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(54) Titre : DERIVES DE SULFONAMIDE ET UTILISATION ASSOCIEE POUR INHIBER UN PROCEDE DEPENDANT DE
L'INTEGRINE $\alpha 4 \beta 7$

(54) Title: SULFONAMIDE DERIVATIVES AND THEIR USE IN THE INHIBITION OF $\alpha 4 \beta 7$ INTEGRIN-DEPENDENT
PROCESS

(57) Abrégé/Abstract:

Provided are sulfonamide derivatives of a specific chemical structure in which a sulfonamide group having, as a substituent, a phenyl group or a heterocyclic group having a hetero atom(s) as a constituent element(s) is present at its terminal, and pharmaceutically acceptable salts thereof. These compounds are novel compounds having excellent $\alpha 4$ integrin-inhibitory action.

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Abstract

Provided are sulfonamide derivatives of a specific chemical structure in which a sulfonamide group having, as a substituent, a phenyl group or a heterocyclic group having a
5 hetero atom(s) as a constituent element(s) is present at its terminal, and pharmaceutically acceptable salts thereof. These compounds are novel compounds having excellent $\alpha 4$ integrin-inhibitory action.

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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.

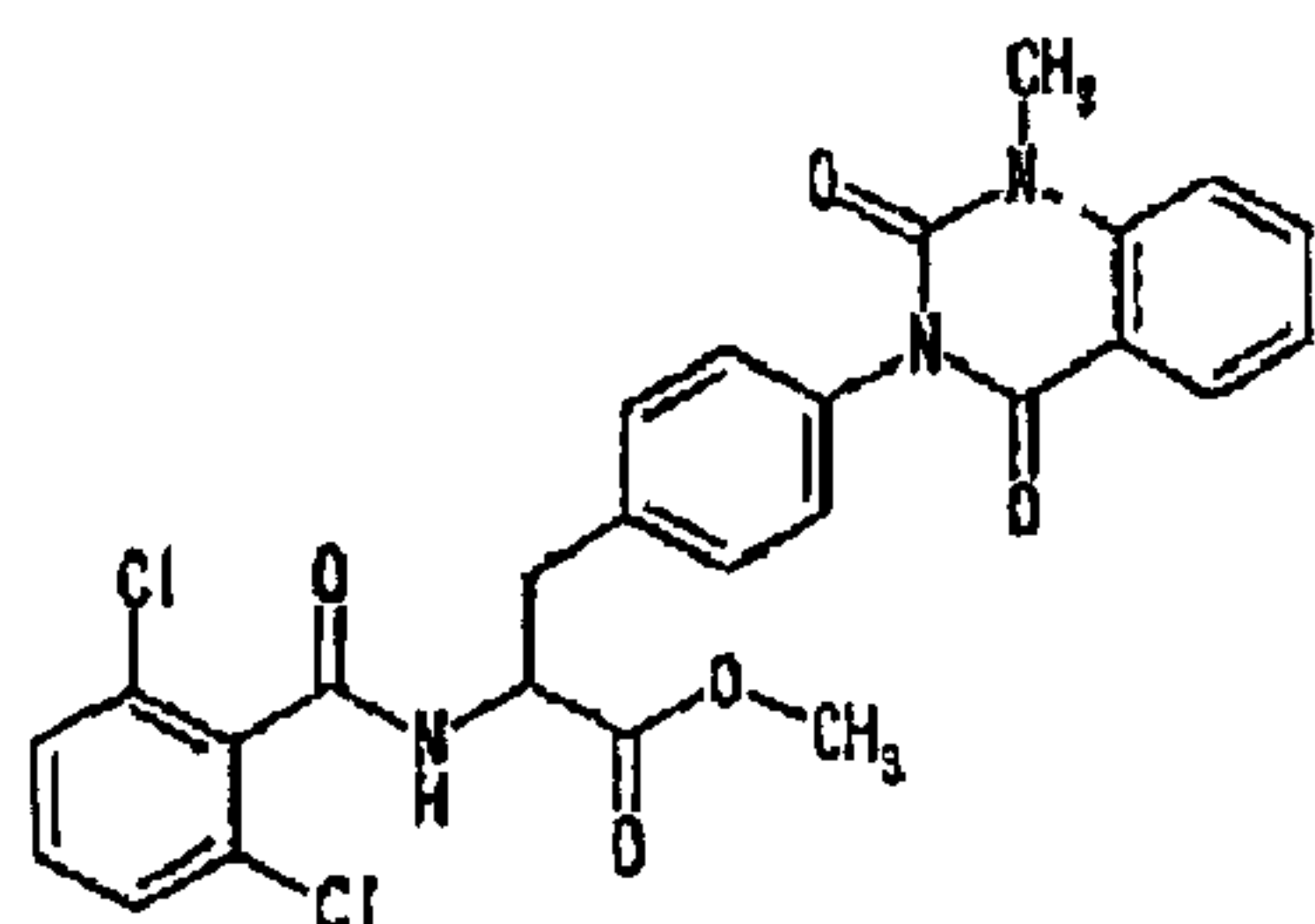
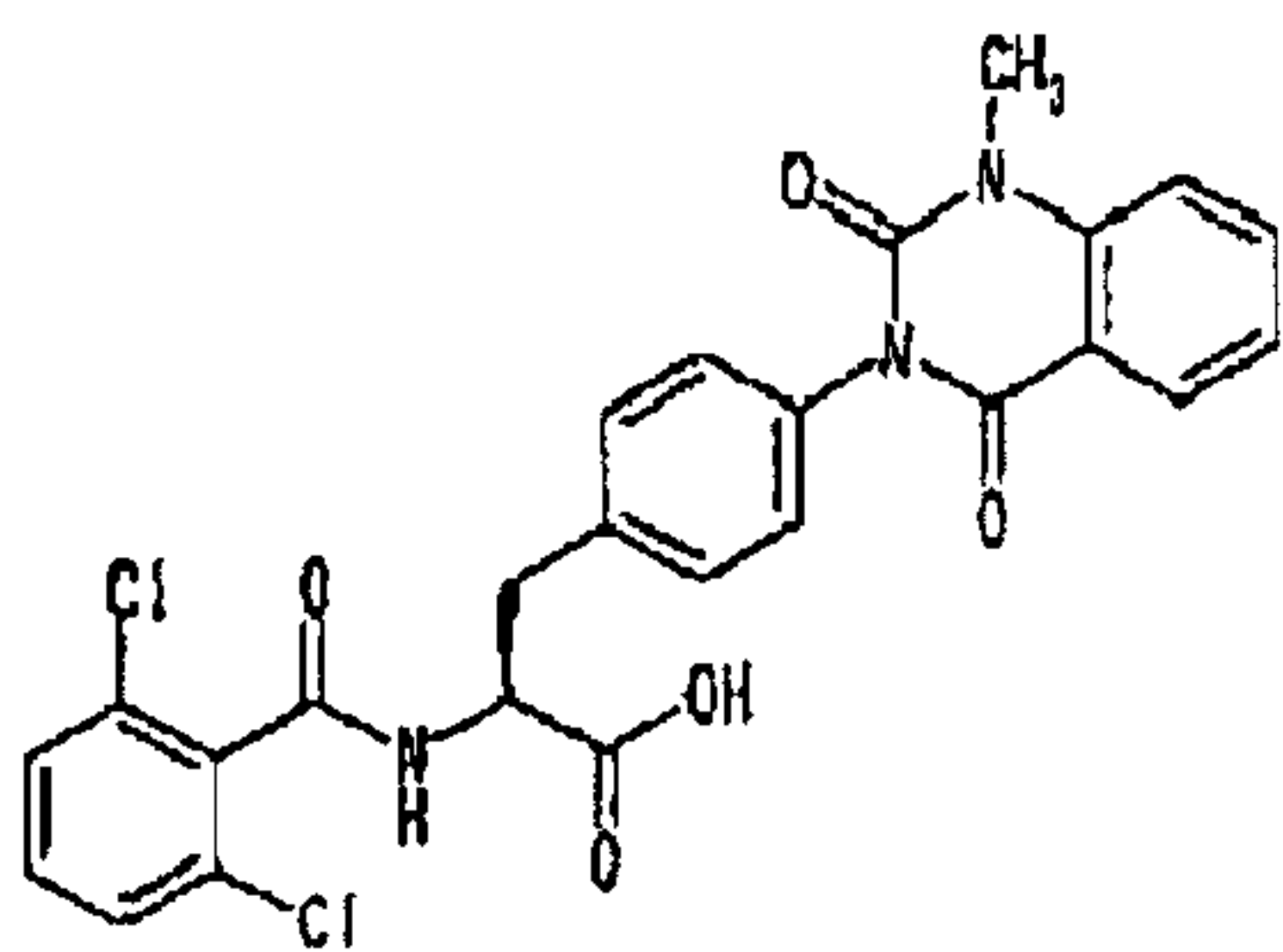
SULFONAMIDE DERIVATIVES AND THEIR USE IN THE INHIBITION OF $\alpha 4\beta 7$
INTEGRIN-DEPENDENT PROCESS

Technical Field

5 The present disclosure relates to a sulfonamide
derivative, a pharmaceutically acceptable salt thereof, and a
pharmaceutical composition comprising any of these compounds
as an active ingredient. Especially, the present disclosure
relates to a compounds useful for inhibiting an $\alpha 4\beta 7$ integrin,
10 and as such, may be useful as a drug for treating or preventing
an inflammatory disease in which an $\alpha 4\beta 7$ integrin-dependent
adhesion process is associated with a pathological condition.

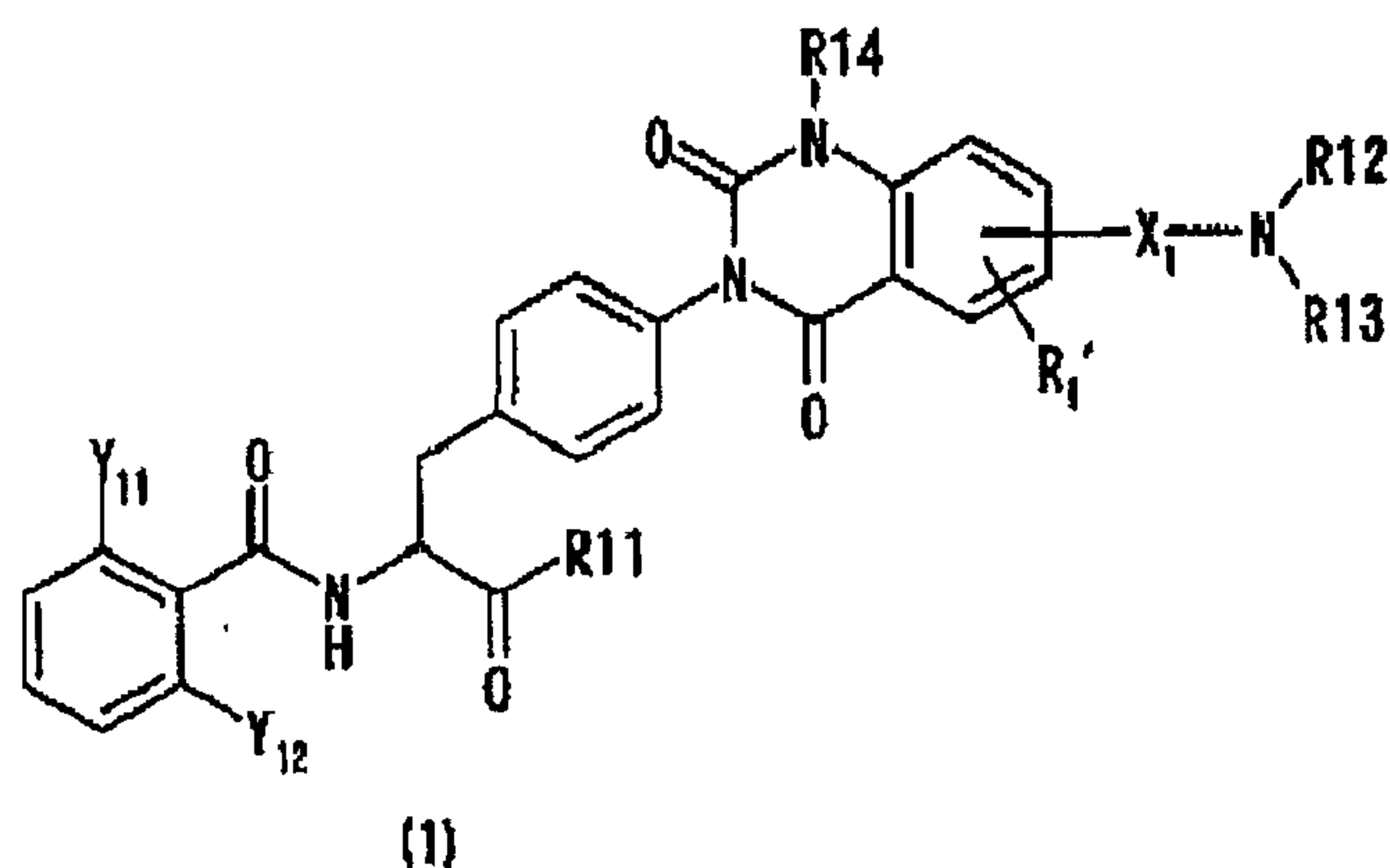
Background Art

Orally administrable compounds have been already known
15 which have $\alpha 4$ integrin-inhibitory action and which are useful
as drugs for treating or preventing an inflammatory disease in
which an $\alpha 4$ integrin-dependent adhesion process is associated
with a pathological condition. For example, Patent Literature
1 discloses a phenylalanine derivative represented by general
20 formula (1) and a pharmaceutically acceptable salt thereof, and
representative compounds thereof have the following chemical
structures.



In addition, Patent Literature 1 shows results of VCAM inhibition activities (VCAM-1/ α 4 β 1 Binding Assay) and (VCAM-1/ α 4 β 7 Binding Assay).

5 Moreover, Patent Literature 2 discloses a phenylalanine derivative being represented by the following general formula (1) and having an R12(R13)N-X1- group at its terminal or a pharmaceutically acceptable salt thereof.



10 This compound was shown to have higher VCAM-1/ α 4 β 1 integrin inhibition activity in the presence of serum than the compound of Example 1 of Patent Literature 1. In addition, Patent Literature 3 also discloses a compound having α 4

integrin-inhibitory action.

Citation List

Patent Literatures

Patent Literature 1: WO02/16329A1

5 Patent Literature 2: WO05/061466A1

Patent Literature 3: WO03/070709A1

Summary of The Disclosure

The present disclosure provides novel compounds having a chemical structural formula which is not known yet and having
10 excellent $\alpha 4$ integrin-inhibitory action.

The present disclosure provides novel compounds having $\alpha 4\beta 7$ integrin-inhibitory selectivity over $\alpha 4\beta 1$.

The present disclosure may therefore provide orally administrable compounds having $\alpha 4\beta 7$ integrin-inhibitory
15 action.

The present disclosure provides a pharmaceutical composition comprising the above-described novel compounds and a pharmaceutically acceptable carrier.

The present disclosure therefore provides
20 compounds that may be useful for treating or preventing an inflammatory disease in which an $\alpha 4\beta 7$ integrin-dependent adhesion process is associated with a pathological condition.

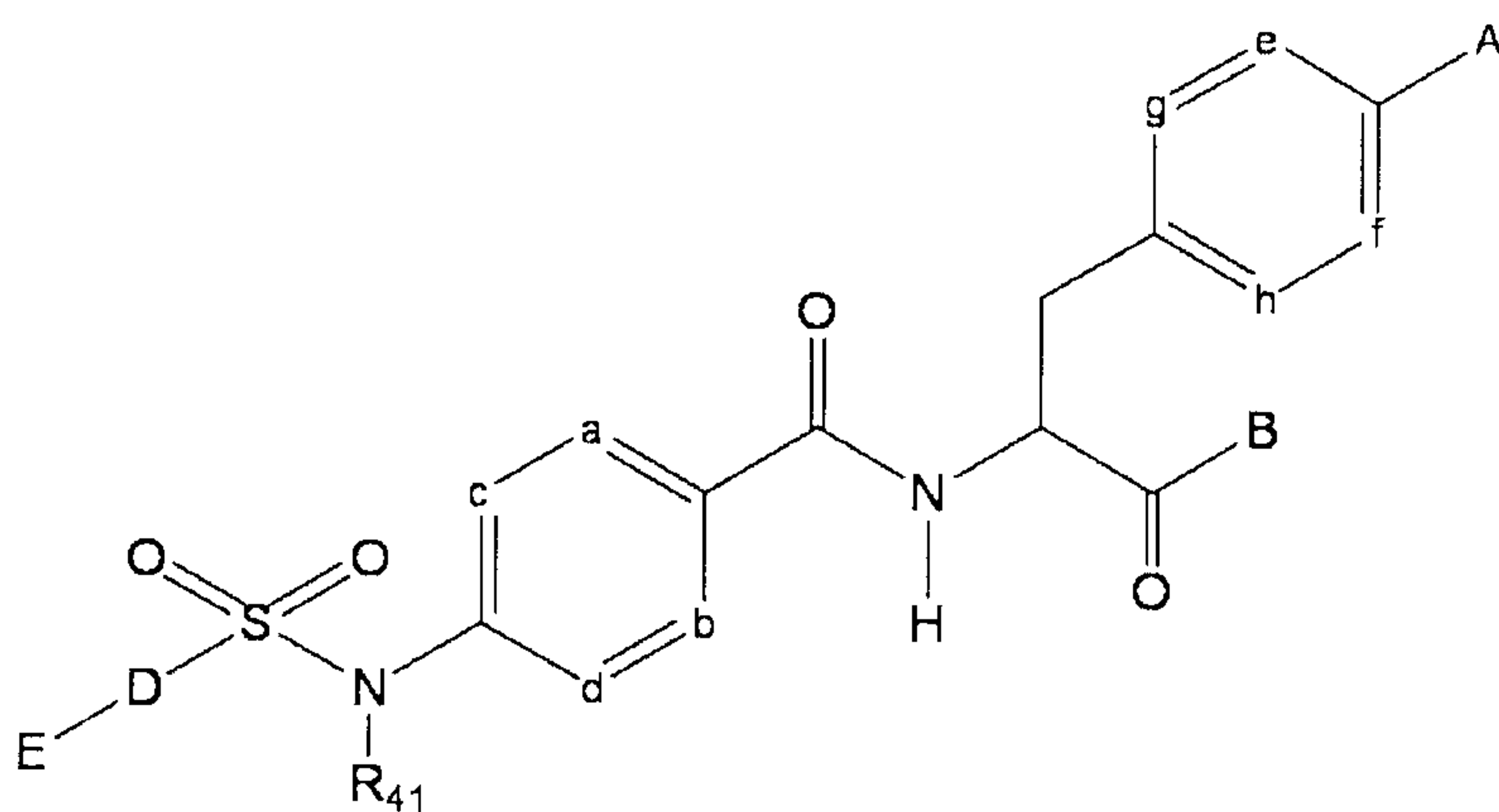
The present disclosure provides an $\alpha 4\beta 7$ integrin inhibitor.

25 The present disclosure has been made on the basis of findings that sulfonamide derivatives having a specific

chemical structure in which a sulfonamide group having, as a
 substituent, a phenyl group or a heterocyclic group containing
 a hetero atom(s) as constituent elements is present at its
 5 terminal and pharmaceutically acceptable salts thereof have
 $\alpha 4\beta 7$ integrin inhibition activity, and that the above-described
 aspects may be achieved by using these compounds.

Specifically, the present disclosure includes the
 following modes [1] to [17].

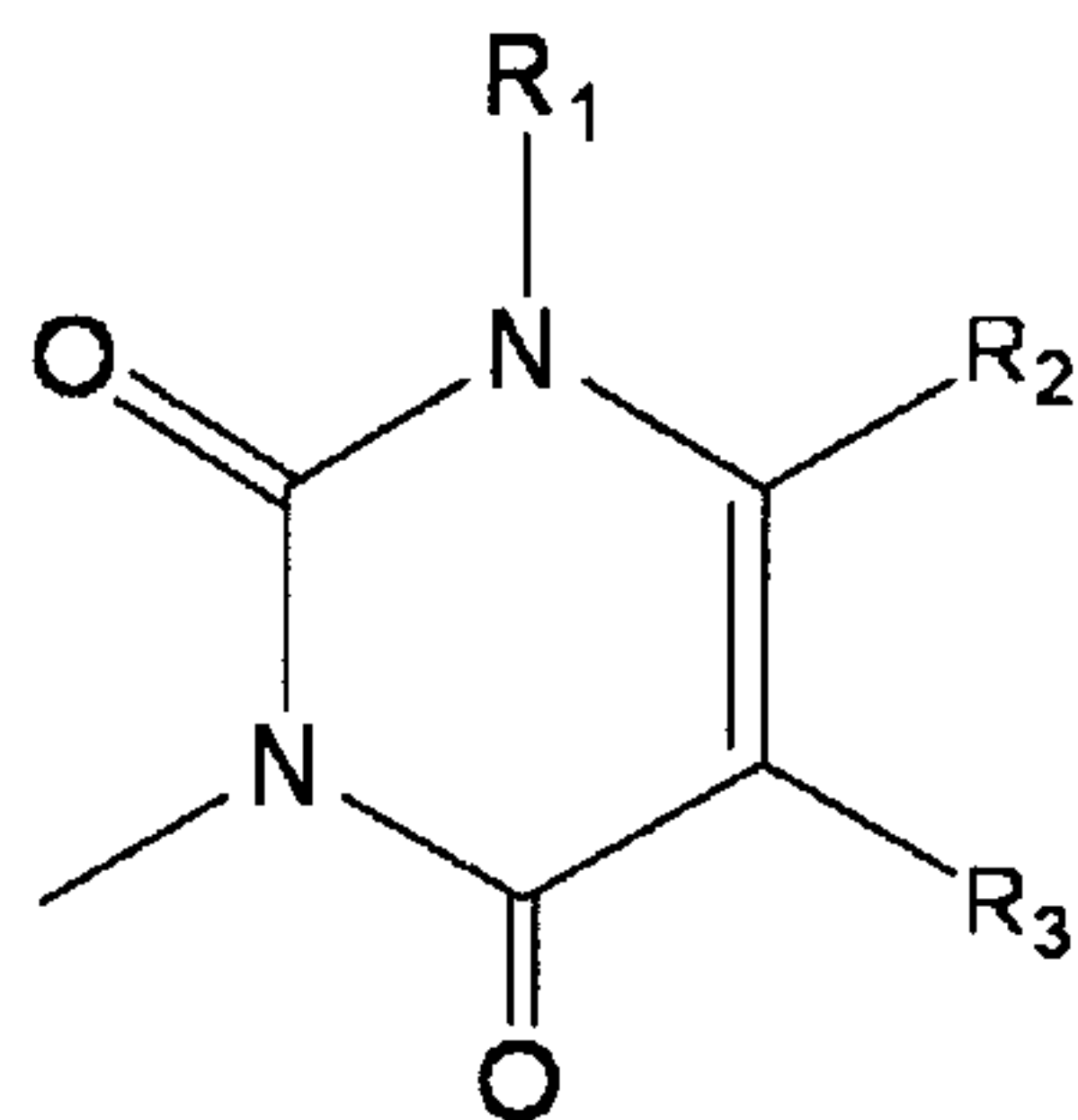
10 [1] A sulfonamide derivative represented by the following
 general formula (1) or a pharmaceutically acceptable salt
 thereof:



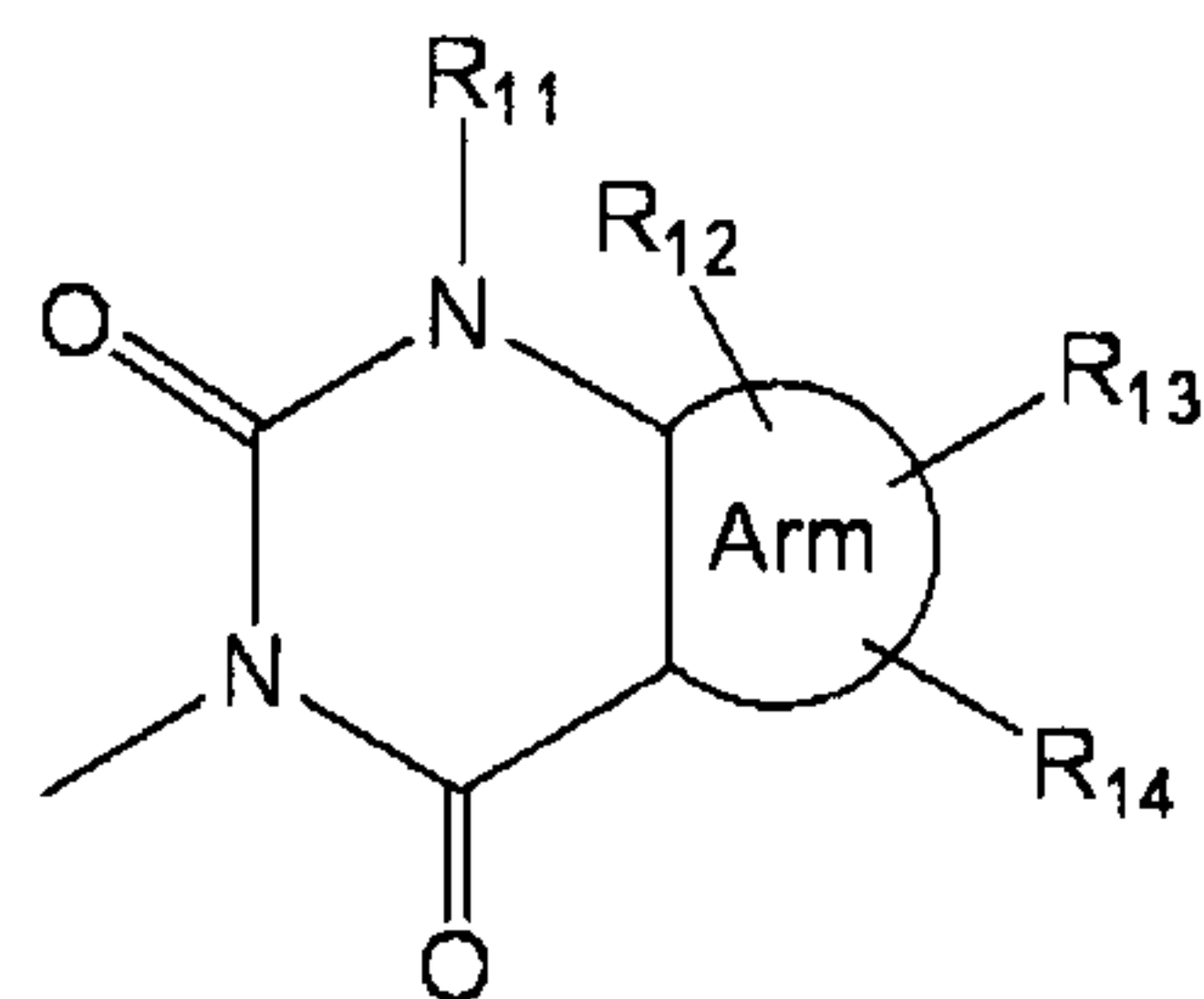
(1),

15 wherein

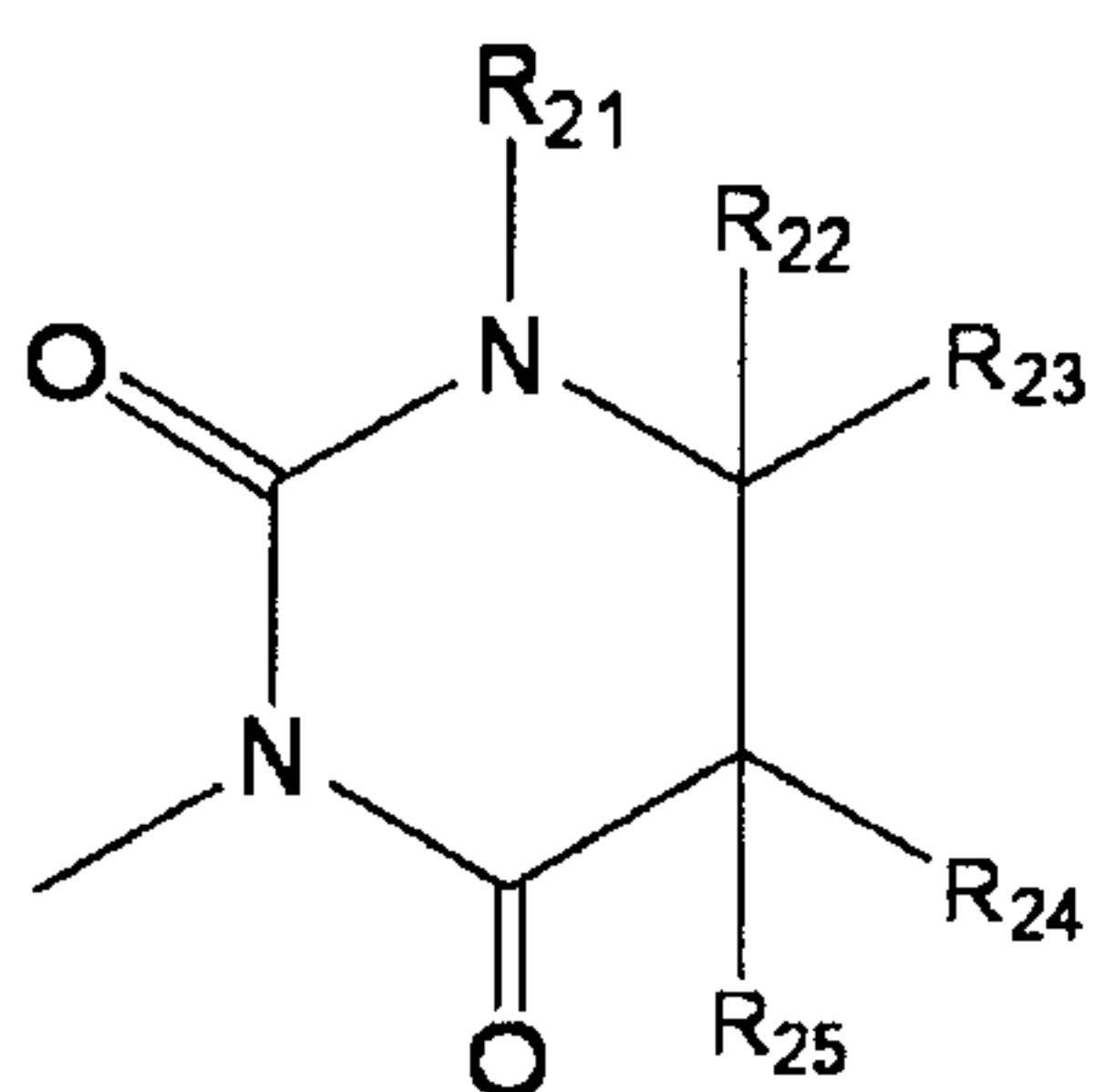
A represents a group represented by the following general
 formula (2-1), (2-2), or (2-3),



(2 - 1)



(2 - 2)



(2 - 3)

, wherein

Arm is a cyclic alkyl group or aromatic ring containing 0, 1, 2, 3, or 4 hetero atoms selected from oxygen atoms, sulfur atoms, and nitrogen atoms,

R1, R11, and R21 each independently represent any one of a hydrogen atom, a halogen atom, a hydroxyl group, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a lower alkoxy group, a lower alkylthio group, a lower hydroxyalkyl group, a lower hydroxyalkenyl group, a lower hydroxyalkoxy group, a lower halogenoalkyl group, a lower halogenoalkoxy group, a lower halogenoalkylthio group, a lower halogenoalkenyl group, a nitro group, a cyano group, an amino group, a lower alkylamino group, a (lower alkylamino)lower alkyl group, a carboxyl group, a lower alkyloxycarbonyl group, a carbamoyl group, a lower alkanoyl group, an aroyl group, a lower alkylsulfonyl group, a sulfamoyl group, and an ammonium group,

R12, R13, and R14 each independently represent any one of a hydrogen atom, a halogen atom, a hydroxyl group, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a lower alkoxy group, a lower alkylthio group, a lower hydroxyalkyl group, a lower hydroxyalkenyl group, a lower hydroxyalkoxy group, a lower halogenoalkyl group, a lower halogenoalkoxy group, a lower halogenoalkylthio group, a lower halogenoalkenyl group, a nitro group, a cyano group, an amino group, a lower alkylamino group, a (lower alkylamino)lower alkyl group, a carboxyl group, a lower alkyloxycarbonyl group, a carbamoyl group, a lower alkanoyl group, an aroyl group, a lower alkylsulfonyl group, a sulfamoyl group, and an ammonium group,

R2, R3, R22, R23, R24, and R25 each independently represent any one of a hydrogen atom, a halogen atom, a hydroxyl group, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a lower alkoxy group, a lower alkylthio group, a lower hydroxyalkyl group, a lower hydroxyalkenyl group, a lower hydroxyalkoxy group, a lower halogenoalkyl group, a lower halogenoalkoxy group, a lower halogenoalkylthio group, a lower halogenoalkenyl group, a nitro group, a cyano group, an amino group, a lower alkylamino group, a (lower alkylamino)lower alkyl group, a carboxyl group, a lower alkyloxycarbonyl group, a carbamoyl group, a lower alkanoyl group, an aroyl group, a lower alkylsulfonyl group, a sulfamoyl group, and an ammonium group,

B represents any one of a lower alkoxy group optionally substituted with an aryl group(s), a hydroxyl group(s), a lower alkyl group(s), a lower alkylamino group(s), and/or a heterocyclic group(s), a hydroxyl group, and a hydroxyamino

group,

R41 represents a hydrogen atom or a lower alkyl group,
a, b, c, and d each independently represent C-R31, C-R32,
C-R33, and C-R34, respectively, but one or two of a, b, c, and
5 d may each represent a nitrogen atom,

R31, R32, R33, and R34 each independently represent any
one of a hydrogen atom, a halogen atom, a lower alkyl group,
a lower alkoxy group, and a nitro group, provided that any one
of R31, R32, R33, and R34 is a halogen atom or a lower alkyl
10 group,

e, f, g, and h each independently represent C-R35, C-R36,
C-R37, and C-R38, respectively, but one or two of e, f, g, and
h may each represent a nitrogen atom,

R35, R36, R37, and R38 are each independently any one of
15 a hydrogen atom, a halogen atom, a lower alkyl group, a lower
alkoxy group, and a nitro group,

D represents a phenyl group or heterocyclic group
optionally having a substituent(s) selected from the group
consisting of halogen atoms, hydroxyl groups, lower alkyl
20 groups, lower alkenyl groups, lower alkynyl groups, lower
alkoxy groups, lower alkylthio groups, lower hydroxyalkyl
groups, lower hydroxyalkenyl groups, lower hydroxyalkoxy
groups, lower halogenoalkyl groups, lower halogenoalkoxy
groups, lower halogenoalkylthio groups, lower halogenoalkenyl
25 groups, nitro groups, cyano groups, amino groups, carboxyl
groups, lower alkyloxycarbonyl groups, carbamoyl groups, lower
alkanoyl groups, aroyl groups, lower alkylsulfonyl groups,
sulfamoyl groups, and ammonium groups, and

E represents a 5- or 6-membered heterocyclic group
30 optionally having a substituent(s) selected from the group

consisting of halogen atoms, hydroxyl groups, lower alkyl
 groups, lower alkenyl groups, lower alkynyl groups, lower
 alkoxy groups, lower alkylthio groups, lower hydroxyalkyl
 groups, lower hydroxyalkenyl groups, lower hydroxyalkoxy
 5 groups, lower halogenoalkyl groups, lower halogenoalkoxy
 groups, lower halogenoalkylthio groups, lower halogenoalkenyl
 groups, nitro groups, cyano groups, amino groups, 4- to
 6-membered cyclic amino groups, carboxyl groups, lower
 alkyloxycarbonyl groups, carbamoyl groups, lower alkanoyl
 10 groups, aroyl groups, lower alkylsulfonyl groups, sulfamoyl
 groups, and ammonium groups; an aminocarbonyl group optionally
 having a substituent(s) selected from the group consisting of
 hydroxyl groups, lower alkyl groups, lower alkenyl groups,
 lower alkynyl groups, lower alkoxy groups, lower hydroxyalkyl
 15 groups, lower hydroxyalkenyl groups, lower hydroxyalkoxy
 groups, lower halogenoalkyl groups, lower halogenoalkoxy
 groups, lower halogenoalkenyl groups, amino groups, lower
 alkylamino groups, aryl groups, heterocyclic groups,
 heterocycle-substituted lower alkyl groups, lower
 20 alkylsulfonyl groups, and sulfamoyl groups; a hydrogen atom,
 a halogen atom, a hydroxyl group, a lower alkyl group, a lower
 alkenyl group, a lower alkynyl group, a lower alkoxy group, a
 lower alkylthio group, a lower hydroxyalkyl group, a lower
 hydroxyalkenyl group, a lower hydroxyalkoxy group, a lower
 25 halogenoalkyl group, a lower halogenoalkoxy group, a lower
 halogenoalkylthio group, a lower halogenoalkenyl group, a nitro
 group, a cyano group, an amino group, a carboxyl group, a
 dihydroxyboryl group, a lower alkylcarbonyl group, a lower
 alkyloxycarbonyl group, a carbamoyl group, a lower alkanoyl
 30 group, an aroyl group, a lower alkylsulfonyl group, a sulfamoyl

group, an ammonium group, or a lower alkylaminoalkylene group, provided that the lower alkylcarbonyl group and the lower alkyloxycarbonyl group may each be bonded to the phenyl group represented by D to form a condensed ring.

5 [2] The sulfonamide derivative according to [1] or a pharmaceutically acceptable salt thereof, wherein

E represents a 5- or 6-membered heterocyclic group optionally having a substituent(s) selected from the group consisting of halogen atoms, hydroxyl groups, lower alkyl
10 groups, lower alkenyl groups, lower alkynyl groups, lower alkoxy groups, lower alkylthio groups, lower hydroxyalkyl groups, lower hydroxyalkenyl groups, lower hydroxyalkoxy groups, lower halogenoalkyl groups, lower halogenoalkoxy groups, lower halogenoalkylthio groups, lower halogenoalkenyl
15 groups, nitro groups, cyano groups, amino groups, carboxyl groups, lower alkyloxycarbonyl groups, carbamoyl groups, lower alkanoyl groups, aroyl groups, lower alkylsulfonyl groups, sulfamoyl groups, and ammonium groups; an aminocarbonyl group optionally having a substituent(s) selected from the group
20 consisting of hydroxyl groups, lower alkyl groups, lower alkenyl groups, lower alkynyl groups, lower alkoxy groups, lower hydroxyalkyl groups, lower hydroxyalkenyl groups, lower hydroxyalkoxy groups, lower halogenoalkyl groups, lower halogenoalkoxy groups, lower halogenoalkenyl groups, amino
25 groups, lower alkylamino groups, aryl groups, heterocyclic groups, lower alkylsulfonyl groups, and sulfamoyl groups; a hydrogen atom, a halogen atom, a hydroxyl group, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a lower alkoxy group, a lower alkylthio group, a lower hydroxyalkyl
30 group, a lower hydroxyalkenyl group, a lower hydroxyalkoxy

group, a lower halogenoalkyl group, a lower halogenoalkoxy group, a lower halogenoalkylthio group, a lower halogenoalkenyl group, a nitro group, a cyano group, an amino group, a carboxyl group, a dihydroxyboryl group, a lower alkyloxycarbonyl group, a carbamoyl group, a lower alkanoyl group, an aroyl group, a lower alkylsulfonyl group, a sulfamoyl group, an ammonium group, or a lower alkylaminoalkylene group.

[3] The sulfonamide derivative according to [1] or a pharmaceutically acceptable salt thereof, wherein

10 D is a phenyl group optionally having a substituent(s) selected from the group consisting of lower alkyl groups, halogen atoms, hydroxyl groups, and lower alkoxy groups.

[4] The sulfonamide derivative according to [1] or a pharmaceutically acceptable salt thereof, wherein

15 D is a 6-membered aromatic heterocyclic group containing a nitrogen atom(s) as a ring-constituent atom(s) and optionally having a substituent(s) selected from the group consisting of lower alkyl groups, halogen atoms, and lower alkoxy groups.

[5] The sulfonamide derivative according to [4] or a pharmaceutically acceptable salt thereof, wherein

the heterocyclic group represented by D is a pyridyl group or pyrrole group optionally having a substituent(s) selected from the group consisting of lower alkyl groups, halogen atoms, and lower alkoxy groups.

25 [6] The sulfonamide derivative according to any one of [1] to [5] or a pharmaceutically acceptable salt thereof, wherein

E is a 5- or 6-membered aromatic heterocyclic group containing 1, 2, 3, or 4 hetero atoms selected from oxygen atoms, sulfur atoms, and nitrogen atoms and optionally having a

30

substituent(s) selected from the group consisting of lower alkyl groups, lower alkoxy groups, and halogen atoms.

[7] The sulfonamide derivative according to [6] or a pharmaceutically acceptable salt thereof, wherein

5 the aromatic heterocyclic group is selected from the group consisting of a pyridyl group, a pyridazyl group, a pyrimidyl group, a pyrazinyl group, a pyrrolyl group, a furanyl group, a thiophenyl group, a thiazolyl group, an oxazolyl group, a triazolyl group, and a tetrazole group.

10 [8] The sulfonamide derivative according to any one of [1] to [4] or a pharmaceutically acceptable salt thereof, wherein

E is an aminocarbonyl group or lower alkylaminoalkylene group optionally substituted with a lower alkyl group(s), a
15 heterocyclic group(s), and/or a heterocycle-substituted lower alkyl group(s).

[9] The sulfonamide derivative according to any one of [1] to [6] and [8] or a pharmaceutically acceptable salt thereof, wherein

20 each lower alkyl group is a linear, branched, or cyclic alkyl group.

[10] The sulfonamide derivative according to any one of [1] to [9] or a pharmaceutically acceptable salt thereof, wherein

25 R1, R11, and R21 are lower alkyl groups.

[11] The sulfonamide derivative according to any one of [1] to [10] or a pharmaceutically acceptable salt thereof, wherein

Arm is selected from the group consisting of a phenyl group,
30 a pyridyl group, and an imidazolyl group.

[12] The sulfonamide derivative according to any one of [1] to [11] or a pharmaceutically acceptable salt thereof, wherein

one of R31, R32, R33, and R34 is a halogen atom, and the
5 rest are hydrogen atoms, or

two of R31, R32, R33, and R34 are halogen atoms, and the rest are hydrogen atoms.

[13] The sulfonamide derivative according to [1] or a pharmaceutically acceptable salt thereof, wherein

10 A is a group represented by general formula (2-1) or (2-2), in which Arm is a pyridyl group or an imidazolyl group, and R1 and R11 are lower alkyl groups,

two of R31, R32, R33, and R34 are halogen atoms, and the rest are hydrogen atoms,

15 g is a carbon or nitrogen atom,

e is a carbon or nitrogen atom,

D is a phenyl group optionally having a halogen atom(s), a lower alkyl group(s), and/or a lower alkoxy group(s), a furyl group, or a pyridyl group optionally having a halogen atom(s),
20 a lower alkyl group(s), and/or a lower alkoxy group(s), and

E is a pyridyl group, pyrimidyl group, triazolyl group, or pyrrolyl group optionally having a lower alkyl group(s) and/or a 4- to 6-membered cyclic amino group(s), or an aminocarbonyl group optionally substituted with a lower alkyl
25 or heterocycle-substituted lower alkyl group(s).

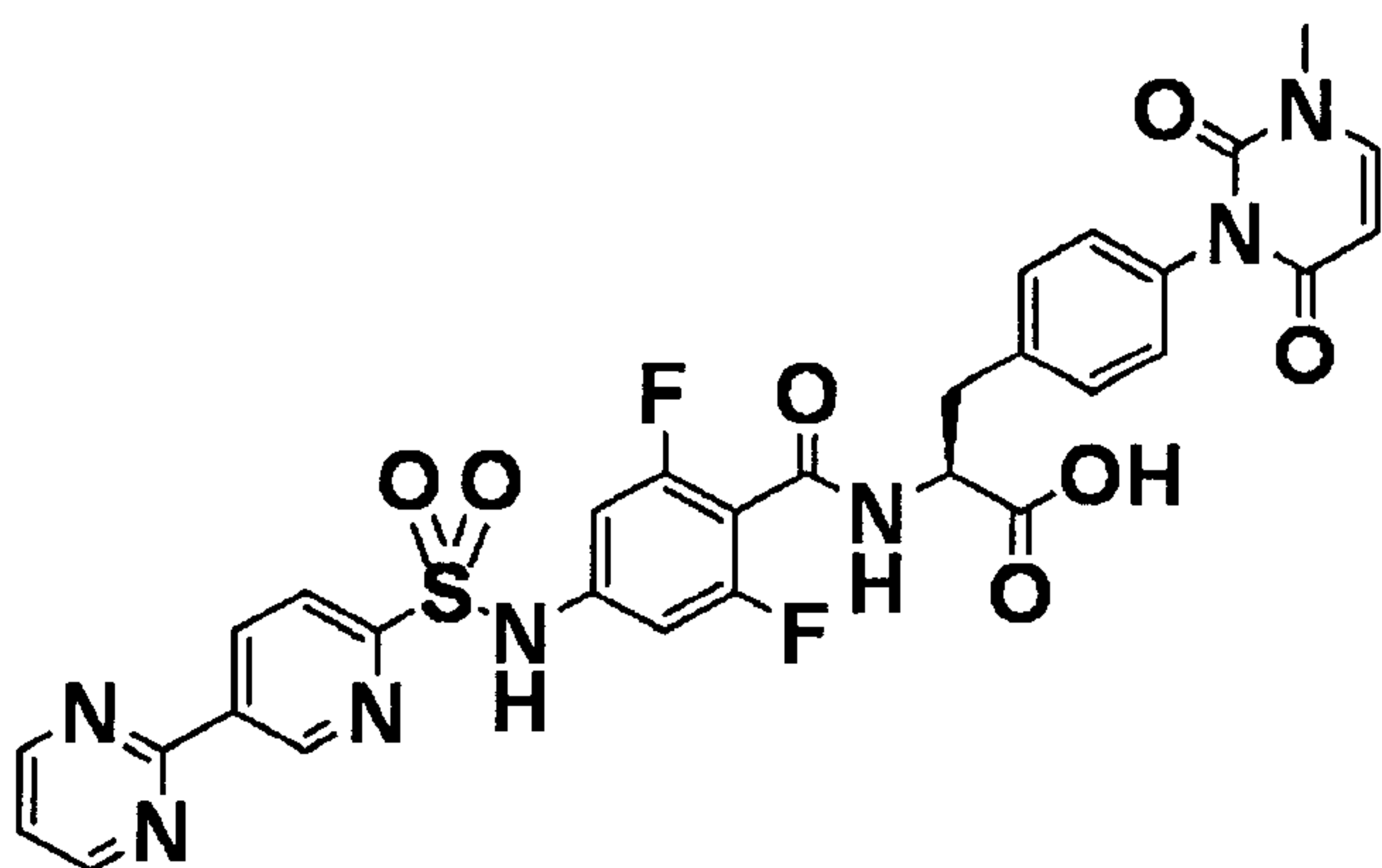
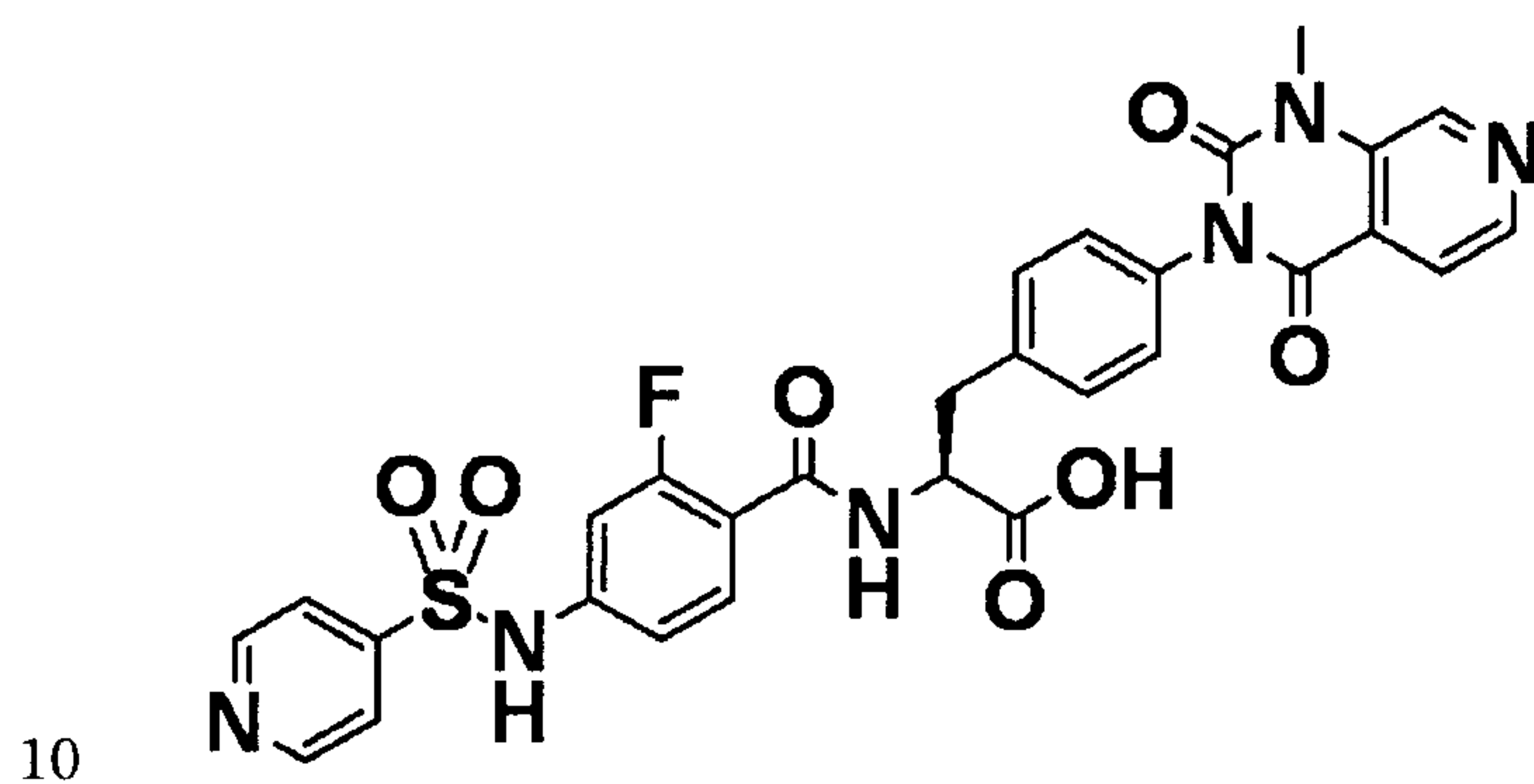
[14] A pharmaceutical composition comprising the sulfonamide derivative according to any one of [1] to [13] or a pharmaceutically acceptable salt thereof.

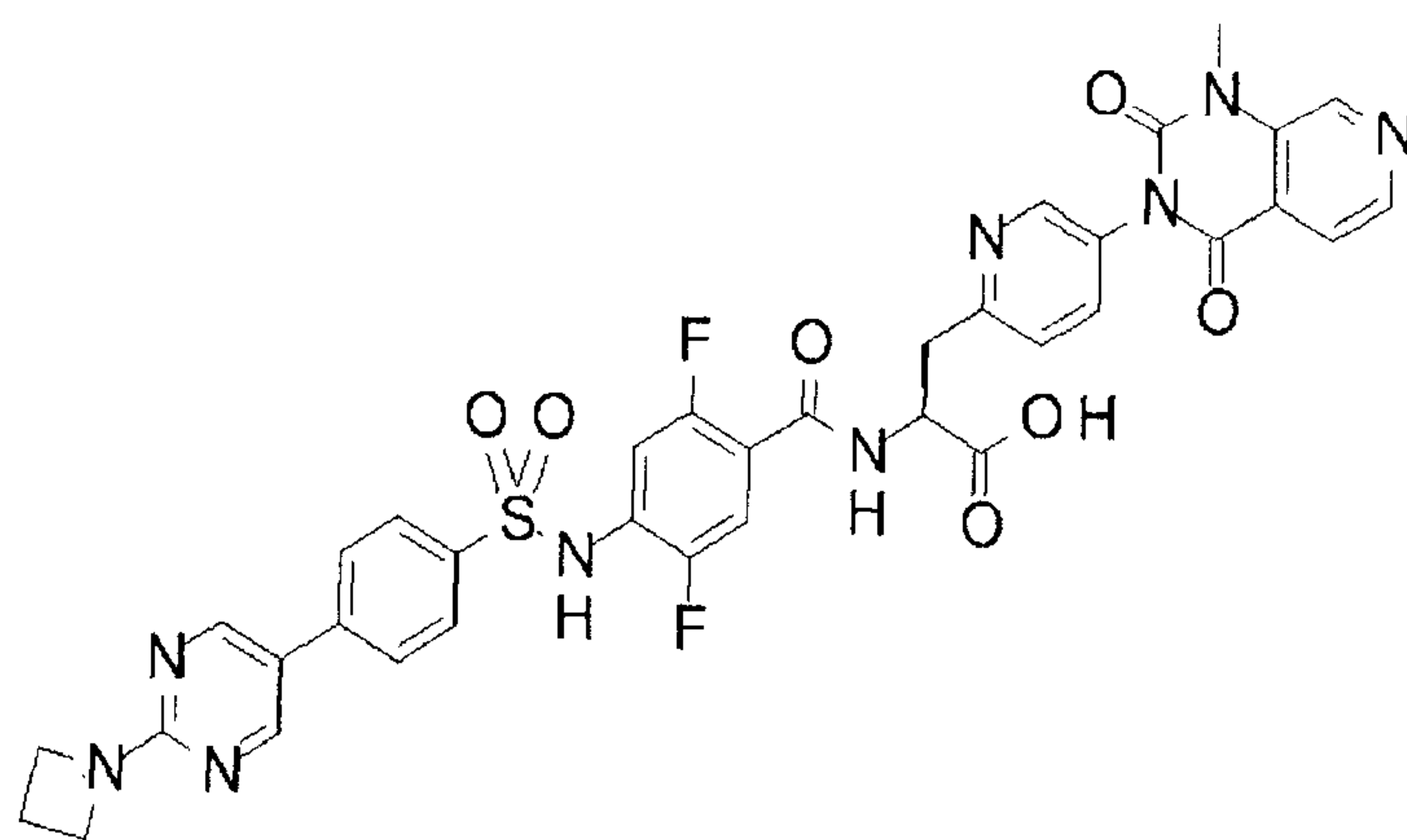
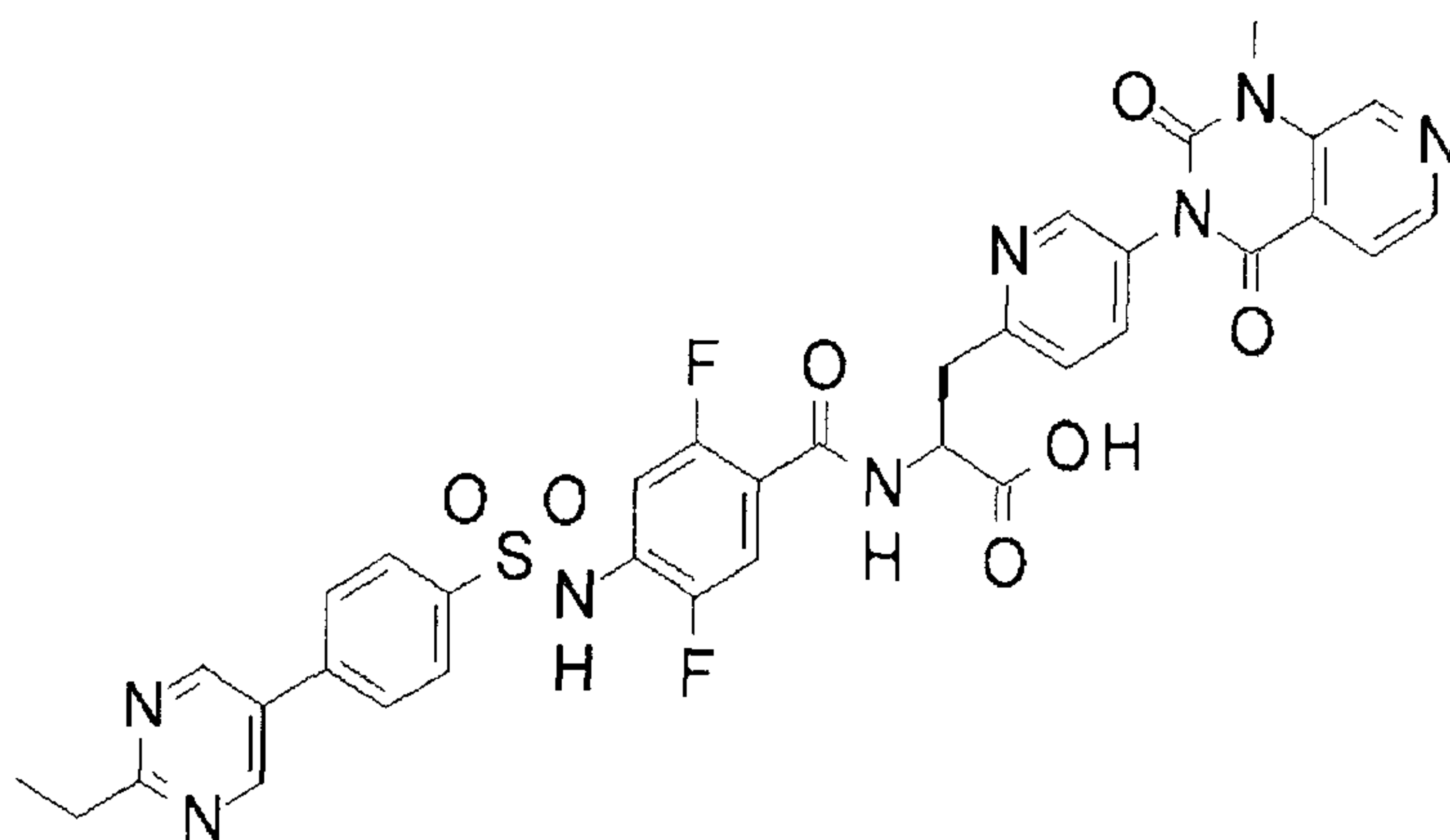
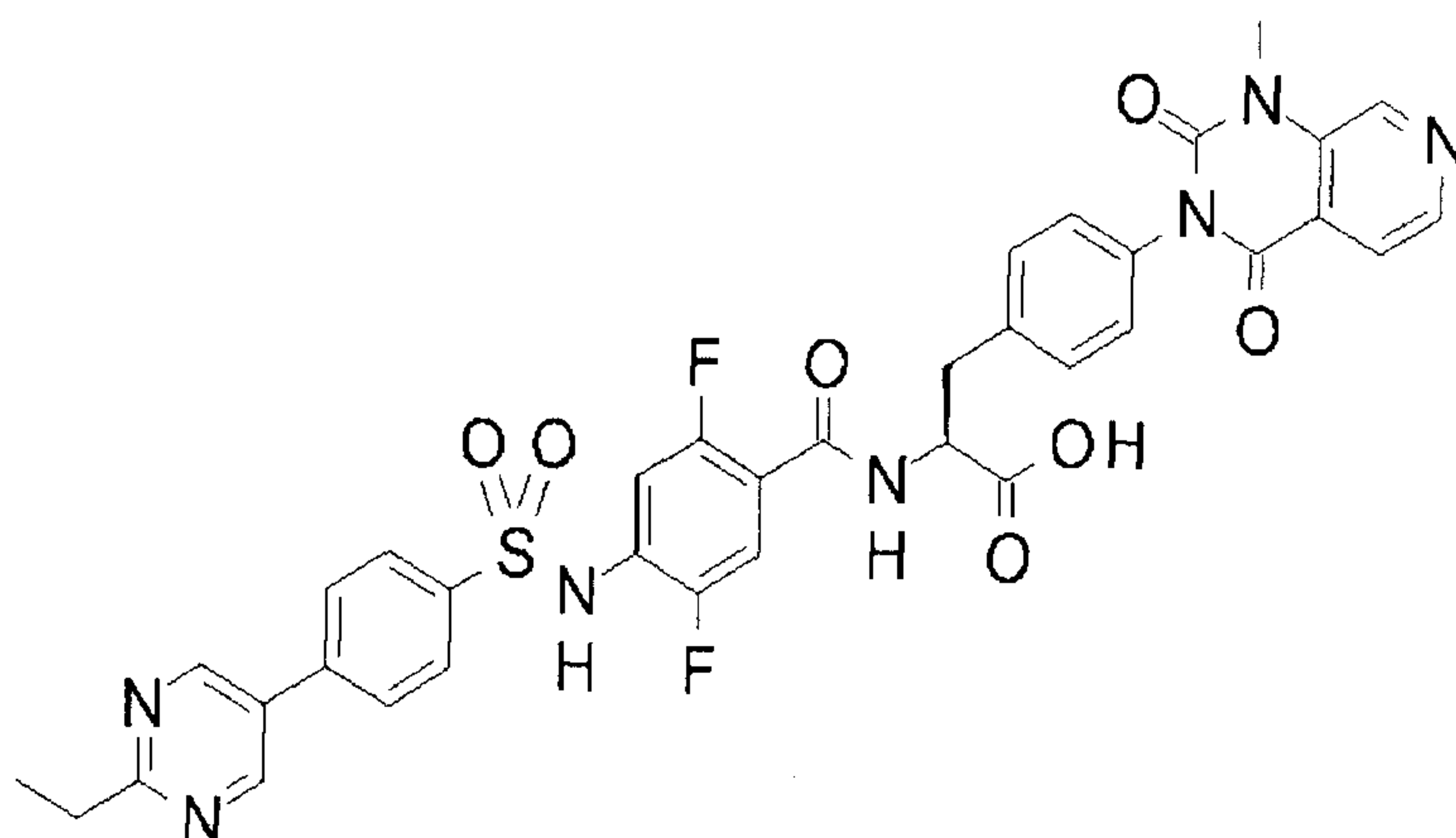
[15] An agent or composition that may be useful
30 for treating or preventing an inflammatory disease in which an $\alpha 4 \beta 7$ integrin-dependent adhesion process

is associated with a pathological condition, the agent comprising, as an active ingredient, the sulfonamide derivative according to any one of [1] to [13] or a pharmaceutically acceptable salt thereof.

5 [16] An $\alpha 4 \beta 7$ integrin inhibitor comprising, as an active ingredient, the sulfonamide derivative according to any one of [1] to [13] or a pharmaceutically acceptable salt thereof.

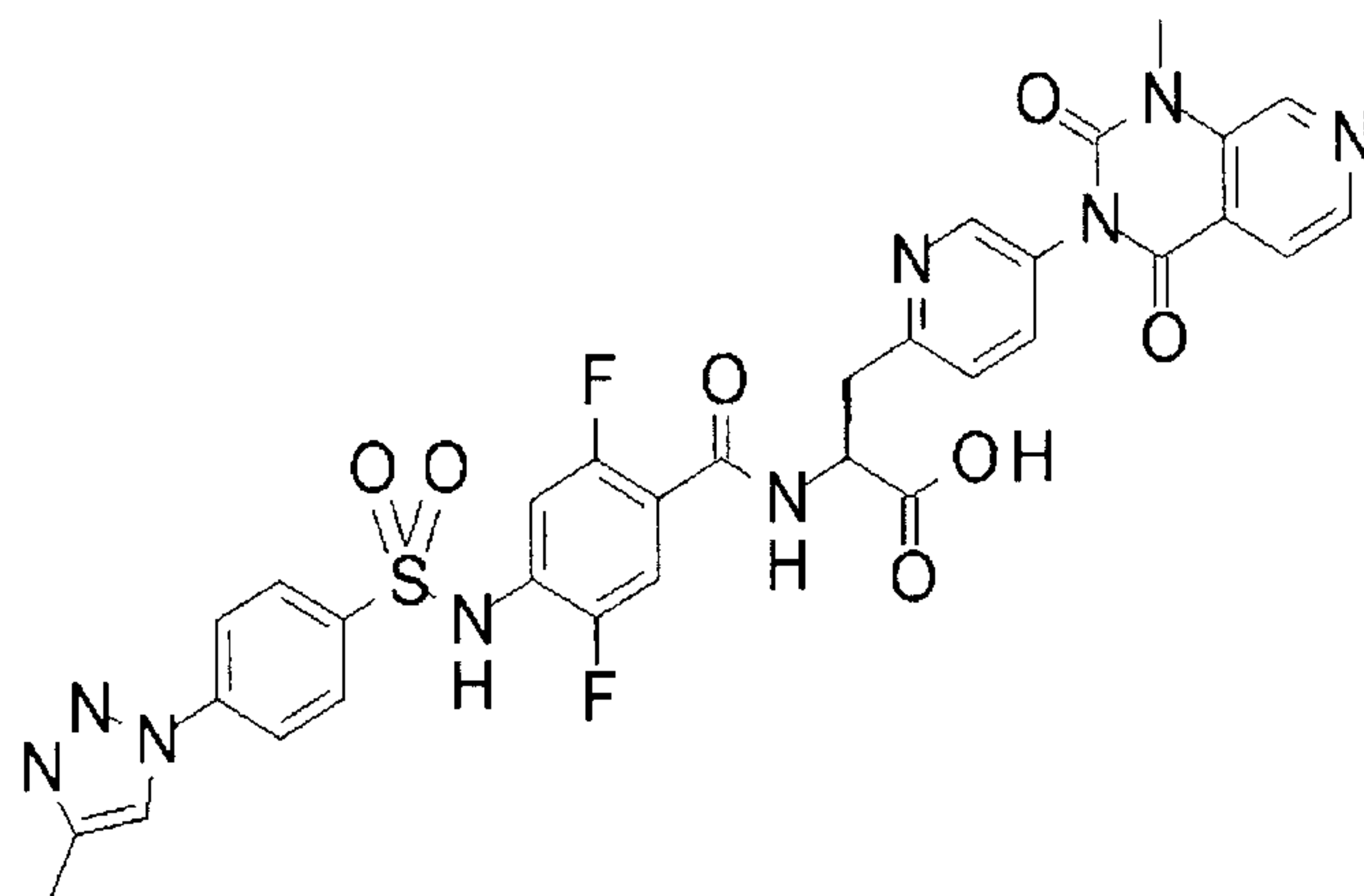
[17] A compound represented by any one of the following formulae or a pharmaceutically acceptable salt thereof:





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, and



Description of Embodiments

In this specification, the term "lower" in a lower alkyl group and the like means that the group has 1 to 6 carbon atoms, and preferably the number of carbon atoms is 1 to 4. An alkyl group, an alkenyl group, or an alkynyl group as a constituent in an alkyl group, an alkenyl group, an alkynyl group, an alkoxy group, an alkylthio group, an alkanoyl group, an alkylamino group, or the like may be linear, branched, or cyclic. Examples of the alkyl group include a methyl group, an ethyl group, a propyl group, an isopropyl group, a butyl group, a secondary butyl group, a tertiary butyl group, a pentyl group, a hexyl group, a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cyclopropylmethyl group, a cyclopropylethyl group, and the like. The alkyl group preferably has 1 to 6 carbon atoms and more preferably has 1 to 4 carbon atoms. The alkenyl group may be a vinyl group, a propenyl group, a butenyl group, a pentenyl group, or the like, and preferably has 2 to 6 carbon atoms, and more preferably has 2 to 4 carbon atoms. The alkynyl group may be an ethynyl group, a propynyl group, a butynyl group, or the like, and preferably has 2 to 6 carbon atoms and more preferably has 2 to 4 carbon atoms.

The alkoxy group may be a methoxy group, an ethoxy group, a propyloxy group, an isopropyloxy group, or the like, and preferably has 1 to 6 carbon atoms, and more preferably has 1 to 4 carbon atoms. A hetero atom may be a nitrogen atom, an oxygen atom, a sulfur atom, or the like. A halogen atom represents a fluorine atom, a chlorine atom, a bromine atom, or an iodine atom. A halogenoalkyl group may be a chloromethyl group, a trichloromethyl group, a trifluoromethyl group, a trifluoroethyl group, a pentafluoromethyl group, or the like. A halogenoalkoxy group may be a trichloromethoxy group, a trifluoromethoxy group, or the like. A hydroxyalkyl group may be a hydroxymethyl group, a hydroxyethyl group, or the like.

In this specification, an aryl group means a substituted or unsubstituted aryl group, and may be a phenyl group, a 1-naphthyl group, a 2-naphthyl group, or the like. The aryl group is preferably a phenyl group or a substituted phenyl group. Here, halogen atoms, alkoxy groups, alkyl groups, hydroxyl groups, halogenoalkyl groups, and halogenoalkoxy groups are particularly preferable as the substituents. A heterocyclic group means a heteroatom-containing cyclic group which is constituted of carbon with nitrogen, oxygen, sulfur, and/or the like, and which is made of one to three 4- to 7-membered substituted or unsubstituted rings. Specific examples of the heterocyclic group include a pyridyl group, a dihydropyranyl group, a tetrahydropyranyl group, a pyridazyl group, a pyrimidyl group, a pyrazyl group, a pyrrolyl group, a furyl group, a thienyl group, a thiazolyl group, a triazolyl group, an isoxazolyl group, an isothiazolyl group, an oxazolyl group, an indolyl group, a quinolyl group, an isoquinolyl group, a benzoimidazolyl group, a pyrazolyl group, an imidazolyl group,

a thiadiazolyl group, a pyrrolidyl group, a piperidyl group, a piperazyl group, a morpholyl group, an oxetanyl ring, an isoindolyl group, a benzofuryl group, an isobenzofuryl group, a benzothienyl group, a benzopyrazolyl group, a benzoimidazolyl group, a benzoxazolyl group, a benzothiazolyl group, and the like. The heterocyclic group is preferably a pyridyl group, a pyrazyl group, a pyrimidyl group, a furyl group, a thienyl group, a substituted pyridyl group, a substituted furyl group, a substituted thienyl group, or the like. Here, halogen atoms, alkoxy groups, alkyl groups, hydroxyl groups, halogenoalkyl groups, halogenoalkoxy groups are particularly preferable as the substituents.

In general formula (1) of the present disclosure, it is preferable that (i) D be a phenyl group optionally having a substituent(s) selected from the group consisting of lower alkyl groups, halogen atoms, hydroxyl groups, and lower alkoxy groups, or that (ii) D be a 6-membered aromatic heterocyclic group containing a nitrogen atom(s) as a ring-constituent atom(s) and optionally having a substituent(s) selected from the group consisting of lower alkyl groups, halogen atoms, and lower alkoxy groups. Here, the heterocyclic group represented by D is particularly preferably a pyridyl group or a pyrrole group.

Moreover, in general formula (1) of the present disclosure or in combination with the above-described (i) or (ii), E is preferably a 5- or 6-membered aromatic heterocyclic group containing 1, 2, 3, or 4 hetero atoms selected from oxygen atoms, sulfur atoms, and nitrogen atoms and optionally having a substituent(s) selected from the group consisting of lower alkyl groups, lower alkoxy groups, and halogen atoms. Here,

the aromatic heterocyclic group is preferably selected from the group consisting of a pyridyl group, a pyridazyl group, a pyrimidyl group, a pyrazinyl group, a pyrrolyl group, a furanyl group, a thiophenyl group, a thiazolyl group, an oxazolyl group, 5 a triazolyl group, and a tetrazole group.

Alternatively, in general formula (1) of the present disclosure or in combination with the above-described (i) or (ii), E is preferably an aminocarbonyl group or lower alkylaminoalkylene group optionally substituted with a lower 10 alkyl, heterocyclic, or heterocycle-substituted lower alkyl group(s). Moreover, it is also preferable that E be a pyridyl group, pyrimidyl group, triazolyl group, or pyrrolyl group optionally having a lower alkyl group(s) and/or a 4- to 6-membered cyclic amino group(s), or an aminocarbonyl group 15 optionally substituted with a lower alkyl or heterocycle-substituted lower alkyl group(s). Here the 4- to 6-membered cyclic amino group may be an azetidiny group or the like, and the heterocycle-substituted lower alkyl group may be a tetrapyran lower alkyl group or the like.

20 In addition, when E represents a lower alkylcarbonyl group or a lower alkyloxycarbonyl group, a condensed ring formed by such a group bonded to the phenyl group of D may be a 1-oxoindanyl group, a 3-oxo-1H-isobenzofuranyl group, or the like.

25 Further, in general formula (1) of the present disclosure or in any one of the above-described preferred modes, R1, R11, and R21 are preferably lower alkyl groups.

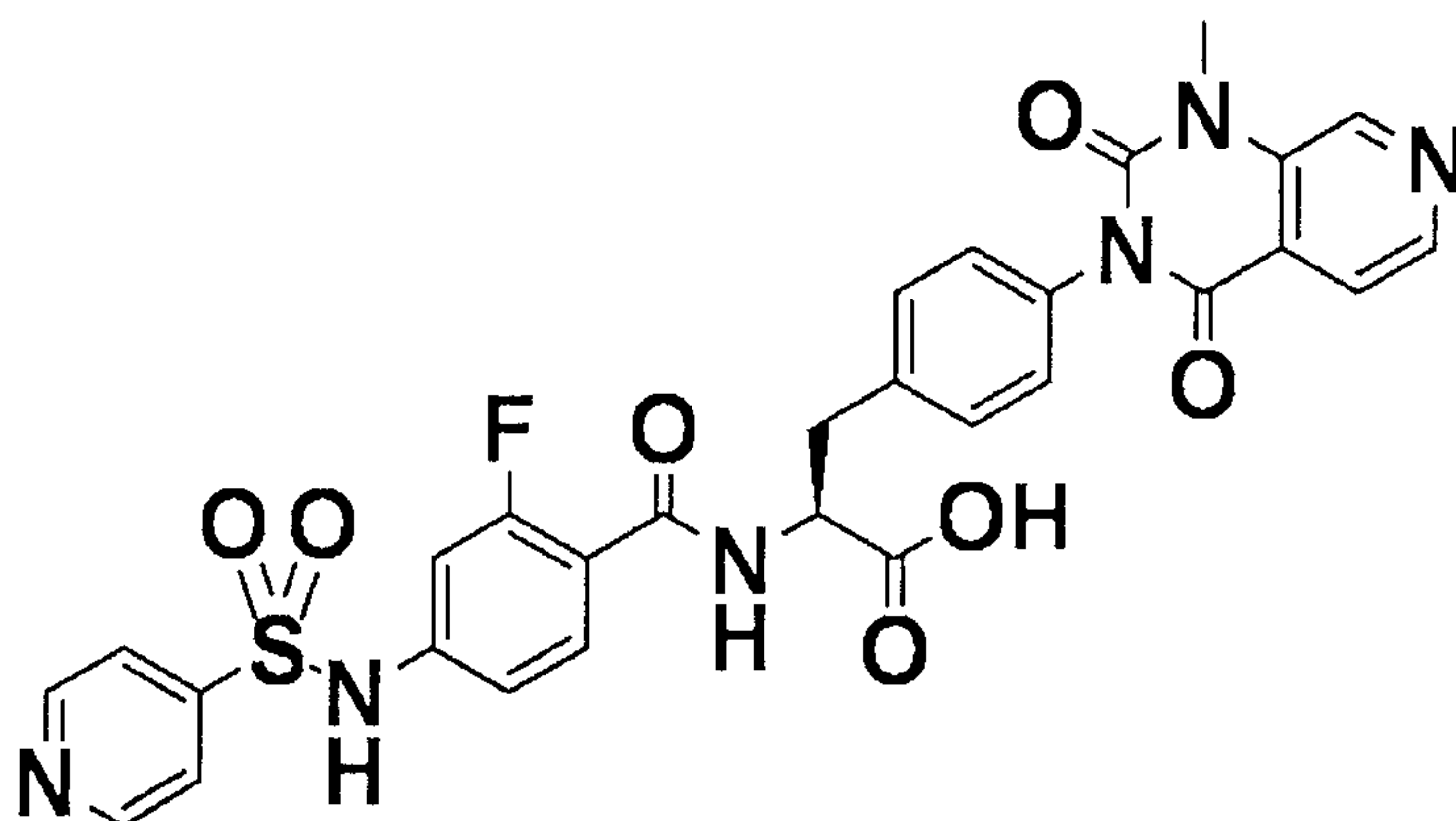
Further, in general formula (1) of the present disclosure or in any one of the above-described preferred modes, Arm is 30 preferably selected from the group consisting of a phenyl group,

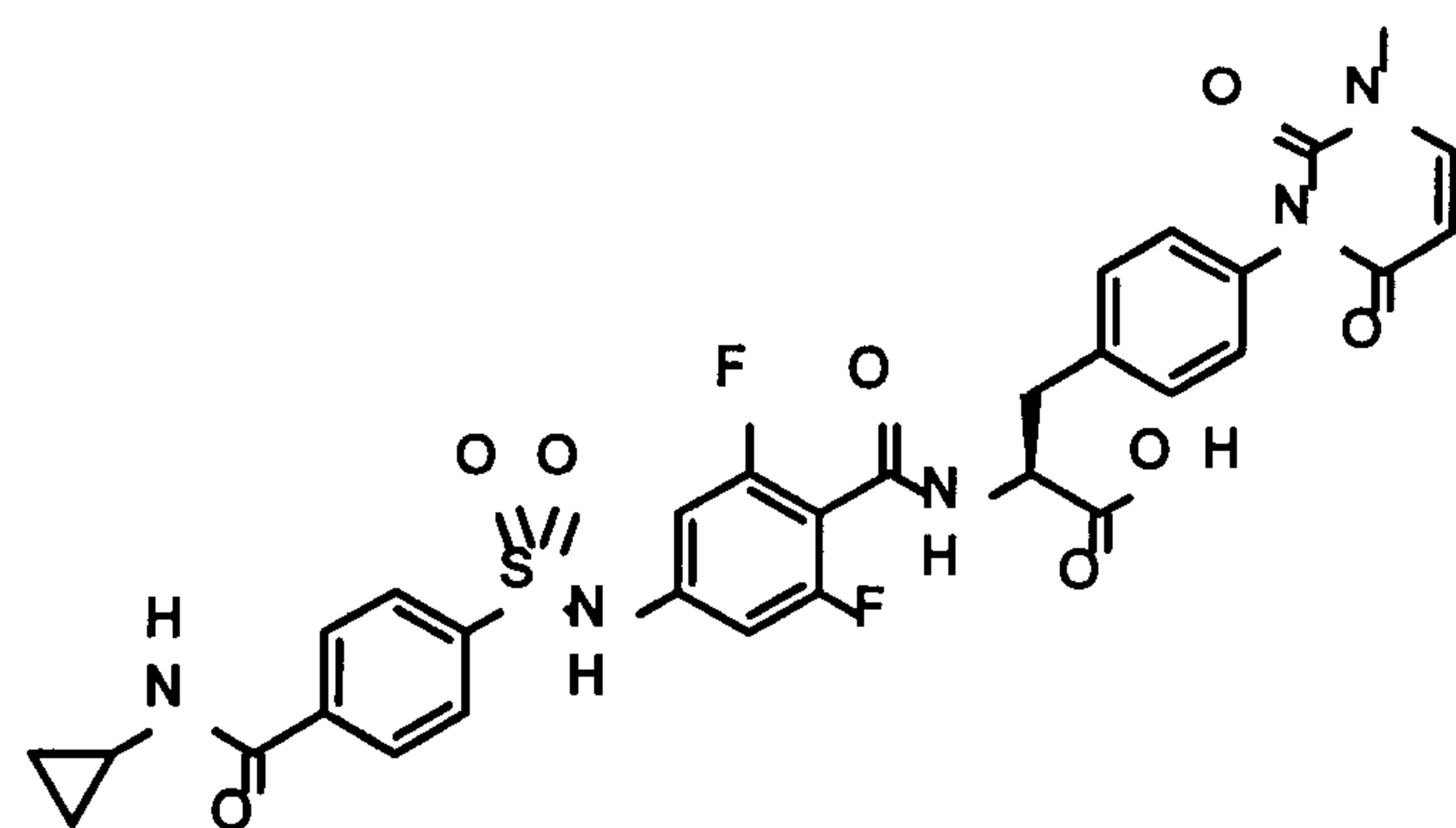
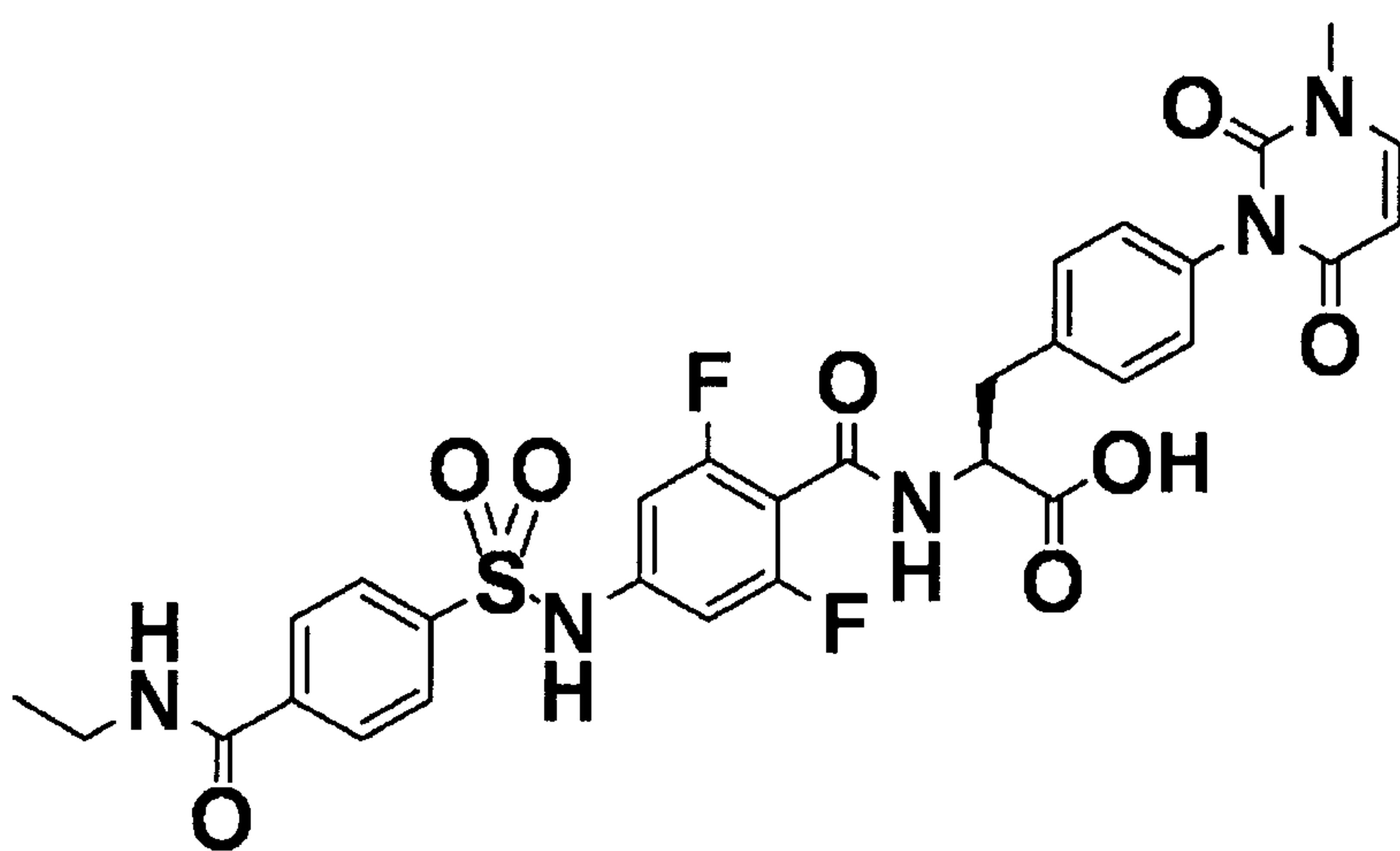
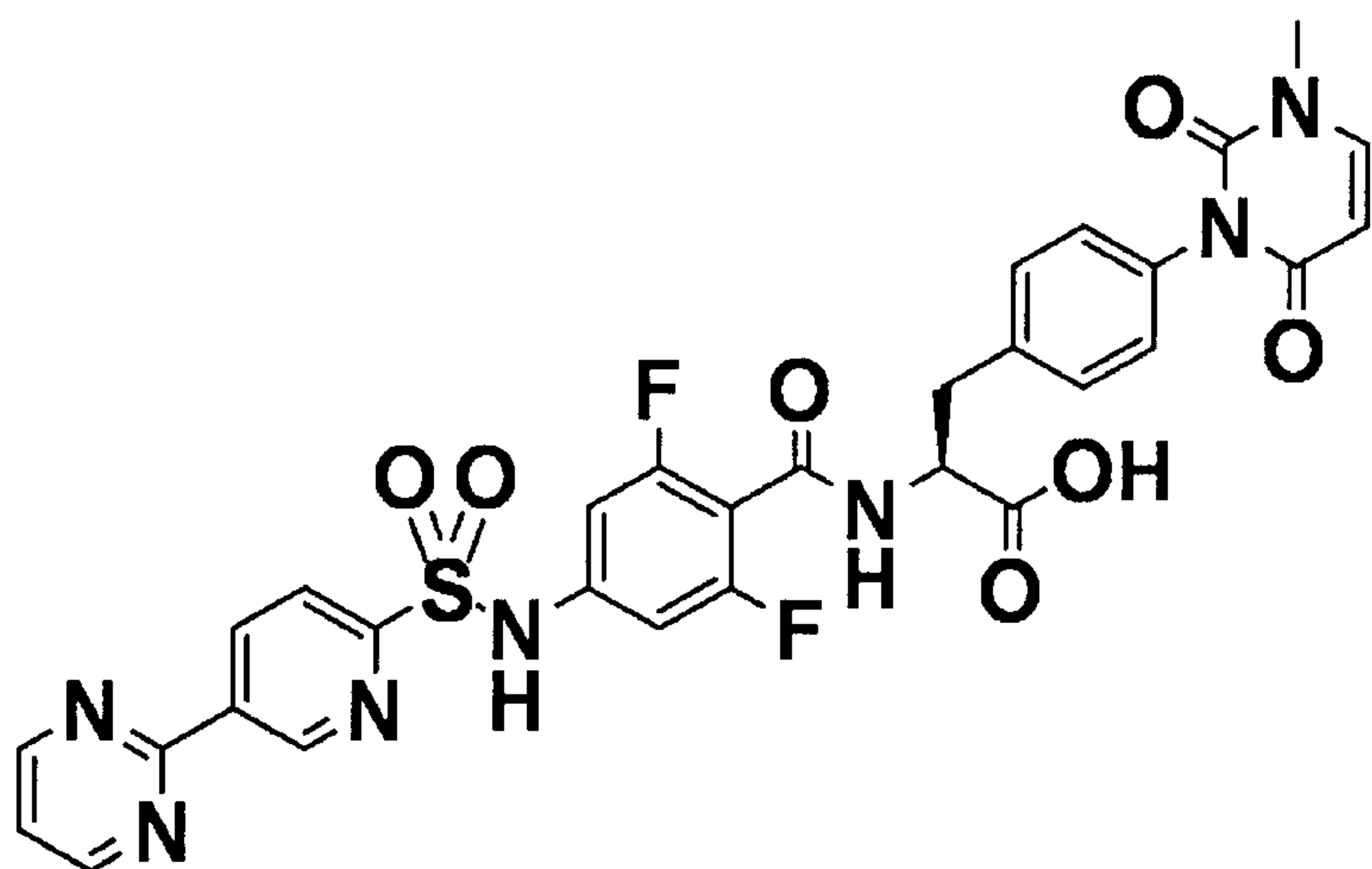
a pyridyl group, and an imidazolyl group.

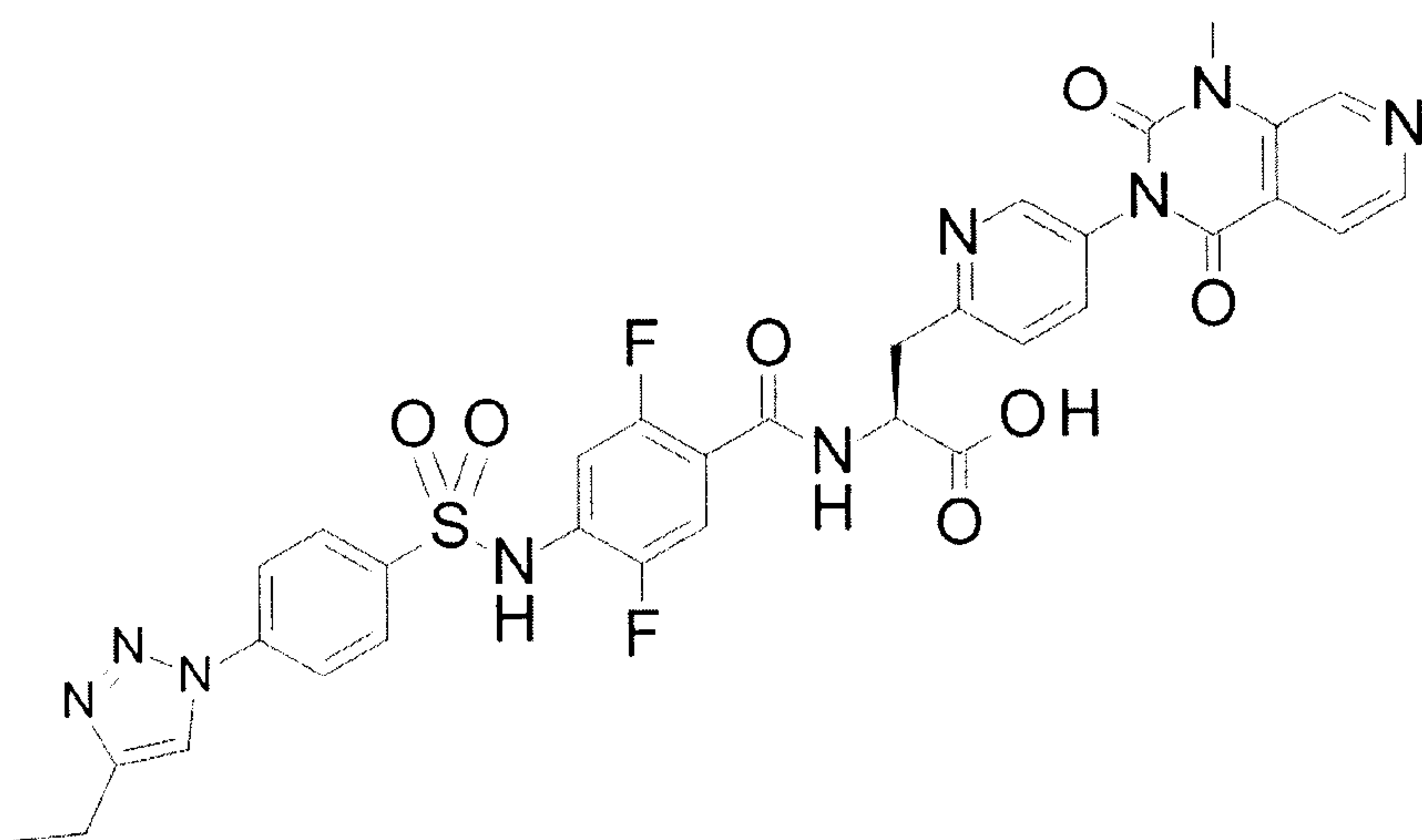
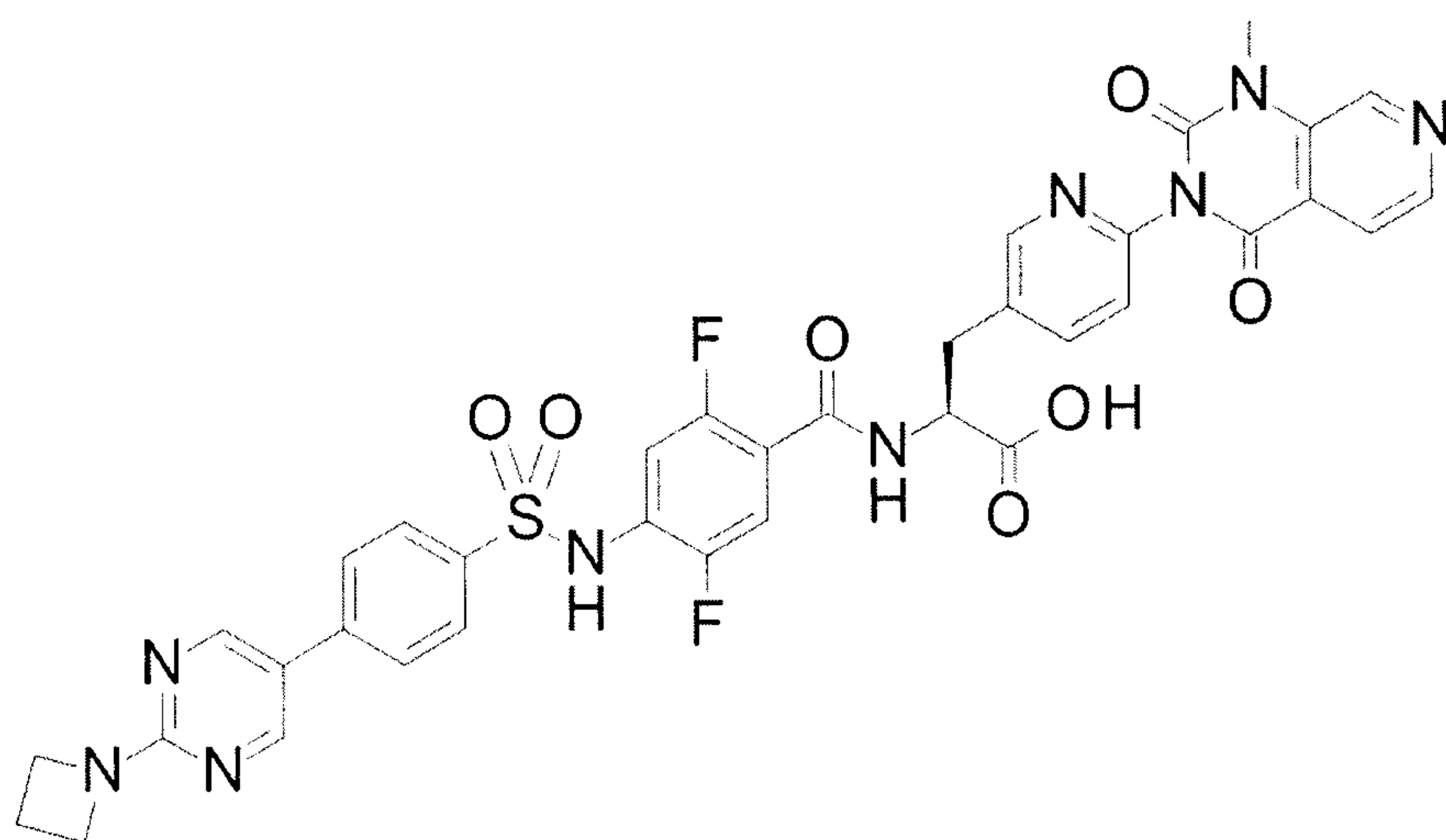
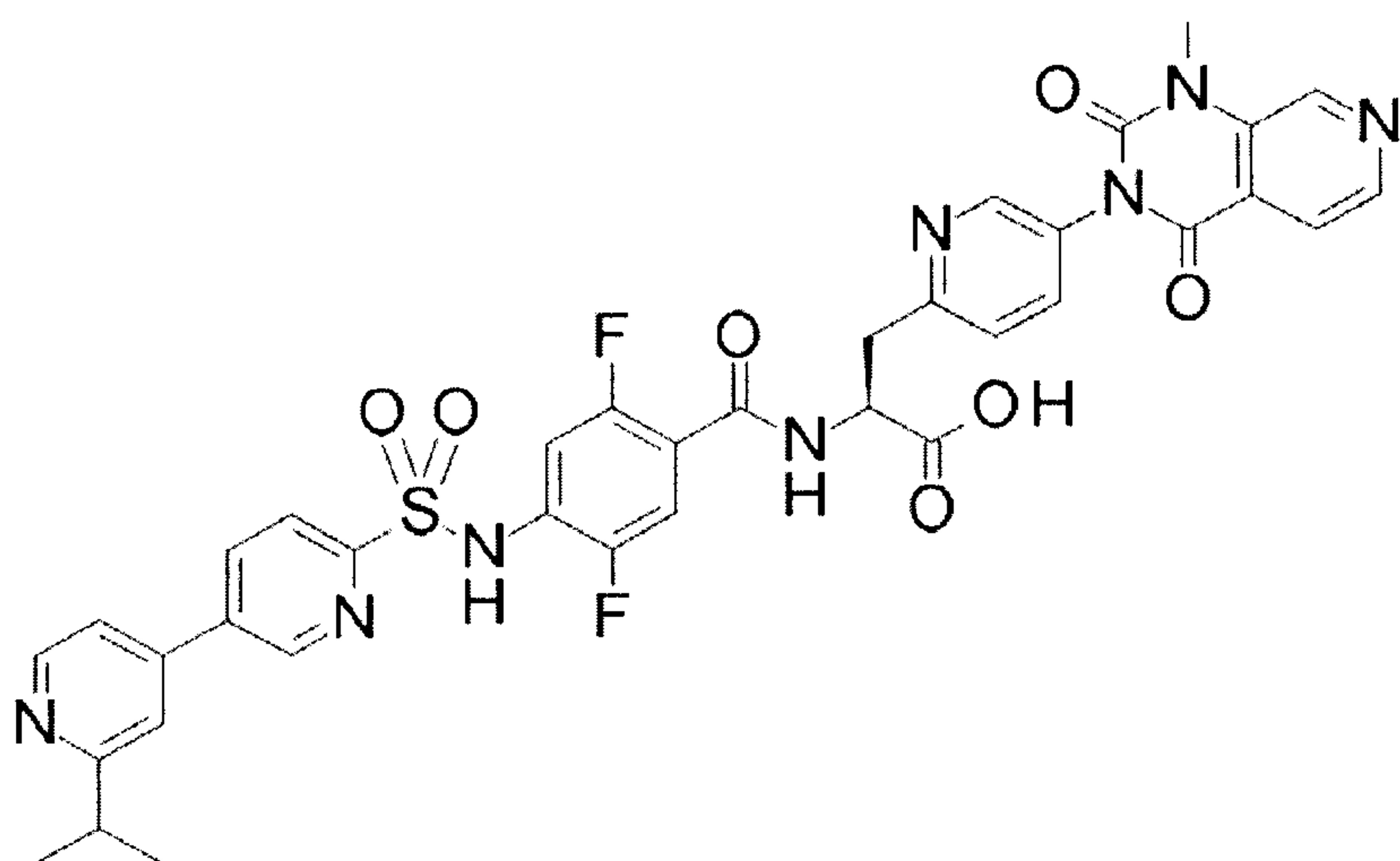
Further, in general formula (1) of the present disclosure or in any one of the above-described preferred modes, it is
5 preferable that one of R31, R32, R33, and R34 be a halogen atom, and the rest be hydrogen atoms, or that two of R31, R32, R33, and R34 be halogen atoms, and the rest be hydrogen atoms.

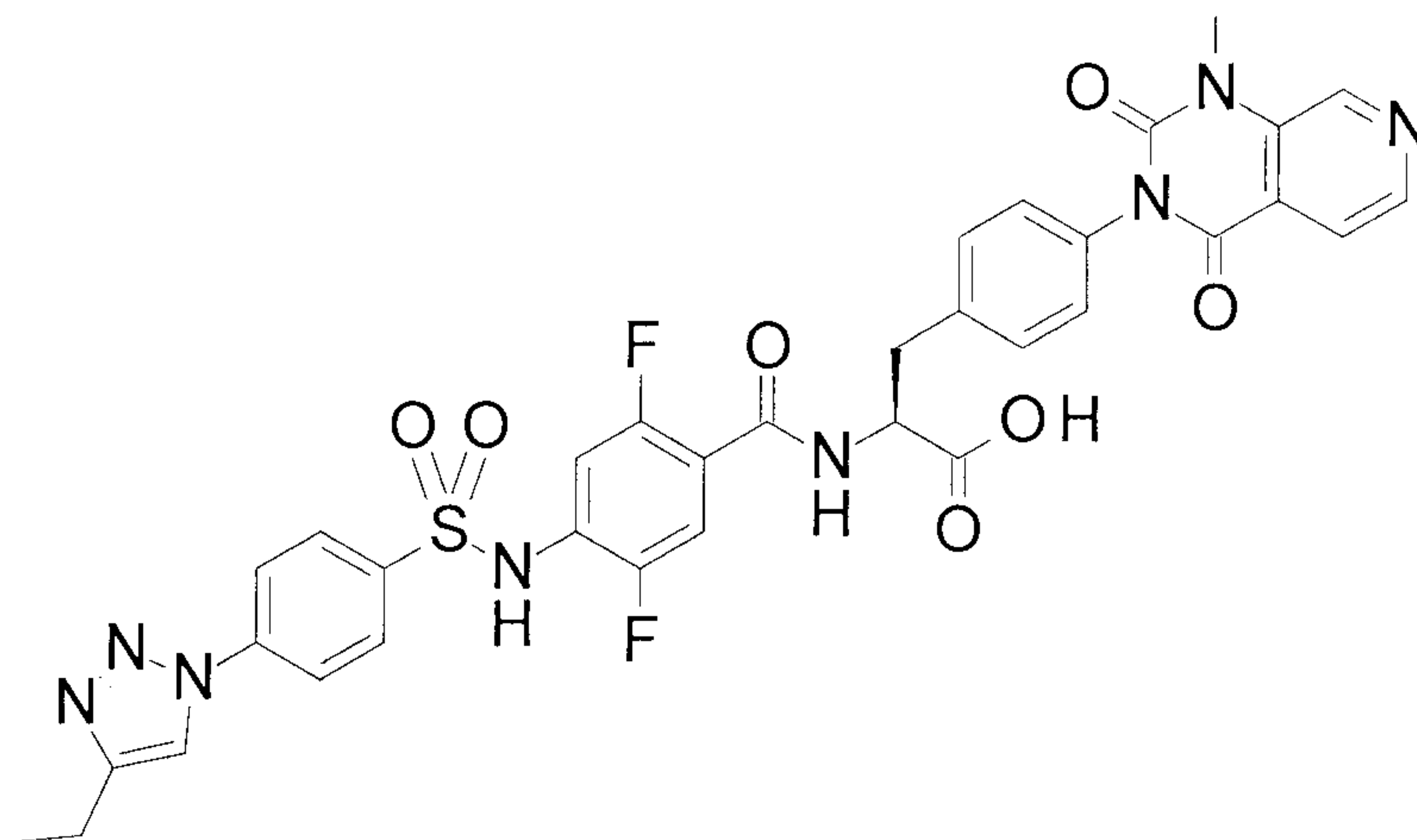
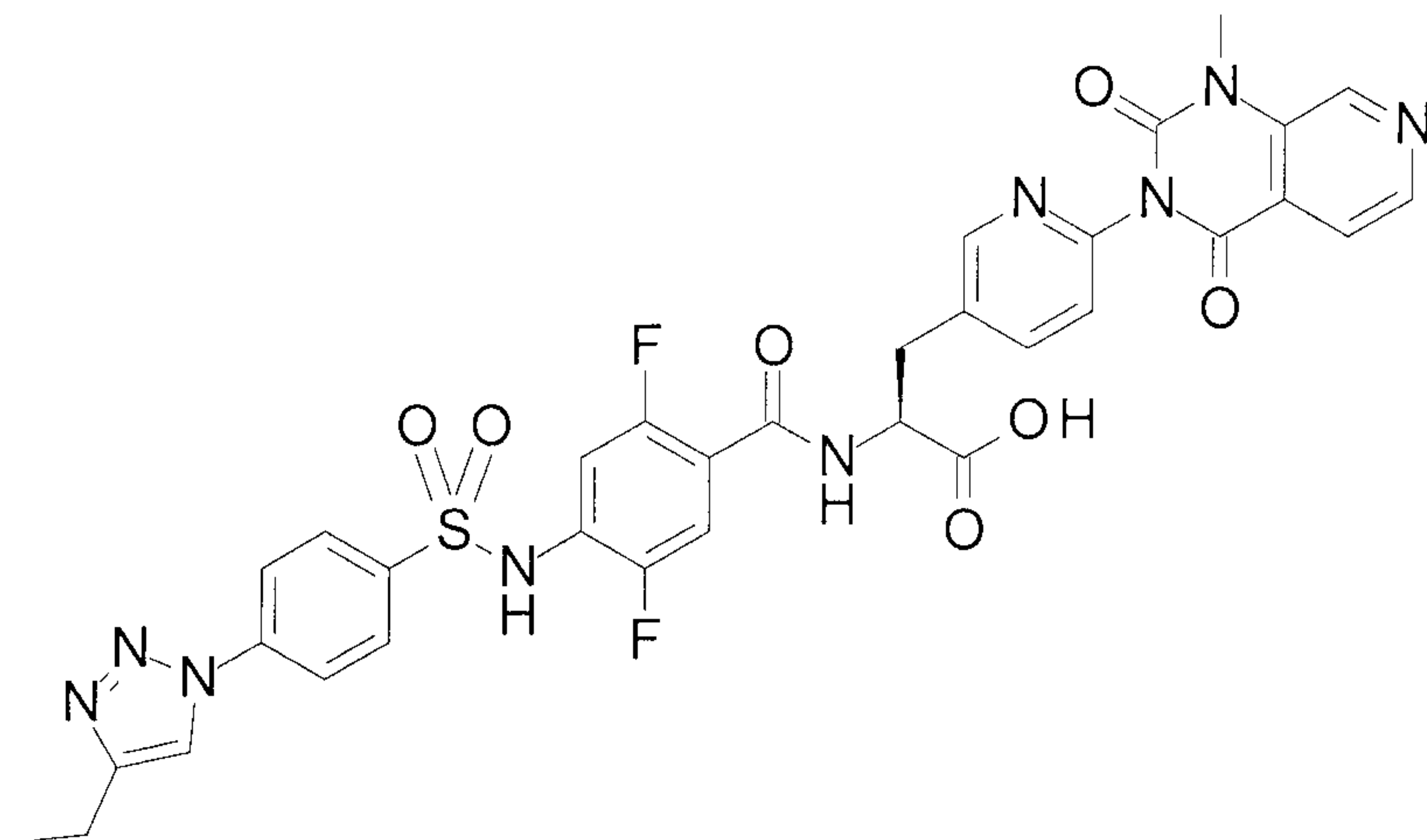
Further, in general formula (1) of the present disclosure or in any one of the above-described preferred modes, it is
10 preferable that g be a carbon or nitrogen atom, and e be a carbon or nitrogen atom.

In the present disclosure, compounds represented by the following formulae and pharmaceutically acceptable salts thereof are particularly preferable. In addition, prodrugs of
15 these compounds and pharmaceutically acceptable salts thereof are also preferable.









5 Furthermore, compounds of Examples 140, 237, 229, 232, 234, 246, 247, 248, 249, 253-256 and 257 and salts and prodrugs thereof are also preferable.

When the compound represented by general formula (1) of the present disclosure can be in the form of a salt, the salt
 10 only needs to be pharmaceutically acceptable one. Examples of the salt for an acidic group such as a carboxyl group in the formula include ammonium salt, salts with alkali metals such as sodium and potassium, salts with alkaline earth metals such as calcium and magnesium, aluminum salt, zinc salt, salts with

organic amines such as triethylamine, ethanolamine, morpholine, piperidine, and dicyclohexylamine, and salts with basic amino acids such as arginine and lysine. In a case where a basic group
5 is present in the formula, examples of the salt for the basic group include salts with inorganic acids such as hydrochloric acid, sulfuric acid, and phosphoric acid, salts with organic carboxylic acids such as acetic acid, citric acid, benzoic acid, maleic acid, fumaric acid, tartaric acid, and succinic acid,
10 and salts with organic sulfonic acids such as methanesulfonic acid and p-toluenesulfonic acid. A method for forming the salt may be a method in which the compound of general formula (1) is mixed with a necessary acid or base at an appropriate amount ratio in a solvent or a dispersion medium, or the salt can be
15 obtained also by subjecting the compound of general formula (1) in the form of another salt to cation exchange or anion exchange.

The compound of the present disclosure may include solvates of the compound represented by general formula (1), such as a hydrate and alcohol adducts.

20 The compound of the present disclosure includes prodrug forms of the compound represented by general formula (1). A prodrug of the compound of the present disclosure refers to a compound which is converted to the compound represented by general formula (1) by a reaction due to an enzyme, gastric acid, or the like in a living organism
25 under physiological conditions, namely, a compound which undergoes enzymatic oxidation, reduction, hydrolysis, or the like, and thus converted to the compound represented by general formula (1), or a compound which undergoes hydrolysis or the like due to gastric acid or the like, and thus converted to the compound represented
30 by general formula (1). Examples of the prodrug of the compound

represented by general formula (1) include compounds illustrated in Examples, but are not limited thereto. When the compound represented by general formula (1) has an amino, examples of compounds used as the prodrugs include compounds in which the amino is subjected to acylation, alkylation, or phosphorylation (for example, compounds in which the amino of the compound represented by general formula (1) is subjected to eicosanoylation, alanylation, pentylaminocarbonylation, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methoxycarbonylation, tetrahydrofuranylation, pyrrolidylmethylation, pivaloyloxymethylation, or tert-butylation), etc. When the compound represented by general formula (1) has a hydroxy, examples of compounds used as the prodrugs include compounds in which the hydroxy is subjected to acylation, alkylation, phosphorylation, or boration (for example, compounds in which the hydroxy of the compound represented by general formula (1) is subjected to acetylation, palmitoylation, propanoylation, pivaloylation, succinylation, fumarylation, alanylation, or dimethylaminomethylcarbonylation), etc. When the compound represented by general formula (1) has a carboxyl, examples of compounds used as the prodrugs include compounds in which the carboxyl is subjected to esterification or amidation (for example, compounds in which the carboxyl of the compound represented by general formula (1) is subjected to ethyl esterification, phenyl esterification, isopropyl esterification, isobutyl esterification, cyclopentyl esterification, cyclohexyl esterification, cycloheptyl esterification, cyclohexylmethyl esterification, normal-hexyl esterification, sec-butyl esterification, tert-butyl esterification, (4-tetrahydropyranyl)methyl

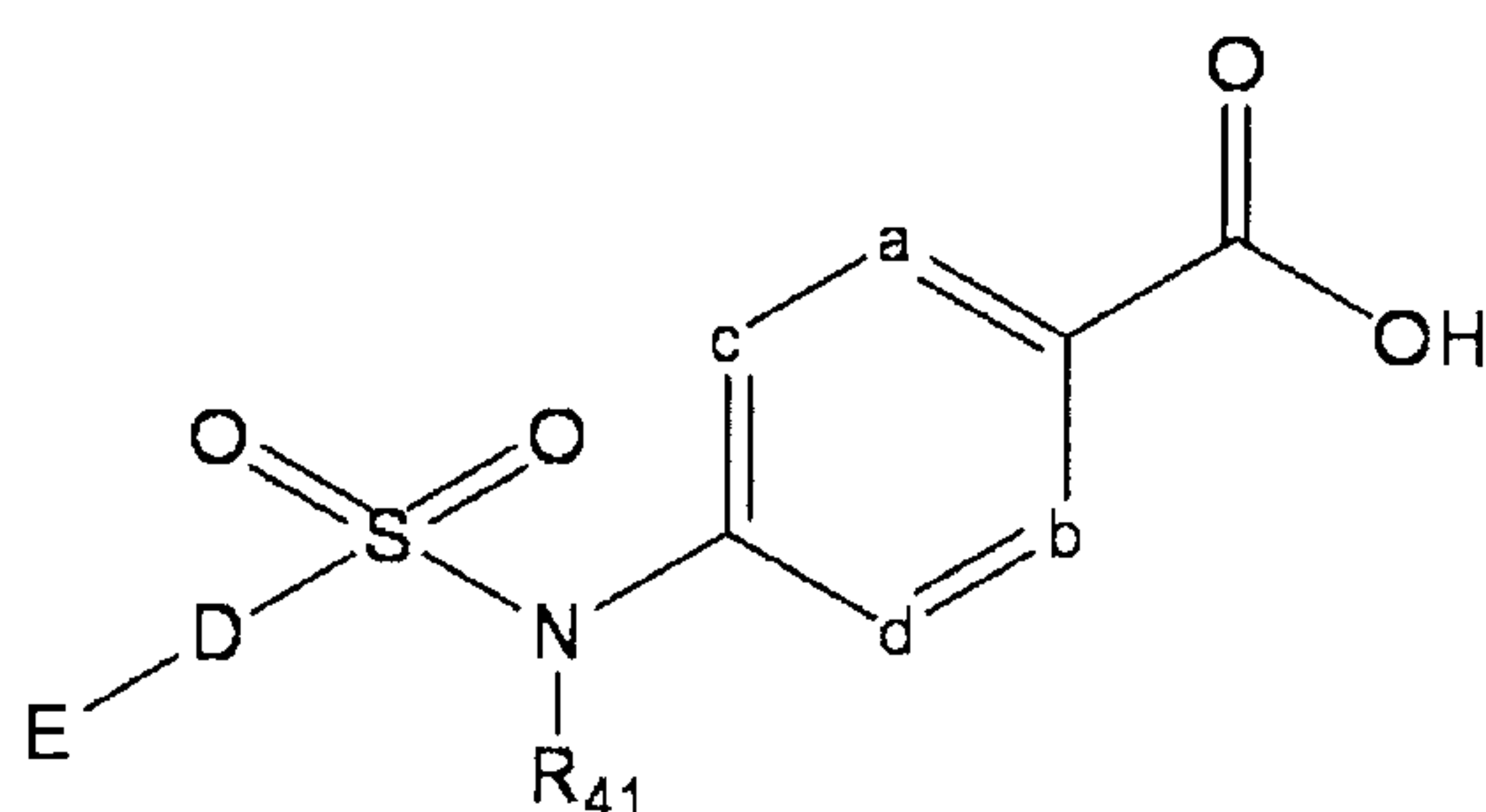
esterification, (4-tetrahydropyranyl) esterification,
 carboxymethyl esterification, dimethylaminomethyl
 esterification, pivaloyloxymethyl esterification,
 5 ethoxycarbonyloxyethyl esterification, phthalidyl
 esterification, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl
 esterification, cyclohexyloxycarbonyl ethyl esterification,
 or methyl amidation), etc. These compounds can be produced from
 the compound represented by general formula (1) by methods known
 10 per se.

Moreover, the prodrug of compound (1) may be a compound
 which is converted to compound (1) under physiological
 conditions as described on Pages 163 to 198 of "IYAKUJIN NO
 KAIHATSU (Pharmaceutical Research and Development)," Vol. 7,
 15 BUNSHI SEKKEI (Molecular Design), published by Hirokawa Shoten.,
 1990.

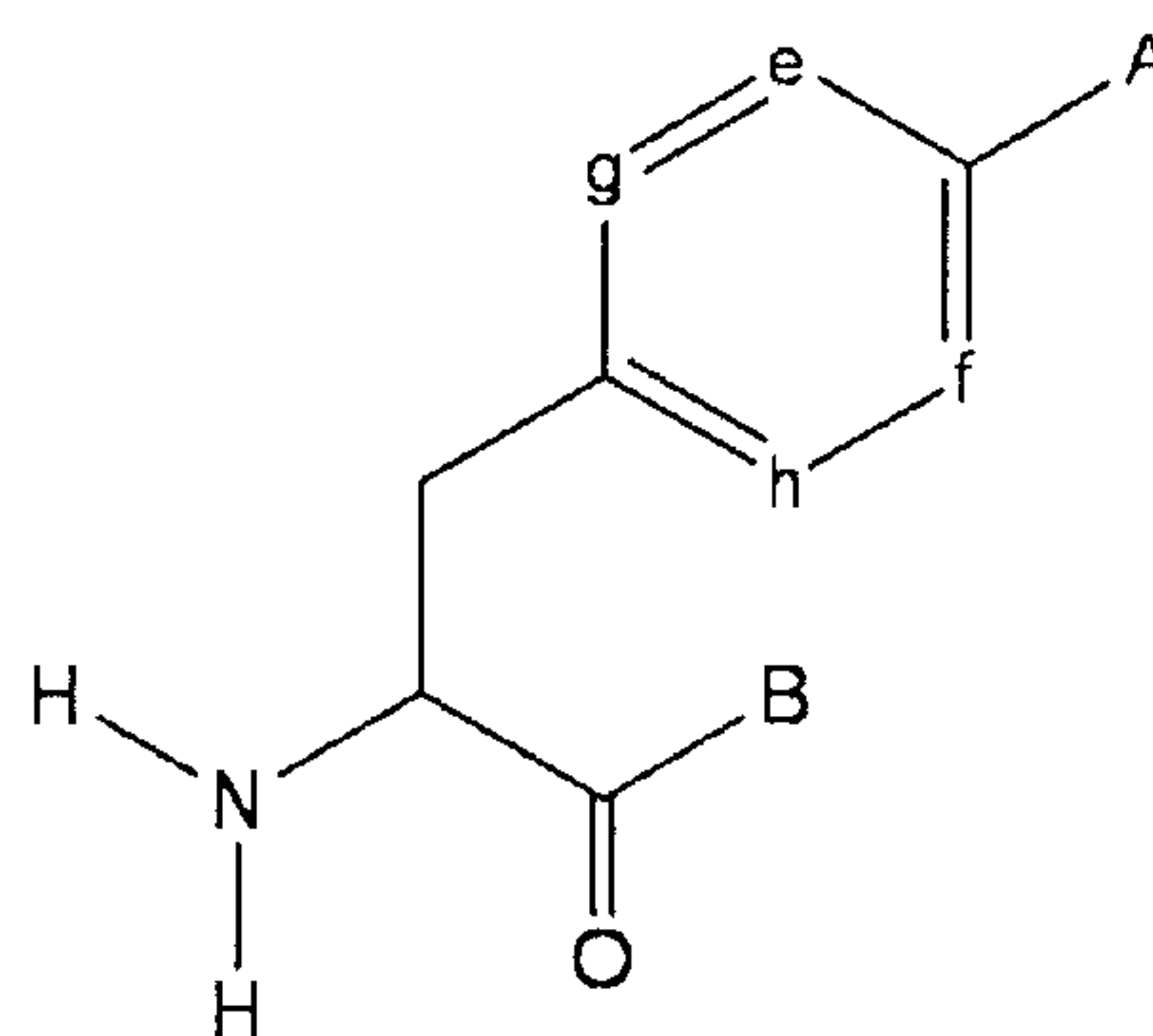
The present disclosure includes all isotopically substituted
 forms of the compound represented by formula (1). An isotopically
 substituted form of the compound of the present disclosure refers
 20 to one in which at least one atom is replaced by an atom having the
 same atomic number (proton number) but having different mass number
 (the sum of the proton number and the neutron number). Examples
 of the isotopes contained in the compound of the present disclosure
 include hydrogen atoms, carbon atoms, nitrogen atoms, oxygen atoms,
 25 phosphorus atoms, sulfur atoms, fluorine atoms, chlorine atoms, and
 the like, and include ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{17}O , ^{18}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F ,
 ^{36}Cl , and the like. Especially, radioisotopes such as ^3H and ^{14}C ,
 which are unstable and which exhibit radioactivity and release
 neutrons, are useful for a body tissue distribution test of
 30 drugs or compounds, and the like. Stable isotopes can be used

safely, because they do not decay, undergo little change in the abundance, and do not have radioactivity. The isotope in the compound of the present disclosure can be introduced in a usual
 5 manner by replacing a reagent used for synthesis with a corresponding reagent containing the isotope.

The compound represented by general formula (1) of the present disclosure can be produced by, for example, a dehydration reaction between an intermediate being represented
 10 by general formula (M-I) and having an amino group at its terminal and an intermediate being represented by general formula (M-II) and having a carboxyl group at its terminal.



(M-II)



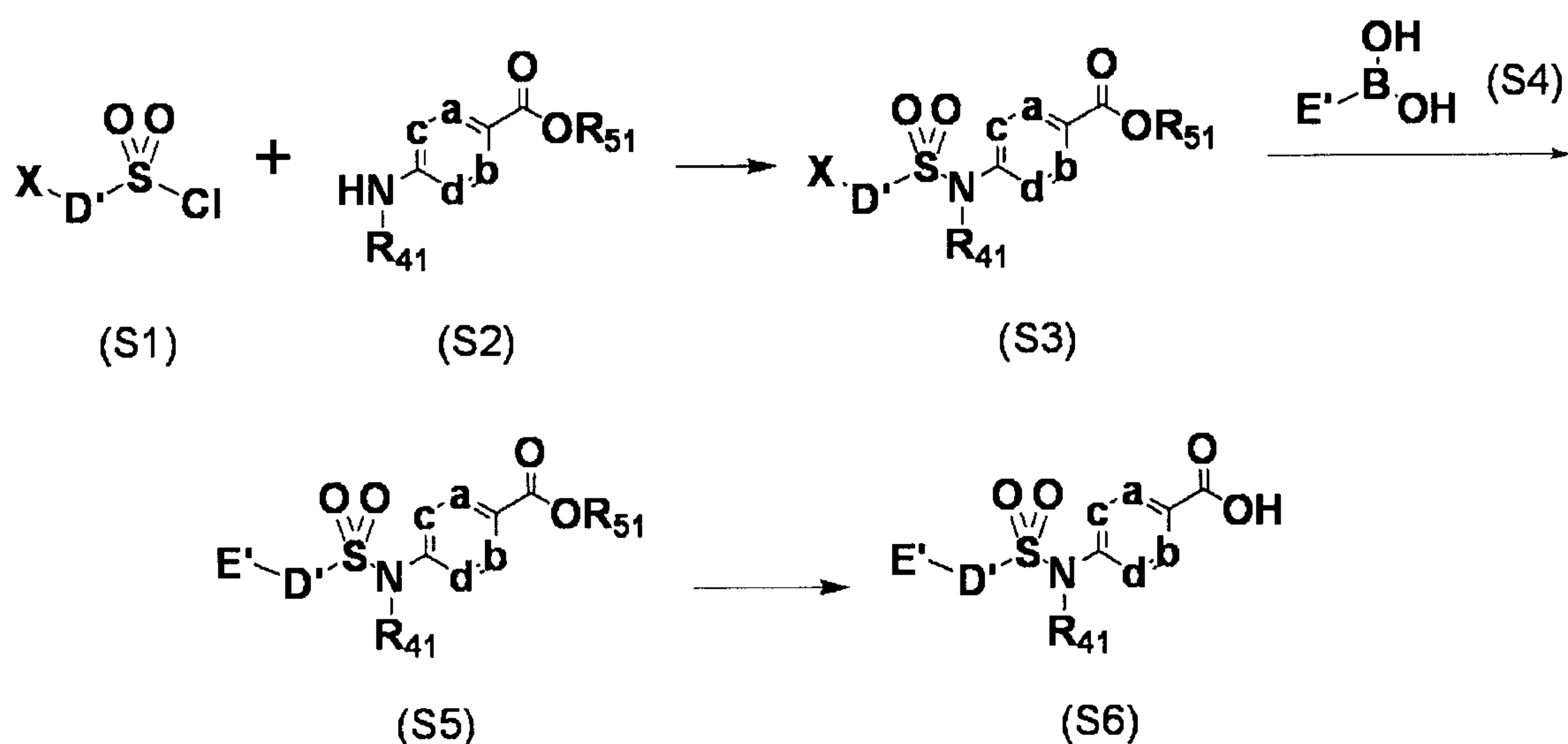
(M-I)

15 Of these intermediates, the intermediate being represented by general formula (M-II) and having a carboxyl group at its terminal can be produced by, for example, the following methods.

The following are methods for producing representative
 20 compounds among intermediates being represented by general formula (M-II) and having a carboxyl group at their terminal, which are compounds of the present disclosure. Note that, in the following description, the signs in the formulae are the same as those defined in formula (I) above, unless otherwise noted.

(1) Intermediate (S6) having a carboxyl group at its terminal and being represented by general formula (M-II), in which D is a phenyl group or pyridyl group optionally having a substituent(s) selected from the group consisting of lower alkyl groups and halogen atoms, and E is a 5-membered or 6-membered aromatic heterocyclic group containing 1, 2, 3, or 4 hetero atoms selected from oxygen atoms, sulfur atoms, and nitrogen atoms and optionally having a substituent(s) selected from lower alkyl groups and halogen atoms can be synthesized by employing, for example, one of the methods described below (production methods A, B, C, and D).

<Production Method A>



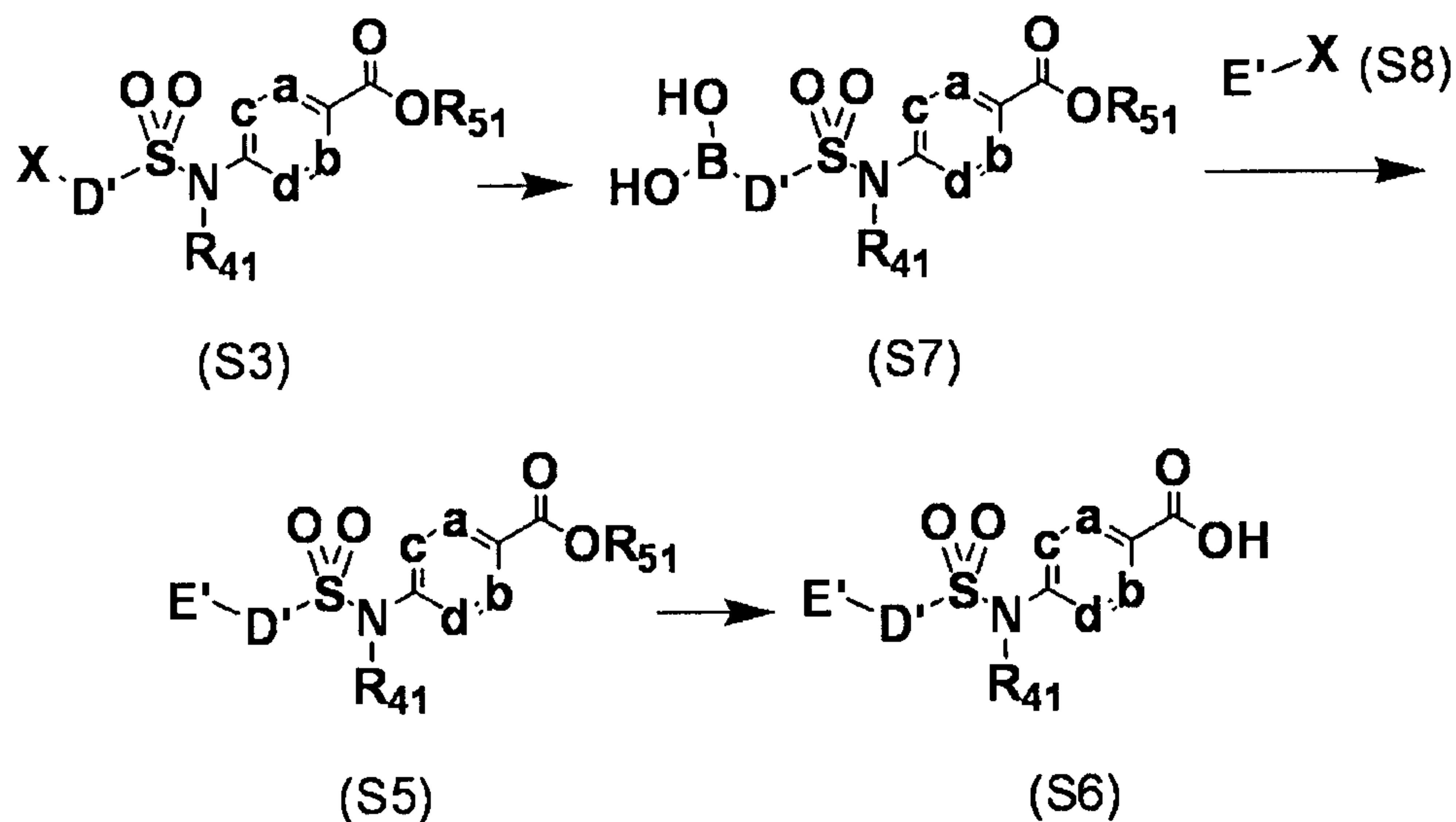
In the formulae, D' represents the above-described substituent represented by D or a substituent which can be easily converted to D by an operation such as deprotection. In the formulae, E' represents the above-described substituent represented by E or a substituent which can be easily converted to E by an operation such as deprotection. Meanwhile, R₅₁ represents, for example, an ordinary ester substituent such as a lower alkyl group.

Sulfonyl chloride derivative (S1) (in the formula, X represents a halogen atom such as a chlorine, bromine, or iodine atom or a leaving group such as a trifluoromethanesulfonyloxy group) is reacted with amine derivative (S2) in a solvent which does not affect this reaction such as methylene chloride in the presence of a base such as pyridine. Thus, sulfonamide derivative (S3) can be synthesized. The obtained sulfonamide derivative (S3) can be converted to the corresponding sulfonamide derivative (S5) by the Suzuki coupling reaction with boronic acid derivative (S4). Subsequently, the obtained sulfonamide derivative (S5) is subjected to deprotection in a solvent which does not affect this reaction such as tetrahydrofuran, methanol, or ethanol, by alkali hydrolysis using a base such as sodium hydroxide, acid hydrolysis using, for example, hydrochloric acid or trifluoroacetic acid, or the like. Thus, the target intermediate (S6) having a carboxyl group at its terminal can be produced.

The Suzuki coupling reaction is known, and is carried out by reacting a boronic acid derivative or a boronic acid ester derivative with a halogen derivative, a trifluoromethanesulfonate, or a methanesulfonate in a solvent which does not affect this reaction such as 1,4-dioxane, tetrahydrofuran, toluene, dimethyl sulfoxide, or 1,2-dimethoxyethane in the presence or absence of a co-solvent such as water, by using a transition metal catalyst such as tetrakis(triphenylphosphine)palladium(0), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II), or tris(dibenzylideneacetone)dipalladium(0) or using a transition metal catalyst such as palladium(II) acetate and a ligand such as triphenylphosphine, in the presence of a base

such as potassium carbonate, sodium carbonate, potassium phosphate, sodium methoxide, or sodium hydroxide.

<Production Method B>



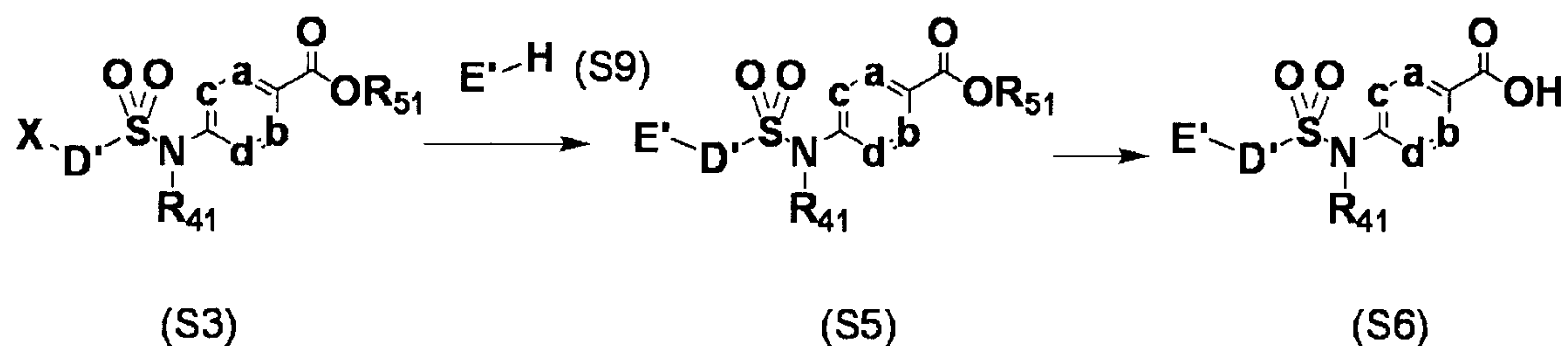
5 In the formulae, D' represents the above-described
substituent represented by D or a substituent which can be
easily converted to D by an operation such as deprotection. In
the formulae, E' represents the above-described substituent
represented by E or a substituent which can be easily converted
10 to E by an operation such as deprotection. Meanwhile, R₅₁
represents an ordinary ester substituent such as a lower alkyl
group.

Sulfonamide derivative (S3), which is the intermediate described in <Production Method A>, and a borane derivative such as bis(pinacolato)diborane are converted to the corresponding boronic acid ester derivative by a coupling reaction in a solvent which does not affect this reaction such as N,N-dimethylformamide, in the presence of a base such as potassium acetate, using a metal catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II). Subsequently, the obtained boronic acid ester derivative is

treated in a solvent which does not affect this reaction such as acetone by adding, for example, sodium periodate, ammonium acetate, and water to remove the boronic acid ester. Thus, the corresponding boronic acid derivative (S7) can be synthesized.

5 The obtained boronic acid derivative (S7) can be converted to the corresponding sulfonamide derivative (S5) by the Suzuki coupling reaction (described above) with halogen derivative (S8) (in the formula, X represents a halogen atom such as a chlorine, bromine, or iodine atom or a leaving group such as a trifluoromethanesulfonyloxy group). By deprotecting sulfonamide derivative (S5) by hydrolysis or the like using the method described in <Production Method A>, the target intermediate (S6) having a carboxyl group at its terminal can be produced.

15 <Production Method C>

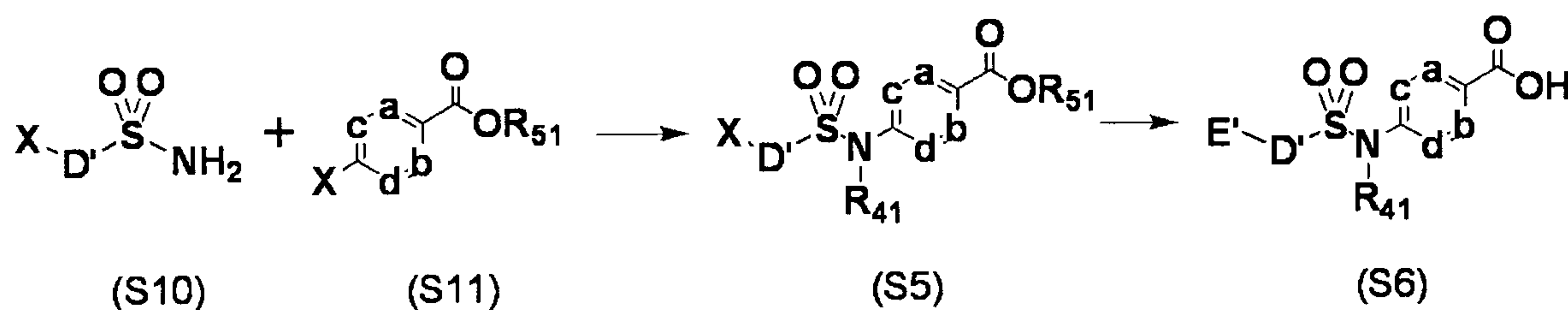


In the formulae, D' represents the above-described substituent represented by D or a substituent which can be easily converted to D by an operation such as deprotection. In the formulae, E' represents the above-described substituent represented by E or a substituent which can be easily converted to E by an operation such as deprotection. Meanwhile, R51 represents an ordinary ester substituent such as a lower alkyl group.

25 Sulfonamide derivative (S3), which is the intermediate described in <Production Method A>, (in the formula, X

represents a halogen atom such as a chlorine, bromine, or iodine atom or a leaving group such as a trifluoromethanesulfonyloxy group) and aromatic heterocycle (S9) can be converted to the corresponding sulfonamide derivative (S5) by a coupling
 5 reaction in a solvent which does not affect this reaction such as N-methylpyrrolidone in the presence of a ligand generally used in organic synthesis such as trans-N,N'-dimethylcyclohexane-1,2-diamine and a base such as potassium phosphate by using a metal catalyst such as copper(I)
 10 iodide. Subsequently, the obtained sulfonamide derivative (S5) is deprotected by hydrolysis or the like by employing the method described in <Production Method A>. Thus, the target intermediate (S6) having a carboxyl group at its terminal can be produced.

15 <Production Method D>

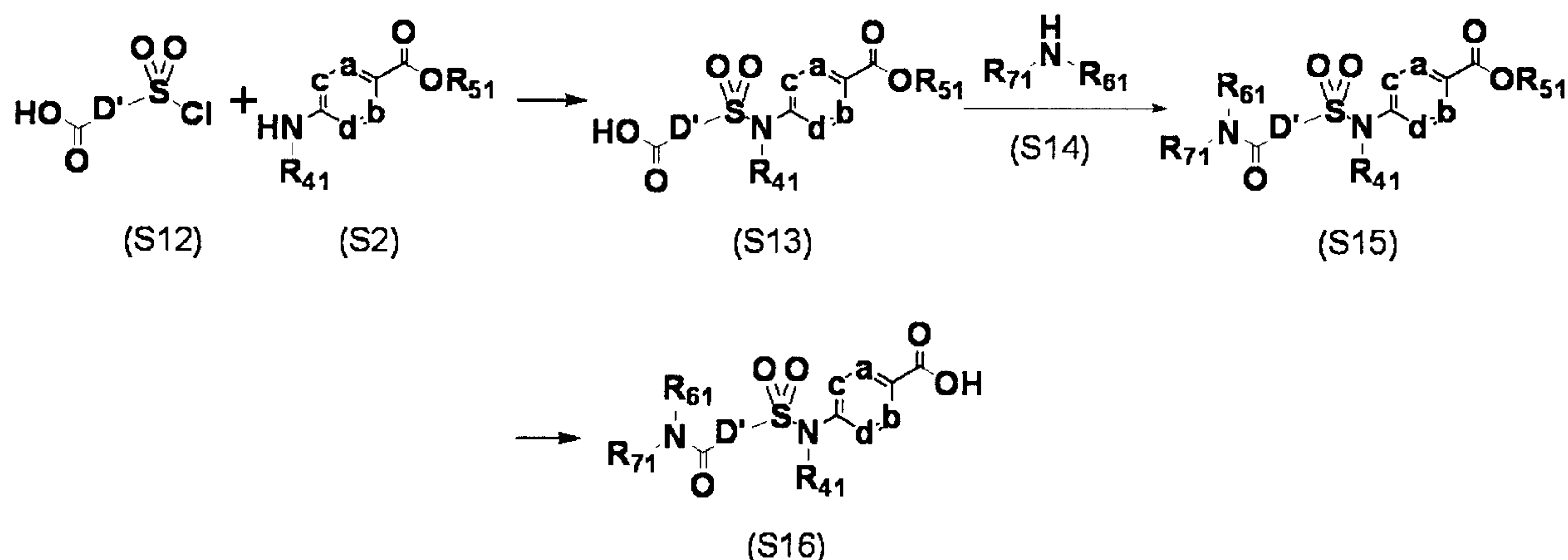


In the formulae, D' represents the above-described substituent represented by D or a substituent which can be easily converted to D by an operation such as deprotection. In
 20 the formulae, E' represents the above-described substituent represented by E or a substituent which can be easily converted to E by an operation such as deprotection. Meanwhile, R51 represents an ordinary ester substituent such as a lower alkyl group.

25 Sulfonamide derivative (S10) (in the formula, X represents a halogen atom such as a chlorine, bromine, or iodine

atom or a leaving group such as a trifluoromethanesulfonyloxy group) and halogen derivative (S11) can be converted to the corresponding sulfonamide derivative (S5) by carrying out a coupling reaction in a solvent which does not affect this
 5 reaction such as 1,4-dioxane in the presence of a metal catalyst such as tris(dibenzylideneacetone)dipalladium(0), a ligand generally used in organic synthesis such as XantPHOS, and a base such as cesium carbonate. Subsequently, the obtained sulfonamide derivative (S5) is deprotected by hydrolysis or the
 10 like by the method described in <Production Method A>. Thus, the target intermediate (S6) having a carboxyl group at its terminal can be produced.

The intermediate having a carboxyl group at its terminal and being represented by general formula (M-II), in which D is
 15 a phenyl group or pyridyl group optionally having a substituent(s) selected from the group consisting of lower alkyl groups and halogen atoms, and E is an aminocarbonyl group optionally substituted with lower alkyl, heterocycle, or heterocycle-substituted lower alkyl can be synthesized by
 20 employing the method described below (Production Method E).
 <Production Method E>



In the formulae, D' represents the above-described

substituent represented by D or a substituent which can be easily converted to D by an operation such as deprotection. R51 represents an ordinary ester substituent such as a lower alkyl group. R61 and R71 each represent an ordinary substituent on
5 an amine, such as a lower alkyl group, a heterocyclic group, or a heterocycle-substituted lower alkyl group.

Sulfonyl chloride derivative (S12) having a carboxylic acid or a substituent which can be easily converted to a carboxylic acid and amine derivative (S2) are reacted with each
10 other in a solvent which does not affect this reaction such as methylene chloride in the presence of a base such as pyridine. Thus, the corresponding carboxylic acid derivative (S13) can be synthesized. By amidation between the obtained carboxylic acid derivative (S13) and amine derivative (S14), the
15 corresponding amide derivative (S15) can be synthesized. Subsequently, the obtained amide derivative (S15) is deprotected by hydrolysis or the like by employing the method described in <Production Method A>. Thus, intermediate (S16) having a carboxyl group at its terminal can be produced.

20 The amidation reaction is known, and examples thereof include (1) a method using a condensation agent, (2) a method using an acid halide, and the like.

The method (1) using a condensation agent is carried out by a reaction between, for example, a carboxylic acid and an
25 amine or a salt thereof in a solvent which does not affect this reaction such as dichloromethane, tetrahydrofuran, 1,4-dioxane, N,N-dimethylformamide, or acetonitrile in the presence or absence of a base such as pyridine, triethylamine, or N-ethyldiisopropylamine and in the presence or absence of
30 a condensation aid such as 1-hydroxybenzotriazole (HOBt),

1-hydroxy-7-azabenzotriazole (HOAt), or N-hydroxysuccinimide (HOSu) by using a condensation agent such as 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (WSC), 1,3-dicyclohexylcarbodiimide (DCC), or
5 O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU).

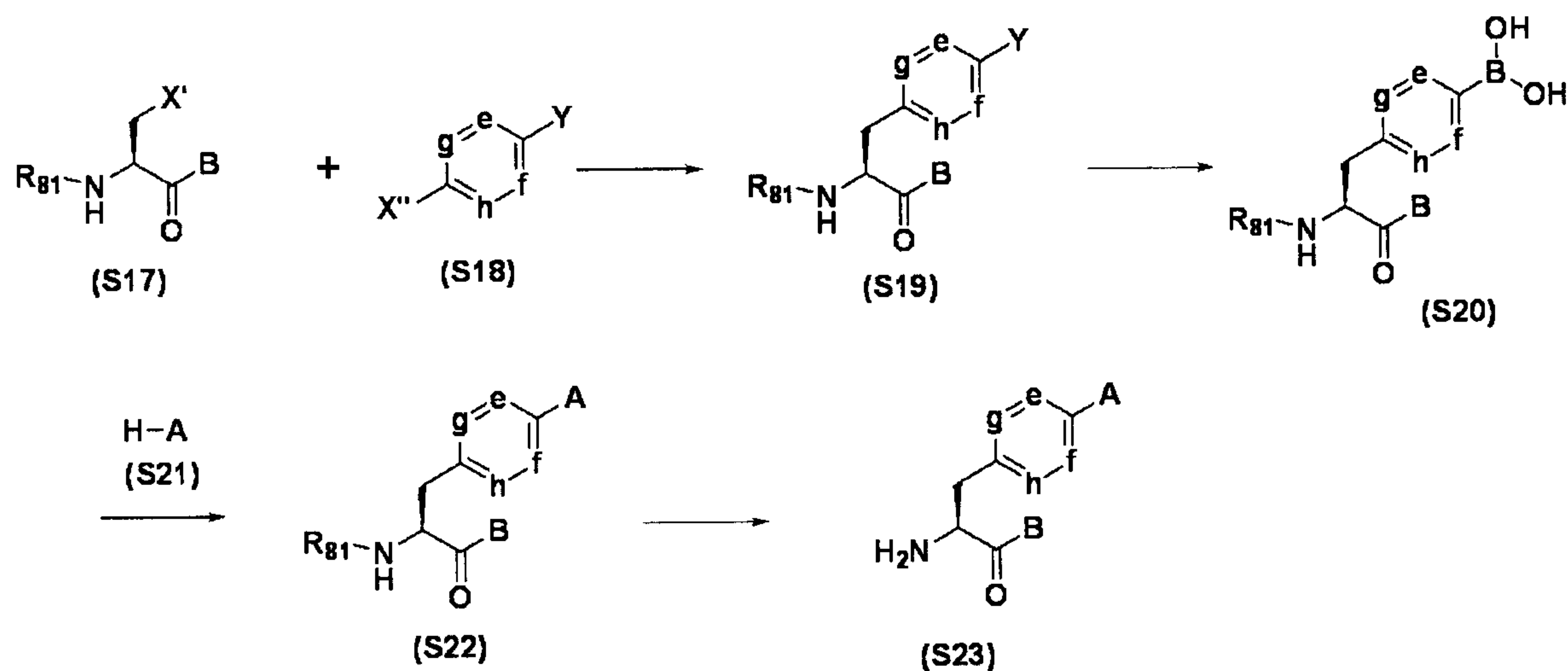
The method (2) using an acid halide is carried out by a reaction of an acid halide, which is obtained by a reaction of a carboxylic acid with, for example, thionyl chloride, oxalyl
10 chloride, thionyl bromide, or the like in a solvent which does not affect this reaction such as dichloromethane or in the absence of any solvent in the presence or absence of a catalyst such as N,N-dimethylformamide, with an amine or a salt thereof in a solvent which does not affect this reaction such as
15 dichloromethane or tetrahydrofuran in the presence of a base such as pyridine, triethylamine, or N-ethyldiisopropylamine.

In each step, the compound can be synthesized by using generally exchangeable reaction conditions, and the reaction conditions should be selected, as appropriate, according to the
20 types of the raw material compounds and the like. Note that the compounds of the present invention obtained by the above-described methods can be purified by employing a method generally used in organic synthesis, such as extraction, distillation, crystallization, or column chromatography.

25 The intermediate having an amino group at its terminal and being represented by general formula (M-I), which is the compound of the present disclosure, can be synthesized by, for example, the method described in Patent Literature 1, a production method (Production Method F) shown below, or the like.
30 Note that, in the following description, signs in the formulae

have the same definitions as those in formula (I) described above, unless otherwise noted.

<Production Method F>



5 In the formulae, R81 represents an ordinary substituent on an amine such as a tert-butoxycarbonyl group or a benzyloxycarbonyl group, which can be removed by an operation such as deprotection. In the formulae, X', X'', and Y each independently represent a halogen atom such as a chlorine, bromine, or iodine atom or a leaving group such as a trifluoromethanesulfonyloxy group.
 10

Amino acid derivative (S17) and halogen derivative (S18) are converted to the corresponding amino acid derivative (S19) by a coupling reaction in a solvent which does not affect this reaction such as N,N-dimethylformamide in the presence of a metal such as zinc by using a metal catalyst such as tetrakis(triphenylphosphine)palladium. Subsequently, the obtained amino acid derivative (S19) is subjected to a coupling reaction with a boronic acid derivative such as bis(2,2,3,3-tetramethyl-2,3-butanedionato)diboron in a solvent which does not affect this reaction such as 1,4-dioxane in the presence of a base such as potassium acetate by using
 15
 20

a metal catalyst such as [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II). Thus, the corresponding boronic acid derivative (S20) can be synthesized. The obtained boronic acid derivative (S20) is
5 subjected to a coupling reaction with compound (S21) in a solvent which does not affect this reaction such as dichloromethane in the presence of a base such as triethylamine by using a metal catalyst such as copper(II) acetate. Thus, amino acid derivative (S22) can be produced. The obtained amino
10 acid derivative (S22) is deprotected by acid hydrolysis using, for example, hydrochloric acid or trifluoroacetic acid, a hydrogenation reaction using a catalyst such as palladium carbon in the presence of hydrogen, or the like. Thus, the target intermediate (S23) having an amino group at its terminal
15 can be produced.

The compound represented by general formula (1) or a salt thereof is administered as it is or in the forms of various pharmaceutical compositions. Examples of dosage forms of the pharmaceutical compositions include tablets, powders, pills,
20 granules, capsules, suppositories, liquids, sugar-coated agents, depots, and syrups, which can be produced in a usual manner using ordinary excipients.

For example, the tablets can be obtained by mixing the sulfonamide derivative, which is an active ingredient of the
25 present invention, with any of known auxiliary substances including inactive diluents such as lactose, calcium carbonate, and calcium phosphate; binders such as gum arabic, corn starch, and gelatin; bulking agents such as alginic acid, corn starch, and pregelatinized starch; sweeteners such as sucrose, lactose,
30 or saccharin; flavoring agents such as peppermint, Gaultheria

adenothrix oil, and cherry; lubricating and wetting agents such as magnesium stearate, talc, and carboxymethyl cellulose; vehicles for soft gelatin capsules or suppositories such as fats, waxes, semi-solid or liquid polyols, natural oils, and hydrogenated oils; and vehicles for solutions such as water, alcohol, glycerol, polyol, sucrose, inverted sugar syrup, glucose, and vegetable oil.

The inhibitor comprising, as an active ingredient, the compound represented by general formula (1) or a salt thereof can be used as an agent for treating or preventing any one of inflammatory diseases, rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, Sjögren's syndrome, asthma, psoriasis, allergy, diabetes mellitus, cardiovascular diseases, arteriosclerosis, restenosis, tumor growth, tumor metastasis, and transplant rejection, in which an $\alpha 4$ integrin-dependent adhesion process is associated with a pathological condition.

The administered amount of the compound represented by general formula (1) or a salt thereof used for the above-described purpose is determined according to the target therapeutic effect, the administration method, the treating period, the age, the body weight, and the like. The administered amount varies between oral routes and parenteral routes, and, in general, it is preferable that the amount administered to a human adult be 1 μ g to 5 g per day for oral administration, and 0.01 μ g to 1 g per day for parenteral administration.

Examples

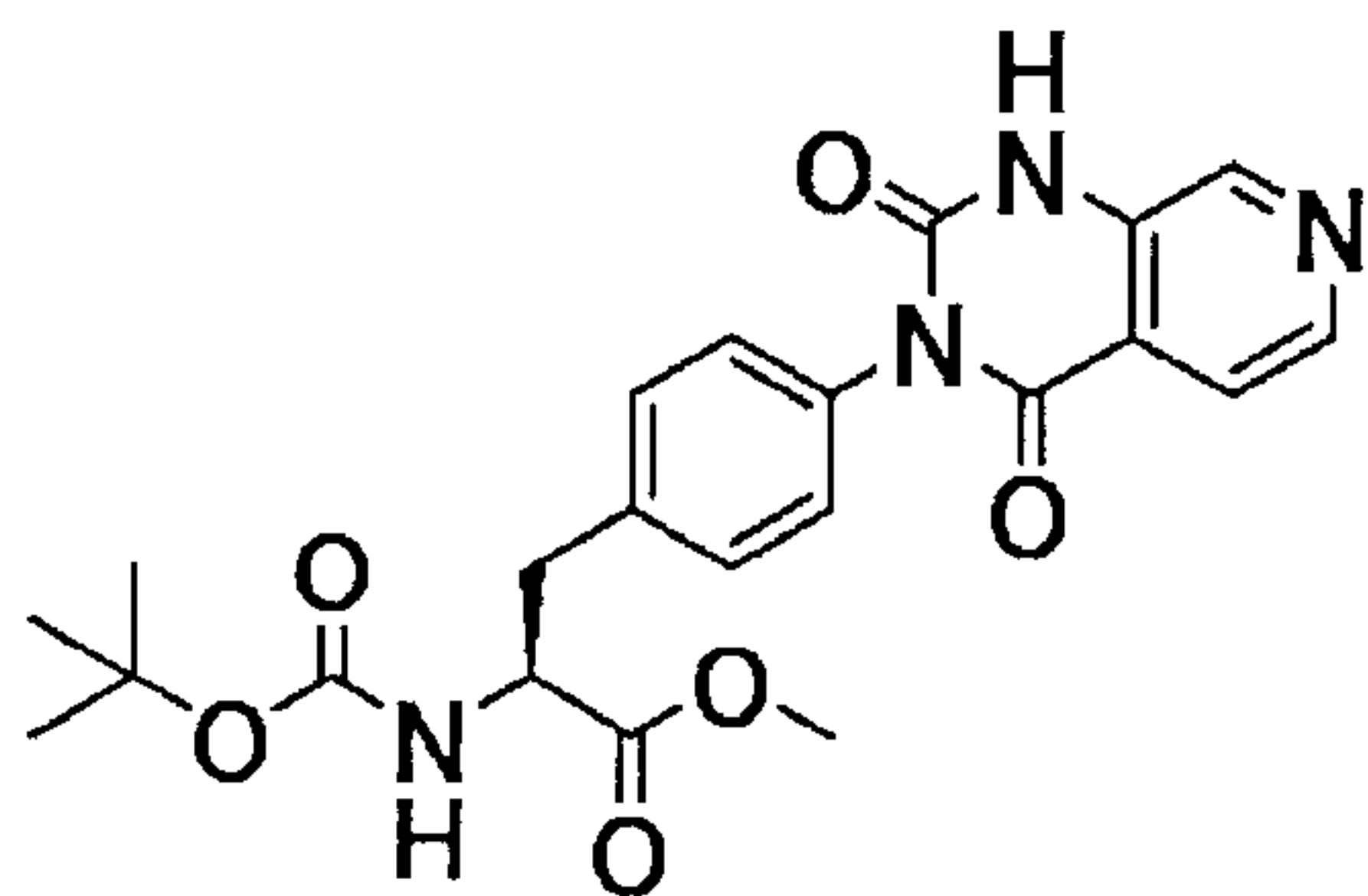
The present disclosure will be described in detail with reference to the following Examples, which are preferred

embodiments of the present disclosure. The present disclosure is not limited to these Examples.

Note that Examples 1 to 5, 97 to 103, and 186 to 188 show Synthesis Examples of intermediates represented by general formula (M-I) and having an amino group at their terminals, and Examples 6 to 38, 104 to 136, 189 to 210, and 240 to 245 show Synthesis Examples of intermediates represented by general formula (M-II) and having a carboxyl group at their terminals. Examples 39 to 96, 137 to 185, 211 to 239, and 246 to 257 are Synthesis Examples of compounds of the present disclosure. Of these, B-1 to B-5, B-7, B-9, B-10, B-12 to B-15, B-17 to B-20, B-22 to B-24, B-26 to B-32, and B-36 to B-40 in Examples 39 to 78, B-41 to B-54, B-56 to B-57, and B-59 to B-88 in Examples 79 to 96 and Examples 137 to 185, B-90 to B-113 and B-115 to B-118 in Examples 211 to 239, and B-119 to B-130 in Examples 246 to 257 show Synthesis Examples of prodrugs.

Example 1: Synthesis of M-1

(Step 1) Methyl N-(tert-Butoxycarbonyl)-4-(2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate

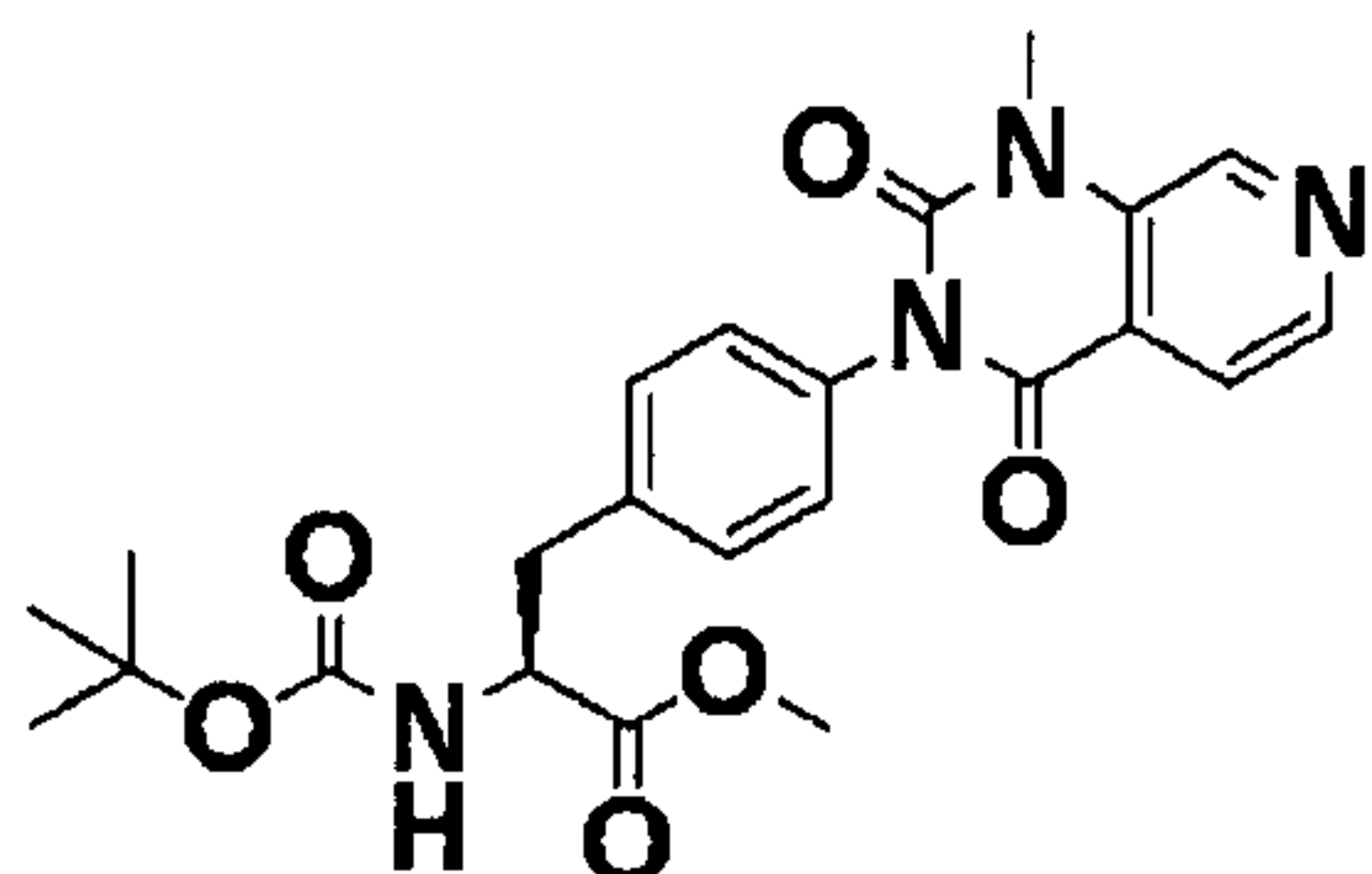


Methyl 3-aminoisonicotinate (10.0 g, 65.0 mmol) was dissolved in methylene chloride (100 ml), and diisopropylethylamine (17.0 g, 130 mmol) and triphosgene (6.40 g, 22.0 mmol) were added thereto, followed by stirring at 0°C

for 3 hours. To the solution, methyl 4-amino-N-(tert-butoxycarbonyl)-L-phenylalaninate (19.0 g, 65.0 mmol) was added, and the mixture was stirred for 12 hours, while the temperature was gradually raised from 0°C to room temperature. After the reaction solution was concentrated under reduced pressure, ethyl acetate was added, and the mixture was washed with water and saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. After the solvent was removed under reduced pressure, purification was conducted by silica gel column chromatography (petroleum ether/ethyl acetate=1:1). The obtained compound was dissolved in N,N-dimethylformamide (200 ml), and an aqueous solution of potassium carbonate (1.20 g, 8.70 mmol) was added, followed by stirring at room temperature for 3 hours. After the reaction solution was concentrated under reduced pressure, ethyl acetate was added, and the mixture was washed with water and saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. After the solvent was removed under reduced pressure, purification was conducted by silica gel column chromatography (petroleum ether/ethyl acetate=1:1) to obtain the title compound (12.0 g, 43% over two steps).

¹H NMR (CDCl₃, 400 MHz): δ 10.07 (1H, s), 8.54 (d, J = 5.2 Hz, 1H), 8.14 (s, 1H), 7.92 (d, J = 8.8 Hz, 1H), 7.35 (d, J = 7.6 Hz, 2H), 7.23 (d, J = 8.0 Hz, 2H), 6.12-6.10 (m, 1H), 4.73-4.69 (m, 1H), 3.71 (s, 3H), 3.22-3.21 (m 2H), 1.44 (s, 9H).

(Step 2) Methyl N-(tert-Butoxycarbonyl)-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate

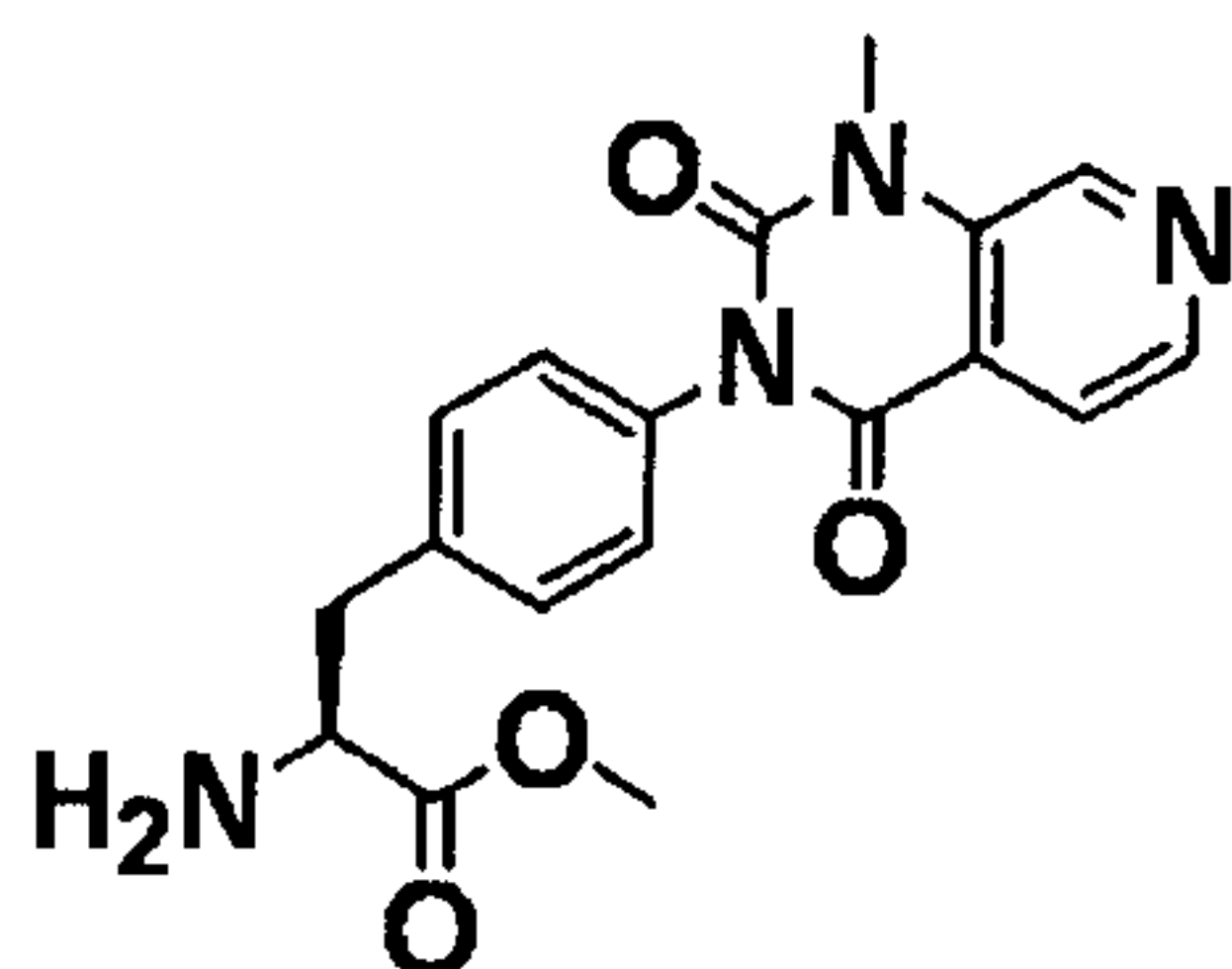


Methyl

N-(tert-butoxycarbonyl)-4-(2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (8.00 g, 18.5 mmol)
 5 was dissolved in N,N-dimethylformamide (100 ml), and potassium carbonate (5.10 g, 37.0 mmol) and methyl iodide (1.9 ml, 37 mmol) were added thereto, followed by stirring at room temperature for 3 hours. The suspension was filtered, and the filtrate was concentrated under reduced pressure. Then, purification was
 10 conducted by silica gel column chromatography (petroleum ether/ethyl acetate=1:1) to obtain the title compound (3.5 g, 43%).

¹H NMR (CDCl₃, 400 MHz): δ 8.81 (1H, s), 8.60 (d, J = 4.8 Hz, 1H), 8.03 (d, J = 4.8 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.19
 15 (d, J = 8.4 Hz, 2H), 5.05-5.03 (m, 1H), 4.65-4.63 (m, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.18-3.16 (m 2H), 1.44 (s, 9H).; MS (ESI) m/z 355 (M+H-Boc)⁺

(Step 3) Methyl
4-(1-Methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2
 20 H)-yl)-L-phenylalaninate (M-1)



·2HCl

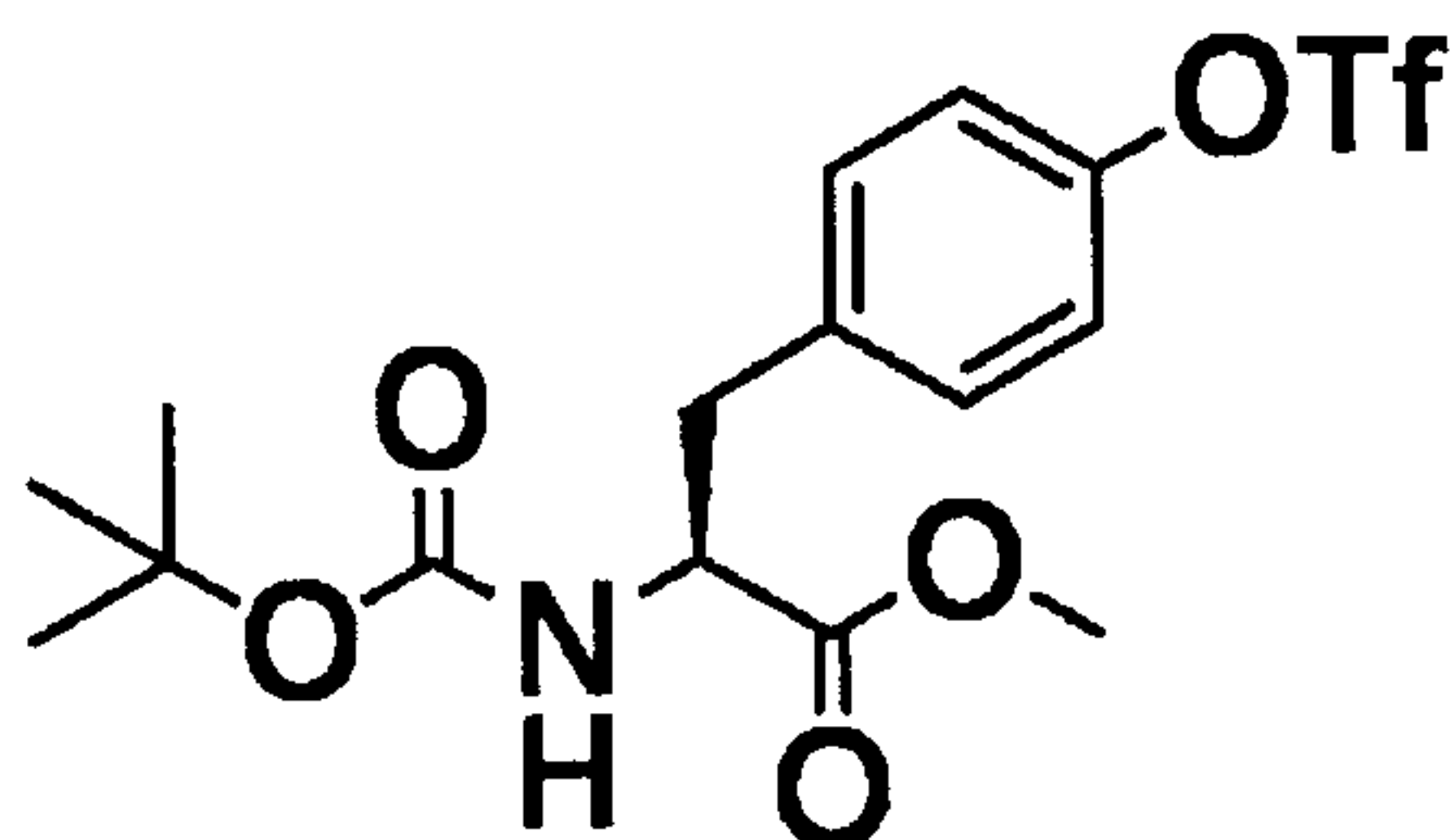
Methyl

N-(tert-butoxycarbonyl)-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (3.5 g, 7.7 mmol) was dissolved in a 4 N hydrogen chloride/ethyl acetate solution (40 ml), followed by stirring at room temperature for 1 hour. After the reaction liquid was filtered, the obtained solid was dried under reduced pressure to obtain the title compound (3.0 g, 94%).

¹H NMR (CD₃OD, 400 MHz): δ 9.28 (s, 1H), 8.76 (d, J = 0.8 Hz, 1H), 8.56 (d, J = 1.6 Hz, 1H), 7.51 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 4.48-4.44 (m, 1H), 3.90 (s, 3H), 3.76 (s, 3H), 3.49-3.44 (m, 1H), 3.30-3.24 (m, 1H).; MS (ESI) m/z 355 (M+H)⁺

Example 2: Synthesis of M-2

(Step 1) Methyl N-(tert-Butoxycarbonyl)-O-[(trifluoromethyl)sulfonyl]-L-tyrosinate



Methyl N-(tert-butoxycarbonyl)-L-tyrosinate (60.0 g, 203 mmol) was dissolved in tetrahydrofuran, and N-phenyl bis(trifluoromethanesulfonamide) (79.8 g, 224 mmol) and diisopropylethylamine (90.0 g, 714 mmol) were added thereto, followed by stirring at room temperature for 12 hours. After the reaction solution was concentrated under reduced pressure, the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=3:1) to obtain the title compound (74 g, 85%).

