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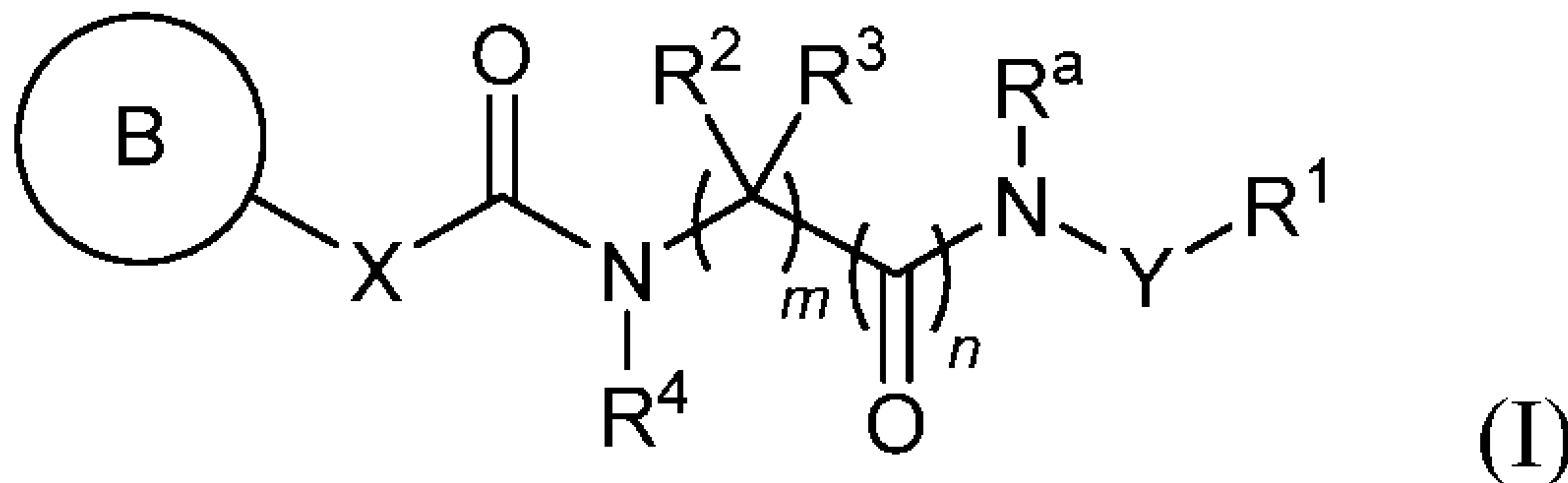
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(54) Titre : COMPOSES BENZOPYRAZOLE ET ANALOGUES DE CEUX-CI
(54) Title: BENZOPYRAZOLE COMPOUNDS AND ANALOGUES THEREOF



(57) **Abrégé/Abstract:**

Disclosed are compounds of formula (I), and pharmaceutically acceptable salts thereof. The compounds are inhibitors of the complement system. Also provided are pharmaceutical compositions comprising a compound of formula (I), and methods involving use of the compounds and compositions in the treatment and prevention of diseases and conditions characterized by aberrant complement system activity.

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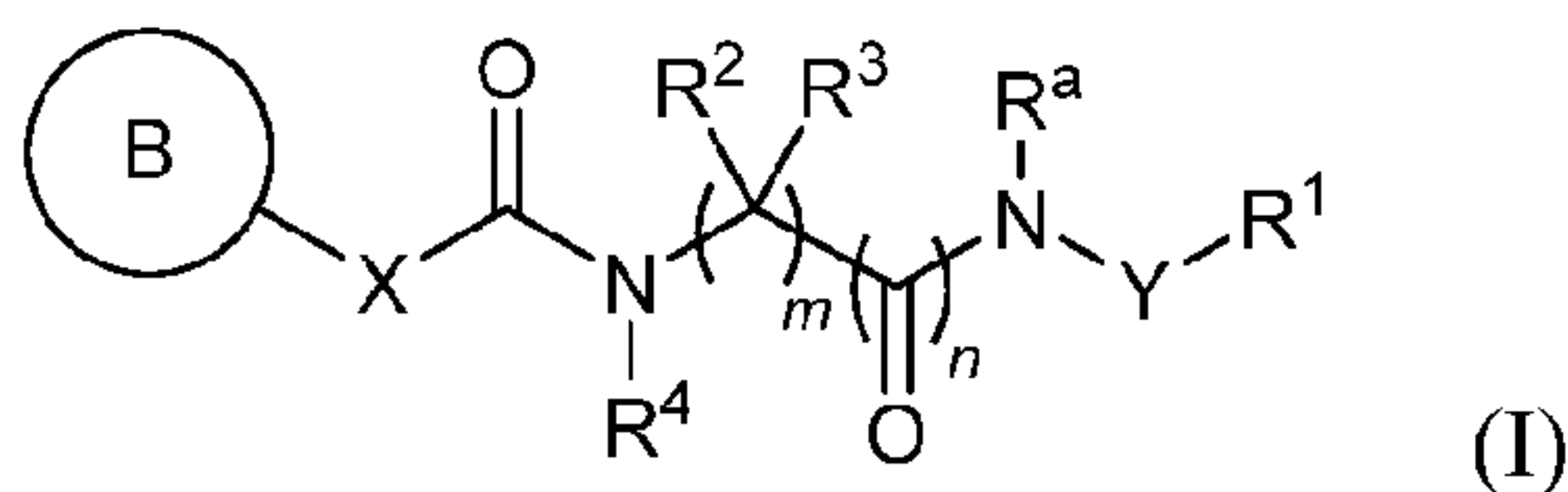
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(57) Abstract: Disclosed are compounds of formula (I), and pharmaceutically acceptable salts thereof. The compounds are inhibitors of the complement system. Also provided are pharmaceutical compositions comprising a compound of formula (I), and methods involving use of the compounds and compositions in the treatment and prevention of diseases and conditions characterized by aberrant complement system activity.

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CECI EST LE TOME 1 DE 2
CONTENANT LES PAGES 1 À 331

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JUMBO APPLICATIONS/PATENTS

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

THIS IS VOLUME 1 OF 2
CONTAINING PAGES 1 TO 331

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RELATED APPLICATIONS

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5 Application serial number 62/289,653, filed February 1, 2016, the contents of which are
hereby incorporated by reference.

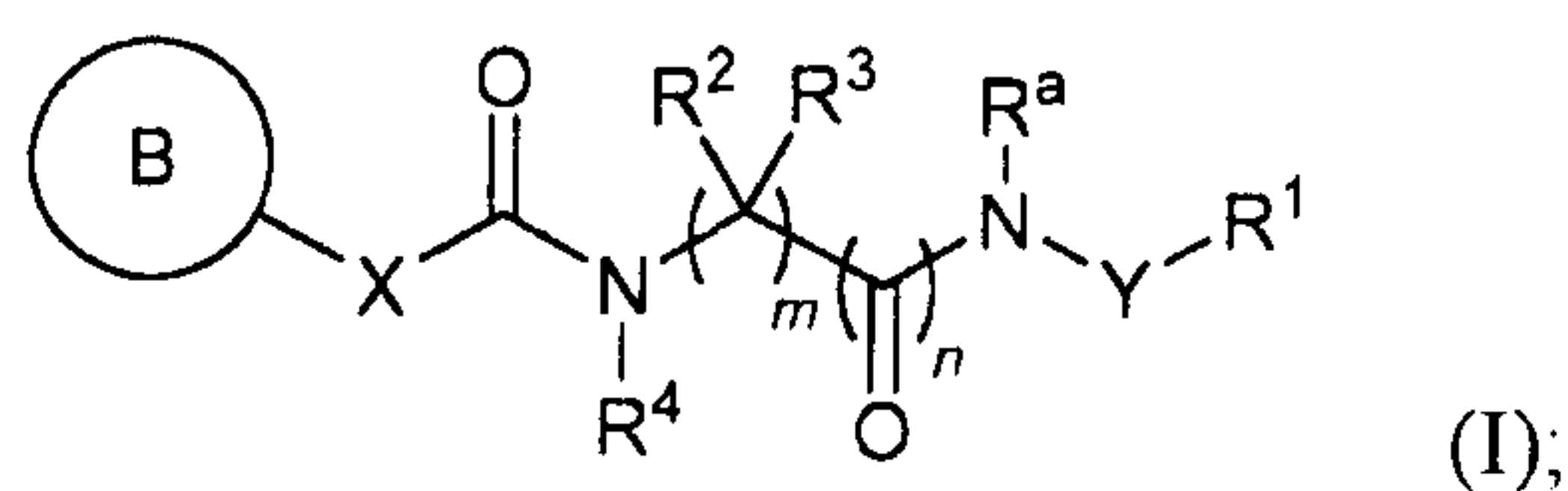
BACKGROUND OF THE INVENTION

The complement system is a branch of an organism's immune system that enhances
the ability of antibodies and phagocytic cells to destroy and remove foreign particles (e.g.,
10 pathogens) from the organism. The complement system comprises a set of plasma proteins
that act together to attack extracellular forms of pathogens and induce a series of
inflammatory responses to help fight infection. Complement activation can occur through
several pathways. For example, complement activation can occur spontaneously in response
to certain pathogens or by antibody binding to a pathogen. When complement proteins are
15 activated a cascade is triggered by which one complement protein induces the activation of
the next protein in the sequence. The activation of a small number of complement proteins at
the start of the pathway is hugely amplified by each successive enzymatic reaction, resulting
in the rapid generation of a disproportionately large complement response. (Marrides, S.
Pharmacological Reviews 1998, Vol. 50, pages 59-88). In healthy organisms there are
20 regulatory mechanisms to prevent uncontrolled complement activation.

When activated, complement proteins can bind to a pathogen, opsonizing them for
engulfment by phagocytes bearing receptors for complement. Then, small fragments of some
complement proteins act as chemoattractants to recruit more phagocytes to the site of
complement activation, and also to activate these phagocytes. Next, the complement proteins
25 create holes or pores in the invading organisms, leading to their destruction. While
complement plays an important role in protecting the body from foreign organisms, it can
also destroy healthy cells and tissue. The inappropriate activation of complement is
implicated in a long list of disease pathologies (Morgan, B. *Eur J Clin Invest* 1994, Vol. 24,
pages 219-228) affecting the immune, renal, cardiovascular, and neurological systems.

30 **SUMMARY OF THE INVENTION**

In certain aspects, the invention provides compounds of formula (I), and
pharmaceutically acceptable salts thereof:



wherein, independently for each occurrence:

R^1 represents optionally substituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, or alkenyl;

5 R^2 and R^3 each independently represent H, F, or optionally substituted alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, (alkylthio)alkyl, aralkyl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl;

or R^2 and R^3 , taken together with the carbon atom to which they are bonded, form an optionally substituted cycloalkyl or heterocycloalkyl ring;

10 R^4 represents H or optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aralkyl, heteroaralkyl, hydroxyalkyl, or haloalkyl;

X represents NH, CH₂, CHF, CF₂, CH(C₁-C₆)alkyl, or C((C₁-C₆)alkyl)₂;

15 Y is absent or represents CH₂, C(O), CR¹⁵R¹⁶, S(O)₂, or optionally substituted (C₃-C₇)cycloalkylene, arylene, or heteroarylene;

R^a represents H or optionally substituted (C₁-C₆)alkyl, (heterocycloalkyl)alkyl, or (C₃-C₇)cycloalkyl;

m is an integer from 1-6;

n is 0 or 1;

20 R^{15} and R^{16} are each independently selected from the group consisting of H, hydroxy, halogen, -C(O)OR¹⁷, -OR¹⁷, -C(O)NR¹⁷R¹⁸, -NR¹⁷R¹⁸, alkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, and (heterocycloalkyl)alkyl, wherein alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, and (heterocycloalkyl)alkyl are
25 optionally substituted with one or more substituents selected from the group consisting of -CN, -OR¹⁷, -NR¹⁷R¹⁸, halo, and alkyl;

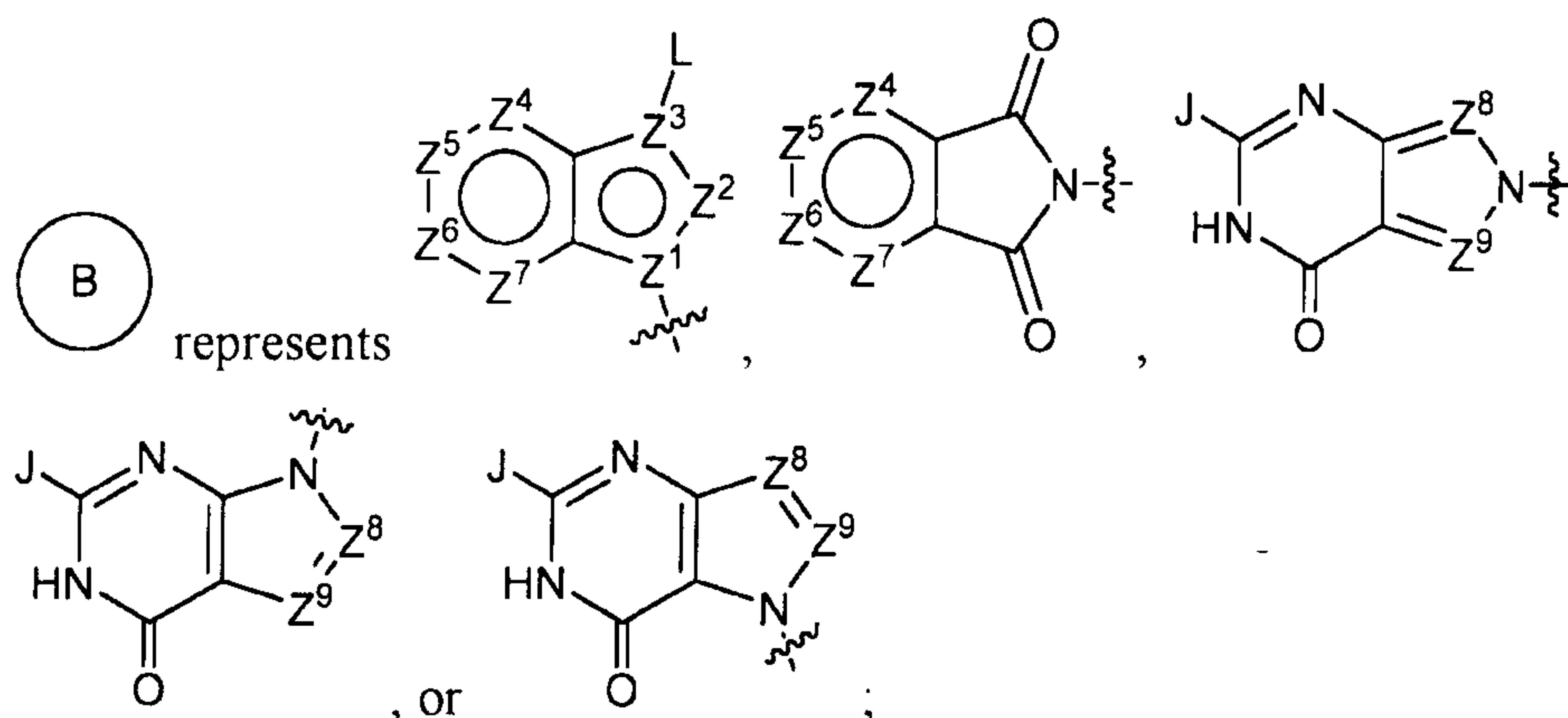
or R^{15} and R^{16} may be taken together with the intervening atom to form an optionally substituted carbocyclic or heterocyclic ring;

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R^{17} and R^{18} are each independently selected from the group consisting of H, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, and (heterocycloalkyl)alkyl;

or R^{17} and R^{18} , when attached to the same atom, may be taken together with the
 5 intervening atom to form an optionally substituted heterocyclic ring;



Z^1 and Z^3 each independently represent C or N;

Z^2 represents N, CH, or CF;

10 Z^4 represents N or CR^8 ;

Z^5 represents N or CR^5 ;

Z^6 represents N or CR^6 ;

Z^7 represents N or CR^9 ;

Z^8 and Z^9 each independently represent N or CR^{19} ;

15 R^5 and R^6 each independently represent H, halogen, $-CN$, $-NO_2$, $-OR^{13}$, $-NR^{13}R^{14}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-OC(O)NR^{13}R^{14}$, $-OC(O)OR^{13}$, $-NR^{13}C(O)OR^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-OS(O)_p(R^{13})$, $-NR^{13}S(O)_p(R^{14})$, or optionally substituted alkyl, alkenyl, alkynyl, haloalkyl, aralkyl, heteroaralkyl, heteroaryl, aryl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl;

20 L represents $-H$, $-CN$, $-C(O)R^7$, $-CH(OH)R^7$, or $-S(O)_p(\text{alkyl})$;

R^7 , independently for each occurrence, represents H, NH_2 , CH_3 , OH , CF_3 , CH_2OH , $(C_1-C_6)\text{alkyl}$, hydroxy $(C_1-C_6)\text{alkyl}$, $(C_1-C_6)\text{alkoxy}(C_1-C_6)\text{alkyl}$, halo $(C_1-C_6)\text{alkyl}$, $NH(C_1-C_6)\text{alkyl}$, $N((C_1-C_6)\text{alkyl})_2$;

R^8 and R^9 each independently represent H, halogen, $-OR^{13}$, $-NR^{13}R^{14}$, $-C(O)R^{13}$,
 25 $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-OC(O)NR^{13}R^{14}$, $-OC(O)OR^{13}$,

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$-\text{NR}^{13}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{13}\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $-\text{OS}(\text{O})_p(\text{R}^{13})$, $-\text{NR}^{13}\text{S}(\text{O})_p(\text{R}^{14})$, or optionally substituted alkyl, alkenyl, alkynyl, haloalkyl, aralkyl, heteroaralkyl, heteroaryl, or aryl;

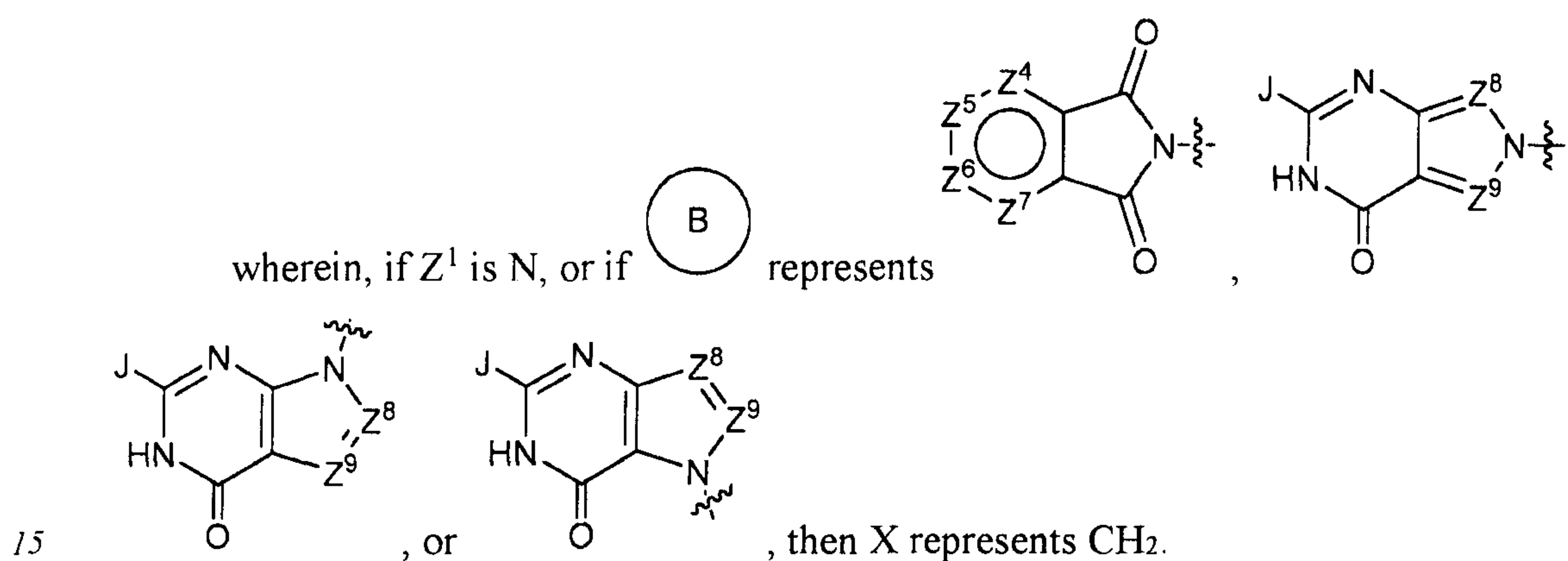
or R^5 and R^8 , or R^5 and R^6 , or R^6 and R^9 may be taken together with the intervening atoms to form an optionally substituted heterocyclic or carbocyclic ring;

5 R^{13} and R^{14} , independently for each occurrence, represent H or optionally substituted alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl; or, when R^{13} and R^{14} are attached to the same atom, R^{13} and R^{14} taken together with the atom may form an optionally substituted heterocyclic ring;

10 R^{19} , independently for each occurrence, represents H, F, CN, $-\text{C}(\text{O})\text{R}^7$, $-\text{CH}(\text{OH})\text{R}^7$, or $-\text{S}(\text{O})_p(\text{alkyl})$;

J represents H or NH_2 ; and

p is 0, 1, or 2;



In certain aspects, the invention provides a pharmaceutical composition, comprising a compound of the invention, or a pharmaceutically acceptable salt thereof; and a pharmaceutically acceptable carrier.

In certain aspects, the invention provides a method of treating or preventing a disease
 20 or condition characterized by aberrant complement system activity. The method comprises the step of administering to a subject in need thereof a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, thereby treating or preventing the disease or condition characterized by aberrant complement system activity. In certain embodiments, the disease or condition characterized by aberrant complement system
 25 activity is an immunological disorder. In certain embodiments, the disease or condition characterized by aberrant complement system activity is a disease of the central nervous

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system. In certain embodiments, the disease or condition characterized by aberrant complement system activity is a neurodegenerative disease or neurological disease. In certain embodiments, the disease or condition characterized by aberrant complement system activity is a renal disease. In certain embodiments, the disease or condition characterized by aberrant complement system activity is a cardiovascular disease. In certain embodiments, the disease or condition characterized by aberrant complement system activity is selected from the group consisting of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, organ transplant rejection, myasthenia gravis, neuromyelitis optica, membranoproliferative glomerulonephritis, dense-deposit disease, cold agglutinin disease, and catastrophic antiphospholipid syndrome.

DETAILED DESCRIPTION

Inhibitors of the complement system have been reported and are useful in therapeutic methods and compositions suitable for use in treating or preventing various immunological disorders, neurodegenerative diseases, and diseases of the central nervous system. Provided herein are compounds of formula (I) that are useful treating or preventing a disease or condition characterized by aberrant complement system activity.

Definitions

The articles “a” and “an” are used herein to refer to one or to more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

The term “heteroatom” is art-recognized and refers to an atom of any element other than carbon or hydrogen. Illustrative heteroatoms include boron, nitrogen, oxygen, phosphorus, sulfur and selenium, and alternatively oxygen, nitrogen or sulfur.

The term “alkyl” as used herein is a term of art and refers to saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. In certain embodiments, a straight-chain or branched-chain alkyl has about 30 or fewer carbon atoms in its backbone (e.g., C₁-C₃₀ for straight chain, C₃-C₃₀ for branched chain), and alternatively, about 20 or fewer, or 10 or fewer. In certain embodiments, the term “alkyl” refers to a C₁-C₁₀ alkyl group. In certain embodiments, the term “alkyl” refers to a C₁-C₆ alkyl group, for example a C₁-C₆ straight-chain alkyl group. In certain embodiments, the term “alkyl” refers to a C₃-C₁₂ branched-chain alkyl group. In certain embodiments, the

term “alkyl” refers to a C₃-C₈ branched-chain alkyl group. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, and n-hexyl.

The term “cycloalkyl” means mono- or bicyclic or bridged saturated carbocyclic rings, each having from 3 to 12 carbon atoms. Certain cycloalkyls have from 5-12 carbon atoms in their ring structure, and may have 6-10 carbons in the ring structure. Preferably, cycloalkyl is (C₃-C₇)cycloalkyl, which represents a monocyclic saturated carbocyclic ring, having from 3 to 7 carbon atoms. Examples of monocyclic cycloalkyls include cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, and cyclooctyl. Bicyclic cycloalkyl ring systems include bridged monocyclic rings and fused bicyclic rings. Bridged monocyclic rings contain a monocyclic cycloalkyl ring where two non-adjacent carbon atoms of the monocyclic ring are linked by an alkylene bridge of between one and three additional carbon atoms (*i.e.*, a bridging group of the form -(CH₂)_w-, where *w* is 1, 2, or 3). Representative examples of bicyclic ring systems include, but are not limited to, bicyclo[3.1.1]heptane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[3.2.2]nonane, bicyclo[3.3.1]nonane, and bicyclo[4.2.1]nonane. Fused bicyclic cycloalkyl ring systems contain a monocyclic cycloalkyl ring fused to either a phenyl, a monocyclic cycloalkyl, a monocyclic cycloalkenyl, a monocyclic heterocyclyl, or a monocyclic heteroaryl. The bridged or fused bicyclic cycloalkyl is attached to the parent molecular moiety through any carbon atom contained within the monocyclic cycloalkyl ring. Cycloalkyl groups are optionally substituted. In certain embodiments, the fused bicyclic cycloalkyl is a 5 or 6 membered monocyclic cycloalkyl ring fused to either a phenyl ring, a 5 or 6 membered monocyclic cycloalkyl, a 5 or 6 membered monocyclic cycloalkenyl, a 5 or 6 membered monocyclic heterocyclyl, or a 5 or 6 membered monocyclic heteroaryl, wherein the fused bicyclic cycloalkyl is optionally substituted.

The term “(cycloalkyl)alkyl” as used herein refers to an alkyl group substituted with one or more cycloalkyl groups. An example of cycloalkylalkyl is cyclohexylmethyl group.

The term “heterocycloalkyl” as used herein refers to a radical of a non-aromatic ring system, including, but not limited to, monocyclic, bicyclic, and tricyclic rings, which can be completely saturated or which can contain one or more units of unsaturation, for the avoidance of doubt, the degree of unsaturation does not result in an aromatic ring system, and having 3 to 12 atoms including at least one heteroatom, such as nitrogen, oxygen, or sulfur. For purposes of exemplification, which should not be construed as limiting the scope of this invention, the following are examples of heterocyclic rings: aziridinyl, azirinyl, oxiranyl,

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thiiranyl, thiirenyl, dioxiranyl, diazirinyl, diazepanyl, 1,3-dioxanyl, 1,3-dioxolanyl, 1,3-dithiolanyl, 1,3-dithianyl, imidazolidinyl, isothiazolinyl, isothiazolidinyl, isoxazolinyl, isoxazolidinyl, azetyl, oxetanyl, oxetyl, thietanyl, thietyl, diazetidinyl, dioxetanyl, dioxetenyl, dithietanyl, dithietyl, dioxalanyl, oxazolyl, thiazolyl, triazinyl, isothiazolyl, isoxazolyl, azepines, azetidiny, morpholinyl, oxadiazolinyl, oxadiazolidinyl, oxazolinyl, oxazolidinyl, oxopiperidinyl, oxopyrrolidinyl, piperazinyl, piperidinyl, pyranyl, pyrazolinyl, pyrazolidinyl, pyrrolinyl, pyrrolidinyl, quinuclidinyl, thiomorpholinyl, tetrahydropyranyl, tetrahydrofuranly, tetrahydrothienyl, thiadiazolinyl, thiadiazolidinyl, thiazolinyl, thiazolidinyl, thiomorpholinyl, 1,1-dioxidothiomorpholinyl (thiomorpholine sulfone), thiopyranly, and trithianyl. A heterocycloalkyl group is optionally substituted by one or more substituents as described below.

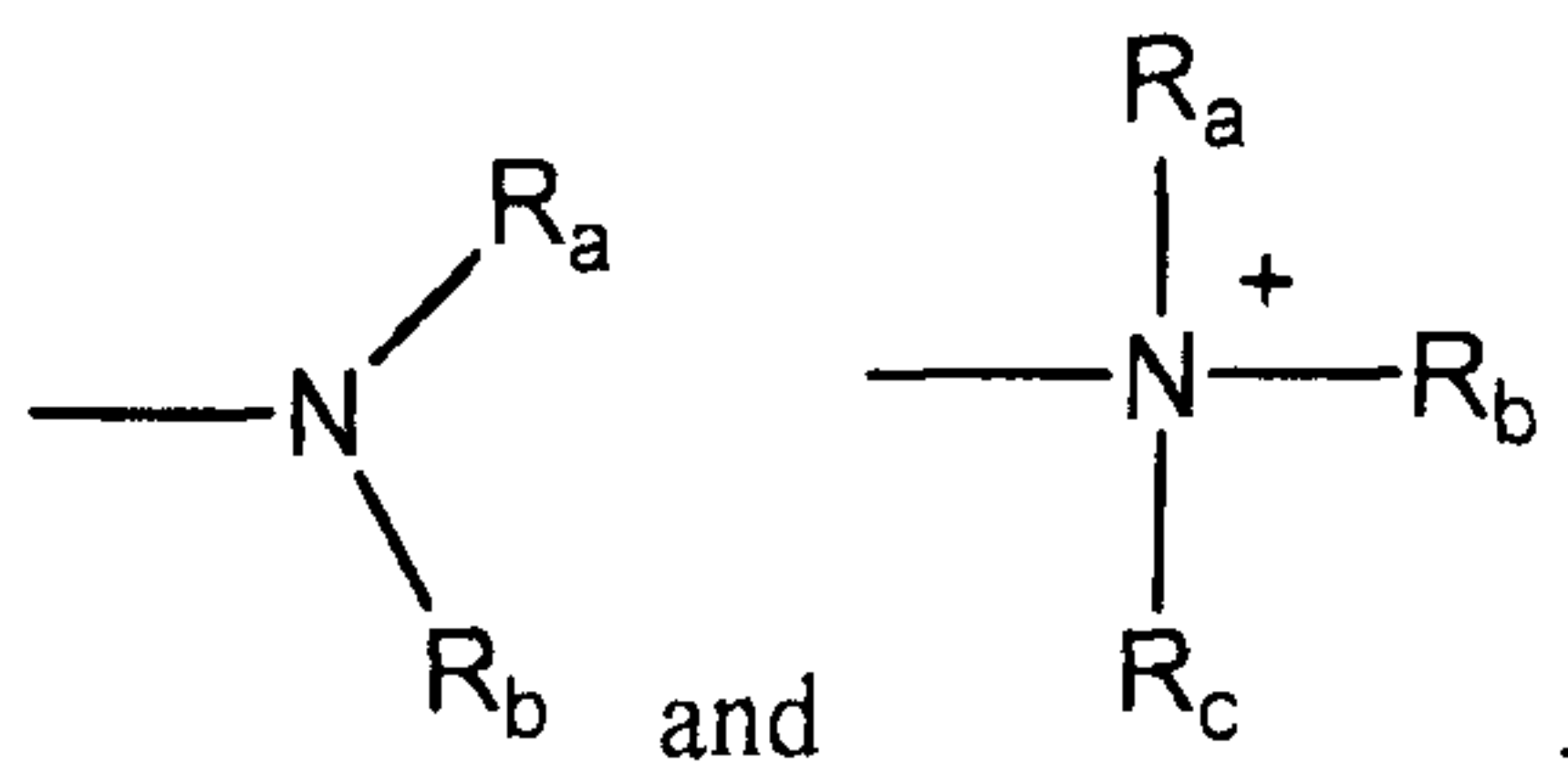
The term “(heterocycloalkyl)alkyl” as used herein refers to an alkyl group substituted with one or more heterocycloalkyl (i.e., heterocyclyl) groups.

The term “alkenyl” as used herein means a straight or branched chain hydrocarbon radical containing from 2 to 10 carbons and containing at least one carbon-carbon double bond formed by the removal of two hydrogens. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-1-heptenyl, and 3-decenyl. The unsaturated bond(s) of the alkenyl group can be located anywhere in the moiety and can have either the (Z) or the (E) configuration about the double bond(s).

The term “alkynyl” as used herein means a straight or branched chain hydrocarbon radical containing from 2 to 10 carbon atoms and containing at least one carbon-carbon triple bond. Representative examples of alkynyl include, but are not limited, to acetylenyl, 1-propynyl, 2-propynyl, 3-butyly, 2-pentyly, and 1-butyly.

The term “alkylene” is art-recognized, and as used herein pertains to a diradical obtained by removing two hydrogen atoms of an alkyl group, as defined above. In one embodiment an alkylene refers to a disubstituted alkane, i.e., an alkane substituted at two positions with substituents such as halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, fluoroalkyl (such as trifluoromethyl), cyano, or the like. That is, in one embodiment, a “substituted alkyl” is an “alkylene”.

The term “amino” is a term of art and as used herein refers to both unsubstituted and substituted amines, e.g., a moiety that may be represented by the general formulas:



wherein R_a , R_b , and R_c each independently represent a hydrogen, an alkyl, an alkenyl, $-(CH_2)_x-R_d$, or R_a and R_b , taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R_d represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocyclyl or a polycyclyl; and x is zero or an integer in the range of 1 to 8. In certain embodiments, only one of R_a or R_b may be a carbonyl, e.g., R_a , R_b , and the nitrogen together do not form an imide. In other embodiments, R_a and R_b (and optionally R_c) each independently represent a hydrogen, an alkyl, an alkenyl, or $-(CH_2)_x-R_d$. In certain embodiments, the term “amino” refers to $-NH_2$.

In certain embodiments, the term “alkylamino” refers to $-NH(\text{alkyl})$.

In certain embodiments, the term “dialkylamino” refers to $-N(\text{alkyl})_2$.

The term “amido”, as used herein, means $-NHC(=O)-$, wherein the amido group is bound to the parent molecular moiety through the nitrogen. Examples of amido include alkylamido such as $CH_3C(=O)N(H)-$ and $CH_3CH_2C(=O)N(H)-$.

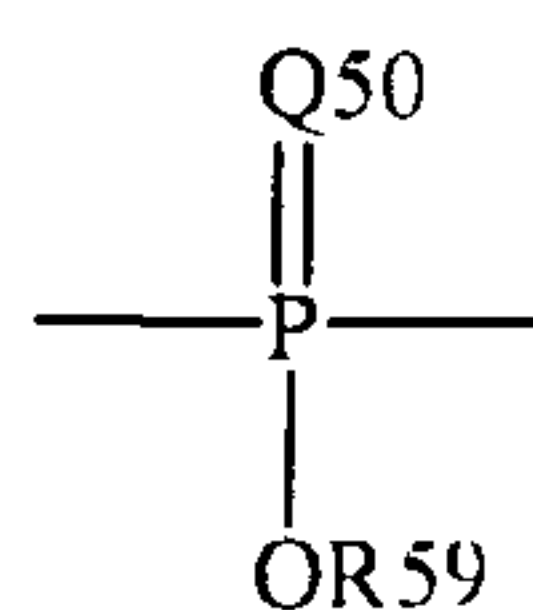
The term “acyl” is a term of art and as used herein refers to any group or radical of the form $RCO-$ where R is any organic group, e.g., alkyl, aryl, heteroaryl, aralkyl, and heteroaralkyl. Representative acyl groups include acetyl, benzoyl, and malonyl.

The term “aminoalkyl” as used herein refers to an alkyl group substituted with one or more one amino groups. In one embodiment, the term “aminoalkyl” refers to an aminomethyl group.

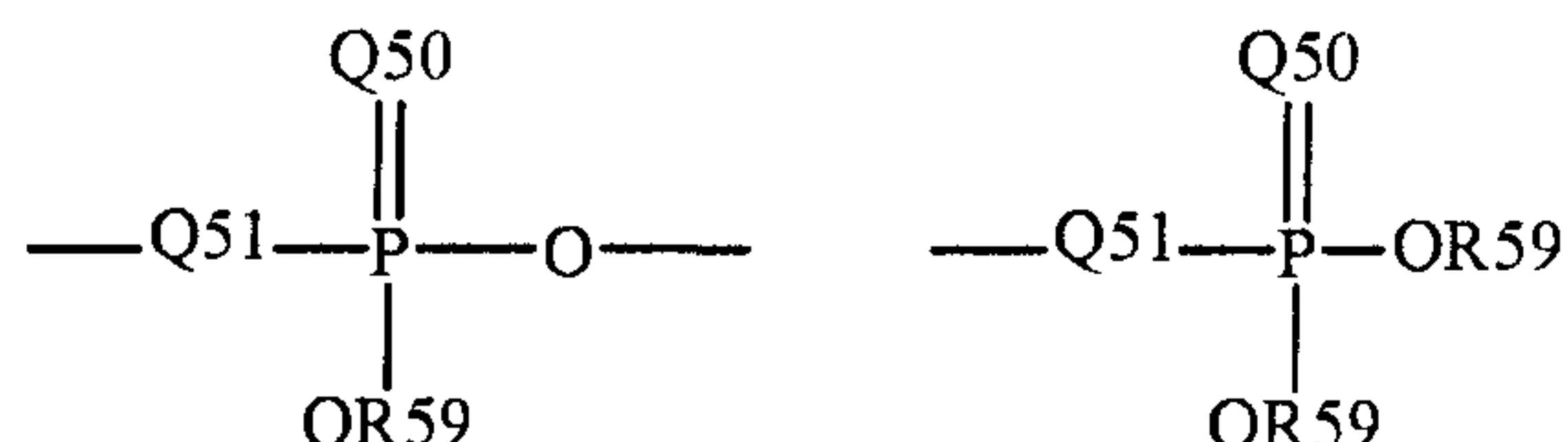
The term “aminoacyl” is a term of art and as used herein refers to an acyl group substituted with one or more amino groups.

The term “aminothionyl” as used herein refers to an analog of an aminoacyl in which the O of $RC(O)-$ has been replaced by sulfur, hence is of the form $RC(S)-$.

The term “phosphoryl” is a term of art and as used herein may in general be represented by the formula:



wherein Q50 represents S or O, and R59 represents hydrogen, a lower alkyl or an aryl; for example, -P(O)(OMe)- or -P(O)(OH)₂. When used to substitute, e.g., an alkyl, the phosphoryl group of the phosphorylalkyl may be represented by the general formulas:



wherein Q50 and R59, each independently, are defined above, and Q51 represents O, S or N; for example, -O-P(O)(OH)OMe or -NH-P(O)(OH)₂. When Q50 is S, the phosphoryl moiety is a “phosphorothioate.”

The term “aminophosphoryl” as used herein refers to a phosphoryl group substituted with at least one amino group, as defined herein; for example, -P(O)(OH)NMe₂.

The term “azide” or “azido”, as used herein, means an -N₃ group.

The term “carbonyl” as used herein refers to -C(=O)-.

The term “thiocarbonyl” as used herein refers to -C(=S)-.

The term “alkylphosphoryl” as used herein refers to a phosphoryl group substituted with at least one alkyl group, as defined herein; for example, -P(O)(OH)Me.

The term “alkylthio” as used herein refers to alkyl-S-. The term “(alkylthio)alkyl” refers to an alkyl group substituted by an alkylthio group.

The term “carboxy”, as used herein, means a -CO₂H group.

The term “aryl” is a term of art and as used herein refers to includes monocyclic, bicyclic and polycyclic aromatic hydrocarbon groups, for example, benzene, naphthalene, anthracene, and pyrene. Typically, an aryl group contains from 6-10 carbon ring atoms (i.e., (C₆-C₁₀)aryl). The aromatic ring may be substituted at one or more ring positions with one or more substituents, such as halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, fluoroalkyl (such as trifluoromethyl), cyano, or the like. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are “fused rings”) wherein at least one of the rings is an aromatic hydrocarbon, e.g., the other

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cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocycllys. In certain embodiments, the term “aryl” refers to a phenyl group.

The term “heteroaryl” is a term of art and as used herein refers to a monocyclic, bicyclic, and polycyclic aromatic group having 3 to 12 total atoms including one or more heteroatoms such as nitrogen, oxygen, or sulfur in the ring structure. Exemplary heteroaryl groups include azaindolyl, benzo(b)thienyl, benzimidazolyl, benzofuranyl, benzoxazolyl, benzothiazolyl, benzothiadiaazolyl, benzotriazolyl, benzoxadiazolyl, furanyl, imidazolyl, imidazopyridinyl, indolyl, indolinyl, indazolyl, isoindolinyl, isoxazolyl, isothiazolyl, isoquinolinyl, oxadiazolyl, oxazolyl, purinyl, pyranyl, pyrazinyl, pyrazolyl, pyridinyl, pyrimidinyl, pyrrolyl, pyrrolo[2,3-d]pyrimidinyl, pyrazolo[3,4-d]pyrimidinyl, quinolinyl, quinazolinyl, triazolyl, thiazolyl, thiophenyl, tetrahydroindolyl, tetrazolyl, thiadiazolyl, thienyl, thiomorpholinyl, triazolyl or tropanyl, and the like. The “heteroaryl” may be substituted at one or more ring positions with one or more substituents such as halogen, azide, alkyl, aralkyl, alkenyl, alkynyl, cycloalkyl, hydroxyl, alkoxyl, amino, nitro, sulfhydryl, imino, amido, phosphonate, phosphinate, carbonyl, carboxyl, silyl, ether, alkylthio, sulfonyl, sulfonamido, ketone, aldehyde, ester, heterocyclyl, aromatic or heteroaromatic moieties, fluoroalkyl (such as trifluoromethyl), cyano, or the like. The term “heteroaryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings (the rings are “fused rings”) wherein at least one of the rings is an aromatic group having one or more heteroatoms in the ring structure, e.g., the other cyclic rings may be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocycllys.

The term “aralkyl” or “arylalkyl” is a term of art and as used herein refers to an alkyl group substituted with an aryl group, wherein the moiety is appended to the parent molecule through the alkyl group.

The term “heteroaralkyl” or “heteroarylalkyl” is a term of art and as used herein refers to an alkyl group substituted with a heteroaryl group, appended to the parent molecular moiety through the alkyl group.

The term “alkoxy” as used herein means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy.

The term “alkoxyalkyl” refers to an alkyl group substituted by an alkoxy group.

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The term “alkoxycarbonyl” means an alkoxy group, as defined herein, appended to the parent molecular moiety through a carbonyl group, represented by -C(=O)- , as defined herein. Representative examples of alkoxycarbonyl include, but are not limited to, methoxycarbonyl, ethoxycarbonyl, and *tert*-butoxycarbonyl.

5 The term “alkylcarbonyl”, as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of alkylcarbonyl include, but are not limited to, acetyl, 1-oxopropyl, 2,2-dimethyl-1-oxopropyl, 1-oxobutyl, and 1-oxopentyl.

The term “arylcarbonyl”, as used herein, means an aryl group, as defined herein,
10 appended to the parent molecular moiety through a carbonyl group, as defined herein. Representative examples of arylcarbonyl include, but are not limited to, benzoyl and (2-pyridinyl)carbonyl.

The term “alkylcarbonyloxy” and “arylcarbonyloxy”, as used herein, means an alkylcarbonyl or arylcarbonyl group, as defined herein, appended to the parent molecular
15 moiety through an oxygen atom. Representative examples of alkylcarbonyloxy include, but are not limited to, acetyloxy, ethylcarbonyloxy, and *tert*-butylcarbonyloxy. Representative examples of arylcarbonyloxy include, but are not limited to phenylcarbonyloxy.

The term “alkenoxy” or “alkenoxyl” means an alkenyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples
20 of alkenoxyl include, but are not limited to, 2-propen-1-oxyl (i.e., $\text{CH}_2=\text{CH}-\text{CH}_2\text{-O-}$) and vinyloxy (i.e., $\text{CH}_2=\text{CH}-\text{O-}$).

The term “aryloxy” as used herein means an aryl group, as defined herein, appended to the parent molecular moiety through an oxygen atom.

The term “heteroaryloxy” as used herein means a heteroaryl group, as defined herein,
25 appended to the parent molecular moiety through an oxygen atom.

The term “carbocyclyl” as used herein means a monocyclic or multicyclic (e.g., bicyclic, tricyclic, etc.) hydrocarbon radical containing from 3 to 12 carbon atoms that is completely saturated or has one or more unsaturated bonds, and for the avoidance of doubt, the degree of unsaturation does not result in an aromatic ring system (e.g., phenyl).
30 Examples of carbocyclyl groups include 1-cyclopropyl, 1-cyclobutyl, 2-cyclopentyl, 1-cyclopentenyl, 3-cyclohexyl, 1-cyclohexenyl and 2-cyclopentenylmethyl.

The term “cyano” is a term of art and as used herein refers to -CN .

The term “halo” is a term of art and as used herein refers to -F , -Cl , -Br , or -I .

The term “haloalkyl” as used herein refers to an alkyl group, as defined herein, wherein some or all of the hydrogens are replaced with halogen atoms.

The term “hydroxy” is a term of art and as used herein refers to –OH.

The term “hydroxyalkyl”, as used herein, means at least one hydroxy group, as
5 defined herein, is appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of hydroxyalkyl include, but are not limited to, hydroxymethyl, 2-hydroxyethyl, 3-hydroxypropyl, 2,3-dihydroxypentyl, and 2-ethyl-4-hydroxyheptyl.

The term “silyl”, as used herein, includes hydrocarbyl derivatives of the silyl ($\text{H}_3\text{Si}-$)
10 group (i.e., $(\text{hydrocarbyl})_3\text{Si}-$), wherein a hydrocarbyl groups are univalent groups formed by removing a hydrogen atom from a hydrocarbon, e.g., ethyl, phenyl. The hydrocarbyl groups can be combinations of differing groups which can be varied in order to provide a number of silyl groups, such as trimethylsilyl (TMS), tert-butyldiphenylsilyl (TBDPS), tert-butyldimethylsilyl (TBS/TBDMS), triisopropylsilyl (TIPS), and [2-
15 (trimethylsilyl)ethoxy]methyl (SEM).

The term “silyloxy”, as used herein, means a silyl group, as defined herein, is appended to the parent molecule through an oxygen atom.

Certain compounds contained in compositions of the present invention may exist in particular geometric or stereoisomeric forms. In addition, compounds of the present
20 invention may also be optically active. The present invention contemplates all such compounds, including *cis*- and *trans*-isomers, (*R*)- and (*S*)-enantiomers, diastereoisomers, (*D*)-isomers, (*L*)-isomers, the racemic mixtures thereof, and other mixtures thereof, as falling within the scope of the invention. Additional asymmetric carbon atoms may be present in a substituent such as an alkyl group. All such isomers, as well as mixtures thereof, are
25 intended to be included in this invention.

If, for instance, a particular enantiomer of compound of the present invention is desired, it may be prepared by asymmetric synthesis, or by derivation with a chiral auxiliary, where the resulting diastereomeric mixture is separated and the auxiliary group cleaved to provide the pure desired enantiomers. Alternatively, where the molecule contains a basic
30 functional group, such as amino, or an acidic functional group, such as carboxyl, diastereomeric salts are formed with an appropriate optically-active acid or base, followed by resolution of the diastereomers thus formed by fractional crystallization or chromatographic means well known in the art, and subsequent recovery of the pure enantiomers.

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It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, fragmentation,
5 decomposition, cyclization, elimination, or other reaction.

The term “substituted” is also contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and nonaromatic substituents of organic compounds. Illustrative substituents include, for example, those
10 described herein above. The permissible substituents may be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. This invention is not intended to be limited in any manner by the permissible substituents of
15 organic compounds.

The phrase “protecting group”, as used herein, means temporary substituents which protect a potentially reactive functional group from undesired chemical transformations. Examples of such protecting groups include esters of carboxylic acids, silyl ethers of alcohols, and acetals and ketals of aldehydes and ketones, respectively. The field of
20 protecting group chemistry has been reviewed (Greene, T.W.; Wuts, P.G.M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991). Protected forms of the inventive compounds are included within the scope of this invention.

For purposes of the invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 67th
25 Ed., 1986-87, inside cover.

Other chemistry terms herein are used according to conventional usage in the art, as exemplified by The McGraw-Hill Dictionary of Chemical Terms (ed. Parker, S., 1985), McGraw-Hill, San Francisco, incorporated herein by reference). Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly
30 understood by one of ordinary skill in the art to which this invention pertains.

The term “pharmaceutically acceptable salt” as used herein includes salts derived from inorganic or organic acids including, for example, hydrochloric, hydrobromic, sulfuric, nitric, perchloric, phosphoric, formic, acetic, lactic, maleic, fumaric, succinic, tartaric, glycolic, salicylic, citric, methanesulfonic, benzenesulfonic, benzoic, malonic, trifluoroacetic,

trichloroacetic, naphthalene-2-sulfonic, and other acids. Pharmaceutically acceptable salt forms can include forms wherein the ratio of molecules comprising the salt is not 1:1. For example, the salt may comprise more than one inorganic or organic acid molecule per molecule of base, such as two hydrochloric acid molecules per molecule of compound of Formula I. As another example, the salt may comprise less than one inorganic or organic acid molecule per molecule of base, such as two molecules of compound of Formula I per molecule of tartaric acid.

The terms “carrier” and “pharmaceutically acceptable carrier” as used herein refer to a diluent, adjuvant, excipient, or vehicle with which a compound is administered or formulated for administration. Non-limiting examples of such pharmaceutically acceptable carriers include liquids, such as water, saline, and oils; and solids, such as gum acacia, gelatin, starch paste, talc, keratin, colloidal silica, urea, and the like. In addition, auxiliary, stabilizing, thickening, lubricating, flavoring, and coloring agents may be used. Other examples of suitable pharmaceutical carriers are described in *Remington's Pharmaceutical Sciences* by E.W. Martin, herein incorporated by reference in its entirety.

The term “treat” as used herein means prevent, halt or slow the progression of, or eliminate a disease or condition in a subject. In one embodiment “treat” means halt or slow the progression of, or eliminate a disease or condition in a subject. In one embodiment, “treat” means reduce at least one objective manifestation of a disease or condition in a subject.

The term “effective amount” as used herein refers to an amount that is sufficient to bring about a desired biological effect.

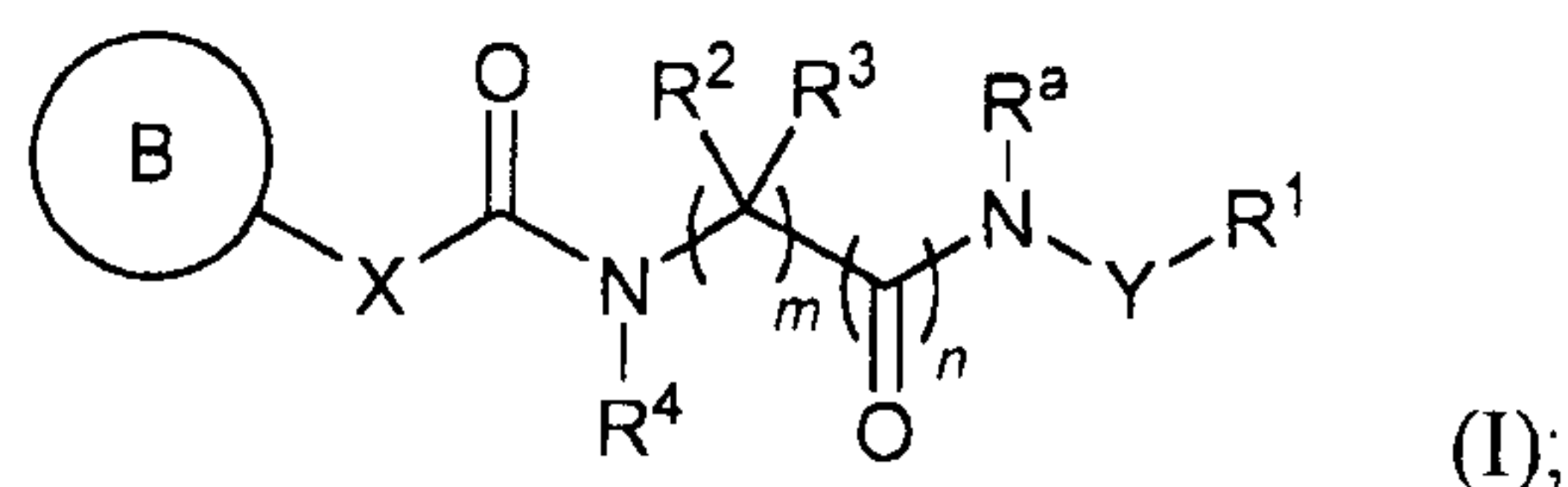
The term “therapeutically effective amount” as used herein refers to an amount that is sufficient to bring about a desired therapeutic effect.

The term “inhibit” as used herein means decrease by an objectively measurable amount or extent. In various embodiments “inhibit” means decrease by at least 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, or 95 percent compared to relevant control. In one embodiment “inhibit” means decrease 100 percent, i.e., halt or eliminate.

The term “subject” as used herein refers to a mammal. In various embodiments, a subject is a mouse, rat, rabbit, cat, dog, pig, sheep, horse, cow, or non-human primate. In one embodiment, a subject is a human.

Compounds

The present invention provides compounds of Formula (I), or pharmaceutically acceptable salts thereof:



5 wherein, independently for each occurrence:

R¹ represents optionally substituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, or alkenyl;

R² and R³ each independently represent H, F, or optionally substituted alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, (alkylthio)alkyl, aralkyl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl;

or R² and R³, taken together with the carbon atom to which they are bonded, form an optionally substituted cycloalkyl or heterocycloalkyl ring;

R⁴ represents H or optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aralkyl, heteroaralkyl, hydroxyalkyl, or haloalkyl;

X represents NH, CH₂, CHF, CF₂, CH(C₁-C₆)alkyl, or C((C₁-C₆)alkyl)₂;

Y is absent or represents CH₂, C(O), CR¹⁵R¹⁶, S(O)₂, or optionally substituted (C₃-C₇)cycloalkylene, arylene, or heteroarylene;

R^a represents H or optionally substituted (C₁-C₆)alkyl, (heterocycloalkyl)alkyl, or (C₃-C₇)cycloalkyl;

m is an integer from 1-6;

n is 0 or 1:

R¹⁵ and R¹⁶ are each independently selected from the group consisting of H, hydroxy, halogen, -C(O)OR¹⁷, -OR¹⁷, -C(O)NR¹⁷R¹⁸, -NR¹⁷R¹⁸, alkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, and (heterocycloalkyl)alkyl, wherein alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, and (heterocycloalkyl)alkyl are optionally substituted with one or more substituents selected from the group consisting of -CN, -OR¹⁷, -NR¹⁷R¹⁸, halo, and alkyl;

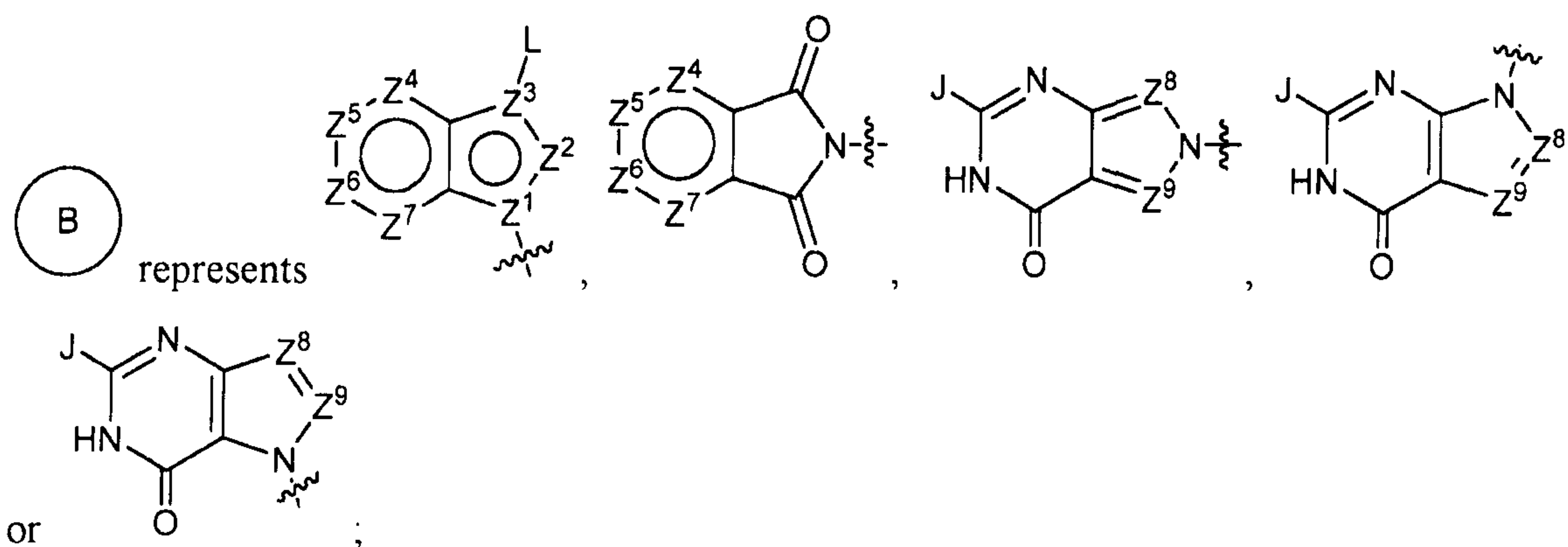
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or R^{15} and R^{16} may be taken together with the intervening atom to form an optionally substituted carbocyclic or heterocyclic ring;

R^{17} and R^{18} are each independently selected from the group consisting of H, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, and (heterocycloalkyl)alkyl;

or R^{17} and R^{18} , when attached to the same atom, may be taken together with the intervening atom to form an optionally substituted heterocyclic ring;



Z^1 and Z^3 each independently represent C or N;

Z^2 represents N, CH, or CF;

Z^4 represents N or CR^8 ;

Z^5 represents N or CR^5 ;

Z^6 represents N or CR^6 ;

Z^7 represents N or CR^9 ;

Z^8 and Z^9 each independently represent N or CR^{19} ;

R^5 and R^6 each independently represent H, halogen, $-CN$, $-NO_2$, $-OR^{13}$, $-NR^{13}R^{14}$,

$-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$,

$-OC(O)NR^{13}R^{14}$, $-OC(O)OR^{13}$, $-NR^{13}C(O)OR^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$,

$-OS(O)_p(R^{13})$, $-NR^{13}S(O)_p(R^{14})$, or optionally substituted alkyl, alkenyl, alkynyl, haloalkyl, aralkyl, heteroaralkyl, heteroaryl, aryl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl;

L represents $-H$, $-CN$, $-C(O)R^7$, $-CH(OH)R^7$, or $-S(O)_p(alkyl)$;

R^7 , independently for each occurrence, represents H, NH_2 , CH_3 , OH, CF_3 , CH_2OH , $(C_1-C_6)alkyl$, hydroxy $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)alkyl$, halo $(C_1-C_6)alkyl$, $NH(C_1-C_6)alkyl$, $N((C_1-C_6)alkyl)_2$;

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R^8 and R^9 each independently represent H, halogen, $-OR^{13}$, $-NR^{13}R^{14}$, $-C(O)R^{13}$,
 $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-OC(O)NR^{13}R^{14}$,
 $-OC(O)OR^{13}$, $-NR^{13}C(O)OR^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-OS(O)_p(R^{13})$,
 $-NR^{13}S(O)_p(R^{14})$, or optionally substituted alkyl, alkenyl, alkynyl, haloalkyl, aralkyl,
 5 heteroaralkyl, heteroaryl, or aryl;

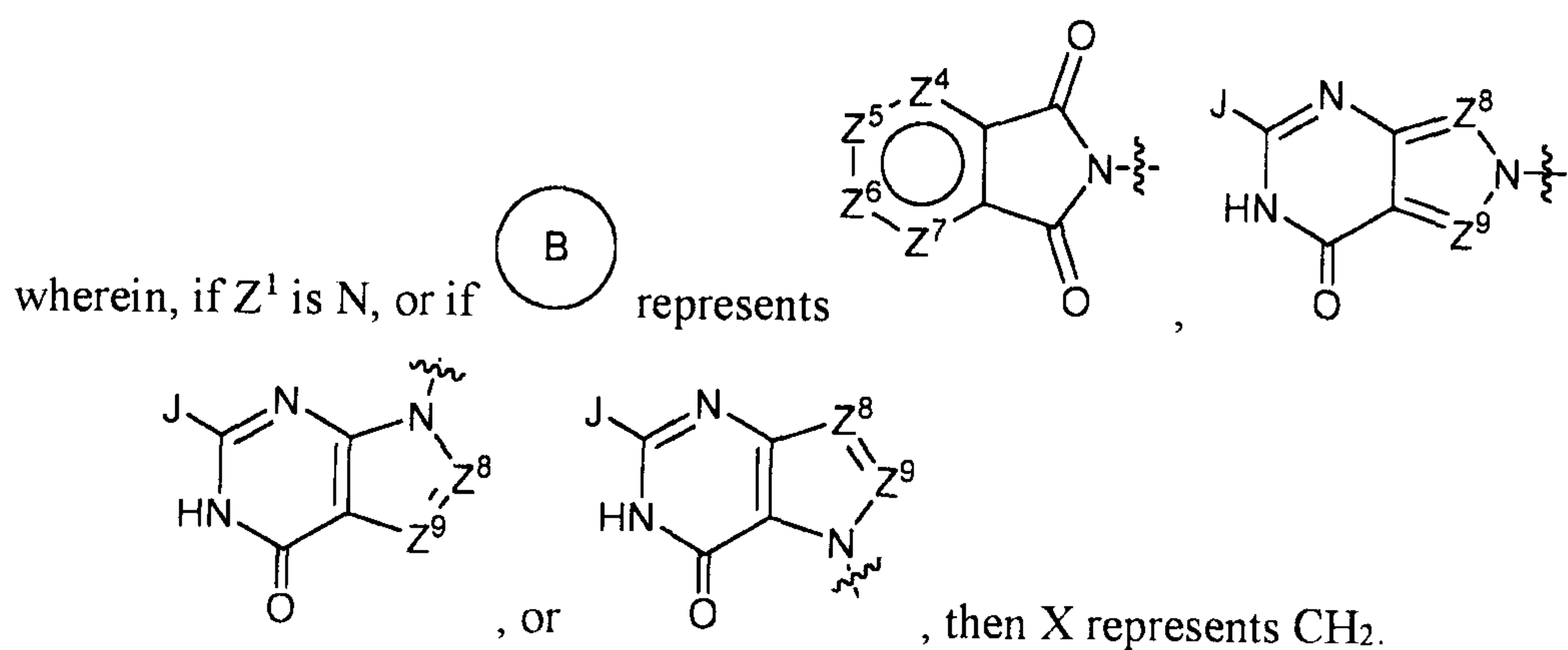
or R^5 and R^8 , or R^5 and R^6 , or R^6 and R^9 may be taken together with the intervening atoms to
 form an optionally substituted heterocyclic or carbocyclic ring;

R^{13} and R^{14} , independently for each occurrence, represent H or optionally substituted alkyl,
 alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl,
 10 heterocycloalkyl, or (heterocycloalkyl)alkyl; or, when R^{13} and R^{14} are attached to the
 same atom, R^{13} and R^{14} taken together with the atom may form an optionally
 substituted heterocyclic ring;

R^{19} , independently for each occurrence, represents H, F, CN, $-C(O)R^7$, $-CH(OH)R^7$, or
 $-S(O)_p(\text{alkyl})$;

15 J represents H or NH_2 ; and

p is 0, 1, or 2;



In preferred embodiments, n is 1.

20 In certain embodiments, R^1 represents aryl or heteroaryl, optionally substituted by one
 or more substituents independently selected from the group consisting of halogen, $-CN$,
 alkoxy, haloalkoxy, alkyl, haloalkyl, alkenyl, dialkylamino, heterocycloalkyl, aryl, and
 heteroaryl.

In certain embodiments, R^1 represents aryl or heteroaryl, optionally substituted by one
 25 or more substituents independently selected from the group consisting of halogen, alkoxy,
 haloalkoxy, alkyl, haloalkyl, alkenyl, dialkylamino, aryl, and heteroaryl.

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In embodiments in which R^1 represents aryl or heteroaryl substituted by one or more substituents including an aryl or heteroaryl substituent, the aryl or heteroaryl substituent may be further substituted by one or more substituents selected from the group consisting of alkyl and halogen.

5 In certain embodiments, R^1 represents aryl or heteroaryl, optionally substituted by one or more substituents independently selected from the group consisting of halogen, alkoxy, haloalkoxy, alkyl, haloalkyl, alkenyl, and dialkylamino.

In certain embodiments, R^1 represents aryl or heteroaryl, substituted by one or more substituents, at least one of which is halogen. For example, R^1 may represent phenyl,
10 substituted by a chloro and a fluoro group.

In other embodiments, R^1 represents phenyl, pyridinyl, pyrazinyl, or pyrimidinyl, optionally substituted by one or more substituents selected from the group consisting of halogen, alkoxy (e.g., methoxy), haloalkoxy (e.g., trifluoromethoxy), alkyl (e.g., methyl), haloalkyl (e.g., trifluoromethyl), alkenyl (e.g., vinyl), and dialkylamino (e.g.,
15 dimethylamino).

In alternative embodiments, R^1 is optionally substituted alkyl or alkenyl. For example, R^1 may be (C₁-C₆)alkyl or (C₂-C₆)alkenyl, optionally substituted by halogen, hydroxy, alkoxy, or haloalkoxy.

In other embodiments, R^1 is optionally substituted cycloalkyl or heterocycloalkyl.
20 For example, R^1 may be cycloalkyl or heterocycloalkyl, optionally substituted by one or more substituents selected from the group consisting of halo, hydroxy, (C₁-C₆)alkyl, (C₁-C₆)alkoxy, and halo(C₁-C₆)alkyl. In some embodiments, R^1 is a heterocycloalkyl that is fused at two adjacent positions to an aryl or heteroaryl ring (e.g., a tetrahydroquinolinyl group).

In certain embodiments, R^1 is optionally substituted heteroaryl and Y is absent; or, R^1
25 is optionally substituted aryl and Y is CH₂.

In certain embodiments, Y is absent or represents CH₂.

In certain embodiments, Y is absent. Alternatively, Y is CH₂.

Alternatively, Y can be optionally substituted (C₃-C₇)cycloalkylene. For example, Y can be cyclopropylene substituted by fluoro.

In other alternative embodiments, Y can be optionally substituted arylene or heteroarylene. For example, Y can be phenylene or pyridinylene, optionally substituted by halo or alkyl.

In alternative embodiments, Y is $CR^{15}R^{16}$. In certain such embodiments, R^{15} and R^{16} are selected from the group consisting of H, alkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, aralkyl, heteroaralkyl, (cycloalkyl)alkyl, and (heterocycloalkyl)alkyl, wherein alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, and (heterocycloalkyl)alkyl are optionally substituted with one or more substituents selected from the group consisting of -CN, -OR¹⁷, -NR¹⁷R¹⁸, halo, and alkyl, and further wherein R¹⁷ and R¹⁸ are each independently selected from the group consisting of H and alkyl.

Alternatively, Y is $CR^{15}R^{16}$ and R^{15} and R^{16} are taken together with the intervening atom to form an optionally substituted carbocyclic or heterocyclic ring, e.g., a cyclopropyl ring.

In certain embodiments, Y represents $CH(C_1-C_6)alkyl$. Alternatively, Y represents $CH(C_1-C_6)alkyl$, wherein the $(C_1-C_6)alkyl$ is substituted by hydroxy, alkoxy, or di(alkyl)amino.

In certain embodiments, R^2 and R^3 each independently represent H or optionally substituted alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, (alkylthio)alkyl, aralkyl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl.

In certain embodiments, R^2 is H and R^3 represents H or optionally substituted alkyl, alkoxyalkyl, hydroxyalkyl, (alkylthio)alkyl, aralkyl, heteroaralkyl, cycloalkyl, or (cycloalkyl)alkyl.

In certain embodiments, both R^2 and R^3 represent H.

Alternatively, both R^2 and R^3 may represent alkyl, e.g., methyl.

In further embodiments, R^2 and R^3 , taken together with the intervening atom, form an optionally substituted carbocyclic or heterocyclic ring.

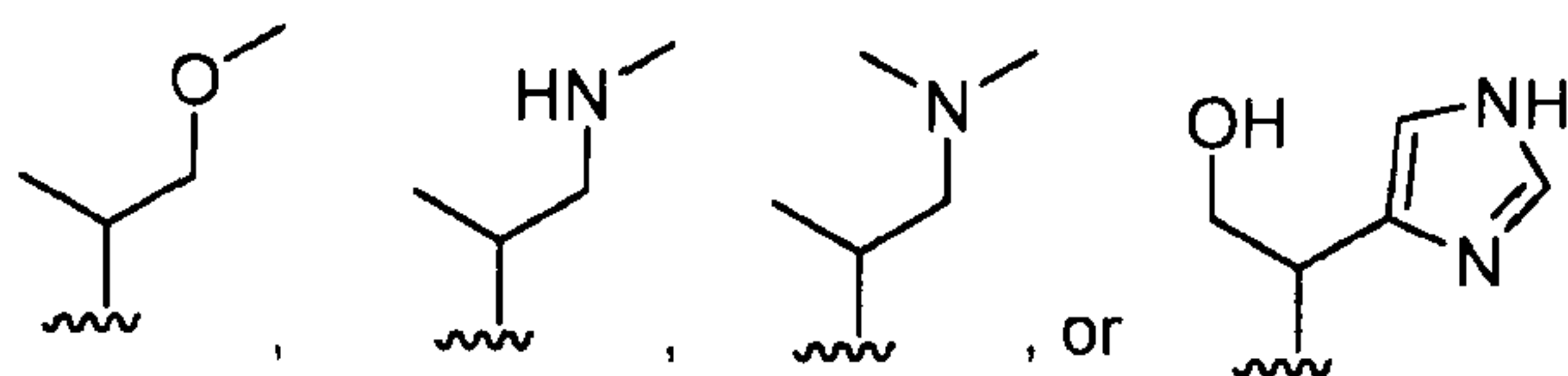
In certain embodiments, R^4 represents H or optionally substituted alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, aralkyl, hydroxyalkyl, or haloalkyl; preferably R^4 represents H or optionally substituted alkyl or cycloalkyl.

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In certain embodiments, R^4 represents H or alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aralkyl, heteroaralkyl, hydroxyalkyl, or haloalkyl, each optionally substituted by one or more substituents independently selected from the group consisting of halo, alkoxy, alkyl, hydroxy, hydroxyalkyl, haloalkyl, $-NH_2$, $-NH(alkyl)$, $-N(alkyl)_2$, $-C(O)O(alkyl)$, $-C(O)NH_2$, $-S(O)_2(alkyl)$, $-NHS(O)_2(alkyl)$, and $-NHC(O)(O(alkyl))$.

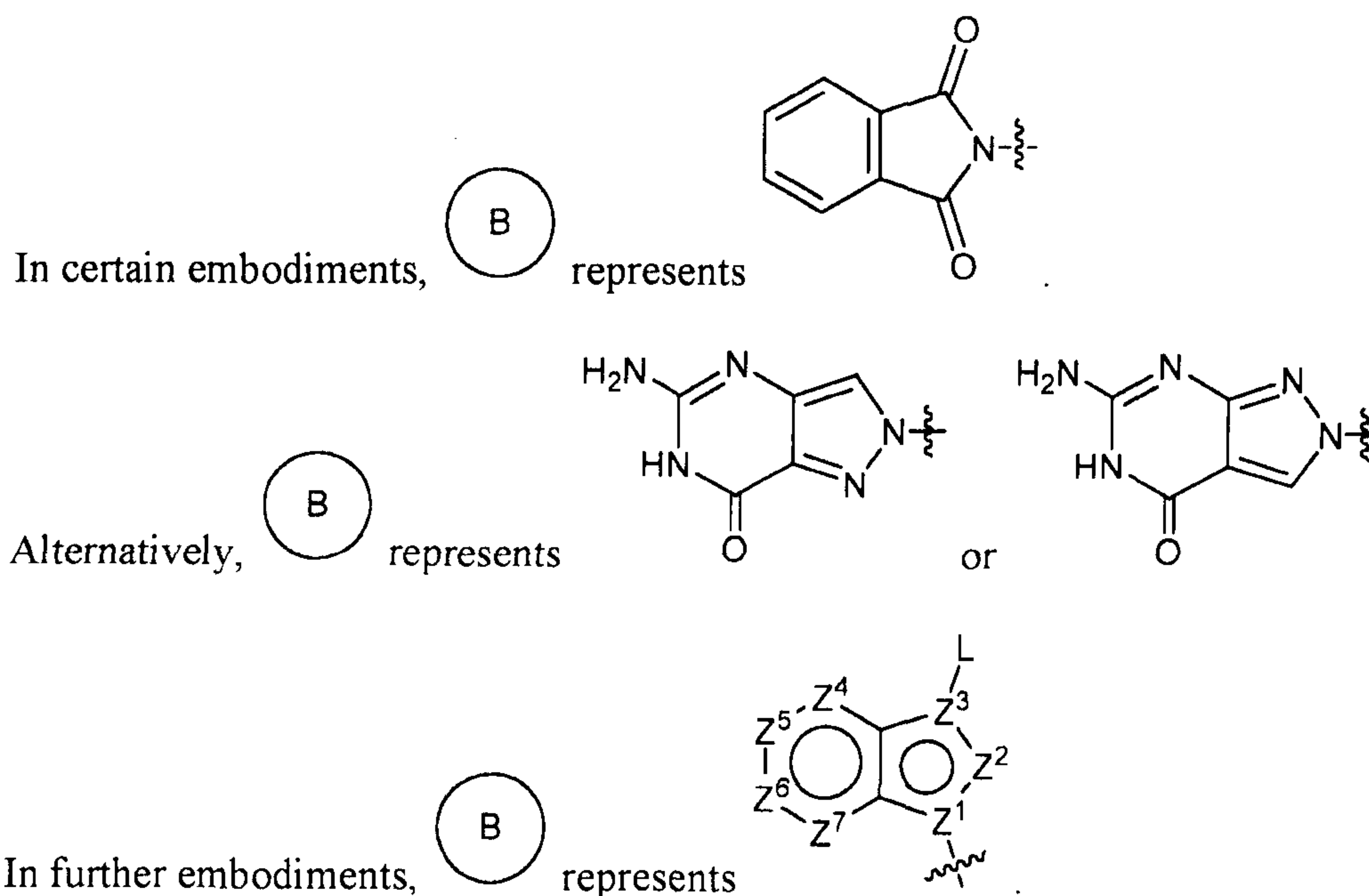
In exemplary embodiments, R^4 represents



In certain embodiments, R^a represents $(C_1-C_6)alkyl$, (heterocycloalkyl)alkyl, or $(C_3-C_7)cycloalkyl$, optionally substituted by hydroxy or dialkylamino.

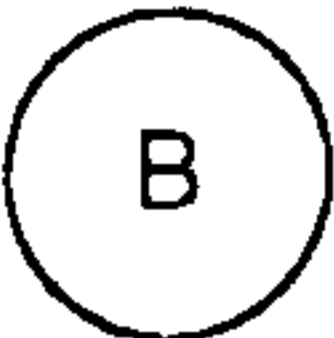
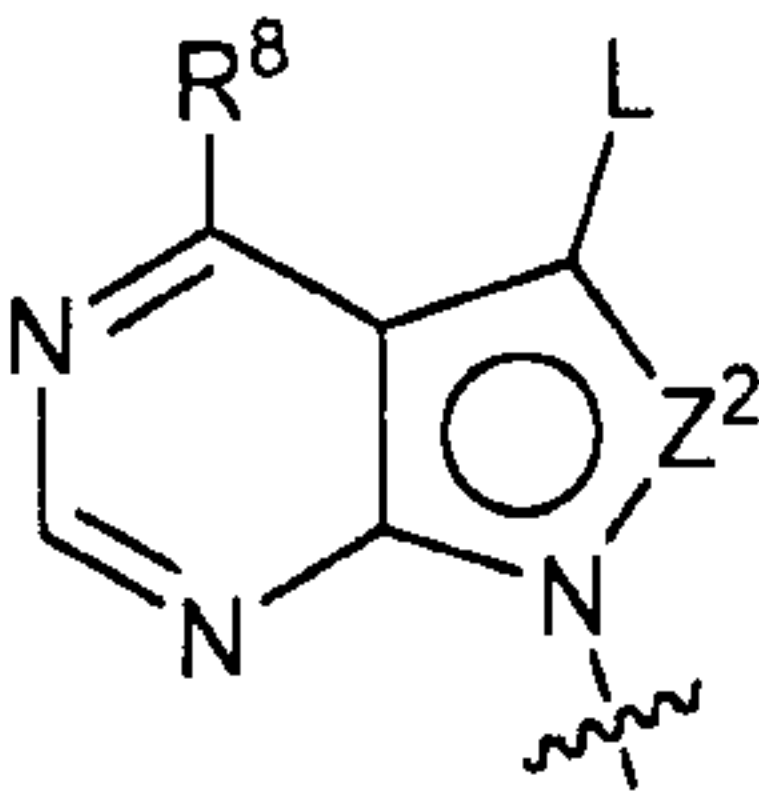
In certain embodiments, R^a represents H, $(C_1-C_6)alkyl$, or $(C_3-C_7)cycloalkyl$. In further embodiments, R^a represents H. Alternatively, in some embodiments, R^a represents $(C_1-C_6)alkyl$.

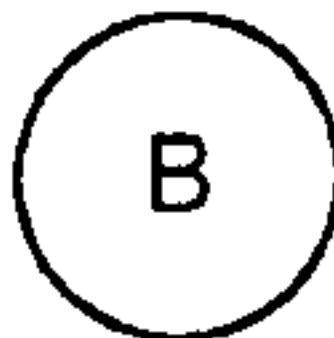
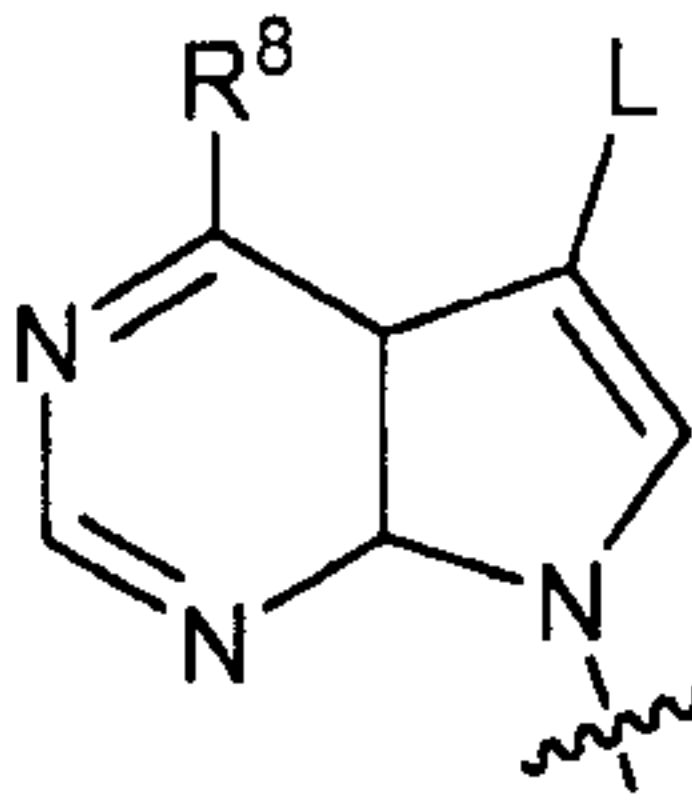
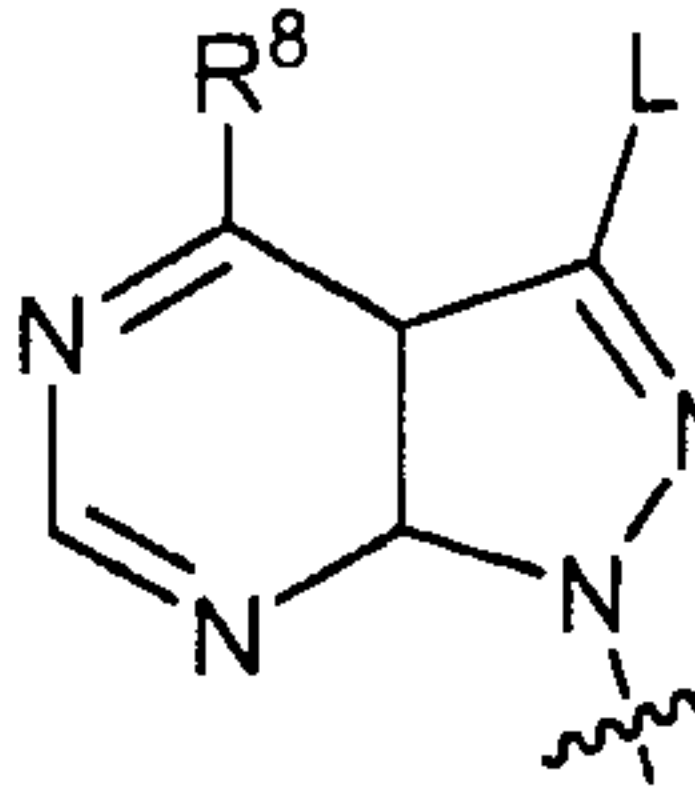
In certain embodiments, m is an integer from 1-4. In some embodiments, m is 1 or 2. Preferably, m is 1.



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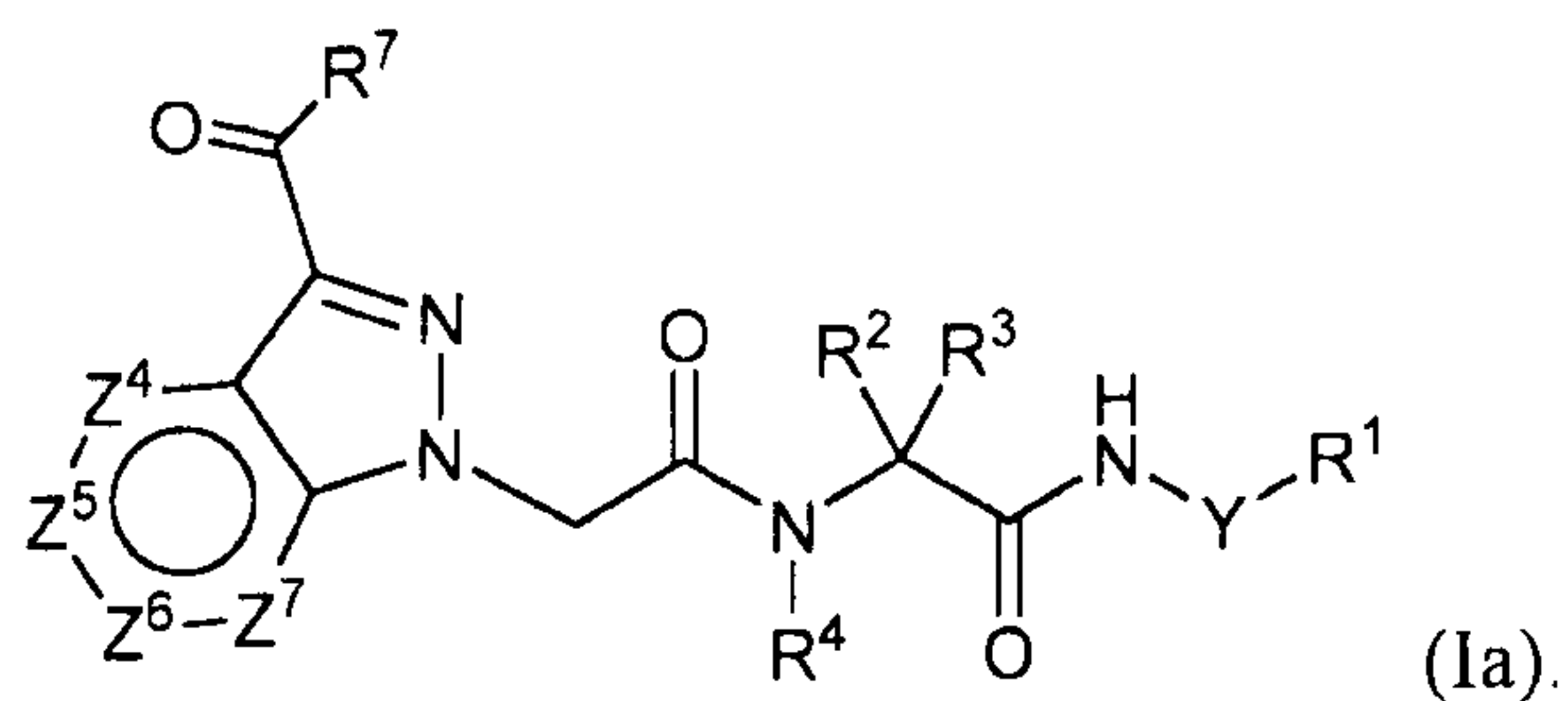
In some embodiments,  may represent , wherein R⁸, L, and Z²

are as defined above. For example,  may represent  or .

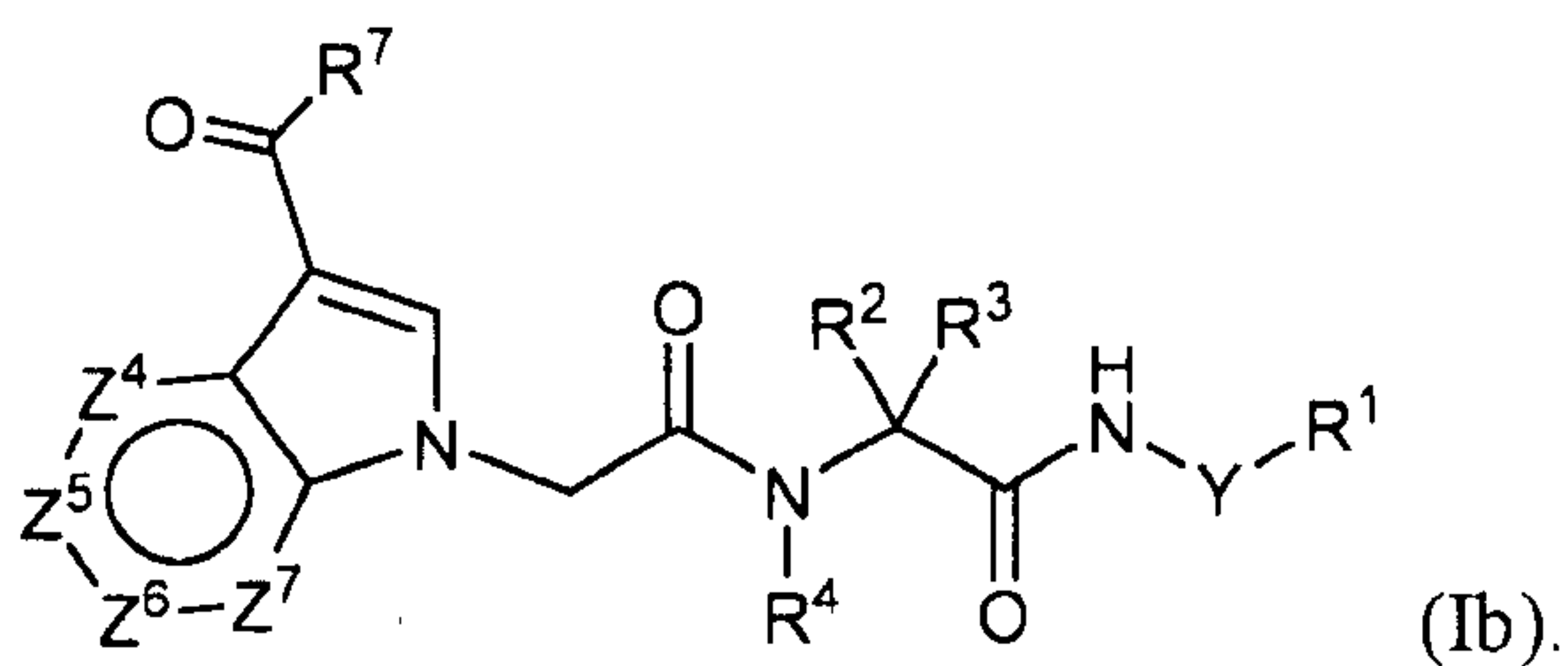
In certain such embodiments, R⁸ is preferably H, NH₂, or Cl. In further such embodiments, L represents H or CN.

5 In certain embodiments, L represents -C(O)R⁷.

In certain embodiments, the compound of Formula (I) has the structure of Formula (Ia):



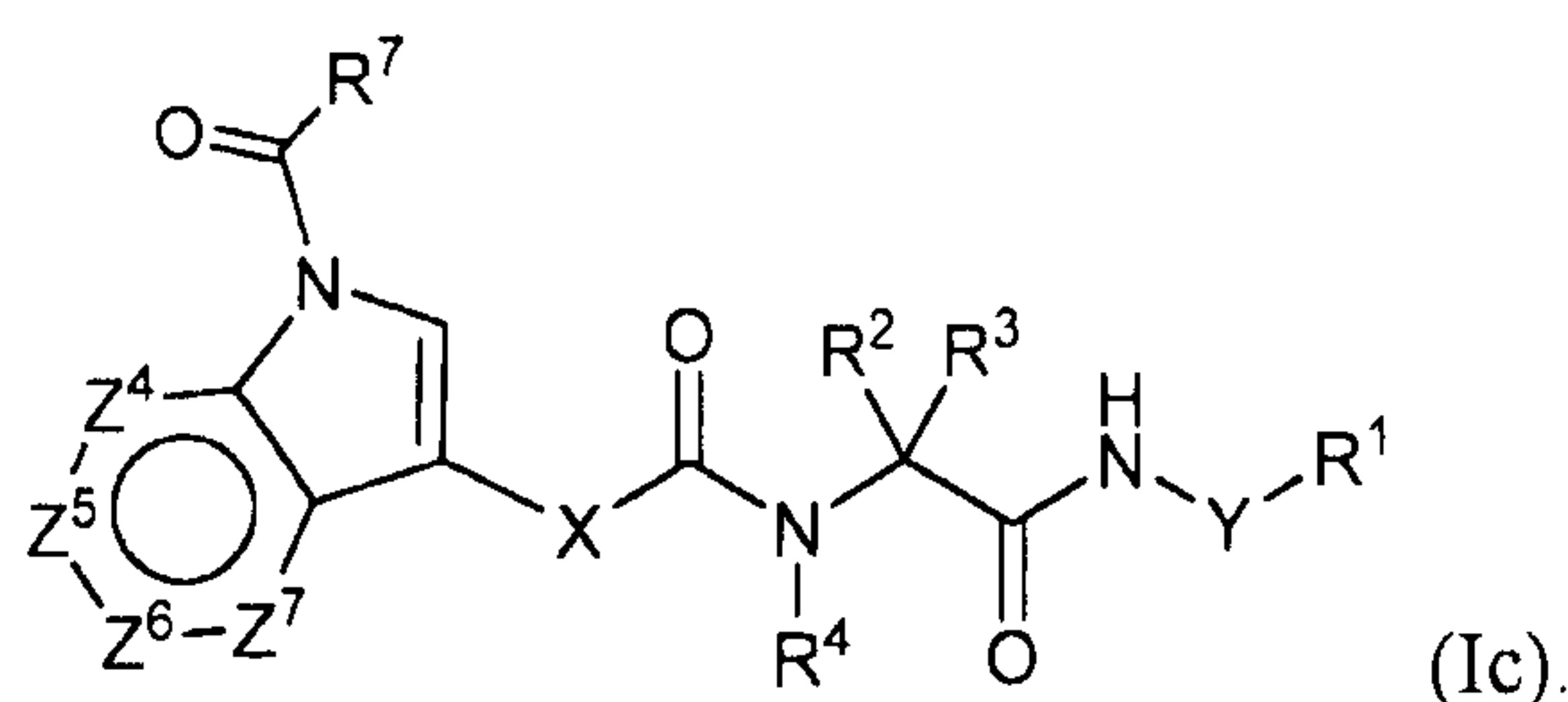
10 In certain embodiments, the compound of Formula (I) has the structure of Formula (Ib):



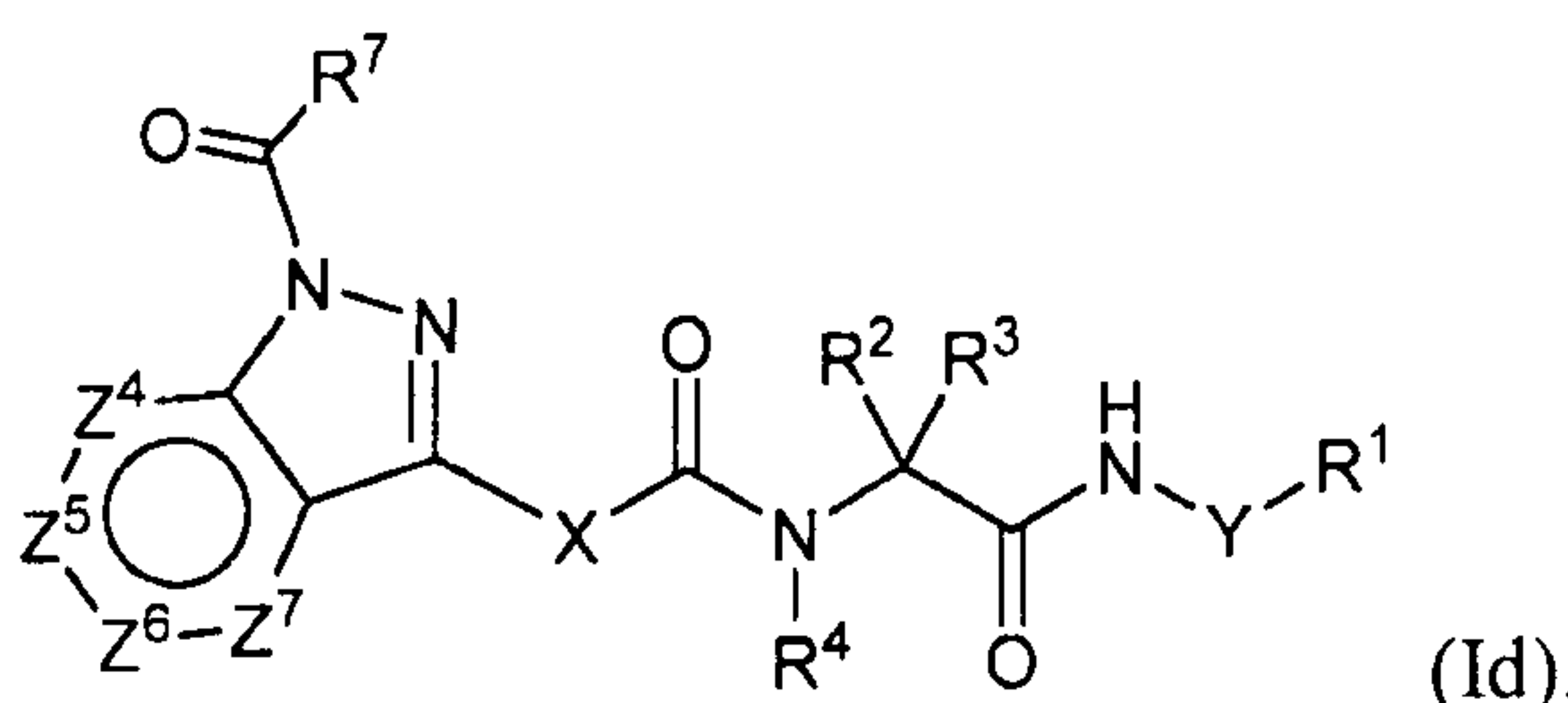
In certain embodiments, the compound of Formula (I) has the structure of Formula (Ic):

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In certain embodiments, the compound of Formula (I) has the structure of Formula (Id):



5 In certain embodiments of the compounds of formulae (Ic) or (Id), X is NH .

In certain embodiments of the compounds of formula (I), if Z^1 is N , then X is CH_2 . In further embodiments, Z^1 is C , then X is NH .

In certain embodiments of the compounds of formulae (Ia), (Ib), (Ic), or (Id), Z^4 represents CR^8 , Z^5 represents CR^5 , Z^6 represents CR^6 , and Z^7 represents CR^9 .

10 In certain embodiments, Z^4 and Z^7 each represent CH .

In certain embodiments, Z^5 represents CR^5 and Z^6 represents CR^6 ; and

R^5 and R^6 each independently represent H , halogen, $-NR^{13}R^{14}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{14}$, $-NHC(O)NR^{13}R^{14}$, $-NHS(O)_2(R^{14})$, or optionally substituted alkyl, alkenyl, alkynyl, heteroaryl, or aryl.

15 In certain such embodiments, R^{13} and R^{14} , independently for each occurrence, represent H or optionally substituted aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, or (cycloalkyl)alkyl.

In further embodiments, R^5 and R^6 each independently represent H or alkyl, alkenyl, alkynyl, heteroaryl, or aryl, optionally substituted with one or more substituents selected from the group consisting of aryl, heteroaryl, silyl, alkyl, amino, alkylamino, dialkylamino, $-C(O)(alkyl)$, heterocycloalkyl, and halogen. Alternatively, R^5 and R^6 each independently represent H or alkyl, alkenyl, alkynyl, heteroaryl, or aryl, optionally substituted with one or

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more substituents selected from the group consisting of aryl, heteroaryl, silyl, alkyl, amino, alkylamino, dialkylamino, $-C(O)(alkyl)$, and halogen.

In certain embodiments, R^{13} and R^{14} , independently for each occurrence, represent H or alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl, optionally substituted by one or more substituents independently selected from halo, alkoxy, alkyl, hydroxy, hydroxyalkyl, haloalkyl, $-NH_2$, $-NH(alkyl)$, $-N(alkyl)_2$, $-C(O)O(alkyl)$, $-C(O)NH_2$, $-S(O)_2(alkyl)$, $-NHS(O)_2(alkyl)$, and $-NHC(O)(O(alkyl))$.

In certain embodiments, R^5 and R^6 each independently represent H, halogen, $-OR^{13}$, $-NR^{13}R^{14}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-OC(O)NR^{13}R^{14}$, $-OC(O)OR^{13}$, $-NR^{13}C(O)OR^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-OS(O)_p(R^{13})$, $-NR^{13}S(O)_p(R^{14})$, or optionally substituted alkyl, alkenyl, alkynyl, haloalkyl, aralkyl, heteroaralkyl, heteroaryl, aryl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl.

In certain embodiments, R^5 , R^6 , R^8 , and R^9 each independently represent H or alkyl, alkenyl, alkynyl, haloalkyl, aralkyl, heteroaralkyl, heteroaryl, aryl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl, optionally substituted with one or more substituents selected from the group consisting of aryl, heteroaryl, silyl, alkyl, amino, alkylamino, dialkylamino, $-C(O)(alkyl)$, hydroxy, alkoxy, aryloxy, heteroaryloxy, and halogen.

In certain embodiments, R^5 , R^6 , R^8 , and R^9 each independently represent H or alkyl, alkenyl, alkynyl, heteroaryl, or aryl, optionally substituted with one or more substituents selected from the group consisting of aryl, heteroaryl, silyl, alkyl, amino, alkylamino, dialkylamino, $-C(O)(alkyl)$, hydroxy, alkoxy, aryloxy, heteroaryloxy, and halogen.

In certain embodiments, R^5 , R^6 , R^8 , and R^9 each independently represent H or $-CH(OH)R^{50}$, $-CH(NH_2)R^{50}$, $-CH(OR^{51})R^{50}$, $-CH(NHR^{51})R^{50}$, $-C(NH_2)(R^{51})(R^{50})$, $-C(OH)(R^{51})(R^{50})$, and $-NH(CO)CR^5R^6R^{50}$; wherein for each occurrence R^{50} and R^{51} are each independently selected from alkyl, alkenyl, alkynyl, haloalkyl, aralkyl, heteroaralkyl, heteroaryl, aryl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, and (heterocycloalkyl)alkyl.

In certain embodiments, R^5 , R^6 , and R^8 are each H.

In certain embodiments, R^5 , R^6 , and R^9 are each H.

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In certain embodiments, R^5 , R^8 , and R^9 are each H.

In certain embodiments, R^6 , R^8 , and R^9 are each H.

In certain embodiments, R^7 represents NH_2 , CH_3 , or CF_3 .

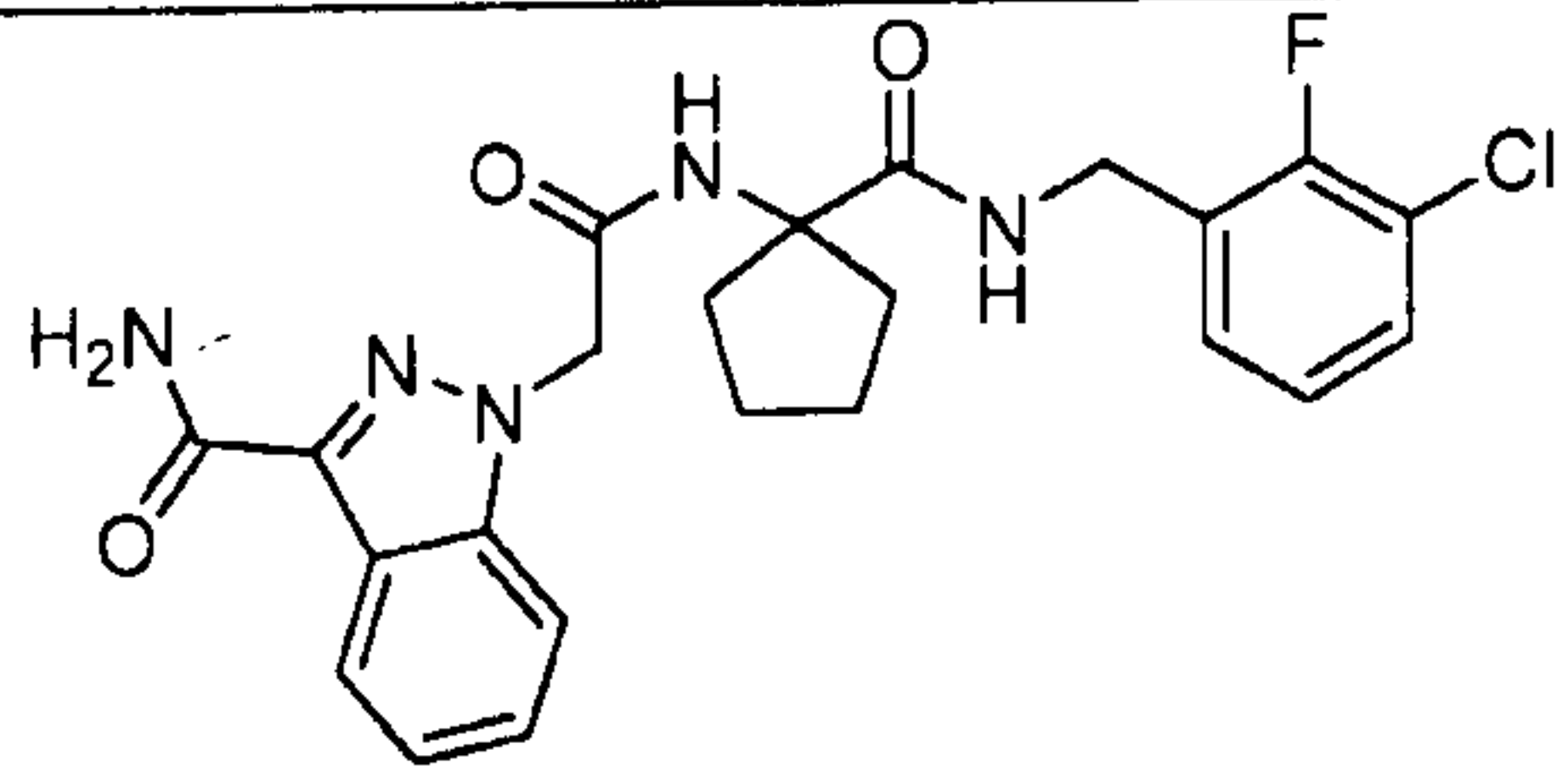
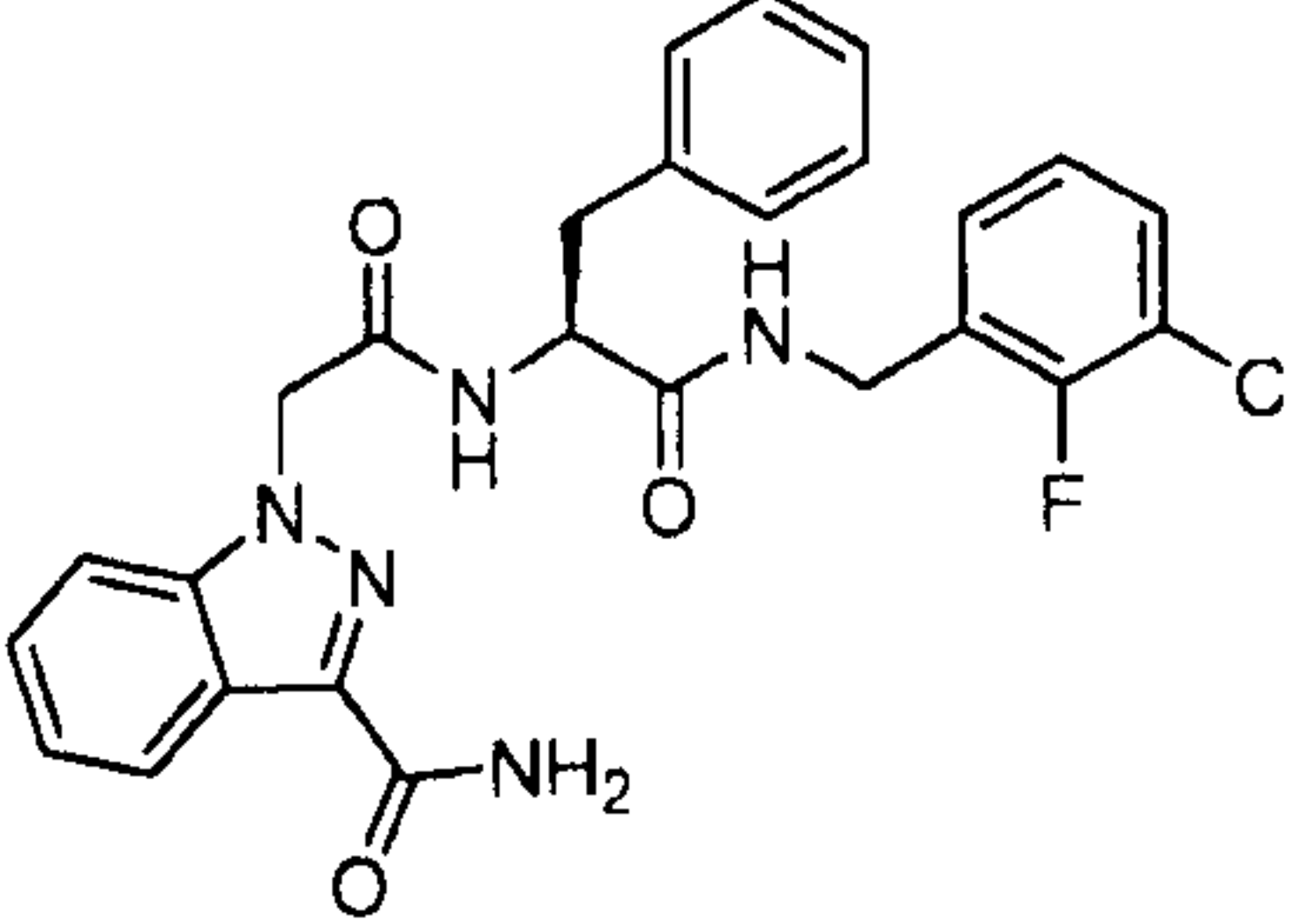
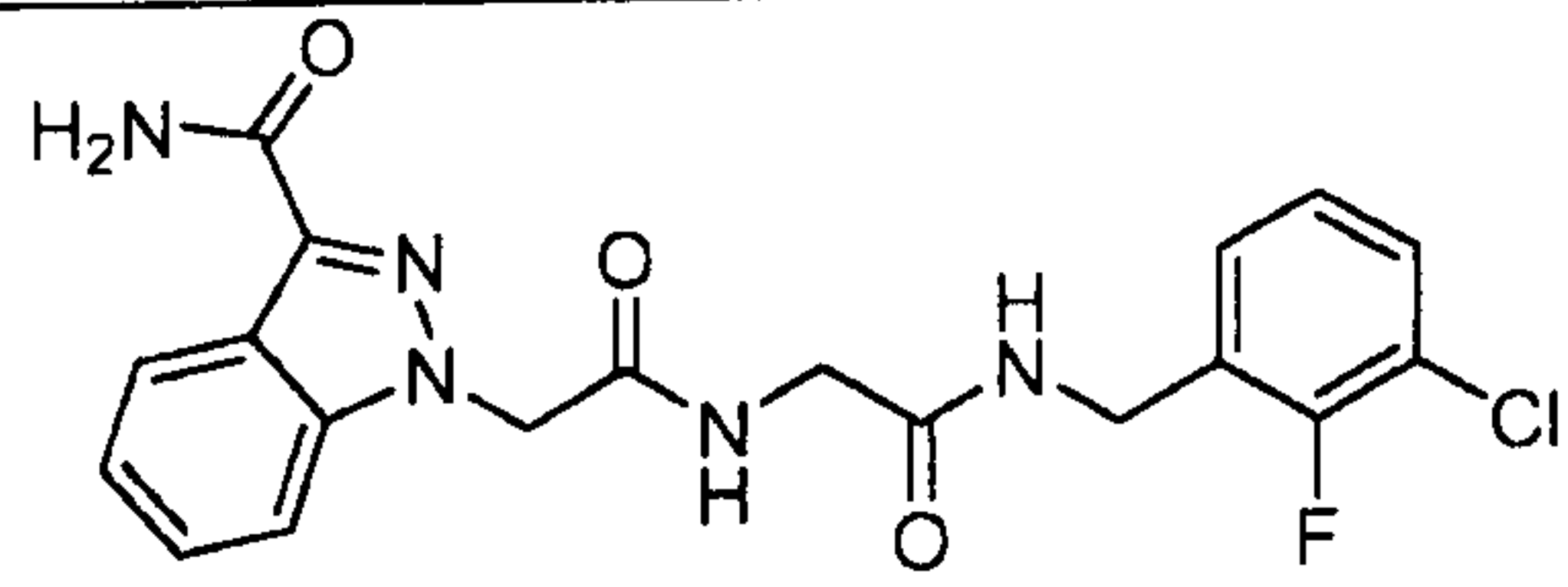
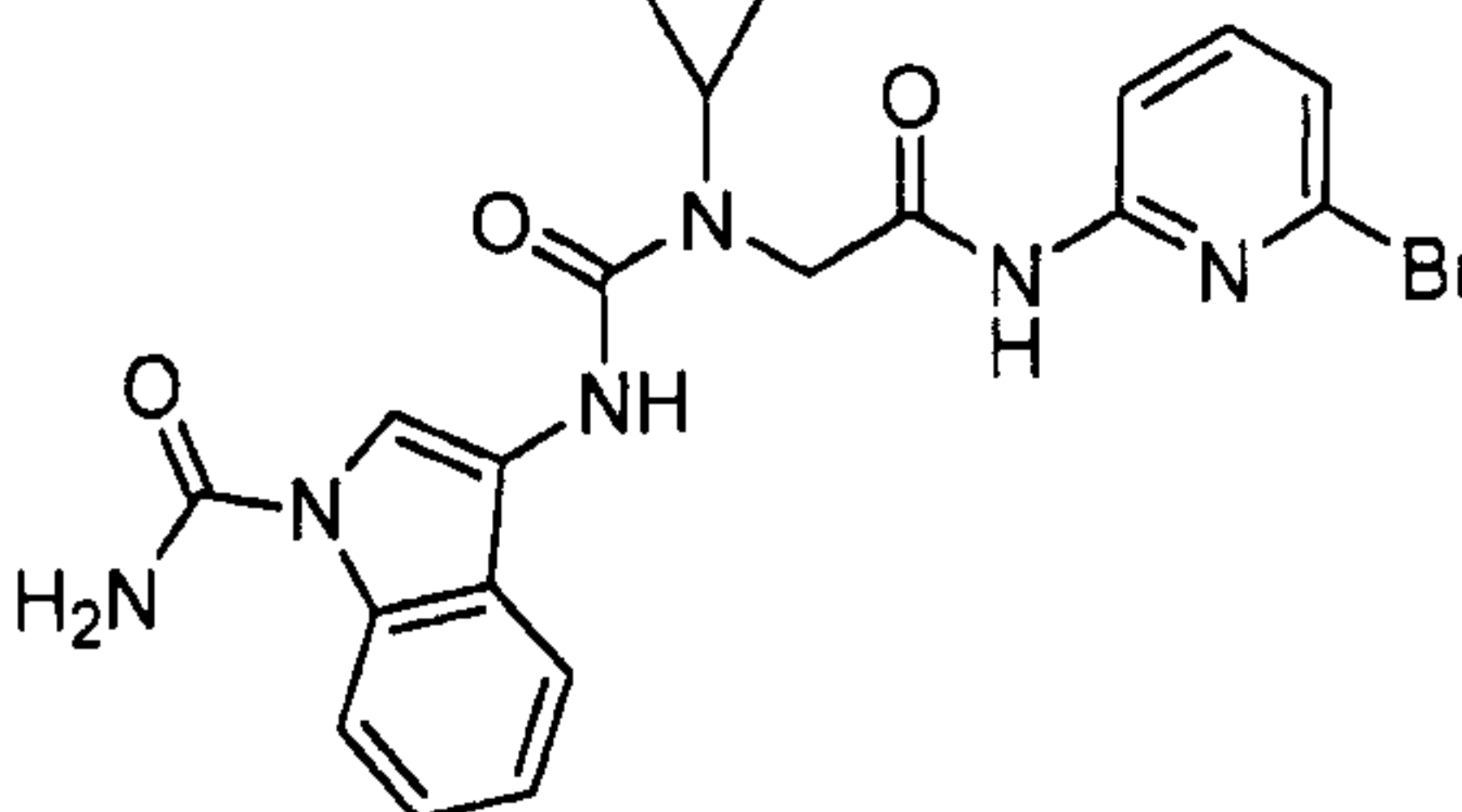
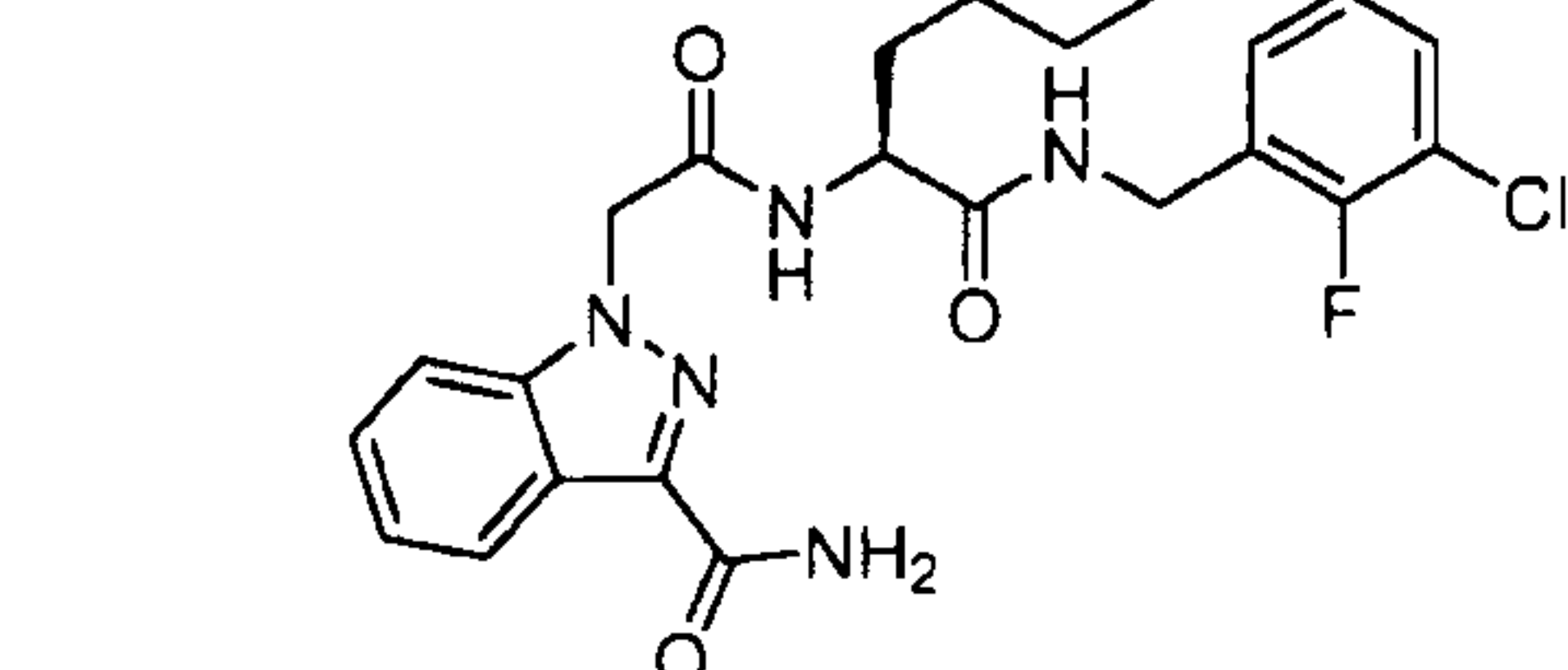
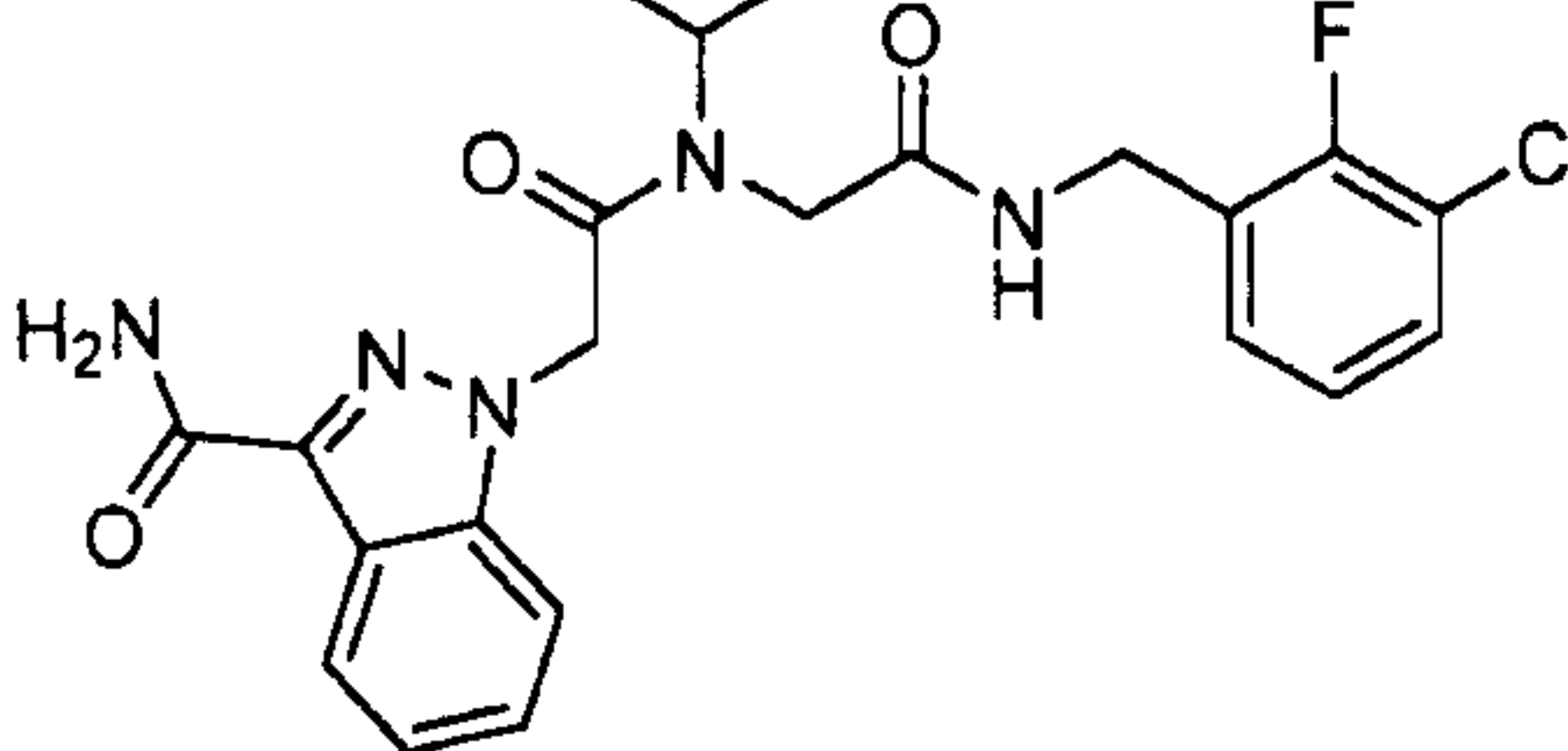
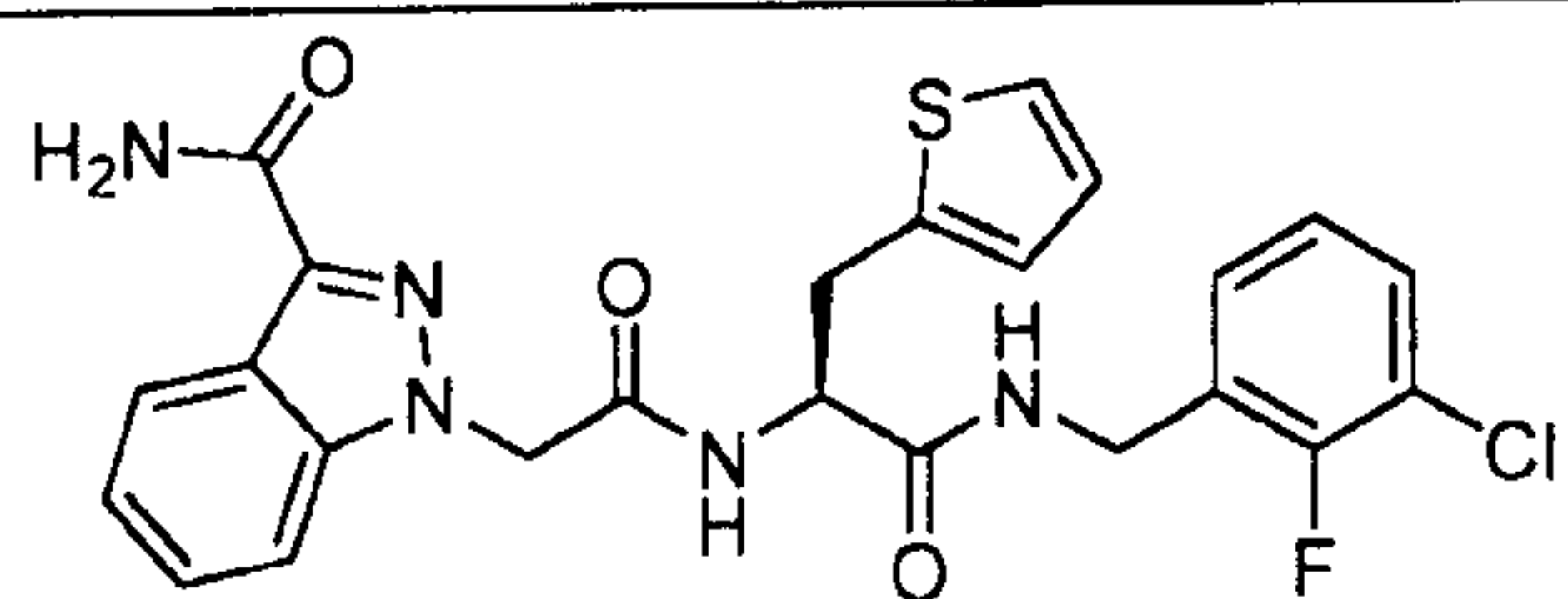
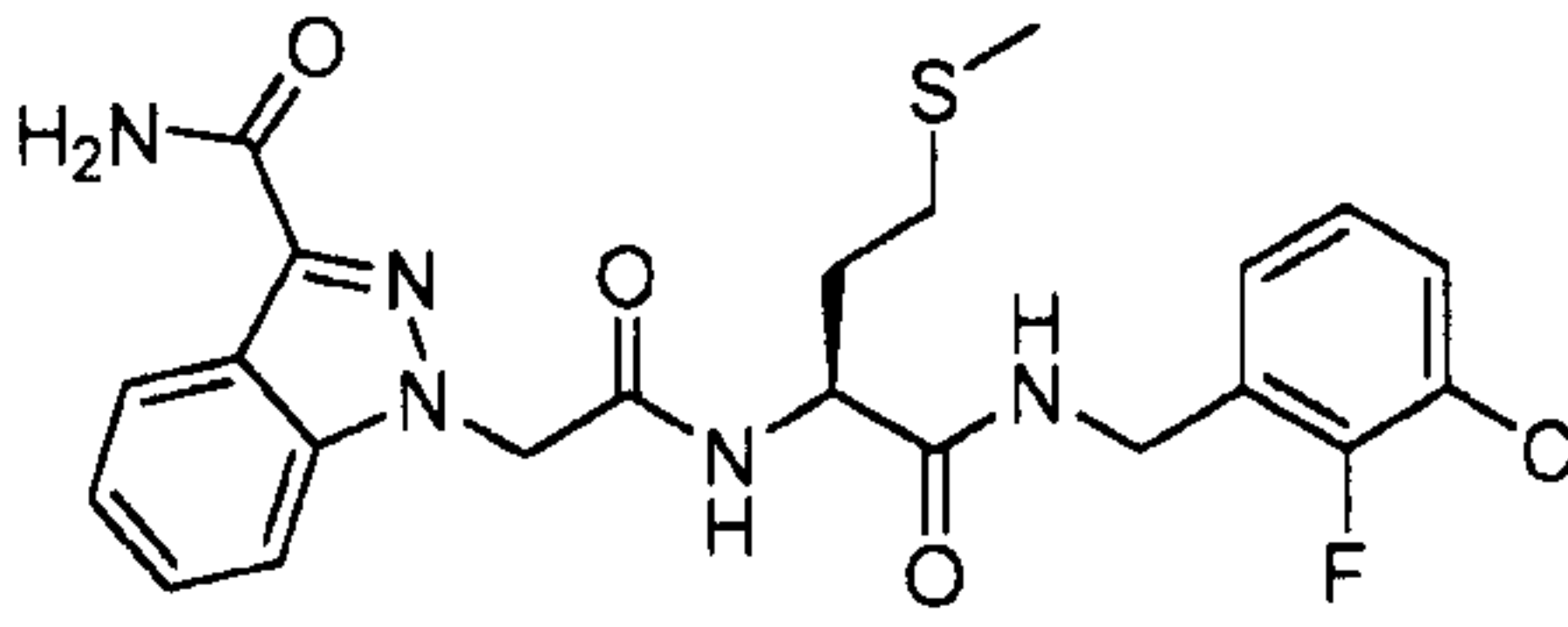
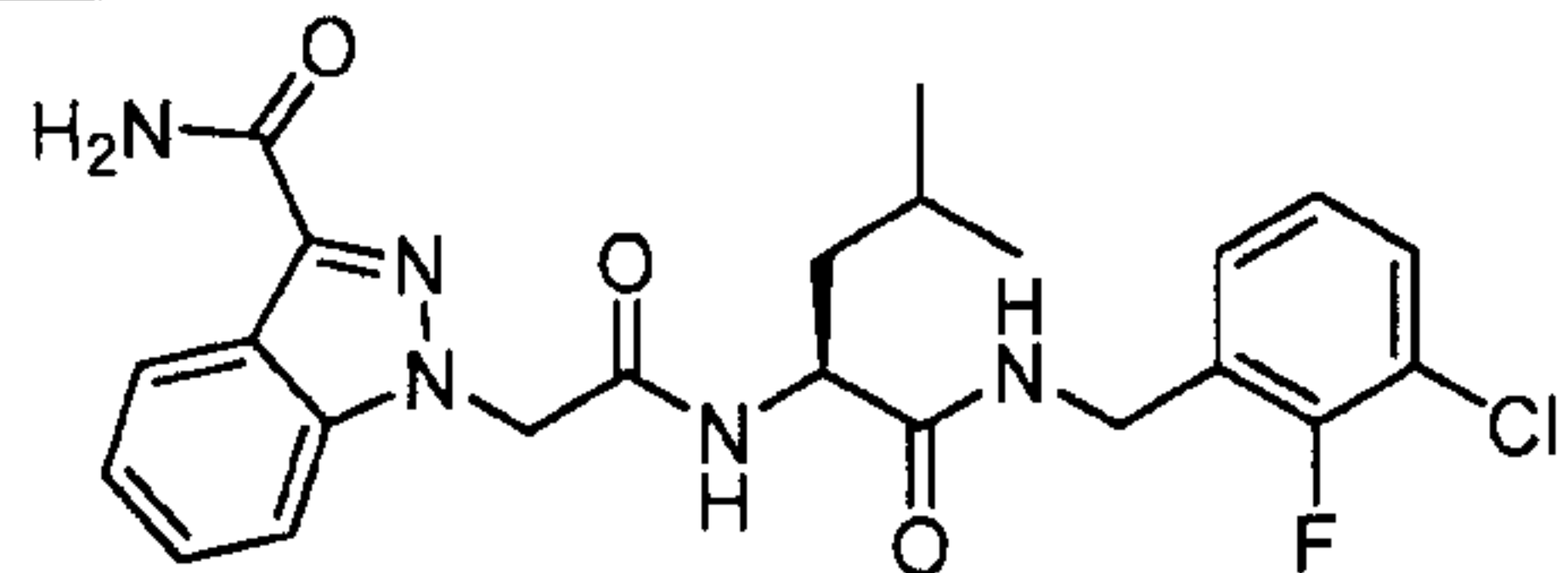
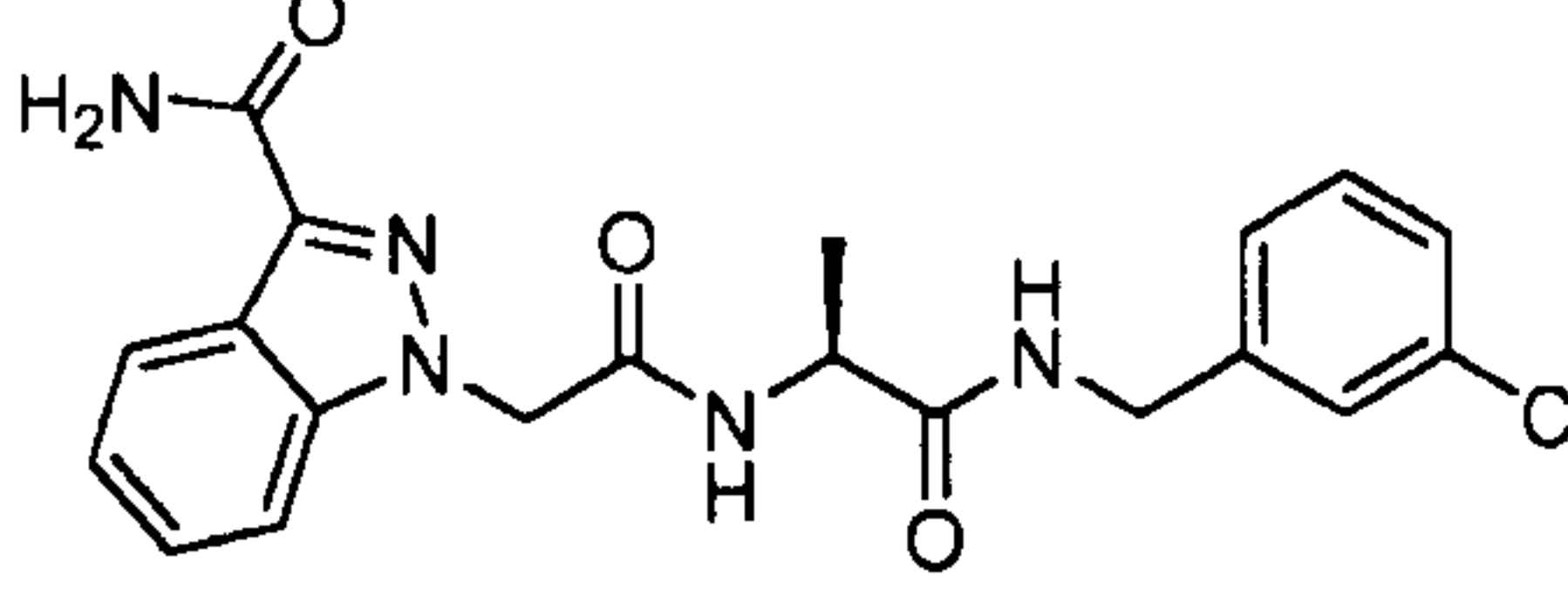
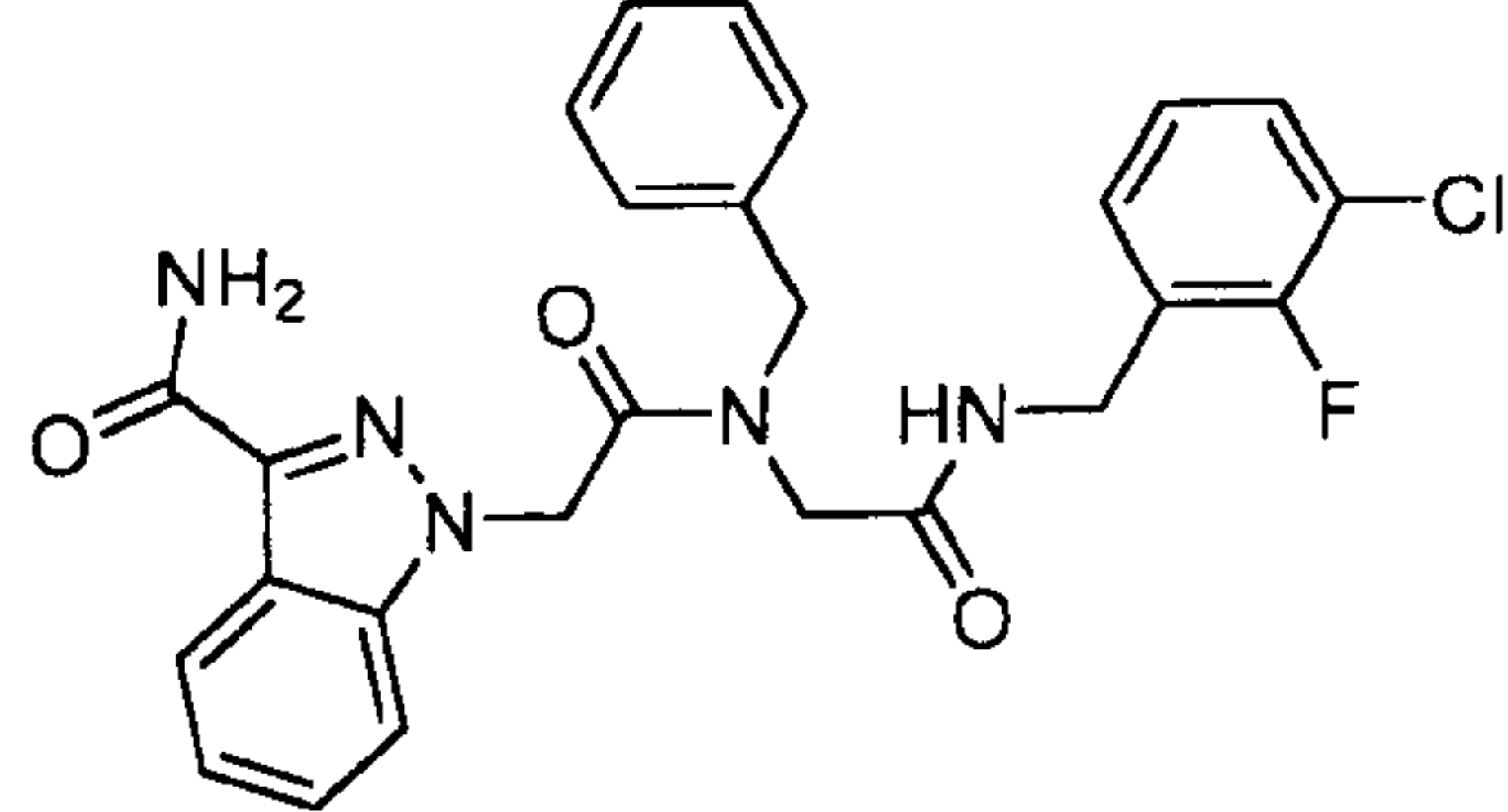
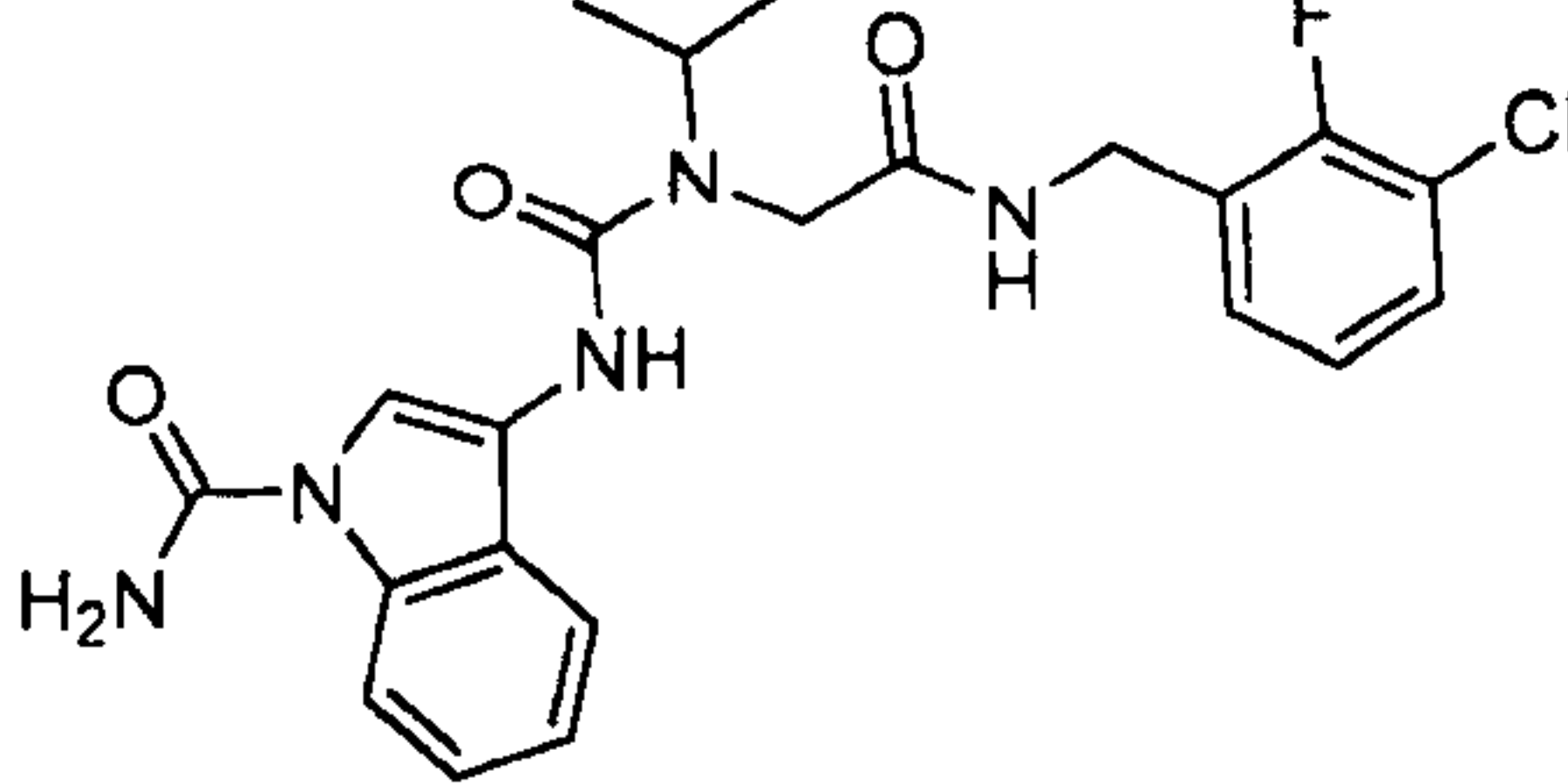
In certain embodiments, R^7 represents NH_2 .

