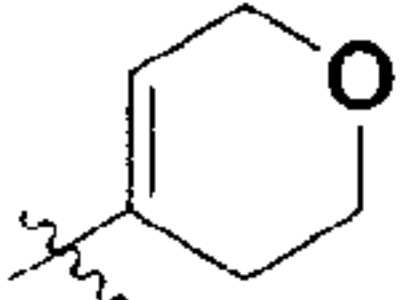
wherein $\textcircled{B}$ is selected from phenyl, pyridine,
pyrimidine, thiazole, indole, indazole, piperazine, quinoline,
furan, tetrahydropyridine, piperidine, or the following
10 group:

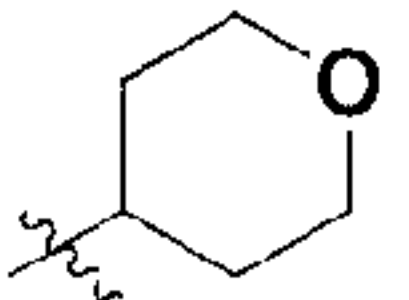


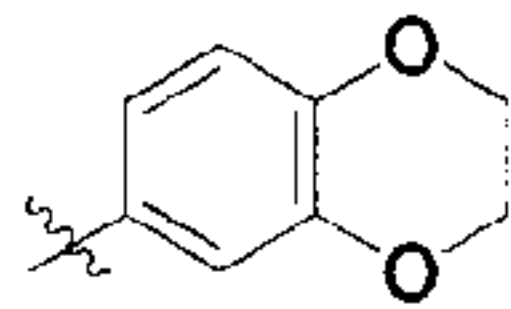
the indazole of $\textcircled{B}$ may be indazol-5-yl or indazol-6-yl,
15 the pyridine of $\textcircled{B}$ may be pyridine-3-yl,
the indole of $\textcircled{B}$ may be indol-4-yl, indol-5-yl or
indol-6-yl,

the pyrimidine of $\textcircled{B}$ may be pyrimidin-5-yl,
the quinoline of $\textcircled{B}$ may be quinolin-7yl,
20 the furan of $\textcircled{B}$ may be furan-3-yl,
the tetrahydropyridine of $\textcircled{B}$ may be 1,2,3,6-
tetrahydropyridin-4-yl,
the piperidine of $\textcircled{B}$ may be piperidin-4-yl,

the  of  may be benzo[d][1,3]dioxol-5-yl,

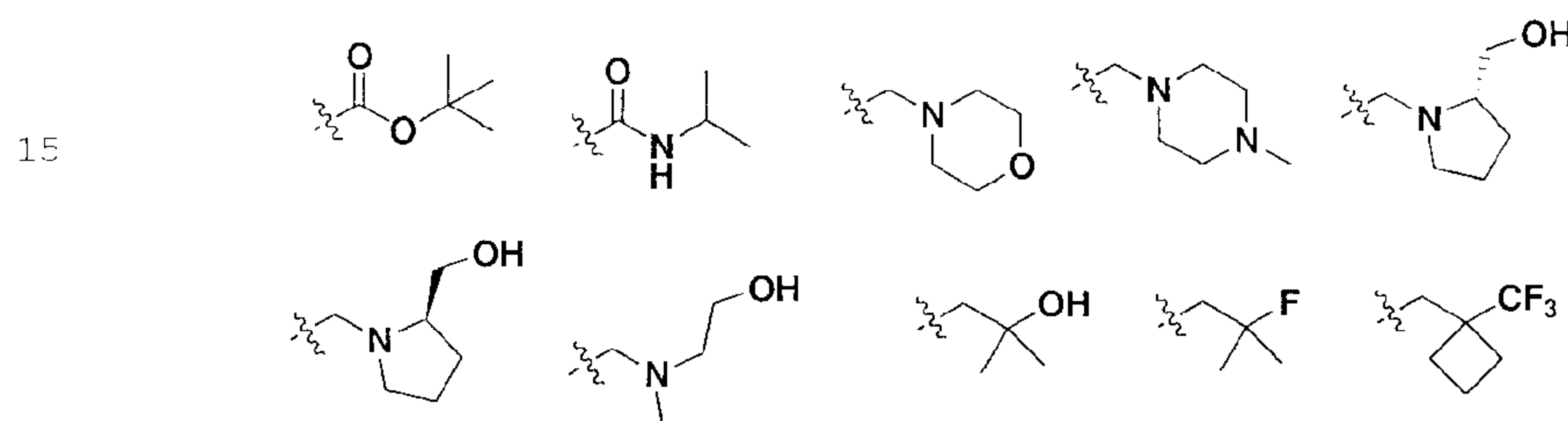
the  of  may be 3,6-dihydro-2H-pyran-4-yl,

the  of  may be tetrahydro-2H-pyran-4-yl,

the  of  may be 2,3-
5 dihydrobenzo[b][1,4]dioxin-6-yl,

x, y and z are each independently an integer of 0 or 1,
and

R_{q1}, R_{q2} and R_{q3} are each independently selected from
hydrogen; hydroxy; -C₁₋₃ alkyl; -CF₃; -C₁₋₆ straight or
10 branched chain alkoxy; -C₂₋₆ straight or branched chain alkyl
alkoxy; -C(=O)CH₃; -C₁₋₄ straight or branched chain alcohol; -
N(CH₃)₂; -F; -Cl; -Br; -I; phenyl; -S(=O)₂CH₃; or the
following group:



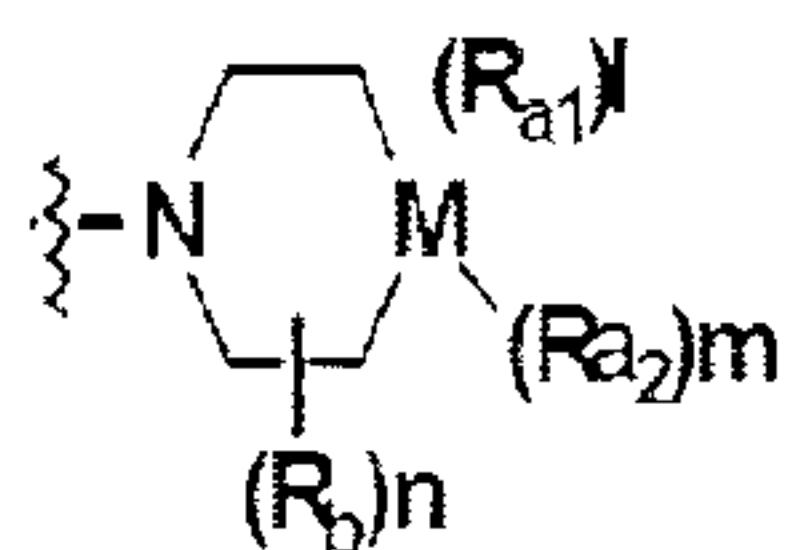
According to embodiments of the present invention, the
compound represented by the above Formula II may preferably

include following structure:

wherein

a is an integer of 0, 1 or 2,

K is independently hydrogen, -F, -Cl, -Br or -I,



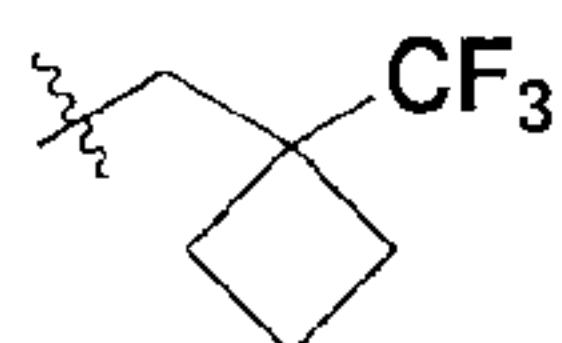
5 Y is ,

M is C, O or N,

l and m are each independently an integer of 0 or 1,

10 Ra1 and Ra2 are each independently hydrogen; hydroxy; -C1-4 straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br or I; -C1-4 straight or branched chain alcohol; benzhydryl; -C1-4 straight or branched chain alkyl substituted with a saturated or unsaturated 5- to 7-membered heterocyclic compound comprising 1 to 3 heteroatoms selected from N, O, and S as a ring member (wherein the heterocyclic compound may be unsubstituted or at least one hydrogen may be optionally substituted with OH, OCH3, CH3, CH2CH3, F, Cl, Br, or I); a saturated or unsaturated 5- to 7-membered heterocyclic compound comprising 1 to 3 heteroatoms selected from N, O, and S as a ring member (wherein the heterocyclic compound may be unsubstituted or at least one hydrogen may be optionally substituted with OH, OCH3, CH3, CH2CH3, F, Cl, Br, or I); phenyl, unsubstituted or substituted with one or more F, Cl, Br, I, C1-4 alkoxy, C1-2

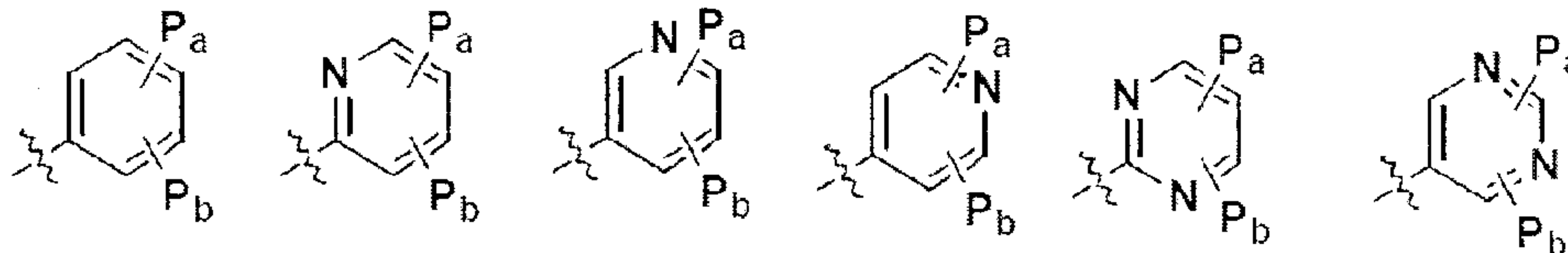
alkyl, or hydroxy; benzyl, unsubstituted or substituted with one or more F, Cl, Br, I, C₁₋₄ alkoxy, C₁₋₂ alkyl, or hydroxy; -S((=O)₂)CH₃; -F; -Cl; -Br; -I; -C₁₋₆ straight or branched chain alkoxy; -C₂₋₆ alkyl alkoxy; -C(=O)R_x, wherein R_x is
 5 straight or branched C₁₋₃ alkyl or C₃₋₁₀ cycloalkyl; or,



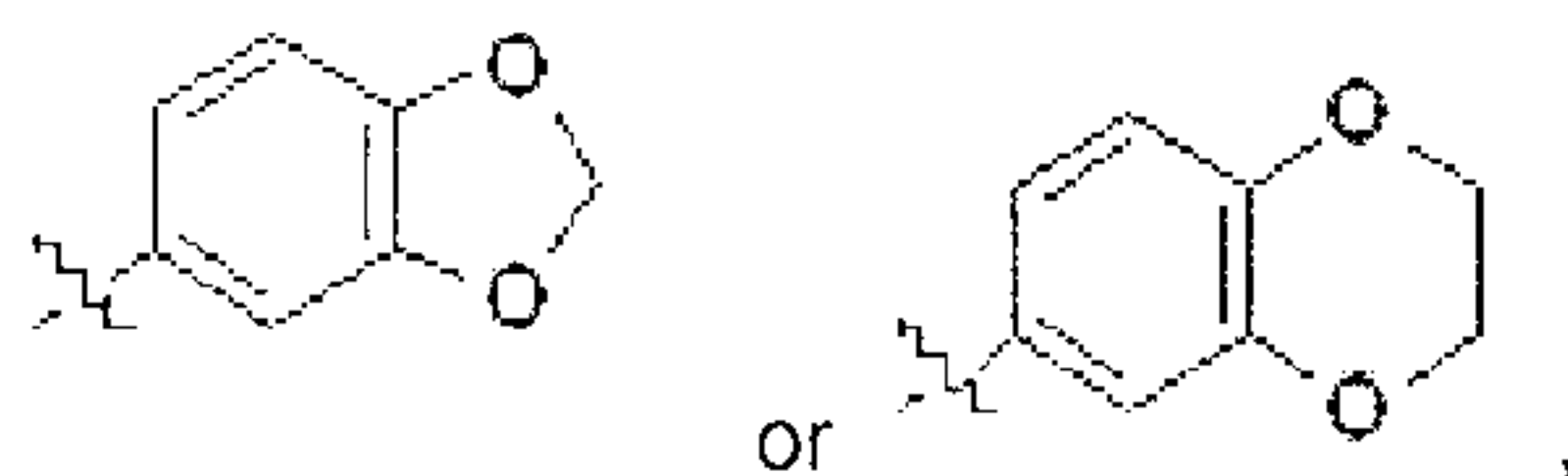
n is an integer of 0, 1, or 2,

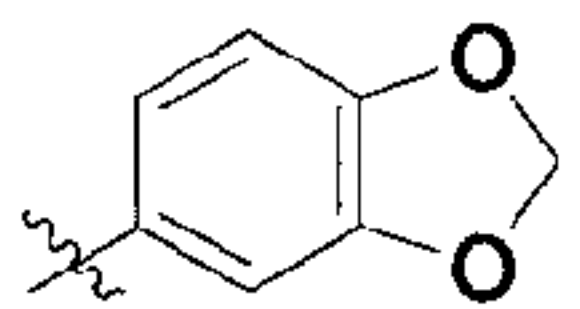
R_b is hydrogen; -C₁₋₆ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br, or
 10 I; and

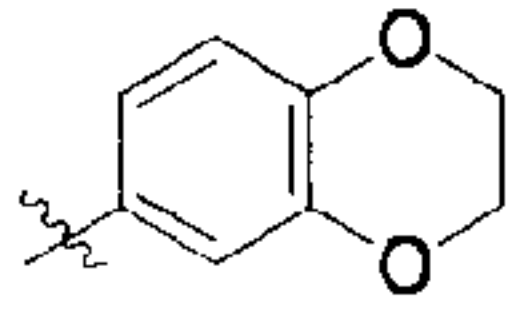
Z is selected from the group consisting of the following compounds:



wherein P_a and P_b are each independently hydrogen; hydroxy; -
 15 C₁₋₄ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br or I; -F; -Cl; -Br; -I; -CF₃; -OCF₃; -CN; -C₁₋₆ straight or branched alkoxy; -C₂₋₆ straight or branched alkyl alkoxy; -CH₂F; -C₁₋₃ alcohol;

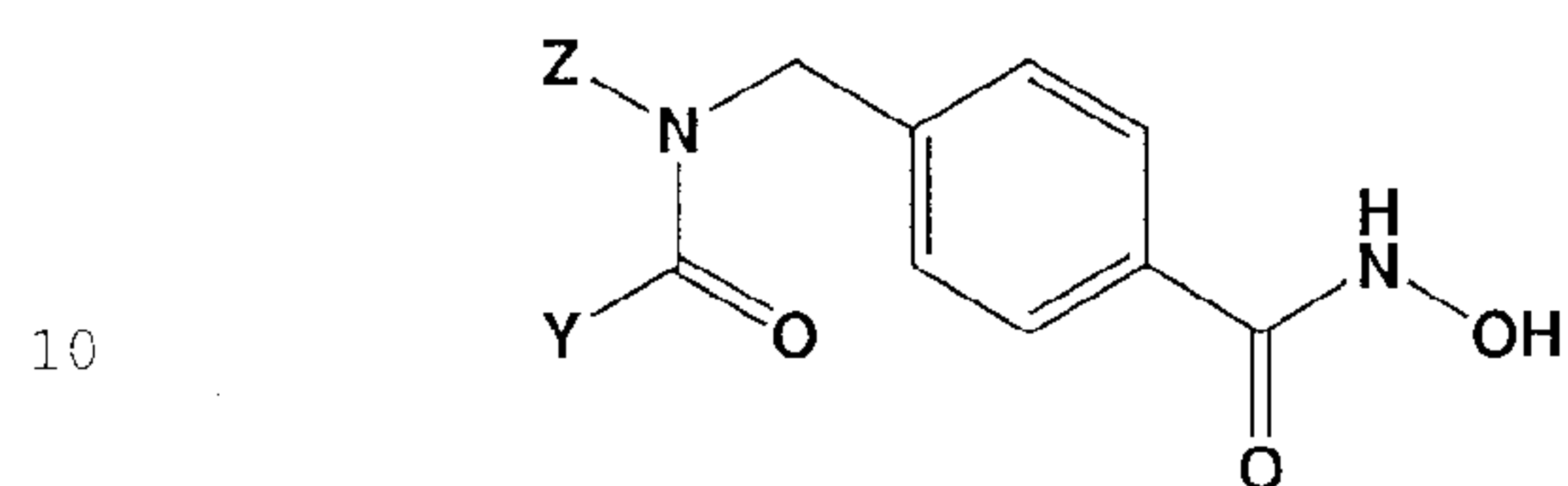


the  may be benzo[d][1,3]dioxol-5-yl,

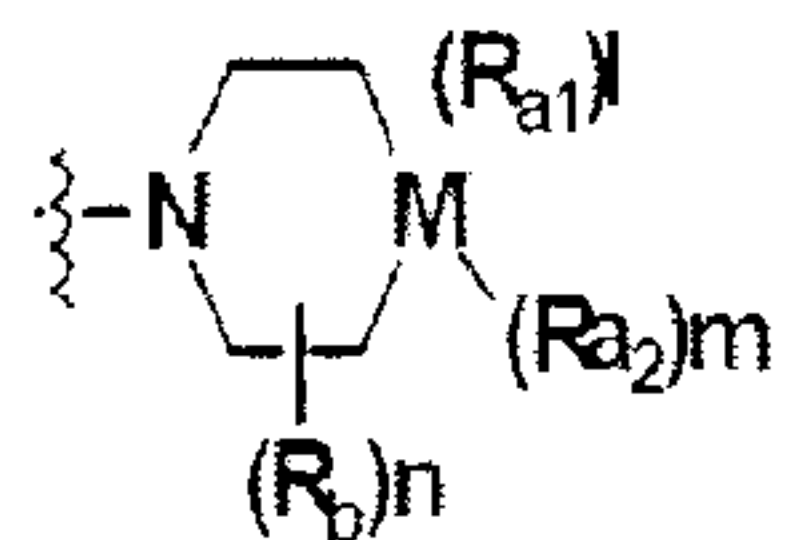
the  may be 2,3-dihydrobenzo[b][1,4]dioxin-6-yl.

More preferably, the compound represented by the above
 5 Formula II may be a compound represented by the following
 Formula III:

[Formula III]



wherein



Y is

15 M is C, O or N,

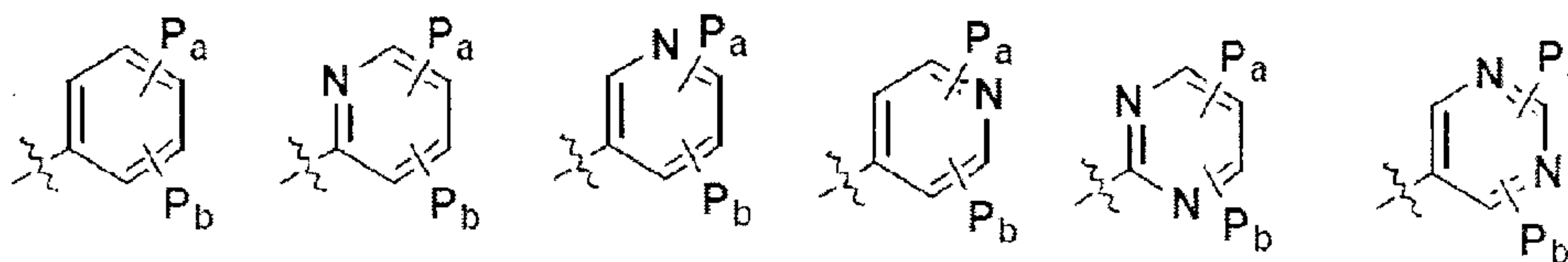
l and m are each independently an integer of 0 or 1,

Ra1 and Ra2 are each independently hydrogen; -C1-4
 straight or branched chain alkyl, unsubstituted or
 substituted with one or more F, Cl, Br or I; -C1-4 straight or
 20 branched chain alkyl substituted with a phenyl, pyridine or

pyrimidine (wherein the phenyl, pyridine or pyrimidine may be unsubstituted or at least one hydrogen may be optionally substituted with OH, OCH₃, CH₃, CH₂CH₃, F, Cl, Br, or I);
n is an integer of 0, 1, or 2,

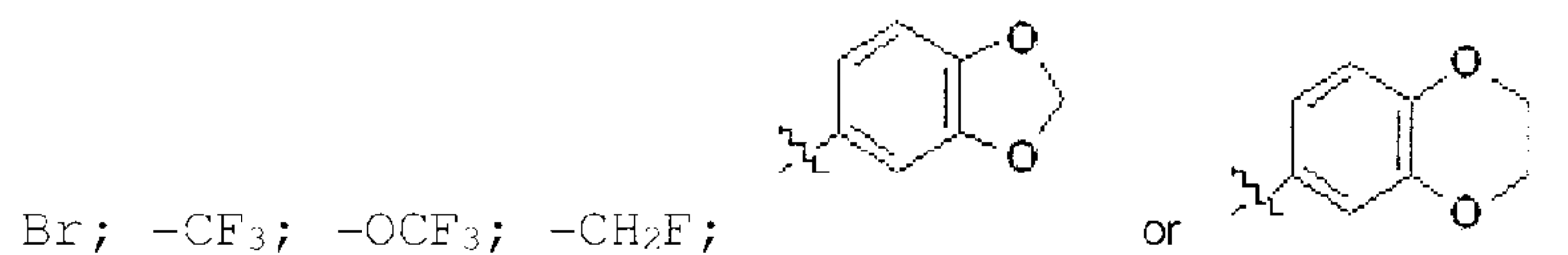
5 R_b is hydrogen; -C₁₋₆ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br, or I; and

Z is selected from the group consisting of the following compounds:



10

wherein P_a and P_b are each independently hydrogen; -F; -Cl; -



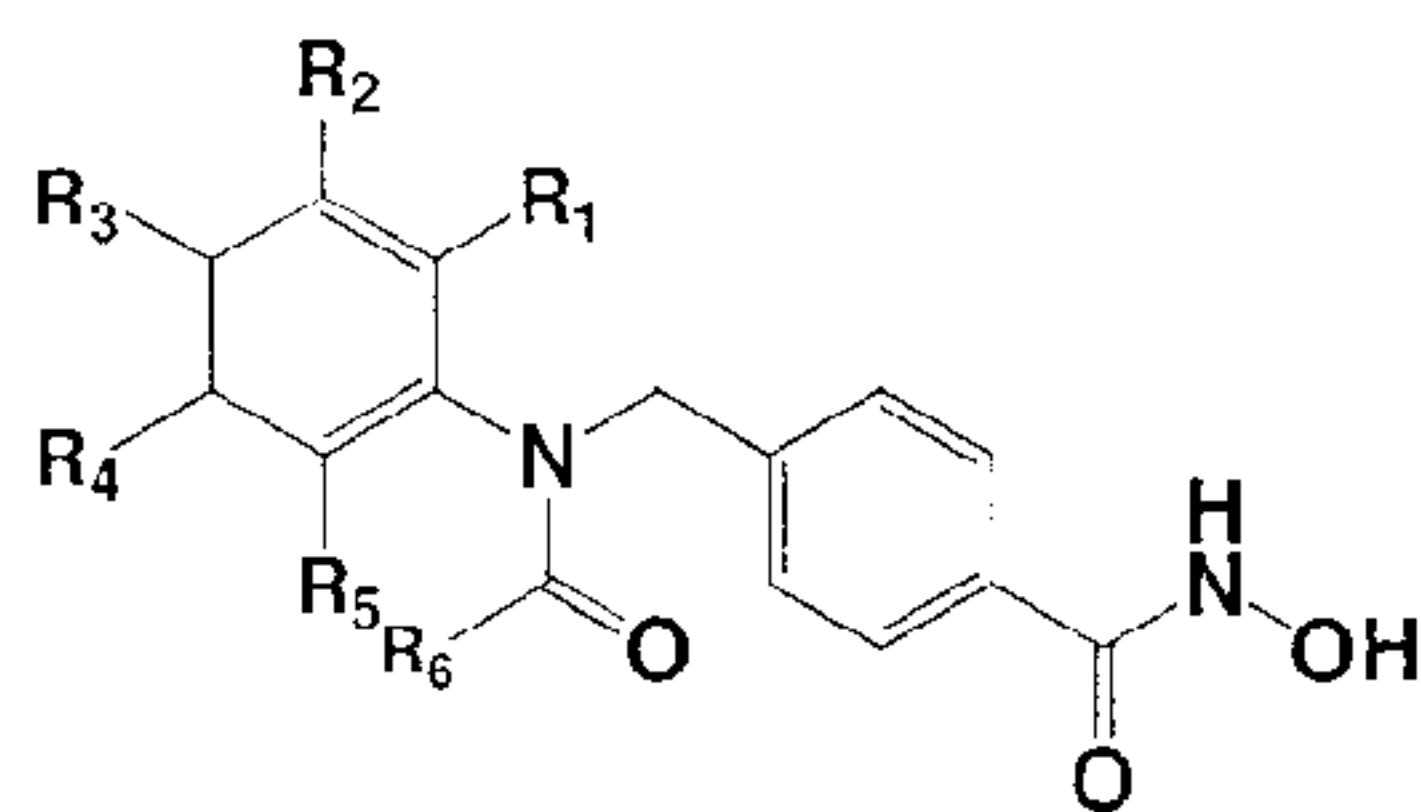
the may be benzo[d][1,3]dioxol-5-yl,

the may be 2,3-dihydrobenzo[b][1,4]dioxin-6-yl.

15

The compound represented by the above Formula I may be a compound represented by the following Formula I-1:

[Formula I-1]



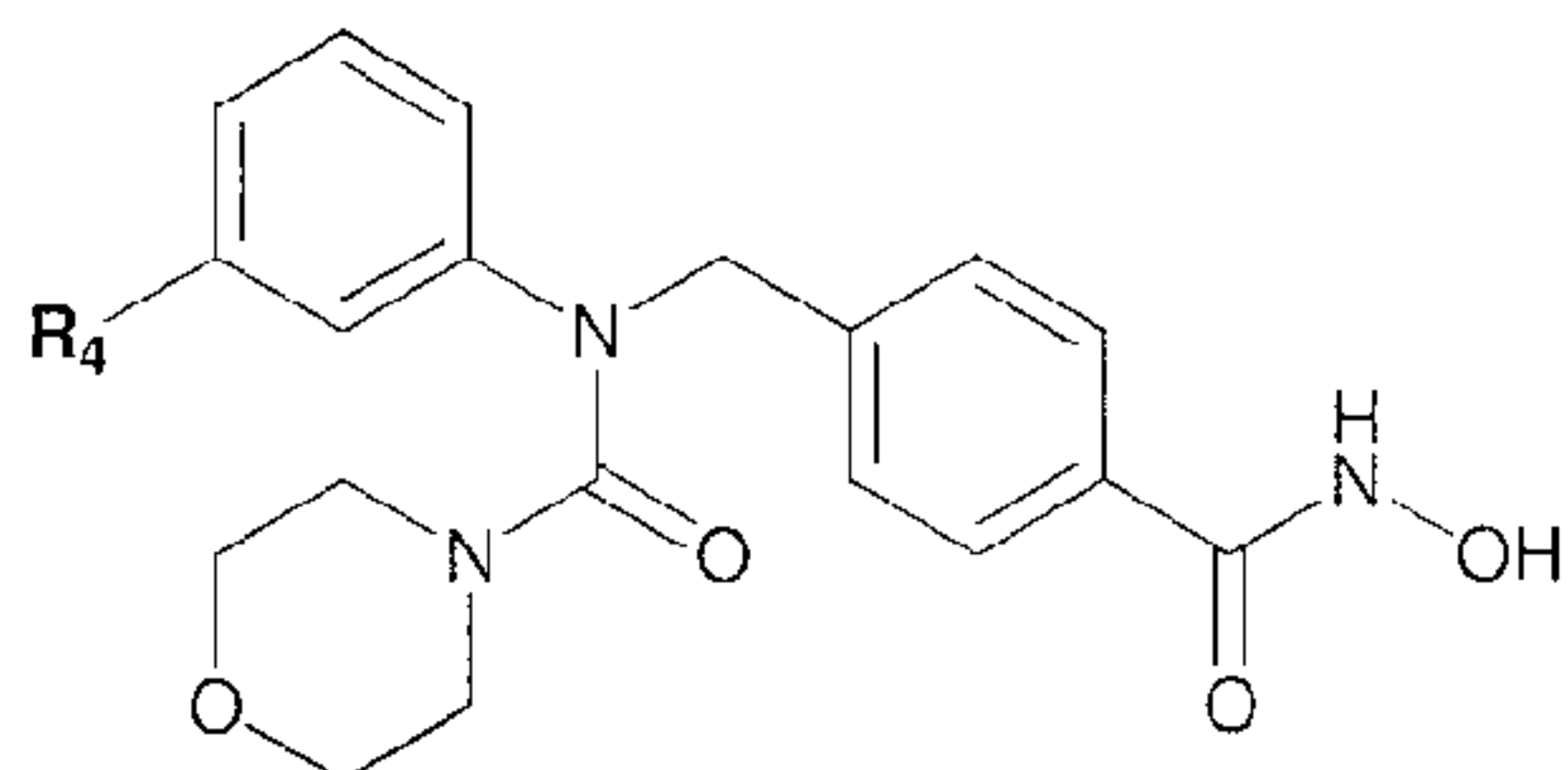
wherein R_1 to R_5 are each independently hydrogen, -F, -Cl, -Br, -I, -CF₃, -CH₃, -CH₂CH₃, -OCH₃, or -OCF₃ and

R_6 is piperidine; piperidine substituted with one or
 5 more C₁₋₃ alkyl; morpholine; morpholine substituted with one
 or more C₁₋₃ alkyl; piperazine; piperazine substituted with
 one or more C₁₋₃ alkyl, -C(=O)CH₃, benzhydryl, phenyl, benzyl,
 pyridine, -C₁₋₂ alkyl morpholine, or morpholine ethanone
 (wherein phenyl or benzyl may be unsubstituted or at least
 10 one hydrogen may be optionally substituted with -OCH₃, -CH₃, -
 CH₂CH₃, -F, -Cl, -Br, or -I); (piperazinyl)ethanone; (R)-3-
 fluoropyrrolidine; (S)-3-fluoropyrrolidine; (R)-pyrrolidin-2-
 yl-methanol; (S)-2-(trifluoromethyl)pyrrolidine; azetidine;
 difluoroazetidine; phenylpiperidinol; or oxazepane.

15 Preferably, the compound represented by the above
 Formula I-1 may be Compound 255, 256, 279, 374, 385, 386, 389,
 390, 391, 392, 393, 394, 413, 414, 415, 416, 438, 439, 440,
 441, 453, 454, 455, 456, 457, 458, 459, 460, 461, 477, 478,
 479, 480, 481, 482, 484, 485, 486, 494, 495, 496, 497, 498,
 20 520, 521, 522, 529, 530, 543, 544, 545, 580, 683, 684, 717,
 718, 771, 772, 773, 774, 776, 791, 800 or 801 described in
 the present invention.

The compound represented by the above Formula I may be a compound represented by the following Formula I-2:

[Formula I-2]

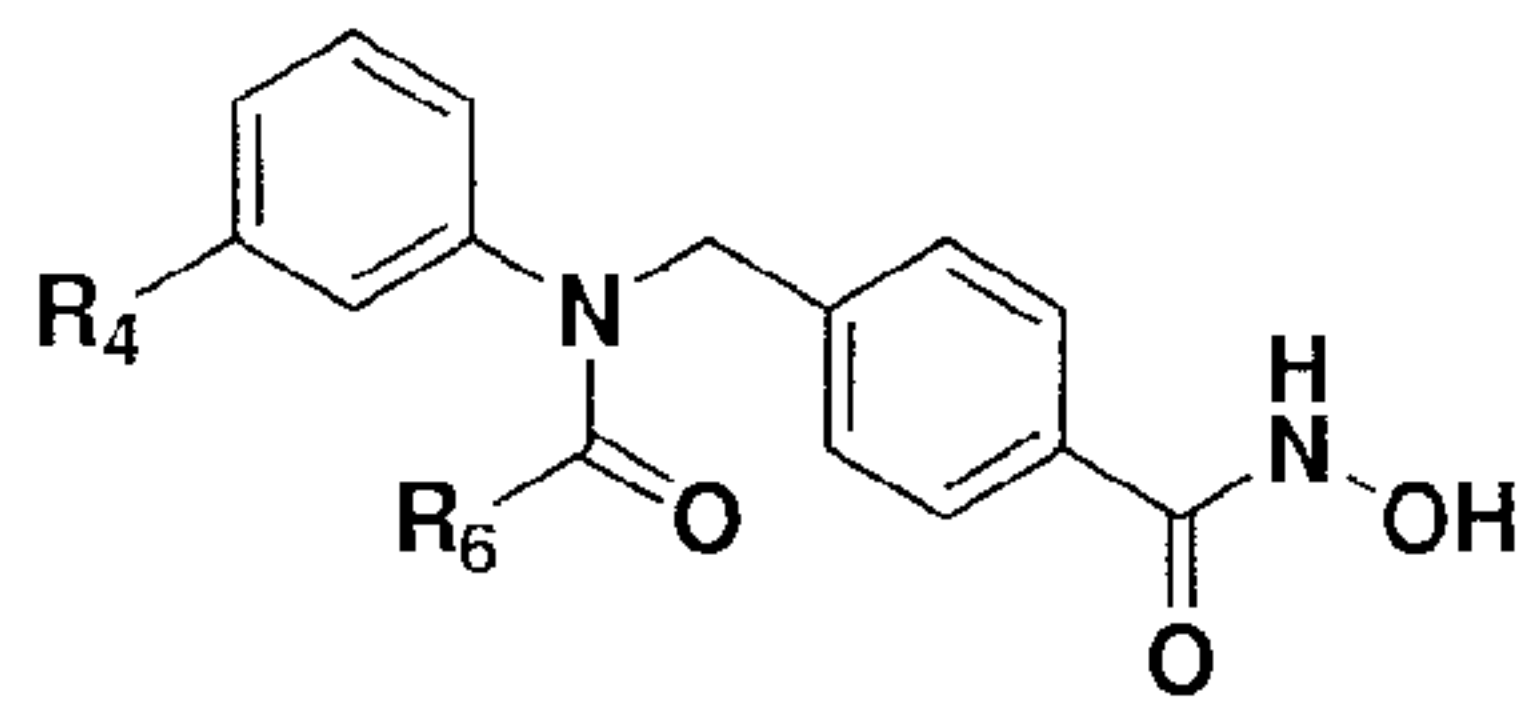


wherein R₄ is indole, pyridine, difluorophenyl, (dimethylamino)pyridine, pyrimidine, bis(trifluorophenyl)phenyl, 2,3-dihydrobenzo[b][1,4]dioxin, trimethoxyphenyl, dimethylphenyl, furan, 3,6-dihydro-2H-pyran, 1-methyl-1,2,3,6-tetrahydropyridine, 1-Boc-1,2,3,6-tetrahydropyridine, benzo[d][1,3]dioxole, or tetrahydro-2H-pyran.

Preferably, the compound represented by the above Formula I-2 may be Compound 261, 262, 263, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 418 or 483 described in the present invention.

The compound represented by the above Formula I may be a compound represented by the following Formula I-3:

[Formula I-3]

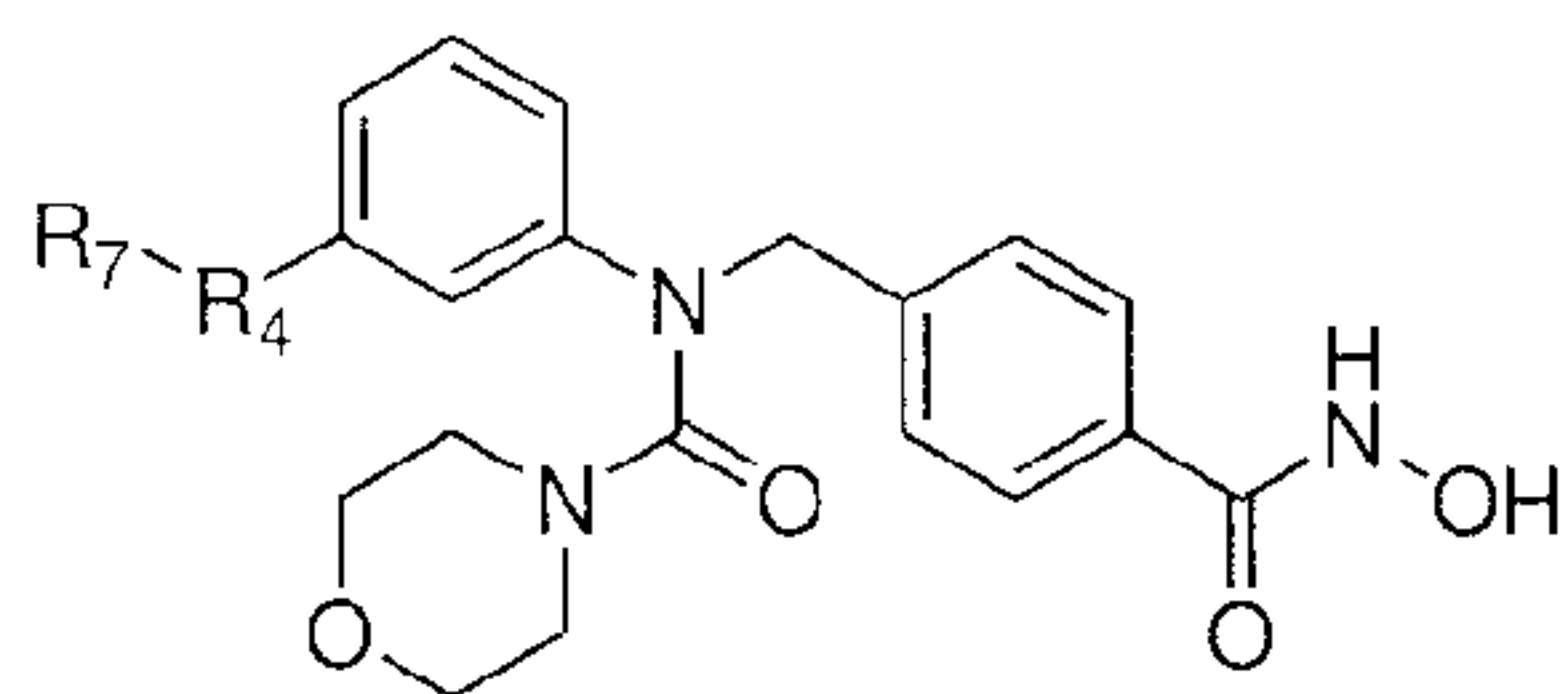


wherein R_4 is 1- C_{1-3} alkyl-1H-indazole and R_6 is morpholine, piperidine, or piperazine, wherein the piperazine is unsubstituted or substituted with $-C_{1-3}$ alkyl.

5 Preferably, the compound represented by the above Formula I-3 may be Compound 252, 253, 254 or 260 described in the present invention.

The compound represented by the above Formula I may be a
10 compound represented by the following Formula I-4:

[Formula I-4]

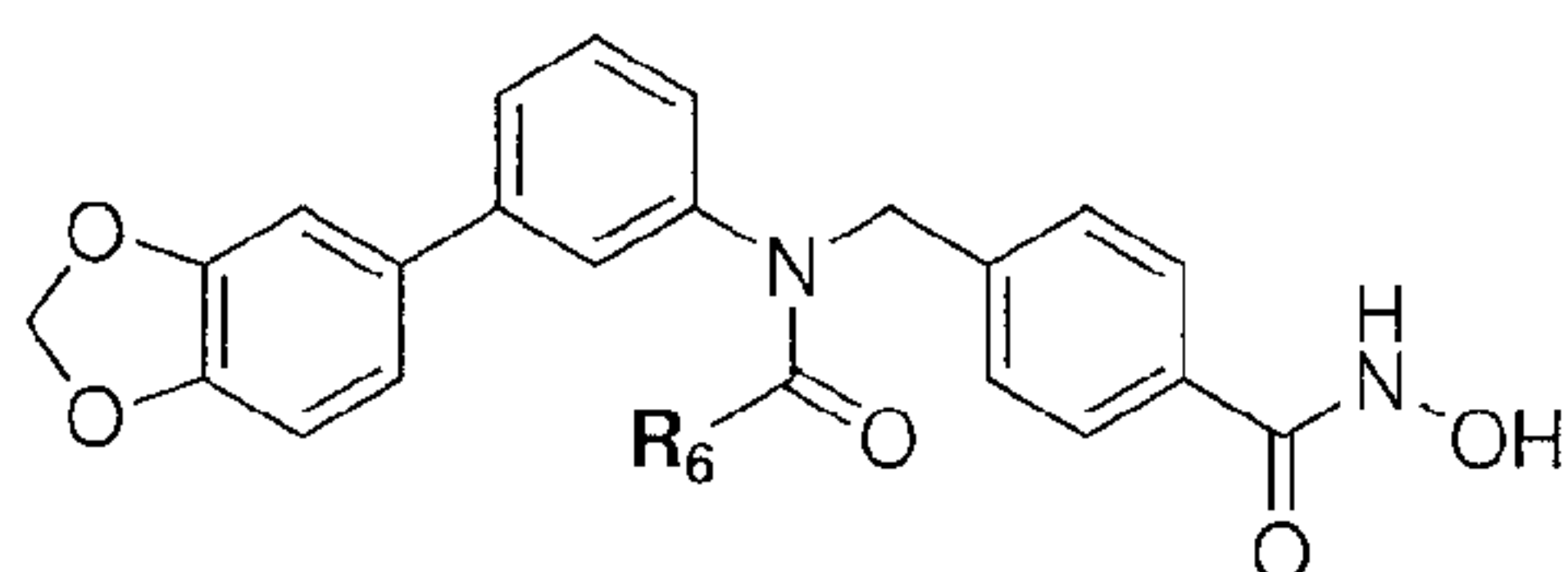


wherein R_4 is tetrahydropyridine or piperidine and R_7 is nothing, acetyl, methylsulfonyl, N-isopropylcarbamoyl, 2-hydroxy-2-methylpropyl, 2-fluoro-2-methylpropyl, t-butylcarboxylate.
15

Preferably, the compound represented by the above Formula I-4 may be Compound 419, 420, 489, 490, 491, 492, 493, 517 or 518 described in the present invention.

The compound represented by the above Formula I may be a compound represented by the following Formula I-5:

[Formula I-5]



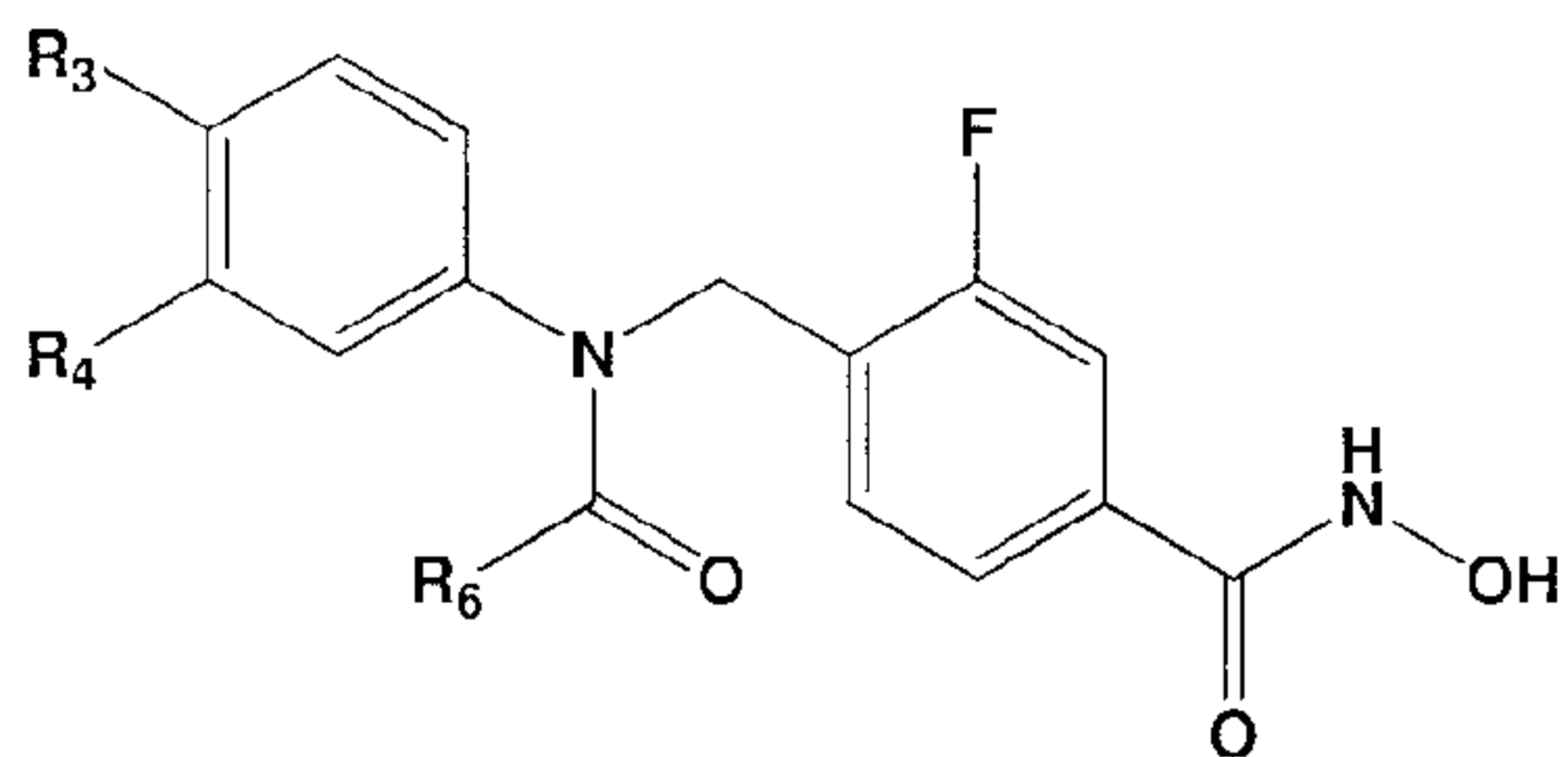
5

wherein R₆ is piperidine, piperidinol, dimethylmorpholine, phenylpiperidinol, methylpiperazine, 2-(piperazin-1-yl)ethanol, pyrrolidine, (S)-pyrrolidin-2-ylmethanol, cyclopropyl(piperazin-1-yl)methanol, or azetidine.

10 Preferably, the compound represented by the above Formula I-5 may be Compound 462, 463, 464, 465, 466, 467, 468, 469, 470 or 471 described in the present invention.

The compound represented by the above Formula I may be a compound represented by the following Formula I-6:

[Formula I-6]



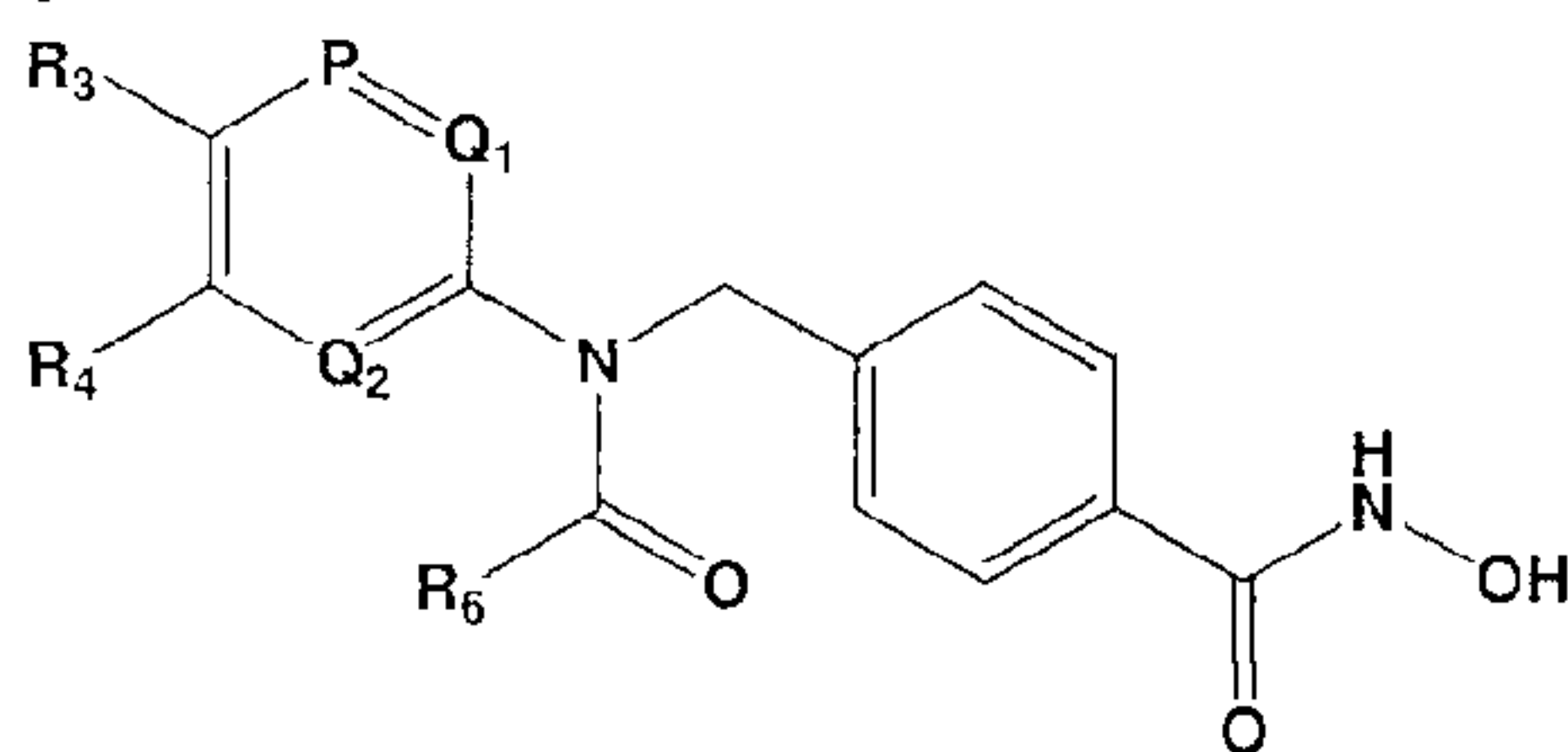
wherein R_3 and R_4 are each independently hydrogen, -F, -Cl, -Br, -I, -CF₃, benzo[d][1,3]dioxole or dihydro-2H-pyran, and R_6 is morpholine, hydroxypiperidine or difluoroazetidine.

Preferably, the compound represented by the above
 5 Formula I-6 may be Compound 487, 488, 511, 512, 513, 514, 532, 577 or 578 described in the present invention.

The compound represented by the above Formula I may be a compound represented by the following Formula I-7:

10

[Formula I-7]



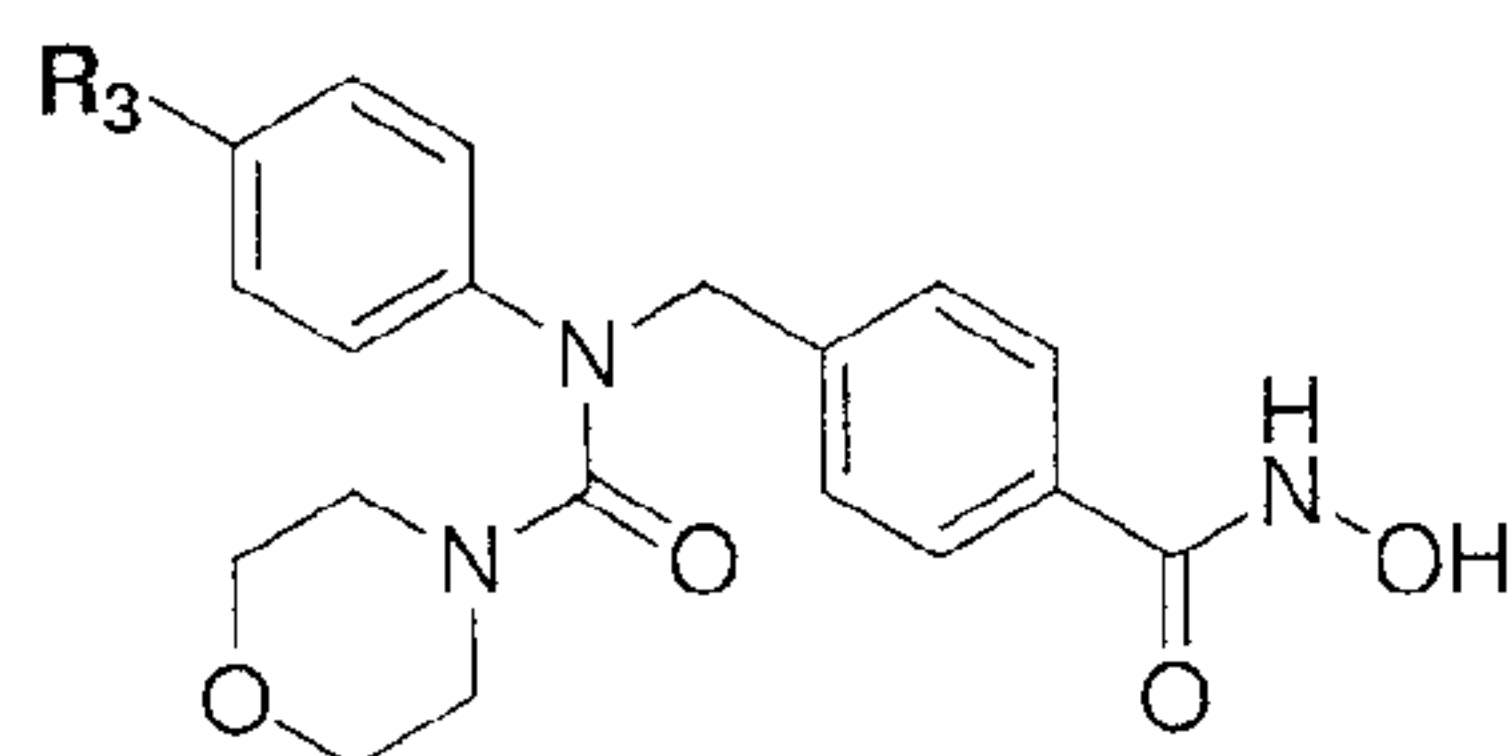
wherein P, Q₁ and Q₂ are each independently C or N, R_3 and R_4 are each independently hydrogen, -F, -Cl, -Br, -I, or -CF₃, and R_6 is piperidine, piperidine substituted with one or
 15 more C₁₋₃ alkyl, morpholine, morpholine substituted with one or more C₁₋₃ alkyl, phenyltetrahydropyridine, piperazine substituted with one or more C₁₋₃ alkyl, benzylpiperazine, phenylpiperidinol, (methoxyphenyl)piperazine, (fluorophenyl)piperazine, pyrrolidine, diazepane substituted
 20 with one or more C₁₋₃ alkyl, azetidine, (dimethylphenyl)piperazine, (1,4-diazepan-1-yl)ethanone,

cyclopropyl(piperazin-1-yl)methanone, or fluoropyrrolidine.

Preferably, the compound represented by the above
Formula I-7 may be Compound 280, 281, 309, 311, 312, 313, 341,
342, 343, 352, 353, 354, 355, 356, 357, 358, 376, 377, 379,
5 450, 451, 533, 778, 826, 827, 828 or 829 described in the
present invention.

The compound represented by the above Formula I may be a
compound represented by the following Formula I-8:

10 [Formula I-8]

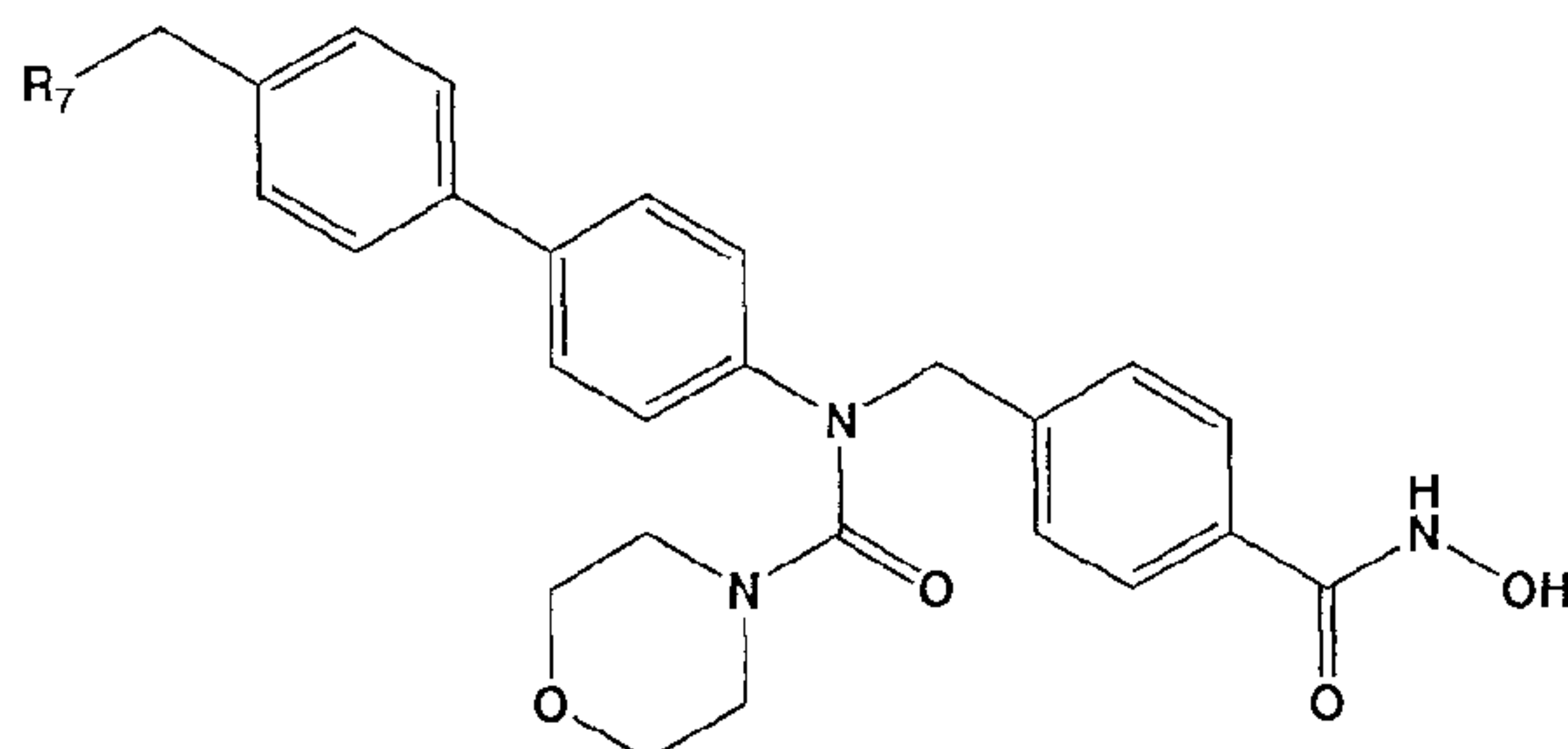


wherein R₃ is 1-methyl-1H-indazole, phenyl,
difluorophenyl, pyridine, pyrimidine, quinoline, biphenyl,
indole, trimethoxyphenyl, bis(trifluoromethyl)phenyl, -F, -Cl,
-Br, or -I.

15 Preferably, the compound represented by the above
Formula I-8 may be Compound 329, 330, 331, 332, 333, 334, 335,
336, 337, 338, 339, 340 or 372 described in the present
invention.

20 The compound represented by the above Formula I may be a
compound represented by the following Formula I-9:

[Formula I-9]

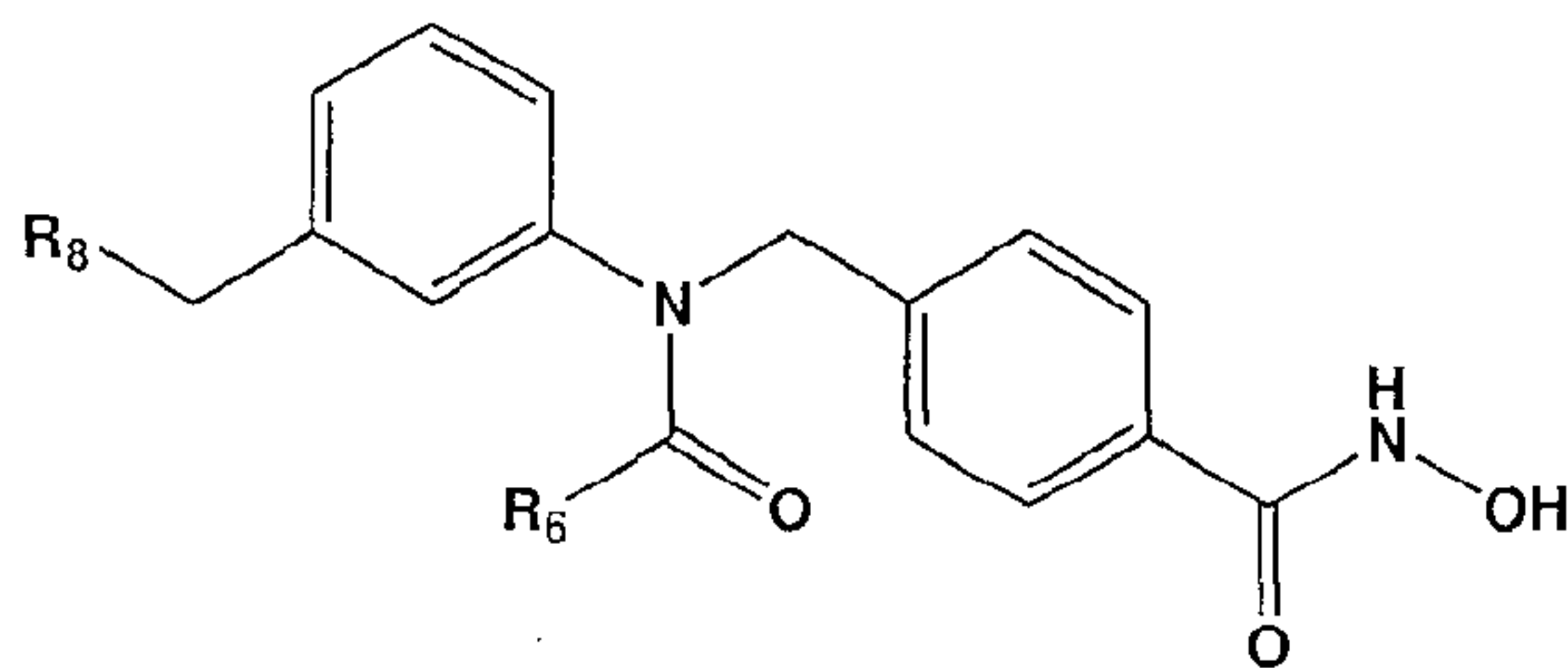


wherein R₇ is morpholine, piperazine substituted with
 one or more C₁₋₃ alkyl, (S)-pyrrolidin-2-ylmethanol, or
 5 (methylamino)ethanol.

Preferably, the compound represented by the above
 Formula I-9 may be Compound 380, 381, 382 or 383 described in
 the present invention.

10 The compound represented by the above Formula I may be a
 compound represented by the following Formula I-10:

[Formula I-10]

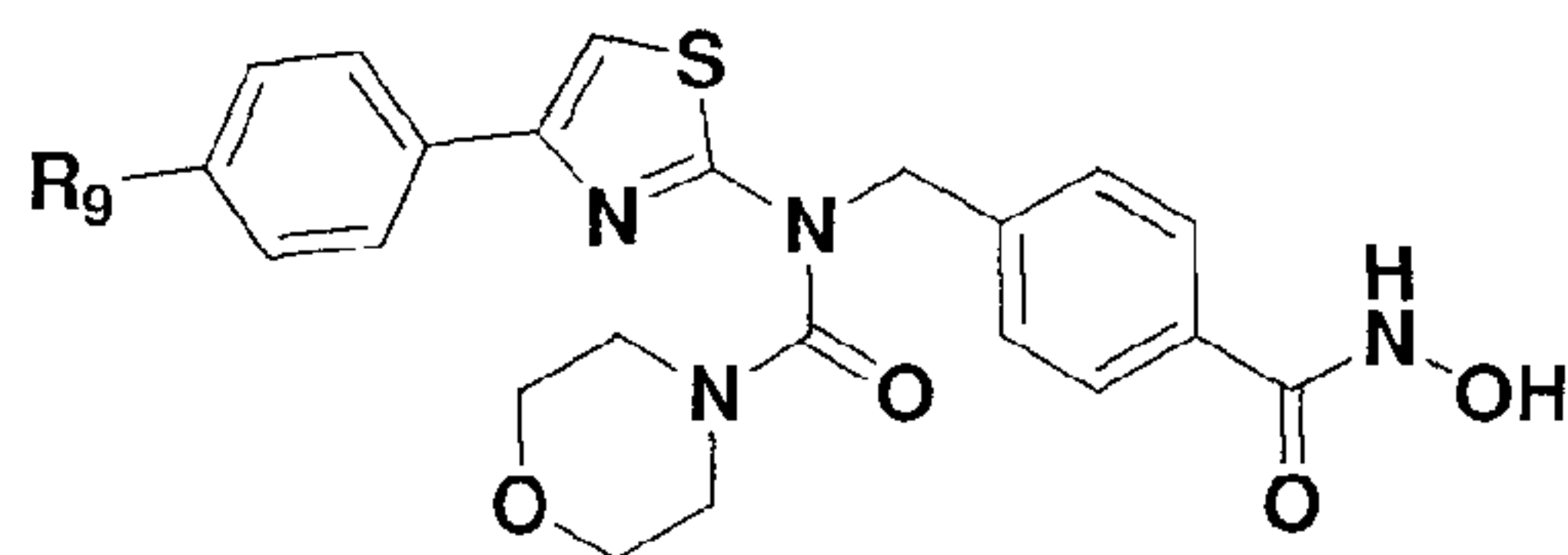


wherein R₈ is hydroxy, -F, -Cl, -Br, or -I and R₉ is
 15 morpholine, ethylpiperazine, or piperazinyl-2-fluoro-2-
 methylpropyl.

Preferably, the compound represented by the above
Formula I-10 may be Compound 499, 500, 765 or 766 described in
the present invention.

5 The compound represented by the above Formula I may be a
compound represented by the following Formula I-11:

[Formula I-11]

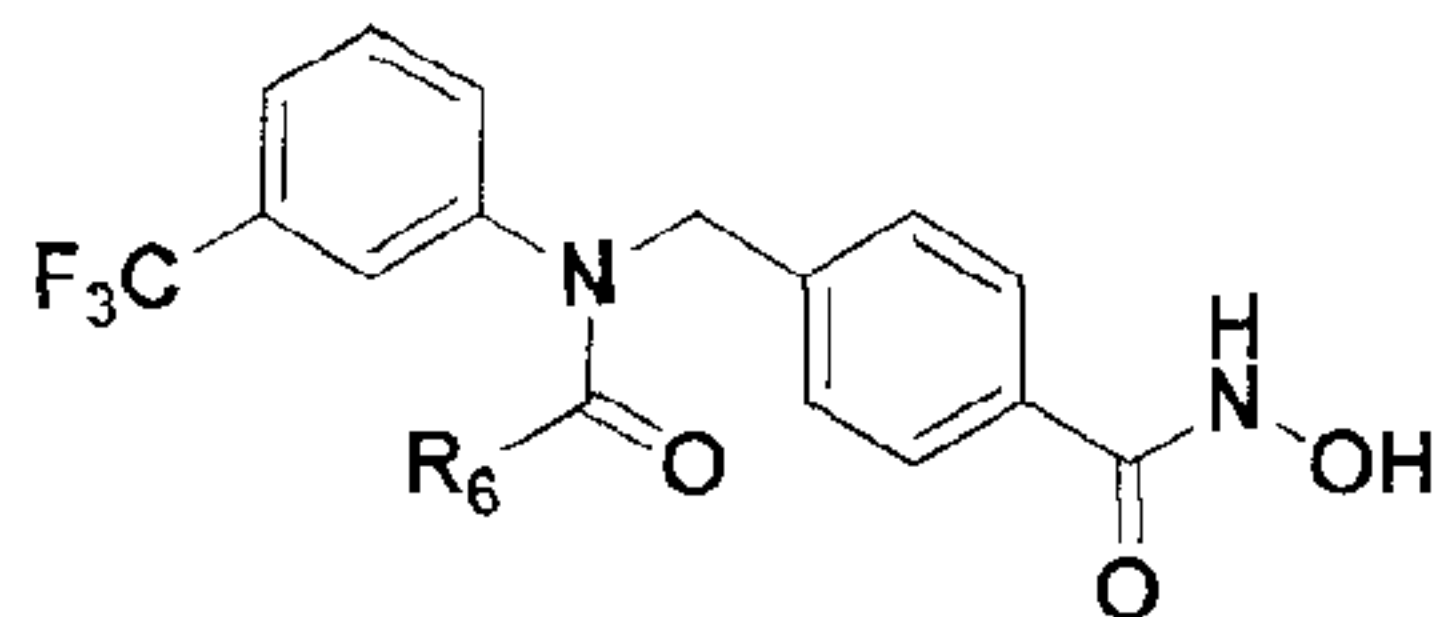


wherein R₉ is hydrogen, hydroxy, -F, -Cl, -Br, or -I.

10 Preferably, the compound represented by the above
Formula I-11 may be Compound 370 or 371 described in the
present invention.

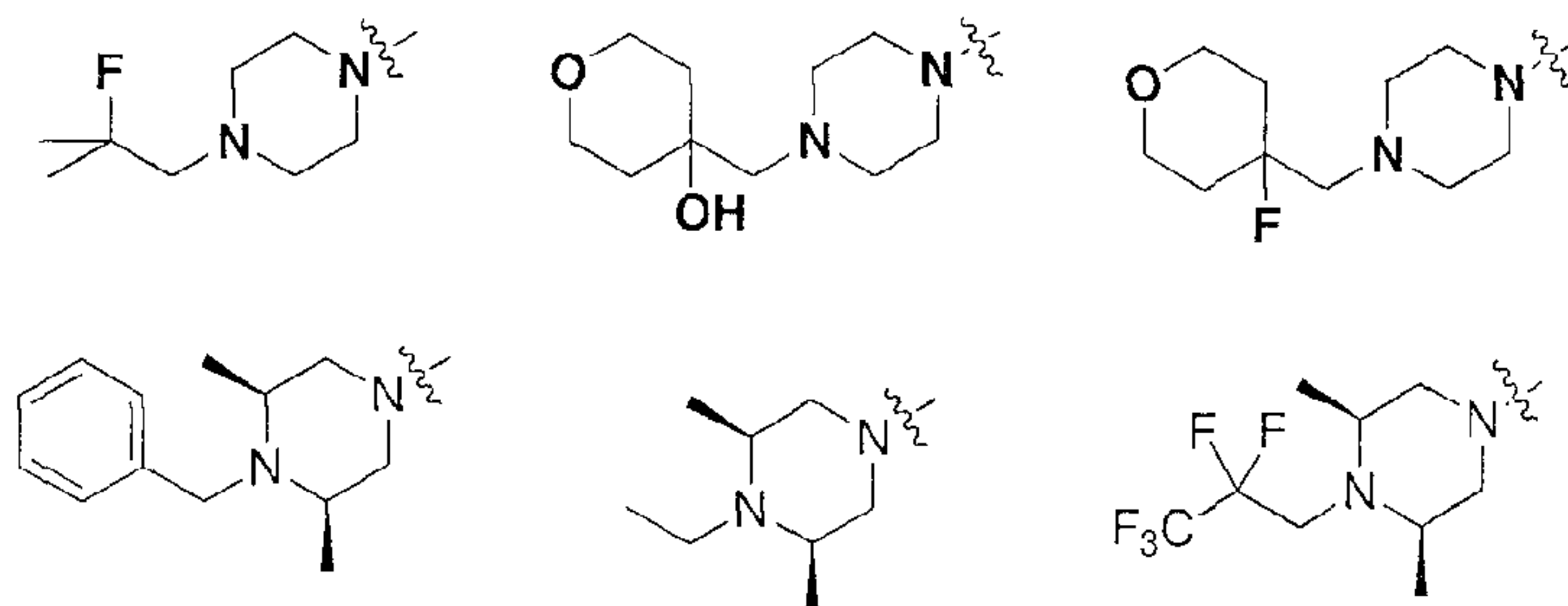
The compound represented by the above Formula I may be a
15 compound represented by the following Formula I-12:

[Formula I-12]



20

wherein R₆ may be selected from the following group:



Preferably, the compound represented by the above Formula I-12 may be Compound 531, 651, 716, 797, 802 or 803 described in the present invention.

5

The compounds represented by Formulas I and I-1 to I12 are as follows:

252	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-methyl-1H-indazol-5-yl)phenyl)morpholine-4-carboxamide
253	N-(4-(hydroxycarbamoyl)benzyl)-4-methyl-N-(3-(1-methyl-1H-indazol-5-yl)phenyl)piperazine-1-carboxamide
254	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-methyl-1H-indazol-6-yl)phenyl)morpholine-4-carboxamide
255	N-(3-bromophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
256	N-(3-bromophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide
260	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-methyl-1H-indazol-5-yl)phenyl)piperidine-1-carboxamide
261	N-(3-(1H-indol-6-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
262	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(pyridin-3-yl)phenyl)morpholine-4-carboxamide
263	N-(3-(1H-indol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
279	N-(4-(hydroxycarbamoyl)benzyl)-N-phenylmorpholine-4-

	carboxamide
280	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)morpholine-4-carboxamide
281	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-3-yl)morpholine-4-carboxamide
309	4-benzyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyrimidin-2-yl)piperazine-1-carboxamide
311	4-hydroxy-N-(4-(hydroxycarbamoyl)benzyl)-4-phenyl-N-(pyrimidin-2-yl)piperidine-1-carboxamide
312	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyrimidin-2-yl)morpholine-4-carboxamide
313	N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(pyrimidin-2-yl)morpholine-4-carboxamide
329	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(1-methyl-1H-indazol-6-yl)phenyl)morpholine-4-carboxamide
330	N-(biphenyl-4-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
331	N-(3',5'-difluorobiphenyl-4-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
332	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(pyridin-3-yl)phenyl)morpholine-4-carboxamide
333	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(pyrimidin-5-yl)phenyl)morpholine-4-carboxamide
334	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(quinolin-7-yl)phenyl)morpholine-4-carboxamide
335	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(biphenyl-3-yl)phenyl)morpholine-4-carboxamide
336	N-(4-(1H-indol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
337	N-(4-(1H-indol-6-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
338	N-(4-(hydroxycarbamoyl)benzyl)-N-(3',4',5'-trimethoxybiphenyl-4-yl)morpholine-4-carboxamide
339	N-(3',5'-bis(trifluoromethyl)biphenyl-4-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
340	N-(4-(1H-indol-4-yl)phenyl)-N-(4-

	(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
341	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperidine-1-carboxamide
342	N-(4-(hydroxycarbamoyl)benzyl)-4-methyl-N-(pyridin-2-yl)piperidine-1-carboxamide
343	N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(pyridin-2-yl)morpholine-4-carboxamide
352	N-(4-(hydroxycarbamoyl)benzyl)-4-phenyl-N-(pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxamide
353	N-(4-(hydroxycarbamoyl)benzyl)-4-methyl-N-(pyridin-2-yl)piperazine-1-carboxamide
354	4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide
355	4-benzyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide
356	N-(4-(hydroxycarbamoyl)benzyl)-4-(2-methoxyphenyl)-N-(pyridin-2-yl)piperazine-1-carboxamide
357	4-(4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide
358	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)pyrrolidine-1-carboxamide
370	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-phenylthiazol-2-yl)morpholine-4-carboxamide
371	N-(4-(4-chlorophenyl)thiazol-2-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
372	N-(4-bromophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
374	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)morpholine-4-carboxamide
376	N-(4-(hydroxycarbamoyl)benzyl)-4-methyl-N-(pyridin-2-yl)-1,4-diazepane-1-carboxamide
377	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)azetidine-1-carboxamide
379	4-(3,4-dimethylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide
380	N-(4-(hydroxycarbamoyl)benzyl)-N-(4'-

	(morpholinomethyl)biphenyl-4-yl)morpholine-4-carboxamide
381	N-(4-(hydroxycarbamoyl)benzyl)-N-(4'-((4-methylpiperazin-1-yl)methyl)biphenyl-4-yl)morpholine-4-carboxamide
382	(S)-N-(4-(hydroxycarbamoyl)benzyl)-N-(4'-((2-(hydroxymethyl)pyrrolidin-1-yl)methyl)biphenyl-4-yl)morpholine-4-carboxamide
383	N-(4-(hydroxycarbamoyl)benzyl)-N-(4'-((2-hydroxyethyl)(methyl)amino)ethyl)biphenyl-4-yl)morpholine-4-carboxamide
385	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)morpholine-4-carboxamide
386	N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(3-(trifluoromethyl)phenyl)morpholine-4-carboxamide
389	N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperidine-1-carboxamide
390	N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperidine-1-carboxamide
391	N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
392	N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylmorpholine-4-carboxamide
393	N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide
394	N-(4-chloro-3-(trifluoromethyl)phenyl)-4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
395	N-(3',5'-difluorobiphenyl-3-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
396	N-(3-(6-(dimethylamino)pyridin-3-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
397	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(pyrimidin-5-yl)phenyl)morpholine-4-carboxamide
398	N-(3',5'-bis(trifluoroethyl)biphenyl-3-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
399	N-(3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
400	N-(4-(hydroxycarbamoyl)benzyl)-N-(3',4',5'-

	trimethoxybiphenyl-3-yl)morpholine-4-carboxamide
401	N-(2',6'-dimethylbiphenyl-3-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
402	N-(3-(furan-3-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
403	N-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
404	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-carboxamide
405	tert-butyl-4-(3-(N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamido)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate
413	N-(2,4-difluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
414	N-(2,4-difluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperidine-1-carboxamide
415	N-(2,4-difluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylmorpholine-4-carboxamide
416	N-(2,4-difluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide
418	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
419	N-(3-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
420	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-carboxamide
438	N-(2-fluoro-4-methylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperidine-1-carboxamide
439	N-(2-fluoro-4-methylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
440	N-(2-fluoro-4-methylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylmorpholine-4-carboxamide
441	N-(2-fluoro-4-methylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide
450	4-acetyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)-1,4-diazepane-1-carboxamide

451	4-(cyclopropanecarbonyl)-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide
453	4-ethyl-N-(2-fluoro-4-methylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
454	N-(2-fluoro-4-methylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-(2-methoxyphenyl)piperazine-1-carboxamide
455	N-(2-fluoro-4-methylphenyl)-4-(4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
456	N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperidine-1-carboxamide
457	N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperidine-1-carboxamide
458	N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
459	N-(4-(hydroxycarbamoyl)benzyl)-4-methyl-N-(3-(trifluoromethyl)phenyl)piperidine-1-carboxamide
460	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperidine-1-carboxamide
461	4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
462	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperidine-1-carboxamide
463	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-4-hydroxy-N-(4-(hydroxycarbamoyl)benzyl)piperidine-1-carboxamide
464	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylmorpholine-4-carboxamide
465	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-4-hydroxy-N-(4-(hydroxycarbamoyl)benzyl)-4-phenylpiperidine-1-carboxamide
466	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide
467	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-(2-hydroxyethyl)piperazine-1-carboxamide
468	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)pyrrolidine-1-carboxamide
469	(S)-N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-

	(hydroxycarbamoyl)benzyl)-2 (hydroxymethyl)pyrrolidine-1-carboxamide
470	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-4-(cyclopropanecarbonyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
471	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)azetidine-1-carboxamide
477	N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylmorpholine-4-carboxamide
478	N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide
479	N-(3-chloro-4-fluorophenyl)-4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
480	4-benzyl-N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
481	N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-(2-methoxyphenyl)piperazine-1-carboxamide
482	N-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
483	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(tetrahydro-2H-pyran-4-yl)phenyl)morpholine-4-carboxamide
484	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-methoxyphenyl)morpholine-4-carboxamide
485	3,3-difluoro-N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)azetidine-1-carboxamide
486	4-hydroxy-N-(4-(hydroxycarbamoyl)benzyl)-4-phenyl-N-(4-(trifluoromethyl)phenyl)piperidine-1-carboxamide
487	N-(3-bromophenyl)-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
488	N-(3-bromophenyl)-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)-4-hydroxypiperidine-1-carboxamide
489	tert-butyl-4-(3-(N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamido)phenyl)piperidine-1-carboxylate
490	N-(3-(1-acetylpiperidin-4-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
491	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-(methylsulfonyl)piperidin-4-yl)phenyl)morpholine-4-

	carboxamide
492	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-(isopropylcarbamoyl)piperidin-4-yl)phenyl)morpholine-4-carboxamide
493	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(piperidin-4-yl)phenyl)morpholine-4-carboxamide hydrochloride
494	4-acetyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
495	(R)-3-fluoro-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide
496	(S)-3-fluoro-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide
497	(R)-N-(4-(hydroxycarbamoyl)benzyl)-2-(hydroxymethyl)-N-(3-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide
498	(S)-N-(4-(hydroxycarbamoyl)benzyl)-2-(trifluoromethyl)-N-(3-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide
499	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(hydroxymethyl)phenyl)morpholine-4-carboxamide
500	N-(3-(fluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
511	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
512	N-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
513	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)-4-hydroxypiperidine-1-carboxamide
514	N-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)-4-hydroxypiperidine-1-carboxamide
517	N-(3-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
518	N-(3-(1-(2-fluoro-2-methylpropyl)piperidin-4-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
520	(R)-3-fluoro-N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide
521	(S)-3-fluoro-N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide

522	(R)-N-(4-(hydroxycarbamoyl)benzyl)-2-(hydroxymethyl)-N-(4-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide
529	4-acetyl-N-(3-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
530	N-(3-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
531	4-(2-fluoro-2-methylpropyl)-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
532	N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)morpholine-4-carboxamide
533	N-(5-chloropyridin-2-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
543	N-(4-(hydroxycarbamoyl)benzyl)-4-(2-morpholinoethyl)-N-(4-(trifluoromethyl)phenyl)piperazine-1-carboxamide
544	N-(4-(hydroxycarbamoyl)benzyl)-4-(pyridin-4-yl)-N-(4-(trifluoromethyl)phenyl)piperazine-1-carboxamide
545	N-(4-(hydroxycarbamoyl)benzyl)-4-(2-morpholino-2-oxoethyl)-N-(4-(trifluoromethyl)phenyl)piperazine-1-carboxamide
577	N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)morpholine-4-carboxamide
578	3,3-difluoro-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)azetidine-1-carboxamide
580	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)-1,4-oxazepane-4-carboxamide
651	N-(4-(hydroxycarbamoyl)benzyl)-4-((4-hydroxytetrahydro-2H-pyran-4-yl)methyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
683	4-benzyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
684	N-(4-(hydroxycarbamoyl)benzyl)-4-(3-methoxyphenyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
716	4-((4-fluorotetrahydro-2H-pyran-4-yl)methyl)-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
717	N-(4-(hydroxycarbamoyl)benzyl)-4-phenyl-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
718	4-benzhydryl-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-

	(trifluoromethyl)phenyl)piperazine-1-carboxamide
765	4-ethyl-N-(3-(fluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
766	4-(2-fluoro-2-methylpropyl)-N-(3-(fluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
771	N-(4-(hydroxycarbamoyl)benzyl)-N-(2-(trifluoromethoxy)phenyl)morpholine-4-carboxamide
772	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethoxy)phenyl)morpholine-4-carboxamide
773	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethoxy)phenyl)morpholine-4-carboxamide
774	N-(4-(hydroxycarbamoyl)benzyl)-N-(2-methoxy-5-(trifluoromethyl)phenyl)morpholine-4-carboxamide
776	N-(2-chloro-5-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
778	N-(4-(hydroxycarbamoyl)benzyl)-N-(6-(trifluoromethyl)pyridin-2-yl)morpholine-4-carboxamide
791	N-(2,3 difluorophenyl) N (4 (hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
797	(3S,5R)-4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
800	N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(3-(trifluoromethoxy)phenyl)morpholine-4-carboxamide
801	N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(2-(trifluoromethoxy)phenyl)morpholine-4-carboxamide
802	(3S,5R)-4-benzyl-N-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
803	(3S,5R)-N-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1 carboxamide
826	4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(6-(trifluoromethyl)pyridin-2-yl)piperazine-1-carboxamide
827	N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(6-(trifluoromethyl)pyridin-2-yl)morpholine-4-carboxamide
828	N-(4-(hydroxycarbamoyl)benzyl)-N-(6-(trifluoromethyl)pyridin-2-yl)piperidine-1-carboxamide

329	(S)-3-flucro-N-(4-(hydroxycarbamoyl)benzyl)-N-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidine-1-carboxamide
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In the present invention, the pharmaceutically acceptable salt refers to salts commonly used in the pharmaceutical industry, such as inorganic ion salts formed with calcium, potassium, sodium, magnesium, etc., inorganic acid salts formed with hydrochloric acid, nitric acid, phosphoric acid, bromic acid, iodic acid, perchloric acid, tartaric acid, sulfuric acid, etc., organic acid salts formed with acetic acid, trifluoroacetic acid, citric acid, maleic acid, succinic acid, oxalic acid, benzoic acid, tartaric acid, fumaric acid, mandelic acid, propionic acid, citric acid, lactic acid, glycolic acid, gluconic acid, galacturonic acid, glutamic acid, glutaric acid, glucuronic acid, aspartic acid, ascorbic acid, carbonic acid, vanillic acid, hydroiodic acid, etc, sulfonic acid salts formed with methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, etc., amino acid salts formed with glycine, arginine, lysine, etc., and amine salts formed with trimethylamine, triethylamine, ammonia, pyridine, picoline, but the types of salts used in the present invention are not limited to the above-mentioned salts.

In the present invention, a preferred salt is a hydrochloric acid salt, and preferred examples of this

compound include Compounds 461 and 493 described in the present specification.

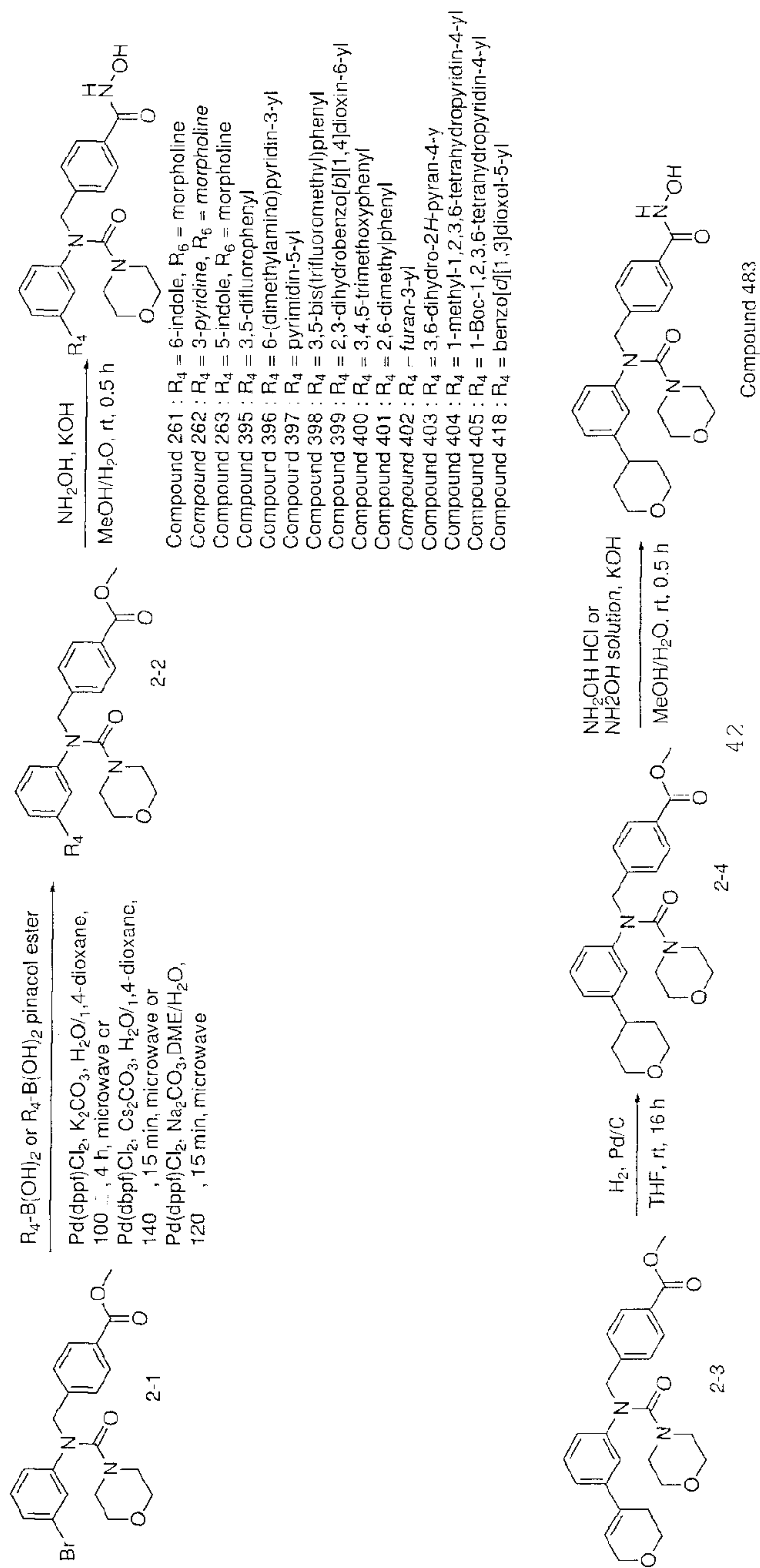
A specific preparation method of a novel compound of
5 Formula I, an optical isomer thereof, or a pharmaceutically acceptable salt thereof is shown in the following reaction schemes 1 to 12.

[Reaction Scheme

In reaction scheme 1, the compound of Formula 1-2 was synthesized by the reductive amination of the compound of Formula 1-1 with methyl 4-formylbenzoate at room temperature for 12 to 24 hours or with methyl 4-(bromomethyl)benzoate at room temperature for 16 hours, and the compound of Formula 1-3 was synthesized by the reaction of the compound of Formula 1-2 with 4-nitrophenyl carbonochloridate at room temperature for 12 to 24 hours.

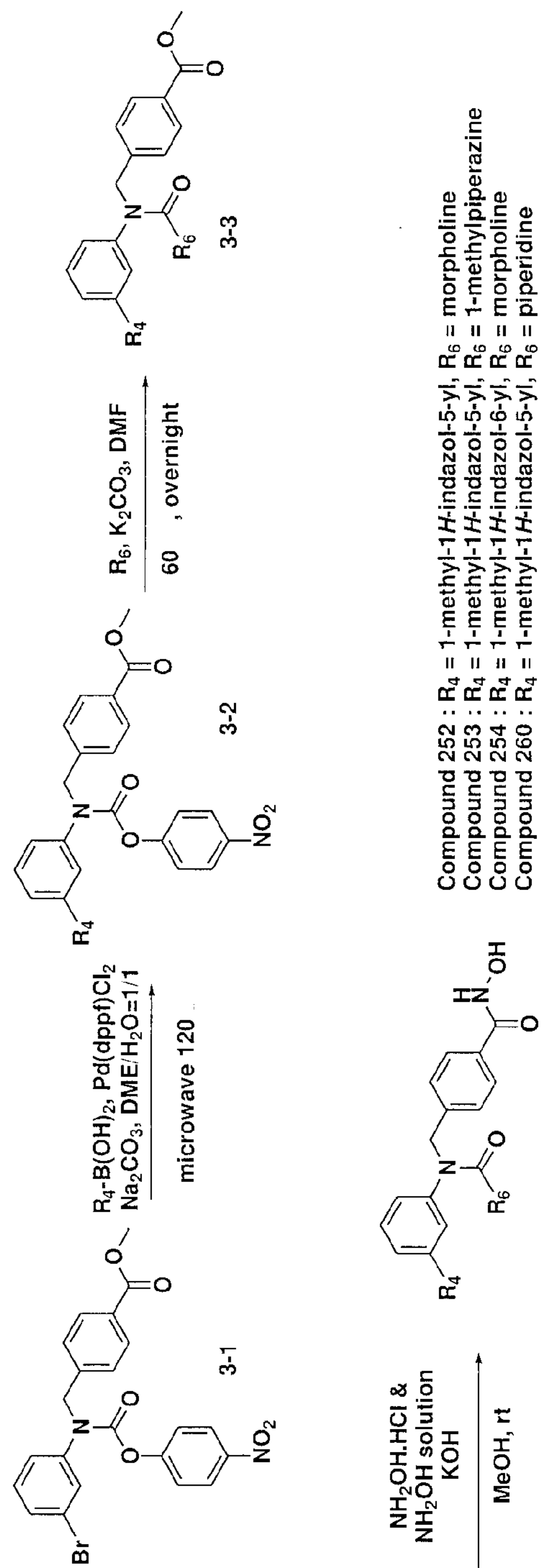
10 Then, the compound of Formula 1-4 was synthesized by the reaction of the compound of Formula 1-3 with amine derivative (R_6) in the presence of dimethylformamide solvent at room temperature or at 60 °C for 1 to 2 days. Finally, the target compound 255, 256, 279, 374, 385, 386, 389, 390, 391, 392,
15 393, 394, 413, 414, 415, 416, 438, 439, 440, 441, 453, 454, 455, 456, 457, 458, 459, 460, 461, 477, 478, 479, 480, 481, 482, 484, 485, 486, 494, 495, 496, 497, 498, 520, 521, 522, 529, 530, 543, 544, 545, 580, 683, 684, 717, 718, 771, 772, 773, 774, 776, 791, 800 or 801 was synthesized by the
20 reaction of the compound of Formula 1-4 with potassium hydroxide (KOH), methanol and hydroxylamine hydrochloride ($\text{HCNH}_2 \text{HCl}$) at room temperature or with hydroxylamine (NH_2OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added dropwise, at room temperature.

[Reaction Scheme 2]



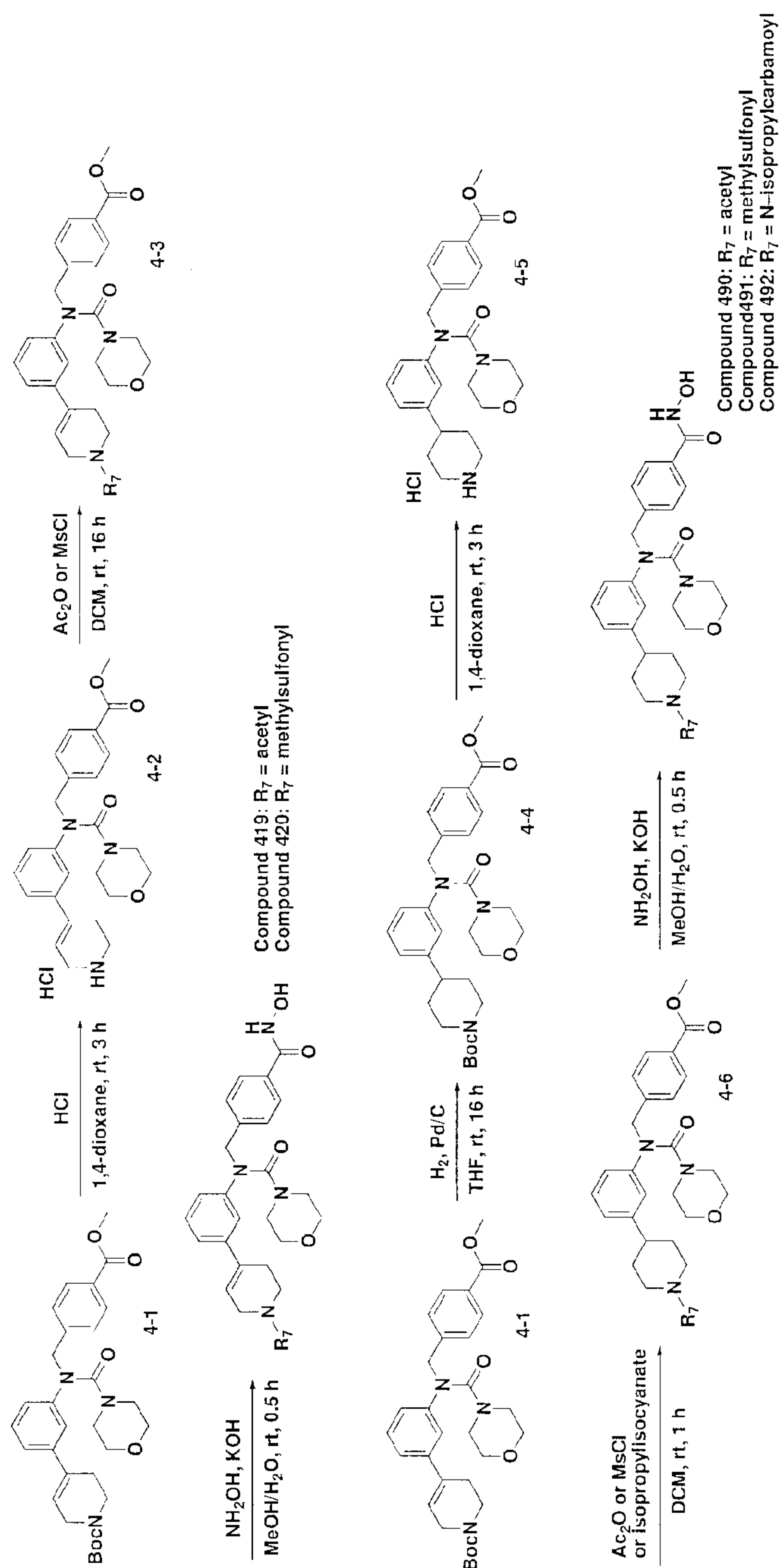
In reaction scheme 2, the compound of Formula 2-2 was synthesized by the Suzuki reaction of the compound of Formula 2-1 with boronic acid, and then the compound of Formula 2-4 was synthesized by the reduction of the compound of Formula 2-3 with hydrogen and palladium. Finally, the target
5 compound 261, 262, 263, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 418 or 483 was synthesized by dissolving the compound of Formula 2-2 or 2-4 in methanol, followed by the reaction with hydroxylamine hydrochloride ($\text{HONH}_2 \text{HCl}$) and
10 potassium hydroxide (KOH) at room temperature or with hydroxylamine (NH_2OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added dropwise, at room temperature.

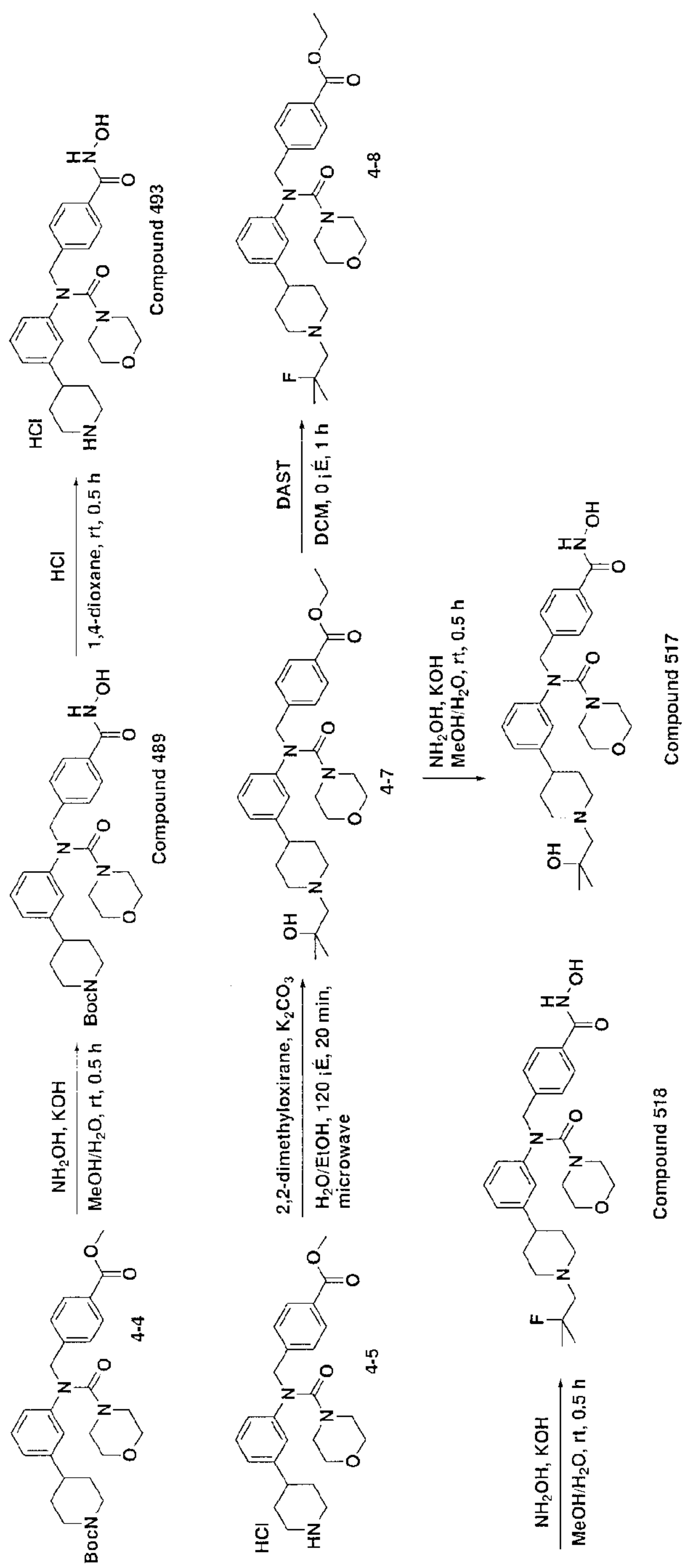
[Reaction Scheme 3]



In reaction scheme 3, the compound of Formula 3-2 was synthesized by the Suzuki reaction of the compound of Formula 3-1 with boronic acid, and then the compound of Formula 3-3 was synthesized by the reaction of the compound of Formula 3-2 with amine derivative (R_5) at 50 to 60 °C. Finally, the target compound 252, 253, 254 or 260 was synthesized by dissolving the compound of Formula 3-3 in methanol, followed by the reaction with hydroxylamine hydrochloride, potassium hydroxide (KOH), and hydroxylamine aqueous solution (50 wt%), which were added dropwise, at room temperature.

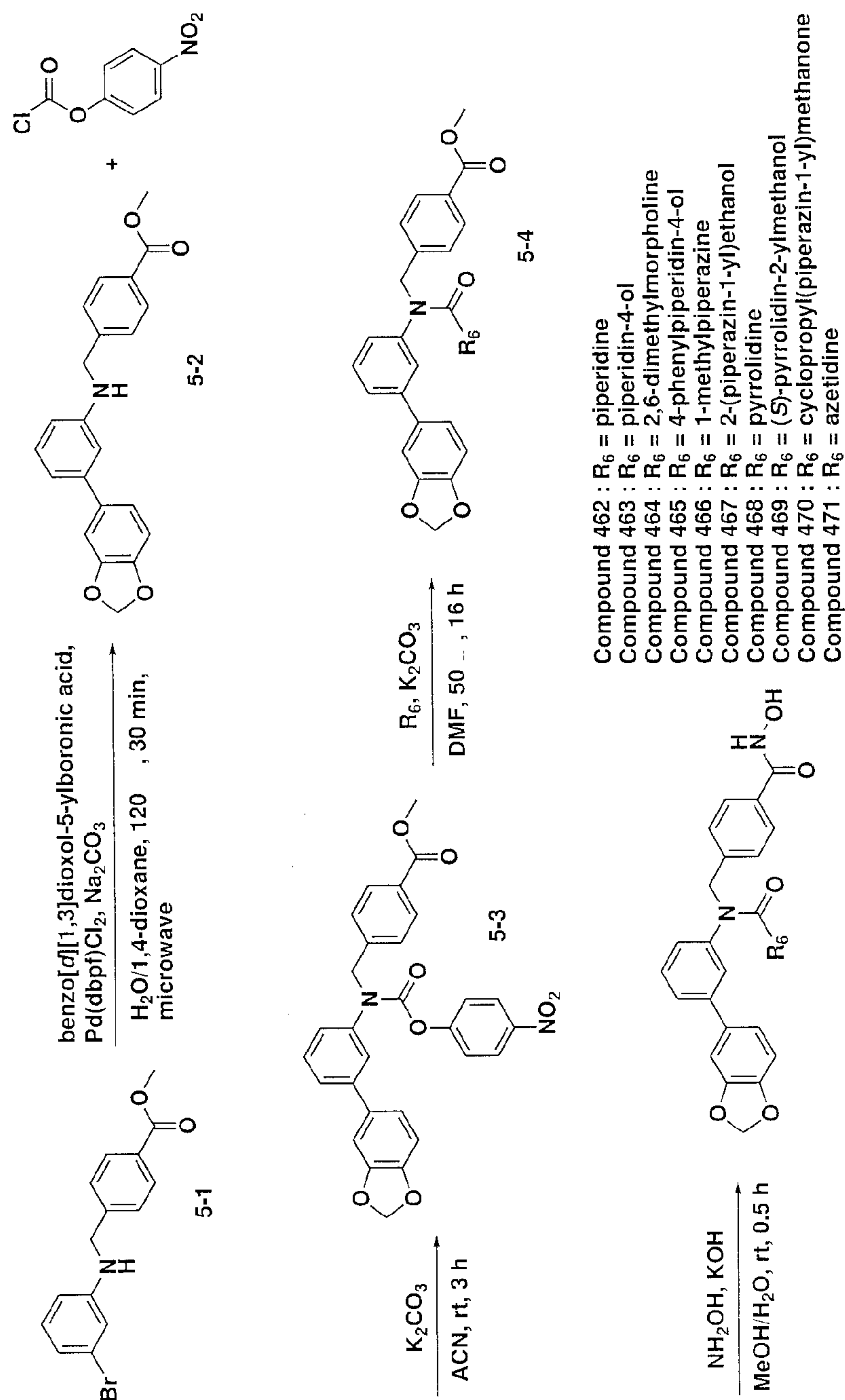
[Reaction Scheme 4]



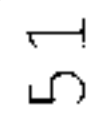


In reaction scheme 4, the compound of Formula 4-2 was synthesized by the reaction of the compound of Formula 4-1 with hydrogen chloride, and then the compound of Formula 4-3 was synthesized using acetic acid anhydride or methane sulfonyl chloride. Next, the compound of Formula 4-4 was synthesized by the reduction of the compound of Formula 4-1 with hydrogen and palladium, and the compound of Formula 4-6 was synthesized by the same method. Subsequently, the compound of Formula 4-7 was synthesized by the reaction of the compound of Formula 4-5 with 2,2-dimethyloxane in a microwave reactor at 120 °C, and then the compound of Formula 4-8 was synthesized using diethylaminosulfur trifluoride (DAST). Finally, the target compound 419, 420, 489, 490, 491, 492, 493, 517 or 518 was synthesized by dissolving compound formula 4-3, 4-6, 4-4, 4-7 or 4-8 in methanol, followed by the reaction with hydroxylamine (NH₂OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added dropwise, at room temperature.

[Reaction Scheme 5]

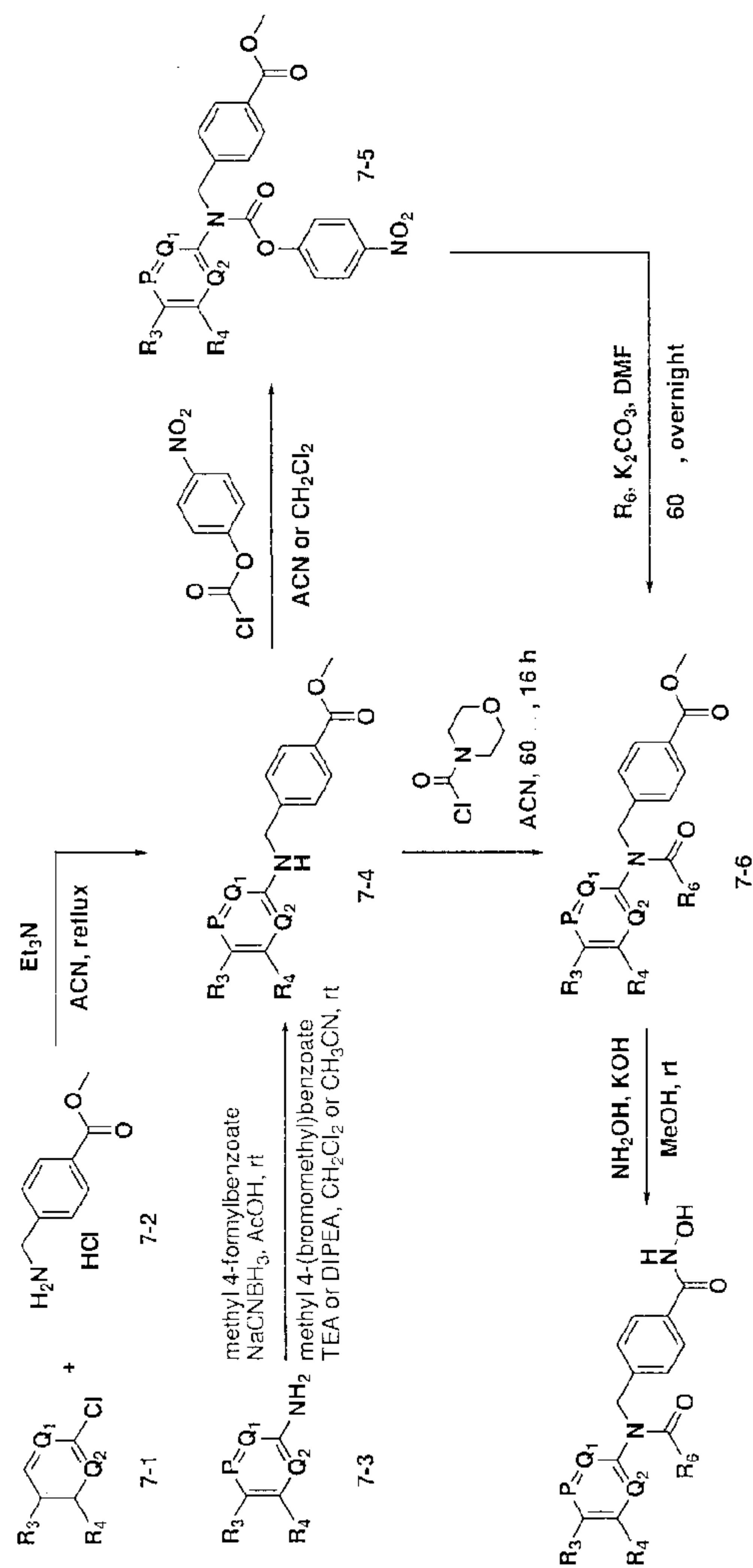


In reaction scheme 5, the compound of Formula 5-2 was synthesized by the Suzuki reaction of the compound of Formula 5-1 with boronic acid, and then the compound of Formula 5-3 was synthesized by the reaction of the compound of Formula 5-2 with 4-nitrophenyl chloroformate at room temperature. Next, the compound of Formula 5-4 was synthesized by the reaction of the compound of Formula 5-3 with amine derivative (R_6) at 50 °C. Finally, the target compound 462, 463, 464, 465, 466, 467, 468, 469, 470 or 471 was synthesized by dissolving the compound of Formula 5-4 in methanol, followed by the reaction with hydroxylamine (NH_2OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added dropwise, at room temperature.



In reaction scheme 6, the compound of Formula 6-2 was synthesized by the substitution of the compound of Formula 1-1 with the compound of Formula 6-1, and then the compound of Formula 6-3 was synthesized by the hydrolysis of the compound of Formula 6-2 with lithium hydroxide (LiOH). Next, the compound of Formula 6-4 was synthesized by the reaction of the compound of Formula 6-3 with methanol, 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole hydrate (HOBt), and then the compound of Formula 6-5 was synthesized by the reaction of the compound of Formula 6-4 with 4-nitrophenyl chloroformate at room temperature. Subsequently, the compound of Formula 6-6 was synthesized by the reaction of the compound of Formula 6-5 with amine derivative (R_6) at 50 °C, and then the compound of Formula 6-7 was synthesized by the Suzuki reaction of the compound of Formula 6-6 with boronic acid, if necessary. Finally, the target compound 487, 488, 511, 512, 513, 514, 532, 577 or 578 was synthesized by dissolving the compound of Formula 6-6 or 6-7 in methanol, followed by the reaction with hydroxylamine (NH_2OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added dropwise, at room temperature.

[Reaction Reaction scheme 7:



Q₁ = C, P = C, Q₂ = N, R_{3,4} = H

Compound 341 : R₆ = piperidine

Compound 342 : R₆ = 4-methylpiperidine

Compound 343 : R₆ = 2,6-dimethylmorpholine

Compound 352 : R₆ = 4-phenyl-1,2,3,6-tetrahydropyridine

Compound 353 : R₆ = 1-methylpiperazine

Compound 354 : R₆ = 1-ethylpiperazine

Compound 355 : R₆ = 1-benzylpiperazine

Q₁ = N, P = C, Q₂ = N, R_{3,4} = H

Compound 309 : R₆ = 1-benzylpiperazine

Compound 311 : R₆ = 4-phenylpiperidin-4-ol

Compound 312 : R₆ = morpholine

Compound 313 : R₆ = 2,6-dimethylmorpholine

Q₁ = C, P = C, Q₂ = N, R_{3,4} = H

Compound 356 : R₆ = 1-(2-methoxyphenyl)piperazine

Compound 357 : R₆ = 1-(4-fluorophenyl)piperazine

Compound 358 : R₆ = pyrrolidine

Compound 376 : R₆ = 1-methyl-1,4-diazepane

Compound 379 : R₆ = azetidine

Compound 450 : R₆ = 1-(3,4-dimethylphenyl)piperazine

Compound 451 : R₆ = 1-(1,4-diazepan-1-yl)ethanone

Compound 451 : R₆ = cyclopropyl(piperazin-1-yl)methanone

Compound 280 : P = C, Q₁ = N, Q₂ = C, R_{3,4} = H, R₆ = morpholine

Compound 281 : P = N, Q₁ = C, Q₂ = C, R_{3,4} = H, R₆ = morpholine

Compound 533 : Q₁ = C, P = C, Q₂ = N, R₃ = Cl, R₄ = H, R₆ = morpholine

Compound 778 : Q₁ = C, P = C, Q₂ = N, R₃ = H, R₄ = CF₃, R₆ = morpholine

Compound 826 : Q₁ = C, P = C, Q₂ = N, R₃ = H, R₄ = CF₃, R₆ = 1-ethylpiperazine

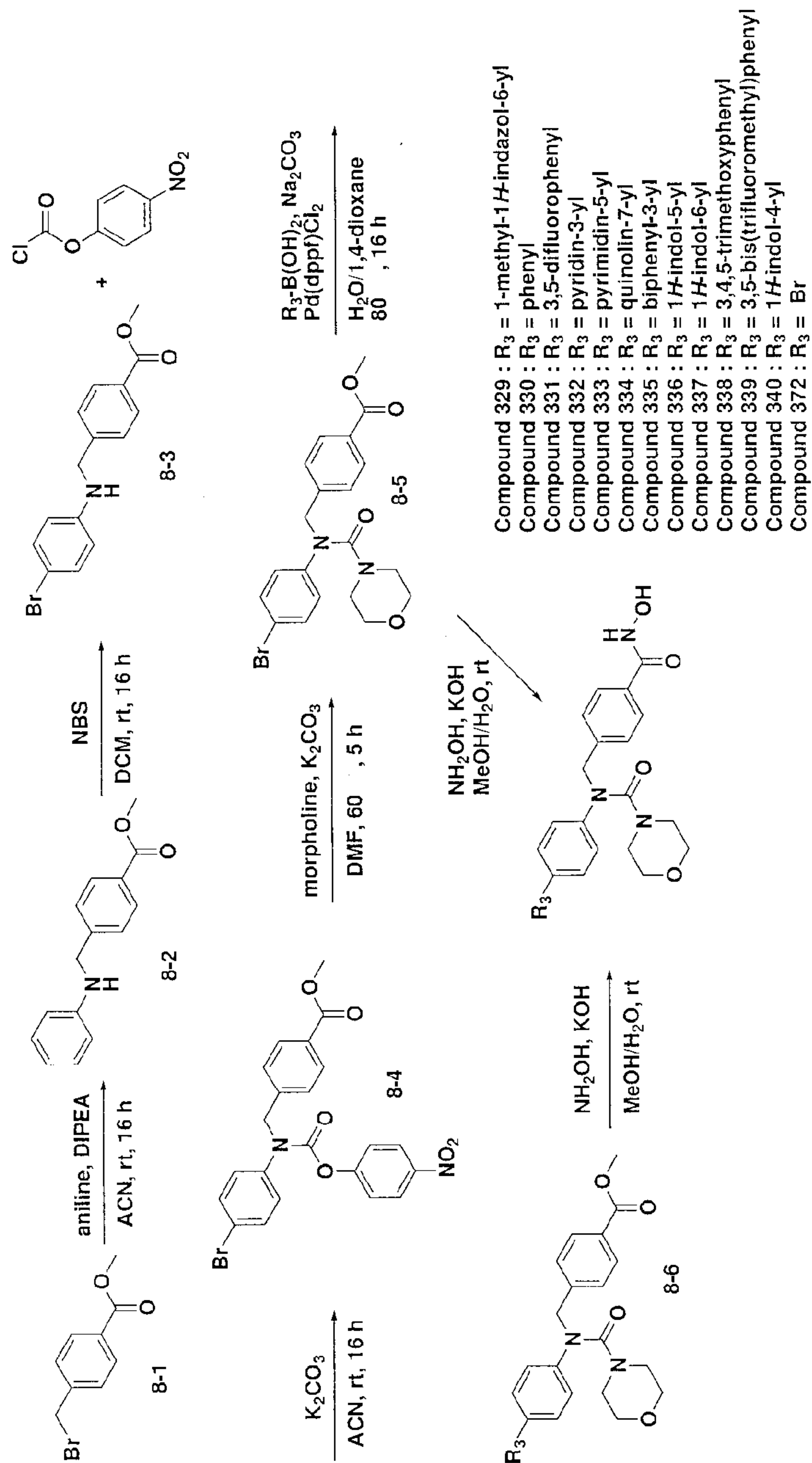
Compound 827 : Q₁ = C, P = C, Q₂ = N, R₃ = H, R₄ = CF₃, R₆ = 2,6-dimethylmorpholine

Compound 828 : Q₁ = C, P = C, Q₂ = N, R₃ = H, R₄ = CF₃, R₆ = piperidine

Compound 829 : Q₁ = C, P = C, Q₂ = N, R₃ = H, R₄ = CF₃, R₆ = (S)-3-fluoropyrrolidine

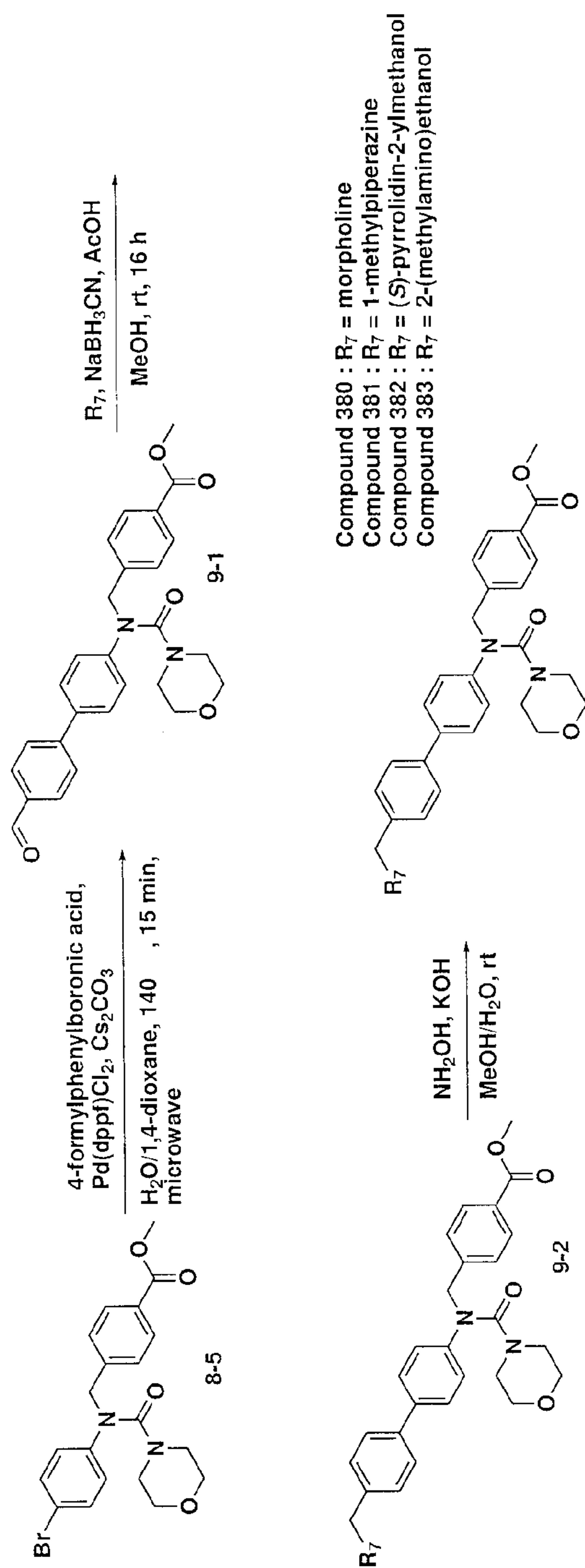
In reaction scheme 7, the compound of Formula 7-4 was synthesized by the reductive amination of the compound of Formula 7-3 or by the substitution of the compound of Formula 7-1 with the compound of Formula 7-2. Then, the compound of Formula 7-5 was synthesized by the reaction of the compound of Formula 7-4 with 4-nitrophenyl chloroformate at room temperature or at 60 °C. Subsequently, the compound of Formula 7-6 was synthesized by the reaction of the compound of Formula 7-5 with amine derivative (R_5) at 60 °C or by adding acyl chloride to the compound of Formula 7-4. Finally, the target compound 280, 281, 309, 311, 312, 313, 341, 342, 343, 352, 353, 354, 355, 356, 357, 358, 376, 377, 379, 450, 451, 533, 778, 826, 827, 828 or 829 was synthesized by dissolving the compound of Formula 7-6 in methanol, followed by the reaction with hydroxylamine (NH_2OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added dropwise, at room temperature.

[Reaction Scheme 8]



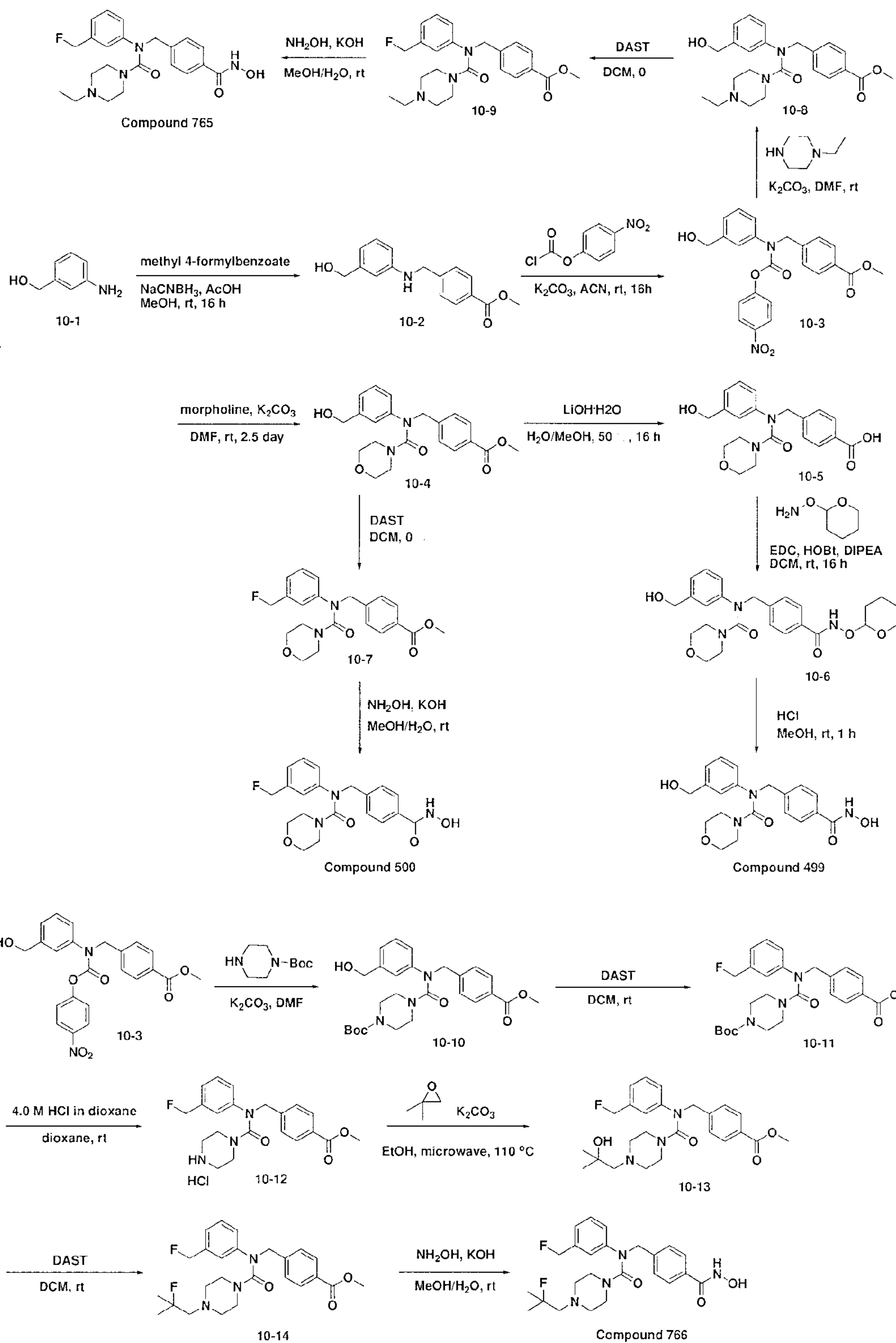
In reaction scheme 8, the compound of Formula 8-2 was synthesized by the substitution of the compound of Formula 8-1 with aniline, and then the compound of Formula 8-3 was synthesized by the reaction of the compound of Formula 8-2 with N-bromosuccinimide at room temperature. Next, the compound of Formula 8-4 was synthesized by the reaction of the compound of Formula 8-3 with 4-nitrophenyl chloroformate at room temperature, and then the compound of Formula 8-5 was synthesized by the substitution of the compound of Formula 8-4 with morpholine at 60 °C. Subsequently, the compound of Formula 8-6 was synthesized by the Suzuki reaction of the compound of Formula 8-5 with boronic acid. Finally, the target compound 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340 or 372 was synthesized by dissolving the compound of Formula 8-5 or 8-6 in methanol, followed by the reaction with hydroxylamine (NH₂OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added dropwise, at room temperature.