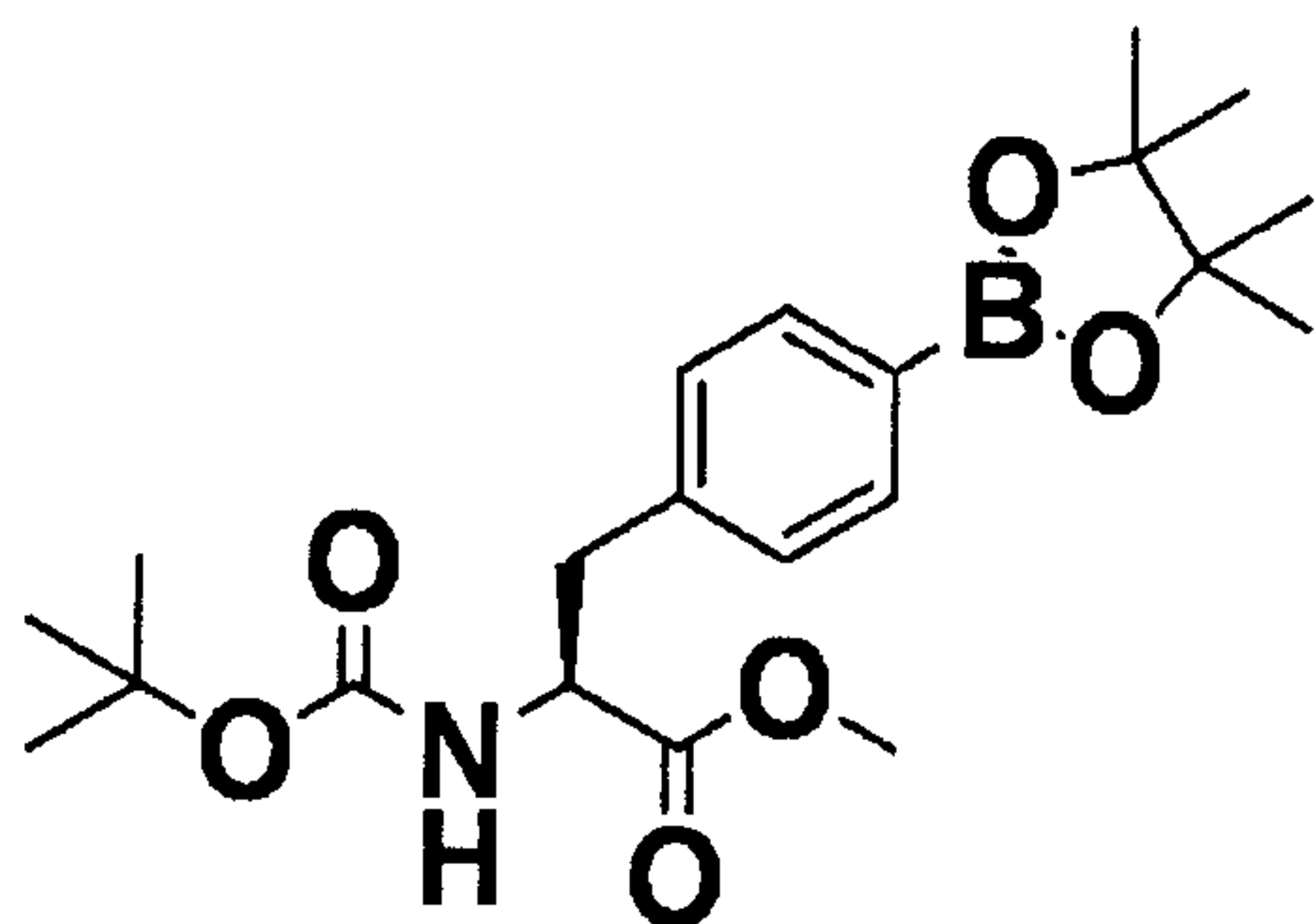
^1H NMR (CDCl_3 , 400 MHz): δ 7.25-7.19 (m, 4H), 5.08-5.06 (m, 1H), 4.61-4.59 (m, 1H), 3.71 (3H, s), 3.19-3.15 (m, 1H), 3.06-3.01 (m, 1H), 1.41 (s, 9H).; MS (ESI) m/z 328 ($\text{M}+\text{H}-\text{Boc}$) $^+$

(Step

2)

Methyl

5 N-(tert-Butoxycarbonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-L-phenylalaninate



Methyl

N-(tert-butoxycarbonyl)-O-[(trifluoromethyl)sulfonyl]-L-tyrosinate (74.0 g, 173 mmol) and bis(pinacolato)diborane (66.0 g, 260 mmol) were dissolved in N,N-dimethylformamide (1 L). To the solution, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (13.6 g, 18.6 mmol) and potassium acetate (60.0 g, 612 mmol) were added, followed by stirring at 95°C for 12 hours. After cooling to room temperature, the reaction solution was filtered through Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=4:1) to obtain the title compound (45.0 g, 65%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.73 (d, J = 8 Hz, 2H), 7.12 (d, J = 8 Hz, 2H), 4.59-4.57 (m, 1H), 3.70 (3H, s), 3.11-3.06 (m, 2H), 1.41 (s, 9H), 1.13 (s, 12H).; MS (ESI) m/z 306 ($\text{M}+\text{H}-\text{Boc}$) $^+$

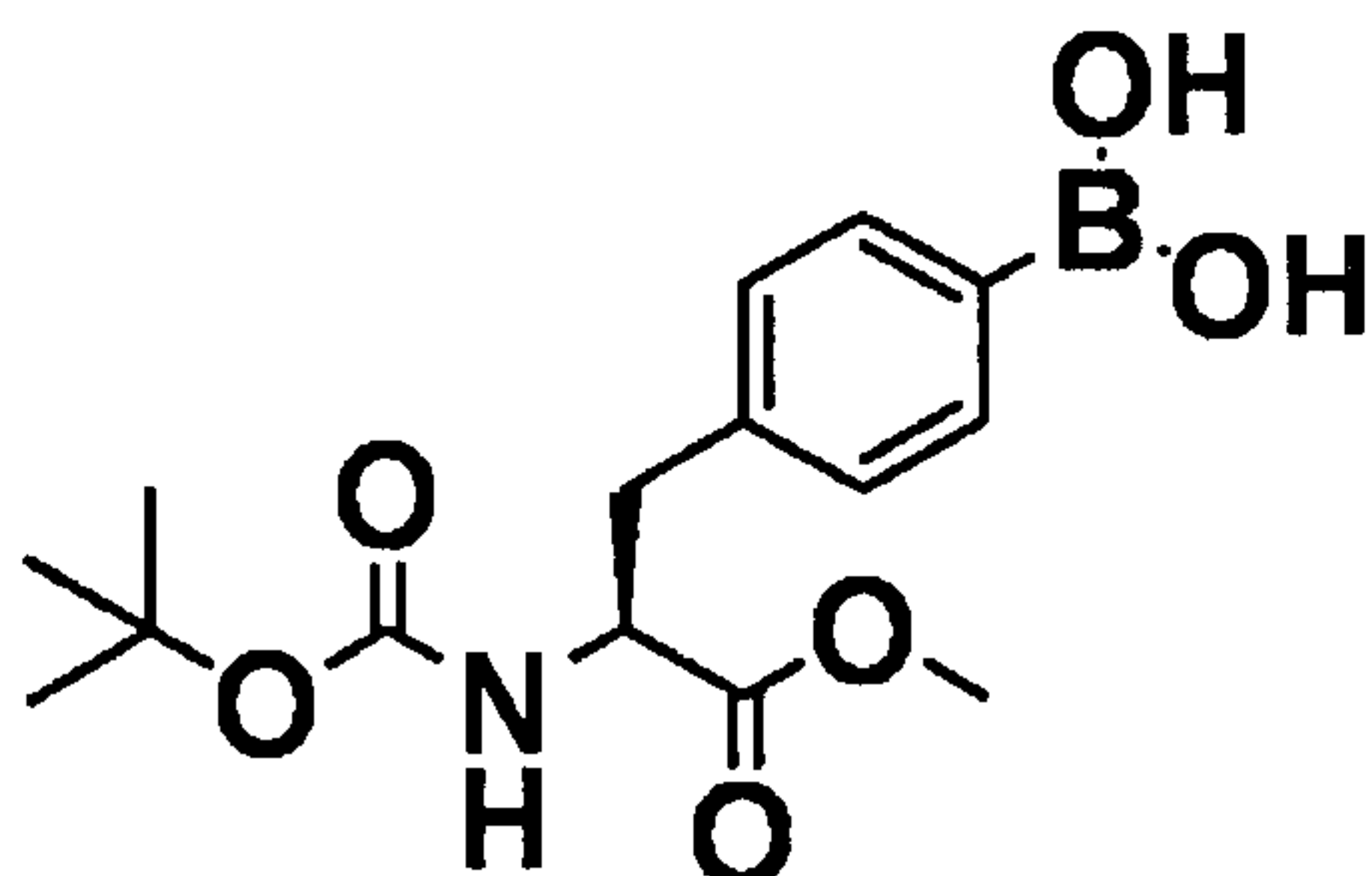
(Step

3)

Methyl

25 N-(tert-Butoxycarbonyl)-4-(dihydroxyboryl)-L-phenylalaninate

e

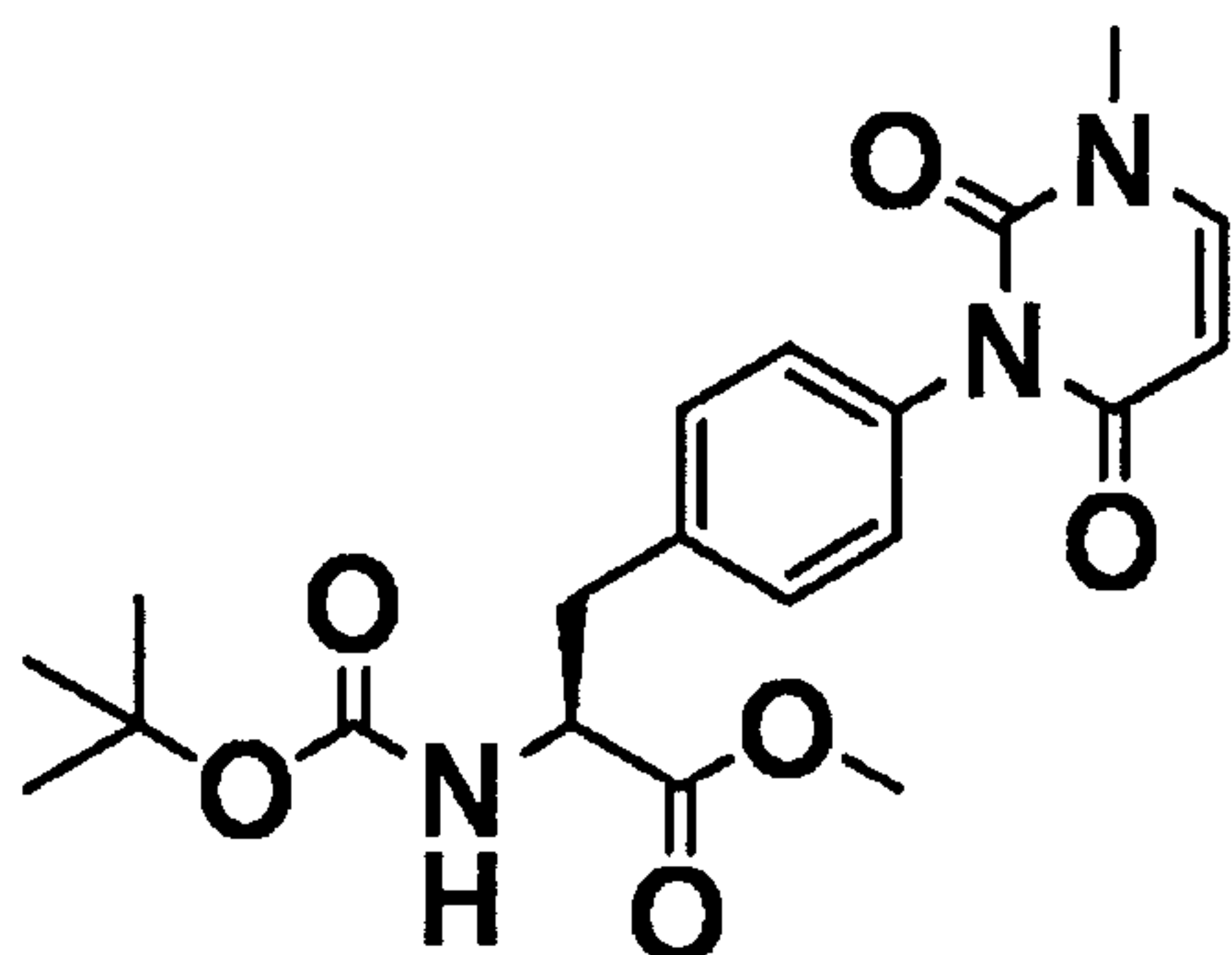


Methyl

N-(tert-butoxycarbonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxab
 5 orolan-2-yl)-L-phenylalaninate (67.0 g, 165 mmol) was
 dissolved in acetone (700 ml). To the solution, sodium
 periodate (71.0 g, 330 mmol), ammonium acetate (25.0 g, 330
 mmol), and water (300 ml) were added, followed by stirring at
 room temperature for 55 hours. After the reaction solution was
 10 filtered, the filtrate was concentrated under reduced pressure,
 and ethyl acetate was added. The mixture was washed with water
 and saturated aqueous sodium chloride, and dried over anhydrous
 sodium sulfate. The solvent was removed under reduced pressure,
 and the precipitated solid was washed with a mixture solvent
 15 of petroleum ether/ethyl acetate (1:10) and dried to obtain the
 title compound (29 g, 55%).

¹H NMR (CDCl₃, 400 MHz): δ: 7.71-7.56 (m, 2H), 7.25-7.16 (m,
 2H), 4.39-4.37 (m, 1H), 3.71 (s, 3H), 3.14-3.10 (m, 1H),
 2.96-2.90 (m, 1H), 1.40 (s, 9H).; MS (ESI) m/z 224 (M+H-Boc)⁺

20 (Step 4) Methyl
N-(tert-Butoxycarbonyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropy
rimidin-1(2H)-yl)-L-phenylalaninate



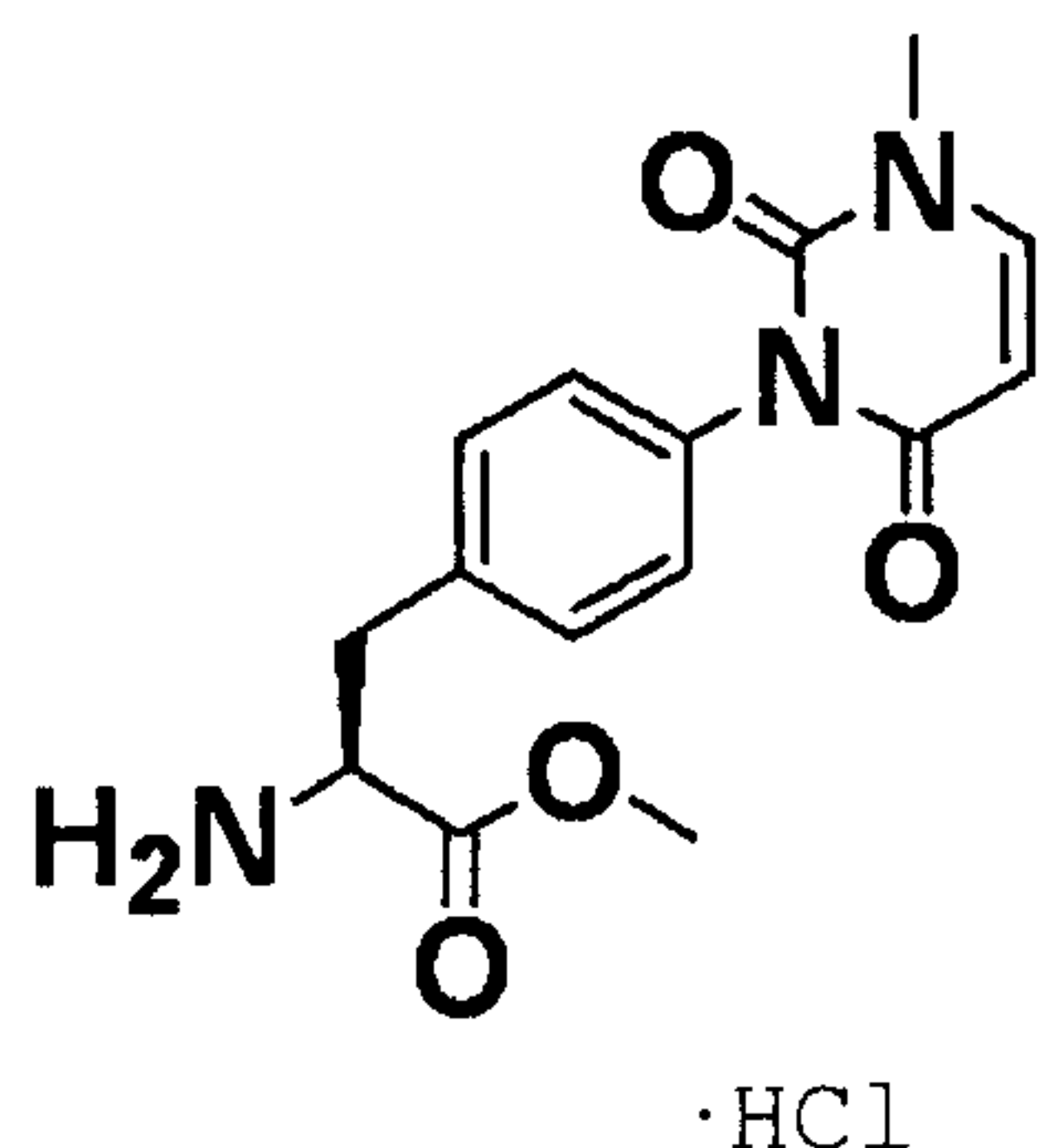
Pyrimidine-2,4 (1H,3H) -dione (30.0 g, 268 mmol),
 1,1,1,3,3,3-hexamethyldisilazane (550 ml), and
 trimethylchlorosilane (55 ml) were stirred at 130°C for 5 hours.
 5 After the reaction solution was cooled to 60°C, methyl iodide
 (200 ml) was added, followed by stirring at 60°C for 30 hours.
 The reaction solution was cooled to 0°C, and acetic acid (500
 ml) was slowly added. Then, the solvent was removed under
 reduced pressure. To the residue, 2-propanol (1600 ml) was
 10 added, followed by vigorous stirring. Then, the obtained solid
 was filtered, and washed with water (500 ml) to obtain a white
 solid (22 g, 67%). Methyl
 N-(tert-butoxycarbonyl)-4-(dihydroxyboryl)-L-phenylalaninate
 (49.0 g, 152 mmol) was dissolved in methylene chloride (500
 15 ml), and then the obtained white solid (22.0 g, 175 mmol)
 copper(II) acetate (18.0 g, 98.9 mmol), and triethylamine (40
 ml) were added thereto, followed by stirring at room temperature
 for 60 hours. After the reaction solution was concentrated
 under reduced pressure, the obtained residue was purified by
 20 silica gel column chromatography (petroleum ether/ethyl
 acetate=1:1) to obtain the title compound (6.0 g, 10%) as white
 crystals.

¹H NMR (d-DMSO, 400 MHz): δ 7.77 (d, J = 8.0 Hz, 1H), 7.38 (d,
 J = 8.0 Hz, 1H), 7.32 (d, J = 8.8 Hz, 2H), 7.11 (d, J = 8.4 Hz,

2H), 5.76 (d, $J = 8.0$ Hz, 1H), 4.22-4.19 (m, 1H), 3.60 (s, 3H), 3.32 (s, 3H), 3.03-3.02 (m, 1H), 2.94-2.90 (m, 1H), 1.36 (s, 9H).; MS (ESI) m/z 421 ($M+H+NH_3$)⁺

(Step 5) Methyl

5 4-(3-Methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate ((M-2))



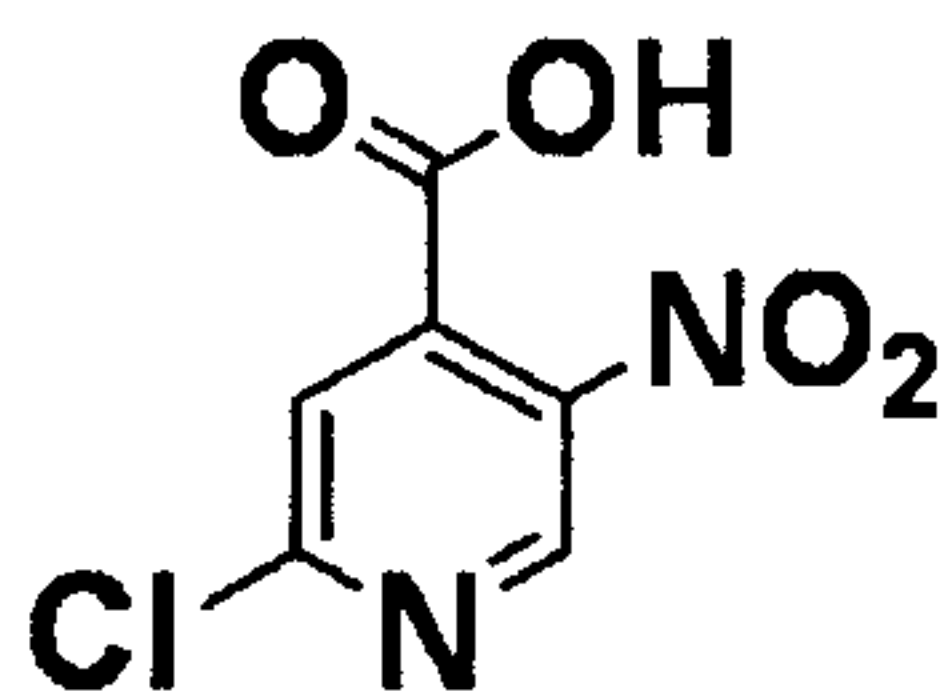
Methyl

10 N-(tert-butoxycarbonyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (6.00 g, 15.0 mmol) was dissolved in a 3 N hydrogen chloride/ethyl acetate solution (100 ml), followed by stirring at room temperature for 1 hour. After the solvent was removed under reduced pressure, ethyl acetate
15 (50 ml) was added, followed by stirring at room temperature for further 0.5 hours. The suspension was filtered, and the obtained solid was dried to obtain the title compound (4.0 g, 80%) as a white solid.

1H NMR (CD₃OD, 500 MHz): δ 7.72 (d, $J = 8$ Hz, 1H), 7.45 (d, $J = 8$ Hz, 2H), 7.29 (d, $J = 8$ Hz, 2H), 5.85 (d, $J = 8$ Hz, 1H),
20 = 8 Hz, 2H), 4.44-4.41 (m, 1H), 3.91 (s, 3H), 3.49-3.45 (m, 4H), 3.23-3.17 (m, 1H).; MS (ESI) m/z 304 ($M+H$)⁺

Example 3: Synthesis of M-3

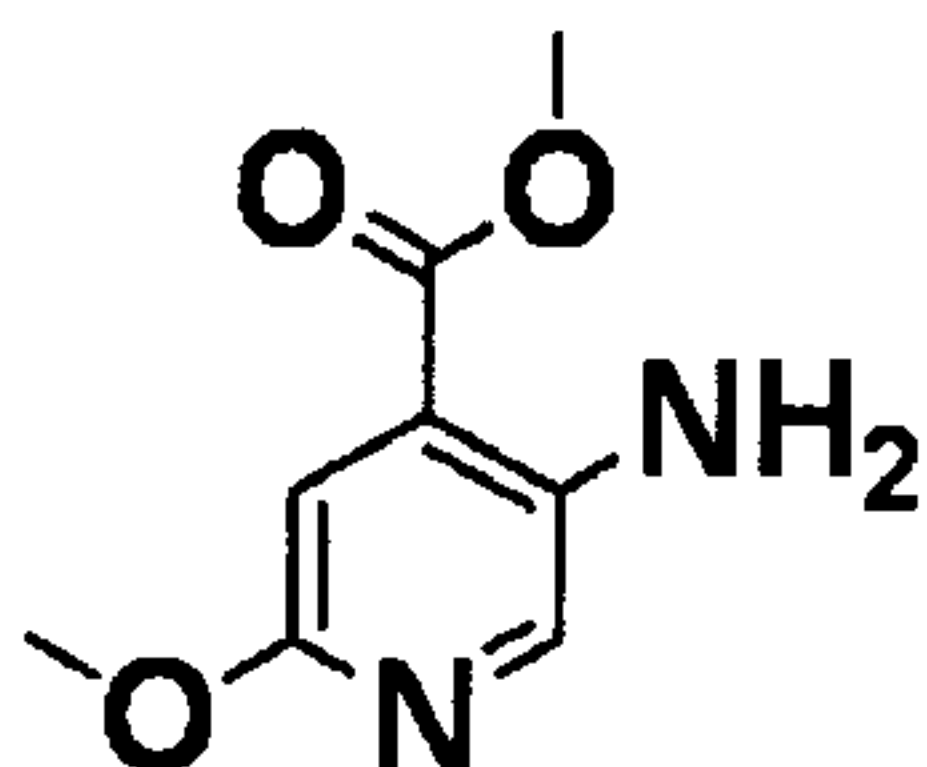
(Step 1) 2-Chloro-5-nitroisonicotinic Acid



2-Chloro-4-methyl-5-nitropyridine (20.5 g, 119 mmol) was dissolved in concentrated sulfuric acid (200 ml), and chromium trioxide (40.0 g, 400 mmol) was added thereto, followed by stirring at 0°C for 1 hour. Then, the temperature was gradually raised from 0°C to room temperature, followed by stirring for 12 hours. The reaction solution was poured into ice-water (2000 ml), and the temperature was raised from 0°C to room temperature. The precipitated solid was filtered and dried under reduced pressure to obtain the title compound (18 g, 75%).

¹H NMR (CD₃OD, 400 MHz): δ 10.8 (1H, br, s), 9.13 (1H, s), 7.70 (1H, s).

(Step 2) Methyl 5-Amino-2-methoxyisonicotinate

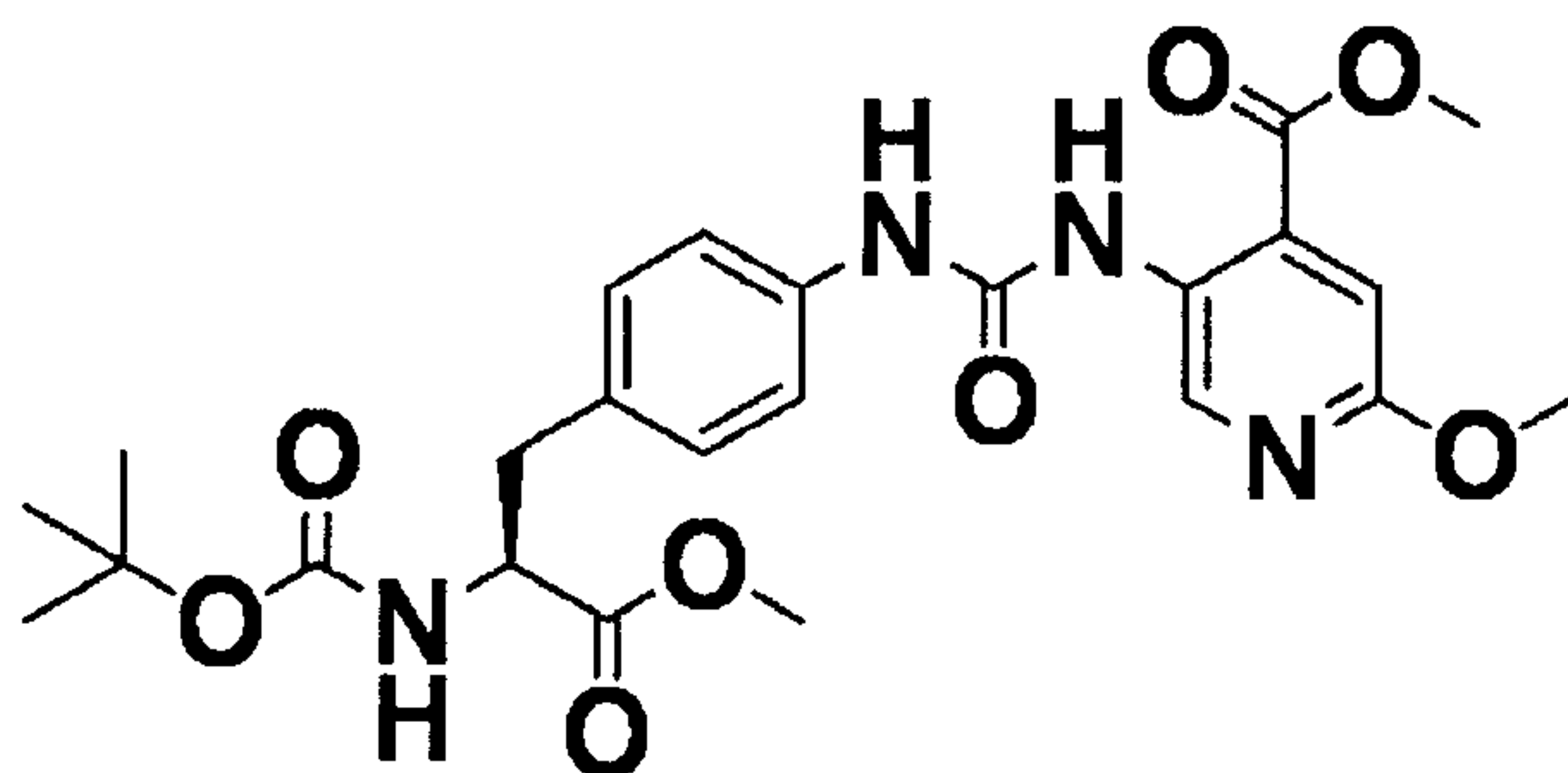


Potassium hydroxide (90 g) was dissolved in diethyl ether (300 ml) and water (30 ml), and N-methyl-N-nitrosourea (30.9 g, 300 mmol) was slowly added thereto. After stirring at 0°C for 20 minutes, the organic layer (ether solution) was separated. 2-Chloro-5-nitroisonicotinic acid (20.2 g, 100 mmol) was dissolved in ethyl acetate (100 ml), and the mixture was cooled to 0°C. Then, the above-described ether solution was added to this mixture, followed by stirring for 1 hour. The solvent was removed under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum

ether/ethyl acetate=6:1 to 2:1). The obtained compound (10.8 g, 50.0 mmol) was dissolved in methanol (100 ml), and sodium methoxide (8.10 g, 150 mmol) was added thereto, followed by stirring at 65°C for 4 hours. After cooling to room temperature, the reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=8:1 to 4:1). The obtained compound (8.0 g, 37 mmol) was dissolved in methanol (100 ml), and iron (10.6 g, 175 mmol) and a saturated aqueous ammonium chloride solution (50 ml) were added thereto, followed by stirring at 65°C for 2 hours. After cooling to room temperature, the pH was adjusted to 7 or higher by adding a saturated aqueous sodium hydrogen carbonate solution. Then, ethyl acetate (100 ml×3) was added, and the organic layer was washed with water and saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=4:1 to 1:1) to obtain the title compound (5.8 g, 58% over three steps).

¹H NMR (CDCl₃, 400 MHz): δ 7.80 (s, 1H), 7.15 (s, 1H), 5.10 (s, 2H), 3.90 (s, 3H), 3.84 (s, 3H).

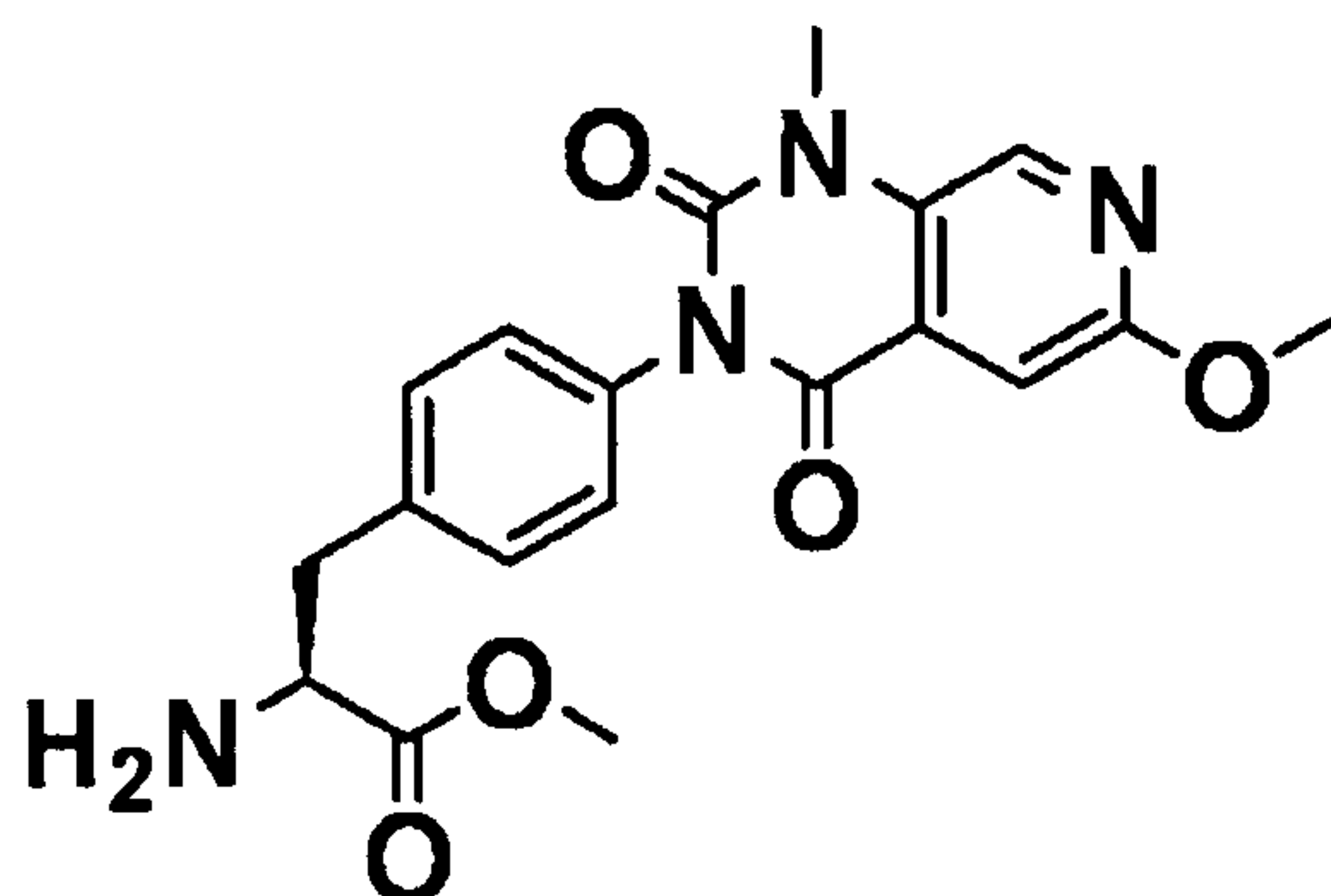
(Step 3) Methyl
N-(tert-Butoxycarbonyl)-4-[(6-methoxy-4-(methoxycarbonyl)
pyridin-3-yl]amino}carbonyl)amino]-L-phenylalaninate



Methyl 5-amino-2-methoxyisonicotinate (5.0 g, 27 mmol) was dissolved in methylene chloride (100 ml), and a solution of triphosgene (2.6 g, 9.0 mmol) in methylene chloride and diisopropylethylamine (10.0 g, 82.0 mmol) were added thereto, followed by stirring at 0°C for 3 hours. Then, methyl 4-amino-N-(tert-butoxycarbonyl)-L-phenylalaninate (7.9 g, 27 mmol) was added thereto, followed by stirring at room temperature for 12 hours. After the solvent was removed under reduced pressure, ethyl acetate was added, and the mixture was washed with a saturated aqueous sodium hydrogen carbonate solution, water, and saturated aqueous sodium chloride and dried over anhydrous sodium sulfate. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1) to obtain the title compound.

MS (ESI) m/z 503 (M+H)⁺

(Step 4) Methyl 4-(6-Methoxy-1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (M-3)



·2HCl

Methyl

N-(tert-butoxycarbonyl)-4-[(6-methoxy-4-(methoxycarbonyl)pyridin-3-yl)amino]carbonyl-L-phenylalaninate was dissolved in N,N-dimethylformamide (20 ml), and an aqueous potassium carbonate solution (0.75 g, 5.3 mmol) was added thereto, followed by stirring at room temperature for 3 hours. To this reaction solution, methyl 4-methylbenzenesulfonate (5.5 g, 30 mmol) and potassium carbonate (7.5 g, 54 mmol) were added, followed by stirring at room temperature for 12 hours. The reaction solution was diluted with water (200 ml), followed by extraction with ethyl acetate. The extraction liquids were combined and dried over anhydrous sodium sulfate, and then the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1).

The obtained compound (6.0 g, 12 mmol) was dissolved in a 3 N hydrogen chloride/ethyl acetate solution (30 ml), followed by stirring at room temperature for 1 hour. The precipitated solid was filtered and dried under reduced pressure to obtain the title compound (4.6 g, 45% over three steps).

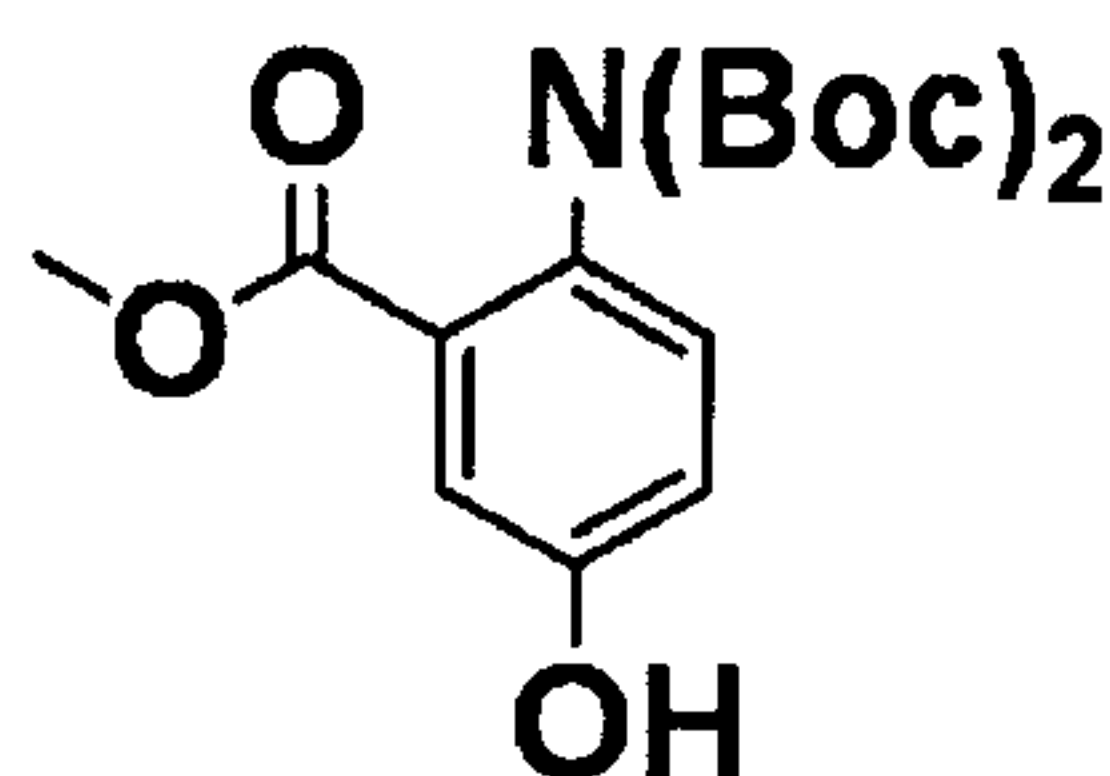
¹H NMR (CD₃OD, 400 MHz): δ 8.50 (s, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.42 (s, 1H), 7.36 (d, J = 8.0 Hz, 2H), 4.69-4.35 (m, 1H),

4.01 (s, 3H), 3.91 (s, 3H), 3.67 (s, 3H), 3.49-3.44 (m 1H),
3.26-3.22 (m, 1H).; MS (ESI) m/z 385 (M+H)⁺

Example 4: Synthesis of M-4

(Step 1) Methyl

5 2-[Bis(tert-butoxycarbonyl)amino]-5-hydroxybenzoate

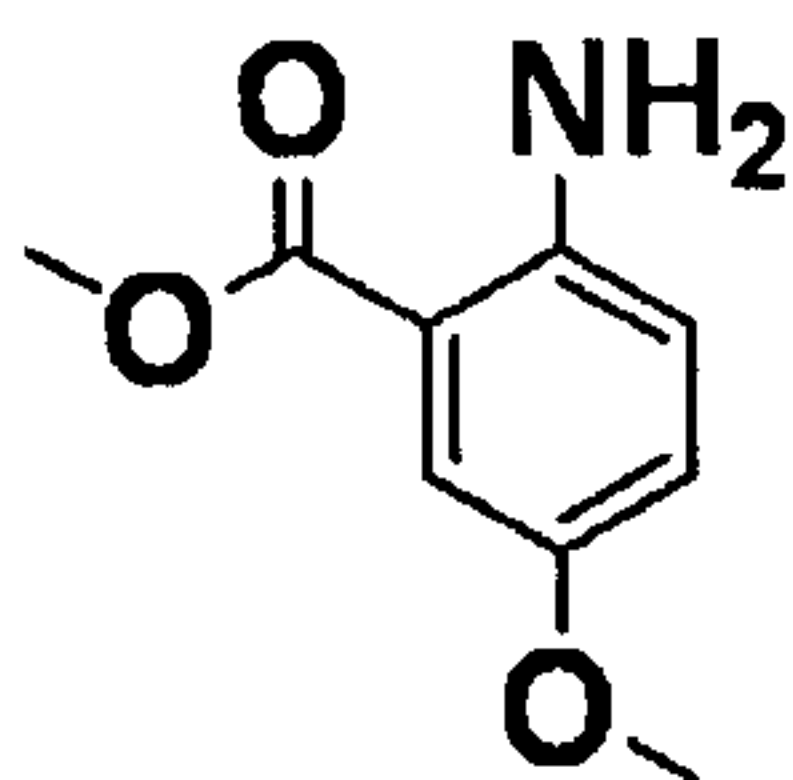


2-Amino-5-hydroxybenzoic acid (10.0 g, 65.3 mmol) was dissolved in methanol (200 ml). To the solution, concentrated sulfuric acid (10 ml) was slowly added dropwise, followed by
10 stirring at 65°C for 48 hours. After cooling to room temperature, the reaction solution was neutralized with sodium hydrogen carbonate, and concentrated under reduced pressure. Water (150 ml) was added to the obtained residue, and then the pH was adjusted to 7 or higher by adding sodium hydrogen
15 carbonate. The precipitated solid was filtered, washed with water, and then dried under reduced pressure.

A portion (6.0 g, 36 mmol) of the obtained solid was dissolved in methylene chloride (300 ml), and di-tert-butyl-dicarbonate (18.8 g, 86.0 mmol) and
20 N,N-dimethyl-4-aminopyridine (1.1 g, 8.7 mmol) were added thereto, followed by stirring at room temperature for 12 hours. After the reaction solution was concentrated under reduced pressure, the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=10:1 to 4:1) to
25 obtain the title compound (8.1 g, 54% over two steps).

MS (ESI) m/z 368 (M+H)⁺

(Step 2) Methyl 2-Amino-5-methoxybenzoate



Methyl

2-[bis(tert-butoxycarbonyl)amino]-5-hydroxybenzoate (3.67 g, 10.0 mmol) was dissolved in tetrahydrofuran (50 ml), and 60% sodium hydride (667 mg, 27.8 mmol) and methyl iodide (2.9 ml, 46 mmol) were added thereto, followed by stirring at room temperature for 1 hour. Then, the temperature was raised to 65°C, followed by stirring for 3 hours. The reaction solution was cooled to room temperature, and diluted with an aqueous ammonium chloride solution, followed by extraction with ethyl acetate. The extraction liquids were combined and dried over anhydrous sodium sulfate, and then the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=6:1 to 2:1). The obtained compound (9.0 g, 23 mmol) was cooled to 0°C, and then a 3 N hydrogen chloride/ethyl acetate solution (100 ml) was added thereto, followed by stirring at room temperature for 1 hour. The reaction solution was concentrated under reduced pressure, and the obtained residue was diluted with a saturated aqueous sodium hydrogen carbonate solution, followed by extraction with ethyl acetate. The extraction liquids were combined, and dried over anhydrous sodium sulfate. Then, the solvent was removed to obtain the title compound (3.8 g, 70% over two steps).

MS (ESI) m/z 182 (M+H)⁺

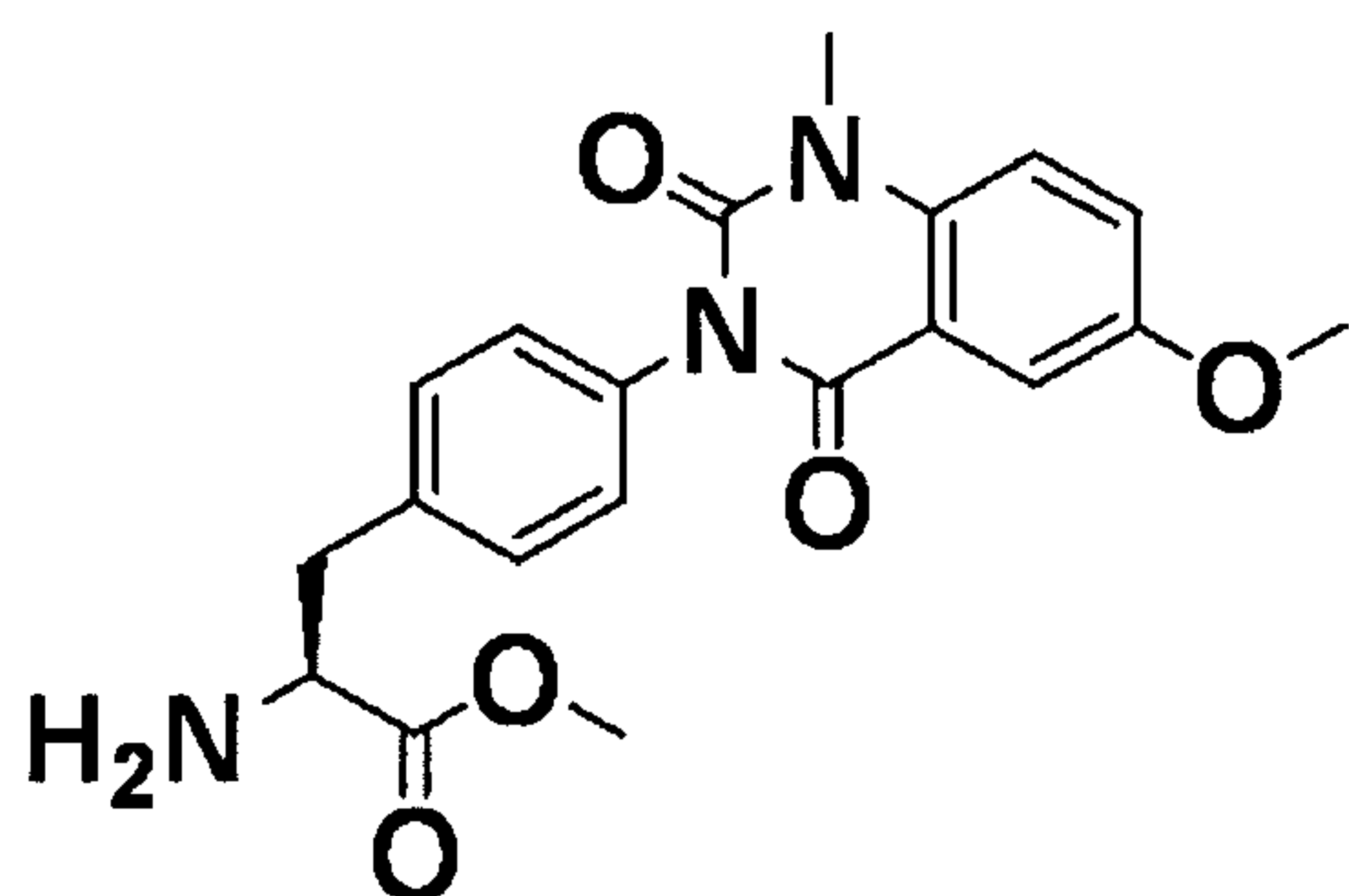
(Step

3)

Methyl

4-(6-Methoxy-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)

-yl)-L-phenylalaninate (M-4)



·HCl

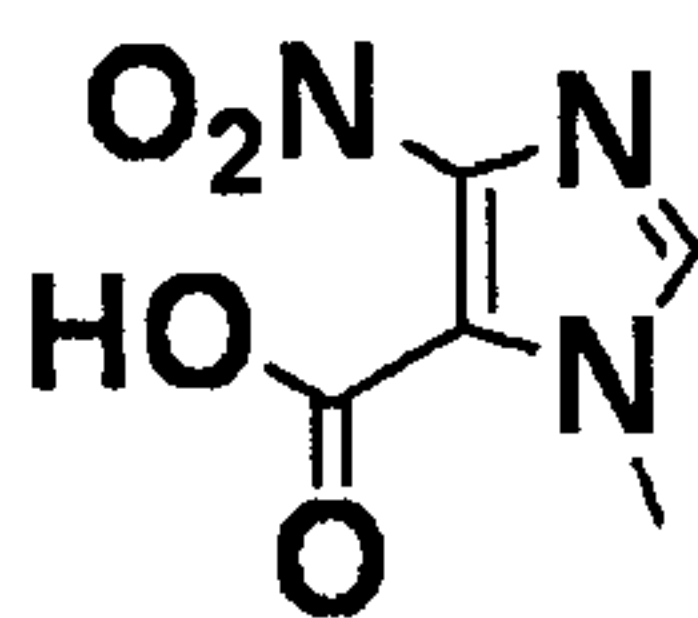
Carbonyldiimidazole (5.1 g, 32 mmol) was dissolved in
 5 N,N-dimethylformamide (100 ml), and methyl
 2-amino-5-methoxybenzoate (5.4 g, 30 mmol) and methyl
 4-amino-N-(tert-butoxycarbonyl)-L-phenylalaninate (8.8 g, 30
 mmol) were added thereto, followed by stirring at 50°C for 2
 hours. The reaction solution was diluted with ethyl acetate,
 10 then washed with a saturated aqueous sodium hydrogen carbonate
 solution and saturated aqueous sodium chloride, and dried over
 anhydrous sodium sulfate. The solvent was removed under
 reduced pressure, and the obtained residue was purified by
 silica gel column chromatography (petroleum ether/ethyl
 15 acetate=2:1 to 1:1). The obtained compound was dissolved in
 N,N-dimethylformamide (50 ml), and an aqueous solution of
 potassium carbonate (1.0 g, 7.2 mmol) was added thereto,
 followed by stirring at room temperature for 3 hours. To this
 reaction solution, methyl 4-methylbenzenesulfonate (7.7 g, 42
 20 mmol) and potassium carbonate (7.5 g, 54 mmol) were added,
 followed by stirring at room temperature for 12 hours. The
 reaction solution was diluted with water (50 ml), followed by
 extraction with ethyl acetate. The extraction liquids were
 combined, and dried over anhydrous sodium sulfate, and then the
 25 solvent was removed. The obtained residue was purified by

silica gel column chromatography (petroleum ether/ethyl acetate=1:1). Further, the obtained compound (9.6 g, 20 mmol) was dissolved in ethyl acetate, and a 3 N hydrogen chloride/ethyl acetate solution (50 ml) was added thereto, followed by stirring at room temperature for 1 hour. The precipitated solid was filtered, and dried under reduced pressure to obtain the title compound (7.0 g, 46% over four steps).

¹H NMR (CD₃OD, 400 MHz): δ 7.65 (d, J = 2.8 Hz, 1H), 7.52-7.45 (m, 4H), 7.36 (d, J = 8.4 Hz, 2H), 4.47-4.43 (m, 1H), 3.92 (s, 3H), 3.90 (s, 3H), 3.65 (s, 3H), 3.51-3.47 (m, 1H), 3.24-3.21 (m, 1H).; MS (ESI) m/z 384 (M+H)⁺

Example 5: Synthesis of M-5

(Step 1) 1-Methyl-4-nitro-1H-imidazole-5-carboxylic Acid



15

5-Chloro-1-methyl-4-nitro-1H-imidazole (3.21 g, 20.0 mmol) was suspended in ethanol (50 ml), and then potassium cyanide (3.91 g, 60.0 mmol) and potassium iodide (10.0 g, 60.0 mmol) were added thereto, followed by stirring at 70°C for 16 hours. After cooling to room temperature, diethyl ether was added to the reaction solution, which was then washed with water and saturated aqueous sodium chloride, and then dried over anhydrous sodium sulfate. After the solvent was concentrated under reduced pressure, water (20 ml), concentrated sulfuric acid (20 ml), and sodium nitrite (1.38 g, 20.0 mmol) were added to the obtained residue, followed by stirring at 80°C for 16 hours. After cooling to room temperature, water was added, and the precipitated solid was filtered to obtain the title compound

25

(1.36 g, 45%).

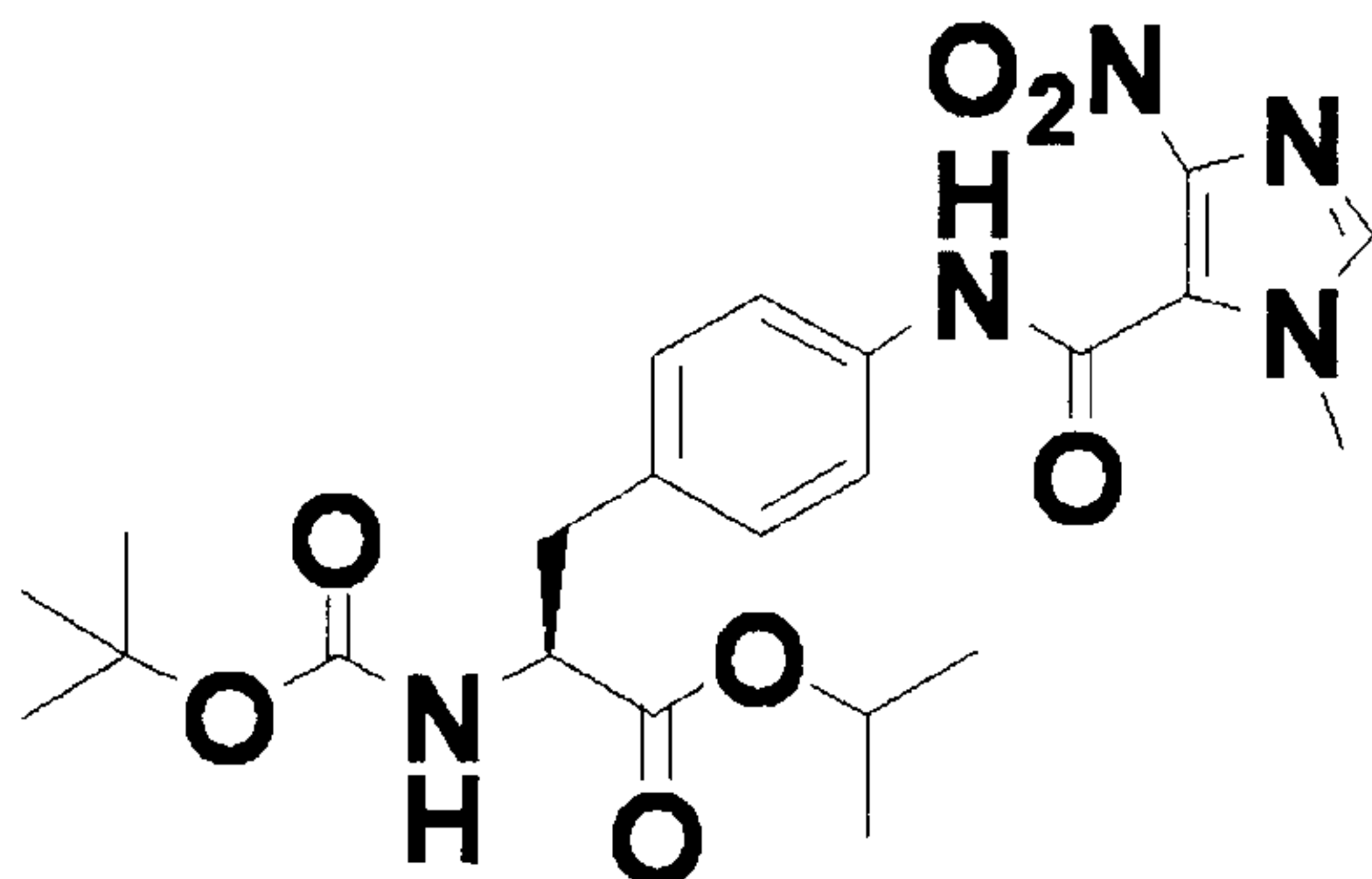
MS (ESI) m/z 172 (M+H)⁺

(Step

2)

Isopropyl

N-(tert-Butoxycarbonyl)-4-{[(1-methyl-4-nitro-1H-imidazol-5
-yl)carbonyl]amino}-L-phenylalaninate



1-Methyl-4-nitro-1H-imidazole-5-carboxylic acid (1.71 g, 10.0 mmol) was suspended in thionyl chloride (20 ml), followed by stirring at 60°C for 6 hours. After concentration under reduced pressure, dichloromethane (20 ml), 3-(4-amino-phenyl)-2-tert-butoxycarbonylaminopropanoic acid isopropyl ester (3.22 g, 10.0 mmol), and triethylamine (2.8 ml, 20 mmol) were added to the obtained residue, followed by stirring at room temperature for 2 hours. After the solvent was removed under reduced pressure, ethyl acetate was added to the reaction solution, which was then washed with an aqueous sodium hydrogen carbonate solution, water, and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The solvent was removed by distillation under reduced pressure, and purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the title compound (2.46 g, 52%).

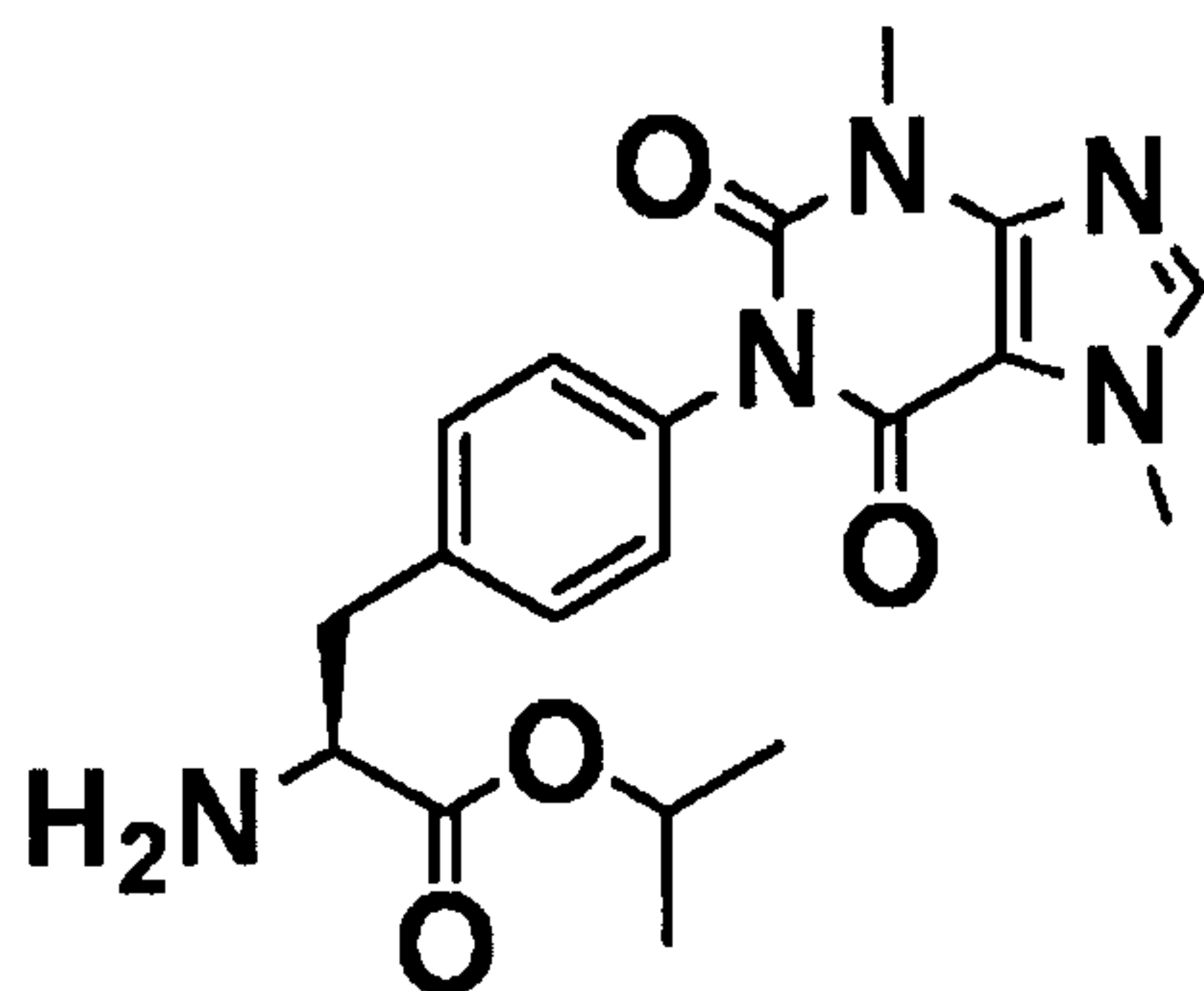
MS (ESI) m/z 476 (M+H)⁺

(Step

3)

Isopropyl

4-(3,7-Dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)

-L-phenylalaninate (M-5)

·TFA

Isopropyl

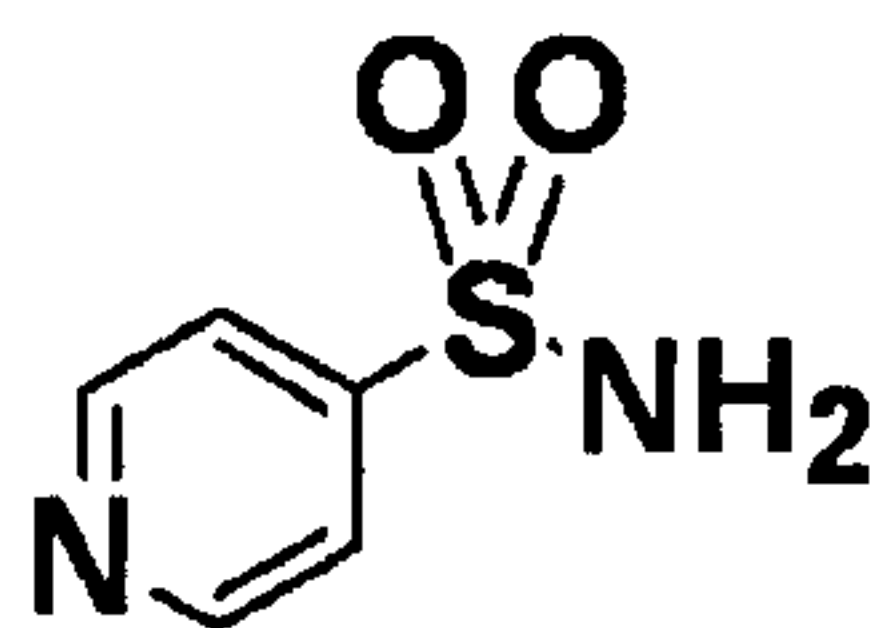
- 5 N-(tert-butoxycarbonyl)-4-([(1-methyl-4-nitro-1H-imidazol-5-yl)carbonyl]amino)-L-phenylalaninate (2.38 g, 5.00 mmol) was dissolved in ethanol (100 mL), and reduction reaction of the nitro group was conducted in a hydrogenation reactor H-Cube (10% Pd/C catalyst, 40°C, hydrogen: 2.0 atm, flow rate: 1.0 ml/min).
- 10 The solution was concentrated under reduced pressure, and then acetonitrile (20 mL) and carbonyldiimidazole (1.62 g, 10.0 mmol) were added thereto, followed by stirring at 60°C for 6 hours. After the solvent was removed under reduced pressure, ethyl acetate was added to the reaction solution, which was then
- 15 washed with an aqueous sodium hydrogen carbonate solution, water, and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. After the solvent was concentrated under reduced pressure, dimethylformamide (20 mL), methyl iodide (1.42 g, 10.0 mmol), and potassium carbonate (2.07 g,
- 20 15.0 mmol) were added to the obtained residue, followed by stirring at room temperature for 2 hours. After the solvent was removed under reduced pressure, ethyl acetate was added to the reaction solution, which was then washed with an aqueous sodium hydrogen carbonate solution, water, and saturated
- 25 aqueous sodium chloride, and dried over anhydrous sodium

sulfate. After the solvent was concentrated under reduced pressure, TFA (5.0 mL) was added to the obtained residue, followed by stirring at room temperature for 1 hour. After removal of TFA under reduced pressure, purification was
 5 conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (1.20 g, 48%) of the title compound.

MS (ESI) m/z 386 (M+H)⁺

Example 6: Synthesis of M-6

10 (Step 1) Pyridine-4-sulfonamide

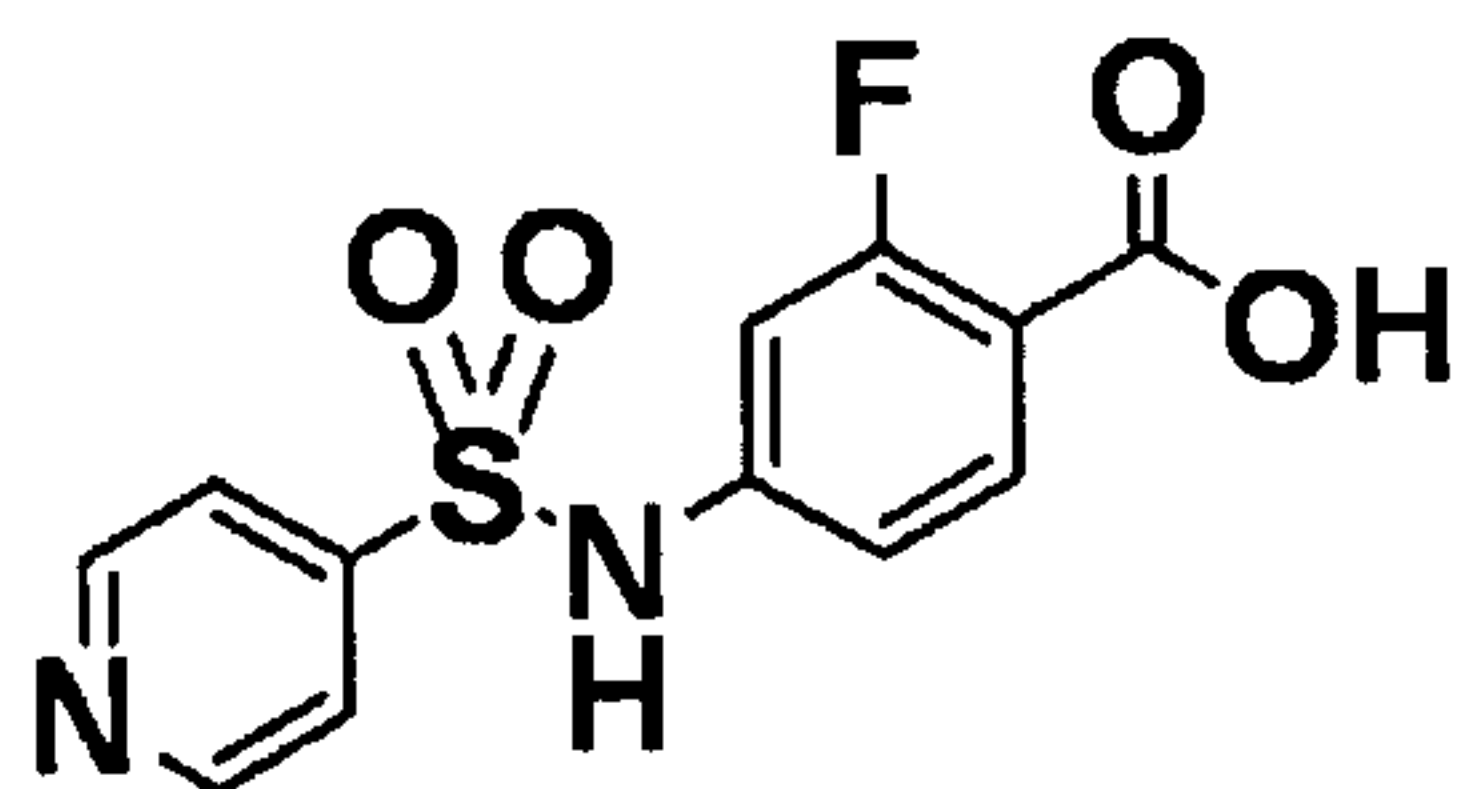


4-Pyridinethiol (16.7 g, 15.0 mmol) was dissolved in concentrated hydrochloric acid (110 ml) and water (30 ml). After cooling to 0°C, chlorine gas generated by adding
 15 concentrated hydrochloric acid (200 ml) to manganese dioxide (300 g) at room temperature was bubbled into the reaction liquid for 1 hour. After the reaction liquid was poured into ice-water (75 g), ammonia (600 mg) was added thereto, followed by stirring at room temperature for 12 hours. The reaction liquid was
 20 stored at 0°C for 12 hours, and the obtained solid was filtered and dried under reduced pressure to obtain the title compound (10.6 g, 45%) as a yellow solid.

¹H NMR (d-DMSO, 400 MHz,) δ 8.85-8.38 (m, 2H), 7.78-7.77 (m, 4H) .;

MS (ESI) m/z 159 (M+H)⁺

25 (Step 2) 2-Fluoro-4-[(pyridin-4-yl-sulfonyl)amino]benzoic Acid (M-6)

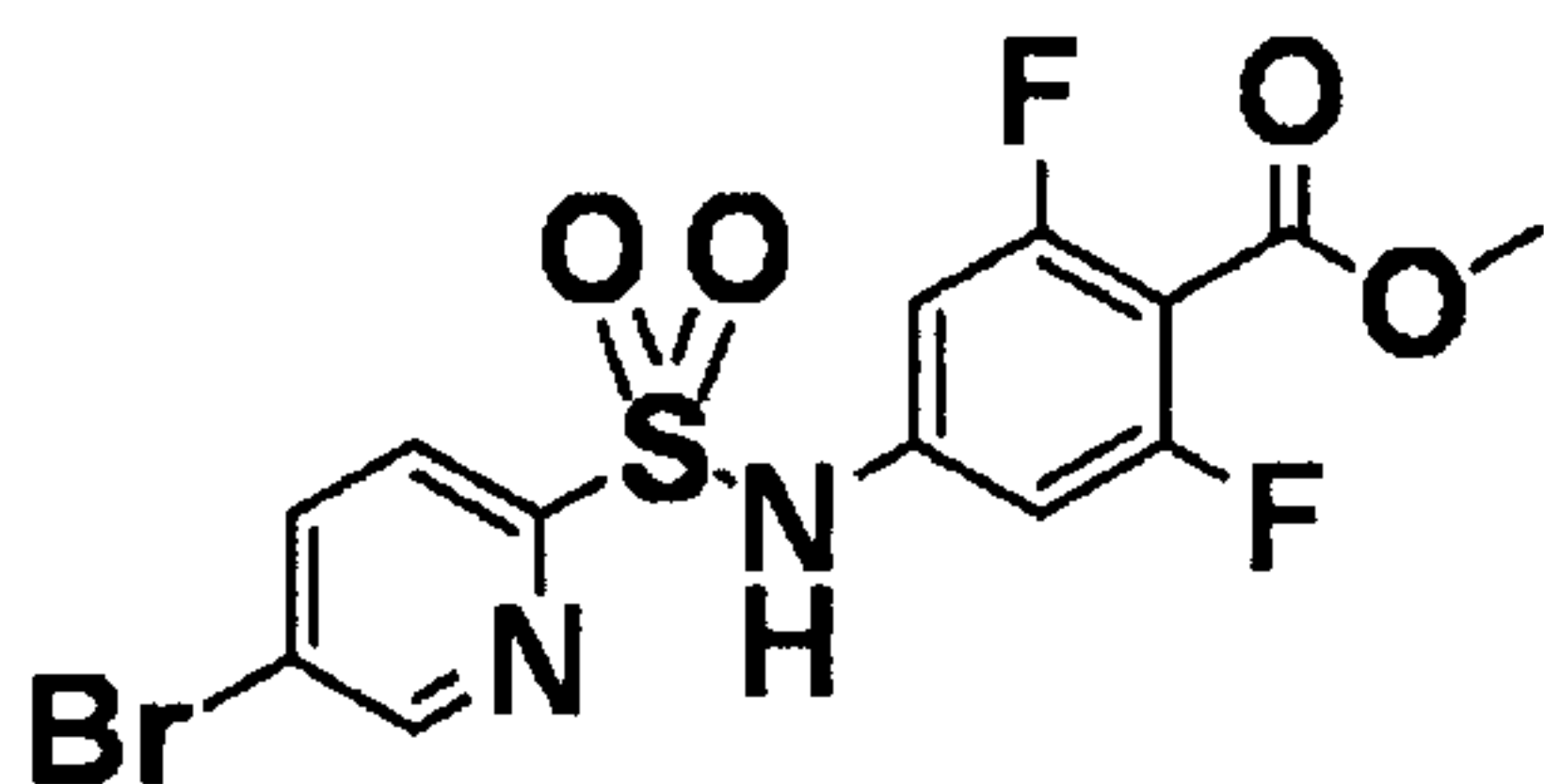


Pyridine-4-sulfonamide (14.0 g, 90.0 mmol) and methyl
4-bromo-2-fluorobenzoate (14.0 g, 60.0 mmol) were suspended in
1,4-dioxane (300 ml). To the solution,
5 tris(dibenzylideneacetone)dipalladium(0) (2.84 g, 3.00 mmol),
XantPHOS (3.42 g, 3.00 mmol), and cesium carbonate (38.0 g, 120
mmol) were added, followed by stirring at 100°C for 16 hours
in the presence of nitrogen gas. After cooling to room
temperature, the reaction solution was filtered through Celite,
10 and the filtrate was concentrated under reduced pressure. The
obtained residue was purified by silica gel column
chromatography (petroleum ether/ethyl acetate=5:1 to 1:1). A
compound (9.30 g, 30.0 mmol) obtained by repeating the
above-described process was dissolved in methanol (30 ml), and
15 a 2 N aqueous sodium hydroxide solution (30 ml) was added thereto,
followed by stirring at room temperature for 1 hour. The pH
was adjusted to 4.0 by adding 2 N hydrochloric acid, and the
precipitated solid was filtered, and then dried under reduced
pressure to obtain the title compound (8.1 g, 36% over two
20 steps).

^1H NMR (400 MHz, CD_3OD) δ 8.82-8.80 (m, 2H), 7.88-7.82 (m, 3H),
7.05-7.00 (m, 2H).; MS (ESI) m/z 297 ($\text{M}+\text{H}$) $^+$

Example 7: Synthesis of M-7

(Step 1) Methyl
25 4-{[(5-Bromopyridin-2-yl)sulfonyl]amino}-2,6-difluorobenzoa
te

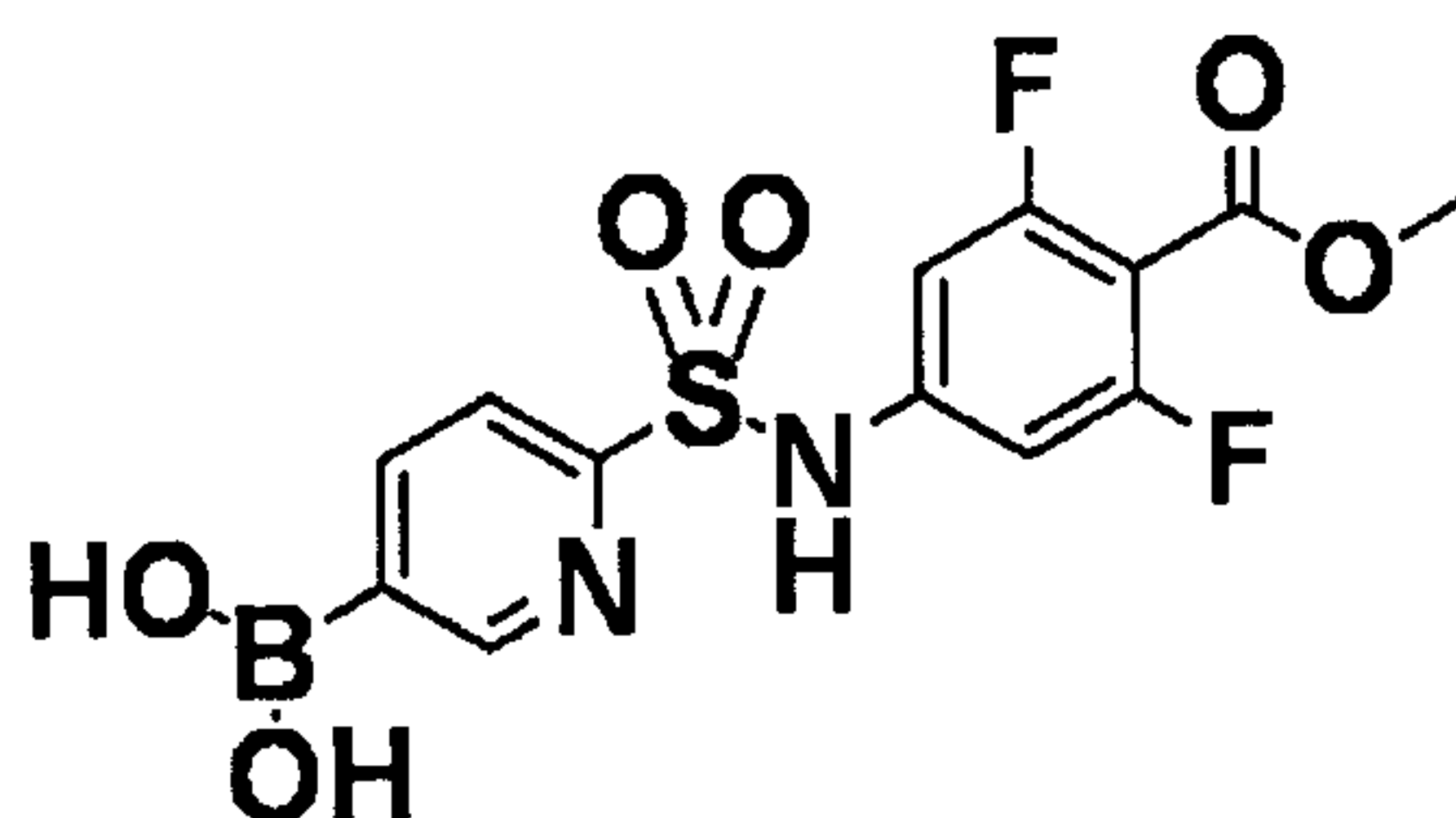


Phenylmethanethiol (80.0 g, 645 mmol) was dissolved in anhydrous tetrahydrofuran (600 ml), and 60% sodium hydride (45.0 g, 1.13 mol) was added thereto, followed by stirring at room temperature for 30 minutes. To this reaction solution, 5-bromo-2-chloropyridine (123 g, 640 mmol) was added, followed by stirring at room temperature for 3 hours. The reaction solution was diluted with water, followed by extraction with diethyl ether. The extraction liquids were combined, washed with a saturated aqueous sodium hydrogen carbonate solution and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. A compound (250 g, 0.90 mol) obtained by repeating the-above described process was suspended in a mixture solvent of acetic acid (2250 ml) and water (750 ml), and N-chlorosuccinimide (340 g, 2.60 mol) was added thereto, followed by stirring at room temperature for 2 hours. The reaction solution was diluted with water, followed by extraction with methylene chloride. The extraction liquids were combined, washed with a saturated aqueous sodium hydrogen carbonate solution and water, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=30:1). The obtained compound (47.0 g, 185 mmol) and methyl 4-amino-2,6-difluorobenzoate (26.0 g, 139 mmol) were suspended in methylene chloride (1000 ml), and pyridine (30 ml) was added thereto, followed by stirring at room temperature for 12 hours.

The reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=4:1) to obtain the title compound (50 g, 15% over three steps).

5 ^1H NMR (d-DMSO, 400 MHz): δ 8.92 (d, J = 1.6 Hz, 1H), 8.41-8.38 (m, 1H), 8.07 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 10 Hz, 2H), 3.81 (s, 3H).; MS (ESI) m/z 407 ($M+H$)⁺
(Step 2)

10 [6-({[3,5-Difluoro-4-(methoxycarbonyl)phenyl]amino}sulfonyl)pyridin-3-yl]boronic Acid



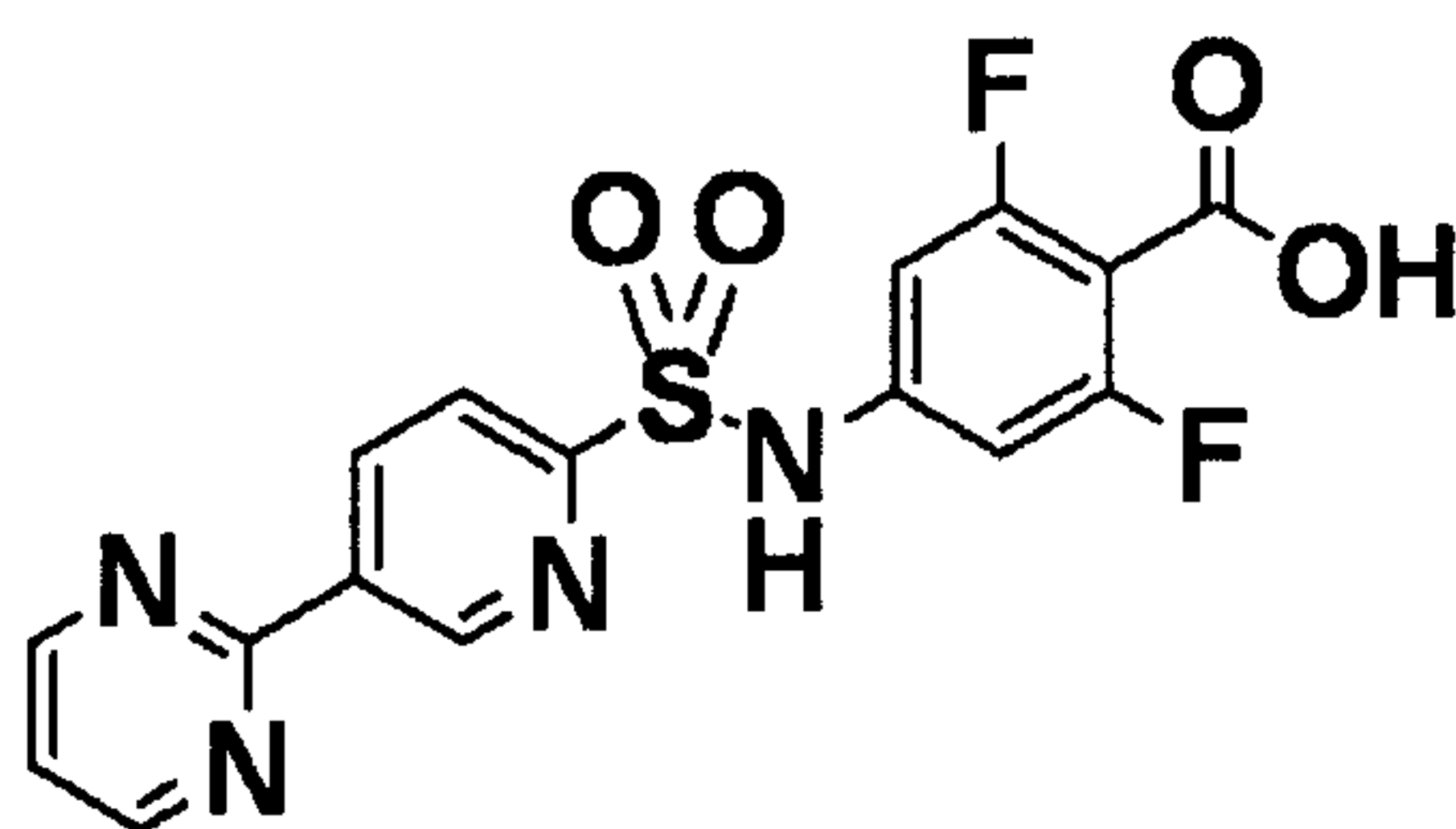
Methyl

4-({[5-bromopyridin-2-yl]sulfonyl]amino}-2,6-difluorobenzoate (25 g, 61.7 mmol) and bis(pinacolato)diborane (18.7 g, 73.6 mmol) were dissolved in N,N-dimethylformamide (500 ml). To the solution,
[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.30 g, 1.80 mmol) and potassium acetate (18.0 g, 184 mmol) were added, followed by stirring at 90°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction solution was diluted with water, followed by extraction with ethyl acetate. The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (ethyl acetate) to obtain the title compound

(11.0 g, 50%).

^1H NMR (CD_3OD , 400 MHz): δ 8.91 (s, 1H), 8.33 (d, $J = 7.2$ Hz, 1H), 8.04 (d, $J = 7.6$ Hz, 1H), 6.93 (d, $J = 10$ Hz, 2H), 3.87 (s, 3H).; MS (ESI) m/z 373 ($\text{M}+\text{H}$) $^+$

5 (Step 3)
2,6-Difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl]amino}benzoic Acid (M-7)



[6-({[3,5-Difluoro-4-(methoxycarbonyl)phenyl]amino}sulfonyl)pyridin-3-yl]boronic acid (11.0 g, 26.9 mmol) and 2-bromopyrimidine (9.40 g, 59.2 mmol) were dissolved in a mixture solvent of N,N-dimethylformamide (200 ml) and water (20 ml). To the solution, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (650 mg, 0.89 mmol) and sodium carbonate (9.40 g, 88.8 mmol) were added, followed by stirring at 90°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction solution was diluted with water, followed by extraction with ethyl acetate. The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:2 to 1:10).

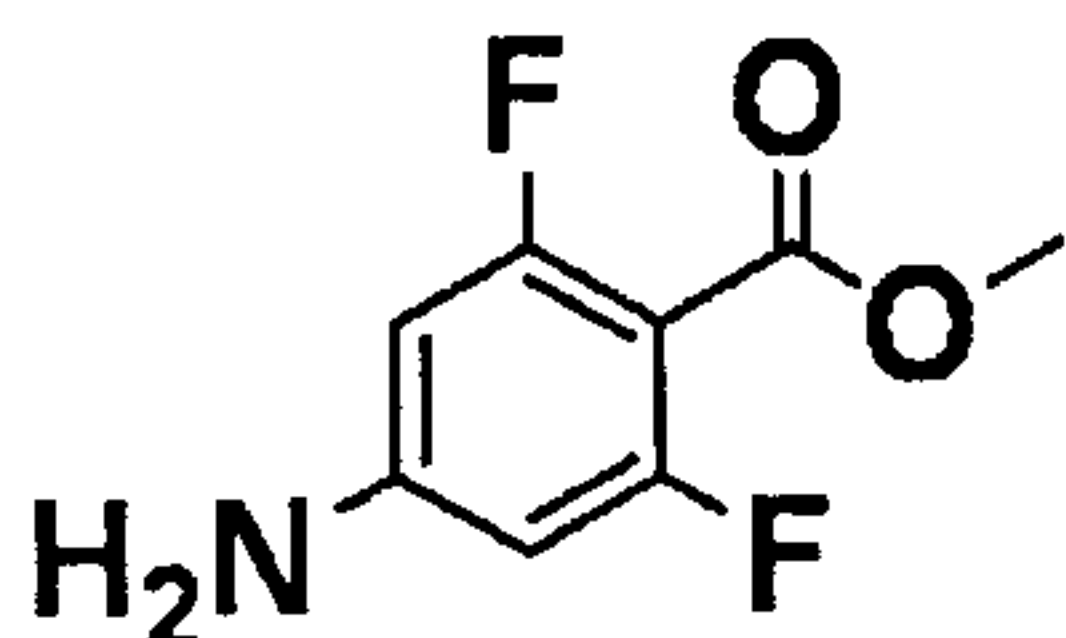
The obtained compound (6.60 g, 16.2 mmol) was dissolved in methanol (300 ml), and a 6 N aqueous sodium hydroxide solution (300 ml) was added thereto, followed by stirring at room

temperature for 30 minutes. The pH was adjusted to 4.0 by adding 4 N hydrochloric acid, and the precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (5.8 g, 50% over two steps).

5 ^1H NMR (CD_3OD , 400 MHz): δ 9.65 (d, $J = 1.6$ Hz, 1H), 9.01 (dd, $J = 8.4$, 2.0 Hz, 1H), 8.94 (d, $J = 5.2$ Hz, 2H), 8.23 (d, $J = 8.0$ Hz, 1H), 7.49 (t, $J = 4.8$ Hz, 1H), 6.97 (d, $J = 10.0$ Hz, 2H).; MS (ESI) m/z 393 ($\text{M}+\text{H}$) $^+$

Example 8: Synthesis of M-8

10 (Step 1) Methyl 4-Amino-2,6-difluorobenzoate

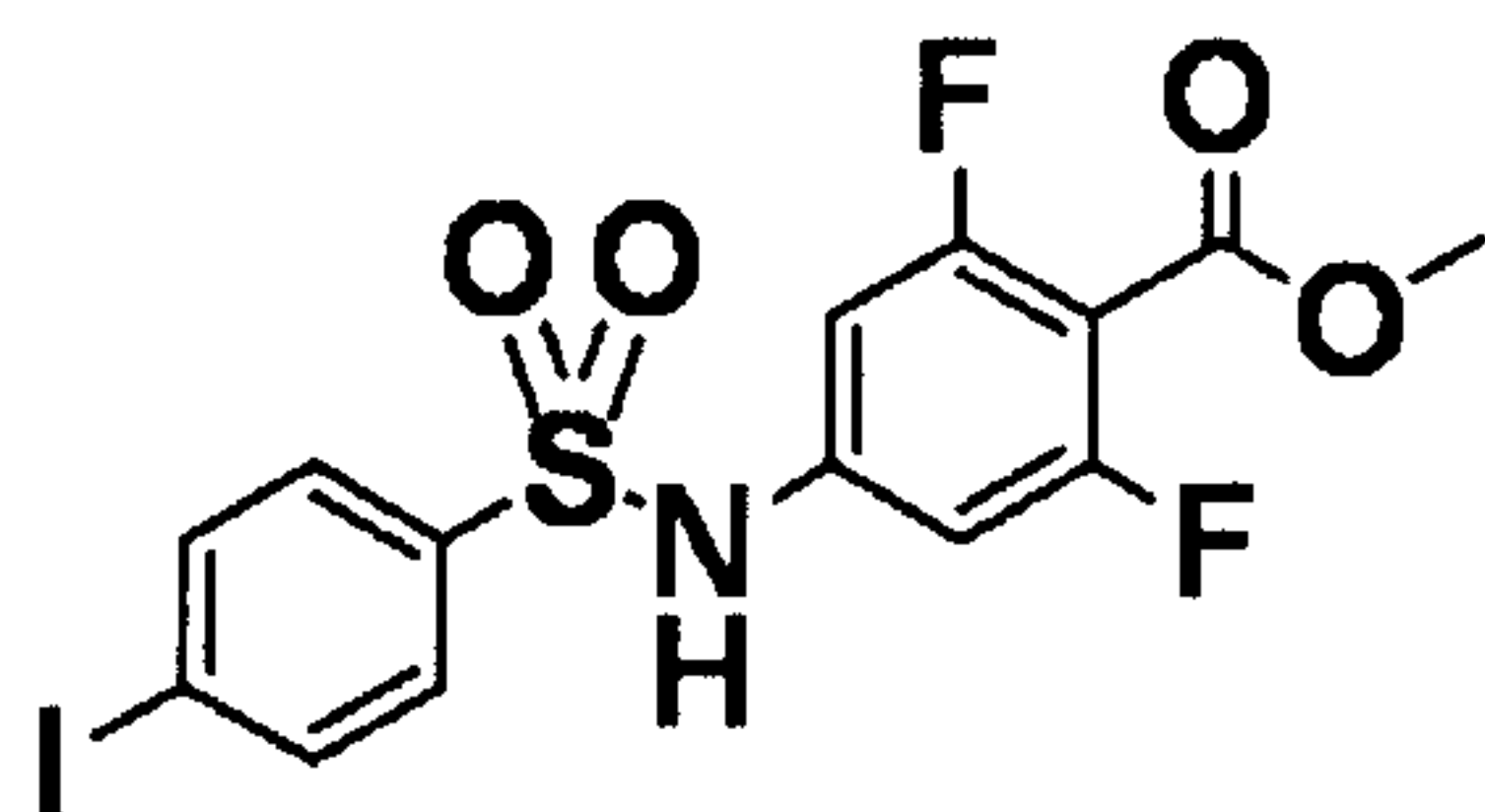


4-Bromo-2,6-difluorobenzoic acid (5.30 g, 23.7 mmol) was dissolved in methanol (35 ml). After cooling to 0°C, thionyl chloride (10 ml) was added dropwise thereto. The reaction solution was heated, and stirred at 95°C for 12 hours. After the solvent was removed under reduced pressure, the obtained residue was dissolved in toluene (135 ml). To the solution, benzophenone imine (5.1 ml, 31 mmol), palladium(II) acetate (135 mg, 0.60 mmol), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (500 mg, 0.80 mmol), and cesium carbonate (13.0 g, 40.0 mmol) were added. After purging with nitrogen gas, the mixture was stirred at 110°C for 14 hours. After cooling to room temperature, the reaction solution was filtered through Celite, and the filtrate was concentrated under reduced pressure. The obtained residue was dissolved in a mixture solvent of tetrahydrofuran (80 ml) and water (30 ml), and concentrated hydrochloric acid (30 ml) was added thereto, followed by stirring at room temperature for

2 hours. The reaction solution was neutralized with an aqueous sodium hydrogen carbonate solution, followed by extraction with ethyl acetate. The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=6:1 to 2:1) to obtain the title compound (3.6 g, 81% over three steps).

(Step 2) Methyl

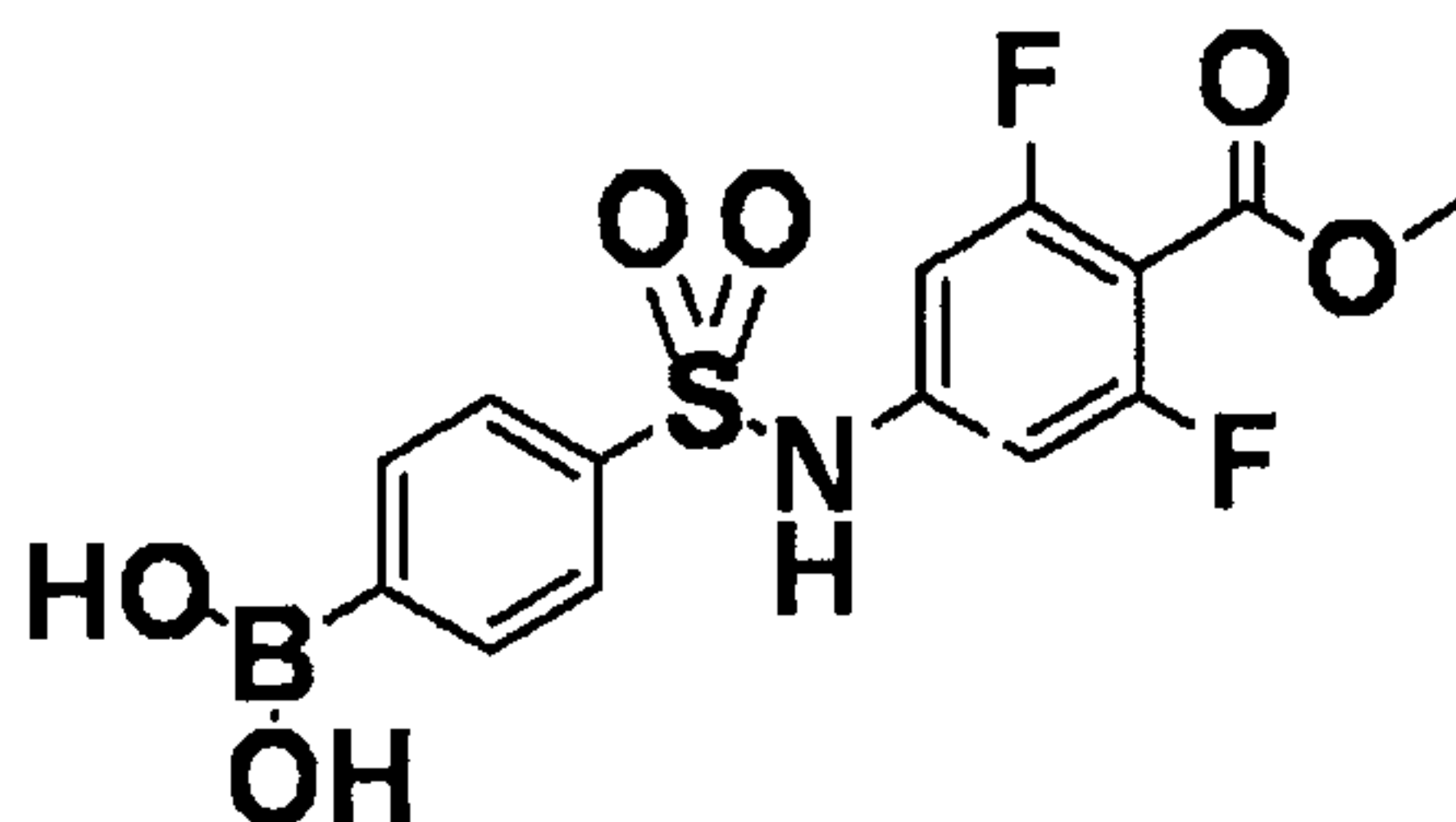
10 2,6-Difluoro-4-{[(4-iodophenyl)sulfonyl]amino}benzoate



Methyl 4-amino-2,6-difluorobenzoate (3.60 g, 19.2 mmol) was suspended in methylene chloride (1.5 L), and 4-iodobenzenesulfonyl chloride (7.50 g, 25.0 mmol) and pyridine (6.0 ml) were added thereto, followed by stirring at 80°C for 12 hours. After the reaction solution was concentrated under reduced pressure, 4 N hydrochloric acid was added. After stirring for 10 minutes, the obtained suspension was filtered. The obtained solid was stirred in a mixture solvent of petroleum ether/ethyl acetate (8:1) for 1 hour, and then filtered and dried under reduced pressure to obtain the title compound (7.4 g, 85%) as a white solid.

(Step 3)

25 [4-({[3,5-Difluoro-4-(methoxycarbonyl)phenyl]amino}sulfonyl)phenyl]boronic Acid



Methyl

2,6-difluoro-4-{[(4-iodophenyl)sulfonyl]amino}benzoate
(6.00 g, 13.2 mmol) and bis(pinacolato)diborane (4.00 g, 16.1
5 mmol) were dissolved in N,N-dimethylformamide (100 ml). To the
solution,

[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
(289 mg, 0.390 mmol) and potassium acetate (3.84 g, 39.1 mmol)
were added, followed by stirring at 90°C for 12 hours in the
10 presence of nitrogen gas. After cooling to room temperature,
the reaction solution was diluted with water, followed by
extraction with ethyl acetate. The extraction liquids were
combined, washed with saturated aqueous sodium chloride, and
dried over anhydrous sodium sulfate. Then, the solvent was
15 removed. The obtained residue was purified by silica gel column
chromatography (petroleum ether/ethyl acetate=4:1 to 2:1).

The obtained compound was dissolved in acetone (30 ml),
and sodium periodate (2.84 g, 13.2 mmol), ammonium acetate (1.00
g, 13.2 mmol), and water (10 ml) were added thereto, followed
20 by stirring at room temperature for 55 hours. After the
reaction solution was concentrated under reduced pressure, the
residue was diluted with water, followed by extraction with
ethyl acetate (500 ml×3). The extraction liquids were combined,
washed with saturated aqueous sodium chloride, and dried over
25 anhydrous sodium sulfate. Then, the solvent was removed. The
obtained residue was washed with a mixture solvent of petroleum

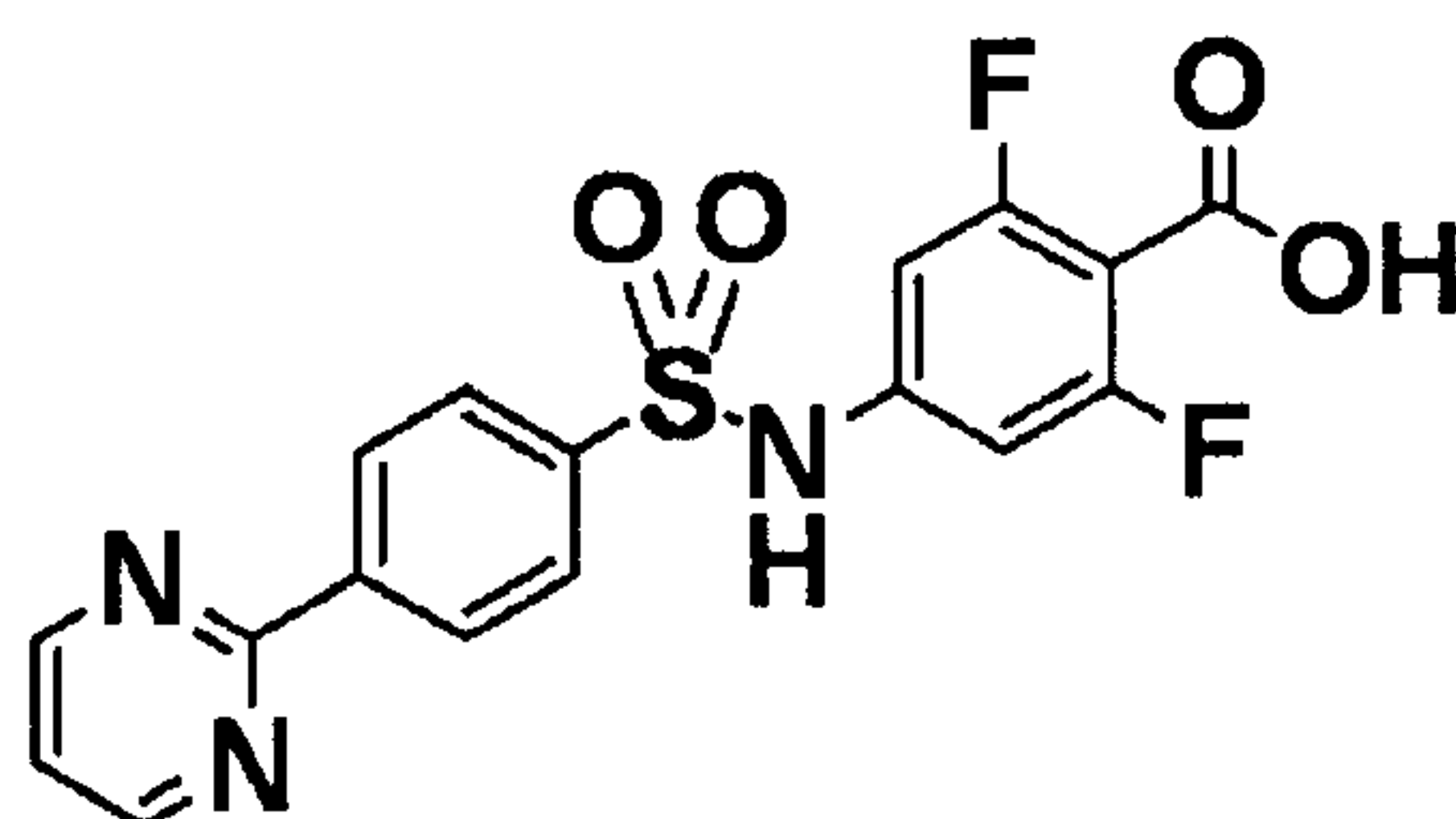
ether/ethyl acetate (1/10), and dried under reduced pressure to obtain the title compound (2.5 g, 36% over two steps).

¹H NMR (d-DMSO, 400 MHz): δ 8.37 (s, 2H), 7.94 (d, J = 8.0 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 10.4 Hz, 2H), 3.79 (s, 3H).; MS (ESI) m/z 372 (M+H)⁺

(Step

4)

2,6-Difluoro-4-{[(4-pyrimidin-2-yl-phenyl)sulfonyl]amino}benzoic Acid (M-8)



[4-({[3,5-Difluoro-4-(methoxycarbonyl)phenyl]amino}sulfonyl)phenyl]boronic acid (3.0 g, 8.1 mmol) and 2-bromopyrimidine (4.5 g, 28 mmol) were dissolved in a mixture solvent of N,N-dimethylformamide (100 ml) and water (10 ml). To the solution,

[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (592 mg, 0.81 mmol) and sodium carbonate (2.5 g, 24 mmol) were added, followed by stirring at 90°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction solution was diluted with water, followed by extraction with ethyl acetate. The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1 to 1:4).

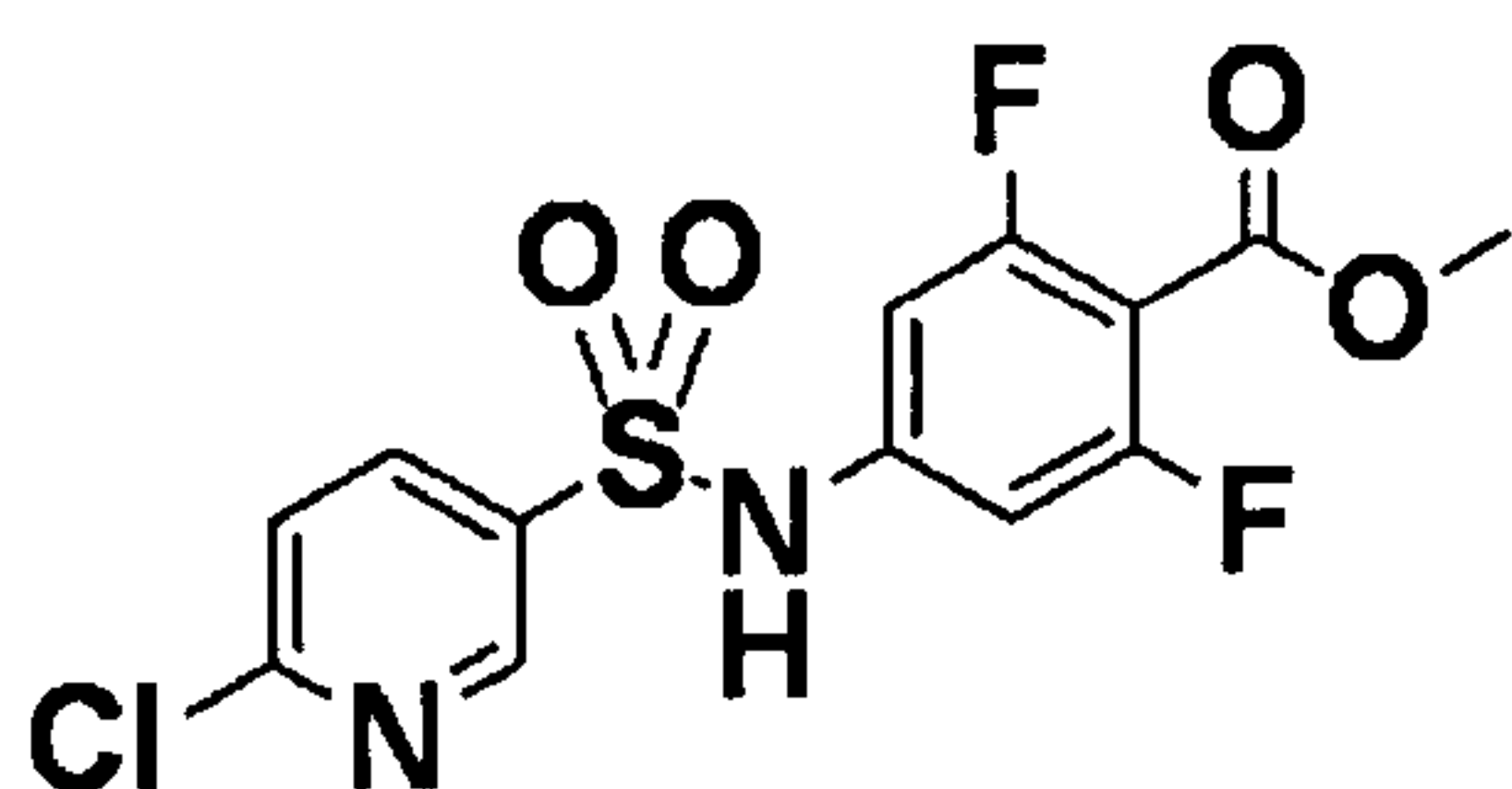
The obtained compound (400 mg, 0.98 mmol) was dissolved in methanol (20 ml), and a 6 N aqueous sodium hydroxide solution

(20 ml) was added thereto, followed by stirring at room temperature for 30 minutes. The pH was adjusted to 4.0 by adding 4 N hydrochloric acid, and the precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (313 mg, 10% over two steps).

^1H NMR (CD₃OD, 300 MHz): δ 8.88 (d, J = 4.8 Hz, 2H), 8.59 (d, J = 8.4 Hz, 2H), 8.0 (d, J = 8.4 Hz, 2H), 7.40 (t, J = 4.8 Hz, 1H), 6.84 (d, J = 9.6 Hz, 2H).; MS (ESI) m/z 392 (M+H)⁺

Example 9: Synthesis of M-9

(Step 1) Methyl 4-{[(6-Chloropyridin-3-yl)sulfonyl]amino}-2,6-difluorobenzoate



6-Chloropyridine-3-sulfonyl chloride (10.0 g, 47.0 mmol) was dissolved in methylene chloride (300 ml), and methyl 4-amino-2,6-difluorobenzoate (7.5 g, 40 mmol) and pyridine (9.0 ml, 102 mmol) were added thereto, followed by stirring at room temperature for 12 hours. The reaction solution was washed with water and 2 N hydrochloric acid, followed by extraction with methylene chloride. The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was recrystallized from a mixture solvent of petroleum ether/ethyl acetate (1:2). The precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (12.0 g, 83%) as a white solid.

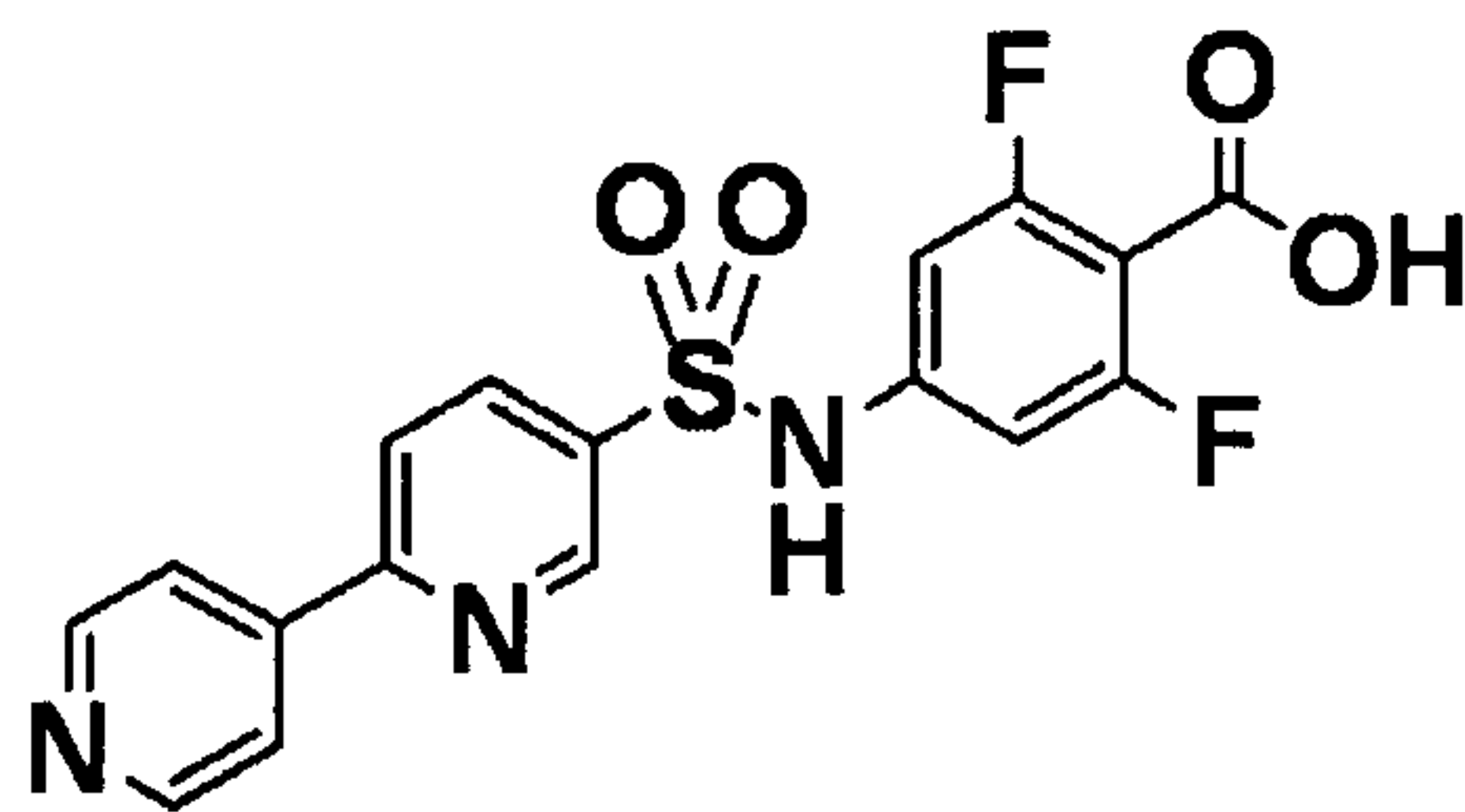
^1H NMR (CD₃OD, 300 MHz): δ 8.82 (d, J = 2.4 Hz, 1H), 8.20 (dd,

$J = 2.4 \text{ Hz}, 8.7 \text{ Hz } (1\text{H}), 7.86\text{--}7.82 \text{ (t, } 1\text{H}), 7.04 \text{ (d, } J = 10 \text{ Hz, } 2\text{H}), 3.86 \text{ (s, } 3\text{H})$

(Step 2)

4-[(2,4'-Bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoic

5 Acid (M-9)



Methyl

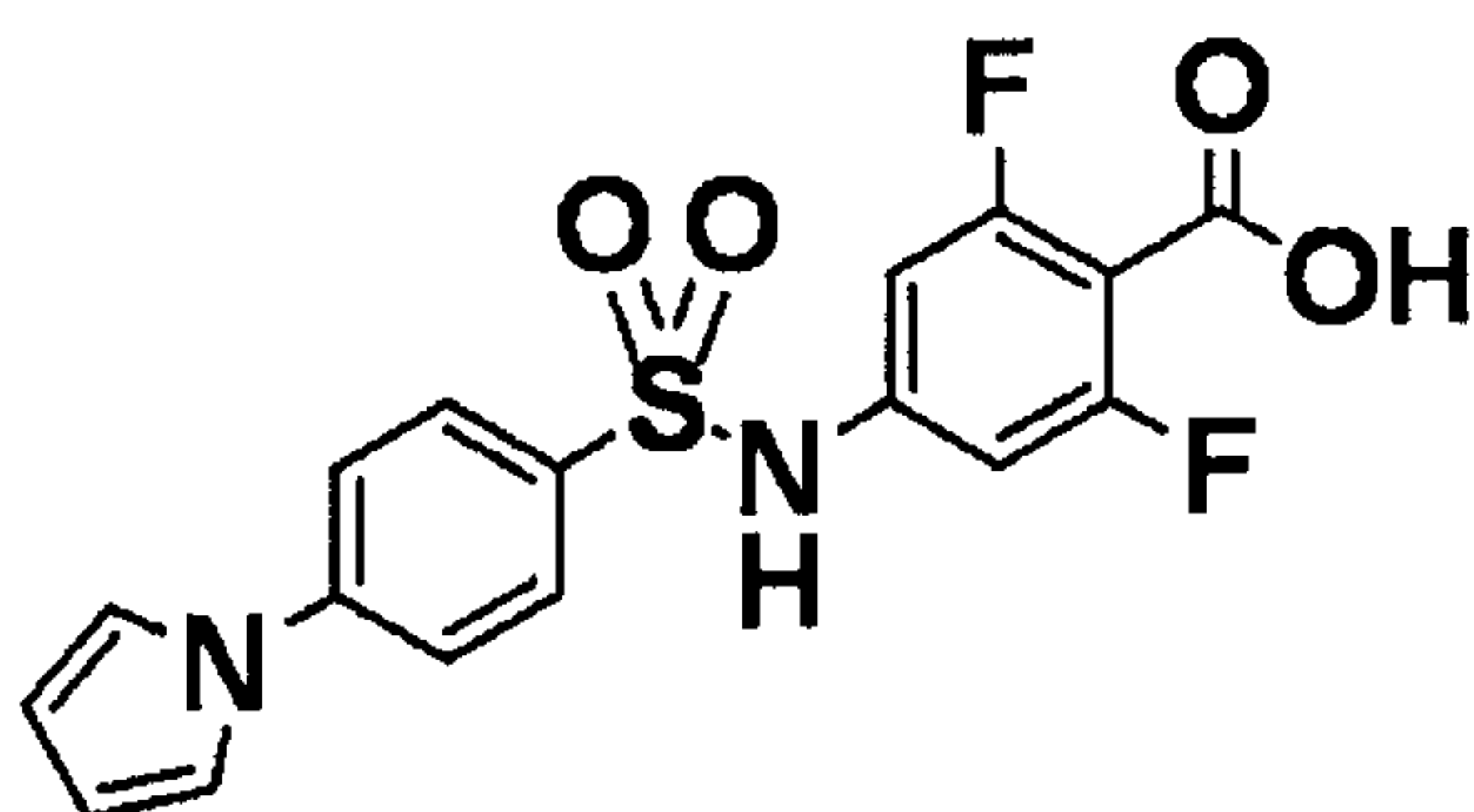
4-{[(6-chloropyridin-3-yl)sulfonyl]amino}-2,6-difluorobenzoate (688 mg, 2.00 mmol) and 4-pyridylboronic acid (492 mg, 4.00 mmol) were dissolved in a mixture solvent of 1,4-dioxane (20 ml) and water (2.0 ml). To the solution, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (162 mg, 0.20 mmol) and sodium carbonate (212 mg, 2.00 mmol) were added, followed by stirring at 130°C for 30 minutes under microwave irradiation. After cooling to room temperature, the reaction solution was diluted with methanol and filtered through Celite. The filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1 to 1:1). A compound (810 mg, 2.00 mmol) obtained by repeating the-above described process was dissolved in methanol (15 ml), and a 6 N aqueous sodium hydroxide solution (5.0 ml) was added thereto, followed by stirring at room temperature for 30 minutes. The pH was adjusted to 4.0 by adding 4 N hydrochloric acid. The precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (620 mg, 47% over two

steps) as a white solid.

^1H NMR (CD_3OD , 400 MHz): δ 9.18 (d, J = 2.4 Hz, 1H), 8.77-8.75 (m, 2H), 8.41 (d, J = 2.0 Hz, 1H), 8.35 (d, J = 8.4 Hz, 1H), 8.10-8.08 (m, 2H), 6.93 (d, J = 10 Hz, 2H).; MS (ESI) m/z 392 ($\text{M}+\text{H}$)⁺

Example 10: Synthesis of M-10

2,6-Difluoro-4-([4-(1H-pyrrol-1-yl)phenyl]sulfonyl)amino)benzoic Acid (M-10)



10 Methyl

2,6-difluoro-4-([4-(4-iodophenyl)sulfonyl]amino)benzoate (7.40 g, 16.3 mmol) was dissolved in N-methylpyrrolidone (30 ml), and copper(I) iodide (1.9 g, 9.8 mmol), potassium phosphate (8.6 g, 41 mmol), pyrrole (2.2 g, 33 mmol), and trans-N,N'-dimethylcyclohexane-1,2-diamine (1.2 g, 8.2 mmol) were added thereto, followed by stirring at 145°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction solution was diluted with water, followed by extraction with methylene chloride (50 ml×2). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1), followed by drying under reduced pressure to obtain a white solid. The obtained compound (1.3 g, 3.3 mmol) was dissolved in a mixture solvent of methanol (40 ml) and

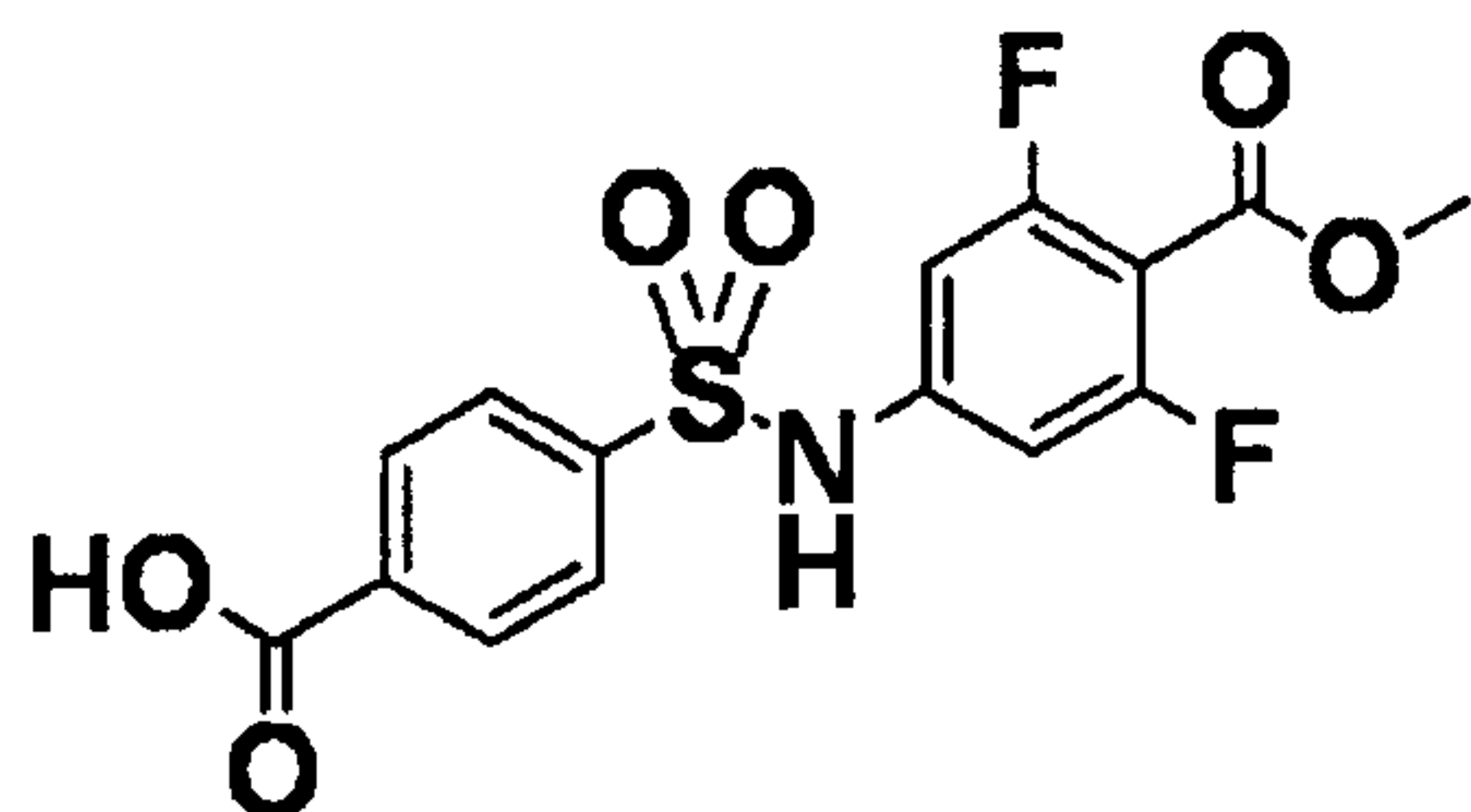
tetrahydrofuran (40 ml), and a 6 N aqueous sodium hydroxide solution (60 ml) was added thereto, followed by stirring at room temperature for 4 hours. The pH was adjusted to 4.0 by adding 4 N hydrochloric acid, and the precipitated solid was filtered
 5 and dried under reduced pressure to obtain the title compound (1.1 g, 18% over two steps) as a white solid.

¹H NMR (CD₃OD, 400 MHz): δ 7.96 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.8 Hz, 2H), 7.32 (s, 2H), 6.85 (d, J = 9.6 Hz, 2H), 6.34 (s, 2H).; MS (ESI) m/z 379 (M+H)⁺

10 Example 11: Synthesis of M-11

(Step 1)

4-({[3,5-Difluoro-4-(methoxycarbonyl)phenyl]amino}sulfonyl)benzoic Acid



15 4-(Chlorosulfonyl)benzoic acid (25.0 g, 113 mmol) and methyl 4-amino-2,6-difluorobenzoate (19.0 g, 101 mmol) were dissolved in methylene chloride (500 ml), and pyridine (25.0 ml, 285 mmol) was added thereto, followed by stirring at room temperature for 12 hours. The reaction solution was
 20 concentrated under reduced pressure. The obtained residue was diluted with water, and then the pH was adjusted to 1.0 by adding 6 N hydrochloric acid. The precipitated solid was filtered, and washed with water. The obtained solid was resuspended in water, and washed with a saturated aqueous sodium hydrogen
 25 carbonate solution, followed by extraction with ethyl acetate (100 ml×2). The pH of the obtained aqueous layer was adjusted

to 6.0 by adding 6 N hydrochloric acid thereto, followed by extraction with ethyl acetate (100 ml×2). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the

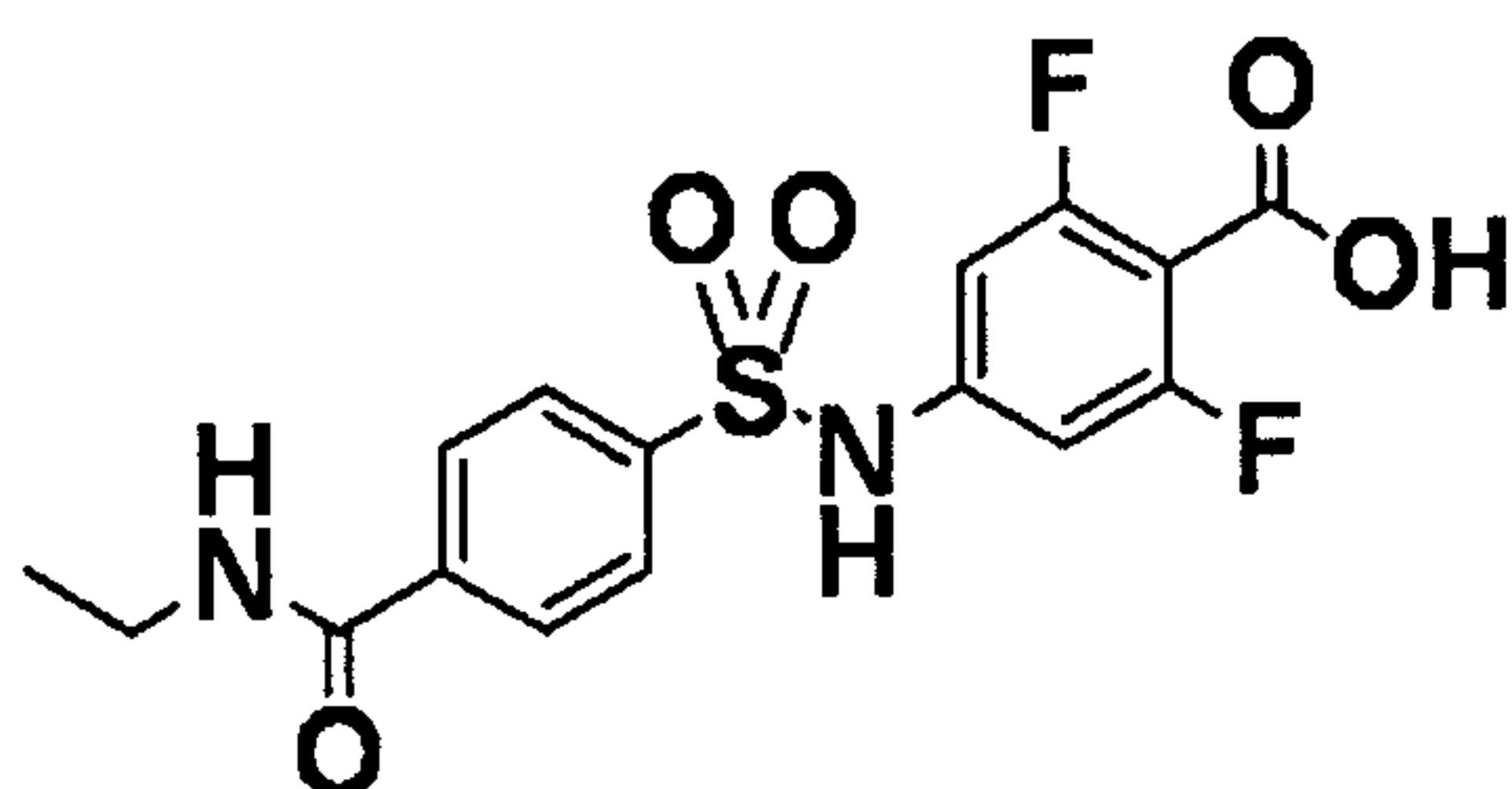
5 solvent was removed to obtain the title compound (15.0 g, 36%).

¹H NMR (d-DMSO, 400 MHz): δ 11.50 (s, 1H), 8.14 (d, J = 8.4 Hz, 2H), 8.01 (d, J = 8.4 Hz, 2H), 6.67 (d, J = 10.4 Hz, 2H), 3.87 (s, 3H), ; MS (ESI) m/z 372 (M+H)⁺

(Step

2)

10 4-[(4-[(Ethylamino)carbonyl]phenyl)sulfonyl]amino]-2,6-difluorobenzoic Acid (M-11)



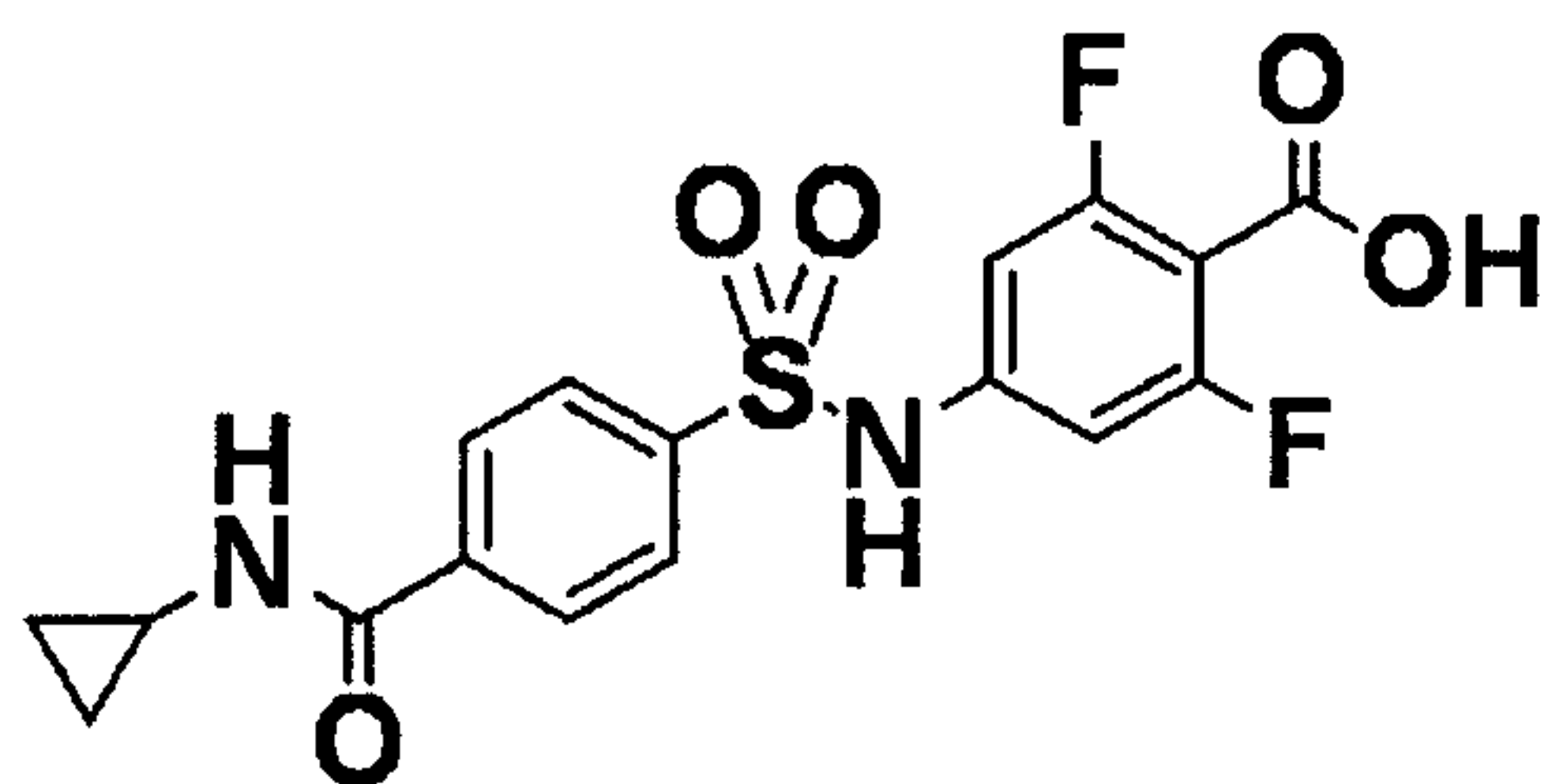
4-([3,5-Difluoro-4-(methoxycarbonyl)phenyl]amino)sulfonyl)benzoic acid (1.5 g, 4.0 mmol) was dissolved in thionyl chloride (40 ml), followed by stirring at 75°C for 4 hours. The reaction solution was cooled to room temperature, and then concentrated under reduced pressure. The obtained residue was dissolved in methylene chloride (30 ml), and ethylamine hydrochloride (648 mg, 8.00 mmol) and triethylamine (808 mg, 8.00 mmol) were added thereto, followed by stirring at room temperature for 30 minutes. The solvent was removed under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1 to 1:1). The obtained compound (800 mg, 2.00 mmol) was dissolved in methanol (30 ml), and a 6 N aqueous sodium hydroxide solution (10 ml) was added thereto, followed by

stirring at room temperature for 30 minutes. The pH was adjusted to 4.0 by adding 6 N hydrochloric acid. The precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (691 mg, 50% over two steps) as a white solid.

^1H NMR (CD_3OD , 400 MHz): δ 7.98-7.92 (m, 4H), 6.80 (d, J = 14.8 Hz, 2H), 3.43-3.40 (m, 2H), 1.23-1.14 (m, 3H).; MS (ESI) m/z 385 ($\text{M}+\text{H}$) $^+$

Example 12: Synthesis of M-12

4-[(4-[(Cyclopropylamino)carbonyl]phenyl)sulfonyl]amino]-2,6-difluorobenzoic Acid (M-12)



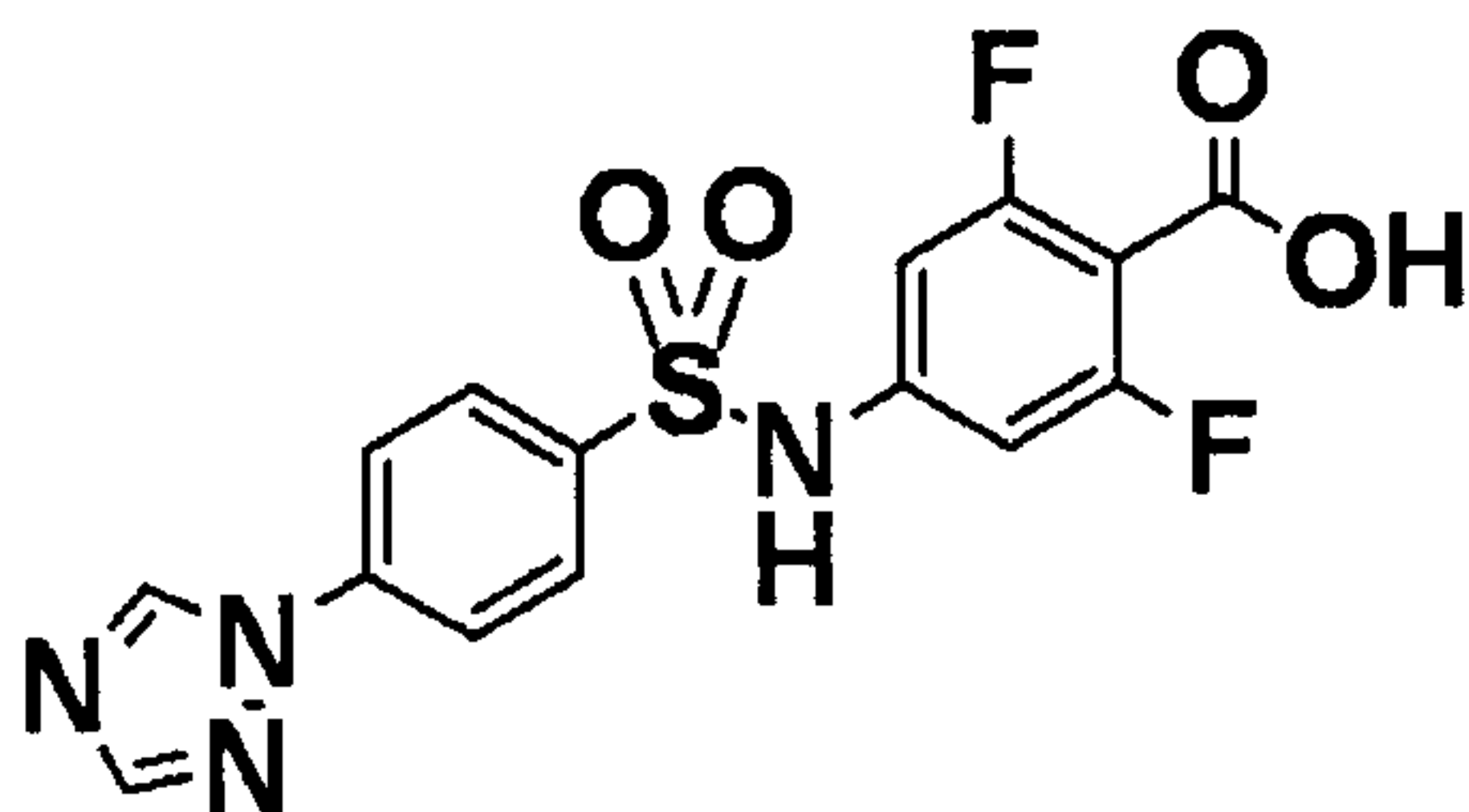
4-([3,5-Difluoro-4-(methoxycarbonyl)phenyl]amino)sulfonylbenzoic acid (1.5 g, 4.0 mmol) was dissolved in thionyl chloride (40 ml), followed by stirring at 75°C for 4 hours. The reaction solution was cooled to room temperature, and then concentrated under reduced pressure. The obtained residue was dissolved in methylene chloride (30 ml), and cyclopropylamine (680 mg, 12.0 mmol) was added thereto, followed by stirring at room temperature for 30 minutes. The solvent was removed under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1 to 1:1). A portion (740 mg, 1.8 mmol) of the obtained compound was dissolved in methanol (15 ml), and a 3 N aqueous sodium hydroxide solution (5.0 ml) was added thereto, followed by stirring at room temperature for 30 minutes. The

pH was adjusted to 4.0 by adding 6 N hydrochloric acid. The precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (670 mg, 51% over two steps) as a white solid.

5 ^1H NMR (d-DMSO, 400 MHz): δ 7.79-7.72 (m, 4H), 6.62 (d, J = 10.0 Hz, 2H), 2.67-2.65 (m, 1H), 0.63-0.59 (m, 2H), 0.45-0.43 (m, 2H), ; MS (ESI) m/z 397 ($M+H$) $^+$

Example 13: Synthesis of M-13

2,6-Difluoro-4-({[4-(1H-1,2,4-triazol-1-yl)phenyl]sulfonyl}
10 amino)benzoic Acid (M-13)



Methyl

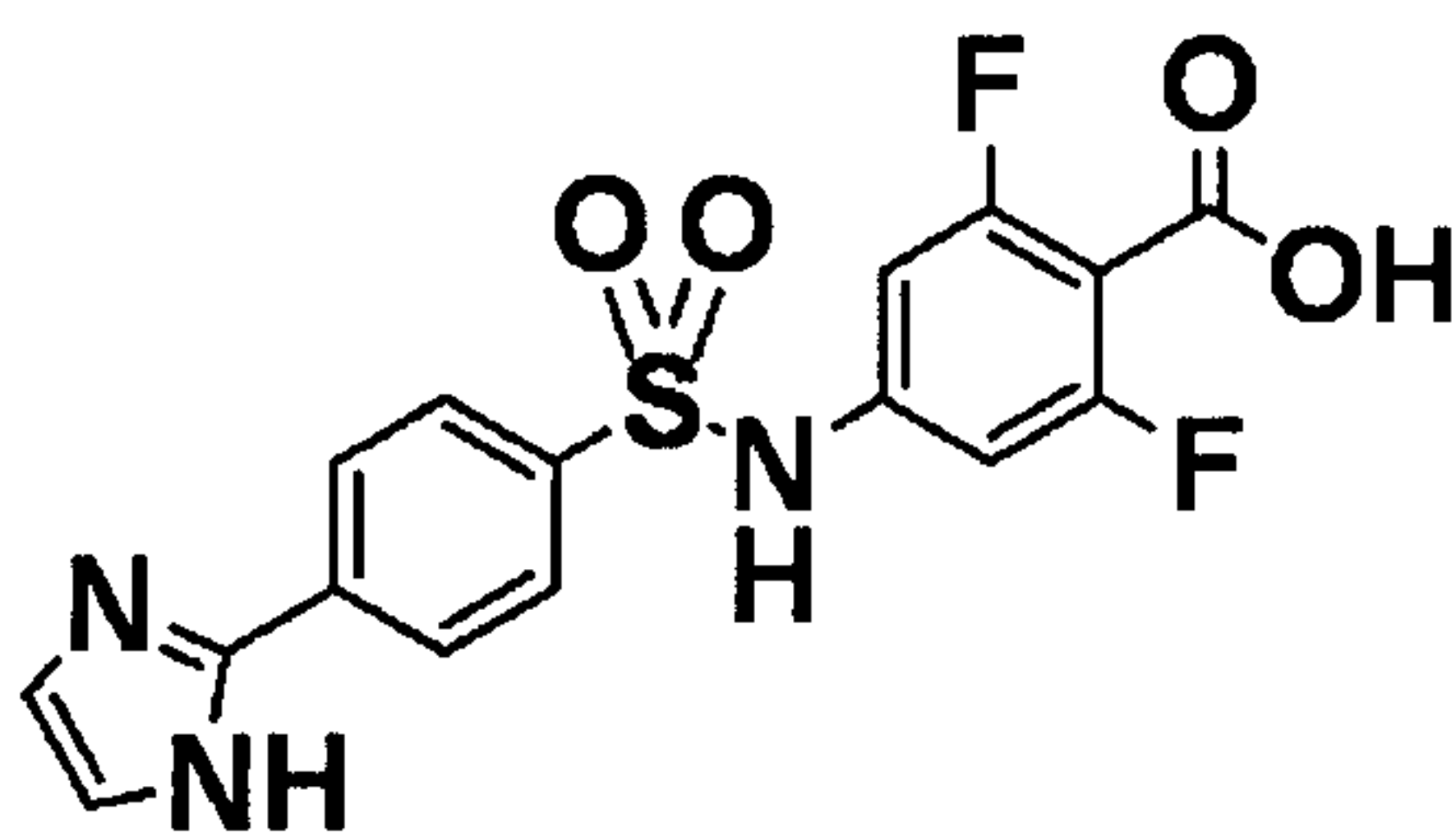
2,6-difluoro-4-{{[(4-iodophenyl)sulfonyl]amino}benzoate
(1.50 g, 3.30 mmol) was dissolved in N-methylpyrrolidone (15
15 ml), and copper(I) iodide (400 mg, 2.10 mmol), potassium
phosphate (2.0 g, 9.4 mmol), 1,2,4-triazole (500 mg, 7.2 mmol),
and trans-N,N'-dimethylcyclohexane-1,2-diamine (500 mg, 3.50
mmol) were added thereto, followed by stirring at 145°C for 12
hours in the presence of nitrogen gas. After cooling to room
20 temperature, the reaction solution was diluted with water,
followed by extraction with methylene chloride (50 ml $\times$ 2). The
extraction liquids were combined, washed with saturated aqueous
sodium chloride, and dried over anhydrous sodium sulfate. Then,
the solvent was removed. The obtained residue was purified by
25 silica gel column chromatography (petroleum ether/ethyl
acetate=1:1), followed by drying under reduced pressure to

obtain a white solid. The obtained compound (230 mg, 0.580 mmol) was dissolved in methanol (10 ml), and a 6 N aqueous sodium hydroxide solution (10 ml) was added thereto, followed by stirring at room temperature for 30 minutes. The pH was
 5 adjusted to 4.0 by adding 3 N hydrochloric acid, and the precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (165 mg, 14% over two steps) as a white solid.

¹H NMR (CD₃OD, 400 MHz): δ 9.10 (s, 1H), 8.01 (s, 1H), 7.96 (s, 4H), 6.73 (d, J = 10.0 Hz, 2H).; MS (ESI) m/z 381 (M+H)⁺
 10

Example 14: Synthesis of M-14

2,6-Difluoro-4-([4-(1H-imidazol-2-yl)phenyl]sulfonyl)amino
)benzoic Acid (M-14)



15 Methyl

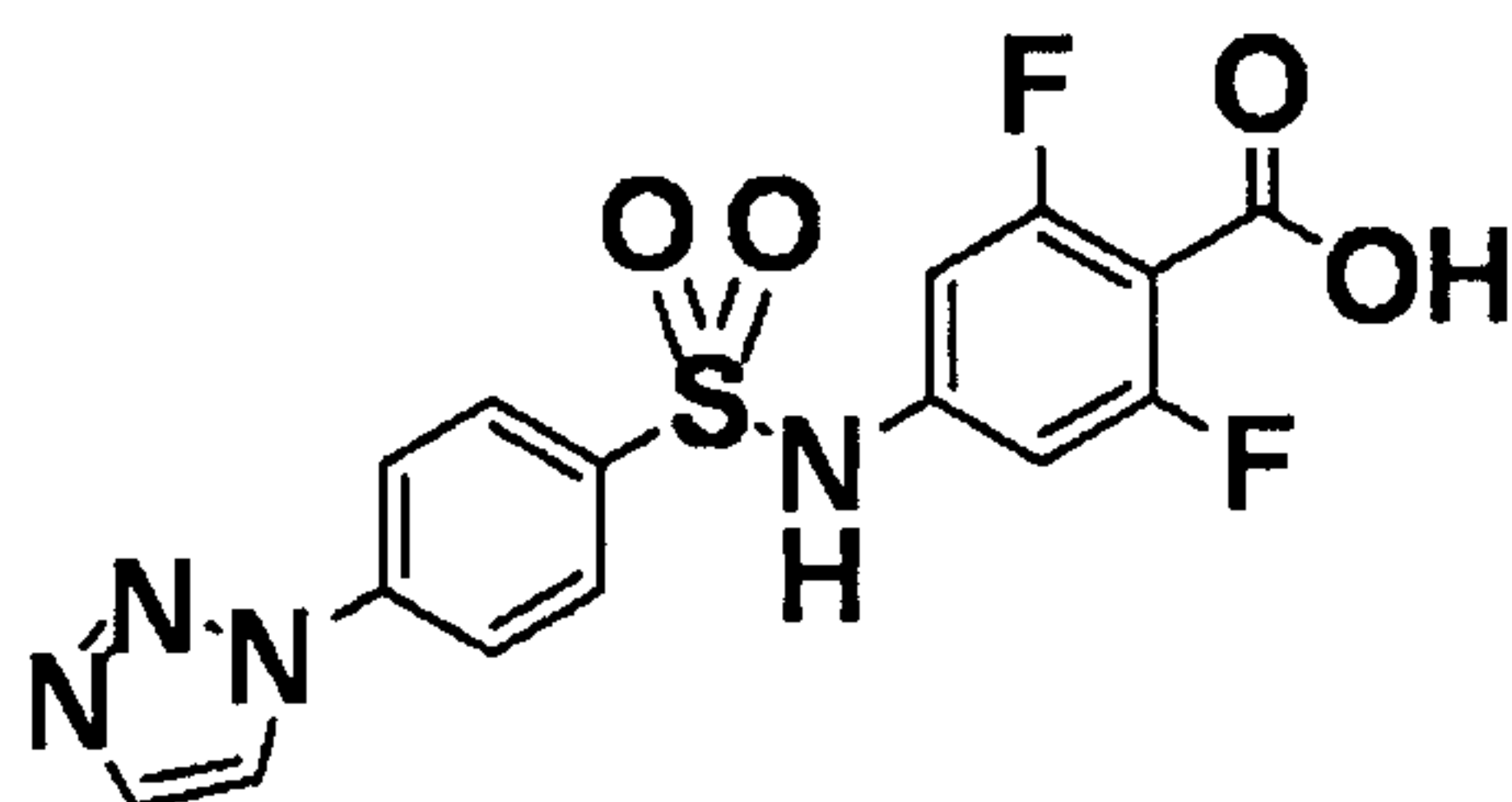
2,6-difluoro-4-{[(4-iodophenyl)sulfonyl]amino}benzoate (3.0 g, 6.6 mmol) was dissolved in N,N-dimethylformamide (50 ml), and copper(I) iodide (2.50 g, 13.2 mmol), palladium acetate (148 mg, 0.66 mmol), and imidazole (450 mg, 26.4 mmol) were added
 20 thereto, followed by stirring at 148°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction solution was diluted with a saturated aqueous ammonium chloride solution, followed by extraction with ethyl acetate (50 ml×3). The extraction liquids were combined,
 25 washed with water and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was

removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1 to 1:1), followed by drying under reduced pressure to obtain a yellow solid. The obtained compound (450 mg, 1.15 mmol) was dissolved
 5 in methanol (20 ml), and a 6 N aqueous sodium hydroxide solution (20 ml) was added thereto, followed by stirring at room temperature for 30 minutes. The pH was adjusted to 4.0 by adding 4 N hydrochloric acid. The precipitated solid was filtered and then dried under reduced pressure to obtain the title compound
 10 (220 mg, 9% over two steps) as a white solid.

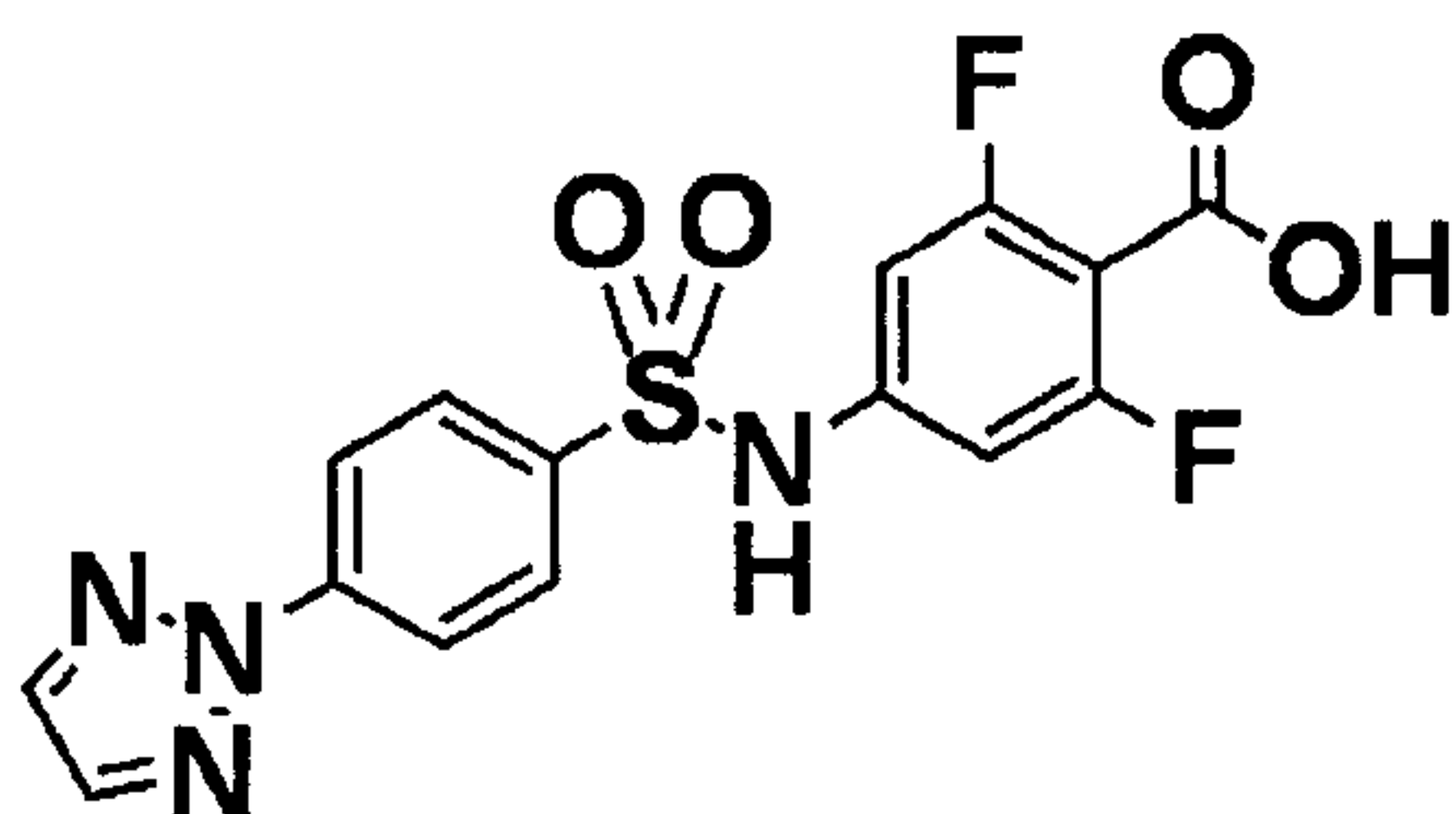
^1H NMR (CD₃OD, 400 MHz): δ 8.01-7.95 (m, 4H), 7.53 (s, 2H), 6.73 (d, J = 9.6 Hz, 2H).; MS (ESI) m/z 380 ($M+H$)⁺

Examples 15 to 18: Synthesis of M-15 to M-18

2,6-Difluoro-4-([4-(1H-1,2,3-triazol-1-yl)phenyl]sulfonyl)
 15 amino)benzoic Acid (M-15)



2,6-Difluoro-4-([4-(2H-1,2,3-triazol-2-yl)phenyl]sulfonyl)
amino)benzoic Acid (M-16)



20 Methyl

2,6-difluoro-4-{[(4-iodophenyl)sulfonyl]amino}benzoate (4.5 g, 9.9 mmol) was dissolved in N-methylpyrrolidone (90 ml), and

1,2,3-triazole (1.50 g, 21.7 mmol), copper(I) iodide (1.20 g, 6.30 mmol), potassium phosphate (6.0 g, 28 mmol), and trans-N,N'-dimethylcyclohexane-1,2-diamine (1.50 g, 10.5 mmol) were added thereto, followed by stirring at 145°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction solution was diluted with water, followed by extraction with ethyl acetate (150 ml×5). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1 to 1:1) to obtain methyl 2,6-difluoro-4-({[4-(1H-1,2,3-triazol-1-yl)phenyl]sulfonyl}amino)benzoate (M-17) (650 mg, 17%) and methyl 2,6-difluoro-4-({[4-(2H-1,2,3-triazol-2-yl)phenyl]sulfonyl}amino)benzoate (M-18) (800 mg, 20%).

¹H NMR (400 MHz, CD₃OD) for M-17: 8.63 (s, 1H), 8.12-8.07 (m, 4H), 7.91 (s, 1H), 6.85 (d, J = 10.0 Hz, 2H), 3.84 (s, 3H).; MS (ESI) m/z 395 (M+H)⁺

¹H NMR (400 MHz, CD₃OD) for M-18: 8.26 (d, J = 8.8 Hz, 2H), 8.03 (d, J = 8.8 Hz, 2H), 7.91 (s, 2H), 6.83 (d, J = 10.0 Hz, 2H), 3.87 (s, 3H).; MS (ESI) m/z 395 (M+H)⁺

The obtained methyl 2,6-difluoro-4-({[4-(1H-1,2,3-triazol-1-yl)phenyl]sulfonyl}amino)benzoate (M-17) (650 mg, 1.60 mmol) was dissolved in methanol (30 ml), and a 6 N aqueous sodium hydroxide solution (30 ml) was added thereto, followed by stirring at room temperature for 12 hours. The pH was adjusted to 4.0 by adding 6 N hydrochloric acid, and the precipitated solid was filtered and then dried under reduced pressure to obtain the title

compound (M-15, 470 mg, 75%).

^1H NMR (CD_3OD , 400 MHz) for M-15: δ 8.66 (d, $J = 1.2$ Hz, 1H), 8.13-8.12 (m, 4H), 7.94 (d, $J = 1.2$ Hz, 1H), 6.87 (d, $J = 10.0$ Hz, 2H).; MS (ESI) m/z 381 ($\text{M}+\text{H}$) $^+$

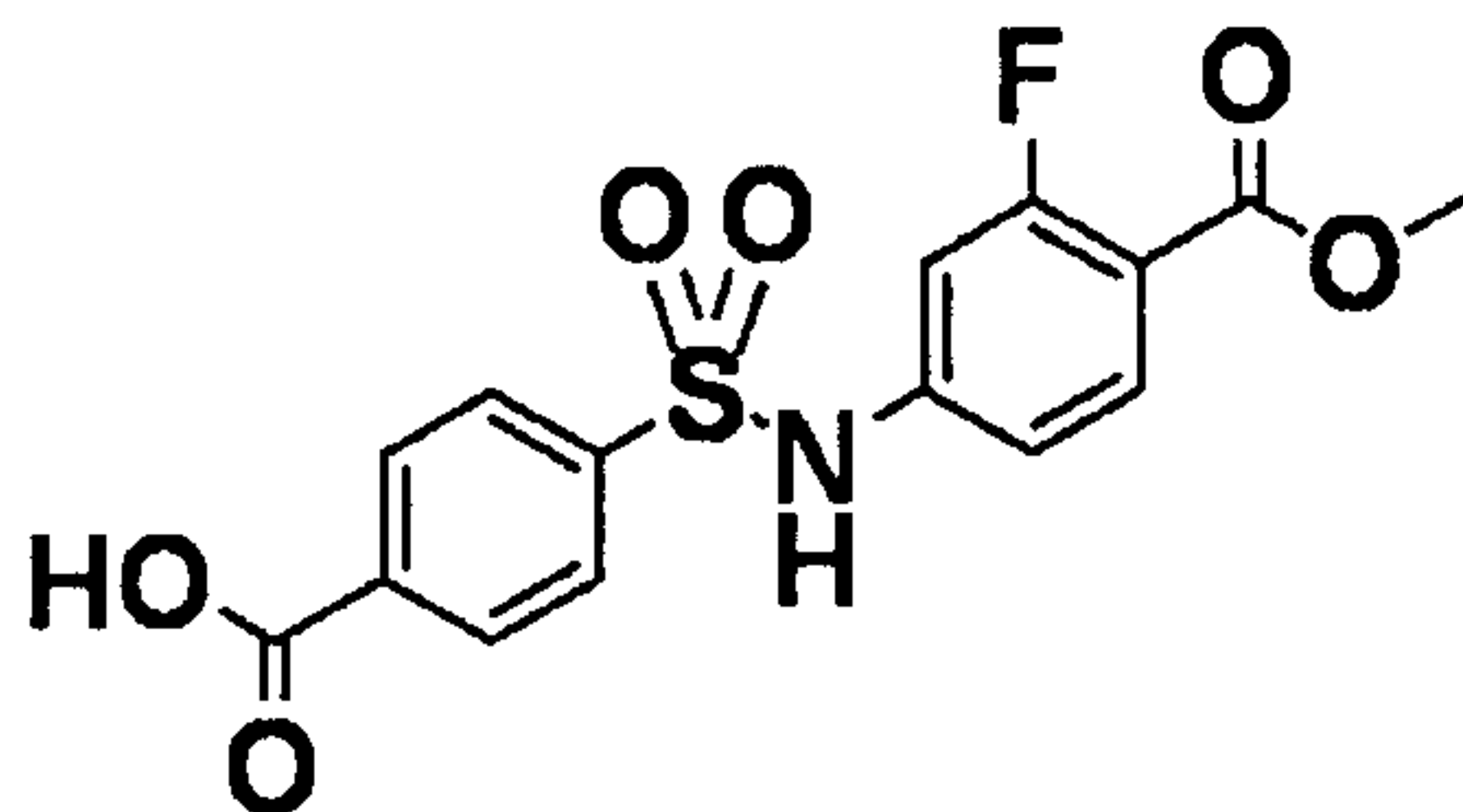
5 The title compound (M-16, 740 mg, 96%) was obtained by subjecting the obtained 2,6-difluoro-4-({[4-(2H-1,2,3-triazol-2-yl)phenyl]sulfonyl} amino)benzoate (M-18) to the same method.

^1H NMR (400 MHz, CD_3OD) for M-16: δ 8.31 (d, $J = 8.8$ Hz, 2H), 8.06 (d, $J = 8.8$ Hz, 2H), 8.00 (s, 2H), 6.86 (d, $J = 9.6$ Hz, 2H).; MS (ESI) m/z 381 ($\text{M}+\text{H}$) $^+$

Example 19: Synthesis of M-19

(Step 1)

15 4-({[3-Fluoro-4-(methoxycarbonyl)phenyl]amino}sulfonyl)benzoic Acid

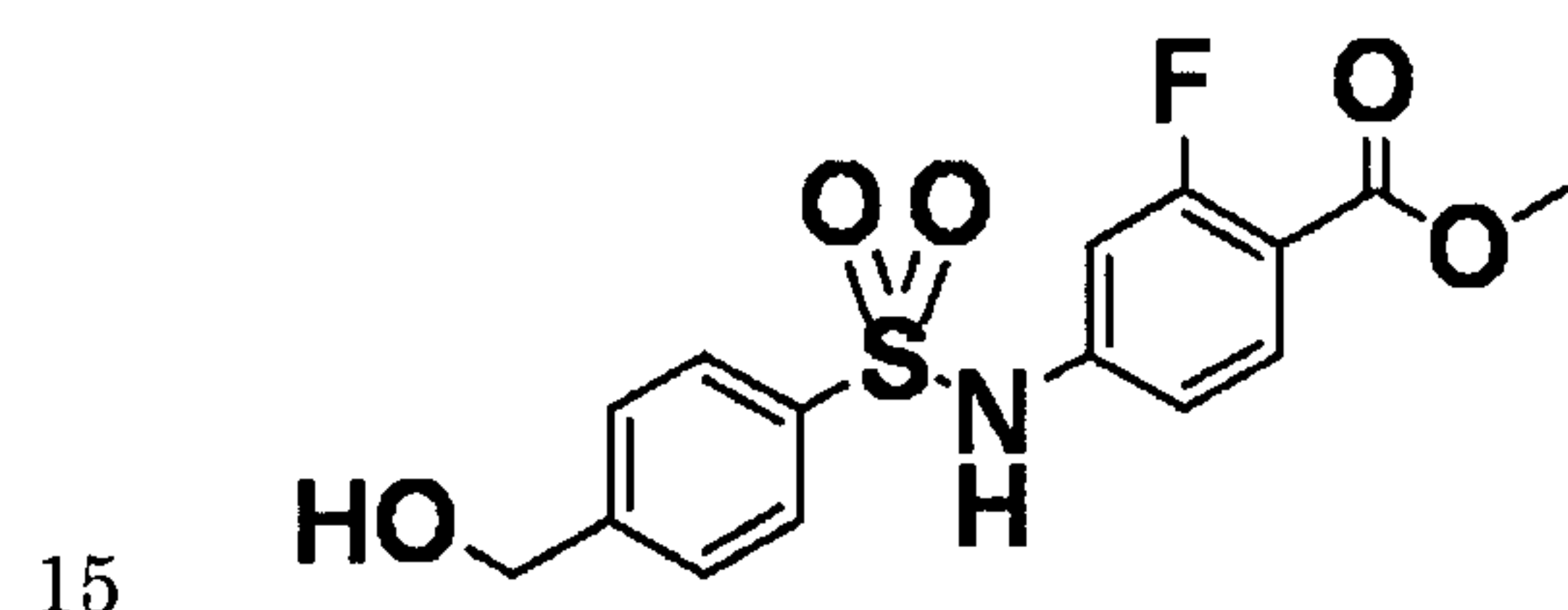


4-(Chlorosulfonyl)benzoic acid (17.0 g, 76.9 mmol) and methyl 4-amino-2-fluorobenzoate (10.0 g, 59.2 mmol) were dissolved in methylene chloride (250 ml), and pyridine (15.0 ml, 171 mmol) was added thereto, followed by stirring at room temperature for 12 hours. The reaction solution was concentrated under reduced pressure, and the obtained residue was diluted with water. Then, the pH was adjusted to 1.0 by adding 6 N hydrochloric acid. The precipitated solid was filtered, and washed with water. The obtained solid was resuspended in water, and washed with a saturated aqueous sodium

hydrogen carbonate solution, followed by extraction with ethyl acetate (50 ml×2). The pH of the obtained aqueous layer was adjusted to 6.0 by adding 6 N hydrochloric acid thereto, followed by extraction with ethyl acetate (80 ml×3). The
 5 extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed to obtain the title compound (5.0 g, 24%).

H NMR (CD₃OD, 400 MHz): δ 8.11 (d, J = 11.2 Hz, 2H), 7.96 (d, J = 11.6 Hz, 2H), 7.79-7.76 (m, 1H), 7.06-6.97 (m, 2H), 3.78 (s, 3H).

(Step 2) Methyl
2-Fluoro-4-([4-(hydroxymethyl)phenyl]sulfonyl)amino)benzoate

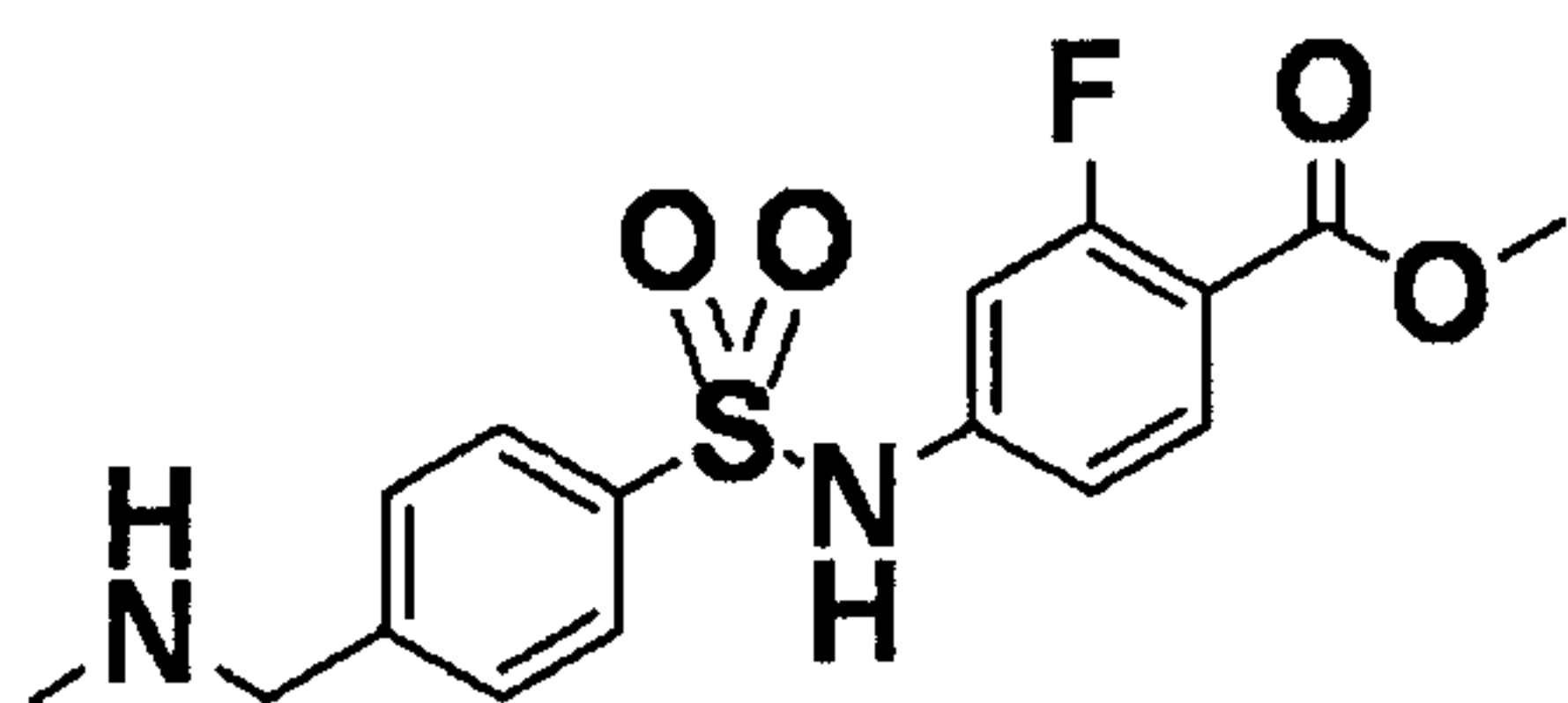


4-([3-Fluoro-4-(methoxycarbonyl)phenyl]amino)sulfonyl)benzoic acid was dissolved in a 1 N borane/tetrahydrofuran solution (25 ml) at 0°C, followed by stirring at room temperature for 15 minutes. To the reaction solution, water
 20 (20 ml) was slowly added dropwise. The precipitated solid was filtered, then washed with water, and dried under reduced pressure to obtain the title compound (4.3 g, 90%).