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In certain embodiments, the compound of the invention is selected from the group consisting of the following table of compounds, or a pharmaceutically acceptable salt thereof:

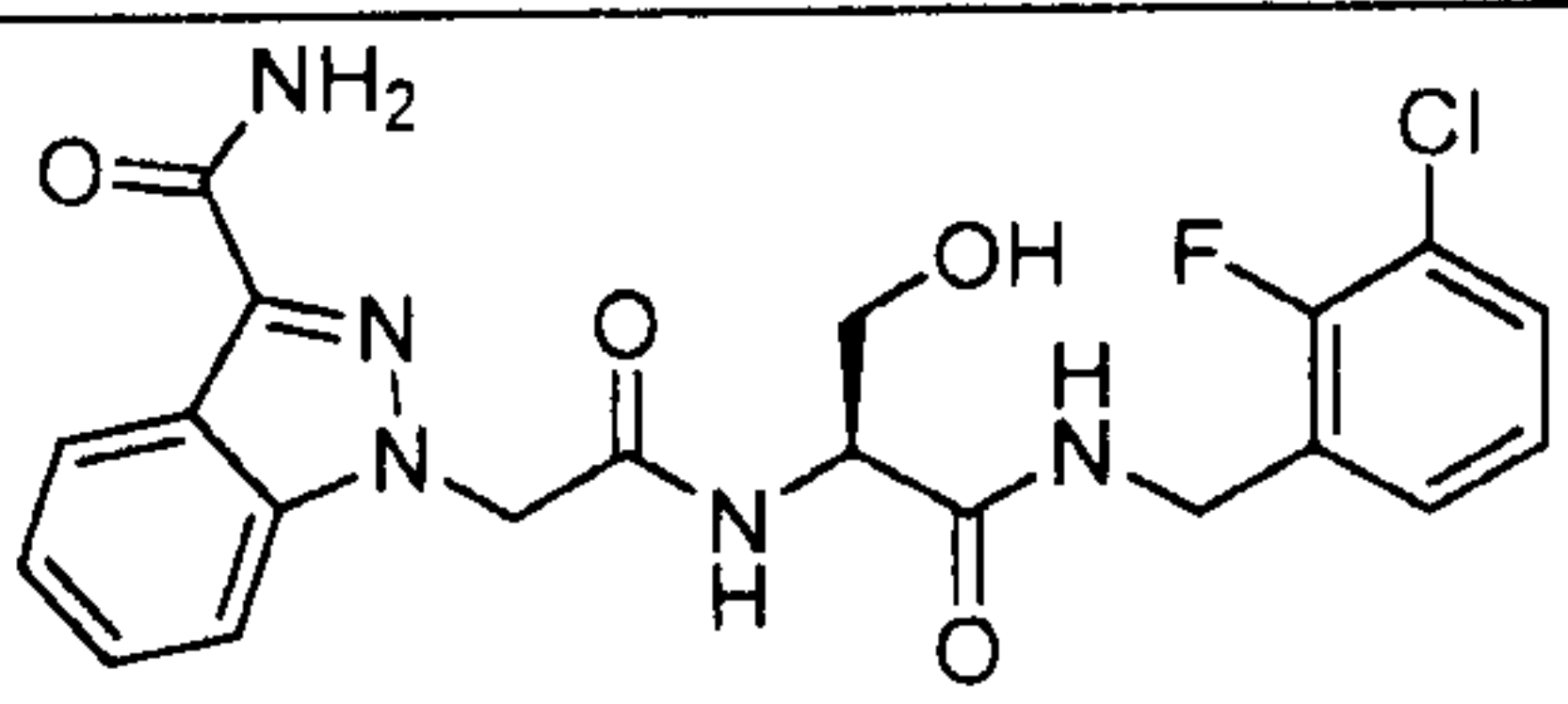
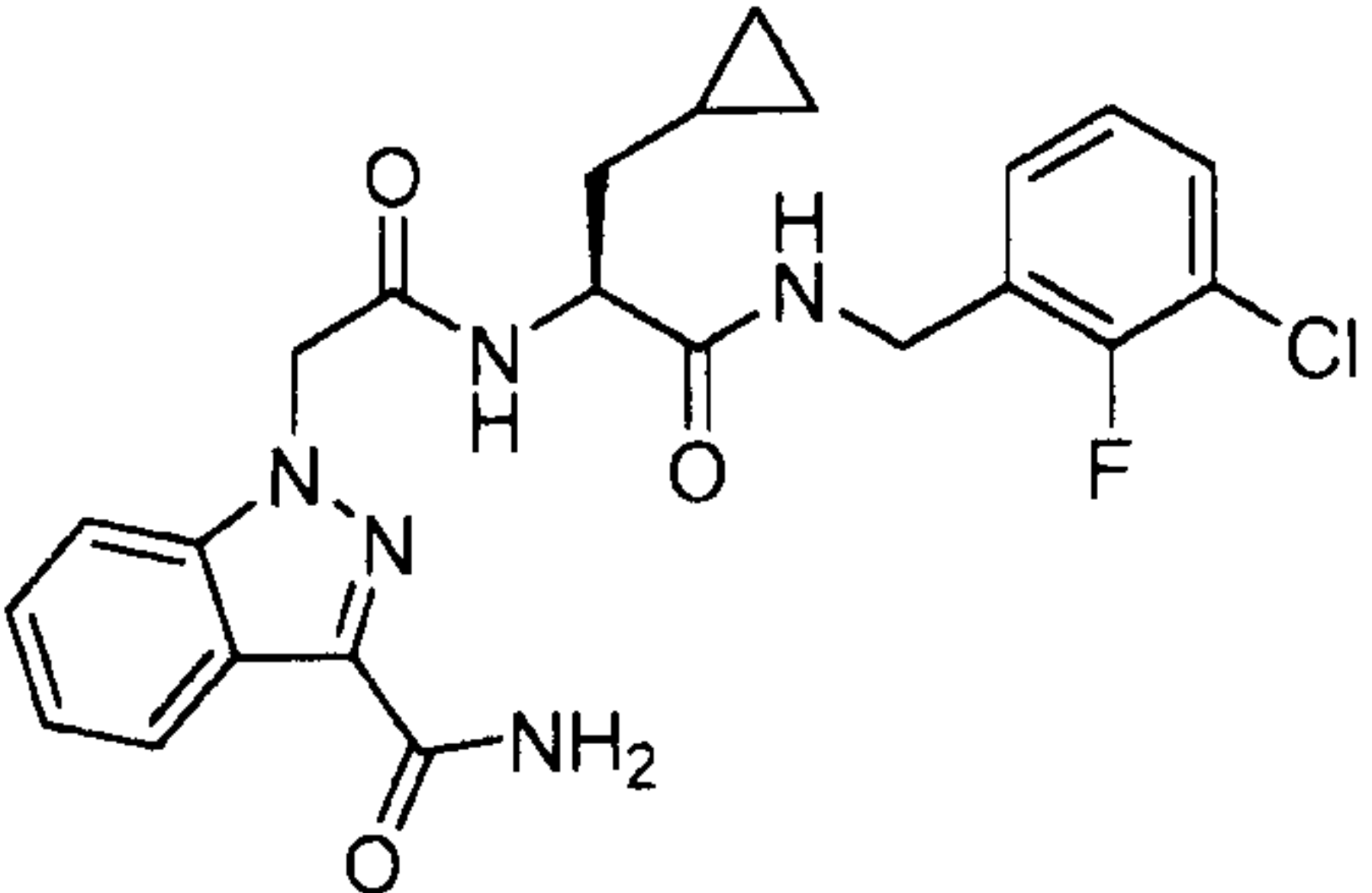
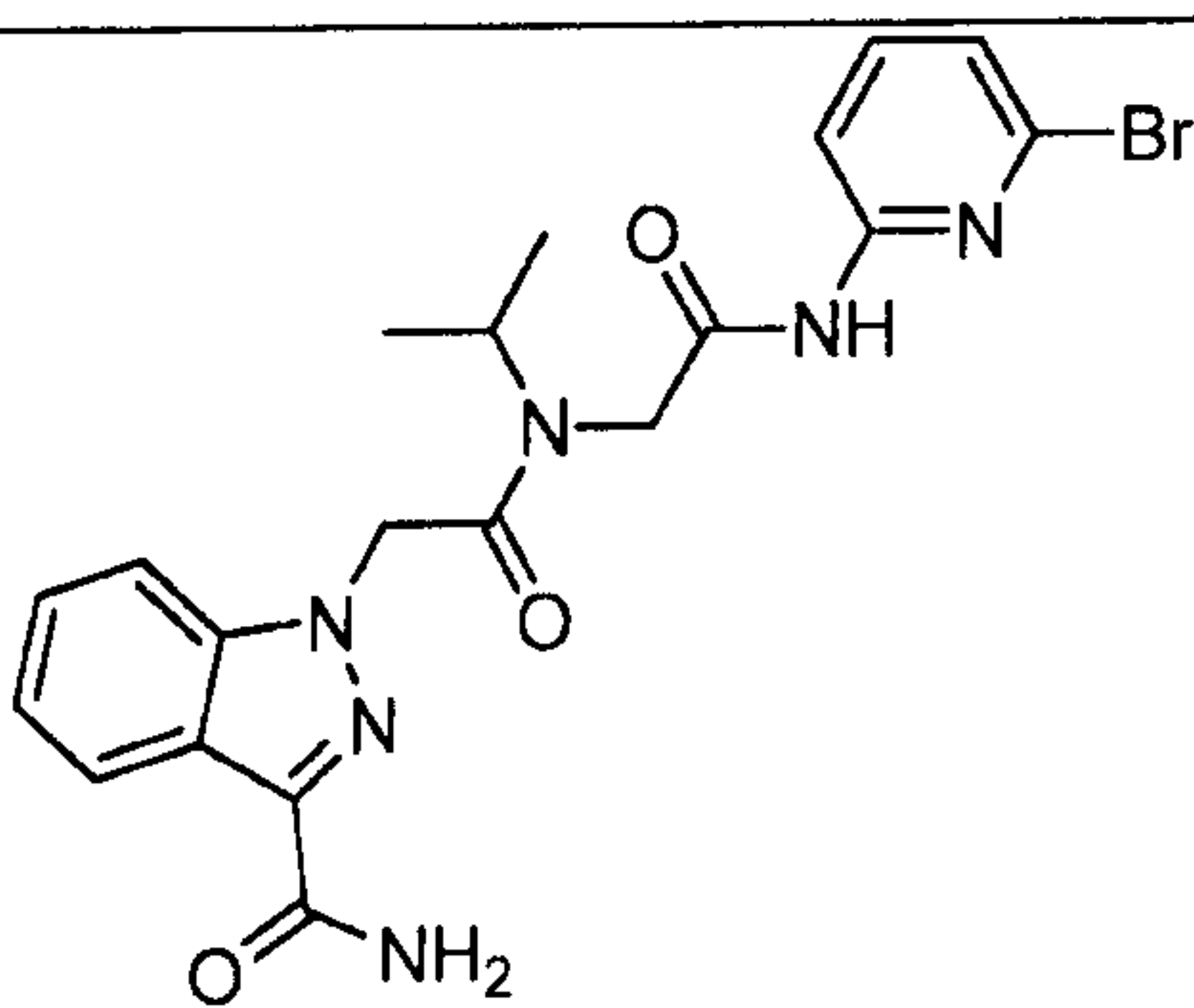
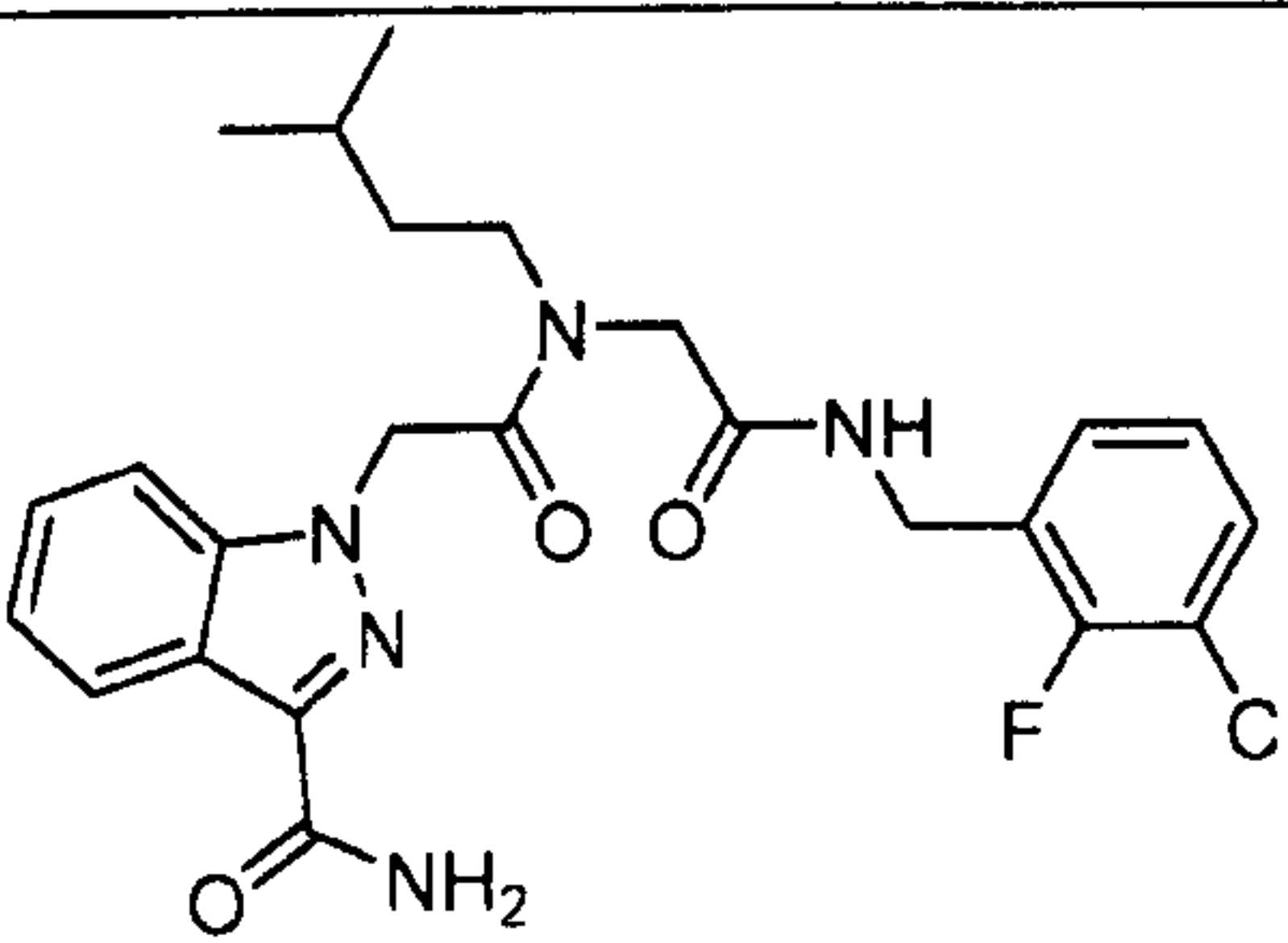
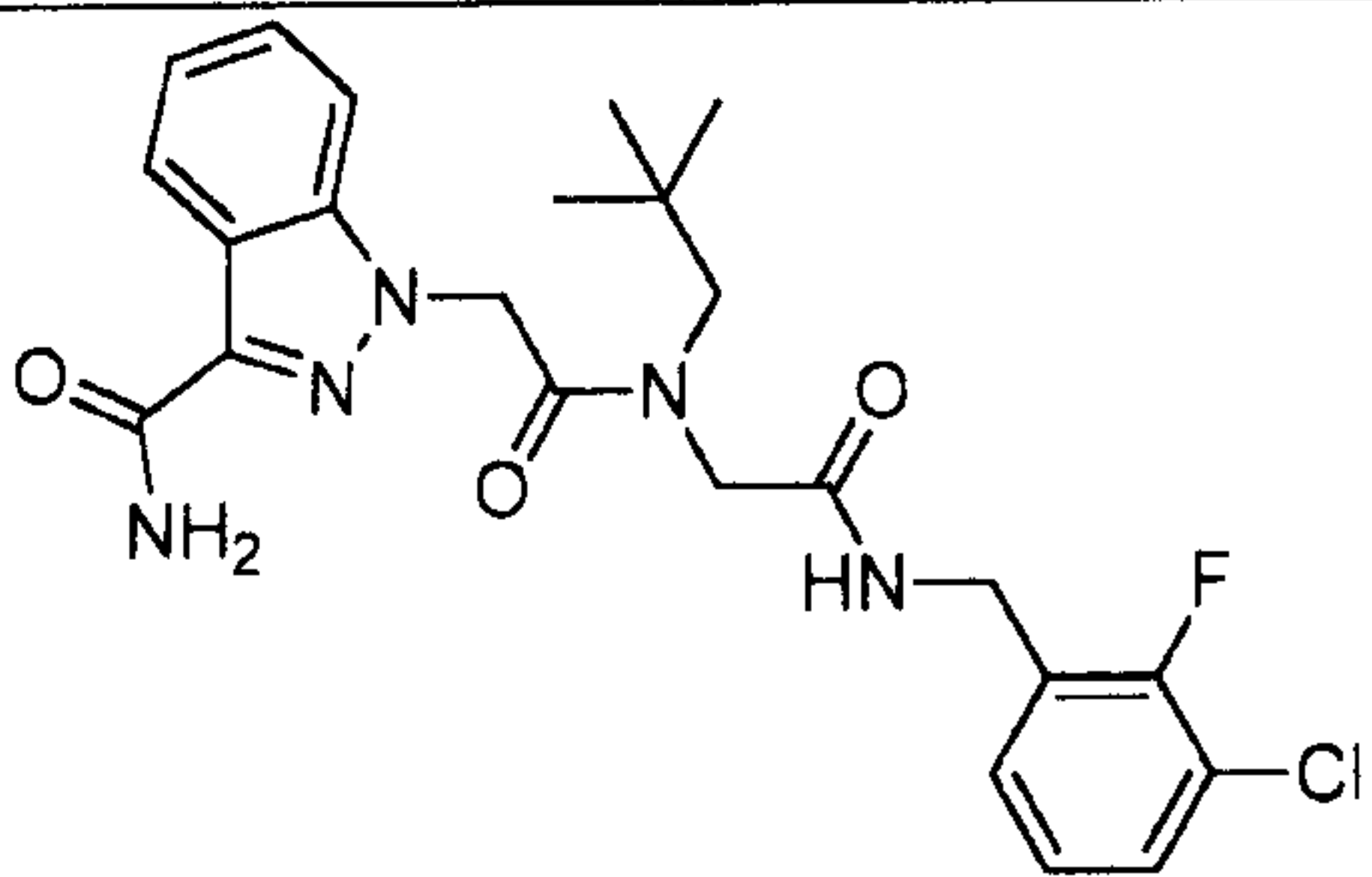
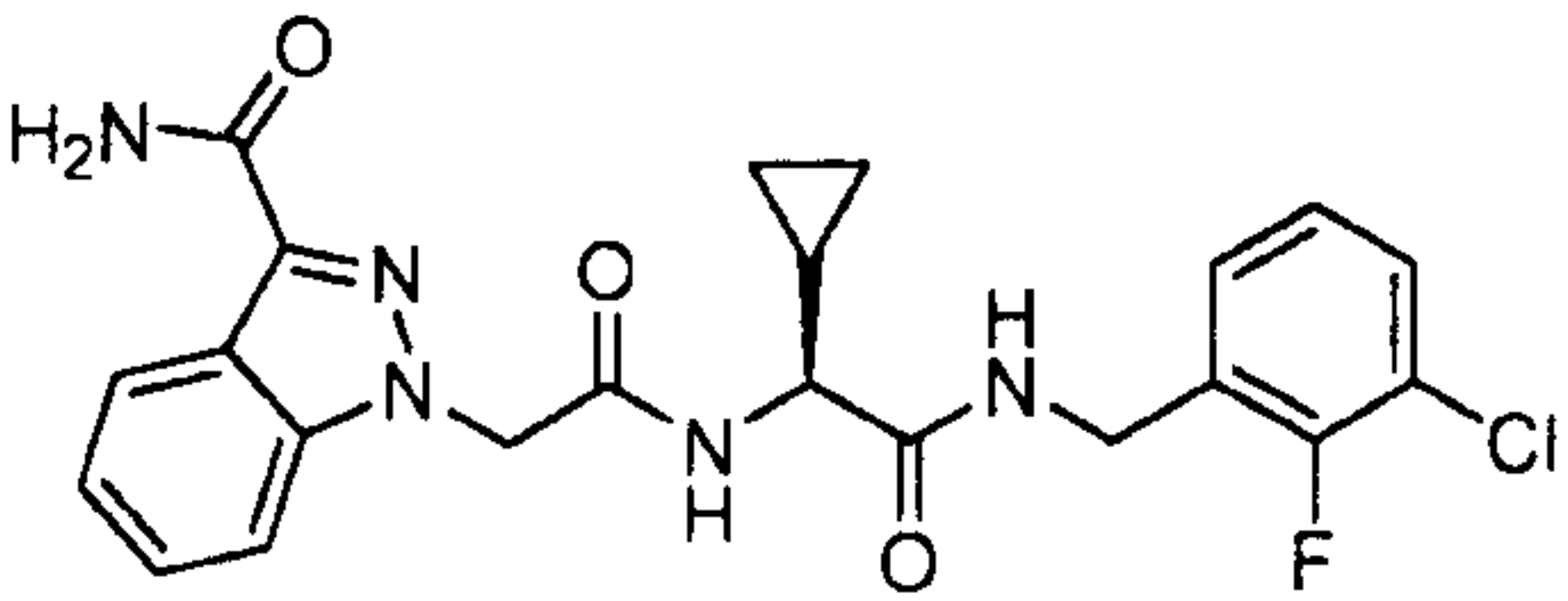
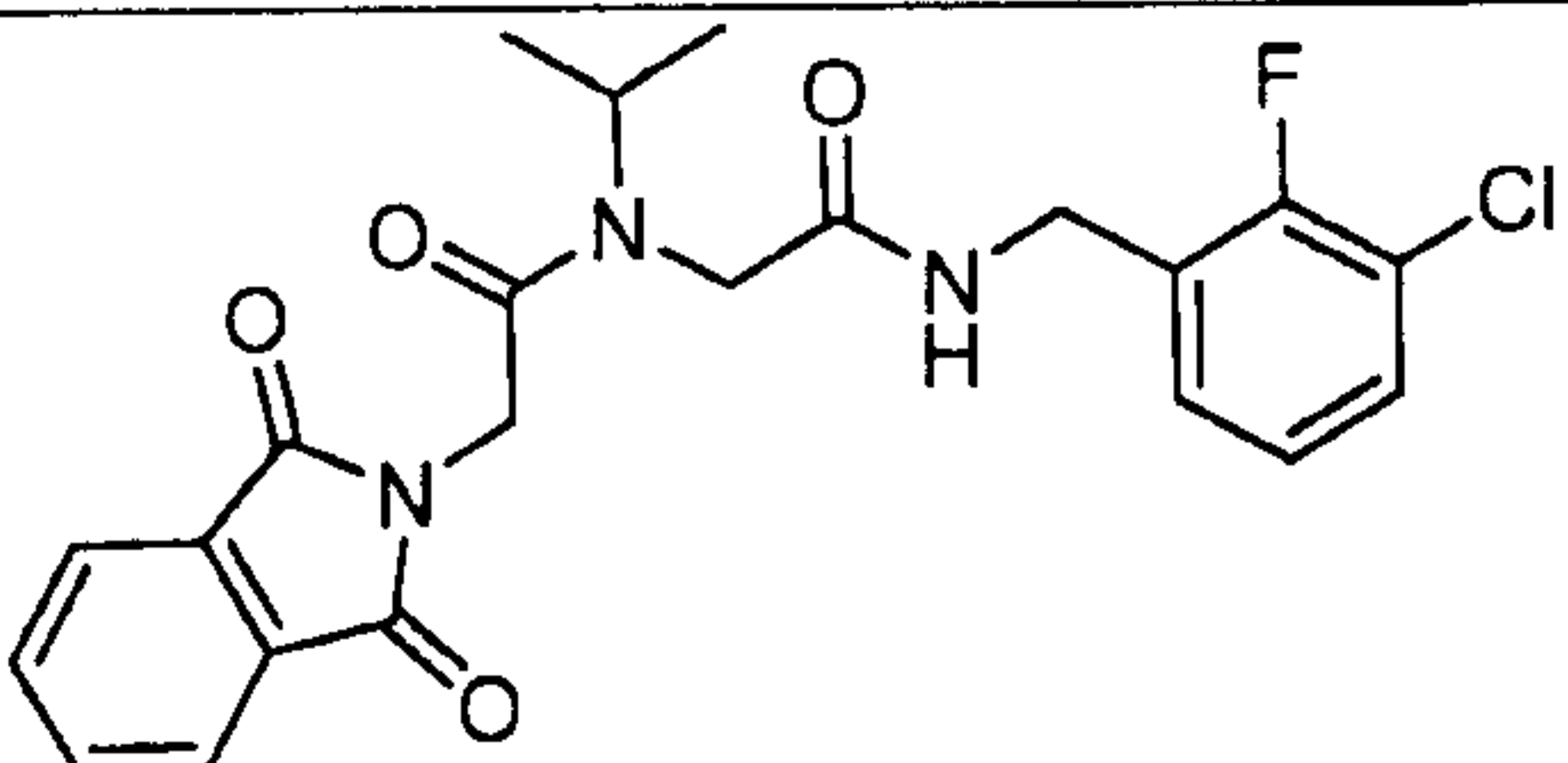
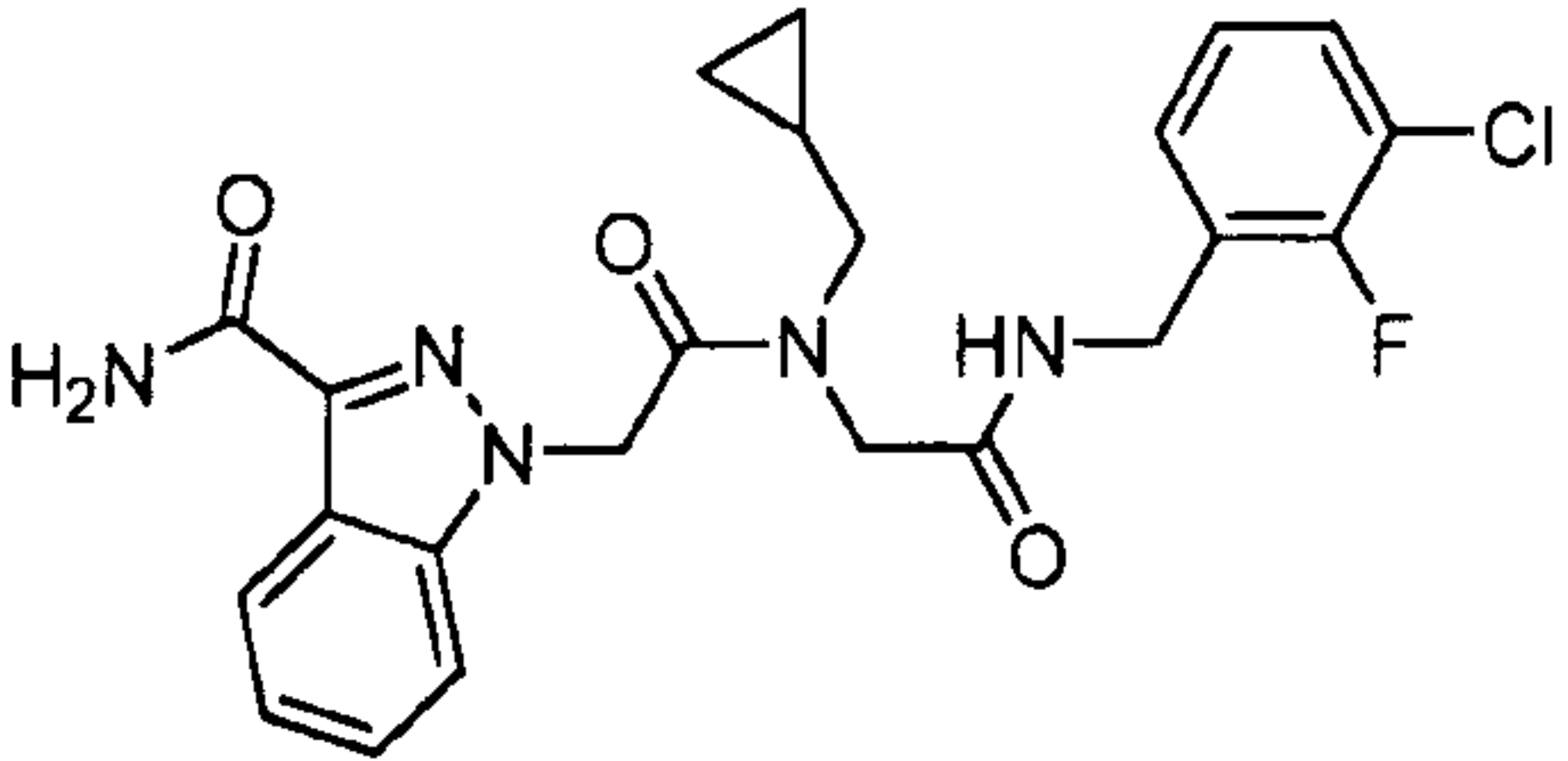
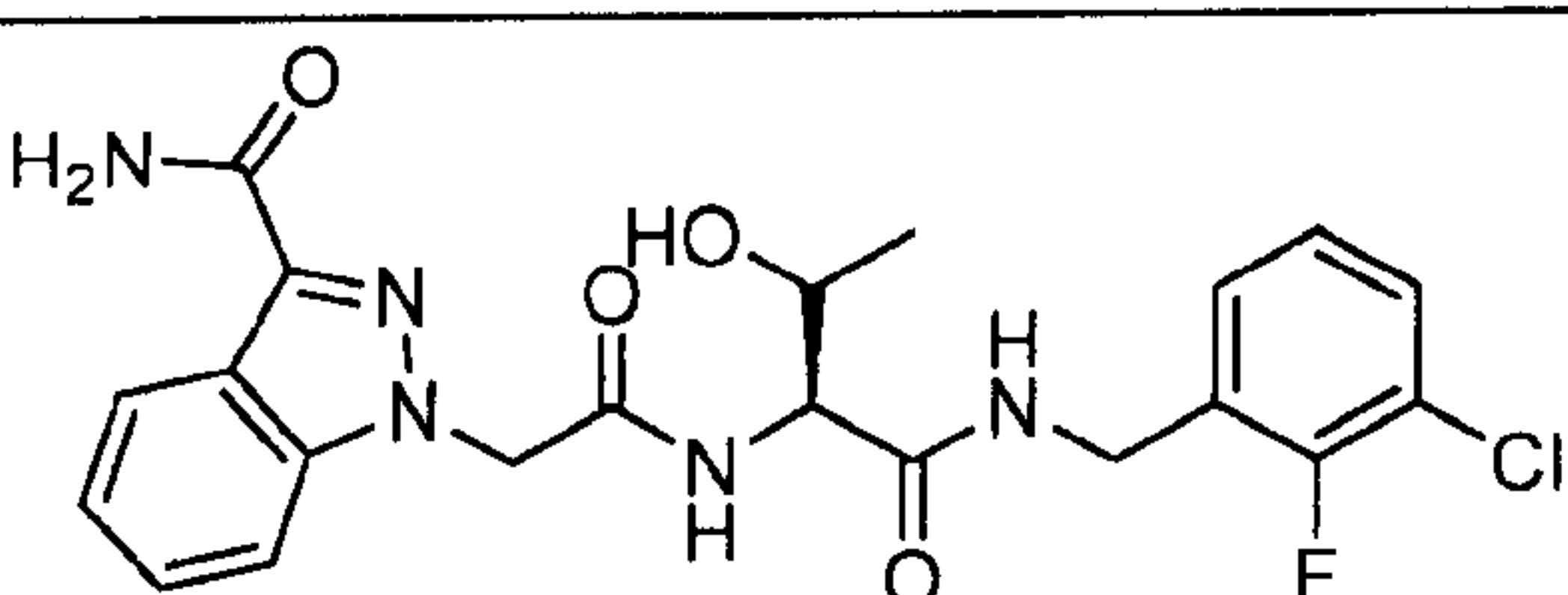
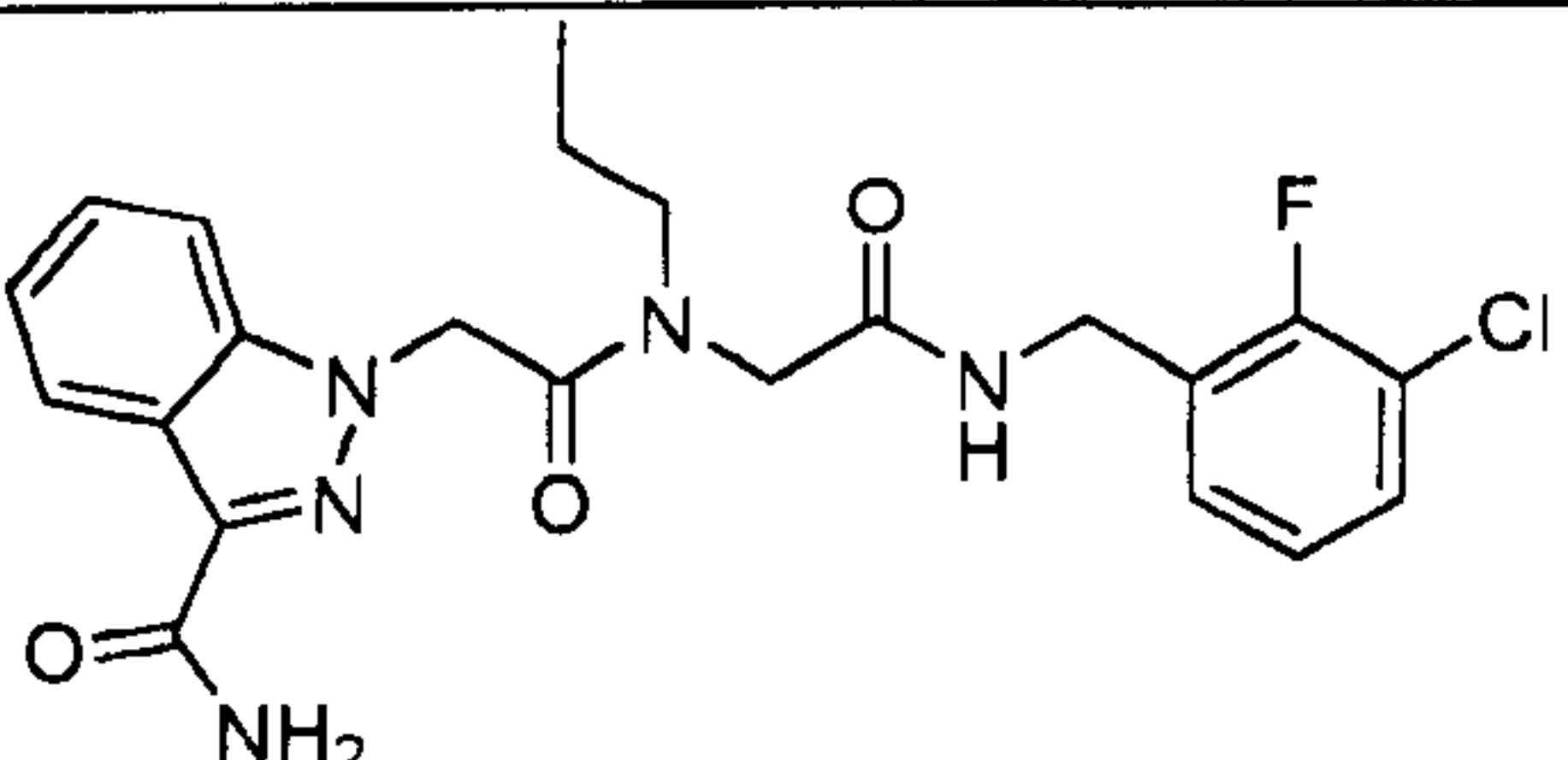
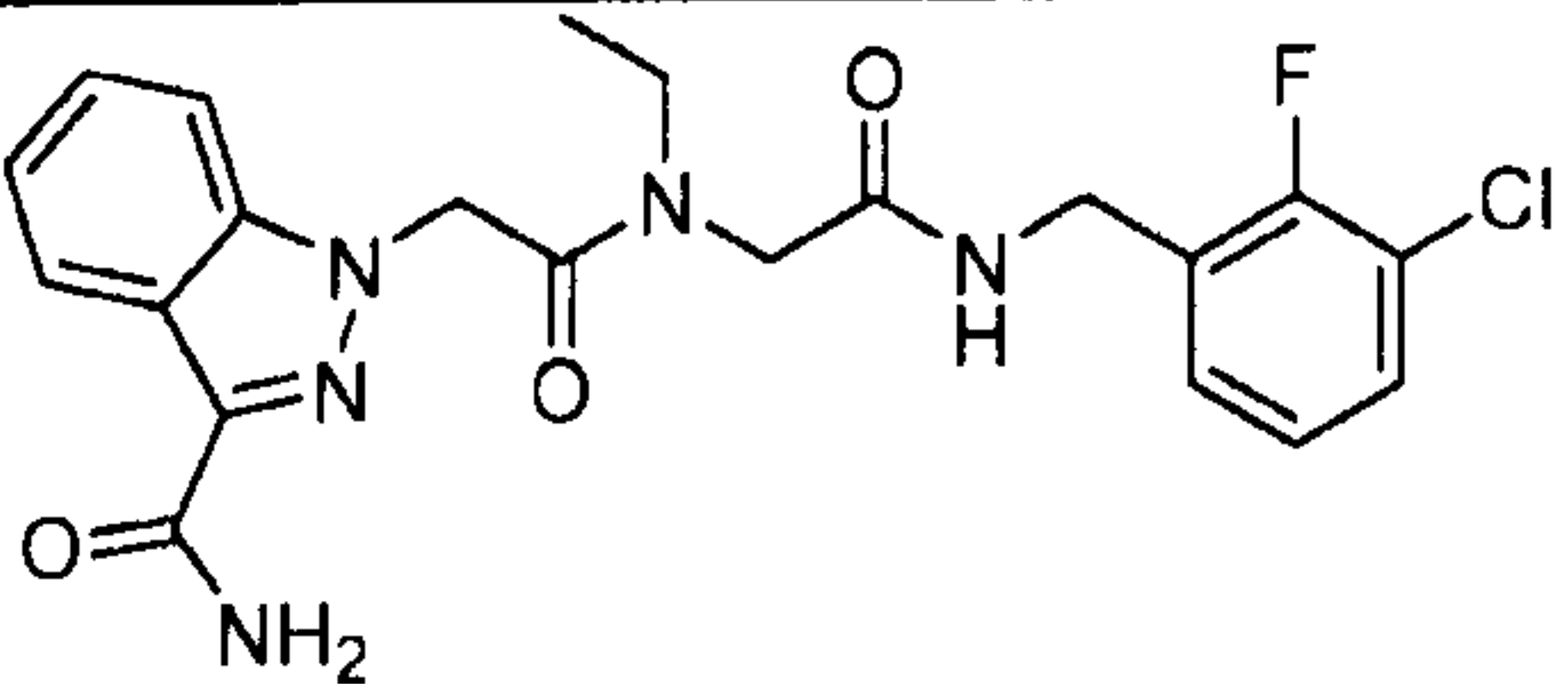
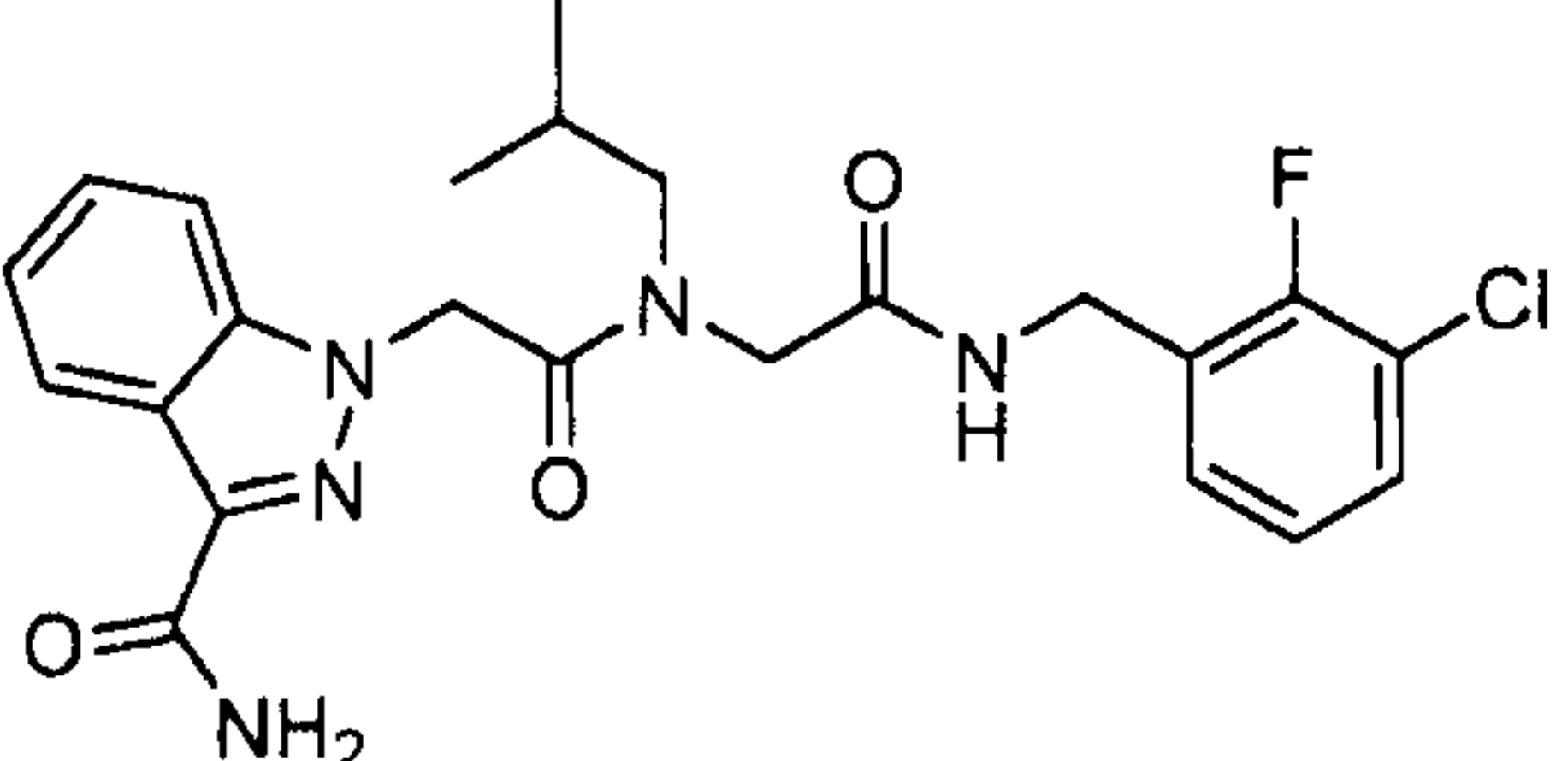
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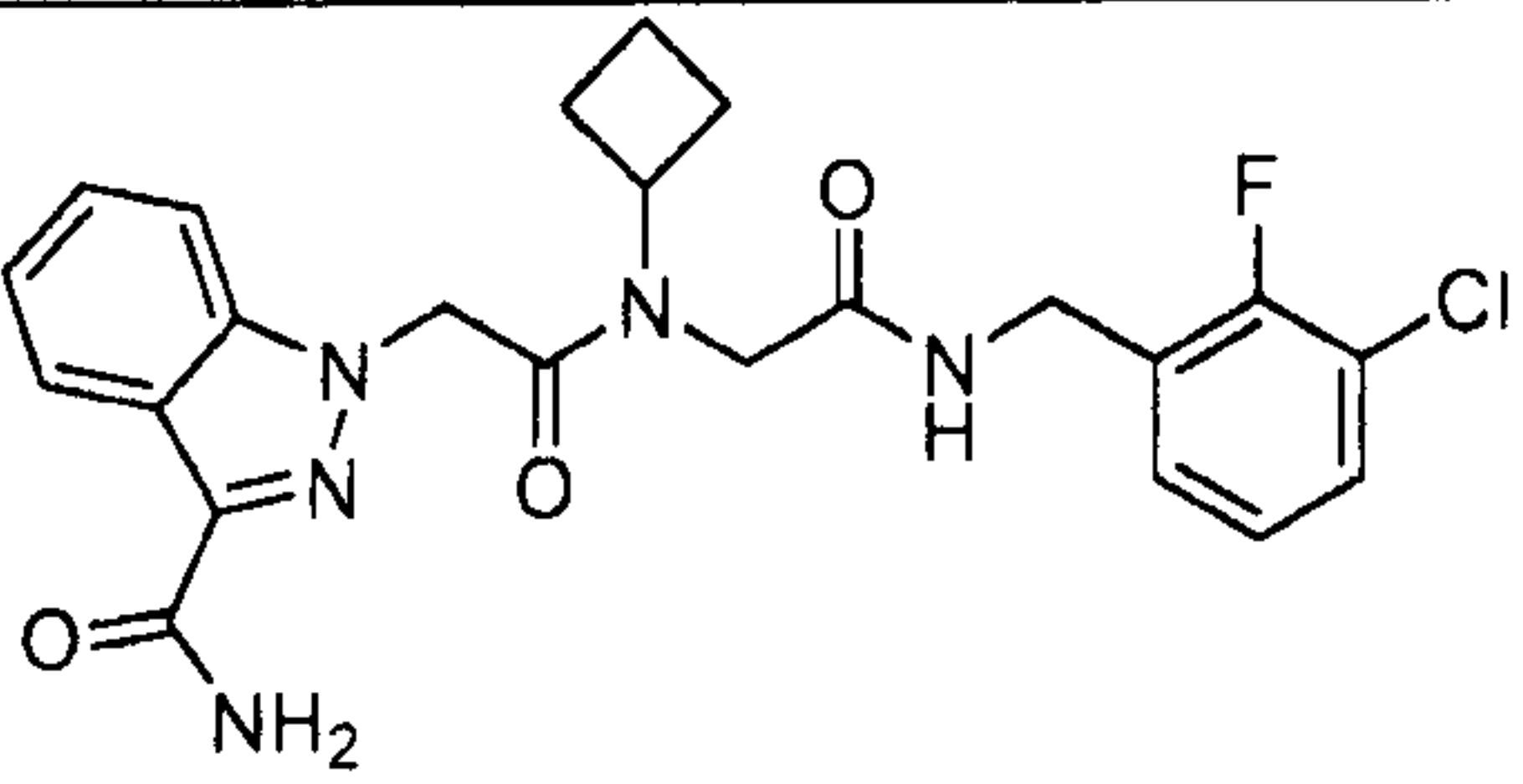
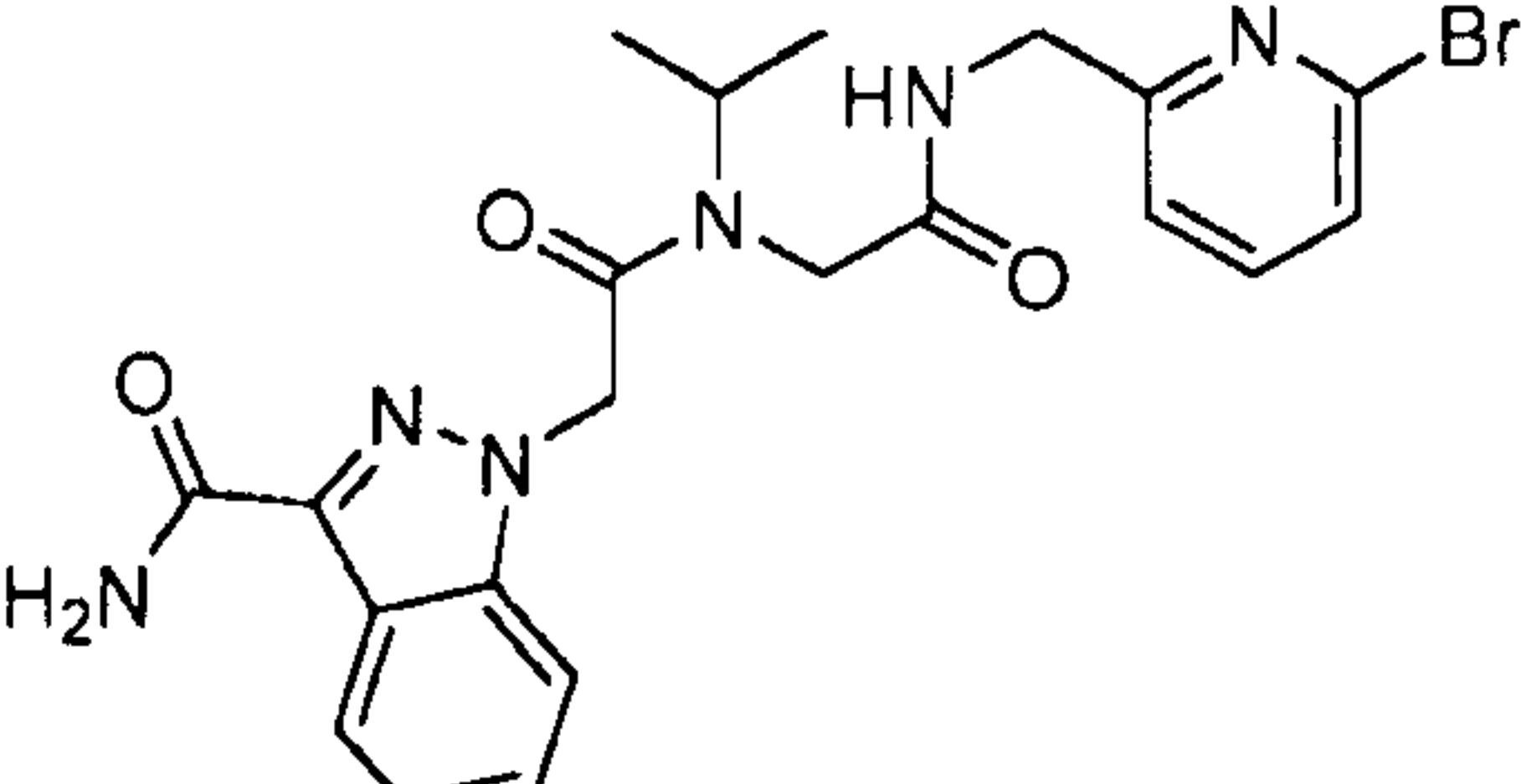
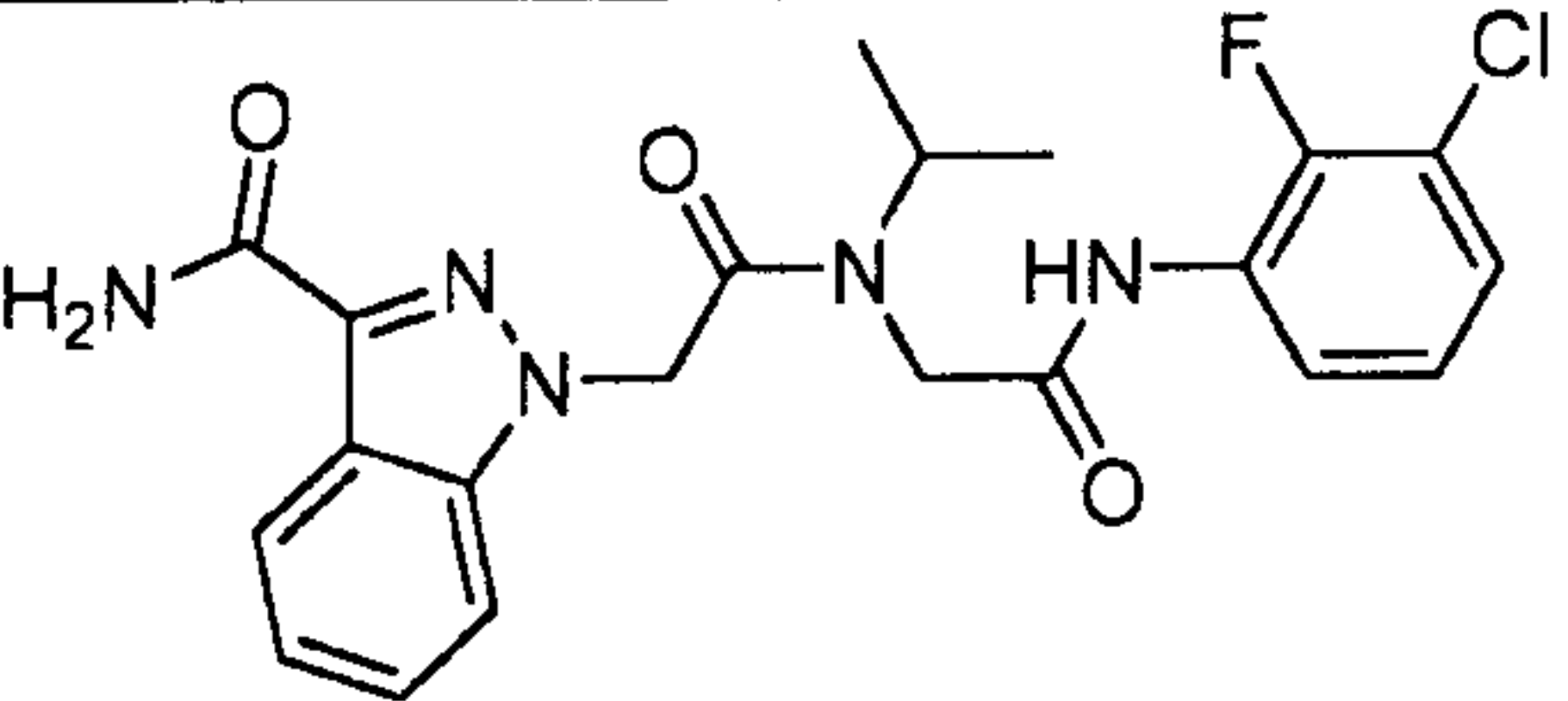
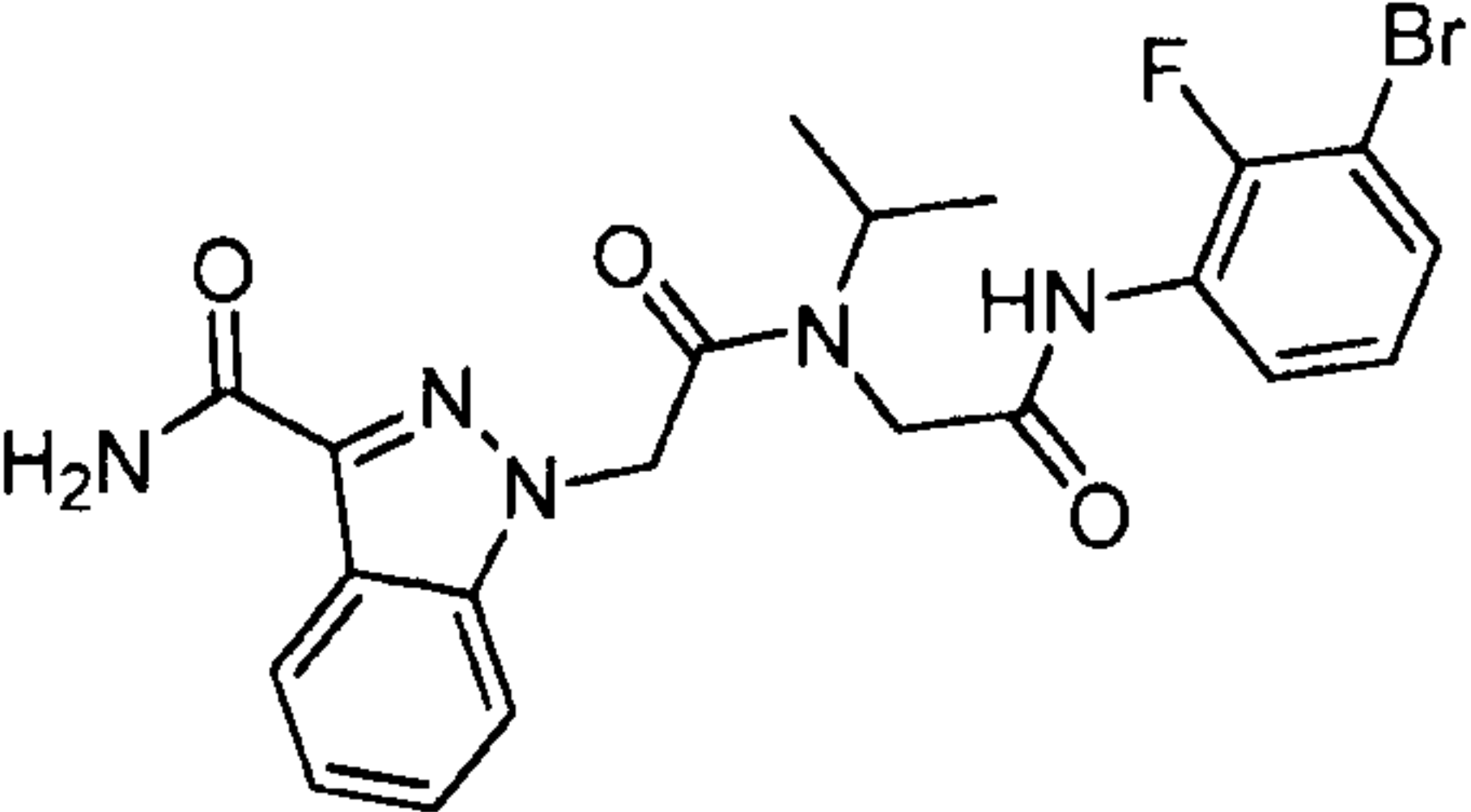
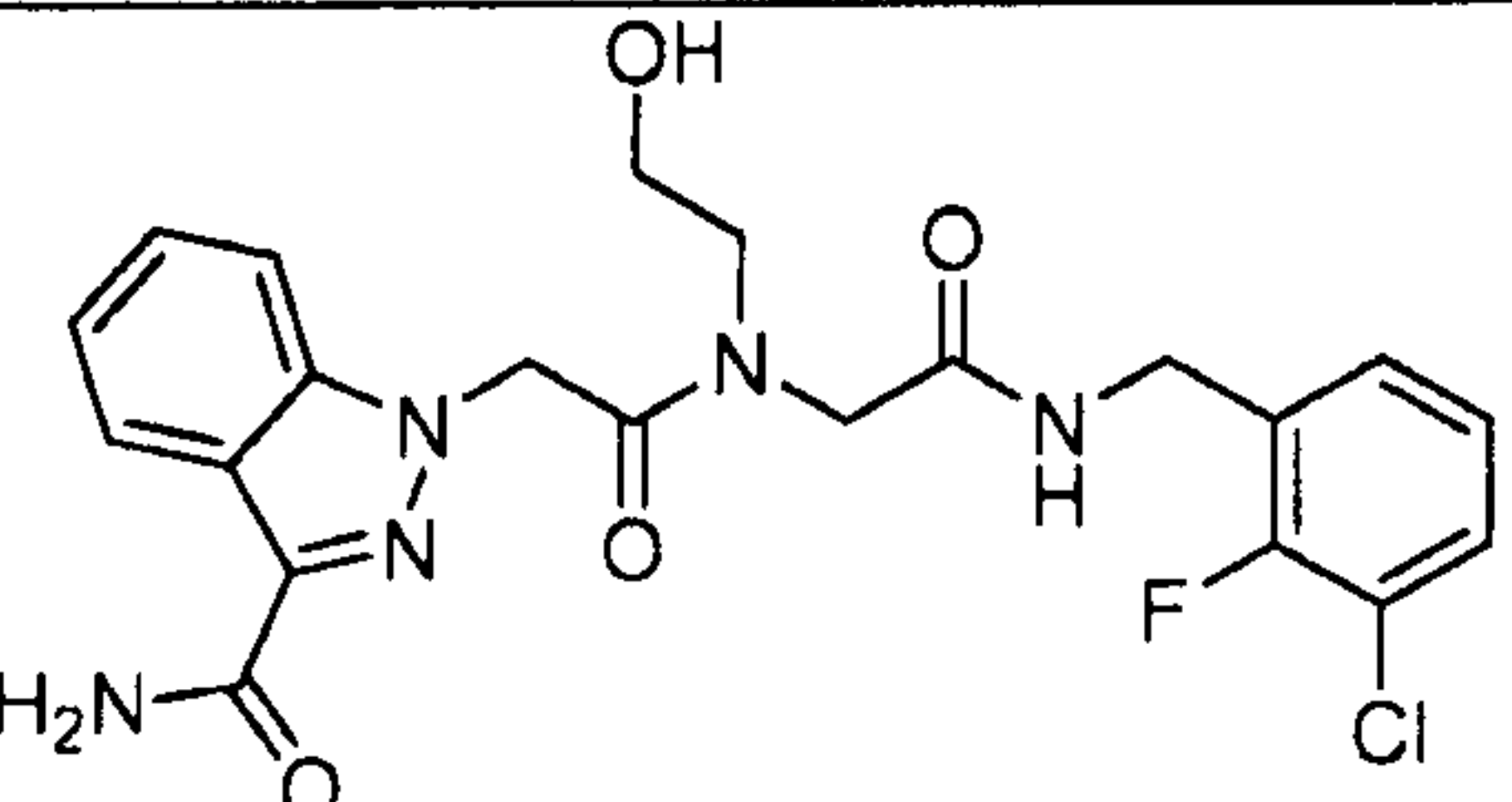
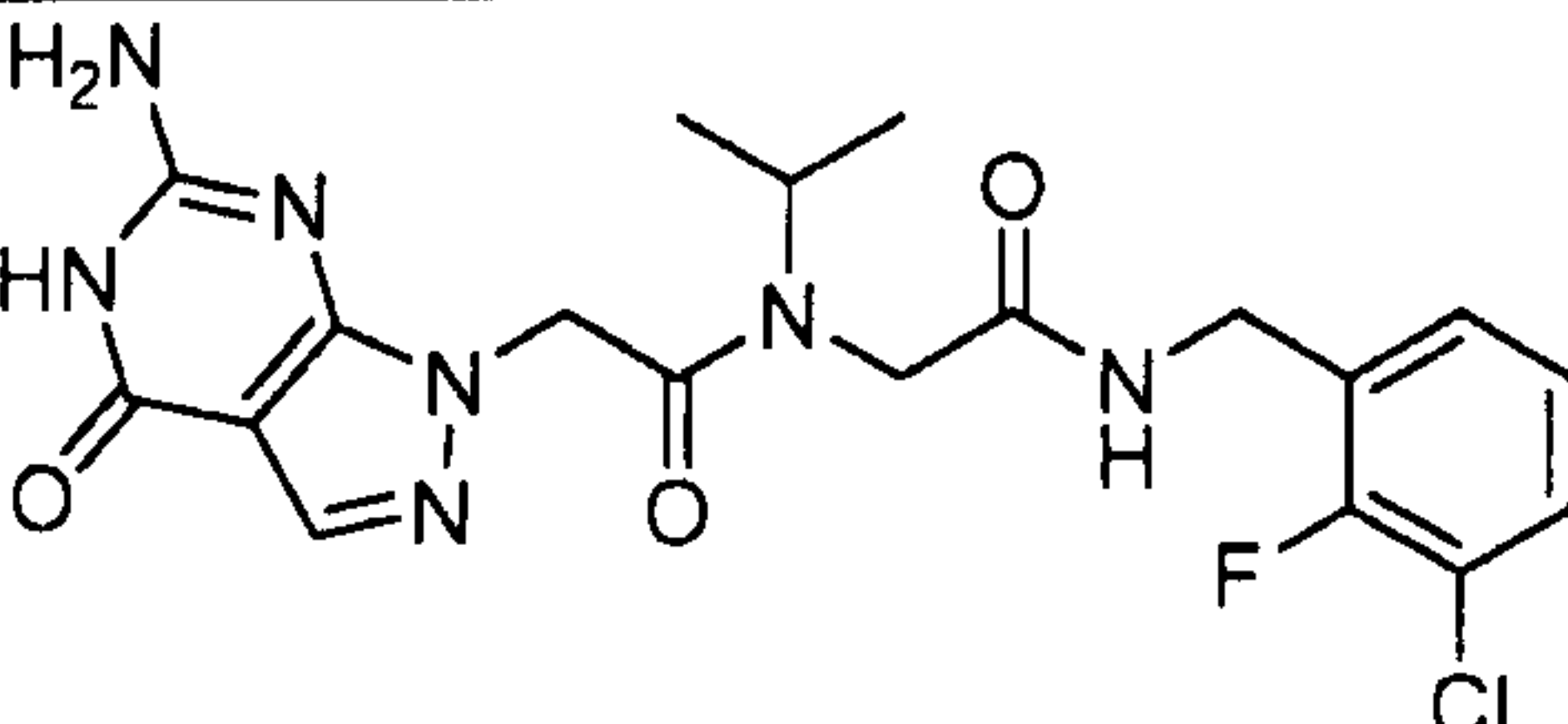
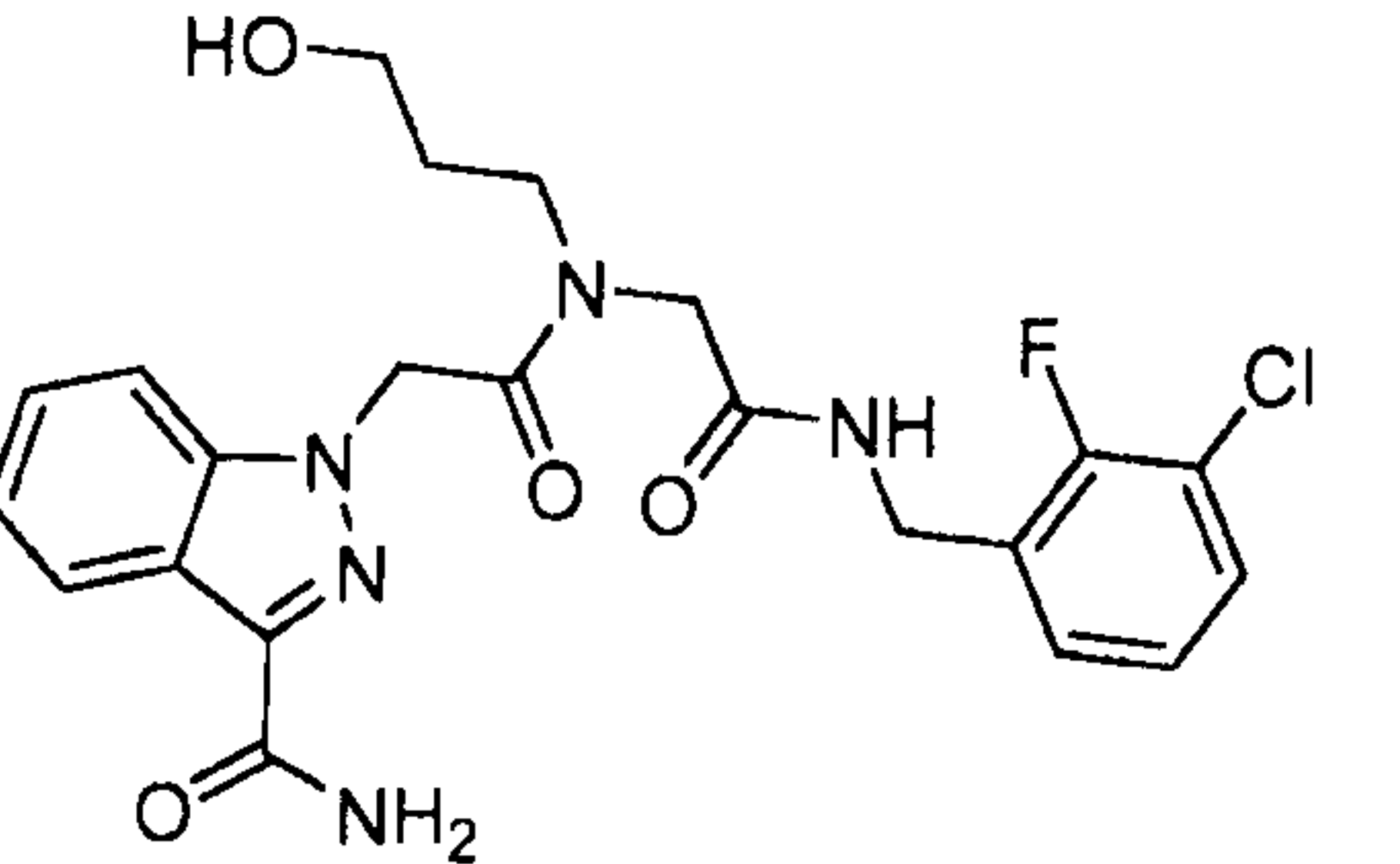
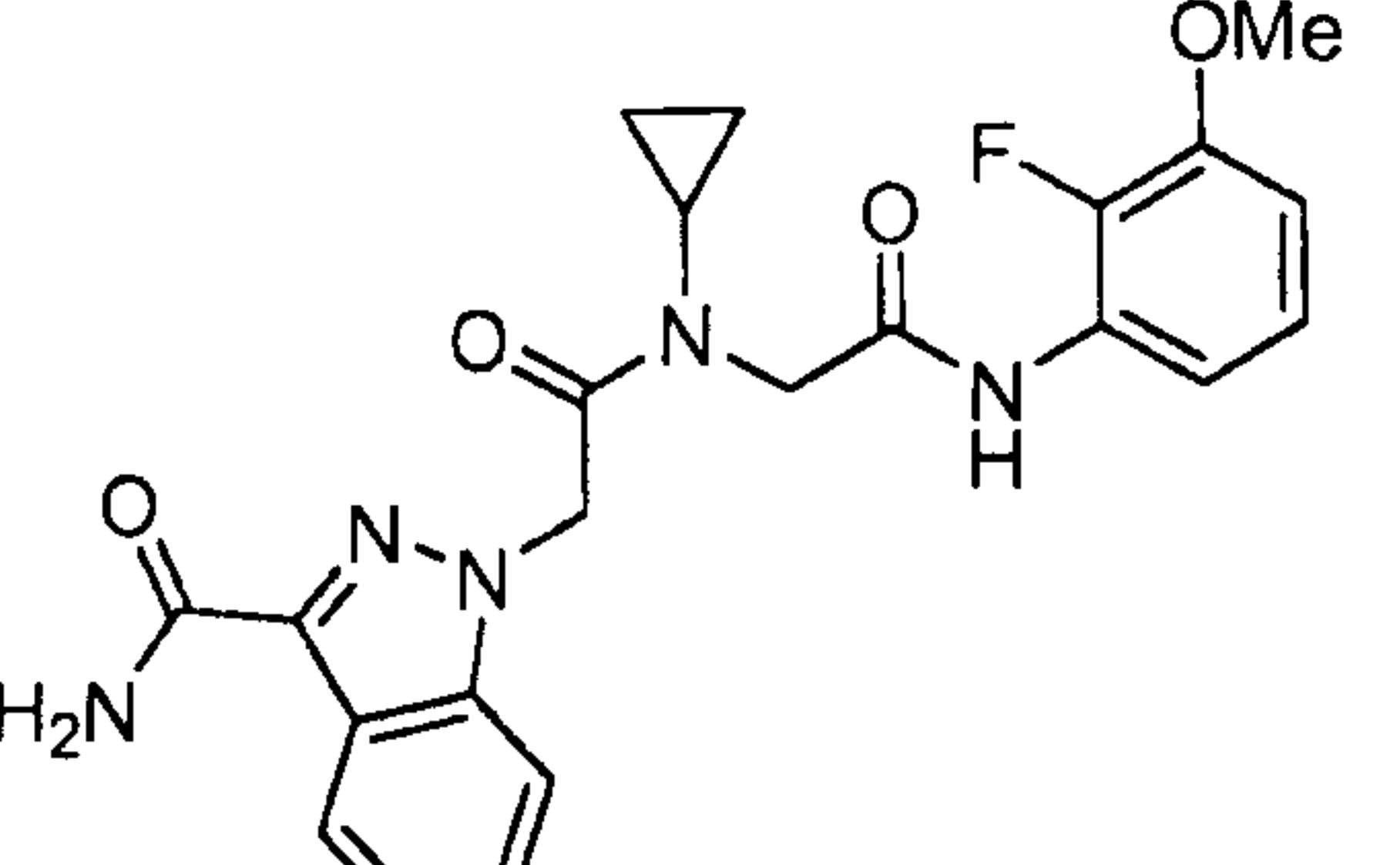
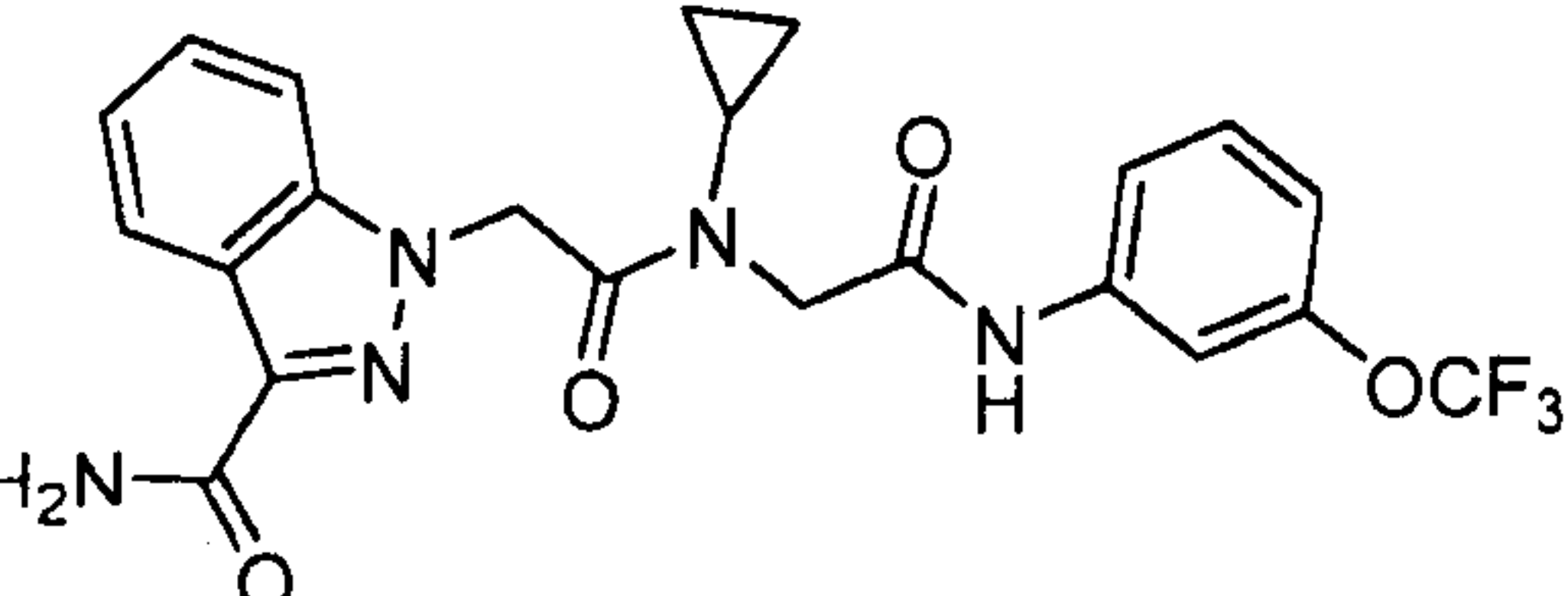
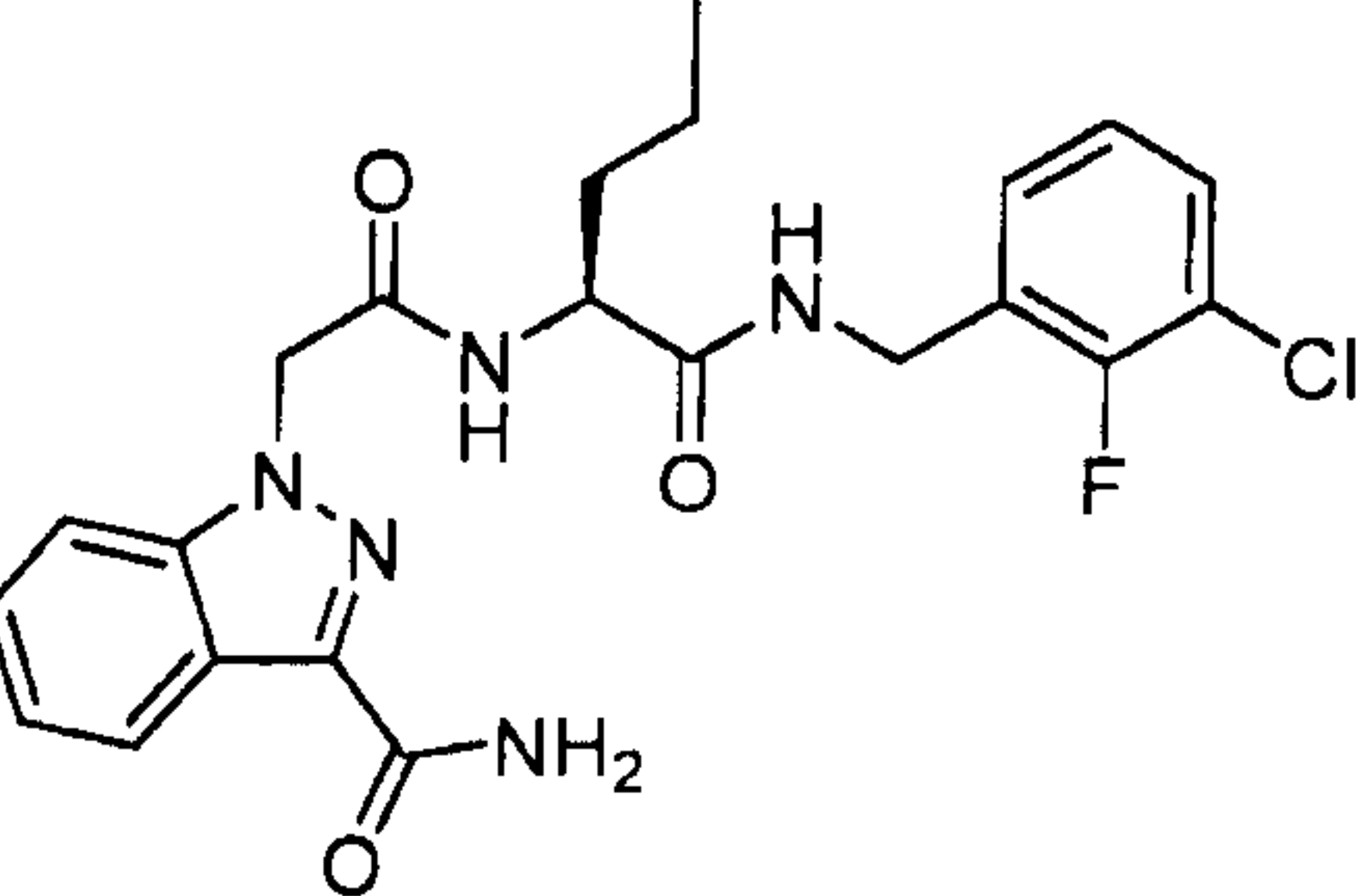
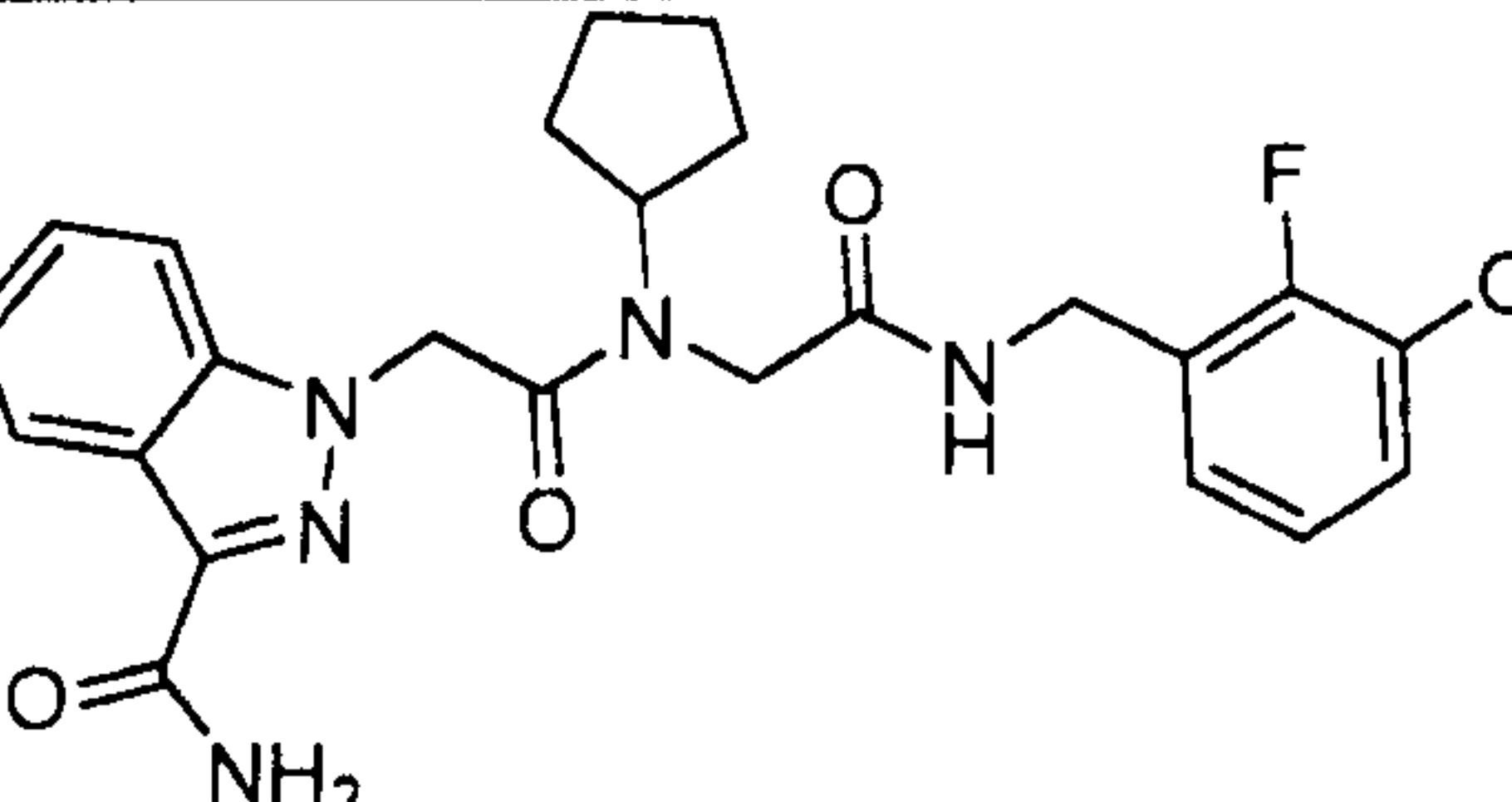
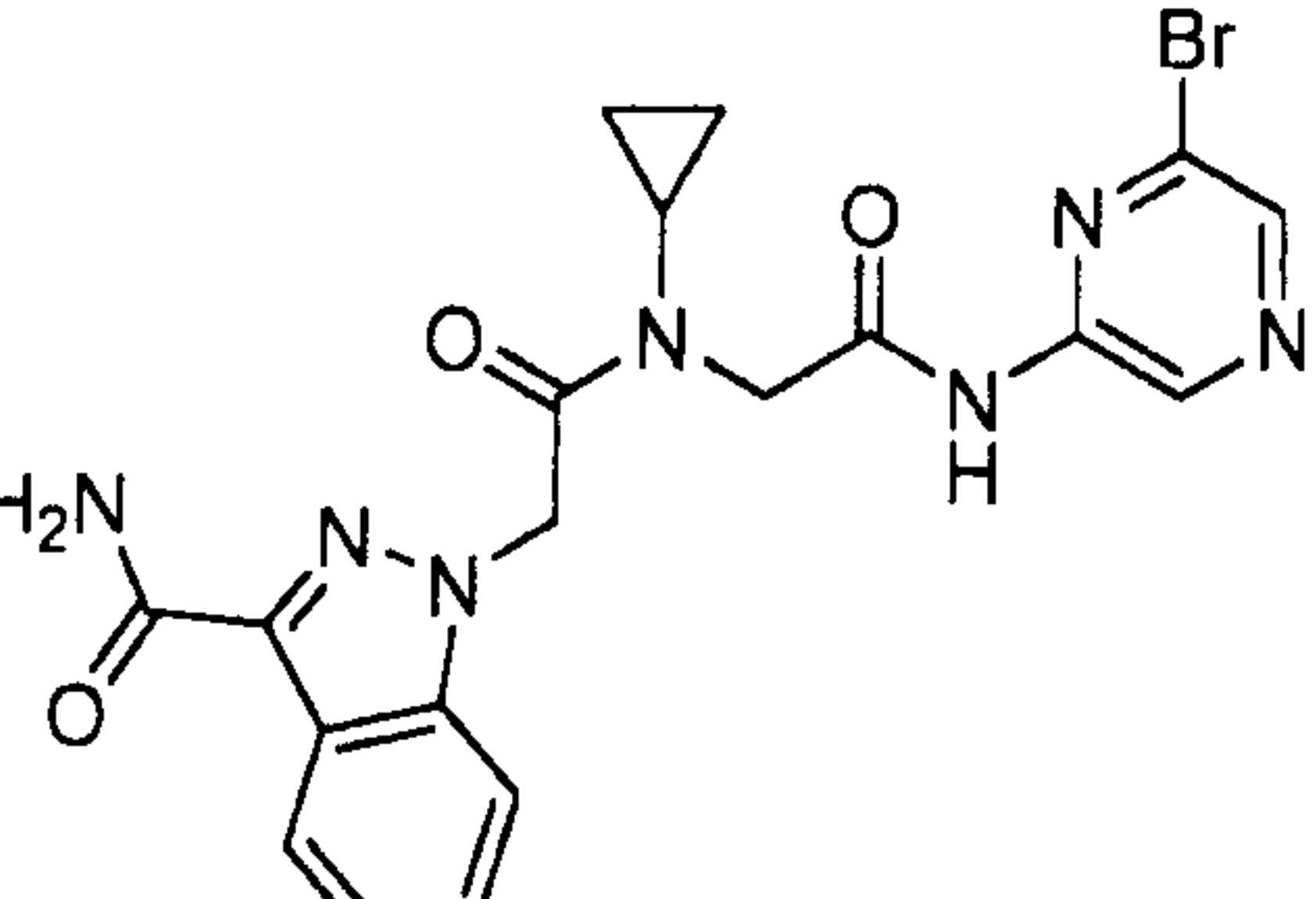
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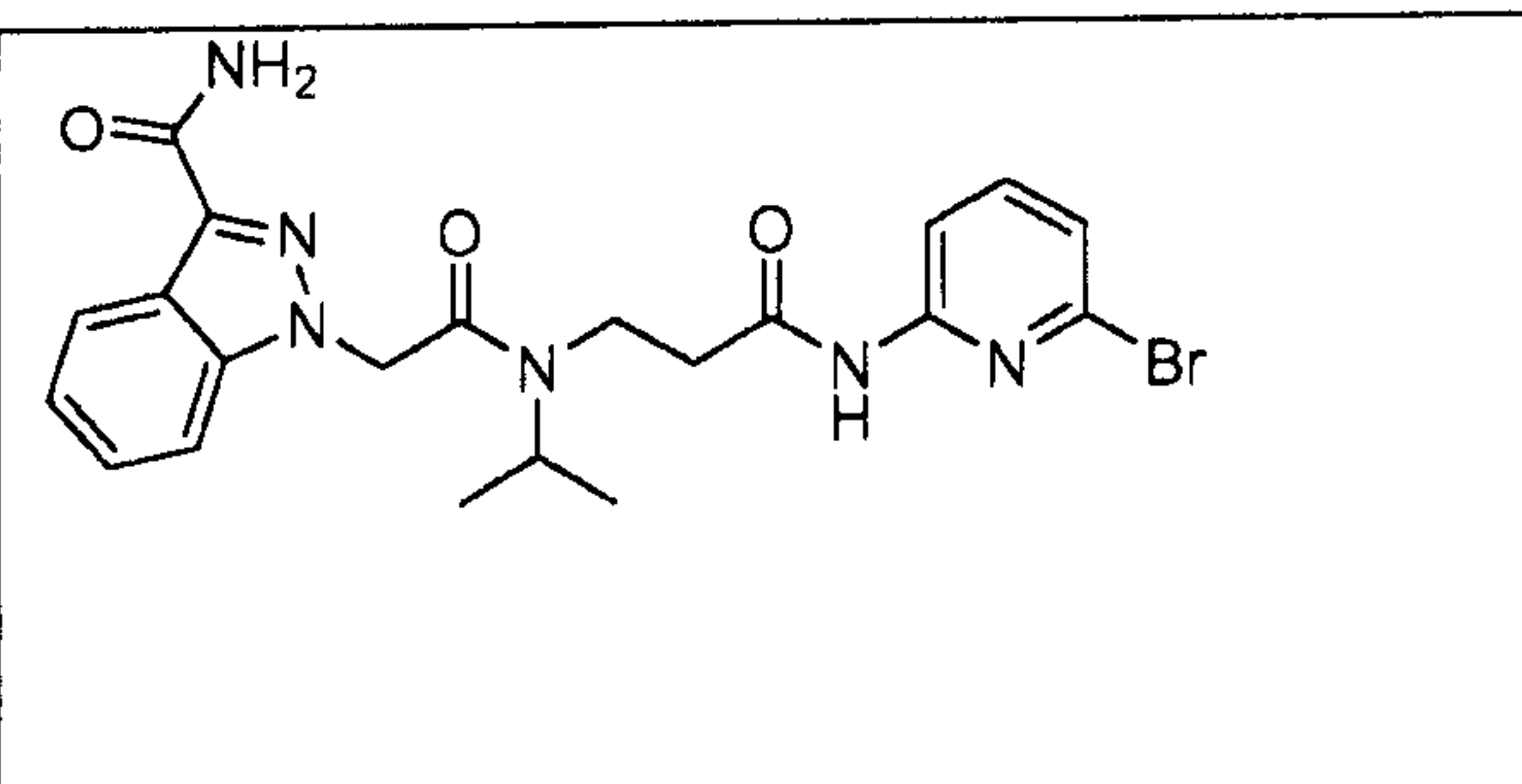
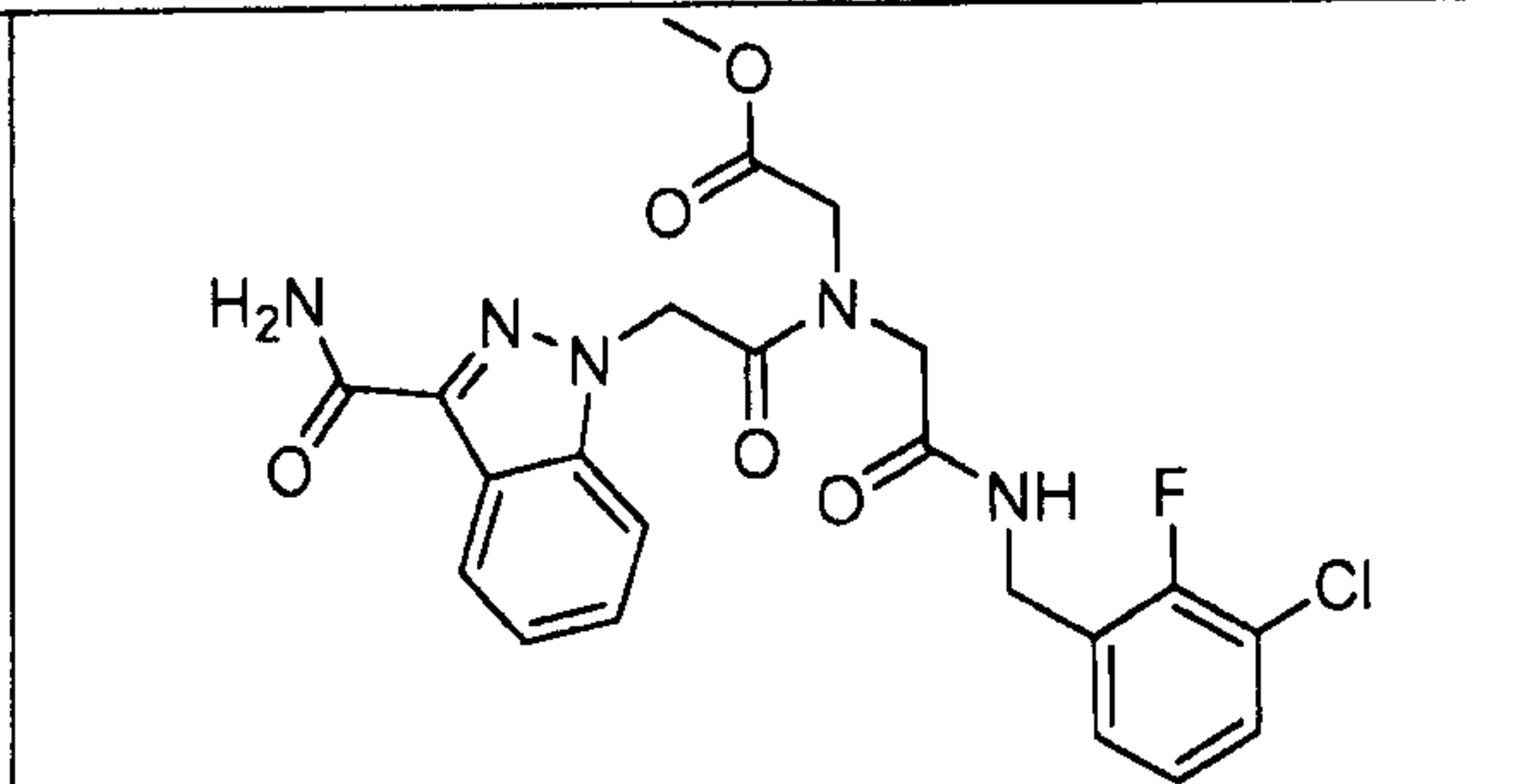
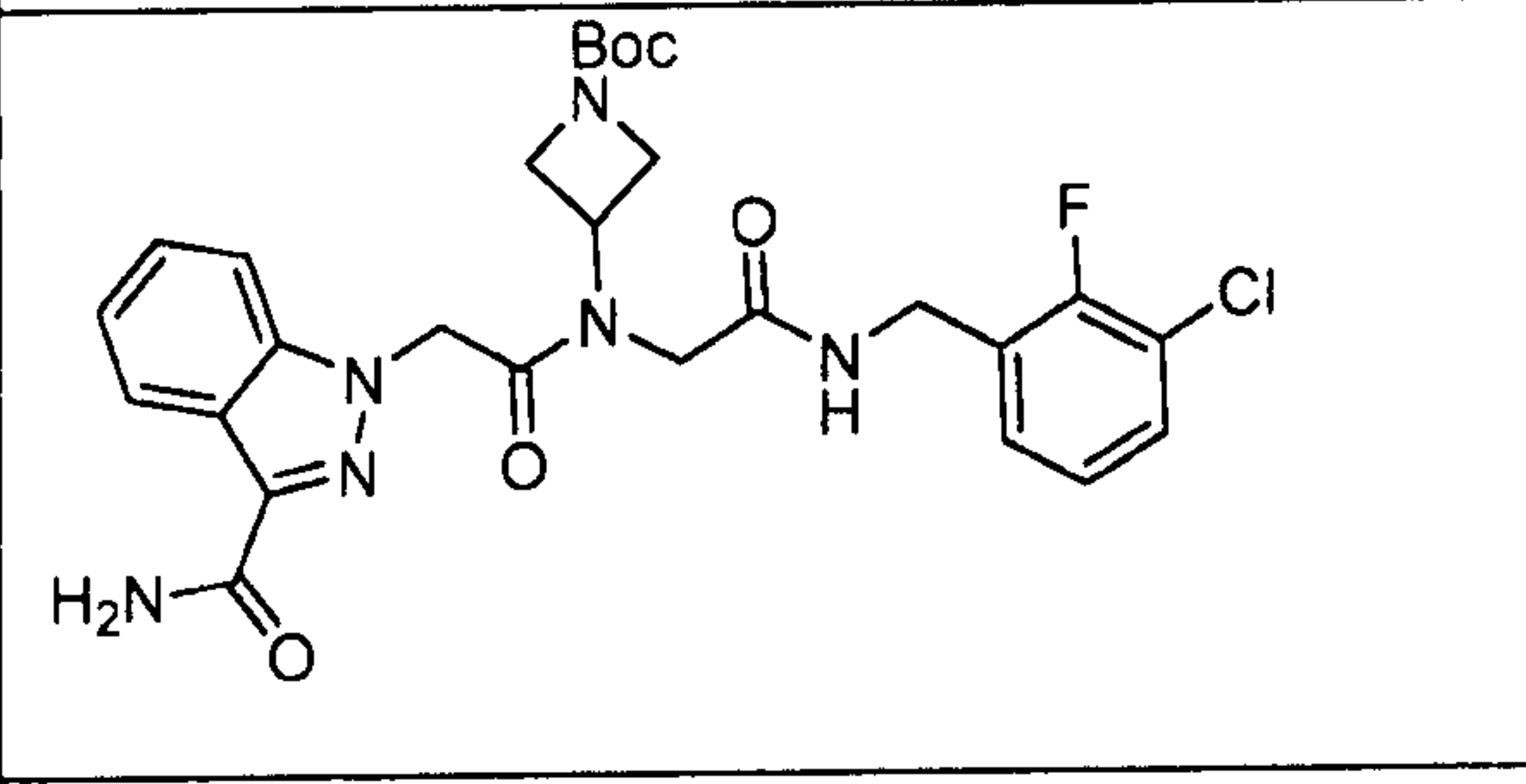
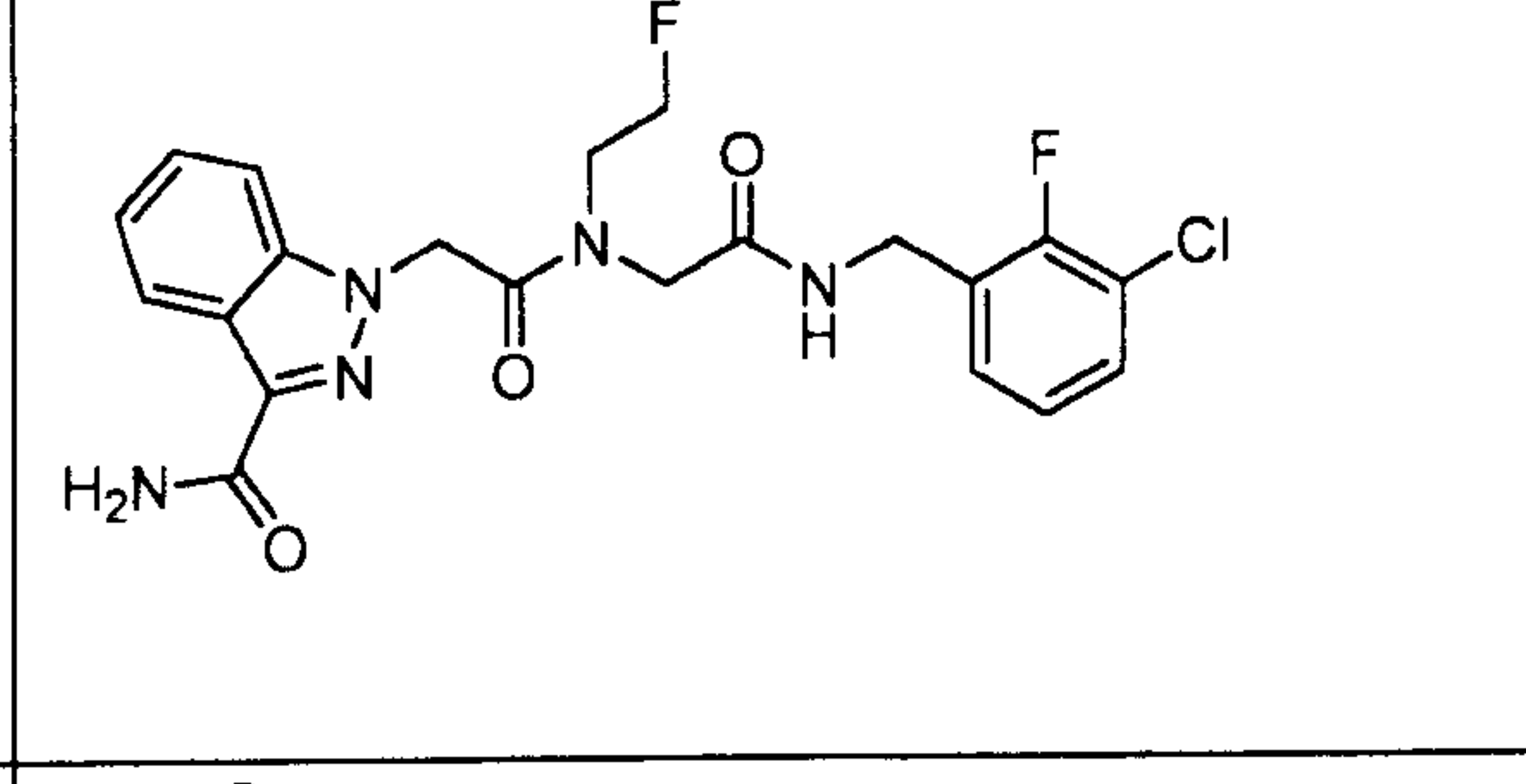
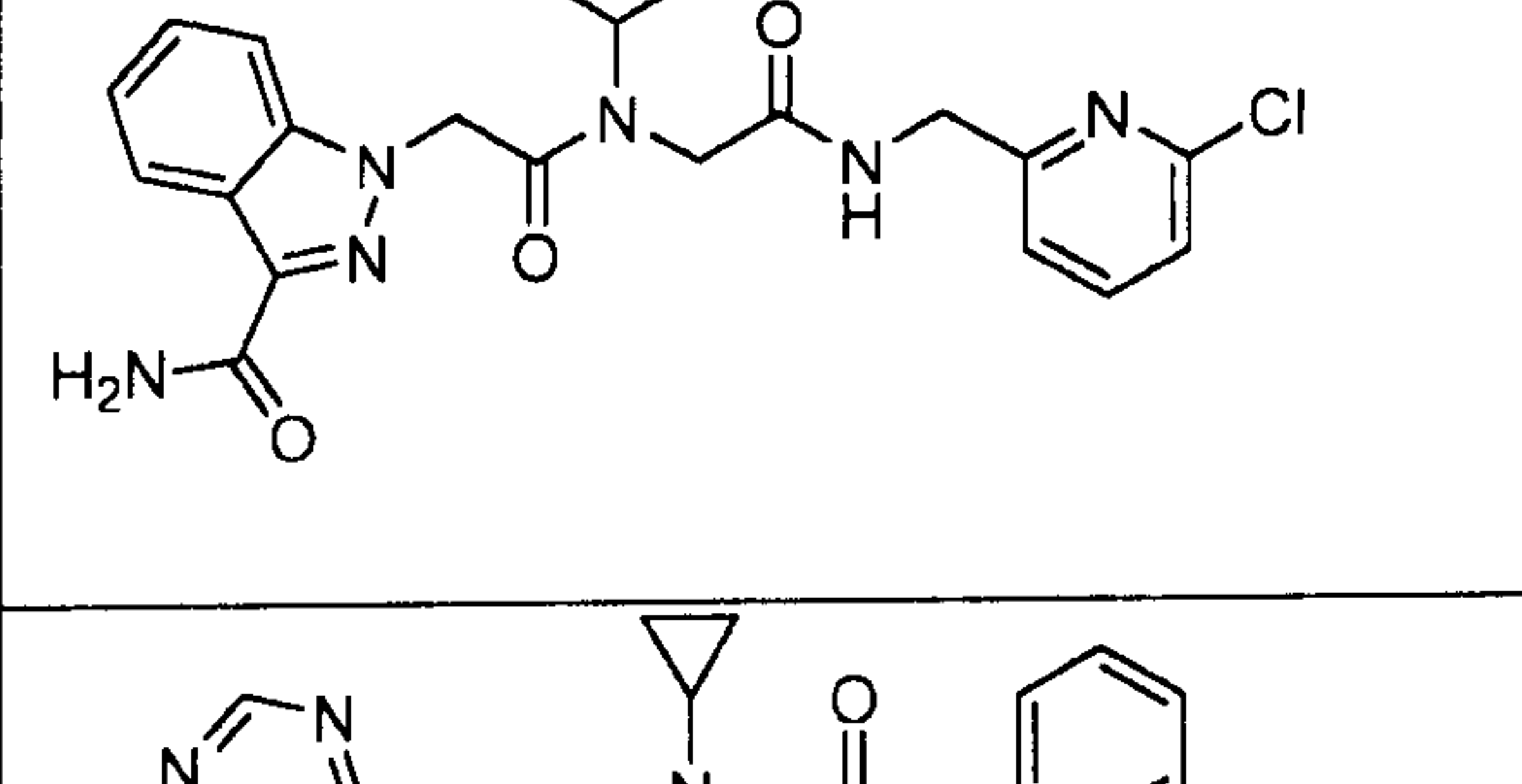
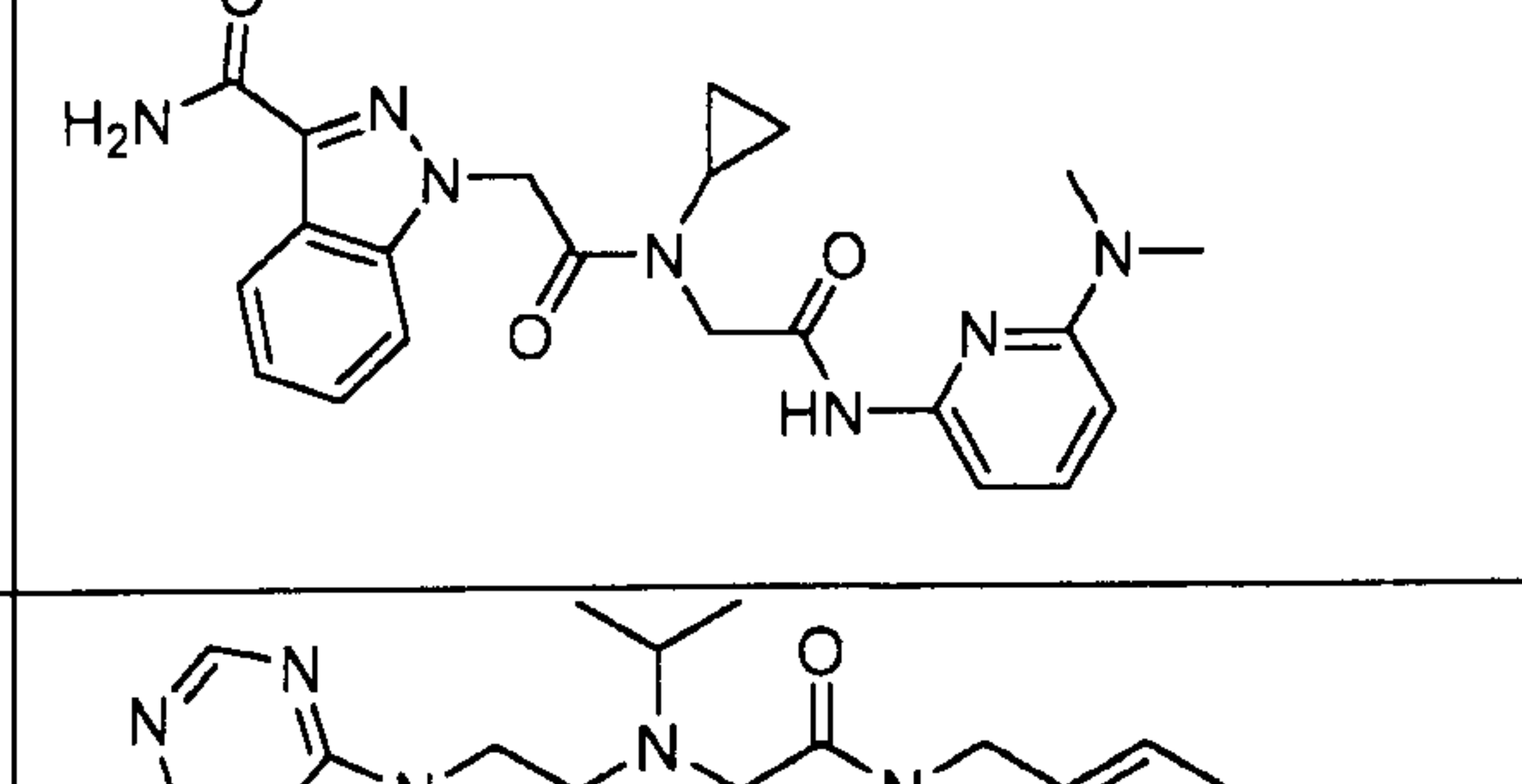
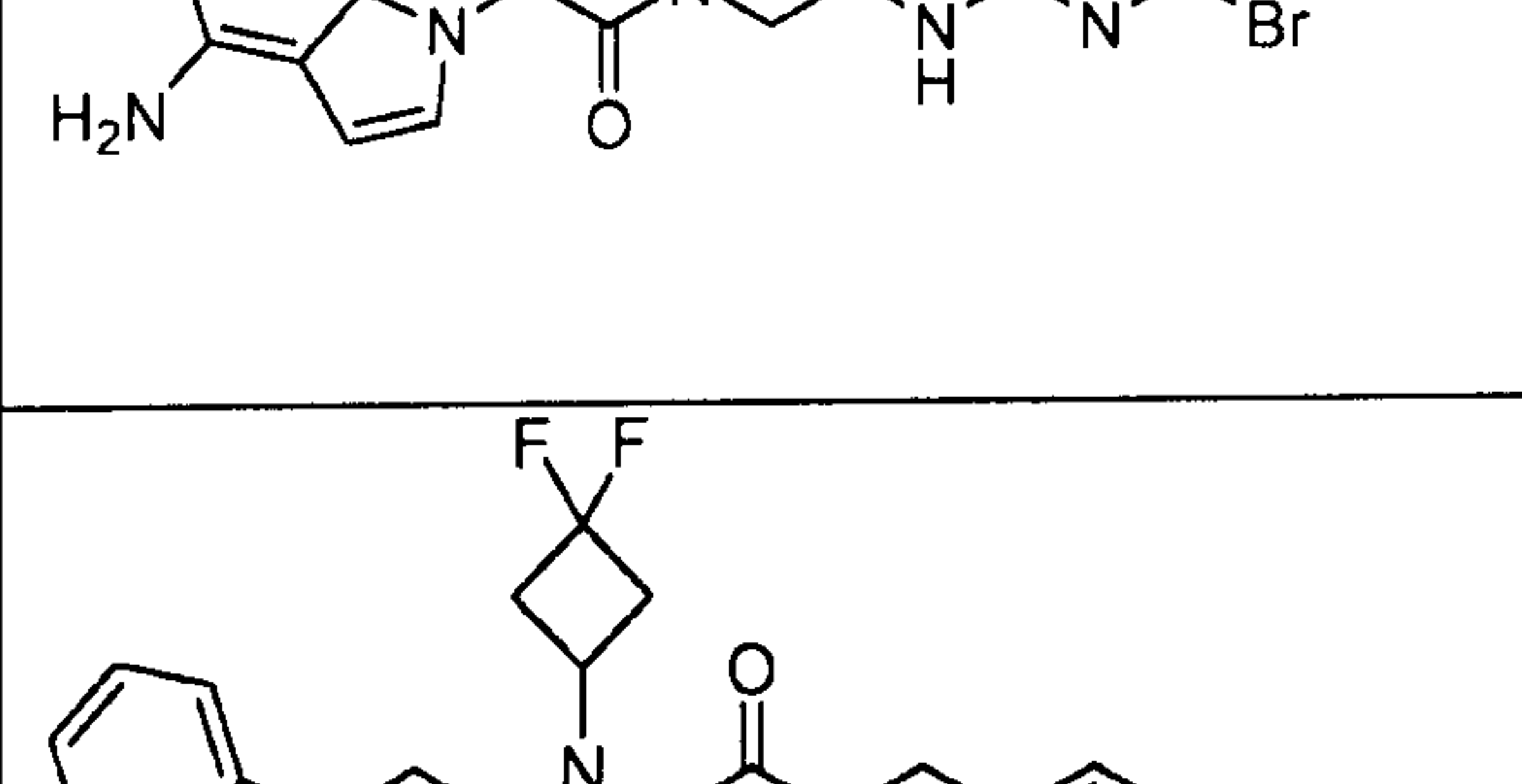
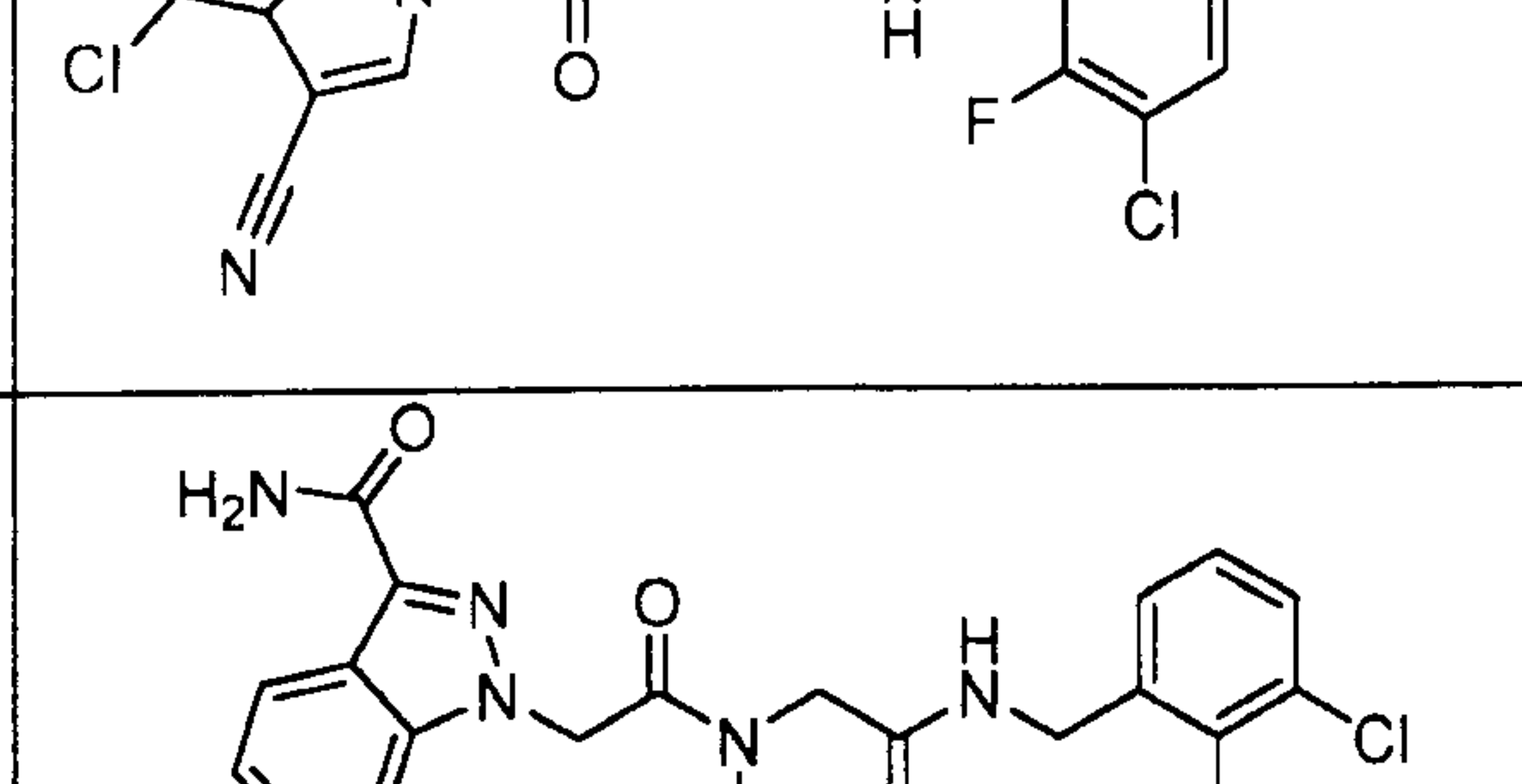
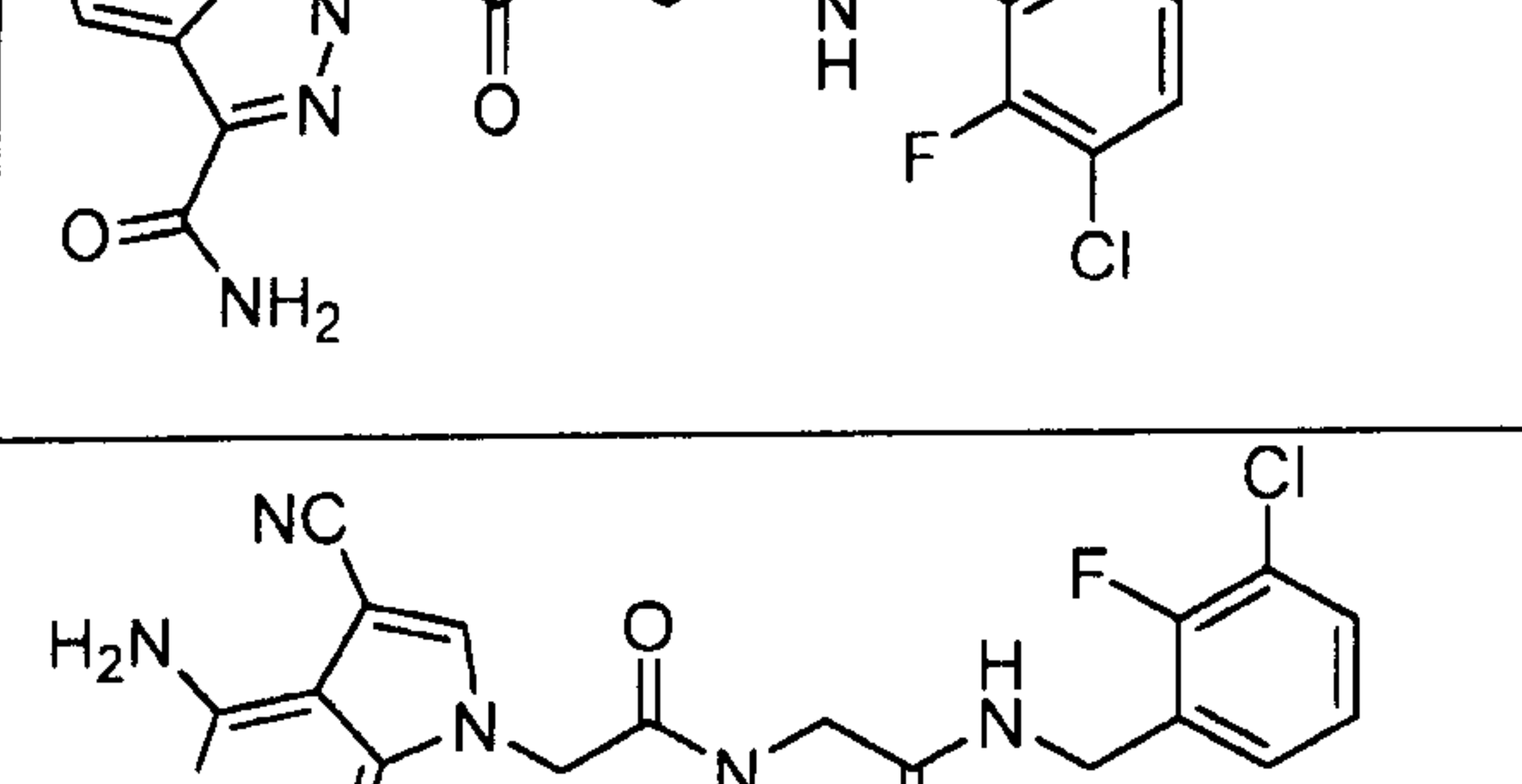
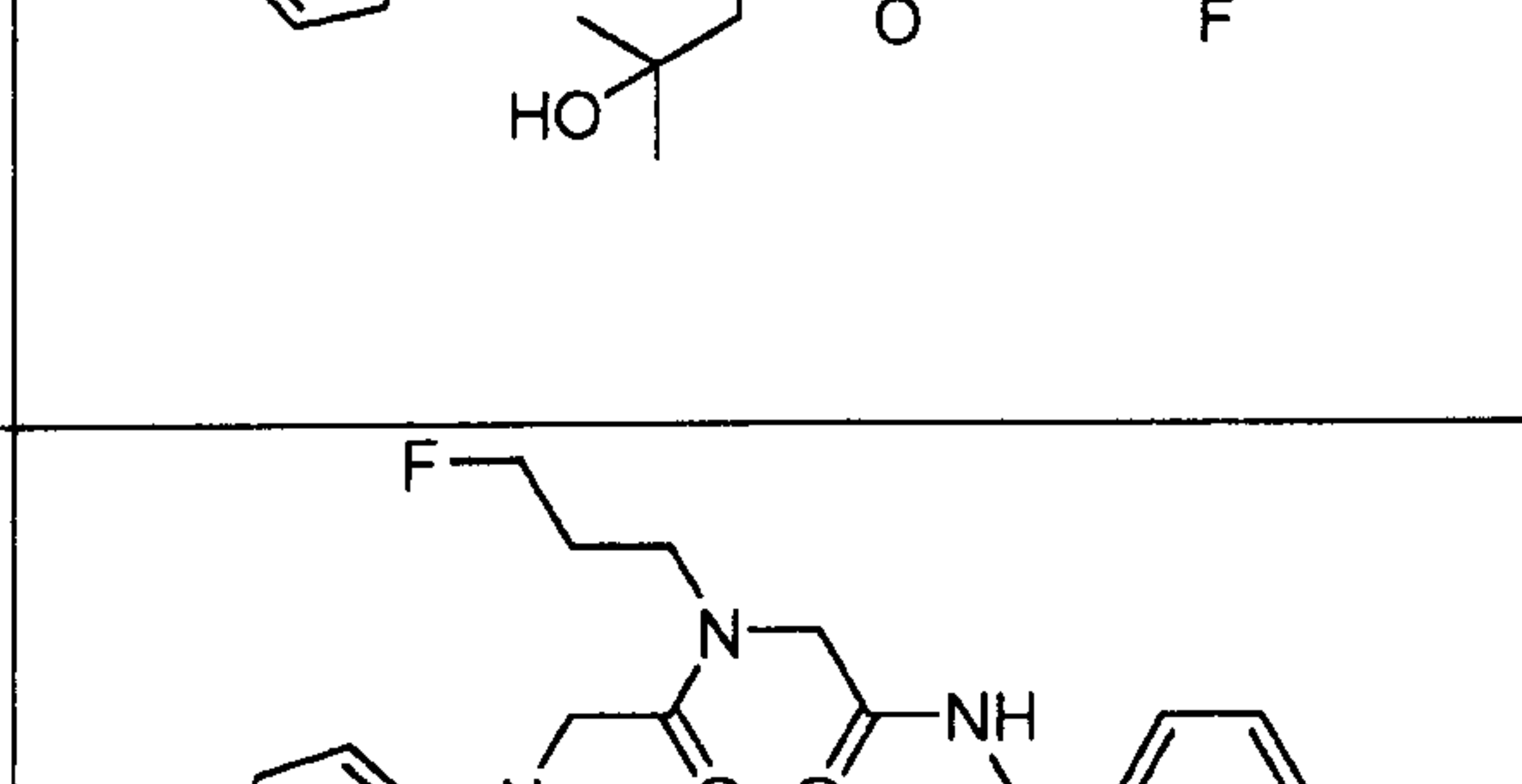
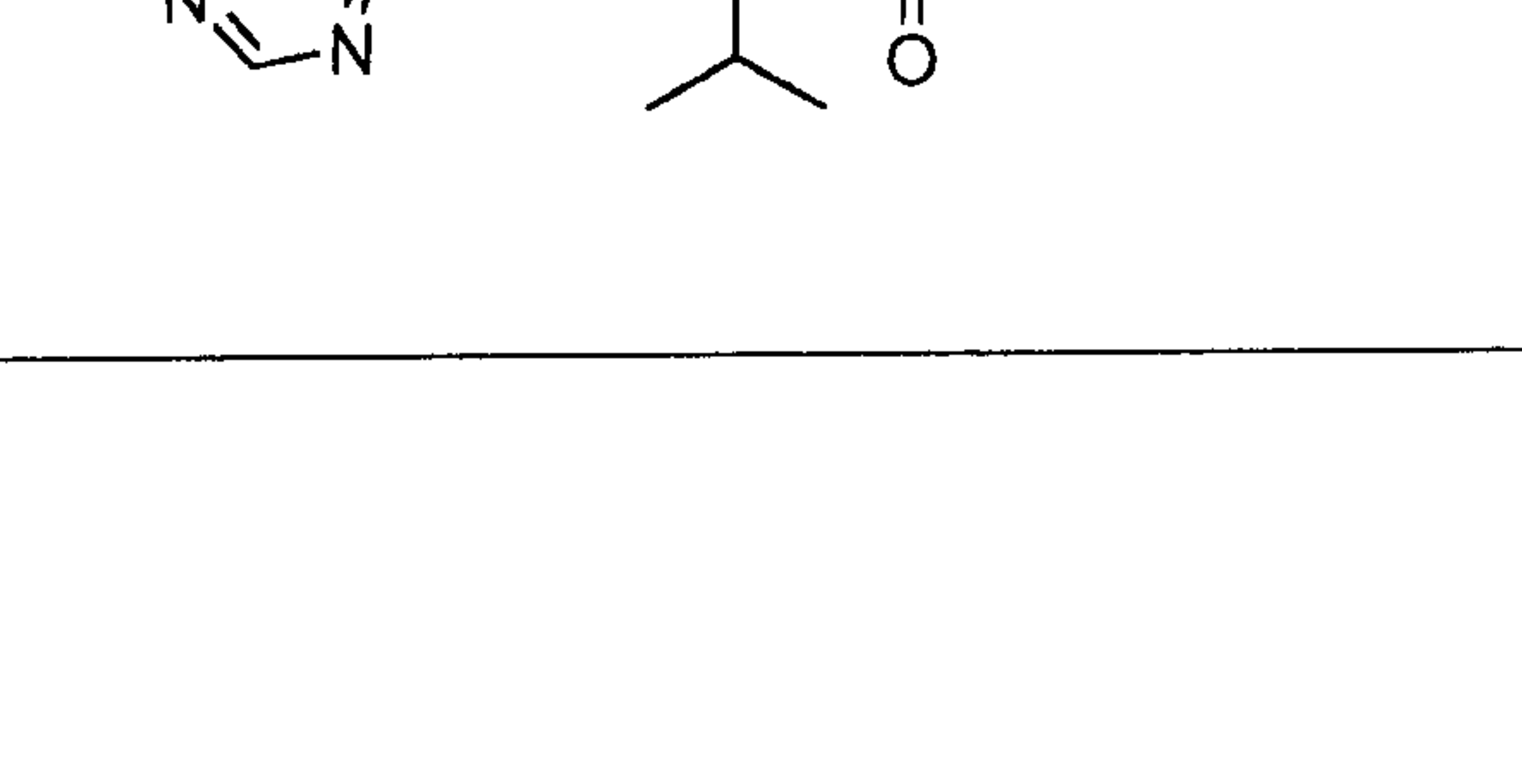
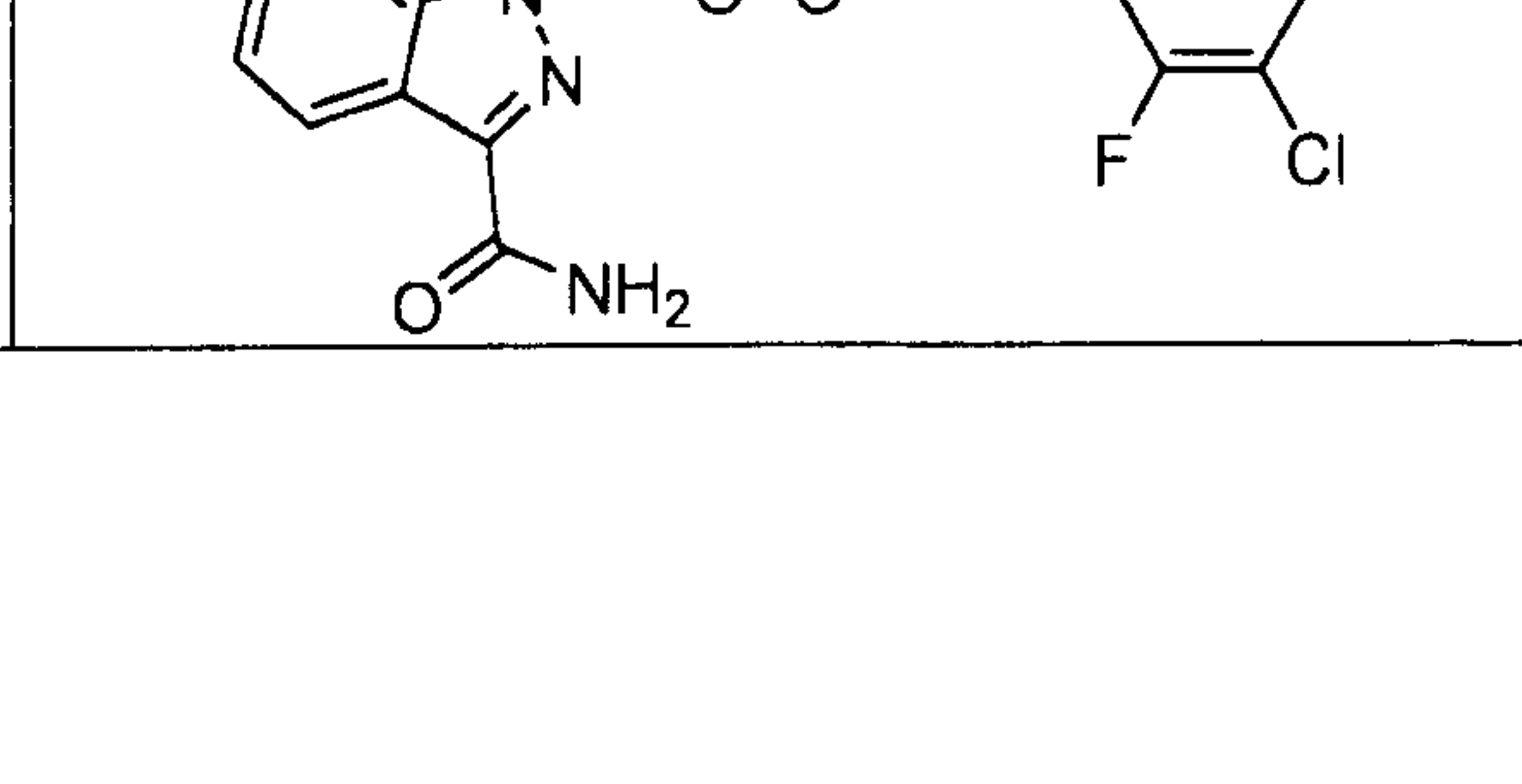
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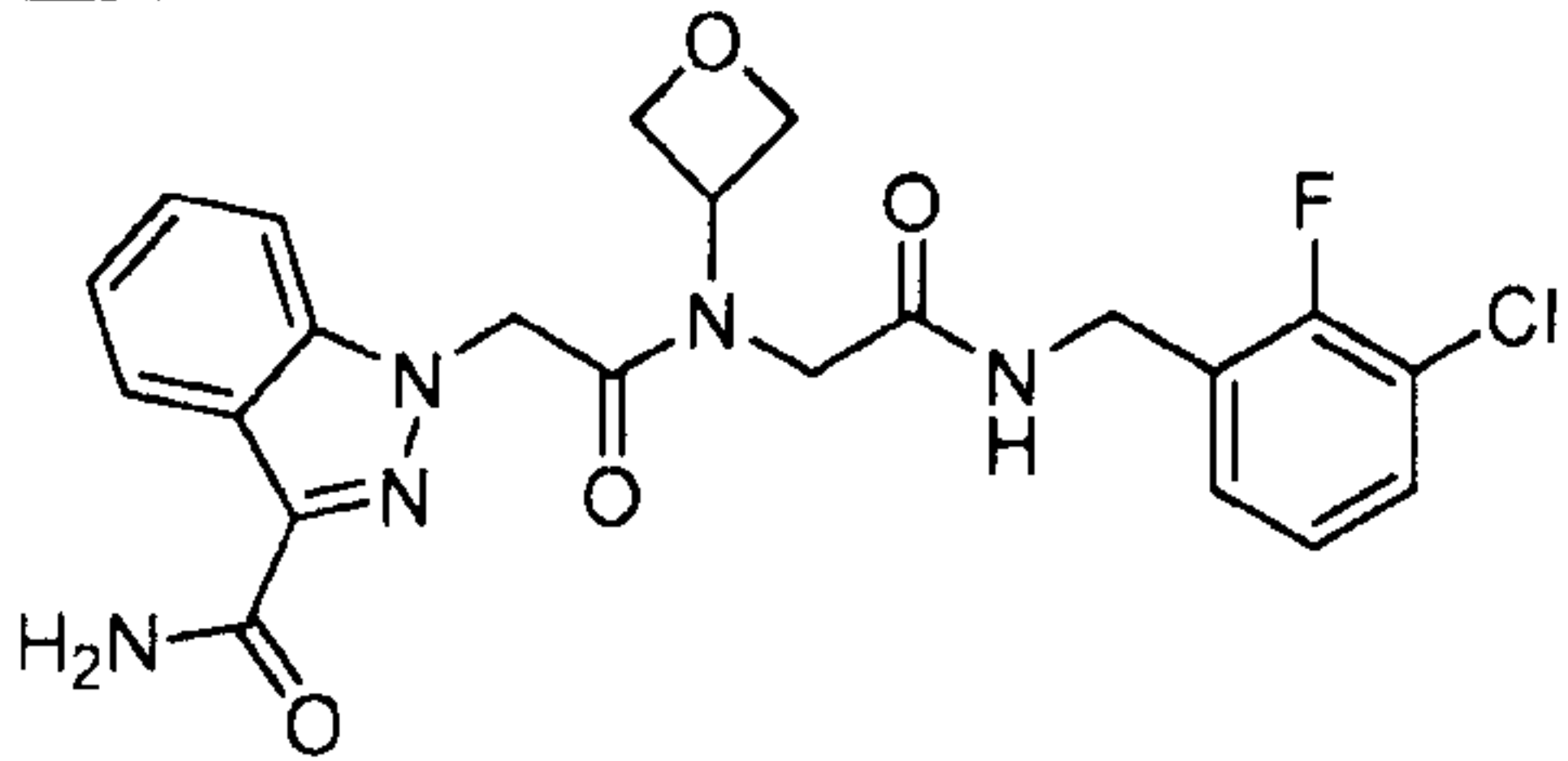
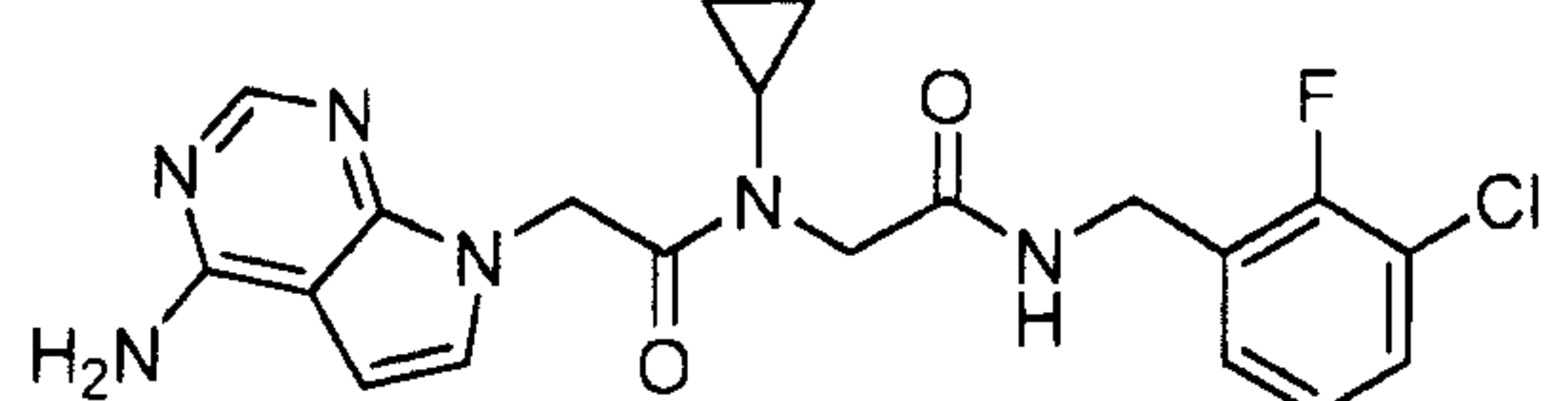
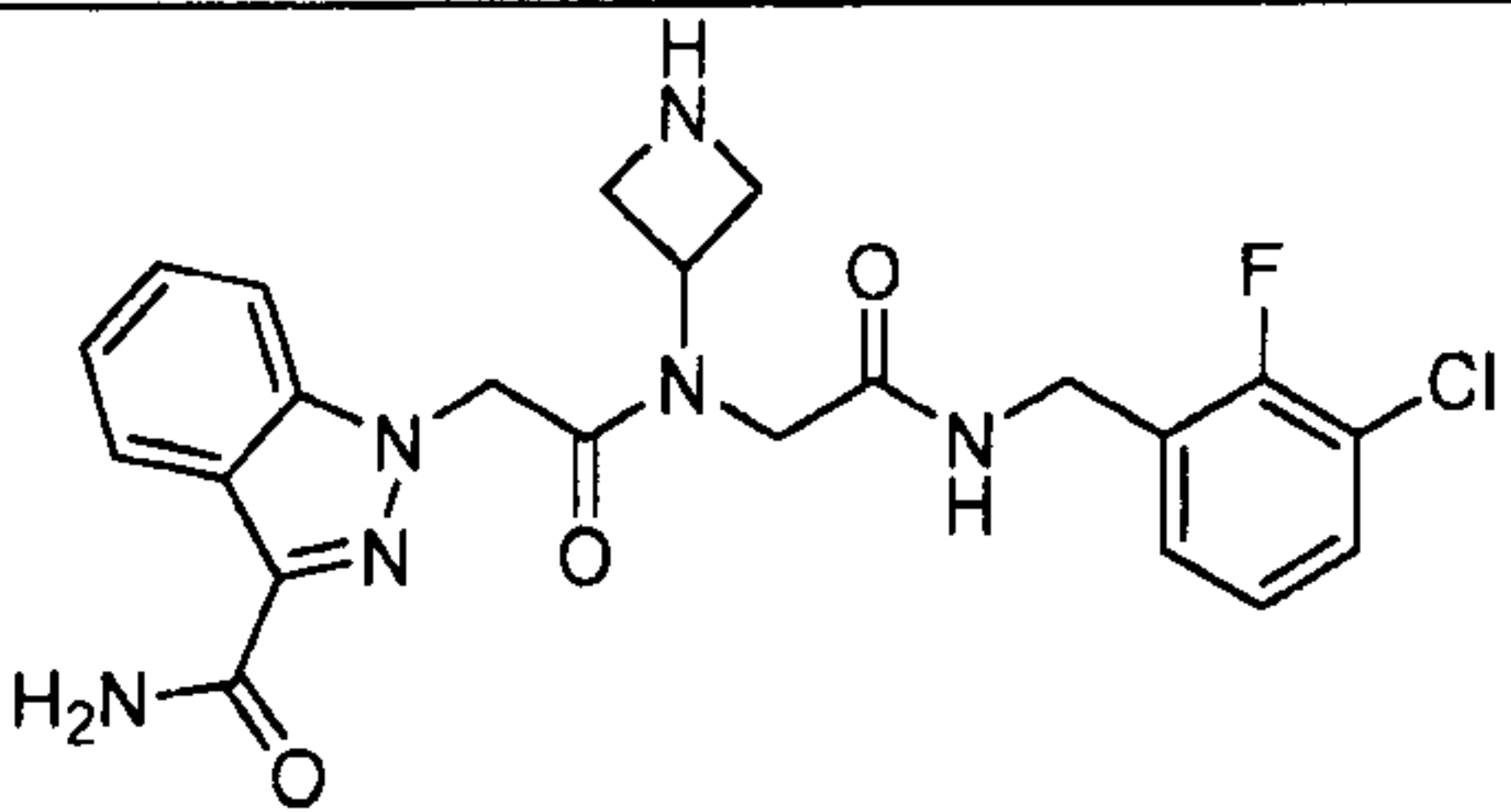
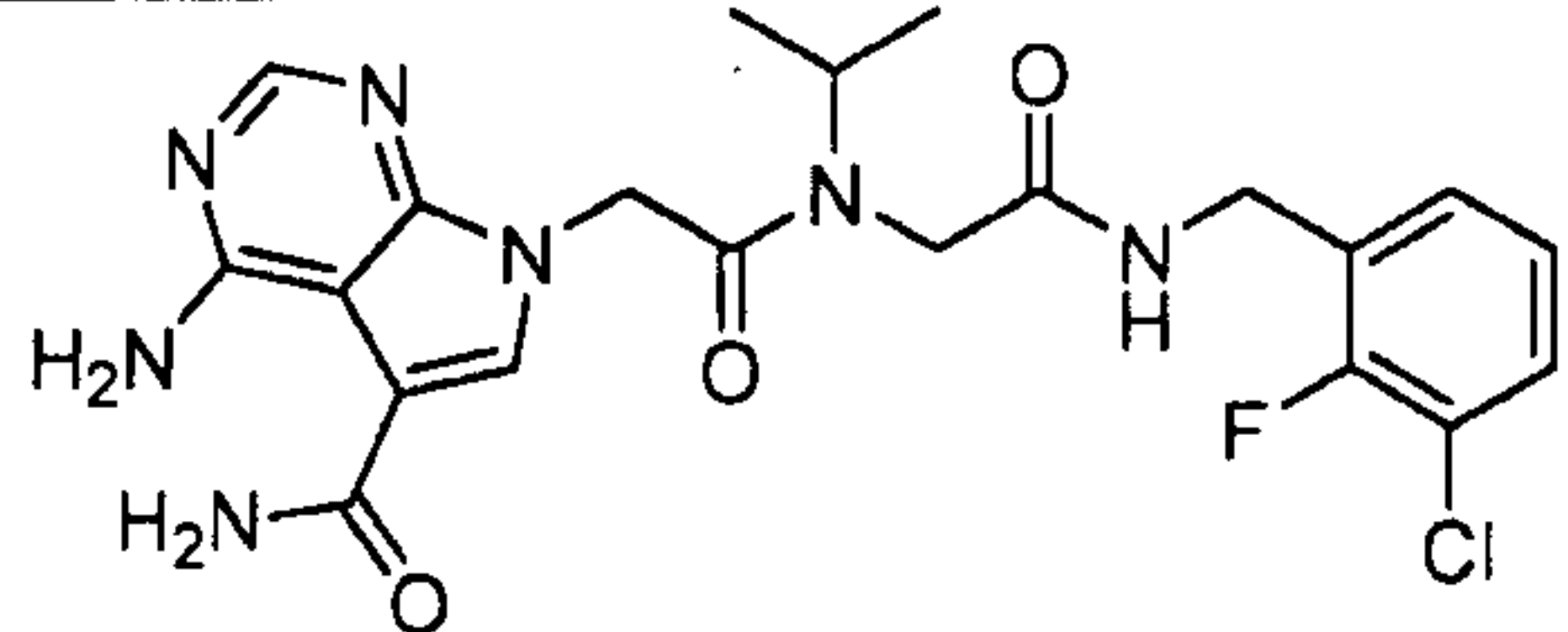
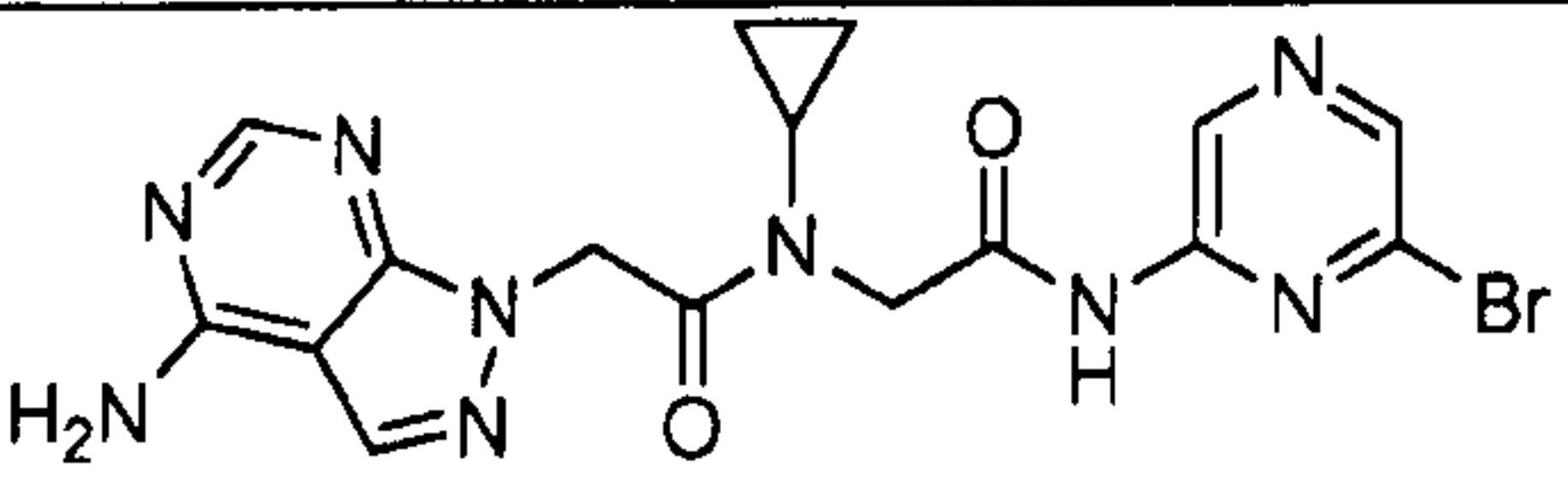
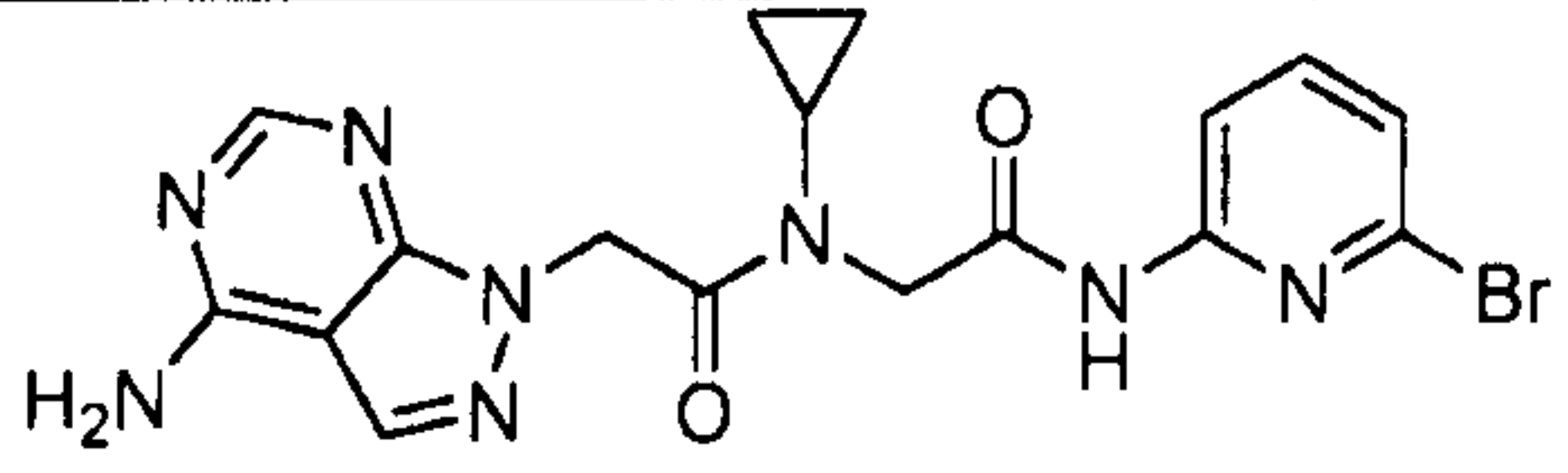
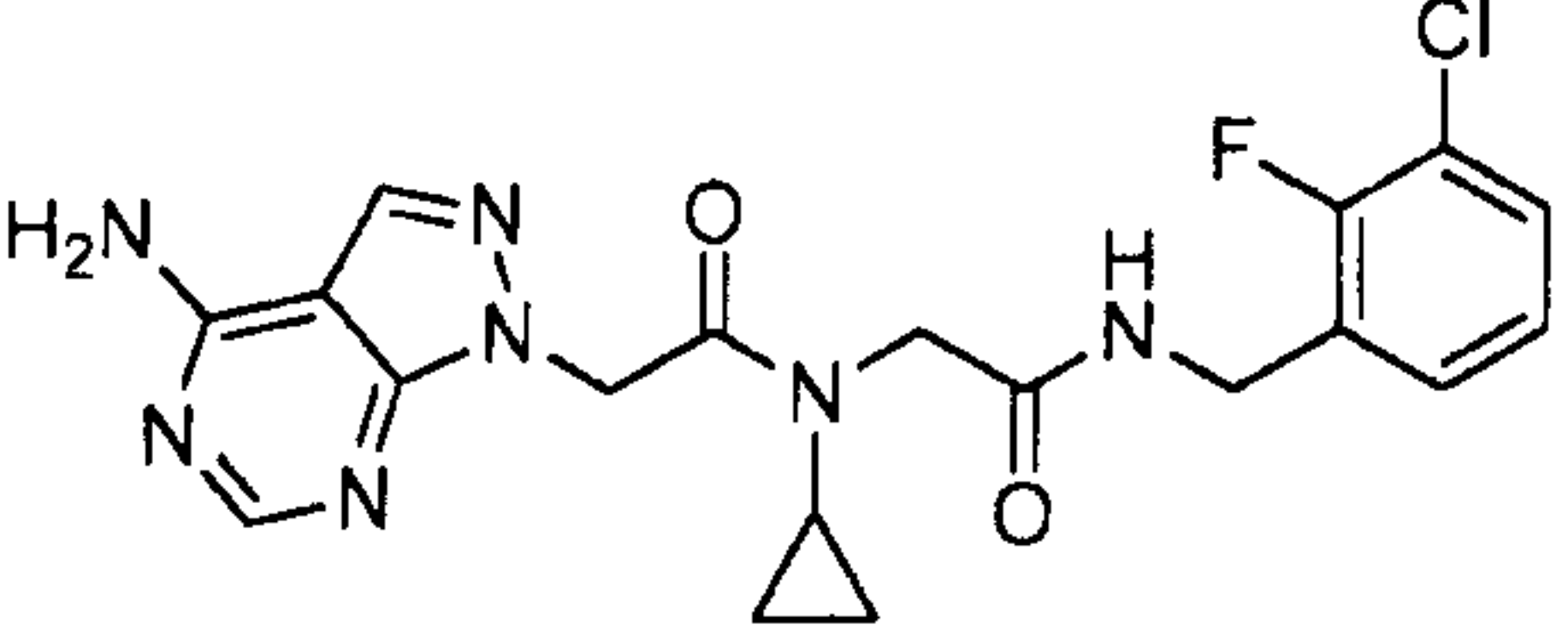
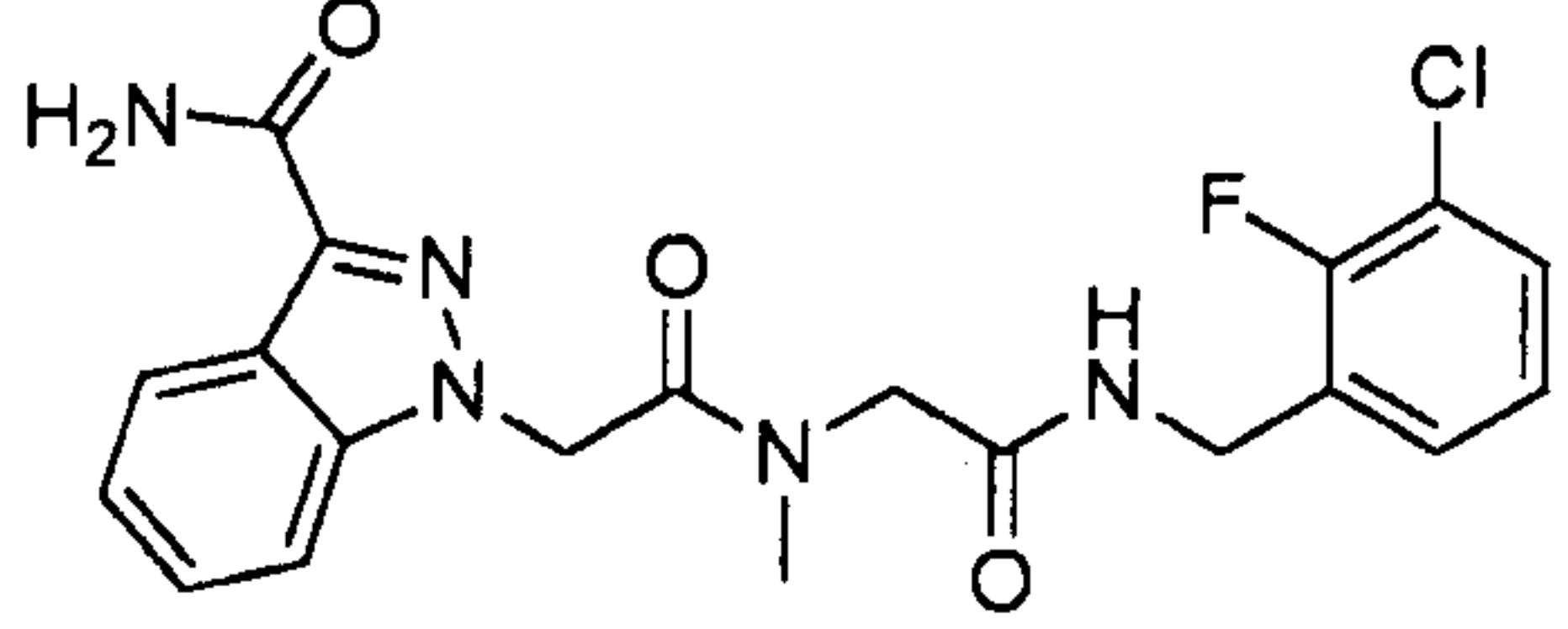
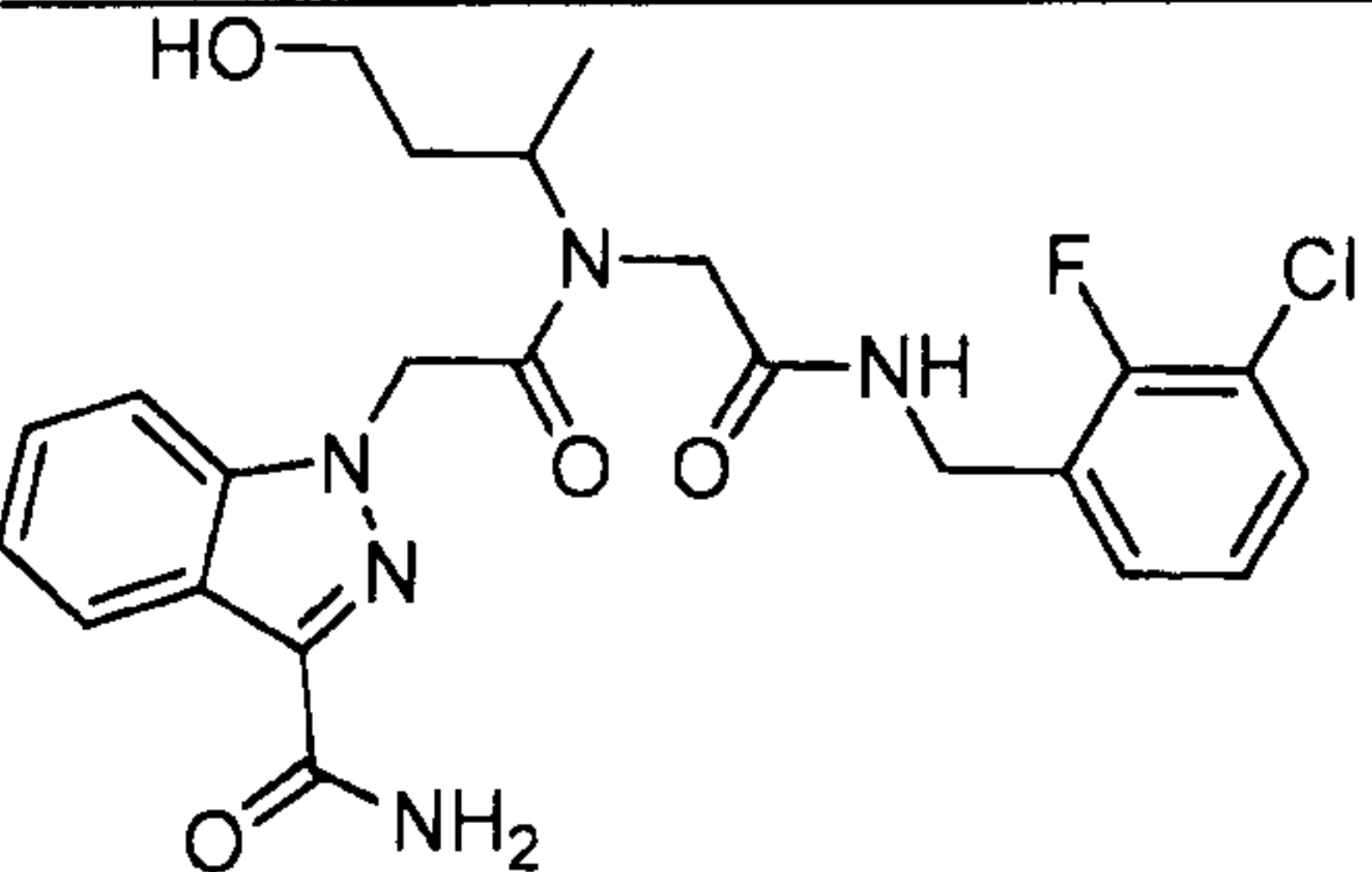
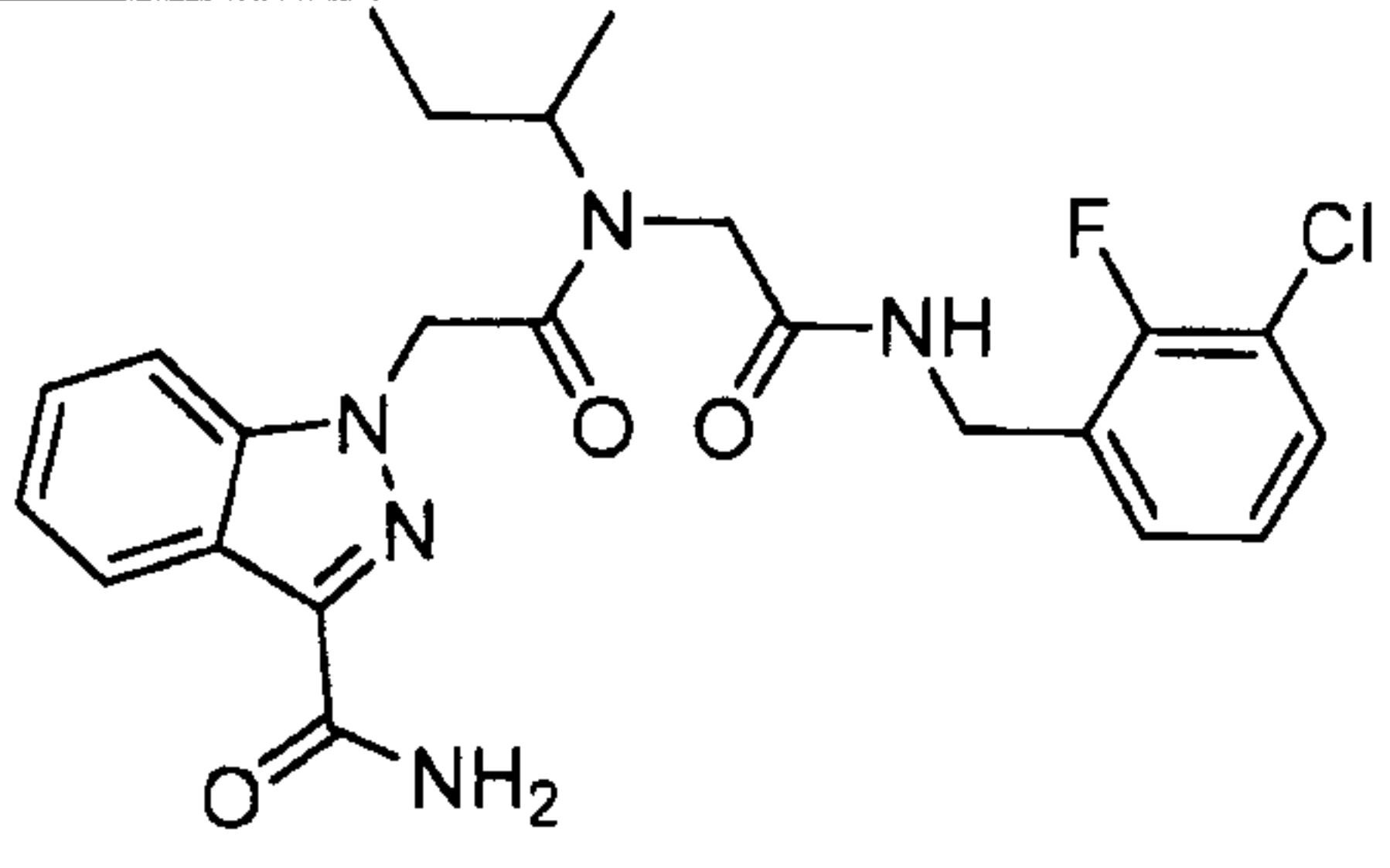