[Reaction Scheme 9]



In reaction scheme 9, the compound of Formula 9-1 was synthesized by the Suzuki reaction of the compound of Formula 8-5 with 4-formylphenylboronic acid, and then the compound of Formula 9-2 was synthesized by the reductive amination of the
5 compound of Formula 9-1 with amine derivative (R_7). Finally, the target compound 380, 381, 382 or 383 was synthesized by dissolving the compound of Formula 9-2 in methanol, followed by the reaction with hydroxylamine (NH_2OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added
10 dropwise, at room temperature.

[Reaction Scheme 10]



In reaction scheme 10, the compound of Formula 10-2 was synthesized by the reductive amination of the compound of Formula 10-1 with methyl 4-formylbenzoate, and the compound of Formula 10-3 was synthesized by the reaction of the compound of Formula 10-2 with 4-nitrophenyl chloroformate at room temperature. Next, the compound of Formula 10-4 was synthesized by the substitution of the compound of Formula 10-3 with morpholine at room temperature, and then the compound of Formula 10-5 was synthesized by the hydrolysis of the compound of Formula 10-4 with lithium hydroxide (LiOH). Subsequently, the compound of Formula 10-6 was synthesized by the reaction of the compound of Formula 10-5 with (tetrahydropyran-2-yl)hydroxylamine, 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole hydrate (HOBt) at room temperature. Then, the target Compound 499 was synthesized by dissolving the compound of Formula 10-6 in methanol and adding hydrogen chloride at room temperature.

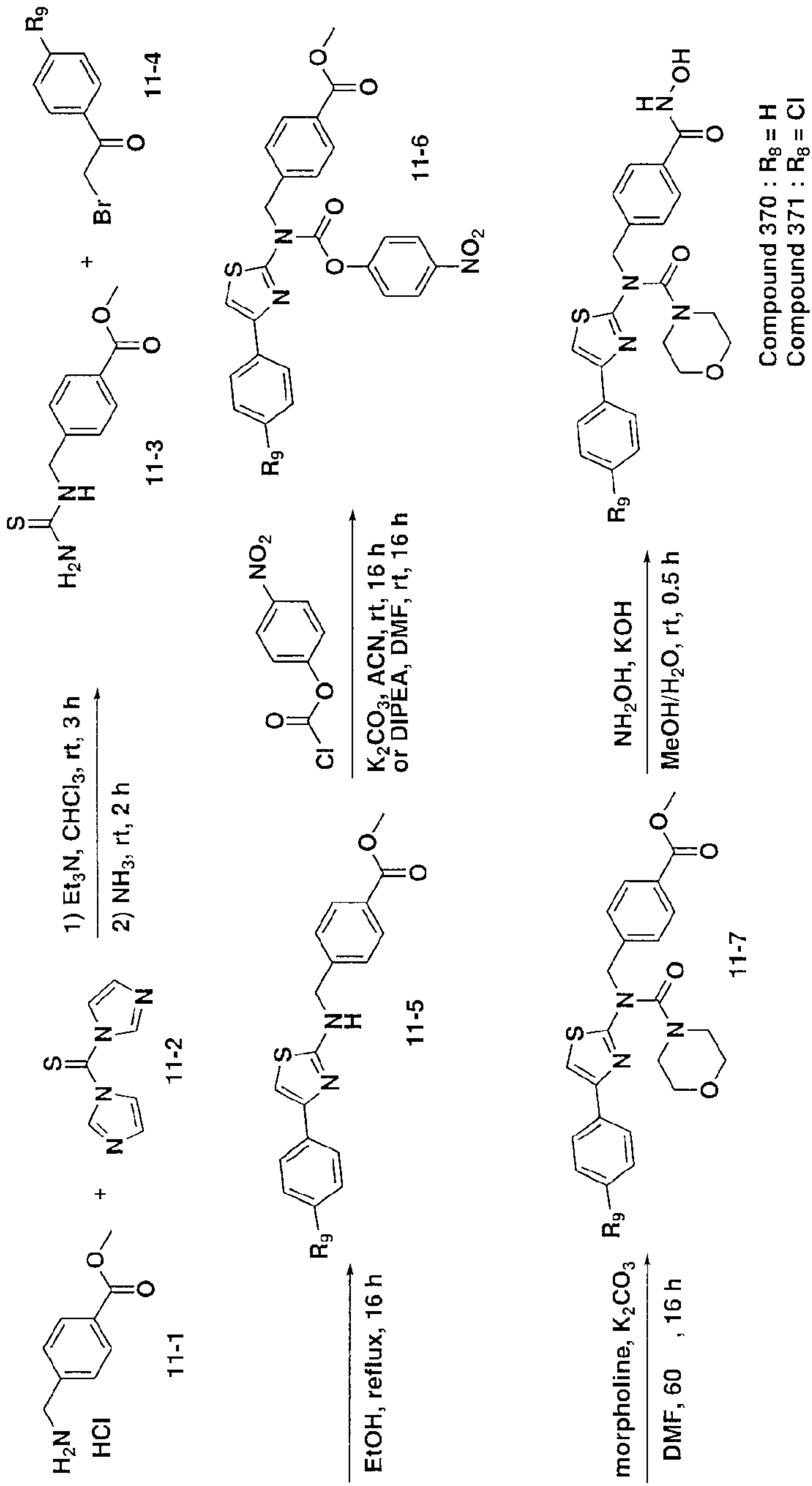
The compound of Formula 10-7 was synthesized by the reaction of the compound of Formula 10-4 with diethylaminosulfur trifluoride (DAST), and then the target Compound 500 was synthesized by dissolving the compound of Formula 10-7 in methanol, followed by the reaction with hydroxylamine (NH₂OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added dropwise, at

room temperature.

The compound of Formula 10-8 was synthesized by the substitution of the compound of Formula 10-3 with ethylpiperazine, and then the compound of Formula 10-9 was synthesized using diethylaminosulfur trifluoride (DAST).
5 Next, the target Compound 765 was synthesized by dissolving the compound of Formula 10-9 in methanol, followed by the reaction with hydroxylamine (NH_2OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added
10 dropwise, at room temperature.

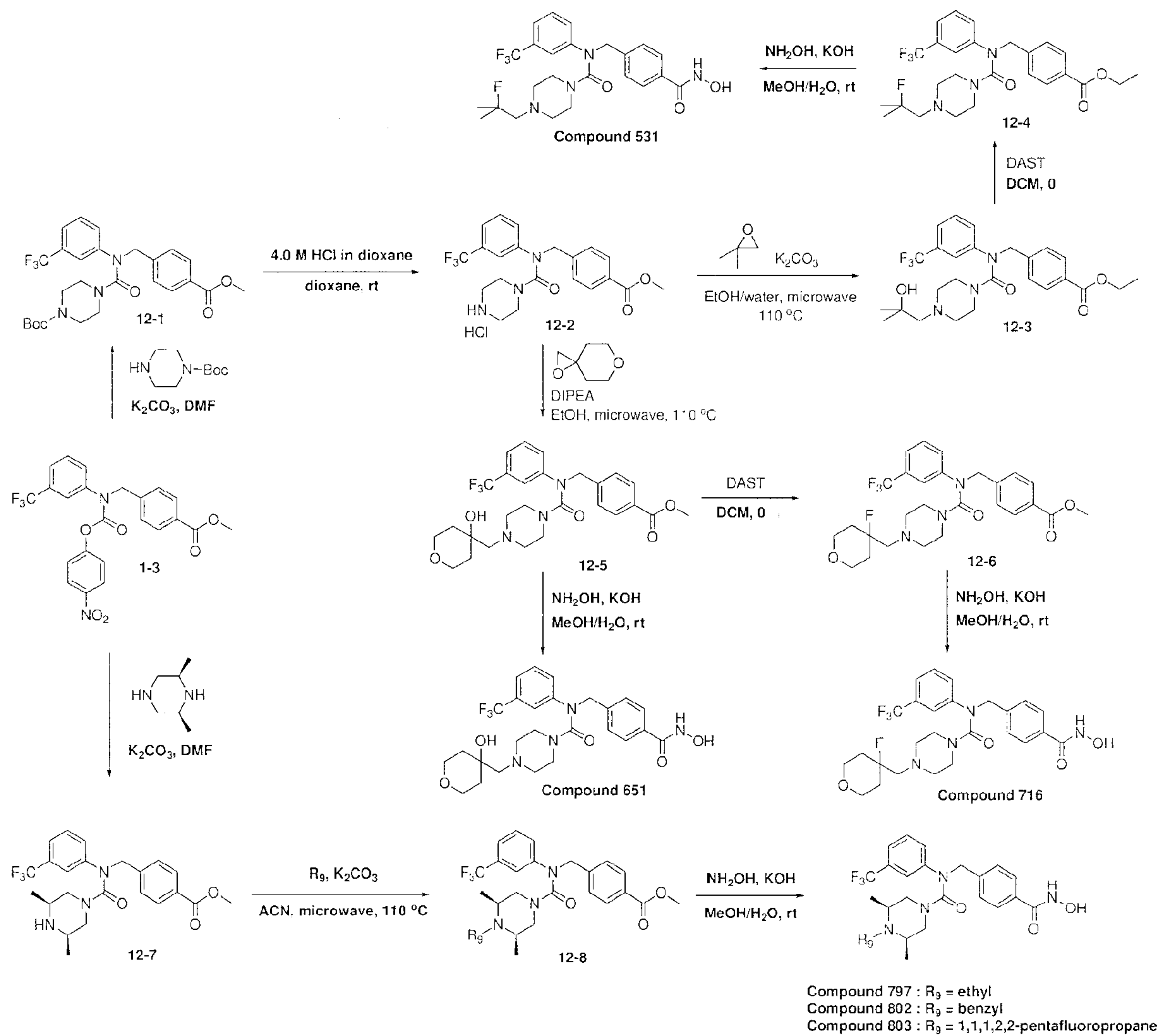
The compound of Formula 10-11 was synthesized by the introduction of Boc-piperazine into the compound of Formula 10-3, followed by the reaction with diethylaminosulfur trifluoride (DAST). And then, the compound of Formula 10-12
15 was synthesized by Boc-deprotection under acidic conditions. Next, the compound of Formula 10-13 was synthesized by the reaction of the compound of Formula 10-12 with 2,2-dimethyloxirane under microwave irradiation, and then the compound of Formula 10-14 was synthesized using
20 diethylaminosulfur trifluoride (DAST). Finally, the target Compound 766 was synthesized by dissolving the compound of Formula 10-14 in methanol, followed by the reaction with hydroxylamine (NH_2OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added dropwise, at
25 room temperature.

[Reaction Scheme 11]



In reaction scheme 11, the compound of Formula 11-3 was synthesized by the substitution of the compound of Formula 11-2 with the compound of Formula 11-1 twice, and then the compound of Formula 11-5 was synthesized by the cyclization
5 of the compound of Formula 11-3 with the compound of Formula 11-4 by stirring under reflux in the presence of ethanol solvent. Next, the compound of Formula 11-6 was synthesized by the reaction of the compound of Formula 11-5 with 4-nitrophenyl chloroformate at room temperature, and then the
10 compound of Formula 11-7 was synthesized by the substitution of the compound of Formula 11-6 with morpholine at 60 °C. Finally, the target Compounds 370 or 731 were synthesized by dissolving the compound of Formula 11-7 in methanol, followed by the reaction with hydroxylamine (NH₂OH) aqueous solution
15 and potassium hydroxide (KOH), which were sequentially added dropwise, at room temperature.

[Reaction Scheme 12]



In reaction scheme 12, the compound of Formula 12-1 was synthesized by the reaction of the compound of Formula 1-3 with N-boc-piperazine, and then the compound of Formula 12-2 was synthesized by Boc-deprotection under acidic conditions. 5 Next, the compound of Formula 12-3 was synthesized by the reaction of the compound of Formula 12-2 with 2,2-dimethyloxirane under microwave irradiation, and then the compound of Formula 12-4 was synthesized using diethylaminosulfur trifluoride (DAST). Then, the Compound 10 531 was synthesized by dissolving the compound of Formula 12-4 in methanol, followed by the reaction with hydroxylamine (NH₂OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added dropwise, at room temperature.

The compound of Formula 12-5 was synthesized by the 15 reaction of the compound of Formula 12-2 with 1,6-dioxaspiro[2,5]octane under microwave irradiation, and then the Compound 651 was synthesized by dissolving the compound of Formula 12-5 in methanol, followed by the reaction with hydroxylamine (NH₂OH) aqueous solution and potassium 20 hydroxide (KOH), which were sequentially added dropwise, at room temperature.

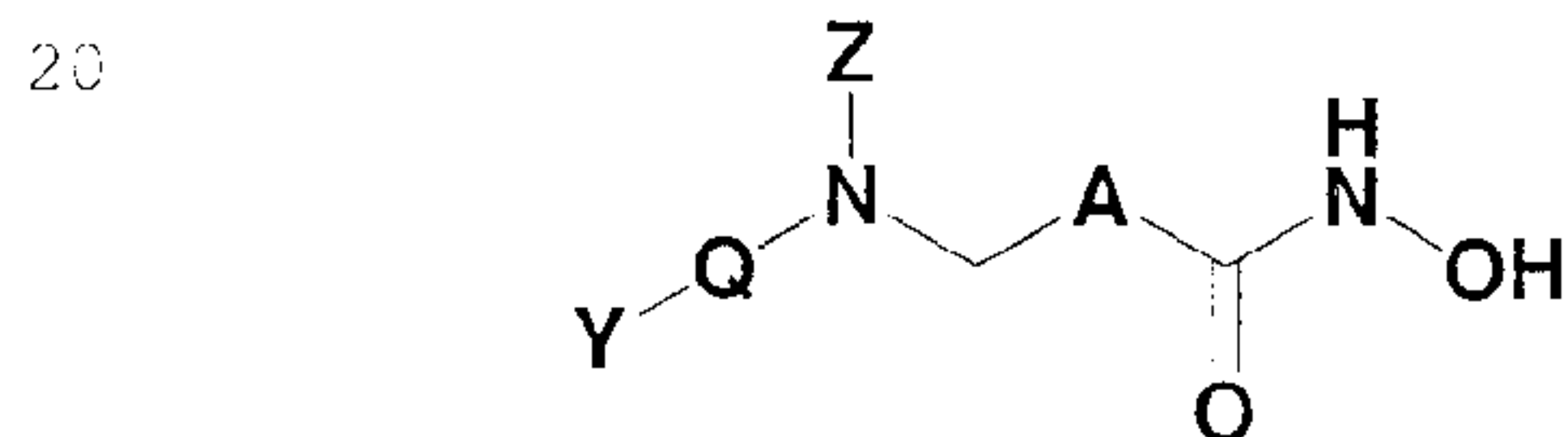
The compound of Formula 12-6 was synthesized by the reaction of the compound of Formula 12-5 with DAST, and then the Compound 716 was synthesized by dissolving the compound 25 of Formula 12-6 in methanol, followed by the reaction with

hydroxylamine (NH₂OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added dropwise, at room temperature.

The compound of Formula 12-8 was synthesized by the introduction of amine derivative (R₆) into the compound of Formula 1-3, followed by the substitution, and then the target compound 797, 802 or 803 was synthesized by dissolving the compound of Formula 12-8 in methanol, followed by the reaction with hydroxylamine (NH₂OH) aqueous solution and potassium hydroxide (KOH), which were sequentially added dropwise, at room temperature.

The present invention provides a pharmaceutical composition for the prevention or treatment of histone deacetylase-mediated diseases, comprising a compound represented by the following Formula I, an optical isomer thereof, or a pharmaceutically acceptable salt thereof as an active ingredient.

[Formula I]



wherein Y, Q, Z and A are the same as defined above.

25 Examples of histone deacetylase-mediated diseases may

include cell proliferative diseases including malignant tumors such as cancers, etc., inflammatory diseases, autosomal dominant diseases such as Huntington's diseases, etc., inherited metabolic diseases such as cystic fibrosis, hepatic fibrosis, kidney fibrosis, pulmonary fibrosis, skin fibrosis, etc, autoimmune diseases such as rheumatoid arthritis, etc., acute and chronic neurological diseases such as diabetes, stroke, etc., hypertrophy such as cardiac hypertrophy, etc., hemorrhagic heart failure, amyotrophic lateral sclerosis, glaucoma, ocular diseases (associated with angiogenesis), neurodegenerative diseases, etc., and further include symptoms and diseases associated with abnormal function of histone deacetylase.

The compound represented by Formula I of the present invention may be one of the compounds represented by the above Formula I-1 to I-12, Formula II or Formula III.

The pharmaceutically acceptable salt is the same as those described with respect to the compound represented by the above Formula I.

For administration, the pharmaceutical composition of the present invention may further comprise one or more pharmaceutically acceptable carriers in addition to the compound represented by the above Formula I, an optical isomer thereof or a pharmaceutically acceptable salt thereof. Examples of the pharmaceutically acceptable carrier include

saline, sterile water, Ringer's solution, buffered saline, dextrose solution, maltodextrin solution, glycerol, ethanol and combinations thereof. If necessary, other general additives, such as antioxidant, buffer solution, anti-
5 bacterial agent, etc., may be added to the composition. Moreover, the pharmaceutical composition of the present invention may be formulated into injections such as aqueous solution, suspension, emulsion, etc., pills, capsules, granule, or tablets by adding diluent, dispersant,
10 surfactant, binder, and lubricant. Accordingly, the composition of the present invention can be presented as patches, liquids, pills, capsules, granules, tablets, suppositories, etc. These formulations may be formulated by suitable methods in the art or methods described in
15 Remington's Pharmaceutical Science (latest edition), Mack Publishing Company, Easton PA, depending on the disease and/or ingredients.

The composition of the present invention may be administered orally or parenterally (e.g., intravenously,
20 subcutaneously, intraperitoneally, or topically) at a dose depending on various factors including the patient's weight, age, gender, state of health, diet, administration time, administration route, excretion rate, severity of disease, etc. The daily dose of the composition of the present
25 invention may be about 1 to 500 mg/kg, preferably 5 to 100

mg/kg, and the composition of the present invention may be administered once or several times a day.

The pharmaceutical composition of the present invention may further comprise one or more active ingredients having
5 the same or similar efficacy in addition to the compound represented by the above Formula I, an optical isomer thereof or a pharmaceutically acceptable salt thereof.

The present invention provides a method for the prevention or treatment of histone deacetylase-mediated
10 diseases, comprising administering a therapeutically effective amount of a compound represented by the above Formula I, an optical isomer thereof or a pharmaceutically acceptable salt thereof.

As used herein, the term "therapeutically effective
15 amount" refers to the amount of a compound represented by the above Formula I, which is effective for the prevention or treatment of histone deacetylase-mediated diseases.

Moreover, the present invention provides a method for inhibiting histone deacetylase (HDAC), comprising
20 administering an effective amount of a compound represented by the above Formula I, an optical isomer thereof or a pharmaceutically acceptable salt thereof to a mammal including a human.

The method for the prevention or treatment of histone
25 deacetylase-mediated diseases according to the present

invention further includes managing the disease itself before the onset of symptoms as well as inhibiting or avoiding the symptoms by administering the compound represented by the above Formula I. In the management of the disease, the preventive or therapeutic dose of a specific active ingredient may vary depending on the nature and severity of the disease or condition and the administration route of the active ingredient. The dose and the frequency of the dose may vary depending on the individual patient's age, weight, and response. The suitable dose and use may be easily selected by those having ordinary skill in the art based on these factors. Moreover, the method for the prevention or treatment of histone deacetylase-mediated diseases according to the present invention may further comprise administering a therapeutically effective amount of an additional active ingredient that improve the treatment of disease together with the compound represented by the above Formula I. The additional active ingredient may exhibit a synergistic or additive effect together with the compound represented by the above Formula I.

The present invention further provides the use of a compound represented by the above Formula I, an optical isomer thereof or a pharmaceutically acceptable salt thereof in the preparation of medicaments for the treatment of HDAC-

mediated diseases. The compound represented by the above
Formula I for the preparation of medicaments may comprise a
pharmaceutically acceptable adjuvant, diluent, carrier, etc.
and may be prepared into combined formulations together with
5 other active ingredients to have synergistic activities.

The matters mentioned in the use, the composition, and
the treatment method of the present invention are applied
equally unless they are contradictory to each other.

10 **【Advantageous Effects】**

The compound represented by the above Formula I, an
optical isomer thereof or a pharmaceutically acceptable salt
thereof according to the present invention can selectively
inhibit HDAC and thus have excellent effects on the
15 prevention and treatment of histone deacetylase-mediated
diseases.

【Description of Drawings】

FIG. 1 shows the acetylation levels of Tubulin, Histone
20 H3 and Histone H4 after the treatment with Compound 255.

FIG. 2 shows the acetylation levels of Tubulin, Histone
H3 and Histone H4 after the treatment with Compound 374.

FIG. 3 shows the improvement of arthritis after the
treatment with Compound 254 or Compound 255 to collagen-
25 induced arthritis models.

FIG. 4 shows the improvement of arthritis after the treatment with Compound 374 to collagen-induced arthritis models.

FIG. 5 shows the improvement of arthritis after the treatment with Compound 255, 374 or 461 to adjuvant-induced arthritis models.

FIG. 6 shows the recovery of weight after the treatment with Compound 254 or 255 to colitis models.

FIG. 7 shows the combination index after the combination treatment of Compound 255 and Velcade.

【Mode for Invention】

Hereinafter, the present invention will be described in further detail with reference to examples, preparation examples and test examples. It is to be understood, however, that these examples are for illustrative purposes only and are not intended to limit the scope of the present invention.

Unless otherwise stated, reagents and solvents mentioned below were those available from Sigma-Aldrich and TCI, HPLC was Waters e2695, silica gel for column chromatography was Merck(230~400 mesh), ¹H NMR data was

measured using Bruker 400 MHz and Mass spectrum was agilent 1100 series.

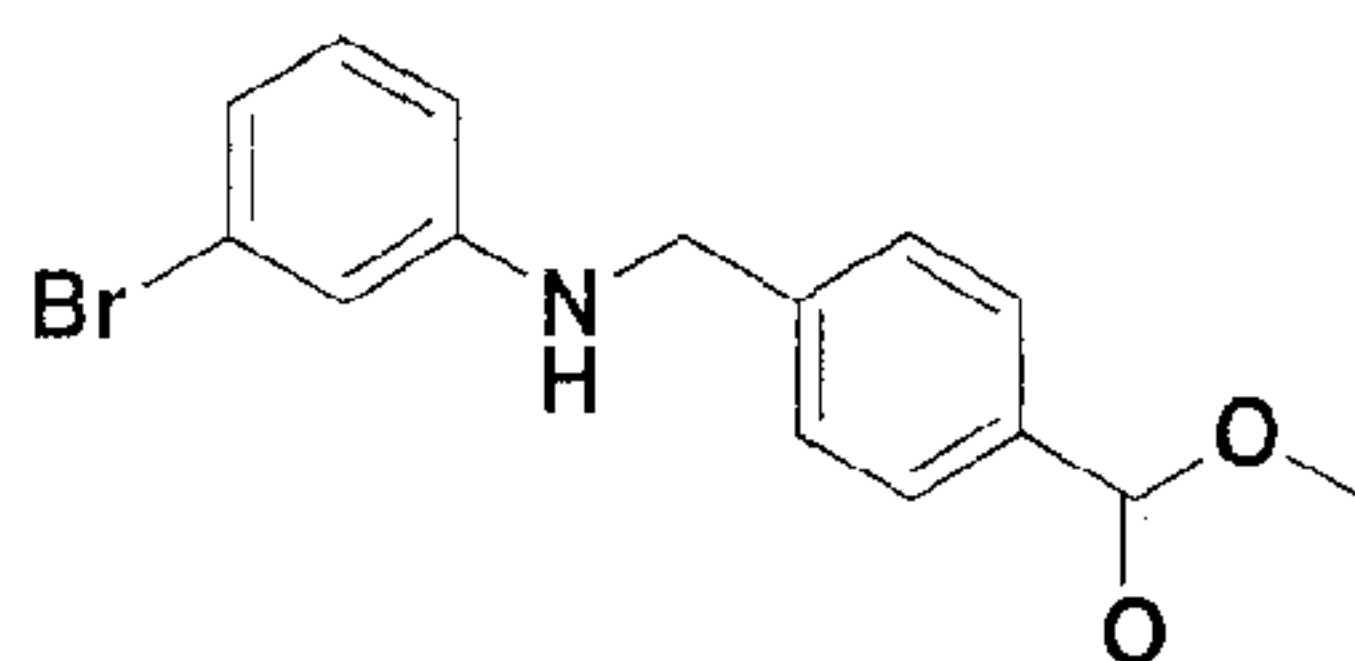
Preparation of novel urea compounds

5 Preparing methods of compound of formula 1 are described with reaction formula.

Example 1: Synthesis of Compound 252

(Formula 1-2: methyl 4-((3-

10 bromophenylamino)methyl)benzoate)

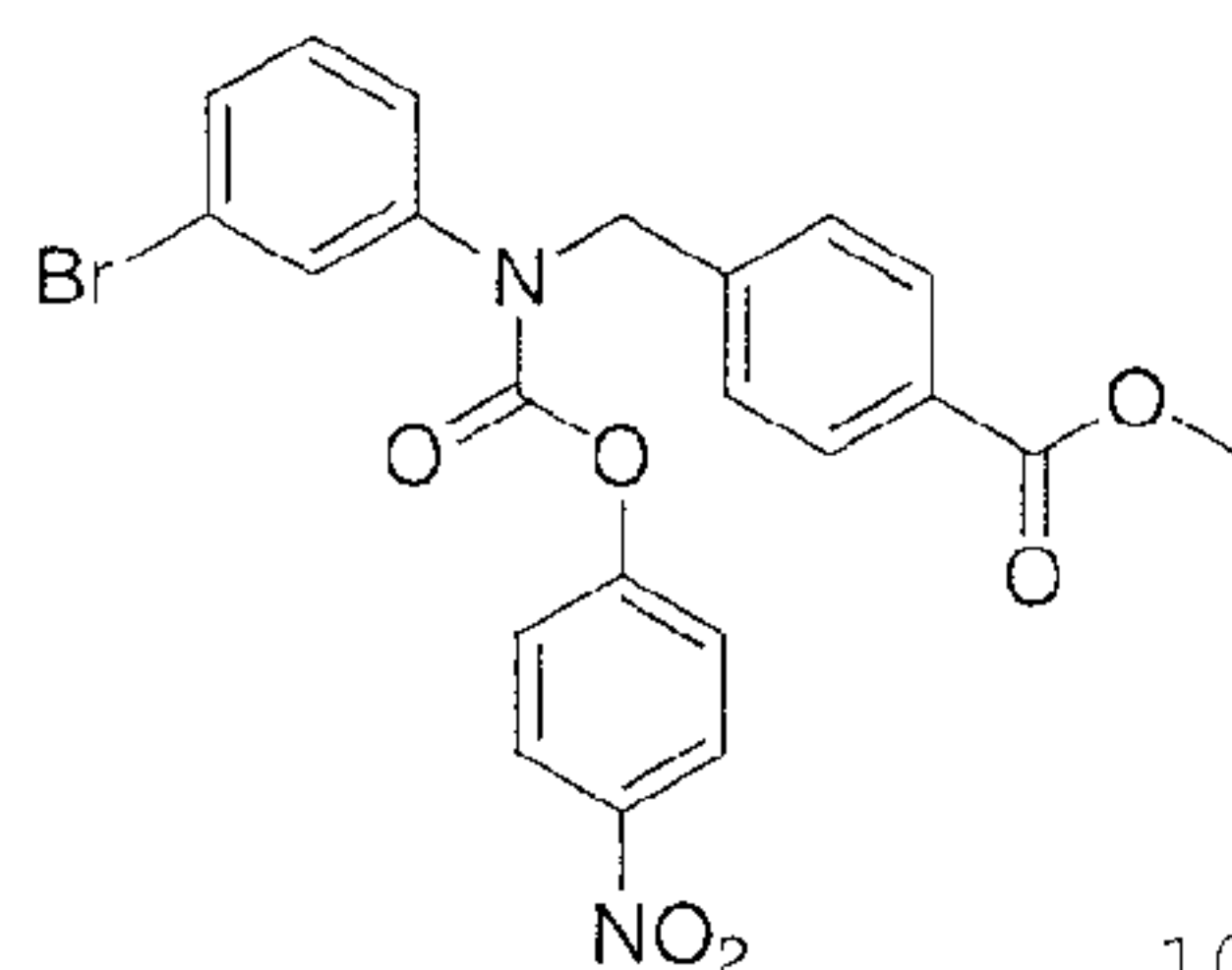


Compound of **Formula 1-1** (3-

15 bromobenzenamine; 5 g, 29 mmol) was dissolved in dichloromethane (200 mL), and then methyl 4-formylbenzoate (5.7 g, 35 mmol) and acetic acid (1.74 mL, 29 mmol) were added and stirred for 1 hour. Then, sodium cyanoborohydride (2.2 g, 35 mmol) was slowly added dropwise and stirred for 1
20 day. Water was poured into the reaction mixture, and the organic layer was extracted. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated

by column chromatography (silica; ethyl acetate/hexane-20%) to give the desired compound of **Formula 1-2** (7.8 g, 84%) in the form of a white solid.

(**Formula 3-1**: methyl 4-(((3-bromophenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate)

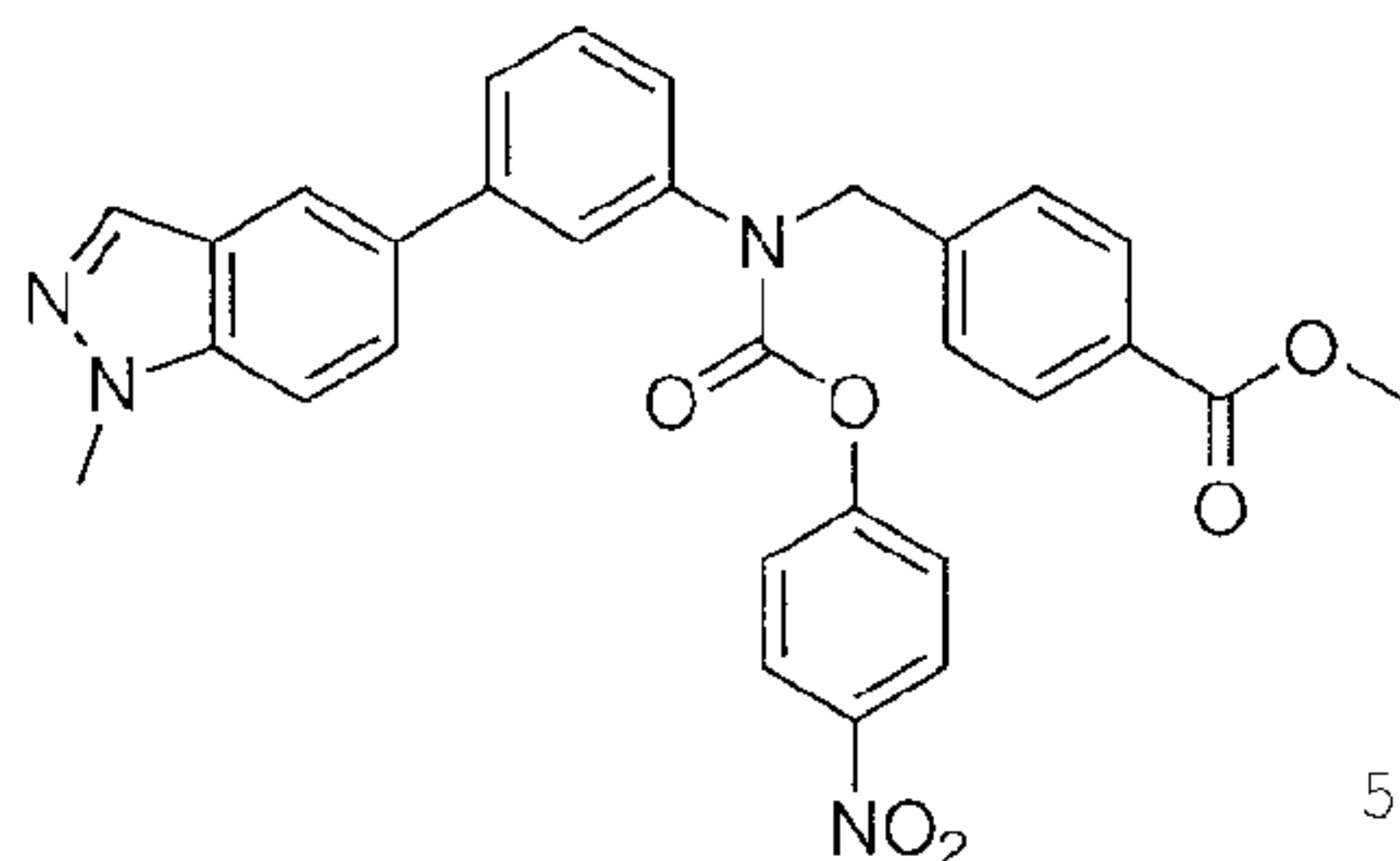


10

Compound of **Formula 1-2**

(methyl 4-(((3-bromophenylamino)methyl)benzoate; 5.90 g, 18.4 mmol) was dissolved in acetonitrile (200 mL), and then potassium carbonate (5.09 g, 36.9 mmol) and 4-nitrophenyl chloroformate (4.09 g, 20.3 mmol) were added. Then, the mixture was heated and stirred at 50 °C for 1 day. Water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane=1%) to give the desired compound of **Formula 3-1** (7.3 g, 82%) in the form of a white solid.

(**Formula 3-2**: methyl 4-(((3-(1-methyl-1H-indazol-5-yl)phenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate)



5

Compound of **Formula****3-****1** (methyl 4-(((3-

bromophenyl))((4-nitrophenoxy)carbonyl)amino)methyl)benzoate;

1.00 g, 2.06 mmol), 1-methyl-1H-indazol-5-ylboronic acid

(0.435 g, 2.473 mmol), Pd(dppf)Cl₂ (0.168 g, 0.206 mmol), and

10 sodium carbonate (0.693 g, 4.53 mmol) were mixed with

dimethoxyethane (5 mL)/H₂O (5 mL), heated at 120 °C for 15

minutes under microwave irradiation, and then the temperature

was lowered to room temperature. Water was poured into the

reaction mixture, and the organic layer was extracted with

15 ethyl acetate. The organic layer was washed with saturated

sodium chloride aqueous solution, dehydrated with anhydrous

magnesium sulfate, and then concentrated under reduced

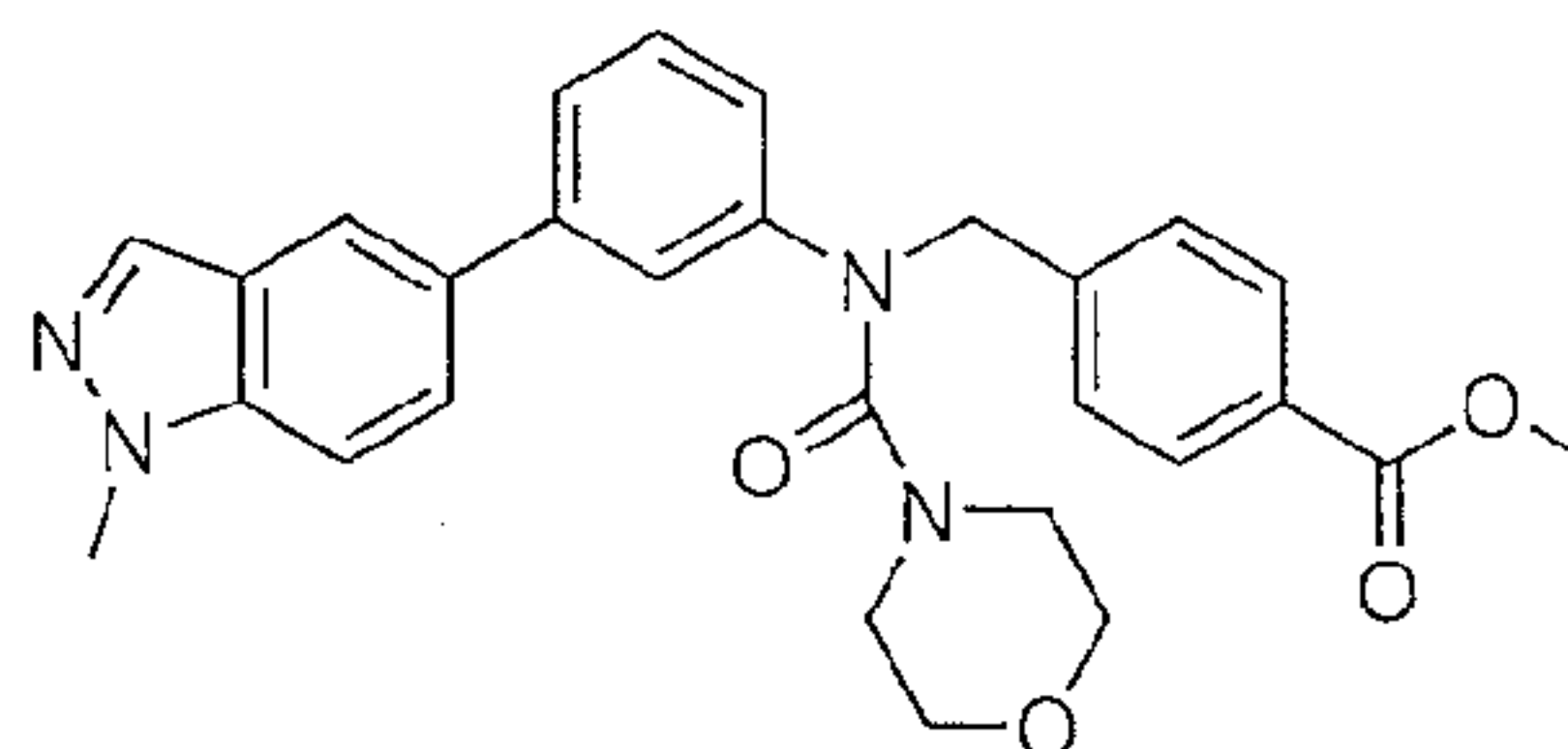
pressure. The residue was purified and concentrated by

column chromatography (silica; ethyl acetate/hexane=30%) to

20 give the desired compound of **Formula 3-2** (0.620 g, 56%) in

the form of a white solid.

(**Formula 3-3**: methyl 4-((N-(3-(1-methyl-1H-indazol-5-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)

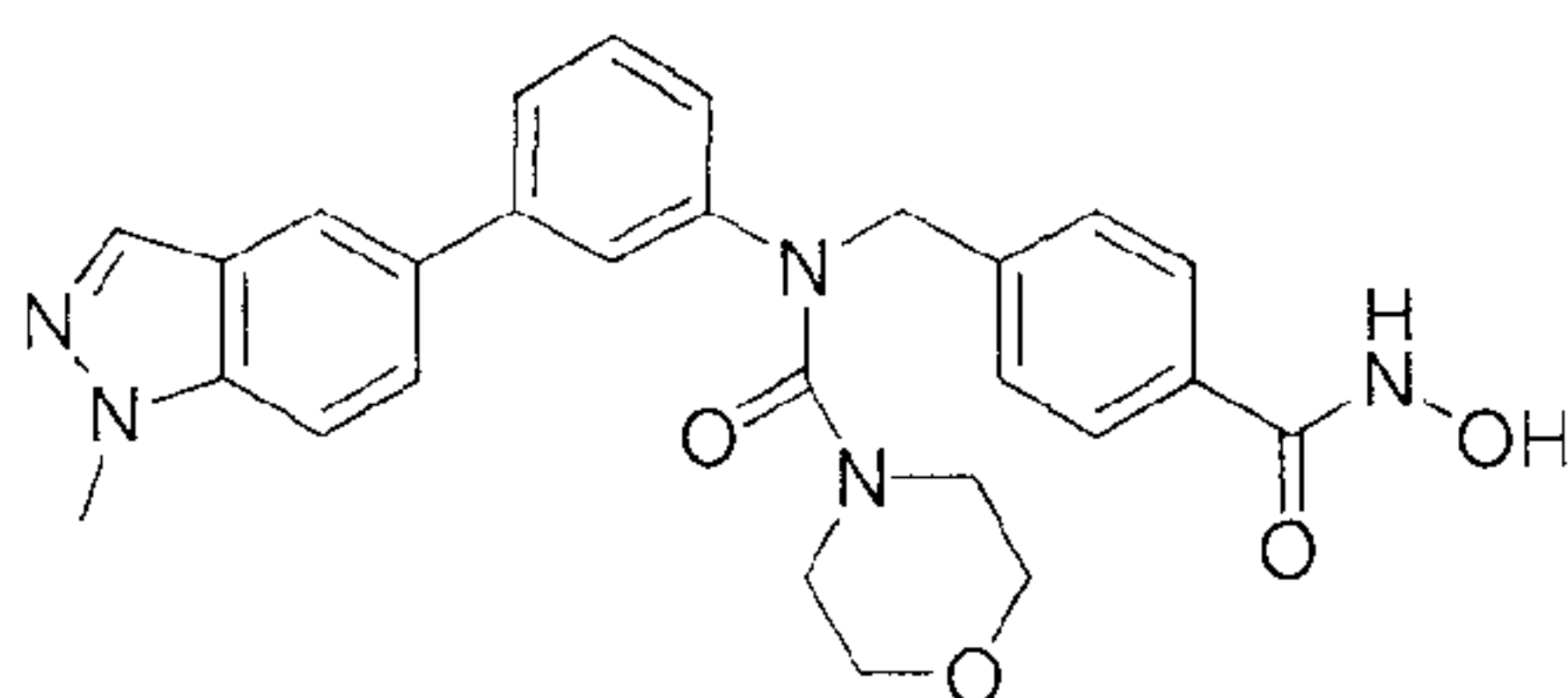


75

Compound of **Formula 3-2** (methyl 4-(((3-(1-methyl-1H-indazol-5-yl)phenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.05 g, 0.093 mmol) was dissolved in dimethylformamide (10 mL), and then morpholine (0.012 mL, 0.14 mmol) and potassium carbonate (0.039 g, 0.28 mmol) were added. Then, the mixture was heated and stirred at 60 °C for 12 hours. Water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 3-3** (0.035 g, 77%) in the form of a colorless liquid.

(Compound 252: N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-methyl-1H-indazol-5-yl)phenyl)morpholine-4-carboxamide)

20

Compound of **Formula**

3-3 (methyl 4-((N-(3-(1-methyl-1H-indazol-5-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.035 g,

25

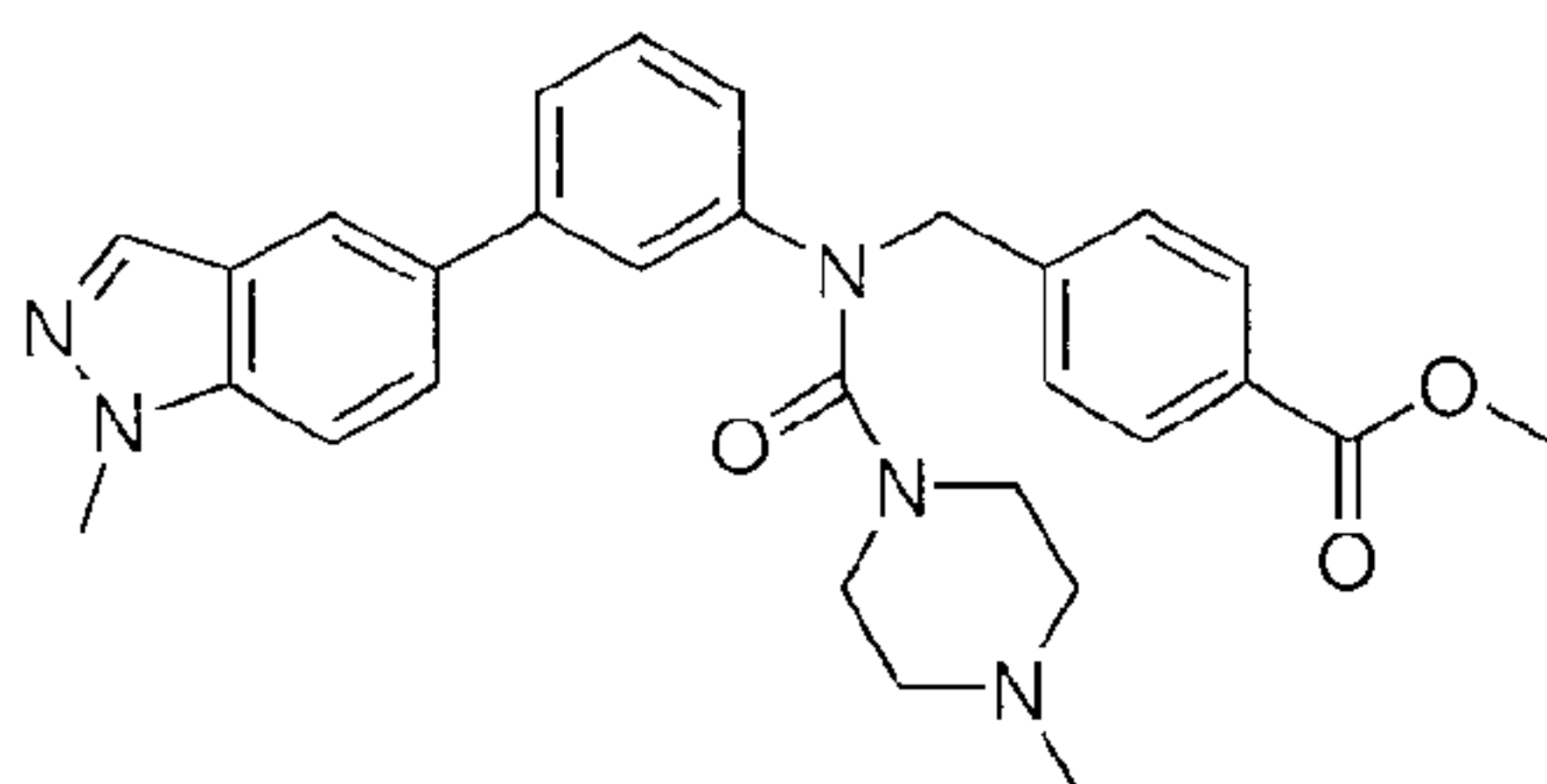
0.072 mmol) was dissolved in methanol (10 mL), and then hydroxylamine hydrochloride (0.025 g, 0.361 mmol), potassium hydroxide (0.041 g, 0.722 mmol), and hydroxylamine (50 wt% aqueous solution; 0.186 mL, 1.445 mmol) were added dropwise and stirred at room temperature for 6 hours. After completion of the reaction, the methanol was removed under reduced pressure, and then 2 N hydrogen chloride was added to precipitate a solid. Then, the resulting solid was filtered and dried to give the desired **Compound 252** (0.016 g, 46%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 8.08 (s, 1 H), 7.97 (s, 1 H), 7.69 – 7.64 (m, 4 H), 7.43 – 7.35 (m, 5 H), 7.08 (d, 1 H, J = 7.0 Hz), 4.93 (s, 2 H), 4.05 (s, 3 H), 3.40 – 3.37 (m, 4 H), 3.19 – 3.16 (m, 4 H); MS (ESI) m/z 486.1 (M⁺ + H).

15

Example 2: Synthesis of Compound 253

(**Formula 3-3**: methyl 4-((4-methyl-N-(3-(1-methyl-1H-



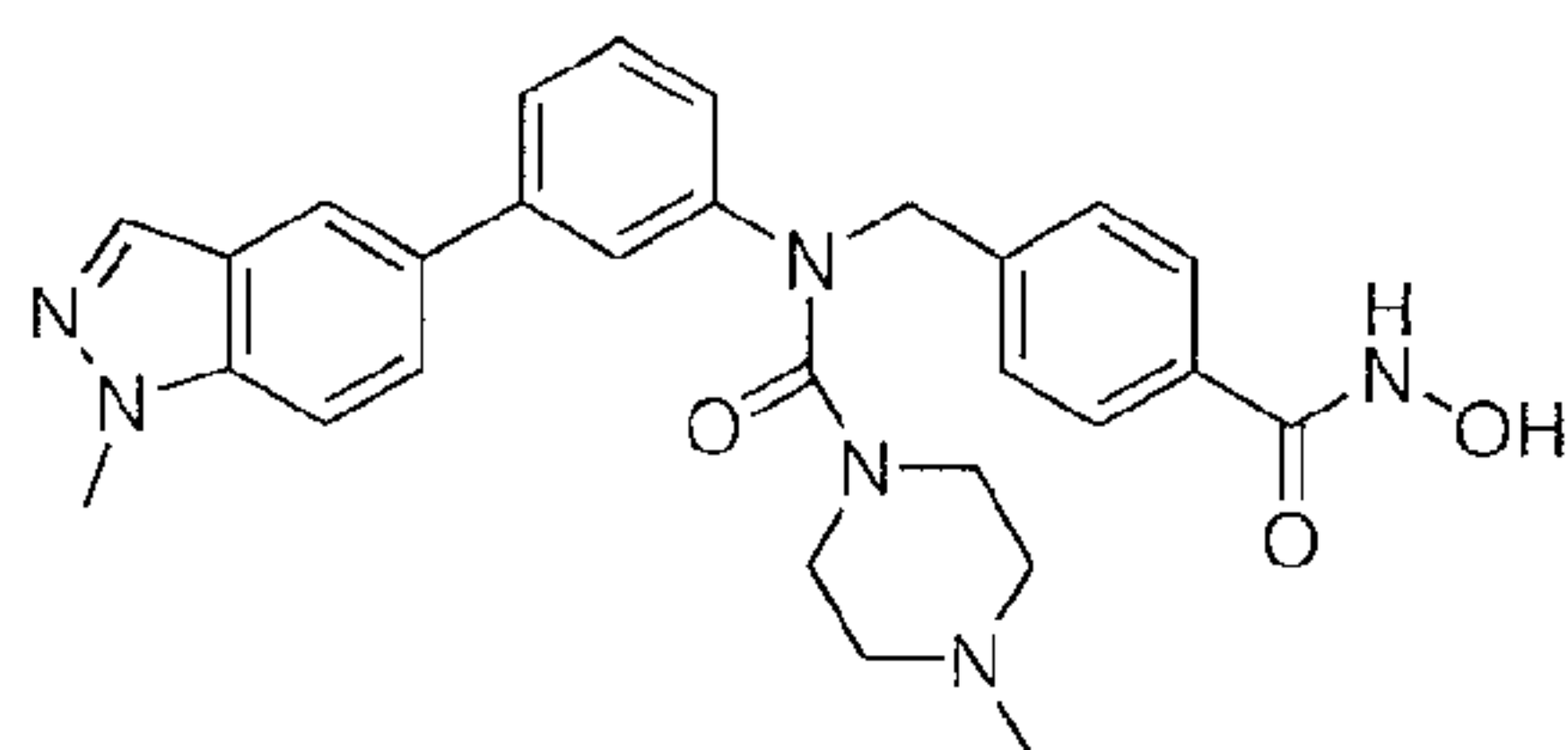
indazol-5-yl)phenyl)piperazine-1-carboxamido)methyl)benzoate)

20

Compound of **Formula 3-2** (methyl 4-((3-(1-methyl-1H-

indazol-5-yl)phenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.05 g, 0.093 mmol) was dissolved in dimethylformamide (10 mL), and then n-methylpiperazine (0.016 mL, 0.14 mmol) and potassium carbonate (0.039 g, 0.28 mmol) were added. Then, the mixture was heated and stirred at 55 °C for 12 hours. Water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane=5%) to give the desired compound of **Formula 3-3** (0.044 g, 95%) in the form of a colorless liquid.

(**Compound 253**: N-(4-(hydroxycarbamoyl)benzyl)-4-methyl-N-(3-(1-methyl-1H-indazol-5-yl)phenyl)piperazine-1-carboxamide)

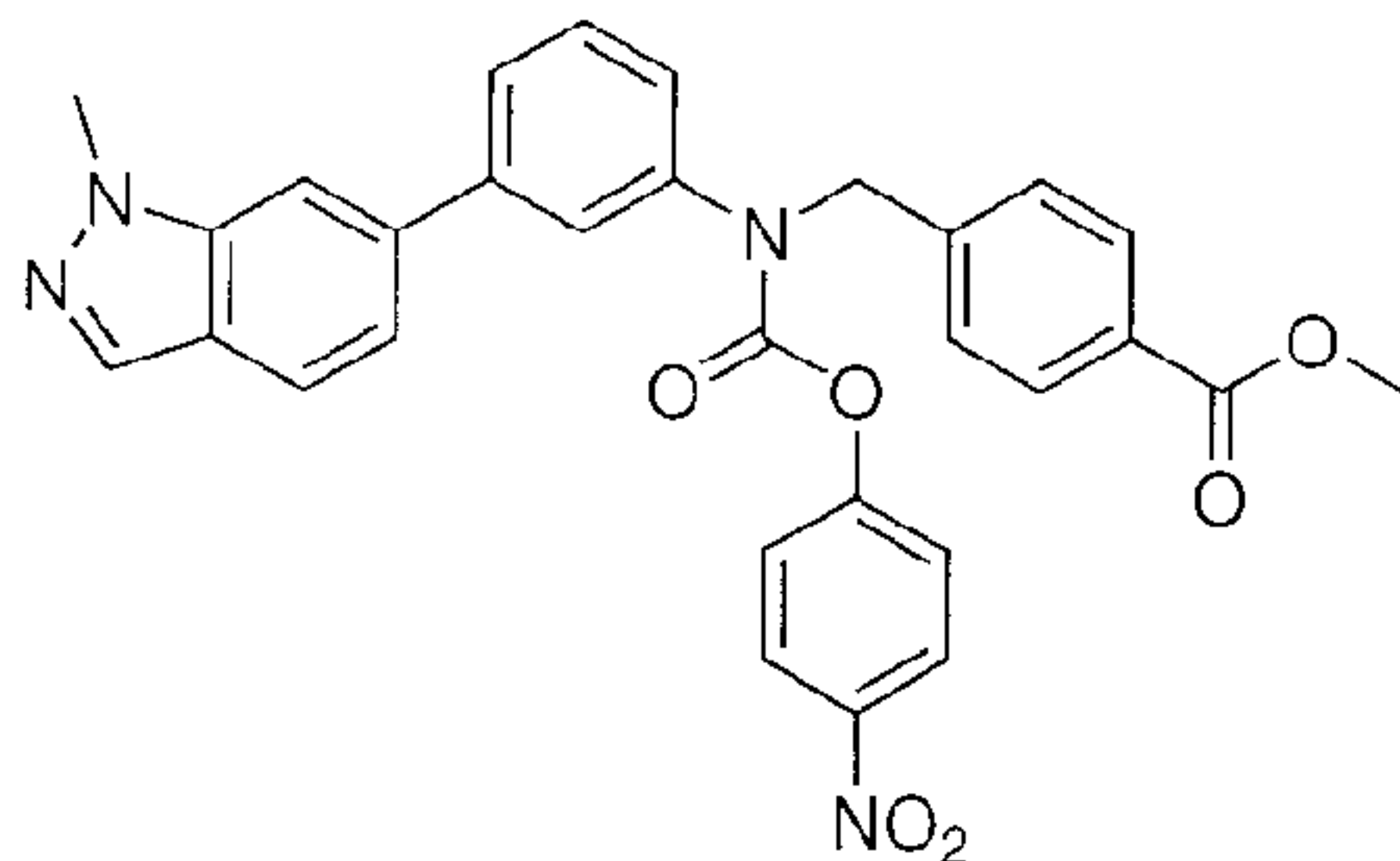


Compound of **Formula 3-3** (methyl 4-((4-methyl-N-(3-(1-methyl-1H-indazol-5-yl)phenyl)piperazine-1-carboxamido)methyl)benzoate; 0.044 g, 0.088 mmol) was dissolved in methanol (5 mL), and then hydroxylamine hydrochloride (0.031 g, 0.442 mmol), potassium hydroxide (0.049 g, 0.884 mmol), and hydroxylamine (50 wt% aqueous solution; 0.228 mL, 1.77 mmol) were added dropwise and stirred at room temperature for 6 hours. After completion of the reaction, the methanol was removed under reduced pressure, and then 2 N hydrogen chloride was added to precipitate a white solid. Then, the resulting solid was filtered and dried to give the desired **Compound 253** (0.02 g, 45%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 8.08 (s, 1 H), 7.97 (s, 1 H),
15 7.69 – 7.64 (m, 4 H), 7.41 – 7.37 (m, 5 H), 7.07 – 7.06 (m, 1
H), 4.92 (s, 2 H), 4.06 (s, 3 H), 3.20 – 3.19 (m, 4 H), 2.13
– 2.11 (m, 4 H), 2.06 (s, 3 H); MS (ESI) m/z 499.2 (M⁺ + H).

Example 3: Synthesis of Compound 254

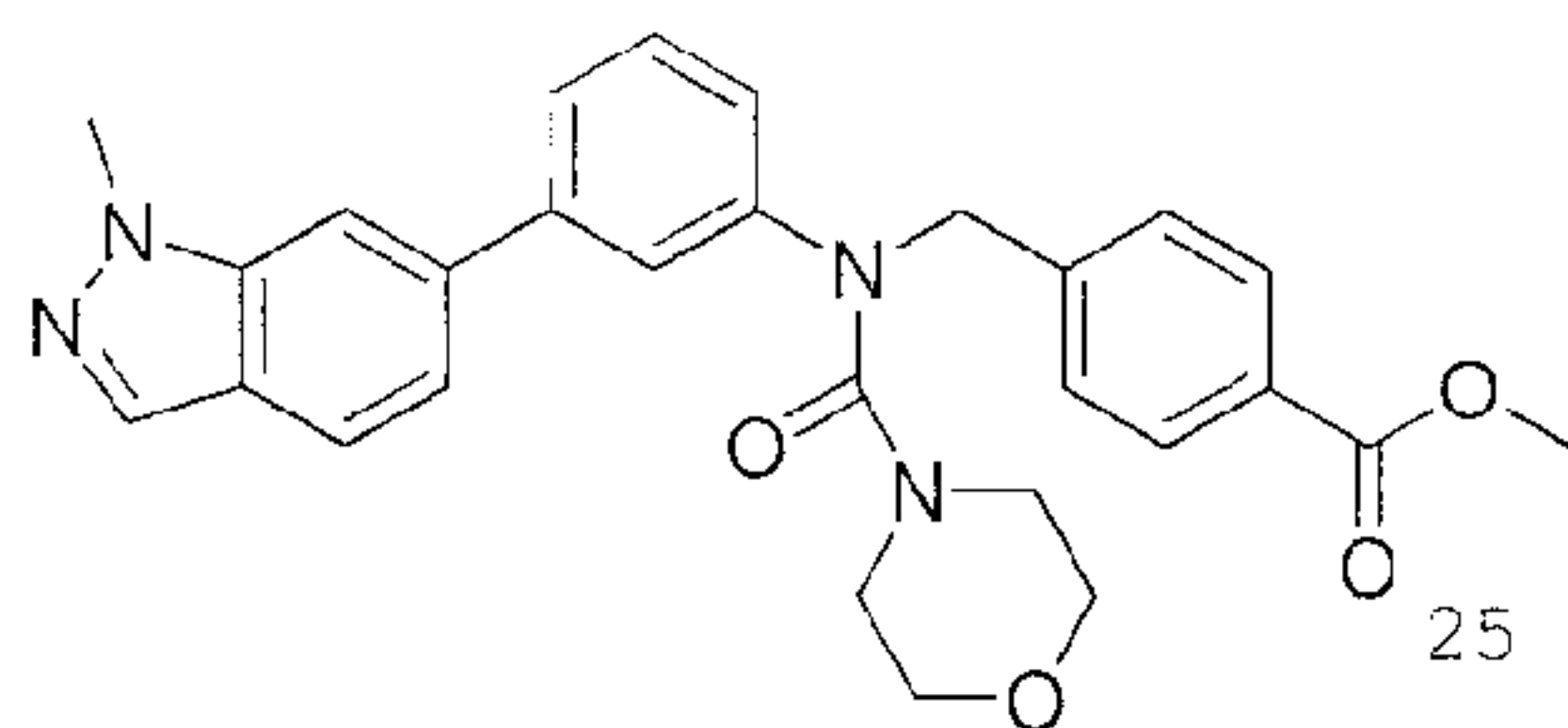
20 (Formula 3-2: methyl 4-(((3-(1-methyl-1H-indazol-6-



yl)phenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate)

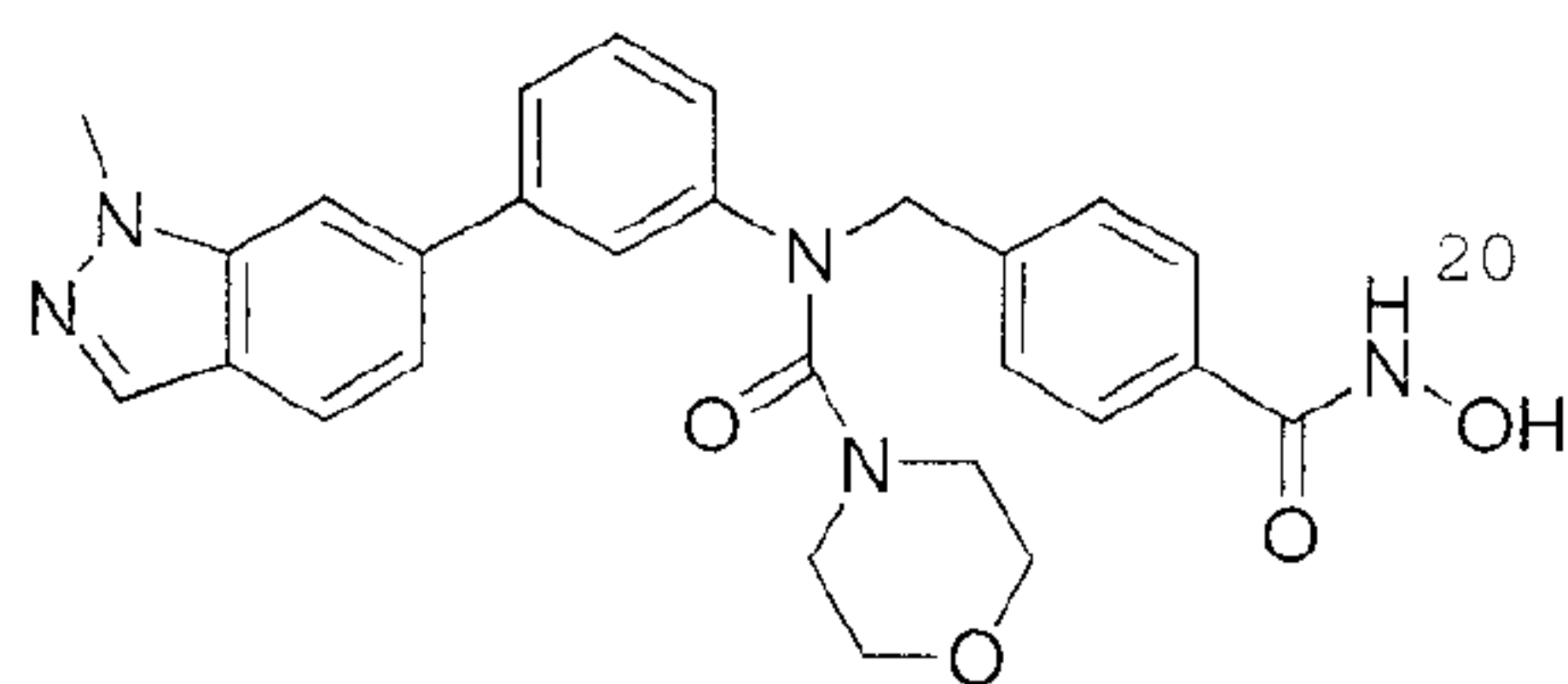
Compound of **Formula 3-1** (methyl 4-(((3-bromophenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate; 1.00 g, 2.06 mmol), 1-methyl-1H-indazol-6-ylboronic acid (0.435 g, 2.47 mmol), Pd(dppf)Cl₂ (0.168 g, 0.206 mmol), and sodium carbonate (0.693 g, 4.53 mmol) were mixed with dimethoxyethane (5 mL)/H₂O (5 mL), heated at 120 °C for 15 minutes under microwave irradiation, and then the temperature was lowered to room temperature. Water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30 %) to give the desired compound of **Formula 3-2** (1.03 g, 93%) in the form of a white solid.

(Formula 3-3: methyl 4-((N-(3-(1-methyl-1H-indazol-6-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)



Compound of **Formula 3-2** (methyl 4-(((3-(1-methyl-1H-indazol-6-yl)phenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.05 g, 0.093 mmol) was dissolved in dimethylformamide (10 mL), and then morpholine (0.011 mL, 0.14 mmol) and potassium carbonate (0.0386 g, 0.28 mmol) were added. Then, the mixture was heated and stirred at 60 °C for 12 hours. Water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 3-3** (0.035 g, 78%) in the form of a white solid.

(Compound 254: N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-methyl-1H-indazol-6-yl)phenyl)morpholine-4-carboxamide)



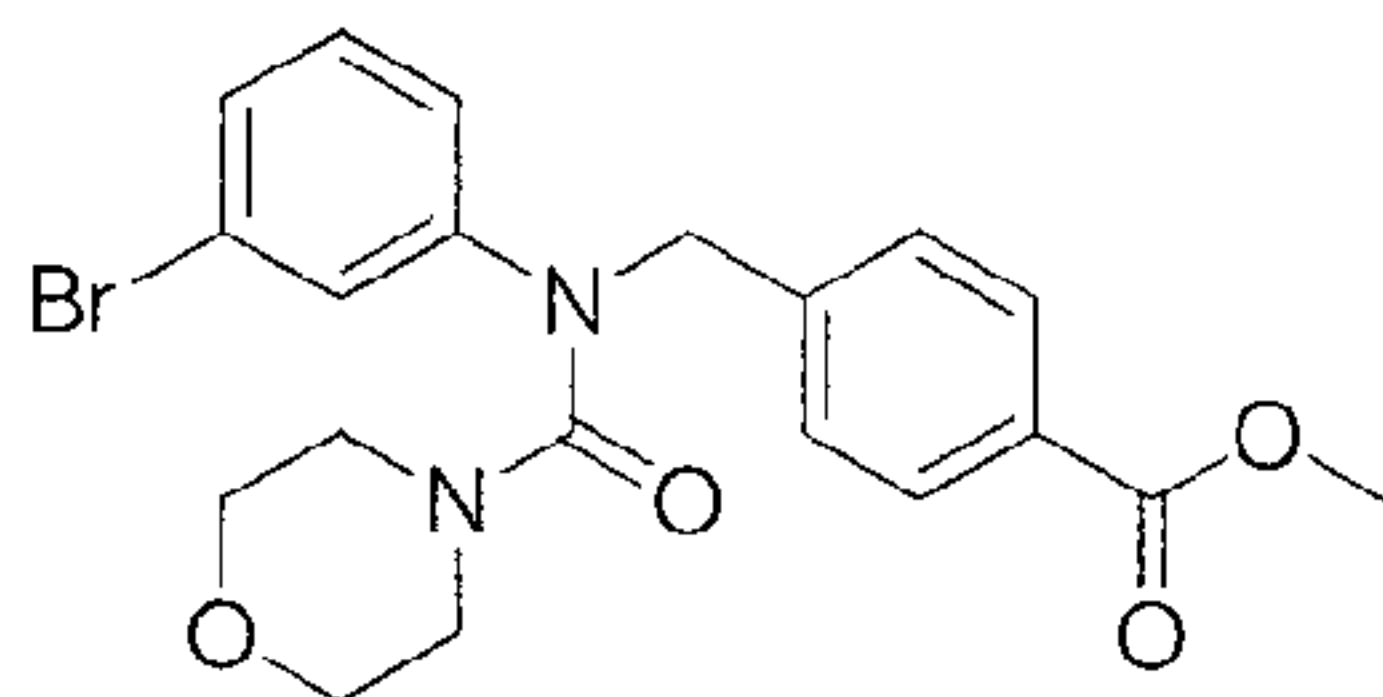
Compound of **Formula 3-3** (methyl 4-((N-(3-(1-methyl-1H-indazol-6-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate;

0.035 g, 0.072 mmol) was dissolved in methanol (5 mL), and then hydroxylamine hydrochloride (0.025 g, 0.361 mmol), potassium hydroxide (0.041 g, 0.722 mmol), and hydroxylamine (50 wt% aqueous solution; 0.186 mL, 1.45 mmol) were added dropwise and stirred at room temperature for 6 hours. After completion of the reaction, the methanol was removed under reduced pressured, and then 2 N hydrogen chloride was added to precipitate a solid. Then, the resulting solid was filtered and dried to give the desired **Compound 254** (0.024 g, 68%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 8.04 (s, 1 H), 7.83 (s, 1 H), 7.80 (d, 1 H, J = 8.4 Hz), 7.65 (d, 2 H, J = 8.2 Hz), 7.52 (s, 1 H), 7.48 (d, 1 H, J = 7.9 Hz), 7.43 - 7.38 (m, 4 H), 7.14 (d, 1 H, J = 7.9 Hz), 4.95 (s, 2 H), 4.09 (s, 2 H), 3.41 - 3.40 (m, 4 H), 3.19 - 3.18 (m, 4 H); **MS** (ESI) m/z 486.1 (M⁺ + H).

Example 4: Synthesis of Compound 255

(**Formula 1-4**: methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate)

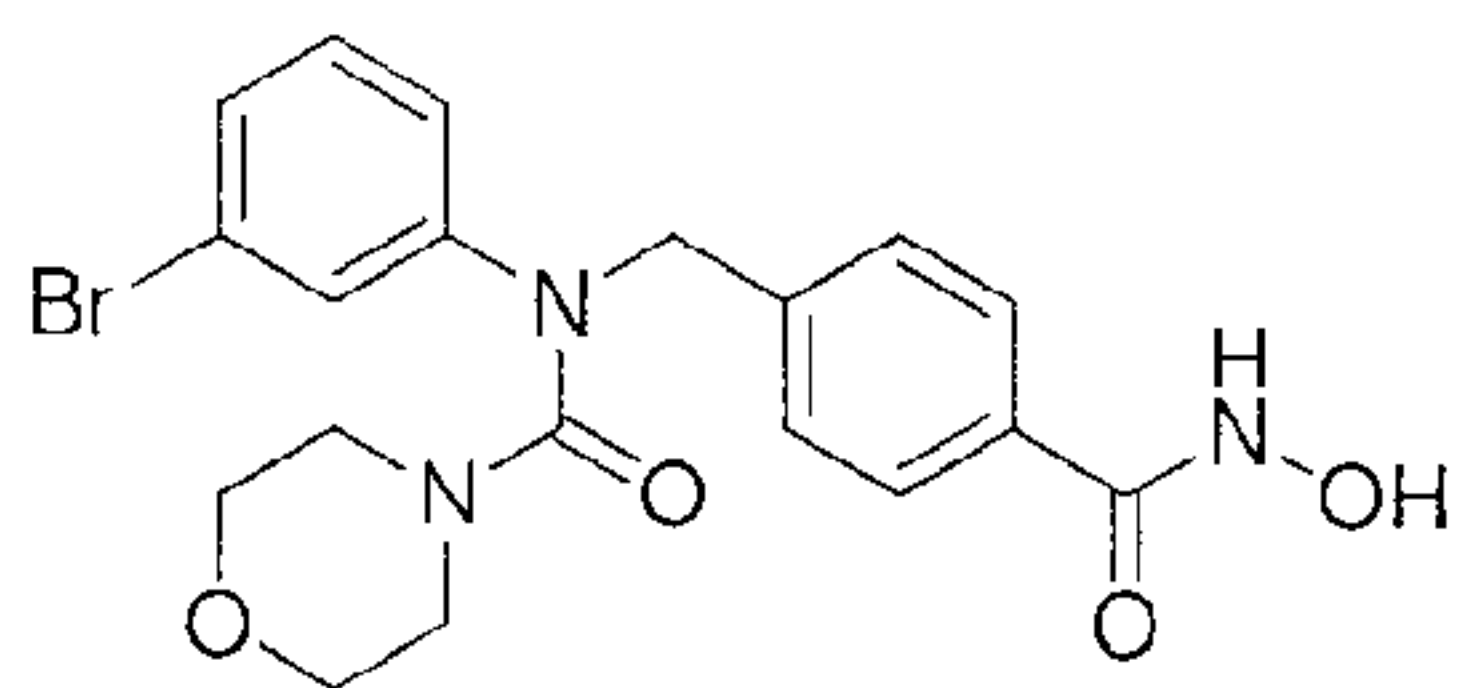


Compound of **Formula 1-3**

(methyl 4-(((3-bromophenyl)-(4-

nitrophenoxy)carbonyl)amino)methyl)benzoate; 1.5 g, 3.09 mmol) was dissolved in acetonitrile (50 ml), and potassium carbonate (1.28 g, 9.3 mmol) and morpholine (0.40 mL, 4.64 mmol) were slowly added. Then, the temperature was slowly raised and the mixture was stirred at 80 °C for 3 hours. The temperature was lowered to room temperature, and dimethylformamide (50 ml) was further added and stirred at 80 °C for 5 hours. Then, the reaction was completed, and the organic layer was washed three times with saturated ammonium chloride aqueous solution, dehydrated with sodium sulfate, and filtered. Then, the filtrate was then concentrated under reduced pressure, and the concentrate was purified by column chromatography (silica; ethyl acetate/hexane=0-50%) to give the desired compound of **Formula 1-4** (0.45 g, 33.6%) in the form of a transparent oil.

(Compound 255: N-(3-bromophenyl)-N-(4-(hydroxycarbonyl)benzyl)morpholine-4-carboxamide)



Compound of **Formula 1-4**

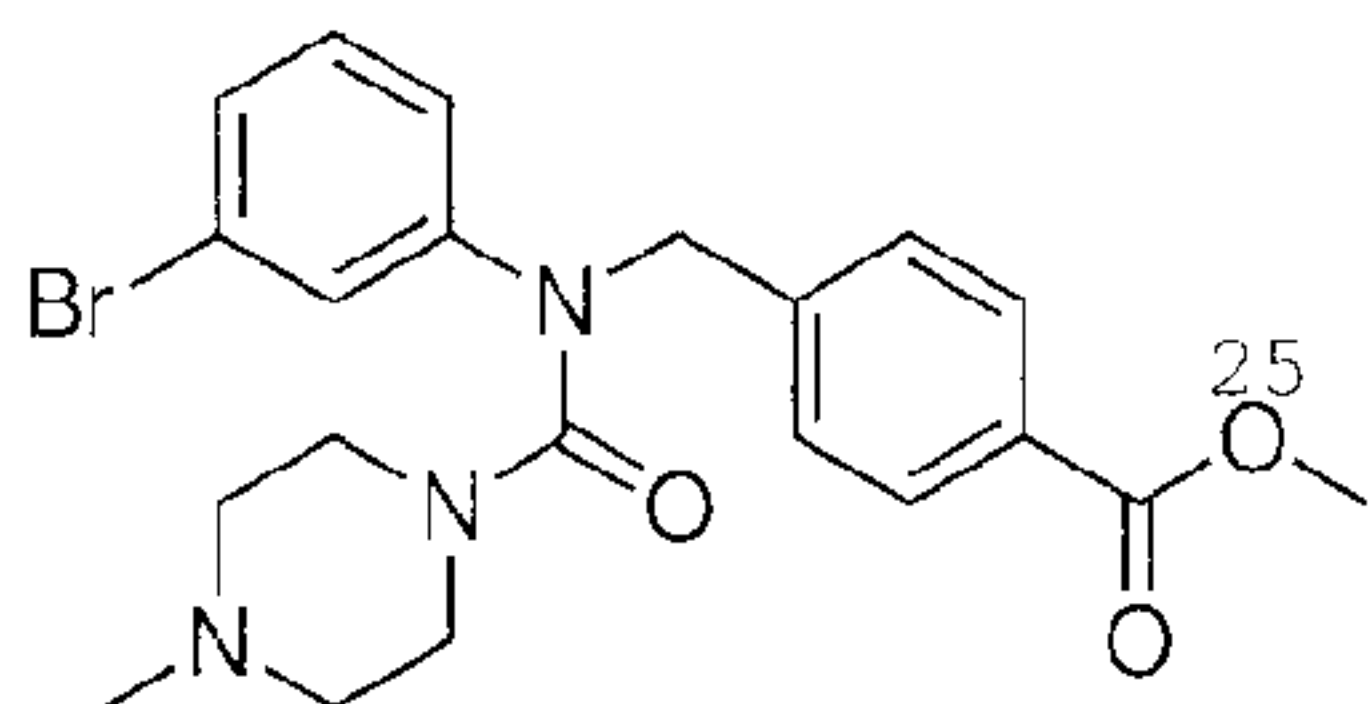
(methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.05 g, 0.12 mmol) was dissolved in methanol (2 ml), and hydroxylamine hydrochloride (0.040 g, 0.58 mmol) was slowly added. Then, potassium hydroxide

(0.065 g, 1.15 mmol) was added and stirred at room temperature for 10 minutes, and hydroxylamine (50.0 wt% aqueous solution; 0.14 mL, 2.31 mmol) was added. The mixture was stirred at room temperature for 1 day, and the organic solvent was then concentrated under reduced pressure and then neutralized by adding 2 N hydrochloric acid. Then, organic layer was washed three times with saturated sodium chloride aqueous solution, dehydrated with anhydrous sodium sulfate, and filtered, and the filtrate was then concentrated under reduced pressure. The concentrate was purified by column chromatography (silica; ethyl acetate/hexane=0-80%) to give the desired **Compound 255** (0.036 g, 72%) in the form of a white solid.

¹H NMR (400 MHz, CDCl₃-d₆) δ 7.63 (d, 2 H, *J* = 7.8 Hz), 7.27 - 7.20 (m, 4 H), 7.13 (t, 1 H, *J* = 7.8 Hz), 6.96 (d, 1 H, *J* = 7.1 Hz), 4.83 (s, 2 H), 3.49 (brs, 4 H), 3.23 (brs, 4 H); MS (ESI) *m/z* 436 (M⁺ + H).

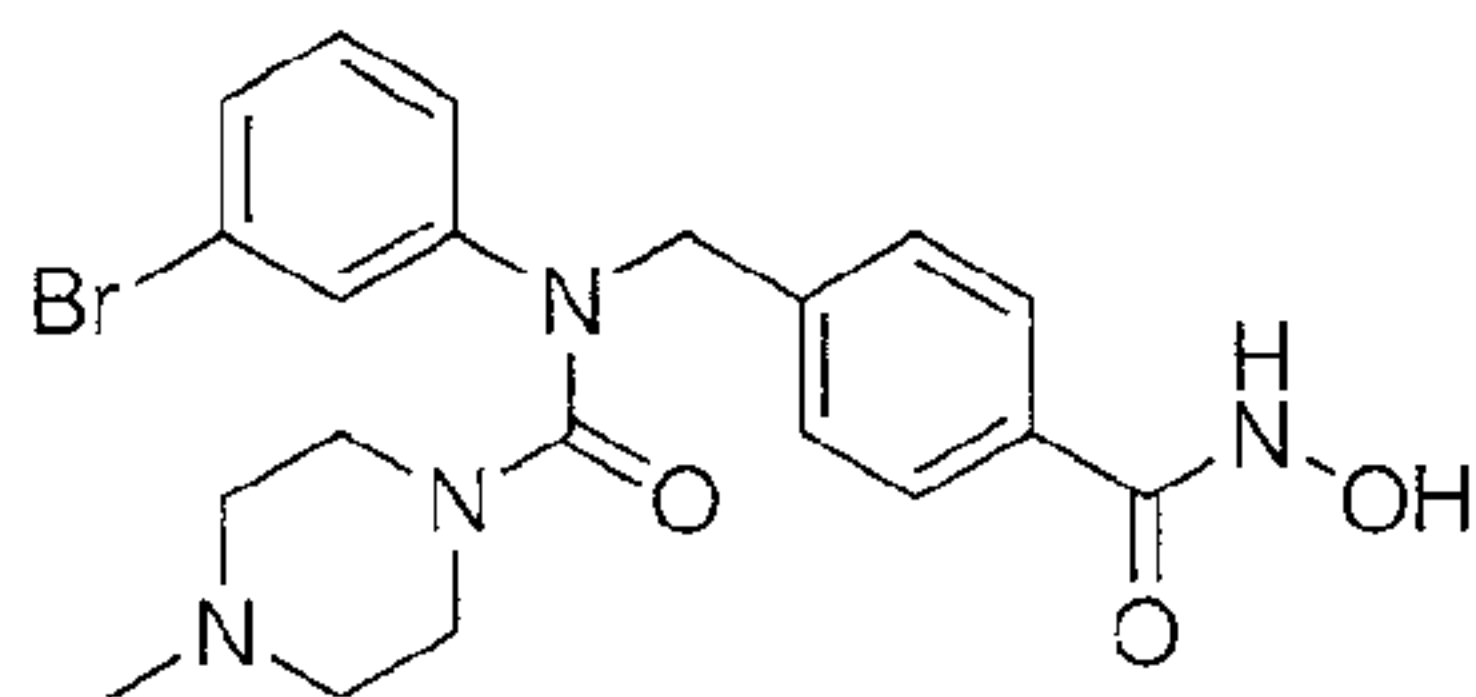
Example 5: Synthesis of Compound 256

(**Formula 1-4**: methyl 4-((N-(3-bromophenyl)-4-methylpiperazine-1-carboxamido)methyl)benzoate)



Compound of **Formula 1-3** (methyl 4-(((3-bromophenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate; 1.5 g, 3.09
 5 mmol) was dissolved in acetonitrile (50 ml), and potassium carbonate (1.28 g, 9.3 mmol) and 1-methylpiperazine (0.52 mL, 4.64 mmol) were slowly added. Then, the temperature was slowly raised and the mixture was stirred at 80 °C for 3 hours. The temperature was lowered to room temperature, and
 10 dimethylformamide (50 ml) was further added and stirred at 80 °C for 5 hours. Then, the reaction was completed, and the organic layer was washed three times with saturated ammonium chloride aqueous solution, dehydrated with sodium sulfate, and filtered. Then, the filtrate was then concentrated under
 15 reduced pressure, and the concentrate was purified by column chromatography (silica; ethyl acetate/hexane-0-50%) to give the desired compound of **Formula 1-4** (0.9 g, 65%) in the form of a transparent oil.

(Compound 256: N-(3-bromophenyl)-N-(4-(hydroxycarbonyl)benzyl)methylpiperazine-1-carboxamide)
 20



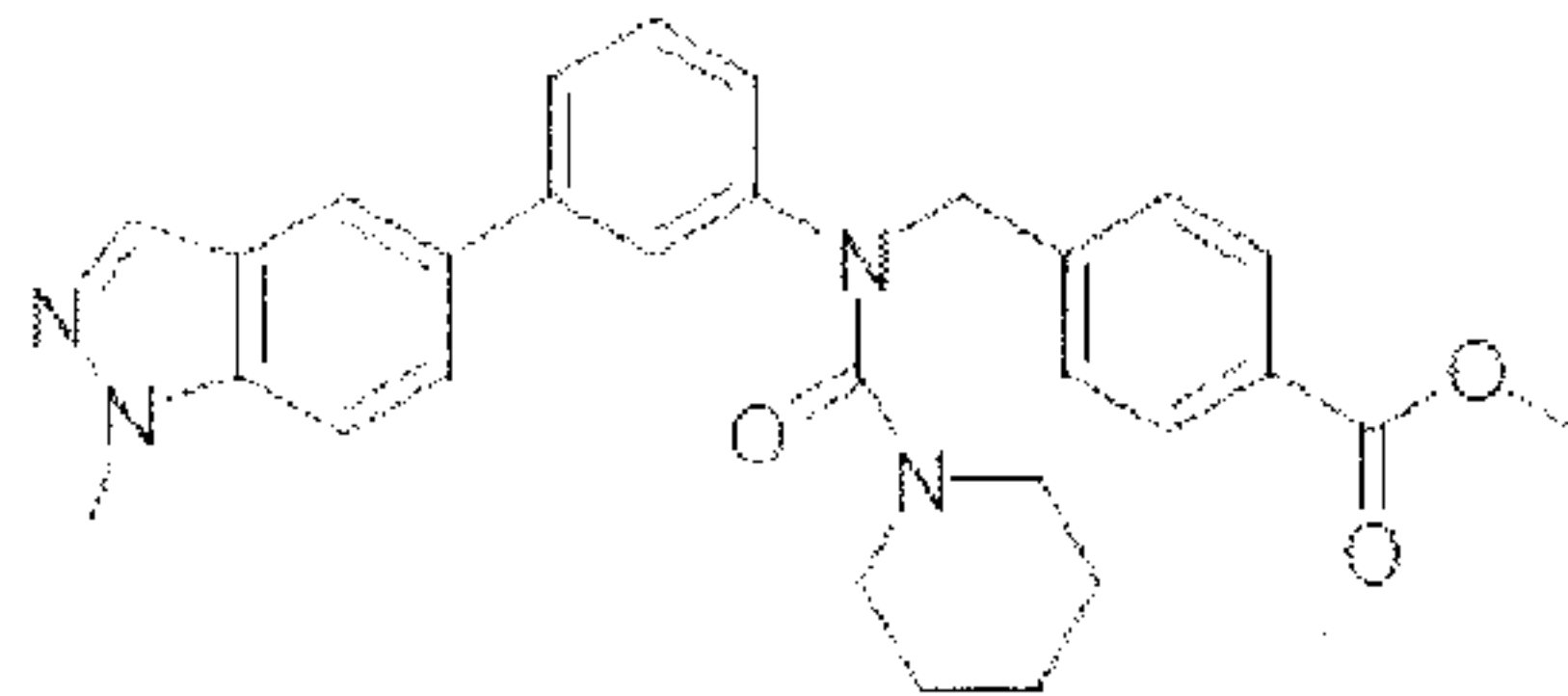
25 Compound of **Formula 1-4** (methyl 4-((N-(3-bromophenyl)-4-

methylpiperazine-1-carboxamido)methyl)benzoate; 0.05 g, 0.12
 mmol) was dissolved in methanol (2 ml), and hydroxylamine
 hydrochloride (0.039 g, 0.56 mmol) was slowly added. Then,
 potassium hydroxide (0.063 g, 1.12 mmol) was added and
 5 stirred at room temperature for 10 minutes, and hydroxylamine
 (50.0 wt% aqueous solution; 0.14 mL, 2.24 mmol) was added.
 The mixture was stirred at room temperature for 1 day, and
 the organic solvent was then concentrated under reduced
 pressure and then neutralized by adding 2 N hydrochloric acid.
 10 Then, organic layer was washed three times with saturated
 sodium chloride aqueous solution, dehydrated with anhydrous
 sodium sulfate, and filtered to give the desired **Compound 256**
 (0.05 g, 99%) in the form of a yellow solid.

¹H NMR (400 MHz, MeOD-d₃) δ 7.65 (d, 2 H, *J* = 8.2 Hz),
 15 7.39 (d, 2 H, *J* = 8.0 Hz), 7.30 – 7.09 (m, 4 H), 4.91 (brs, 2
 H), 3.26 (m, 4 H), 2.26 (m, 4 H), 2.22 (s, 3 H); **MS** (ESI) *m/z*
 449 (M⁺ + H).

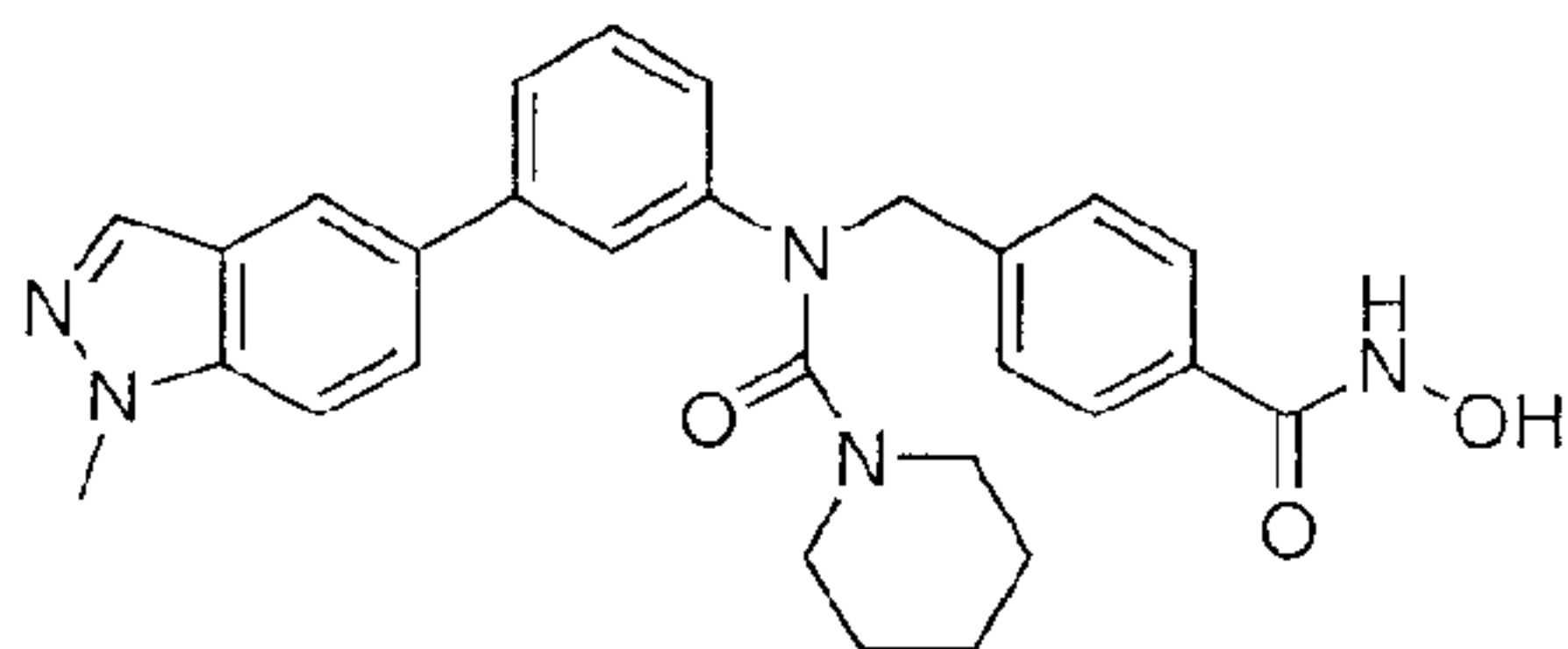
Example 6: Synthesis of Compound 260

20 **(Formula 3-3: methyl 4-((N-(3-(1-methyl-1H-indazol-5-
 yl)phenyl)piperidine-1-carboxamido)methyl)benzoate)**



Compound of **Formula 3-2** (methyl 4-(((3-(1-methyl-1H-indazol-5-yl)phenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.05 g, 0.093 mmol) was dissolved in dimethylformamide (3 mL), and then
 5 piperidine (0.012 mL, 0.14 mmol) and potassium carbonate (0.039 g, 0.28 mmol) were added. Then, the mixture was heated and stirred at 60 °C for 12 hours. Water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated
 10 sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane= 20-30 %) to give the desired compound of **Formula 3-3** (0.042 g, 93.4%) in
 15 the form of a colorless liquid.

(Compound 260: N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-methyl-1H-indazol-5-yl)phenyl)piperidine-1-carboxamide)



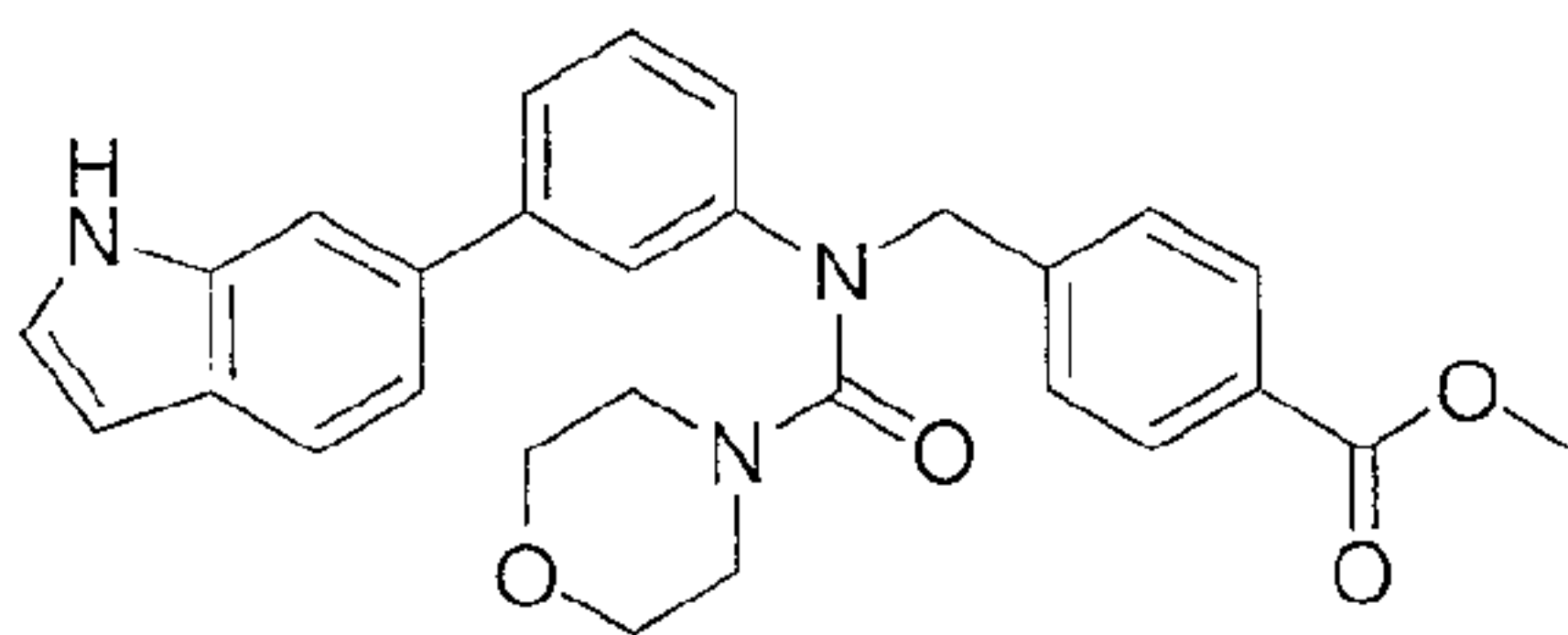
Compound of **Formula 3-3** (methyl 4-((N-(3-(1-methyl-1H-indazol-5-yl)phenyl)piperidine-1-carboxamido)methyl)benzoate;
 20 0.042 g, 0.087 mmol) was dissolved in methanol (5 mL), and

then hydroxylamine hydrochloride (0.030 g, 0.435 mmol),
 potassium hydroxide (0.049 g, 0.87 mmol), and hydroxylamine
 (50 wt% aqueous solution; 0.224 mL, 1.74 mmol) were added
 dropwise and stirred at room temperature for 6 hours. After
 5 completion of the reaction, the methanol was removed under
 reduced pressured, and then 2 N hydrogen chloride was added
 to precipitate a solid. Then, the resulting solid was
 filtered and dried to give the desired **Compound 260** (0.036 g,
 85.5%) in the form of a white solid.

10 ¹H NMR (400 MHz, DMSO-d₆) δ 8.08 (s, 1 H), 7.95 (s, 1 H),
 7.71 - 7.64 (m, 4 H), 7.37 - 7.36 (m, 5 H), 7.04 - 7.03 (m, 1
 H), 4.90 (s, 2 H), 4.05 (s, 3 H), 3.18 - 3.17 (m, 4 H), 1.42
 - 1.41 (m, 2 H), 1.29 - 1.28 (m, 4 H); **MS** (ESI) m/z 483.56
 (M⁺ + H).

15 **Example 7: Synthesis of Compound 261**

(**Formula 2-2**: methyl 4-((N-(3-(1H-indol-6-
 yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)

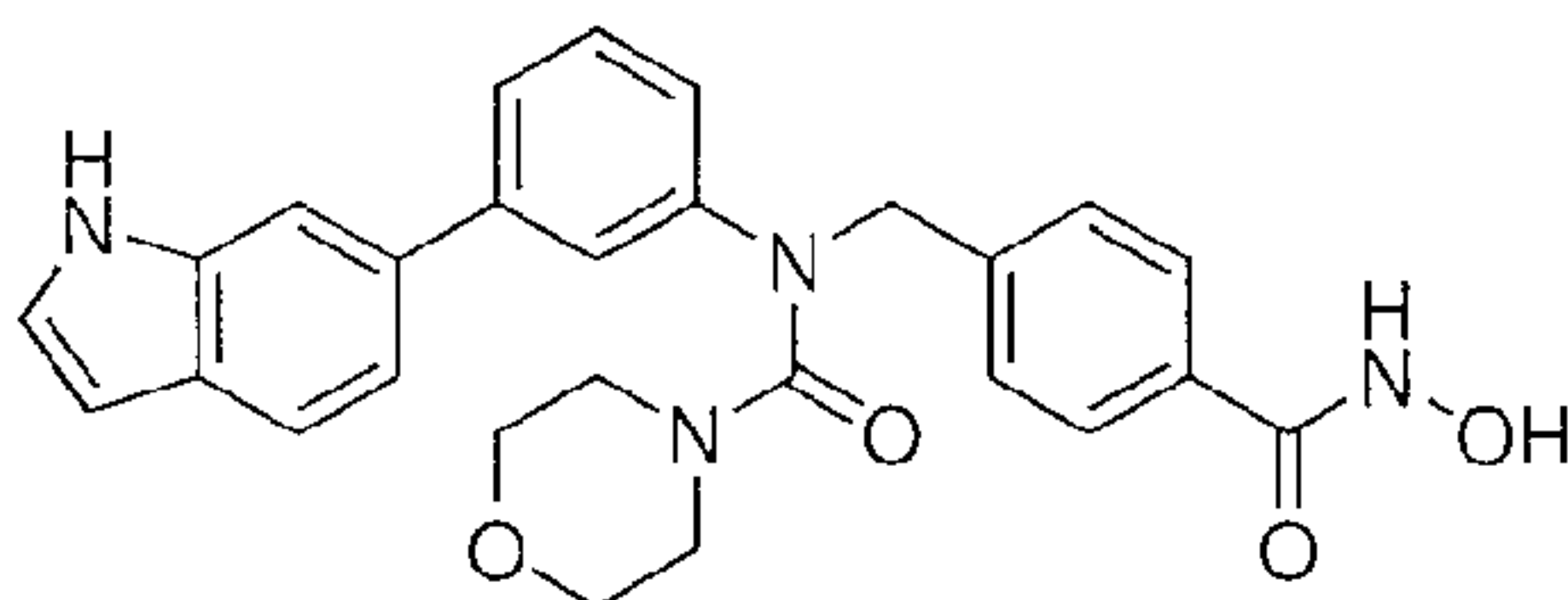


Compound of **Formula**

2-1 (methyl 4-((N-(3-bromophenyl)morpholine-4-
 carboxamido)methyl)benzoate; 0.12 g, 0.28 mmol) was placed in
 25 a microwave reactor, and then dimethoxyethane (5 mL) was

added. Then, indole-6-boronic acid (0.054 g, 0.33 mmol) and Pd(dppf)Cl₂ (0.023 g, 0.028 mmol) were slowly added, and saturated sodium carbonate aqueous solution (0.093 g, 0.61 mmol) was then added. The mixture was stirred at 120 °C for 15 minutes under microwave irradiation, and then the reaction was completed. After washing three times with saturated sodium chloride aqueous solution, the organic layer was dehydrated with sodium sulfate, filtered, and concentrated. Then, the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (silica; ethyl acetate/hexane=0-80%) to give the desired compound of **Formula 2-2** (0.091 g, 70%) in the form of a white solid.

(**Compound 261**: N-(3-(1H-indol-6-yl)phenyl)-N-(4-(hydroxycarbonyl)benzyl)morpholine-4-carboxamide)

Compound of **Formula**

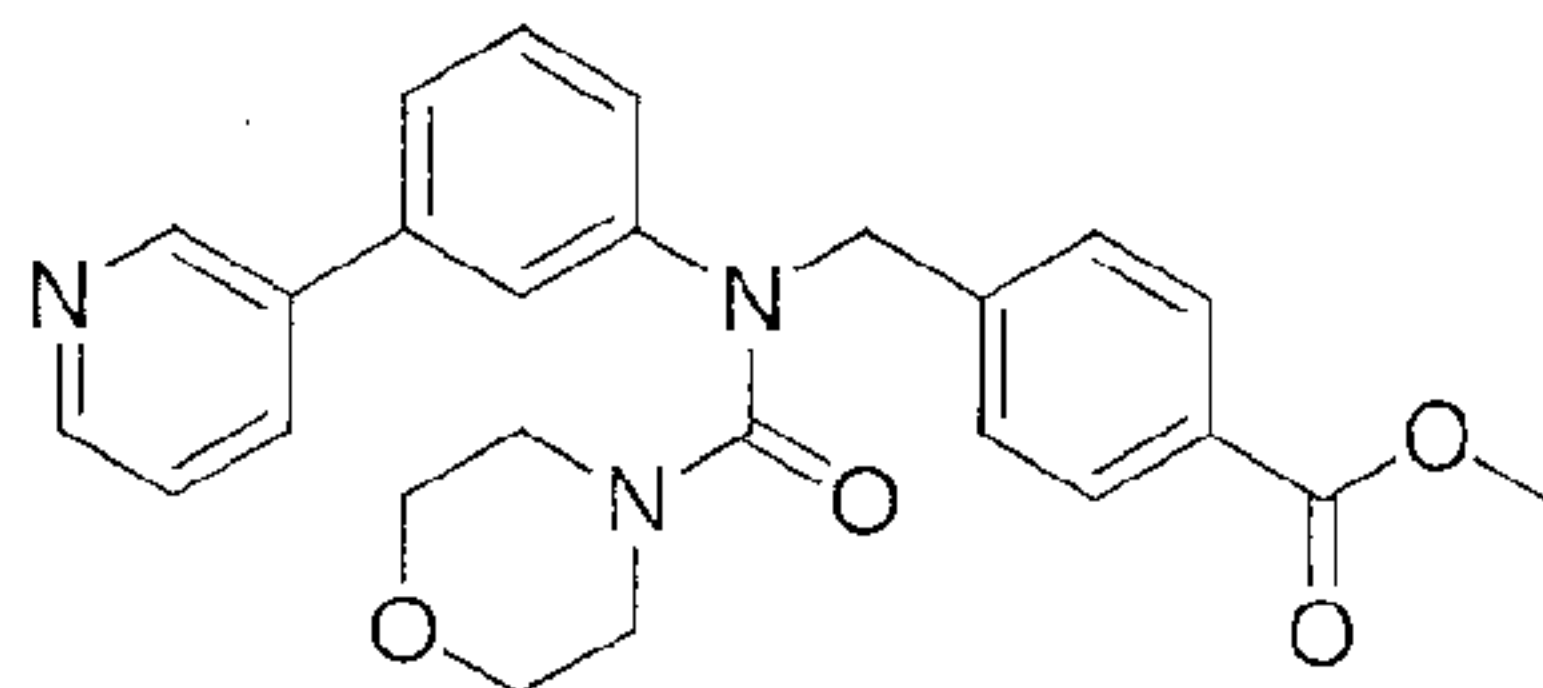
2-2 (methyl 4-((N-(3-(1H-indol-6-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.09 g, 0.19 mmol) was dissolved in methanol (10 mL), and then hydroxylamine hydrochloride (0.067 g, 0.96 mmol) was slowly added. Then, potassium hydroxide (0.11 g, 1.92 mmol) was added and stirred at room temperature for 10 minutes, and then hydroxylamine (50.0 wt%

aqueous solution; 0.23 mL, 3.83 mmol) was added and stirred at room temperature for 1 day. The organic solvent was concentrated under reduced pressure and then neutralized by adding 2 N hydrochloric acid. Then, the produced solid was
 5 filtered and dried to give the desired **Compound 261** (0.05 g, 55%) in the form of a yellow solid.

¹H NMR (400 MHz, CDCl₃-d₆) δ 7.65 (d, 2 H, *J* = 8.2 Hz), 7.60 – 7.57 (m, 2 H), 7.40 – 7.36 (m, 6 H, *J* = 7.8 Hz), 7.24 (d, 1 H, *J* = 8.2 Hz), 7.09 – 7.07 (m, 1 H), 6.43 (s, 1 H),
 10 4.93 (s, 2 H), 3.50 (m, 4 H), 4.93 (m, 4 H), 2.49 (s, 3H); **MS** (ESI) *m/z* 471 (*M*⁺ + H).

Example 8: Synthesis of Compound 262

(**Formula 2-2**: methyl 4-((N-(3-(pyridin-3-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)
 15

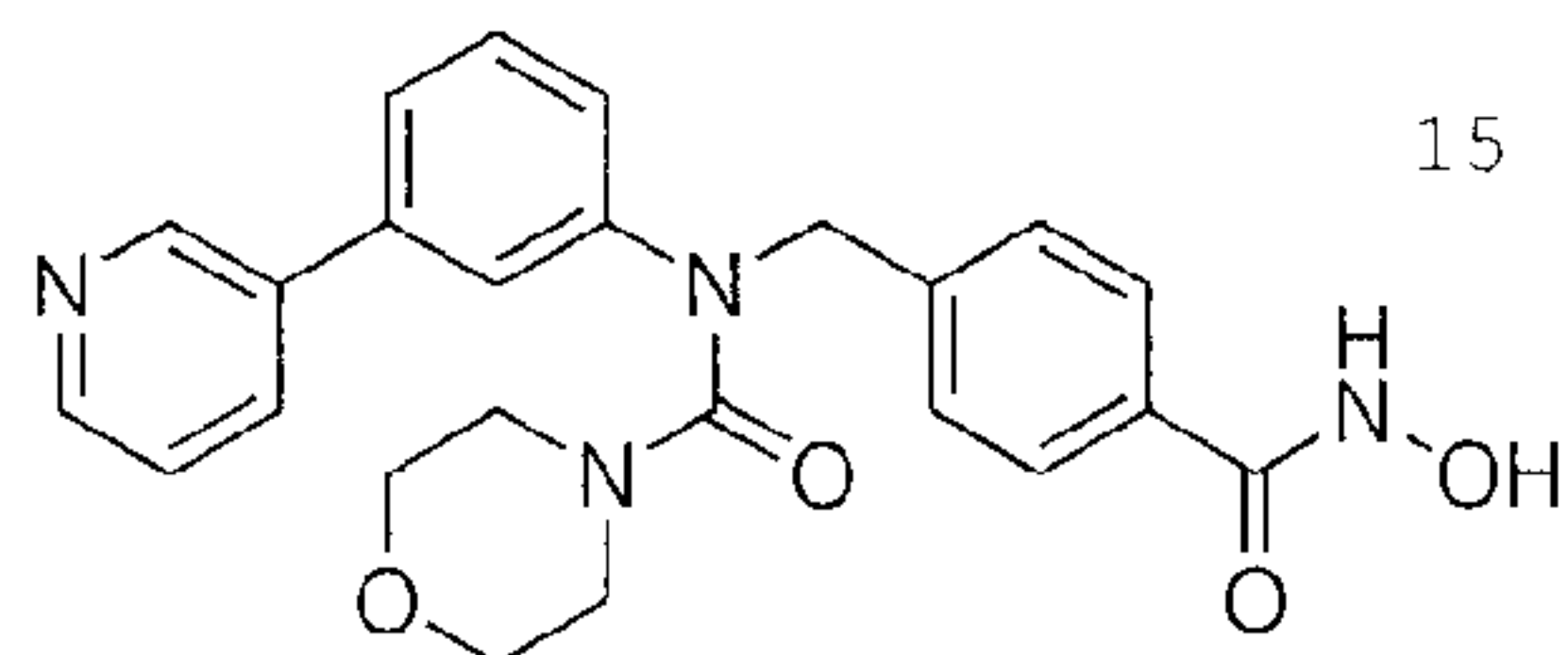


20

Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.11 g, 0.25 mmol) was placed in a microwave reactor, and then dimethoxyethane (5 mL) was added. Then, pyridine-3-boronic
 25 acid (0.037 g, 0.31 mmol) and Pd(dppf)Cl₂ (0.021 g, 0.025

mmol) were slowly added, and saturated sodium carbonate aqueous solution (0.085 g, 0.56 mmol) was then added. The mixture was stirred at 120 °C for 15 minutes under microwave irradiation, and then the reaction was completed. After
 5 washing three times with saturated sodium chloride aqueous solution, the organic layer was dehydrated with sodium sulfate, filtered, and concentrated. Then, the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (silica; ethyl
 10 acetate/hexane=0-80 %) to give the desired compound of **Formula 2-2** (0.064 g, 58%) in the form of a whit solid.

(**Compound 262**: N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(pyridin-3-yl)phenyl)morpholine-4-carboxamide)



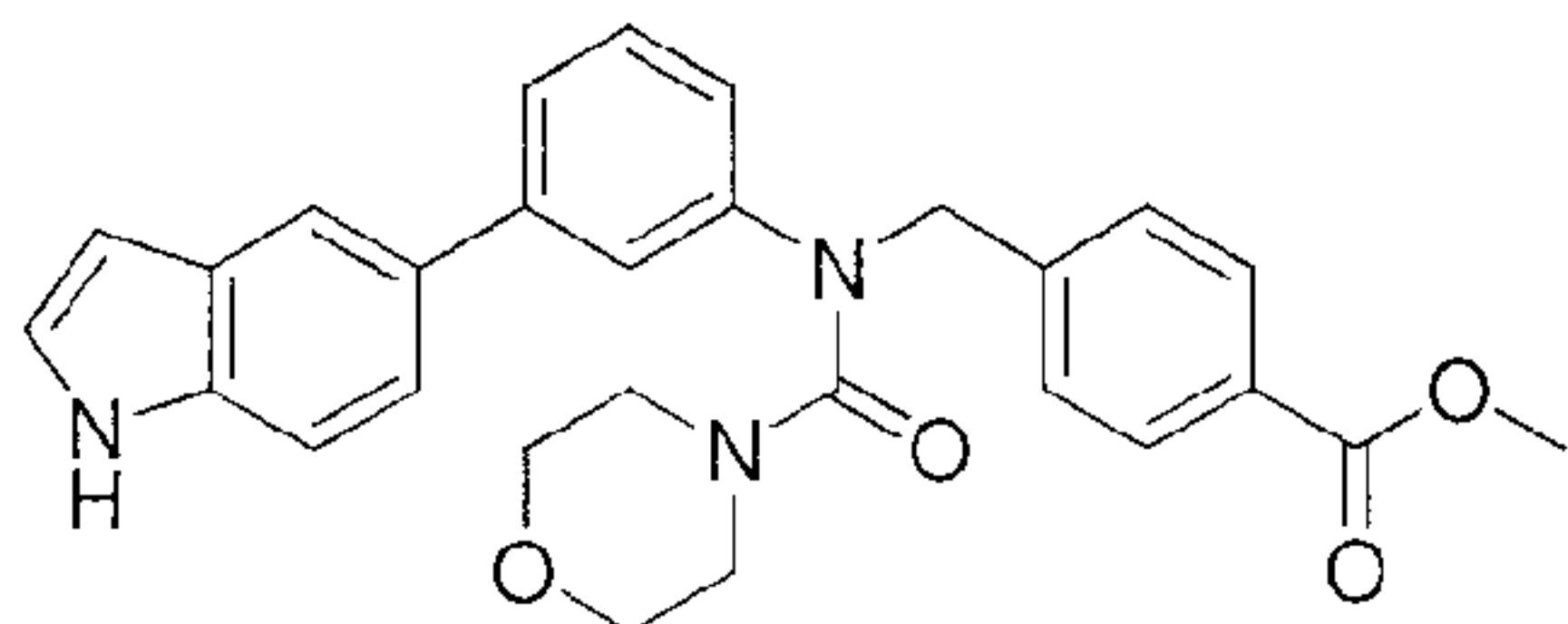
Compound of **Formula 2-2** (methyl 4-((N-(3-(pyridin-3-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.06 g,
 20 0.14 mmol) was dissolved in methanol (10 mL), and then hydroxylamine hydrochloride (0.048 g, 0.70 mmol) was slowly added. Then, potassium hydroxide (0.078 g, 1.40 mmol) was added and stirred at room temperature for 10 minutes, and
 25 then hydroxylamine (50.0 wt% aqueous solution; 0.17 mL, 2.78

mmol) was added and stirred at room temperature for 1 day. The organic solvent was concentrated under reduced pressure and then neutralized by adding 2 N hydrochloric acid. The organic layer was washed with ether and three times with
 5 saturated sodium chloride aqueous solution, dehydrated with anhydrous sodium sulfate, and then filtered to give the desired **Compound 262** (0.045 g, 75%) in the form of a white solid.

¹H NMR (400 MHz, MeOD-d₃) δ 8.86 (s, 1 H), 8.64 (d, 1 H, *J* = 4.0 Hz), 8.29 (d, 1 H, *J* = 8.1 Hz), 7.24 - 7.26 (m, 9 H),
 10 5.02 (m, 4 H), 3.30 (m, 4 H); **MS** (ESI) *m/z* 433 (*M*⁺ + H).

Example 9: Synthesis of Compound 263

(**Formula 2-2**: methyl 4-((N-(3-(1H-indole-5-
 15 yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)

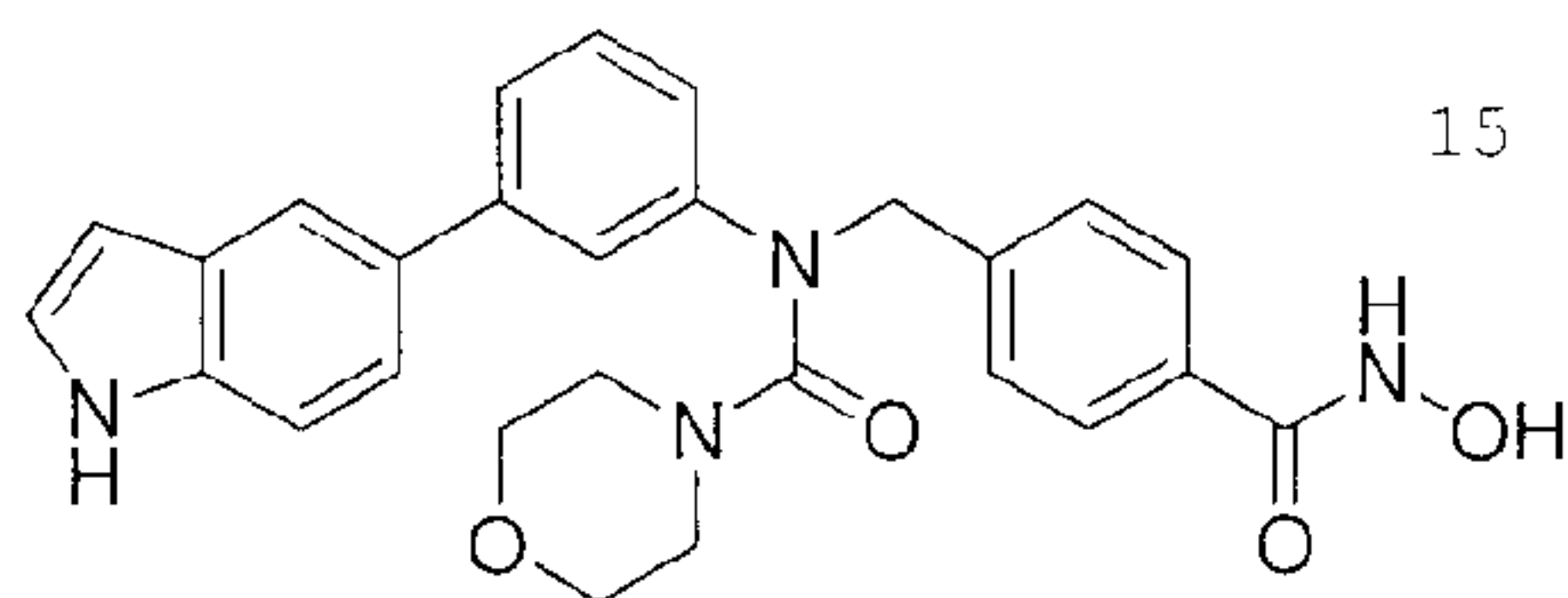


20

Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.05 g, 0.12 mmol) was placed in a microwave reactor, and then dimethoxyethane (5 mL) was added. Then, indole-5-boronic
 25 acid (0.023 g, 0.14 mmol) and Pd(dppf)Cl₂ (0.009 g, 0.012

mmol) were slowly added, and saturated sodium carbonate aqueous solution (0.039 g, 0.25 mmol) was then added. The mixture was stirred at 120 °C for 15 minutes under microwave irradiation, and then the reaction was completed. After
 5 washing three times with saturated sodium chloride aqueous solution, the organic layer was dehydrated with sodium sulfate, filtered, and concentrated. Then, the filtrate was concentrated under reduced pressure. The concentrate was purified by column chromatography (silica; ethyl
 10 acetate/hexane=0-80 %) to give the desired compound of **Formula 2-2** (0.040 g, 74%) in the form of a whit solid.

(**Compound 263**: N-(3-(1H-indol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide)



Compound of **Formula 2-2** (methyl 4-((N-(3-(1H-indole-5-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.040 g,
 20 0.085 mmol) was dissolved in methanol (2 mL), and then hydroxylamine hydrochloride (0.030 g, 0.43 mmol) was slowly added. Then, potassium hydroxide (0.48 g, 0.85 mmol) was added and stirred at room temperature for 10 minutes, and
 25 then hydroxylamine (50.0 wt% aqueous solution; 0.11 mL, 1.70

mmol) was added and stirred at room temperature for 1 day.

The organic solvent was concentrated under reduced pressure and then neutralized by adding 2 N hydrochloric acid. Then, the produced solid was filtered and dried to give the desired

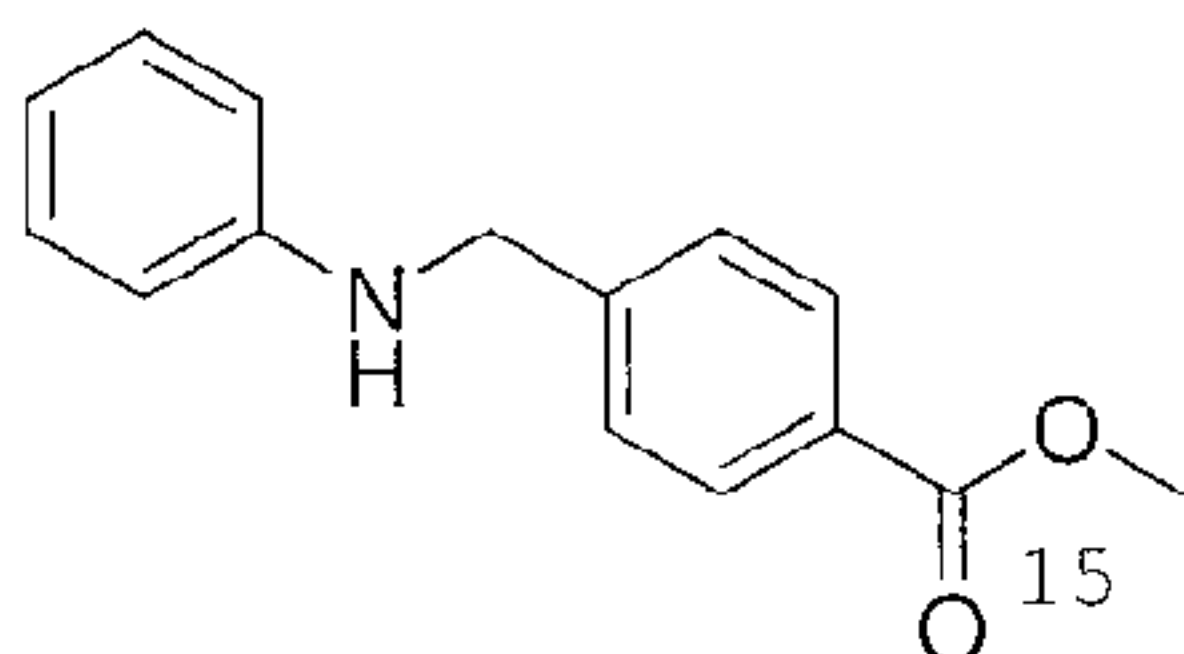
5 **Compound 263** (0.03 g, 82%) in the form of a yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 8.99 (brs, 1 H), 7.75 (s, 1 H), 7.64 (d, 1 H, *J* = 7.8 Hz), 7.44 – 7.05 (m, 9 H), 6.46 (s, 1 H), 4.93 (s, 2 H), 3.39 (m, 4 H), 3.17 (m, 4 H); **MS** (ESI) *m/z* 471 (M⁺ + H).

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Example 10: Synthesis of Compound 279

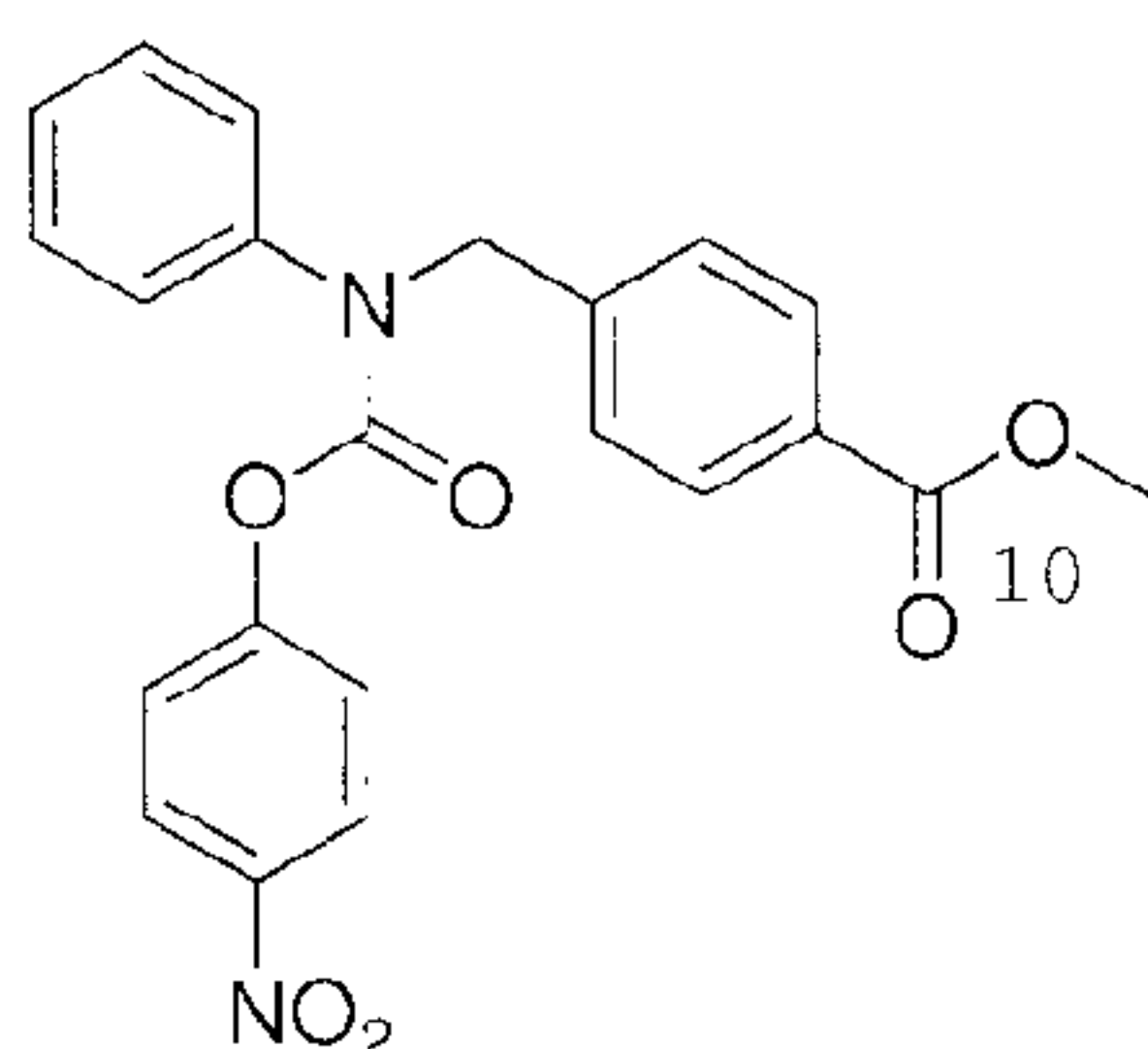
(**Formula 1-2**: methyl 4-((phenylamino)methyl)benzoate)



Compound of **Formula 1-1** (aniline; 0.20 g, 2.15 mmol) was dissolved in dichloroethane (10 mL), and then triethylamine (0.45 mL, 3.22 mmol) was slowly added. Then, methyl 4-
 20 (bromomethyl)benzoate (0.74 g, 3.22 mmol) was added, the temperature was slowly raised to 60 °C, and the mixture was stirred for 1 hour. The reaction was completed, and the organic layer was washed three times with saturated sodium chloride aqueous solution, dehydrated with anhydrous sodium
 25 sulfate, and then filtered. The filtrate was concentrated

under reduced pressure, and then the concentrate was purified by column chromatography (silica; ethyl acetate/hexane= 0-50%) to give the desired compound of **Formula 1-2** (0.15 g, 29%) in the form of a yellow oil.

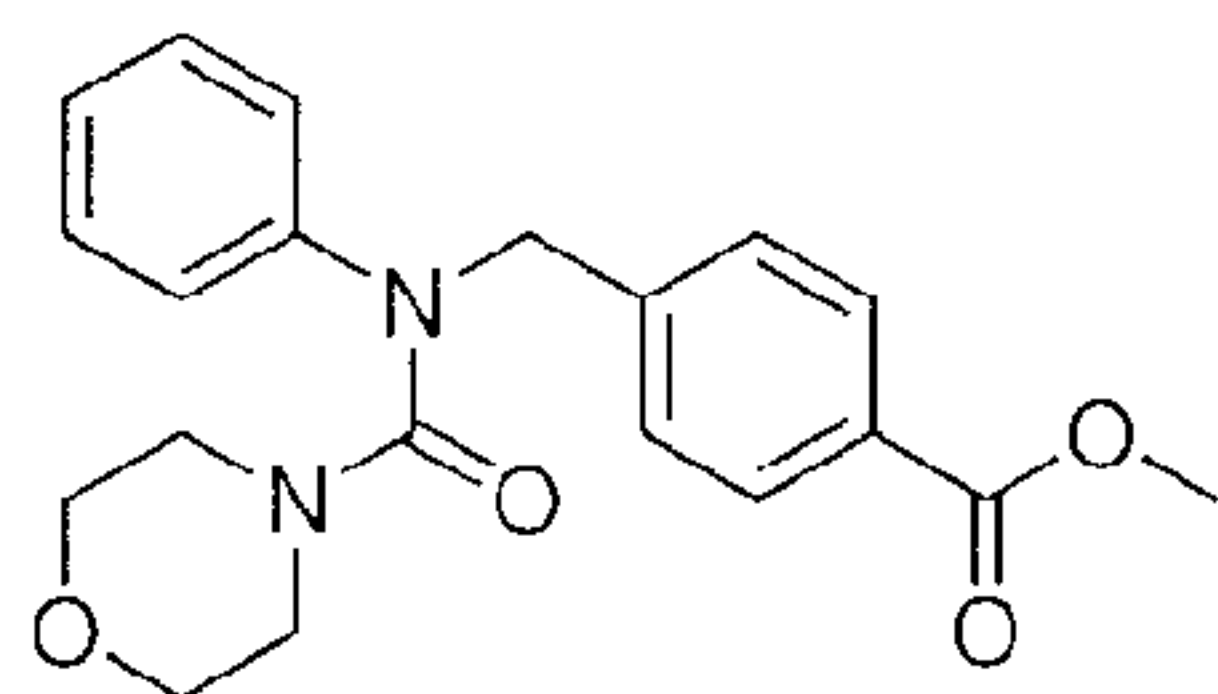
5 **(Formula 1-3: methyl 4-((((4-nitrophenoxy)carbonyl)(phenyl)amino)methyl)benzoate)**



Compound of Formula 1-2 (methyl 4-
 15 ((phenylamino)methyl)benzoate; 0.15 g, 0.62 mmol) was dissolved in acetonitrile (3 mL), and then potassium carbonate (0.17 g, 1.24 mmol) was slowly added and stirred at room temperature for 10 minutes. Then, 4-nitrophenyl
 chloroformate (0.14 g, 0.68 mmol) was added, the temperature
 20 was slowly raised to 50 °C, and the mixture was stirred for 12 hours. After completion of the reaction, the solvent was evaporated under reduced pressure, and the ethyl acetate layer was washed three times with saturated sodium chloride aqueous solution, and then the organic layer was dehydrated
 25 with sodium sulfate, and then filtered. The filtrate was

concentrated under reduced pressure, and then the concentrate was purified by column chromatography (silica; ethyl acetate/hexane=0-20%) to give the desired compound of **Formula 1-3** (0.18 g, 71%) in the form of a transparent oil.