¹H NMR (d-DMSO, 400 MHz): δ 11.11 (s, 1H), 7.84-7.76 (m, 3H), 7.52 (d, J = 8.4 Hz, 2H), 7.05-6.96 (m, 2H), 5.40 (m, 1H), 4.55
 25 (d, J = 5.2 Hz, 2H), 3.79 (s, 3H).; MS (ESI) m/z 340 (M+H)⁺

(Step 3) Methyl
2-Fluoro-4-([(4-(methylamino)methyl)phenyl]sulfonyl)amino]

benzoate



Methyl

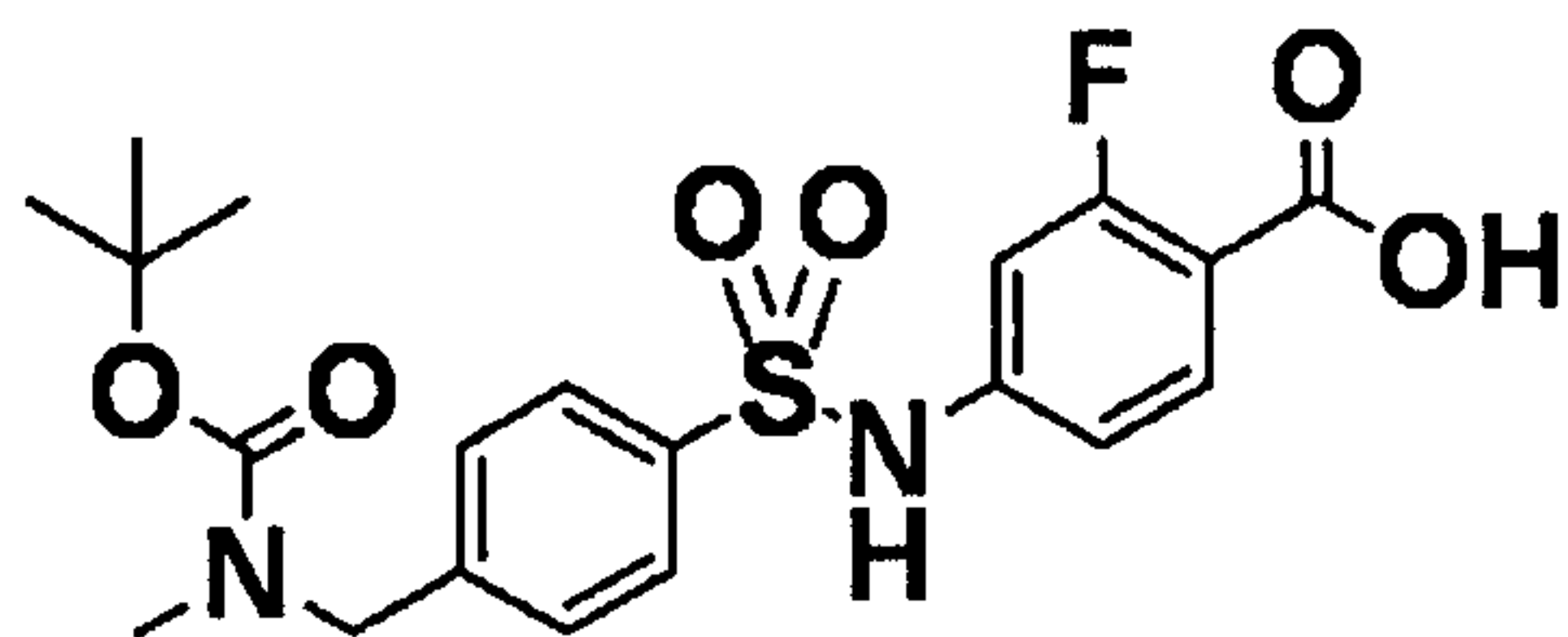
2-fluoro-4-((4-((hydroxymethyl)amino)phenyl)sulfonyl)aminobenzoate (2.80 g, 8.30 mmol) and manganese dioxide (2.90 g, 33.0 mmol) were suspended in chloroform (35 ml), followed by stirring at 60°C for 4 hours. The mixture was cooled to room temperature, and then filtered. The filtrate was concentrated under reduced pressure. The obtained residue was dissolved in tetrahydrofuran (50 ml), and a 2 N methylamine/tetrahydrofuran solution (7.0 ml) was added thereto, followed by stirring at room temperature for 5 minutes. To the reaction liquid, sodium cyanoborohydride (2.0 g, 32 mmol) was added, followed by stirring at room temperature for 20 hours. The reaction solution was filtered, and the filtrate was concentrated under reduced pressure. The obtained residue was dissolved in ethyl acetate (60 ml), and washed with a saturated aqueous ammonium chloride solution (50 ml×2). The organic layer was concentrated under reduced pressure to obtain the title compound (1.7 g, 60% over two steps).

MS (ESI) m/z 353 (M+H)⁺

(Step

4)

4-{[(4-{[(tert-Butoxycarbonyl)(methyl)amino]methyl}phenyl)sulfonyl]amino}-2-fluorobenzoic Acid (M-19)



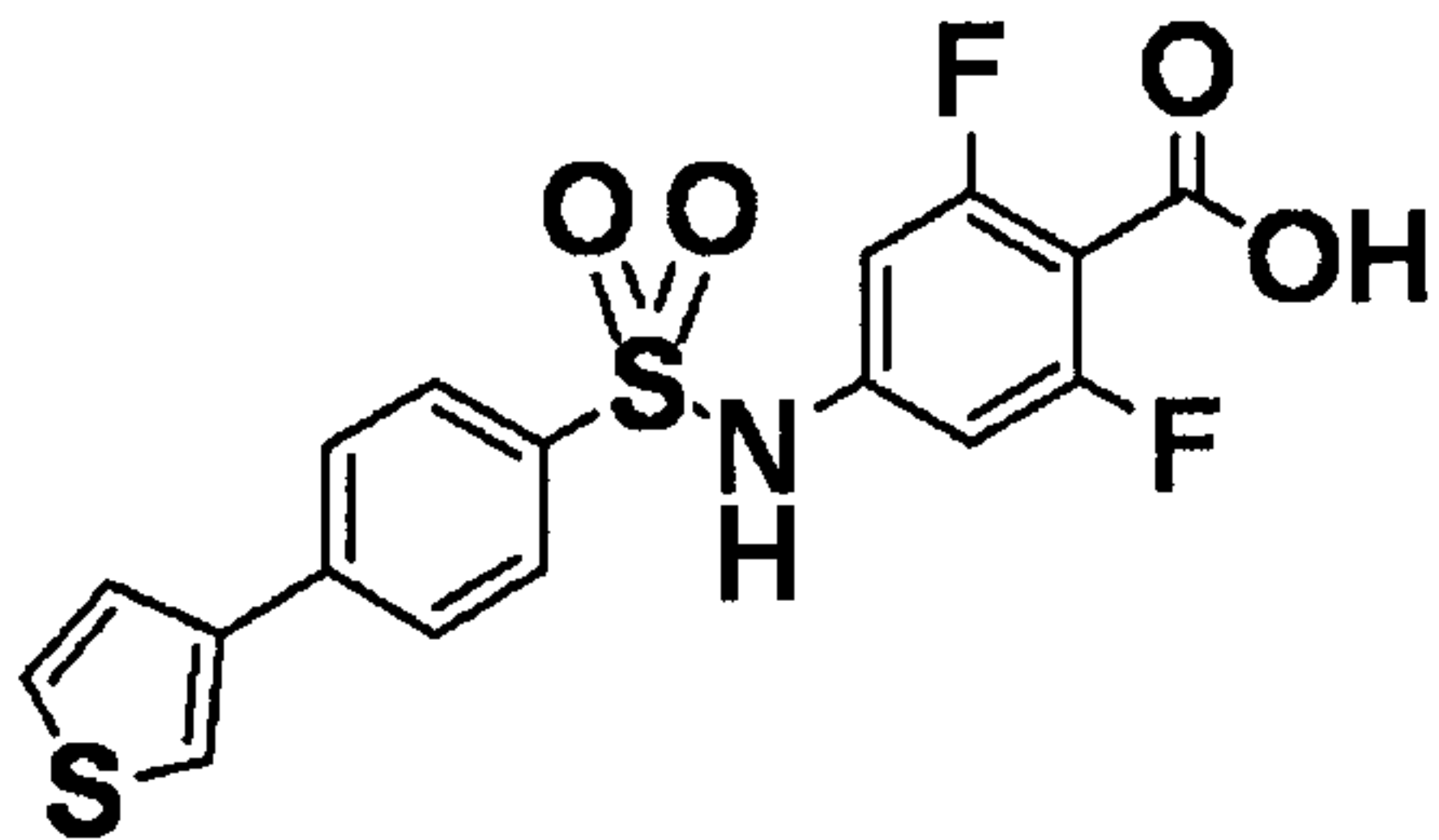
Methyl

2-fluoro-4-[(4-[(methylamino)methyl]phenyl)sulfonyl]amino benzoate (1.7 g, 4.8 mmol) and N,N'-dimethyl-4-aminopyridine
 5 (0.20 g, 1.6 mmol) were dissolved in tetrahydrofuran (45 ml), followed by stirring at room temperature for 15 minutes. The reaction liquid was cooled to 5°C, and then triethylamine (1.0 ml) and di-tert-butyl dicarbonate (1.1 g, 5.3 mmol) were added thereto, followed by stirring for further 20 minutes. After
 10 the reaction liquid was concentrated under reduced pressure, the obtained residue was diluted with water (30 ml), followed by extraction with ethyl acetate (30 ml×3). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the
 15 solvent was removed, followed by purification by silica gel column chromatography (methylene chloride/methanol=10:1). The obtained compound was dissolved in a 6 N aqueous lithium hydroxide solution (21 ml), followed by stirring at room temperature for 30 minutes. The pH was adjusted to 3.0 by adding
 20 citric acid. The precipitated solid was filtered, washed with water, and dried under reduced pressure to obtain the title compound (610 mg, 38% over two steps) as a white solid.

¹H NMR (CD₃OD, 400 MHz): δ 7.74 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 6.86-6.83 (m, 2H),
 25 4.36 (s, 2H), 2.80-2.68 (m, 3H) 1.38-1.17 (m, 9H).; MS (ESI) m/z 339 (M+H-Boc)⁺

Example 20: Synthesis of M-20

2,6-Difluoro-4-([4-(3-thienyl)phenyl]sulfonyl)amino)benzoic Acid (M-20)



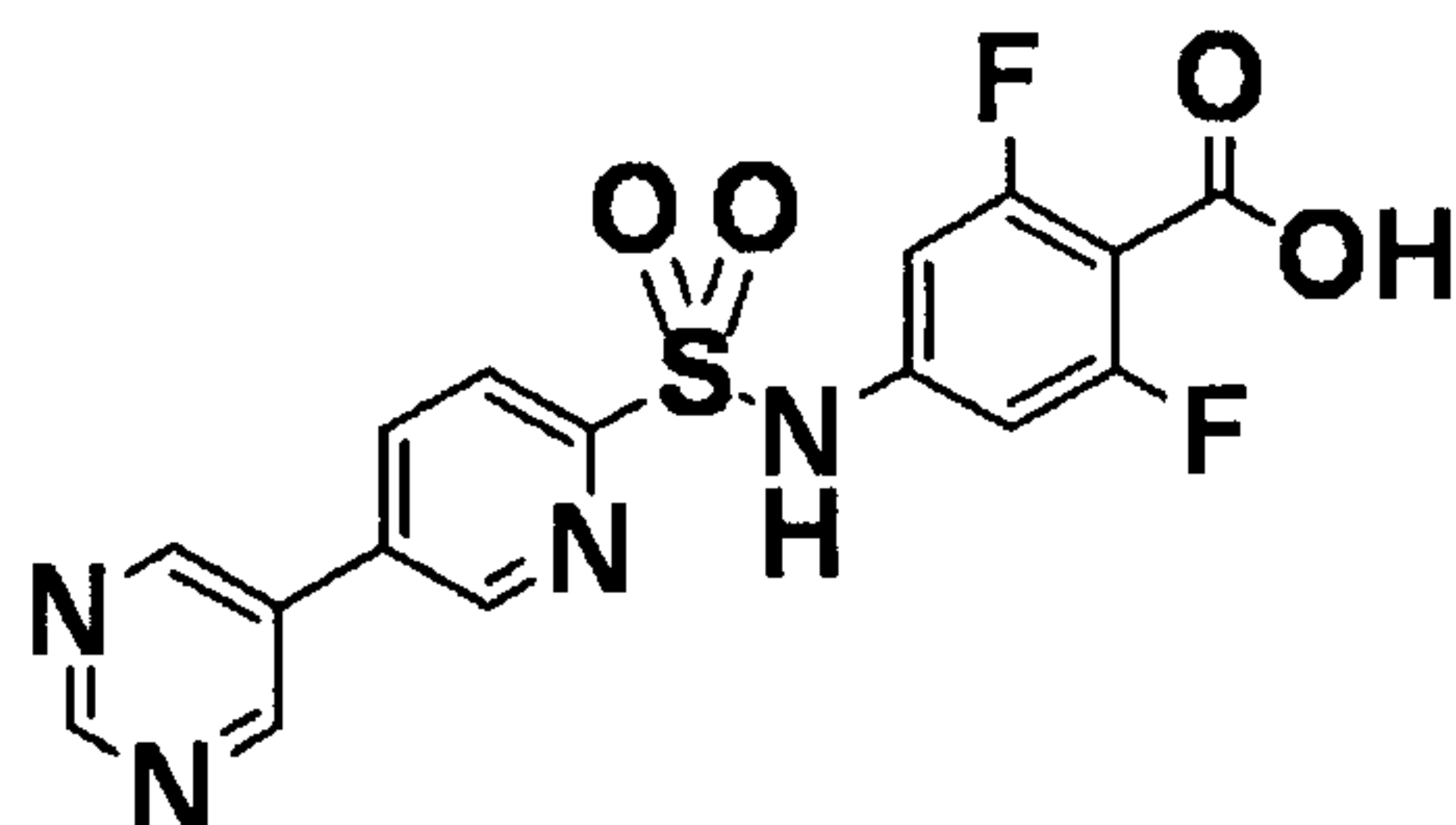
Methyl

- 5 2,6-difluoro-4-([4-(3-thienyl)phenyl]sulfonyl)amino)benzoate (3.00 g, 6.60 mmol) and 3-thienylboronic acid (1.70 g, 13.0 mmol) were dissolved in a mixture solvent of N,N-dimethylformamide (130 ml) and water (20 ml). To the solution,
- 10 [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.76 g, 0.66 mmol) and sodium carbonate (2.1 g, 20 mmol) were added, followed by stirring at 110°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction solution was diluted with water, followed by
- 15 extraction with ethyl acetate. The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=5:1 to 1:4).
- 20 The obtained compound (1.20 g, 2.90 mmol) was dissolved in a 6 N aqueous lithium hydroxide solution (20 ml), followed by stirring at room temperature for 30 minutes. The pH was adjusted to 3.0 by adding 6 N hydrochloric acid. The precipitated solid was filtered and then dried under reduced
- 25 pressure to obtain the title compound (1.0 g, 86% over two steps).

^1H NMR (CD_3OD , 400 MHz): δ 7.93-7.82 (m, 5H), 7.53 (t, $J = 1.2$ Hz, 2H), 6.85 (d, $J = 10.0$ Hz, 2H).; MS (ESI) m/z 394 ($\text{M}-\text{H}$) $^+$

Example 21: Synthesis of M-21

2,6-Difluoro-4-{\[(5-pyrimidin-5-yl-pyridin-2-yl)sulfonyl]amino\}benzoic Acid (M-21)



Methyl

4-{\[(5-bromopyridin-2-yl)sulfonyl]amino\}-2,6-difluorobenzoate (3.30 g, 8.10 mmol) and pyrimidin-5-yl-boronic acid (2.00 g, 16.3 mmol) were dissolved in a mixture solvent of N,N-dimethylformamide (50 ml) and water (20 ml). To the solution,

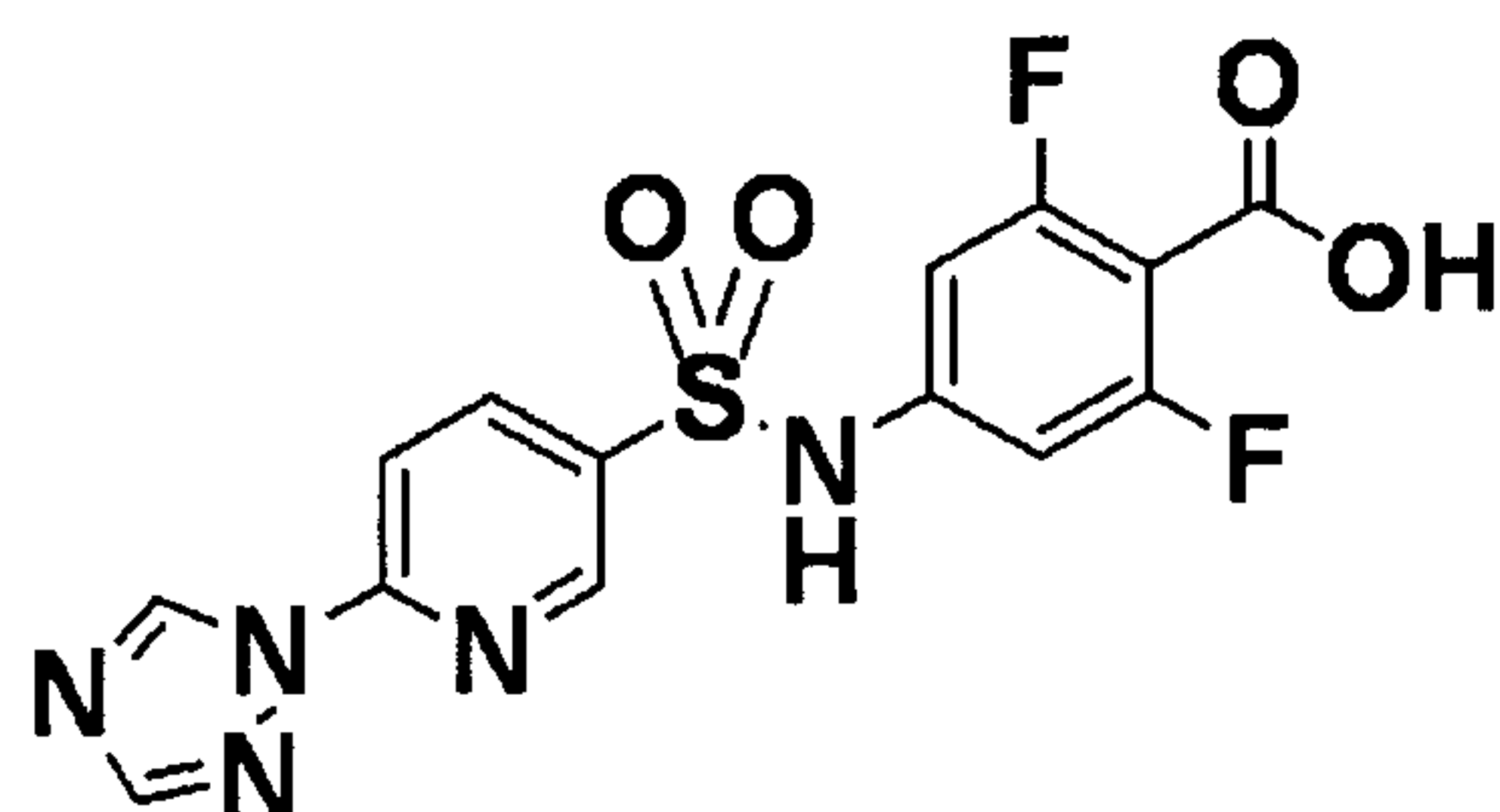
[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (0.60 g, 0.81 mmol) and sodium carbonate (2.6 g, 24 mmol) were added, followed by stirring at 120°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction solution was diluted with water (200 ml), followed by extraction with ethyl acetate (70 ml $\times$ 10). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1 to 1:2). The obtained compound (1.20 g, 3.00 mmol) was dissolved in methanol (40 ml) and tetrahydrofuran (40 ml), and a 6 N aqueous sodium hydroxide solution (60 ml) was added, followed by stirring at room temperature for 4 hours. The pH

was adjusted to 4.0 by adding 4 N hydrochloric acid. The precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (1.05 g, 33% over two steps).

5 ^1H NMR (CD_3OD , 400 MHz): δ 9.26 (s, 1H), 9.20 (s, 2H), 9.08 (d, J = 1.6 Hz, 1H), 8.45 (dd, J = 8.4, 2.0 Hz, 1H), 8.26 (d, J = 8.4 Hz, 1H), 6.97 (d, J = 10.0 Hz, 2H).; MS (ESI) m/z 393 ($\text{M}+\text{H}$) $^+$

Example 22: Synthesis of M-22

2,6-Difluoro-4-({[6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl]sul
10 fonyl}amino)benzoic Acid (M-22)



Methyl

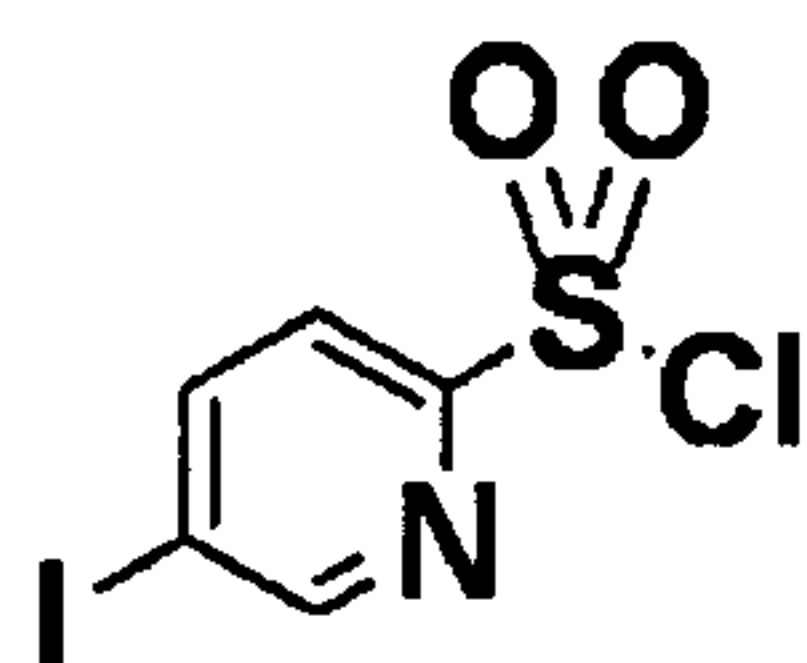
4-{{[6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl]sulfonyl}amino}-2,6-difluorobenzoate (1.90 g, 5.00 mmol) was dissolved in N-methylpyrrolidone
15 (30 ml), and 1,2,4-triazole (0.76 g, 11 mmol), copper(I) iodide (0.76 g, 4.0 mmol), potassium phosphate (3.0 g, 14 mmol), and trans-N,N'-dimethylcyclohexane-1,2-diamine (0.15 g, 1.0 mmol) were added thereto, followed by stirring at 145°C for 12 hours in the presence of nitrogen gas. After cooling to room
20 temperature, the reaction solution was diluted with water (50 ml), followed by extraction with ethyl acetate (50 ml×3). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by
25 silica gel column chromatography (petroleum ether/ethyl acetate=2:1 to 1:1). A portion (800 mg, 2.00 mmol) of the

obtained compound was dissolved in methanol (15 ml), and a 6 N aqueous sodium hydroxide solution (5.0 ml) was added thereto, followed by stirring at room temperature for 1 hour. The pH was adjusted to 4.0 by adding 4 N hydrochloric acid, and the precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (668 mg, 36% over two steps) as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 13.69 (s, 1H), 11.49 (s, 1H), 9.44 (d, J = 6.4 Hz, 1H), 8.99 (d, J = 2.0 Hz, 1H), 8.50-8.47 (m, 1H), 8.38 (s, 1H), 8.07 (d, J = 8.4 Hz, 1H), 6.90 (d, J = 9.6 Hz, 2H).; MS (ESI) m/z 382 (M+H)⁺

Example 23: Synthesis of M-23

(Step 1) 5-Iodopyridine-2-sulfonyl Chloride

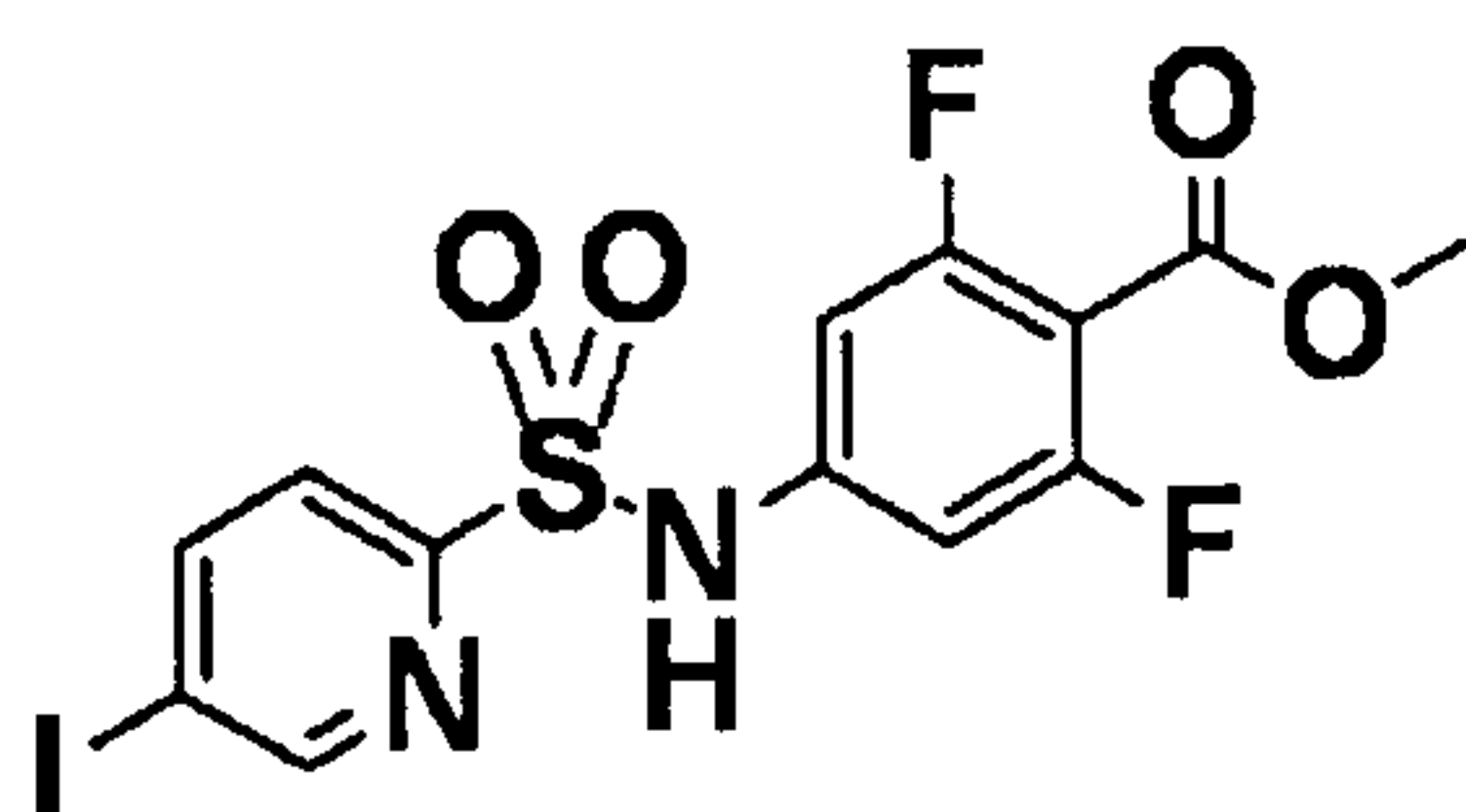


Phenylmethanethiol (9.3 g, 75 mmol) was dissolved in dimethyl formaldehyde (120 ml). After cooling to 0°C, 60% sodium hydride (3.8 g, 95 mmol) was added thereto, followed by stirring at room temperature for 30 minutes. To this reaction solution, 2-chloro-5-iodopyridine (15 g, 63 mmol) was added, followed by stirring at room temperature for 1 hour. The reaction solution was diluted with water, followed by extraction with ethyl acetate (200 ml×2). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. A portion (11.3 g, 35.0 mmol) of the obtained compound was suspended in a mixture solvent of acetic acid (75 ml) and water (25 ml), and N-chlorosuccinimide (18.4 g, 138 mmol) was added thereto, followed by stirring at room

temperature for 1 hour. The reaction solution was diluted with water, followed by extraction with methylene chloride (100 ml×2). The extraction liquids were combined, washed with a saturated aqueous sodium hydrogen carbonate solution and water, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=30:1) to obtain the title compound (2.6 g, 23% over two steps) as a white solid.

(Step 2) Methyl

10 2,6-Difluoro-4-{[(5-iodopyridin-2-yl)sulfonyl]amino}benzoate
e

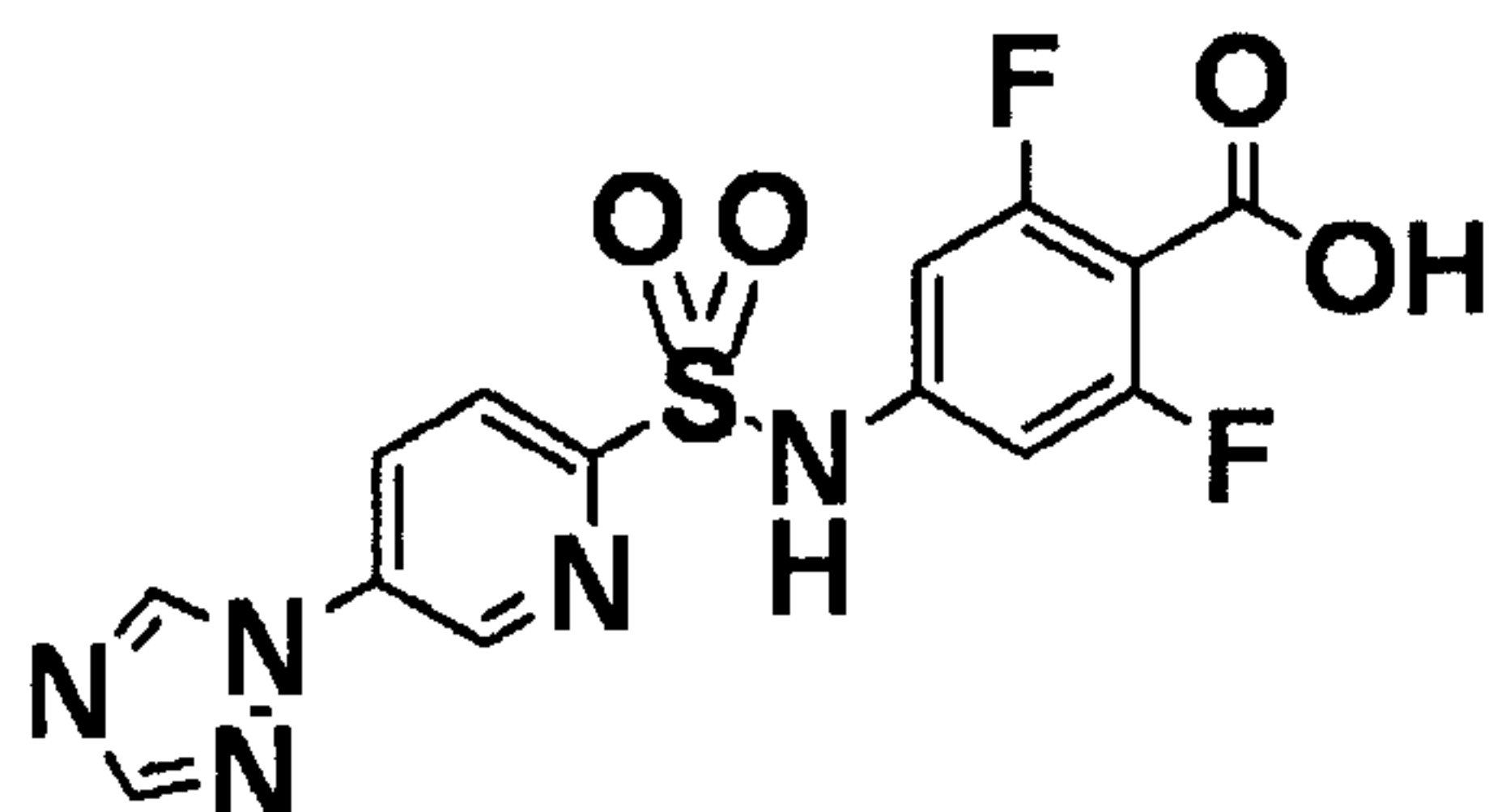


5-Iodopyridine-2-sulfonyl chloride (5.1 g, 17 mmol) and methyl 4-amino-2,6-difluorobenzoate (2.5 g, 13 mmol) were dissolved in methylene chloride (25 ml), and pyridine (5.0 ml) was added thereto, followed by stirring at room temperature for 12 hours. The reaction solution was concentrated under reduced pressure. To the obtained residue, 6 N hydrochloric acid (100 ml) was added. The precipitated solid was filtered, and dried under reduced pressure to obtain the title compound (3.0 g, 69%).

¹H NMR (d-DMSO, 400 MHz): δ 11.58 (br, 1H), 9.00 (d, J = 2.0 Hz, 1H), 8.54-8.51 (dd, J = 8.4, 2.0 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 10.4 Hz, 2H), 3.81 (s, 3H).; MS (ESI) m/z 455 (M+H)⁺

(Step 3)

2,6-Difluoro-4-([5-(1H-1,2,4-triazol-1-yl)pyridin-2-yl]sul

fonyl}amino)benzoic Acid (M-23)

Methyl

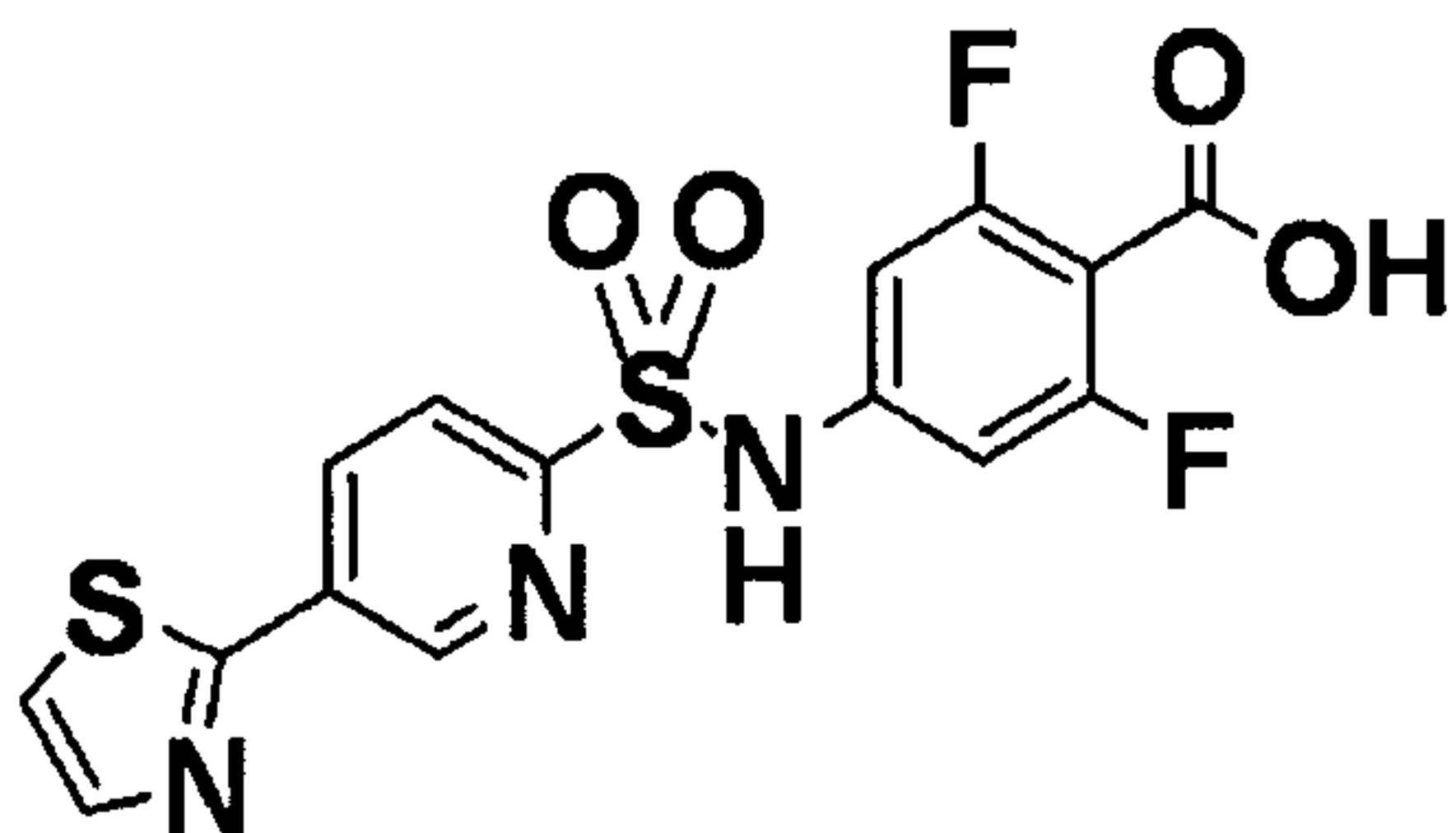
2,6-difluoro-4-[(5-iodopyridin-2-yl)sulfonyl]amino}benzoate (3.0 g, 6.6 mmol) was dissolved in N-methylpyrrolidone (20 ml), and 1,2,4-triazole (0.68 g, 9.9 mmol), copper(I) iodide (0.63 g, 3.3 mmol), potassium phosphate (2.8 g, 13 mmol), and trans-N,N'-dimethylcyclohexane-1,2-diamine (0.94 g, 6.6 mmol) were added thereto, followed by stirring at 145°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction solution was diluted with water (40 ml), followed by extraction with ethyl acetate (50 ml×4). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained black residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1). A portion (800 mg, 2.00 mmol) of the obtained compound was dissolved in methanol (50 ml), and a 4 N aqueous sodium hydroxide solution (5.0 ml) was added thereto, followed by stirring at room temperature for 12 hours. The pH was adjusted to 4.0 by adding 6 N hydrochloric acid. The precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (0.49 g, 19% over two steps) as a white solid.

¹H NMR (d₆-DMSO, 400 MHz): δ 13.70 (br, 1H), 11.58 (br, 1H), 9.50 (s, 1H), 9.31 (d, J = 2.0 Hz, 1H), 8.57-8.54 (m, 1H),

8.38-8.33 (m, 2H), 6.95 (d, $J = 10.0$ Hz, 2H).; MS (ESI) m/z 382
($M+H$)⁺

Example 24: Synthesis of M-24

2,6-Difluoro-4-([5-(1,3-thiazol-2-yl)pyridin-2-yl]sulfonyl
5 }amino)benzoic Acid (M-24)



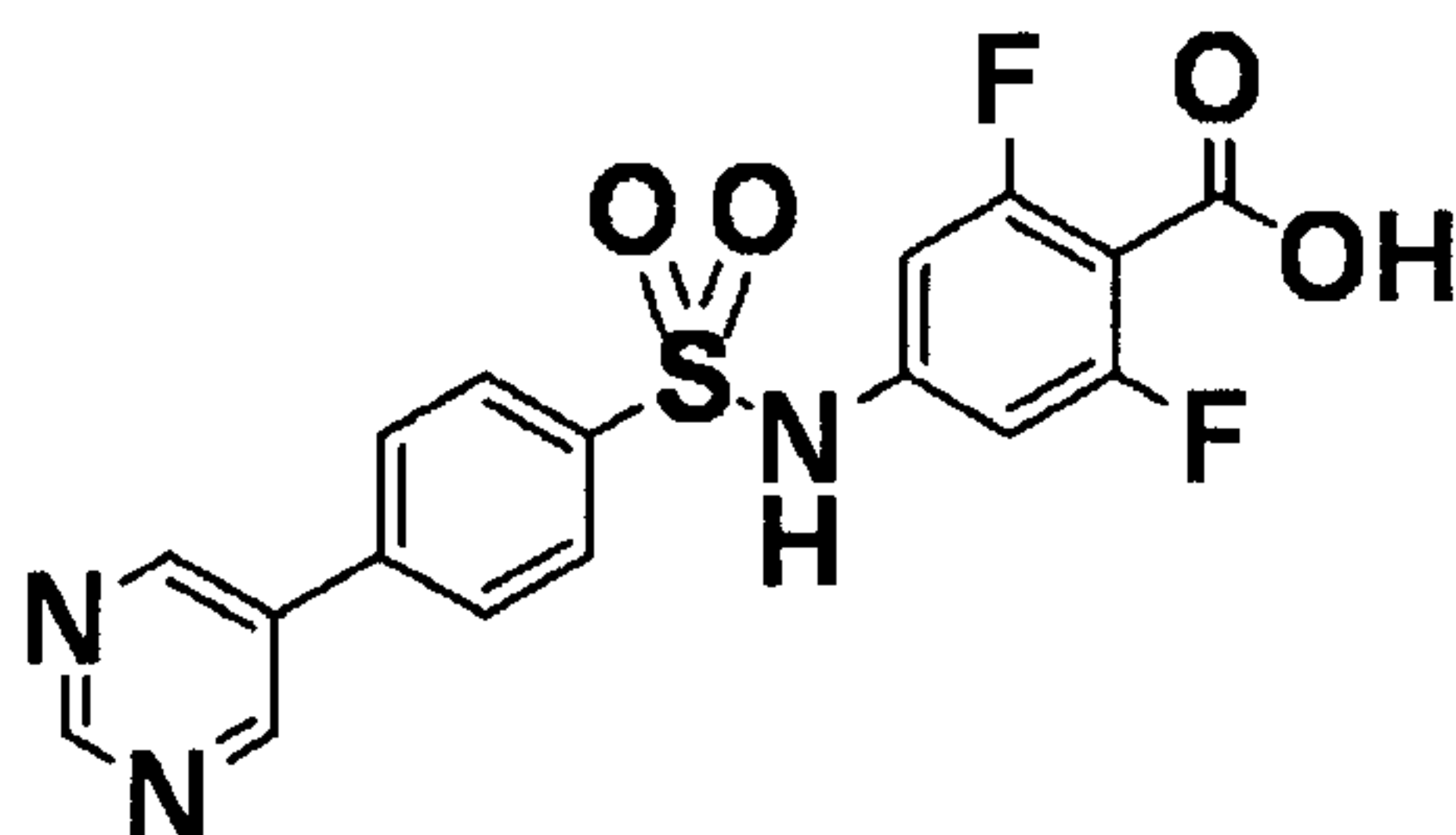
[6-([3,5-Difluoro-4-(methoxycarbonyl)phenyl]amino)sulfonyl]pyridin-3-yl]boronic acid (5.00 g, 13.4 mmol) and 2-bromo-1,3-thiazole (7.6 g, 47 mmol) were dissolved in a mixture solvent of N,N-dimethylformamide (100 ml) and water (40 ml). To the solution, [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (980 mg, 1.34 mmol) and sodium carbonate (4.30 g, 40.6 mmol) were added, followed by stirring at 120°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction solution was diluted with water (200 ml), followed by extraction with ethyl acetate (80 ml×3). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:2). The obtained compound (1.20 g, 2.92 mmol) was dissolved in methanol (50 ml) and tetrahydrofuran (50 ml), and a 6 N aqueous sodium hydroxide solution (70 ml) was added thereto, followed by stirring at room temperature for 5 hours. The pH was adjusted to 4.0 by adding 4 N hydrochloric acid. The

precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (1.08 g, 20% over two steps) as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 13.6 (br, 1H), 11.60 (br, 1H), 9.29 (d, J = 1.2 Hz, 1H), 8.64 (dd, J = 8.0, 2.0 Hz, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.10 (d, J = 2.8 Hz, 1H), 8.03 (d, J = 2.8 Hz, 1H), 6.95 (t, J = 10.0 Hz, 2H).; MS (ESI) m/z 398 (M+H)⁺

Example 25: Synthesis of M-25

2,6-Difluoro-4-{[(4-pyrimidin-5-yl-phenyl)sulfonyl]amino}benzoic Acid (M-25)



Methyl

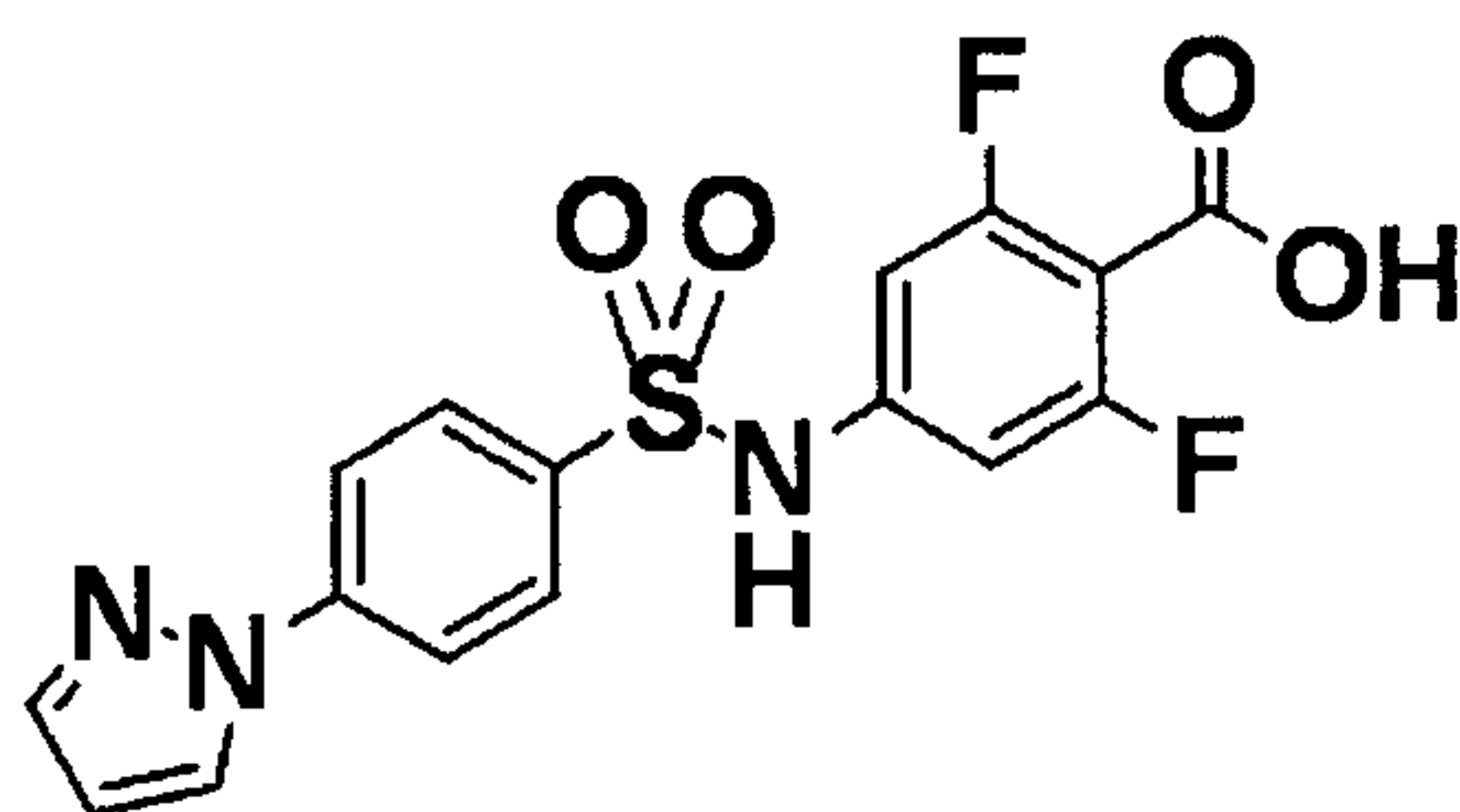
2,6-difluoro-4-{[(4-iodophenyl)sulfonyl]amino}benzoate (3.0 g, 6.6 mmol) and pyrimidin-5-yl-boronic acid (0.89 g, 7.3 mmol) were dissolved in a mixture solvent of N,N-dimethylformamide (50 ml) and water (10 ml). To the solution, tetrakis(triphenylphosphine)palladium (0.76 g, 0.66 mmol) and sodium carbonate (2.00 g, 18.8 mmol) were added, followed by stirring at 100°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction solution was diluted with water, followed by extraction with ethyl acetate. The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:2 to 1:4).

The obtained compound (640 mg, 1.58 mmol) was dissolved in methanol (15 ml), and a 6 N aqueous sodium hydroxide solution (5.0 ml) was added thereto, followed by stirring at room temperature for 30 minutes. The pH was adjusted to 4.0 by adding 4 N hydrochloric acid. The precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (550 mg, 21% over two steps) as a white solid.

^1H NMR (CD_3OD , 400 MHz): δ 9.18 (s, 1H), 9.11 (s, 2H), 8.04 (d, $J = 8.0$ Hz, 2H), 7.94 (d, $J = 8.4$ Hz, 2H), 6.84 (d, $J = 9.6$ Hz, 2H).; MS (ESI) m/z 392 ($\text{M}+\text{H}$) $^+$

Example 26: Synthesis of M-26

2,6-Difluoro-4-([4-(1H-pyrazol-1-yl)phenyl]sulfonyl)amino
benzoic Acid (M-26)



15 Methyl

2,6-difluoro-4-([4-(4-iodophenyl)sulfonyl]amino)benzoate (3.0 g, 6.4 mmol) was dissolved in N-methylpyrrolidone (30 ml), and 1H-pyrazole (900 mg, 13.2 mmol), copper(I) iodide (0.84 g, 4.4 mmol), potassium phosphate (3.50 g, 16.5 mmol), and trans-N,N'-dimethylcyclohexane-1,2-diamine (0.28 g, 2.0 mmol) were added thereto, followed by stirring at 145°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction solution was diluted with water (50 ml), followed by extraction with ethyl acetate (50 ml $\times$ 3). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then,

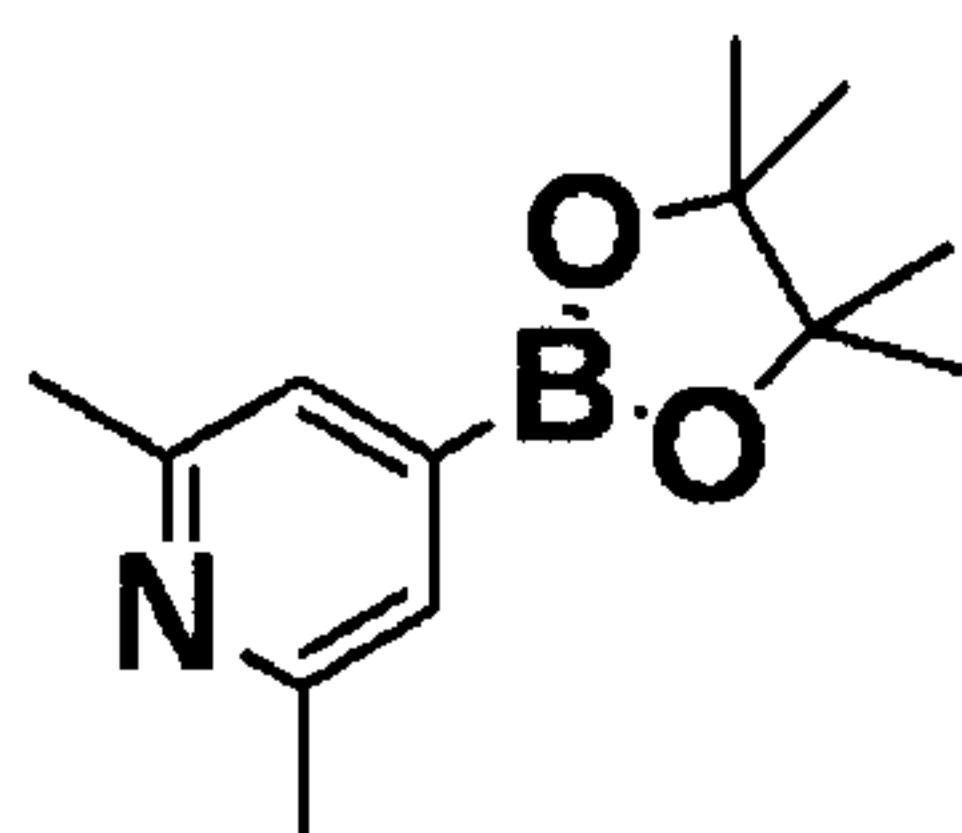
the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1 to 1:1). The obtained compound (1.1 g, 2.8 mmol) was dissolved in methanol (20 ml), and a 6 N aqueous sodium hydroxide solution (5.0 ml) was added thereto, followed by stirring at room temperature for 1 hour. The pH was adjusted to 4.0 by adding 4 N hydrochloric acid. The precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (960 mg, 40% over two steps) as a white solid.

10 ^1H NMR (CD_3OD , 400 MHz): δ 8.23 (d, $J = 3.2$ Hz, 1H), 7.88 (s, 4H), 7.66 (d, $J = 1.6$ Hz, 1H), 6.73 (d, $J = 10.0$ Hz, 2H), 6.46-6.45 (m, 1H).; MS (ESI) m/z 380 ($\text{M}+\text{H}$)⁺

Example 27: Synthesis of M-27

(Step 1)

15 2,6-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine



2,6-Dimethylpyridine (10 g, 93 mmol), 4,4'-bis(1,1'-tert-butyl)-2'-bipyridine (1.56 g, 5.80 mmol), 20 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (25.4 g, 100 mmol), and (1,5-cyclooctadiene)(methoxy)iridium(I) dimer (1.96 g, 3.00 mmol) were dissolved in tetrahydrofuran (500 ml), followed by stirring at 65°C for 16 hours in the presence of nitrogen gas.

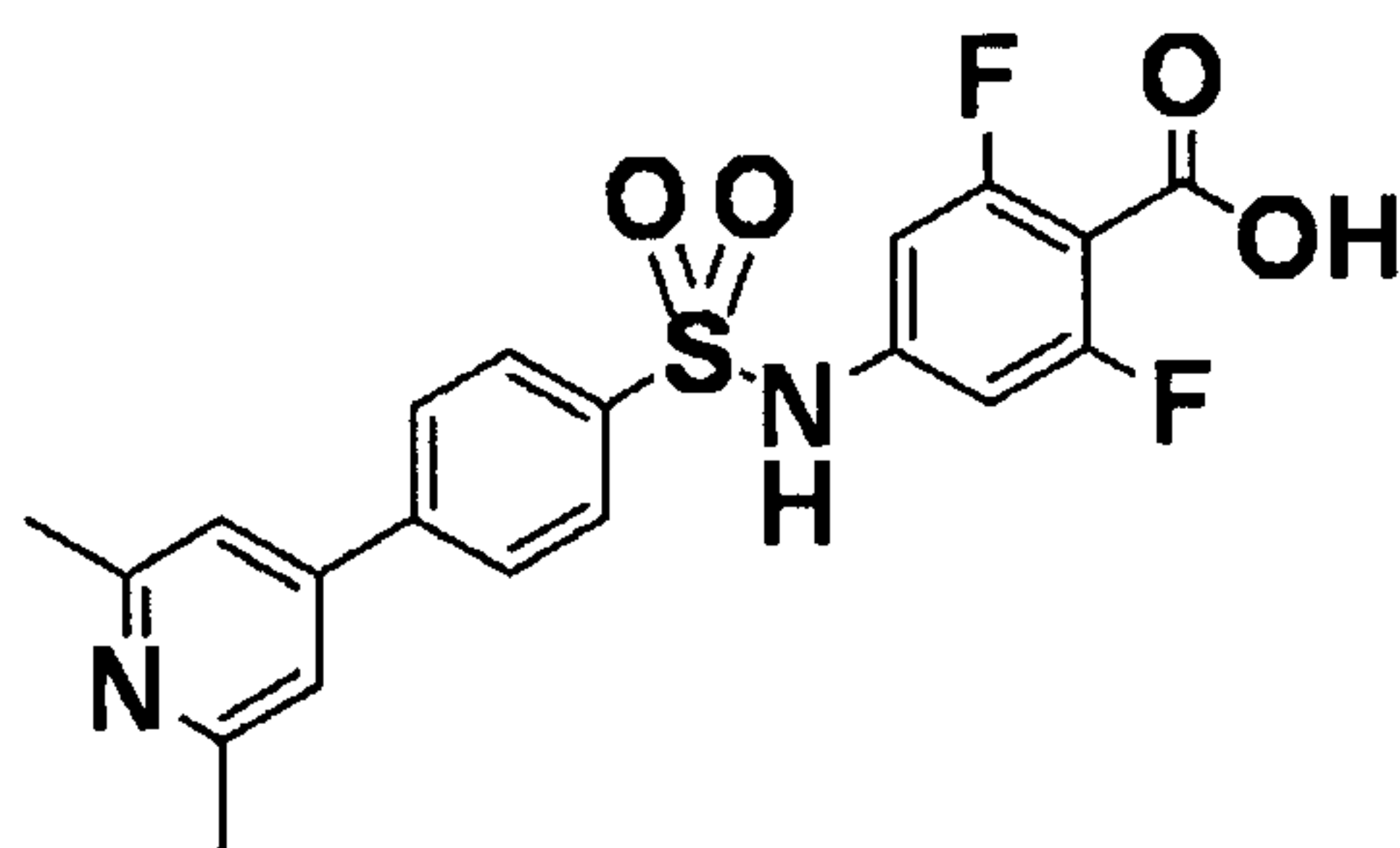
25 The reaction solution was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=100:1) to

obtain the title compound (15.0 g, 66%).

¹H NMR (CDCl₃, 300 MHz): δ 7.38 (s, 2H), 2.53 (s, 6H), 1.37 (s, 12H).; MS (ESI) m/z 234 (M+H)⁺

(Step 2)

5 4-({[4-(2,6-Dimethylpyridin-4-yl)phenyl]sulfonyl}amino)-2,6-difluorobenzoic Acid (M-27)



Methyl

2,6-difluoro-4-{{[4-(2,6-dimethylpyridin-4-yl)phenyl]sulfonyl}amino}benzoate

10 (29.1 g, 64.3 mmol) and 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridine (18.0 g, 76.9 mmol) were dissolved in a mixture solvent of N,N-dimethylformamide (750 ml) and water (75 ml). To the solution,

15 [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (1.7 g, 2.3 mmol) and sodium carbonate (24.4 g, 155 mmol) were added, followed by stirring at 90°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction solution was diluted with water, followed by

20 extraction with ethyl acetate. The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:2 to 1:10).

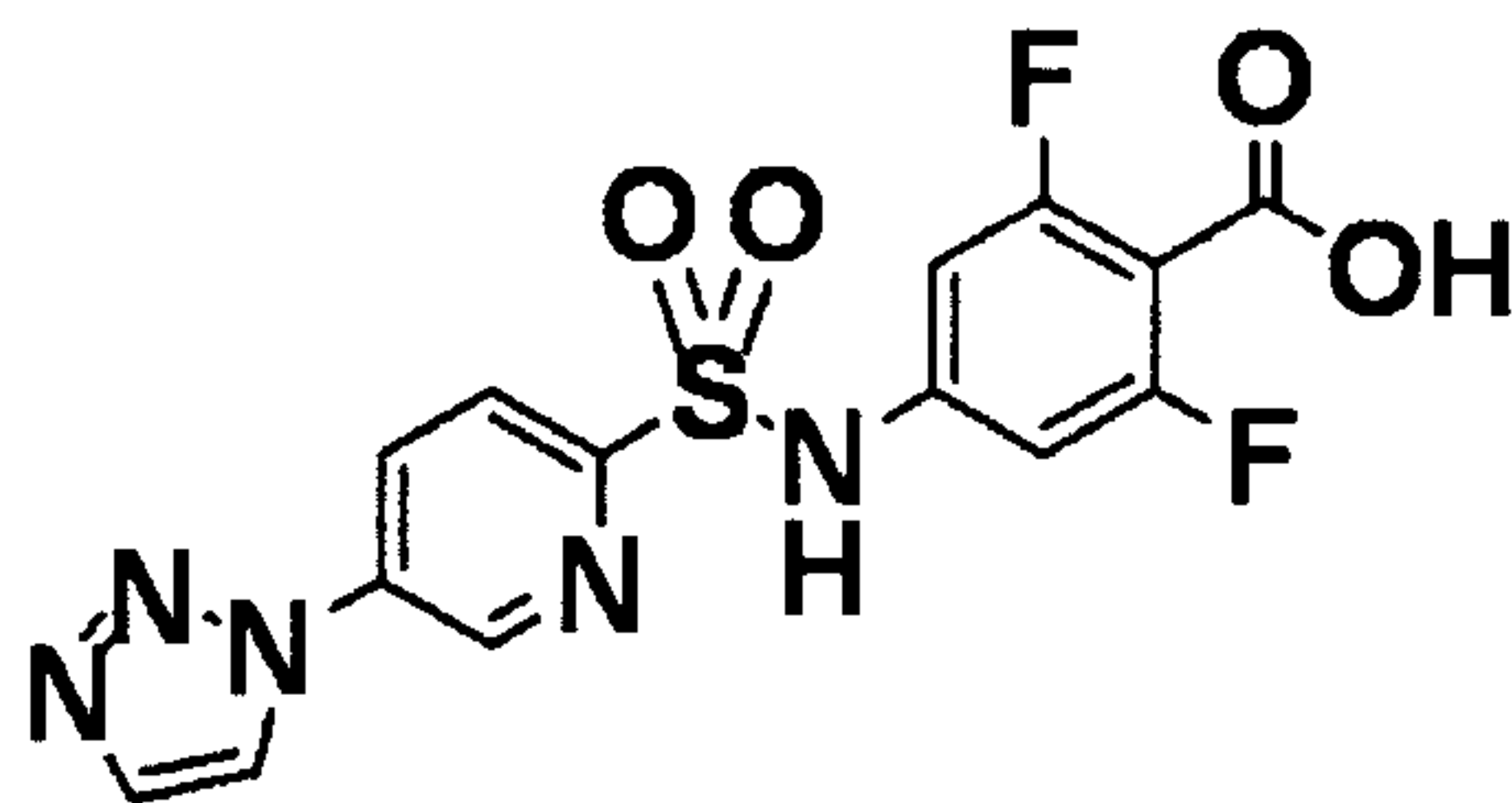
25 The obtained compound (13.0 g, 30.0 mmol) was dissolved in methanol (90 ml), and a 6 N aqueous sodium hydroxide solution

(30 ml) was added thereto, followed by stirring at room temperature for 30 minutes. The pH was adjusted to 4.0 by adding 4 N hydrochloric acid. The precipitated solid was filtered and then dried under reduced pressure to obtain the title compound
 5 (10.5 g, 39% over two steps) as a white solid.

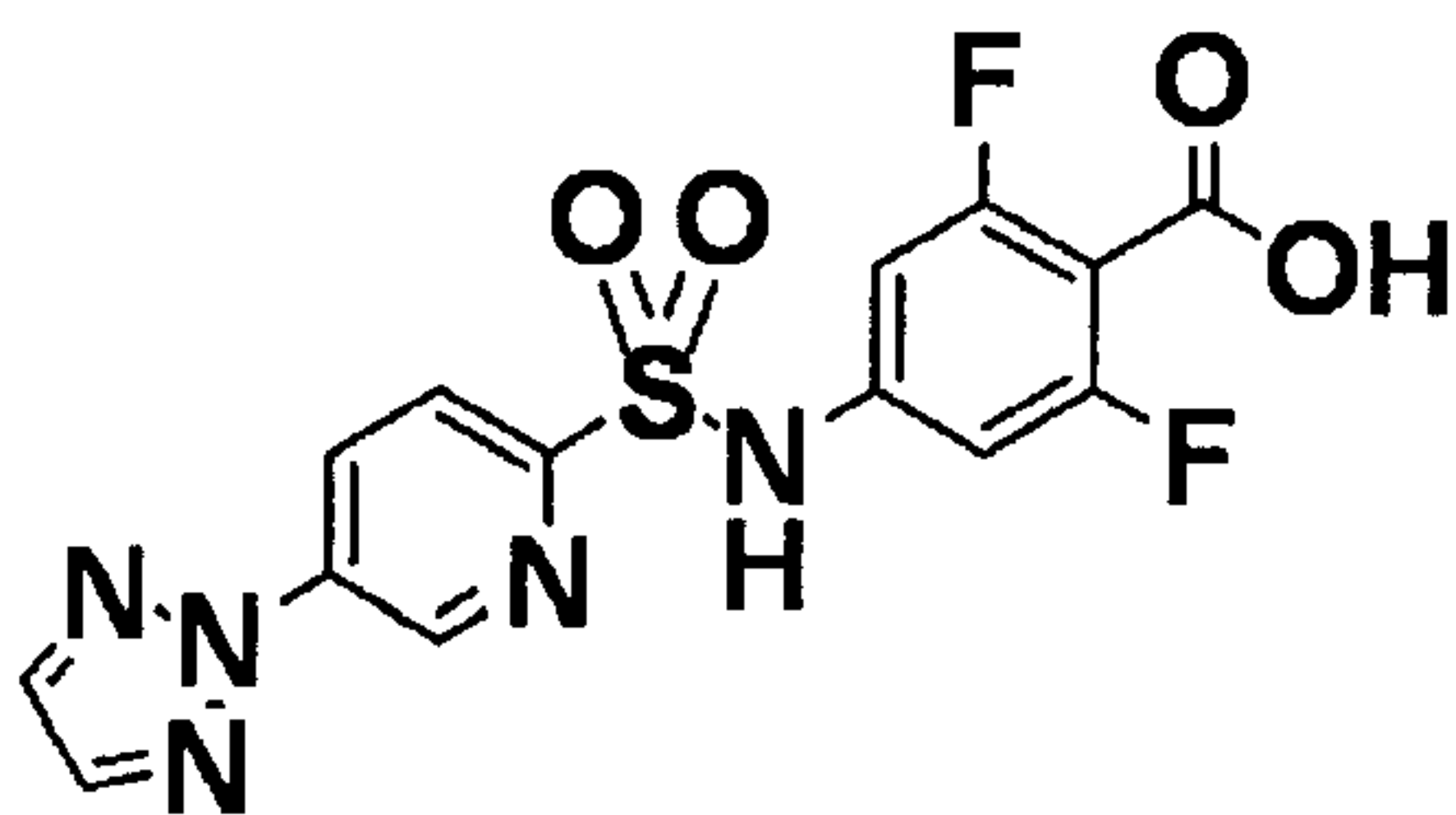
^1H NMR (d-DMSO, 400 MHz): δ 8.02 (s, 4H), 7.57 (s, 2H), 6.88 (d, J = 10.0 Hz, 2H), 2.53 (s, 6H).; MS (ESI) m/z 419 ($M+H$) $^+$

Examples 28 to 31: Synthesis of M-28 to M-31

2,6-Difluoro-4-({[5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl]sulfonyl}amino)benzoic Acid (M-28)
 10



2,6-Difluoro-4-({[5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl]sulfonyl}amino)benzoic Acid (M-29)



15 Methyl

4-{{[5-bromopyridin-2-yl]sulfonyl}amino}-2,6-difluorobenzoate (8.0 g, 20 mmol) was dissolved in N-methylpyrrolidone (120 ml), and 1,2,3-triazole (2.0 g, 30 mmol), copper(I) iodide (1.9 g, 10 mmol), potassium phosphate (8.4 g, 40 mmol), and
 20 N,N-dimethylcyclohexylamine (2.8 g, 20 mmol) were added thereto, followed by stirring at 145°C for 12 hours in the presence of nitrogen gas. After cooling to room temperature, the reaction

solution was diluted with water (300 ml), followed by extraction with ethyl acetate (150 ml×5). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1 to 1:1) to obtain methyl

2,6-difluoro-4-({[5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl]sulfonyl}amino)benzoate (M-30: methyl ester of M-28) (1.5 g, 19%)

10 and methyl 2,6-difluoro-4-({[5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl]sulfonyl}amino)benzoate (M-31: methyl ester of M-29) (2.0 g, 25%).

The obtained methyl 2,6-difluoro-4-({[5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl]sulfonyl}amino)benzoate (M-30) (800 mg, 2.00 mmol) was dissolved in methanol (50 ml), and a 4 N aqueous sodium hydroxide solution (50 ml) was added thereto, followed by stirring at room temperature for 12 hours. The pH was adjusted to 4.0 by adding 6 N hydrochloric acid. The precipitated solid was filtered and then dried under reduced pressure to obtain the title compound (M-28, 920 mg, 63%).

¹H NMR (CD₃OD, 400 MHz) for M-28: δ 9.30 (d, J = 3.2 Hz, 1H), 8.76 (d, J = 1.6 Hz, 1H), 8.62 (dd, J = 11.6, 3.2 Hz, 1H), 8.33 (d, J = 11.6 Hz, 1H), 7.99 (d, J = 1.2 Hz, 1H), 6.98 (d, J = 13.2 Hz, 2H).; MS (ESI) m/z 382 (M+H)⁺

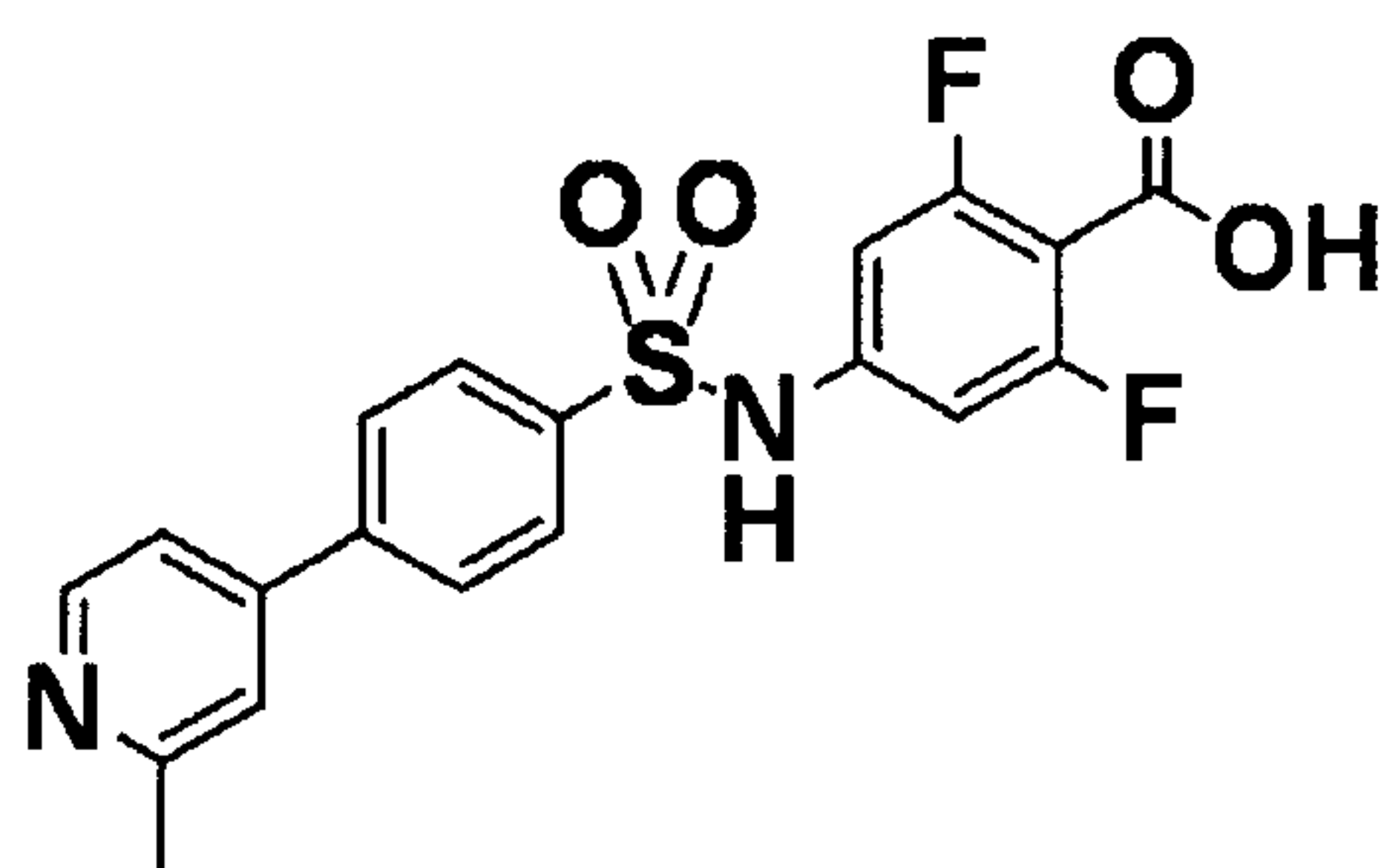
The title compound (M-29, 910 mg, 46%) was obtained by subjecting the obtained methyl 2,6-difluoro-4-({[5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl]sulfonyl}amino)benzoate (M-31) to the same method.

30 ¹H NMR (d-DMSO, 400 MHz) for M-29: δ 13.58 (br, 1H), 11.72 (br,

1H), 9.38 (d, J = 1.6 Hz, 1H), 8.65 (dd, J = 8.4, 2.0 Hz, 1H), 8.30-8.27 (m, 3H), 6.95 (d, J = 10.0 Hz, 2H).; MS (ESI) m/z 382 (M+H)⁺

Example 32: Synthesis of M-32

5 2,6-Difluoro-4-({[4-(2-methylpyridin-4-yl)phenyl]sulfonyl}amino)benzoic Acid (M-32)



·TFA

Methyl

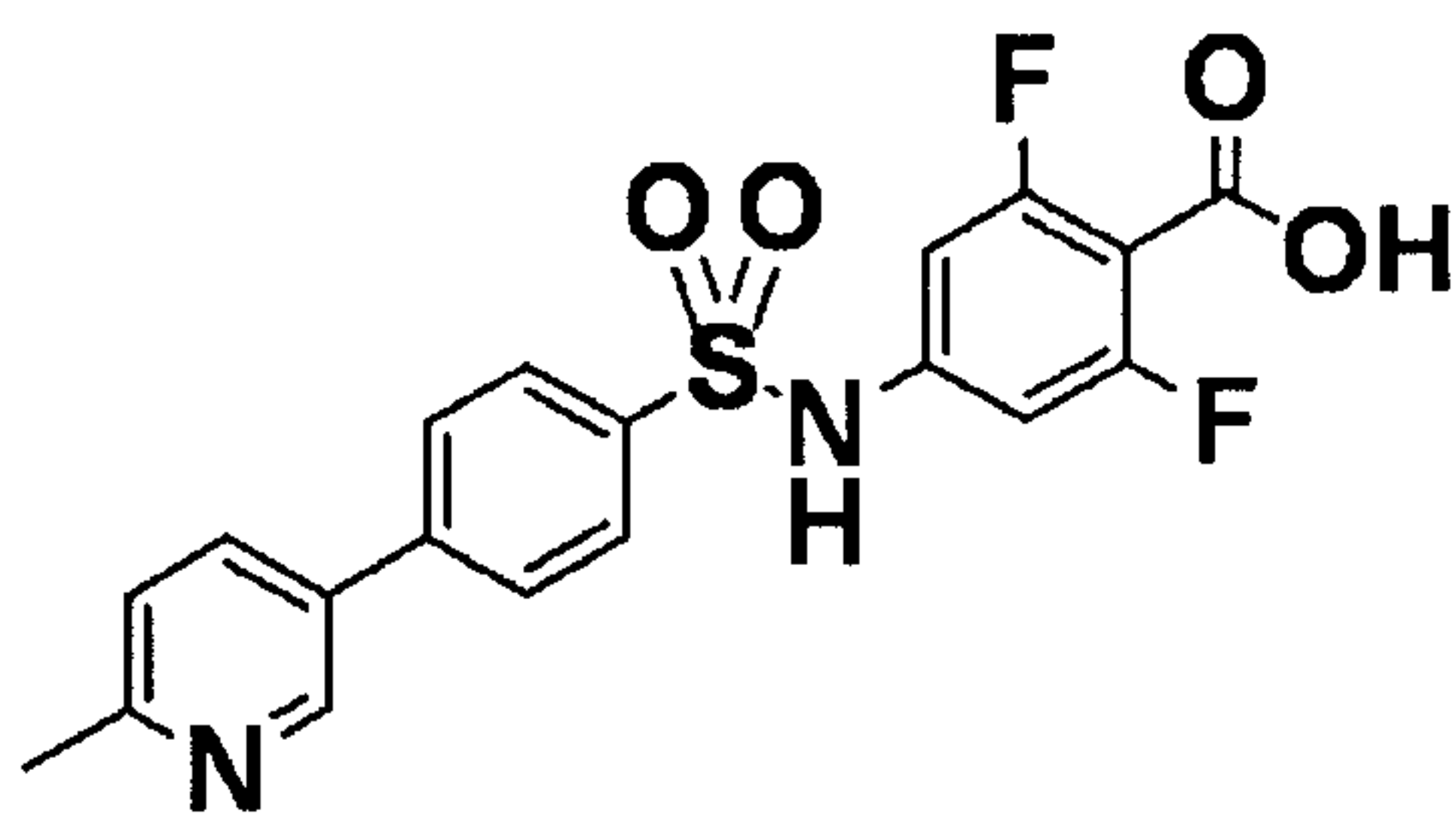
10 4-{{[4-bromophenyl]sulfonyl}amino}-2,6-difluorobenzoate (200 mg, 0.440 mmol) was dissolved in 1,4-dioxane (9.0 ml), and 2-methylpyridine-4-boronic acid (132 mg, 0.970 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (32.0 mg, 44.0 μmol), and a 1 M aqueous sodium carbonate solution
15 (3.0 ml) were added thereto. This solution was degassed under reduced pressure, and purged with argon gas. Then, the solution was stirred at 80°C for 3 hours. After the stirring, the solvent was removed by distillation, and the obtained residue was suspended in methanol (3.0 ml). The suspension was filtered,
20 and the solvent was removed by distillation from the obtained residue. To this residue, tetrahydrofuran (4.0 ml), water (1.0 ml), and a 2 N aqueous sodium hydroxide solution (2.0 ml) were added, followed by stirring at 60°C for 3 hours. After the reaction liquid was concentrated under reduced pressure,
25 purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (85.0

mg, 0.210 mmol, 48%) of the title compound.

MS (ESI) m/z 405 (M+H)⁺

Example 33: Synthesis of M-33

2,6-Difluoro-4-({[4-(6-methylpyridin-3-yl)phenyl]sulfonyl}a
5 mino)benzoic Acid (M-33)



·TFA

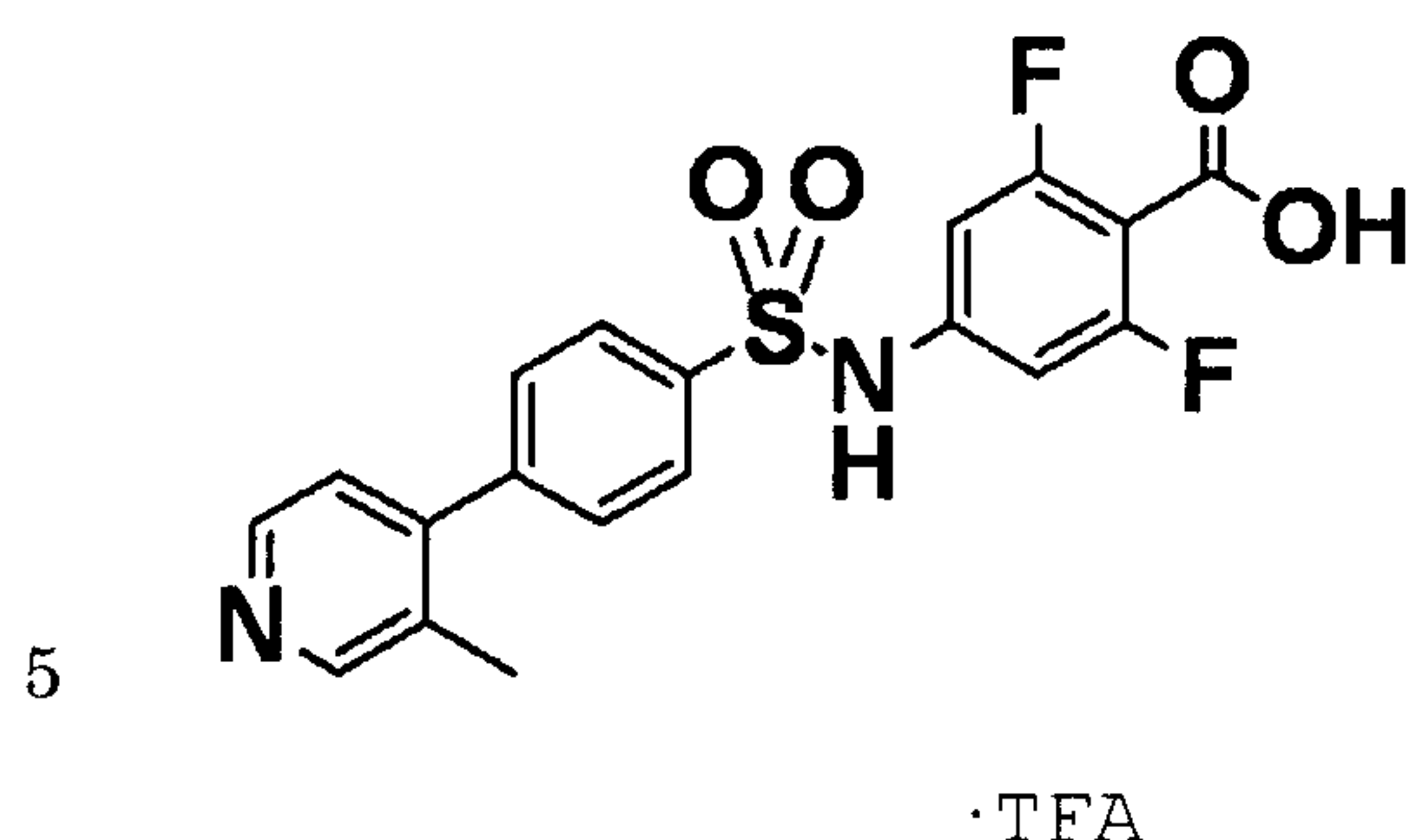
Methyl

4-{[(4-bromophenyl)sulfonyl]amino}-2,6-difluorobenzoate
10 (150 mg, 0.371 mmol) was dissolved in 1,4-dioxane (9.0 ml), and
2-picoline-5-boronic acid (120 mg, 0.777 mmol),
[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
(30.0 mg, 40.0 μ mol), and a 1 M aqueous sodium carbonate solution
(3.0 ml) were added thereto. This solution was degassed under
15 reduced pressure, and purged with argon gas, followed by
stirring at 80°C for 3 hours. After the stirring, the solvent
was removed by distillation, and the obtained residue was
suspended in methanol (3.0 ml). The suspension was filtered,
and the solvent was removed by distillation from the obtained
20 residue. To this residue, tetrahydrofuran (4.0 ml), water (1.0
ml), and a 2 N aqueous sodium hydroxide solution (2.0 ml) were
added, followed by stirring at 60°C for 3 hours. After the
reaction liquid was concentrated, purification was conducted
by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system)
25 to obtain the TFA salt (112 mg, 0.277 mmol, 75%) of the title
compound.

MS (ESI) m/z 405 (M+H)⁺

Example 34: Synthesis of M-34

2,6-Difluoro-4-({[4-(3-methylpyridin-4-yl)phenyl]sulfonyl}amino)benzoic Acid (M-34)



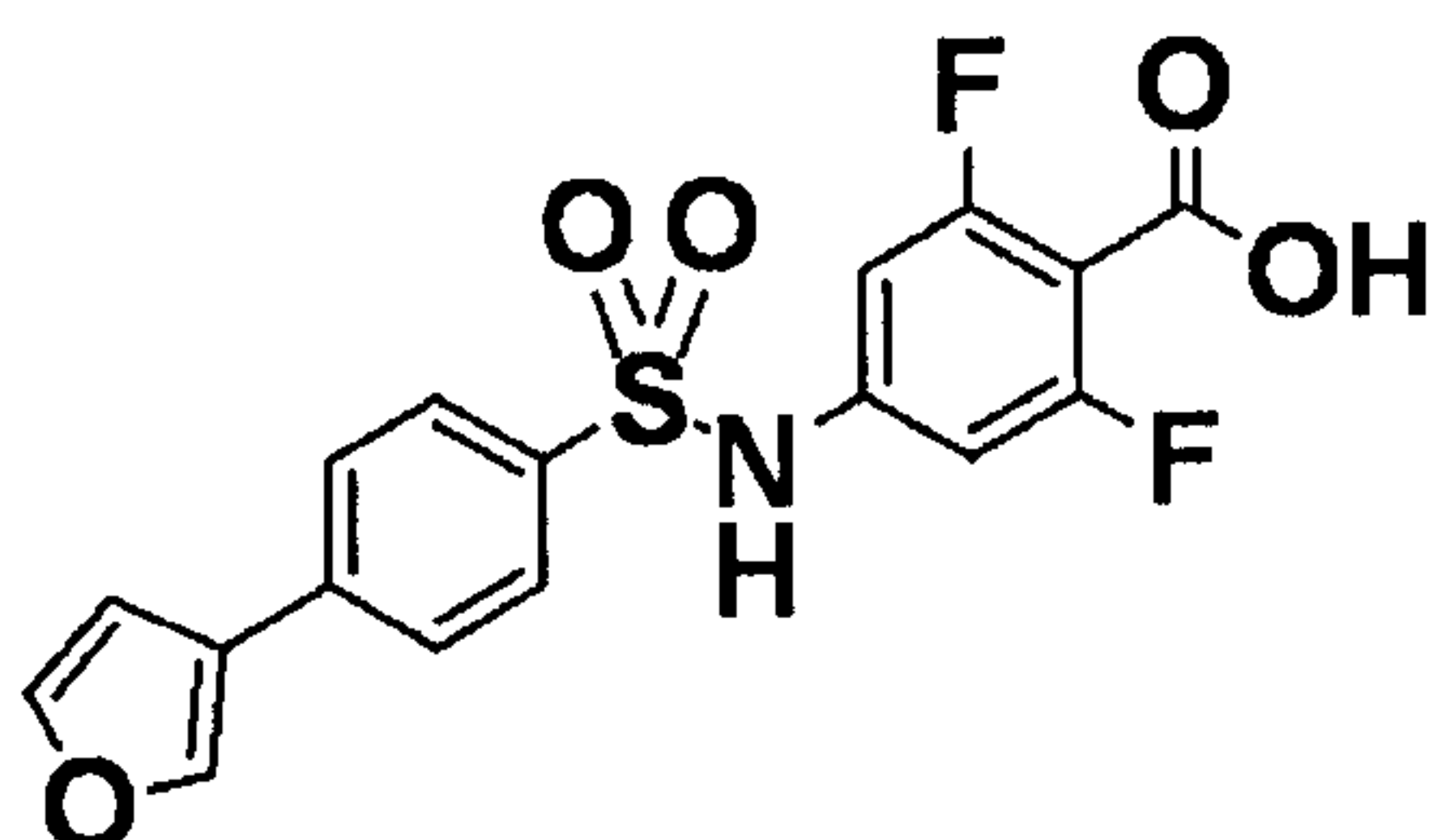
Methyl

4-{{[4-bromophenyl]sulfonyl}amino}-2,6-difluorobenzoate (40.0 mg, 0.100 mmol) was dissolved in 1,4-dioxane (4.0 ml), and 3-picoline-4-boronic acid (30.0 mg, 0.219 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (7.30 mg, 10.0 μmol), and a 1 M aqueous sodium carbonate solution (1.0 ml) were added thereto. This solution was degassed under reduced pressure, and purged with argon gas, followed by stirring at 80°C for 3 hours. After the stirring, the solvent was removed by distillation from the reaction solution, and the obtained residue was suspended in methanol (3.0 ml). The suspension was filtered, and the solvent was removed by distillation from the obtained residue. To this residue, tetrahydrofuran (2.0 ml), water (0.5 ml), and a 2 N aqueous sodium hydroxide solution (1.0 ml) were added, followed by stirring at 50°C for 3 hours. After the reaction liquid was concentrated, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (22.0 mg, 54.5 μmol, 55%) of the title compound.

MS (ESI) m/z 405 (M+H)⁺

Example 35: Synthesis of M-35

2,6-Difluoro-4-({[4-(3-furyl)phenyl]sulfonyl}amino)benzoic
Acid (M-35)



5

Methyl

4-{{[4-(3-furyl)phenyl]sulfonyl}amino}-2,6-difluorobenzoate
 (150 mg, 0.372 mmol) was dissolved in 1,4-dioxane (15 ml), and
 2-(furan-3-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (158
 mg, 0.814 mmol),
 10 [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
 (27.0 mg, 40.0 μ mol), and a 1 M aqueous sodium carbonate solution
 (5.0 ml) were added thereto. This solution was degassed under
 reduced pressure, and purged with argon gas, followed by
 stirring at 85°C for 3 hours. After the stirring, the solvent
 15 was removed by distillation, and the obtained residue was
 suspended in methanol (3.0 ml). The suspension was filtered,
 and the solvent was removed by distillation from the obtained
 residue. To this residue, tetrahydrofuran (4.0 ml), water (1.0
 ml), and a 2 N aqueous sodium hydroxide solution (2.0 ml) were
 20 added, followed by stirring at 60°C for 3 hours. After the
 reaction liquid was concentrated, purification was conducted
 by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system)
 to obtain the title compound (100 mg, 0.264 mmol, 71%).

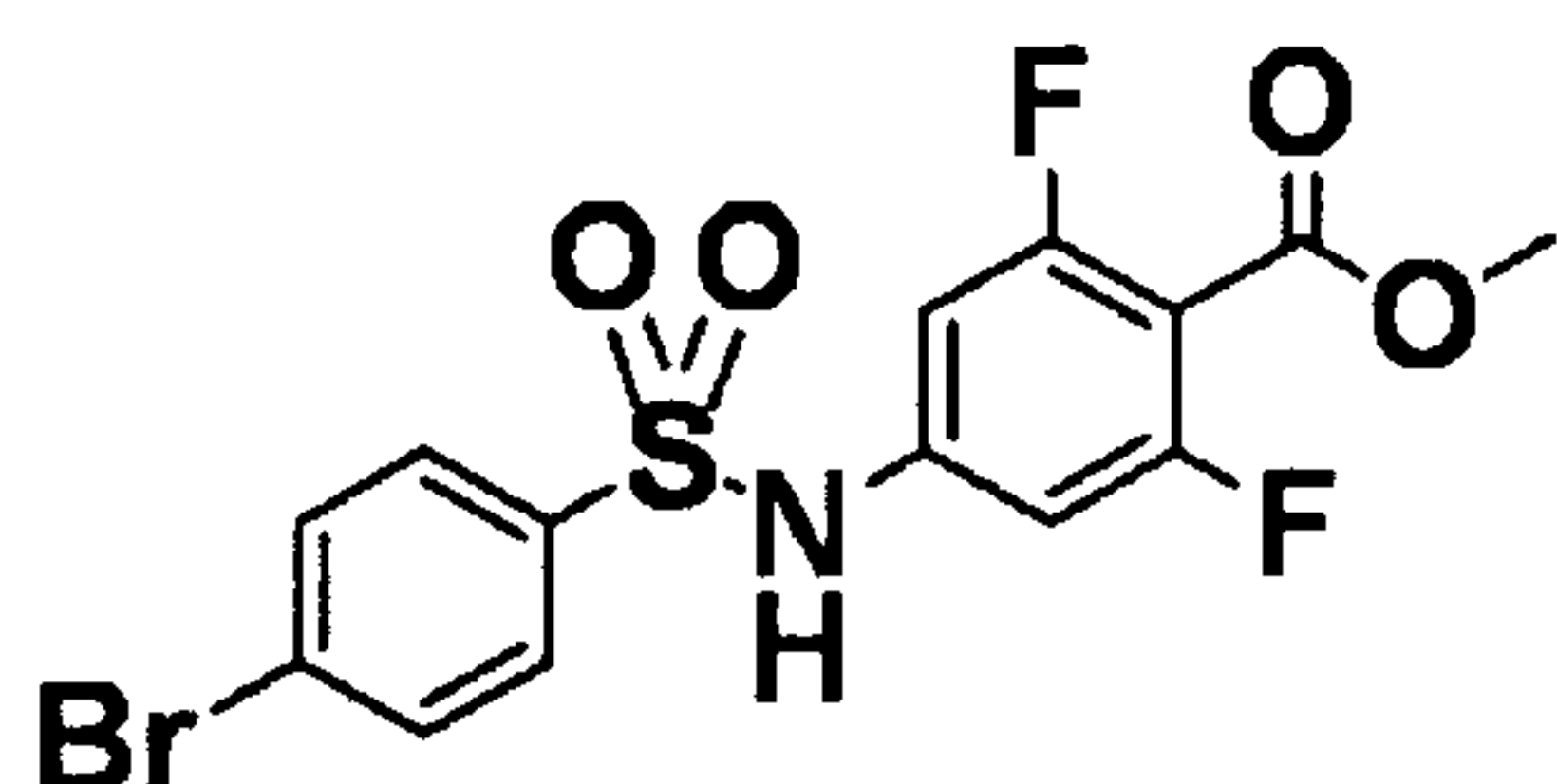
MS (ESI) m/z 380 (M+H)⁺

25 Example 36: Synthesis of M-36

(Step

1)

Methyl

4-{[(4-Bromophenyl)sulfonyl]amino}-2,6-difluorobenzoate

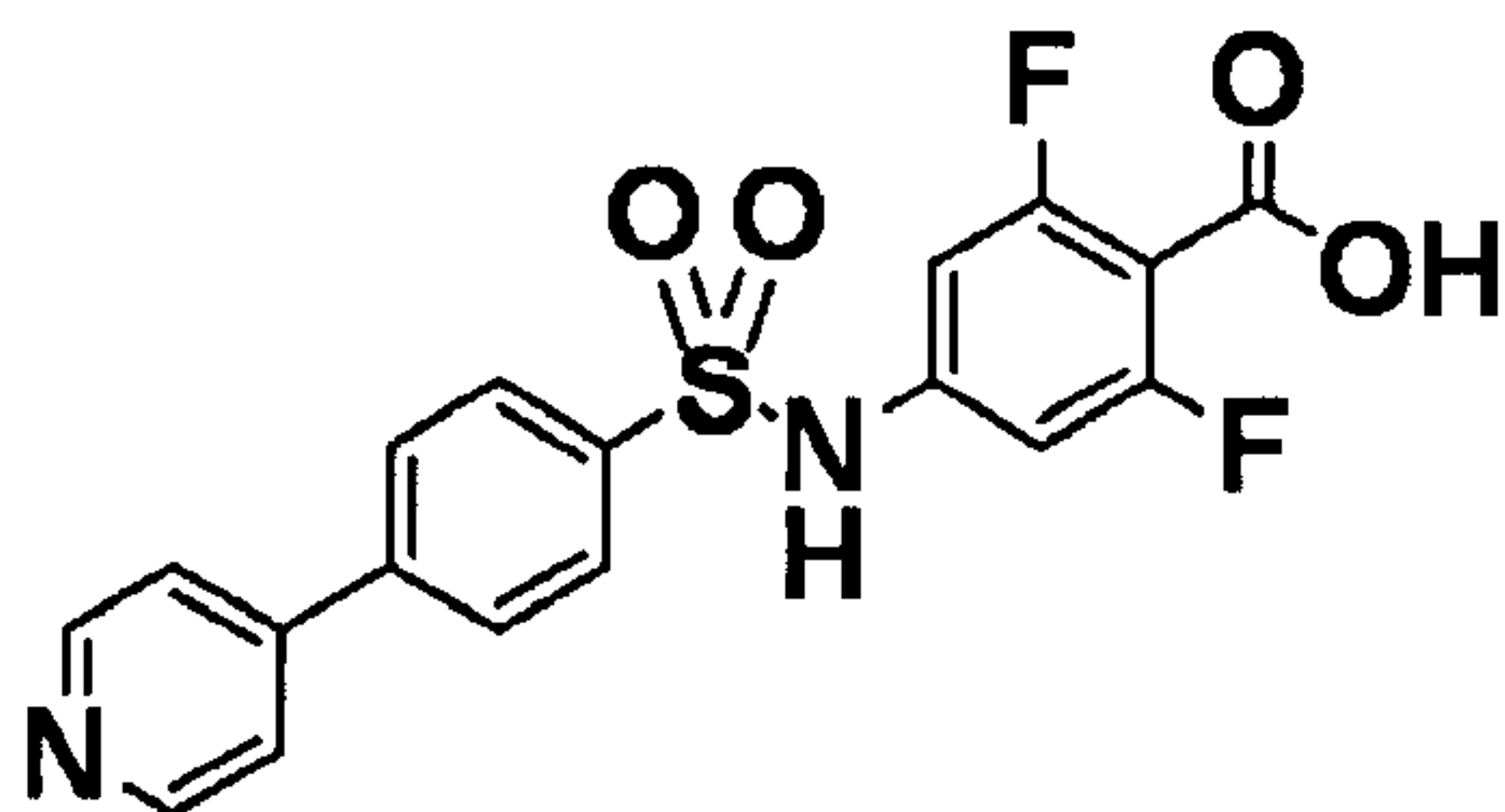
Methyl 4-amino-2,6-difluorobenzoate (5.00 g, 26.7 mmol) was dissolved in dichloromethane (100 ml), and
 5 p-bromobenzenesulfonyl chloride (7.50 g, 29.4 mmol) and pyridine (6.5 ml, 80 mmol) were added, followed by stirring at room temperature for 12 hours. The reaction solution was concentrated under reduced pressure, and purification was conducted by silica gel column chromatography
 10 (dichloromethane/methanol=95:5) to obtain the title compound (8.50 g, 21.0 mmol, 79%).

MS (ESI) m/z 406 (M+H)⁺

(Step

2)

2,6-Difluoro-4-{[(4-pyridin-4-yl-phenyl)sulfonyl]amino}benz
 15 oic Acid (M-36)



·TFA

Methyl

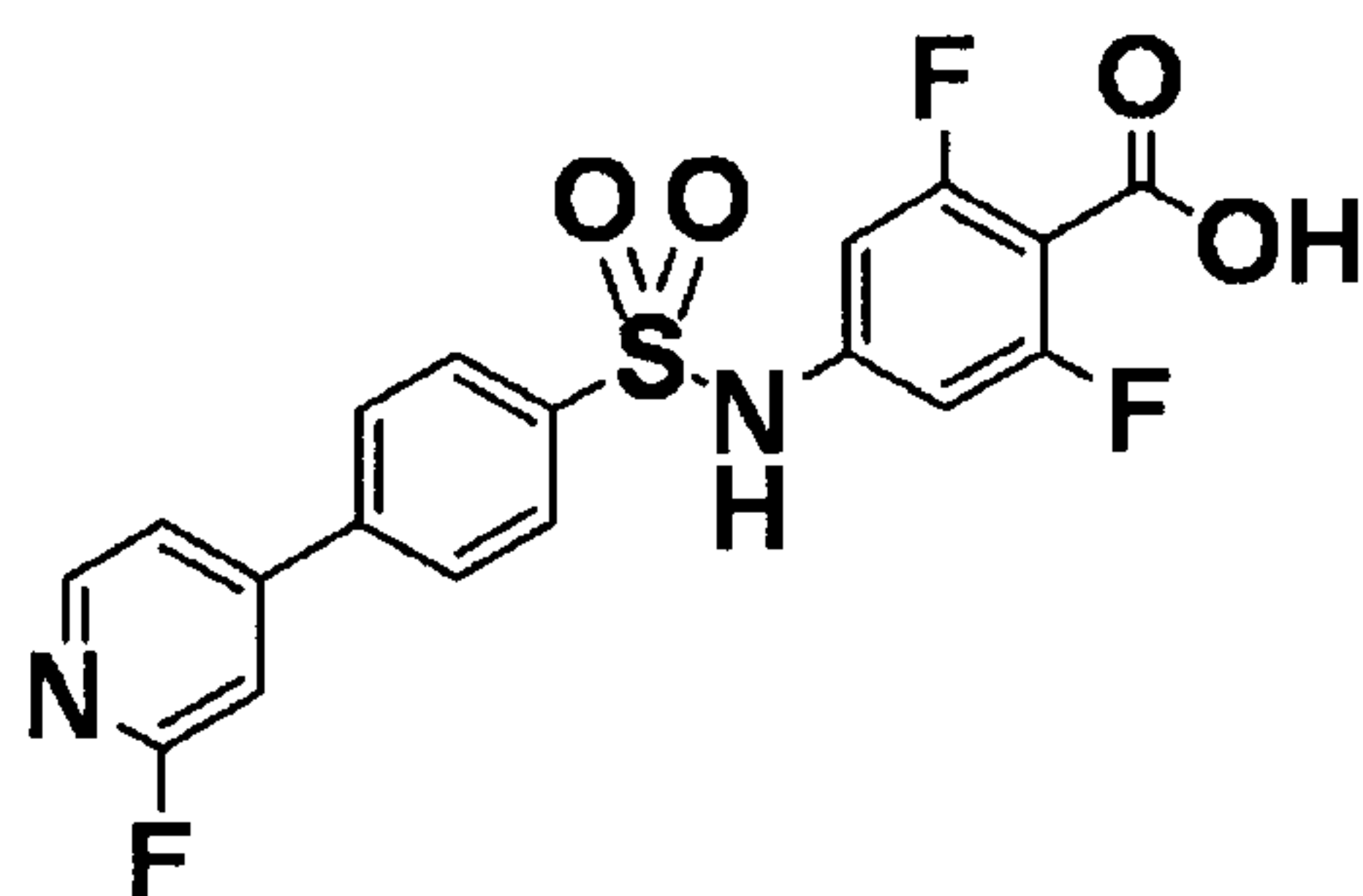
4-{[(4-bromophenyl)sulfonyl]amino}-2,6-difluorobenzoate
 20 (300 mg, 0.743 mmol) was dissolved in 1,4-dioxane (15 ml), and pyridine-4-boronic acid (200 mg, 1.63 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (30.0 mg, 40.0 μmol), and a 1 M aqueous sodium carbonate solution

(5.0 ml) were added. This solution was degassed under reduced pressure, and purged with argon gas, followed by stirring at 85°C for 3 hours. After the stirring, the solvent was removed by distillation, and the obtained residue was suspended in methanol (3.0 ml). The suspension was filtered, and the solvent was removed by distillation from the obtained residue. To this residue, tetrahydrofuran (4.0 ml), water (1.0 ml), and a 2 N aqueous sodium hydroxide solution (2.0 ml) were added, followed by stirring at 60°C for 3 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (182 mg, 0.467 mmol, 63%) of the title compound.

MS (ESI) m/z 391 (M+H)⁺

Example 37: Synthesis of M-37

2,6-Difluoro-4-({[4-(2-fluoropyridin-4-yl)phenyl]sulfonyl}amino)benzoic Acid (M-37)



·TFA

20 Methyl

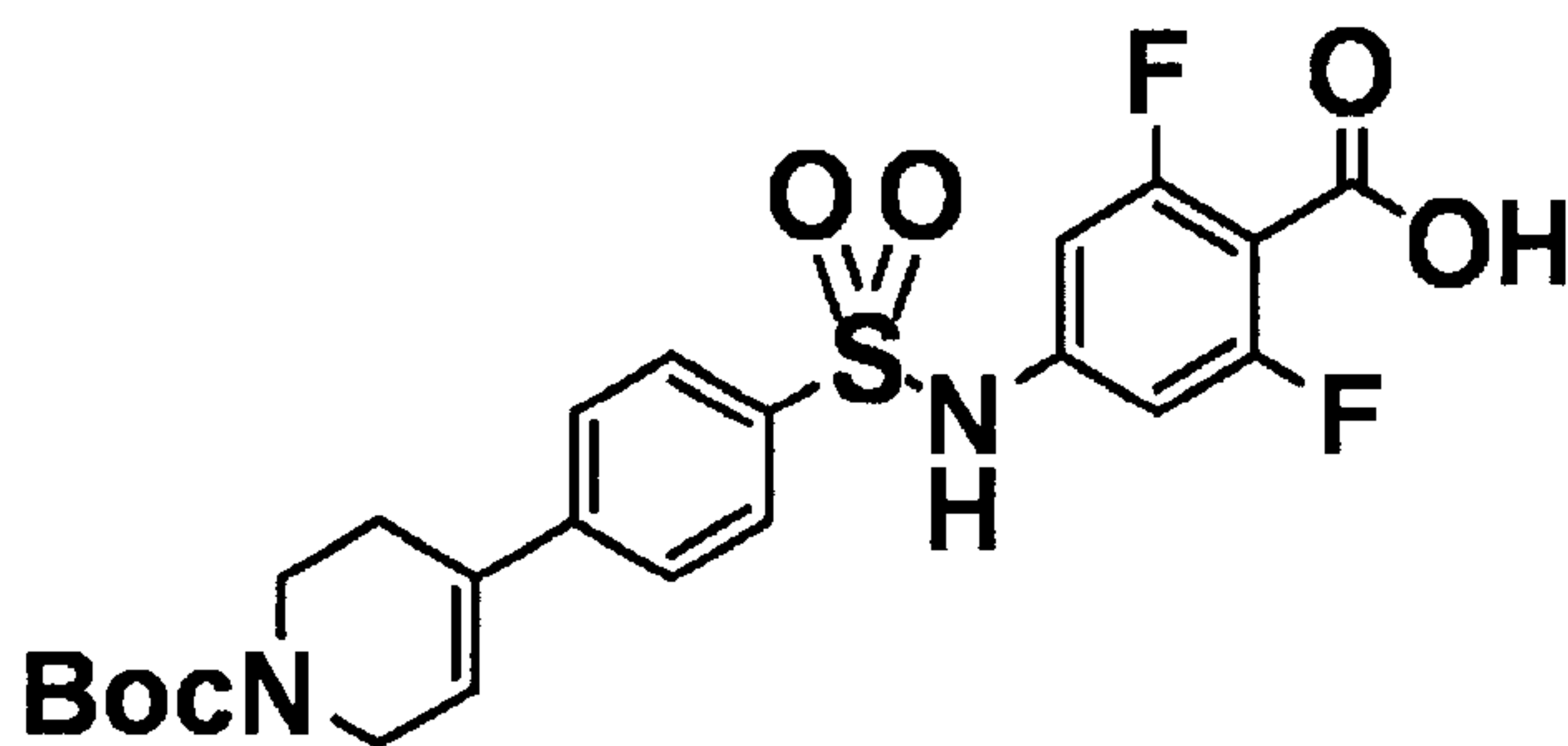
4-{{[4-(2-fluoropyridin-4-yl)phenyl]sulfonyl}amino}-2,6-difluorobenzoate (150 mg, 0.371 mmol) was dissolved in 1,4-dioxane (9.0 ml), and 2-fluoropyridine-4-boronic acid (110 mg, 0.777 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (30.0 mg, 40.0 μmol), and a 1 M aqueous sodium carbonate solution

(3.0 ml) were added thereto. This solution was degassed under reduced pressure, and purged with argon gas, followed by stirring at 80°C for 3 hours. After the stirring, the solvent was removed by distillation, and the obtained residue was suspended in methanol (3.0 ml). The suspension was filtered, and the solvent was removed by distillation from the obtained residue. To this residue, tetrahydrofuran (4.0 ml), water (1.0 ml), and a 2 N aqueous sodium hydroxide solution (2.0 ml) were added, followed by stirring at 50°C for 3 hours. After the reaction liquid was concentrated, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (114 mg, 0.279 mmol, 75%) of the title compound.

MS (ESI) m/z 409 (M+H)⁺

Example 38: Synthesis of M-38

4-[(4-[1-(tert-Butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]phenyl)sulfonyl]amino]-2,6-difluorobenzoic Acid (M-38)



Methyl

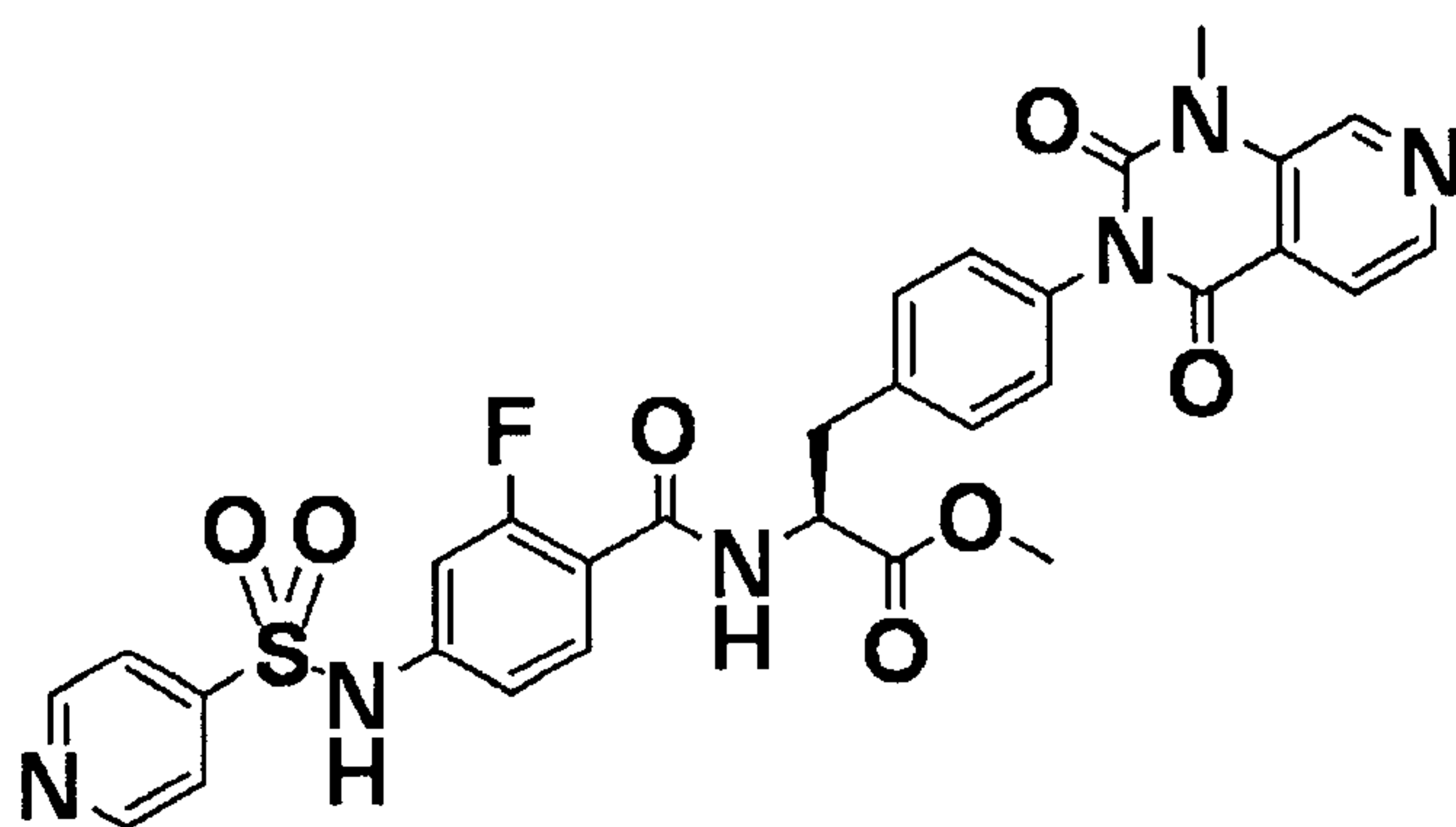
4-[(4-bromophenyl)sulfonyl]amino]-2,6-difluorobenzoate (150 mg, 0.371 mmol) was dissolved in 1,4-dioxane (9.0 ml), and 2-fluoropyridine-4-boronic acid (110 mg, 0.777 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (30.0 mg, 40.0 μmol), and a 1 M aqueous sodium carbonate solution (3.0 ml) were added thereto. This solution was degassed under

reduced pressure, and purged with argon gas, followed by stirring at 80°C for 3 hours. After the stirring, the solvent was removed by distillation, and the obtained residue was suspended in methanol (3.0 ml). The suspension was filtered, and the solvent was removed by distillation from the obtained residue. To this residue, tetrahydrofuran (4.0 ml), water (1.0 ml), and a 2 N aqueous sodium hydroxide solution (2.0 ml) were added, followed by stirring at 50°C for 3 hours. After the reaction liquid was concentrated, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the title compound (102 mg, 0.206 mmol, 56%).

MS (ESI) m/z 495 (M+H)⁺

Example 39: Synthesis of A-1 and B-1

(Step 1) Methyl N-{2-Fluoro-4-[(pyridin-4-yl-sulfonyl)amino]benzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-1)



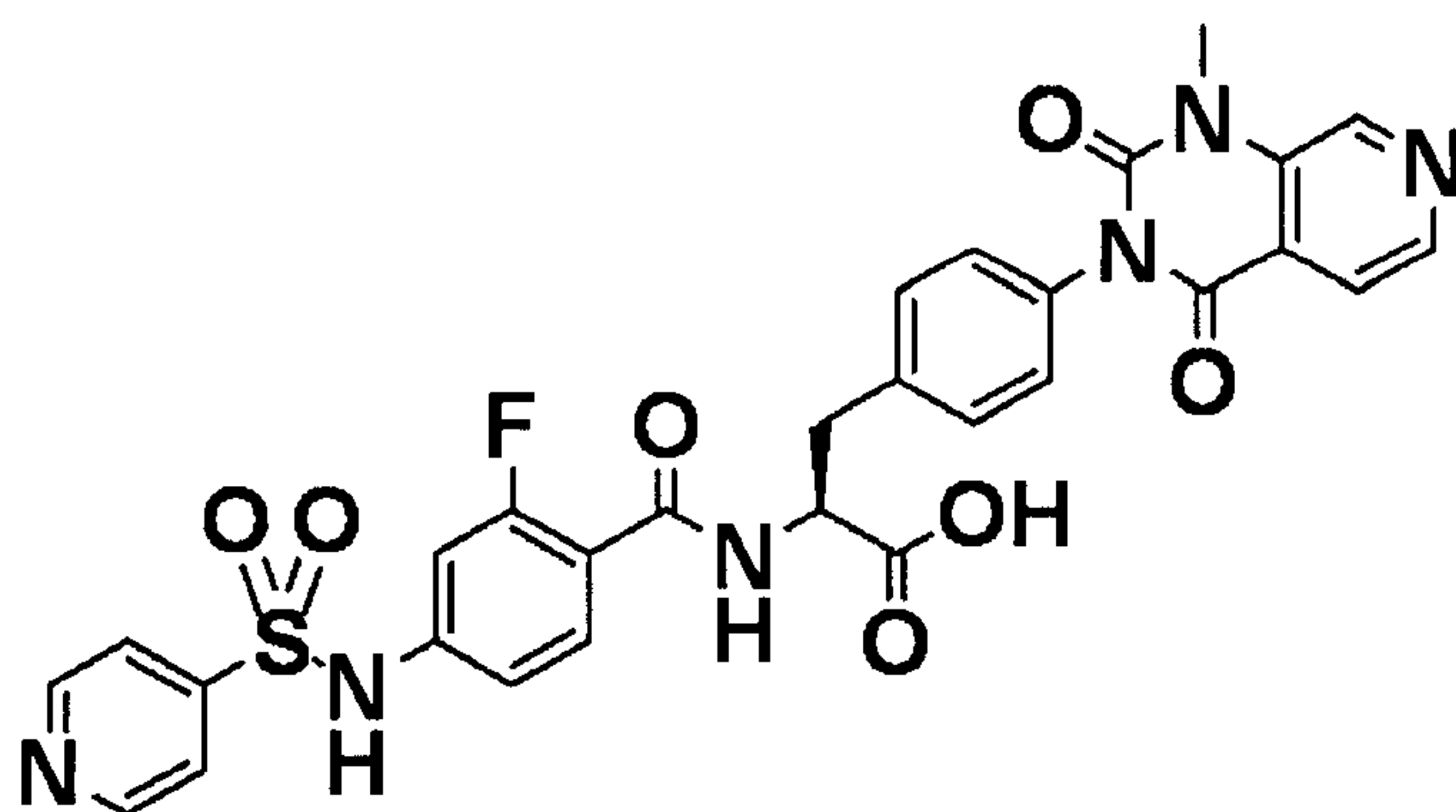
·2TFA

Methyl 4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (M-1) (100 mg, 0.234 mmol) and 2-fluoro-4-[(pyridin-4-yl-sulfonyl)amino]benzoic acid (M-6) (69.0 mg, 0.234 mmol) were suspended in methylene chloride (2.0

ml), and HATU (131 mg, 0.351 mmol) and diisopropylethylamine (0.160 ml, 0.920 mmol) were added thereto, followed by stirring at room temperature for 12 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (120 mg, 61%) of the title compound.

¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 8.97 (s, 1H), 8.86 (dd, J = 4.4, 1.6 Hz, 2H), 8.63 (dd, J = 7.6, 2.0 Hz, 1H), 8.56 (d, J = 4.8 Hz, 1H), 7.89 (dd, J = 4.8, 0.4 Hz, 1H), 7.76 (dd, J = 4.8, 1.6 Hz, 2H), 7.41 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.01-6.95 (m, 2H), 4.69-4.63 (m, 1H), 3.65 (s, 3H), 3.60 (s, 3H), 3.22-3.06 (m, 2H).; MS (ESI) m/z 633 (M+H)⁺

(Step 2)
N-{2-Fluoro-4-[(pyridin-4-yl-sulfonyl)amino]benzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-1)



20 ·2TFA

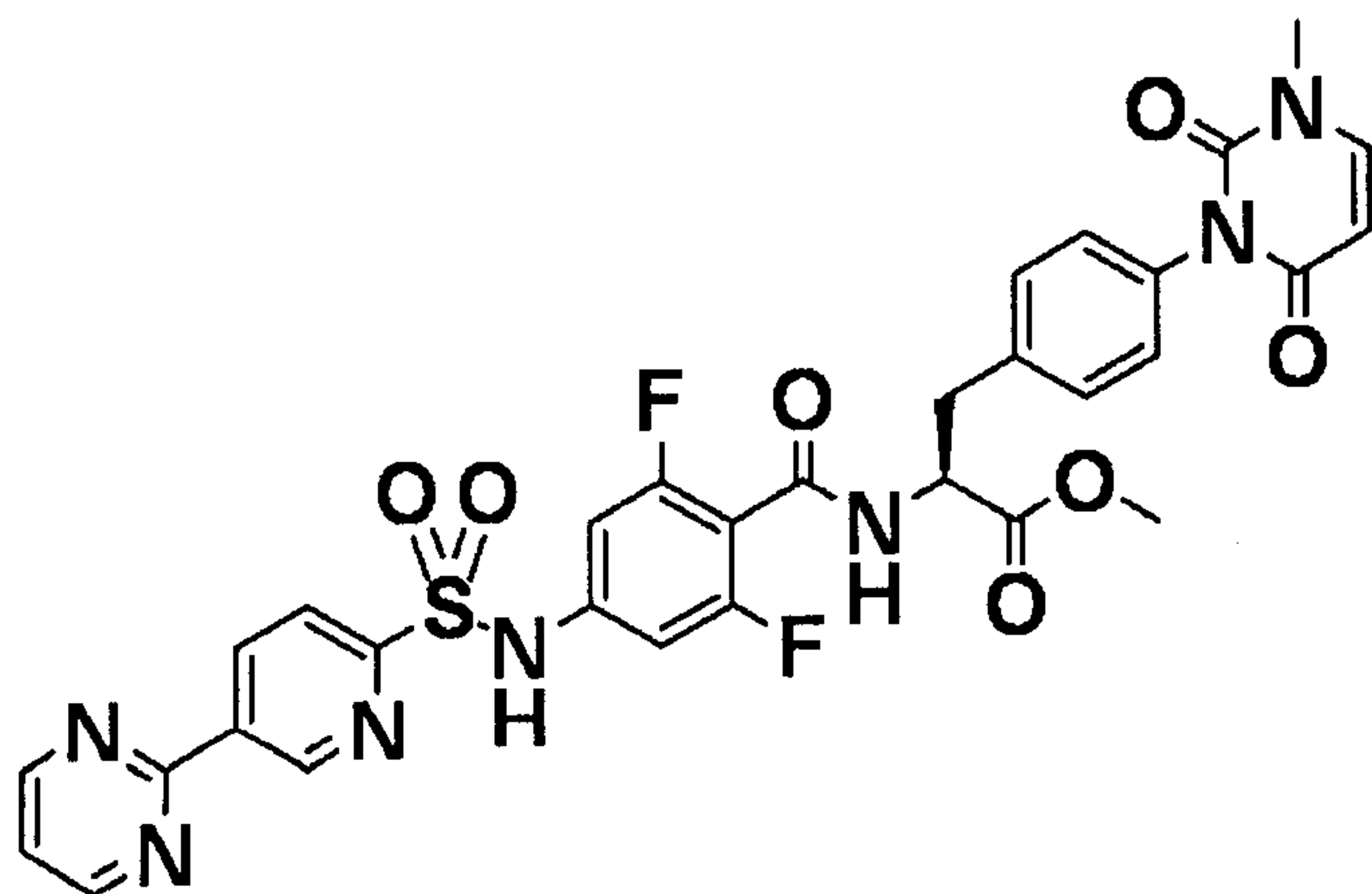
To the TFA salt (60.0 mg, 70.0 μmol) of methyl N-{2-fluoro-4-[(pyridin-4-yl-sulfonyl)amino]benzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-1), a 4 N hydrogen chloride/dioxane

solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (45 mg, 76%) of the title compound.

¹H NMR (d-DMSO, 400 MHz): δ 11.1 (s, 1H), 8.90 (s, 1H), 8.79 (d, J = 6.0 Hz, 2H), 8.49 (d, J = 5.2 Hz, 1H), 8.38 (d, J = 5.6 Hz, 1H), 7.82 (d, J = 5.2 Hz, 1H), 7.69 (d, J = 6.0 Hz, 2H), 7.36 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 6.94-6.88 (m, 2H), 4.57-4.52 (m, 1H), 3.53 (s, 3H), 3.17-3.00 (m, 2H).; MS (ESI) m/z 619 (M+H)⁺

Example 40: synthesis of A-2 and B-2

(Step 1) Methyl N-(2,6-Difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (B-2)



·2TFA

Methyl

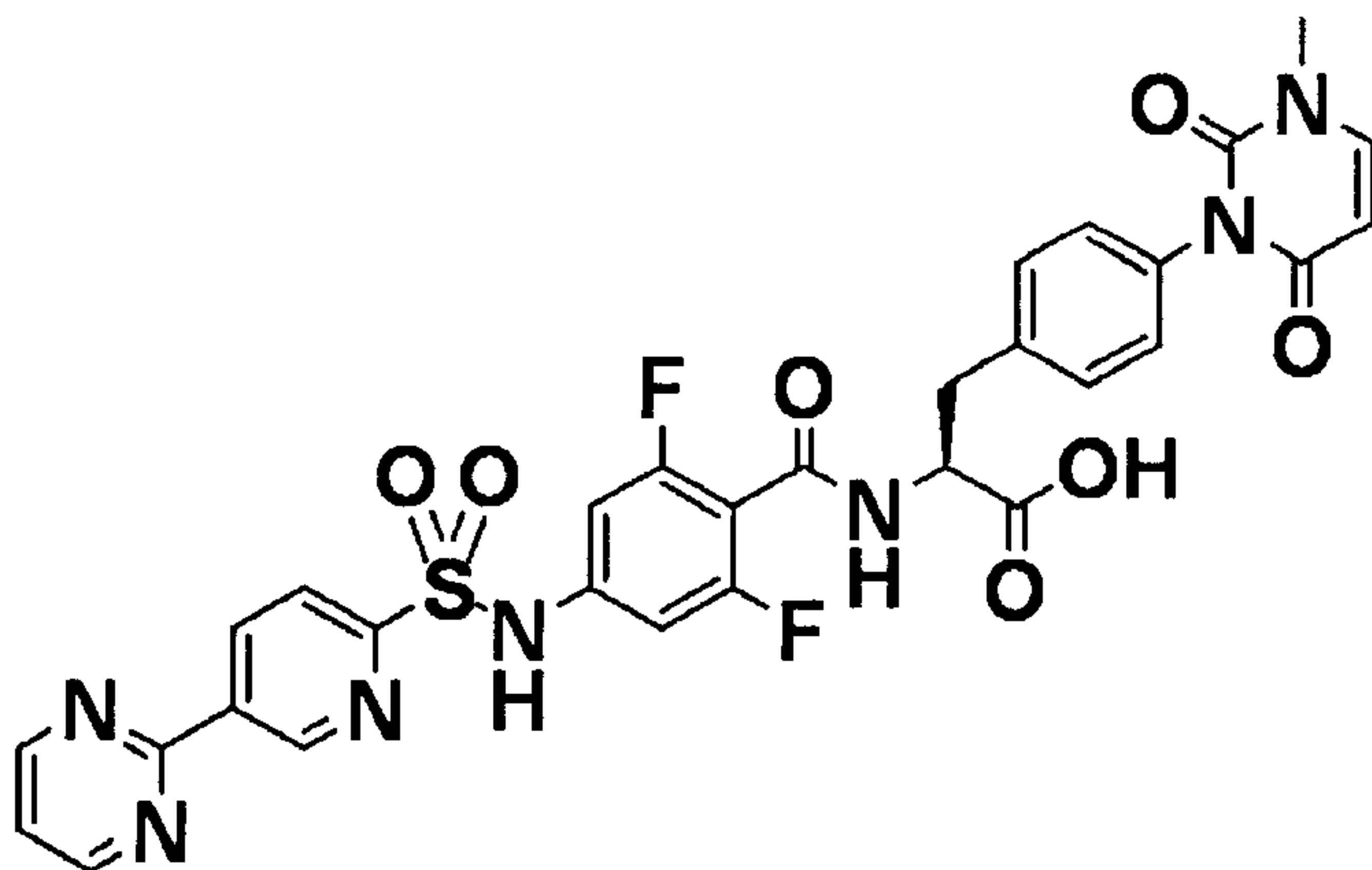
4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (M-2) (80 mg, 0.24 mmol) and 2,6-difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl]amino}benzoic acid (M-7) (103 mg, 0.240 mmol) were suspended in

methylene chloride (2.0 ml), and HATU (137 mg, 0.360 mmol) and diisopropylethylamine (0.167 ml, 0.96 mmol) were added thereto, followed by stirring at room temperature for 2 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (80 mg, 37%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.4 (s, 1H), 9.58 (dd, J = 2.4, 0.8 Hz, 1H), 9.16 (d, J = 7.6 Hz, 1H), 9.01 (d, J = 4.8 Hz, 2H), 8.95 (dd, J = 8.0, 2.0 Hz, 1H), 8.28 (dd, J = 8.4, 0.8 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 4.8 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 9.2 Hz, 2H), 5.74 (d, J = 7.6 Hz, 1H), 4.62-4.57 (m, 1H), 3.62 (s, 3H), 3.30 (s, 3H), 3.14-2.97 (m, 2H).; MS (ESI) m/z 678 (M+H)⁺

(Step 2)

N-(2,6-Difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-2)



20 ·2TFA

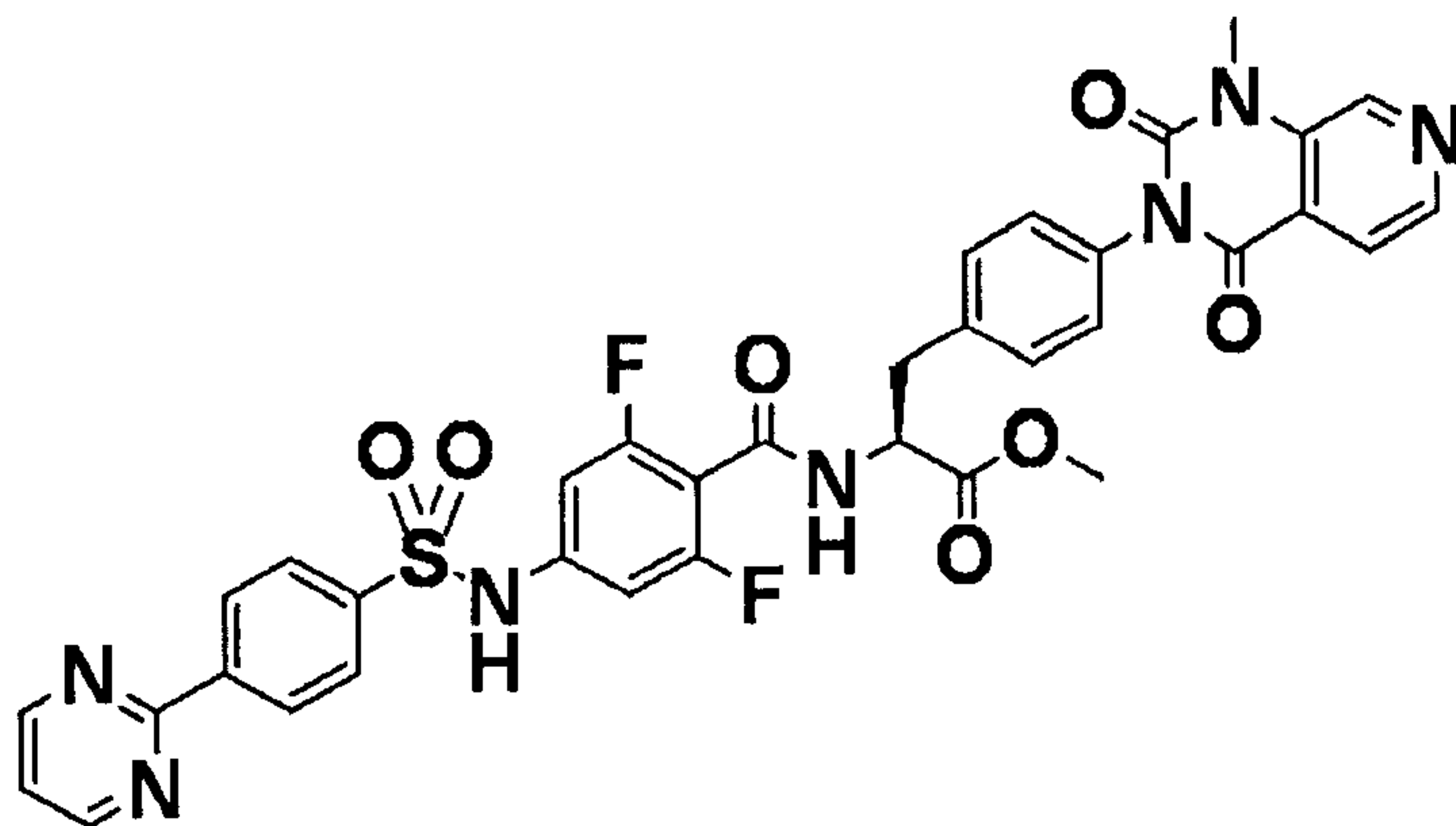
To the TFA salt (60.0 mg, 66.0 μmol) of methyl N-(2,6-difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-

1 (2H)-yl)-L-phenylalaninate (B-2), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification
 5 was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (42.3 mg, 72%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.46 (s, 1H), 9.64 (dd, J = 2.1, 0.7 Hz, 1H), 9.09 (d, J = 8.0 Hz, 1H), 9.06 (d, J = 4.9 Hz, 2H),
 10 9.01 (dd, J = 8.2, 2.1 Hz, 1H), 8.33 (dd, J = 8.2, 0.7 Hz, 1H), 7.81 (d, J = 7.9 Hz, 1H), 7.66 (t, J = 4.9 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.94 (d, J = 9.2 Hz, 2H), 5.80 (d, J = 7.9 Hz, 1H), 4.68-4.55 (m, 1H), 3.36 (s, 3H), 3.19 (dd, J = 14.2, 4.6 Hz, 1H), 3.02 (dd, J = 14.2, 9.7 Hz,
 15 1H).; MS (ESI) m/z 664 (M+H)⁺

Example 41: Synthesis of A-3 and B-3

(Step 1) Methyl
N-(2,6-Difluoro-4-{[(4-pyrimidin-2-yl-phenyl)sulfonyl]amino}
}benzoyl)-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyr
 20 imidin-3(2H)-yl)-L-phenylalaninate (B-3)



·2TFA

Methyl

4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2

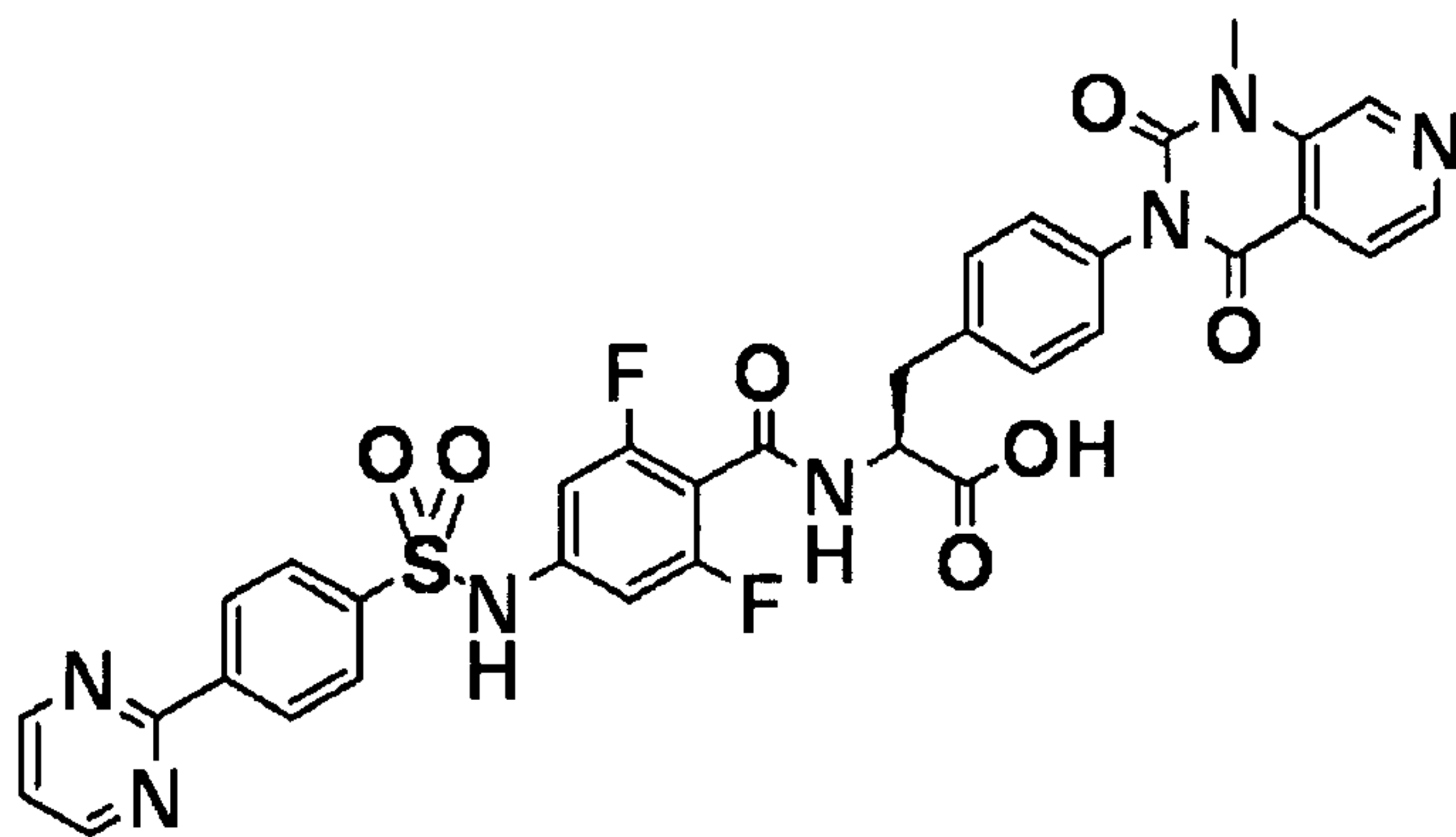
H)-yl)-L-phenylalaninate (M-1) (100 mg, 0.234 mmol) and 2,6-difluoro-4-{[(4-pyrimidin-2-yl-phenyl)sulfonyl]amino}benzoic acid (M-8) (90.0 mg, 0.230 mmol) were suspended in methylene chloride (2.0 ml), and HATU (133 mg, 0.351 mmol) and diisopropylethylamine (0.160 ml, 0.920 mmol) were added thereto, followed by stirring at room temperature for 12 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (100 mg, 45%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.16 (d, J = 7.6 Hz, 1H), 8.97 (s, 2H), 8.95 (s, 1H), 8.59-8.02 (m, 3H), 8.03 (dd, J = 6.8, 1.6 Hz, 2H), 7.88 (d, J = 4.4 Hz, 1H), 7.54 (t, J = 4.8 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.65-4.59 (m, 1H), 3.63 (s, 3H), 3.59 (s, 3H), 3.17-2.98 (m, 2H).; MS (ESI) m/z 728 (M+H)⁺

(Step

2)

N-(2,6-Difluoro-4-{[(4-pyrimidin-2-yl-phenyl)sulfonyl]amino}benzoyl)-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-3)



·2TFA

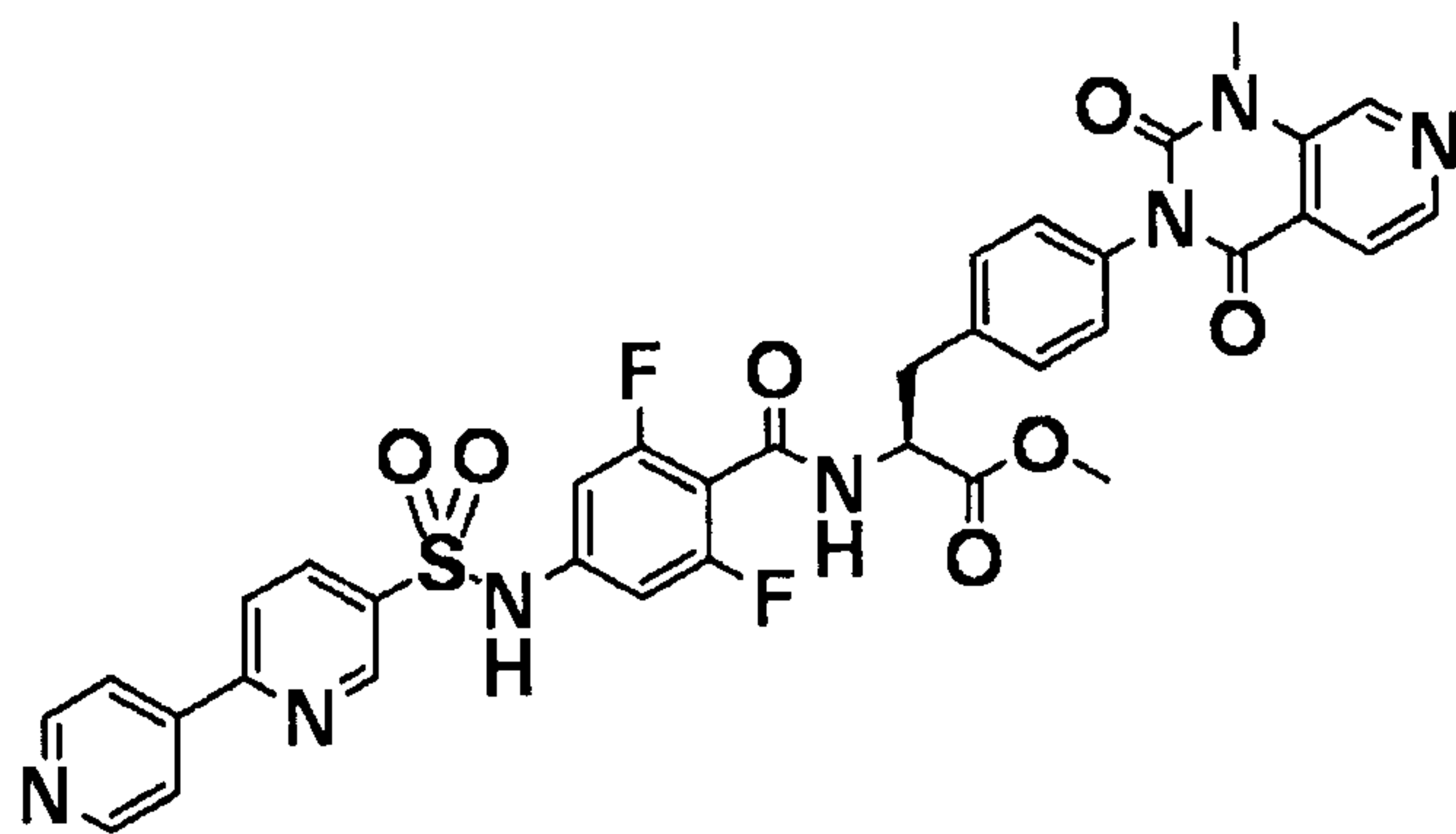
To the TFA salt (80 mg, 84 μmol) of methyl N-(2,6-difluoro-4-{[(4-pyrimidin-2-yl-phenyl)sulfonyl]amino

}benzoyl)-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-3), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (52.7 mg, 67%) of the title compound.

¹H NMR (d-DMSO, 400 MHz): δ 11.18 (s, 1H), 9.03 (d, J = 7.9 Hz, 1H), 8.96 (d, J = 4.9 Hz, 3H), 8.61-8.53 (m, 3H), 8.06-7.99 (m, 2H), 7.88 (dd, J = 5.0, 0.6 Hz, 1H), 7.54 (t, J = 4.9 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 9.1 Hz, 2H), 4.70-4.28 (m, 1H), 3.59 (s, 3H), 3.16 (dd, J = 14.0, 4.7 Hz, 1H), 2.98 (dd, J = 14.2, 9.8 Hz, 1H).; MS (ESI) m/z 714 (M+H)⁺

Example 42: Synthesis of A-4 and B-4

(Step 1) Methyl N-{4-[(2,4'-Bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-4)



·3TFA

Methyl

4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2

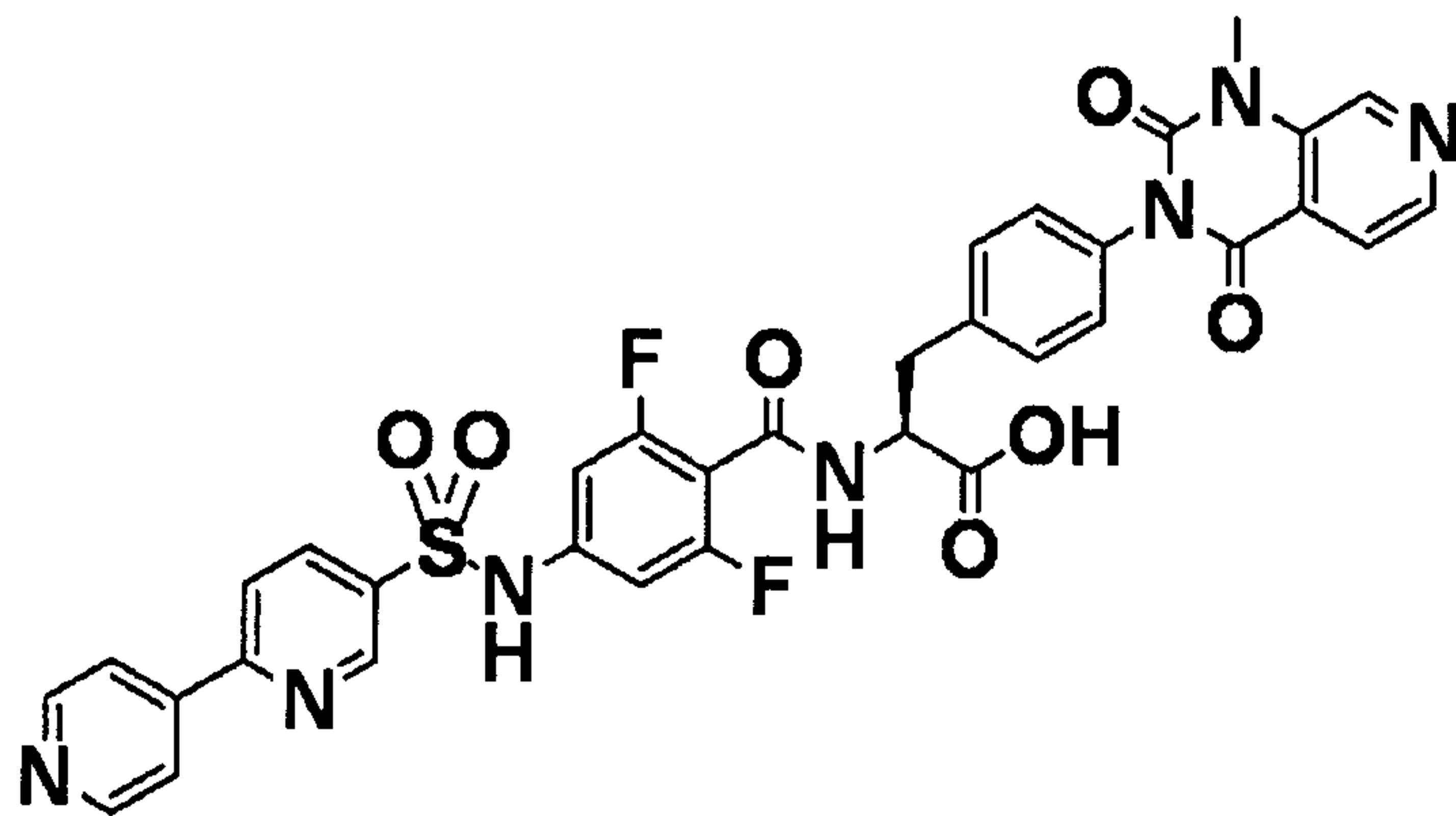
H)-yl)-L-phenylalaninate (M-1) (100 mg, 0.234 mmol) and 4-[(2,4'-bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoic acid (M-9) (90.0 mg, 0.230 mmol) were suspended in methylene chloride (1.0 ml), and HATU (133 mg, 0.351 mmol) and diisopropylethylamine (0.160 ml, 0.920 mmol) were added thereto, followed by stirring at room temperature for 2 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (105 mg, 43%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.5 (s, 1H), 9.27-9.24 (m, 2H), 9.03 (s, 1H), 8.90 (dd, J = 4.8, 1.6 Hz, 2H), 8.62 (d, J = 4.8 Hz, 1H), 8.52-8.46 (m, 2H), 8.30 (dd, J = 4.8, 1.2 Hz, 2H), 7.94 (dd, J = 4.8, 0.4 Hz, 1H), 7.40 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 4.72-4.67 (m, 1H), 3.70 (s, 3H), 3.65 (s, 3H), 3.23-3.01 (m, 2H).; MS (ESI) m/z 728 (M+H)⁺

(Step

2)

N-{4-[(2,4'-Bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-4)



·3TFA

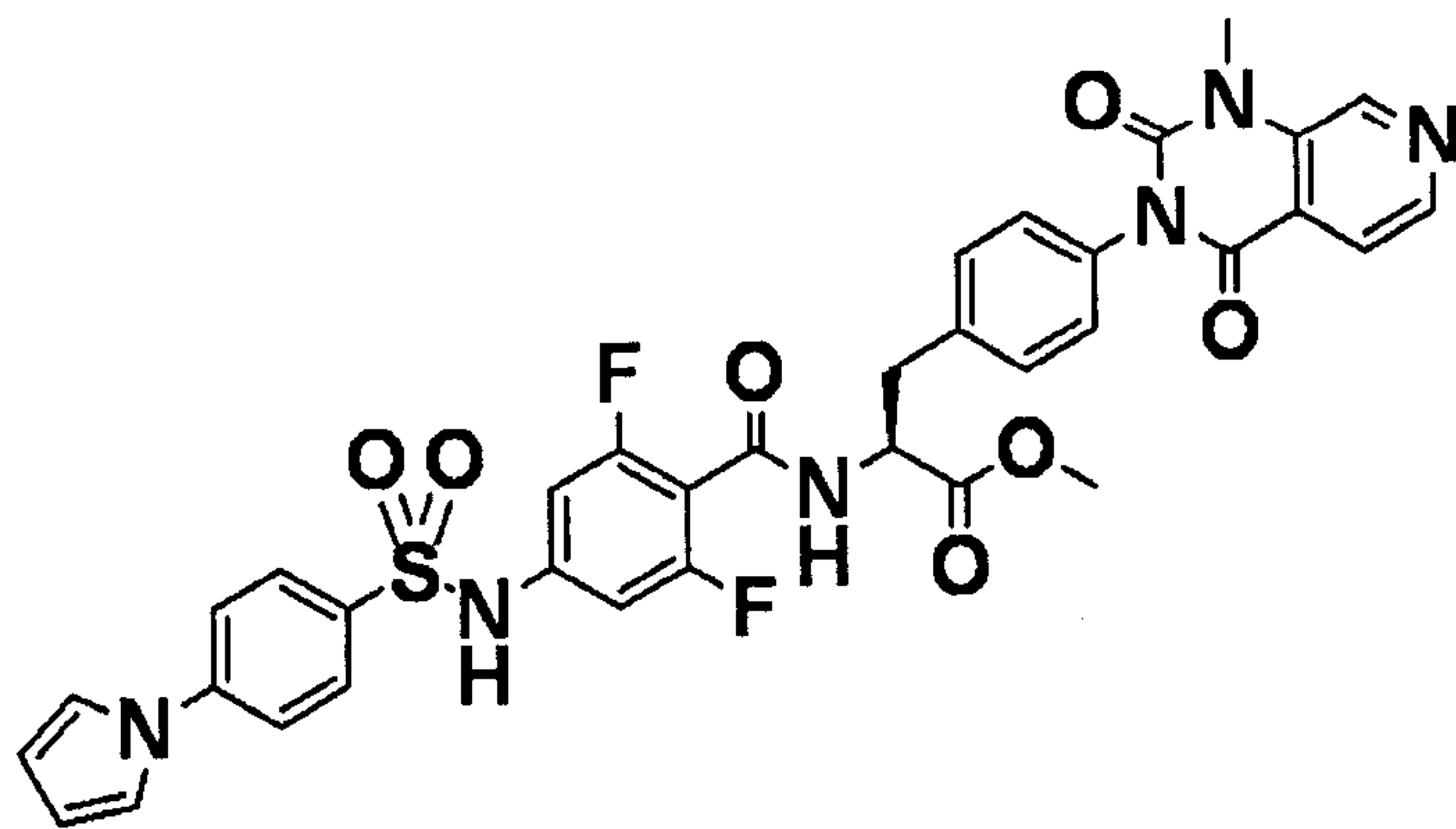
To the TFA salt (85 mg, 79 μmol) of methyl

N-{4-[(2,4'-bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-4), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (51.5 mg, 62%) of the title compound.

¹H NMR (d-DMSO, 400 MHz): δ 11.34 (s, 1H), 9.16-9.06 (m, 1H), 9.00 (d, J = 7.9 Hz, 1H), 8.90 (s, 1H), 8.81-8.70 (m, 2H), 8.49 (d, J = 4.9 Hz, 1H), 8.42-8.29 (m, 2H), 8.25-8.09 (m, 2H), 7.81 (d, J = 5.0 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 4.58-4.43 (m, 1H), 3.53 (s, 3H), 3.10 (dd, J = 14.2, 4.4 Hz, 1H), 2.92 (dd, J = 14.2, 9.8 Hz, 1H).; MS (ESI) m/z 714 (M+H)⁺

Example 43: Synthesis of A-5 and B-5

(Step 1) Methyl N-[2,6-difluoro-4-({[4-(1H-pyrrol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-5)



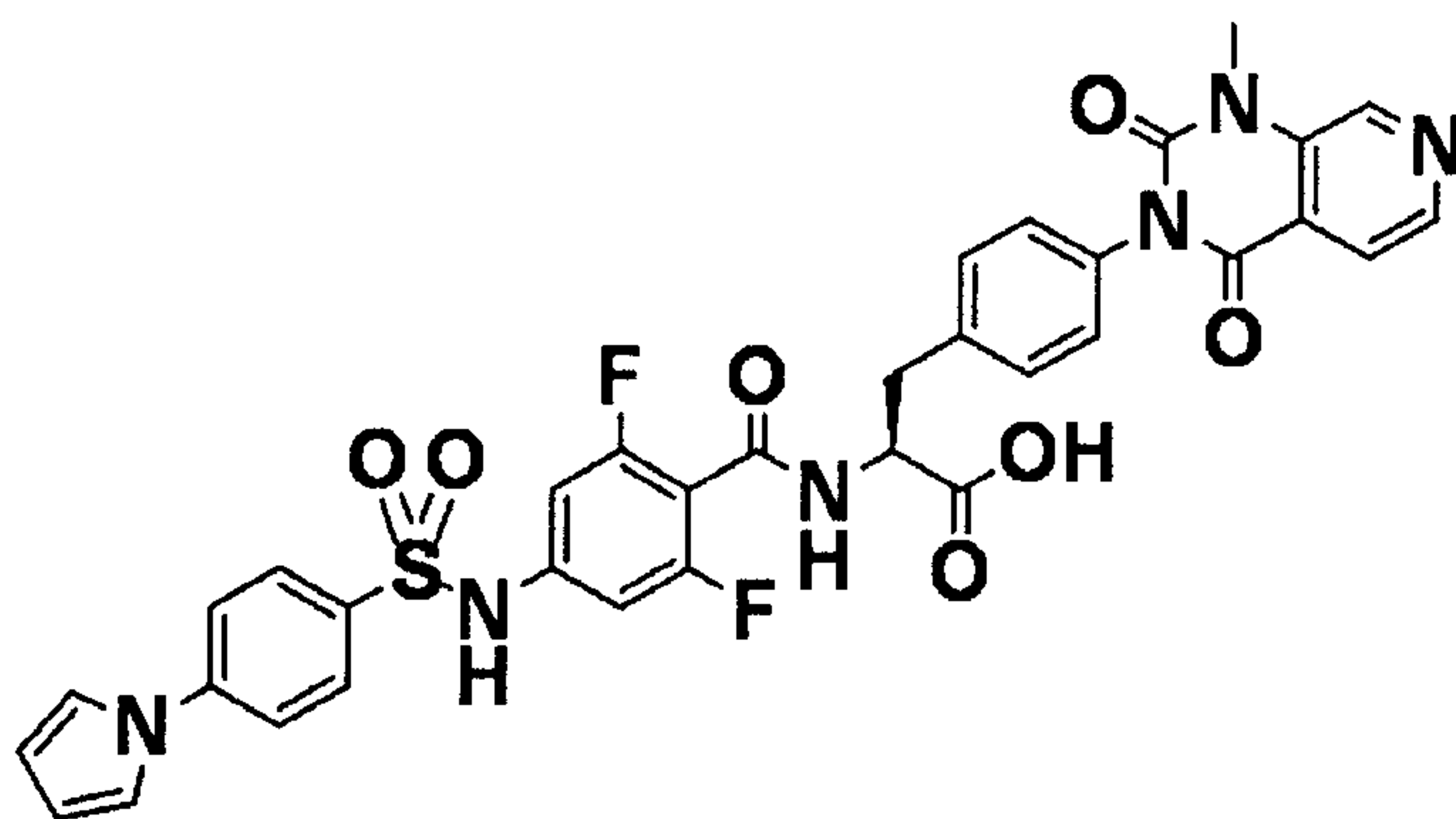
·TFA

Methyl

4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (M-1) (100 mg, 0.234 mmol) and 2,6-difluoro-4-({[4-(1H-pyrrol-1-yl)phenyl]sulfonyl}amino)benzoic acid (M-10) (87.0 mg, 0.230 mmol) were suspended in methylene chloride (2.0 ml), and HATU (133 mg, 0.351 mmol) and diisopropylethylamine (0.160 ml, 0.920 mmol) were added thereto, followed by stirring at room temperature for 20 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (100 mg, 46%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.1 (s, 1H), 9.17 (d, J = 7.6 Hz, 1H), 8.97 (s, 1H), 8.55 (d, J = 5.2 Hz, 1H), 7.92-7.88 (m, 3H), 7.83 (dd, J = 6.8, 2.0 Hz, 2H), 7.50 (t, J = 2.0 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 9.2 Hz, 2H), 6.32 (t, J = 2.0 Hz, 2H), 4.65-4.60 (m, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 3.16-2.99 (m, 2H).; MS (ESI) m/z 715 (M+H)⁺ (Step 2)

N-[2,6-Difluoro-4-({[4-(1H-pyrrol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-5)



·TFA

To the TFA salt (80 mg, 85 μ mol) of methyl

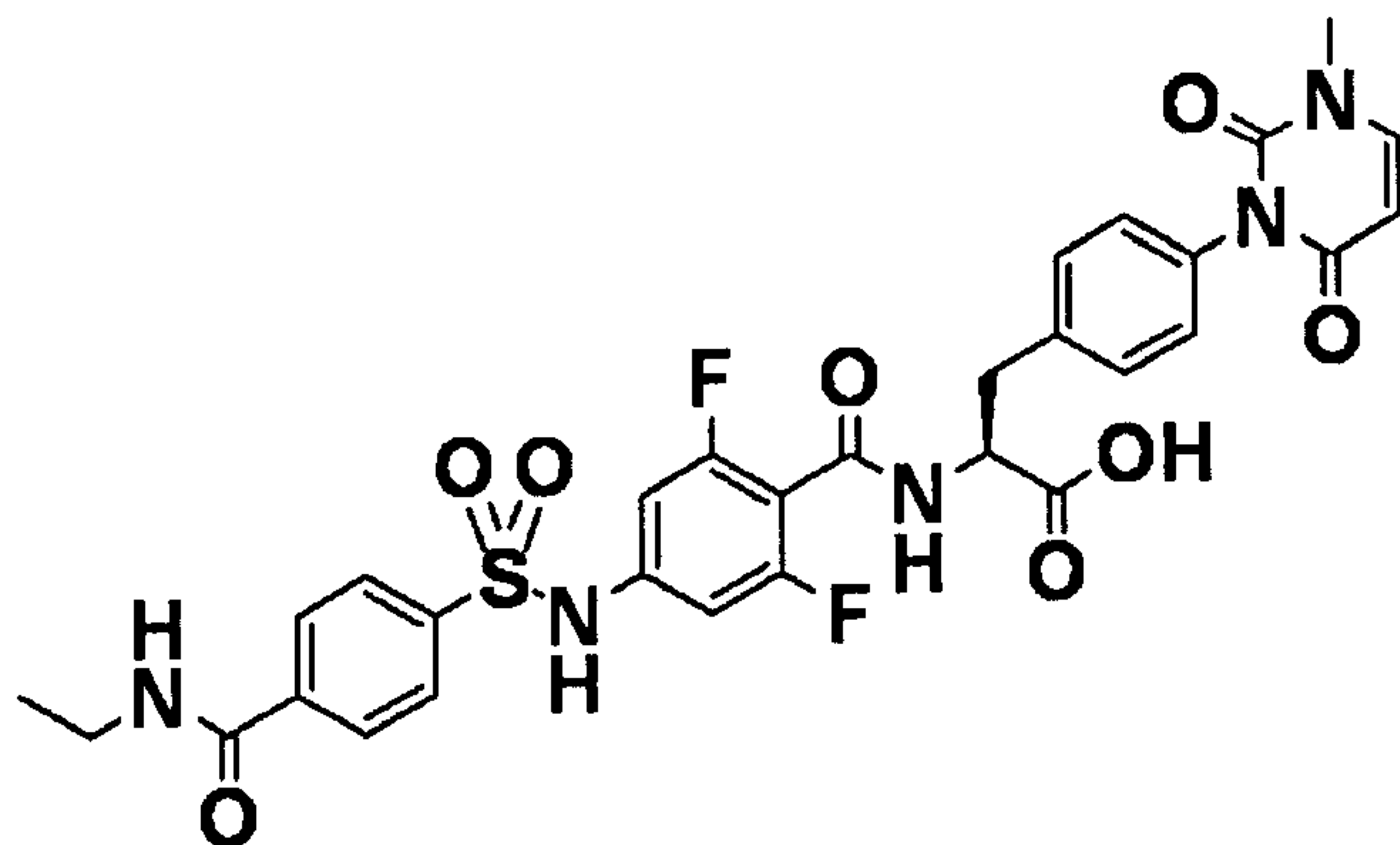
N-[2,6-difluoro-4-({[4-(1H-pyrrol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-5), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (41.0 mg, 52%) of the title compound.