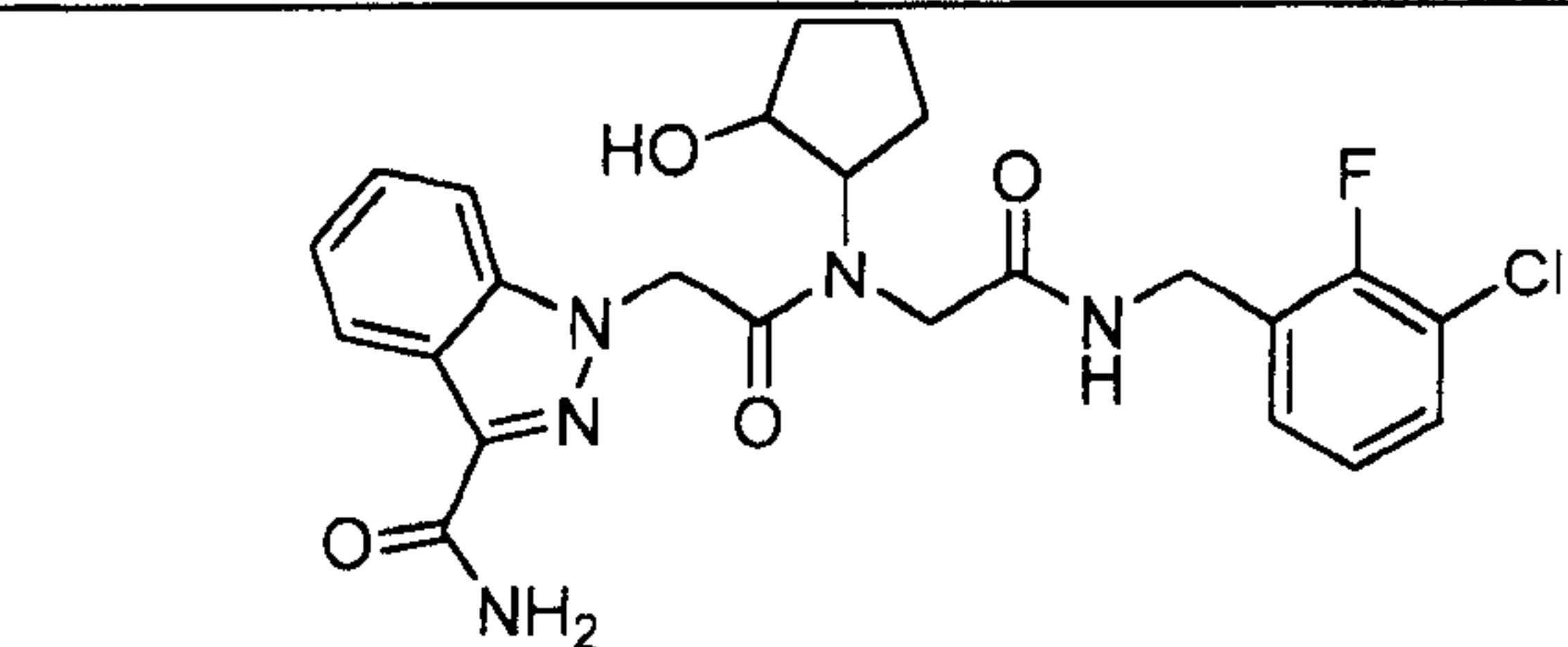
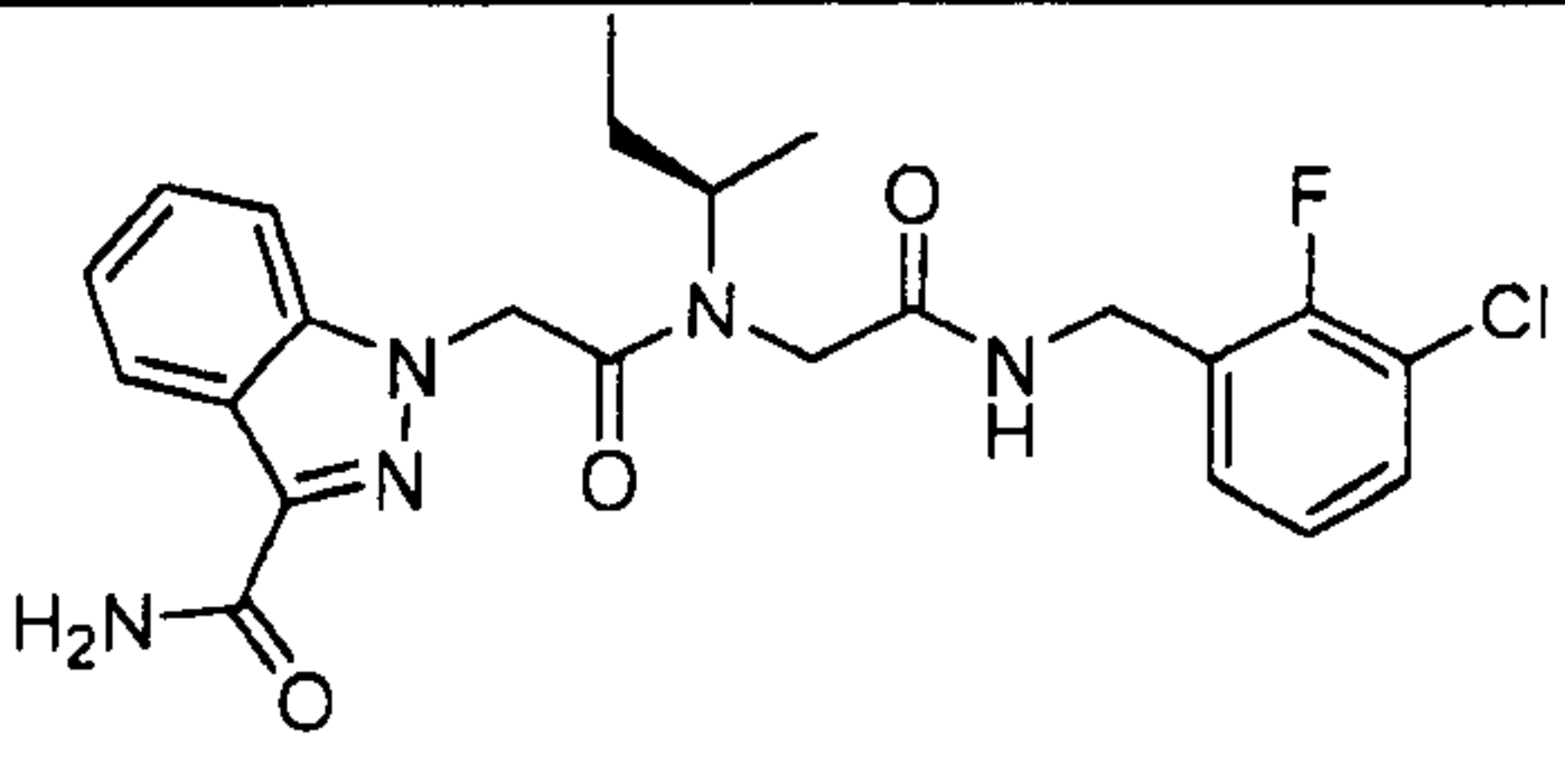
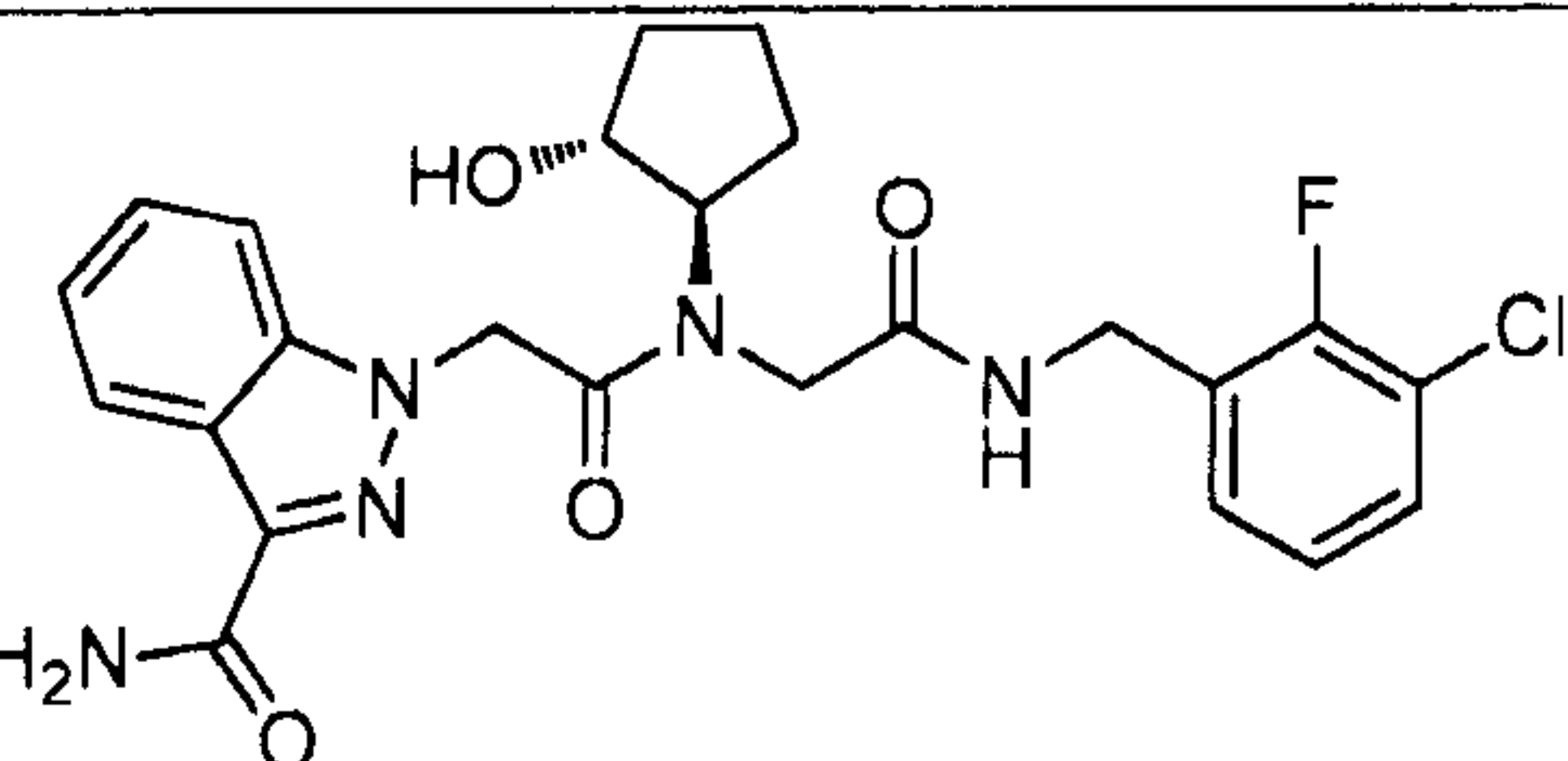
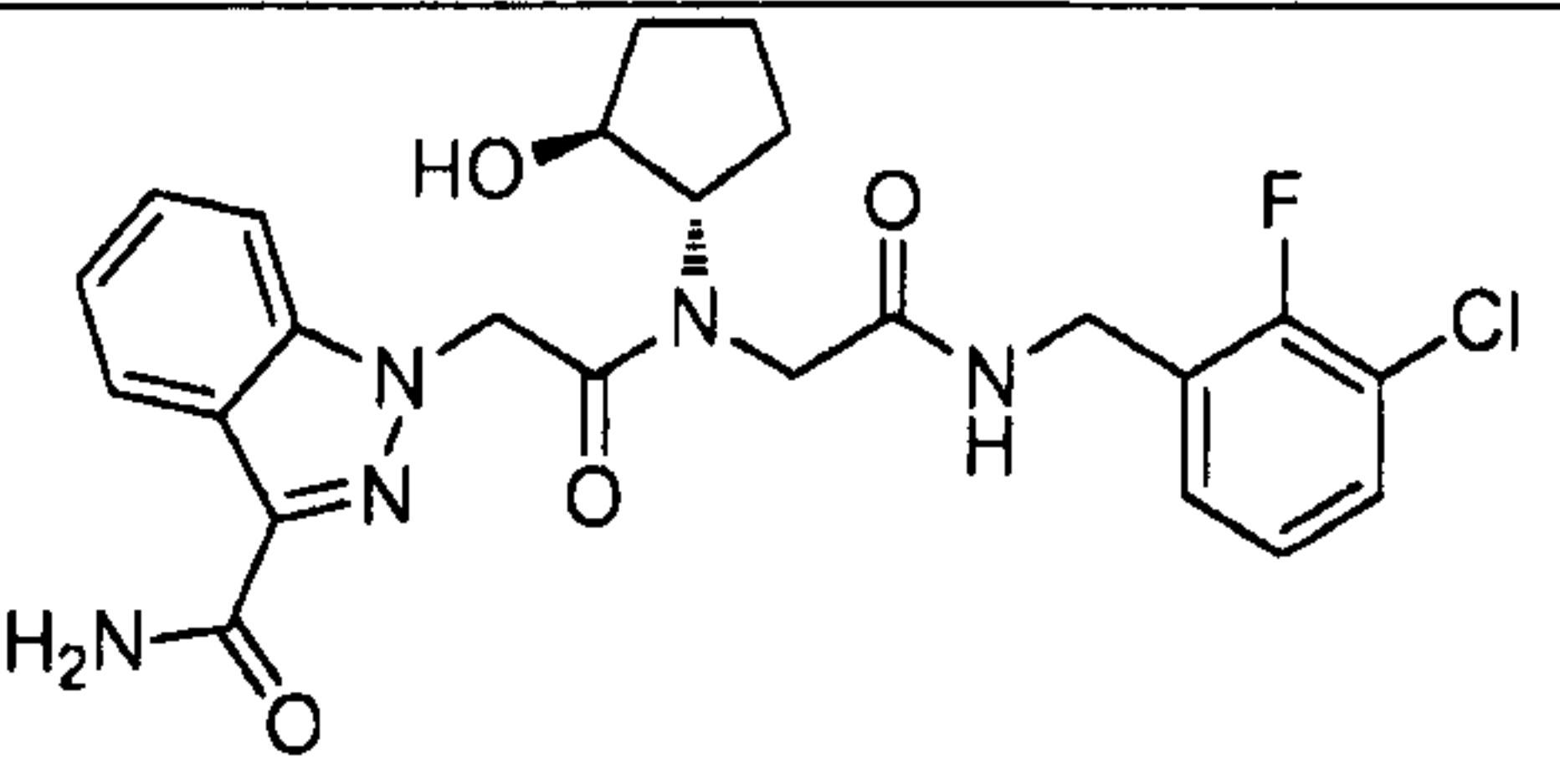
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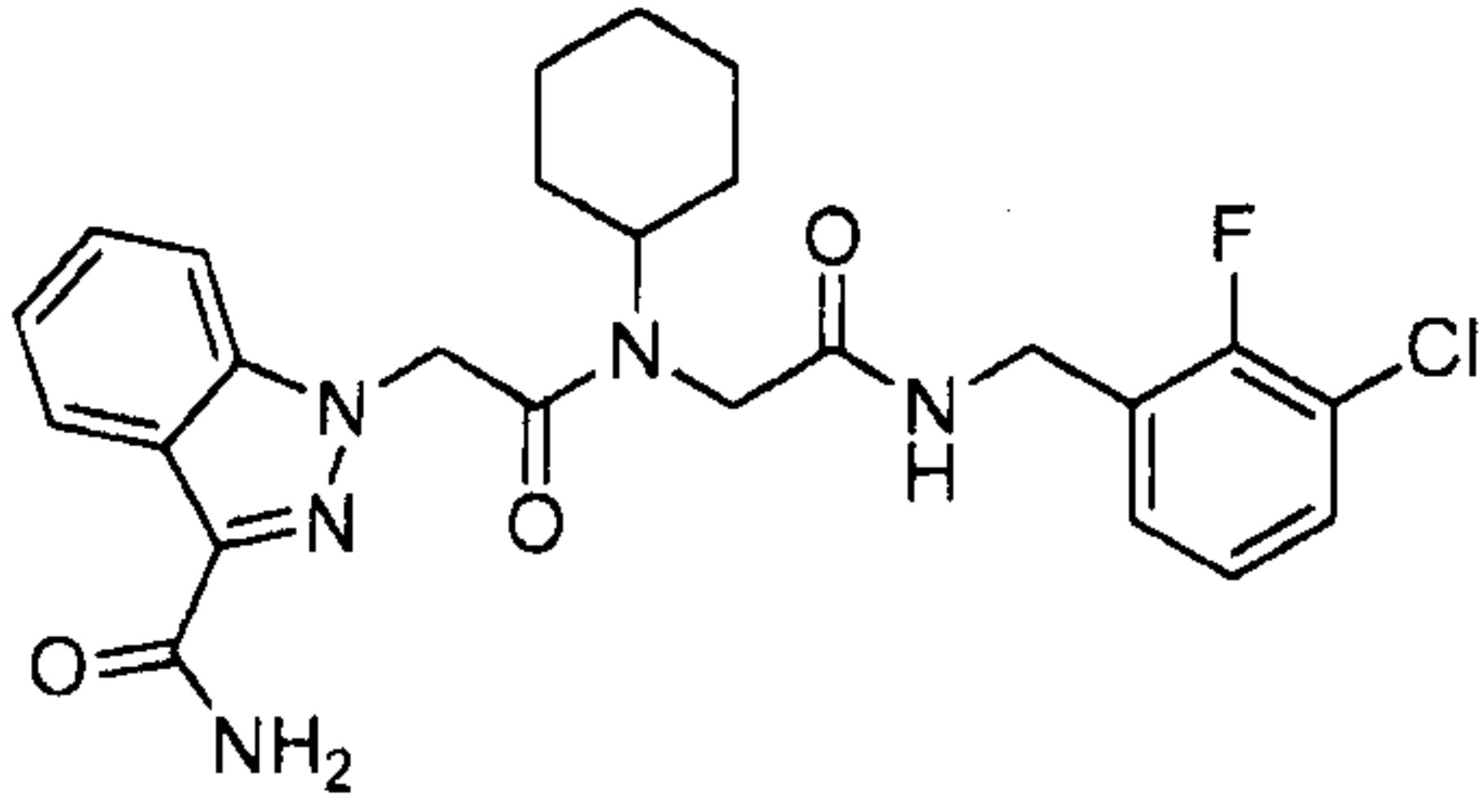
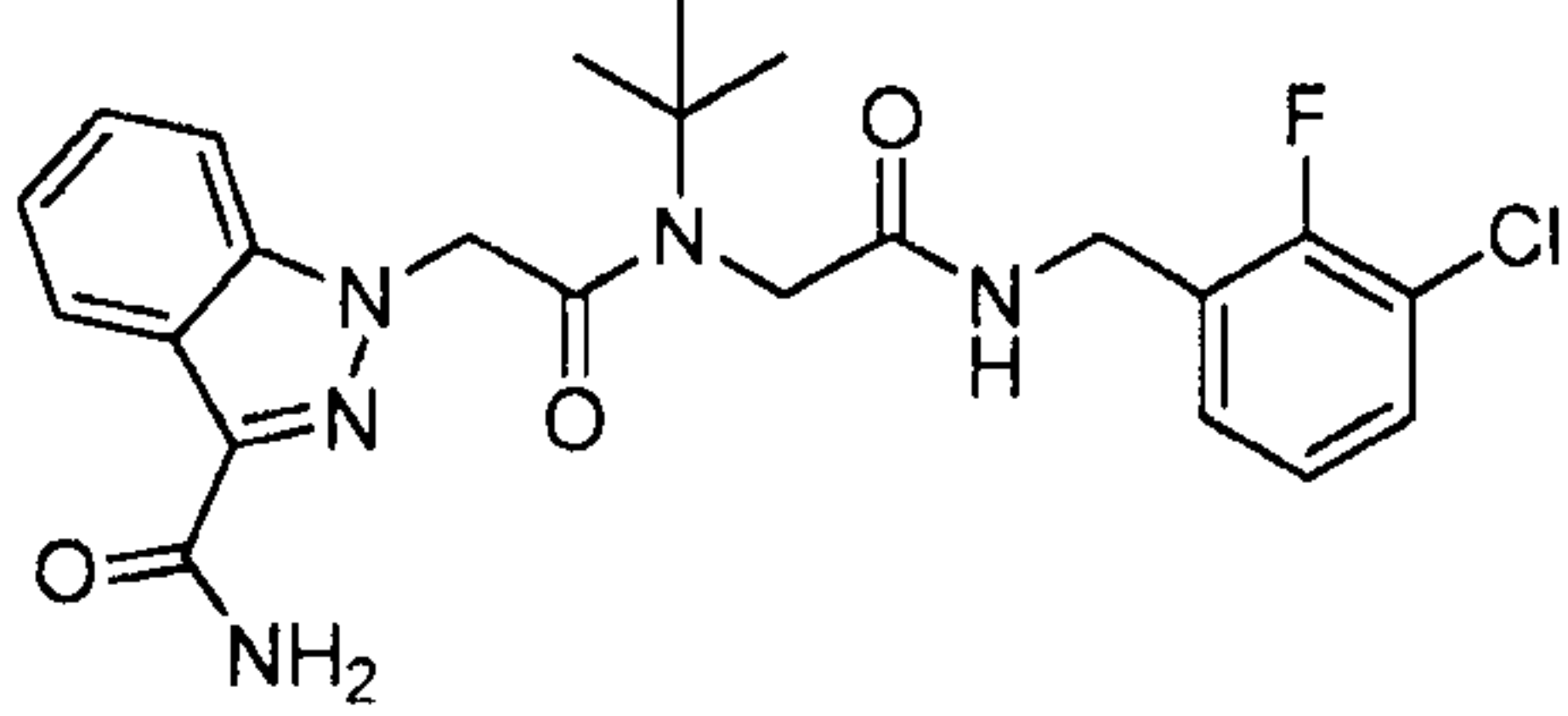
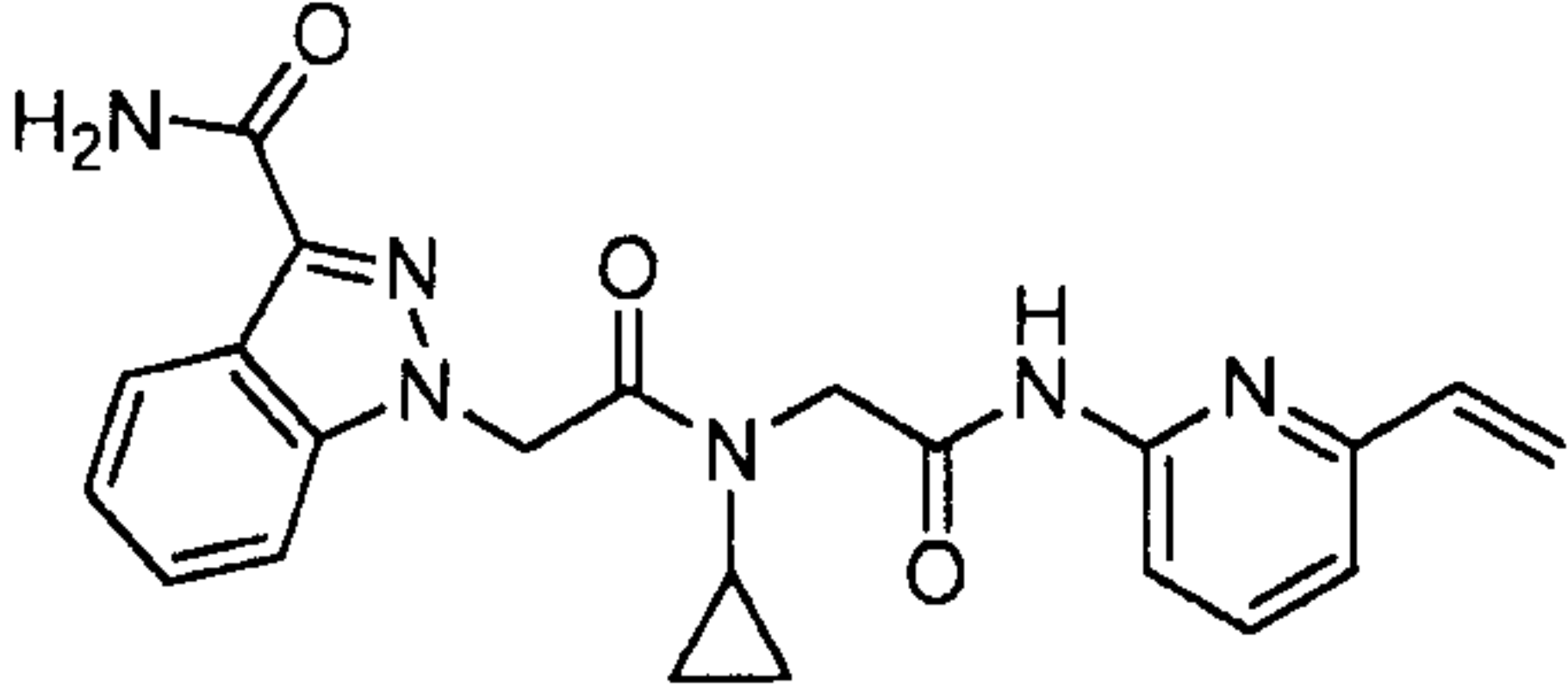
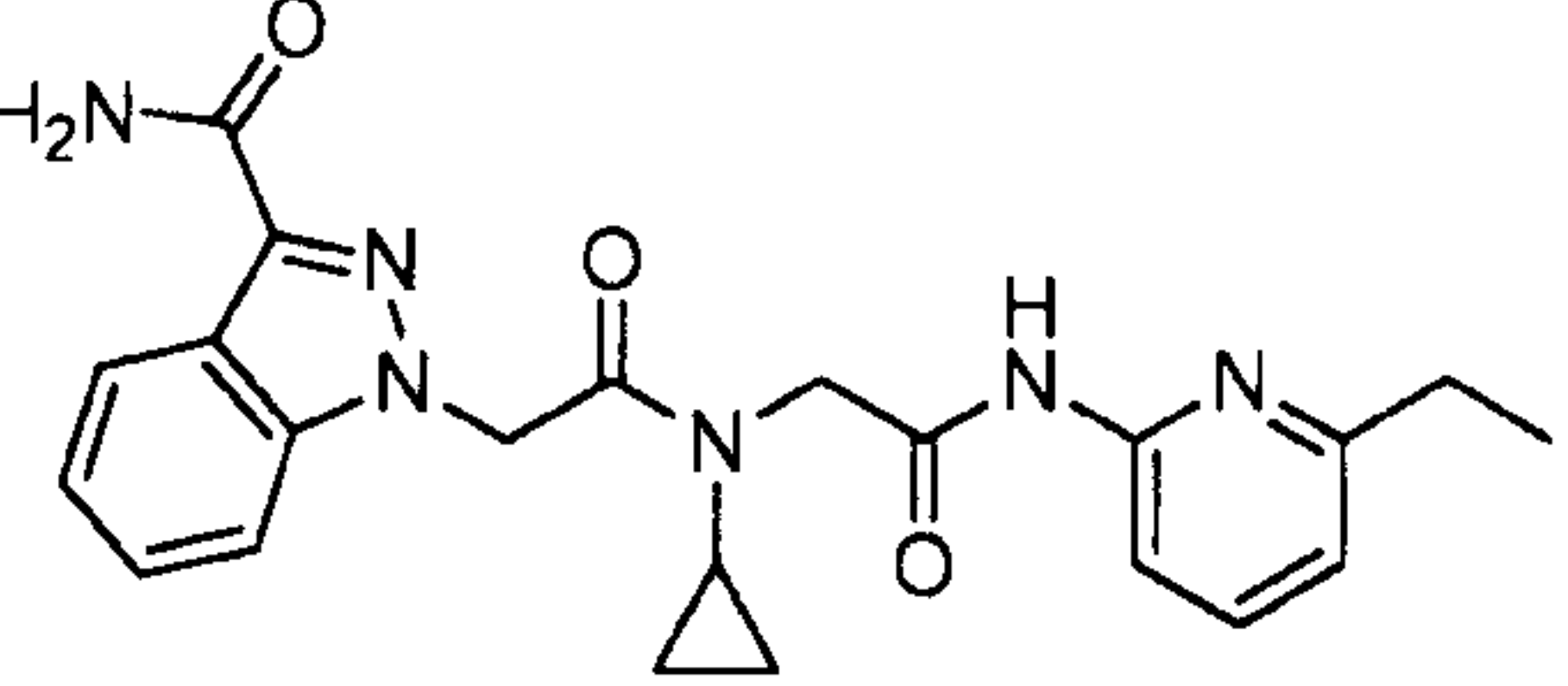
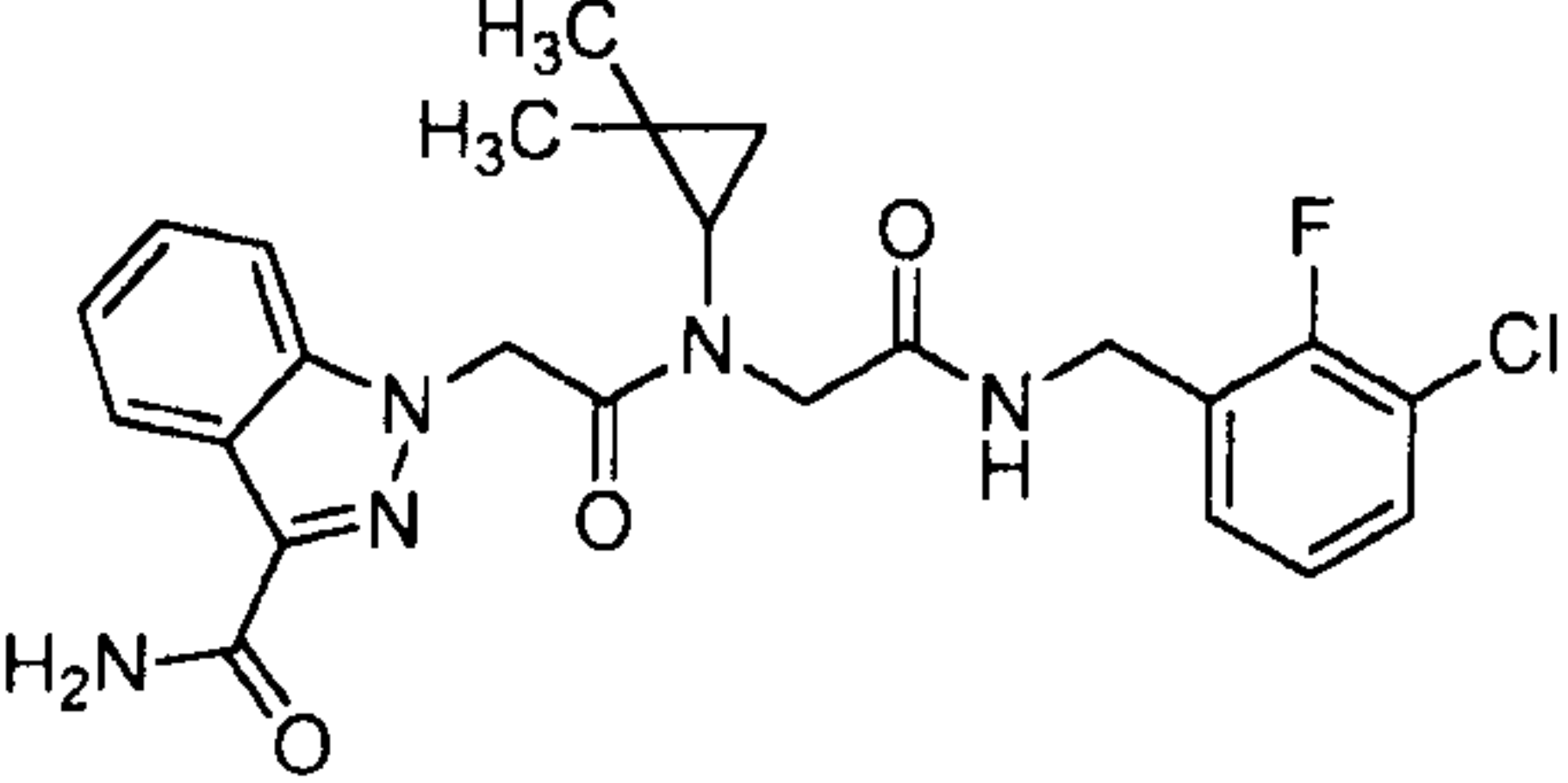
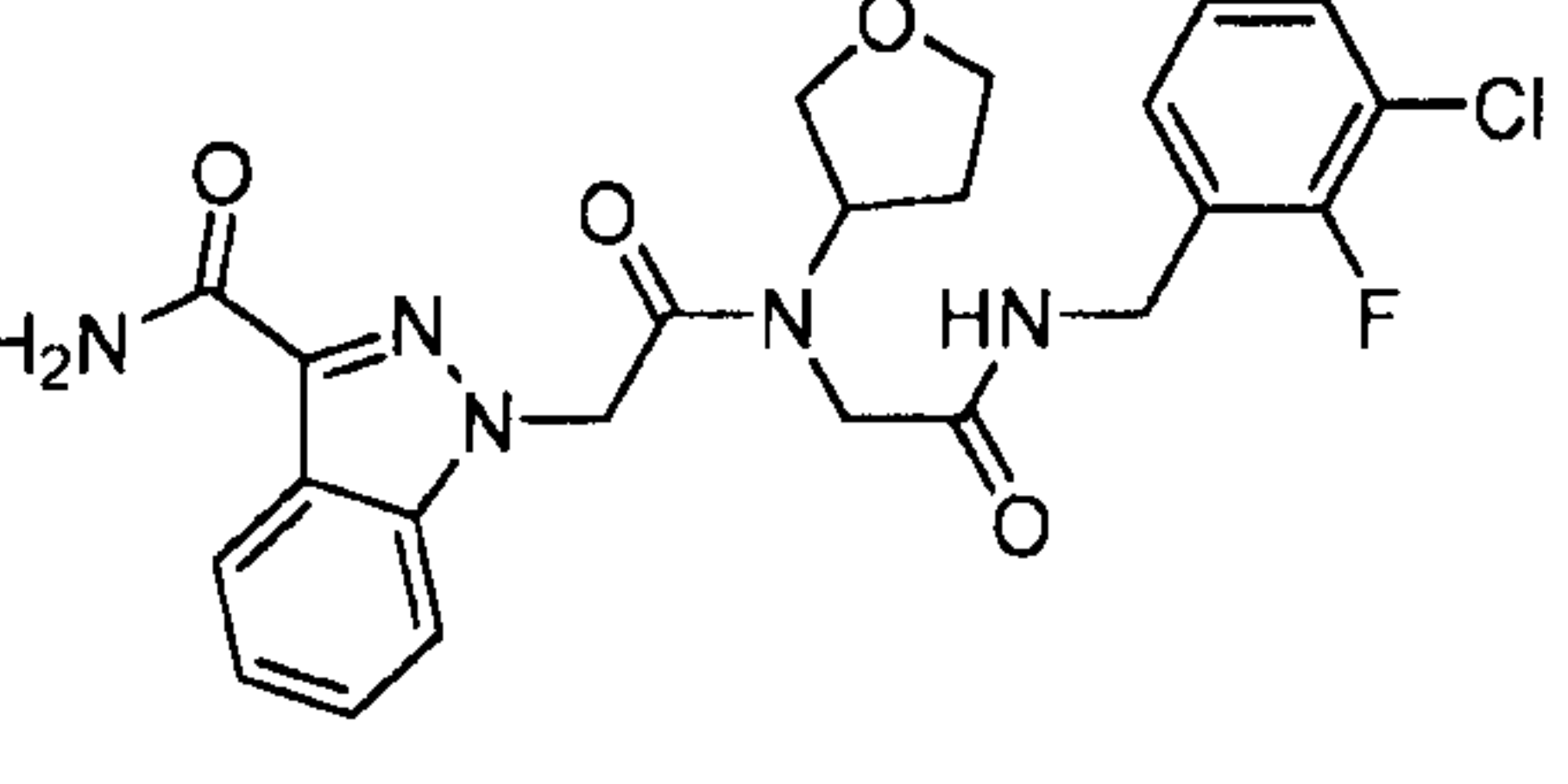
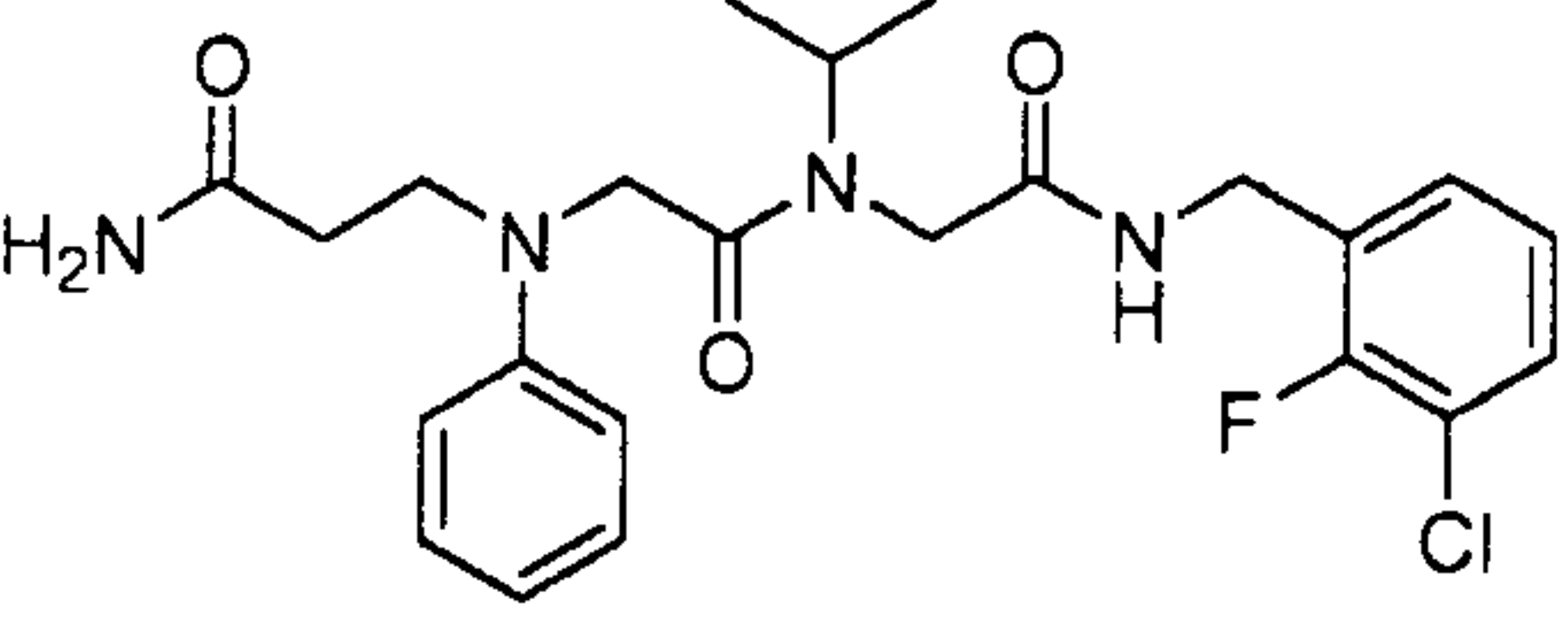
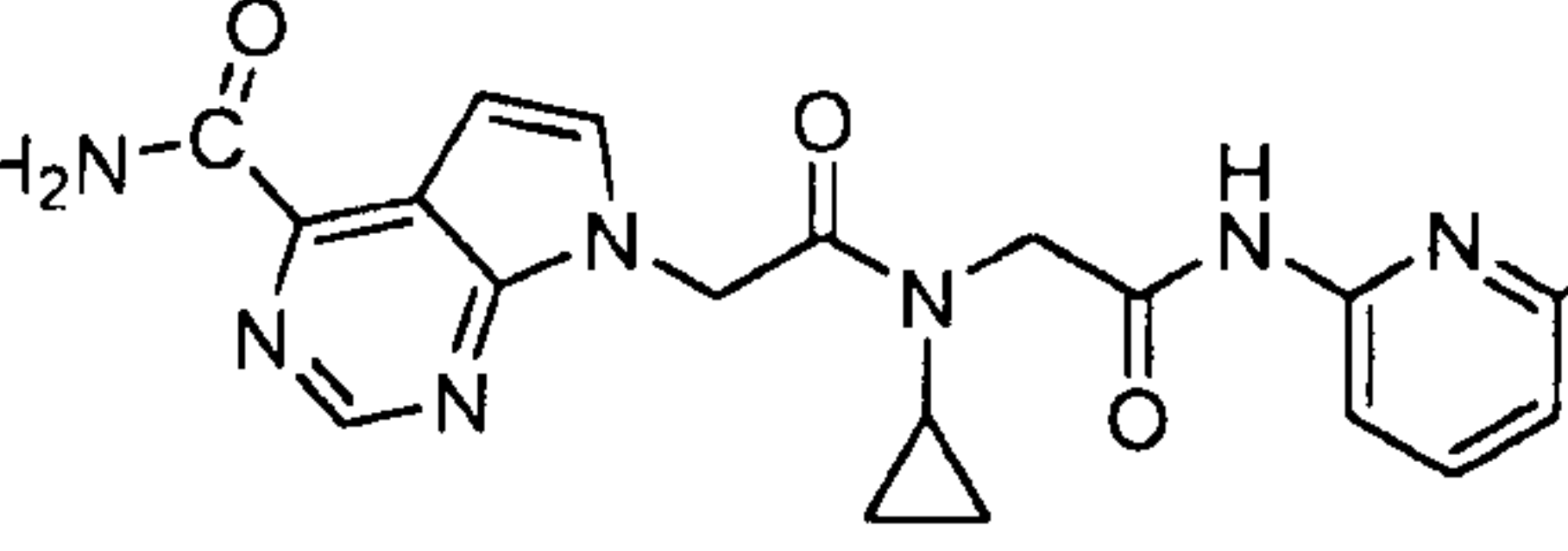
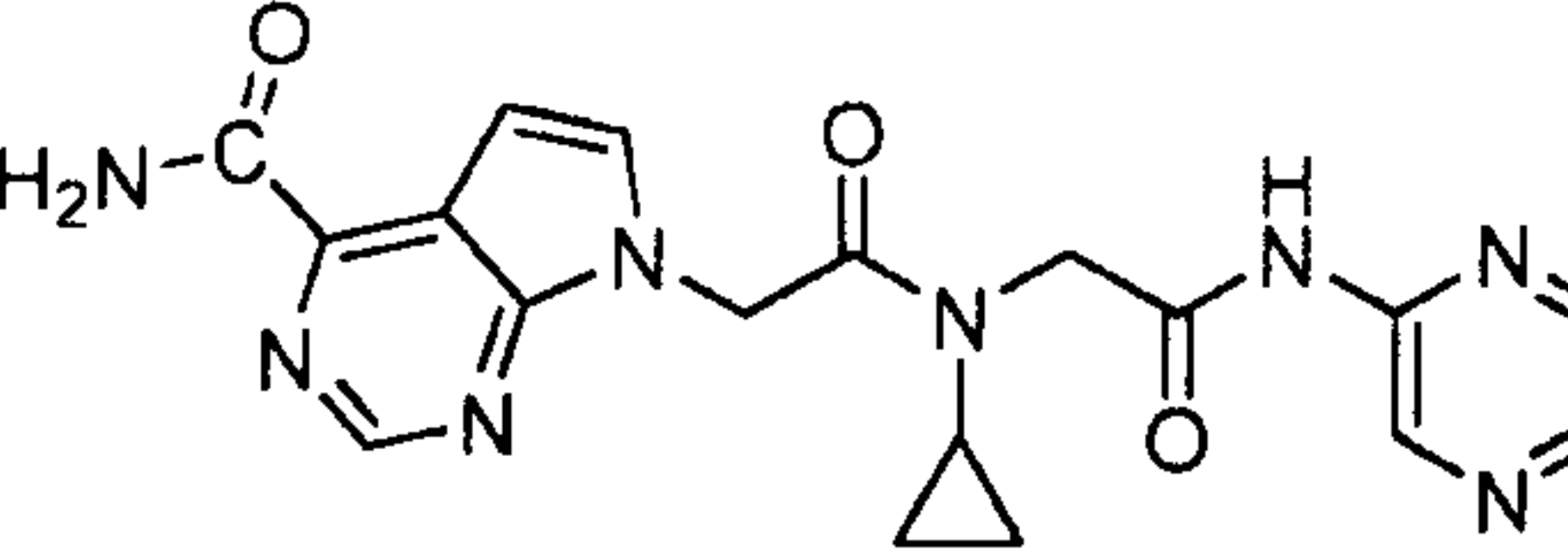
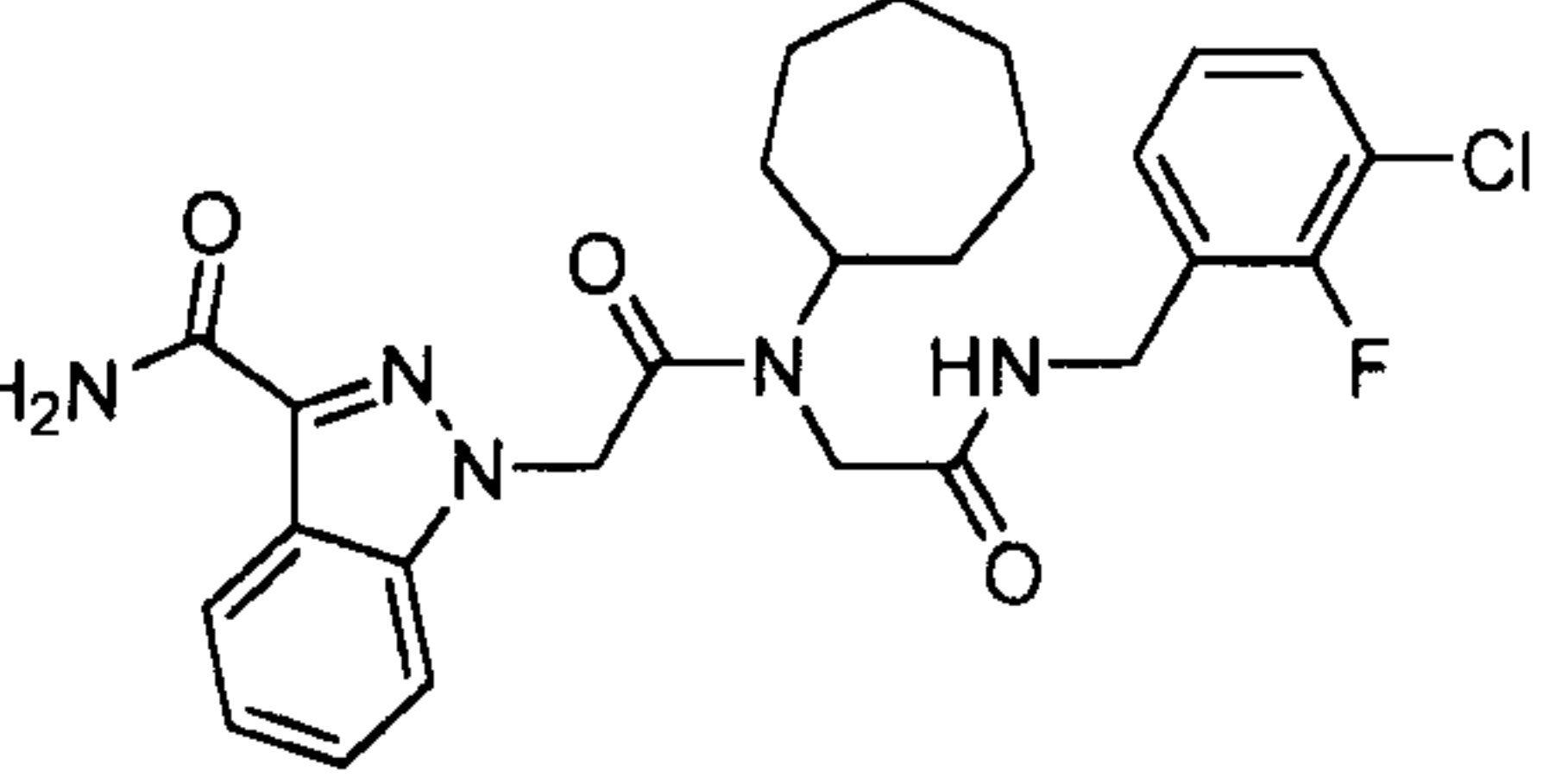
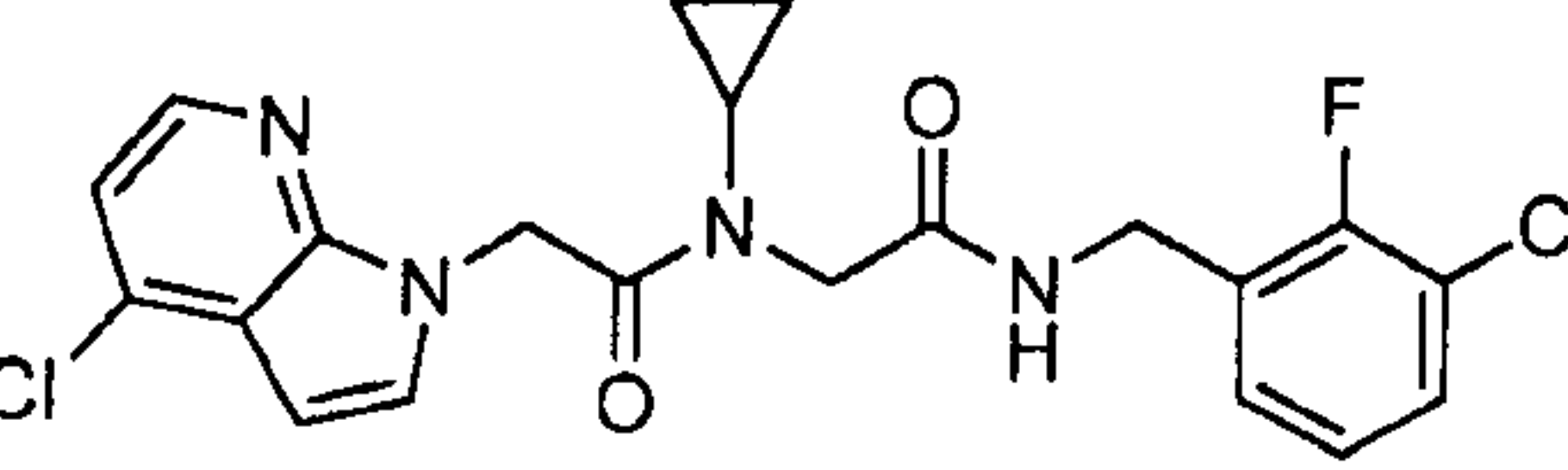
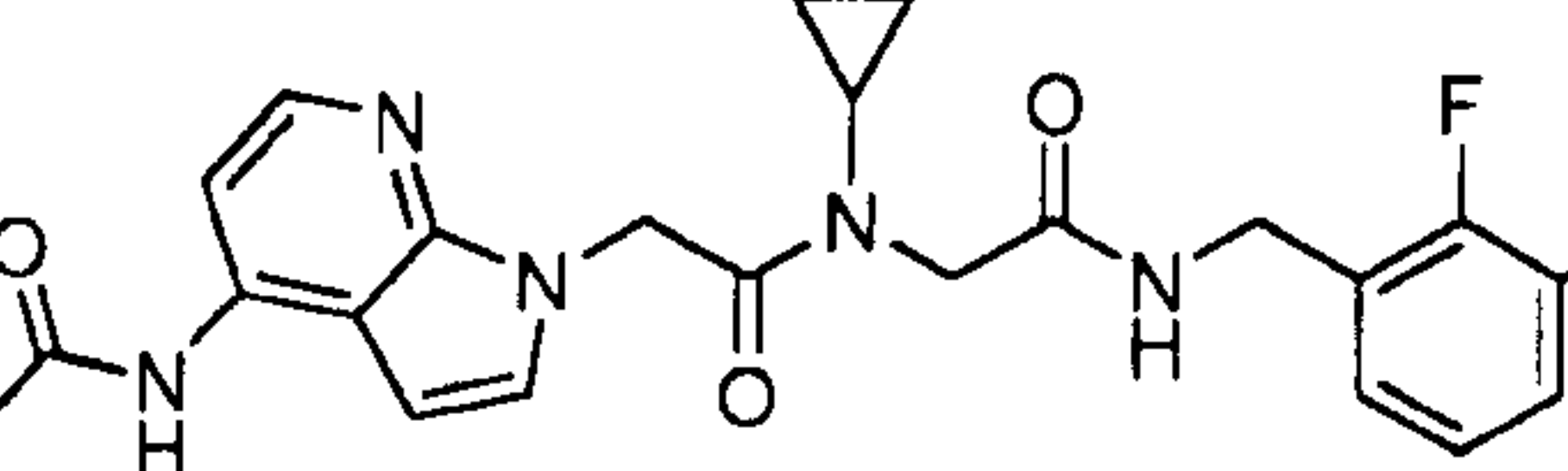
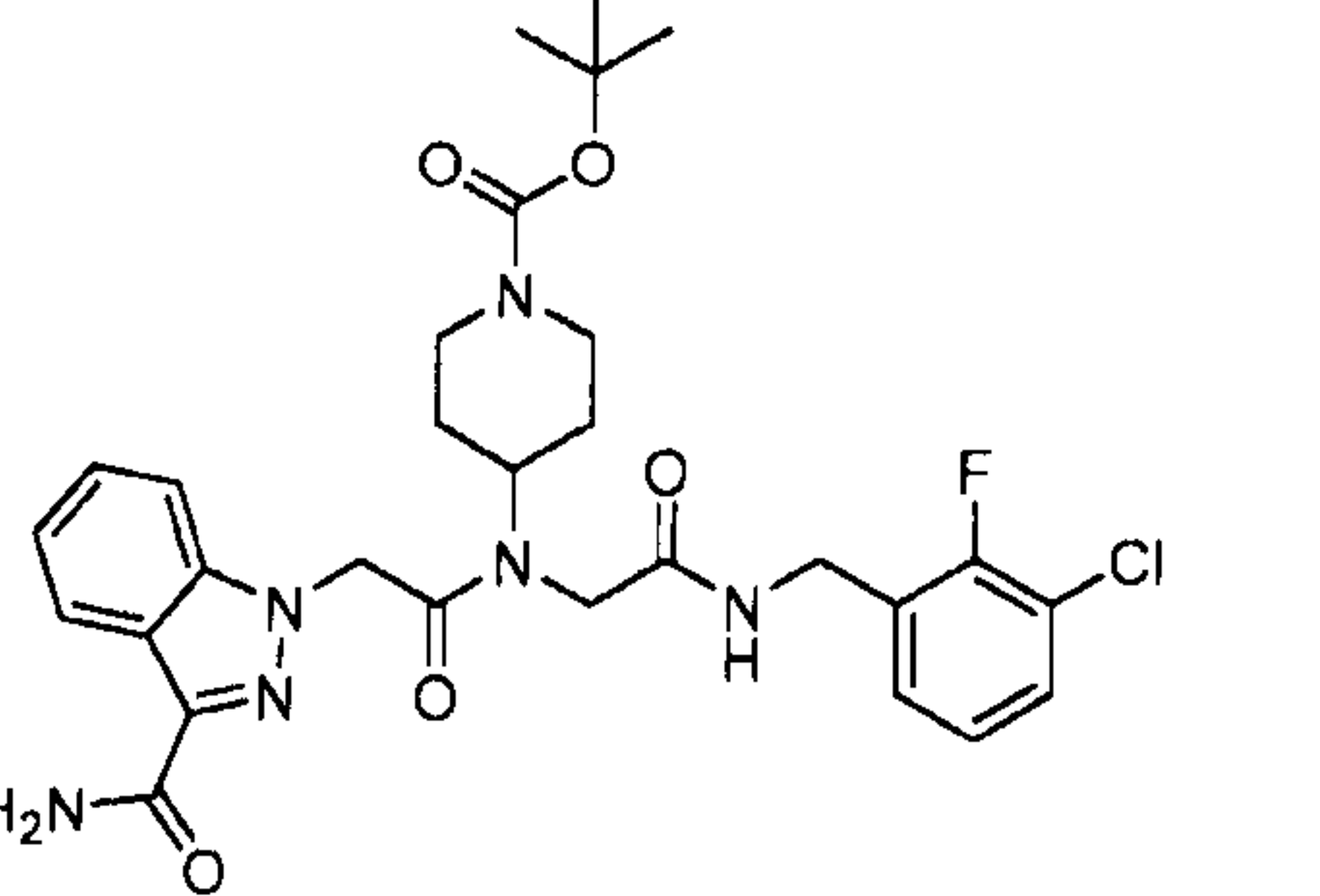
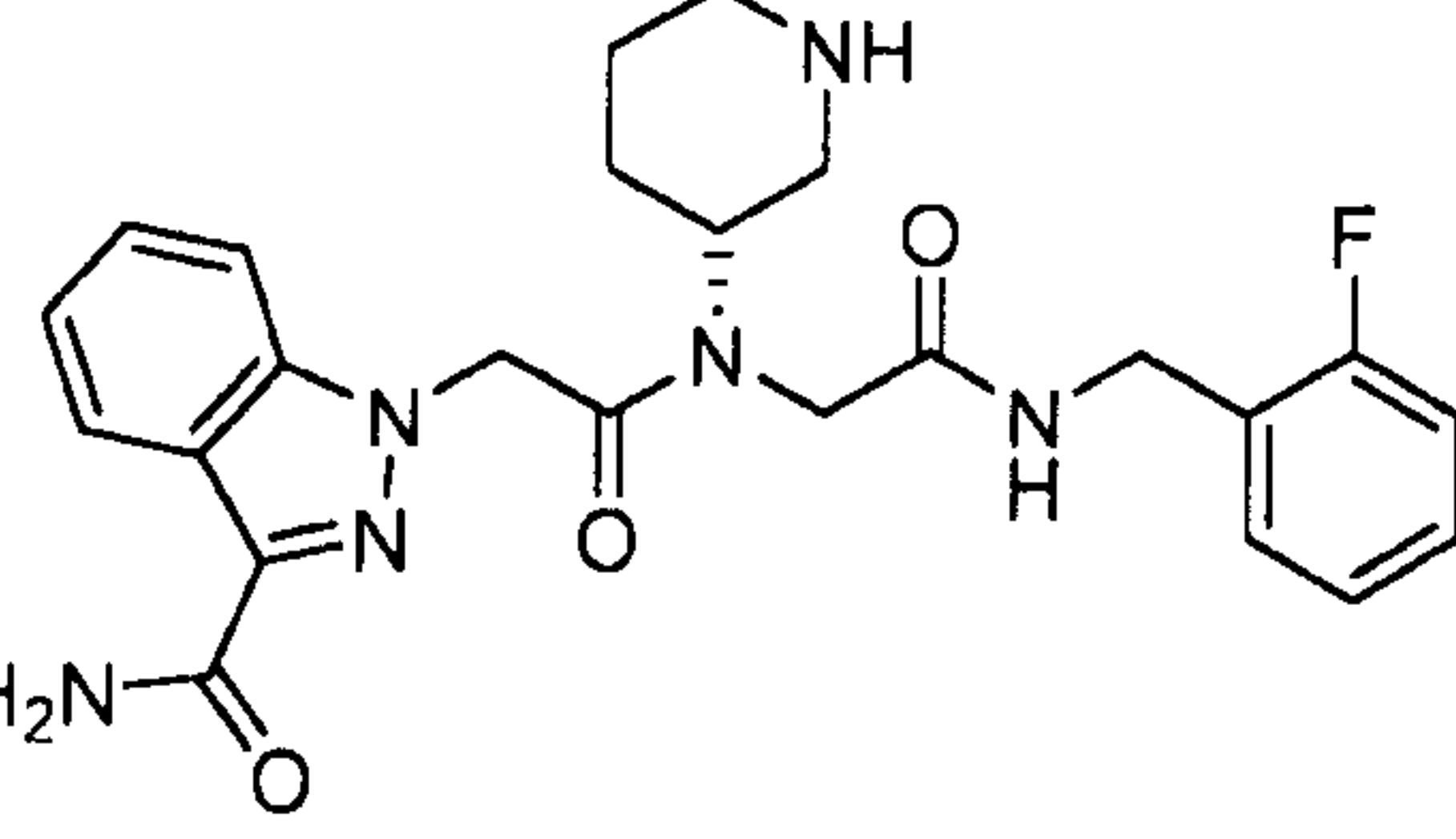
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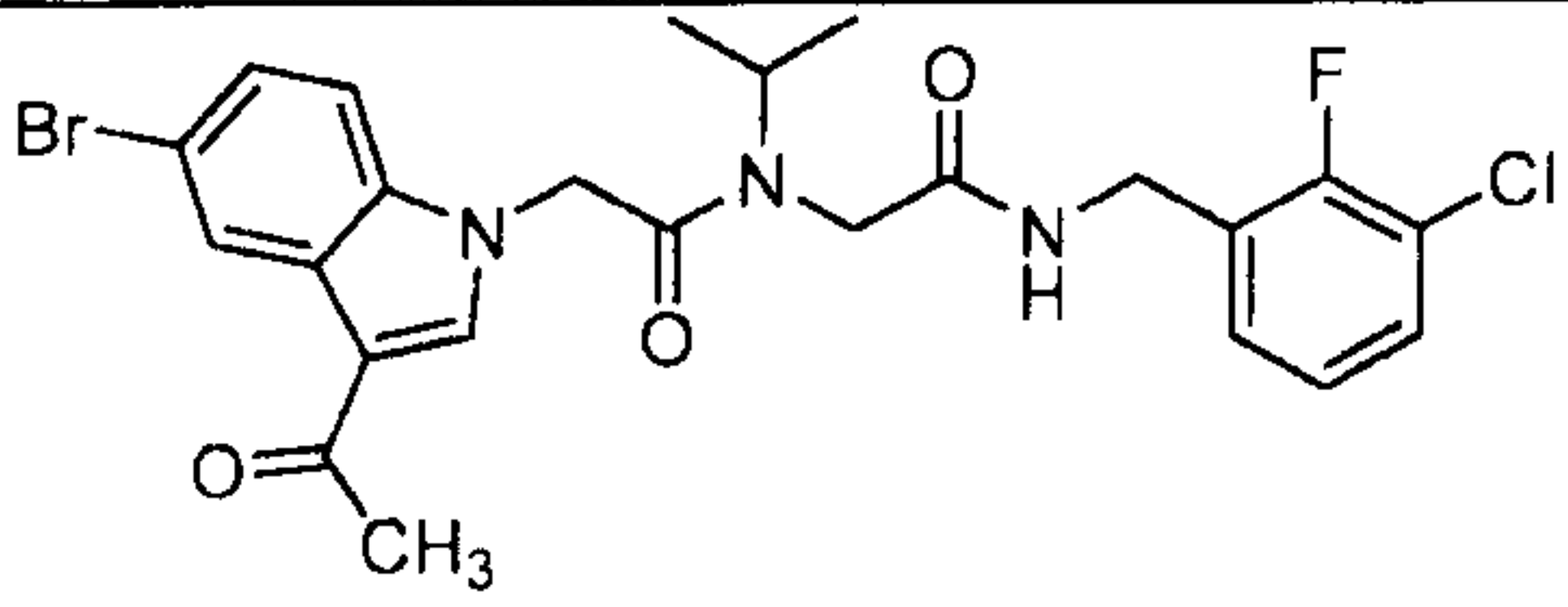
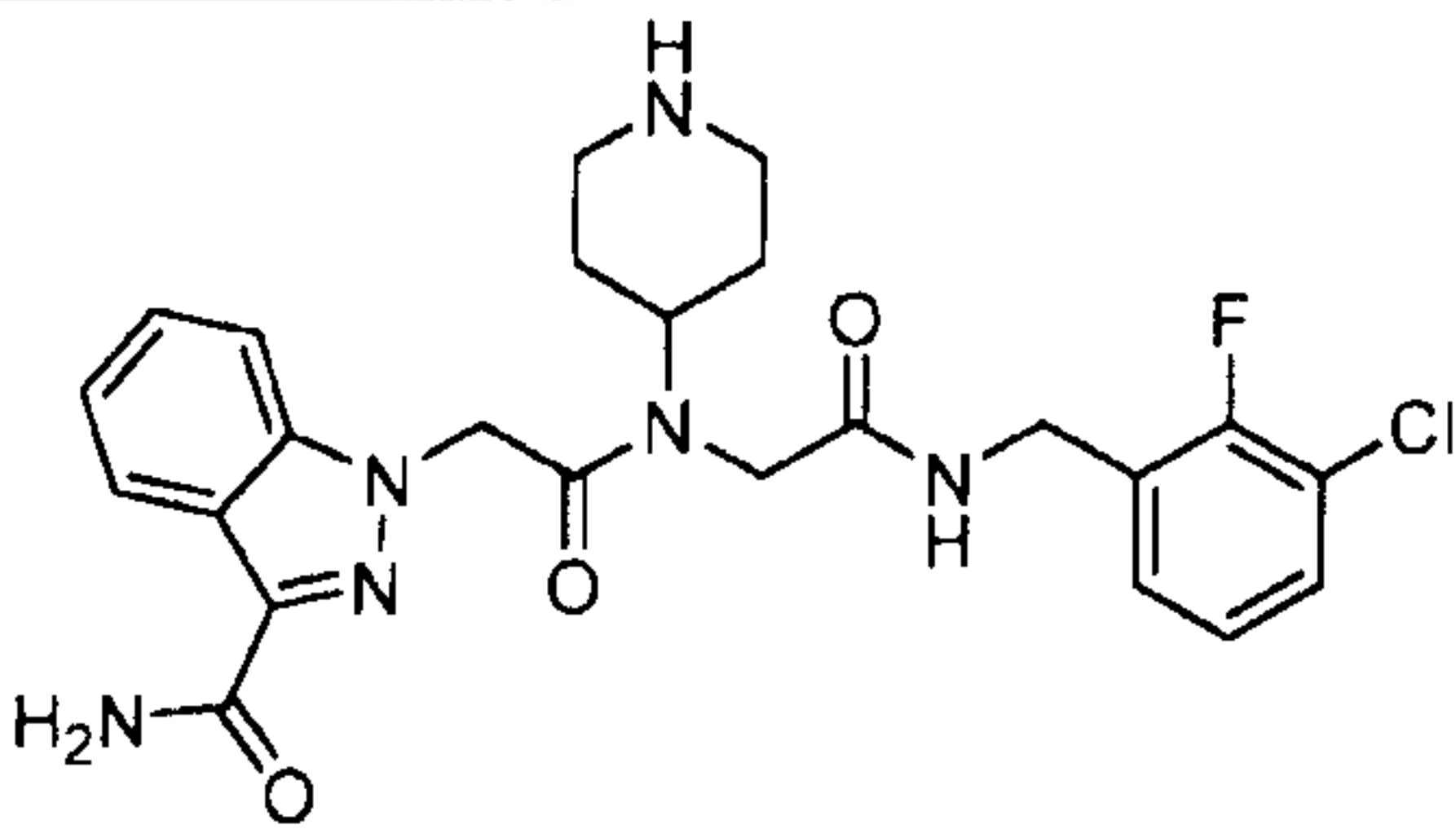
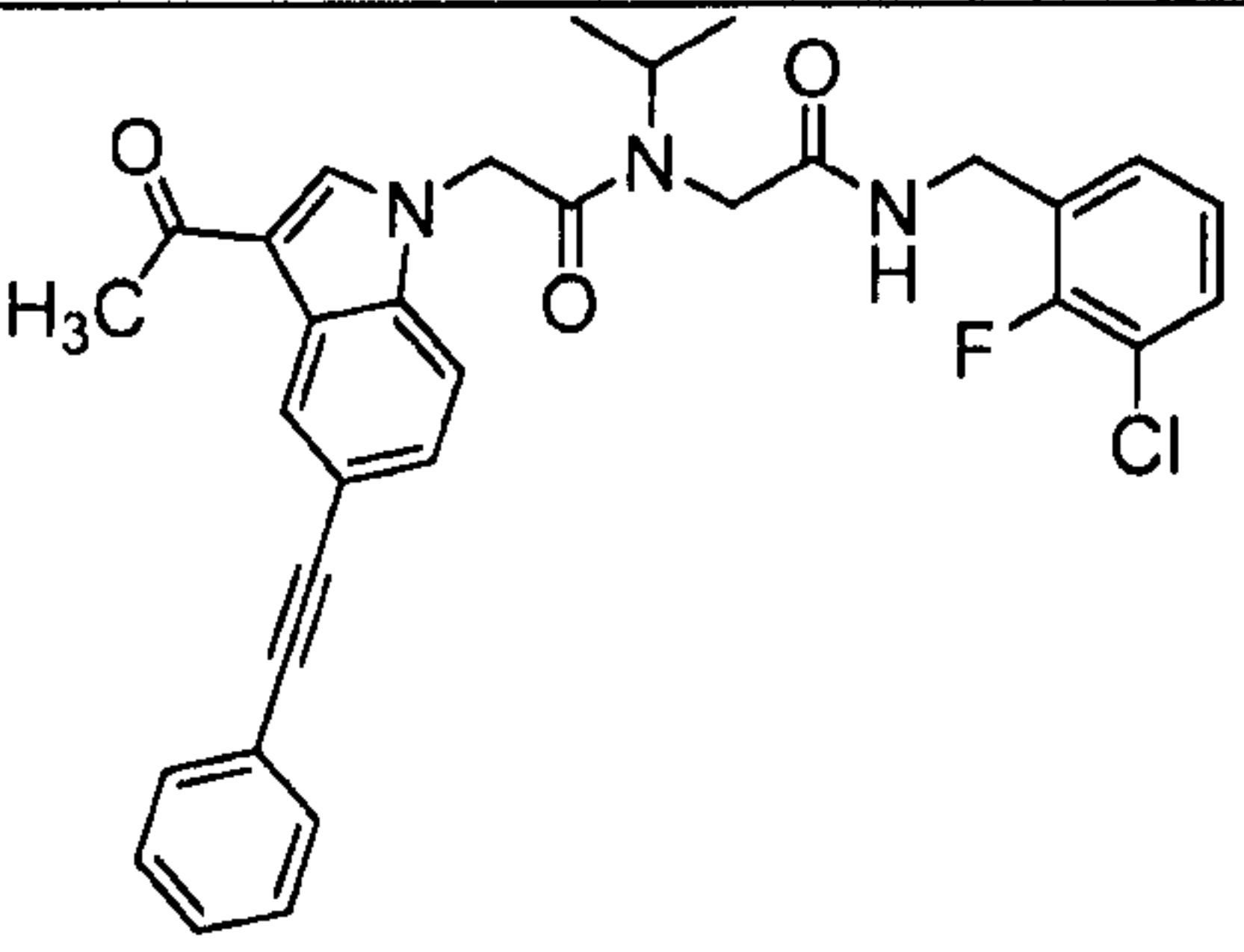
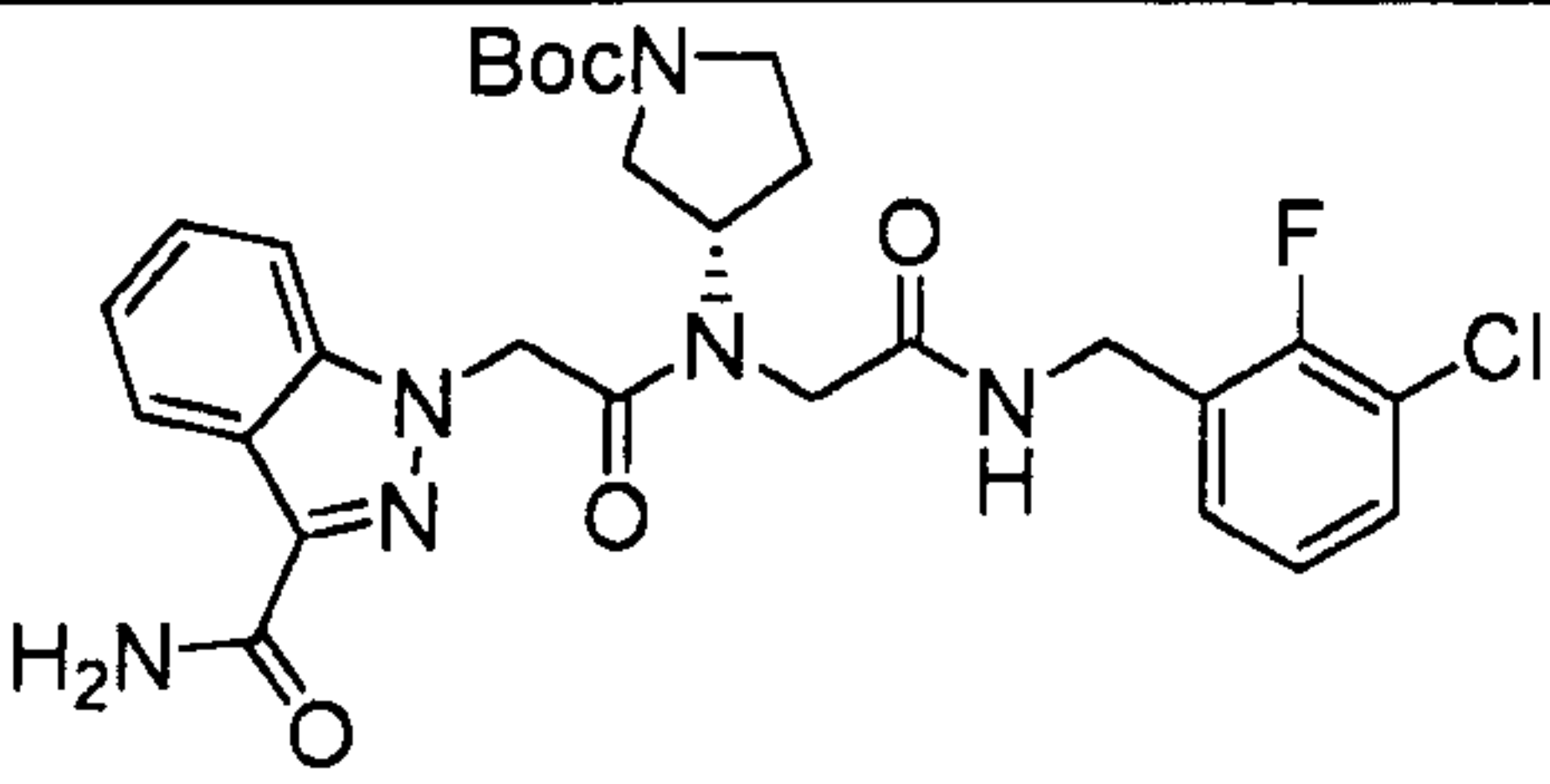
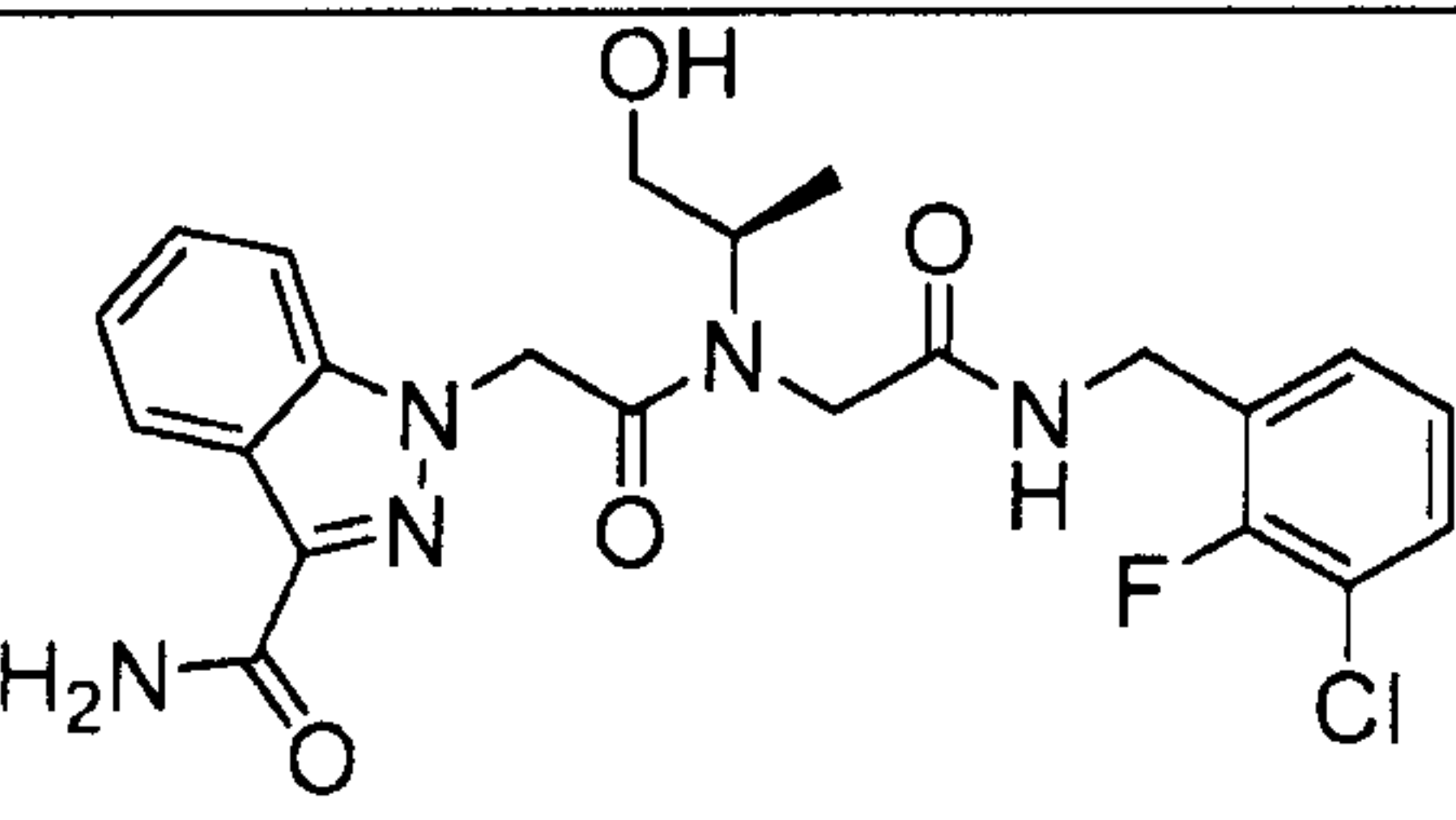
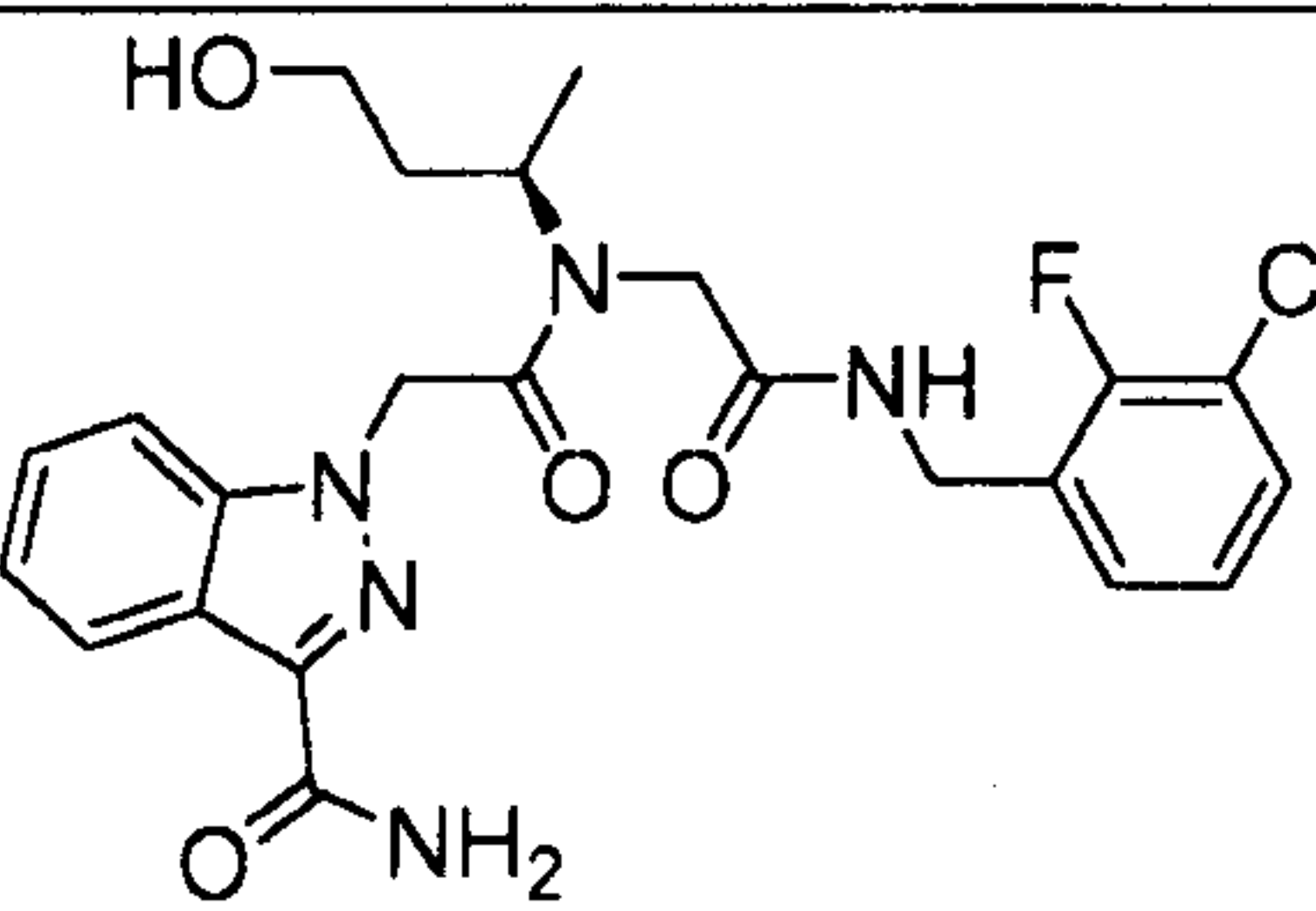
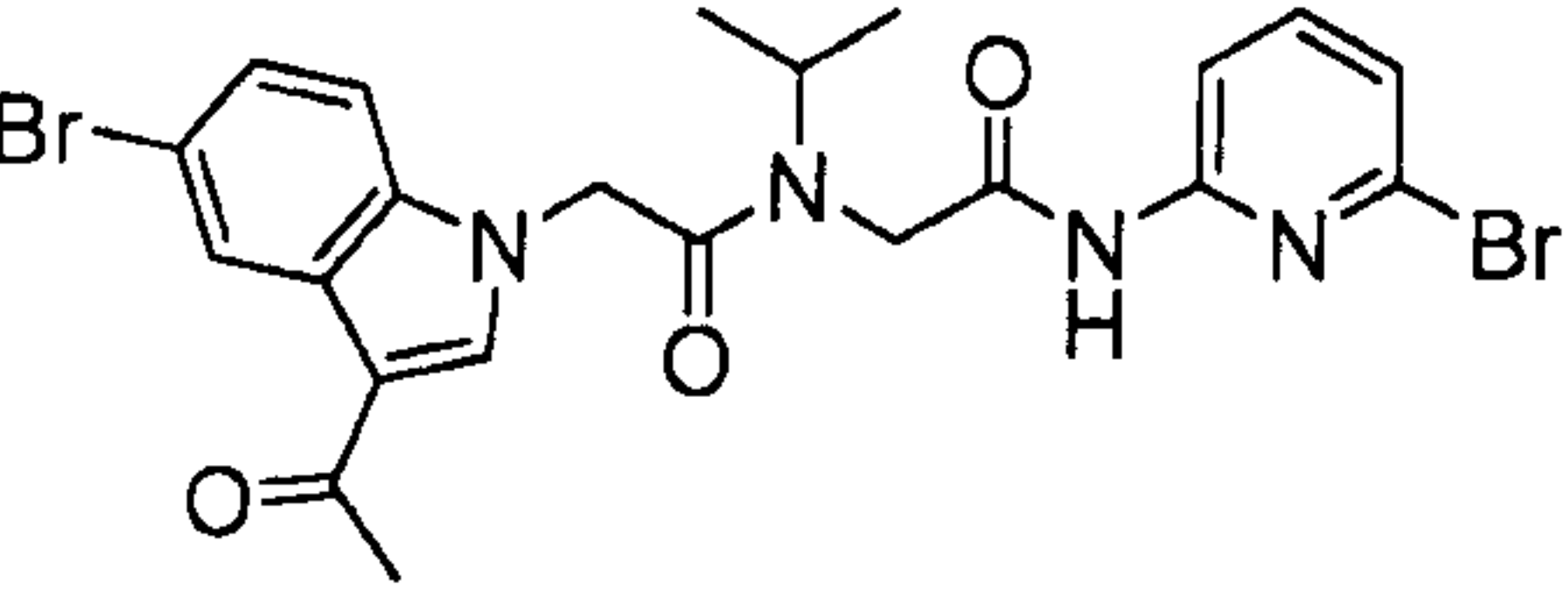
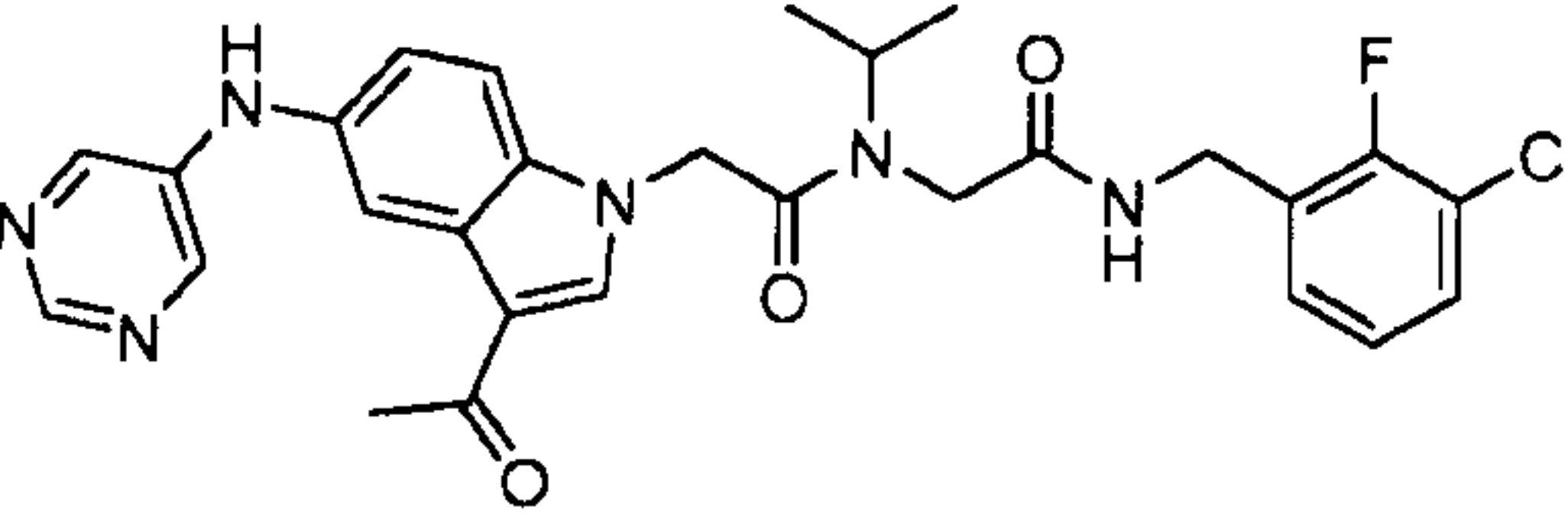
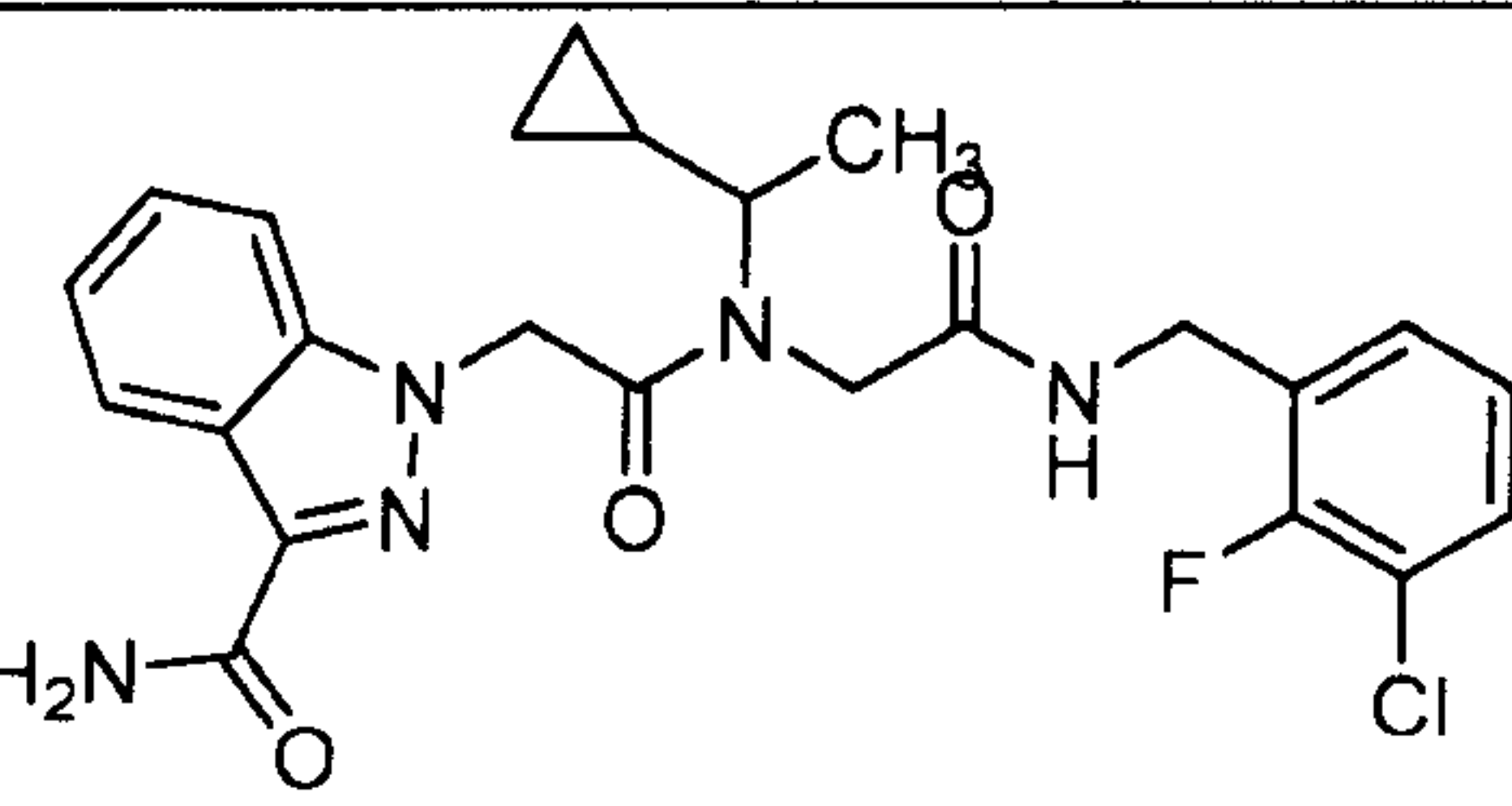
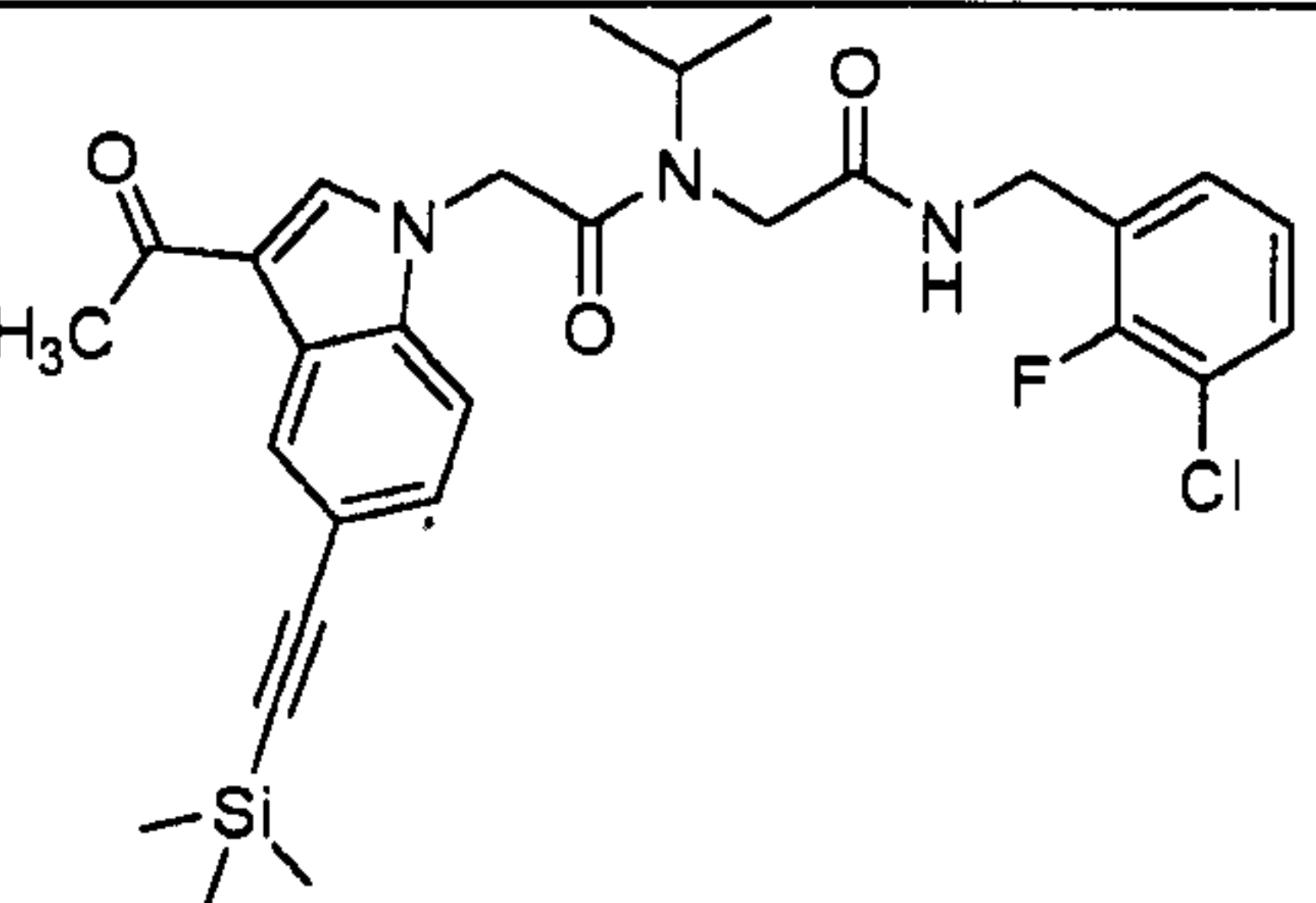
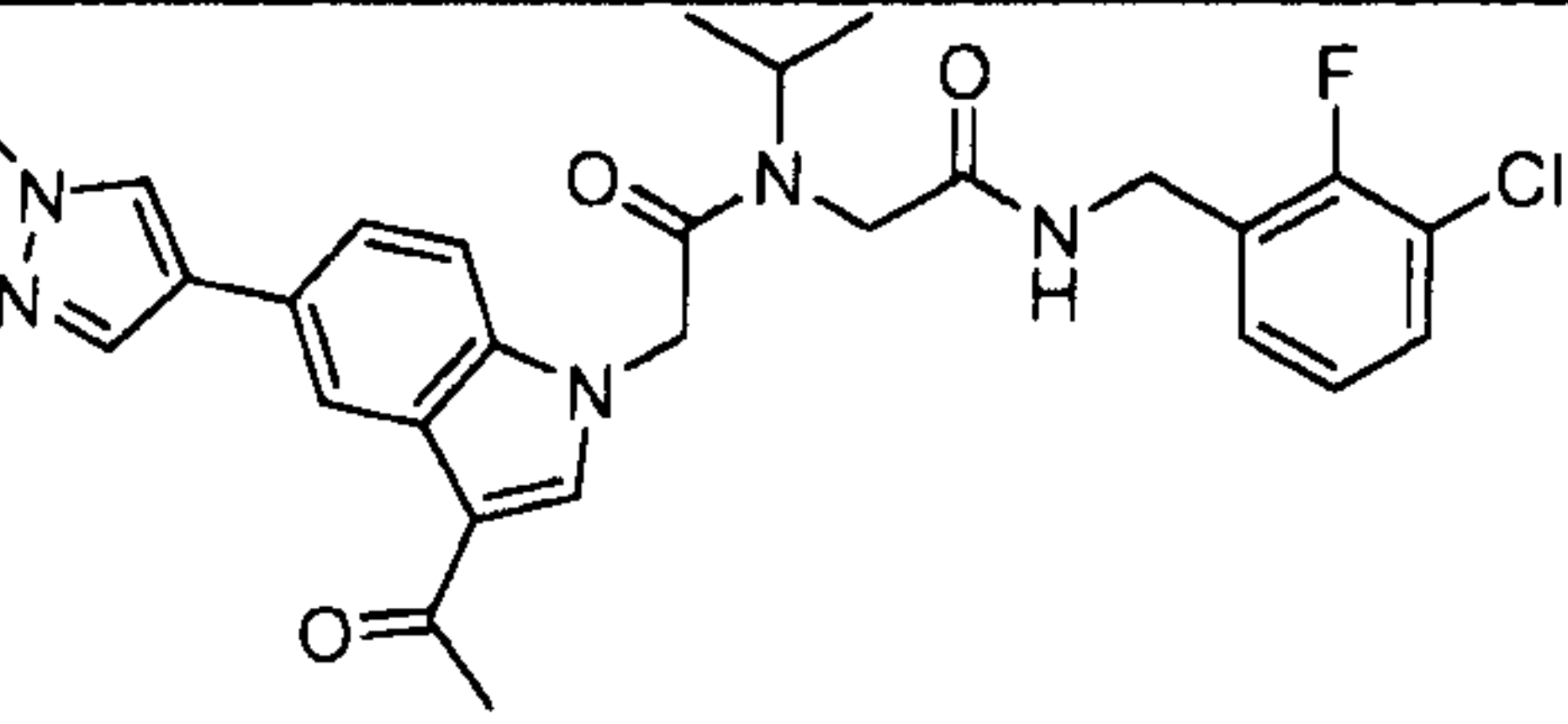
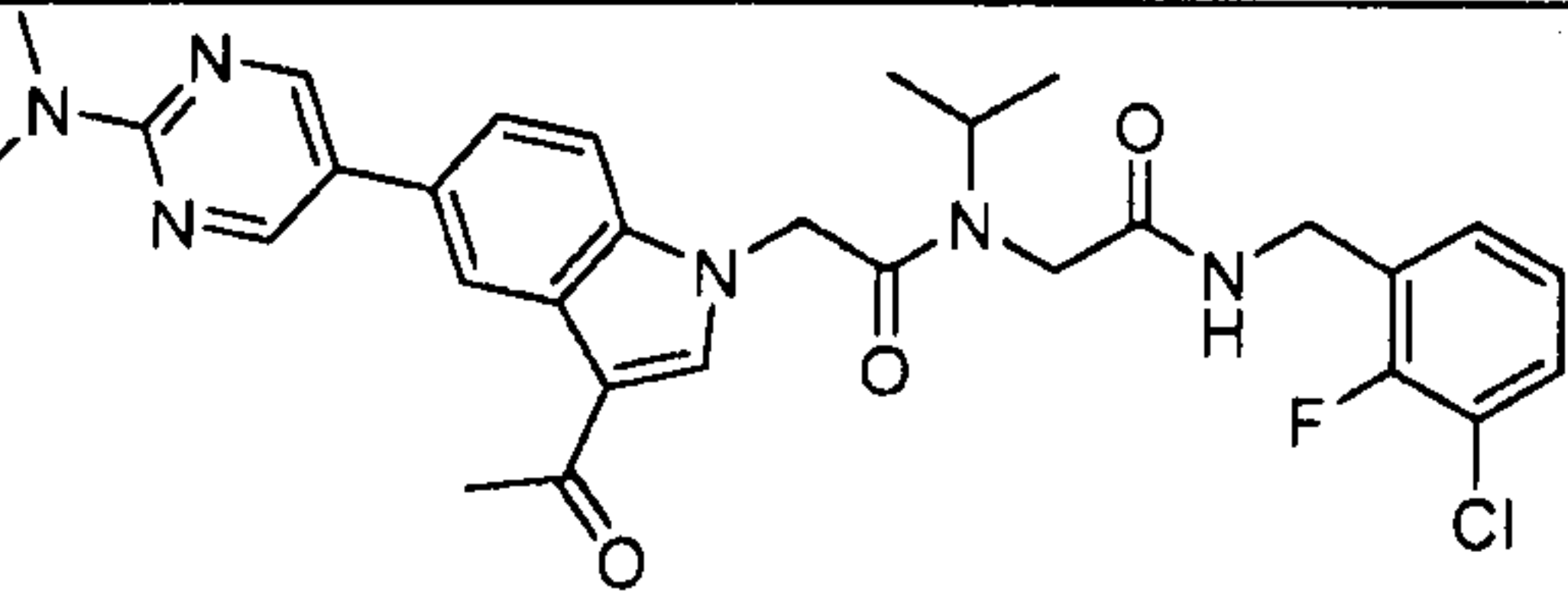
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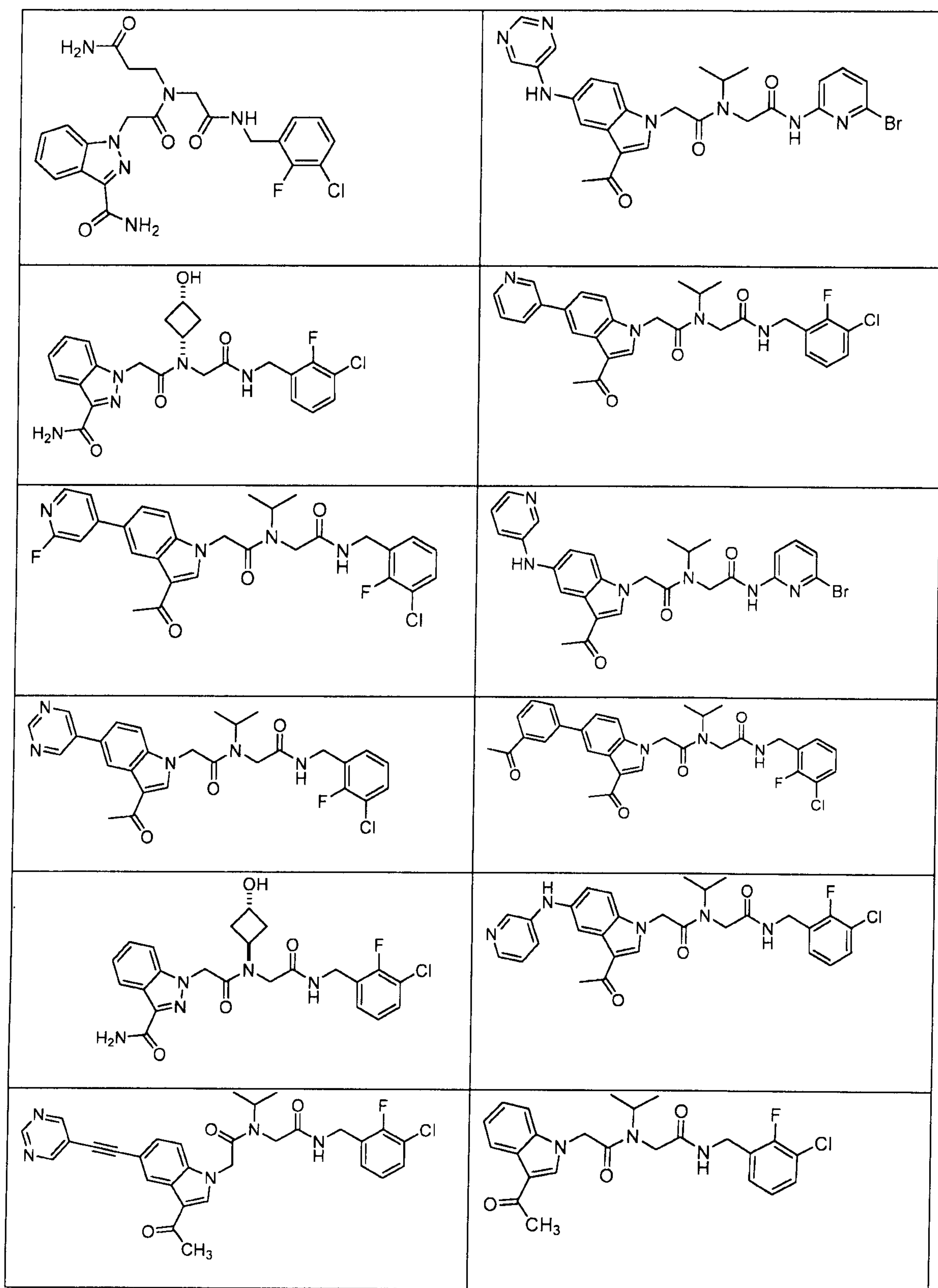
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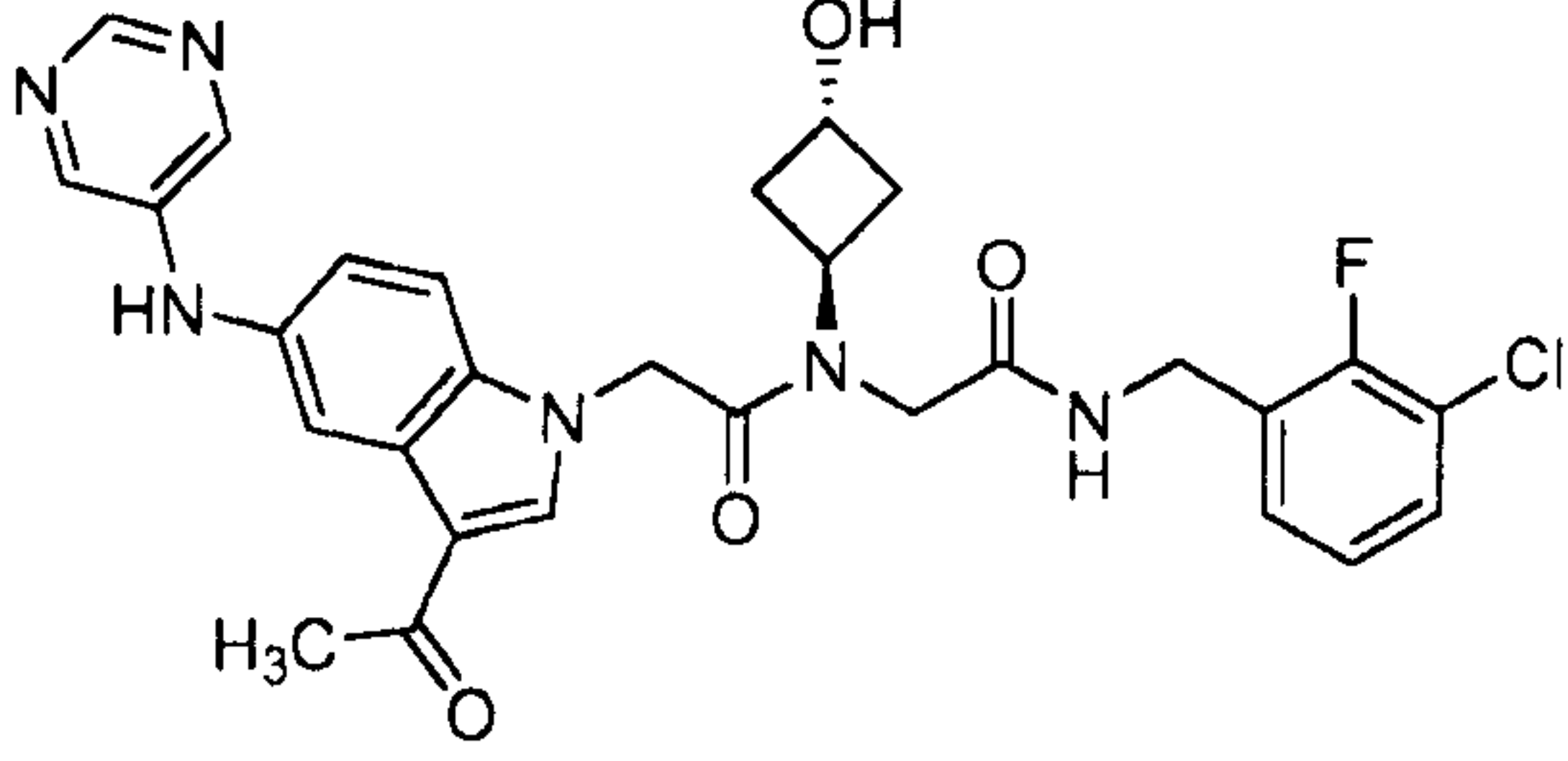
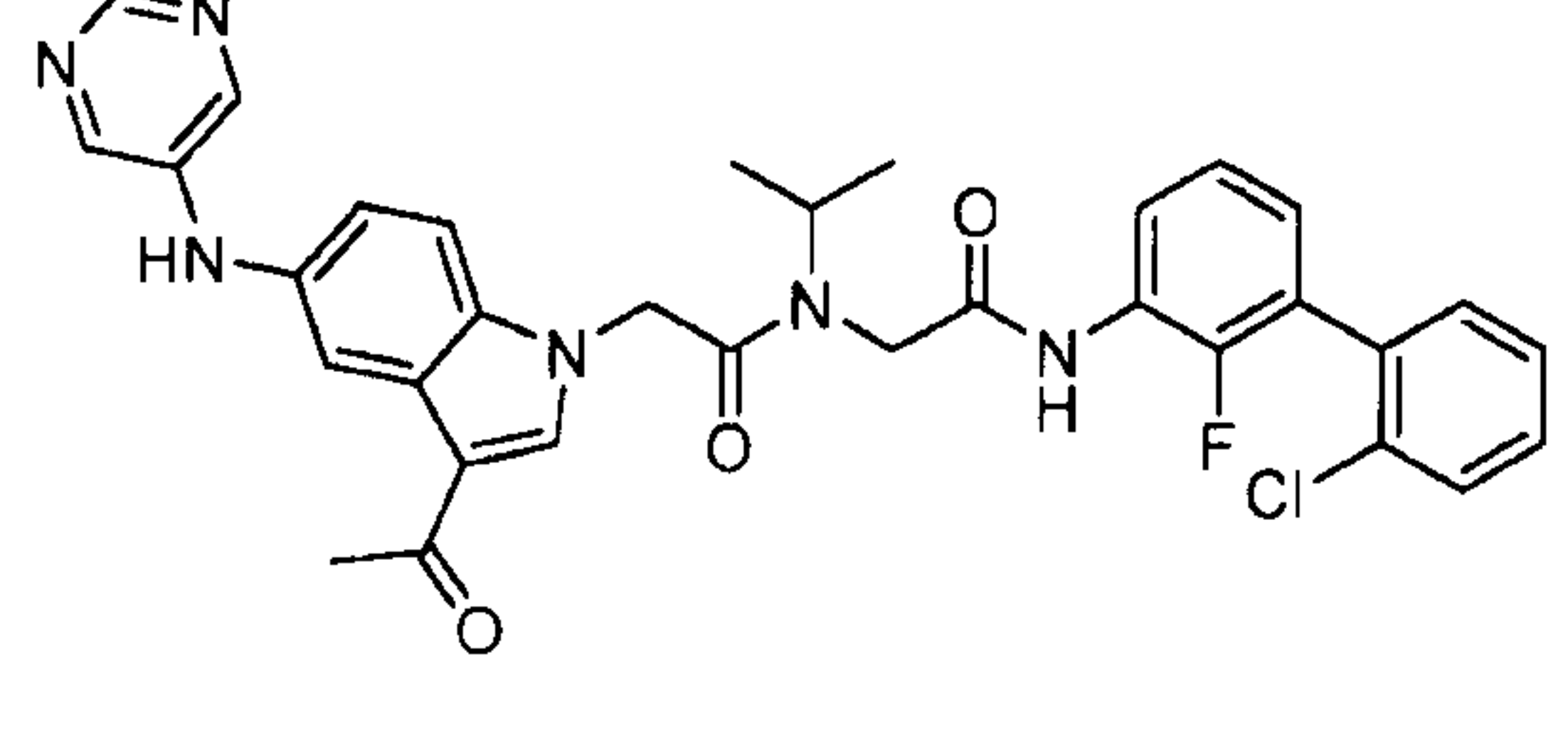
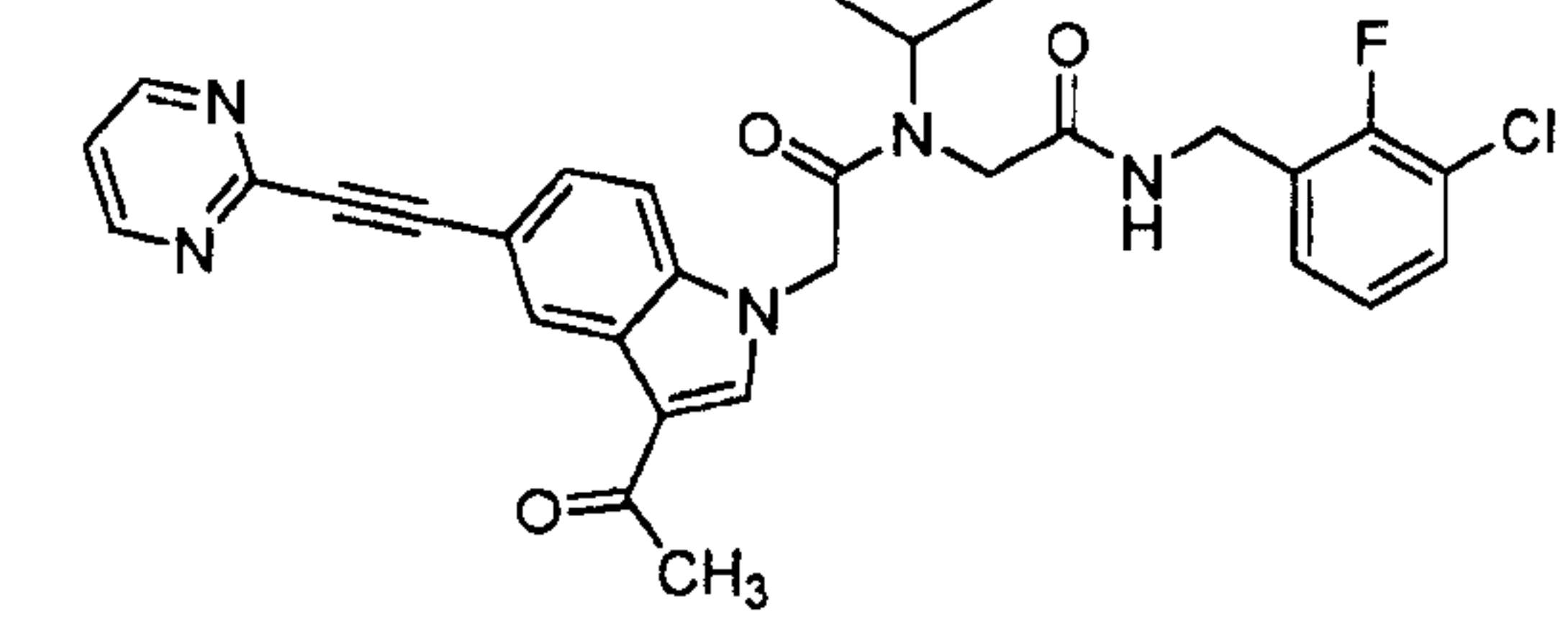
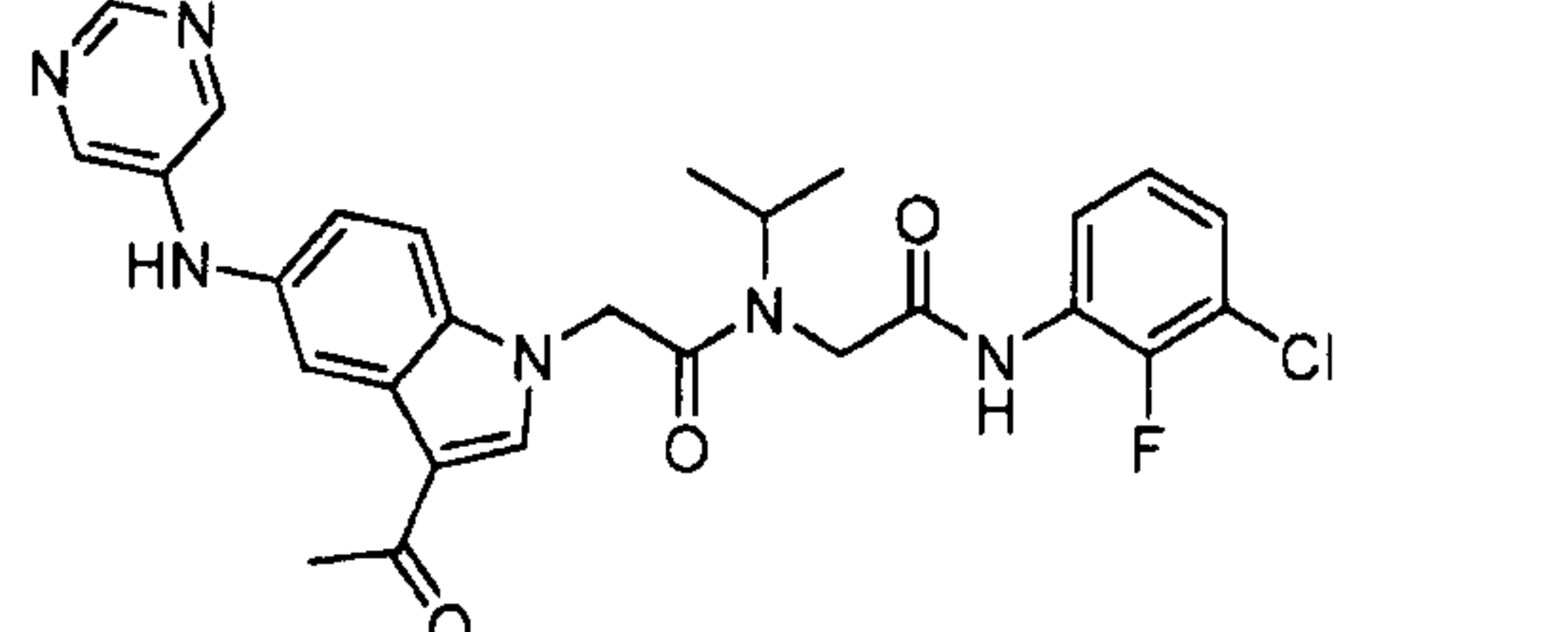
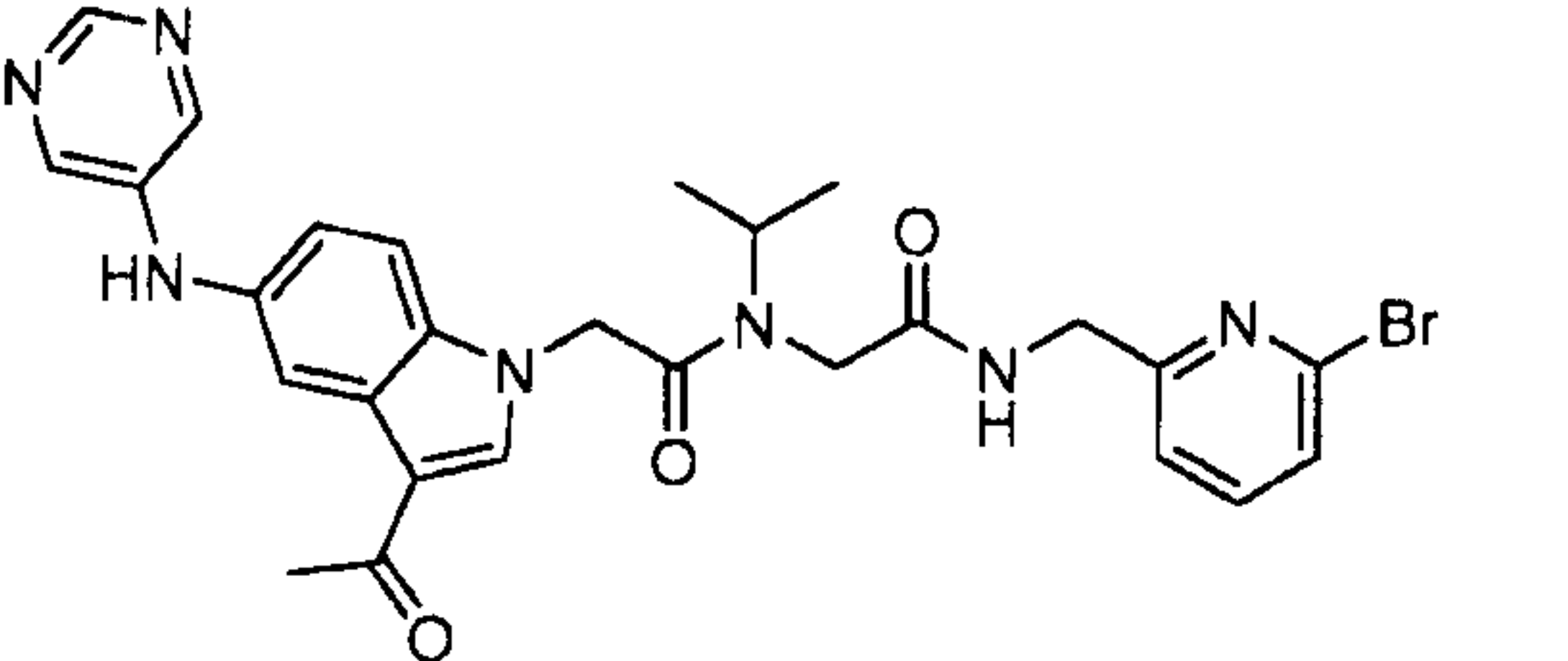
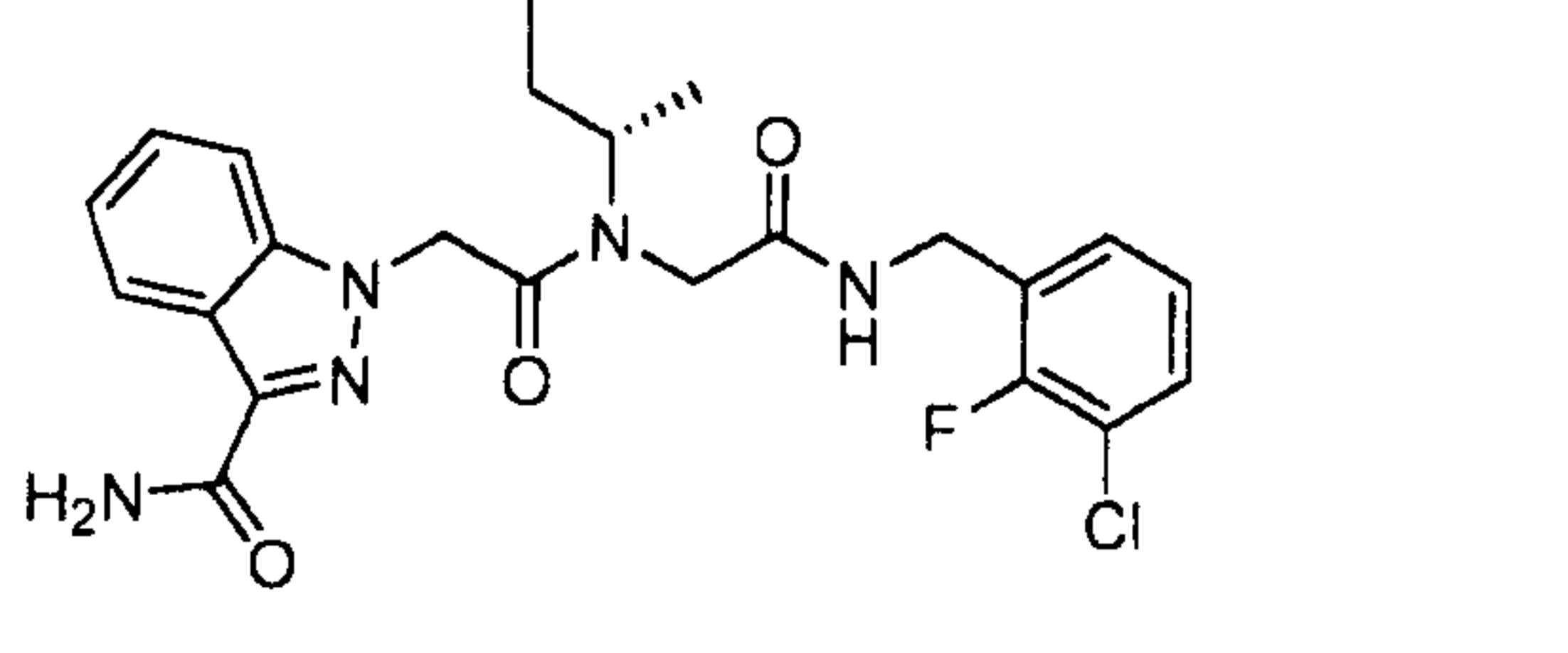
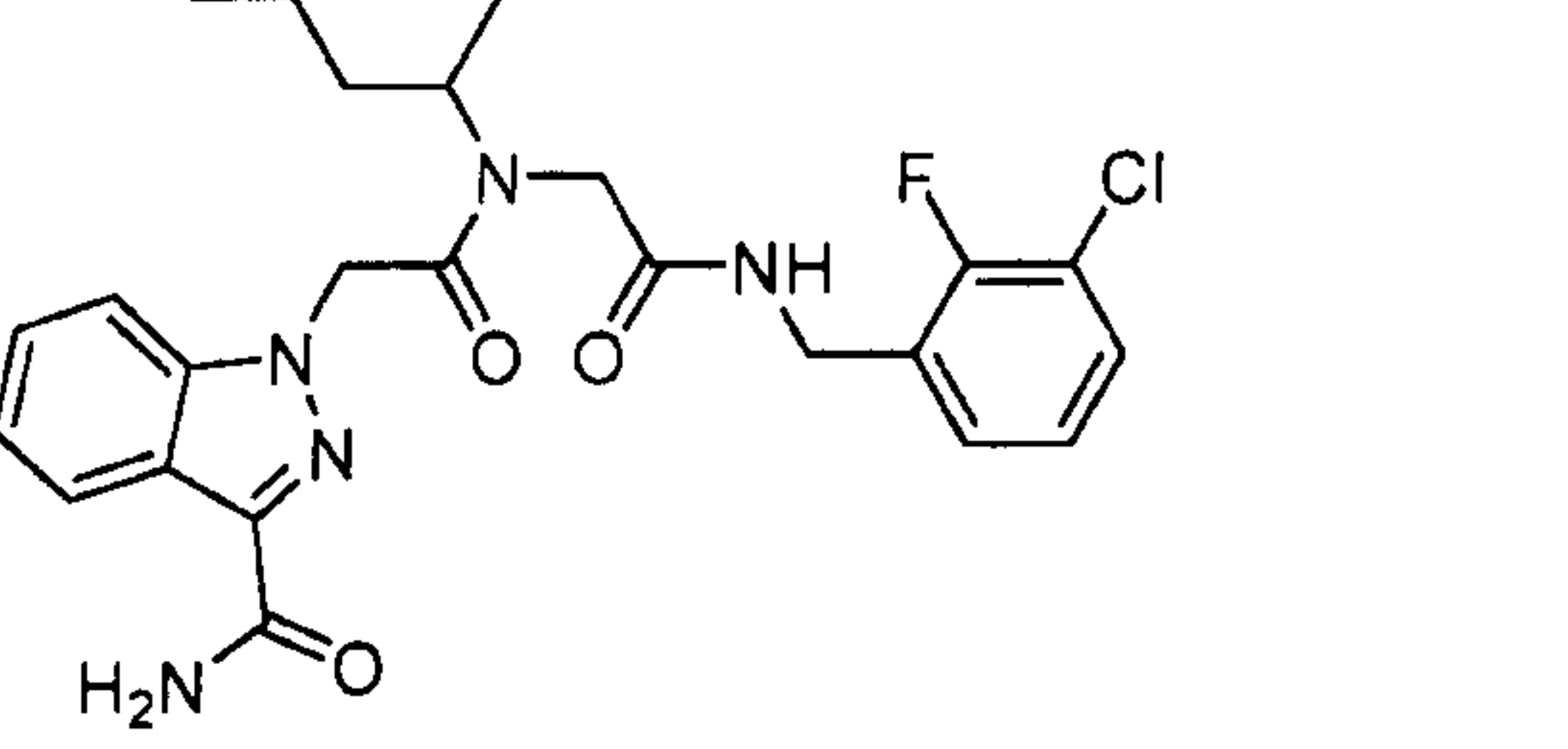
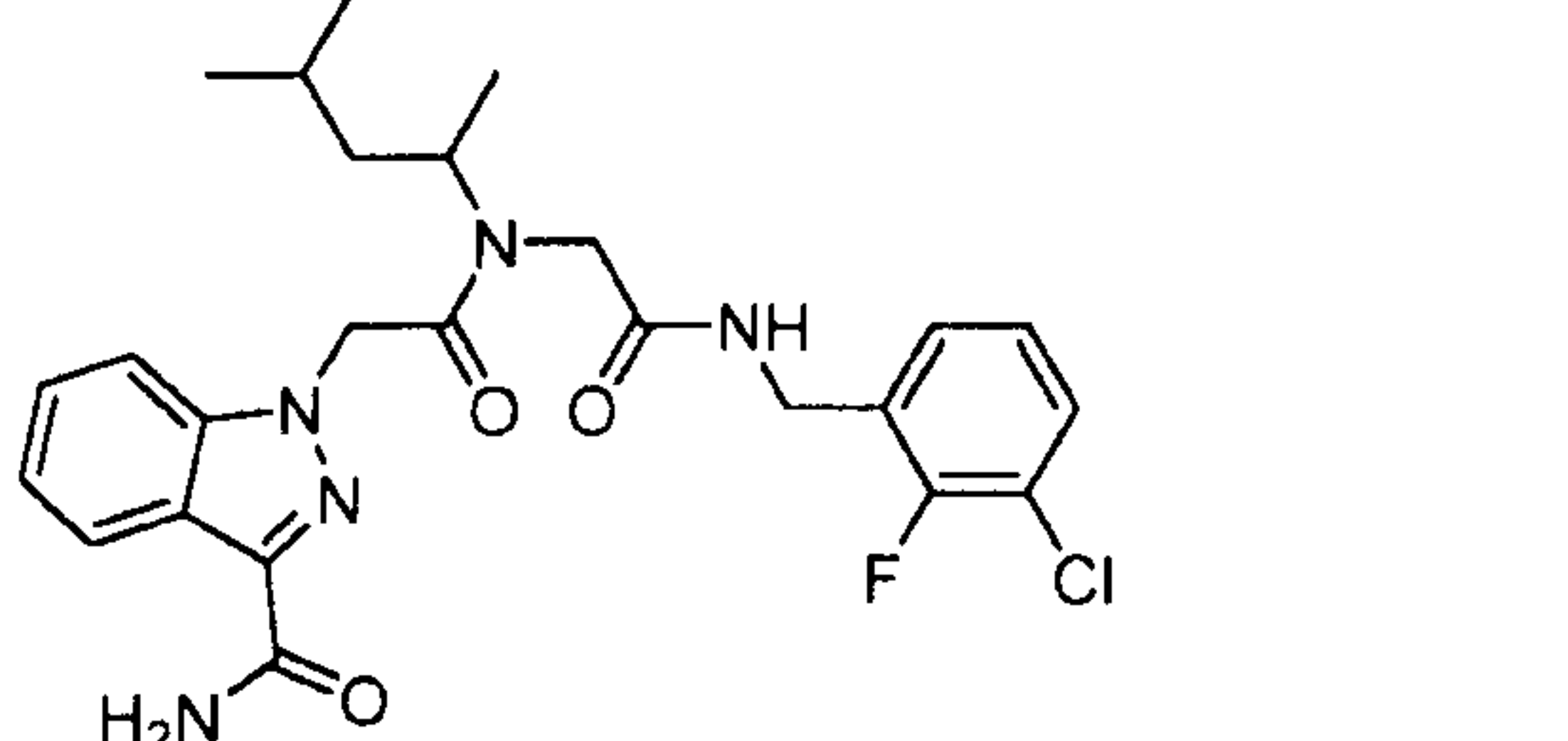
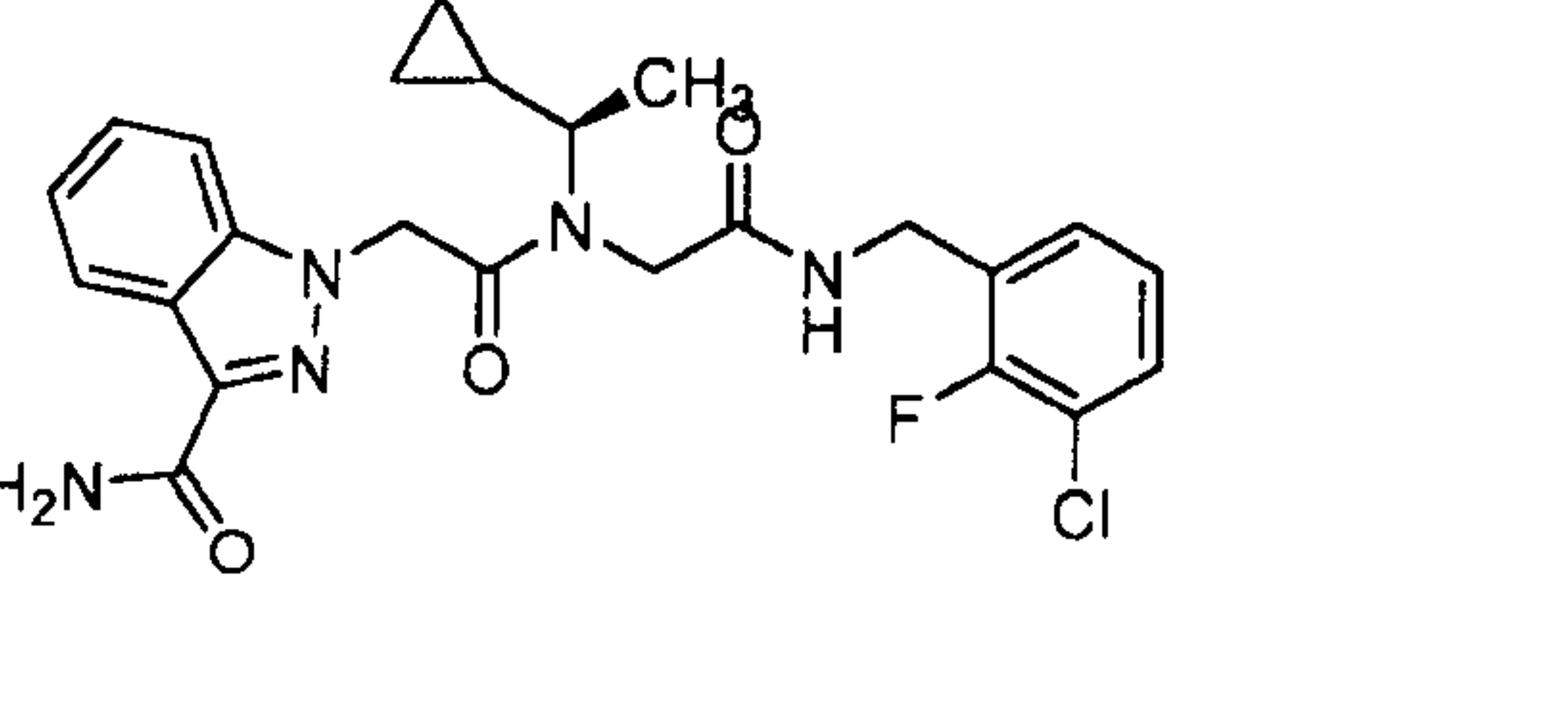
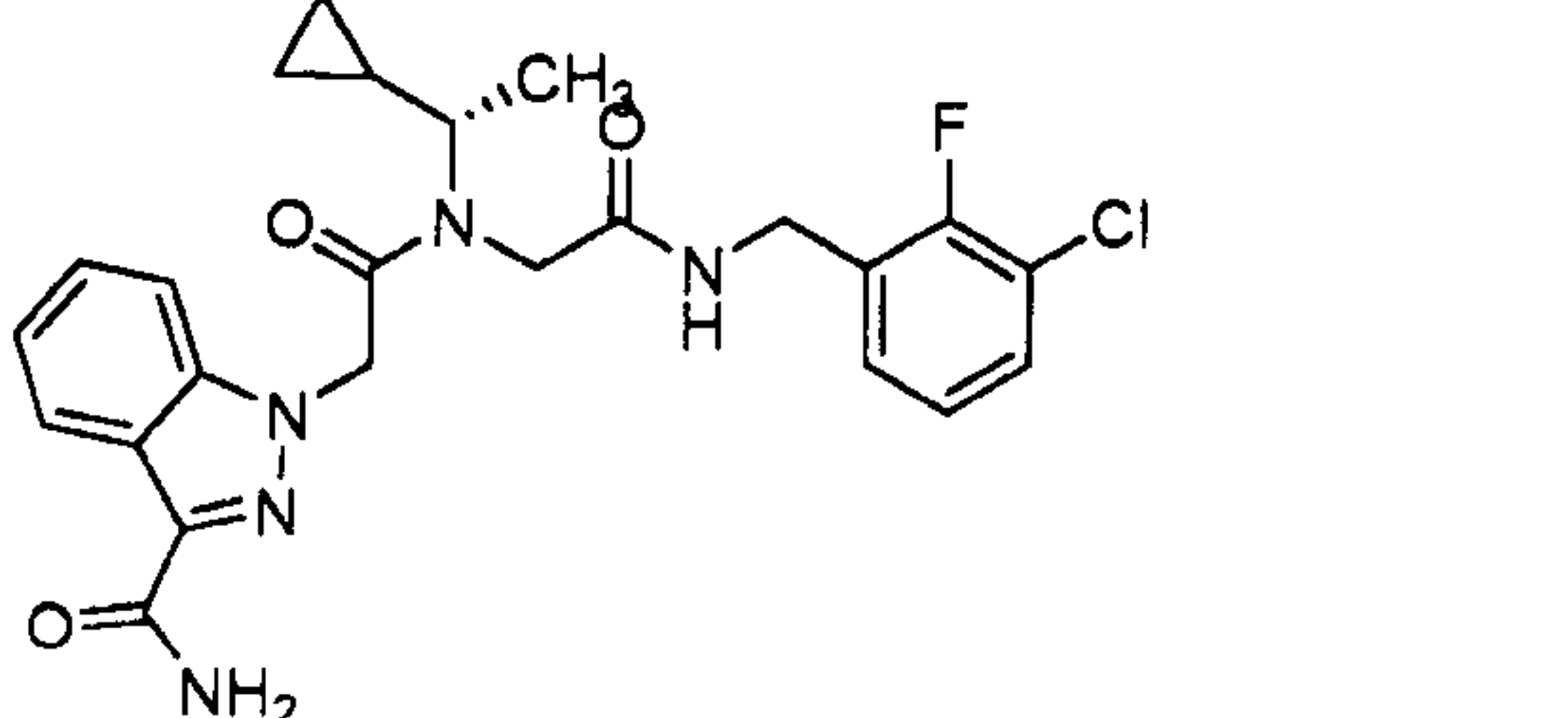
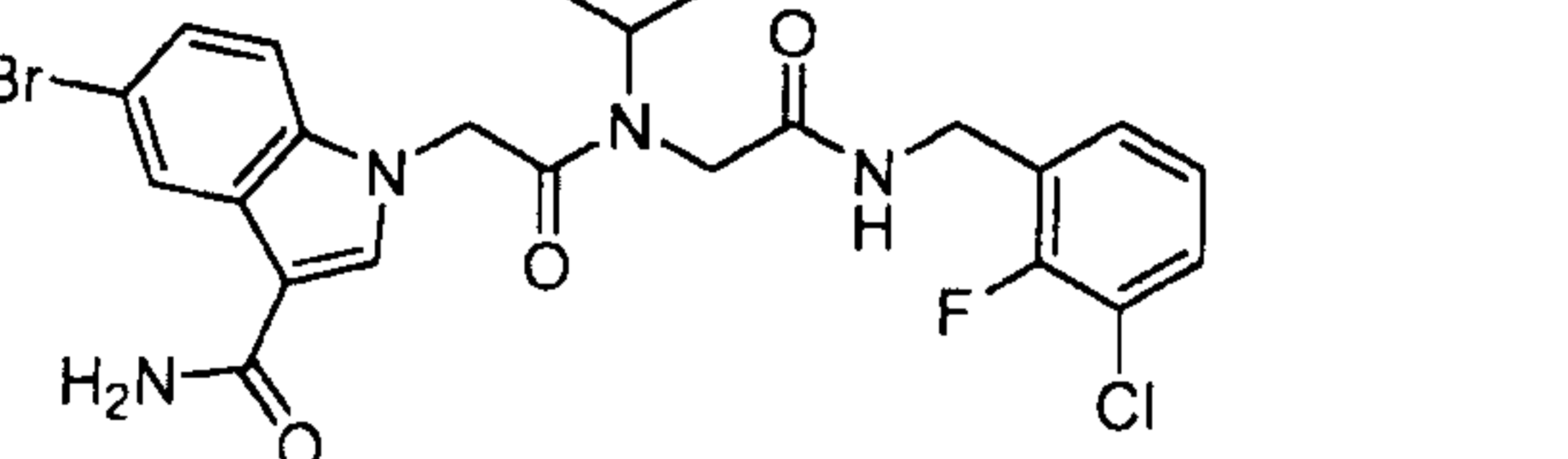
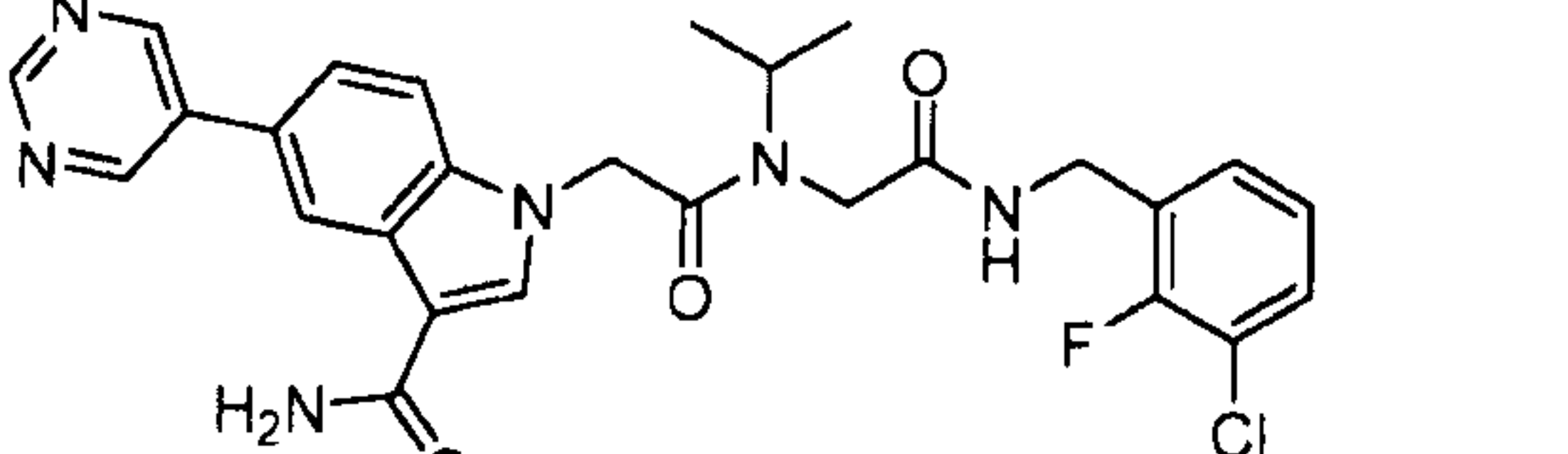
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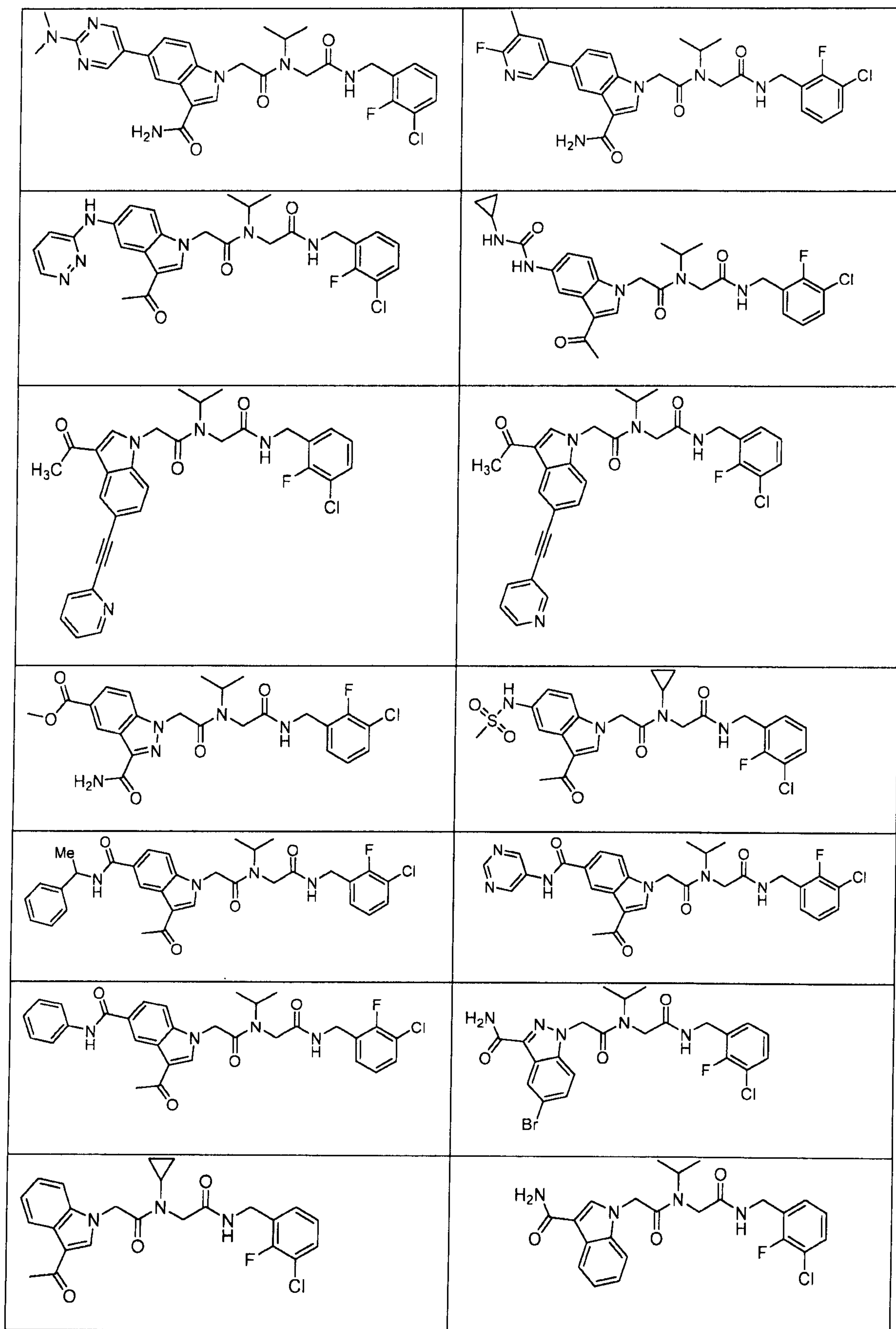
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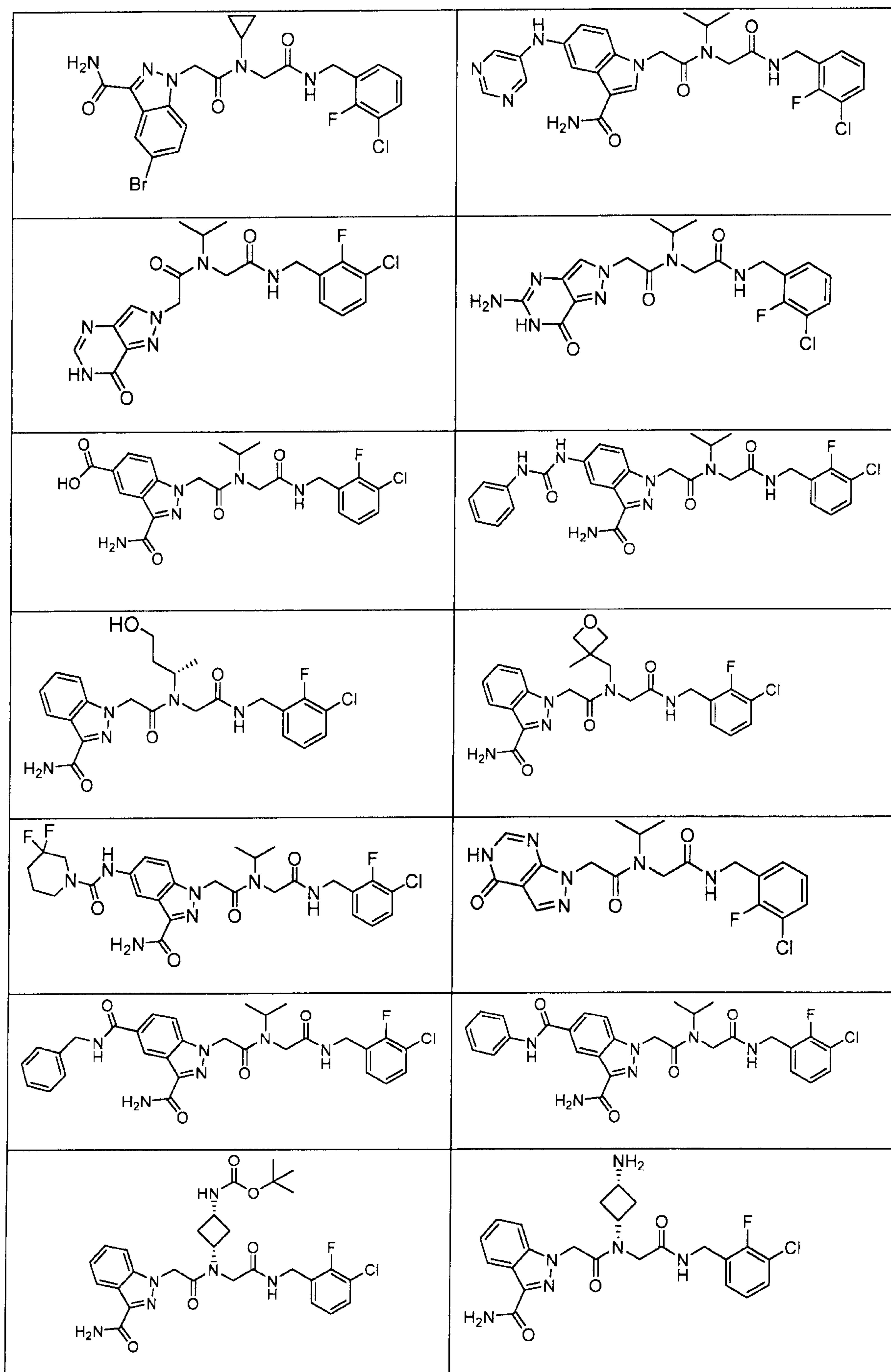
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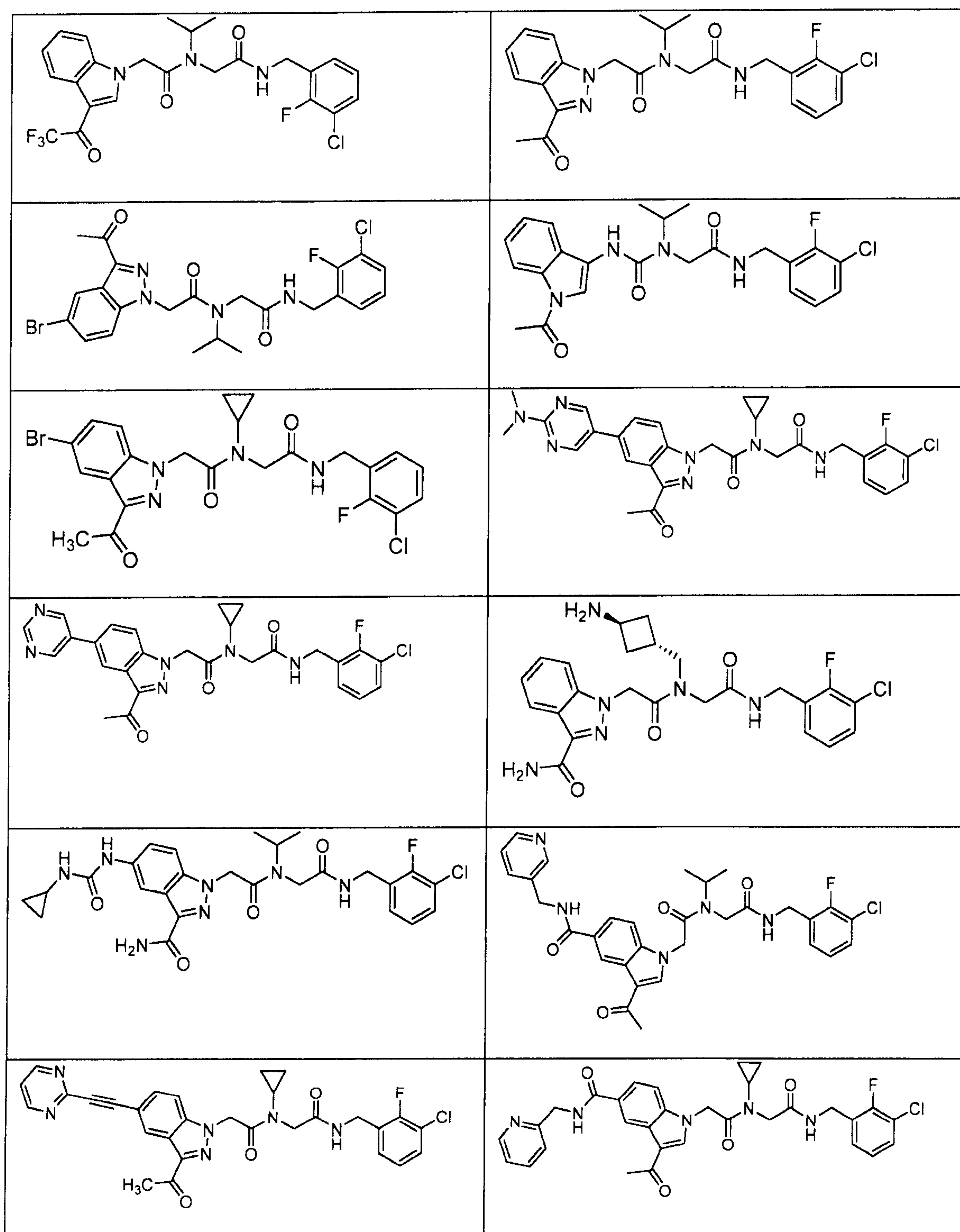