5 **(Formula 1-3: methyl 4-((N-(phenylmorpholine-4-carboxamido)methyl)benzoate)**

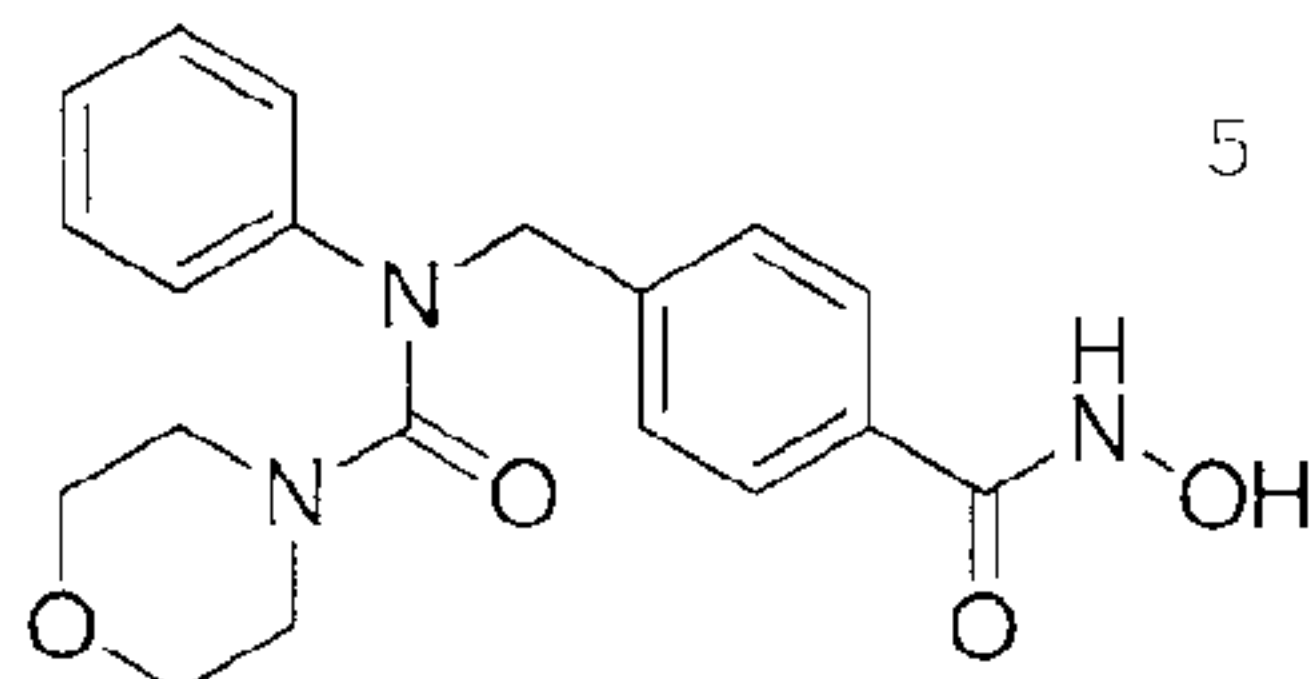


10

Compound of **Formula 1-4** (methyl 4-(((4-nitrophenoxy)carbonyl)(phenyl)amino)methyl)benzoate; 0.18 g, 0.44 mmol) was dissolved in dimethylformamide (5 mL), and then potassium carbonate (0.18 g, 1.33 mmol) and morpholine
 15 (0.060 g, 0.67 mmol) were slowly added. The temperature was lowered to room temperature, and dimethylformamide (50 ml) was further added. Then, the temperature was slowly raised to 80 °C, and the mixture was stirred for 3 hours. Then, the temperature was raised again to 80 °C, and the mixture was
 20 stirred for 5 hours. The reaction was completed, and the organic layer was washed three times with saturated ammonium chloride aqueous solution, dehydrated with sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the concentrate was purified by column
 25 chromatography (silica; ethyl acetate/hexane=0-50%) to give

the desired compound of **Formula 1-4** (0.10 g, 64%) in the form of a pale yellow solid.

(Compound 279: N-(4-(hydroxycarbamoyl)benzyl)-N-phenylmorpholine-4-carboxamide)



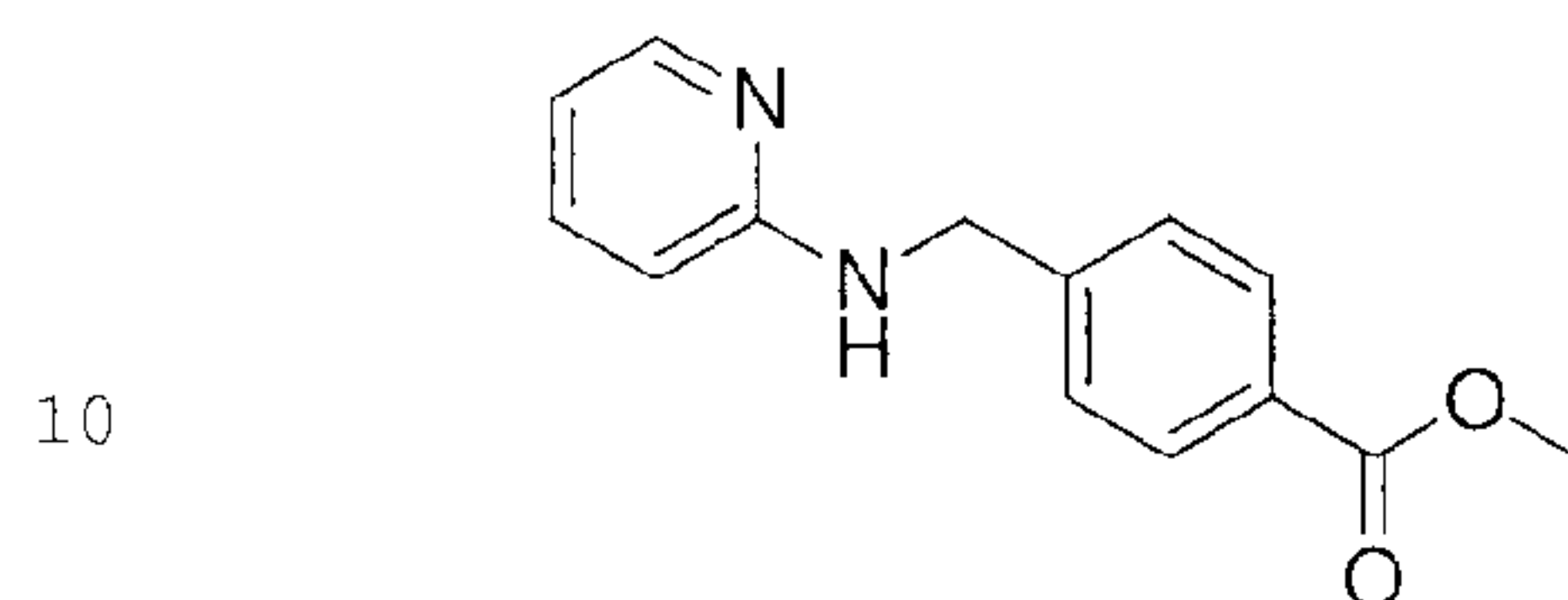
Compound of **Formula 1-4** (methyl 4-((N-phenylmorpholine-4-carboxamido)methyl)benzoate; 0.15 g, 0.42 mmol) was dissolved in methanol (5 ml), and then hydroxylamine hydrochloride (0.15 g, 2.12 mmol) was slowly added. Then, potassium hydroxide (0.24 g, 4.23 mmol) was added and stirred at room temperature for about 10 minutes, and then hydroxylamine (50.0 wt% aqueous solution; 0.56 mL, 8.46 mmol) was added and stirred at room temperature for 1 day. The organic solvent was concentrated under reduced pressure, washed twice with ether after adding water, neutralized by adding 2 N hydrochloric acid, and then further extracted with ethyl acetate. Then, the organic layer was washed twice with saturated sodium chloride aqueous solution, dehydrated with anhydrous sodium sulfate, and then filtered to give the desired **Compound 279** (0.080 g, 53%) in the form of a white solid.

¹H NMR (400 MHz, MeOD-d₃) δ 7.66 (d, 2 H, J = 8.1 Hz),

7.41 (d, 2 H, $J = 8.1$ Hz), 7.34 (t, 2 H, $J = 7.8$ Hz), 7.15 (d, 2 H, $J = 8.4$ Hz), 4.92 (s, 2 H), 3.46 (t, 4 H, $J = 4.7$ Hz), 3.22 (t, 4 H, $J = 4.7$ Hz); **MS** (ESI) m/z 356 ($M^+ + H$).

5 **Example 11: Synthesis of Compound 280**

(**Formula 7-4**: methyl 4-((pyridin-2-ylamino)methyl)benzoate)



Compound of **Formula 7-3**

(pyridin-2-amine, 0.2 g, 2.13 mmol) was dissolved in methanol (10 mL), and then methyl 4-formylbenzoate (0.35 g, 2.13 mmol) was added and stirred at room temperature for 20 minutes.

15 Then, sodium cyanoborohydride (0.13 g, 2.13 mmol) and acetic acid (0.12 mL, 2.13 mmol) were slowly added and stirred at room temperature for 5 hours. The organic layer was washed three times with saturated sodium chloride aqueous solution, dehydrated with sodium sulfate, and then filtered. The

20 filtrate was concentrated under reduced pressure, and the concentrate was purified by column chromatography (silica; ethyl acetate/hexane=0-30%) to give the desired compound of **Formula 7-4** (0.10 g, 19%) in the form of a transparent oil.

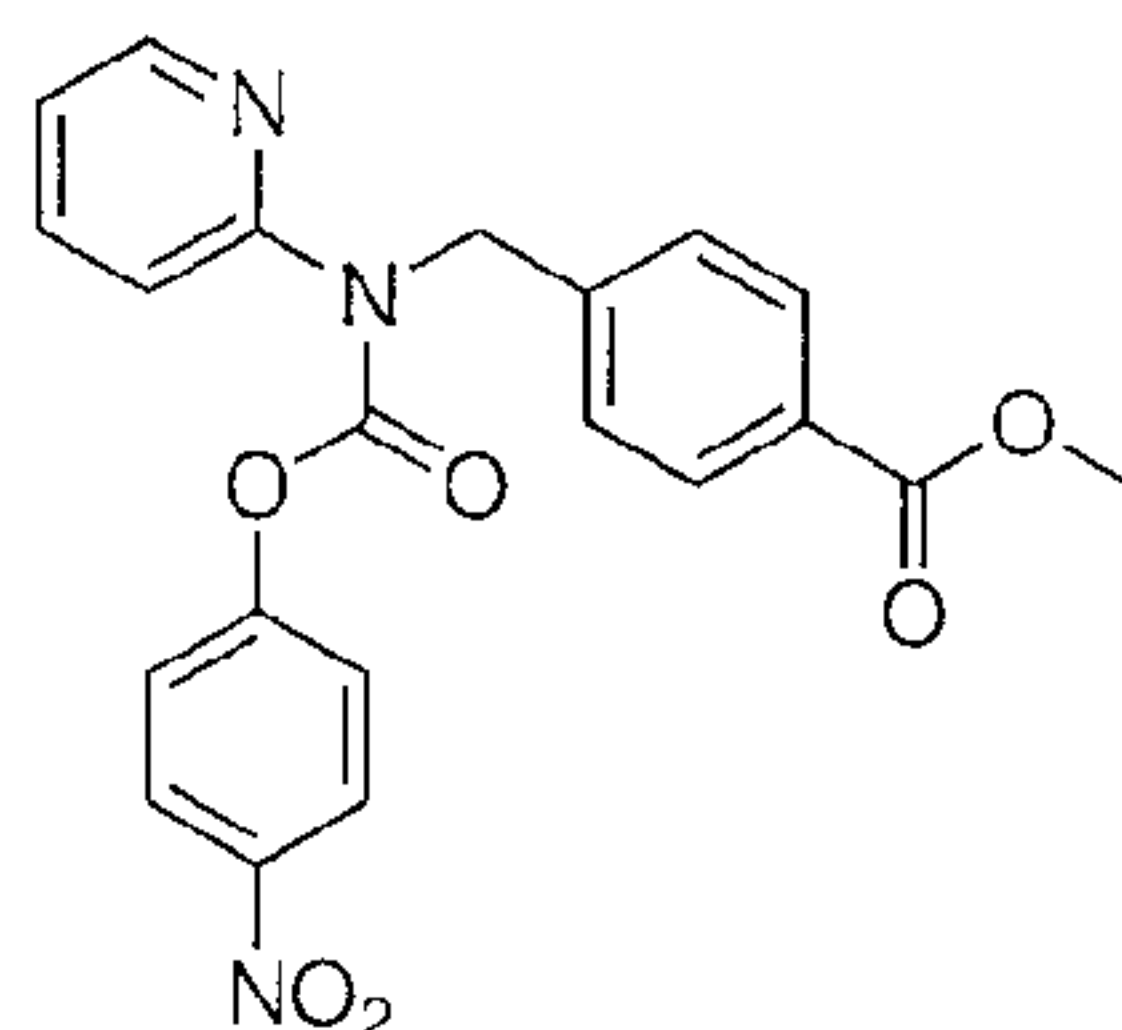
¹H NMR (400 MHz, CDCl₃) δ 8.17 (d, 1 H, $J = 5.8$ Hz), 8.06 (d, 2 H, $J = 8.4$ Hz), 7.66 (t, 1 H, $J = 7.8$ Hz), 7.44 (d, 2 H,

25

$J = 8.0$ Hz), 6.76 (t, 1 H, $J = 6.7$ Hz), 6.58 (d, 1 H, $J = 8.6$ Hz), 4.67 (d, 2 H, $J = 6.0$ Hz), 3.92 (s, 3 H)

(Formula 7-5: methyl 4-(((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate)

5



10

Formula 7-4 (methyl 4-

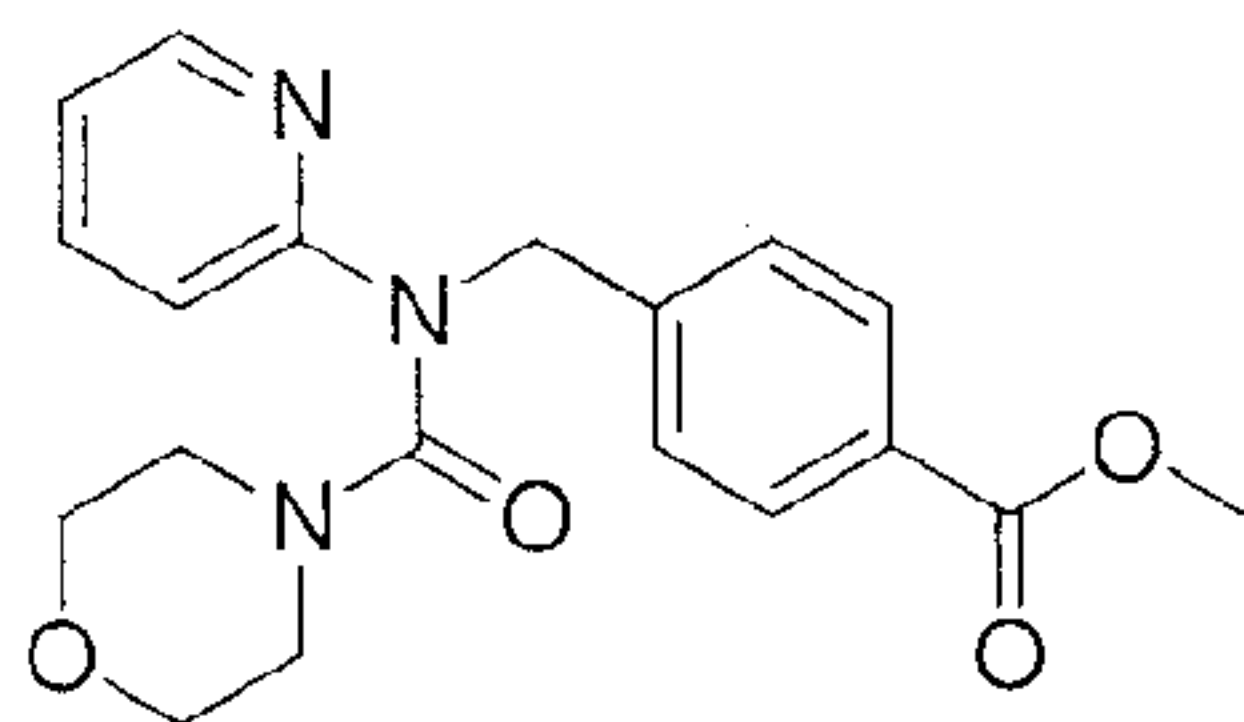
((pyridin-2-ylamino)methyl)benzoate; 0.040 g, 0.16 mmol) was dissolved in dimethylformamide (3 mL), and then potassium carbonate (0.046 g, 0.33 mmol) was slowly added. Then, 4-nitrophenyl chloroformate (0.037 g, 0.18 mmol) was added, the temperature was slowly raised to 50 °C, and the mixture was stirred for 2 days hours. After completion of the reaction, the ethyl acetate layer was washed three times with saturated ammonium chloride aqueous solution, and then the organic layer was dehydrated with sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and then the concentrate was purified by column chromatography (silica; ethyl acetate/hexane=0-50%) to give the desired compound of **Formula 7-5** (0.048 g, 71%) in the form of a yellow oil.

25

¹H NMR (400 MHz, CDCl₃) δ 8.49 – 8.48 (m, 1 H), 8.24 (dd, 2 H, J = 7.0, 2.2 Hz), 8.17 (dd, 2 H, J = 7.2, 2.0 Hz), 8.00 (d, 2 H, J = 8.4 Hz), 7.78 (t, 1 H, J = 3.8 Hz), 7.44 (d, 2 H, J = 8.0 Hz), 6.91 (dd, 2 H, J = 7.3, 2.1 Hz), 5.39 (brs, 2 H), 3.92 (s, 3 H); MS (ESI) m/z 408 (M⁺ + H)

(Formula 7-6: methyl 4-((N-(pyridin-2-yl)morpholine-4-carboxamido)methyl)benzoate)

10



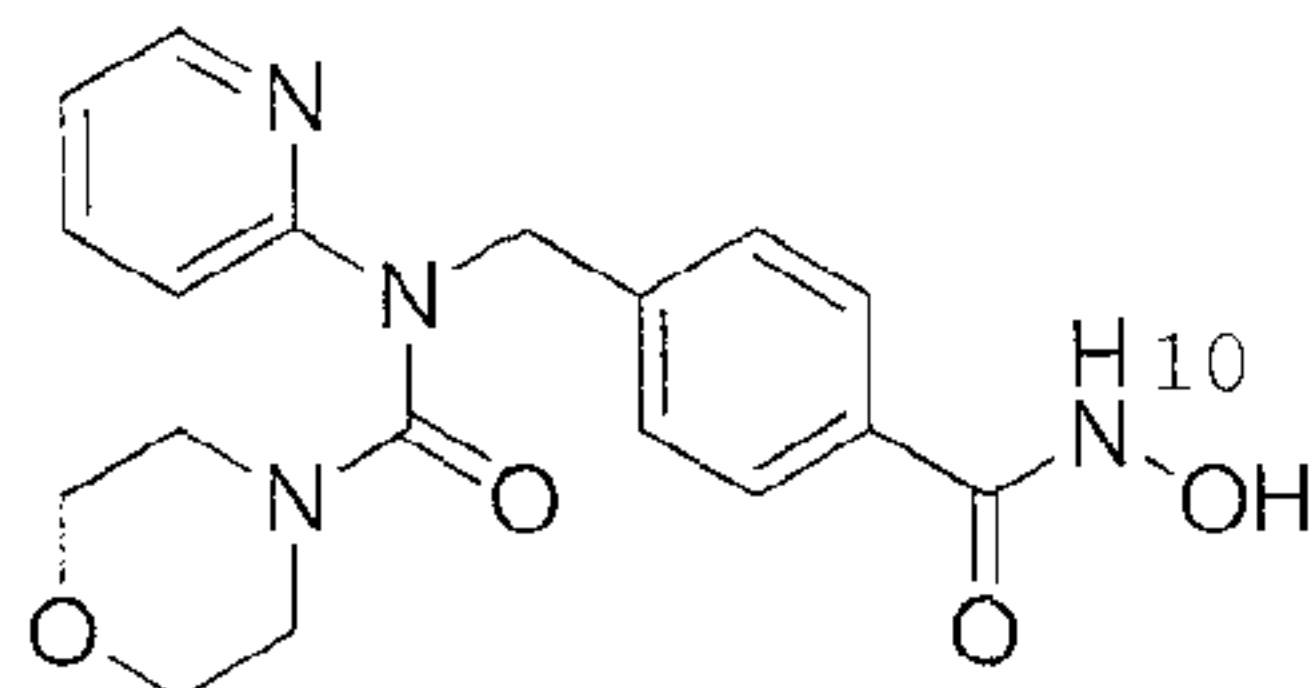
Compound of Formula 7-5

(methyl 4-(((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate; 0.040 g, 0.098 mmol) was dissolved in dimethylformamide (5 ml), and then potassium carbonate (0.040 g, 0.30 mmol) and morpholine (0.013 mL, 0.15 mmol) were slowly added. Then, the temperature was slowly raised to 80 °C, and the mixture was stirred for 3 hours. The reaction was completed, and the organic layer was washed three times with saturated ammonium chloride, dehydrated with sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and then the concentrate was purified by column chromatography (silica; ethyl

acetate/hexane=0-50%) to give the desired compound of **Formula 7-6** (0.022 g, 63%) in the form of a pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 8.37 - 8.35 (m, 1 H), 7.95 (d, 2 H, *J* = 8.4 Hz), 7.60 - 7.58 (m, 1 H), 7.47 (d, 2 H, *J* = 8.4 Hz), 6.94 - 6.89 (m, 2 H), 5.13 (s, 2 H), 3.89 (s, 3 H), 3.53 - 3.51 (m, 4 H), 3.31 - 3.29 (m, 4 H)

(**Compound 280**: N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)morpholine-4-carboxamide)



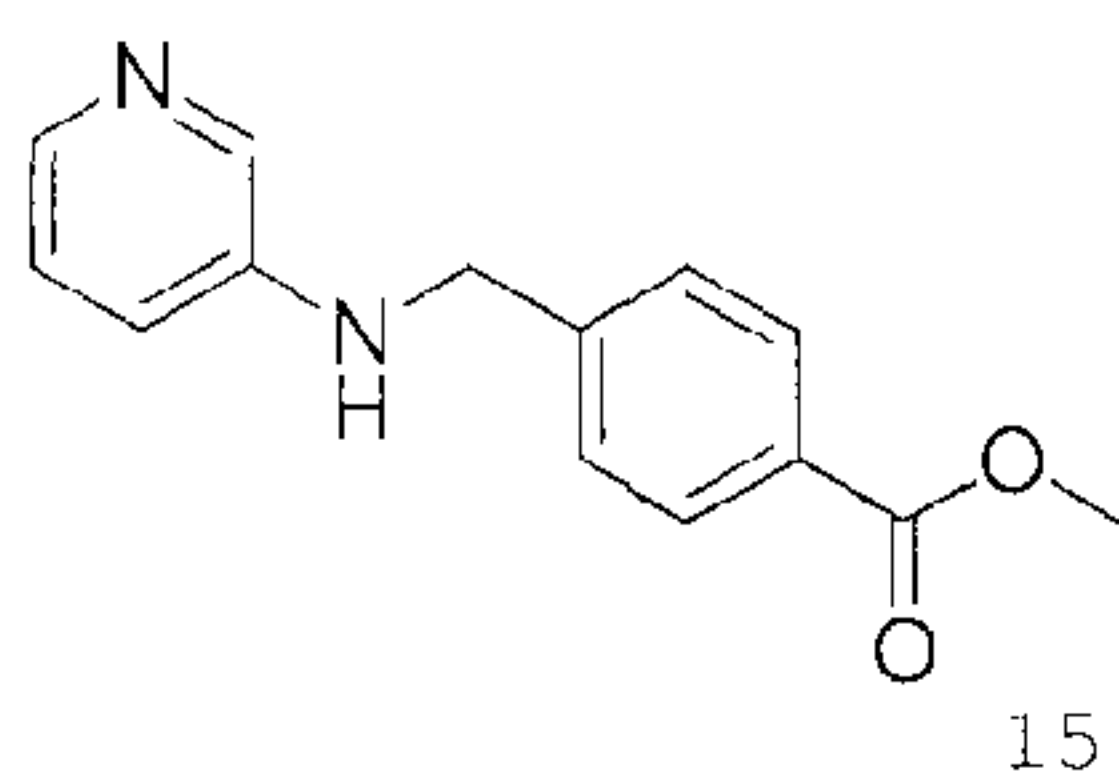
Compound of **Formula 7-6** (methyl 4-((N-(pyridin-2-yl)morpholine-4-carboxamido)methyl)benzoate; 0.022 g, 0.062 mmol) was dissolved in methanol (2 mL), and then hydroxylamine hydrochloride (0.022 g, 0.31 mmol) was slowly added. Then, potassium hydroxide (0.035 g, 0.62 mmol) was added and stirred at room temperature for about 10 minutes, and then hydroxylamine (50.0 wt% aqueous solution; 0.082 mL, 1.24 mmol) was added and stirred at room temperature for 1 day. Then, the organic solvent was concentrated under reduced pressure and then neutralized by adding 2 N hydrochloric acid. Then, the organic layer was washed three times with saturated sodium chloride aqueous solution, dehydrated with anhydrous sodium sulfate, and then filtered

to give the desired **Compound 280** (0.007 g, 32%) in the form of a white solid.

¹H NMR (400 MHz, MeOD-d₃) δ 8.32 (d, 1 H, *J* = 3.6 Hz), 7.72 (t, 1 H, *J* = 6.6 Hz), 7.67 (d, 2 H, *J* = 8.2 Hz), 7.48 (d, 2 H, *J* = 8.2 Hz), 7.08-7.01 (m, 2 H), 5.08 (s, 2 H), 3.52 (t, 4 H, *J* = 4.8 Hz), 3.29 (t, 4 H, *J* = 4.8 Hz); **MS** (ESI) *m/z* 357 (M⁺ + H).

Example 12: Synthesis of Compound 281

(**Formula 7-4**: methyl 4-((pyridin-3-ylamino)methyl)benzoate)



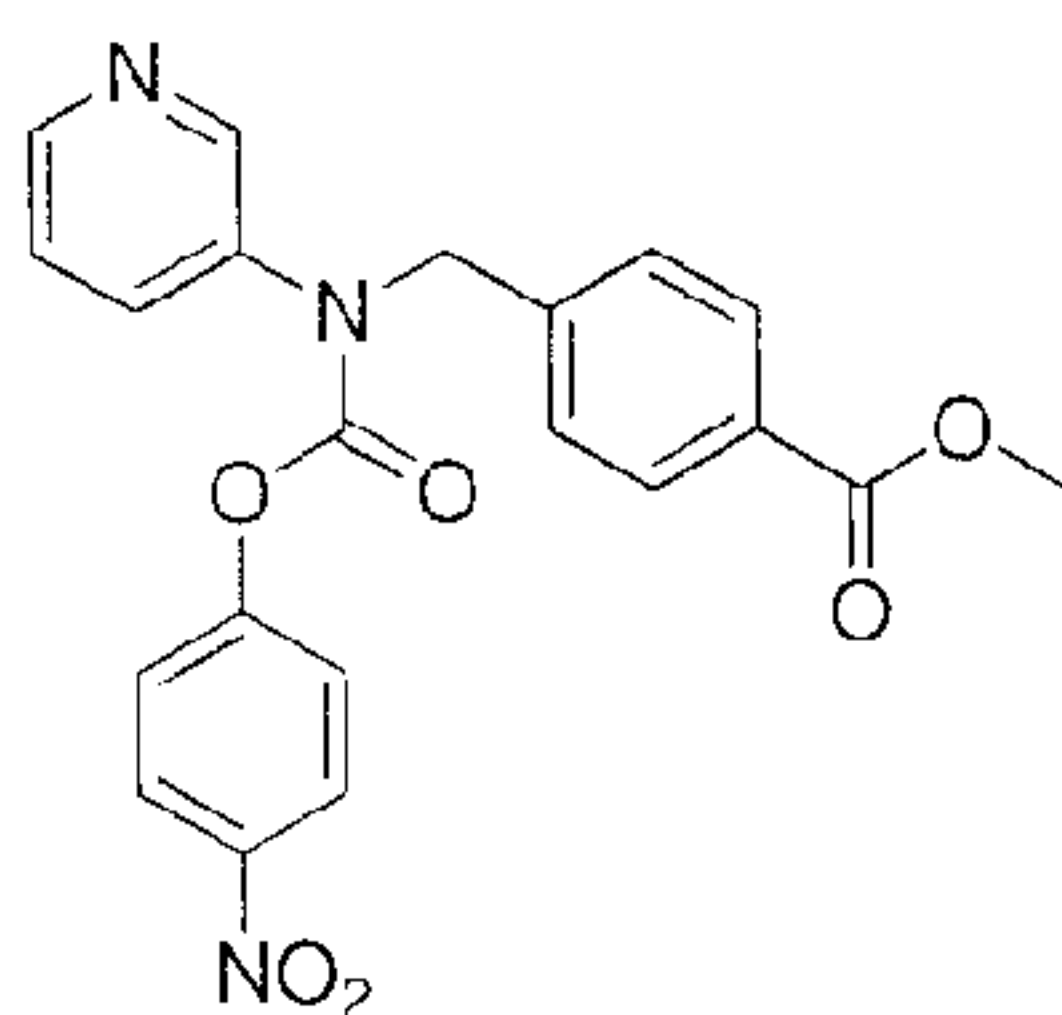
Compound of **Formula 7-3**

(pyridin-3-amine, 0.5 g, 5.31 mmol) was dissolved in methanol (10 mL), and then methyl 4-formylbenzoate (1.03 g, 5.31 mmol) was added and stirred at room temperature for 20 minutes. Then, sodium cyanoborohydride (0.33 g, 5.31 mmol) and acetic acid (0.32 mL, 5.31 mmol) were slowly added and stirred at room temperature for 5 hours. The organic layer was washed three times with saturated sodium chloride aqueous solution, dehydrated with sodium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and the concentrate was purified by column chromatography (silica;

ethyl acetate/hexane=0-30%) to give the desired compound of **Formula 7-4** (0.85 g, 66%) in the form of a white solid.

(**Formula 7-5**: methyl 4-(((4-nitrophenoxy)carbonyl)(pyridin-3-yl)amino)methyl)benzoate)

5



Compound of **Formula 7-4** (methyl

10 4-

((pyridin-3-ylamino)methyl)benzoate;

0.20 g, 0.83 mmol) was dissolved in dimethylformamide (3 mL),

and then 4-nitrophenyl chloroformate (0.18 g, 0.90 mmol) and

potassium carbonate (0.23 g, 1.65 mmol) were added. Then,

the temperature was slowly raised to 90 °C, and the mixture

15 was stirred for 1 day. After completion of the reaction, the

ethyl acetate layer was washed three times with saturated

ammonium chloride aqueous solution, and then the organic

layer was dehydrated with sodium sulfate, and then filtered.

The filtrate was concentrated under reduced pressure, and

20 then the concentrate was purified by column chromatography

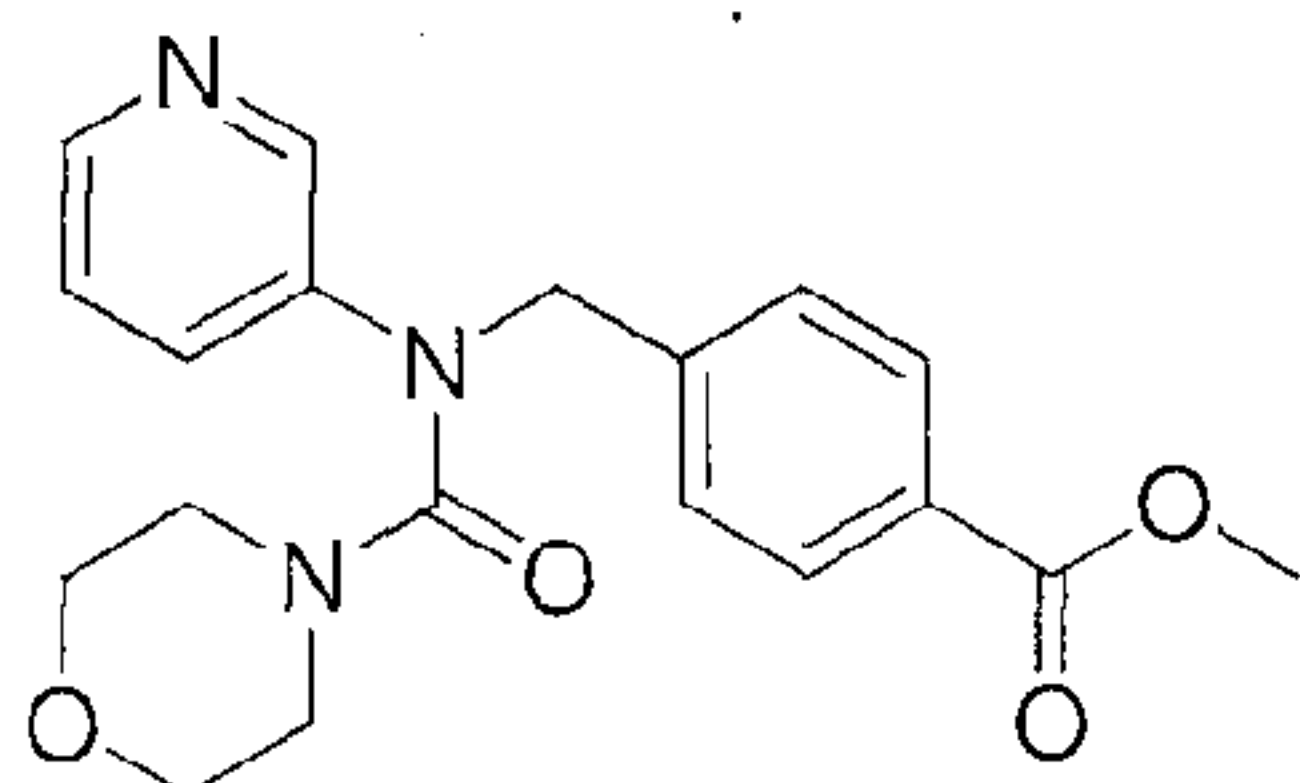
(silica; ethyl acetate/hexane=0-100%) to give the desired

compound of **Formula 7-5** (0.030 g, 8%) in the form of a white

solid.

(**Formula 7-6**: methyl 4-((N-(pyridin-3-yl)morpholine-4-

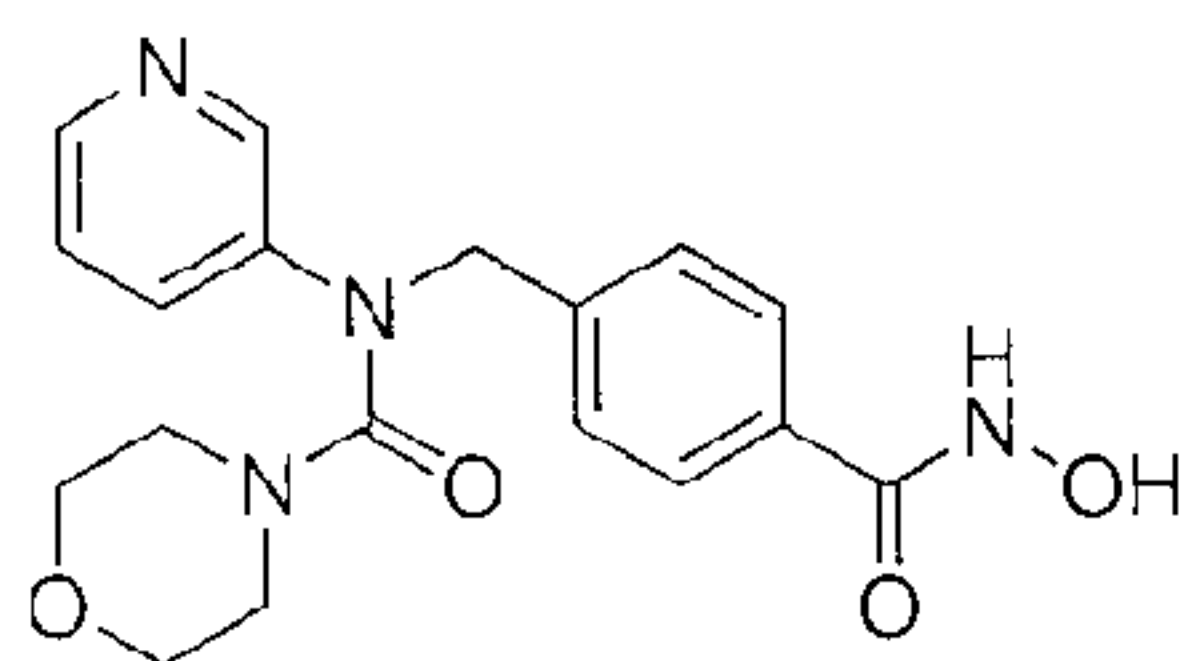
25 carboxamido)methyl)benzoate)



Compound of **Formula 7-5** (methyl 4-(((4-

5 nitrophenoxy)carbonyl)(pyridin-3-yl)amino)methyl)benzoate;
 0.025 g, 0.061 mmol) was dissolved in dimethylformamide (1
 mL), and then potassium carbonate (0.025 g, 0.184 mmol) and
 morpholine (0.008 g, 0.092 mmol) were added. Then, the
 temperature was slowly raised to 60 °C, and the mixture was
 10 stirred for 3 hours. After completion of the reaction, the
 ethyl acetate layer was washed three times with saturated
 ammonium chloride aqueous solution, and then the organic
 layer was dehydrated with sodium sulfate, and then filtered.
 The filtrate was concentrated under reduced pressure, and
 15 then the concentrate was purified by column chromatography
 (silica; methanol/dichloromethane=0-10%) to give the desired
 compound of **Formula 7-6** (0.018 g, 83%) in the form of a pale
 yellow solid.

(**Compound 281**: N-(4-(hydroxycarbonyl)benzyl)-N-
 20 (pyridin-3-yl)morpholine-4-carboxamide)



Compound of **Formula 7-6**

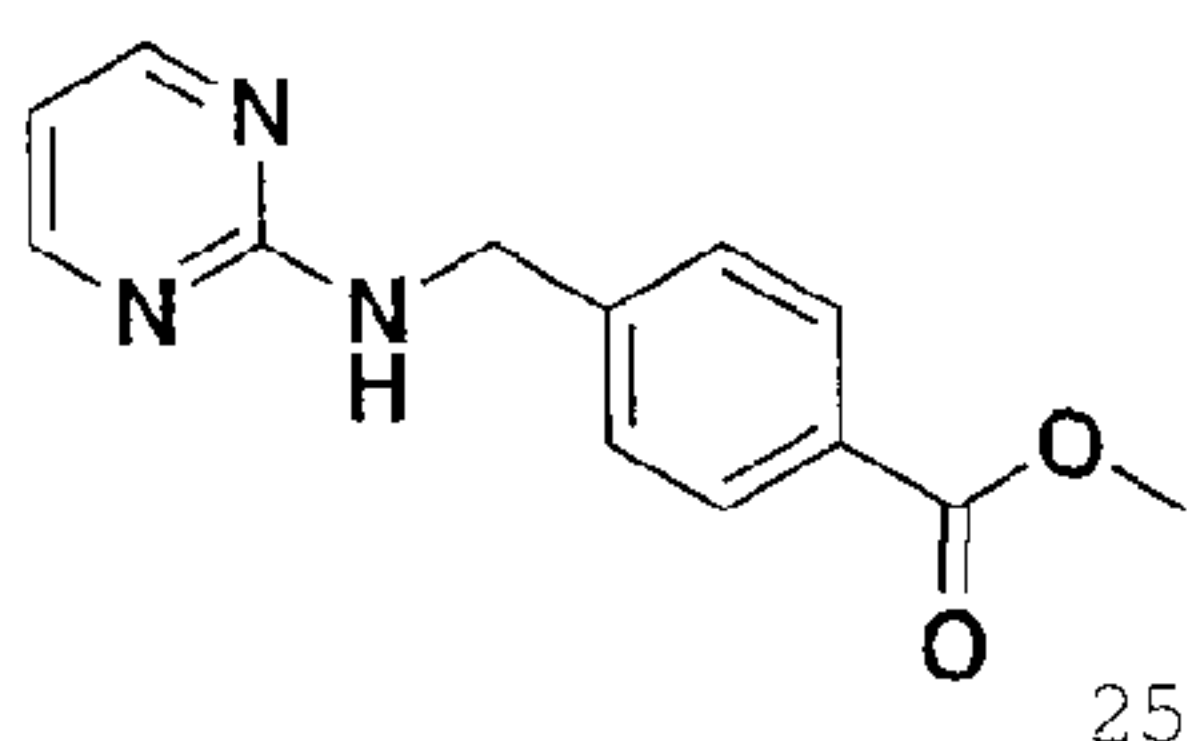
25 (methyl 4-((N-(pyridin-3-yl)morpholine-4-

carboxamido)methyl)benzoate; 0.018 g, 0.051 mmol) was dissolved in methanol (5 mL), and then hydroxylamine hydrochloride (0.018 g, 0.25 mmol) was slowly added. Then, potassium hydroxide (0.028 g, 0.51 mmol) was added and
 5 stirred at room temperature for about 10 minutes, and then hydroxylamine (50.0 wt% aqueous solution; 0.067 mL, 1.0 mmol) was added and stirred at room temperature for 1 day. Then, the organic layer was concentrated under reduced pressure and then neutralized by adding 2 N hydrochloric acid. Then, the
 10 organic layer was washed three times with saturated sodium chloride aqueous solution, dehydrated with anhydrous sodium sulfate, and then filtered to give the desired **Compound 281** (0.010 g, 55%) in the form of a white solid.

¹H NMR (400 MHz, MeOD-d₃) δ 8.11 (s, 1 H), 8.06 (d, 1 H, *J* = 4.1 Hz), 8.03 (d, 2 H, *J* = 8.3 Hz), 7.42 (d, 2 H, *J* = 2.8 Hz), 7.27 - 7.21 (m, 2 H), 4.93 (s, 2 H), 3.51 (t, 4 H, *J* = 4.7 Hz), 3.25 (t, 4 H, *J* = 4.8 Hz); **MS** (ESI) *m/z* 357 (M⁺ + H).

Example 13: Synthesis of Compound 309

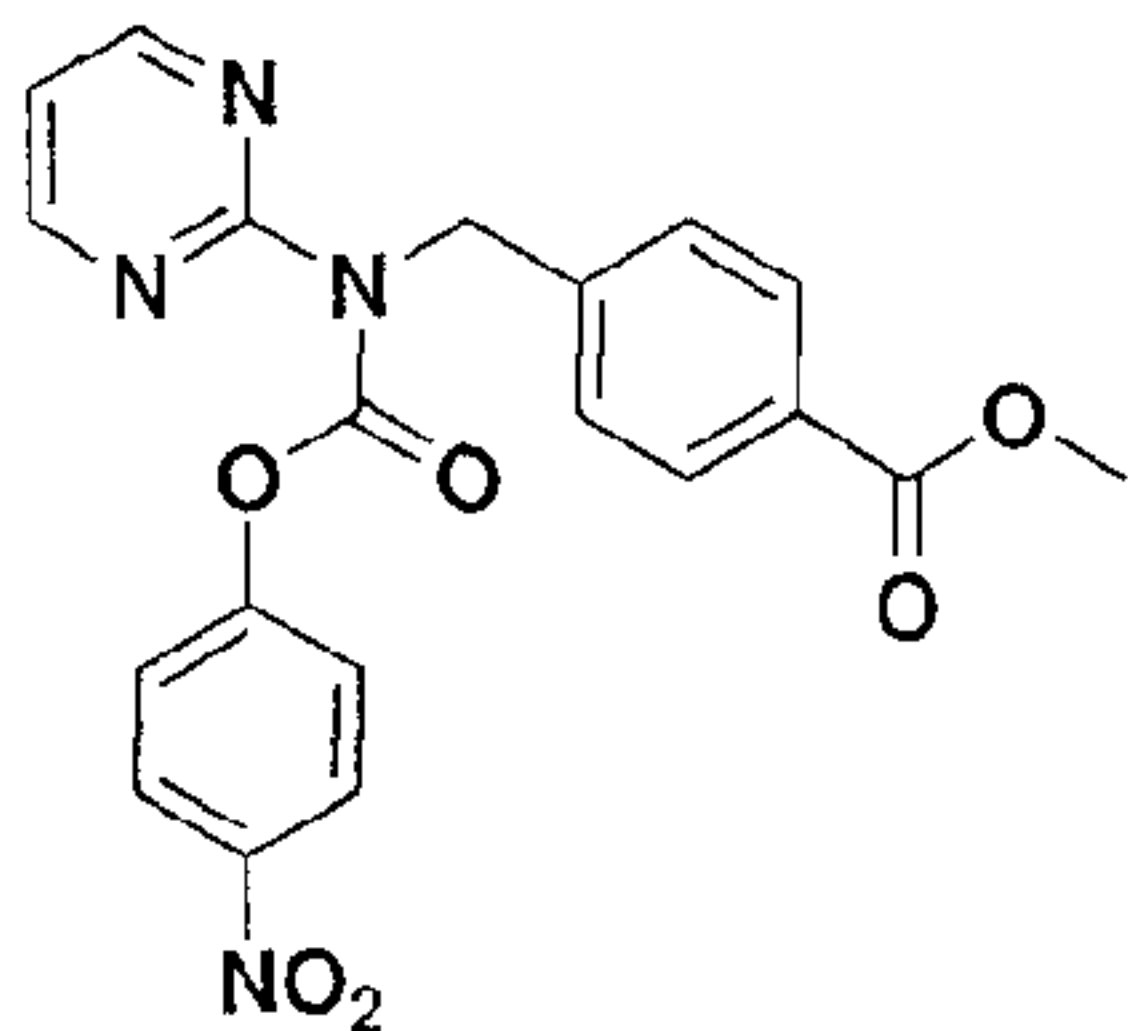
20 **(Formula 7-4: methyl 4-((pyrimidin-2-ylamino)methyl)benzoate)**



Compound of **Formula 7-1** (2-

chloropyrimidine; 6.25 g, 54.6 mmol) and compound of **Formula 7-2** (methyl 4-(aminomethyl)benzoate hydrochloride; 10.0 g, 49.6 mmol) were dissolved in ethanol (150 mL), and the triethylamine (17.0 mL, 124 mmol) was added and stirred under
 5 reflux for 3 days. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution, dehydrated with anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and then the residue
 10 was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 7-4** (8.06 g, 67%) in the form of a white solid.

(**Formula 7-5**: methyl 4-(((4-
 15 nitrophenoxy)carbonyl)(pyrimidin-2-yl)amino)methyl)benzoate)



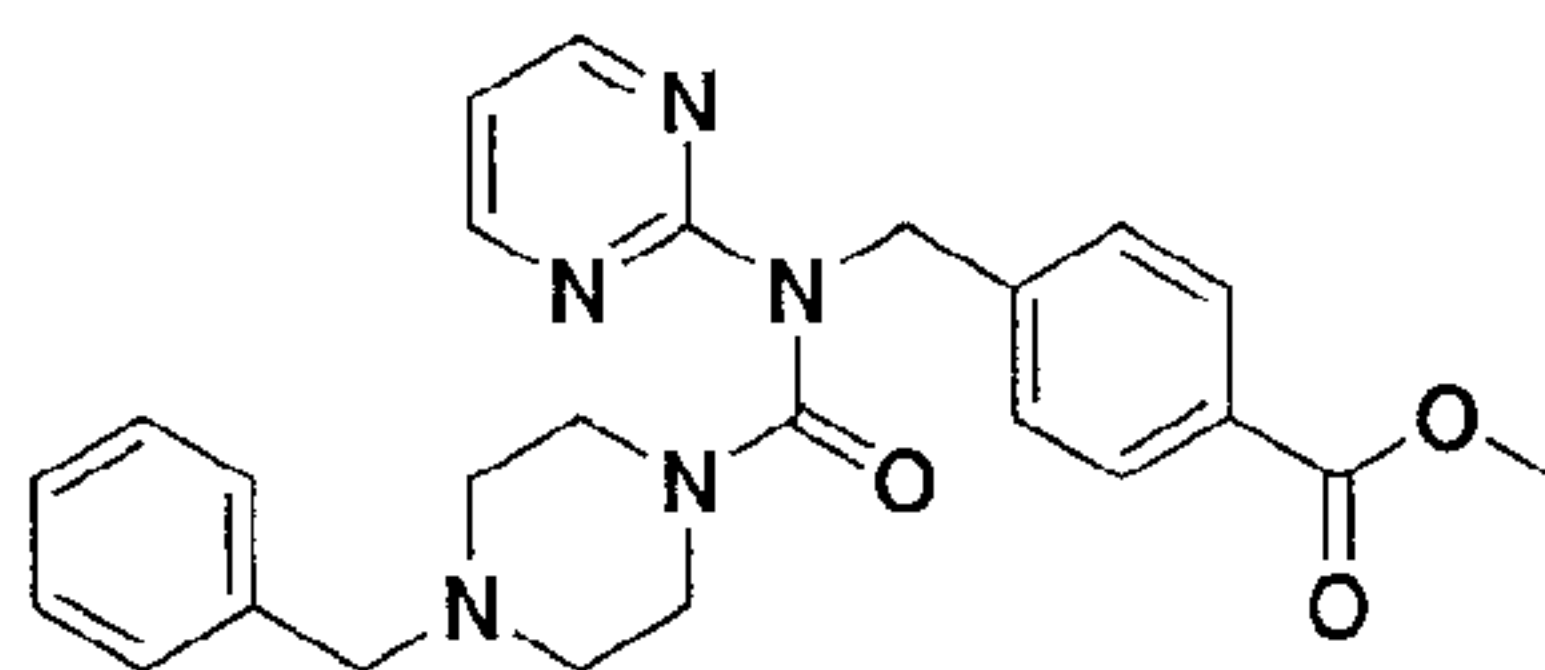
20

Compound of **Formula 7-4** (methyl

4-((pyrimidin-2-ylamino)methyl)benzoate; 8.06 g, 33.1 mmol) and 4-nitrophenyl chloroformate (7.01 g, 34.8 mmol) were dissolved in acetonitrile (150 mL), and then potassium
 25 carbonate (6.87 g, 49.7 mmol) was added and stirred at room

temperature for 16 hours. Then, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution, dehydrated with anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 7-5** (1.50 g, 11%) in the form of a light yellow liquid.

(**Formula 7-6**: methyl 4-((4-benzyl-N-(pyrimidin-2-yl)piperazine-1-carboxamido)methyl)benzoate)



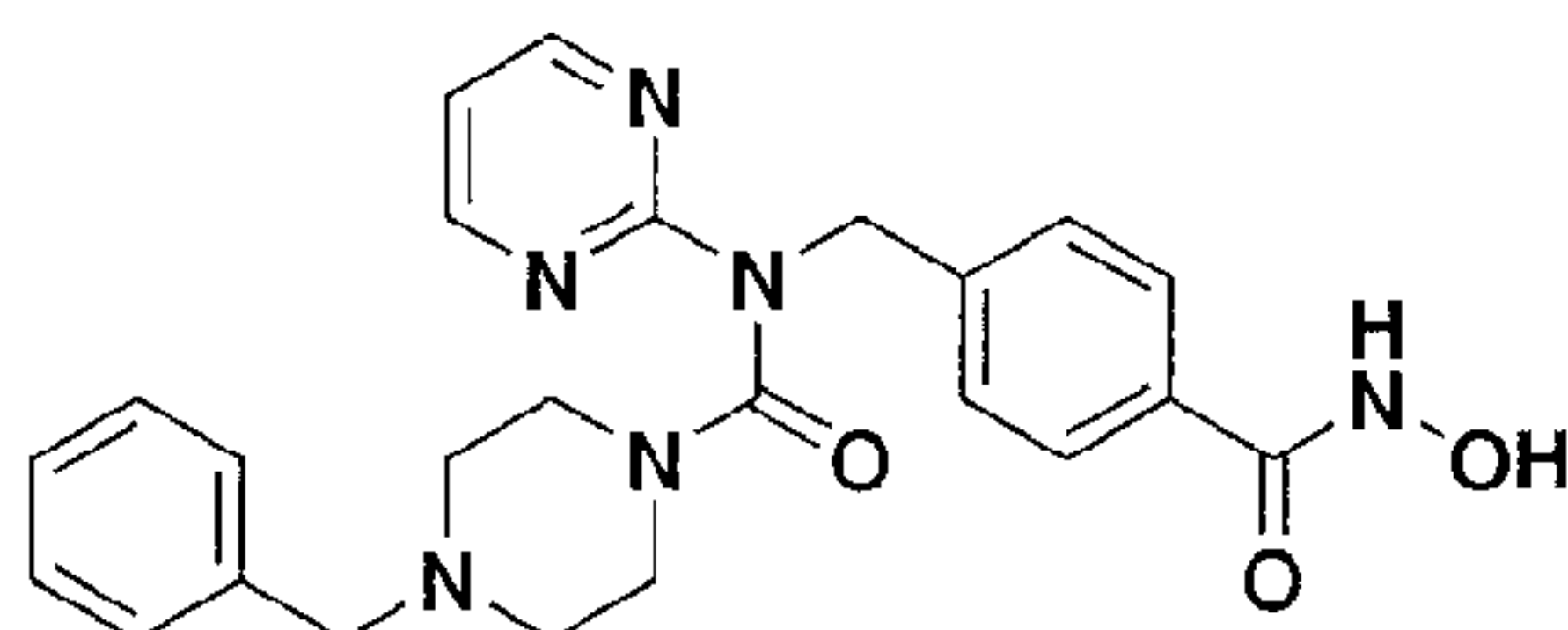
15

Compound of **Formula 7-5** (methyl 4-(((4-nitrophenoxy)carbonyl)(pyrimidin-2-yl)amino)methyl)benzoate; 0.150 g, 0.367 mmol) was dissolved in dimethylformamide (1 mL), and then 1-benzylpiperazine (0.130 g, 0.735 mmol) and potassium carbonate (0.152 g, 1.10 mmol) were added and stirred at 60 °C for 16 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica;

25

ethyl acetate/hexane=50%) to give the desired compound of **Formula 7-6** (0.132 g, 81%) in the form of a yellow liquid.

(**Compound 309**: 4-benzyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyrimidin-2-yl)piperazine-1-carboxamide)



Compound of **Formula 7-6** (methyl 4-((4-benzyl-N-(pyrimidin-2-yl)piperazine-1-carboxamido)methyl)benzoate; 0.132 g, 0.296 mmol) was dissolved in methanol (5 mL), and then hydroxylamine (50.0 wt% aqueous solution; 0.906 mL, 14.8 mmol) and potassium hydroxide (0.166 g, 2.96 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 2 mL, and saturated sodium hydrogen carbonate aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 309** (0.079 g, 60%) in the form of a light yellow solid.

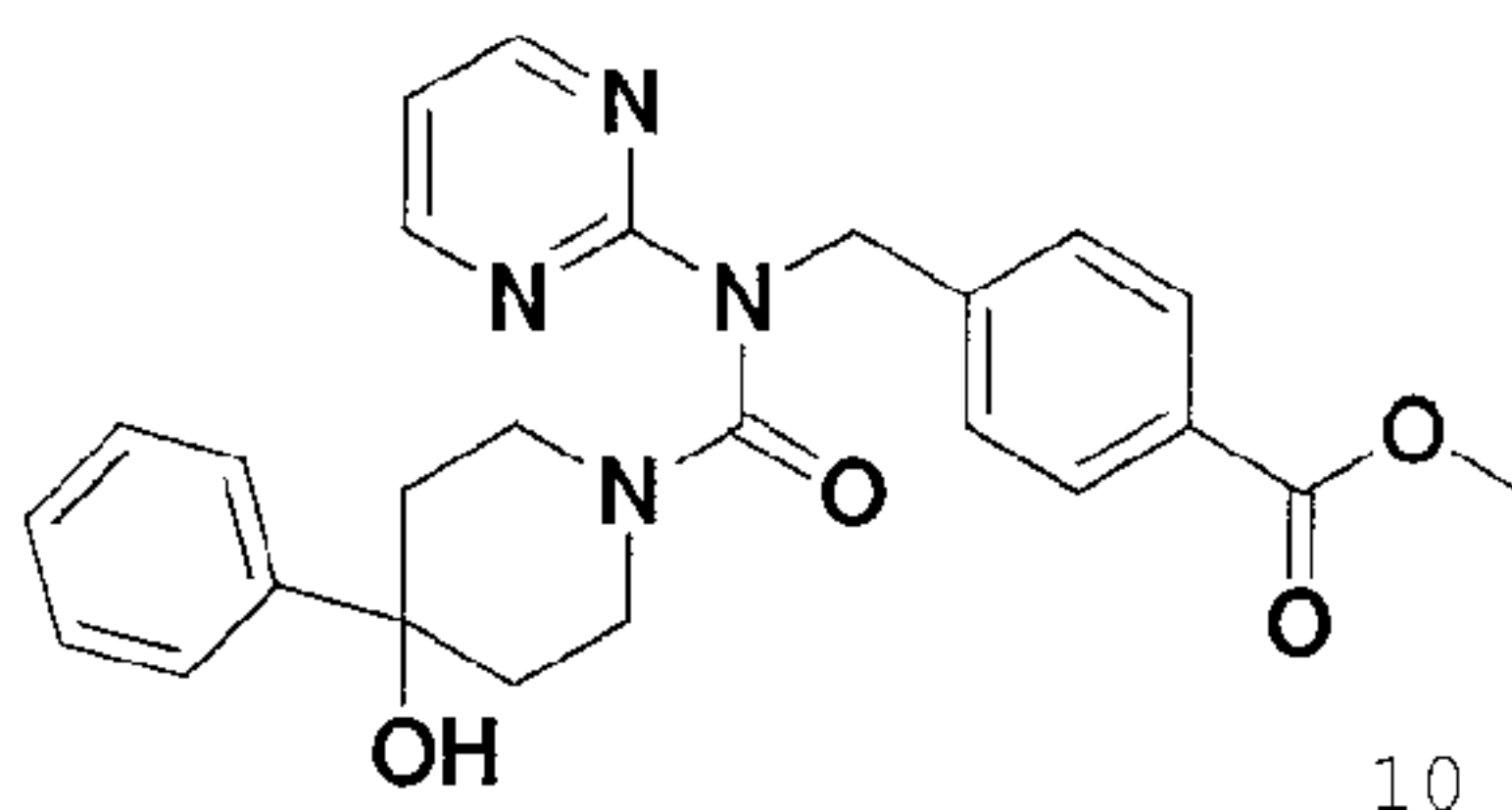
¹H NMR (400 MHz, DMSO-d₆) δ 11.18 (s, 1 H), 9.03 (s, 1 H), 8.50 (d, 2 H, J = 4.8 Hz), 7.68 (d, 2 H, J = 8.4 Hz), 7.39 (d, 2 H, J = 8.4 Hz), 7.32 - 7.21 (m, 5 H) 6.93 (t, 1 H, J = 4.8 Hz), 4.97 (s, 2 H), 3.40 (s, 2 H), 3.29 (m, 4 H), 2.19 (m, 4

25

H). **MS** (ESI) m/z 447 ($M^+ + H$).

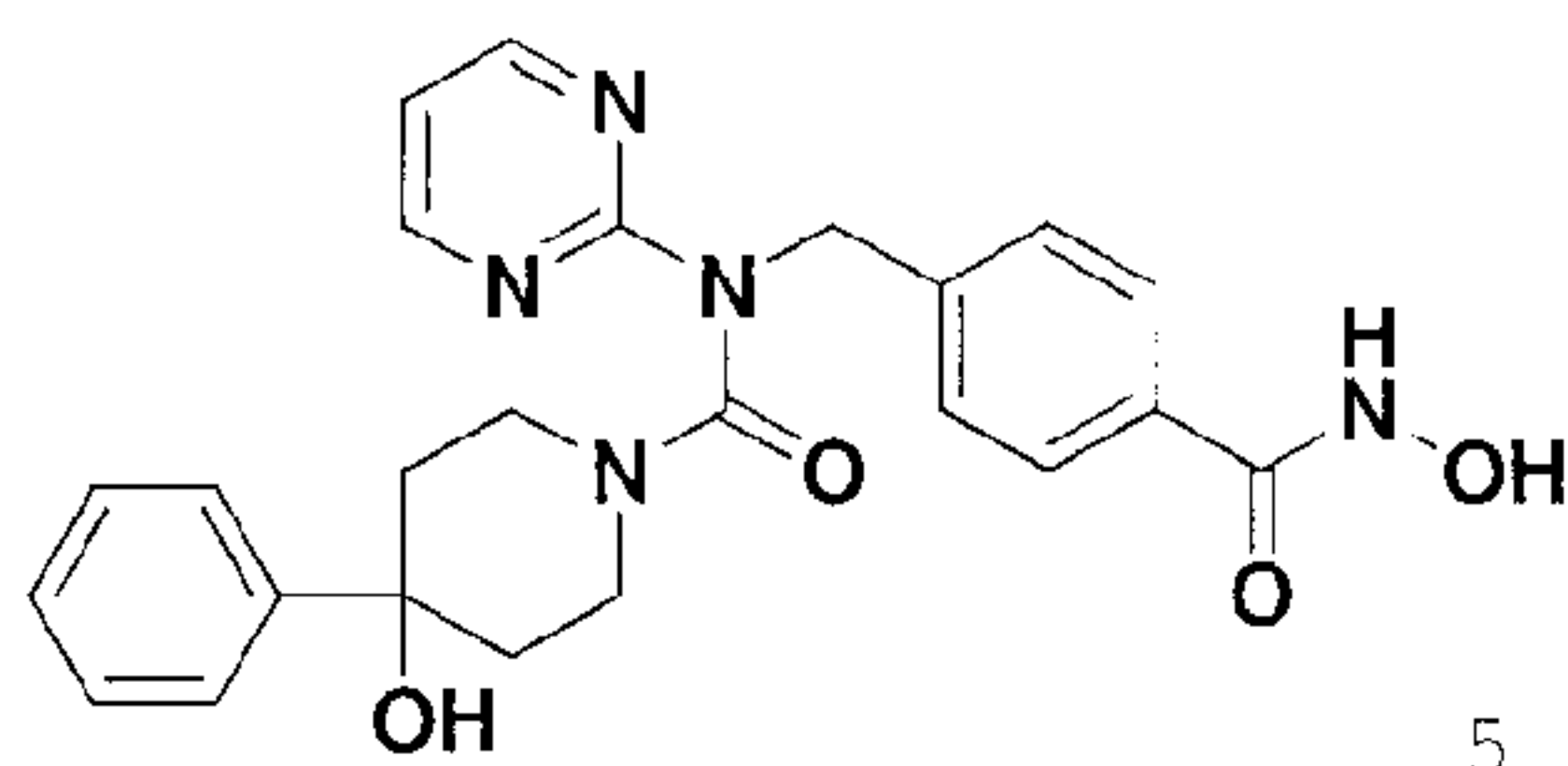
Example 14: Synthesis of Compound 311

(**Formula 7-6**: methyl 4-((4-hydroxy-4-phenyl-N-(pyrimidin-2-yl)piperidine-1-carboxamido)methyl)benzoate)



Compound of **Formula 7-5** (methyl 4-(((4-nitrophenoxy)carbonyl)(pyrimidin-2-yl)amino)methyl)benzoate; 0.150 g, 0.367 mmol) was dissolved in dimethylformamide (1 mL), and then 4-phenylpiperidine-4-ol (0.130 g, 0.735 mmol) and potassium carbonate (0.152 g, 1.10 mmol) were added and stirred at 60 °C for 16 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane-30%) to give the desired compound of **Formula 7-6** (0.104 g, 63%) in the form of a light yellow liquid.

(**Compound 311**: 4-hydroxy-N-(4-(hydroxycarbonyl)benzyl)-4-phenyl-N-(pyrimidin-2-yl)piperidine-1-carboxamide)



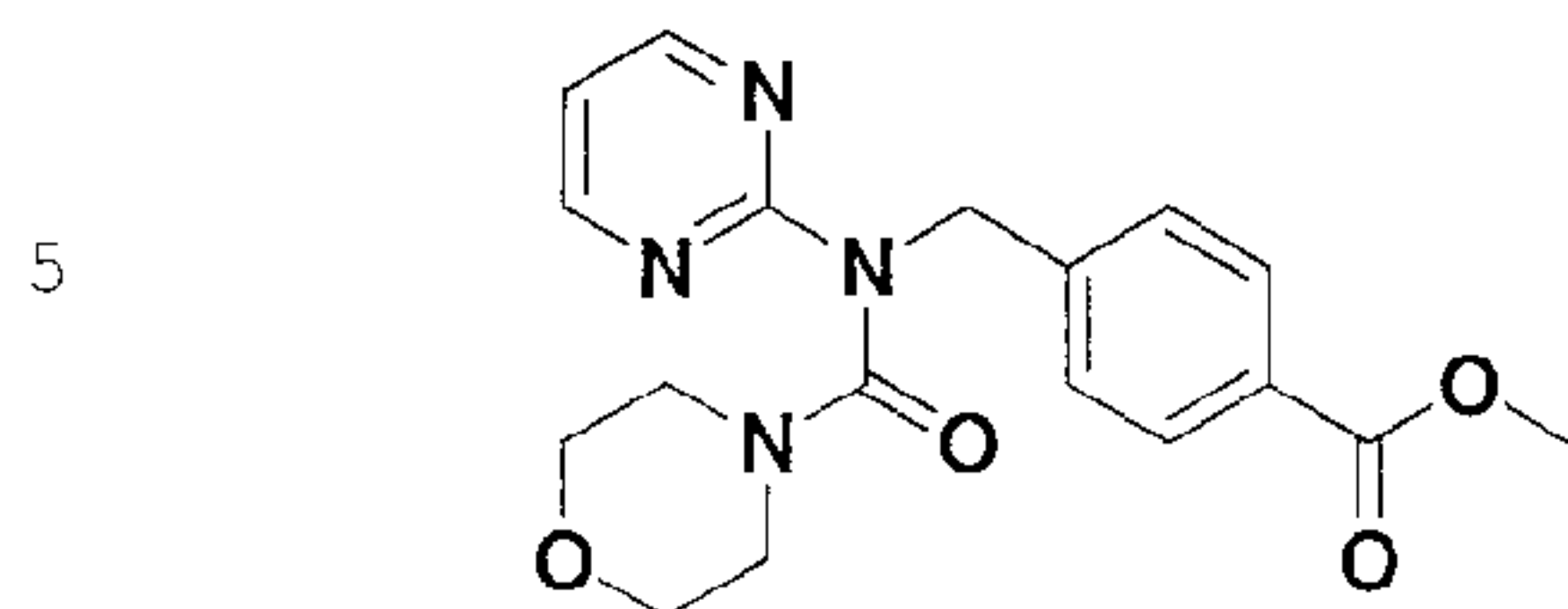
Compound of **Formula 7-6** (methyl 4-((4-hydroxy-4-phenyl-N-(pyrimidin-2-yl)piperidine-1-carboxamido)methyl)benzoate; 0.104 g, 0.233 mmol) was dissolved in methanol (5 mL), and then hydroxylamine (50.0 wt% aqueous solution; 1.43 mL, 23.3 mmol) and potassium hydroxide (0.131 g, 2.33 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 2 mL, and saturated sodium hydrogen carbonate aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 311** (0.072 g, 69%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.19 (s, 1 H), 9.04 (s, 1 H), 8.54 (d, 2 H, J = 4.8 Hz), 7.73 (d, 2 H, J = 8.3 Hz), 7.45 (d, 2 H, J = 8.3 Hz), 7.30 - 7.26 (m, 4 H), 7.19 (m, 1 H), 6.93 (t, 1 H, J = 4.8 Hz), 5.08 (s, 1 H), 5.01 (brs, 2 H), 3.73 (brs, 2 H), 3.18 - 3.11 (m, 2 H), 1.56 - 1.47 (m, 4 H). **MS** (ESI) m/z 448 (M⁺ + H).

25

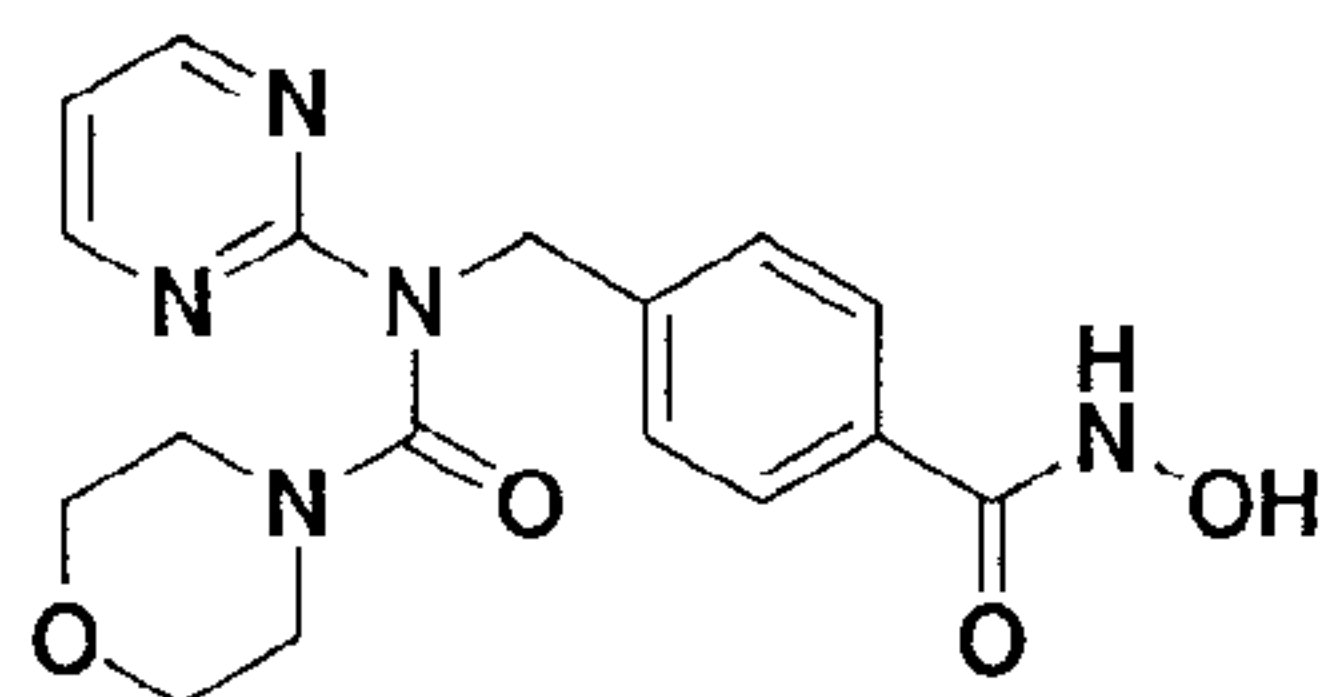
Example 15: Synthesis of Compound 312

(**Formula 7-6**: methyl 4-((N-(pyrimidin-2-yl)morpholine-4-carboxamido)methyl)benzoate)

Compound of **Formula 7-4**

(methyl 4-((pyrimidin-2-ylamino)methyl)benzoate; 0.200 g, 0.822 mmol) was dissolved in acetonitrile (2 mL), and then morpholine-4-carbonyl chloride (0.185 g, 1.23 mmol) and N,N-diisopropylethylamine (0.291 mL, 1.64 mmol) were added and stirred at 60 °C for 16 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 7-6** (0.179 g, 61%) in the form of a light yellow solid.

20 (**Compound 312**: N-(4-(hydroxycarbamoyl)benzyl)-N-(pyrimidin-2-yl)morpholine-4-carboxamide)



25

Compound of **Formula 7-6**

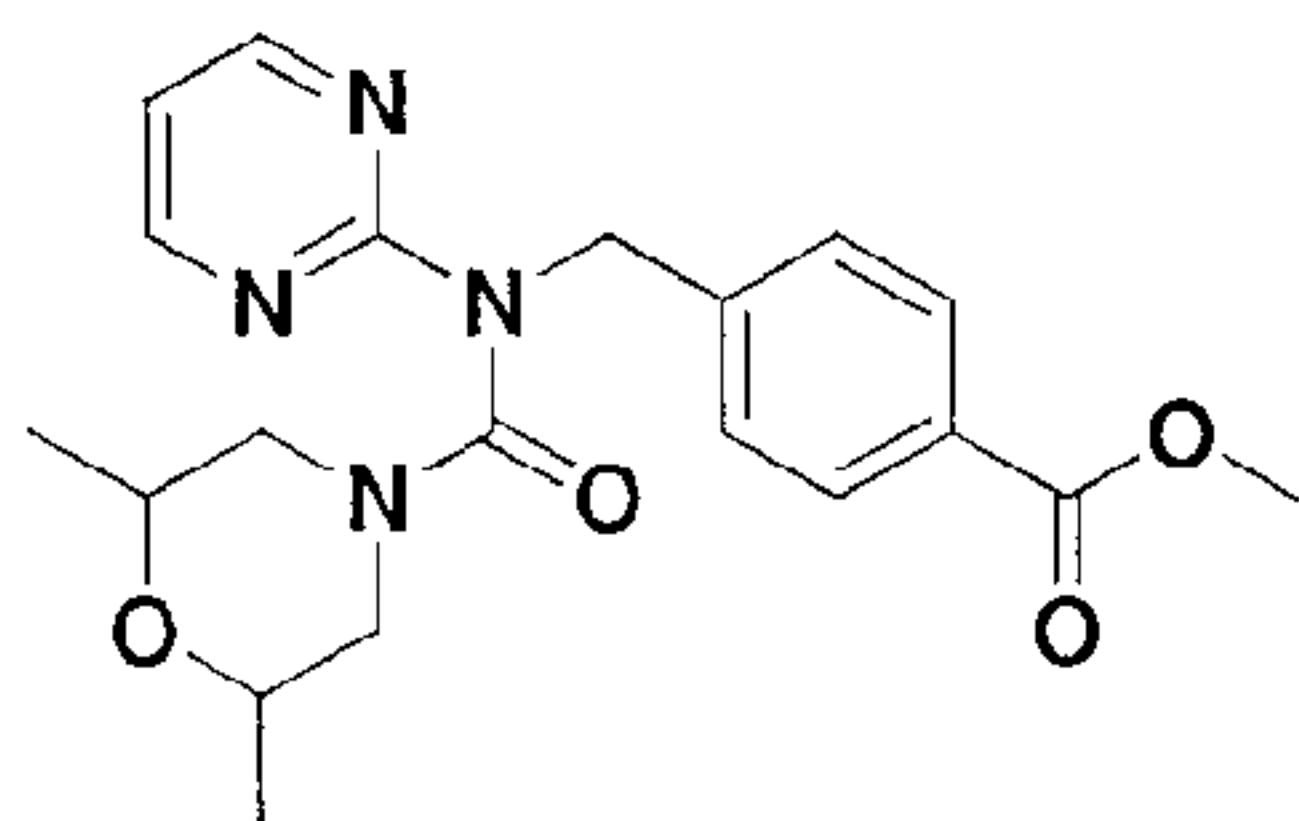
(methyl 4-((N-(pyrimidin-2-yl)morpholine-4-carboxamido)methyl)benzoate; 0.179 g, 0.502 mmol) was dissolved in methanol (5 mL), and then hydroxylamine (50.0 wt% aqueous solution; 2.15 mL, 35.2 mmol) and potassium hydroxide (0.282 g, 5.02 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 2 mL, and the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution. The organic layer was washed three times with water, dehydrated with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The residue was recrystallized with diethylether and hexane to give the desired **Compound 312** (0.036 g, 20%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.18 (s, 1 H), 8.53 (d, 2 H, J = 4.8 Hz), 7.68 (d, 2 H, J = 7.6 Hz), 7.40 (d, 2 H, J = 8.1 Hz), 6.96 (t, 1 H, J = 4.8 Hz), 4.98 (s, 2 H), 3.40 (m, 4 H), 3.28 (m, 4 H). MS (ESI) m/z 358 (M⁺ + H).

Example 16: Synthesis of Compound 313

(Formula 7-6: methyl 4-((2,6-dimethyl-N-(pyrimidin-2-yl)morpholine-4-carboxamido)methyl)benzoate)

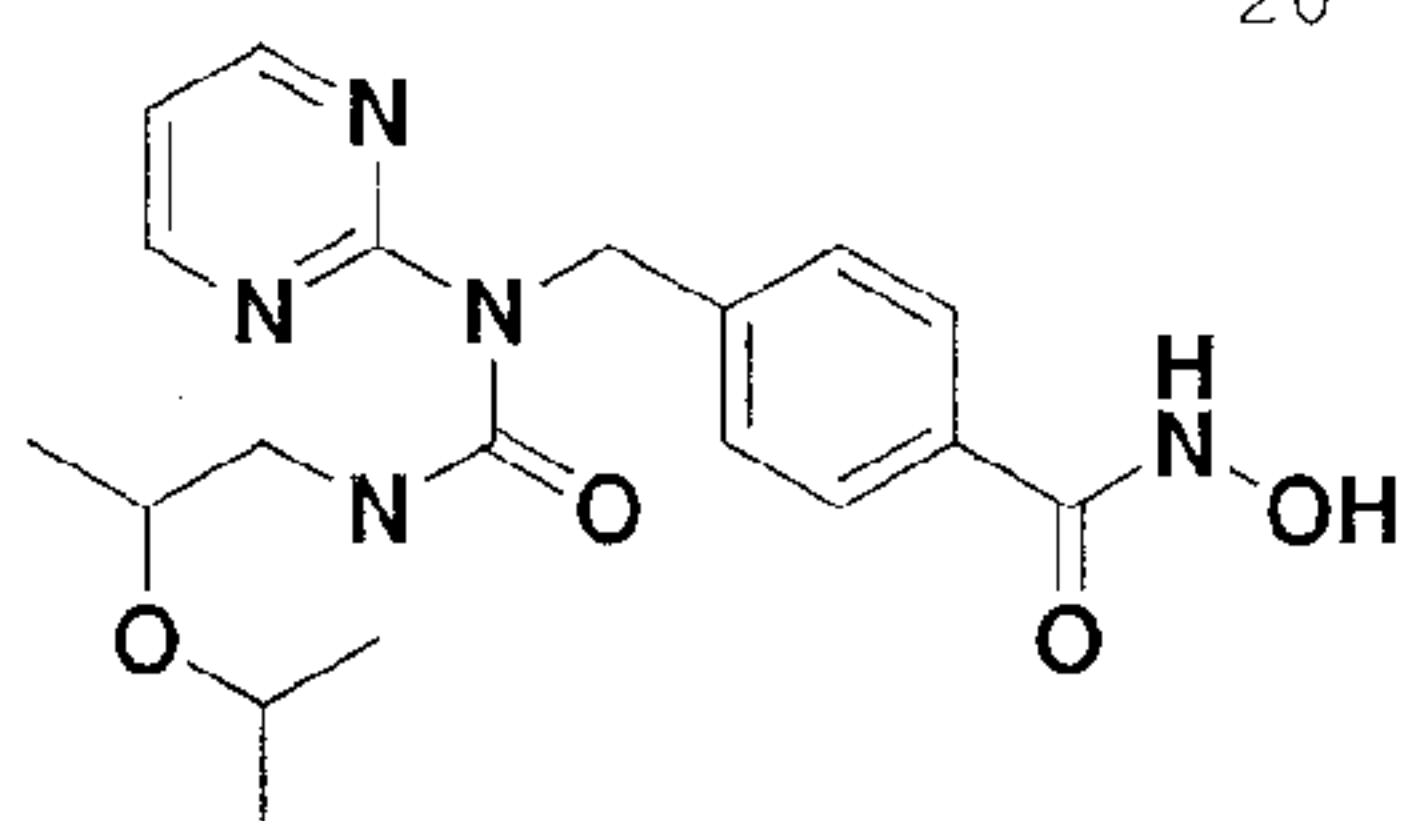
25



5 Compound of **Formula 7-5** (methyl 4-(((4-nitrophenoxy)carbonyl)(pyrimidin-2-yl)amino)methyl)benzoate; 0.150 g, 0.367 mmol) was dissolved in dimethylformamide (1 mL), and then 2,6-dimethylmorpholine (0.085 g, 0.735 mmol) and potassium carbonate (0.152 g, 1.10 mmol) were added and
10 stirred at 60 °C for 16 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica;
15 ethyl acetate/hexane=50%) to give the desired compound of **Formula 7-6** (0.062 g, 44%) in the form of a yellow liquid.

(**Compound 313**: N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(pyrimidin-2-yl)morpholine-4-carboxamide)

20



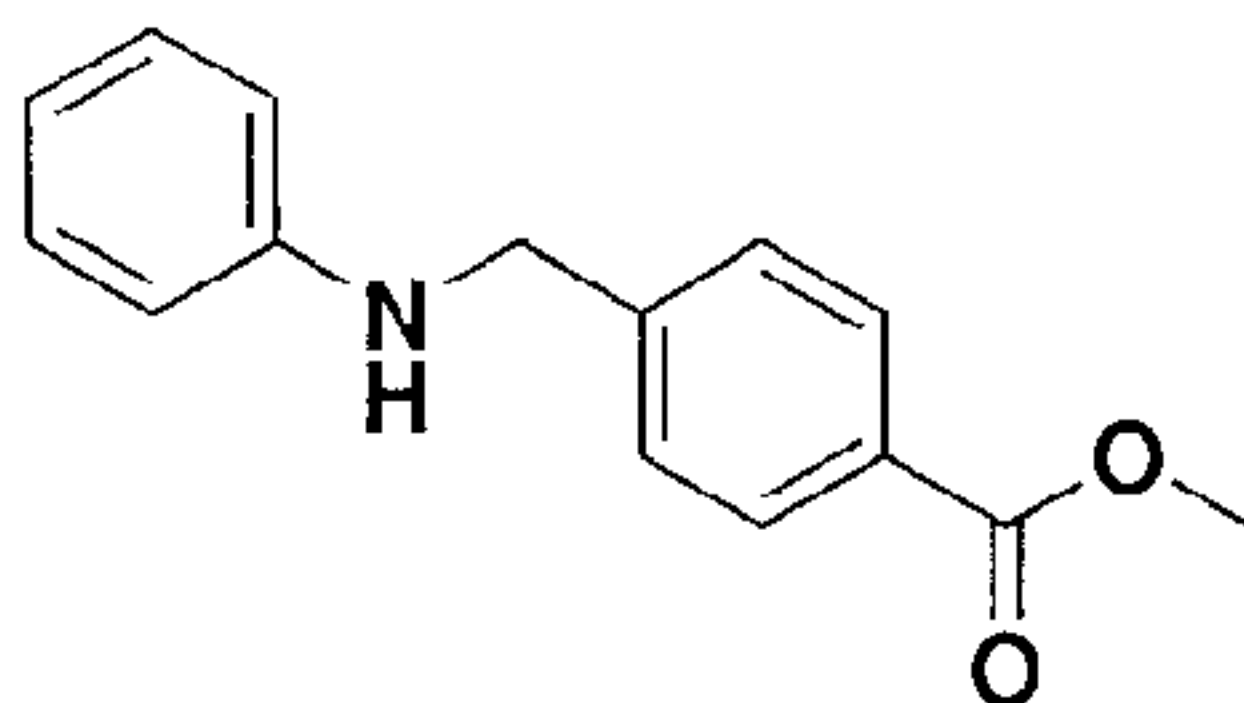
25 Compound of **Formula 7-6** (methyl 4-((2,6-dimethyl-N-

(pyrimidin-2-yl)morpholine-4-carboxamido)methyl)benzoate;
 0.062 g, 0.161 mmol) was dissolved in methanol (5 mL), and
 then hydroxylamine (50.0 wt% aqueous solution; 0.986 mL, 16.1
 mmol) and potassium hydroxide (0.091 g, 1.61 mmol) were added
 5 sequentially and then stirred at room temperature for 30
 minutes. After completion of the reaction, the reaction
 solution was concentrated under reduced pressure until its
 volume became about 2 mL, and the organic layer was extracted
 with ethyl acetate and saturated sodium hydrogen carbonate
 10 aqueous solution. The organic layer was washed three times
 with water, dehydrated with anhydrous magnesium sulfate,
 filtered, and then concentrated under reduced pressure. The
 residue was recrystallized with diethylether and hexane to
 give the desired **Compound 313** (0.037 g, 60%) in the form of a
 15 white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.18 (s, 1 H), 9.02 (s, 1 H),
 8.52 (d, 2 H, *J* = 4.4 Hz), 7.68 (d, 2 H, *J* = 7.8 Hz), 7.40 (d,
 2 H, *J* = 7.8 Hz), 6.95 (t, 1 H, *J* = 4.6 Hz), 4.98 (s, 2 H),
 3.68 (brs, 2 H), 3.21 (brs, 2 H), 2.44 - 2.41 (m, 2 H), 0.97
 20 (s, 3 H), 0.96 (s, 3 H). **MS** (ESI) *m/z* 386 (*M*⁺ + H).

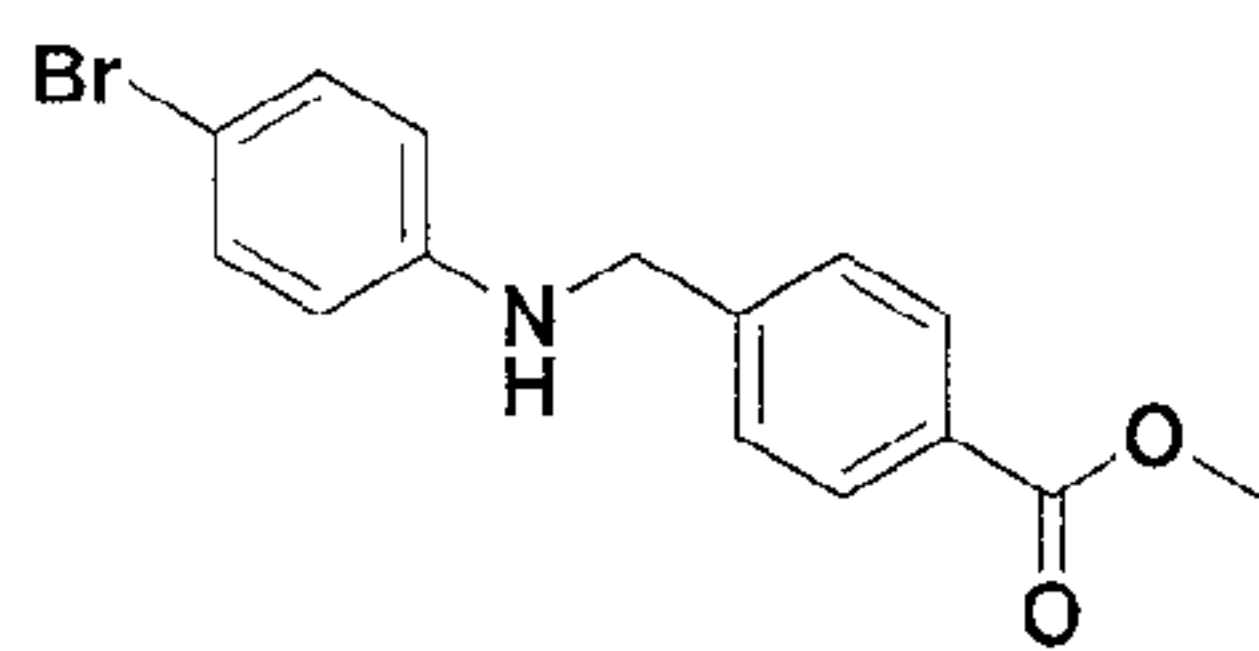
Example 17: Synthesis of Compound 329

(**Formula 8-2**: methyl 4-((phenylamino)methyl)benzoate)

Compound of **Formula 8-1**

(methyl 4-(bromomethyl)benzoate; 12.5 g, 54.8 mmol) and aniline (5.00 mL, 54.8 mmol) were dissolved in acetonitrile (70 mL), and then N,N-diisopropylethylamine (11.6 mL, 65.7 mmol) were added and stirred at room temperature for 16 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution, dehydrated with anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane-15%) to give the desired compound of **Formula 8-2** (9.13 g, 69%) in the form of a yellow liquid.

(**Formula 8-3**: methyl 4-((4-bromophenylamino)methyl)benzoate)



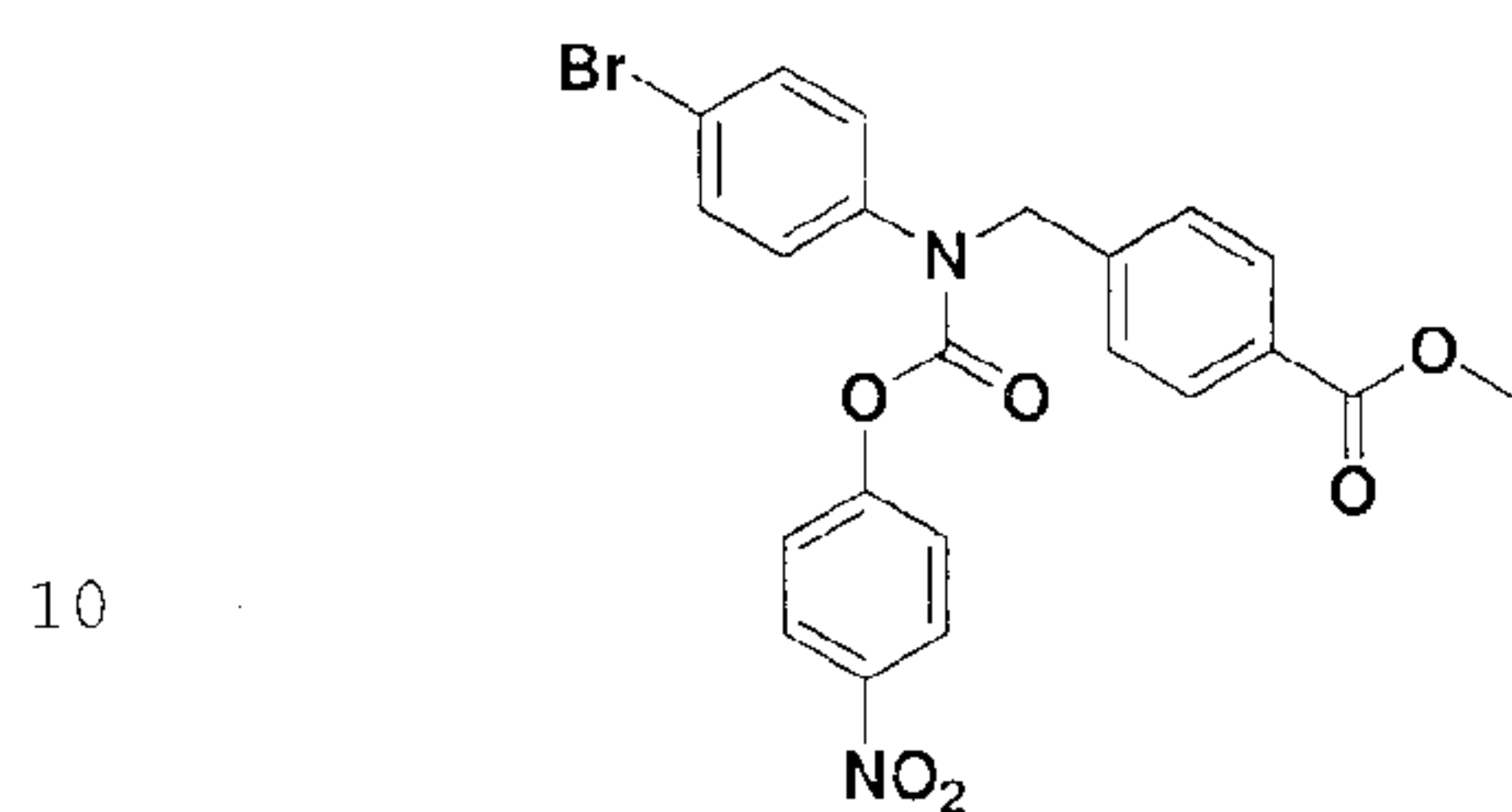
20

Compound of **Formula 8-2**

(methyl 4-((phenylamino)methyl)benzoate; 9.13 g, 37.8 mmol) was dissolved in dichloromethane (70 mL), and the N-bromosuccinimide (7.07 g, 39.7 mmol) was added and stirred at room temperature for 16 hours. After completion of the reaction, the organic layer was concentrated under reduced

pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=15%) to give the desired compound of **Formula 8-3** (9.57 g, 79%) in the form of a white solid.

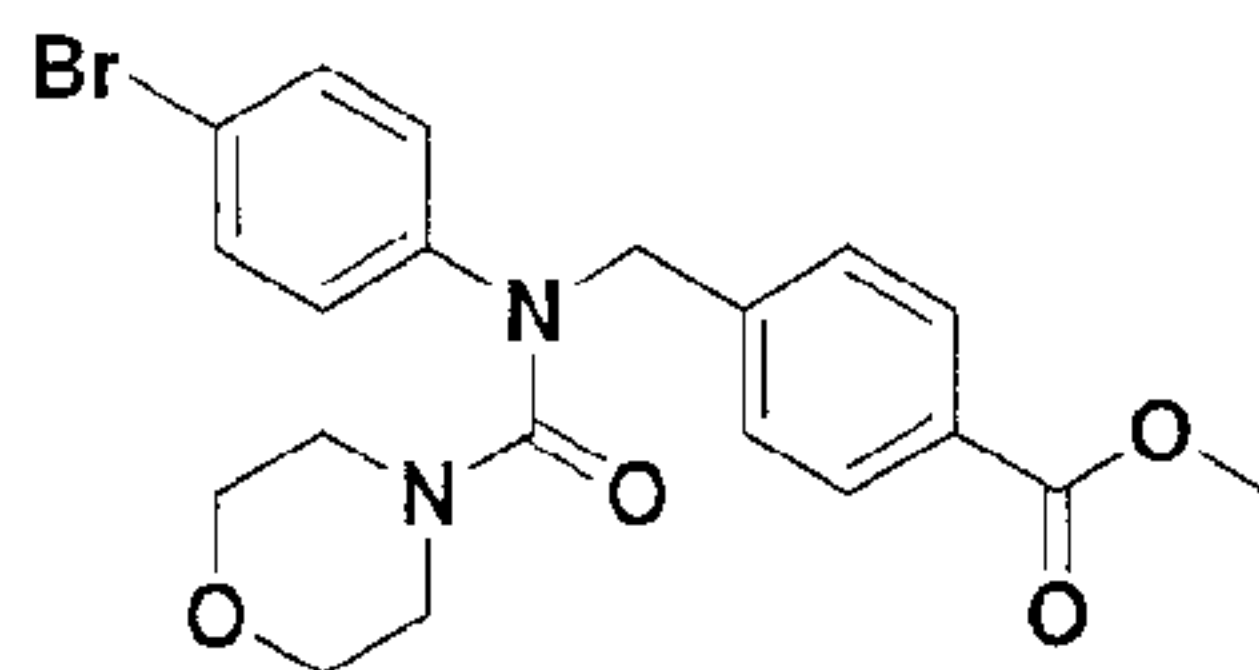
5 **(Formula 8-4:** methyl 4-(((4-bromophenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate)



(methyl 4-(((4-bromophenylamino)methyl)benzoate; 7.67 g, 24.0 mmol) and 4-nitrophenyl chloroformate (5.31 g, 26.4 mmol) were dissolved in acetonitrile (70 mL), and then potassium carbonate (4.97 g, 35.9 mmol) was added and stirred at room temperature for 16 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution, dehydrated with anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=20%) to give the desired compound of **Formula 8-4** (11.2 g, 96%) in the form of a yellow liquid.

25 **(Formula 8-5:** methyl 4-((N-(4-bromophenyl)morpholine-4-

carboxamido)methyl)benzoate)



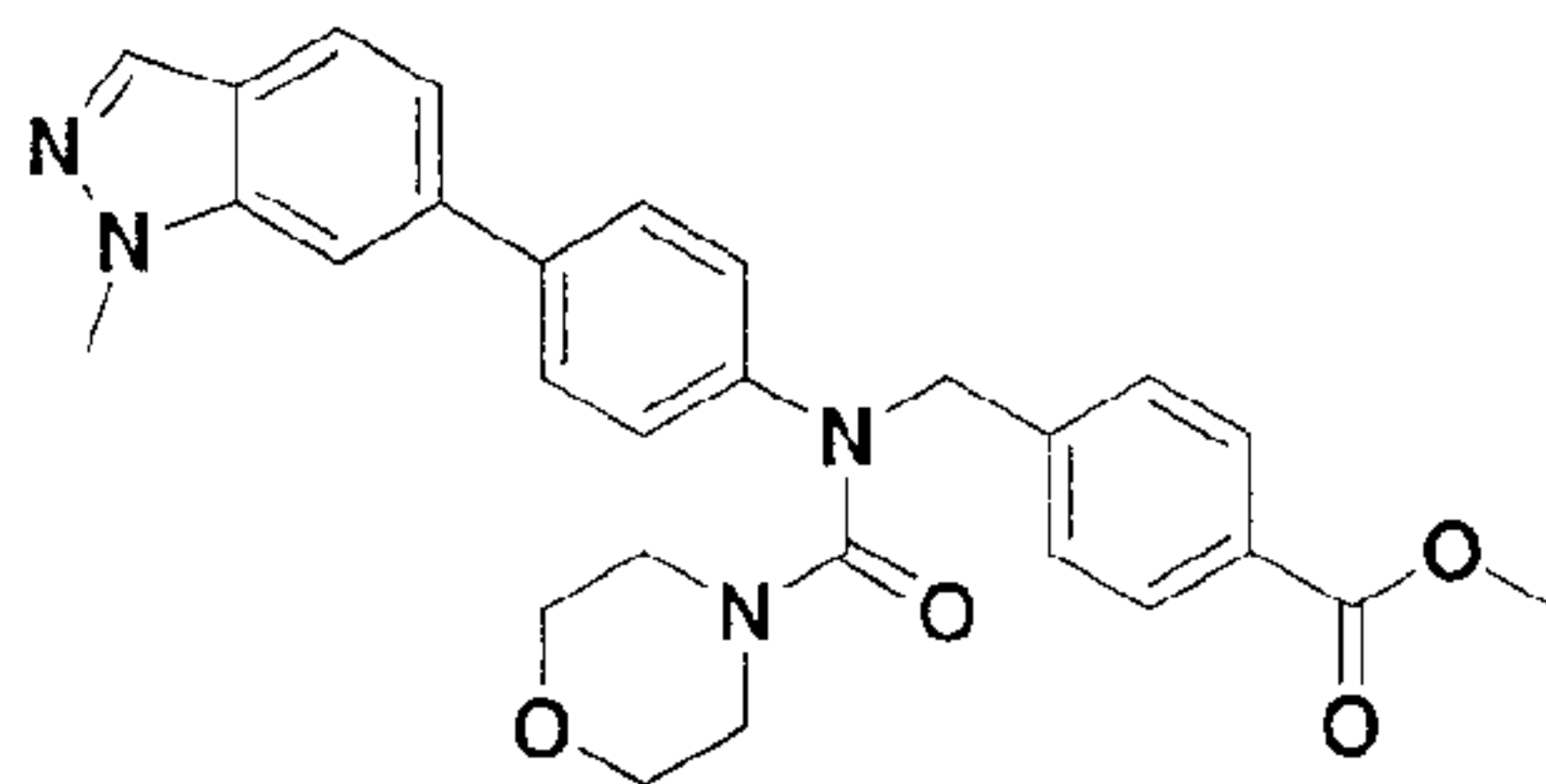
5 Compound of **Formula 8-4** (methyl 4-((4-bromophenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate; 5.00 g, 10.3 mmol) was dissolved in dimethylformamide (20 mL), and then morpholine (1.35 g, 15.5 mmol) and potassium carbonate (2.85 g, 20.6 mmol) were added and stirred at 60 °C for 5 hours.

10 After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated ammonium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and then the residue was purified and

15 concentrated by column chromatography (silica; ethyl acetate/hexane= 30%) to give the desired compound of **Formula 8-5** (3.86 g, 87%) in the form of a yellow solid.

(**Formula 8-6**: methyl 4-((N-(4-(1-methyl-1H-indazol-6-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)

20

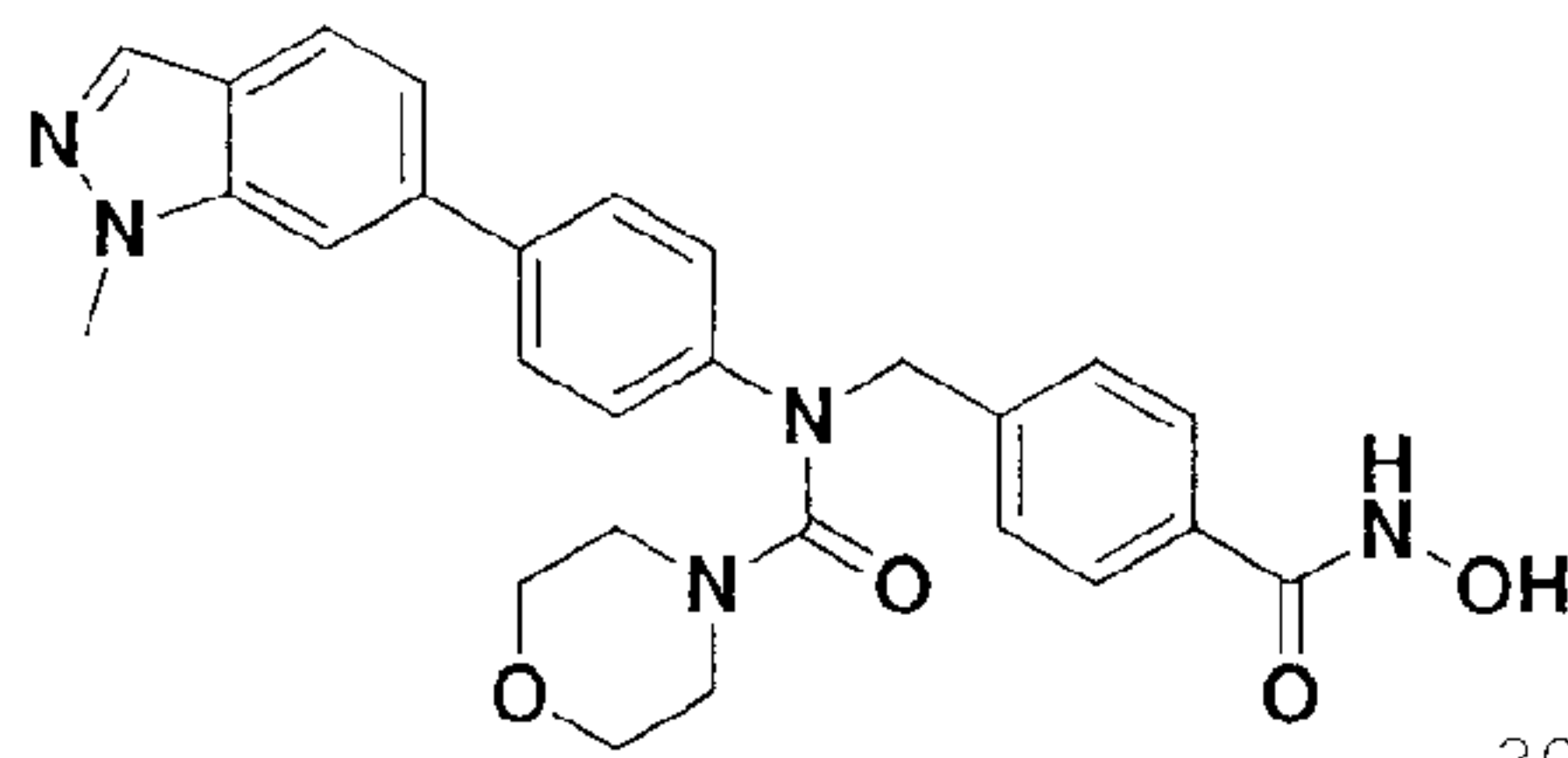


Compound of **Formula 8-5**

25 (methyl 4-((N-(4-bromophenyl)morpholine-4-

carboxamido)methyl)benzoate; 0.185 g, 0.427 mmol), 1-methyl-indazol-6-ylboronic acid (0.090 g, 0.512 mmol), and Pd(dppf)Cl₂ (0.035 g, 0.043 mmol) were dissolved in 1,4-dioxane (3 mL), and then sodium carbonate (0.181 g, 1.71 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 80 °C for 16 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 8-6** (0.112 g, 71%) in the form of a white solid.

(**Compound 329**: N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(1-methyl-1H-indazol-6-yl)phenyl)morpholine-4-carboxamide)



20

Compound of **Formula**

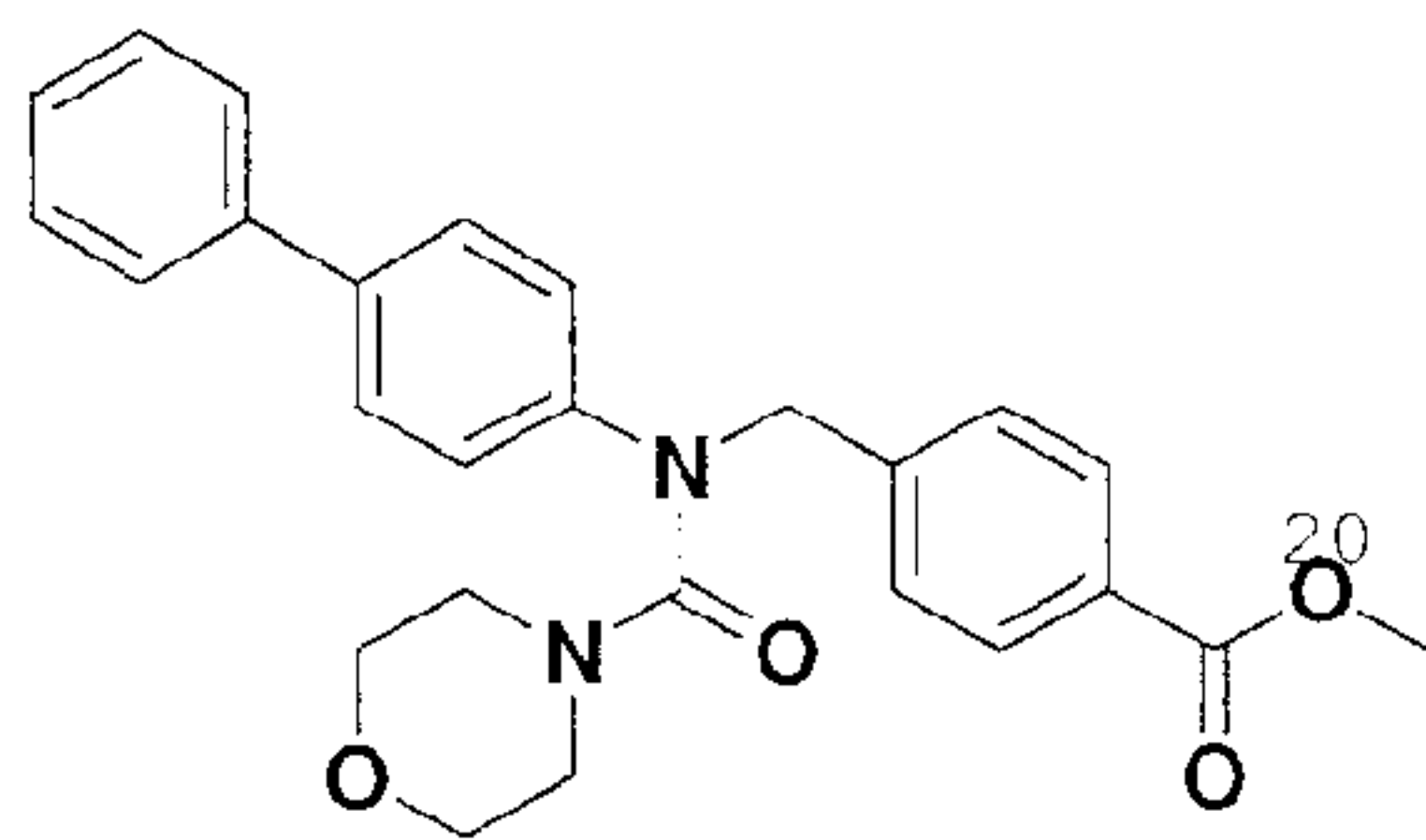
8-6 (methyl 4-((N-(4-(1-methyl-1H-indazol-6-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.112 g, 0.231 mmol) was dissolved in methanol (5 mL), and then hydroxylamine (50.0 wt% aqueous solution; 1.41 mL, 23.1 mmol) and potassium hydroxide (0.130 g, 2.31 mmol) added

sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 2 mL, and saturated ammonium chloride
 5 aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 329** (0.096 g, 86%) in the form of a light brown solid.

¹H NMR (400 MHz, DMSO-d₆) δ 8.02 (s, 1 H), 7.88 (s, 1 H),
 10 7.77 (d, 1 H, J = 8.4 Hz), 7.73 (d, 2 H, J = 8.6 Hz), 7.66 (d, 2 H, J = 8.2 Hz), 7.42 - 7.39 (m, 3 H), 7.26 (d, 2 H, J = 8.5 Hz), 4.93 (s, 2 H), 4.07 (s, 3 H), 3.47 - 3.43 (m, 4 H), 3.22-3.17 (m, 4 H). **MS** (ESI) m/z 486 (M⁺ + H).

15 **Example 18: Synthesis of Compound 330**

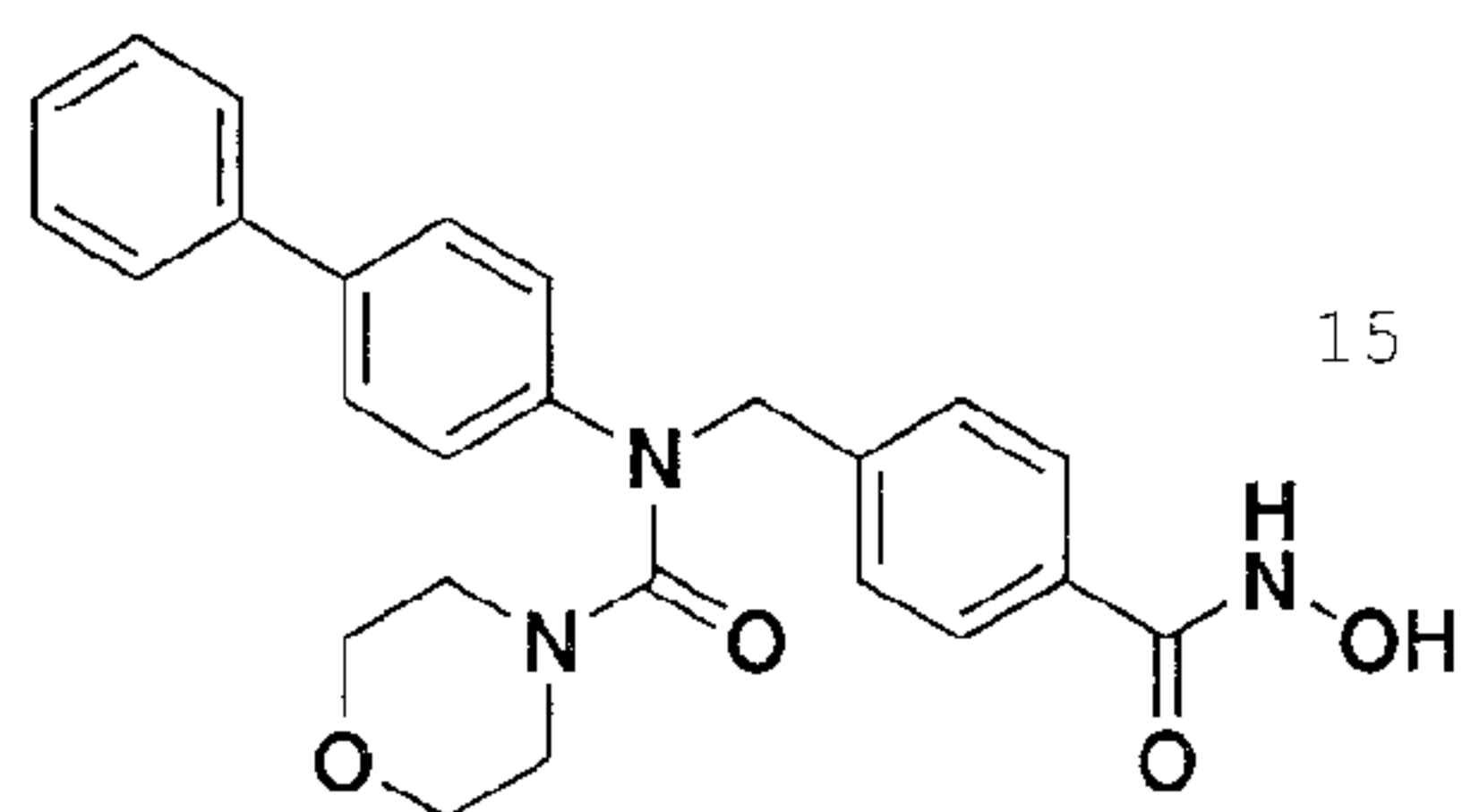
(**Formula 8-6**: methyl 4-((N (biphenyl-4-yl)morpholine-4-carboxamido)methyl)benzoate)



Compound of **Formula 8-5** (methyl 4-((N-(4-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g,
 25 0.462 mmol), phenylboronic acid (0.068 g, 0.554 mmol), and

Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and then sodium carbonate (0.196 g, 1.85 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 6 hours. After completion
 5 of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=60%) to give the
 10 desired compound of **Formula 8-6** (0.160 g, 81%) in the form of a white solid.

(**Compound 330**: N-(biphenyl-4-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide)



Compound of **Formula 8-6**

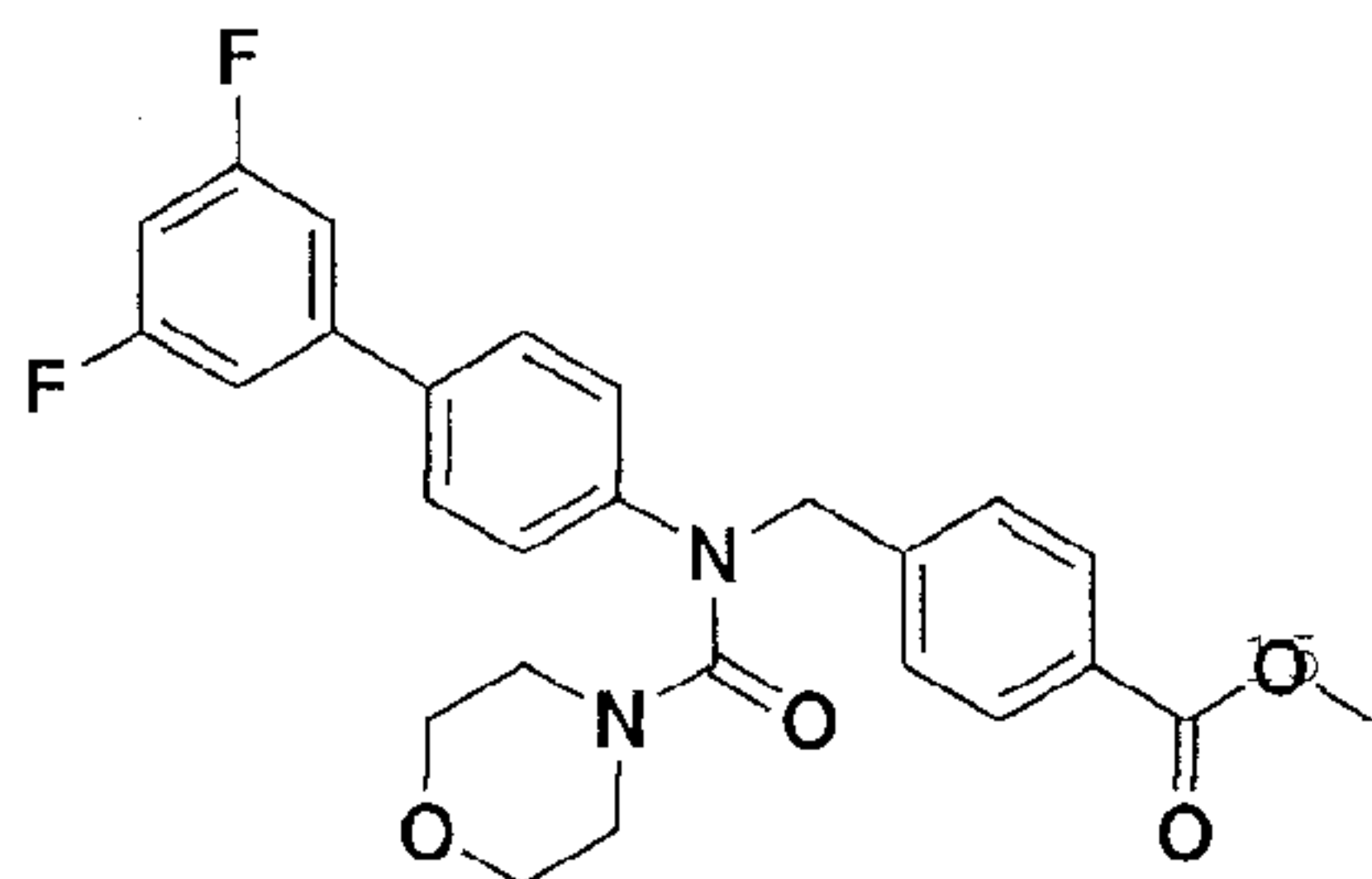
(methyl 4-((N-(biphenyl-4-yl)morpholine-4-carboxamido)methyl)benzoate; 0.160 g, 0.372
 20 mmol) was dissolved in methanol (10 mL), and then hydroxylamine (50.0 wt% aqueous solution; 2.27 mL, 37.2 mmol) and potassium hydroxide (0.209 g, 3.72 mmol) added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction
 25 solution was concentrated under reduced pressure until its

volume became about 3 mL, and saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 330** (0.120 g, 75%)
 5 in the form of a light brown solid.

MS (ESI) m/z 432 ($M^+ + H$).

Example 19: Synthesis of Compound 331

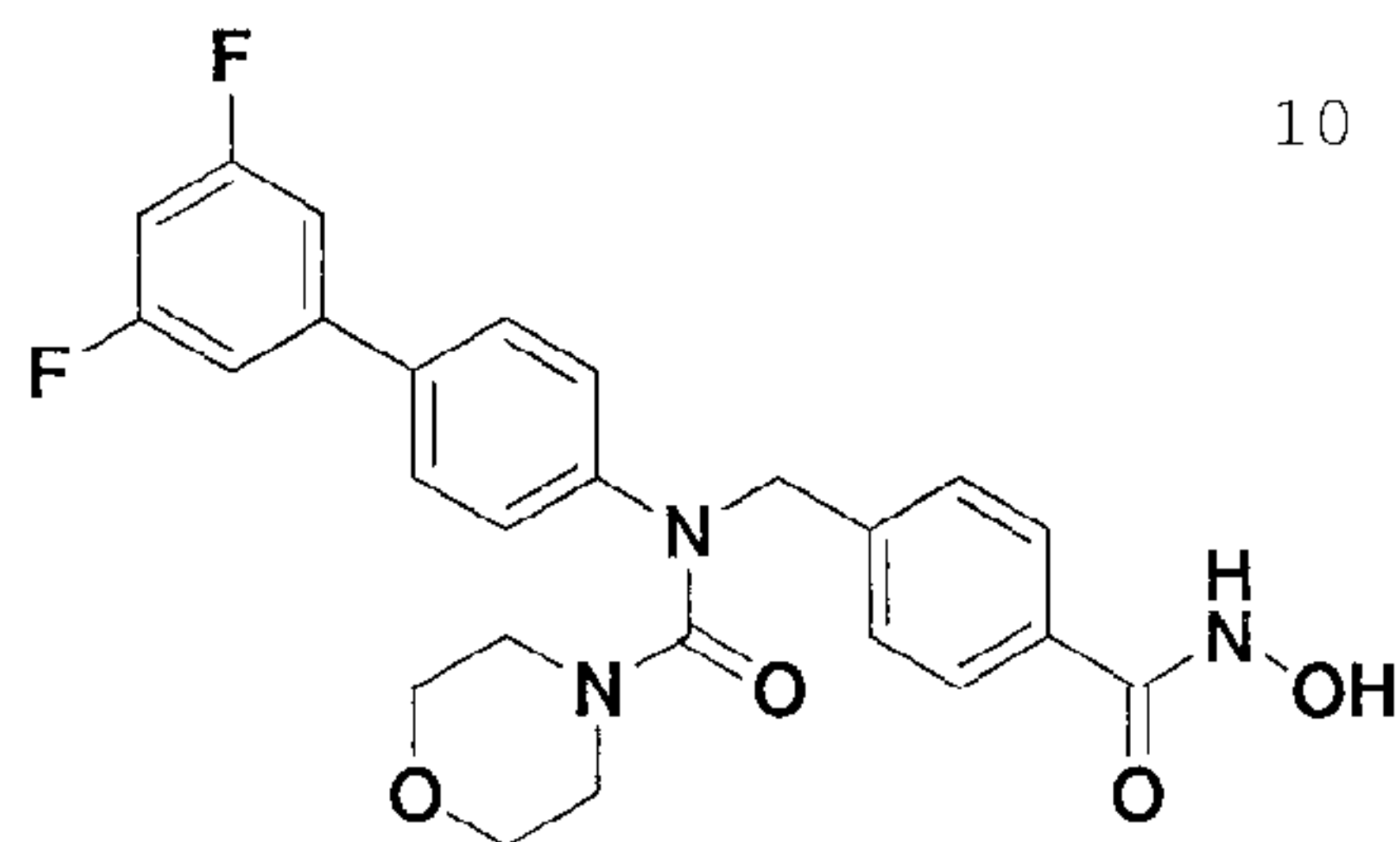
(**Formula 8-6**: methyl 4-((N-(3',5'-difluorobiphenyl-4-yl)morpholine-4-carboxamido)methyl)benzoate)
 10



Compound of **Formula 8-5** (methyl 4-((N-(4-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), 3',5'-difluorophenylboronic acid (0.088 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and then sodium carbonate (0.196 g, 1.85 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 6 hours. After
 25 completion of the reaction, the organic layer was extracted

with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=60%) to give the
 5 desired compound of **Formula 8-6** (0.169 g, 79%) in the form of a white solid.

(**Compound 331**: N-(3',5'-difluorobiphenyl-4-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide)



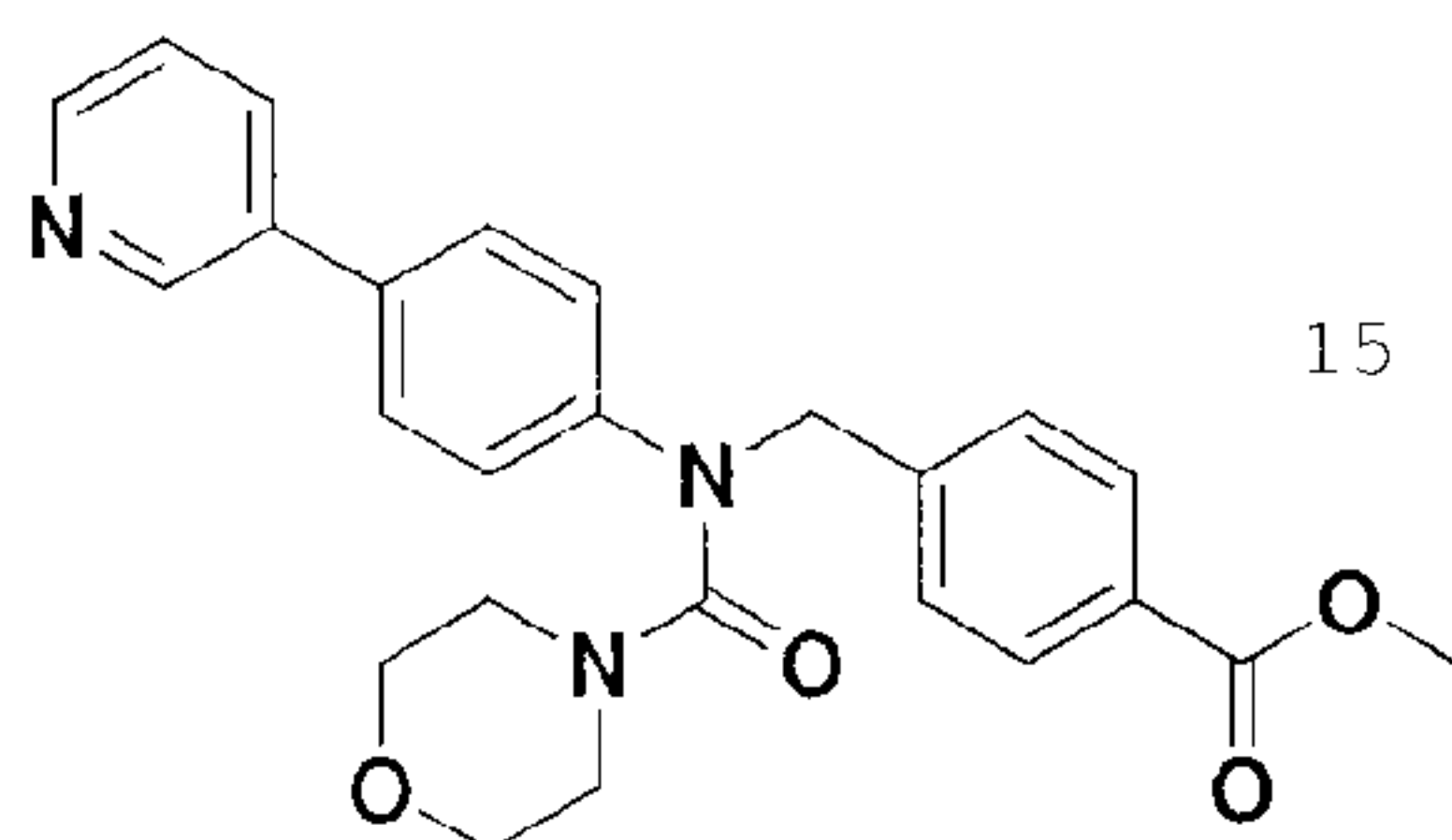
Compound of **Formula 8-6** (methyl 4-((N-(3',5'-difluorobiphenyl-4-yl)morpholine-4-carboxamido)methyl)benzoate; 0.169 g, 0.362 mmol) was dissolved in methanol (10 mL), and then hydroxylamine (50.0
 20 wt% aqueous solution; 2.22 mL, 36.2 mmol) and potassium hydroxide (0.203 g, 3.62 mmol) added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 3 mL, and
 25 saturated ammonium chloride aqueous solution (1-2 mL) was

added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 331** (0.102 g, 60%) in the form of a light brown solid.