¹H NMR (d-DMSO, 400 MHz): δ 11.07 (s, 1H), 9.04 (d, J = 7.9 Hz, 1H), 8.97 (s, 1H), 8.56 (d, J = 4.9 Hz, 1H), 7.94-7.87 (m, 3H), 7.83 (d, J = 8.9 Hz, 2H), 7.59-7.44 (m, 2H), 7.35 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 6.81 (d, J = 9.1 Hz, 2H), 6.40-6.23 (m, 2H), 4.66-4.46 (m, 1H), 3.60 (s, 3H), 3.17 (dd, J = 14.1, 4.3 Hz, 1H), 2.99 (dd, J = 14.1, 9.9 Hz, 1H).; MS (ESI) m/z 701 (M+H)⁺

Example 44: Synthesis of A-6

(Step 2)

N-{4-[(4-[(Ethylamino)carbonyl]phenyl)sulfonyl]amino}-2,6-difluorobenzoyl}-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-6)



Methyl

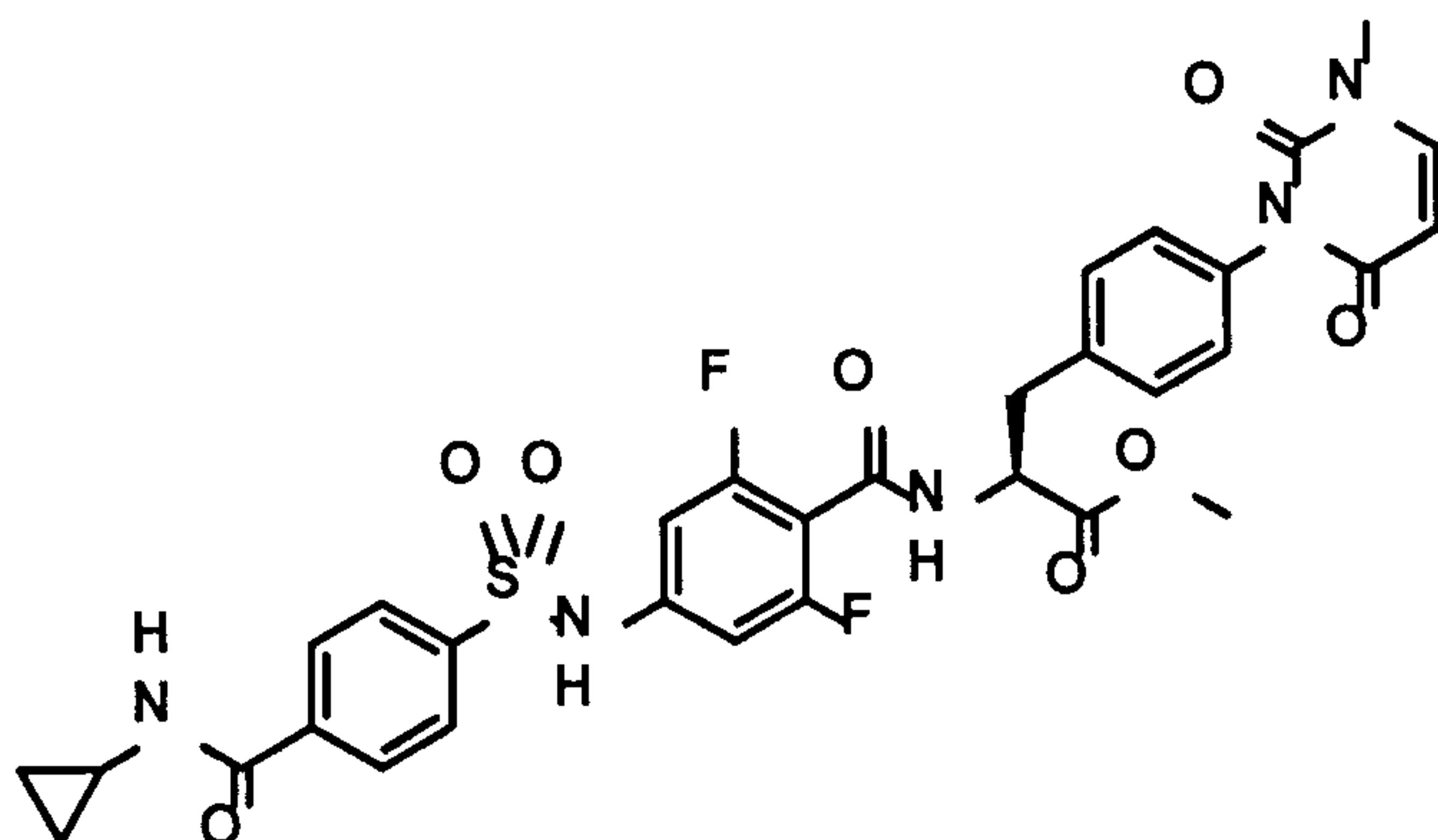
4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phen

ylalaninate (M-2) (100 mg, 0.290 mmol) and
 4-[(4-[(ethylamino)carbonyl]phenyl)sulfonyl)amino]-2,6-difluorobenzoic acid (M-11) (111 mg, 0.290 mmol) were suspended
 in methylene chloride (2.0 ml), and HATU (165 mg, 0.440 mmol)
 5 and diisopropylethylamine (0.202 ml, 1.16 mmol) were added
 thereto, followed by stirring at room temperature for 16 hours.
 After the reaction liquid was concentrated under reduced
 pressure, purification was conducted by reversed-phase HPLC
 (H₂O containing 0.1% TFA/CH₃CN system). To the obtained white
 10 solid, a 4 N hydrogen chloride/dioxane solution (3.0 ml) and
 water (2.0 ml) were added, followed by stirring at 80°C for 1
 hour. After the reaction liquid was concentrated under reduced
 pressure, purification was conducted by reversed-phase HPLC
 (H₂O containing 0.1% TFA/CH₃CN system) to obtain the title
 15 compound (80.0 mg, 42%) as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 12.85 (s, 1H), 11.14 (s, 1H), 9.04
 (d, J = 7.8 Hz, 1H), 8.67 (d, J = 5.4 Hz, 1H), 8.01-7.91 (m,
 4H), 7.75 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.09
 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 9.1 Hz, 2H), 5.74 (d, J = 7.9
 20 Hz, 1H), 4.60-4.49 (m, 1H), 3.34-3.22 (m, 5H), 3.14 (dd, J =
 14.3, 4.6 Hz, 1H), 2.96 (dd, J = 14.3, 9.7 Hz, 1H), 1.10 (t,
 J = 7.2 Hz, 3H).; MS (ESI) m/z 656 (M+H)⁺

Example 45: Synthesis of A-7 and B-7

(Step 1) Methyl
 25 N-{4-[(4-[(Cyclopropylamino)carbonyl]phenyl)sulfonyl)amino]-2,6-difluorobenzoyl}-4-(3-methyl-2,6-dioxo-3,6-dihydropyr
imidin-1(2H)-yl)-L-phenylalaninate (B-7)



Methyl

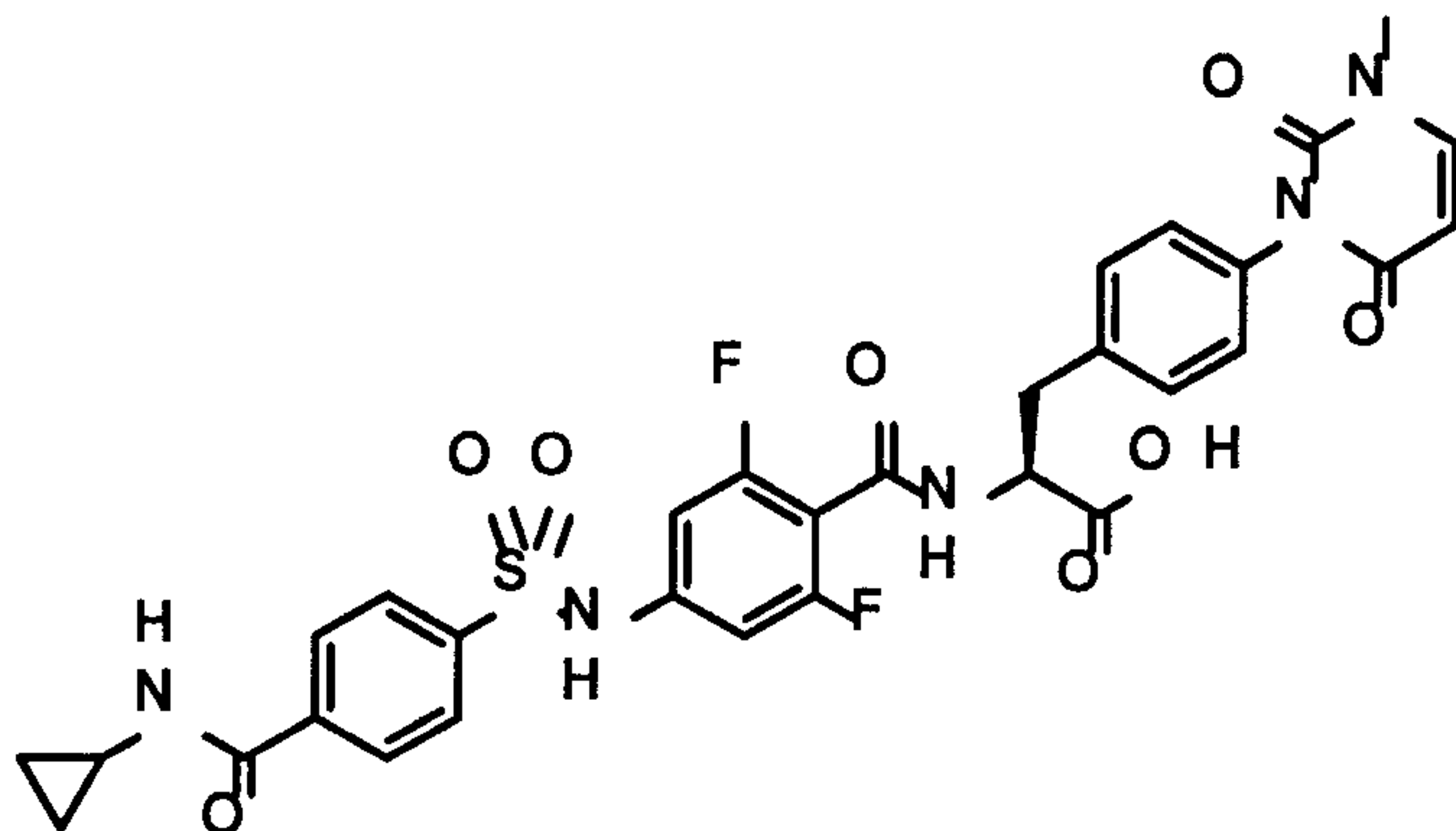
4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (M-2) (77.0 mg, 0.230 mmol) and
 5 4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino]-2,6-difluorobenzic acid (M-12) (75.0 mg, 0.190 mmol) were
 suspended in methylene chloride (2.0 ml), and HATU (108 mg, 0.290 mmol) and diisopropylethylamine (0.132 ml, 0.760 mmol)
 were added, followed by stirring at room temperature for 20
 10 hours. After the reaction liquid was concentrated under
 reduced pressure, purification was conducted by reversed-phase
 HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA
 salt (80.0 mg, 62%) of the title compound as a white solid.
¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.17 (d, J = 7.6 Hz,
 15 1H), 8.64 (d, J = 4.4 Hz, 1H), 7.96-7.91 (m, 4H), 7.75 (d, J
 = 8.0 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz,
 2H), 6.79 (d, J = 9.2 Hz, 2H), 5.74 (d, J = 8.0 Hz, 1H), 4.63-4.57
 (m, 1H), 3.63 (s, 3H), 3.31 (s, 3H), 3.14-2.97 (m, 2H), 2.86-2.80
 (m, 1H), 0.71-0.69 (m, 2H), 0.57-0.53 (m, 2H).; MS (ESI) m/z
 20 682 (M+H)⁺

(Step

2)

N-{4-[(4-[(Cyclopropylamino)carbonyl]phenyl)sulfonyl]amino}-2,6-difluorobenzoyl}-4-(3-methyl-2,6-dioxo-3,6-dihydropyr

imidin-1(2H)-yl)-L-phenylalanine (A-7)

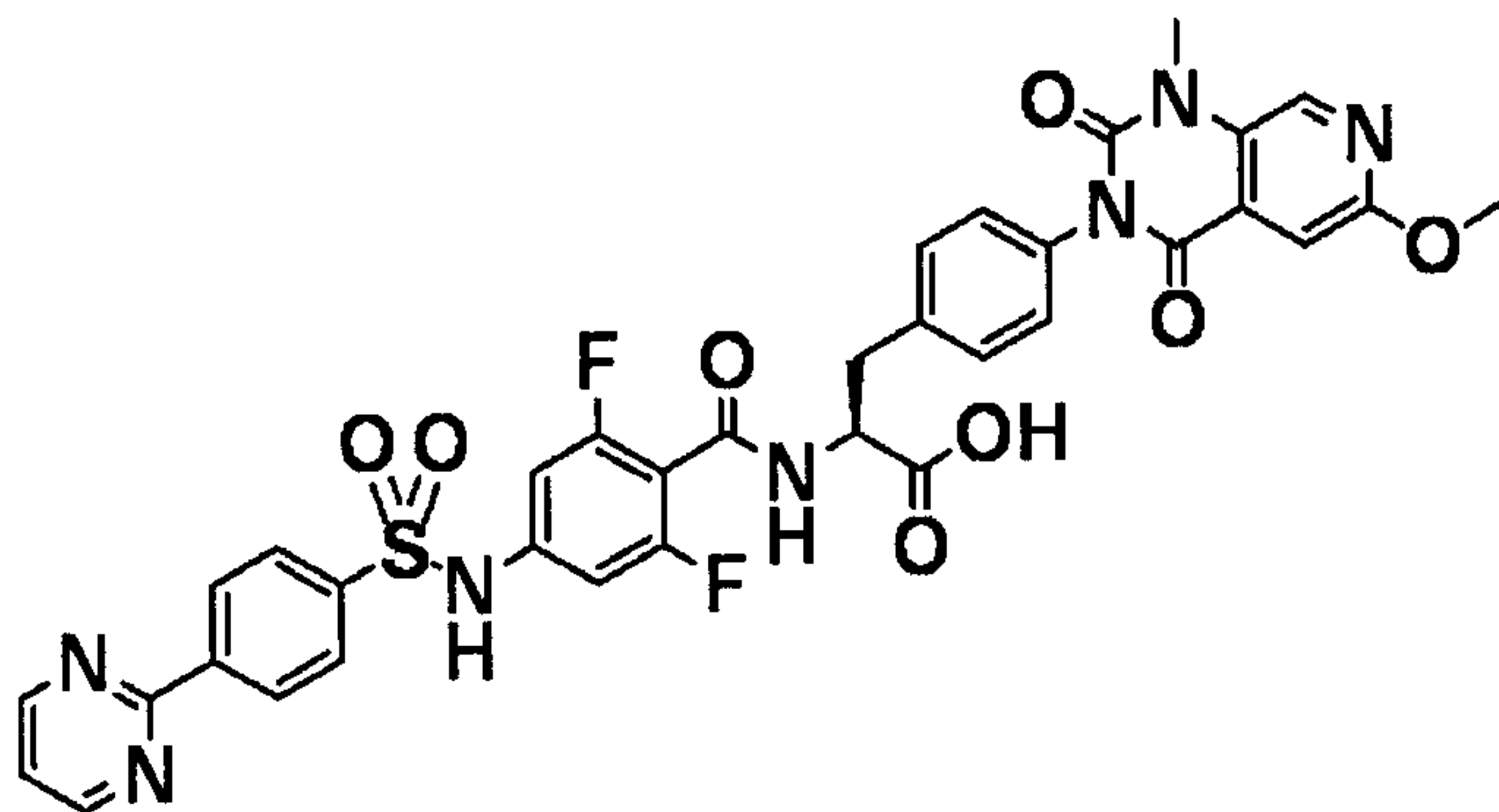


To the TFA salt (60 mg, 88 μ mol) of methyl
 N-{4-[(4-{4-[(cyclopropylamino)carbonyl]phenyl}sulfonyl)amino
 5]-2,6-difluorobenzoyl}-4-(3-methyl-2,6-dioxo-3,6-dihydropyr
 imidin-1(2H)-yl)-L-phenylalaninate (B-7), a 4 N hydrogen
 chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added,
 followed by stirring at 80°C for 1 hour. After the reaction
 liquid was concentrated under reduced pressure, purification
 10 was conducted by reversed-phase HPLC (H₂O containing 0.1%
 TFA/CH₃CN system) to obtain the title compound (32.4 mg, 55%).
¹H NMR (d-DMSO, 400 MHz): δ 11.14 (s, 1H), 9.04 (d, J = 7.8 Hz,
 1H), 8.64 (d, J = 4.3 Hz, 1H), 8.03-7.86 (m, 4H), 7.75 (d, J
 = 7.9 Hz, 1H), 7.30 (d, J = 8.3 Hz, 2H), 7.09 (d, J = 8.3 Hz,
 15 2H), 6.78 (d, J = 9.0 Hz, 2H), 5.74 (d, J = 7.9 Hz, 1H), 4.61-4.47
 (m, 1H), 3.31 (s, 3H), 3.14 (dd, J = 14.2, 4.5 Hz, 1H), 2.96
 (dd, J = 14.2, 9.8 Hz, 1H), 2.88-2.78 (m, 1H), 0.74-0.63 (m,
 2H), 0.60-0.50 (m, 2H).; MS (ESI) m/z 668 (M+H)⁺

Example 46: Synthesis of A-8

20 (Step 2)

N-(2,6-Difluoro-4-{[(4-pyrimidin-2-yl-phenyl)sulfonyl]amino
 }benzoyl)-4-(6-methoxy-1-methyl-2,4-dioxo-1,4-dihydropyrido
 [3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-8)



·2TFA

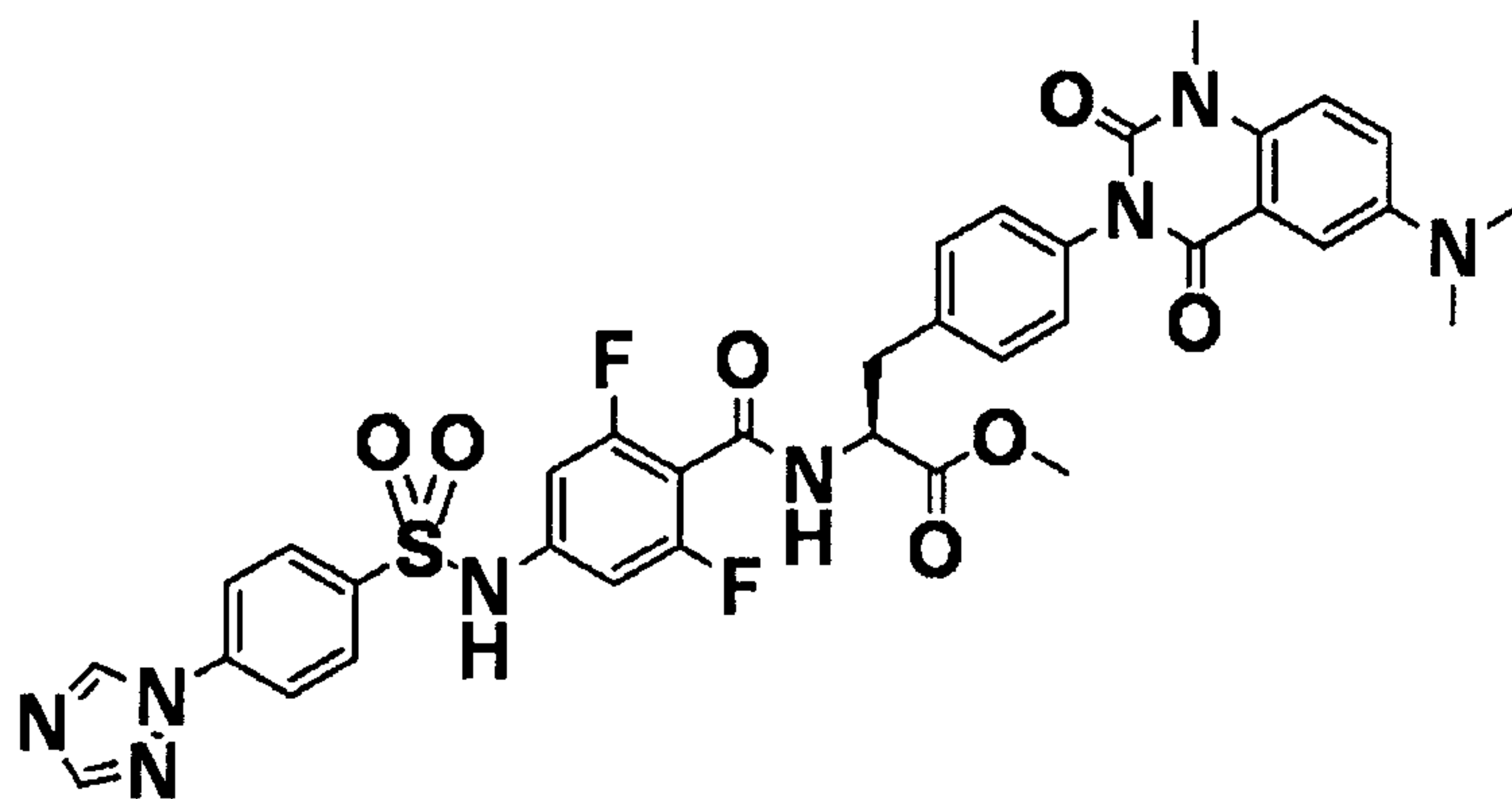
Methyl

4-(6-methoxy-1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyr
 5 imidin-3(2H)-yl)-L-phenylalaninate (M-3) (100 mg, 0.220 mmol)
 and
 2,6-difluoro-4-{[(4-pyrimidin-2-yl-phenyl)sulfonyl]amino}be
 nzoic acid (M-8) (65.0 mg, 0.170 mmol) were suspended in
 methylene chloride (2.0 ml), and HATU (125 mg, 0.330 mmol) and
 10 diisopropylethylamine (0.153 ml, 0.880 mmol) were added thereto,
 followed by stirring at room temperature for 1 hour. After the
 reaction liquid was concentrated under reduced pressure,
 purification was conducted by reversed-phase HPLC (H₂O
 containing 0.1% TFA/CH₃CN system). To the obtained compound,
 15 a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0
 ml) were added, followed by stirring at 80°C for 1 hour. After
 the reaction liquid was concentrated under reduced pressure,
 purification was conducted by reversed-phase HPLC (H₂O
 containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (18.0
 20 mg, 11% over two steps) of the title compound as a white solid.
¹H NMR (d-DMSO, 400 MHz): δ 11.18 (s, 1H), 9.03 (d, J = 7.8 Hz,
 1H), 8.96 (d, J = 4.9 Hz, 2H), 8.58 (d, J = 8.6 Hz, 2H), 8.53
 (s, 1H), 8.02 (d, J = 8.6 Hz, 2H), 7.53 (t, J = 4.9 Hz, 1H),
 7.33 (d, J = 8.3 Hz, 2H), 7.26 (s, 1H), 7.19 (d, J = 8.3 Hz,

2H), 6.82 (d, $J = 9.1$ Hz, 2H), 4.64-4.45 (m, 1H), 3.93 (s, 3H), 3.54 (s, 3H), 3.16 (dd, $J = 14.2, 4.3$ Hz, 1H), 2.98 (dd, $J = 14.1, 9.9$ Hz, 1H).; MS (ESI) m/z 744 ($M+H$)⁺

Example 47: Synthesis of A-9 and B-9

5 (Step 1) Methyl N-[2,6-Difluoro-4-({[4-(1H-1,2,4-triazol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-[6-(dimethylamino)-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl]-L-phenylalaninate (B-9)



10 ·2TFA

Methyl

4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (80.0 mg, 0.170 mmol) and 2,6-difluoro-4-({[4-(1H-1,2,4-triazol-1-yl)phenyl]sulfonyl}amino)benzoic acid (M-13) (65.0 mg, 0.170 mmol) were suspended in methylene chloride (2.0 ml), and HATU (97.0 mg, 0.260 mmol) and diisopropylethylamine (0.118 ml, 0.680 mmol) were added thereto, followed by stirring at room temperature for 2 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (100 mg, 67%) of the title compound as a yellow solid.

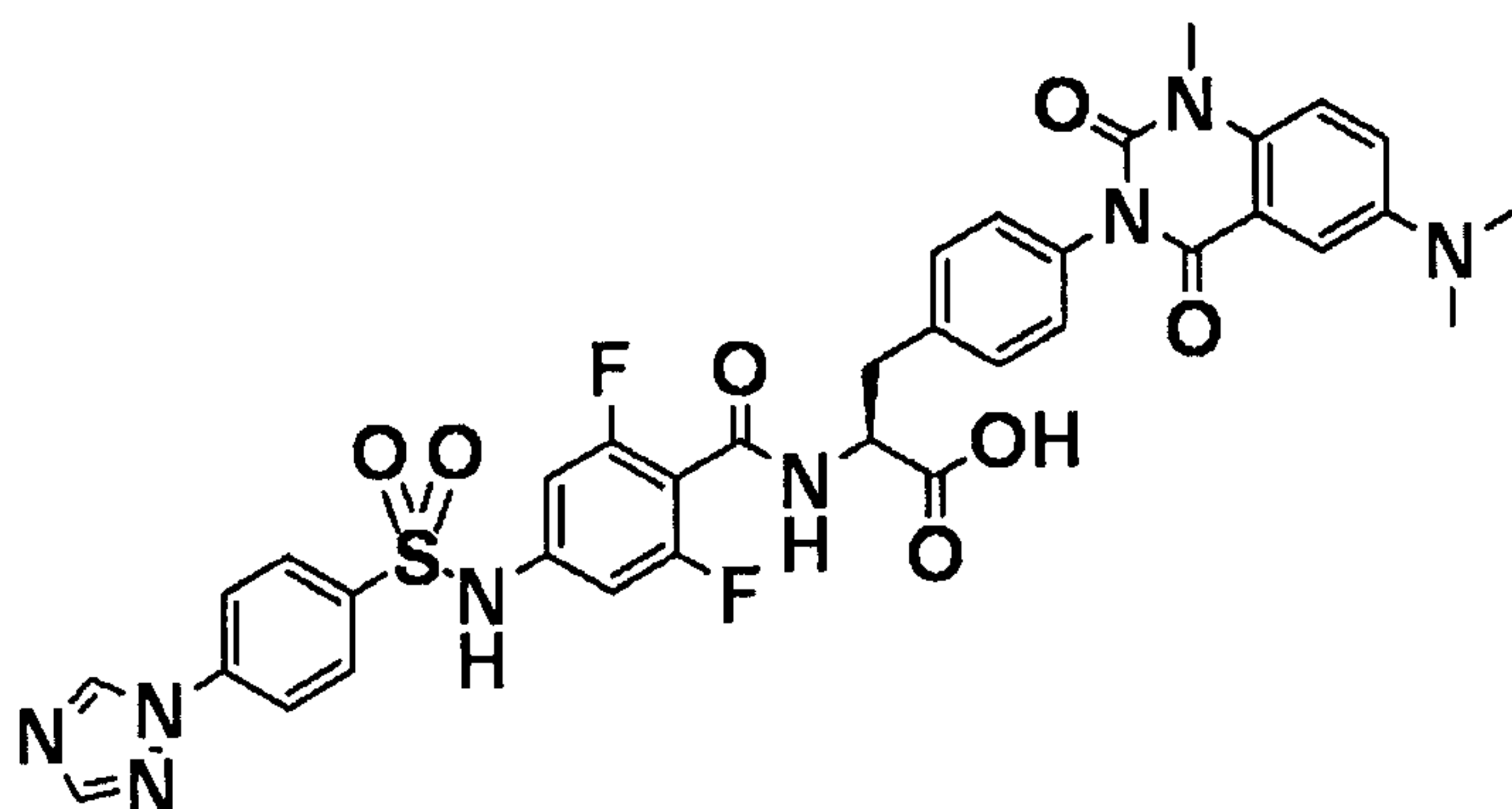
¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.41 (s, 1H), 9.19 (d, $J = 7.6$ Hz, 1H), 8.30 (s, 1H), 8.11 (dd, $J = 6.8, 2.4$ Hz,

2H), 8.05 (dd, $J = 6.8, 2.4$ Hz, 2H), 7.41-7.27 (m, 5H), 7.17 (d, $J = 8.0$ Hz, 2H), 6.83 (d, $J = 9.2$ Hz, 2H), 4.65-4.60 (m, 1H), 3.63 (s, 3H), 3.49 (s, 3H), 3.16-2.99 (m, 2H), 2.95 (s, 6H).; MS (ESI) m/z 759 ($M+H$)⁺

5 (Step

2)

N-[2,6-Difluoro-4-({[4-(1H-1,2,4-triazol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-[6-(dimethylamino)-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl]-L-phenylalanine (A-9)



10

·2TFA

To the TFA salt (80 mg, 92 μ mol) of methyl N-[2,6-difluoro-4-({[4-(1H-1,2,4-triazol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-[6-(dimethylamino)-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl]-L-phenylalaninate (B-9), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (58.2 mg, 74%) of the title compound.

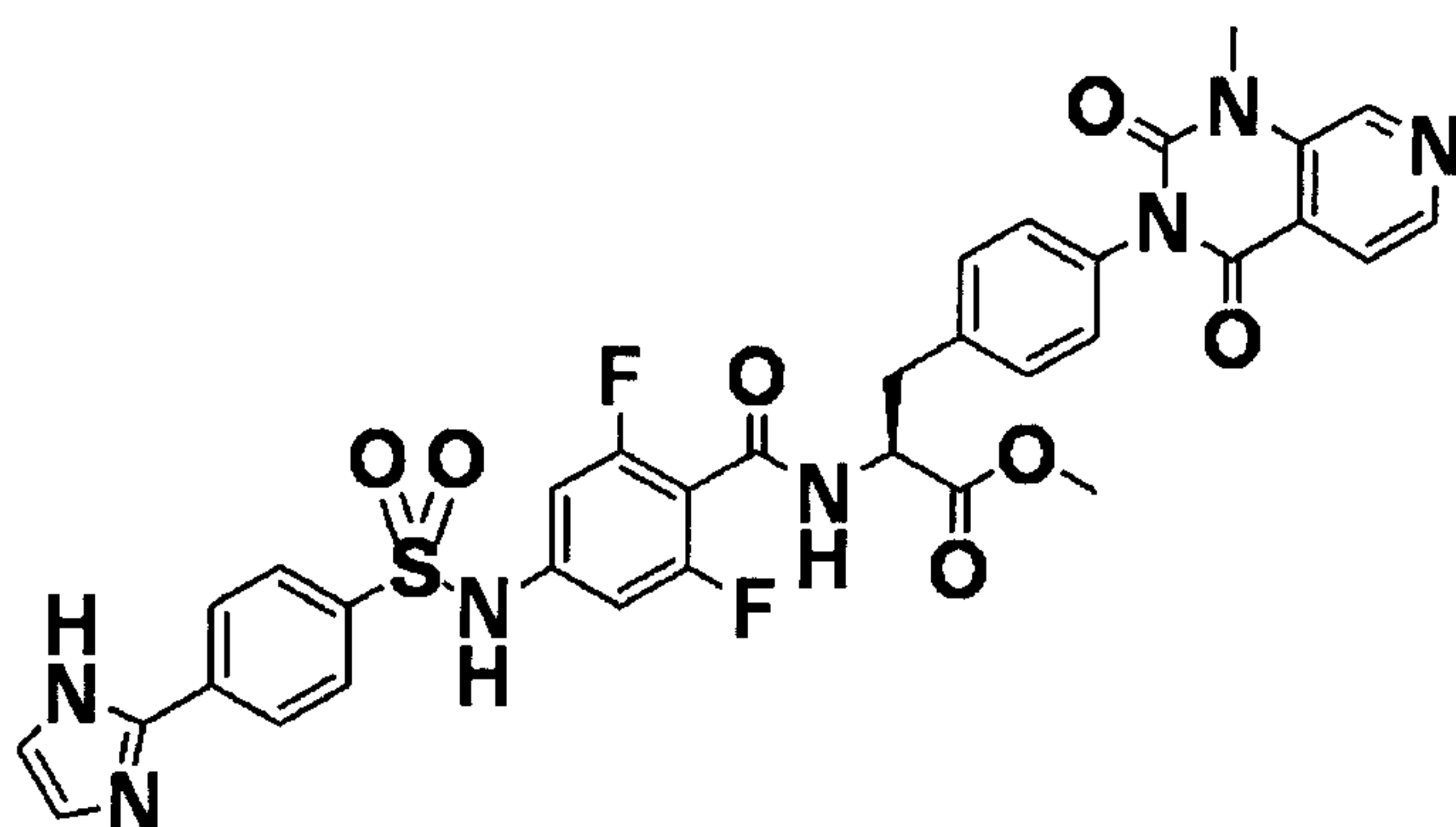
20

¹H NMR (d-DMSO, 400 MHz): δ 11.18 (s, 1H), 9.40 (s, 1H), 9.06 (d, $J = 7.9$ Hz, 1H), 8.30 (s, 1H), 8.16-8.08 (m, 2H), 8.08-8.00 (m, 2H), 7.45-7.30 (m, 5H), 7.17 (d, $J = 8.3$ Hz, 2H), 6.83 (d, $J = 9.0$ Hz, 2H), 4.69-4.44 (m, 1H), 3.50 (s, 3H), 3.16 (dd, J

= 14.2, 4.4 Hz, 1H), 3.05-2.93 (m, 7H).; MS (ESI) m/z 745 (M+H)⁺

Example 48: Synthesis of A-10 and B-10

(Step 1) Methyl
N-[2,6-Difluoro-4-({[4-(1H-imidazol-2-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-10)



·2TFA

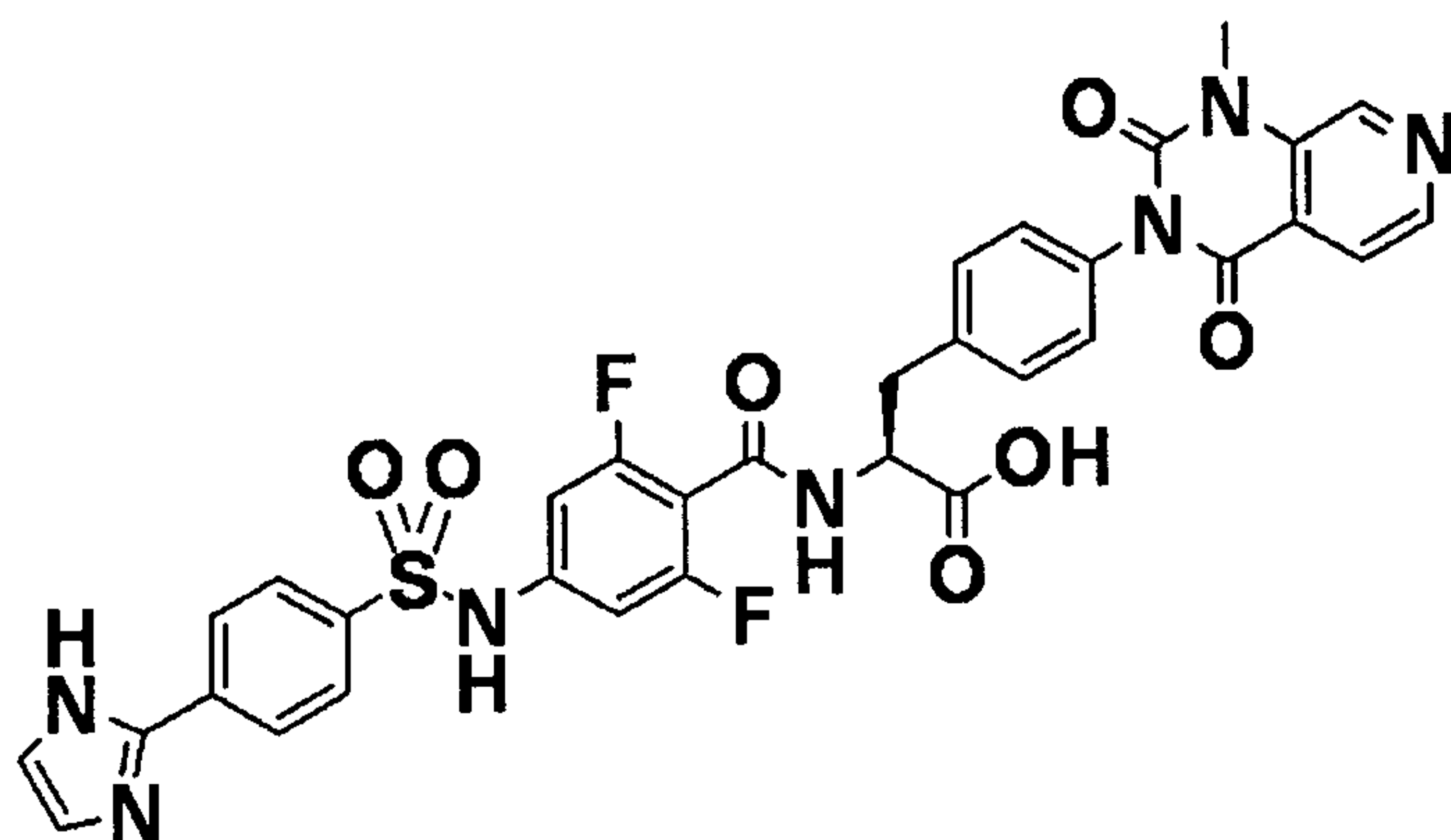
Methyl

4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (M-1) (100 mg, 0.234 mmol) and 2,6-difluoro-4-({[4-(1H-imidazol-2-yl)phenyl]sulfonyl}amino)benzoic acid (M-14) (87.0 mg, 0.234 mmol) were suspended in methylene chloride (2.0 ml), and HATU (133 mg, 0.351 mmol) and diisopropylethylamine (0.160 ml, 0.920 mmol) were added thereto, followed by stirring at room temperature for 17 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (120 mg, 55%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.20 (d, J = 7.6 Hz, 1H), 8.98 (s, 1H), 8.56 (d, J = 4.8 Hz, 1H), 8.16 (d, J = 8.8 Hz, 2H), 8.09 (d, J = 8.4 Hz, 2H), 7.94 (d, J = 8.4 Hz, 1H), 7.81-7.75 (m, 2H), 7.34 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4

Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 4.66-4.60 (m, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 3.17-2.99 (m, 2H).; MS (ESI) m/z 716 (M+H)⁺
(Step 2)

N-[2,6-Difluoro-4-({[4-(1H-imidazol-2-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-10)



·2TFA

To the TFA salt (100 mg, 0.110 mmol) of methyl
10 N-[2,6-difluoro-4-({[4-(1H-imidazol-2-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (A-10), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction
15 liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (54.9 mg, 54%) of the title compound.

¹H NMR (d-DMSO, 400 MHz): δ 11.24 (s, 1H), 9.07 (d, J = 7.8 Hz, 1H), 8.97 (s, 1H), 8.56 (d, J = 4.9 Hz, 1H), 8.16 (d, J = 8.5 Hz, 2H), 8.09 (d, J = 8.6 Hz, 2H), 7.88 (d, J = 4.9 Hz, 1H), 7.76 (s, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 4.62-4.51 (m, 1H), 3.60 (s, 3H), 3.14 (dd, J = 15.2, 4.4 Hz, 1H), 2.99 (dd, J = 14.2, 9.9 Hz,

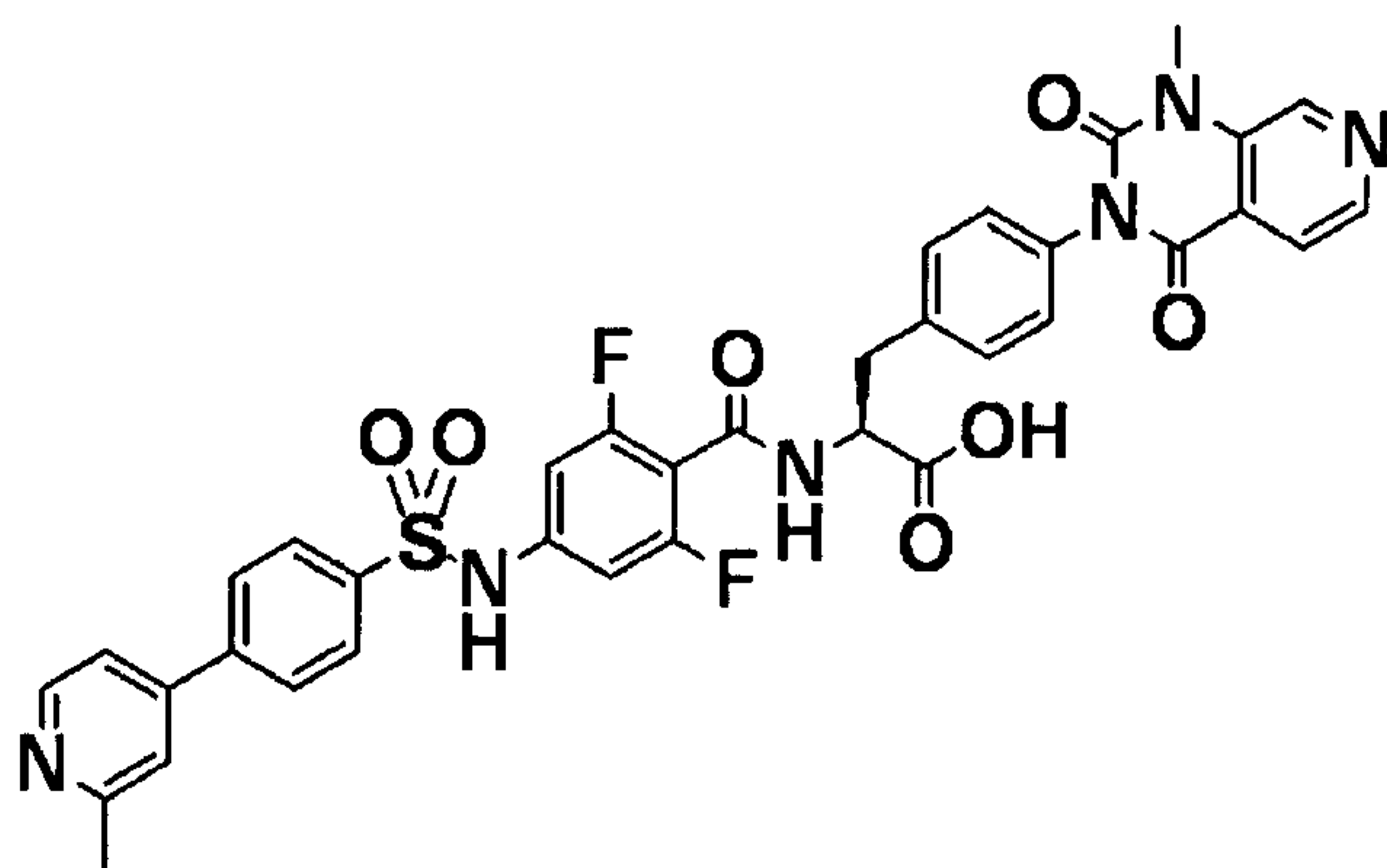
¹H).; MS (ESI) m/z 702 (M+H)⁺

Example 49: Synthesis of A-11

(Step

2)

N- [2,6-Difluoro-4- ({ [4- (2-methylpyridin-4-yl)phenyl]sulfonyl}amino)benzoyl] -4- (1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl) -L-phenylalanine (A-11)



·2TFA

Methyl

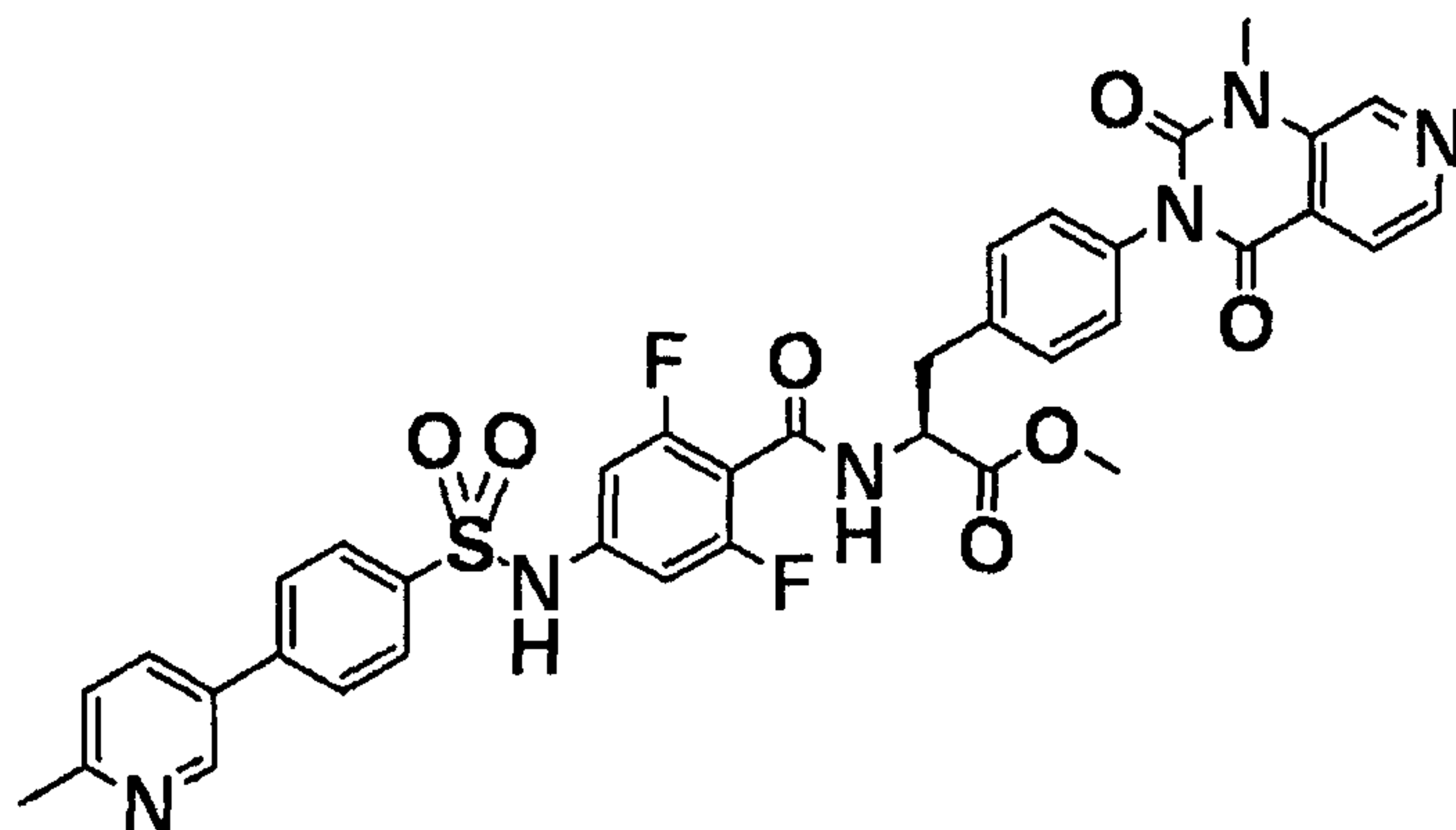
4- (1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl) -L-phenylalaninate (M-1) (100 mg, 0.234 mmol) and 2,6-difluoro-4- ({ [4- (2-methylpyridin-4-yl)phenyl]sulfonyl}amino)benzoic acid (M-32) (93.0 mg, 0.234 mmol) were suspended in methylene chloride (2.0 ml), and HATU (133 mg, 0.351 mmol) and diisopropylethylamine (0.160 ml, 0.920 mmol) were added thereto, followed by stirring at room temperature for 17 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system). To the obtained compound, a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt

(40.0 mg, 18%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.22 (s, 1H), 9.07 (d, J = 7.9 Hz, 1H), 8.97 (s, 1H), 8.73 (d, J = 5.7 Hz, 1H), 8.55 (d, J = 4.9 Hz, 1H), 8.11 (d, J = 8.6 Hz, 2H), 8.06-7.98 (m, 3H), 7.95-7.81 (m, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 4.61-4.53 (m, 1H), 3.60 (s, 3H), 3.17 (dd, J = 14.1, 4.4 Hz, 1H), 2.98 (dd, J = 14.1, 9.9 Hz, 1H), 2.64 (s, 3H).; MS (ESI) m/z 727 (M+H)⁺

Example 50: Synthesis of A-12 and Synthesis of B-12

10 (Step 1) Methyl
N-[2,6-Difluoro-4-({[4-(6-methylpyridin-3-yl)phenyl]sulfonyl
1}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,
4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-12)



15 ·2TFA

Methyl

4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (M-1) (75.0 mg, 0.180 mmol) and 2,6-difluoro-4-({[4-(6-methylpyridin-3-yl)phenyl]sulfonyl}amino)benzoic acid (M-33) (73.0 mg, 0.180 mmol) were suspended in methylene chloride (2.0 ml), and HATU (91.0 mg, 0.240 mmol) and diisopropylethylamine (0.111 ml, 0.640 mmol) were added thereto, followed by stirring at room temperature for 1 hour. After the reaction liquid was concentrated under reduced

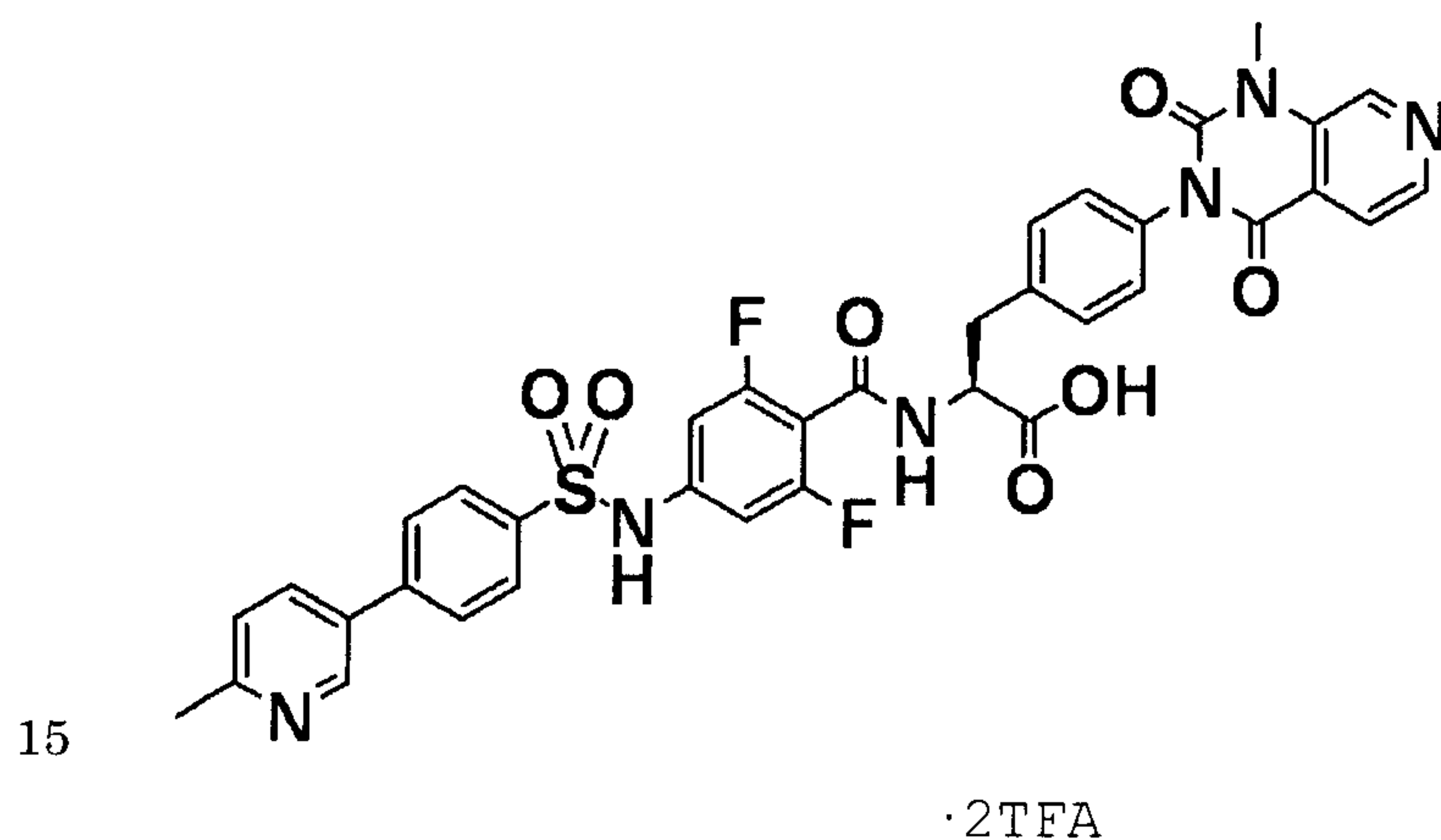
pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (70.0 mg, 40%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.14 (d, J = 7.6 Hz, 1H), 8.90-8.88 (m, 2H), 8.49 (d, J = 5.2 Hz, 1H), 8.27 (d, J = 7.6 Hz, 1H), 7.95-7.91 (m, 4H), 7.82 (d, J = 5.2 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 9.2 Hz, 2H), 4.59-4.53 (m, 1H), 3.57 (s, 3H), 3.53 (s, 3H), 3.10-2.92 (m, 2H), 2.54 (s, 3H).; MS (ESI) m/z 741 (M+H)⁺

(Step

2)

N-[2,6-Difluoro-4-({[4-(6-methylpyridin-3-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-12)



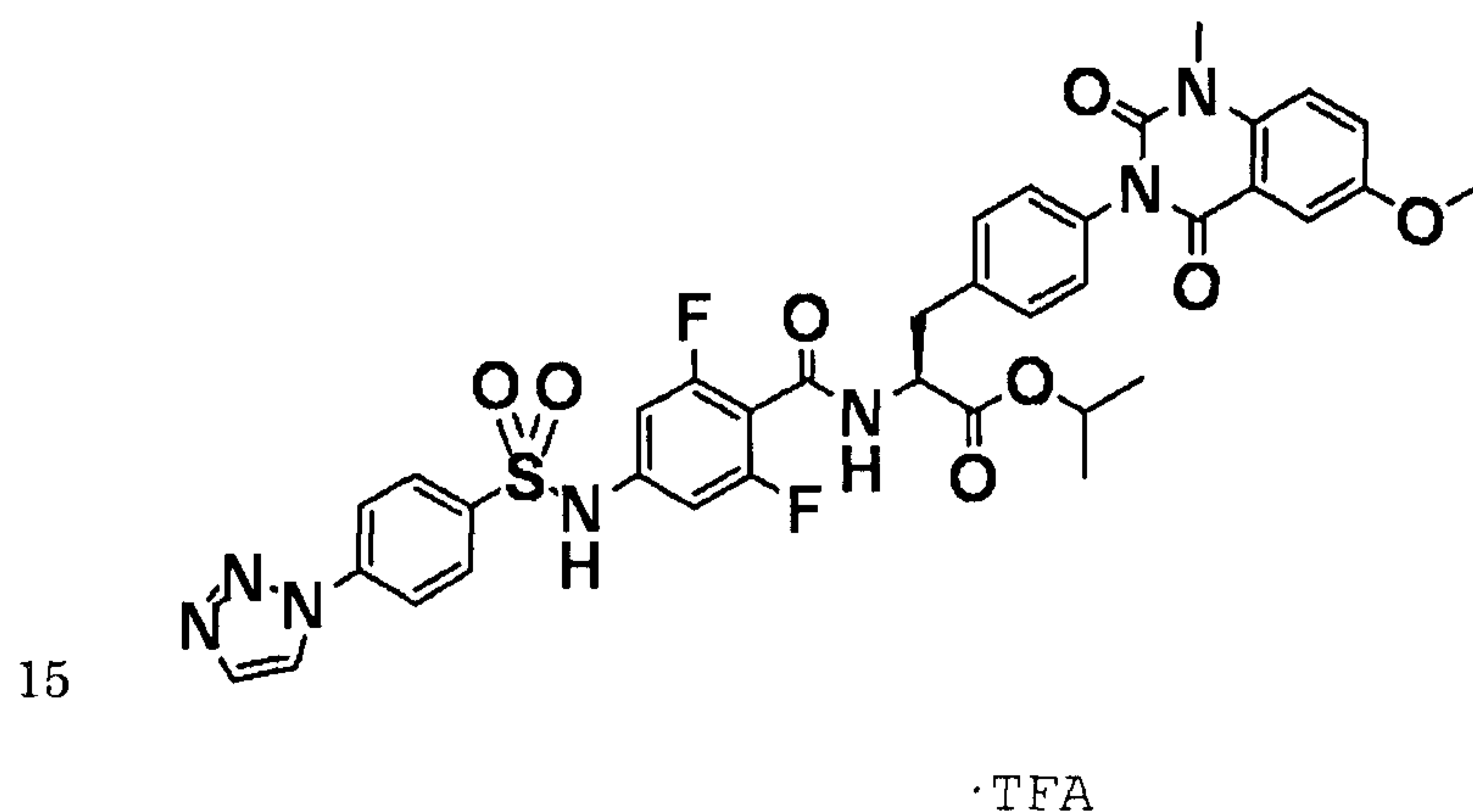
To the TFA salt (50.0 mg, 52.0 μmol) of methyl N-[2,6-difluoro-4-({[4-(6-methylpyridin-3-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-12), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O

containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (30.8 mg, 62%) of the title compound.

¹H NMR (d-DMSO, 400 MHz): δ 11.12 (s, 1H), 9.00 (d, J = 7.9 Hz, 1H), 8.90 (s, 1H), 8.87 (s, 1H), 8.49 (d, J = 4.9 Hz, 1H), 8.24 (d, J = 8.3 Hz, 1H), 7.98-7.89 (m, 4H), 7.82 (d, J = 4.9 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.76 (d, J = 9.1 Hz, 2H), 4.56-4.43 (m, 1H), 3.53 (s, 3H), 3.10 (dd, J = 14.1, 4.4 Hz, 1H), 2.91 (dd, J = 14.2, 9.9 Hz, 1H), 2.53 (s, 3H).; MS (ESI) m/z 727 (M+H)⁺

Example 51: Synthesis of A-13 and B-13

(Step 1) Isopropyl N-[2,6-Difluoro-4-({[4-(1H-1,2,3-triazol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(6-methoxy-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-L-phenylalaninate (B-13)



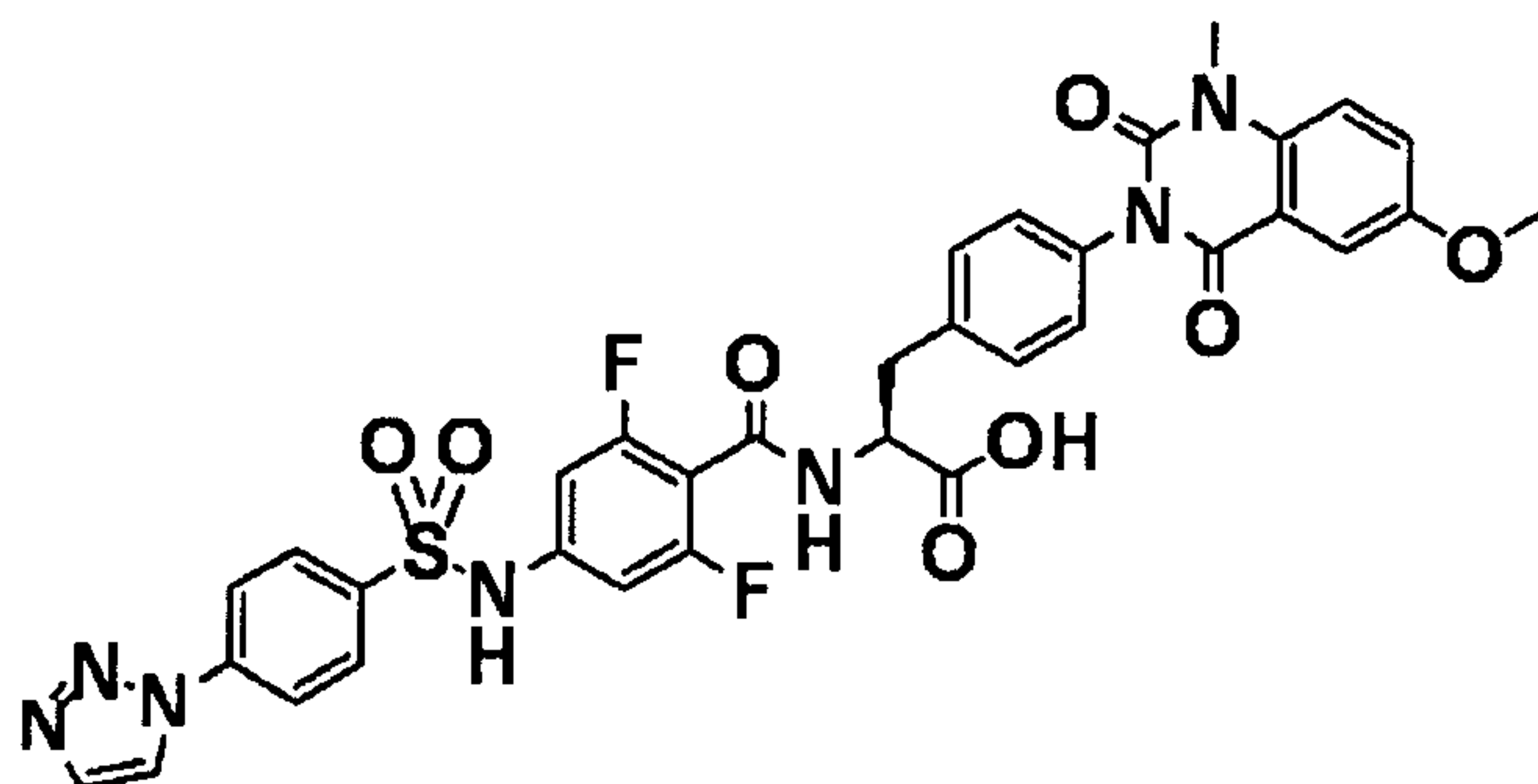
Isopropyl

4-(6-methoxy-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-L-phenylalaninate (M-4) (82.0 mg, 0.200 mmol) and 2,6-difluoro-4-({[4-(1H-1,2,3-triazol-1-yl)phenyl]sulfonyl}amino)benzoic acid (M-15) (76.0 mg, 0.200 mmol) were suspended in methylene chloride (2.0 ml), and HATU (111 mg, 0.290 mmol) and diisopropylethylamine (0.136 ml, 0.780 mmol) were added thereto, followed by stirring at room temperature for 18 hours.

After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (80.0 mg, 52%) of the title compound.

5 ¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.16 (d, J = 7.6 Hz, 1H), 8.94 (d, J = 1.2 Hz, 1H), 8.18 (dd, J = 6.8, 2.0 Hz, 2H), 8.09 (dd, J = 6.8, 2.0 Hz, 2H), 8.02 (d, J = 1.2 Hz, 1H), 7.49-7.42 (m, 3H), 7.33 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 4.91-4.85 (m, 1H), 4.56-4.51 (m, 1H),
10 3.83 (s, 3H), 3.51 (s, 3H), 3.12-2.99 (m, 2H), 1.17 (d, J = 6.0 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H).; MS (ESI) m/z 774 (M+H)⁺
(Step 2)

N-[2,6-Difluoro-4-({[4-(1H-1,2,3-triazol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(6-methoxy-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-L-phenylalanine (A-13)
15



·TFA

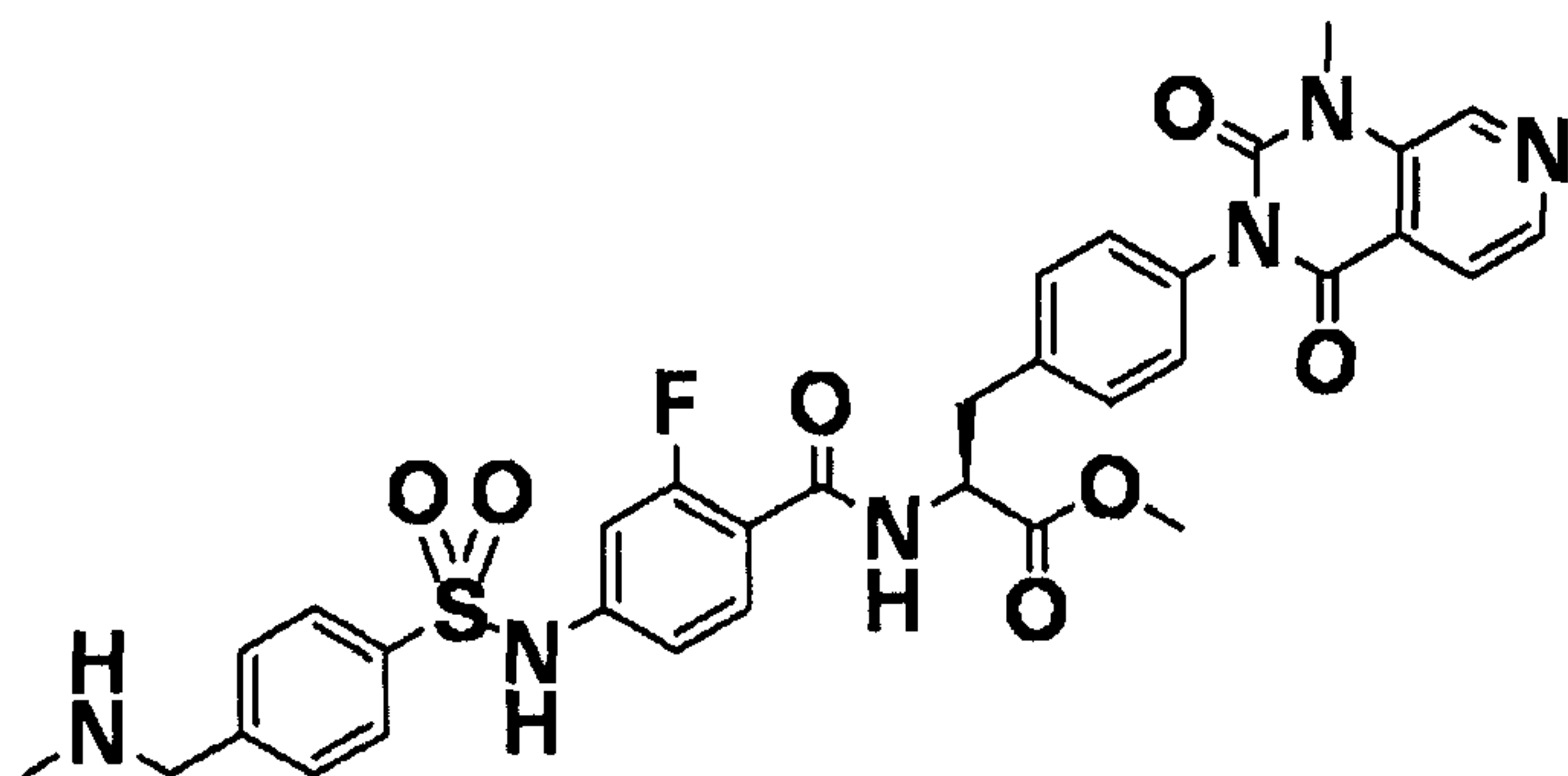
To the TFA salt (20.0 mg, 26.0 μmol) of isopropyl N-[2,6-difluoro-4-({[4-(1H-1,2,3-triazol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(6-methoxy-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-L-phenylalaninate (B-13), a 4 N
20 hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure,
25 purification was conducted by reversed-phase HPLC (H₂O

containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (11.9 mg, 63%) of the title compound.

¹H NMR (d-DMSO, 400 MHz): δ 11.21 (s, 1H), 9.06 (d, J = 7.9 Hz, 1H), 8.93 (d, J = 1.2 Hz, 1H), 8.22-8.14 (m, 2H), 8.12-8.05 (m, 2H), 8.01 (d, J = 1.2 Hz, 1H), 7.51-7.41 (m, 3H), 7.33 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 4.62-4.53 (m, 1H), 3.83 (s, 3H), 3.51 (s, 3H), 3.20-3.14 (m, 1H), 2.98 (dd, J = 14.2, 9.8 Hz, 1H).; MS (ESI) m/z 732 (M+H)⁺

Example 52: Synthesis of A-14 and B-14

10 (Step 1) Methyl
N-{2-Fluoro-4-[(4-[(methylamino)methyl]phenyl)sulfonyl]amino}benzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]p
yrimidin-3(2H)-yl)-L-phenylalaninate (B-14)



15

·2TFA

Methyl

4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (M-1) (100 mg, 0.234 mmol) and 4-[[4-[(tert-butoxycarbonyl)(methyl)amino]methyl]phenyl)sulfonyl]amino}-2-fluorobenzoic acid (M-19) (101 mg, 0.230 mmol) were suspended in methylene chloride (2.0 ml), and HATU (131 mg, 0.350 mmol) and diisopropylethylamine (0.160 ml, 0.920 mmol) were added thereto, followed by stirring at room temperature for 19 hours. After the reaction liquid was concentrated under reduced pressure, trifluoroacetic acid (2.0

20

25

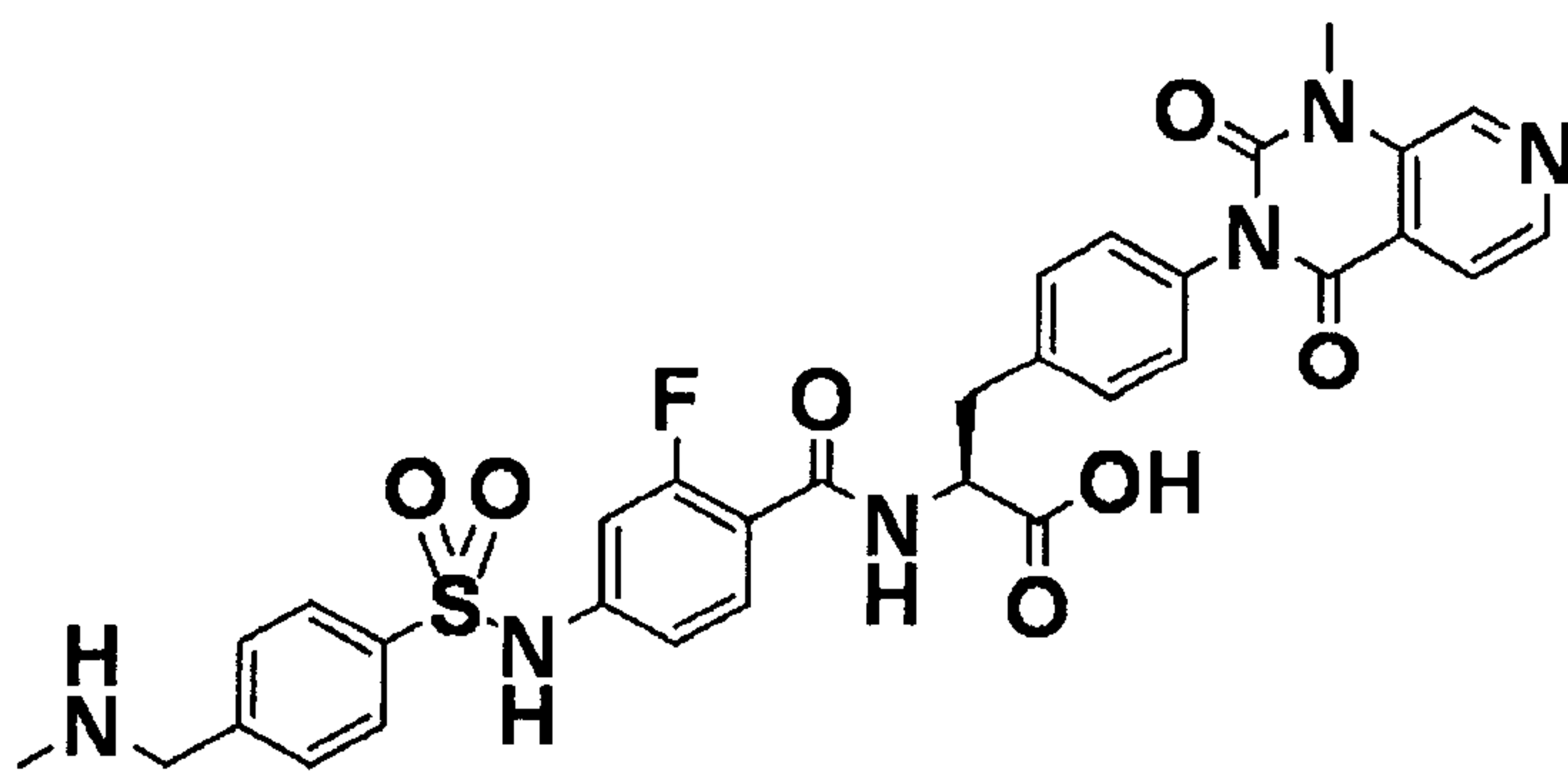
ml) was added thereto, followed by stirring at room temperature for 30 minutes. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to
 5 obtain the TFA salt (120 mg, 58%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.0 (s, 1H), 8.98 (s, 1H), 8.79 (br, 1H), 8.60 (dd, J = 7.6, 2.0 Hz, 1H), 8.56 (d, J = 4.8 Hz, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.89 (d, J = 4.8 Hz, 1H), 7.66
 10 (d, J = 8.4 Hz, 2H), 7.43-7.35 (m, 3H), 7.22 (d, J = 8.4 Hz, 2H), 7.01-6.94 (m, 2H), 4.67-4.63 (m, 1H), 4.17 (t, J = 5.6 Hz, 2H), 3.66 (s, 3H), 3.60 (s, 3H), 3.22-3.06 (m, 2H), 2.57 (t, J = 5.2 Hz, 3H).; MS (ESI) m/z 675 (M+H)⁺

(Step

2)

15 N-{2-Fluoro-4-[(4-[(methylamino)methyl]phenyl)sulfonyl]amino}benzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-14)



·2TFA

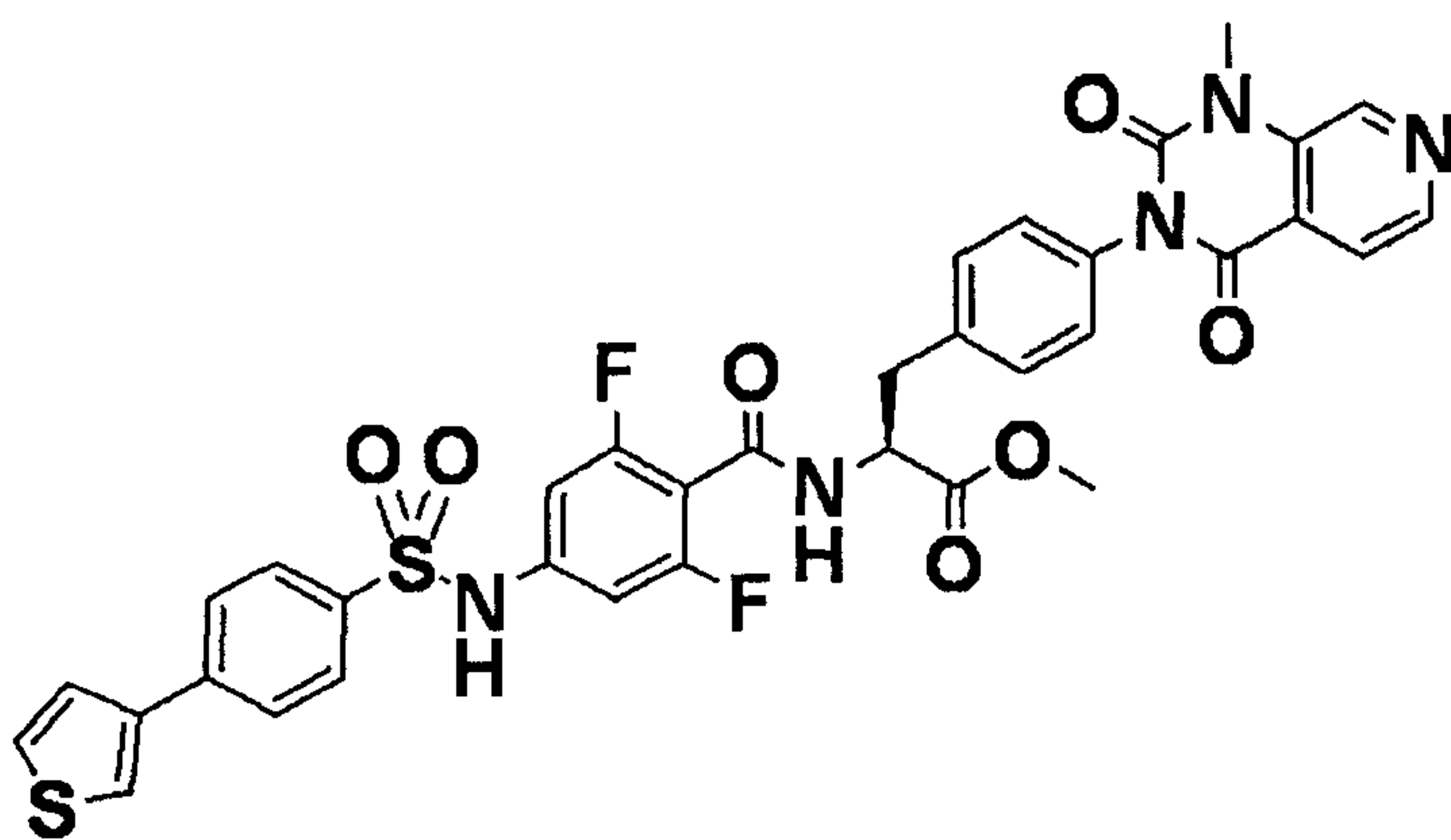
20 To the TFA salt (100 mg, 0.110 mmol) of methyl N-{2-fluoro-4-[(4-[(methylamino)methyl]phenyl)sulfonyl]amino}benzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-14), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added,

followed by stirring at 70°C for 2 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (89.5 mg, 92%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.03 (s, 1H), 8.98 (s, 1H), 8.87 (s, 2H), 8.56 (d, J = 4.9 Hz, 1H), 8.41 (dd, J = 7.8, 2.8 Hz, 1H), 7.96-7.83 (m, 3H), 7.66 (d, J = 8.4 Hz, 2H), 7.42 (t, J = 8.4 Hz, 1H), 7.37 (d, J = 8.3 Hz, 2H), 7.22 (d, J = 8.3 Hz, 2H), 7.04-6.92 (m, 2H), 4.66-4.55 (m, 1H), 4.17 (s, 2H), 3.60 (s, 3H), 3.22 (dd, J = 14.0, 4.4 Hz, 1H), 3.08 (dd, J = 14.0, 9.9 Hz, 1H), 2.57 (s, 3H).; MS (ESI) m/z 661 (M+H)⁺

Example 53: Synthesis of A-15 and B-15

(Step 1) Methyl N-[2,6-Difluoro-4-({[4-(3-thienyl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-15)



·TFA

20 Methyl

4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (M-1) (100 mg, 0.234 mmol) and 2,6-difluoro-4-({[4-(3-thienyl)phenyl]sulfonyl}amino)benzoi

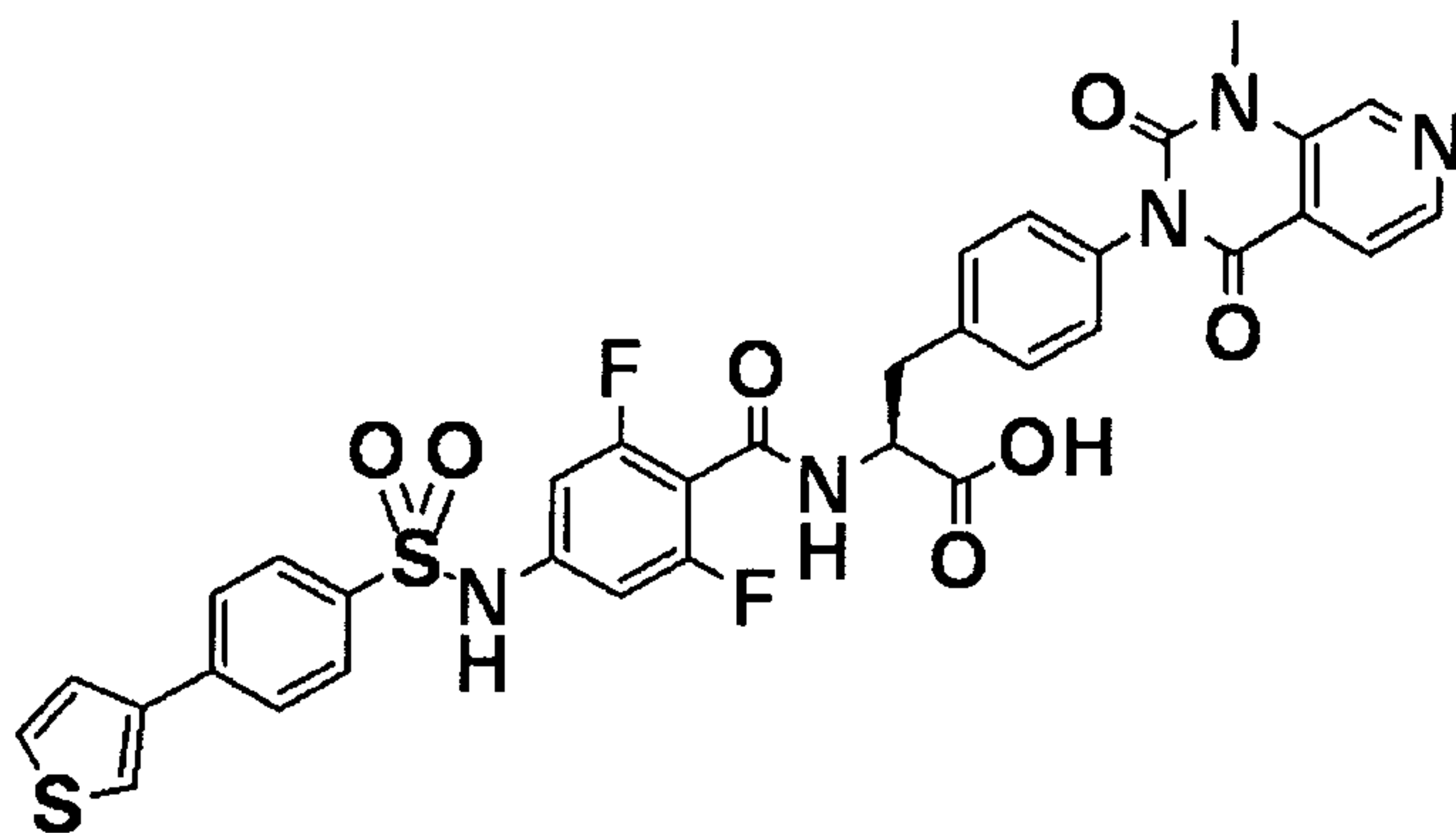
c acid (M-20) (91.0 mg, 0.234 mmol) were suspended in methylene chloride (2.0 ml), and HATU (133 mg, 0.350 mmol) and diisopropylethylamine (0.160 ml, 0.920 mmol) were added thereto, followed by stirring at room temperature for 1 hour. After the
 5 reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (150 mg, 77%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.23 (d, J = 7.6 Hz, 1H), 9.03 (s, 1H), 9.26 (d, J = 4.8 Hz, 1H), 8.14 (dd, J = 2.8, 1.2 Hz, 1H), 8.02 (d, J = 8.4 Hz, 2H), 7.95-7.93 (m, 3H), 7.76 (dd, J = 4.8, 0.8 Hz, 1H), 7.68 (dd, J = 4.8, 1.2 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 9.2 Hz, 2H), 4.71-4.65 (m, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.17-3.04
 10 (m, 2H).; MS (ESI) m/z 732 (M+H)⁺

(Step

2)

N-[2,6-Difluoro-4-({[4-(3-thienyl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-15)



20

·TFA

To the TFA salt (130 mg, 0.150 mmol) of methyl N-[2,6-difluoro-4-({[4-(3-thienyl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimid

in-3(2H)-yl)-L-phenylalaninate (B-15), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification
 5 was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (95.6 mg, 73%) of the title compound.

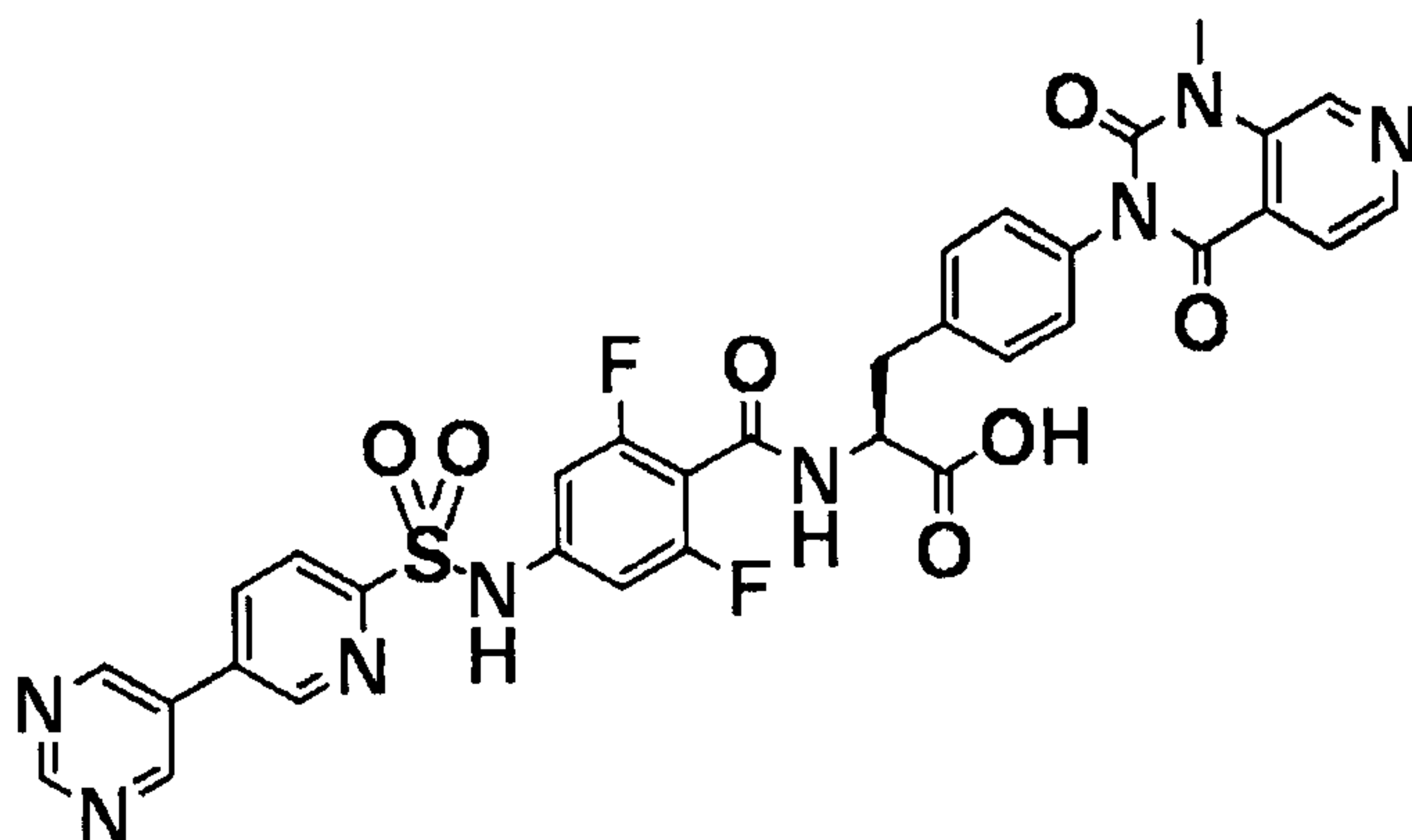
¹H NMR (d-DMSO, 400 MHz): δ 11.02 (s, 1H), 8.97 (d, J = 7.9 Hz, 1H), 8.90 (s, 1H), 8.49 (d, J = 4.9 Hz, 1H), 8.01 (dd, J = 2.8, 1.3 Hz, 1H), 7.89 (d, J = 8.6 Hz, 2H), 7.85-7.76 (m, 3H), 7.62 (dd, J = 5.0, 2.9 Hz, 1H), 7.55 (dd, J = 5.1, 1.2 Hz, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 6.74 (d, J = 9.1 Hz, 2H), 4.57-4.43 (m, 1H), 3.53 (s, 3H), 3.10 (dd, J = 14.2, 4.4 Hz, 1H), 2.91 (dd, J = 14.1, 9.9 Hz, 1H).; MS (ESI) m/z 718
 15 (M+H)⁺

Example 54: Synthesis of A-16

(Step

2)

N-(2,6-Difluoro-4-{[(5-pyrimidin-5-yl-pyridin-2-yl)sulfonyl]amino}benzoyl)-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-
 20 -d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-16)



·3TFA

Methyl

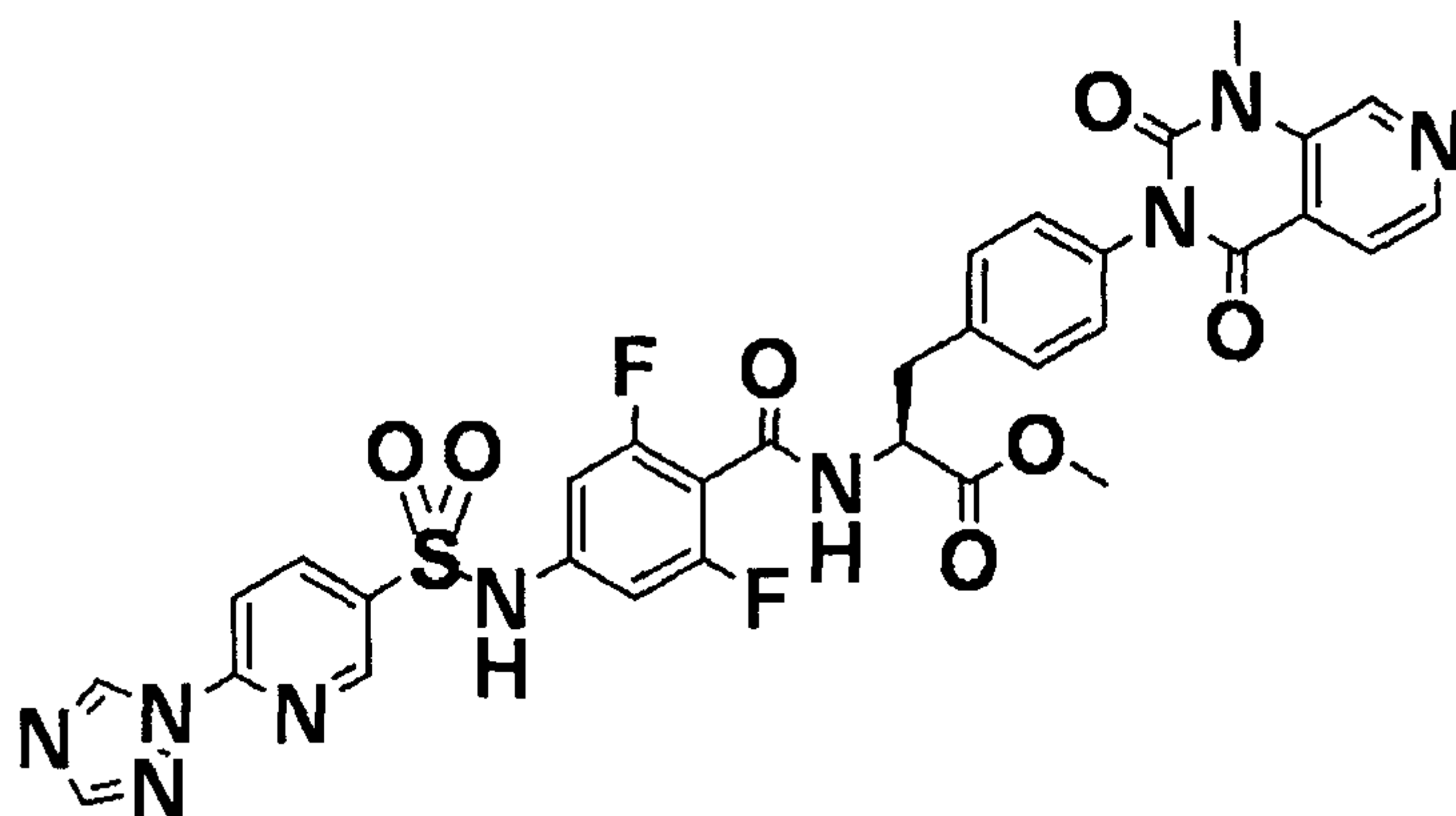
4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2

H)-yl)-L-phenylalaninate (M-1) (100 mg, 0.234 mmol) and 2,6-difluoro-4-{[(5-pyrimidin-5-yl-pyridin-2-yl)sulfonyl]amino}benzoic acid (M-21) (99.0 mg, 0.234 mmol) were suspended in methylene chloride (2.0 ml), and HATU (133 mg, 0.350 mmol) and diisopropylethylamine (0.160 ml, 0.920 mmol) were added thereto, followed by stirring at room temperature for 3 days. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system). To the obtained compound, a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (150 mg, 62%) of the title compound as a yellow solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.41 (s, 1H), 9.28 (d, J = 1.3 Hz, 3H), 9.20 (dd, J = 2.3, 0.7 Hz, 1H), 9.07 (d, J = 7.9 Hz, 1H), 8.97 (s, 1H), 8.61-8.50 (m, 2H), 8.26 (dd, J = 8.2, 0.7 Hz, 1H), 7.89 (dd, J = 5.0, 0.5 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 9.2 Hz, 2H), 4.62-4.49 (m, 1H), 3.60 (s, 3H), 3.17 (dd, J = 14.2, 4.3 Hz, 1H), 2.99 (dd, J = 14.1, 9.9 Hz, 1H).; MS (ESI) m/z 715 (M+H)⁺

Example 55: Synthesis of A-17 and B-17

(Step 1) Methyl N-[2,6-Difluoro-4-({[6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-17)



·3TFA

Methyl

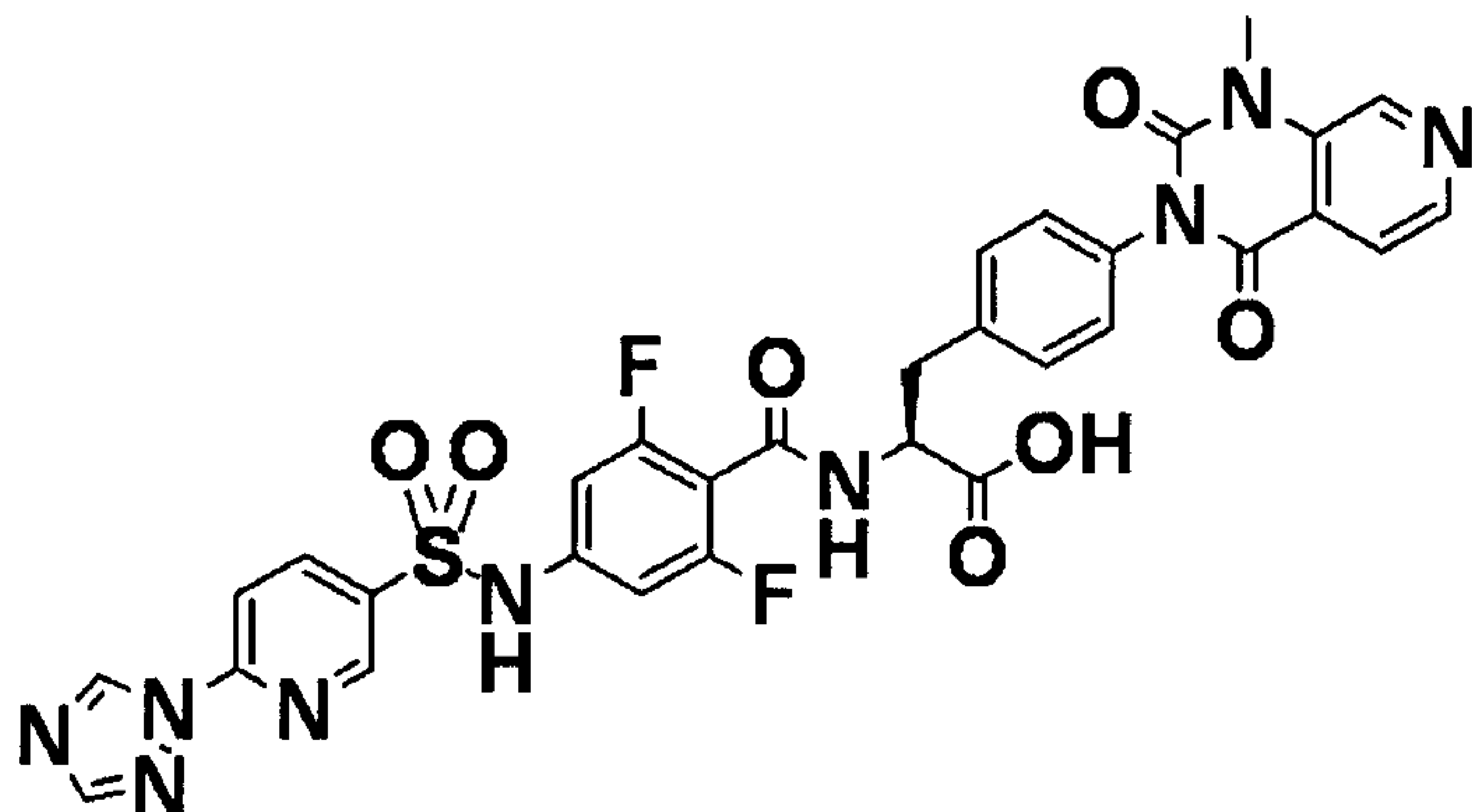
4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2
 5 H)-yl)-L-phenylalaninate (M-1) (100 mg, 0.234 mmol) and
 2,6-difluoro-4-([6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl]sul
 fonyl)amino)benzoic acid (M-22) (88.0 mg, 0.230 mmol) were
 suspended in methylene chloride (1.0 ml), and HATU (133 mg,
 0.350 mmol) and diisopropylethylamine (0.160 ml, 0.920 mmol)
 10 were added thereto, followed by stirring at room temperature
 for 2 hours. After the reaction liquid was concentrated under
 reduced pressure, purification was conducted by reversed-phase
 HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA
 salt (150 mg, 69%) of the title compound as a white solid.
 15 ¹H NMR (d-DMSO, 400 MHz): δ 11.4 (s, 1H), 9.51 (s, 1H), 9.26
 (d, J = 7.6 Hz, 1H), 9.03 (s, 2H), 8.62 (d, J = 5.2 Hz, 1H),
 8.55 (dd, J = 8.8, 2.4 Hz, 1H), 8.44 (s, 1H), 8.14 (dd, J = 8.8,
 0.4 Hz, 1H), 7.95 (dd, J = 5.2, 0.4 Hz, 1H), 7.40 (d, J = 8.4
 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 9.2 Hz, 2H),
 20 4.73-4.67 (m, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 3.21 (dd, J =
 14.0, 9.2 Hz, 1H), 3.09 (dd, J = 14.4, 10.0 Hz, 1H).; MS (ESI)
 m/z 718 (M+H)⁺

(Step

2)

N-[2,6-Difluoro-4-([6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl]

sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-17)



·3TFA

5 To the TFA salt (130 mg, 0.140 mmol) of methyl N-[2,6-difluoro-4-({[6-(1H-1,2,4-triazol-1-yl)pyridin-3-yl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-17), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0
10 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (106 mg, 81%) of the title compound.

15 ¹H NMR (d-DMSO, 400 MHz): δ 11.28 (s, 1H), 9.38 (s, 1H), 9.00 (d, J = 7.9 Hz, 1H), 8.95-8.84 (m, 2H), 8.49 (d, J = 4.9 Hz, 1H), 8.42 (dd, J = 8.7, 2.4 Hz, 1H), 8.31 (s, 1H), 8.01 (dd, J = 8.7, 0.6 Hz, 1H), 7.82 (dd, J = 5.0, 0.5 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.9 Hz, 2H), 4.59-4.45 (m, 1H), 3.53 (s, 3H), 3.10 (dd, J = 14.2, 4.4
20 Hz, 1H), 2.92 (dd, J = 14.2, 9.8 Hz, 1H).; MS (ESI) m/z 704 (M+H)⁺

Example 56: Synthesis of A-18 and B-18

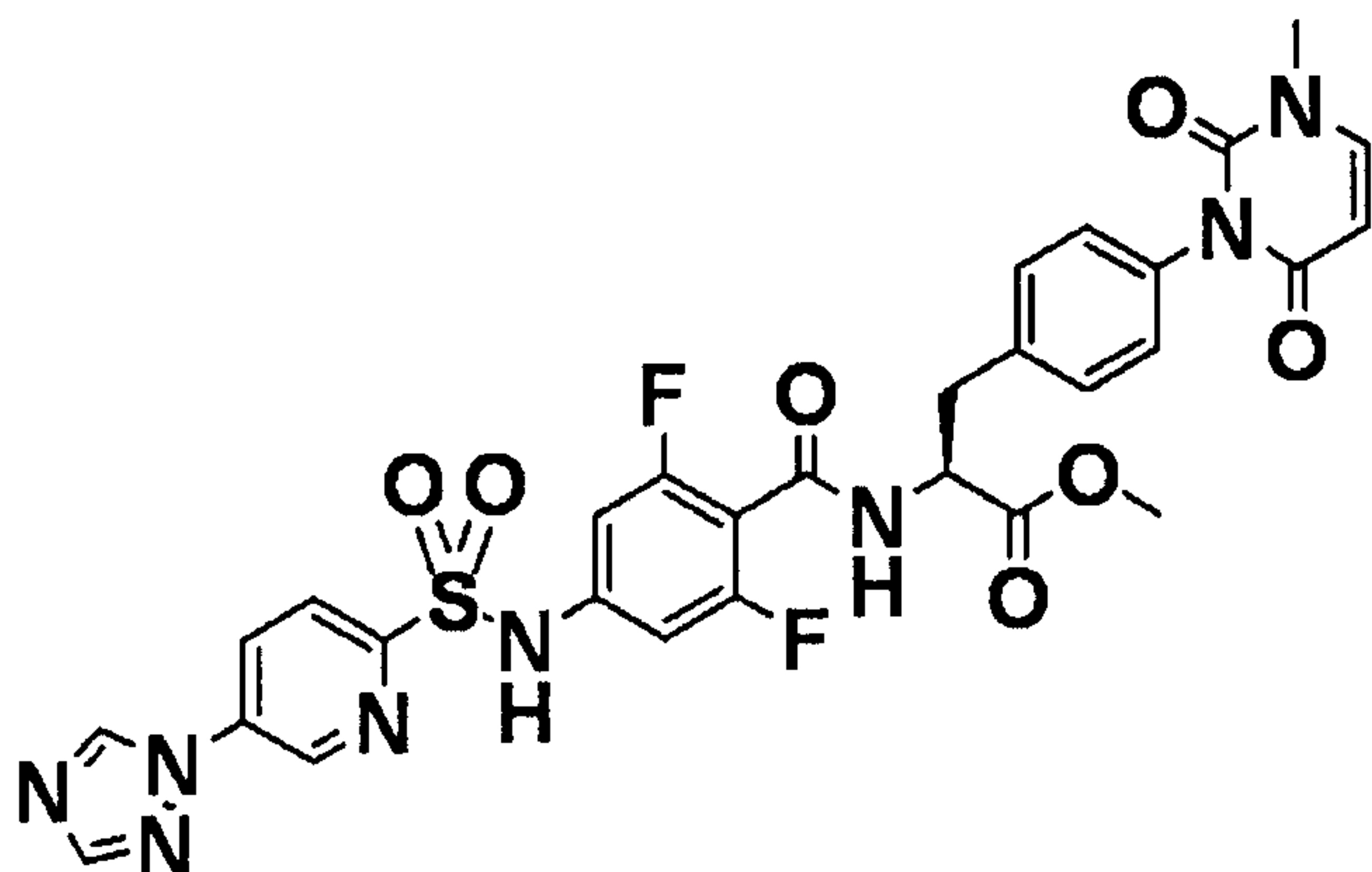
(Step

1)

Methyl

N-[2,6-Difluoro-4-({[5-(1H-1,2,4-triazol-1-yl)pyridin-2-yl]

sulfonyl}amino)benzoyl]-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (B-18)



·2TFA

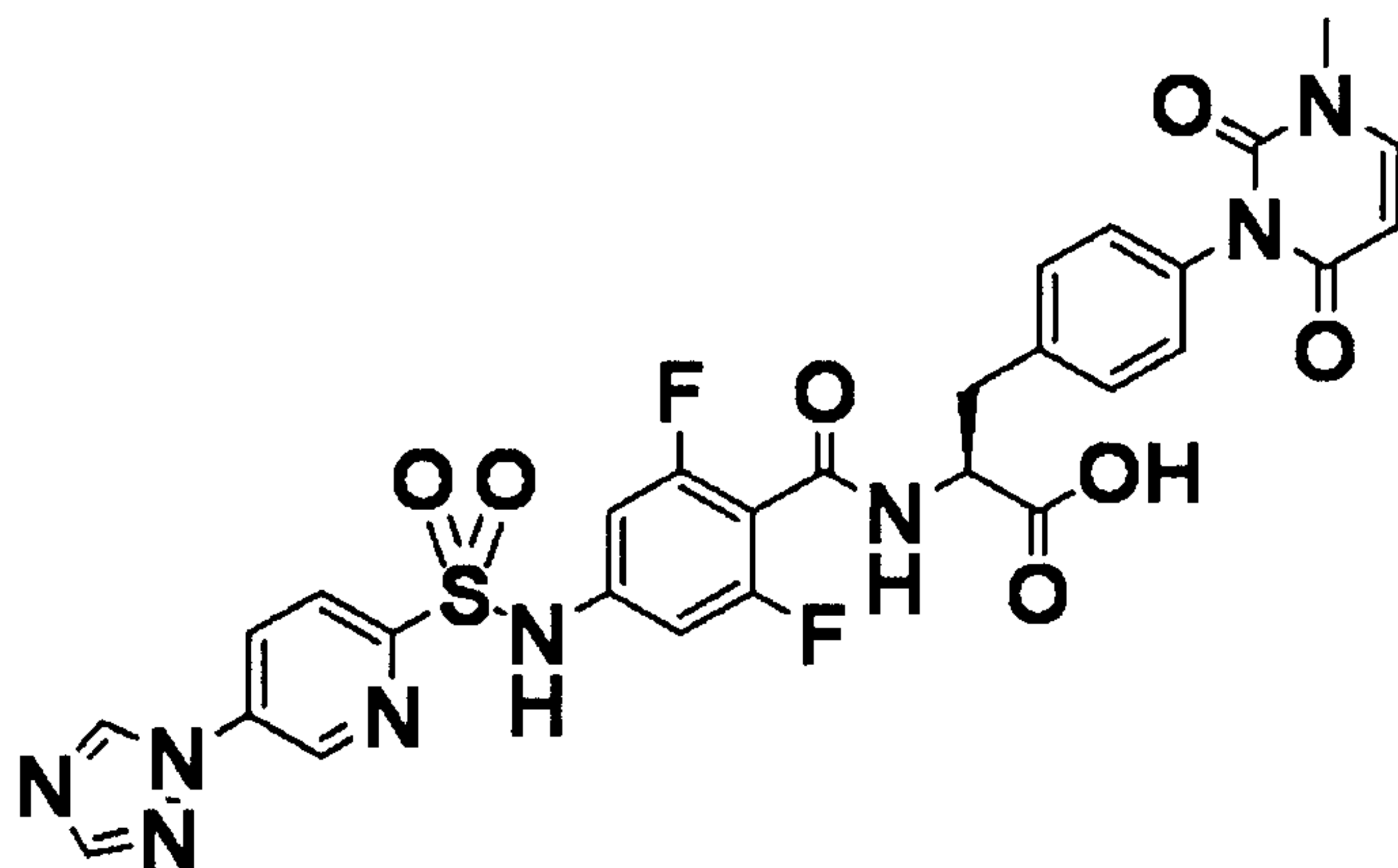
5 Methyl

4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (M-2) (80.0 mg, 0.240 mmol) and 2,6-difluoro-4-([5-(1H-1,2,4-triazol-1-yl)pyridin-2-yl]sulfonyl}amino)benzoic acid (M-23) (91.0 mg, 0.240 mmol) were
 10 suspended in methylene chloride (2.0 ml), and HATU (137 mg, 0.360 mmol) and diisopropylethylamine (0.167 ml, 0.960 mmol) were added thereto, followed by stirring at room temperature for 20 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase
 15 HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (38.0 mg, 26%) of the title compound as a white solid.
¹H NMR (d-DMSO, 400 MHz): δ 11.3 (s, 1H), 9.41 (s, 1H), 9.22 (d, J = 2.4 Hz, 1H), 9.11 (d, J = 7.6 Hz, 1H), 8.48 (dd, J = 8.8, 2.4 Hz, 1H), 8.30 (s, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 5.67 (d, J = 8.0 Hz, 1H), 4.60-4.51 (m, 1H), 3.56 (s, 3H), 3.24 (s, 3H), 3.08-2.91 (m, 2H).; MS (ESI) m/z 667 (M+H)⁺

(Step

2)

N-[2,6-Difluoro-4-({[5-(1H-1,2,4-triazol-1-yl)pyridin-2-yl]sulfonyl}amino)benzoyl]-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-18)



5

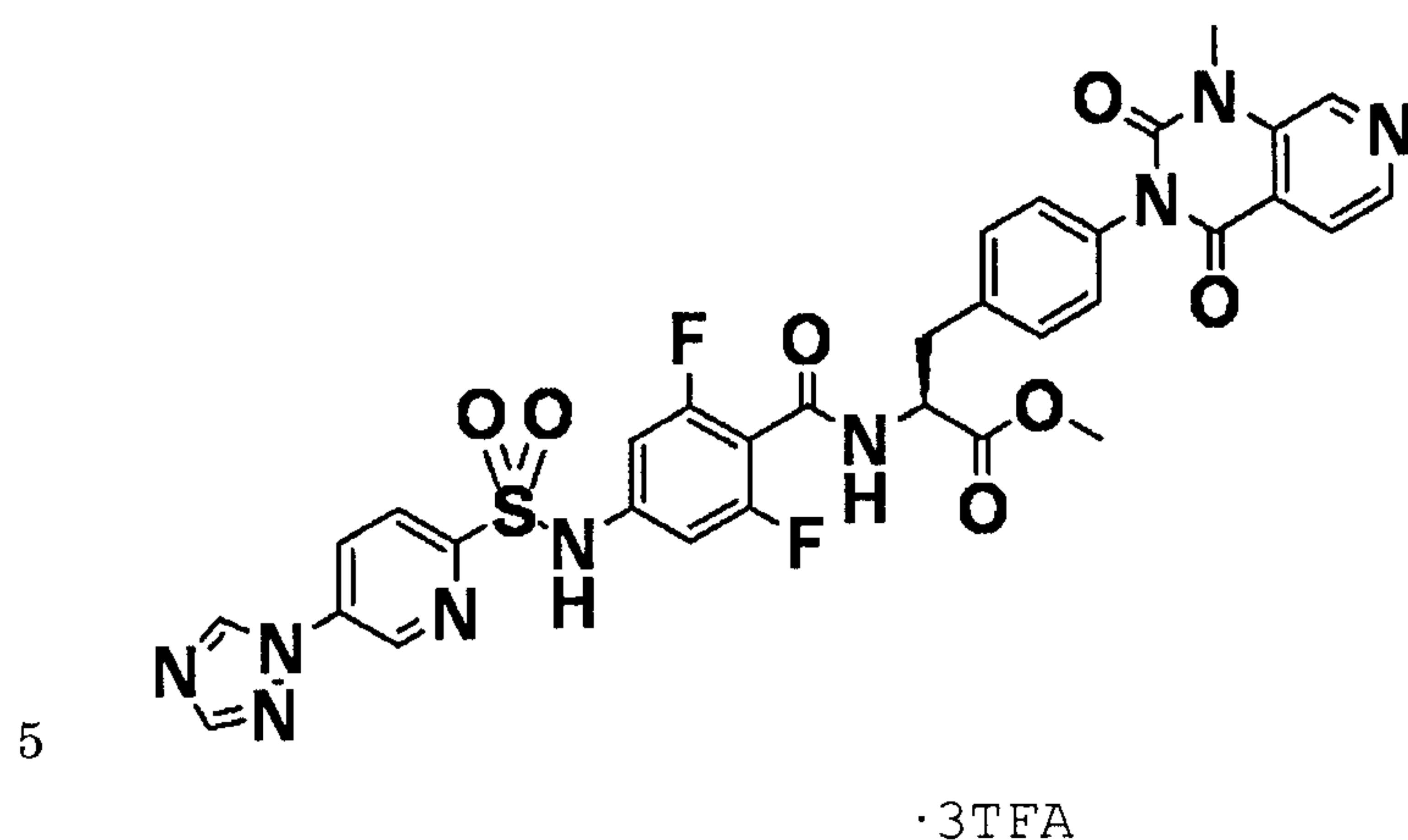
·2TFA

To the TFA salt (38 mg, 49 μmol) of methyl N-[2,6-difluoro-4-({[5-(1H-1,2,4-triazol-1-yl)pyridin-2-yl]sulfonyl}amino)benzoyl]-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (B-18), a 4 N hydrogen
 10 chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H_2O containing 0.1% TFA/ CH_3CN system) to obtain the TFA salt (22.9 mg, 61%) of the
 15 title compound.

^1H NMR (d-DMSO, 400 MHz): δ 11.46 (s, 1H), 9.54 (s, 1H), 9.35 (d, $J = 1.9$ Hz, 1H), 9.10 (d, $J = 7.8$ Hz, 1H), 8.63-8.58 (m, 1H), 8.45-8.35 (m, 3H), 7.80 (d, $J = 7.9$ Hz, 1H), 7.37 (d, $J = 8.3$ Hz, 2H), 7.15 (d, $J = 8.3$ Hz, 2H), 6.94 (d, $J = 9.2$ Hz, 2H), 5.80 (d, $J = 7.9$ Hz, 1H), 4.66-4.55 (m, 1H), 3.36 (s, 3H),
 20 3.20 (dd, $J = 14.1, 4.4$ Hz, 1H), 3.03 (dd, $J = 14.1, 9.8$ Hz, 1H).; MS (ESI) m/z 653 ($\text{M}+\text{H}$) $^+$

Example 57: Synthesis of A-19 and B-19

(Step 1) Methyl
N-[2,6-Difluoro-4-({[5-(1H-1,2,4-triazol-1-yl)pyridin-2-yl]
sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropy
rido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-19)



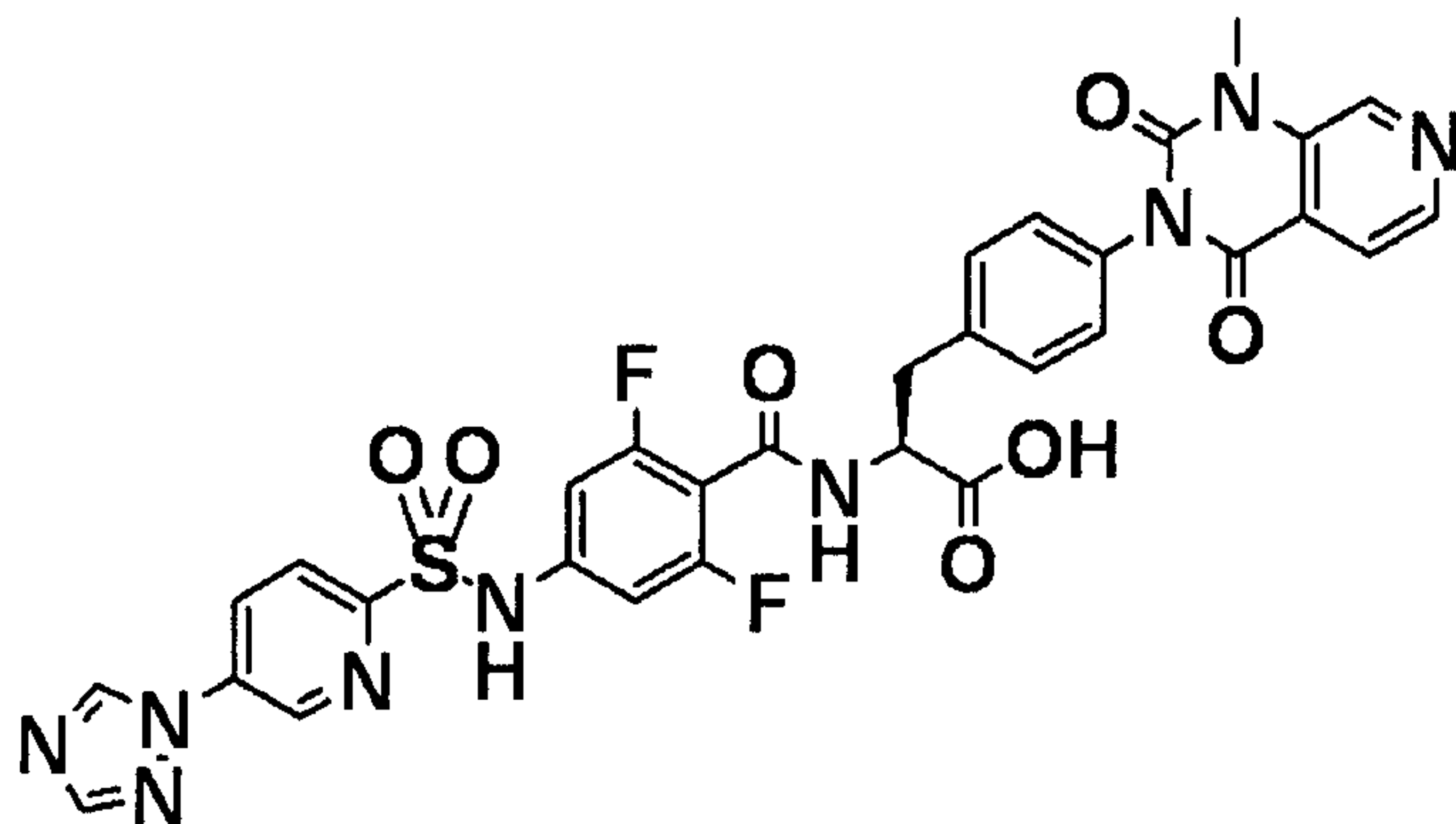
Methyl
 4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2
 H)-yl)-L-phenylalaninate (M-1) (100 mg, 0.234 mmol) and
 10 2,6-difluoro-4-({[5-(1H-1,2,4-triazol-1-yl)pyridin-2-yl]sul
 fonyl}amino)benzoic acid (M-23) (89.0 mg, 0.230 mmol) were
 suspended in methylene chloride (2.0 ml), and HATU (133 mg,
 0.350 mmol) and diisopropylethylamine (0.160 ml, 0.920 mmol)
 were added thereto, followed by stirring at room temperature
 15 for 2 hours. After the reaction liquid was concentrated under
 reduced pressure, purification was conducted by reversed-phase
 HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA
 salt (45.0 mg, 21%) of the title compound as a white solid.
¹H NMR (d-DMSO, 400 MHz): δ 11.4 (s, 1H), 9.49 (s, 1H), 9.30
 20 (d, J = 2.0 Hz, 1H), 9.19 (d, J = 7.6 Hz, 1H), 8.97 (s, 1H),
 8.56-8.54 (m, 2H), 8.37 (s, 1H), 8.33 (dd, J = 8.4, 0.4 Hz, 1H),
 7.89 (dd, J = 4.8, 0.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.21
 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.67-4.61 (m,
 1H), 3.69 (s, 3H), 3.60 (s, 3H), 3.17-3.00 (m, 2H).; MS (ESI)

m/z 718 (M+H)⁺

(Step

2)

N-[2,6-Difluoro-4-({[5-(1H-1,2,4-triazol-1-yl)pyridin-2-yl]
sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropy
5 rido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-19)



·3TFA

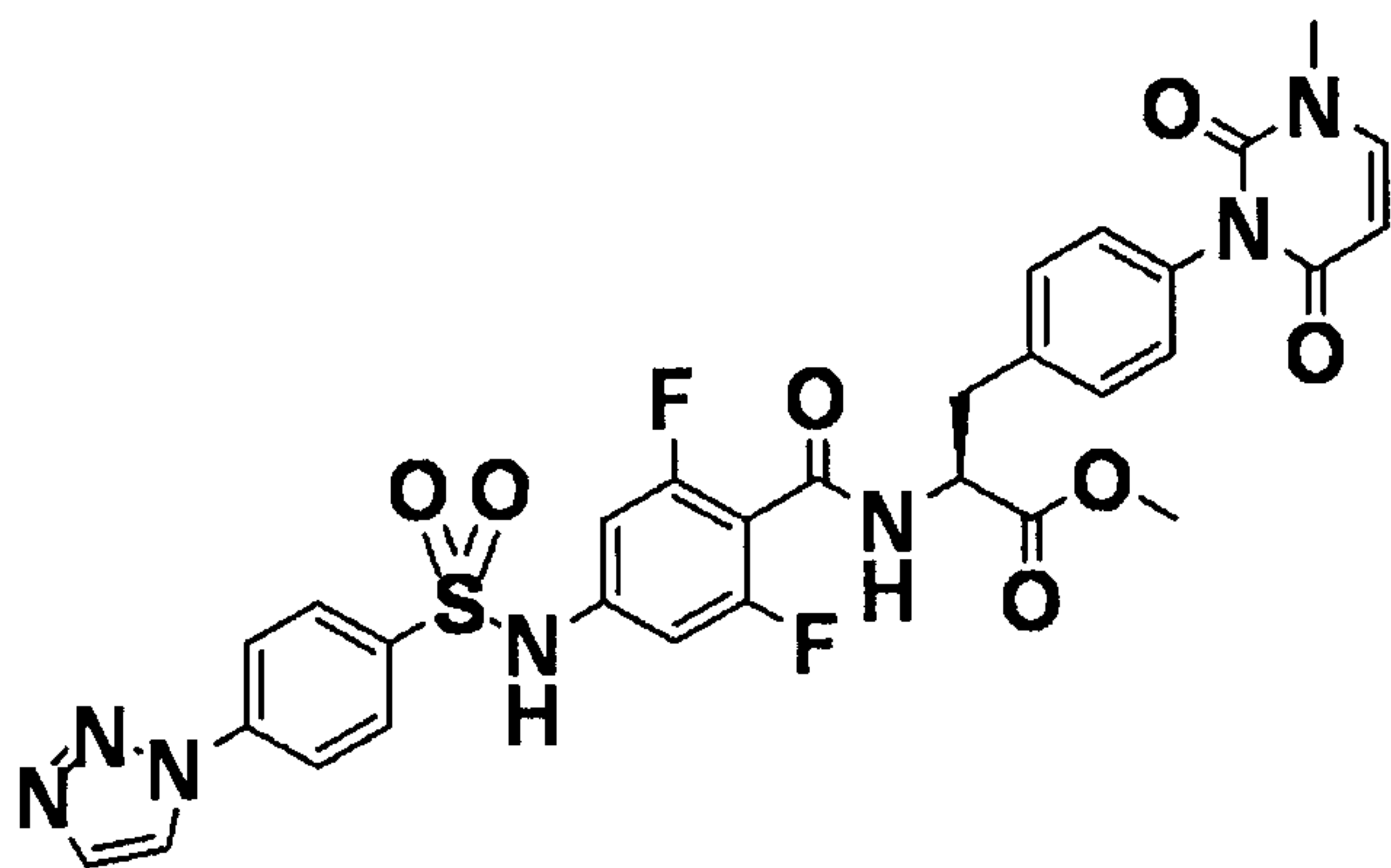
To the TFA salt (25.0 mg, 26.0 μmol) of methyl
N-[2,6-difluoro-4-({[5-(1H-1,2,4-triazol-1-yl)pyridin-2-yl]
10 sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropy
rido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-19), a 4
N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0
ml) were added, followed by stirring at 80°C for 1 hour. After
the reaction liquid was concentrated under reduced pressure,
15 purification was conducted by reversed-phase HPLC (H₂O
containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (13.1
mg, 54%) of the title compound.

¹H NMR (d-DMSO, 400 MHz): δ 11.40 (s, 1H), 9.48 (s, 1H), 9.30
(d, J = 2.2 Hz, 1H), 9.05 (d, J = 7.9 Hz, 1H), 8.97 (s, 1H),
20 8.61-8.50 (m, 2H), 8.37 (s, 1H), 8.32 (d, J = 8.5 Hz, 1H), 7.89
(d, J = 4.9 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.3
Hz, 2H), 6.89 (d, J = 9.2 Hz, 2H), 4.63-4.53 (m, 1H), 3.60 (s,
3H), 3.17 (dd, J = 14.2, 4.3 Hz, 1H), 2.99 (dd, J = 14.1, 9.9
Hz, 1H).; MS (ESI) m/z 704 (M+H)⁺

Example 58: Synthesis of A-20 and B-20

(Step 1) Methyl

N-[2,6-Difluoro-4-({[4-(1H-1,2,3-triazol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (B-20)



·TFA

Methyl

4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (M-2) (80.0 mg, 0.240 mmol) and 2,6-difluoro-4-({[4-(1H-1,2,3-triazol-1-yl)phenyl]sulfonyl}amino)benzoic acid (M-15) (91.0 mg, 0.240 mmol) were suspended in methylene chloride (2.0 ml), and HATU (137 mg, 0.360 mmol) and diisopropylethylamine (0.167 ml, 0.960 mmol) were added thereto, followed by stirring at room temperature for 20 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (70.0 mg, 44%) of the title compound as a white solid.

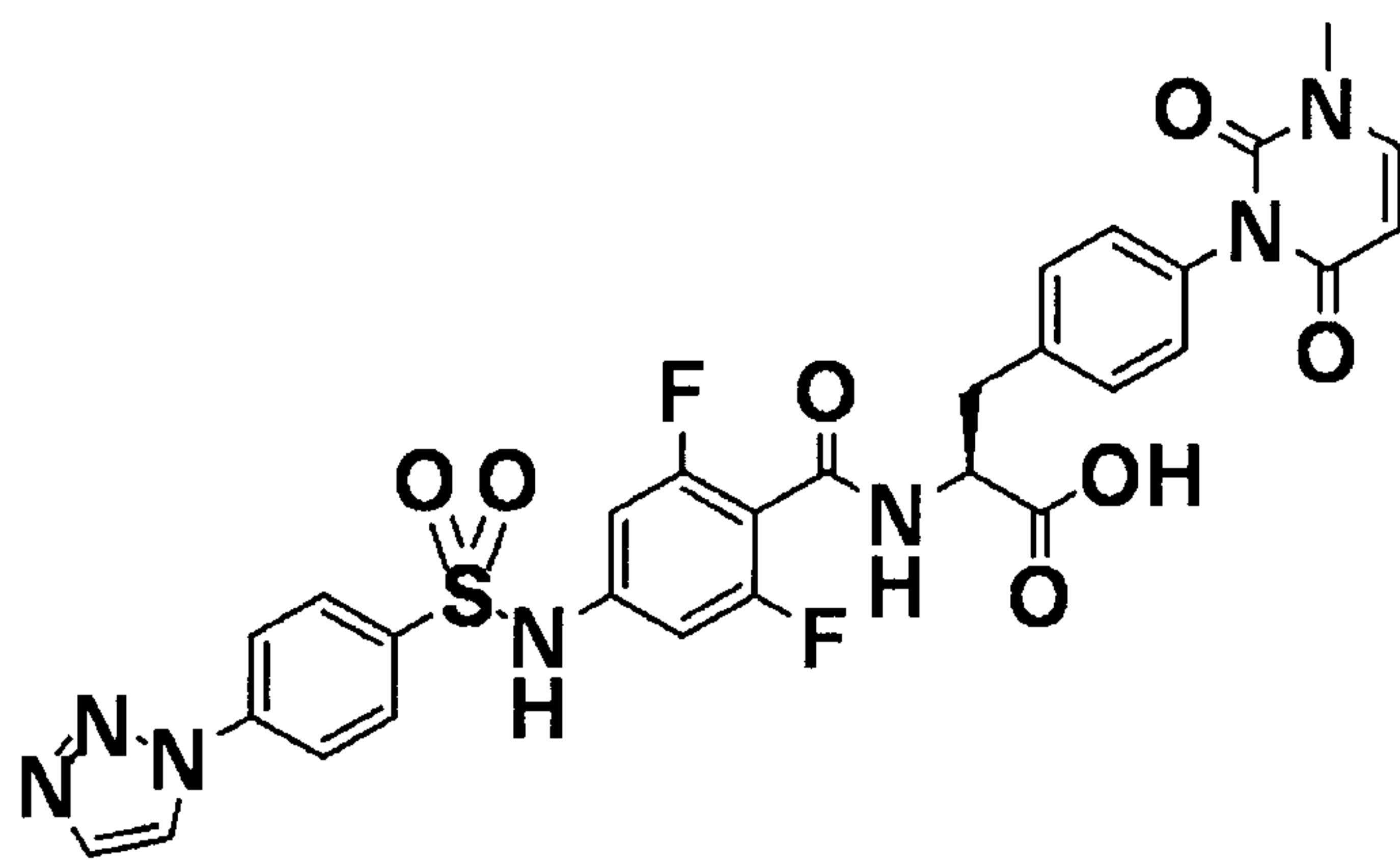
¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.17 (d, J = 7.6 Hz, 1H), 8.93 (d, J = 1.2 Hz, 1H), 8.18 (dd, J = 7.2, 2.0 Hz, 2H), 8.08 (dd, J = 6.8, 1.6 Hz, 2H), 8.02 (d, J = 1.2 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 5.74 (d, J = 8.0 Hz, 1H),

4.63-4.57 (m, 1H), 3.62 (s, 3H), 3.30 (s, 3H), 3.14-2.97 (m, 2H) 4.67-4.61 (m, 1H), 3.69 (s, 3H), 3.60 (s, 3H), 3.17-3.00 (m, 2H).; MS (ESI) m/z 666 (M+H)⁺

(Step

2)

5 N-[2,6-Difluoro-4-({[4-(1H-1,2,3-triazol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-20)



·TFA

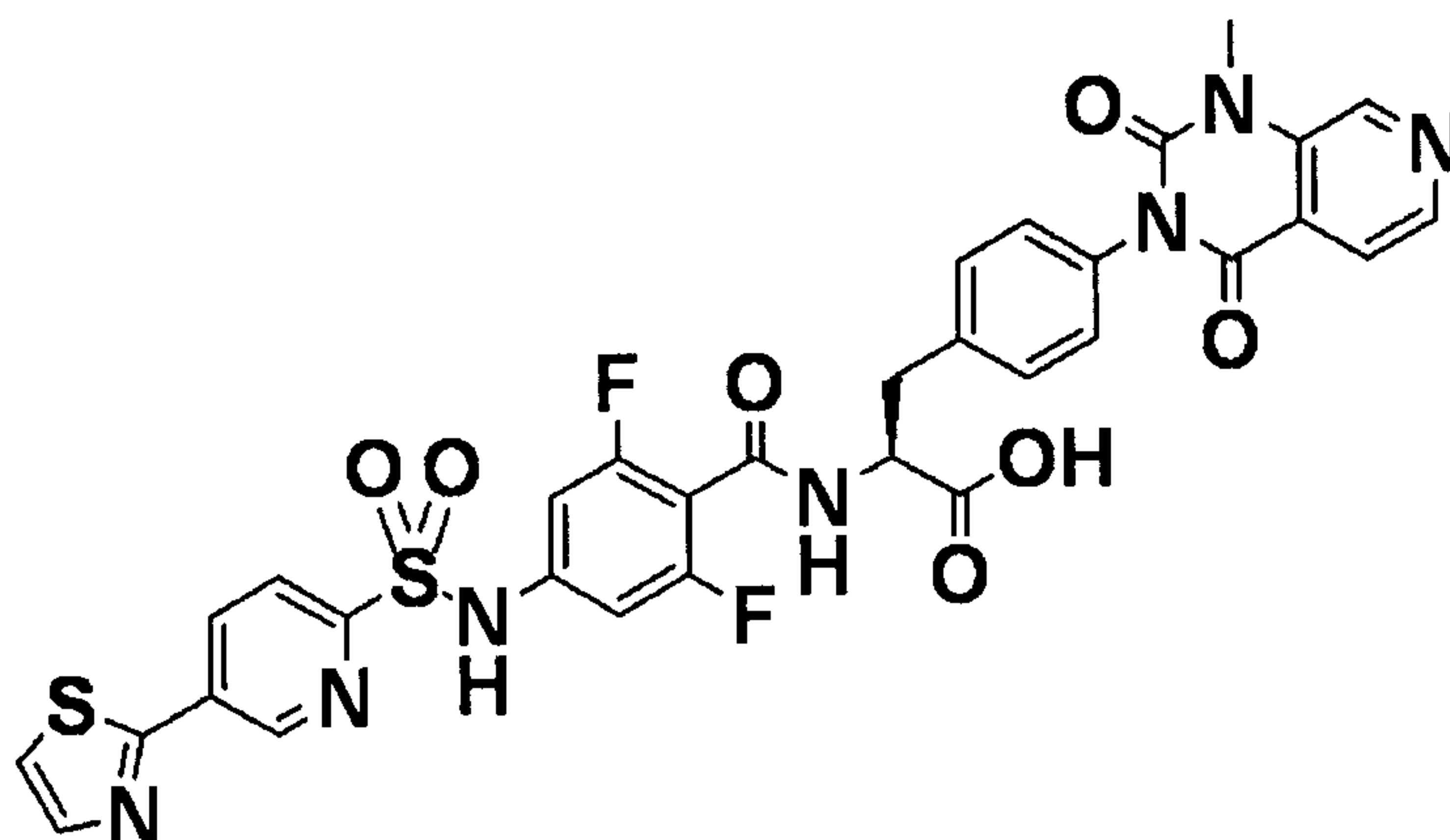
10 To the TFA salt (50 mg, 75 μ mol) of methyl N-[2,6-difluoro-4-({[4-(1H-1,2,3-triazol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (B-20), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (34.7 mg, 71%) of the title compound as a white solid.

20 ¹H NMR (d-DMSO, 400 MHz): δ 11.14 (s, 1H), 8.97 (d, J = 7.8 Hz, 1H), 8.85 (d, J = 1.2 Hz, 1H), 8.16-8.05 (m, 2H), 8.05-7.97 (m, 2H), 7.95 (d, J = 1.2 Hz, 1H), 7.67 (d, J = 7.9 Hz, 1H), 7.23 (d, J = 8.3 Hz, 2H), 7.02 (d, J = 8.3 Hz, 2H), 6.76 (d, J = 9.0

Hz, 2H), 5.67 (d, J = 7.9 Hz, 1H), 4.54-4.42 (m, 1H), 3.23 (s, 3H), 3.07 (dd, J = 14.2, 4.5 Hz, 1H), 2.90 (dd, J = 14.2, 9.7 Hz, 1H).; MS (ESI) m/z 652 (M+H)⁺

Example 59: Synthesis of A-21

5 (Step 2)
N-[2,6-Difluoro-4-({[5-(1,3-thiazol-2-yl)pyridin-2-yl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-21)



10 ·2TFA

Methyl

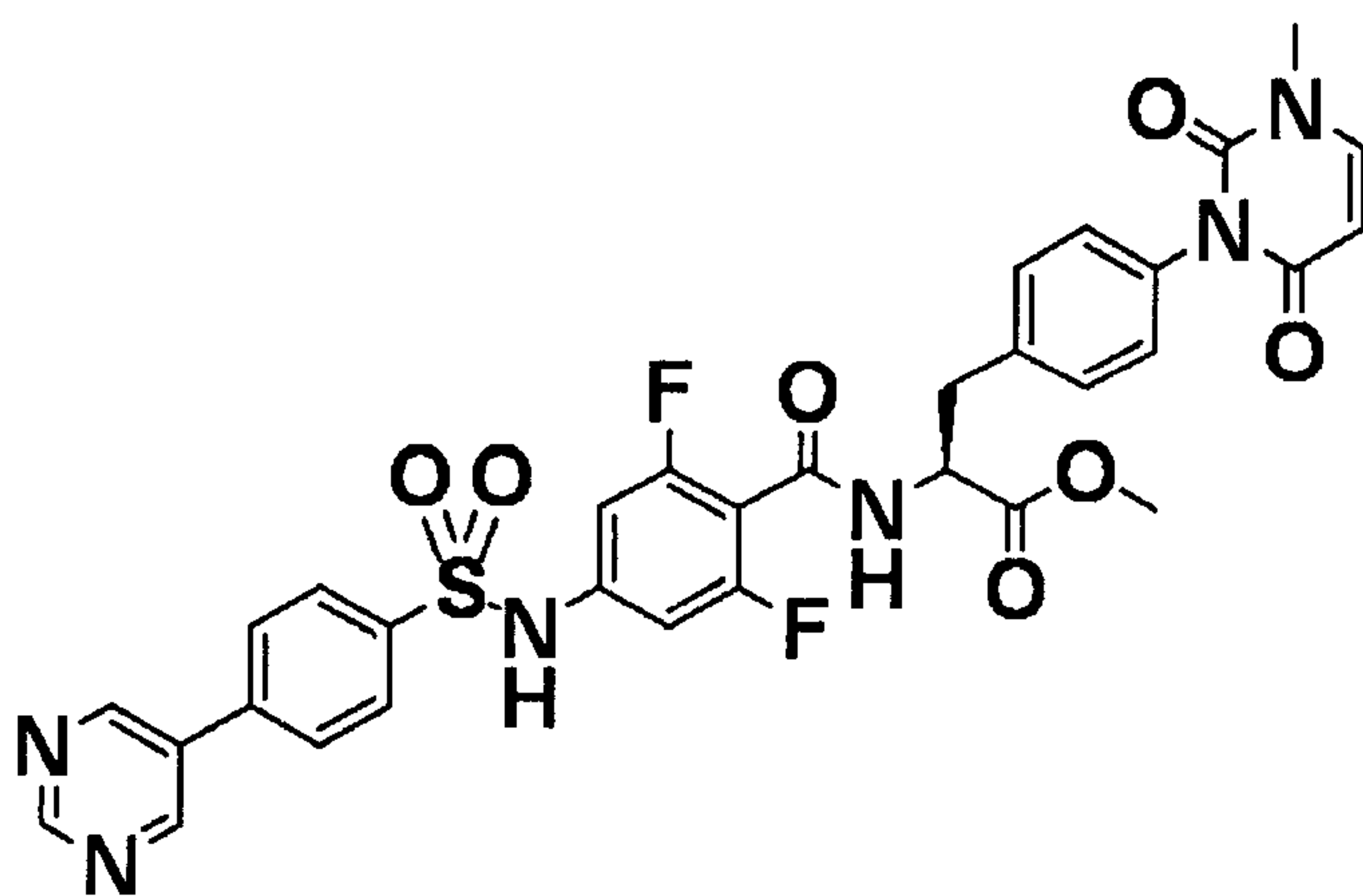
4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (M-1) (98.0 mg, 0.230 mmol) and 2,6-difluoro-4-({[5-(1,3-thiazol-2-yl)pyridin-2-yl]sulfonyl}amino)benzoic acid (M-24) (91.0 mg, 0.230 mmol) were suspended
 15 in methylene chloride (2.0 ml), and HATU (133 mg, 0.350 mmol) and diisopropylethylamine (0.160 ml, 0.920 mmol) were added thereto, followed by stirring at room temperature for 4 days. After the reaction liquid was concentrated under reduced
 20 pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system). To the obtained compound, a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1

hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (18.6 mg, 8% over two steps) of the title compound.

5 ¹H NMR (d-DMSO, 400 MHz): δ 12.85 (s, 1H), 11.39 (s, 1H), 9.29 (dd, J = 2.2, 0.7 Hz, 1H), 9.04 (d, J = 7.9 Hz, 1H), 8.97 (s, 1H), 8.61 (dd, J = 8.2, 2.2 Hz, 1H), 8.55 (d, J = 4.9 Hz, 1H), 8.22 (dd, J = 8.3, 0.7 Hz, 1H), 8.08 (d, J = 3.2 Hz, 1H), 8.02 (d, J = 3.2 Hz, 1H), 7.88 (dd, J = 5.0, 0.6 Hz, 1H), 7.35 (d, 10 J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 9.2 Hz, 2H), 4.62-4.52 (m, 1H), 3.60 (s, 3H), 3.17 (dd, J = 14.2, 4.5 Hz, 1H), 2.99 (dd, J = 14.1, 9.8 Hz, 1H).; MS (ESI) m/z 720 (M+H)⁺

Example 60: Synthesis of A-22 and B-22

(Step 1) Methyl
15 N-(2,6-Difluoro-4-{[(4-pyrimidin-5-yl-phenyl)sulfonyl]amino}
}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-
yl)-L-phenylalaninate (B-22)



·TFA

20

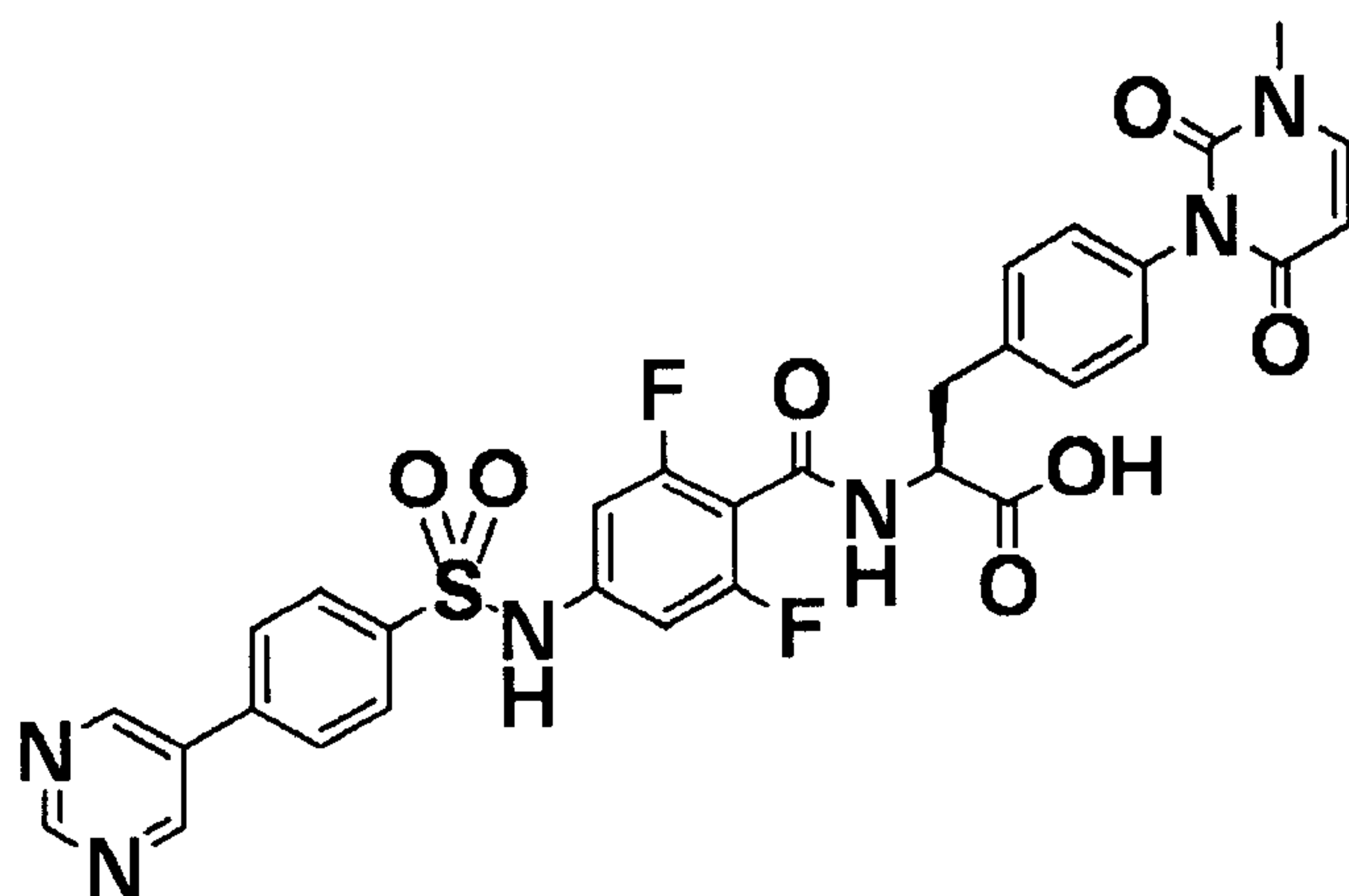
Methyl

4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (M-2) (80.0 mg, 0.240 mmol) and 2,6-difluoro-4-{[(4-pyrimidin-5-yl-phenyl)sulfonyl]amino}be

nzoic acid (M-25) (94.0 mg, 0.240 mmol) were suspended in methylene chloride (2.0 ml), and HATU (137 mg, 0.360 mmol) and diisopropylethylamine (0.167 ml, 0.960 mmol) were added thereto, followed by stirring at room temperature for 16 hours. After
 5 the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (80.0 mg, 42%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.24 (s, 1H), 9.20-9.15
 10 (m, 3H), 8.06 (dd, J = 6.8, 2.0 Hz, 2H), 8.01 (dd, J = 6.8, 2.0 Hz, 2H), 7.75 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 9.2 Hz, 2H), 5.74 (d, J = 8.0 Hz, 1H), 4.63-4.57 (m, 1H), 3.62 (s, 3H), 3.30 (s, 3H), 3.17-2.97 (m, 2H).; MS (ESI) m/z 677 (M+H)⁺

15 (Step 2)
N-(2,6-Difluoro-4-{[(4-pyrimidin-5-yl-phenyl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-22)



20

·TFA

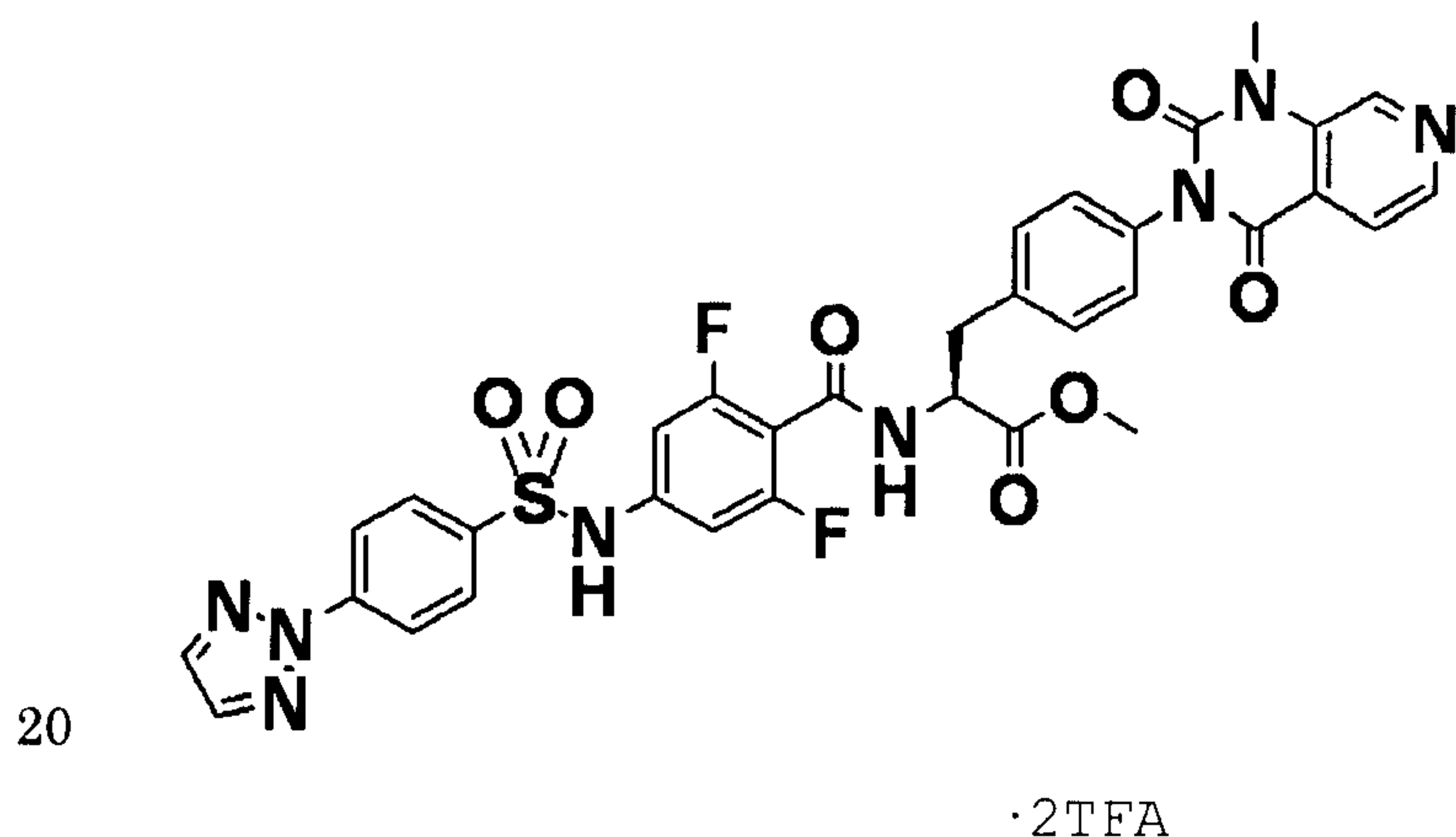
To the TFA salt (60 mg, 76 μmol) of methyl N-(2,6-difluoro-4-{[(4-pyrimidin-5-yl-phenyl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-

yl)-L-phenylalaninate (B-22), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was
 5 conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (34.8 mg, 59%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.22 (s, 1H), 9.22 (d, J = 18.0 Hz, 3H), 9.05 (d, J = 7.8 Hz, 1H), 8.06 (d, J = 8.5 Hz, 2H),
 10 8.01 (d, J = 8.5 Hz, 2H), 7.75 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.08 (d, J = 8.2 Hz, 2H), 6.83 (d, J = 9.0 Hz, 2H), 5.74 (d, J = 7.9 Hz, 1H), 4.61-4.49 (m, 1H), 3.30 (s, 3H), 3.14 (dd, J = 14.2, 4.3 Hz, 1H), 2.96 (dd, J = 14.1, 9.8 Hz, 1H).; MS (ESI) m/z 663 (M+H)⁺

15 Example 61: Synthesis of A-23 and B-23

(Step 1) Methyl N-[2,6-Difluoro-4-({[4-(2H-1,2,3-triazol-2-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-23)



Methyl

4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (M-1) (100 mg, 0.234 mmol) and

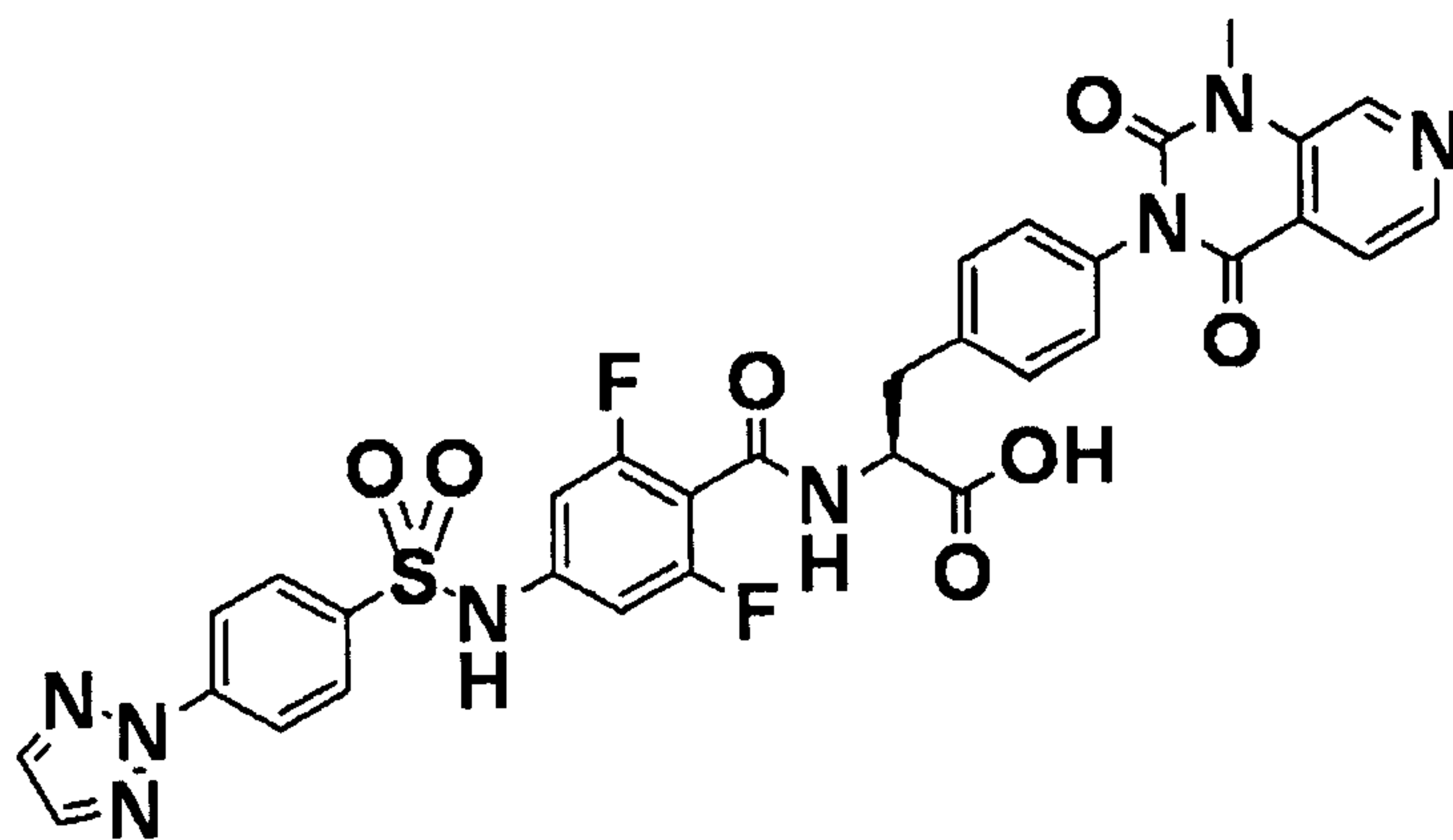
2,6-difluoro-4-({[4-(2H-1,2,3-triazol-2-yl)phenyl]sulfonyl} amino)benzoic acid (M-16) (87.0 mg, 0.230 mmol) were suspended in methylene chloride (2.0 ml), and HATU (133 mg, 0.350 mmol) and diisopropylethylamine (0.160 ml, 0.920 mmol) were added thereto, followed by stirring at room temperature for 17 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (120 mg, 63%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.3 (s, 1H), 9.23 (d, J = 7.6 Hz, 1H), 9.03 (s, 1H), 8.62 (d, J = 5.2 Hz, 1H), 8.32-8.28 (m, 4H), 8.12 (dd, J = 7.2, 2.0 Hz, 2H), 7.95 (d, J = 4.8 Hz, 1H), 7.39 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 9.2 Hz, 2H), 4.71-4.66 (m, 1H), 3.69 (s, 3H), 3.66 (s, 3H), 3.26-3.05 (m, 2H).; MS (ESI) m/z 717 (M+H)⁺

(Step

2)

N-[2,6-Difluoro-4-({[4-(2H-1,2,3-triazol-2-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-23)



20

·2TFA

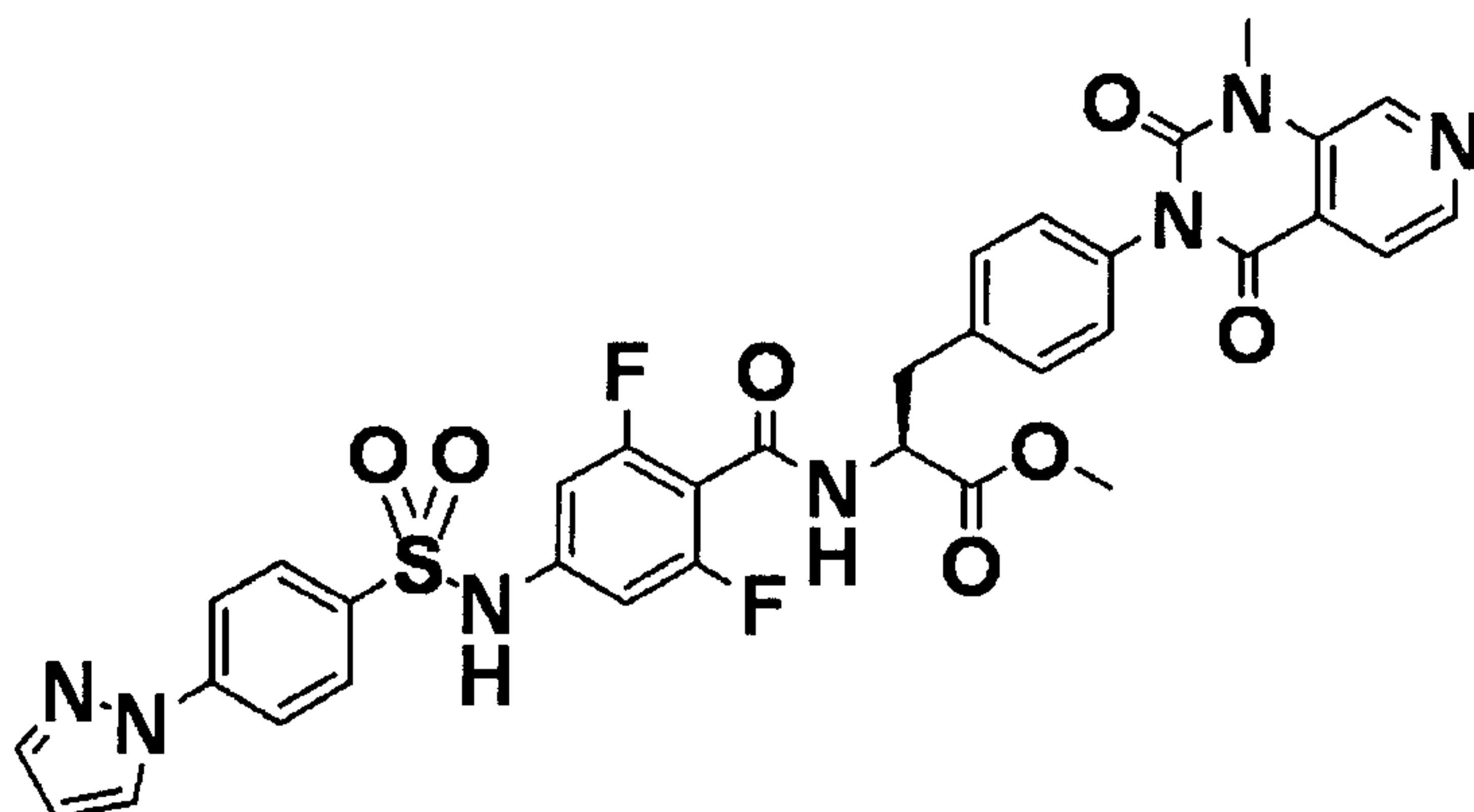
To the TFA salt (100 mg, 0.120 mmol) of methyl N-[2,6-difluoro-4-({[4-(2H-1,2,3-triazol-2-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-23)

yl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-23), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the
 5 reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (79.4 mg, 81%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.11 (s, 1H), 8.97 (d, J = 7.9 Hz, 1H), 8.90 (s, 1H), 8.49 (d, J = 4.9 Hz, 1H), 8.18 (d, J = 8.9 Hz, 2H), 8.15 (s, 2H), 8.02-7.95 (m, 2H), 7.82 (d, J = 4.9 Hz, 1H), 7.27 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 6.74 (d, J = 9.0 Hz, 2H), 4.57-4.44 (m, 1H), 3.53 (s, 3H), 3.10 (dd, J = 14.1, 4.4 Hz, 1H), 2.91 (dd, J = 14.1, 9.8 Hz, 1H).; MS (ESI)
 15 m/z 703 (M+H)⁺

Example 62: Synthesis of A-24 and B-24

(Step 1) Methyl N-[2,6-Difluoro-4-({[4-(1H-pyrazol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]p
 20 yrimidin-3(2H)-yl)-L-phenylalaninate (B-24)



·2TFA

Methyl

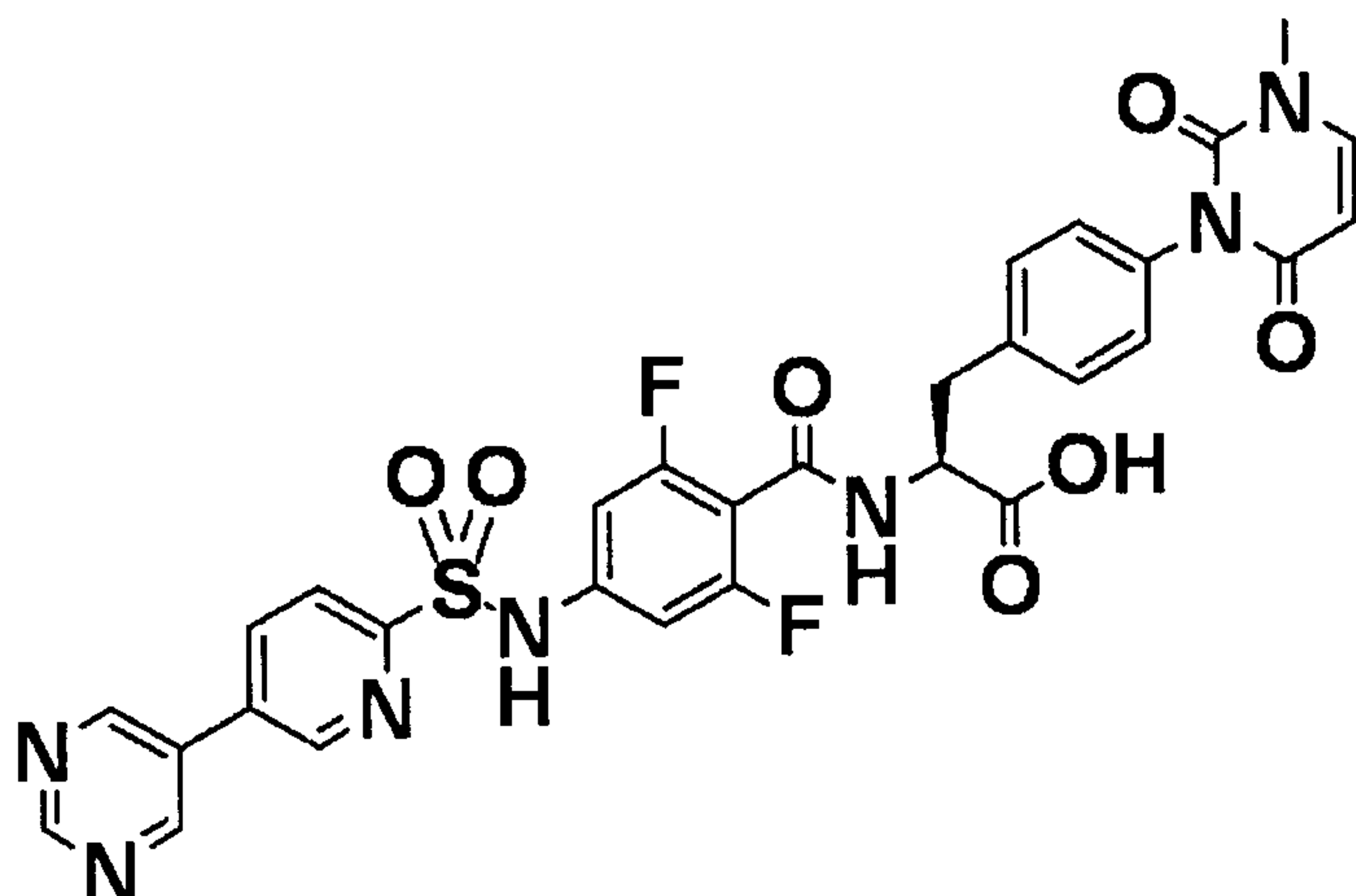
4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2

To the TFA salt (100 mg, 0.110 mmol) of methyl N-[2,6-difluoro-4-({[4-(1H-pyrazol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-24), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (77.6 mg, 76%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 11.03 (s, 1H), 8.96 (d, J = 7.9 Hz, 1H), 8.90 (s, 1H), 8.54 (d, J = 2.6 Hz, 1H), 8.49 (d, J = 4.9 Hz, 1H), 8.01 (d, J = 8.9 Hz, 2H), 7.90 (d, J = 8.9 Hz, 2H), 7.82 (d, J = 5.0 Hz, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.28 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 6.74 (d, J = 9.1 Hz, 2H), 6.54 (dd, J = 2.5, 1.8 Hz, 1H), 4.57-4.43 (m, 1H), 3.53 (s, 3H), 3.10 (dd, J = 14.2, 4.4 Hz, 1H), 2.91 (dd, J = 14.1, 9.8 Hz, 1H).; MS (ESI) m/z 702 (M+H)⁺

Example 63: Synthesis of A-25

(Step 2)
N-(2,6-Difluoro-4-{[(5-pyrimidin-5-yl-pyridin-2-yl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-25)



·2TFA

Methyl

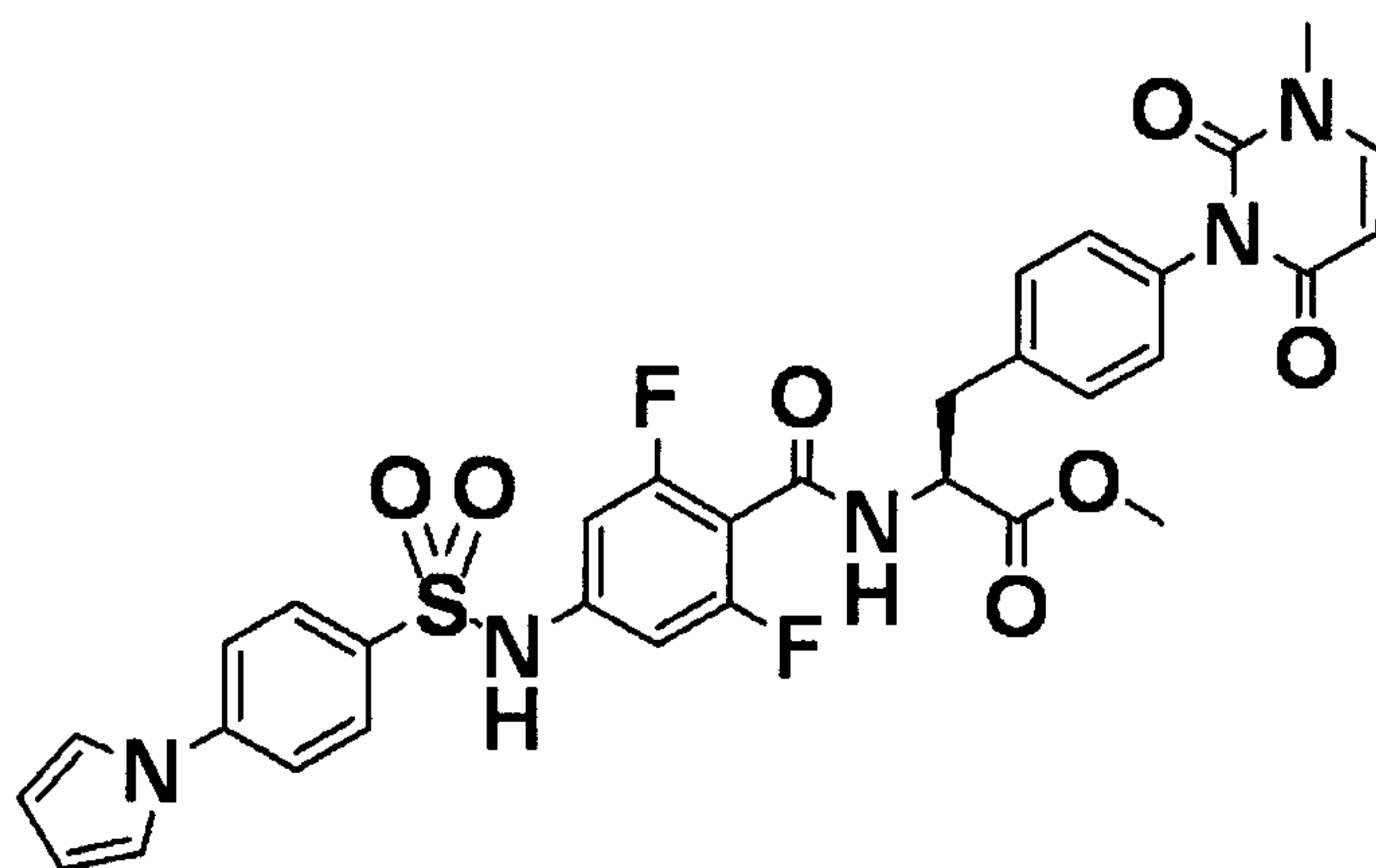
4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phen
 5 ylalaninate (M-2) (100 mg, 0.290 mmol) and
 2,6-difluoro-4-{[(5-pyrimidin-5-yl-pyridin-2-yl)sulfonyl]am
 ino}benzoic acid (M-21) (124 mg, 0.290 mmol) were suspended in
 methylene chloride (2.0 ml), and HATU (165 mg, 0.440 mmol) and
 diisopropylethylamine (0.202 ml, 1.16 mmol) were added thereto,
 10 followed by stirring at room temperature for 3 days. After the
 reaction liquid was concentrated under reduced pressure,
 purification was conducted by reversed-phase HPLC (H₂O
 containing 0.1% TFA/CH₃CN system). To the obtained compound,
 a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (2.0
 15 ml) were added, followed by stirring at 80°C for 1 hour. After
 the reaction liquid was concentrated under reduced pressure,
 purification was conducted by reversed-phase HPLC (H₂O
 containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (120
 mg, 46%) of the title compound.

20 ¹H NMR (d-DMSO, 400 MHz): δ 12.86 (s, 1H), 11.41 (s, 1H), 9.28
 (s, 3H), 9.20 (dd, J = 2.3, 0.7 Hz, 1H), 9.05 (d, J = 7.8 Hz,
 1H), 8.56 (dd, J = 8.2, 2.3 Hz, 1H), 8.26 (dd, J = 8.2, 0.6 Hz,
 1H), 7.75 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.09

(d, $J = 8.4$ Hz, 2H), 6.90 (d, $J = 9.2$ Hz, 2H), 5.74 (d, $J = 7.9$ Hz, 1H), 4.60-4.46 (m, 1H), 3.30 (s, 3H), 3.14 (dd, $J = 14.1$, 4.4 Hz, 1H), 2.97 (dd, $J = 14.0$, 9.7 Hz, 1H).; MS (ESI) m/z 664 (M+H)⁺

5 Example 64: Synthesis of A-26 and B-26

(Step 1) Methyl N-[2,6-Difluoro-4-([4-(1H-pyrrol-1-yl)phenyl]sulfonyl)amino]benzoyl]-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (B-26)



10

Methyl

4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (M-2) (73.0 mg, 0.220 mmol) and 2,6-difluoro-4-([4-(1H-pyrrol-1-yl)phenyl]sulfonyl)amino]benzoic acid (M-10) (69.0 mg, 0.180 mmol) were suspended in methylene chloride (2.0 ml), and HATU (103 mg, 0.270 mmol) and diisopropylethylamine (0.125 ml, 0.720 mmol) were added thereto, followed by stirring at room temperature for 2 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the title compound (70.0 mg, 59%) as a white solid.

20

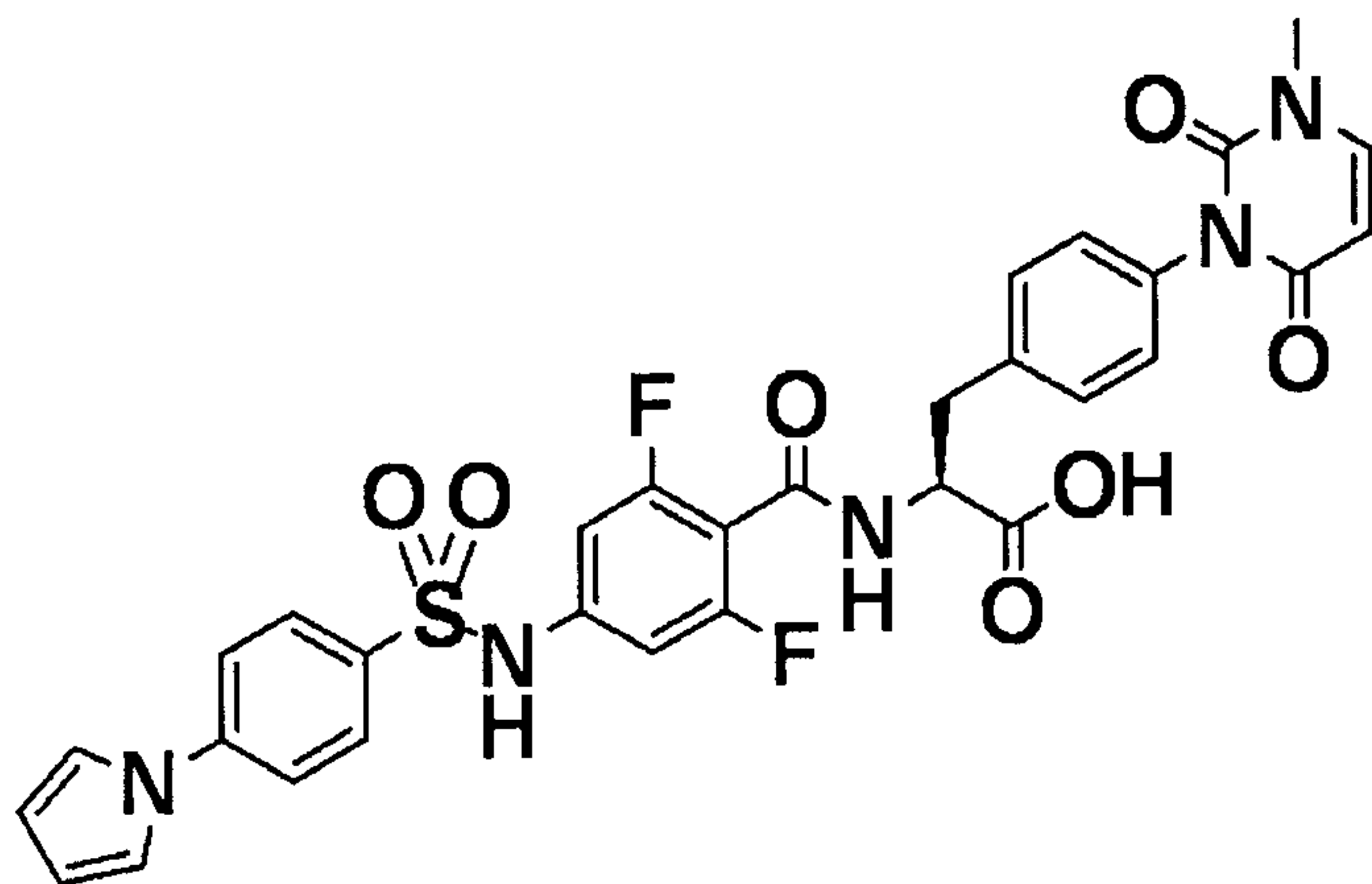
¹H NMR (d-DMSO, 400 MHz): δ 11.1 (s, 1H), 9.16 (d, $J = 7.6$ Hz,

1H), 7.90 (dd, J = 7.2, 2.0 Hz, 2H), 7.82 (dd, J = 7.2, 2.4 Hz, 2H), 7.75 (d, J = 8.0 Hz, 1H), 7.49 (t, J = 2.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 6.32 (t, J = 2.0 Hz, 2H), 5.74 (d, J = 8.0 Hz, 1H),
 5 4.62-4.57 (m, 1H), 3.62 (s, 3H), 3.30 (s, 3H), 3.14-2.96 (m, 2H).; MS (ESI) m/z 664 (M+H)⁺

(Step

2)

N-[2,6-Difluoro-4-({[4-(1H-pyrrol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-26)



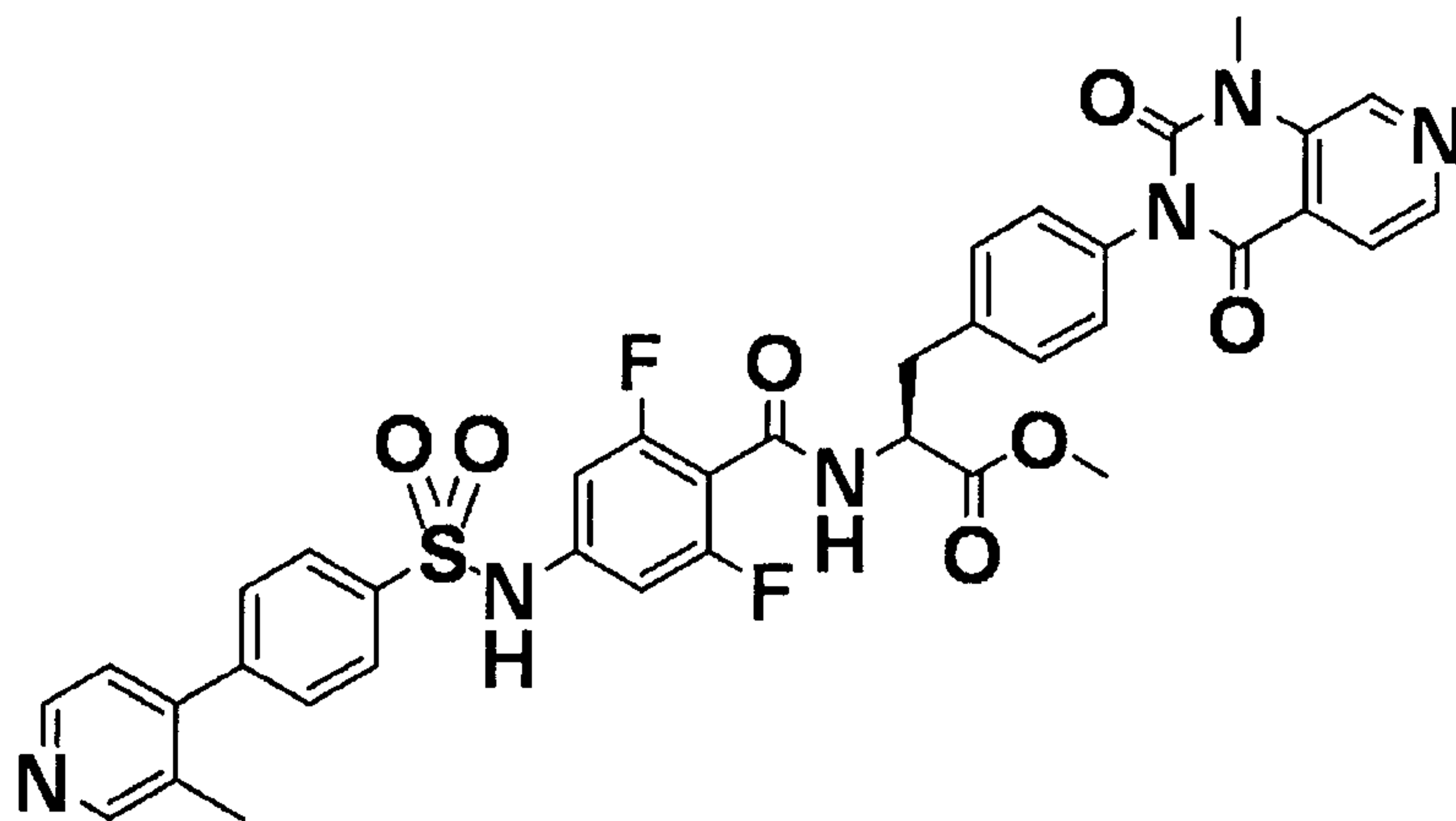
To the TFA salt (50 mg, 75 μmol) of methyl N-[2,6-difluoro-4-({[4-(1H-pyrrol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (B-26), a 4 N hydrogen chloride/dioxane
 15 solution (2.0 ml) and water (2.0 ml) were added, followed by stirring at 80°C for 1 hour. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN
 20 system) to obtain the title compound (15.0 mg, 31%) as a white solid.