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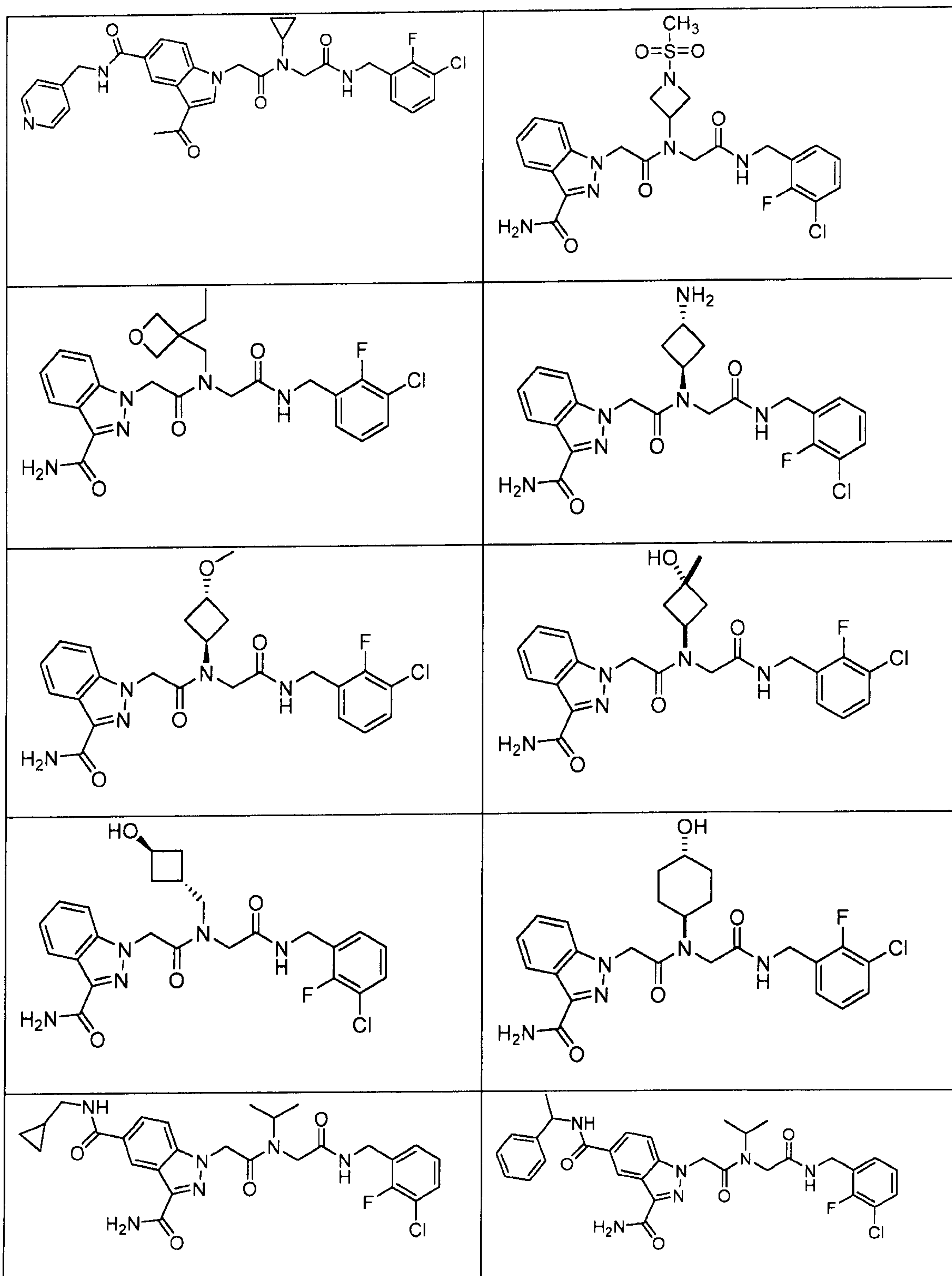
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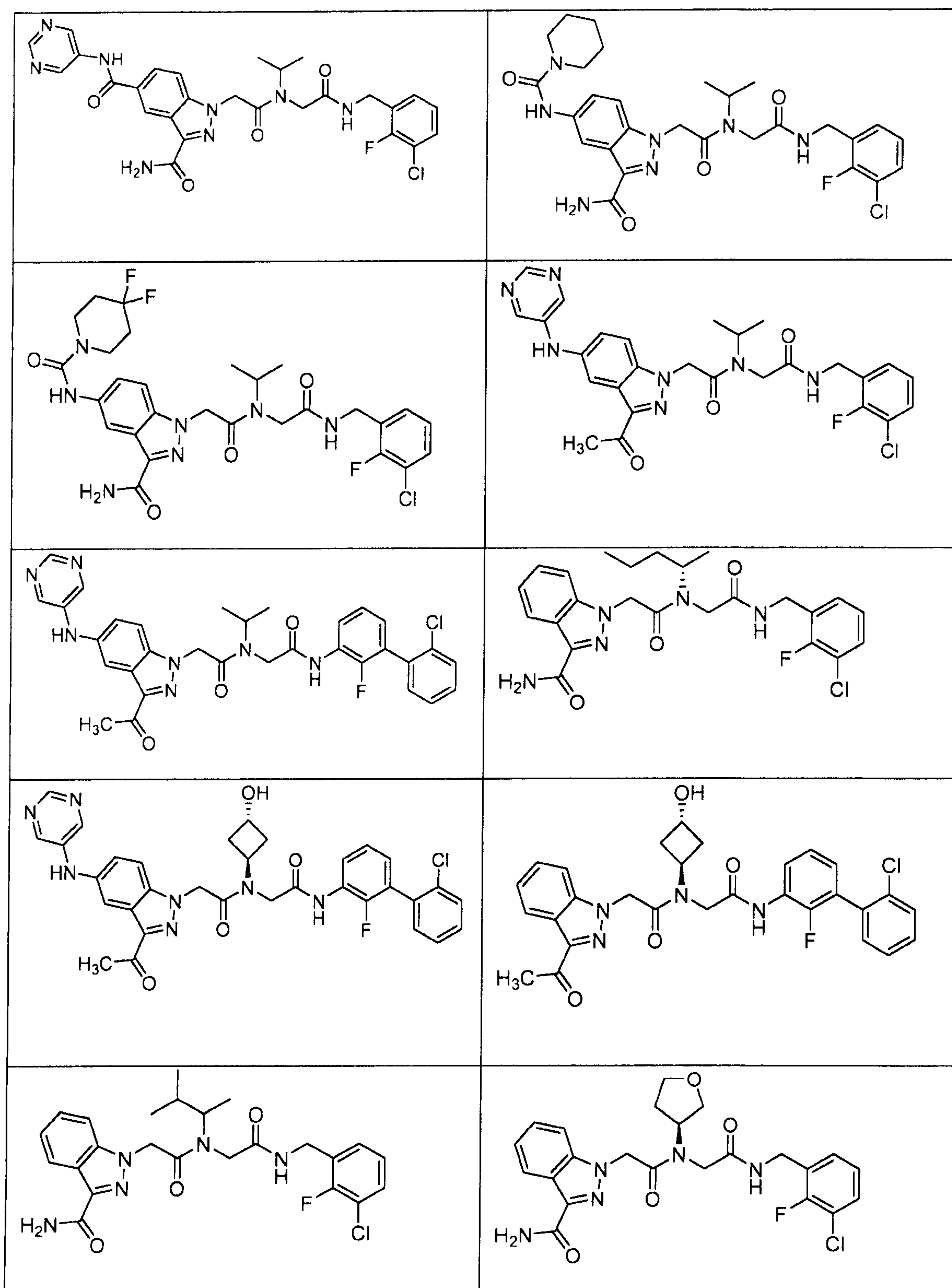
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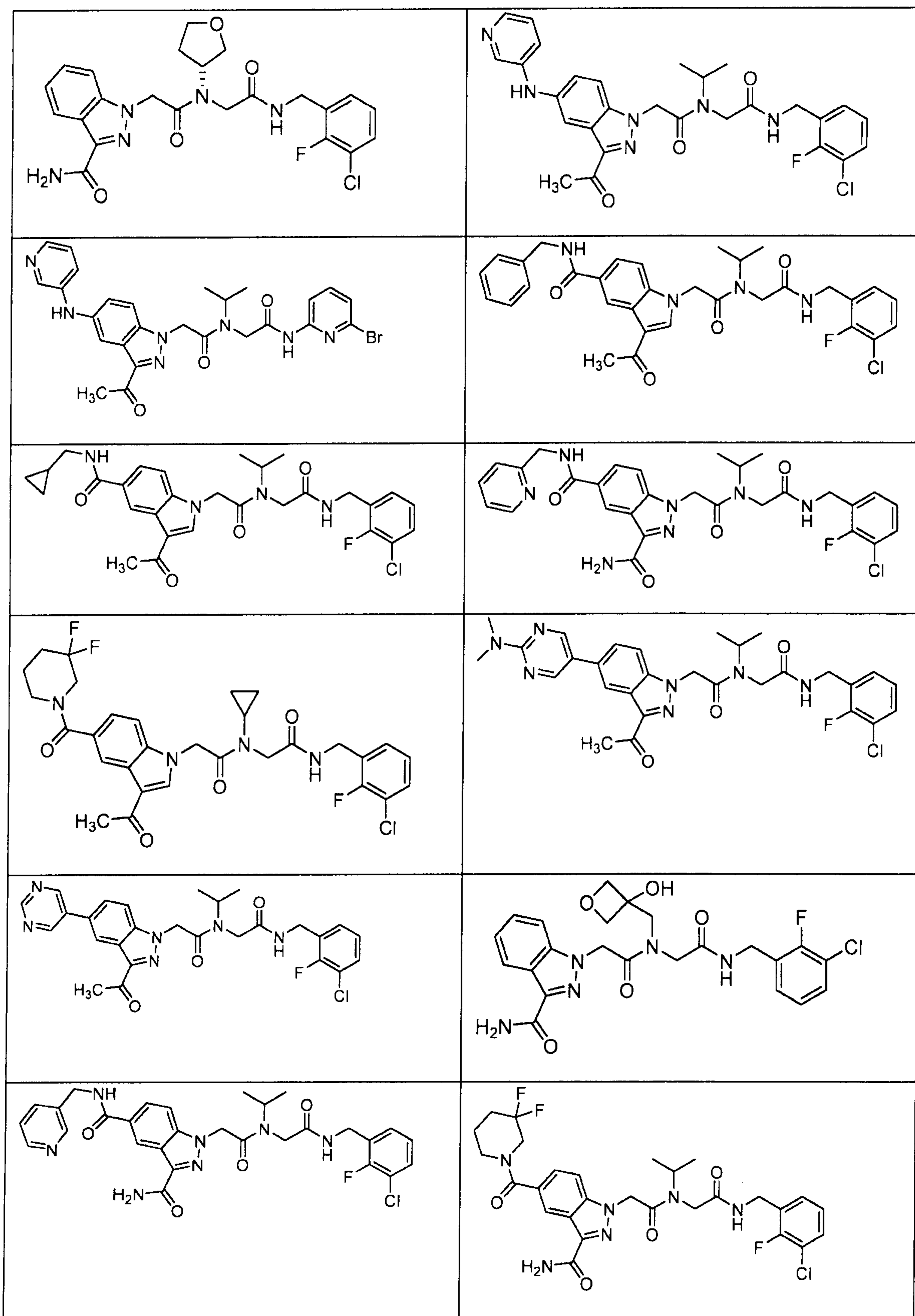
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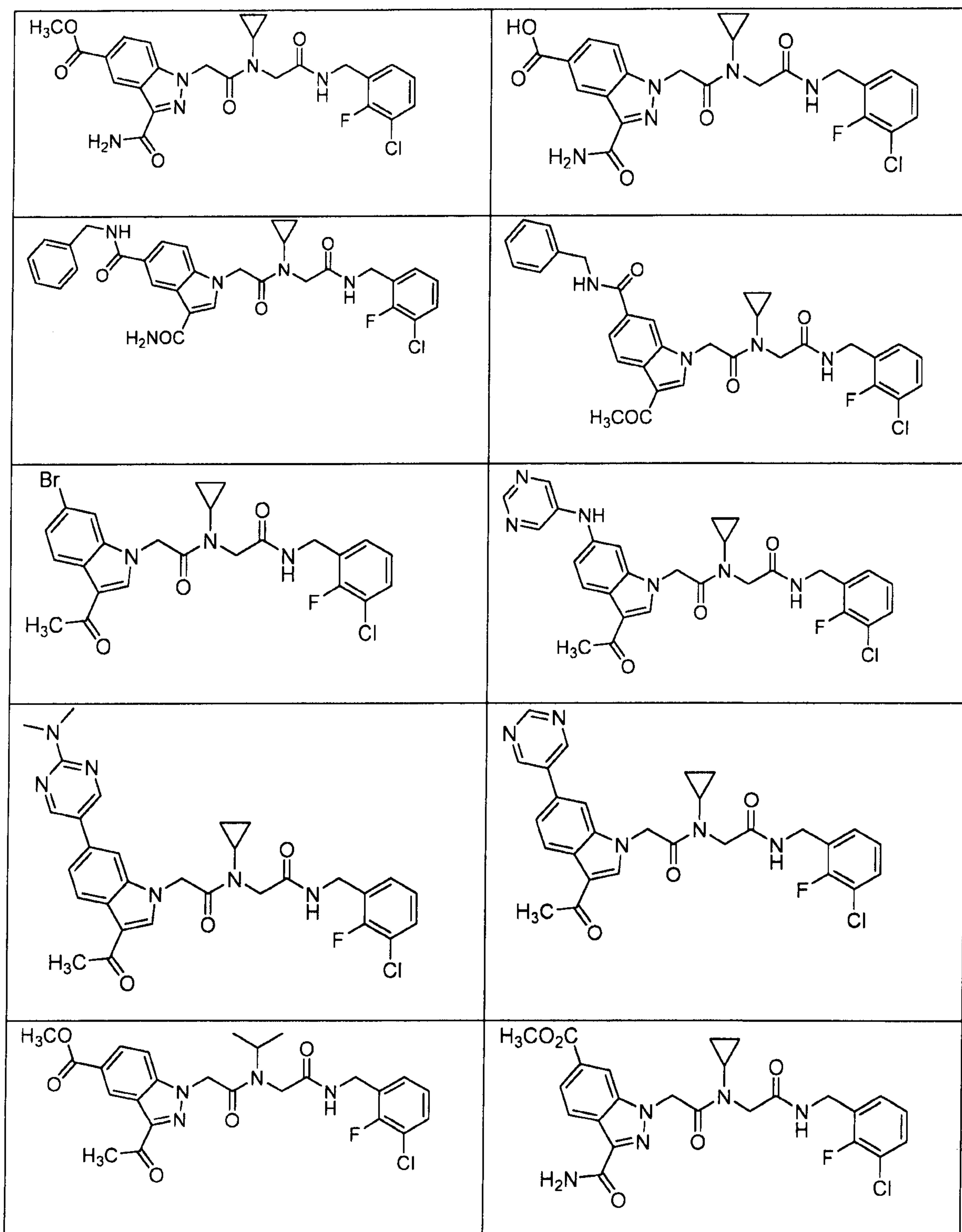
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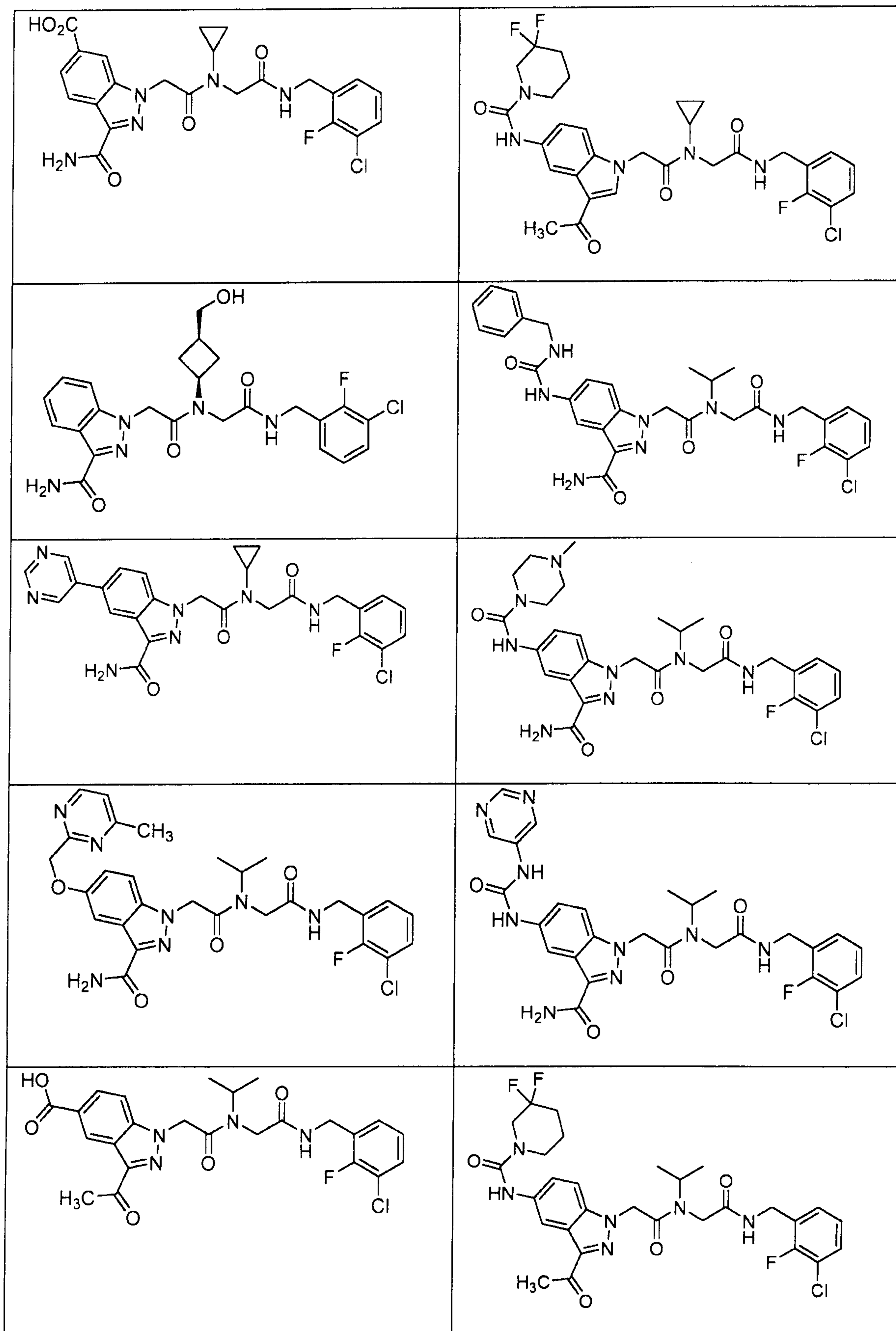
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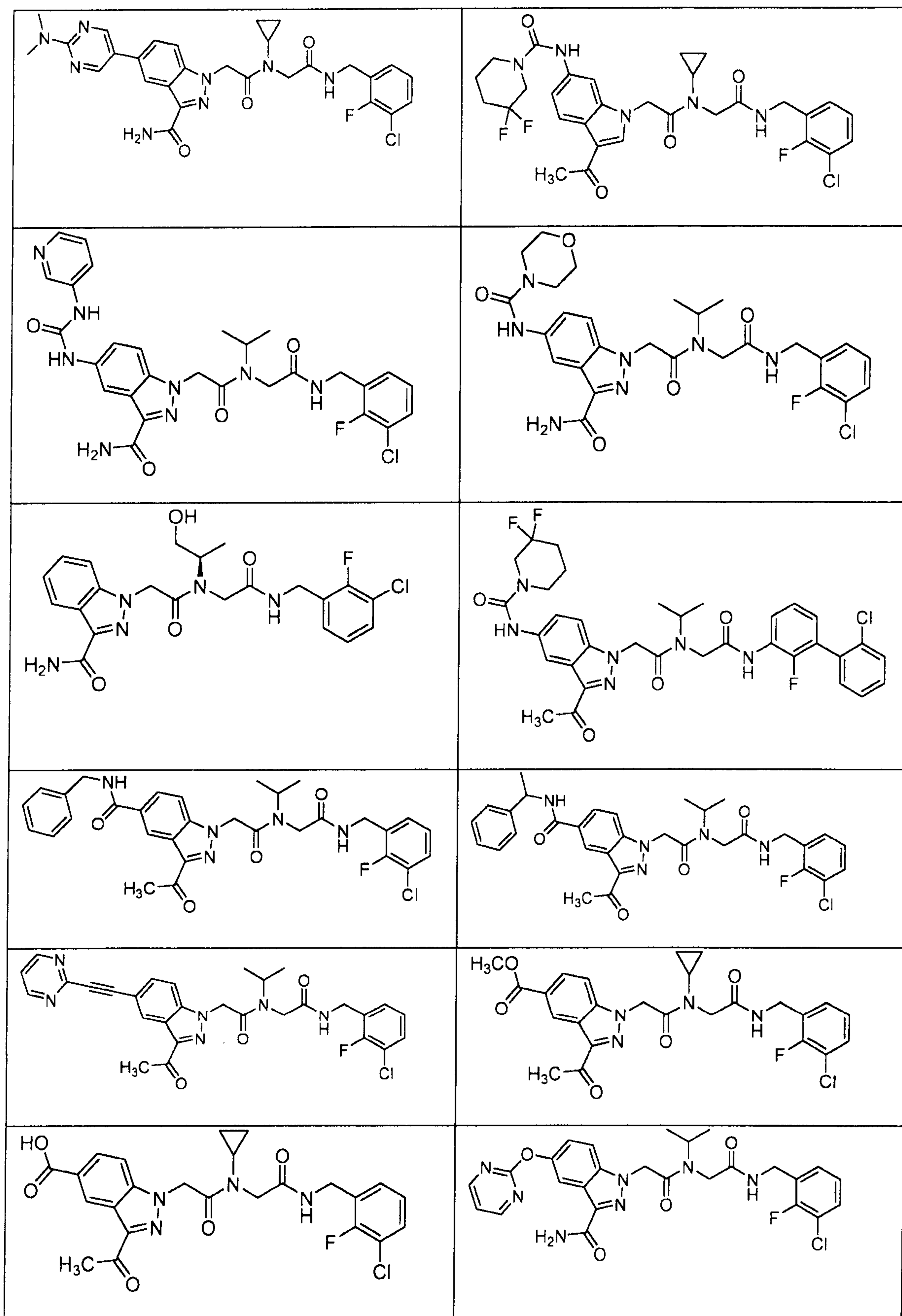
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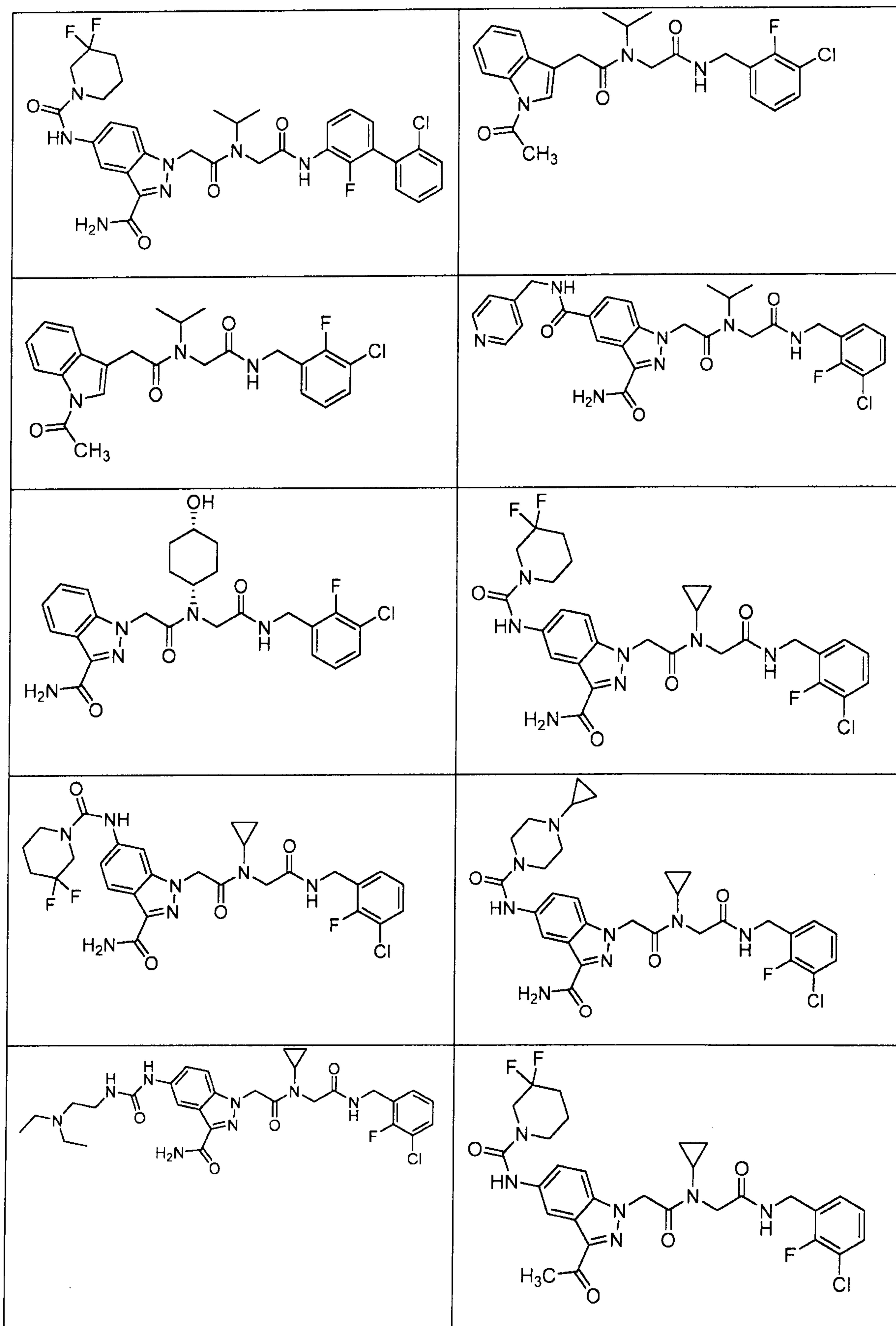
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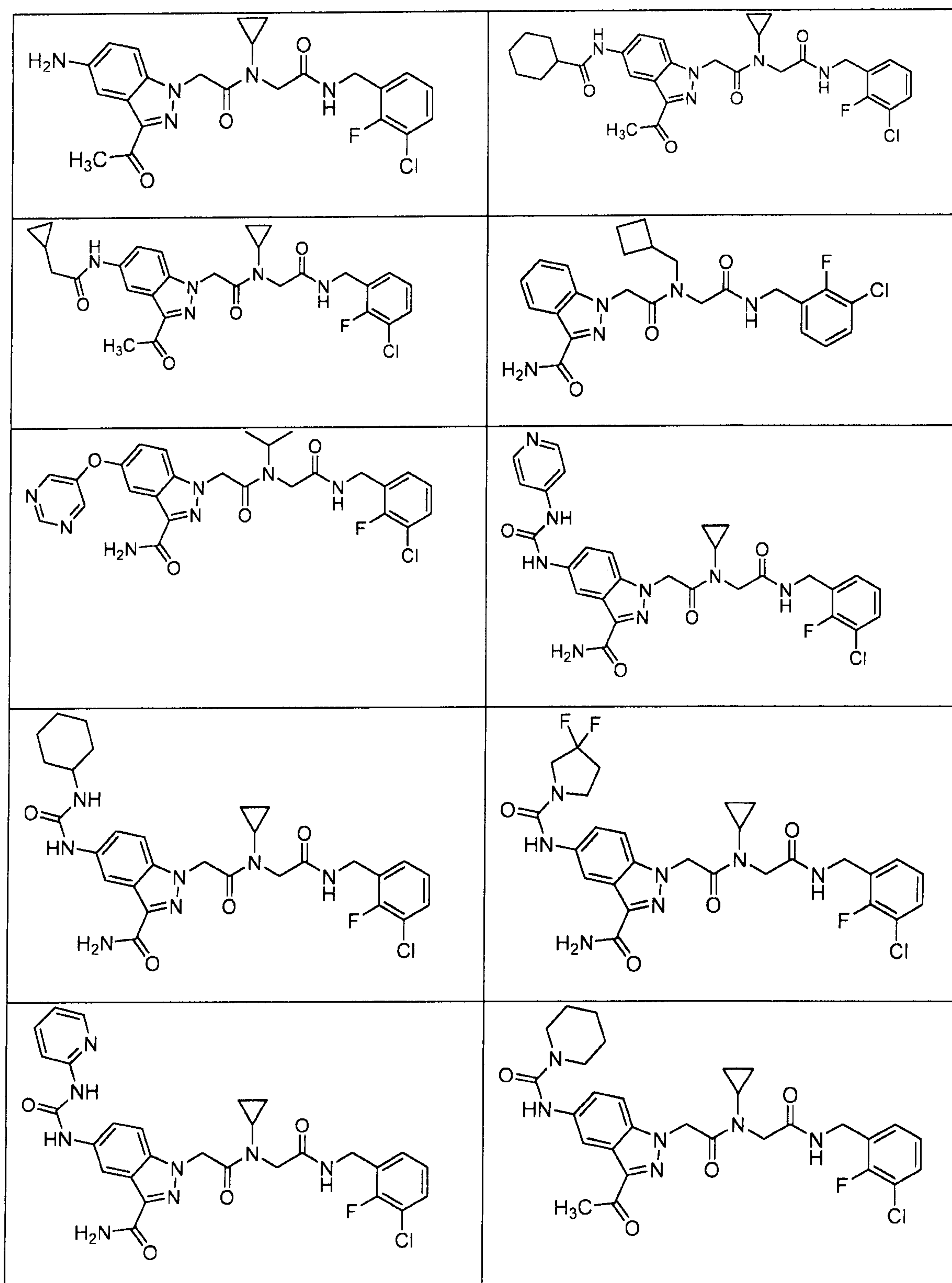
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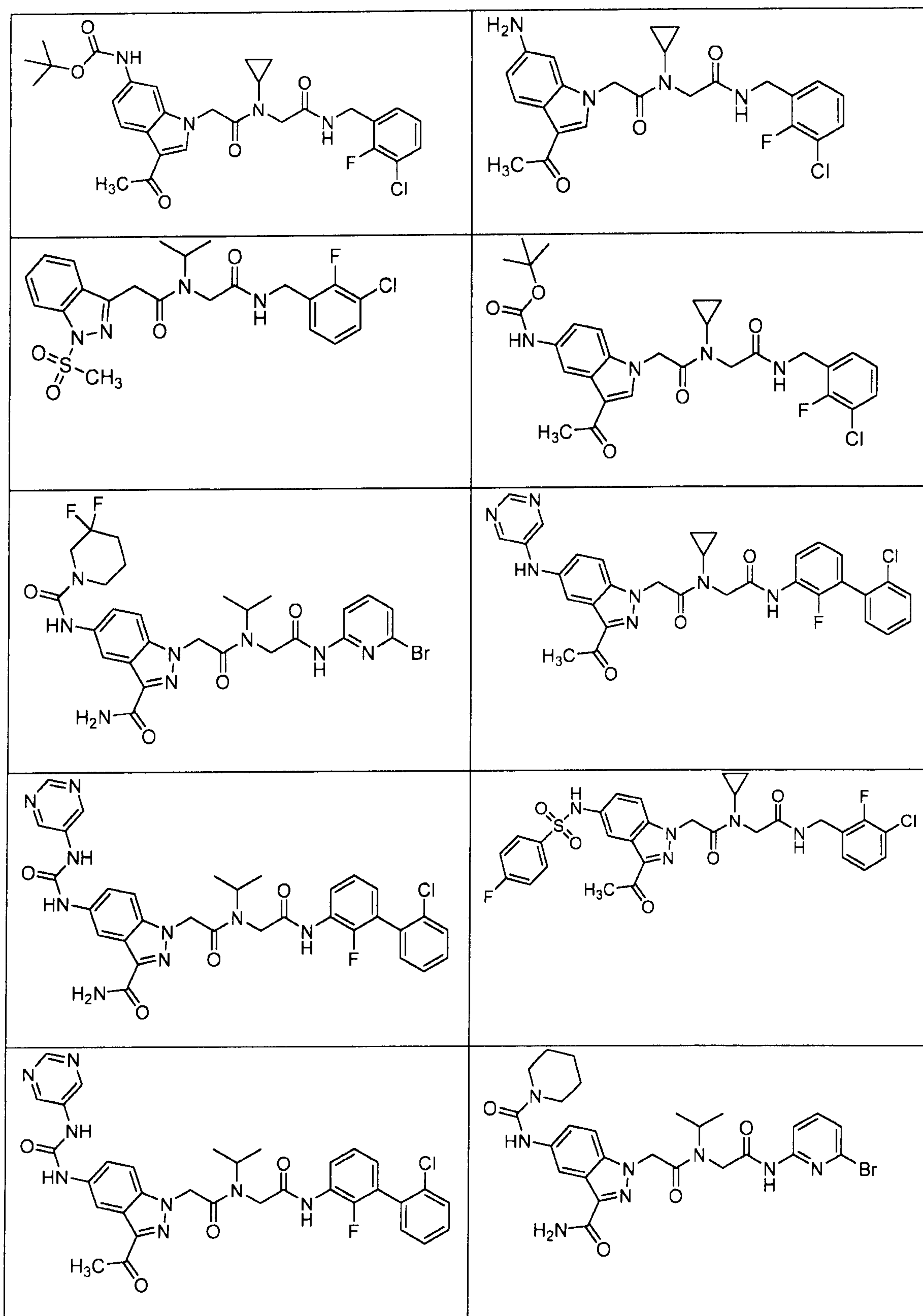
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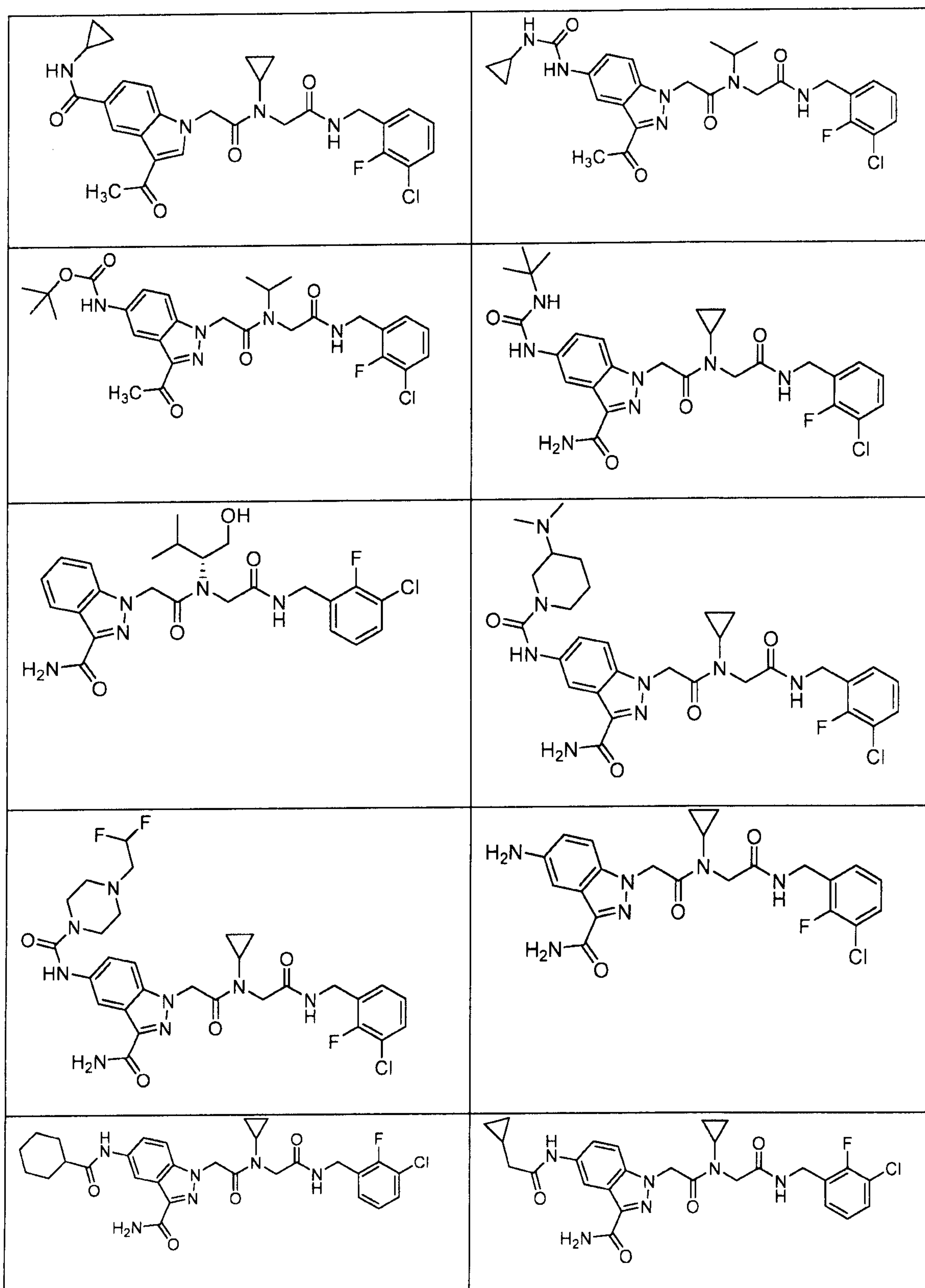
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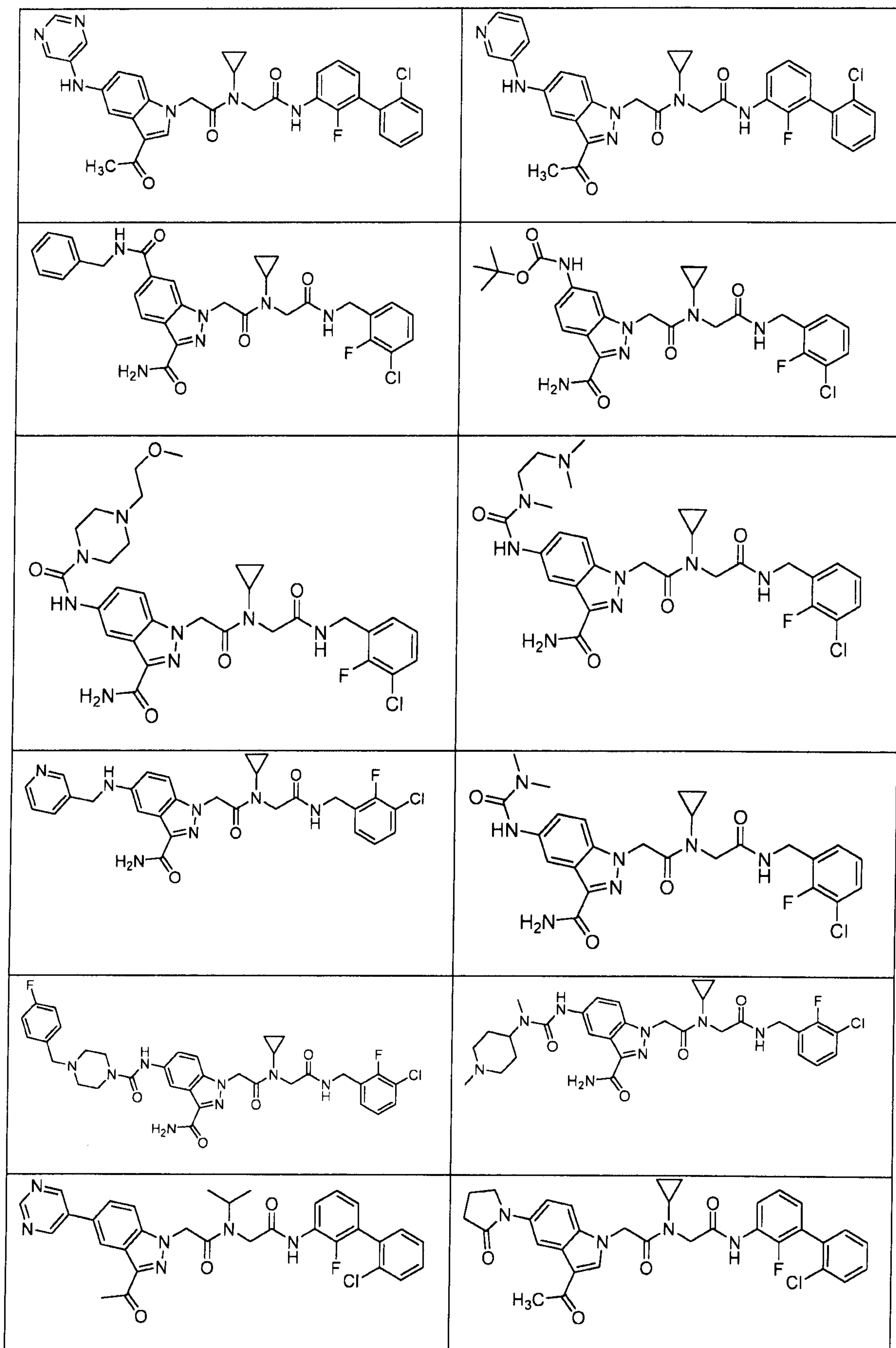
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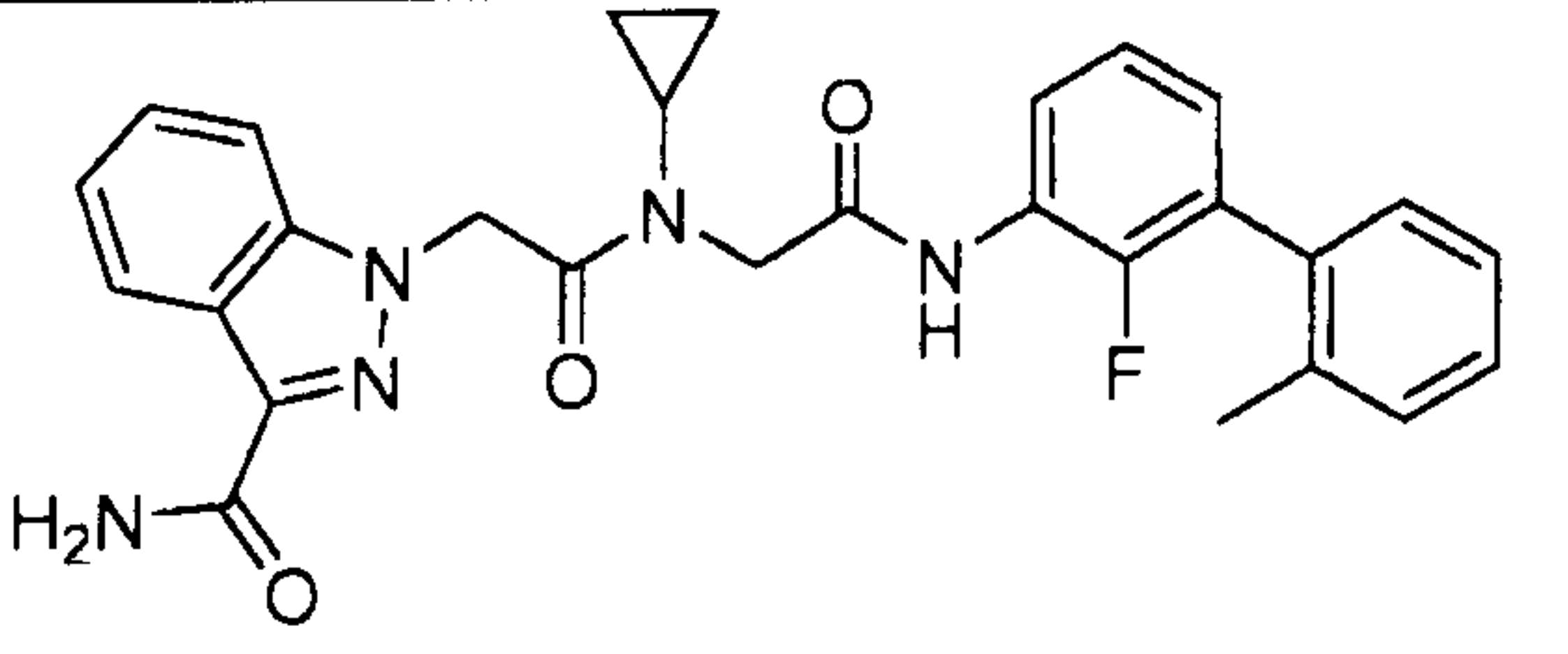
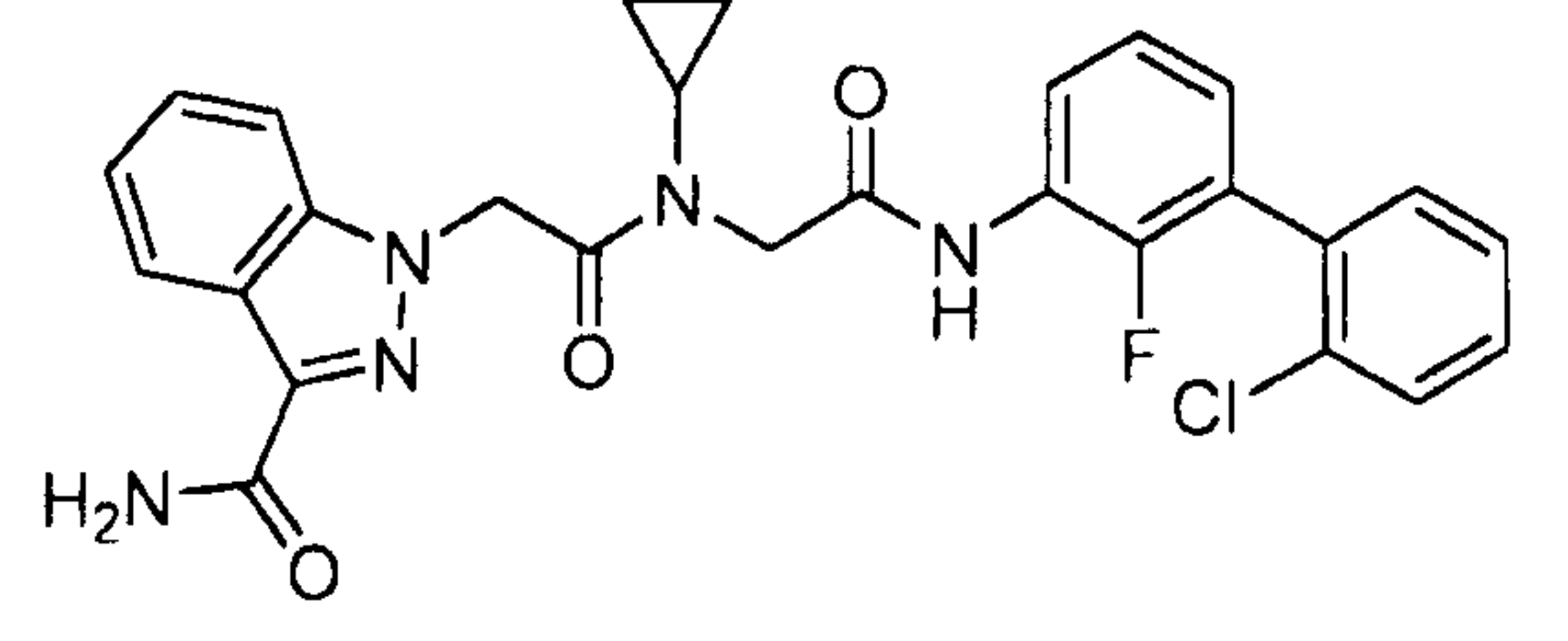
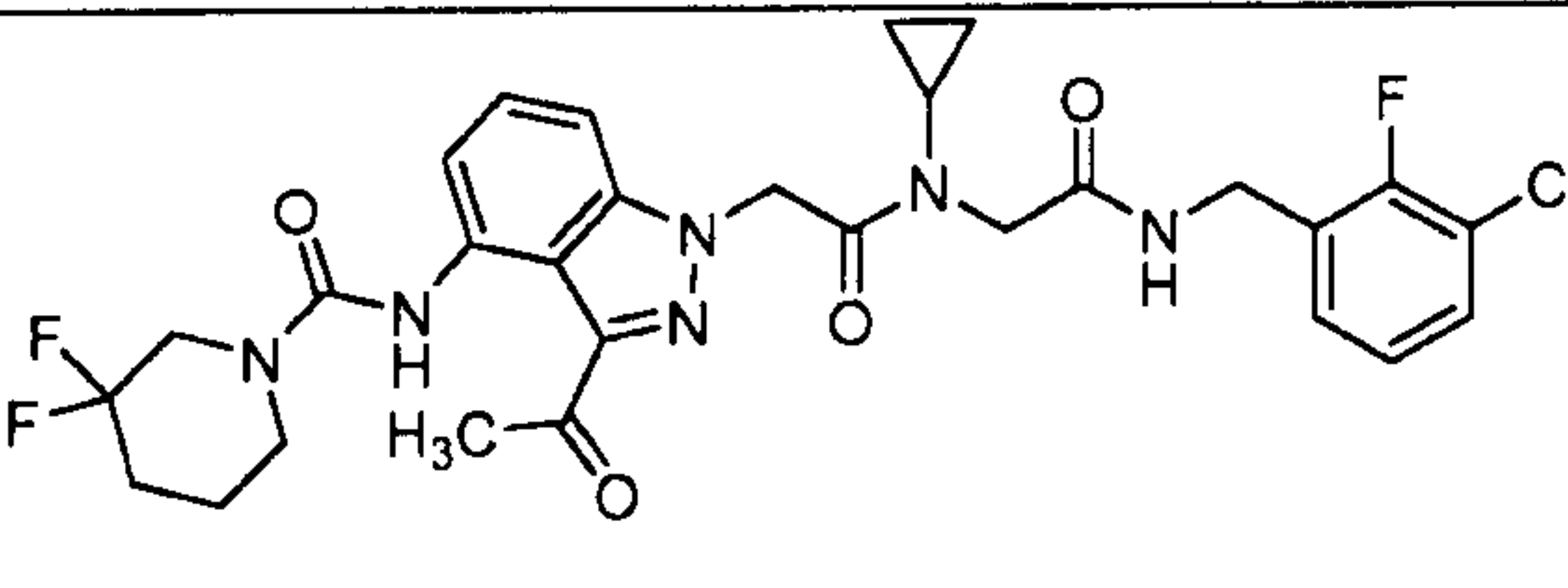
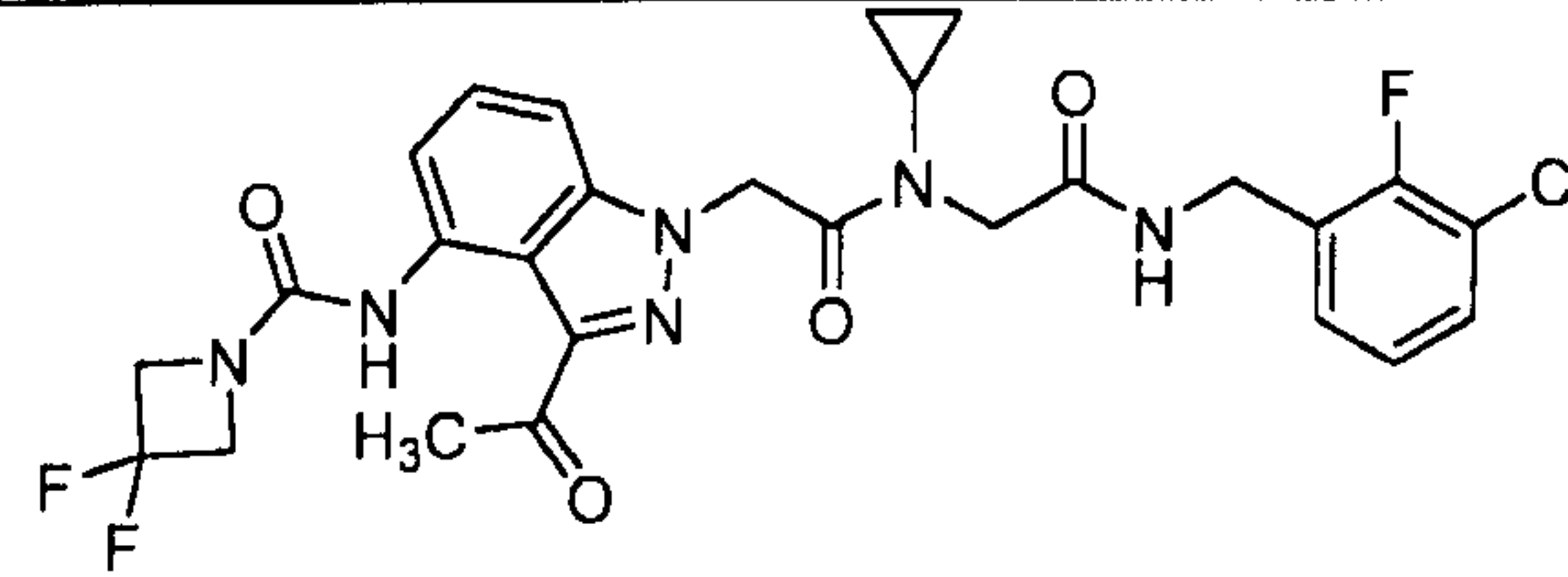
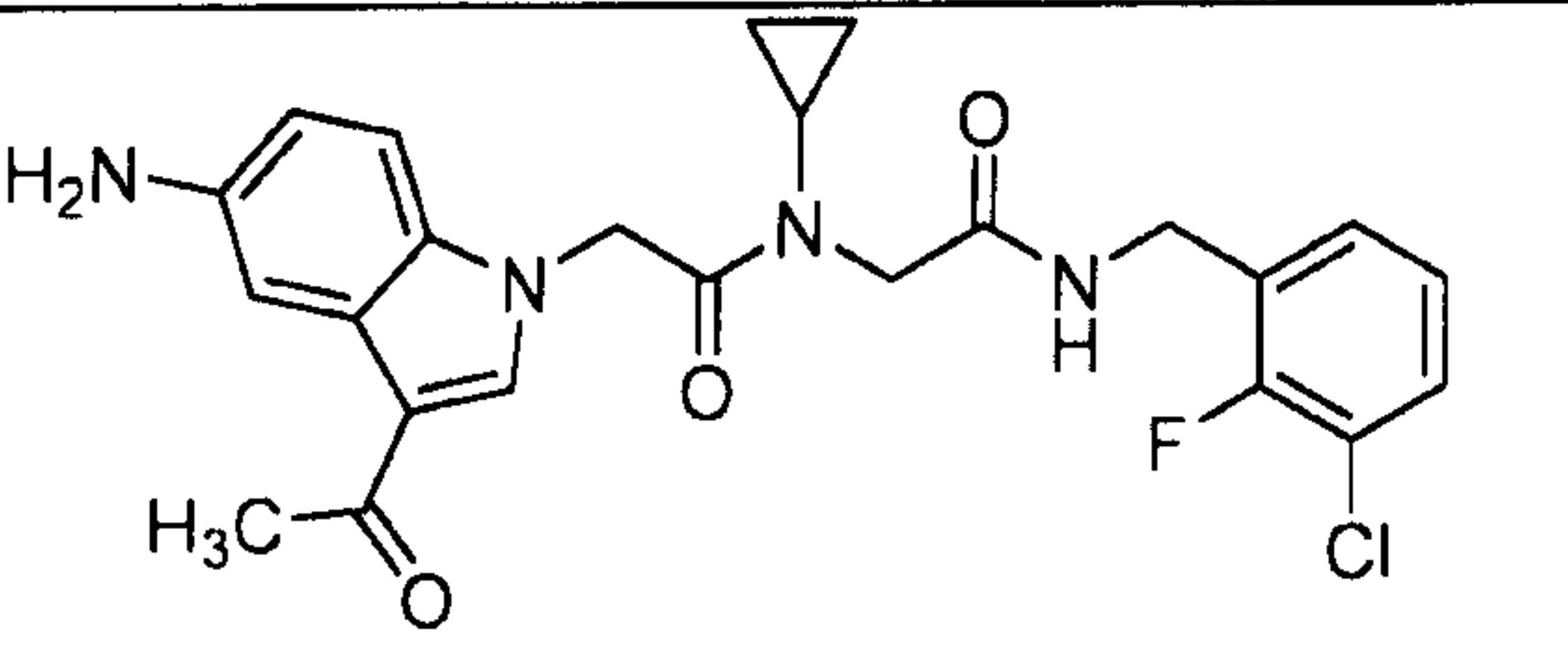
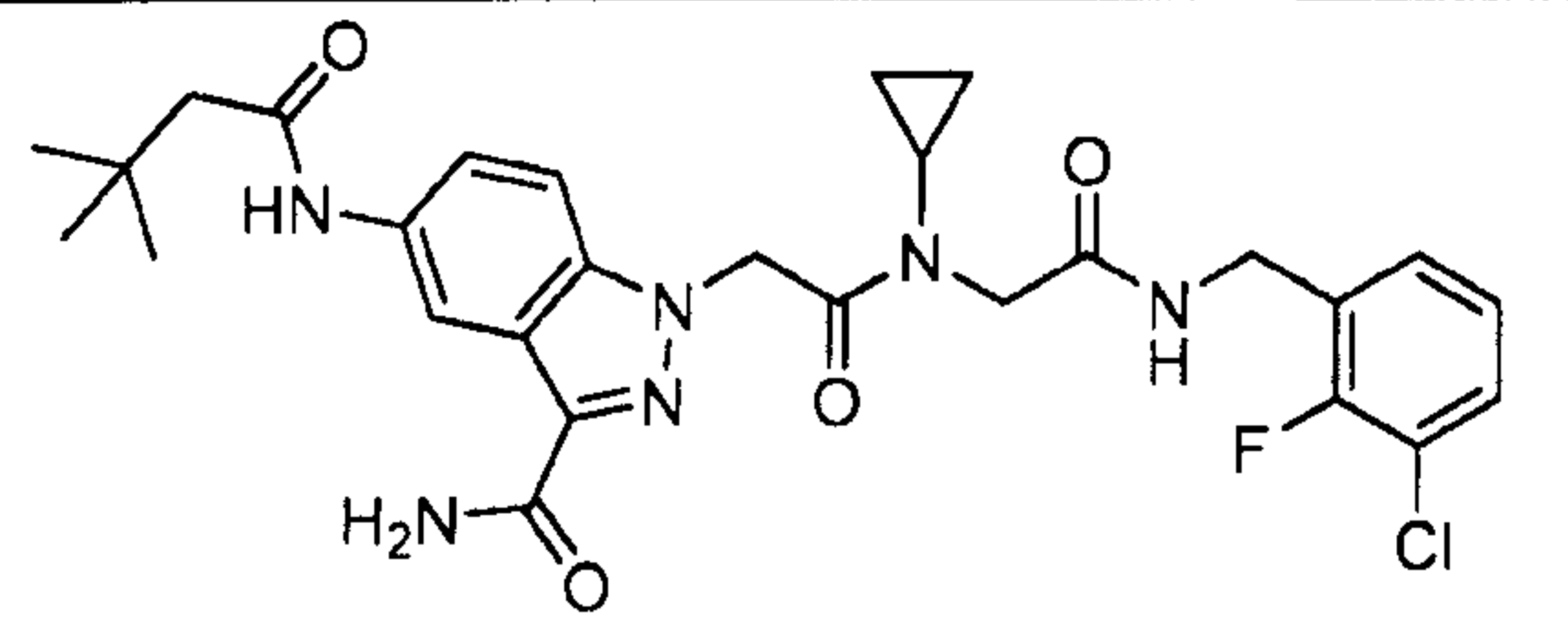
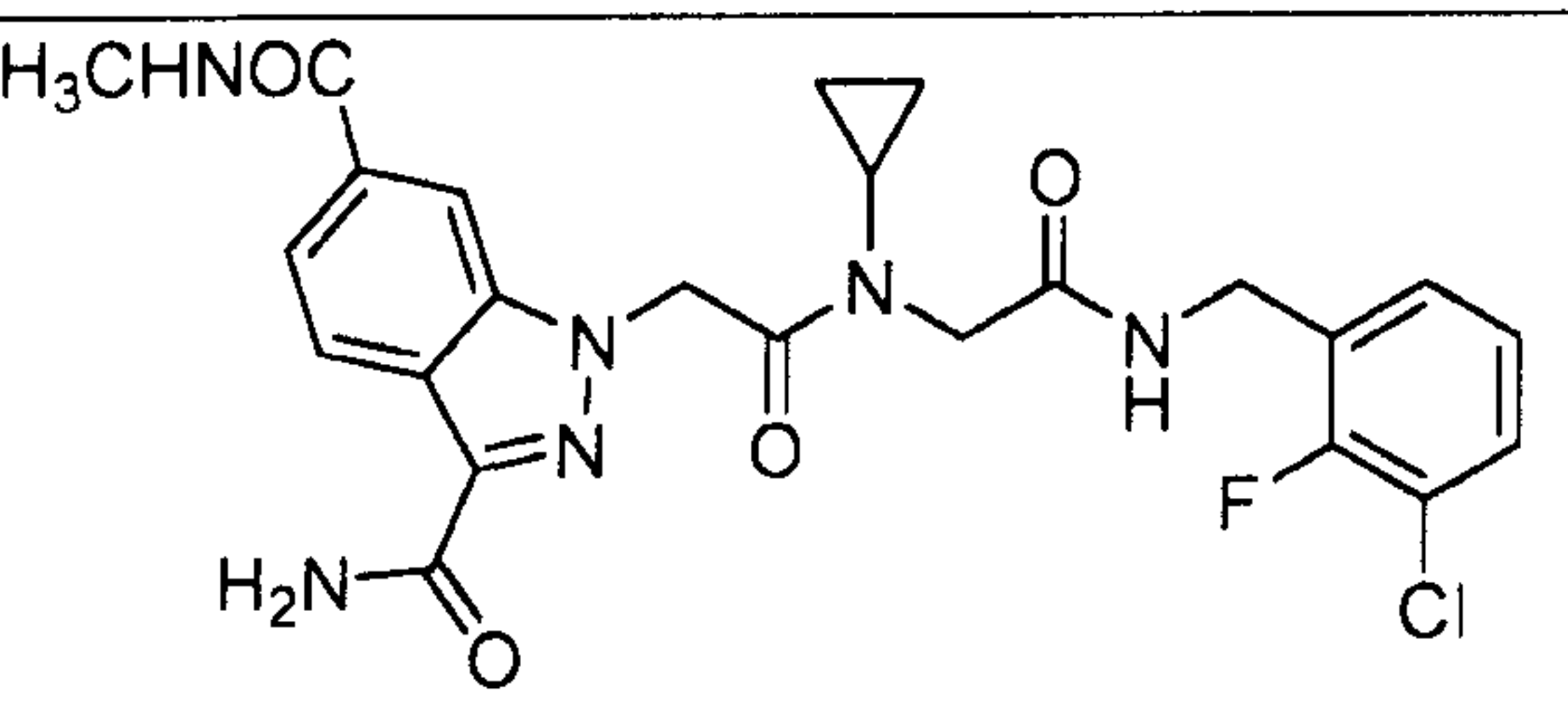
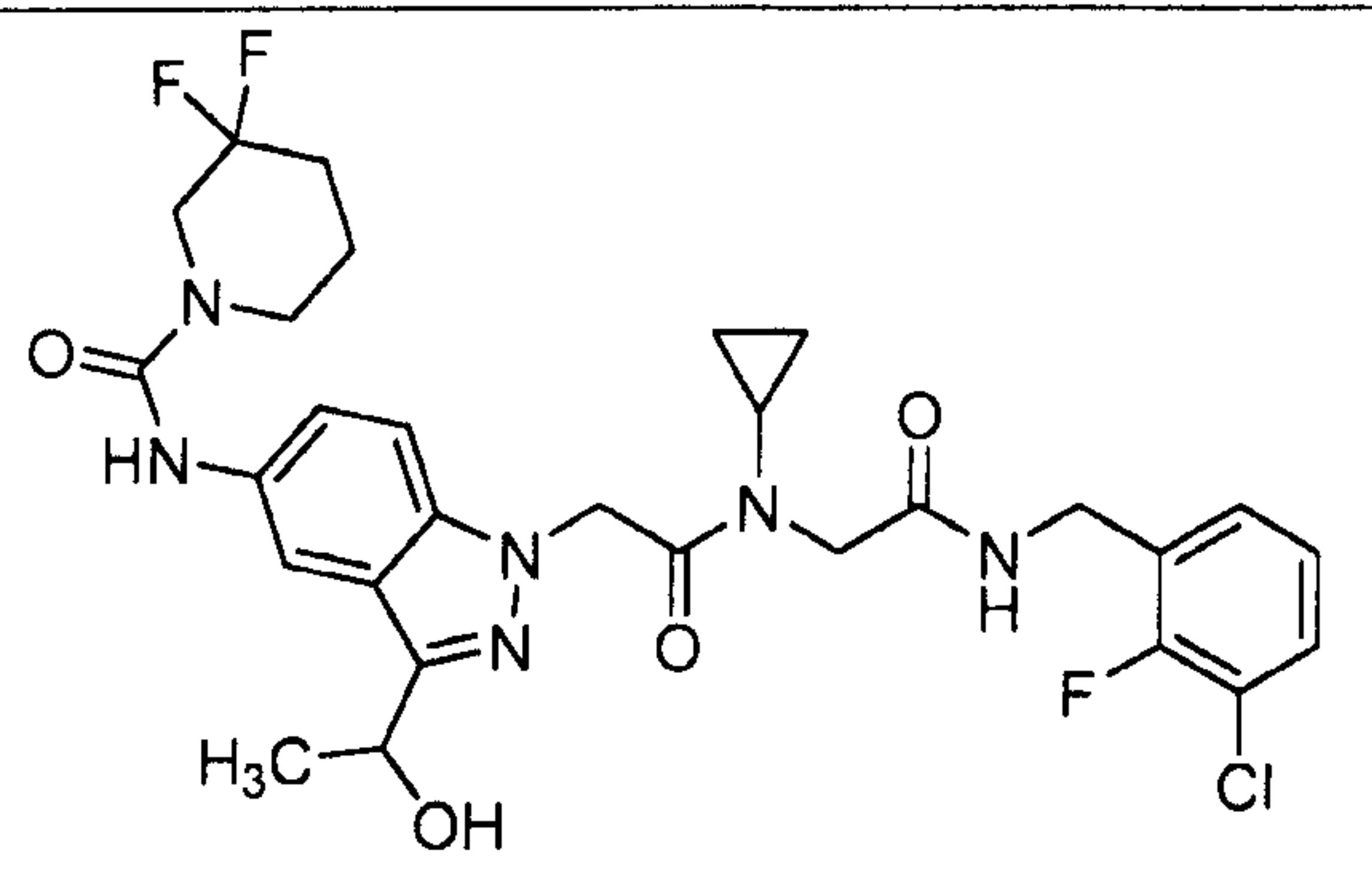
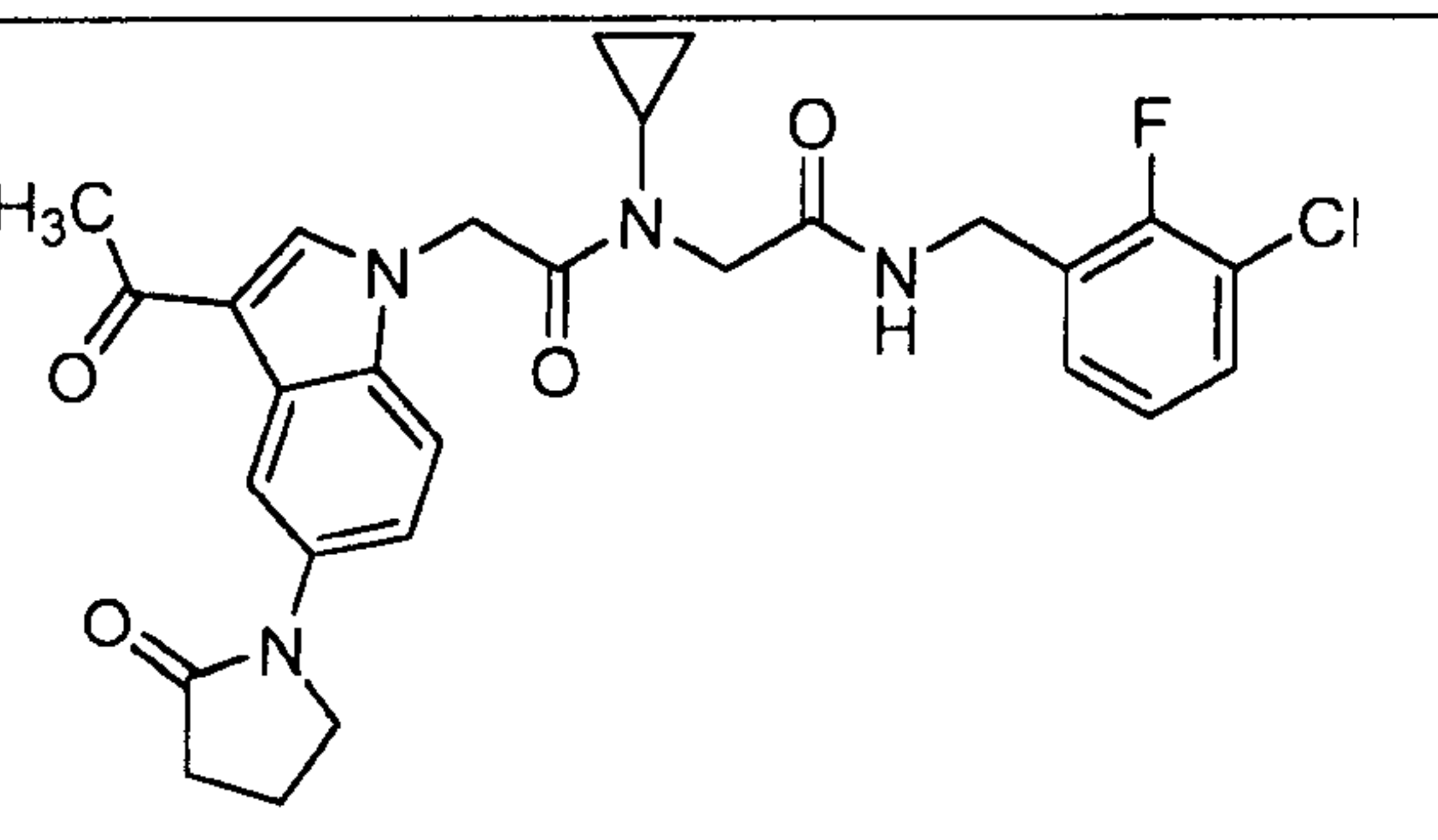
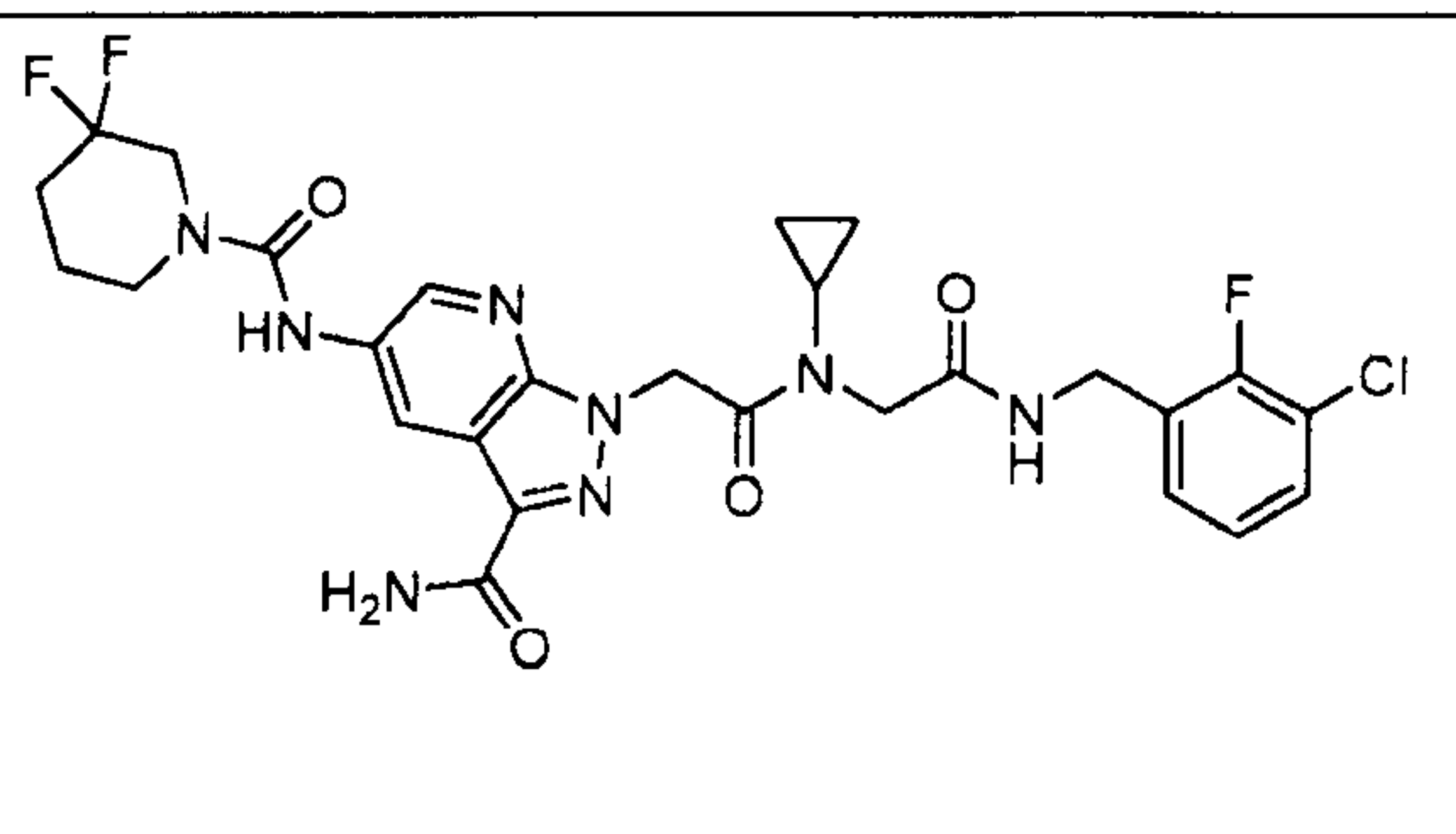
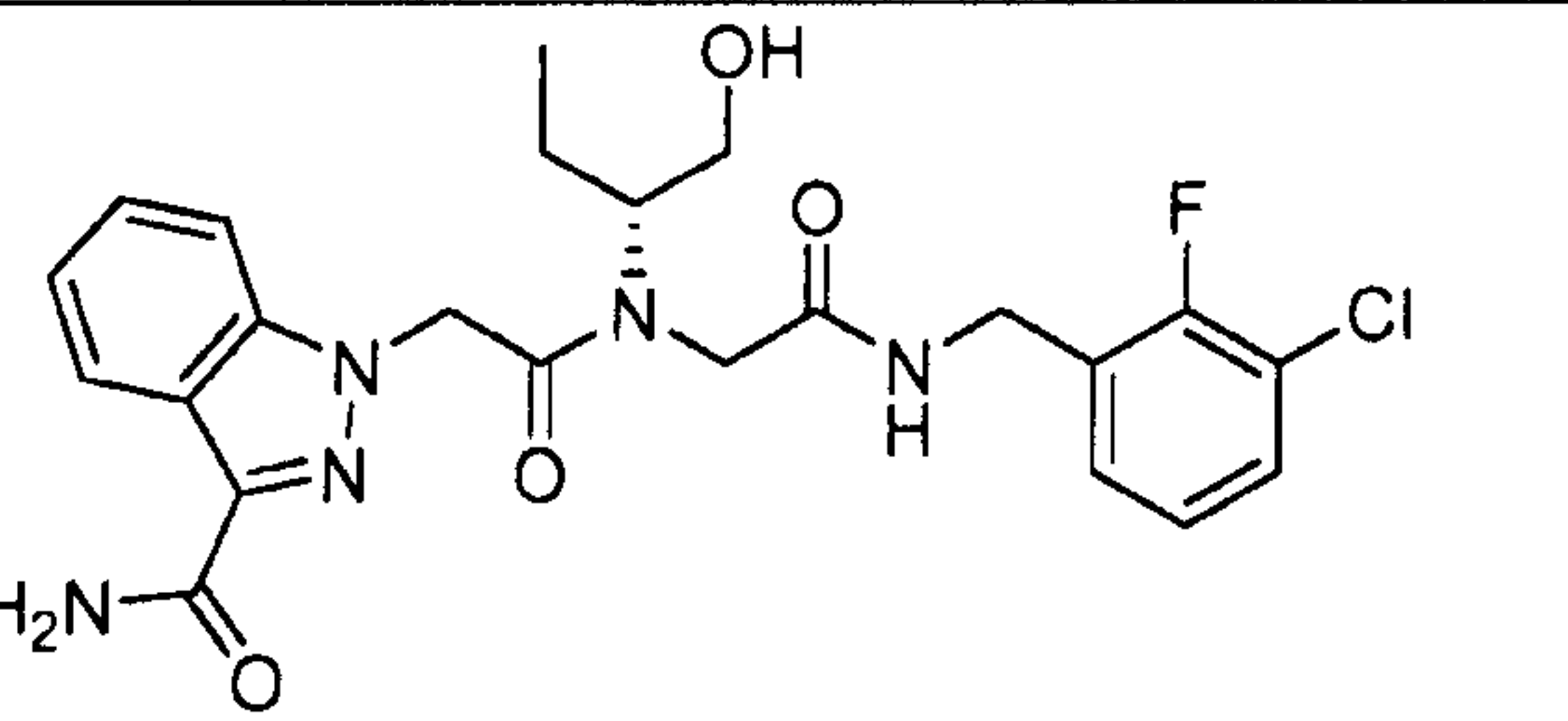
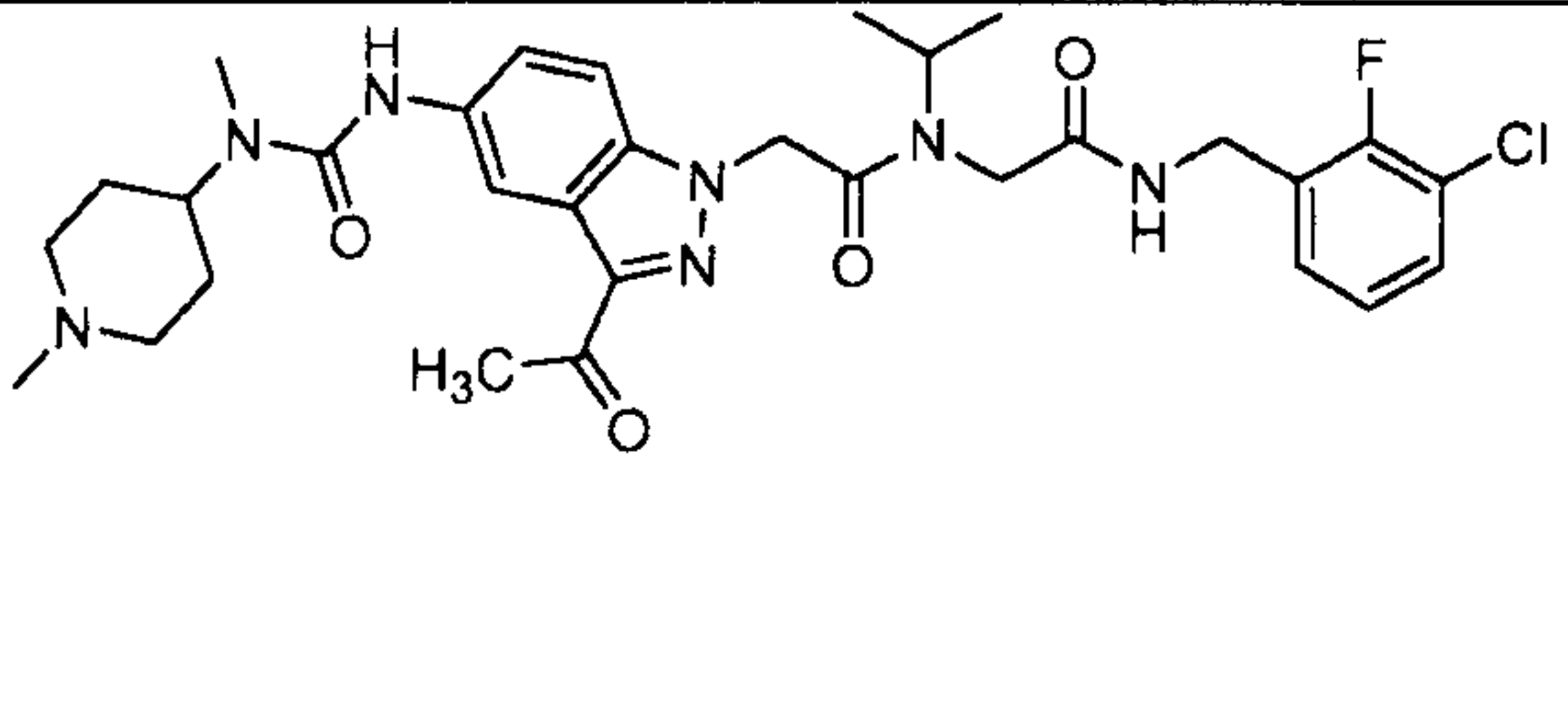
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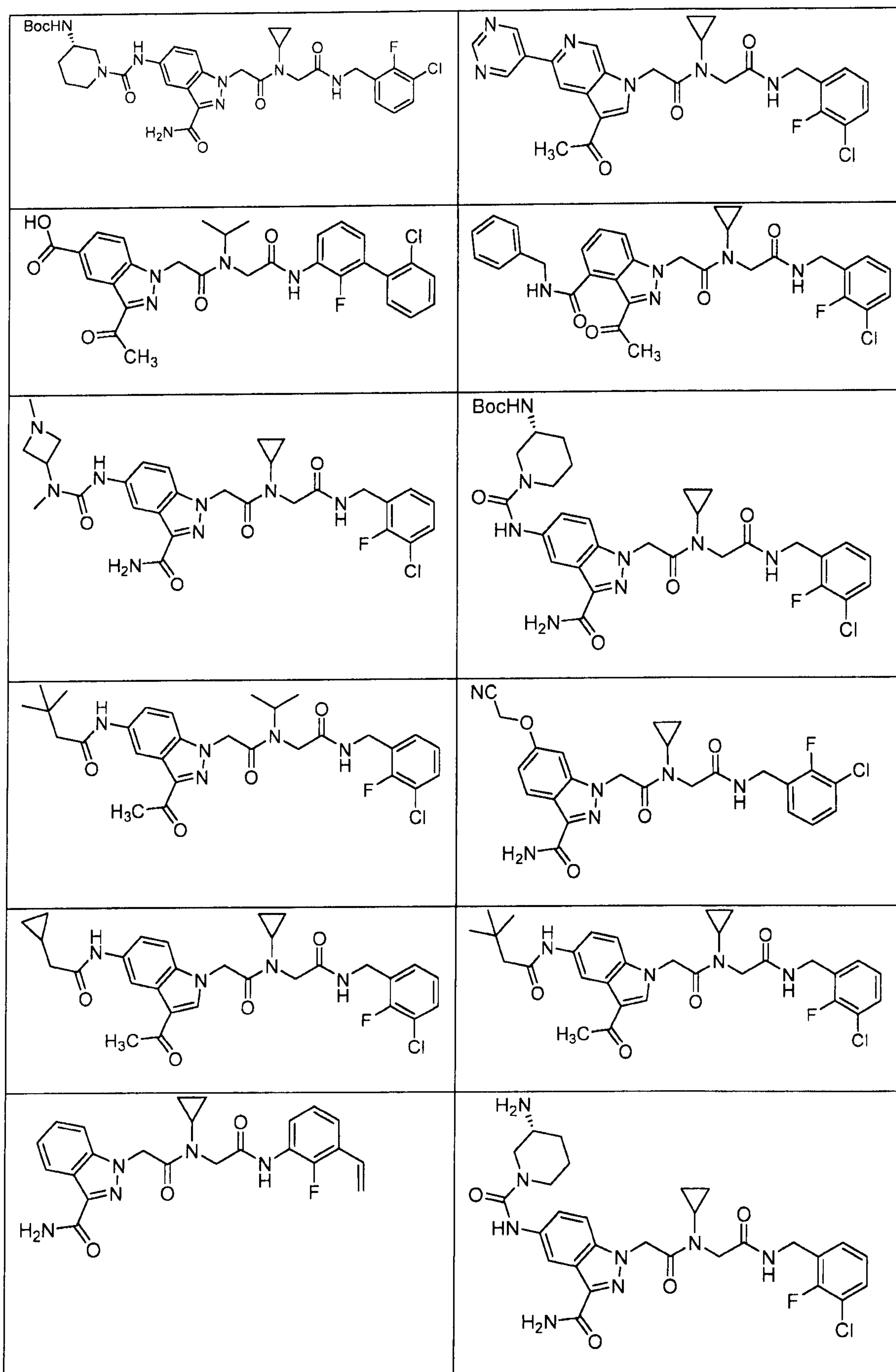
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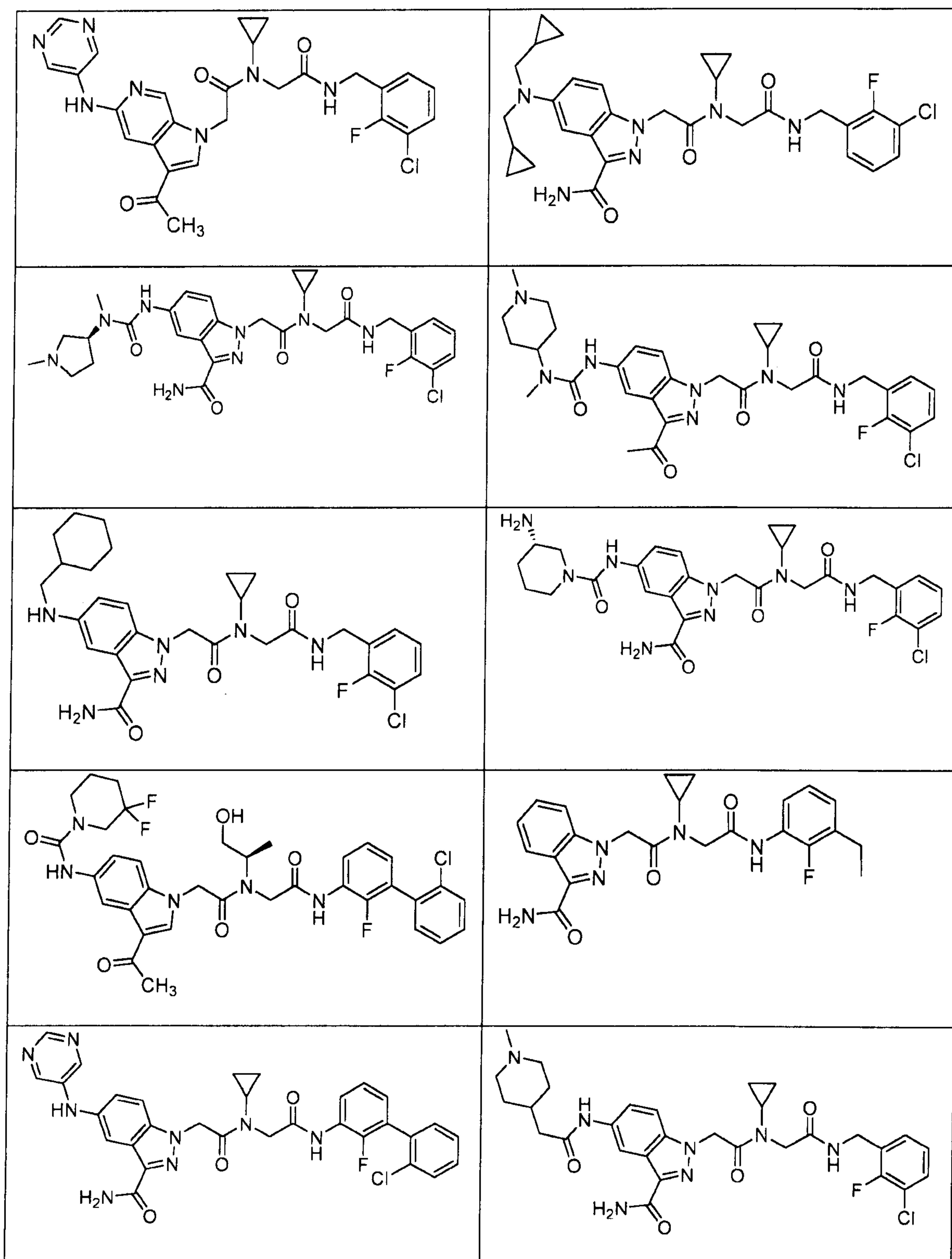
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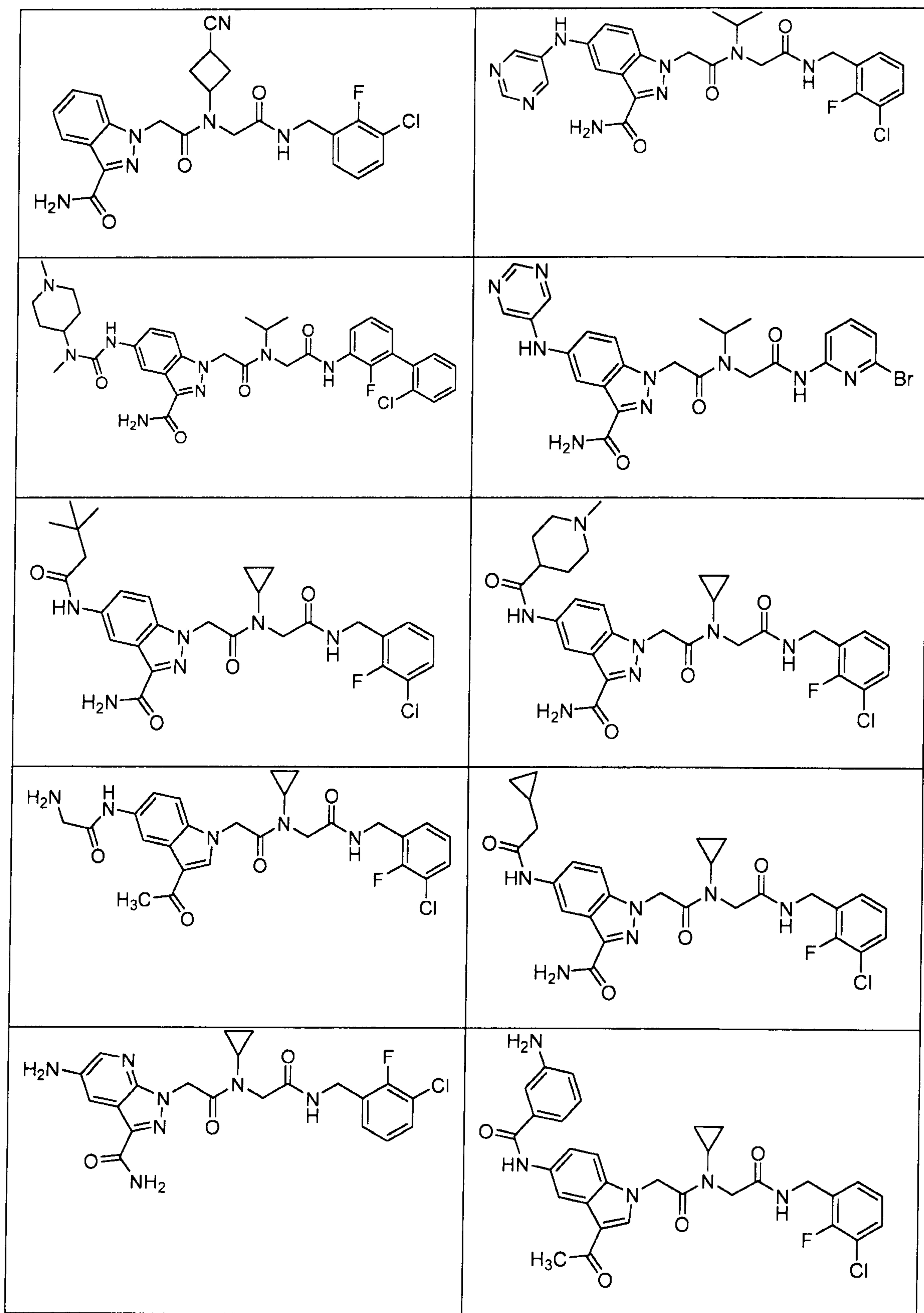
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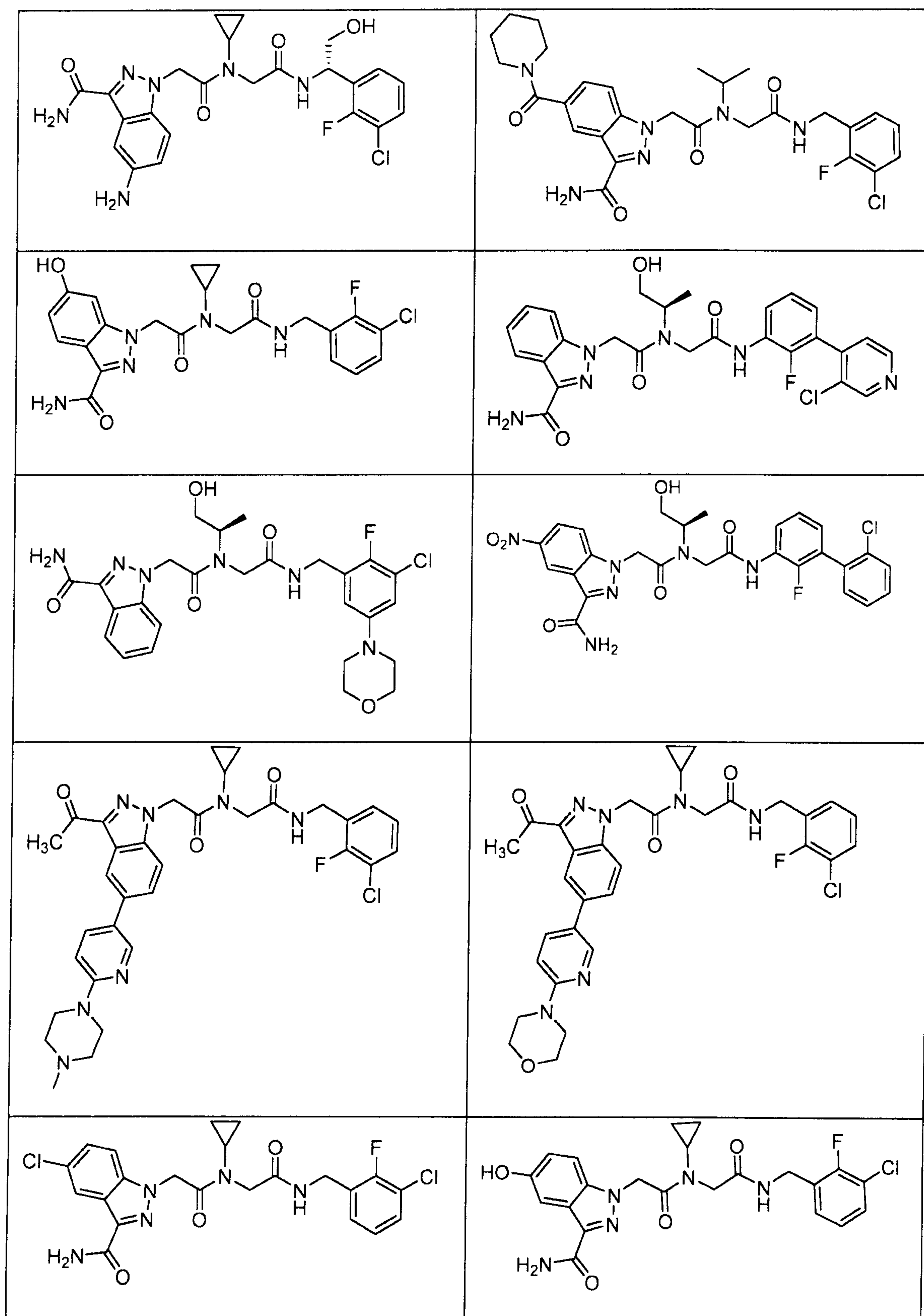
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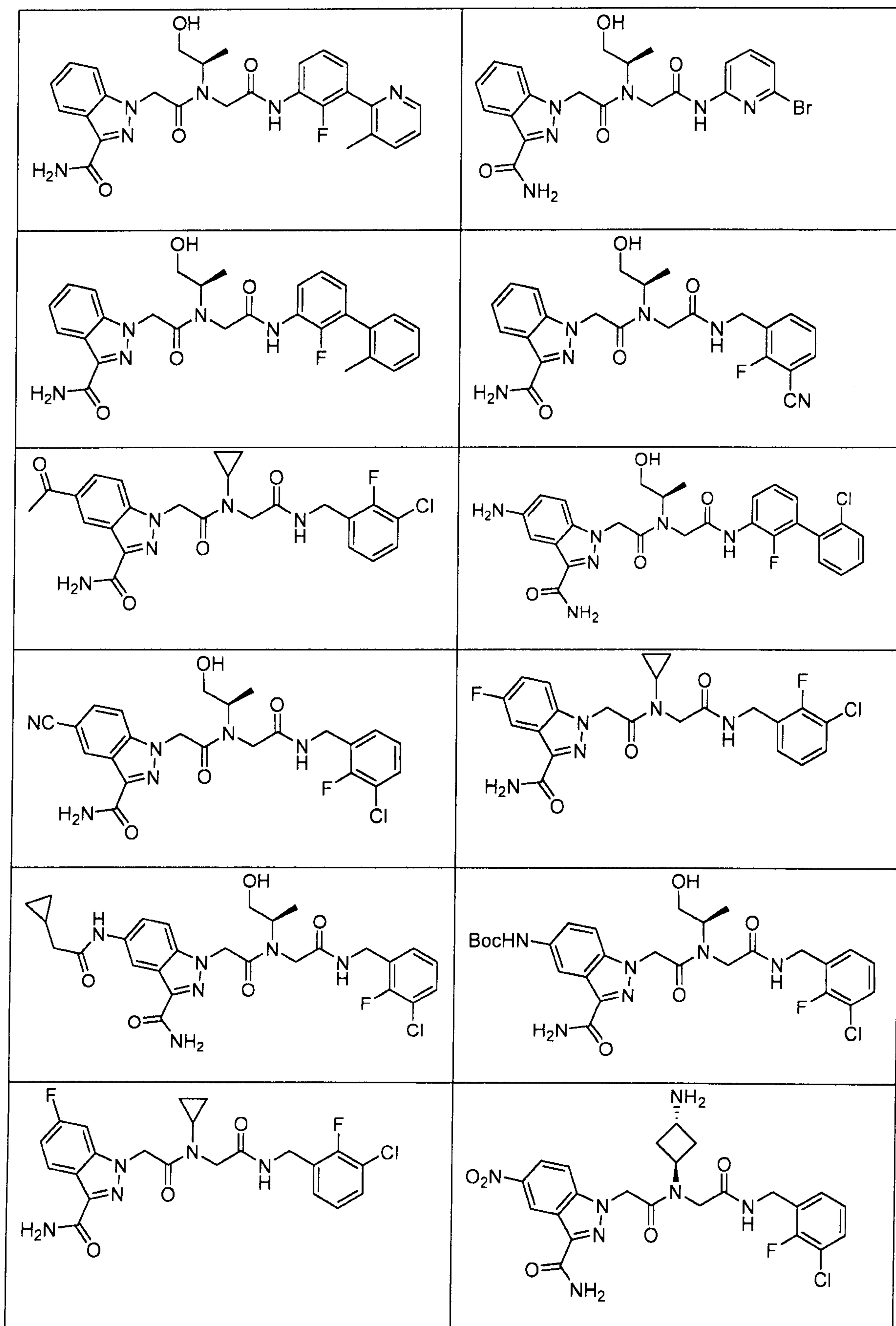
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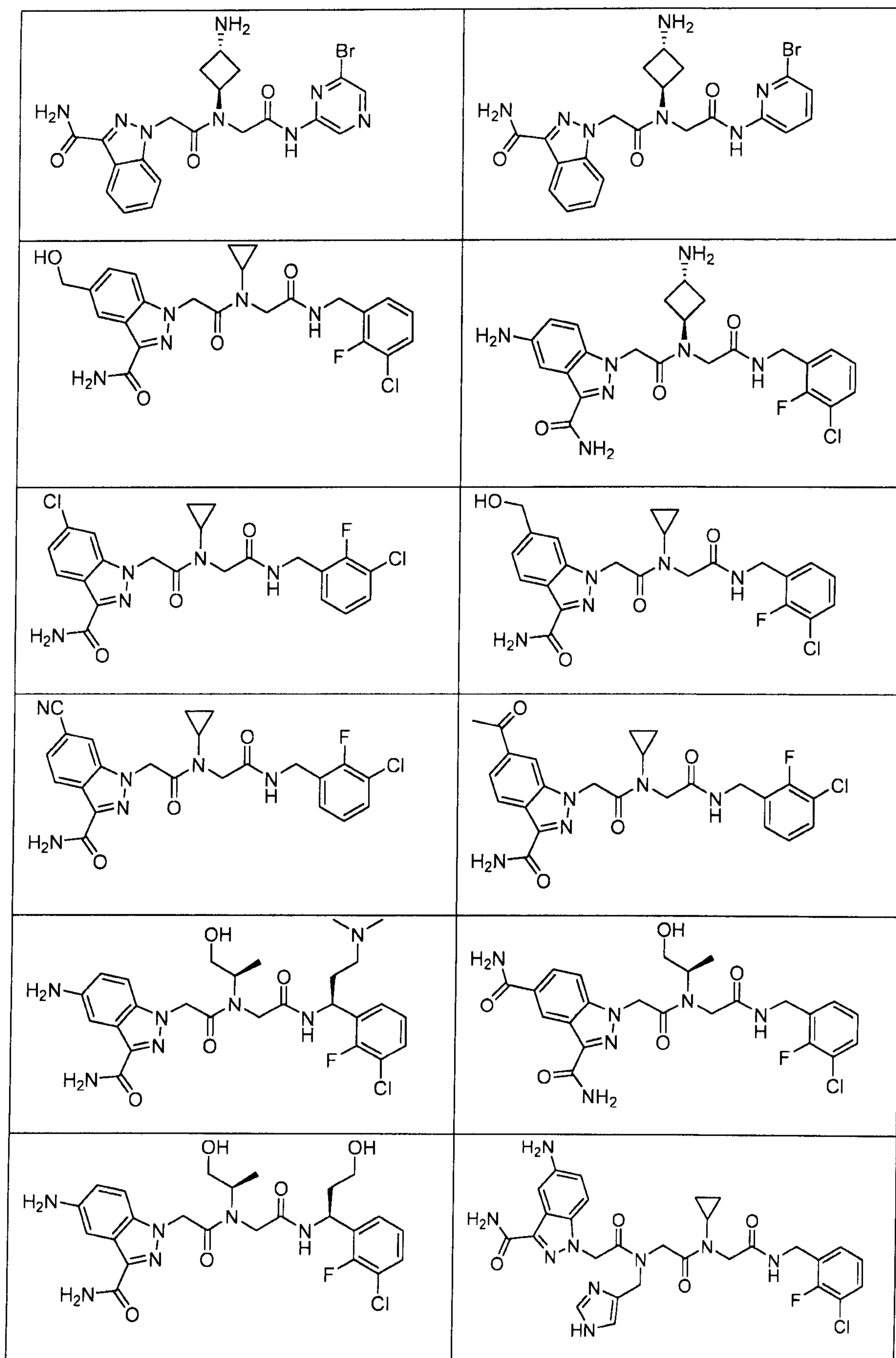
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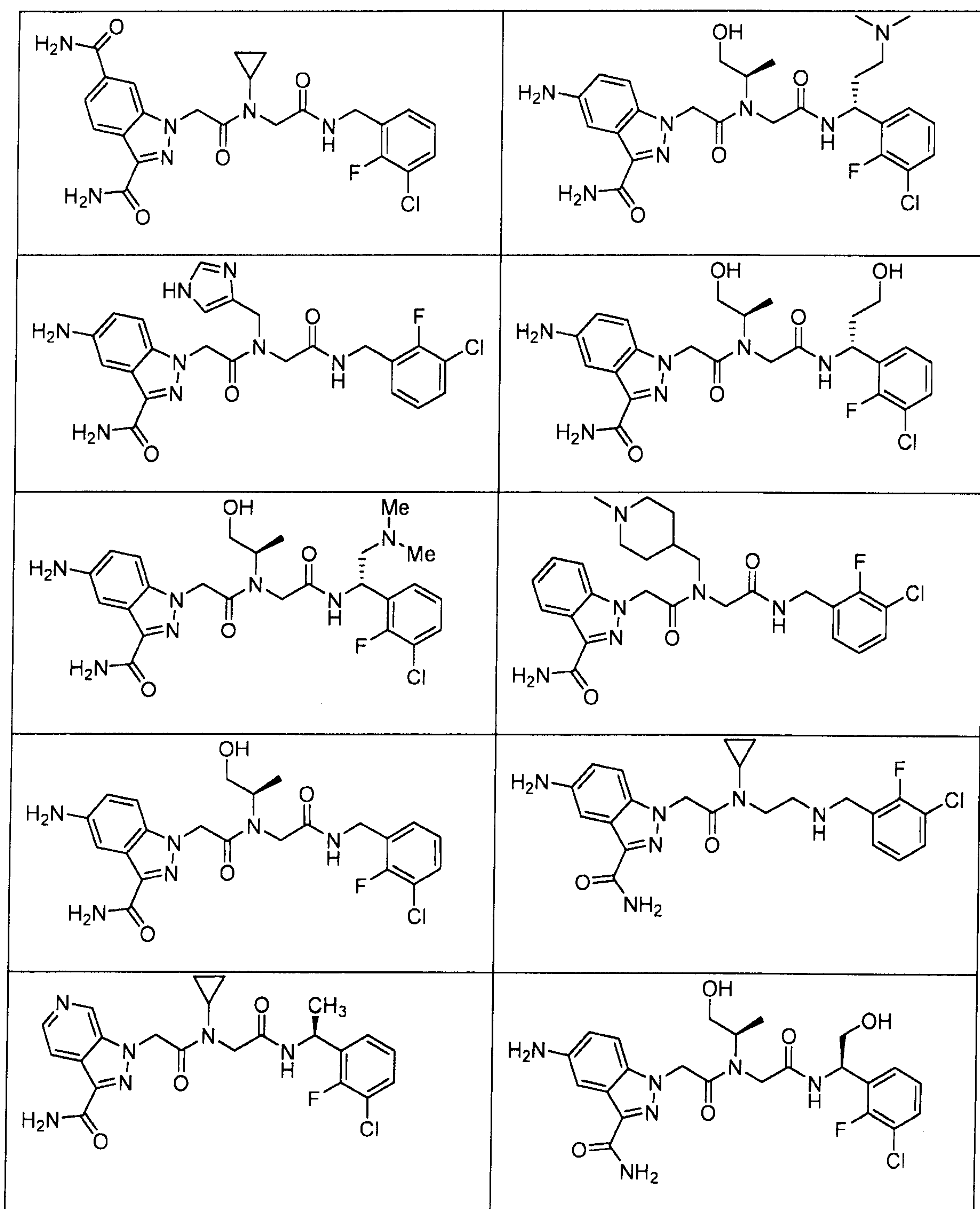
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Pharmaceutical Compositions