5 ^1H NMR (400 MHz, DMSO- d_6) δ 7.70 (d, 2 H, J = 8.8 Hz), 7.65 (d, 2 H, J = 8.3 Hz), 7.43 - 7.37 (m, 4 H), 7.22 (d, 2 H, J = 8.8 Hz), 7.17 (m, 1 H), 4.92 (s, 2 H), 3.44 (t, 4 H, J = 4.6 Hz), 3.18 (t, 4 H, J = 4.6 Hz). **MS** (ESI) m/z 468 (M^+ + H).

10 **Example 20: Synthesis of Compound 332**

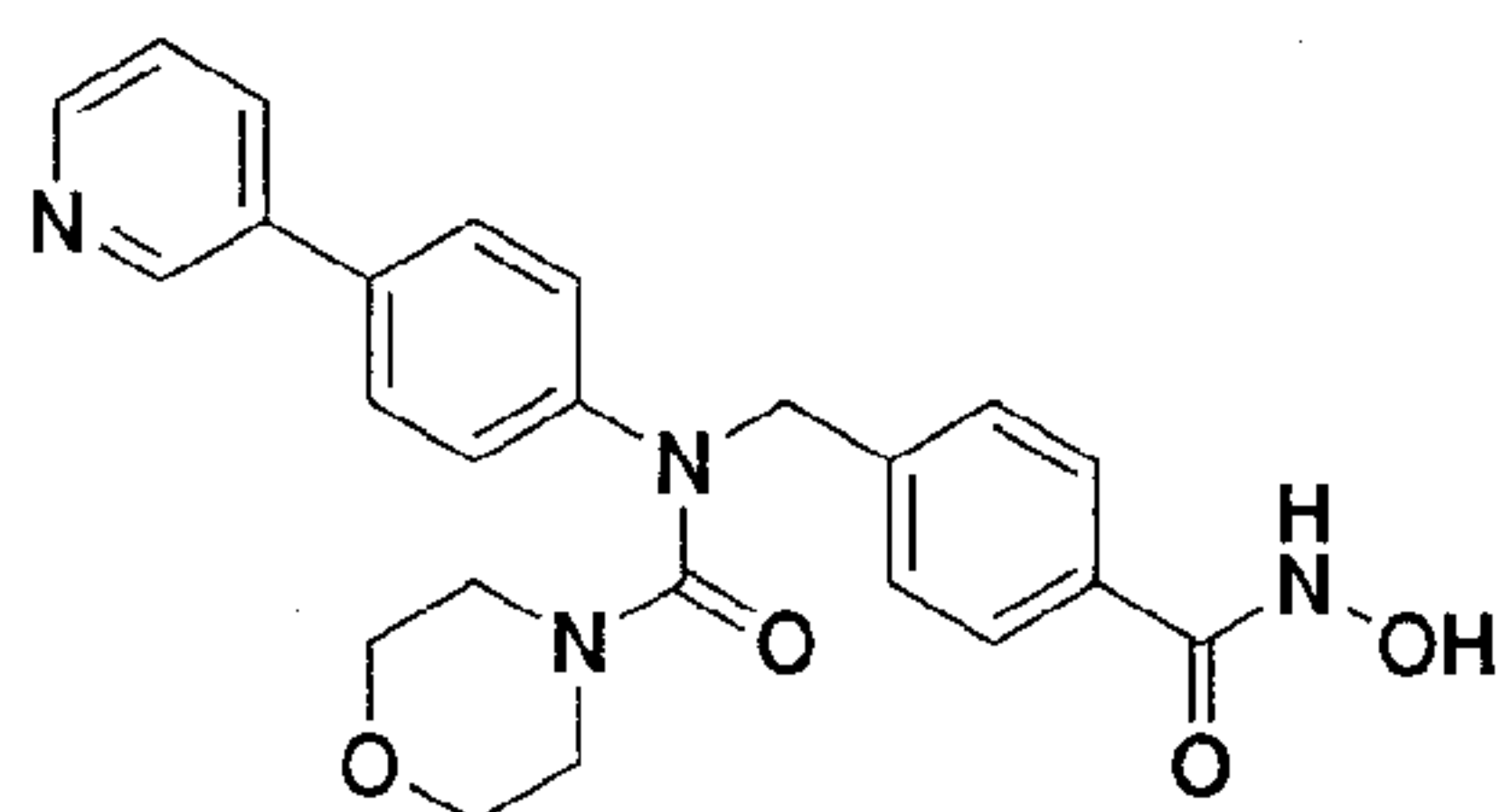
(**Formula 8-6**: methyl 4-((N-(4-(pyridine-3-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)



20 Compound of **Formula 8-5** (methyl 4-((N-(4-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), pyridine-3-ylboronic acid (0.068 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and then sodium carbonate (0.196 g, 1.85
25 mmol) dissolved in water (1 mL) was added to the reaction

solution and stirred at 100 °C for 6 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then
 5 the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=75%) to give the desired compound of **Formula 8-6** (0.132 g, 66%) in the form of a white solid.

(**Compound 332**: N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(pyridin-3-yl)phenyl)morpholine-4-carboxamide)
 10



15

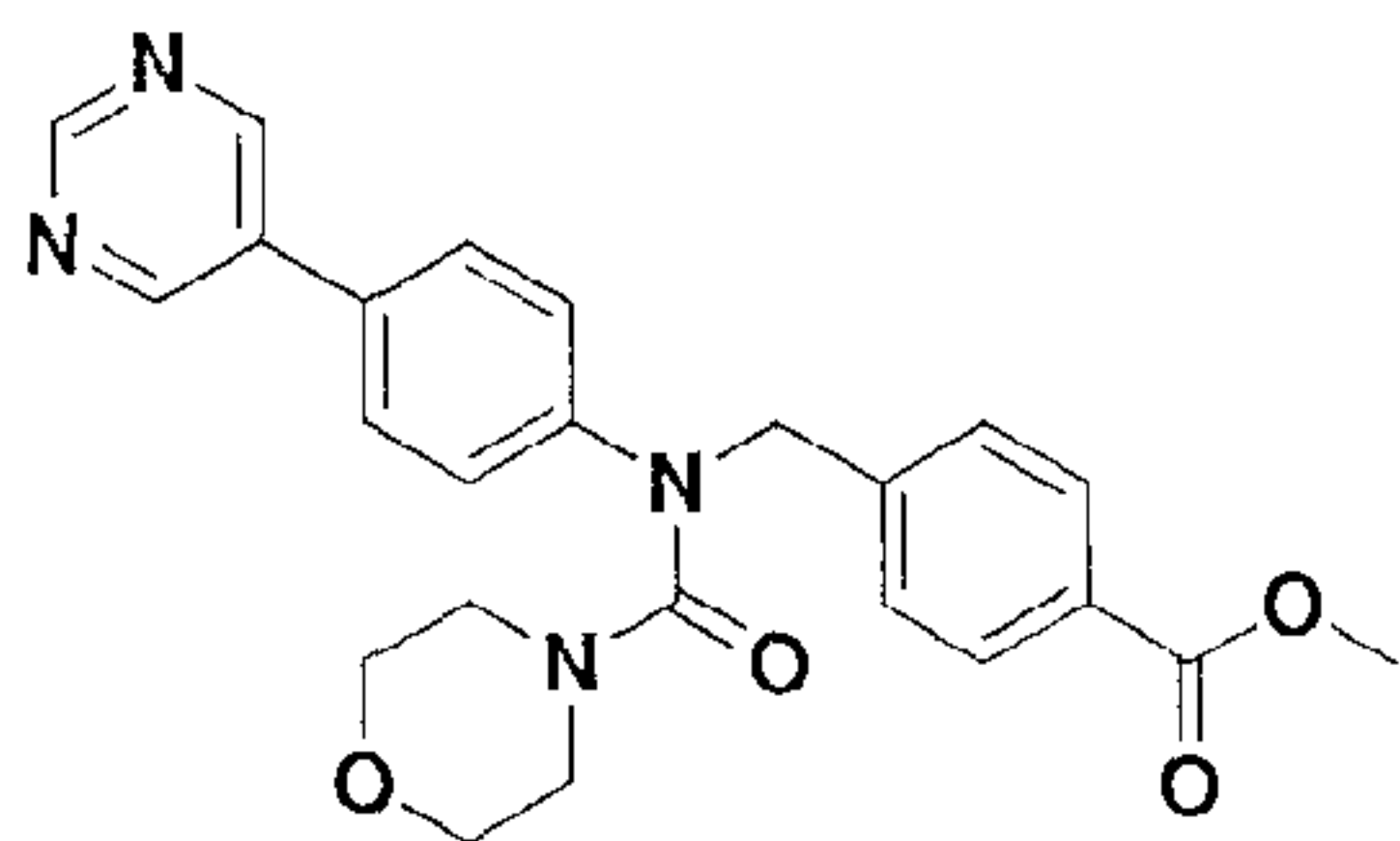
Compound of **Formula 8-6** (methyl 4-((N-(4-(pyridine-3-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.132 g, 0.306 mmol) was dissolved in methanol (10 mL), and then
 20 hydroxylamine (50.0 wt% aqueous solution; 1.87 mL, 30.6 mmol) and potassium hydroxide (0.172 g, 3.06 mmol) added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its
 25 volume became about 3 mL, and saturated ammonium chloride

aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 332** (0.051 g, 39%) in the form of a brown solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.15 (s, 1 H), 9.00 (s, 1 H), 8.86 (s, 1 H), 8.52 (s, 1 H), 8.04 (d, 1 H, *J* = 5.2 Hz), 7.71 - 7.65 (m, 4 H), 7.43 - 7.38 (m, 3 H), 7.26 (d, 2 H, *J* = 6.8 Hz), 4.93 (s, 2 H), 3.44 (m, 4 H), 3.19 (m, 4 H). **MS** (ESI) *m/z* 433 (M⁺ + H).

Example 21: Synthesis of Compound 333

(**Formula 8-6**: methyl 4-((N-(4-(pyrimidin-5-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)

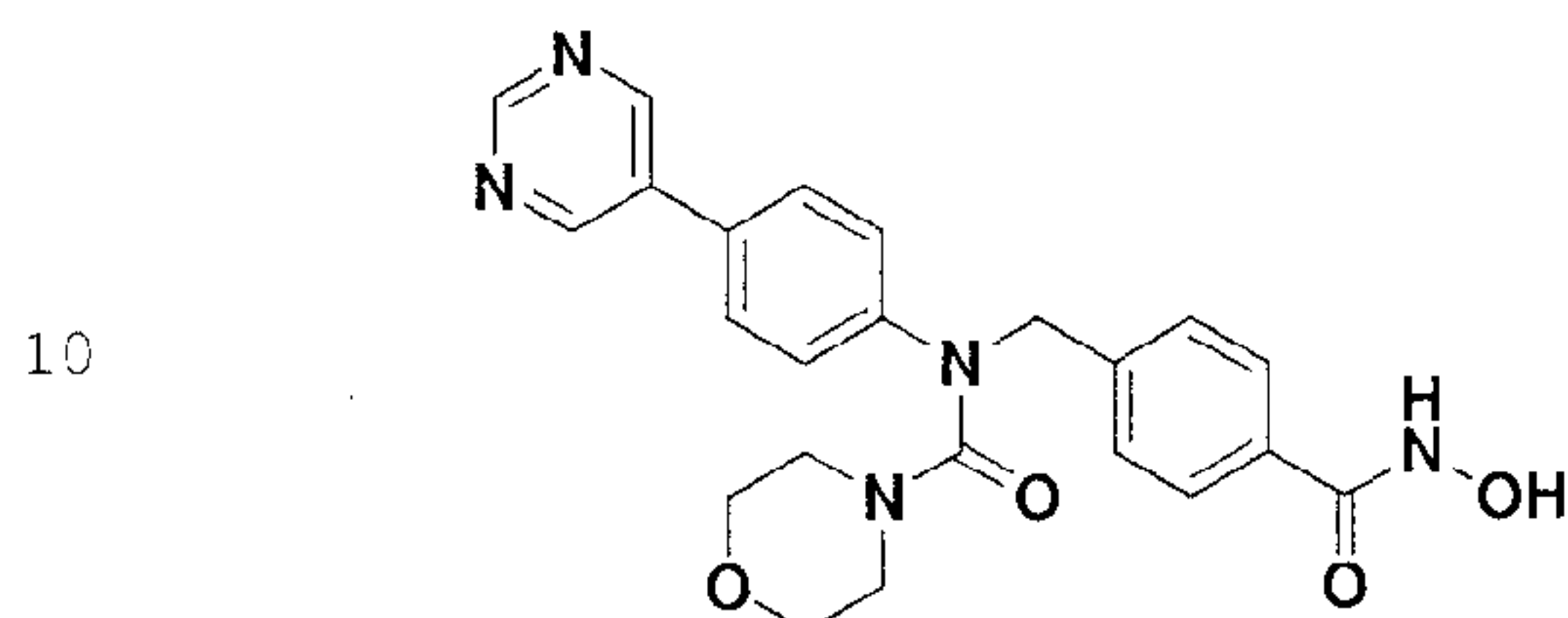


Compound of **Formula 8-5**

(methyl 4-((N-(4-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), pyrimidin-5-ylboronic acid (0.069 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and then sodium carbonate (0.196 g, 1.85 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 6 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated

sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=75%) to give the desired compound of **Formula 8-6** (0.148 g, 74%) in the form of a white solid.

(**Compound 333**: N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(pyrimidin-5-yl)phenyl)morpholine-4-carboxamide)



Compound of **Formula 8-6**

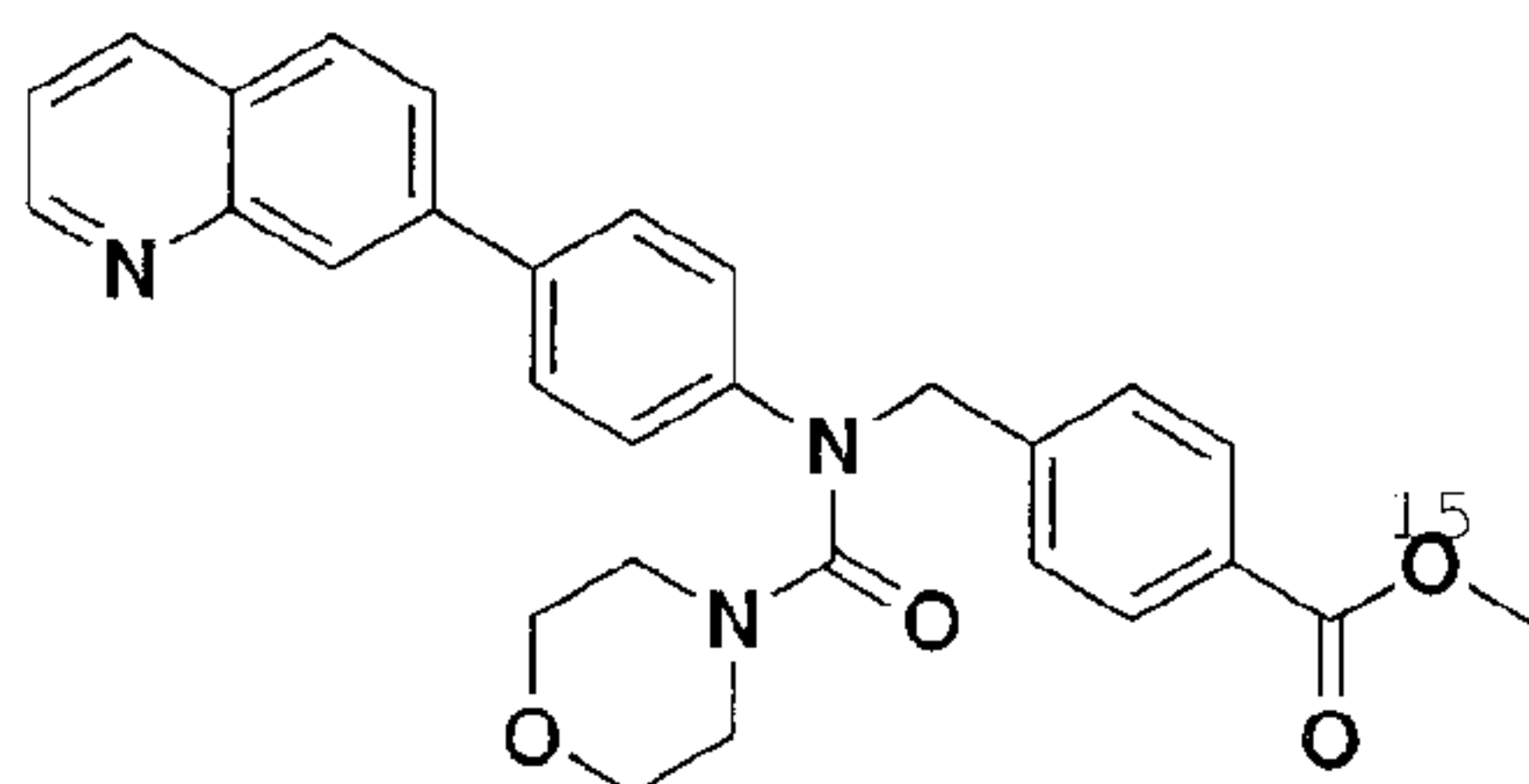
(methyl 4-((N-(4-(pyrimidin-5-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.148 g, 0.342 mmol) was dissolved in methanol (10 mL), and then hydroxylamine (50.0 wt% aqueous solution; 2.09 mL, 34.2 mmol) and potassium hydroxide (0.192 g, 3.42 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 3 mL, and the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution. The organic layer was dehydrated with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The residue was recrystallized with

dichloromethane and hexane to give the desired **Compound 333** (0.060 g, 40%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 9.13 (s, 1 H), 9.10 (s, 2 H), 7.77 (d, 2 H, *J* = 8.7 Hz), 7.65 (d, 2 H, *J* = 8.3 Hz), 7.39 (d, 2 H, *J* = 8.2 Hz), 7.29 (d, 2 H, *J* = 8.7 Hz), 4.94 (s, 2 H), 3.45 (t, 4 H, *J* = 4.6 Hz), 3.19 (t, 4 H, *J* = 4.6 Hz). MS (ESI) *m/z* 434 (M⁺ + H).

Example 22: Synthesis of Compound 334

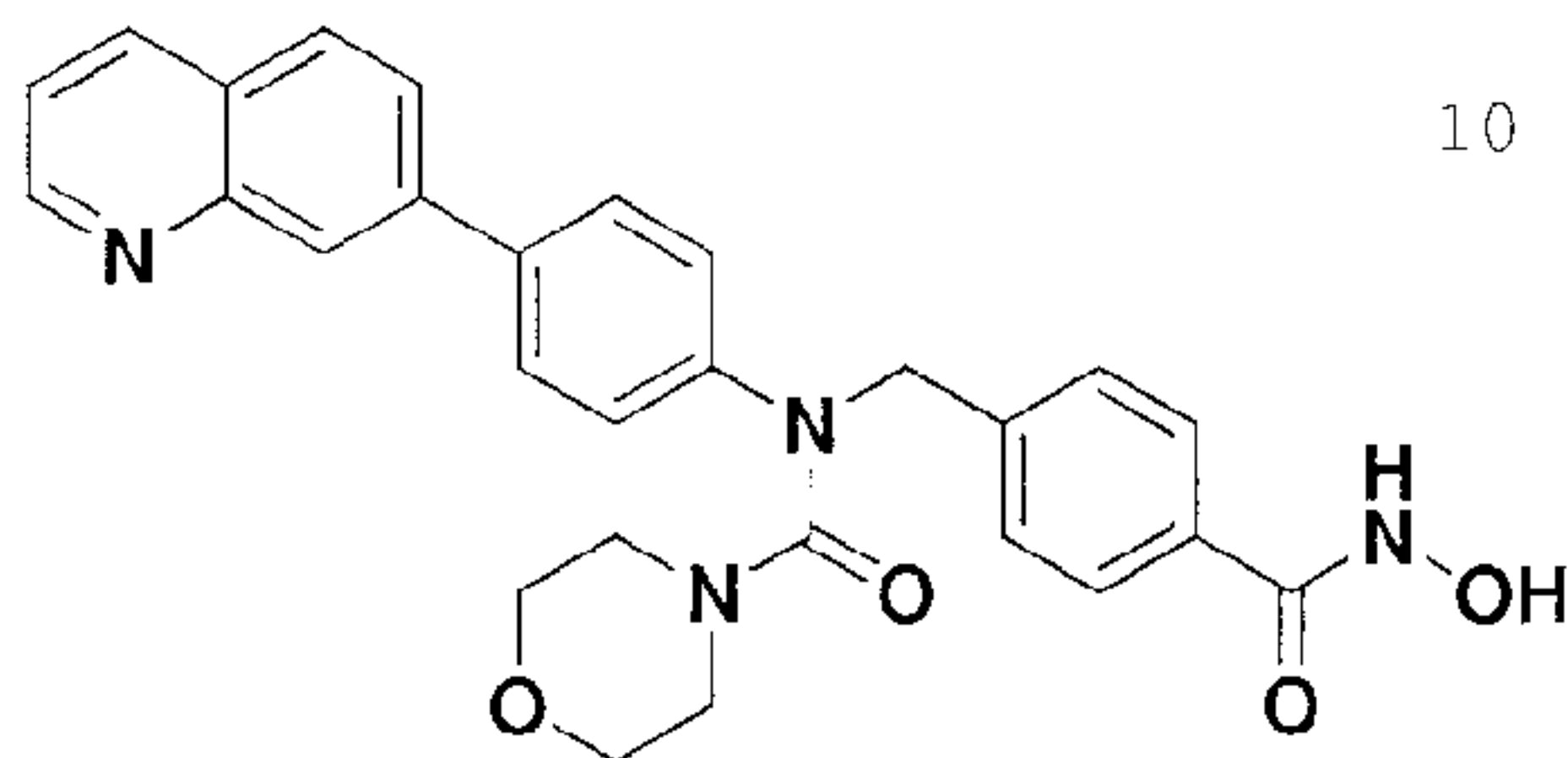
(**Formula 8-6**: methyl 4-((N-(4-(quinolin-7-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)



Compound of **Formula 8-5** (methyl 4-((N-(4-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), quinolin-7-ylboronic acid (0.096 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and then sodium carbonate (0.196 g, 1.85 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 6 hours. After completion

of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=70%) to give the desired compound of **Formula 8-6** (0.192 g, 86%) in the form of a light brown solid.

(**Compound 334**: N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(quinolin-7-yl)phenyl)morpholine-4-carboxamide)



15

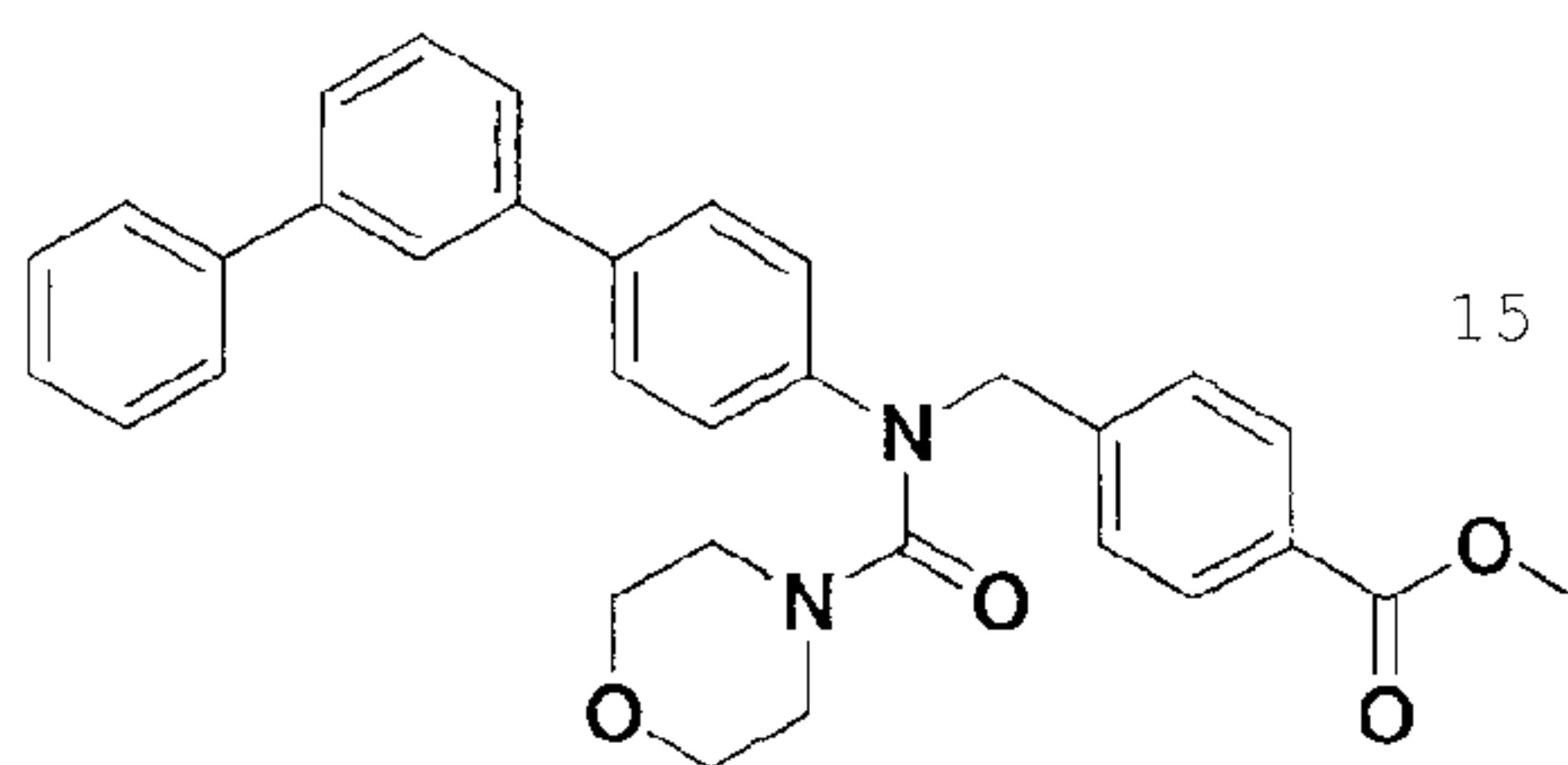
Compound of **Formula 8-6** (methyl 4-((N-(4-(quinolin-7-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.192 g, 0.399 mmol) was dissolved in methanol (10 mL), and then hydroxylamine (50.0 wt% aqueous solution; 2.44 mL, 39.9 mmol) and potassium hydroxide (0.224 g, 3.99 mmol) added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 3 mL, and saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the

solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 334** (0.173 g, 90%) in the form of a light brown solid.

¹H NMR (400 MHz, DMSO-d₆) δ 8.89 (m, 1 H), 8.41 (dd, 1 H, *J* = 8.3, 1.7 Hz), 7.96 (m, 1 H), 7.74 (m, 1 H), 7.71 – 7.63 (m, 5 H), 7.55 (dd, 1 H, *J* = 8.2, 4.1 Hz), 7.43 (d, 2 H, *J* = 8.2 Hz), 7.25 (d, 2 H, *J* = 8.6 Hz), 4.95 (s, 2 H), 3.48 – 3.45 (m, 4 H), 3.24 – 3.20 (m, 4 H). **MS**(ESI) *m/z* 483 (M⁺ + H).

10 **Example 23: Synthesis of Compound 335**

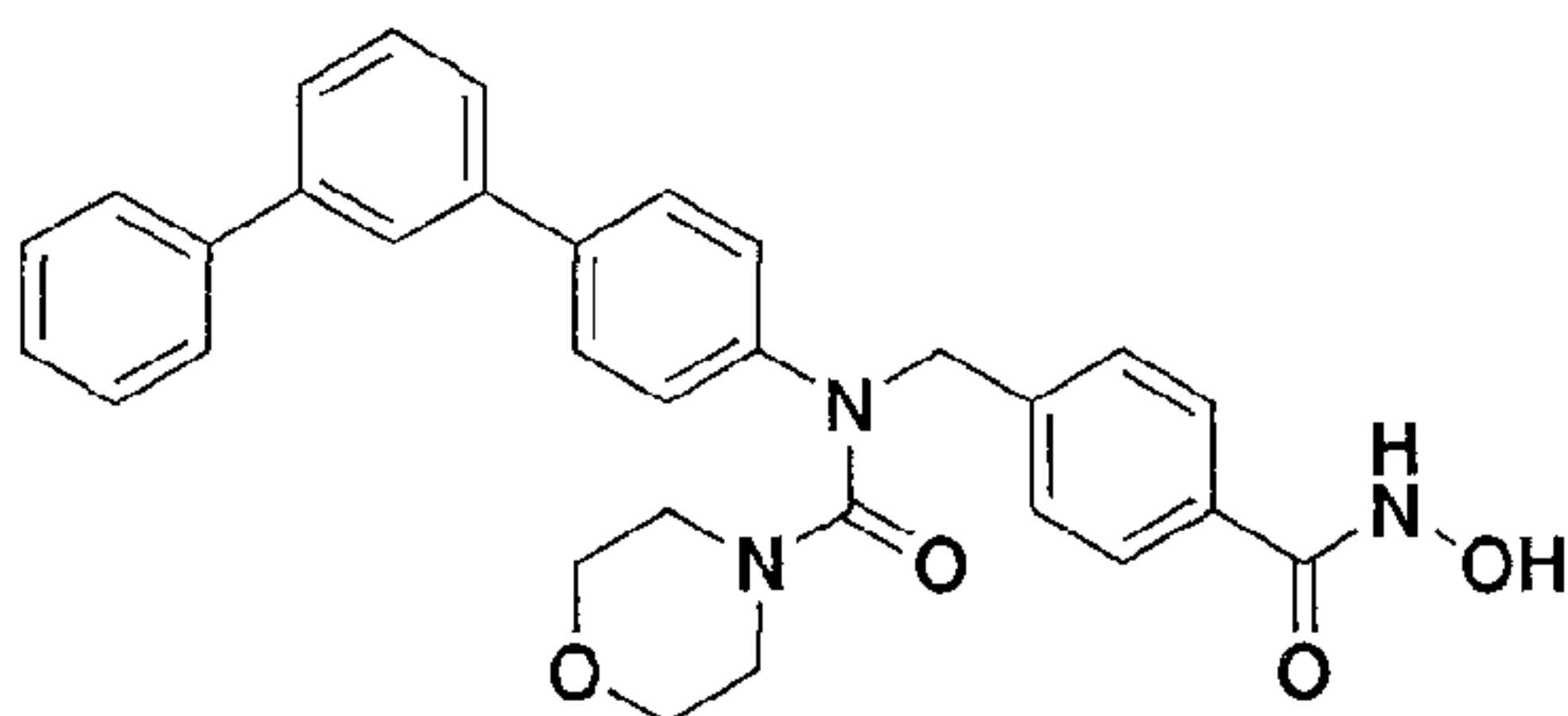
(**Formula 8-6**: methyl 4-((N-(4-(biphenyl-3-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)



20 Compound of **Formula 8-5** (methyl 4-((N-(4-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), biphenyl-3-ylboronic acid (0.110 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and then sodium carbonate (0.196 g, 1.85
25 mmol) dissolved in water (1 mL) was added to the reaction

solution and stirred at 100 °C for 6 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then
 5 the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=70%) to give the desired compound of **Formula 8-6** (0.230 g, 98%) in the form of a white solid.

(**Compound 335**: N-(4-(hydroxycarbamoyl)benzyl) N-(4-(biphenyl-3-yl)phenyl)morpholine-4-carboxamide)
 10



15

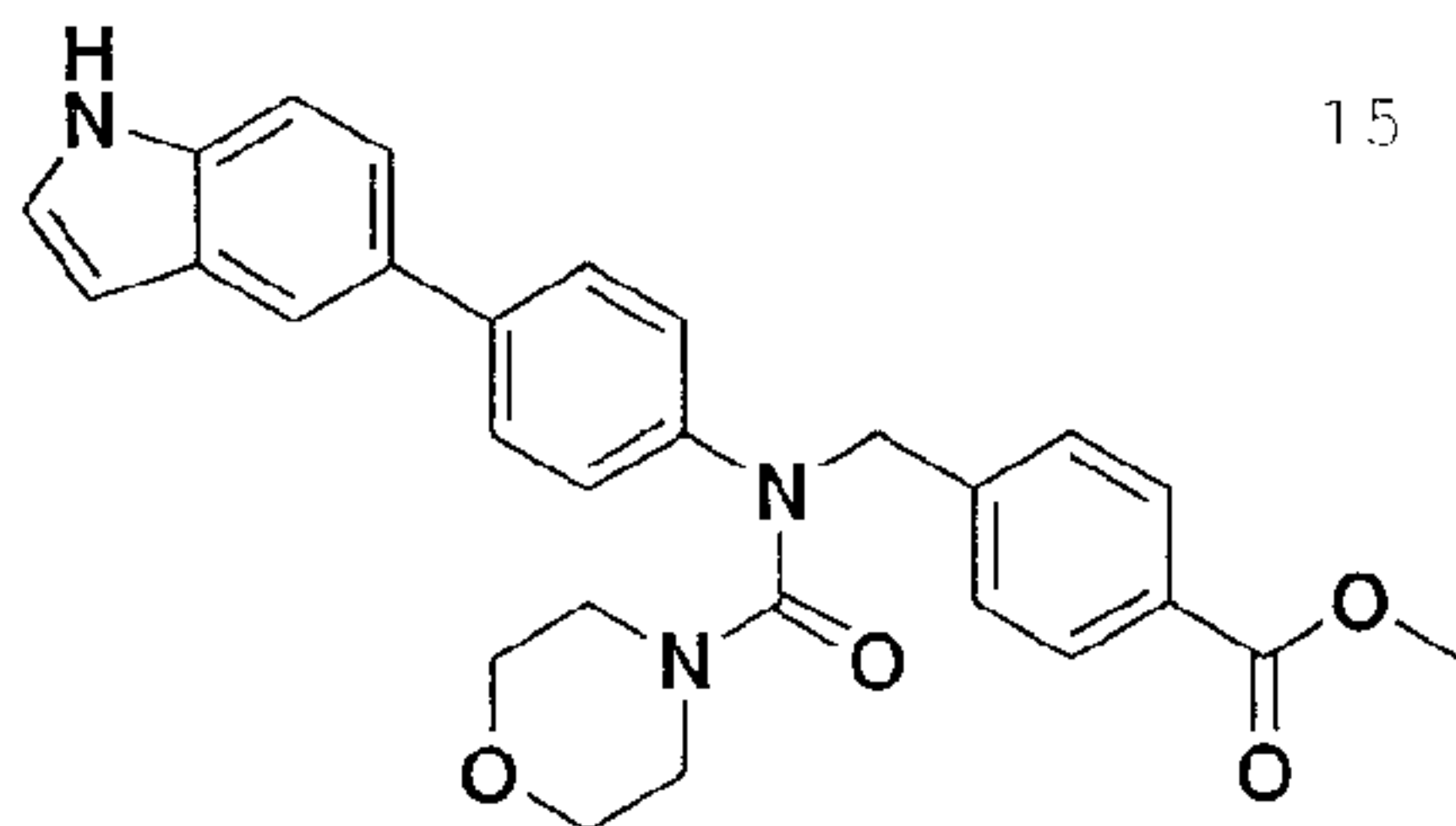
Compound of **Formula 8-6** (methyl 4-((N-(4-(biphenyl-3-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.230 g, 0.454 mmol) was dissolved in methanol (10 mL), and then
 20 hydroxylamine (50.0 wt% aqueous solution; 2.78 mL, 45.4 mmol) and potassium hydroxide (0.255 g, 4.54 mmol) added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its
 25 volume became about 3 mL, and saturated ammonium chloride

aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 335** (0.220 g, 96%) in the form of a light brown solid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.86 (s, 1 H), 7.75 - 7.70 (m, 4 H), 7.67 (d, 2 H, *J* = 8.3 Hz), 7.63 - 7.60 (m, 2 H), 7.53 - 7.45 (m, 3 H), 7.41 - 7.39 (m, 3 H), 7.24 (d, 2 H, *J* = 8.6 Hz), 4.92 (s, 2 H), 3.44 - 3.42 (m, 4 H), 3.19 - 3.17 (m, 4 H). **MS** (ESI) *m/z* 508 (*M*⁺ + H).

Example 24: Synthesis of Compound 336

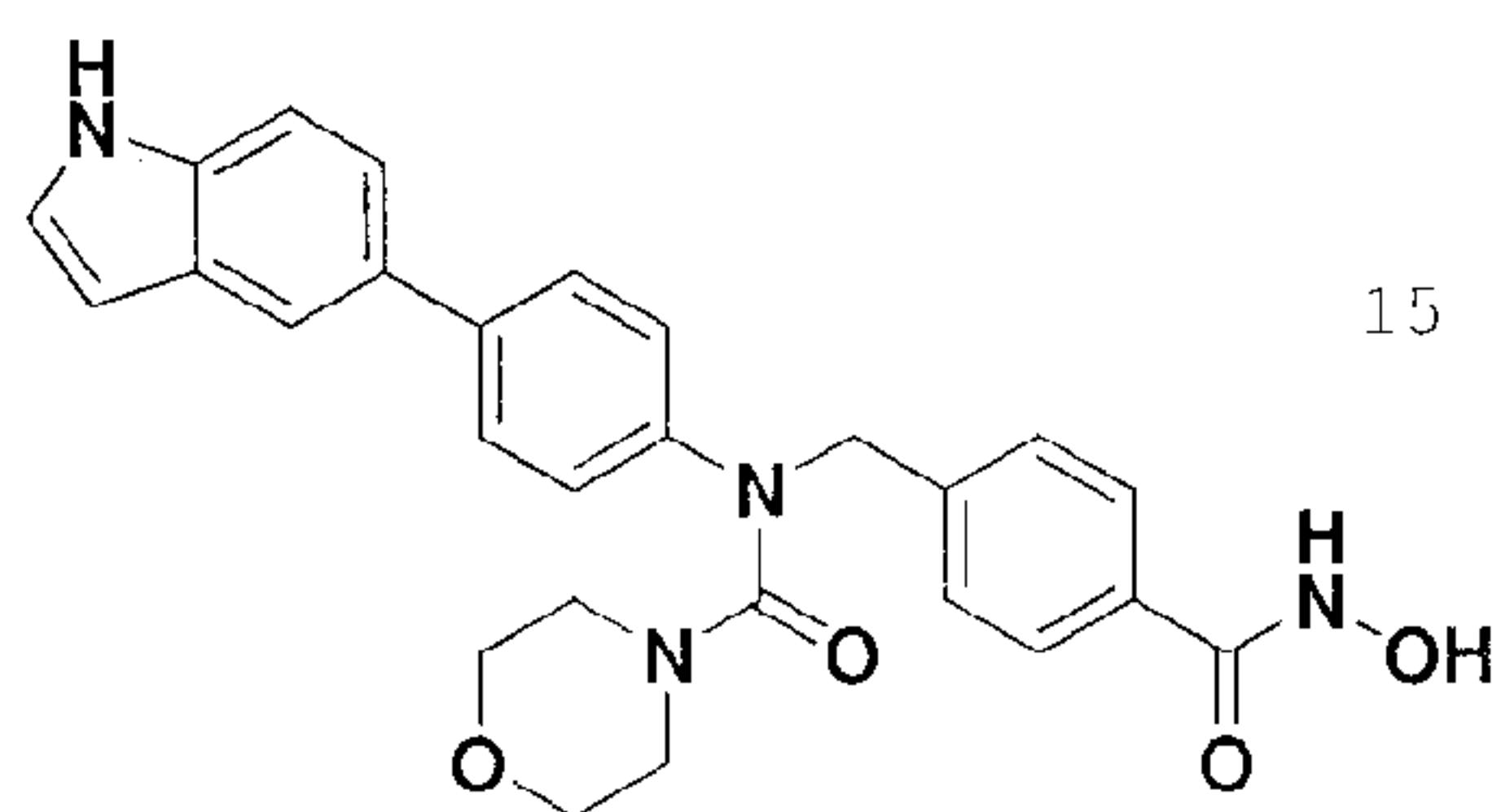
(**Formula 8-6**: methyl 4-((N-(4-(1H-indol-5-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)



Compound of **Formula 8-5** (methyl 4-((N-(4-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), indol-5-ylboronic acid (0.089 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and then sodium carbonate (0.196 g, 1.85

mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 6 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=70%) to give the desired compound of **Formula 8-6** (0.191 g, 88%) in the form of a light brown solid.

10 **(Compound 336: N-(4-(1H-indol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide)**



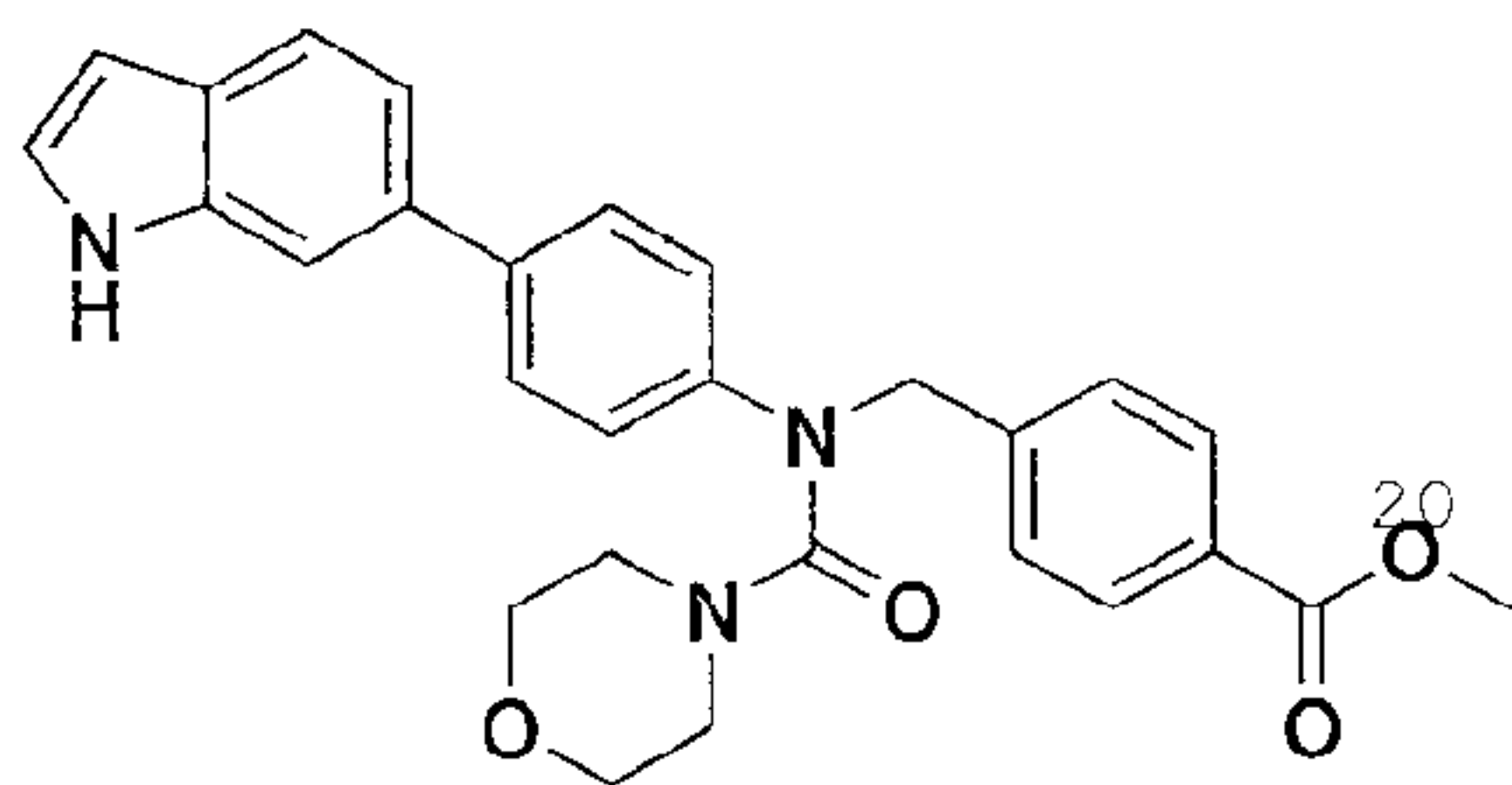
Compound of **Formula 8-6** (methyl 4-((N-(4-(1H-indol-5-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.191 g, 0.407 mmol) was dissolved in methanol (10 mL), and then hydroxylamine (50.0 wt% aqueous solution; 2.49 mL, 40.7 mmol) and potassium hydroxide (0.228 g, 4.07 mmol) added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction

solution was concentrated under reduced pressure until its volume became about 3 mL, and saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then
 5 vacuum dried to give the desired **Compound 336** (0.185 g, 97%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.14 (s, 1 H), 7.77 (s, 1 H), 7.66 (d, 2 H, *J* = 8.2 Hz), 7.61 (d, 2 H, *J* = 8.6 Hz), 7.44 - 7.38 (m, 3 H), 7.36 - 7.33 (m, 2 H), 7.19 (d, 2 H, *J* = 8.6
 10 Hz), 6.44 (s, 1 H), 4.90 (s, 2 H), 3.45 - 3.41 (m, 4 H), 3.21 - 3.17 (m, 4H). **MS** (ESI) *m/z* 471 (M⁺ + H).

Example 25: Synthesis of Compound 337

(**Formula 8-6**: methyl 4-((N-(4-(1H-indol-6-
 15 yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)

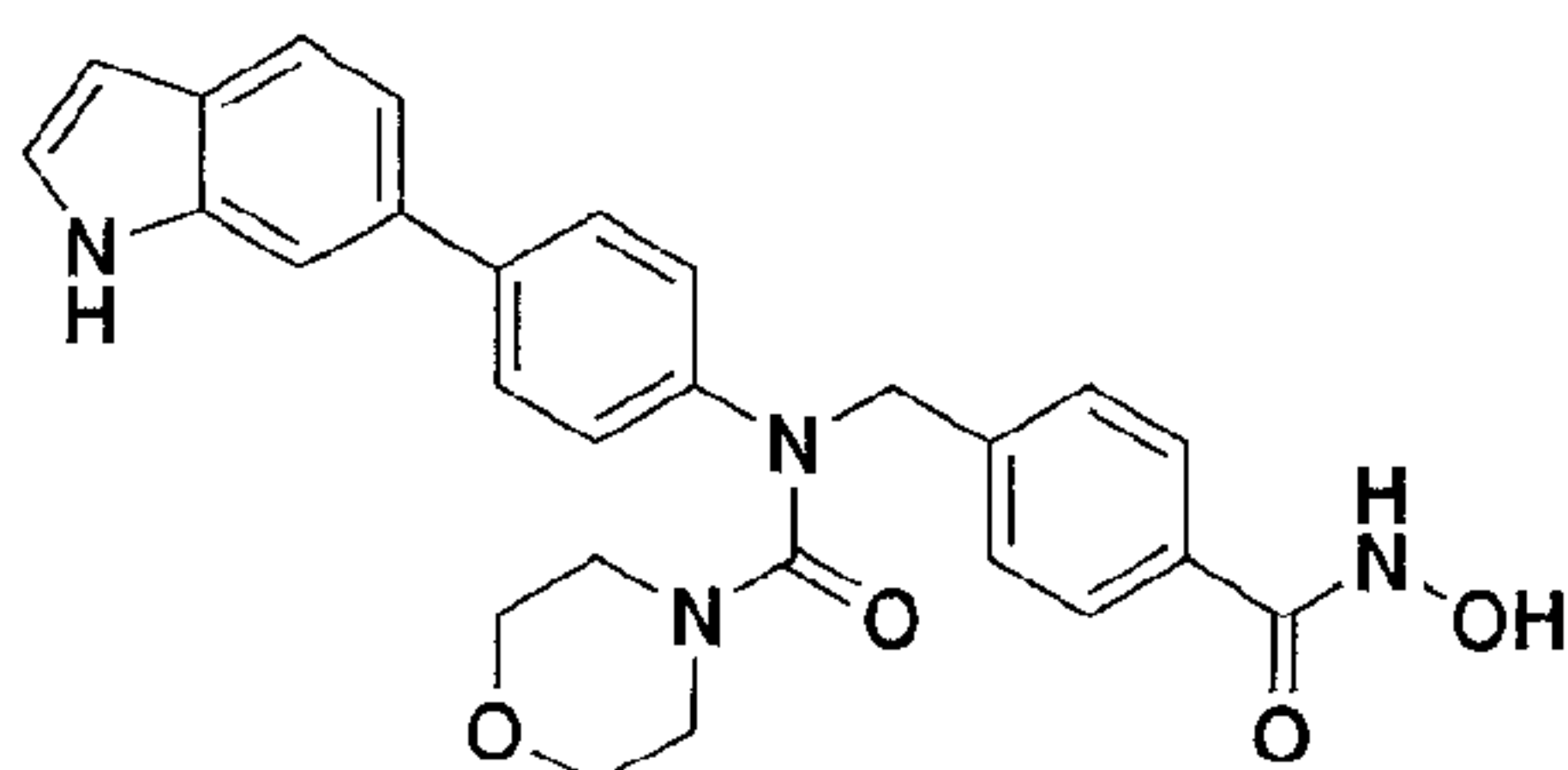


Compound of **Formula 8-5** (methyl 4-((N-(4-
 25 bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g,

0.462 mmol), indol-6-ylboronic acid (0.089 g, 0.554 mmol),
 and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-
 dioxane (3 mL), and then sodium carbonate (0.196 g, 1.85
 mmol) dissolved in water (1 mL) was added to the reaction
 5 solution and stirred at 100 °C for 6 hours. After completion
 of the reaction, the organic layer was extracted with ethyl
 acetate and saturated sodium hydrogen carbonate aqueous
 solution and concentrated under reduced pressure, and then
 the residue was purified and concentrated by column
 10 chromatography (silica; ethyl acetate/hexane=70%) to give the
 desired compound of **Formula 8-6** (0.201 g, 93%) in the form of
 a light brown solid.

(**Compound 337**: N-(4-(1H-indol-6-yl)phenyl)-N-(4-
 (hydroxycarbonyl)benzyl)morpholine-4-carboxamide)

15



20

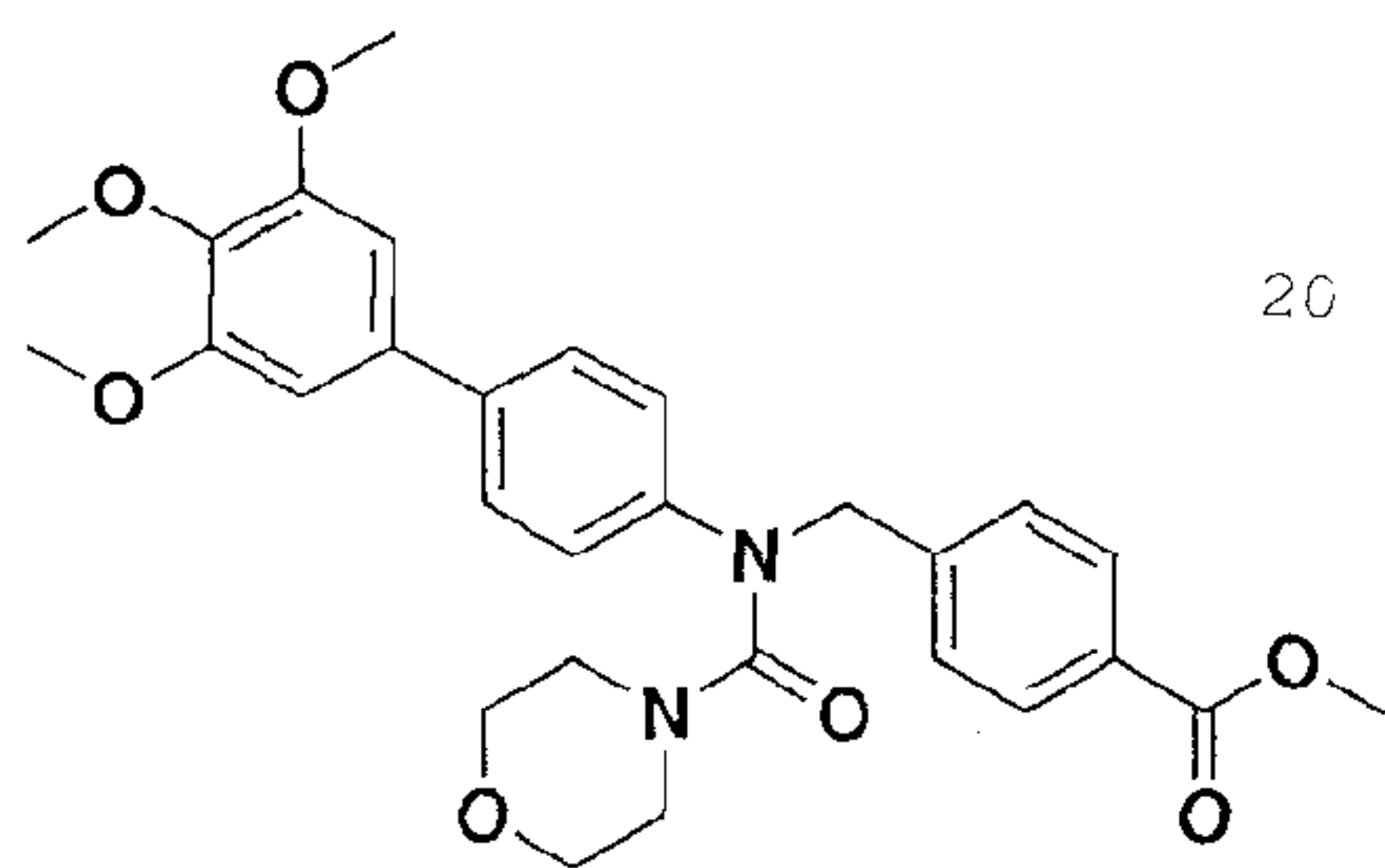
Compound of **Formula 8-6** (methyl 4-((N-(4-(1H-indol-6-
 yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.201 g,
 0.428 mmol) was dissolved in methanol (10 mL), and then
 hydroxylamine (50.0 wt% aqueous solution; 2.62 mL, 42.8 mmol)
 25 and potassium hydroxide (0.240 g, 4.28 mmol) added

sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 3 mL, and saturated ammonium chloride
 5 aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 337** (0.195 g, 97%) in the form of a light brown solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.15 (s, 1 H), 7.67 (d, 2 H, *J* = 8.2 Hz), 7.63 - 7.56 (m, 4H), 7.39 (d, 2 H, *J* = 8.2 Hz), 7.36 (m, 1 H), 7.26 (m, 1 H), 7.21 (d, 2 H, *J* = 8.6 Hz), 6.42 (s, 1 H), 4.91 (s, 2 H), 3.44 - 3.42 (m, 4 H), 3.19 - 3.17 (m, 4 H). MS (ESI) *m/z* 471 (M⁺ + H).

15 **Example 26: Synthesis of Compound 338**

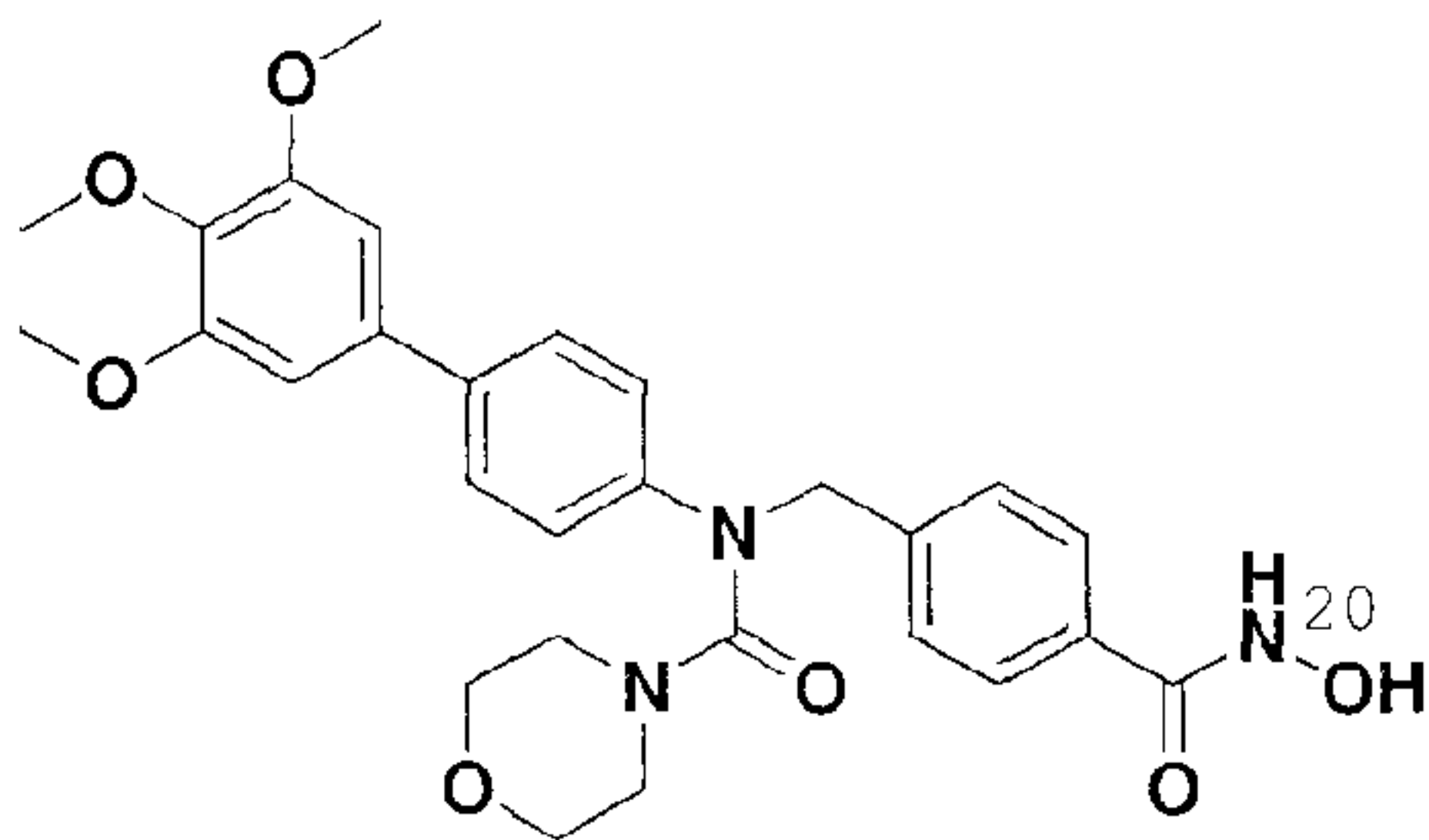
(**Formula 8-6**: methyl 4-((N-(3',4',5'-trimethoxybiphenyl-4-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)



25

Compound of **Formula 8-5** (methyl 4-((N-(4-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), 3,4,5-trimethoxyphenylboronic acid (0.117 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and then sodium carbonate (0.196 g, 1.85 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 6 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=70%) to give the desired compound of **Formula 8-6** (0.121 g, 50%) in the form of a white solid.

(**Compound 338**: N-(4-(hydroxycarbamoyl)benzyl)-N-(3',4',5'-trimethoxybiphenyl-4-yl)morpholine-4-carboxamide)



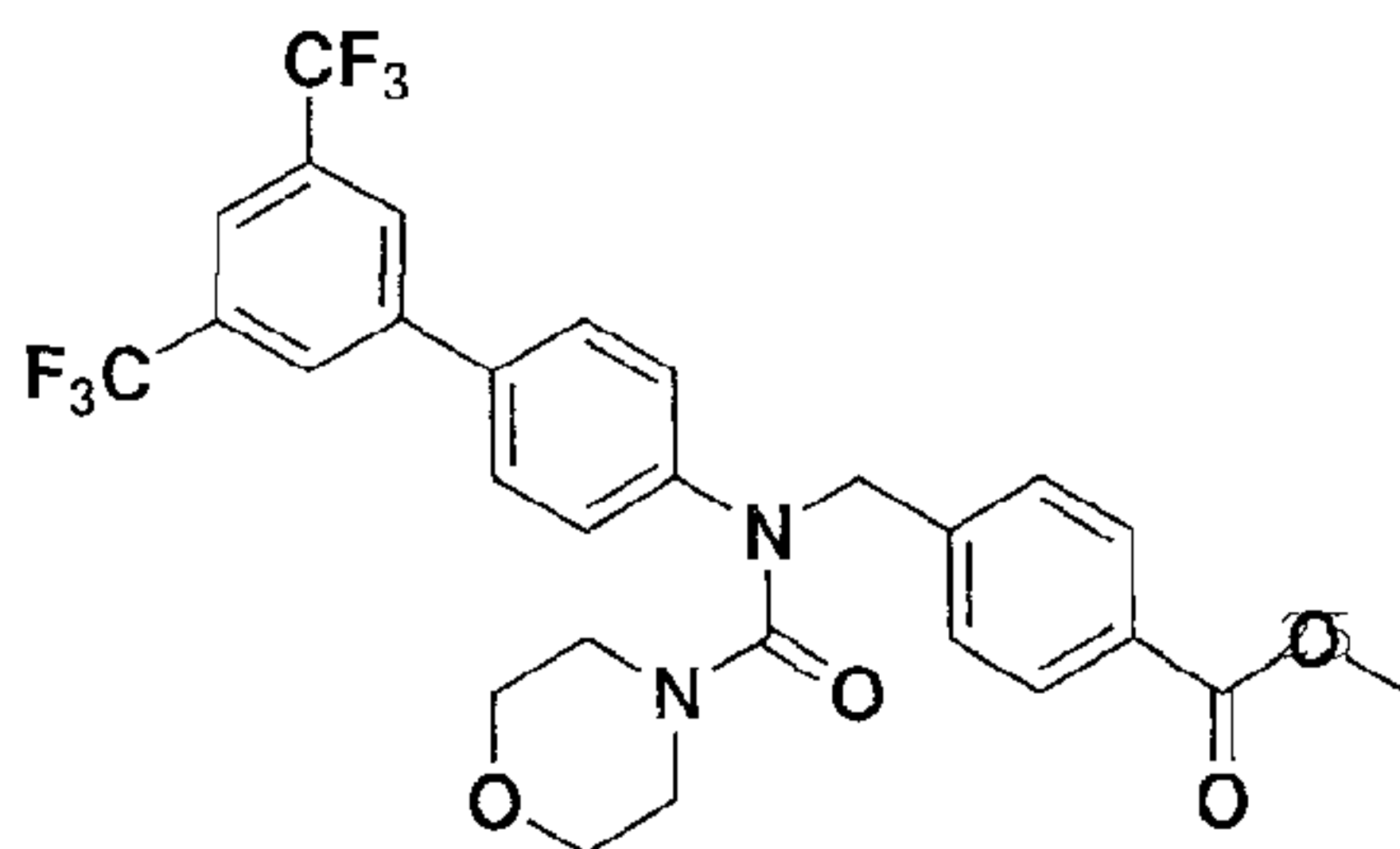
Compound of **Formula 8-6** (methyl 4-((N-(3',4',5'-trimethoxybiphenyl-4-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.121 g, 0.232 mmol) was

dissolved in methanol (10 mL), and then hydroxylamine (50.0
 wt% aqueous solution; 1.42 mL, 23.2 mmol) and potassium
 hydroxide (0.130 g, 2.32 mmol) added sequentially and then
 stirred at room temperature for 30 minutes. After completion
 5 of the reaction, the reaction solution was concentrated under
 reduced pressure until its volume became about 3 mL, and
 saturated ammonium chloride aqueous solution (1-2 mL) was
 added and stirred. Then, the solid product was filtered,
 washed with water, and then vacuum dried to give the desired
 10 **Compound 338** (0.038 g, 31%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.66 -7.61 (m, 4 H), 7.38 (d,
 2 H, J = 8.2 Hz), 7.20 (d, 2 H, J = 8.6 Hz), 6.86 (s, 2 H),
 4.91 (s, 2 H), 3.83 (s, 6 H), 3.66 (s, 3 H), 3.44 (t, 4 H, J
 = 4.3 Hz), 3.17 (t, 4 H, J = 4.4 Hz). **MS** (ESI) m/z 522 (M⁺ +
 15 H).

Example 27: Synthesis of Compound 339

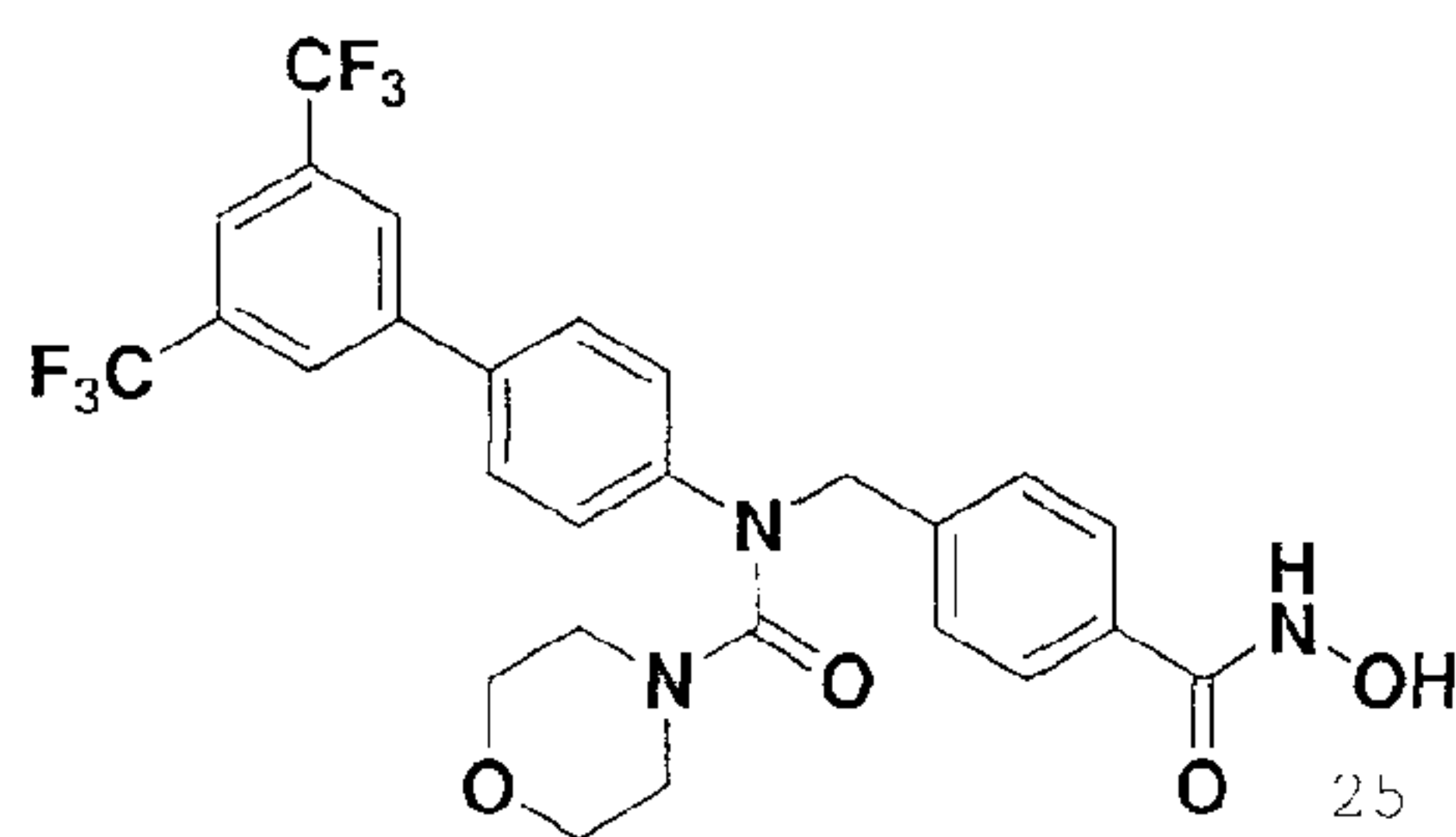
(Formula 8-6: methyl 4-((N-(3',5'-
 bis(trifluoromethyl)biphenyl-4-yl))morpholine-4-
 20 carboxamido)methyl)benzoate)



Compound of **Formula 8-5** (methyl 4-((N-(4-
 5 bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g,
 0.462 mmol), 3,5- bis(trifluoromethyl)phenylboronic acid
 (0.143 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol)
 were dissolved in 1,4-dioxane (3 mL), and then sodium
 carbonate (0.196 g, 1.85 mmol) dissolved in water (1 mL) was
 10 added to the reaction solution and stirred at 100 °C for 6
 hours. After completion of the reaction, the organic layer
 was extracted with ethyl acetate and saturated sodium
 hydrogen carbonate aqueous solution and concentrated under
 reduced pressure, and then the residue was purified and
 15 concentrated by column chromatography (silica; ethyl
 acetate/hexane=50%) to give the desired compound of **Formula**
8-6 (0.203 g, 78%) in the form of a white solid.

(**Compound 339**: N-(3',5'-bis(trifluoromethyl)biphenyl-4-
 yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide)

20



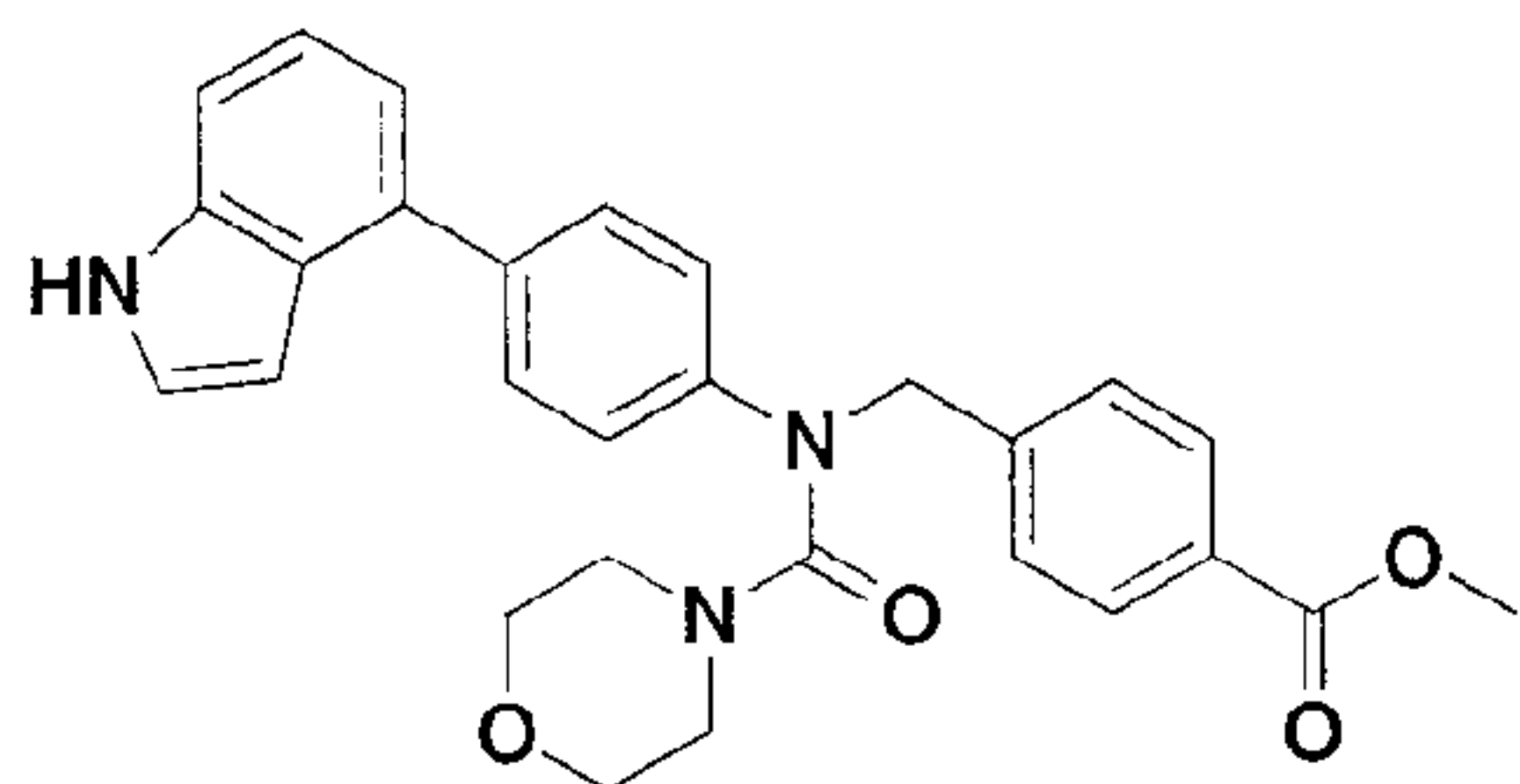
Compound of **Formula 8-6** (methyl 4-((N-(3',5'-bis(trifluoromethyl)biphenyl-4-yl))morpholine-4-carboxamido)methyl)benzoate; 0.203 g, 0.358 mmol) was
 5 dissolved in methanol (10 mL), and then hydroxylamine (50.0 wt% aqueous solution; 2.19 mL, 35.8 mmol) and potassium hydroxide (0.201 g, 3.58 mmol) added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under
 10 reduced pressure until its volume became about 3 mL, and saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 339** (0.197 g, 97%) in the form of a light brown
 15 solid.

¹H NMR (400 MHz, DMSO-d₆) δ 8.29 (s, 2 H), 8.03 (s, 1 H), 7.82 (d, 2 H, J = 8.6 Hz), 7.66 (d, 2 H, J = 8.2 Hz), 7.40 (d, 2 H, J = 8.2 Hz), 7.28 (d, 2 H, J = 8.6 Hz), 4.94 (s, 2 H), 3.47 - 3.43 (m, 4 H), 3.21 - 3.15 (m, 4 H). **MS** (ESI) m/z 568
 20 (M⁺ + H).

Example 28: Synthesis of Compound 340

(**Formula 8-6**: methyl 4-((N-(4-(1H-indol-4-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)

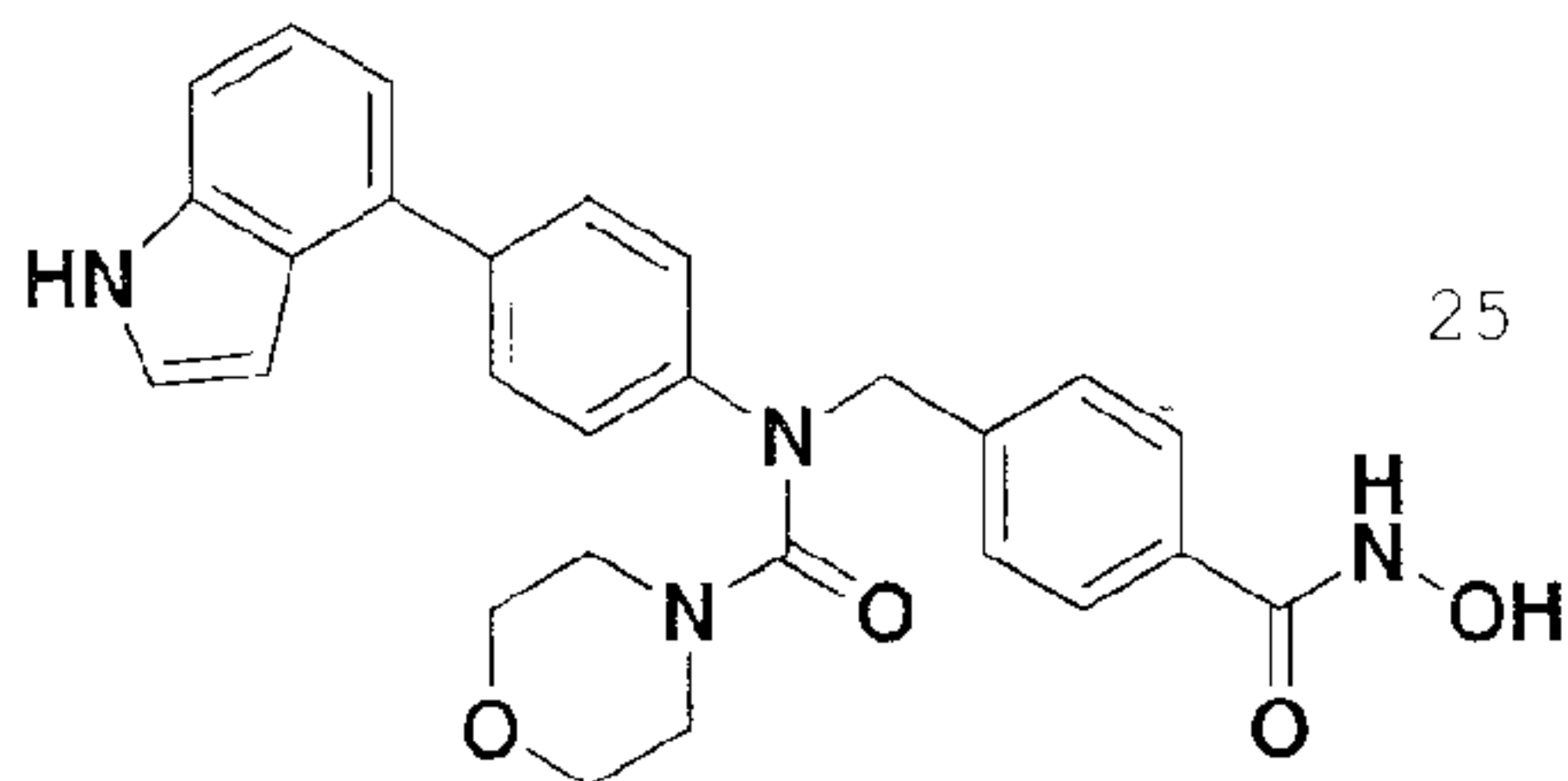
25



5

Compound of **Formula 8-5** (methyl 4-((N-(4-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), indol-4-ylboronic acid (0.089 g, 0.554 mmol),
 10 and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and then sodium carbonate (0.196 g, 1.85 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 6 hours. After completion of the reaction, the organic layer was extracted with ethyl
 15 acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=70%) to give the desired compound of **Formula 8-6** (0.142 g, 66%) in the form of
 20 a light yellow solid.

(Compound 340: N-(4-(1H-indol-4-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide)



25

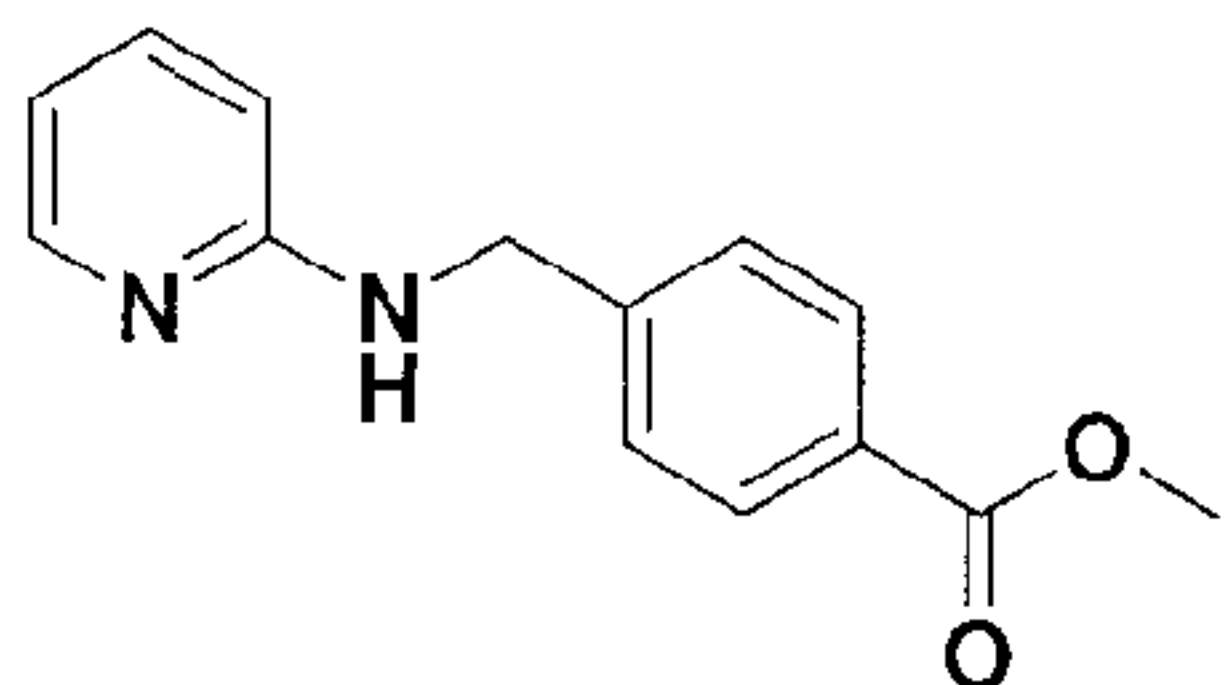
140

Compound of **Formula 8-6** (methyl 4-((N-(4-(1H-indol-4-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.142 g, 0.302 mmol) was dissolved in methanol (10 mL), and then hydroxylamine (50.0 wt% aqueous solution; 1.85 mL, 30.2 mmol) and potassium hydroxide (0.170 g, 3.02 mmol) added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 3 mL, and saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 340** (0.105 g, 74%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.25 (s, 1 H), 7.68 (d, 2 H, *J* = 8.3 Hz), 7.61 (d, 2 H, *J* = 8.6 Hz), 7.41 - 7.36 (m, 4 H), 7.25 (d, 2 H, *J* = 8.6 Hz), 7.14 (t, 1 H, *J* = 7.7 Hz), 7.04 (d, 1 H, *J* = 7.3 Hz), 6.51 (s, 1 H), 4.92 (s, 2 H), 3.45 - 3.43 (m, 4 H), 3.22 - 3.20 (m, 4 H). **MS** (ESI) *m/z* 471 (M⁺ + H).

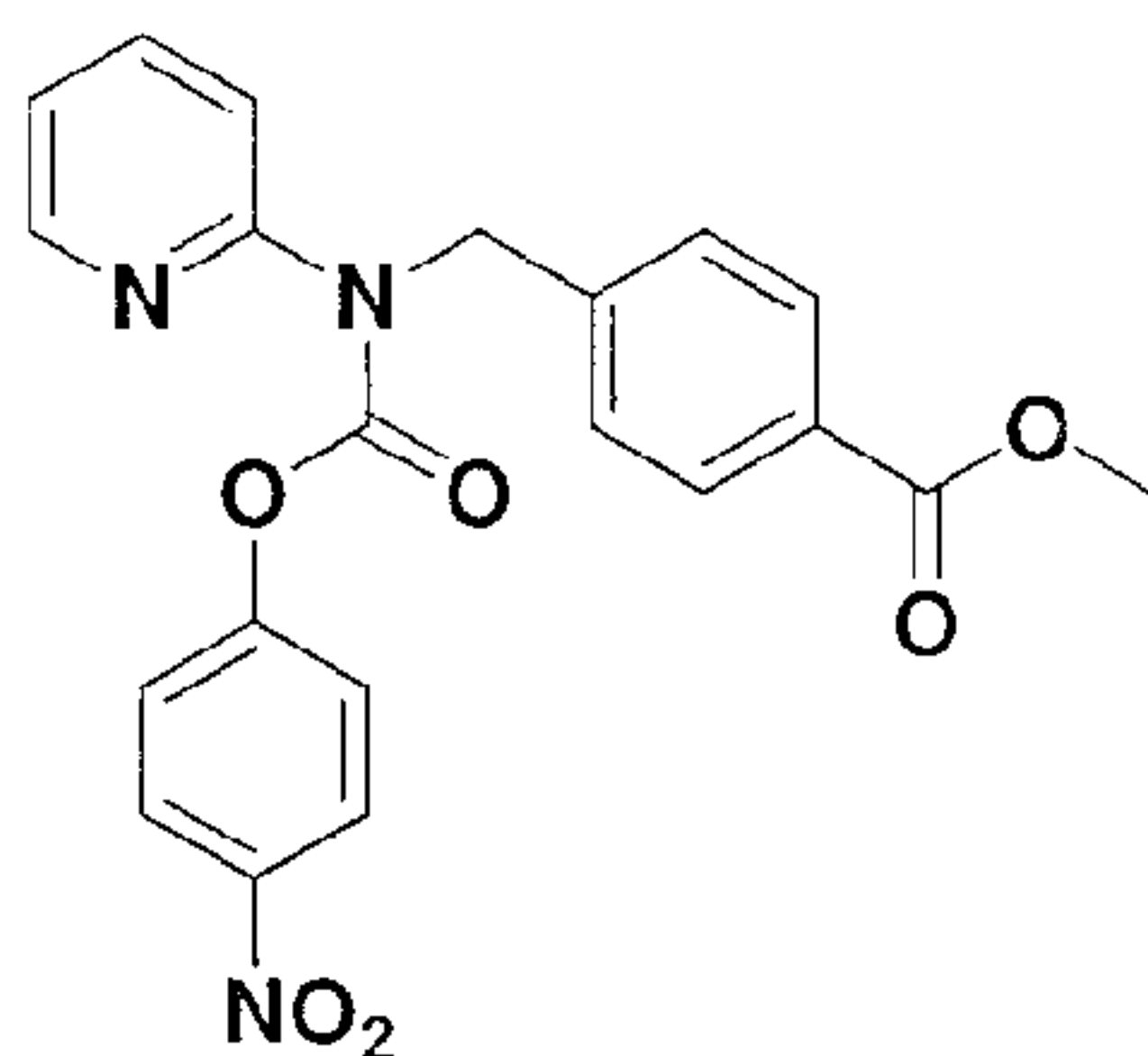
Example 29: Synthesis of Compound 341

(**Formula 7-4**: methyl 4-((pyridin-2-ylamino)methyl)benzoate)

Compound of **Formula 7-3** (pyridin-

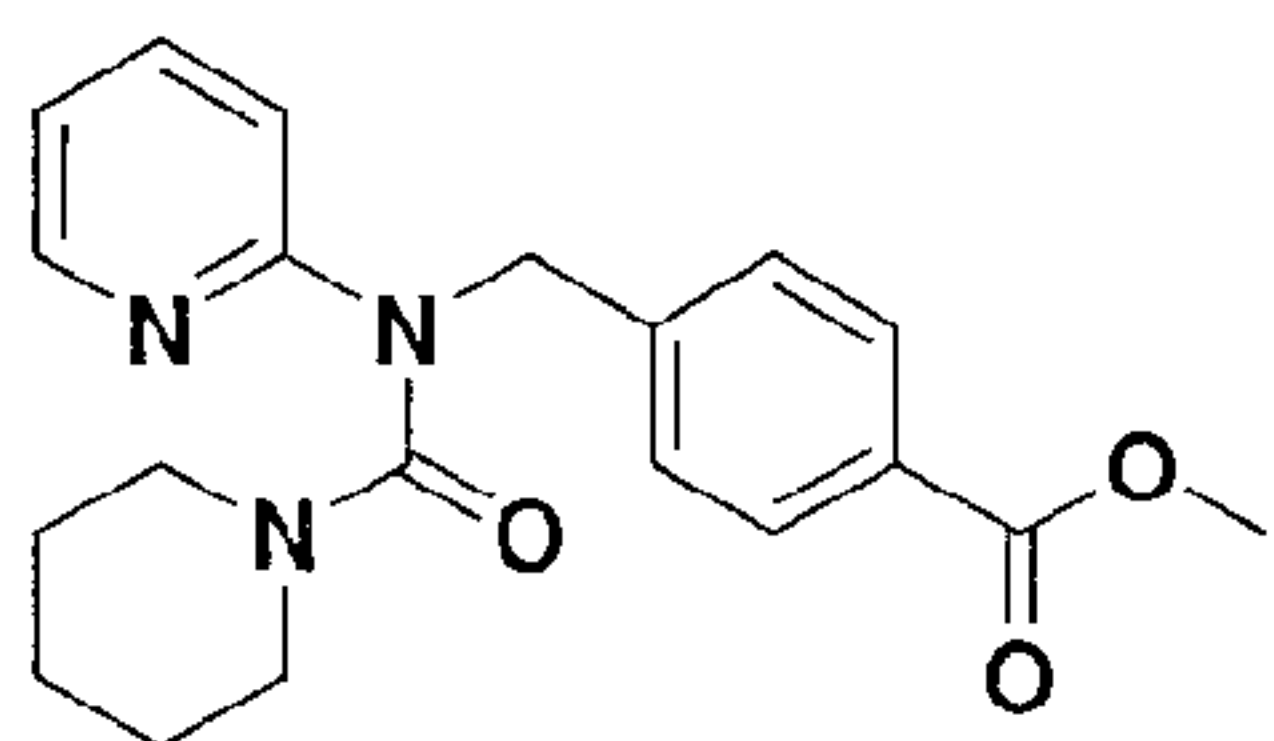
5 2-amine; 10.0 g, 106 mmol) was dissolved in methanol (100 mL),
 and then methyl 4-formylbenzoate (17.4 g, 106 mmol) and
 acetic acid (6.08 mL, 106 mmol) were added and stirred for 1
 day. Then, sodium cyanoborohydride (22.5 g, 106 mmol) was
 added and stirred for 1 day. After completion of the
 10 reaction, the produced solid was filtered, and the organic
 layer was washed with saturated sodium chloride aqueous
 solution, dehydrated with anhydrous magnesium sulfate, and
 then concentrated under reduced pressure. The residue was
 purified and concentrated by column chromatography (silica;
 15 dichloromethane/ethyl acetate=5%) to give the desired
 compound of **Formula 7-4** (8.0 g, 31%) in the form of a white
 solid.

(**Formula 7-5:** methyl 4-(((4-
 nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate)



Compound of **Formula 7-4** (methyl 4-((pyridin-2-ylamino)methyl)benzoate; 1.80 g, 7.43 mmol) was dissolved in acetonitrile (50 mL), and then potassium carbonate (3.08 g, 22.3 mmol) and 4-nitrophenyl chloroformate (2.24 g, 11.1 mmol) were added. Then, the mixture was heated and stirred at about 50 °C for 1 day. Water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; hexane/ethyl acetate=30%) to give the desired compound of **Formula 7-5** (0.98, 32%) in the form of a white solid.

(**Formula 7-6**: methyl 4-((N-(pyridin-2-yl)piperidine-1-carboxamido)methyl)benzoate)



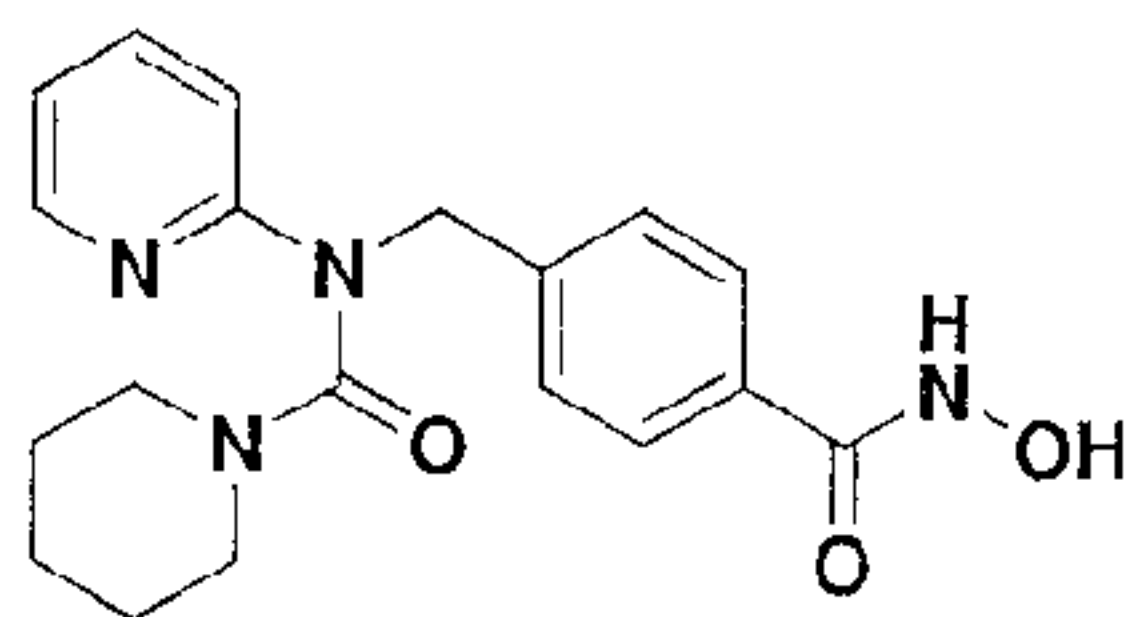
Compound of **Formula 7-5**

(methyl 4-(((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate; 0.30 g, 0.736 mmol) was dissolved in dimethylformamide (4 mL), and then piperidine (0.06 mL, 0.736 mmol) and potassium carbonate (0.122 g, 0.884 mmol)

were added, and the mixture was heated and stirred at 60 °C for 12 hours. Then, the dimethylformamide was removed under reduced pressure, water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 7-6** (0.27 g, 104%) in the form of a yellow oil.

(Compound 341: N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperidine-1-carboxamide)

15



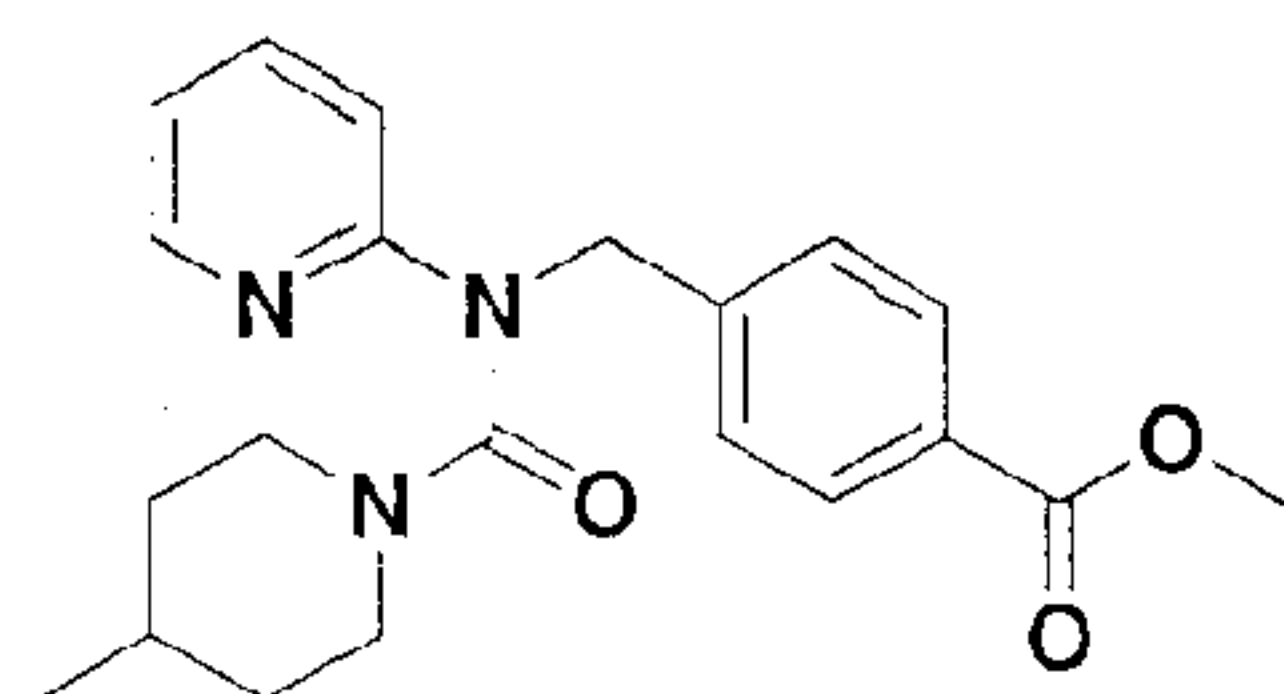
Compound of **Formula 7-6** (methyl 4-((N-(pyridin-2-yl)piperidine-1-carboxamido)methyl)benzoate; 0.13 g, 0.38 mmol) was dissolved in methanol (10 mL), and then hydroxylamine (0.13 g, 1.89 mmol) and potassium hydroxide (0.21 g, 3.79 mmol) were added and stirred for 5 minutes. Then, hydroxylamine (50 wt% aqueous solution; 0.98 mL, 7.58 mmol) was added dropwise and stirred at room temperature for 12 hours. After completion of the reaction, 2 N hydrogen

chloride was added, and the organic layer was extracted with ethyl acetate, washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was
 5 purified and concentrated by column chromatography (silica; methanol/dichloromethane =5%) to give the desired **Compound 341** (0.09 g, 70%) in the form of a white solid.

¹H NMR (400 MHz, MeOD-d₃) δ 8.31 - 8.29 (m, 1 H), 7.72 - 7.66 (m, 3 H), 7.49 (d, 2 H, *J* = 8.3 Hz), 7.01 - 6.98 (m, 2
 10 H), 5.07 (s, 2 H), 3.27 (t, 4 H, *J* = 5.5 Hz), 1.57 - 1.53 (m, 2 H), 1.45 - 1.41 (m, 4 H); **MS** (ESI) *m/z* 355.2 (*M*⁺ + H).

Example 30: Synthesis of Compound 342

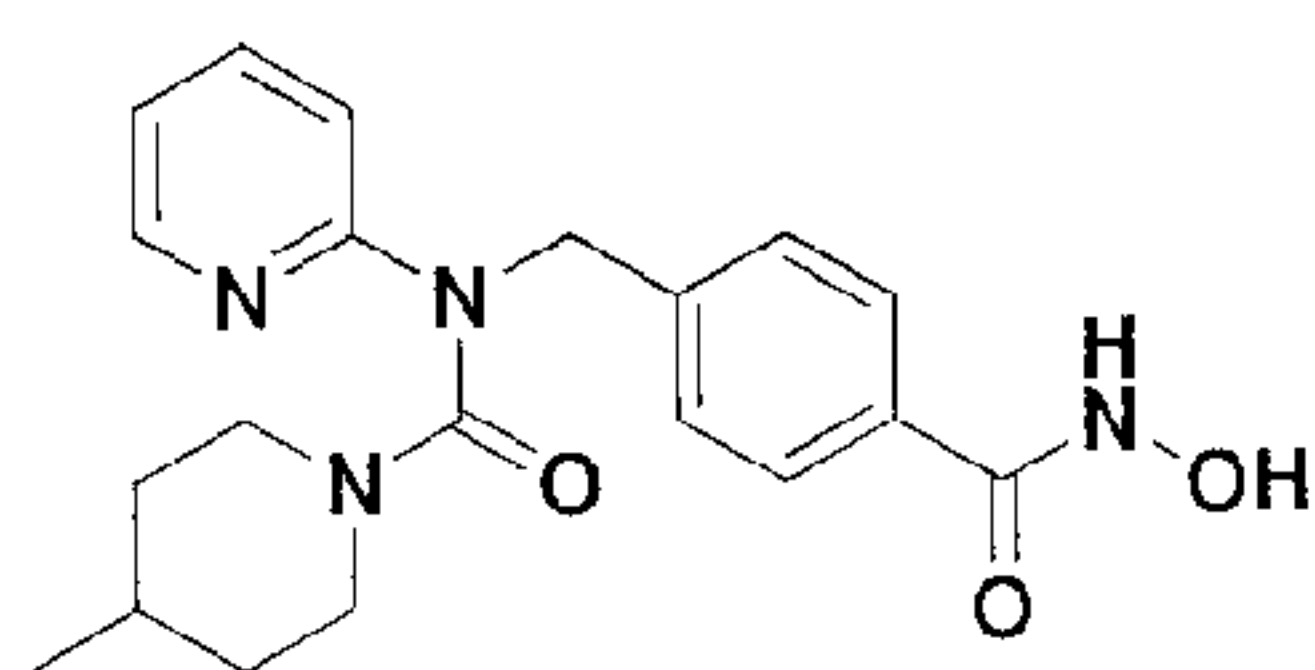
(**Formula 7-6**: methyl 4-(((4-methyl-N-(pyridin-2-yl)piperidine-1-carboxamido)methyl)benzoate)



20 Compound of **Formula 7-5** (methyl 4-(((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate; 0.300 g, 0.736 mmol) was dissolved in dimethylformamide (4 mL), and then 4-methylpiperidine (0.07 g, 0.736 mmol) and potassium carbonate (0.122 g, 0.884 mmol) were added, and the
 25 mixture was heated and stirred at 60 °C for 12 hours. Then,

the dimethylformamide was removed under reduced pressure, water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, 5 dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 7-6** (0.27 g, 100%) in the form of a yellow oil.

10 **(Compound 342:** N-(4-(hydroxycarbamoyl)benzyl)-4-methyl-N-(pyridin-2-yl)piperidine-1-carboxamide)



15

Compound of **Formula 7-6** (methyl 4-((4-methyl-N-(pyridin-2-yl)piperidine-1-carboxamido)methyl)benzoate; 0.15 g, 0.40 mmol) was dissolved in methanol (10 mL), and then hydroxylamine (0.14 g, 2.00 mmol) and potassium hydroxide 20 (0.22 g, 4.00 mmol) were added and stirred for 5 minutes. Then, hydroxylamine (50 wt% aqueous solution; 1.03 mL, 8.00 mmol) was added dropwise and stirred at room temperature for 12 hours. After completion of the reaction, 2 N hydrogen chloride was added, and the organic layer was extracted with 25 ethyl acetate, washed with saturated sodium chloride aqueous

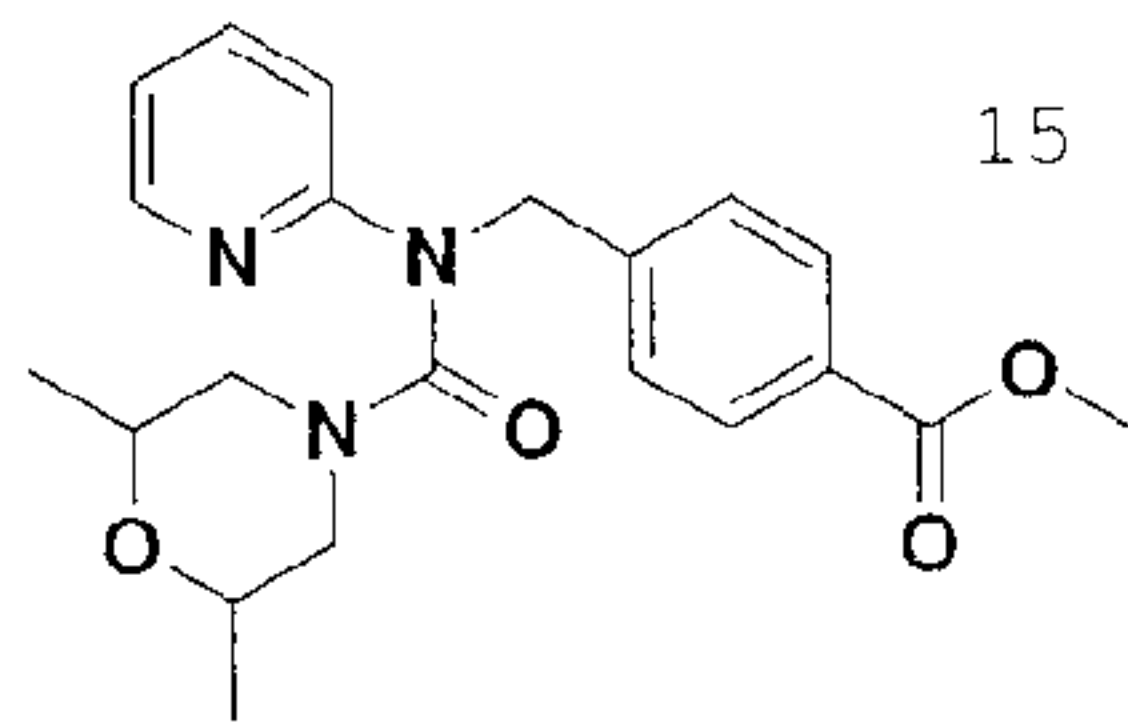
solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane =5%) to give the desired **Compound**

5 **342** (0.09 g, 64%) in the form of a colorless oil.

¹H NMR (400 MHz, MeOD-d₃) δ 8.31 - 8.29 (m, 1 H), 7.71 - 7.67 (m, 3 H), 7.48 (d, 2 H, *J* = 8.3 Hz), 7.01 - 6.98 (m, 2 H), 5.07 (s, 2 H), 3.83 (d, 2 H, *J* = 13.2 Hz), 2.72 (td, 2 H, *J* = 12.6, 2.0 Hz), 1.55 - 1.50 (m, 3 H), 0.97 - 0.93 (m, 2 H),
10 0.95 (m, 3 H); **MS** (ESI) *m/z* 369.1 (*M*⁺ + H).

Example 31: Synthesis of Compound 343

(**Formula 7-6**: methyl 4-((2,6-dimethyl-N-(pyridin-2-yl)morpholine-4-carboxamido)methyl)benzoate)

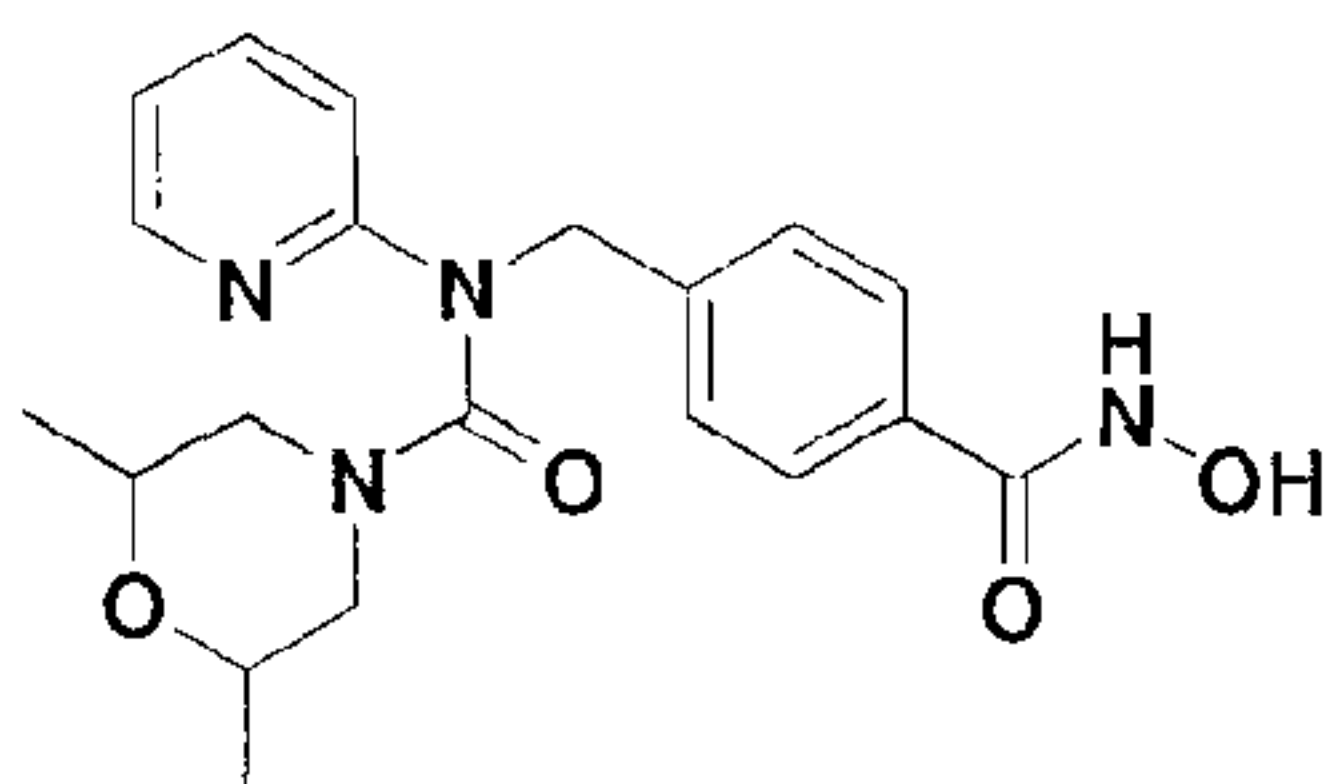


Compound of **Formula 7-5** (methyl 4-

(((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate; 0.300 g, 0.736 mmol) was dissolved
20 in dimethylformamide (4 mL), and then 2,6-dimethylmorpholine (0.085 g, 0.736 mmol) and potassium carbonate (0.122 g, 0.884 mmol) were added, and the mixture was heated and stirred at 60 °C for 12 hours. Then, the dimethylformamide was removed
25 under reduced pressure, water was poured into the reaction

mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane-30%) to give the desired compound of **Formula 7-6** (0.17 g, 60%) in the form of a white oil.

(Compound 343: N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(pyridin-2-yl)morpholine-4-carboxamide)



Compound of **Formula 7-6** (methyl 4-((2,6-dimethyl-N-(pyridin-2-yl)morpholine-4-carboxamidomethyl)benzoate; 0.116 g, 0.303 mmol) was dissolved in methanol (10 mL), and then hydroxylamine (0.105 g, 1.51 mmol) and potassium hydroxide (0.169 g, 3.02 mmol) were added and stirred for 5 minutes. Then, hydroxylamine (50 wt% aqueous solution; 0.778 mL, 6.05 mmol) was added dropwise and stirred at room temperature for 12 hours. After completion of the reaction, 2 N hydrogen chloride was added, and the organic layer was extracted with ethyl acetate, washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and

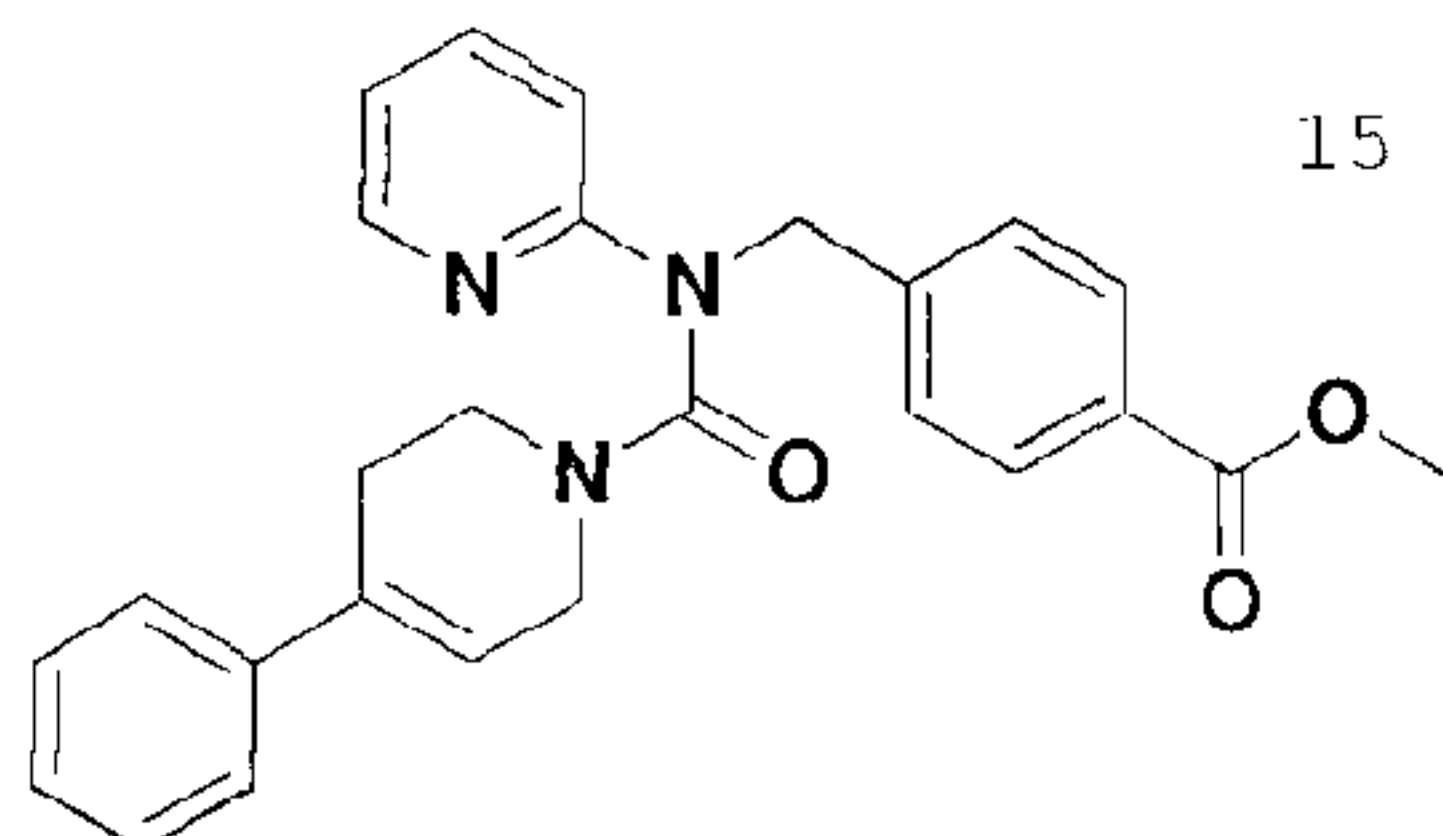
then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane -5%) to give the desired **Compound 343** (0.107 g, 92%) in the form of a colorless oil.

5 ^1H NMR (400 MHz, MeOD- d_3) δ 8.32 (dd, 1 H, $J = 4.9, 1.1$ Hz), 7.74 - 7.69 (m, 1 H), 7.67 (d, 2 H, $J = 8.2$ Hz), 7.48 (d, 2 H, $J = 8.2$ Hz), 7.05 - 7.02 (m, 2 H), 5.08 (s, 2 H), 3.65 (d, 2 H, $J = 12.9$ Hz), 3.43 - 3.37 (m, 2 H), 2.46 - 2.40 (m, 2 H), 1.03 (d, 6 H, $J = 6.2$ Hz); **MS** (ESI) m/z 385.1 ($\text{M}^+ + \text{H}$).

10

Example 32: Synthesis of Compound 352

(**Formula 7-6**: methyl 4-((4-phenyl-N-(pyridin-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxamido)methyl)benzoate)



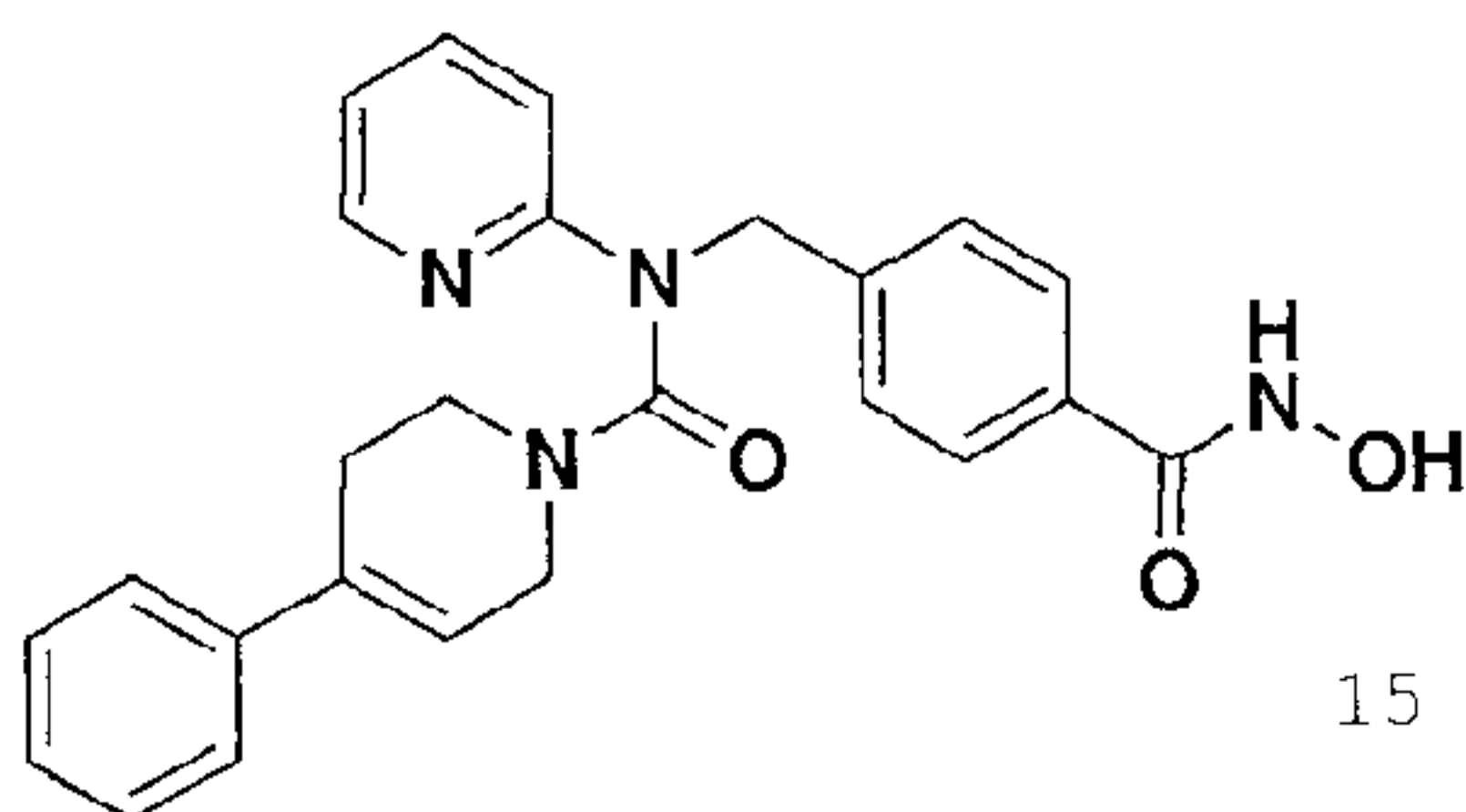
Compound of **Formula 7-5** (methyl

4-(((4-

20 nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate;
0.50 g, 1.23 mmol) was dissolved in dimethylformamide (3 mL),
and then 4-phenyl-1,2,3,6-tetrahydropyridine (0.264 g, 1.35
mmol) and potassium carbonate (0.339 g, 2.46 mmol) were added,
and the mixture was heated and stirred at 55 °C for 12 hours.
25 Then, the dimethylformamide was removed under reduced

pressure, water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=25%) to give the desired compound of **Formula 7-6** (0.57 g, 108%) in the form of a yellow oil.

(**Compound 352**: N-(4-(hydroxycarbamoyl)benzyl)-4-phenyl-N-(pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxamide)



Compound of **Formula 7-6**

(methyl 4-((4-phenyl-N-(pyridin-2-yl)-1,2,3,6-tetrahydropyridine-1-carboxamido)methyl)benzoate; 0.386 g, 0.903 mmol) was dissolved in methanol (20 mL), and then hydroxylamine (0.313 g, 4.51 mmol) and potassium hydroxide (0.507 g, 9.03 mmol) were added and stirred for 5 minutes. Then, hydroxylamine (50 wt% aqueous solution; 2.33 mL, 18.1 mmol) was added dropwise and stirred at room temperature for 12 hours. After completion of the reaction, the methanol was evaporated under reduced pressure, and the solid was

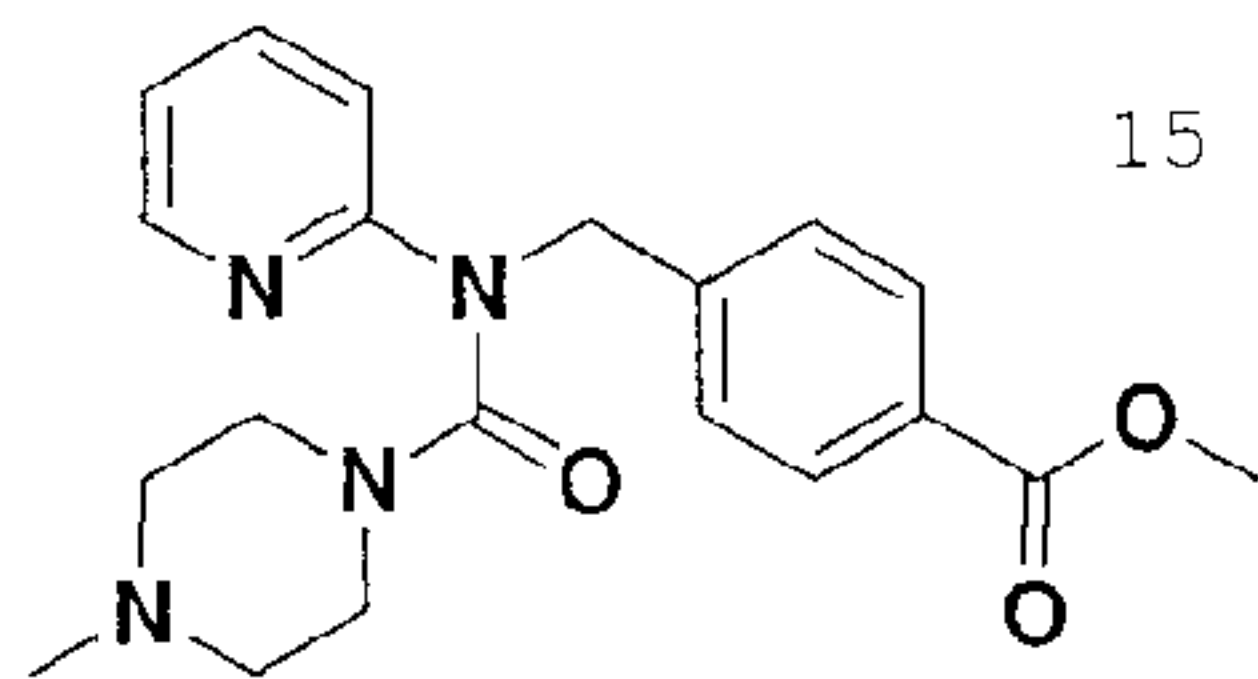
precipitated by adding 2 N hydrogen chloride. The solid was filtered and dried to give the desired **Compound 352** (0.22 g, 57%) in the form of a white solid.

¹H NMR (400 MHz, MeOD-d₃) δ 8.33 (dd, 1 H, *J* = 5.0, 1.2 Hz), 7.74 - 7.70 (m, 1 H), 7.65 (d, 2 H, *J* = 8.3 Hz), 7.49 (d, 2 H, *J* = 8.3 Hz), 7.36 - 7.23 (m, 5 H), 7.09 - 7.02 (m, 2 H), 5.97 (t, 1 H, *J* = 3.2 Hz), 5.12 (s, 2 H), 3.90 (d, 2 H, *J* = 3.0 Hz), 3.59 (t, 2 H, *J* = 5.7 Hz), 2.43 (d, 2 H, *J* = 5.7 Hz); **MS** (ESI) *m/z* 429.1 (M⁺ + H).

10

Example 33: Synthesis of Compound 353

(**Formula 7-6**: methyl 4-((4-methyl-N-(pyridin-2-yl)-piperazine-1-carboxamido)methyl)benzoate)



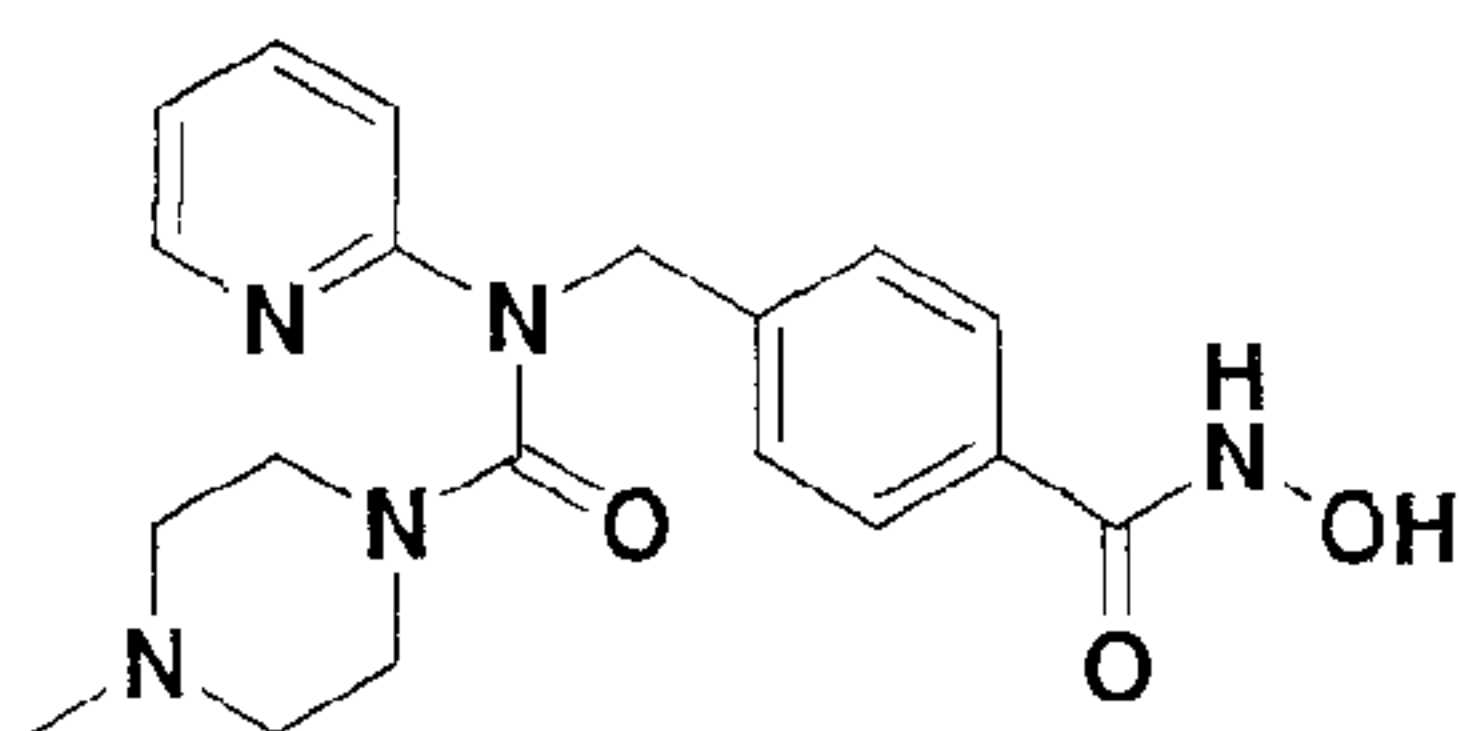
Compound of **Formula 7-5** (methyl 4-(((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate; 0.5 g, 1.23 mmol) was dissolved in dimethylformamide (3 mL), and then 1-methylpiperazine (0.15 mL, 1.35 mmol) and potassium carbonate (0.339 g, 2.46 mmol) were added, and the mixture was heated and stirred at 55 °C for 12 hours. Then, the dimethylformamide was removed under reduced pressure, water was poured into the reaction mixture, and the

25

organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was
 5 purified and concentrated by column chromatography (silica; methanol/dichloromethane=5%) to give the desired compound of **Formula 7-6** (0.33 g, 73%) in the form of a yellow oil.