¹H NMR (d-DMSO, 400 MHz): δ 12.78 (s, 1H), 10.99 (s, 1H), 8.96 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 8.9 Hz, 2H), 7.75 (d, J = 8.9

Hz, 2H), 7.68 (d, $J = 7.9$ Hz, 1H), 7.46-7.39 (m, 2H), 7.23 (d, $J = 8.3$ Hz, 2H), 7.02 (d, $J = 8.3$ Hz, 2H), 6.73 (d, $J = 9.1$ Hz, 2H), 6.32-6.18 (m, 2H), 5.67 (d, $J = 7.9$ Hz, 1H), 4.55-4.41 (m, 1H), 3.23 (s, 3H), 3.06 (dd, $J = 14.1, 4.5$ Hz, 1H), 2.89 (dd, $J = 14.2, 9.7$ Hz, 1H).; MS (ESI) m/z 650 ($M+H$)⁺

Example 65: Synthesis of A-27 and B-27

(Step 1) Methyl N-[2,6-Difluoro-4-({[4-(3-methylpyridin-4-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-27)



·2TFA

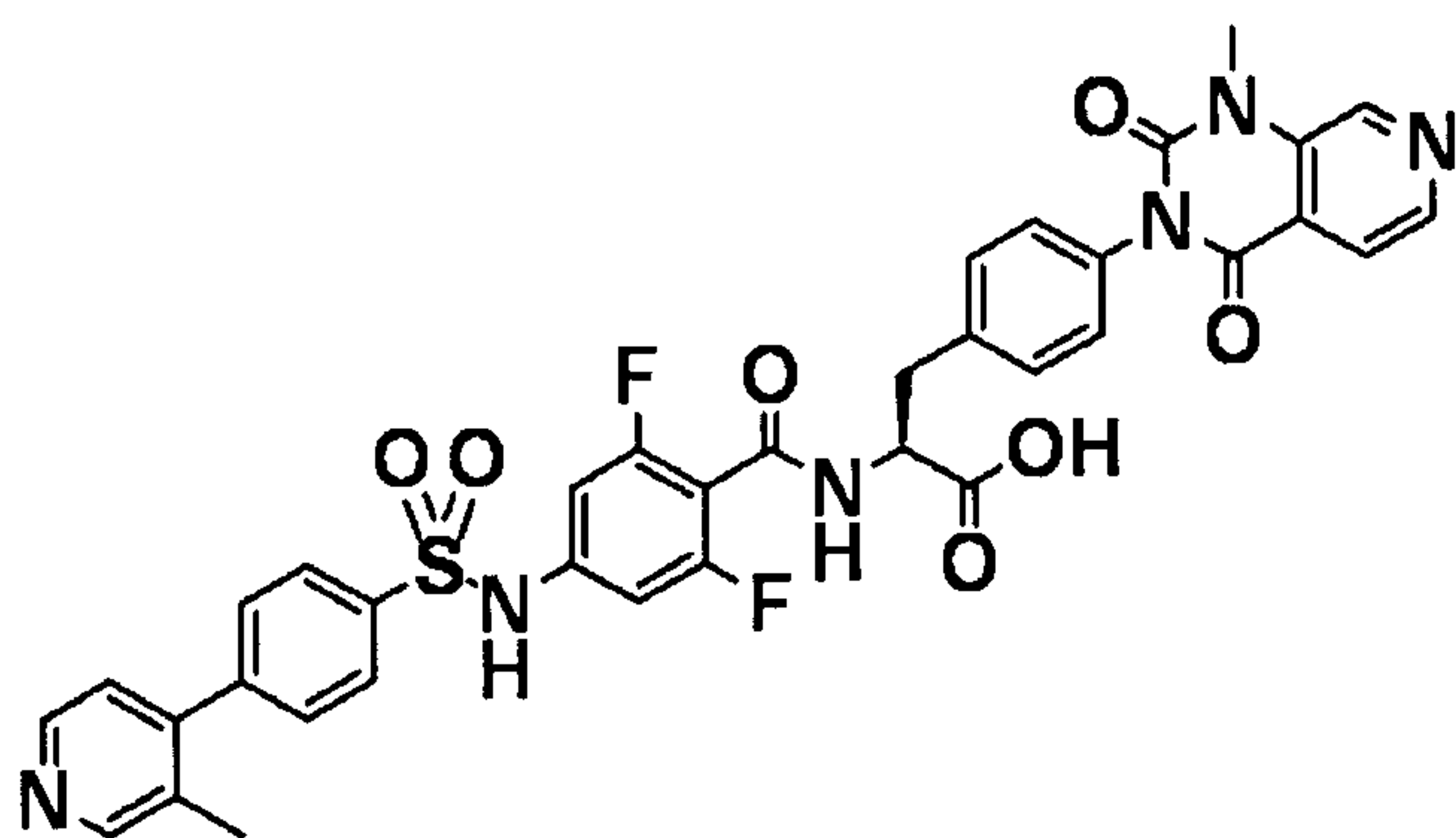
Methyl

4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (M-1) (43.0 mg, 0.100 mmol) and 2,6-difluoro-4-({[4-(3-methylpyridin-4-yl)phenyl]sulfonyl}amino)benzoic acid (M-34) (40.0 mg, 77.2 μ mol) were suspended in methylene chloride (4.0 ml), and HATU (53.0 mg, 0.140 mmol) and diisopropylethylamine (52 μ l, 0.30 mmol) were added thereto, followed by stirring at room temperature for 3 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H_2O containing 0.1% TFA/ CH_3CN system) to obtain the TFA salt (32.0

mg, 42%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz,) δ 11.2 (s, 1H), 9.22 (d, J = 7.6 Hz 1H), 8.97 (s, 1H), 8.66 (s, 1H), 8.60 (d, J = 5.2 Hz 1H), 8.55 (d, J = 5.2 Hz 1H), 8.00 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 4.8 Hz, 1H), 7.72 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 5.2 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 9.2 Hz, 2H), 4.67-4.61 (m, 1H), 3.64 (s, 3H), 3.60 (s, 3H), 3.18-3.01 (m, 2H), 2.27 (s, 3H). ; MS (ESI) m/z 741 (M+H)⁺ (Step 2)

10 N-[2,6-Difluoro-4-({[4-(3-methylpyridin-4-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-27)



·2TFA

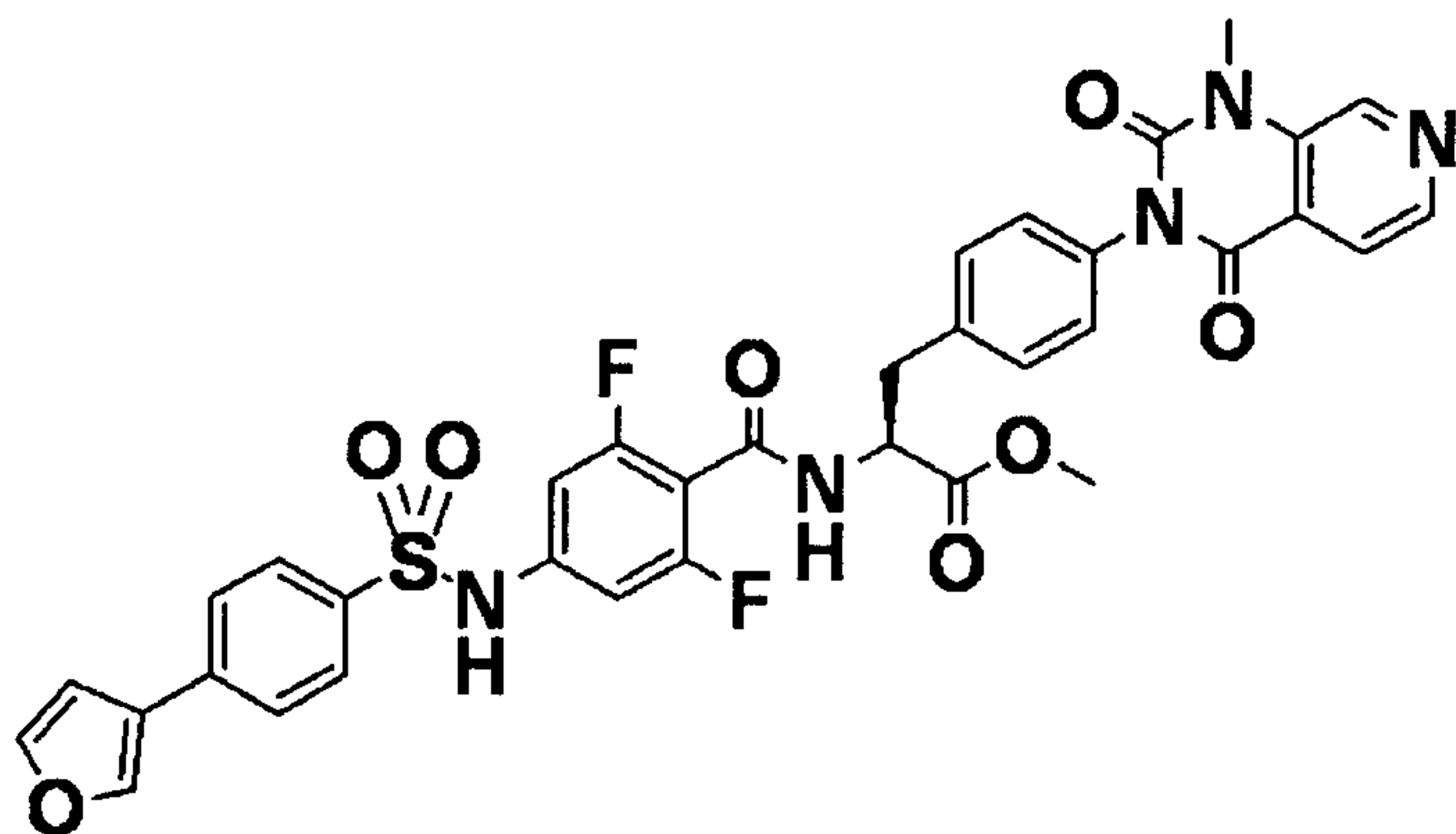
15 To the TFA salt (15.0 mg, 15.5 μmol) of methyl N-[2,6-difluoro-4-({[4-(3-methylpyridin-4-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-27), a 4 N hydrogen chloride/dioxane solution (4.0 ml) and water (1.0 ml) were added, followed by stirring at 70°C for 6 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (10.0 mg, 65%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz) δ 11.2 (s, 1H), 9.08 (d, J = 8.0 Hz 1H), 8.97 (s, 1H), 8.59 (s, 1H), 8.56-8.52 (m, 2H), 7.98 (d, J = 8.4 Hz 2H), 7.88 (d, J = 4.8 Hz 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.39-7.35 (m, 3H), 7.21 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 4.60-4.56 (m, 1H), 3.60 (s, 3H), 3.21-2.97 (m, 2H), 2.24 (s, 3H). ; MS (ESI) m/z 727 (M+H)⁺

Example 66: Synthesis of A-28 and B-28

(Step 1) Methyl

N-[2,6-Difluoro-4-({[4-(3-furyl)phenyl]sulfonyl}amino)benzo
yl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin
-3(2H)-yl)-L-phenylalaninate (B-28)



·TFA

Methyl

4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2
H)-yl)-L-phenylalaninate (M-1) (122 mg, 0.286 mmol) and
2,6-difluoro-4-({[4-(3-furyl)phenyl]sulfonyl}amino)benzoic
acid (M-35) (100 mg, 0.264 mmol) were suspended in methylene
chloride (4.0 ml), and HATU (138 mg, 0.364 mmol) and
diisopropylethylamine (0.140 ml, 0.780 mmol) were added thereto,
followed by stirring at room temperature for 3 hours. After
the reaction liquid was concentrated under reduced pressure,
purification was conducted by reversed-phase HPLC (H₂O
containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (64.0

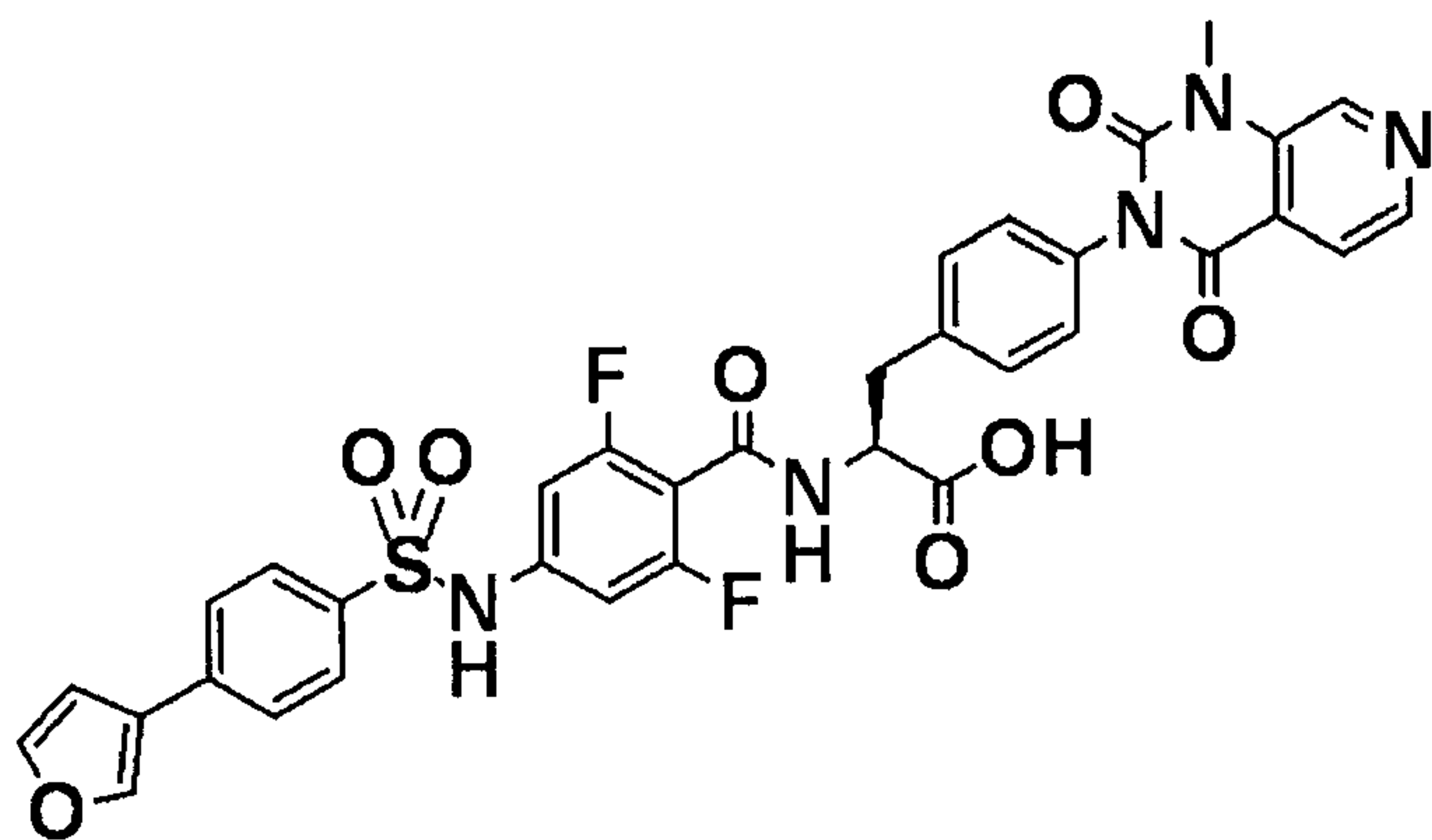
mg, 34%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz) δ 11.1 (s, 1H), 9.17 (d, J = 7.6 Hz, 1H), 8.97 (s, 1H), 8.56 (d, J = 5.2 Hz, 1H), 8.34 (s, 1H), 7.89 (d, J = 4.8 Hz, 1H), 7.85-7.79 (m, 5H), 7.33 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 7.03 (d, J = 1.6 Hz, 1H), 6.81 (d, J = 9.2 Hz, 2H), 4.65-4.60 (m, 1H), 3.63 (s, 3H), 3.60 (s, 3H), 3.19-2.99 (m, 2H). ; MS (ESI) m/z 716 (M+H)⁺

(Step

2)

N-[2,6-Difluoro-4-({[4-(3-furyl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-28)



·TFA

To the TFA salt (20.0 mg, 24.0 μmol) of methyl N-[2,6-difluoro-4-({[4-(3-furyl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-28), a 4 N hydrogen chloride/dioxane solution (4.0 ml) and water (1.0 ml) were added, followed by stirring at room temperature for 6 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (12.0 mg, 61%) of the title compound as a white solid.

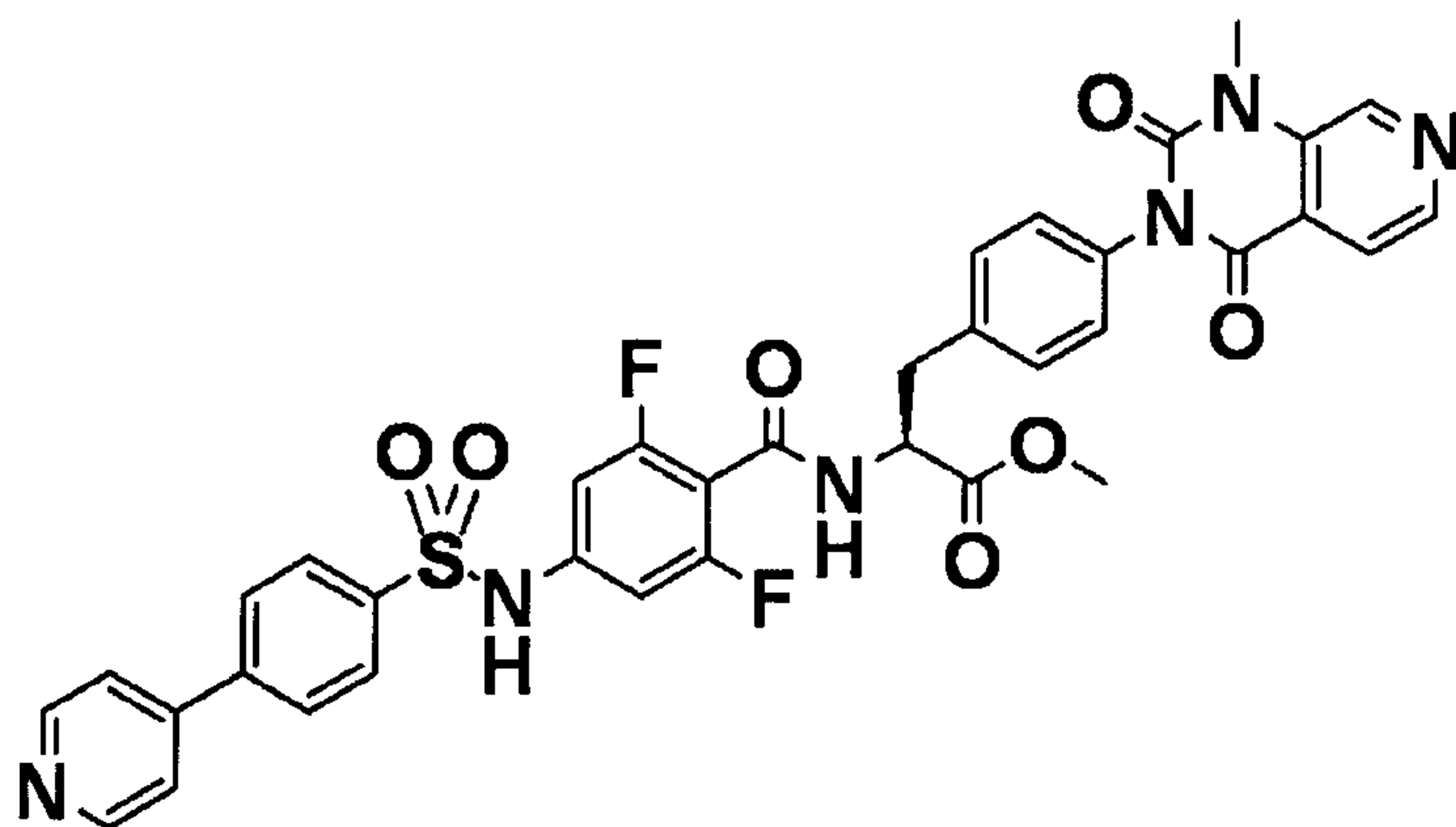
¹H NMR (d-DMSO, 400 MHz) δ 11.0 (s, 1H), 9.04 (d, J = 7.6 Hz,

1H), 8.97 (s, 1H), 8.55 (d, J = 4.8 Hz, 2H), 8.33 (s, 1H), 7.88 (d, J = 4.8 Hz 1H), 7.79-7.85 (m, 5H), 7.34 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.02 (s, 1H), 6.80 (d, J = 9.2 Hz, 2H), 4.53-4.59 (m, 1H), 3.60 (s, 3H), 2.95-3.23-2.88 (m, 2H), ;

5 MS (ESI) m/z 702 (M+H)⁺

Example 67: Synthesis of A-29 and B-29

(Step 1) Methyl N-(2,6-Difluoro-4-{[(4-pyridin-4-yl-phenyl)sulfonyl]amino}benzoyl)-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-29)



·2TFA

Methyl

4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2
15 H)-yl)-L-phenylalaninate (M-1) (235 mg, 0.550 mmol) and
2,6-difluoro-4-{[(4-pyridin-4-yl-phenyl)sulfonyl]amino}benz
oic acid (M-36) (195 mg, 0.500 mmol) were suspended in
dimethylformamide (4.0 ml), and HATU (266 mg, 0.700 mmol) and
diisopropylethylamine (0.350 ml, 2.00 mmol) were added thereto,
20 followed by stirring at room temperature for 3 hours. After
the reaction liquid was concentrated under reduced pressure,
purification was conducted by reversed-phase HPLC (H₂O
containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (73.0

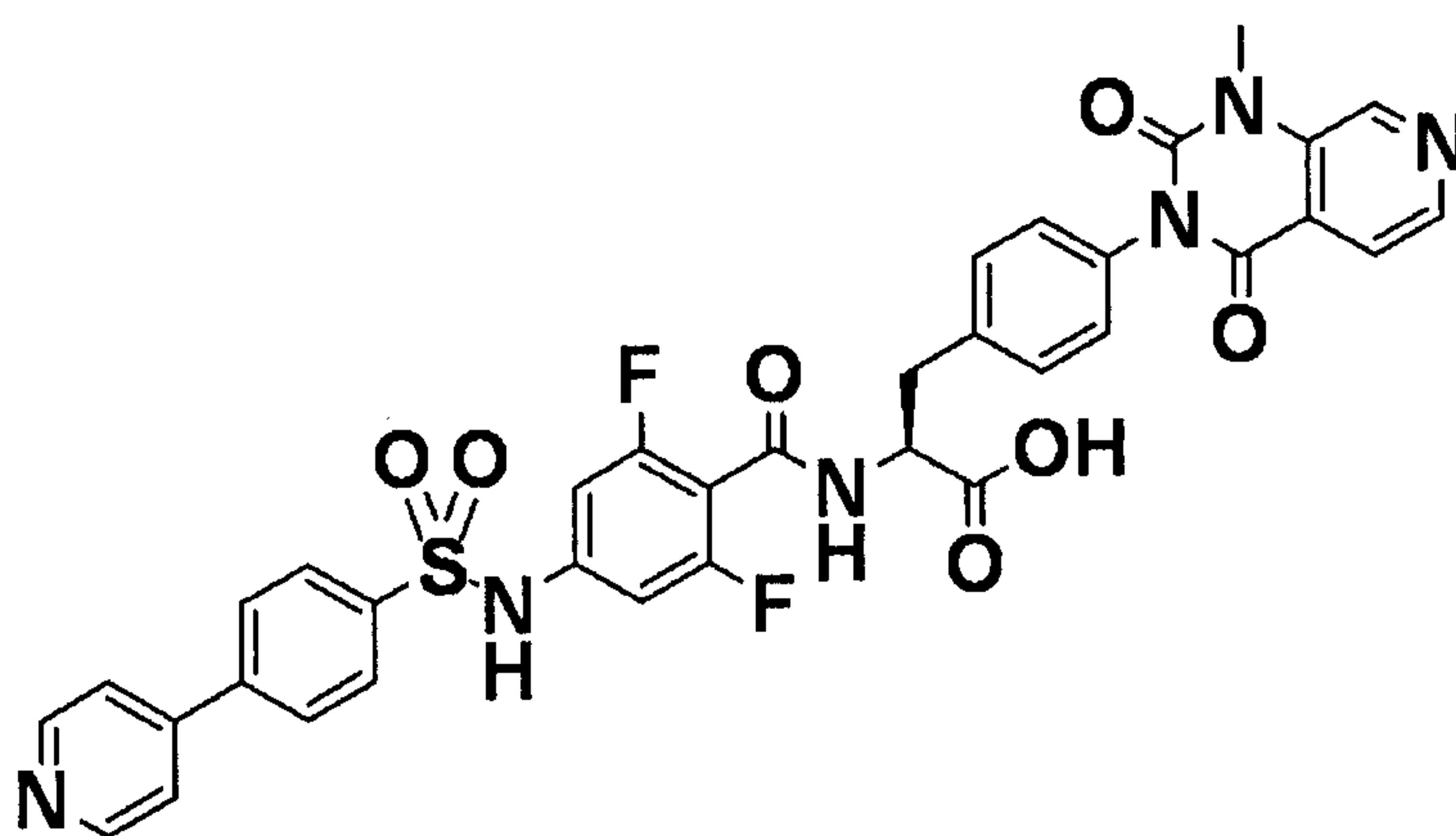
mg, 15%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz) δ 11.2 (s, 1H), 9.19 (d, J = 7.6 Hz, 1H), 8.99 (d, J = 2.4 Hz, 1H), 8.97 (s, 1H), 8.67 (dd, J = 4.8, 1.6 Hz, 1H), 8.55 (d, J = 4.8 Hz, 1H), 8.25 (d, J = 7.6 Hz, 1H), 8.027.97 (m, 4H), 7.88 (d, J = 4.8 Hz, 1H), 7.61 (dd, J = 8.0, 4.8 Hz, 1H), 7.33 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 9.2 Hz, 2H), 4.66-4.60 (m, 1H), 3.63 (s, 3H), 3.59 (s, 3H), 3.17-2.99 (m, 2H).; MS (ESI) m/z 727 (M+H)⁺

(Step

2)

10 N-(2,6-Difluoro-4-{[(4-pyridin-4-yl-phenyl)sulfonyl]amino}benzoyl)-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-29)



·2TFA

15 To the TFA salt (50.0 mg, 52.4 μmol) of methyl N-(2,6-difluoro-4-{[(4-pyridin-4-yl-phenyl)sulfonyl]amino}benzoyl)-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-29), a 4 N hydrogen chloride/dioxane solution (4.0 ml) and water (1.0 ml) were added, followed by stirring at 70°C for 6 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (27.0 mg, 55%) of the

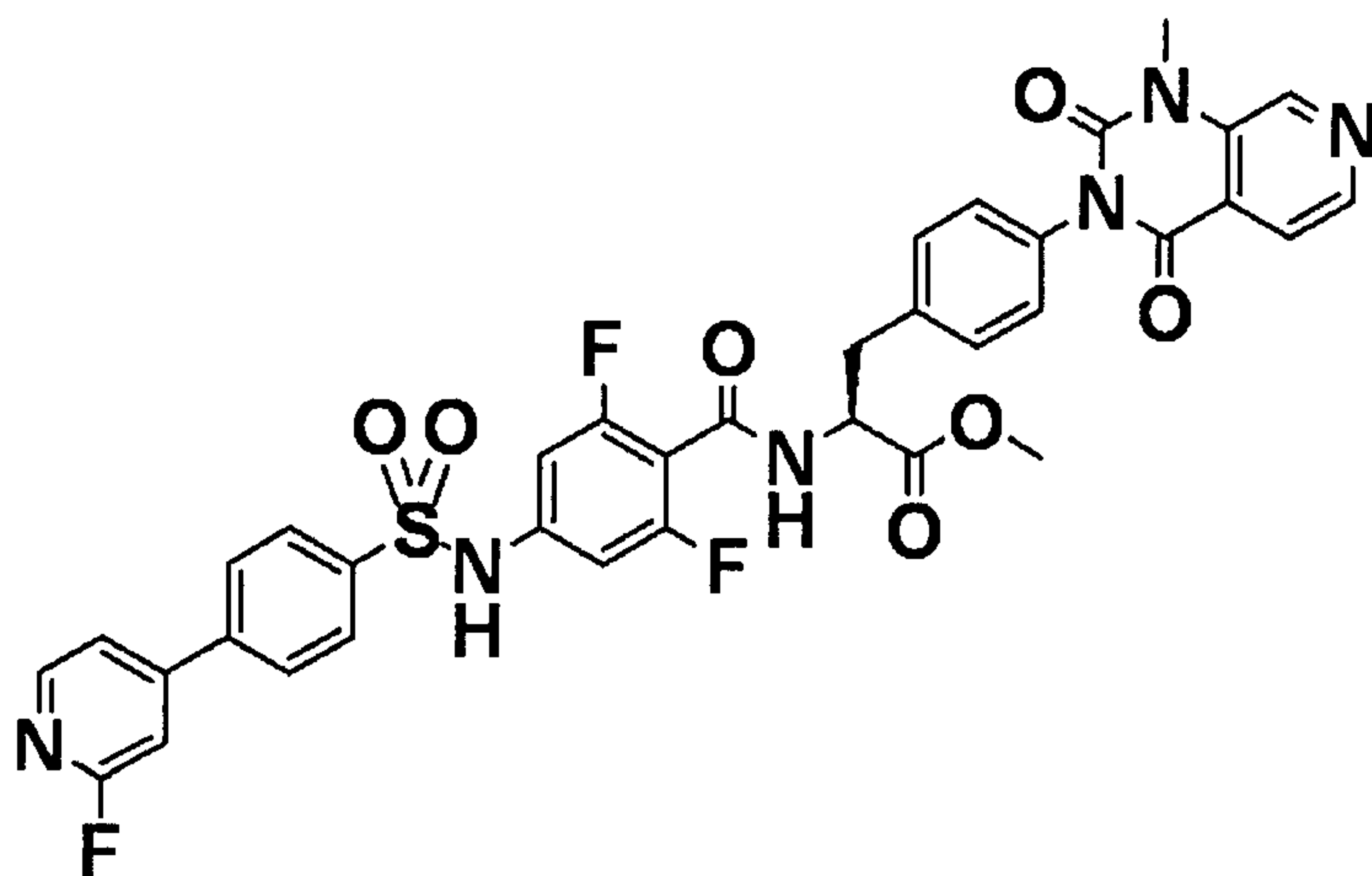
20

title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz) δ 11.2 (s, 1H), 9.00 (d, J = 7.6 Hz, 2H), 8.90 (s, 1H), 8.73 (d, J = 6.4 Hz, 2H), 8.49 (d, J = 5.2 Hz, 1H), 8.04 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 8.4 Hz, 2H),
 5 7.81 (d, J = 4.8 Hz, 1H), 7.93 (d, J = 6.4 Hz, 2H), 7.28 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 9.2 Hz, 2H), 4.53-4.48 (m, 1H), 3.12-2.88 (m, 2H).; MS (ESI) m/z 713 (M+H)⁺

Example 68: Synthesis of A-30 and B-30

10 (Step 1) Methyl
N-[2,6-Difluoro-4-([4-(2-fluoropyridin-4-yl)phenyl]sulfonyl
amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,
4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-30)



15 ·2TFA

Methyl

4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2
 H)-yl)-L-phenylalaninate (M-1) (100 mg, 0.234 mmol) and
 2,6-difluoro-4-([4-(2-fluoropyridin-4-yl)phenyl]sulfonyl)a
 20 mino)benzoic acid (M-37) (94.0 mg, 0.230 mmol) were suspended
 in methylene chloride (2.0 ml), and HATU (133 mg, 0.350 mmol)
 and diisopropylethylamine (0.160 ml, 0.920 mmol) were added

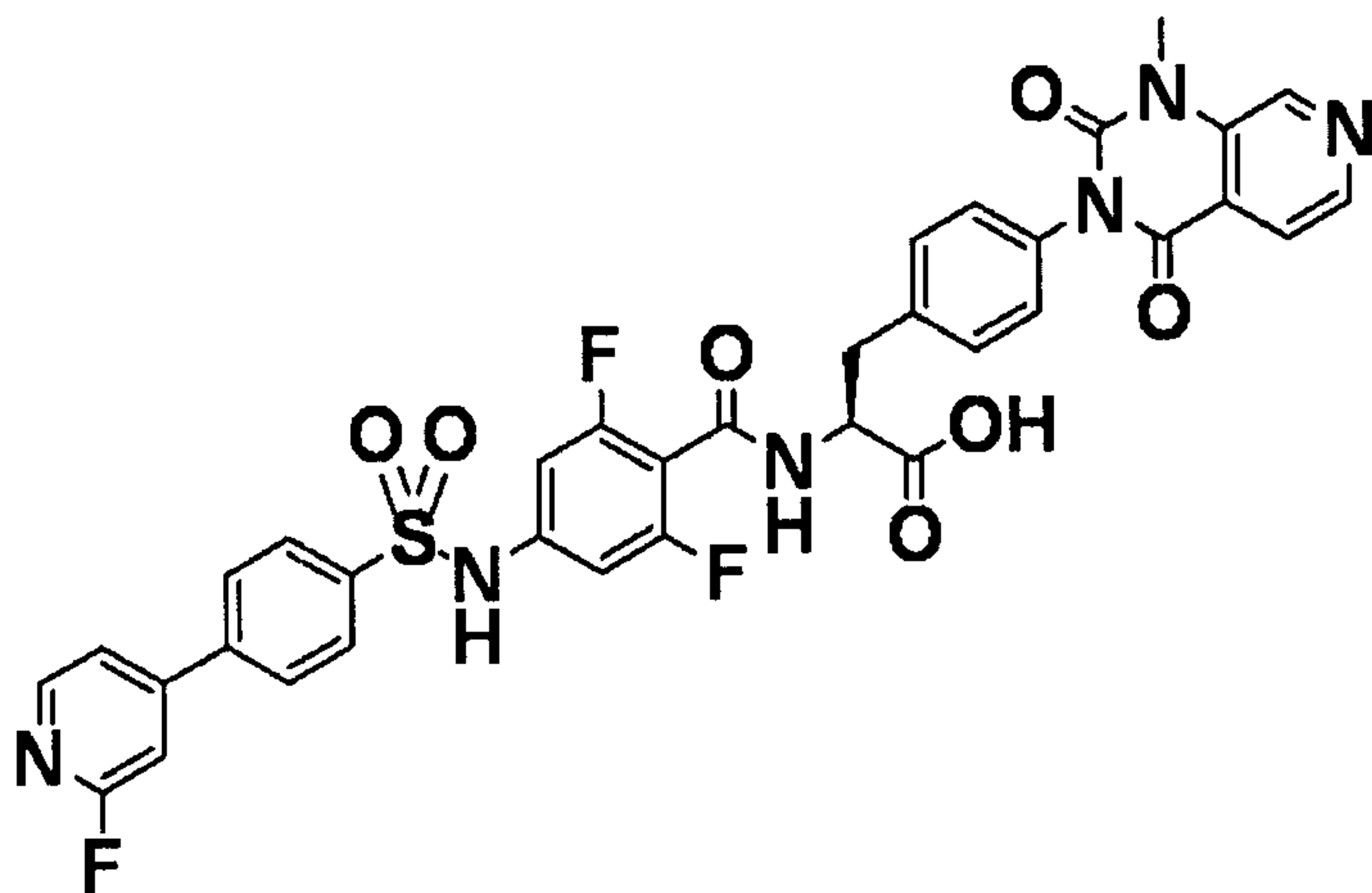
thereto, followed by stirring at room temperature for 16 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (30.0 mg, 13%) of the title compound as a white solid.

MS (ESI) m/z 745 (M+H)⁺

(Step

2)

N-[2,6-Difluoro-4-({[4-(2-fluoropyridin-4-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-30)



·2TFA

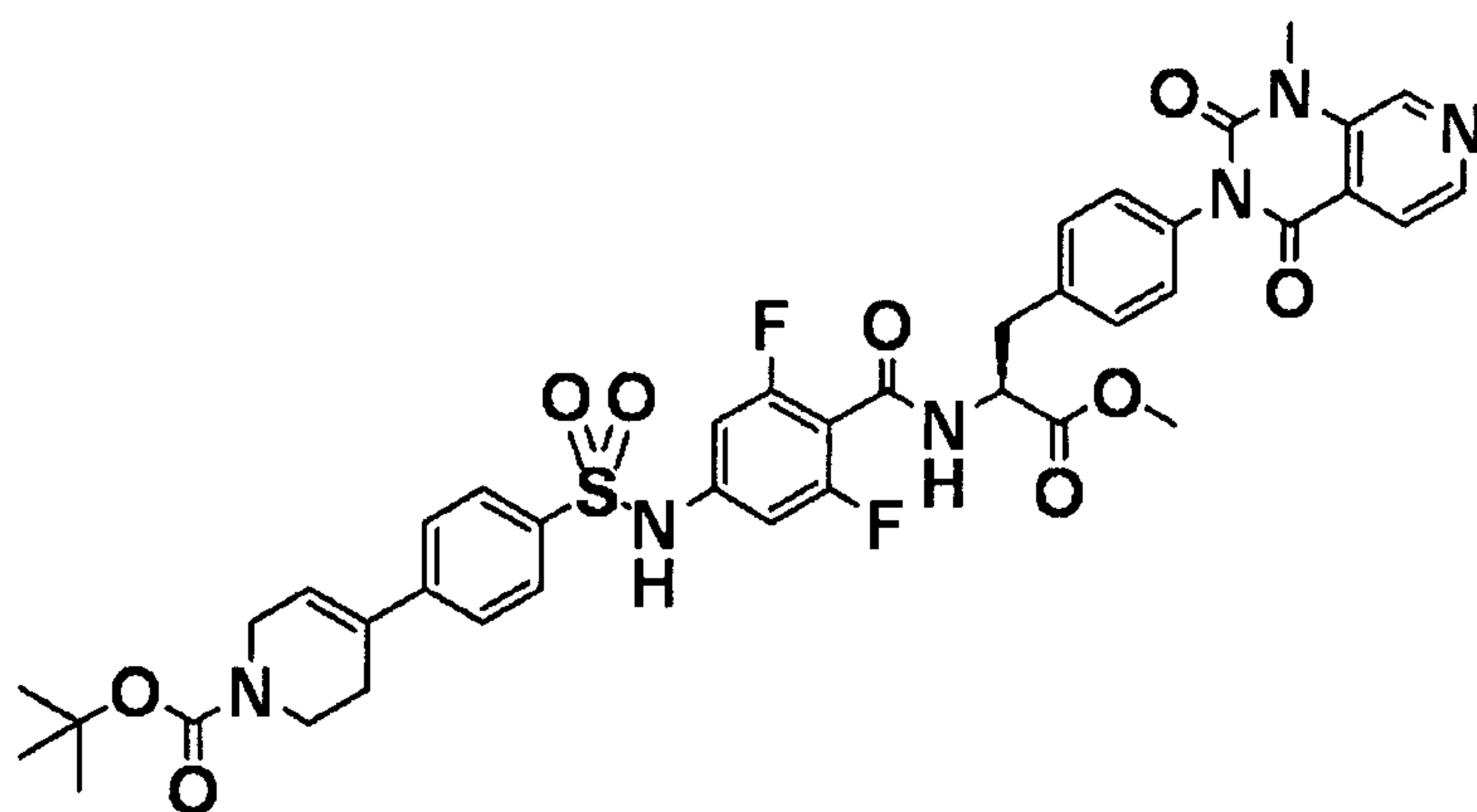
To the TFA salt (20.0 mg, 20.6 μmol) of methyl N-[2,6-difluoro-4-({[4-(2-fluoropyridin-4-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-30), a 4 N hydrogen chloride/dioxane solution (4.0 ml) and water (1.0 ml) were added, followed by stirring at 70°C for 6 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (11.0 mg, 56%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz) δ 11.2 (s, 1H), 9.06 (d, J = 7.6 Hz,

1H), 8.97 (s, 1H), 8.55 (d, J = 5.2 Hz, 1H), 8.35 (d, J = 5.2 Hz, 1H), 8.08 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 8.4 Hz, 2H), 7.88 (d, J = 4.8 Hz, 1H), 7.75 (d, J = 5.2 Hz, 1H), 7.61 (s, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 4.60-4.54 (m, 1H), 3.60 (s, 3H), 3.26-2.95 (m, 2H); MS (ESI) m/z 731 (M+H)⁺

Example 69: Synthesis of A-31 and B-31

(Step 1) Methyl N-{4-[(4-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]phenyl)sulfonyl]amino}-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-31)



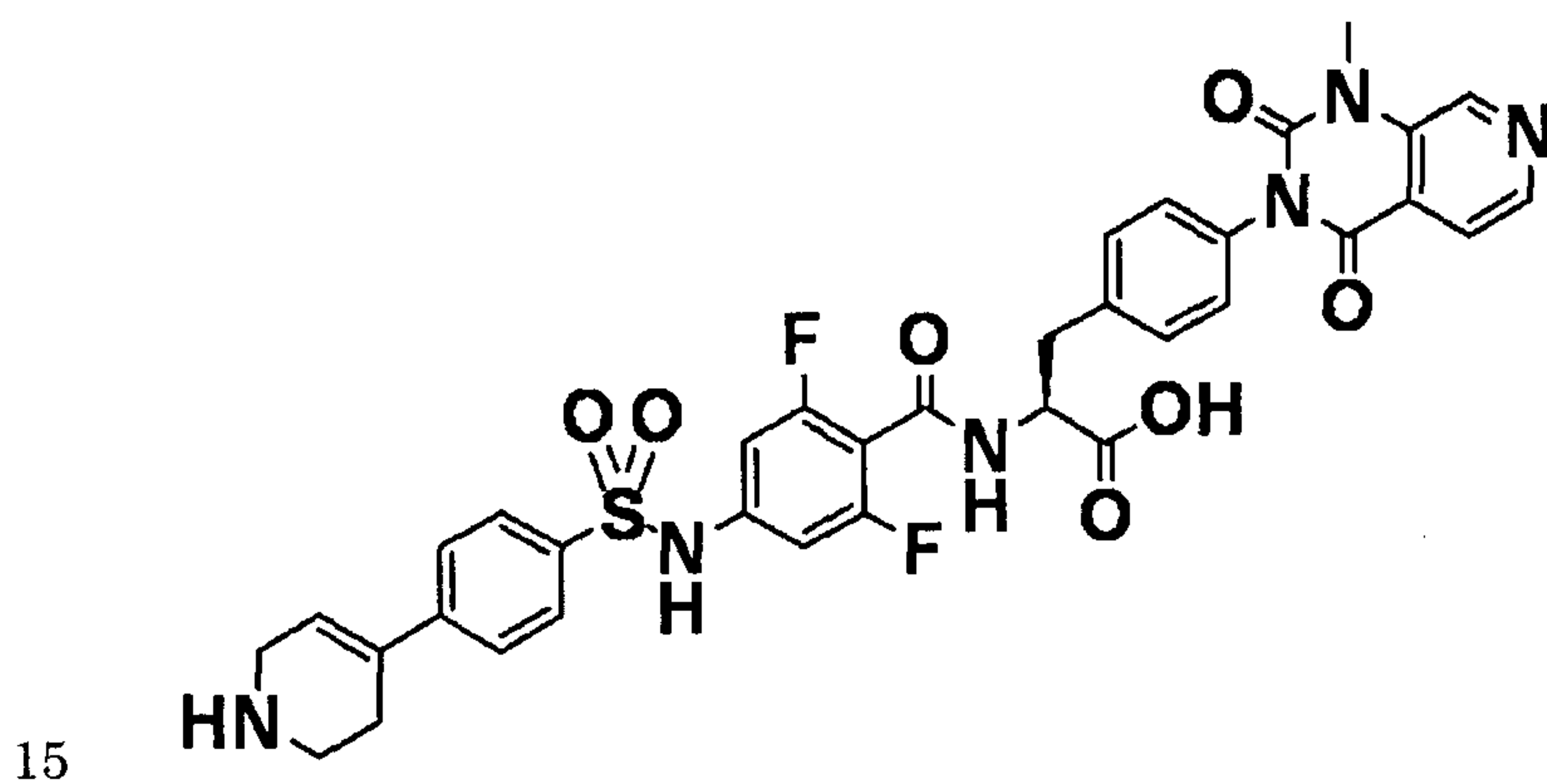
·TFA

15 Methyl
4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (M-1) (141 mg, 0.330 mmol) and 4-[(4-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]phenyl)sulfonyl]amino}-2,6-difluorobenzoic acid (M-38) (130 mg, 0.300 mmol) were suspended in methylene chloride (5.0 ml), and HATU (160 mg, 0.420 mmol) and diisopropylethylamine (0.210 ml, 1.50 mmol) were added thereto, followed by stirring at room temperature for 3 hours. After the reaction liquid was

concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (22.0 mg, 8%) of the title compound as a white solid.

5 ¹H NMR (d-DMSO, 400 MHz) δ 11.1 (s, 1H), 9.18 (d, J = 6.4 Hz, 1H), 8.97 (s, 1H), 8.56 (d, J = 4.8 Hz, 1H), 7.89 (d, J = 4.4 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 9.2 Hz, 2H), 6.34 (br, 1H), 4.66-4.58 (m, 1H), 4.01 (br, 2H), 3.64 (s, 3H), 3.60 (s, 10 3H), 3.17-3.00 (m, 2H), 1.41 (s, 9H); MS (ESI) m/z 731 (M+H-Boc)⁺ (Step 2)

N-[2,6-Difluoro-4-({[4-(1,2,3,6-tetrahydropyridin-4-yl)phenyl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydr
opyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-31)



·2TFA

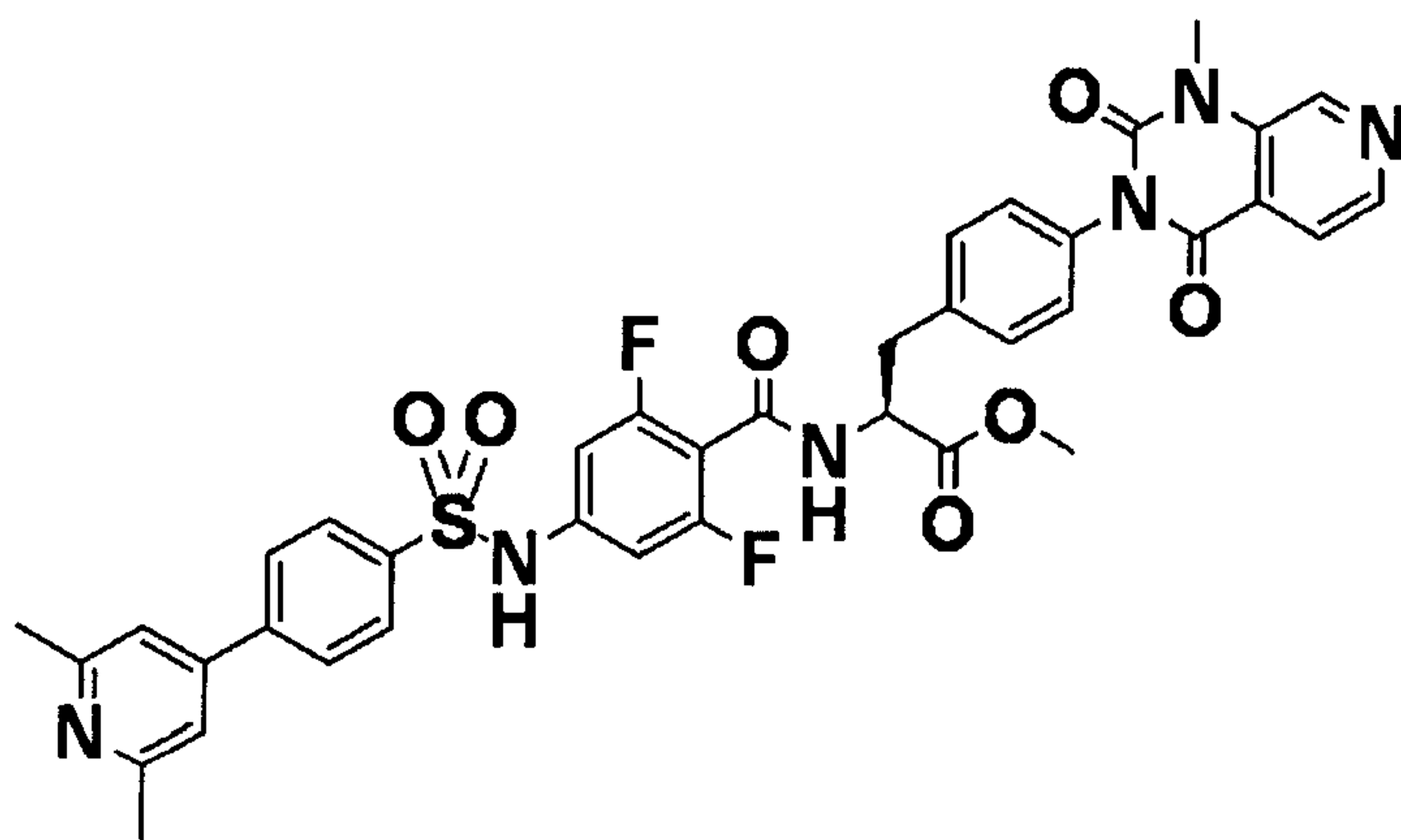
To the TFA salt (10.0 mg, 10.6 μmol) of methyl N-{4-[(4-[1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl]phenyl)sulfonyl]amino}-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-31), a 4 N hydrogen chloride/dioxane solution (4.0 ml) and water (1.0 ml) were added, followed by stirring at 70°C for 6 hours. After the reaction liquid was concentrated under reduced pressure, purification was

conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (6.0 mg, 59%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz) δ 11.1 (s, 1H), 9.07 (d, J = 8.0 Hz, 1H), 8.98 (s, 1H), 8.77 (br, 1H), 8.56 (d, J = 5.2 Hz, 1H), 7.90 (d, J = 4.4 Hz, 1H), 7.88 (d, J = 5.6 Hz, 2H), 7.71 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 9.2 Hz, 2H), 6.37 (br, 1H), 4.59-4.55 (m, 1H), 3.78 (br, 2H), 3.78 (s, 3H), 3.23-2.96 (m, 2H); MS (ESI) m/z 717 (M+H)⁺

Example 70: Synthesis of A-32 and B-32

(Step 1) Methyl N-[4-({[4-(2,6-Dimethylpyridin-4-yl)phenyl]sulfonyl}amino)-2,6-difluorobenzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyridido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (B-32)



15

·2TFA

Methyl

4-(1-methyl-2,4-dioxo-1,4-dihydropyridido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (M-1) (64.0 mg, 75.0 μ mol) and 4-({[4-(2,6-dimethylpyridin-4-yl)phenyl]sulfonyl}amino)-2,6-difluorobenzoic acid (M-27) (63.0 mg, 0.118 mmol) were suspended in methylene chloride (4.0 ml), and HATU (80.0 mg, 0.165 mmol) and diisopropylethylamine (80 μ L, 0.18 mmol) were

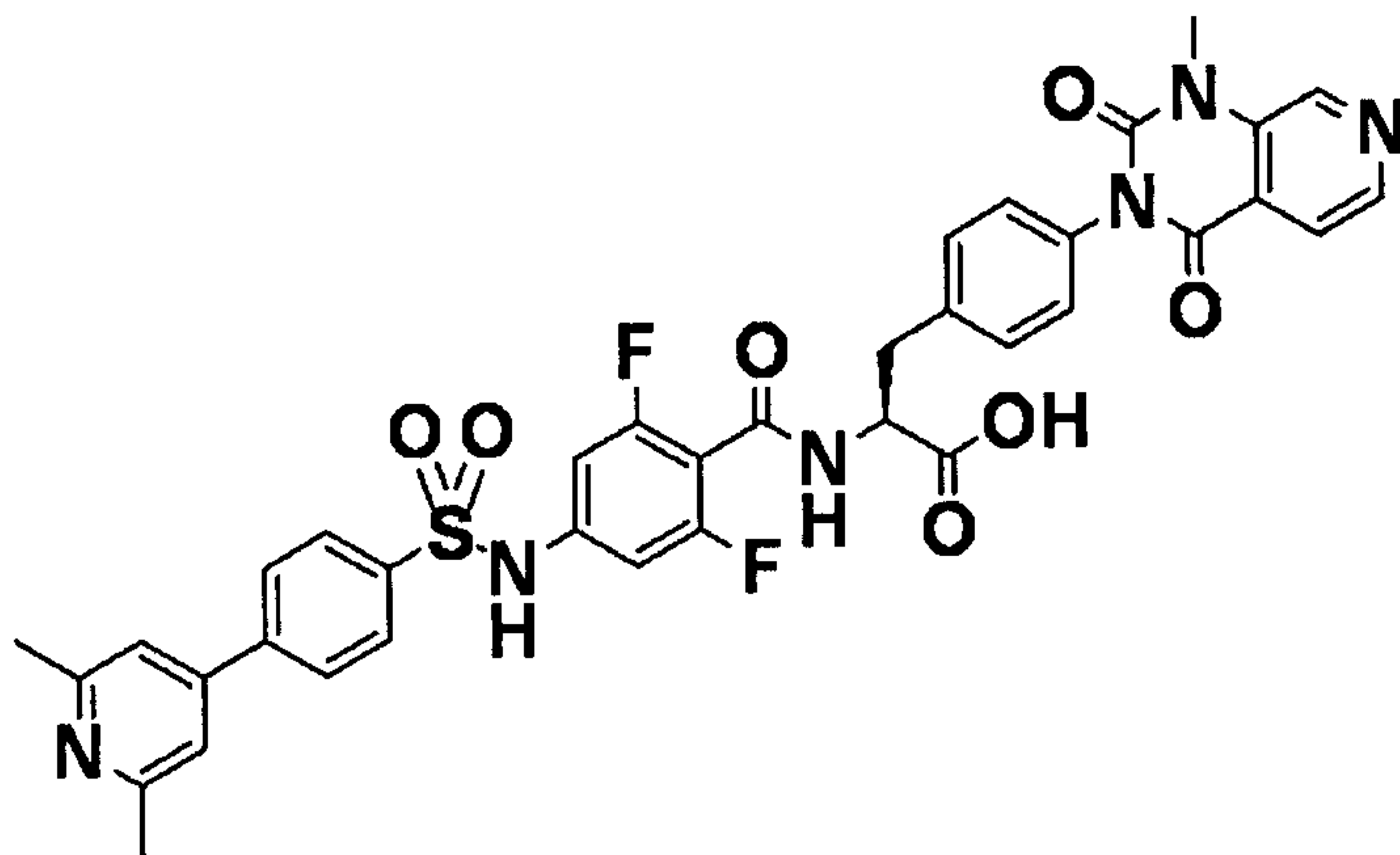
20

added thereto, followed by stirring at room temperature for 3 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (40.0 mg, 34%) of the title compound as a white solid.
 MS (ESI) m/z 755 (M+H)⁺

(Step

2)

N-[4-({[4-(2,6-Dimethylpyridin-4-yl)phenyl]sulfonyl}amino)-2,6-difluorobenzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrid
o[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-32)



·2TFA

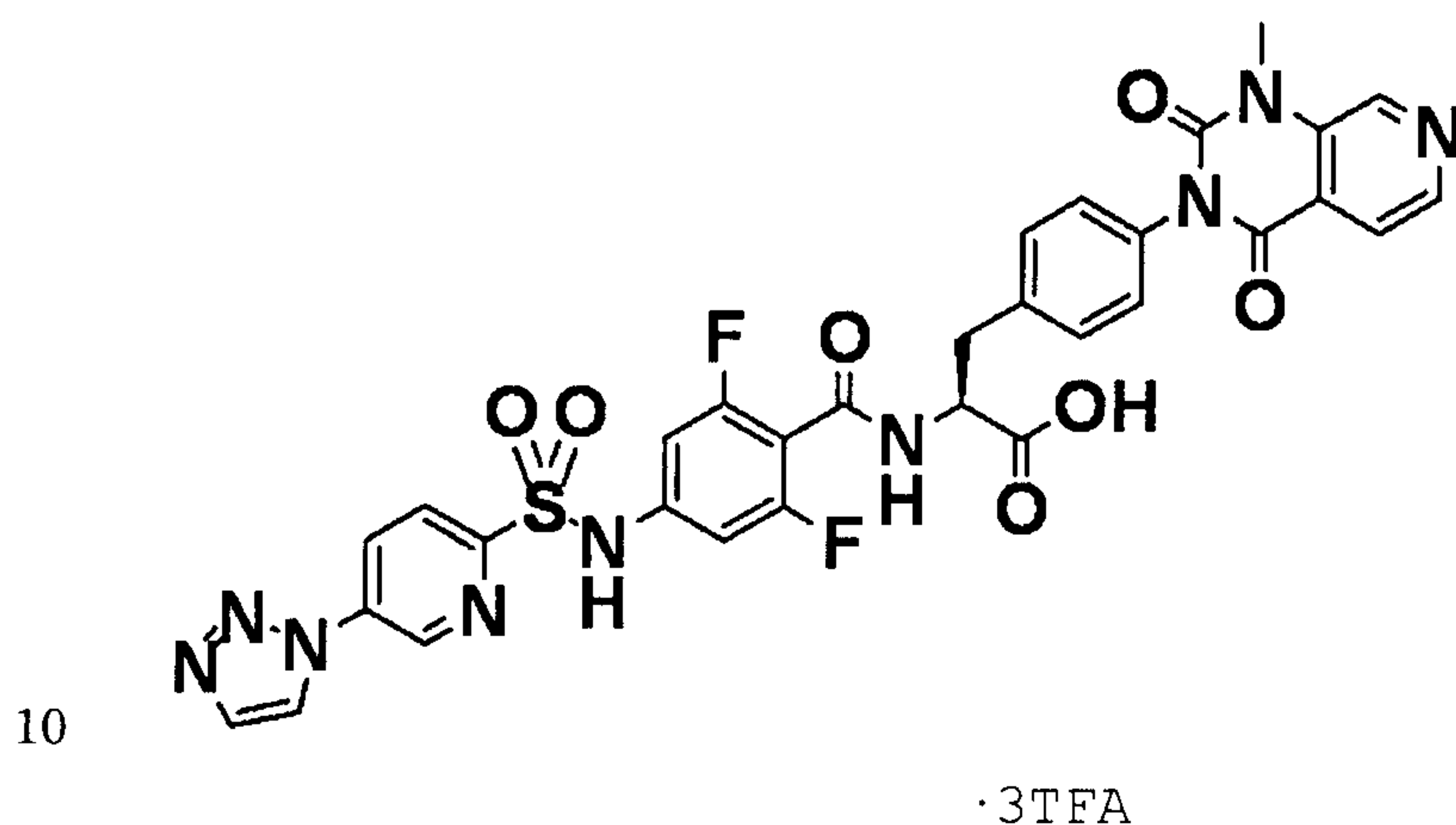
To the TFA salt (20.0 mg, 20.6 μmol) of methyl N-[4-({[4-(2,6-dimethylpyridin-4-yl)phenyl]sulfonyl}amino)-2,6-difluorobenzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyridine-3-carboxamide)-L-phenylalaninate (B-32), a 4 N hydrogen chloride/dioxane solution (4.0 ml) and water (1.0 ml) were added, followed by stirring at 70°C for 6 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (11.0 mg, 56%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz) δ 11.2 (s, 1H), 9.07 (d, J = 7.6 Hz,

1H), 8.97 (s, 1H), 8.56 (d, J = 4.8 Hz, 1H), 8.10 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.4 Hz, 2H), 7.94 (br, 2H), 7.88 (d, J = 5.2 Hz, 1H), 7.35 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 4.60-4.54 (m, 1H), 3.60 (s, 3H),
 5 3.19-2.98 (m, 2H), 2.65 (s, 6H).; MS (ESI) m/z 741 (M+H)⁺

Example 71: Synthesis of A-33

N-[2,6-Difluoro-4-({[5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl]sulfonyl}amino)benzoyl]-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-33)



Methyl

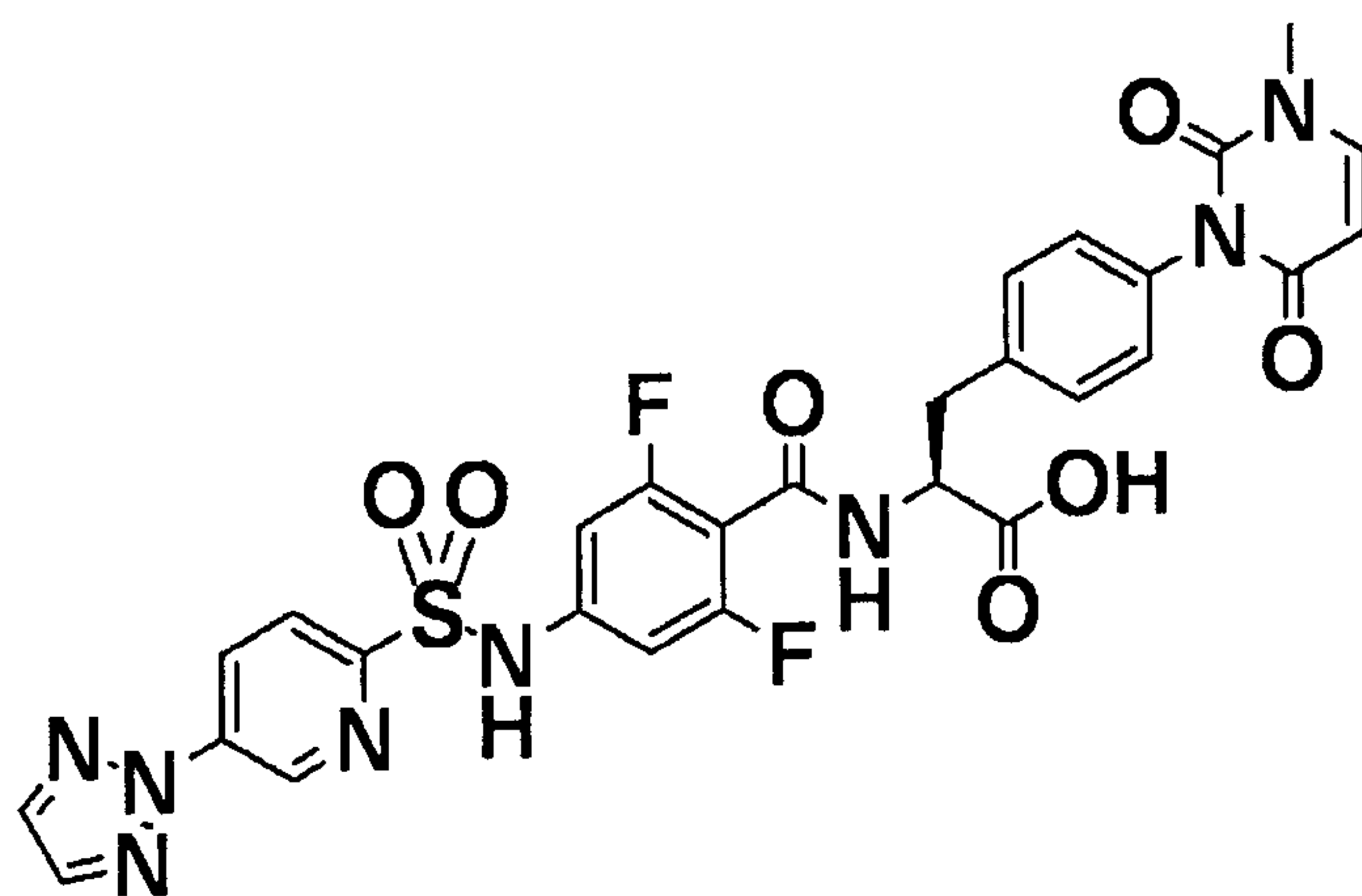
4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (M-1) (100 mg, 0.230 mmol) and
 15 2,6-difluoro-4-({[5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl]sulfonyl}amino)benzoic acid (M-28) (106 mg, 0.253 mmol) were suspended in methylene chloride (4.0 ml), and HATU (122 mg, 0.322 mmol) and diisopropylethylamine (0.120 ml, 0.690 mmol) were added thereto, followed by stirring at room temperature
 20 for 3 hours. After the reaction liquid was concentrated under reduced pressure, a 4 N hydrogen chloride/dioxane solution (4.0 ml) and water (1.0 ml) were added thereto, followed by stirring at 70°C for 6 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by

reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (63.0 mg, 29%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz) δ 11.4 (s, 1H), 9.35 (d, J = 2.0 Hz, 1H), 9.06 (d, J = 8.0 Hz, 1H), 9.02 (d, J = 1.2 Hz, 1H), 8.98 (s, 1H), 8.66 (dd, J = 2.8, 8.8 Hz, 1H), 8.56 (d, J = 4.8 Hz, 1H), 8.36 (d, J = 8.8 Hz, 1H), 8.07 (d, J = 1.2 Hz, 1H), 7.89 (d, J = 4.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 4.61-4.56 (m, 1H), 3.60 (s, 3H), 3.22-2.99 (m, 2H).; MS (ESI) m/z 704 (M+H)⁺

Example 72: Synthesis of A-34

N-[2,6-Difluoro-4-({[5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl]sulfonyl}amino)benzoyl]-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-34)



·2TFA

Methyl

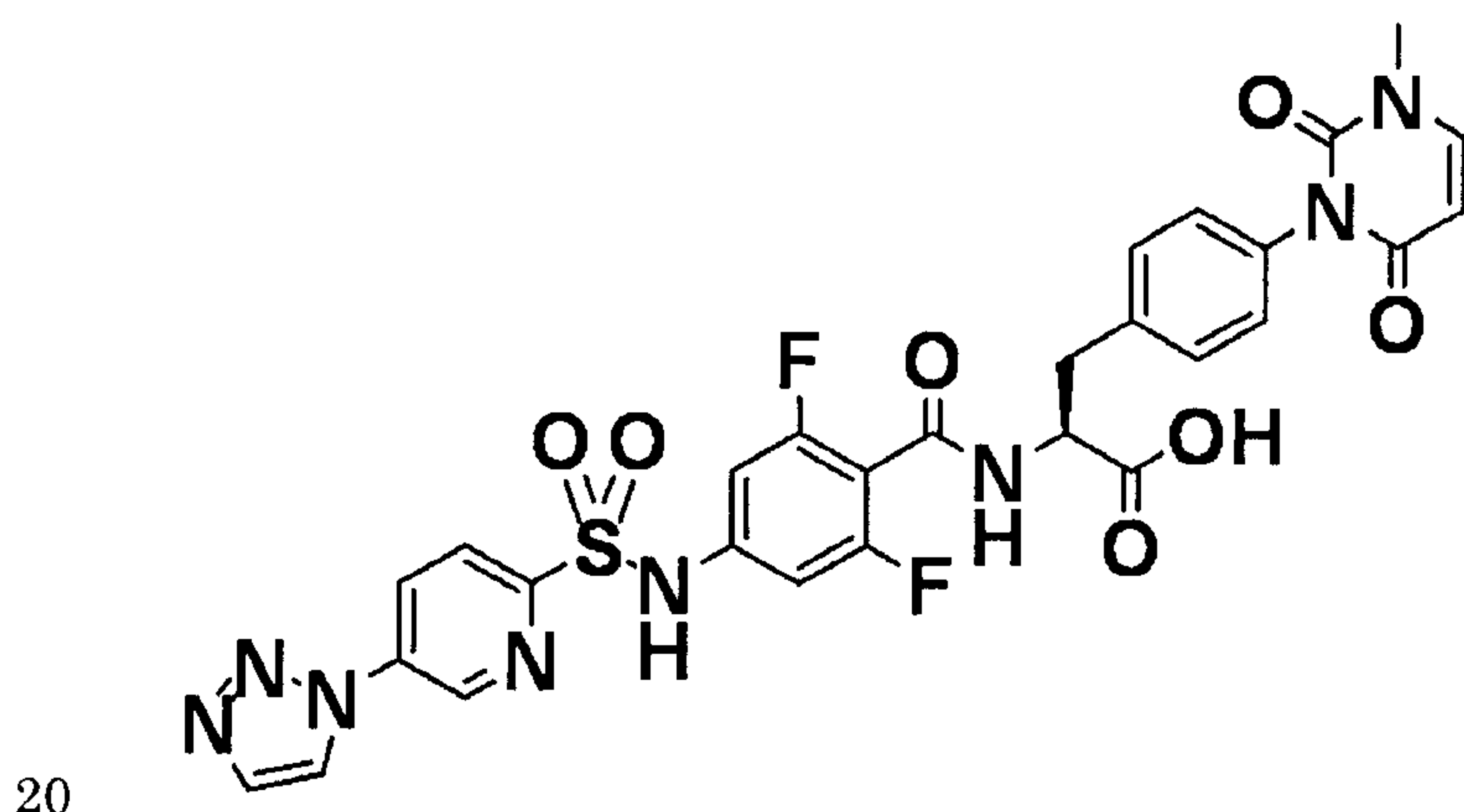
4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (M-2) (100 mg, 0.290 mmol) and 2,6-difluoro-4-({[5-(2H-1,2,3-triazol-2-yl)pyridin-2-yl]sulfonyl}amino)benzoic acid (M-29) (133 mg, 0.319 mmol) were suspended in methylene chloride (4.0 ml), and HATU (154 mg, 0.406 mmol) and diisopropylethylamine (0.150 ml, 0.870 mmol)

were added thereto, followed by stirring at room temperature for 3 hours. After the reaction liquid was concentrated under reduced pressure, a 4 N hydrogen chloride/dioxane solution (4.0 ml) and water (1.0 ml) were added thereto, followed by stirring
 5 at 70°C for 6 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (78.0 mg, 35%) of the title compound as a white solid.

10 ¹H NMR (d-DMSO, 400 MHz) δ 11.4 (s, 1H), 9.38 (d, J = 2.4 Hz, 1H), 9.03 (d, J = 7.6 Hz, 1H), 8.65 (dd, J = 2.8, 8.8 Hz, 1H), 8.32-8.30 (m, 3H), 7.75 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 9.2 Hz, 2H), 5.74 (d, J = 8.0 Hz, 1H), 4.58-4.52 (m, 1H), 3.31 (s, 3H),
 15 3.17-2.94 (m, 2H).; MS (ESI) m/z 653 (M+H)⁺

Example 73: Synthesis of A-35

N-[2,6-Difluoro-4-({[5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl]sulfonyl}amino)benzoyl]-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-35)



·2TFA

Methyl

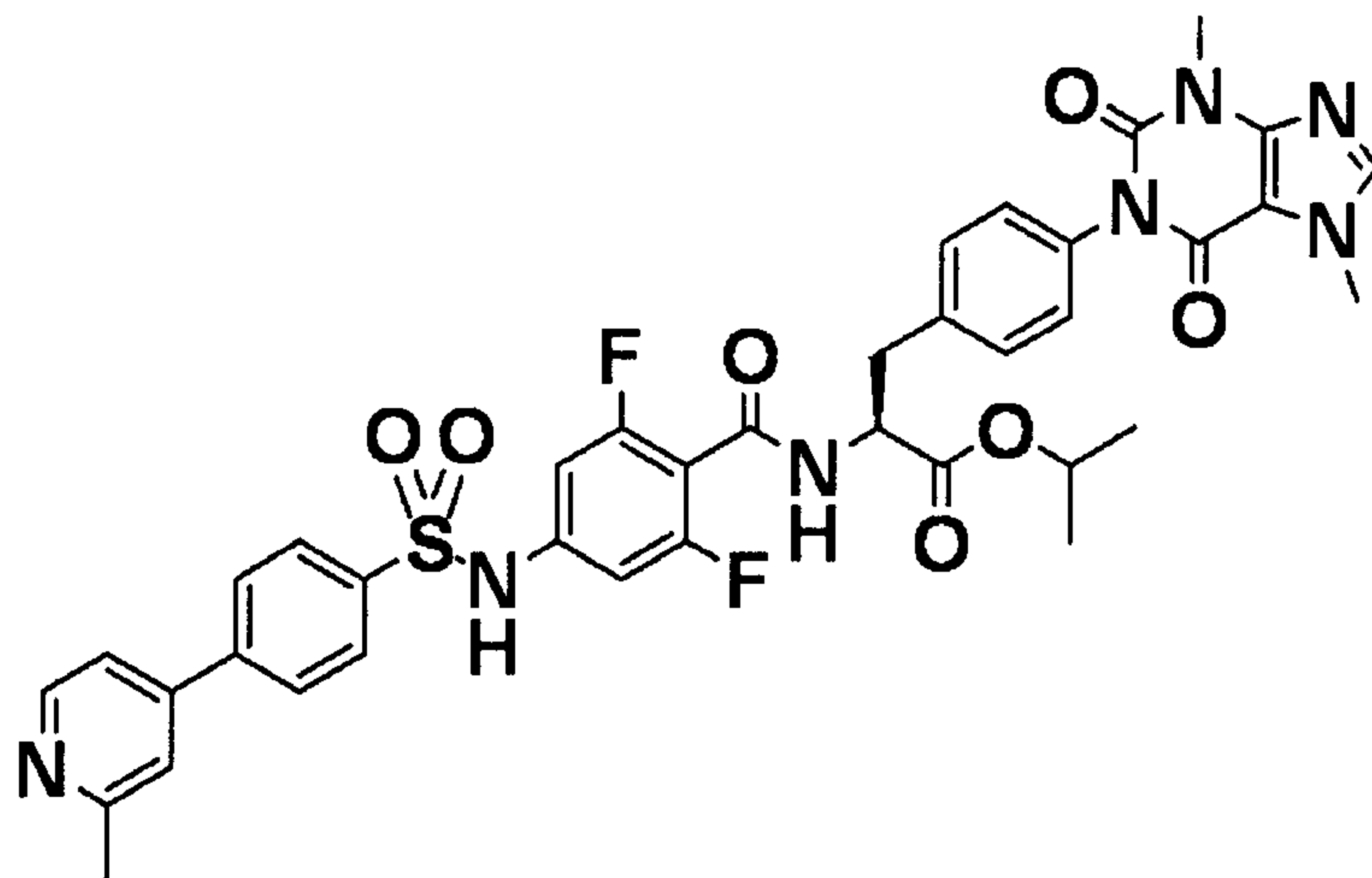
4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phen

ylalaninate (M-2) (100 mg, 0.290 mmol) and 2,6-difluoro-4-({[5-(1H-1,2,3-triazol-1-yl)pyridin-2-yl]sulfonyl}amino)benzoic acid (M-28) (133 mg, 0.319 mmol) were suspended in methylene chloride (4.0 ml), and HATU (154 mg, 0.406 mmol) and diisopropylethylamine (0.150 ml, 0.870 mmol) were added thereto, followed by stirring at room temperature for 3 hours. After the reaction liquid was concentrated under reduced pressure, a 4 N hydrogen chloride/dioxane solution (4.0 ml) and water (1.0 ml) were added thereto, followed by stirring at 70°C for 6 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (62.0 mg, 28%) of the title compound as a white solid.

¹H NMR (d-DMSO, 400 MHz) δ 11.4 (s, 1H), 9.34 (d, J = 2.4 Hz, 1H), 9.05-9.02 (m, 2H), 8.66 (dd, J = 2.8, 8.8 Hz, 1H), 8.36 (d, J = 8.8 Hz, 1H), 8.07 (s, 1H), 7.75 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 9.2 Hz, 2H), 5.74 (d, J = 8.0 Hz, 1H), 4.58-4.53 (m, 1H), 3.31 (s, 3H), 3.17-2.95 (m, 2H).; MS (ESI) m/z 653 (M+H)⁺

Example 74: Synthesis of A-36 and B-36

(Step 1) Isopropyl N-[2,6-Difluoro-4-({[4-(2-methylpyridin-4-yl)phenyl]sulfonyl}amino)benzoyl]-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-L-phenylalaninate (B-36)



·TFA

Isopropyl

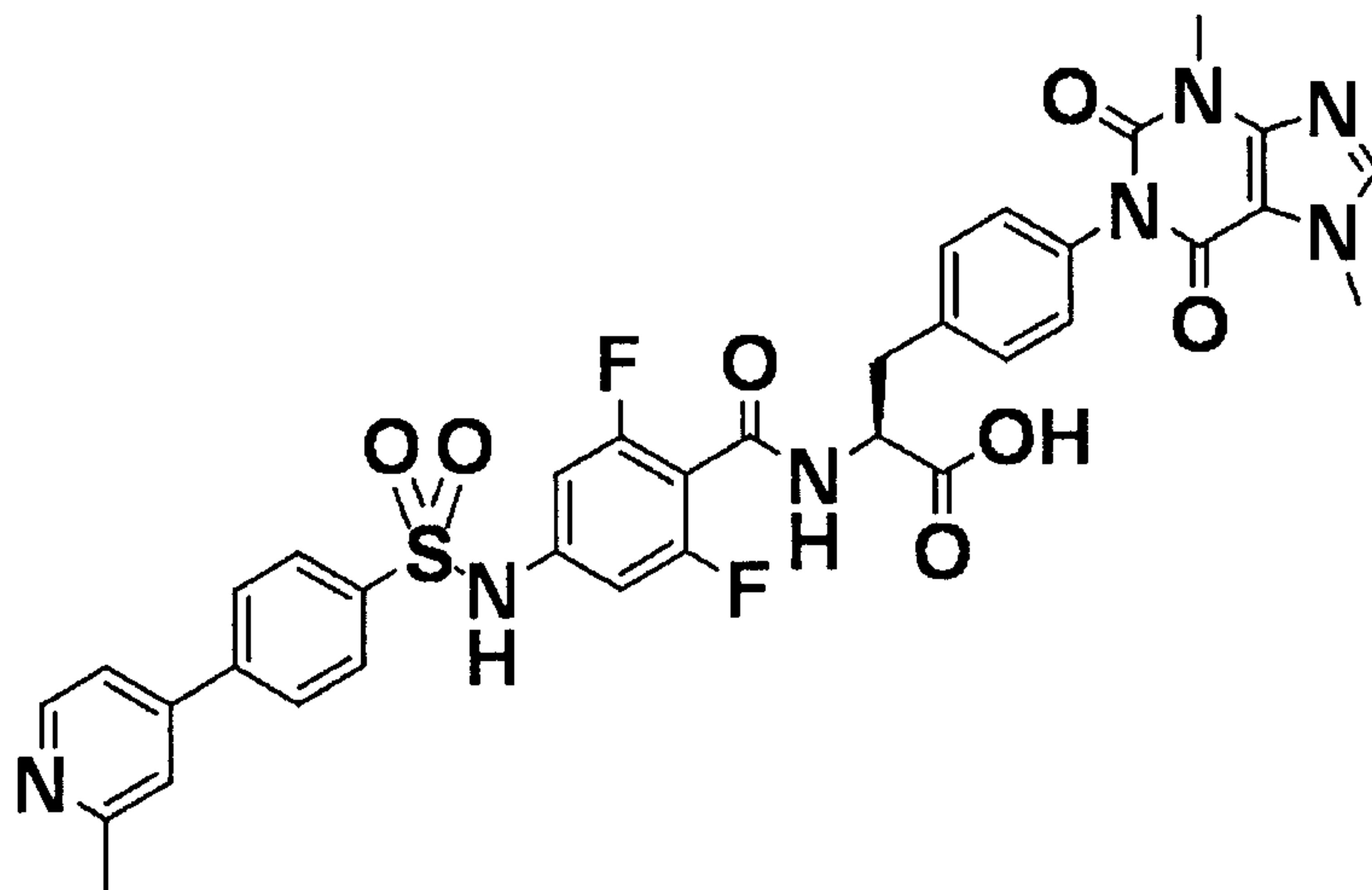
4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)
 5 -L-phenylalaninate (M-5) (99.9 mg, 0.200 mmol) and
 2,6-difluoro-4-([4-(2-methylpyridin-4-yl)phenyl]sulfonyl)amino)benzoic acid (M-32) (80.9 mg, 0.200 mmol) were suspended
 in methylene chloride (4.0 ml), and HATU (114 mg, 0.300 mmol),
 HOAt (40.8 mg, 0.300 mmol), and triethylamine (70 μ L, 0.50 mmol)
 10 were added thereto, followed by stirring at room temperature
 for 2 hours. After the reaction liquid was concentrated under
 reduced pressure, purification was conducted by reversed-phase
 HPLC (H_2O containing 0.1% TFA/ CH_3CN system) to obtain the TFA
 salt (19.8 mg, 11%) of the title compound.

15 ^1H NMR (d -DMSO, 400 MHz): δ 11.24 (s, 1H), 9.17 (d, J = 7.3 Hz,
 1H), 8.70 (d, J = 6.0 Hz, 1H), 8.12-8.01 (m, 5H), 7.96 (s, 1H),
 7.86 (s, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz,
 2H), 6.85 (d, J = 9.1 Hz, 2H), 4.91-4.85 (m, 1H), 4.57-4.47 (dd,
 J = 14.2, 8.2 Hz, 1H), 3.86 (s, 3H), 3.42 (s, 3H), 3.12-2.97
 20 (m, 2H), 2.63 (s, 3H), 1.17 (d, J = 6.3 Hz, 3H), 1.11 (d, J =
 6.2 Hz, 3H).; MS (ESI) m/z 772 ($M+H$) $^+$

(Step

2)

N-[2,6-Difluoro-4-({[4-(2-methylpyridin-4-yl)phenyl]sulfonyl
amino)benzoyl]-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahyd
ro-1H-purin-1-yl)-L-phenylalanine (A-36)



5

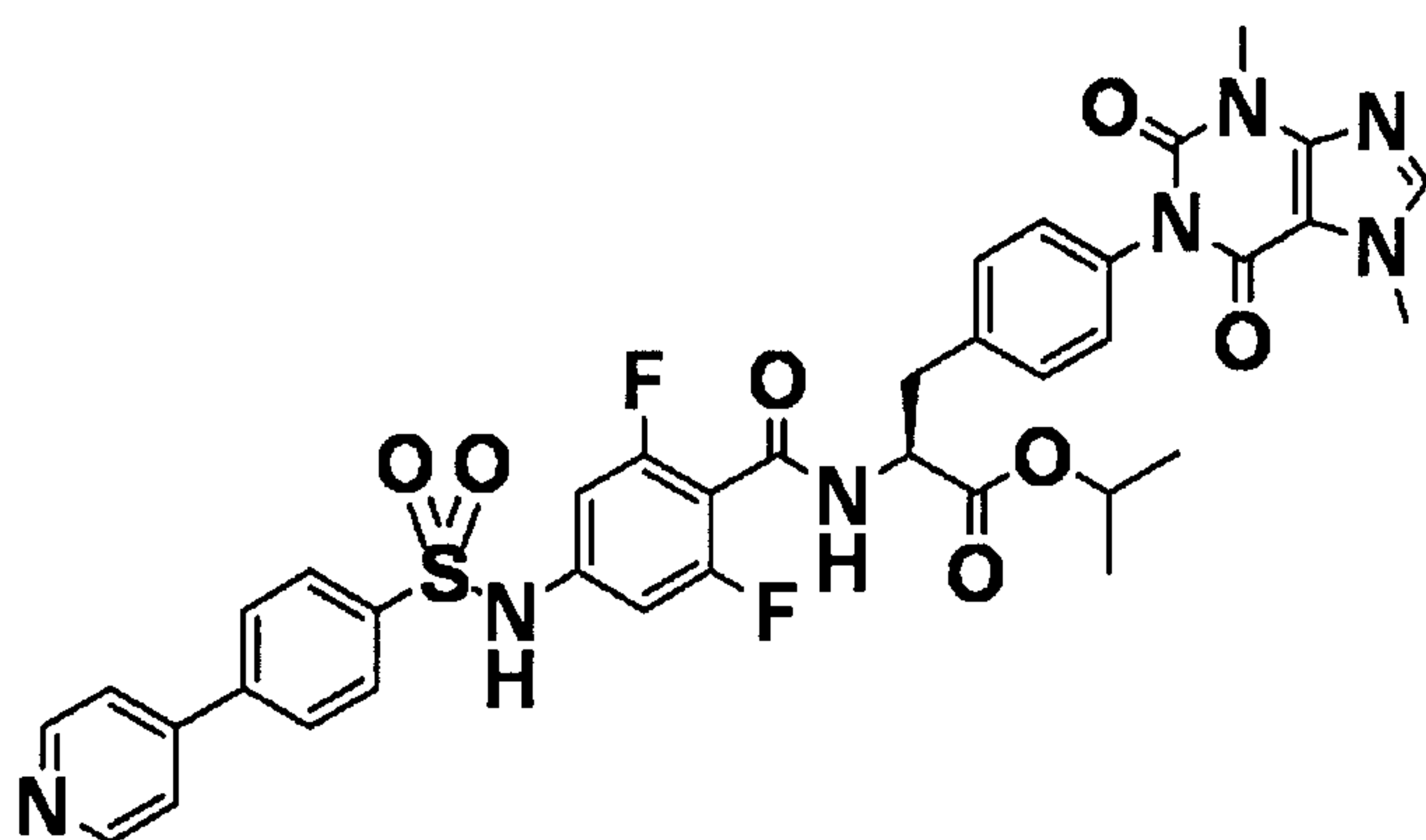
·TFA

To the TFA salt (19.8 mg, 22.3 μmol) of isopropyl
 N-[2,6-difluoro-4-({[4-(2-methylpyridin-4-yl)phenyl]sulfonyl
 amino)benzoyl]-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahyd
 ro-1H-purin-1-yl)-L-phenylalaninate (B-36), a 4 N hydrogen
 10 chloride/dioxane solution (2.0 ml) and water (4.0 ml) were added,
 followed by stirring at 70°C for 6 hours. After the reaction
 liquid was concentrated under reduced pressure, purification
 was conducted by reversed-phase HPLC (H_2O containing 0.1%
 TFA/ CH_3CN system) to obtain the TFA salt (4.7 mg, 25%) of the
 15 title compound.

^1H NMR ($d\text{-DMSO}$, 400 MHz): δ 11.20 (s, 1H), 9.06 (d, $J = 7.9$ Hz,
 1H), 8.66 (d, $J = 4.8$ Hz, 1H), 8.08-7.97 (m, 5H), 7.87 (s, 1H),
 7.78 (s, 1H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 8.3$ Hz,
 2H), 6.83 (d, $J = 9.0$ Hz, 2H), 4.58-4.52 (m, 1H), 3.86 (s, 3H),
 20 3.42 (s, 3H), 3.15 (dd, $J = 13.3, 3.2$ Hz, 1H), 2.97 (dd, $J =$
 14.1, 9.6 Hz, 1H), 2.60 (s, 3H).; MS (ESI) m/z 730 ($\text{M}+\text{H}$) $^+$

Example 75: Synthesis of A-37 and B-37

(Step 1) Isopropyl
N-(2,6-Difluoro-4-{[(4-pyridin-4-yl-phenyl)sulfonyl]amino}benzoyl)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-L-phenylalaninate (B-37)



5

·TFA

Isopropyl

4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)
 -L-phenylalaninate (M-5) (49.9 mg, 0.100 mmol) and
 10 2,6-difluoro-4-{[(4-pyridin-4-yl-phenyl)sulfonyl]amino}benz
 oic acid (M-36) (39.0 mg, 0.100 mmol) were suspended in
 methylene chloride (2.0 ml), and HATU (57.0 mg, 0.150 mmol),
 HOAt (20.4 mg, 0.150 mmol), and triethylamine (28 μ L, 0.20 mmol)
 were added thereto, followed by stirring at room temperature
 15 for 2 hours. After the reaction liquid was concentrated under
 reduced pressure, purification was conducted by reversed-phase
 HPLC (H_2O containing 0.1% TFA/ CH_3CN system) to obtain the TFA
 salt (7.4 mg, 8%) of the title compound.

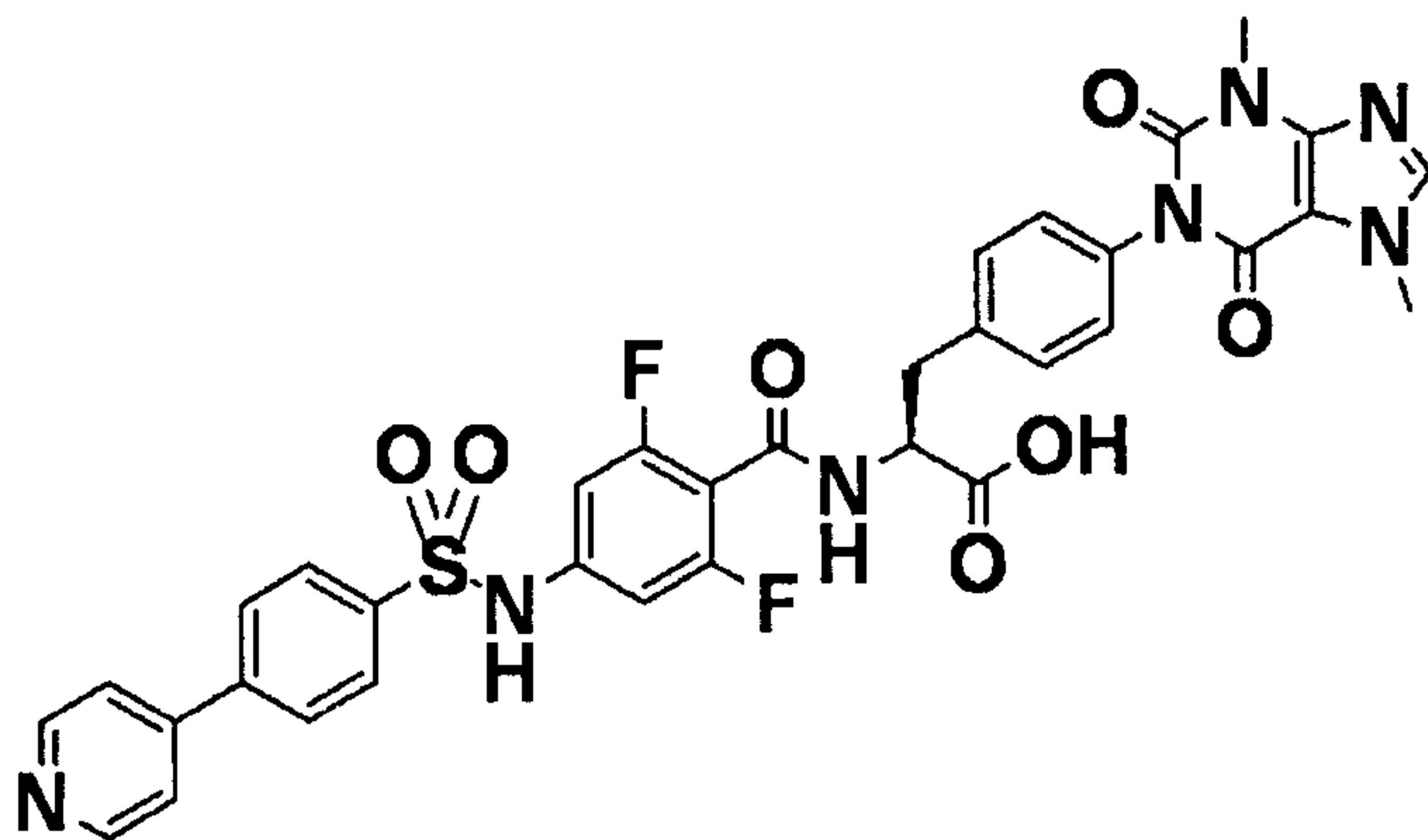
^1H NMR (d -DMSO, 400 MHz): δ 11.23 (s, 1H), 9.16 (d, J = 7.4 Hz,
 1H), 8.73 (d, J = 5.4 Hz, 2H), 8.10-8.04 (m, 3H), 8.01 (d, J
 20 = 8.5 Hz, 2H), 7.85 (d, J = 5.9 Hz, 2H), 7.31 (d, J = 8.3 Hz,
 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.85 (d, J = 9.0 Hz, 2H), 4.91-4.84
 (m, 1H), 4.54-4.49 (m, 1H), 3.85 (s, 3H), 3.42 (s, 3H), 3.14-2.97
 (m, 2H), 1.17 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H);

MS (ESI) m/z 758 (M+H)⁺

(Step

2)

N-(2,6-Difluoro-4-{[(4-pyridin-4-yl-phenyl)sulfonyl]amino}benzoyl)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-L-phenylalanine (A-37)



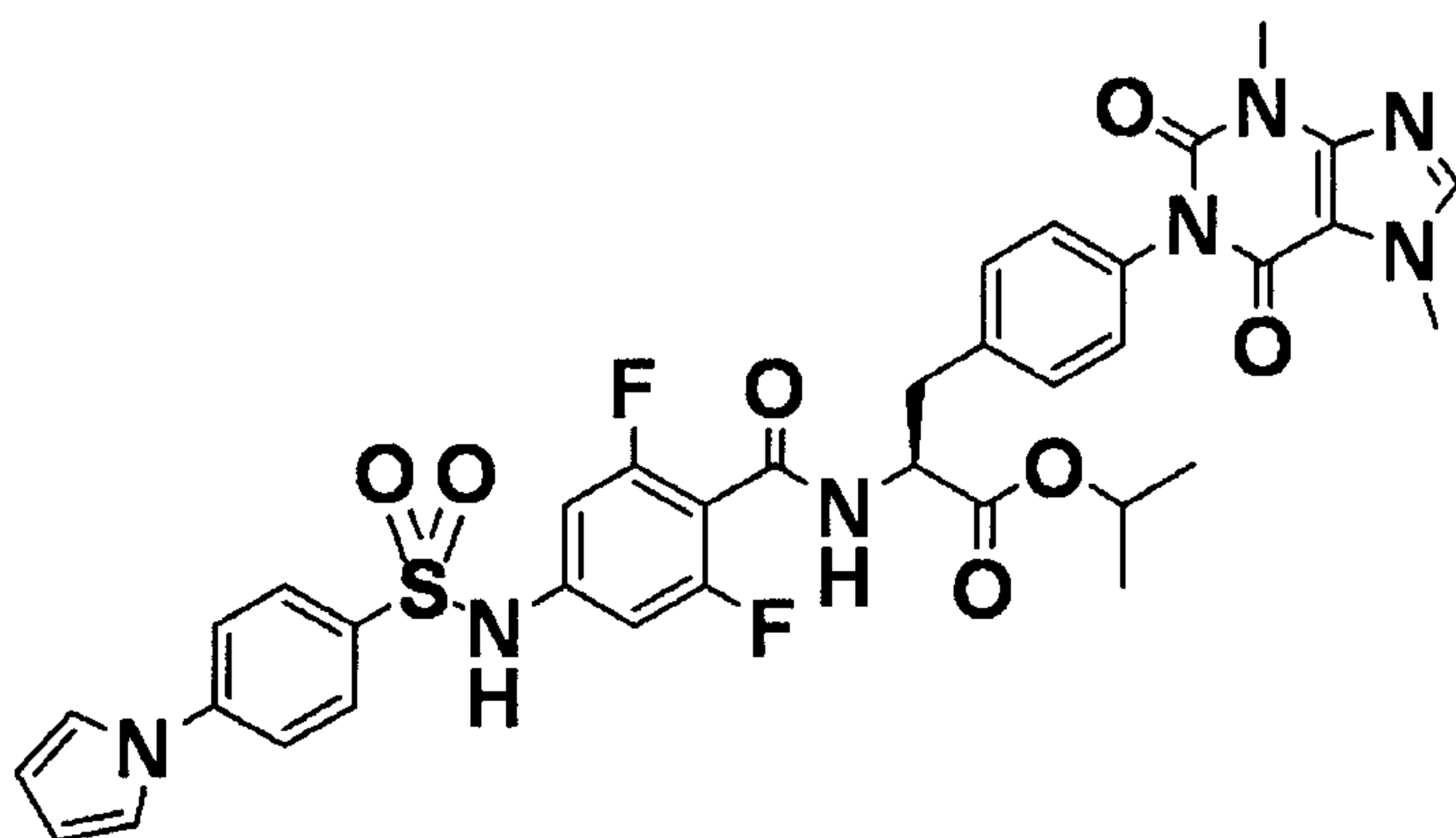
·TFA

To the TFA salt (7.4 mg, 8.5 μ mol) of isopropyl N-(2,6-difluoro-4-{[(4-pyridin-4-yl-phenyl)sulfonyl]amino}benzoyl)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-L-phenylalaninate (B-37), a 4 N hydrogen chloride/dioxane solution (1.0 ml) and water (2.0 ml) were added, followed by stirring at 70°C for 6 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (2.8 mg, 53%) of the title compound.

¹H NMR (d-DMSO, 400 MHz): δ 11.20 (s, 1H), 9.05 (d, J = 7.8 Hz, 1H), 8.73 (d, J = 4.3 Hz, 2H), 8.08-8.05 (m, 3H), 8.00 (d, J = 8.6 Hz, 2H), 7.85 (d, J = 4.5 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 9.1 Hz, 2H), 4.62-4.48 (m, 1H), 3.85 (s, 3H), 3.42 (s, 3H), 3.15 (dd, J = 13.8, 3.7 Hz, 1H), 2.97 (dd, J = 15.5, 8.8 Hz, 1H); MS (ESI) m/z 716 (M+H)⁺

Example 76: Synthesis of A-38 and B-38

(Step 1) Isopropyl
N-[2,6-Difluoro-4-({[4-(1H-pyrrol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-L-phenylalaninate (B-38)



5

Isopropyl

4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-L-phenylalaninate (M-5) (99.9 mg, 0.200 mmol) and 2,6-difluoro-4-({[4-(1H-pyrrol-1-yl)phenyl]sulfonyl}amino)benzoic acid (M-10) (75.7 mg, 0.200 mmol) were suspended in methylene chloride (4.0 ml), and HATU (114 mg, 0.300 mmol), HOAt (40.8 mg, 0.300 mmol), and triethylamine (70 μ L, 0.50 mmol) were added thereto, followed by stirring at room temperature for 2 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H_2O containing 0.1% TFA/ CH_3CN system) to obtain the title compound (27.8 mg, 16%).

^1H NMR (d -DMSO, 400 MHz): δ 11.08 (s, 1H), 9.14 (d, J = 7.3 Hz, 1H), 8.07 (s, 1H), 7.91 (d, J = 9.0 Hz, 2H), 7.83 (d, J = 9.0 Hz, 2H), 7.52-7.46 (m, 2H), 7.31 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 9.0 Hz, 2H), 6.33-6.29 (m, 2H), 4.92-4.84 (m, 1H), 4.56-4.48 (m, 1H), 3.86 (s, 3H), 3.42 (s, 3H), 3.10-2.97 (m, 2H), 1.17 (d, J = 6.2 Hz, 3H), 1.11 (d, J

20

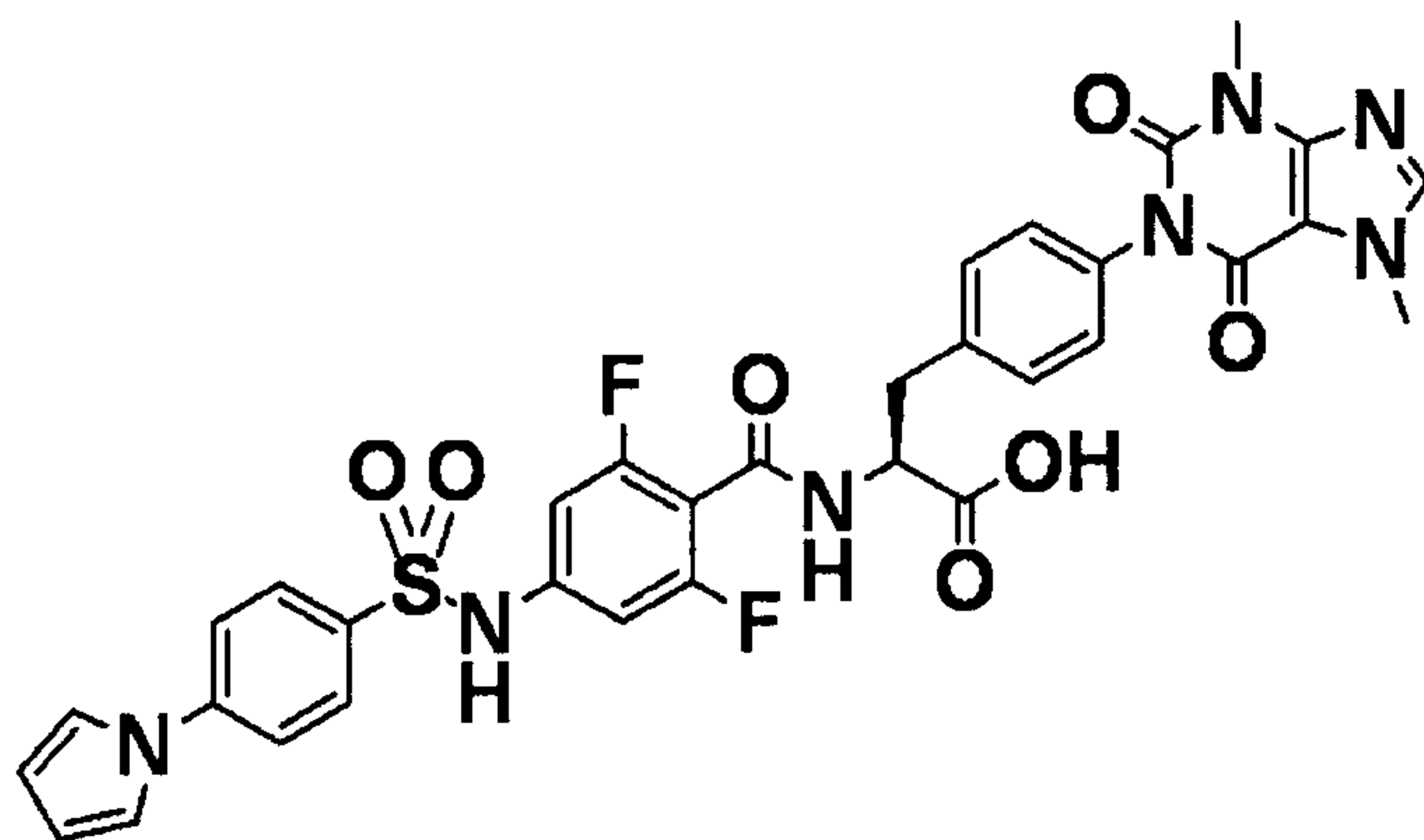
= 6.2 Hz, 3H); MS (ESI) m/z 746 (M+H)⁺

(Step

2)

N-[2,6-Difluoro-4-({[4-(1H-pyrrol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-L-phenylalanine (A-38)

5



To

isopropyl

N-[2,6-difluoro-4-({[4-(1H-pyrrol-1-yl)phenyl]sulfonyl}amino)benzoyl]-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)-L-phenylalaninate (B-38) (27.8 mg, 32.3 μmol), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (4.0 ml) were added, followed by stirring at 70°C for 6 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the title compound (7.6 mg, 29%).

¹H NMR (d-DMSO, 400 MHz): δ 11.06 (s, 1H), 9.03 (d, J = 7.8 Hz, 1H), 8.07 (d, J = 0.5 Hz, 1H), 7.90 (d, J = 8.9 Hz, 2H), 7.82 (d, J = 8.9 Hz, 2H), 7.51-7.47 (m, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.81 (d, J = 9.1 Hz, 2H), 6.34-6.27 (m, 2H), 4.59-4.51 (m, 1H), 3.86 (s, 3H), 3.42 (s, 3H), 3.17-3.06 (m, 1H), 2.97 (dd, J = 14.2, 9.7 Hz, 1H); MS (ESI) m/z 704 (M+H)⁺

20

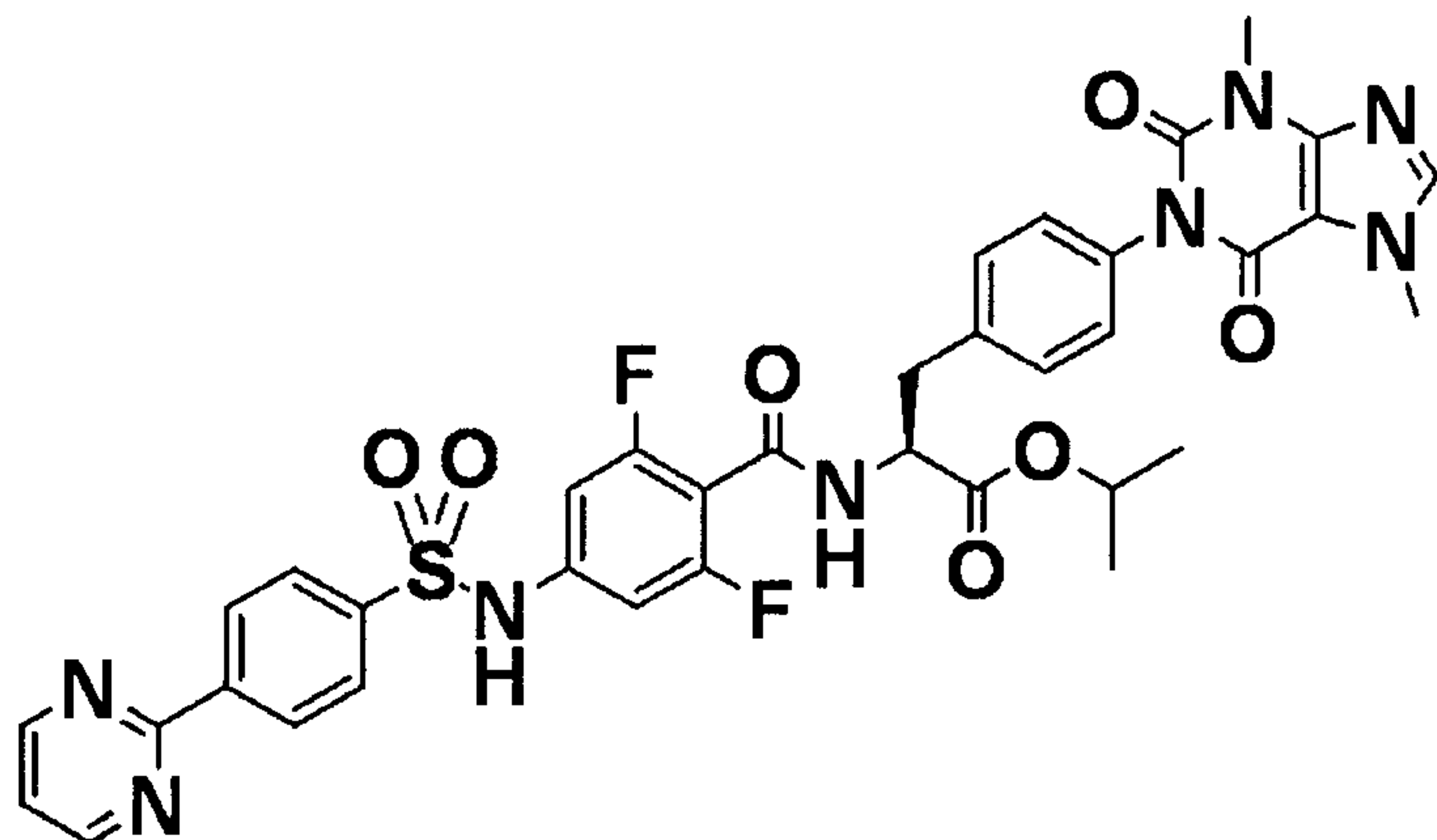
Example 77: Synthesis of A-39 and B-39

(Step

1)

Isopropyl

N-(2,6-Difluoro-4-{[(4-pyrimidin-2-yl-phenyl)sulfonyl]amino}
}benzoyl)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-p
urin-1-yl)-L-phenylalaninate (B-39)



5

·TFA

Isopropyl

4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)
 -L-phenylalaninate (M-5) (99.9 mg, 0.200 mmol) and
 2,6-difluoro-4-{[(4-pyrimidin-2-yl-phenyl)sulfonyl]amino}be
 10 nzoic acid (M-8) (78.3 mg, 0.200 mmol) were suspended in
 methylene chloride (4.0 ml), and HATU (114 mg, 0.300 mmol), HOAt
 (40.8 mg, 0.300 mmol), and triethylamine (70 μ L, 0.50 mmol) were
 added thereto, followed by stirring at room temperature for 2
 hours. After the reaction liquid was concentrated under
 15 reduced pressure, purification was conducted by reversed-phase
 HPLC (H_2O containing 0.1% TFA/ CH_3CN system) to obtain the TFA
 salt (28.4 mg, 16%) of the title compound.

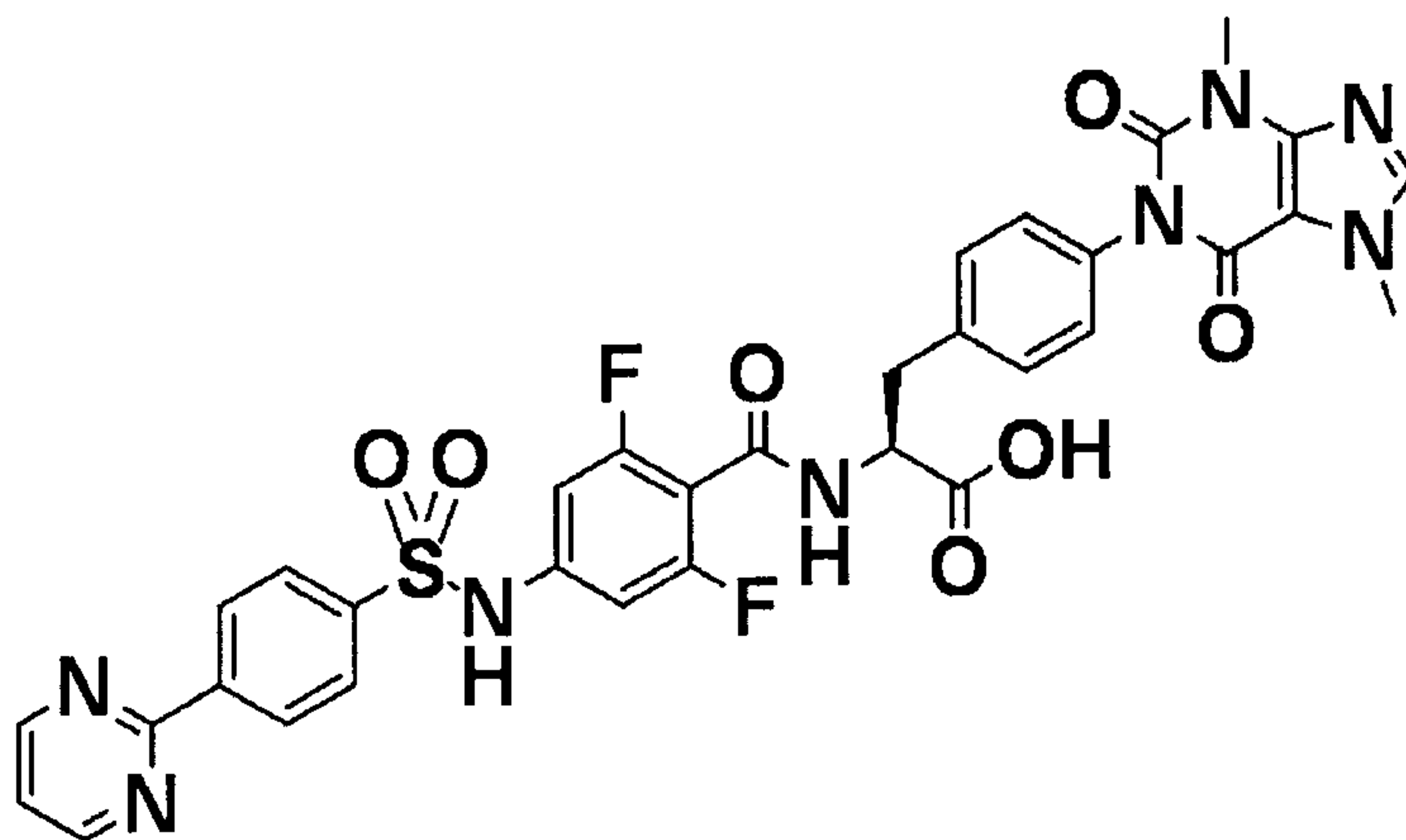
^1H NMR (d-DMSO, 400 MHz): δ 11.19 (s, 1H), 9.14 (d, J = 7.4 Hz,
 1H), 8.96 (d, J = 4.9 Hz, 2H), 8.64-8.53 (m, 2H), 8.10-7.97 (m,
 20 3H), 7.54 (t, J = 4.9 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.13
 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 9.1 Hz, 2H), 4.95-4.78 (m,
 1H), 4.59-4.44 (m, 1H), 3.86 (s, 3H), 3.42 (s, 3H), 3.12-2.96
 (m, 2H), 1.16 (d, J = 6.2 Hz, 3H), 1.11 (d, J = 6.2 Hz, 3H);

MS (ESI) m/z 759 (M+H)⁺

(Step

2)

N-(2,6-Difluoro-4-{[(4-pyrimidin-2-yl-phenyl)sulfonyl]amino}
benzoyl)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-p
 5 urin-1-yl)-L-phenylalanine (A-39)



·TFA

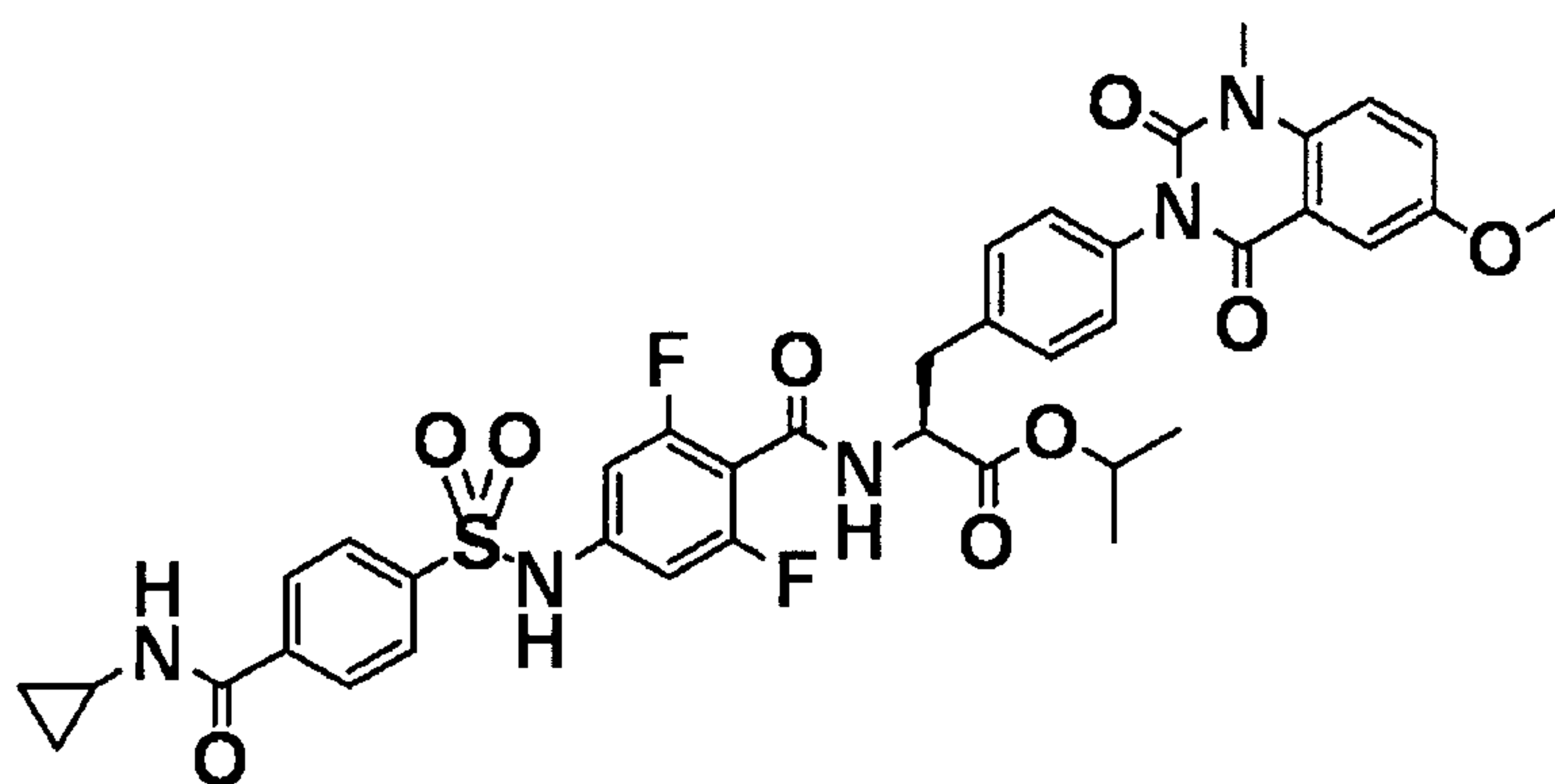
To the TFA salt (28.4 mg, 32.5 μ mol) of isopropyl
 N-(2,6-difluoro-4-{[(4-pyrimidin-2-yl-phenyl)sulfonyl]amino
 10 }benzoyl)-4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-p
 urin-1-yl)-L-phenylalaninate (B-39), a 4 N hydrogen
 chloride/dioxane solution (2.0 ml) and water (4.0 ml) were added,
 followed by stirring at 70°C for 6 hours. After the reaction
 liquid was concentrated under reduced pressure, purification
 15 was conducted by reversed-phase HPLC (H₂O containing 0.1%
 TFA/CH₃CN system) to obtain the TFA salt (9.7 mg, 36%) of the
 title compound.

¹H NMR (d-DMSO, 400 MHz): δ 11.17 (s, 1H), 9.03 (d, J = 7.9 Hz,
 1H), 8.96 (d, J = 4.9 Hz, 2H), 8.58 (d, J = 8.7 Hz, 2H), 8.06
 20 (s, 1H), 8.02 (d, J = 8.7 Hz, 2H), 7.53 (t, J = 4.9 Hz, 1H),
 7.31 (d, J = 8.3 Hz, 2H), 7.12 (d, J = 8.3 Hz, 2H), 6.81 (d,
 J = 9.1 Hz, 2H), 4.57-4.51 (m, 1H), 3.86 (s, 3H), 3.42 (s, 3H),
 3.14 (dd, J = 14.4, 4.4 Hz, 1H), 2.96 (dd, J = 13.9, 9.7 Hz,

1H); MS (ESI) m/z 717 (M+H)⁺

Example 78: Synthesis of A-40 and B-40

(Step 1) Isopropyl
N-{4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino
5 -2,6-difluorobenzoyl}-4-(6-methoxy-1-methyl-2,4-dioxo-1,4-
dihydroquinazolin-3(2H)-yl)-L-phenylalaninate (B-40)



Isopropyl

4-(3,7-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-1-yl)
 10 -L-phenylalaninate (M-4) (105 mg, 0.200 mmol) and
 4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino-2,
 6-difluorobenzoic acid (M-12) (79.3 mg, 0.200 mmol) were
 suspended in methylene chloride (4.0 ml), and HATU (114 mg,
 0.300 mmol), HOAt (40.8 mg, 0.300 mmol), and triethylamine (56
 15 μ L, 0.40 mmol) were added thereto, followed by stirring at room
 temperature for 2 hours. After the reaction liquid was
 concentrated under reduced pressure, purification was
 conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN
 system) to obtain the title compound (24.2 mg, 15%).

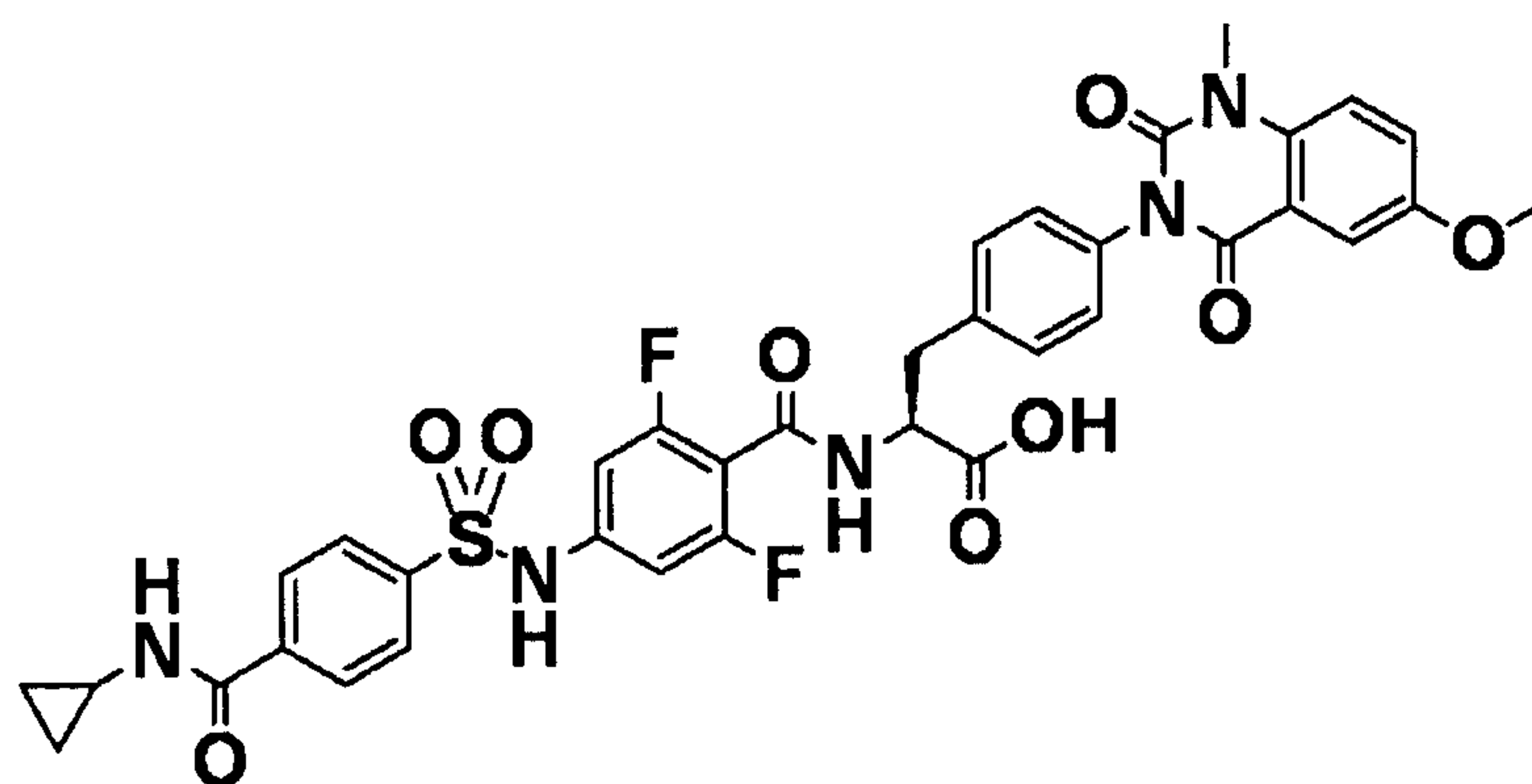
20 ¹H NMR (d-DMSO, 400 MHz): δ 11.18 (s, 1H), 9.17 (d, J = 7.4 Hz,
 1H), 8.65 (d, J = 4.3 Hz, 1H), 7.99-7.89 (m, 4H), 7.51-7.43 (m,
 3H), 7.34 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.3 Hz, 2H), 6.81
 (d, J = 9.0 Hz, 2H), 4.97-4.81 (m, 1H), 4.59-4.47 (m, 1H), 3.84
 (s, 3H), 3.52 (s, 3H), 3.16-2.98 (m, 2H), 2.91-2.78 (m, 1H),

1.18 (d, $J = 6.2$ Hz, 3H), 1.12 (d, $J = 6.2$ Hz, 3H), 0.73-0.65 (m, 2H), 0.60-0.50 (m, 2H); MS (ESI) m/z 790 (M+H)⁺

(Step

2)

N-{4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino}-2,6-difluorobenzoyl-4-(6-methoxy-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-L-phenylalanine (A-40)



To

isopropyl

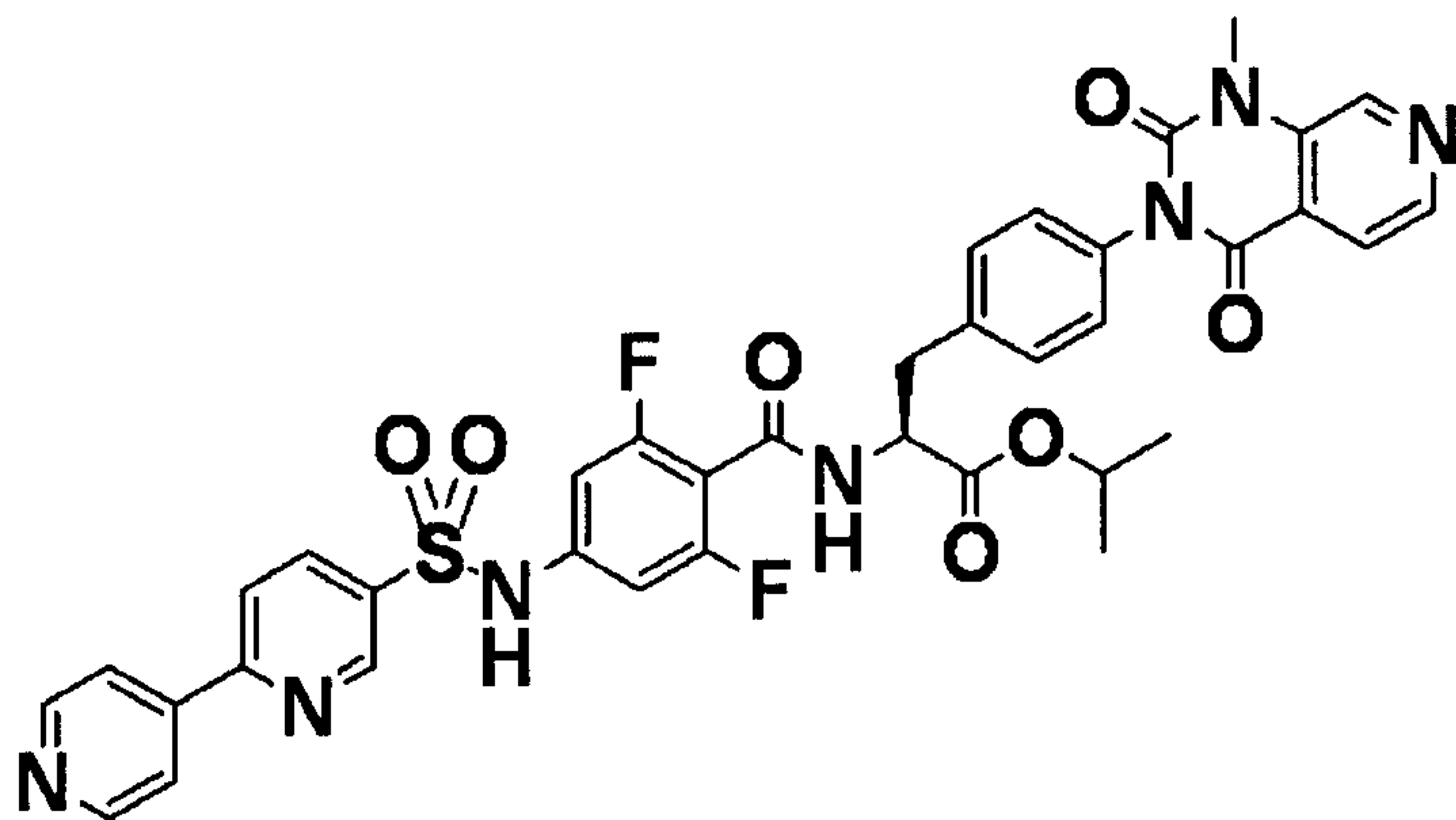
N-{4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino}-2,6-difluorobenzoyl-4-(6-methoxy-1-methyl-2,4-dioxo-1,4-dihydroquinazolin-3(2H)-yl)-L-phenylalaninate (B-40) (24.2 mg, 30.6 μ mol), a 4 N hydrogen chloride/dioxane solution (2.0 ml) and water (4.0 ml) were added, followed by stirring at 70°C for 6 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the title compound (10.3 mg, 45%).

¹H NMR (d-DMSO, 400 MHz): δ 11.15 (s, 1H), 9.06 (d, $J = 7.7$ Hz, 1H), 8.64 (d, $J = 4.1$ Hz, 1H), 7.98-7.89 (m, 4H), 7.51-7.45 (m, 3H), 7.34 (d, $J = 8.2$ Hz, 2H), 7.19 (d, $J = 8.2$ Hz, 2H), 6.79 (d, $J = 9.0$ Hz, 2H), 4.61-4.54 (m, 1H), 3.84 (s, 3H), 3.52 (s, 3H), 3.16-3.06 (m, 1H), 2.99 (dd, $J = 14.4, 9.5$ Hz, 1H), 2.87-2.79 (m, 1H), 0.75-0.63 (m, 2H), 0.59-0.51 (m, 2H).; MS (ESI) m/z 748 (M+H)⁺

Example 79: Synthesis of C-1

Isopropyl

N-{4-[(2,4'-Bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (C-1)



·3TFA

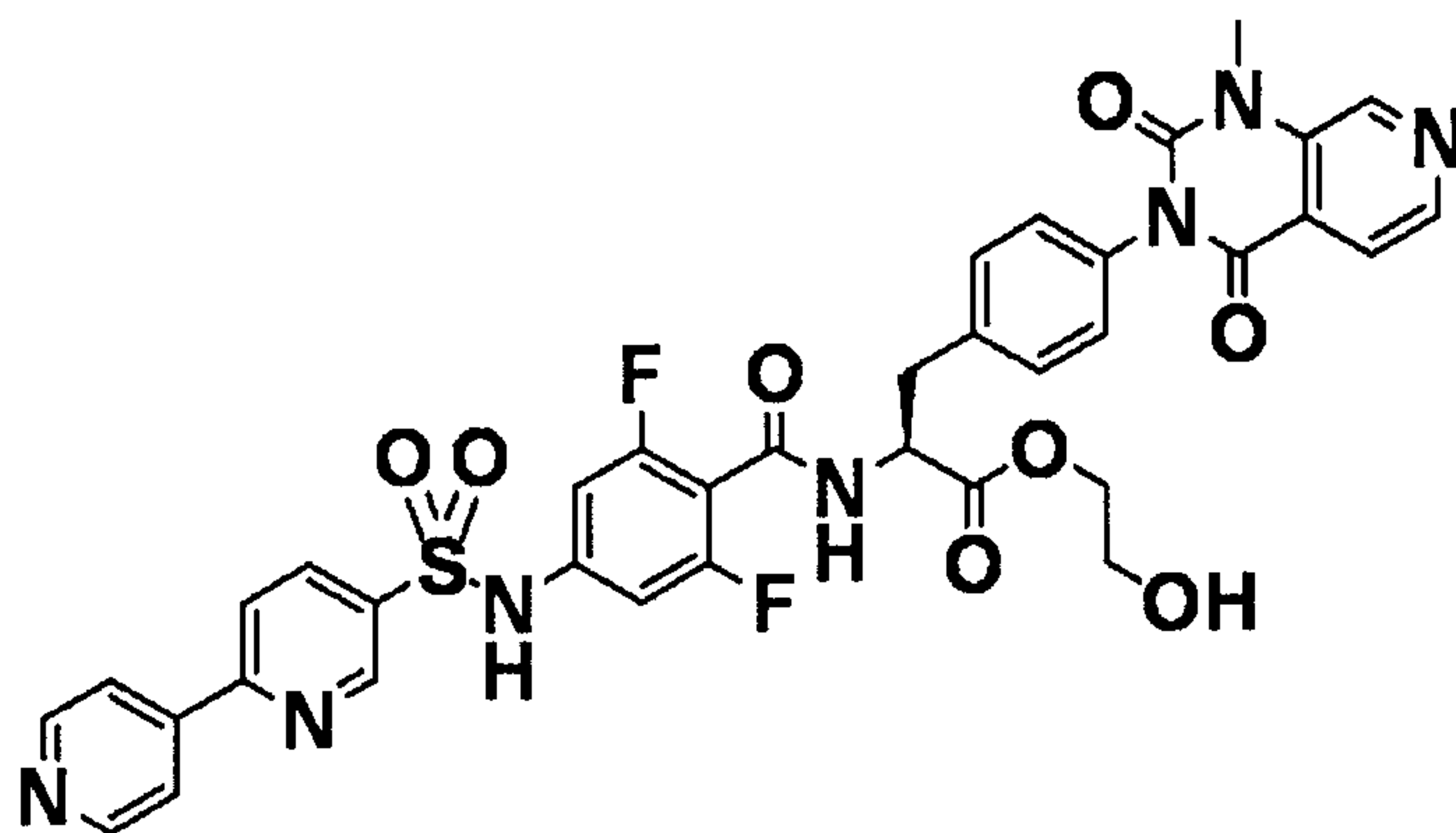
N-{4-[(2,4'-Bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-4) (30.0 mg, 28.4 μ mol) was dissolved in a 4 N hydrogen chloride/dioxane solution (2.0 ml), and isopropyl alcohol (1.0 ml) was added thereto, followed by stirring at 70°C for 2 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system) to obtain the TFA salt (22.3 mg, 72%) of the title compound.

¹H NMR (d-DMSO, 400 MHz): δ 11.4 (s, 1H), 9.19-9.17 (m, 2H), 8.98 (s, 1H), 8.83 (dd, J = 4.8, 1.2 Hz, 2H), 8.56 (d, J = 4.8 Hz, 1H), 8.44-8.43 (m, 2H), 8.22 (d, J = 6.0 Hz, 2H), 7.89 (d, J = 4.8 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 4.92-4.86 (m, 1H), 4.58-4.52 (m, 1H), 3.60 (s, 3H), 3.13-3.00 (m, 2H), 1.18 (d, J = 6.0 Hz, 3H), 1.12 (d, J = 6.4 Hz, 3H).; MS (ESI) m/z 756 (M+H)⁺

Example 80: Synthesis of C-2

2-Hydroxyethyl

N-{4-[(2,4'-Bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (C-2)



·3TFA

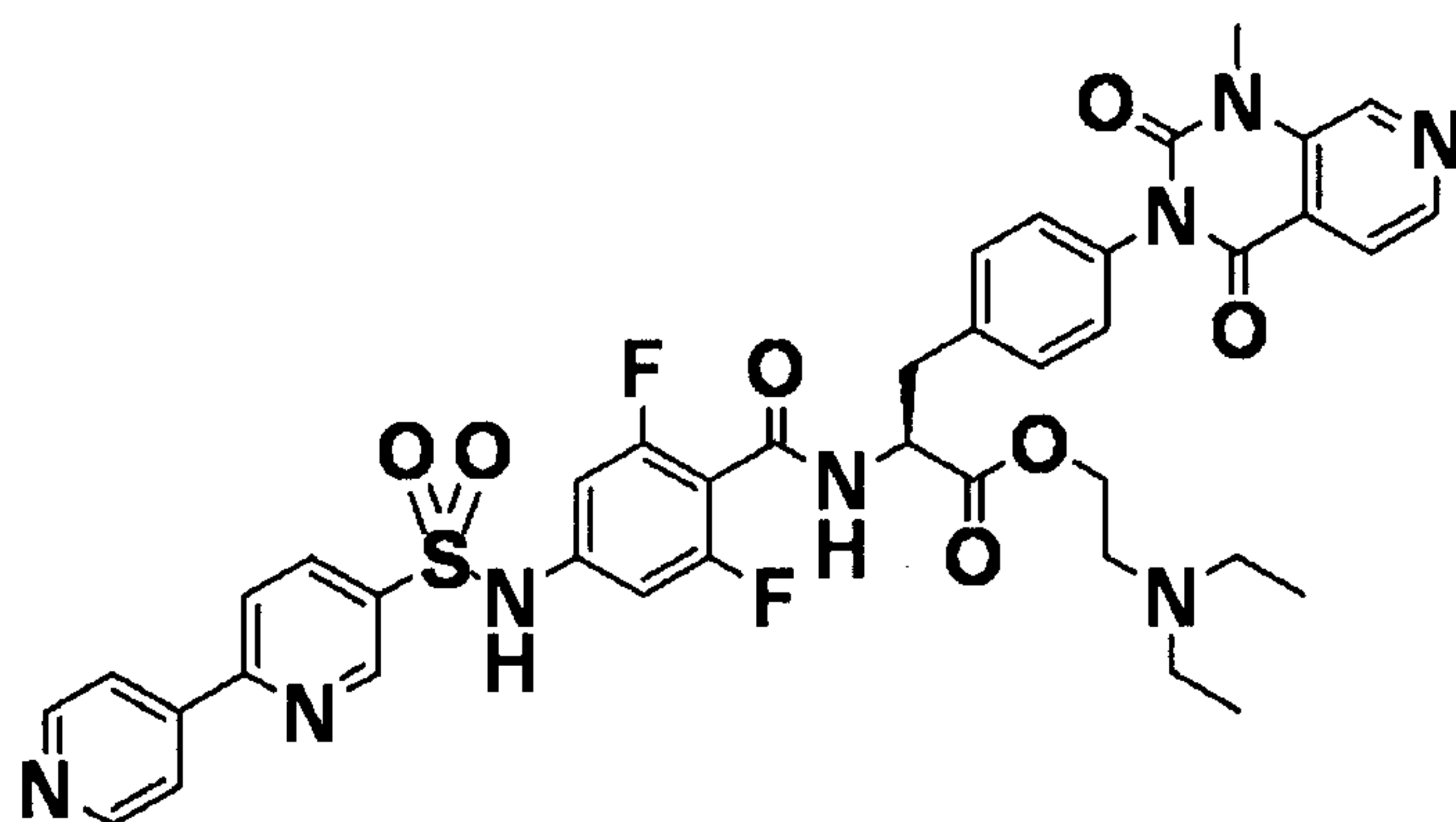
The title compound was obtained by subjecting N-{4-[(2,4'-bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-4) to the same method as described above.

¹H NMR (d-DMSO, 400 MHz): δ 11.4 (s, 1H), 9.13-9.11 (m, 2H), 8.90 (s, 1H), 8.79 (d, J = 4.8 Hz, 2H), 8.49 (d, J = 4.8 Hz, 1H), 8.40-8.35 (m, 2H), 8.21 (br, 2H), 7.81 (d, J = 4.8 Hz, 1H), 7.28 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.62-4.56 (m, 1H), 4.01 (t, J = 5.2 Hz, 2H), 3.53 (s, 3H), 3.14-2.93 (m, 2H).; MS (ESI) m/z 758 (M+H)⁺

Example 81: Synthesis of C-3

20 2-(Diethylamino)ethyl

N-{4-[(2,4'-Bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (C-3)



·4TFA

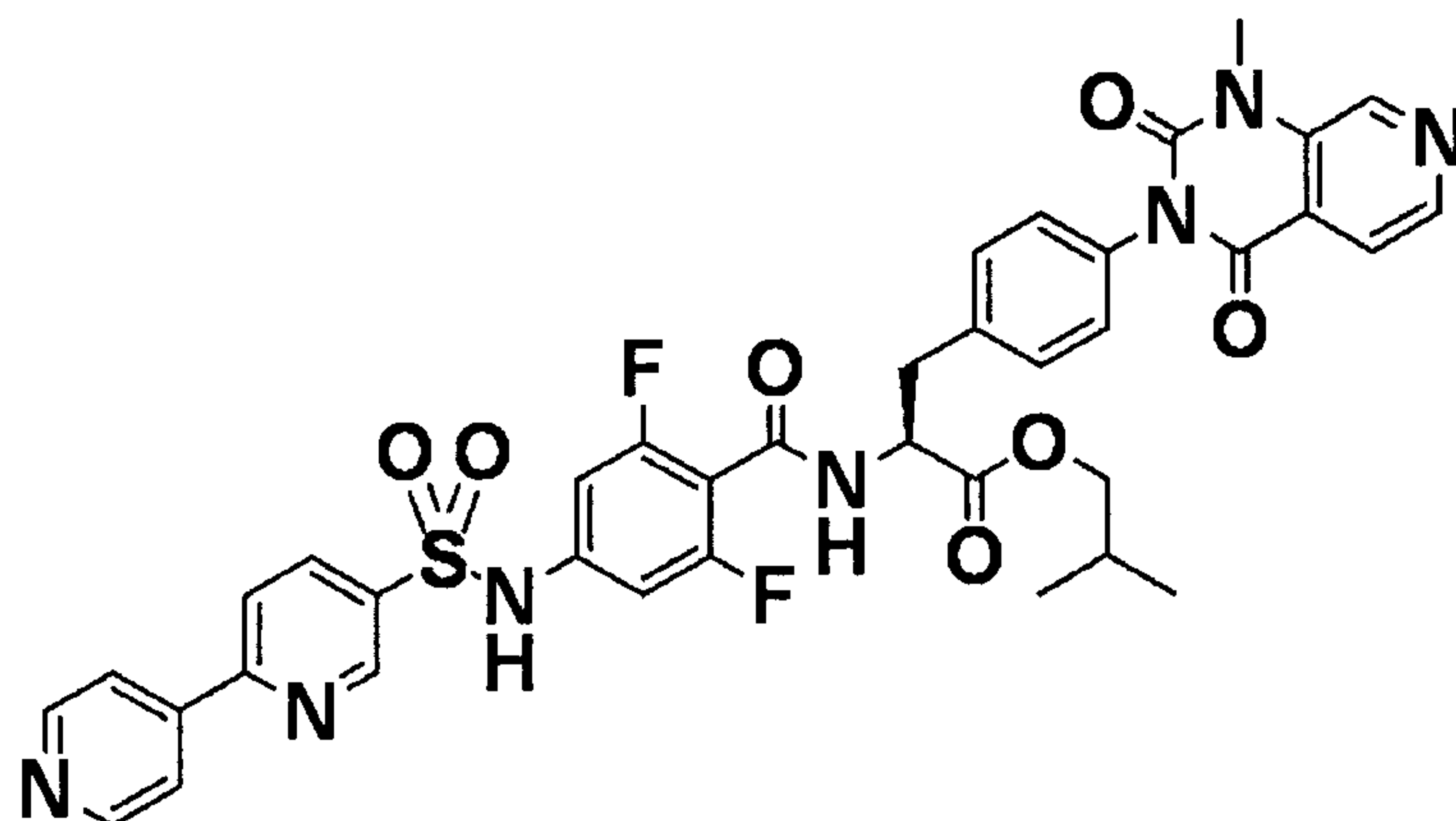
The title compound was obtained by subjecting N-{4-[(2,4'-bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-4) to the same method as described above.

¹H NMR (d-DMSO, 400 MHz): δ 11.4 (s, 1H), 9.29 (d, J = 7.2 Hz, 1H), 9.17 (d, J = 2.0 Hz, 1H), 8.99 (s, 1H), 8.79 (dd, J = 4.8, 1.6 Hz, 2H), 8.57 (d, J = 4.8 Hz, 1H), 8.45-8.38 (m, 2H), 8.13 (dd, J = 4.8, 1.6 Hz, 2H), 7.88 (d, J = 5.2 Hz, 1H), 7.36 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H), 6.91 (d, J = 9.2 Hz, 2H), 4.73-4.67 (m, 1H), 4.40-4.27 (m, 2H), 4.26 (s, 3H), 3.32 (br, 2H), 3.17-3.08 (m, 6H), 1.20-1.15 (m, 6H).; MS (ESI) m/z 813 (M+H)⁺

Example 82: Synthesis of C-4

Isobutyl

N-{4-[(2,4'-Bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (C-4)



·3TFA

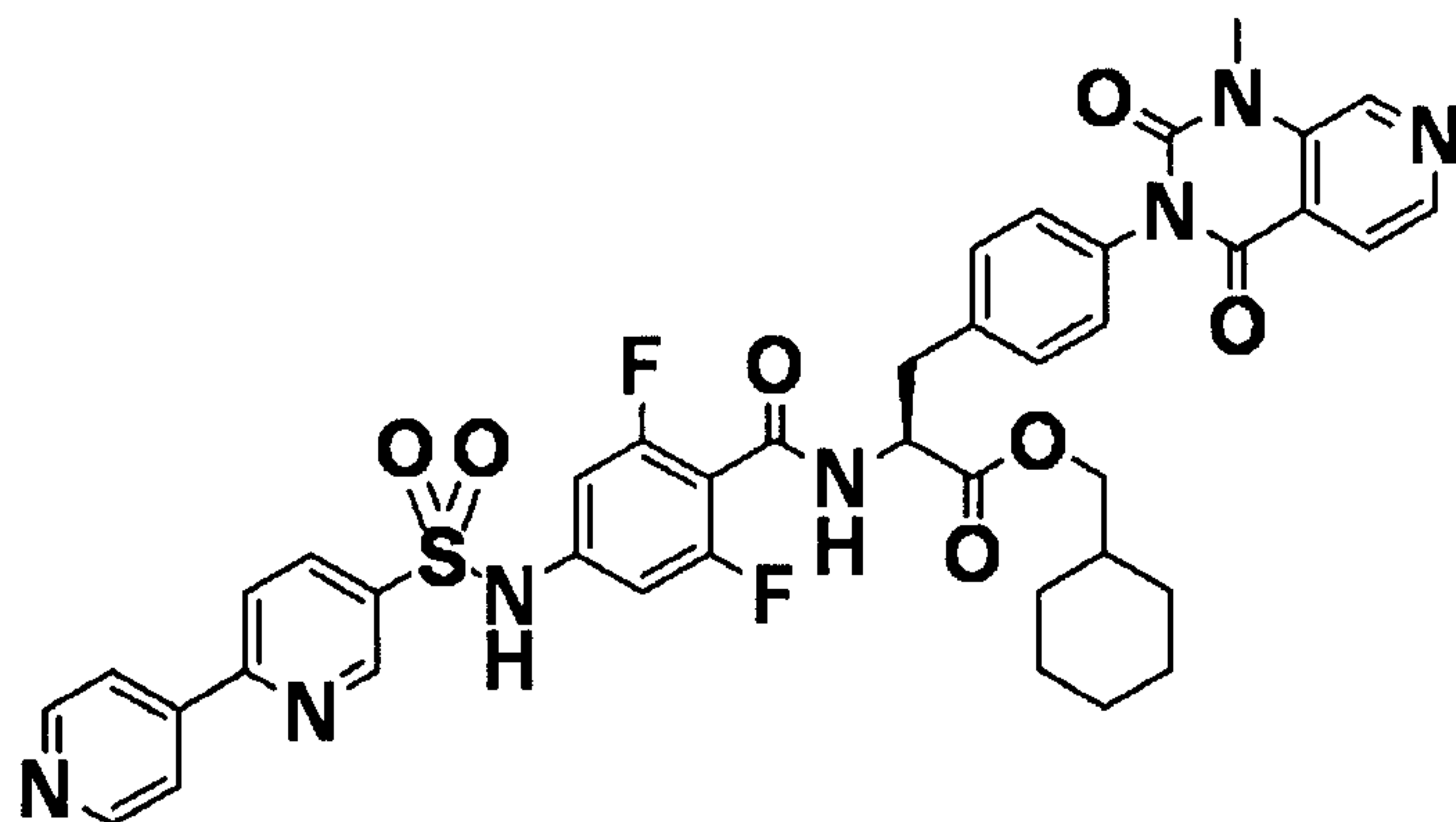
The title compound was obtained by subjecting N-{4-[(2,4'-bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-4) to the same method as described above.

¹H NMR (d-DMSO, 400 MHz): δ 11.4 (s, 1H), 9.20-9.17 (m, 2H), 8.97 (s, 1H), 8.81 (dd, J = 4.8, 1.6 Hz, 2H), 8.55 (d, J = 5.2 Hz, 1H), 8.45-8.39 (m, 2H), 8.19 (dd, J = 4.8, 1.6 Hz, 2H), 7.88 (dd, J = 5.2, 0.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 4.67-4.62 (m, 1H), 3.85 (d, J = 5.6 Hz, 2H), 3.59 (s, 3H), 3.18-3.00 (m, 2H), 1.88-1.81 (m, 1H), 0.87 (d, J = 6.8 Hz, 6H).; MS (ESI) m/z 770 (M+H)⁺

Example 83: Synthesis of C-5

Cyclohexylmethyl

N-{4-[(2,4'-Bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (C-5)



·3TFA

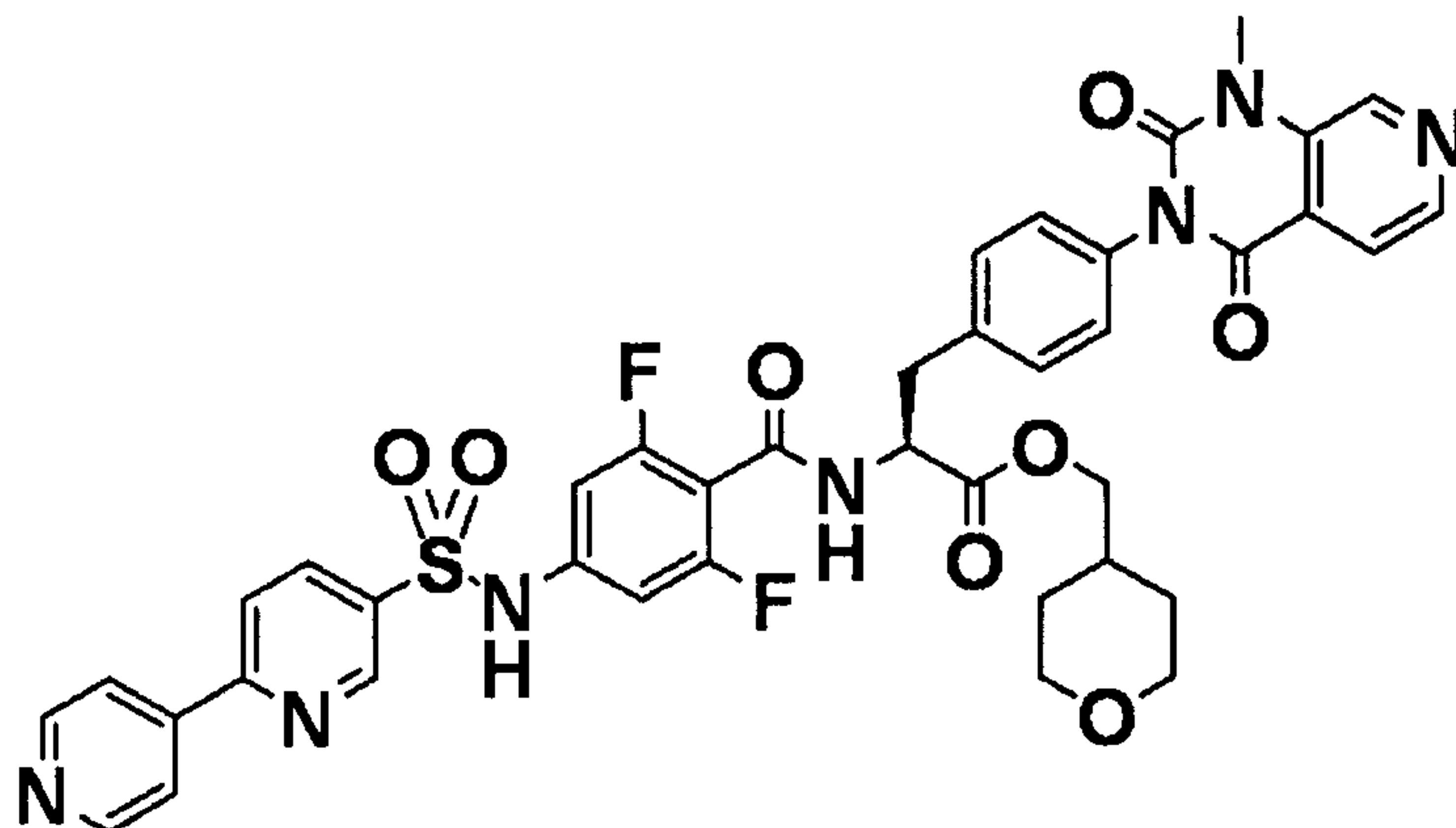
The title compound was obtained by subjecting N-{4-[(2,4'-bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-4) to the same method as described above.

¹H NMR (d-DMSO, 400 MHz): δ 11.4 (s, 1H), 9.12-9.10 (m, 2H), 8.90 (s, 1H), 8.76 (d, J = 5.2 Hz, 2H), 8.49 (d, J = 4.8 Hz, 1H), 8.39-8.33 (m, 2H), 8.16 (br, 2H), 7.81 (d, J = 4.8 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.58-4.54 (m, 1H), 3.80 (dd, J = 6.4, 2.0 Hz, 2H), 3.52 (s, 3H), 3.12-2.92 (m, 2H), 1.60-1.47 (m, 6H), 1.16-1.01 (m, 3H), 0.89-0.76 (m, 2H).; MS (ESI) m/z 810 (M+H)⁺

Example 84: Synthesis of C-6

Tetrahydro-2H-pyran-4-yl-methyl

N-{4-[(2,4'-Bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalaninate (C-6)



·3TFA

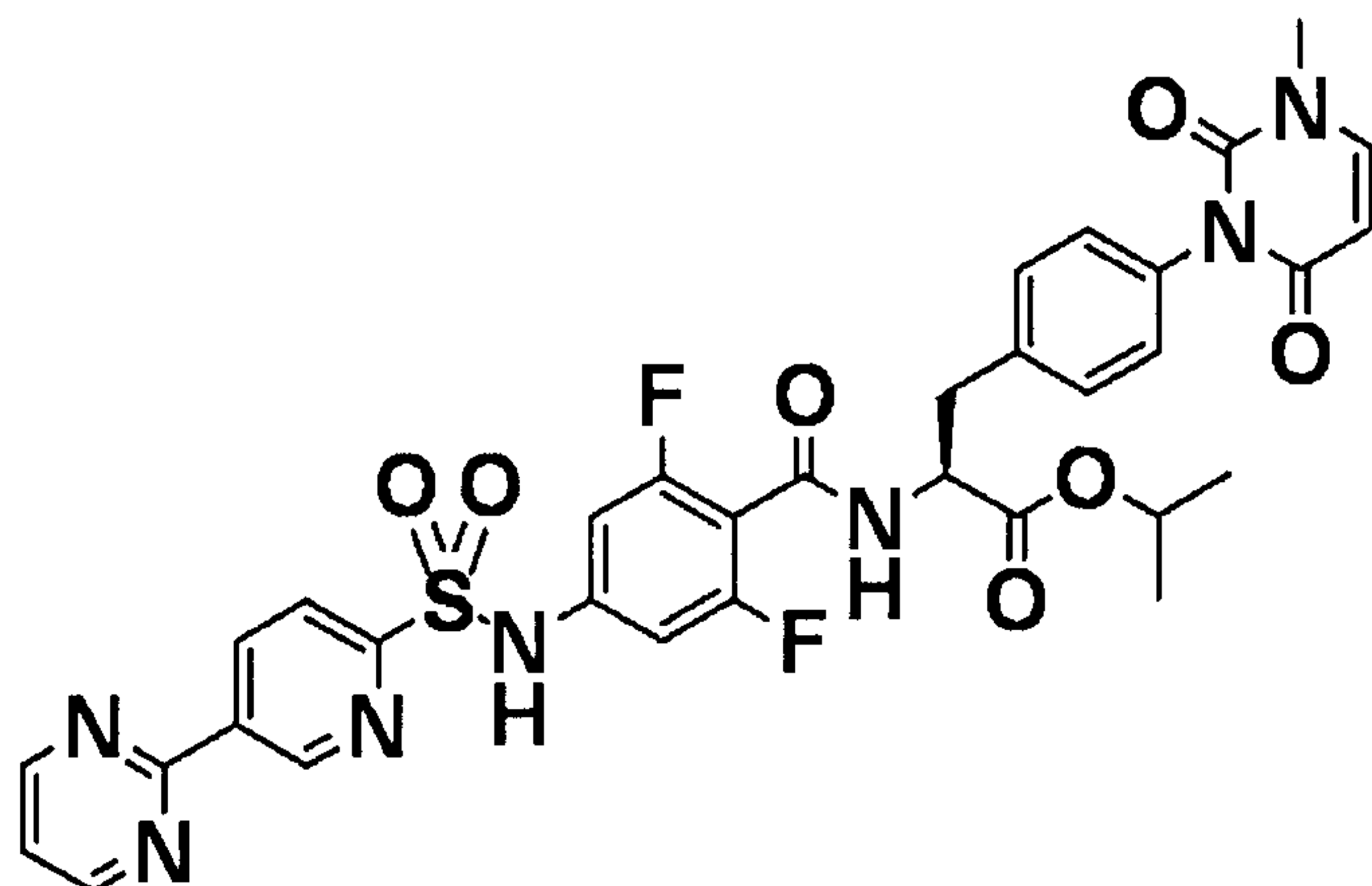
The title compound was obtained by subjecting N-{4-[(2,4'-bipyridin-5-yl-sulfonyl)amino]-2,6-difluorobenzoyl}-4-(1-methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)-L-phenylalanine (A-4) to the same method as described above.

¹H NMR (d-DMSO, 400 MHz): δ 11.4 (s, 1H), 9.19-9.18 (m, 2H), 8.97 (s, 1H), 8.84 (dd, J = 4.8, 1.6 Hz, 2H), 8.55 (d, J = 5.2 Hz, 1H), 8.47-8.41 (m, 2H), 8.25 (dd, J = 4.8, 1.2 Hz, 2H), 7.88 (dd, J = 5.2, 0.4 Hz, 1H), 7.34 (d, J = 8.4 Hz, 2H), 7.21 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.65-4.62 (m, 1H), 3.91 (d, J = 6.4 Hz, 2H), 3.83-3.80 (m, 2H), 3.59 (s, 3H), 3.28-3.22 (m, 2H), 3.16-3.01 (m, 2H), 1.83-1.77 (m, 1H), 1.53-1.50 (m, 2H), 1.24-1.14 (m, 2H).; MS (ESI) m/z 812 (M+H)⁺

Example 85: Synthesis of C-7

Isopropyl

N-(2,6-Difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (C-7)



·2TFA

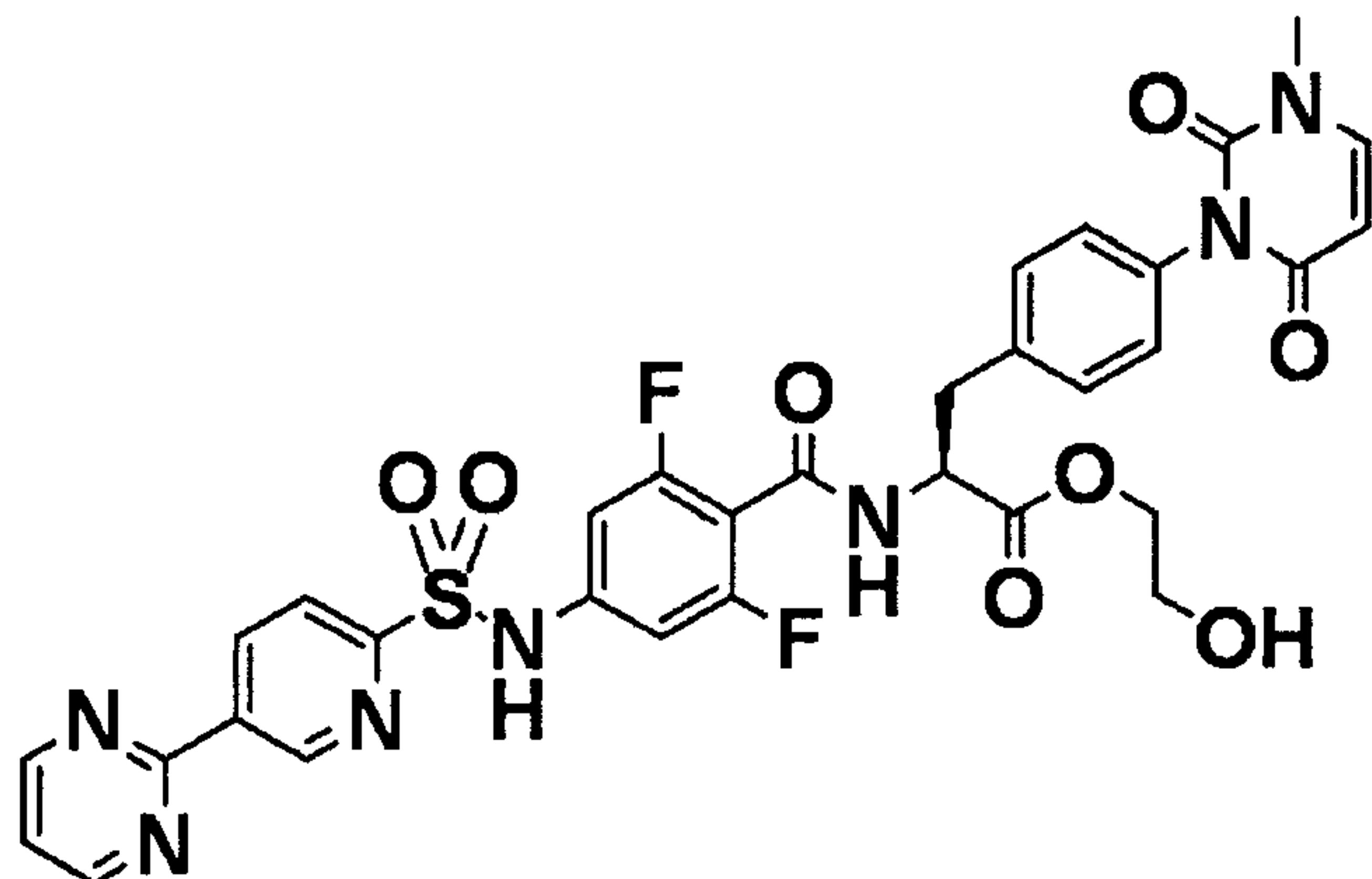
The title compound was obtained by subjecting N-(2,6-difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-2) to the same method as described above .

¹H NMR (d-DMSO, 400 MHz): δ 11.4 (s, 1H), 9.59 (dd, J = 2.0, 0.8 Hz, 1H), 9.14 (d, J = 7.2 Hz, 1H), 9.01 (d, J = 4.8 Hz, 2H), 8.96 (dd, J = 8.4, 2.0 Hz, 1H), 8.29 (dd, J = 8.0, 0.4 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.61 (t, J = 4.8 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 9.2 Hz, 2H), 5.74 (d, J = 8.0 Hz, 1H), 4.90-4.84 (m, 1H), 4.53-4.48 (m, 1H), 3.31 (s, 3H), 3.10-2.98 (m, 2H), 1.16 (d, J = 6.4 Hz, 3H), 1.10 (d, J = 6.0 Hz, 3H).; MS (ESI) m/z 706 (M+H)⁺

Example 86: Synthesis of C-8

2-Hydroxyethyl

N-(2,6-Difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (C-8)



·2TFA

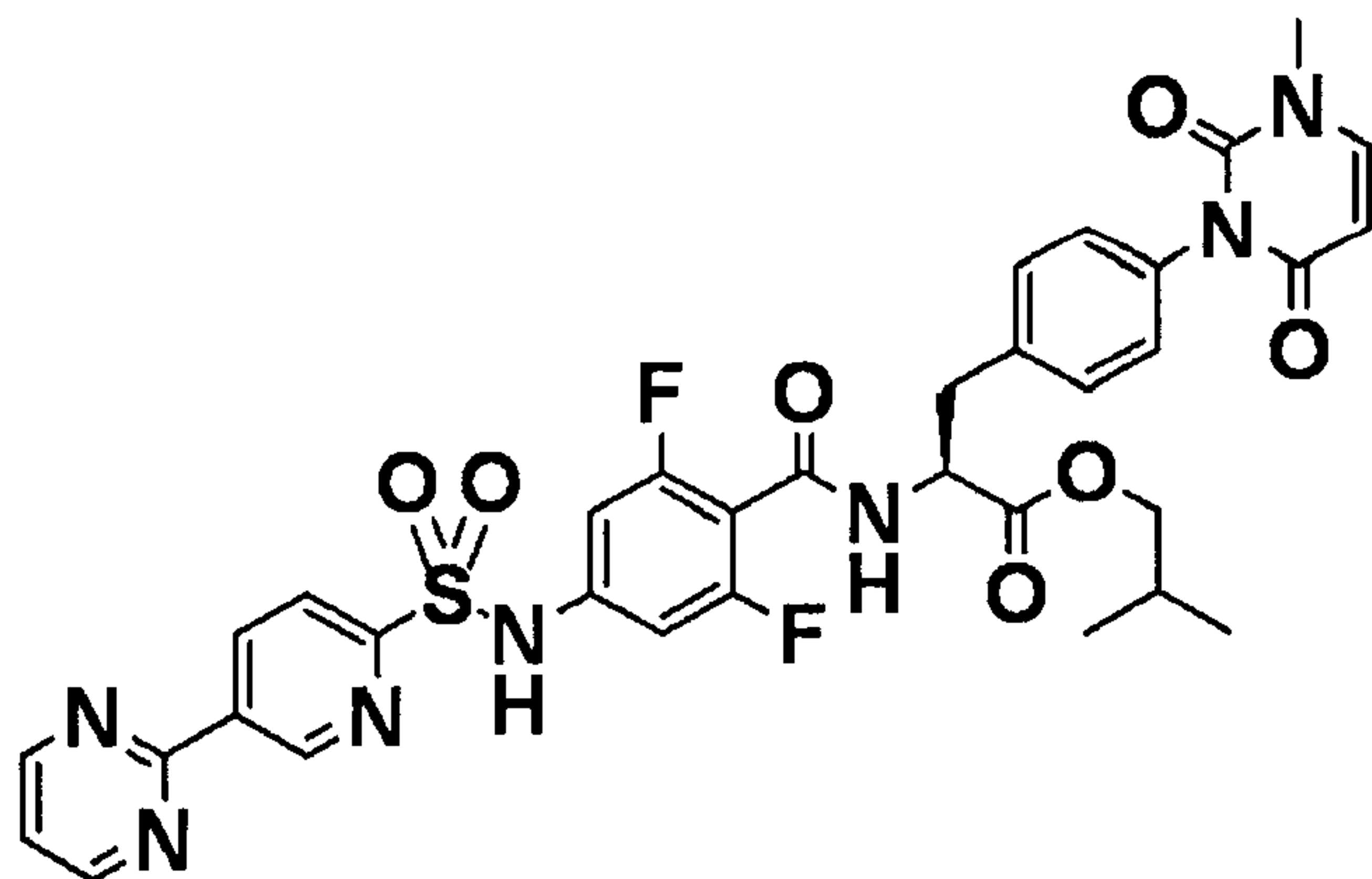
The title compound was obtained by subjecting
 N-(2,6-difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl
 5]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-
 1(2H)-yl)-L-phenylalanine (A-2) to the same method as described
 above.

MS (ESI) m/z 708 (M+H)⁺

Example 87: Synthesis of C-9

10 Isobutyl

N-(2,6-Difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl
]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-
 1(2H)-yl)-L-phenylalaninate (C-9)



·2TFA

15

The title compound was obtained by subjecting

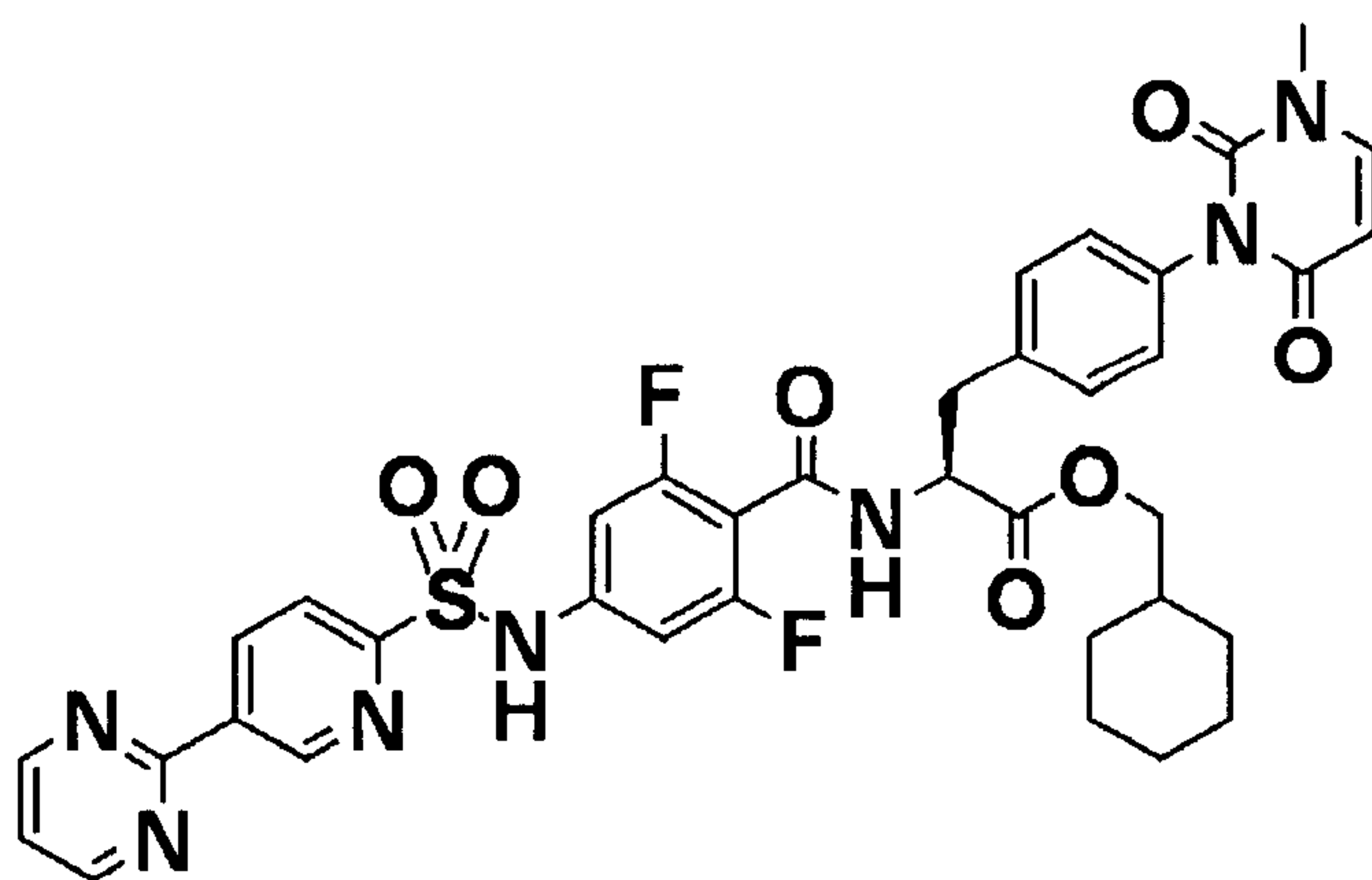
N-(2,6-difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-2) to the same method as described above.