The invention provides pharmaceutical compositions, each comprising one or more compounds of the invention and a pharmaceutically acceptable carrier. In certain embodiments, the pharmaceutical composition comprises a compound of the invention and a pharmaceutically acceptable carrier. In certain embodiments, the pharmaceutical

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composition comprises a plurality of compounds of the invention and a pharmaceutically acceptable carrier.

In certain embodiments, a pharmaceutical composition of the invention further comprises at least one additional pharmaceutically active agent other than a compound of the invention. The at least one additional pharmaceutically active agent can be an agent useful in
5 the treatment of a disease or condition characterized by aberrant complement system activity.

Pharmaceutical compositions of the invention can be prepared by combining one or more compounds of the invention with a pharmaceutically acceptable carrier and, optionally, one or more additional pharmaceutically active agents.

10 *Methods of Use*

The present invention provides compounds that useful for treating or preventing a disease or condition characterized by aberrant complement system activity.

In certain aspects, the invention provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for use as a medicament.

15 In certain aspects, the invention provides methods of treating or preventing a disease or condition characterized by aberrant complement system activity. The method includes the step of administering to a subject in need thereof a therapeutically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof, thereby treating or preventing the disease or condition characterized by aberrant complement system activity.
20 By reducing complement system activity in the subject, the disease or condition characterized by aberrant complement system activity is treated.

Alternatively, in certain aspects, the invention provides a compound of the invention, or a pharmaceutically acceptable salt thereof, for treatment of a disease or condition characterized by aberrant complement system activity.

25 Alternatively, in certain aspects, the invention provides the use of a compound of the invention, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use in treatment of a disease or condition characterized by aberrant complement system activity.

As used herein, a “disease or condition characterized by aberrant complement system
30 activity” refers to any disease or condition in which it is desirable to reduce complement system activity. For example, it may be desirable to reduce complement system activity in the setting of inappropriate activation or hyperactivation of the complement system.

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In certain embodiments, the disease or condition characterized by aberrant complement system activity is an immunological disorder.

In certain embodiments, the disease or condition characterized by aberrant complement system activity is a disease of the central nervous system.

5 In certain embodiments, the disease or condition characterized by aberrant complement system activity is a renal disease.

In certain embodiments, the disease or condition characterized by aberrant complement system activity is a cardiovascular disease.

10 In certain embodiments, the disease or condition characterized by aberrant complement system activity is a neurodegenerative disease or neurological disease

In certain embodiments, the disease or condition characterized by aberrant complement system activity is selected from the group consisting of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, organ transplant rejection, myasthenia gravis, neuromyelitis optica, membranoproliferative glomerulonephritis, dense-deposit
15 disease, cold agglutinin disease, and catastrophic antiphospholipid syndrome.

In certain embodiments, the disease or condition is paroxysmal nocturnal hemoglobinuria.

In certain embodiments, the disease or condition is atypical hemolytic uremic syndrome.

20 In certain embodiments, the disease or condition is organ transplant rejection.

In certain embodiments, the disease or condition is myasthenia gravis.

In certain embodiments, the disease or condition is neuromyelitis optica.

In certain embodiments, the disease or condition is membranoproliferative glomerulonephritis.

25 In certain embodiments, the disease or condition is dense-deposit disease.

In certain embodiments, the disease or condition is cold agglutinin disease.

In certain embodiments, the disease or condition is catastrophic antiphospholipid syndrome.

30 In other embodiments, the the disease or condition characterized by aberrant complement system activity is adult respiratory distress syndrome, myocardial infarct, lung inflammation, hyperacute rejection (transplantation rejection), sepsis, cardiopulmonary bypass, burns, asthma, restenosis, multiple organ dysfunction syndrome, Guillain-Barré syndrome, hemorrhagic shock, paroxysmal nocturnal hemoglobinuria, glomerulonephritis, systemic lupus erythematosus, rheumatoid arthritis, infertility, Alzheimer's disease, organ

rejection (transplantation), myasthenia gravis, multiple sclerosis, platelet storage, or hemodialysis.

Formulations, Routes of Administration, and Dosing

The compounds of the invention can be formulated as pharmaceutical compositions
5 and administered to a mammalian host, such as a human patient, in a variety of forms adapted to the chosen route of administration, e.g., orally or parenterally, by intravenous, intraperitoneal, intramuscular, topical, or subcutaneous routes. Additional routes of administration are also contemplated by the invention.

Thus, the present compounds may be systemically administered, e.g., orally, in
10 combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs,
15 suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2% to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

20 The tablets, troches, pills, capsules, and the like may also contain the following diluents and carriers: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint,
25 oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or
30 elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically

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acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water or physiologically acceptable aqueous solution, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation can include vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of the invention to the skin are known in the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392; incorporated herein by reference), Geria (U.S. Pat. No. 4,992,478; incorporated herein by reference), Smith et al. (U.S. Pat. No. 4,559,157; incorporated herein by reference), and Wortzman (U.S. Pat. No. 4,820,508; incorporated herein by reference).

Useful dosages of the compounds of the invention can be determined, at least initially, by comparing their *in vitro* activity and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known in the art; for example, see U.S. Pat. No. 4,938,949 (incorporated herein by reference).

The amount of the compound, or an active salt thereof, required for use in treatment will vary not only with the particular compound or salt selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 0.5 to about 100 mg/kg body weight of the recipient per day, e.g., from about 3 to about 90 mg/kg of body weight per day, from about 6 to about 75 mg per kilogram of body weight per day, from about 10 to about 60 mg/kg of body weight per day, or from about 15 to about 50 mg/kg of body weight per day.

Compounds of the invention can be conveniently formulated in unit dosage form; for example, containing 5 to 1000 mg, 10 to 750 mg, or 50 to 500 mg of active ingredient per unit dosage form. In one embodiment, the invention provides a composition comprising a compound of the invention formulated in such a unit dosage form. The desired dose may

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conveniently be presented in a single dose or as divided doses to be administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations.

5 Compounds of the invention can also be administered in combination with other therapeutic agents, for example, other agents that are useful for treating or preventing ischemia, blood loss, or reperfusion injury.

Other delivery systems can include time-release, delayed release, or sustained release delivery systems such as are well-known in the art. Such systems can avoid repeated
10 administrations of the active compound, increasing convenience to the subject and the physician. Many types of release delivery systems are available and known to those of ordinary skill in the art. Use of a long-term sustained release implant may be desirable. Long-term release, as used herein, means that the delivery system or is implant constructed and arranged to deliver therapeutic levels of the active ingredient for at least 30 days, and
15 preferably 60 days.

In certain embodiments, a compound of the invention is formulated for intraocular administration, for example direct injection or insertion within or in association with an intraocular medical device.

The compounds of the invention may be formulated for depositing into a medical
20 device, which may include any of a variety of conventional grafts, stents, including stent grafts, catheters, balloons, baskets, or other device that can be deployed or permanently implanted within a body lumen. As a particular example, it would be desirable to have devices and methods which can deliver compounds of the invention to the region of a body which has been treated by interventional technique.

25 In exemplary embodiment, a compound of the invention may be deposited within a medical device, such as a stent, and delivered to the treatment site for treatment of a portion of the body.

Stents have been used as delivery vehicles for therapeutic agents (i.e., drugs). Intravascular stents are generally permanently implanted in coronary or peripheral vessels.
30 Stent designs include those of U.S. Pat. No. 4,733,655 (Palmaz), U.S. Pat. No. 4,800,882 (Gianturco), or U.S. Pat. No. 4,886,062 (Wiktor). Such designs include both metal and polymeric stents, as well as self-expanding and balloon-expandable stents. Stents may also be used to deliver a drug at the site of contact with the vasculature, as disclosed in U.S. Pat. No. 5,102,417 (Palmaz), U.S. Pat. No. 5,419,760 (Narciso, Jr.), U.S. Pat. No. 5,429,634

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(Narciso, Jr.), and in International Patent Application Nos. WO 91/12779 (Medtronic, Inc.) and WO 90/13332 (Cedars-Sinai Medical Center), for example.

The term “deposited” means that the compound is coated, adsorbed, placed, or otherwise incorporated into the device by methods known in the art. For example, the compound may be embedded and released from within (“matrix type”) or surrounded by and released through (“reservoir type”) polymer materials that coat or span the medical device. In the latter example, the compound may be entrapped within the polymer materials or coupled to the polymer materials using one or more the techniques for generating such materials known in the art. In other formulations, the compound may be linked to the surface of the medical device without the need for a coating, for example by means of detachable bonds, and release with time or can be removed by active mechanical or chemical processes. In other formulations, the compound may be in a permanently immobilized form that presents the compound at the implantation site.

In certain embodiments, the compound may be incorporated with polymer compositions during the formation of biocompatible coatings for medical devices, such as stents. The coatings produced from these components are typically homogeneous and are useful for coating a number of devices designed for implantation.

The polymer may be either a biostable or a bioabsorbable polymer depending on the desired rate of release or the desired degree of polymer stability, but frequently a bioabsorbable polymer is preferred for this embodiment since, unlike a biostable polymer, it will not be present long after implantation to cause any adverse, chronic local response. Bioabsorbable polymers that could be used include, but are not limited to, poly(L-lactic acid), polycaprolactone, polyglycolide (PGA), poly(lactide-co-glycolide) (PLLA/PGA), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D-lactic acid), poly(L-lactic acid), poly(D, L-lactic acid), poly(D, L-lactide) (PLA), poly(L-lactide) (PLLA), poly(glycolic acid-co-trimethylene carbonate) (PGA/PTMC), polyethylene oxide (PEO), polydioxanone (PDS), polyphosphoester, polyphosphoester urethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters) (e.g., PEO/PLA), polyalkylene oxalates, polyphosphazenes and biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates, cross linked or amphipathic block copolymers of hydrogels, and other suitable bioabsorbable polymers known in the art. Also, biostable polymers with a relatively low chronic tissue

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response such as polyurethanes, silicones, and polyesters could be used, and other polymers could also be used if they can be dissolved and cured or polymerized on the medical device such as polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride; 5 polyvinylpyrrolidone; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidene chloride; polyacrylonitrile, polyvinyl ketones; polyvinyl aromatics, such as polystyrene, polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, acrylonitrile-styrene copolymers, ABS resins, and 10 ethylene-vinyl acetate copolymers; pyran copolymer; polyhydroxy-propyl-methacrylamide-phenol; polyhydroxyethyl-aspartamide-phenol; polyethyleneoxide-polylysine substituted with palmitoyl residues; polyamides, such as Nylon 66 and polycaprolactam; alkyd resins, polycarbonates; polyoxymethylenes; polyimides; polyethers; epoxy resins, polyurethanes; rayon; rayon-triacetate; cellulose, cellulose acetate, cellulose butyrate; cellulose acetate 15 butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers; and carboxymethyl cellulose.

Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

In certain embodiments of the invention, the compound of the invention is coupled to 20 a polymer or semipermeable polymer matrix that is formed as a stent or stent-graft device.

Typically, polymers are applied to the surface of an implantable device by spin coating, dipping, or spraying. Additional methods known in the art can also be utilized for this purpose. Methods of spraying include traditional methods as well as microdeposition techniques with an inkjet type of dispenser. Additionally, a polymer can be deposited on an 25 implantable device using photo-patterning to place the polymer on only specific portions of the device. This coating of the device provides a uniform layer around the device which allows for improved diffusion of various analytes through the device coating.

In certain embodiments of the invention, the compound is formulated for release from the polymer coating into the environment in which the medical device is placed. Preferably, 30 the compound is released in a controlled manner over an extended time frame (e.g., months) using at least one of several well-known techniques involving polymer carriers or layers to control elution. Some of these techniques are described in U.S. Patent Application 2004/0243225A1, the entire disclosure of which is incorporated herein in its entirety.

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Moreover, as described for example in U.S. Pat. No. 6,770,729, which is incorporated herein in its entirety, the reagents and reaction conditions of the polymer compositions can be manipulated so that the release of the compound from the polymer coating can be controlled. For example, the diffusion coefficient of the one or more polymer coatings can be modulated
5 to control the release of the compound from the polymer coating. In a variation on this theme, the diffusion coefficient of the one or more polymer coatings can be controlled to modulate the ability of an analyte that is present in the environment in which the medical device is placed (e.g., an analyte that facilitates the breakdown or hydrolysis of some portion of the polymer) to access one or more components within the polymer composition (and for
10 example, thereby modulate the release of the compound from the polymer coating). Yet another embodiment of the invention includes a device having a plurality of polymer coatings, each having a plurality of diffusion coefficients. In such embodiments of the invention, the release of the compound from the polymer coating can be modulated by the plurality of polymer coatings.

15 In yet another embodiment of the invention, the release of the compound from the polymer coating is controlled by modulating one or more of the properties of the polymer composition, such as the presence of one or more endogenous or exogenous compounds, or alternatively, the pH of the polymer composition. For example, certain polymer compositions can be designed to release a compound in response to a decrease in the pH of
20 the polymer composition.

Kits

The invention also provides a kit, comprising a compound of the invention, or a pharmaceutically acceptable salt thereof, at least one other therapeutic agent, packaging material, and instructions for administering the compound of the invention or the
25 pharmaceutically acceptable salt thereof and the other therapeutic agent or agents to a mammal to treat or prevent a disease or condition characterized by aberrant complement system activity. In one embodiment, the mammal is a human.

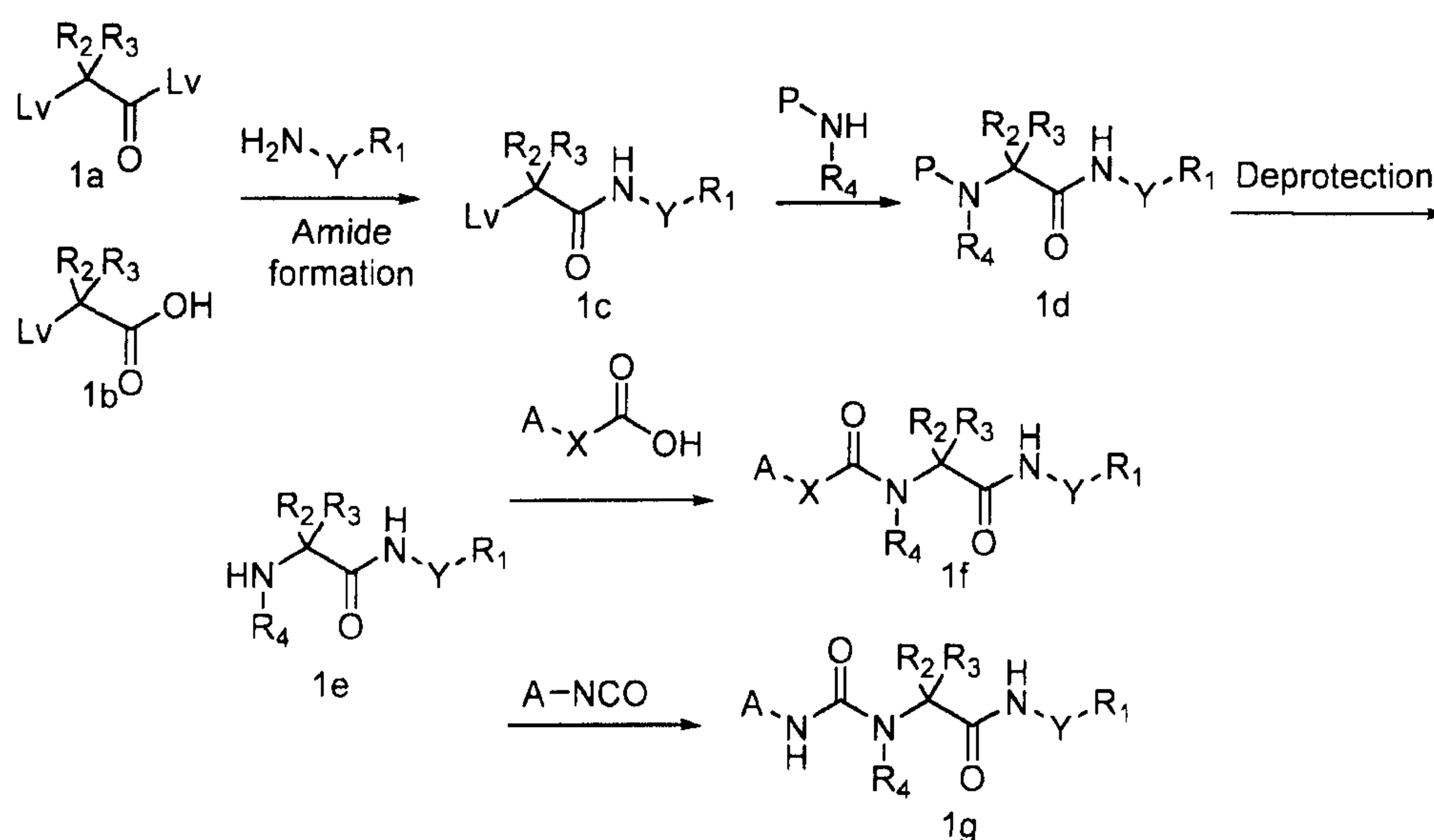
It will be understood by one of ordinary skill in the relevant arts that other suitable modifications and adaptations to the compositions and methods described herein are readily
30 apparent from the description of the invention contained herein in view of information known to the ordinarily skilled artisan, and may be made without departing from the scope of the invention or any embodiment thereof.

EXAMPLES

Having now described the present invention in detail, the same will be more clearly understood by reference to the following examples, which are included herewith for purposes of illustration only and are not intended to be limiting of the invention.

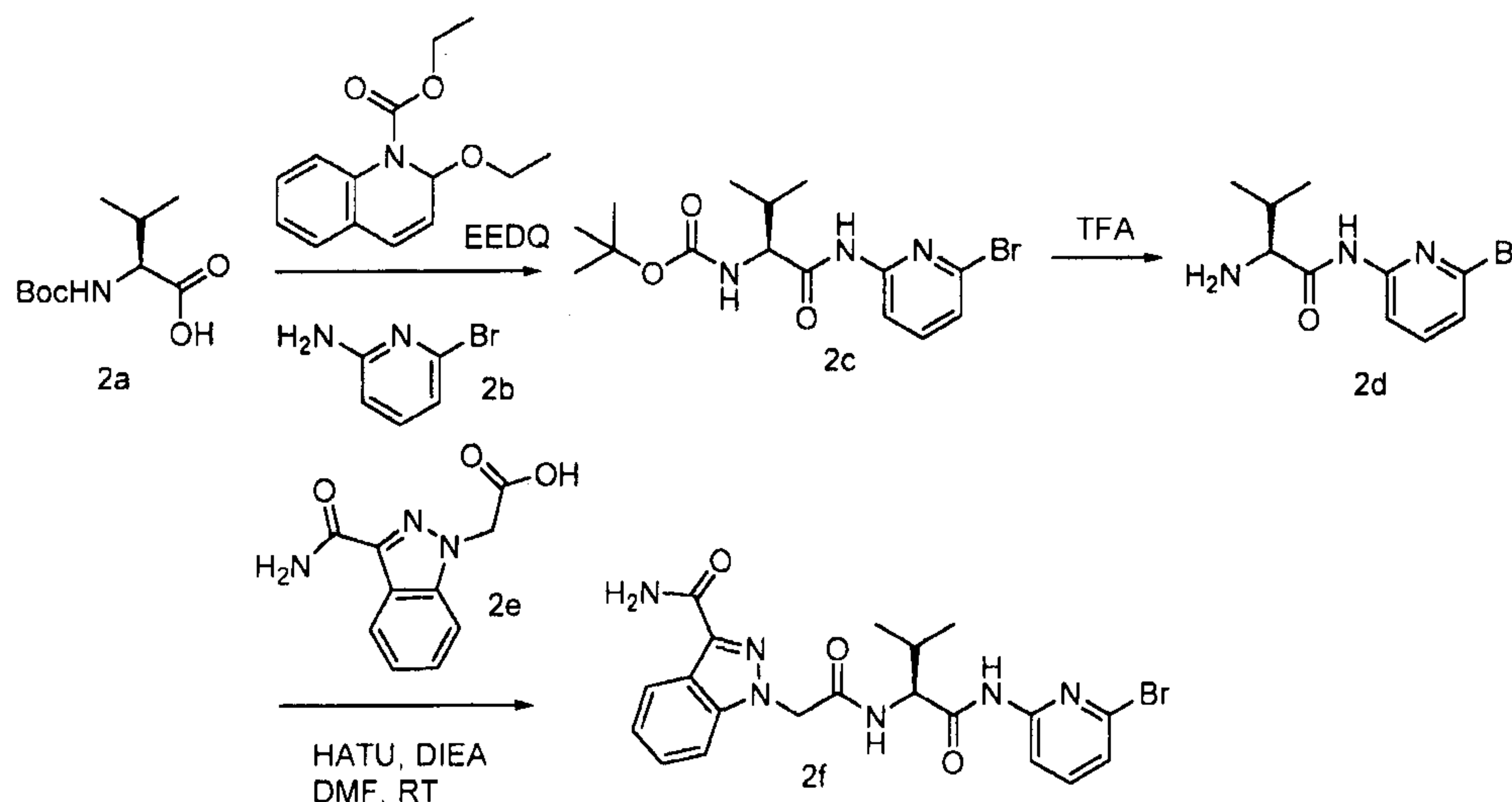
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Scheme 1



Scheme 1 depicts general synthesis of compounds of type (1f) and/or (1g). These compounds were prepared in a manner wherein (1a) or (1b) consisting of an activated carbonyl compound bearing a leaving group (Lv) upon reacting with free or protected amine under coupling conditions yields (1c). The compound (1d) was prepared by reaction of free or protected amine with (1c); the protecting group was removed using standard conditions to form (1e). In the final step, compound (1e) was coupled with activated carbonyl group using a coupling reagent to form amide compounds (1f), subsequently substituted urea compounds (1g) were prepared from (1e) using structurally diverse isocyanate.

Scheme 2



Preparation of (*S*)-1-(2-((1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-2-oxoethyl)-1*H*-indazole-3-carboxamide (**2f**)

- 5 Step-1: Preparation of (*S*)-*tert*-butyl 1-(6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (**2c**)

To a solution of Boc-L-valine (**2a**) (1.32 g, 6.07 mmol) and 6-bromopyridin-2-amine (**2b**) (1.0 g, 5.78 mmol) in THF (20 mL) was added ethyl 2-ethoxyquinoline-1(2*H*)-carboxylate (EEDQ, 1.43 g, 5.78 mmol). The resulting mixture was refluxed for 4 days, cooled to room
 10 temperature, diluted with EtOAc (100 mL), washed with KHSO₄ (1 N, 2 x 30 mL) and brine (20 mL). The organic layer was dried, concentrated in vacuum and the residue obtained was purified by flash column chromatography [silica gel (12 g), eluting with EtOAc (0-50 %) in hexane] to afford (*S*)-*tert*-butyl 1-(6-bromopyridin-2-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (**2c**) (121 mg, 0.325 mmol, 6% yield) as a semi-solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.78 (s, 1H), 8.09 (d, *J* = 8.1 Hz, 1H), 7.73 (t, *J* = 7.9 Hz, 1H), 7.34 (d, *J* = 7.7
 15 Hz, 1H), 6.98 (d, *J* = 8.4 Hz, 1H), 4.06 – 3.94 (m, 1H), 2.05 – 1.92 (m, 1H), 1.37 (s, 9H), 0.93 – 0.86 (m, 6H); MS (ES⁺): 394.4 (M+Na).

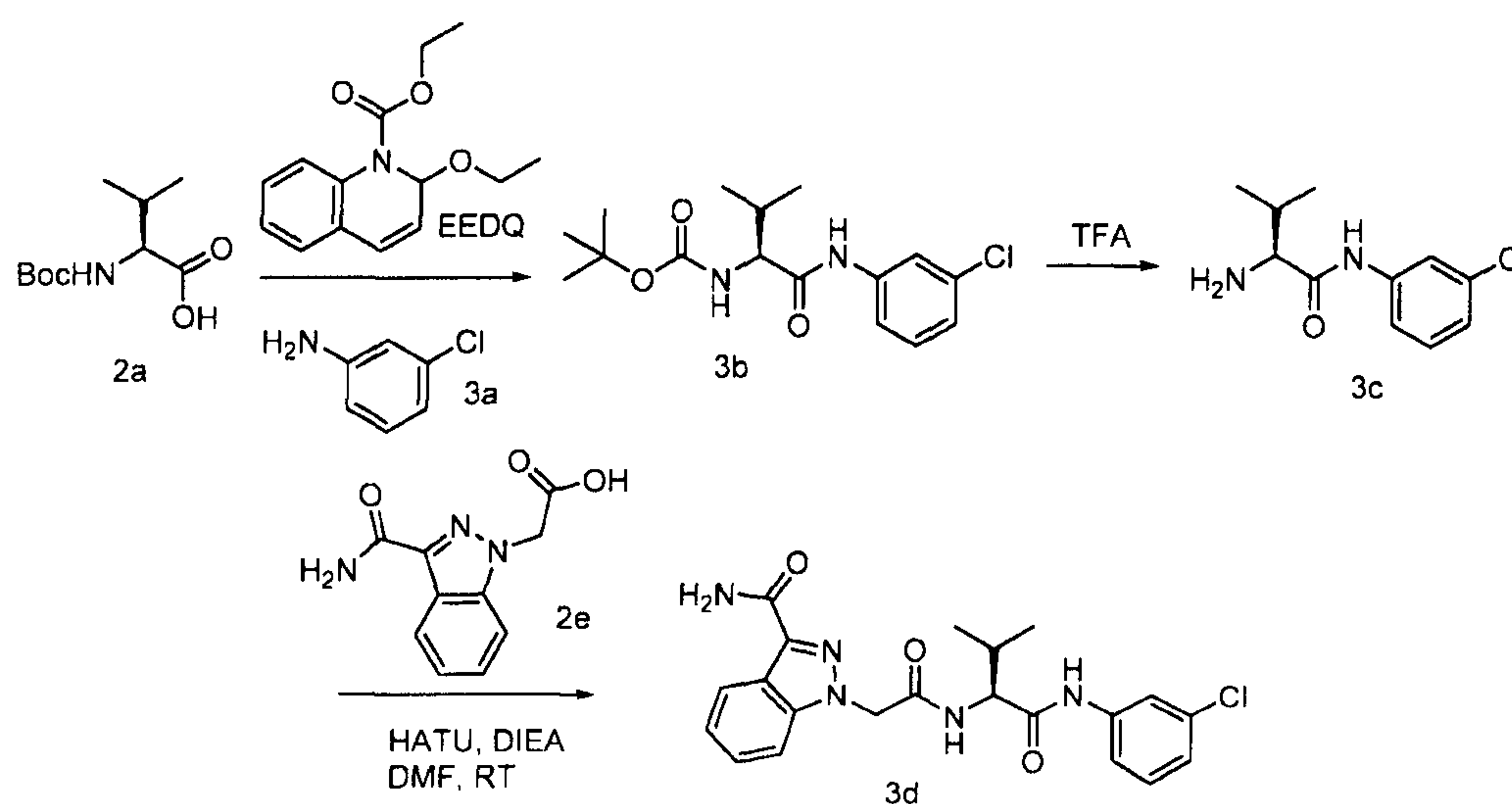
Step-2: Preparation of (*S*)-2-amino-N-(6-bromopyridin-2-yl)-3-methylbutanamide (**2d**)

To a stirred solution of (*S*)-*tert*-butyl 1-(6-bromopyridin-2-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (**2c**) (120 mg, 0.322 mmol) in DCM (10 mL) was added TFA (368 mg, 3.22
 20 mmol) at room temperature and stirred for 16 h. The reaction mixture was concentrated in vacuum to remove DCM and excess TFA to furnish (*S*)-2-amino-N-(6-bromopyridin-2-yl)-3-methylbutanamide (**2d**) which was used as such in the next step without further purification; MS (ES⁺): 273.3 (M+1).

Step-3: Preparation of (*S*)-1-(2-((1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-2-oxoethyl)-1*H*-indazole-3-carboxamide (**2f**)

To the above TFA salt of (*S*)-2-amino-N-(6-bromopyridin-2-yl)-3-methylbutanamide (**2d**) (120 mg, 0.441 mmol) in DMF (4 mL) was added 2-(3-carbamoyl-1*H*-indazol-1-yl)acetic acid (**2e**) (116 mg, 0.529 mmol, prepared according to procedure reported by Altmann, Eva et al; in PCT Int. Appl., WO 2012/093101), DIPEA (0.308 mL, 1.764 mmol), HATU (201 mg, 0.529 mmol) and stirred at room temperature overnight. The reaction mixture was diluted with EtOAc (100 mL), washed with water (3x), brine, dried, filtered and concentrated in vacuum to dryness. The residue obtained was purified by flash column chromatography [silica gel (12 g) eluting with 0-60% EtOAc/MeOH (9:1) in hexane] to furnish (*S*)-1-(2-((1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-2-oxoethyl)-1*H*-indazole-3-carboxamide (**2f**) (38 mg, 18% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.01 (s, 1H), 8.57 (d, *J* = 8.1 Hz, 1H), 8.13 (dd, *J* = 21.3, 8.2 Hz, 2H), 7.81 - 7.56 (m, 3H), 7.39 (dd, *J* = 23.5, 7.5 Hz, 3H), 7.25 (t, *J* = 7.5 Hz, 1H), 5.41 - 5.23 (m, 2H), 4.46 (t, *J* = 7.2 Hz, 1H), 2.15 - 2.00 (m, 1H), 1.00 - 0.83 (m, 7H); MS (ES⁺): 496.4 (M+Na).

Scheme 3



Preparation of (*S*)-1-(2-((1-((3-chlorophenyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-2-oxoethyl)-1*H*-indazole-3-carboxamide (**3d**)

Step-1: Preparation of (*S*)-*tert*-butyl 1-(3-chlorophenylamino)-3-methyl-1-oxobutan-2-ylcarbamate (**3b**)

Reaction of Boc-L-valine (**2a**) (1.73 g, 7.84 mmol) with 3-chloroaniline (**3a**) (1.0 g, 7.84 mmol) according to the procedure reported in step-1 of Scheme 2 gave after workup and purification (*S*)-*tert*-butyl 1-(3-chlorophenylamino)-3-methyl-1-oxobutan-2-ylcarbamate (**3b**)

(1.72 g, 5.26 mmol, 67% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.20 (s, 1H), 7.84 (s, 1H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.34 (t, $J = 8.0$ Hz, 1H), 7.11 (d, $J = 7.4$ Hz, 1H), 6.99 (d, $J = 8.1$ Hz, 1H), 3.89 (t, $J = 7.7$ Hz, 1H), 2.09 – 1.80 (m, 1H), 1.39 (s, 9H), 0.89 (d, $J = 6.4$ Hz, 6H); MS (ES^+): 349.4 ($\text{M}+\text{Na}$).

5 Step-2: Preparation of (*S*)-2-amino-*N*-(3-chlorophenyl)-3-methylbutanamide (**3c**)

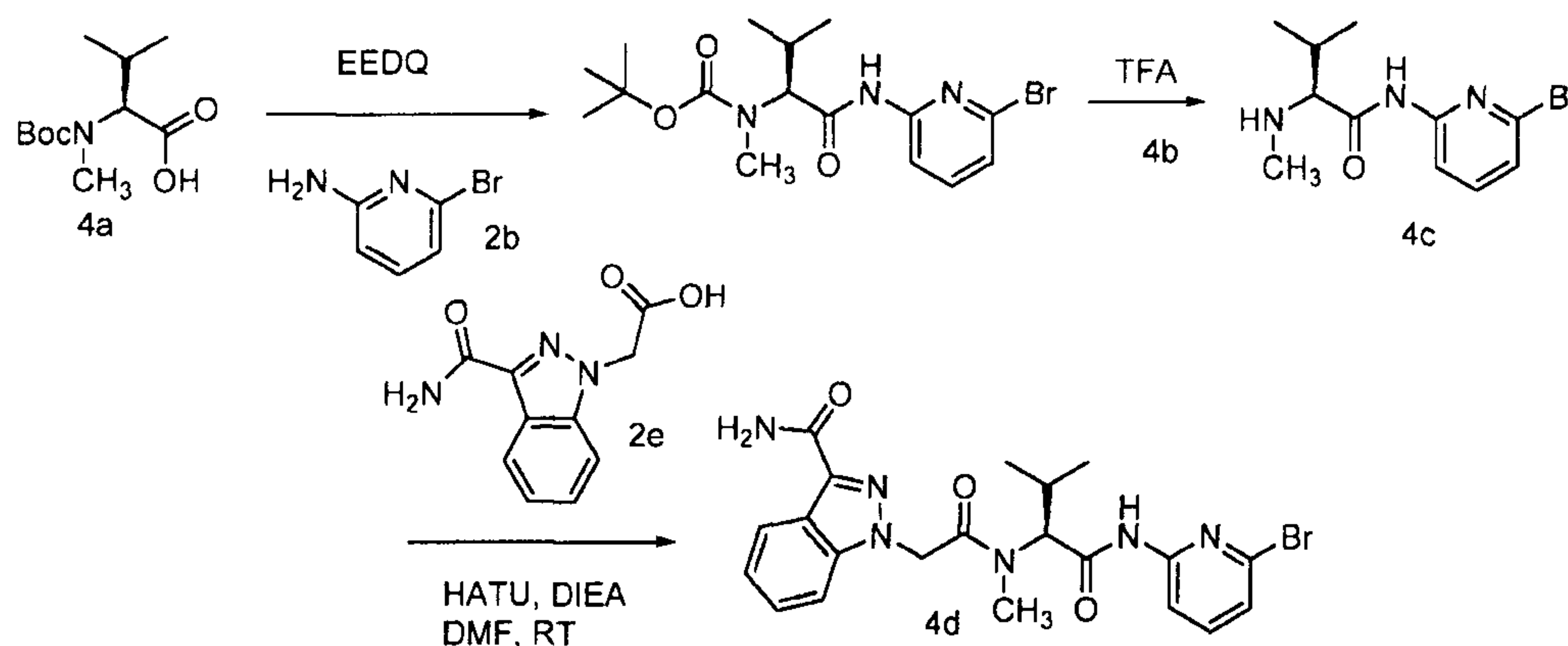
Reaction of (*S*)-*tert*-butyl 1-(3-chlorophenylamino)-3-methyl-1-oxobutan-2-ylcarbamate (**3b**) (750 mg, 2.30 mmol) with TFA (2.62 g, 22.95 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and purification by chromatography [silica (12 g) eluting with EtOAc/MeOH (9:1) in hexane from 0 to 60%] (*S*)-2-amino-*N*-(3-chlorophenyl)-3-methylbutanamide (**3c**) (355 mg, 1.57 mmol, 68% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.86 – 7.78 (m, 1H), 7.49 (d, $J = 7.9$ Hz, 1H), 7.39 (t, $J = 7.9$ Hz, 1H), 7.18 (d, $J = 7.8$ Hz, 1H), 3.66 (d, $J = 5.6$ Hz, 1H), 2.21 – 2.05 (m, 1H), 0.97 (t, $J = 7.1$ Hz, 6H); MS (ES^+): 227.3 ($\text{M}+1$).

15 Step-3: Preparation of (*S*)-1-(2-((1-((3-chlorophenyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**3d**)

Reaction of (*S*)-2-amino-*N*-(3-chlorophenyl)-3-methylbutanamide (**3c**) (145 mg, 0.64 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane] (*S*)-1-(2-((1-((3-chlorophenyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**3d**) (50 mg, 0.117 mmol, 18% yield) as a yellow solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.38 (s, 1H), 8.69 (d, $J = 8.3$ Hz, 1H), 8.18 (d, $J = 7.9$ Hz, 1H), 7.83 (s, 1H), 7.76 – 7.59 (m, 2H), 7.52 – 7.31 (m, 4H), 7.26 (t, $J = 7.2$ Hz, 1H), 7.13 (d, $J = 7.7$ Hz, 1H), 5.43 – 5.22 (m, 2H), 4.33 (t, $J = 7.5$ Hz, 1H), 2.22 – 1.86 (m, 1H), 0.95 (t, $J = 6.5$ Hz, 6H); MS (ES^+): 450.4 ($\text{M}+\text{Na}$).

25

Scheme 4



Preparation of (S)-1-(2-((1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**4d**)

Step-1: Preparation of (S)-tert-butyl (1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamate (**4b**)

- 5 Reaction of (S)-2-(*tert*-butoxycarbonyl(methyl)amino)-3-methylbutanoic acid (**4a**) (500 mg, 2.16 mmol) with 6-bromopyridin-2-amine (**2b**) (374 mg, 2.16 mmol) according to the procedure reported in step-1 of Scheme 2 gave after workup and purification by chromatography on silica gel (12 g) of (S)-tert-butyl (1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamate (**4b**) (135 mg, 0.35 mmol, 16% yield) as a semi-
10 solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.92 (s, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.74 (t, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 2.85 (s, 3H), 2.75 (s, 1H), 2.21 – 2.07 (m, 1H), 1.40 (s, 9H), 0.93 – 0.83 (m, 6H); MS (ES⁺): 410.4 (M+Na); (ES⁻), 386.3 (M-1).

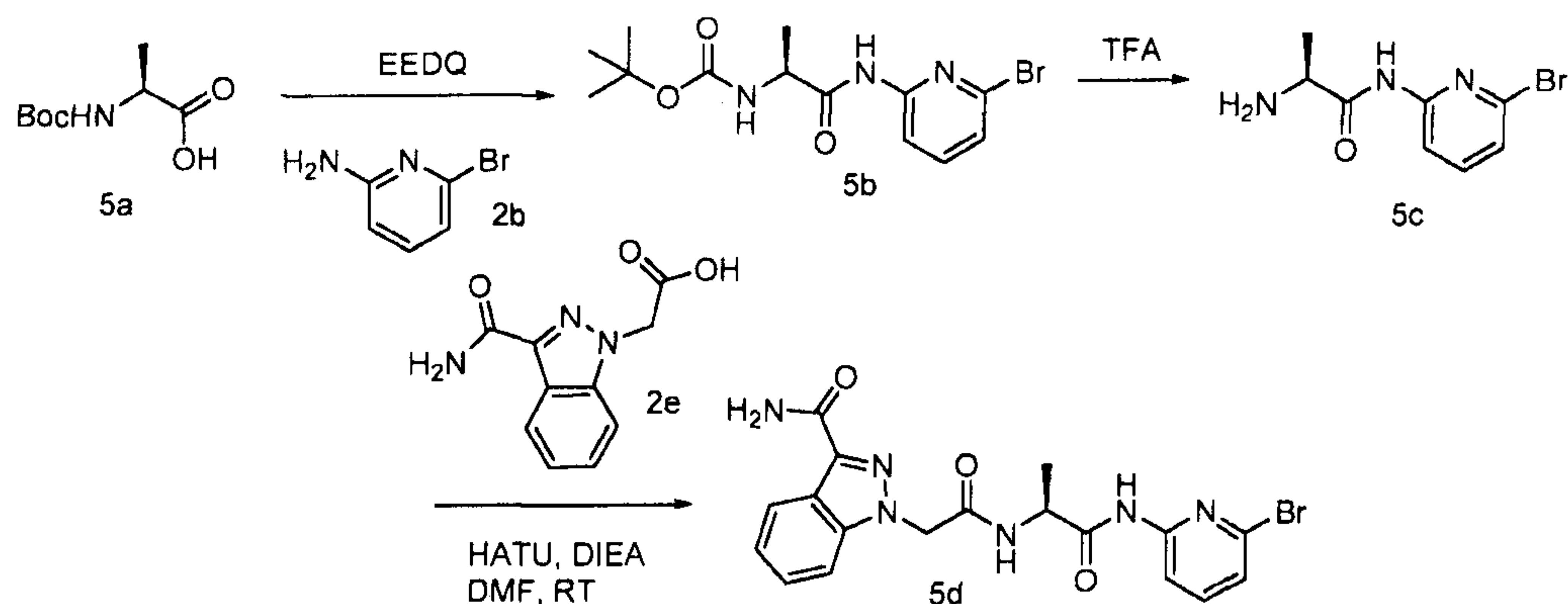
Step-2: Preparation of (S)-N-(6-bromopyridin-2-yl)-3-methyl-2-(methylamino)butanamide (**4c**)

- 15 Reaction of (S)-tert-butyl (1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)carbamate (**4b**) (125 mg, 0.32 mmol) with TFA (369 mg, 3.24 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup (S)-N-(6-bromopyridin-2-yl)-3-methyl-2-(methylamino)butanamide (**4c**) as a TFA salt which was used as such in next step without further purification; MS (ES⁺): 288.3 (M+1).

- 20 Step-3: Preparation of (S)-1-(2-((1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**4d**)

- Reaction of above TFA salt of (S)-N-(6-bromopyridin-2-yl)-3-methyl-2-(methylamino)butanamide (**4c**) (99 mg, 0.247 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (65.1 mg, 0.297 mmol) according to the procedure reported in step-3 of
25 Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane] (S)-1-(2-((1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)(methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**4d**) (53 mg, 0.11 mmol, 44% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.92 (s, 1H), 8.25 - 8.02 (m, 2H), 7.87 - 7.65 (m, 1H), 7.65 - 7.50 (m, 2H), 7.46 - 7.31 (m, 3H), 7.31 - 7.18 (m,
30 1H), 5.78 - 5.44 (m, 2H), 4.84 (d, *J* = 10.8 Hz, 1H), 3.27 - 2.88 (m, 3H), 2.44 - 2.09 (m, 1H), 1.12 - 0.79 (m, 6H); MS (ES⁺): 488.4 (M+1).

Scheme 5



Preparation of (S)-1-(2-((1-((6-bromopyridin-2-yl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**5d**)

5 Step-1: Preparation of (S)-tert-butyl (1-((6-bromopyridin-2-yl)amino)-1-oxopropan-2-yl)carbamate (**5b**)

Reaction of (S)-2-(tert-butoxycarbonylamino)propanoic acid (**5a**) (1.15 g, 6.07 mmol) with 6-bromopyridin-2-amine (**2b**) (1.0 g, 5.78 mmol) according to the procedure reported in step-1 of Scheme 2 gave after workup and purification by chromatography (S)-tert-butyl (1-((6-bromopyridin-2-yl)amino)-1-oxopropan-2-yl)carbamate (**5b**) (250 mg, 0.73 mmol, 13%
10 yield) as a clear oil; MS (ES⁻): 342.4 (M-1).

Step-2: Preparation of (S)-2-amino-N-(6-bromopyridin-2-yl)propanamide (**5c**)

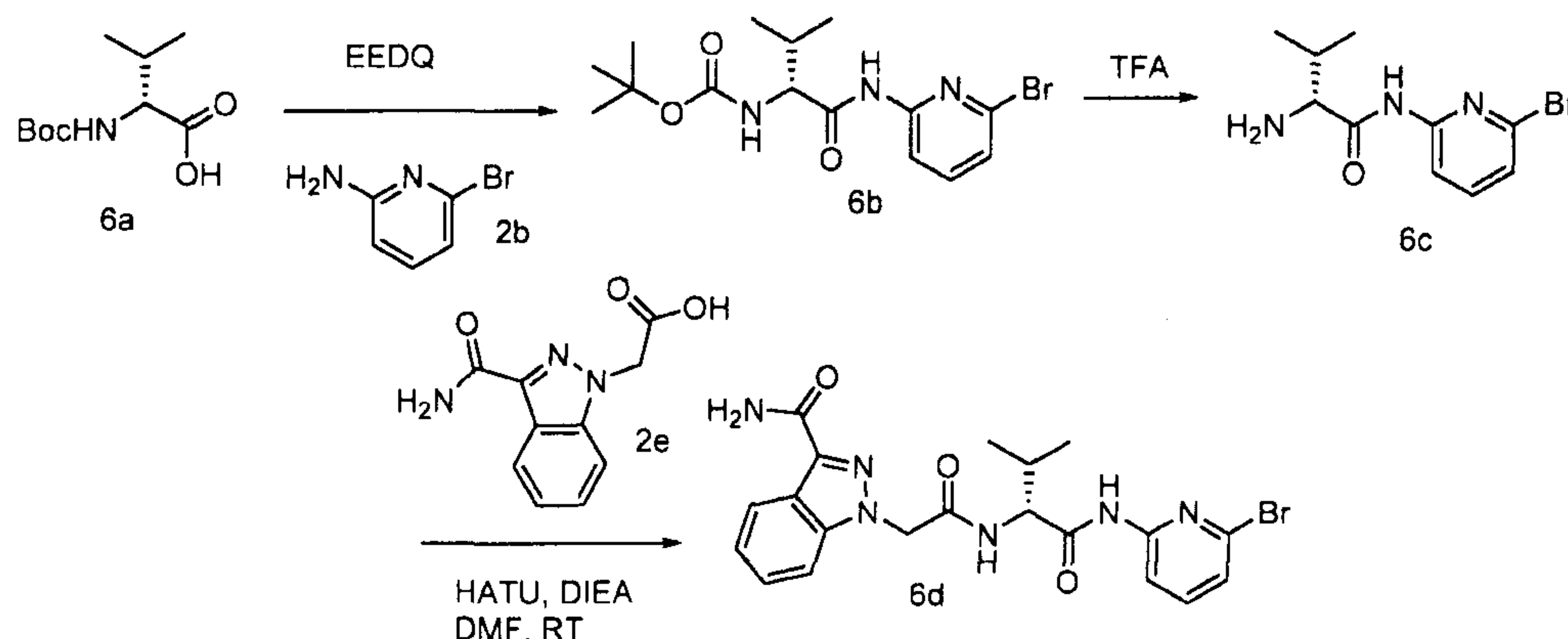
Reaction of (S)-tert-butyl (1-((6-bromopyridin-2-yl)amino)-1-oxopropan-2-yl)carbamate (**5b**) (225 mg, 0.65 mmol) with TFA (745 mg, 6.54 mmol) according to the procedure reported in
15 step-2 of Scheme 2 gave after workup (S)-2-amino-N-(6-bromopyridin-2-yl)propanamide (**5c**) as TFA salt which was used in next step without further purification; MS (ES⁺): 245.2 (M+1).

Step-3: Preparation of (S)-1-(2-((1-((6-bromopyridin-2-yl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**5d**)

20 Reaction of above TFA salt of (S)-2-amino-N-(6-bromopyridin-2-yl)propanamide (**5c**) (125 mg, 0.35 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (92 mg, 0.419 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with 0-60% EtOAc/MeOH (9:1) in hexane] (S)-1-(2-((1-((6-bromopyridin-2-yl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**5d**) (18 mg, 12% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ
25 10.96 (s, 1H), 8.75 (d, *J* = 6.9 Hz, 1H), 8.16 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 8.2 Hz, 1H),

7.79 - 7.56 (m, 3H), 7.47 - 7.30 (m, 3H), 7.30 - 7.18 (m, 1H), 5.26 (s, 2H), 4.71 - 4.36 (m, 1H), 1.34 (d, $J = 7.1$ Hz, 3H); MS (ES⁺): 467.4 (M+Na).

Scheme 6



- 5 Preparation of (R)-1-(2-((1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**6d**)

Step-1: Preparation of (R)-tert-butyl (1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (**6b**)

Reaction of (R)-2-((tert-butoxycarbonyl)amino)-3-methylbutanoic acid (**6a**) (1.0 g, 4.6
 10 mmol) with 6-bromopyridin-2-amine (**2b**) (1.0 g, 5.80 mmol) according to the procedure reported in step-1 of Scheme 2 gave after workup and purification by chromatography (R)-tert-butyl (1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (**6b**) (523mg, 31% yield) as a white semi-solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.78 (s, 1H), 8.09 (d, $J = 8.2$ Hz, 1H), 7.83 – 7.66 (m, 1H), 7.34 (d, $J = 7.6$ Hz, 1H), 6.97 (d, $J = 8.4$ Hz, 1H), 4.03 (t, $J = 7.8$ Hz, 1H), 2.07 – 1.87 (m, 1H), 1.40 (s, 9H), 0.92 – 0.84 (m, 6H); MS
 15 (ES⁺): 394.4 (M+Na).

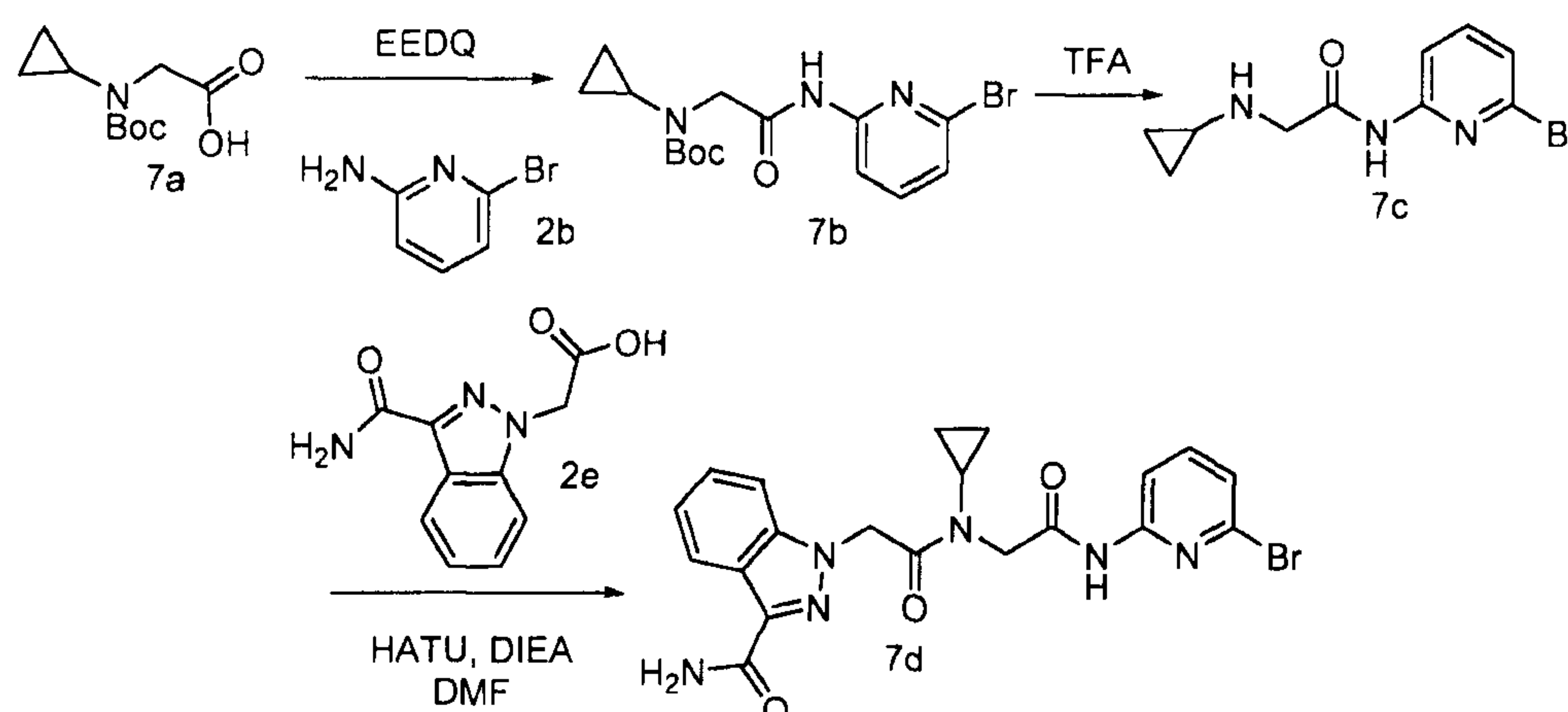
Step-2: Preparation of (R)-2-amino-N-(6-bromopyridin-2-yl)-3-methylbutanamide (**6c**)

Reaction of (R)-tert-butyl (1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (**6b**) (490 mg, 1.32 mmol) with TFA (750 mg, 6.58 mmol) according to the
 20 procedure reported in step-2 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with MeOH in CHCl₃ 0 to 20%] to give (R)-2-amino-N-(6-bromopyridin-2-yl)-3-methylbutanamide (**6c**) (185 mg, 0.680 mmol, 52% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.13 (d, $J = 8.1$ Hz, 1H), 7.74 (t, $J = 7.9$ Hz, 1H), 7.34 (d, $J = 7.7$ Hz, 1H), 3.22 (d, $J = 5.2$ Hz, 1H), 2.02 – 1.85 (m, 1H), 0.91 (d, $J = 6.8$
 25 Hz, 3H), 0.82 (d, $J = 6.8$ Hz, 3H); MS (ES⁺): 272.3 (M+1).

Step-3: Preparation of (R)-tert-butyl (1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (**6b**)

Reaction of (R)-2-amino-N-(6-bromopyridin-2-yl)-3-methylbutanamide (**6c**) (91 mg, 0.33 mmol) with 2-(3-carbamoyl-1*H*-indazol-1-yl)acetic acid (**2e**) (88 mg, 0.4 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 40%] to give (R)-tert-butyl (1-((6-bromopyridin-2-yl)amino)-3-methyl-1-oxobutan-2-yl)carbamate (**6b**) (65 mg, 0.14 mmol, 41% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.12 – 10.90 (m, 1H), 8.58 (d, *J* = 7.8 Hz, 1H), 8.14 (dd, *J* = 21.5, 8.0 Hz, 2H), 7.84 – 7.53 (m, 3H), 7.50 – 7.10 (m, 4H), 5.43 – 5.19 (m, 2H), 4.57 – 4.34 (m, 1H), 2.18 – 2.00 (m, 1H), 0.94 (s, 6H); MS (ES⁺): 473.4 (M+1).

Scheme 7



Preparation of 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1*H*-indazole-3-carboxamide (**7d**)

Step-1: Preparation of tert-butyl (2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl) carbamate (**7b**)

Reaction of 2-((tert-butoxycarbonyl)(cyclopropyl)amino)acetic acid (**7a**) (0.5 g, 2.32 mmol) with 6-bromopyridin-2-amine (**2b**) (0.4 g, 2.32 mmol) according to the procedure reported in step-1 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with MeOH in CHCl₃ from 0-20%] tert-butyl (2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl) carbamate (**7b**) contaminated with 6-bromopyridin-2-amine (**2b**).

Step-2: Preparation of N-(6-bromopyridin-2-yl)-2-(cyclopropylamino)acetamide (**7c**)

Reaction of tert-butyl (2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl) carbamate (**7b**) from above step-1 with TFA (0.9 mL, 11.61 mmol) according to the procedure reported

in step-2 of Scheme 2 gave after workup N-(6-bromopyridin-2-yl)-2-(cyclopropylamino)acetamide (**7c**) as a TFA salt; MS (ES⁺): 272.3 (M+2).

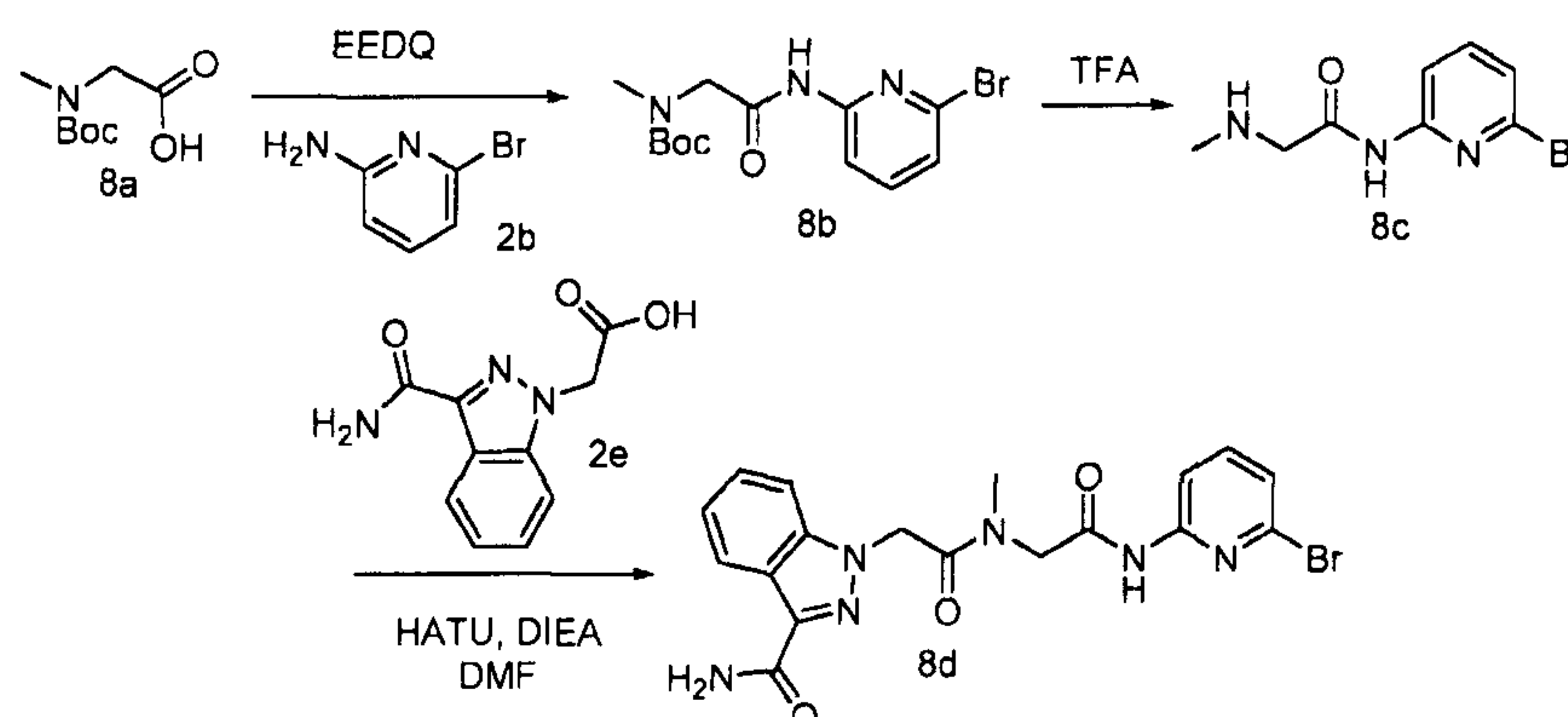
Step-3: Preparation of 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**7d**)

- 5 Reaction of N-(6-bromopyridin-2-yl)-2-(cyclopropylamino)acetamide (**7c**) TFA salt from above step-2 (90 mg, 0.33 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (88 mg, 0.4 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 40%] 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**7d**) (24 mg, 0.051 mmol, 15% yield for three steps) as a white solid.

¹H NMR (300 MHz, DMSO-*d*₆) δ 10.96 (s, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 8.1 Hz, 1H), 7.81 – 7.59 (m, 3H), 7.51 – 7.18 (m, 4H), 5.70 (s, 2H), 4.18 (s, 2H), 3.15 – 3.05 (m, 1H), 1.15 – 0.77 (m, 4H); MS (ES⁺): 471.4 (M+1).

15

Scheme 8



Preparation of 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**8d**)

Step-1: Preparation of tert-butyl (2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(methyl)carbamate (**8b**)

- 20 Reaction of 2-((tert-butoxycarbonyl)(methyl)amino)acetic acid (**8a**) (2 g, 10.57 mmol) with 6-bromopyridin-2-amine (**2b**) (1.52 g, 8.81 mmol) according to the procedure reported in step-1 of Scheme 2 gave after workup and purification by chromatography [silica gel (24 g), eluting with EtOAc (0-50 %) in hexane] tert-butyl (2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(methyl)carbamate (**8b**) (685 mg, 1.99 mmol, 23% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.90 (d, 1H), 8.06 (t, *J* = 7.8 Hz, 1H), 7.74 (td, *J* = 8.0, 3.6 Hz, 1H),

7.34 (d, $J = 7.7$ Hz, 1H), 4.01 (d, $J = 7.5$ Hz, 2H), 2.84 (d, $J = 8.0$ Hz, 3H), 1.35 (d, $J = 27.9$ Hz, 9H); MS (ES⁺): 344.3 (M+1).

Step-2: Preparation of N-(6-bromopyridin-2-yl)-2-(methylamino)acetamide (**8c**)

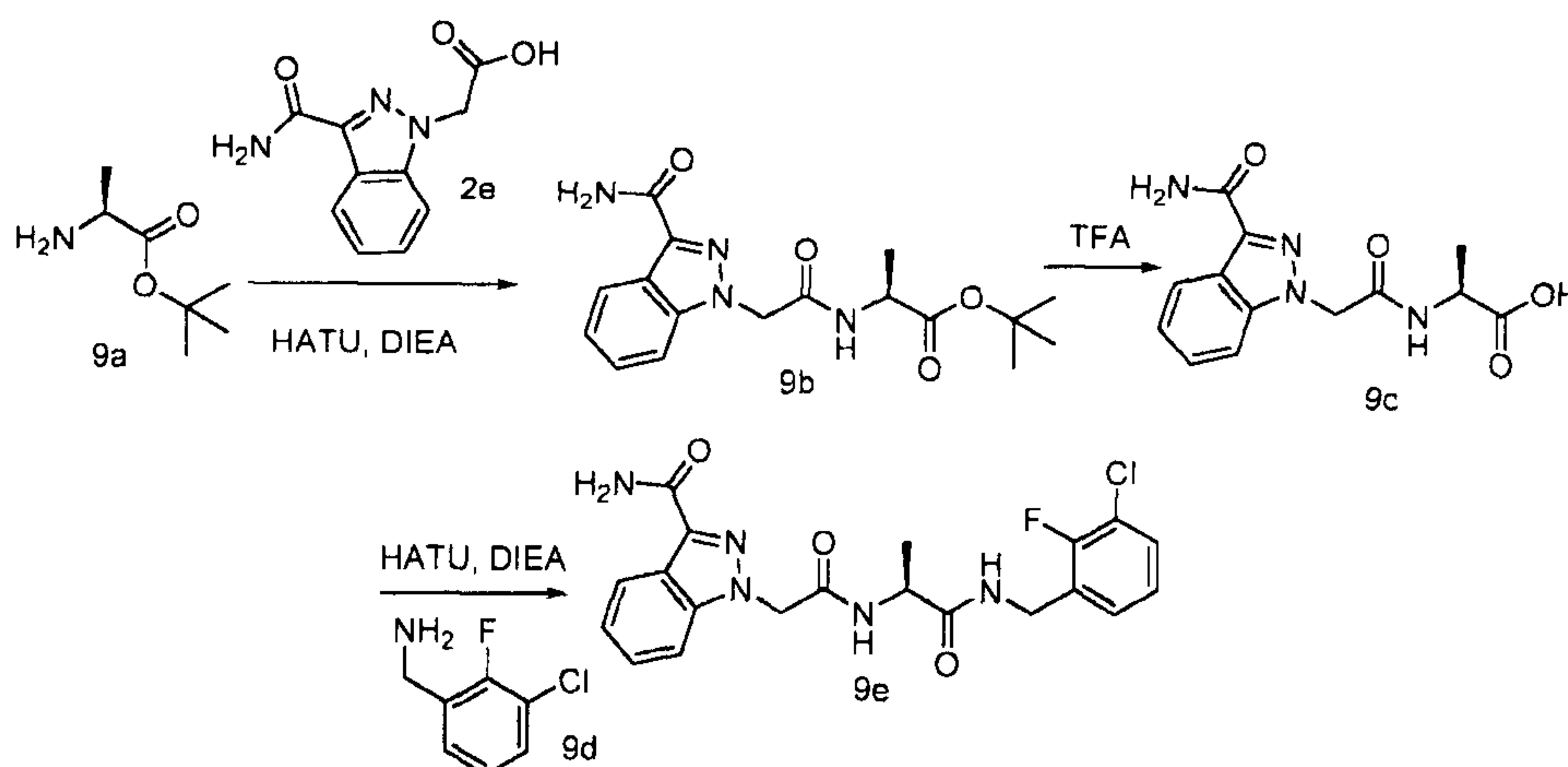
Reaction of tert-butyl (2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(methyl)carbamate (**8b**)

5 (650 mg, 1.89 mmol) with TFA (0.73 mL, 9.44 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with MeOH in CHCl₃ 0 to 20%] N-(6-bromopyridin-2-yl)-2-(methylamino)acetamide (**8c**) (285 mg, 1.17 mmol, 62% yield) as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.38 (s, 1H), 8.93 (s, 2H), 8.05 (d, $J = 7.9$ Hz, 1H), 7.81 (t, $J = 8.0$ Hz, 1H), 7.51 – 7.32 (m, 1H), 3.98 (s, 2H), 2.62 (s, 3H); MS (ES⁺): 244.3 (M+1).

Step-3: Preparation of 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**8d**)

Reaction of N-(6-bromopyridin-2-yl)-2-(methylamino)acetamide (**8c**) (90 mg, 0.37 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (88 mg, 0.4 mmol) according to the
15 procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 30%] 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**8d**) (67 mg, 0.15 mmol, 41% yield for three steps) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.30 – 10.84 (2s at 11.22, 10.94, 1H), 8.23 – 8.00 (m, 2H), 7.87 – 7.56 (m, 3H), 7.49 – 7.21 (m, 4H), 5.54 (2s at 5.61, 5.46, 2H), 4.34 (2 s at 4.47, 4.20, 2H), 3.04 (2 s at 3.23, 2.85, 3H); MS (ES⁺): 467.4 (M+Na).

Scheme 9



Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**9e**)
25

Step-1: Preparation of (S)-tert-butyl 2-(2-(3-carbamoyl-1H-indazol-1-yl)acetamido)propanoate (**9b**)

Reaction of (S)-tert-butyl 2-aminopropanoate (**9a**) (767 mg, 4.22 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (1.02 g, 4.64 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (40 g), eluting with CMA80 in CHCl₃ 0 to 40%] (S)-tert-butyl 2-(2-(3-carbamoyl-1H-indazol-1-yl)acetamido)propanoate (**9b**) (965 mg, 2.79 mmol, 66% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.73 (d, *J* = 7.1 Hz, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.77 – 7.57 (m, 2H), 7.49 – 7.33 (m, 2H), 7.26 (t, *J* = 7.5 Hz, 1H), 5.22 (s, 2H), 4.23 – 4.06 (m, 1H), 1.38 (s, 9H), 1.30 (d, *J* = 7.3 Hz, 3H); MS (ES⁺): 369.5 (M+Na); 345.4 (M-1).

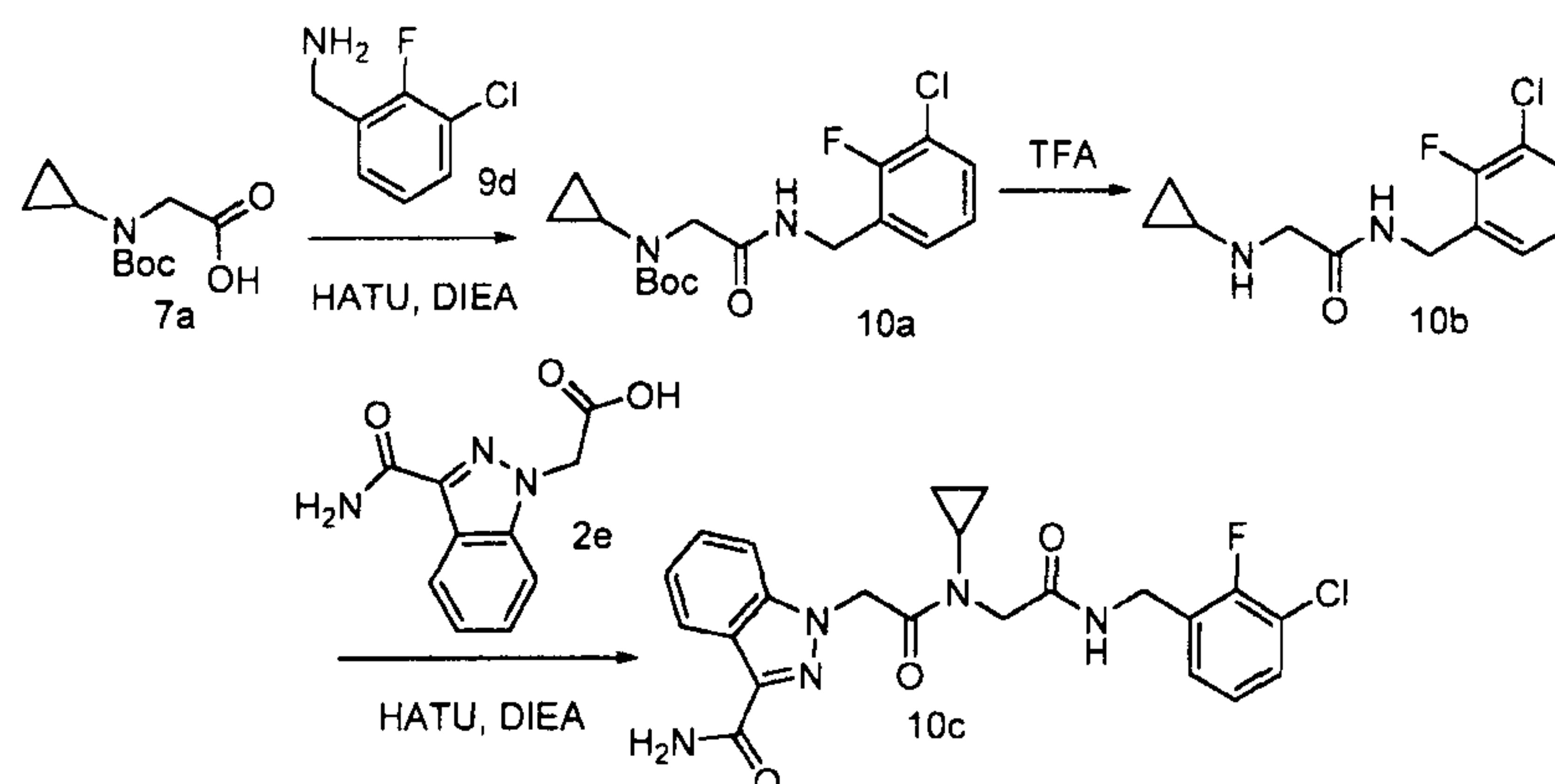
Step-2: Preparation of (S)-2-(2-(3-carbamoyl-1H-indazol-1-yl)acetamido)propanoic acid (**9c**)

Reaction of (S)-tert-butyl 2-(2-(3-carbamoyl-1H-indazol-1-yl)acetamido)propanoate (**9b**) (900 mg, 2.6 mmol) with TFA (1.2 mL, 15.59 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup (S)-2-(2-(3-carbamoyl-1H-indazol-1-yl)acetamido)propanoic acid (**9c**) (750 mg, 2.58 mmol, 99% yield) as a TFA salt which was used in the next step without further purification.

Step-3: Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**9e**)

Reaction of (S)-2-(2-(3-carbamoyl-1H-indazol-1-yl)acetamido)propanoic acid (**9c**) (100 mg, 0.35 mmol) TFA salt from above step-2 with 3-chloro-2-fluorobenzylamine (**9d**) (66.0 mg, 0.413 mmol), according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by [silica (12 g), eluting with CMA80 in CHCl₃ from 0 to 50%] (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**9e**) (22 mg, 0.05 mmol, 15% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.68 (d, *J* = 7.2 Hz, 1H), 8.64 – 8.57 (m, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.72 (s, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.57 – 7.33 (m, 3H), 7.34 – 7.19 (m, 2H), 7.19 – 7.06 (m, 1H), 5.25 (s, 2H), 4.44 – 4.20 (m, 3H), 1.28 (d, *J* = 6.9 Hz, 3H); MS (ES⁺): 454.4 (M+Na); 430.4 (M-1).

Scheme 10



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**10c**)

- 5 Step-1: Preparation of tert-butyl (2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)carbamate (**10a**)

Reaction of 2-((tert-butoxycarbonyl)(cyclopropyl)amino)acetic acid (**7a**) (250 mg, 1.16 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (185 mg, 1.16 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by
 10 chromatography [silica (40 g), eluting with EtOAc in hexane 0 to 50%] tert-butyl (2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)carbamate (**10a**) (365 mg, 1.02 mmol, 88% yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.42 (t, *J* = 5.9 Hz, 1H), 7.53 – 7.42 (m, 1H), 7.34 – 7.23 (m, 1H), 7.22 – 7.11 (m, 1H), 4.33 (d, *J* = 5.7 Hz, 2H), 3.76 (s, 2H), 2.67 – 2.54 (m, 1H), 1.46 – 1.10 (m, 9H), 0.68 – 0.43 (m, 4H); MS (ES⁺): 379.4
 15 (M+Na).

Step-2: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**)

Reaction of tert-butyl (2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)carbamate (**10a**) (365 mg, 1.02 mmol) with TFA (0.54 mL, 6.97 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (265 mg, 0.715 mmol, 61.5%
 20 yield) as a TFA salt, which was used in the next step without further purification; MS (ES⁺) 257.3 (M+1).

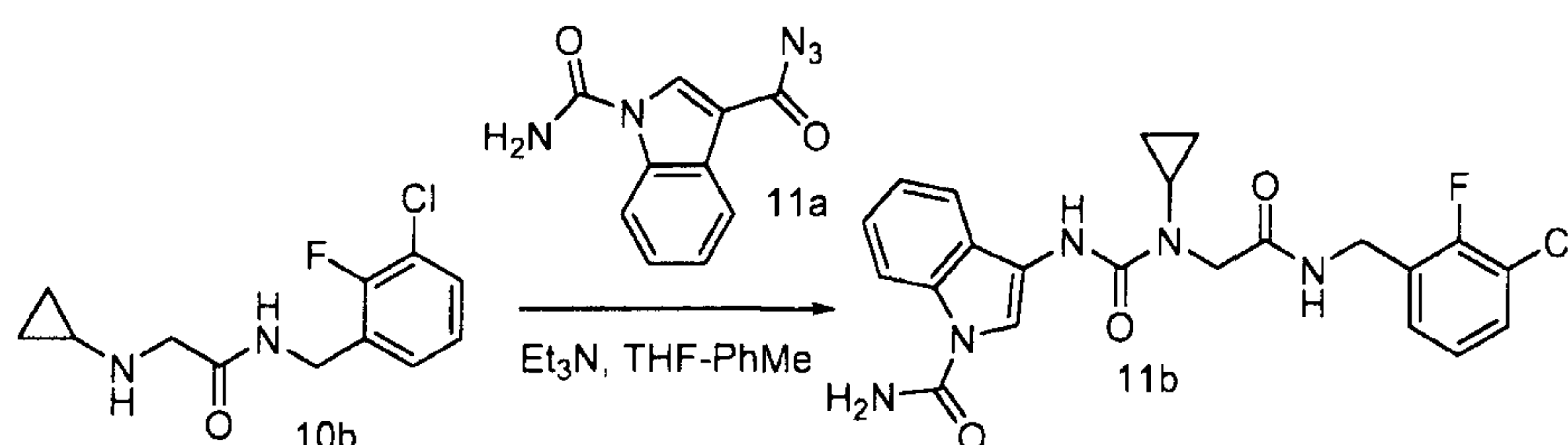
Step-3: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**10c**)

25 Reaction of N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (150 mg, 0.41 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid

(**2e**) (106 mg, 0.49 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by [silica (12 g), eluting with CMA80 in CHCl₃ from 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**10c**) (85 mg, 0.19 mmol, 46% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.51 (t, *J* = 5.8 Hz, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.74 (s, 1H), 7.64 (d, *J* = 8.5 Hz, 1H), 7.52 – 7.33 (m, 3H), 7.31 – 7.16 (m, 2H), 7.16 – 7.05 (m, 1H), 5.67 (s, 2H), 4.33 (d, *J* = 5.5 Hz, 2H), 3.98 (s, 2H), 3.14 – 2.99 (m, 1H), 1.08 – 0.95 (m, 2H), 0.95 – 0.86 (m, 2H); ¹⁹F NMR (282 MHz, DMSO) δ -121.33; MS (ES⁺): 458.5 (M+1); 456.5 (M-1).

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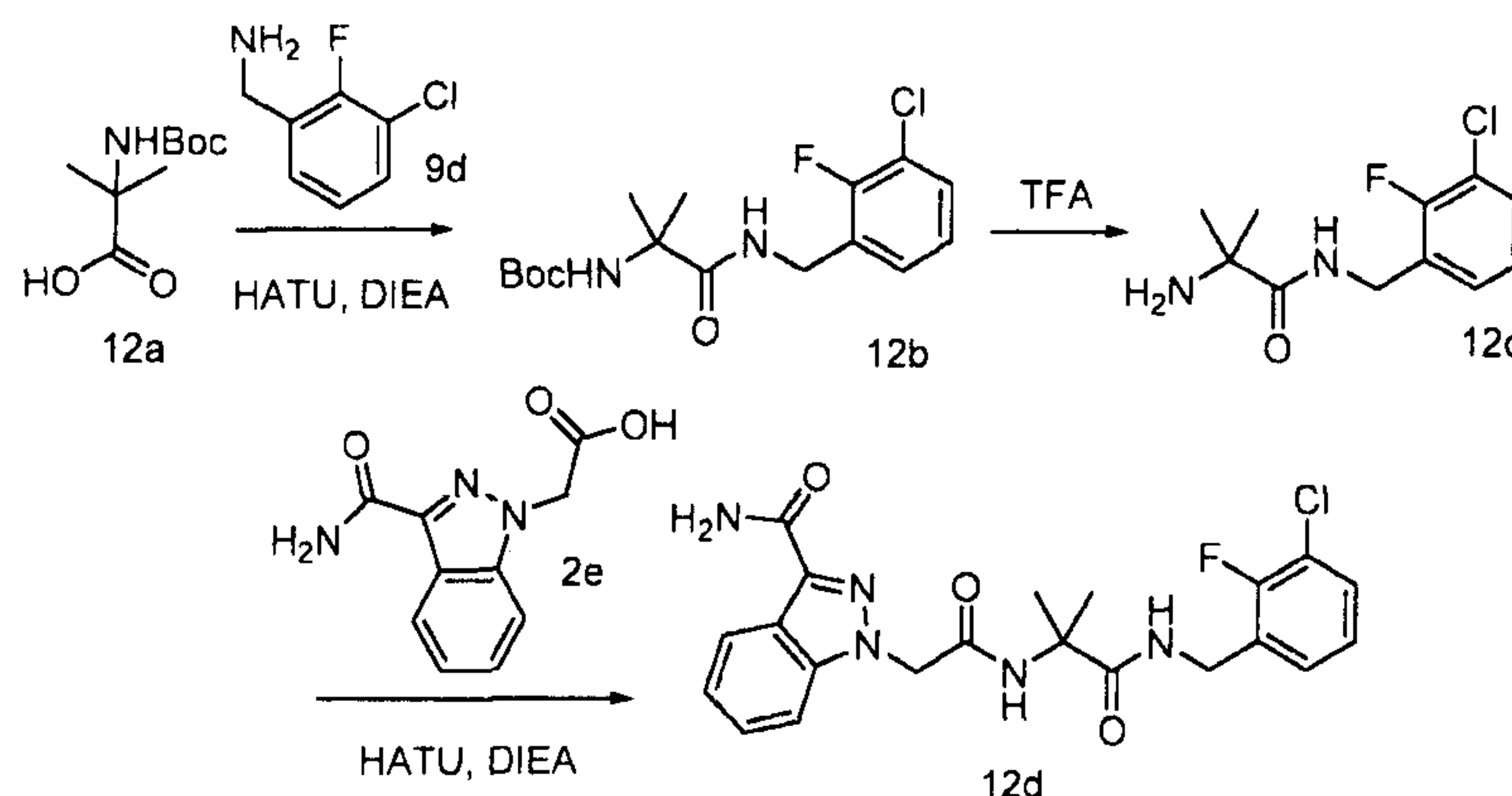
Scheme 11



Preparation of 3-(3-(2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)-3-cyclopropylureido)-1H-indole-1-carboxamide (**11b**)

A suspension of 1-carbamoyl-1H-indole-3-carbonyl azide (**11a**) (50 mg, 0.22 mmol, prepared according to procedure reported by Altmann, Eva et al; in PCT Int. Appl., WO 2012/093101) in toluene (10 mL) was refluxed for 1.5 h. The resulting clear solution was cooled to room temperature and added a solution of N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (56.0 mg, 0.22 mmol) in THF (5 mL), and triethylamine (0.061 μL, 0.44 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated in vacuum. The residue obtained was purified by flash column chromatography [Silica gel (24 g) eluting with CMA80 in CHCl₃ 0 to 40%] to afford 3-(3-(2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)-3-cyclopropylureido)-1H-indole-1-carboxamide (**11b**) (42 mg, 0.092 mmol, 42% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.47 (t, *J* = 5.9 Hz, 1H), 8.33 - 8.23 (m, 2H), 8.03 (s, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.55 - 7.39 (m, 1H), 7.37 - 7.23 (m, 2H), 7.23 - 7.14 (m, 2H), 4.36 (d, *J* = 5.7 Hz, 2H), 3.99 (s, 2H), 2.99 - 2.84 (m, 1H), 1.01 - 0.88 (m, 2H), 0.80 (d, *J* = 3.8 Hz, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.33 (t, *J* = 6.9 Hz); MS (ES⁺) 458.5 (M+1).