(**Compound 353**: N-(4-(hydroxycarbamoyl)benzyl)-4-methyl-N-(pyridin-2-yl)piperazine-1-carboxamide)

10



Compound of **Formula 7-6** (methyl

15 4-((4-methyl-N-(pyridin-2-yl)-piperazine-1-carboxamido)methyl)benzoate; 0.23 g, 0.624 mmol) was dissolved in methanol (20 mL), and then hydroxylamine (0.217 g, 3.12 mmol) and potassium hydroxide (0.35 g, 6.24 mmol) were added and stirred for 5 minutes. Then, hydroxylamine
 20 (50 wt% aqueous solution; 1.61 mL, 12.49 mmol) was added dropwise and stirred at room temperature for 12 hours. After completion of the reaction, the methanol was evaporated under reduced pressure, 2 N hydrogen chloride was added, and the organic layer was extracted with ethyl acetate. The organic
 25 layer was washed with saturated sodium chloride aqueous

solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane=10%) to give the desired **Compound**

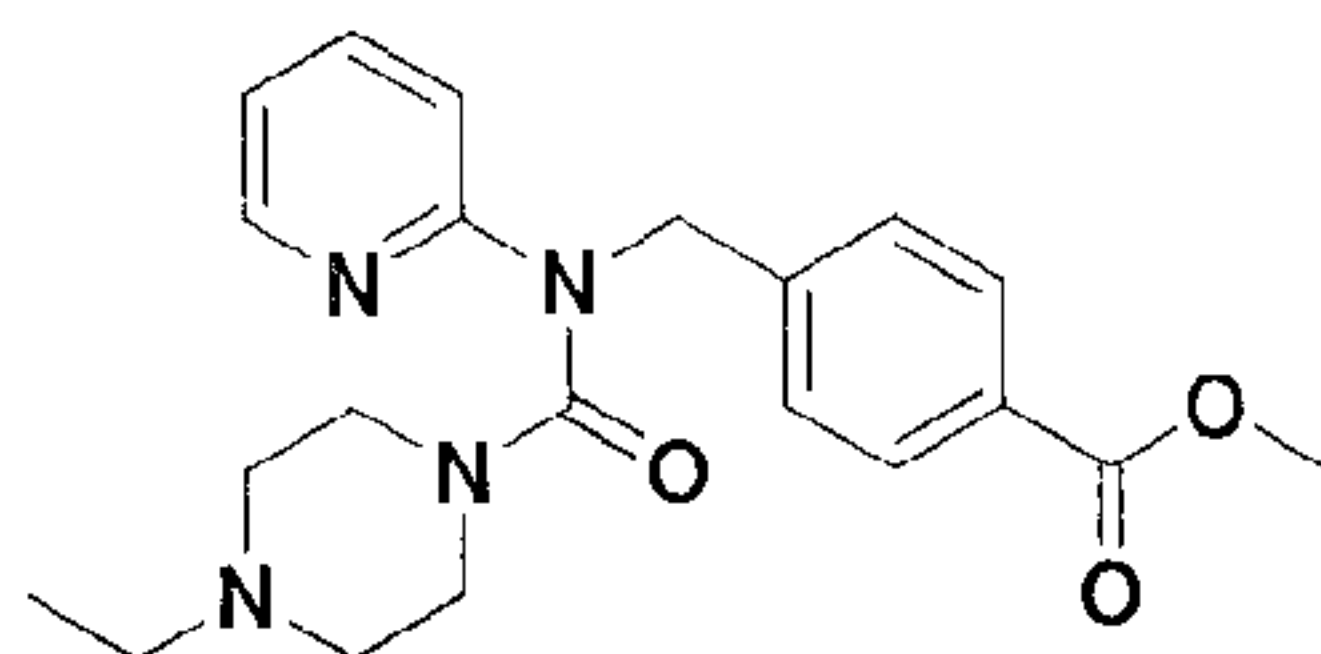
5 **353** (0.04 g, 17%) in the form of a colorless oil.

¹H NMR (400 MHz, MeOD-d₃) δ 8.33 (dd, 1 H, *J* = 4.9, 1.6 Hz), 7.75 – 7.71 (m, 1 H), 7.68 (d, 2 H, *J* = 8.2 Hz), 7.48 (d, 2 H, *J* = 8.1 Hz), 7.09 (d, 1 H, *J* = 8.2 Hz), 7.06 – 7.03 (m, 1 H), 5.08 (s, 2 H), 3.41 – 3.38 (m, 4 H), 2.59 – 2.57 (m, 4
10 H), 2.44 (s, 3 H); **MS** (ESI) *m/z* 370.1 (*M*⁺ + H).

Example 34: Synthesis of Compound 354

(**Formula 7-6**: methyl 4-(((4-ethyl-N-(pyridin-2-yl)-piperazine-1-carboxamido)methyl)benzoate)

15

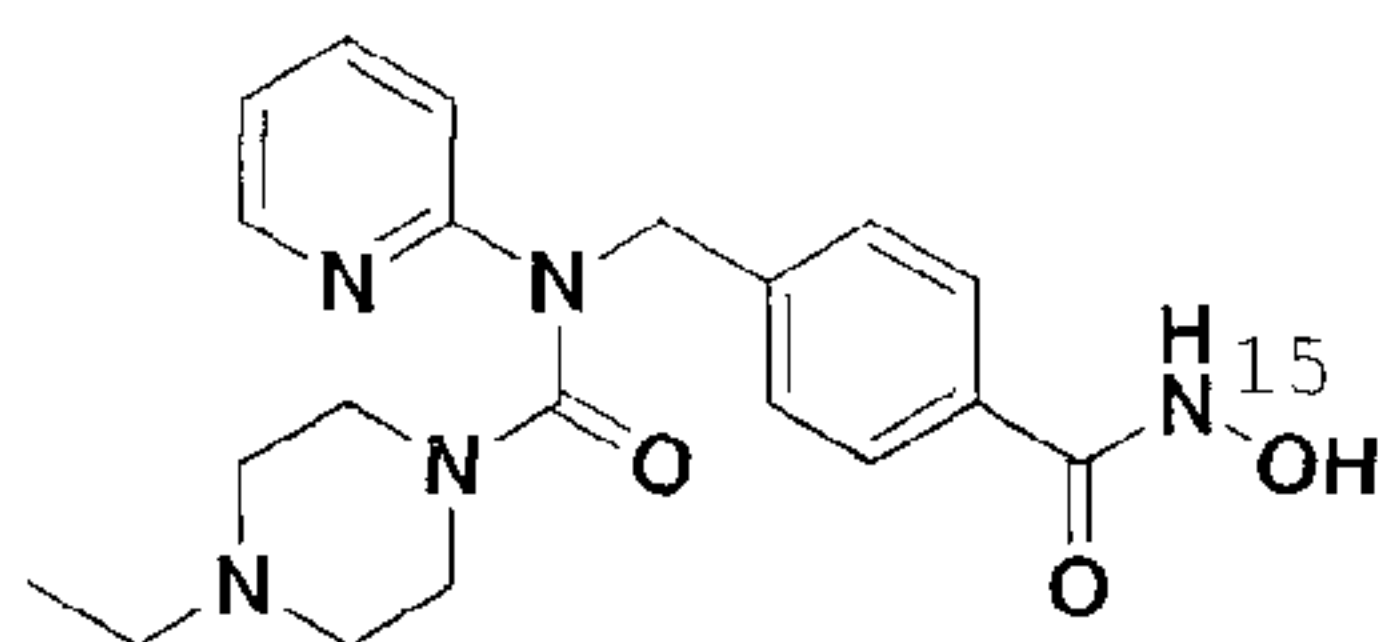


Compound of **Formula 7-5** (methyl

20 4-((((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate; 0.50 g, 1.23 mmol) was dissolved in dimethylformamide (3 mL), and then 1-ethylpiperazine (0.154 g, 1.35 mmol) and potassium carbonate (0.339 g, 2.45 mmol) were added, and the mixture was heated and stirred at 55 °C for 12
25 hours. Then, the dimethylformamide was removed under reduced

pressure, water was poured into the reaction mixture, and the organic layer was extracted with dichloromethane. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane=30%) to give the desired compound of **Formula 7-6** (0.3 g, 64%) in the form of a yellow oil.

10 **(Compound 354:** 4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide)



Compound of **Formula 7-6** (methyl 4-((4-ethyl-N-(pyridin-2-yl)-piperazine-1-carboxamido)methyl)benzoate; 0.23 g, 0.60 mmol) was dissolved in methanol (20 mL), and then hydroxylamine (0.209 g, 3.01 mmol) and potassium hydroxide (0.337 g, 6.01 mmol) were added and stirred for 5 minutes. Then, hydroxylamine (50 wt% aqueous solution; 1.55 mL, 12.02 mmol) was added dropwise and stirred at room temperature for 12 hours. After completion of the reaction, 2 N hydrogen chloride was added and the

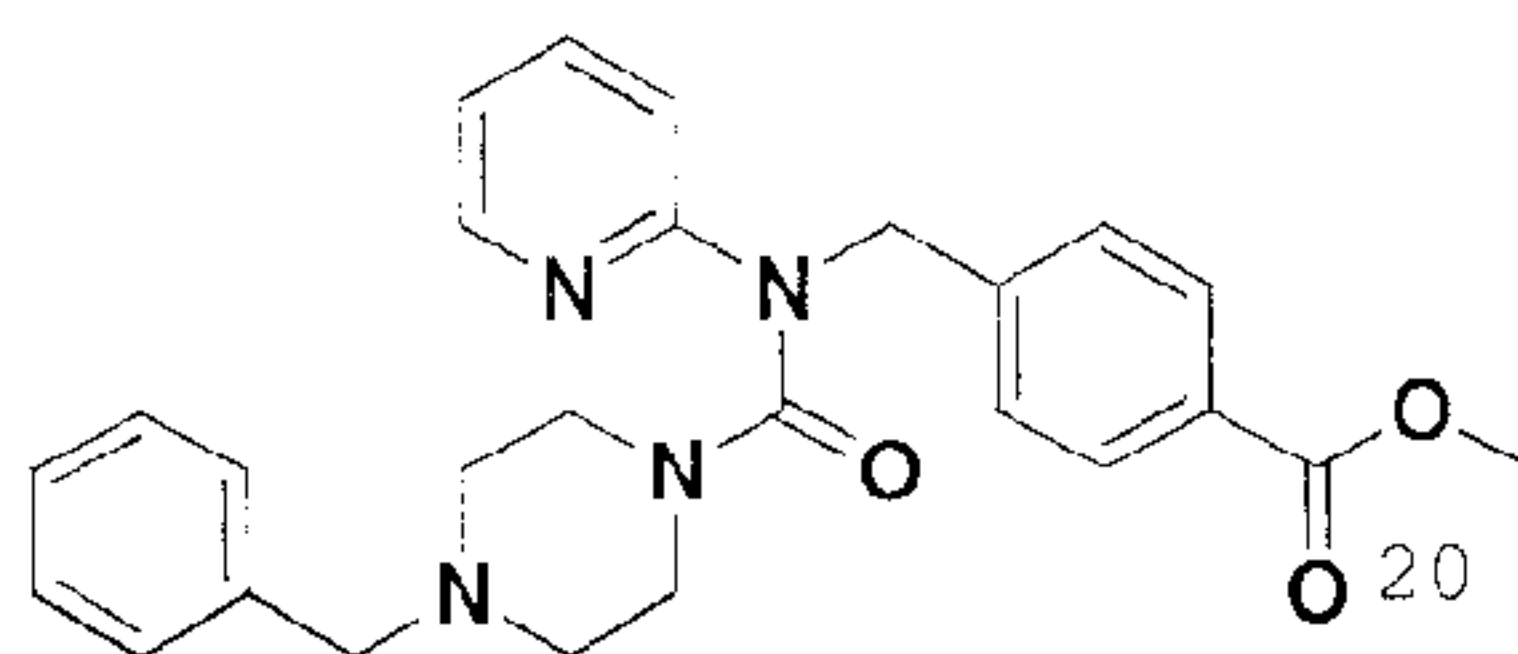
25

organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was
 5 purified and concentrated by column chromatography (silica; methanol/dichloromethane =10%) to give the desired **Compound 354** (0.038 g, 17%) in the form of a colorless oil.

¹H NMR (400 MHz, MeOD-d₃) δ 8.31 (dd, 1 H, *J* = 4.8, 1.2 Hz), 7.73 - 7.66 (m, 3 H), 7.48 (d, 2 H, *J* = 8.2 Hz), 7.06 -
 10 7.01 (m, 2 H), 5.08 (s, 2 H), 3.36 - 3.31 (m, 4 H), 2.46 - 2.37 (m, 6 H), 1.07 (t, 3 H, *J* = 7.2 Hz); **MS** (ESI) *m/z* 384.1 (M⁺ + H).

Example 35: Synthesis of Compound 355

15 **(Formula 7-6: methyl 4-(((4-benzyl-N-(pyridin-2-yl)-piperazine-1-carboxamido)methyl)benzoate)**

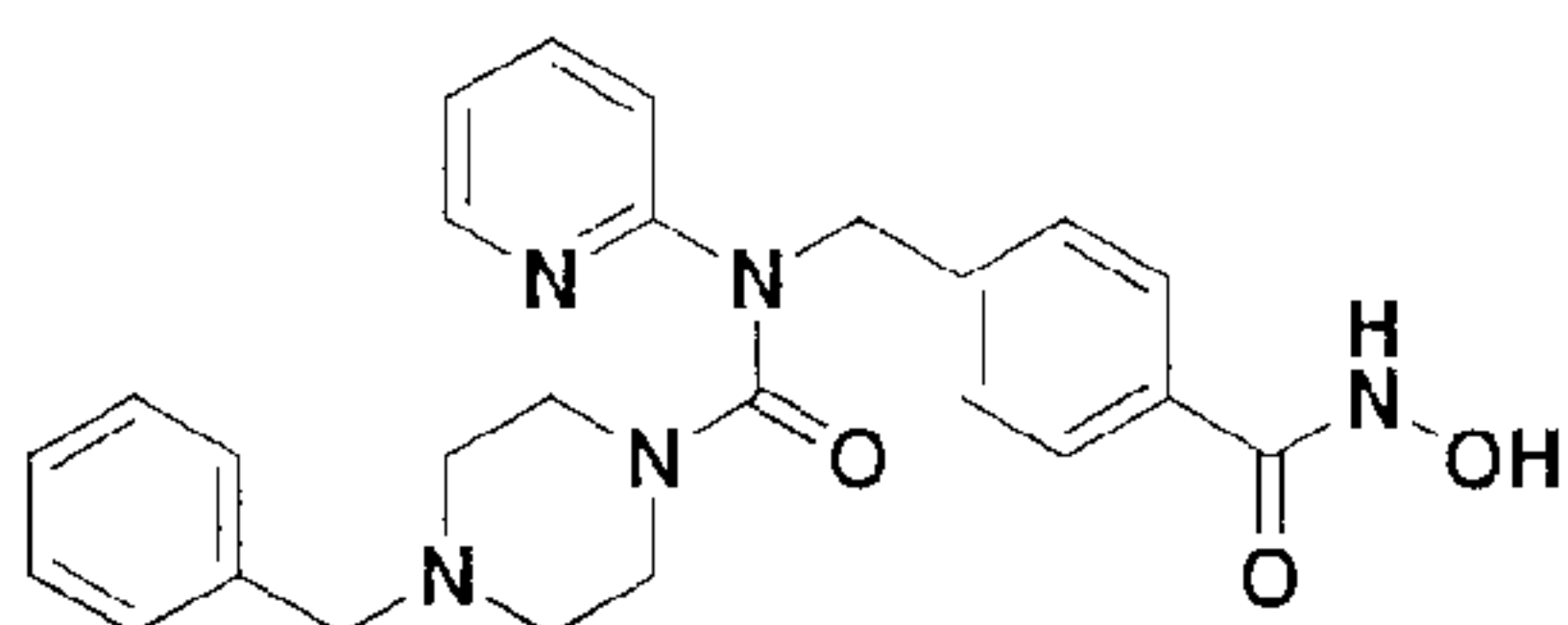


Compound of **Formula 7-5**

(methyl 4-(((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate; 0.50 g, 1.23 mmol) was dissolved in dimethylformamide (3 mL), and then 1-benzylpiperazine (0.231
 25 mL, 1.35 mmol) and potassium carbonate (0.339 g, 2.46 mmol)

were added, and the mixture was heated and stirred at 55 °C for 12 hours. Then, the dimethylformamide was removed under reduced pressure, water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=25%) to give the desired compound of **Formula 7-6** (0.185 g, 34%) in the form of a yellow oil.

(Compound 355: 4-benzyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide)



Compound of **Formula 7-6**

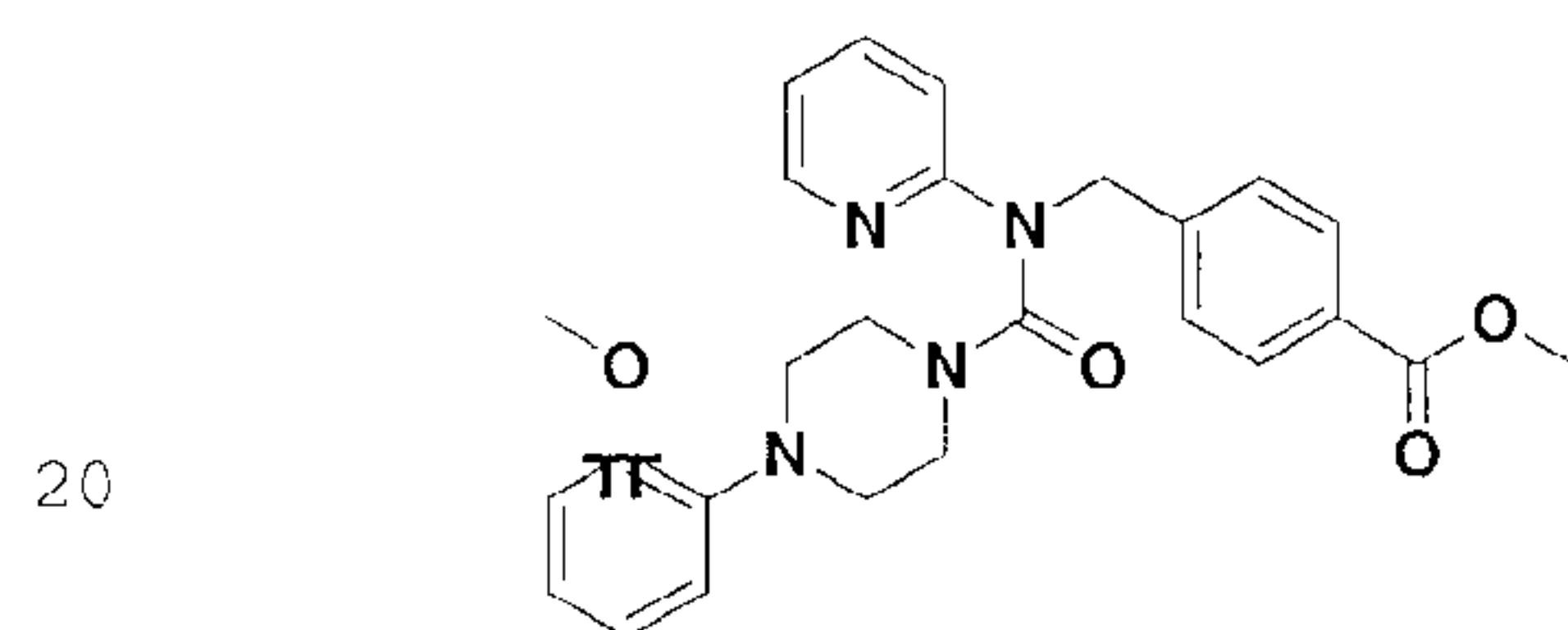
(methyl 4-((4-benzyl-N-(pyridin-2-yl)-piperazine-1-carboxamido)methyl)benzoate; 0.136 g, 0.31 mmol) was dissolved in methanol (20 mL), and then hydroxylamine (0.106 g, 1.53 mmol) and potassium hydroxide (0.172 g, 3.06 mmol) were added and stirred for 5 minutes. Then, hydroxylamine (50 wt% aqueous solution; 0.788 mL, 6.12 mmol) was added

dropwise and stirred at room temperature for 12 hours. After completion of the reaction, the methanol was evaporated under reduced pressure, and the solid was precipitated by adding 2 N hydrogen chloride. The solid was filtered to give the
 5 desired **Compound 355** (0.077 g, 57%) in the form of a white solid.

¹H NMR (400 MHz, MeOD-d₃) δ 8.31 (dd, 1 H, *J* = 4.8, 0.9 Hz), 7.72 – 7.65 (m, 3 H), 7.47 (d, 2 H, *J* = 8.2 Hz), 7.32 – 7.24 (m, 5 H), 7.03 – 7.00 (m, 2 H), 5.07 (s, 2 H), 3.48 (s,
 10 2 H), 3.31 – 3.30 (m, 4 H), 2.32 – 2.29 (m, 4 H); **MS** (ESI) *m/z* 446.1 (M⁺ + H).

Example 36: Synthesis of Compound 356

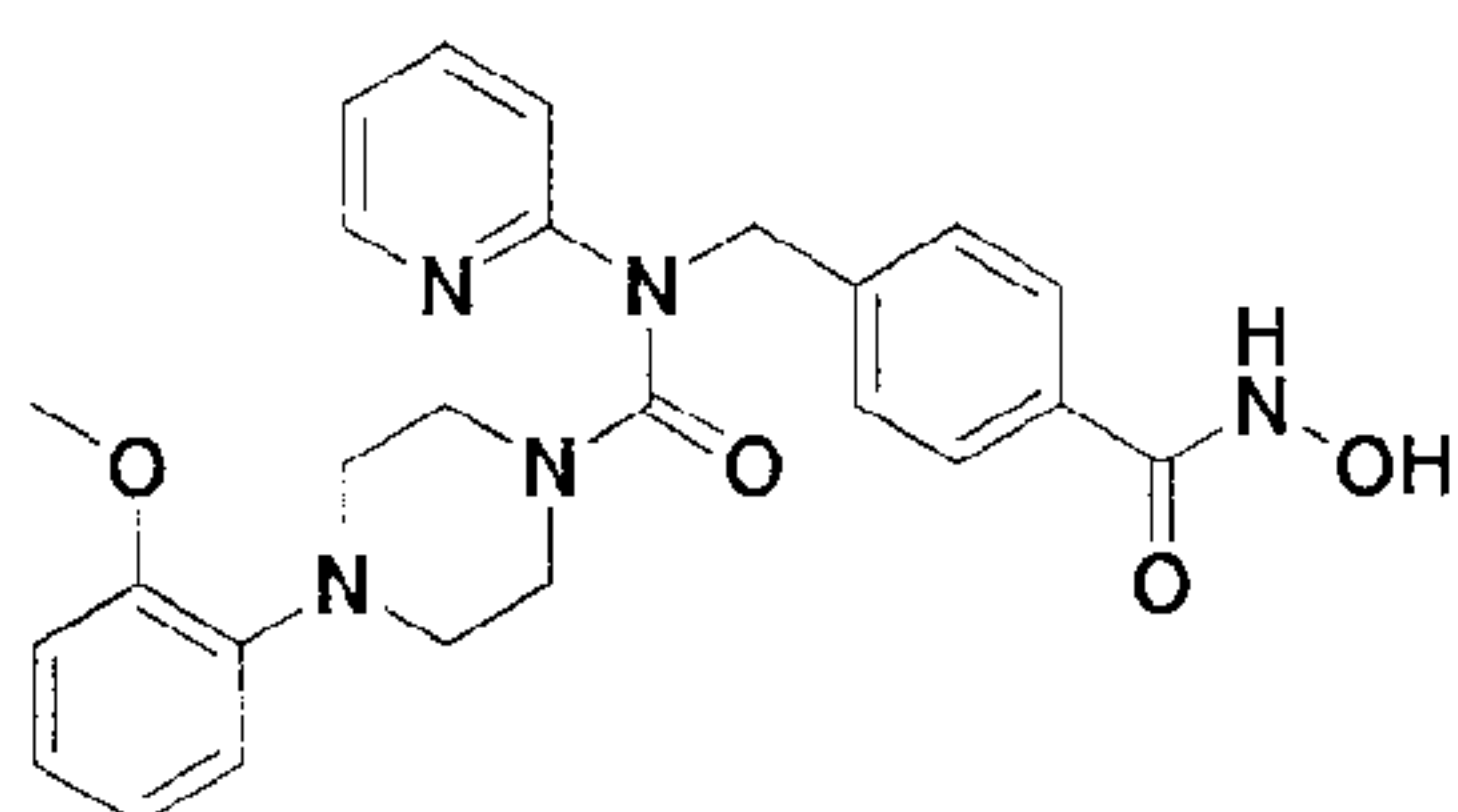
(**Formula 7-6**: methyl 4-((4-(2-methoxyphenyl)-N-(pyridin-
 15 2-yl)piperazine-1-carboxamido)methyl)benzoate)



Compound of **Formula 7-5** (methyl 4-(((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate;
 0.50 g, 1.23 mmol) was dissolved in dimethylformamide (3 mL),
 25 and then 1-(2-methoxyphenyl)piperazine (0.236 mL, 1.35 mmol)

and potassium carbonate (0.339 g, 2.46 mmol) were added, and the mixture was heated and stirred at 55 °C for 12 hours. Then, the dimethylformamide was removed under reduced pressure, water was poured into the reaction mixture, and the organic layer was extracted with dichloromethane. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 7-6** (0.565 g, 100%) in the form of a yellow oil.

(**Compound 356**: N-(4-(hydroxycarbonyl)benzyl)-4-(2-methoxyphenyl)-N-(pyridin-2-yl)piperazine-1-carboxamide)



Compound of **Formula 7-6**

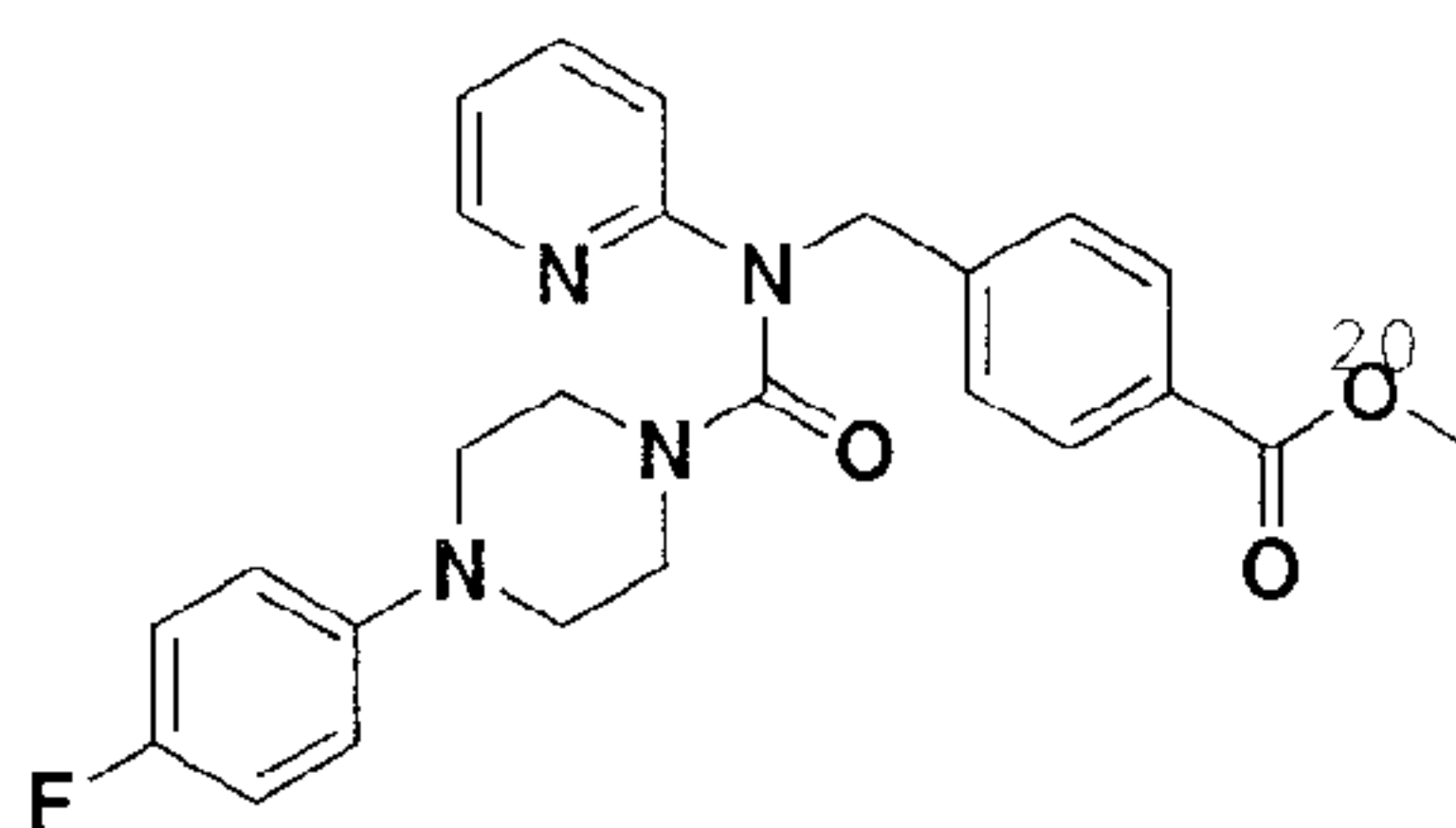
(methyl 4-((4-(2-methoxyphenyl)-N-(pyridin-2-yl)piperazine-1-carboxamido)methyl)benzoate; 0.395 g, 0.858 mmol) was dissolved in methanol (20 mL), and then hydroxylamine (0.298 g, 4.29 mmol) and potassium hydroxide (0.481 g, 8.58 mmol) were added and stirred for 5 minutes. Then, hydroxylamine (50 wt% aqueous solution; 2.21 mL, 17.15 mmol) was added

dropwise and stirred at room temperature for 12 hours. After completion of the reaction, 2 N hydrogen chloride was added, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane =10%) to give the desired **Compound 356** (0.28 g, 70%) in the form of a colorless oil.

¹H NMR (400 MHz, MeOD-d₃) δ 8.33 (dd, 1 H, *J* = 4.9, 1.2 Hz), 7.74 - 7.71 (m, 1 H), 7.68 (d, 2 H, *J* = 8.2 Hz), 7.51 (d, 2 H, *J* = 8.2 Hz), 7.09 - 6.87 (m, 6 H), 5.11 (s, 2 H), 3.82 (s, 3 H), 3.47 - 3.44 (m, 4 H), 2.87 - 2.85 (m, 4 H); **MS** (ESI) *m/z* 446.1 (*M*⁺ - H).

Example 37: Synthesis of Compound 357

(**Formula 7-6**: methyl 4-((4-(4-fluorophenyl)-N-(pyridin-2-yl)piperazine-1-carboxamido)methyl)benzoate)

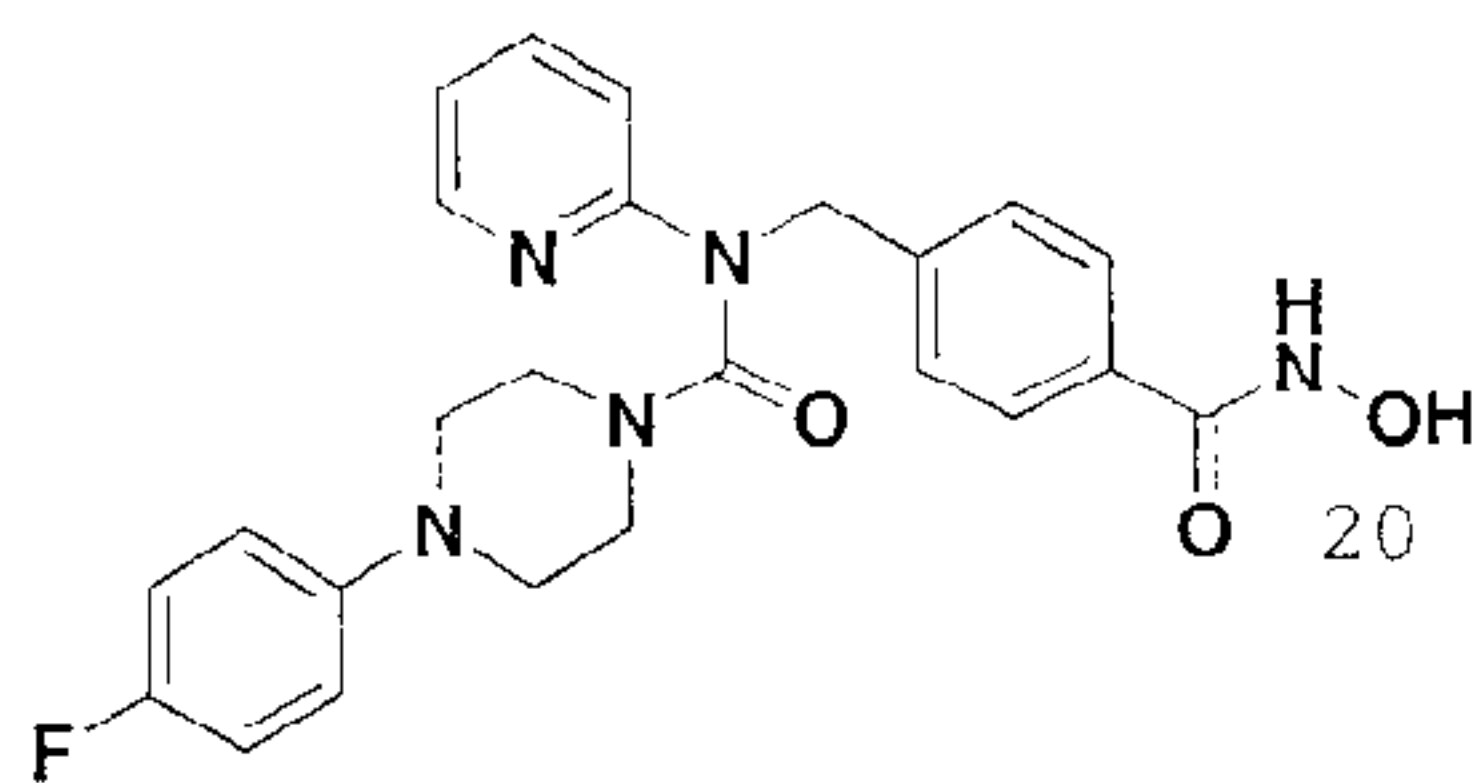


Compound of **Formula 7-5** (methyl 4-(((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate;

0.50 g, 1.23 mmol) was dissolved in dimethylformamide (3 mL), and then 1-(4-fluorophenyl)piperazine (0.243 mL, 1.35 mmol) and potassium carbonate (0.339 g, 2.46 mmol) were added, and the mixture was heated and stirred at 55 °C for 12 hours.

5 Then, the dimethylformamide was removed under reduced pressure, water was poured into the reaction mixture, and the organic layer was extracted with dichloromethane. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate,
10 and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane-25%) to give the desired compound of **Formula 7-6** (0.54 g, 98%) in the form of a yellow oil.

15 **(Compound 357: 4-(4-fluorophenyl)-N-(4-(hydroxycarbonyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide)**



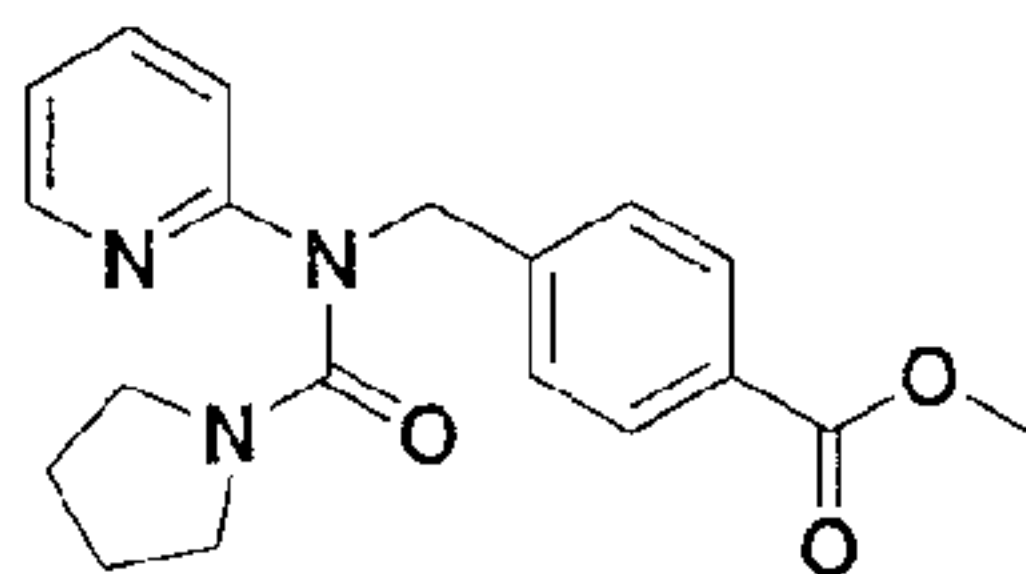
Compound of **Formula 7-6** (methyl 4-((4-(4-fluorophenyl)-N-(pyridin-2-yl)piperazine-1-carboxamido)methyl)benzoate;
0.31 g, 0.691 mmol) was dissolved in methanol (20 mL), and
25 then hydroxylamine (0.24 g, 3.46 mmol) and potassium

hydroxide (0.3881 g, 6.91 mmol) were added and stirred for 5 minutes. Then, hydroxylamine (50 wt% aqueous solution; 1.78 mL, 13.8 mmol) was added dropwise and stirred at room temperature for 12 hours. After completion of the reaction, 5 2 N hydrogen chloride was added, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated 10 by column chromatography (silica; methanol/dichloromethane =10%) to give the desired **Compound 357** (0.27 g, 87%) in the form of a colorless oil.

¹H NMR (400 MHz, MeOD-d₃) δ 8.34 - 8.33 (m, 1 H), 7.75 - 7.71 (m, 1 H), 7.67 (d, 2 H, J = 8.2 Hz), 7.51 (d, 2 H, J = 15 8.2 Hz), 7.09 (d, 1 H, J = 8.3 Hz), 7.05 - 6.89 (m, 5 H), 5.11 (s, 2 H), 3.46 - 3.44 (m, 4 H), 2.96 - 2.93 (m, 4 H); MS (ESI) m/z 450.1 (M⁺ + H).

Example 38: Synthesis of Compound 358

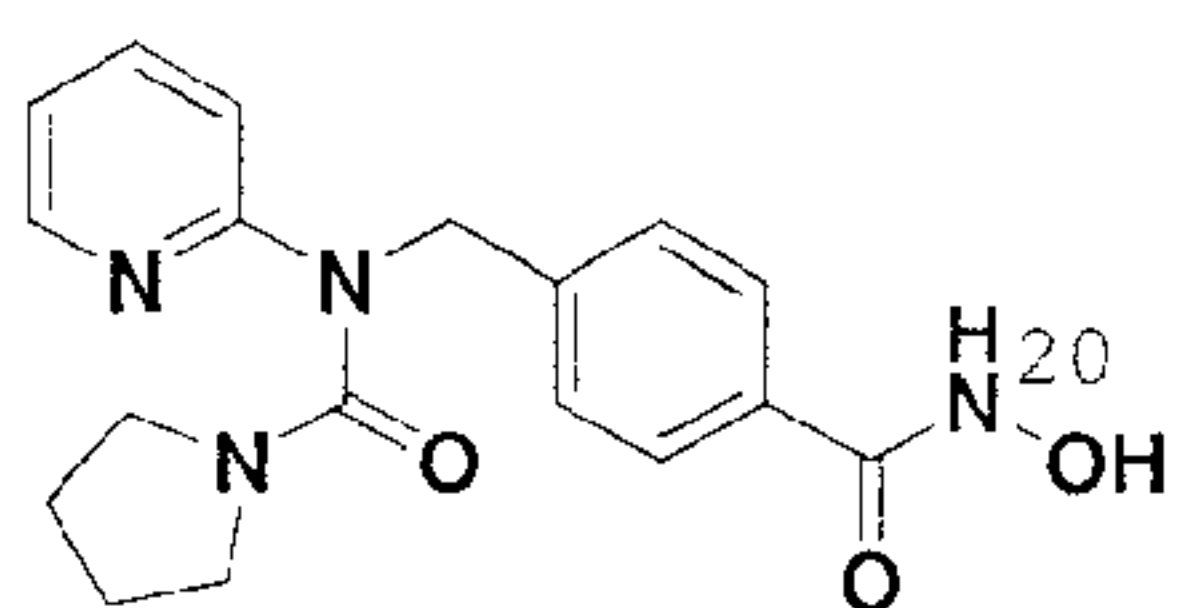
20 (Formula 7-6: methyl 4-((N-(pyridin-2-yl)pyrrolidine-1-carboxamido)methyl)benzoate)



25

Compound of **Formula 7-5** (methyl 4-(((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate;
 0.20 g, 0.491 mmol) was dissolved in dimethylformamide (4 mL),
 and then pyrrolidine (0.035 mL, 0.491 mmol) and potassium
 5 carbonate (0.081 g, 0.589 mmol) were added, and the mixture
 was heated and stirred at 55 °C for 12 hours. Then, the
 dimethylformamide was removed under reduced pressure, water
 was poured into the reaction mixture, and the organic layer
 was extracted with ethyl acetate. The organic layer was
 10 washed with saturated sodium chloride aqueous solution,
 dehydrated with anhydrous magnesium sulfate, and then
 concentrated under reduced pressure. The residue was
 purified and concentrated by column chromatography (silica;
 ethyl acetate/hexane=30%) to give the desired compound of
 15 **Formula 7-6** (0.031 g, 19%) in the form of a colorless oil.

(**Compound 358**: N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)pyrrolidine-1-carboxamide)



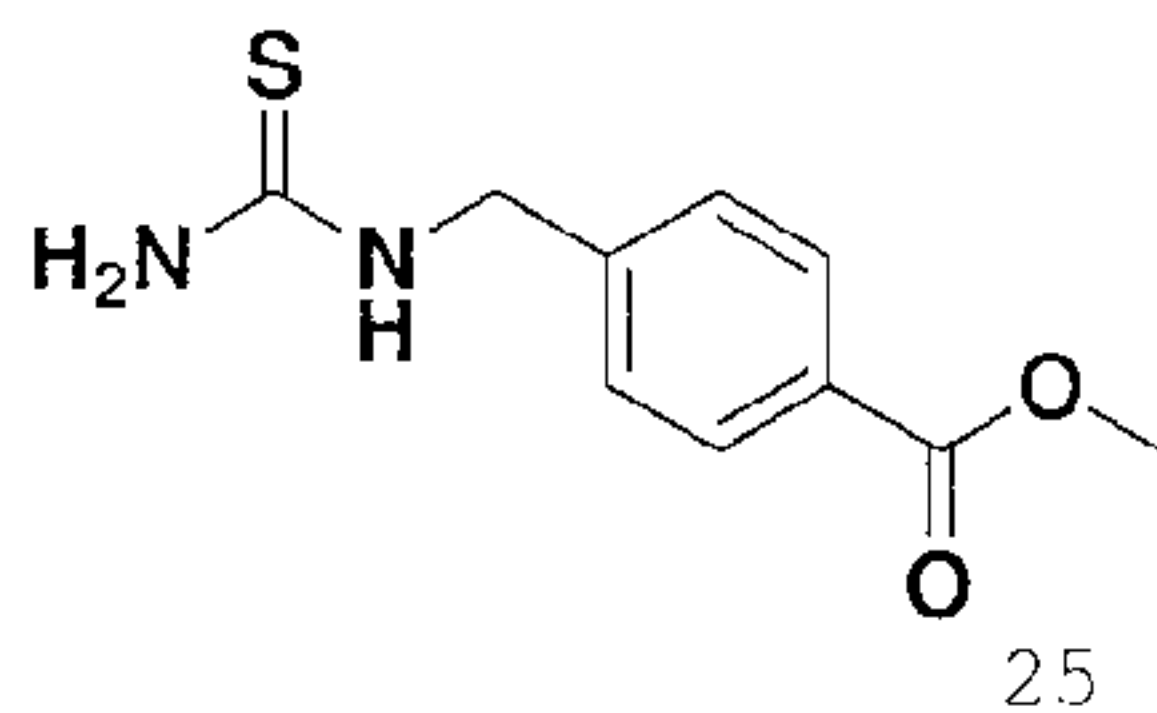
Compound of **Formula 7-6** (methyl 4-
 ((N-(pyridin-2-yl)pyrrolidine-1-carboxamido)methyl)benzoate;
 0.031 g, 0.091 mmol) was dissolved in methanol (4 mL), and
 25 then hydroxylamine (0.032 g, 0.457 mmol) and potassium

hydroxide (0.051 g, 0.913 mmol) were added and stirred for 5 minutes. Then, hydroxylamine (50 wt% aqueous solution; 0.135 mL, 1.83 mmol) was added dropwise and stirred at room temperature for 12 hours. After completion of the reaction, the methanol was evaporated under reduced pressure, 2 N hydrogen chloride was added, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane=10%) to give the desired **Compound 358** (0.012 g, 39%) in the form of a colorless oil.

¹H NMR (400 MHz, MeOD-d₃) δ 8.31 (dd, 1 H, *J* = 4.9, 1.3 Hz), 7.73 – 7.69 (m, 1 H), 7.65 (d, 2 H, *J* = 8.2 Hz), 7.47 (d, 2 H, *J* = 8.2 Hz), 7.07 – 7.02 (m, 2 H), 5.08 (s, 2 H), 3.19 – 3.18 (m, 4 H), 1.80 – 1.77 (m, 4 H); **MS** (ESI) *m/z* 341.2 (*M*⁺ + H).

Example 39: Synthesis of Compound 370

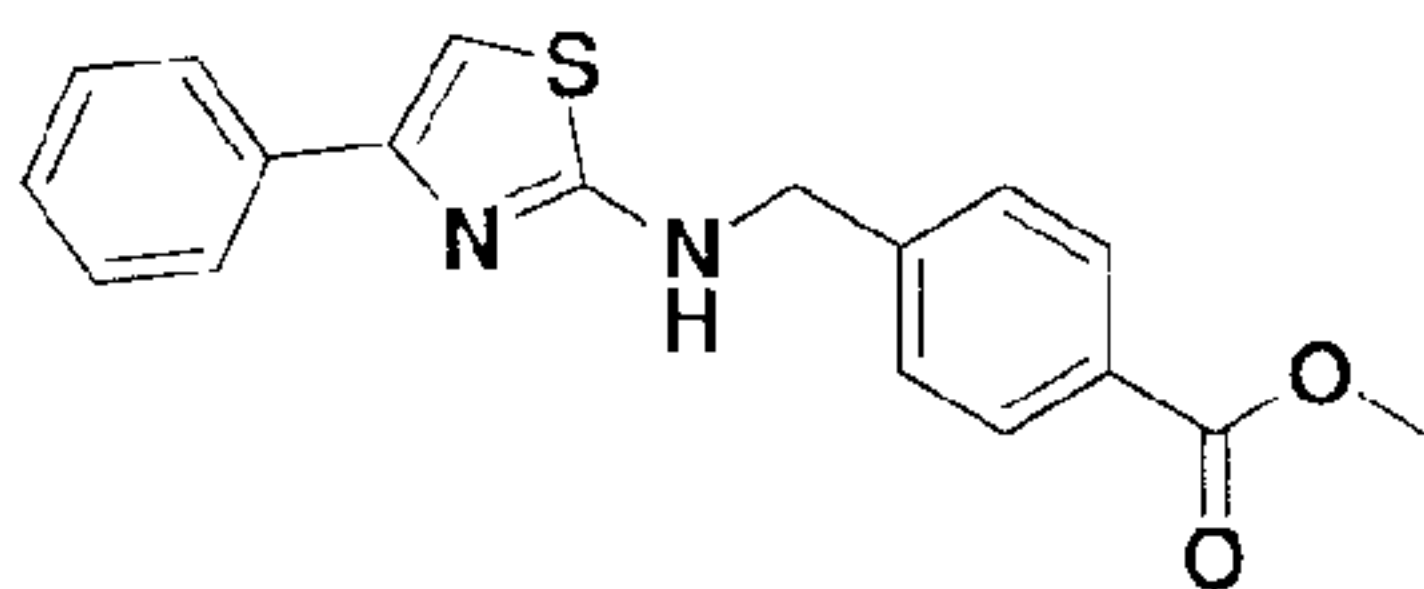
(Formula 11-3: methyl 4-(thioureidomethyl)benzoate)



Compound of **Formula 11-2** (1,1'-

thiocarbonyldiimidazole; 8.26 g, 46.4 mmol) was dissolved in hydrogen chloride (40 mL), and then triethylamine (6.34 mL, 46.4 mmol) and compound of **Formula 11-1** (4-(aminomethyl)benzoate hydrochloride; 8.50 g, 42.2 mmol) were
 5 slowly added sequentially and then stirred at room temperature for 3 hours. Then, ammonia (28.0 wt% aqueous solution; 30 mL) and methanol (10 mL) were added to the mixture and stirred at room temperature for 2 hours, and then hexane (85 mL) and water (45 mL) were further added and
 10 stirred at the same temperature for 1 hour. The solid product was filtered, washed with hexane and then with water, and then vacuum dried to give the desired compound of **Formula 11-3** (9.40 g, 99%) in the form of a light brown solid.

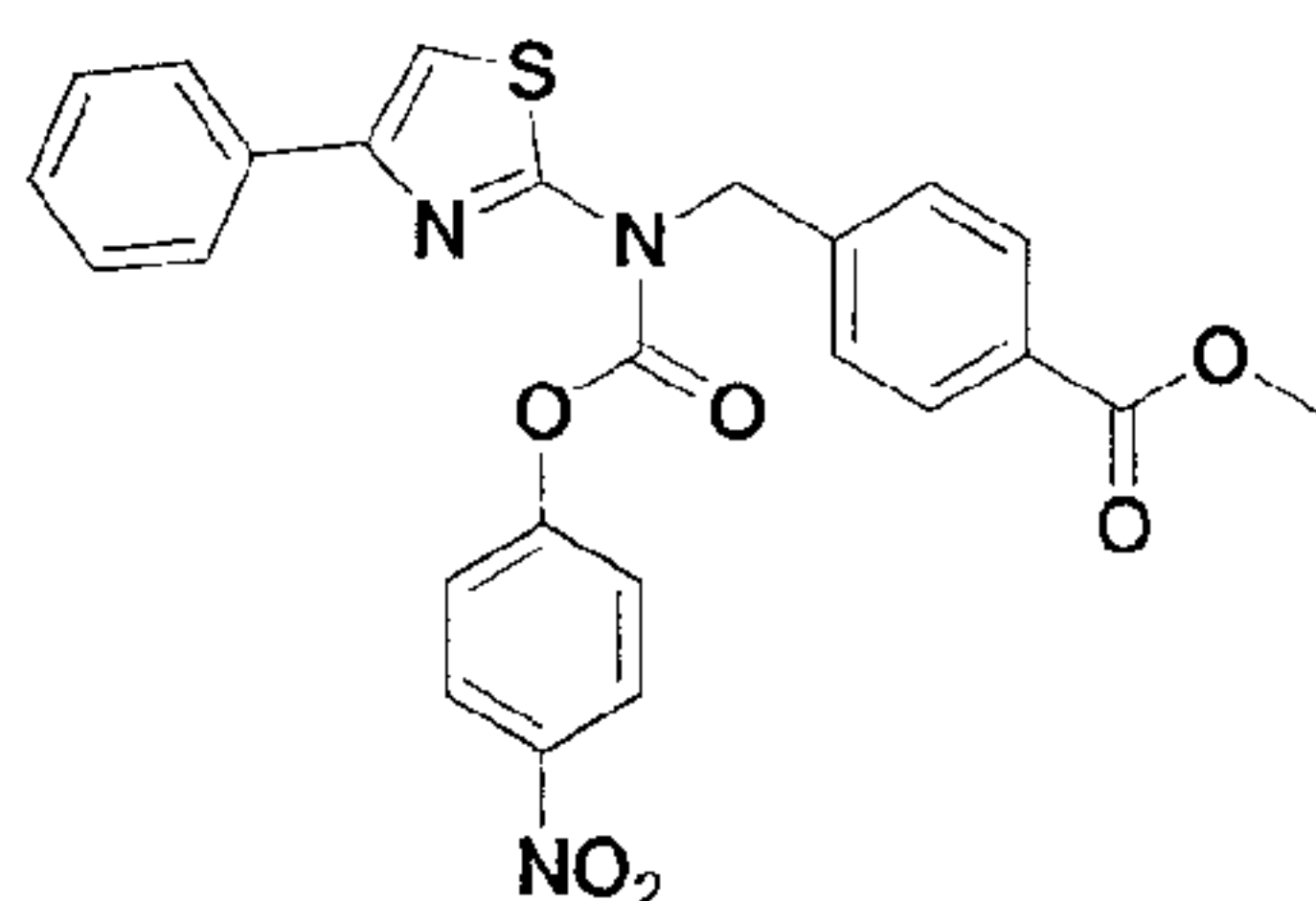
(**Formula 11-5**: methyl 4-((4-phenylthiazol-2-ylamino)methyl)benzoate)



Compound of **Formula 11-3** (methyl 4-(thioureidomethyl)benzoate; 0.180 g, 0.803 mmol) and compound
 20 of **Formula 11-4** (2-bromoacetophenone; 0.084 g, 0.843 mmol) were dissolved in ethanol (5 mL) and then stirred under reflux for 16 hours. After completion of the reaction, the temperature reaction solution was cooled to room temperature,
 25 and then ethyl acetate and hexane were added and stirred.

Then, the solid product was filtered and vacuum dried to give the desired compound of **Formula 11-5** (0.175 g, 67%) in the form of a light brown solid.

(**Formula 11-6**: methyl 4-(((4-nitrophenoxy)carbonyl)(4-phenylthiazol-2-yl)amino)methyl)benzoate)

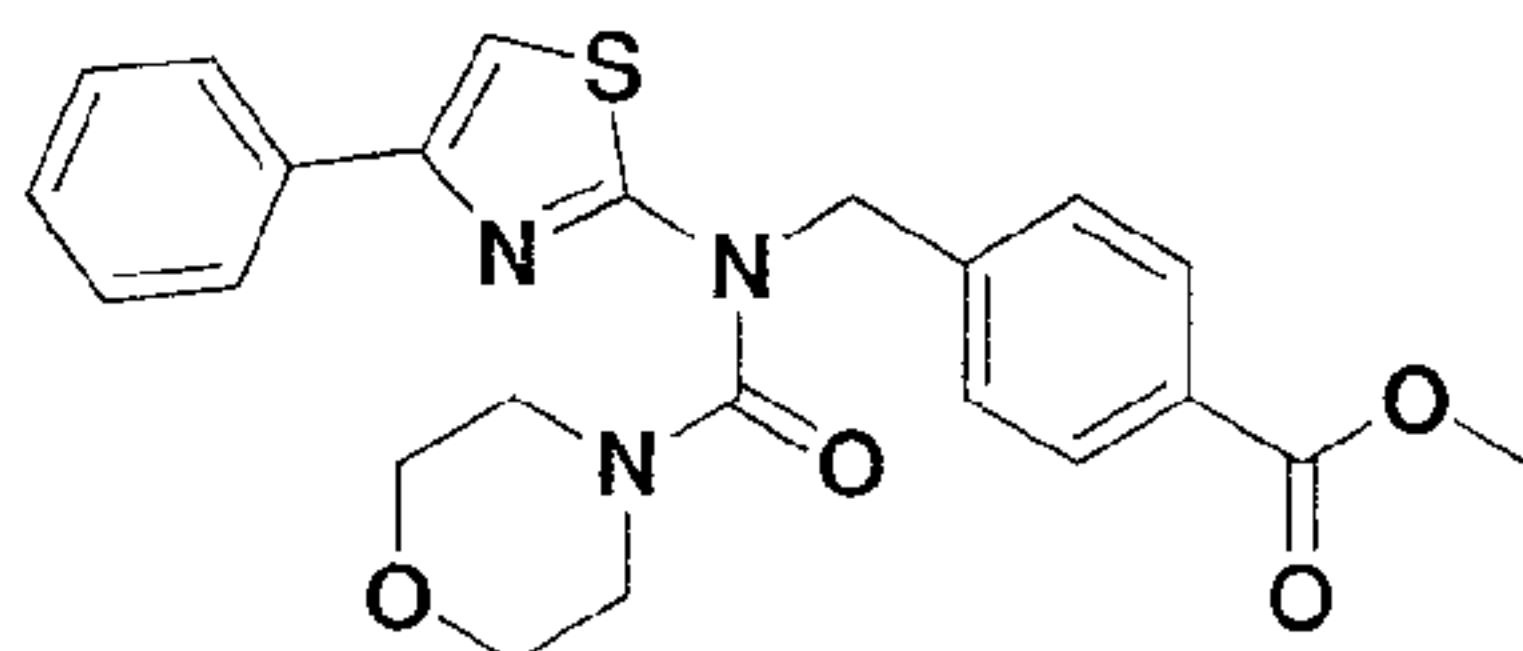


10

Compound of **Formula 11-5**

(methyl 4-((4-phenylthiazol-2-ylamino)methyl)benzoate; 0.175 g, 0.539 mmol) and 4-nitrophenyl chloroformate (0.141 g, 0.701 mmol) were dissolved in acetonitrile (10 mL), and then potassium carbonate (0.112 g, 0.809 mmol) was added and stirred at room temperature for 16 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution, dehydrated with anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane= 20%) to give the desired compound of **Formula 11-6** (0.160 g, 61%) in the form of a yellow solid.

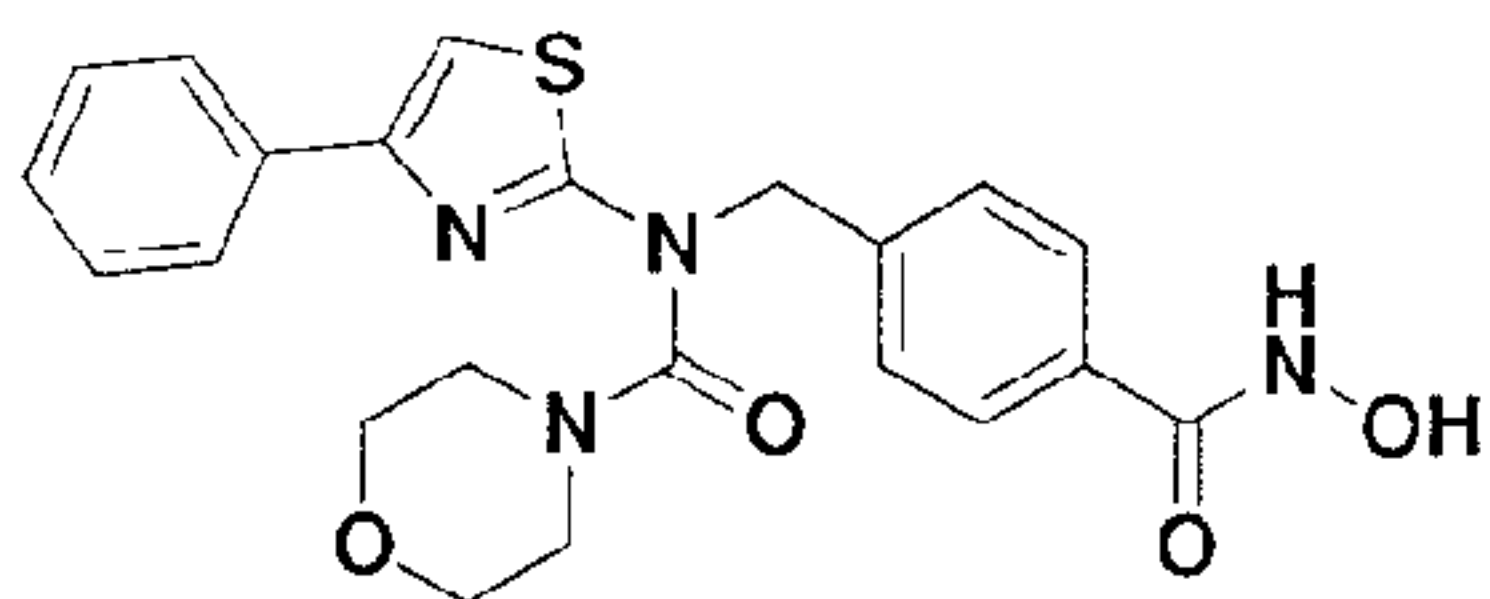
(**Formula 11-7**: methyl 4-((N-(4-phenylthiazol-2-yl)morpholine-4-carboxamido)methyl)benzoate)

Compound of **Formula 11-6**

5 (methyl 4-(((4-nitrophenoxy)carbonyl)(4-phenylthiazol-2-yl)amino)methyl)benzoate; 0.160 g, 0.327 mmol) was dissolved in dimethylformamide (5 mL), and then morpholine (0.057 g, 0.654 mmol) and potassium carbonate (0.136 g, 0.981 mmol) were added and stirred at 60 °C for 16 hours. After
 10 completion of the reaction, the organic layer was extracted with ethyl acetate and saturated ammonium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and then the residue was purified and concentrated
 15 by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 11-7** (0.085 g, 59%) in the form of a light yellow solid.

(**Compound 370**: N-(4-(hydroxycarbamoyl)benzyl)-N-(4-phenylthiazol-2-yl)morpholine-4-carboxamide)

20

Compound of **Formula 11-7**

(methyl 4-((N-(4-phenylthiazol-2-yl)morpholine-4-carboxamido)methyl)benzoate; 0.085 g, 0.194 mmol) was
 25

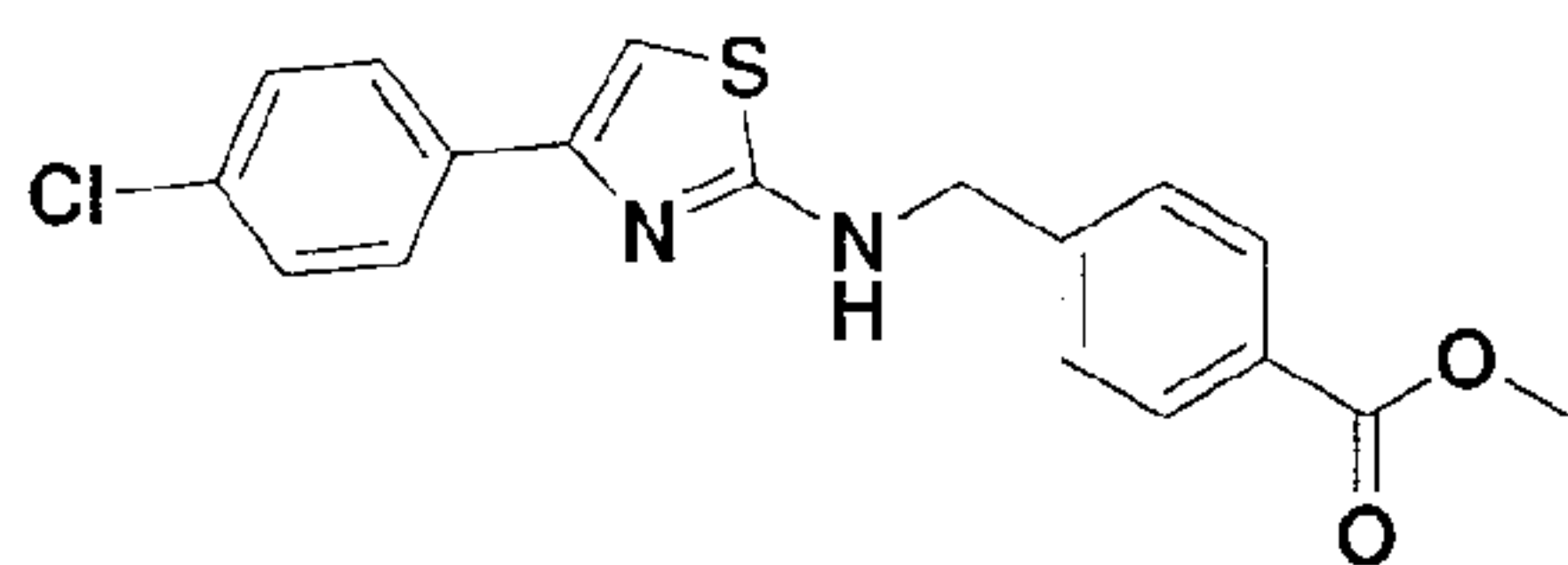
dissolved in methanol (5 mL), and then hydroxylamine (50.0 wt% aqueous solution; 1.19 mL, 19.4 mmol) and potassium hydroxide (0.109 g, 1.94 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After
 5 completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 1 mL, and saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give
 10 the desired **Compound 370** (0.059 g, 69%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.82 (d, 2 H, J = 8.5 Hz), 7.67 (d, 2 H, J = 8.3 Hz), 7.55 (s, 1 H), 7.41 - 7.35 (m, 4 H), 7.29 (m, 1 H), 5.13 (s, 2 H), 3.59 - 3.57 (m, 4 H), 3.39
 15 - 3.36 (m, 4 H). MS (ESI) m/z 439 (M⁺ + H).

Example 40: Synthesis of Compound 371

(**Formula 11-5**: methyl 4-((4-(4-chlorophenyl)thiazol-2-ylamino)methyl)benzoate)

20

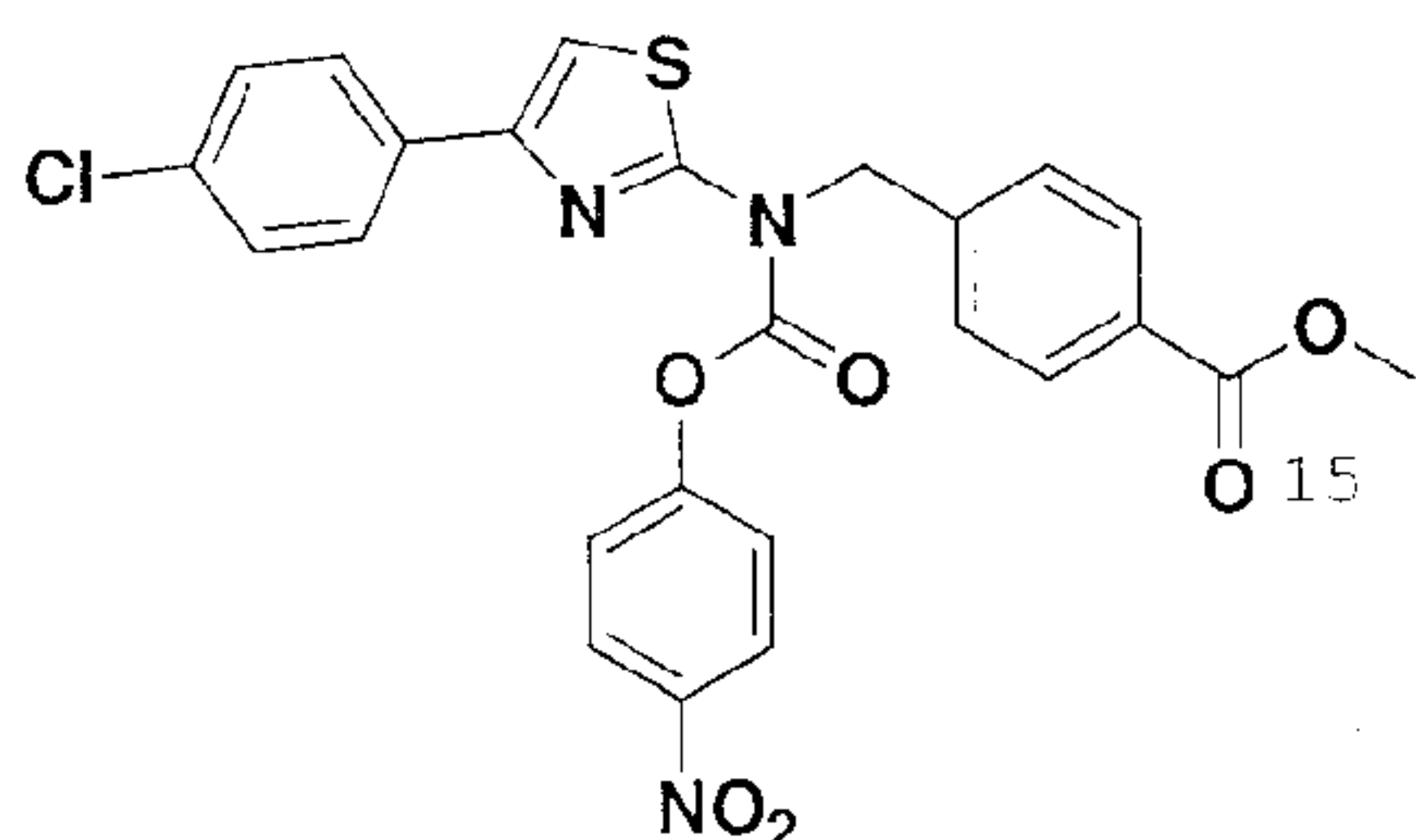


25

Compound of **Formula 11-3** (methyl 4-

(thioureidomethyl)benzoate; 0.500 g, 2.23 mmol) and 2-bromo-4-chloroacetophenone (0.573 g, 2.45 mmol) were dissolved in ethanol (20 mL) and then stirred under reflux for 16 hours. After completion of the reaction, the temperature reaction
 5 solution was cooled to room temperature, and then ethyl acetate and hexane were added and stirred. Then, the solid product was filtered and vacuum dried to give the desired compound of **Formula 11-5** (0.700 g, 88%) in the form of a white solid.

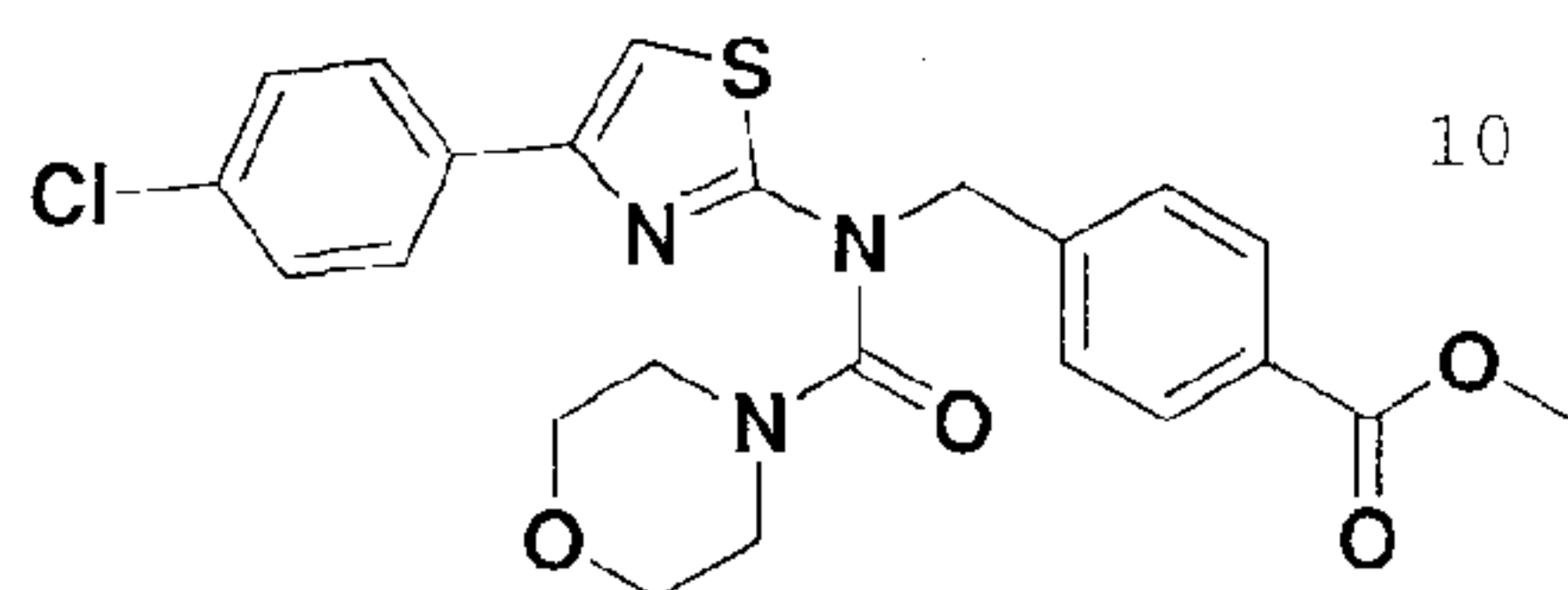
10 **(Formula 11-6: methyl 4-(((4-(4-chlorophenyl)thiazol-2-yl) ((4-nitrophenoxy)carbonyl)amino)methyl)benzoate)**



Compound of **Formula 11-5** (methyl 4-((4-(4-chlorophenyl)thiazol-2-ylamino)methyl)benzoate; 0.500 g, 1.39
 20 mmol) and 4-nitrophenyl chloroformate (0.337 g, 1.67 mmol) were dissolved in dimethylformamide (10 mL), and then N,N-diisopropylethylamine (0.370 mL, 2.09 mmol) was added and stirred at room temperature for 16 hours. After completion of the reaction, the organic layer was extracted with ethyl
 25 acetate and saturated sodium hydrogen carbonate aqueous

solution, dehydrated with anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane= 15%) to give the desired compound of **Formula 11-6** (0.520 g, 71%) in the form of a yellow solid.

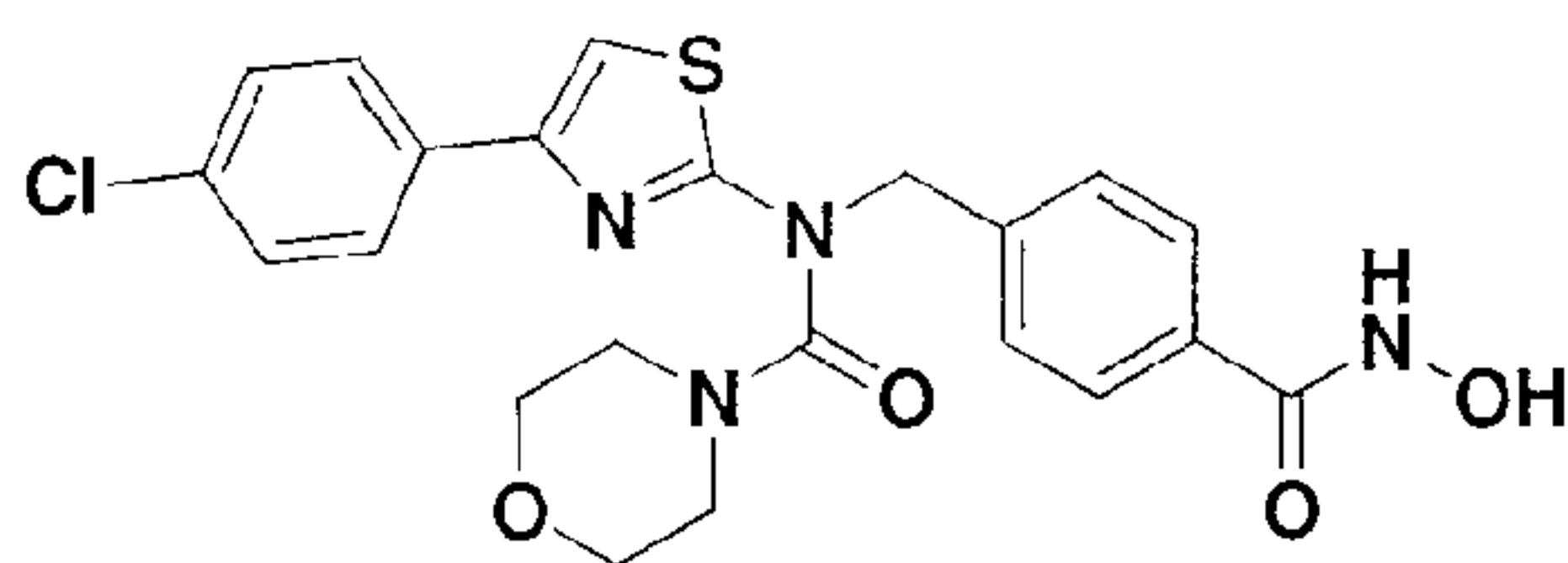
(**Formula 11-7**: methyl 4-((N-(4-(4-chlorophenyl)thiazol-2-yl)morpholine-4-carboxamido)methyl)benzoate)



Compound of **Formula 11-6** (methyl 4-(((4-(4-chlorophenyl)thiazol-2-yl))((4-nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.520 g, 0.992 mmol) was dissolved in dimethylformamide (5 mL), and then morpholine (0.173 g, 1.99 mmol) and potassium carbonate (0.412 g, 2.98 mmol) were added and stirred at 60 °C for 16 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated ammonium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and then the residue was

purified and concentrated by column chromatography (silica; ethyl acetate/hexane=50%) to give the desired compound of **Formula 11-7** (0.460 g, 98%) in the form of a white solid.

(**Compound 371**: N-(4-(4-chlorophenyl)thiazol-2-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide)



10

Compound of **Formula 11-7** (methyl 4-((N-(4-(4-chlorophenyl)thiazol-2-yl)morpholine-4-carboxamido)methyl)benzoate; 0.460 g, 0.975 mmol) was dissolved in methanol (10 mL), and then hydroxylamine (50.0 wt% aqueous solution; 2.98 mL, 48.7 mmol) and potassium hydroxide (0.547 g, 9.75 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 1 mL, and saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 371** (0.435 g, 94%) in the form of a white solid.

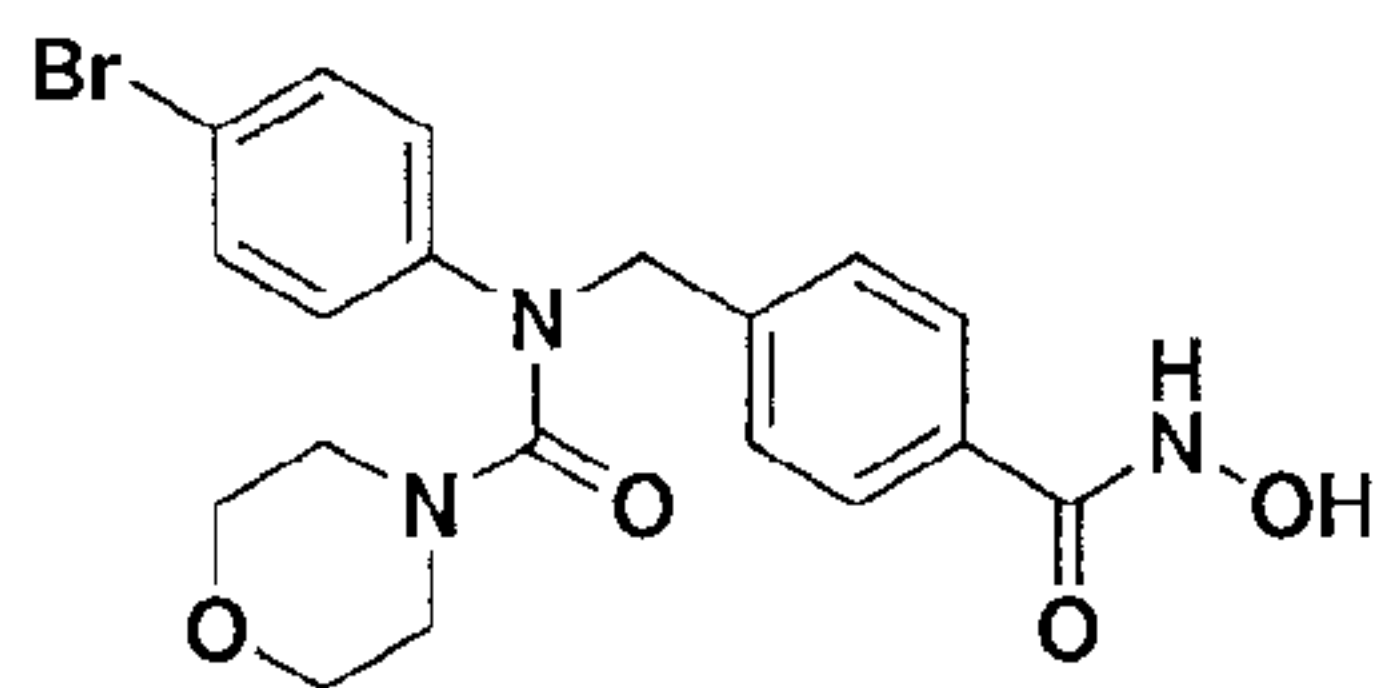
¹H NMR (400 MHz, DMSO-d₆) δ 11.14 (s, 1 H), 9.00 (s, 1 H),

7.83 (d, 2 H, $J = 8.5$ Hz), 7.67 (d, 2 H, $J = 8.2$ Hz), 7.62 (s, 1 H), 7.45 (d, 2 H, $J = 8.6$ Hz), 7.39 (d, 2 H, $J = 8.0$ Hz), 5.14 (s, 2 H), 3.60 – 3.57 (m, 4 H), 3.41 – 3.38 (m, 4 H). **MS** (ESI) m/z 473 ($M^+ + H$).

5

Example 41: Synthesis of Compound 372

(Compound 372: N-(4-bromophenyl)-N-(4-



(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide)

10

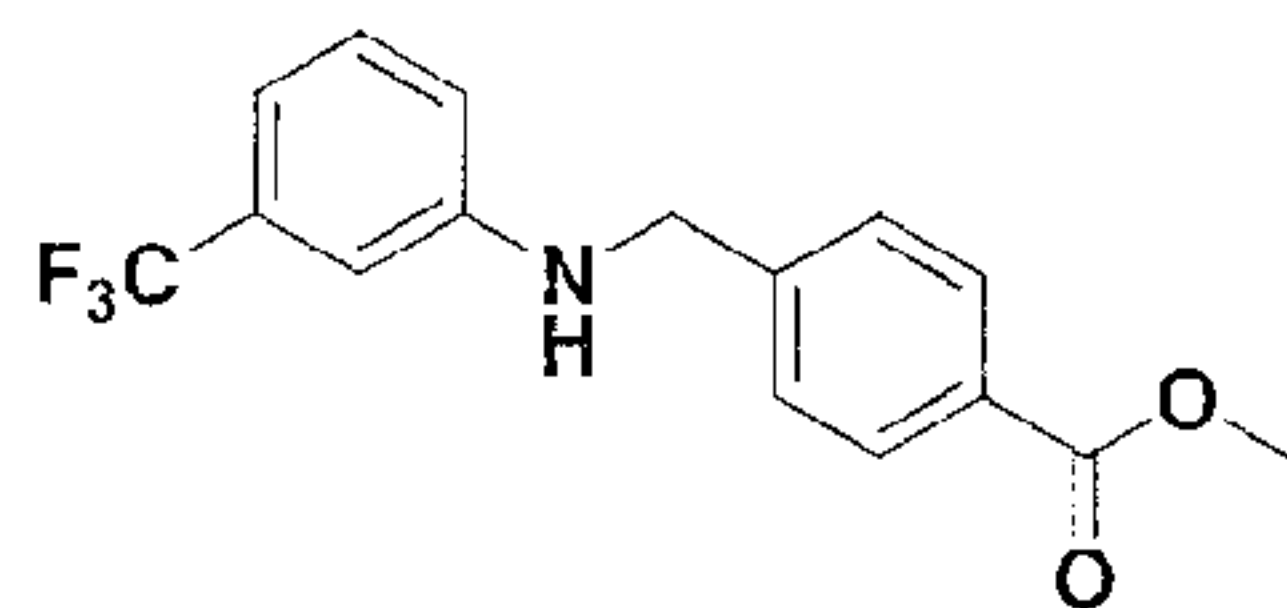
Compound of **Formula 8-5** (methyl 4-((N-(4-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.085 g, 0.196 mmol) was dissolved in methanol (5 mL), and then
 15 hydroxylamine (50.0 wt% aqueous solution; 1.20 mL, 19.6 mmol) and potassium hydroxide (0.110 g, 1.96 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its
 20 volume became about 1 mL, and saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the

solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 372** (0.049 g, 58%) in the form of a light yellow solid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.64 (d, 2 H, *J* = 8.4 Hz),
 5 7.45 (dd, 2 H, *J* = 6.8, 2.1 Hz), 7.33 (d, 2 H, *J* = 8.2 Hz),
 7.09 (dd, 2 H, *J* = 6.8, 2.1 Hz), 4.85 (s, 2H), 3.41 (t, 4 H,
J = 4.7 Hz), 3.13 (t, 4 H, *J* = 4.6 Hz). **MS** (ESI) *m/z* 434, 436
 (M⁺ + H).

10 **Example 42: Synthesis of Compound 374**

(**Formula 1-2**: methyl 4-((3-



(trifluoromethyl)phenylamino)methyl)benzoate)

15

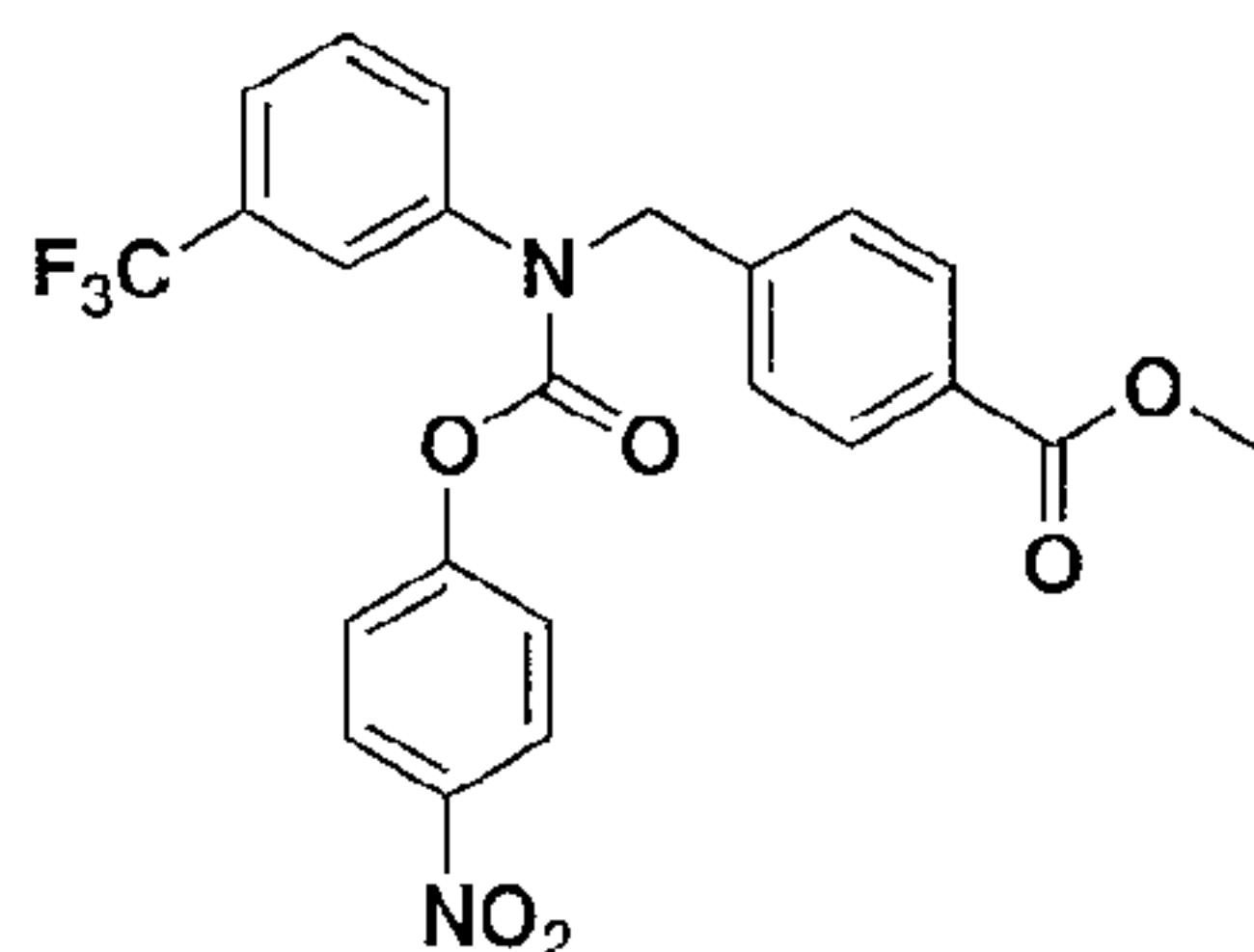
Compound **Formula 1-1** (3-(trifluoromethyl)benzenamine;
 0.30 g, 1.84 mmol) and potassium carbonate (0.76 g, 5.53
 mmol) were dissolved in dimethylformamide (DMF, 5 mL), and
 methyl 4-(bromomethyl)benzoate (0.42 g, 1.84 mmol) was then
 20 added. The mixture was reacted at room temperature for 1 day
 and then diluted with ethyl acetate. The reaction mixture

was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica; ethyl

5 acetate/hexane =20%) to give the desired compound of **Formula 1-2** (0.37 g, 65%).

¹H NMR (400 MHz, DMSO-d₆) δ 7.93 (d, 2 H, J = 8.3 Hz), 7.49 (d, 2 H, J = 8.3 Hz), 7.24 (t, 1 H, J = 7.9 Hz), 6.88-6.78 (m, 4 H), 4.42 (d, 2 H, J = 6.1 Hz), 3.83 (s, 3H), MS
10 (ESI) m/z 310 (M⁺ + H).

(**Formula 1-3**: methyl 4-(((4-nitrophenoxy)carbonyl)(3-(trifluoromethyl)phenyl)amino)methyl)benzoate)



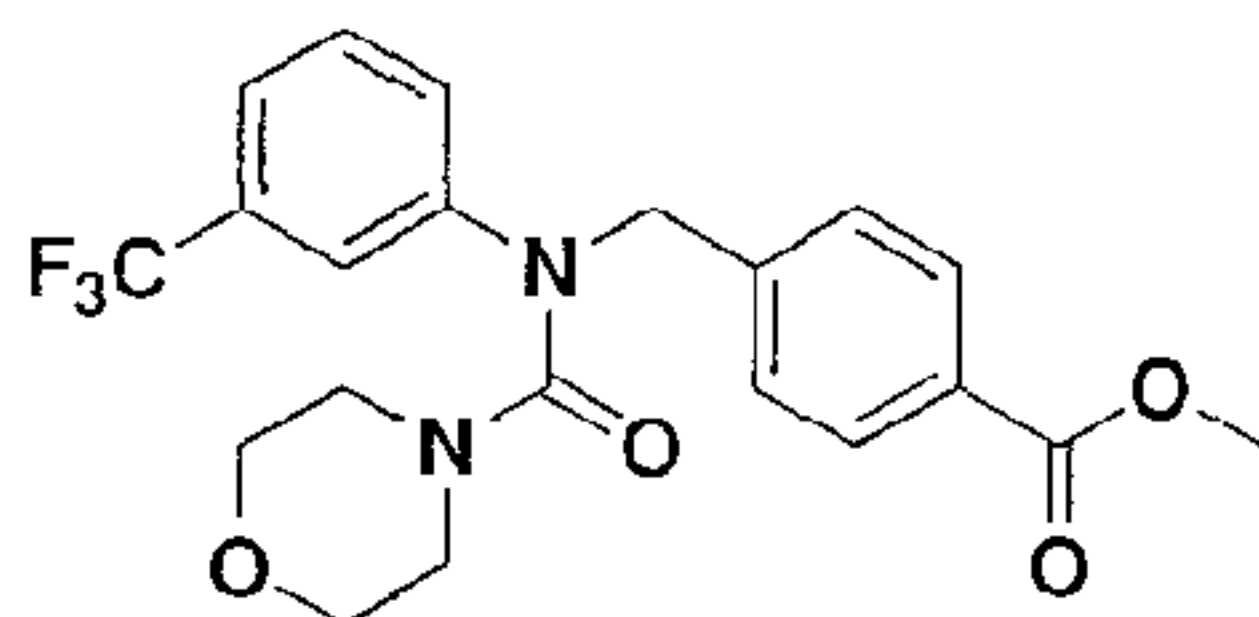
Compound of **Formula 1-2**

(methyl 4-((3-(trifluoromethyl)phenylamino)methyl)benzoate;
0.26 g, 0.82 mmol) and 4-nitrophenyl carbonochloridate (0.33
20 g, 1.65 mmol) were dissolved in acetonitrile (10 mL), and potassium carbonate (0.34 g, 2.47 mmol) was then added. The mixture was reacted at room temperature for 1 day and then diluted with ethyl acetate. The reaction mixture was washed with saturated sodium chloride aqueous solution, dehydrated
25 with anhydrous sodium sulfate, filtered, and then

concentrated under reduced pressure. The residue was purified by column chromatography (silica; ethyl acetate/hexane-20%) to give the desired compound of **Formula 1-3** (0.35 g, 89%) in the form of a colorless oil.

5 $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.20 (d, 2 H, $J = 10.2$ Hz), 8.01 (d, 2 H, $J = 7.8$ Hz), 7.56-7.46 (m, 3H), 7.35 (d, 3 H, $J = 8.0$ Hz), 7.26 (d, 2 H, $J = 8.1$ Hz), 5.01 (bs, 2H), 3.90 (s, 3H).

(**Formula 1-4**: methyl 4-((N-(3-(trifluoromethyl)phenyl)morpholine-4-carboxamido)methyl)benzoate)



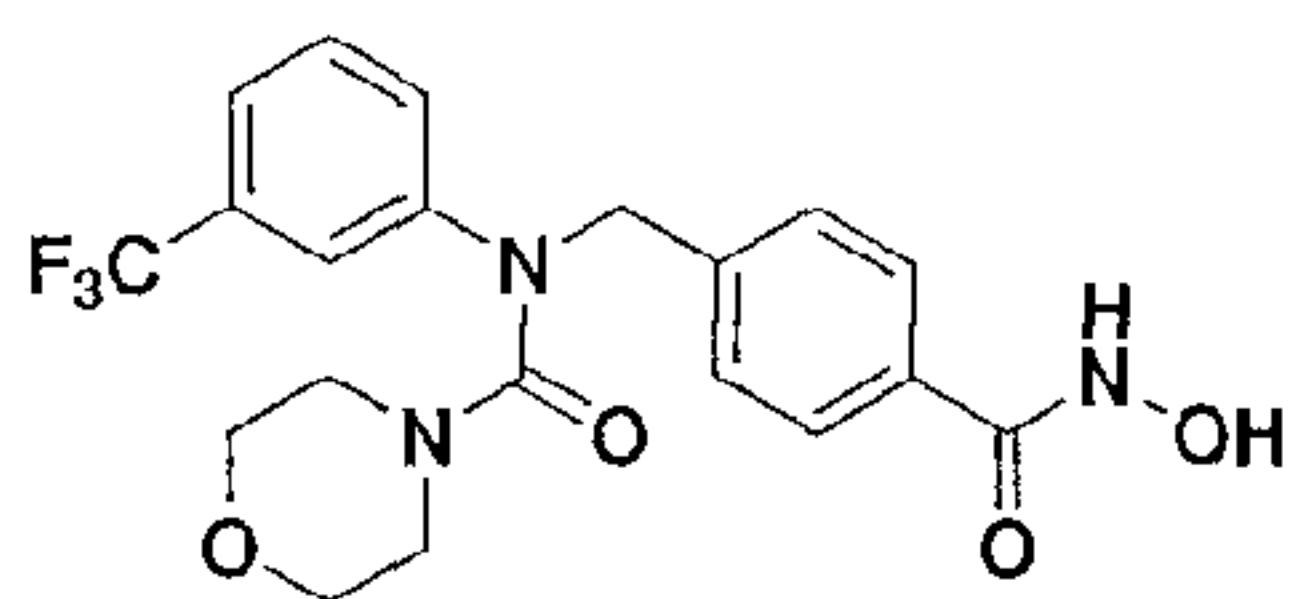
15 Compound of **Formula 1-3** (methyl 4-(((4-nitrophenoxy)carbonyl)(3-(trifluoromethyl)phenyl)amino)methyl)benzoate; 0.29 g, 0.60 mmol) was dissolved in dimethylformamide (10 mL), and potassium carbonate (0.25 g, 1.81 mmol) and morpholine (0.05 mL, 0.60 mmol) were then added. The mixture was reacted at 60 °C for 2 days and then diluted with saturated ammonium chloride solution. The organic layer was extracted with ethyl acetate, dehydrated with anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure. The
20 residue was purified by column chromatography (silica; ethyl
25

acetate/hexane=50%) to give the desired compound of **Formula 1-4** (0.15 g, 60%).

¹H NMR (400 MHz, DMSO-d₆) δ 7.97 (d, 2 H, J = 8.2 Hz), 7.43-7.32 (m, 5H), 7.20 (d, 1 H, J = 8.0 Hz), 4.94 (s, 2H),
 5 3.90 (s, 3H), 3.50 (t, 4 H, J = 4.8 Hz), 3.25 (t, 4 H, J = 4.8 Hz), **MS** (ESI) m/z 423 (M⁺ + H).

(Compound 374: N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)morpholine-4-carboxamide)

10

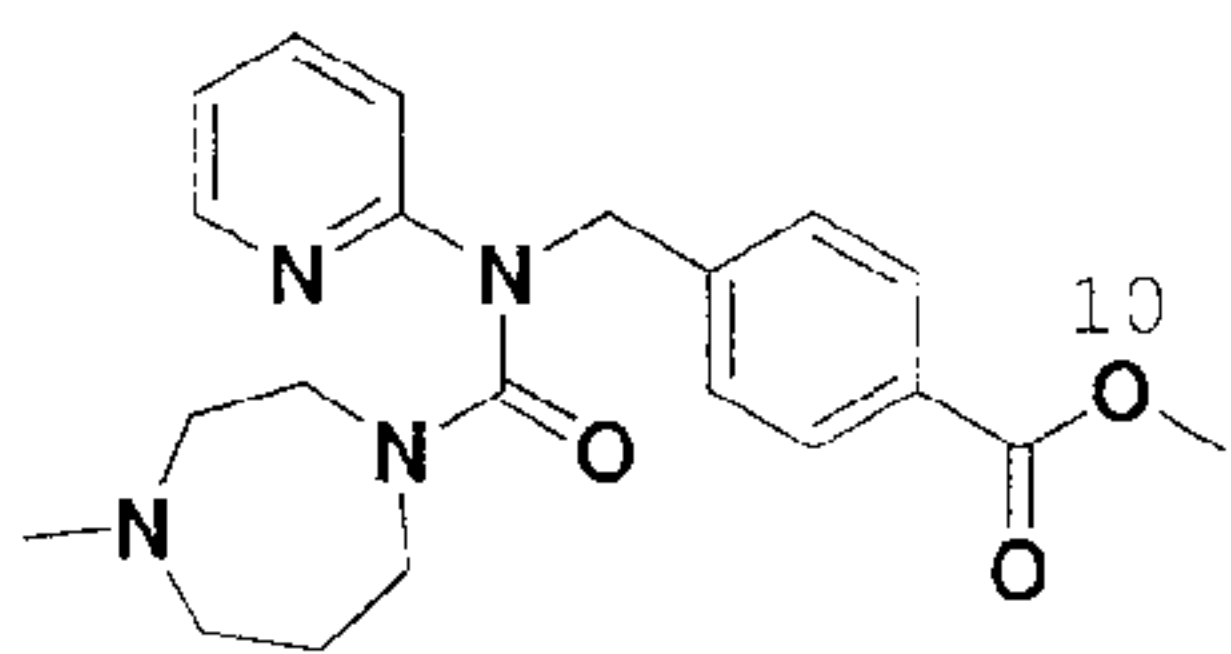
Compound of **Formula 1-4**

(methyl 4-((N-(3-(trifluoromethyl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.15 g, 0.36 mmol) was dissolved
 15 in methanol (5 mL), and hydroxylamine aqueous solution (50 wt%, 1 mL) and potassium hydroxide (0.10 g, 1.81 mmol) were then added and stirred overnight. After completion of the reaction, the methanol was removed by distillation under reduced pressure, and the organic layer was extracted with
 20 ethyl acetate and water, dehydrated with anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure. The residue was stirred in diethyl ether to give a solid product, and the resulting solid was filter and dried to give the desired **Compound 374** (0.082 g, 54%) in the form
 25 of a white solid.

^1H NMR (400 MHz, MeOD- d_3) δ 11.14 (brs, 1 H), 8.99 (brs, 1 H), 7.85 (d, 2 H, $J = 8.0$ Hz), 7.66–7.27 (m, 6 H), 4.94 (s, 2 H), 3.41 (s, 2 H), 3.15 (s, 2 H). **MS** (ESI) m/z 424 ($M^+ + H$).

5 **Example 43: Synthesis of Compound 376**

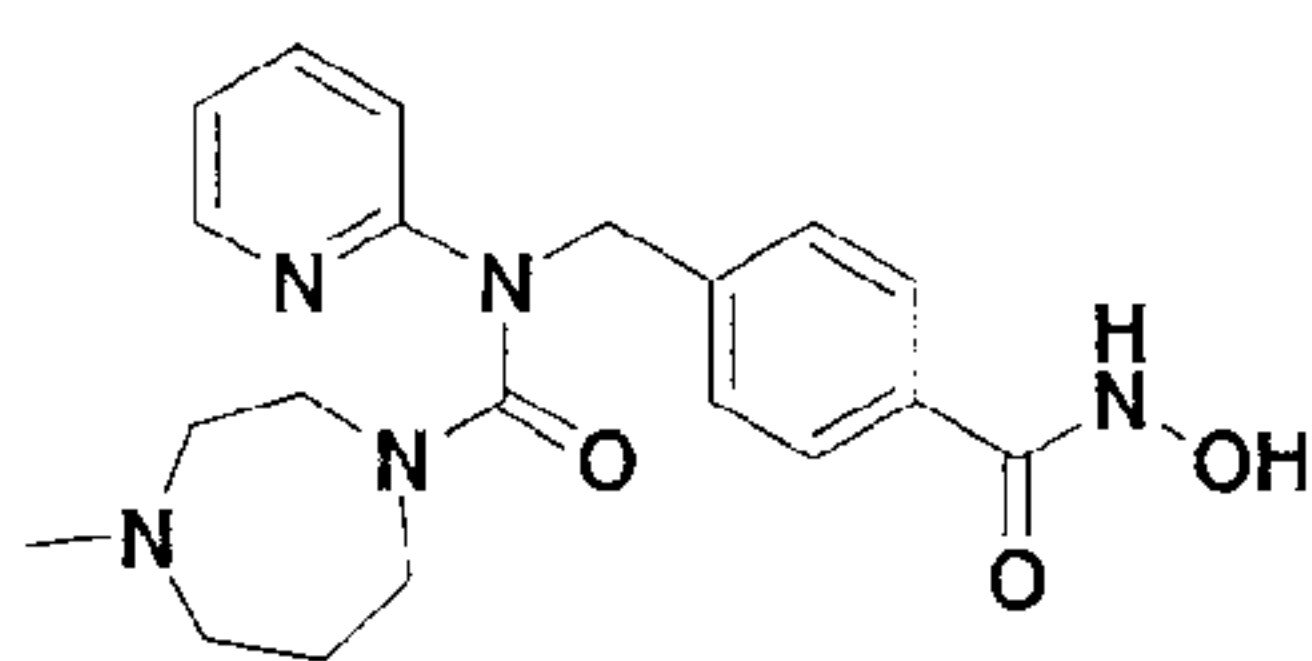
(**Formula 7-6**: methyl 4-((4-methyl-N-(pyridin-2-yl)-1,4-diazepane-1-carboxamido)methyl)benzoate)



Compound of **Formula 7-5** (methyl 4-(((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate;
 15 0.50 g, 1.23 mmol) was dissolved in dimethylformamide (4 mL),
 and then 1-methyl-1,4-diazepane (0.183 mL, 1.47 mmol) and
 potassium carbonate (0.339 g, 2.45 mmol) were added, and the
 mixture was heated and stirred at 55 °C for 12 hours. Then,
 the dimethylformamide was removed under reduced pressure,
 20 saturated ammonium chloride aqueous solution was poured into
 the reaction mixture, and the organic layer was extracted
 with dichloromethane. The organic layer was washed with
 saturated sodium chloride aqueous solution, dehydrated with
 anhydrous magnesium sulfate, and then concentrated under
 25 reduced pressure. The residue was purified and concentrated

by column chromatography (silica; ethyl acetate/hexane=50%)
to give the desired compound of **Formula 7-6** (0.32 g, 68%) in
the form of a pale yellow oil.

(**Compound 376**: N-(4-(hydroxycarbonyl)benzyl)-4-methyl-
5 N-(pyridin-2-yl)-1,4-diazepane-1-carboxamide)



10

Compound of **Formula 7-6** (methyl

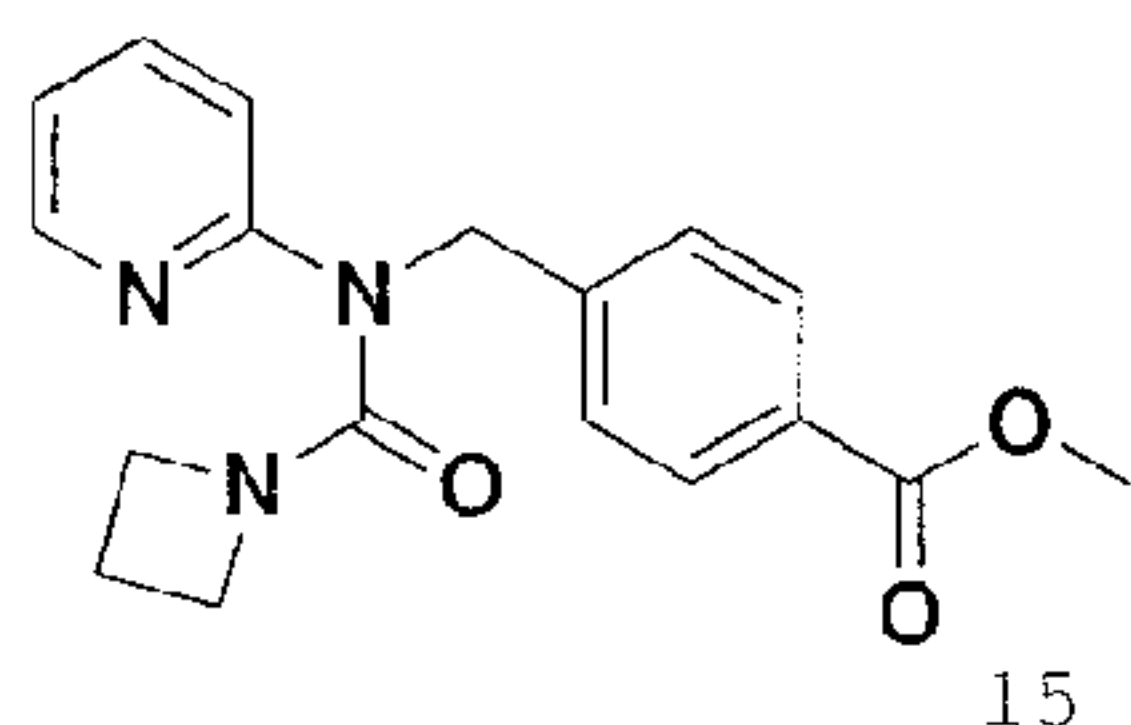
4-((4-methyl-N-(pyridin-2-yl)-1,4-diazepane-1-
carboxamido)methyl)benzoate; 0.15 g, 0.39 mmol) was dissolved
in methanol (20 mL), and then hydroxylamine (0.136 g, 1.96
mmol) and potassium hydroxide (0.22 g, 3.92 mmol) were added
15 and stirred for 5 minutes. Then, hydroxylamine (50 wt%
aqueous solution; 1.01 mL, 7.84 mmol) was added dropwise and
stirred at room temperature for 6 hours. After completion of
the reaction, the methanol was evaporated by reduced pressure,
1 N hydrogen chloride was added, and the organic layer was
20 extracted with ethyl acetate. The organic layer was washed
with saturated sodium chloride aqueous solution, dehydrated
with anhydrous magnesium sulfate, and then concentrated under
reduced pressure. The residue was purified and concentrated
by column chromatography (silica;
25 methanol/dichloromethane=5%) to give the desired **Compound 376**

(0.009 g, 6%) in the form of a white solid.

¹H NMR (400 MHz, MeOD-d₃) δ 8.33 - 8.31 (m, 1 H), 7.74 - 7.72 (m, 1 H), 7.67 (d, 2 H, *J* = 8.3 Hz), 7.50 (d, 2 H, *J* = 8.2 Hz), 7.10 - 7.04 (m, 2 H), 5.09 (d, 2 H, *J* = 2.4 Hz),
 5 3.96 - 3.93 (m, 2 H), 3.56 - 2.95 (m, 6 H), 2.88 (s, 3 H),
 2.06 - 2.02 (m, 2H); MS (ESI) *m/z* 384.1 (M⁺ + H).

Example 44: Synthesis of Compound 377

(Formula 7-6: methyl 4-((N-(pyridin-2-yl)azetidine-1-
 10 carboxamido)methyl)benzoate)

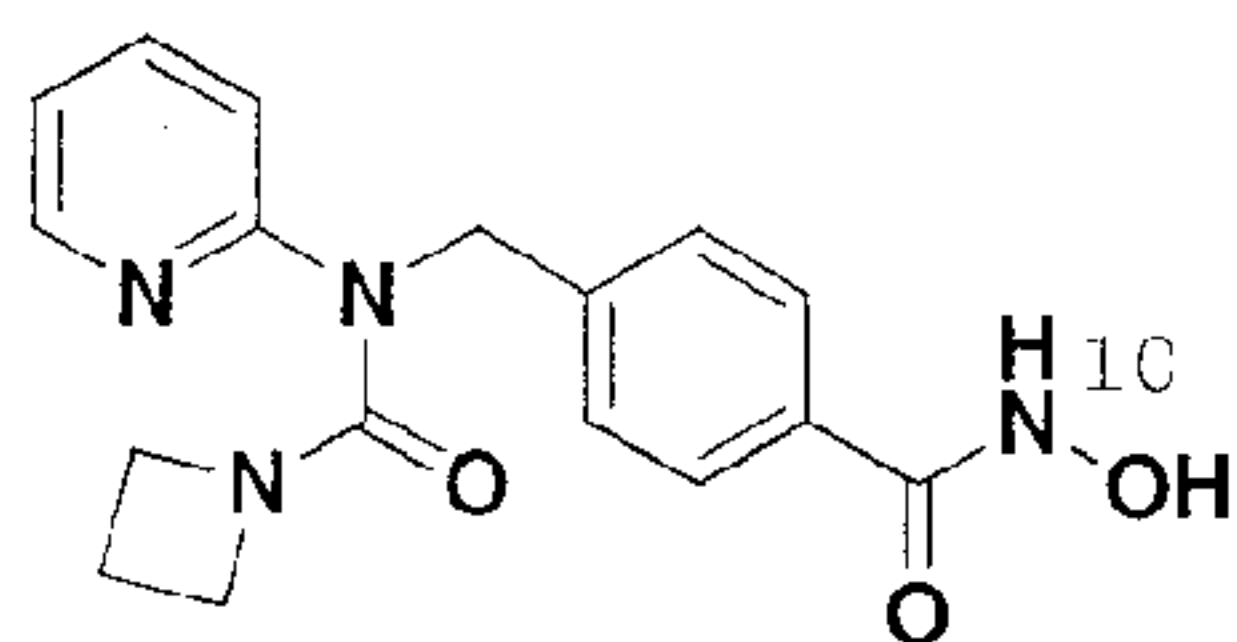


Compound of **Formula 7-5** (methyl 4-(((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate;
 0.50 g, 1.23 mmol) was dissolved in dimethylformamide (4 mL),
 and then azetidine (0.183 g, 1.47 mmol) and potassium
 20 carbonate (0.339 g, 2.45 mmol) were added, and the mixture
 was heated and stirred at 55 °C for 1 day. Then, the
 dimethylformamide was removed under reduced pressure, water
 was poured into the reaction mixture, and the organic layer
 was extracted with dichloromethane. The organic layer was
 25 washed with saturated sodium chloride aqueous solution,

dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of

5 **Formula 7-6** (0.03 g, 8%) in the form of a white solid.

(**Compound 377**: N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)azetidine-1-carboxamide)



Compound of **Formula 7-6** (methyl 4-((N-(pyridin-2-yl)azetidine-1-carboxamido)methyl)benzoate; 0.03 g, 0.09 mmol) was dissolved in methanol (20 mL), and

15 then hydroxylamine (0.032 g, 0.092 mmol) and potassium hydroxide (0.052 g, 0.922 mmol) were added and stirred for 5 minutes. Then, hydroxylamine (50 wt% aqueous solution; 0.238 mL, 1.84 mmol) was added dropwise and stirred at room temperature for 6 hours. After completion of the reaction, 1

20 N hydrogen chloride was added and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated

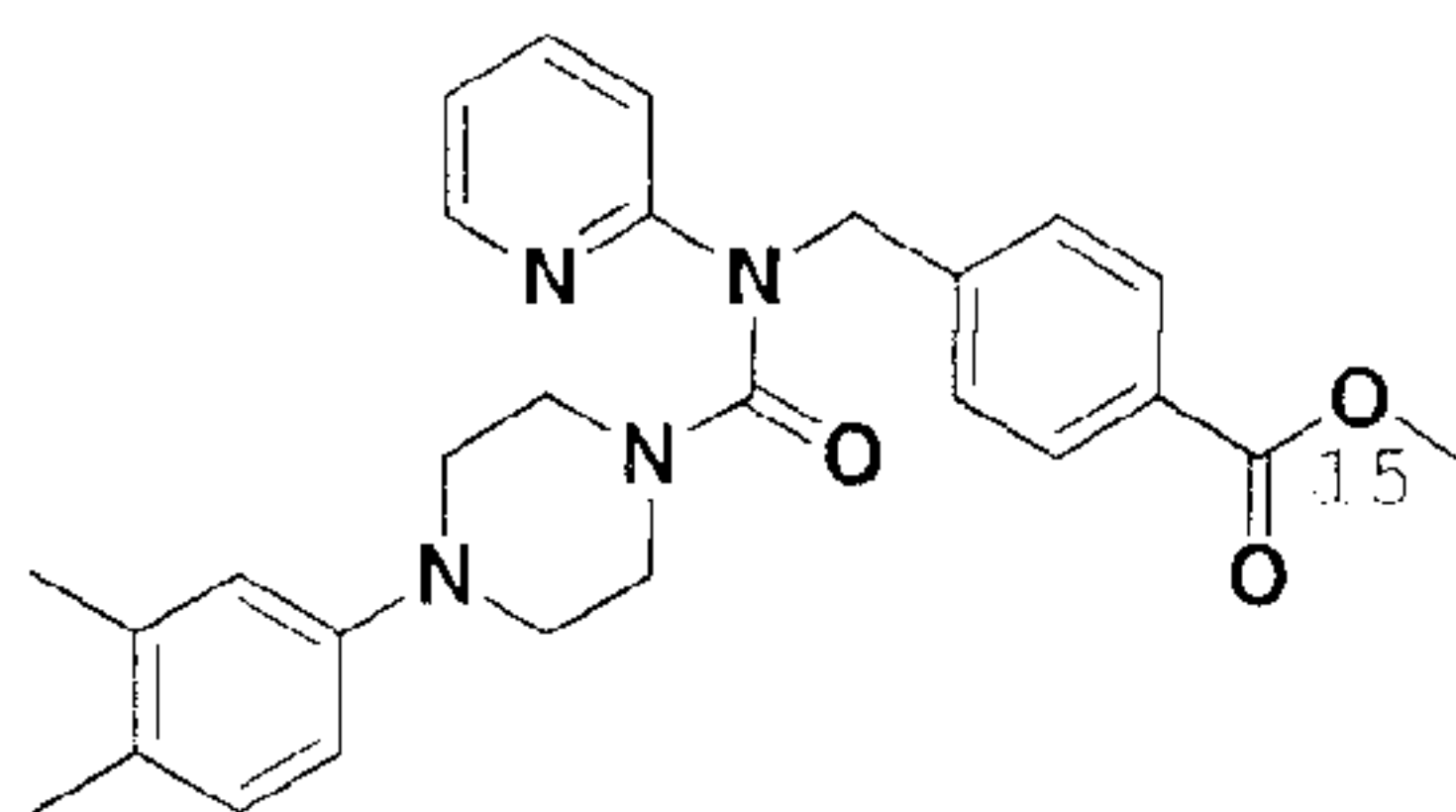
25 by column chromatography (silica;

methanol/dichloromethane=5%) to give the desired **Compound 377** (0.013 g, 43%) in the form of a white solid.

¹H NMR (400 MHz, MeOD-d₃) δ 8.38 - 8.36 (m, 1 H), 7.78 - 7.74 (m, 1 H), 7.64 (d, 2 H, *J* = 8.3 Hz), 7.40 (d, 2 H, *J* = 8.3 Hz), 7.24 (d, 1 H, *J* = 8.2 Hz), 7.15 - 7.11 (m, 1 H), 5.09 (s, 2 H), 3.73 (t, 4 H, *J* = 7.7 Hz), 2.12 (tt, 2H, *J* = 7.7 Hz); **MS** (ESI) *m/z* 327.2 (*M*⁺ - H).

Example 45: Synthesis of Compound 379

(**Formula 7-6**: methyl 4-((4-(3,4-dimethylphenyl)-N-(pyridin-2-yl)piperazine-1-carboxamido)methyl)benzoate)

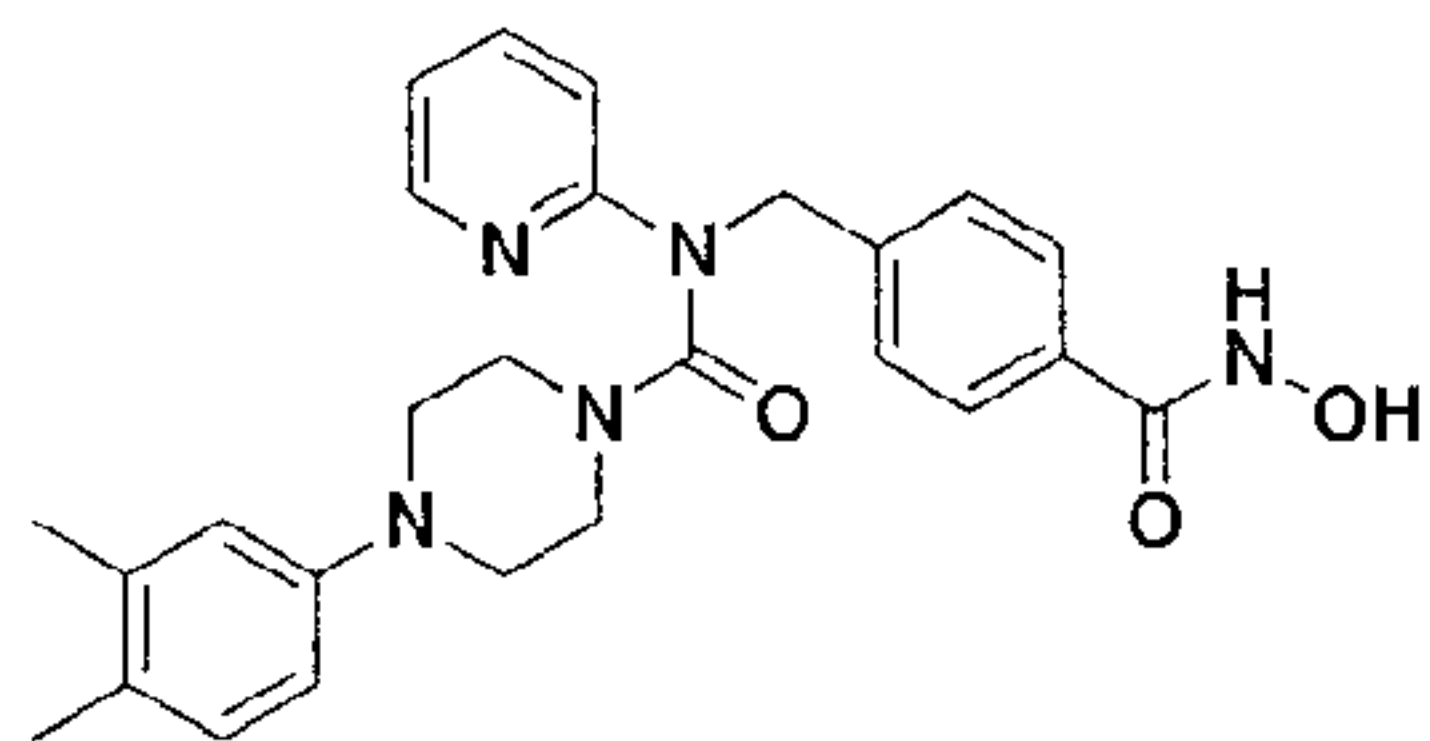


Compound of **Formula 7-5**

(methyl 4-(((4-nitrophenoxy)carbonyl)(pyridin-2-yl)amino)methyl)benzoate; 0.50 g, 1.23 mmol) was dissolved in dimethylformamide (4 mL), and then 1-(3,4-dimethylphenyl)piperazine (0.28 g, 1.47 mmol) and potassium carbonate (0.339 g, 2.46 mmol) were added, and the mixture was heated and stirred at 55 °C for 1 day. Then, the dimethylformamide was removed under reduced pressure, water was poured into the reaction mixture, and the organic layer

was extracted with dichloromethane. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 7-6** (0.4 g, 71%) in the form of a yellow oil.

(**Compound 379**: 4-(3,4-dimethylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide)



Compound of **Formula 7-6** (methyl 4-((4-(3,4-dimethylphenyl)-N-(pyridin-2-yl)piperazine-1-carboxamido)methyl)benzoate; 0.1 g, 0.218 mmol) was dissolved in methanol (20 mL), and then hydroxylamine (0.076 g, 1.09 mmol) and potassium hydroxide (0.122 g, 2.18 mmol) were added and stirred for 5 minutes. Then, hydroxylamine (50 wt% aqueous solution; 0.56 mL, 4.36 mmol) was added dropwise and stirred at room temperature for 6 hours. After completion of the reaction, 2 N hydrogen chloride was added and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution,

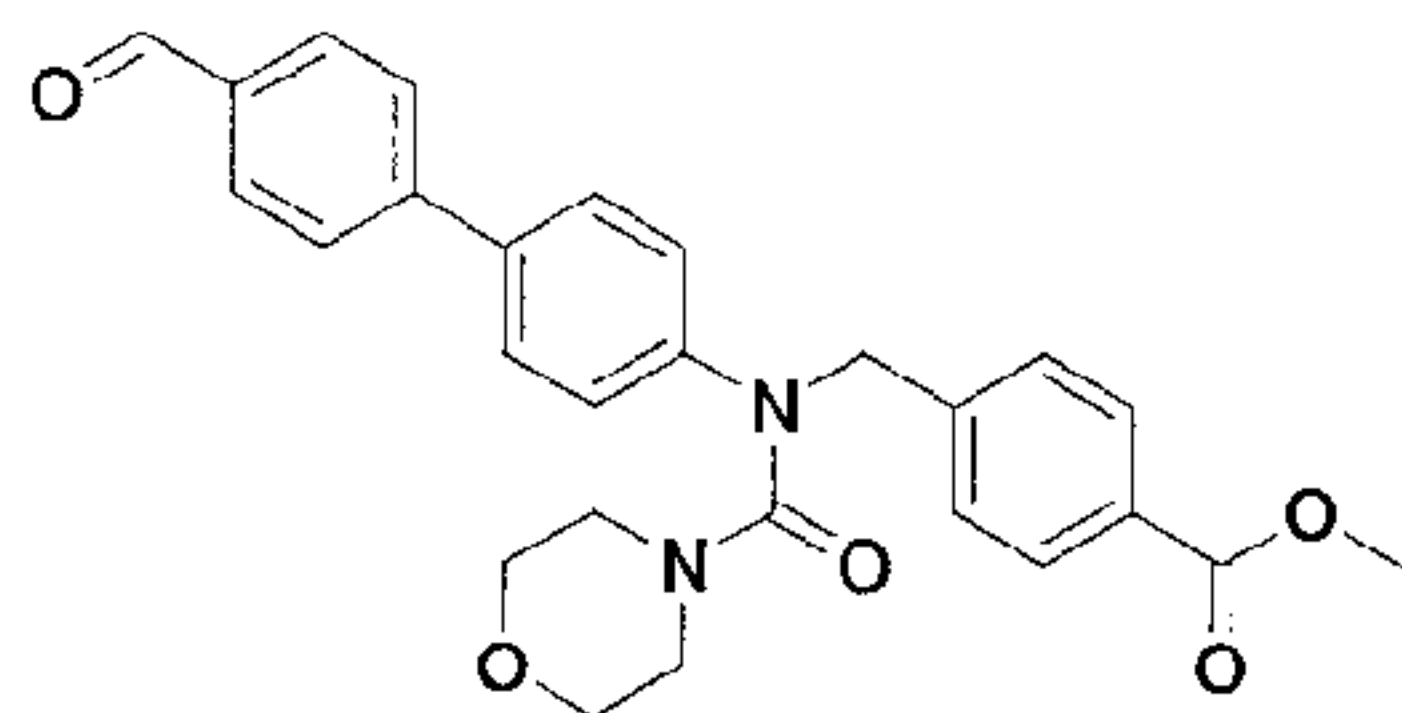
dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane=5%) to give the desired **Compound 379**

5 (0.05 g, 52%) in the form of a white solid.

¹H NMR (400 MHz, MeOD-d₃) δ 8.33 (dd, 1 H, *J* = 4.9, 1.2 Hz), 7.74 - 7.70 (m, 1 H), 7.67 (d, 2 H, *J* = 8.3 Hz), 7.50 (d, 2 H, *J* = 8.3 Hz), 7.08 (d, 1 H, *J* = 8.3 Hz), 7.05 - 7.02 (m, 1 H), 6.97 (d, 1 H, *J* = 8.3 Hz), 6.72 (d, 1 H, *J* = 2.2 Hz),
10 6.63 (dd, 1 H, *J* = 8.2, 2.4 Hz), 5.10 (s, 2 H), 3.45 - 3.43 (m, 4 H), 2.95 - 2.93 (m, 4 H), 2.20 (s, 3 H), 2.15 (s, 3 H);
MS (ESI) *m/z* 460.2 (M⁺ + H).