5 ¹H NMR (d-DMSO, 400 MHz): δ 11.4 (s, 1H), 9.59 (d, J = 1.6 Hz, 1H), 9.16 (d, J = 7.6 Hz, 1H), 9.01 (d, J = 5.2 Hz, 2H), 8.96 (dd, J = 8.4, 2.0 Hz, 1H), 8.29 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.61 (t, J = 5.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 9.2 Hz, 2H), 5.74
10 (d, J = 8.0 Hz, 1H), 4.64-4.58 (m, 1H), 3.83 (dd, J = 8.4, 6.8 Hz, 2H), 3.31 (s, 3H), 3.15-2.98 (m, 2H), 1.89-1.79 (m, 1H), 0.86 (d, J = 6.8 Hz, 6H).; MS (ESI) m/z 720 (M+H)⁺

Example 88: Synthesis of C-10

Cyclohexylmethyl

15 N-(2,6-Difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (C-10)



·2TFA

20 The title compound was obtained by subjecting N-(2,6-difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-2) to the same method as described

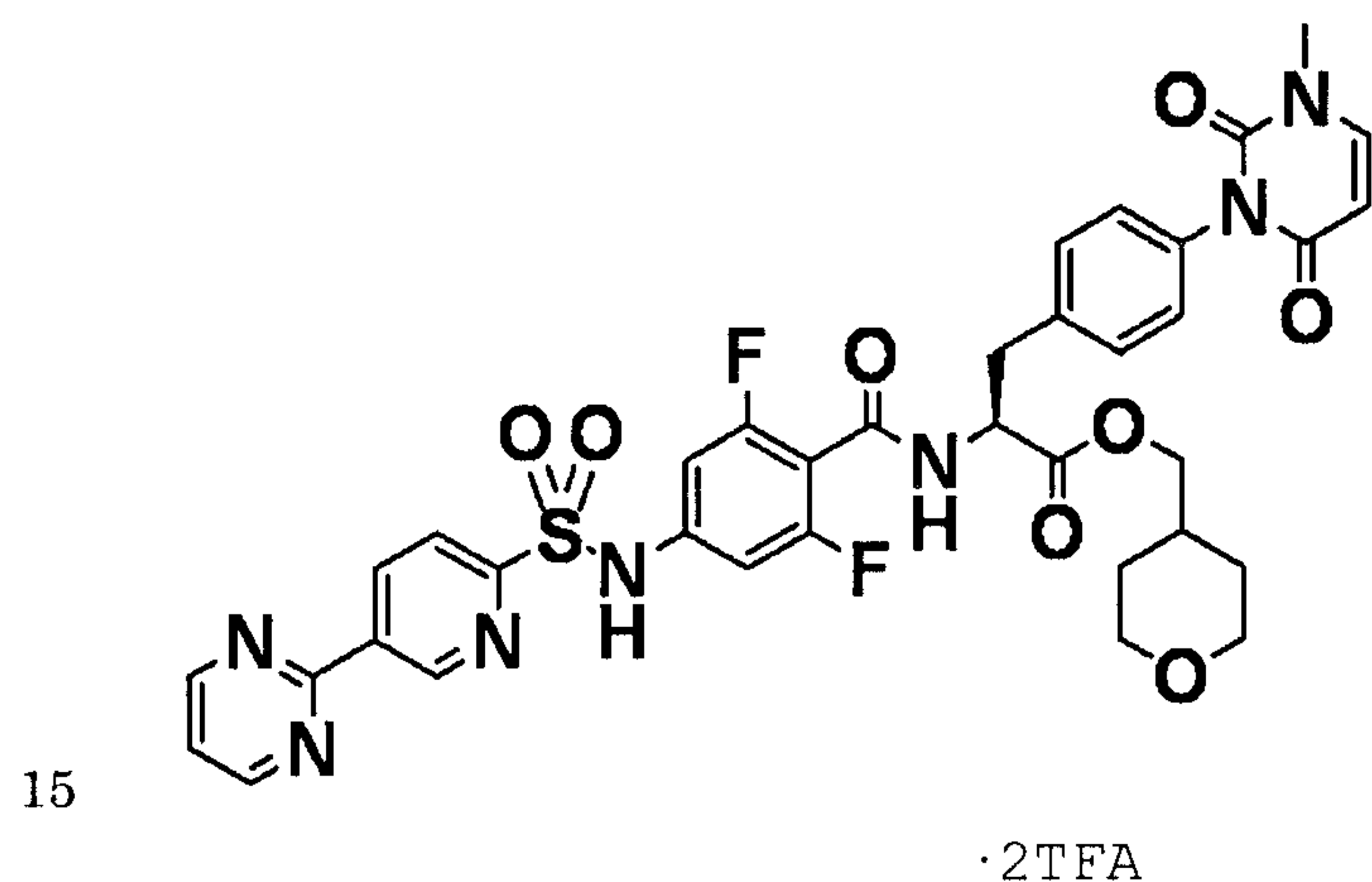
above.

¹H NMR (d-DMSO, 400 MHz): δ 11.4 (s, 1H), 9.51 (d, J = 2.0 Hz, 1H), 9.07 (d, J = 7.6 Hz, 1H), 8.94 (d, J = 4.8 Hz, 2H), 8.88 (dd, J = 8.0, 2.0 Hz, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.53 (t, J = 5.2 Hz, 1H), 7.23 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 9.2 Hz, 2H), 5.67 (d, J = 7.6 Hz, 1H), 4.54-4.52 (m, 1H), 3.80-3.76 (m, 1H), 3.23 (s, 3H), 3.08-2.90 (m, 2H), 1.59-1.47 (m, 6H), 1.11-1.03 (m, 3H), 0.88-0.83 (m, 2H).; MS (ESI) m/z 760 (M+H)⁺

10 Example 89: Synthesis of C-11

Tetrahydro-2H-pyran-4-yl-methyl

N-(2,6-Difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (C-11)



The title compound was obtained by subjecting N-(2,6-difluoro-4-{[(5-pyrimidin-2-yl-pyridin-2-yl)sulfonyl]amino}benzoyl)-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-2) to the same method as described above.

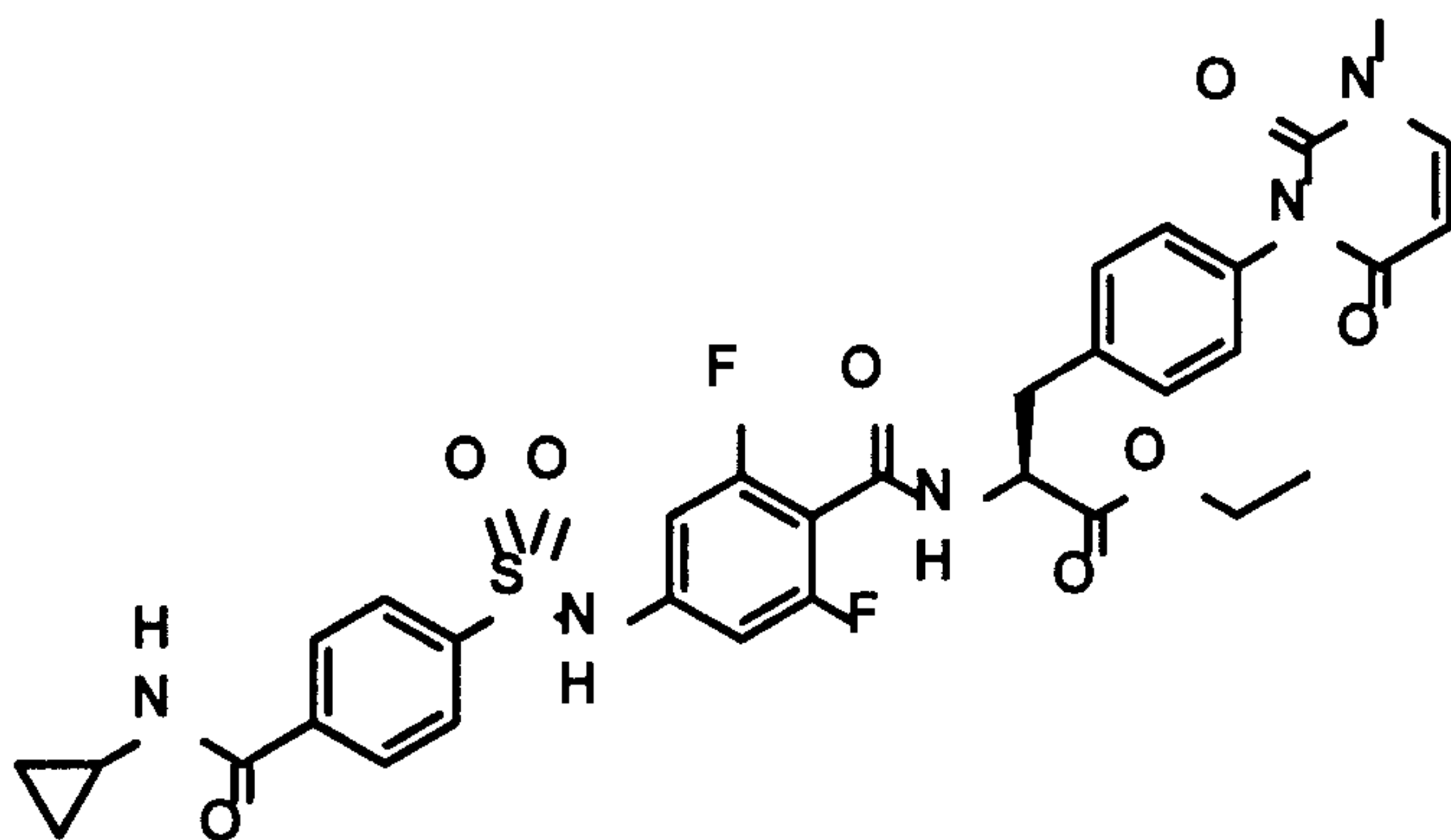
¹H NMR (d-DMSO, 400 MHz): δ 11.4 (s, 1H), 9.59-9.59 (m, 1H), 9.17 (d, J = 7.6 Hz, 1H), 9.01 (dd, J = 5.2, 0.8 Hz, 2H), 8.96 (dd, J = 8.4, 1.6 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 7.75 (d,

J = 8.0 Hz, 1H), 7.61 (t, J = 5.2 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 5.74 (dd, J = 8.0, 0.4 Hz, 1H), 4.63-4.57 (m, 1H), 3.90 (d, J = 6.4 Hz, 2H), 3.81-3.79 (m, 2H), 3.31 (s, 3H), 3.27-3.21 (m, 2H),
 5 3.14-2.98 (m, 2H), 1.83-1.76 (m, 1H), 1.52-1.49 (m, 2H), 1.23-1.13 (m, 2H).; MS (ESI) m/z 762 (M+H)⁺

Example 90: Synthesis of C-12

Ethyl

N-{4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino
 10]-2,6-difluorobenzoyl}-4-(3-methyl-2,6-dioxo-3,6-dihydropyr
imidin-1(2H)-yl)-L-phenylalaninate (C-12)



The title compound was obtained by subjecting
 N-{4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino
 15]-2,6-difluorobenzoyl}-4-(3-methyl-2,6-dioxo-3,6-dihydropyr
 imidin-1(2H)-yl)-L-phenylalanine (A-7) to the same method as
 described above.

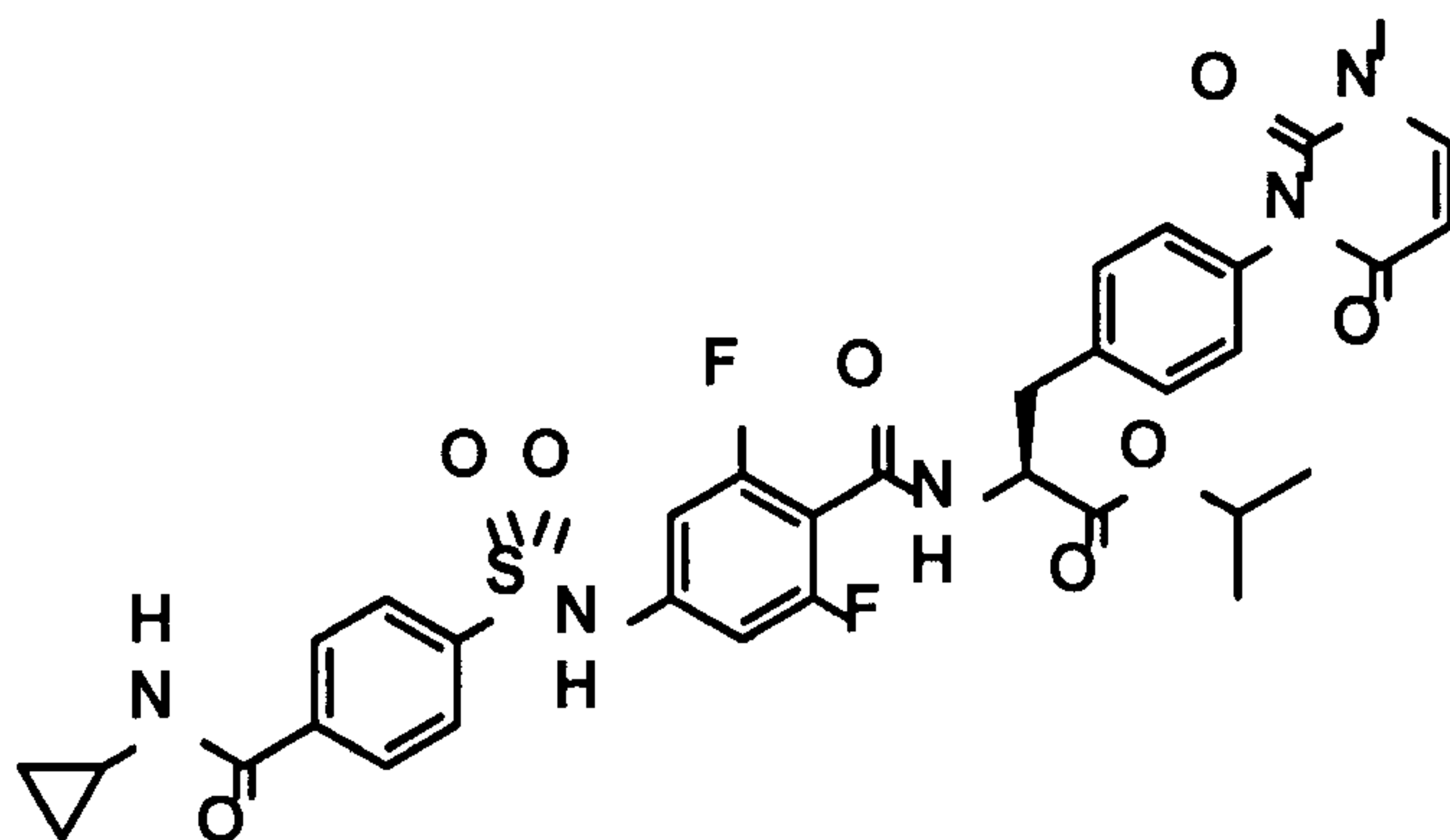
¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.17 (br, 1H), 8.64 (s, 1H), 7.95 (br, 4H), 7.76 (dd, J = 7.6, 4.4 Hz, 1H), 7.30 (d, J = 3.6 Hz, 2H), 7.10 (d, J = 4.0 Hz, 2H), 6.82-6.78 (m, 2H), 5.75 (dd, J = 8.0, 5.2 Hz, 1H), 4.57 (br, 1H), 4.10-4.04 (m, 2H), 3.32 (s, 3H), 3.18-2.98 (m, 2H), 2.87-2.81 (m, 1H),
 20 1.16-1.11 (m, 3H), 0.70 (br, 2H), 0.56 (br, 2H).; MS (ESI) m/z

696 (M+H)⁺

Example 91: Synthesis of C-13

Isopropyl

N-{4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino
5]-2,6-difluorobenzoyl}-4-(3-methyl-2,6-dioxo-3,6-dihydropyr
imidin-1(2H)-yl)-L-phenylalaninate (C-13)



The title compound was obtained by subjecting
N-{4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino
10]-2,6-difluorobenzoyl}-4-(3-methyl-2,6-dioxo-3,6-dihydropyr
imidin-1(2H)-yl)-L-phenylalanine (A-7) to the same method as
described above.

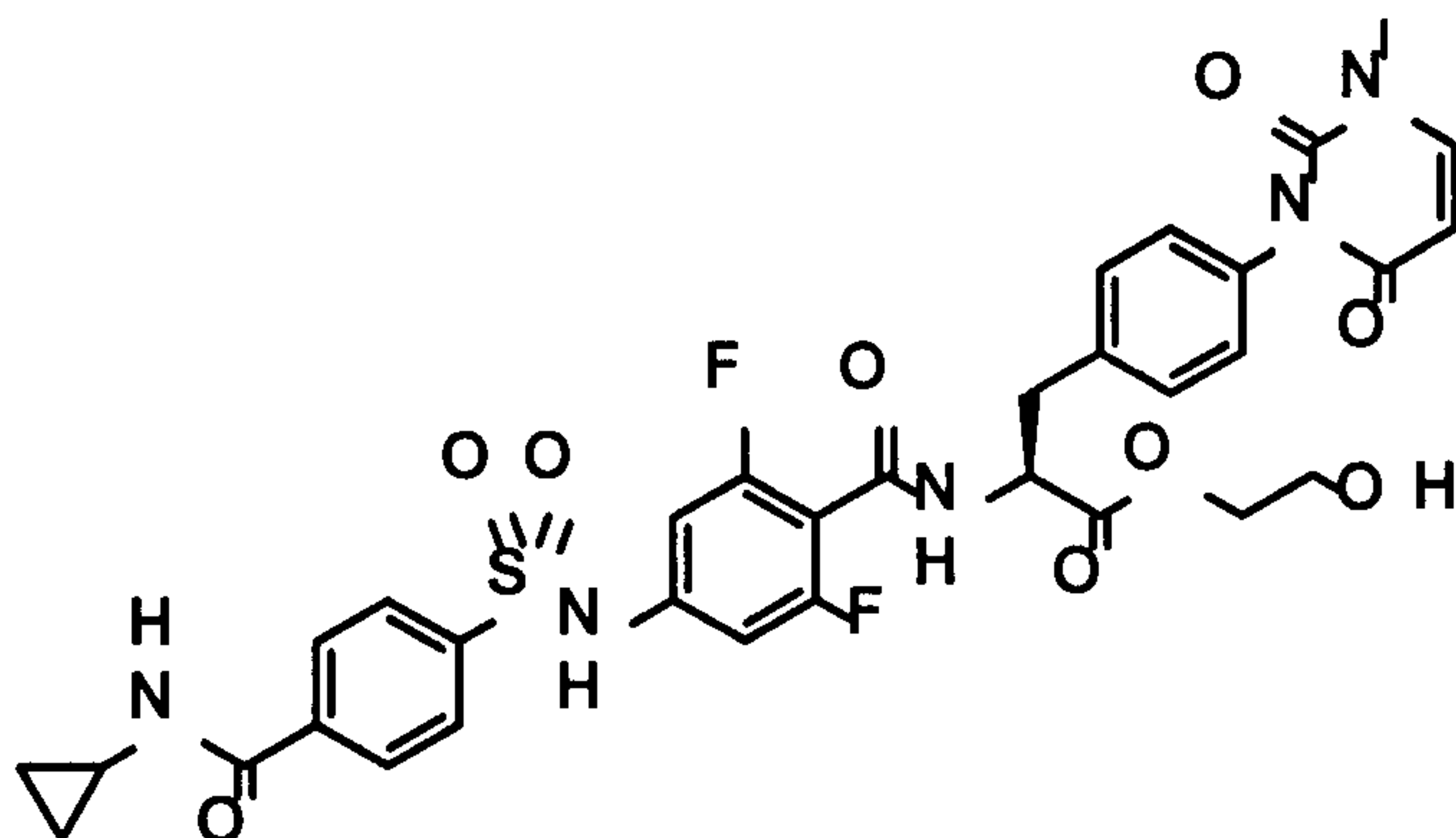
¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.15 (d, J = 7.2 Hz,
1H), 8.64 (d, J = 4.0 Hz, 1H), 7.95 (dd, J = 12.8, 8.8 Hz, 4H),
15 7.76 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.10 (d,
J = 8.0 Hz, 2H), 6.80 (d, J = 9.2 Hz, 2H), 5.75 (d, J = 8.0 Hz,
1H), 4.91-4.85 (m, 1H), 4.54-4.49 (m, 1H), 3.31 (s, 3H),
3.11-2.98 (m, 2H), 2.86-2.81 (m, 1H), 1.17 (d, J = 6.0 Hz, 3H),
1.11 (d, J = 6.4 Hz, 3H), 0.71-0.67 (m, 2H), 0.58-0.54 (m, 2H). ;
20 MS (ESI) m/z 710 (M+H)⁺

Example 92: Synthesis of C-14

2-Hydroxyethyl

N-{4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino

] -2,6-difluorobenzoyl}-4-(3-methyl-2,6-dioxo-3,6-dihydropyr
imidin-1(2H)-yl)-L-phenylalaninate (C-14)



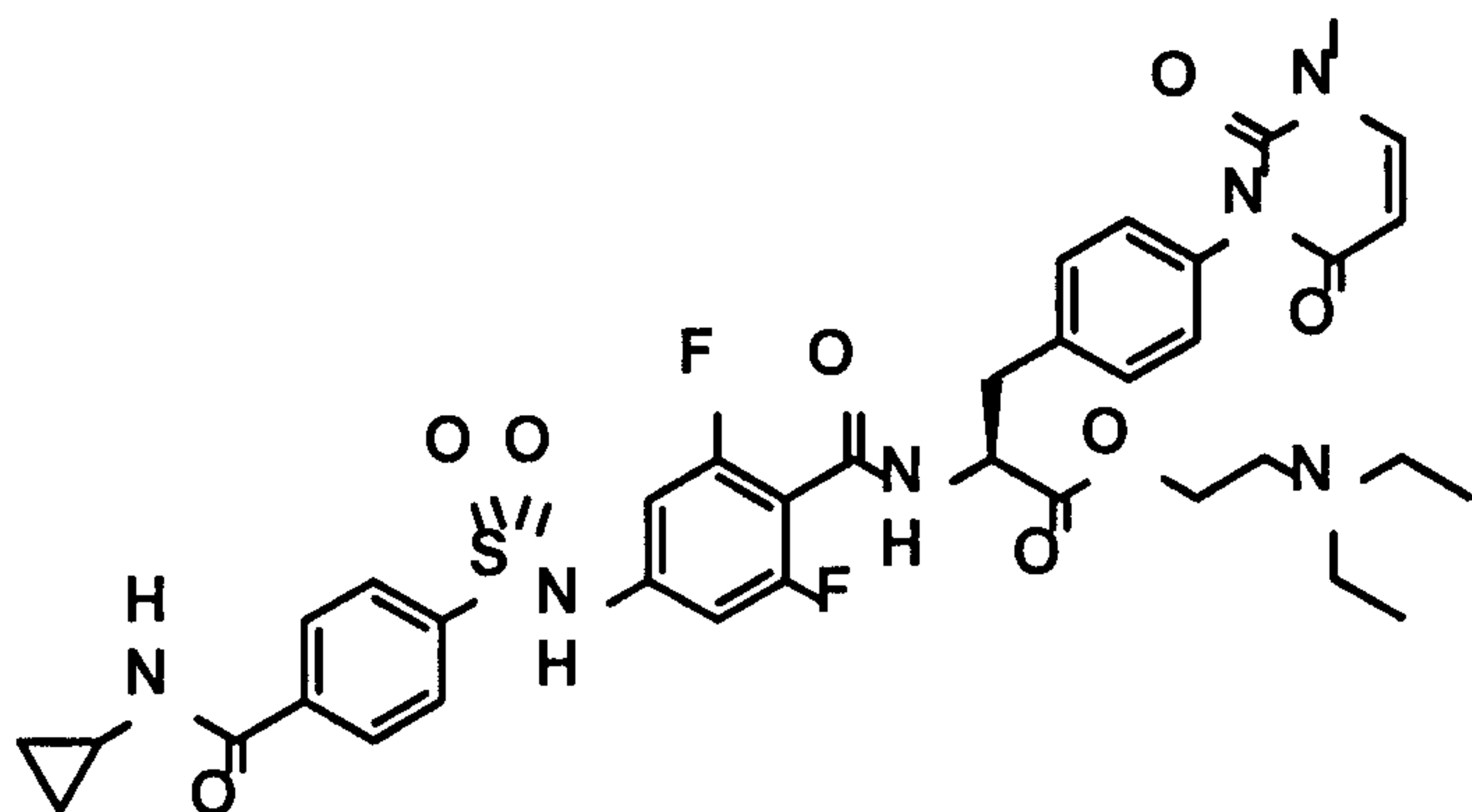
The title compound was obtained by subjecting
5 N-{4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino
]-2,6-difluorobenzoyl}-4-(3-methyl-2,6-dioxo-3,6-dihydropyr
imidin-1(2H)-yl)-L-phenylalanine (A-7) to the same method as
described above.

¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.16 (d, J = 7.6 Hz,
10 1H), 8.63 (d, J = 4.4 Hz, 1H), 7.94 (dd, J = 12.8, 8.8 Hz, 4H),
7.76 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.09 (d,
J = 8.4 Hz, 2H), 6.79 (dd, J = 9.2, 2.0 Hz, 2H), 5.75 (d, J =
7.6 Hz, 1H), 4.65-4.60 (m, 1H), 4.06 (t, J = 5.2 Hz, 2H), 3.54
(t, J = 6.0 Hz, 2H), 3.31 (s, 3H), 3.17-2.98 (m, 2H), 2.85-2.80
15 (m, 1H), 0.71-0.67 (m, 2H), 0.57-0.53 (m, 2H).; MS (ESI) m/z
712 (M+H)⁺

Example 93: Synthesis of C-15

2-(Diethylamino)ethyl

N-{4-[(4-[(Cyclopropylamino)carbonyl]phenyl)sulfonyl]amino
20] -2,6-difluorobenzoyl}-4-(3-methyl-2,6-dioxo-3,6-dihydropyr
imidin-1(2H)-yl)-L-phenylalaninate (C-15)



·TFA

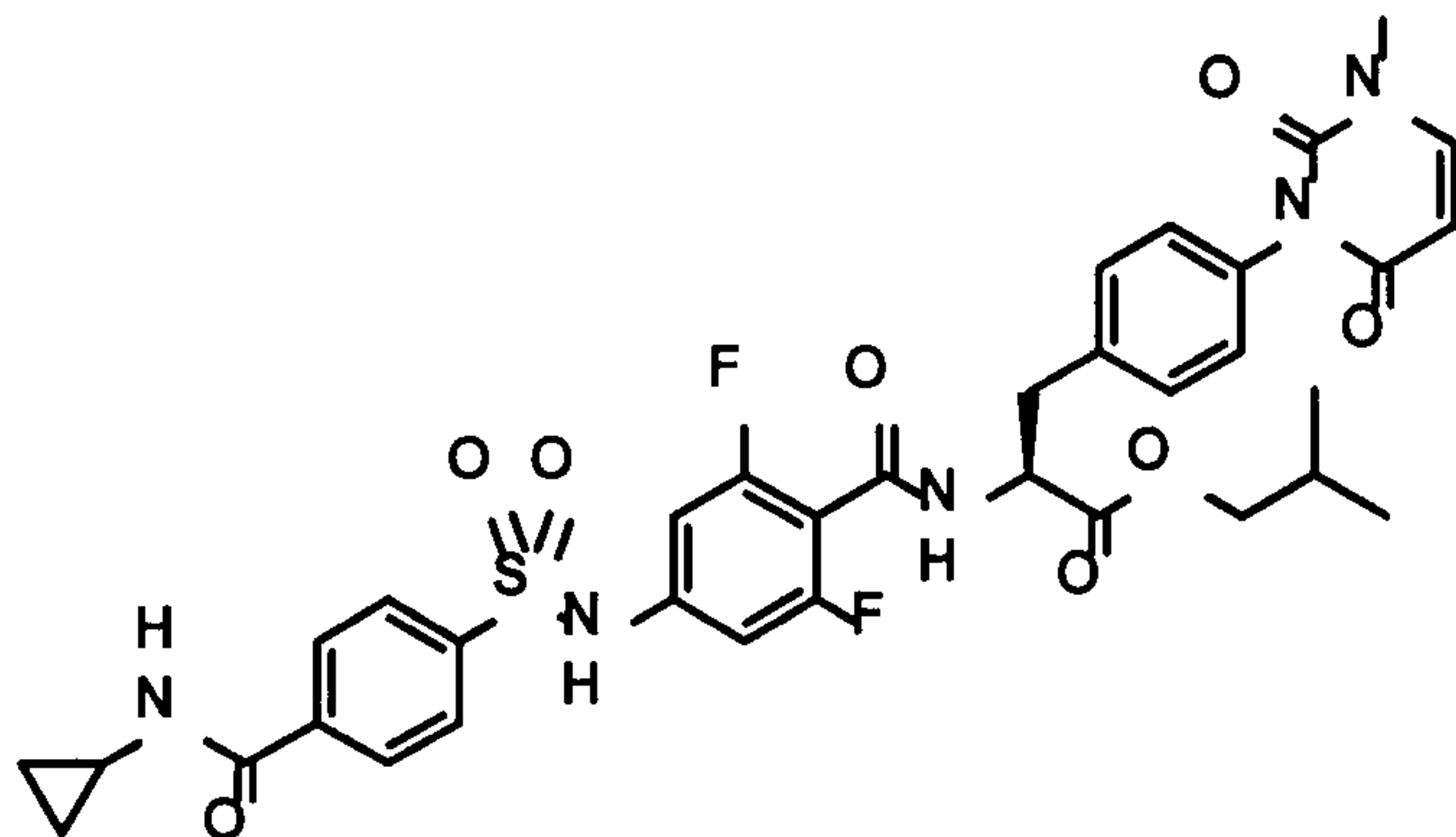
The title compound was obtained by subjecting N-{4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino}-2,6-difluorobenzoyl-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-7) to the same method as described above.

¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.26 (d, J = 6.8 Hz, 1H), 8.64 (d, J = 4.4 Hz, 1H), 7.94 (dd, J = 14.4, 8.8 Hz, 4H), 7.77 (d, J = 7.6 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.13 (d, J = 8.4 Hz, 2H), 6.81 (dd, J = 9.2, 1.6 Hz, 2H), 5.76 (d, J = 8.0 Hz, 1H), 4.69-4.63 (m, 1H), 4.39-4.33 (m, 1H), 4.29-4.23 (m, 1H), 3.35-3.27 (m, 5H), 3.14-3.07 (m, 6H), 2.87-2.80 (m, 1H), 1.18-1.14 (m, 6H), 0.71-0.68 (m, 2H), 0.57-0.54 (m, 2H).; MS (ESI) m/z 767 (M+H)⁺

Example 94: Synthesis of C-16

Isobutyl

N-{4-[(4-[(Cyclopropylamino)carbonyl]phenyl)sulfonyl]amino}-2,6-difluorobenzoyl-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (C-16)



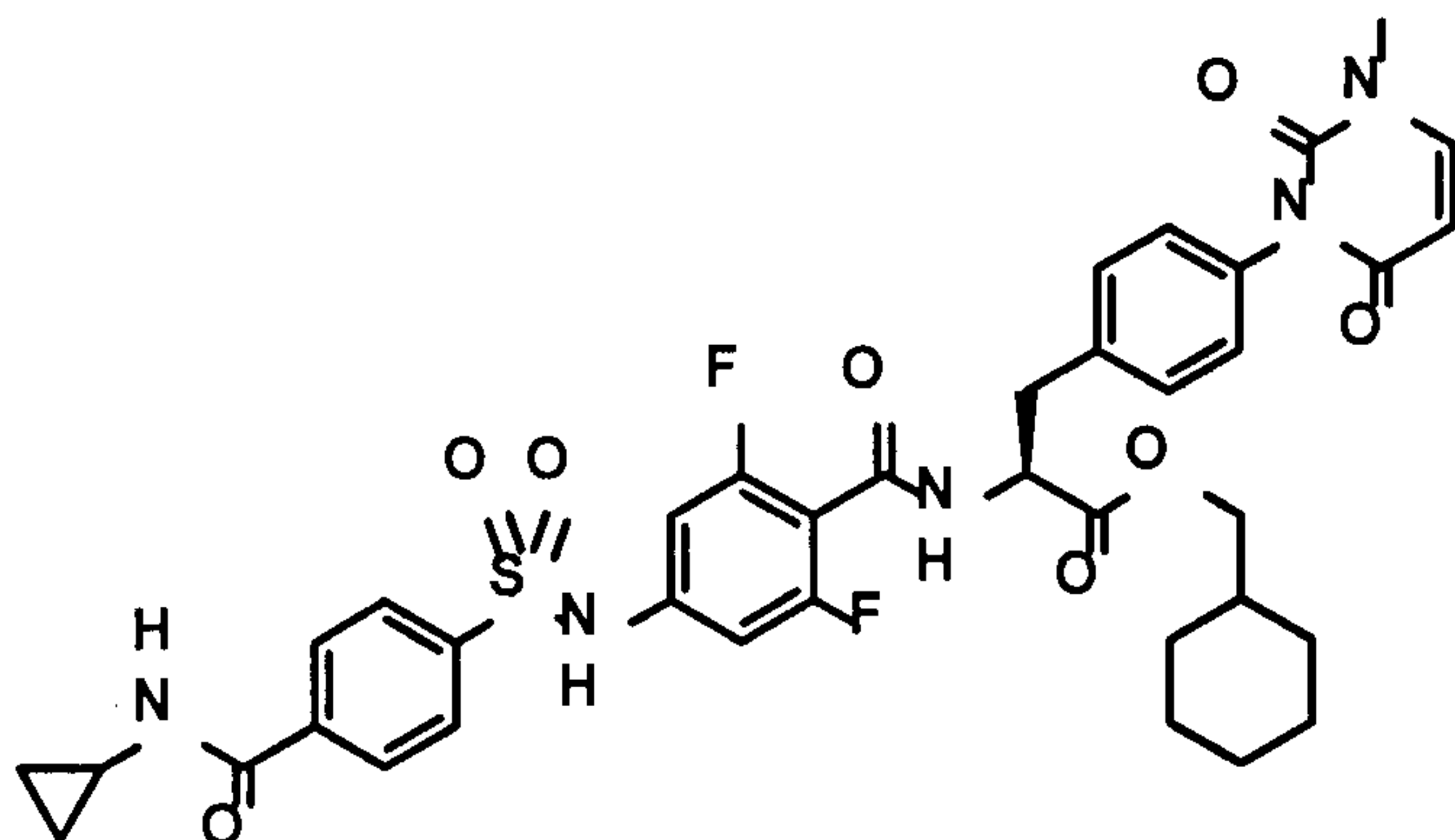
The title compound was obtained by subjecting N-{4-[(4-{4-[(cyclopropylamino)carbonyl]phenyl}sulfonyl)amino]-2,6-difluorobenzoyl}-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-7) to the same method as described above.

^1H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.17 (d, $J = 7.6$ Hz, 1H), 8.64 (d, $J = 4.0$ Hz, 1H), 7.94 (dd, $J = 12.0, 8.8$ Hz, 4H), 7.76 (d, $J = 8.0$ Hz, 1H), 7.31 (d, $J = 8.4$ Hz, 2H), 7.10 (d, $J = 8.4$ Hz, 2H), 6.79 (d, $J = 9.2$ Hz, 2H), 5.75 (d, $J = 7.6$ Hz, 1H), 4.65-4.59 (m, 1H), 3.84 (dd, $J = 6.8, 1.2$ Hz, 2H), 3.31 (s, 3H), 3.16-2.98 (m, 2H), 2.86-2.81 (m, 1H), 1.88-1.81 (m, 1H), 0.86 (d, $J = 6.4$ Hz, 6H), 0.72-0.67 (m, 2H), 0.57-0.53 (m, 2H).; MS (ESI) m/z 724 ($M+H$) $^+$

Example 95: Synthesis of C-17

Cyclohexylmethyl

N-{4-[(4-{4-[(Cyclopropylamino)carbonyl]phenyl}sulfonyl)amino]-2,6-difluorobenzoyl}-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (C-17)



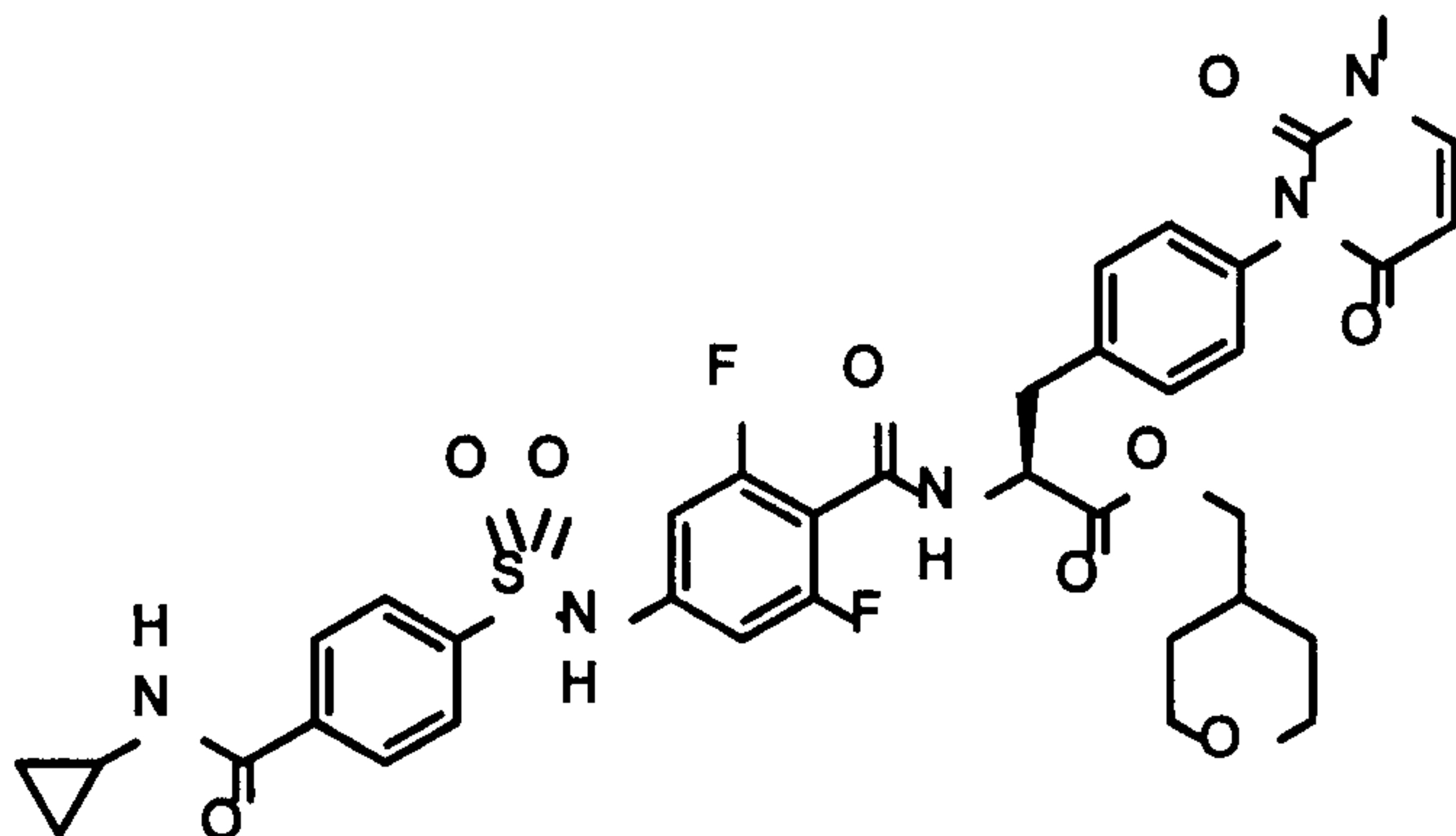
The title compound was obtained by subjecting N-{4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino}-2,6-difluorobenzoyl-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-7) to the same method as described above.

¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.15 (d, J = 7.6 Hz, 1H), 8.63 (d, J = 4.4 Hz, 1H), 7.94 (dd, J = 12.8, 8.8 Hz, 4H), 7.75 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 9.2 Hz, 2H), 5.74 (d, J = 8.0 Hz, 1H), 4.63-4.58 (m, 1H), 3.86 (d, J = 4.8 Hz, 2H), 3.31 (s, 3H), 3.15-2.97 (m, 2H), 2.85-2.81 (m, 1H), 1.66-1.57 (m, 6H), 1.23-1.09 (m, 3H), 0.96-0.88 (m, 2H), 0.71-0.69 (m, 2H), 0.57-0.53 (m, 2H).; MS (ESI) m/z 764 (M+H)⁺

Example 96: Synthesis of C-18

Tetrahydro-2H-pyran-4-yl-methyl

N-{4-[(4-[(Cyclopropylamino)carbonyl]phenyl)sulfonyl]amino}-2,6-difluorobenzoyl-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (C-18)

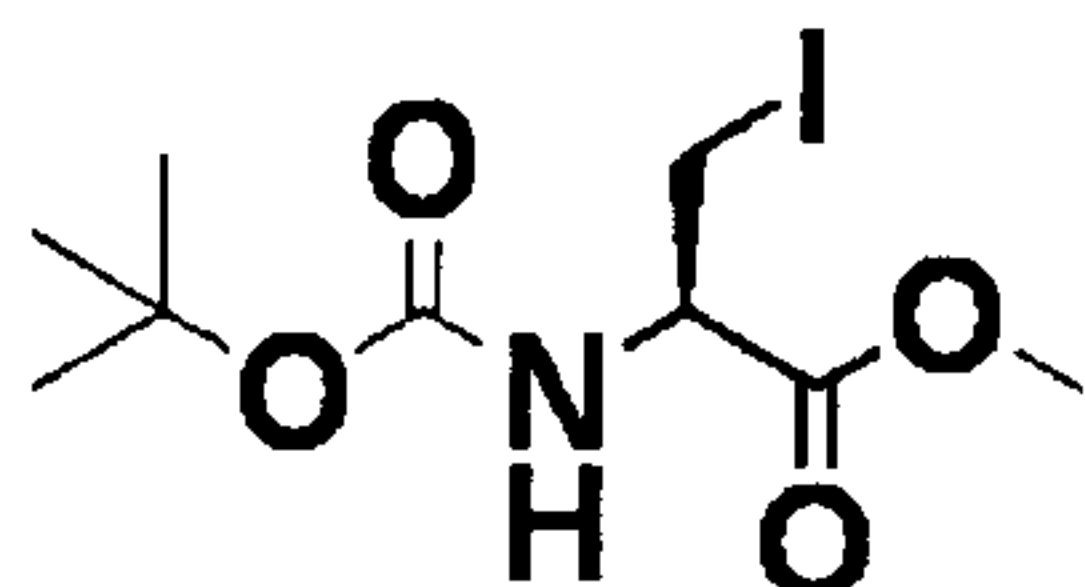


The title compound was obtained by subjecting N-{4-[(4-[(cyclopropylamino)carbonyl]phenyl)sulfonyl]amino}-2,6-difluorobenzoyl-4-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalanine (A-7) to the same method as described above.

¹H NMR (d-DMSO, 400 MHz): δ 11.2 (s, 1H), 9.18 (d, J = 7.6 Hz, 1H), 8.64 (d, J = 4.4 Hz, 1H), 7.94 (dd, J = 12.8, 9.2 Hz, 4H), 7.76 (d, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 5.75 (d, J = 8.0 Hz, 1H), 4.64-4.58 (m, 1H), 3.90 (d, J = 6.4 Hz, 2H), 3.82-3.81 (m, 2H), 3.31 (s, 3H), 3.28-3.23 (m, 2H), 3.14-2.99 (m, 2H), 2.87-2.80 (m, 1H), 1.84-1.76 (m, 1H), 1.53-1.50 (m, 2H), 1.24-1.14 (m, 2H), 0.72-0.69 (m, 2H), 0.57-0.54 (m, 2H).; MS (ESI) m/z 766 (M+H)⁺

Example 97: Synthesis of M-39

(Step 1) Methyl N-(tert-Butoxycarbonyl)-3-iodo-L-alaninate

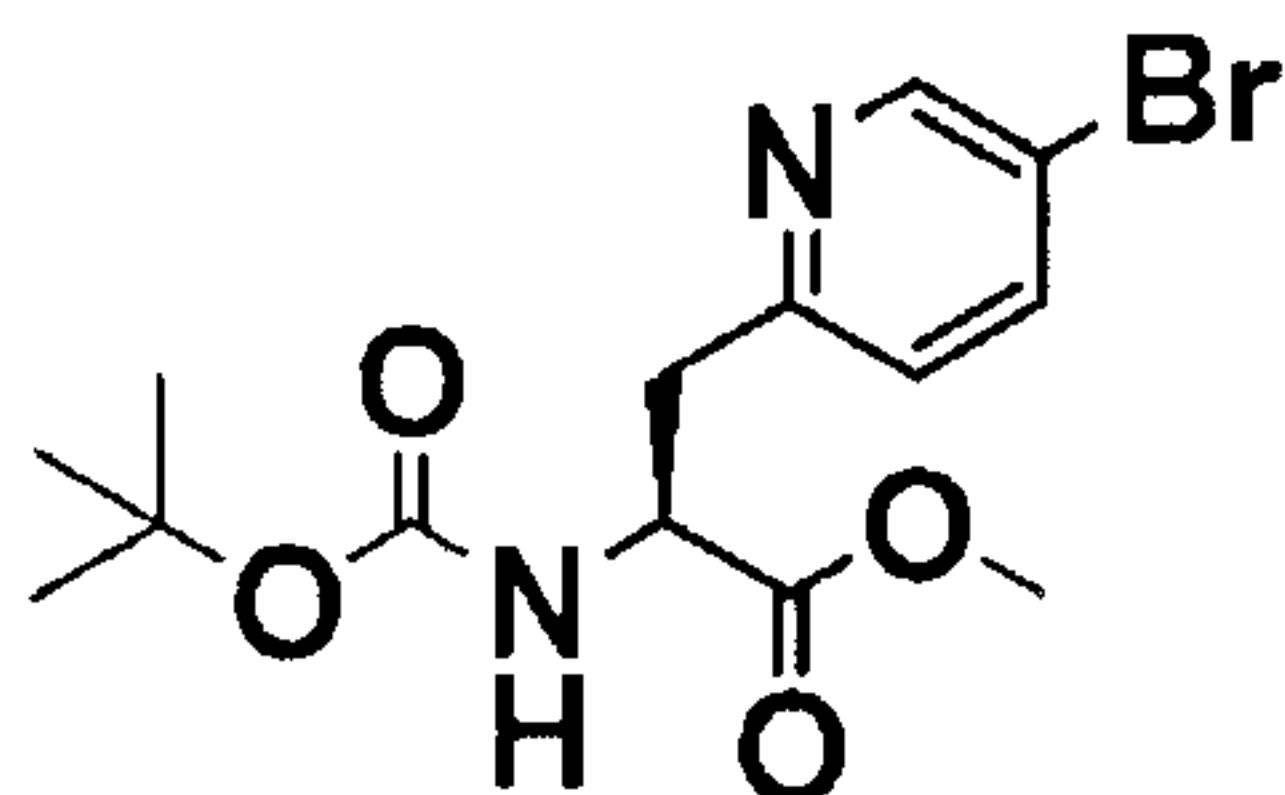


Triphenylphosphine (66.0 g, 0.250 mol) and imidazole (17.1 g, 0.250 mol) were dissolved in methylene chloride (900

ml). After cooling to 0°C, iodine (64.0 g, 0.250 mol) was added thereto, and the temperature was gradually raised from 0°C to room temperature in the presence of nitrogen gas, followed by stirring for 10 minutes. After cooling to 0°C, a methylene chloride solution (100 ml) of methyl N-(tert-butoxycarbonyl)-L-serinate (45.0 g, 0.200 mol) was slowly added dropwise over one hour, followed by stirring at room temperature for 2 hours. After the reaction solution was filtered, the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1 to 1:2) to obtain the title compound (43.8 g, 65%).

¹H NMR (CDCl₃, 400 MHz): δ 5.36-5.34 (m, 1H), 4.53-4.51 (m, 1H), 3.80 (s, 3H), 3.61-3.53 (m, 2H), 1.46 (s, 9H).

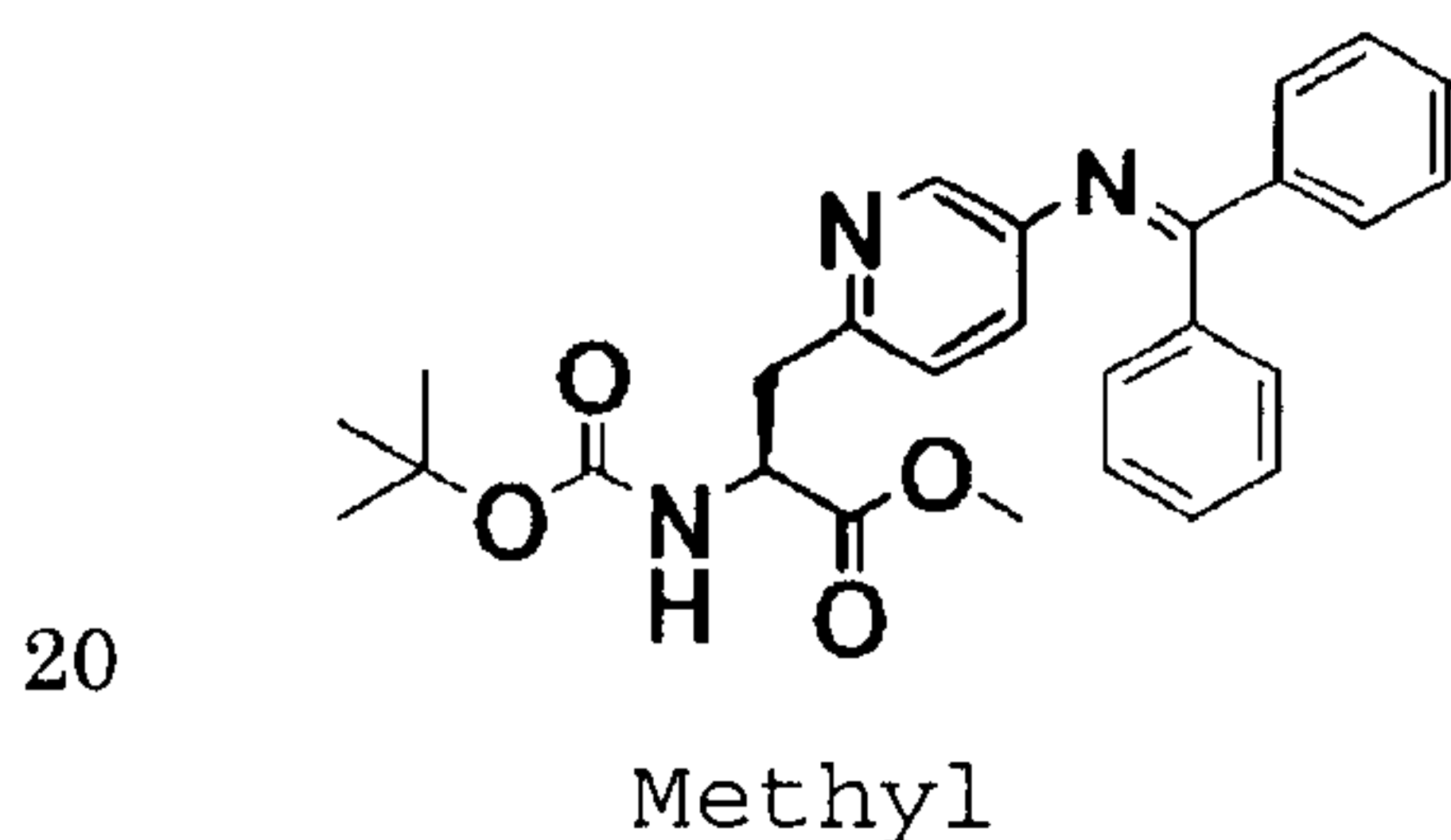
(Step 2) Methyl 3-(5-Bromopyridin-2-yl)-N-(tert-butoxycarbonyl)-L-alaninate



An operation in which zinc (24.0 g, 0.360 mol) was heated at 200°C for 30 minutes and cooled to room temperature was repeated three times, and then an N,N'-dimethylformamide solution (50 ml) of dibromoethane (3.40 g, 18.2 mmol) was added thereto. An operation in which the obtained reaction mixture was heated to 90°C and then cooled to room temperature was repeated twice, and then chlorotrimethylsilane (0.400 g, 3.64 mmol) was added to the reaction mixture, followed by stirring at room temperature for 30 minutes. An N,N'-dimethylformamide solution (70 ml) of methyl

N-(tert-butoxycarbonyl)-3-iodo-L-alaninate (20.0 g, 60.7 mmol) was added dropwise, followed by stirring at 35°C for 2.5 hours. Then, 2,5-dibromopyridine (19.0 g, 80.7 mmol) and bis(triphenylphosphine)palladium(II) chloride (2.30 g, 3.30 mmol) were further added to the reaction solution, followed by stirring at 70°C for 2 hours. After cooling to room temperature, the reaction solution was diluted with water, followed by extraction with ethyl acetate (200 ml×3). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1 to 1:2) to obtain the title compound (11.7 g, 54%).
¹H NMR (CDCl₃, 400 MHz): δ 8.61 (s, 1H), 7.98-7.96 (m, 1H), 7.29-7.25 (m, 2H), 4.45-4.39 (m, 1H), 3.60 (s, 3H), 3.12-2.97 (m, 2H), 1.32 (s, 9H).

(Step 3) Methyl N-(tert-Butoxycarbonyl)-3-{5-[(diphenylmethylene)amino]pyridin-2-yl}-L-alaninate



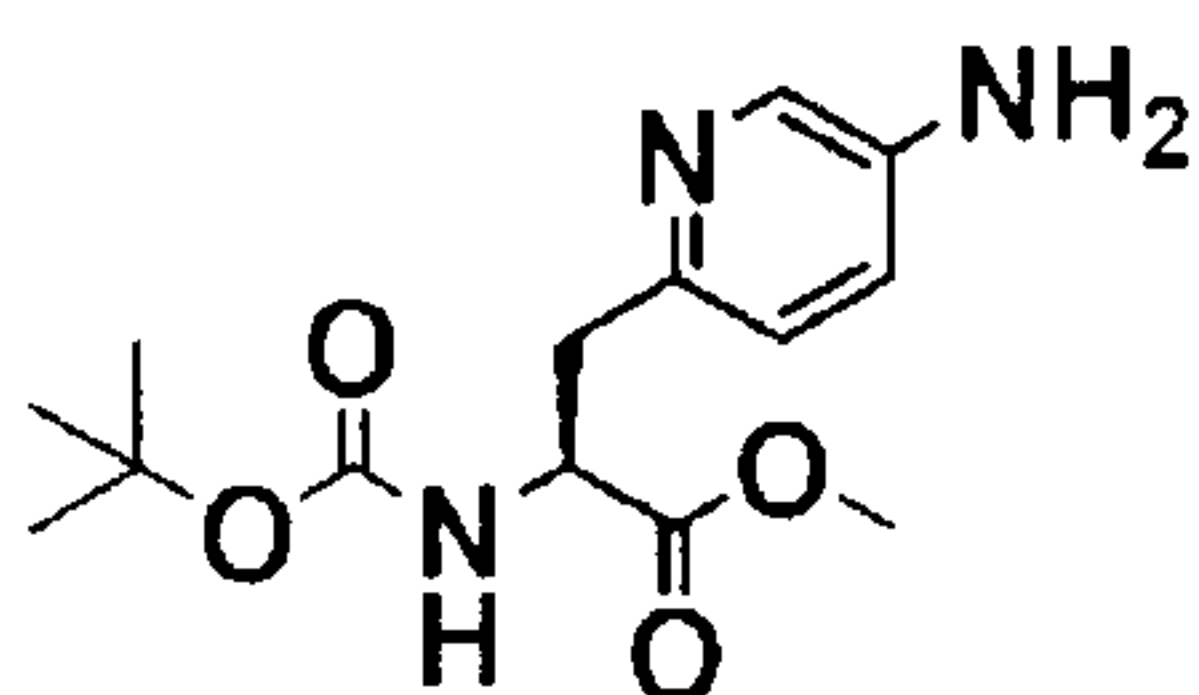
3-(5-bromopyridin-2-yl)-N-(tert-butoxycarbonyl)-L-alaninate (15.0 g, 40.0 mmol) and BINAP (1.58 g, 2.40 mmol) were dissolved in toluene (150 ml). To the solution, palladium(II) acetate (537 mg, 2.40 mmol), cesium carbonate (27.0 g, 84.0 mmol), and benzophenone imine (11.0 g, 60.0 mmol) were added, followed by stirring at 110°C for 10 hours. After cooling to room

temperature, the liquid was filtered through Celite, followed by washing with ethyl acetate. The obtained filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1 to 1:2) to obtain the title compound (14.6 g, 76%).

¹H NMR (DMSO-d₆, 400 MHz): δ 7.87 (s, 1H), 7.67-7.35 (m, 2H), 7.56-7.45 (m, 3H), 7.34-7.33 (m, 3H), 7.19-7.15 (m, 3H), 7.06 (s, 1H), 4.34-4.32 (m, 1H), 3.51 (s, 3H), 2.95-2.90 (m, 2H), 1.33 (s, 9H).; MS (ESI) m/z 460 (M+H)⁺

(Step 4) Methyl

3-(5-Aminopyridin-2-yl)-N-(tert-butoxycarbonyl-L-alaninate



Methyl

N-(tert-butoxycarbonyl)-3-{5-[(diphenylmethylene)amino]pyridin-2-yl}-L-alaninate (14.6 g, 32.0 mmol) and palladium hydroxide carbon (5.0 g, 7.0 mmol) were suspended in methanol (100 ml), and ammonium formate (2.0 g, 32 mmol) was added thereto, followed by stirring at 60°C for 3 hours. After the reaction solution was filtered, the solvent was removed under reduced pressure. The obtained compound (14.6 g, 31.0 mmol) and palladium hydroxide carbon (5.0 g, 7.0 mmol) were suspended in methanol (100 ml), and ammonium formate (2.0 g, 32 mmol) was added thereto, followed by stirring at 60°C for 6 hours. After the reaction solution was filtered, the filtrate was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum

ether/ethyl acetate=1:1 to 1:2) to obtain the title compound (7.9 g, 84%).

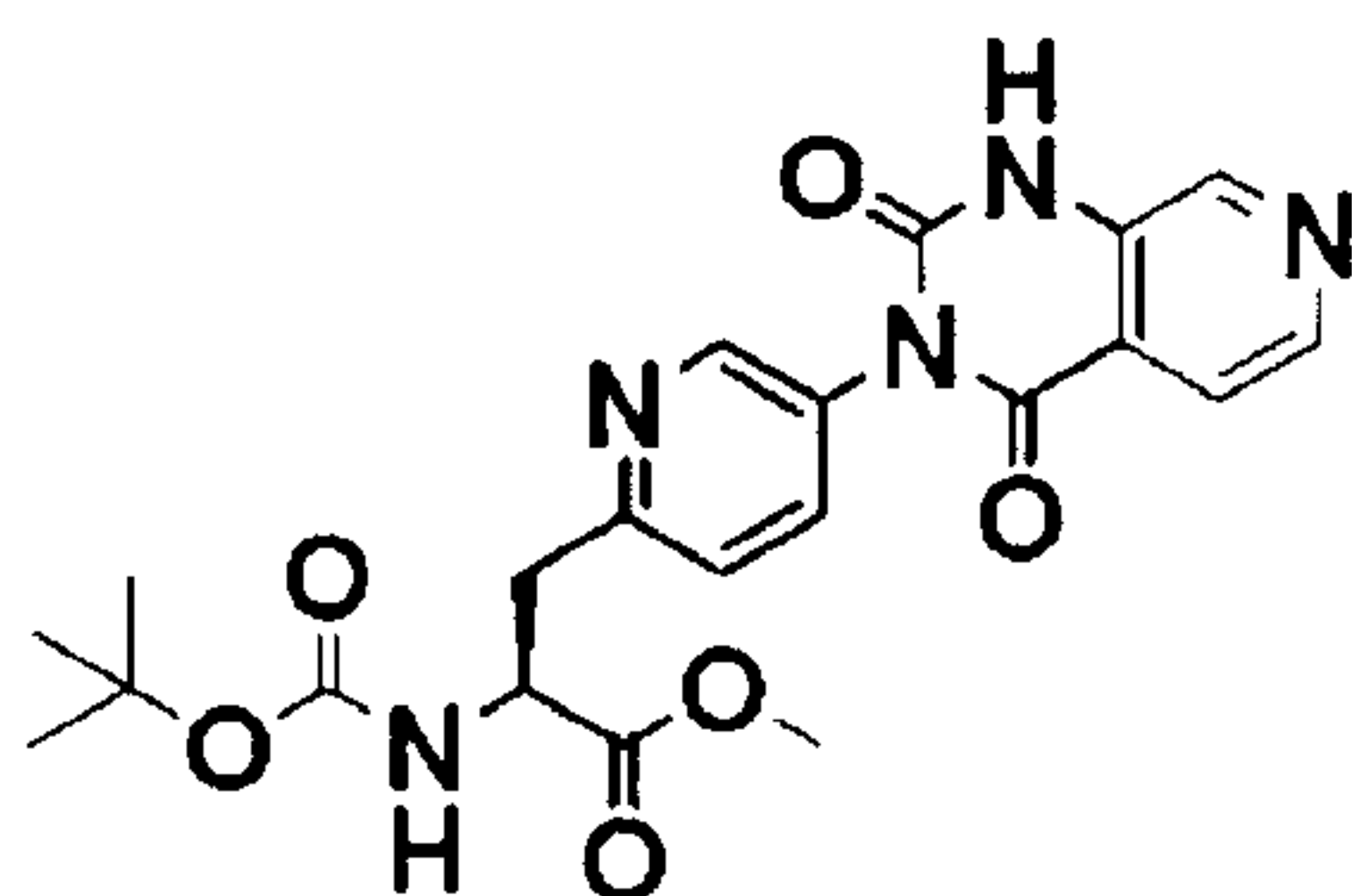
MS (ESI) m/z 296 (M+H)⁺

(Step

5)

Methyl

5 N-(tert-Butoxycarbonyl)-3-[5-(2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)pyridin-2-yl]-L-alaninate



Methyl 3-aminoisonicotinate (4.80 g, 32.0 mmol) and diisopropylethylamine (8.20 g, 64.0 mmol) were dissolved in methylene chloride (100 ml), and a methylene chloride solution (20 ml) of triphosgene (3.10 g, 10.6 mmol) was added thereto, followed by stirring at 0°C for 3 hours. To this solution, methyl

3-(5-aminopyridin-2-yl)-N-(tert-butoxycarbonyl)-L-alaninate (7.90 g, 26.7 mmol) was added, followed by stirring at room temperature for further 12 hours. The reaction solution was concentrated under reduced pressure, and then ethyl acetate was added thereto. The mixture was washed with a saturated aqueous sodium hydrogen carbonate solution, water, and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1 to 1:2) to obtain the title compound (7.6 g).

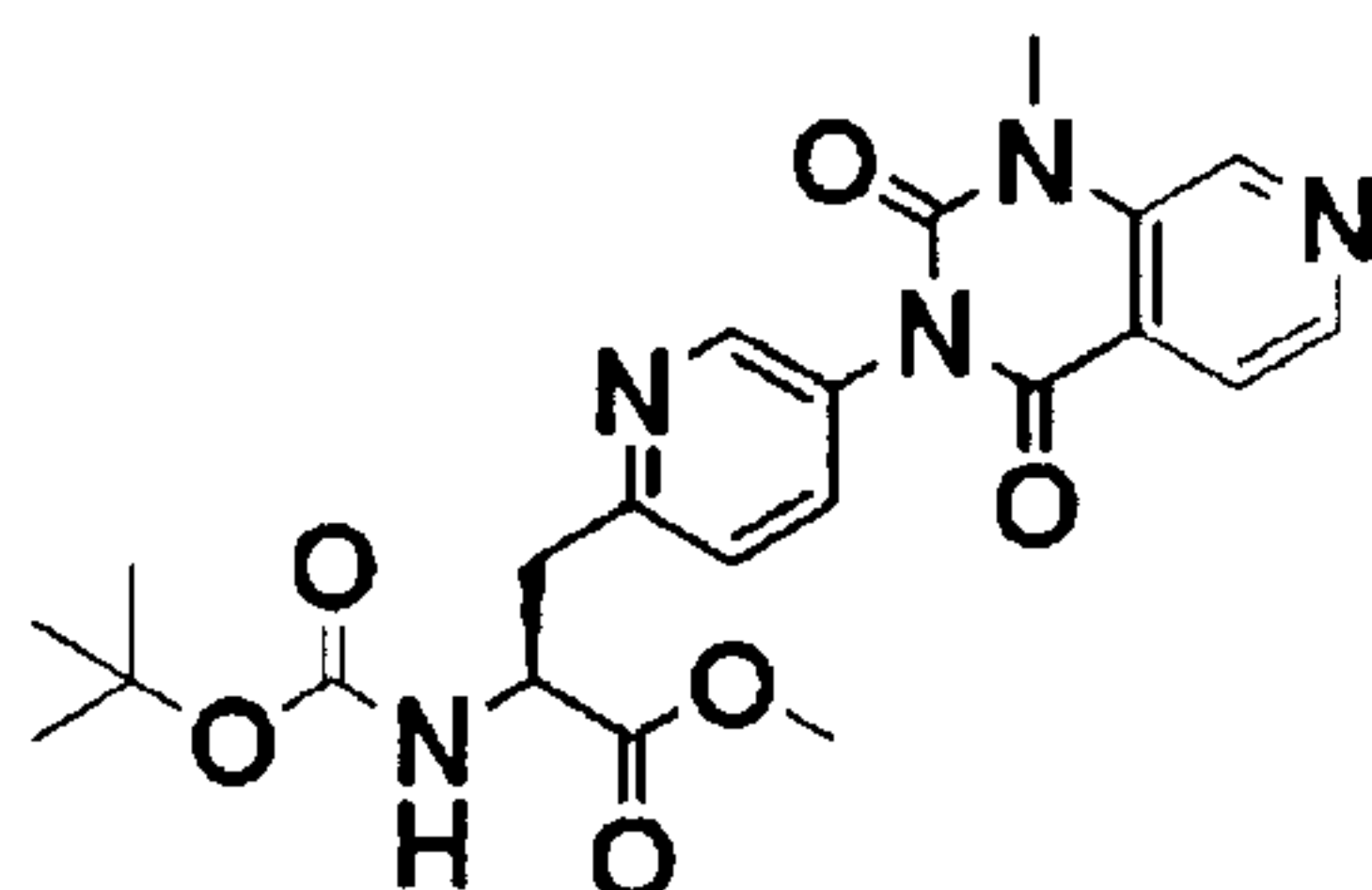
25 MS (ESI) m/z 442 (M+H)⁺

(Step

6)

Methyl

N-(tert-Butoxycarbonyl)-3-[5-(1-methyl-2,4-dioxo-1,4-dihydr
opyrido[3,4-d]pyrimidin-3(2H)-yl)pyridin-2-yl]-L-alaninate



Methyl

5 N-(tert-butoxycarbonyl)-3-[5-(2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)pyridin-2-yl]-L-alaninate (7.6 g) was dissolved in N,N'-dimethylformamide (60 ml), and an aqueous solution (4.0 ml) of potassium carbonate (0.60 g, 4.3 mmol) was added thereto, followed by stirring at room temperature for 3
10 hours. To this reaction solution, p-toluenesulfonic acid methyl ester (4.4 g, 24 mmol) and potassium carbonate (2.00 g, 14.4 mmol) were added, followed by stirring at room temperature for 12 hours. The reaction solution was diluted with water (100 ml), followed by extraction with ethyl acetate (100 ml×3). The
15 extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1) to obtain the title
20 compound (6.0 g, 84%).

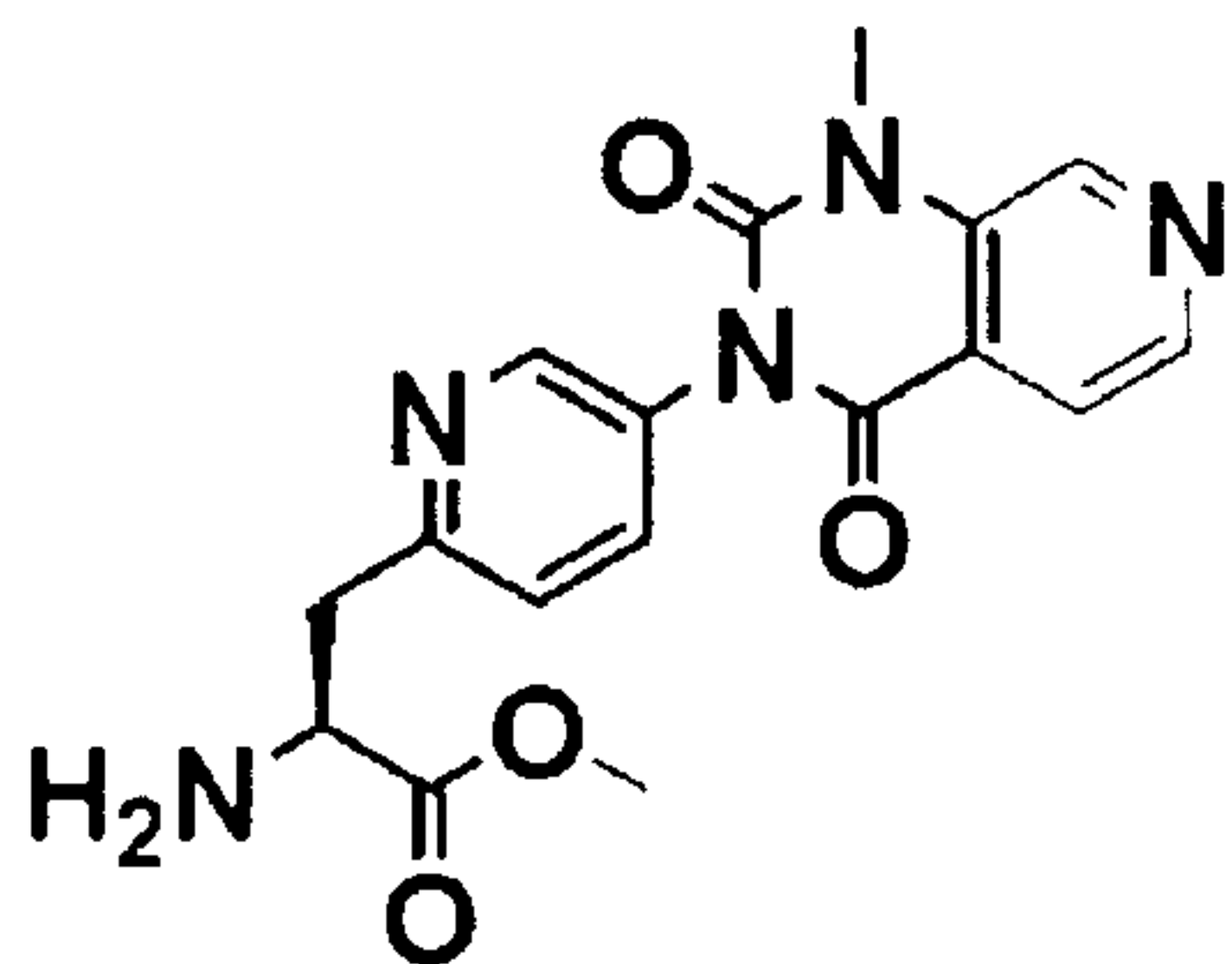
¹H NMR (DMSO-d₆, 400 MHz): δ 8.99 (s, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.45 (d, J = 2.0 Hz, 1H), 7.92 (d, J = 4.8 Hz, 1H), 7.73-7.71 (m, 1H), 7.42 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 4.55-4.49 (m, 1H), 3.19-3.15 (m, 2H), 3.71 (s, 3H), 3.52 (s,
25 3H), 1.35 (s, 9H).; MS (ESI) m/z 456 (M+H)⁺

(Step

7)

Methyl

3-[5-(1-Methyl-2,4-dioxo-1,4-d-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)pyridin-2-yl]-L-alaninate (M-39)



To

methyl

5 N-(tert-butoxycarbonyl)-3-[5-(1-methyl-2,4-dioxo-1,4-dihydr
opyrido[3,4-d]pyrimidin-3(2H)-yl)pyridin-2-yl]-L-alaninate
(6.00 g, 13.2 mmol), 4 N hydrogen chloride/ethyl acetate (50
ml) was added, followed by stirring at room temperature for 1
hour. The obtained white solid was filtered and dried under
10 reduced pressure to obtain the title compound (M-39) (4.8 g,
93%).

¹H NMR (CD₃OD, 400 MHz): δ 9.25 (s, 1H), 8.71 (d, J = 5.6 Hz,
1H), 8.66 (s, 1H), 8.54 (d, J = 5.6 Hz, 1H), 8.08 (d, J = 2.8
Hz, 1H), 7.78-7.58 (m, 1H), 4.65-4.62 (m, 1H), 3.78 (s, 3H),
15 3.71 (s, 3H), 3.62-3.61 (m 2H).; MS (ESI) m/z 356 (M+H)⁺

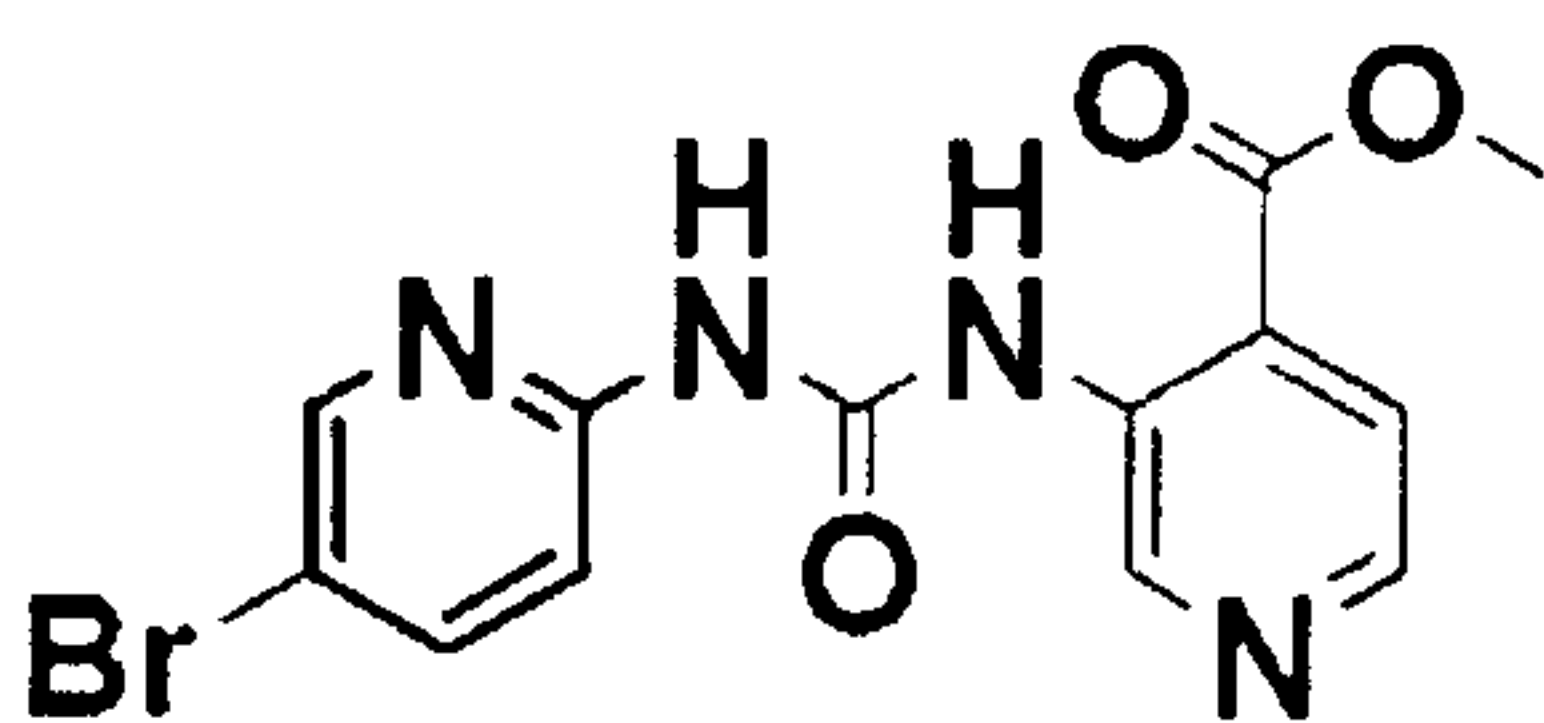
Example 98: Synthesis of M-40

(Step

1)

Methyl

3-({[(5-Bromopyridin-2-yl)amino]carbonyl}amino)isonicotinat
e



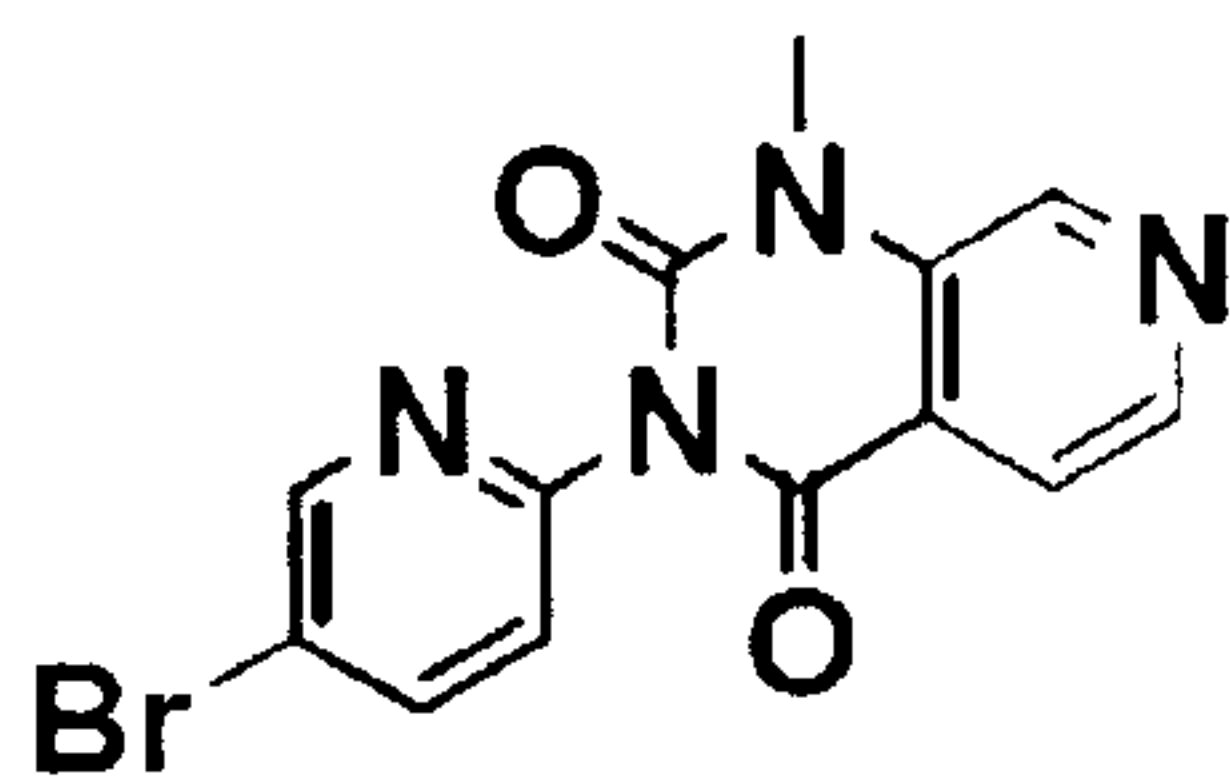
20

Methyl 3-aminoisonicotinate (4.80 g, 32.0 mmol) and
diisopropylethylamine (8.20 g, 64.0 mmol) were dissolved in
methylene chloride (100 ml), and a methylene chloride solution

(20 ml) of triphosgene (3.10 g, 10.4 mmol) was added thereto, followed by stirring at 0°C for 3 hours. To this solution, 5-bromopyridine-2-amine (4.60 g, 26.6 mmol) was added, followed by stirring at room temperature for further 12 hours. After the reaction solution was concentrated under reduced pressure, ethyl acetate was added. The mixture was washed with a saturated aqueous sodium hydrogen carbonate solution, water, and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1 to 1:2) to obtain the title compound (6.2 g, 67%).

¹H NMR (400 MHz, DMSO-d₆): δ 11.0 (s, 1H), 10.3 (s, 1H), 9.4 (s, 1H), 8.39 (d, J = 5.2 Hz, 2H), 8.0 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 4.8 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 3.92 (s, 3H). (Step 2)

3-(5-Bromopyridin-2-yl)-1-methylpyrido[3,4-d]pyrimidine-2,4
(1H,3H)-dione



20 Methyl

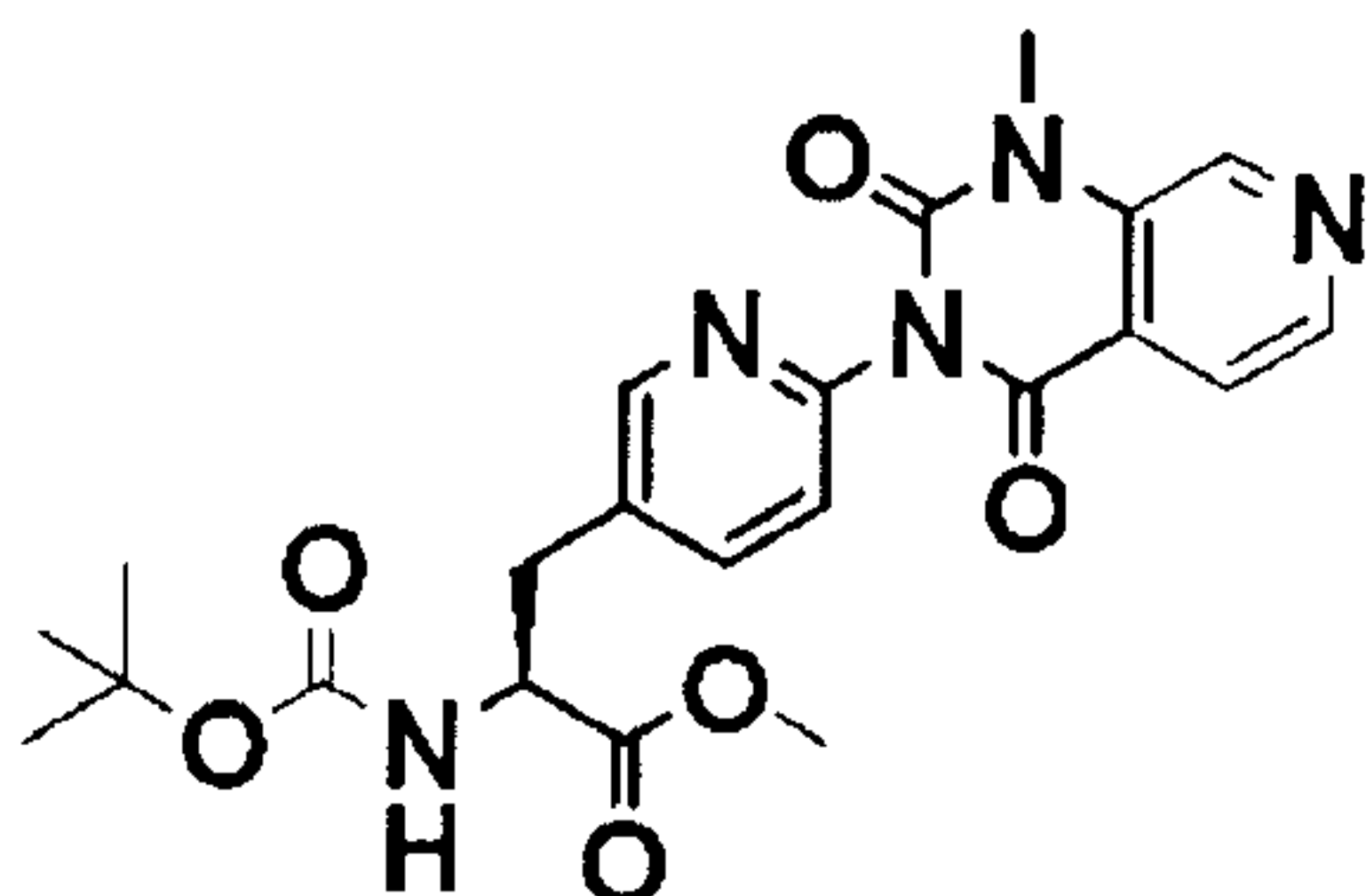
3-({[(5-bromopyridin-2-yl)amino]carbonyl}amino)isonicotinate (6.20 g, 17.7 mmol) was dissolved in N,N'-dimethylformamide (60 ml), and an aqueous solution (4.0 ml) of potassium carbonate (600 mg, 4.34 mmol) was added thereto, followed by stirring at room temperature for 3 hours. To this reaction solution, p-toluenesulfonic acid methyl ester (4.40 g, 23.6 mmol) and potassium carbonate (3.00 g, 21.7 mmol) were added, followed

by stirring at room temperature for 12 hours. The reaction solution was diluted with water (100 ml), followed by extraction with ethyl acetate (100 ml×3). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and
 5 dried over anhydrous sodium sulfate. Then, the solvent was removed under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1) to obtain the title compound (5.2 g, 88%).

10 ^1H NMR (400 MHz, DMSO- d_6): δ 9.00 (s, 1H), 8.77 (d, J = 2.4 Hz, 1H), 8.58 (d, J = 4.8 Hz, 1H), 8.32-8.30 (m, 1H), 7.91 (d, J = 4.8 Hz, 1H), 7.52 (d, J = 8.8 Hz, 1H), 3.61 (s, 3H).

(Step 3) Methyl

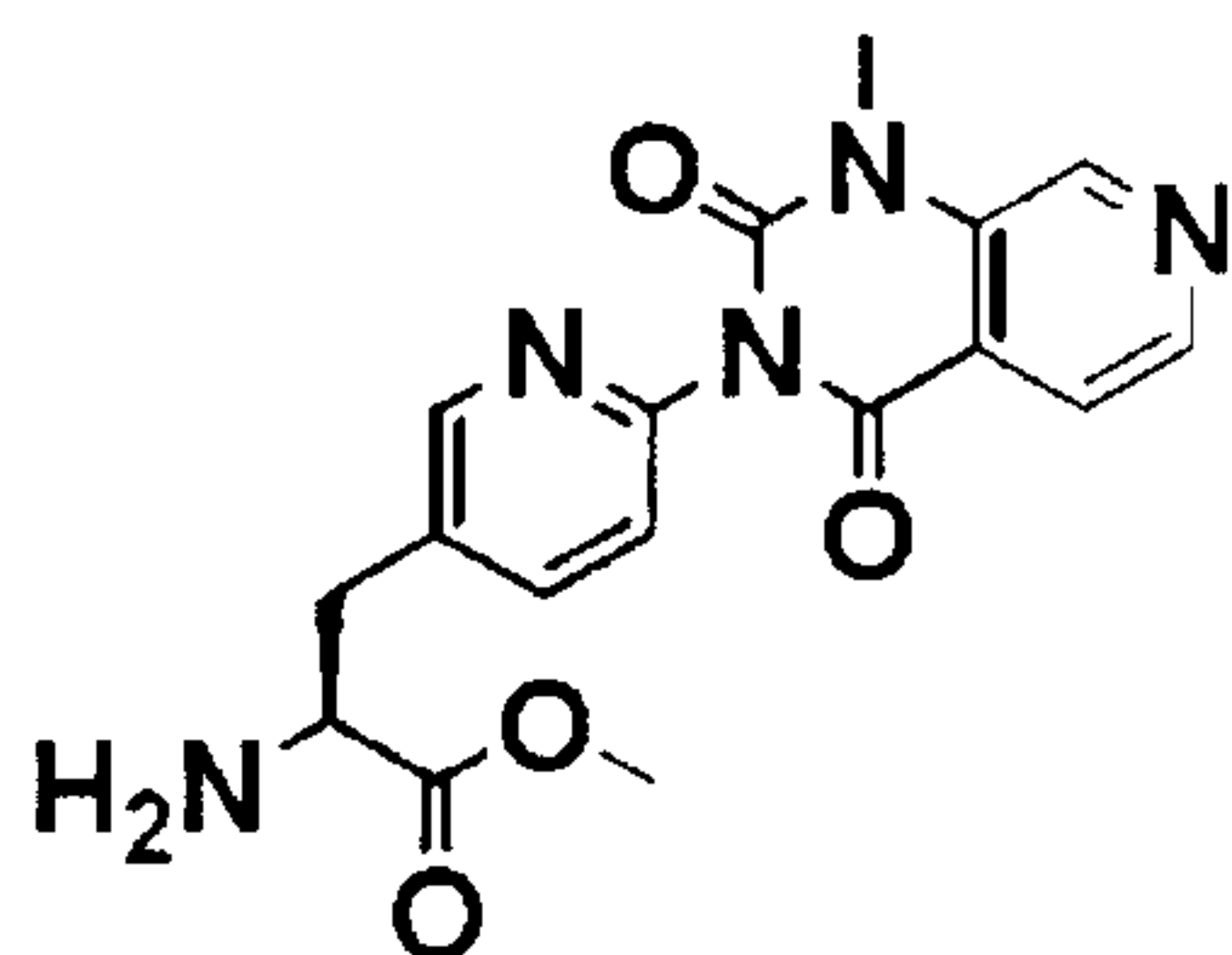
N-(tert-Butoxycarbonyl)-3-[6-(1-methyl-2,4-dioxo-1,4-dihydr
 15 opyrido[3,4-d]pyrimidin-3(2H)-yl)pyridin-3-yl]-L-alaninate



An operation in which zinc (2.40 g, 36.7 mmol) was heated at 200°C for 30 minutes and cooled to room temperature was repeated three times, and then an N,N'-dimethylformamide
 20 solution (5.0 ml) of dibromoethane (0.340 g, 1.82 mmol) was added thereto. An operation in which the obtained reaction mixture was heated to 90°C and then cooled to room temperature was repeated twice, and then chlorotrimethylsilane (40.0 mg, 0.364 mmol) was added to the reaction mixture, followed by
 25 stirring at room temperature for 30 minutes. An N,N'-dimethylformamide solution (5.0 ml) of methyl

N-(tert-butoxycarbonyl)-3-iodo-L-alaninate (2.00 g, 6.08 mmol) was added dropwise, followed by stirring at 35°C for 2.5 hours. Then, 3-(5-bromopyridin-2-yl)-1-methylpyrido[3,4-d]pyrimidine-2,4 (1H,3H)-dione (2.60 g, 7.80 mmol) and bis(triphenylphosphine)palladium(II) chloride (230 mg, 0.328 mmol) were further added to the reaction solution, followed by stirring at 70°C for 2 hours. After cooling to room temperature, the reaction solution was diluted with water, followed by extraction with ethyl acetate (20 ml×3). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1 to 1:2) to obtain the title compound (300 mg, 11%).
¹H NMR (400 MHz, CDCl₃): δ 8.83 (s, 1H), 8.62 (d, J = 3.6 Hz, 1H), 8.46 (s, 1H), 8.05 (d, J = 3.2 Hz, 1H), 7.75 (d, J = 4.4 Hz, 1H), 7.29-7.27 (m, 1H), 5.16-5.12 (m, 1H), 4.69-4.67 (m, 1H), 3.76 (s, 3H), 3.72 (s, 3H), 3.23-3.20 (m, 2H), 1.45 (s, 9H).

(Step 4) Methyl 3-[6-(1-Methyl-2,4-dioxo-1,4-dihydropyrido[3,4-d]pyrimidin-3(2H)-yl)pyridin-3-yl]-L-alaninate (M-40)



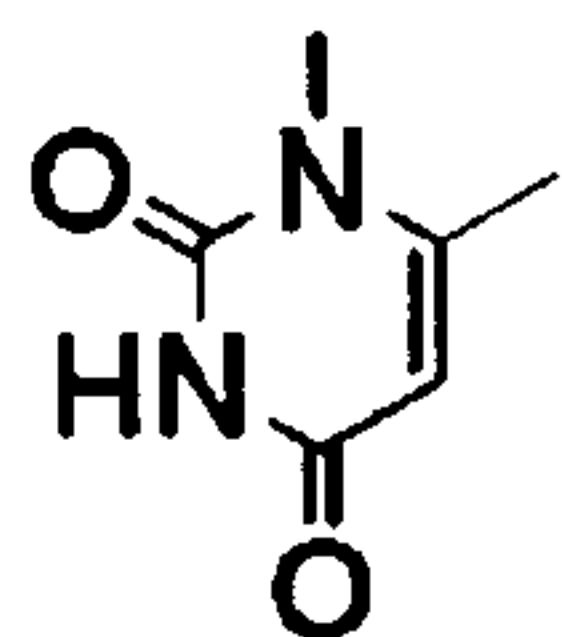
To methyl N-(tert-butoxycarbonyl)-3-[6-(1-methyl-2,4-dioxo-1,4-dihydr

opyrido[3,4-d]pyrimidin-3(2H)-yl)pyridin-3-yl]-L-alaninate
(300 mg, 0.659 mmol), 4 N hydrogen chloride/ethyl acetate (5.0
ml) was added, followed by stirring at room temperature for 1
hour. The obtained white solid was filtered and dried under
5 reduced pressure to obtain a hydrochloride of the title compound
(M-40) (253 mg, 98%).

¹H NMR (400 MHz, CD₃OD): δ 9.29 (s, 1H), 8.77 (d, J = 6.0 Hz,
1H), 8.62 (d, J = 2.0 Hz, 1H), 8.57 (d, J = 5.6 Hz, 1H), 8.09
(dd, J = 8.0, 2.0 Hz, 1H), 7.64 (dd, J = 15.6, 8.0 Hz, 1H),
10 4.55-4.51 (m, 1H), 3.88 (s, 3H), 3.76 (s, 3H), 3.52-3.48 (m,
1H), 3.46-3.41 (m, 1H).; MS (ESI) m/z 356 (M+H)⁺

Example 100: Synthesis of M-42

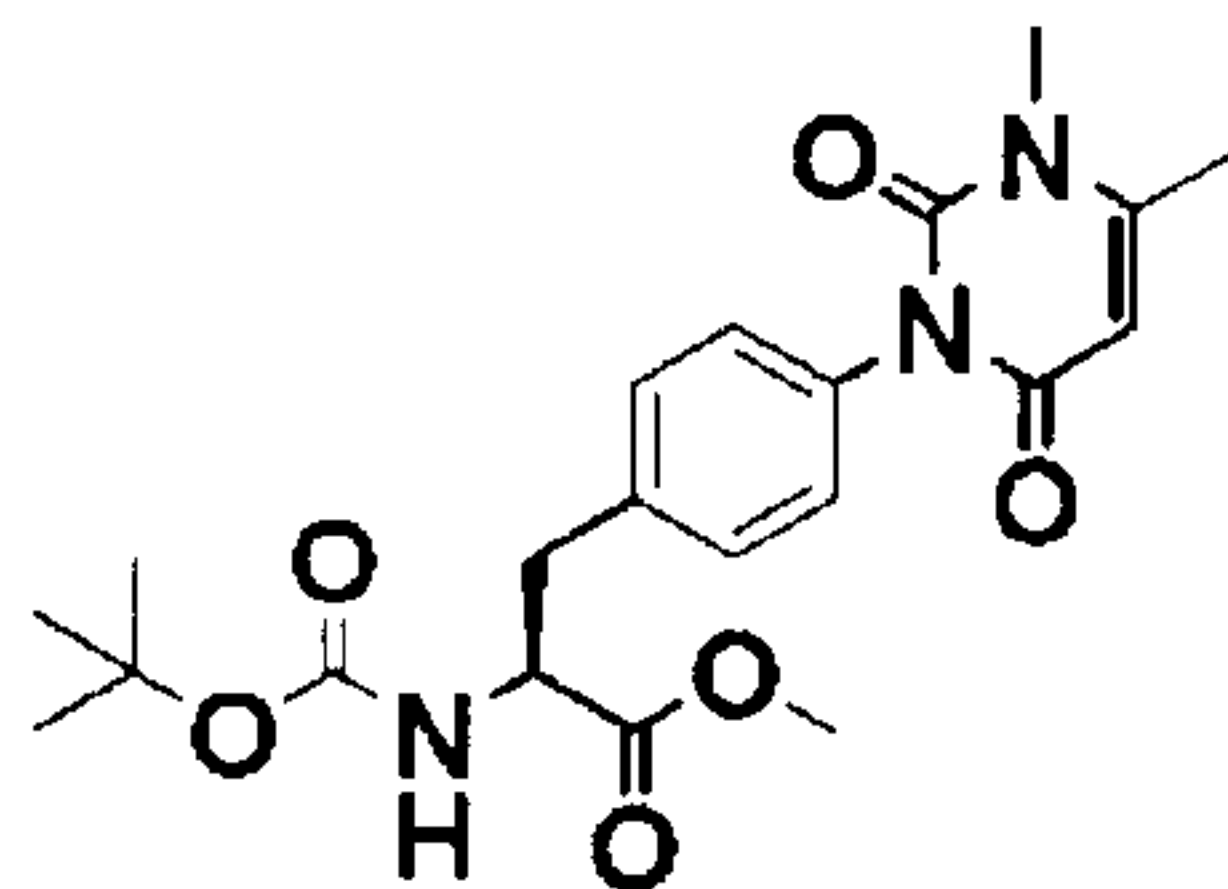
(Step 1) 1,6-Dimethylpyrimidine-2,4(1H,3H)-dione



15 4-Methyleneaxetan-2-one (8.0 g, 95 mmol) and
N-methylurea (5.0 g, 68 mmol) were dissolved in acetic acid (50
ml), followed by stirring at 120°C for 12 hours. The solvent
was removed under reduced pressure. To the obtained residue,
ethyl acetate (50 ml) was added, followed by stirring for 30
20 minutes. After the precipitated solid was filtered,
purification was conducted by reversed-phase HPLC (H₂O
containing 0.1% FTA/CH₃CN system) to obtain the title compound
(1.3 g, 14%).

¹H NMR (400 MHz, CD₃OD): δ 5.59 (s, 1H), 3.39 (s, 3H), 2.32 (s,
25 3H).

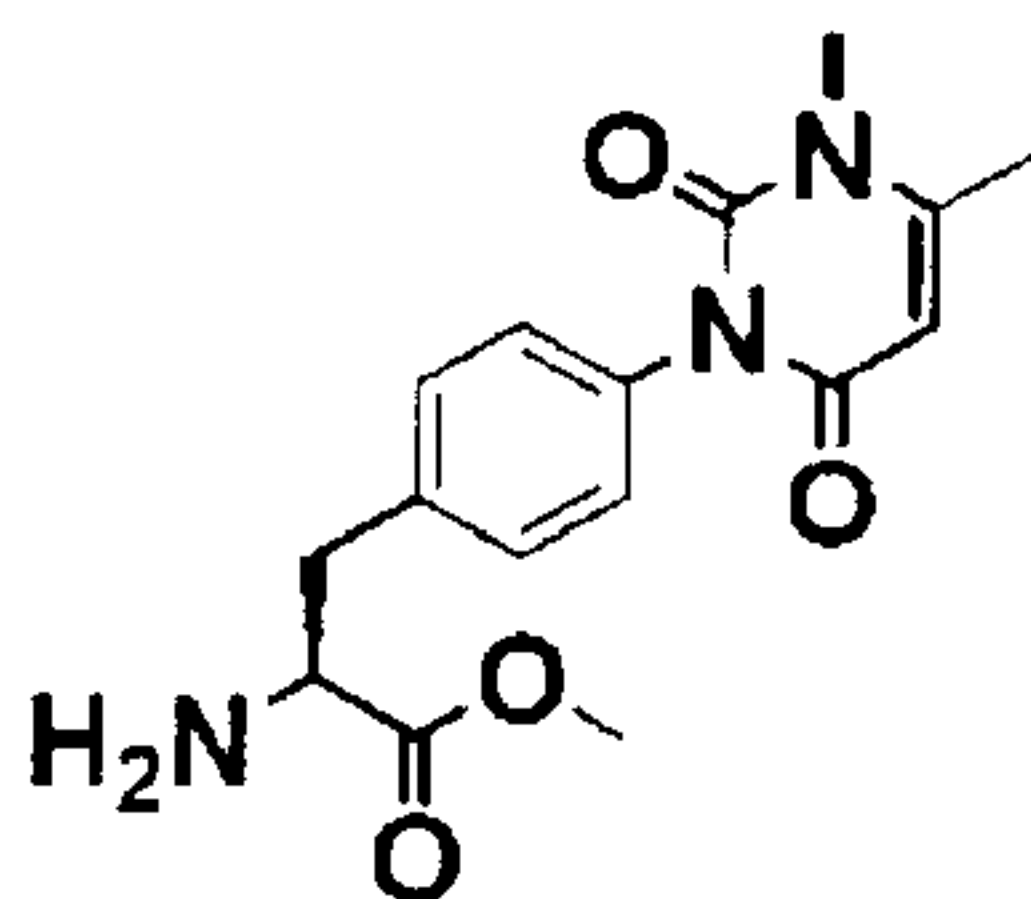
(Step 2) Methyl
N-(tert-Butoxycarbonyl)-4-(3,4-dimethyl-2,6-dioxo-3,6-dihyd
ropyrimidin-1(2H)-yl)-L-phenylalaninate



1,6-Dimethylpyrimidine-2,4(1H,3H)-dione (1.3 g, 9.3 mmol) and methyl N-(tert-butoxycarbonyl)-4-(dihydroxyboryl)-L-phenylalaninate (2.0 g, 6.2 mmol) were dissolved in methylene chloride (500 ml), and copper(II) acetate (3.0 g, 15 mmol) and triethylamine (6.0 ml) were added thereto, followed by stirring at room temperature for 2.5 days. The reaction liquid was concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1) to obtain the title compound (250 mg, 9.7%) as a white solid.

¹H NMR (400 MHz, CD₃OD): δ 7.35 (d, J = 8.0 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 5.78 (s, 1H), 4.45-4.41 (m, 1H), 3.74 (s, 3H), 3.45 (s, 3H), 3.20-3.02 (m, 2H), 2.39 (s, 3H), 1.41 (s, 9H).

(Step 3) Methyl 4-(3,4-Dimethyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (M-42)



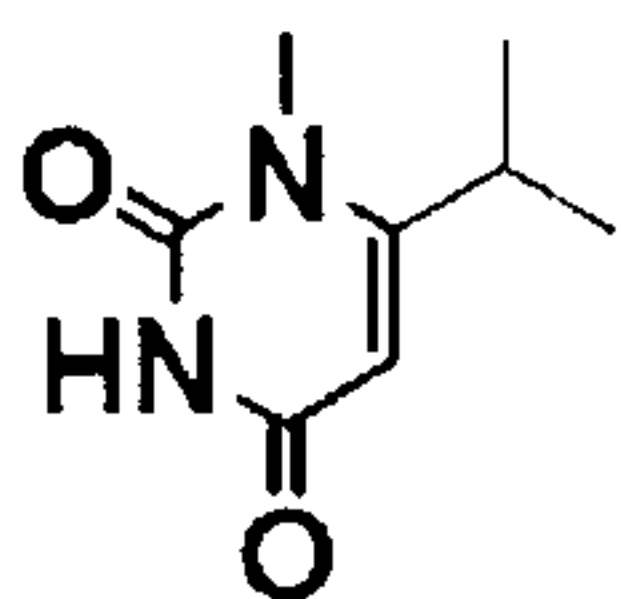
To methyl N-(tert-butoxycarbonyl)-4-(3,4-dimethyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (250 mg, 0.599 mmol),

3 N hydrogen chloride/ethyl acetate (5.0 ml) was added, followed by stirring at room temperature for 1 hour. The obtained white solid was filtered and dried under reduced pressure to obtain a hydrochloride of the title compound (M-42) (150 mg, 71%) as
 5 a white solid.

^1H NMR (400 MHz, CD_3OD): δ 7.36 (d, $J = 8.0$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 2H), 5.75 (s, 1H), 4.35 (dd, $J = 8.4, 5.6$ Hz, 1H), 3.84 (s, 3H), 3.40 (s, 3H), 3.42-3.37 (m, 1H), 3.15-3.09 (m, 1H), 2.34 (s, 3H).; MS (ESI) m/z 318 ($\text{M}+\text{H}$) $^+$

10 Example 101: Synthesis of M-43

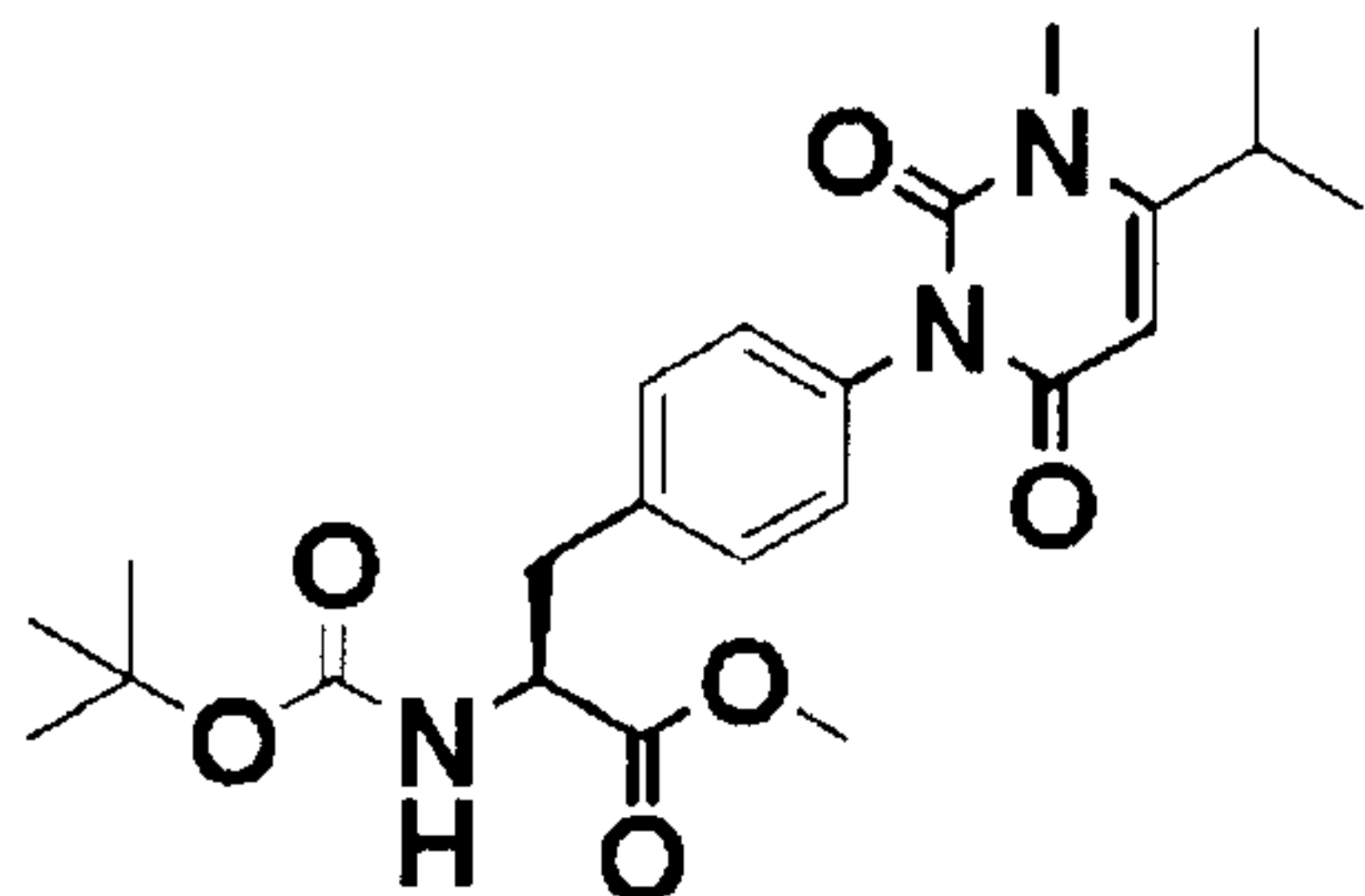
(Step 1) 6-Isopropyl-1-methylpyrimidine-2,4(1H,3H)-dione



Methyl 4-methyl-3-oxopentanoate (5.0 g, 35 mmol) and N-methylurea (1.9 g, 26 mmol) were dissolved in acetic acid (50
 15 ml), followed by stirring at 120°C for 12 hours. The solvent was removed under reduced pressure, and the obtained residue was purified by silica gel column chromatography (methylene chloride/ethyl acetate=2:1 to 1:2) to obtain the title compound (1.5 g, 34%).

20 ^1H NMR (400 MHz, CD_3OD): δ 9.96 (s, 1H), 3.34 (s, 3H), 2.66-2.60 (m, 1H), 1.26 (s, 3H), 1.25 (s, 3H).

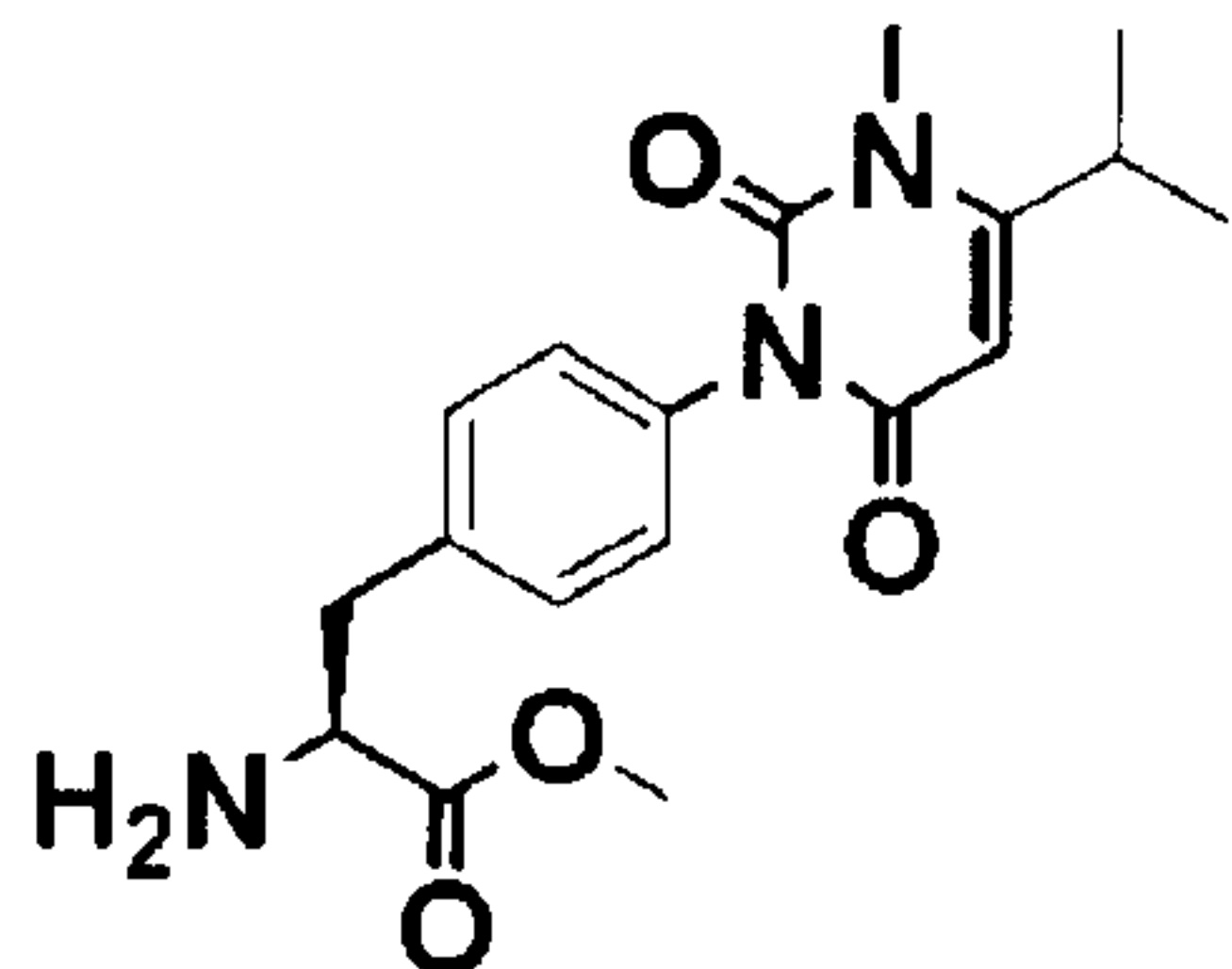
(Step 2) Methyl N-(tert-Butoxycarbonyl)-4-(4-isopropyl-3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate



6-Isopropyl-1-methylpyrimidine-2,4(1H,3H)-dione (1.5 g, 8.9 mmol) and methyl N-(tert-butoxycarbonyl)-4-(dihydroxyboryl)-L-phenylalaninate (1.5 g, 4.6 mmol) were dissolved in methylene chloride (50 ml), and copper(II) acetate (3.0 g, 15 mmol) and triethylamine (3.0 ml) were added thereto, followed by stirring at room temperature for 2.5 days. The reaction liquid was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1) to obtain the title compound (352 mg, 17%) as a white solid.

^1H NMR (400 MHz, CD_3OD): δ 7.37 (d, $J = 8.0$ Hz, 2H), 7.22 (d, $J = 8.0$ Hz, 2H), 5.60 (s, 1H), 4.43-4.40 (m, 1H), 3.79 (s, 3H), 3.38 (s, 3H), 3.19-3.01 (m, 2H), 2.67-2.62 (m, 1H), 1.42 (s, 9H), 1.26 (s, 3H), 1.25 (s, 3H).

(Step 3) Methyl 4-(4-Isopropyl-3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (M-43)



20

To

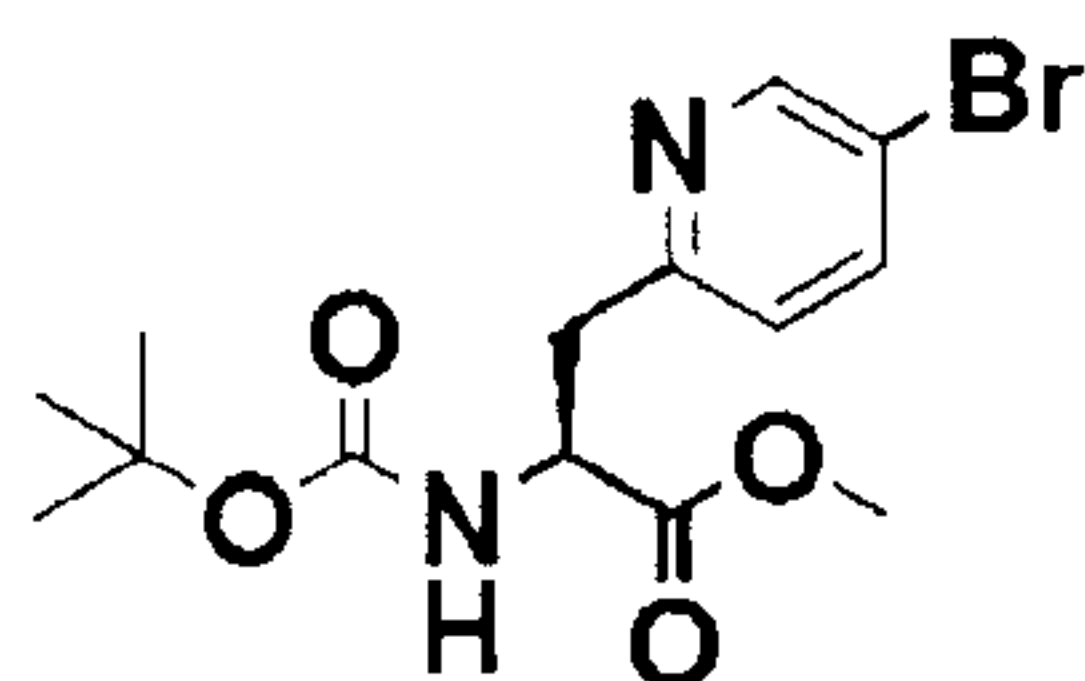
methyl

N-(tert-butoxycarbonyl)-4-(4-isopropyl-3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (352 mg, 0.790 mmol), 3 N hydrogen chloride/ethyl acetate (10.0 ml) was added, followed by stirring at room temperature for 1 hour. The
 5 obtained white solid was filtered and dried under reduced pressure to obtain a hydrochloride of the title compound (M-43) (250 mg, 83%) as a white solid.

¹H NMR (400 MHz, CD₃OD): δ 7.33 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 5.72 (s, 1H), 4.32-4.31 (m, 1H), 3.81 (s, 3H),
 10 3.38 (s, 3H), 3.42-3.34 (m, 1H), 3.11-3.03 (m, 2H), 1.25 (s, 3H), 1.23 (s, 3H).; MS (ESI) m/z 346 (M+H)⁺

Example 102: Synthesis of M-44

(Step 1) Methyl
3-(5-Bromopyridin-2-yl)-N-(tert-butoxycarbonyl)-L-alaninate

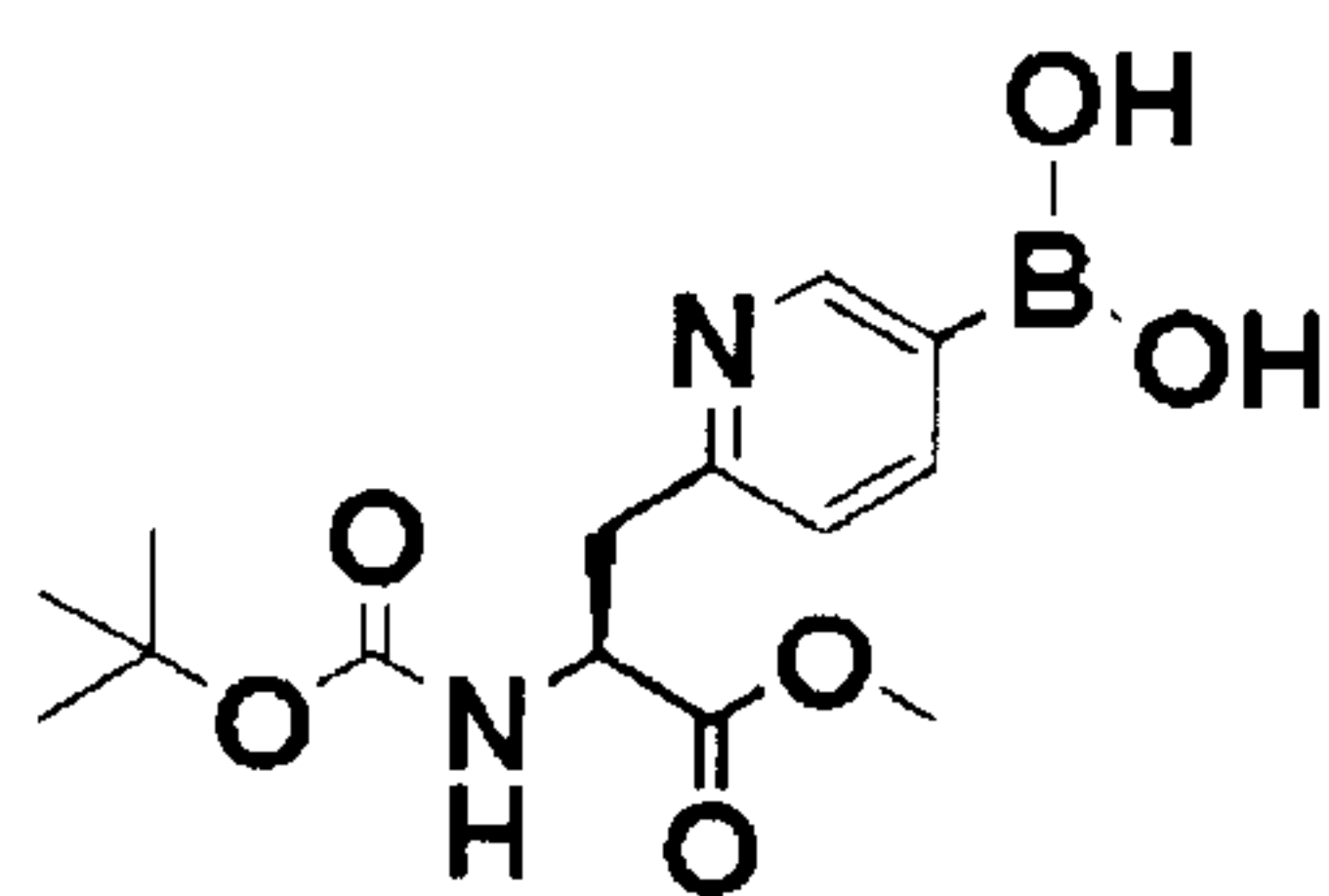


15

An operation in which zinc (130 g, 2.00 mol) was heated at 200°C for 30 minutes and cooled to room temperature was repeated three times, and then an N,N'-dimethylformamide solution (350 ml) of dibromoethane (10.0 ml, 0.11 mol) was added
 20 thereto. An operation in which the obtained reaction mixture was heated to 90°C and then cooled to room temperature was repeated twice, and then chlorotrimethylsilane (3.00 ml, 23.5 mmol) was added thereto, followed by stirring at room temperature for 30 minutes. An N,N'-dimethylformamide
 25 solution (250 ml) of methyl N-(tert-butoxycarbonyl)-3-iodo-L-alaninate (110 g, 0.330 mol) was added dropwise, followed by stirring at 35°C for 2.5 hours.

Then, 2,5-dibromopyridine (100 g, 0.420 mol) and bis(triphenylphosphine)palladium(II) chloride (12.0 g, 17.0 mmol) were further added to the reaction solution, followed by stirring at 70°C for 2 hours. After cooling to room temperature, the reaction solution was diluted with water, followed by extraction with ethyl acetate (200 ml×3). The extraction liquids were combined, washed with saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1 to 1:2) to obtain the title compound (65 g, 54%).
¹H NMR (CDCl₃, 400 MHz): δ 8.61 (s, 1H), 7.98-7.96 (m, 1H), 7.29-7.25 (m, 2H), 4.45-4.39 (m, 1H), 3.60 (s, 3H), 3.12-2.97 (m, 2H), 1.32 (s, 9H).

(Step 2)
(6-{(2S)-2-[(tert-Butoxycarbonyl)amino]-3-methoxy-3-oxopropyl}pyridin-3-yl)boronic Acid



Methyl

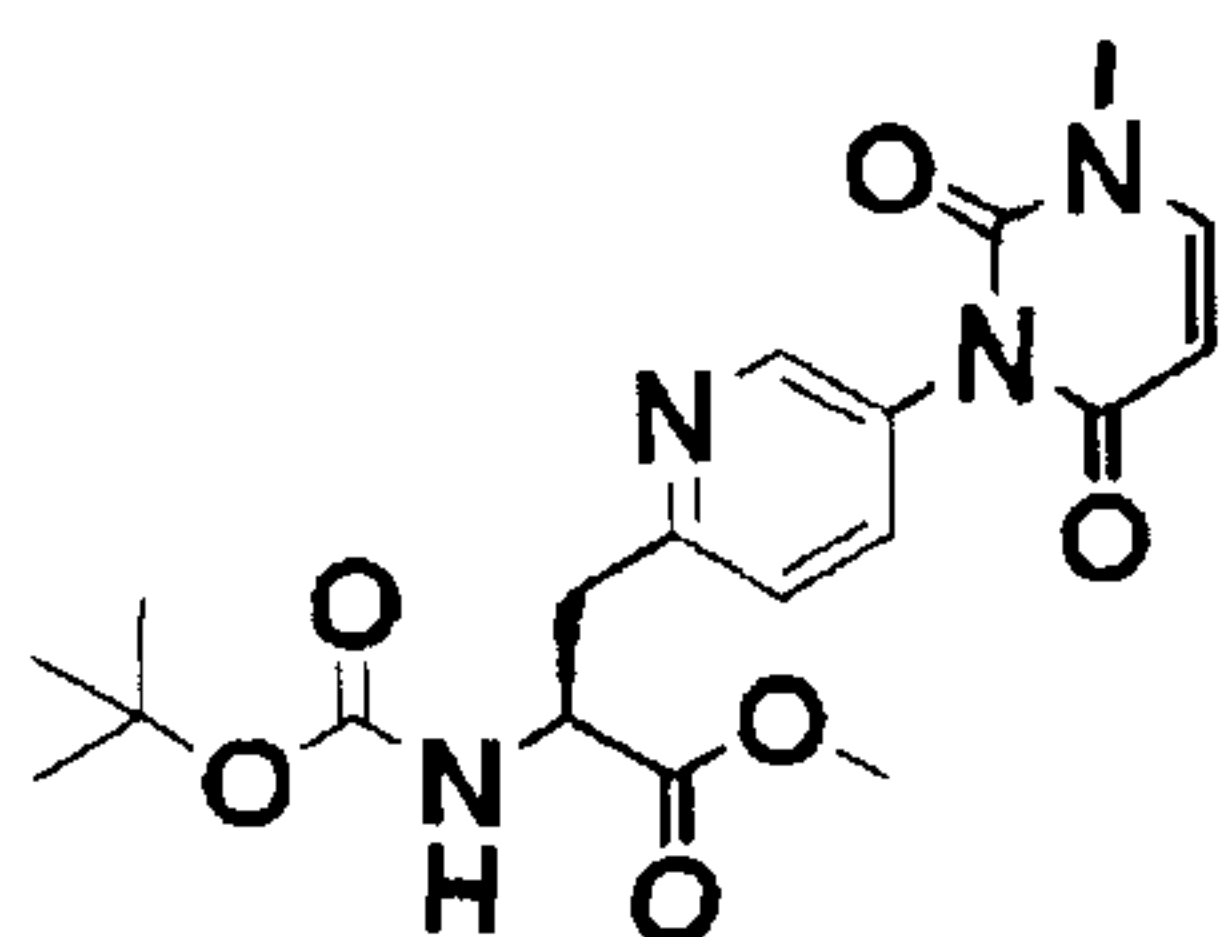
3-(5-bromopyridin-2-yl)-N-(tert-butoxycarbonyl)-L-alaninate (55.0 g, 153 mmol) and bis(pinacolato)diborane (58.5 g, 230 mmol) were dissolved in N,N'-dimethylformamide (1.0 L), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (5.60 g, 7.68 mmol) and potassium acetate (45.1 g, 461 mol) were added thereto, followed by stirring at 95°C for 12 hours in the presence of nitrogen gas. The reaction liquid was cooled to

room temperature, and filtered through Celite. Then, the filtrate was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=4:1 to 1:1).

5 The obtained compound was dissolved in acetone (700 ml), and sodium periodate (71.0 g, 330 mmol), ammonium acetate (25.0 g, 330 mmol), and water (300 ml) were added thereto, followed by stirring at room temperature for 55 hours. After the reaction liquid was filtered, the solvent was removed under
10 reduced pressure, and the obtained residue was diluted with water. After extraction with ethyl acetate (500 ml×3), the extraction liquids were combined, and dried over anhydrous sodium sulfate. After the solvent was removed under reduced pressure, the residue was washed with petroleum ether/ethyl
15 acetate=10:1, and the obtained solid was filtered to obtain the title compound (42.0 g, 85%).

¹H NMR (400 MHz, CDCl₃): δ 8.90-8.84 (m, 1H), 8.39-8.28 (m, 1H), 7.27-7.15 (m, 2H), 5.95 (s, 1H), 4.66-4.59 (m, 1H), 3.68 (s, 3H), 3.22-3.15 (m, 2H), 1.45 (s, 9H).

20 (Step 3) Methyl
N-(tert-Butoxycarbonyl)-3-[5-(3-methyl-2,6-dioxo-3,6-dihydr
opyrimidin-1(2H)-yl)pyridin-2-yl]-L-alaninate



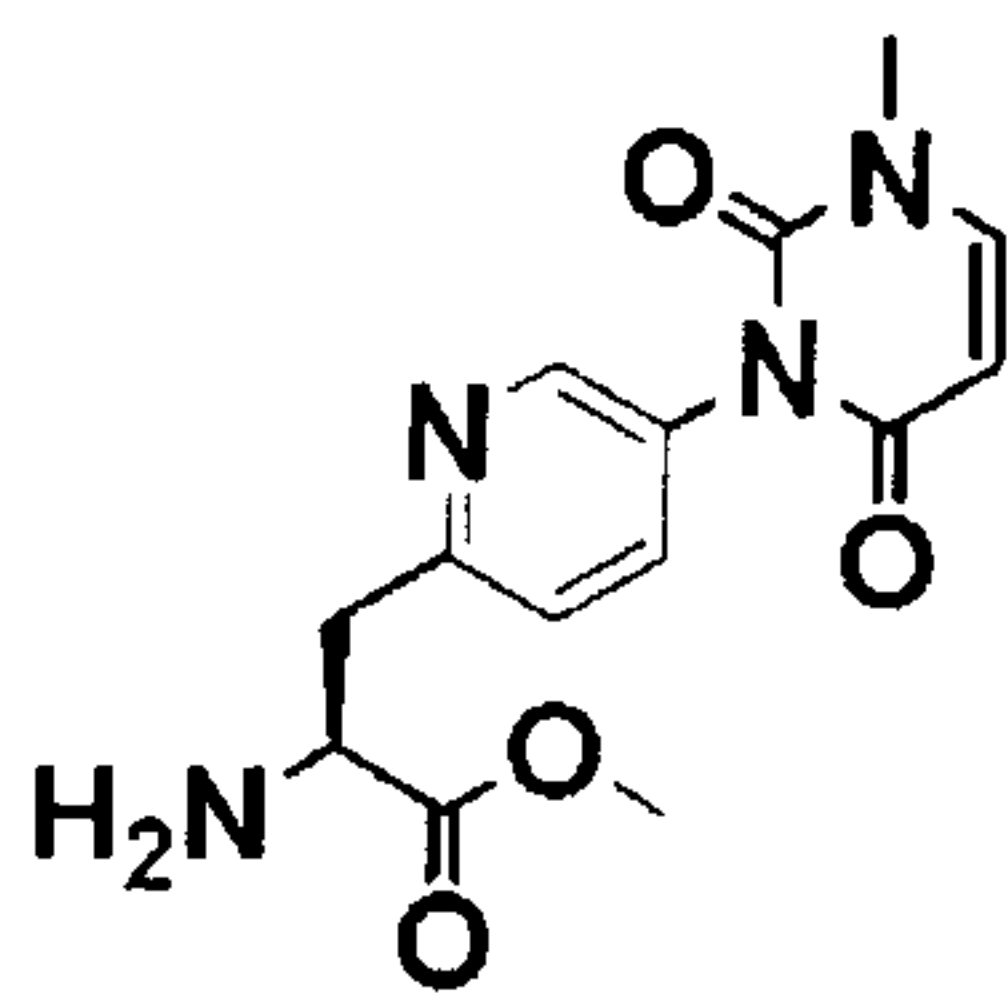
25 and
1-Methylpyrimidine-2,4(1H,3H)-dione (15.5 g, 123 mmol)
(6-{(2S)-2-[(tert-butoxycarbonyl)amino]-3-methoxy-3-oxoprop

yl}pyridin-3-yl)boronic acid (40.0 g, 123 mmol) were dissolved in methylene chloride (800 ml), and copper(II) acetate (27.0 g, 148 mmol), 4A MS (30 g), and triethylamine (50 ml) were added thereto, followed by stirring at room temperature for 3 days.

- 5 The reaction liquid was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1) to obtain the title compound (9.94 g, 20%) as a white solid.

MS (ESI) m/z 405 (M+H)⁺

- 10 (Step 4) Methyl 3-[5-(3-Methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)pyridin-2-yl]-L-alaninate (M-44)



To

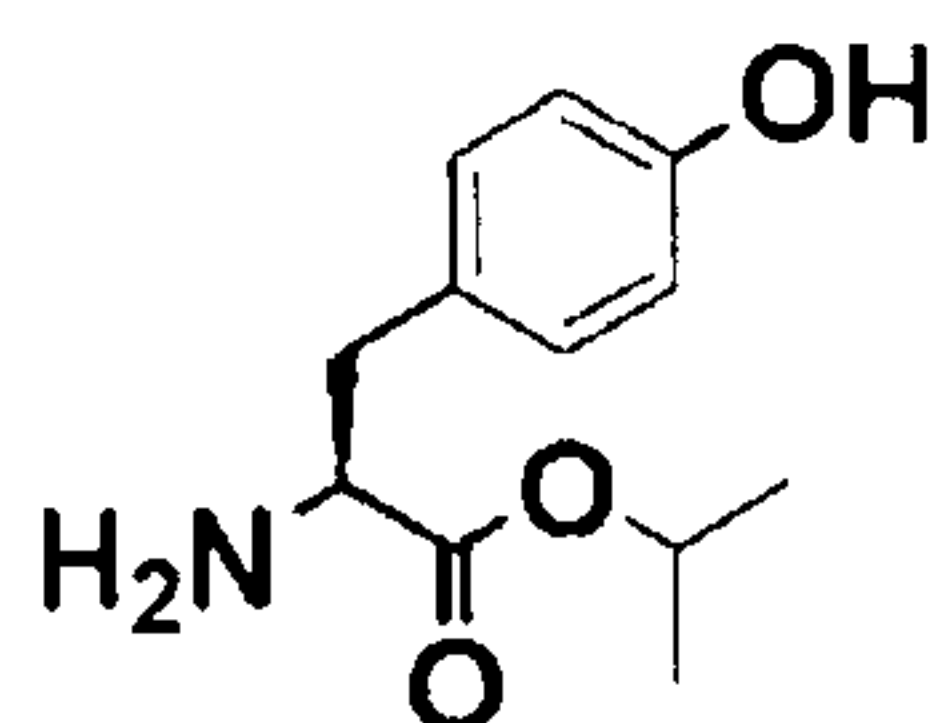
methyl

- 15 N-(tert-butoxycarbonyl)-3-[5-(3-methyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)pyridin-2-yl]-L-alaninate (4.20 g, 10.4 mmol), 4 N hydrogen chloride/ethyl acetate (30 ml) was added, followed by stirring at room temperature for 1 hour. The obtained white solid was filtered and dried under reduced pressure to obtain a hydrochloride of the title compound (M-44) (3.40 g, 95%) as a white solid.

¹H NMR (400 MHz, CD₃OD): δ 8.37 (s, 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.53 to 7.49 (m, 2H), 5.67 (d, J = 8.0 Hz, 1H), 4.46 to 4.43 (m, 1H), 3.65 (s, 3H), 3.45 to 3.38 (m, 2H), 3.24 (s, 3H).;

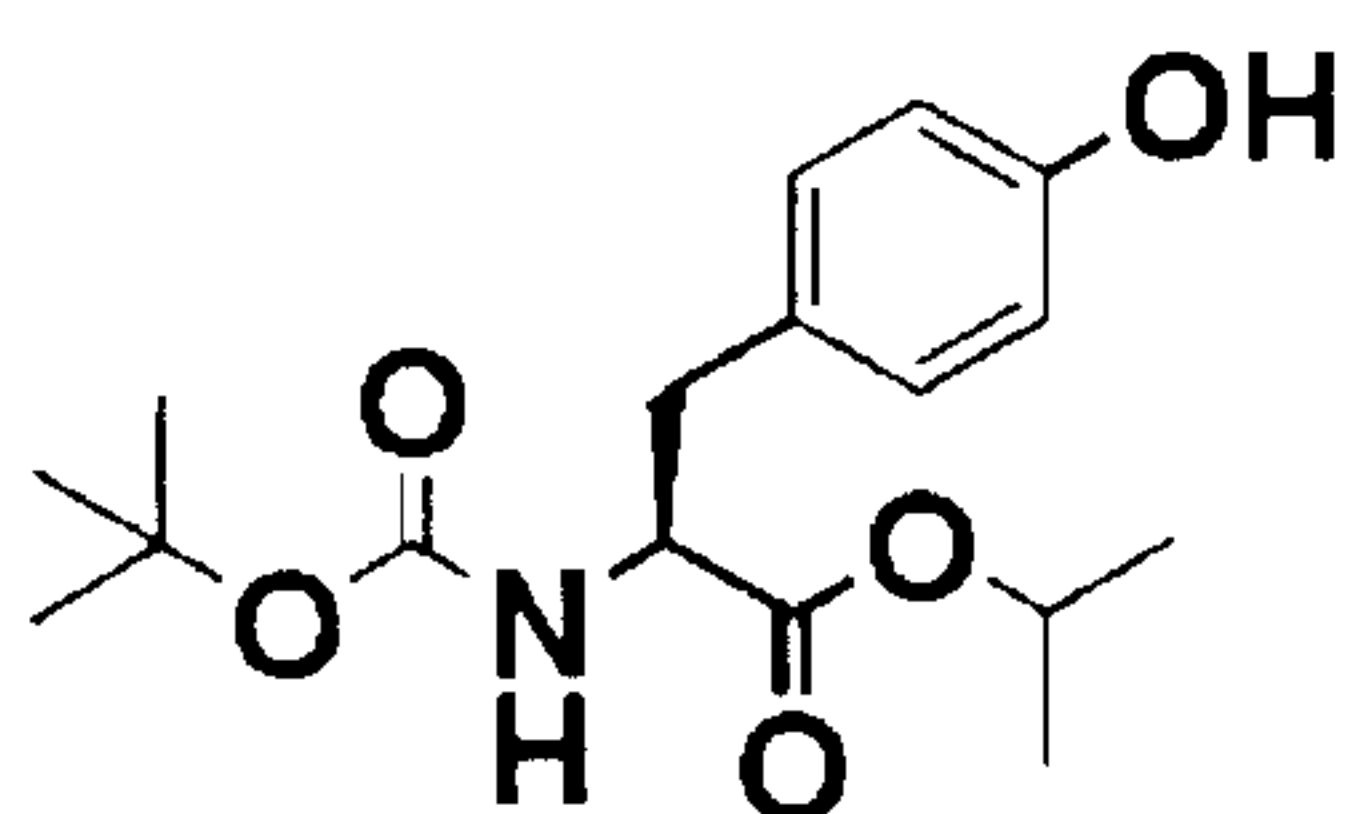
- 25 MS (ESI) m/z 305 (M+H)⁺

Example 103: Synthesis of M-45

(Step 1) Isopropyl L-Tyrosinate

L-Tyrosine (100 g, 552 mmol) was dissolved in 2-propanol (1.00 L), and then concentrated sulfuric acid (60 ml) was added dropwise thereto, followed by stirring at 80°C for 2 days. The reaction liquid was concentrated under reduced pressure, and then a saturated aqueous hydrogen carbonate solution was added to the residue, followed by stirring. The obtained solid was filtered and dried under reduced pressure to obtain the title compound (129 g, 85%) as a white solid.

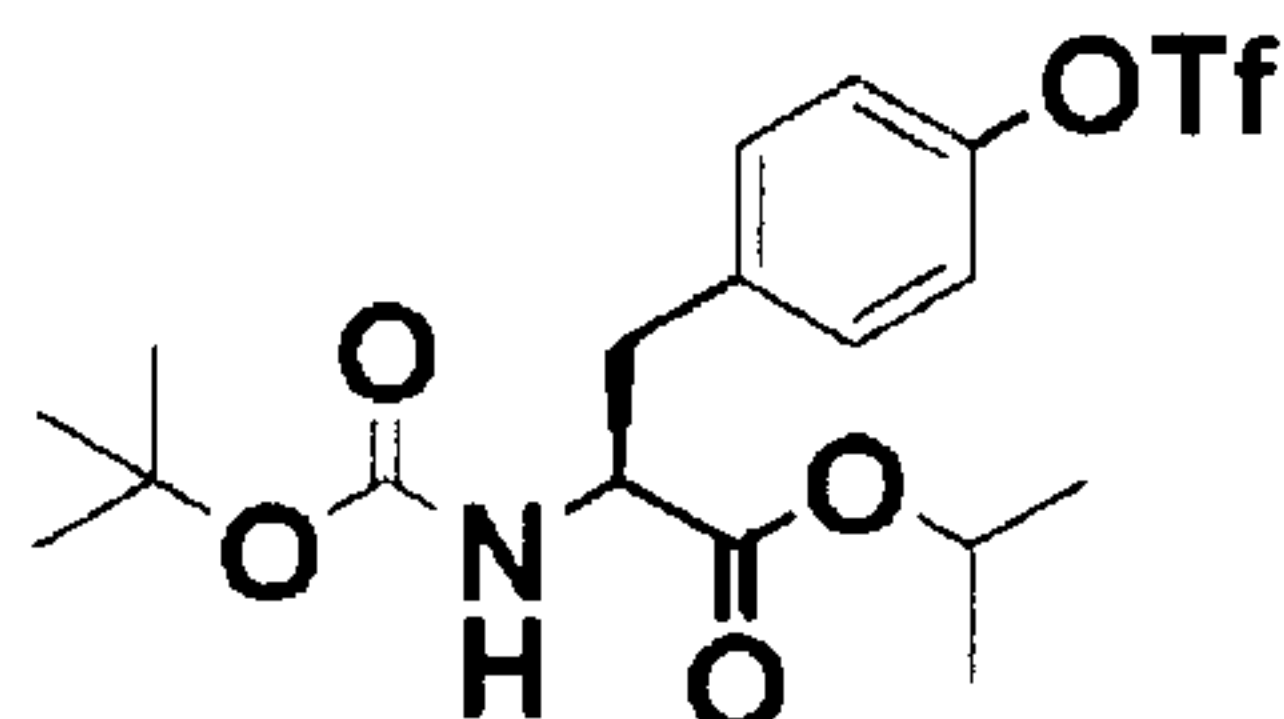
^1H NMR (CD_3OD , 400 MHz): δ 7.01 (d, $J = 8.0$ Hz, 2H), 6.71 (d, $J = 8.4$ Hz, 2H), 4.96-4.90 (m, 1H), 3.62 (t, $J = 6.8$ Hz, 1H), 2.91-2.80 (m, 2H), 1.15 (d, $J = 6.4$ Hz, 6H).; MS (ESI) m/z 224 ($\text{M}+\text{H}$) $^+$

15 (Step 2) Isopropyl N-(tert-Butoxycarbonyl)-L-tyrosinate

Isopropyl L-tyrosinate (120 g, 538 mmol) was dissolved in tetrahydrofuran (1.3 L), and di-tert-butyl dicarbonate (123 g, 565 mmol) and triethylamine (80 ml) were added thereto, followed by stirring at room temperature for 2 hours. The reaction liquid was concentrated under reduced pressure to obtain the title compound (174 g, 91%).

MS (ESI) m/z 324 ($\text{M}+\text{H}$) $^+$

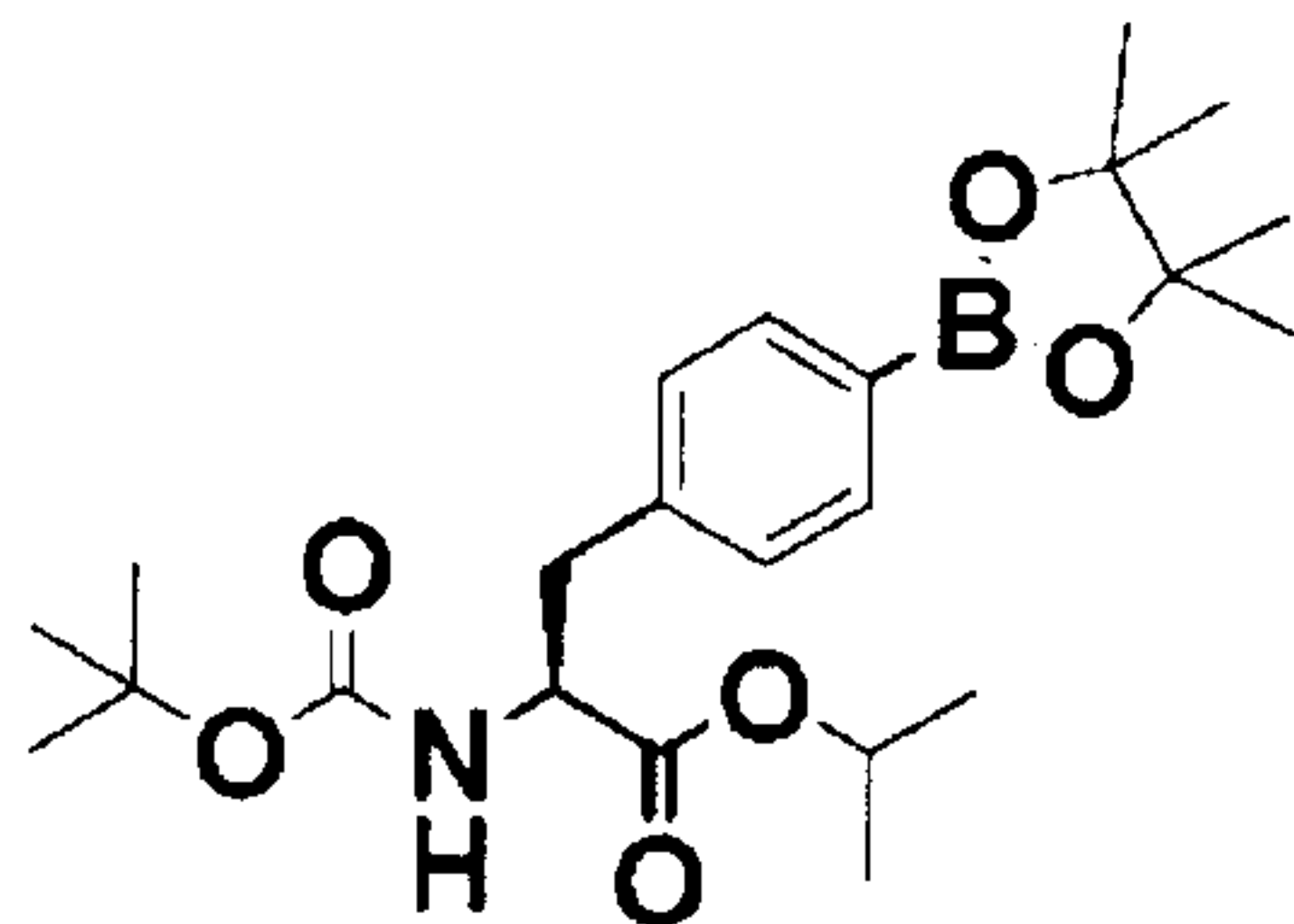
(Step 3) Isopropyl
N-(tert-Butoxycarbonyl)-O-[(trifluoromethyl)sulfonyl]-L-tyr
osinate



- 5 Isopropyl N-(tert-butoxycarbonyl)-L-tyrosinate (170 g, 526 mmol) was dissolved in methylene chloride (1.2 L). After the mixture was cooled to 0°C, trifluoromethanesulfonic anhydride (148 g, 526 mmol) and pyridine (200 ml) were added dropwise, followed by stirring at room temperature for 12 hours.
- 10 The reaction liquid was diluted with water (800 ml), and then washed with a 0.5 N aqueous sodium hydroxide solution (800 ml), water (800 ml), 1 N hydrochloric acid (800 ml), and saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Then, the solvent was removed under reduced pressure
- 15 to obtain the title compound (214 g, 89%).

¹H NMR (CDCl₃, 400 MHz): δ 7.28-7.19 (m, 4H), 5.08-4.97 (m, 2H), 4.55-4.51 (m, 1H), 3.16-3.03 (m, 2H), 1.43 (s, 9H), 1.23 (q, J = 8.4 Hz, 6H).; MS (ESI) m/z 456 (M+H)⁺

(Step 4) Isopropyl
 20 N-(tert-Butoxycarbonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxab
orolan-2-yl)-L-phenylalaninate



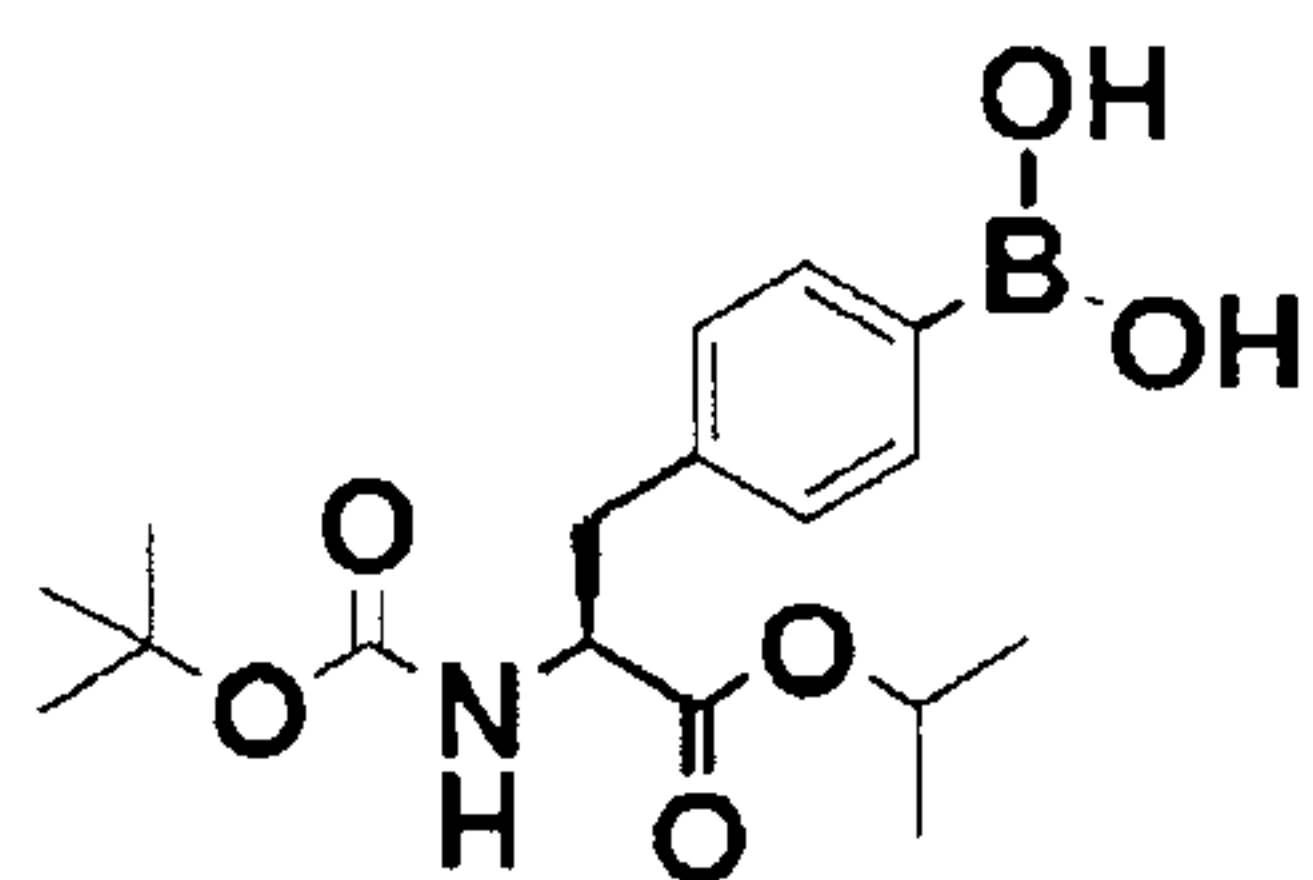
Isopropyl

N-(tert-butoxycarbonyl)-O-[(trifluoromethyl)sulfonyl]-L-tyr
osinate (230 g, 505 mmol) and bis(pinacolato)diborane (192 g,
758 mmol) were dissolved in N,N'-dimethylformamide (1.0 L), and
[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
5 (18.5 g, 25.3 mmol) and potassium acetate (149 g, 1.52 mol) were
added thereto, followed by stirring at 95°C for 12 hours in the
presence of nitrogen gas. The reaction liquid was cooled to
room temperature, and then filtered through Celite. The
filtrate was concentrated under reduced pressure, and the
10 obtained residue was purified by silica gel column
chromatography (petroleum ether/ethyl acetate=20:1) to obtain
the title compound (180 g, 82%) as a yellow oil.

¹H NMR (CDCl₃, 400 MHz): δ 7.74 (d, J = 8.4 Hz, 2H), 7.16 (d,
J = 7.6 Hz, 2H), 5.03-4.99 (m, 1H), 4.97 (d, J = 8.4 Hz, 1H),
15 4.54-4.49 (m, 1H), 3.16-3.05 (m, 2H), 1.42 (s, 9H), 1.34 (s,
12H), 1.24 (t, J = 6.0 Hz, 6H).; MS (ESI) m/z 434 (M+H)⁺

(Step 5) Isopropyl

N-(tert-Butoxycarbonyl)-4-(dihydroxyboryl)-L-phenylalaninate
e



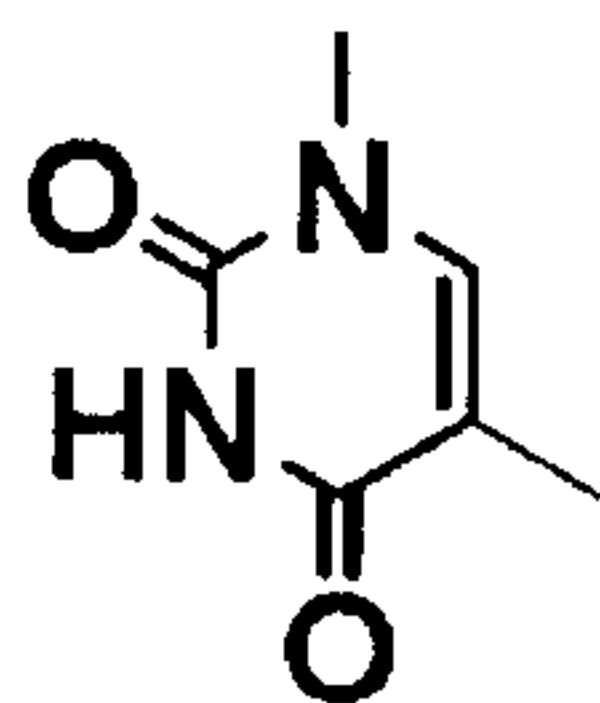
20

Isopropyl

N-(tert-butoxycarbonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxab
orolan-2-yl)-L-phenylalaninate (71.4 g, 165 mmol) was
dissolved in acetone (700 ml), and sodium periodate (71.0 g,
25 330 mmol), ammonium acetate (25.0 g, 330 mmol), and water (300
ml) were added thereto, followed by stirring at room temperature

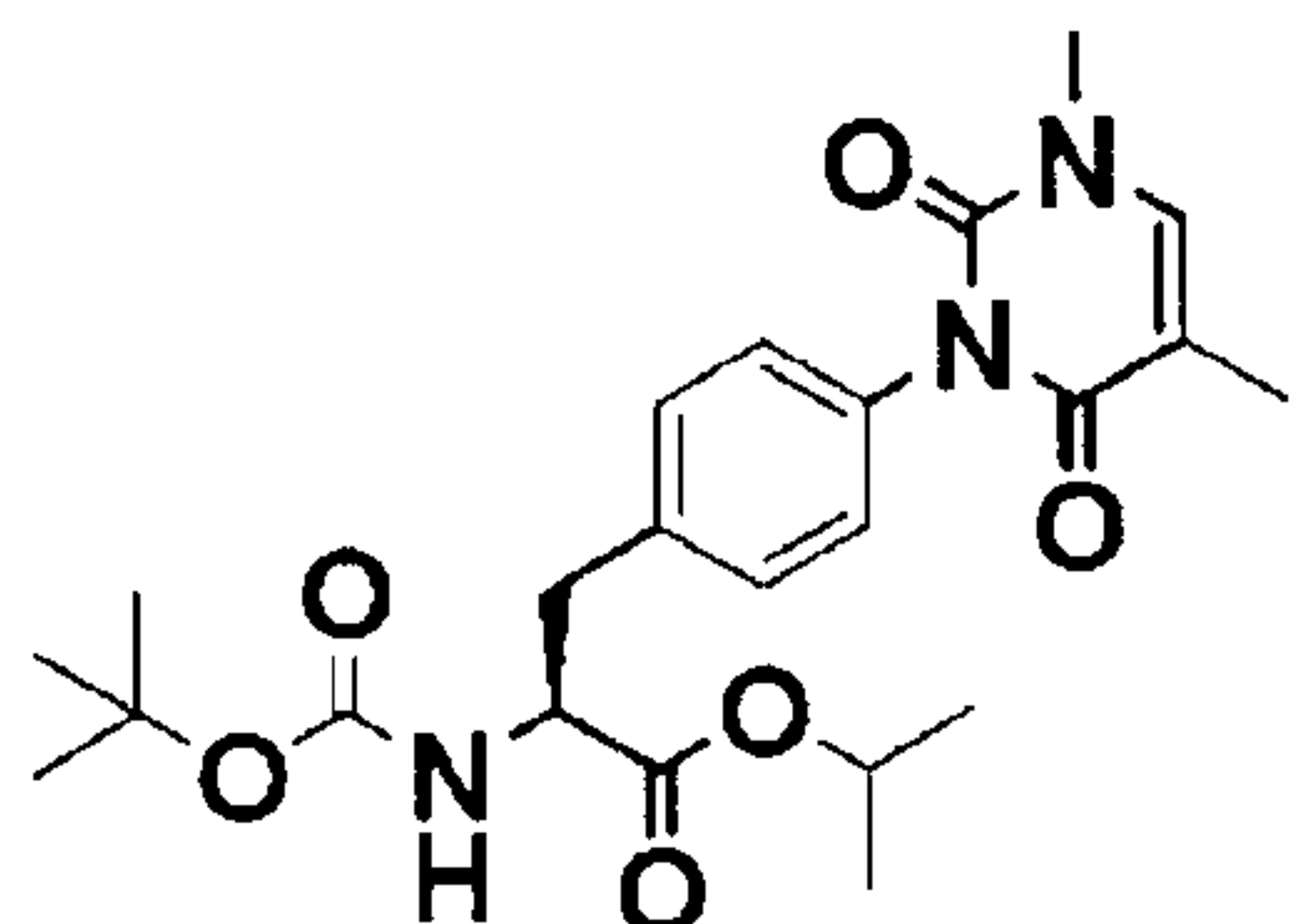
for 72 hours. After the reaction liquid was filtered, the solvent was removed under reduced pressure, and the obtained residue was diluted with water. After extraction with ethyl acetate (500 ml×3), the extraction liquids were combined, and
 5 dried over anhydrous sodium sulfate. After the solvent was removed under reduced pressure, the residue was washed with petroleum ether/ethyl acetate=10:1, and the obtained solid was filtered to obtain the title compound (45.8 g, 79%).

¹H NMR (DMSO-d₆, 400 MHz): δ: 7.98 (s, 2H), 7.70 (d, J = 7.6
 10 Hz, 2H), 7.27 (d, J = 7.6 Hz, 1H), 7.20 (d, J = 8.0 Hz, 2H), 4.89-4.83 (m, 1H), 4.10-4.00 (m, 1H), 2.97-2.82 (m, 2H), 1.33 (s, 9H), 1.20-1.05 (m, 6H).; MS (ESI) m/z 252 (M+H-boc)⁺
 (Step 6) 1,5-Dimethylpyrimidine-2,4(1H,3H)-dione



15 5-Methylpyrimidine-2,4(1H,3H)-dione (33.8 g, 268 mmol), bis(trimethylsilyl)amine (550 ml), and chlorotrimethylsilane (55.0 ml) were stirred at 130°C for 5 hours. Then, the mixture was cooled to 60°C, and methyl iodide (200 ml, 3.2 mol) was added thereto, followed by stirring at 60°C for further 30 hours.
 20 After cooling to 0°C, acetic acid (500 ml) was added, followed by stirring. The reaction liquid was concentrated under reduced pressure, and 2-propanol (1.6 L) was added thereto, followed by vigorous stirring. The solid obtained by filtration was purified by recrystallization from water (500
 25 ml) to obtain the title compound (25.1 g, 67%) as a white solid.
¹H NMR (DMSO-d₆, 400 MHz): δ 11.24 (br, 1H), 7.51 (s, 1H), 3.19 (s, 3H), 1.74 (s, 3H).; MS (ESI) m/z 141 (M+H)⁺

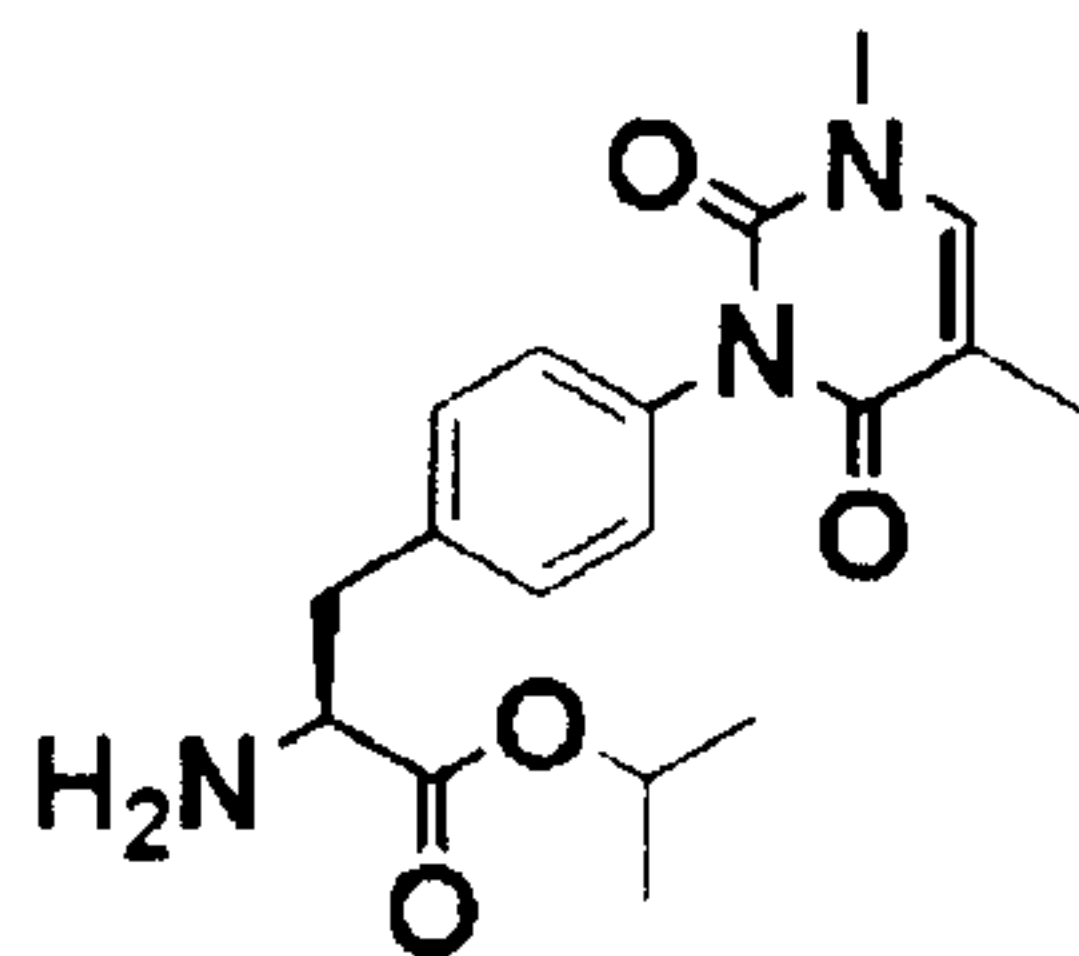
(Step 7) Isopropyl
N-(tert-Butoxycarbonyl)-4-(3,5-dimethyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate



5 1,5-Dimethylpyrimidine-2,4(1H,3H)-dione (15.0 g, 107 mmol) and methyl N-(tert-butoxycarbonyl)-4-(dihydroxyboryl)-L-phenylalaninate (37.6 g, 107 mmol) were dissolved in methylene chloride (500 ml), and copper(II) acetate (19.5 g, 107 mmol) and triethylamine
 10 (40 ml) were added thereto, followed by stirring at room temperature for 3 days. The reaction liquid was concentrated under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=1:1) to obtain the title compound (3.4 g, 7%) as a yellow
 15 solid.

^1H NMR (CDCl_3 , 400 MHz): δ 7.28 (d, $J = 6.4$ Hz, 1H), 7.19 (d, $J = 5.6$ Hz, 2H), 7.08 (s, 1H), 5.06 (d, $J = 8.4$ Hz, 1H), 5.03-4.98 (m, 1H), 4.56 (d, $J = 4.0$ Hz, 1H), 3.40 (s, 3H), 3.13-3.06 (m, 2H), 1.94 (s, 3H), 1.42 (s, 9H), 1.22 (t, $J = 6.8$ Hz, 6H).; MS
 20 (ESI) m/z 363 ($\text{M}+\text{H}+17(\text{NH}_3)-\text{boc}$) $^+$

(Step 8) Isopropyl
4-(3,5-Dimethyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (M-45)



To

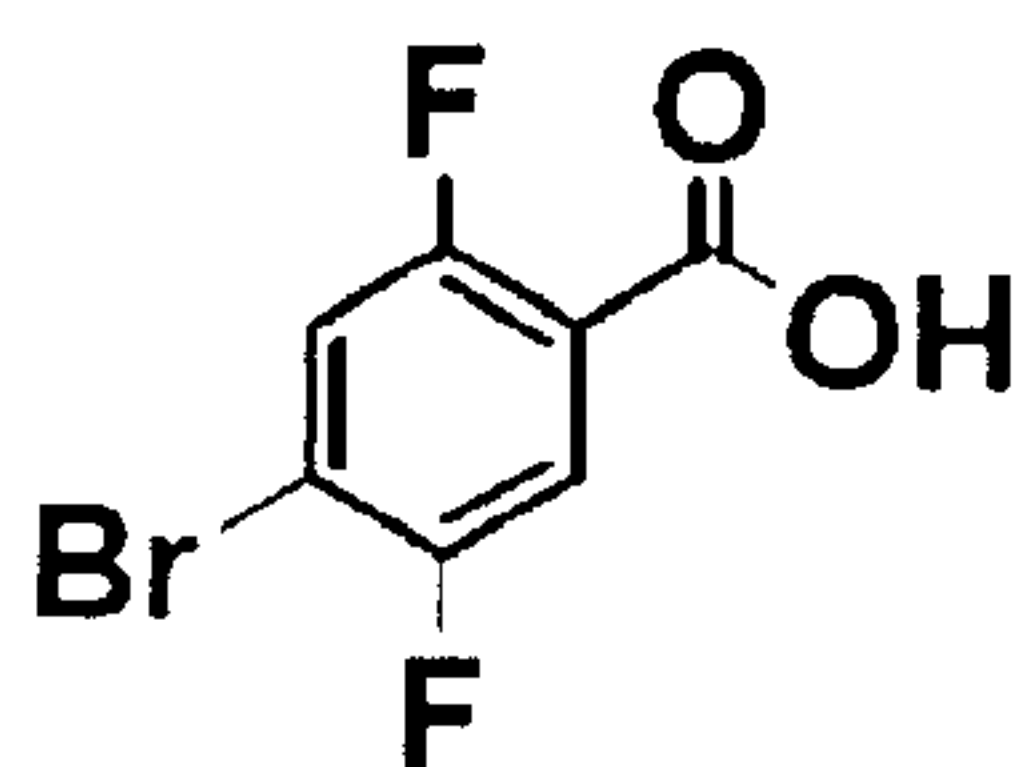
isopropyl

N-(tert-butoxycarbonyl)-4-(3,5-dimethyl-2,6-dioxo-3,6-dihydropyrimidin-1(2H)-yl)-L-phenylalaninate (6.0 g, 15 mmol), 3 N
 5 hydrogen chloride/ethyl acetate (100 ml) was added, followed by stirring at room temperature for 1 hour. The obtained white solid was filtered and dried under reduced pressure to obtain a hydrochloride of the title compound (M-45) (2.66 g, 91%) as a white solid.

10 ^1H NMR (CD_3OD , 400 MHz): δ 7.59 (s, 1H), 7.47 (d, J = 8.4 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 5.21-5.16 (m, 1H), 4.38-4.34 (m, 1H), 3.46-3.43 (m, 1H), 3.42 (s, 3H), 3.22-3.16 (m, 1H), 1.97 (s, 3H), 1.36 (t, J = 4.8 Hz, 6H).; MS (ESI) m/z 346 ($\text{M}+\text{H}$) $^+$

Example 104: Synthesis of M-46

15 (Step 1) 4-Bromo-2,5-difluorobenzoic Acid

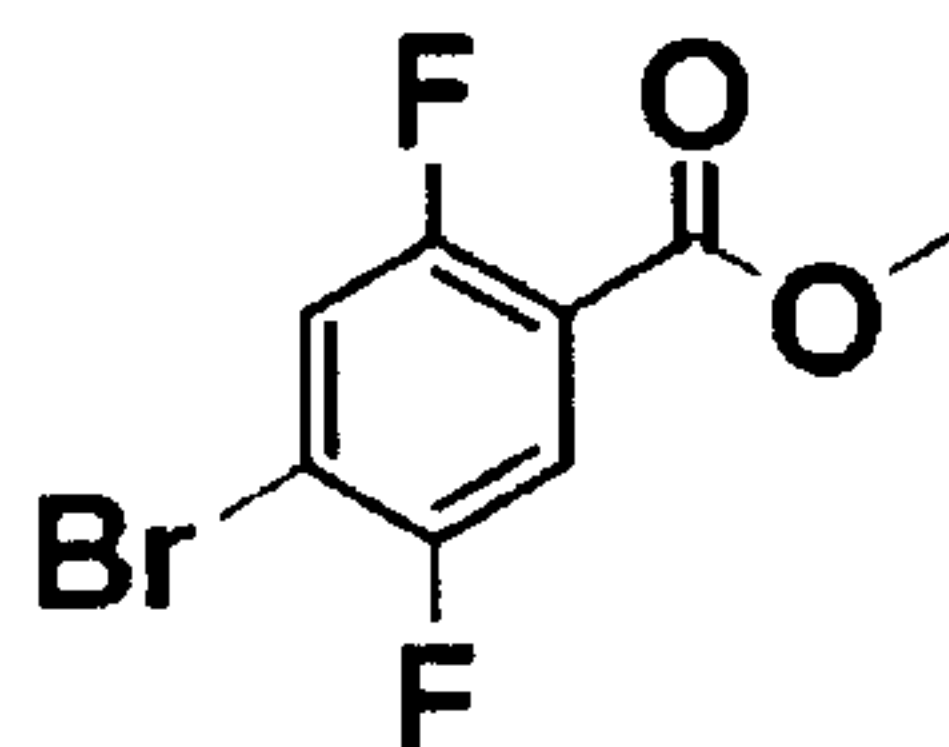


1,4-Dibromo-2,5-difluorobenzene (51.2 g, 188 mmol) was dissolved in 1,2-diethoxyethane (400 ml), and a 2.5 M n-butyllithium/hexane solution (76.0 ml, 190 mmol) was slowly
 20 added dropwise thereto at -78°C in the presence of nitrogen gas. After the reaction solution was stirred at -78°C for 30 minutes, dry ice was added thereto, followed by stirring for further 30 minutes. After the temperature was gradually raised to room

temperature, water (200 ml) was added to the reaction liquid. The reaction liquid was diluted with ethyl acetate, and washed with a 10% aqueous sodium carbonate solution (200 ml×2). Then, the obtained aqueous layers were combined, and made acidic by adjustment with 1 N hydrochloric acid. The precipitated yellow solid was filtered and dried to obtain the title compound (30.0 g, 67%).