Scheme 12



Preparation of 1-(2-(1-(3-chloro-2-fluorobenzylamino)-2-methyl-1-oxopropan-2-ylamino)-2-oxoethyl)-1H-indazole-3-carboxamide (**12d**)

- 5 Step-1: Preparation of tert-butyl 2-(2-(3-chloro-2-fluorophenyl)propan-2-ylamino)-2-oxoethylcarbamate (**12b**)

Reaction of 2-(tert-butoxycarbonylamino)-2-methylpropanoic acid (**12a**) (650 mg, 3.2 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (425 mg, 2.67 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica
10 (12 g), eluting with EtOAc in hexane from 0-50%] tert-butyl 2-(2-(3-chloro-2-fluorophenyl)propan-2-ylamino)-2-oxoethylcarbamate (**12b**) (752 mg, 2.18 mmol, 82% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.16 (s, 1H), 7.51 – 7.28 (m, 2H), 7.18 – 7.04 (m, 1H), 6.99 (s, 1H), 4.29 (d, *J* = 5.5 Hz, 2H), 1.46 – 1.33 (m, 9H), 1.30 (s, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.85; MS (ES⁺): 345.4 (M+1), 367.4 (M+Na).

- 15 Step-2: Preparation of 2-amino-N-(2-(3-chloro-2-fluorophenyl)propan-2-yl)acetamide (**12c**)

Reaction of tert-butyl 2-(2-(3-chloro-2-fluorophenyl)propan-2-ylamino)-2-oxoethylcarbamate (**12b**) (700 mg, 2.030 mmol) with TFA (0.94 mL, 12.18 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup 2-amino-N-(2-(3-chloro-2-fluorophenyl)propan-2-yl)acetamide (**12c**) TFA salt (725 mg, 2.02 mmol, 100% yield) as a
20 semi-solid, which was used in the next step without further purification; ¹H NMR (300 MHz, DMSO-*d*₆) 8.93 (t, *J* = 5.6 Hz, 1H), 8.21 (s, 2H), 7.50 (td, *J* = 7.4, 2.1 Hz, 1H), 7.31 – 7.14 (m, 2H), 4.40 (d, *J* = 5.5 Hz, 2H), 1.48 (s, 6H); ¹⁹F NMR (282 MHz, DMSO) δ -73.40, -121.12; MS (ES⁺): 245.3 (M+1).

Step-3: Preparation of 1-(2-(1-(3-chloro-2-fluorobenzylamino)-2-methyl-1-oxopropan-2-ylamino)-2-oxoethyl)-1H-indazole-3-carboxamide (**12d**)

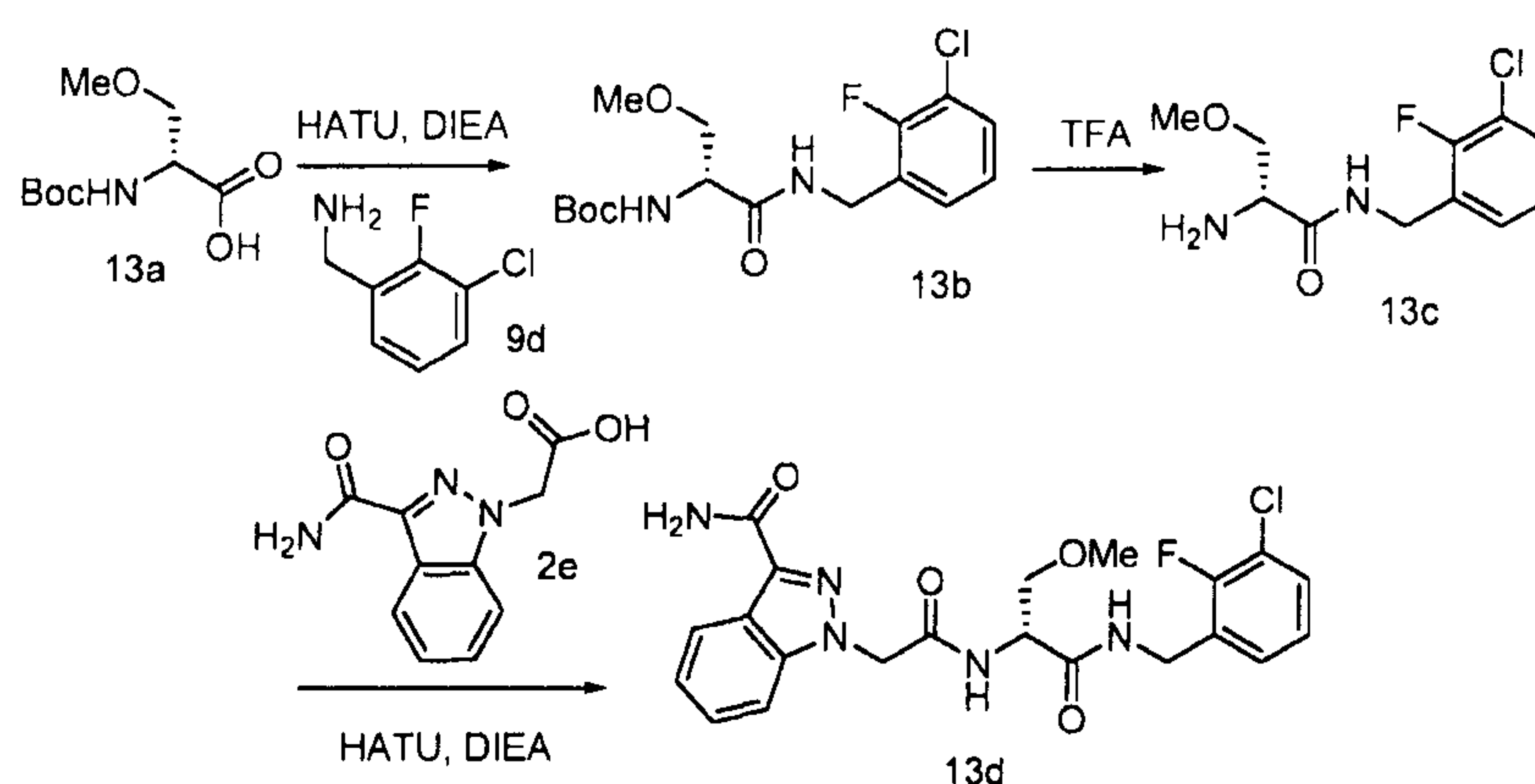
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Reaction of 2-amino-N-(2-(3-chloro-2-fluorophenyl)propan-2-yl)acetamide (**12c**) (300 mg, 0.836 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (220 mg, 1.0 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by [silica (12 g), eluting with CMA80 in CHCl₃ from 0 to 40%] 1-(2-(1-(3-chloro-2-fluorobenzylamino)-2-methyl-1-oxopropan-2-ylamino)-2-oxoethyl)-1H-indazole-3-carboxamide (**12d**) (185 mg, 0.42 mmol, 50% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.58 (s, 1H), 8.36 (t, *J* = 5.9 Hz, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 7.69 (s, 1H), 7.62 – 7.53 (m, 1H), 7.46 – 7.32 (m, 3H), 7.30 – 7.14 (m, 2H), 6.92 (t, *J* = 7.9 Hz, 1H), 5.24 (s, 2H), 4.32 (d, *J* = 5.6 Hz, 2H), 1.41 (s, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.89; MS (ES⁺) 446.5 (M+1), 468.5 (M+Na).

Scheme 13



Preparation of (R)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-3-methoxy-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**13d**)

Step-1: Preparation of (R)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-3-methoxy-1-oxopropan-2-yl)carbamate (**13b**)

Reaction of (R)-2-((tert-butoxycarbonyl)amino)-3-methoxypropanoic acid (**13a**) (382 mg, 1.74 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (232 mg, 1.45 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup (R)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-3-methoxy-1-oxopropan-2-yl)carbamate (**13b**) which was used as such in next step; MS (ES⁺): 383.4 (M+Na).

Step-2: Preparation of (R)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-methoxypropanamide (**13c**)

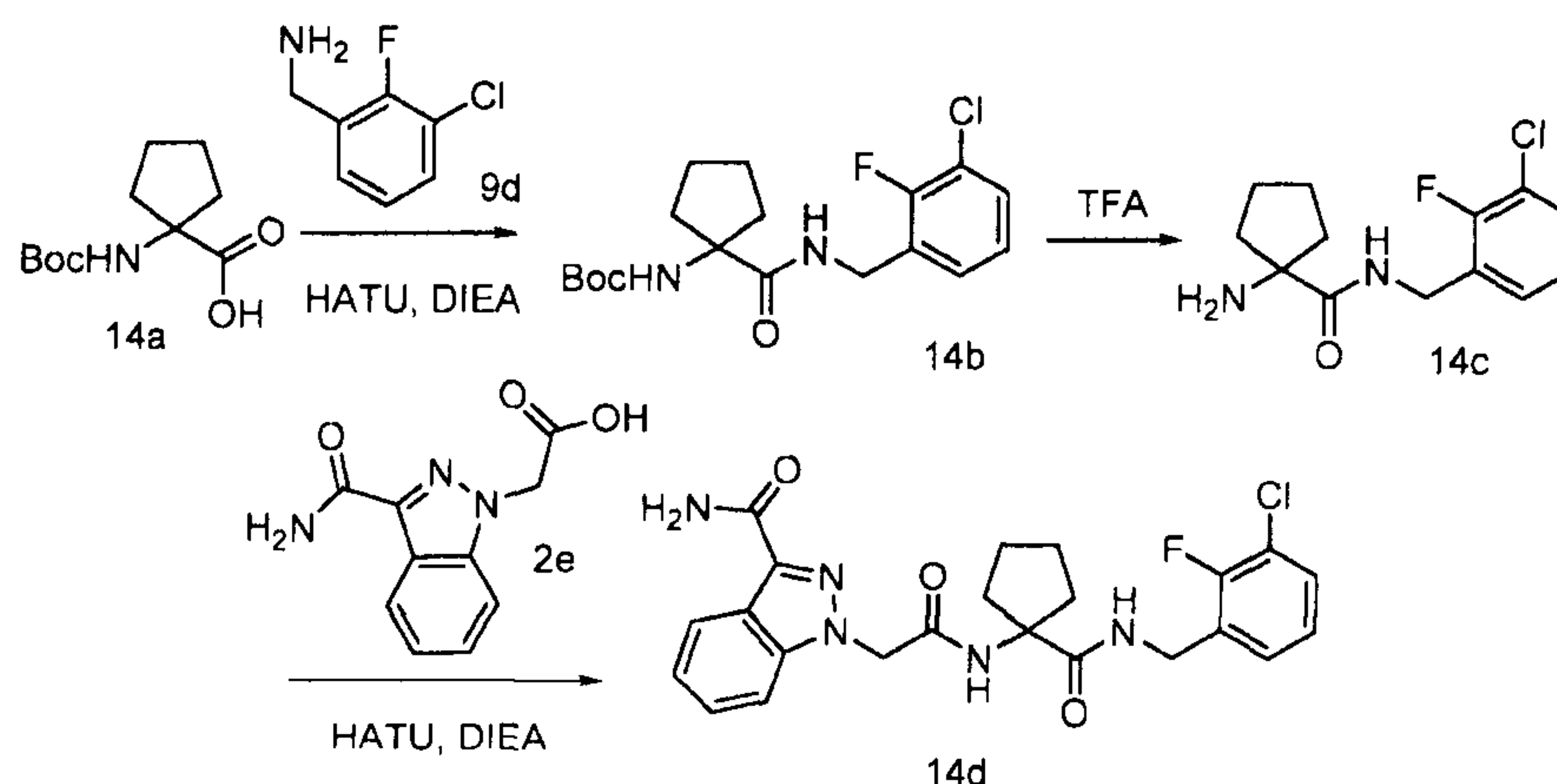
Reaction of (R)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-3-methoxy-1-oxopropan-2-yl)carbamate (**13b**) (525 mg, 1.45 mmol) with TFA (2.02 mL, 26.2 mmol) according to the

procedure reported in step-2 of Scheme 2 gave after workup (R)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-methoxypropanamide (**13c**) TFA salt (379 mg, 1.45 mmol, 100% yield) which was used in the next step without further purification; MS (ES⁺): 261.3 (M+1).

Step-3: Preparation of (R)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-3-methoxy-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**13d**)

Reaction of (R)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-methoxypropanamide (**13c**) (379 mg, 1.45 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (382 mg, 1.75 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (24 g), eluting with MeOH in CHCl₃ from 0 to 40%] (R)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-3-methoxy-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**13d**) (32 mg, 5% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.78 – 8.66 (m, 2H), 8.18 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.72 (s, 1H, D₂O exchangeable), 7.64 (d, *J* = 8.5 Hz, 1H), 7.54 – 7.35 (m, 3H, 1H, D₂O exchangeable), 7.31 – 7.22 (m, 2H), 7.20 – 7.10 (m, 1H), 5.30 (d, *J* = 2.3 Hz, 2H), 4.57 – 4.47 (m, 1H), 4.46 – 4.28 (m, 2H), 3.65 – 3.50 (m, 2H), 3.28 (s, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.28; MS (ES⁺): 484.5 (M+Na); (ES⁻) 496.4 (M+Cl).

Scheme 14



Preparation of 1-(2-((1-((3-chloro-2-fluorobenzyl)carbamoyl)cyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**14d**)

Step-1: Preparation of tert-butyl (1-((3-chloro-2-fluorobenzyl)carbamoyl)cyclopentyl)carbamate (**14b**)

Reaction of 1-((tert-butoxycarbonyl)amino)cyclopentanecarboxylic acid (**14a**) (650 mg, 2.85 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (379 mg, 2.37 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by

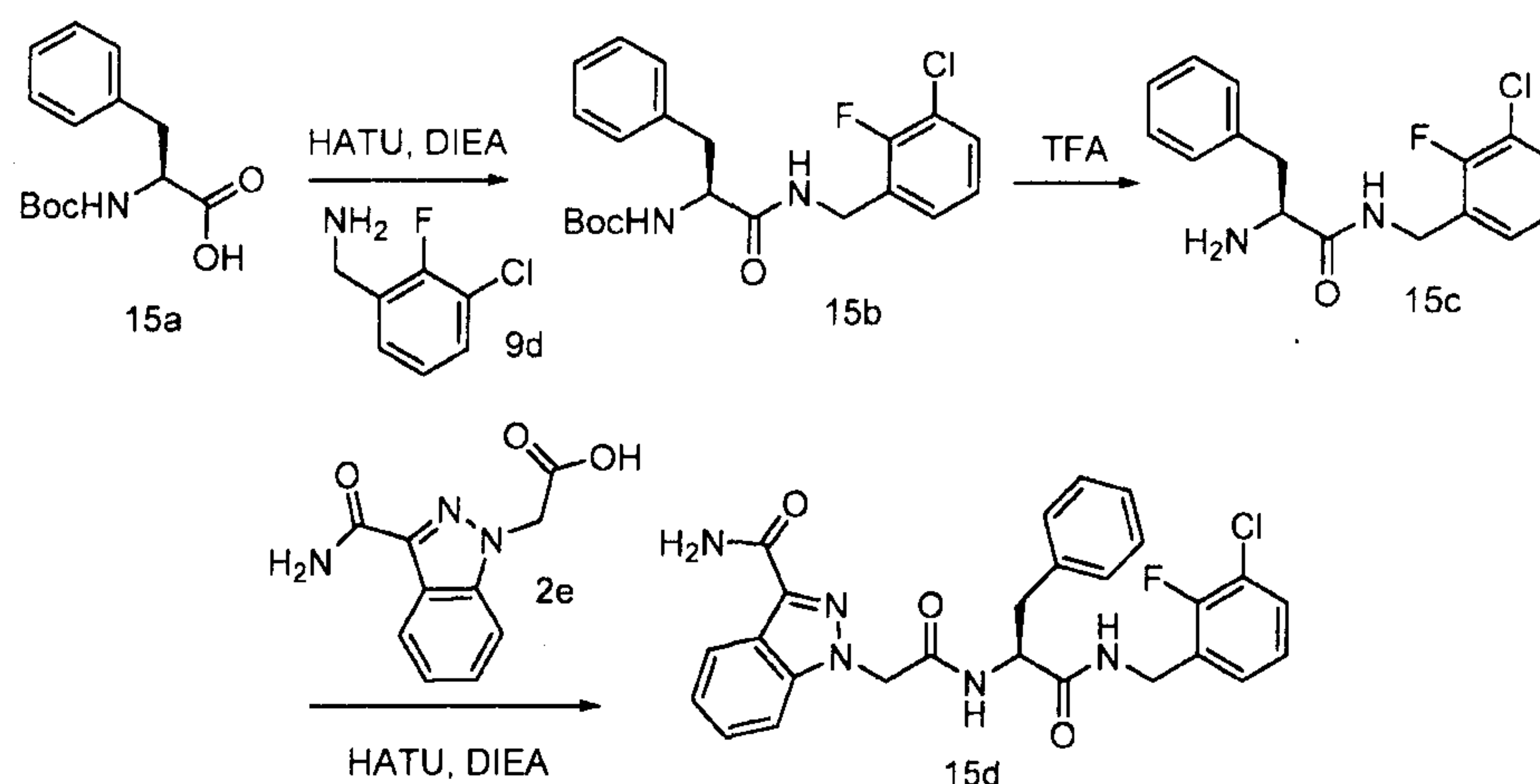
chromatography [silica gel (12 g), eluting with EtOAc in hexane, 0-50 %] tert-butyl (1-((3-chloro-2-fluorobenzyl)carbamoyl)cyclopentyl)carbamate (**14b**) (650 mg, 1.73 mmol, 74% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) 8.15 – 8.06 (m, 1H), 7.43 (t, *J* = 7.1 Hz, 1H), 7.35 (t, *J* = 7.1 Hz, 1H), 7.19 – 7.06 (m, 2H), 4.31 (d, *J* = 5.9 Hz, 2H), 2.07 – 1.92 (m, 2H), 1.89 – 1.71 (m, 3H), 1.65 – 1.55 (m, 3H), 1.38 (s, 9H); MS (ES⁺): 371.4 (M+1), 393.4 (M+Na).

Step-2: Preparation of 1-amino-N-(3-chloro-2-fluorobenzyl)cyclopentanecarboxamide (**14c**)
Reaction of tert-butyl (1-((3-chloro-2-fluorobenzyl)carbamoyl)cyclopentyl)carbamate (**14b**) (650 mg, 1.75 mmol) with TFA (1.35 mL, 17.53 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup 1-amino-N-(3-chloro-2-fluorobenzyl)cyclopentanecarboxamide (**14c**) TFA salt (675 mg, 1.75 mmol, 100% yield) as a clear oil which was used in the next step without further purification; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.86 (t, *J* = 5.2 Hz, 1H), 8.17 (s, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.32 – 7.13 (m, 2H), 4.40 (d, *J* = 5.2 Hz, 2H), 4.13 (s, 1H), 2.10 (s, 2H), 1.86 (d, *J* = 15.6 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO) δ -73.25 (TFA); -121.06; MS (ES⁺): 271.3 (M+1).

Step-3: Preparation of 1-(2-((1-((3-chloro-2-fluorobenzyl)carbamoyl)cyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**14d**)

Reaction of 1-amino-N-(3-chloro-2-fluorobenzyl)cyclopentanecarboxamide (**14c**) (117 mg, 0.53 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (116 mg, 0.53 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 40%] 1-(2-((1-((3-chloro-2-fluorobenzyl)carbamoyl)cyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**14d**) (62 mg, 0.13 mmol, 30% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.63 (s, 1H), 8.37 (t, *J* = 5.9 Hz, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 7.65 (s, 1H), 7.57 (d, *J* = 8.5 Hz, 1H), 7.45 – 7.31 (m, 3H), 7.31 – 7.20 (m, 1H), 7.20 – 7.09 (m, 1H), 6.91 (t, *J* = 7.9 Hz, 1H), 5.25 (s, 2H), 4.33 (d, *J* = 5.7 Hz, 2H), 2.15 – 1.97 (m, 2H), 1.96 – 1.80 (m, 2H), 1.77 – 1.59 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.99; MS (ES⁺): 472.5 (M+1).

Scheme 15



Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**15d**)

Step-1: Preparation of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**15b**)

- 5 Reaction of (S)-2-((tert-butoxycarbonyl)amino)-3-phenylpropanoic acid (**15a**) (475 mg, 1.79 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (238 mg, 1.49 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**15b**) which was used as such in the next step; MS (ES⁻): 441.4 (M+Cl).

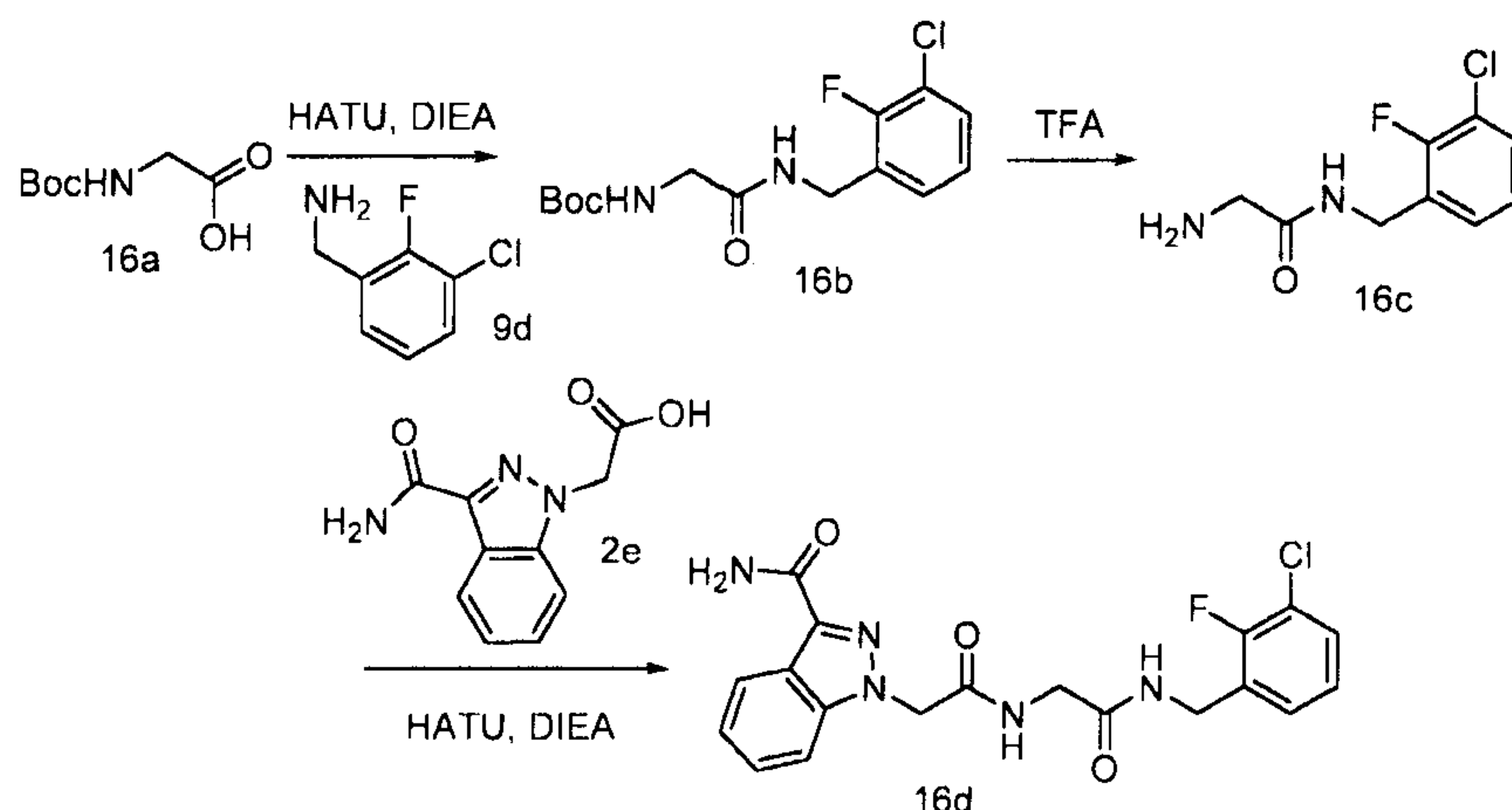
- 10 Step-2: Preparation of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-phenylpropanamide (**15c**)
Reaction of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-1-oxo-3-phenylpropan-2-yl)carbamate (**15b**) (607 mg, 1.5 mmol) with TFA according to the procedure reported in step-2 of Scheme 2 gave after workup (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-phenylpropanamide (**15c**) TFA salt (458 mg, 1.49 mmol, 83%) which was used in next step
15 without further purification; MS (ES⁺): 307.4 (M+1), (ES⁻) 305.2 (M-1).

Step-3: Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**15d**)

- Reaction of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-phenylpropanamide (**15c**) (458 mg, 1.49 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid
20 (**2e**) (393 mg, 1.79 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (24 g), eluting with MeOH in CHCl₃ 0 to 40%] (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxo-3-phenylpropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**15d**) (66 mg, 13% yield) as an off-white solid; ¹H

NMR (300 MHz, DMSO-*d*₆) δ 8.79 – 8.67 (m, 2H), 8.15 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.65 (s, 1H), 7.47 (td, *J* = 7.5, 1.9 Hz, 1H), 7.42 – 7.35 (m, 3H), 7.30 – 7.19 (m, 6H), 7.14 – 7.00 (m, 2H), 5.31 – 5.08 (m, 2H), 4.64 – 4.53 (m, 1H), 4.44 – 4.21 (m, 2H), 3.11 – 2.97 (m, 1H), 2.92 – 2.75 (m, 1H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.21; MS (ES⁺): 530.5 (M+Na); (ES⁻): 506.5 (M-1), 542.4 (M+Cl).

Scheme 16



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**16d**)

Step-1: Preparation of tert-butyl (2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)carbamate (**16b**)

Reaction of 2-((tert-butoxycarbonyl)amino)acetic acid (**16a**) (4 g, 22.83 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (3.31 g, 20.76 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (80g), eluting with EtOAc in hexane from 0 to 60%] tert-butyl (2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)carbamate (**16b**) (4.09 g, 12.91 mmol, 62% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.37 (t, *J* = 5.8 Hz, 1H), 7.53 – 7.41 (m, 1H), 7.35 – 7.23 (m, 1H), 7.24 – 7.12 (m, 1H), 7.05 (t, *J* = 6.0 Hz, 1H), 4.33 (d, *J* = 5.8 Hz, 2H), 3.57 (d, 2H), 1.38 (s, 9H); ¹⁹F NMR (282 MHz, DMSO) δ -121.38; MS (ES⁺): 339.4 (M+Na)

Step-2: Preparation of 2-amino-N-(3-chloro-2-fluorobenzyl)acetamide (**16c**)

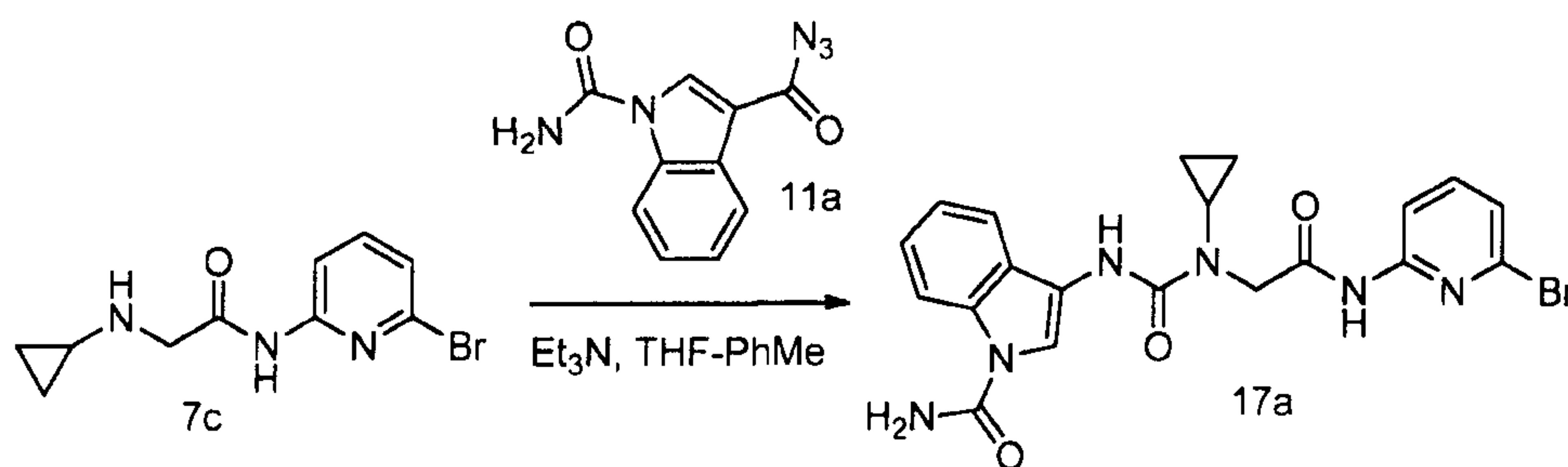
Reaction of tert-butyl (2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)carbamate (**16b**) (4.08 g, 12.88 mmol) with TFA (4.96 mL, 64.4 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup 2-amino-N-(3-chloro-2-fluorobenzyl)acetamide (**16c**) TFA salt (9.07 mmol, 70% yield) as a white solid, which was used in the next step without further purification; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.94 (t, *J* = 5.7 Hz, 1H), 8.04 (s, 3H), 7.56 –

7.45 (m, 1H), 7.40 – 7.29 (m, 1H), 7.27 – 7.15 (m, 1H), 4.41 (d, $J = 5.7$ Hz, 2H), 3.62 (s, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -73.32, -120.87; MS (ES^+) 217.2 ($\text{M}+1$).

Step-3: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**16d**)

Reaction of 2-amino-N-(3-chloro-2-fluorobenzyl)acetamide (**16c**) (160 mg, 0.48 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (127 mg, 0.58 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl_3 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**16d**) (120 mg, 0.29 mmol, 59% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.59 (t, $J = 5.7$ Hz, 1H), 8.54 (t, $J = 5.7$ Hz, 1H), 8.18 (d, $J = 8.0$ Hz, 1H), 7.75 – 7.61 (m, 2H), 7.54 – 7.34 (m, 3H), 7.33 – 7.20 (m, 2H), 7.20 – 7.10 (m, 1H), 5.26 (s, 2H), 4.36 (d, $J = 5.6$ Hz, 2H), 3.82 (d, $J = 5.5$ Hz, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.23; MS (ES^+): 418.5 ($\text{M}+1$), 440.4 ($\text{M}+\text{Na}$); 416.3 ($\text{M}-1$).

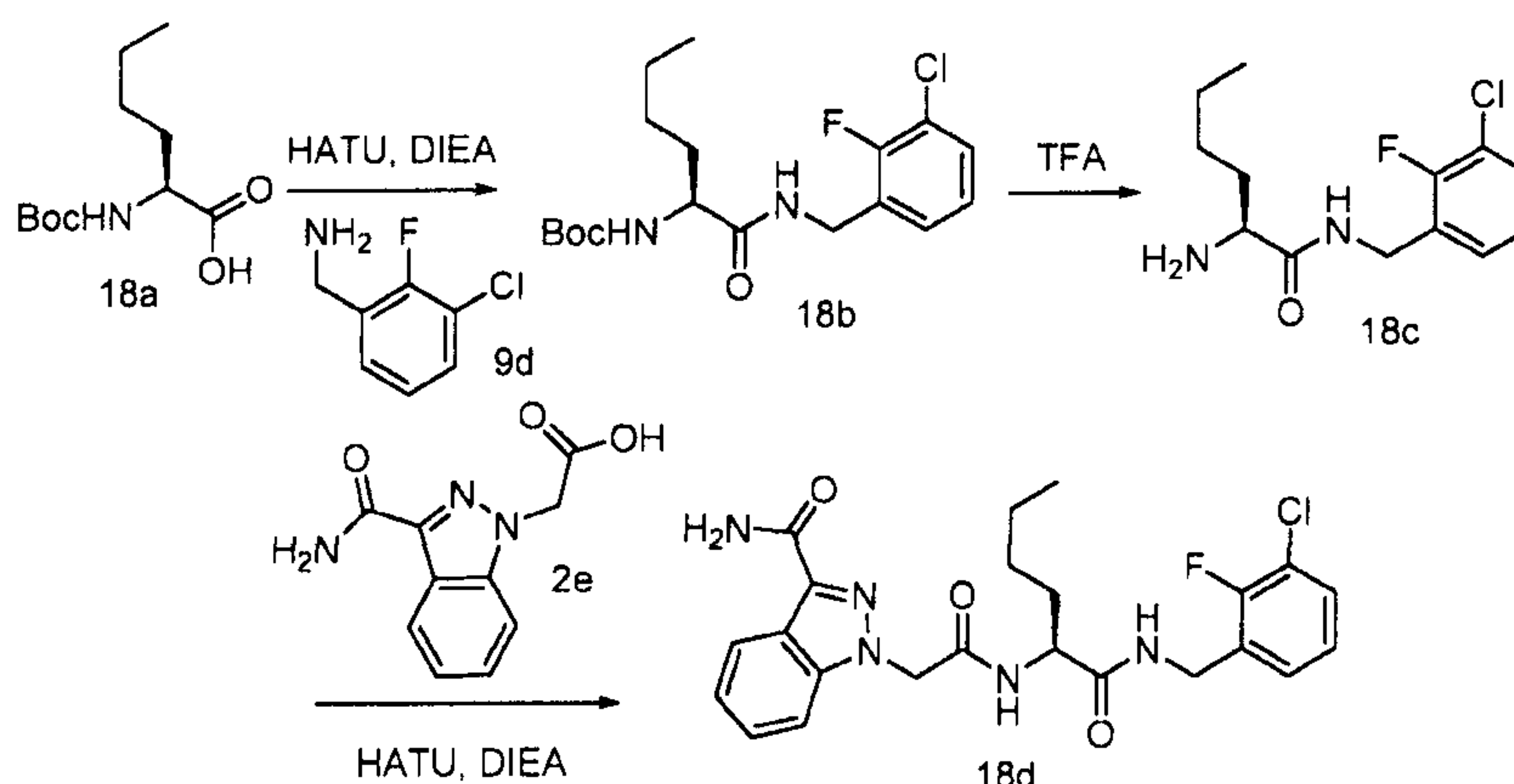
Scheme 17



Preparation of 3-(3-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-3-cyclopropylureido)-1H-indole-1-carboxamide (**17a**)

Reaction of N-(6-bromopyridin-2-yl)-2-(cyclopropylamino)acetamide (**7c**) with 1-carbamoyl-1H-indole-3-carbonyl azide (**11a**) (50 mg, 0.22 mmol) according to the procedure reported in Scheme 11 gave after workup and purification by flash column chromatography (Silica gel, 24 g eluting with CHCl_3 -CMA80 0-40%) 3-(3-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-3-cyclopropylureido)-1H-indole-1-carboxamide (**17a**) (108 mg, 0.23 mmol, 76% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.95 (s, 1H), 8.35 - 8.22 (m, 2H), 8.07 (d, $J = 8.2$ Hz, 1H), 8.02 (s, 1H), 7.78 - 7.64 (m, 2H), 7.42 (s, 2H), 7.34 (d, $J = 7.7$ Hz, 1H), 7.31 - 7.15 (m, 2H), 4.19 (s, 2H), 3.06 - 2.89 (m, 1H), 1.05 - 0.87 (m, 2H), 0.85 - 0.72 (m, 2H); MS (ES^+): 471.4 ($\text{M}+1$), 493.4 ($\text{M}+\text{Na}$).

Scheme 18



Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxohexan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**18d**)

5 Step-1: Preparation of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-1-oxohexan-2-yl)carbamate (**18b**)

Reaction of (S)-2-((tert-butoxycarbonyl)amino)hexanoic acid (**18a**) (0.42 g, 1.8 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (0.239 g, 1.5 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-1-oxohexan-2-yl)carbamate (**18b**) which was used as such in the next step.

Step-2: Preparation of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)hexanamide (**18c**)

Reaction of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-1-oxohexan-2-yl)carbamate (**18b**) (0.56 g, 1.5 mmol) with TFA (2.08 mL, 26.9 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup (S)-2-amino-N-(3-chloro-2-fluorobenzyl)hexanamide (**18c**) TFA salt (9.07 mmol, 70% yield) which was used as such in the next step; MS (ES⁺): 273.4 (M+1).

Step-3: Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxohexan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**18d**)

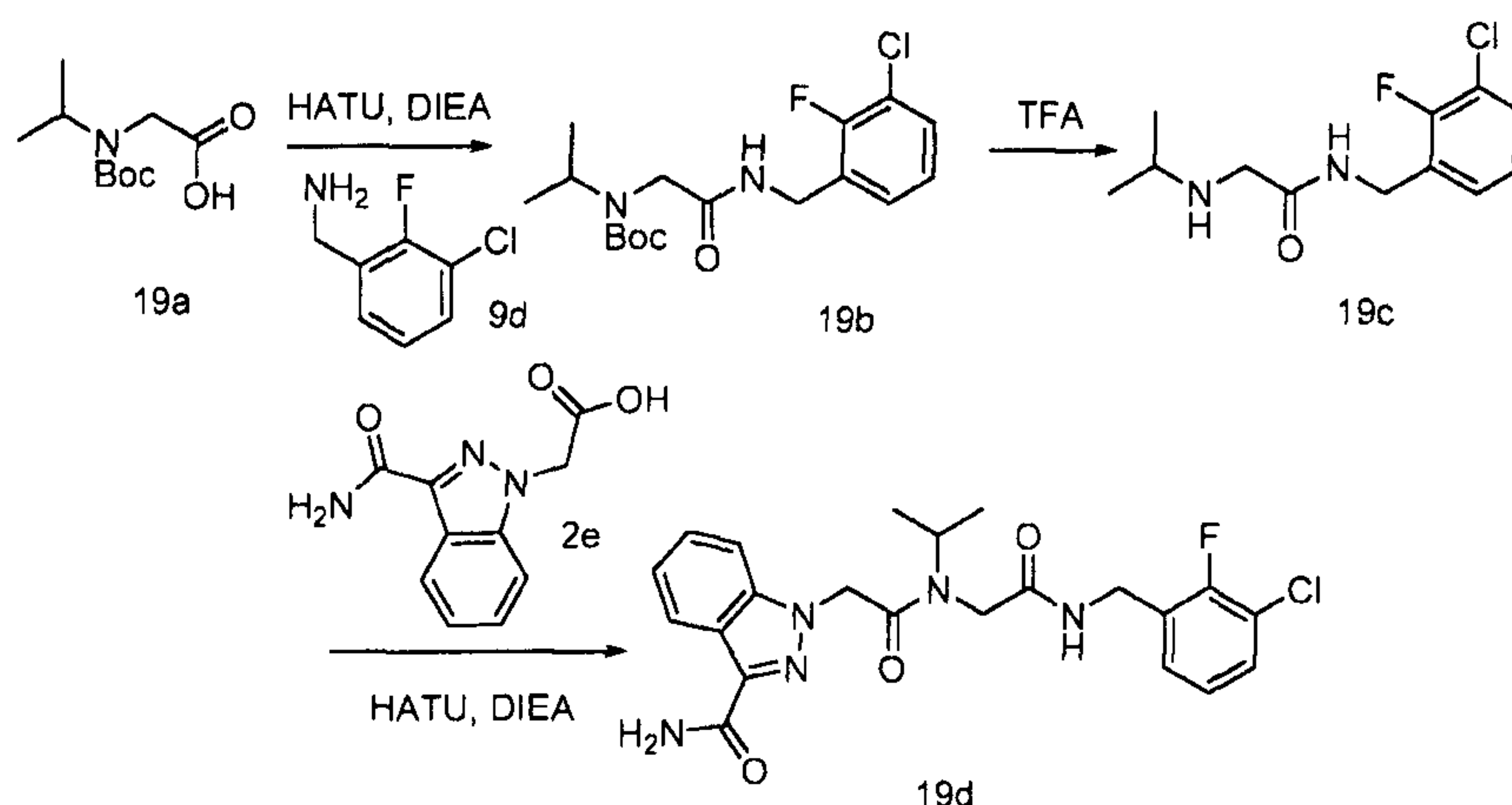
Reaction of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)hexanamide (**18c**) (408 mg, 1.5 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (393 mg, 1.8 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup gave (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxohexan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**18d**) (56 mg, 0.12 mmol, 8% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.76 – 8.62 (m, 2H, D₂O exchangeable), 8.24 (d, *J* = 8.1 Hz, 1H), 7.76 (s, 1H, D₂O exchangeable), 7.69 (d, *J* = 8.6 Hz, 1H), 7.60 – 7.42 (m, 3H), 7.32 (t, *J* = 7.7 Hz, 2H), 7.20 (t, *J* = 7.8 Hz, 1H), 5.32 (s, 2H), 4.53 – 4.26 (m, 3H), 1.81 – 1.56 (m, 2H), 1.31

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(s, 4H), 0.96 – 0.86 (m, 3H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -121.09; MS (ES⁺): 496.5 (M+Na), 472.5 (M-1).

Scheme 19



- 5 Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**19d**)

Step-1: Preparation of tert-butyl (2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)carbamate (**19b**)

Reaction of 2-((tert-butoxycarbonyl)(isopropyl)amino)acetic acid (**19a**) (300 mg, 1.38 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (200 mg, 1.26 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with EtOAc in hexane 0 to 60%] tert-butyl (2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)carbamate (**19b**) (395 mg, 1.1 mmol, 88% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 8.35 (s, 1H), 7.47 (t, $J = 7.5$ Hz, 1H), 7.37 – 7.25 (m, 1H), 7.23 – 7.10 (m, 1H), 4.32 (d, $J = 5.7$ Hz, 2H), 4.28 – 3.95 (m, 1H), 3.75 – 3.57 (m, 2H), 1.40 (s, 3H), 1.26 (s, 6H), 1.12 – 0.95 (m, 6H); MS (ES⁺) 381.4 (M+Na).

Step-2: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**)

Reaction of tert-butyl (2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)carbamate (**19b**) (340 mg, 0.95 mmol) with TFA (0.37 mL, 4.74 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) TFA salt (348 mg, 0.93 mmol, 99% yield) as a white solid, which was used in the next step without further purification; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 9.04 (t, $J = 5.7$ Hz, 1H), 8.81 (s, 2H), 7.57 – 7.46 (m, 1H), 7.40 – 7.30 (m, 1H), 7.26 – 7.16 (m, 1H), 4.42 (d, $J = 5.6$ Hz, 2H), 3.78 – 3.77 (m, 2H), 3.37 – 3.20 (m, 1H), 1.20 (d, $J = 6.5$ Hz, 6H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -73.83 (TFA peak), -120.79; MS (ES⁺) 259.4 (M+1).

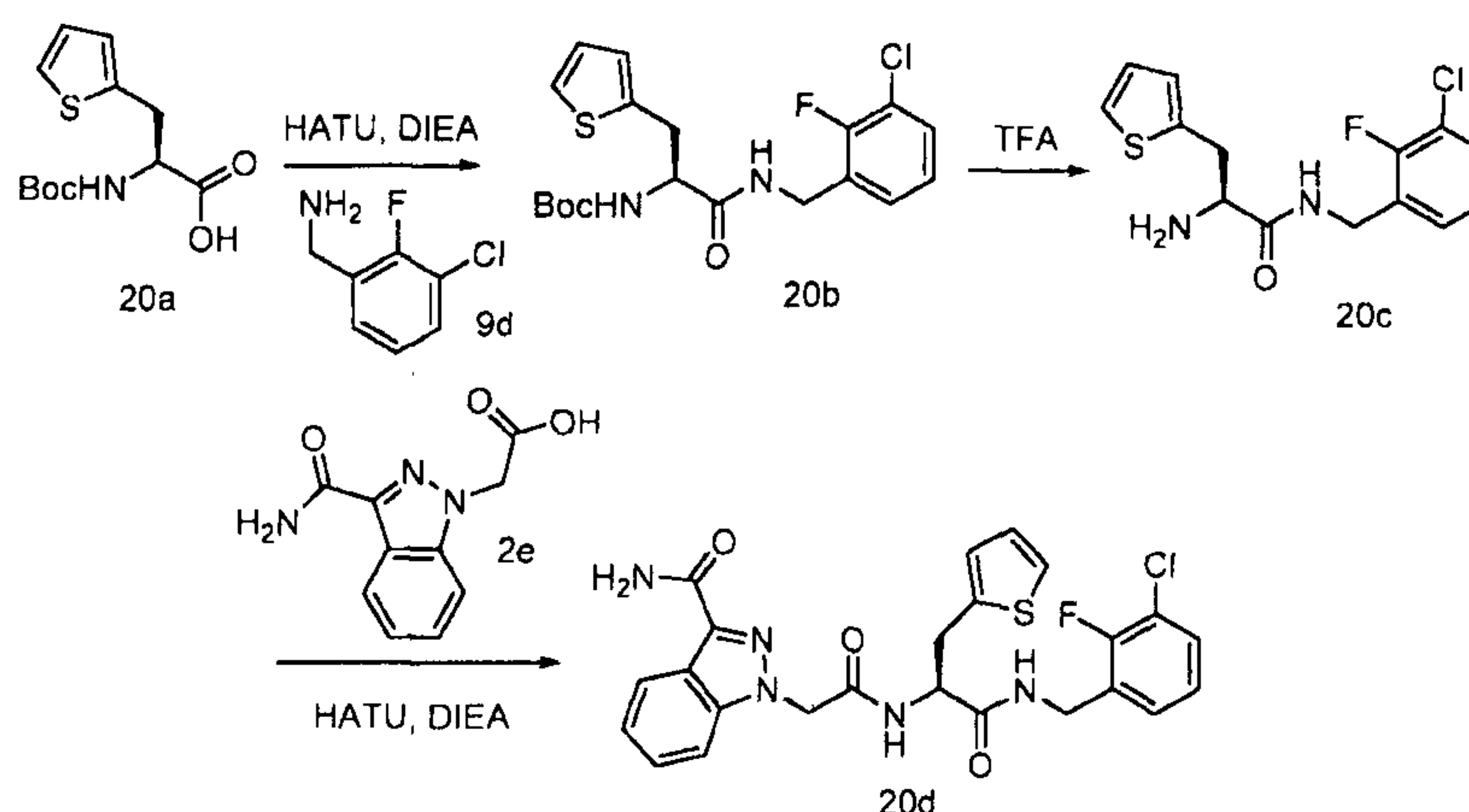
Step-3: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**19d**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (160 mg, 0.43 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**)

5 (113 mg, 0.52 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**19d**) (115 mg, 0.25 mmol, 58% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.83, 8.36 (2t, *J* = 5.7 Hz, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.71 (s, 1H), 7.63 – 7.47 (m, 2H), 7.47 – 7.31 (m, 3H), 7.29 – 6.99 (m, 2H), 5.59, 5.45 (2s, 2H), 4.61 – 4.39 (m, 2H), 4.36 – 4.10 (m, 2H), 3.91 – 3.75 (m, 1H), 1.23, 0.99 (2dd, *J* = 72.0, 6.4 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -120.94, -121.48; MS (ES⁺): 460.5 (M+1); (ES⁻): 458.5 (M-1); (based on NMR the compound is a mixture of rotamers with 2:3 ratio)

15

Scheme 20



Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxo-3-(thiophen-2-yl)propan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**20d**)

Step-1: Preparation of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-1-oxo-3-(thiophen-2-yl)propan-2-yl)carbamate (**20b**)

20

Reaction of (S)-2-((tert-butoxycarbonyl)amino)-3-(thiophen-2-yl)propanoic acid (**20a**) (428 mg, 1.58 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (252 mg, 1.58 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-1-oxo-3-(thiophen-2-yl)propan-2-yl)carbamate (**20b**) which was used

25

as such in the next step; MS (ES⁻): 448.4 (M+Cl).

Step-2: Preparation of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-(thiophen-2-yl)propanamide (**20c**)

Reaction of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-1-oxo-3-(thiophen-2-yl)propan-2-yl)carbamate (**20b**) (652 mg, 1.58 mmol) with TFA (2.19 mL, 28.4 mmol)

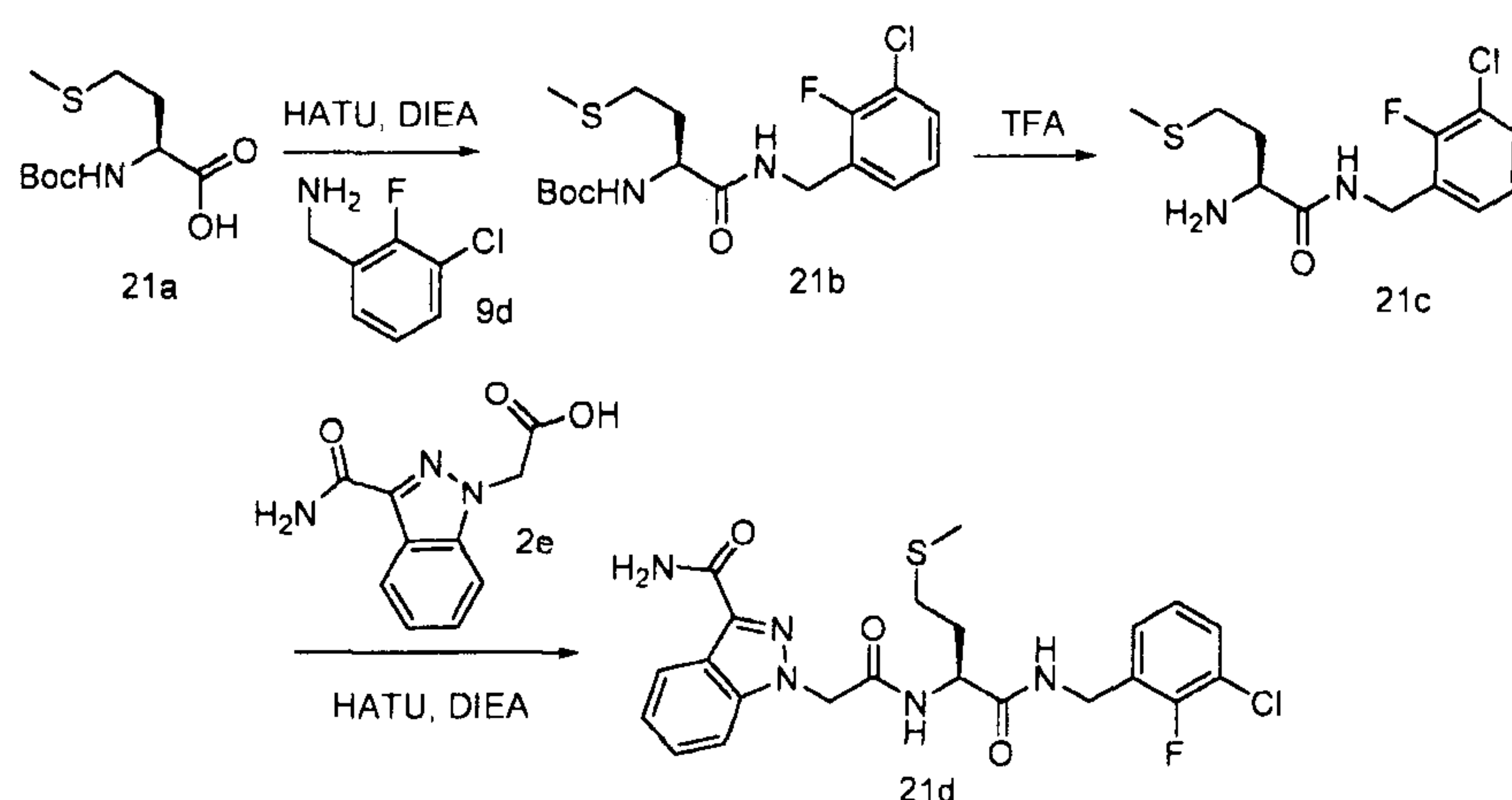
5 according to the procedure reported in step-2 of Scheme 2 gave after workup (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-(thiophen-2-yl)propanamide (**20c**) TFA salt which was used in next step without further purification; MS (ES⁺): 313.3 (M+1).

Step-3: Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxo-3-(thiophen-2-yl)propan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**20d**)

10 Reaction of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-phenylpropanamide (**15c**) (494 mg, 1.58 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (415 mg, 1.9 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxo-3-(thiophen-2-yl)propan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**20d**) (86 mg, 11% yield) as an off-white
15 solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.91 – 8.70 (m, 2H), 8.17 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.67 (s, 1H), 7.55 – 7.35 (m, 5H), 7.30 – 7.21 (m, 1H), 7.17 – 7.04 (m, 2H), 6.98 – 6.92 (m, 1H), 6.92 – 6.87 (m, 1H), 5.37 – 5.09 (m, 2H), 4.66 – 4.50 (m, 1H), 4.46 – 4.22 (m, 2H), 3.33 – 3.21 (m, 1H), 3.17 – 2.99 (m, 1H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.19; MS (ES⁺): 514.53 (M+1), 536.5 (M+Na), 512.5 (M-1).

20

Scheme 21



Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-4-(methylthio)-1-oxobutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**21d**)

Step-1: Preparation of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (**21b**)

25

Reaction of (S)-2-((tert-butoxycarbonyl)amino)-4-(methylthio)butanoic acid (**21a**) (391 mg, 1.57 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (250 mg, 1.57 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (**21b**) which was used as
 5 such in the next step; MS (ES⁻): 391.4 (M-1).

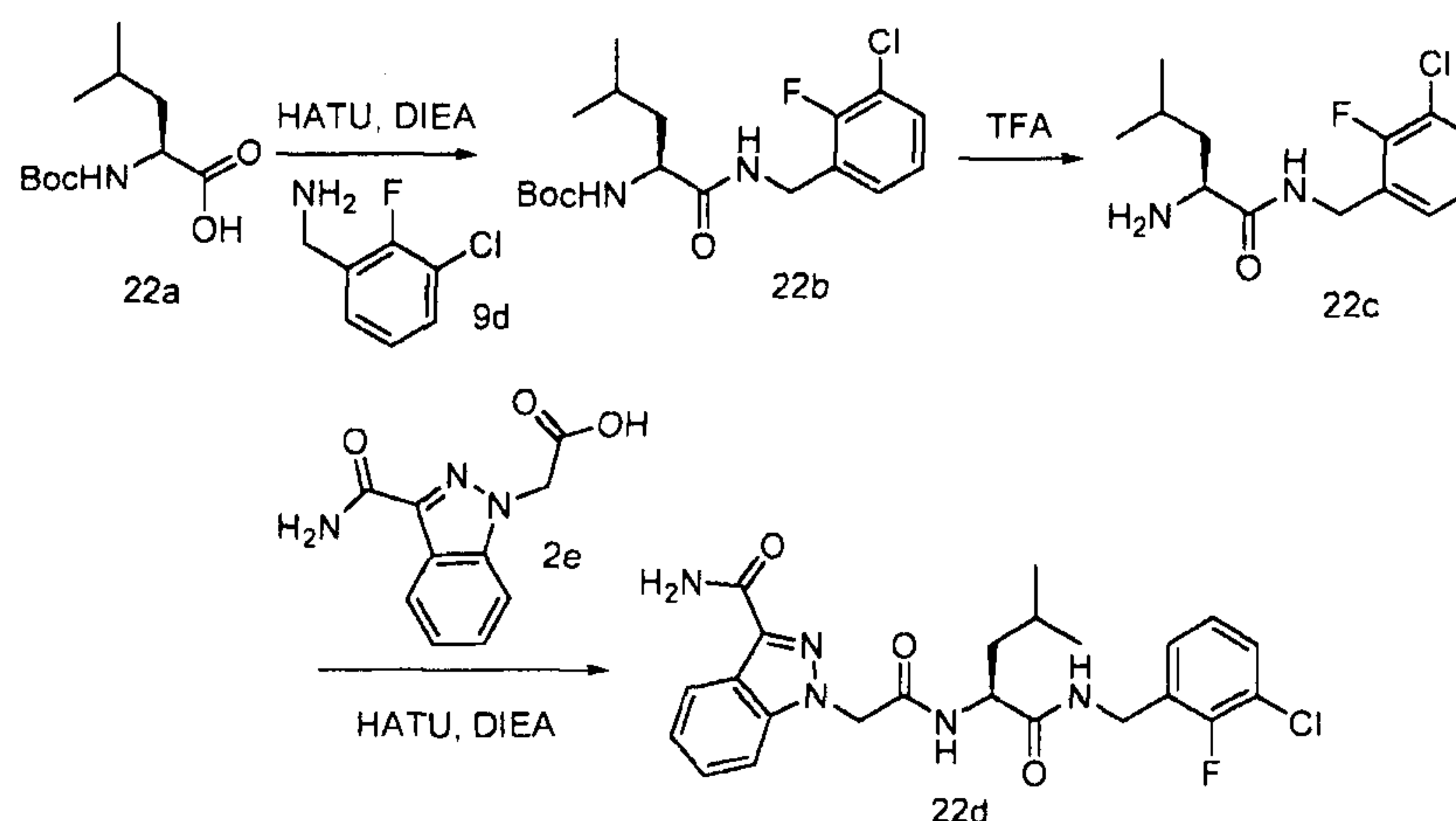
Step-2: Preparation of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-4-(methylthio)butanamide (**21c**)

Reaction of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-4-(methylthio)-1-oxobutan-2-yl)carbamate (**21b**) from above step with TFA (3 mL) according to the procedure reported in
 10 step-2 of Scheme 2 gave after workup (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-4-(methylthio)butanamide (**21c**)TFA salt which was used in next step without further purification; MS (ES⁺): 291.3 (M+1).

Step-3: Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-4-(methylthio)-1-oxobutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**21d**)

15 Reaction of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-4-(methylthio)butanamide (**21c**) (0.254 g, 0.931 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (136 mg, 0.62 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (24 g), eluting with CMA80 in CHCl₃ 0 to 40%] (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-4-(methylthio)-1-oxobutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**21d**) (33 mg, 0.067 mmol,
 20 11% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.75 - 8.60 (m, 2H), 8.17 (d, *J* = 8.1 Hz, 1H), 7.71 (s, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.58 - 7.35 (m, 3H), 7.31 - 7.20 (m, 2H), 7.15 (q, *J* = 8.8, 7.8 Hz, 1H), 5.27 (s, 2H), 4.47 - 4.27 (m, 3H), 2.48 - 2.36 (m, 2H), 2.04 (s, 1H), 2.02 (s, 2H), 2.01 - 1.67 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.12 (d, *J* =
 25 7.1 Hz); MS (ES⁺): 492.5 (M+1); MS (ES⁻): 490.5 (M-1); 526.5 (M+Cl).

Scheme 22



Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-4-methyl-1-oxopentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**22d**)

5 Step-1: Preparation of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (**22b**)

Reaction of (S)-2-((tert-butoxycarbonyl)amino)-4-methylpentanoic acid (**22a**) (362 mg, 1.57 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (250 mg, 1.57 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (**22b**) which was used as such in the next step; MS (ES⁺): 395.4 (M+Na).

Step-2: Preparation of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-4-methylpentanamide (**22c**)

Reaction of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-4-methyl-1-oxopentan-2-yl)carbamate (**22b**) from above step with TFA (3 mL) according to the procedure reported in step-2 of Scheme 2 gave after workup (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-4-methylpentanamide (**22c**) TFA salt which was used in next step without further purification; MS (ES⁺): 273.4 (M+1).

Step-3: Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-4-methyl-1-oxopentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**22d**)

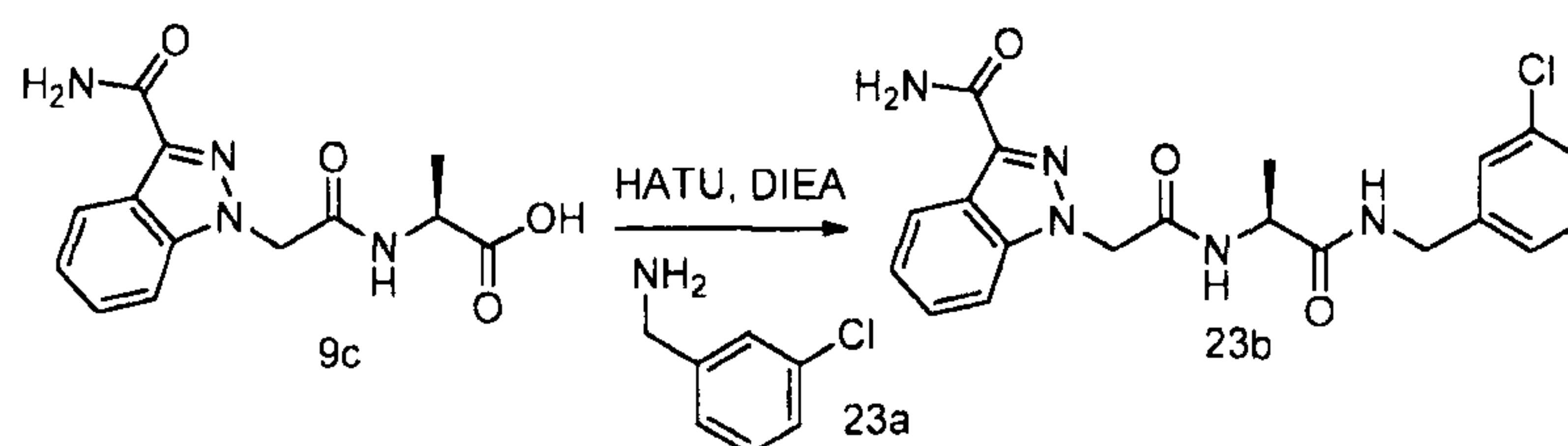
20 Reaction of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-4-methylpentanamide (**22c**) (0.25 g, 0.93 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (136 mg, 0.62 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (24 g), eluting with CMA80 in CHCl₃; 0 to 40%] (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-4-methyl-1-oxopentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**22d**) (65 mg, 0.14 mmol,

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22% yield) as a pale white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.69 (t, $J = 5.8$ Hz, 1H), 8.62 (d, $J = 8.0$ Hz, 1H), 8.17 (d, $J = 8.1$ Hz, 1H), 7.70 (s, 1H), 7.61 (d, $J = 8.5$ Hz, 1H), 7.52 - 7.35 (m, 3H), 7.32 - 7.19 (m, 2H), 7.13 (t, $J = 7.9$ Hz, 1H), 5.25 (s, 2H), 4.42 - 4.24 (m, 3H), 1.70 - 1.54 (m, 1H), 1.55 - 1.42 (m, 2H), 0.90 (d, $J = 6.4$ Hz, 3H), 0.83 (d, $J = 6.4$ Hz, 3H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.23; MS (ES+) 474.5 (M+1), 496.5 (M+Na); MS (ES-) 508.5

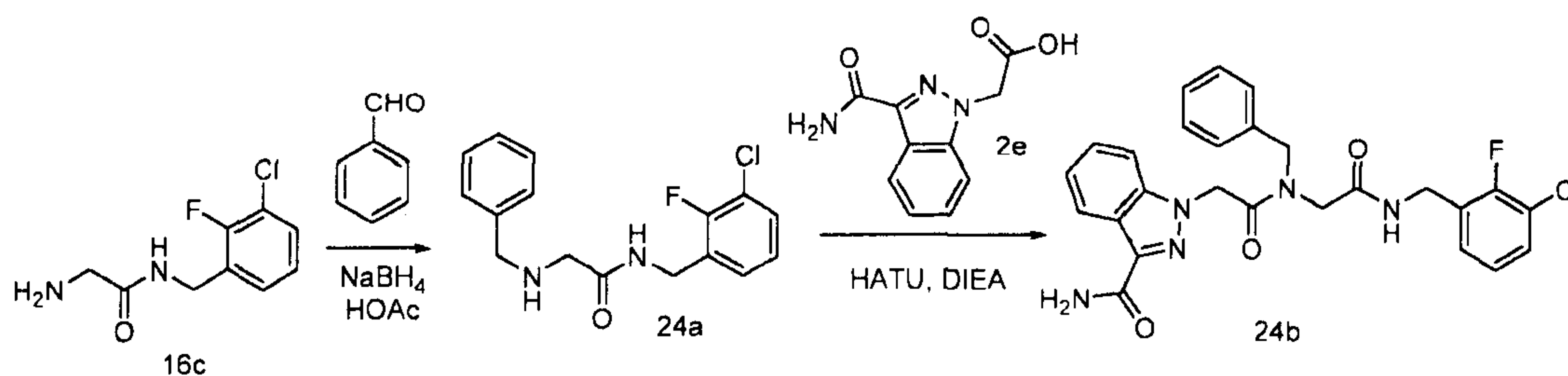
Scheme 23



Preparation of (S)-1-(2-((1-((3-chlorobenzyl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**23b**)

Reaction of (S)-2-(2-(3-carbamoyl-1H-indazol-1-yl)acetamido)propanoic acid (**9c**) (200 mg, 0.69 mmol) TFA salt with (3-chlorophenyl)methanamine (**23a**) (98 mg, 0.69 mmol), according to the procedure reported in step-3 of Scheme 2 gave after workup (S)-1-(2-((1-((3-chlorobenzyl)amino)-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**23b**) (126 mg, 0.3 mmol, 44% yield) as a yellow solid; ^1H NMR(300 MHz, $\text{DMSO}-d_6$) δ 8.67 (d, $J = 7.4$ Hz, 1H), 8.59 (t, $J = 6.0$ Hz, 1H), 8.17 (d, $J = 8.1$ Hz, 1H), 7.72 (s, 1H), 7.64 (d, $J = 8.5$ Hz, 1H), 7.47 - 7.15 (m, 7H), 5.41 - 5.16 (m, 2H), 4.43 - 4.23 (m, 3H), 1.29 (d, $J = 7.0$ Hz, 3H); MS (ES+): 414.5 (M+1); ES(-): 412.4 (M-1).

Scheme 24



Preparation of 1-(2-(benzyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**24b**)

Step-1: Preparation of 2-(benzylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**24a**)

To a solution of 2-amino-N-(3-chloro-2-fluorobenzyl)acetamide (**16c**) (320 mg, 1.48 mmol) in THF (10 mL) was added benzaldehyde (143 mg, 1.343 mmol) and acetic acid (0.12 mL,

2.01 mmol). The resulting mixture was stirred for 50 min, NaBH₄ (102 mg, 2.69 mmol) was added and stirred at room temperature overnight. The reaction was quenched with aqueous NaHCO₃ (2N, 20 mL), stirred for 30min-and diluted with EtOAc (100 mL). The organic layer was separated washed with brine, dried, filtered and concentrated in vacuum to afford 2-

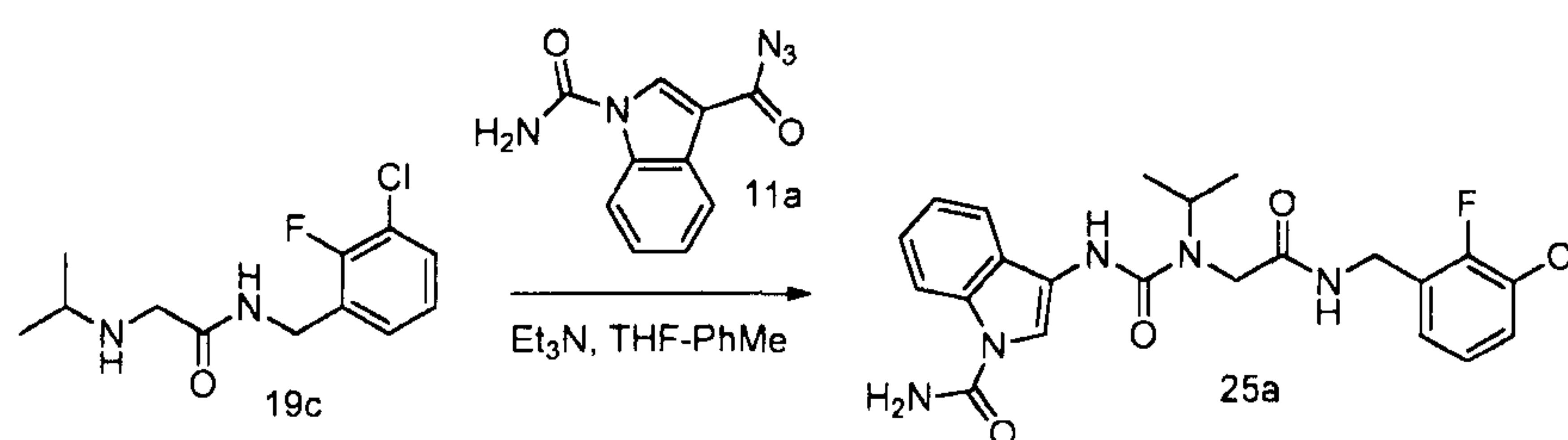
5 (benzylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**24a**) (240 mg, 0.78 mmol, 58% yield), which was used in the next step without further purification. MS (ES⁺): 307.3 (M+1)

Step-2: Preparation of 1-(2-(benzyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**24b**)

Reaction of 2-(benzylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**24a**) (240 mg, 0.78 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (171 mg, 0.78 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl₃; 0 to 40%] 1-(2-(benzyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**24b**) (38 mg, 0.075 mmol, 10% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.79 and 8.52 (2t, *J* = 5.9 Hz, 1H), 8.25 – 8.11 (m, 1H), 7.80 – 7.66 (m, 1H), 7.66 – 7.56 (m, 1H), 7.56 – 7.36 (m, 5H), 7.34 – 7.10 (m, 6H), 5.58 (s, 2H), 4.83 and 4.46 (2s, 2H), 4.43 and 4.34 (2d, *J* = 5.6 Hz, 2H), 4.21 and 3.95 (s, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.06, -121.35; MS (ES⁺): 508.5 (M+1); (ES⁻) 506.5 (M-1); (*based on NMR the compound is a mixture of rotamers 2:1 ratio*)

20

Scheme 25



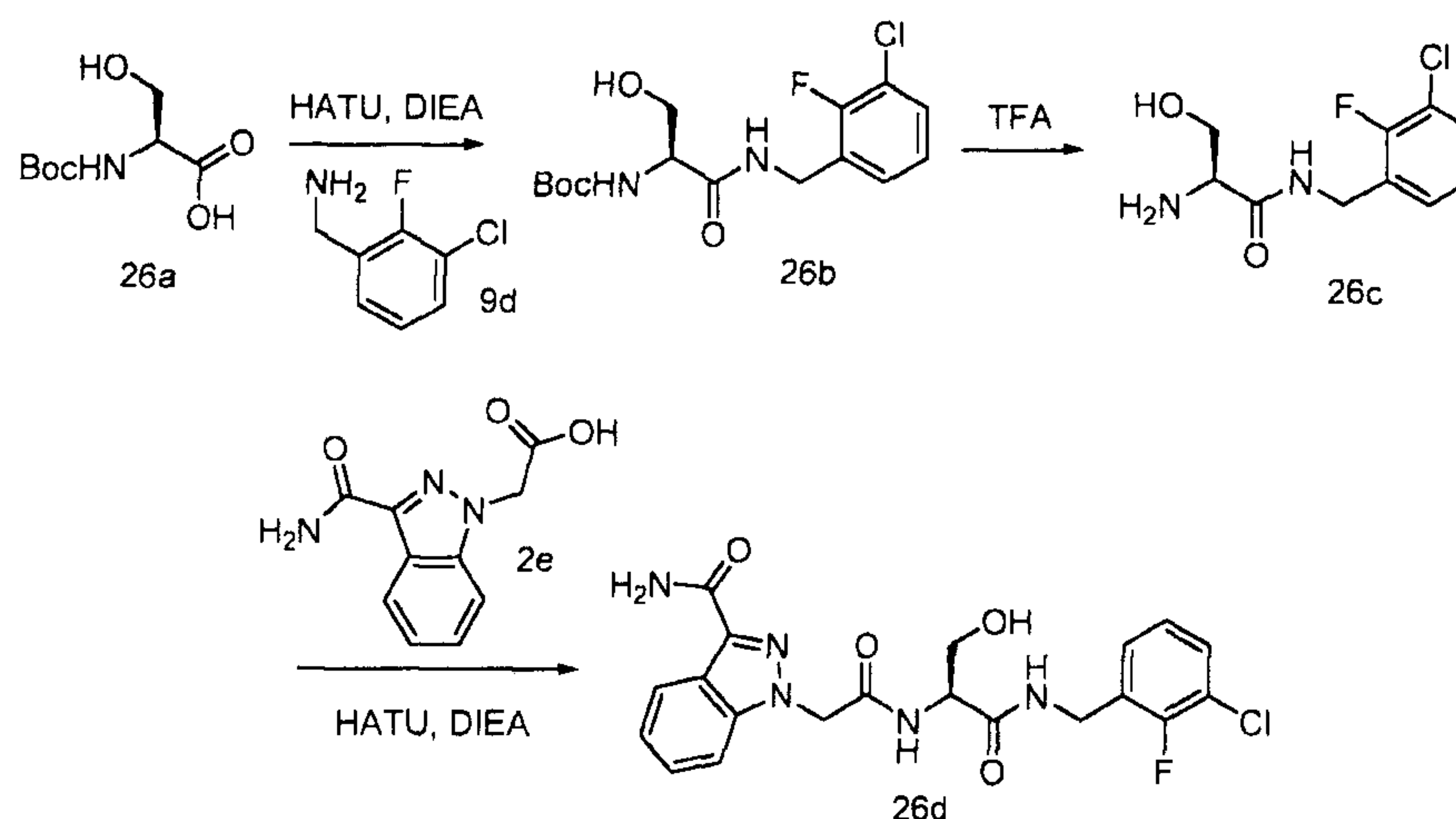
Preparation of 3-(3-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-3-isopropylureido)-1H-indole-1-carboxamide (**25a**)

25 Reaction of N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (90 mg, 0.35 mmol) with 1-carbamoyl-1H-indole-3-carbonyl azide (**11a**) (80 mg, 0.35 mmol) according to the procedure reported in Scheme 11 gave after workup and purification by flash column chromatography (Silica gel, 24 g eluting with CMA80 in CHCl₃ from 0-30%) 3-(3-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-3-isopropylureido)-1H-indole-1-carboxamide (**25a**) (9 mg, 6% yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.92 (s, 1H, D₂O

30

exchangeable), 8.82 – 8.70 (m, 1H, D₂O exchangeable), 8.30 – 8.22 (m, 1H), 7.98 (s, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.54 – 7.32 (m, 4H, 2H, D₂O exchangeable), 7.30 – 7.21 (m, 1H), 7.20 – 7.11 (m, 2H), 4.56 – 4.33 (m, 3H), 3.97 (s, 2H), 1.10 (d, *J* = 6.6 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.07; MS (ES⁺): 460.5 (M+1), 482.49 (M+Na); MS (ES⁻): 458.44 (M-1).

Scheme 26



Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-3-hydroxy-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**26d**)

10 Step-1: Preparation of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (**26b**)

Reaction of (S)-2-((tert-butoxycarbonyl)amino)-3-hydroxypropanoic acid (**26a**) (389 mg, 1.9 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (252 mg, 1.58 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (**26b**) which was used as such
15 in the next step; MS (ES⁺): 369.4 (M+Na), MS (ES⁻): 381.3 (M+Cl).

Step-2: Preparation of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-hydroxypropanamide (**26c**)

Reaction of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-3-hydroxy-1-oxopropan-2-yl)carbamate (**26b**) (548 mg, 1.58 mmol) from above step with TFA (2.19 mL, 28.4 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-hydroxypropanamide (**26c**) TFA salt which was used in next
20 step without further purification; MS (ES⁺): 247.3 (M+1).

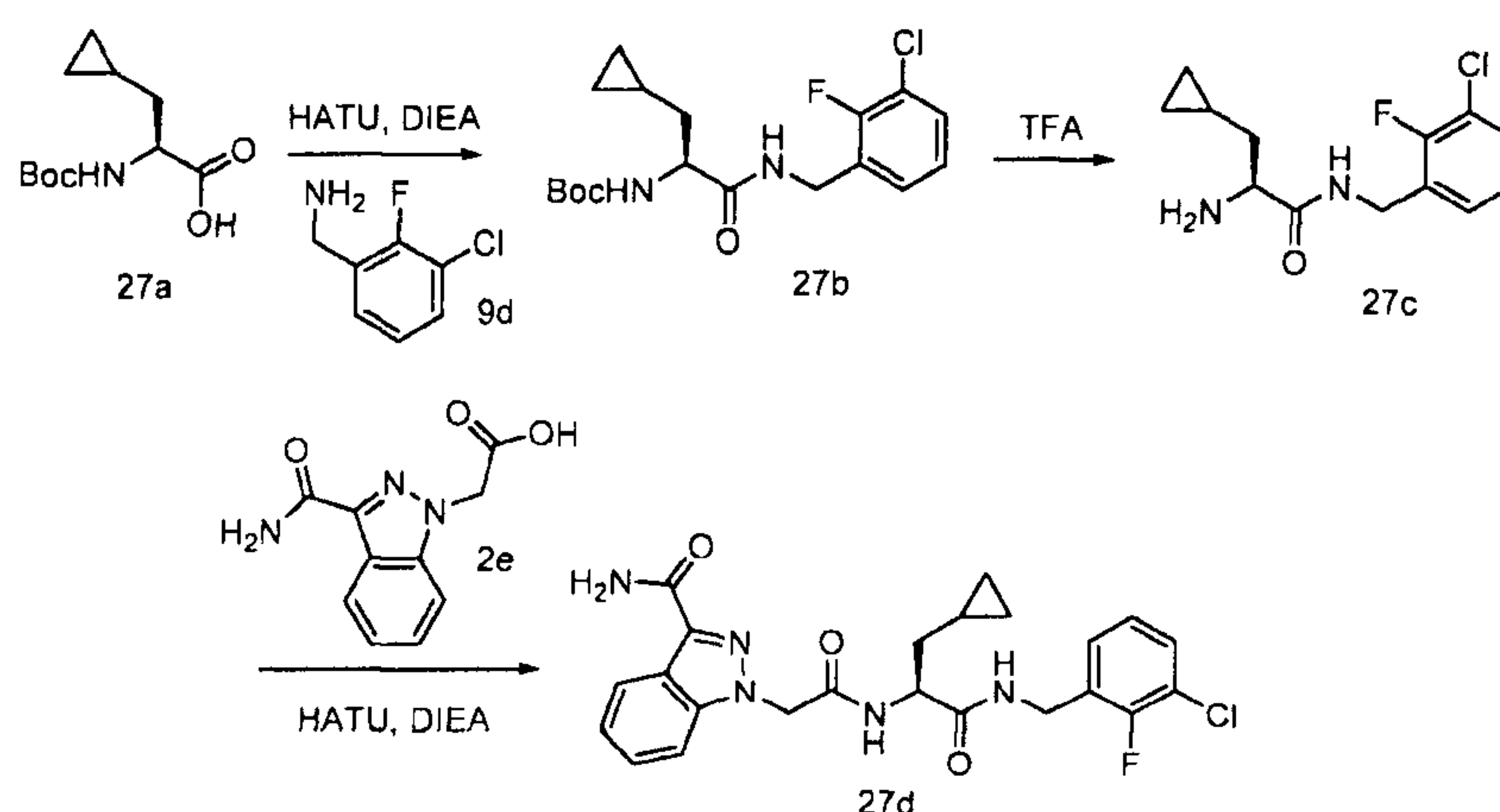
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Step-3: Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-3-hydroxy-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**26d**)

Reaction of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-hydroxypropanamide (**26c**) (390 g, 1.58 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (416 mg, 1.9 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (24 g), eluting with CMA80 in CHCl₃; 0 to 100%] (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-3-hydroxy-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**26d**) (16 mg, 2% yield) as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.67 – 8.57 (m, 2H, D₂O exchangeable), 8.18 (dt, *J* = 8.2, 1.0 Hz, 1H), 7.73 (s, 1H, D₂O exchangeable), 7.64 (dt, *J* = 8.6, 0.9 Hz, 1H), 7.52 – 7.37 (m, 3H), 7.33 – 7.22 (m, 2H), 7.17 – 7.09 (m, 1H), 5.40 – 5.22 (m, 2H), 5.13 (t, *J* = 5.3 Hz, 1H, D₂O exchangeable), 4.42 – 4.29 (m, 3H), 3.70 – 3.59 (m, 2H); ¹H NMR (300 MHz, DMSO-*d*₆ D₂O) δ 8.17 – 8.09 (m, 1H), 7.62 – 7.55 (m, 1H), 7.46 – 7.36 (m, 2H), 7.34 – 7.17 (m, 2H), 7.06 (t, *J* = 7.9 Hz, 1H), 5.40 – 5.14 (m, 2H), 4.32 (s, 2H), 4.28 (t, *J* = 5.4 Hz, 1H), 3.76 – 3.54 (m, 2H); MS (ES⁺): 448.5 (M+1), 470.5 (M+Na); MS (ES⁻): 446.4 (M-1), 482.4 (M+Cl).

Scheme 27



Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**27d**)

Step-1: Preparation of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamate (**27b**)

Reaction of (S)-2-((tert-butoxycarbonyl)amino)-3-cyclopropylpropanoic acid (**27a**) (575 mg, 2.51 mmol, prepared according to method reported by Hendricks, Robert Than et al; in U.S. Pat. Appl. Publ., 20110230462) according to the procedure reported in step-3 of Scheme 2

gave after workup (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamate (**27b**) which was used as such in the next step; MS (ES⁺): 393.3 (M+Na); MS (ES⁻): 405.4 (M+Cl).

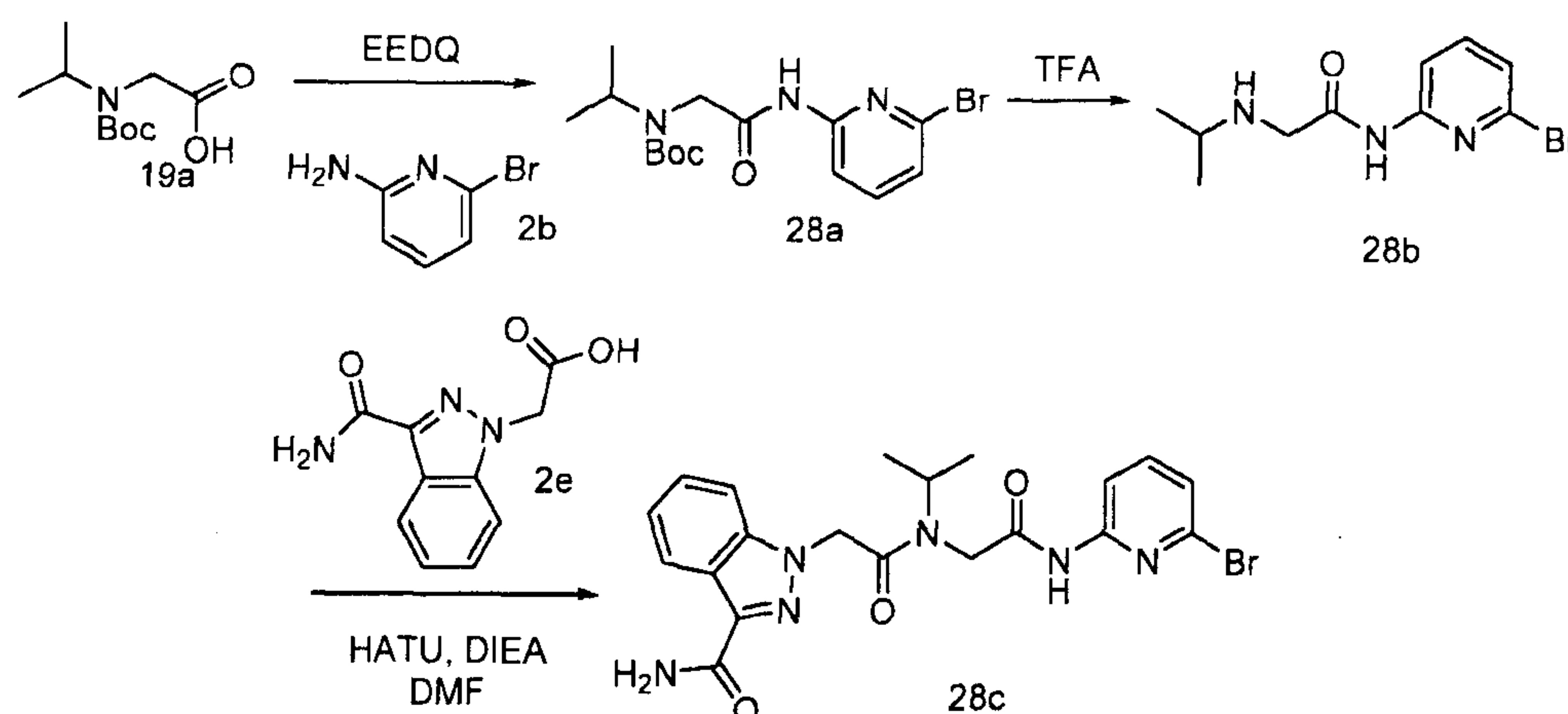
Step-2: Preparation of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-cyclopropylpropanamide (**27c**)

Reaction of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)carbamate (**27b**) (930 mg, 2.51 mmol) from above step with TFA (3.48 mL, 45.1 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-cyclopropylpropanamide (**27c**) TFA salt which was used in next step without further purification; MS (ES⁺): 271.3 (M+1).

Step-3: Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**27d**)

Reaction of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-cyclopropylpropanamide (**27c**) (679 g, 2.51 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (660 mg, 3.01 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-3-cyclopropyl-1-oxopropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**27d**) (93 mg, 8% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.73 – 8.56 (m, 2H), 8.17 (d, *J* = 8.1 Hz, 1H), 7.69 (s, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.36 (m, 3H), 7.25 (t, *J* = 7.4 Hz, 2H), 7.13 (t, *J* = 7.9 Hz, 1H), 5.26 (s, 2H), 4.45 – 4.25 (m, 3H), 1.73 – 1.36 (m, 2H), 0.79 – 0.63 (m, 1H), 0.46 – 0.25 (m, 2H), 0.15 – 0.01 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ 120.97; MS (ES⁺): 472.5 (M+1), 494.5 (M+Na); (ES⁻): 470.4 (M-1), 506.5 (M+Cl).

Scheme 28



Preparation of 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**28c**)

Step-1: Preparation of tert-butyl (2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)carbamate (**28a**)

5 Reaction of 2-((tert-butoxycarbonyl)(isopropyl)amino)acetic acid (**19a**) (0.65 g, 2.99 mmol) with 6-bromopyridin-2-amine (**2b**) (0.78 g, 4.49 mmol) according to the procedure reported in step-1 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with MeOH in CHCl₃ from 0-20%] tert-butyl (2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)carbamate (**28a**) which was used in the next step without further
10 purification.

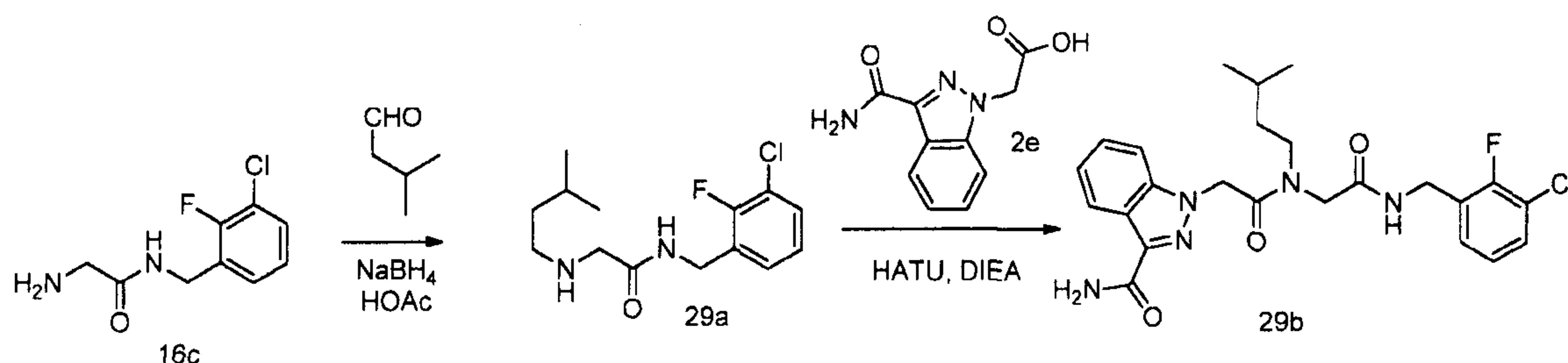
Step-2: Preparation of N-(6-bromopyridin-2-yl)-2-(isopropylamino)acetamide (**28b**)

Reaction of tert-butyl (2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)carbamate (**28a**) from above step-1 with TFA (1.15 mL, 14.96 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and purification by chromatography [silica
15 (12 g), eluting with CMA80 in CHCl₃ 0 to 20%] N-(6-bromopyridin-2-yl)-2-(isopropylamino)acetamide (**28b**) (340 mg, 1.25 mmol, 42%) which was used in the next step without further purification; MS (ES⁺): 272.3 (M+1).

Step-3: Preparation of 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**28c**)

20 Reaction of N-(6-bromopyridin-2-yl)-2-(isopropylamino)acetamide (**28b**) (100 mg, 0.26 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (62 mg, 0.29 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 40%] 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-
25 carboxamide (**28c**) (70 mg, 0.15 mmol, 57% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.17 and 10.77 (2s, 1H), 8.24 – 7.95 (m, 2H), 7.87 – 7.54 (m, 3H), 7.51 – 7.14 (m, 4H), 5.62 and 5.46 (2s, 2H), 4.606 – 4.332 (m, 1H), 4.43 and 4.03 (2s, 2H), 1.25 (d, *J* = 6.3 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H); MS (ES⁺): 473.4 (M+1); (based on NMR the compound is a mixture of rotamers with 1.2:1 ratio)

Scheme 29



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**29b**)

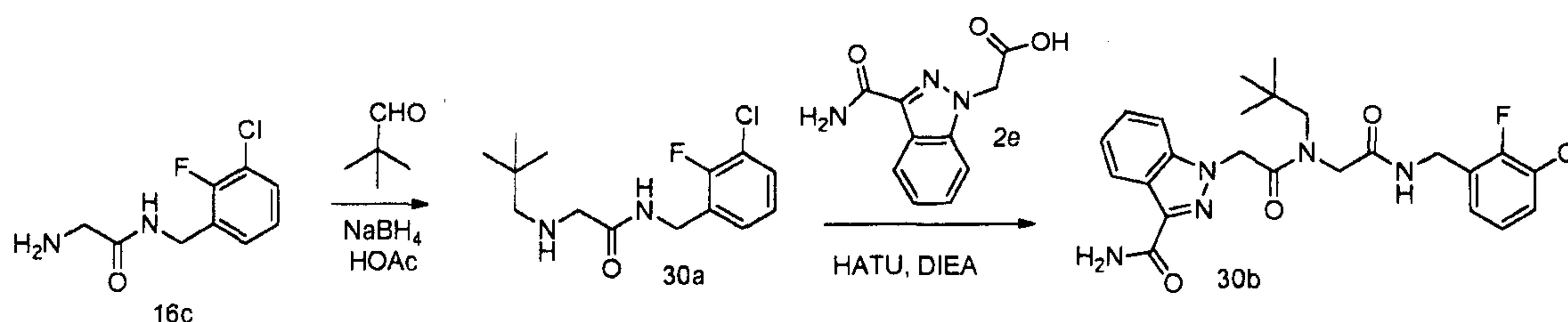
Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(isopentylamino)acetamide (**29a**)

Reaction of 2-amino-N-(3-chloro-2-fluorobenzyl)acetamide (**16c**) (337 mg, 1.56 mmol) with
 5 isovaleraldehyde (147 mg, 1.711 mmol) according to the procedure reported in step-1 of
 Scheme 24 gave after work and purification by flash column chromatography [silica (12 g),
 eluting with EtOAc in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-
 (isopentylamino)acetamide (**29a**) (120 mg, 0.42 mmol, 27% yield) as a clear oil; ¹H NMR
 (300 MHz, DMSO-*d*₆) δ 8.34 (t, *J* = 5.8 Hz, 1H), 7.52 – 7.39 (m, 1H), 7.32 – 7.23 (m, 1H),
 10 7.21 – 7.11 (m, 1H), 4.36 (d, *J* = 5.9 Hz, 2H), 3.11 (s, 2H), 2.48 – 2.39 (m, 2H), 1.66 – 1.43
 (m, 1H), 1.36 – 1.16 (m, 3H), 0.82 (d, *J* = 6.6 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -
 121.38; MS (ES⁺): 287.4 (M+1); (ES⁻): 285.3 (M-1).

Step-2: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(isopentylamino)acetamide (**29a**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(isopentylamino)acetamide (**29a**) (100 mg, 0.35
 15 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (84 mg, 0.384 mmol) according
 to the procedure reported in step-3 of Scheme 2 gave after workup and purification by
 chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 40%] N-(3-chloro-2-
 fluorobenzyl)-2-(isopentylamino)acetamide (**29a**) (100 mg, 0.21 mmol, 59% yield) as a white
 solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.85 and 8.49 (2t, *J* = 5.6 Hz, 1H), 8.18 (d, *J* = 8.1
 20 Hz, 1H), 7.76 – 7.66 (m, 1H), 7.62 – 7.47 (m, 2H), 7.47 – 7.33 (m, 3H), 7.29 – 7.09 (m, 2H),
 5.56 and 5.47 (2s, 2H), 4.46 and 4.34 (2d, *J* = 5.4 Hz, 2H), 4.23 and 3.94 (2s, 2H), 3.52 –
 3.39 (m, 1H), 3.30 – 3.15 (m, 1H), 1.66 – 1.37 (m, 2H), 1.37 – 1.15 (m, 1H), 0.93 and 0.80
 (2d, *J* = 6.4 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -120.92, -121.31; MS (ES⁺): 473.4
 (M+1); (based on NMR the compound is a mixture of rotamers with 3:2 ratio).

Scheme 30



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(neopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**30b**)

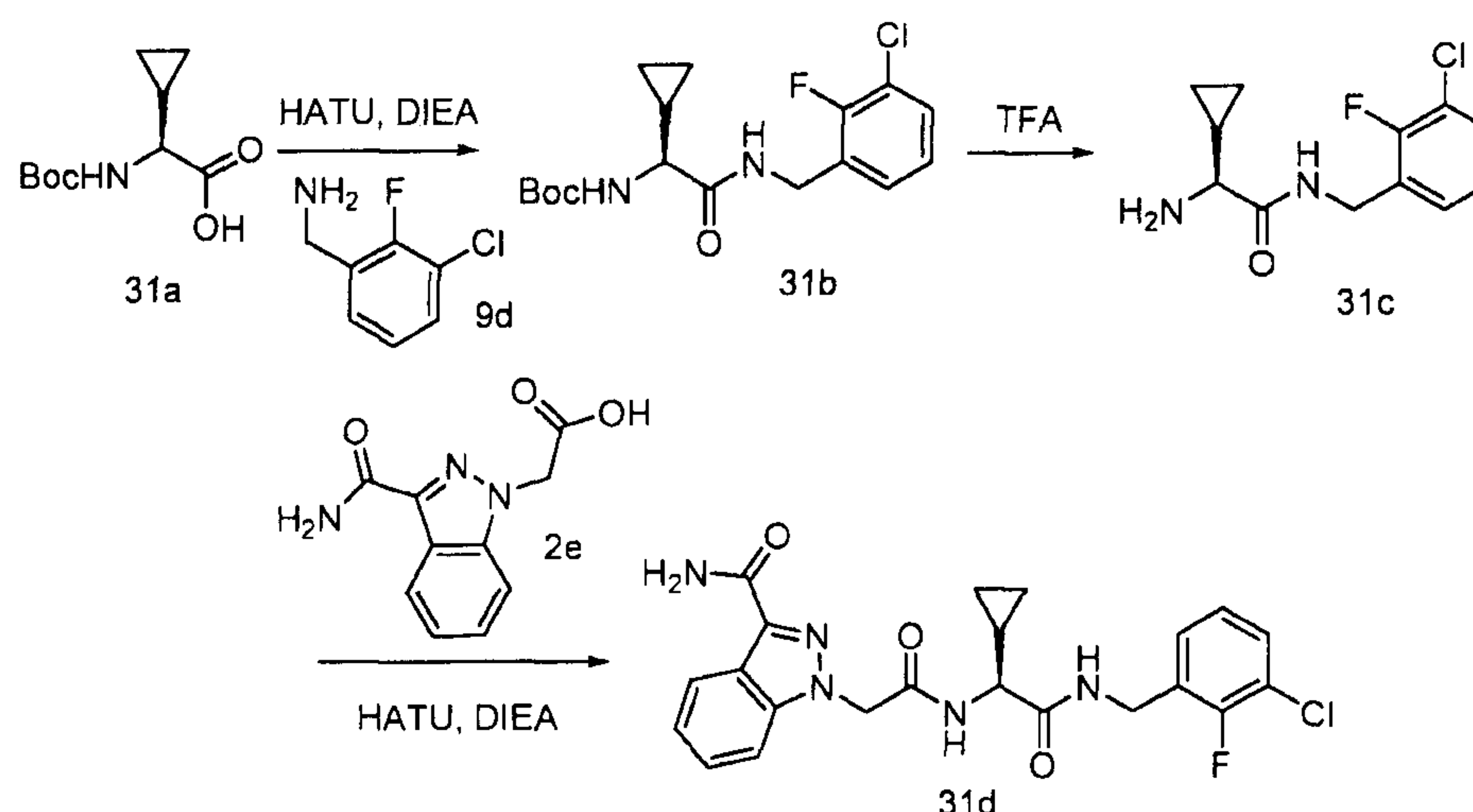
Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(neopentylamino)acetamide (**30a**)

Reaction of 2-amino-N-(3-chloro-2-fluorobenzyl)acetamide (**16c**) (300 mg, 1.39 mmol) with
 5 trimethylacetaldehyde (131 mg, 1.523 mmol) according to the procedure reported in step-1 of
 Scheme 24 gave after work and purification by flash column chromatography [silica (12 g),
 eluting with EtOAc in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-
 (neopentylamino)acetamide (**30a**) (200 mg, 0.7 mmol, 50% yield) as a clear oil; ¹H NMR
 (300 MHz, DMSO-*d*₆) δ 8.55 (d, *J* = 5.5 Hz, 1H), 7.79 (t, *J* = 7.5 Hz, 1H), 7.60 (t, *J* = 7.1 Hz,
 10 1H), 7.50 (t, *J* = 7.8 Hz, 1H), 4.69 (d, *J* = 5.9 Hz, 2H), 3.44 (s, 2H), 2.90 – 2.74 (m, 2H), 2.41
 (s, 1H), 1.16 (d, *J* = 2.9 Hz, 9H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.08; MS (ES+):
 287.4 (M+1); (ES-) 285.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(neopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**30b**)

15 Reaction of N-(3-chloro-2-fluorobenzyl)-2-(neopentylamino)acetamide (**30a**) (130 mg, 0.45
 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (109 mg, 0.5 mmol) according
 to the procedure reported in step-3 of Scheme 2 gave after workup and purification by
 chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 40%] 1-(2-((2-((3-chloro-
 2-fluorobenzyl)amino)-2-oxoethyl)(neopentyl)amino)-2-oxoethyl)-1H-indazole-3-
 20 carboxamide (**30b**) (100 mg, 0.21 mmol, 45% yield) as a white solid; ¹H NMR (300 MHz,
 DMSO-*d*₆) δ 8.83 (t, *J* = 5.7 Hz, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.81 – 7.58 (m, 1H), 7.57 –
 7.46 (m, 2H), 7.46 – 7.31 (m, 3H), 7.30 – 7.15 (m, 2H), 5.61 – 5.37 (m, 2H), 4.47 (d, *J* = 5.4
 Hz, 2H), 4.32 (s, 2H), 3.04 (s, 2H), 1.14 – 0.71 (m, 9H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -
 120.96; MS (ES+): 488.5 (M+1); (ES-): 486.5 (M-1).

Scheme 31



Preparation of (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-1-cyclopropyl-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**31d**)

Step-1: Preparation of (S)-tert-butyl (2-((3-chloro-2-fluorobenzyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (**31b**)

- 5 Reaction of (S)-2-((tert-butoxycarbonyl)amino)-2-cyclopropylacetic acid (**31a**) (232 mg, 1.08 mmol, prepared according to method reported by Hendricks, Robert Than et al; in U.S. Pat. Appl. Publ., 2011/0230462) with 3-chloro-2-fluorobenzylamine (**9d**) (172 mg, 1.08 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup (S)-tert-butyl (2-((3-chloro-2-fluorobenzyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (**31b**) which was
10 used as such in the next step; MS (ES⁻): 391.3 (M+Cl).

Step-2: Preparation of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-2-cyclopropylacetamide (**31c**)

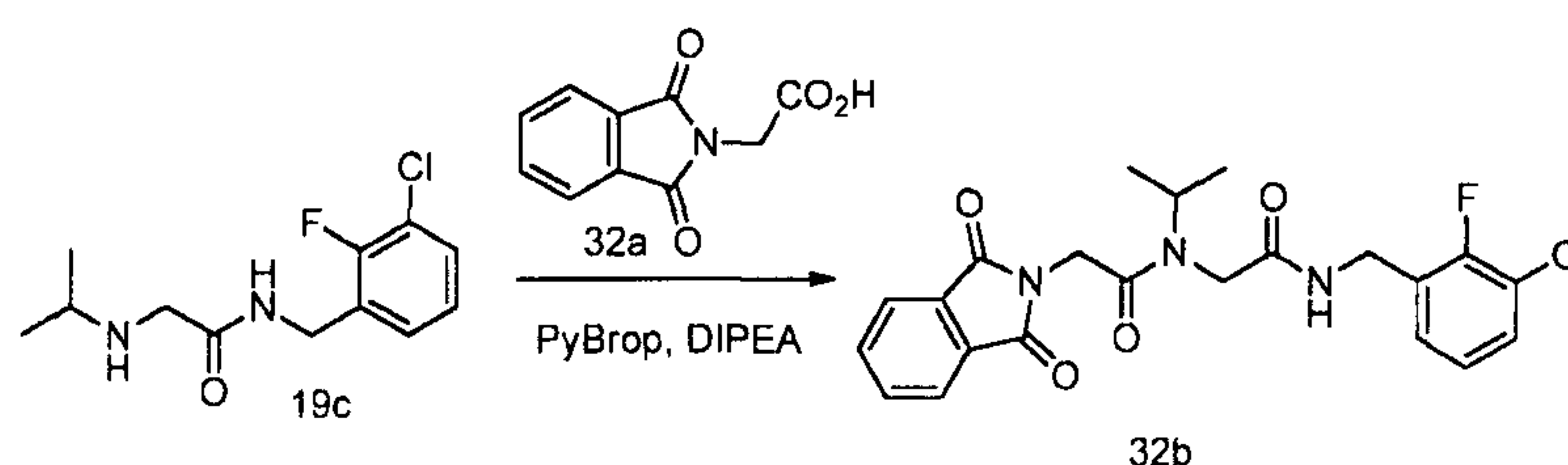
- Reaction of (S)-tert-butyl (2-((3-chloro-2-fluorobenzyl)amino)-1-cyclopropyl-2-oxoethyl)carbamate (**31b**) (378 mg, 1.06 mmol) from above step-1 with TFA (1.5 mL, 19.07
15 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-2-cyclopropylacetamide (**31c**)TFA salt which was used in next step without further purification; MS (ES⁺): 257.3 (M+1).

Step-3: Preparation of (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-1-cyclopropyl-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**31d**)

- 20 Reaction of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)-2-cyclopropylacetamide (**31c**) (272 mg, 1.06 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (279 mg, 1.27 mmol) according to the procedure reported in step-3 of Scheme 2 gave

after workup and purification by flash column chromatography [silica gel (24 g), eluting with CMA80 in CHCl₃; 0 to 30%] (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-1-cyclopropyl-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**31d**) (21 mg, 0.046 mmol, 4% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.80 (d, *J* = 7.8 Hz, 1H, D₂O exchangeable), 8.62 (t, *J* = 5.8 Hz, 1H, D₂O exchangeable), 8.17 (d, *J* = 8.1 Hz, 1H), 7.81 – 7.60 (m, 2H), 7.54 – 7.36 (m, 3H), 7.32 – 7.20 (m, 2H), 7.14 (t, *J* = 7.9 Hz, 1H), 5.27 (s, 2H), 4.49 – 4.24 (m, 2H), 3.77 (t, *J* = 8.1 Hz, 1H), 1.17 – 1.00 (m, 1H), 0.59 – 0.41 (m, 3H), 0.37 – 0.22 (m, 1H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.16; MS (ES⁺): 480.5 (M+Na); (ES⁻): 456.4 (M-1), 492.4 (M+Cl).

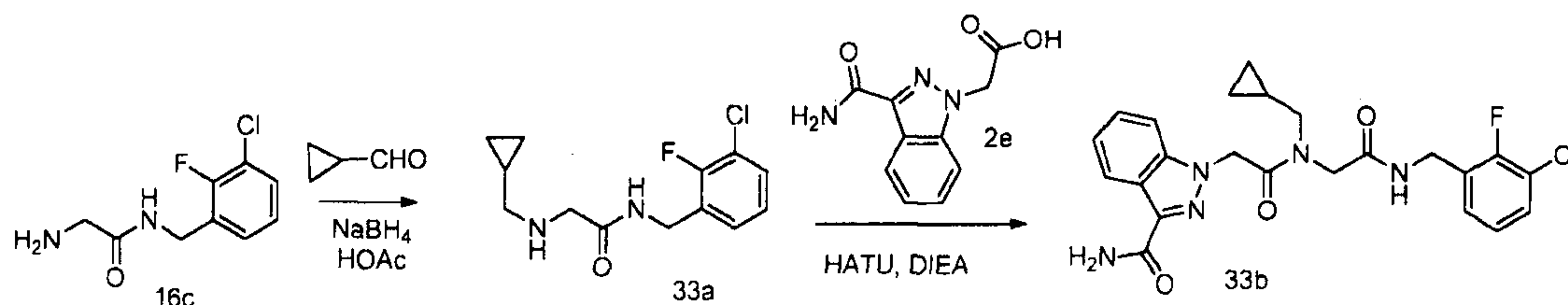
Scheme 32



Preparation of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-(1,3-dioxoisindolin-2-yl)-N-isopropylacetamide (**32b**)

To solution of N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (195 mg, 0.75 mmol), N-ethyl-N-isopropylpropan-2-amine (0.66 mL, 3.77 mmol), 2-(1,3-dioxoisindolin-2-yl)acetic acid (**32a**) (186 mg, 0.9 mmol), in DMF (6 mL) was added bromo-tris-pyrrolidino phosphoniumhexafluorophosphate(PyBrop, 422 mg, 0.9 mmol) and stirred at room temperature for 14 h. The reaction mixture was diluted with brine (100 mL) and extracted with EtOAc (3 x 100 mL). The organic layers were combined, dried, filtered and evaporated to dryness. The residue obtained was purified by flash column chromatography [silica gel (24 g), eluting with MeOH in CHCl₃ 0-100%] to afford N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-(1,3-dioxoisindolin-2-yl)-N-isopropylacetamide (**32b**) (103 mg, 0.23 mmol, 31% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.73 & 8.34 (2t, *J* = 5.9 Hz, 1H), 7.97 – 7.82 (m, 4H), 7.55 – 7.33 (m, 2H), 7.28 – 7.06 (m, 1H), 4.64 – 4.17 (m, 5H), 4.13 & 3.81 (2s, 2H), 1.20 & 0.96 (2d, *J* = 6.6 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.07, -121.49 (*based on NMR the compound is a mixture of two rotamers with ~1:1 ratio*); MS (ES⁺): 446.5 (M+1), 468.4 (M+Na); (ES⁻) 444.5 (M-1); Analysis calculated for C₂₂H₂₁ClFN₃O₄: C, 59.26; H, 4.75; N, 9.42; Found: C, 58.86; H, 4.84; N, 9.36.

Scheme 33



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropylmethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**33b**)

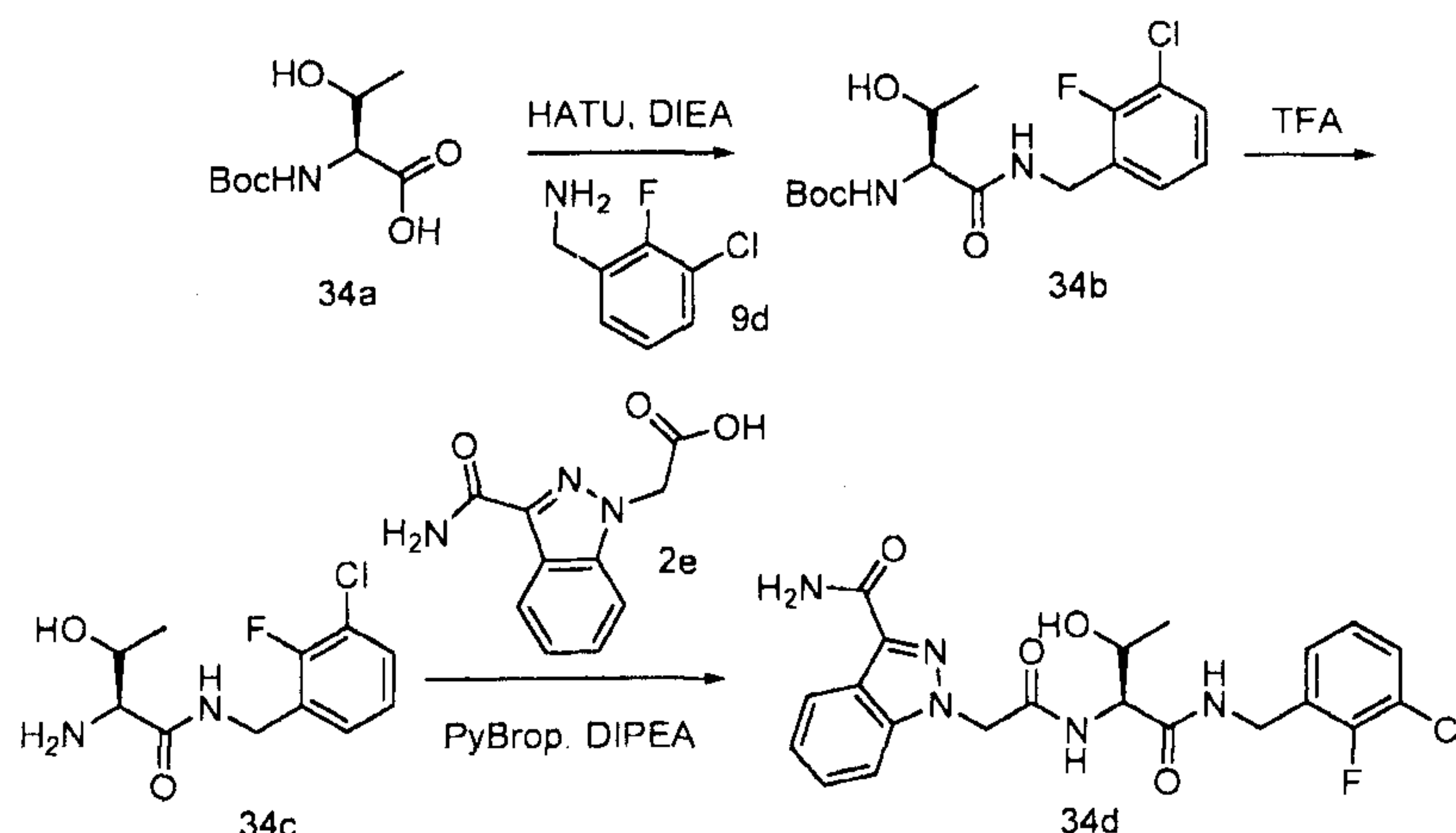
5 Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((cyclopropylmethyl)amino)acetamide (**33a**)

Reaction of 2-amino-N-(3-chloro-2-fluorobenzyl)acetamide (**16c**) (250 mg, 1.15 mmol) with cyclopropanecarbaldehyde (89 mg, 1.27 mmol) according to the procedure reported in step-1 of Scheme 24 gave after workup and purification by flash column chromatography N-(3-chloro-2-fluorobenzyl)-2-((cyclopropylmethyl)amino)acetamide (**33a**) (190mg, 38% yield);
 10 MS (ES⁺): 271.3 (M+1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropylmethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**33b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-((cyclopropylmethyl)amino)acetamide (**33a**) (190 mg, 0.7 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (169 mg, 0.77 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropylmethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**33b**) (41 mg, 0.087 mmol, 12% yield) as a white solid; ¹H NMR
 15 (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 8.96 – 8.39 (m, 1H), 8.18 (d, *J* = 7.5 Hz, 1H), 7.87 – 7.66 (m, 1H), 7.62 – 7.03 (m, 7H), 5.54 (2s, 2H), 4.57 – 3.98 (m, 4H), 3.46 – 3.39 (m, 1H), 3.22 – 2.99 (m, 1H), 1.22 – 0.69 (m, 1H), 0.62 – 0.04 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -120.74, 121.14; MS (ES⁺): 472.5 (M+1), 494.5 (M+Na); 470.6 (M-1).

Scheme 34



Preparation of 1-(2-(((2S,3R)-1-((3-chloro-2-fluorobenzyl)amino)-3-hydroxy-1-oxobutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**34d**)

- 5 Step-1: Preparation of tert-butyl ((2S,3R)-1-((3-chloro-2-fluorobenzyl)amino)-3-hydroxy-1-oxobutan-2-yl)carbamate (**34b**)

Reaction of (2S,3R)-2-((tert-butoxycarbonyl)amino)-3-hydroxybutanoic acid (**34a**) (481 mg, 2.19 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (350 mg, 2.19 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup tert-butyl ((2S,3R)-1-((3-chloro-2-fluorobenzyl)amino)-3-hydroxy-1-oxobutan-2-yl)carbamate (**34b**) which was used as such
10 in the next step.

Step-2: Preparation of (2S,3R)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-hydroxybutanamide (**34c**)

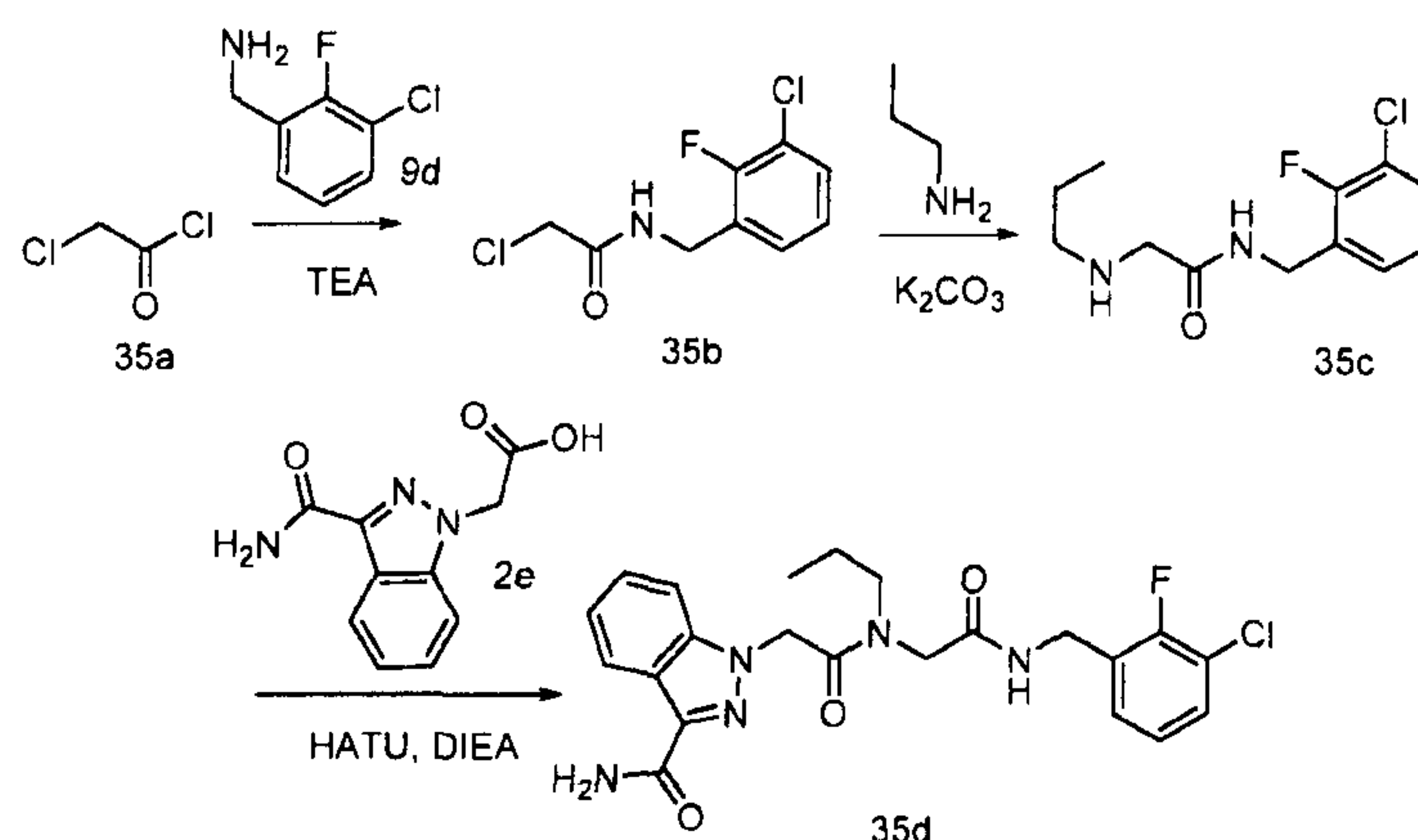
Reaction of tert-butyl ((2S,3R)-1-((3-chloro-2-fluorobenzyl)amino)-3-hydroxy-1-oxobutan-2-yl)carbamate (**34b**) (791 mg, 2.19 mmol) from above step-1 with TFA (3.04 mL, 39.5 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup (2S,3R)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-hydroxybutanamide (**34c**) TFA salt which was used in
15 next step without further purification.

- Step-3: Preparation of 1-(2-(((2S,3R)-1-((3-chloro-2-fluorobenzyl)amino)-3-hydroxy-1-oxobutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**34d**)
20

Reaction of (2S,3R)-2-amino-N-(3-chloro-2-fluorobenzyl)-3-hydroxybutanamide (**34c**) (680 mg, 2.61 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (572 mg, 2.61 mmol) according to the procedure reported in Scheme 32 gave after workup 1-(2-(((2S,3R)-1-((3-chloro-2-fluorobenzyl)amino)-3-hydroxy-1-oxobutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**34d**) (28 mg, 0.061 mmol, 2% yield) as
25 an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.50 (t, *J* = 5.8 Hz, 1H, D₂O

exchangeable), 8.39 (d, $J = 8.3$ Hz, 1H, D₂O exchangeable), 8.17 (d, $J = 8.1$ Hz, 1H), 7.71 (s, 1H, D₂O exchangeable), 7.62 (d, $J = 8.5$ Hz, 1H), 7.52 – 7.36 (m, 3H), 7.34 – 7.22 (m, 2H), 7.18 – 7.05 (m, 1H), 5.36 (s, 2H), 5.07 (d, $J = 4.7$ Hz, 1H, D₂O exchangeable), 4.37 (t, $J = 4.7$ Hz, 2H), 4.20 (dd, $J = 8.3, 3.9$ Hz, 1H), 4.13 – 4.02 (m, 1H), 1.07 (d, $J = 6.2$ Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.36; MS (ES⁺): 484.5 (M+Na); (ES⁻) 460.5 (M-1), 496.4 (M+Cl).

Scheme 35



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(propyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**35d**)

Step-1: Preparation of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**)

To a solution of 2-chloroacetyl chloride (**35a**) (1.04 g, 9.21 mmol) and triethylamine (1.93 mL, 13.81 mmol) in THF (10 mL) at 0 °C was added (3-chloro-2-fluorophenyl)methanamine (**9d**) (1.47 g, 9.21 mmol). The reaction mixture was stirred at room temperature overnight, quenched with water (20 mL) and extracted with DCM (3 x 20 mL). The organic layers were combined, dried, filtered and concentrated in vacuum to dryness. The residue obtained was purified by chromatography [silica (24 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 40%] to afford 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (1.2 g, 5.08 mmol, 55% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.81 (t, $J = 5.2$ Hz, 1H), 7.50 (td, $J = 7.8, 1.8$ Hz, 1H), 7.35 – 7.26 (m, 1H), 7.25 – 7.15 (m, 1H), 4.37 (d, $J = 5.8$ Hz, 2H), 4.13 (s, 2H); ¹⁹F NMR (282 MHz, DMSO) δ -121.08; MS (ES⁺) 236.2 (M+1); 234.1 (M-2).

Step-2: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(propylamino)acetamide (**35c**)

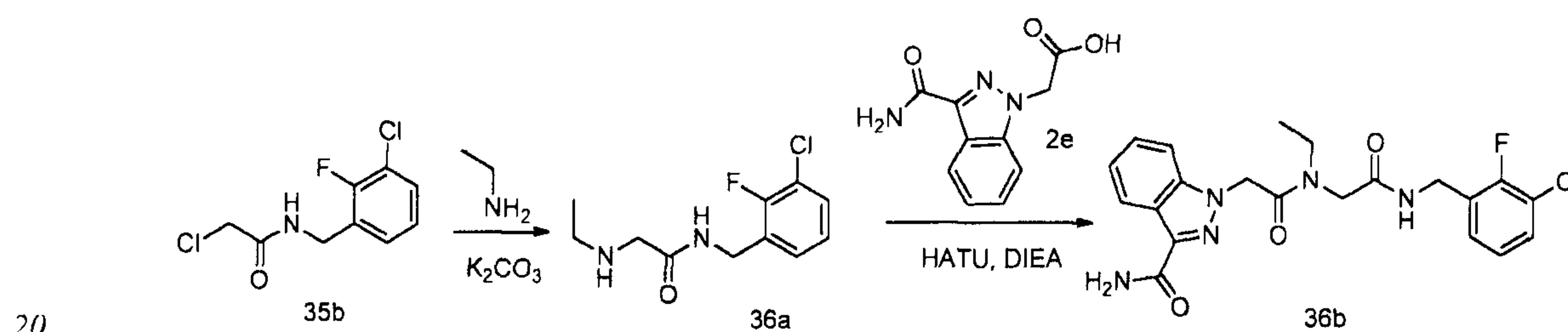
To a solution of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (600 mg, 2.54 mmol) in CH₃CN (10 mL) was added propan-1-amine (300 mg, 5.08 mmol), K₂CO₃ (878 mg, 6.35 mmol) and heated at 60 °C for 5h. The inorganic solid was removed by filtration and filtrate was concentrated in vacuum to dryness. The residue obtained was purified by

chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] to give *N*-(3-chloro-2-fluorobenzyl)-2-(propylamino)acetamide (**35c**) (468 mg, 1.81 mmol, 71% yield) as a yellow oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.35 (t, *J* = 5.9 Hz, 1H), 7.53 – 7.39 (m, 1H), 7.34 – 7.22 (m, 1H), 7.22 – 7.11 (m, 1H), 4.37 (d, *J* = 6.0 Hz, 2H), 3.12 (s, 2H), 2.41 (t, *J* = 7.1 Hz, 2H), 2.16 (s, 1H), 1.50 – 1.29 (m, 2H), 0.84 (t, *J* = 7.4 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO) δ -121.68; MS (ES+) 259.4 (M+1); 257.3 (M-1).

Step-3: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(propyl)amino)-2-oxoethyl)-1*H*-indazole-3-carboxamide (**35d**)

Reaction of *N*-(3-chloro-2-fluorobenzyl)-2-(propylamino)acetamide (**35c**) (130 mg, 0.50 mmol) with 2-(3-carbamoyl-1*H*-indazol-1-yl)acetic acid (**2e**) (121 mg, 0.55 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(propyl)amino)-2-oxoethyl)-1*H*-indazole-3-carboxamide (**35d**) (155 mg, 0.34 mmol, 67% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 8.84 and 8.48 (2t, *J* = 5.8 Hz, 1H), 8.23 – 8.13 (m, 1H), 7.71 (d, *J* = 8.3 Hz, 1H), 7.61 – 7.03 (m, 7H), 5.56 and 5.47 (2s, 2H), 4.46 and 4.33 (2d, *J* = 5.7 Hz, 2H), 4.24 and 3.95 (2s, 2H), 3.49 – 3.38 (m, 1H), 3.25 – 3.13 (m, 1H), 1.53 (m, 2H), 0.93 and 0.77 (2t, *J* = 7.3 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.25, 121.63; MS (ES+) 482.5 (M+Na); 458.4 (M-1).