Example 46: Synthesis of Compound 380

15 **(Formula 9-1: methyl 4-((N-(4'-formylbiphenyl-4-yl)morpholine-4-carboxamido)methyl)benzoate)**



20

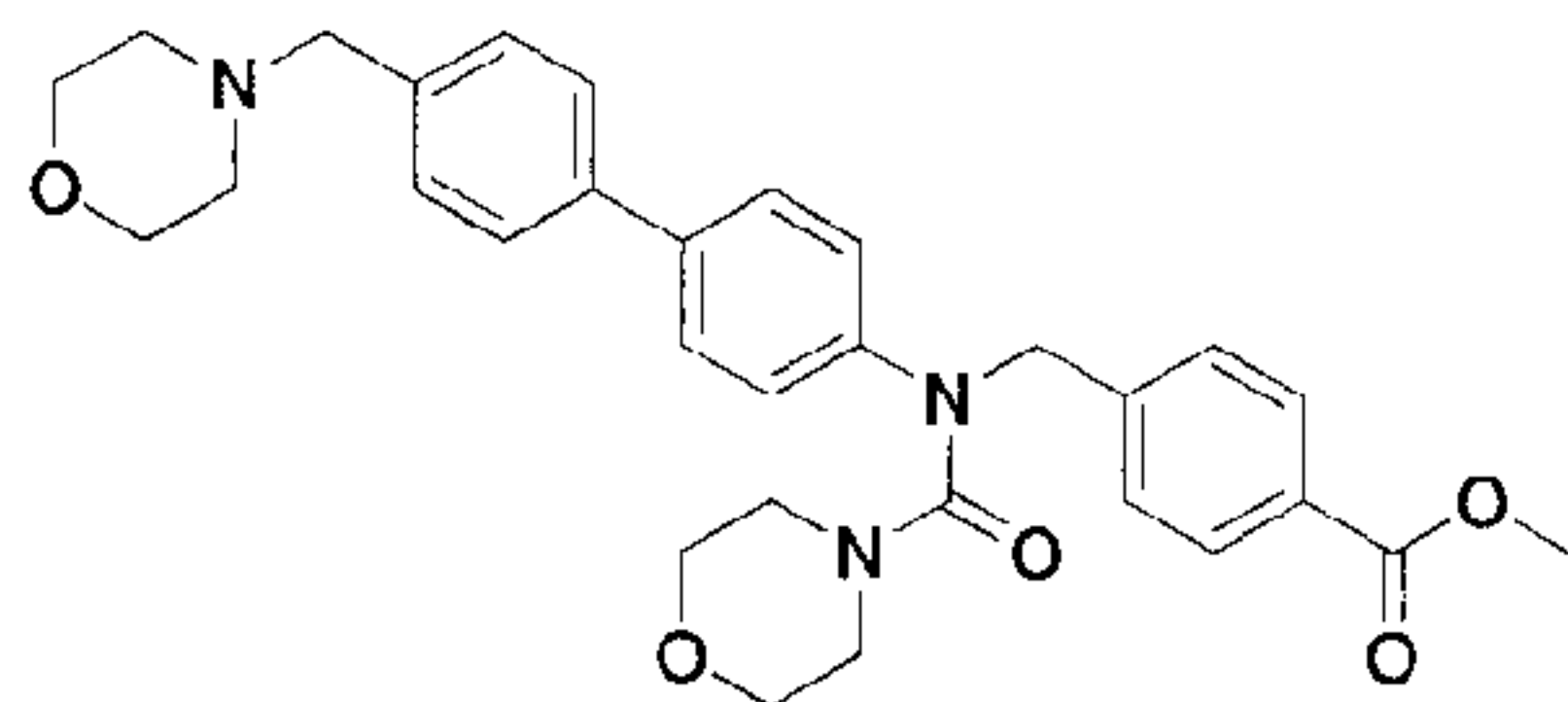
Compound of **Formula 8-5** (methyl 4-((N-(4-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 1.00 g, 2.31 mmol), 4-formylphenylboronic acid (0.415 g, 2.77 mmol), and Pd(dppf)Cl₂ (0.094 g, 0.115 mmol) were dissolved in 1,4-dioxane (12 mL), and then cesium carbonate (2.24 g, 6.92

25

mmol) dissolved in water (3 mL) was added to the reaction solution and then stirred at 140 °C for 15 minutes in a microwave reactor. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution, dehydrated with anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=50%) to give the desired compound of **Formula 9-1** (0.750 g, 71%) in the form of a light yellow solid.

(**Formula 9-2**: methyl 4-((N-(4'-(morpholinomethyl)biphenyl-4-yl)morpholine-4-carboxamido)methyl)benzoate)

15

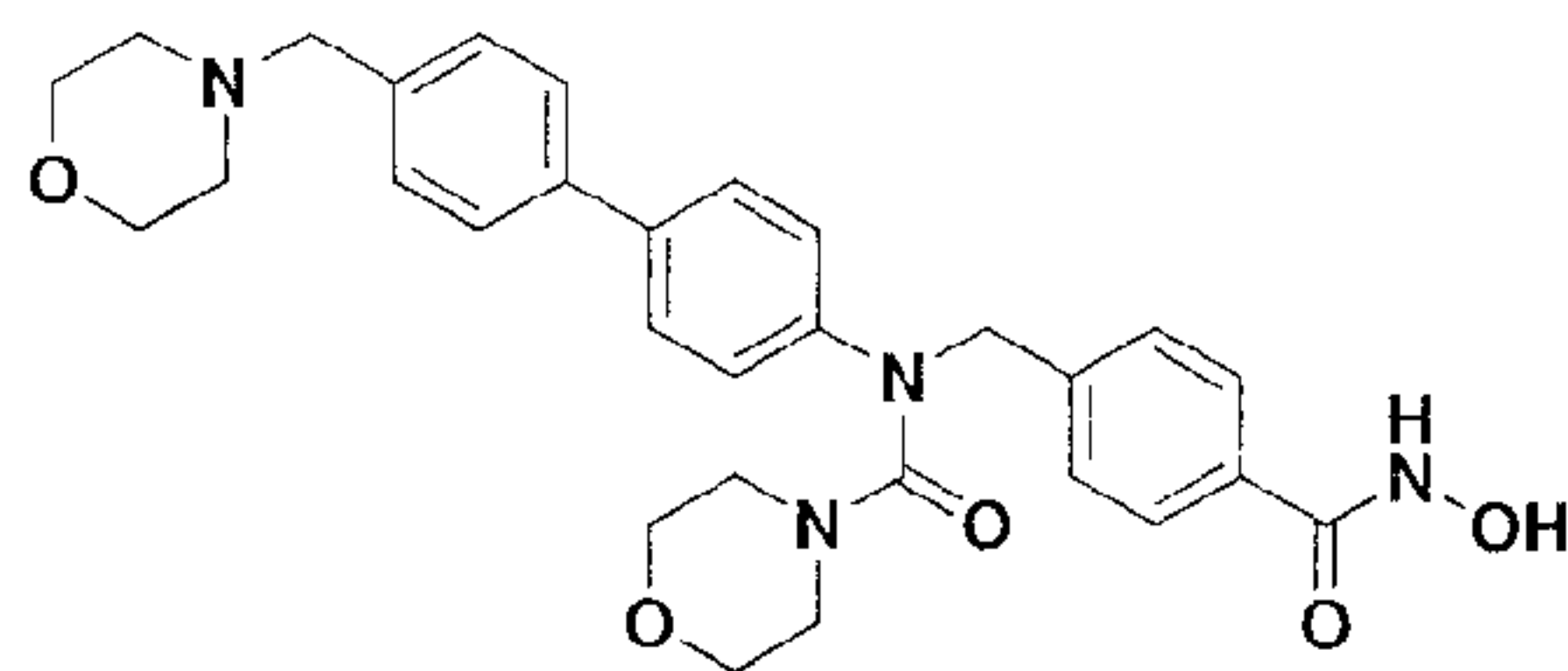


Compound of **Formula 9-1** (methyl 4-((N-(4'-formylbiphenyl-4-yl)morpholine-4-carboxamido)methyl)benzoate; 0.150 g, 0.327 mmol) was dissolved in methanol (5 mL), and then morpholine (0.086 g, 0.981 mmol) and acetic acid (0.094 mL, 1.64 mmol) were added and stirred at room temperature for 1 hour. Then, sodium cyanoborohydride (0.041 g, 0.654 mmol) was added and stirred at the same temperature for 16 hours.

After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure. Then, the organic layer was dehydrated with
 5 anhydrous magnesium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. Then, the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=25%) to give the desired compound of **Formula 9-2** (0.136 g, 79%) in the form of
 10 a white solid.

(**Compound 380**: N-(4-(hydroxycarbamoyl)benzyl)-N-(4'-(morpholinomethyl)biphenyl-4-yl)morpholine-4-carboxamide)

15



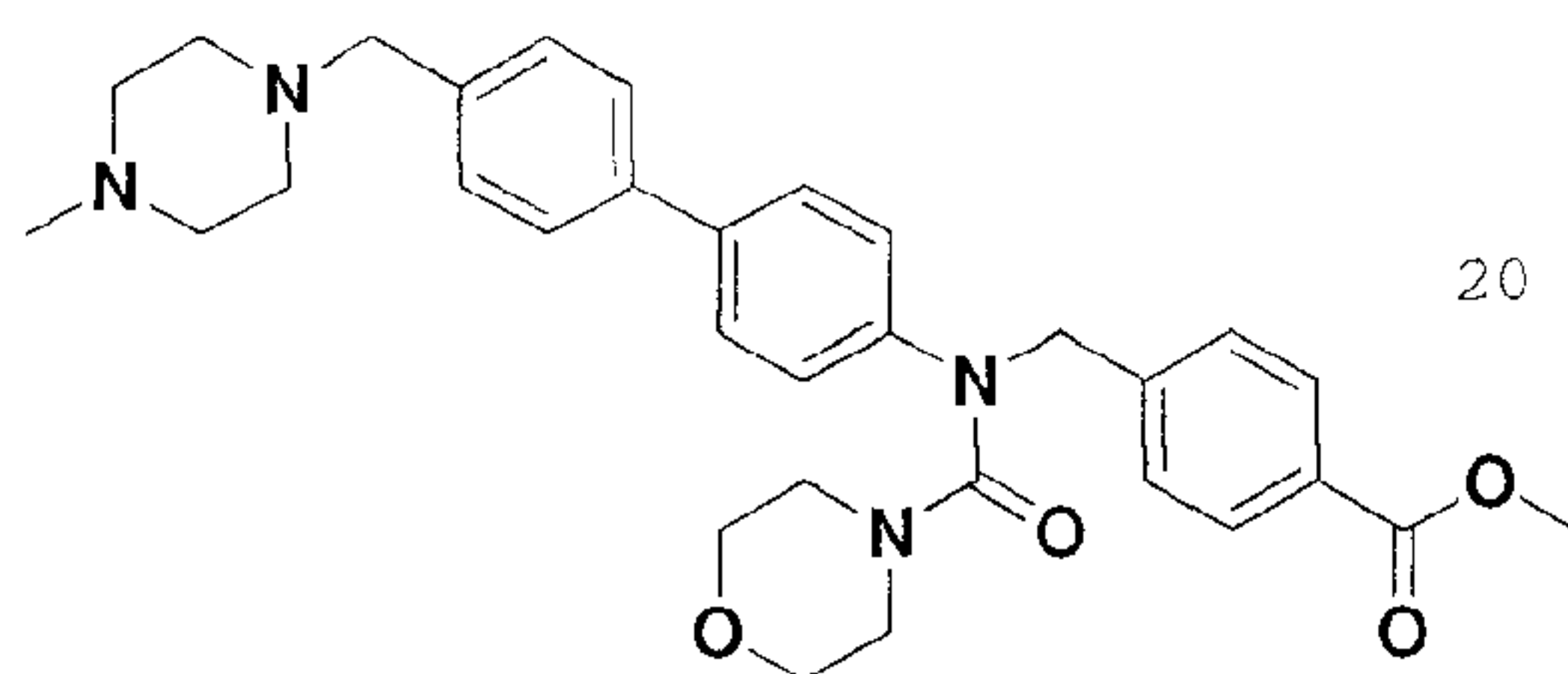
Compound of **Formula 9-2** (methyl 4-((N-(4'-(morpholinomethyl)biphenyl-4-yl)morpholine-4-carboxamido)methyl)benzoate; 0.130 g, 0.245 mmol) was
 20 dissolved in methanol (10 mL), and hydroxylamine (50.0 wt% aqueous solution; 1.50 mL, 24.5 mmol) and potassium hydroxide (0.138 g, 2.46 mmol) were added and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure
 25 until its volume became about 2 mL, and the organic layer was

extracted with ethyl acetate and saturated ammonium chloride aqueous solution. The organic layer was dehydrated with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The residue was
 5 recrystallized with dichloromethane and hexane to give the desired **Compound 380** (0.073 g, 56%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.14 (brs, H), 9.14 (brs, 1 H), 7.65 (d, 2 H, J = 8.1 Hz), 7.62 - 7.56 (m, 4 H), 7.39 -
 10 7.33 (m, 4 H), 7.21 (d, 2 H, J = 8.5 Hz), 4.90 (s, 2 H), 3.58 - 3.55 (m, 4 H), 3.46 (s, 2 H), 3.42 - 3.37 (m, 8 H), 3.17 (m, 4 H). MS (ESI) m/z 529 (M⁺ + H).

Example 47: Synthesis of Compound 381

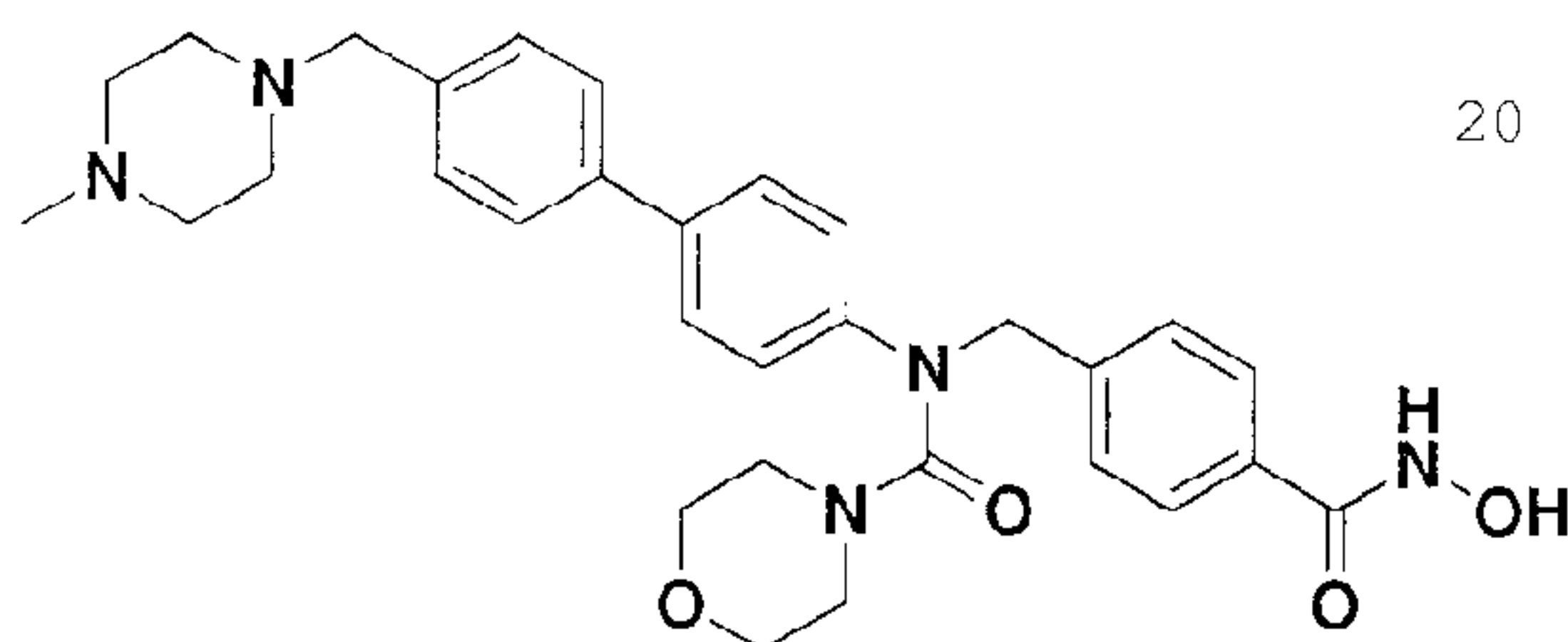
15 (Formula 9-2: methyl 4-((N-(4'-((4-methylpiperazin-1-yl)methyl)biphenyl-4-yl)morpholine-4-carboxamido)methyl)benzoate)



Compound of **Formula 9-1** (methyl 4-((N-(4'-
 25 formylbiphenyl-4-yl)morpholine-4-carboxamido)methyl)benzoate;

0.150 g, 0.327 mmol) was dissolved in methanol (5 mL), and then 1-methylpiperazine (0.098 g, 0.981 mmol) and acetic acid (0.094 mL, 1.64 mmol) were added and stirred at room temperature for 1 hour. Then, sodium cyanoborohydride (0.041 g, 0.654 mmol) was added and stirred at the same temperature for 16 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure. Then, the organic layer was dehydrated with anhydrous magnesium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. Then, the residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane -10%) to give the desired compound of **Formula 9-2** (0.140 g, 79%) in the form of a white solid.

(Compound 381: N-(4-(hydroxycarbonyl)benzyl)-N-(4'-((4-methylpiperazin-1-yl)methyl)biphenyl-4-yl)morpholine-4-carboxamide)



Compound of **Formula 9-2** (methyl 4-((N-(4'-((4-

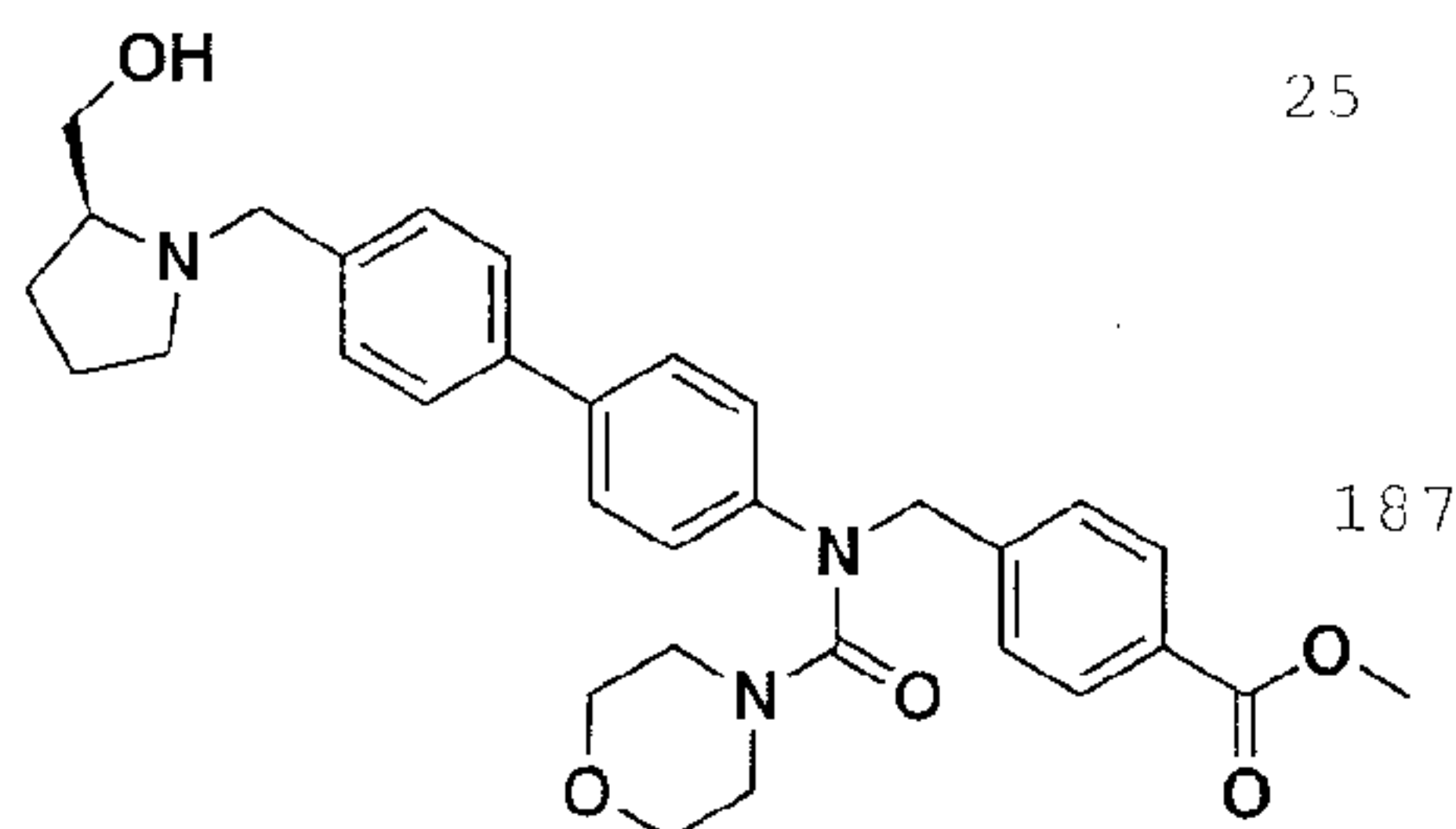
methylpiperazin-1-yl)methyl)biphenyl-4-yl)morpholine-4-
 carboxamido)methyl)benzoate; 0.140 g, 0.258 mmol) was
 dissolved in methanol (10 mL), and hydroxylamine (50.0 wt%
 aqueous solution; 1.58 mL, 25.8 mmol) and potassium hydroxide
 5 (0.145 g, 2.58 mmol) were added and then stirred at room
 temperature for 30 minutes. After completion of the reaction,
 the reaction solution was concentrated under reduced pressure
 until its volume became about 2 mL, and the organic layer was
 extracted with ethyl acetate and saturated ammonium chloride
 10 aqueous solution. The organic layer was dehydrated with
 anhydrous magnesium sulfate, filtered, and then concentrated
 under reduced pressure. The residue was recrystallized with
 dichloromethane and hexane to give the desired **Compound 381**
 (0.093 g, 66%) in the form of a white solid.

15 ¹H NMR (400 MHz, DMSO-d₆) δ 7.65 (d, 2 H, *J* = 7.8 Hz),
 7.61 – 7.56 (m, 4 H), 7.38 (d, 2 H, *J* = 8.0 Hz), 7.32 (d, 2 H,
J = 7.6 Hz), 7.21 (d, 2 H, *J* = 8.5 Hz), 4.90 (s, 2 H), 3.59 –
 3.39 (m, 10 H), 3.17 (m, 4 H), 2.40 – 2.23 (m, 4 H), 2.18 (s,
 3 H). MS (ESI) *m/z* 544 (M⁺ + H).

20

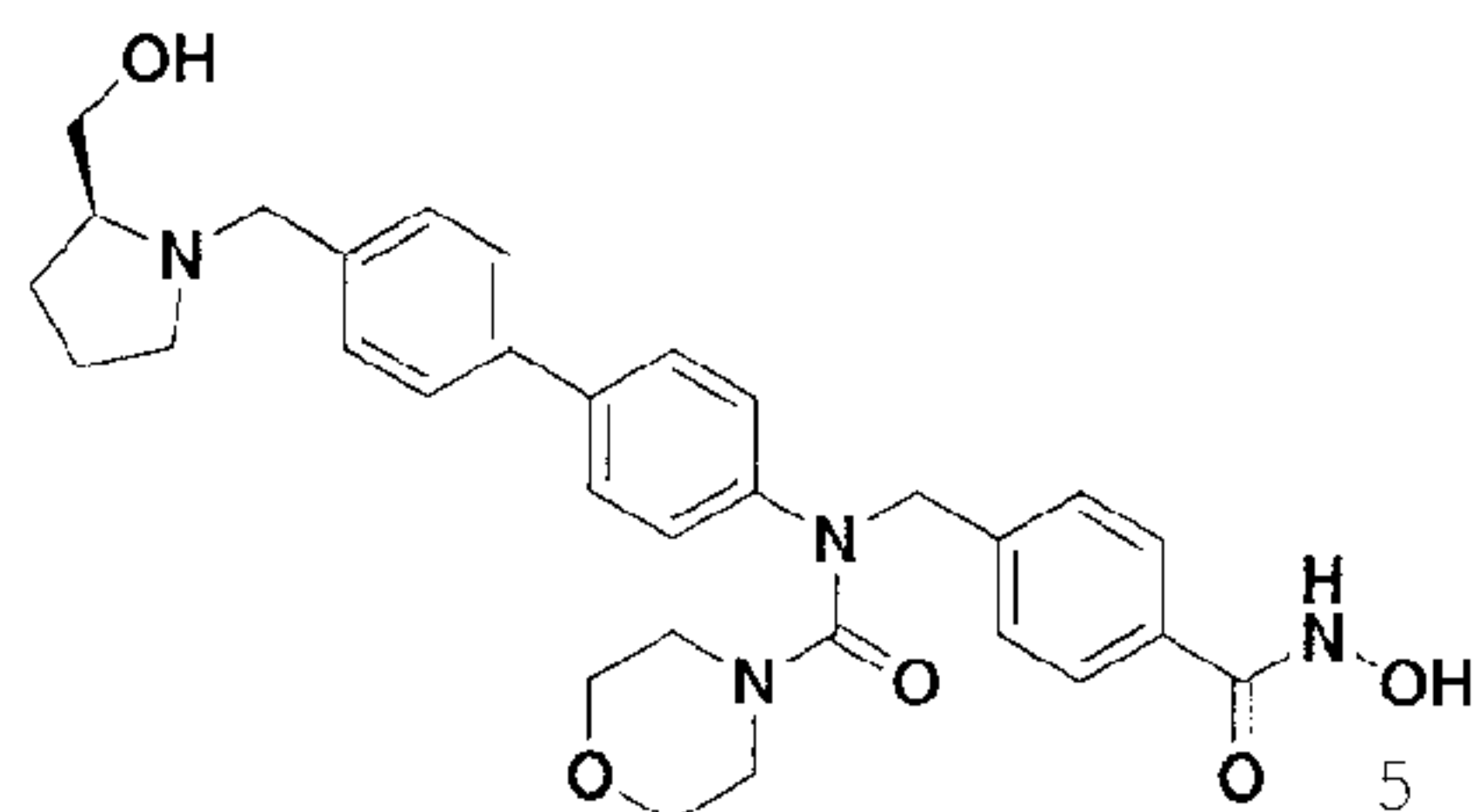
Example 48: Synthesis of Compound 382

(Formula 9-2: (S)-methyl 4-((N-(4'-((2-
 (hydroxymethyl)pyrrolidin-1-yl)methyl)biphenyl-4-
 yl)morpholine-4-carboxamido)methyl)benzoate)



5 Compound of **Formula 9-1** (methyl 4-((N-(4'-
formylbiphenyl-4-yl)morpholine-4-
carboxamido)methyl)benzoate; 0.150 g, 0.327 mmol) was
dissolved in methanol (5 mL), and then (S)-pyrrolidin-2-yl-
methanol (0.099 g, 0.981 mmol) and acetic acid (0.094 mL,
10 1.64 mmol) were added and stirred at room temperature for 1
hour. Then, sodium cyanoborohydride (0.041 g, 0.654 mmol)
was added and stirred at the same temperature for 16 hours.
After completion of the reaction, the organic layer was
extracted with ethyl acetate and saturated sodium hydrogen
15 carbonate aqueous solution and concentrated under reduced
pressure. Then, the organic layer was dehydrated with
anhydrous magnesium sulfate and filtered, and then the
filtrate was concentrated under reduced pressure. Then, the
residue was purified and concentrated by column
20 chromatography (silica; methanol/dichloromethane = 10%) to
give the desired compound of **Formula 9-2** (0.123 g, 69%) in
the form of a white solid.

(**Compound 382**: (S)-N-(4-(hydroxycarbamoyl)benzyl)-N-(4'-
((2-(hydroxymethyl)pyrrolidin-1-yl)methyl)biphenyl-4-
25 yl)morpholine-4-carboxamide)



Compound of **Formula 9-2** ((S)-methyl 4-((N-(4'-(2-(hydroxymethyl)pyrrolidin-1-yl)methyl)biphenyl-4-

yl)morpholine-4-carboxamido)methyl)benzoate; 0.120 g, 0.221

mmol) was dissolved in methanol (10 mL), and hydroxylamine

10 (50.0 wt% aqueous solution; 1.35 mL, 22.1 mmol) and potassium

hydroxide (0.124 g, 2.21 mmol) were added and then stirred at

room temperature for 30 minutes. After completion of the

reaction, the reaction solution was concentrated under

reduced pressure until its volume became about 2 mL, and the

15 organic layer was extracted with ethyl acetate and saturated

ammonium chloride aqueous solution. The organic layer was

dehydrated with anhydrous magnesium sulfate, filtered, and

then concentrated under reduced pressure to give the desired

Compound 382 (0.036 g, 30%) in the form of a colorless liquid.

20 ¹H NMR (400 MHz, DMSO-d₆) δ 7.65 (d, 2 H, *J* = 7.8 Hz),

7.61 – 7.55 (m, 4 H), 7.39 – 7.34 (m, 4 H), 7.21 (d, 2 H, *J* =

8.3 Hz), 4.90 (s, 2 H), 4.06 (m, 1 H), 3.47 – 3.39 (m, 6 H),

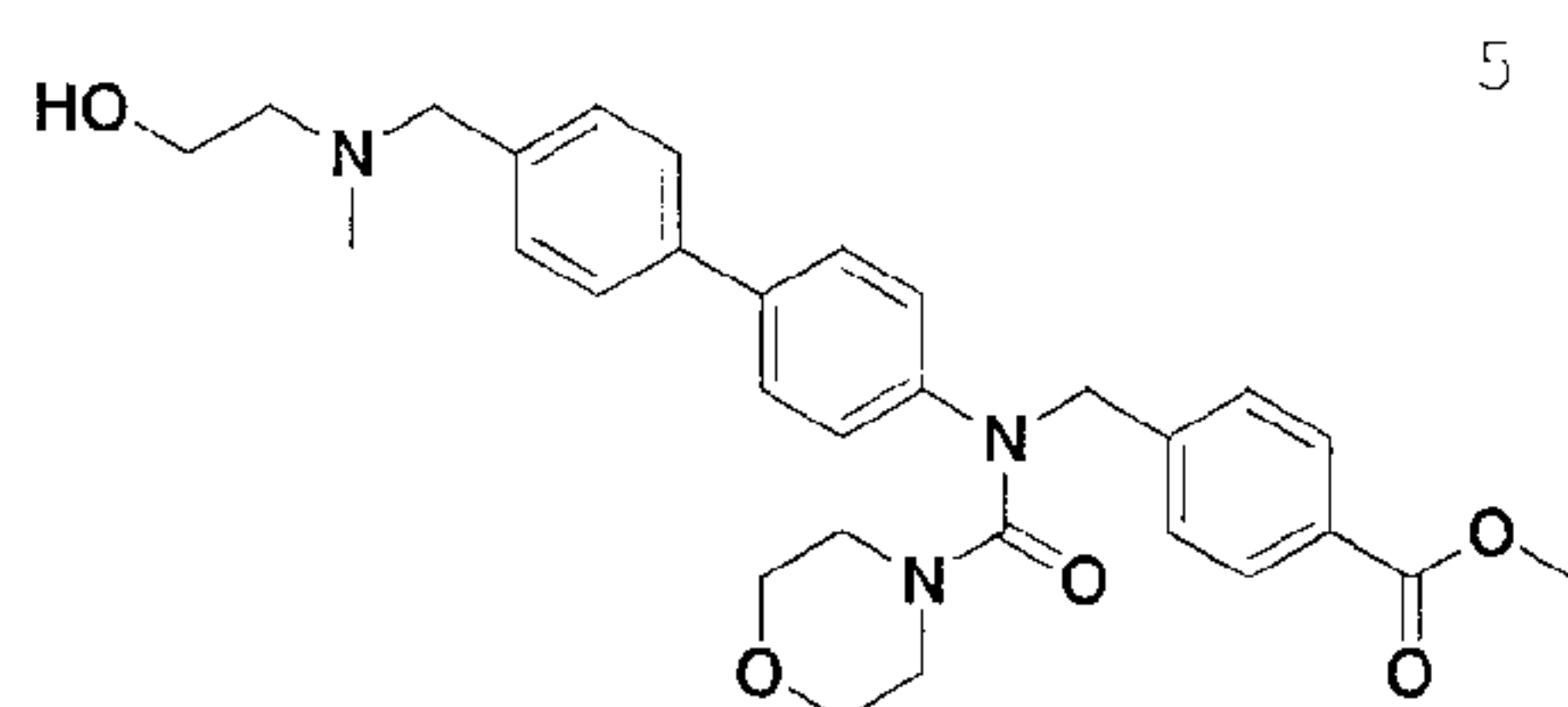
3.37 – 3.35 (m, 2 H), 3.17 (m, 4 H), 2.24 – 2.20 (m, 2 H),

1.64 – 1.52 (m, 5 H). **MS** (ESI) *m/z* 545 (M⁺ + H).

25

Example 49: Synthesis of Compound 383

(**Formula 9-2**: methyl 4-((N-(4'-((2-(hydroxyethyl)(methyl)amino)methyl)biphenyl-4-yl)morpholine-4-carboxamido)methyl)benzoate)

Compound of **Formula 9-1**

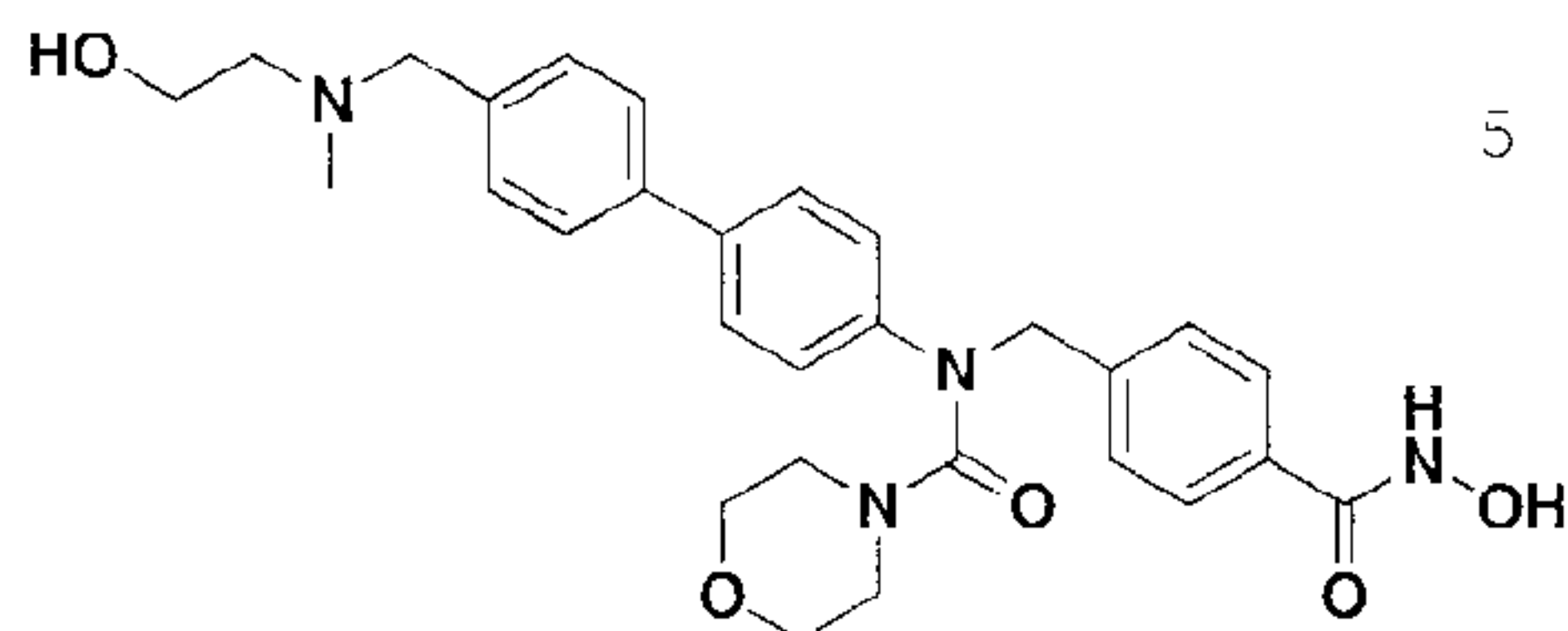
10 (methyl 4-((N-(4'-formylbiphenyl-4-yl)morpholine-4-carboxamido)methyl)benzoate; 0.150 g, 0.327 mmol) was dissolved in methanol (5 mL), and then 2-(methylamino)ethanol (0.074 g, 0.981 mmol) and acetic acid (0.094 mL, 1.64 mmol) were added and stirred at room temperature for 1 hour. Then,

15 sodium cyanoborohydride (0.041 g, 0.654 mmol) was added and stirred at the same temperature for 16 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure.

20 Then, the organic layer was dehydrated with anhydrous magnesium sulfate and filtered, and then the filtrate was concentrated under reduced pressure. Then, the residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane= 7%) to give the desired compound of

25 **Formula 9-2** (0.152 g, 90%) in the form of a white solid.

(**Compound 383**: N-(4-(hydroxycarbamoyl)benzyl)-N-(4'-(((2-hydroxyethyl)(methyl)amino)methyl)biphenyl-4-yl)morpholine-4-carboxamide)



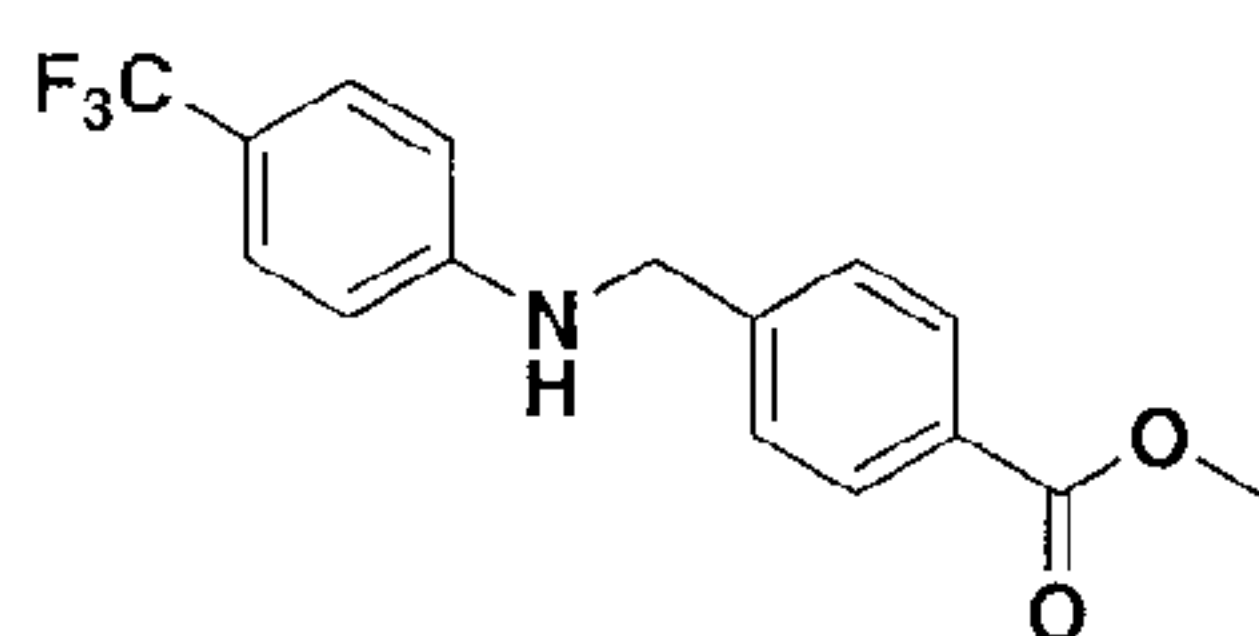
Compound of **Formula 9-2** (methyl 4-((N-(4'-(((2-hydroxyethyl)(methyl)amino)methyl)biphenyl-4-yl)morpholine-4-carboxamido)methyl)benzoate; 0.150 g, 0.290 mmol) was dissolved in methanol (10 mL), and hydroxylamine (50.0 wt% aqueous solution; 1.77 mL, 29.0 mmol) and potassium hydroxide (0.163 g, 2.90 mmol) were added and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 2 mL, and the organic layer was extracted with ethyl acetate and saturated ammonium chloride aqueous solution. The organic layer was dehydrated with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to give the desired **Compound 383** (0.023 g, 15%) in the form of a colorless liquid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.66 - 7.56 (m, 6 H), 7.39 - 7.34 (m, 4 H), 7.21 (d, 2 H, J = 8.6 Hz), 4.90 (s, 2 H), 3.51 - 3.48 (m, 4 H), 3.42 - 3.37 (m, 4 H), 3.17 (m, 4 H), 2.45 -

2.43 (m, 2 H), 2.22 (m, 1 H), 2.15 (s, 3 H). **MS** (ESI) m/z 519 (M⁺ + H).

Example 50: Synthesis of Compound 385

5 **(Formula 1-2: methyl 4-((4-(trifluoromethyl)phenylamino)methyl)benzoate)**

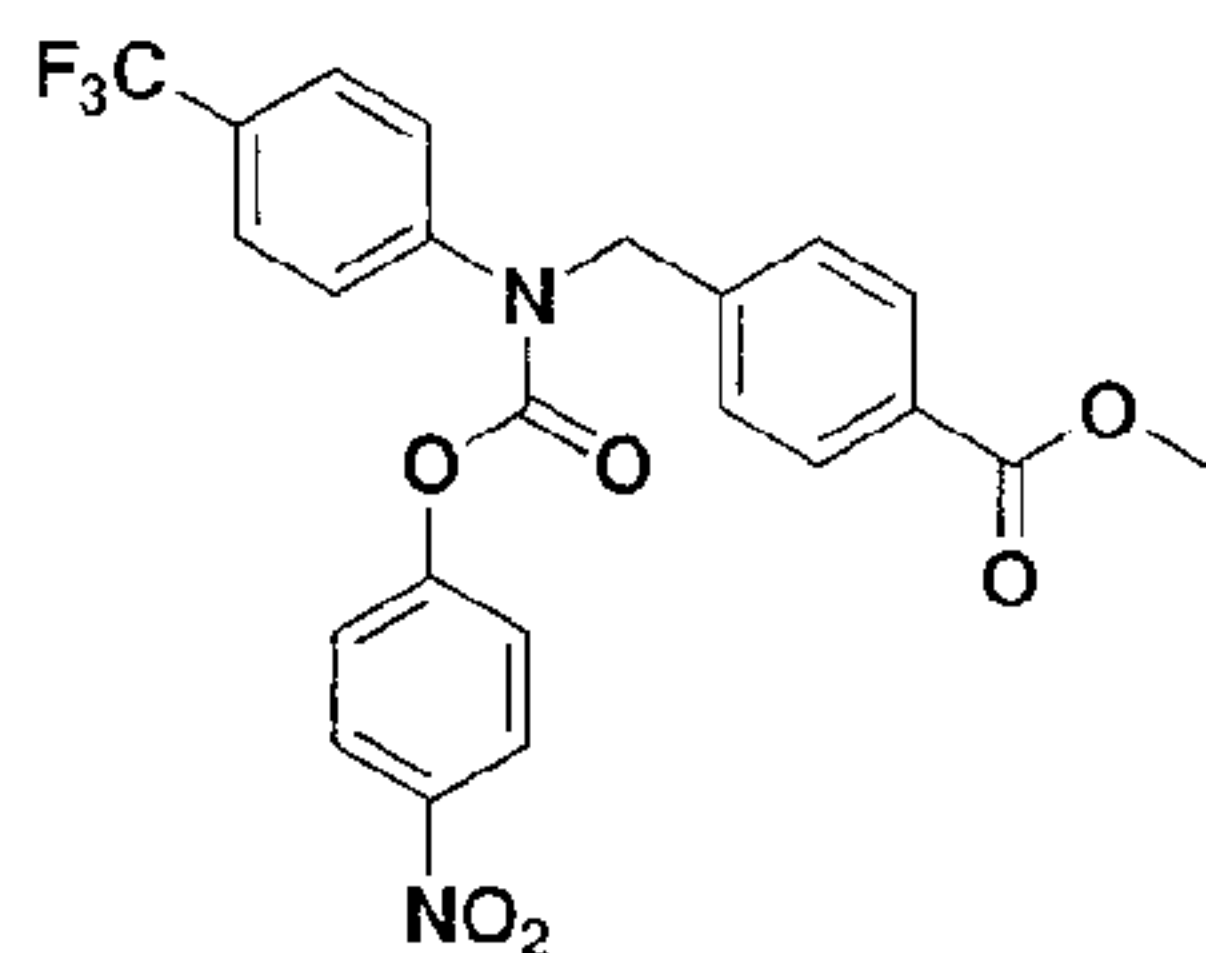


10

Compound of **Formula 1-1** (4-(trifluoromethyl)benzenamine; 0.30 g, 1.84 mmol) and potassium carbonate (0.76 g, 5.53 mmol) were dissolved in dimethylformamide (10 mL), and methyl 4-(bromomethyl)benzoate (0.84 g, 3.67 mmol) was then added. 15 The mixture was reacted at room temperature for 1 day and then diluted with ethyl acetate. The reaction mixture was washed with water and saturated sodium chloride aqueous solution, dehydrated with anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure. The residue 20 was purified by column chromatography (silica; ethyl acetate/hexane =20%) to give the desired compound of **Formula 1-2** (0.27 g, 4%).

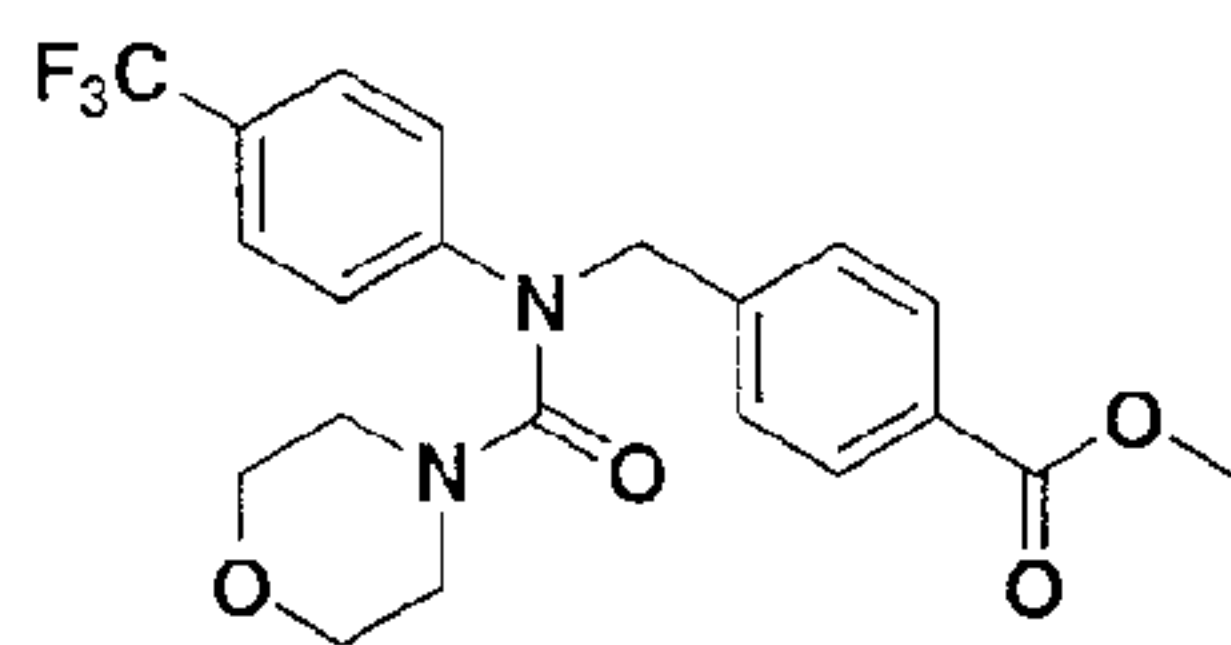
(Formula 1-3: methyl 4-((((4-nitrophenoxy)carbonyl)(4-(trifluoromethyl)phenyl)amino)methyl)benzoate)

25



5 Compound of **Formula 1-2** (methyl 4-((4-(trifluoromethyl)phenylamino)methyl)benzoate; 0.27 g, 0.87 mmol) and 4-nitrophenyl carbonylchloride (0.35 g, 1.74 mmol) were dissolved in acetonitrile (10 mL), and potassium carbonate (0.36 g, 2.61 mmol) was then added. The mixture
10 was reacted at room temperature for 1 day and then diluted with ethyl acetate. The reaction mixture was washed with water and saturated sodium chloride aqueous solution, dehydrated with anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure. The residue was
15 purified by column chromatography (silica; ethyl acetate/hexane =20%) to give the desired compound of **Formula 1-3** (0.40 g, 97%).

(**Formula 1-4**: methyl 4-((N-(4-(trifluoromethyl)phenyl)morpholine-4-carboxamido)methyl)benzoate)

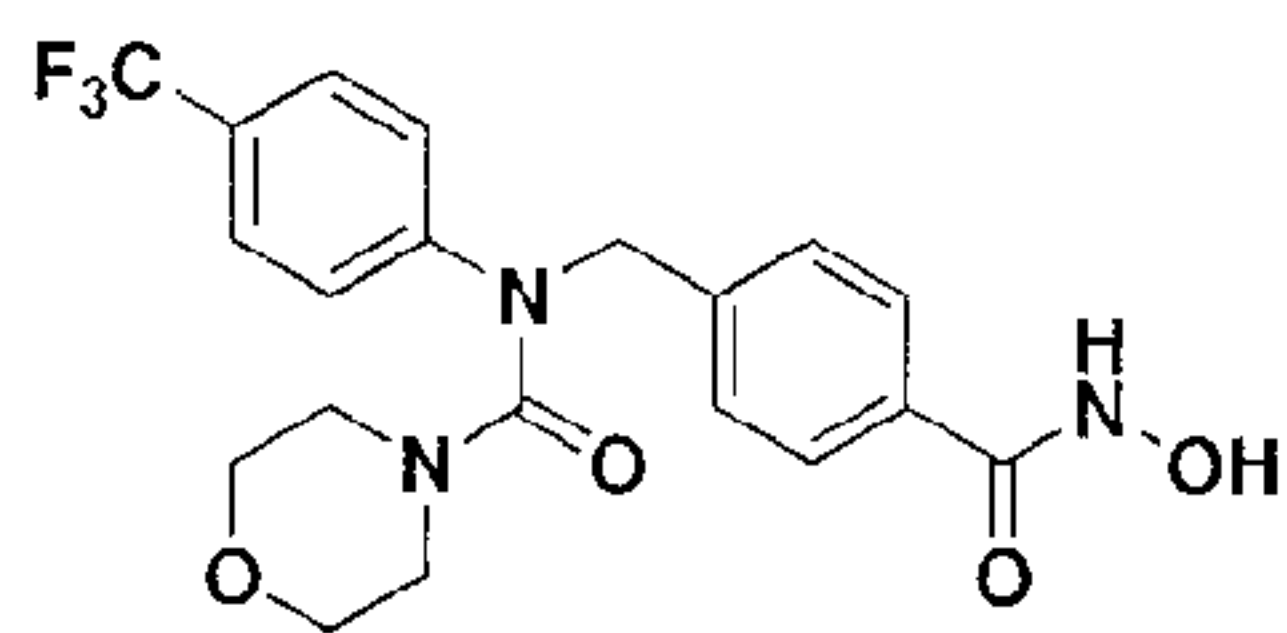
Compound of **Formula 1-3**

25 (methyl 4-(((4-nitrophenoxy)carbonyl)(4-

(trifluoromethyl)phenyl)amino)methyl)benzoate; 0.39 g, 0.84 mmol) was dissolved in dimethylformamide, and potassium carbonate (0.25 g, 1.81 mmol) and morpholine (10 mL) were then added. The mixture was reacted at 60 °C for 2 days and
 5 diluted with saturated ammonium chloride solution. The organic layer was extracted with ethyl acetate, dehydrated with anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica; ethyl
 10 acetate/hexane =50%) to give the desired compound of **Formula 1-4** (0.20 g, 60%).

(**Compound 385**, N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)morpholine-4-carboxamide)

15

Compound of **Formula 1-4**

(methyl 4-((N-(4-(trifluoromethyl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.20 g, 0.48 mmol) was dissolved
 20 in methanol, and hydroxylamine (50 wt% aqueous solution; 0.29 mL) and potassium hydroxide (0.13 g, 2.39 mmol) were then added and stirred overnight. After completion of the reaction, the methanol was removed by distillation under reduced pressure, and the organic layer was extracted with
 25 ethyl acetate and water, dehydrated with anhydrous sodium

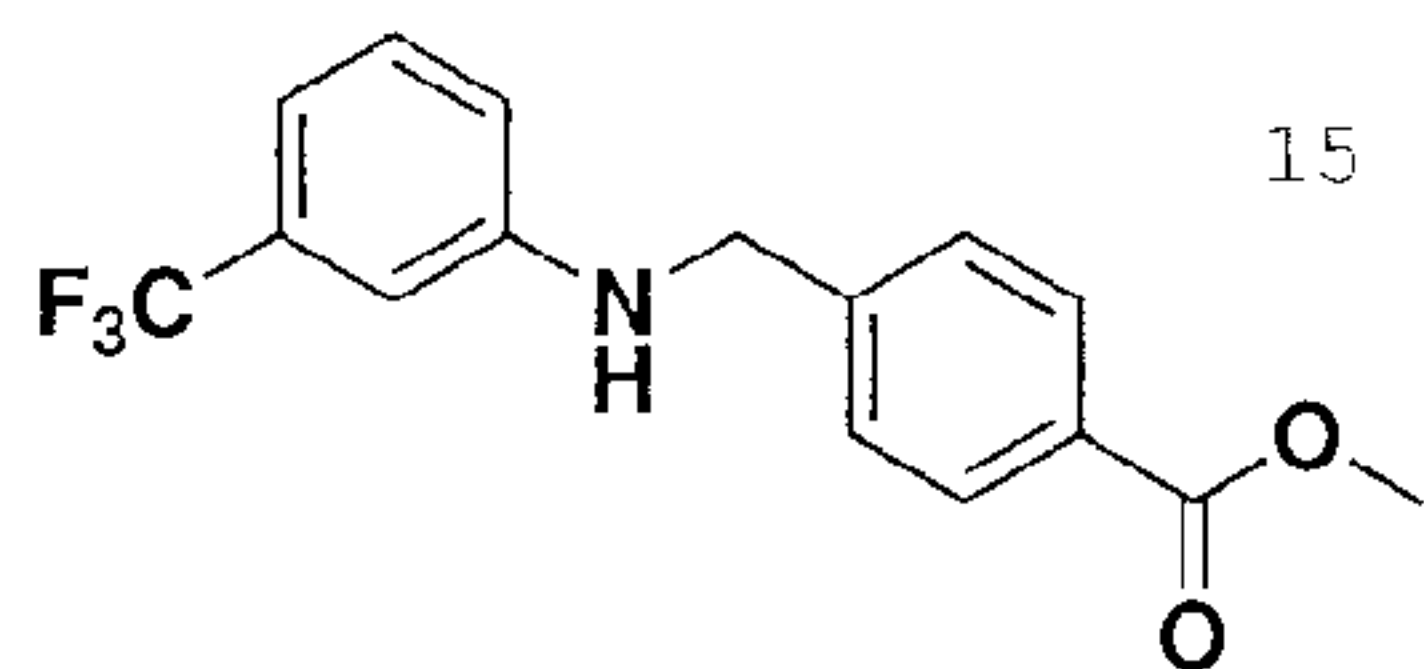
sulfate, filtered, and then concentrated under reduced pressure. The residue was stirred in diethyl ether to give a white solid, and the resulting solid was filter and dried to give the desired **Compound 385** (0.10 g, 50%) in the form of a
 5 white solid.

^1H NMR (400 MHz, DMSO- d_6) δ 11.14 (brs, 1 H), 8.99 (brs, 1 H), 7.67 - 7.62 (m, 4 H), 7.38 (d, 2 H, $J = 8.2$ Hz), 7.29 (d, 2 H, $J = 8.5$ Hz), 4.94 (s, 2 H), 3.47 - 3.44 (m, 4 H), 3.21 - 3.18 (m, 4 H). **MS** (ESI) m/z 424 ($M^+ + H$).

10

Example 51: Synthesis of Compound 386

(**Formula 1-2**: methyl 4-((3-(trifluoromethyl)phenylamino)methyl)benzoate)

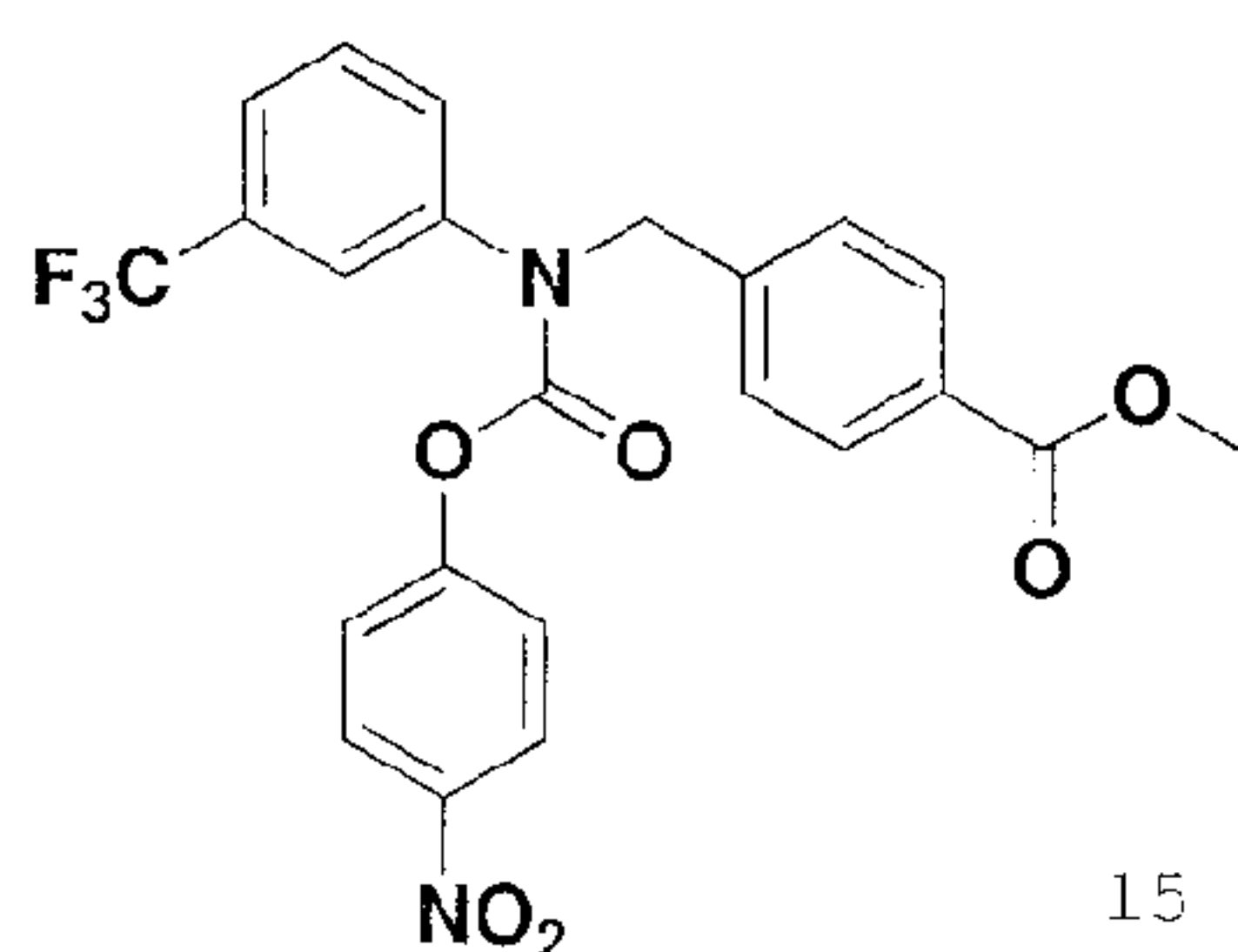


Compound of **Formula 1-1** (3-(trifluoromethyl)benzenamine;
 20 1.00 g, 6.21 mmol) and methyl 4-formylbenzoate (1.02 g, 6.21 mmol) were dissolved in methanol(10 ml), and sodium cyanoborohydride(NaCNBH_3) (0.41 g, 6.21 mmol) and acetic acid (0.71 mL, 2.00 mmol) was added. The mixture was reacted at room temperature for 2 day and then the methanol was
 25 evaporated by reduced pressure. The reaction was completed by

adding saturated sodium hydrogen carbonate solution. The reaction mixture was extracted with ethyl acetate, dehydrated with anhydrous sodium sulfate, filtered, and then concentrated under reduced pressure. The residue was
 5 purified by column chromatography (silica; ethyl acetate/hexane=20%) to give the desired compound of **Formula 1-2** (1.43 g, 74.5%).

(**Formula 1-3**: methyl 4-((((4-nitrophenoxy)carbonyl)(3-(trifluoromethyl)phenyl)amino)methyl)benzoate)

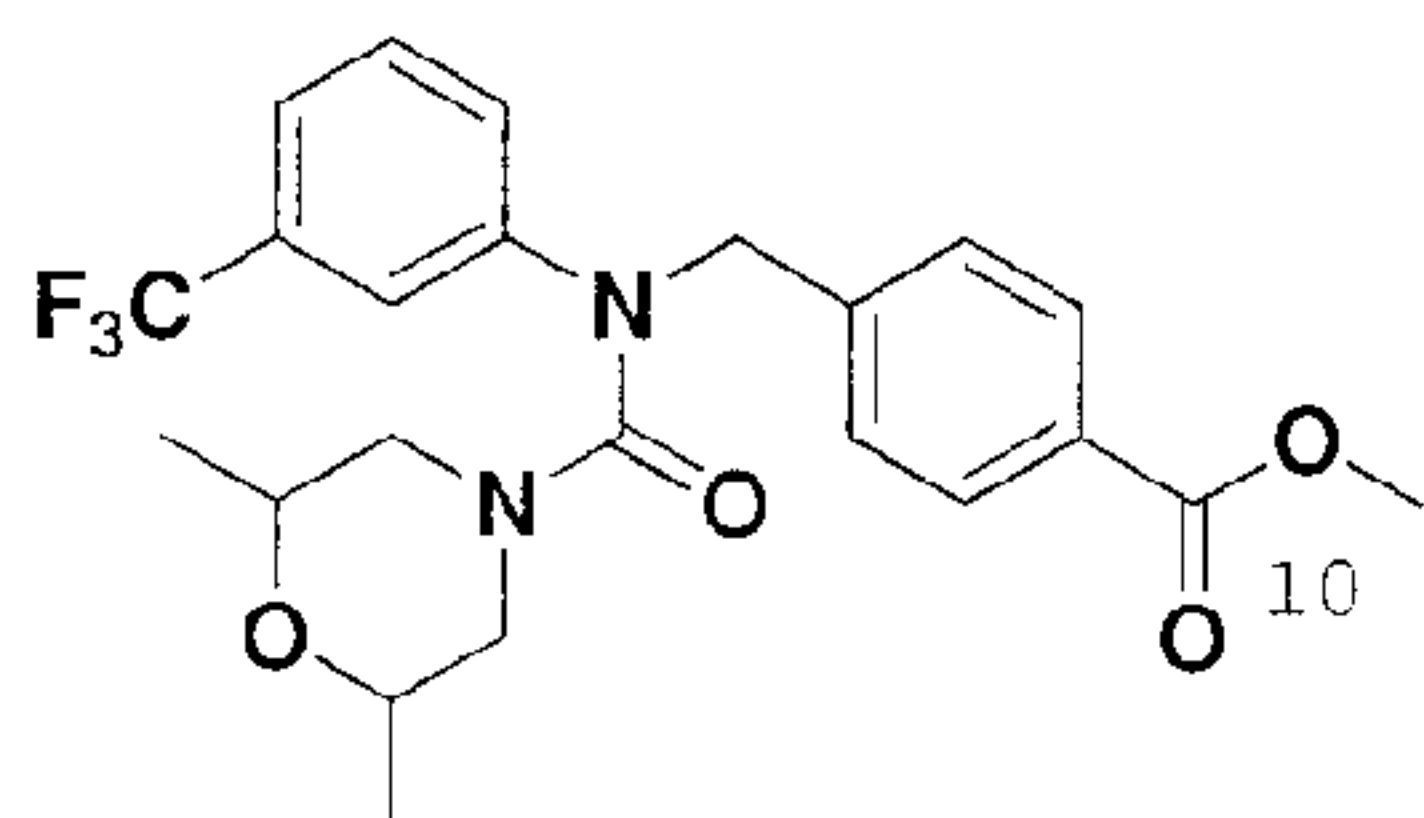
10



Compound of **Formula 1-2** (methyl 4-((3-(trifluoromethyl)phenylamino)methyl)benzoate; 1.04 g, 3.36 mmol) and 4-nitrophenyl carbonochloridate (1.36 g, 6.73 mmol)
 20 were dissolved in acetonitrile (30 mL), and potassium carbonate (1.39 g, 10.1 mmol) was then added. The mixture was reacted at room temperature for 1 day and then diluted with ethyl acetate. The reaction mixture was washed with water and saturated sodium chloride aqueous solution and
 25 water, dehydrated with anhydrous sodium sulfate, filtered,

and then concentrated under reduced pressure. The residue was purified by column chromatography (silica; ethyl acetate/hexane-20%) to give the desired compound of **Formula 1-3** (1.51 g, 95%).

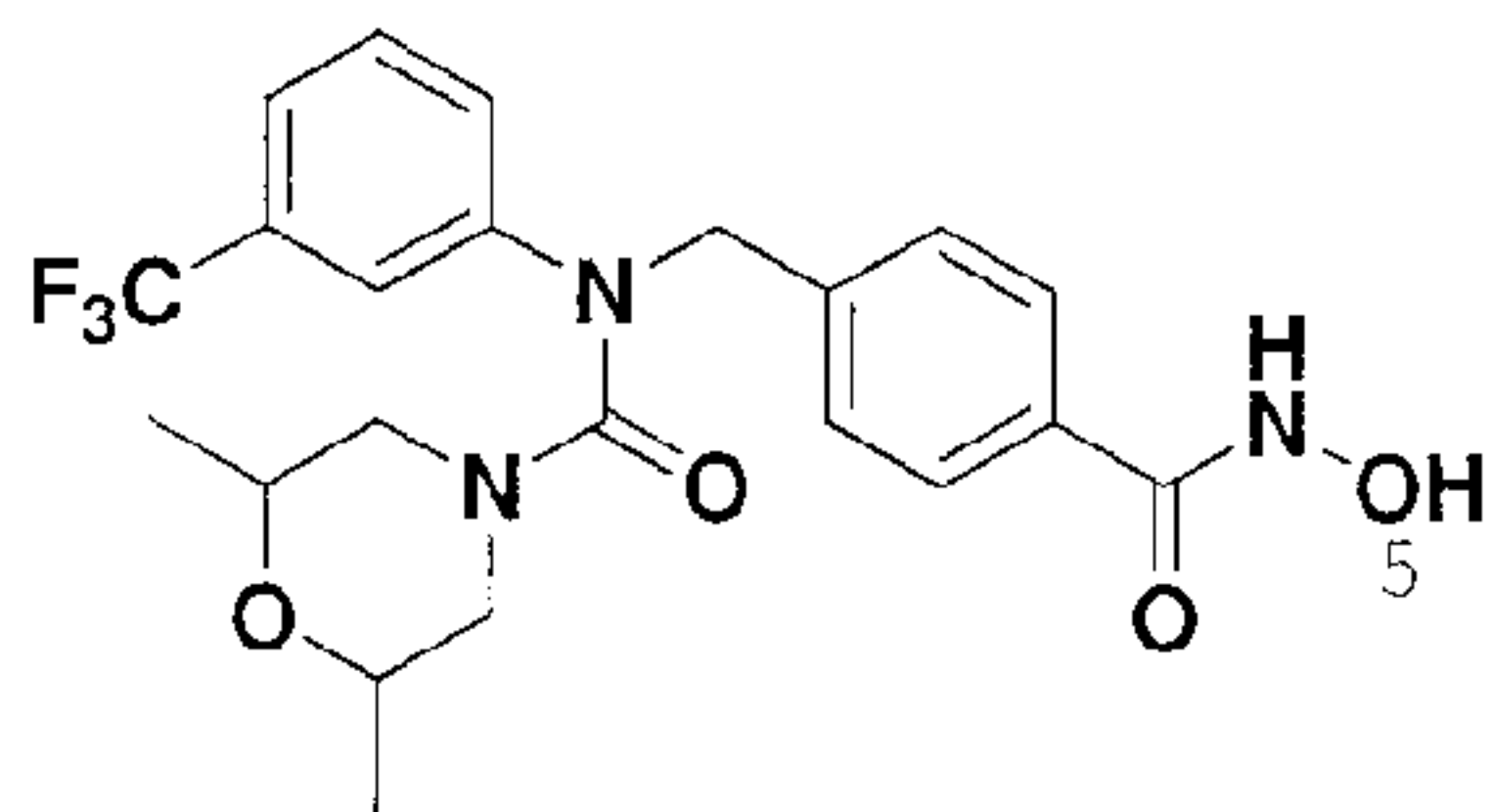
5 **(Formula 1-4: methyl 4-((2,6-dimethyl-N-(3-(trifluoromethyl)phenyl)morpholine-4-carboxamido)methyl)benzoate)**



Compound of **Formula 1-3** (methyl 4-(((4-nitrophenoxy)carbonyl)(3-(trifluoromethyl)phenyl)amino)methyl)benzoate; 0.38 g, 0.80 mmol) was dissolved in dimethylformamide (10ml), and potassium carbonate (0.33 g, 2.38 mmol) and 2,6-dimethylmorpholine (0.09, 0.80 mmol) were then added. The mixture was reacted at 60 °C for 2 days and then it was diluted with ethyl acetate and washed with saturated ammonium chloride solution. The organic layer was dehydrated with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The residue was purified by column chromatography (silica; ethyl acetate/hexane =50%) to give the desired compound of **Formula 1-4** (0.21 g, 59%).

25 **(Compound 386, N-(4-(hydroxycarbonyl)benzyl)-2,6-**

dimethyl-N-(3-(trifluoromethyl)phenyl)morpholine-4-carboxamide)



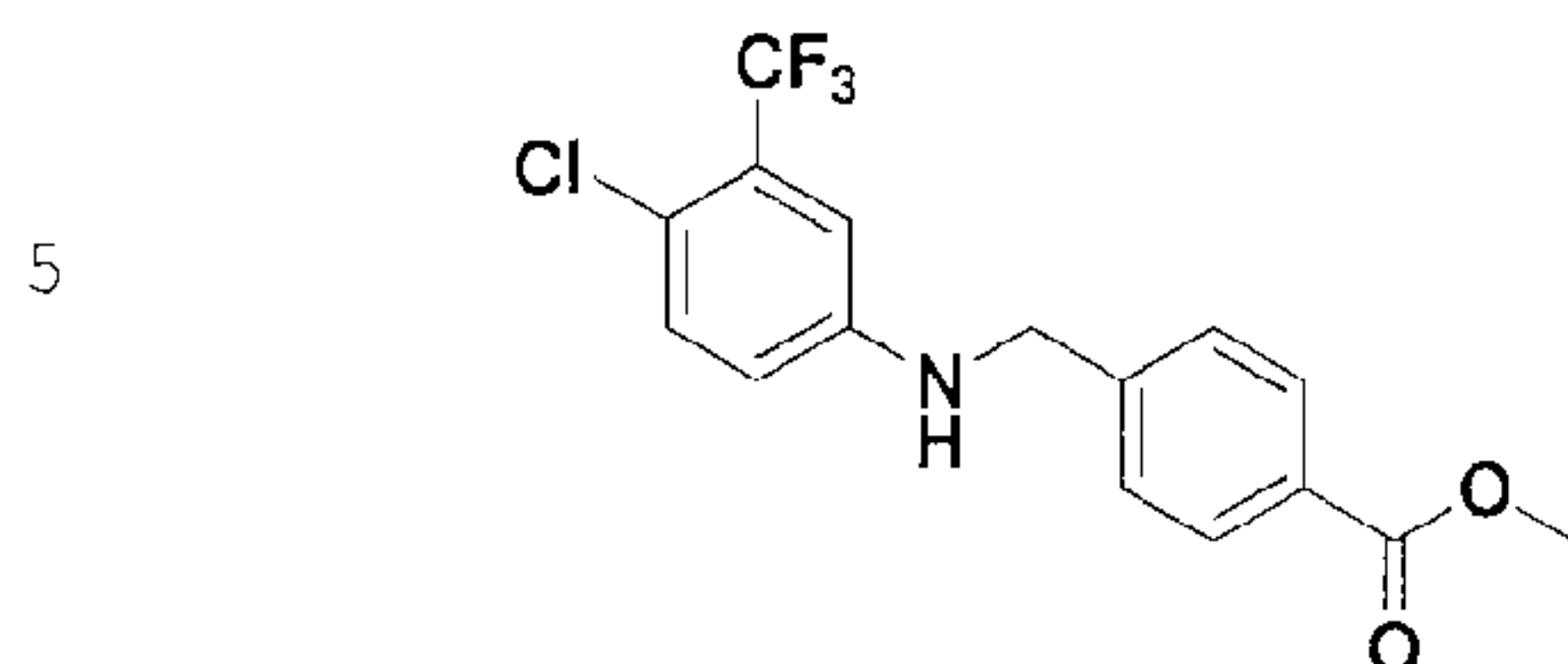
Compound of **Formula 1-4** (methyl 4-((2,6-dimethyl-N-(3-(trifluoromethyl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.21 g, 0.47 mmol) was dissolved
 10 in methanol (50 mL), and hydroxylamine aqueous solution (50 wt%, 0.29 mL) and potassium hydroxide (0.13 g, 2.35 mmol) were then added and stirred overnight. After completion of the reaction, the methanol was removed by distillation under reduced pressure, and the organic layer was extracted with
 15 ethyl acetate and water, dehydrated with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure. The residue was stirred in diethyl ether to give a white solid, and the resulting solid was filter and dried to give the desired **Compound 386** (0.10 g, 48%) in the
 20 form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.13 (brs, 1 H), 8.98 (brs, 1 H), 7.65 (d, 2 H, J = 8.3 Hz), 7.54-7.50 (m, 1 H), 7.43-7.36 (m, 5 H), 3.55 (d, 2 H, J = 12.4 Hz), 2.36-2.31 (m, 2 H), 0.94 (s, 3 H), 0.93 (s, 3 H). **MS** (ESI) m/z 452 (M⁺ + H).

25

Example 52: Synthesis of Compound 389

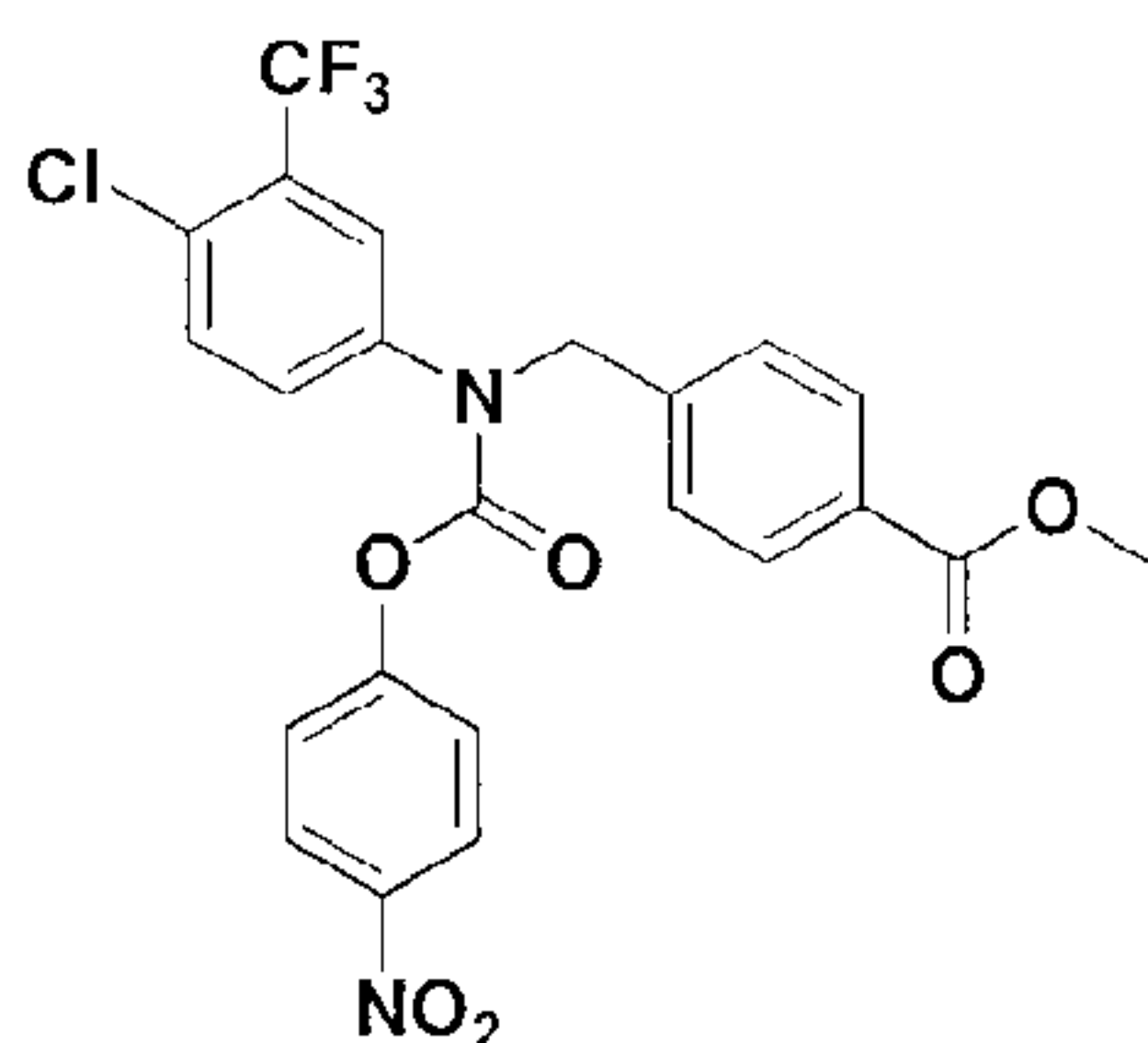
(**Formula 1-2**: methyl 4-((4-chloro-3-(trifluoromethyl)phenylamino)methyl)benzoate)



Compound of **Formula 1-1** (4-chloro-3-(trifluoromethyl)benzenamine; 5 g, 25.6 mmol) and methyl 4-formylbenzoate (4.19 g, 25.6 mmol) were dissolved in methanol (100 mL) and stirred for 1 hour. Then, acetic acid (1.58 mL, 25.6 mmol) and sodium cyanoborohydride (1.61 g, 25.6 mmol) were added and stirred for 1 day. The methanol was partially removed by air-drying to precipitate a solid, and the resulting solid was filtered and dried to give the desired compound of **Formula 1-2** (3.4 g, 39%) in the form of a white solid.

(**Formula 1-3**: methyl 4-(((4-chloro-3-(trifluoromethyl)phenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate)

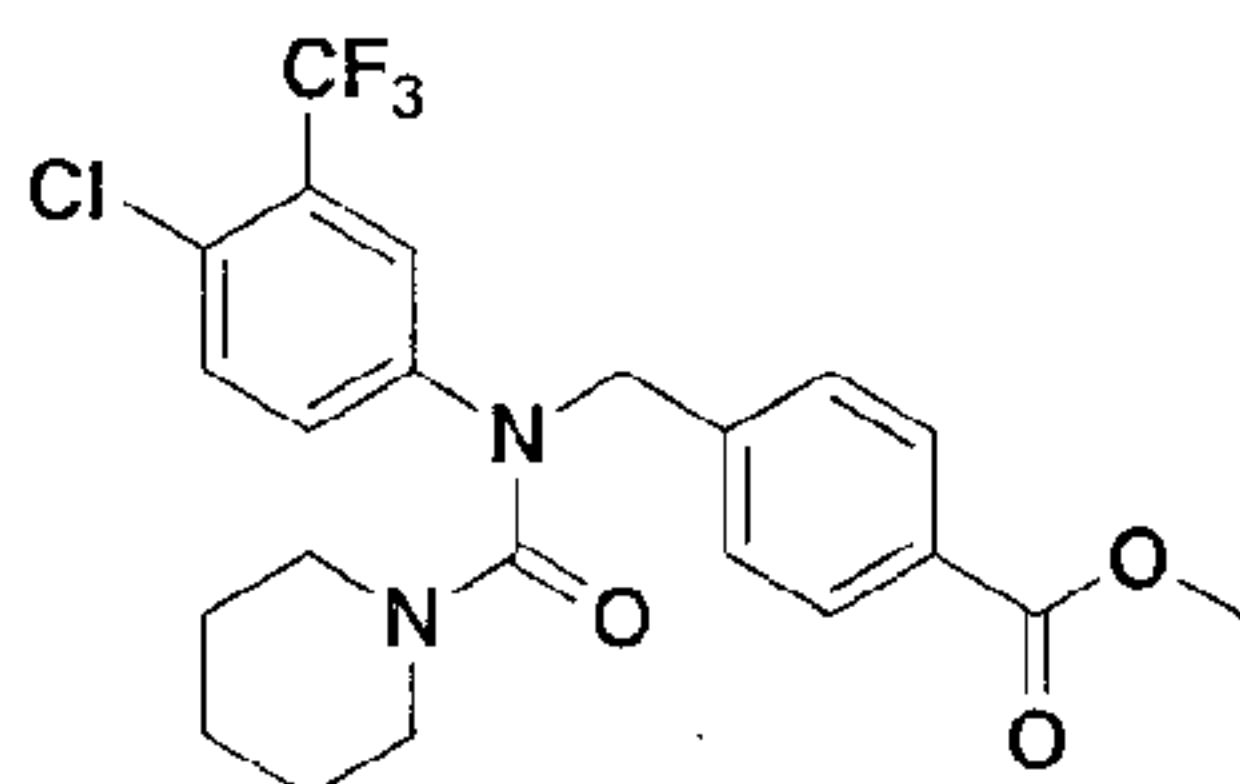
20



Compound of **Formula 1-2** (methyl 4-((4-chloro-3-
 5 (trifluoromethyl)phenylamino)methyl)benzoate; 2 g, 5.82 mmol)
 and 4-nitrophenyl chloroformate (1.17 g, 5.82 mmol) were
 dissolved in dichloromethane (50 mL) and stirred at room
 temperature for 2 days to precipitate a solid, and the
 resulting solid was filter and dried to give the desired
 10 compound of **Formula 1-3** (3.14 g, 106%) in the form of a
 yellow solid.

(**Formula 1-4**: methyl 4-((N-(4-chloro-3-
 (trifluoromethyl)phenyl)piperidine-1-
 carboxamido)methyl)benzoate)

15

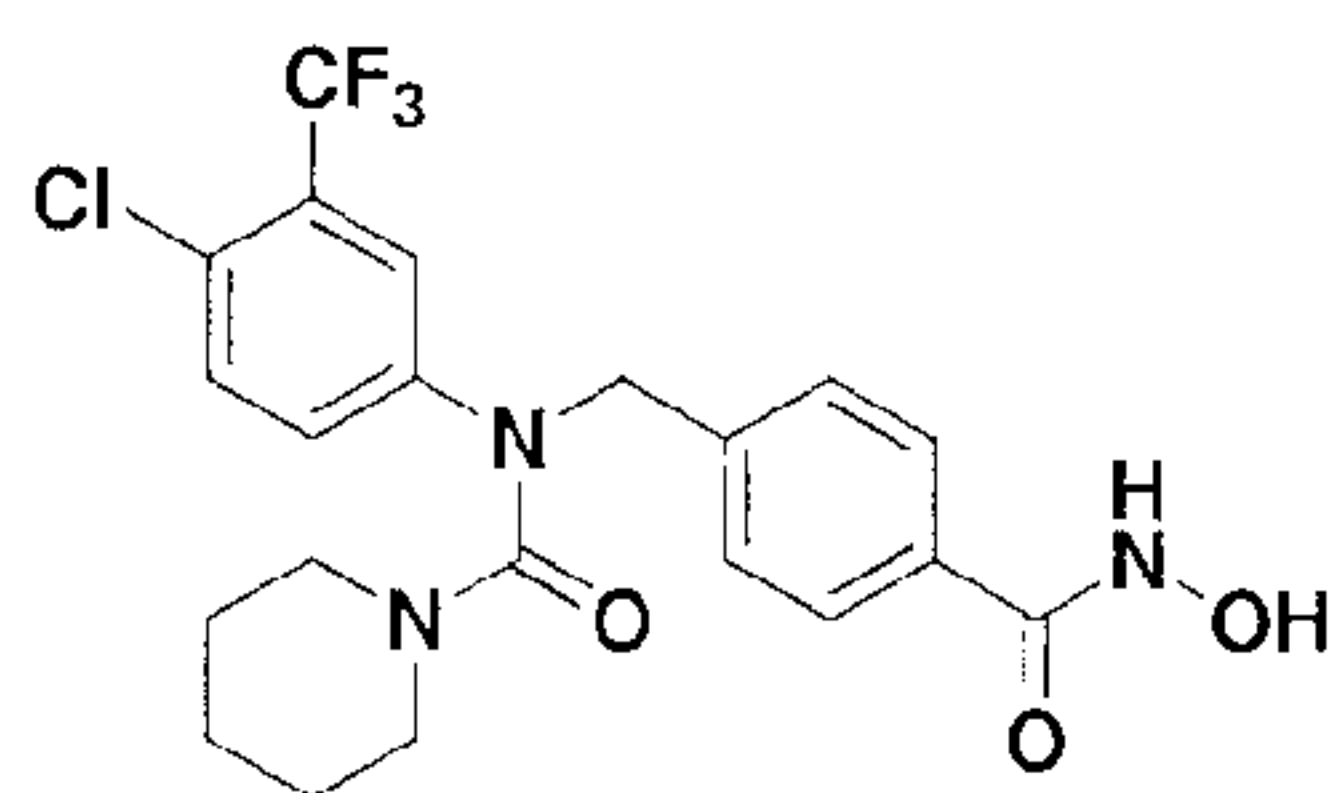


Compound of **Formula 1-3**

20 (methyl 4-(((4-chloro-3-(trifluoromethyl)phenyl)((4-
 nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.50 g, 0.983
 mmol) and piperidine (0.097 mL, 0.983 mmol) were dissolved in
 dimethylformamide (10 mL), and the mixture was heated and
 stirred at 60 °C for 2 days. Then, the dimethylformamide was
 25 removed under reduced pressure, water was poured into the

reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced
 5 pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=20%) to give the desired compound of **Formula 1-4** (0.425 g, 95%) in the form of a colorless oil.

(**Compound 389**: N-(4-chloro-3-(trifluoromethyl)phenyl)-N-
 10 (4-(hydroxycarbonyl)benzyl)piperidine-1-carboxamide)



15

Compound of **Formula 1-4**

(methyl 4-((N-(4-chloro-3-(trifluoromethyl)phenyl)piperidine-1-carboxamido)methyl)benzoate; 0.263 g, 0.578 mmol) was dissolved in methanol (20 mL), and hydroxylamine hydrochloride (0.201 g, 2.89 mmol) and potassium hydroxide
 20 (0.324 g, 5.78 mmol) were added and stirred. Then, hydroxylamine (50 wt% aqueous solution; 1.49 mL, 11.56 mmol) was added dropwise and stirred at room temperature for 6 hours. After completion of the reaction, the methanol was removed under reduced pressure, saturated sodium hydrogen
 25 carbonate aqueous solution was added to precipitate a solid,

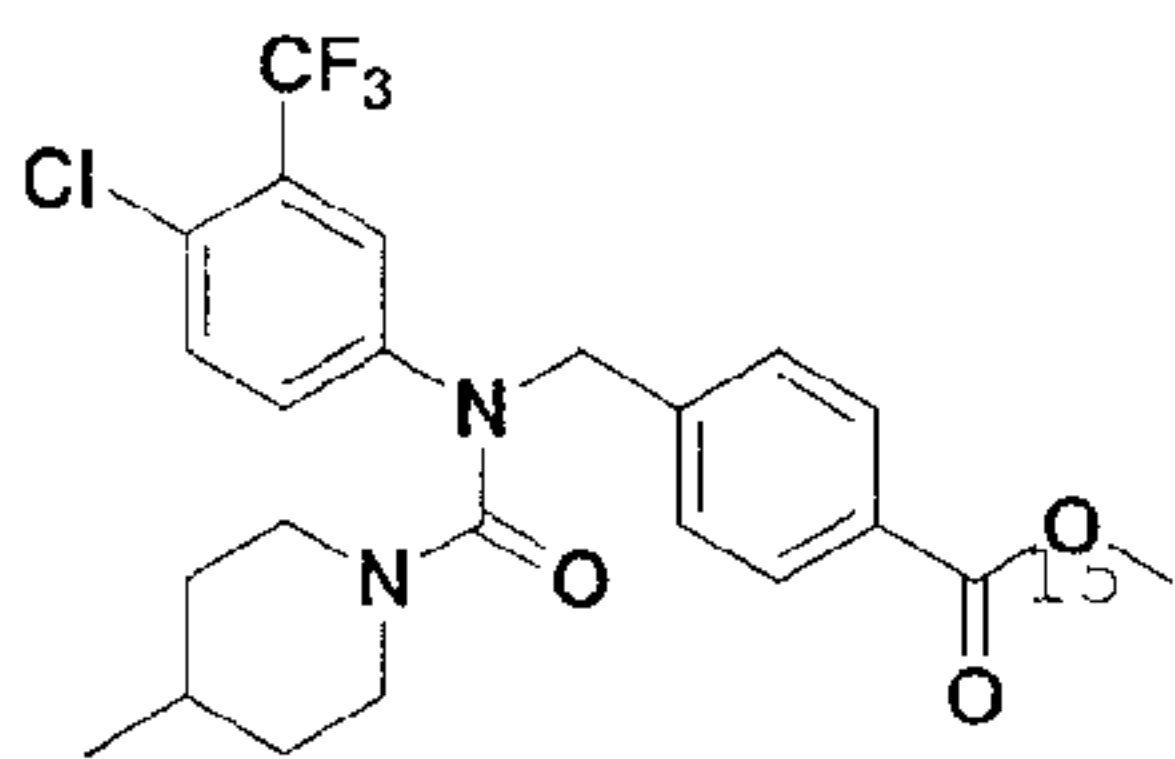
and the resulting solid was filter and dried to give the desired **Compound 389** (0.18 g, 68%) in the form of an apricot solid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.64 (d, 2 H, *J* = 8.1 Hz),
 5 7.58 (d, 1 H, *J* = 8.7 Hz), 7.43 (d, 1 H, *J* = 2.6 Hz), 7.35
 (dd, 1 H, *J* = 8.8, 2.6 Hz), 7.28 (d, 2 H, *J* = 8.1 Hz), 4.87
 (s, 2 H), 3.71 – 3.68 (m, 2 H), 2.69 – 2.63 (m, 2 H), 1.50 –
 1.44 (m, 2 H), 0.87 – 0.81 (m, 4 H); **MS** (ESI) *m/z* 456.1 (M⁺ +
 H).

10

Example 53: Synthesis of Compound 390

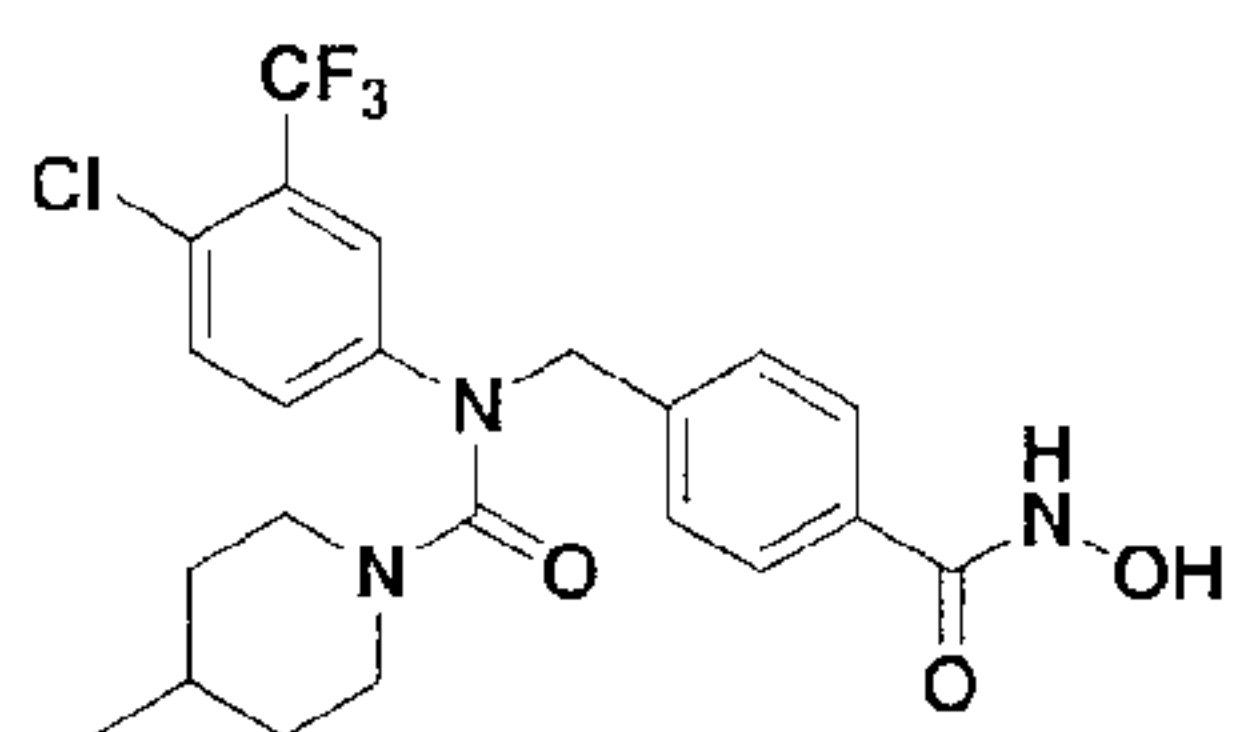
(**Formula 1-4**: methyl 4-((N-(4-chloro-3-
 (trifluoromethyl)phenyl)-4-
 methylpiperidine-1-
 carboxamido)methyl)benzoate)



Compound of **Formula 1-3** (methyl 4-(((4-chloro-3-
 20 (trifluoromethyl)phenyl)((4-
 nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.50 g, 0.983
 mmol) and 4-methylpiperidine (0.116 mL, 0.983 mmol) were
 dissolved in dimethylformamide (10 mL), and the mixture was
 heated and stirred at 60 °C for 2 days. Then, the
 25 dimethylformamide was removed under reduced pressure, water

was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=20%) to give the desired compound of **Formula 1-4** (0.369 g, 80%) in the form of a white oil.

(Compound 390: N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperidine-1-carboxamide)



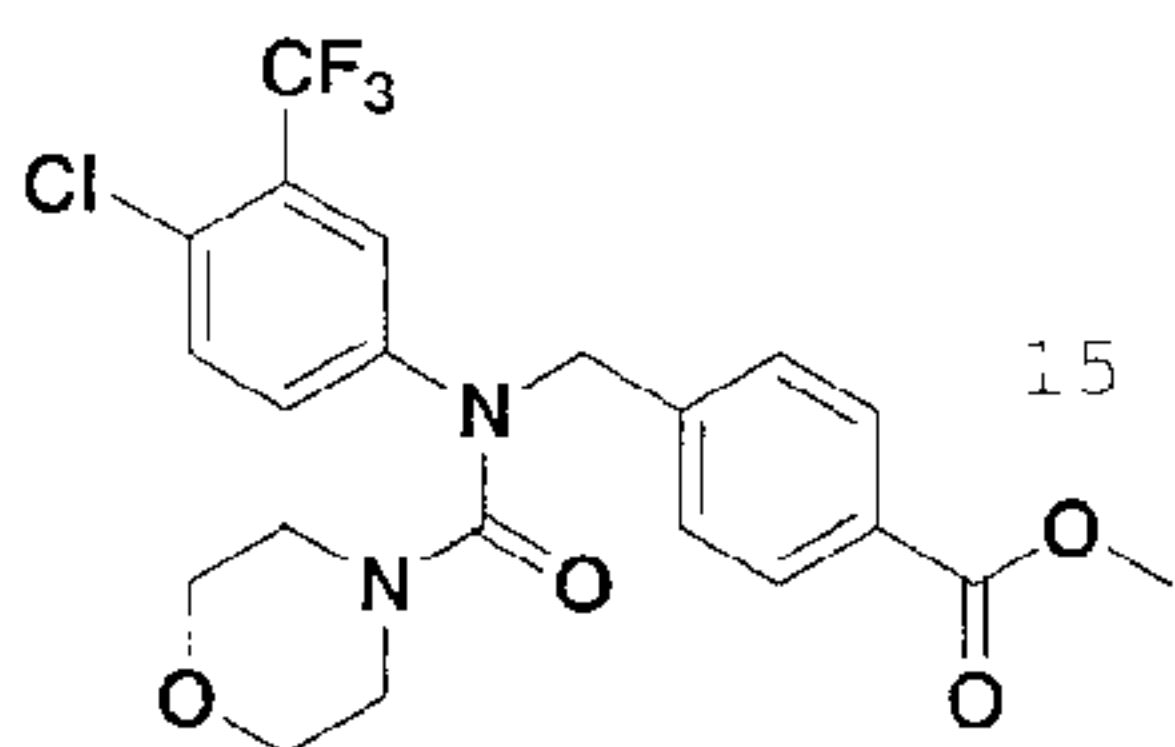
Compound of **Formula 1-4** (methyl 4-((N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methylpiperidine-1-carboxamido)methyl)benzoate, 0.239 g, 0.51 mmol) was dissolved in methanol (20 mL), and hydroxylamine hydrochloride (0.177 g, 2.55 mmol) and potassium hydroxide (0.286 g, 5.09 mmol) were added and stirred. Then, hydroxylamine (50 wt% aqueous solution; 1.31 mL, 10.19 mmol) was added dropwise and stirred at room temperature for 6 hours. After completion of the reaction, the methanol was removed under reduced pressure, saturated sodium hydrogen carbonate aqueous solution was added to precipitate a solid,

and the resulting solid was filter and dried to give the desired **Compound 390** (0.175 g, 73%) in the form of an apricot solid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.64 (d, 2 H, *J* = 8.2 Hz),
 5 7.58 (d, 1 H, *J* = 8.8 Hz), 7.44 (d, 1 H, *J* = 2.6 Hz), 7.34
 (dd, 1 H, *J* = 8.8, 2.6 Hz), 7.29 (d, 2 H, *J* = 8.2 Hz), 4.88
 (s, 2 H), 3.18 - 3.15 (m, 4 H), 1.46 - 1.45 (m, 3 H), 1.33 -
 1.32 (m, 5 H); **MS** (ESI⁻) *m/z* 470.1 (M⁺ + H).

10 **Example 54: Synthesis of Compound 391**

(**Formula 1-4**: methyl 4-((N-(4-chloro-3-(trifluoromethyl)phenyl)morpholine-4-carboxamido)methyl)benzoate)

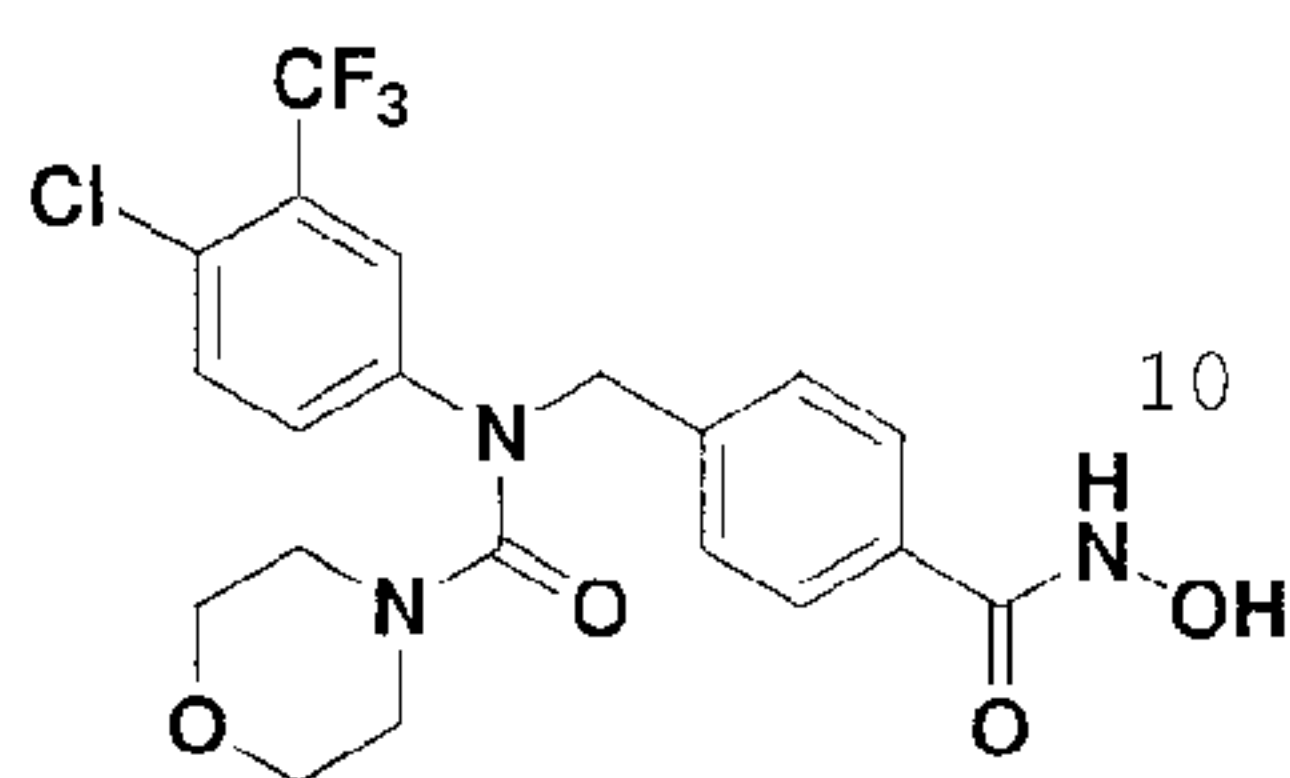


Compound of **Formula 1-3** (methyl 4-

((4-chloro-3-(trifluoromethyl)phenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.50 g, 0.983
 20 mmol) and morpholine (0.086 mL, 0.983 mmol) were dissolved in dimethylformamide (10 mL), and the mixture was heated and stirred at 60 °C for 2 days. Then, the dimethylformamide was removed under reduced pressure, water was poured into the reaction mixture, and the organic layer was extracted with
 25 ethyl acetate. The organic layer was washed with saturated

sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=20%) to
 5 give the desired compound of **Formula 1-4** (0.229 g, 51%) in the form of a white oil.

(**Compound 391**: N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbonyl)benzyl)morpholine-4-carboxamide)



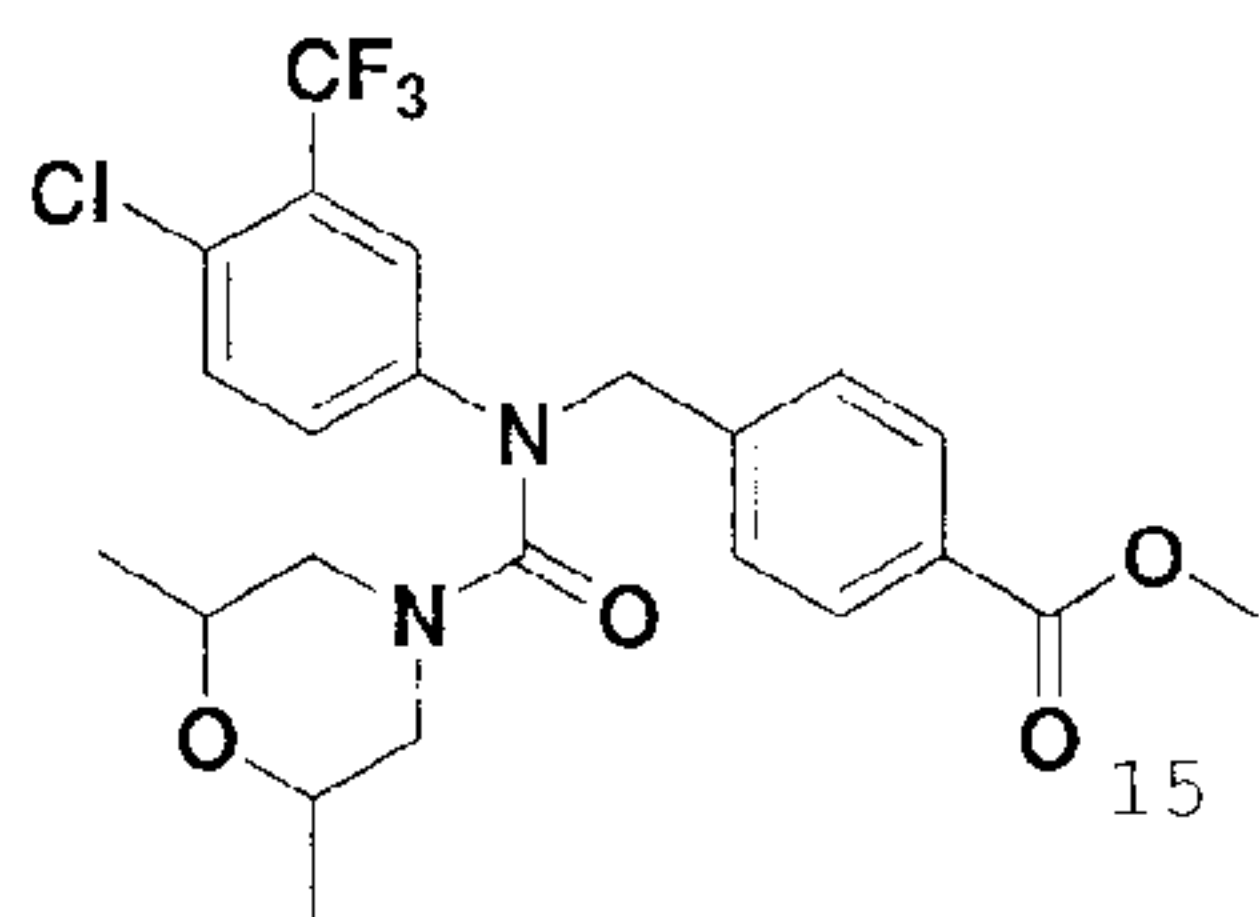
Compound of **Formula 1-4** (methyl 4-((N-(4-chloro-3-(trifluoromethyl)phenyl)morpholine-4-carboxamido)methyl)benzoate, 0.138 g, 0.302 mmol) was
 15 dissolved in methanol (20 mL), and hydroxylamine hydrochloride (0.105 g, 1.51 mmol) and potassium hydroxide (0.169 g, 3.02 mmol) were added and stirred. Then, hydroxylamine (50 wt% aqueous solution; 0.778 mL, 6.04 mmol)
 20 was added dropwise and stirred at room temperature for 6 hours. After completion of the reaction, the methanol was removed under reduced pressure, saturated sodium hydrogen carbonate aqueous solution was added to precipitate a solid, and the resulting solid was filter and dried to give the
 25 desired **Compound 391** (0.089 g, 64%) in the form of a white

solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.13 (s, 1 H), 8.99 (s, 1 H), 7.65 (d, 2 H, J = 8.3 Hz), 7.60 (d, 1 H, J = 8.7 Hz), 7.54 (d, 1 H, J = 2.6 Hz), 7.43 - 7.40 (m, 1 H), 7.36 (d, 2 H, J = 8.2 Hz), 4.94 (s, 2 H), 3.44 - 3.42 (m, 4 H), 3.18 - 3.16 (m, 4 H); MS (ESI) m/z 458.1 (M⁺ + H).

Example 55: Synthesis of Compound 392

(Formula 1-4: methyl 4-((N-(4-chloro-3-(trifluoromethyl)phenyl)-2,6-dimethylmorpholine-4-carboxamido)methyl)benzoate)

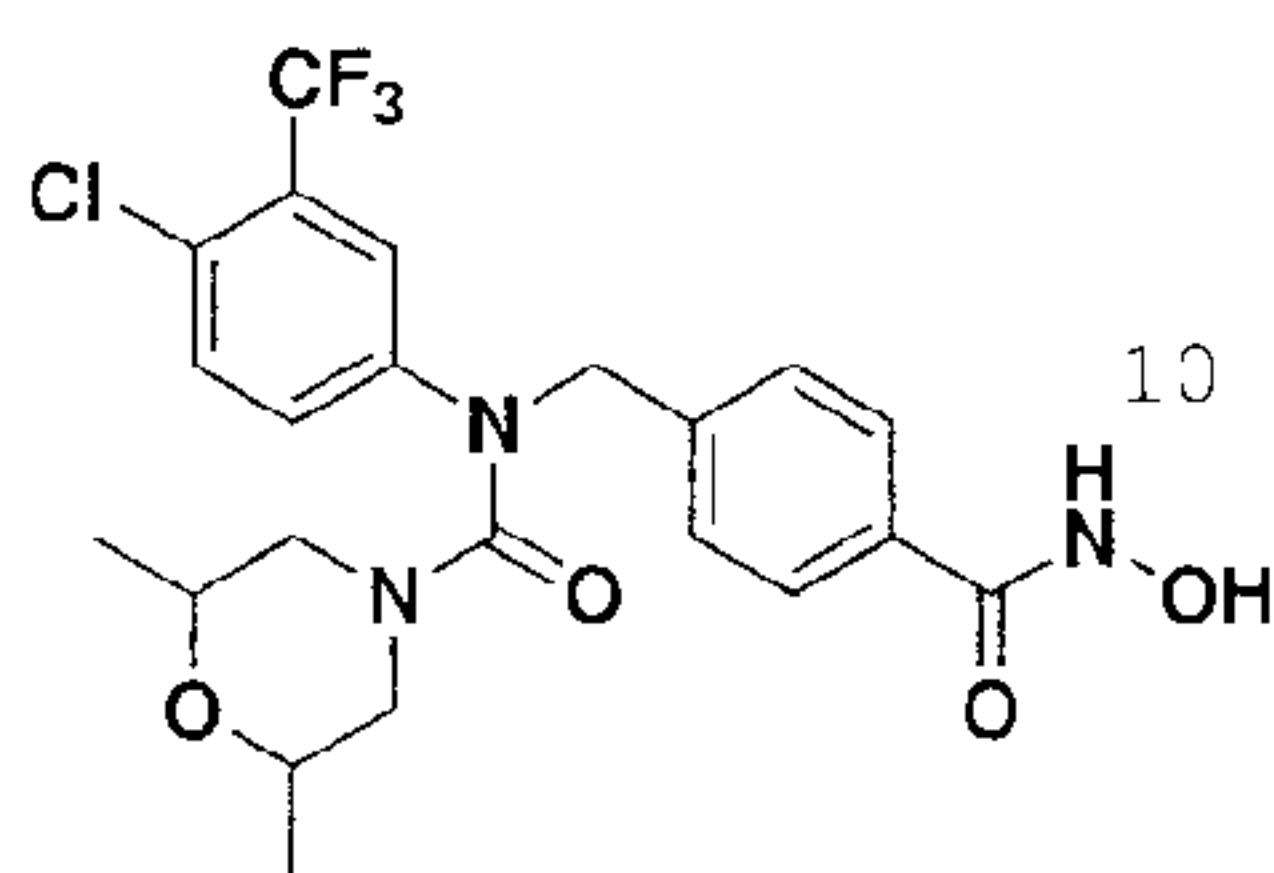


Compound of **Formula 1-3** (methyl 4-(((4-chloro-3-(trifluoromethyl)phenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.50 g, 0.983 mmol) and 2,6-dimethylmorpholine (0.12 mL, 0.983 mmol) were dissolved in dimethylformamide (10 mL), and the mixture was heated and stirred at 60 °C for 2 days. Then, the dimethylformamide was removed under reduced pressure, water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution,

dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=20%) to give the desired compound of

5 **Formula 1-4** (0.2 g, 42%) in the form of a white oil.

(**Compound 392**: N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbonyl)benzyl)-2,6-dimethylmorpholine-4-carboxamide)



Compound of **Formula 1-4** (methyl 4-

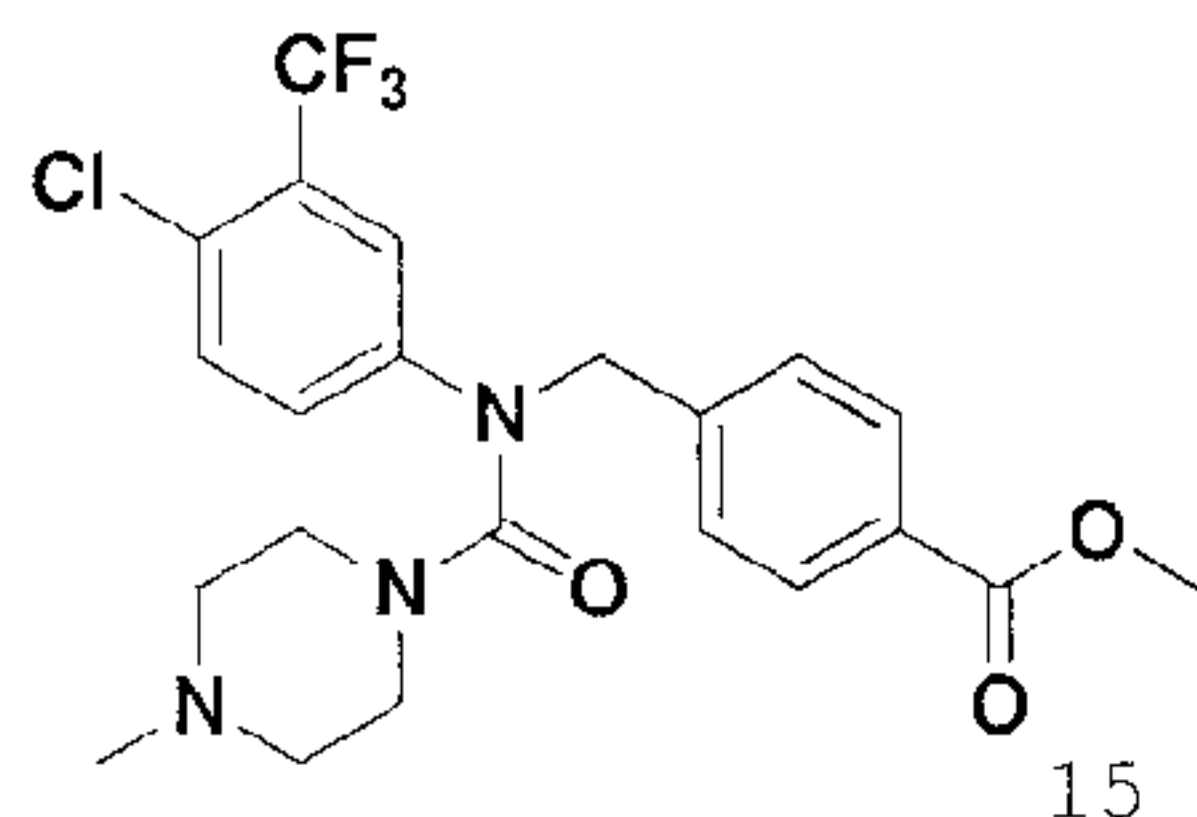
((N-(4-chloro-3-(trifluoromethyl)phenyl)-2,6-dimethylmorpholine-4-carboxamido)methyl)benzoate, 0.121 g, 0.250 mmol) was dissolved in methanol (20 mL), and hydroxylamine hydrochloride (0.087 g, 1.25 mmol) and potassium hydroxide (0.14 g, 2.49 mmol) were added and stirred. Then, hydroxylamine (50 wt% aqueous solution; 0.643 mL, 4.99 mmol) was added dropwise and stirred at room temperature for 6 hours. After completion of the reaction, the methanol was removed under reduced pressure, saturated sodium hydrogen carbonate aqueous solution was added to precipitate a solid, and the resulting solid was filter and dried to give the desired **Compound 392** (0.056 g, 46%) in the

form of an white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.64 (d, 2 H, J = 8.3 Hz),
7.59 (d, 1 H, J = 8.8 Hz), 7.49 (d, 1 H, J = 2.6 Hz), 7.39 -
7.36 (m 1 H), 7.30 (d, 2 H, J = 8.2 Hz), 4.89 (s, 2 H), 3.58
5 - 3.55 (m, 2 H), 2.40 - 2.32 (m, 4 H), 0.96 (d, 6 H, J = 6.2
Hz); MS (ESI) m/z 486.1 (M⁺ + H).

Example 56: Synthesis of Compound 393

(Formula 1-4: methyl 4-((N-(4-chloro-3-
10 (trifluoromethyl)phenyl)-4-methylpiperazine-1-
carboxamido)methyl)benzoate)

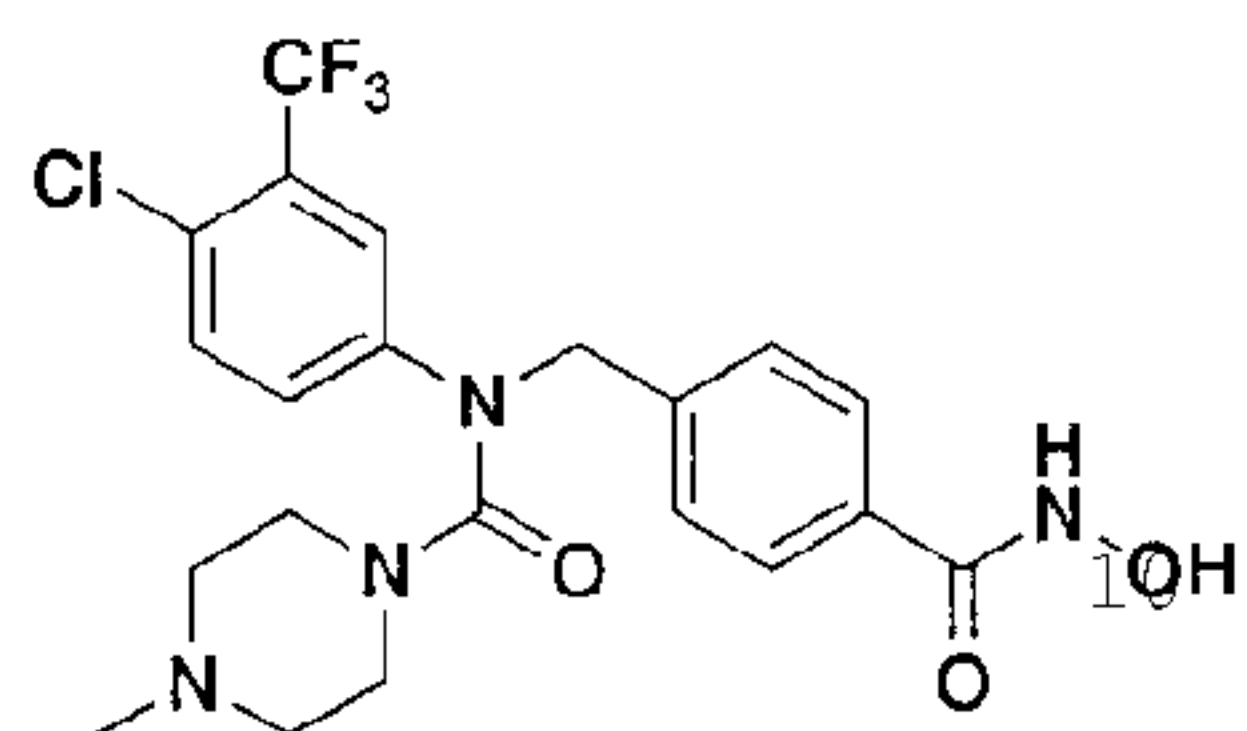


Compound of **Formula 1-3** (methyl 4-(((4-chloro-3-
(trifluoromethyl)phenyl)((4-
nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.50 g, 0.983
mmol) and 1-methylpiperazine (0.109 mL, 0.983 mmol) were
20 dissolved in dimethylformamide (10 mL), and the mixture was
heated and stirred at 60 °C for 2 days. Then, the
dimethylformamide was removed under reduced pressure, water
was poured into the reaction mixture, and the organic layer
was extracted with ethyl acetate. The organic layer was
25 washed with saturated sodium chloride aqueous solution,

dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane= 5%) to give the desired compound of

5 **Formula 1-4** (0.420 g, 91%) in the form of a yellow oil.

(**Compound 393**: N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide)



Compound of **Formula 1-4** (methyl 4-((N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methylpiperazine-1-carboxamido)methyl)benzoate, 0.251 g, 0.534 mmol) was

15 dissolved in methanol (20 mL), and hydroxylamine hydrochloride (0.185 g, 2.67 mmol) and potassium hydroxide (0.299 g, 5.34 mmol) were added and stirred. Then, hydroxylamine (50 wt% aqueous solution; 1.38 mL, 10.7 mmol)

20 was added dropwise and stirred at room temperature for 6 hours. After completion of the reaction, the methanol was removed under reduced pressure, saturated sodium hydrogen carbonate aqueous solution was added to precipitate a solid, and the resulting solid was filter and dried to give the

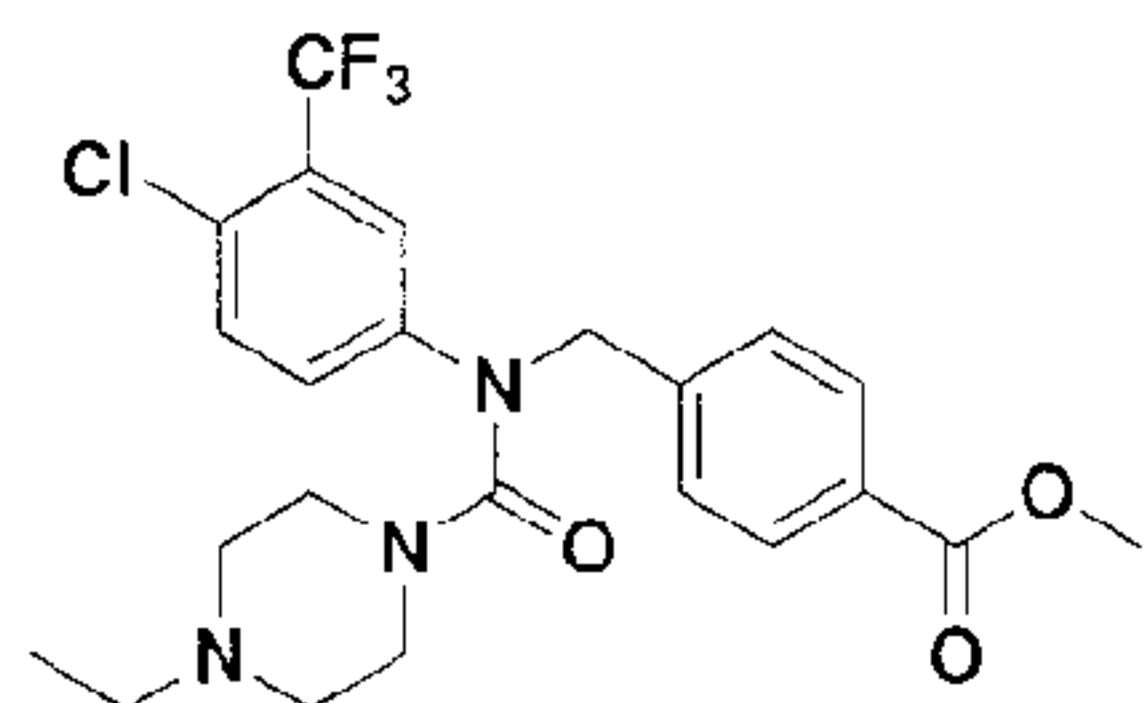
25 desired **Compound 393** (0.19 g, 75%) in the form of a white

solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.13 (s, 1 H), 8.99 (s, 1 H), 7.65 (d, 2 H, J = 8.1 Hz), 7.60 (d, 1 H, J = 8.7 Hz), 7.49 (d, 1 H, J = 2.4 Hz), 7.40 - 7.35 (m, 3 H), 5.75 (s, 1 H), 4.92 (s, 2 H), 3.17 (m, 4 H), 2.14 (m, 4 H), 2.10 (s, 3 H); MS (ESI) m/z 471.1 (M⁺ + H).

Example 57: Synthesis of Compound 394

(Formula 1-4: methyl 4-((N-(4-chloro-3-(trifluoromethyl)phenyl)-4-ethylpiperazine-1-carboxamido)methyl)benzoate)



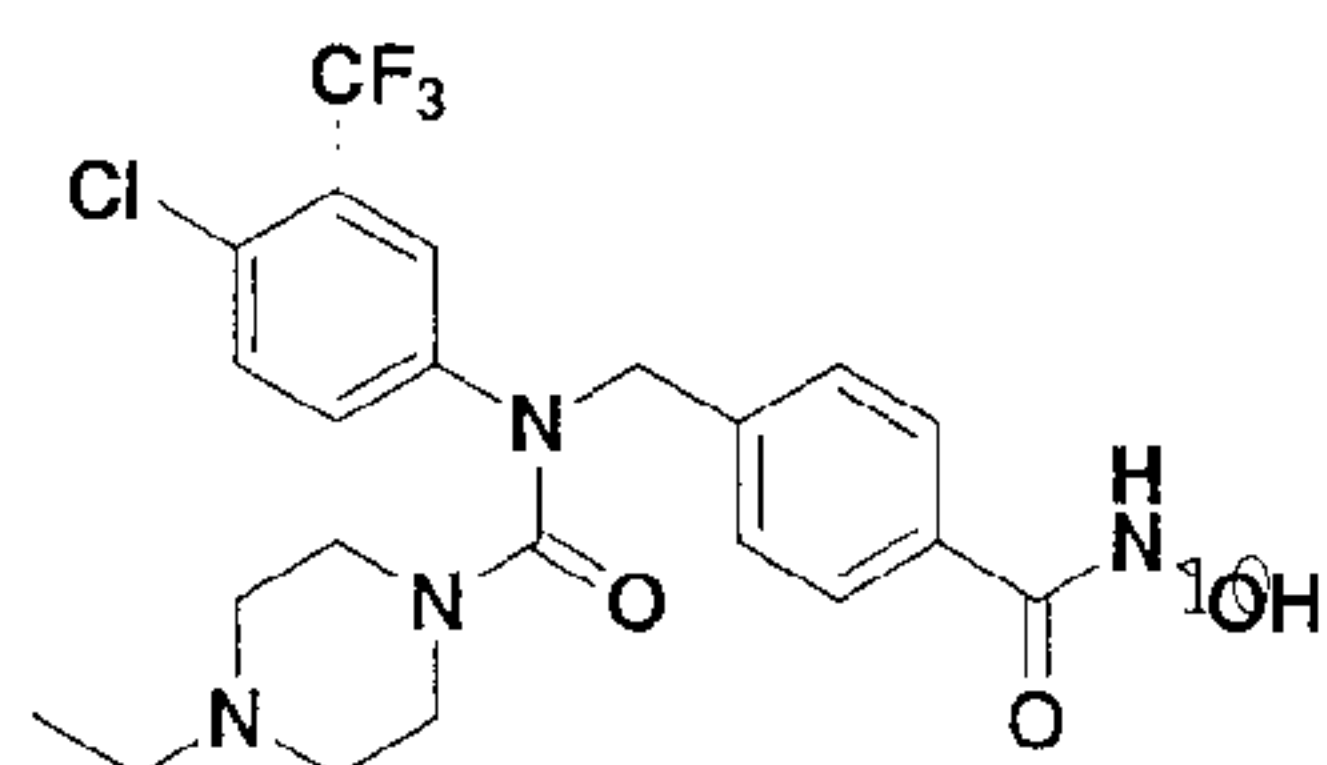
15

Compound of **Formula 1-3** (methyl 4-

((4-chloro-3-(trifluoromethyl)phenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.5 g, 0.983 mmol) and 1-ethylpiperazine (0.125 mL, 0.983 mmol) were dissolved in dimethylformamide (10 mL), and the mixture was heated and stirred at 60 °C for 2 days. Then, the dimethylformamide was removed under reduced pressure, water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then

concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane = 5%) to give the desired compound of **Formula 1-4** (0.411 g, 86%) in the form of a yellow oil.