^1H NMR (DMSO- d_6 , 400 MHz): δ 7.90-7.87 (m, 1H), 7.79-7.75 (m, 1H).; MS (ESI) m/z 191 ($M+H-44$) $^+$

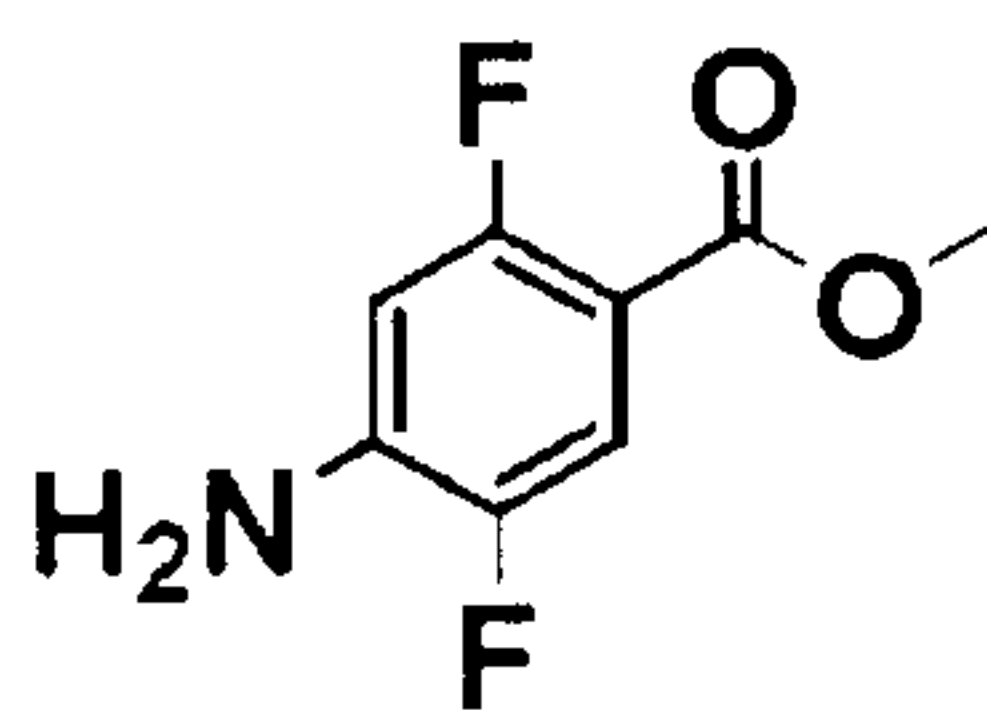
10 (Step 2) Methyl 4-Bromo-2,5-difluorobenzoate



4-Bromo-2,5-difluorobenzoic acid (30.0 g, 127 mmol) was dissolved in ethyl acetate (500 ml). After the mixture was cooled to 0°C, an ether solution of diazomethane was added thereto. The reaction liquid was stirred at 0°C for 1 hour, and the solvent was removed under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=6:1 to 2:1) to obtain the title compound (25.0 g, 78%).

20 ^1H NMR (DMSO- d_6 , 400 MHz): δ 7.93-7.89 (m, 1H), 7.80-7.77 (m, 1H), 3.86 (s, 3H).

(Step 3) Methyl 4-Amino-2,5-difluorobenzoate



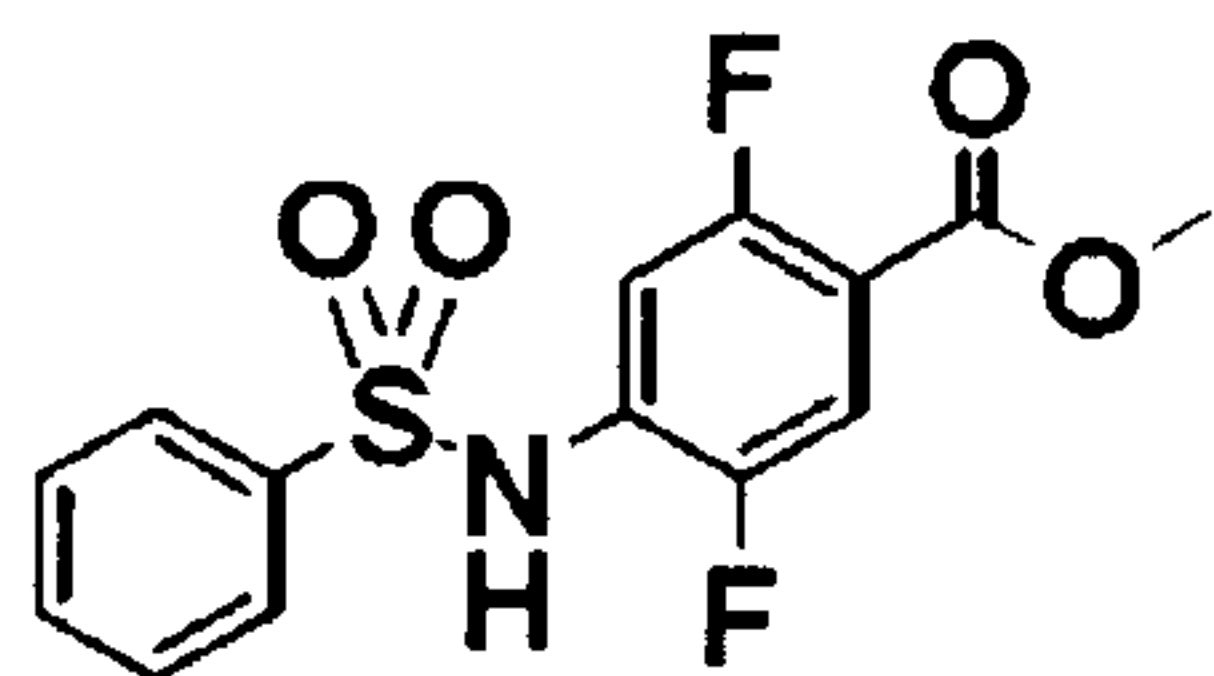
Methyl 4-bromo-2,5-difluorobenzoate (25.0 g, 99.6 mmol)

and BINAP (1.86 g, 3.00 mmol) were dissolved in toluene (500 ml). To the solution, palladium(II) acetate (672 mg, 3.00 mmol), cesium carbonate (52.0 g, 160 mmol), and benzophenone imine (25.3 g, 140 mmol) were added, followed by stirring at 110°C
 5 for 12 hours. After cooling to room temperature, the mixture was filtered through Celite, followed by washing with ethyl acetate. The obtained filtrate was concentrated under reduced pressure.

The obtained compound was dissolved in water (30 ml) and
 10 tetrahydrofuran (80 ml), and concentrated hydrochloric acid (30 ml) was added thereto, followed by stirring at room temperature for 2 hours. The precipitated solid was filtered to obtain a white solid. In addition, the filtrate was concentrated under reduced pressure, until a white solid precipitated. The
 15 obtained solid was filtered. These white solids were combined and dried to obtain the title compound (9.8 g, 53% over two steps).

^1H NMR (CD_3OD , 400 MHz): δ 7.53-7.49 (m, 1H), 6.60-6.56 (m, 1H), 3.85 (s, 3H).; MS (ESI) m/z 188 ($\text{M}+\text{H}$) $^+$

20 (Step 4) Methyl
2,5-Difluoro-4-[(phenylsulfonyl)amino]benzoate

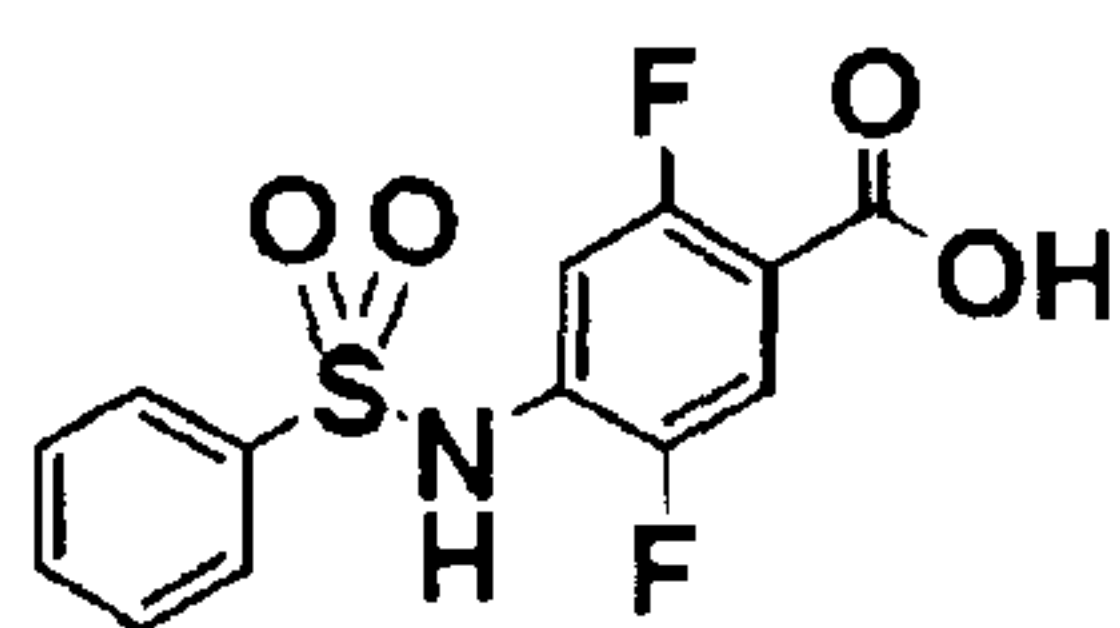


Methyl 4-amino-2,5-difluorobenzoate (20.0 g, 107 mmol) was dissolved in methylene chloride (200 ml), and
 25 benzenesulfonyl chloride (37.8 g, 214 mmol) and pyridine (67.0 ml) were added thereto, followed by stirring at room temperature for 12 hours. The reaction liquid was concentrated under

reduced pressure. Then, the pH of the obtained residue was adjusted to 1.0 by adding 6 N hydrochloric acid thereto. The obtained solid was filtered, washed with water and methylene chloride, and dried to obtain the title compound (21.0 g, 60%).

5 ^1H NMR ($\text{DMSO}-d_6$, 300 MHz): δ 11.1 (s, 1H), 7.87-7.84 (m, 2H), 7.67-7.58 (m, 4H), 7.29-7.23 (m, 1H), 3.80 (s, 3H).; MS (ESI) m/z 326 (M-1)

(Step 5) 2,5-Difluoro-4-[(phenylsulfonyl)amino]benzoic Acid
(M-46)



10

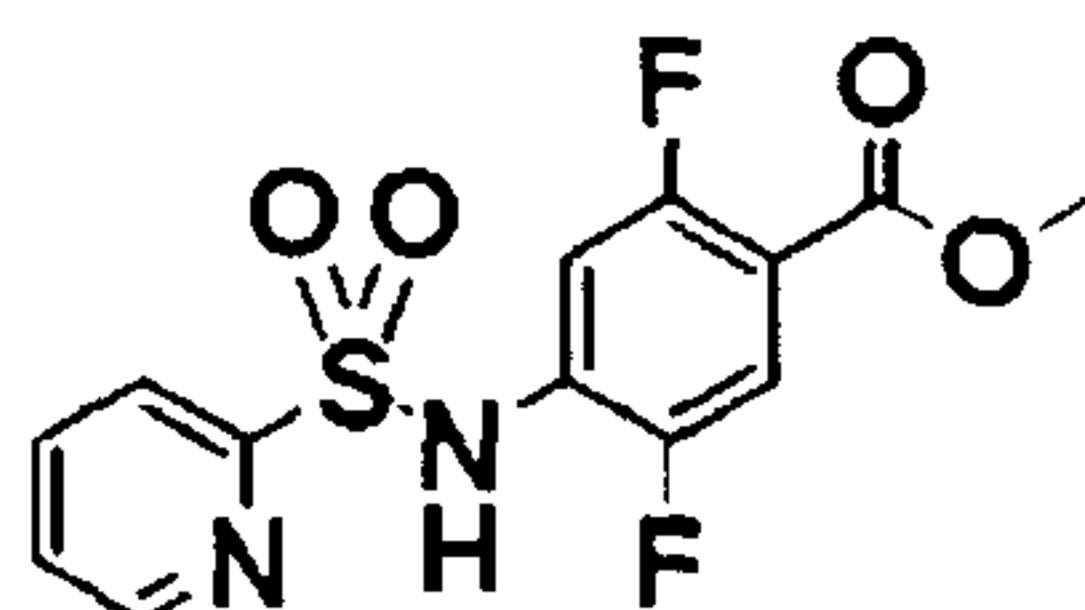
Methyl 2,5-difluoro-4-[(phenylsulfonyl)amino]benzoate (21.0 g, 64.2 mmol) was dissolved in a saturated aqueous lithium hydroxide solution, followed by stirring at room temperature for 30 minutes. The pH of the reaction liquid was adjusted to lower than 6.0 by adding 8 N hydrochloric acid thereto, and the obtained white solid was filtered and dried to obtain the title compound (19.2 g, 95%).

15 ^1H NMR (CD_3OD , 400 MHz): δ 7.92-7.90 (m, 2H), 7.67-7.64 (m, 1H), 7.60-7.50 (m, 3H), 7.40 (dd, $J = 11.6, 6.4$ Hz, 1H).; MS (ESI) m/z 312 (M-1)

20

Example 105: Synthesis of M-47

(Step 1) Methyl 2,5-Difluoro-4-[(pyridin-2-ylsulfonyl)amino]benzoate



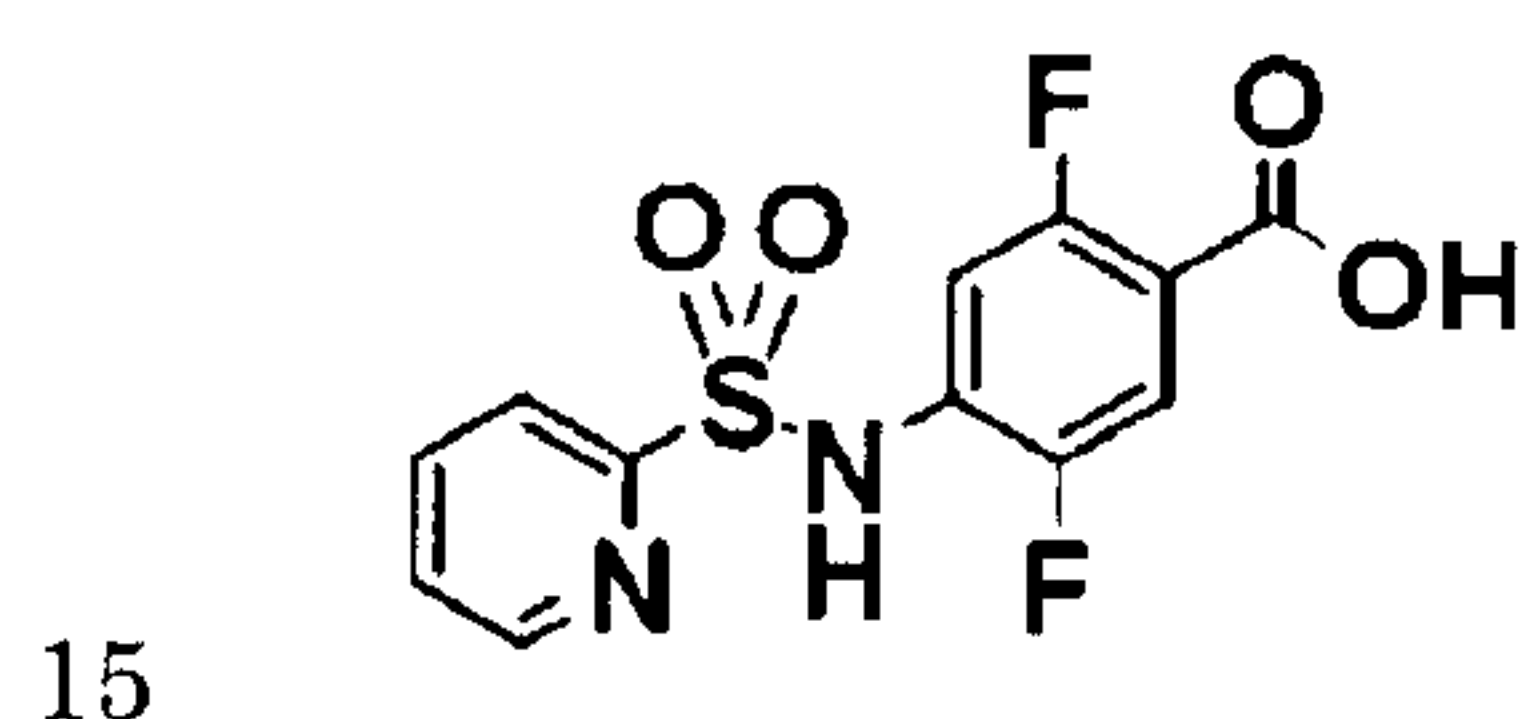
25

Methyl 4-bromo-2,5-difluorobenzoate (500 mg, 1.99 mmol)

<see (Step 3) of Example 104>, pyridine-2-sulfonamide (262 mg, 1.66 mmol), potassium carbonate (683 mg, 4.94 mmol), diisopropylethylamine (72.0 mg, 0.82 mmol), and copper(I) iodide (26.0 mg, 0.140 mmol) were dissolved in acetonitrile, followed by stirring at 140°C for 2 hours under microwave irradiation. The reaction liquid was cooled to room temperature and then filtered. The obtained filtrate was concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1) to obtain the title compound (160 mg, 29%).

MS (ESI) m/z 327 (M-1)

(Step 2) 2,5-Difluoro-4-[(pyridin-2-ylsulfonyl)amino]benzoic Acid (M-47)

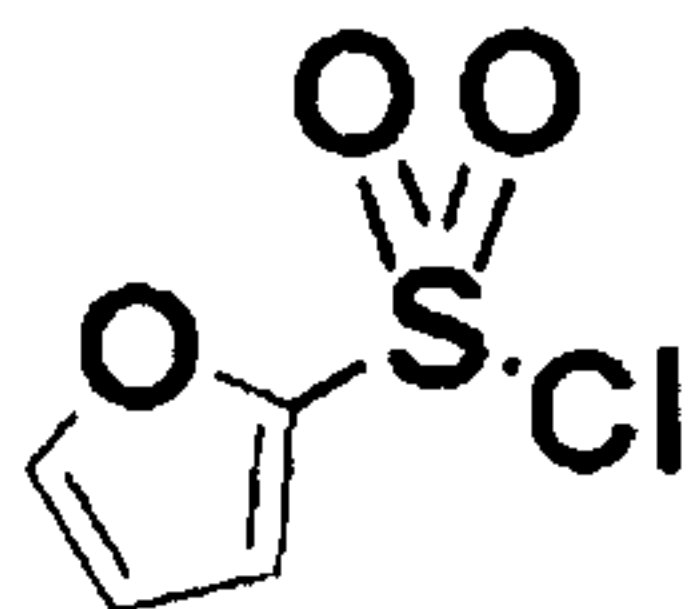


Methyl

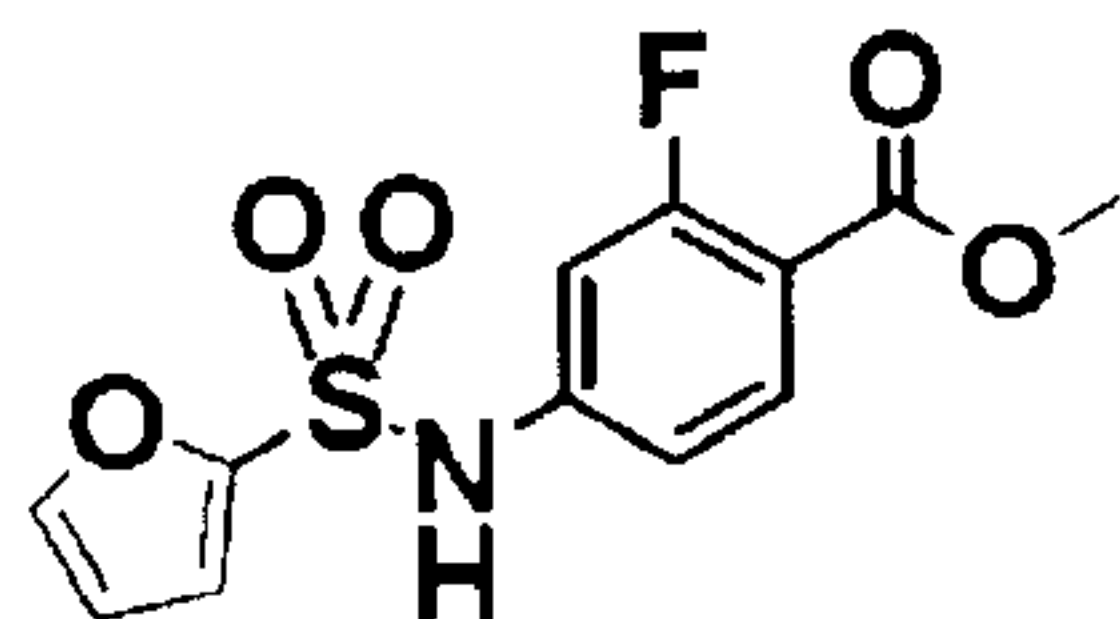
2,5-difluoro-4-[(pyridin-2-ylsulfonyl)amino]benzoate (2.30 g, 7.00 mmol) was dissolved in methanol (30 ml), and a 6 N aqueous lithium hydroxide solution (20 ml) was added thereto, followed by stirring at room temperature for 30 minutes. The pH of the reaction liquid was adjusted to a range from 4.0 to 5.0 by adding 4 N hydrochloric acid thereto, and the precipitated yellow solid was filtered and dried to obtain the title compound (2.05 g, 93%).

25 ¹H NMR (CD₃OD, 400 MHz): δ 8.56 (d, J = 4.4 Hz, 1H), 7.97 (dd, J = 6.4, 1.6 Hz, 2H), 7.54-7.41 (m, 3H).; MS (ESI) m/z 315 (M+H)⁺

Example 106: Synthesis of M-48

(Step 1) Furan-2-sulfonyl Chloride

Furan (3.67 g, 53.9 mmol) was dissolved in diethyl ether (50 ml). After the solution was cooled to 0°C, a t-butyllithium/hexane solution (1.3 mol/l, 50 ml) was slowly added dropwise, followed by stirring for 15 minutes. Sulfur dioxide was added to the reaction liquid, followed by stirring for further 15 minutes. Subsequently, N-chlorosuccinimide (8.65 g, 64.8 mmol) was added thereto, followed by stirring at room temperature for 30 minutes. The reaction liquid was diluted with water. After extraction with ethyl acetate (100 ml×2), the extraction liquids were combined, and dried over anhydrous sodium sulfate. After the solvent was removed under reduced pressure, the residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=10:1 to 5:1) to obtain the title compound (3.2 g, 36%).

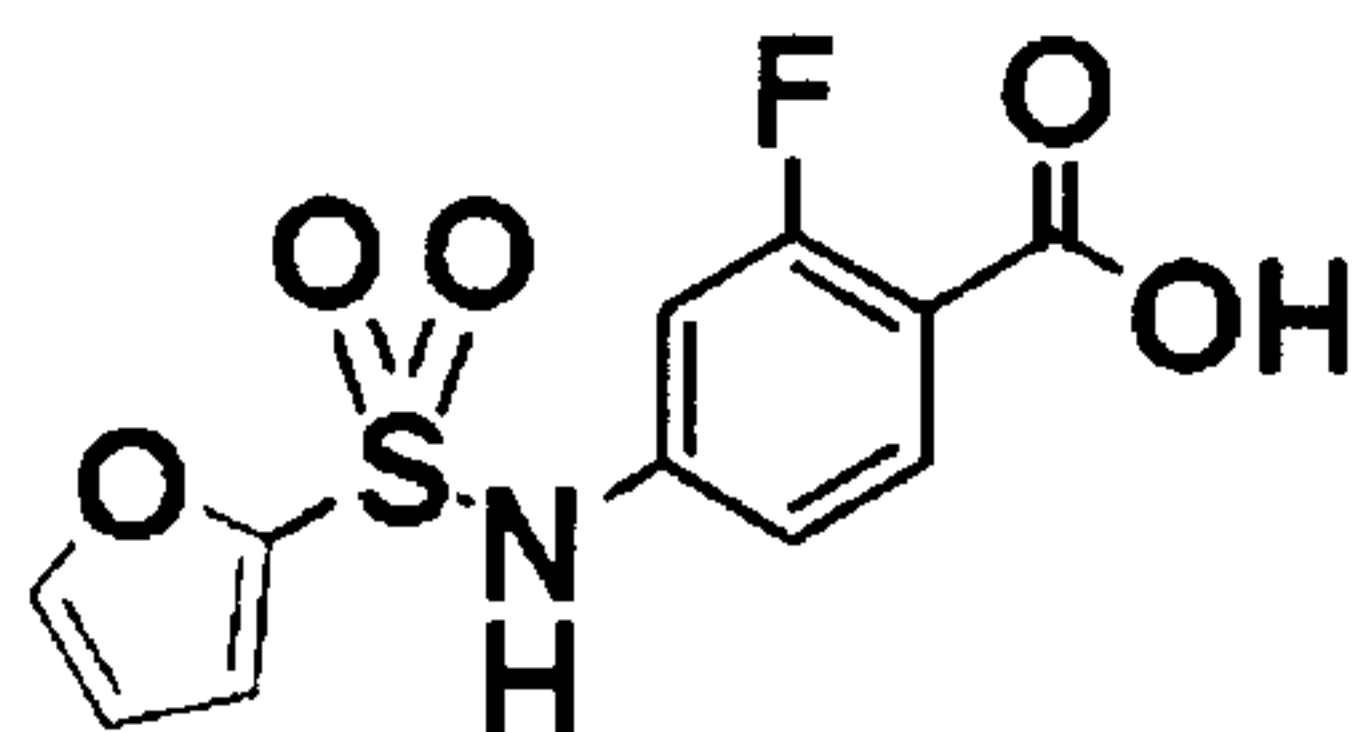
(Step 2) Methyl 2-Fluoro-4-[(2-furylsulfonyl)amino]benzoate

The title compound was obtained by subjecting furan-2-sulfonyl chloride and methyl 4-amino-2-fluorobenzoate to the same method as in (Step 4) of Example 104.

¹H NMR (400 MHz, DMSO-d₆): δ 11.48 (s, 1H), 8.00 (d, J = 0.8 Hz, 1H), 7.85-7.80 (m, 1H), 7.40-7.39 (m, 1H), 7.08-6.99 (m, 2H), 6.69-6.68 (m, 1H), 3.80 (s, 3H).

25 (Step 3) 2-Fluoro-4-[(2-furylsulfonyl)amino]benzoic Acid

(M-48)

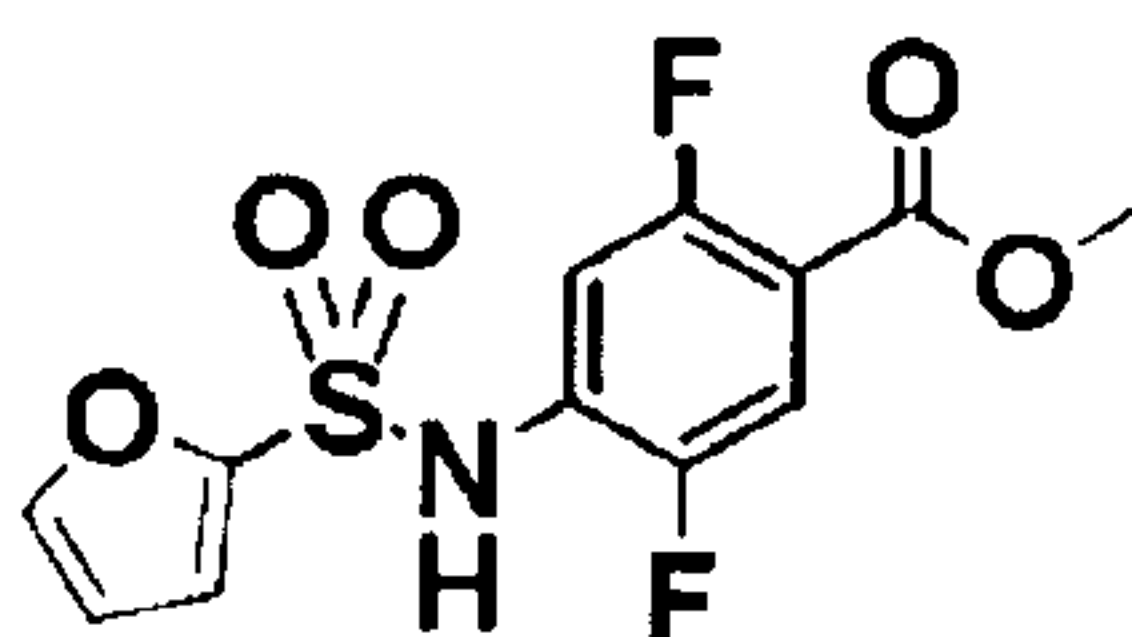


The title compound (M-48) was obtained by subjecting methyl 2-fluoro-4-[(2-furylsulfonyl)amino]benzoate to the same method as in (Step 5) of Example 104.

^1H NMR (400 MHz, CD_3OD): δ 7.78 (t, $J = 8.8$ Hz, 1H), 7.67 (d, $J = 0.8$ Hz, 1H), 7.15-7.14 (m, 1H), 6.99-6.95 (m, 2H), 6.51 (dd, $J = 3.6, 2.0$ Hz, 1H).

Example 107: Synthesis of M-49

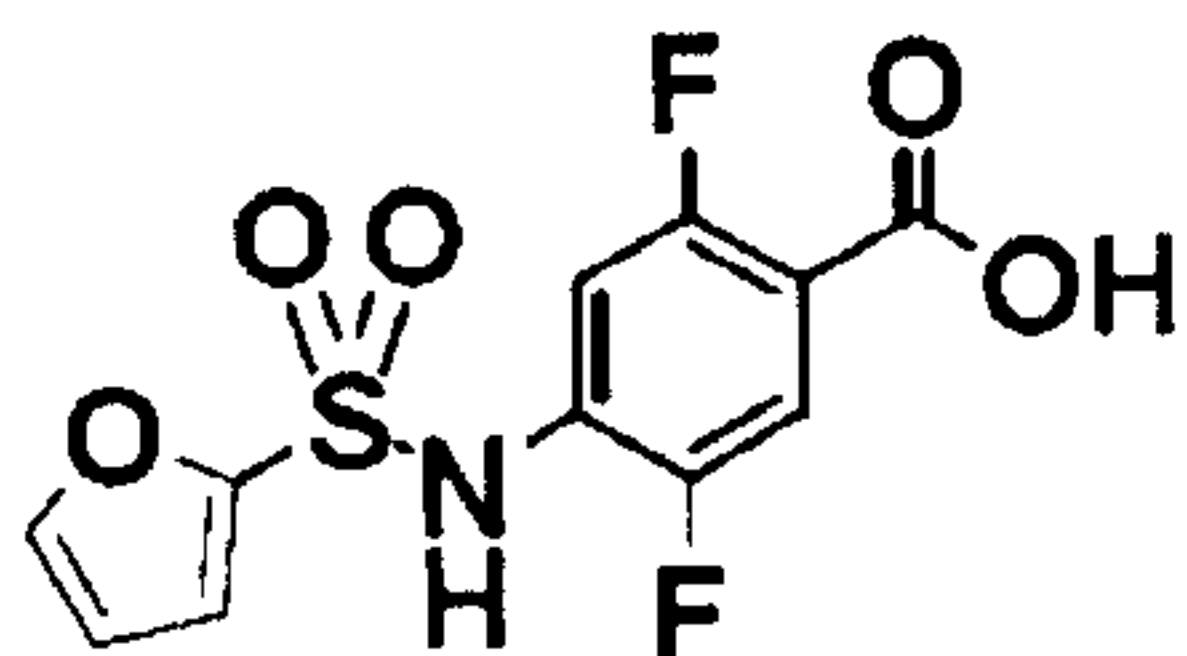
(Step 1) Methyl 2,5-Difluoro-4-[(2-furylsulfonyl)amino]benzoate



The title compound (800 mg, 34%) was obtained as a gray solid by subjecting methyl 4-amino-2,5-difluorobenzoate (1.40 g, 7.48 mmol) <see (Step 3) of Example 104> and furan-2-sulfonyl chloride (3.00 g, 18.0 mmol) <see (Step 1) of Example 106> to the same method as in (Step 4) of Example 104.

^1H NMR ($\text{DMSO}-d_6$, 400 MHz): δ 8.02 (s, 1H), 7.71-6.66 (m, 1H), 7.32-7.25 (m, 2H), 6.70-6.66 (m, 1H), 3.82 (s, 3H).; MS (ESI) m/z 318 ($\text{M}+\text{H}$) $^+$

(Step 2) 2,5-Difluoro-4-[(2-furylsulfonyl)amino]benzoic Acid (M-49)



The title compound (M-49) (600 mg, 79%) was obtained by
subjecting methyl

2,5-difluoro-4-[(2-furysulfonyl)amino]benzoate (800 mg,
5 2.52 mmol) to the same method as in (Step 5) of Example 104.

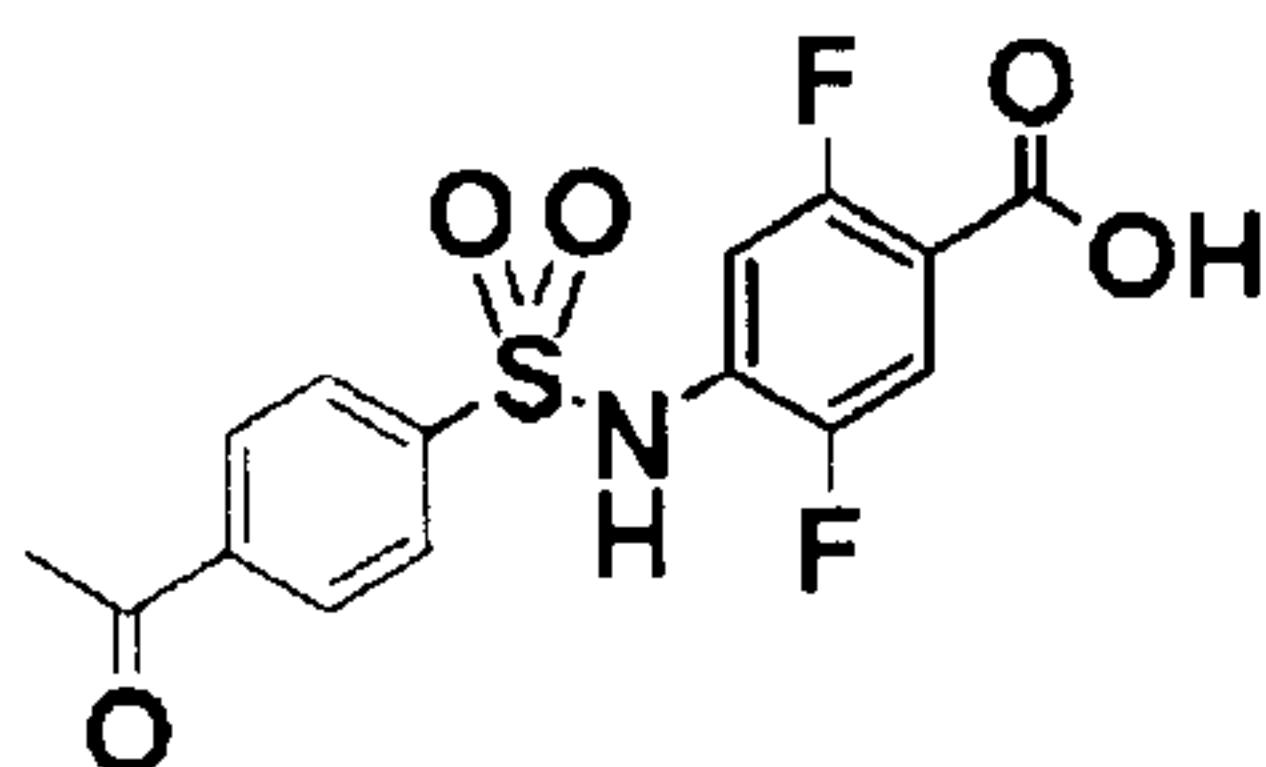
^1H NMR (CD_3OD , 400 MHz): δ 7.74 (dd, $J = 2.4, 1.6$ Hz, 1H), 7.61
(dd, $J = 14.4, 8.4$ Hz, 1H), 7.38 (dd, $J = 15.6, 8.4$ Hz, 1H),
7.18 (dd, $J = 4.8, 1.6$ Hz, 1H), 6.58 (dd, $J = 4.8, 2.4$ Hz, 1H). ;
MS (ESI) m/z 304 ($\text{M}+\text{H}$) $^+$

10 Example 108: Synthesis of M-50

(Step

1)

4-{[(4-Acetylphenyl)sulfonyl]amino}-2,5-difluorobenzoic
Acid (M-50)

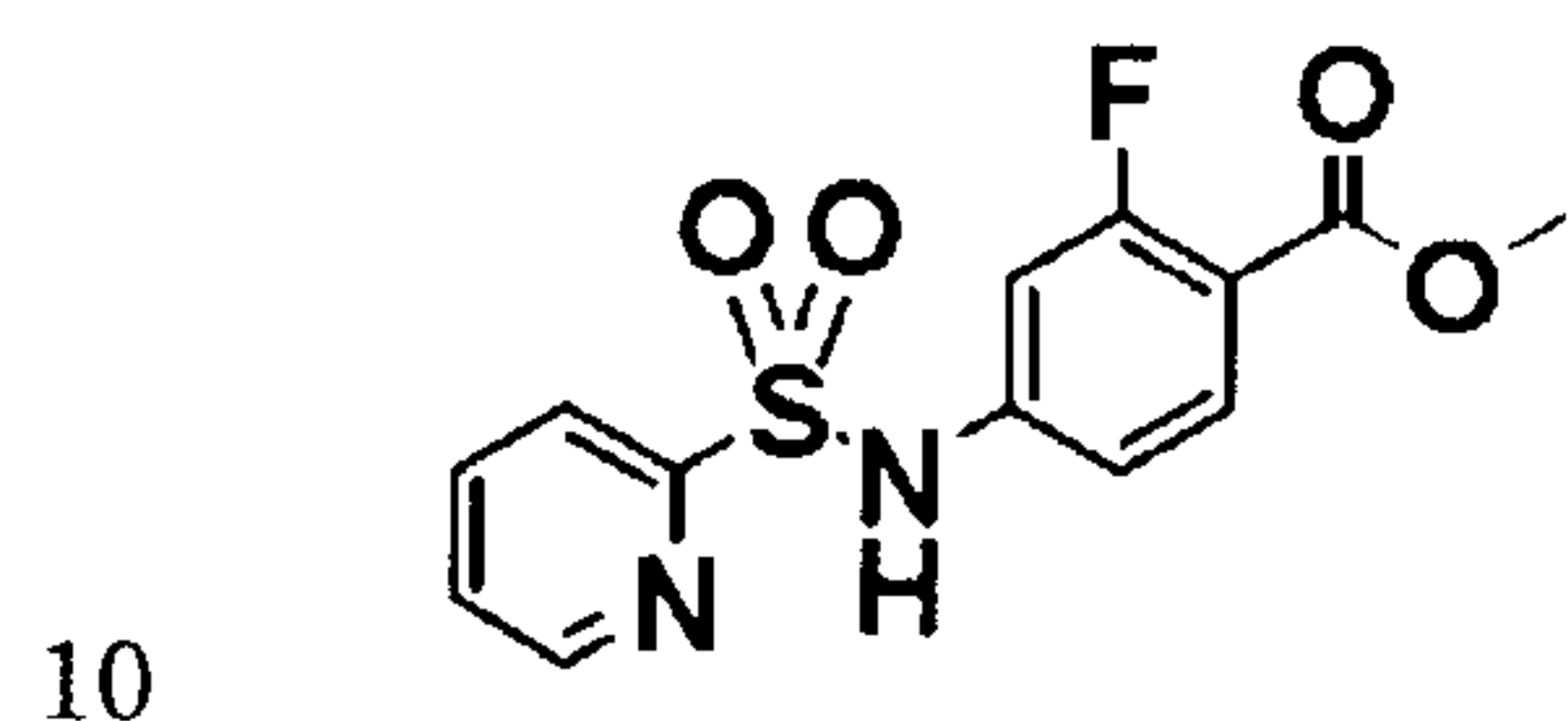


15 To 4-acetylbenzenesulfonyl chloride (700 mg, 3.21 mmol)
and methyl 4-amino-2,5-difluorobenzoate (600 mg, 3.21 mmol),
dichloromethane (10 ml) and pyridine (5.2 ml) were added,
followed by stirring at room temperature overnight. Water was
added to the reaction solution, followed by extraction with
20 ethyl acetate. The extraction liquid was washed with saturated
aqueous sodium chloride, and dried over anhydrous magnesium
sulfate. After concentration under reduced pressure, the
residue was suspended in 1,4-dioxane (5.0 ml), and a 2 N aqueous
lithium hydroxide solution (3.20 ml, 6.40 mmol) was added

dropwise thereto, followed by stirring at room temperature overnight. The mixture was neutralized with 2 N hydrochloric acid, and concentrated under reduced pressure. Then, the obtained residue was purified by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system), followed by freeze-drying, to obtain the title compound (390 mg, 34% over two steps).

Example 109: Synthesis of M-51

(Step 1) Methyl 2-Fluoro-4-[(pyridin-2-ylsulfonyl)amino]benzoate



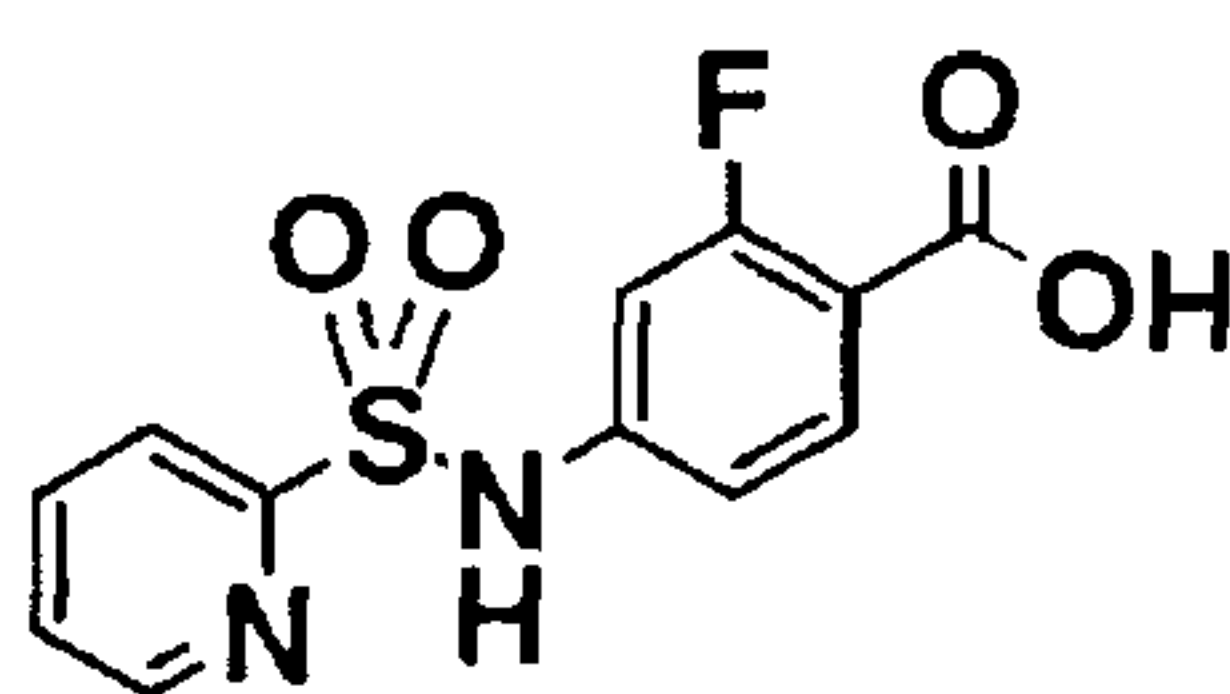
4-Pyridinethiol (16.7 g, 15.0 mmol) was dissolved in concentrated hydrochloric acid (110 ml) and water (30 ml). After the solution was cooled to 0°C, chlorine gas was injected for 1 hour. The reaction liquid was poured onto ice (80.0 g), and then neutralized slowly by adding sodium hydrogen carbonate. With the solution being cooled to 5 to 10°C, extraction was conducted with methylene chloride (150 ml×3), and the extraction liquids were combined and dried over anhydrous sodium sulfate. Then, with the combined liquid being cooled to 5 to 10°C, the solvent was removed under reduced pressure.

The obtained compound was dissolved in methylene chloride, and the solution was cooled to -10°C. Then, a methylene chloride solution (200 ml) of methyl 4-amino-2-fluorobenzoate (16.9 g, 100 mmol) and pyridine (10 ml) was added thereto, followed by stirring at room temperature for 2 hours. The reaction solution was washed with 0.1 N hydrochloric acid (200 ml×2). Then, the organic layers were combined and dried over

anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1 to 1:1) to obtain the title compound (12.4 g, 40%).

5 MS (ESI) m/z 311 ($M+H$)⁺

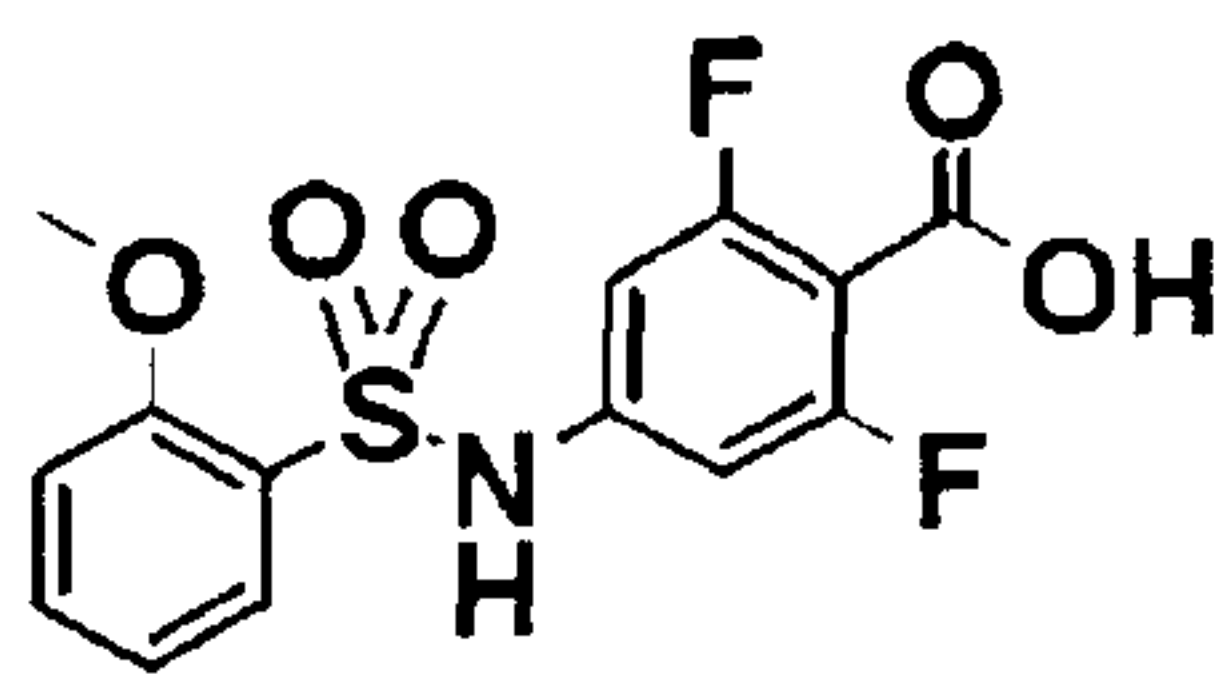
(Step 2) 2-Fluoro-4-[(pyridin-2-ylsulfonyl)amino]benzoic Acid (M-51)



The title compound (M-51) (10.5 g, 92%) was obtained by
 10 subjecting methyl
 2-fluoro-4-[(pyridin-2-ylsulfonyl)amino]benzoate (12.0 g, 38.7 mmol) to the same method as in (Step 5) of Example 104.
¹H NMR (400 MHz, CD₃OD): δ 8.66 (d, J = 4.4 Hz, 1H), 8.08-8.01 (m, 2H), 7.79 (t, J = 8.4 Hz, 1H), 7.61-7.57 (m, 1H), 7.10-7.02
 15 (m, 2H).; MS (ESI) m/z 297 ($M+H$)⁺

Example 110: Synthesis of M-52

(Step 1)
2,6-Difluoro-4-[(2-methoxyphenyl)sulfonyl]amino}benzoic Acid (M-52)



20

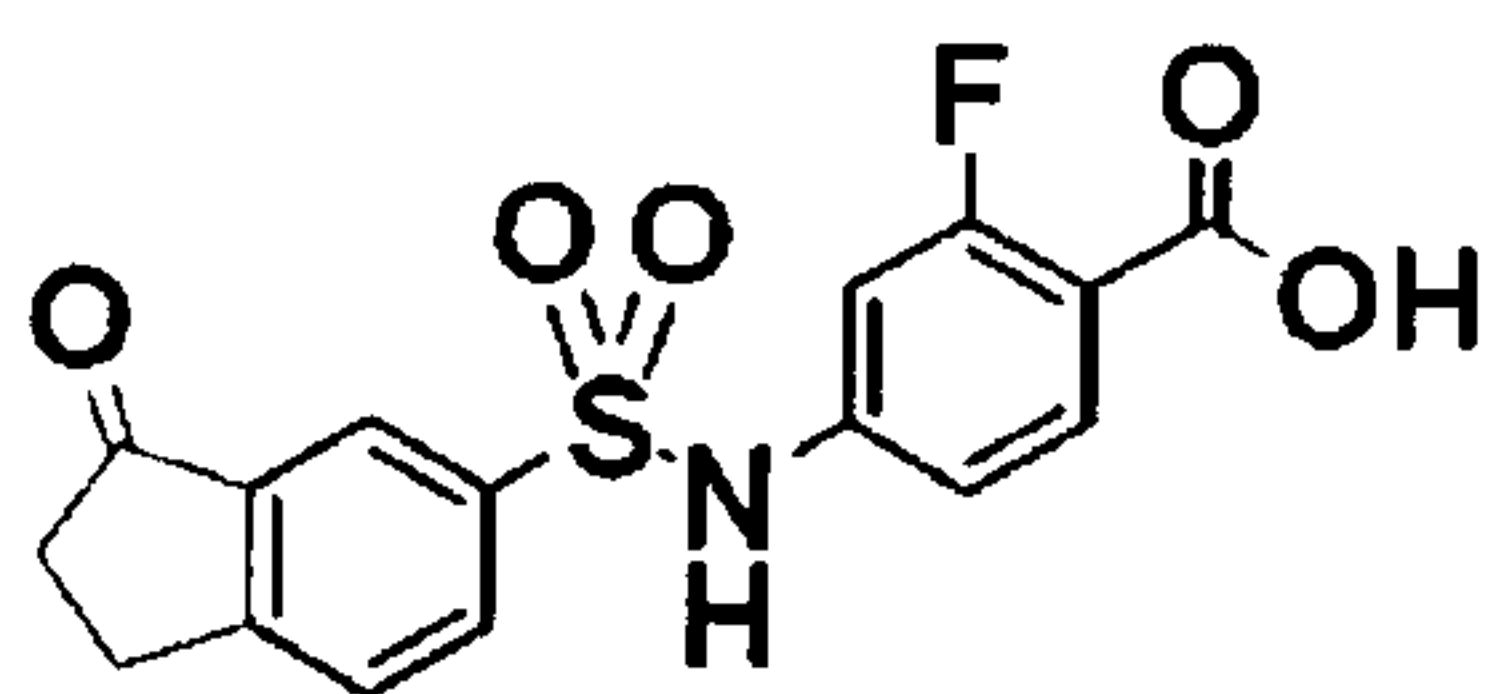
To 5-bromo-2-methoxy-benzenesulfonyl chloride (500 mg, 1.76 mmol) and methyl 4-amino-2,6-difluorobenzoate (395 mg, 2.11 mmol), dichloromethane (12 ml) and pyridine (427 μ l, 5.28 mmol) were added, followed by stirring at room temperature

overnight. The reaction solution was concentrated under reduced pressure, diluted with dichloromethane, washed with 2 N hydrochloric acid, water, and saturated aqueous sodium chloride, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The obtained product was dissolved in ethanol (5.0 ml) and DMF (5.0 ml), and 10% Pd/C (50 mg) was added thereto, followed by stirring overnight in a hydrogen atmosphere at 3 atm. After filtration through Celite, the filtrate was concentrated under reduced pressure, and tetrahydrofuran (5.0 ml) and water (1.0 ml) were added thereto. Then, a 2 N aqueous sodium hydroxide solution (2.0 ml) was added dropwise thereto, followed by stirring at room temperature for 4 hours. The mixture was neutralized with 2 N hydrochloric acid, and concentrated under reduced pressure. Then, the obtained residue was purified by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system), followed by freeze-drying, to obtain the title compound.

MS (ESI) m/z 344 (M+H)⁺

Example 111: Synthesis of M-53

(Step 1)
2-Fluoro-4-{[(3-oxo-2,3-dihydro-1H-inden-5-yl)sulfonyl]amino}benzoic Acid (M-53)

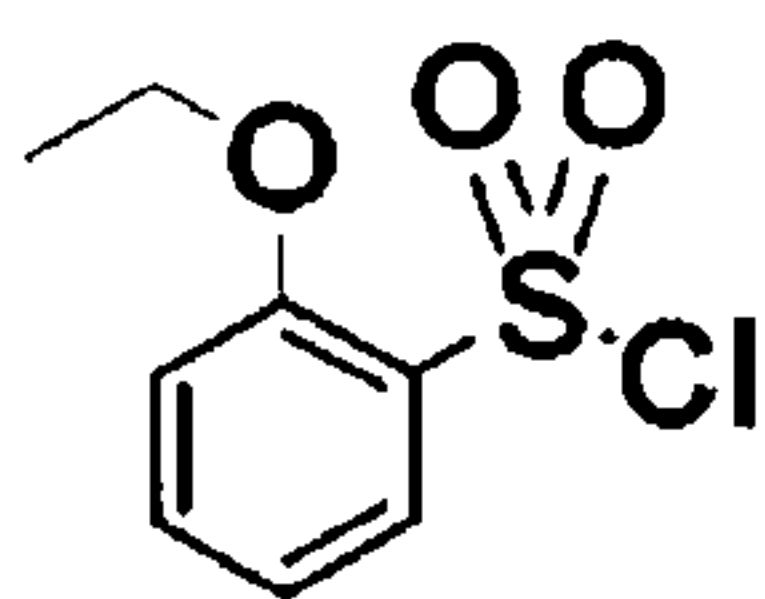


To 3-oxo-indane-5-sulfonyl chloride (500 mg, 2.17 mmol) and 4-amino-2-fluorobenzenecarboxylic acid (336 mg, 2.17 mmol), dichloromethane (10 ml) and pyridine (5.2 ml) were added, followed by stirring at room temperature for 12 hours. After

the mixture was concentrated under reduced pressure, the obtained residue was purified by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system), followed by freeze-drying, to obtain the title compound (412 mg, 54%).

5 Example 112: Synthesis of M-54

(Step 1) 2-Ethoxybenzenesulfonyl Chloride



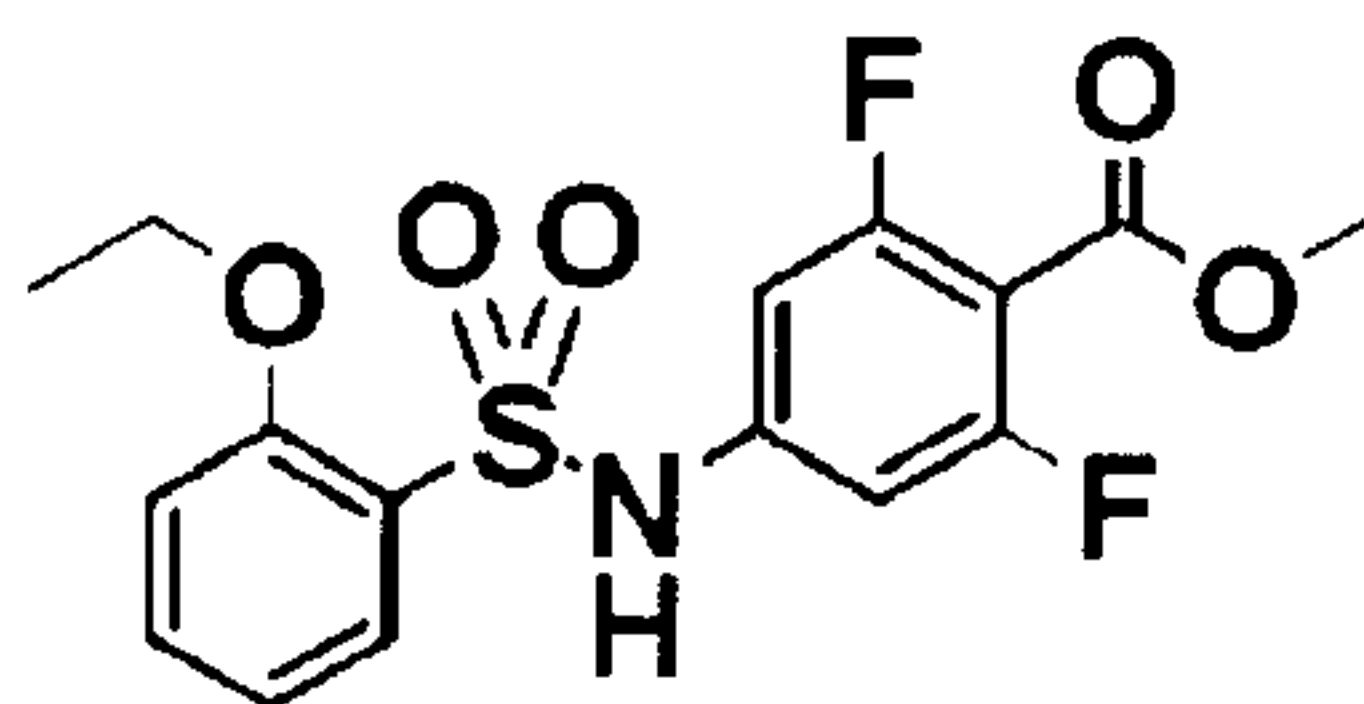
Tetramethylethylenediamine (15.2 ml, 101 mmol) was dissolved in diethyl ether (200 ml). After the solution was cooled to 0°C, n-butyllithium (2.5 mol/l, 40.0 ml, 100 mmol) was added thereto, followed by stirring for 5 minutes. To the reaction liquid, ethoxybenzene (11.0 ml, 87.1 mmol) was added, followed by stirring for further 1 hour. The reaction liquid was cooled to -78°C, and sulfur dioxide was added with a syringe over 30 minutes. After that, the temperature was raised to room temperature with stirring over 1 hour. To the reaction liquid, thionyl chloride (8.80 ml, 110 mmol) was added, followed by stirring at room temperature for 6 hours. The reaction liquid was diluted with diethyl ether, and washed with water and saturated aqueous sodium chloride. Then, the organic layer was dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain the title compound (8.1 g, 42%).

(Step

2)

Methyl

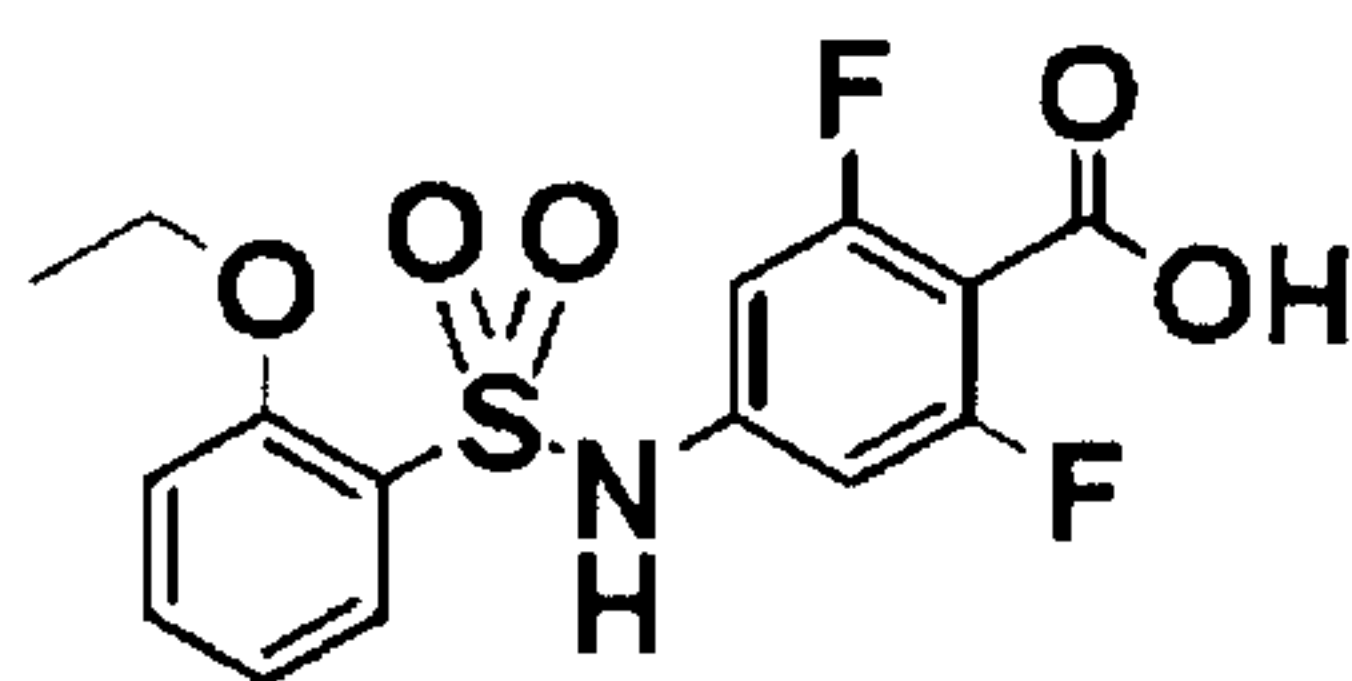
25 4 - { [(2-Ethoxyphenyl) sulfonyl] amino } - 2,6-difluorobenzoate



The title compound (1.4 g, 71%) was obtained by subjecting methyl 4-amino-2,6-difluorobenzoate (1.00 g, 5.34 mmol) and 2-ethoxybenzenesulfonyl chloride (3.00 g, 13.6 mmol) to the same method as in (Step 4) of Example 104.

¹H NMR (DMSO-d₆, 400 MHz): δ 10.97 (s, 1H), 7.93-7.91 (m, 1H), 7.64-7.60 (m, 1H), 7.22-7.20 (m, 1H), 7.13-7.09 (m, 1H), 6.81-6.78 (m, 2H), 4.21-4.16 (m, 2H), 3.79 (s, 3H), 1.27-1.24 (m, 3H).

(Step 3)
4-{[(2-Ethoxyphenyl)sulfonyl]amino}-2,6-difluorobenzoic Acid (M-54)

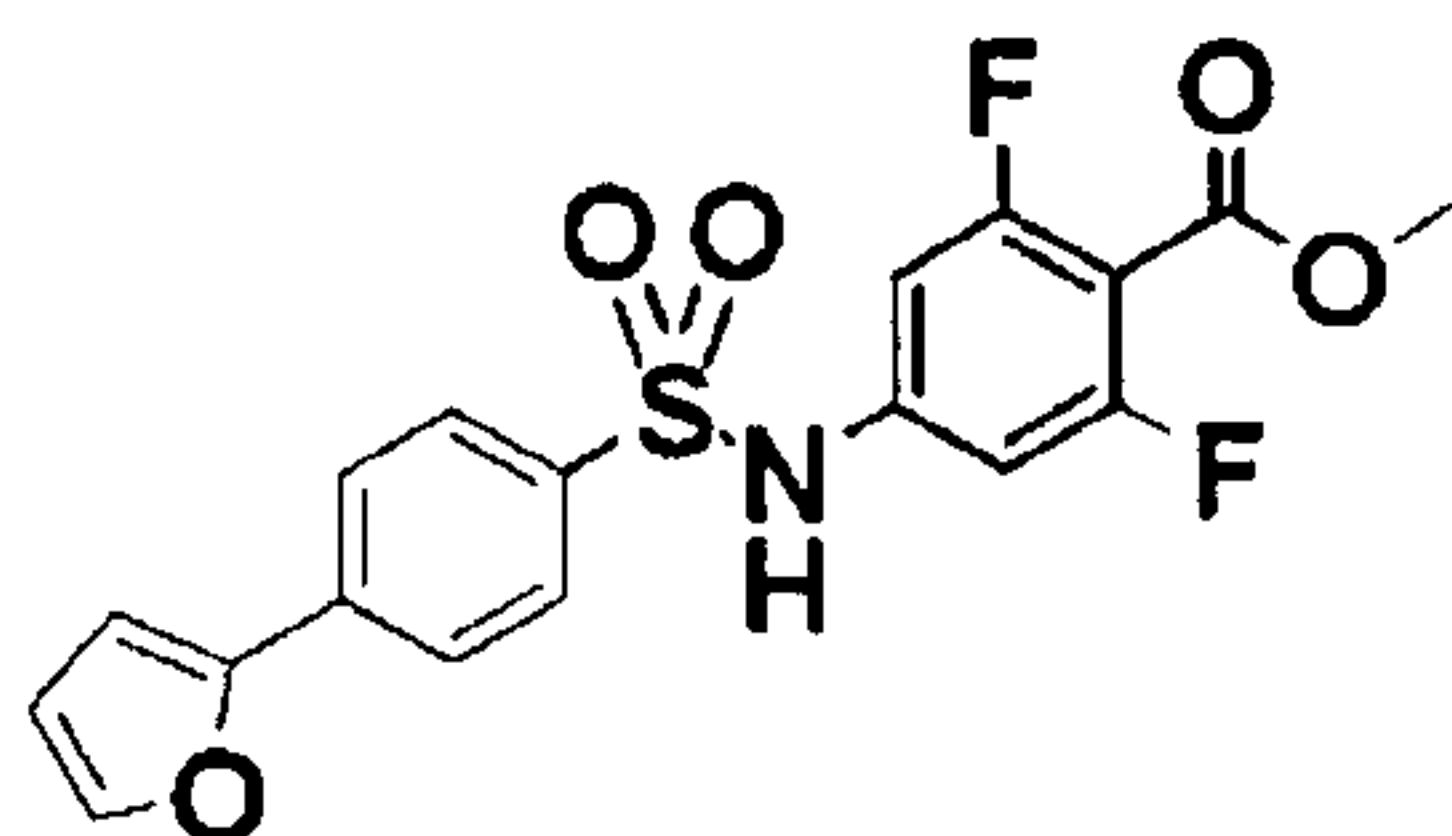


The title compound (M-54) (1.05 g, 78%) was obtained as a yellow solid by subjecting methyl 4-{[(2-ethoxyphenyl)sulfonyl]amino}-2,6-difluorobenzoate (1.40 g, 3.77 mmol) to the same method as in (Step 5) of Example 104.

¹H NMR (CD₃OD, 400 MHz): δ 7.86 (dd, J = 8.0, 1.6 Hz, 1H), 7.50-7.46 (m, 1H), 7.04 (d, J = 8.4 Hz, 1H), 7.00-6.96 (m, 1H), 6.66 (d, J = 10.4 Hz, 2H), 4.13 (q, J = 6.8 Hz, 2H), 1.31 (t, J = 6.8 Hz, 3H).; MS (ESI) m/z 356 (M-H)

Example 113: Synthesis of M-55

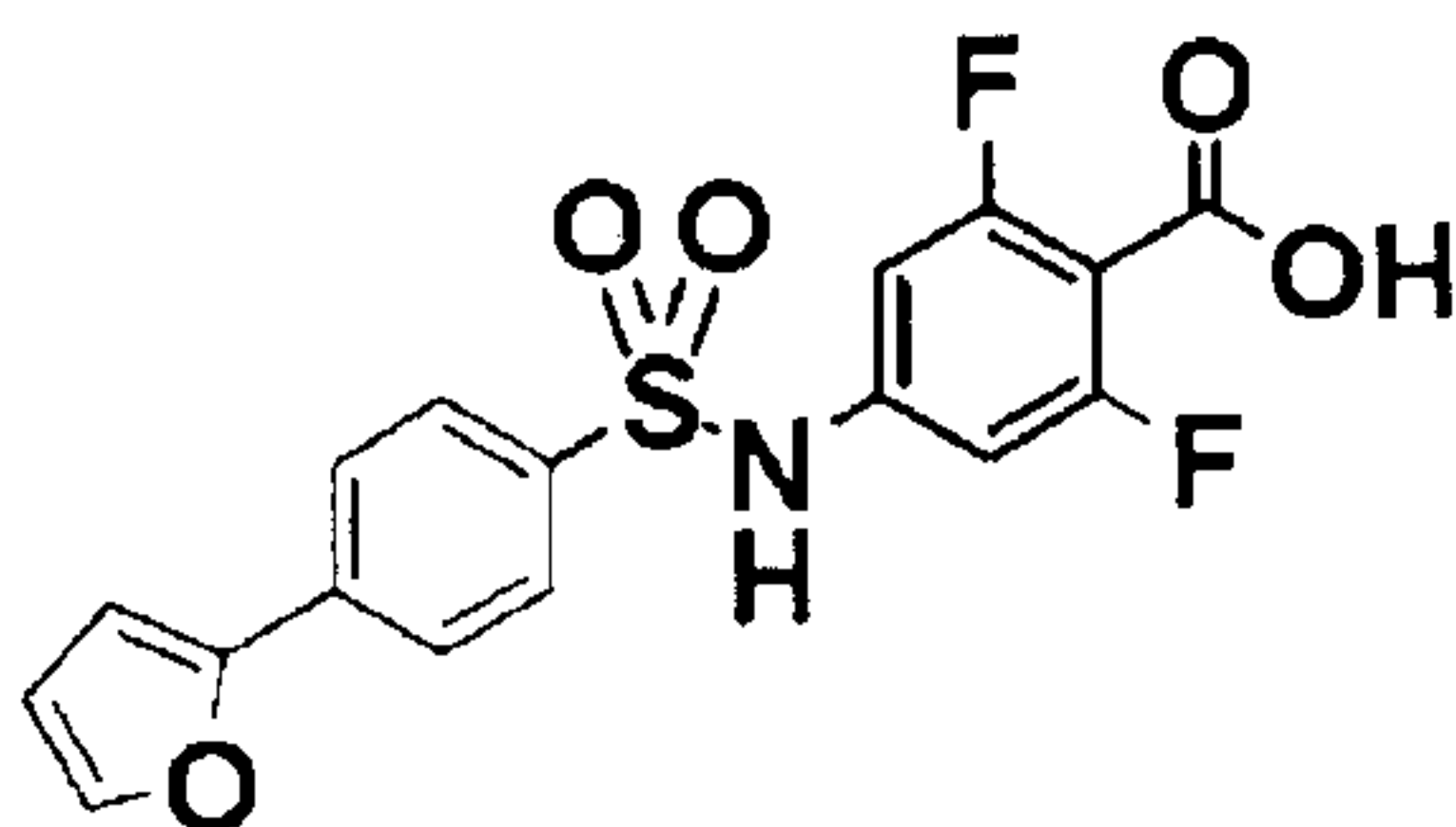
(Step 1) Methyl

2,6-Difluoro-4-[[4-(2-furyl)phenyl]sulfonylamino]benzoate

The title compound (1.00 g, 77%) was obtained as a brown solid by subjecting methyl 2,6-difluoro-4-[(4-iodophenyl)sulfonylamino]benzoate <see (Step 2) of Example 8> (1.50 g, 3.31 mmol) and 2-furylboronic acid (556 mg, 4.97 mmol) to the same method as in Example 20. ¹H NMR (400 MHz, DMSO-d₆): δ 11.3(s, 1H), 7.90 (s, 4H), 7.85 (d, J = 1.2 Hz, 1H), 7.18 (d, J = 3.2 Hz, 1H), 6.85 (d, J = 10.0 Hz, 2H), 6.68-6.65 (m, 1H), 3.55 (s, 3H).

(Step 2)

2,6-Difluoro-4-[[4-(2-furyl)phenyl]sulfonylamino]benzoic Acid (M-55)



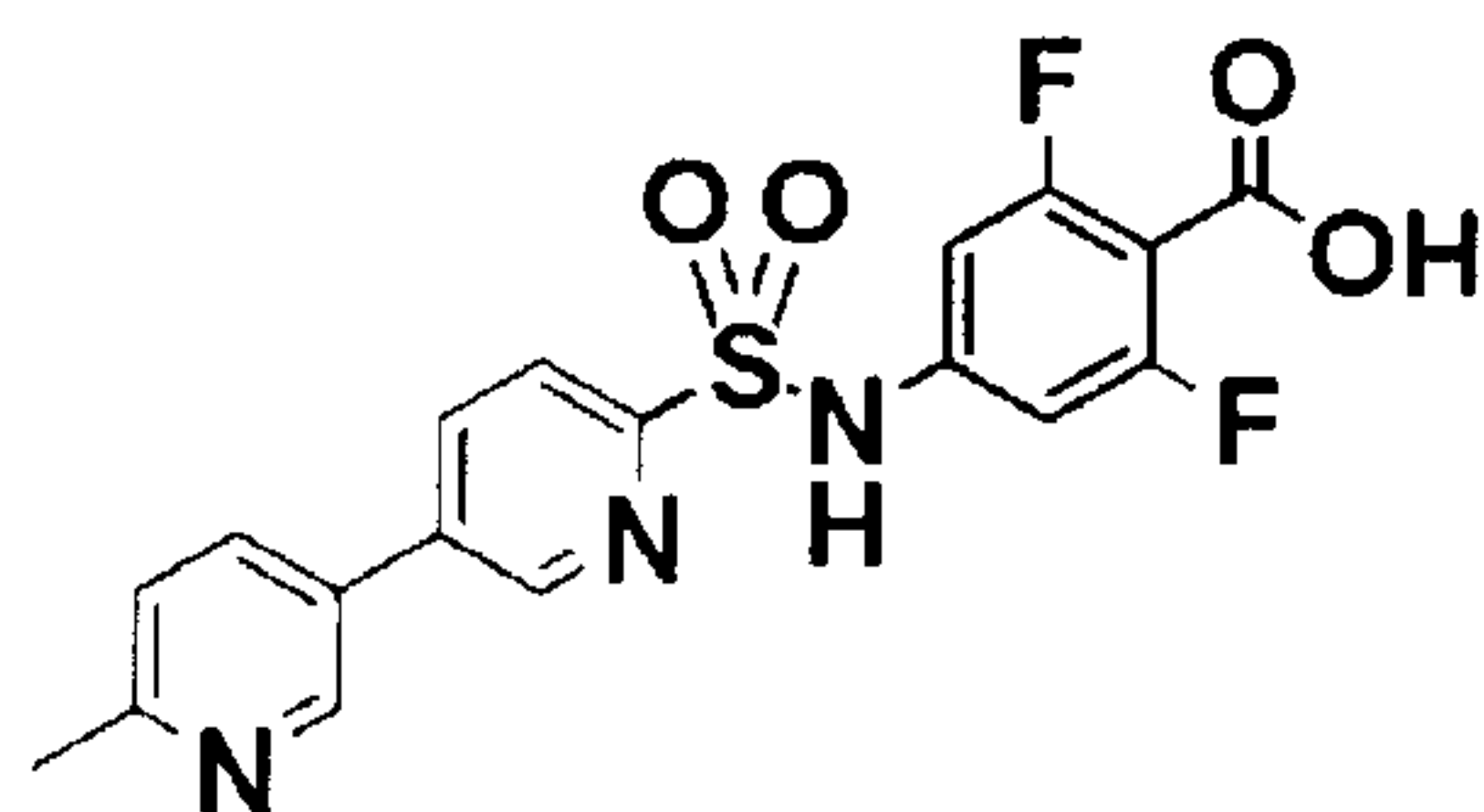
The title compound (839 mg, 88%) was obtained as a white solid by subjecting methyl 2,6-difluoro-4-[[4-(2-furyl)phenyl]sulfonylamino]benzoate <see (Step 1)> (1.00 g, 2.50 mmol) to the same method as in (Step 5) of Example 104.

¹H NMR (400 MHz, CD₃OD): δ 7.84-7.78 (m, 4H), 7.57 (d, J = 1.6 Hz, 1H), 6.92 (d, J = 3.6 Hz, 1H), 6.76 (d, J = 9.6 Hz, 2H), 6.51-6.49 (m, 1H).; MS (ESI) m/z 378 (M-1)

Example 114: Synthesis of M-56

(Step 1)

2,6-Difluoro-4-{[(6'-methyl-3,3'-bipyridin-6-yl)sulfonyl]amino}benzoic Acid (M-56)

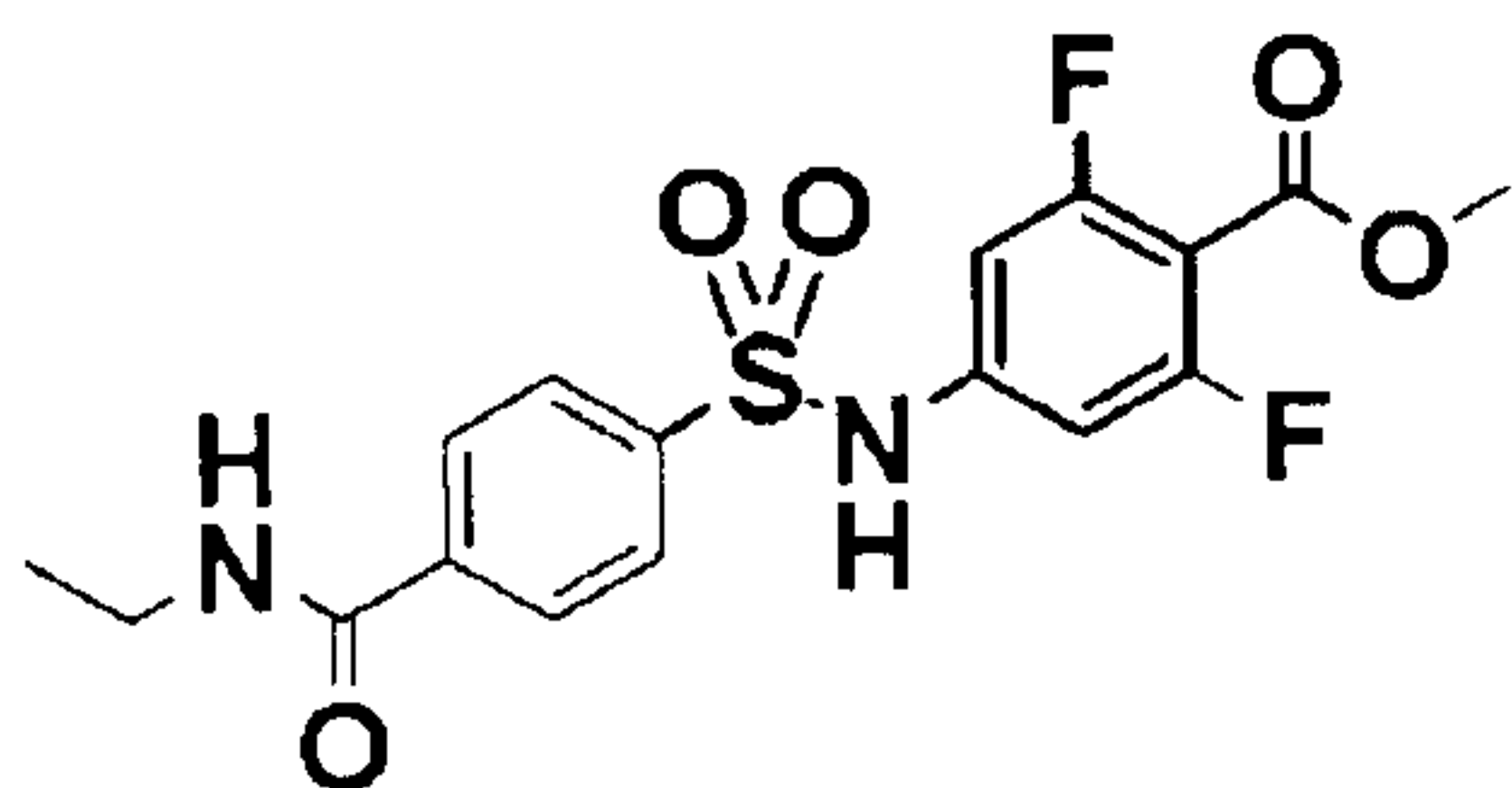


Methyl

5 2,6-difluoro-4-{[(5-iodopyridin-2-yl)sulfonyl]amino}benzoate (52 mg, 0.11 mmol) <see (Step 3) of Example 120>, 2-methyl-pyridine-5-boronic acid (34 mg, 0.22 mmol), Pd(dppf)Cl₂ (8 mg, 0.011 mmol), 1,4-dioxane (4.0 ml), and a 1 N aqueous sodium hydrogen carbonate solution (1.0 ml) were added
10 sequentially. The reaction solution was degassed, and stirred at 80°C overnight. The reaction solution was concentrated under reduced pressure, and tetrahydrofuran (2.0 ml) and water (0.50 ml) were added thereto. Then, a 2 N aqueous sodium hydroxide solution (0.50 ml) was added dropwise thereto,
15 followed by stirring at 50°C. The mixture was neutralized with 2 N hydrochloric acid, and concentrated under reduced pressure. Then, the obtained residue was purified by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system), followed by freeze-drying, to obtain a TFA salt (52 mg, 91% over two steps)
20 of the title compound.

Example 115: Synthesis of M-57

(Step 1) Methyl 4-[(4-[(Ethylamino)carbonyl]phenyl)sulfonyl]amino-2,6-difluorobenzoate



To

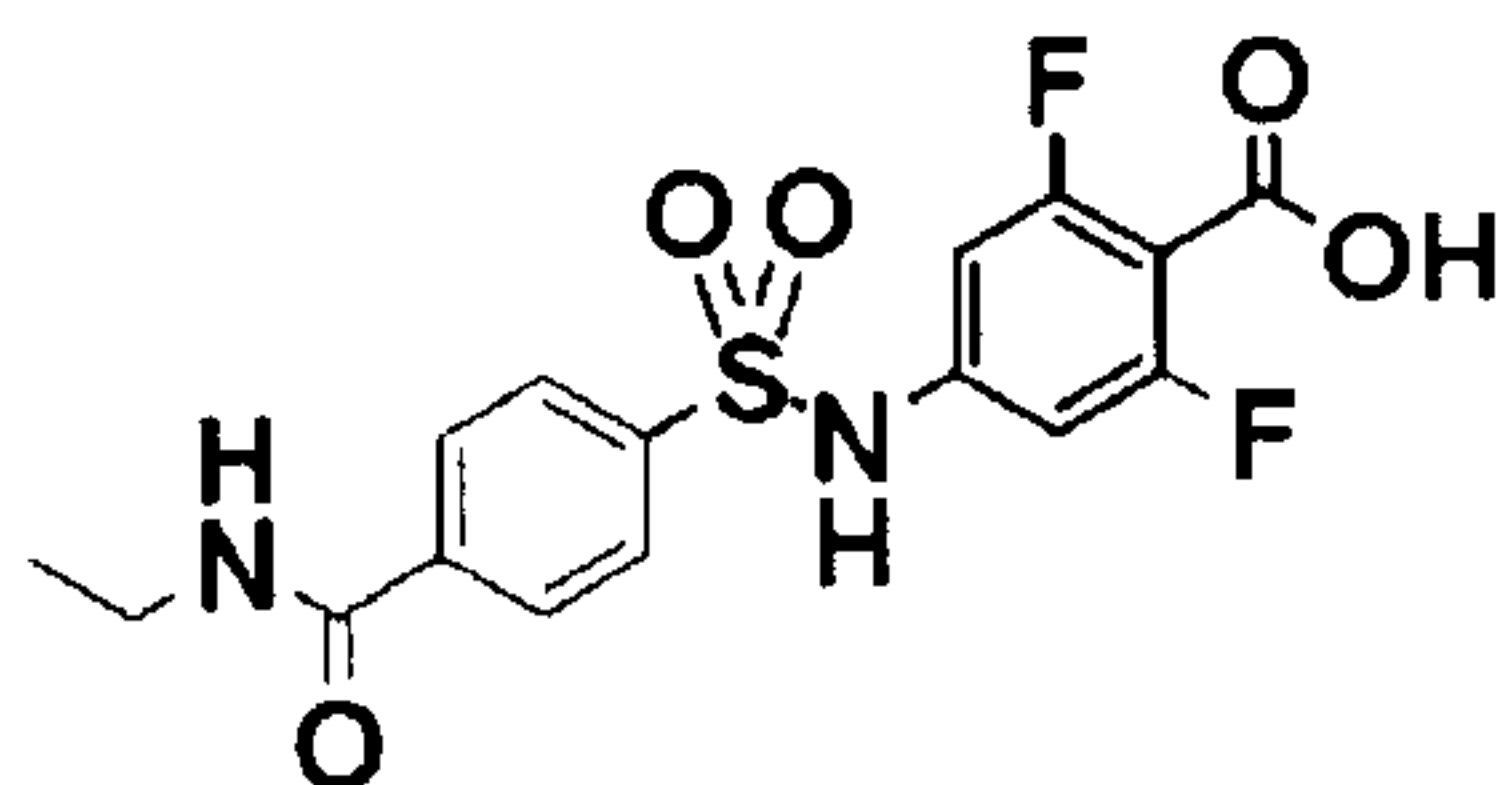
4-([3,5-difluoro-4-(methoxycarbonyl)phenyl]amino)sulfonyl) benzoic acid (1.5 g, 4.0 mmol) <see (Step 1) of Example 11>, 5 thionyl chloride (40 ml) was added, followed by stirring at 75°C for 4 hours. The reaction liquid was concentrated under reduced pressure, and the concentrate was dissolved in methylene chloride (30 ml). Ethylamine hydrochloride (648 mg, 8.00 mmol) and triethylamine (8.00 ml) were added thereto, followed by 10 stirring at room temperature for 30 minutes. The solvent was removed under reduced pressure, and the obtained residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate=2:1 to 1:1) to obtain the title compound (0.85 g, 53%).

15 ^1H NMR (CD_3OD , 400 MHz): δ 7.97-7.92 (m, 4H), 6.82 (d, J = 9.6 Hz, 2H), 3.85 (s, 1H), 3.42-3.36 (m, 2H), 1.23-1.18 (m, 3H).; MS (ESI) m/z 399 ($\text{M}+\text{H}$) $^+$

(Step

2)

20 4-[(4-[(Ethylamino)carbonyl]phenyl)sulfonyl]amino]-2,6-difluorobenzoic Acid (M-57)



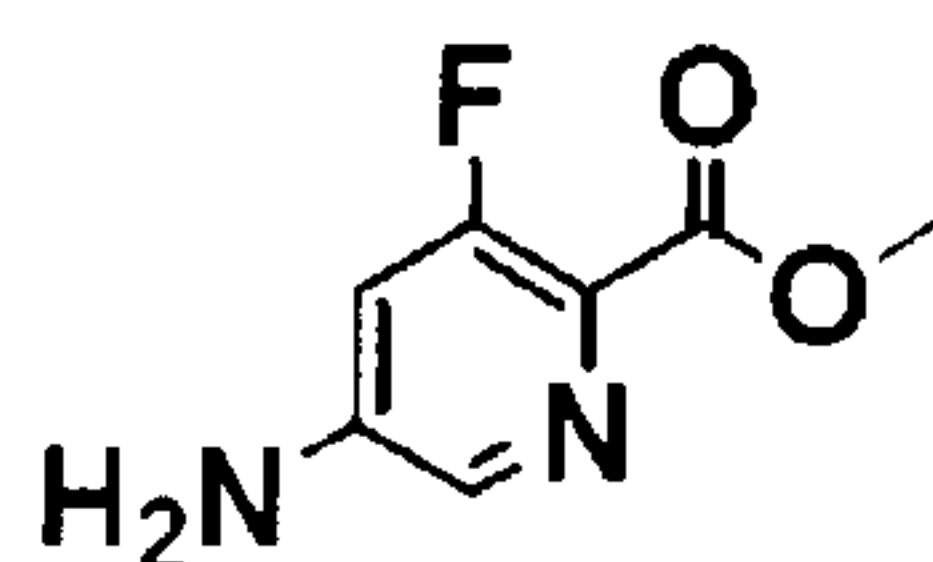
The title compound (M-57) (1.12 g, 90%) was obtained by subjecting methyl

4-[(4-[(ethylamino)carbonyl]phenyl)sulfonyl]amino]-2,6-difluorobenzoate (1.30 g, 3.30 mmol) to the same method as in (Step 5) of Example 104.

¹H NMR (CD₃OD, 400 MHz): δ 7.98-7.92 (m, 4H), 6.80 (d, J = 14.8 Hz, 2H), 3.43-3.40 (m, 2H), 1.23-1.14 (m, 3H).; MS (ESI) m/z 385 (M+H)⁺

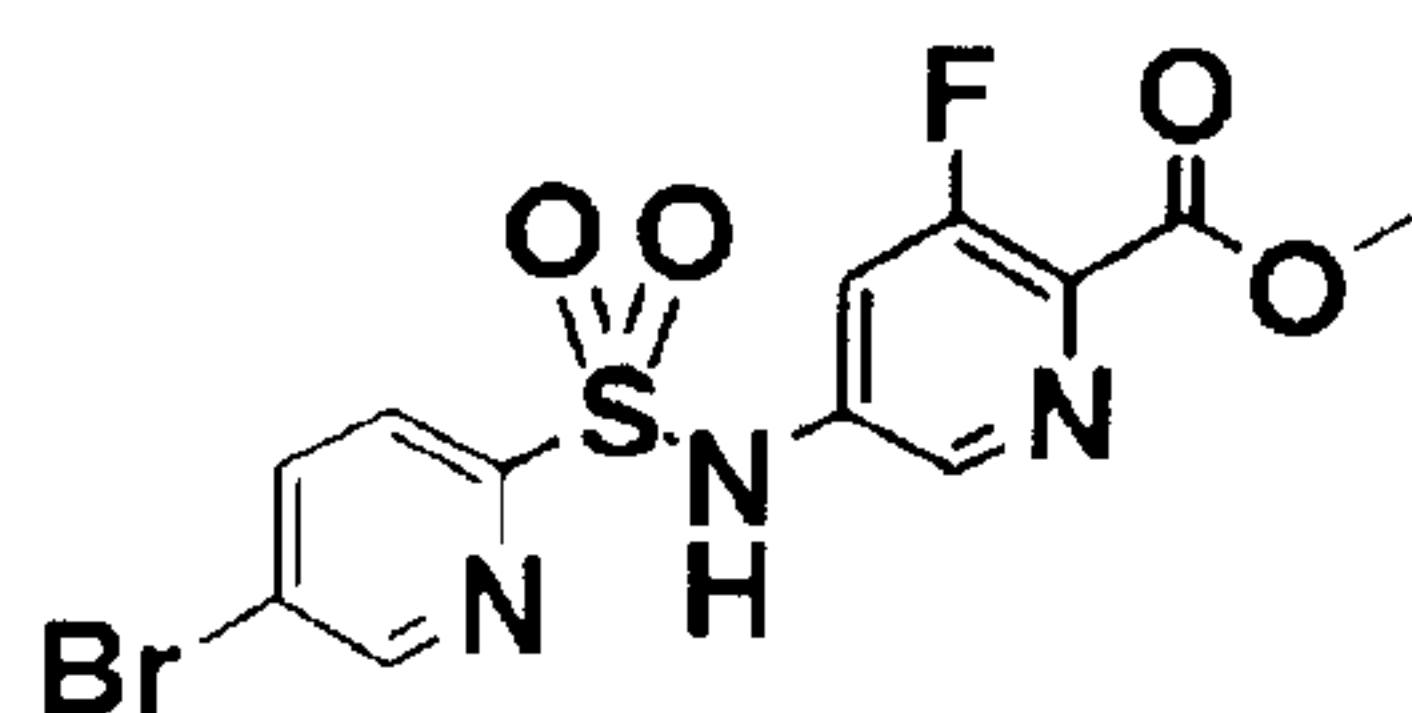
Example 116: Synthesis of M-58

(Step 1) Methyl 5-Amino-3-fluoropyridine-2-carboxylate



The title compound (19.0 g, 49% over three steps) was obtained by subjecting 5-bromo-3-fluoropyridine-2-benzoic acid (50.0 g, 227 mmol) to the same methods as in (Step 1), (Step 2), and (Step 3) of Example 104.

(Step 2) Methyl 5-{[(5-Bromopyridin-2-yl)sulfonyl]amino}-3-fluoropyridine-2-carboxylate



Methyl 5-amino-3-fluoropyridine-2-carboxylate (5.30 g, 31.2 mmol) and 5-bromopyridine-2-sulfonyl chloride (12.0 g, 46.8 mmol) <see (Step 1) of Example 7> were dissolved in methylene chloride (350 ml), and pyridine (20 ml) was added thereto, followed by stirring at room temperature for 12 hours. The reaction liquid was concentrated under reduced pressure, and the pH was adjusted to 4.0 by adding 4 N hydrochloric acid, followed by stirring for 10 minutes. Further, methylene

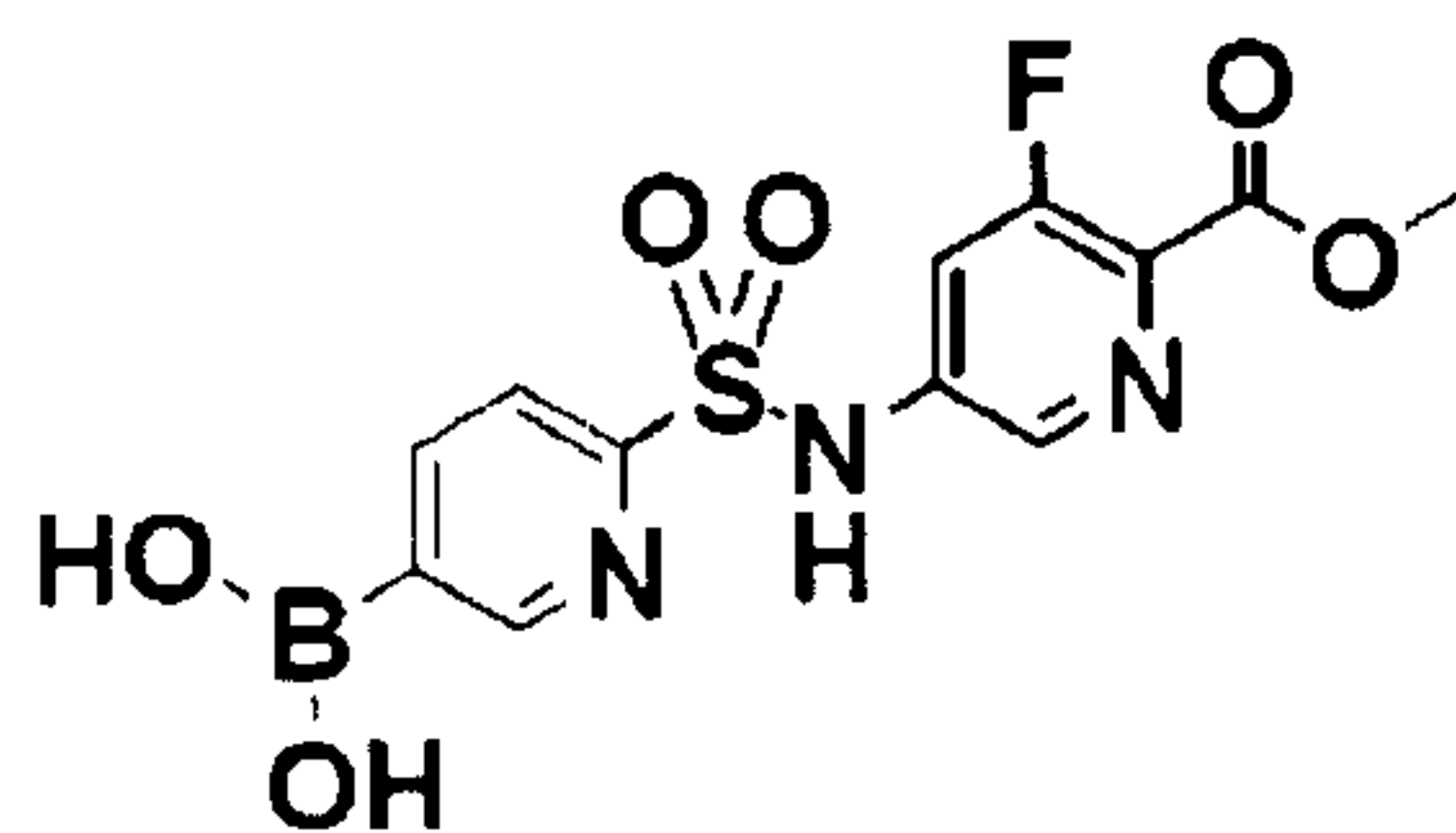
chloride (100 ml) was added thereto, followed by stirring at room temperature for 1 hour. The obtained solid was filtered and dried to obtain the title compound (6.0 g, 49%) as a white solid.

5 MS (ESI) m/z 390 and 392 (M+H)⁺

(Step

3)

[6-({[5-Fluoro-6-(methoxycarbonyl)pyridin-3-yl]amino}sulfonyl)pyridin-3-yl]boronic Acid



10 Methyl

5-{{[(5-bromopyridin-2-yl)sulfonyl]amino}-3-fluoropyridine-2-carboxylate (6.00 g, 15.4 mmol) and bis(pinacolato)diborane (4.70 g, 18.5 mmol) were dissolved in N,N'-dimethylformamide (150 ml), and

15 [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (338 mg, 0.460 mmol) and potassium acetate (4.50 g, 46.3 mmol) were added thereto, followed by stirring at 85°C for 12 hours in the presence of nitrogen gas. The reaction liquid was cooled to room temperature, and diluted with water, followed by
20 extraction with methylene chloride four times. The organic layers were combined, concentrated under reduced pressure, and then diluted with water. The obtained solid was filtered and dried to obtain the title compound (4.8 g, 88%).

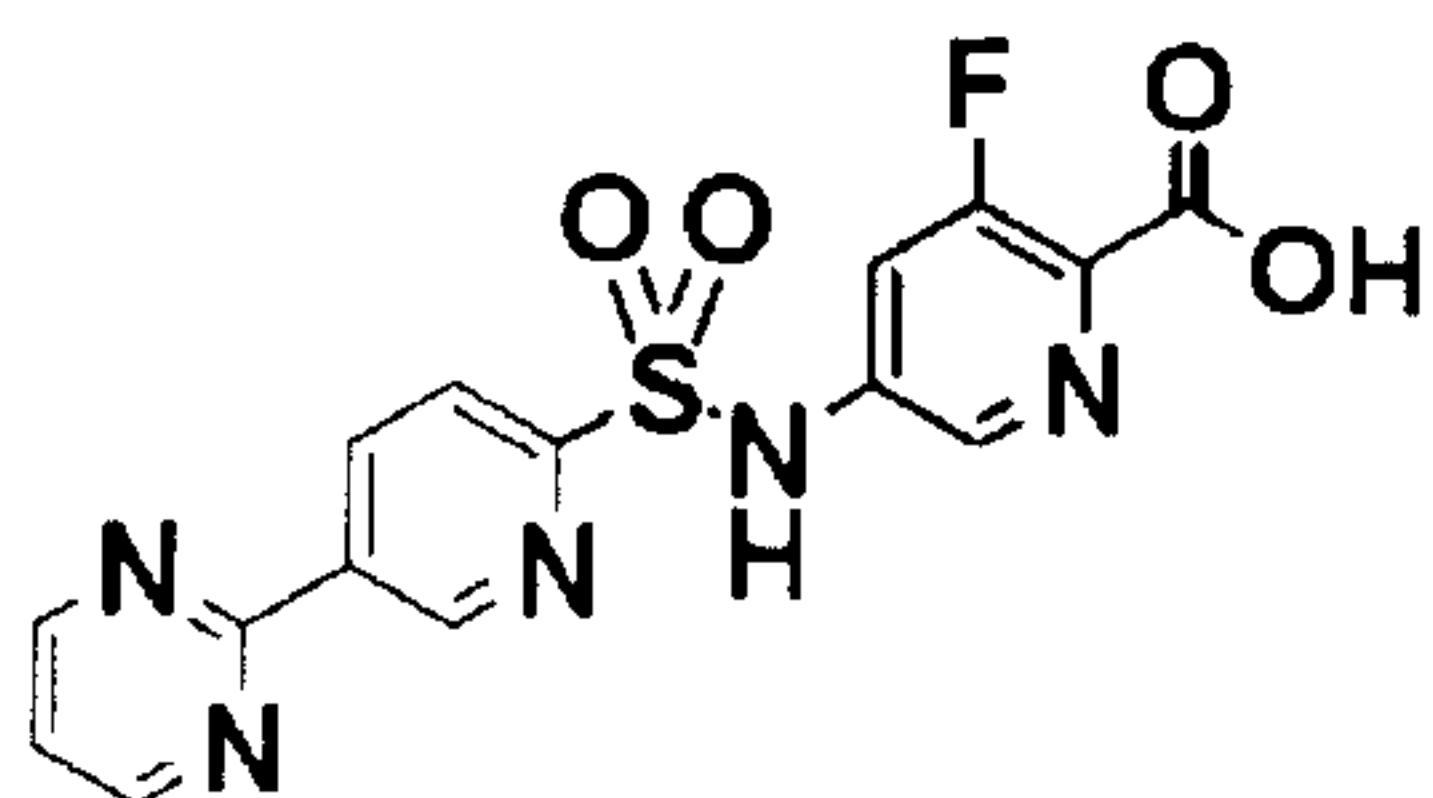
¹H NMR (CD₃OD, 400 MHz): δ 8.83 (s, 1H), 8.28-8.26 (m, 2H), 8.03 (d, J = 8.0 Hz, 1H), 7.72 (d, J = 12.0 Hz, 1H), 3.91 (s, 3H).;

25 MS (ESI) m/z 356 (M+H)⁺

(Step

4)

3-Fluoro-5-{[(5-pyrimidin-2-ylpyridin-2-yl)sulfonyl]amino}pyridine-2-carboxylic Acid (M-58)



[6-({[5-Fluoro-6-(methoxycarbonyl)pyridin-3-yl]amino} sulfonyl)pyridin-3-yl]boronic acid (4.80 g, 13.5 mmol) and 2-bromopyrimidine (4.30 g, 27.0 mmol) were dissolved in N,N'-dimethylformamide (150 ml) and water (60 ml), and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (989 mg, 1.35 mmol) and sodium carbonate (4.30 g, 40.6 mmol) were added thereto, followed by stirring at 95°C for 12 hours in the presence of nitrogen gas. The reaction liquid was cooled to room temperature, and diluted with water. Then, the pH was adjusted to 5.0 by adding 6 N hydrochloric acid. The precipitated white solid was filtered and dried to obtain a hydrochloride (720 mg, 13%) of the title compound (M-58).

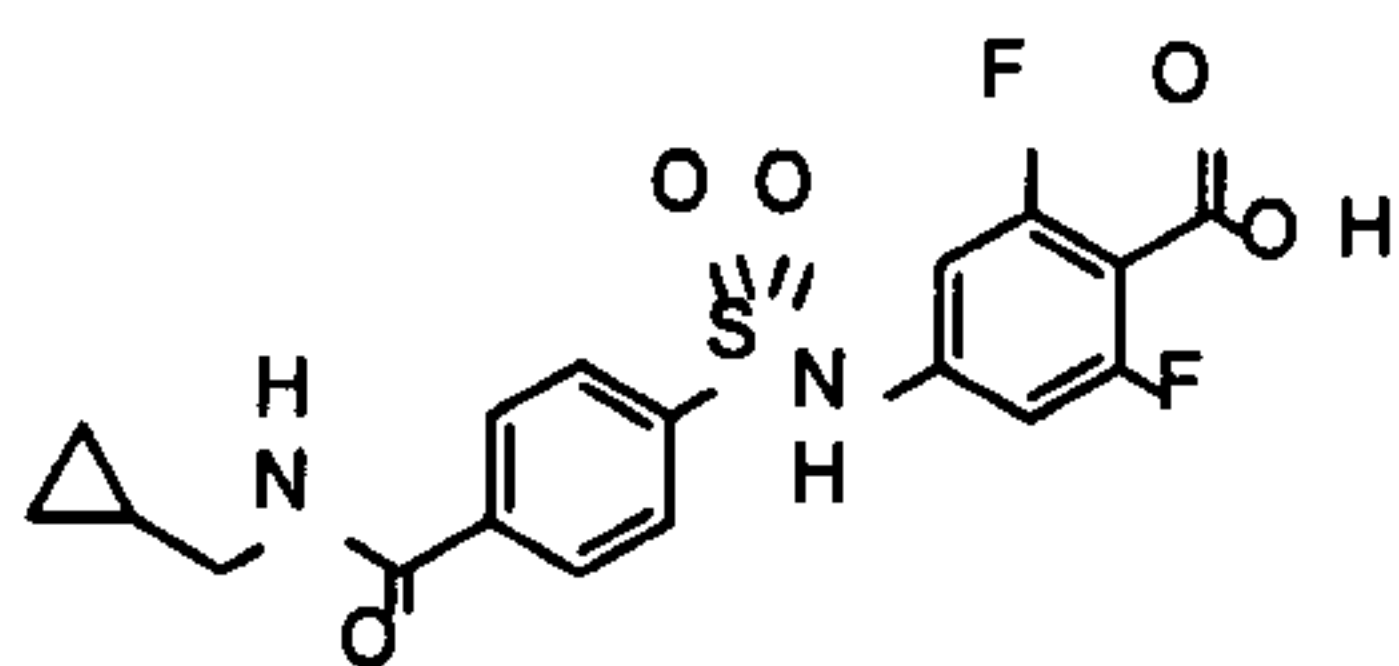
¹H NMR (CD₃OD, 400 MHz): δ 9.59 (s, 1H), 8.98 (d, J = 8.0 Hz, 1H), 8.89 (d, J = 4.8 Hz, 2H), 8.36 (s, 1H), 8.21 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 12.0 Hz, 1H), 7.45 (t, J = 4.8 Hz, 1H).; MS (ESI) m/z 376 (M+H)⁺

Example 117: Synthesis of M-59

(Step

1)

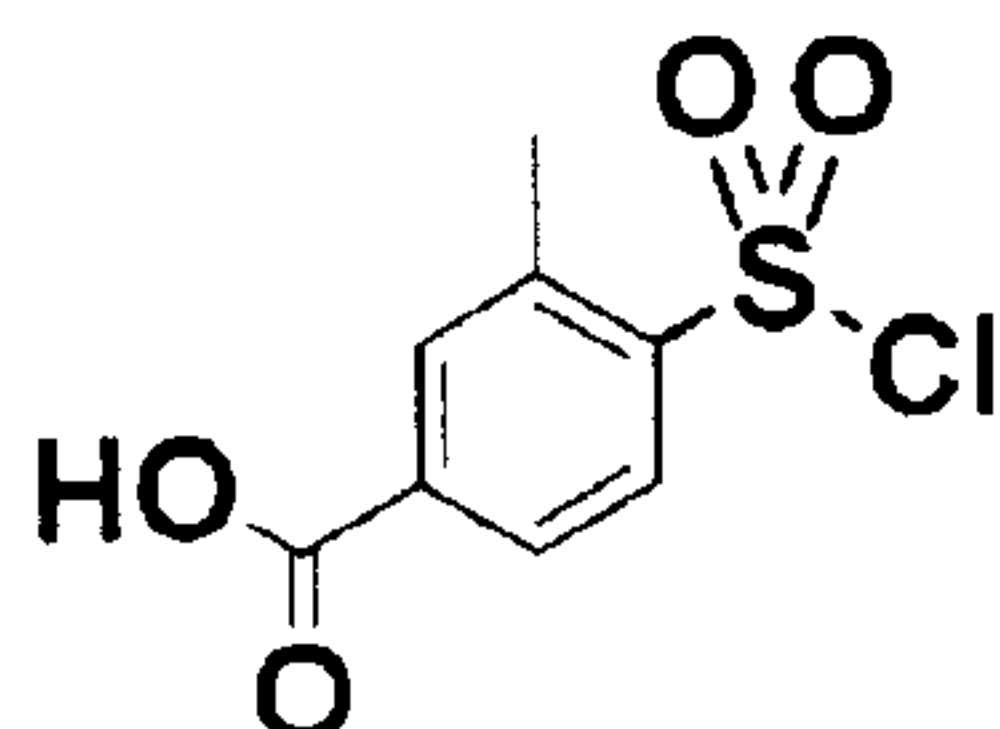
4-{[(4-{[(Cyclopropylmethyl)amino]carbonyl}phenyl)sulfonyl]amino}-2,6-difluorobenzoic Acid



4-([3,5-Difluoro-4-(methoxycarbonyl)phenyl]amino)sulfonyl)benzoic acid <see (Step 1) of Example 11> (68 mg, 0.20 mmol) and cyclopropylmethylaniline (7.1 mg, 0.10 mmol) were suspended in dichloromethane (3.0 ml), and HATU (57.0 mg, 0.150 mmol), HOAt (20.0 mg, 0.150 mmol), and triethylamine (28 μ l, 0.20 mmol) were added thereto, followed by stirring at room temperature for 2 hours. The reaction liquid was concentrated under reduced pressure, and then a 4 N hydrochloric acid/1,4-dioxane solution (2.0 ml) and water (4.0 ml) were added thereto, followed by stirring at 70°C for 6 hours. After the reaction liquid was concentrated under reduced pressure, purification was conducted by reversed-phase HPLC (H₂O containing 0.1% TFA/CH₃CN system), followed by freeze-drying, to obtain the title compound (27.6 mg, 67% over two steps).

Example 118: Synthesis of M-60

(Step 1) 4-(Chlorosulfonyl)-3-methylbenzoic Acid



4-Amino-3-methylbenzoic acid (15.0 g, 0.933 mol) was dissolved in concentrated hydrochloric acid (60 ml) and glacial acetic acid (20 ml), and the solution was cooled to -10°C. Then, an aqueous solution (20 ml) of sodium nitrite (10.0 g, 0.149 mol) was added dropwise thereto, followed by stirring at -10°C for 45 minutes, to obtain a diazonium salt. Another reaction vessel was filled with glacial acetic acid (480 ml), and sulfur dioxide (gas) was bubbled thereinto for 30 minutes. To the reaction liquid, copper(II) chloride (8.0 g) was added, and sulfur dioxide (gas) was bubbled for further 30 minutes. This

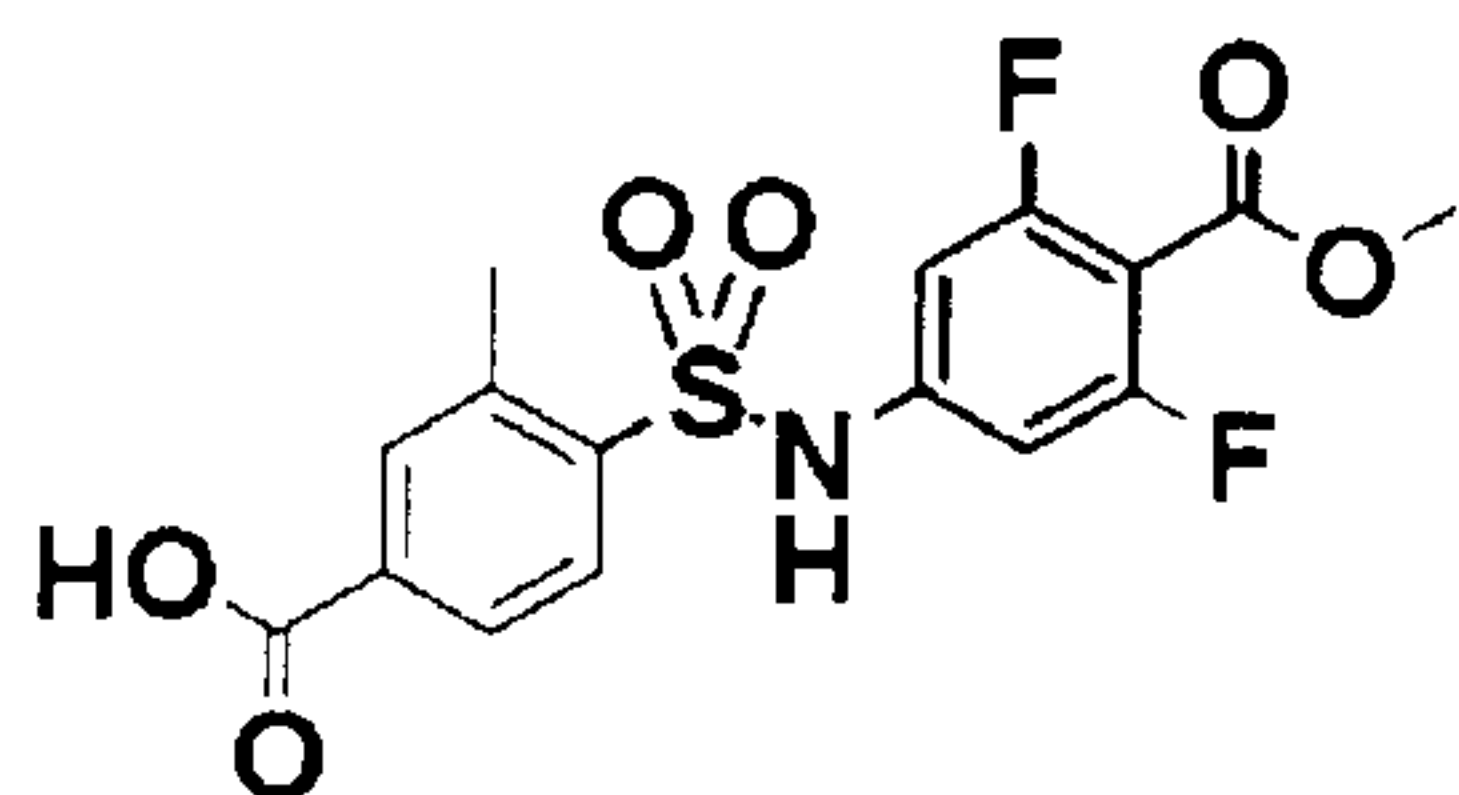
reaction solution was cooled to -30°C , and the above-described solution of the diazonium salt was slowly added dropwise thereto, followed by stirring at room temperature for 1 hour. After the reaction, the mixture was diluted with water, and the precipitated solid was filtered and dried to obtain the title compound (5.1 g, 22%).

^1H NMR ($\text{DMSO}-d_6$, 300 MHz): δ 8.23-8.13 (m, 3H), 2.89 (s, 3H).

(Step 2)

4-([3,5-Difluoro-4-(methoxycarbonyl)phenyl]amino)sulfonyl)

10 -3-methylbenzoic Acid



The title compound (610 mg, 14%) was obtained by subjecting 4-(chlorosulfonyl)-3-methylbenzoic acid (4.17 g, 17.8 mmol) to the same method as in (Step 4) of Example 104.

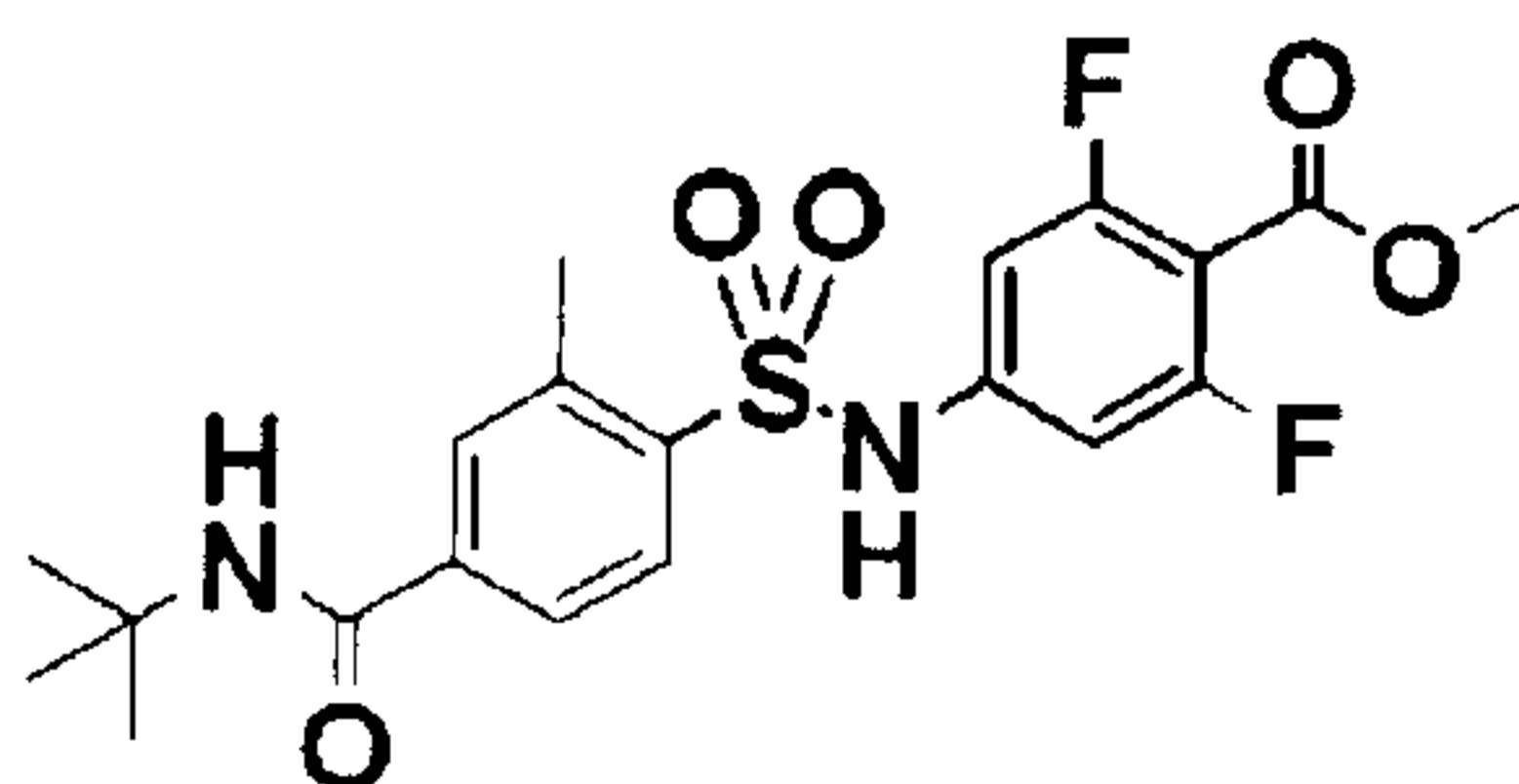
15 MS (ESI) m/z 386 ($\text{M}+\text{H}$) $^{+}$

(Step

3)

Methyl

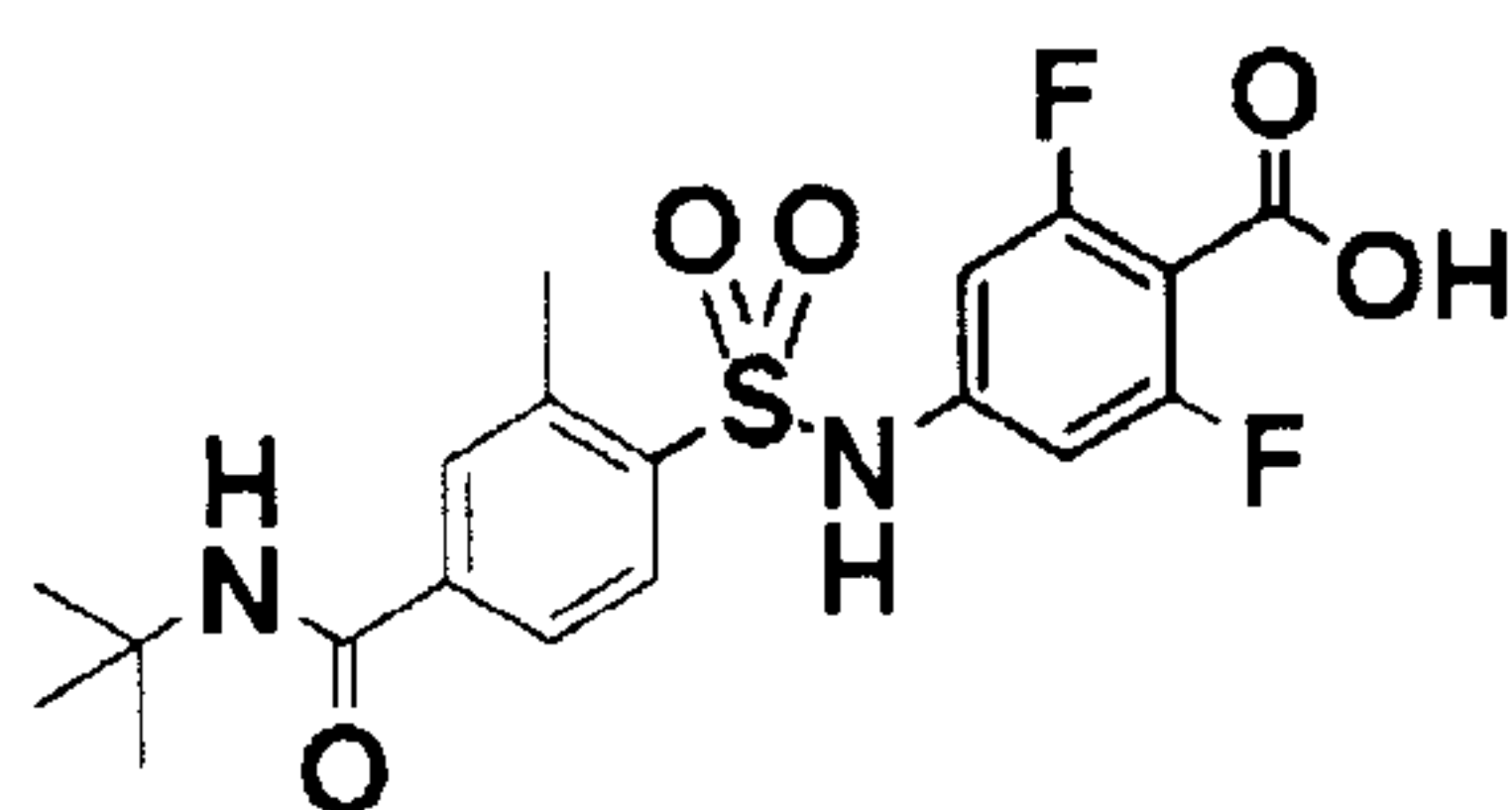
4-([4-[(tert-Butylamino)carbonyl]-2-methylphenyl]sulfonyl)amino]-2,6-difluorobenzoate



20 4-([3,5-Difluoro-4-(methoxycarbonyl)phenyl]amino)sulfonyl)-3-methylbenzoic acid (610 mg, 1.58 mmol) was dissolved in thionyl chloride (80 ml), followed by stirring at 100°C for 3.5 hours. The reaction solvent was removed under reduced pressure, and the obtained residue was suspended in methylene

chloride (anhydrous) (40 ml), and t-butylamine (10 ml) was added thereto, followed by stirring at room temperature for 12 hours. The obtained white solid was filtered, and further the solid was stirred in 6 N hydrochloric acid (50 ml) for 30 minutes, filtered, and dried to obtain the title compound (615 mg, 73%).
¹H NMR (DMSO-d₆, 400 MHz): δ 11.57 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 7.96 (s, 1H), 7.75-7.74 (m, 2H), 6.79 (d, J = 10.4 Hz, 2H), 3.79 (s, 3H), 2.62 (s, 3H), 1.35 (s, 9H).; MS (ESI) m/z 441 (M+H)⁺

10 (Step 4)
4-[(4-[(tert-Butylamino)carbonyl]-2-methylphenyl)sulfonyl]amino]-2,6-difluorobenzoic Acid (M-60)

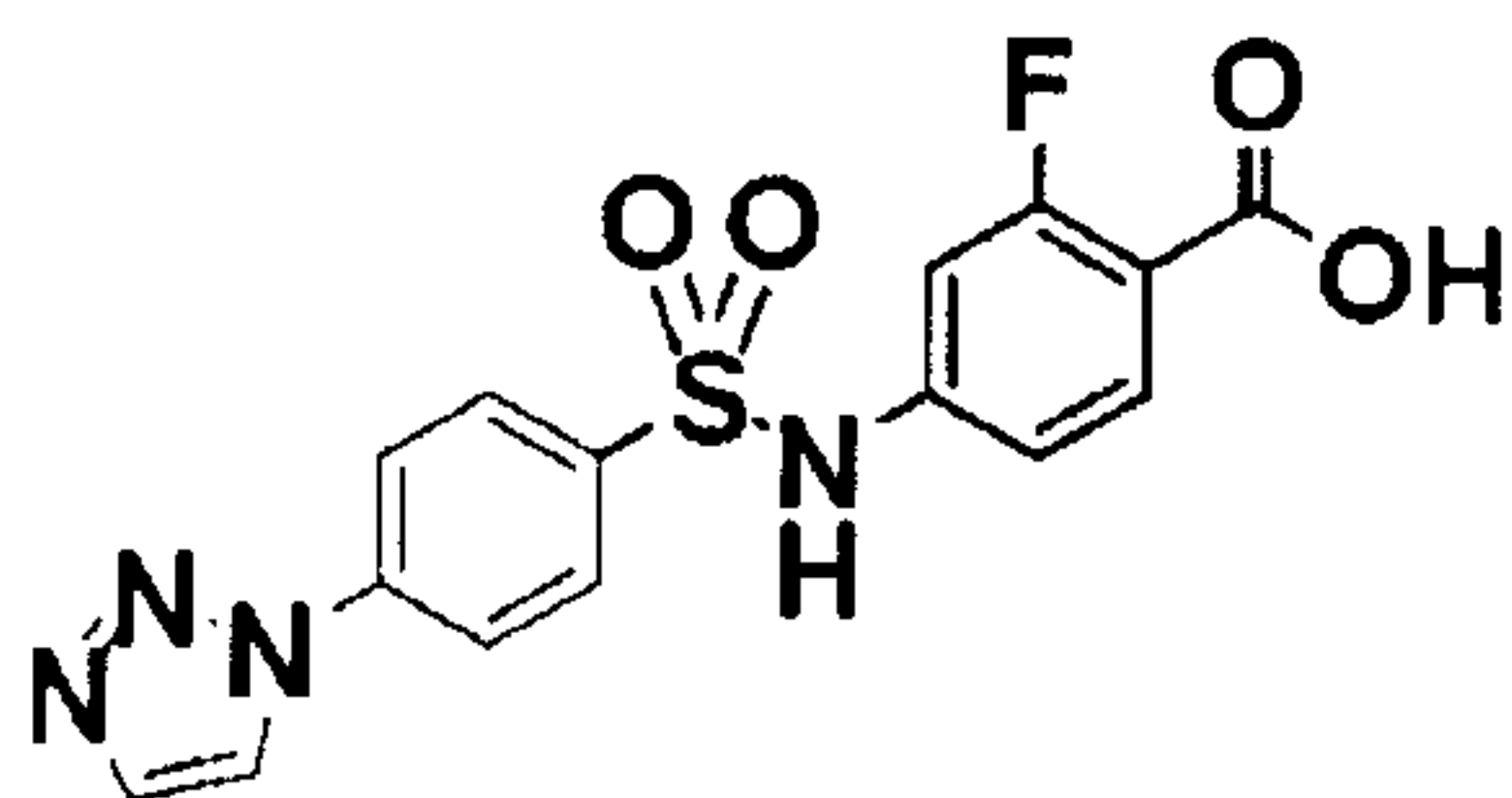


The title compound (M-60) (483 mg, 96%) was obtained by
 15 subjecting methyl
 4-[(4-[(tert-butylamino)carbonyl]-2-methylphenyl)sulfonyl]amino]-2,6-difluorobenzoate (615 mg, 1.17 mmol) to the same method as in (Step 5) of Example 104.

¹H NMR (CD₃OD, 300 MHz): δ 8.10 (d, J = 8.7 Hz, 1H), 7.69-7.67 (m, 2H), 6.74 (d, J = 7.2 Hz, 2H), 2.70 (s, 3H), 1.43 (s, 9H).; MS (ESI) m/z 425 (M-1)

Example 119: Synthesis of M-61

(Step 1)
2-Fluoro-4-([4-(1H-1,2,3-triazol-1-yl)phenyl]sulfonyl)amino]benzoic Acid (M-61)
 25



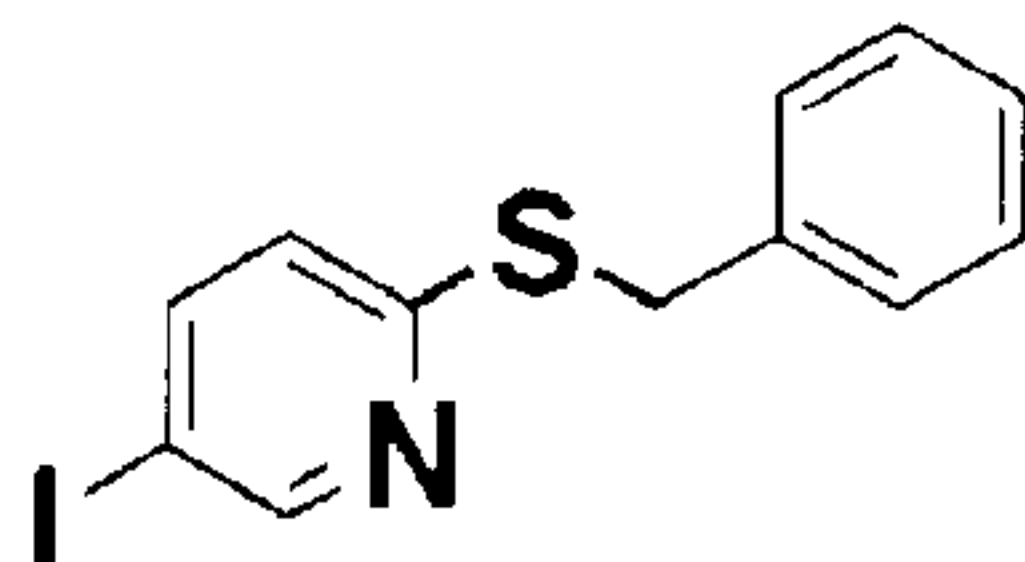
The title compound (M-61) (1.2 g, 13%) was obtained by
subjecting methyl

2-fluoro-4-{[(4-iodophenyl)sulfonyl]amino}benzoate (10.3 g,
23.1 mmol) to the same methods as in Examples 15 to 18.

^1H NMR (CD_3OD , 400 MHz): δ 8.64 (d, $J = 0.8$ Hz, 2H), 8.10 (m, 4H), 7.93 (d, $J = 1.2$ Hz, 1H), 7.83 (t, $J = 8.4$ Hz, 1H), 7.06-7.00 (m, 2H).; MS (ESI) m/z 363.0 ($\text{M}+\text{H}$) $^+$

Example 120: Synthesis of M-62

(Step 1) 2-(Benzylthio)-5-iodopyridine

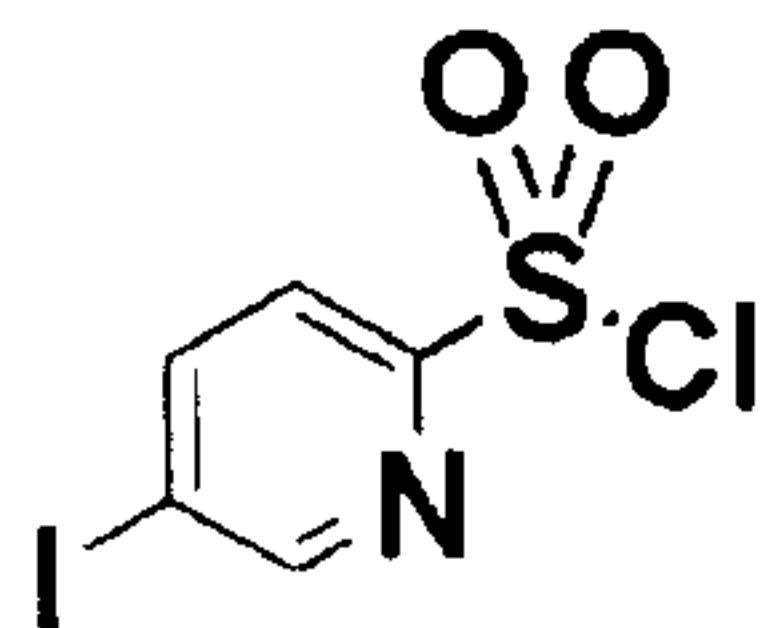


2-Chloro-5-iodopyridine (9.30 g, 75.0 mmol) was dissolved in N,N' -dimethylformamide (120 ml). After the solution was cooled to 0°C , 60% sodium hydride (3.8 g, 95 mmol) was added thereto, followed by stirring at 0°C for 30 minutes. To this reaction liquid, an N,N' -dimethylformamide solution (30 ml) of phenylmethanethiol (15 g, 63 mmol) was added, followed by stirring at room temperature for 1 hour. After the reaction, the reaction liquid was diluted with water, followed by extraction with ethyl acetate (200 ml $\times$ 2). The organic layers were combined and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to obtain the title compound (18.4 g, 90%).

^1H NMR (CDCl_3 , 400 MHz): δ 8.64 (d, $J = 1.6$ Hz, 1H), 7.73-7.70 (m, 1H), 7.39 (d, $J = 7.6$ Hz, 2H), 7.33-7.23 (m, 3H), 6.98-6.95

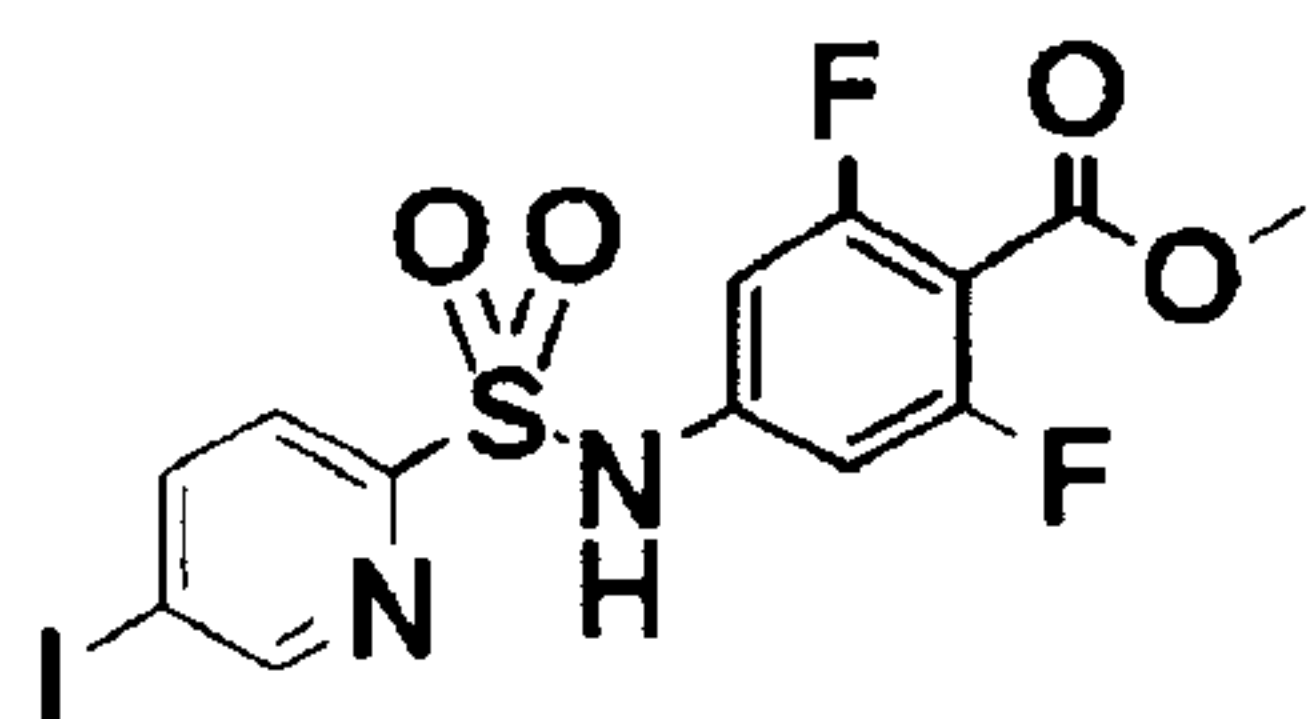
(m, 1H), 4.39 (s, 2H).; MS (ESI) m/z 328 (M+H)⁺

(Step 2) 5-Iodopyridine-2-sulfonyl Chloride



2-(Benzylthio)-5-iodopyridine (11.3 g, 35.0 mmol) was
 5 suspended in a mixture solvent of water (25 ml) and acetic acid
 (75 ml), and N-chlorosuccinimide (18.4 g, 138 mmol) was added
 thereto, followed by stirring at room temperature for 1 hour.
 The reaction liquid was diluted with water, followed by
 extraction with methylene chloride (100 ml×2). The organic
 10 layers were combined, then washed with a 3 N aqueous sodium
 hydroxide solution (80 ml) and saturated aqueous sodium
 chloride, and dried over anhydrous sodium sulfate. The solvent
 was removed under reduced pressure. The obtained residue was
 purified by silica gel column chromatography (petroleum
 15 ether/ethyl acetate=30:1) to obtain the title compound (2.6 g,
 25%) as a white solid.

(Step 3) Methyl
2,6-Difluoro-4-{[(5-iodopyridin-2-yl)sulfonyl]amino}benzoate
e



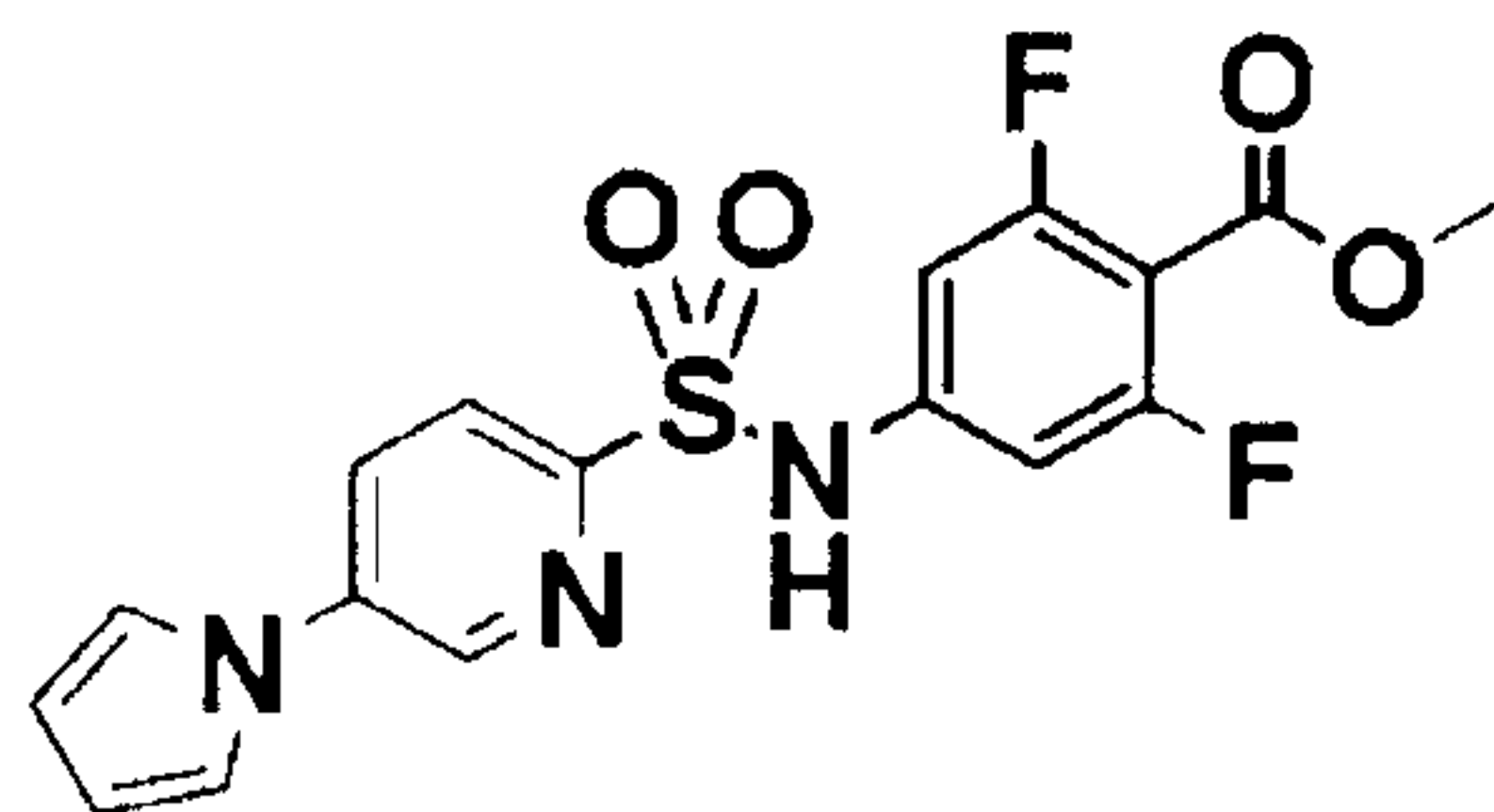
20

The title compound (3.0 g, 69%) was obtained by subjecting
 5-iodopyridine-2-sulfonyl chloride (5.1 g, 17 mmol) to the same
 method as in (Step 4) of Example 104.

¹H NMR (DMSO-d₆, 400 MHz): δ 11.58 (br, 1H), 9.00 (d, J = 2.0
 25 Hz, 1H), 8.53 (dd, J = 8.4, 2.0 Hz, 1H), 7.92 (d, J = 8.0 Hz,

1H), 6.94 (d, J = 10.4 Hz, 2H), 3.81 (s, 3H).; MS (ESI) m/z 455 (M+H)⁺

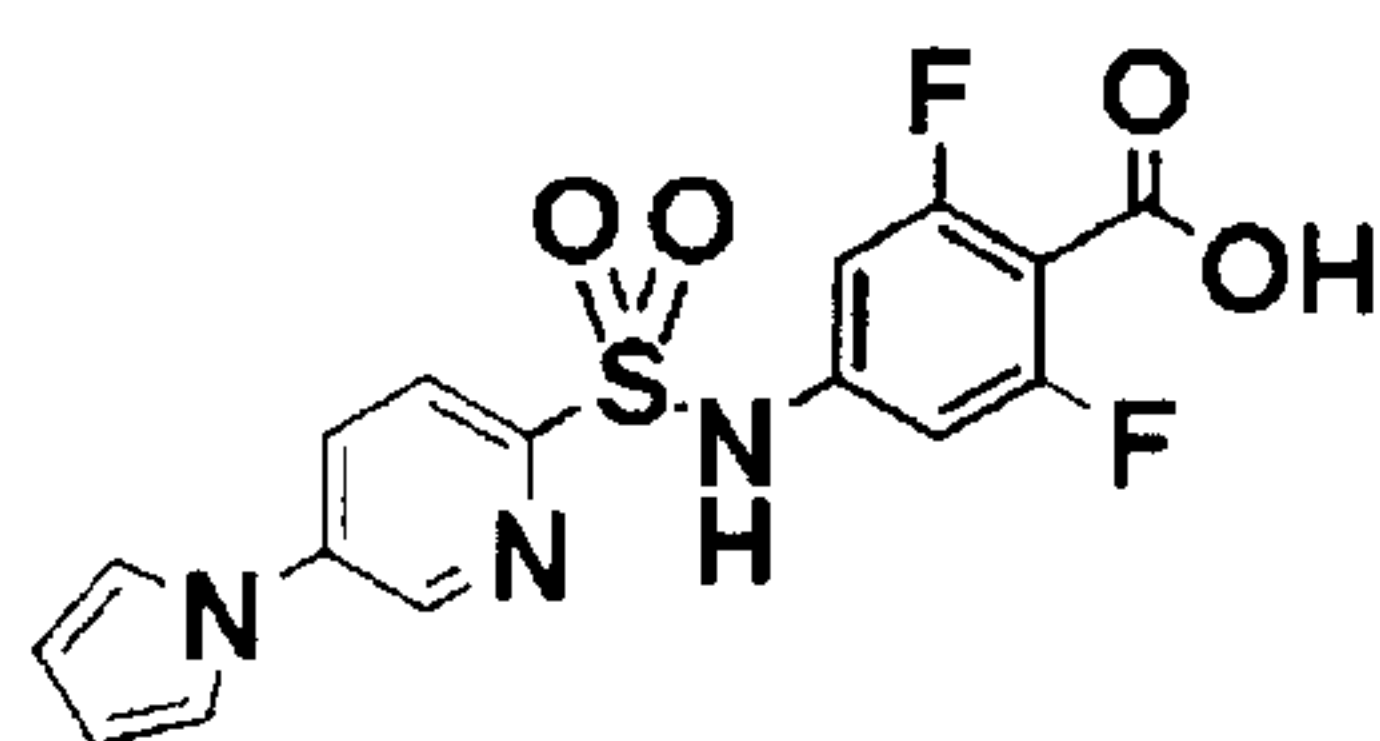
(Step 4) Methyl 2,6-Difluoro-4-([5-(1H-pyrrol-1-yl)pyridin-2-yl]sulfonyl)amino)benzoate



The title compound (0.80 g, 31%) was obtained as a white solid by subjecting methyl 2,6-difluoro-4-([5-(1H-pyrrol-1-yl)pyridin-2-yl]sulfonyl)amino)benzoate (3.0 g, 6.6 mmol) to the same method as in Example 10.

MS (ESI) m/z 394 (M+H)⁺

(Step 5) 2,6-Difluoro-4-([5-(1H-pyrrol-1-yl)pyridin-2-yl]sulfonyl)amino)benzoic Acid (M-62)

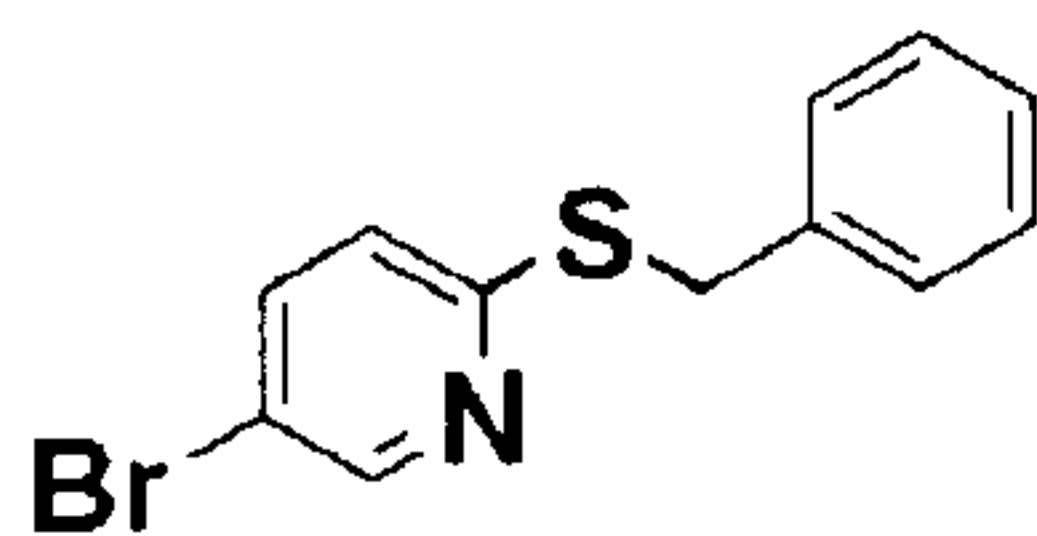


The title compound (M-62) (306 mg, 79%) was obtained by subjecting methyl 2,6-difluoro-4-([5-(1H-pyrrol-1-yl)pyridin-2-yl]sulfonyl)amino)benzoate (400 mg, 1.01 mmol) to the same method as in (Step 5) of Example 104.

¹H NMR (CD₃OD, 300 MHz): δ 8.92 (s, 1H), 8.14 (d, J = 1.2 Hz, 2H), 7.39 (t, J = 1.8 Hz, 2H), 6.93 (d, J = 9.9 Hz, 2H), 6.39 (d, J = 1.8 Hz, 2H).; MS (ESI) m/z 378 (M-1)

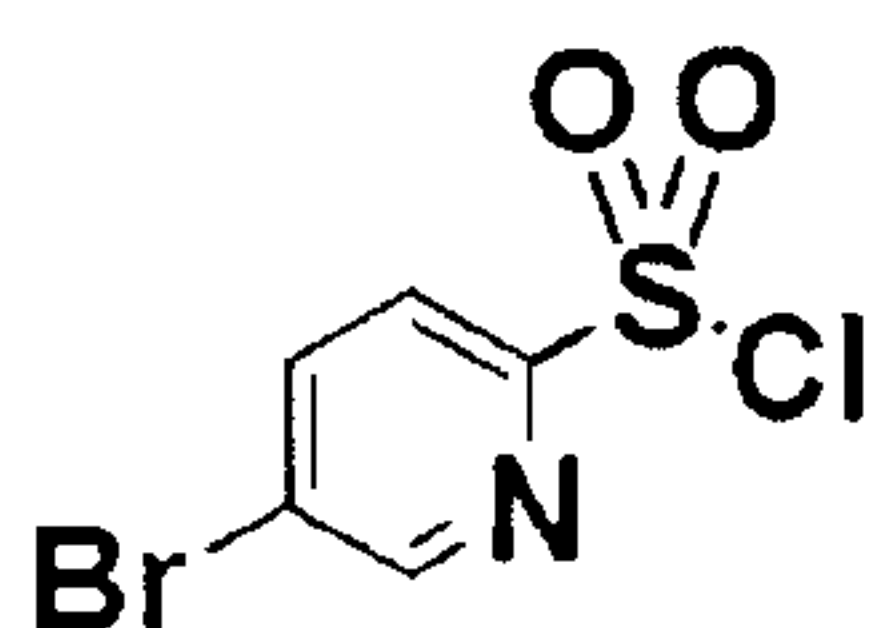
Example 121: Synthesis of M-63

(Step 1) 2-(Benzylthio)-5-bromopyridine



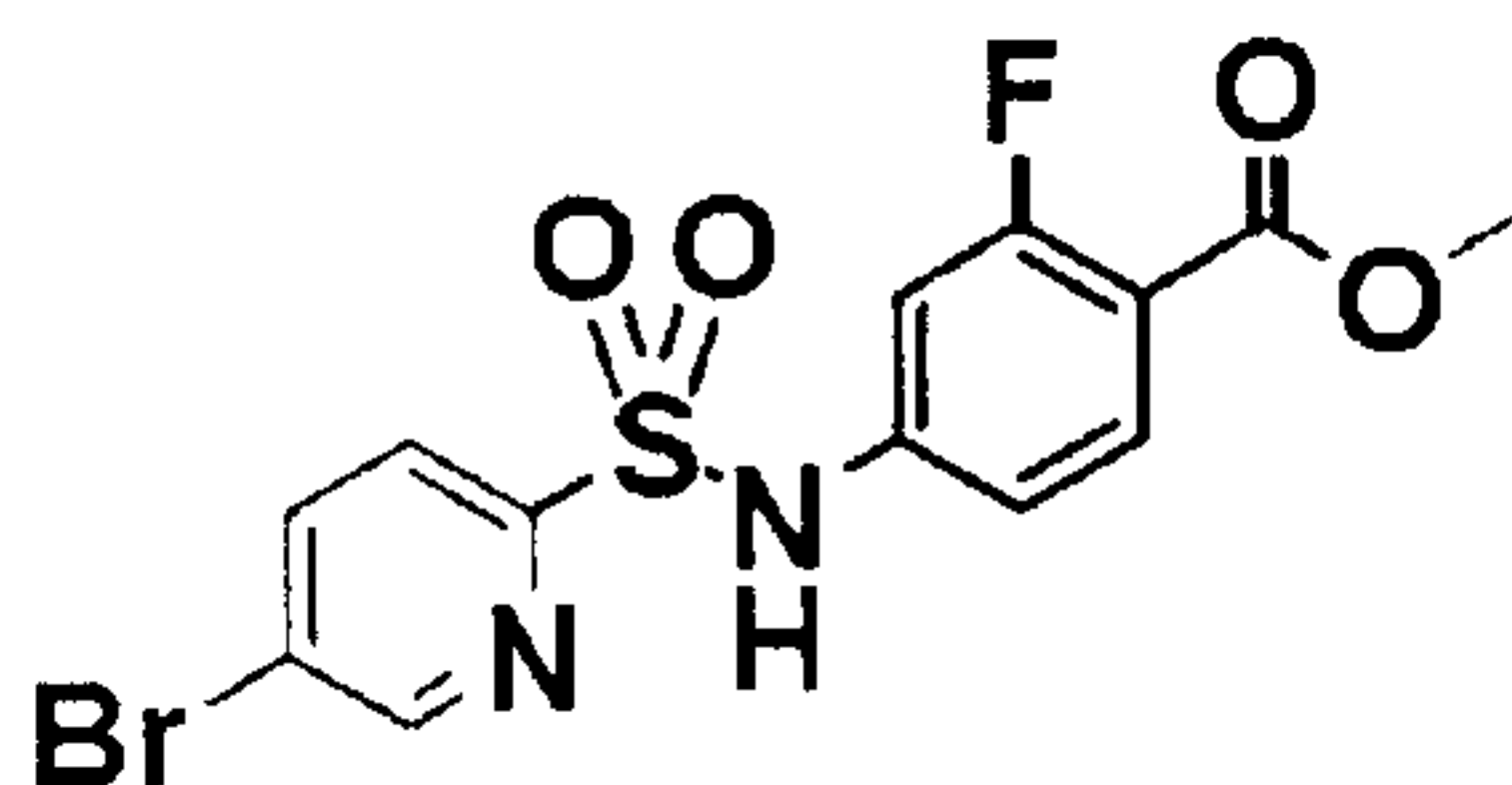
The title compound (143 g, 80%) was obtained by subjecting 2-chloro-5-bromopyridine (123 g, 640 mmol) to the same method as in (Step 1) of Example 120.

(Step 2) 5-Bromopyridine-2-sulfonyl Chloride



The title compound (4.70 g, 21%) was obtained by subjecting 2-(benzylthio)-5-bromopyridine (25.0 g, 90.0 mmol) to the same method as in (Step 2) of Example 120.

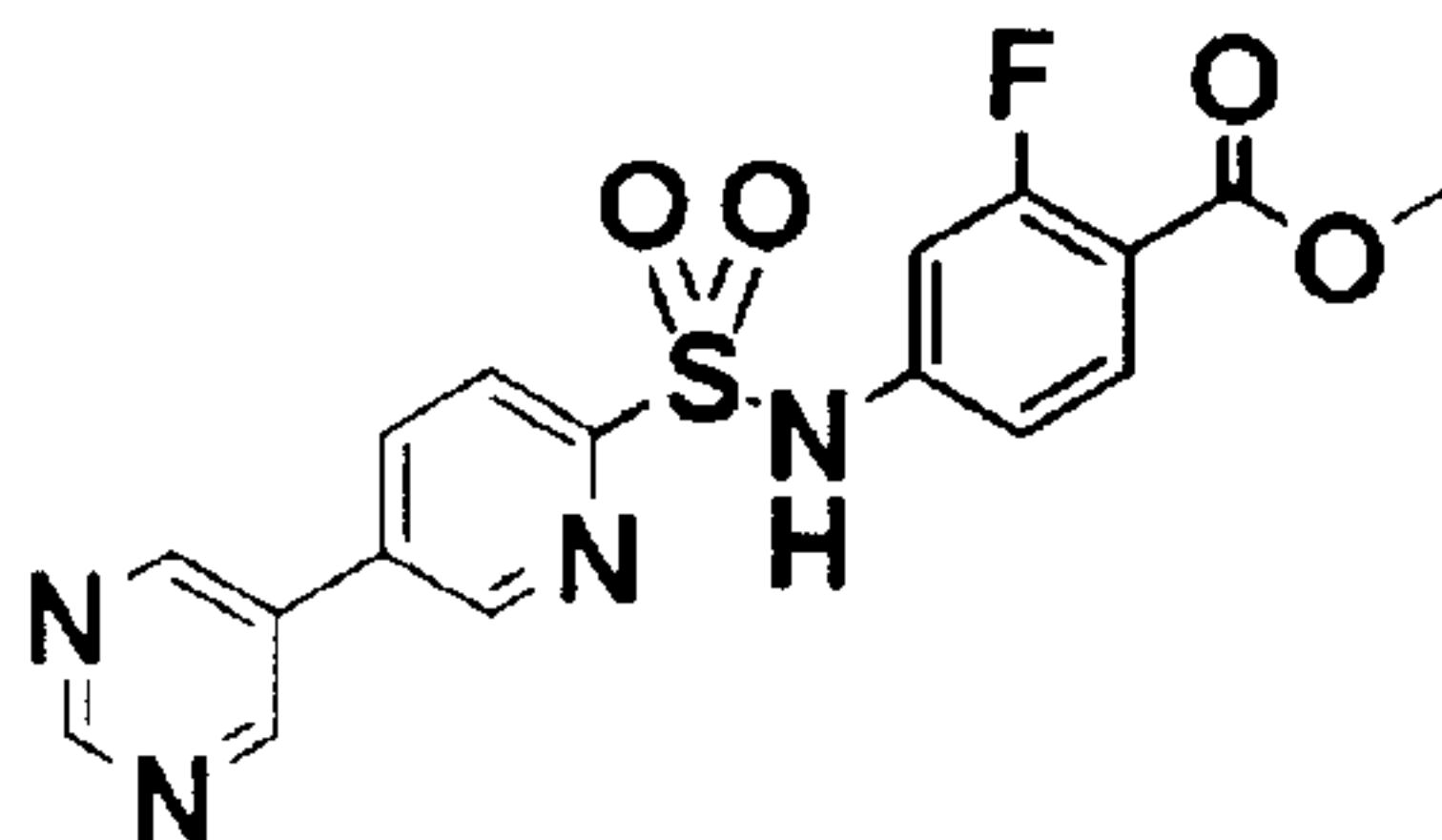
(Step 3) Methyl 4-{[(5-Bromopyridin-2-yl)sulfonyl]amino}-2-fluorobenzoate



The title compound (3.97 g, 85%) was obtained by subjecting 5-bromopyridine-2-sulfonyl chloride (4.70 g, 18.0 mmol) to the same method as in (Step 4) of Example 104.

¹H NMR (CDCl₃, 300 MHz): δ 8.75 (d, J = 2.1 Hz, 1H), 8.07-8.04 (m, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.86-7.80 (m, 1H), 7.12 (dd, J = 11.7, 2.1 Hz, 1H), 7.02 (dd, J = 8.4, 2.1 Hz, 1H), 3.89 (s, 3H).; MS (ESI) m/z 389 (M+H)⁺

(Step 4) Methyl 2-Fluoro-4-{[(5-pyrimidin-5-ylpyridin-2-yl)sulfonyl]amino}benzoate



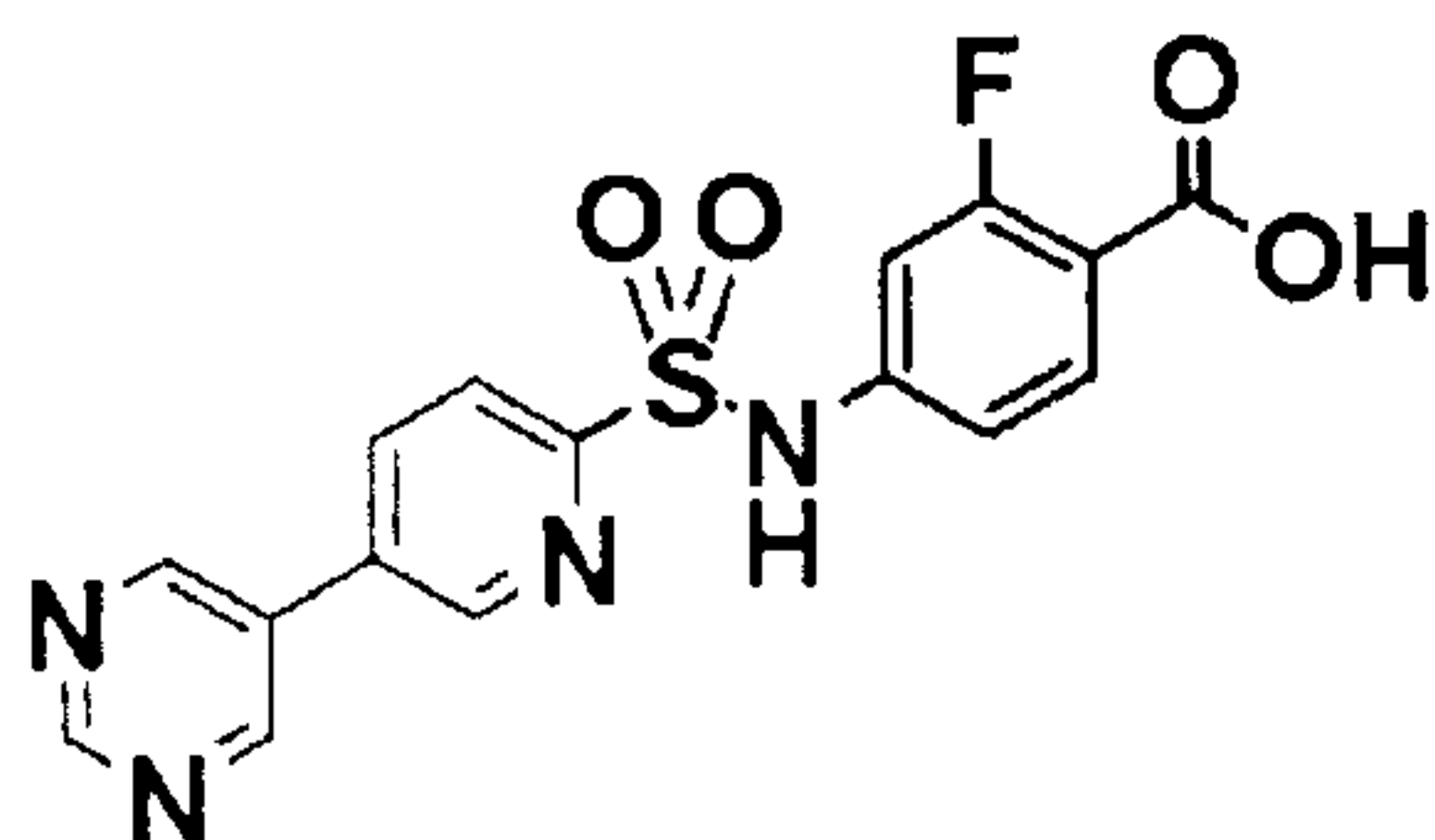
Methyl

4-{{[(5-bromopyridin-2-yl)sulfonyl]amino}-2-fluorobenzoate
(4.20 g, 10.8 mmol) and pyrimidin-5-ylboronic acid (2.70 g, 17.8
5 mmol) were dissolved in N,N'-dimethylformamide (50 ml) and
water (10 ml), and
[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II)
(366 mg, 0.500 mmol) and sodium carbonate (2.50 g, 23.6 mmol)
were added thereto, followed by stirring at 90°C for 12 hours
10 in the presence of nitrogen gas. The reaction liquid was cooled
to room temperature and diluted with water, and then ethyl
acetate was added thereto for extraction. The organic layers
were combined, washed with saturated aqueous sodium chloride,
and dried over anhydrous sodium sulfate. Then, the solvent was
15 removed under reduced pressure. The obtained residue was
purified by silica gel column chromatography (petroleum
ether/ethyl acetate=1:2 to 1:10) to obtain the title compound
(2.3 g, 55%).

MS (ESI) m/z 389 (M+H)⁺

20 (Step 5)

2-Fluoro-4-{{[(5-pyrimidin-5-yl)pyridin-2-yl]sulfonyl}amino}b
enzoic Acid (M-63)

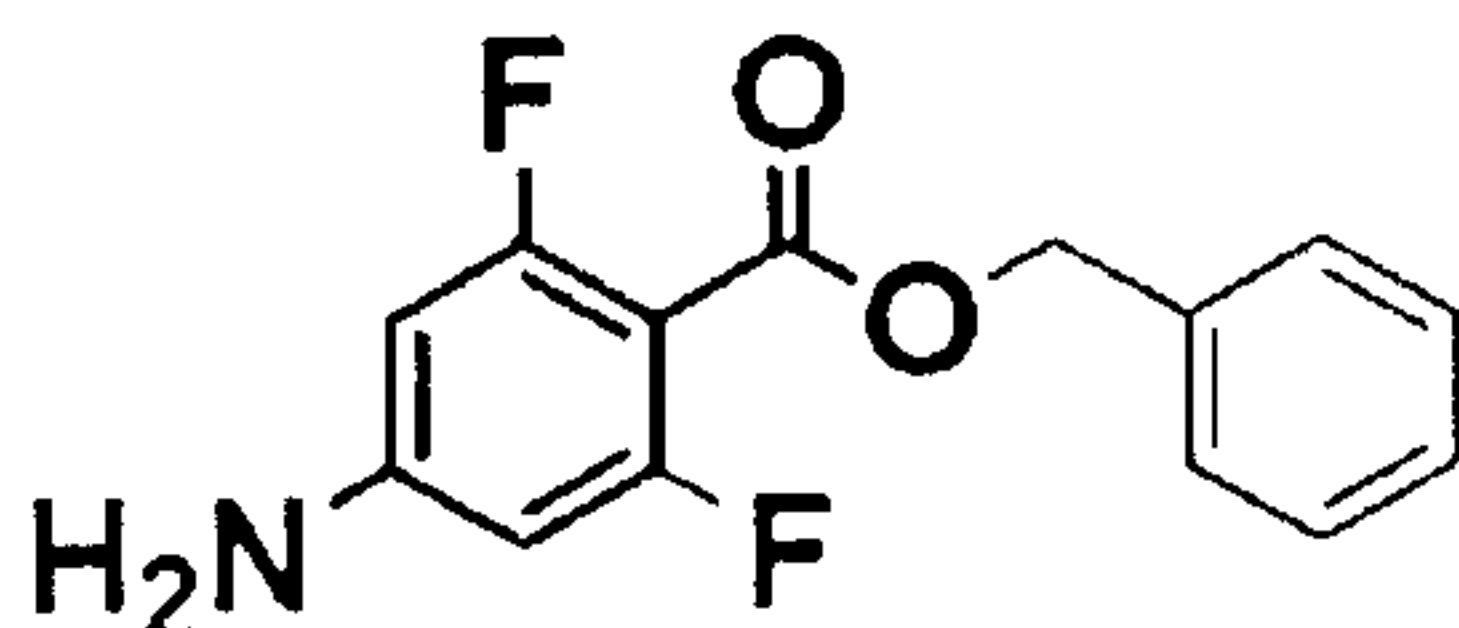


The title compound (M-63) (1.38 g, 90%) was obtained as a white solid by subjecting methyl 2-fluoro-4-{[(5-pyrimidin-5-ylpyridin-2-yl)sulfonyl]amino}benzoate (1.6 g, 4.1 mmol) to the same method as in (Step 5) of Example 104.