Scheme 36



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(ethyl)amino)-2-oxoethyl)-1*H*-indazole-3-carboxamide (**36b**)

Step-1: Preparation of *N*-(3-chloro-2-fluorobenzyl)-2-(ethylamino)acetamide (**36a**)

Reaction of 2-chloro-*N*-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (600 mg, 2.54 mmol) with ethanamine hydrochloride (415 mg, 5.08 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup *N*-(3-chloro-2-fluorobenzyl)-2-(ethylamino)acetamide (**36a**) (494 mg, 2.02 mmol, 79% yield) as a yellow oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.39 (t, *J* = 5.8 Hz, 1H), 7.53 – 7.40 (m, 1H), 7.33 – 7.23 (m, 1H), 7.23 – 7.13 (m, 1H), 4.37 (d, *J* = 5.9

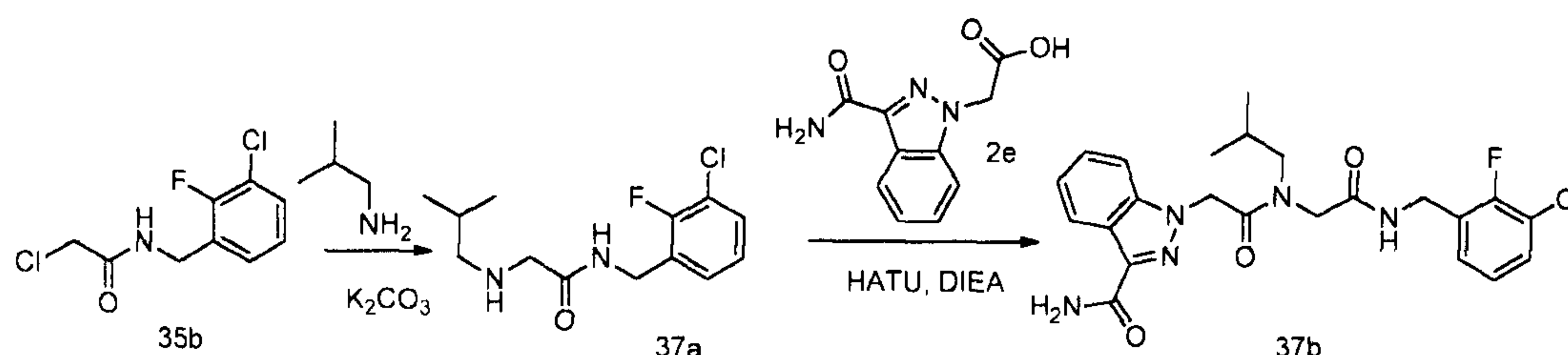
Hz, 2H), 3.14 (s, 2H), 2.50 (q, $J = 7.1$ Hz, 2H), 2.25 (s, 1H), 1.00 (t, $J = 7.1$ Hz, 3H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.72; MS (ES+) 245.3 (M+1); 243.2 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(ethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**36b**)

5 Reaction of N-(3-chloro-2-fluorobenzyl)-2-(ethylamino)acetamide (**36a**) (174 mg, 0.71 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (171 mg, 0.78 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(ethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**36b**) (69 mg, 0.156 mmol, 22% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) (a mixture of two rotamers) δ 8.85 and 8.49 (2t, $J = 5.5$ Hz, 1H), 8.18 (d, $J = 8.1$ Hz, 1H), 7.71 (d, $J = 7.4$ Hz, 1H), 7.62 – 7.09 (m, 7H), 5.57 and 5.45 (2s, 2H), 4.46 and 4.34 (2d, $J = 5.5$ Hz, 2H), 4.24 and 3.95 (2s, 2H), 3.56 – 3.24 (m, 2H), 1.23 and 0.97 (2t, $J = 7.1$ Hz, 3H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.28, 121.65; MS (ES+) 468.5 (M+Na); 444.5 (M-1);
 10 [based on NMR, this compound is a mixture of rotamers with 1:1 ratio]

15

Scheme 37



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**37b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(isobutylamino)acetamide (**37a**)

20 Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (200 mg, 0.85 mmol) with isobutylamine (124 mg, 1.7 mmol), according to the procedure reported in step-2 of Scheme 35 gave after workup N-(3-chloro-2-fluorobenzyl)-2-(isobutylamino)acetamide (**37a**) (50 mg, 0.18 mmol, 22% yield) as a yellow oil; MS (ES+): 273.4 (M+1); (ES-) 271.3 (M-1)

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-

25 oxoethyl)(isobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**37b**)

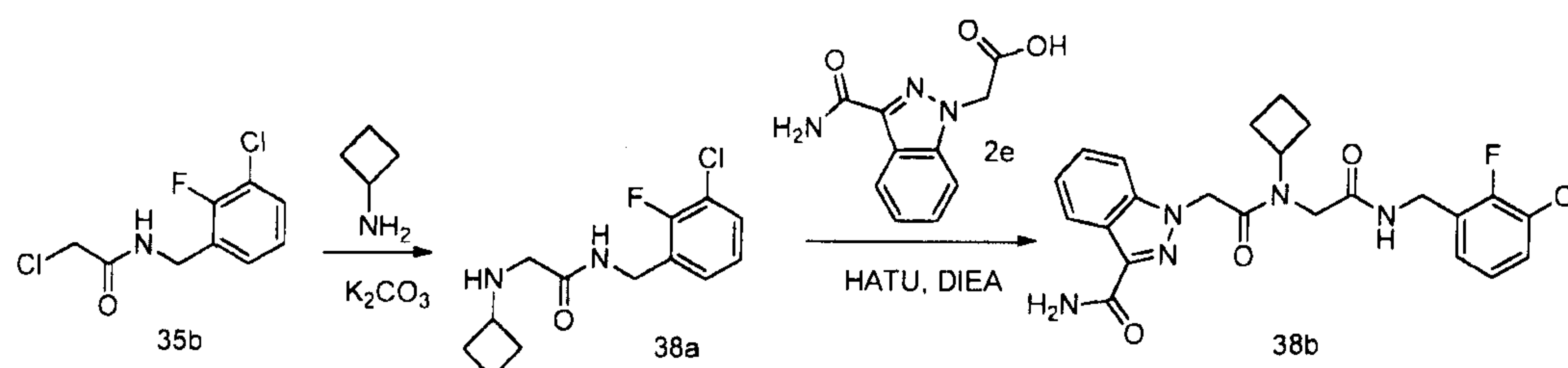
Reaction of N-(3-chloro-2-fluorobenzyl)-2-(isobutylamino)acetamide (**37a**) (54 mg, 0.2 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (48 mg, 0.22 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by column chromatography [silica (12 g), eluting with CMA80 in CHCl_3 from 0 to 40%] to give

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1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**37b**) (48 mg, 0.1 mmol, 51% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.84 and 8.48 (2t, *J* = 5.6 Hz, 1H), 8.18 (d, *J* = 8.2 Hz, 1H), 7.78 – 7.65 (m, 1H), 7.59 – 7.00 (m, 7H), 5.54 and 5.50 (2s, 2H), 4.53 – 3.86 (m, 4H), 3.34 – 2.97 (m, 2H), 2.10 – 1.65 (m, 1H), 0.99 and 0.79 (2d, *J* = 6.6 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.22, 121.64; MS (ES⁺): 474.5 (M+1); (ES⁻): 472.4 (M-1); [based on NMR, this compound is a mixture of rotamers with 3:2 ratio]

Scheme 38



10 Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**38b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(cyclobutylamino)acetamide (**38a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (530 mg, 2.25 mmol) with cyclobutanamine (319 mg, 4.49 mmol), according to the procedure reported in step-2 of
 15 Scheme 35 gave after workup and purification by chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-(cyclobutylamino)acetamide (**38a**) (523 mg, 1.93 mmol, 86% yield) as a yellow oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.33 (t, *J* = 5.9 Hz, 1H), 7.52 – 7.39 (m, 1H), 7.32 – 7.23 (m, 1H), 7.23 – 7.14 (m, 1H), 4.34 (d, *J* = 6.0 Hz, 2H), 3.18 – 3.07 (m, 1H), 3.05 (s, 2H), 2.37 (s, 1H),
 20 2.11 – 1.96 (m, 2H), 1.75 – 1.44 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.68; MS (ES⁺): 271.4 (M+1); (ES⁻): 269.3 (M-1);

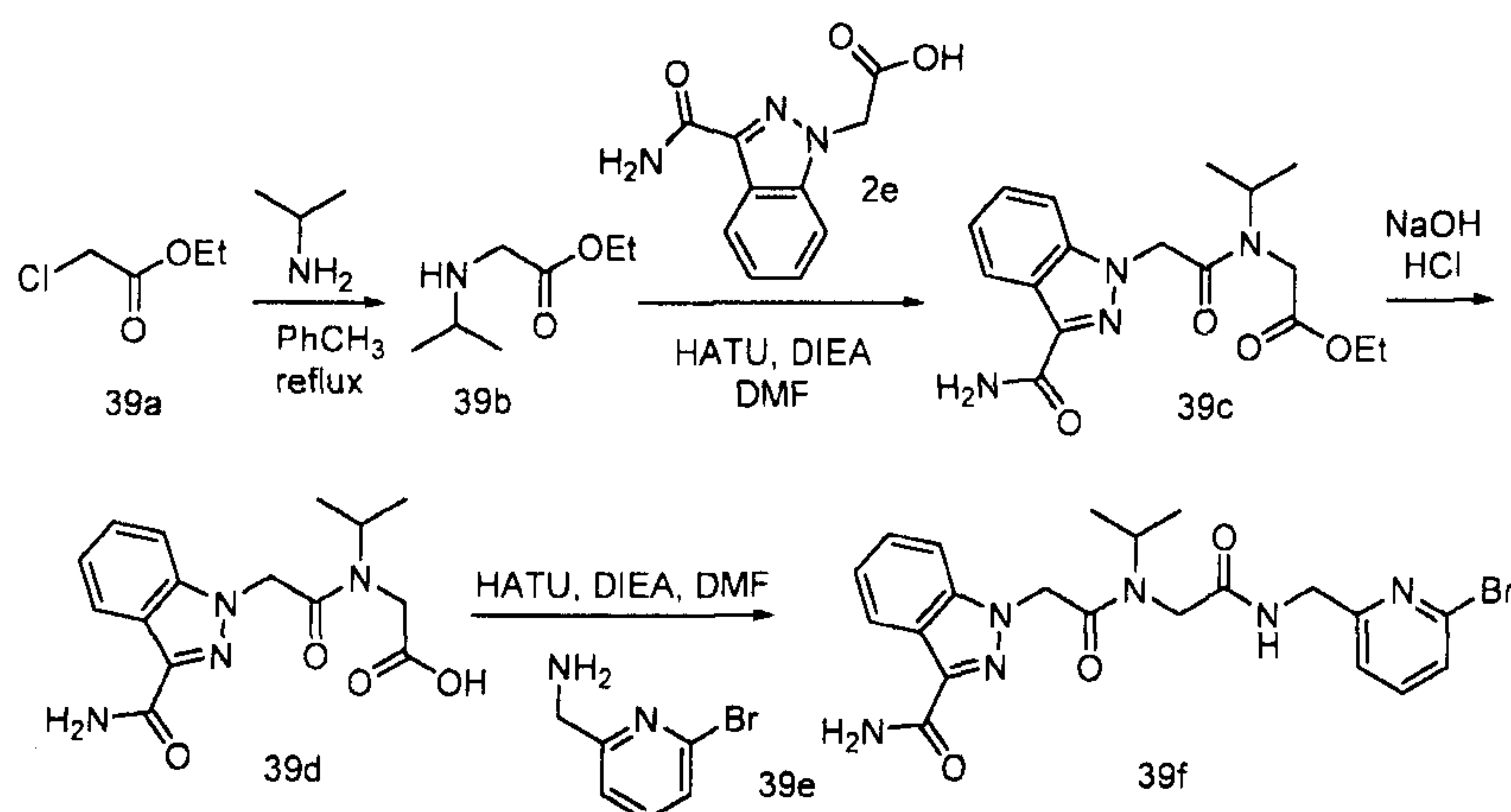
Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**38b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(cyclobutylamino)acetamide (**38a**) (210 mg, 0.78 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (187 mg, 0.85 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**38b**) (298 mg, 0.63 mmol, 81% yield) as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.87 and 8.43 (2t, *J* = 5.8 Hz, 1H), 8.18 (d, *J* = 7.6 Hz, 1H), 7.71 (s, 1H), 7.62 – 7.02 (m,

7H), 5.56 and 5.42 (s, 2H), 4.75 – 4.50 (m, 1H), 4.49 – 4.02 (m, 4H), 2.30 – 2.09 (m, 2H), 2.03 – 1.86 (m, 2H), 1.74 – 1.46 (m, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.23, 121.61; MS (ES $^{+}$): 494.5 (M+Na); ES $^{-}$): 470.4 (M-1); [based on NMR, this compound is a mixture of rotamers with 2:3 ratio].

5

Scheme 39



Preparation of 1-(2-((2-(((6-bromopyridin-2-yl)methyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**39f**)

Step-1: Preparation of ethyl 2-(isopropylamino)acetate (**39b**)

10 A stirred solution of propan-2-amine (22.94 mL, 269 mmol) and ethyl 2-chloroacetate (**39a**) (19.21 mL, 180 mmol) in toluene (200 mL) was heated at reflux for 2 h, cooled to room temperature, diluted with brine (300 mL) and with extracted with EtOAc (2 x 300 mL). The organic layers combined were, dried, filtered and evaporated to dryness. The residue obtained was purified by flash column chromatography [Silica gel, 80 g eluting with EtOAc in
15 hexanes from 0-30%) to afford ethyl 2-(isopropylamino)acetate (**39b**) (18.78 g, 129 mmol, 72% yield) as a yellow semi-solid; MS (ES $^{+}$): 146.2 (M+1); (ES $^{-}$) 180.1 (M+Cl).

Step-2: Preparation of ethyl 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-isopropylacetamido)acetate (**39c**)

Reaction of ethyl 2-(isopropylamino)acetate (**39b**) (4.42 g, 30.4 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (4.00 g, 18.25 mmol) according to the procedure reported in
20 step-3 of Scheme 2 gave after workup ethyl 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-isopropylacetamido)acetate (**39c**) as a dark yellow oil which was used as such in the next step.

Step-3: Preparation of 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-isopropylacetamido)acetic acid (**39d**)
25

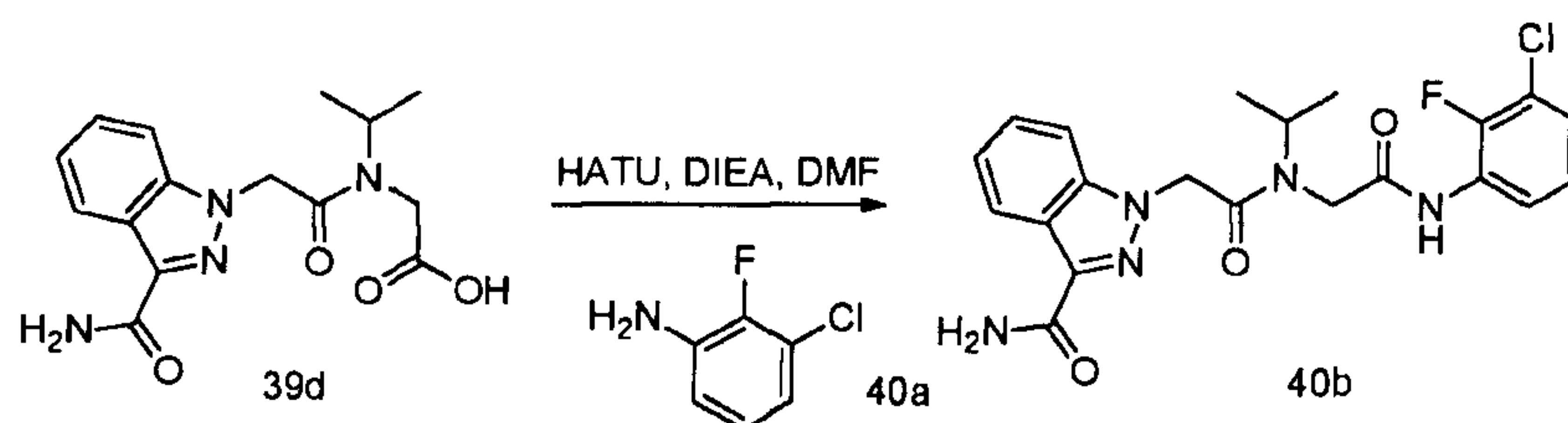
To a solution of ethyl 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-isopropylacetamido)acetate (**39c**) (3.00 g, 8.66 mmol) in of acetonitrile (30 mL) at room temperature was added sodium hydroxide (0.762 g, 19.05 mmol) in 30 mL of H₂O) and stirred overnight. Acetonitrile was removed by evaporation vacuum and the aqueous layer was basified with 1 N NaOH, washed with ether. The basic aqueous layer was acidified with ice-cold 1 N HCl and the solid obtained was collected by filtration, dried in vacuum to afford 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-isopropylacetamido)acetic acid (**39d**) (1.53 g, 4.81 mmol, 55.5% yield) as a yellow solid; MS (ES⁺): 341.4 (M+Na); (ES⁻) 317.4 (M-1).

Step-4: Preparation of 1-(2-((2-(((6-bromopyridin-2-yl)methyl)amino)-2-

oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**39f**)

Reaction of 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-isopropylacetamido)acetic acid (**39d**) (0.15 g, 0.47 mmol) with (6-bromopyridin-2-yl)methanamine (**39e**) (0.115 g, 0.613 mmol), according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [Silica gel, 24 g eluting with MeOH in CHCl₃ 0-100%) 1-(2-((2-(((6-bromopyridin-2-yl)methyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**39f**) (65 mg, 0.13 mmol, 28% yield) as an off-white solid, which was mixture of rotamers from NMR analysis; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.92 & 8.46 (2t, *J* = 6.1 Hz, 1H), 8.23 – 8.12 (m, 1H), 7.78 – 7.18 (m, 8H), 5.59 & 5.46 (2s, 2H), 4.63 – 4.50 (m, 1H), 4.46 (d, *J* = 5.7 Hz) & 4.31 (d, *J* = 6.1 Hz) (2d, 2H), 4.25 & 3.85 (2s, 2H), 1.25 (d, *J* = 6.2 Hz) & 1.02 (dd, *J* = 6.8, 2.0 Hz) (d & dd, 6H); ¹H NMR (300 MHz, DMSO-*d*₆/D₂O) δ 8.17 – 8.09 (m, 1H), 7.69 (t, *J* = 7.7 Hz, 1H), 7.61 – 7.33 (m, 4H), 7.31 – 7.16 (m, 1H), 5.57 (s) & 5.42 (s) (2s, 2H), 4.59 – 4.46 (m, 1H), 4.43 (s) & 4.29 (2s, 2H), 4.19 (s, 1H), 1.22 (d, *J* = 6.4 Hz) & 1.00 (d, *J* = 6.8 Hz) (2d, 6H); MS (ES⁺): 487.5, 489.5 (M+2), 509.5, 511.5 (M+Na); (ES⁻): 485.4, 487.5 (M-1), 521.4, 523.4 (M+Cl).

Scheme 40



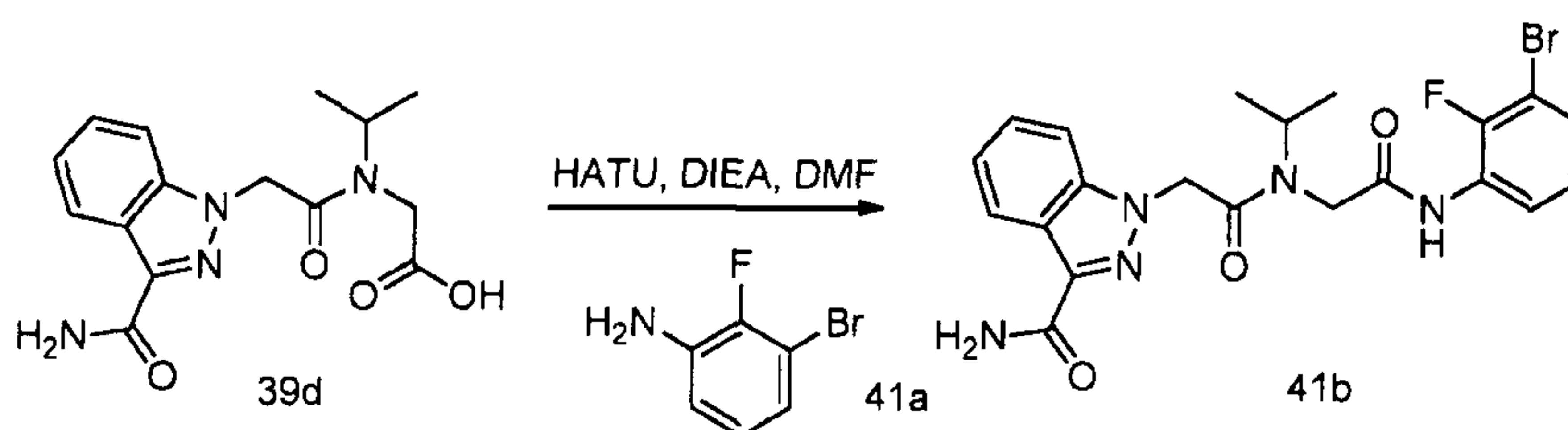
Preparation of 1-(2-((2-((3-chloro-2-fluorophenyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**40b**)

Reaction of 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-isopropylacetamido)acetic acid (**39d**)

(0.15 g, 0.47 mmol) with 3-chloro-2-fluoroaniline (**40a**) (0.089 g, 0.613 mmol) according to

the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [Silica gel, 24 g eluting with MeOH in CHCl₃ 0-30%) 1-(2-((2-((3-chloro-2-fluorophenyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**40b**) (51 mg, 0.11 mmol, 24% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.34 & 9.86 (2s, 1H), 8.29 – 8.10 (m, 1H), 8.02 – 7.51 (m, 3H), 7.51 – 7.06 (m, 5H), 5.63 & 5.48 (s, 2H), 4.79 – 3.92 (m, 3H), 1.26 (d, *J* = 6.6 Hz) & 1.06 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -126.60; (*based on NMR the compound is a mixture of rotamers with ~2:3 ratio*); MS (ES⁺): 446.5 (M+1); MS (ES⁻): 444.4 (M-1), 480.4 (M+Cl).

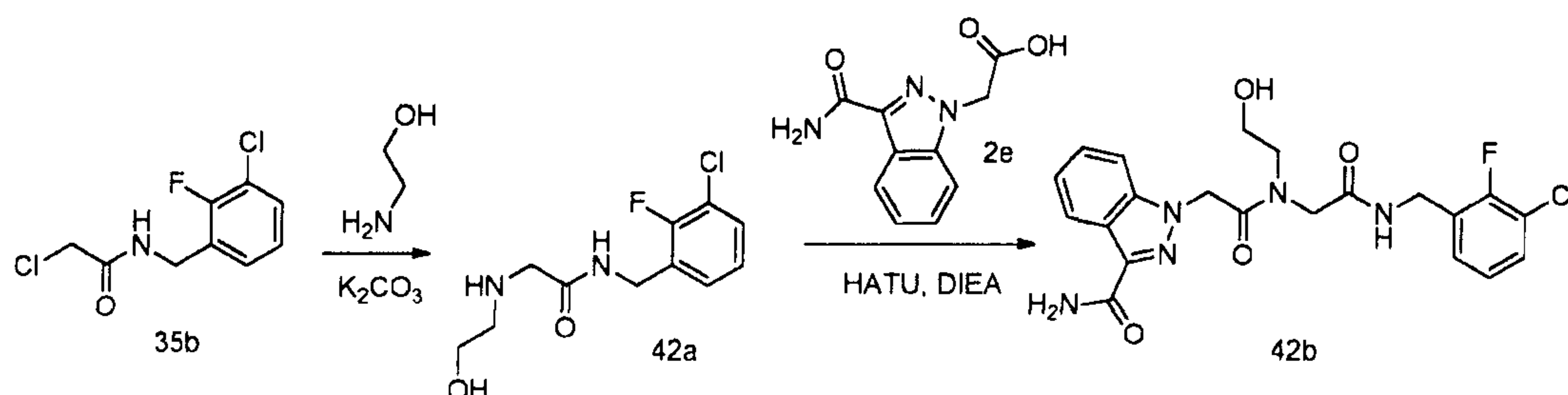
Scheme 41



Preparation of 1-(2-((2-((3-bromo-2-fluorophenyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**41b**)

Reaction of 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-isopropylacetamido)acetic acid (**39d**) (0.15 g, 0.47 mmol) with 3-bromo-2-fluoroaniline (**41a**) (90 mg, 0.47 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [Silica gel, 24 g eluting with MeOH in CHCl₃ from 0-100%) 1-(2-((2-((3-bromo-2-fluorophenyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**41b**) (48 mg, 0.1 mmol, 21% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.34 & 9.85 (2s, 1H), 8.28 – 7.02 (m, 9H), 5.63 & 5.49 (2s, 2H), 4.83 – 3.91 (m, 3H), 1.26 (d, *J* = 6.5 Hz) 1.06 (d, *J* = 6.9 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -118.22 (d, *J* = 3.7 Hz); (*based on NMR the compound is a mixture of rotamers with ~2:3 ratio*); MS (ES⁺): 490.4, 492.5 (M+2); MS (ES⁻): 488.3, 490.3 (M-2).

Scheme 42



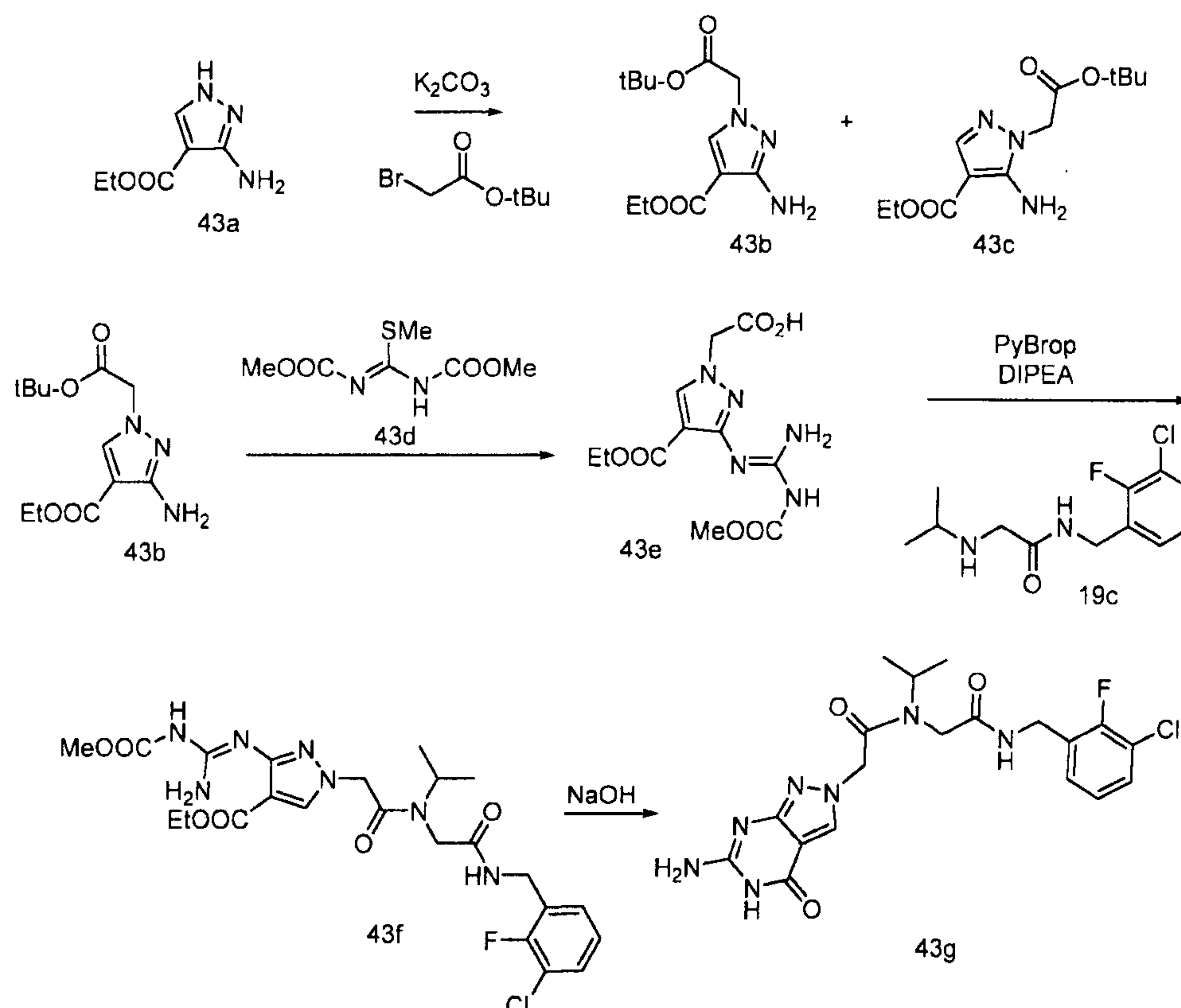
Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2-hydroxyethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**42b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((2-hydroxyethyl)amino)acetamide (**42a**)

- 5 Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 2.12 mmol) with 2-aminoethanol (259 mg, 4.24 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-((2-hydroxyethyl)amino)acetamide (**42a**) (402 mg, 1.54 mmol, 73% yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.45 (t, *J* = 6.0 Hz, 1H), 7.53 – 7.40 (m, 1H), 7.33 – 7.23 (m, 1H), 7.23 – 7.11 (m, 1H), 4.54 (s, 1H), 4.36 (d, *J* = 6.0 Hz, 2H), 3.52 – 3.40 (m, 2H), 3.16 (s, 3H), 2.55 (t, *J* = 5.6 Hz, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -73.53 (TFA peak), -121.72; MS (ES+): 261.3 (M+1), 283.3 (M+Na); (ES-): 259.3 (M-1).

- Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2-hydroxyethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**42b**)
- 15 Reaction of N-(3-chloro-2-fluorobenzyl)-2-((2-hydroxyethyl)amino)acetamide (**42a**) (210 mg, 0.81 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (194 mg, 0.89 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2-hydroxyethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**42b**) (128 mg, 0.28 mmol, 34% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.87 and 8.57(2t, *J* = 5.8 Hz, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.78 – 7.64 (m, 1H), 7.60 – 7.00 (m, 7H), 5.66 and 5.43 (2s, 2H), 5.24 and 4.76 2 (2t, *J* = 5.1 Hz, 1H), 4.49 – 4.32 (m, 2H), 4.00 (s, 1H), 3.72 – 3.55 (m, 3H), 3.51 – 3.39 (m, 1H), 3.34 – 3.26 (m, 1H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.33, 121.63; MS (ES-): 460.5 (M-1); [based on NMR, this
- 25 compound is a mixture of two rotamers with 2:5 ratio].

Scheme 43



Preparation of 2-(6-amino-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)-N-(2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)-N-isopropylacetamide (**43g**)

- 5 Step-1: Preparation of ethyl 3-amino-1-(2-(tert-butoxy)-2-oxoethyl)-1H-pyrazole-4-carboxylate (**43b**)

To a solution of ethyl 3-amino-1H-pyrazole-4-carboxylate (**43a**) (5 g, 31.6 mmol) and tert-butyl 2-bromoacetate (5.60 mL, 37.9 mmol) in DMF (20 mL) was added Potassium carbonate (6.55 g, 47.4 mmol) and stirred at room temperature overnight. The reaction mixture was
 10 diluted with EtOAc (200 mL), washed with water (2 x 100 mL), brine (100 mL), dried, filtered and concentrated in vacuum. The residue was purified by flash column chromatography on silica gel eluting with hexanes/EtOAc (1:0 to 2:1) to afford ethyl 3-amino-1-(2-(tert-butoxy)-2-oxoethyl)-1H-pyrazole-4-carboxylate (**43b**) as a (1.16 g, 14%) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.93 (s, 1H), 5.37 (s, 2H), 4.69 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 1.42 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H); MS (ES⁺: 270.4 (M + 1) and 292.4 (M + Na); and ethyl 5-amino-1-(2-(tert-butoxy)-2-oxoethyl)-1H-pyrazole-4-carboxylate (**43c**) (1.56 g, 18%) as a brown gum. ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.45 (s, 1H), 6.38 (s, 2H), 4.70 (s, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 1.41 (s, 9H), 1.24 (t, *J* = 7.1 Hz, 3H); MS (ES⁺: 268.3 (M-1) and 304.3 (M+Cl).

Step-2: Preparation of (E)-2-(3-(amino(methoxycarbonylamino)methyleneamino)-4-(ethoxycarbonyl)-1H-pyrazol-1-yl)acetic acid (**43e**)

A mixture of ethyl 3-amino-1-(2-(tert-butoxy)-2-oxoethyl)-1H-pyrazole-4-carboxylate (**43b**) (571 mg, 2.12 mmol) and (Z)-(methoxycarbonylamino)(methylthio)methylenecarbamic acid methyl ester (**43d**) (646 mg) in acetic acid (5 mL) was heated with stirring at 100 °C

overnight. The reaction mixture was cooled to room temperature and triturated with CHCl₃ followed by filtration, washing with CHCl₃, and drying under vacuum to afford (E)-2-(3-(amino(methoxycarbonylamino)methyleneamino)-4-(ethoxycarbonyl)-1H-pyrazol-1-yl)acetic acid (**43e**) (290 mg, 44%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.81 (bs, 1H), 8.34 (s, 1H), 8.07 (s, 1H), 4.97 (s, 2H), 4.28 (q, *J* = 7.1 Hz, 2H), 3.54 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 314 (M+1),

Step-3: Preparation of (E)-ethyl 3-(amino(methoxycarbonylamino)methyleneamino)-1-(2-((2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-pyrazole-4-carboxylate (**43f**)

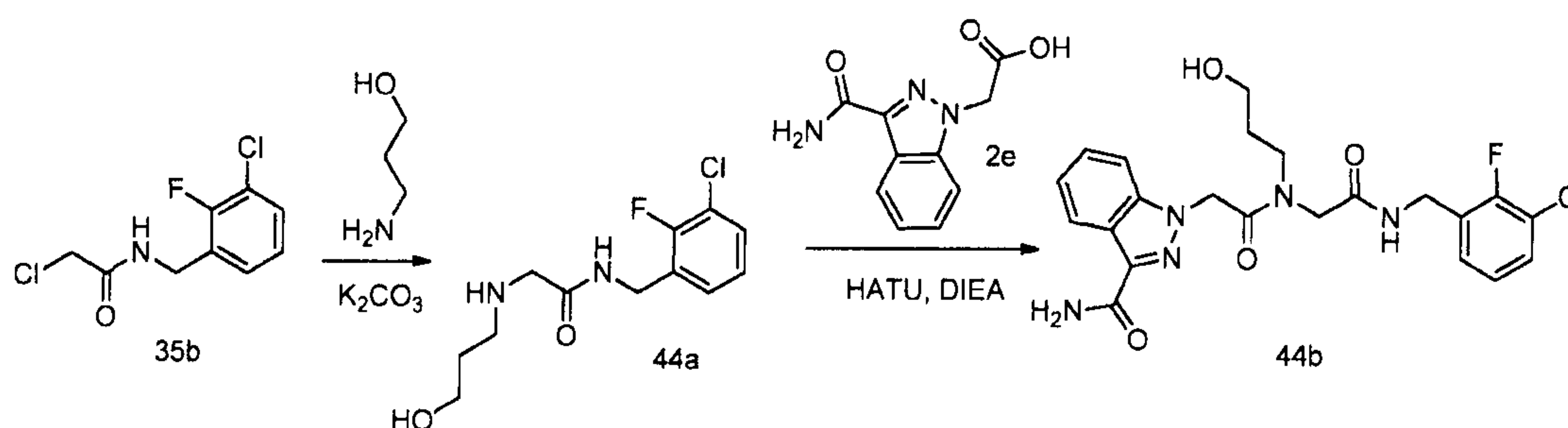
Reaction of (E)-2-(3-(amino(methoxycarbonylamino)methyleneamino)-4-(ethoxycarbonyl)-1H-pyrazol-1-yl)acetic acid (**43e**) (80 mg, 0.26 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (79 mg, 0.306 mmol) according to the procedure reported in step-3 of Scheme-2 gave after workup and purification by flash column chromatography on silica gel eluting with CHCl₃/MeOH (1:0 to 19:1) to give (E)-ethyl 3-(amino(methoxycarbonylamino)methyleneamino)-1-(2-((2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-pyrazole-4-carboxylate (**43f**) (64 mg, 45%) as an off-white solid; ¹H NMR ((300 MHz, DMSO-*d*₆) (as a mixture of two rotamers): δ 11.60 (s, 1H), 8.75 & 8.33 (2t, 1H), 8.26 (s, 1H), 8.22 (s, 1H), 8.06 (d, *J* = 13.5 Hz, 1H), 7.59 – 7.05 (m, 3H), 5.25 & 5.05 (2s, 2H), 4.64 – 4.50 & 4.17 – 3.98 (2m, 1H), 4.46 – 4.22 (m, 4H), 4.07 & 3.83 (2s, 2H), 3.54 (s, 3H), 1.35 – 0.92 (m, 9H); ¹⁹F NMR(282 MHz, DMSO-*d*₆) δ -121.28, -121.69; MS (ES⁺): 554.6 (M+1) & 556.6 (M+3); MS (ES⁻): 588.6 and 590.6 (M+Cl).

Step-4: Preparation of 2-(6-amino-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)-N-(2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)-N-isopropylacetamide (**43g**)

To a solution of (E)-ethyl 3-(amino(methoxycarbonylamino)methyleneamino)-1-(2-((2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-pyrazole-4-carboxylate (**43f**) (54 mg, 0.097 mmol) in MeOH (8 mL) was added with 1 N aqueous sodium hydroxide (0.49 mL, 0.98 mmol) and refluxed for 2.5 h. The reaction mixture was

cooled to room temperature concentrated in vacuum to remove MeOH, diluted with water (10 mL) and acidified with 4 N HCl. The solid obtained was collected by filtration, dried under vacuum to afford 2-(6-amino-4-oxo-4,5-dihydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)-N-(2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)-N-isopropylacetamide (**43g**) (15 mg, 34%) as a white solid; ¹H NMR(300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 10.35 & 10.33 (2s, 1H), 8.74 & 8.36 (2t, 1H), 8.14 & 8.13 (2s, 1H), 7.60 – 7.07 (m, 3H), 6.20 (bs, 2H), 5.21 & 5.03 (2s, 2H), 4.41 (d, *J* = 5.6 Hz) & 4.33 (d, *J* = 5.7 Hz) (2d, 2H), 4.64 – 4.48 & 4.21 – 4.05 (2m, 1H), 4.10 & 3.83 (2s, 2H), 1.15 (d, *J* = 6.4 Hz) & 0.97 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.35, -121.73. MS (ES⁺): 450.5 (M+1).

Scheme 44



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(3-hydroxypropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**44b**)

Step-1: Preparation of *N*-(3-chloro-2-fluorobenzyl)-2-((3-hydroxypropyl)amino)acetamide (**44a**)

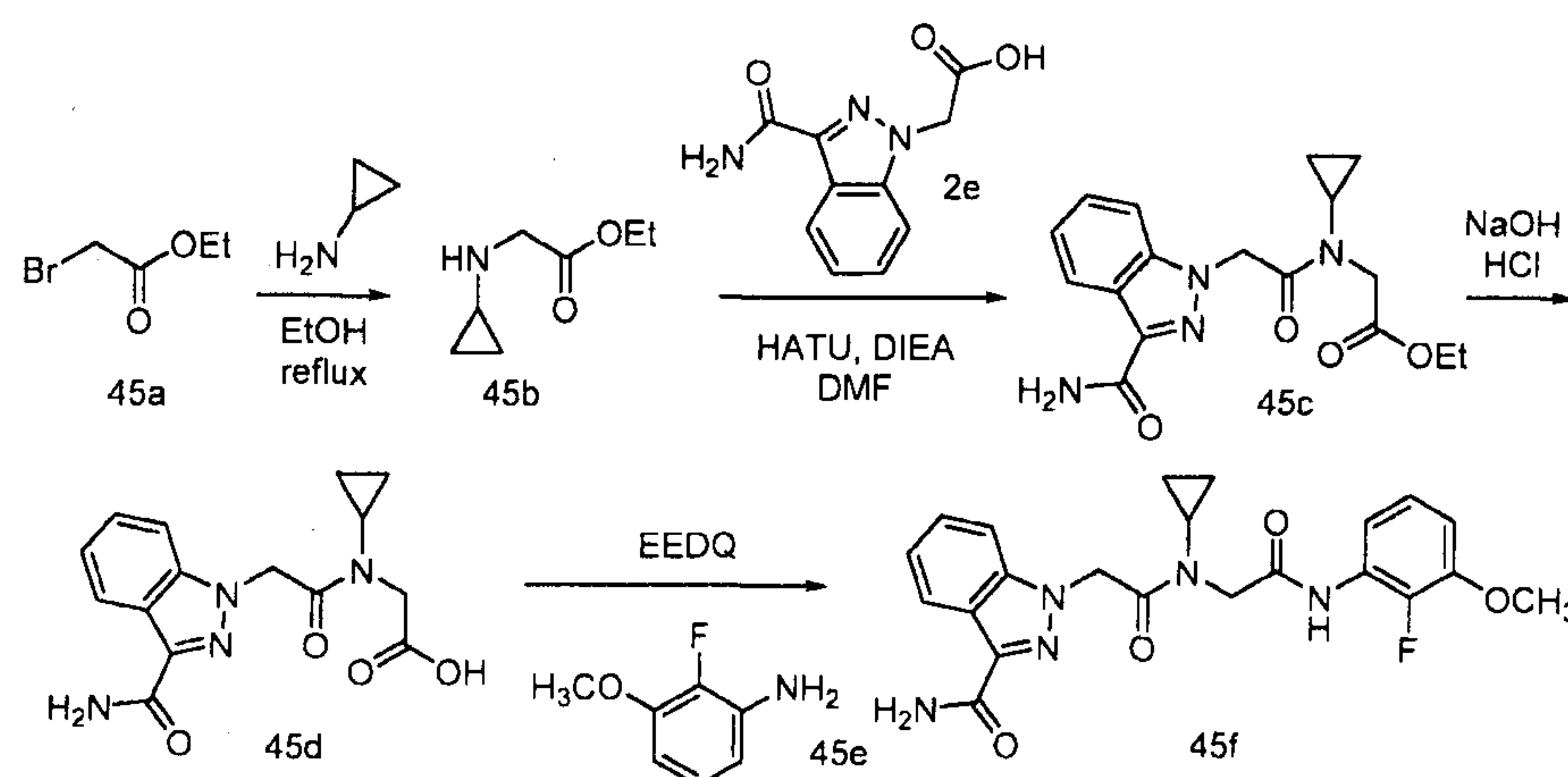
Reaction of 2-chloro-*N*-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 2.12 mmol) with 2-aminoethanol (318 mg, 4.24 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] *N*-(3-chloro-2-fluorobenzyl)-2-((3-hydroxypropyl)amino)acetamide (**44a**) (494 mg, 2.02 mmol, 73% yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.38 (t, *J* = 6.1 Hz, 1H), 7.52 – 7.42 (m, 1H), 7.33 – 7.23 (m, 1H), 7.19 (td, *J* = 7.8, 1.0 Hz, 1H), 4.37 (d, *J* = 5.8 Hz, 2H), 4.14 (s, 1H), 3.45 (t, *J* = 6.3 Hz, 2H), 3.18 (s, 2H), 3.13 (s, 2H), 2.56 – 2.52 (m, 1H), 1.61 – 1.49 (m, 2H); MS (ES⁺) 275.4 (M+1); MS (ES⁻), 273.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(3-hydroxypropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**44b**)

Reaction of *N*-(3-chloro-2-fluorobenzyl)-2-((3-hydroxypropyl)amino)acetamide (**44a**) (120 mg, 0.44 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (105 mg, 0.48 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(3-hydroxypropyl)amino)-2-oxoethyl)-1H-

indazole-3-carboxamide (**44b**) (59 mg, 0.12 mmol, 28% yield) as a white solid; ^1H NMR(300 MHz, DMSO- d_6) (a mixture of two rotamers) δ 8.86 (t, J = 5.5 Hz) & 8.51 (t, J = 5.9 Hz) (2t, 1H), 8.18 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 7.1 Hz, 1H), 7.60 – 7.06 (m, 7H), 5.63 & 5.45 (2s, 2H), 4.82 – 4.29 (m, 3H), 4.26 & 3.94 (2s, 2H), 3.65 – 3.48 (m, 2H), 3.35 – 3.23 (m, 2H), 1.89 – 1.46 (m, 2H); ^{19}F NMR (282 MHz, DMSO) δ -121.30, 121.64; MS (ES $^+$) 476.5 (M+1); MS (ES $^-$), 510.5 (M+Cl); HPLC, Rt 4.005 min, 93.5338% [based on NMR, this compound is a mixture of two rotamers 2:5 ratio].

Scheme 45



Preparation of 1-(2-(cyclopropyl(2-((2-fluoro-3-methoxyphenyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**45f**)

Step-1: Preparation of ethyl 2-(cyclopropylamino)acetate (**45b**)

Reaction of ethyl 2-bromoacetate (**45a**) (10 g, 59.9 mmol) with cyclopropylamine (16.88 mL, 240 mmol) in ethanol (80 mL) at room temperature according to the procedure reported in step-1 of Scheme 39 gave after workup ethyl 2-(cyclopropylamino)acetate (**45b**) (7.2 g, 50.3 mmol, 84% yield) as light orange colored liquid; ^1H NMR (300 MHz, DMSO- d_6) δ 4.09 (q, J = 7.1 Hz, 2H), 3.30 (s, 2H), 2.60 (s, 1H), 2.23 - 2.09 (m, 1H), 1.19 (t, J = 7.1 Hz, 3H), 0.37 - 0.28 (m, 2H), 0.24 - 0.17 (m, 2H); MS (ES $^+$) 144.2 (M+1).

Step-2: Preparation of ethyl 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-cyclopropylacetamido)acetate (**45c**)

Reaction of ethyl 2-(cyclopropylamino)acetate (**45b**) (1.57 g, 10.95 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (2 g, 9.12 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup ethyl 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-cyclopropylacetamido)acetate (**45c**) (2 g, 5.81 mmol, 64% yield) as off-white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.22 - 8.14 (m, 1H), 7.71 (s, 1H), 7.66 - 7.59 (m, 1H), 7.47 - 7.35 (m, 2H), 7.26 (ddd, J = 7.9, 6.9, 0.9 Hz, 1H), 5.69 (s, 2H), 4.16 - 3.99 (m, 4H), 3.15 -

3.02 (m, 1H), 1.31 - 1.21 (m, 2H), 1.17 (t, $J = 7.1$ Hz, 3H), 1.03 - 0.88 (m, 2H); MS (ES⁺): 345.5 (M+1), 367.4 (M+Na), MS (ES⁻): 379.5 (M+Cl).

Step-3: Preparation of 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-cyclopropylacetamido)acetic acid (**45d**)

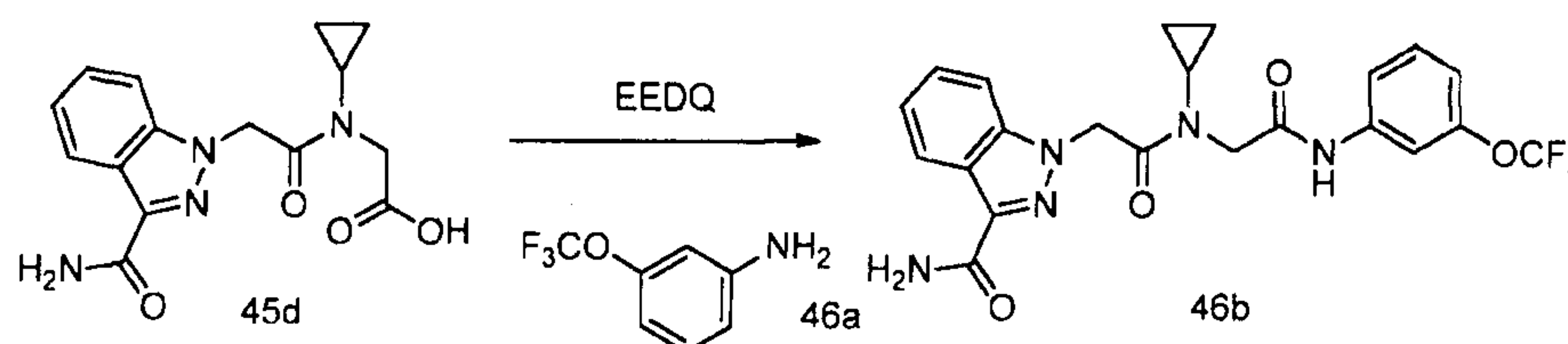
5 Hydrolysis ester of ethyl 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-cyclopropylacetamido)acetate (**45c**) (1.8 g, 5.23 mmol) according to the procedure reported in step-3 of Scheme 39 gave after workup 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-cyclopropylacetamido)acetic acid (**45d**) (1.5 g, 4.74 mmol, 91% yield) as light orange colored foam; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.76 (s, 1H), 8.18 (dt, $J = 8.1, 1.0$ Hz, 1H),
10 7.73 (s, 1H), 7.64 (dt, $J = 8.6, 0.9$ Hz, 1H), 7.47 - 7.36 (m, 2H), 7.26 (ddd, $J = 8.0, 6.8, 0.9$ Hz, 1H), 5.68 (s, 2H), 4.00 (s, 2H), 3.12 - 2.99 (m, 1H), 1.06 - 0.86 (m, 4H).

Step-4: Preparation of 1-(2-(cyclopropyl(2-((2-fluoro-3-methoxyphenyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**45f**)

Reaction of 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-cyclopropylacetamido)acetic acid (**45d**)
15 (0.12 g, 0.38 mmol) with 2-fluoro-3-methoxyaniline (0.054 g, 0.379 mmol) (**45e**) (54 mg, 0.379 mmol), according to the procedure reported in step-1 of Scheme 2 gave after workup and purification by flash column chromatography [Silica gel, 12 g eluting with MeOH/EtOAc (9:1) in hexane 0-100%] 1-(2-(cyclopropyl(2-((2-fluoro-3-methoxyphenyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**45f**) (70 mg, 0.159 mmol, 42%
20 yield) as a white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 9.83 (s, 1H), 8.18 (dt, $J = 8.1, 1.0$ Hz, 1H), 7.74 (s, 1H), 7.66 (d, $J = 8.5$ Hz, 1H), 7.59 - 7.34 (m, 3H), 7.32 - 7.20 (m, 1H), 7.06 (td, $J = 8.3, 1.8$ Hz, 1H), 6.98 - 6.86 (m, 1H), 5.70 (s, 2H), 4.20 (s, 2H), 3.82 (s, 3H), 3.11 (s, 1H), 1.05 - 0.91 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -147.62; MS (ES⁺): 440.5 (M+1), 462.5 (M+Na), MS (ES⁻): 438.5 (M-1).

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Scheme 46

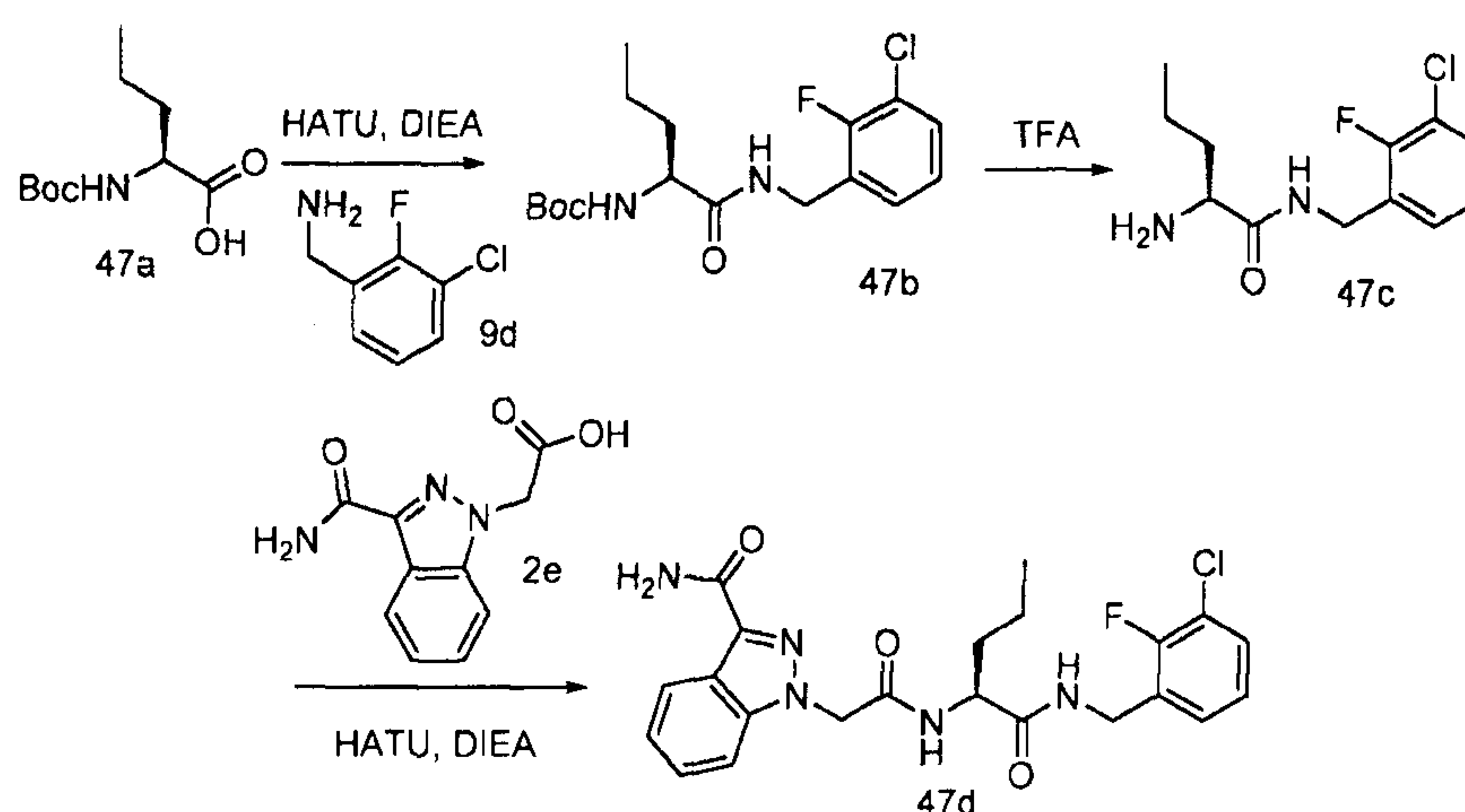


Preparation of 1-(2-(cyclopropyl(2-oxo-2-((3-(trifluoromethoxy)phenyl)amino)ethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**46b**)

Reaction of 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-cyclopropylacetamido)acetic acid (**45d**)
30 (0.12 g, 0.38 mmol) with 2-(trifluoromethoxy)aniline (**46a**) (67 mg, 0.379 mmol) according

to the procedure reported in step-1 of Scheme 2 gave after workup and purification by flash column chromatography [Silica gel, 12 g eluting with MeOH/EtOAc (9:1) in hexane 0-100%] 1-(2-(cyclopropyl(2-oxo-2-((3-(trifluoromethoxy)phenyl)amino)ethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**46b**) (65 mg, 0.137 mmol, 36% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.38 (s, 1H), 8.22 - 8.12 (m, 1H), 7.80 - 7.71 (m, 2H), 7.70 - 7.61 (m, 1H), 7.52 - 7.33 (m, 4H), 7.30 - 7.20 (m, 1H), 7.09 - 6.95 (m, 1H), 5.71 (s, 2H), 4.15 (s, 2H), 3.18 - 3.06 (m, 1H), 1.11 - 0.89 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -56.72; MS (ES⁺): 476.5 (M+1), 498.5 (M+Na), MS (ES⁻): 474.5 (M-1).

Scheme 47



10

Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxopentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**47d**)

Step-1: Preparation of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-1-oxopentan-2-yl)carbamate (**47b**)

15 Reaction of (S)-2-((tert-butoxycarbonyl)amino)pentanoic acid (**47a**) (412 mg, 1.9 mmol) with 3-chloro-2-fluorobenzylamine (**9d**) (252 mg, 1.58 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-1-oxopentan-2-yl)carbamate (**47b**) which was used as such in the next step. MS (ES⁺): 381.45 (M+Na); (ES⁻): 393.34 (M+Cl).

20 Step-2: Preparation of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)pentanamide (**47c**)

Reaction of (S)-tert-butyl (1-((3-chloro-2-fluorobenzyl)amino)-1-oxopentan-2-yl)carbamate (**47b**) (567 mg, 1.58 mmol) with TFA (2.19 mL, 28.4 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup (S)-2-amino-N-(3-chloro-2-fluorobenzyl)pentanamide (**47c**) which was used as such in the next step; MS (ES⁺): 259.4 (M+1).

25

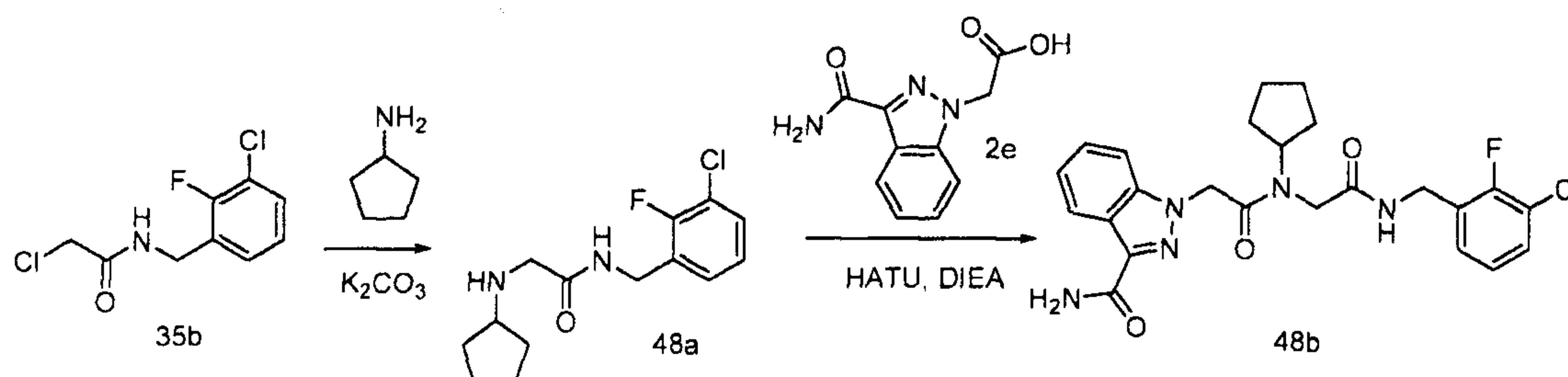
WO 2017/136395

PCT/US2017/015953

Step-3: Preparation of (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxopentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**47d**)

Reaction of (S)-2-amino-N-(3-chloro-2-fluorobenzyl)pentanamide (**47c**) (409 mg, 1.58 mmol) TFA salt from above step-2 with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (416 mg, 1.9 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (24 g), eluting with MeOH in CHCl₃ from 0 to 50%] (S)-1-(2-((1-((3-chloro-2-fluorobenzyl)amino)-1-oxopentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**47d**) (12 mg, 0.026 mmol, 2% yield) as an off-white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.65 (t, *J* = 5.8 Hz, 1H), 8.59 (d, *J* = 7.9 Hz, 1H), 8.17 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.70 (s, 1H), 7.66 – 7.59 (m, 1H), 7.53 – 7.37 (m, 3H), 7.31 – 7.21 (m, 2H), 7.19 – 7.09 (m, 1H), 5.26 (s, 2H), 4.38 – 4.20 (m, 3H), 1.66 – 1.53 (m, 2H), 1.33 – 1.26 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.48; MS (ES⁺): 460.47 (M+1), 482.5 (M+Na); (ES⁻): 458.40 (M-1), 494.41 (M+Cl).

Scheme 48



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**48b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(cyclopentylamino)acetamide (**48a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 2.12 mmol) with cyclopentylamine (216 mg, 2.54 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-(cyclopentylamino)acetamide (**48a**) as a clear oil which was used as such in next step; MS

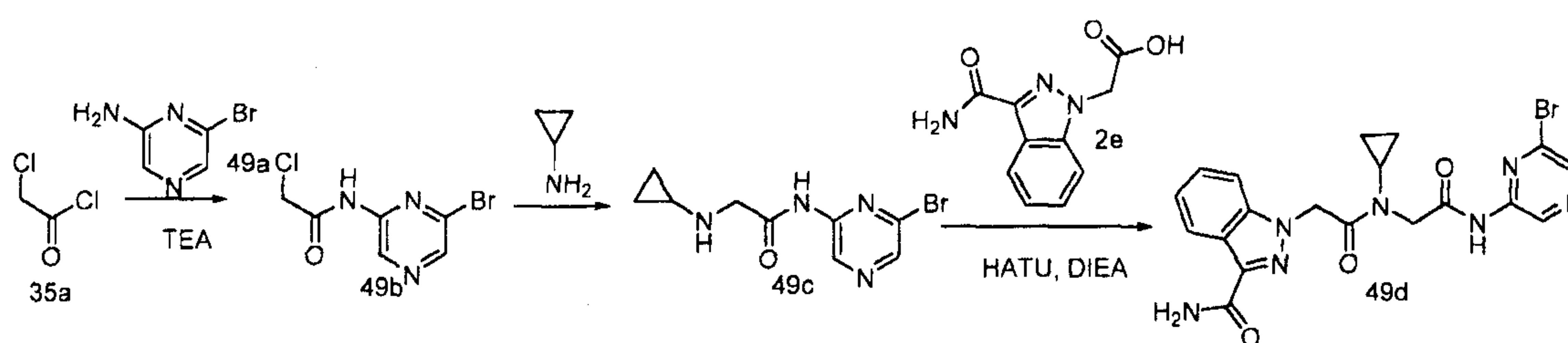
(ES⁺): 285.4 (M+1); MS (ES⁻): 283.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**48b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(cyclopentylamino)acetamide (**48a**) (240 mg, 0.84 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (203 mg, 0.93 mmol) according

to the procedure reported in step-3 of Scheme 2 gave after workup 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**48b**) (315 mg, 0.65 mmol, 77% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.84 (t, *J* = 5.6 Hz) and 8.40 (t, *J* = 5.8 Hz) (2t, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.71 (s, 1H), 7.64 – 7.00 (m, 7H), 5.63 & 5.45 (2s, 2H), 4.67 – 4.24 (m, 3H), 4.19 & 3.82 (2s, 2H), 2.06 – 1.84 (m, 1H), 1.75 – 1.28 (m, 7H); ¹⁹F NMR (282 MHz, DMSO) δ -121.17, 121.71; MS (ES⁺) 486.6 (M+1); MS (ES⁻), 484.4 (M-1); HPLC, Rt 7.134 min, 96.7156% [based on NMR, this compound is a mixture of two rotamers 1:1 ratio].

Scheme 49



Preparation of 1-(2-((2-((6-bromopyrazin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**49d**)

Step-1: Preparation of N-(6-bromopyrazin-2-yl)-2-chloroacetamide (**49b**)

Reaction of 2-chloroacetyl chloride (**35a**) (0.24 mL, 3 mmol) with 6-bromopyrazin-2-amine (**49a**) (350 mg, 2.01 mmol) according to the procedure reported in step-1 of Scheme 35 gave after workup N-(6-bromopyrazin-2-yl)-2-chloroacetamide (**49b**) (45 mg, 1.8 mmol, 89% yield) as a dark orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.51 (s, 1H), 9.28 (d, *J* = 0.6 Hz, 1H), 8.60 (d, *J* = 0.6 Hz, 1H), 4.39 (s, 2H); MS (ES⁺): 250.2, 252.2 (M, M+2), MS (ES⁻): 248.1, 250.1 (M-2, M).

Step-2: Preparation of N-(6-bromopyrazin-2-yl)-2-(cyclopropylamino)acetamide (**49c**)

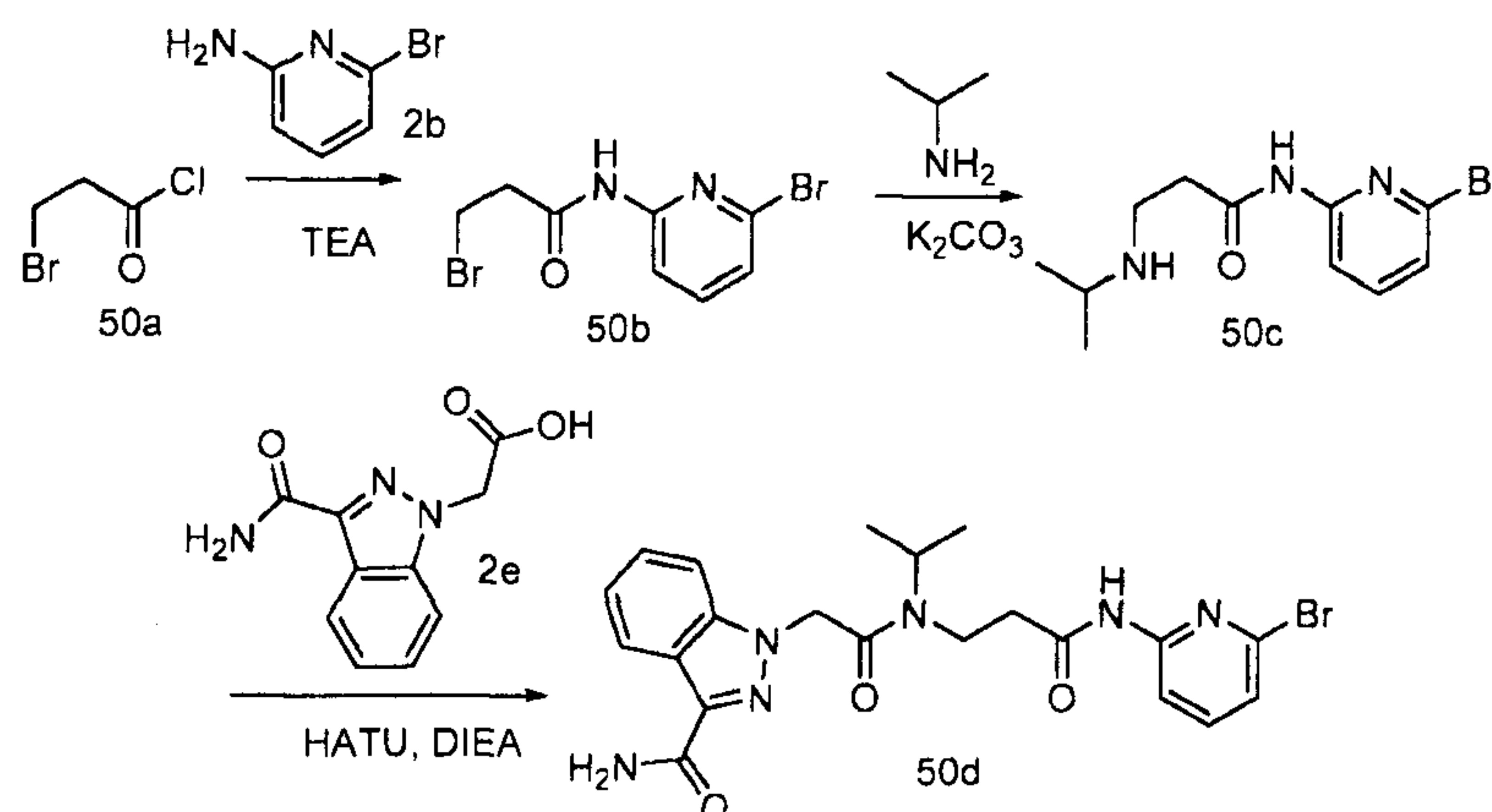
Reaction of N-(6-bromopyrazin-2-yl)-2-chloroacetamide (**49b**) (480 mg, 1.92 mmol) with Cyclopropylamine (0.34 mL, 4.79 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by column chromatography [silica gel (24 g), eluting with EtOAc in hexane 0 to 100%] N-(6-bromopyrazin-2-yl)-2-

(cyclopropylamino)acetamide (**49c**) (33 mg, 1.22 mmol, 64% yield) as an orange colored solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.33 (s, 1H), 8.55 (s, 1H), 4.00 (s, 1H), 3.43 (s, 2H), 2.24 - 2.10 (m, 1H), 0.41 - 0.30 (m, 2H), 0.29 - 0.18 (m, 2H); MS (ES⁻): 269.2, 271.2 (M-2, M).

Step-3: Preparation of 1-(2-((2-((6-bromopyrazin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**49d**)

Reaction of N-(6-bromopyrazin-2-yl)-2-(cyclopropylamino)acetamide (**49c**) (90 mg, 0.33 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (73 mg, 0.33 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup 1-(2-((2-((6-bromopyrazin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**49d**) (110 mg, 0.23 mmol, 70% yield) as white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.29 (s, 1H), 9.25 (s, 1H), 8.54 (s, 1H), 8.17 (d, J = 8.2, 1H), 7.72 (s, 1H), 7.69 - 7.64 (m, 1H), 7.50 - 7.34 (m, 2H), 7.25 (d, J = 7.9, 1H), 5.71 (s, 2H), 4.22 (s, 2H), 3.20 - 3.06 (m, 1H), 1.14 - 0.84 (m, 4H); MS (ES⁺): 472.4, 474.5 (M+1, M+3), MS (ES⁻): 470.4, 472.4.

Scheme 50



Preparation of 1-(2-((3-((6-bromopyridin-2-yl)amino)-3-oxopropyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**50d**)

Step-1: Preparation of 3-bromo-N-(6-bromopyridin-2-yl)propanamide (**50b**)

Reaction of 3-bromopropanoyl chloride (**50a**) (1g, 5.83 mmol) with 6-bromopyridin-2-amine (**2b**) (1.01 g, 5.83 mmol) according to the procedure reported in step-1 of Scheme 35 gave after workup and purification by flash column chromatography [silica (24 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 40%] to give 3-bromo-N-(6-bromopyridin-2-yl)propanamide (**50b**) (1.26 g, 4.09 mmol, 70.1% yield) as a white solid; MS (ES⁺): 307.2 (M+1).

Step-2: Preparation of N-(6-bromopyridin-2-yl)-3-(isopropylamino)propanamide (**50c**)

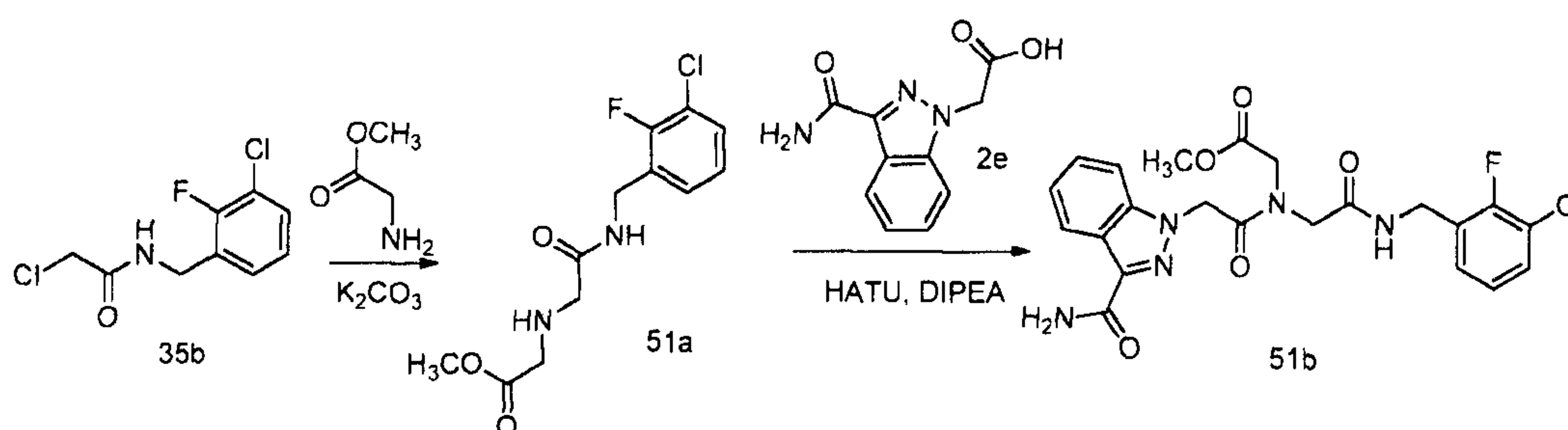
Reaction of 3-bromo-N-(6-bromopyridin-2-yl)propanamide (**50b**) (520 mg, 1.69 mmol) with propan-2-amine (299 mg, 5.07 mmol) according to the procedure reported in step-2 of

Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] *N*-(6-bromopyridin-2-yl)-3-(isopropylamino)propanamide (**50c**) (321 mg, 1.12 mmol, 66% yield) as a clear oil; MS (ES⁺): 286.3 (M+1); MS (ES⁻): 284.3 (M-1).

5 Step-3: Preparation of 1-(2-((3-((6-bromopyridin-2-yl)amino)-3-oxopropyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**50d**)

Reaction of *N*-(6-bromopyridin-2-yl)-3-(isopropylamino)propanamide (**50c**) (230 mg, 0.8 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (194 mg, 0.88 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash
10 column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 40%] 1-(2-((3-((6-bromopyridin-2-yl)amino)-3-oxopropyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**50d**) (325 mg, 0.67 mmol, 83% yield) as an off white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 11.06 & 10.82 (2s, 1H), 8.28 – 7.99 (m, 2H), 7.86 – 7.54 (m, 3H), 7.49 – 7.20 (m, 4H), 5.60 & 5.55 (2s, 2H), 4.41 – 4.12 (m, 1H), 3.71 (t, *J* = 7.1 Hz) & 3.48 – 3.40
15 (m) (t & m, 2H), 2.90 (t, *J* = 7.1 Hz) & 2.63 – 2.60 (m) (t & m, 2H), 1.25 (d, *J* = 6.5 Hz) & 1.15 (d, *J* = 6.8 Hz) (2d, 6H); MS (ES⁺): 487.4 (M+1); [based on NMR, this compound is a mixture of two rotamers with 4:5 ratio].

Scheme 51



20 Preparation of methyl 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)acetate (**51b**)

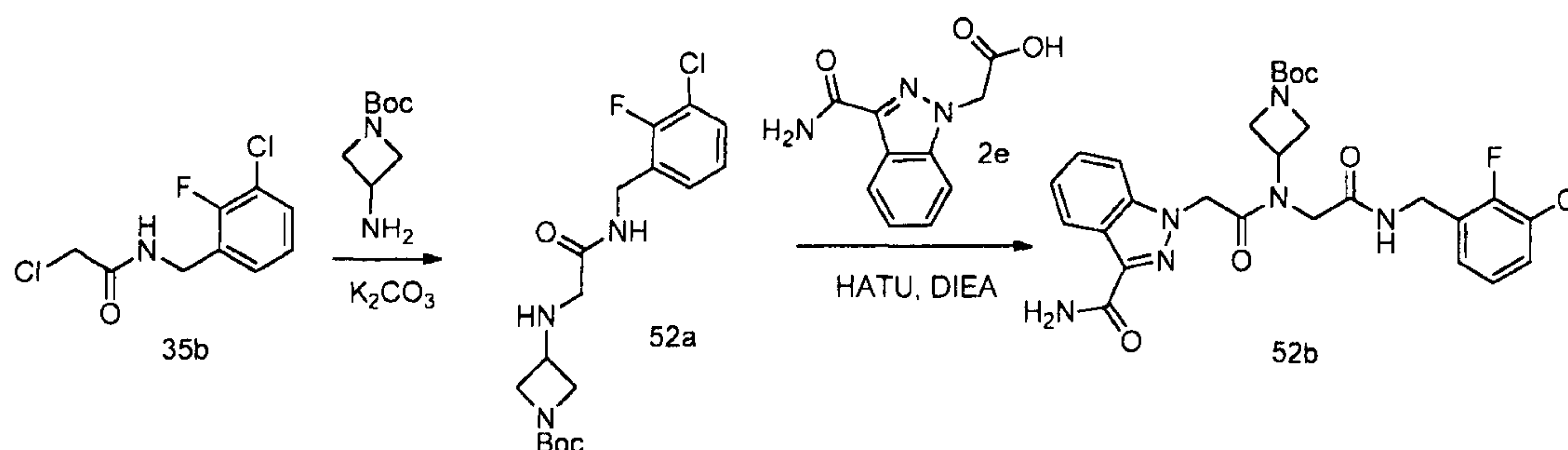
Step-1: Preparation of methyl 2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)acetate (**51a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 2.12 mmol) with
25 methyl 2-aminoacetate (266 mg, 2.12 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] methyl 2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)acetate (**51a**) (293 mg, 1.02 mmol, 48% yield) as a clear oil; MS (ES⁺) 311.3 (M+Na)

Step-2: Preparation of 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)acetate (**51b**)

Reaction of methyl 2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)acetate (**51a**) (200 mg, 0.69 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (167 mg, 0.76 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)acetate (**51b**) (36 mg, 0.073 mmol, 11% yield) as a white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.82 (t, *J* = 5.8 Hz) and 8.53 (t, *J* = 5.3 Hz) (2t, 1H), 8.18 (d, *J* = 7.5 Hz, 1H), 7.74 (s, 1H), 7.52 – 7.09 (m, 7H), 5.54 and 5.51 (2s, 2H), 4.57- 4.28 (m, 4H), 4.08 and 3.99 (2s, 2H), 3.75 and 3.61 (2s, 3H); ¹⁹F NMR (282 MHz, DMSO) δ -121.32, -121.61; MS (ES⁺): 490.5 (M+1), 512.5 (M+Na); MS (ES⁻): 488.4 (M-1); [based on NMR, this compound is a mixture of two rotamers with 5:4 ratio].

Scheme 52



Preparation of tert-butyl 3-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)azetidine-1-carboxylate (**52b**)

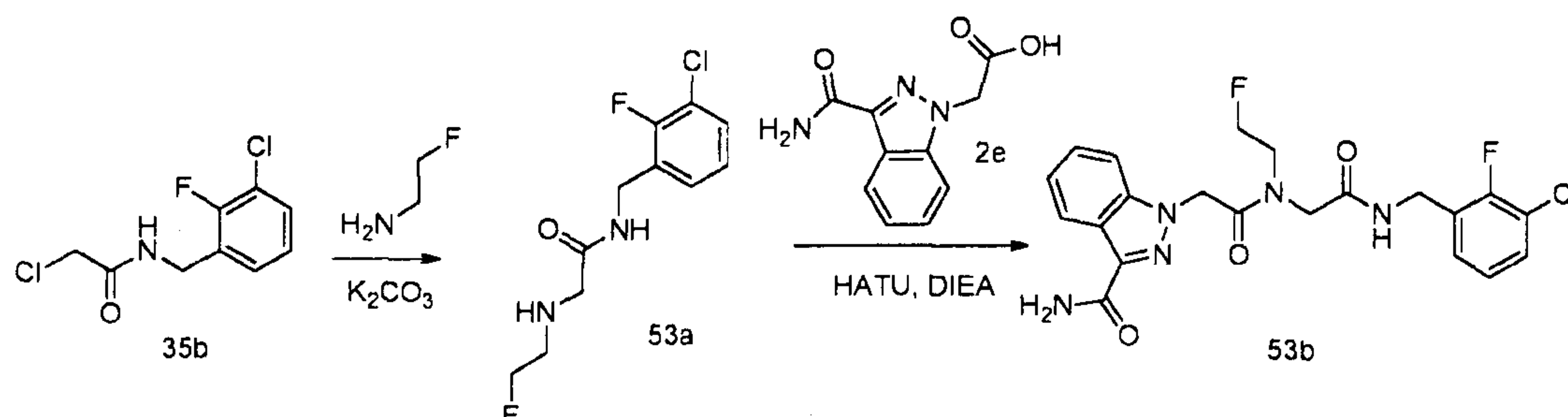
Step-1: Preparation of tert-butyl 3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)azetidine-1-carboxylate (**52a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (925 mg, 3.92 mmol) with tert-butyl 3-aminoazetidine-1-carboxylate (710 mg, 4.12 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] tert-butyl 3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)azetidine-1-carboxylate (**52a**) (785 mg, 2.11 mmol, 51% yield) as a clear oil; MS (ES⁺) 372.4 (M+1); MS (ES⁻): 370.4 (M-1).

Step-2: Preparation of tert-butyl 3-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)azetidine-1-carboxylate (**52b**)

Reaction of *tert*-butyl 3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)azetidine-1-carboxylate (**52a**) (440 mg, 1.18 mmol) with 2-(3-carbamoyl-1*H*-indazol-1-yl)acetic acid (**2e**) (285 mg, 1.3 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] *tert*-butyl 3-(2-(3-carbamoyl-1*H*-indazol-1-yl)-*N*-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)azetidine-1-carboxylate (**52b**) (325 mg, 0.57 mmol, 48% yield) as a white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.93 (t, *J* = 5.6 Hz) and 8.59 (t, *J* = 5.8 Hz) (2t, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.59 – 7.02 (m, 7H), 5.60 & 5.43 (2s, 2H), 5.12 – 4.74 (m, 1H), 4.48 (d, *J* = 5.4 Hz) & 4.33 (d, *J* = 5.6 Hz) (2d, 2H), 4.39 & 4.10 (2s, 2H), 4.16 (t, *J* = 8.7 Hz) & 4.01 – 3.76 (m) (t & m, 4H), 1.39 & 1.35 (2s, 9H); ¹⁹F NMR (282 MHz, DMSO) δ -121.26, 121.61; MS (ES+) 573.7 (M+1); [based on NMR, this compound is a mixture of two rotamers 1:1 ratio].

Scheme 53



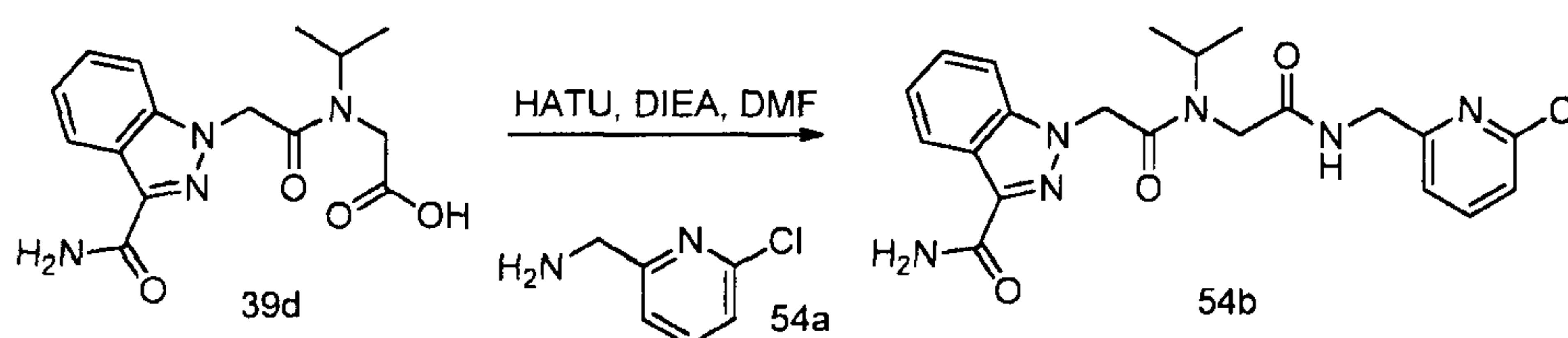
Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2-fluoroethyl)amino)-2-oxoethyl)-1*H*-indazole-3-carboxamide (**53b**)

Step-1: Preparation of *N*-(3-chloro-2-fluorobenzyl)-2-((2-fluoroethyl)amino)acetamide (**53a**)
Reaction of 2-chloro-*N*-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 2.12 mmol) with *tert*-fluoroethanamine hydrochloride (422 mg, 4.24 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] *N*-(3-chloro-2-fluorobenzyl)-2-((2-fluoroethyl)amino)acetamide (**53a**) (224 mg, 0.85 mmol, 40% yield) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.39 (t, *J* = 5.9 Hz, 1H), 7.53 – 7.44 (m, 1H), 7.31 – 7.23 (m, 1H), 7.23 – 7.13 (m, 1H), 4.60 – 4.50 (m, 1H), 4.41 – 4.32 (m, 3H), 3.19 (s, 2H), 2.82 (t, *J* = 5.0 Hz, 1H), 2.72 (t, *J* = 5.0 Hz, 1H), 2.47 – 2.37 (m, 1H); ¹⁹F NMR (282 MHz, DMSO) δ -121.69; MS (ES+) 263.4 (M+1); 261.3 (M-1);

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2-fluoroethyl)amino)-2-oxoethyl)-1*H*-indazole-3-carboxamide (**53b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-((2-fluoroethyl)amino)acetamide (**53a**) (178 mg, 0.68 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (163 mg, 0.745 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] 1-
 5 (2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2-fluoroethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**53b**) (162 mg, 0.349 mmol, 51.5% yield) as a white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.84 (t, *J* = 5.7 Hz) and 8.54 (t, *J* = 5.8 Hz) (2t, 1H), 8.18 (d, *J* = 7.5 Hz, 1H), 7.74 (s, 1H), 7.57 – 7.07 (m, 7H), 5.59 & 5.48 (2s, 2H), 4.88 – 4.62 (m, 1H), 4.61 – 4.29 (m, 3H), 4.35 & 4.03 (2s, 2H), 3.97 – 3.80 (m, 1H), 3.62 (t, *J* = 4.8 Hz) and 3.53
 10 (t, *J* = 4.9 Hz) (2t, 1H); MS (ES⁺): 464.5 (M+1); MS (ES⁻): 462.4 (M-1); [based on NMR, this compound is a mixture of two rotamers with 1:1 ratio].

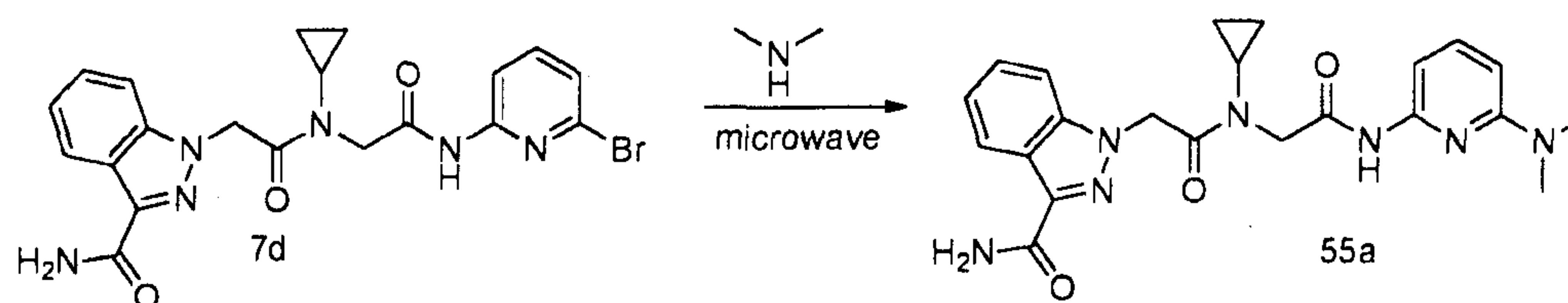
Scheme 54



Preparation of 1-(2-((2-(((6-chloropyridin-2-yl)methyl)amino)-2-oxoethyl)(isopropyl)amino)-
 15 2-oxoethyl)-1H-indazole-3-carboxamide (**54b**)

Reaction of 2-(2-(3-carbamoyl-1H-indazol-1-yl)-N-isopropylacetamido)acetic acid (**39d**) (0.15 g, 0.47 mmol) with (6-chloropyridin-2-yl)methanamine (**54a**) (122 mg, 0.57 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [Silica gel, 24 g eluting with MeOH in CHCl₃ from 0-50%]
 20 1-(2-((2-(((6-chloropyridin-2-yl)methyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**54b**) (101 mg, 0.23 mmol, 48% yield) as an off-white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.93 (t, *J* = 6.0 Hz) & 8.47 (t, *J* = 6.1 Hz) (2t, 1H), 8.22 – 8.13 (m, 1H), 7.85 (t, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 4.4 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.53 (dt, *J* = 8.5, 1.0 Hz, 1H), 7.46 – 7.30 (m, 3H), 7.31 – 7.16 (m, 1H), 5.60 & 5.47 (2s, 2H), 4.62 –
 25 4.50 (m, 1H), 4.47 (d, *J* = 5.8 Hz & 4.32 (d, *J* = 6.0 Hz) (2d, 2H), 4.23 & 3.86 (2s, 2H), 1.25 (d, *J* = 6.5 Hz) & 1.02 (d, *J* = 6.8 Hz) (2d, 6H); (based on NMR the compound is a mixture of two rotamers ~1:2 ratio); MS (ES⁺): 443.5 (M+1), 465.5 (M+Na); (ES⁻): 441.4 (M-1), 477.4 (M+Cl).

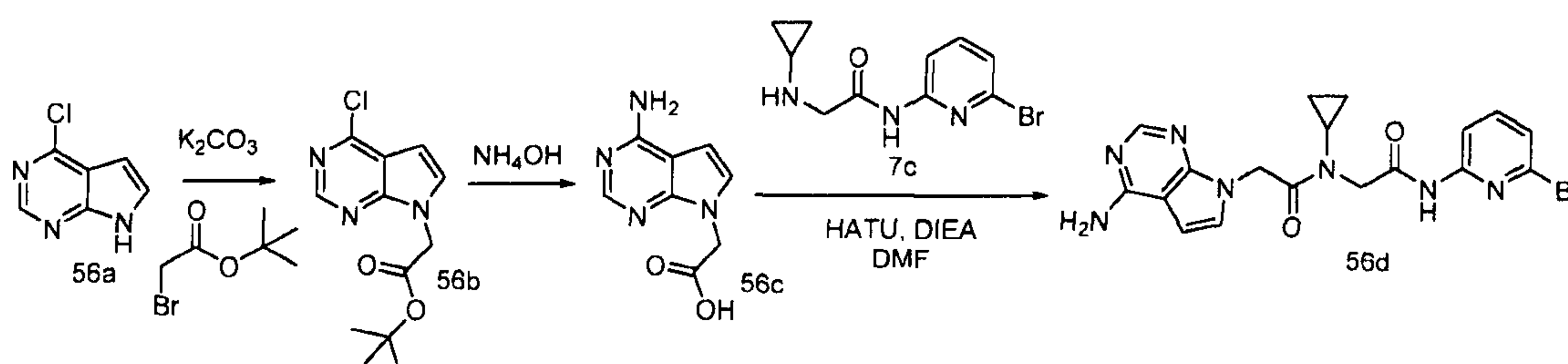
Scheme 55



Preparation of 1-(2-(cyclopropyl(2-((6-(dimethylamino)pyridin-2-yl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**55a**)

- 5 To a solution of 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**7d**) (105 mg, 0.22 mmol) in dioxane (1 mL) was added aqueous dimethylamine (0.56 mL, 4.46 mmol) and heated under microwave irradiation at 150 °C for 3h. The reaction mixture was cooled to room temperature, diluted with water (50 mL) and extracted with EtOAc (2 x 40 mL). The organic layers were combined washed
10 with brine, dried, filtered and concentrated in vacuum. The residue obtained was purified by chromatography [silica gel (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 100%] to afford 1-(2-(cyclopropyl(2-((6-(dimethylamino)pyridin-2-yl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**55a**) (55 mg, 0.13 mmol, 57% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.00 (s, 1H), 8.21 - 8.11 (m, 1H), 7.76 (s, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.52 - 7.34 (m, 3H), 7.30 - 7.15 (m, 2H), 6.31 (d, J = 8.3 Hz, 1H), 5.70 (s, 2H),
15 = 8.5 Hz, 1H), 7.52 - 7.34 (m, 3H), 7.30 - 7.15 (m, 2H), 6.31 (d, J = 8.3 Hz, 1H), 5.70 (s, 2H), 4.19 (s, 2H), 3.17 - 3.05 (m, 1H), 2.98 (s, 6H), 1.08 - 0.86 (m, 4H); MS (ES⁺): 436.6 (M+1); (ES⁻): 470.5 (M+Cl).

Scheme 56



- 20 Preparation of 2-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**56d**)

Step-1: Preparation of tert-butyl 2-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**56b**)

- Reaction of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine (**56a**) (1.5 g, 9.77 mmol) in acetonitrile (60 mL) with tert-butyl 2-bromoacetate (2.16 mL, 14.65 mmol) using Potassium carbonate
25 (2.7 g, 19.54 mmol) as base according to the procedure reported step-2 of Scheme 35 gave

after workup and purification by flash column chromatography [silica gel (40 g), eluting with EtOAc in hexanes 0 to 50%] tert-butyl 2-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**56b**) (2.2 g, 8.22 mmol, 84% yield) as white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.65 (s, 1H), 7.75 (d, *J* = 3.6 Hz, 1H), 6.68 (d, *J* = 3.6 Hz, 1H), 5.09 (s, 2H), 1.41 (s, 9H); MS (ES+) 268.4 (M+1), MS (ES-) 302.3(M+Cl).

Step-2: Preparation of 2-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetic acid (**56c**)

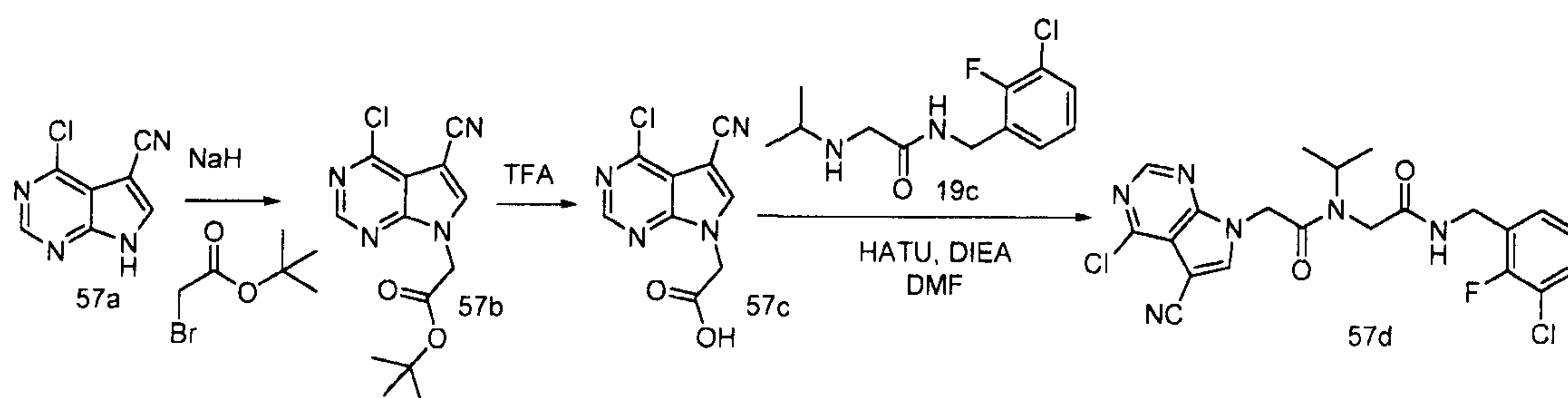
Reaction of tert-butyl 2-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**56b**) (512 mg, 1.91 mmol) with aqueous conc. ammonium hydroxide (1.5 mL, 38.3 mmol) under micro irradiation according to the procedure reported Scheme 55 gave after workup 2-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetic acid (**56c**) (312 mg, 1.62 mmol, 85% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.98 (s, 1H), 7.02 (d, *J* = 3.4 Hz, 1H), 6.82 (s, 2H), 6.43 (d, *J* = 3.5 Hz, 1H), 4.45 (s, 2H); MS (ES+): 193.2 (M+1); (ES-): 191.2 (M-1).

Step-3: Preparation of 2-(4-amino-7 H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**56d**)

Reaction of N-(6-bromopyridin-2-yl)-2-(cyclopropylamino)acetamide (**7c**) (8 mg, 0.3 mmol) with 2-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetic acid (**56c**) (57 mg, 0.3 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 40%] 2-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**56d**) (22 mg, 0.05 mmol, 17% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.93 (s, 1H), 8.07 – 7.95 (m, 2H), 7.72 (t, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.7, 0.7 Hz, 1H), 7.07 (d, *J* = 3.5 Hz, 1H), 6.95 (s, 2H), 6.51 (d, *J* = 3.5 Hz, 1H), 5.27 (s, 2H), 4.16 (s, 2H), 3.11 – 2.95 (m, 1H), 1.02 – 0.85 (m, 4H); MS (ES+): 444.5, 446.4 (M+1, M+3), MS (ES-): 442.3, 444.4.

25

Scheme 57



Preparation of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-isopropylacetamide (**57d**)

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PCT/US2017/015953

Step-1: Preparation of tert-butyl 2-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**57b**)

To a solution of 4-chloro-7H-pyrrolo[2,3-d]pyrimidine-5-carbonitrile (**57a**) (811 mg, 4.54 mmol) in DMF (10 mL) was added at room temperature, NaH (60% in mineral oil, 218 mg, 5.45 mmol) stirred for 5 mins followed by the addition of tert-butyl 2-bromoacetate (0.81 mL, 5.45 mmol). The reaction mixture was stirred for 2 h quenched with EtOAc (50 mL) and brine (75 mL). The organic layer was separated washed with water (50 mL), dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica gel (24 g), eluting with MeOH in CHCl₃ 0 to 30%] to afford tert-butyl 2-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**57b**) (989 mg, 3.38 mmol, 74% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.86 (s, 1H), 8.71 (s, 1H), 5.18 (s, 2H), 1.42 (s, 9H); MS (ES⁺): 293.4 (M+1), 315.3 (M+Na); (ES⁻): 291.3 (M-1), 327.4 (M+Cl).

Step-2: Preparation of 2-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetic acid (**57c**)

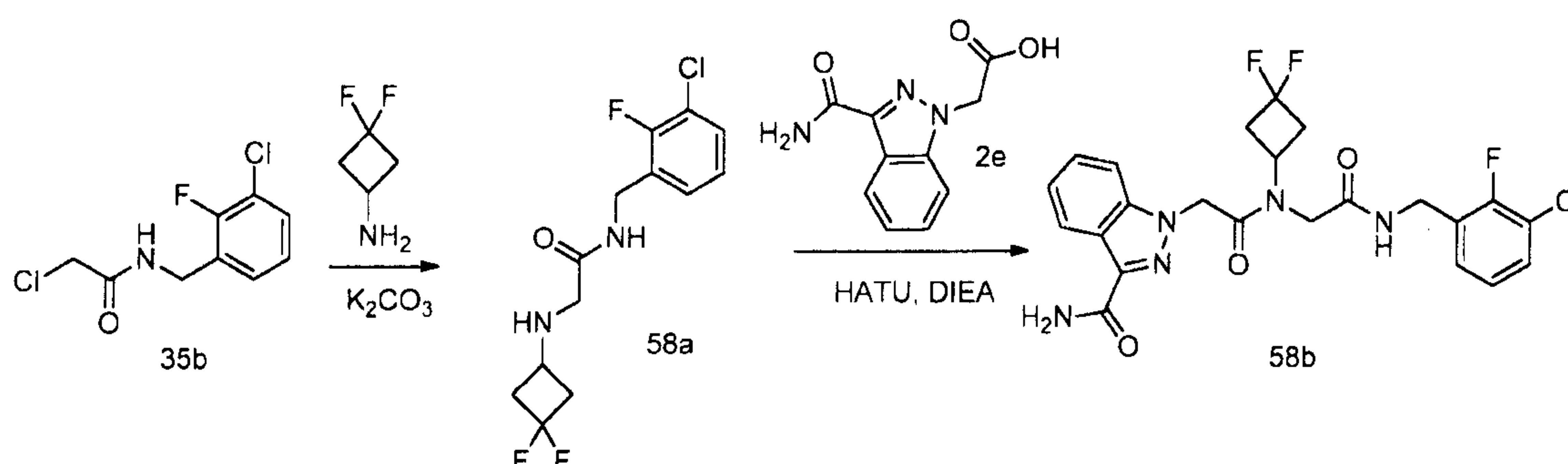
Reaction of tert-butyl 2-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**57b**) (500 mg, 1.71 mmol) with TFA (1.32 mL, 17.08 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup 2-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetic acid (**57c**) (310 mg, 1.31 mmol, 77% yield) which was used as such in the next step without further purification; MS (ES⁺): 237.3 (M+1); (ES⁻): 235.2 (M-1)

Step-3: Preparation of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-isopropylacetamide (**57d**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (387 mg, 1.5 mmol) with 2-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetic acid (**57c**) (295 mg, 1.25 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [First column: Silica gel (24 g), eluting with MeOH in CHCl₃ 0-100%; Second column: Silica gel (24 g) eluting with EtOAc/MeOH (9:1) in hexanes 0-100%;) N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-isopropylacetamide (**57d**) (115 mg, 0.241 mmol, 19% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.82 & 8.82 (2s, 1H), 8.79 & 8.33 (2t, 1H), 8.64 & 8.61 (2s, 1H), 7.57 – 7.33 (m, 2H), 7.30 – 7.03 (m, 1H), 5.46 & 5.33 (2s, 2H), 4.62 – 4.47 & 4.26 – 4.20 (2m, 1H), 4.44 (d, *J* = 5.6 Hz) & 4.30 (d, *J* = 5.8 Hz) (2d, 2H), 4.18 & 3.84 (2s, 2H), 1.24 (d, *J* = 6.4 Hz) & 0.98 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz,

DMSO-*d*₆) δ -121.27, -121.63; [based on NMR the compound is a mixture of two rotamers ~2:3 ratio]; MS (ES⁺): 477.5 (M+1); (ES⁻): 475.5, 477.5 (M-1).

Scheme 58



- 5 Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**58b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((3,3-difluorocyclobutyl)amino)acetamide (**58a**)

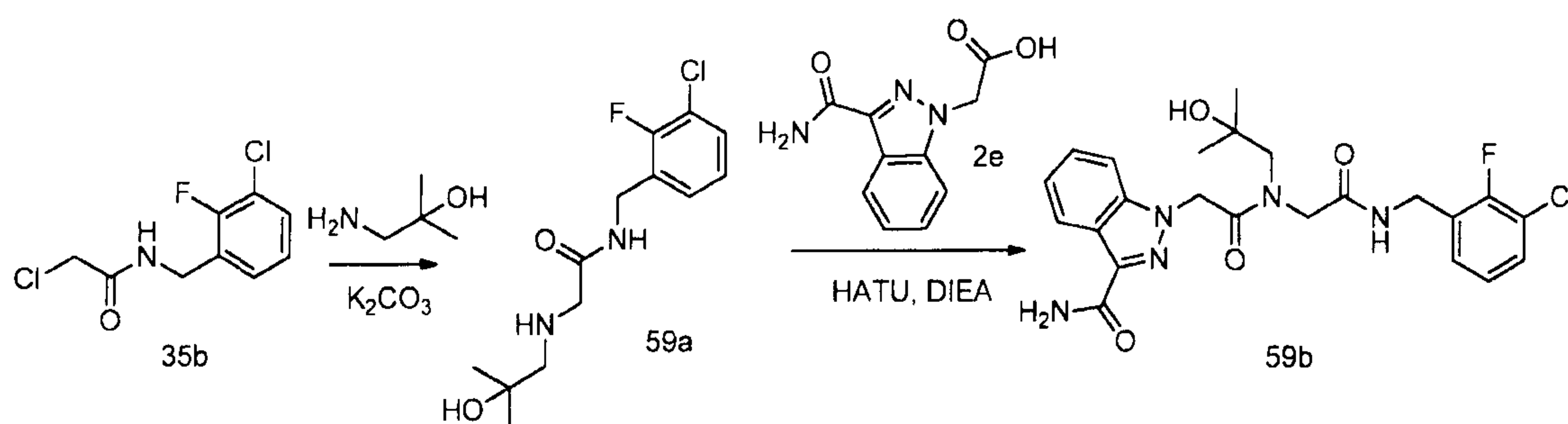
Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 2.12 mmol) with 3,3-difluorocyclobutanamine hydrochloride (502 mg, 3.49 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-((3,3-difluorocyclobutyl)amino)acetamide (**58a**) (110 mg, 0.36 mmol, 17%) as a clear oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.39 (t, *J* = 6.0 Hz, 1H), 7.52 – 7.43 (m, 1H), 7.33 – 7.24 (m, 1H), 7.24 – 7.14 (m, 1H), 4.35 (d, *J* = 5.9 Hz, 2H), 3.17 – 3.03 (m, 3H), 2.80 – 2.61 (m, 3H), 2.41 – 2.22 (m, 2H); MS (ES⁺): 307.3, 309.3 (M+1, M+3)

Step-2: Preparation of tert-butyl 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**58b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-((3,3-difluorocyclobutyl)amino)acetamide (**58a**) (110 mg, 0.36 mmol,) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (86 mg, 0.4 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] tert-butyl 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(3,3-difluorocyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**58b**) (115 mg, 0.23 mmol, 63% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.90 (t, *J* = 5.9 Hz) and 8.57 (t, *J* = 6.6 Hz) (2t, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.79 – 7.63 (m, 1H), 7.56 – 7.07 (m, 7H), 5.65 and 5.43 (2s, 2H), 4.64 – 4.02 (m, 5H), 3.12 – 2.85 (m, 2H), 2.80 – 2.65 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -82.66, -99.20, -121.23, -121.60; MS (ES⁺): 508.5 (M+1);

MS (ES⁺): 506.5 (M-1); [based on NMR, this compound is a mixture of two rotamers 5:1 ratio].

Scheme 59



- 5 Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2-hydroxy-2-methylpropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**59b**)

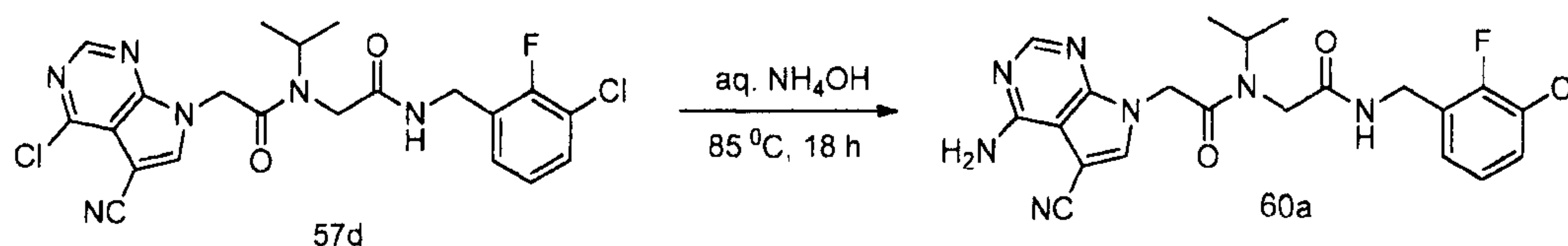
Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((2-hydroxy-2-methylpropyl)amino)acetamide (**59a**)

- Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 2.12mmol) with
 10 1-amino-2-methylpropan-2-ol (378 mg, 4.24 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-((2-hydroxy-2-methylpropyl)amino)acetamide (**59a**) (200 mg, 0.69 mmol, 33%) as a clear oil; MS (ES⁺) 289.4 (M+1); (ES⁻) 287.3.

- 15 Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2-hydroxy-2-methylpropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**59b**)

- Reaction of N-(3-chloro-2-fluorobenzyl)-2-((2-hydroxy-2-methylpropyl)amino)acetamide (**59a**) (200 mg, 0.69 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (167 mg, 0.76 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and
 20 purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2-hydroxy-2-methylpropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**59b**) (239 mg, 0.49 mmol, 70% yield) as a white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.83 (t, *J* = 5.6 Hz and 8.49 (t, *J* = 5.9 Hz) (2t, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 11.8 Hz, 1H), 7.57 – 7.01 (m, 7H), 5.69 and 5.44 (2s, 2H), 5.08 and 4.59 (2s, 1H), 4.52 – 4.28 (m, 3H), 4.07 (s, 1H), 3.50 and 3.20 (2s, 2H), 1.24 and 1.03 (2s, 6H); ¹⁹F NMR (282 MHz, DMSO) δ -121.34, -121.67; MS (ES⁺): 490.5(M+1); MS (ES⁻): 488.5 (M-1); [based on NMR, this compound is a mixture of
 25 two rotamers with 1:1 ratio].

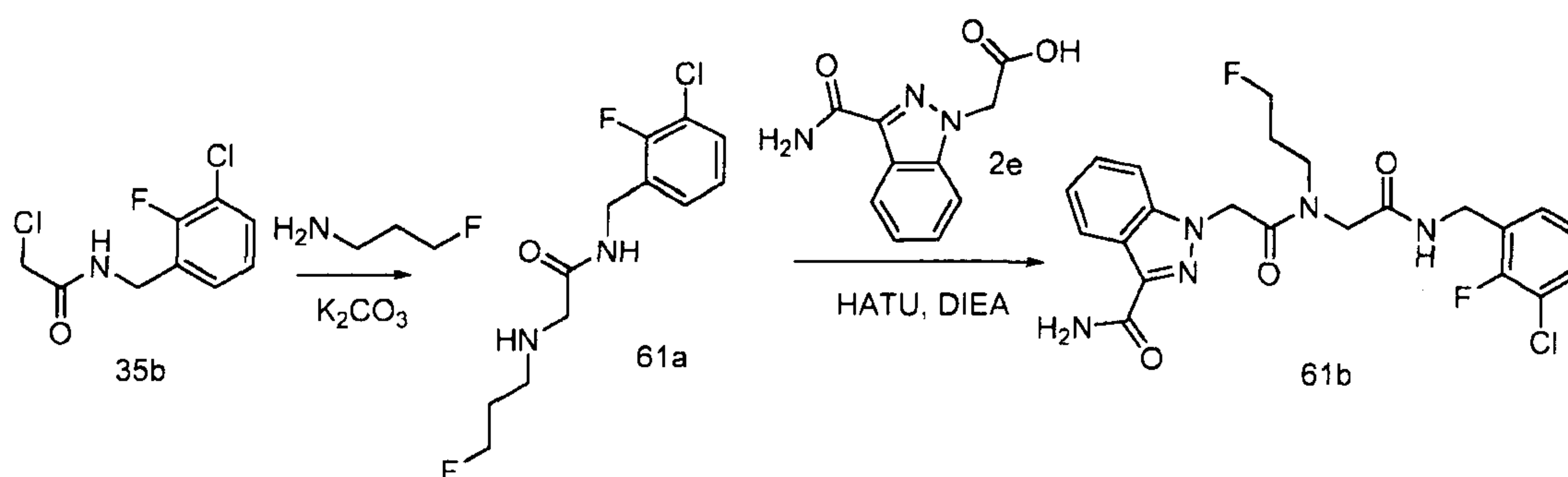
Scheme 60



Preparation of 2-(4-amino-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**60a**)

- To a solution of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-(4-chloro-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-isopropylacetamide (**57d**) (80 mg, 0.17 mmol) in dioxane (3 mL) was added aqueous ammonium hydroxide (1.83 mL, 46.9 mmol) and heated at 85 °C for 18 h. The reaction was cooled to room temperature and excess solvent was removed under reduced pressure. The residue obtained was triturated with CHCl_3 and the solid obtained was collected by filtration, rinsed with MeOH, evaporated to dryness to afford 2-(4-amino-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**60a**) (36 mg, 0.079 mmol, 47% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.77 (t, $J = 5.8$ Hz) and 8.31 (t, $J = 5.9$ Hz) (2t, 1H), 8.18 and 8.18 (2s, 1H), 8.07 and 8.06 (2s, 1H), 7.57 – 7.33 (m, 2H), 7.28 – 7.06 (m, 1H), 6.84 (s, 2H), 5.25 and 5.12 (2s, 2H), 4.63 – 4.48 and 4.26 – 4.19 (2m, 1H), 4.43 (d, $J = 5.6$ Hz) and 4.31 (d, $J = 5.8$ Hz) (2d, 2H), , 4.15 and 3.83 (2s, 2H), 1.21 (d, $J = 6.4$ Hz) and 0.97 (d, $J = 6.8$ Hz) (2d, 6H).; ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.31, -121.67. [based on NMR the compound is a mixture of two rotamers ~1:1 ratio]; MS (ES⁺): 458.5 (M+1), 480.5 (M+Na); (ES⁻): 456.4 (M-1), 492.5 (M+Cl).

Scheme 61



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(3-fluoropropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**61b**)

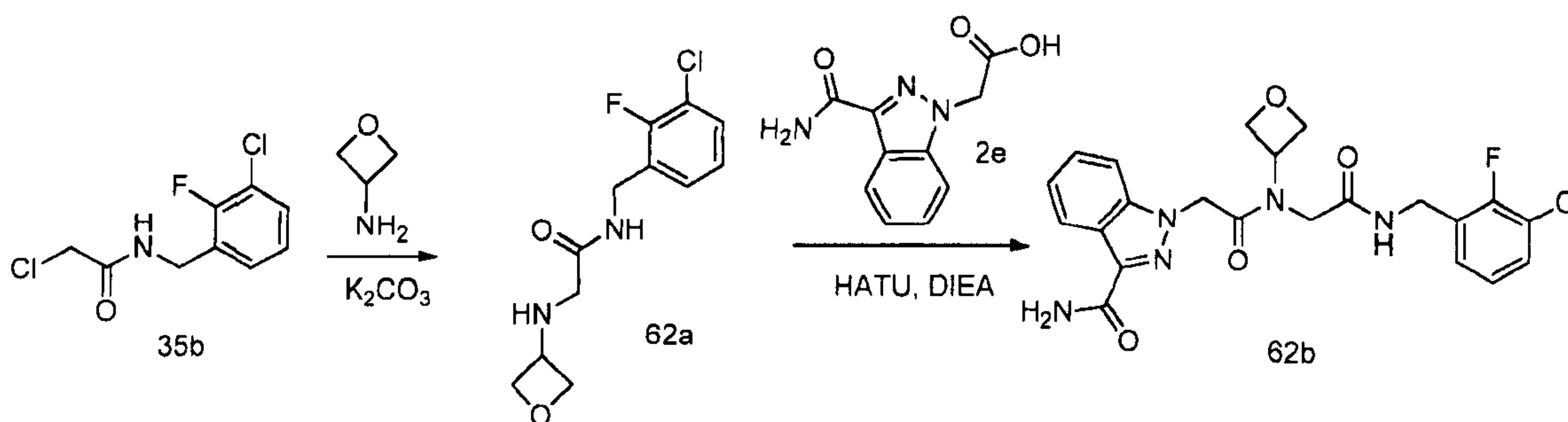
Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((3-fluoropropyl)amino)acetamide (**61a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (494 mg, 2.09 mmol) with 3-fluoropropan-1-amine hydrochloride (250 mg, 2.201 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-((3-fluoropropyl)amino)acetamide (**61a**) (287 mg, 1.04 mmol, 47%) as a clear oil; MS (ES⁺): 277.4, 279.3 (M+1, M+3); (ES⁻): 275.3

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(3-fluoropropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**61b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-((3-fluoropropyl)amino)acetamide (**61a**) (144 mg, 0.52 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (125 mg, 0.57 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(3-fluoropropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**61b**) (145 mg, 0.30 mmol, 58% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.87 (t, *J* = 5.7 Hz) and 8.52 (t, *J* = 5.9 Hz) (2t, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.78 – 7.66 (m, 1H), 7.61 – 7.07 (m, 7H), 5.58 and 5.45 (2s, 2H), 4.70 and 4.54 (2t, *J* = 5.6 Hz, 1H), 4.51 – 4.30 (m, 3H), 4.27 and 3.97 (2s, 2H), 3.62 (t, *J* = 7.1 Hz) and 3.39 – 3.33 (t & m, 2H), 2.17 – 1.96 and 1.90 – 1.68 (2m, 2H); ¹⁹F NMR (282 MHz, DMSO) δ -121.27, -121.62; MS (ES⁺) 478.5 (M+1); MS (ES⁻), 476.5 (M-1); [based on NMR, this compound is a mixture of two rotamers with 5:4 ratio].

Scheme 62



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(oxetan-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**62b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(oxetan-3-ylamino)acetamide (**62a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 2.12 mmol) with oxetan-3-amine (310 mg, 4.24 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting

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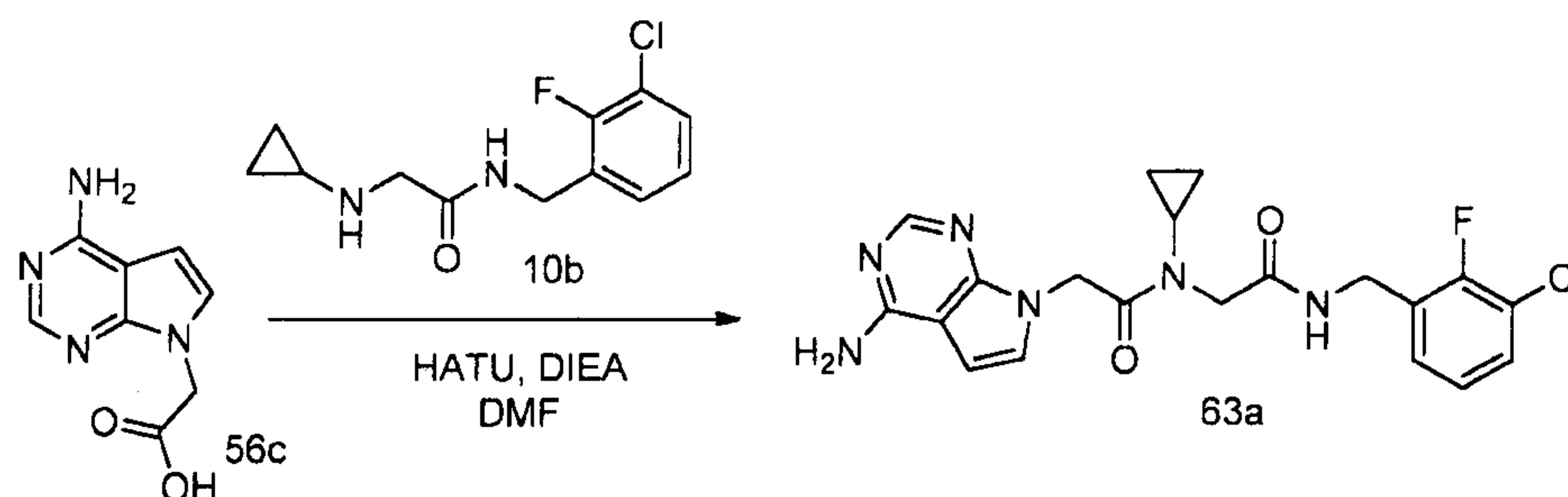
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with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-(oxetan-3-ylamino)acetamide (**62a**) (365 mg, 1.34 mmol, 63% yield) as a yellow oil; MS (ES+) 273.3, 275.3 (M+1, M+3); (ES-): 271.3 (M-1)

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(oxetan-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**62b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(oxetan-3-ylamino)acetamide (**62a**) (200 mg, 0.73 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (177 mg, 0.81 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(oxetan-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**62b**) (192 mg, 0.41 mmol, 55% yield) as a white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.94 (t, *J* = 5.7 Hz) and 8.59 (t, *J* = 5.8 Hz) (2t, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 14.5 Hz, 1H), 7.57 – 7.05 (m, 7H), 5.58 and 5.44 (2s, 2H), 5.12 (t, *J* = 7.4 Hz, 1H), 4.80 (t, *J* = 7.2 Hz) and 4.69 (t, *J* = 6.7 Hz (2t, 2H), 4.58 (t, *J* = 7.2 Hz, 1H), 4.54 – 4.45 (m, 2H), 4.43 and 4.24 (2s, 2H), 4.34 (d, *J* = 5.6 Hz, 1H); ¹⁹F NMR (282 MHz, DMSO) δ -121.26, -121.67; MS (ES+): 474.5 (M+1); MS (ES-): 472.4 (M-1); [based on NMR, this compound is a mixture of two rotamers with 5:4 ratio].

Scheme 63



Preparation of 2-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**63a**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (85 mg, 0.33 mmol) with 2-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetic acid (**56c**) (64 mg, 0.33 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 40%] 2-(4-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**63a**) (42 mg, 0.097 mmol, 29% yield) as a white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.44 (t, *J* = 5.9 Hz, 1H), 8.01 (s, 1H), 7.47 (td, *J* = 7.6, 1.8

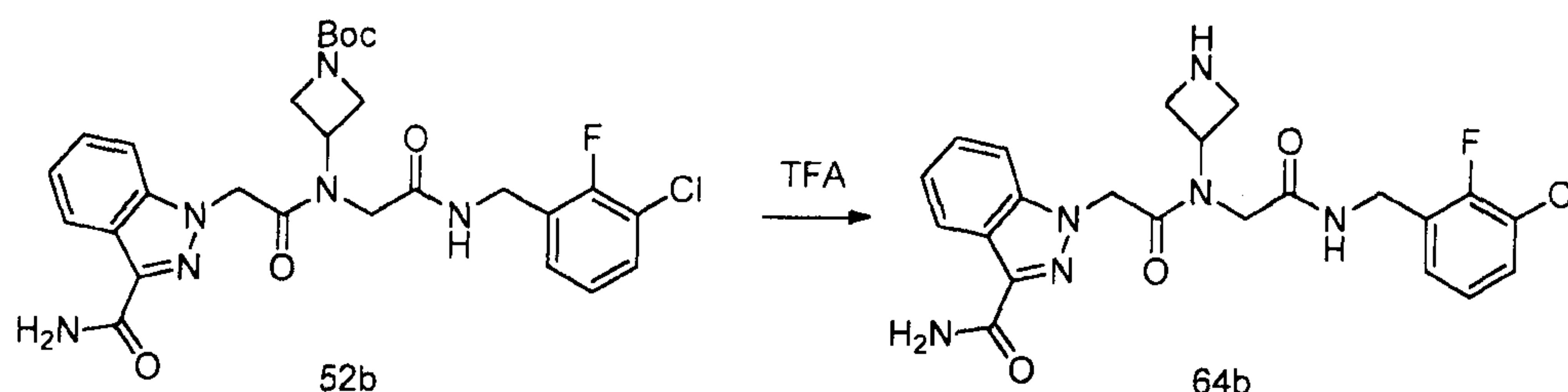
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Hz, 1H), 7.28 – 7.19 (m, 1H), 7.15 (td, $J = 7.8, 1.0$ Hz, 1H), 7.06 (d, $J = 3.5$ Hz, 1H), 6.96 (s, 2H), 6.52 (d, $J = 3.5$ Hz, 1H), 5.25 (s, 2H), 4.33 (d, $J = 5.7$ Hz, 2H), 3.96 (s, 2H), 3.07 – 2.94 (m, 1H), 1.01 – 0.82 (m, 4H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.62; MS (ES+): 431.5 & 433.4 (M+1), MS (ES-): 429.5 (M-1).

5

Scheme 64

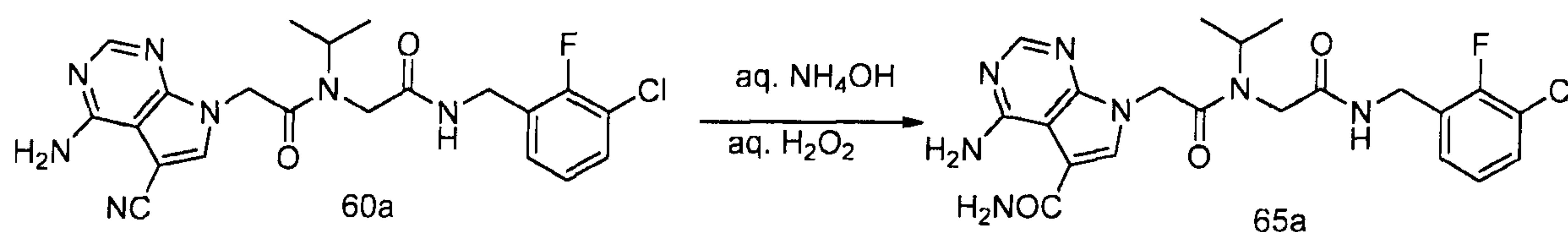


Preparation of 1-(2-(azetidin-3-yl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**64b**)

Reaction of tert-butyl 3-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)azetidine-1-carboxylate (**52b**) (236 mg, 0.41 mmol) with TFA (0.19 mL, 2.47 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl_3 0 to 60%] 1-(2-(azetidin-3-yl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**64b**) (112 mg, 0.24 mmol, 58% yield) as a white solid; ^1H NMR(300 MHz, DMSO- d_6) δ 8.94 (t, $J = 5.7$ Hz) and 8.51 (t, $J = 6.0$ Hz) (2t, 1H), 8.17 (d, $J = 8.2$ Hz, 1H), 7.68 (bs, 1H), 7.52 – 7.22 (m, 7H), 5.55 and 5.41 (2s, 2H), 4.91 (m, 1H), 4.47 (d, $J = 5.3$ Hz) and 4.33 (d, $J = 5.5$ Hz) (2d, 2H), 4.42 and 4.18 (2s, 2H), 3.62 (d, $J = 7.2$ Hz, 2H), 3.41 (d, $J = 7.6$ Hz, 2H), 3.35 (s, 1H); ^{19}F NMR (282 MHz, DMSO) δ -121.28, -121.64; MS (ES+) 473.5 (M+1); MS (ES-), 471.4 (M-1); [based on NMR, this compound is a mixture of two rotamers 1:1 ratio].

20

Scheme 65



Preparation of 4-amino-7-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-

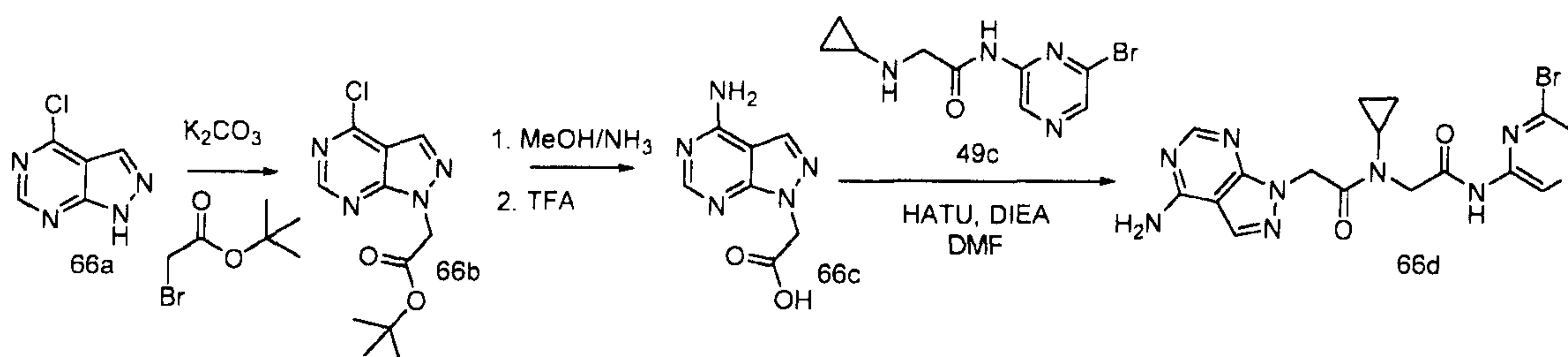
25 oxoethyl)(isopropyl)amino)-2-oxoethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide (**65a**)

To a solution of 2-(4-amino-5-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**60a**) (32 mg, 0.07 mmol) in ethanol (5 mL) was added aq. ammonium hydroxide (0.54 mL, 13.98 mmol) followed by aq. hydrogen peroxide (35%, 0.122 mL, 1.398 mmol) and stirred at room temperature for 16 h.

5 Excess solvent was removed under reduced pressure and the residue obtained was purified by flash column chromatography [Silica gel (12 g), eluting with MeOH in CHCl₃ 0-50%] to afford 4-amino-7-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-7H-pyrrolo[2,3-d]pyrimidine-5-carboxamide (**65a**) (14 mg, 0.029 mmol, 42% yield) as a white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.79 (t, *J* = 5.7 Hz) and 8.35 (t, *J* = 5.9 Hz) (2t, 1H), 8.04 and 8.04 (2s, 1H), 7.90 and 7.88 (2s, 1H), 7.58 – 7.35 (m, 2H), 7.34 – 7.07 (m, 3H), 5.21 and 5.08 (2s, 2H), 4.63 – 4.51 and 4.28 – 4.23 (2m, 1H), 4.43 (d, *J* = 5.6 Hz) and 4.31 (d, *J* = 5.8 Hz) (2d, 2H), , 4.17 and 3.84 (2s, 2H), 1.20 (d, *J* = 6.4 Hz) and 0.97 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.32 , -121.70. [based on

10 NMR the compound is a mixture of two rotamers ~1:1 ratio]; MS (ES⁺): 476.5 (M+1), 498.5 (M+Na); (ES⁻): 474.5 (M-1), 510.3 (M+Cl).

Scheme 66



Preparation of 2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-(2-((6-bromopyrazin-2-yl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**66d**)

20 Step-1: Preparation of tert-butyl 2-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetate (**66b**)

Reaction of 4-chloro-1H-pyrazolo[3,4-d]pyrimidine (**66a**) (6.82 g, 44.16 mmol) with tert-butyl 2-bromoacetate (7.82 mL, 52.96 mmol) using potassium carbonate (9.14 g, 66.13 mmol) as base according to the procedure reported step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica gel (40 g), eluting with EtOAc in

25 hexanes 0 to 60%] tert-butyl 2-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetate (**66b**) (4.5 g, 16.75 mmol, 38% yield) as white solid.

Step-2: Preparation of 2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetic acid (**66c**)

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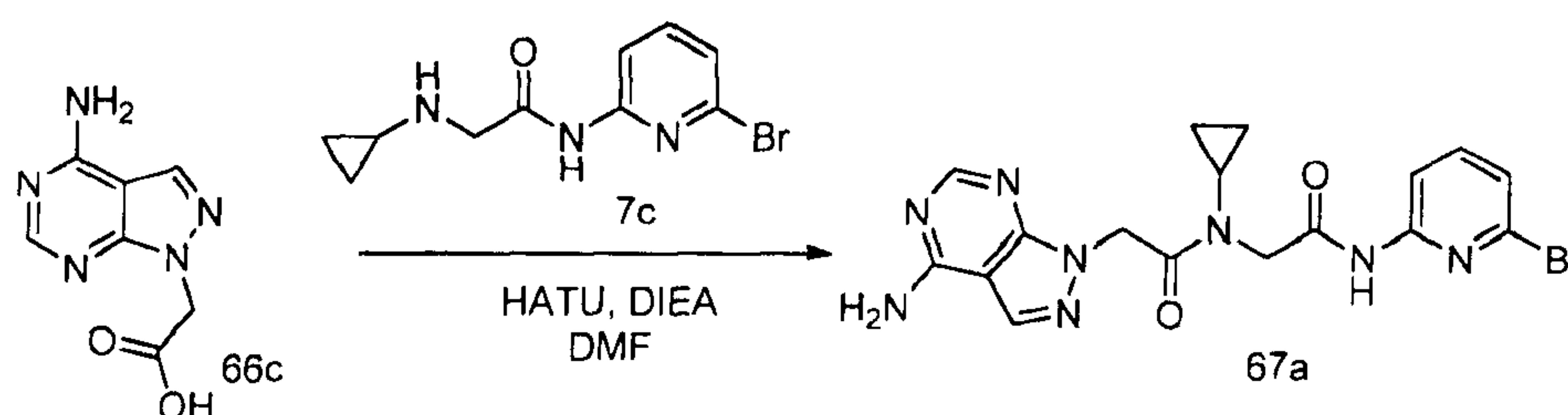
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A solution of tert-butyl 2-(4-chloro-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetate (**66b**) (300 mg, 1.12 mmol) in methanolic ammonia (3.72 mL, 11.16 mmol) was stirred at room temperature for 2d, concentrated in vacuum and the residue was purified by chromatography [silica gel (12 g), eluting with EtOAc/MeOH (9:1) in hexanes 0 to 100%] afforded intermediate product. This material was dissolved in DCM (5 mL), added TFA (0.86 mL, 11.16 mmol) and stirred at room temperature for 4d. The solvent was removed under vacuum and resultant residue was suspended in toluene (10 mL) and evaporated. The solid was dried under vacuum to afford 2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetic acid (**66c**) (0.14 g, 0.73 mmol, 65% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.24 (s, 1H), 8.64 (s, 1H), 8.39 (s, 1H), 8.32 (s, 1H), 5.16 (s, 2H); MS (ES+) 194.2 (M+1).

Step-3: Preparation of 2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-(2-((6-bromopyrazin-2-yl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**66d**)

Reaction of N-(6-bromopyrazin-2-yl)-2-(cyclopropylamino)acetamide (**49c**) (70 mg, 0.26 mmol) with 2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetic acid (**66c**) (50 mg, 0.26 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 40%] 2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-(2-((6-bromopyrazin-2-yl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**66d**) (62 mg, 0.14 mmol, 54% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.27 (s, 1H), 9.25 (s, 1H), 8.54 (s, 1H), 8.15 (s, 1H), 8.08 (s, 1H), 7.87 - 7.54 (m, 2H), 5.45 (s, 2H), 4.19 (s, 2H), 3.14 - 3.02 (m, 1H), 1.02 - 0.88 (m, 4H); MS (ES+): 446.4 & 448.4 (M+1), 468.4 & 470.4 (M+Na).