5 **(Compound 394: N-(4-chloro-3-(trifluoromethyl)phenyl)-4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide)**



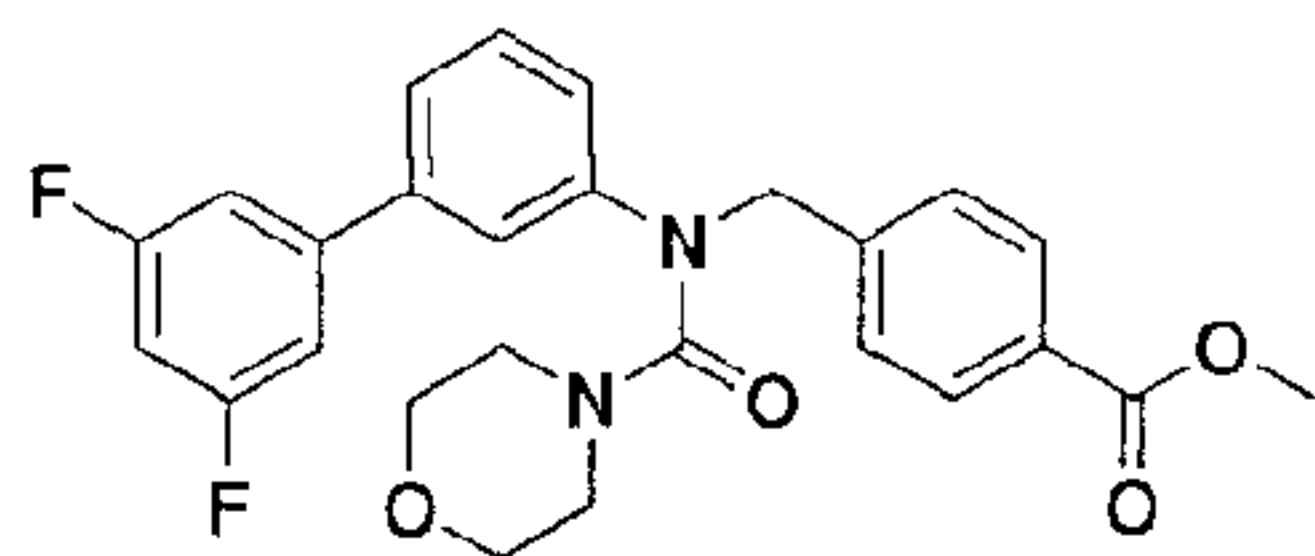
Compound of **Formula 1-4** (methyl 4-((N-(4-chloro-3-(trifluoromethyl)phenyl)-4-ethylpiperazine-1-carboxamido)methyl)benzoate, 0.261 g, 0.539 mmol) was dissolved in methanol (20 mL), and hydroxylamine
 15 hydrochloride (0.187 g, 2.69 mmol) and potassium hydroxide (0.303 g, 5.39 mmol) were added and stirred. Then, hydroxylamine (50 wt% aqueous solution; 1.39 mL, 10.79 mmol) was added dropwise and stirred at room temperature for 6
 20 hours. After completion of the reaction, the methanol was removed under reduced pressure, saturated sodium hydrogen carbonate aqueous solution was added to precipitate a solid, and the resulting solid was filter and dried to give the desired **Compound 394** (0.25 g, 95%) in the form of an pale
 25 yellow solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.13 (s, 1 H), 9.00 (s, 1 H), 7.65 (d, 2 H, J = 8.2 Hz), 7.60 (d, 1 H, J = 8.8 Hz), 7.49 (d, 1 H, J = 2.4 Hz), 7.40 - 7.35 (m, 3 H), 5.75 (s, 2 H), 4.92 (s, 2 H), 3.18 (m, 4 H), 2.24 (q, 2 H, J = 7.2 Hz), 2.19 (m, 4 H), 0.93 (t, 3 H, J = 7.1 Hz); **MS** (ESI) m/z 485.1 (M⁺ + H).

Example 58: Synthesis of Compound 395

(**Formula 2-2**: methyl 4-((N-(3',5'-difluorobiphenyl-3-yl)morpholine-4-carboxamido)methyl)benzoate)

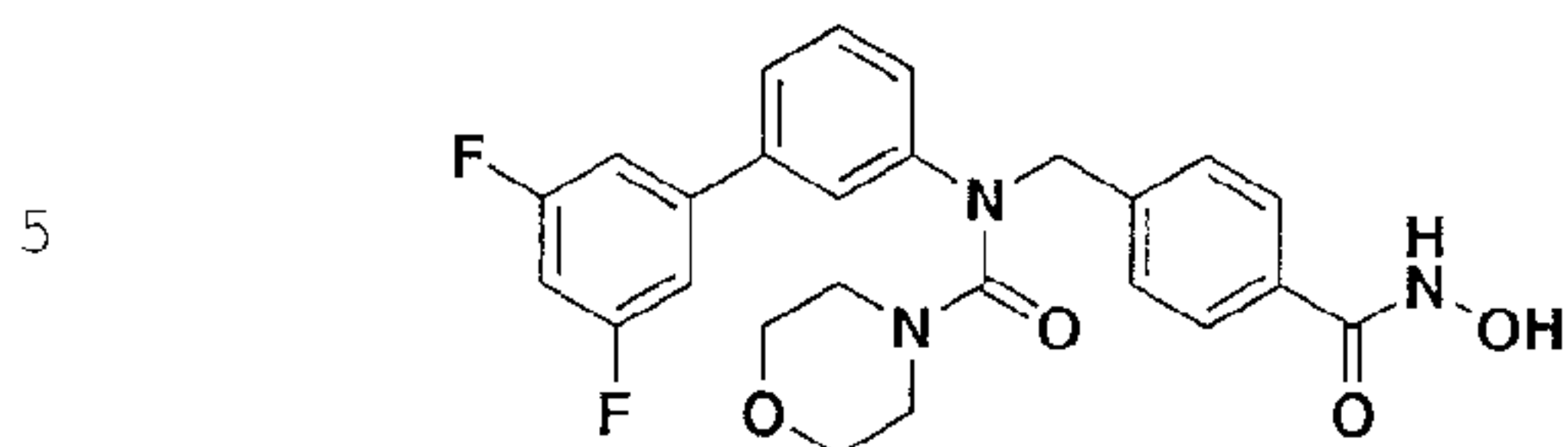
10



Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), 3,5-difluorophenylboronic acid (0.088 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and potassium carbonate (0.128 g, 0.923 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 4 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=50%) to give the desired compound of **Formula 2-2** (0.180 g, 84%) in the form of

a light brown solid.

(Compound 395: N-(3',5'-difluorobiphenyl-3-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide)



Compound of **Formula 2-2**

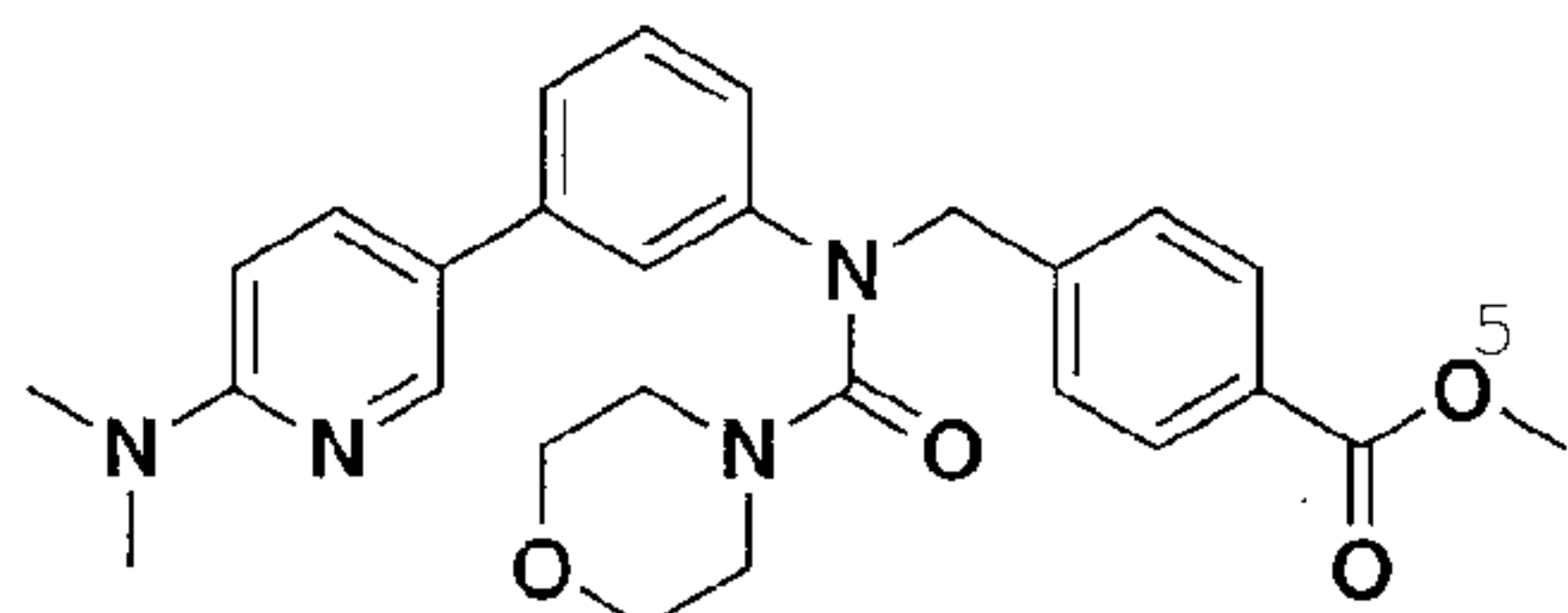
(methyl 4-((N-(3',5'-difluorobiphenyl-3-yl)morpholine-4-carboxamido)methyl)benzoate; 0.180 g, 0.386 mmol) was
 10 dissolved in methanol (10 mL), and hydroxylamine (50.0 wt% aqueous solution; 2.36 mL, 38.6 mmol) and potassium hydroxide (0.217 g, 3.86 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under
 15 reduced pressure until its volume became about 1 mL, and then saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 395** (0.159 g, 88%) in the form of a light brown
 20 solid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.64 (d, 2 H, J = 8.2 Hz), 7.57 (s, 1 H), 7.46 - 7.36 (m, 6 H), 7.23 (m, 1 H), 7.15 (m, 1 H), 4.96 (s, 2 H), 3.40 - 3.37 (m, 4 H), 3.17 - 3.14 (m, 4 H). **MS** (ESI) m/z 468 (M⁺ + H).

25

Example 59: Synthesis of Compound 396

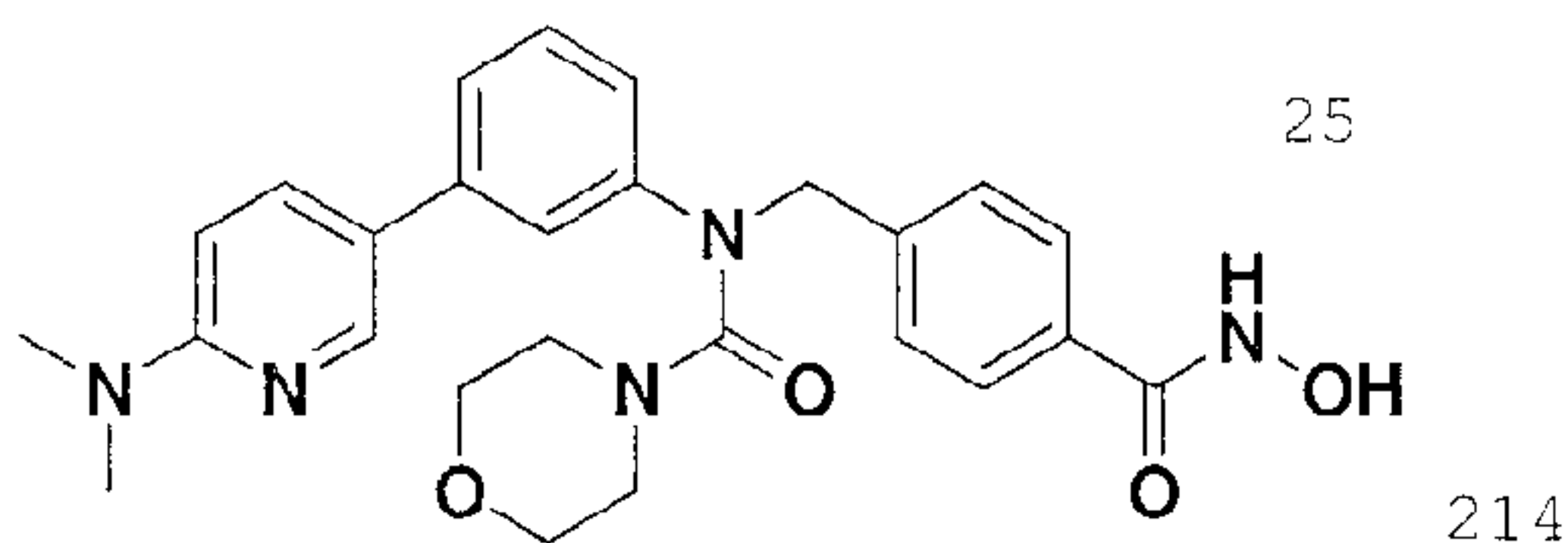
(**Formula 2-2**: methyl 4-((N-(3-(6-(dimethylamino)pyridin-3-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)



Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), 6-dimethylaminopyridin-3-ylboronic acid (0.092 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and potassium carbonate (0.128 g, 0.923 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 4 hours.

After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=50%) to give the desired compound of **Formula 2-2** (0.136 g, 62%) in the form of a light brown solid.

(**Compound 396**: N-(3-(6-(dimethylamino)pyridin-3-yl)phenyl)-N-(4-(hydroxycarbonyl)benzyl)morpholine-4-carboxamide)



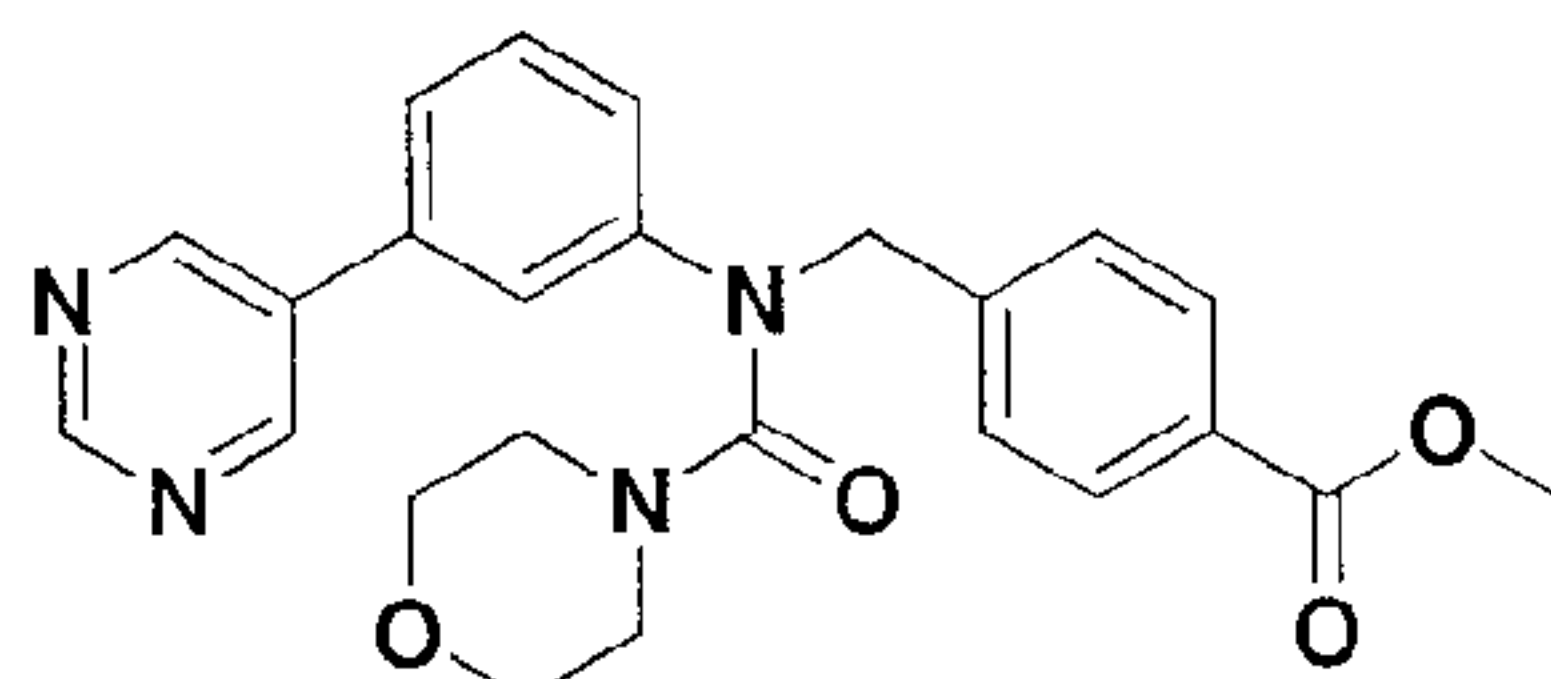
Compound of **Formula 2-2** (methyl 4-((N-(3-(6-
 5 (dimethylamino)pyridin-3 yl)phenyl)morpholine-4-
 carboxamido)methyl)benzoate; 0.136 g, 0.287 mmol) was
 dissolved in methanol (10 mL), and hydroxylamine (50.0 wt%
 aqueous solution; 1.75 mL, 28.7 mmol) and potassium hydroxide
 (0.161 g, 2.87 mmol) were added sequentially and then stirred
 10 at room temperature for 30 minutes. After completion of the
 reaction, the reaction solution was concentrated under
 reduced pressure until its volume became about 1 mL, and then
 saturated ammonium chloride aqueous solution (1-2 mL) was
 added and stirred. Then, the solid product was filtered,
 15 washed with water, and then vacuum dried to give the desired
Compound 396 (0.118 g, 87%) in the form of a light brown
 solid.

¹H NMR (400 MHz, DMSO-d₆) δ 8.38 (d, 1 H, J = 2.5 Hz),
 7.78 (m, 1 H), 7.64 (d, 2 H, J = 8.3 Hz), 7.39 - 7.35 (m, 3
 20 H), 7.32 - 7.29 (m, 2 H), 7.05 (m, 1 H), 6.69 (d, 1 H, J =
 8.9 Hz), 4.93 (s, 2 H), 3.41 - 3.38 (m, 4 H), 3.18 - 3.15 (m,
 4 H), 3.05 (s, 6 H). **MS** (ESI) m/z 476 (M⁺ + H).

Example 60: Synthesis of Compound 397

25 **(Formula 2-2: methyl 4-((N-(3-(pyrimidin-5-**

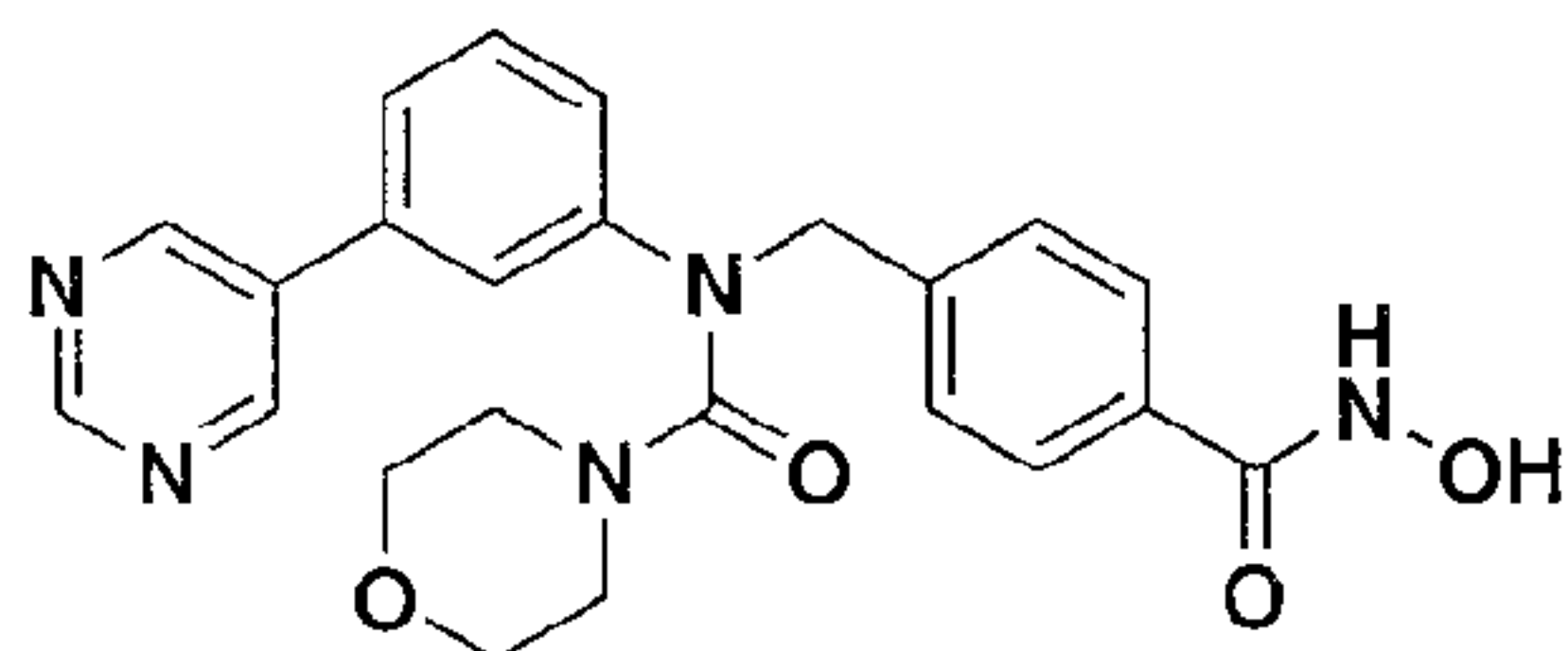
yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)



5

Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), pyrimidin-5-ylboronic acid (0.069 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and potassium carbonate (0.128 g, 0.923 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 4 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=25%) to give the desired compound of **Formula 2-2** (0.120 g, 60%) in the form of a yellow solid.

(**Compound 397**: N-(4-(hydroxycarbonyl)benzyl)-N-(3-(pyrimidin-5-yl)phenyl)morpholine-4-carboxamide)



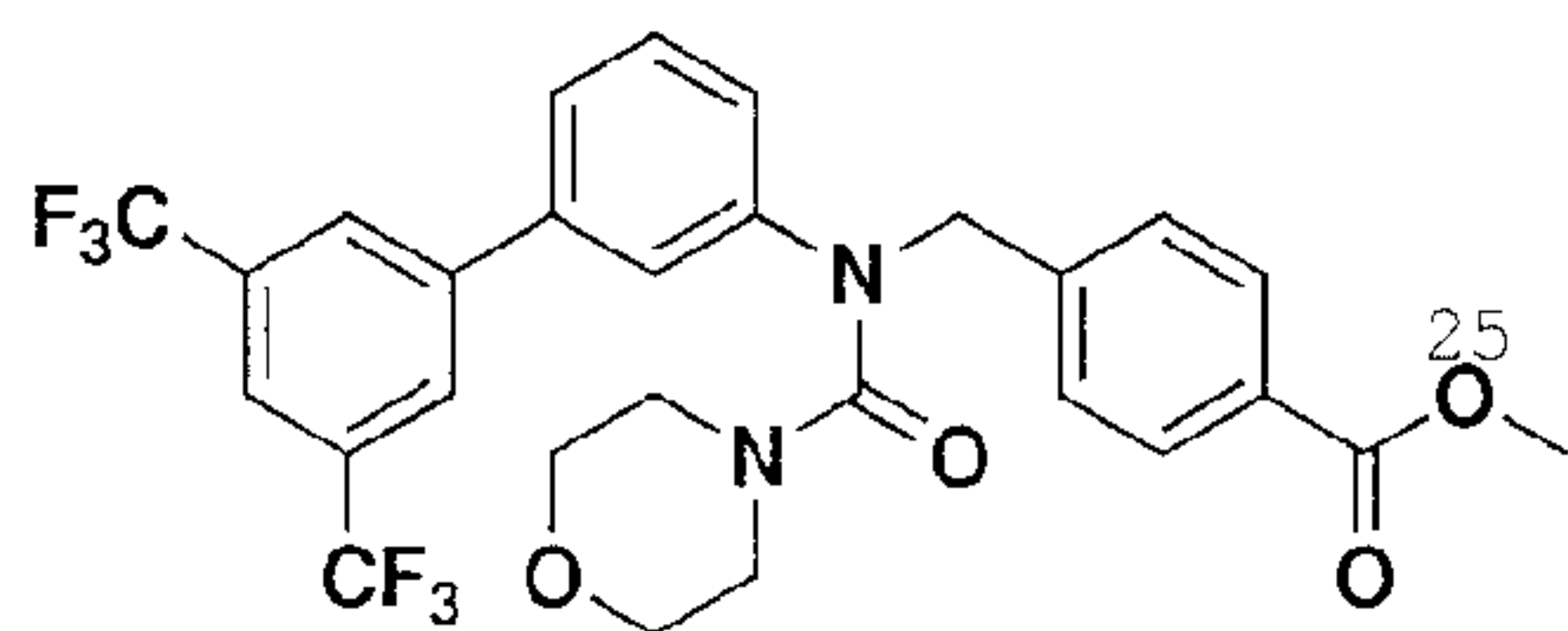
Compound of **Formula 2-2** (methyl 4-((N-(3-(pyrimidin-5-

yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.120 g, 0.277 mmol) was dissolved in methanol (10 mL), and hydroxylamine (50.0 wt% aqueous solution; 1.70 mL, 27.7 mmol) and potassium hydroxide (0.156 g, 2.78 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 2 mL, and then extracted by ethyl acetate and saturated ammonium chloride aqueous solution. Then, the organic layer was dehydrated with anhydrous magnesium sulfate, and filtered, and the filtrate was then concentrated under reduced pressure to give the desired **Compound 397** (0.056 g, 47 %) in the form of a brown solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.21 (brs, 1 H), 9.18 (brs, 1 H), 9.13 (s, 2 H), 8.97 (s, 1 H), 7.66 – 7.63 (m, 3 H), 7.51 – 7.41 (m, 4 H), 7.20 (m, 1 H), 4.97 (s, 2 H), 3.41 – 3.37 (m, 4 H), 3.19 – 3.16 (m, 4 H). **MS** (ESI) m/z 434 (M⁺ + H).

Example 61: Synthesis of Compound 398

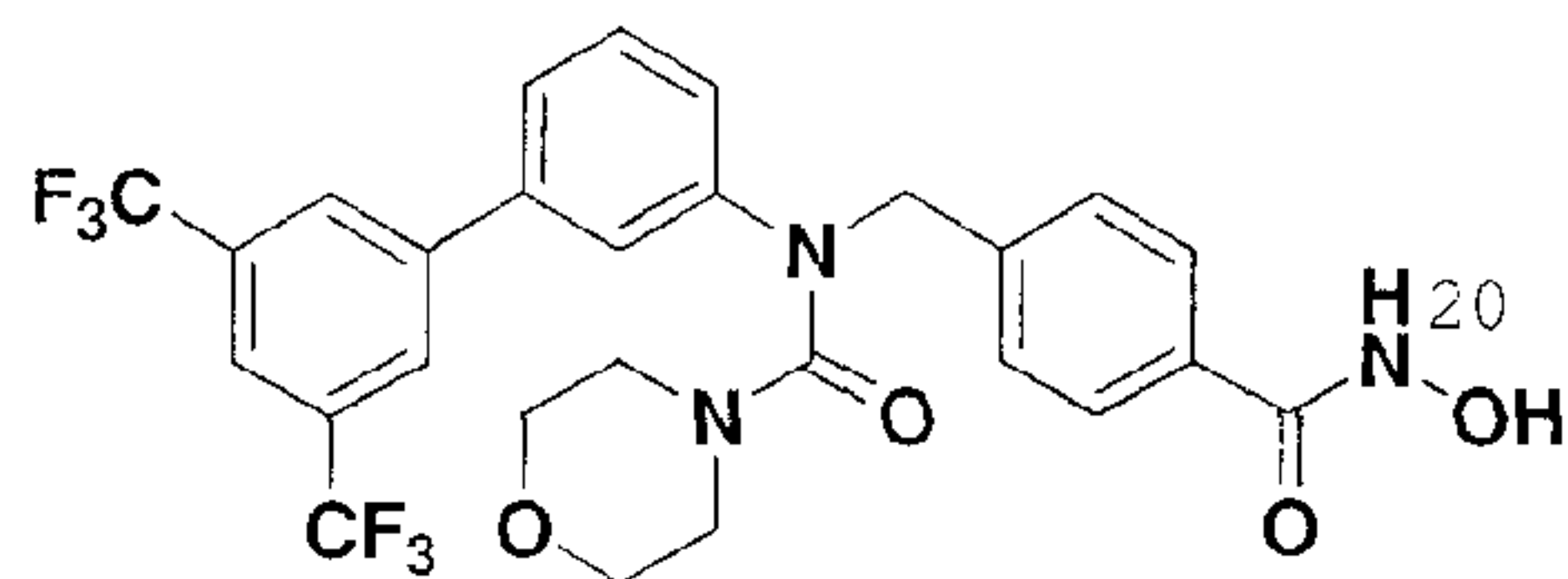
(Formula 2-2: methyl 4-((N-(3',5'-bis(trifluoromethyl)biphenyl-3-yl)morpholine-4-carboxamido)methyl)benzoate)



Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), 3,5-bis(trifluoromethyl)phenylboronic acid (0.143 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and potassium carbonate (0.128 g, 0.923 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 4 hours.

After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 2-2** (0.185 g, 71%) in the form of a white solid.

(**Compound 398**: N-(3',5'-bis(trifluoromethyl)biphenyl-3-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide)



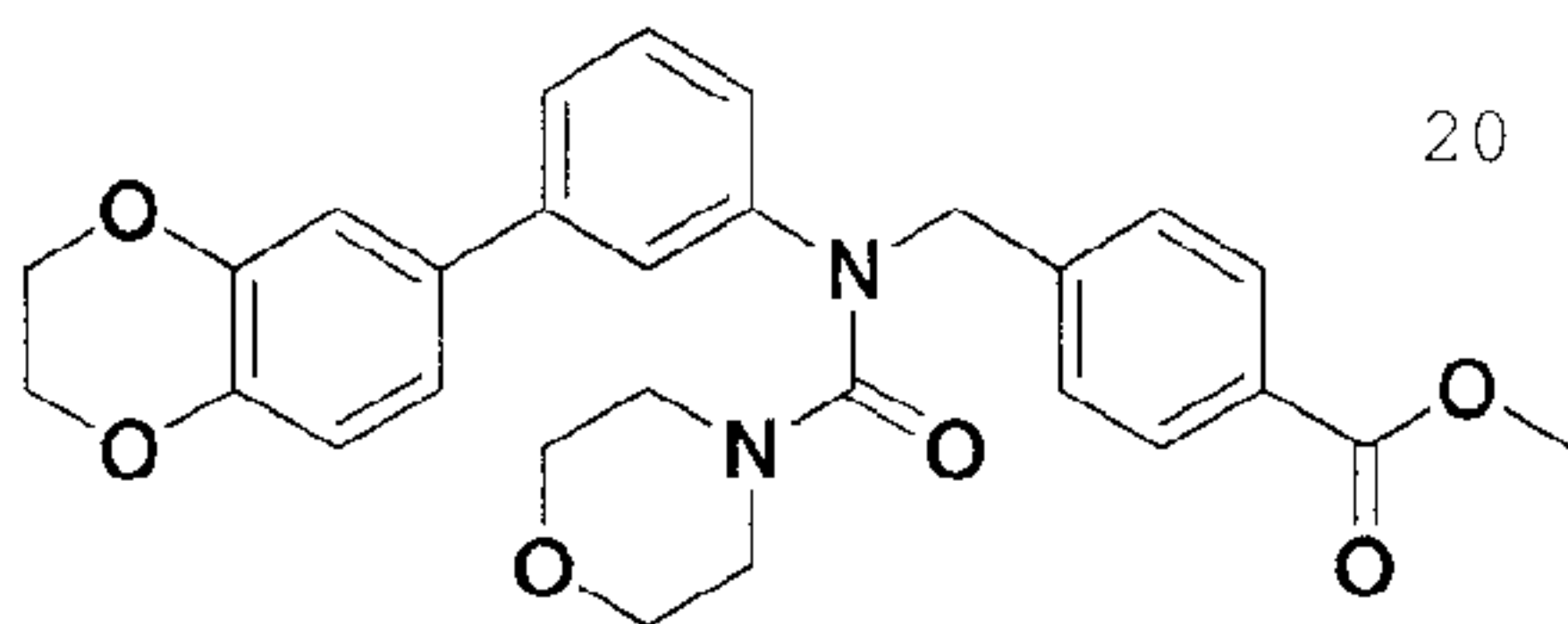
Compound of **Formula 2-2** (methyl 4-((N-(3',5'-bis(trifluoromethyl)biphenyl-3-yl)morpholine-4-carboxamido)methyl)benzoate; 0.185 g, 0.327 mmol) was

dissolved in methanol (10 mL), and hydroxylamine (50.0 wt% aqueous solution; 2.00 mL, 32.7 mmol) and potassium hydroxide (0.183 g, 3.27 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 1 mL, and then saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 398** (0.160 g, 86%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 8.31 (s, 2 H), 8.09 (s, 1 H), 7.74 (s, 1 H), 7.64 (d, 2 H, *J* = 8.4 Hz), 7.57 (m, 1 H), 7.43 - 7.40 (m, 3 H), 7.22 (m, 1 H), 4.98 (s, 2 H), 3.41 - 3.38 (m, 4 H), 3.19 - 3.16 (m, 4 H). **MS** (ESI) *m/z* 568 (M⁺ + H).

Example 62: Synthesis of Compound 399

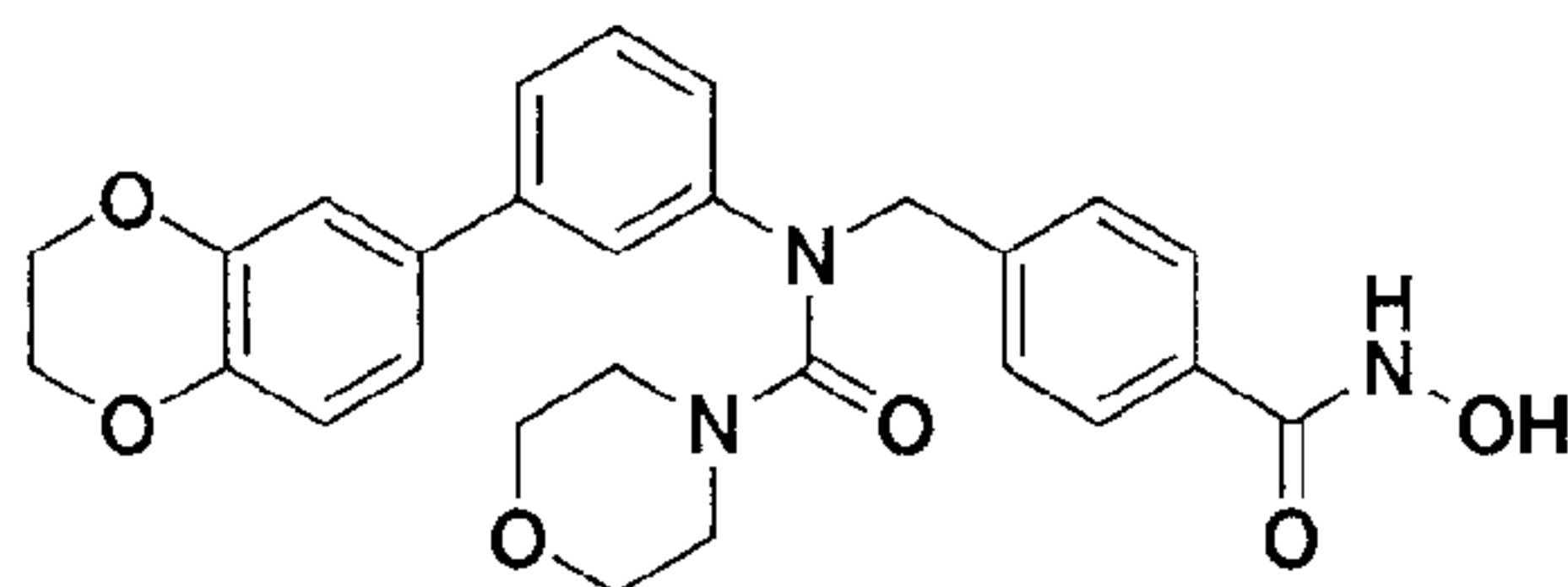
(**Formula 2-2**: methyl 4-((N-(3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)



Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g,

0.462 mmol), 2,3-dihydrobenzo[b][1,4]dioxin-6-ylboronic acid (0.100 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and potassium carbonate (0.128 g, 0.923 mmol) dissolved in water (1 mL) was added to
 5 the reaction solution and stirred at 100 °C for 4 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated
 10 by column chromatography (silica; ethyl acetate/hexane=50%) to give the desired compound of **Formula 2-2** (0.182 g, 81%) in the form of a yellow liquid.

(**Compound 399**: N-(3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)-N-(4-(hydroxycarbonyl)benzyl)morpholine-4-
 15 carboxamide)



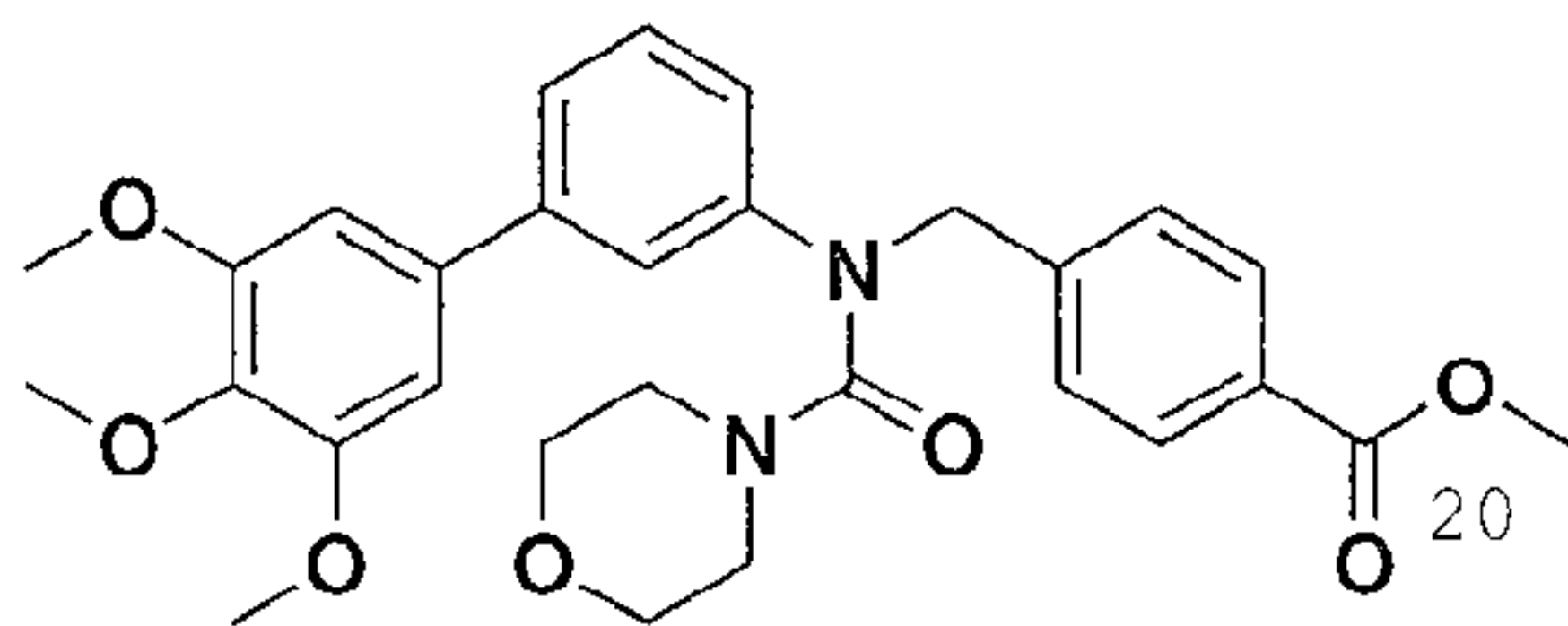
20 Compound of **Formula 2-2** (methyl 4-((N-(3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.182 g, 0.373 mmol) was dissolved in methanol (10 mL), and hydroxylamine (50.0 wt% aqueous solution; 2.28 mL, 37.3 mmol) and potassium hydroxide
 25 (0.209 g, 3.73 mmol) were added sequentially and then stirred

at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 1 mL, and then saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 399** (0.165 g, 91%) in the form of a light brown solid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.64 (d, 2 H, *J* = 8.2 Hz), 7.38 (d, 2 H, *J* = 8.2 Hz), 7.34 - 7.27 (m, 3 H), 7.12 - 7.04 (m, 3 H), 6.91 (d, 1 H, *J* = 8.3 Hz), 4.92 (s, 2 H), 4.26 (s, 4 H), 3.40 - 3.37 (m, 4 H), 3.17 - 3.15 (m, 4 H). **MS** (ESI) *m/z* 490 (M⁺ + H).

Example 63: Synthesis of Compound 400

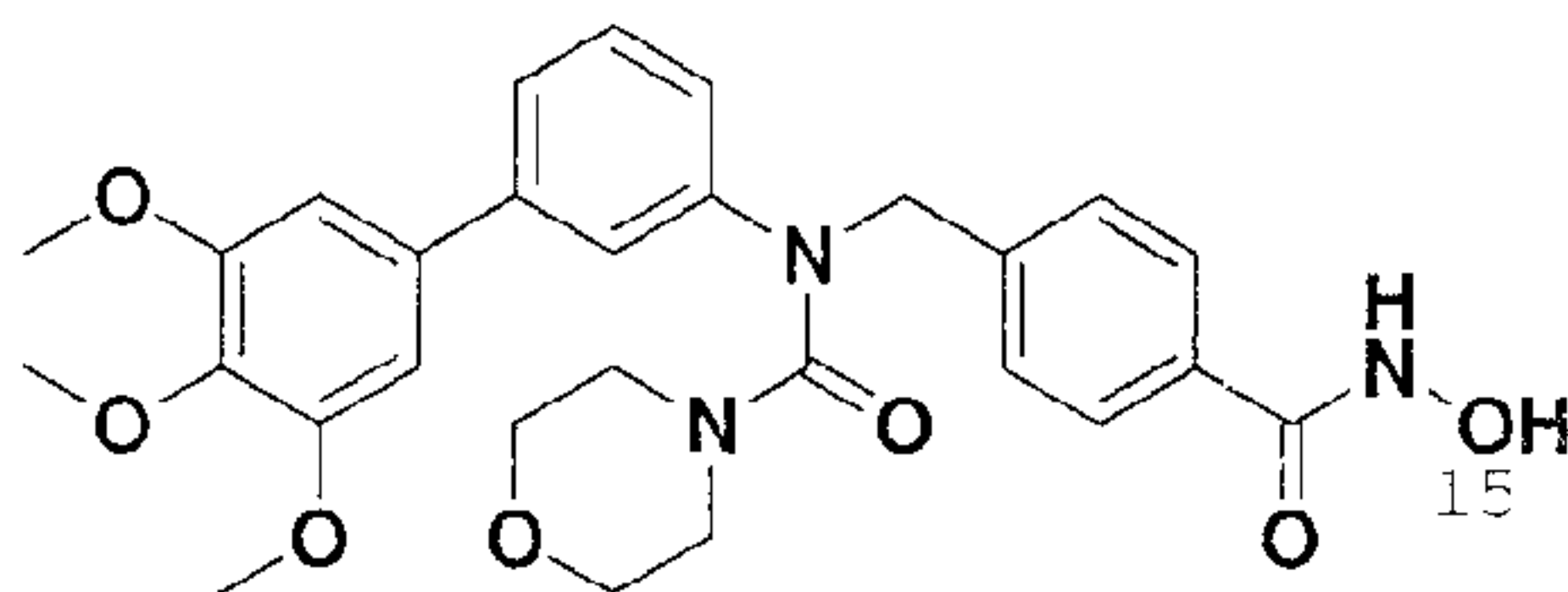
(**Formula 2-2**: methyl 4-((N-(3',4',5'-trimethoxybiphenyl-3-yl)morpholine-4-carboxamido)methyl)benzoate)



Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), 3,4,5-trimethoxyphenylboronic acid (0.117 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were

dissolved in 1,4-dioxane (3 mL), and potassium carbonate (0.128 g, 0.923 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 4 hours. After completion of the reaction, the organic layer was
 5 extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=50%) to give the desired compound of **Formula 2-2** (0.146 g, 61%) in
 10 the form of a white solid.

(**Compound 400**: N-(4-(hydroxycarbamoyl)benzyl)-N-(3',4',5'-trimethoxybiphenyl-3-yl)morpholine-4-carboxamide)



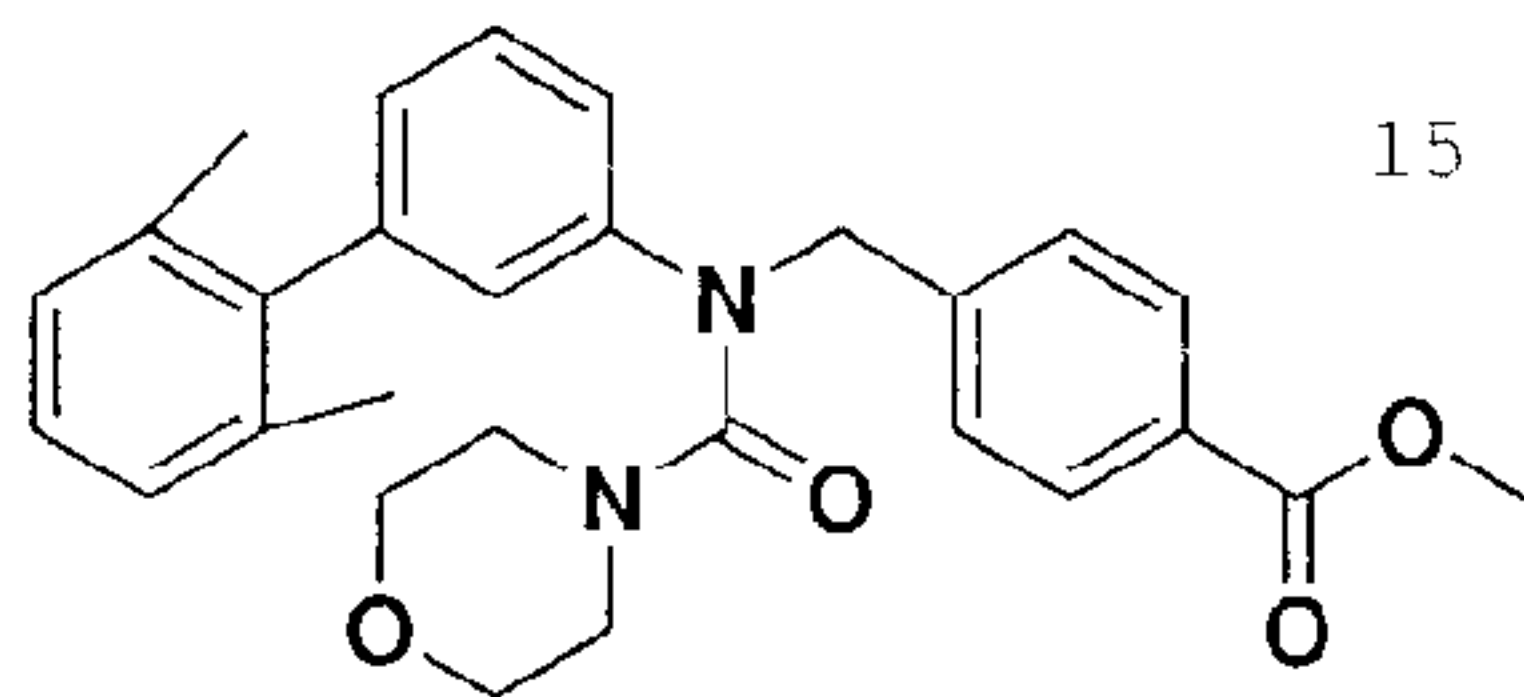
Compound of **Formula 2-2** (methyl 4-((N-(3',4',5'-trimethoxybiphenyl-3-yl)morpholine-4-carboxamido)methyl)benzoate; 0.146 g, 0.280 mmol) was
 20 dissolved in methanol (10 mL), and hydroxylamine (50.0 wt% aqueous solution; 1.72 mL, 28.1 mmol) and potassium hydroxide (0.157 g, 2.81 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under
 25 reduced pressure until its volume became about 1 mL, and then

saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 400** (0.125 g, 86%) in the form of a light brown solid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.65 (d, 2 H, *J* = 8.2 Hz), 7.41 - 7.39 (m, 3 H), 7.37 - 7.35 (m, 2 H), 7.12 (m, 1 H), 6.81 (s, 2 H), 4.95 (s, 2 H), 3.83 (s, 6 H), 3.67 (s, 3 H), 3.43 - 3.40 (m, 4 H), 3.19 - 3.16 (m, 4 H). **MS** (ESI) *m/z* 522 (M⁺ + H).

Example 64: Synthesis of Compound 401

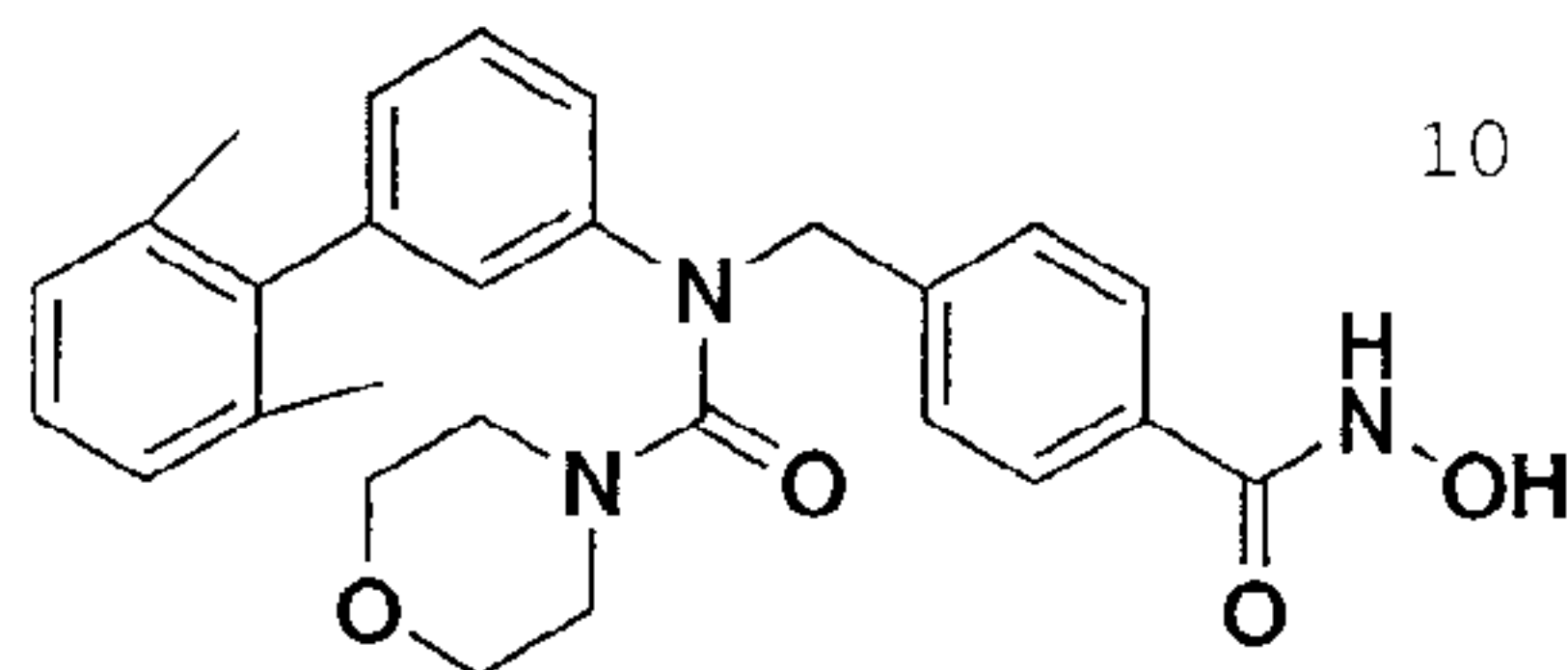
(**Formula 2-2**: methyl 4-((N-(2',6'-dimethylbiphenyl-3-yl)morpholine-4-carboxamido)methyl)benzoate)



Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), 2,6-dimethylphenylboronic acid (0.083 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and potassium carbonate (0.128 g, 0.923 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 4 hours. After

completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=50%) to give the
 5 desired compound of **Formula 2-2** (0.205 g, 97%) in the form of a white solid.

(**Compound 401**: N-(2',6'-dimethylbiphenyl-3-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide)



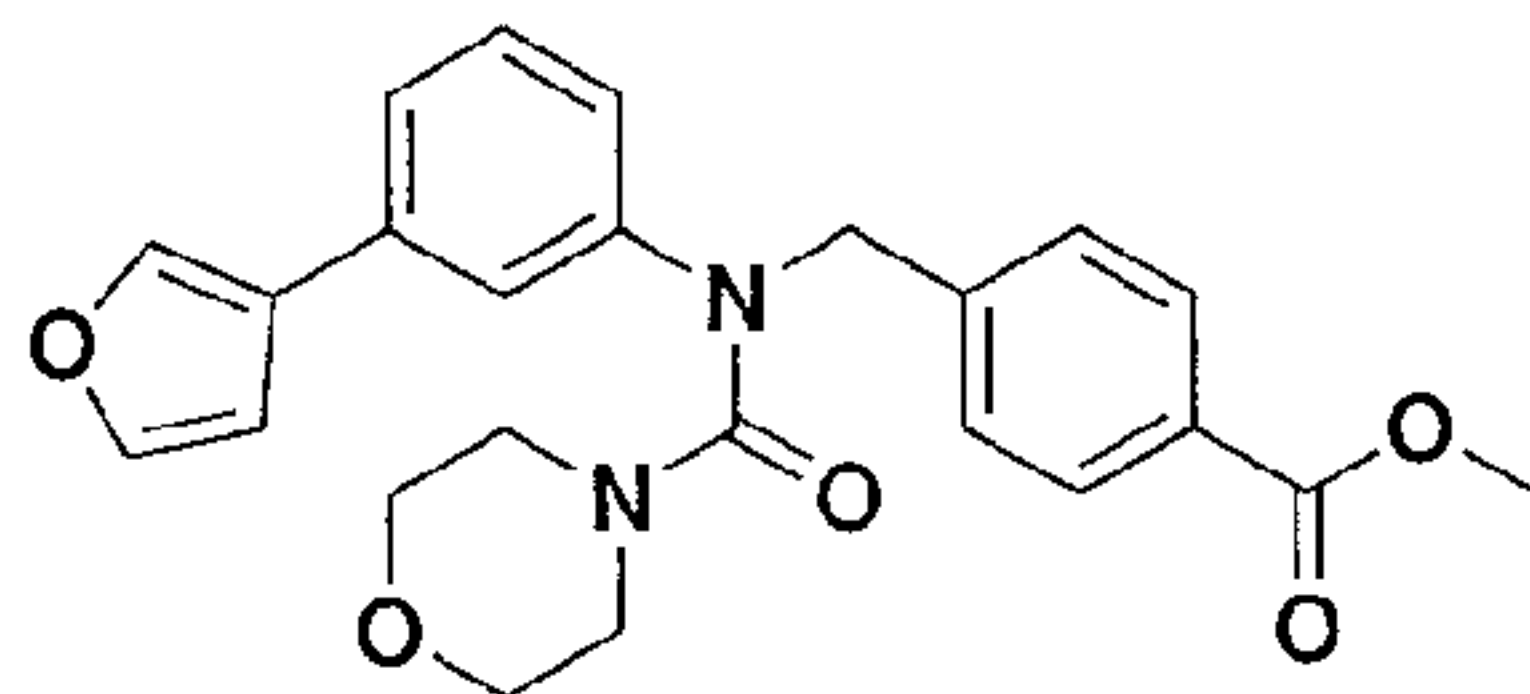
Compound of **Formula 2-2** (methyl 4-((N-(2',6'-
 15 dimethylbiphenyl-3-yl)morpholine-4-carboxamido)methyl)benzoate; 0.205 g, 0.447 mmol) was dissolved in methanol (10 mL), and hydroxylamine (50.0 wt% aqueous solution; 2.74 mL, 44.7 mmol) and potassium hydroxide (0.251 g, 4.47 mmol) were added sequentially and then stirred
 20 at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 1 mL, and then saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered,
 25 washed with water, and then vacuum dried to give the desired

Compound 401 (0.195 g, 95%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.61 (d, 2 H, *J* = 8.2 Hz),
7.38 (t, 1 H, *J* = 7.8 Hz), 7.33 (d, 2 H, *J* = 8.3 Hz), 7.16 -
7.11 (m, 2 H), 7.06 (d, 2 H, *J* = 7.4 Hz), 6.81 (d, 1 H, *J* =
5 7.6 Hz), 6.77 (m, 1 H), 4.86 (s, 2 H), 3.40 - 3.37 (m, 4 H),
3.17 - 3.14 (m, 4 H), 1.83 (s, 6 H). **MS** (ESI) *m/z* 460 (M⁺ +
H).

Example 65: Synthesis of Compound 402

10 **(Formula 2-2: methyl 4-((N-(3-(furan-3-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)**

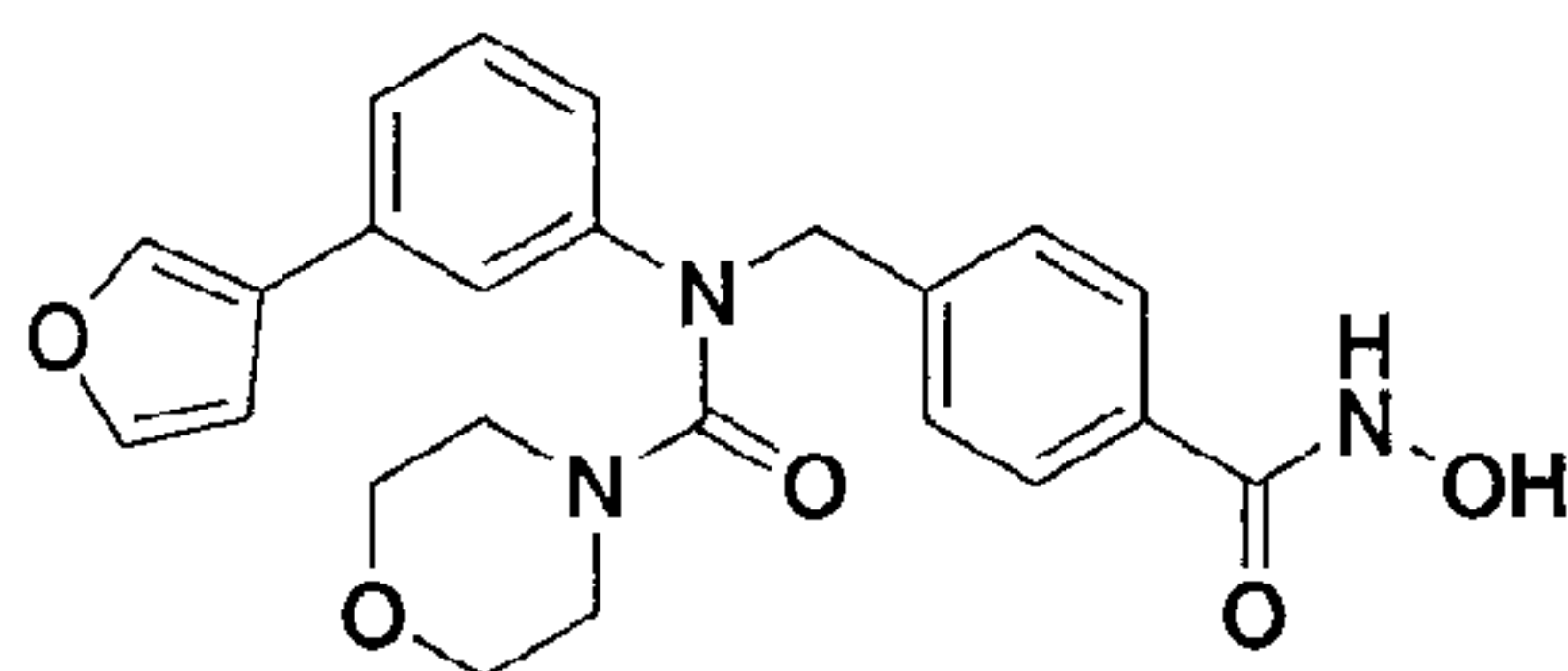


15

Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), furan-3-ylboronic acid (0.062 g, 0.554 mmol), and Pd(dppf)Cl₂ (0.038 g, 0.046 mmol) were dissolved in 1,4-dioxane (3 mL), and potassium carbonate (0.128 g, 0.923 mmol)
20 dissolved in water (1 mL) was added to the reaction solution and stirred at 100 °C for 4 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution and
25 concentrated under reduced pressure, and then the residue was

purified and concentrated by column chromatography (silica; ethyl acetate/hexane=50%) to give the desired compound of **Formula 2-2** (0.113 g, 58%) in the form of a brown solid.

(**Compound 402**: N-(3-(furan-3-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide)



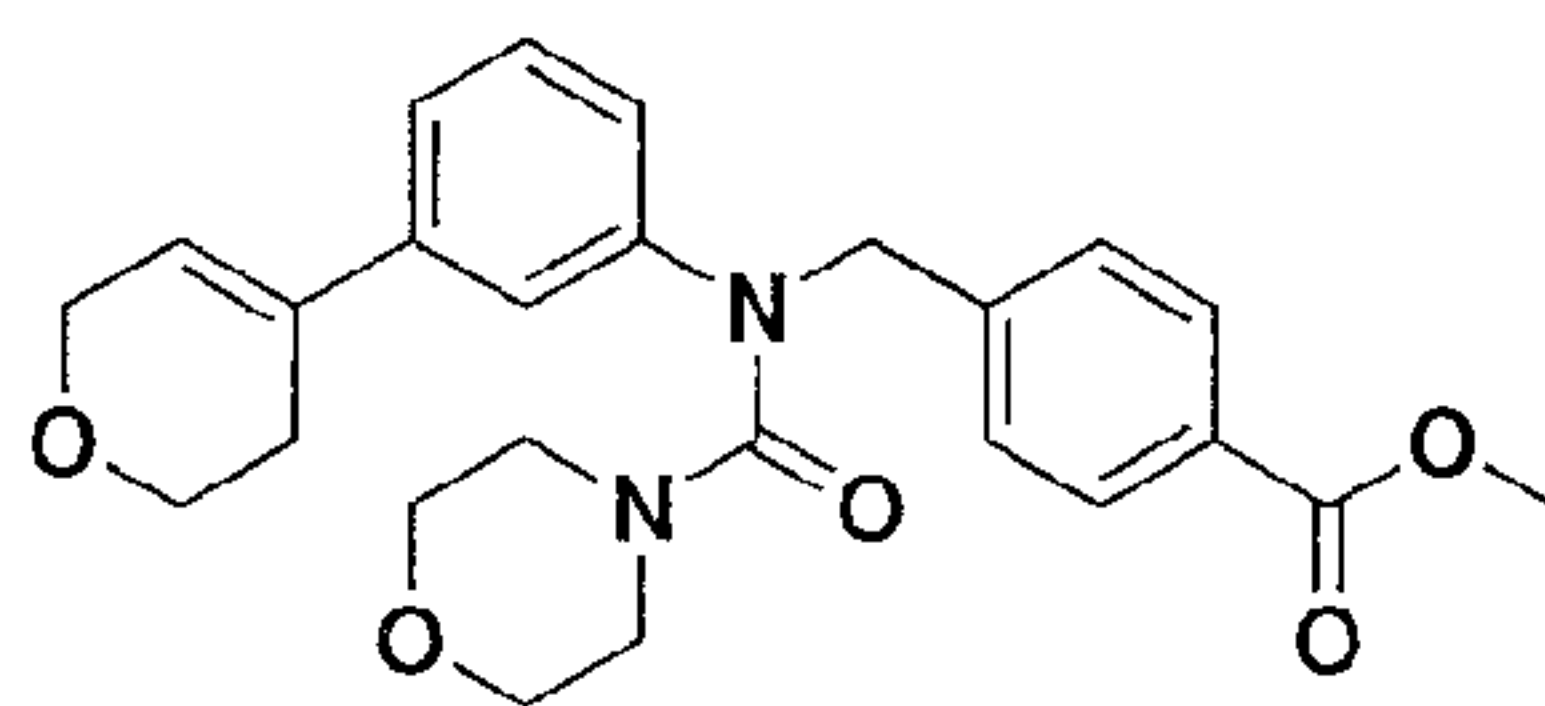
Compound of **Formula 2-2** (methyl 4-((N-(3-(furan-3-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.113 g, 0.269 mmol) was dissolved in methanol (10 mL), and hydroxylamine (50.0 wt% aqueous solution; 1.64 mL, 26.9 mmol) and potassium hydroxide (0.151 g, 2.69 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 1 mL, and then saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 402** (0.060 g, 53%) in the form of a brown solid.

¹H NMR (400 MHz, DMSO-d₆) δ 8.20 (s, 1 H), 7.73 (s, 1 H), 7.63 (d, 2 H, J = 8.1 Hz), 7.43 (s, 1 H), 7.38 (d, 2 H, J = 8.1 Hz), 7.30 - 7.28 (m, 2 H), 7.00 (m, 1 H), 6.95 (m, 1 H),

4.91 (s, 2 H), 3.39 - 3.36 (m, 4 H), 3.16 - 3.13 (m, 4 H). **MS**
(ESI) **m/z** 422 ($M^+ + H$).

Example 66: Synthesis of Compound 403

5 **(Formula 2-2: methyl 4-((N-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)**

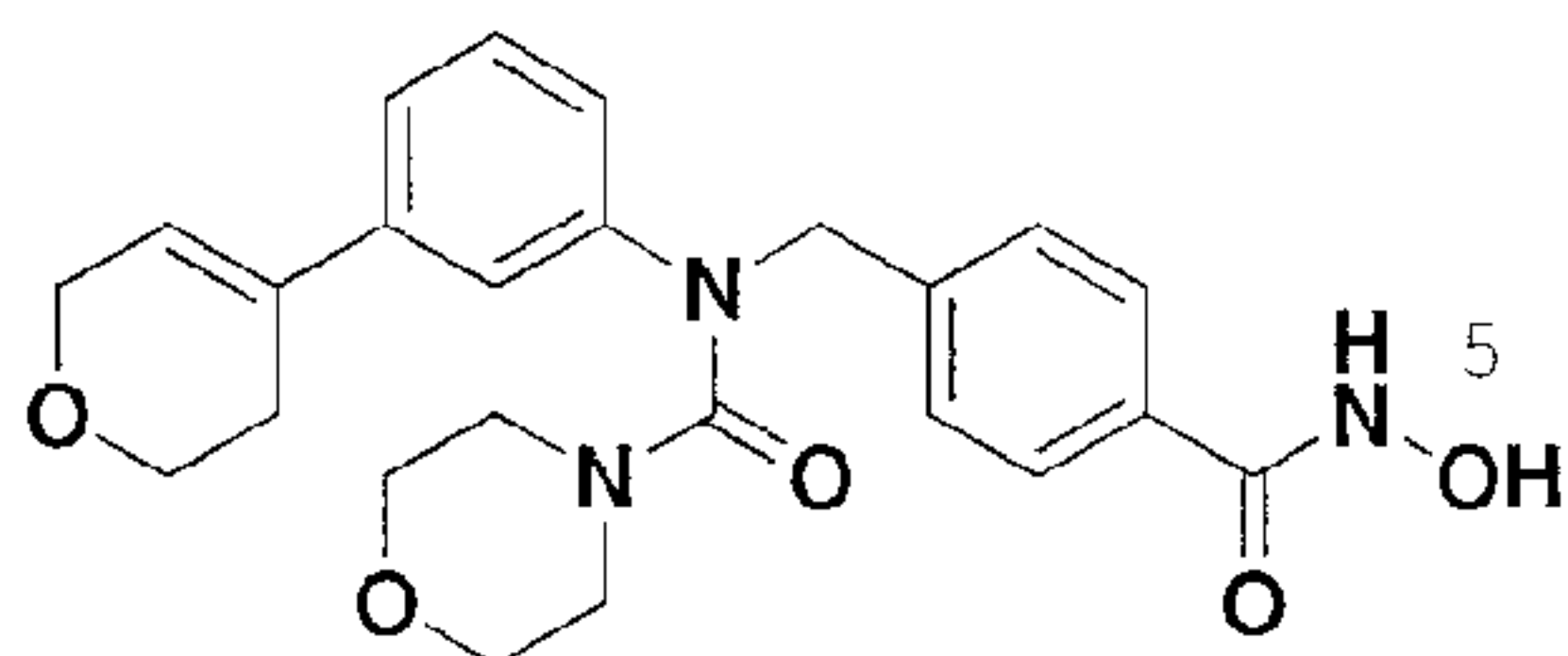


10

Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.400 g, 0.923 mmol), 1,2,3,6-tetrahydropyran-4-boronic acid pinacol ester (0.233 g, 1.11 mmol), and Pd(dppf)Cl₂ (0.030 g, 0.046
15 mmol) were dissolved in 1,4-dioxane (4 mL), and cesium carbonate (0.897 g, 2.77 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 140 °C for 15 minutes by using microwave reactor. After completion of the reaction, the organic layer was extracted with ethyl acetate
20 and saturated sodium hydrogen carbonate aqueous solution. Then, the organic layer dehydrated with anhydrous magnesium sulfate and filtered. It was concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=50%)
25 to give the desired compound of **Formula 2-2** (0.132 g, 33%) in

the form of a brown solid.

(**Compound 403**: N-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)-
N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide)



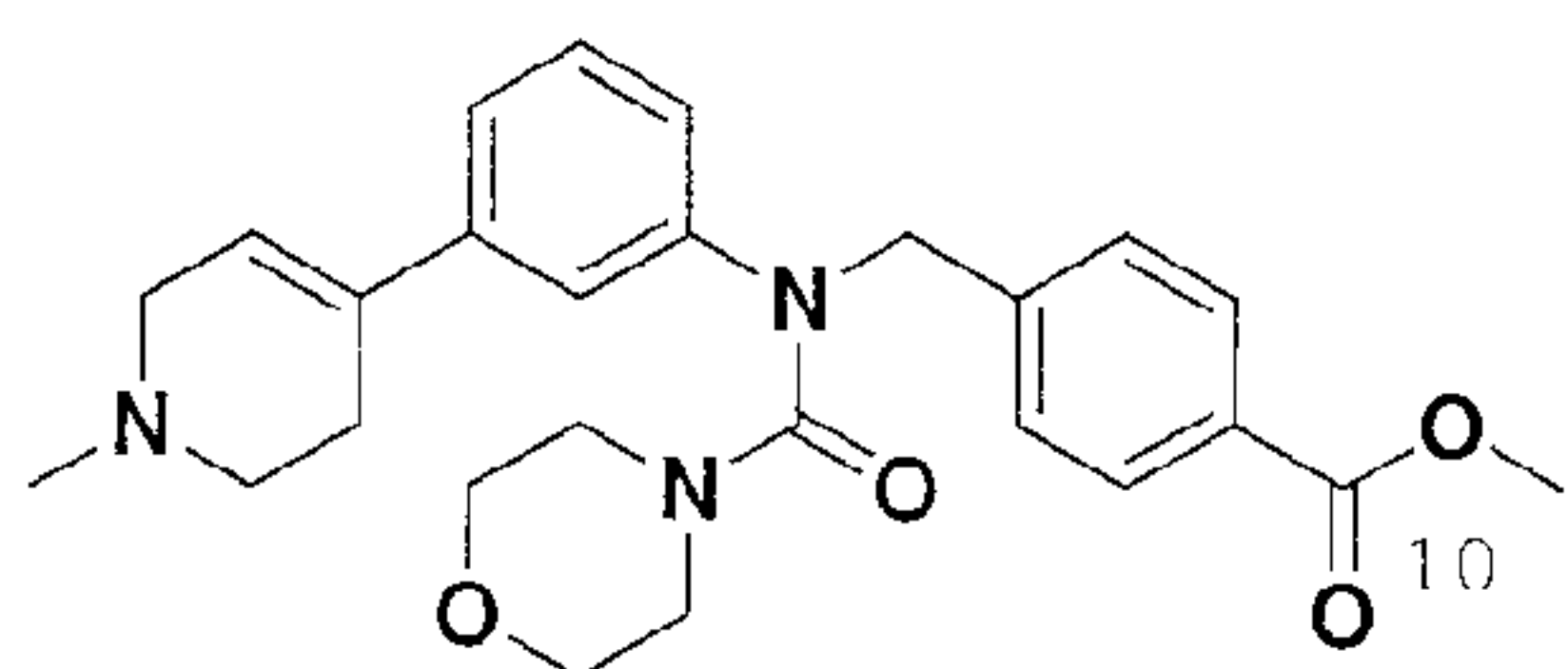
Compound of **Formula 2-2** (methyl 4-((N-(3-(3,6-dihydro-
2H-pyran-4-yl)phenyl)morpholine-4-
10 carboxamido)methyl)benzoate; 0.050 g, 0.115 mmol) was
dissolved in methanol (5 mL), and hydroxylamine (50.0 wt%
aqueous solution; 1.40 mL, 22.9 mmol) and potassium hydroxide
(0.064 g, 1.15 mmol) were added sequentially and then stirred
at room temperature for 30 minutes. After completion of the
15 reaction, the reaction solution was concentrated under
reduced pressure until its volume became about 1 mL, and then
saturated ammonium chloride aqueous solution (1-2 mL) was
added and stirred. Then, the solid product was filtered,
washed with water, and then vacuum dried to give the desired
20 **Compound 403** (0.030 g, 60%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.12 (s, 1 H), 8.97 (s, 1 H),
7.63 (d, 2 H, J = 8.3 Hz), 7.36 (d, 2 H, J = 8.3 Hz), 7.27 (t,
1 H, J = 7.9 Hz), 7.18 (s, 1 H), 7.14 (d, 1 H, J = 7.6 Hz),
7.03 (d, 1 H, J = 7.8 Hz), 6.23 (m, 1H), 4.88 (s, 2 H), 4.19
25 (d, 2 H, J = 2.6 Hz), 3.78 (t, 2 H, J = 5.5 Hz), 3.39 - 3.36

(m, 4 H), 3.14 – 3.11 (m, 4 H), 2.38 – 2.36 (m, 2 H). **MS**
(ESI) **m/z** 438 ($M^+ + H$).

Example 67: Synthesis of Compound 404

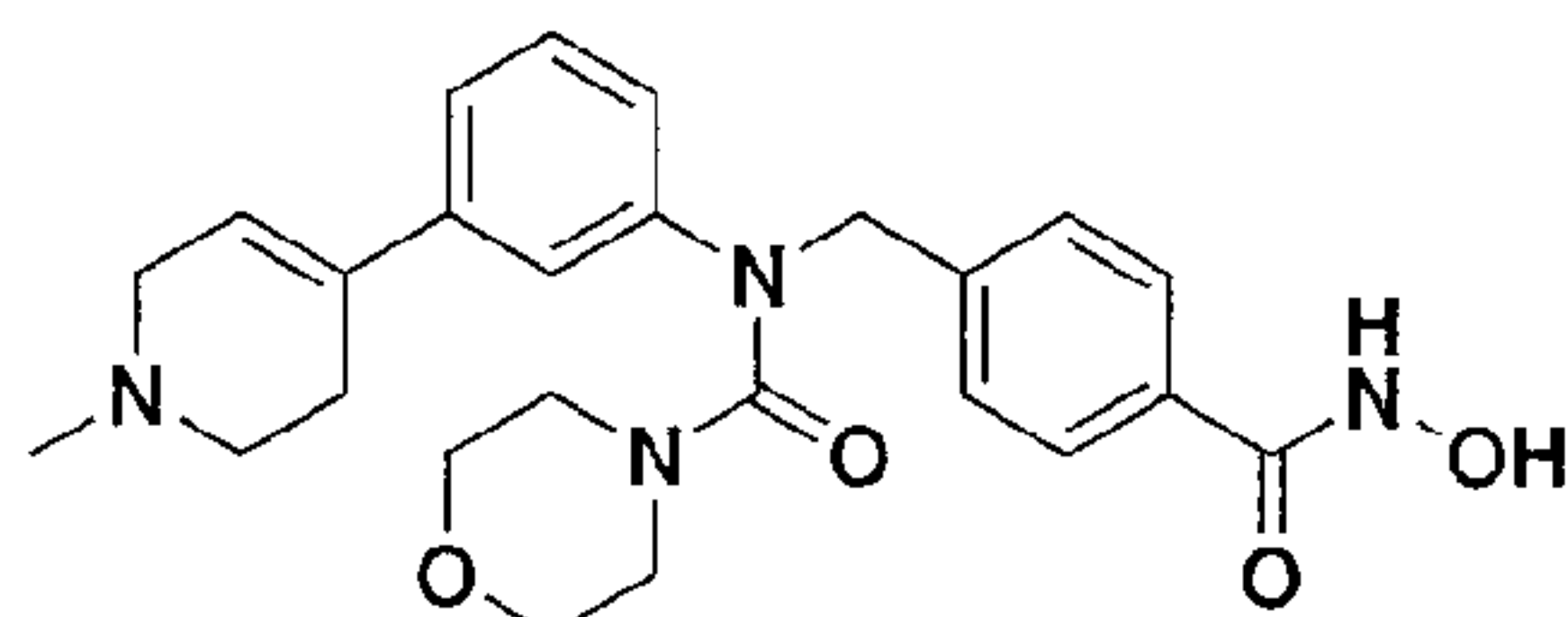
5 **(Formula 2-2: methyl 4-((N-(3-(1-methyl-1,2,3,6-tetrahydropyridn-4-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)**



Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.400 g, 0.923 mmol), 1-methyl-1,2,3,6-tetrahydropyridine-4-boronic
15 acid pinacol ester (0.247 g, 1.11 mmol), and Pd(dppf)Cl₂ (0.030 g, 0.046 mmol) were dissolved in 1,4-dioxane (4 mL), and cesium carbonate (0.897 g, 2.77 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 140 °C for 15 minutes by using microwave reactor. After
20 completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution. Then, the organic layer dehydrated with anhydrous magnesium sulfate and filtered. It was concentrated under reduced pressure, and then the residue was purified and
25 concentrated by column chromatography (silica;

methanol/dichloromethane-10%) to give the desired compound of **Formula 2-2** (0.193 g, 47%) in the form of a brown solid.

(**Compound 404**: N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-carboxamide)

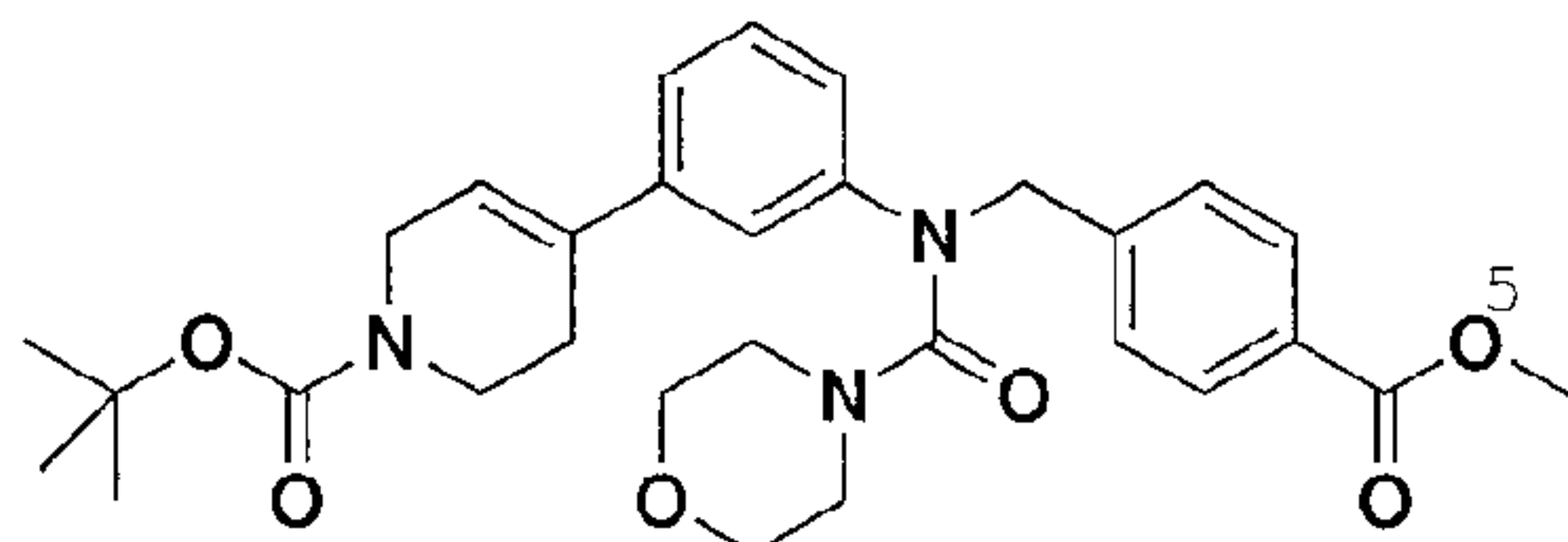


Compound of **Formula 2-2** (methyl 4-((N-(3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.050 g, 0.111 mmol) was dissolved in methanol (5 mL), and hydroxylamine (50.0 wt% aqueous solution; 1.36 mL, 22.2 mmol) and potassium hydroxide (0.062 g, 1.11 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 1 mL, and then saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 404** (0.015 g, 30%) in the form of a brown solid.

MS (ESI) m/z 451 ($M^+ + H$).

Example 68: Synthesis of Compound 405

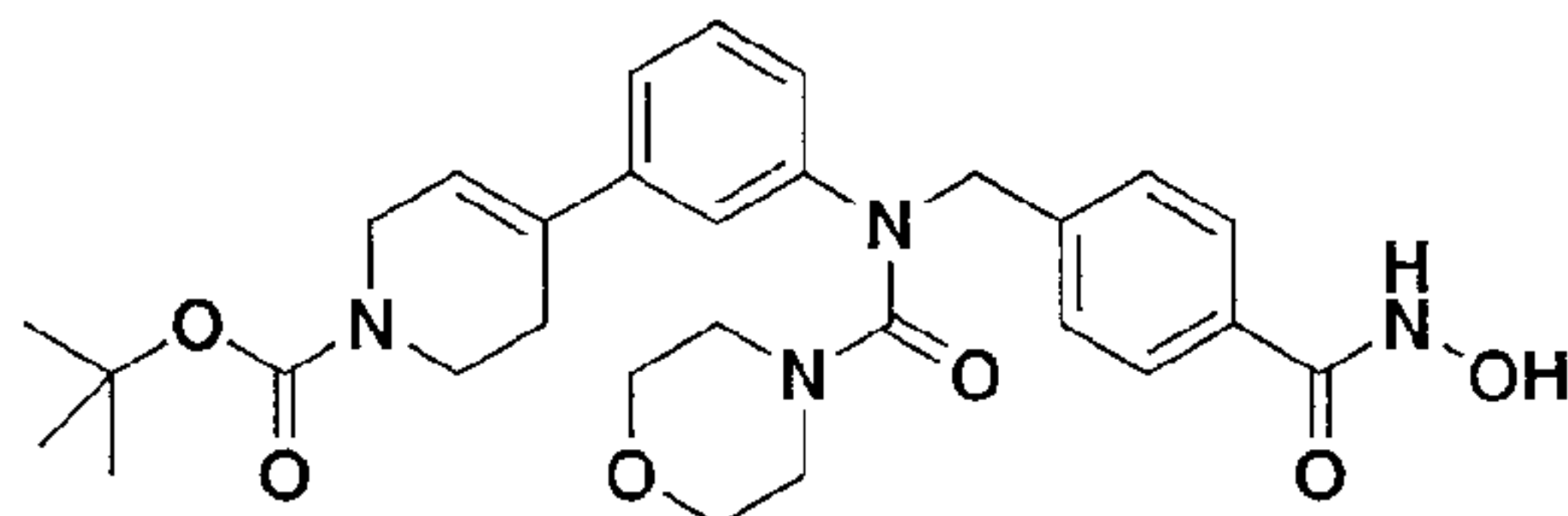
(**Formula 2-2**: tert-butyl 4-(3-(N-(4-(methoxycarbonyl)benzyl)morpholine-4-carboxamido)phenyl)-5,6-dihydropyridin-1(2H)-carboxylate)



Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.800 g, 1.85 mmol), N-Boc-1,2,3,6-tetrahydropyridin-4-boronic acid pinacol ester (0.685 g, 2.22 mmol), and Pd(dppf)Cl₂ (0.060 g, 0.092 mmol) were dissolved in 1,4-dioxane (8 mL), and cesium carbonate (1.79 g, 5.54 mmol) dissolved in water (2 mL) was added to the reaction solution and stirred at 140 °C for 15 minutes by using microwave reactor. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution. Then, the organic layer dehydrated with anhydrous magnesium sulfate and filtered. It was concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=50%) to give the desired compound of **Formula 2-2** (0.832 g, 84%) in the form of a brown solid.

(**Compound 405**: tert-butyl 4-(3-(N-(4-(hydroxycarbonyl)benzyl)morpholine-4-carboxamido)phenyl)-

5,6-dihydropyridine-1(2H)-carboxylate)



5

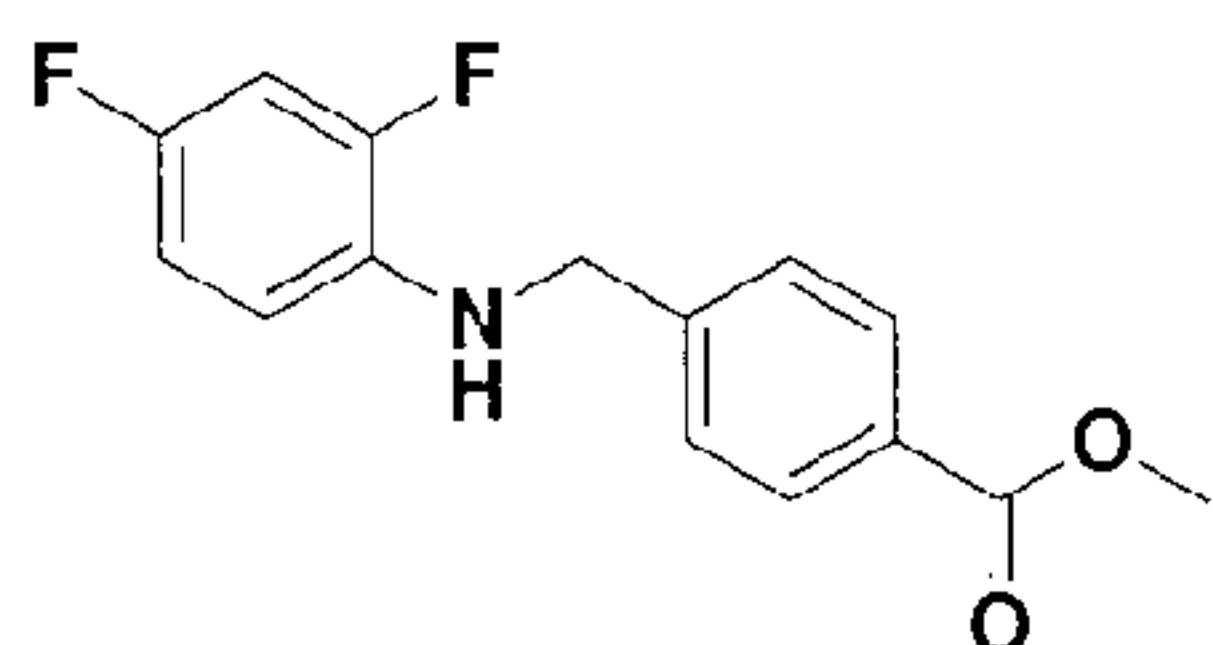
Compound of **Formula 2-2** (tert-butyl 4-(3-(N-(4-(methoxycarbonyl)benzyl)morpholine-4-carboxamido)phenyl)-5,6-dihydropyridin-1(2H)-carboxylate; 0.050 g, 0.093 mmol) was dissolved in methanol (5 mL), and hydroxylamine (50.0 wt% aqueous solution; 1.14 mL, 18.7 mmol) and potassium hydroxide (0.052 g, 0.933 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 1 mL, and then saturated ammonium chloride aqueous solution (1-2 mL) was added and stirred. Then, the solid product was filtered, washed with water, and then vacuum dried to give the desired **Compound 405** (0.030 g, 60%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.63 (d, 2 H, J = 8.3 Hz), 7.35 (d, 2 H, J = 8.2 Hz), 7.26 (t, 1 H, J = 7.9 Hz), 7.18 (s, 1 H), 7.12 (d, 1 H, J = 8.2 Hz), 7.02 (d, 1 H, J = 8.0 Hz), 6.17 (m, 1 H), 4.87 (s, 2 H), 3.97 (brs, 2 H), 3.50 (t, 2 H, J = 5.7 Hz), 3.38 (t, 4 H, J = 4.6 Hz), 3.12 (t, 4 H, J = 4.5 Hz), 2.40 (brs, 2 H), 1.41 (s, 9 H). **MS** (ESI) m/z 537.

25

Example 69: Synthesis of Compound 413

(**Formula 1-2**: methyl 4-((2,4-difluorophenylamino)methyl)benzoate)



Compound of **Formula 1-1** (2,4-

difluorobenzenamine; 3.0 g, 23.2 mmol) and methyl 4-

formylbenzoate (3.81 g, 23.2 mmol) were dissolved in methanol

(500 mL) and stirred at room temperature for 2 hours. Then,

acetic acid (1.33 mL, 23.2 mmol) and sodium cyanoborohydride

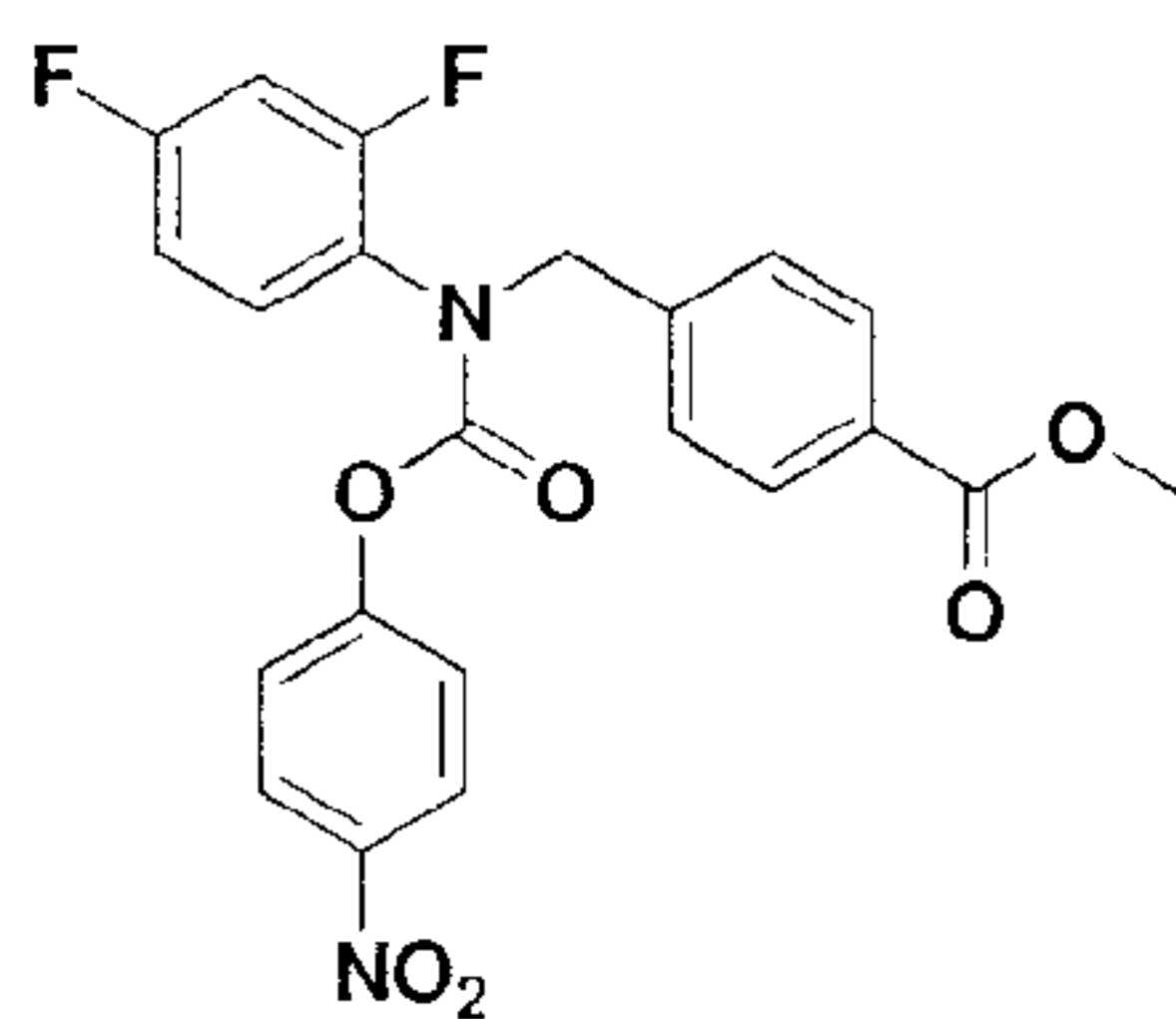
(1.46 g, 23.2 mmol) were added and stirred for 1 day. The

methanol was partially removed by air-drying to precipitate a

solid, and the resulting solid was filtered and dried to give

the desired compound of **Formula 1-2** (2.9 g, 45%) in the form of a white solid.

(**Formula 1-3**: methyl 4-(((2,4-difluorophenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate)

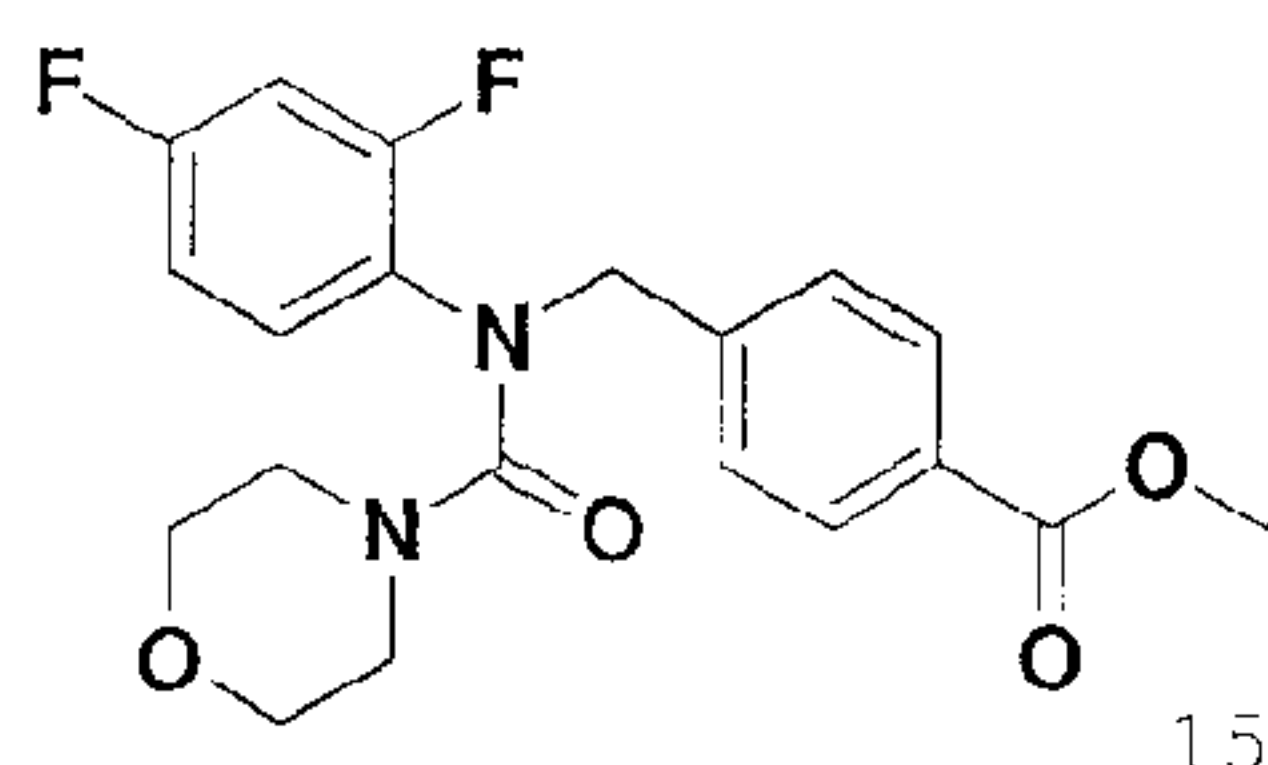


Compound of **Formula 1-2**

(methyl 4-((2,4-difluorophenylamido)methyl)benzoate; 2 g,

7.21 mmol) and 4-nitrophenyl chloroformate (1.45 g, 7.21 mmol) were dissolved in dichloromethane (50 mL) and stirred at room temperature for 3 days. Then, water was added to extract the organic layer. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was dried to give the desired compound of **Formula 1-3** (2.5 g, 78%) in the form of a yellow oil.

(**Formula 1-4**: methyl 4-((N-(2,4-difluorophenyl)morpholine-4-carboxamido)methyl)benzoate)

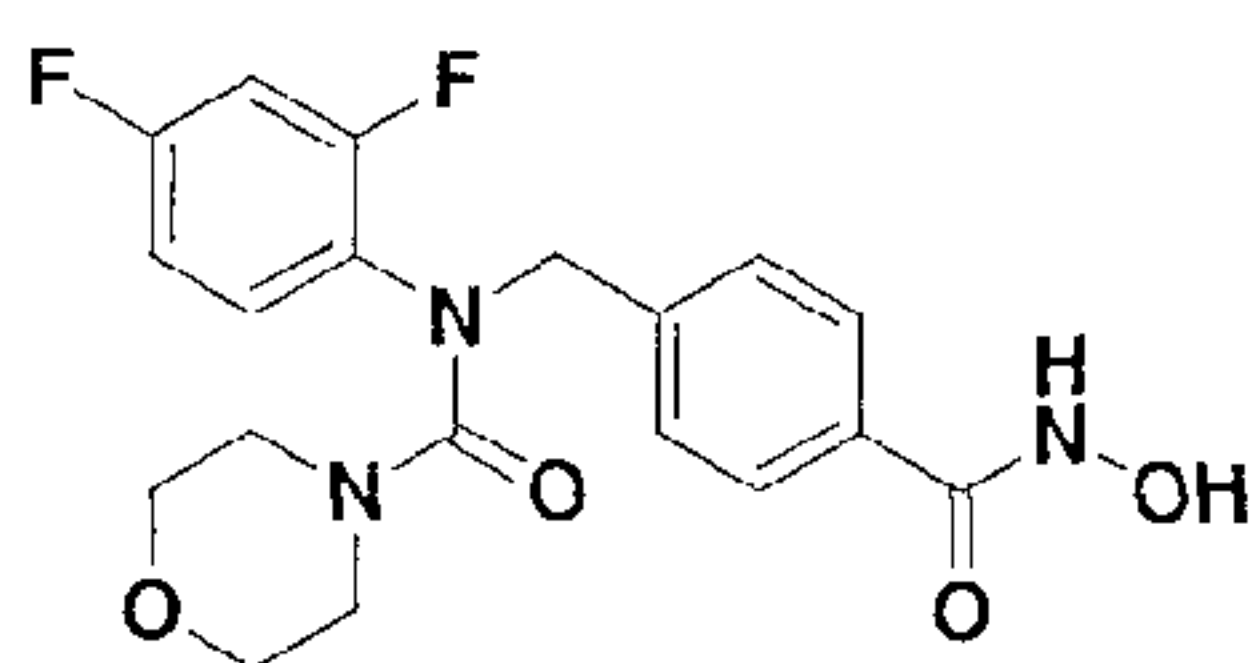


Compound of **Formula 1-3**

(methyl 4-(((2,4-difluorophenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.50 g, 1.13 mmol) and morpholine (0.098 mL, 1.13 mmol) were dissolved in dimethylformamide (10 mL), and the mixture was heated and stirred at 60 °C for 2 days. Then, the dimethylformamide was removed under reduced pressure, water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced

pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 1-4** (0.44 g, 98%) in the form of a colorless oil.

5 **(Compound 413: N-(2,4-difluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine -4-carboxamide)**



10

Compound of **Formula 1-4**

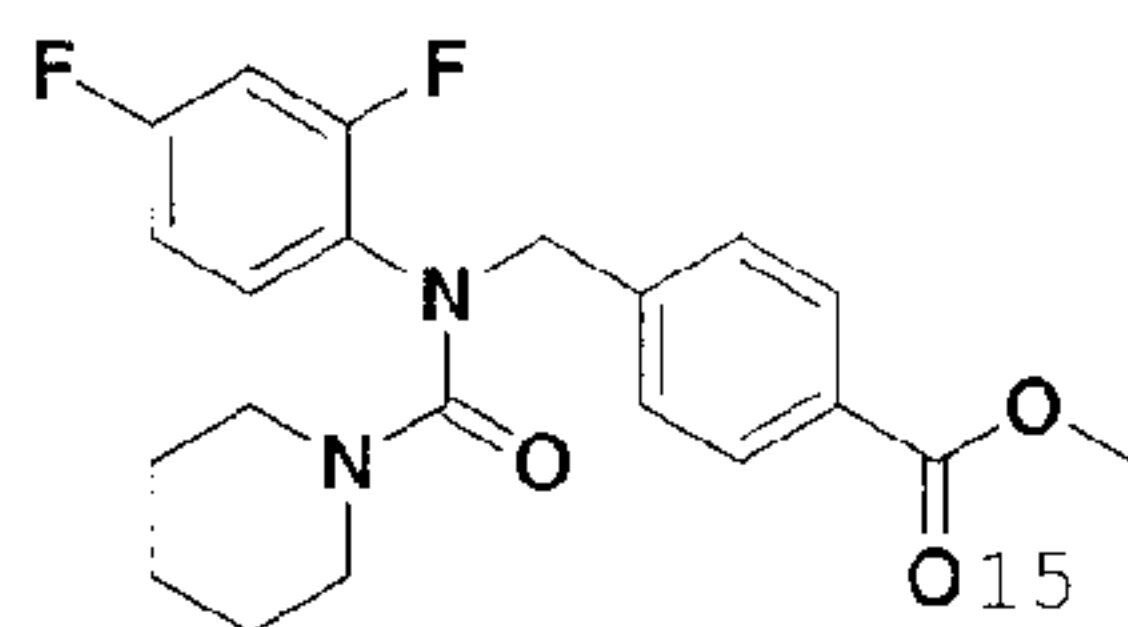
(methyl 4-((N-(2,4-difluorophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.10 g, 0.256 mmol) was dissolved in methanol (20 mL), and hydroxylamine hydrochloride (0.089 g, 1.28 mmol) and potassium hydroxide
 15 (0.144 g, 2.56 mmol) were added and stirred. Then, hydroxylamine (50 wt% aqueous solution; 0.329 mL, 5.12 mmol) was added dropwise and stirred at room temperature for 3 hours. After completion of the reaction, the methanol was removed under reduced pressure, water was poured into the
 20 reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. Then, the residue was dissolved in dichloromethane
 25 and hexane was added to precipitate a solid, and the

resulting solid was filtered and dried to give the desired
Compound 413 (0.076 g, 76%) in the form of a pale yellow
 solid.

¹H NMR (400 MHz, MeOD-d₃) δ 7.65 (d, 2 H, J = 8.3 Hz),
 5 7.41 (d, 2 H, J = 8.2 Hz), 7.27 - 7.25 (m, 1 H), 7.04 - 6.96
 (m, 2 H), 4.80 (s, 2 H), 3.46 - 3.43 (m, 4 H), 3.22 - 3.19 (m,
 4 H); **MS** (ESI) m/z 392.1 (M⁺ + H).

Example 70: Synthesis of Compound 414

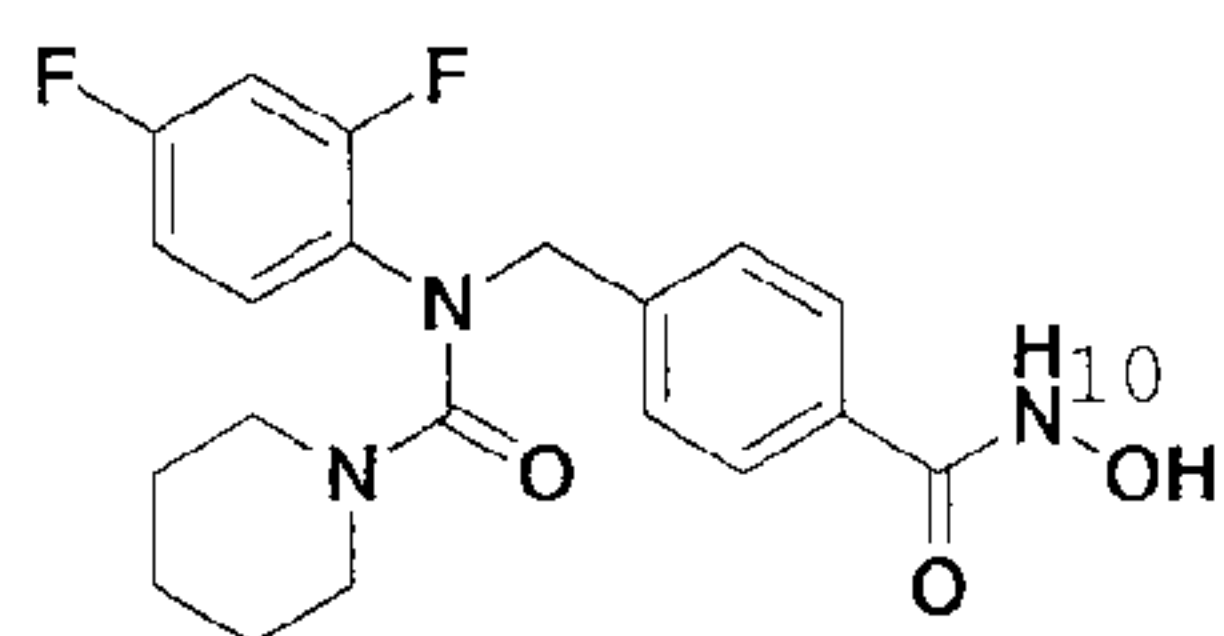
10 **Formula 1-4**: methyl 4-((N-(2,4-
 difluorophenyl)piperidine-1-carboxamido)methyl)benzoate)



Compound of **Formula 1-3** (methyl 4-
 ((2,4-difluorophenyl)((4-
 nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.50 g, 1.13
 mmol) and piperidine (0.112 mL, 1.13 mmol) were dissolved in
 20 dimethylformamide (10 mL), and the mixture was heated and
 stirred at 60 °C for 2 days. Then, the dimethylformamide was
 removed under reduced pressure, water was poured into the
 reaction mixture, and the organic layer was extracted with
 ethyl acetate. The organic layer was washed with saturated
 25 sodium chloride aqueous solution, dehydrated with anhydrous

magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=10%) to give the desired compound of **Formula 1-4** (0.46 g, 104.8%) in the form of a colorless oil.

(**Compound 414**: N-(2,4-difluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperidine-1-carboxamide)



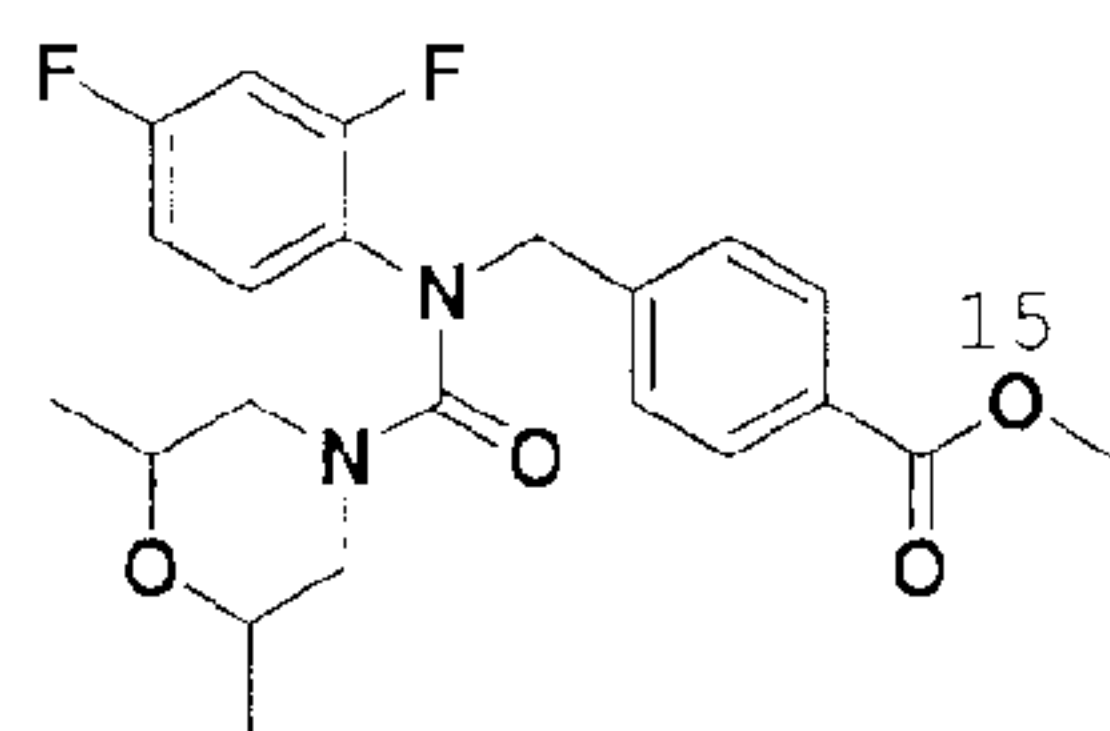
Compound of **Formula 1-4** (methyl 4-((N-(2,4-difluorophenyl)piperidine-1-carboxamido)methyl)benzoate; 0.15 g, 0.386 mmol) was dissolved in methanol (20 mL), and hydroxylamine hydrochloride (0.134 g, 1.93 mmol) and potassium hydroxide (0.217 g, 3.86 mmol) were added and stirred. Then, hydroxylamine (50 wt% aqueous solution; 0.496 mL, 7.72 mmol) was added dropwise and stirred at room temperature for 3 hours. After completion of the reaction, the methanol was removed under reduced pressure, water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced

pressure. Then, the residue was dissolved in dichloromethane and hexane was added to precipitate a solid, and the resulting solid was filtered and dried to give the desired **Compound 414** (0.118 g, 79%) in the form of a pale yellow solid.

^1H NMR (400 MHz, MeCD-d_3) δ 7.65 (d, 2 H, $J = 8.2$ Hz), 7.41 (d, 2 H, $J = 8.1$ Hz), 7.23 – 7.20 (m, 1 H), 7.05 – 6.94 (m, 2 H), 4.77 (s, 2 H), 3.21 – 3.18 (m, 4 H), 1.51 – 1.49 (m, 2 H), 1.32 – 1.31 (m, 4 H); **MS** (ESI) m/z 390.1 ($\text{M}^+ + \text{H}$).

Example 71: Synthesis of Compound 415

Formula 1-4: methyl 4-((N-(2,4-difluorophenyl)2,6-dimethylmorpholine-4-carboxamido)methyl)benzoate)



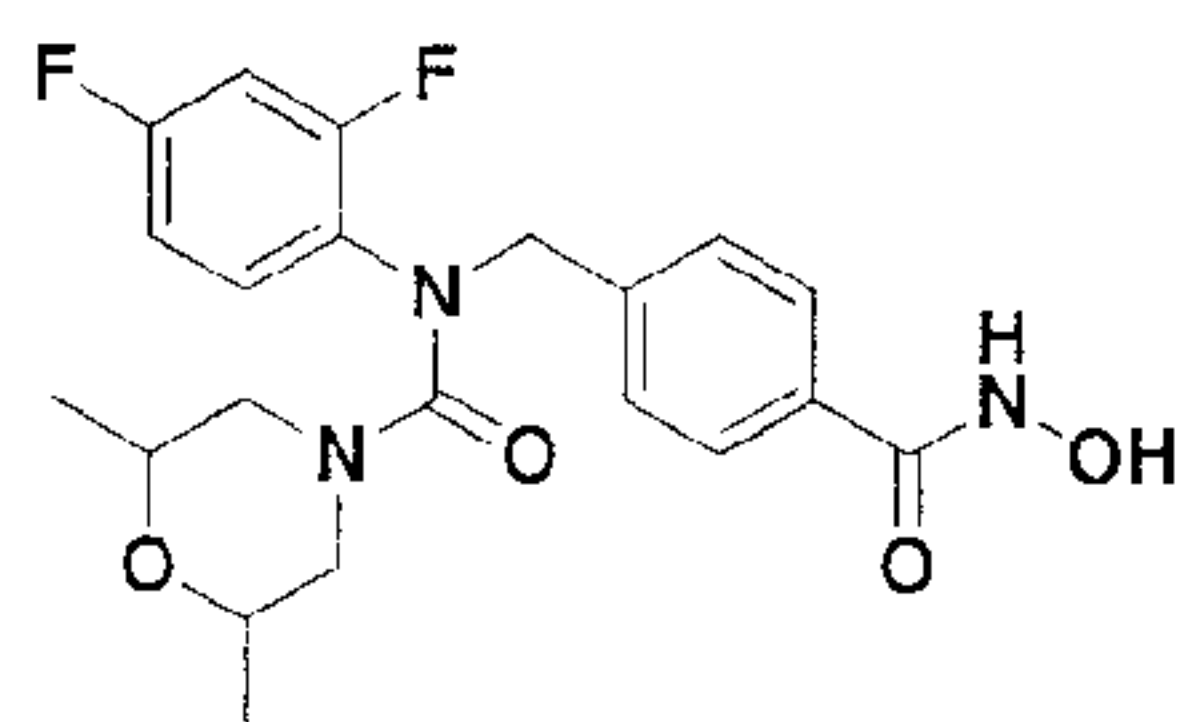
Compound of **Formula 1-3** (methyl 4-((2,4-difluorophenyl)((4-

nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.50 g, 1.13 mmol) and 2,6-dimethylmorpholine (0.138 mL, 1.13 mmol) were dissolved in dimethylformamide (10 mL), and the mixture was heated and stirred at 60 °C for 2 days. Then, the dimethylformamide was removed under reduced pressure, water was poured into the reaction mixture, and the organic layer

was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was

5 purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 1-4** (0.40 g, 85%) in the form of a colorless oil.

(**Compound 415**: N-(2,4-difluorophenyl)-N-(4
(hydroxycarbamoyl)benzyl)-2,6-dimethylmorpholine-4-
10 carboxamide)



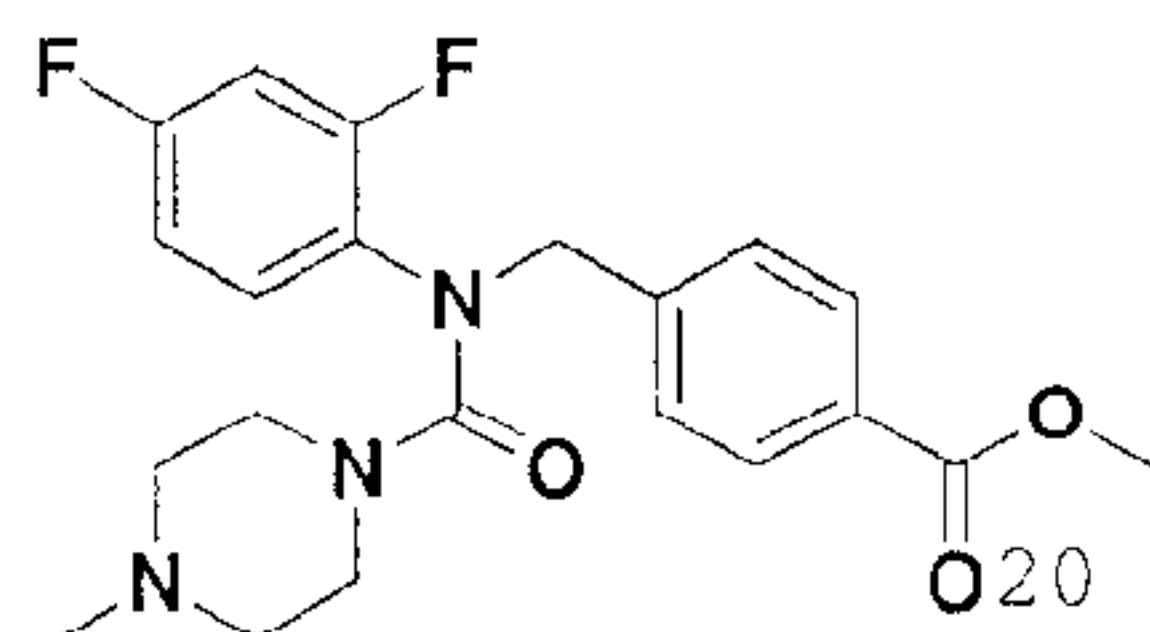
15 Compound of **Formula 1-4** (methyl 4-((N-(2,4-difluorophenyl)2,6-dimethylmorpholine-4-carboxamido)methyl)benzoate; 0.20 g, 0.478 mmol) was dissolved in methanol (20 mL), and hydroxylamine hydrochloride (0.166 g, 2.39 mmol) and potassium hydroxide
20 (0.268 g, 4.78 mmol) were added and stirred. Then, hydroxylamine (50 wt% aqueous solution; 0.614 mL, 9.56 mmol) was added dropwise and stirred at room temperature for 3 hours. After completion of the reaction, the methanol was removed under reduced pressure, water was poured into the
25 reaction mixture, and the organic layer was extracted with

ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. Then, the residue was dissolved in dichloromethane and hexane was added to precipitate a solid, and the resulting solid was filtered and dried to give the desired **Compound 415** (0.086 g, 43%) in the form of a pale yellow solid.

¹H NMR (400 MHz, MeOD-d₃) δ 7.65 (d, 2 H, *J* = 8.0 Hz), 7.41 (d, 2 H, *J* = 8.0 Hz), 7.27 – 7.26 (m, 1 H), 7.04 – 6.94 (m, 2 H), 4.79 (s, 2 H), 3.58 (d, 2 H, *J* = 12.9 Hz), 2.38 – 2.32 (m, 2 H), 1.01 (d, 6 H, *J* = 6.2 Hz); **MS** (ESI) *m/z* 420.1 (*M*⁺ + H).

Example 72: Synthesis of Compound 416

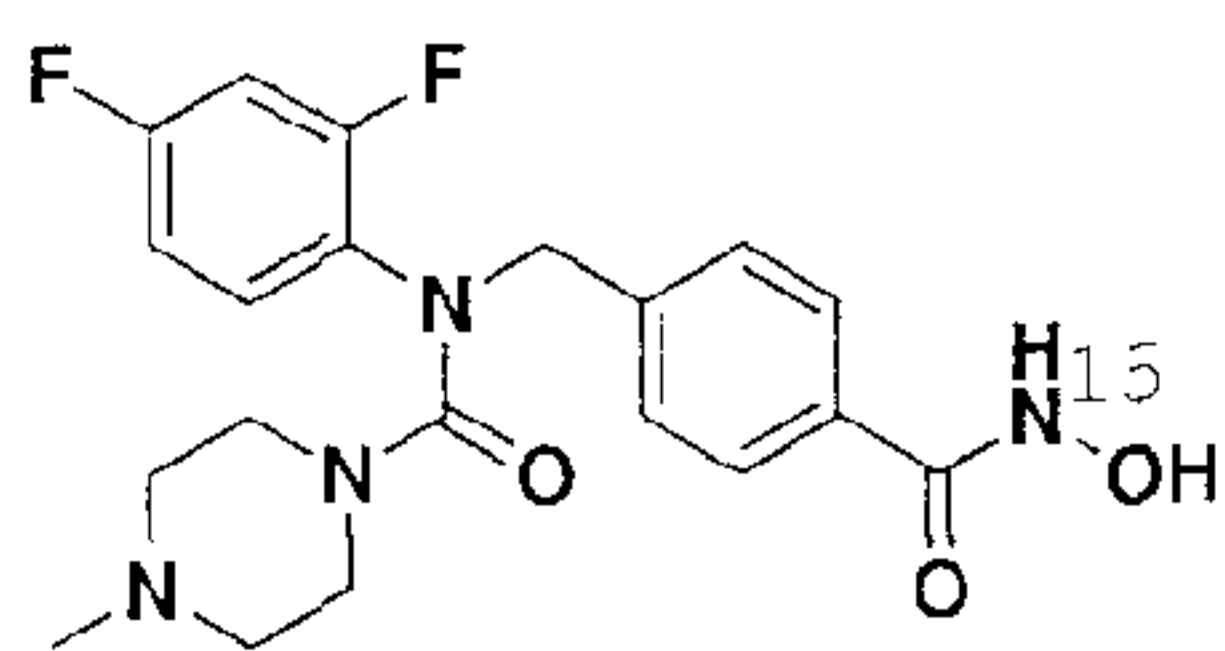
Formula 1-4: methyl 4-((N-(2,4-difluorophenyl)-4-methylpiperazine-1-carboxamido)methyl)benzoate)



Compound of **Formula 1-3** (methyl 4-((2,4-difluorophenyl)((4-nitrophenoxy)carbonyl)amino)methyl)benzoate; 0.50 g, 1.13 mmol) and 1-methylpiperazine (0.126 mL, 1.13 mmol) were dissolved in dimethylformamide (10 mL), and the mixture was

heated and stirred at 60 °C for 2 days. Then, the dimethylformamide was removed under reduced pressure, water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified and concentrated by column chromatography (silica; methanol/dichloromethane=5%) to give the desired compound of **Formula 1-4** (0.46 g, 101%) in the form of a yellow oil.

(**Compound 416**: N-(2,4-difluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide)



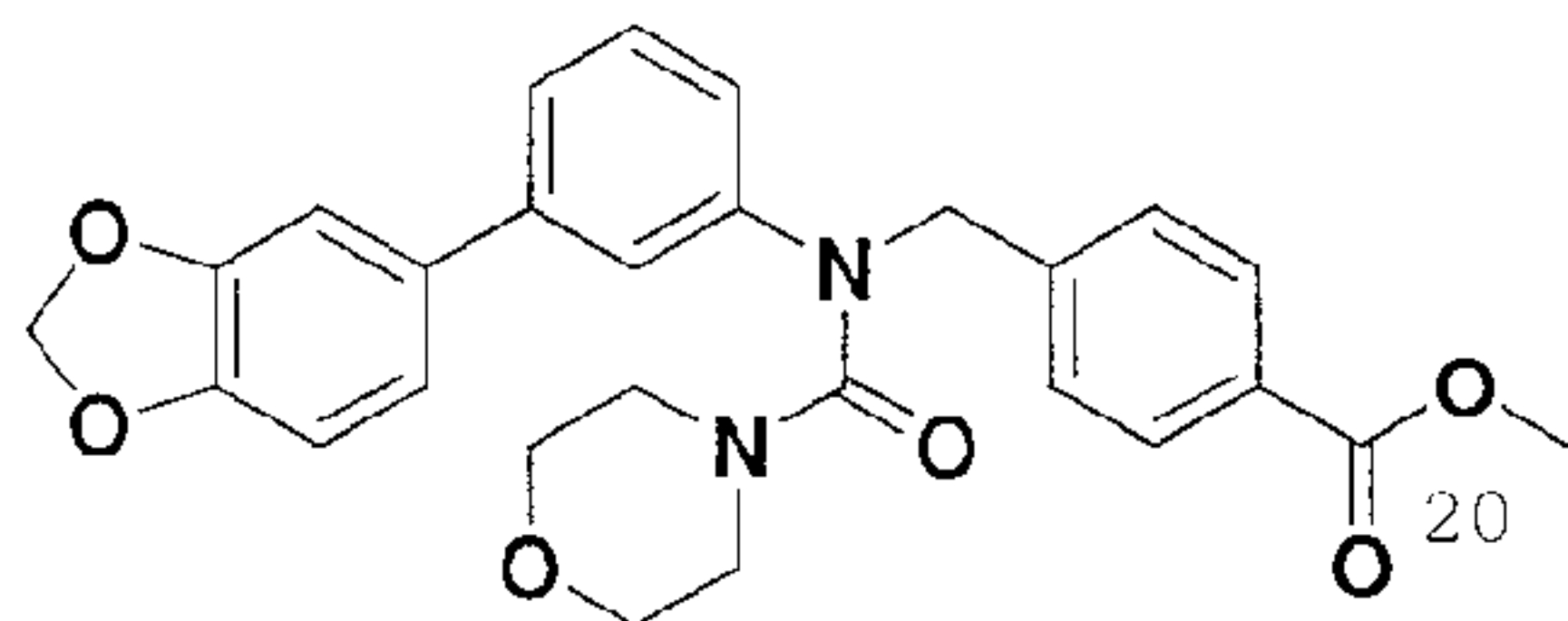
Compound of **Formula 1-4** (methyl 4-((N-(2,4-difluorophenyl)-4-methylpiperazine-1-carboxamido)methyl)benzoate; 0.22 g, 0.545 mmol) was dissolved in methanol (20 mL), and hydroxylamine hydrochloride (0.189 g, 2.73 mmol) and potassium hydroxide (0.306 g, 5.45 mmol) were added and stirred. Then, hydroxylamine (50 wt% aqueous solution; 0.701 mL, 10.9 mmol) was added dropwise and stirred at room temperature for 3 hours. After completion of the reaction, the methanol was

removed under reduced pressure, water was poured into the reaction mixture, and the organic layer was extracted with ethyl acetate. The organic layer was washed with saturated sodium chloride aqueous solution, dehydrated with anhydrous
 5 magnesium sulfate, and then concentrated under reduced pressure. Then, the residue was dissolved in dichloromethane and hexane was added to precipitate a solid, and the resulting solid was filtered and dried to give the desired **Compound 416** (0.154 g, 70%) in the form of a yellow solid.