¹H NMR (DMSO-d₆, 400 MHz): δ 11.47 (s, 1H), 9.27 (s, 3H), 9.18 (d, J = 2.4 Hz, 1H), 8.56 (dd, J = 10.8, 3.2 Hz, 1H), 8.25 (d, J = 11.2 Hz, 1H), 7.77 (t, J = 11.2 Hz, 1H), 7.12 (s, 1H), 7.08 (s, 1H).; MS (ESI) m/z 375 (M+H)⁺

Example 122: Synthesis of M-64

(Step 1) Benzyl 4-Amino-2,6-difluorobenzoate



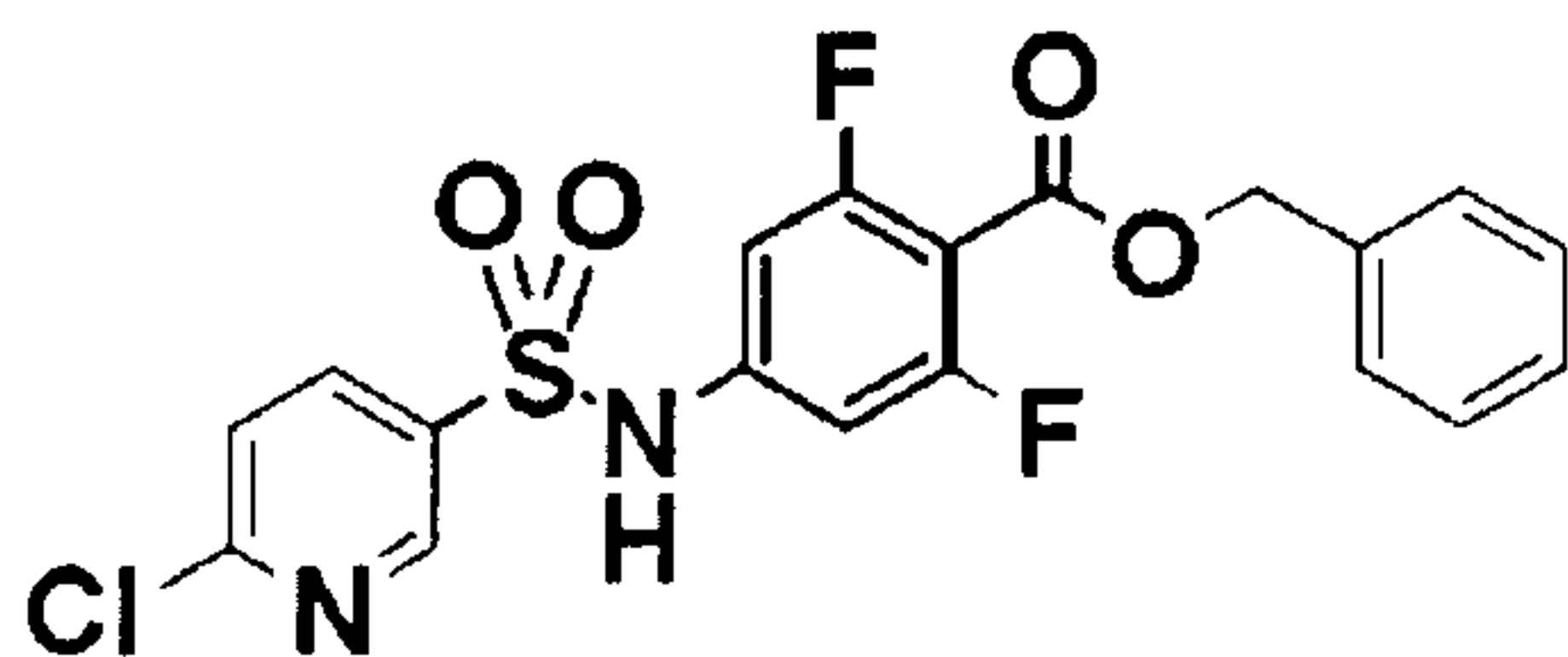
4-Amino-2,6-difluorobenzoic acid (101 g, 0.583 mol) was dissolved in acetonitrile (400 ml), and potassium carbonate (81.0 g, 0.586 mol) and benzyl bromide (100 g, 0.585 mol) were added thereto, followed by stirring at 80°C for 2 hours. The reaction liquid was diluted with water, followed by extraction with ethyl acetate (150 ml). Then, the solvent was removed under reduced pressure to obtain the title compound (115 g, 75%).

¹H NMR (DMSO-d₆, 400 MHz): δ 7.46-7.27 (m, 5H), 6.18-6.13 (m, 2H), 5.35 (s, 2H), 4.23 (s, 2H).

(Step

2)

Benzyl

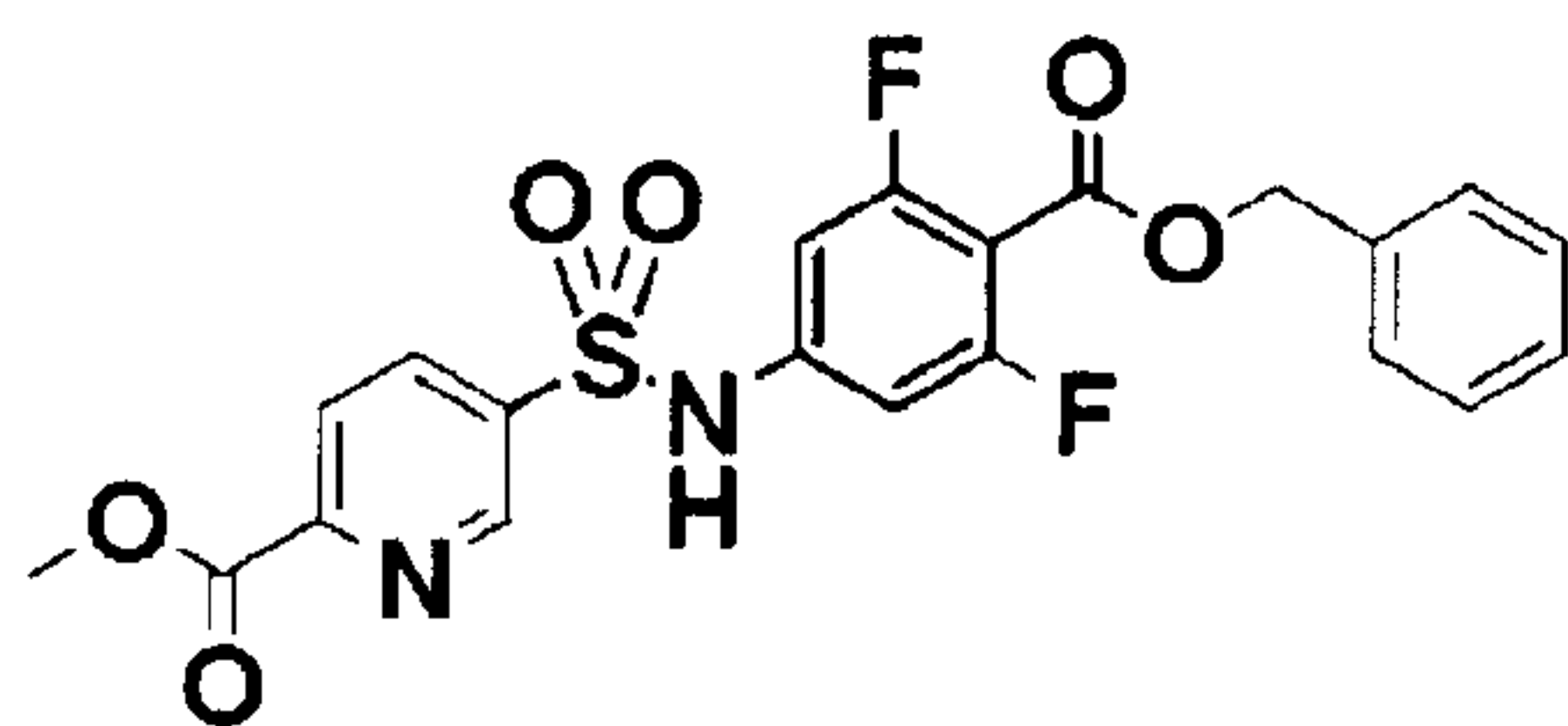
4- { [(6-Chloropyridin-3-yl) sulfonyl] amino} -2,6-benzoate

The title compound (51.0 g, 64%) was obtained by
 subjecting benzyl 4-amino-2,6-difluorobenzoate (48.0 g, 0.182
 5 mol) and 6-chloropyridine-3-sulfonyl chloride (57.0 g, 0.269
 mol) to the same method as in (Step 4) of Example 104.

MS (ESI) m/z 439 (M+H)⁺

(Step 3) Methyl

5- [({4- [(Benzyloxy) carbonyl] -3,5-difluorophenyl} amino) sulfo
 10 nyl]pyridine-2-carboxylate



Benzyl

4- { [(6-chloropyridin-3-yl) sulfonyl] amino} -2,6-benzoate

(43.8 g, 99.8 mmol) was dissolved in methanol (200 ml), and
 15 trans-bis(benzonitrile)palladium(II) dichloride (4.80 g, 13.0
 mmol), 1,3-bis(diphenylphosphino)propane (10.0 g, 25.0 mmol),
 and triethylamine (20.2 g, 0.200 mol) were added thereto,
 followed by stirring at 120°C for 18 hours in the presence of
 carbon monoxide (80 psi). The reaction liquid was concentrated
 20 under reduced pressure, and the obtained residue was purified
 by silica gel column chromatography (petroleum ether/ethyl
 acetate=4:1 to 2:1) to obtain the title compound (27.0 g, 59%).

¹H NMR (DMSO-d₆, 400 MHz): δ 11.6 (s, 1H), 9.14 (d, J = 2.0 Hz,
 1H), 8.44-8.42 (m, 1H), 8.22 (d, J = 8.4 Hz, 1H), 7.45-7.32 (m,

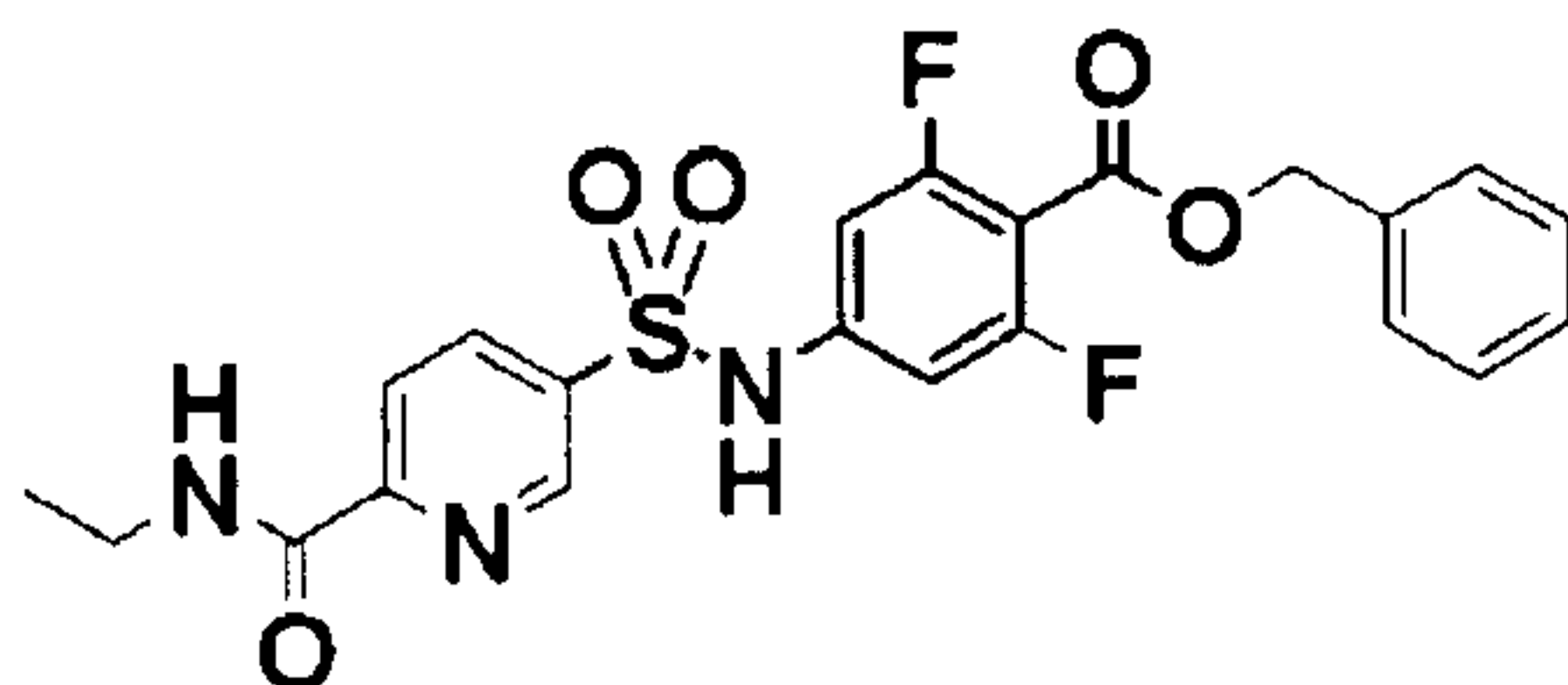
5H), 6.88 (d, $J = 10.4$ Hz, 2H), 5.32 (s, 2H), 3.92 (s, 3H).;

MS (ESI) m/z 463 (M+H)⁺

(Step 4) Benzyl

4-[(6-[(Ethylamino)carbonyl]pyridin-3-yl)sulfonyl]amino]-2

5 ,6-difluorobenzoate



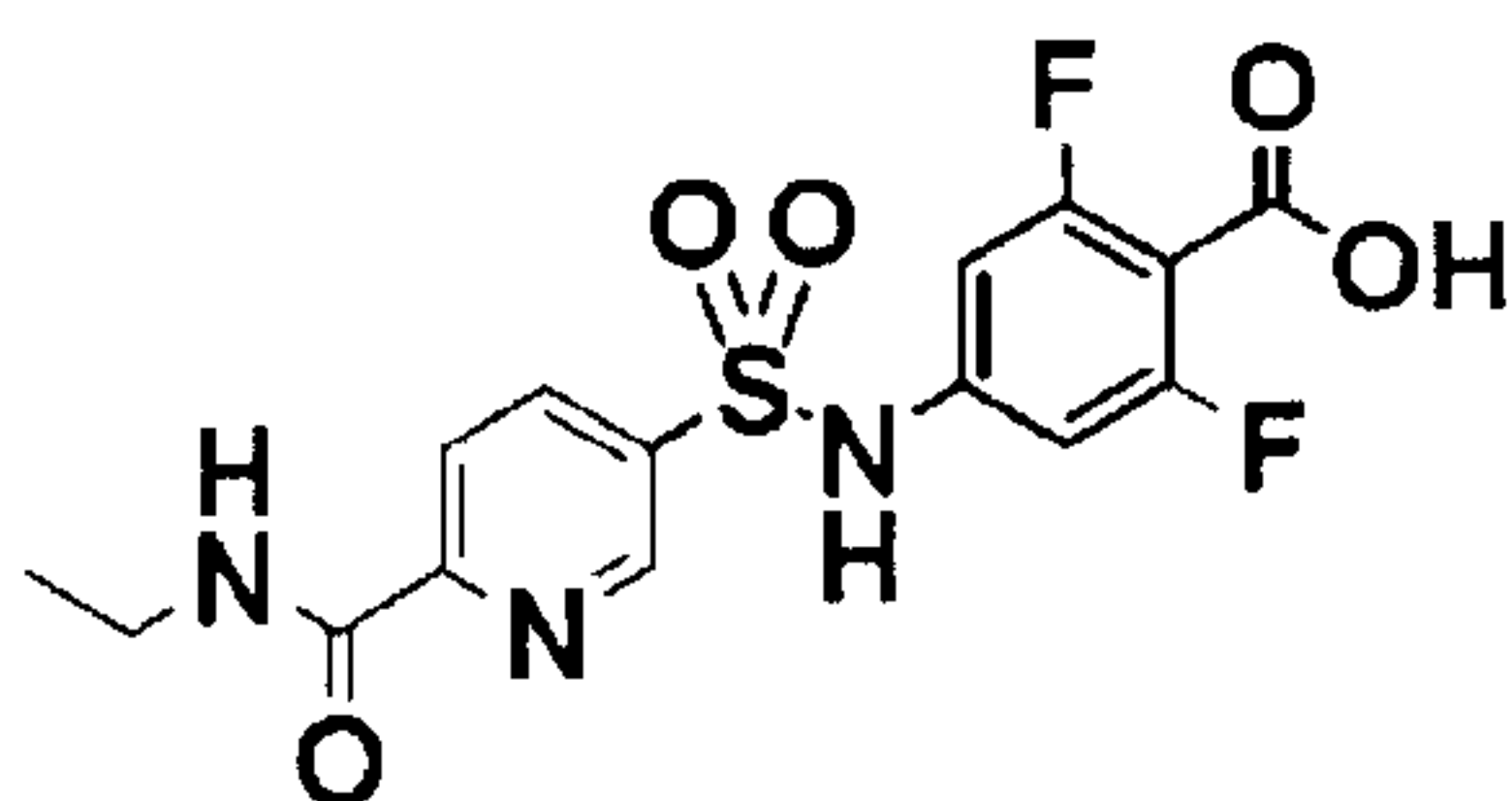
Methyl

5-[(4-[(benzyloxy)carbonyl]-3,5-difluorophenyl)amino)sulfonyl]pyridine-2-carboxylate (8.50 g, 18.4 mmol) was dissolved in tetrahydrofuran (40 ml), and a 2 N ethylamine tetrahydrofuran solution (27.6 ml) was added thereto, followed by stirring at room temperature for 72 hours. The solvent was removed under reduced pressure, and n-hexane (50 ml) was added to the residue. After stirring for 10 minutes, the obtained solid was filtered and dried to obtain the title compound (6.8 g, 78%).

¹H NMR (CD₃OD, 400 MHz): δ 9.03-9.02 (m, 1H), 8.35-8.33 (m, 1H), 8.15-8.13 (m, 1H), 7.42-7.29 (m, 5H), 6.58 (d, $J = 12.0$ Hz, 2H), 5.29 (s, 2H), 3.48-3.42 (m, 2H), 1.30 (t, $J = 8.4$ Hz, 3H).

(Step 5)

20 4-[(6-[(Ethylamino)carbonyl]pyridin-3-yl)sulfonyl]amino]-2
,6-difluorobenzoic Acid (M-64)



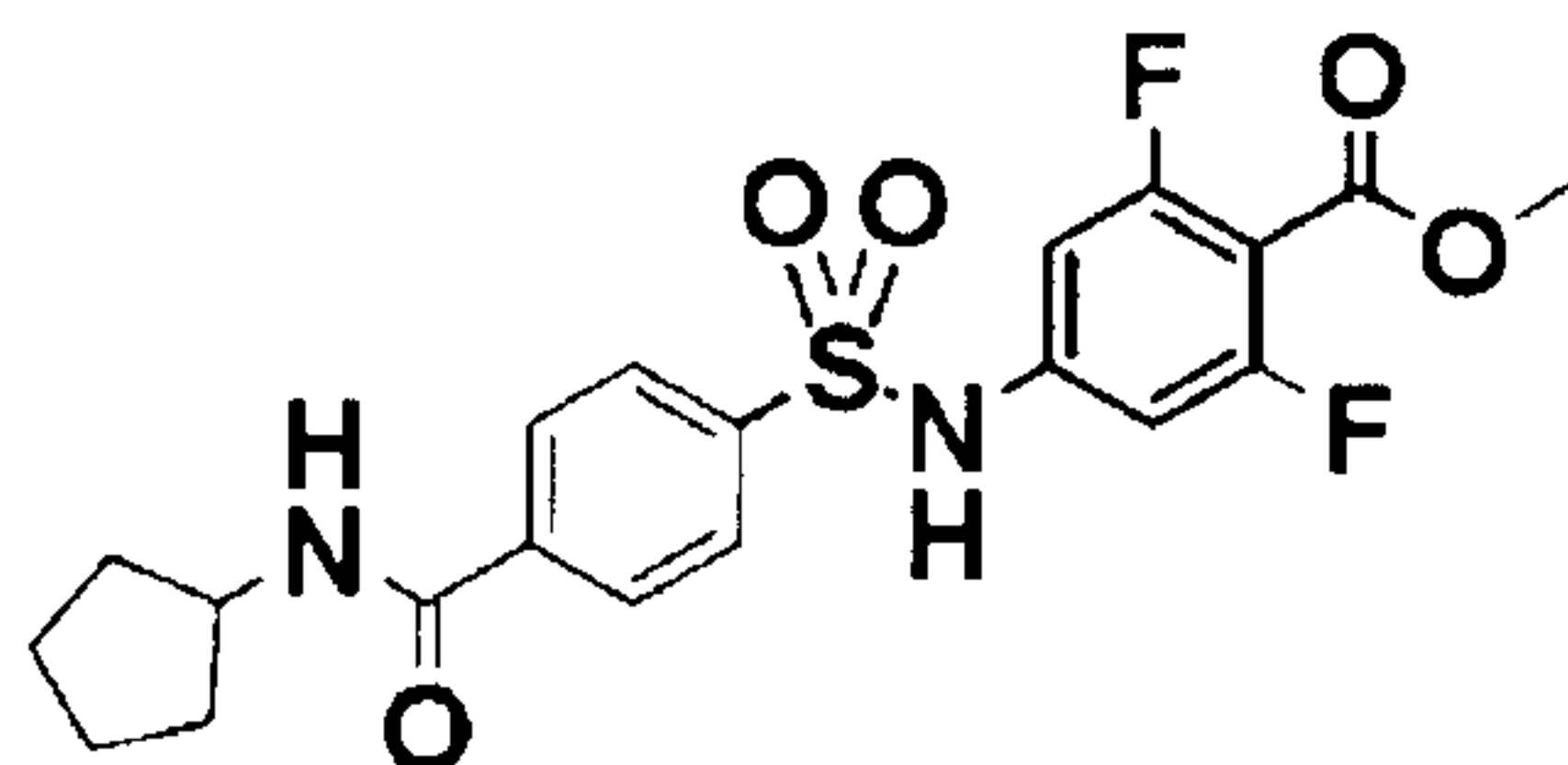
Benzyl

4-[(6-[(ethylamino)carbonyl]pyridin-3-yl)sulfonyl]amino]-2

,6-difluorobenzoate (6.80 g, 14.3 mmol) was dissolved in methanol (150 ml), and 10% palladium carbon (2.0 g) was added thereto, followed by stirring at room temperature for 4 days in the presence of hydrogen gas. The reaction liquid was
 5 filtered, and the filtrate was concentrated under reduced pressure. Then, n-hexane (30 ml) was added to the obtained residue, followed by stirring. The precipitated solid was filtered to obtain the title compound (M-64) (3.4 g, 62%).
¹H NMR (CD₃OD, 400 MHz): δ 9.06 (d, J = 2.0 Hz, 1H), 8.43 (dd, J = 8.0, 2.0 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 6.89 (s, 1H),
 10 6.87 (s, 1H), 3.46 (q, J = 6.8 Hz, 2H), 1.24 (t, J = 6.8 Hz, 3H).; MS (ESI) m/z 386 (M+H)⁺

Example 123: Synthesis of M-65

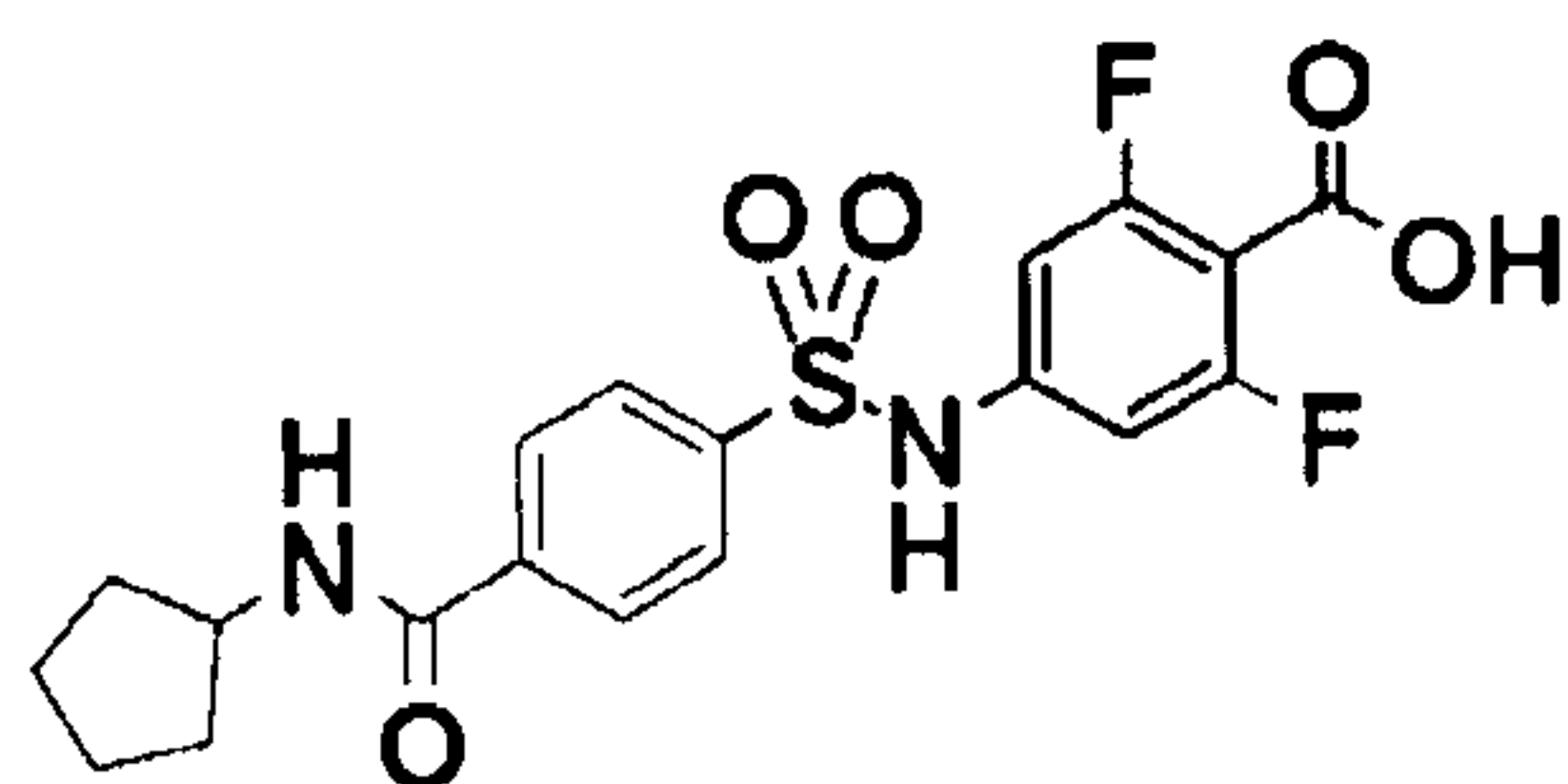
(Step 1) Methyl
 15 4-[(4-[(Cyclopentylamino)carbonyl]phenyl)sulfonyl]amino]-2,6-difluorobenzoate



The title compound (1.4 g, 47%) was obtained by subjecting 4-({[3,5-difluoro-4-(methoxycarbonyl)phenyl]amino}sulfonyl) benzoic acid <see (Step 1) of Example 11> (2.5 g, 4.0 mmol) to
 20 the same method as in (Step 2) of Example 11.

MS (ESI) m/z 439 (M+H)⁺

(Step 2) 2)
4-[(4-[(Cyclopentylamino)carbonyl]phenyl)sulfonyl]amino]-2,6-difluorobenzoic Acid (M-65)
 25



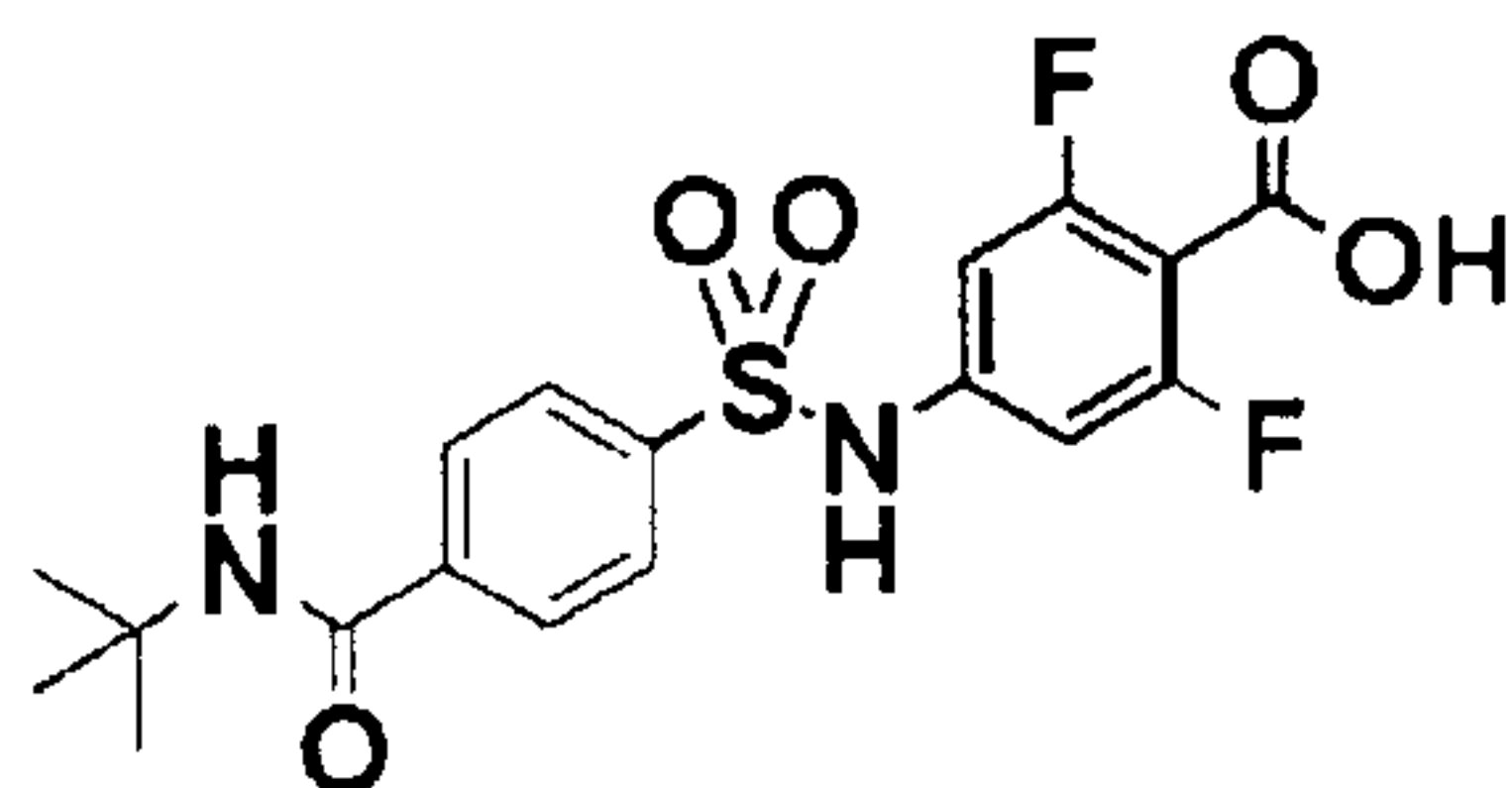
The title compound (M-65) (990 mg, 74%) was obtained as a white solid by subjecting methyl 4-[(4-[(cyclopentylamino)carbonyl]phenyl)sulfonyl]amino]-2,6-difluorobenzoate (1.4 g, 3.2 mmol) to the same method as in (Step 5) of Example 104.

$^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.98-7.92 (m, 4H), 6.83 (d, $J = 10.0$ Hz, 2H), 4.33-4.27 (m, 1H), 2.06-2.00 (m, 2H), 1.79-1.54 (m, 6H).; MS (ESI) m/z 425 ($\text{M}+\text{H}$) $^+$

Example 124: Synthesis of M-66

(Step 1)

4-[(4-[(tert-Butylamino)carbonyl]phenyl)sulfonyl]amino]-2,6-difluorobenzoic Acid (M-66)

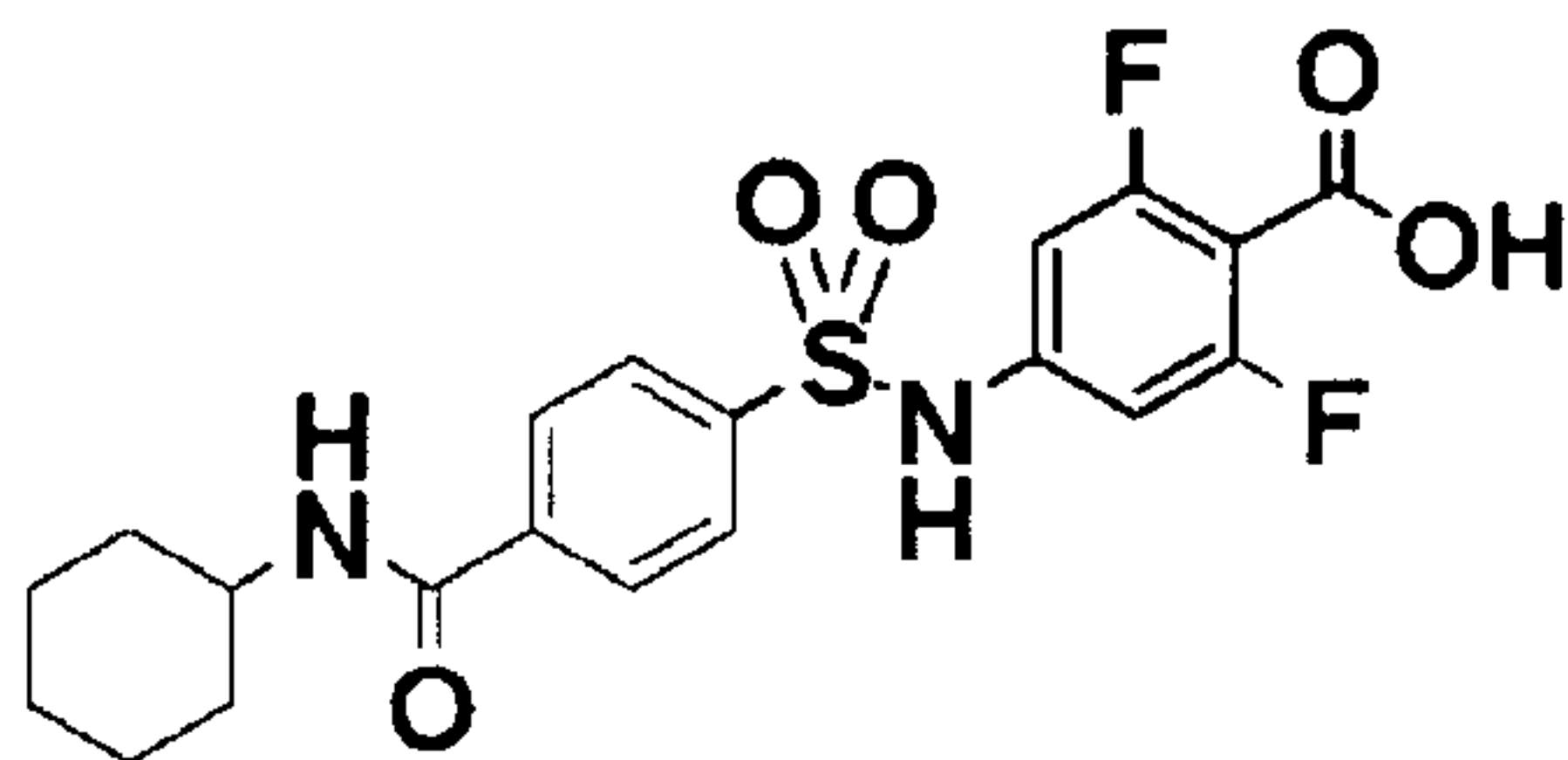


The title compound (M-66) (14.0 g, 74% over two steps) was obtained as a white solid by subjecting 4-[(3,5-difluoro-4-(methoxycarbonyl)phenyl)amino]sulfonyl]benzoic acid <see (Step 1) of Example 11> (17.0 g, 45.8 mmol) to a method including the same two steps as (Step 2) of Example 11 and (Step 5) of Example 104.

$^1\text{H NMR}$ (CD_3OD , 400 MHz): δ 7.95 (d, $J = 8.8$ Hz, 2H), 7.87 (d, $J = 8.4$ Hz, 2H), 6.82 (d, $J = 9.6$ Hz, 2H), 1.44 (s, 9H).; MS (ESI) m/z 413 ($\text{M}+\text{H}$) $^+$

Example 125: Synthesis of M-67

(Step 1)
4-[(4-[(Cyclohexylamino)carbonyl]phenyl)sulfonyl]amino]-2,6-difluorobenzoic Acid (M-67)

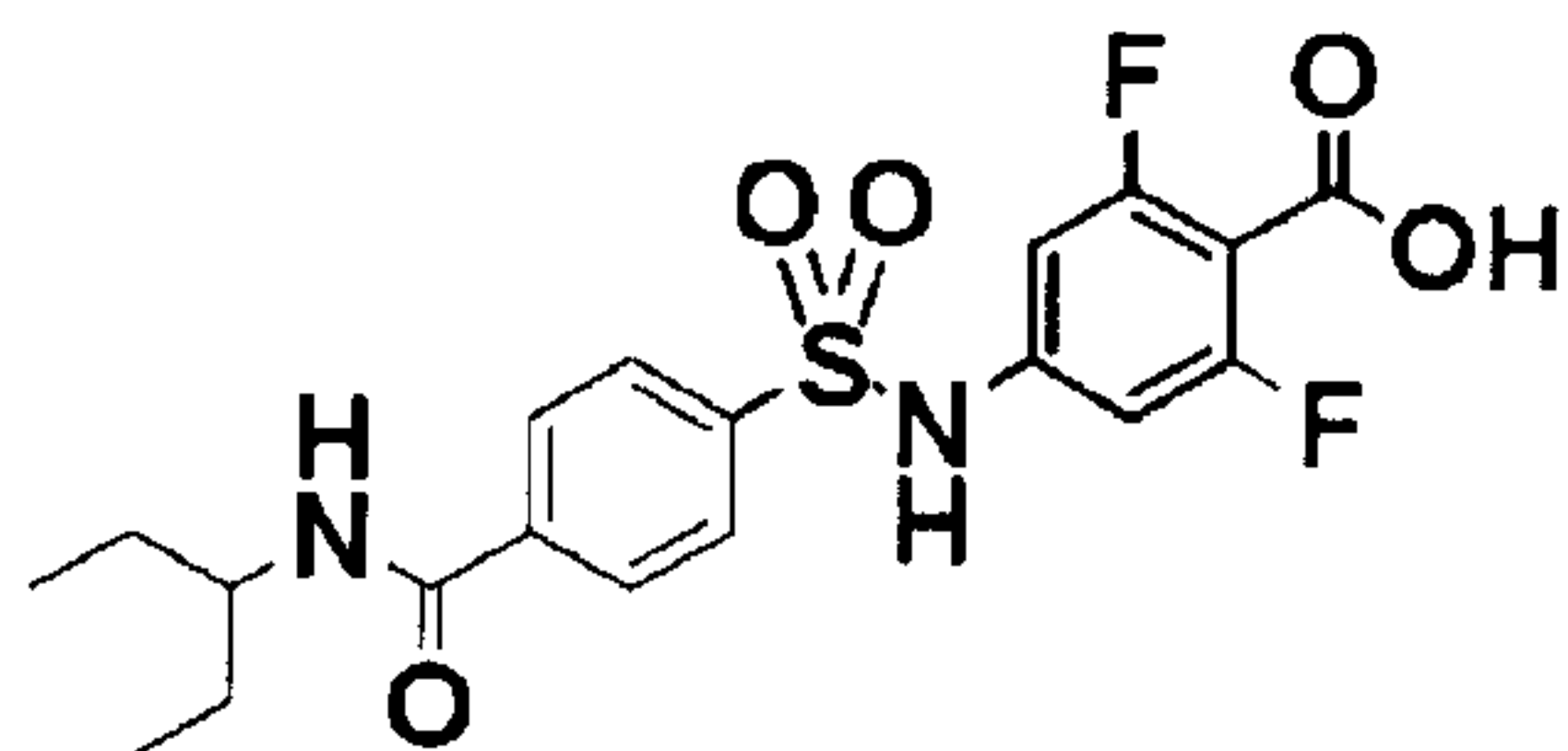


5 The title compound (M-67) (600 mg, 34% over two steps) was obtained as a white solid by subjecting 4-([3,5-difluoro-4-(methoxycarbonyl)phenyl]amino)sulfonyl benzoic acid <see (Step 1) of Example 11> (1.5 g, 4.0 mmol) to a method including the same two steps as (Step 2) of Example 11 and (Step 5) of Example 104.

¹H-NMR (CD₃OD, 300 MHz): δ 7.97-7.90 (m, 4H), 6.84 (d, J = 2.4 Hz, 1H), 6.80 (d, J = 2.4 Hz, 1H), 3.33-3.10 (m, 1H), 1.96-1.92 (m, 2H), 1.82-1.78 (m, 3H), 1.42-1.30 (m, 5H).; MS (ESI) m/z 439 (M+H)⁺

15 Example 126: Synthesis of M-68

(Step 1)
4-{[(4-{[(1-Ethylpropyl)amino]carbonyl}phenyl)sulfonyl]amino}-2,6-difluorobenzoic Acid (M-68)



20 The title compound (M-68) (570 mg, 31% over two steps) was obtained as a white solid by subjecting 4-([3,5-difluoro-4-(methoxycarbonyl)phenyl]amino)sulfonyl benzoic acid <see (Step 1) of Example 11> (1.5 g, 4.0 mmol) to a method including the same two steps as (Step 2) of Example

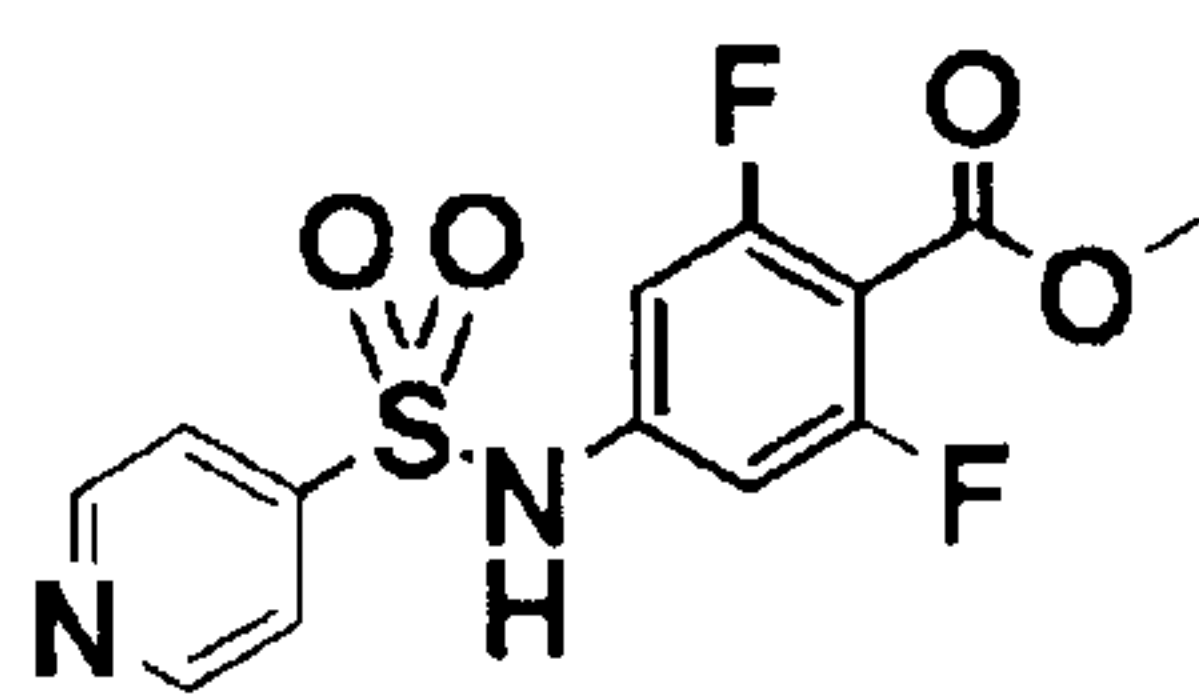
11 and (Step 5) of Example 104.

$^1\text{H-NMR}$ (CD_3OD , 400 MHz): δ 7.95-7.90 (m, 4H), 6.78 (d, J = 9.2 Hz, 2H), 3.83-3.79 (m, 1H), 1.64-1.47 (m, 4H), 0.92 (t, J = 7.2 Hz, 6H).; MS (ESI) m/z 427 ($\text{M}+\text{H}$) $^+$

5 Example 127: Synthesis of M-69

(Step 1) Methyl

2,6-Difluoro-4-[(pyridin-4-ylsulfonyl)amino]benzoate

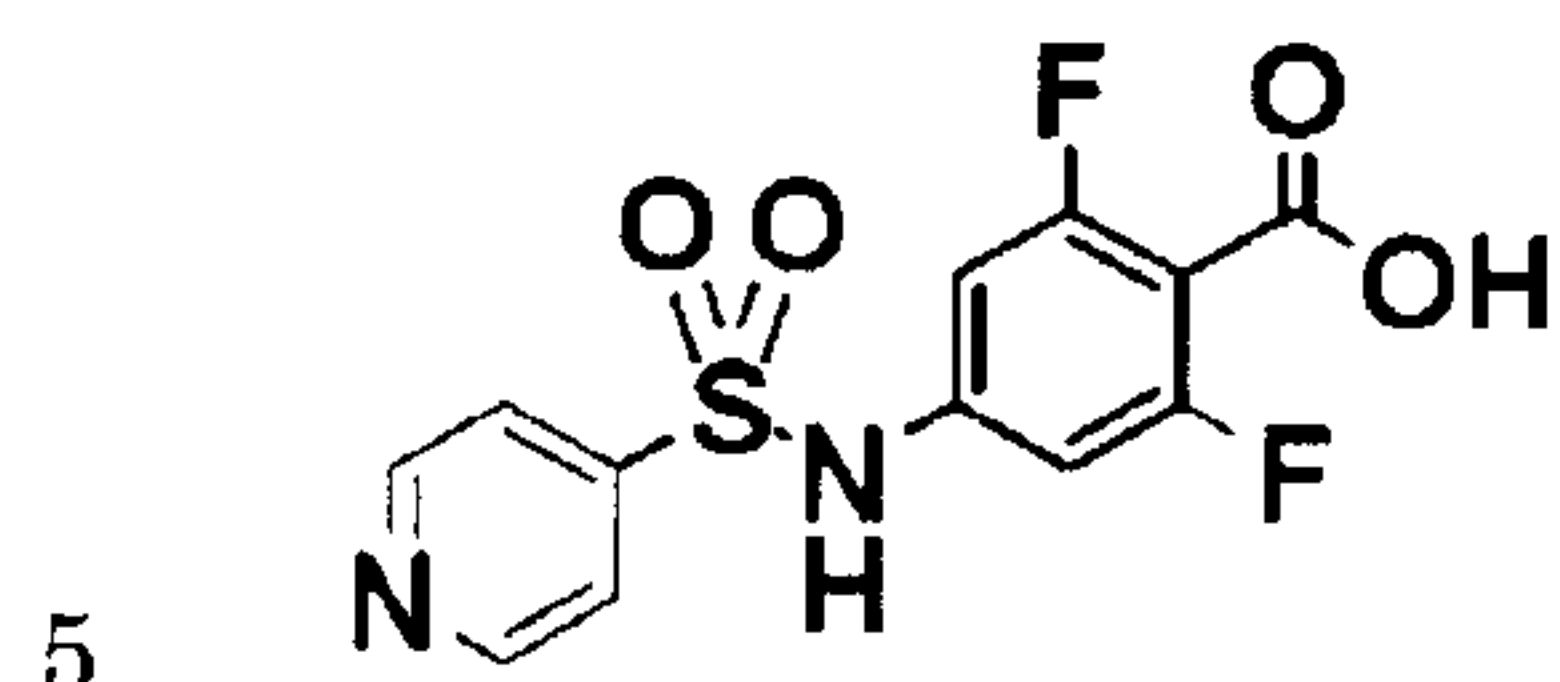


Pyridine-4-thiol (16.7 g, 150 mmol) was dissolved in
 10 concentrated hydrochloric acid (110 ml) and water (30 ml).
 After cooling to 0°C, chlorine gas was bubbled for 1 hour. The
 reaction solution was diluted with ice-water (75 g), and
 neutralized by gradually adding sodium hydrogen carbonate.
 After extraction with methylene chloride (150 ml×3) cooled to
 15 5 to 10°C, the organic layers were combined and dried over
 anhydrous sodium sulfate. Then, the solvent was removed under
 reduced pressure to obtain the corresponding sulfonyl chloride.
 In another reaction vessel, methyl
 4-amino-2,6-difluorobenzoate (16.9 g, 90.3 mmol) and pyridine
 20 (10 ml) were dissolved in methylene chloride (200 ml). After
 cooling to -10°C, the above-described solution of the sulfonyl
 chloride in methylene chloride was added thereto, followed by
 stirring at room temperature for 6 hours. The organic layer
 was washed with 0.1 N hydrochloric acid (200 ml×2), and the
 25 solvent was removed under reduced pressure. The residue was
 purified by silica gel column chromatography (petroleum
 ether/ethyl acetate=2:1 to 1:1) to obtain the title compound

(11.2 g, 38% over two steps).

MS (ESI) m/z 329 (M+H)⁺

(Step 2) 2,6-Difluoro-4-[(pyridin-4-ylsulfonyl)amino]benzoic Acid (M-69)



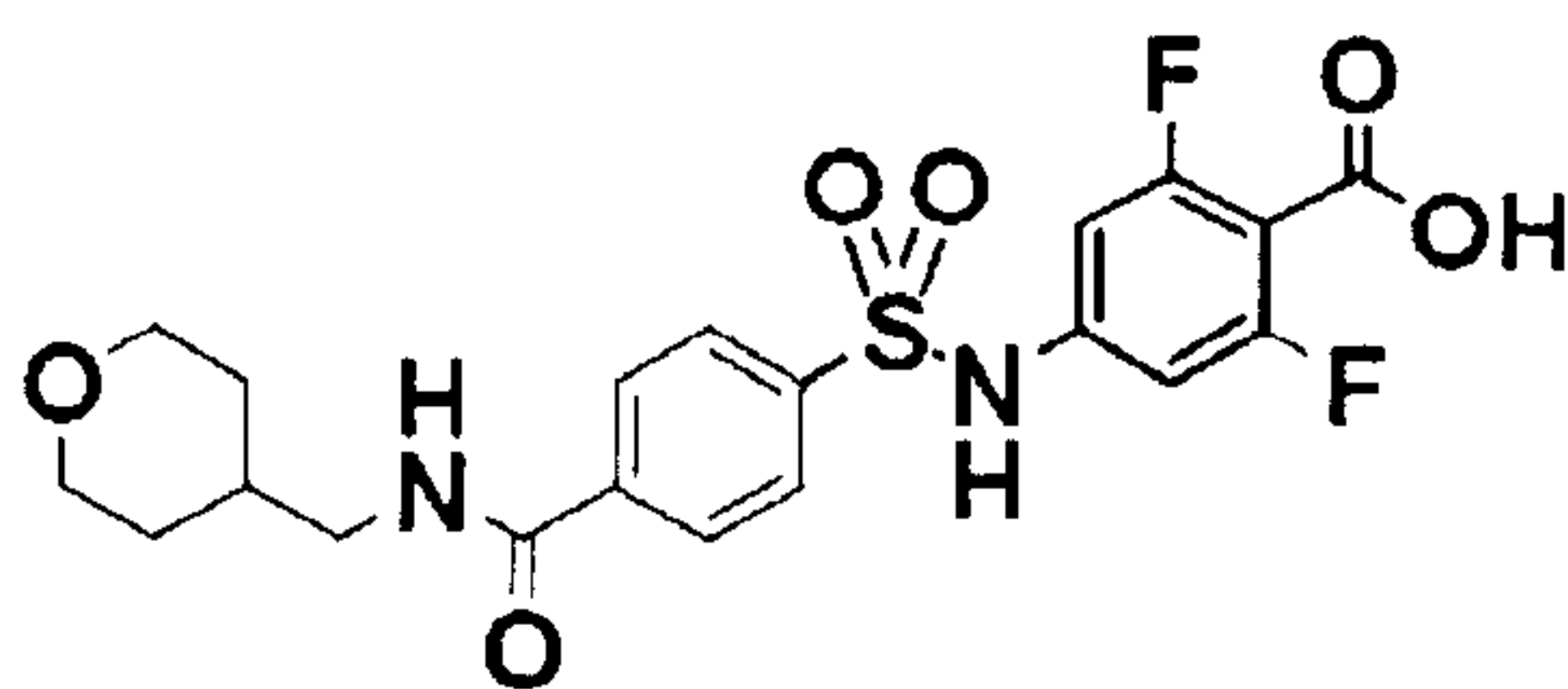
The title compound (M-69) (790 mg, 90%) was obtained by
 subjecting methyl
 2,6-difluoro-4-[(pyridin-4-ylsulfonyl)amino]benzoate (920 mg,
 2.80 mmol) to the same method as in (Step 5) of Example 104.

10 ¹H NMR (CD₃OD, 400 MHz): δ 8.99 (dd, J = 5.2, 1.6 Hz, 2H), 8.27
 (dd, J = 5.2, 1.6 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H).; MS (ESI)
 m/z 315 (M+H)⁺

Example 128: Synthesis of M-70

(Step 1) 1)

15 2,6-Difluoro-4-{[(4-{[(tetrahydro-2H-pyran-4-yl-methyl)amin
 o]carbonyl}phenyl)sulfonyl]amino}benzoic Acid (M-70)



To

4-({[3,5-difluoro-4-(methoxycarbonyl)phenyl]amino}sulfonyl)
 20 benzoic acid <see (Step 1) of Example 11> (85 mg, 0.23 mmol),
 dichloromethane (5.0 ml) was added, and HATU (114 mg, 0.30 mmol),
 C-(tetrahydro-pyran-4-yl)-methylamine (32.0 μl, 0.280 mmol),
 and DIPEA (120 μl, 0.690 mmol) were added sequentially, followed
 by stirring at room temperature overnight. To the reaction

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

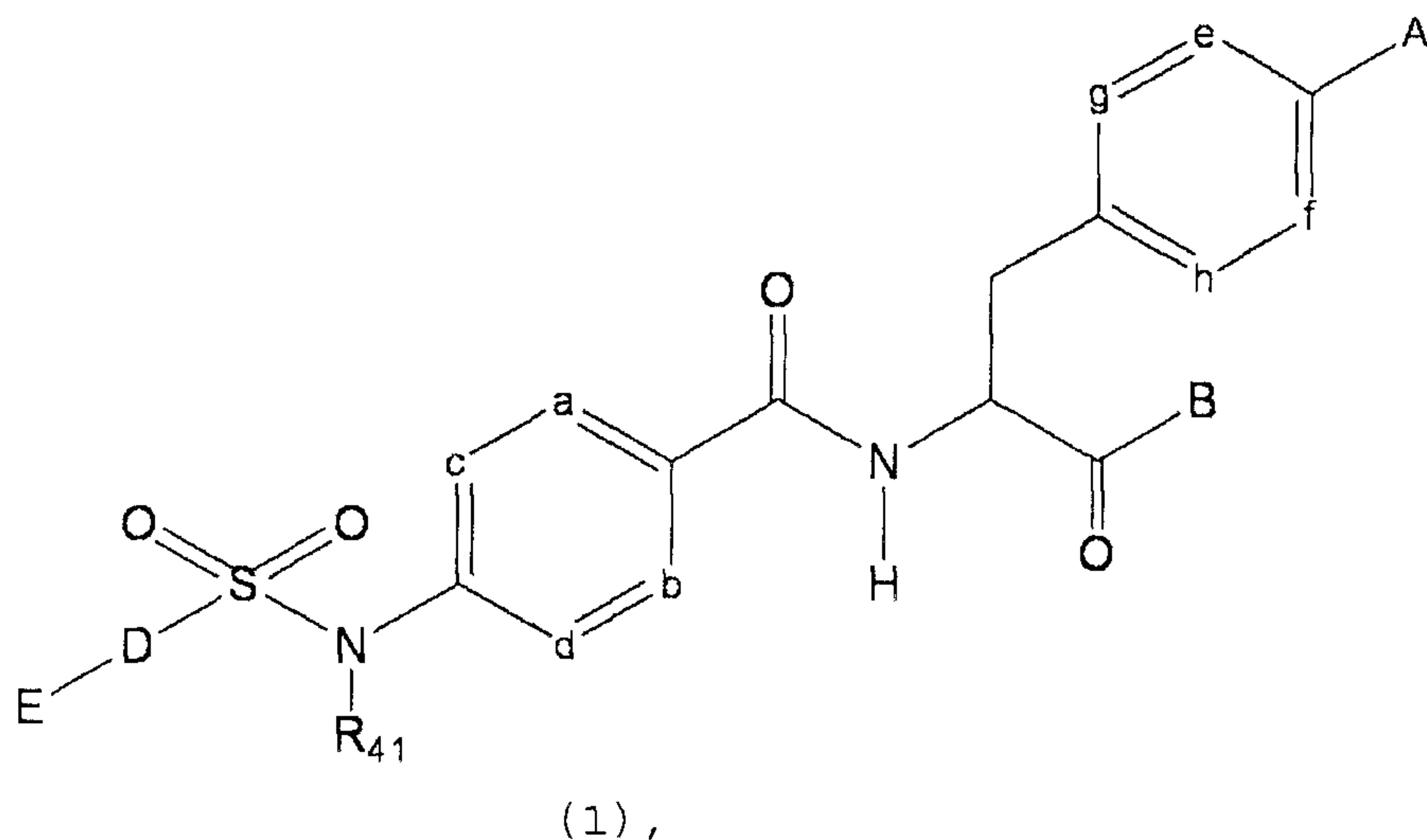
**THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE
THAN ONE VOLUME.**

THIS IS VOLUME __1__ OF __2__

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

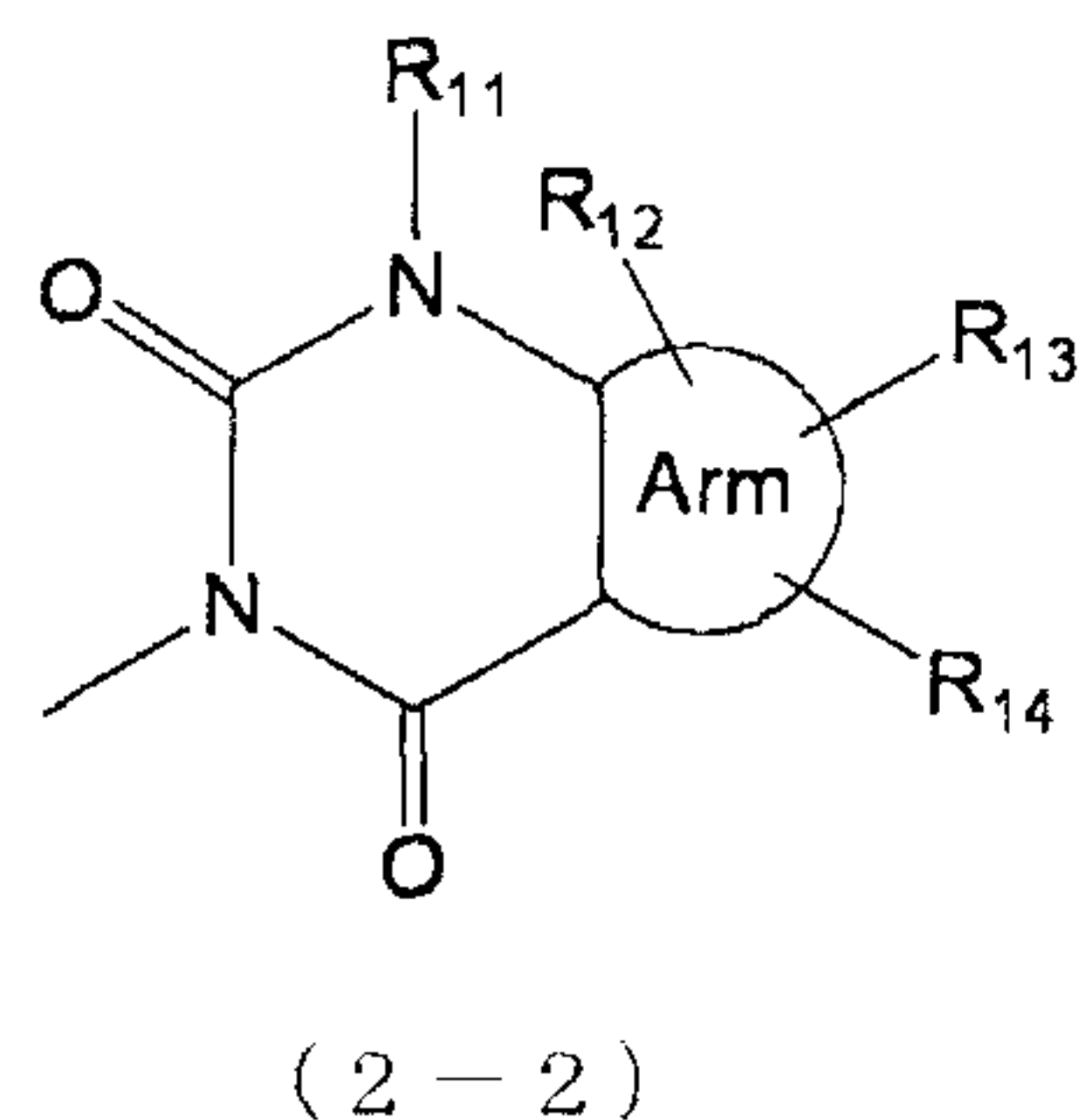
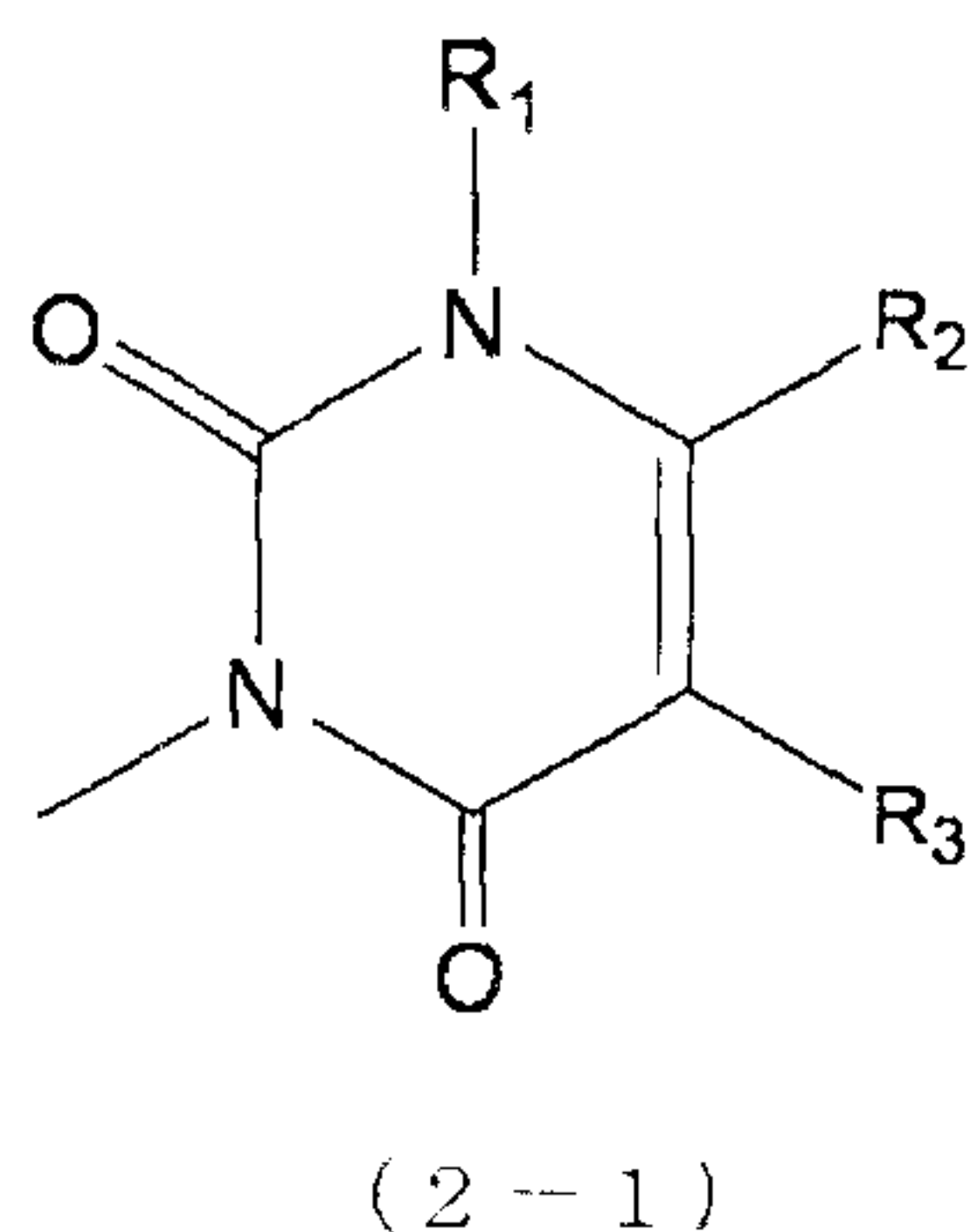
Claims:

1. A sulfonamide derivative represented by the following general formula (1) or a pharmaceutically acceptable salt thereof:



wherein

A represents a group represented by the following general formula (2-1), or (2-2)



, wherein

Arm is selected from the group consisting of a phenyl group, a pyridyl group, and an imidazolyl group,

R₁, and R₁₁ each independently represent any one of a

hydrogen atom, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, and a lower alkoxy group,

R_{12} , R_{13} , and R_{14} each independently represent any one of a hydrogen atom, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, a lower alkoxy group, an amino group, a lower alkylamino group, and a (lower alkylamino)lower alkyl group,

R_2 and R_3 each independently represent any one of a hydrogen atom, a lower alkyl group, a lower alkenyl group, a lower alkynyl group, and a lower alkoxy group,

B represents any one of a lower alkoxy group optionally substituted with a hydroxyl group(s), a lower alkyl group(s), a lower alkylamino group(s), and/or a 5- or 6-membered heterocyclic group(s) containing oxygen atoms, sulfur atoms, or nitrogen atoms, as a ring-constituent atom(s), and a hydroxyl group,

R_{41} represents a hydrogen atom or a lower alkyl group,

a, b, c, and d each independently represent C- R_{31} , C- R_{32} , C- R_{33} , and C- R_{34} , respectively, but one or two of a, b, c, and d may each represent a nitrogen atom,

R_{31} , R_{32} , R_{33} , and R_{34} each independently represent any one of a hydrogen atom, a halogen atom, a lower alkyl group, and a lower alkoxy group,, provided that any one of R_{31} , R_{32} , R_{33} , and R_{34} is a halogen atom or a lower alkyl group,

e, f, g, and h each independently represent C- R_{35} , C- R_{36} , C- R_{37} , and C- R_{38} , respectively, but one or two of e, f, g, and h may each represent a nitrogen atom,

R_{35} , R_{36} , R_{37} , and R_{38} are each independently any one of a hydrogen atom, a lower alkyl group, and a lower alkoxy group,

D represents a phenylene group or 5- or 6-membered heterocyclic group containing oxygen atoms, sulfur atoms, or nitrogen atoms, as a ring-constituent atom(s),

optionally having a substituent(s) selected from the group consisting of hydroxyl groups, lower alkyl groups, lower alkenyl groups, lower alkynyl groups, and lower alkoxy groups, and

E represents

(1) a 5- or 6-membered heterocyclic group containing 1, 2, 3 or 4 heteroatoms selected from the group consisting of oxygen atoms, sulfur atoms, and nitrogen atoms, as a ring-constituent atom(s), optionally having a substituent(s) selected from the group consisting of (1.1) halogen atoms, (1.2) hydroxyl groups, (1.3) lower alkyl groups, (1.4) lower alkenyl groups, (1.5) lower alkynyl groups, (1.6) lower alkoxy groups, (1.7) amino groups -NH_2 , (1.8) 4- to 6-membered cyclic amino groups, (1.9) carboxyl groups, and (1.10) lower alkyloxycarbonyl groups;

(2) an aminocarbonyl group optionally having a substituent(s) selected from the group consisting of (2.1) hydroxyl groups, (2.2) lower alkyl groups, (2.3) lower alkenyl groups, (2.4) lower alkynyl groups, (2.5) lower alkoxy groups, (2.6) 5- or 6-membered heterocyclic groups containing 1, 2, 3 or 4 heteroatoms selected from the group consisting of oxygen atoms, sulfur atoms, and nitrogen atoms, as a ring-constituent atom(s), and (2.7) heterocycle-substituted lower alkyl groups wherein the heterocycle is a 5- or 6-membered heterocyclic groups containing 1, 2, 3 or 4 heteroatoms selected from the group consisting of oxygen atoms, sulfur atoms, and nitrogen atoms, as a ring-constituent atom(s);

(3) a hydrogen atom;

(4) a hydroxyl group;

(5) a lower alkyl group;

(6) a lower alkenyl group;

(7) a lower alkynyl group;

- (8) a lower alkoxy group;
- (9) an amino group -NH₂;
- (10) a lower alkylcarbonyl group;
- (11) a lower alkyloxy carbonyl group; or
- (12) a lower alkylaminoalkylene group,

provided that the lower alkylcarbonyl group and the lower alkyloxy carbonyl group may each be bonded to the phenyl group represented by D to form a condensed ring;

wherein the term "lower alkyl" means that the group has 1 to 6 carbon atoms;

the term "lower alkenyl" means that the group has 2 to 6 carbon atoms;

the term "lower alkynyl" means that the group has 2 to 6 carbon atoms; and

the term "lower alkoxy" means that the group has 1 to 6 carbon atoms.

2. The sulfonamide derivative according to claim 1 or a pharmaceutically acceptable salt thereof, wherein

D is a phenylene group optionally having a substituent(s) selected from the group consisting of lower alkyl groups, hydroxyl groups, and lower alkoxy groups.

3. The sulfonamide derivative according to claim 1 or a pharmaceutically acceptable salt thereof, wherein

D is a 6-membered aromatic heterocyclic group containing a nitrogen atom(s) as a ring-constituent atom(s) and optionally having a substituent(s) selected from the group consisting of lower alkyl groups, and lower alkoxy groups.

4. The sulfonamide derivative according to claim 1 or a

pharmaceutically acceptable salt thereof, wherein

the heterocyclic group represented by D is a pyridyl group or pyrrole group optionally having a substituent(s) selected from the group consisting of lower alkyl groups, and lower alkoxy groups.

5. The sulfonamide derivative according to any one of claims 1 to 4 or a pharmaceutically acceptable salt thereof, wherein

E is a 5- or 6-membered aromatic heterocyclic group containing 1, 2, 3, or 4 hetero atoms selected from the group consisting of oxygen atoms, sulfur atoms, and nitrogen atoms and optionally having a substituent(s) selected from the group consisting of lower alkyl groups, lower alkoxy groups, and halogen atoms.

6. The sulfonamide derivative according to claim 5 or a pharmaceutically acceptable salt thereof, wherein

the aromatic heterocyclic group is selected from the group consisting of a pyridyl group, a pyridazyl group, a pyrimidyl group, a pyrazinyl group, a pyrrolyl group, a furanyl group, a thiophenyl group, a thiazolyl group, an oxazolyl group, a triazolyl group, and a tetrazole group.

7. The sulfonamide derivative according to any one of claims 1 to 3 or a pharmaceutically acceptable salt thereof, wherein

E is an aminocarbonyl group or lower alkylaminoalkylene group optionally substituted with a lower alkyl group(s), a 5- or 6-membered heterocyclic group(s) containing 1, 2, 3 or 4 heteroatoms selected from the group consisting of oxygen atoms, sulfur atoms, and nitrogen atoms, as a ring-constituent atom(s), and/or a heterocycle-substituted lower alkyl group(s) wherein

the heterocycle is a 5- or 6-membered heterocyclic groups containing 1, 2, 3 or 4 heteroatoms selected from the group consisting of oxygen atoms, sulfur atoms, and nitrogen atoms, as a ring-constituent atom(s).

8. The sulfonamide derivative according to any one of claims 1 to 5 and 7 or a pharmaceutically acceptable salt thereof, wherein

each lower alkyl group is a linear, branched, or cyclic alkyl group.

9. The sulfonamide derivative according to any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof, wherein

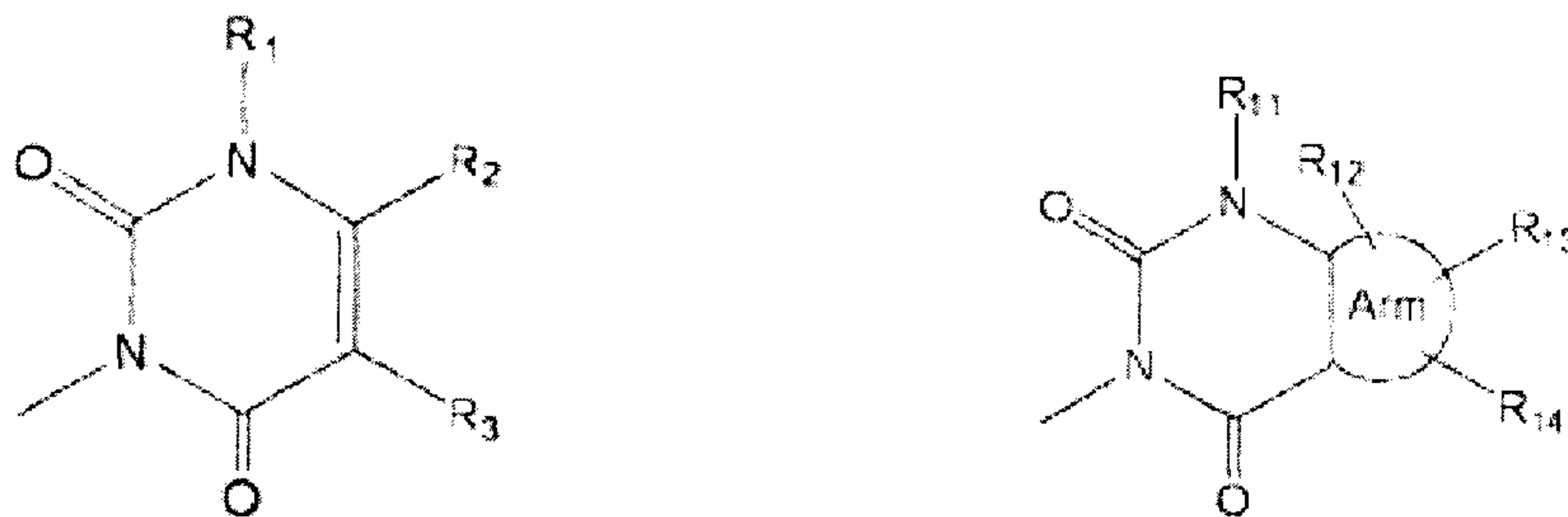
R_1 , and R_{11} are lower alkyl groups.

10. The sulfonamide derivative according to any one of claims 1 to 9 or a pharmaceutically acceptable salt thereof, wherein

one of R_{31} , R_{32} , R_{33} , and R_{34} is a halogen atom, and the rest are hydrogen atoms, or two of R_{31} , R_{32} , R_{33} , and R_{34} are halogen atoms, and the rest are hydrogen atoms.

11. The sulfonamide derivative according to claim 1 or a pharmaceutically acceptable salt thereof, wherein

A is a group represented by general formula:



in which Arm is a pyridyl group or an imidazolyl group,

and R_1 and R_{11} are lower alkyl groups,

two of R_{31} , R_{32} , R_{33} , and R_{34} are halogen atoms, and the rest are hydrogen atoms,

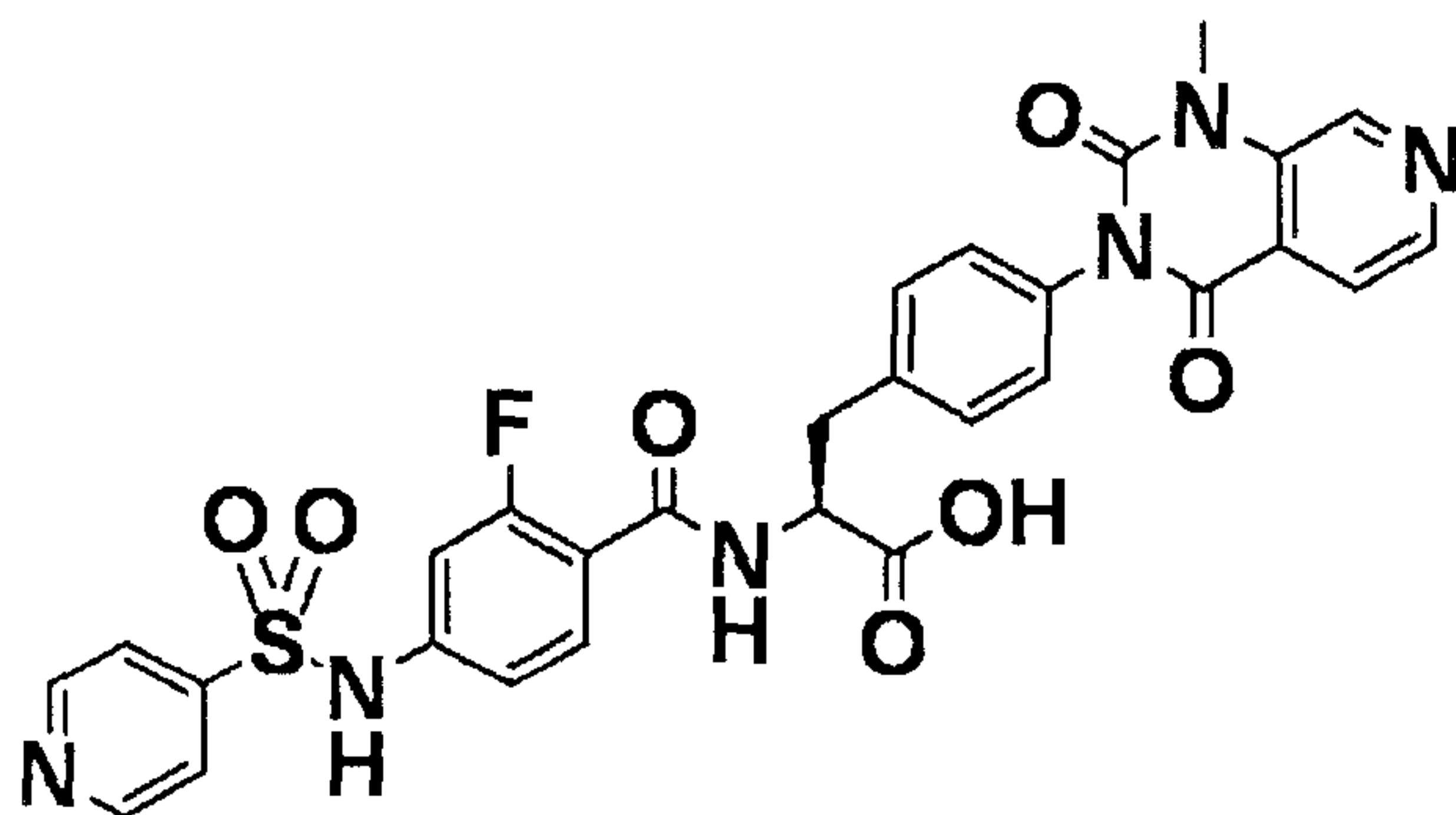
g is a carbon or nitrogen atom,

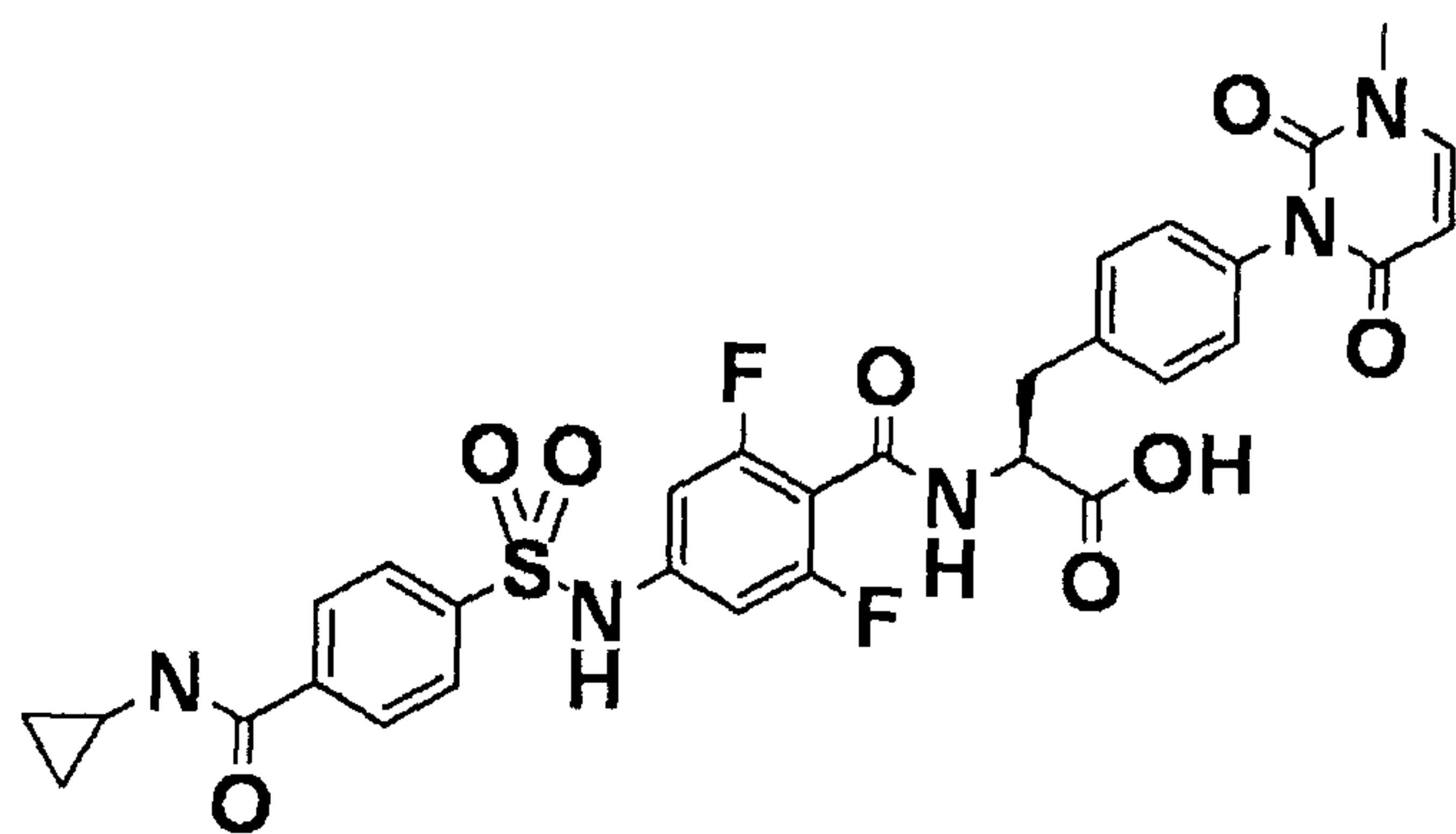
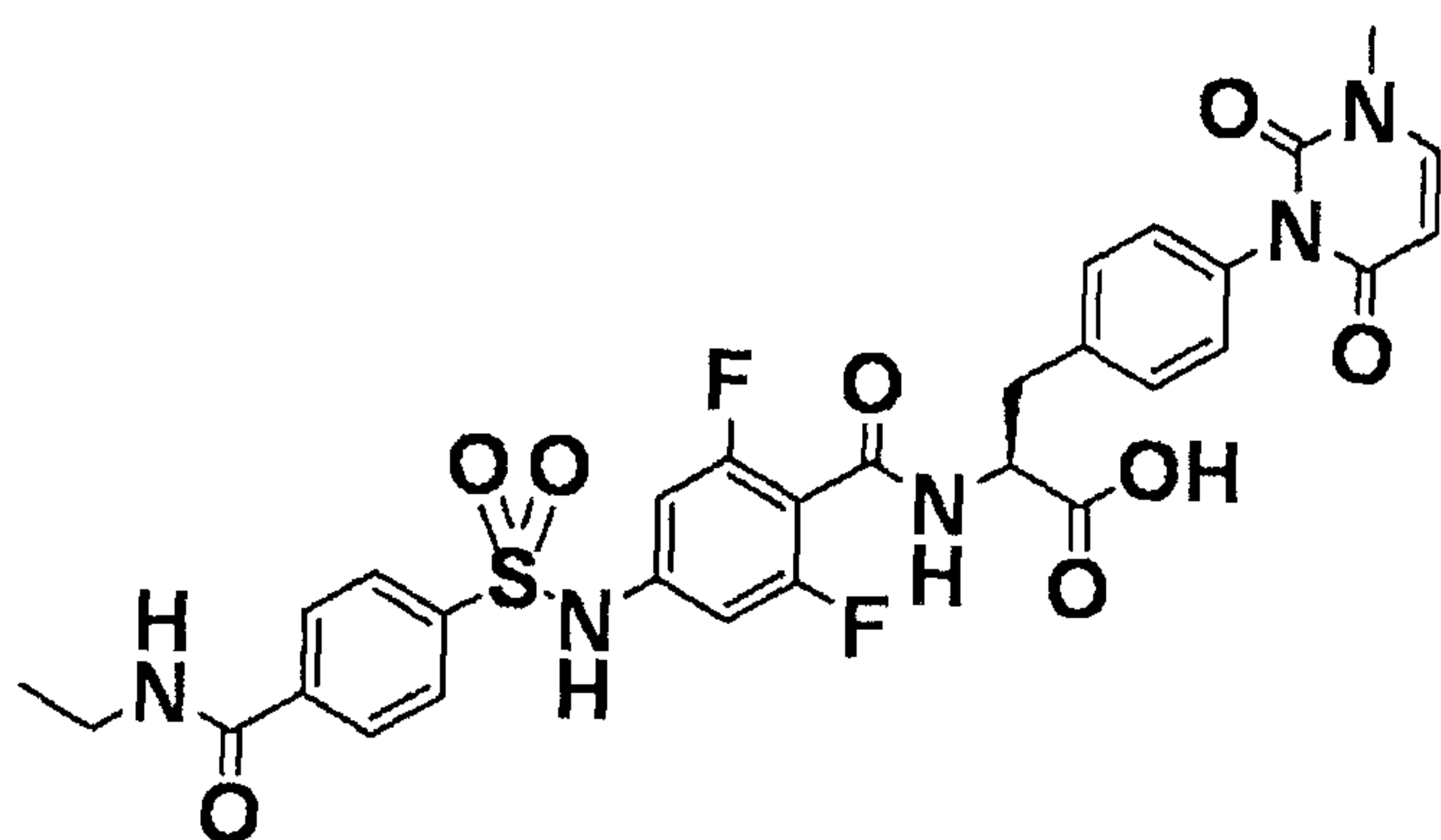
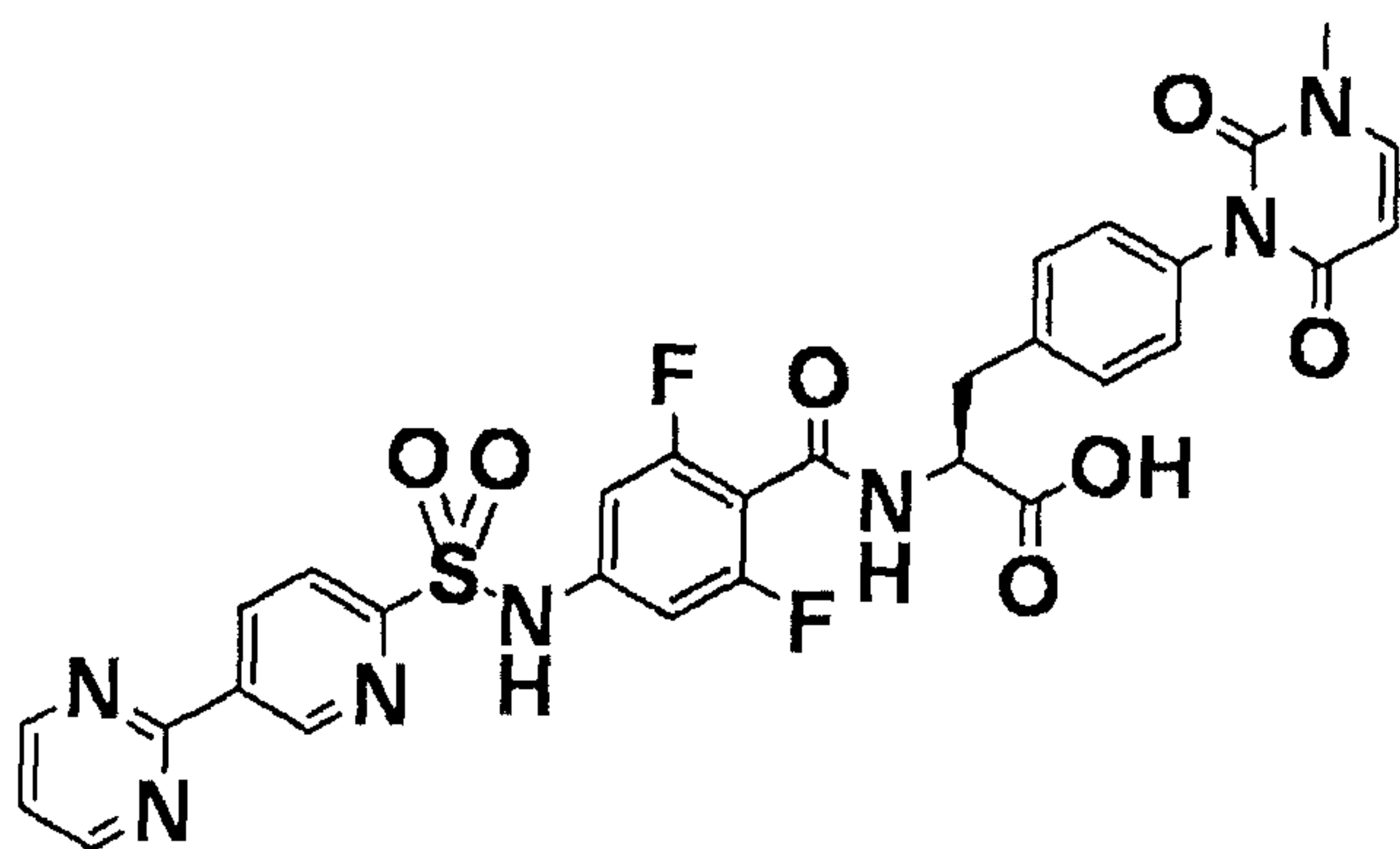
e is a carbon or nitrogen atom,

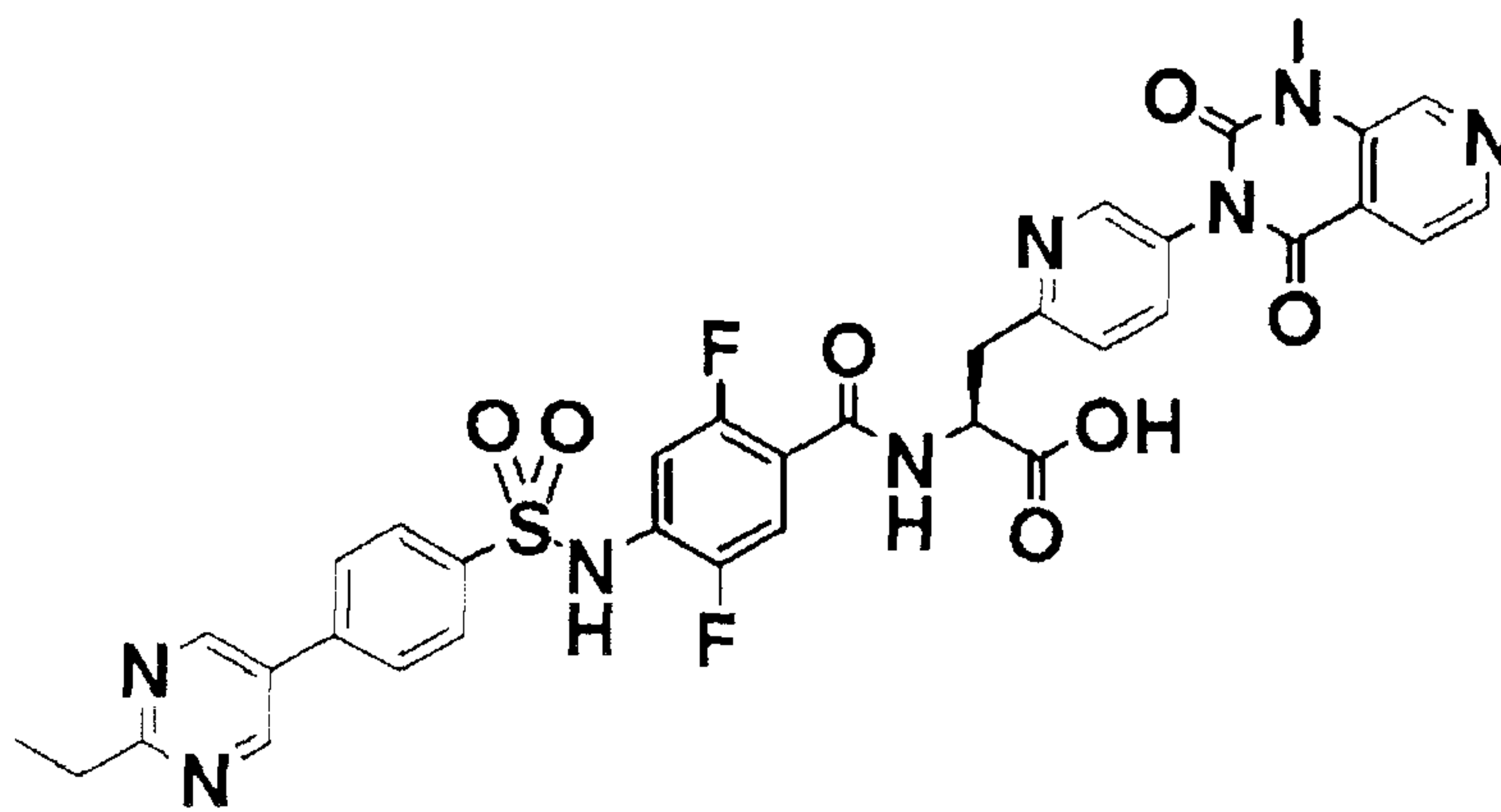
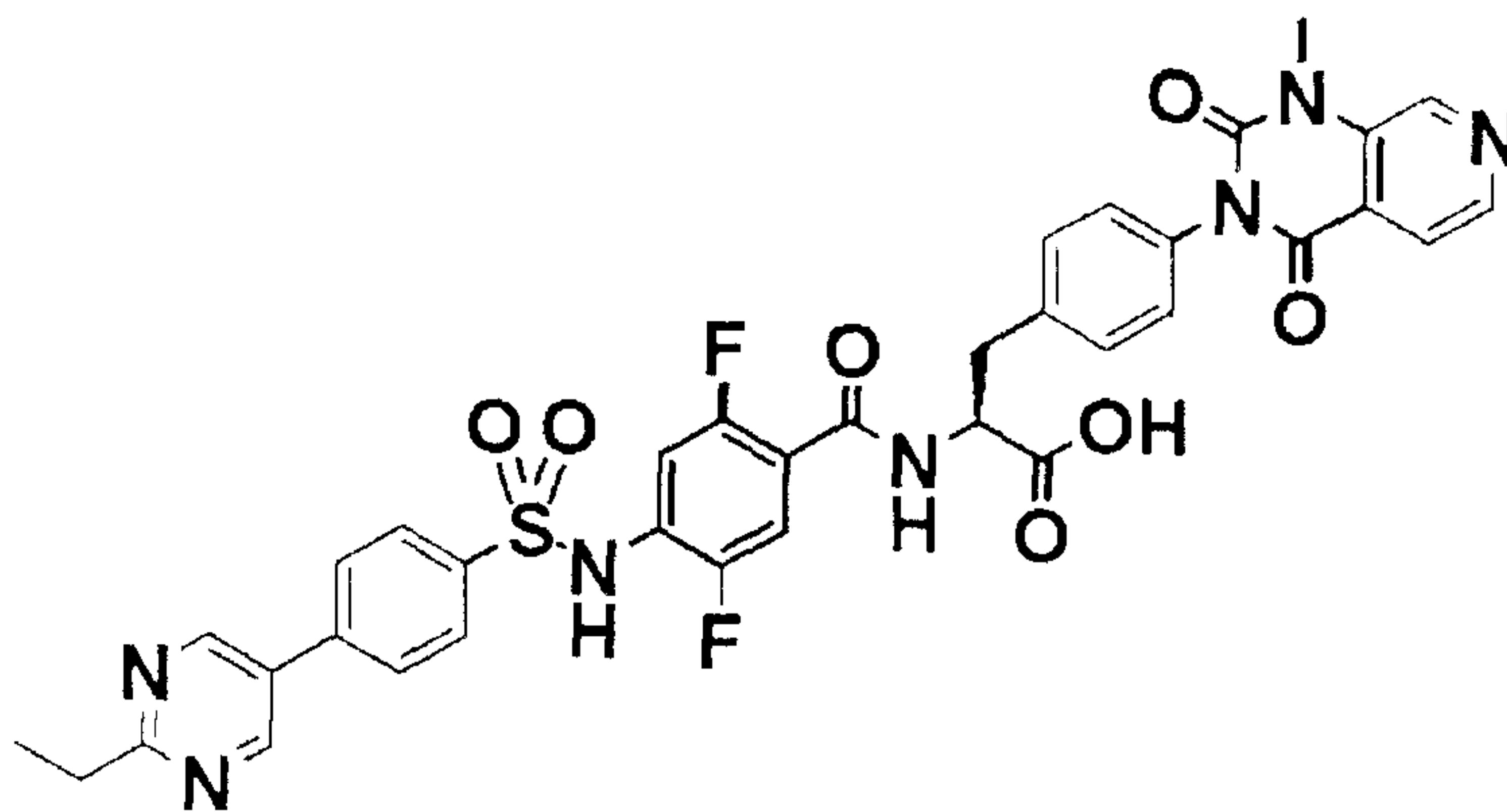
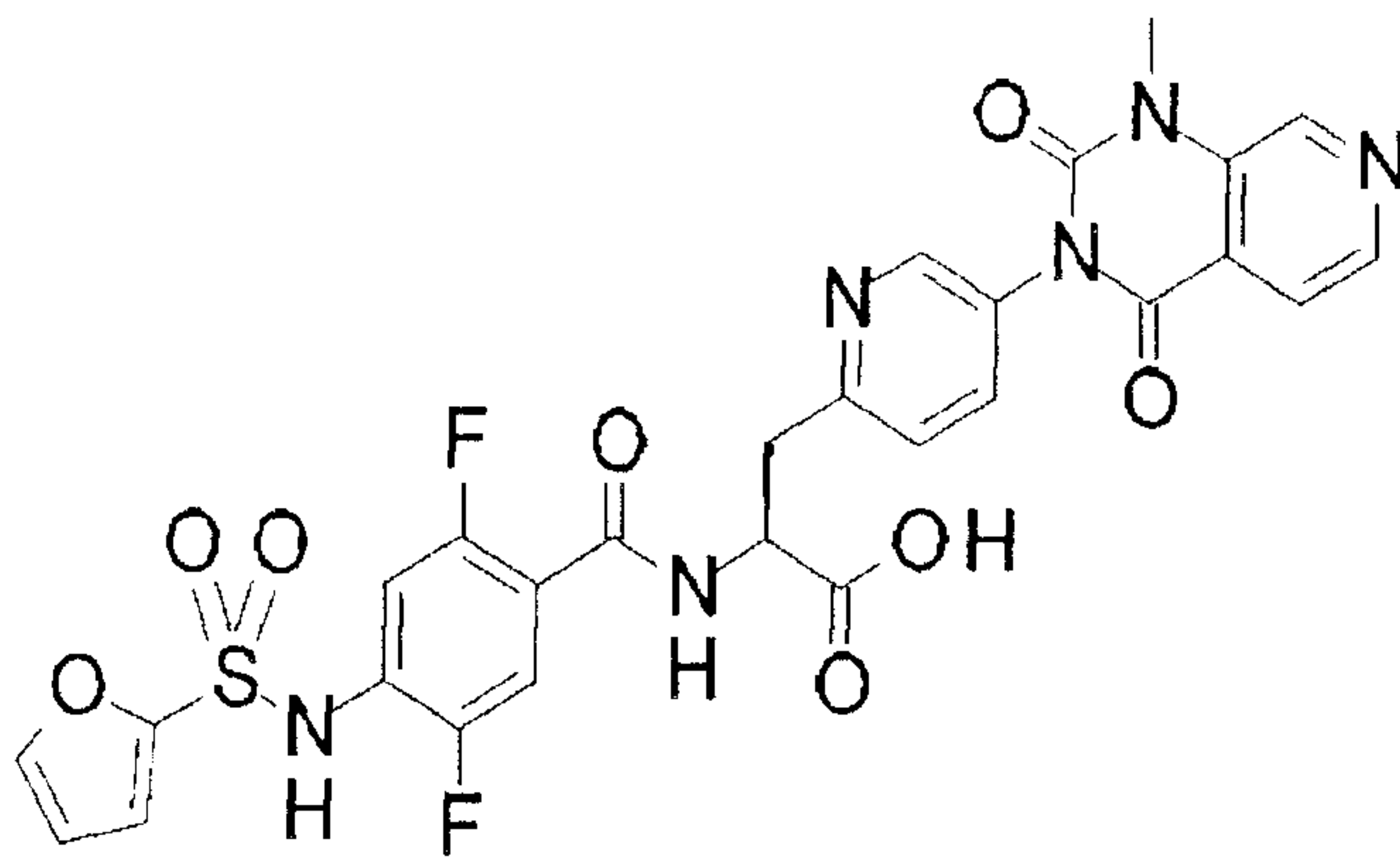
D is a phenylene group optionally having a lower alkyl group(s), and/or a lower alkoxy group(s), a furylene group, or a pyridylene group optionally having a lower alkyl group(s), and/or a lower alkoxy group(s), and

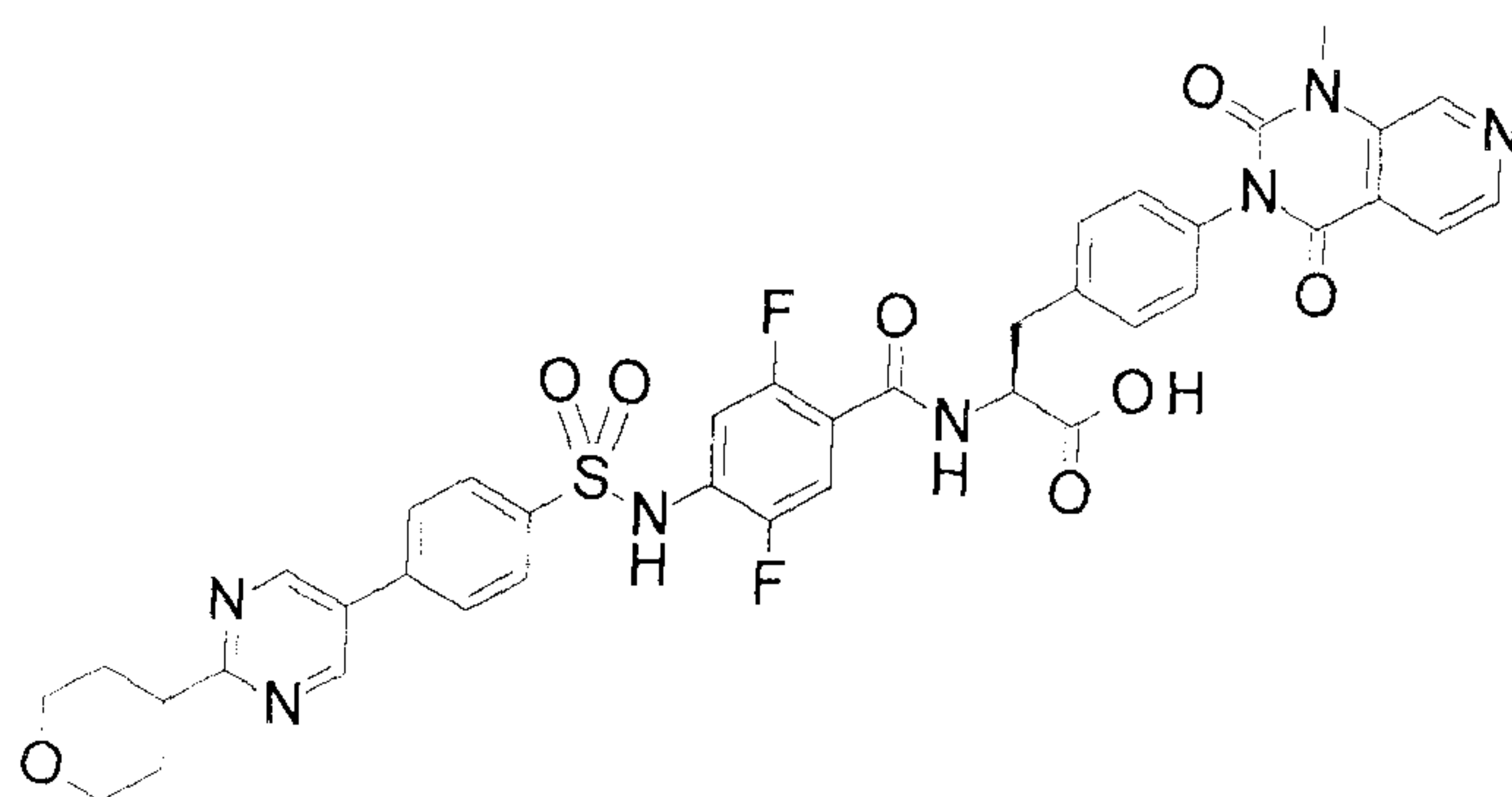
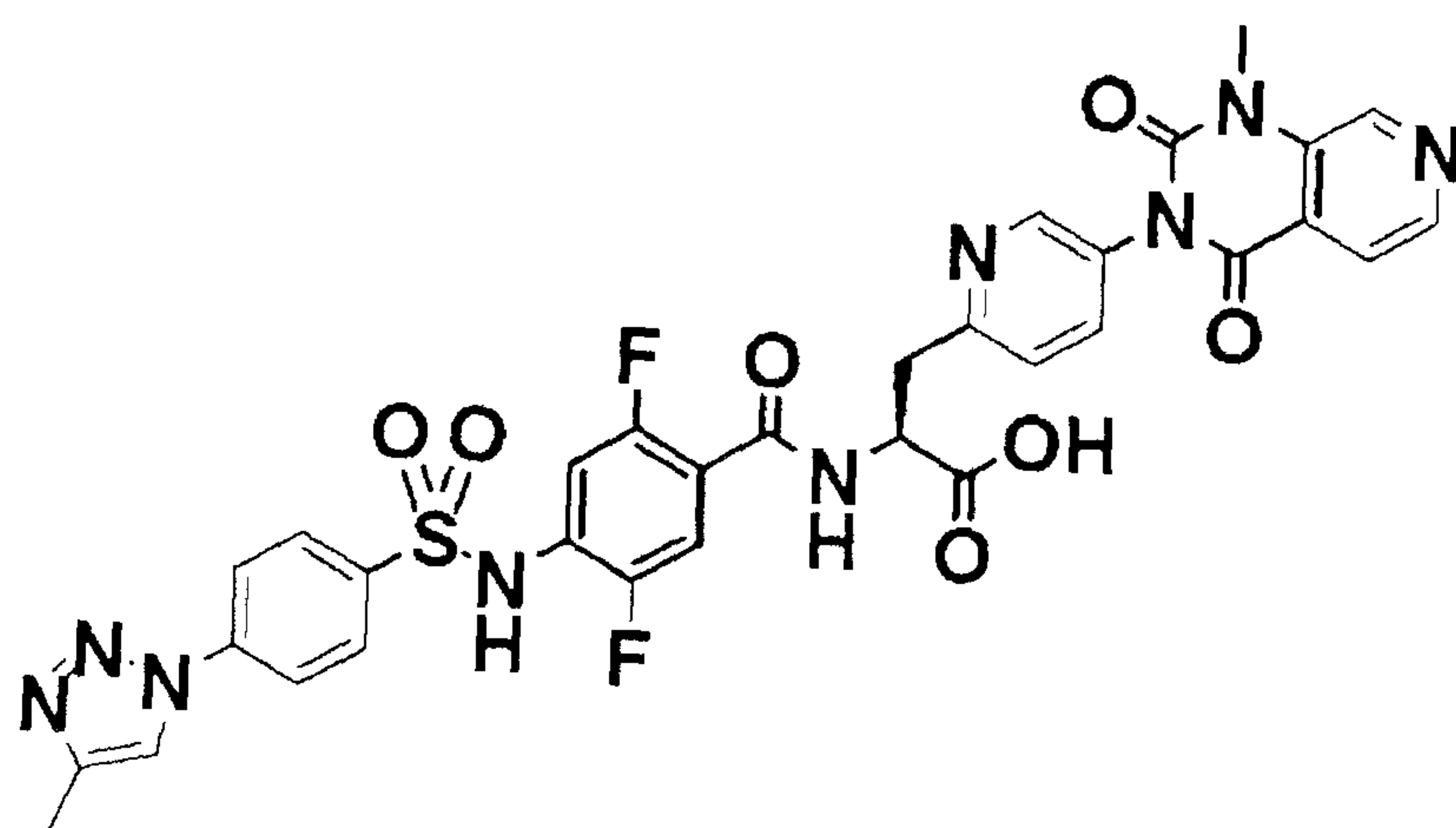
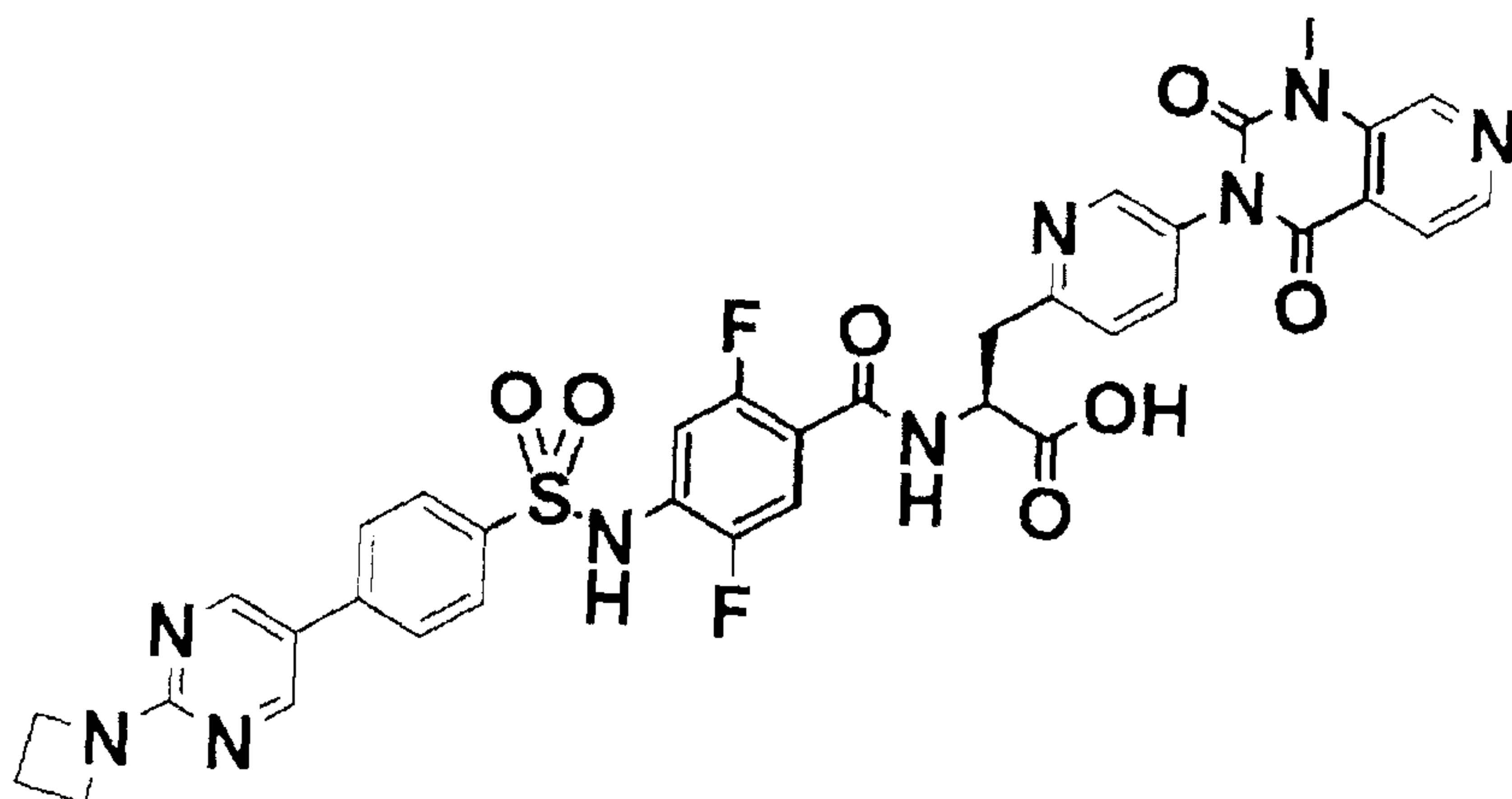
E is a pyridyl group, pyrimidyl group, triazolyl group, or pyrrolyl group optionally having a lower alkyl group(s) and/or a 5- or 6-membered cyclic amino group(s) containing 1, 2, 3 or 4 heteroatoms selected from the group consisting of oxygen atoms, sulfur atoms, and nitrogen atoms, as a ring-constituent atom(s), or an aminocarbonyl group optionally substituted with a lower alky or heterocycle-substituted lower alkyl group(s).

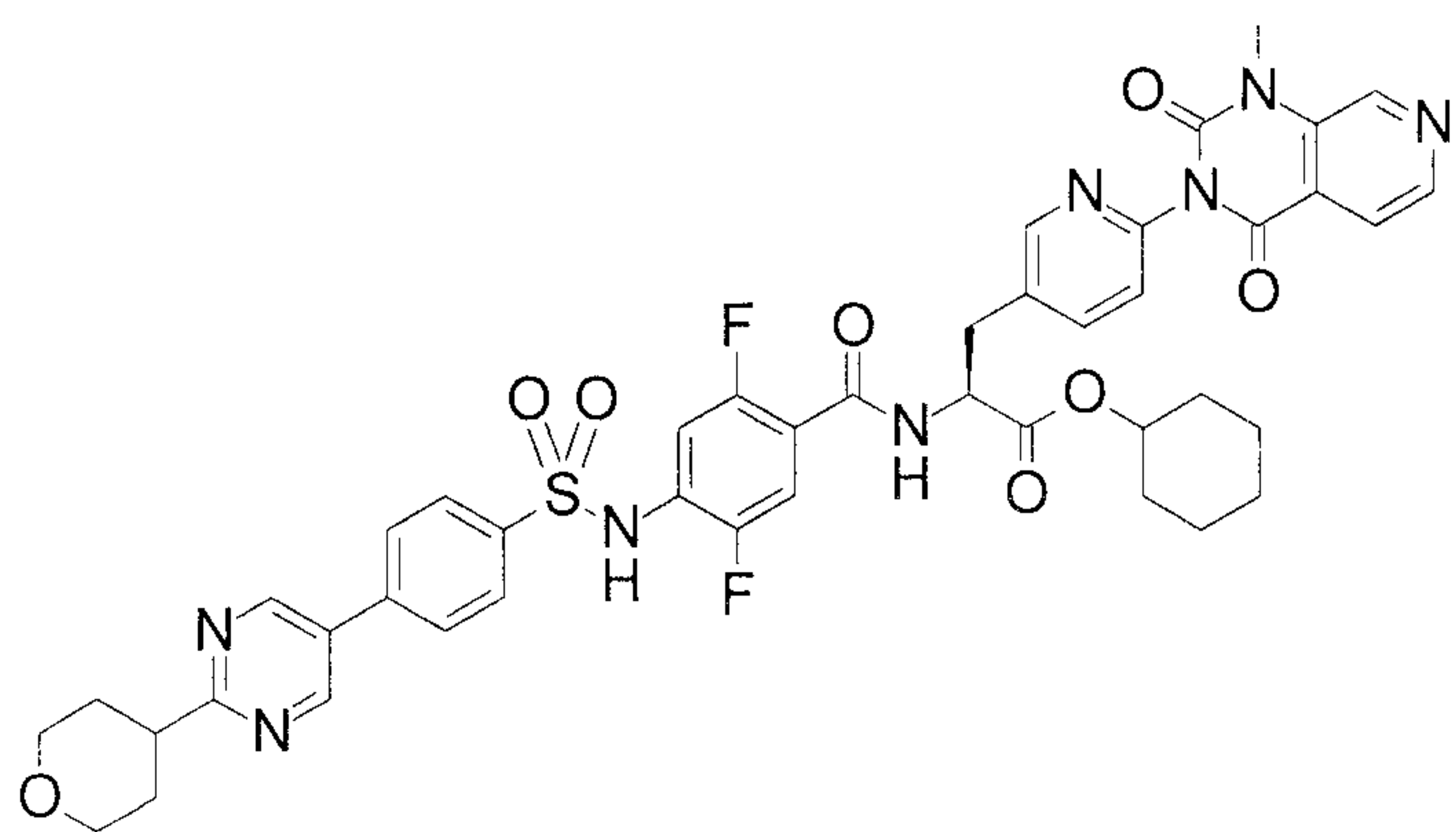
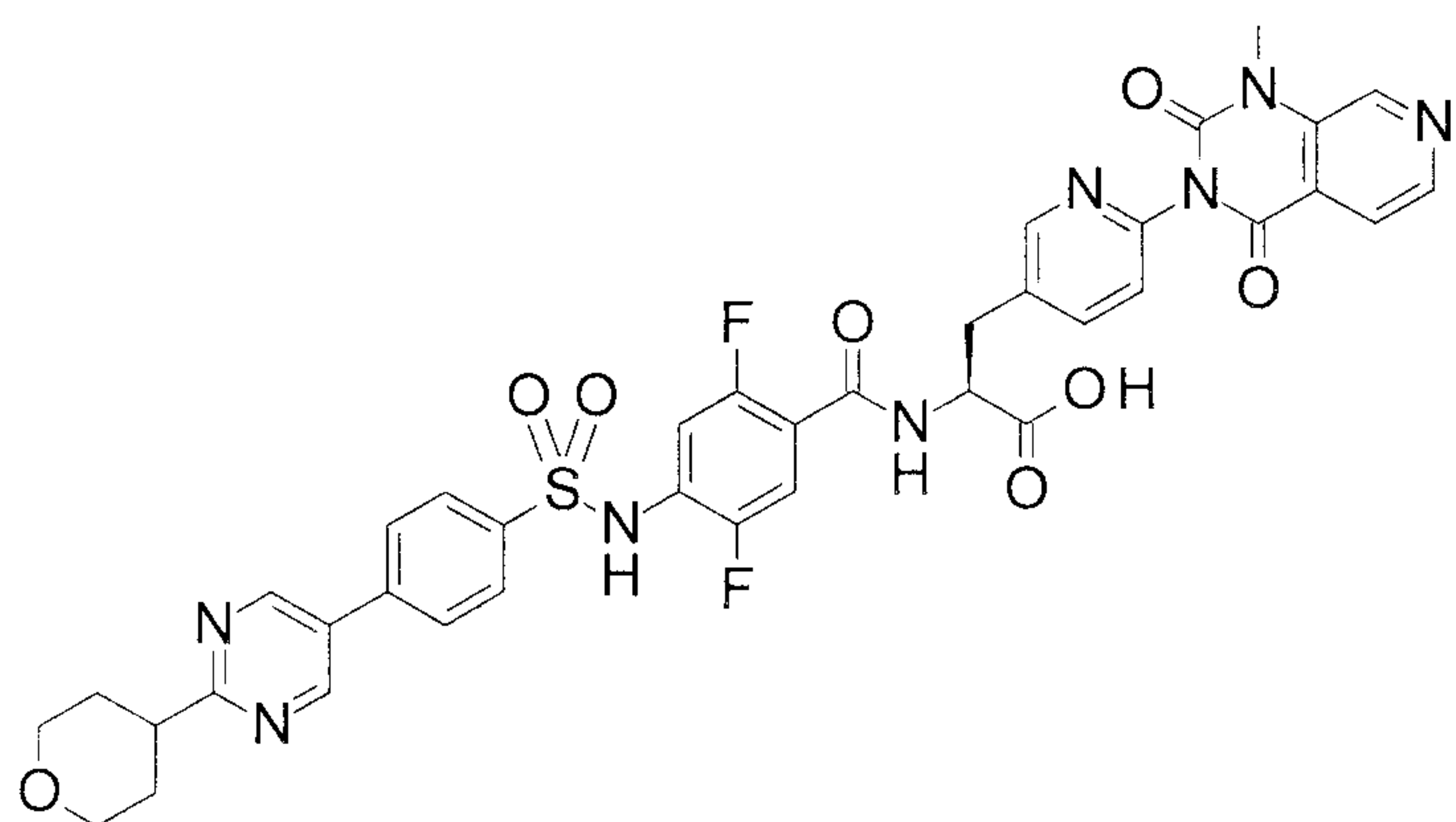
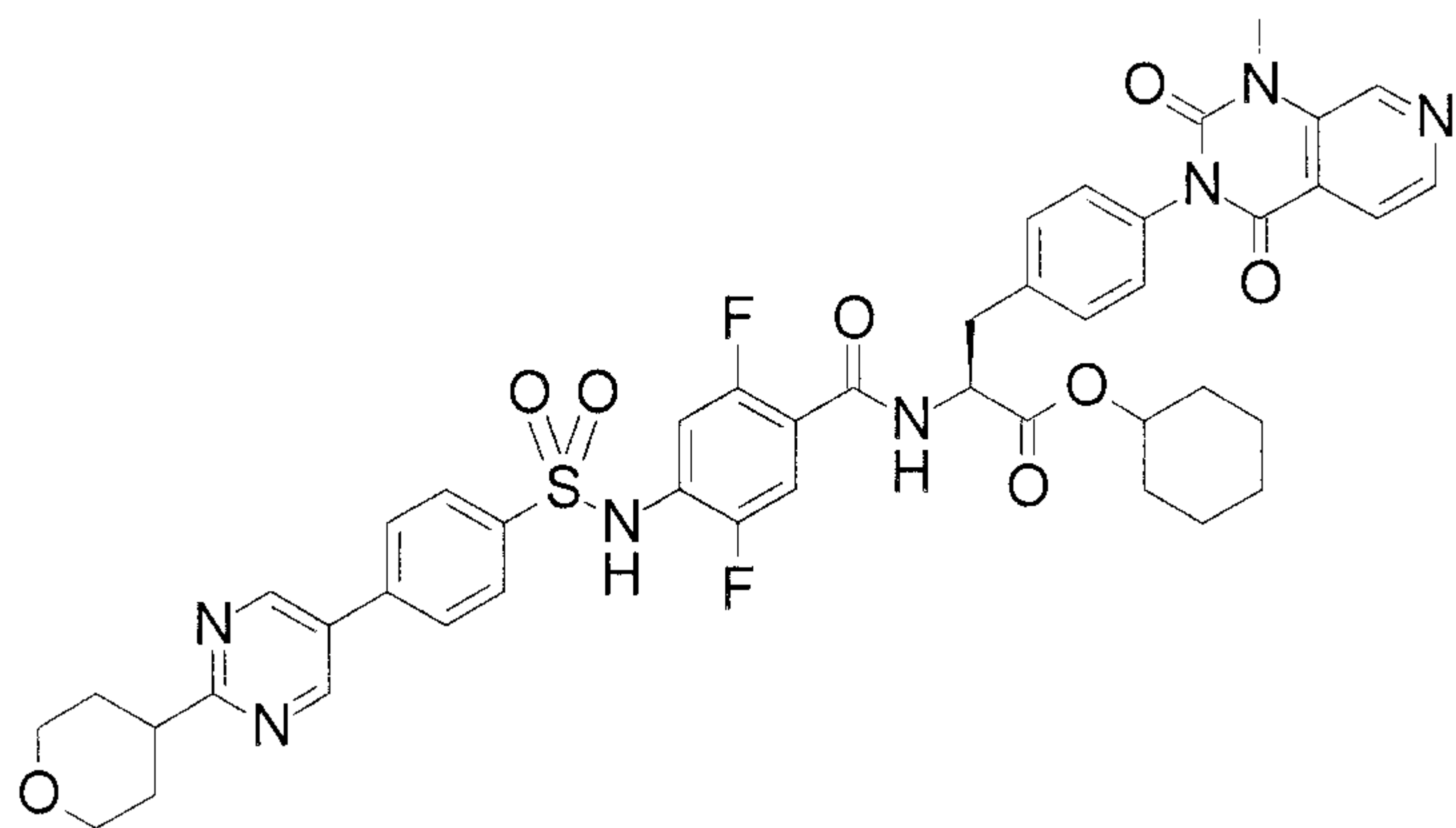
12. A compound represented by any one of the following formulae or a pharmaceutically acceptable salt thereof:

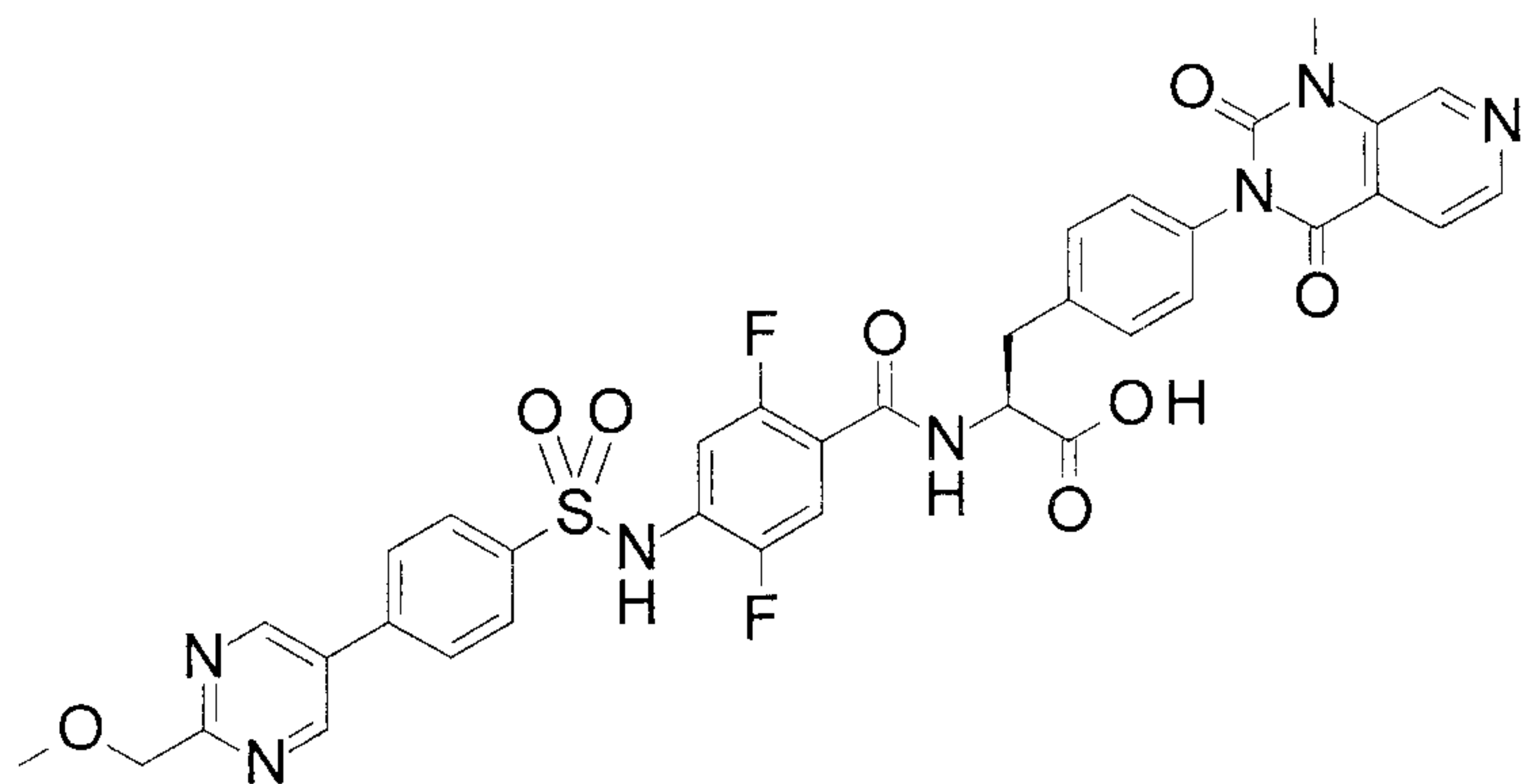




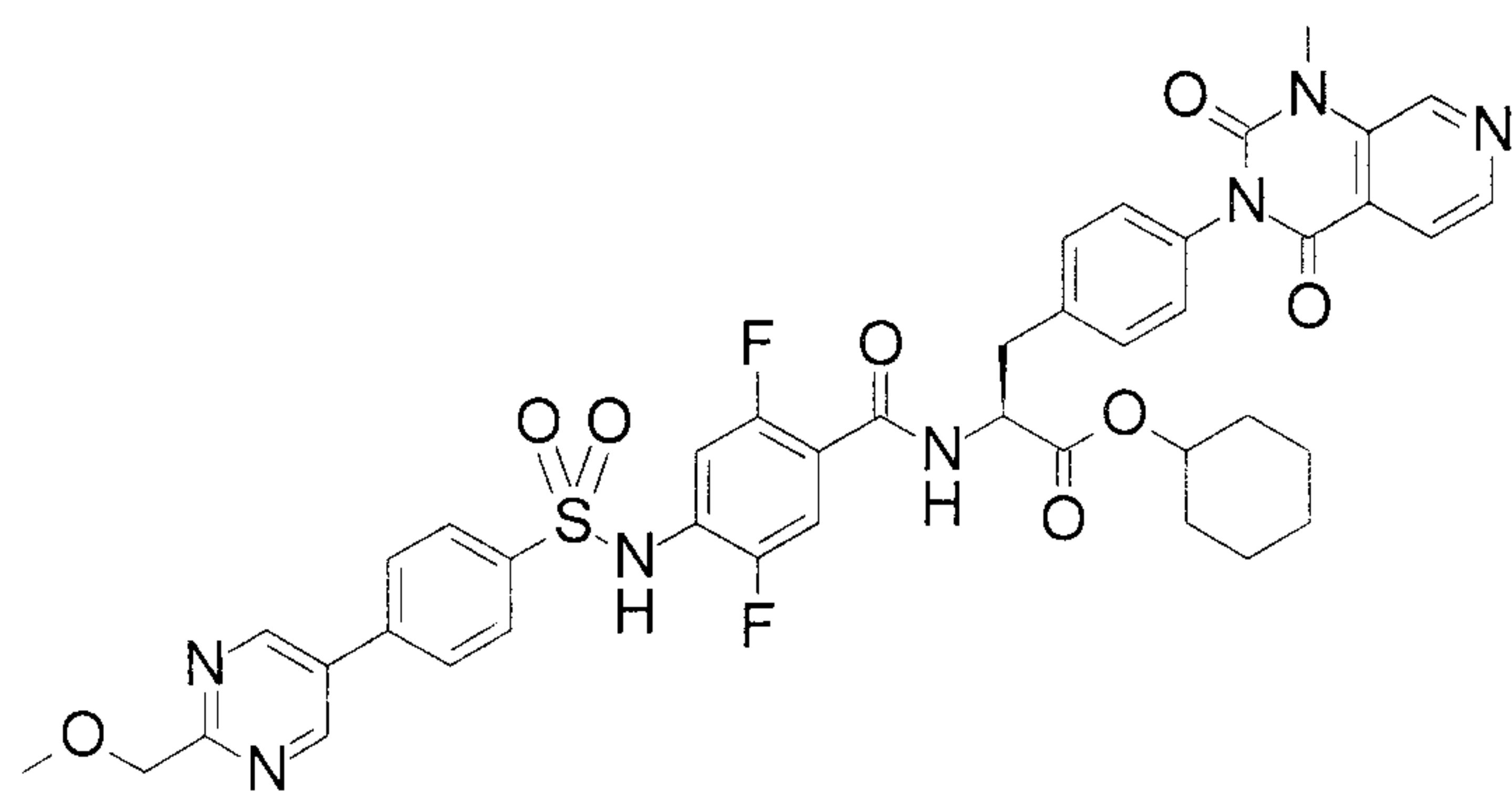




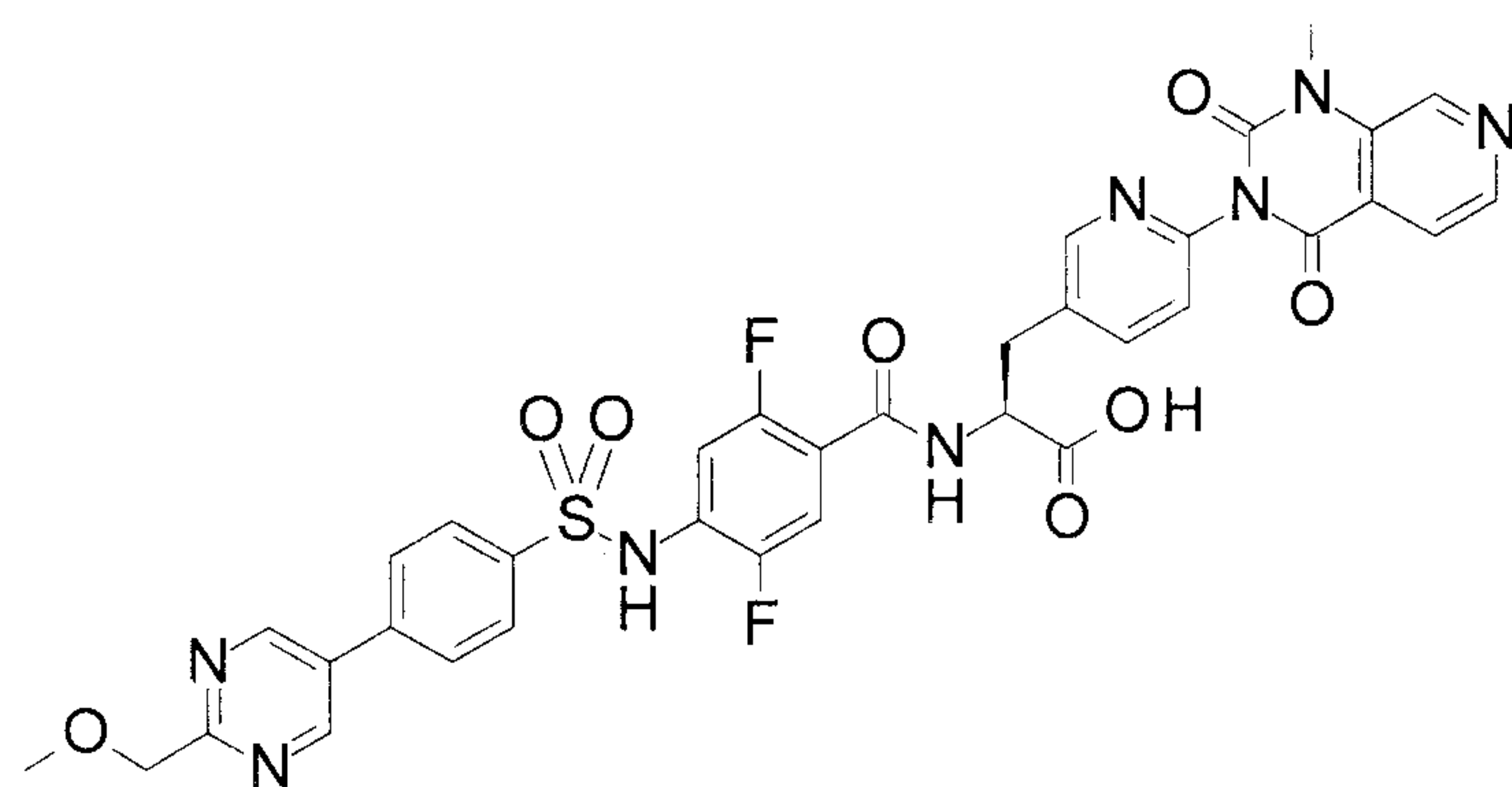




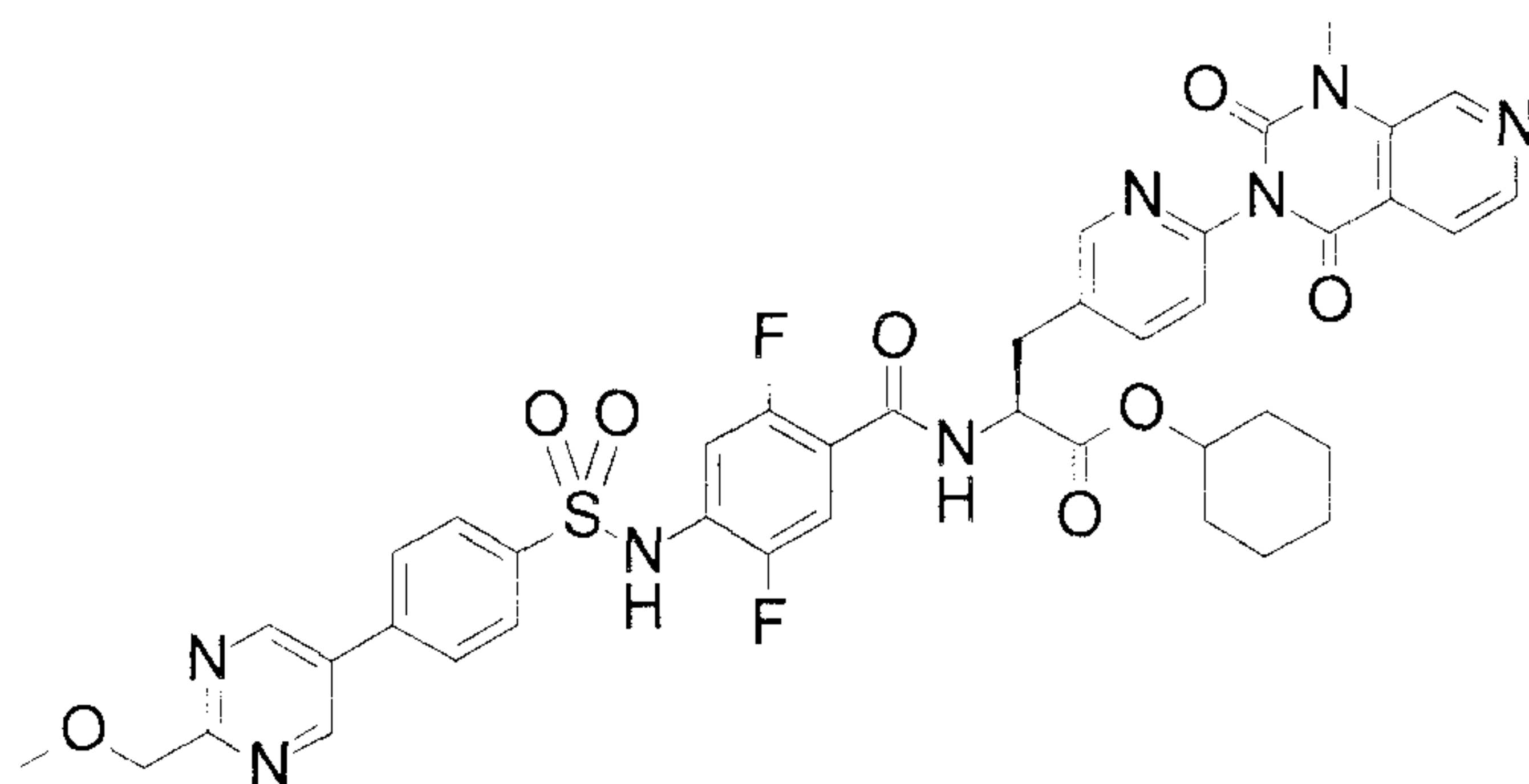
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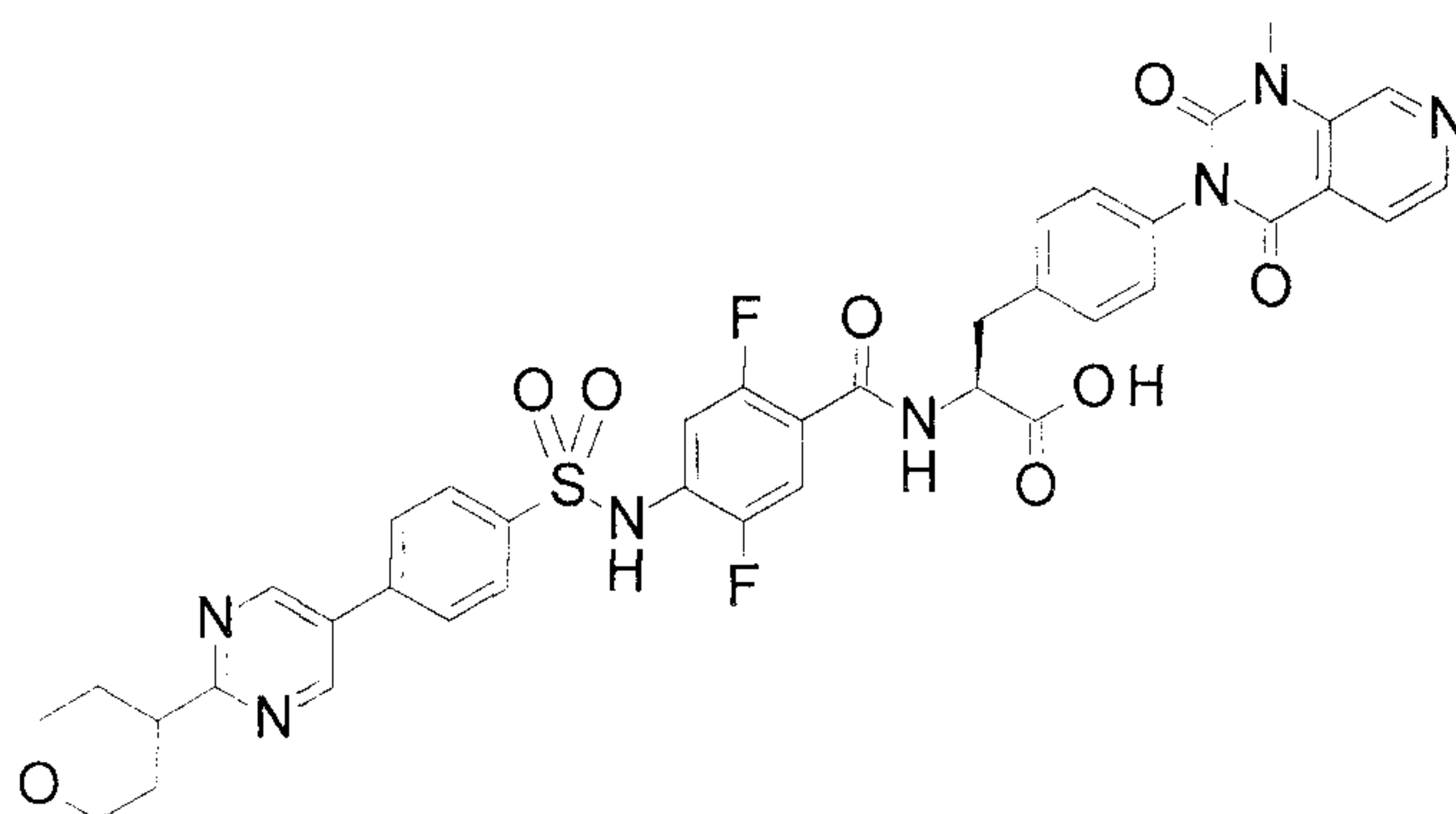
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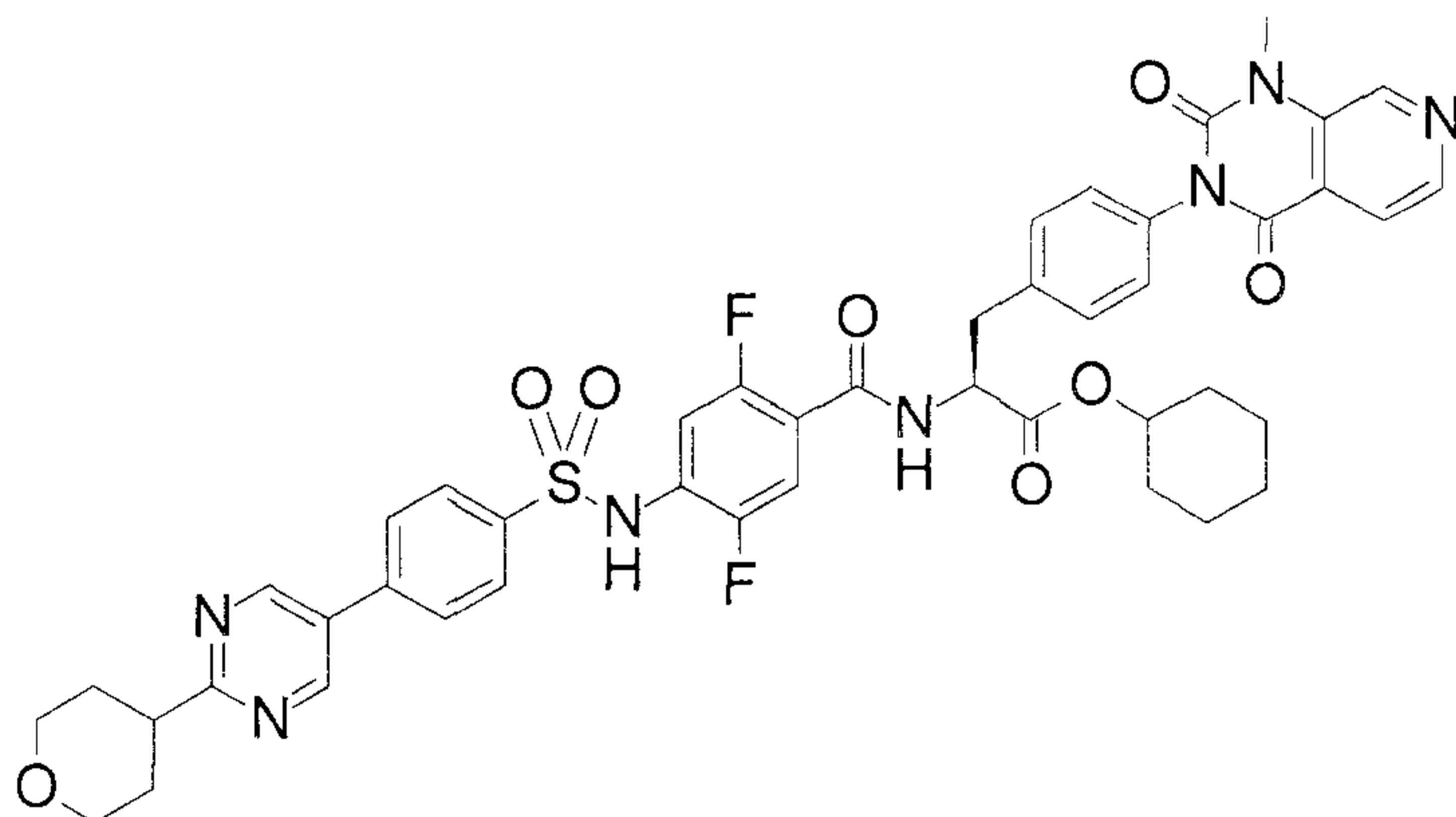


13. A compound of formula:



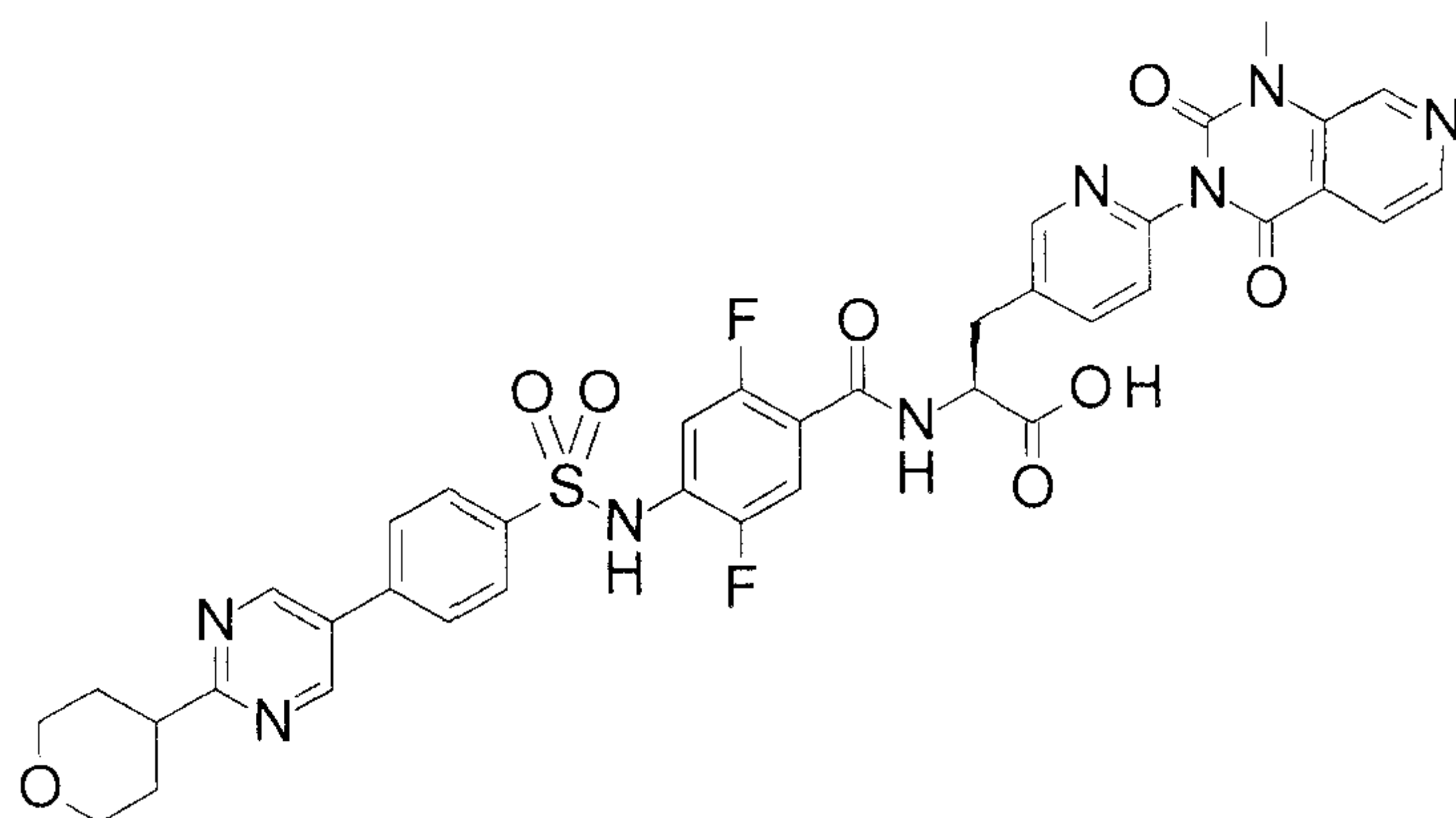
or a pharmaceutically acceptable salt thereof.

14. A compound of formula:



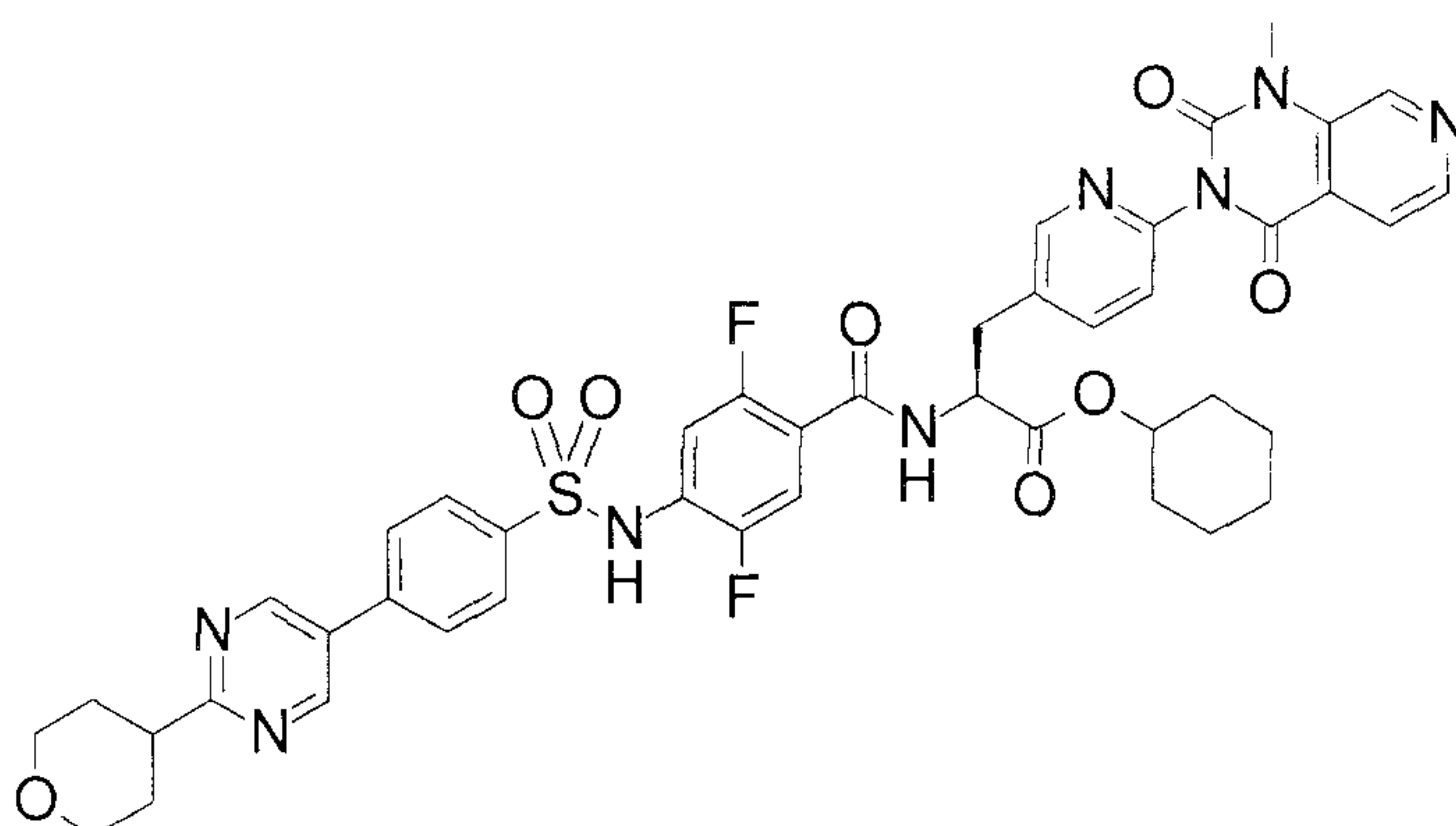
or a pharmaceutically acceptable salt thereof.

15. A compound of formula:



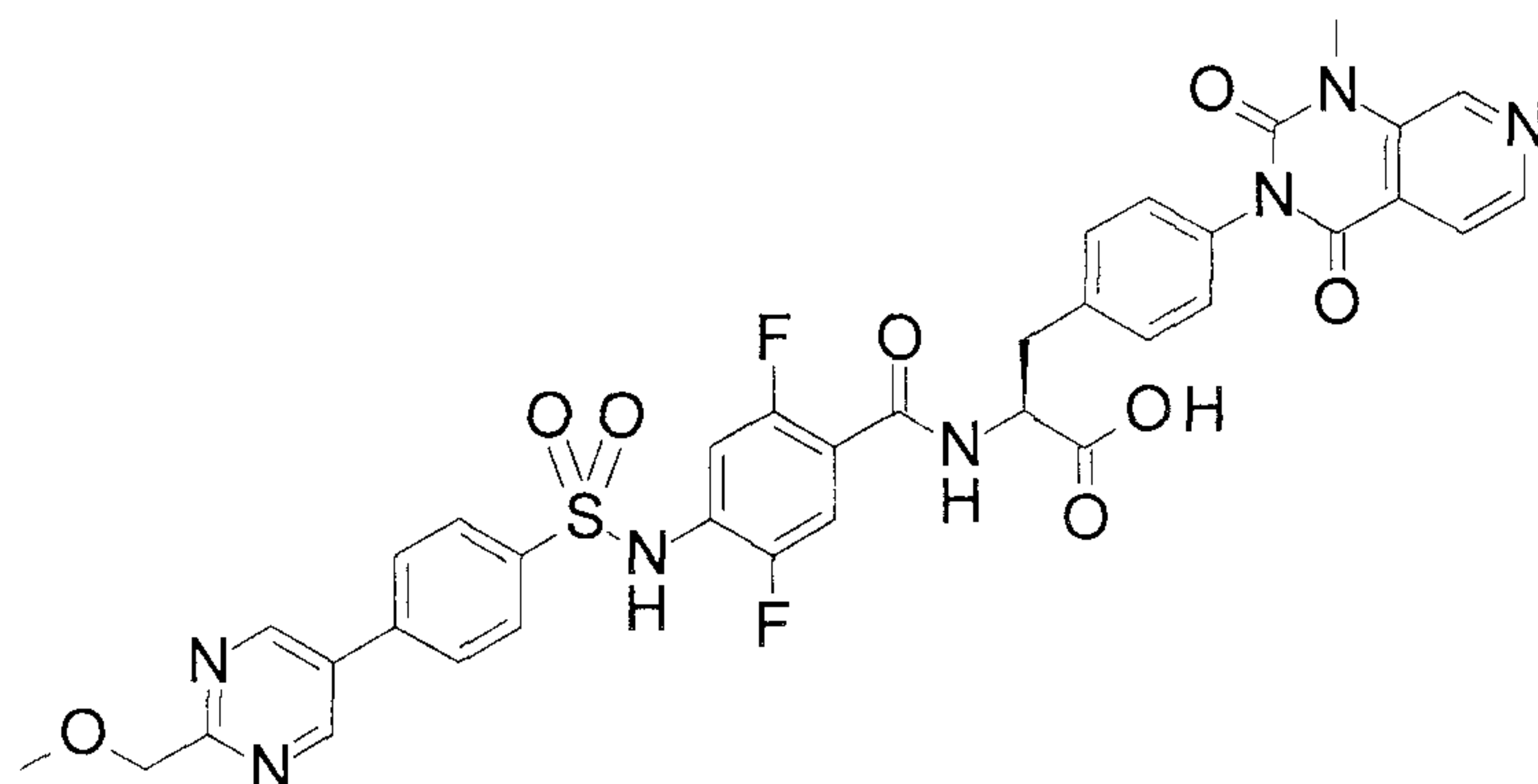
or a pharmaceutically acceptable salt thereof.

16. A compound of formula:



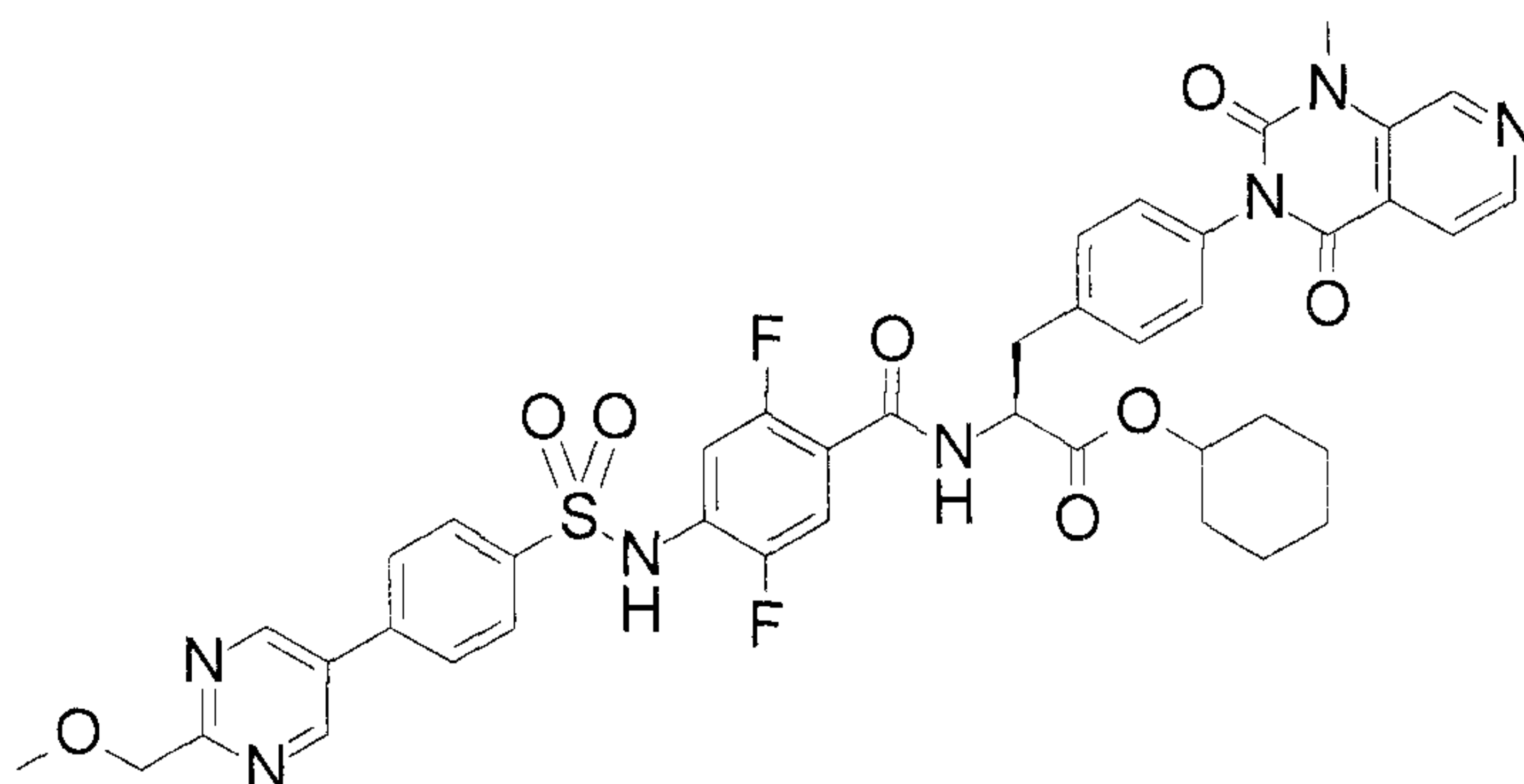
or a pharmaceutically acceptable salt thereof.

17. A compound of formula:



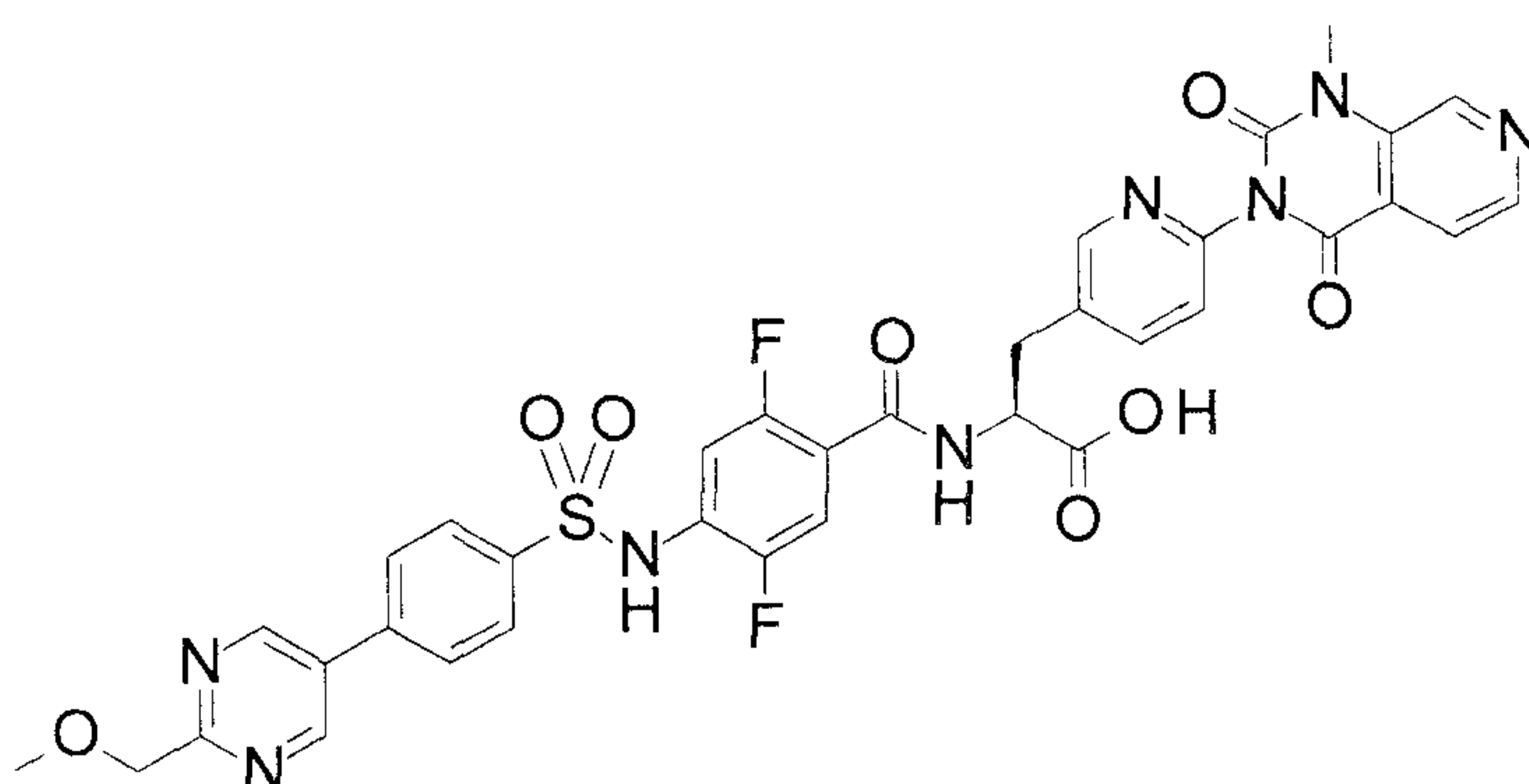
or a pharmaceutically acceptable salt thereof.

18. A compound of formula:



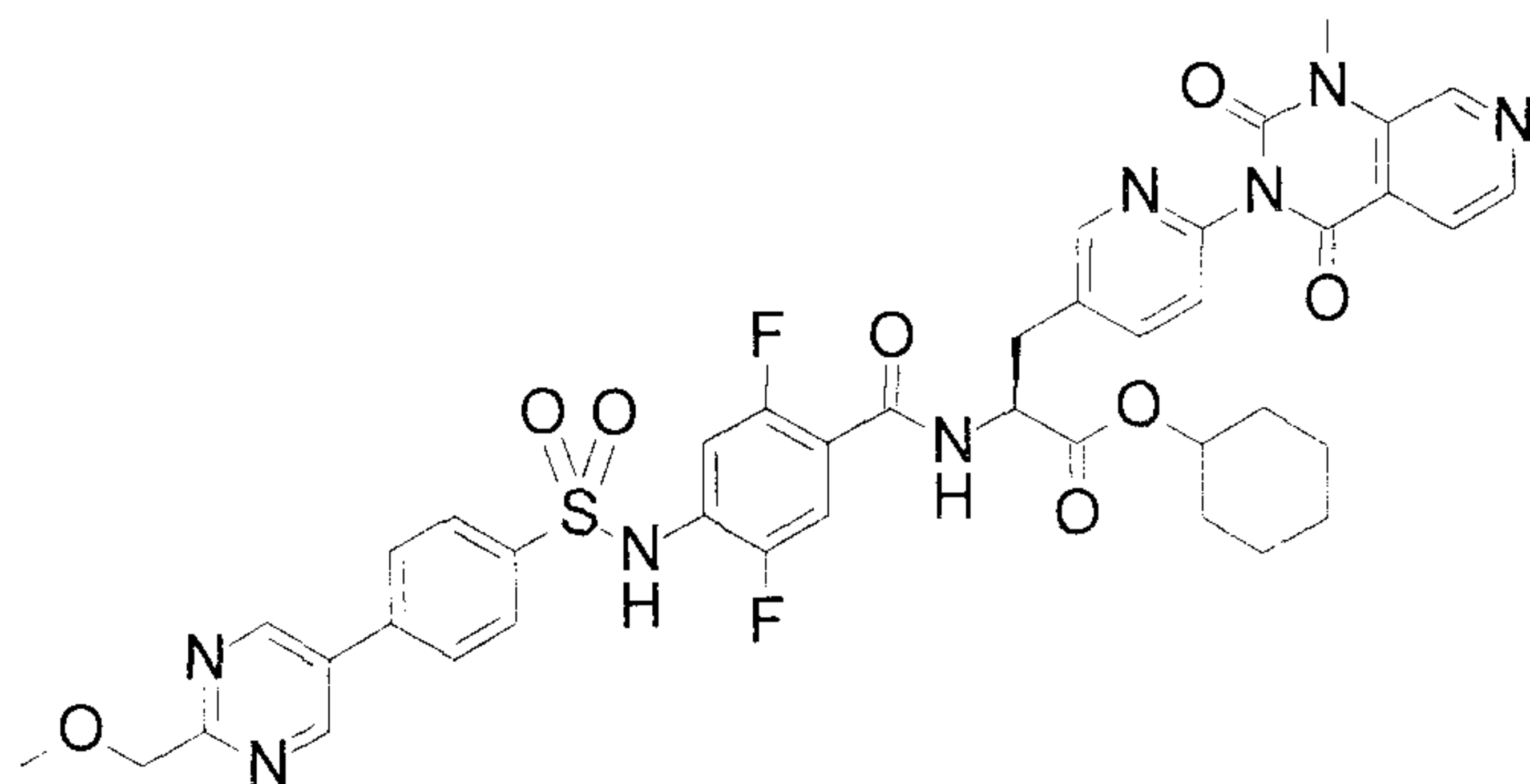
or a pharmaceutically acceptable salt thereof.

19. A compound of formula:



or a pharmaceutically acceptable salt thereof.

20. A compound of formula:



or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition comprising the sulfonamide derivative according to any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

22. Use of an effective amount of the sulfonamide derivative according to any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof for treating or preventing an inflammatory disease or condition involving an $\alpha 4\beta 7$ integrin-dependent adhesion process .

23. The use of claim 22, wherein said disease or condition is rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, Sjögren's syndrome, asthma, psoriasis, allergy, diabetes mellitus, cardiovascular diseases, arteriosclerosis, restenosis, tumor growth, tumor metastasis, or transplant rejection.

24. The sulfonamide derivative according to any one of claims 1 to 20 or a pharmaceutically acceptable salt thereof, for inhibiting an $\alpha 4\beta 7$ integrin.

25. The pharmaceutical composition of claim 21 for treating rheumatoid arthritis, inflammatory bowel disease, systemic lupus erythematosus, multiple sclerosis, Sjögren's syndrome, asthma, psoriasis, allergy, diabetes mellitus, cardiovascular diseases, arteriosclerosis, restenosis, tumor growth, tumor metastasis, or transplant rejection.