10 ^1H NMR (400 MHz, $\text{MeCD}-\text{d}_3$) δ 7.65 (d, 2 H, $J = 8.2$ Hz), 7.40 (d, 2 H, $J = 8.2$ Hz), 7.26 – 7.25 (m, 1 H), 7.04 – 6.96 (m, 2 H), 4.79 (s, 2 H), 3.25 – 3.23 (m, 4 H), 2.24 – 2.21 (m, 7 H); **MS** (ESI) m/z 405.1 ($\text{M}^+ + \text{H}$).

15 **Example 73: Synthesis of Compound 418**

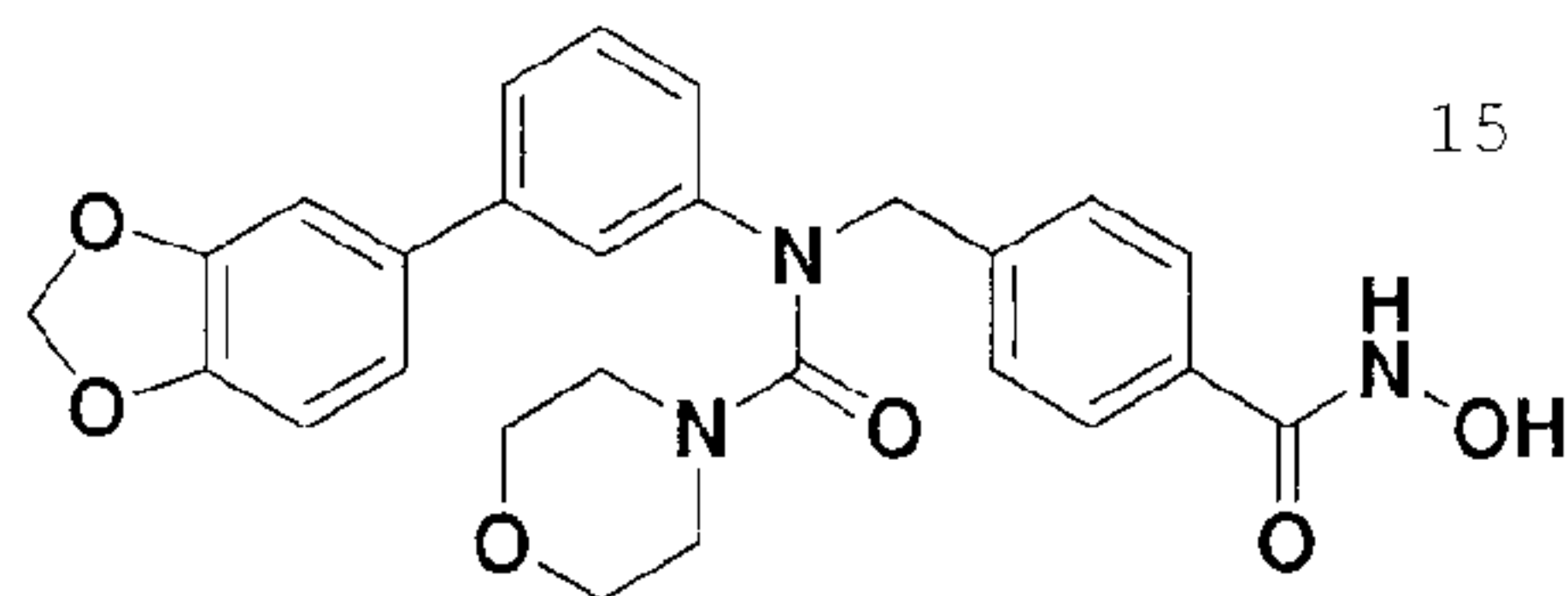
(**Formula 2-2**: methyl 4-((N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)



Compound of **Formula 2-1** (methyl 4-((N-(3-bromophenyl)morpholine-4-carboxamido)methyl)benzoate; 0.200 g, 0.462 mmol), benzo[d][1,3]dioxol-5-ylboronic acid (0.092 g, 0.554 mmol), and $\text{Pd}(\text{dppf})\text{Cl}_2$ (0.015 g, 0.023 mmol) were
 25

dissolved in 1,4-dioxane (4 mL), and cesium carbonate (0.448 g, 1.39 mmol) dissolved in water (1 mL) was added to the reaction solution and stirred at 140 °C for 15 minutes by using microwave reactor. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution. Then, the organic layer dehydrated with anhydrous magnesium sulfate and filtered. It was concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=30%) to give the desired compound of **Formula 2-2** (0.146 g, 67%) in the form of a light brown solid.

(**Compound 418**: N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbonyl)benzyl)morpholine-4-carboxamide)



Compound of **Formula 2-2** (methyl 4-((N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.146 g, 0.308 mmol) was dissolved in methanol (10 mL), and hydroxylamine (50.0 wt% aqueous solution; 1.88 mL, 30.8 mmol) and potassium hydroxide (0.173 g, 3.08 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the

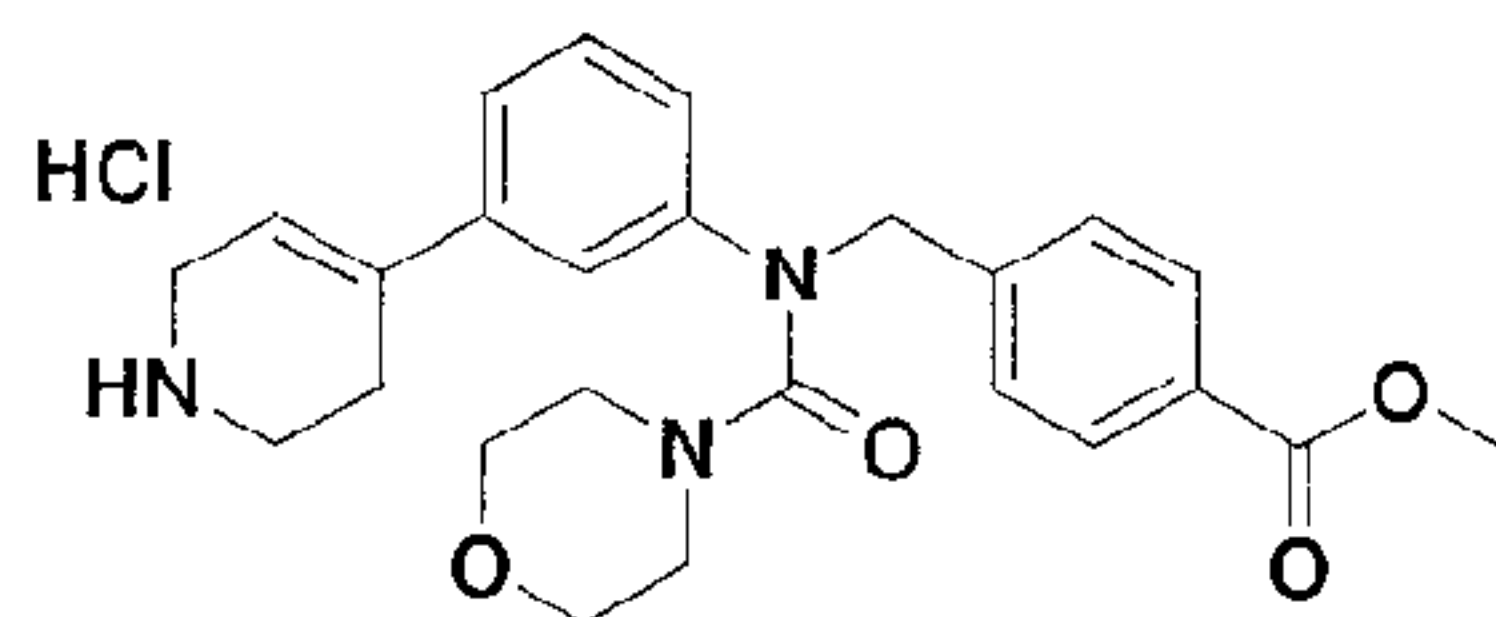
reaction, the reaction solution was concentrated under reduced pressure until its volume became about 2 mL, and then extracted with ethyl acetate and saturated ammonium chloride aqueous solution. Then, the organic layer was washed with water and dehydrated with anhydrous magnesium sulfate. It was filtered and concentrated under reduced pressure to give the desired **Compound 418** (0.121 g, 83%) in the form of a light brown solid.

¹H NMR (400 MHz, DMSO-d₆) δ 7.63 (d, 2 H, *J* = 8.2 Hz), 7.34 – 7.27 (m, 5 H), 7.21 (d, 1 H, *J* = 1.7 Hz), 7.09 (dd, 1 H, *J* = 8.1, 1.8 Hz), 7.05 (d, 1 H, *J* = 7.7 Hz), 6.97 (d, 1 H, *J* = 8.1 Hz), 6.05 (s, 2 H), 4.90 (s, 2 H), 3.39 (t, 4 H, *J* = 4.5 Hz), 3.16 (t, 4 H, *J* = 4.4 Hz). MS (ESI) *m/z* 476 (M⁺ + H).

Example 74: Synthesis of Compound 419

(Formula 4-2: methyl 4-((N-(3-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-

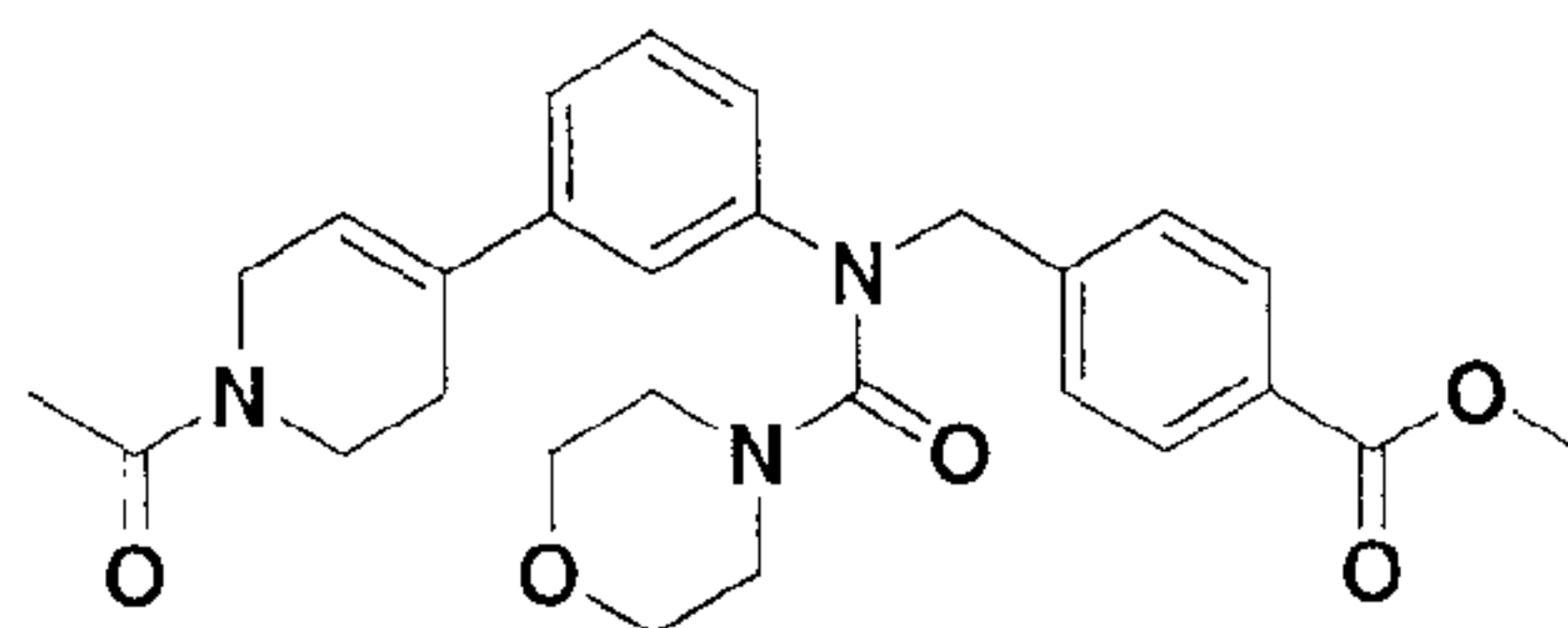
carboxamido)methyl)benzoate hydrochloride)



Compound of **Formula 4-1** (tert-butyl 4-(3-(N-(4-(methoxycarbonyl)benzyl)morpholine-4-carboxamido)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate; 0.510 g, 0.952 mmol) was

dissolved in 1,4-dioxane (5 mL), and then hydrogen chloride (4.0 M 1,4-dioxane solution; 4.76 mL, 19.0 mmol) was added and stirred at room temperature for 3 hours. After completion of the reaction, the organic layer was concentrated under reduced pressure, and the residue was recrystallized with dichloromethane and hexane to give the desired compound of **Formula 4-2** (0.440 g, 98%) in the form of a brown solid.

(**Formula 4-3**: methyl 4-((N-(3-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)

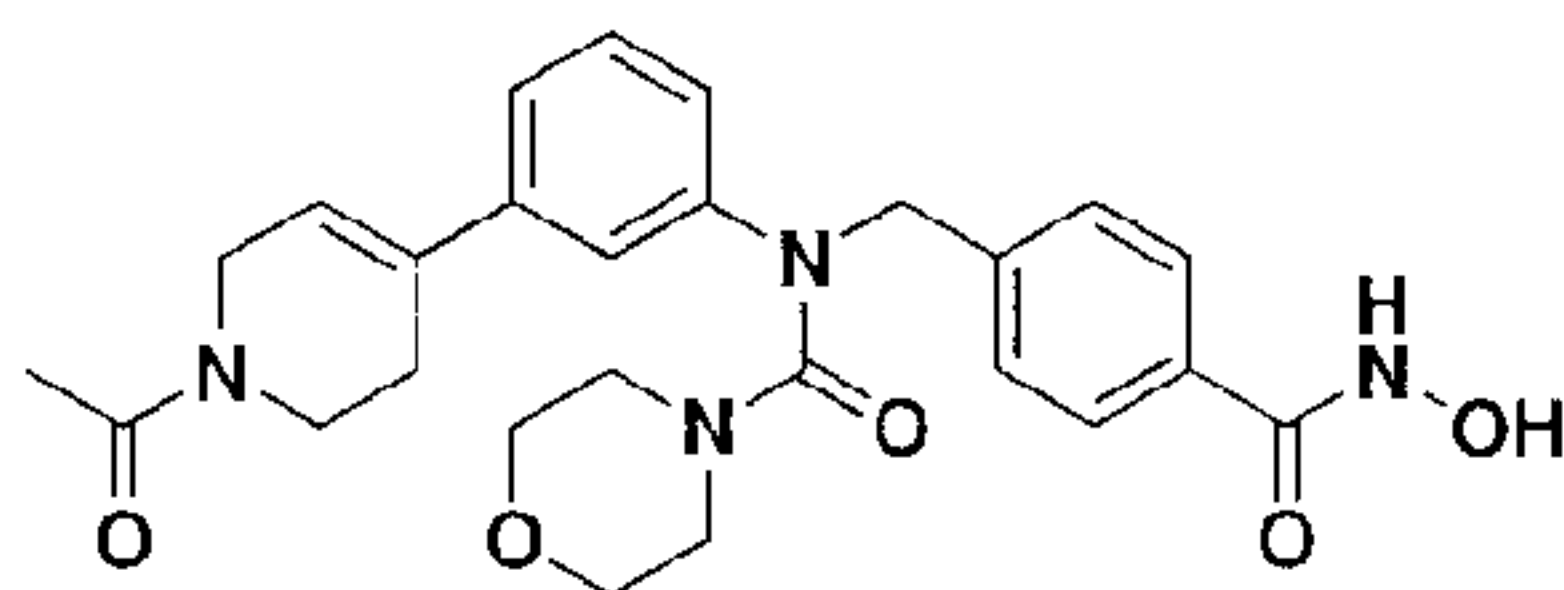


Compound of **Formula 4-2** (methyl 4-((N-(3-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate hydrochloride; 0.140 g, 0.297 mmol) was suspended in dichloromethane (5 mL), and then N,N-diisopropylethylamine (0.158 mL, 0.890 mmol) and acetic acid anhydride (0.036 g, 0.356 mmol) were added sequentially and then stirred at room temperature for 16 hours. After completion of the reaction, the organic layer was extracted with ethyl acetate and saturated sodium hydrogen carbonate aqueous solution, dehydrated with anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under

reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=25%) to give the desired compound of **Formula 4-3** (0.103 g, 73%) in the form of a white solid.

5 **(Compound 419: N-(3-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-N-(4-(hydroxycarbonyl)benzyl)morpholine-4-carboxamide)**

10



15

20

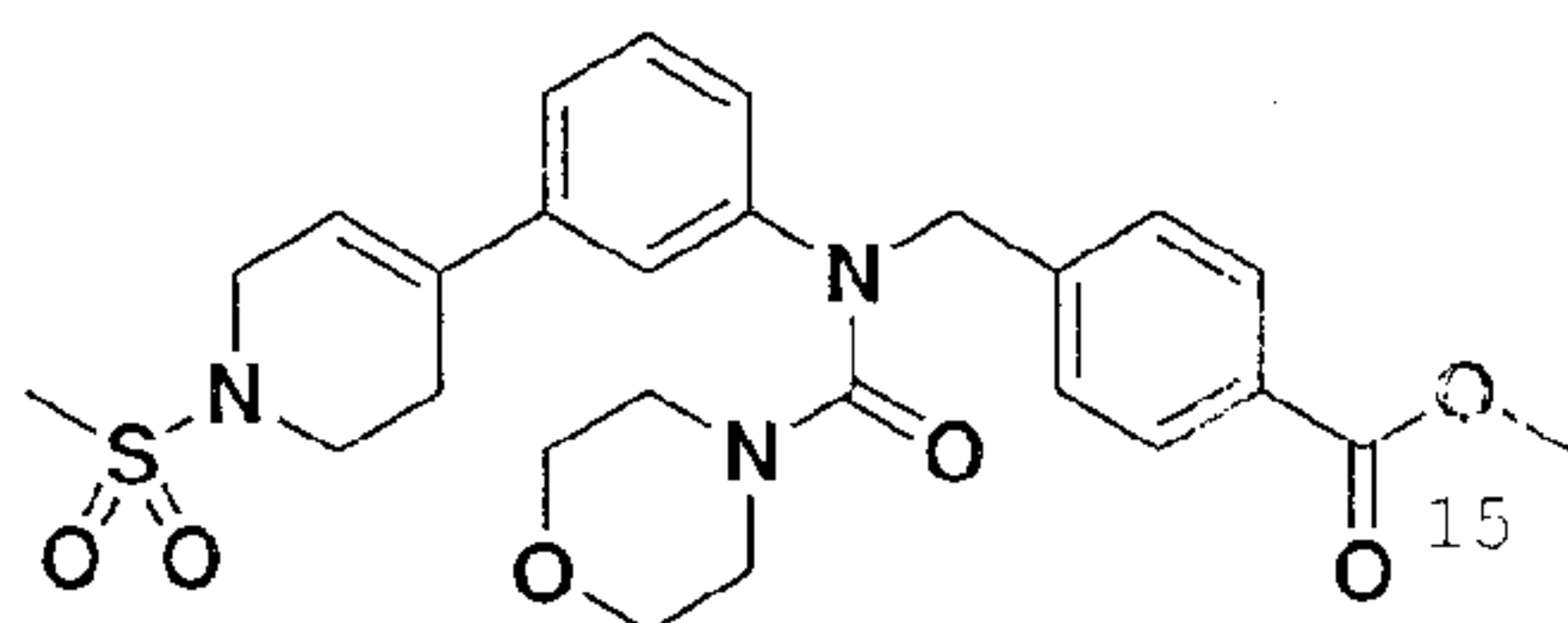
25

Compound of **Formula 4-3** (methyl 4-((N-(3-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.103 g, 0.216 mmol) was dissolved in methanol (10 mL), and then hydroxylamine (50.0 wt% aqueous solution; 1.32 mL, 21.6 mmol) and potassium hydroxide (0.121 g, 2.16 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 2 mL, and the organic layer was extracted with ethyl acetate and saturated ammonium chloride aqueous solution. The organic layer was washed with water, dehydrated with anhydrous magnesium sulfate, filtered, and then concentrated under reduced pressure to give the desired **Compound 419** (0.043 g, 42%) in the form of a white solid.

¹H NMR (400 MHz, DMSO-d₆) δ 11.13 (s, 1 H), 8.98 (s, 1 H), 7.63 (d, 2 H, *J* = 8.2 Hz), 7.36 (d, 2 H, *J* = 8.2 Hz), 7.27 (t, 1 H, *J* = 7.9 Hz), 7.18 – 7.12 (m, 2 H), 7.03 (d, 1 H, *J* = 8.4 Hz), 6.16 (m, 1 H), 4.87 (s, 2 H), 4.12 – 4.06 (m, 2 H), 3.63 – 3.58 (m, 2 H), 3.39 (t, 4 H, *J* = 4.5 Hz), 3.12 (t, 4 H, *J* = 4.4 Hz), 2.38 (brs, 2 H), 2.07 (d, 3 H, *J* = 9.0 Hz). **MS** (ESI) *m/z* 479 (M⁺ + H).

Example 75: Synthesis of Compound 420

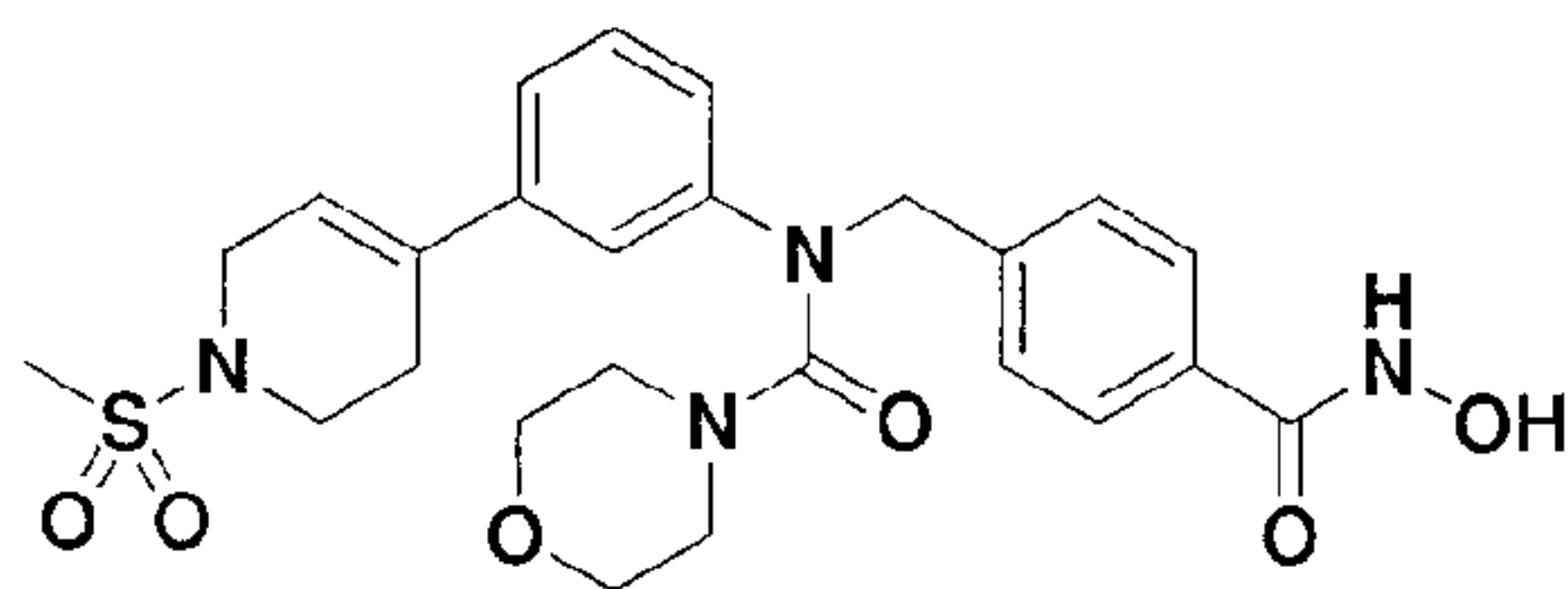
10 (Formula 4-3: methyl 4-((N-(3-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate)



Compound of **Formula 4-2** (methyl 4-((N-(3-(1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate hydrochloride; 0.140 g, 0.297 mmol) was suspended in dichloromethane (5 mL), and then N,N-diisopropylethylamine (0.158 mL, 0.890 mmol) and methylsulfonyl chloride (0.040 g, 0.356 mmol) were added sequentially and then stirred at room temperature for 16 hours. After completion of the reaction, the organic layer
25 was extracted with ethyl acetate and saturated sodium

hydrogen carbonate aqueous solution, dehydrated with anhydrous magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure, and then the residue was purified and concentrated by column chromatography (silica; ethyl acetate/hexane=70%) to give the desired compound of **Formula 4-3** (0.114 g, 75%) in the form of a white solid.

(**Compound 420**: N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-carboxamide)



Compound of **Formula 4-3** (methyl 4-((N-(3-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-carboxamido)methyl)benzoate; 0.114 g, 0.222 mmol) was dissolved in methanol (10 mL), and then hydroxylamine (50.0 wt% aqueous solution; 1.36 mL, 22.2 mmol) and potassium hydroxide (0.125 g, 2.22 mmol) were added sequentially and then stirred at room temperature for 30 minutes. After completion of the reaction, the reaction solution was concentrated under reduced pressure until its volume became about 2 mL, and the organic layer was extracted with ethyl acetate and saturated ammonium chloride aqueous

DEMANDES OU BREVETS VOLUMINEUX

**LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS
COMPREND PLUS D'UN TOME.**

CECI EST LE TOME __1__ DE __2__

NOTE: Pour les tomes additionels, veuillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

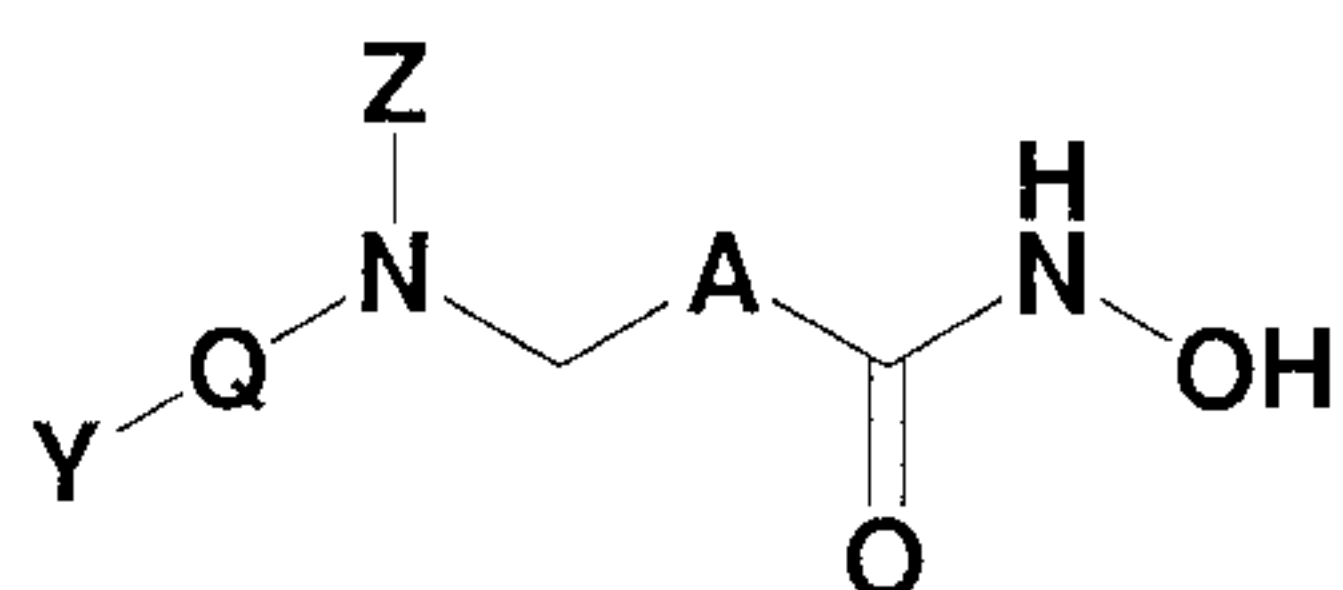
THIS IS VOLUME __1__ OF __2__

NOTE: For additional volumes please contact the Canadian Patent Office.

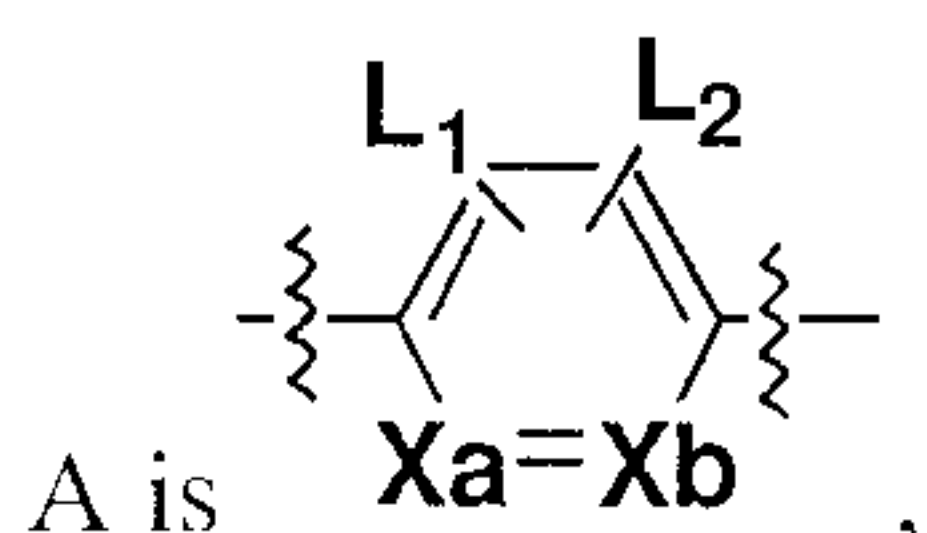
What is claimed is:

1. A compound represented by the following Formula I, optical isomer thereof or pharmaceutically acceptable salt thereof:

[Formula I]

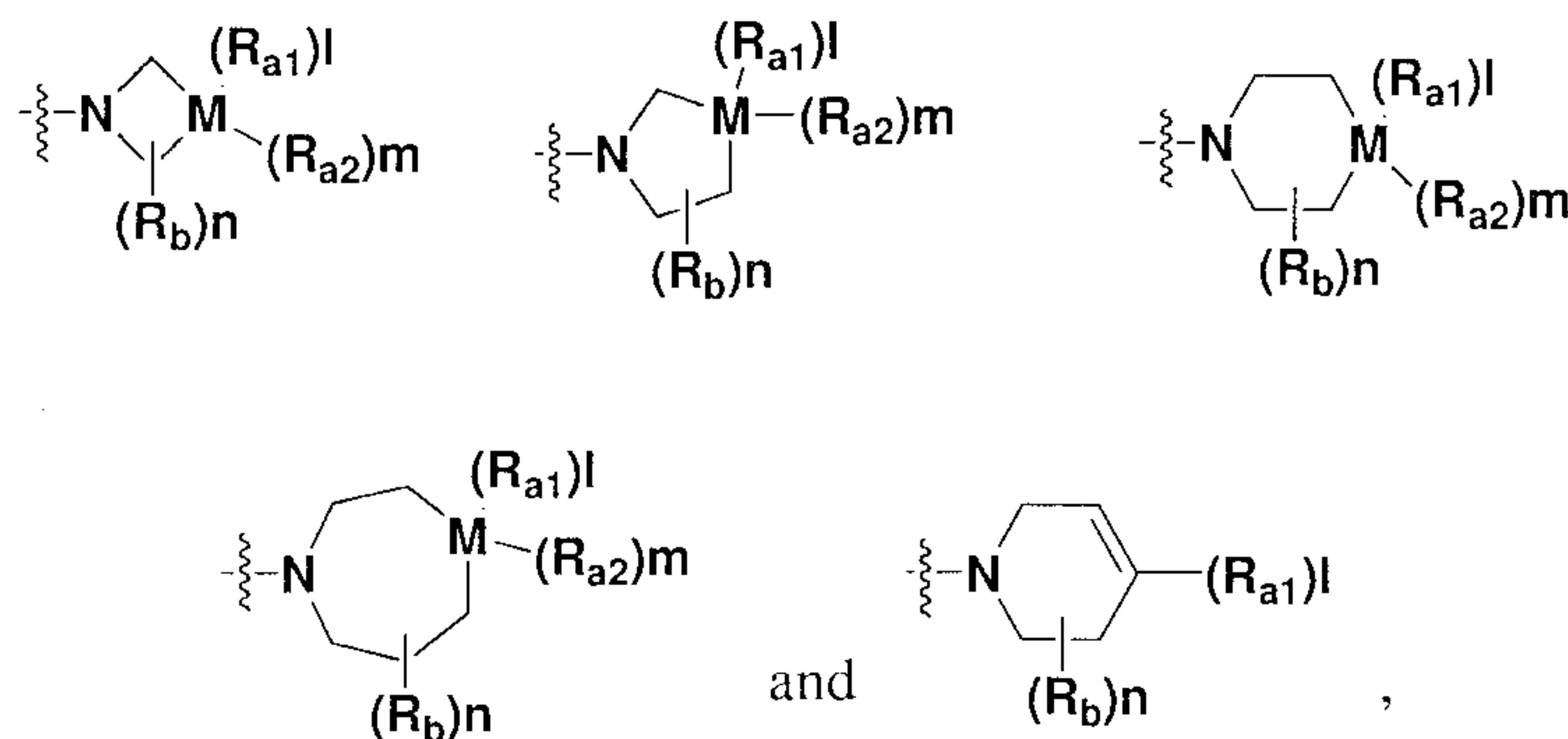


wherein



Xa and Xb are C, L₁ and L₂ are each independently hydrogen, -F, -Cl, -Br, or -I,

Q is C(=O), Y is selected from the group consisting of:



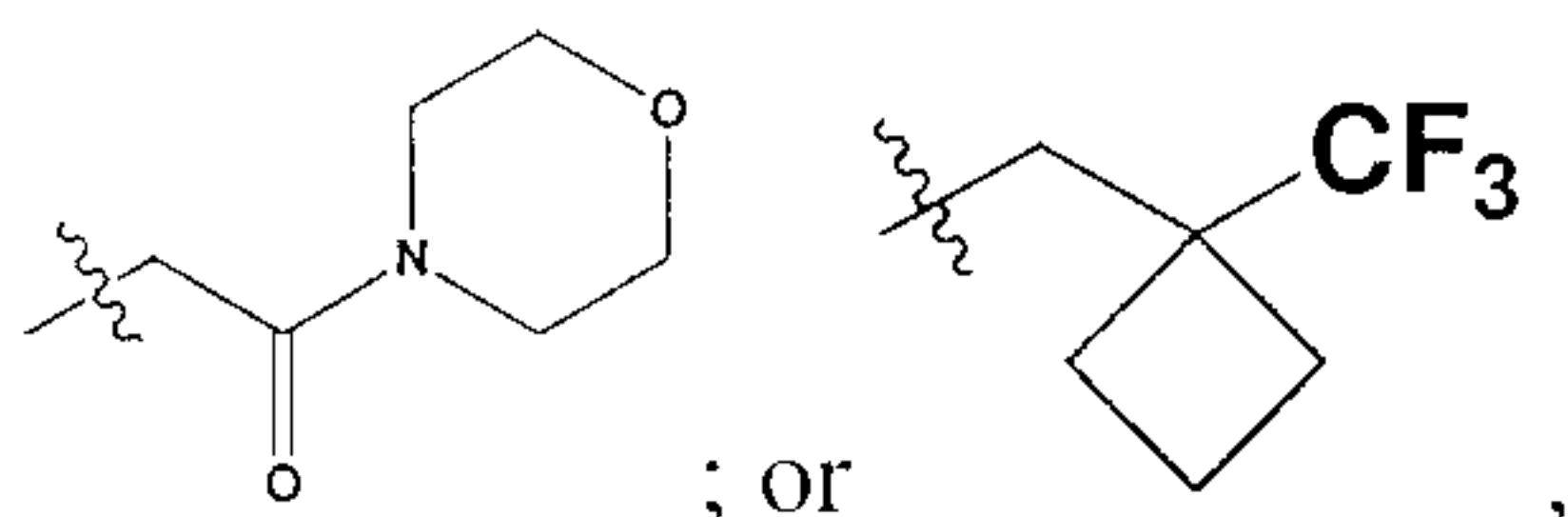
M is C, O, N, S(=O)₂, or S,

l and m are each independently an integer of 0 or 1,

R_{a1} and R_{a2} are each independently hydrogen; hydroxy; -C₁₋₄ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br or I; -C₁₋₄ straight or branched chain alcohol; benzhydryl; -C₁₋₄ straight or branched chain alkyl substituted with a saturated or unsaturated 5- to 7-membered heterocyclic compound comprising 1 to 3 heteroatoms selected from N, O, and S as a ring member (wherein the heterocyclic compound may be unsubstituted or at least one hydrogen may be optionally substituted with OH, OCH₃,

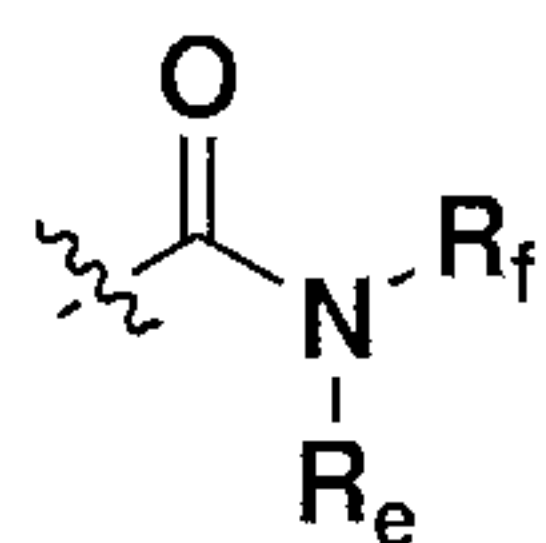
CH₃, CH₂CH₃, F, Cl, Br, or I); a saturated or unsaturated 5- to 7-membered heterocyclic compound comprising 1 to 3 heteroatoms selected from N, O, and S as a ring member (wherein the heterocyclic compound may be unsubstituted or at least one hydrogen may be optionally substituted with OH, OCH₃, CH₃, CH₂CH₃, F, Cl, Br, or I); phenyl, unsubstituted or substituted with one or more F, Cl, Br, I, C₁₋₄ alkoxy, C₁₋₂ alkyl, or hydroxy; benzyl, unsubstituted or substituted with one or more F, Cl, Br, I, C₁₋₄ alkoxy, C₁₋₂ alkyl, or hydroxy; -S((=O)₂)CH₃; -F; -Cl; -Br; -I; -C₁₋₆ straight or branched chain alkoxy; -C₂₋₆ alkyl alkoxy; -C(=O)R_x, wherein R_x is straight or branched C₁₋₃ alkyl or C₃₋₁₀ cycloalkyl;

wherein R_c and R_d are each independently hydrogen, C₁₋₃ straight or branched chain alkyl;



n is an integer of 0, 1, or 2,

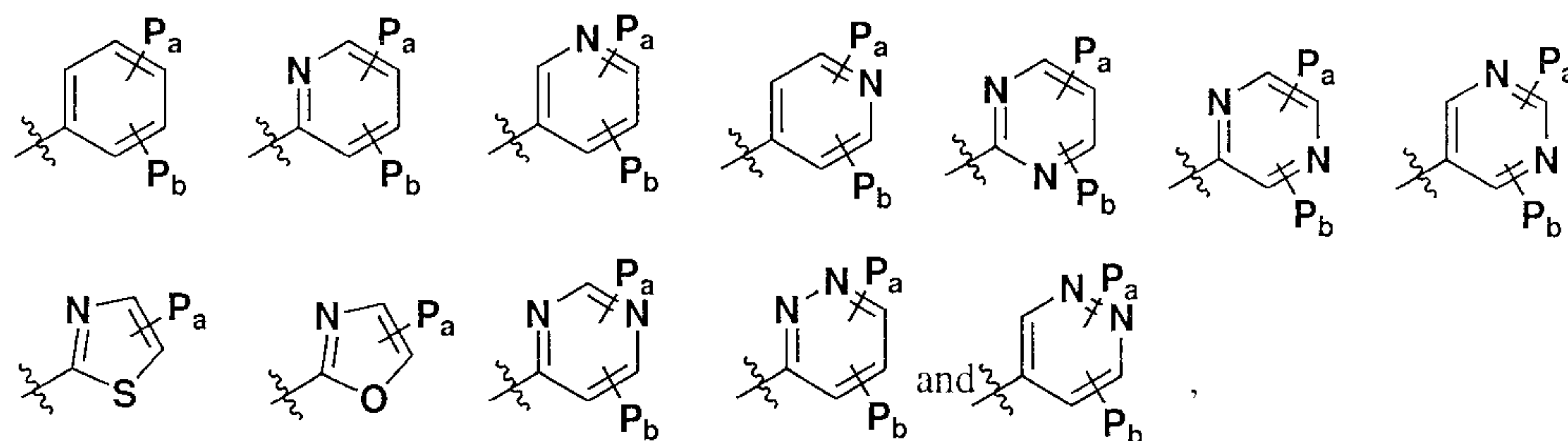
R_b is hydrogen; hydroxy; -C₁₋₆ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br, or I; -C(=O)CH₃; -C₁₋₄ straight or branched chain alcohol; -C₁₋₆ straight or branched chain alkoxy; -C₂₋₆ straight or branched chain alkyl alkoxy;

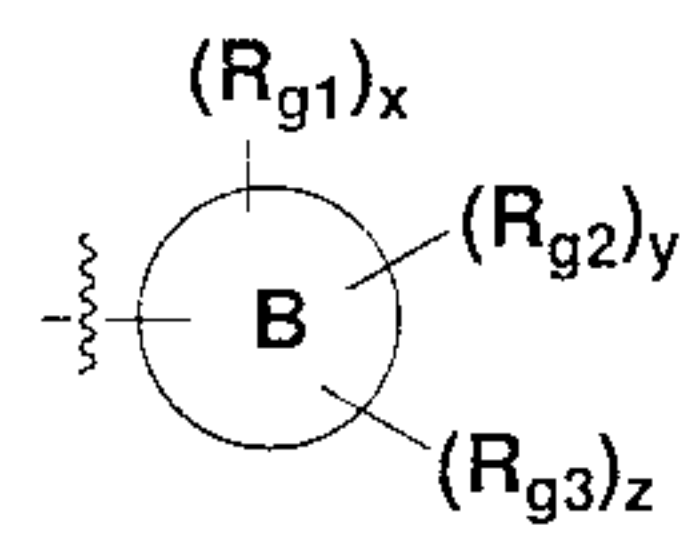


-CF₃; -F; -Cl; -Br; -I; or , wherein R_e and R_f are each independently hydrogen or -C₁₋₃ straight or branched chain alkyl,

and

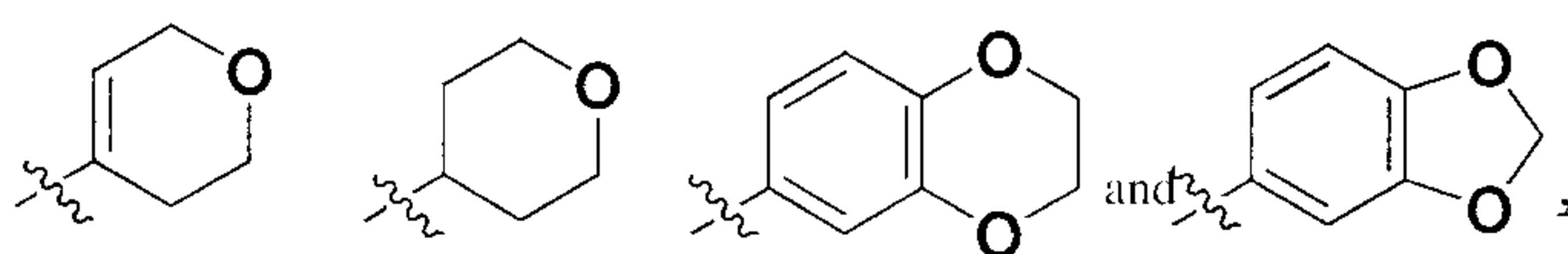
Z is selected from the group consisting of the following compounds:





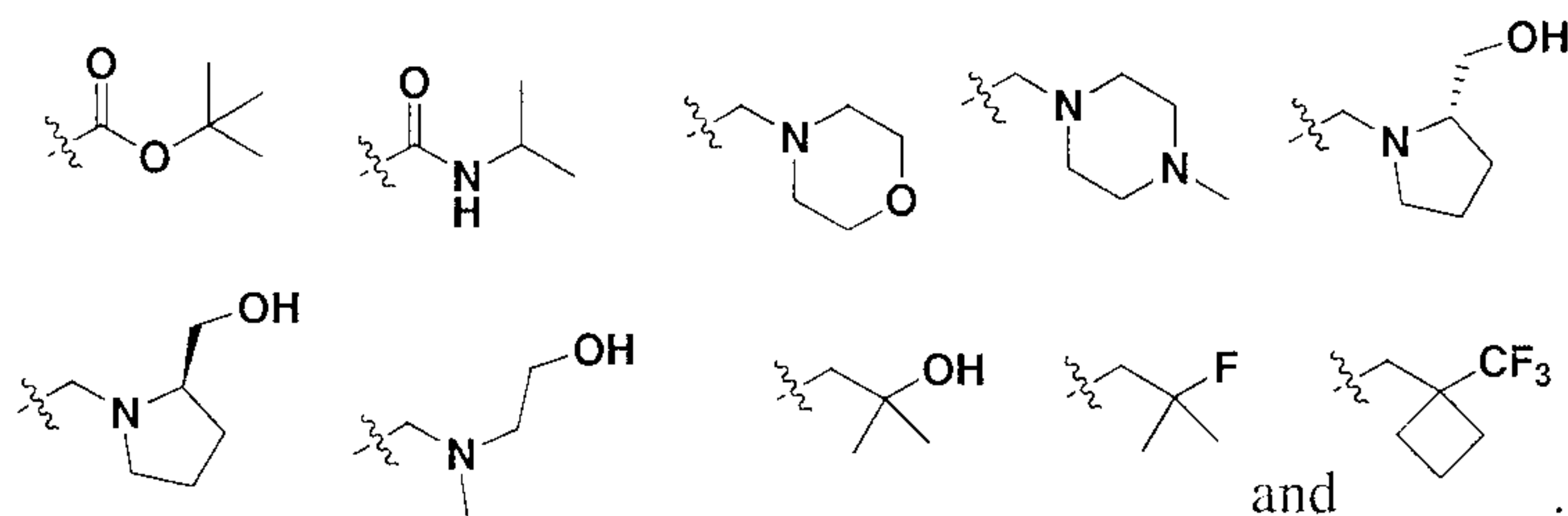
wherein P_a and P_b are each independently straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br or I; -F; -Cl; -Br; -I; -CF₃; -OCF₃; -CN; -C₁₋₆ straight or branched alkoxy; -C₂₋₆ straight or branched alkyl alkoxy; -CH₂F; or -C₁₋₃ alcohol,

wherein  is selected from phenyl, pyridine, pyrimidine, thiazole, indole, indazole, piperazine, quinoline, furan, tetrahydropyridine, piperidine, or the following group:



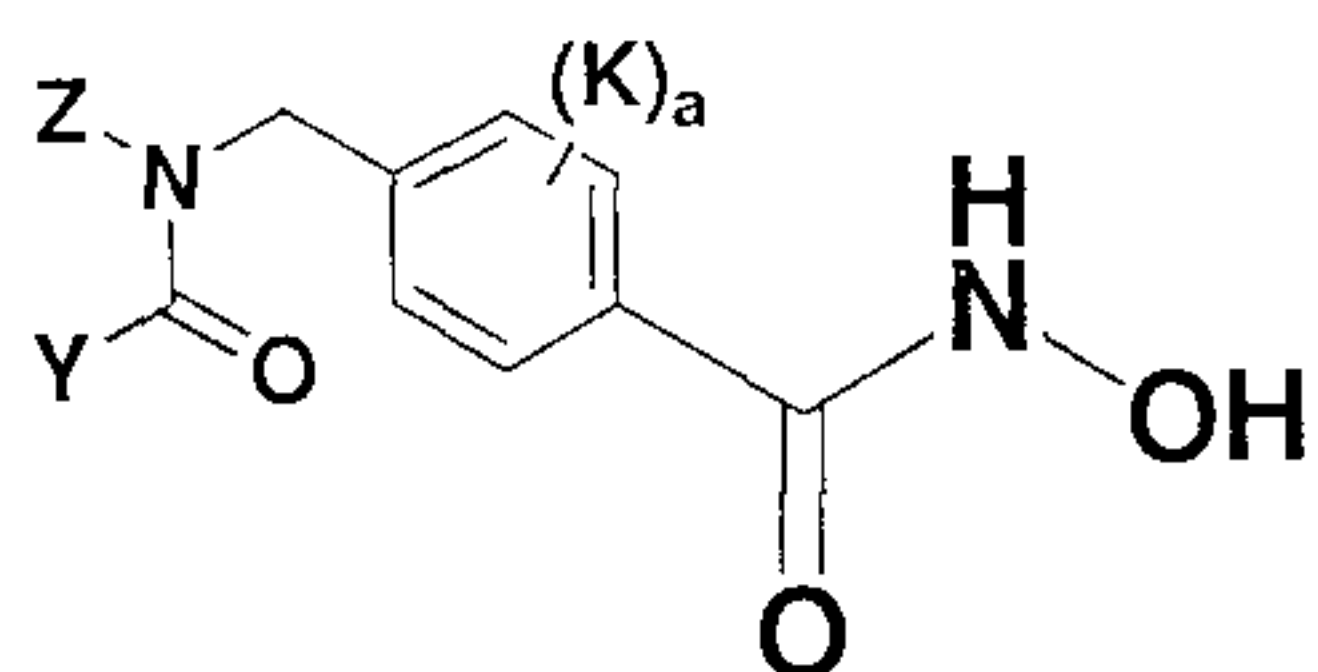
x , y and z are each independently an integer of 0 or 1, and

R_{g1} , R_{g2} and R_{g3} are each independently selected from hydrogen; hydroxy; -C₁₋₃ alkyl; -CF₃; -C₁₋₆ straight or branched chain alkoxy; -C₂₋₆ straight or branched chain alkyl alkoxy; -C(=O)CH₃; -C₁₋₄ straight or branched chain alcohol; -N(CH₃)₂; -F; -Cl; -Br; -I; phenyl; -S((=O)₂)CH₃; or the following group:



2. The compound of Formula I, optical isomer thereof or pharmaceutically acceptable salt thereof according to claim 1, wherein the compound represented by the above Formula I is a compound represented by the following Formula II:

[Formula II]

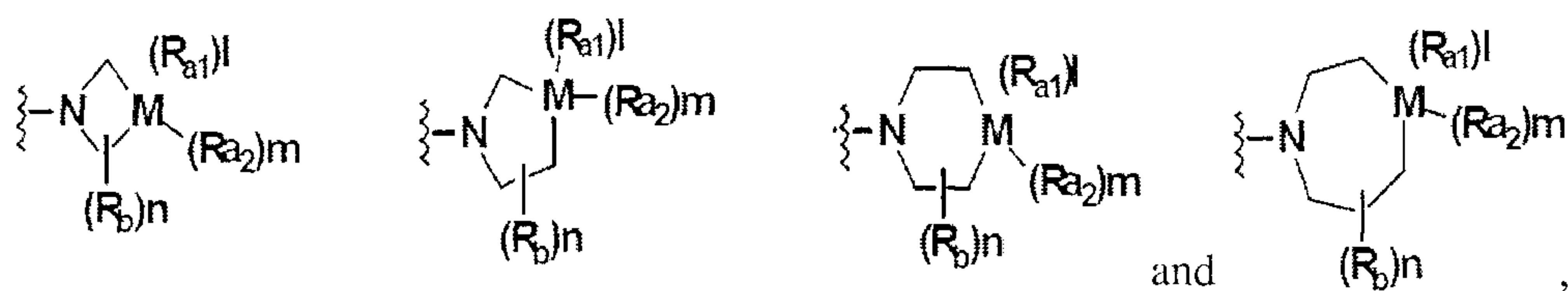


wherein

a is an integer of 0, 1 or 2,

K is independently, hydrogen, -F, -Cl, -Br or -I,

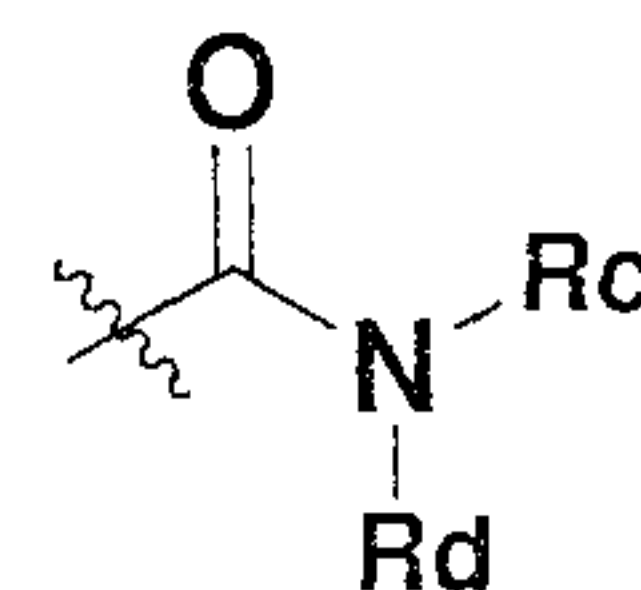
Y is selected from the group consisting of:



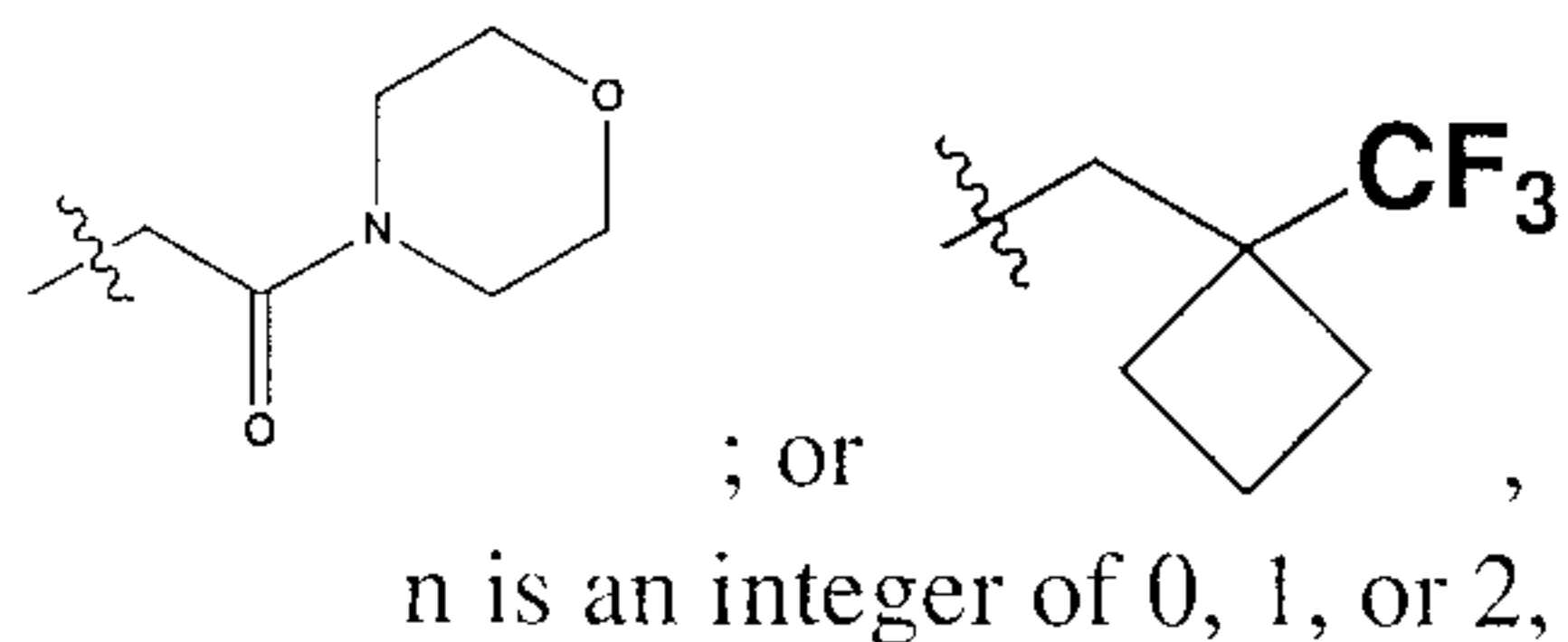
M is C, O or N,

l and m are each independently an integer of 0 or 1,

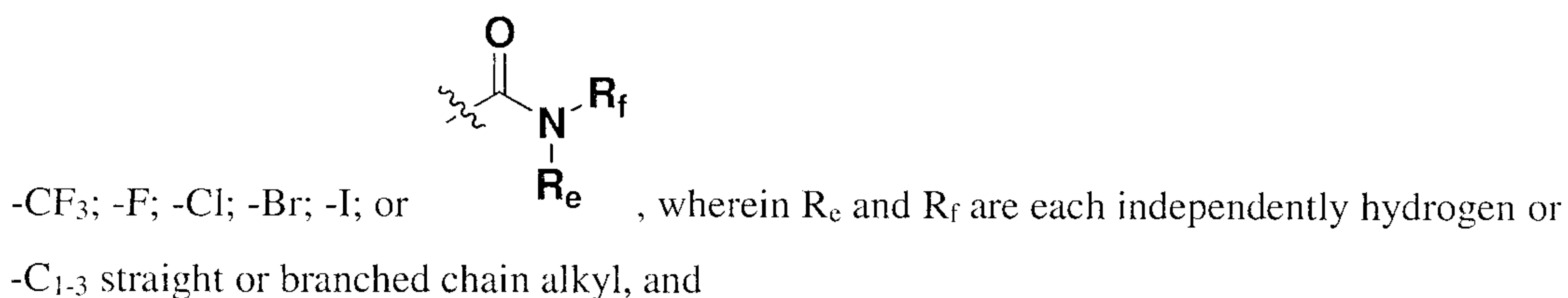
R_{a1} and R_{a2} are each independently hydrogen; hydroxy; $-C_{1-4}$ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br or I; $-C_{1-4}$ straight or branched chain alcohol; benzhydryl; $-C_{1-4}$ straight or branched chain alkyl substituted with a saturated or unsaturated 5- to 7-membered heterocyclic compound comprising 1 to 3 heteroatoms selected from N, O, and S as a ring member (wherein the heterocyclic compound may be unsubstituted or at least one hydrogen may be optionally substituted with OH, OCH_3 , CH_3 , CH_2CH_3 , F, Cl, Br, or I); a saturated or unsaturated 5- to 7-membered heterocyclic compound comprising 1 to 3 heteroatoms selected from N, O, and S as a ring member (wherein the heterocyclic compound may be unsubstituted or at least one hydrogen may be optionally substituted with OH, OCH_3 , CH_3 , CH_2CH_3 , F, Cl, Br, or I); phenyl, unsubstituted or substituted with one or more F, Cl, Br, I, C_{1-4} alkoxy, C_{1-2} alkyl, or hydroxy; benzyl, unsubstituted or substituted with one or more F, Cl, Br, I, C_{1-4} alkoxy, C_{1-2} alkyl, or hydroxy; $-S((=O)_2)CH_3$; -F; -Cl; -Br; -I; $-C_{1-6}$ straight or branched chain alkoxy; $-C_{2-6}$ alkyl alkoxy; $-C(=O)R_x$, wherein R_x is straight or branched C_{1-3} alkyl or C_{3-10} cycloalkyl;



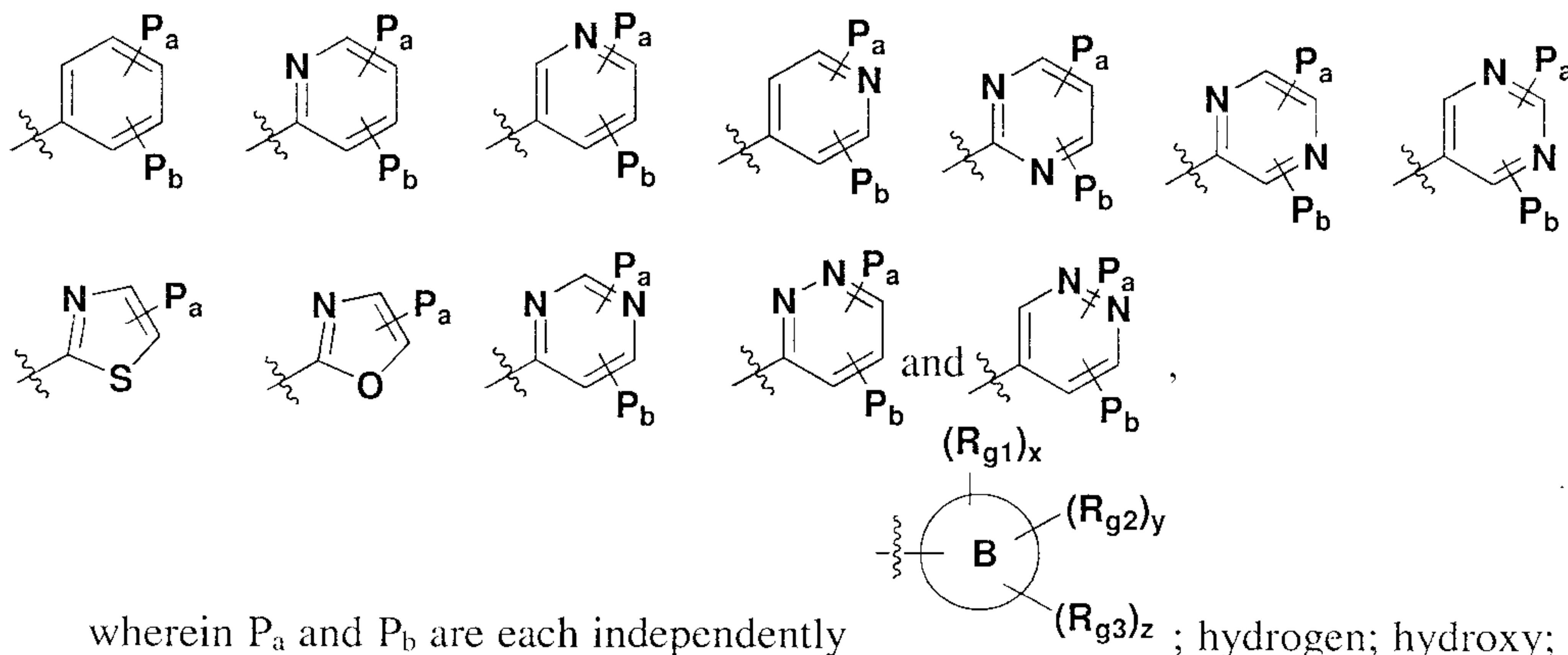
wherein R_c and R_d are each independently hydrogen, C_{1-3} straight or branched chain alkyl;



R_b is hydrogen; hydroxy; $-C_{1-6}$ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br, or I; $-C(=O)CH_3$; $-C_{1-4}$ straight or branched chain alcohol; $-C_{1-6}$ straight or branched chain alkoxy; $-C_{2-6}$ straight or branched chain alkyl alkoxy;



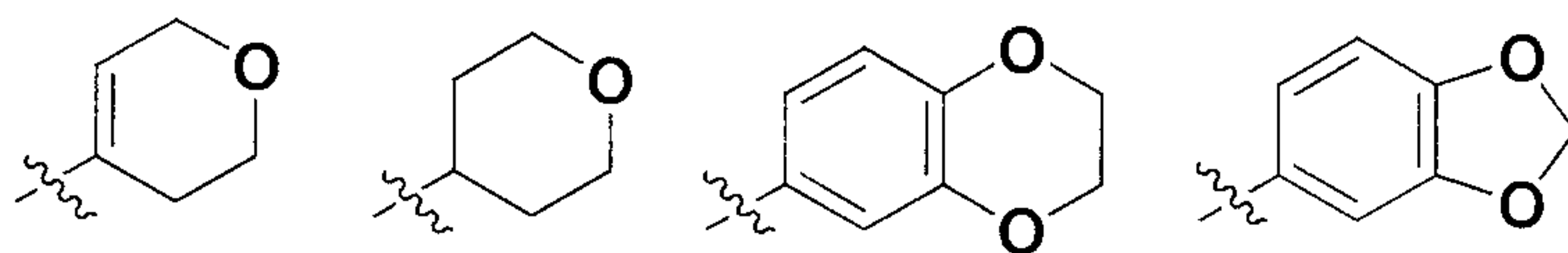
Z is selected from the group consisting of the following compounds:



C_{1-4} straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br or I; $-F$; $-Cl$; $-Br$; $-I$; $-CF_3$; $-OCF_3$; $-CN$; $-C_{1-6}$ straight or branched alkoxy; $-C_{2-6}$ straight or branched alkyl alkoxy; $-CH_2F$; or $-C_{1-3}$ alcohol,

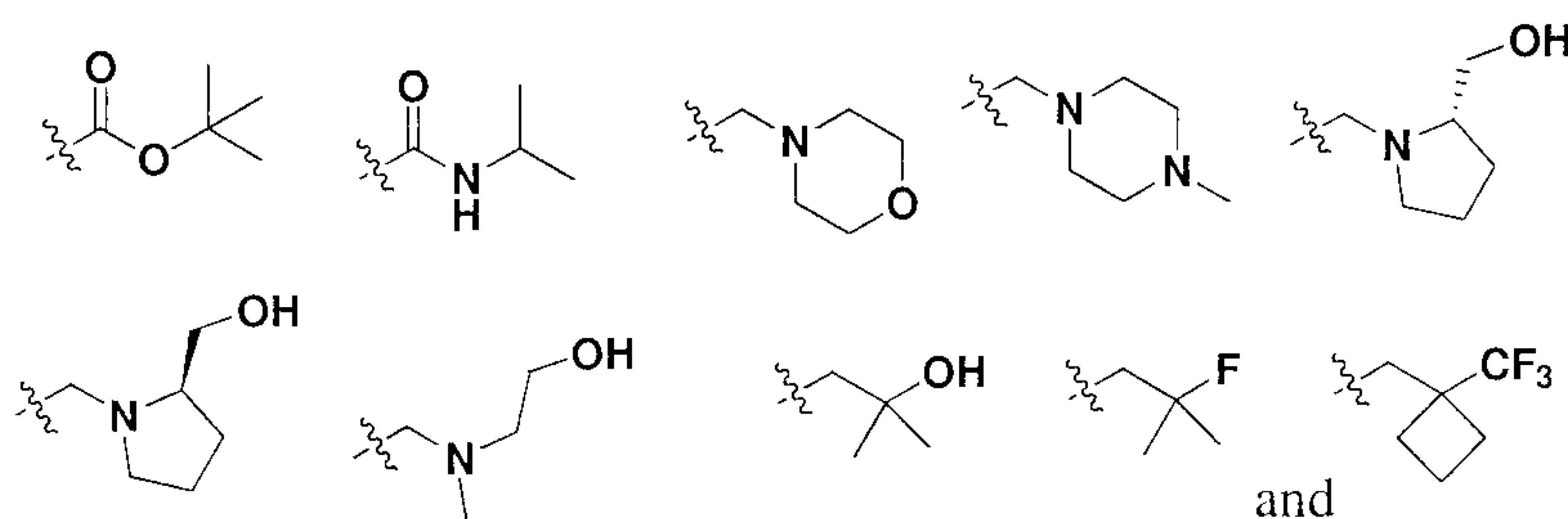
wherein $\textcircled{B}$ is selected from phenyl, pyridine, pyrimidine, thiazole, indole, indazole, piperazine, quinoline, furan, tetrahydropyridine, piperidine, or the following group:

and



x, y and z are each independently an integer of 0 or 1, and

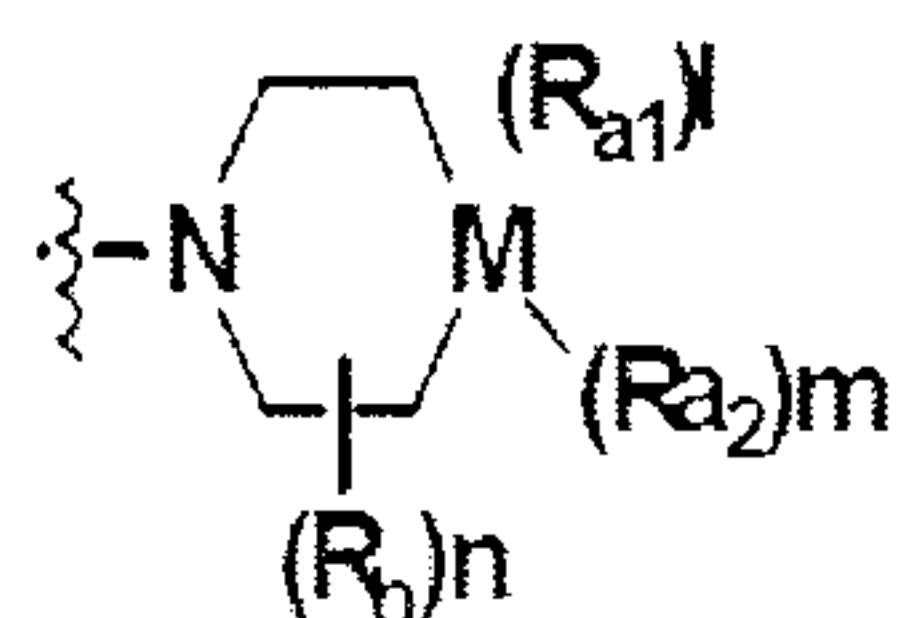
R_{g1} , R_{g2} and R_{g3} are each independently selected from hydrogen; hydroxy; $-C_{1-3}$ alkyl; $-CF_3$; $-C_{1-6}$ straight or branched chain alkoxy; $-C_{2-6}$ straight or branched chain alkyl alkoxy; $-C(=O)CH_3$; $-C_{1-4}$ straight or branched chain alcohol; $-N(CH_3)_2$; $-F$; $-Cl$; $-Br$; $-I$; phenyl; $-S(=O)_2CH_3$; or the following group:



3. The compound of Formula II, optical isomer thereof or pharmaceutically acceptable salt thereof according to claim 2, wherein

a is an integer of 0, 1 or 2,

K is independently hydrogen, $-F$, $-Cl$, $-Br$ or $-I$,



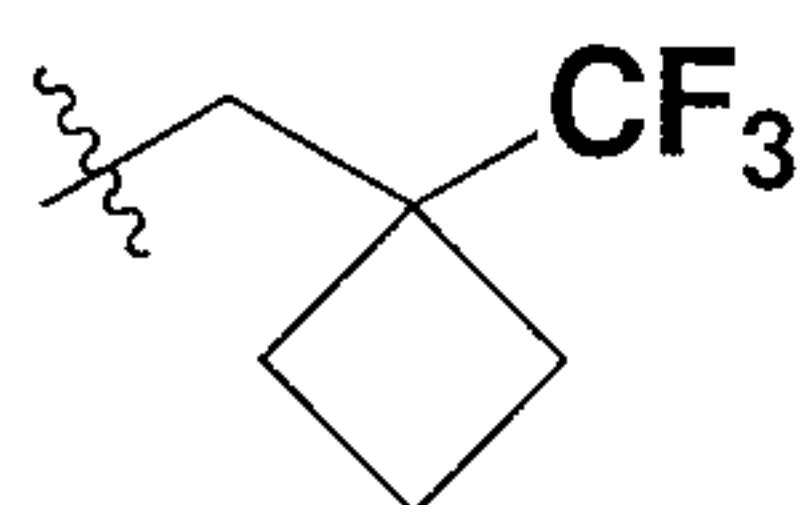
Y is

M is C, O or N,

l and m are each independently an integer of 0 or 1,

R_{a1} and R_{a2} are each independently hydrogen; hydroxy; $-C_{1-4}$ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br or I; $-C_{1-4}$ straight or branched chain alcohol; benzhydryl; $-C_{1-4}$ straight or branched chain alkyl substituted with a saturated or unsaturated 5- to 7-membered heterocyclic compound comprising 1 to 3 heteroatoms selected from N, O, and S as a ring member (wherein the heterocyclic compound may be unsubstituted or at least one hydrogen may be optionally substituted with OH, OCH_3 ,

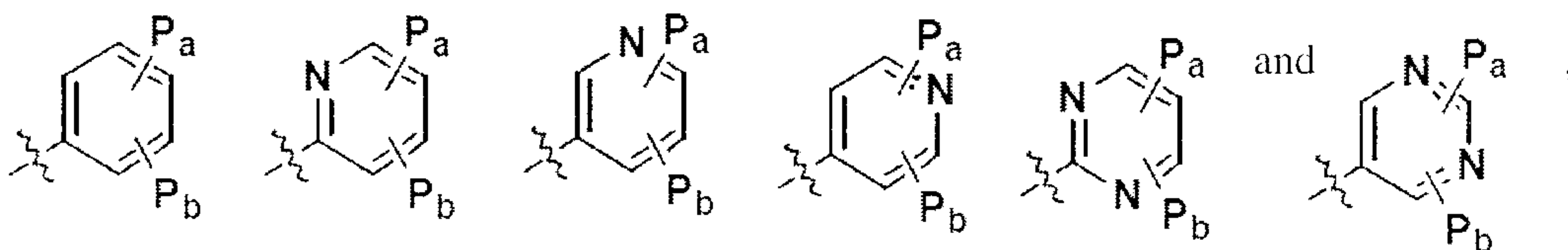
CH₃, CH₂CH₃, F, Cl, Br, or I); a saturated or unsaturated 5- to 7-membered heterocyclic compound comprising 1 to 3 heteroatoms selected from N, O, and S as a ring member (wherein the heterocyclic compound may be unsubstituted or at least one hydrogen may be optionally substituted with OH, OCH₃, CH₃, CH₂CH₃, F, Cl, Br, or I); phenyl, unsubstituted or substituted with one or more F, Cl, Br, I, C₁₋₄ alkoxy, C₁₋₂ alkyl, or hydroxy; benzyl, unsubstituted or substituted with one or more F, Cl, Br, I, C₁₋₄ alkoxy, C₁₋₂ alkyl, or hydroxy; -S((=O)₂)CH₃; -F; -Cl; -Br; -I; -C₁₋₆ straight or branched chain alkoxy; -C₂₋₆ alkyl alkoxy; -C(=O)R_x, wherein R_x is straight or branched C₁₋₃ alkyl or C₃₋₁₀ cycloalkyl; or,



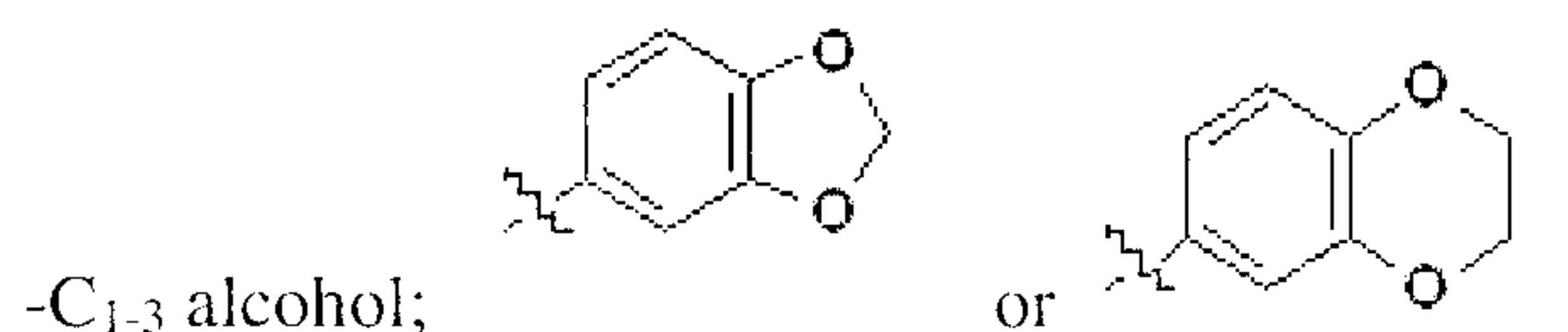
n is an integer of 0, 1, or 2,

R_b is hydrogen; -C₁₋₆ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br, or I; and

Z is selected from the group consisting of the following compounds:



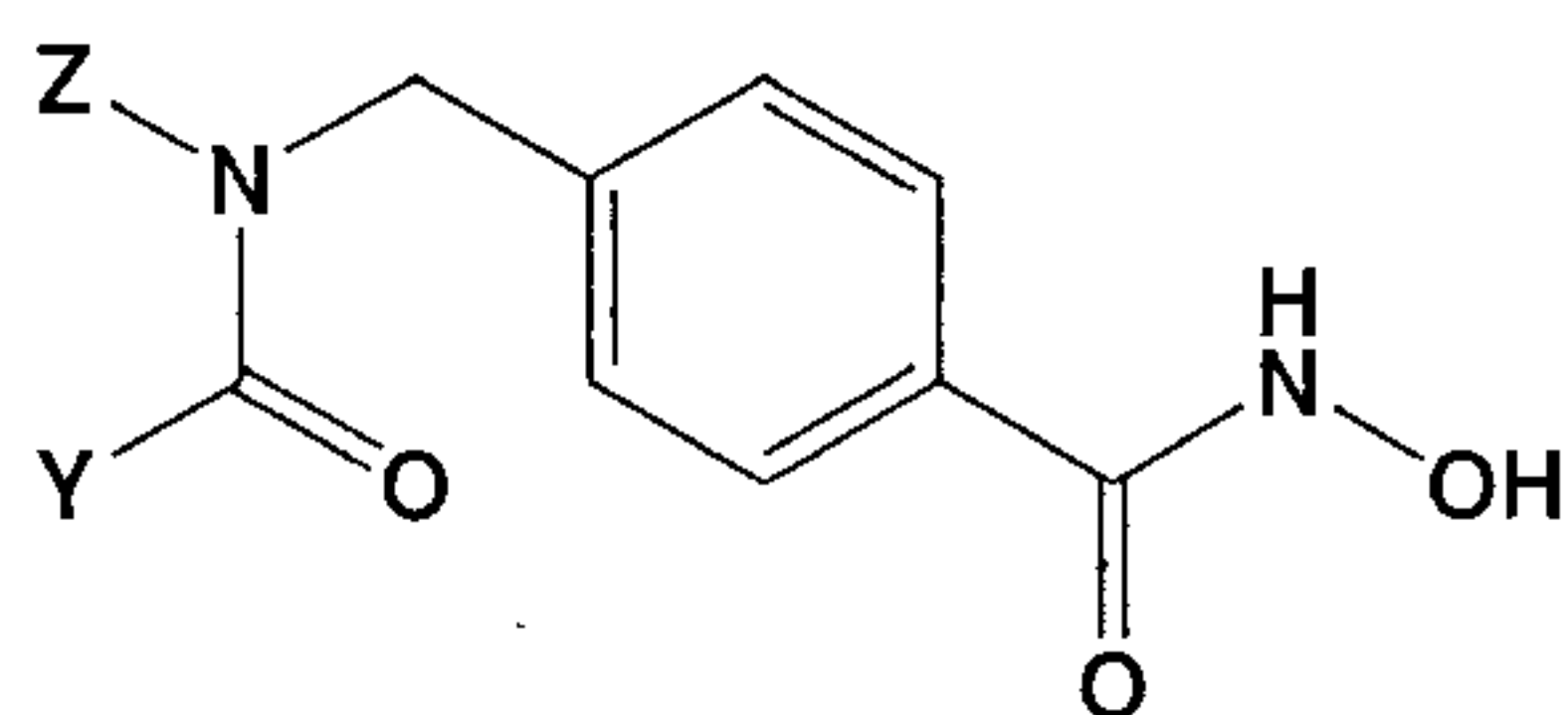
wherein P_a and P_b are each independently hydrogen; hydroxy; -C₁₋₄ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br or I; -F; -Cl; -Br; -I; -CF₃; -OCF₃; -CN; -C₁₋₆ straight or branched alkoxy; -C₂₋₆ straight or branched alkyl alkoxy; -CH₂F;



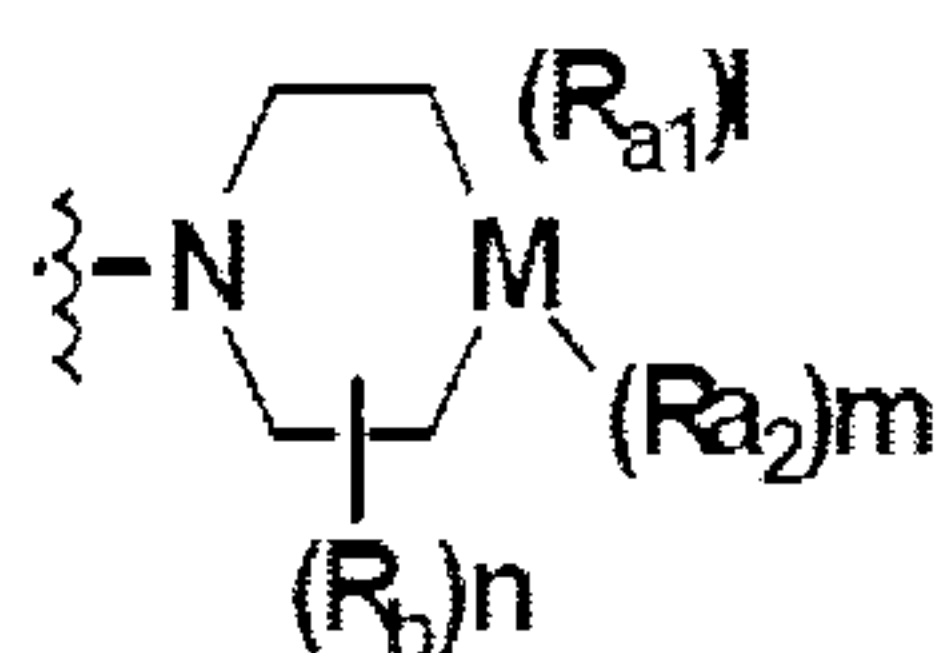
-C₁₋₃ alcohol;

4. The compound of Formula II, optical isomer thereof or pharmaceutically acceptable salt thereof according to claim 2, wherein the compound represented by the above Formula II is a compound represented by the following Formula III:

[Formula III]



wherein



Y is

M is C, O or N,

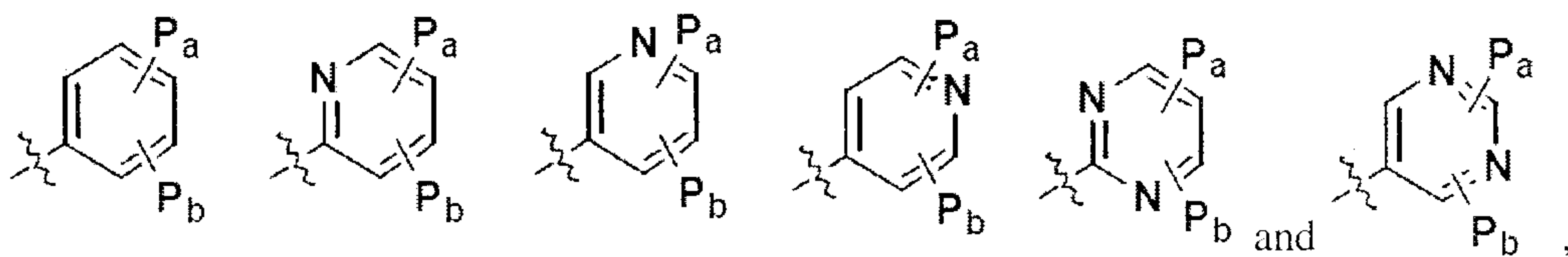
l and m are each independently an integer of 0 or 1,

R_{a1} and R_{a2} are each independently hydrogen; -C₁₋₄ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br or I; -C₁₋₄ straight or branched chain alkyl substituted with a phenyl, pyridine or pyrimidine (wherein the phenyl, pyridine or pyrimidine may be unsubstituted or at least one hydrogen may be optionally substituted with OH, OCH₃, CH₃, CH₂CH₃, F, Cl, Br, or I);

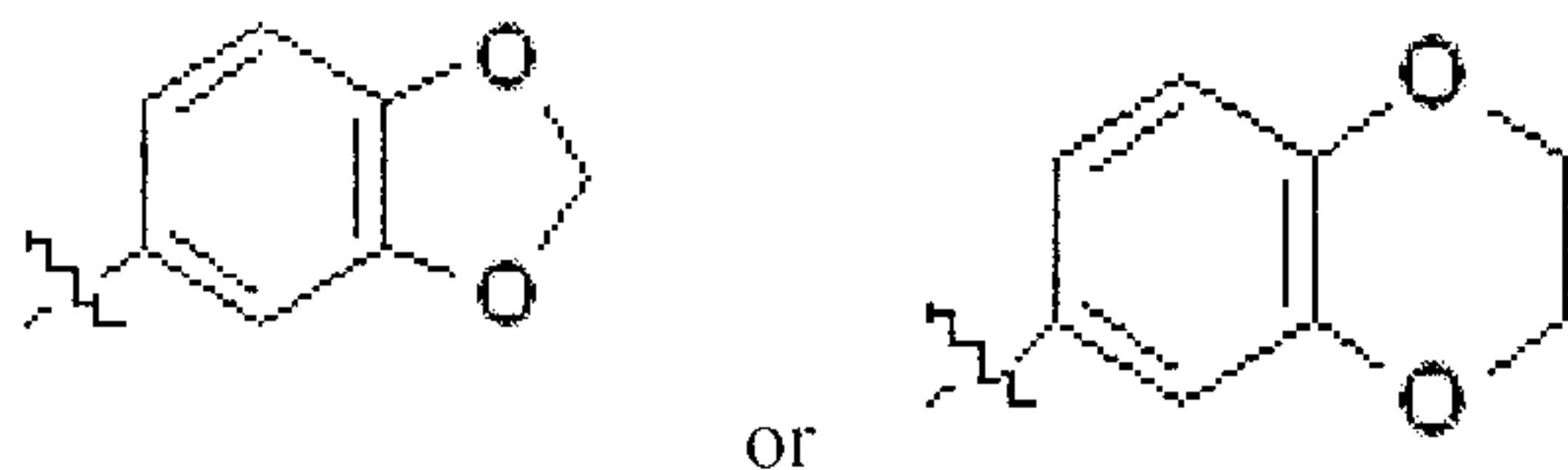
n is an integer of 0, 1, or 2,

R_b is hydrogen; -C₁₋₆ straight or branched chain alkyl, unsubstituted or substituted with one or more F, Cl, Br, or I; and

Z is selected from the group consisting of the following compounds:



wherein P_a and P_b are each independently hydrogen; -F; -Cl; -Br; -CF₃; -OCF₃; -CH₂F;



5. The compounds of Formula I, optical isomers thereof or pharmaceutically acceptable salts thereof according to claim 1, wherein the compounds of Formula I are selected from the group consisting of the following compounds:

252	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-methyl-1H-indazol-5-yl)phenyl)morpholine-4-carboxamide
253	N-(4-(hydroxycarbamoyl)benzyl)-4-methyl-N-(3-(1-methyl-1H-indazol-5-yl)phenyl)piperazine-1-carboxamide
254	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-methyl-1H-indazol-6-yl)phenyl)morpholine-4-carboxamide
255	N-(3-bromophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
256	N-(3-bromophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide
260	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-methyl-1H-indazol-5-yl)phenyl)piperidine-1-carboxamide
261	N-(3-(1H-indol-6-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
262	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(pyridin-3-yl)phenyl)morpholine-4-carboxamide
263	N-(3-(1H-indol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
279	N-(4-(hydroxycarbamoyl)benzyl)-N-phenylmorpholine-4-carboxamide
280	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)morpholine-4-carboxamide
281	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-3-yl)morpholine-4-carboxamide
309	4-benzyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyrimidin-2-yl)piperazine-1-carboxamide
311	4-hydroxy-N-(4-(hydroxycarbamoyl)benzyl)-4-phenyl-N-(pyrimidin-2-yl)piperidine-1-carboxamide
312	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyrimidin-2-yl)morpholine-4-carboxamide
313	N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(pyrimidin-2-yl)morpholine-4-carboxamide
329	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(1-methyl-1H-indazol-6-yl)phenyl)morpholine-4-carboxamide
330	N-(biphenyl-4-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide

331	N-(3',5'-difluorobiphenyl-4-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
332	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(pyridin-3-yl)phenyl)morpholine-4-carboxamide
333	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(pyrimidin-5-yl)phenyl)morpholine-4-carboxamide
334	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(quinolin-7-yl)phenyl)morpholine-4-carboxamide
335	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(biphenyl-3-yl)phenyl)morpholine-4-carboxamide
336	N-(4-(1H-indol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
337	N-(4-(1H-indol-6-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
338	N-(4-(hydroxycarbamoyl)benzyl)-N-(3',4',5'-trimethoxybiphenyl-4-yl)morpholine-4-carboxamide
339	N-(3',5'-bis(trifluoromethyl)biphenyl-4-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
340	N-(4-(1H-indol-4-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
341	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperidine-1-carboxamide
342	N-(4-(hydroxycarbamoyl)benzyl)-4-methyl-N-(pyridin-2-yl)piperidine-1-carboxamide
343	N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(pyridin-2-yl)morpholine-4-carboxamide
352	N-(4-(hydroxycarbamoyl)benzyl)-4-phenyl-N-(pyridin-2-yl)-5,6-dihydropyridine-1(2H)-carboxamide
353	N-(4-(hydroxycarbamoyl)benzyl)-4-methyl-N-(pyridin-2-yl)piperazine-1-carboxamide
354	4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide
355	4-benzyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide
356	N-(4-(hydroxycarbamoyl)benzyl)-4-(2-methoxyphenyl)-N-(pyridin-2-yl)piperazine-1-carboxamide
357	4-(4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide
358	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)pyrrolidine-1-carboxamide

370	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-phenylthiazol-2-yl)morpholine-4-carboxamide
371	N-(4-(4-chlorophenyl)thiazol-2-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
372	N-(4-bromophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
374	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)morpholine-4-carboxamide
376	N-(4-(hydroxycarbamoyl)benzyl)-4-methyl-N-(pyridin-2-yl)-1,4-diazepane-1-carboxamide
377	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)azetidine-1-carboxamide
379	4-(3,4-dimethylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide
380	N-(4-(hydroxycarbamoyl)benzyl)-N-(4'-(morpholinomethyl)biphenyl-4-yl)morpholine-4-carboxamide
381	N-(4-(hydroxycarbamoyl)benzyl)-N-(4'-((4-methylpiperazin-1-yl)methyl)biphenyl-4-yl)morpholine-4-carboxamide
382	(S)-N-(4-(hydroxycarbamoyl)benzyl)-N-(4'-((2-(hydroxymethyl)pyrrolidin-1-yl)methyl)biphenyl-4-yl)morpholine-4-carboxamide
383	N-(4-(hydroxycarbamoyl)benzyl)-N-(4'-(((2-hydroxyethyl)(methyl)amino)methyl)biphenyl-4-yl)morpholine-4-carboxamide
385	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)morpholine-4-carboxamide
386	N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(3-(trifluoromethyl)phenyl)morpholine-4-carboxamide
389	N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperidine-1-carboxamide
390	N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperidine-1-carboxamide
391	N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
392	N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylmorpholine-4-carboxamide
393	N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide
394	N-(4-chloro-3-(trifluoromethyl)phenyl)-4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
395	N-(3',5'-difluorobiphenyl-3-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-

	carboxamide
396	N-(3-(6-(dimethylamino)pyridin-3-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
397	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(pyrimidin-5-yl)phenyl)morpholine-4-carboxamide
398	N-(3',5'-bis(trifluoromethyl)biphenyl-3-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
399	N-(3-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
400	N-(4-(hydroxycarbamoyl)benzyl)-N-(3',4',5'-trimethoxybiphenyl-3-yl)morpholine-4-carboxamide
401	N-(2',6'-dimethylbiphenyl-3-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
402	N-(3-(furan-3-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
403	N-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
404	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-carboxamide
405	tert-butyl 4-(3-(N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamido)phenyl)-5,6-dihydropyridine-1(2H)-carboxylate
413	N-(2,4-difluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
414	N-(2,4-difluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperidine-1-carboxamide
415	N-(2,4-difluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylmorpholine-4-carboxamide
416	N-(2,4-difluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide
418	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
419	N-(3-(1-acetyl-1,2,3,6-tetrahydropyridin-4-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
420	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-(methylsulfonyl)-1,2,3,6-tetrahydropyridin-4-yl)phenyl)morpholine-4-carboxamide
438	N-(2-fluoro-4-methylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperidine-1-carboxamide
439	N-(2-fluoro-4-methylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-

	carboxamide
440	N-(2-fluoro-4-methylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylmorpholine-4-carboxamide
441	N-(2-fluoro-4-methylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide
450	4-acetyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)-1,4-diazepane-1-carboxamide
451	4-(cyclopropanecarbonyl)-N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)piperazine-1-carboxamide
453	4-ethyl-N-(2-fluoro-4-methylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
454	N-(2-fluoro-4-methylphenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-(2-methoxyphenyl)piperazine-1-carboxamide
455	N-(2-fluoro-4-methylphenyl)-4-(4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
456	N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperidine-1-carboxamide
457	N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperidine-1-carboxamide
458	N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
459	N-(4-(hydroxycarbamoyl)benzyl)-4-methyl-N-(3-(trifluoromethyl)phenyl)piperidine-1-carboxamide
460	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperidine-1-carboxamide
461	4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
462	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperidine-1-carboxamide
463	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-4-hydroxy-N-(4-(hydroxycarbamoyl)benzyl)piperidine-1-carboxamide
464	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylmorpholine-4-carboxamide
465	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-4-hydroxy-N-(4-(hydroxycarbamoyl)benzyl)-4-phenylpiperidine-1-carboxamide
466	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide
467	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-(2-

	hydroxyethyl)piperazine-1-carboxamide
468	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)pyrrolidine-1-carboxamide
469	(S)-N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)-2-(hydroxymethyl)pyrrolidine-1-carboxamide
470	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-4-(cyclopropanecarbonyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
471	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)azetidine-1-carboxamide
477	N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethylmorpholine-4-carboxamide
478	N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-methylpiperazine-1-carboxamide
479	N-(3-chloro-4-fluorophenyl)-4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
480	4-benzyl-N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
481	N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)-4-(2-methoxyphenyl)piperazine-1-carboxamide
482	N-(3-chloro-4-fluorophenyl)-4-(4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
483	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(tetrahydro-2H-pyran-4-yl)phenyl)morpholine-4-carboxamide
484	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-methoxyphenyl)morpholine-4-carboxamide
485	3,3-difluoro-N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)azetidine-1-carboxamide
486	4-hydroxy-N-(4-(hydroxycarbamoyl)benzyl)-4-phenyl-N-(4-(trifluoromethyl)phenyl)piperidine-1-carboxamide
487	N-(3-bromophenyl)-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
488	N-(3-bromophenyl)-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)-4-hydroxypiperidine-1-carboxamide
489	tert-butyl 4-(3-(N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamido)phenyl)piperidine-1-carboxylate
490	N-(3-(1-acetylpiperidin-4-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
491	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-(methylsulfonyl)piperidin-4-

	yl)phenyl)morpholine-4-carboxamide
492	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(1-(isopropylcarbamoyl)piperidin-4-yl)phenyl)morpholine-4-carboxamide
493	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(piperidin-4-yl)phenyl)morpholine-4-carboxamide hydrochloride
494	4-acetyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
495	(R)-3-fluoro-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide
496	(S)-3-fluoro-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide
497	(R)-N-(4-(hydroxycarbamoyl)benzyl)-2-(hydroxymethyl)-N-(3-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide
498	(S)-N-(4-(hydroxycarbamoyl)benzyl)-2-(trifluoromethyl)-N-(3-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide
499	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(hydroxymethyl)phenyl)morpholine-4-carboxamide
500	N-(3-(fluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
511	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
512	N-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
513	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)-4-hydroxypiperidine-1-carboxamide
514	N-(3-(3,6-dihydro-2H-pyran-4-yl)phenyl)-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)-4-hydroxypiperidine-1-carboxamide
517	N-(3-(1-(2-hydroxy-2-methylpropyl)piperidin-4-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
518	N-(3-(1-(2-fluoro-2-methylpropyl)piperidin-4-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
520	(R)-3-fluoro-N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide
521	(S)-3-fluoro-N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide
522	(R)-N-(4-(hydroxycarbamoyl)benzyl)-2-(hydroxymethyl)-N-(4-(trifluoromethyl)phenyl)pyrrolidine-1-carboxamide
529	4-acetyl-N-(3-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-

	carboxamide
530	N-(3-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
531	4-(2-fluoro-2-methylpropyl)-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
532	N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)morpholine-4-carboxamide
533	N-(5-chloropyridin-2-yl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
543	N-(4-(hydroxycarbamoyl)benzyl)-4-(2-morpholinoethyl)-N-(4-(trifluoromethyl)phenyl)piperazine-1-carboxamide
544	N-(4-(hydroxycarbamoyl)benzyl)-4-(pyridin-4-yl)-N-(4-(trifluoromethyl)phenyl)piperazine-1-carboxamide
545	N-(4-(hydroxycarbamoyl)benzyl)-4-(2-morpholino-2-oxoethyl)-N-(4-(trifluoromethyl)phenyl)piperazine-1-carboxamide
577	N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)morpholine-4-carboxamide
578	3,3-difluoro-N-(2-fluoro-4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)azetidine-1-carboxamide
580	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethyl)phenyl)-1,4-oxazepane-4-carboxamide
651	N-(4-(hydroxycarbamoyl)benzyl)-4-((4-hydroxytetrahydro-2H-pyran-4-yl)methyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
683	4-benzyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
684	N-(4-(hydroxycarbamoyl)benzyl)-4-(3-methoxyphenyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
716	4-((4-fluorotetrahydro-2H-pyran-4-yl)methyl)-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
717	N-(4-(hydroxycarbamoyl)benzyl)-4-phenyl-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
718	4-benzhydryl-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
765	4-ethyl-N-(3-(fluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
766	4-(2-fluoro-2-methylpropyl)-N-(3-(fluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)piperazine-1-carboxamide
771	N-(4-(hydroxycarbamoyl)benzyl)-N-(2-(trifluoromethoxy)phenyl)morpholine-4-

	carboxamide
772	N-(4-(hydroxycarbamoyl)benzyl)-N-(4-(trifluoromethoxy)phenyl)morpholine-4-carboxamide
773	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethoxy)phenyl)morpholine-4-carboxamide
774	N-(4-(hydroxycarbamoyl)benzyl)-N-(2-methoxy-5-(trifluoromethyl)phenyl)morpholine-4-carboxamide
776	N-(2-chloro-5-(trifluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
778	N-(4-(hydroxycarbamoyl)benzyl)-N-(6-(trifluoromethyl)pyridin-2-yl)morpholine-4-carboxamide
791	N-(2,3-difluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
797	(3S,5R)-4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
800	N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(3-(trifluoromethoxy)phenyl)morpholine-4-carboxamide
801	N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(2-(trifluoromethoxy)phenyl)morpholine-4-carboxamide
802	(3S,5R)-4-benzyl-N-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
803	(3S,5R)-N-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-4-(2,2,3,3,3-pentafluoropropyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
826	4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(6-(trifluoromethyl)pyridin-2-yl)piperazine-1-carboxamide
827	N-(4-(hydroxycarbamoyl)benzyl)-2,6-dimethyl-N-(6-(trifluoromethyl)pyridin-2-yl)morpholine-4-carboxamide
828	N-(4-(hydroxycarbamoyl)benzyl)-N-(6-(trifluoromethyl)pyridin-2-yl)piperidine-1-carboxamide and
829	(S)-3-fluoro-N-(4-(hydroxycarbamoyl)benzyl)-N-(6-(trifluoromethyl)pyridin-2-yl)pyrrolidine-1-carboxamide

6. The compounds of Formula I, optical isomers thereof or pharmaceutically acceptable salts thereof according to claim 5, wherein the compounds of Formula I are selected from the group consisting of the following compounds:

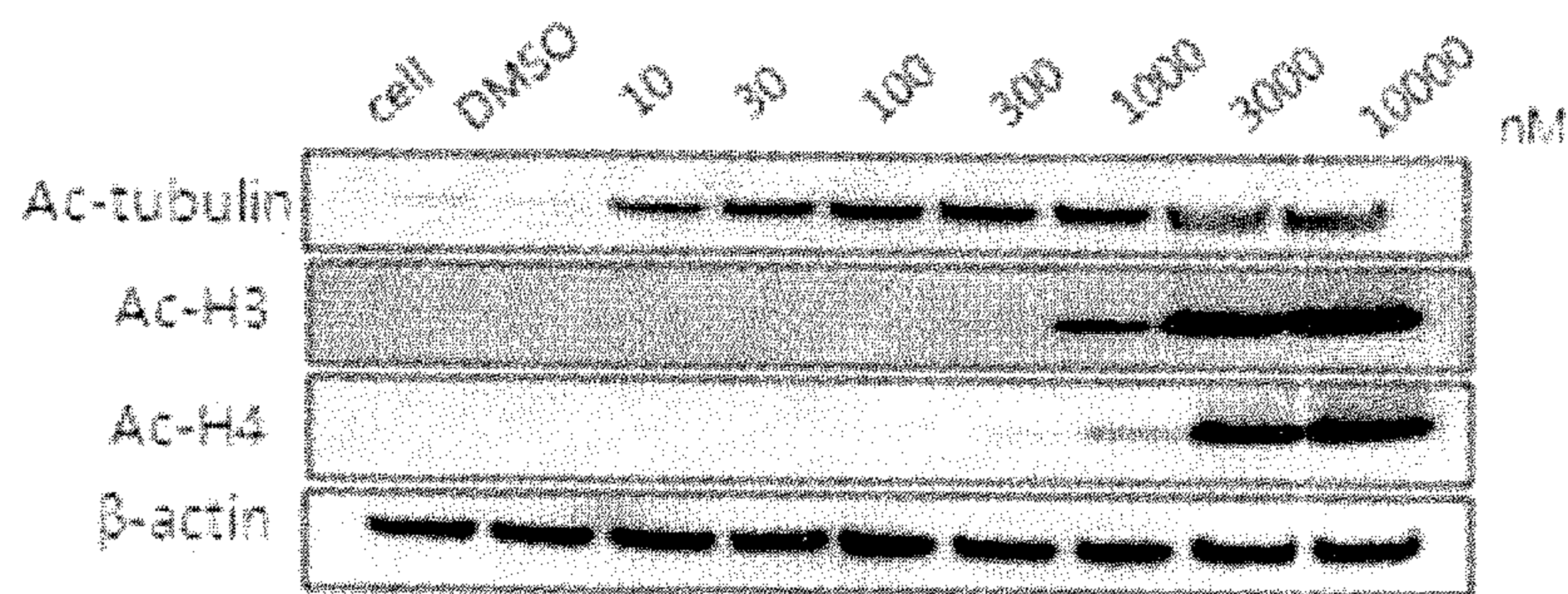
255	N-(3-bromophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
279	N-(4-(hydroxycarbamoyl)benzyl)-N-phenylmorpholine-4-carboxamide
280	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyridin-2-yl)morpholine-4-carboxamide
312	N-(4-(hydroxycarbamoyl)benzyl)-N-(pyrimidin-2-yl)morpholine-4-carboxamide
374	N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)morpholine-4-carboxamide
418	N-(3-(benzo[d][1,3]dioxol-5-yl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
458	N-(3-chloro-4-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
461	4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide
500	N-(3-(fluoromethyl)phenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide
530	N-(3-fluorophenyl)-N-(4-(hydroxycarbamoyl)benzyl)morpholine-4-carboxamide and
797	(3S,5R)-4-ethyl-N-(4-(hydroxycarbamoyl)benzyl)-3,5-dimethyl-N-(3-(trifluoromethyl)phenyl)piperazine-1-carboxamide

7. A pharmaceutical composition for the prevention or treatment of histone deacetylase-mediated diseases, comprising a pharmaceutically acceptable excipient, and a compound, an optical isomer thereof, or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 6 as an active ingredient.

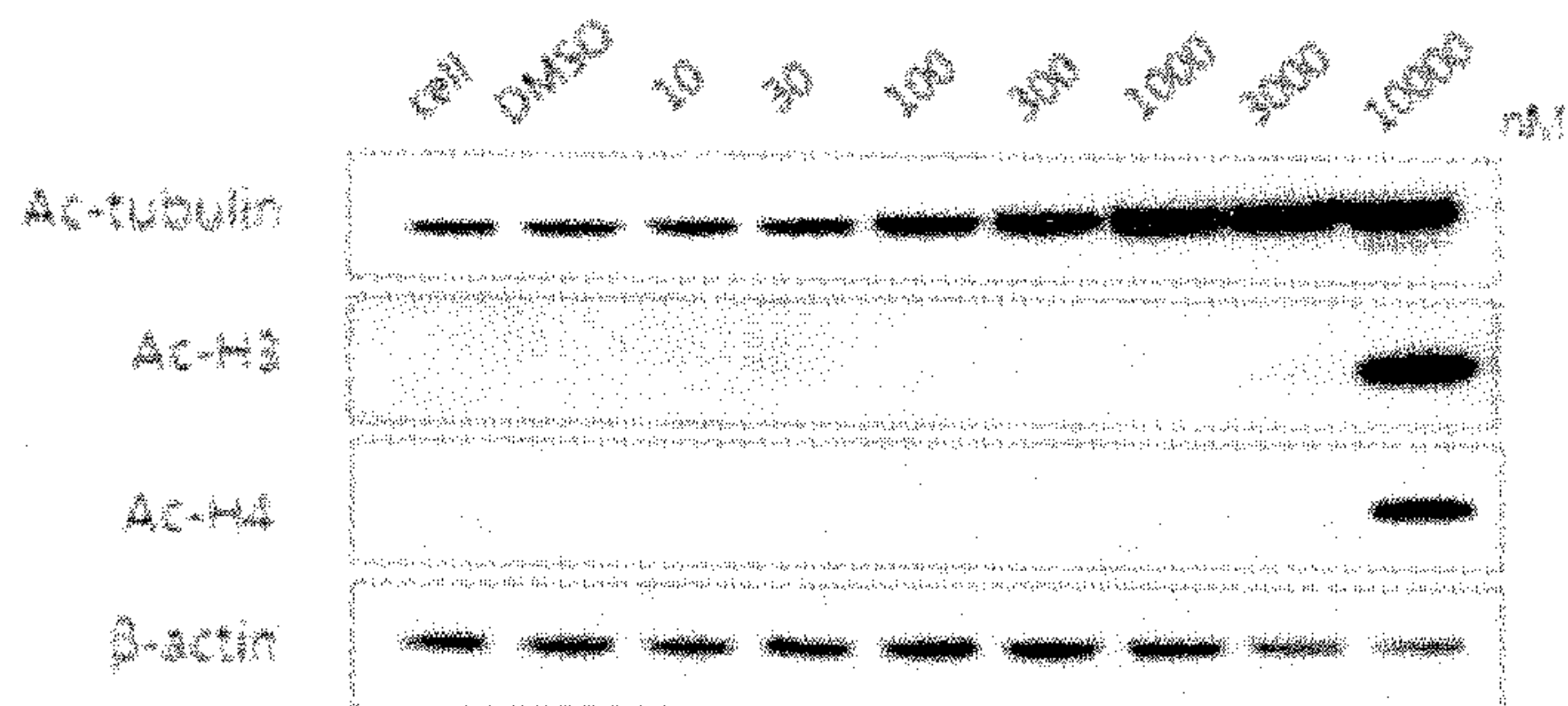
8. Use of a compound, an optical isomer thereof or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 6, for the treatment of histone deacetylase-mediated diseases.

9. The use of a compound, an optical isomer thereof or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 6 in the preparation of medicaments for the treatment of HDAC-mediated diseases.

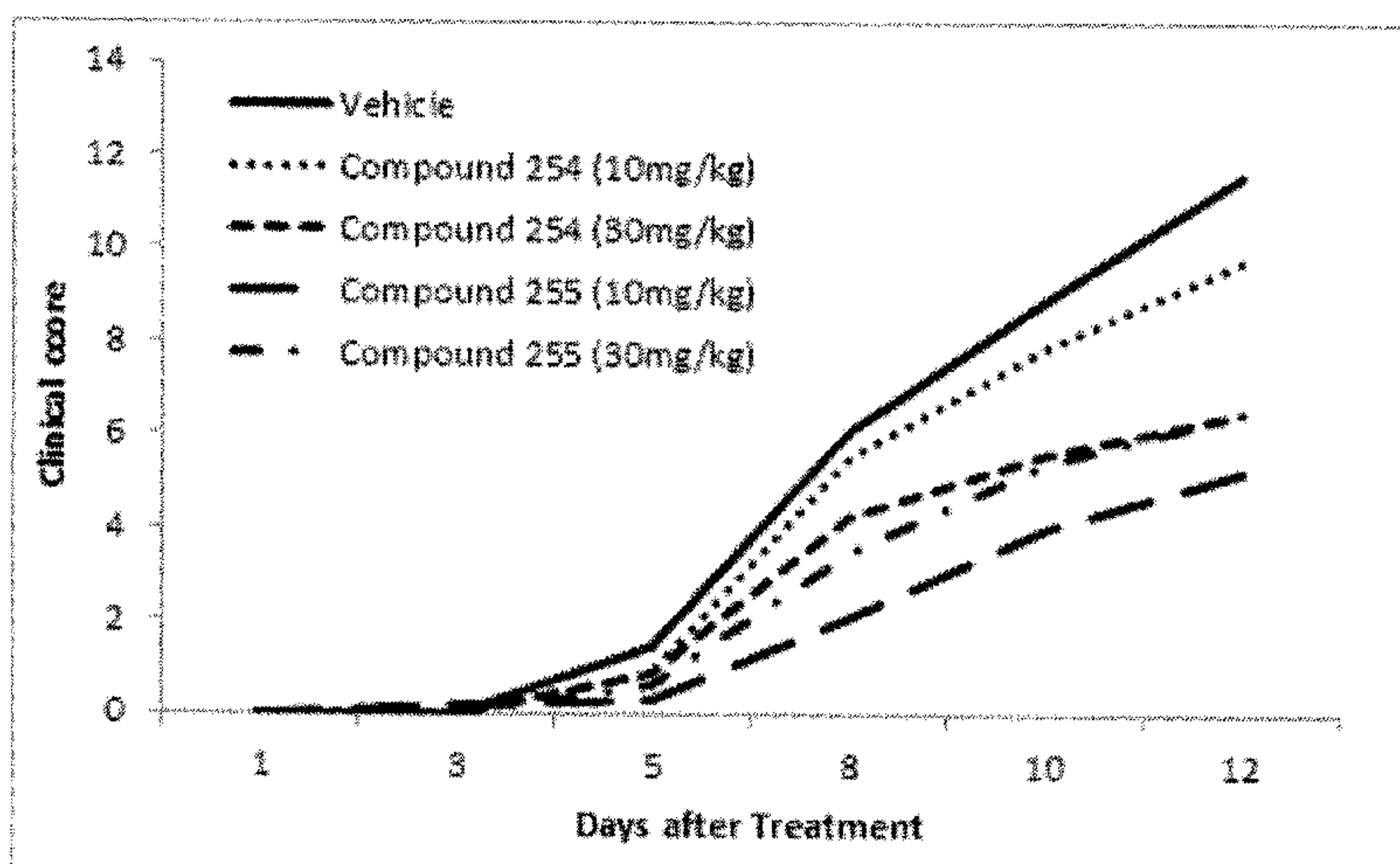
[Fig. 1]



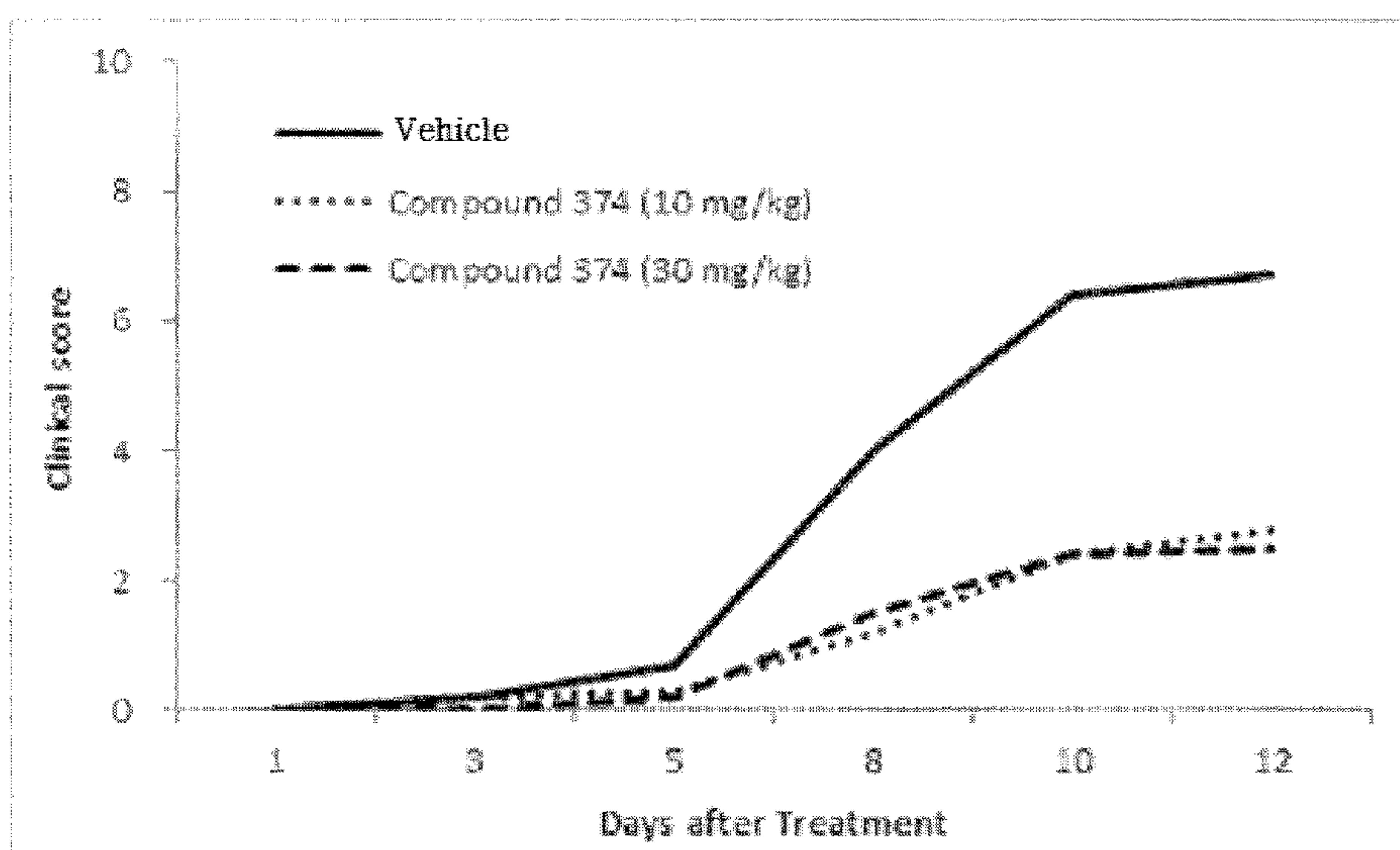
[Fig. 2]



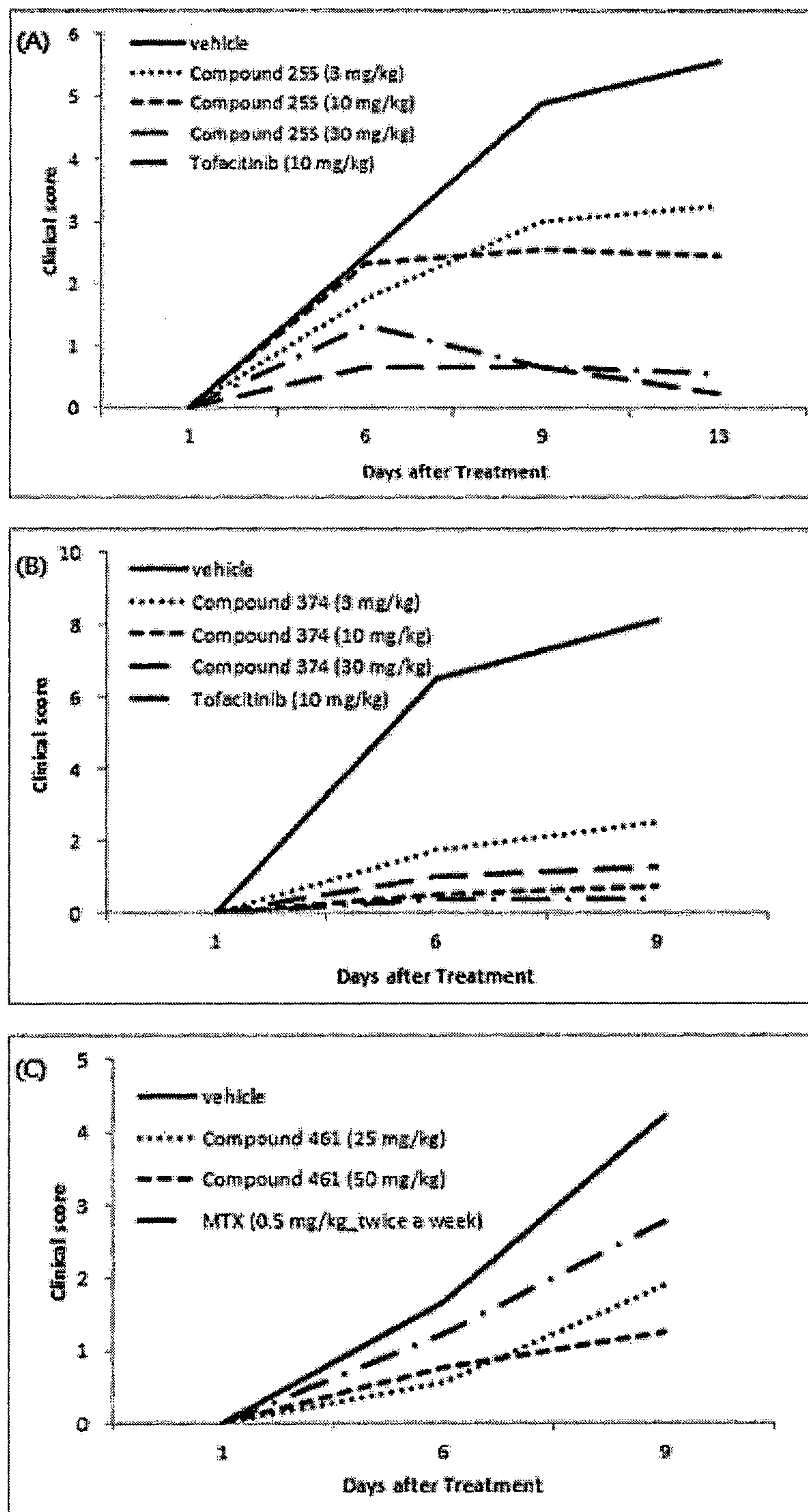
[Fig. 3]



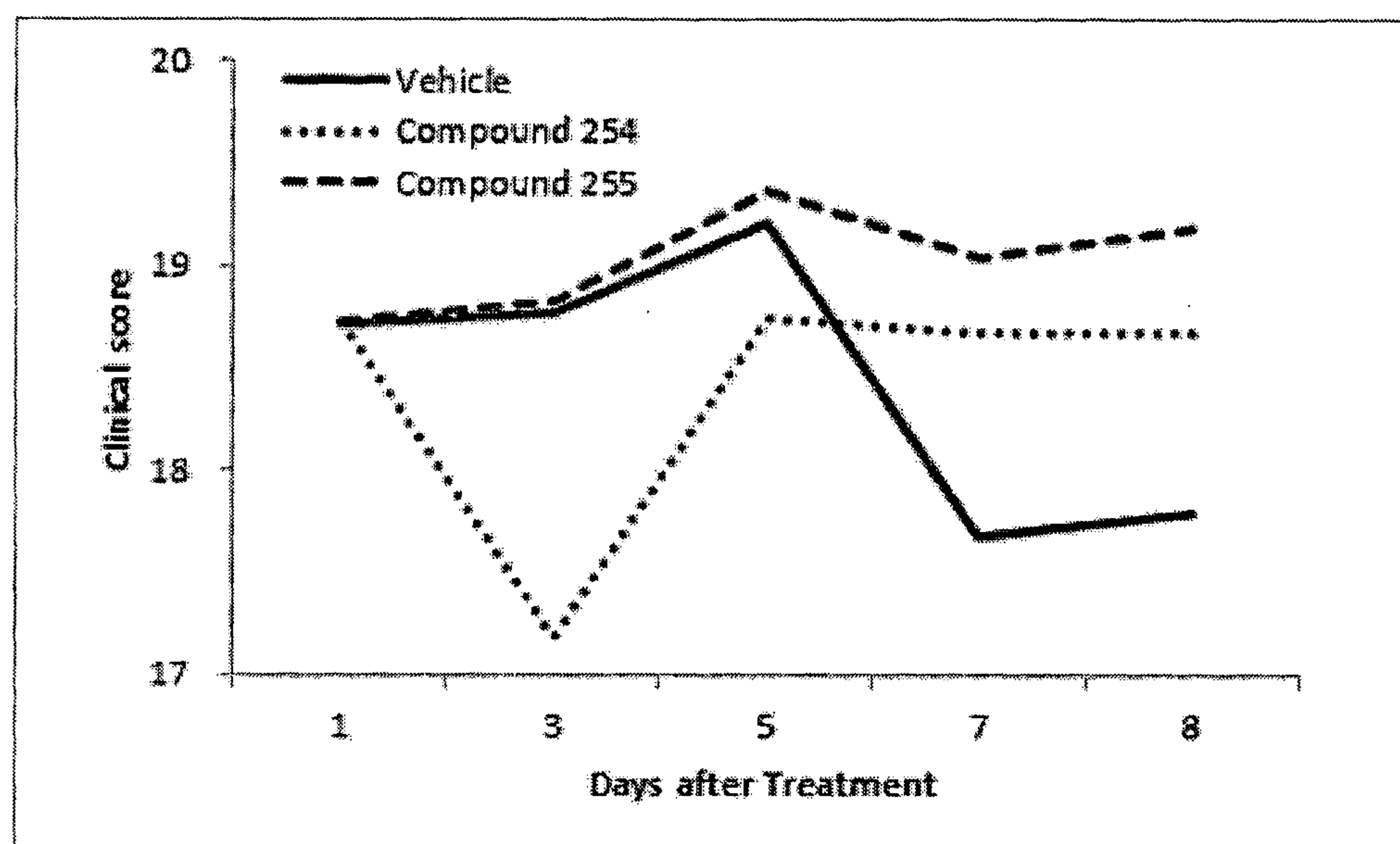
[Fig. 4]



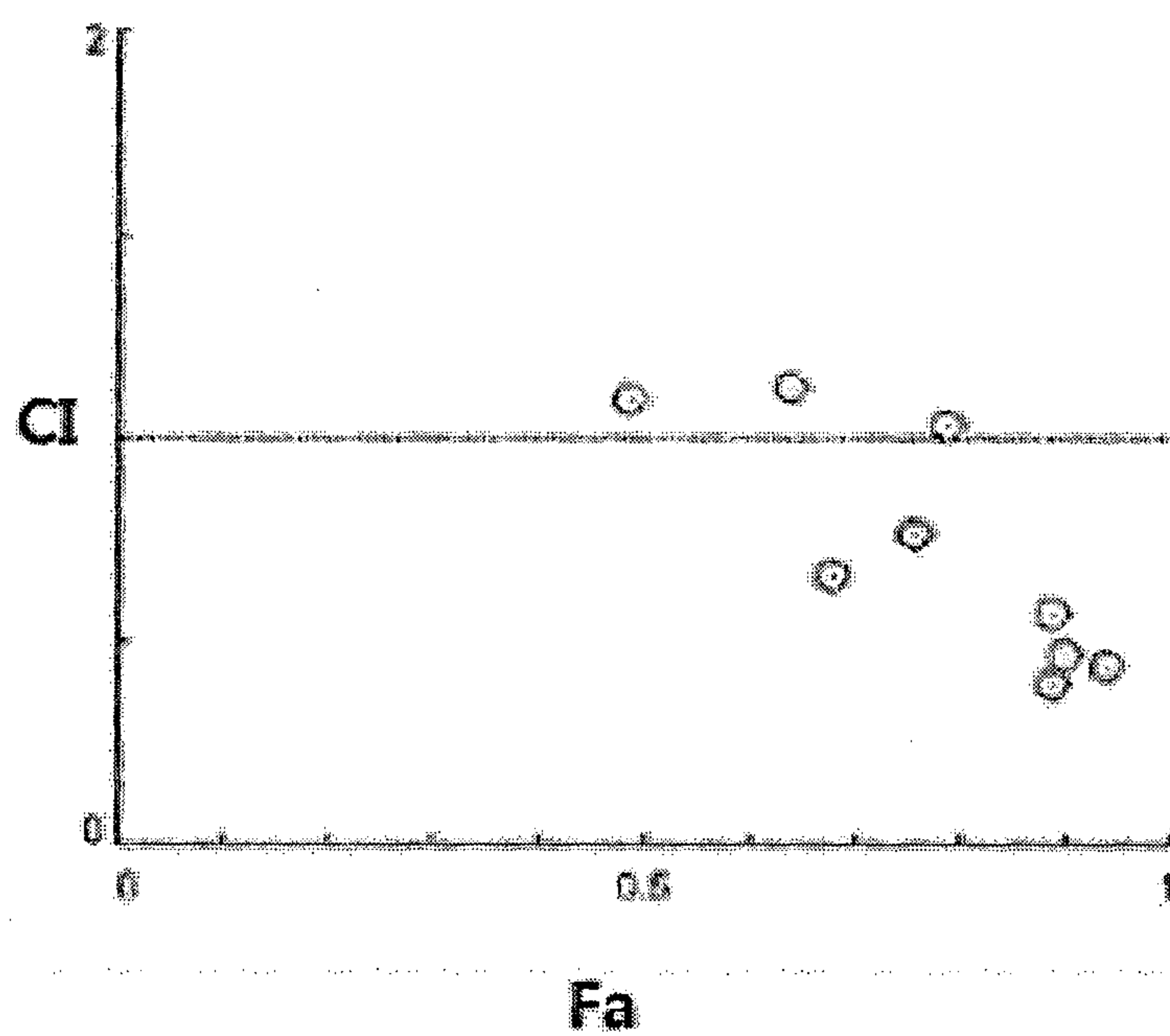
[Fig. 5]



[Fig. 6]



[Fig. 7]



CELL ONE



1000

3000

nm

AC-tubulin

AC-43

AC-HA

3-amin