Scheme 67



Preparation of 2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**67a**)

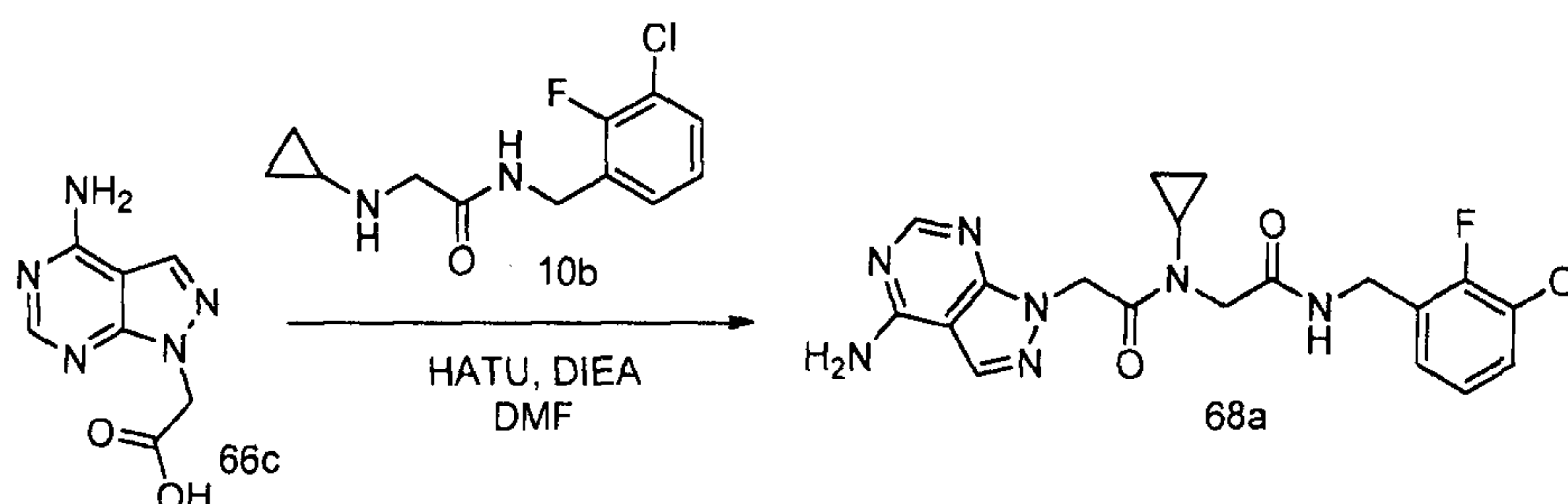
Reaction of N-(6-bromopyrazin-2-yl)-2-(cyclopropylamino)acetamide (**7c**) (70 mg, 0.26 mmol) with 2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetic acid (**66c**) (50 mg, 0.26 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 40%] 2-(4-

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amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**67a**) (68 mg, 0.153 mmol, 59% yield) as a white solid; ^1H NMR(300 MHz, DMSO- d_6) δ 10.93 (s, 1H), 8.15 (s, 1H), 8.08 (s, 1H), 8.02 (d, $J = 8.1$ Hz, 1H), 7.86 – 7.53 (m, 3H), 7.33 (dd, $J = 7.7, 0.7$ Hz, 1H), 5.43 (s, 2H), 4.15 (s, 2H), 3.12 – 3.00 (m, 1H), 1.01 – 0.86 (m, 4H); MS (ES+); 445.4 & 447.4 (M+1), 467.4 & 469.5 (M+Na), MS (ES-): 443.4 & 445.4 (M-1).

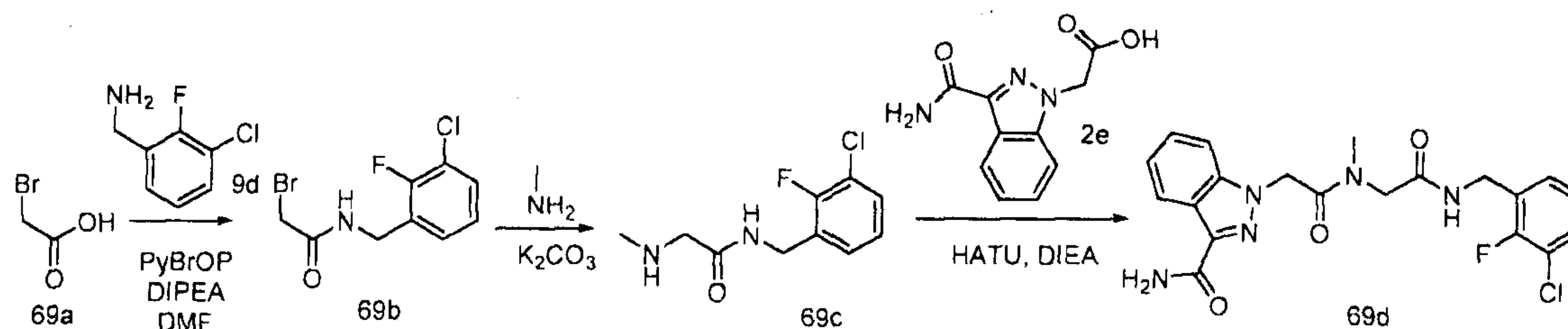
Scheme 68



Preparation of 2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**68a**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (70 mg, 0.27 mmol) with 2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)acetic acid (**66c**) (53 mg, 0.27 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by chromatography [silica (12 g), eluting with CMA80 in CHCl_3 0 to 40%] 2-(4-amino-1H-pyrazolo[3,4-d]pyrimidin-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**68a**) (85 mg, 0.2 mmol, 72% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.45 (t, $J = 5.8$ Hz, 1H), 8.14 (s, 1H), 8.08 (s, 1H), 7.88 - 7.52 (m, 2H), 7.47 (td, $J = 7.6, 1.8$ Hz, 1H), 7.27 - 7.19 (m, 1H), 7.19 - 7.10 (m, 1H), 5.42 (s, 2H), 4.32 (d, $J = 5.7$ Hz, 2H), 3.95 (s, 2H), 3.09 - 2.95 (m, 1H), 0.99 - 0.82 (m, 4H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.62; MS (ES+): 432.5 & 433.5 (M+1), 454.4 (M+23), MS (ES-): 430.4 & 432.4 (M-1).

Scheme 69



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Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**69d**)

Step-1: Preparation of 2-bromo-N-(3-chloro-2-fluorobenzyl)acetamide (**69b**)

Reaction of 2-bromoacetic acid (**69a**) (2.09 g, 15.04 mmol) with 3-chloro-2-

5 fluorobenzylamine (**9d**) (2.0 g, 12.53 mmol) according to the procedure reported in Scheme 32 gave after workup and purification by flash column chromatography [silica gel (40 g), eluting with EtOAc in hexanes 0-100%] 2-bromo-N-(3-chloro-2-fluorobenzyl)acetamide (**69b**) (2.58 g, 9.21 mmol, 74% yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.86 (t, *J* = 5.9 Hz, 1H, D₂O exchangeable), 7.51 (ddd, *J* = 7.9, 7.2, 1.8 Hz, 1H), 7.36 – 7.27 (m, 1H), 7.26 – 7.16 (m, 1H), 4.44 – 4.27 (m, 2H), 3.91 (s, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.04; MS (ES⁺): 280.2, 282.2 (M+2); (ES⁻): 278.2, 280.2 (M-2).

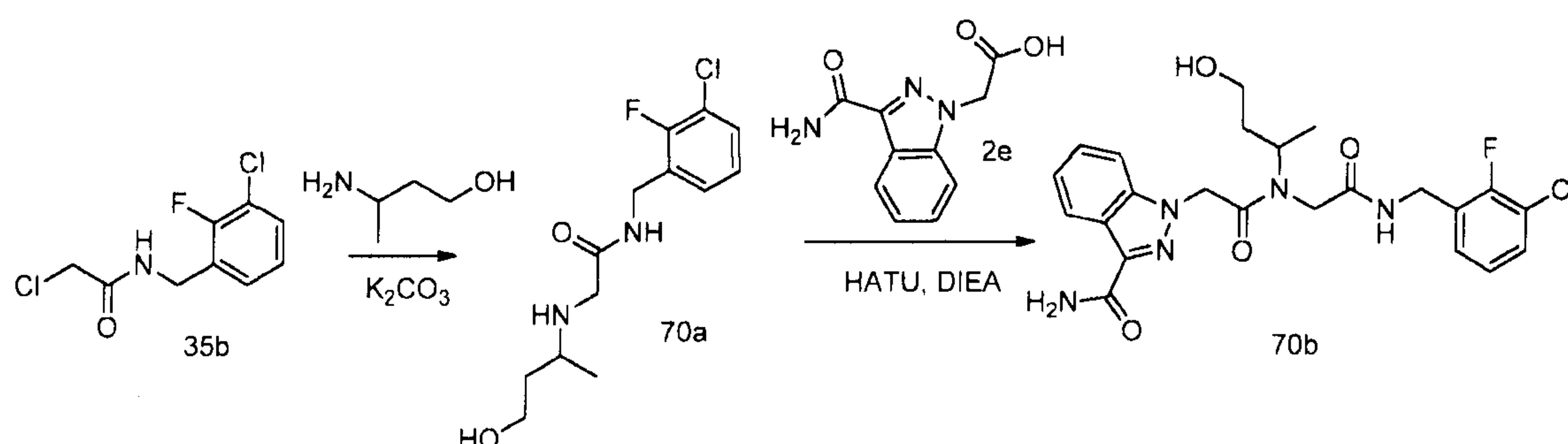
Step-2: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(methylamino)acetamide (**69c**)

Reaction of 2-bromo-N-(3-chloro-2-fluorobenzyl)acetamide (**69b**) (300 mg, 1.07 mmol) with methylamine (2M in MeOH) (0.962 mL, 1.925 mmol) in ethanol (20 mL) according to the
15 procedure reported in step-2 of Scheme 35 gave after workup N-(3-chloro-2-fluorobenzyl)-2-(methylamino)acetamide (**69c**) (217 mg, 0.94 mmol, 88% yield) as a yellow oil which was used as such in the next step; MS (ES⁻): 229.2 (M-1).

Step-3: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**69d**)

20 Reaction of N-(3-chloro-2-fluorobenzyl)-2-(methylamino)acetamide (**69c**) (217 mg, 0.94 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (572 mg, 2.61 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [Silica gel (24 g), eluting with MeOH in CHCl₃ 0-50%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(methyl)amino)-2-oxoethyl)-1H-indazole-3-
25 carboxamide (**69d**) (139 mg, 34% yield) as a pale yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.93 – 8.78 & 8.59 – 8.45 (2m, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.79 – 7.58 (m, 2H), 7.58 – 7.33 (m, 3H), 7.34 – 7.05 (m, 3H), 5.57 & 5.44 (2s, 2H), 4.46 (d, *J* = 5.1 Hz) & 4.35 (d, *J* = 5.6 Hz) (2d, 2H), 4.25 & 4.00 (2s, 2H), 3.19 & 2.81 (s, 3H) ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.40, -121.64 [*based on NMR the compound is a mixture of two rotamers ~2:3 ratio*];
30 MS (ES⁺): 432.5 (M+1).

Scheme 70



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(4-hydroxybutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**70b**)

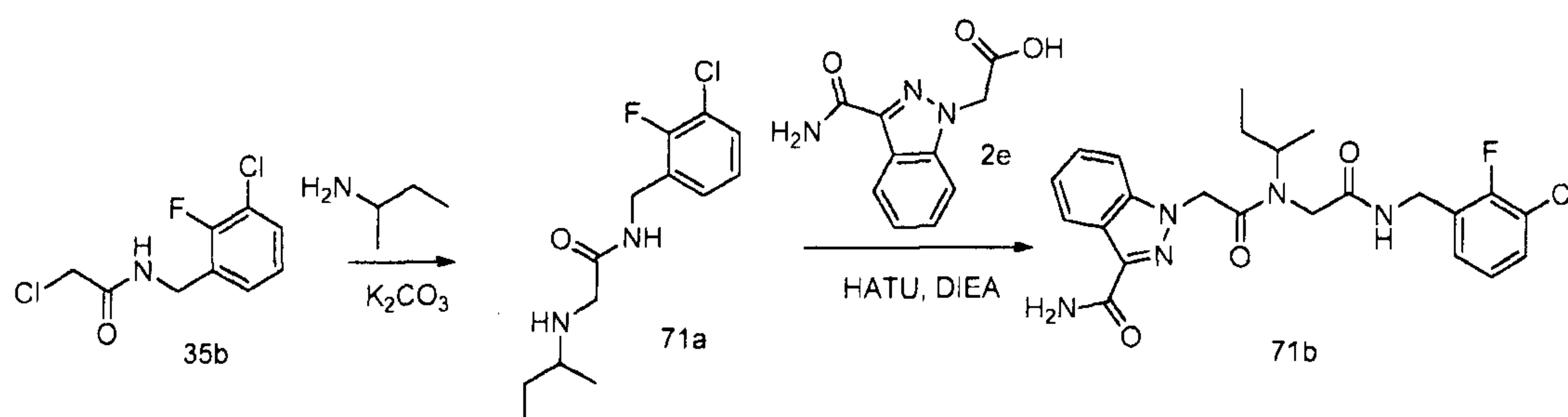
- 5 Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((4-hydroxybutan-2-yl)amino)acetamide (**70a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (494 mg, 2.09 mmol) with 3-aminobutan-1-ol (378 mg, 4.24 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-((4-hydroxybutan-2-yl)amino)acetamide (**70a**) (200 mg, 0.69 mmol, 33%) as a clear oil; MS (ES⁺) 289.4 (M+1); (ES⁻) 287.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(4-hydroxybutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**70b**)

- 15 Reaction of N-(3-chloro-2-fluorobenzyl)-2-((4-hydroxybutan-2-yl)amino)acetamide (**70a**) (200 mg, 0.69 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (167 mg, 0.76 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] followed by prep-HPLC [C18 column, MeOH in water 0-100%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(4-hydroxybutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**70b**) (102 mg, 0.21 mmol, 30% yield) as a white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.83 (t, *J* = 5.5 Hz) and 8.40 (t, *J* = 5.8 Hz) (2t, 1H), 8.18 (d, *J* = 7.9 Hz, 1H), 7.72 (d, *J* = 6.5 Hz, 1H), 7.58 – 7.00 (m, 7H), 5.79 – 5.40 (m, 2H), 4.57 – 3.41 (m, 7H), 3.31 (t, *J* = 6.5 Hz, 1H), 1.80 – 1.41 (m, 2H), 1.25 (d, *J* = 6.5 Hz) & 0.98 (d, *J* = 6.8 Hz) (2d, 3H);
- 20 ¹⁹F NMR (282 MHz, DMSO) δ -74.30 (TFA peak), -121.26, -121.77; MS (ES⁺) 490.5 (M+1); MS (ES⁻), 488.4 (M-1); [based on NMR, this compound is a mixture of two rotamers 4:5 ratio].
- 25

Scheme 71



Preparation of 1-(2-(sec-butyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**71b**)

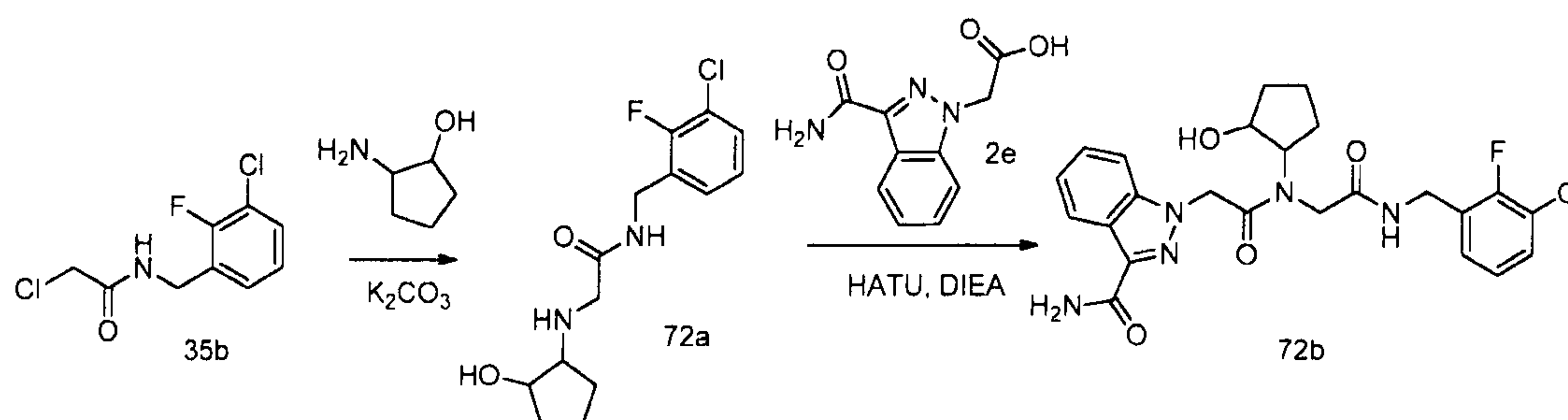
Step-1: Preparation of 2-(sec-butylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**71a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 2.12 mmol) with butan-2-amine (775 mg, 10.59 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] 2-(sec-butylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**71a**) (170 mg, 0.62 mmol, 29%) as a yellow oil; MS (ES⁺): 273.4 (M+1); MS (ES⁻): 271.3 (M-1).

Step-2: Preparation of 1-(2-(sec-butyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**71b**)

Reaction of 2-(sec-butylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**71a**) (170 mg, 0.62 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (150 mg, 0.69 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] 1-(2-(sec-butyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**71b**) (178 mg, 0.38 mmol, 60% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.82 (t, *J* = 5.7 Hz) and 8.36 (t, *J* = 5.9 Hz) (2t, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.77 – 7.67 (m, 1H), 7.60 – 7.02 (m, 7H), 5.66 – 5.39 (m, 2H), 4.57 – 3.71 (m, 5H), 1.69 – 1.28 (m, 2H), 1.26 – 0.61 (m, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.19, -121.76; MS (ES⁺) 474.5 (M+1); MS (ES⁻), 472.5 (M-1); [based on NMR, this compound is a mixture of two rotamers 2:1 ratio].

Scheme 72



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2-hydroxycyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**72b**)

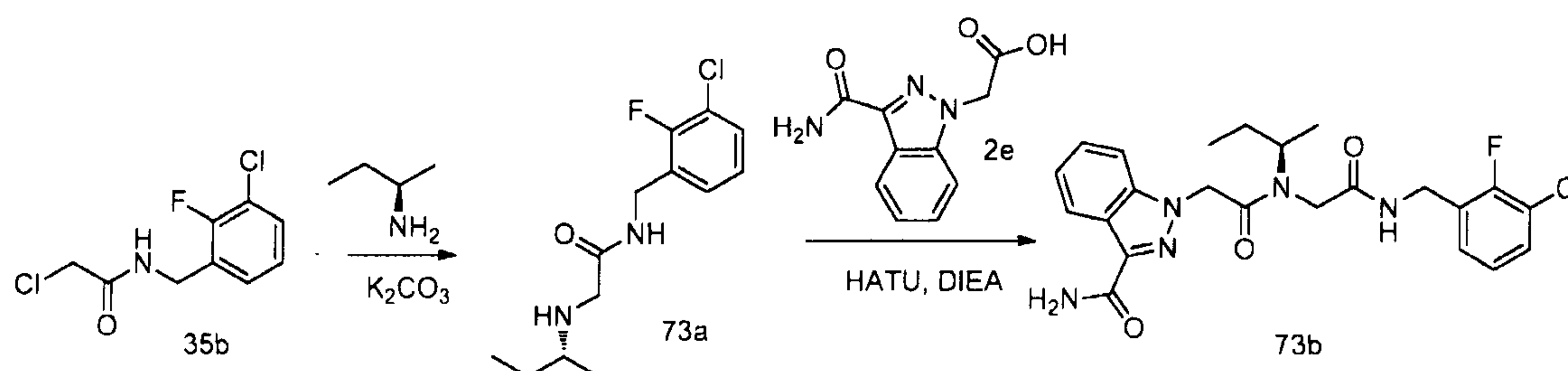
5 Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((2-hydroxycyclopentyl)amino)acetamide (**72a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (350 mg, 1.48 mmol) with 2-aminocyclopentanol (375 mg, 3.71 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-((2-hydroxycyclopentyl)amino)acetamide (**72a**) (158 mg, 0.53 mmol, 36%) as a yellow oil; MS (ES⁺): 301.3; (ES⁻): 299.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2-hydroxycyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**72b**)

15 Reaction of N-(3-chloro-2-fluorobenzyl)-2-((2-hydroxycyclopentyl)amino)acetamide (**72a**) (158 mg, 0.53 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (127 mg, 0.58 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2-hydroxycyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**72b**) (128 mg, 0.26 mmol, 49% yield) as an off white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.87 (t, *J* = 5.7 Hz) and 8.47 (t, *J* = 5.9 Hz) (2t, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.77 – 7.64 (m, 1H), 7.60 – 6.99 (m, 7H), 5.69 and 5.43 (2s, 1H), 5.36 (d, *J* = 4.7 Hz) and 4.75 (d, *J* = 4.8 Hz) (2d, 2H), 4.50 – 3.70 (m, 6H), 2.04 – 1.28 (m, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.22, -121.68; MS (ES⁺) 502.6 (M+1); MS (ES⁻): 500.5 (M-1); [based on NMR, this compound is a mixture of two rotamers 1:3 ratio].

Scheme 73



Preparation of (R)-1-(2-(sec-butyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**73b**)

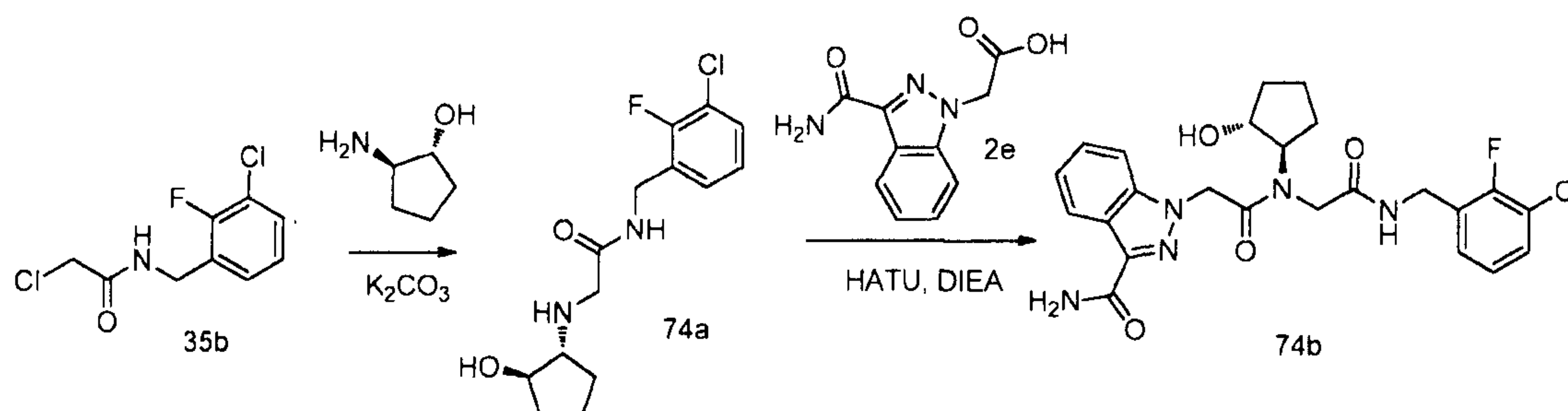
5 Step-1: Preparation of (R)-2-(sec-butylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**73a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (200 mg, 0.85 mmol) with (R)-butan-2-amine (155 mg, 2.12 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] (R)-2-(sec-butylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**73a**) (100 mg, 0.37 mmol, 43%) as a yellow oil; MS (ES⁺): 273.3 (M+1); MS (ES⁻): 271.3 (M-1).

Step-2: Preparation of (R)-1-(2-(sec-butyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**73b**)

Reaction of (R)-2-(sec-butylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**73a**) (100 mg, 0.37 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (88 mg, 0.4 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] (R)-1-(2-(sec-butyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**73b**) (101 mg, 0.21 mmol, 58% yield) as a white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.82 (t, *J* = 5.5 Hz) and 8.36 (t, *J* = 5.7 Hz) (2t, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 7.82 – 7.65 (m, 1H), 7.59 – 7.01 (m, 7H), 5.68 – 5.39 (m, 2H), 4.55 – 3.71 (m, 5H), 1.67 – 1.28 (m, 2H), 1.26 – 0.65 (m, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.19, -121.76; MS (ES⁺) 474.6 (M+1); 496.5 (M+Na); MS (ES⁻), 472.5 (M-1); [based on NMR, this compound is a mixture of rotamers 1:3 ratio].

Scheme 74



Preparation of 1-(2-(((2-(((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((1R,2R)-2-hydroxycyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**74b**)

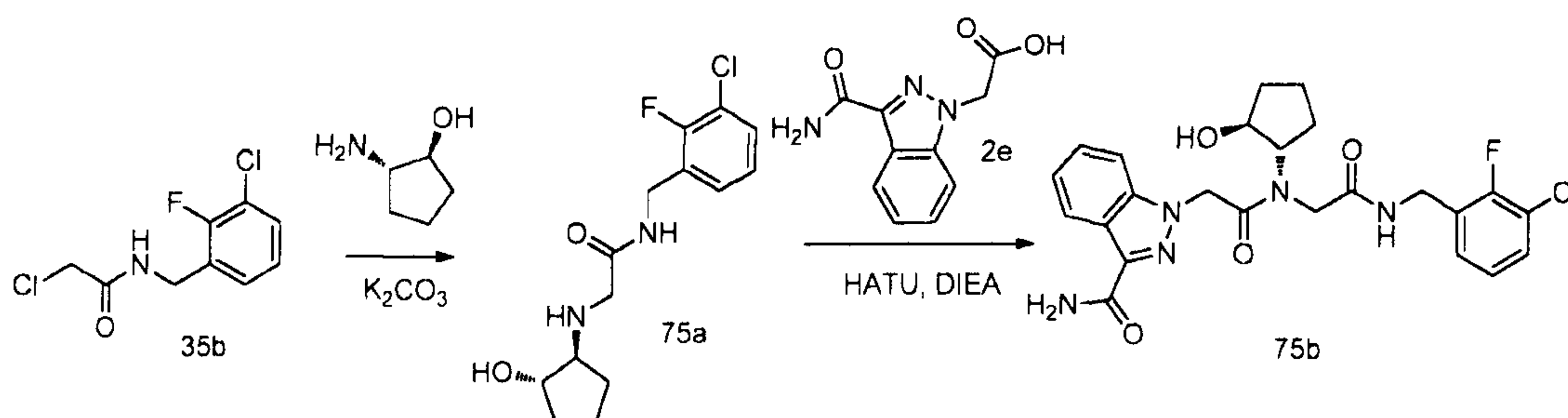
- 5 Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(((1R,2R)-2-hydroxycyclopentyl)amino)acetamide (**74a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (350 mg, 1.48 mmol) with (1R,2R)-2-aminocyclopentanol (510 mg, 3.71 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography
 10 [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-(((1R,2R)-2-hydroxycyclopentyl)amino)acetamide (**74a**) (312 mg, 1.04 mmol, 70%) as a yellow oil; MS (ES⁺): 301.3 (M+1); MS (ES⁻): 299.3 (M-1).

Step-2: Preparation of 1-(2-(((2-(((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((1R,2R)-2-hydroxycyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**74b**)

- 15 Reaction of N-(3-chloro-2-fluorobenzyl)-2-(((1R,2R)-2-hydroxycyclopentyl)amino)acetamide (**74a**) (135 mg, 0.55 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (132 mg, 0.6 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] 1-(2-(((2-(((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((1R,2R)-2-hydroxycyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide
 20 (**74b**) (95 mg, 0.189 mmol, 34.5% yield) as a white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.87 (t, *J* = 5.8 Hz) and 8.47 (t, *J* = 5.9 Hz) (2t, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.71 (d, *J* = 6.5 Hz, 1H), 7.58 – 7.00 (m, 7H), 5.69 and 5.43 (2s, 2H), 5.37 (d, *J* = 4.7 Hz) and 4.76 (d, *J* = 4.8 Hz) (2d, 1H), 4.52 – 3.71 (m, 6H), 2.03 – 1.37 (m, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -
 25 121.22, -121.68; MS (ES⁺) 502.6 (M+1); 524.5 (M+Na); [based on NMR, this compound is a mixture of two rotamers 2:7 ratio].

Scheme 75



Preparation of 1-(2-(((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((1S,2S)-2-hydroxycyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**75b**)

5 Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(((1S,2S)-2-hydroxycyclopentyl)amino)acetamide (**75a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (350 mg, 1.48 mmol) with (1S,2S)-2-aminocyclopentanol (510 mg, 3.71 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography

10 [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-(((1S,2S)-2-hydroxycyclopentyl)amino)acetamide (**75a**) (285 mg, 0.95 mmol, 64%) as a yellow oil; MS (ES⁺): 301.4 (M+1); MS (ES⁻): 299.4 (M-1).

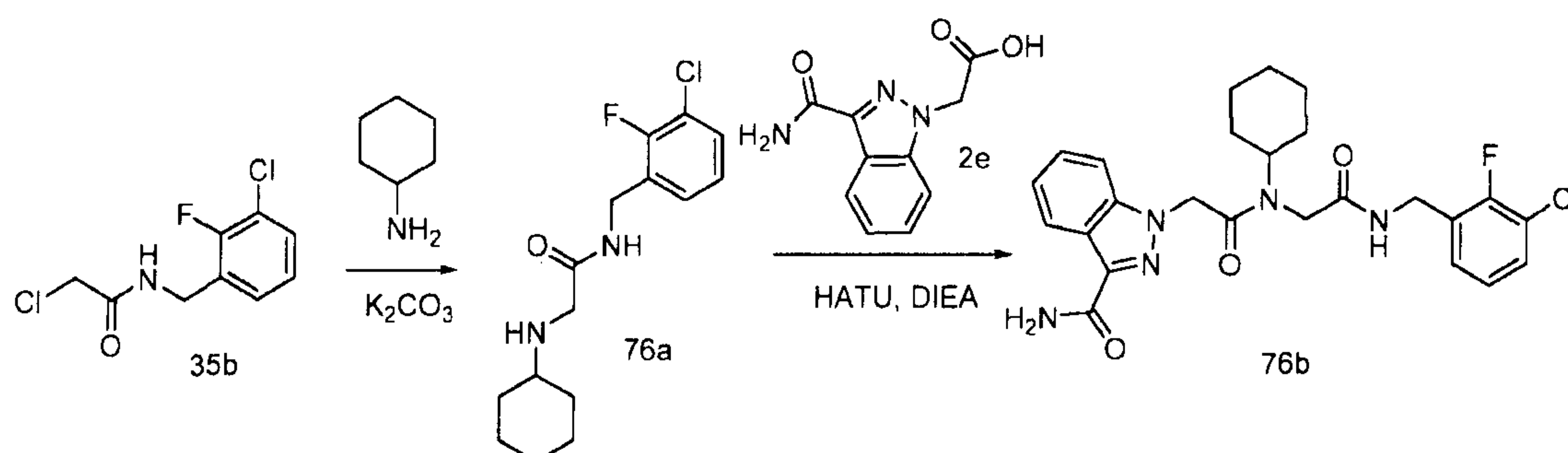
Step-2: Preparation of 1-(2-(((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((1S,2S)-2-hydroxycyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**75b**)

15 Reaction of N-(3-chloro-2-fluorobenzyl)-2-(((1S,2S)-2-hydroxycyclopentyl)amino)acetamide (**75a**) (165 mg, 0.55 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (132 mg, 0.6 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] 1-(2-(((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((1S,2S)-2-

20 hydroxycyclopentyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**75b**) (185 mg, 0.369 mmol, 67.2% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.88 (t, *J* = 5.6 Hz) and 8.48 (t, *J* = 5.7 Hz) (2s, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.78 – 7.63 (m, 1H), 7.57 – 6.99 (m, 7H), 5.69 and 5.44 (2s, 2H), 5.37 (d, *J* = 4.6 Hz) and 4.76 (d, *J* = 4.7 Hz) (2d, 1H), 4.51 – 3.72 (m, 6H), 2.03 – 1.45 (m, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.21, -121.67; MS (ES⁺): 524.5 (M+Na); (ES⁻): 500.5 (M-1); [based on NMR, this compound is a mixture of two rotamers 2:7 ratio].

25

Scheme 76



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclohexyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**76b**)

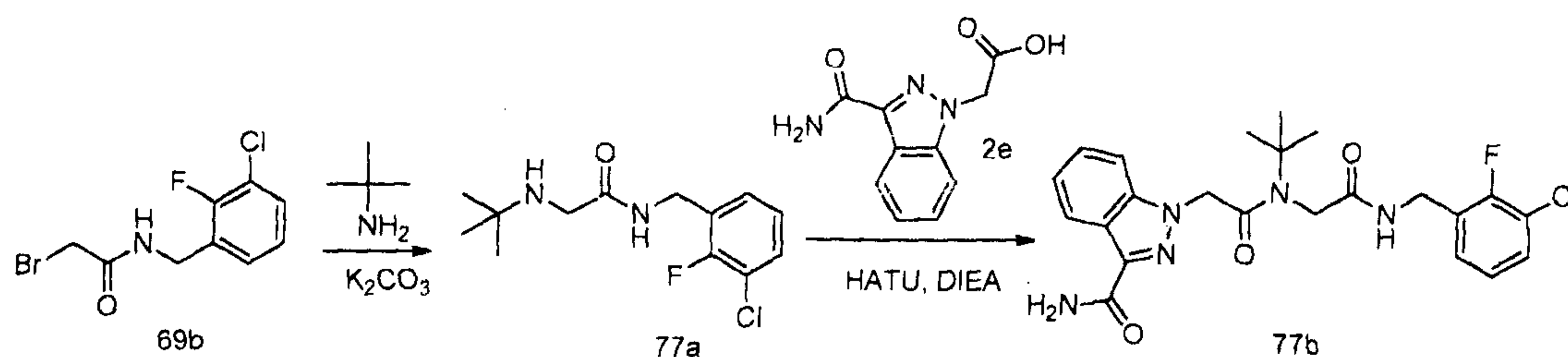
5 Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(cyclohexylamino)acetamide (**76a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (400 mg, 1.69 mmol) with cyclohexylamine (840 mg, 8.87 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-(cyclohexylamino)acetamide (**76a**) (331 mg, 1.11 mmol, 65%) as a yellow oil; MS (ES⁺): 299.4 (M+1); MS (ES⁻): 297.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclohexyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**76b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(cyclohexylamino)acetamide (**76a**) (145 mg, 0.49 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (117 mg, 0.53 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclohexyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**76b**) (176 mg, 0.352 mmol, 72.5% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.82 (t, *J* = 5.7 Hz) and 8.33 (t, *J* = 5.8 Hz) (2t, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.76 – 7.65 (m, 1H), 7.64 – 7.02 (m, 7H), 5.60 and 5.47 (2s, 2H), 4.46 (d, *J* = 5.5 Hz) and 4.32 (d, *J* = 5.7 Hz) (2d, 2H), 4.24 – 3.70 (m, 3H), 1.90 – 0.93 (m, 10H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.11, -121.68; MS (ES⁺): 500.5 (M+1); MS (ES⁻): 498.5 (M-1); [based on NMR, this compound is a mixture of two rotamers with 1:1 ratio].

Scheme 77



Preparation of 1-(2-(tert-butyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**77b**)

5 Step-1: Preparation of 2-(tert-butylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**77a**)

Reaction of 2-bromo-N-(3-chloro-2-fluorobenzyl)acetamide (**69b**) (300 mg, 1.07 mmol) with 2-methylpropan-2-amine (0.2 mL, 1.93 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup 2-(tert-butylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**77a**) (226 mg, 0.83 mmol, 77%) as a yellow oil which was used as such without further

10 purification; ^1H NMR (300 MHz, DMSO- d_6) δ 8.38 (t, $J = 5.9$ Hz, 1H), 7.51 – 7.43 (m, 1H), 7.30 – 7.23 (m, 1H), 7.22 – 7.15 (m, 1H), 4.36 (d, $J = 6.1$ Hz, 2H), 3.09 (s, 2H), 2.28 (s, 1H), 1.00 (s, 9H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.72; MS (ES+): 273.4 (M+1); MS (ES-): 271.3 (M-1).

Step-2: Preparation of 1-(2-(tert-butyl(2-((3-chloro-2-fluorobenzyl)amino)-2-

15 oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**77b**)

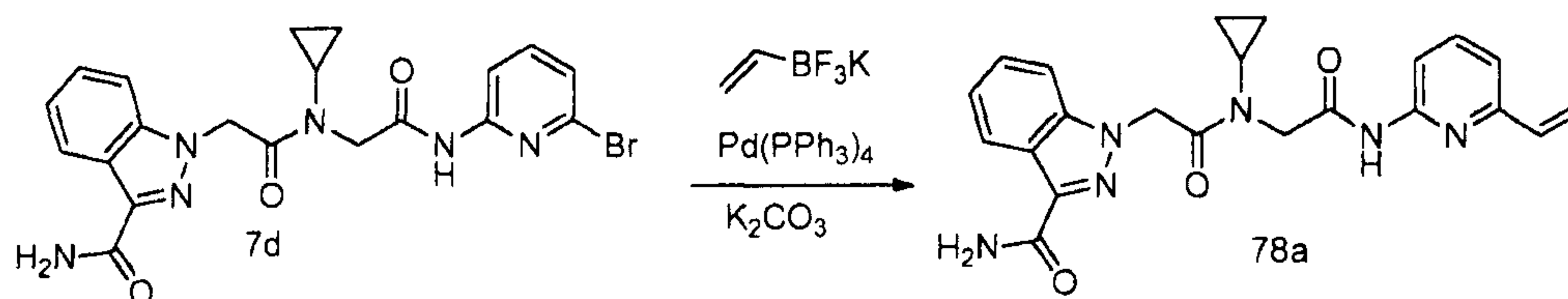
Reaction of 2-(tert-butylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**77a**) (210 mg, 0.77 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (203 mg, 0.92 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash

20 column chromatography [silica (12 g), eluting with MeOH in CHCl_3 0 to 50%] 1-(2-(tert-butyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-

carboxamide (**77b**) (37 mg, 0.078 mmol, 10% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.81 (t, $J = 5.7$ Hz, 1H, D_2O exchangeable), 8.18 (dt, $J = 8.3, 1.0$ Hz, 1H), 7.76 (s, 1H, D_2O exchangeable), 7.60 – 7.48 (m, 2H), 7.47 – 7.33 (m, 3H), 7.31 – 7.16 (m, 2H), 5.39 (s, 2H), 4.47 (d, $J = 5.5$ Hz, 2H), 4.25 (s, 2H), 1.29 (s, 9H); ^{19}F NMR (282 MHz,

25 DMSO- d_6) δ -121.23; MS (ES+): 474.5 (M+1), 496.4 (M+Na); MS (ES-): 508.6 (M+Cl).

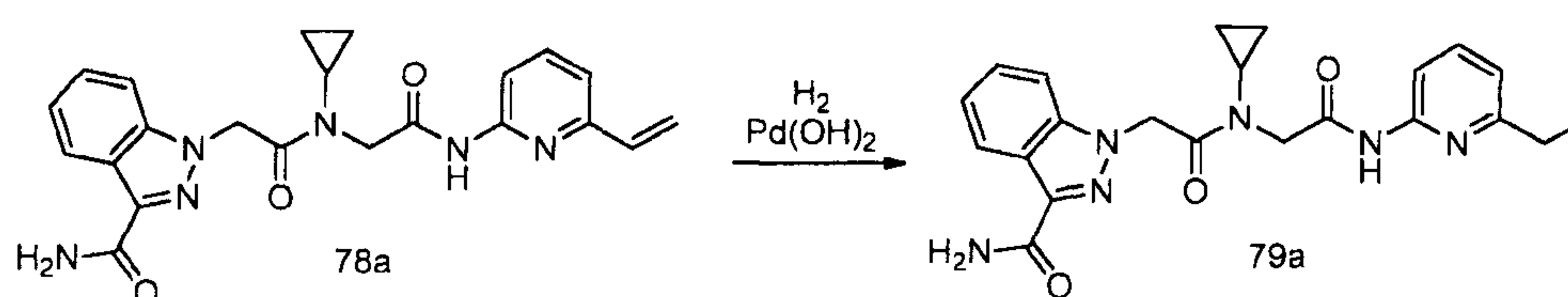
Scheme 78



Preparation of 1-(2-(cyclopropyl(2-oxo-2-((6-vinylpyridin-2-yl)amino)ethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**78a**)

- 5 To a degassed solution of 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (170 mg, 0.36 mmol) in dioxane (5 mL) was added potassium vinyltrifluoroborate (97 mg, 0.72 mmol), tetrakis(triphenylphosphine) Palladium (0) (42 mg, 0.036 mmol), degassed solution of potassium carbonate (100 mg, 0.72 mmol) in water (0.5 mL). The reaction mixture was
- 10 stirred under argon atmosphere for 16 h, quenched with water (30 mL) and EtOAc (40 mL). The organic layers was separated and aqueous layer was extracted with EtOAc (20 mL). The organic layers were combined washed with brine, dried, filtered and concentrated in vacuum. The residue was purified by flash column chromatography [silica gel (12 g), eluting with EtOAc-MeOH (9:1) in hexane 0 to 100%] to afford 1-(2-(cyclopropyl(2-oxo-2-((6-
- 15 vinylpyridin-2-yl)amino)ethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**78a**) (80 mg, 0.191 mmol, 53% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.57 (s, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 7.91 (d, *J* = 8.2 Hz, 1H), 7.81 - 7.70 (m, 2H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.50 - 7.33 (m, 2H), 7.31 - 7.13 (m, 2H), 6.72 (dd, *J* = 17.4, 10.8 Hz, 1H), 6.19 (dd, *J* = 17.5, 1.8 Hz, 1H), 5.70 (s, 2H), 5.46 (dd, *J* = 10.7, 1.7 Hz, 1H), 4.21 (s, 2H), 3.20 - 3.05
- 20 (m, 1H), 1.10 - 0.84 (m, 4H); MS (ES⁺): 419.5 (M+1); (ES⁻) 453.4.5 (M+Cl).

Scheme 79

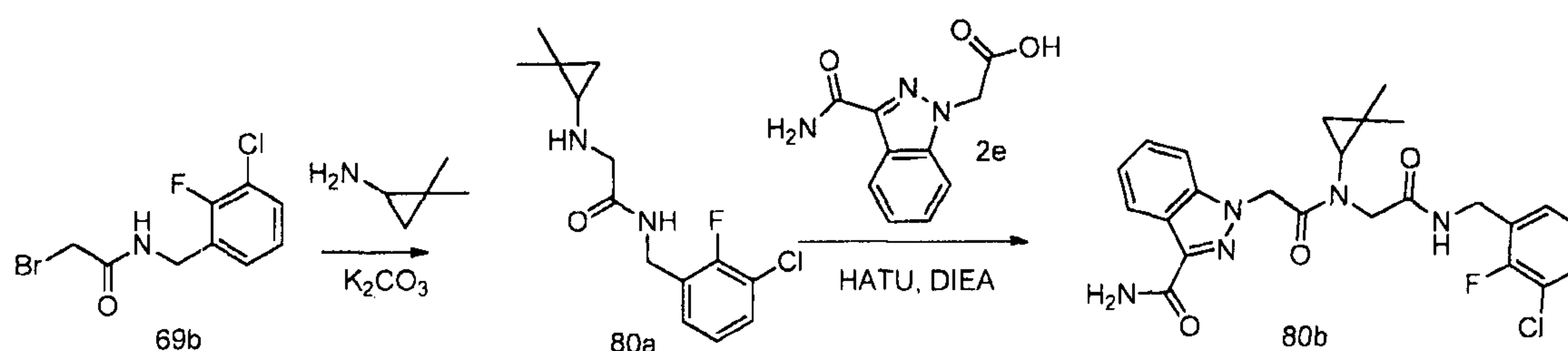


Preparation of 1-(2-(cyclopropyl(2-((6-ethylpyridin-2-yl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**79a**)

- 25 A solution of 1-(2-(cyclopropyl(2-oxo-2-((6-vinylpyridin-2-yl)amino)ethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**78a**) (35 mg, 0.084 mmol) in EtOAc (5 mL) containing Pd(OH)₂ (12 mg, 0.084 mmol) was hydrogenated at atmospheric pressure for 16 h.

The reaction mixture was filtered over a Celite pad to remove catalyst and filtrate was concentrated in vacuum. The residue was purified by flash chromatography [silica gel (4 g), eluting with CMA80 in CHCl₃ 0 to 40%] to afford 1-(2-(cyclopropyl(2-((6-ethylpyridin-2-yl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**79a**) (18 mg, 0.043 mmol, 51% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.53 (s, 1H), 8.17 (d, J = 8.1, 1.0 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.76 (s, 1H), 7.72 - 7.62 (m, 2H), 7.48 - 7.35 (m, 2H), 7.30 - 7.20 (m, 1H), 6.96 (d, J = 7.5 Hz, 1H), 5.70 (s, 2H), 4.19 (s, 2H), 3.17 - 3.05 (m, 1H), 2.65 (q, J = 7.6 Hz, 2H), 1.19 (t, J = 7.6 Hz, 3H), 1.07 - 0.87 (m, 4H); MS (ES⁺): 421.5 (M+1); (ES⁻): 419.5 (M-1).

Scheme 80



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2,2-dimethylcyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**80b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((2,2-dimethylcyclopropyl)amino)acetamide (**80a**)

Reaction of 2-bromo-N-(3-chloro-2-fluorobenzyl)acetamide (**69b**) (300 mg, 1.07 mmol) with 2,2-dimethylcyclopropanamine (182 mg, 2.14 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup N-(3-chloro-2-fluorobenzyl)-2-((2,2-dimethylcyclopropyl)amino)acetamide (**80a**) (305 mg, 1.07 mmol, 100%) as a yellow oil which was used as such without further purification; MS (ES⁺): 285.4 (M+1); MS (ES⁻): 283.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2,2-dimethylcyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**80b**)

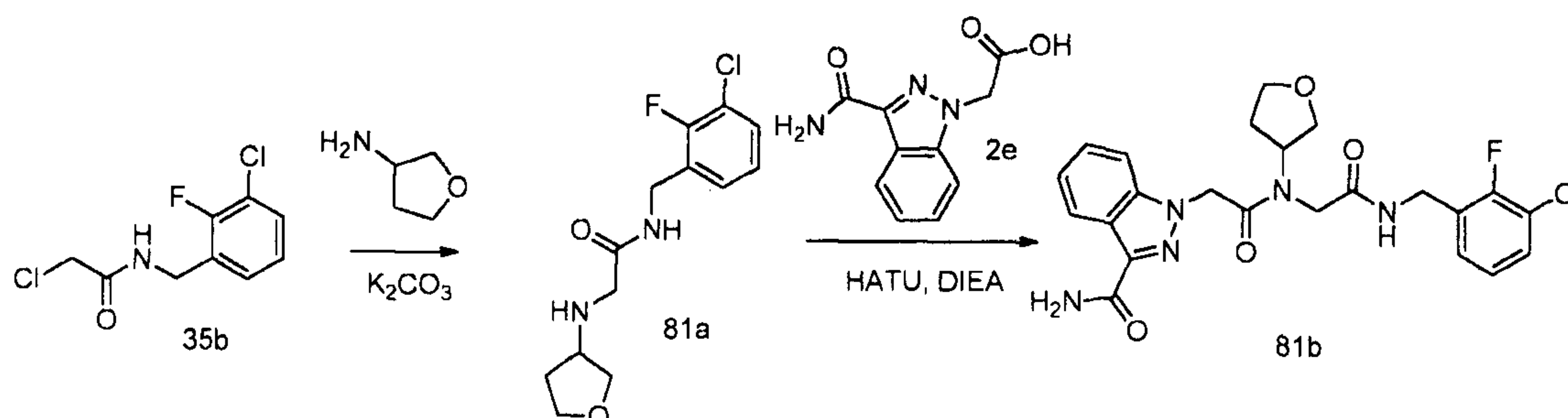
Reaction of N-(3-chloro-2-fluorobenzyl)-2-((2,2-dimethylcyclopropyl)amino)acetamide (**80a**) (305 mg, 1.07 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (282 mg, 1.29 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (24 g), eluting with MeOH in CHCl₃ 0 to 50%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(2,2-dimethylcyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**80b**) (68 mg, 0.14

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mmol, 1% yield) as a white solid in the form of mixture of two rotamers; ^1H NMR (300 MHz, DMSO- d_6) (a mixture of two rotamers) δ 8.83 ($J = 5.7$ Hz) & 8.50 ($J = 5.8$ Hz (2t, 1H), 8.22 – 8.16 (m, 1H), 7.73 & 7.70 (2s, 1H), 7.58 – 7.36 (m, 4H), 7.32 – 7.19 (m, 2H), 7.11 (td, $J = 7.8, 1.0$ Hz, 1H), 5.74 – 5.25 (m, 2H), 4.37 – 4.30 (m, 2H), 4.17 – 3.81 (m, 2H), 2.96 (dd, $J = 8.0, 4.5$ Hz, 1H), 1.28 & 0.96 (2s, 3H), 1.18 & 0.91 (2s, 3H), 0.87 – 0.74 (m, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.23, -121.56; MS (ES+): 486.5 (M+1), 508.5 (M+Na); MS (ES-): 484.5 (M-1), 520.5 (M+Cl).

Scheme 81



10 Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(tetrahydrofuran-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**81b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((tetrahydrofuran-3-yl)amino)acetamide (**81a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (300 mg, 1.27 mmol) with
 15 tetrahydrofuran-3-amine (332 mg, 3.81 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-((tetrahydrofuran-3-yl)amino)acetamide (**81a**) (152 mg, 0.53 mmol, 42% yield) as a clear oil;
 ^1H NMR (300 MHz, DMSO- d_6) δ ^1H NMR (300 MHz, DMSO- d_6) δ 8.37 (t, $J = 6.0$ Hz, 1H, D₂O exchangeable), 7.48 (td, $J = 7.8, 1.8$ Hz, 1H), 7.33 – 7.24 (m, 1H), 7.24 – 7.12 (m, 1H), 4.36 (d, $J = 6.0$ Hz, 2H), 3.83 – 3.55 (m, 3H), 3.46 – 3.36 (m, 1H), 3.30 – 3.18 (m, 1H), 3.14 (s, 2H), 2.35 (s, 1H, D₂O exchangeable), 1.95 – 1.80 (m, 1H), 1.72 – 1.55 (m, 1H); MS (ES+), 287.3 (M+1); (ES-): 285.3 (M-1).

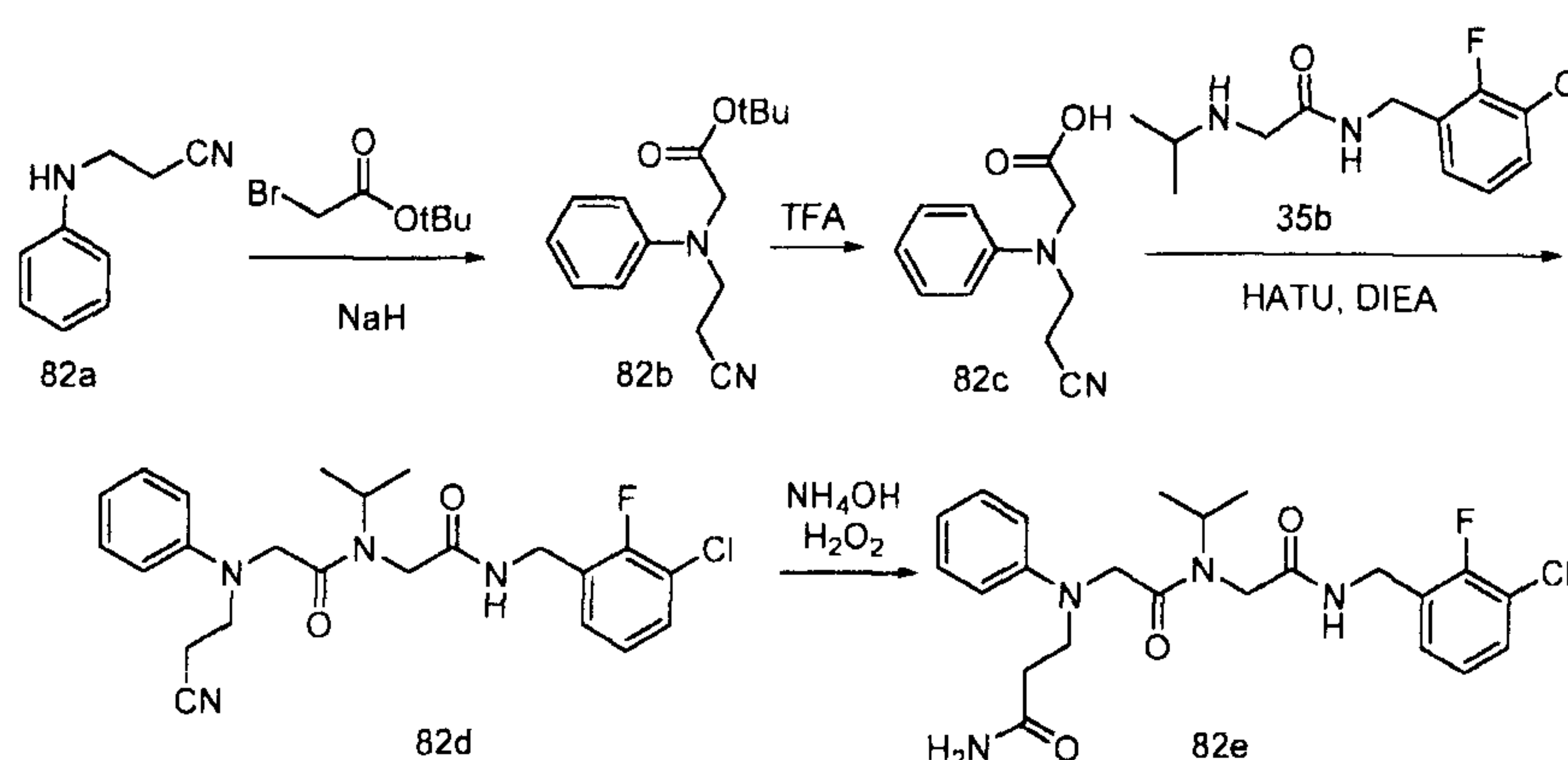
Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(tetrahydrofuran-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**81b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-((tetrahydrofuran-3-yl)amino)acetamide (**81a**) (110 mg, 0.38 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (93 mg, 0.42 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and

purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl_3 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(tetrahydrofuran-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**81b**) (136 mg, 0.28 mmol, 73% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.89 (t, $J = 5.6$ Hz) and 8.49 (t, $J = 5.8$ Hz) (2t, 1H), 8.25 – 8.09 (m, 1H), 7.70 (s, 1H), 7.61 – 7.00 (m, 7H), 5.75 – 5.56 (m) and 5.40 (s) (2H), 4.95 – 4.71 (m, 1H), 4.47 (d, $J = 5.6$ Hz) and 4.31 (d, $J = 5.5$ Hz) (2d, 2H), 4.25 (s) and 4.03 – 3.73 (m) (4H), 3.63 – 3.48 (m, 2H), 2.17 – 1.62 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.27, -121.73; MS (ES+) 488.5 (M+1); 510.5 (M+Na); MS (ES-), 486.5 (M-1); [based on NMR, this compound is a mixture of two rotamers 1:1 ratio].

10

Scheme 82



Preparation of 3-((2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)(phenyl)amino)propanamide (**82e**)

Step-1: Preparation of tert-butyl 2-((2-cyanoethyl)(phenyl)amino)acetate (**82b**)

Reaction of 3-(phenylamino)propanenitrile (**82a**) (1.0 g, 6.84 mmol) with *tert*-butyl 2-bromoacetate (1.11 mL, 7.52 mmol) using sodium hydride (0.274 g, 6.84 mmol) as a base according to the procedure reported in step-1 of Scheme 57 gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane 0 to 50%] tert-butyl 2-((2-cyanoethyl)(phenyl)amino)acetate (**82b**) (148 mg, 0.57 mmol, 8% yield) as a colorless oil; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.24 - 7.11 (m, 2H), 6.76 - 6.51 (m, 3H), 4.09 (s, 2H), 3.70 (t, $J = 6.9$ Hz, 2H), 2.74 (t, $J = 6.8$ Hz, 2H), 1.39 (s, 9H); MS (ES+): 283.5 (M+Na).

Step-2: Preparation of 2-((2-cyanoethyl)(phenyl)amino)acetic acid (**82c**)

Reaction of tert-butyl 2-((2-cyanoethyl)(phenyl)amino)acetate (**82b**) (141 mg, 0.542 mmol) with TFA (0.42 mL, 5.42 mmol) according to the procedure reported in step-2 of Scheme 2

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gave after workup 2-((2-cyanoethyl)(phenyl)amino)acetic acid (**82c**) which was used as such in the next step; MS (ES⁺): 205.3 (M+1); MS (ES⁻): 203.3 (M-1).

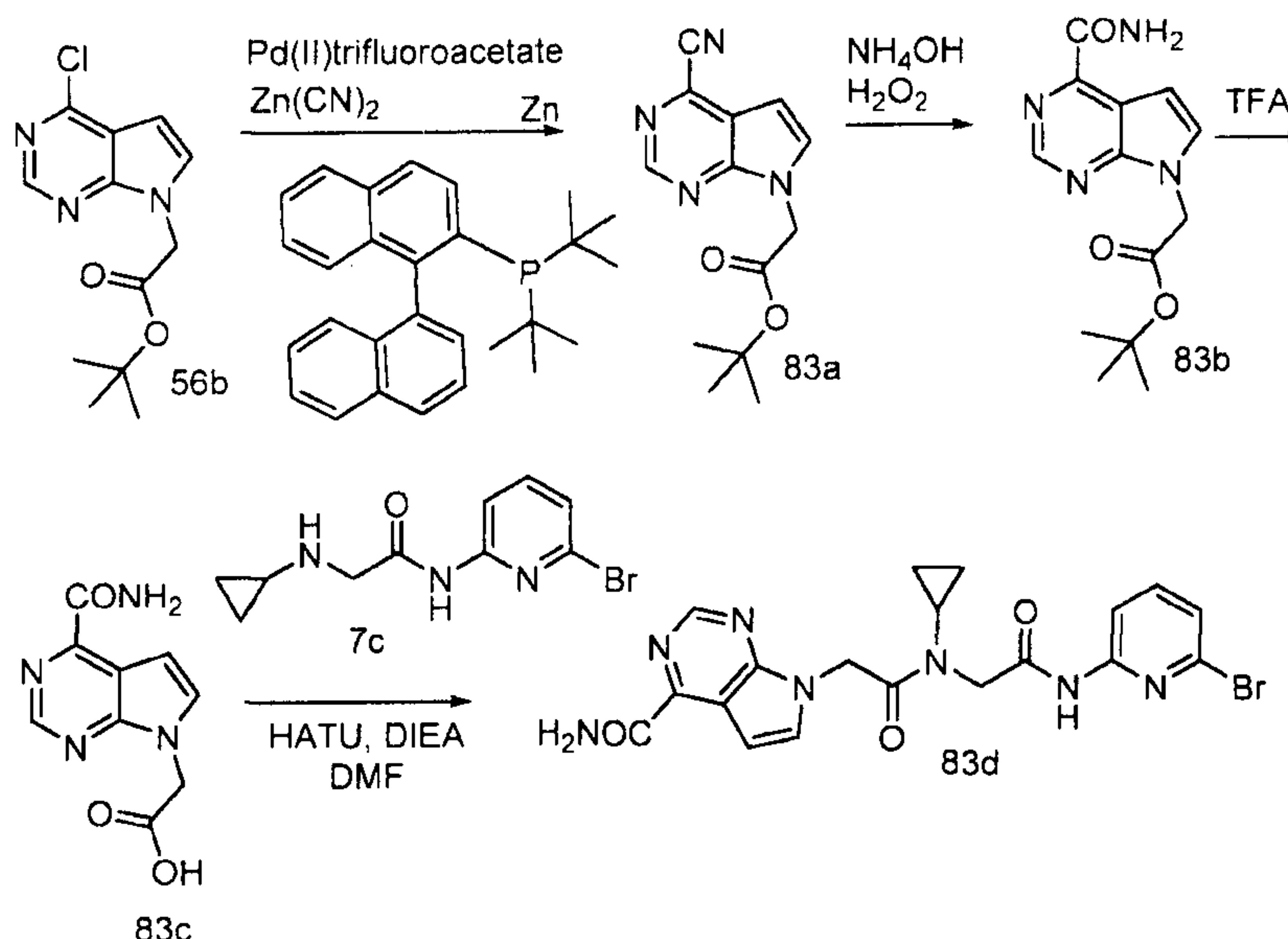
Step-3: Preparation of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-((2-cyanoethyl)(phenyl)amino)-N-isopropylacetamide (**82d**)

- 5 Reaction of 2-((2-cyanoethyl)(phenyl)amino)acetic acid (**82c**) (110 mg, 0.544 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**35b**) (141 mg, 0.54 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-((2-cyanoethyl)(phenyl)amino)-N-isopropylacetamide (**82d**) which was used as such in the next step; MS (ES⁻): 443.5 (M-1).

- 10 Step-4: Preparation of 3-((2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)(phenyl)amino)propanamide (**82e**)

- Reaction of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-((2-cyanoethyl)(phenyl)amino)-N-isopropylacetamide (**82d**) (242 mg, 0.54 mmol) in ethanol (5 mL) using aq. NH₄OH (2.12 mL, 54.4 mmol) and H₂O₂ (aq. 35%, 0.95 mL, 10.88 mmol) according to the procedure reported in Scheme 65 gave after workup and purification by flash column chromatography [First column: silica gel (24 g), eluting with MeOH in CHCl₃ 0-30%; Second column: Silica gel (12 g), eluting with MeOH in CHCl₃ 0-10%] 3-((2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)(phenyl)amino)propanamide (**82e**) (53 mg, 0.11 mmol, 21% yield) as an off-white solid in the form of mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.70 (t, *J* = 5.8 Hz) and 8.28 (t, *J* = 6.0 Hz) (2t, 1H), 7.56 – 7.31 (m, 3H), 7.30 – 7.15 (m, 1H), 7.15 – 7.03 (m, 2H), 6.82 (bs, 1H), 6.70 – 6.49 (m, 3H), 4.67 – 4.52 and 4.19 – 4.05 (m, 1H), 4.46 – 4.30 (m, 2H), 4.30 and 4.14 (2s, 2H), 4.01 and 3.79 (2s, 2H), 3.57 – 3.44 (m, 2H), 2.41 – 2.31 (m, 2H), 1.18 (d, *J* = 6.4 Hz) and 0.97 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.30, -121.90; MS (ES⁺): 463.5 (M+1), 485.5 (M+Na); MS (ES⁻): 461.5 (M-1), 497.5 (M+Cl).
- 15
- 20
- 25

Scheme 83



Preparation of 7-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carboxamide (**83d**)

Step-1: Preparation of tert-butyl 2-(4-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**83a**)

To a degassed solution of tert-butyl 2-(4-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**56b**) (0.54 g, 2.02 mmol) in DMA (10 mL) was added dicyanozinc (237 mg, 2.02 mmol), 1,1'-binaphthyl-2-yl-di-tert-butylphosphine (80 mg, 0.20 mmol), palladium(II)trifluoroacetate (34 mg, 0.10 mmol), Zn (66 mg, 1.01 mmol) and heated at 95 °C for 16 h. Mixture was cooled to room temperature, diluted with EtOAc (20 mL), filtered over Celite pad and washed with EtOAc (2x15 mL). The combined filtrate was washed with water (2 x 40 mL), brine, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica gel (24 g), eluting with EtOAc in hexanes 0 to 100%] to afford tert-butyl 2-(4-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**83a**) (80 mg, 0.31 mmol, 15% yield) as white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.00 (s, 1H), 8.01 (d, J = 3.7 Hz, 1H), 6.90 (d, J = 3.7 Hz, 1H), 5.14 (s, 2H), 1.41 (s, 9H); MS (ES⁻): 257.3 (M-1).

Step-2: Preparation of tert-butyl 2-(4-carbamoyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**83b**)

Reaction of tert-butyl 2-(4-cyano-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**83a**) (350 mg, 1.36 mmol) in ethanol (10 mL) using aq. NH₄OH (1.06 mL, 27.1 mmol) and H₂O₂ (aq. 35%, 0.42 mL, 13.55 mmol) according to the procedure reported in Scheme 65 gave after workup tert-butyl 2-(4-carbamoyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**83b**) (360 mg, 1.30 mmol, 96% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.87 (s, 1H), 8.33 (s,

1H), 7.88 (s, 1H), 7.76 (d, J = 3.6 Hz, 1H), 7.07 (d, J = 3.5 Hz, 1H), 5.09 (s, 2H), 1.41 (s, 9H); MS (ES+): 277.4 (M+1); MS (ES-): 275.3 (M-1).

Step-3: Preparation of 2-(4-carbamoyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetic acid (**83c**)

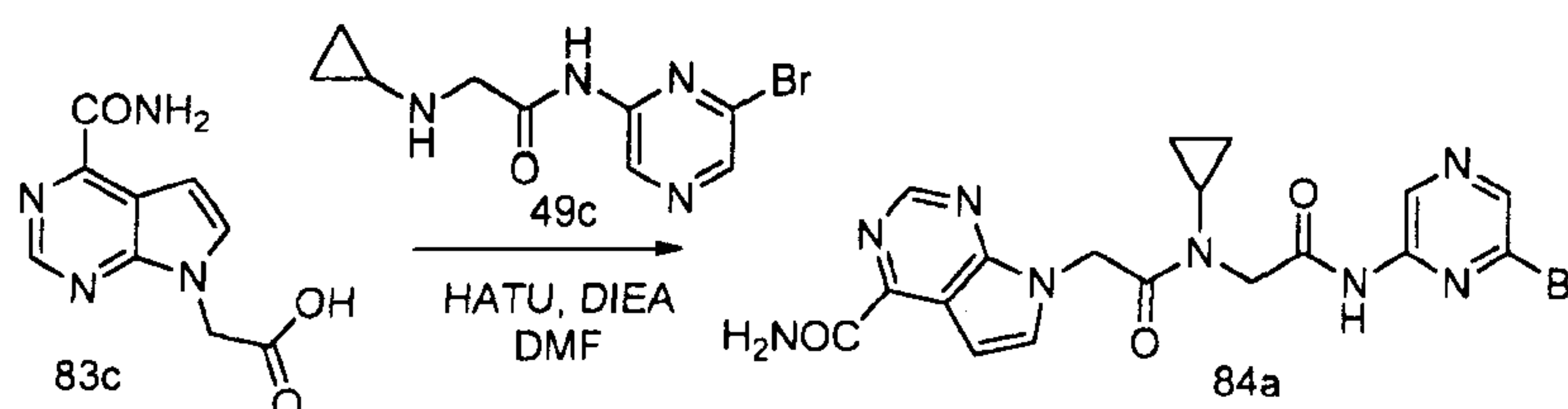
Reaction of tert-butyl 2-(4-carbamoyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**83b**) (340 mg, 1.23 mmol) with TFA (0.95 mL, 12.31 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup 2-(4-carbamoyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetic acid (**83c**) which was used as such in the next step; MS (ES+): 221.3 (M+1); MS (ES-): 219.2 (M-1).

Step-4: Preparation of 7-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-

10 oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carboxamide (**83d**)

Reaction of N-(6-bromopyridin-2-yl)-2-(cyclopropylamino)acetamide (**7c**) (70 mg, 0.26 mmol) with 2-(4-carbamoyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetic acid (**83c**) (57 mg, 0.26 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 40%] 7-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carboxamide (**83d**) (60 mg, 0.13 mmol, 49% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.94 (s, 1H), 8.86 (s, 1H), 8.31 (s, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.86 (s, 1H), 7.77 - 7.65 (m, 2H), 7.32 (dd, J = 7.7, 0.7 Hz, 1H), 7.05 (d, J = 3.5 Hz, 1H), 5.50 (s, 2H), 4.17 (s, 2H), 3.14 - 3.02 (m, 1H), 1.04 - 0.89 (m, 4H); MS (ES+): 472.5, 474.5 (M+1); MS (ES-): 470.4, 472.4 (M-1).

Scheme 84



Preparation of 7-(2-((2-((6-bromopyrazin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carboxamide (**84a**)

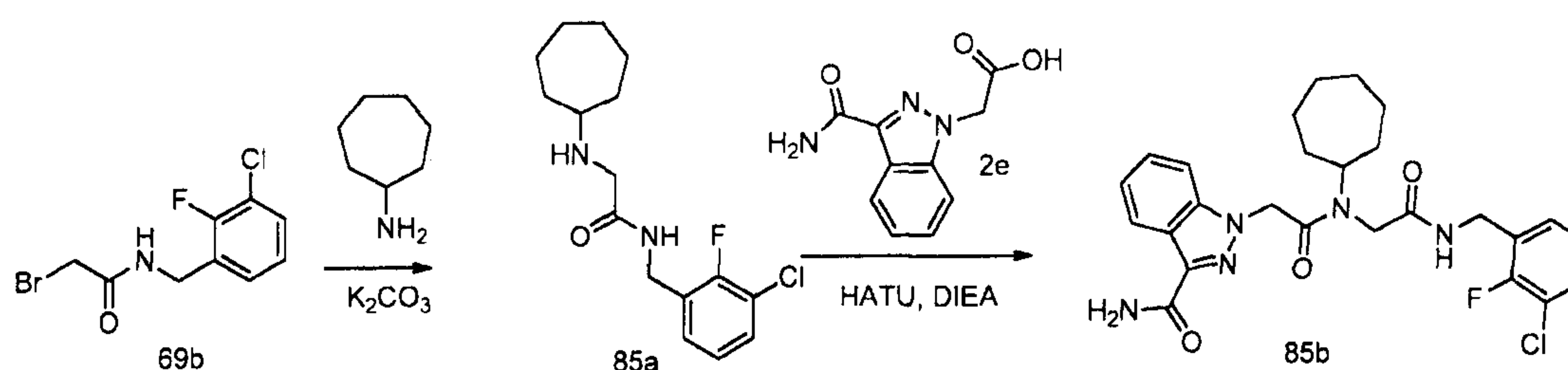
Reaction of N-(6-bromopyrazin-2-yl)-2-(cyclopropylamino)acetamide (**49c**) (70 mg, 0.26 mmol) with 2-(4-carbamoyl-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetic acid (**83c**) (57 mg, 0.26 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in

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CHCl₃ 0 to 40%] 7-(2-((2-((6-bromopyrazin-2-yl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-7H-pyrrolo[2,3-d]pyrimidine-4-carboxamide (**84a**) (55 mg, 0.12 mmol, 45% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.28 (s, 1H), 9.24 (s, 1H), 8.86 (s, 1H), 8.54 (s, 1H), 8.31 (s, 1H), 7.85 (s, 1H), 7.72 (d, *J* = 3.5 Hz, 1H), 7.05 (d, *J* = 3.5 Hz, 1H), 5.51 (s, 2H), 4.22 (s, 2H), 3.15 – 3.05 (m, 1H), 1.06 – 0.92 (m, 4H); MS (ES⁺): 473.4 and 475.4 (M+1); MS (ES⁻): 471.3 and 473.3 (M-1).

Scheme 85



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cycloheptyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**85b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(cycloheptylamino)acetamide (**85a**)
Reaction of 2-bromo-N-(3-chloro-2-fluorobenzyl)acetamide (**69b**) (313 mg, 1.12 mmol) with cycloheptanamine (0.17 mL, 1.34 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup N-(3-chloro-2-fluorobenzyl)-2-(cycloheptylamino)acetamide (**85a**) as a yellow oil which was used as such without further purification; MS (ES⁺): 313.4 (M+1); MS (ES⁻): 311.4 (M-1), 347.4 (M+Cl).

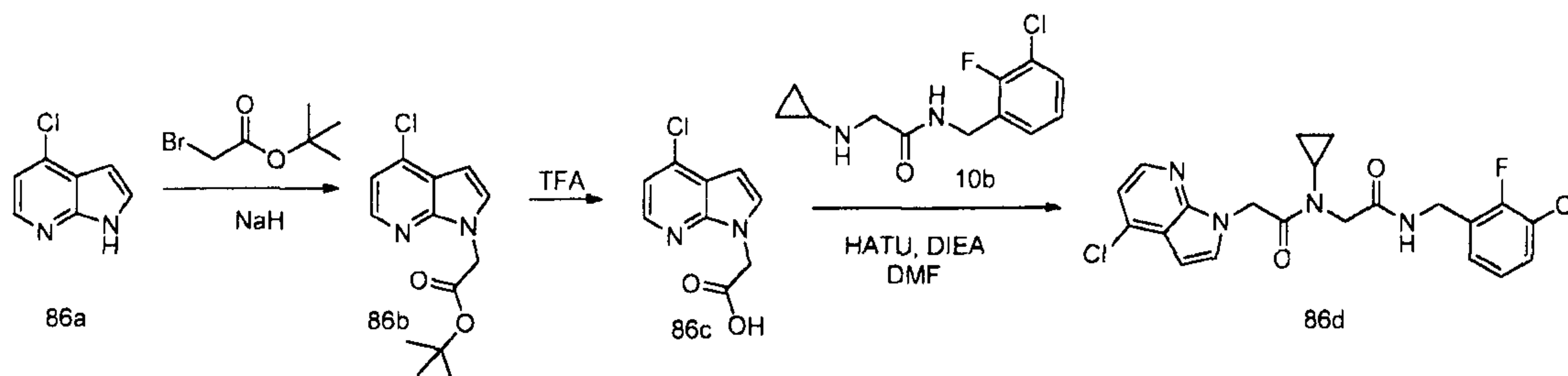
Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cycloheptyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**85b**)
Reaction of N-(3-chloro-2-fluorobenzyl)-2-(cycloheptylamino)acetamide (**85a**) (347 mg, 1.12 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (365 mg, 1.66 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (40 g), eluting with MeOH in CHCl₃ 0 to 10%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cycloheptyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**85b**) (136 mg, 0.27 mmol, 24% yield) as an off-white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.85 (t, *J* = 5.8 Hz) & 8.37 (t, *J* = 5.9 Hz) (2t, 1H), 8.23 – 8.13 (m, 1H), 7.70 (s, 1H), 7.65 – 7.35 (m, 5H), 7.32 – 6.96 (m, 2H), 5.59 & 5.46 (s, 2H), 4.46 (d, *J* = 5.6 Hz) & 4.31 (d, *J* = 5.7 Hz) (2d, 2H), 4.27 – 4.21 & 3.98 – 3.87 (m, 1H), 4.19 & 3.82 (2s, 2H), 1.69 – 1.40 (m, 11H), 1.36 – 1.23 (m, 1H); ¹⁹F NMR (282

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MHz, DMSO-*d*₆) δ -121.10, -121.72; MS (ES⁺): 514.8 and 516.7 (M+1), 536.7 and 538.6 (M+Na); MS (ES⁻): 512.3, 514.6 (M-1), 548.5 (M+Cl).

Scheme 86



- 5 Preparation of 2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**86d**)

Step-1: Preparation of tert-butyl 2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)acetate (**86b**)

Reaction of 4-chloro-1H-pyrrolo[2,3-b]pyridine (**86a**) (2.0 g, 13.11 mmol) with *tert*-butyl 2-bromoacetate (2.32 mL, 15.73 mmol) according to the procedure reported in step-1 of

- 10 Scheme 56 gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane 0 to 50%] tert-butyl 2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)acetate (**86b**) (3 g, 11.25 mmol, 86% yield) as a colorless oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.21 (d, *J* = 5.2 Hz, 1H), 7.66 (d, *J* = 3.6 Hz, 1H), 7.26 (d, *J* = 5.2 Hz, 1H), 6.56 (d, *J* = 3.6 Hz, 1H), 5.05 (s, 2H), 1.40 (s, 9H).

- 15 Step-2: Preparation of 2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)acetic acid (**86c**)

Reaction of tert-butyl 2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)acetate (**86b**) (1.5 g, 5.62 mmol) with TFA (4.33 mL, 56.2 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup 2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)acetic acid (**86c**)

- 20 (940 mg, 4.46 mmol, 79% yield) as light orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.08 (s, 1H), 8.20 (d, *J* = 5.2 Hz, 1H), 7.67 (d, *J* = 3.6 Hz, 1H), 7.26 (d, *J* = 5.2 Hz, 1H), 6.56 (d, *J* = 3.6 Hz, 1H), 5.06 (s, 2H); MS (ES⁺): 211.2 (M+1); (ES⁻) 209.1 (M-1).

Step-3: Preparation of 2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**86d**)

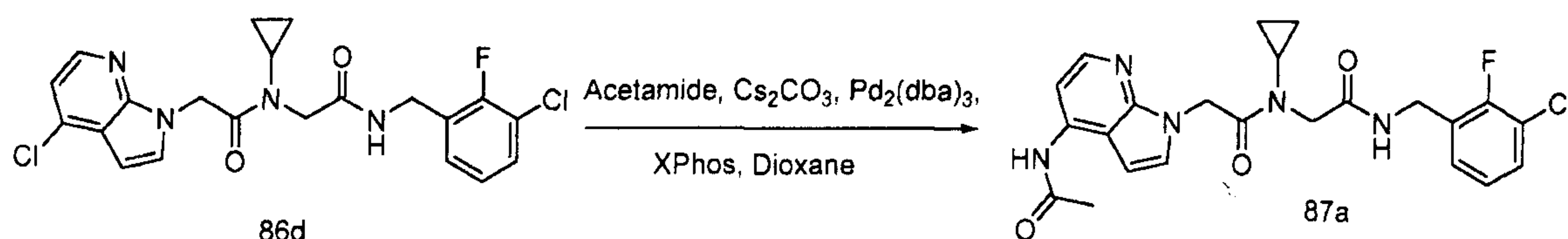
- 25 Reaction of 2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)acetic acid (**86c**) (330 mg, 1.57 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (402 mg, 1.57 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (24 g), eluting with MeOH-EtOAc (1:9) in hexanes 0 to 70%] 2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-

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2-oxoethyl)-N-cyclopropylacetamide (**86d**) (580 mg, 1.29 mmol, 82% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.45 (t, J = 5.8 Hz, 1H), 8.18 (d, J = 5.2 Hz, 1H), 7.61 (d, J = 3.6 Hz, 1H), 7.47 (td, J = 7.6, 1.8 Hz, 1H), 7.29 - 7.18 (m, 2H), 7.18 - 7.10 (m, 1H), 6.56 (d, J = 3.5 Hz, 1H), 5.44 (s, 2H), 4.33 (d, J = 5.7 Hz, 2H), 3.97 (s, 2H), 3.09 - 2.98 (m, 1H), 1.05 - 0.87 (m, 4H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.61; MS (ES $^-$): 447.3 and 449.5 (M-1), 483.4 and 485.4 (M+Cl).

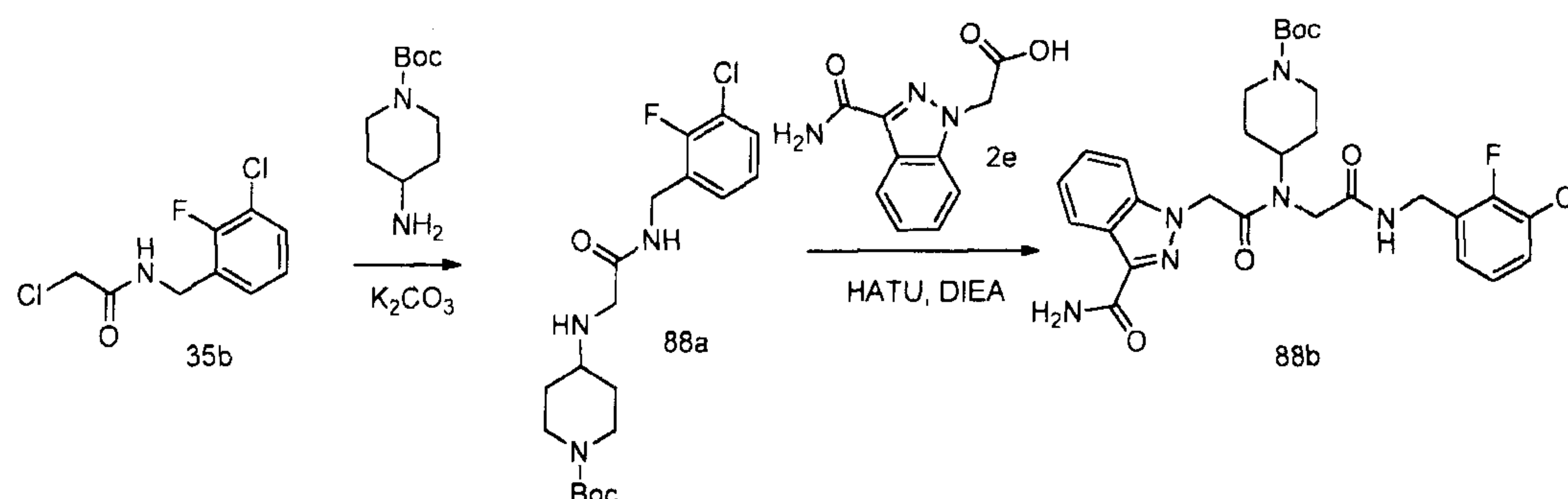
Scheme 87



Preparation of 2-(4-acetamido-1H-pyrrolo[2,3-b]pyridin-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**87a**)

To a degassed solution of 2-(4-chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**86d**) (300 mg, 0.67 mmol) in dioxane (10 mL) was added cesium carbonate (326 mg, 1.0 mmol), acetamide (79 mg, 1.34 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (32 mg, 0.067 mmol), $\text{Pd}_2(\text{dba})_3$ (31 mg, 0.033 mmol) and heated at 80 °C for 16 h. The mixture was cooled to room temperature, diluted with EtOAc (5 mL), filtered over Celite pad and pad was washed with EtOAc (2 x 5 mL). The filtrate was washed with water (2 x 30 mL), brine, dried, filtered and concentrated in vacuum. The residue was purified by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl_3 0 to 40%] to afford 2-(4-acetamido-1H-pyrrolo[2,3-b]pyridin-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**87a**) (105 mg, 0.22 mmol, 33% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 10.05 (s, 1H), 8.44 (t, J = 5.9 Hz, 1H), 8.06 (d, J = 5.4 Hz, 1H), 7.83 (d, J = 5.4 Hz, 1H), 7.51 - 7.41 (m, 1H), 7.35 (d, J = 3.6 Hz, 1H), 7.27 - 7.07 (m, 2H), 6.82 (d, J = 3.6 Hz, 1H), 5.37 (s, 2H), 4.33 (d, J = 5.8 Hz, 2H), 3.97 (s, 2H), 3.09 - 2.97 (m, 1H), 2.20 (s, 3H), 1.03 - 0.84 (m, 4H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.62; MS (ES $^+$) 472.5 (M+1); MS (ES $^-$): 470.5 (M-1), 506.5 (M+Cl).

Scheme 88



Preparation of tert-butyl 4-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)piperidine-1-carboxylate (**88b**)

Step-1: Preparation of tert-butyl 4-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)piperidine-1-carboxylate (**88a**)

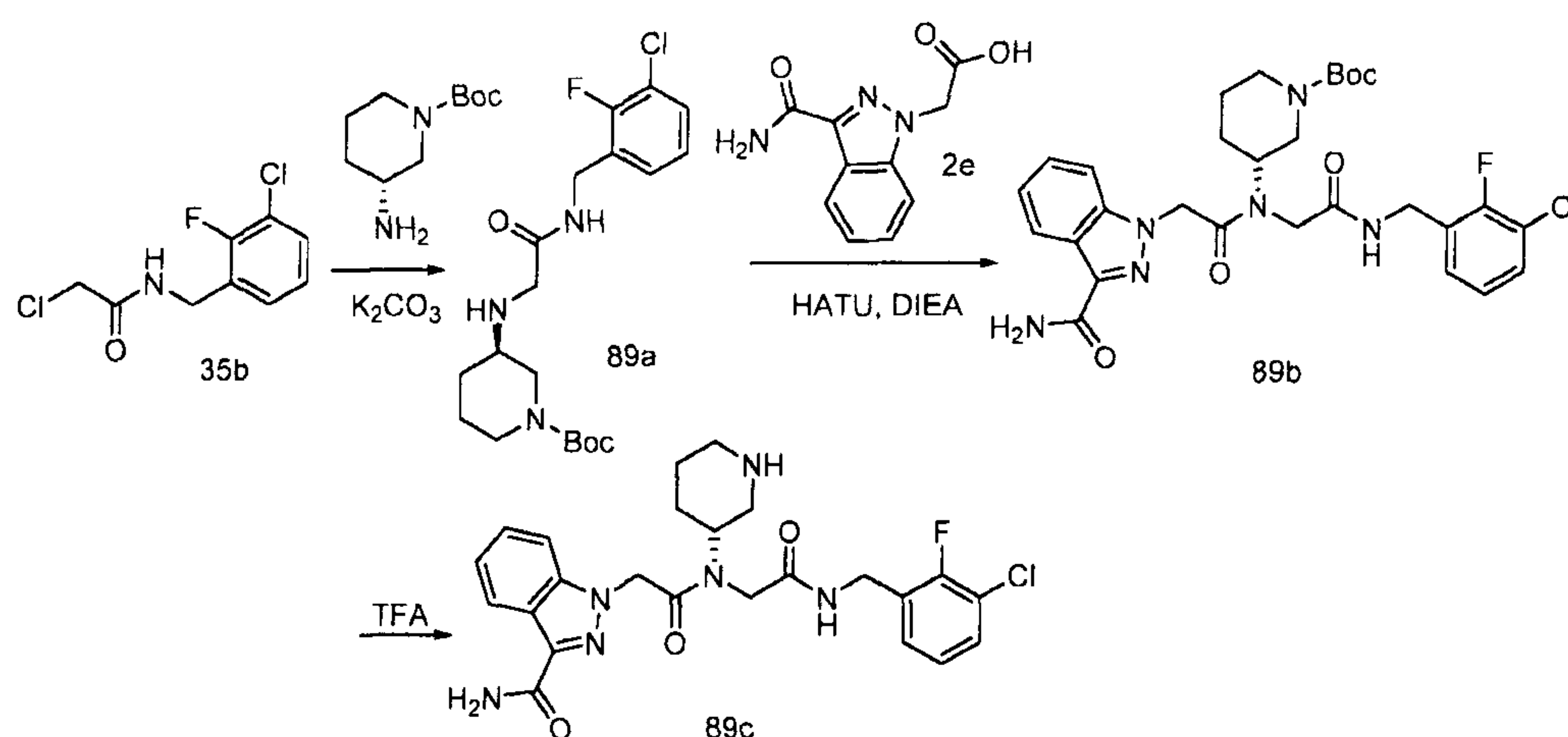
5 Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 5.3 mmol) with tert-butyl 4-aminopiperidine-1-carboxylate (1.06 g, 5.3 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] tert-butyl 4-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)piperidine-1-carboxylate (**88a**) (762 mg, 1.91 mmol, 90 %) as a clear oil. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.38 (t, *J* = 6.1 Hz, 1H), 7.53 – 7.40 (m, 1H), 7.34 – 7.23 (m, 1H), 7.23 – 7.14 (m, 1H), 4.36 (d, *J* = 6.0 Hz, 2H), 3.79 (d, *J* = 13.1 Hz, 2H), 3.16 (s, 2H), 2.87 – 2.63 (m, 2H), 2.48 – 2.40 (m, 1H), 2.27 (s, 1H), 1.79 – 1.64 (m, 2H), 1.38 (s, 9H), 1.20 – 1.01 (m, 2H); MS (ES⁺): 400.5 (M+1); MS (ES⁻): 398.4 (M-1).

Step-2: Preparation of tert-butyl 4-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)piperidine-1-carboxylate (**88b**)

Reaction of tert-butyl 4-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)piperidine-1-carboxylate (**88a**) (660 mg, 1.65 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (398 mg, 1.82 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] tert-butyl 4-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)piperidine-1-carboxylate (**88b**) (442 mg, 0.74 mmol, 45% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.78 (t, *J* = 5.7 Hz) and 8.36 (t, *J* = 5.8 Hz) (2t, 1H), 8.18 (m, 1H), 7.71 (m, 1H), 7.60 – 7.06 (m, 7H), 5.67 and 5.48 (2s, 2H), 4.46 (d, *J* = 3.7 Hz) and 4.31 (d, *J* = 4.9 Hz) (2d, 2H), 4.21 and 3.86 (2s, 2H), 4.37-3.90 (m, 3H), 2.77 (m, 2H), 1.40 (m, 13H); ¹⁹F NMR (282 MHz, DMSO) δ -121.12, -121.67;

MS (ES⁺): 623.6 & 625.7 (M+Na); [based on NMR, this compound is a mixture of rotamers 2:1 ratio].

Scheme 89



- 5 Preparation of (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(piperidin-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**89c**)

Step-1: Preparation of (R)-tert-butyl 3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)piperidine-1-carboxylate (**89a**)

- Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 5.3 mmol) with
 10 (R)-tert-butyl 3-aminopiperidine-1-carboxylate (1.06 g, 5.3 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] (R)-tert-butyl 3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)piperidine-1-carboxylate (**89a**) (850 mg, 2.13 mmol, 100%) as a yellow oil; MS (ES⁺): 400.5 (M+1); MS (ES⁻): 398.4
 15 (M-1).

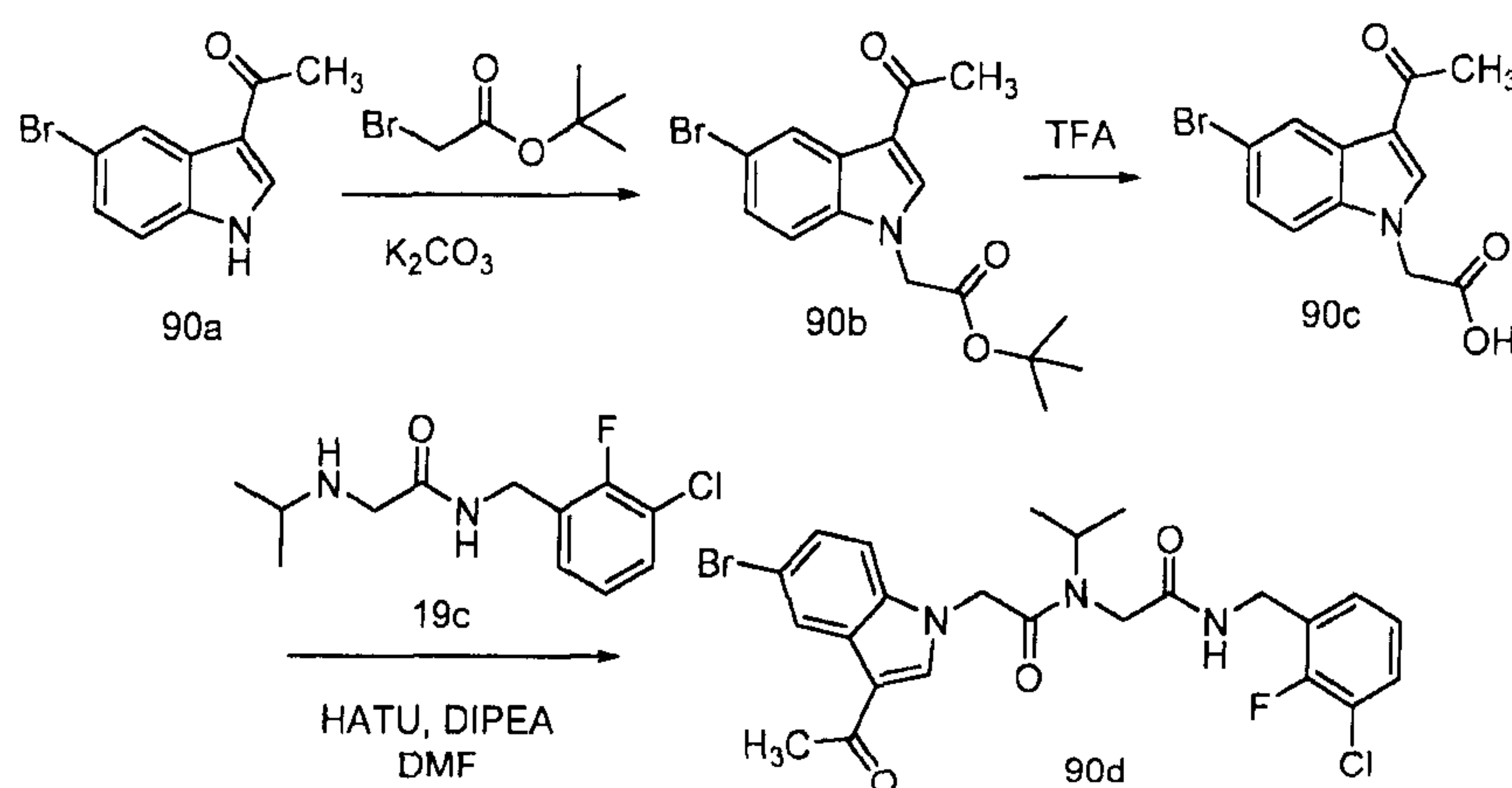
Step-2: Preparation of (R)-tert-butyl 3-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)piperidine-1-carboxylate (**89b**)

- Reaction of (R)-tert-butyl 3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)piperidine-1-carboxylate (**89a**) (710 mg, 1.78 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (428 mg, 1.95 mmol) according to the procedure reported in
 20 step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] (R)-tert-butyl 3-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)piperidine-1-carboxylate (**89b**) (520 mg, 0.87 mmol, 49% yield) as a white solid. MS (ES⁺): 602.6 (M+1).

Step-3: Preparation of (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(piperidin-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**89c**)

Reaction of (R)-tert-butyl 3-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)piperidine-1-carboxylate (**89b**) (495 mg, 0.82 mmol) with TFA (0.32 mL, 4.12 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(piperidin-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**89c**) (300 mg, 0.6 mmol, 73% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.82 (t, *J* = 5.6 Hz) and 8.37 (t, *J* = 5.9 Hz) (2t, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.78 – 7.64 (m, 1H), 7.63 – 7.03 (m, 7H), 5.75 – 5.51 (m) and 5.45 (s) (2H), 4.52 – 4.38 (m, 1H), 4.31 (d, *J* = 5.7 Hz) and 4.22 (d, *J* = 4.6 Hz) (2d, 2H), 4.17 – 4.04 and 3.85-3.75 (2m, 1H), 3.89 and 3.17 (2s, 2H), 3.12 – 2.65 (m, 2H), 2.45 – 2.18 (m, 2H), 1.96 – 1.25 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -73.45 (TFA peak), -121.17, -121.70; MS (ES⁺) 501.5 (M+1); 499.5 (M-1); [based on NMR, this compound is a mixture of rotamers 2:1 ratio].

Scheme 90



Preparation of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**)

Step-1: Preparation of tert-butyl 2-(3-acetyl-5-bromo-1H-indol-1-yl)acetate (**90b**)

Reaction of 1-(5-bromo-1H-indol-3-yl)ethanone (**90a**) (prepared according to the procedure reported By Denis, Jean-Noel et al in PCT Int. Appl., WO 2013/014102, 8.24 g, 34.6 mmol) with *tert*-butyl 2-bromoacetate (6.14 mL, 41.5 mmol) according to the procedure reported in step-1 of Scheme 56 gave after workup tert-butyl 2-(3-acetyl-5-bromo-1H-indol-1-yl)acetate (**90b**) (11.26 g, 32.0 mmol, 92% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆)

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δ 8.38 (s, 1H), 8.35 – 8.29 (m, 1H), 7.54 – 7.36 (m, 2H), 5.14 (s, 2H), 2.44 (s, 3H), 1.43 (s, 9H); MS (ES⁺): 352.2, 354.3 (M+2), 374.4, 376.3 (M+Na); (ES⁻): 350.3, 352.3 (M-2), 386.3, 388.3 (M+Cl).

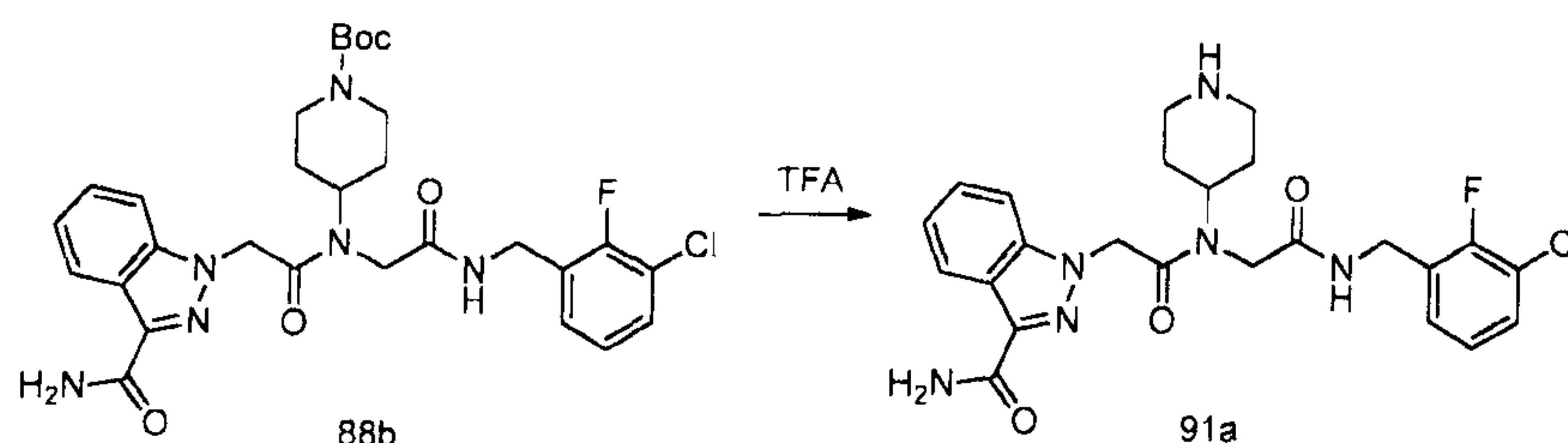
Step-2: Preparation of 2-(3-acetyl-5-bromo-1H-indol-1-yl)acetic acid (**90c**)

5 Reaction of tert-butyl 2-(3-acetyl-5-bromo-1H-indol-1-yl)acetate (**90b**) (11.15 g, 31.7 mmol) with TFA (48.8 mL, 633 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup 2-(3-acetyl-5-bromo-1H-indol-1-yl)acetic acid (**90c**) (11.38 g, 38.4 mmol, 88% yield) as a pink solid in the form of TFA adduct; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.33 (bs, 1H, D₂O exchangeable), 8.40 (s, 1H), 8.32 (d, *J* = 2.0 Hz, 1H), 7.54 (d, *J* = 8.8, 1H), 7.40 (dd, *J* = 8.7, 2.0 Hz, 1H), 5.15 (s, 2H), 2.44 (s, 3H); MS (ES⁺): 296.2, 298.2 (M+2); (ES⁻) 294.2, 296.2 (M-2).

Step-3: Preparation of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**)

Reaction of 2-(3-acetyl-5-bromo-1H-indol-1-yl)acetic acid (**90c**) (1.6 g, 5.4 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (1.4 g, 5.4 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (40 g), eluting with MeOH in CHCl₃ 0-100%] 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**) (1.67 g, 3.11 mmol, 58% yield) as a pale yellow solid as of mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.83 (t, *J* = 5.7 Hz, 1H), 8.36 – 8.28 (m, 2H, another triplet of amide proton of one of the two rotamers were overlapped in this region), 7.56 – 7.29 (m, 4H), 7.22 (td, *J* = 7.9, 1.1 Hz) & 6.99 (td, *J* = 7.9, 1.1 Hz) (2td, 1H), 5.37 & 5.18 (2s, 2H), 4.65 – 4.51 & 4.27 – 4.18 (2m, 1H), 4.47 (d, *J* = 5.6 Hz) & 4.33 (d, *J* = 5.8 Hz) (2d, 2H), 4.17 & 3.84 (2s, 2H), 2.44 & 2.42 (2s, 3H), 1.25 (d, *J* = 6.4 Hz) & 0.99 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.19, -121.76; MS (ES⁺): 536.49 and 538.49 (M+1), 558.5 and 560.5 (M+Na); (ES⁻): 534.36 and 536.41 (M-1), 570.4 and 572.4 (M+Cl).

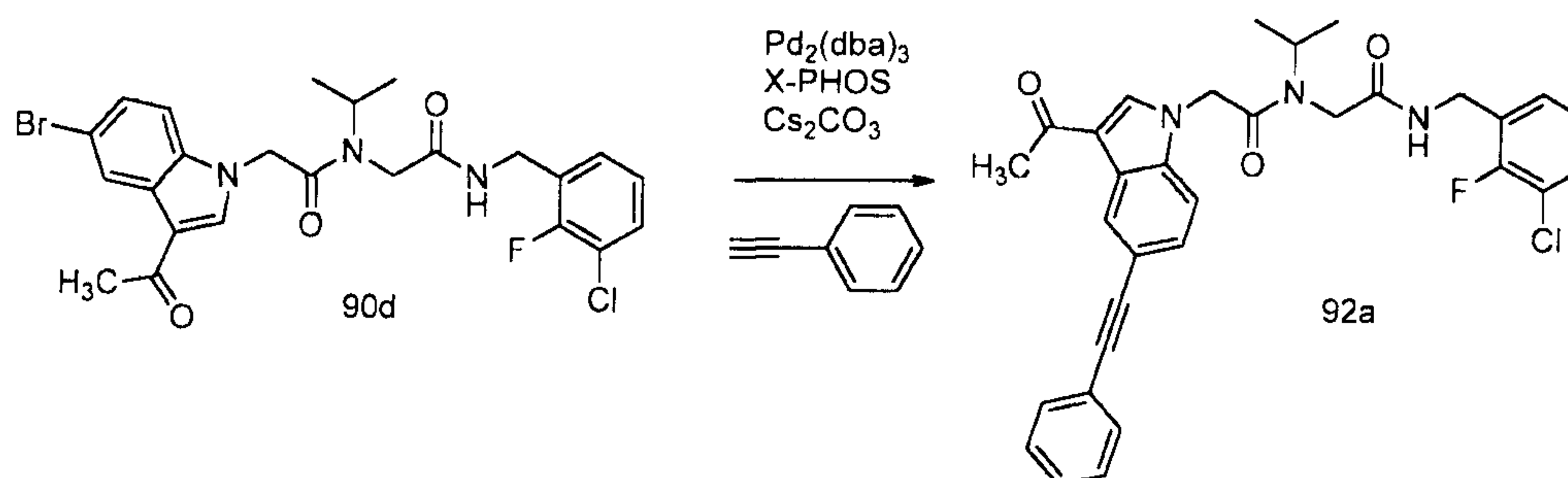
Scheme 91



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(piperidin-4-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**91a**)

Reaction of tert-butyl 4-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)piperidine-1-carboxylate (**88b**) (500 mg, 0.92 mmol) with TFA (0.35 mL, 4.58 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(piperidin-4-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**91a**) (386 mg, 0.77 mmol, 84% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.89 (t, *J* = 5.6 Hz) and 8.42 (t, *J* = 5.9 Hz) (2t, 1H), 8.23 – 8.12 (m, 1H), 7.77 – 7.64 (m, 1H), 7.64 – 7.04 (m, 7H), 5.65 and 5.44 (s, 2H), 4.47 (d, *J* = 5.4 Hz) and 4.32 (d, *J* = 5.7 Hz) (2d, 2H), 4.21 and 3.84 (2s, 2H), 4.32-4.30 and 4.12 – 3.95 (2m, 1H), 3.22 – 3.01 (m, 2H), 2.85 – 2.69 and 2.69 – 2.56 (2m, 2H), 1.94 – 1.40 (m, 4H); ¹⁹F NMR (282 MHz, DMSO) δ -73.53 (TFA peak), -121.18, -121.66; MS (ES⁺): 501.6 (M+1); 499.5 (M-1); [based on NMR, this compound is a mixture of rotamers 3:2 ratio].

Scheme 92

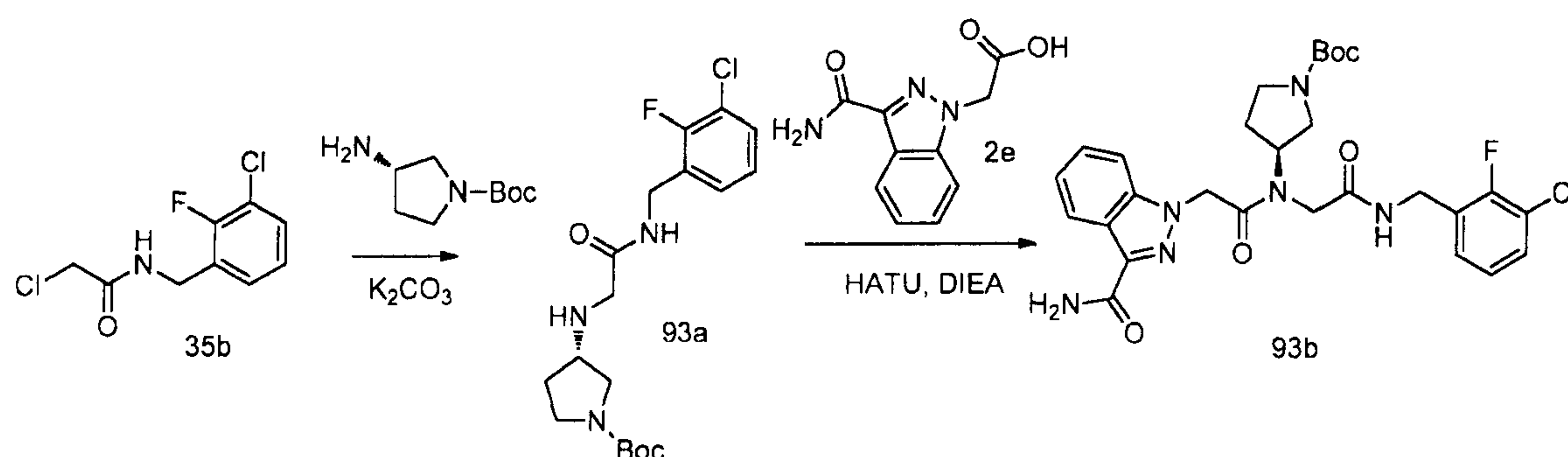


Preparation of 2-(3-acetyl-5-(phenylethynyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**92a**)

A solid mixture of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**) (113 mg, 0.21 mmol), Cs₂CO₃ (69 mg, 0.21 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (X-PHOS, 20 mg, 0.04 mmol), Pd₂(dba)₃ (19 mg, 0.02 mmol) was purged with positive flow of nitrogen for 10 min, then added phenylacetylene (0.023 mL, 0.21 mmol) and anhydrous toluene (10 mL) under a positive flow of nitrogen. The reaction flask was heated at 90 °C for 8 h. The reaction mixture was diluted with EtOAc (50 mL), filtered through a Celite pad, subsequently pad was rinsed with EtOAc (3 x 20 mL). The filtrate was washed with brine, dried, filtered and evaporated to dryness. The residue was purified by flash column chromatography [silica gel (24 g), eluting with MeOH in CHCl₃ 0 to 20%] to afford 2-(3-acetyl-5-(phenylethynyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**92a**)

(63 mg, 54% yield) as a brown solid as a mixture of two rotamers; ^1H NMR (300 MHz, DMSO- d_6) δ 8.84 (t, $J = 5.7$ Hz) and 8.43 – 8.26 (m) (3H), 7.63 – 7.34 (m, 9H), 7.30 – 6.96 (m, 1H), 5.39 & 5.21 (2s, 2H), 4.67 – 4.53 & 4.32 – 4.19 (2m, 1H), 4.48 (d, $J = 5.9$ Hz) & 4.34 (d, $J = 5.8$ Hz) (2d, 2H), 4.19 & 3.86 (2s, 2H), 2.46 & 2.44 (2s, 3H), 1.26 (d, $J = 6.4$ Hz) & 1.01 (d, $J = 6.8$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.18, -121.77; MS (ES+): 558.7 & 560.6 (M+1); (ES-): 556.6 & 558.6 (M-1).

Scheme 93



Preparation of (S)-tert-butyl 3-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)pyrrolidine-1-carboxylate (**93b**)

Step-1: Preparation of (S)-tert-butyl 3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)pyrrolidine-1-carboxylate (**93a**)

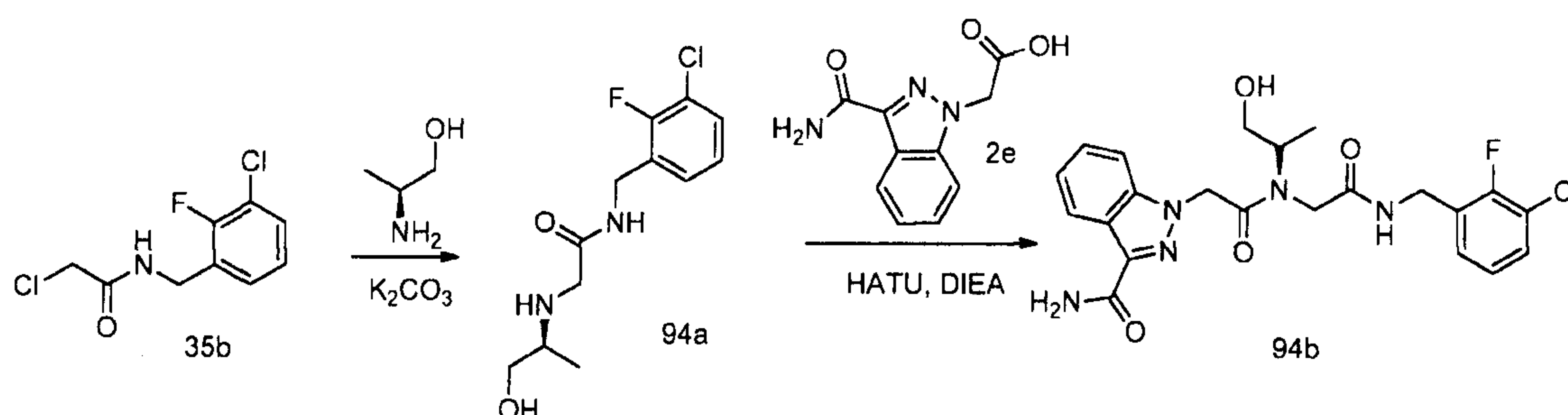
Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (350 mg, 1.48 mmol) with (S)-tert-butyl 3-aminopyrrolidine-1-carboxylate (690 mg, 3.71 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] (S)-tert-butyl 3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)pyrrolidine-1-carboxylate (**93a**) (500 mg, 1.3 mmol, 87%) as a yellow oil; MS (ES+): 386.5 (M+1).

Step-2: Preparation of (S)-tert-butyl 3-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)pyrrolidine-1-carboxylate (**93b**)

Reaction of (S)-tert-butyl 3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)pyrrolidine-1-carboxylate (**93a**) (300 mg, 0.78 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (187 mg, 0.86 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl_3 0 to 60%] (S)-tert-butyl 3-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)pyrrolidine-1-carboxylate (**93b**) (352 mg, 0.6 mmol, 77% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.83 (t, $J = 5.6$ Hz) and 8.44 (t, $J = 5.0$ Hz) (2t, 1H), 8.22 – 8.13 (m, 1H), 7.77 –

7.65 (m, 1H), 7.64 – 7.01 (m, 7H), 5.70 and 5.42 (2s, 2H), 4.84 – 4.63 (m, 1H), 4.47 (d, J = 5.1 Hz) and 4.31 (d, J = 5.7 Hz) (2d, 2H), 4.26 and 3.91 (2s, 2H), 3.46 – 2.95 (m, 2H), 2.19 – 1.80 (m, 2H), 1.41 and 1.37 (2s, 9H), 0.89 – 0.77 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -121.24, -121.68; MS (ES⁺): 587.6 (M+1); MS (ES⁻): 585.6 (M-1); [based on NMR, this compound is a mixture of rotamers]

Scheme 94



Preparation of (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-hydroxypropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**94b**)

Step-1: Preparation of (S)-N-(3-chloro-2-fluorobenzyl)-2-((1-hydroxypropan-2-yl)amino)acetamide (**94a**)

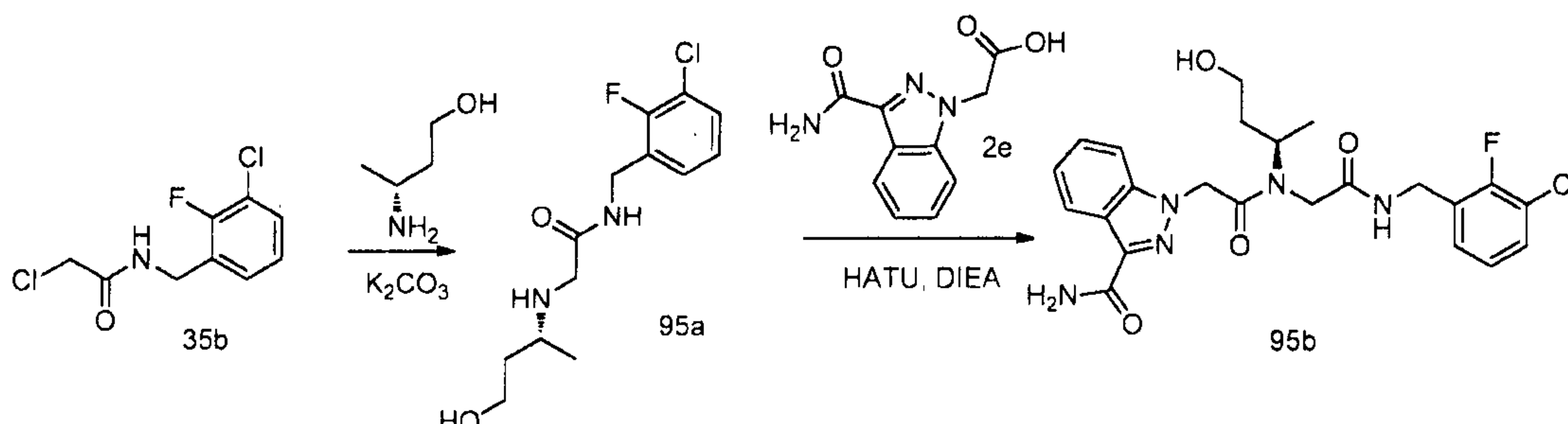
Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (350 mg, 1.48 mmol) with (S)-2-aminopropan-1-ol (278 mg, 3.71 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] (S)-N-(3-chloro-2-fluorobenzyl)-2-((1-hydroxypropan-2-yl)amino)acetamide (**94a**) (200 mg, 0.73 mmol, 49%) as a yellow oil; MS (ES⁺): 275.4, 277.4 (M+1, M+3).

Step-2: Preparation of (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-hydroxypropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**94b**)

Reaction of (S)-N-(3-chloro-2-fluorobenzyl)-2-((1-hydroxypropan-2-yl)amino)acetamide (**94a**) (200 mg, 0.73 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (176 mg, 0.8 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl_3 0 to 60%] (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-hydroxypropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**94b**) (210 mg, 0.44 mmol, 61% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 8.90 – 8.46 (m, 1H), 8.25 – 8.12 (m, 1H), 7.72 (s, 1H), 7.60 – 6.89 (m, 7H), 5.83 – 5.31 (m, 3H), 4.86 – 4.11 (m, 4H), 4.00 – 3.72 (m, 1H), 3.55 – 3.39 (m, 1H), 3.32 – 3.13 (m, 1H), 1.17 – 0.88 (m, 3H); ^{19}F NMR (282 MHz,

DMSO) δ -121.26, -121.65; MS (ES+): 476.5 (M+1); (ES-): 474.5 (M-1); [based on NMR, this compound is a mixture of rotamers]

Scheme 95



- 5 Preparation of (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(4-hydroxybutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**95b**)

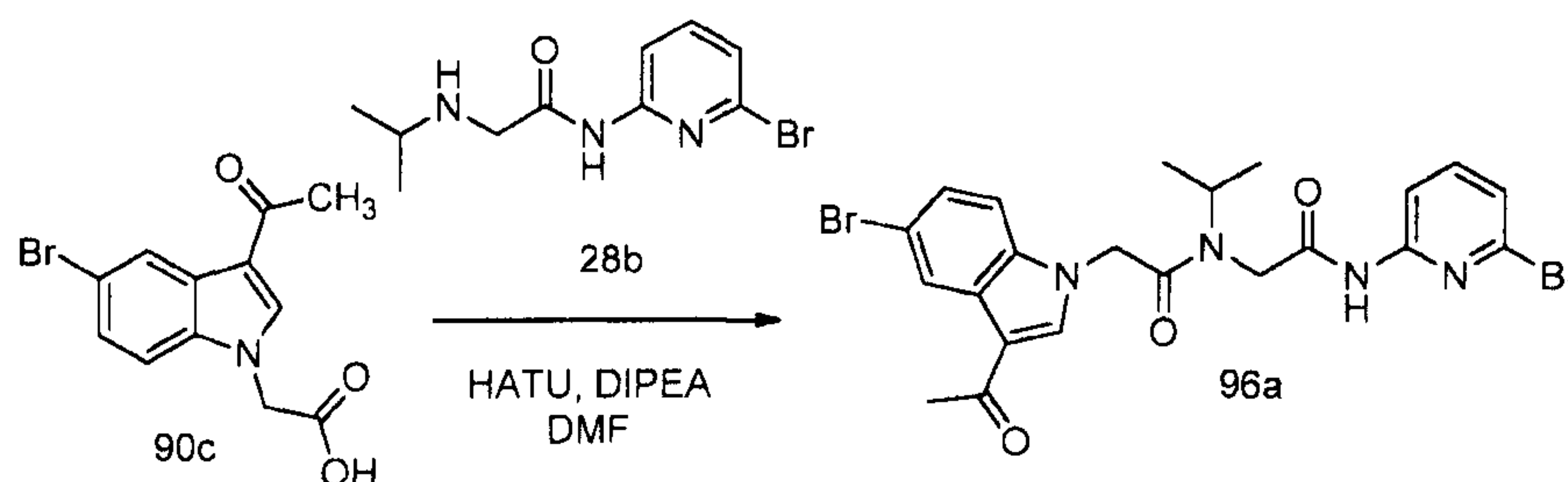
Step-1: Preparation of (R)-N-(3-chloro-2-fluorobenzyl)-2-((4-hydroxybutan-2-yl)amino)acetamide (**95a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 2.12 mmol) with
 10 (R)-3-aminobutan-1-ol (378 mg, 4.24 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] (R)-N-(3-chloro-2-fluorobenzyl)-2-((4-hydroxybutan-2-yl)amino)acetamide (**95a**) (150 mg, 0.52 mmol, 25%) as a yellow oil; MS (ES+): 289.4 (M+1); MS (ES-): 287.3 (M-1).

- 15 Step-2: Preparation of (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(4-hydroxybutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**95b**)

Reaction of (R)-N-(3-chloro-2-fluorobenzyl)-2-((4-hydroxybutan-2-yl)amino)acetamide (**95a**) (150 mg, 0.52 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (125 mg, 0.57 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and
 20 purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(4-hydroxybutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**95b**) (43 mg, 0.088 mmol, 17% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.90 – 8.46 (m, 1H), 8.25 – 8.12 (m, 1H), 7.72 (s, 1H), 7.60 – 6.89 (m, 7H), 5.83 – 5.31 and 4.86 – 4.11 and 4.00 – 3.72 (3m, 8H), 3.55 – 3.39 and 3.32 – 3.13 (2m, 2H), 1.17 – 0.88 (m, 3H); ¹⁹F NMR (282 MHz, DMSO) δ -
 25 121.26, -121.77; MS (ES+): 490.5 (M+1); (ES-): 488.5 (M-1); [based on NMR, this compound is a mixture of rotamers 1:1 ratio].

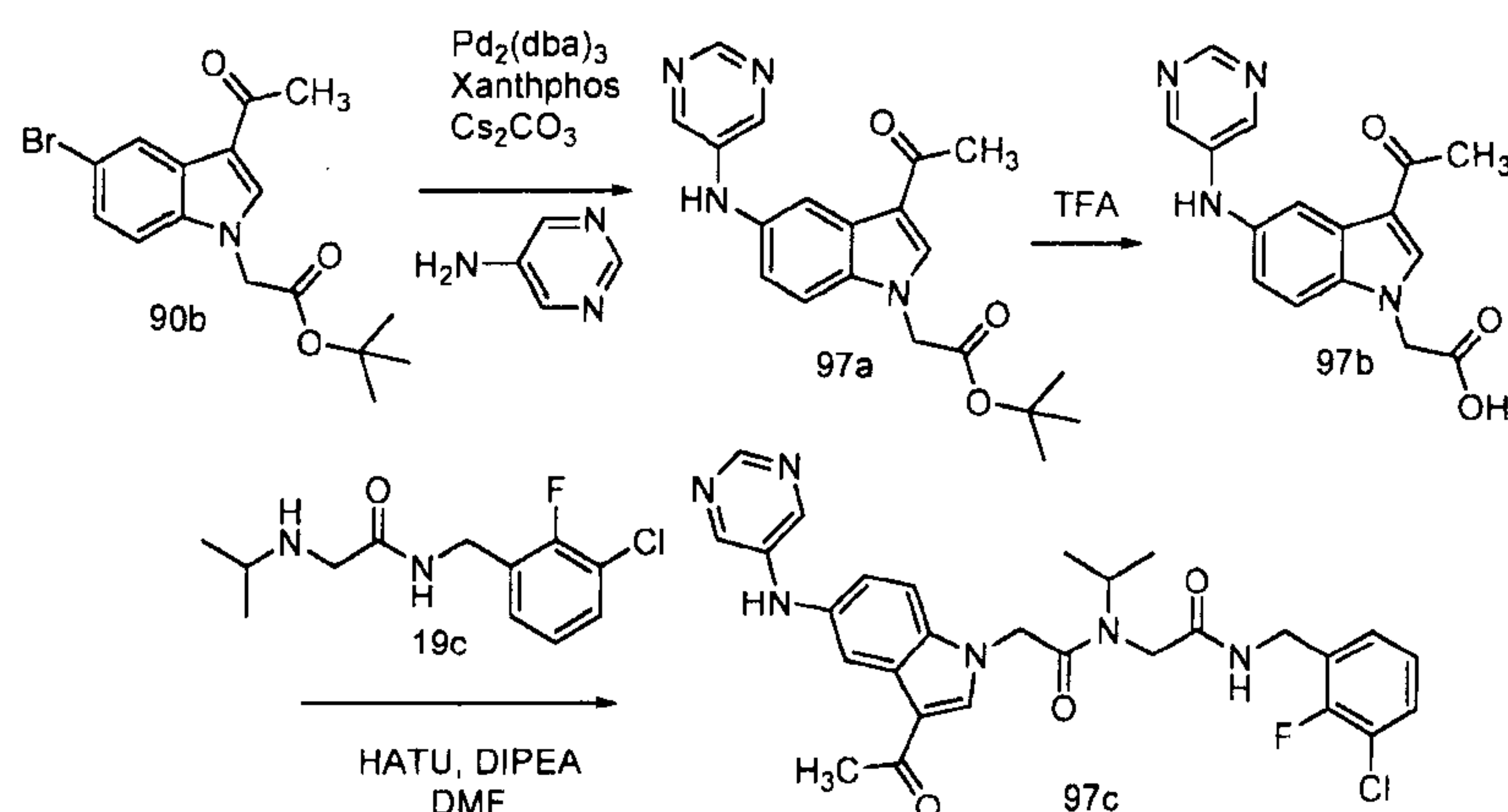
Scheme 96



Preparation of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**96a**)

- 5 Reaction of N-(6-bromopyridin-2-yl)-2-(isopropylamino)acetamide (**28b**) (1.1 g, 4.05 mmol) with 2-(3-acetyl-5-bromo-1H-indol-1-yl)acetic acid (**90c**) (1.2 g, 4.05 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**96a**) (1.5 g, 2.73 mmol, 67% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (as a mixture of
- 10 rotamers) δ 11.20 and 10.81 (2s, 1H), 8.36 – 8.28 (m, 2H), 8.17 and 8.01 (2d, *J* = 8.1 Hz, 1H), 7.81 and 7.70 (2t, *J* = 8.0 Hz, 1H), 7.48 – 7.27 (m, 3H), 5.41 and 5.20 (2s, 2H), 4.69 – 4.55 and 4.32-4.20 (2m, 1H), 4.42 and 4.04 (2s, 2H), 2.44 and 2.43 (2s, 3H), 1.26 and 1.03 (2d, *J* = 6.4 Hz, 6H); MS (ES⁺): 551.4, 553.4 (M+1); MS (ES⁻): 583.4, 585.4 (M+Cl).

Scheme 97



15

Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**97c**)

Step-1: Preparation of tert-butyl 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetate (**97a**)

- 20 To a degassed DMF (12 mL) in a sealed reactor were added tert-butyl 2-(3-acetyl-5-bromo-1H-indol-1-yl)acetate (**90b**) (1.05 g, 2.98 mmol), cesium carbonate (1.94 g, 5.96 mmol),

pyrimidin-5-amine (340 mg, 3.58 mmol), Pd₂(dba)₃ (273 mg, 0.3 mmol), (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (Xanthphos, 172 mg, 0.3 mmol) and heated with stirring at 100 °C for 16 h. The mixture was cooled to room temperature, diluted with EtOAc (30 mL) and filtered over Celite pad. The pad was washed with EtOAc (2 x 15 mL) and

5 combined filtrate was concentrated to give a crude residue which was purified by flash column chromatography [silica gel (40 g), eluting with CMA80 in CHCl₃ 0 to 20%] to afford tert-butyl 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetate (**97a**) (0.34 g, 0.93 mmol, 31% yield) as light yellow solid; MS (ES⁺): 367.5 (M+1), MS (ES⁻): 401.4 (M+Cl).

Step-2: Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**97b**)

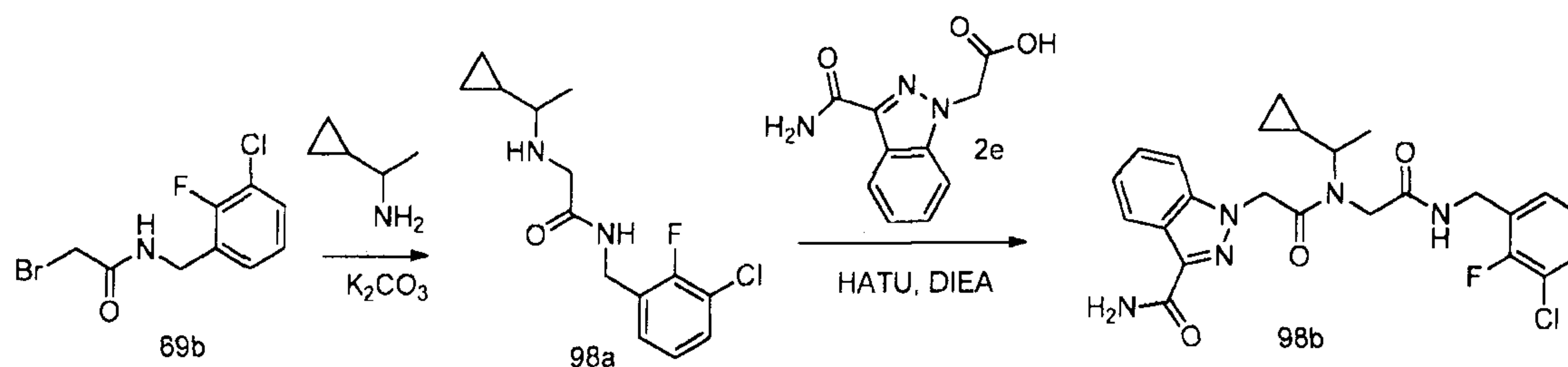
10 Reaction of tert-butyl 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetate (**97a**) (340 mg, 0.93 mmol) with TFA (1.43 mL, 18.56 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**97b**) (250 mg, 0.81 mmol, 87% yield) as light orange solid. ¹H NMR showed product as mixture of rotamers and data is corresponding to the major rotamer; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.7-13.1 (bs, 1H, D₂O exchangeable), 8.67 - 8.51 (m, 2H), 8.48 (s, 2H), 8.31 (s, 1H), 8.01 (d, *J* = 2.2 Hz, 1H), 7.48 (d, *J* = 8.8 Hz, 1H), 7.18 - 7.07 (m, 1H), 5.11 (s, 2H), 2.41 (s, 3H); MS (ES⁺) 311.4 (M+1), MS (ES⁻) 309.3 (M-1).

Step-3: Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**97c**)

20 Reaction of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**97b**) (80 mg, 0.26 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (67 mg, 0.26 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (12 g), eluting with CMA-80 in CHCl₃ 0-100%] 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**97c**) (68 mg, 0.12 mmol, 48% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (as a mixture of two rotamers) δ 8.83 and 8.35 (2t, *J* = 5.8 Hz, 1H), 8.57 and 8.56 (2s, 1H), 8.49 (s, 1H), 8.47 (s, 2H), 8.25 and 8.20 (2s, 1H), 8.00 (d, *J* = 2.2 Hz, 1H), 7.57 - 7.34 (m, 3H), 7.25 - 6.96 (m, 2H), 5.34 and 5.15 (2s, 2H), 4.69 - 4.51 and 4.28 - 4.21 (2m, 1H), 4.47 and 4.34 (2d, *J* = 5.6 Hz, 2H), 4.18 and 3.85 (2s, 2H), 2.41 and 2.40 (2s, 3H), 1.25 and 1.00 (2d, *J* = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) (as a mixture of two rotamers) δ -121.18 and -121.77; MS (ES⁺): 551.6 (M+1), MS (ES⁻): 549.5 (M-1).

30

Scheme 98



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-cyclopropylethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**98b**)

- 5 Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((1-cyclopropylethyl)amino)acetamide (**98a**)

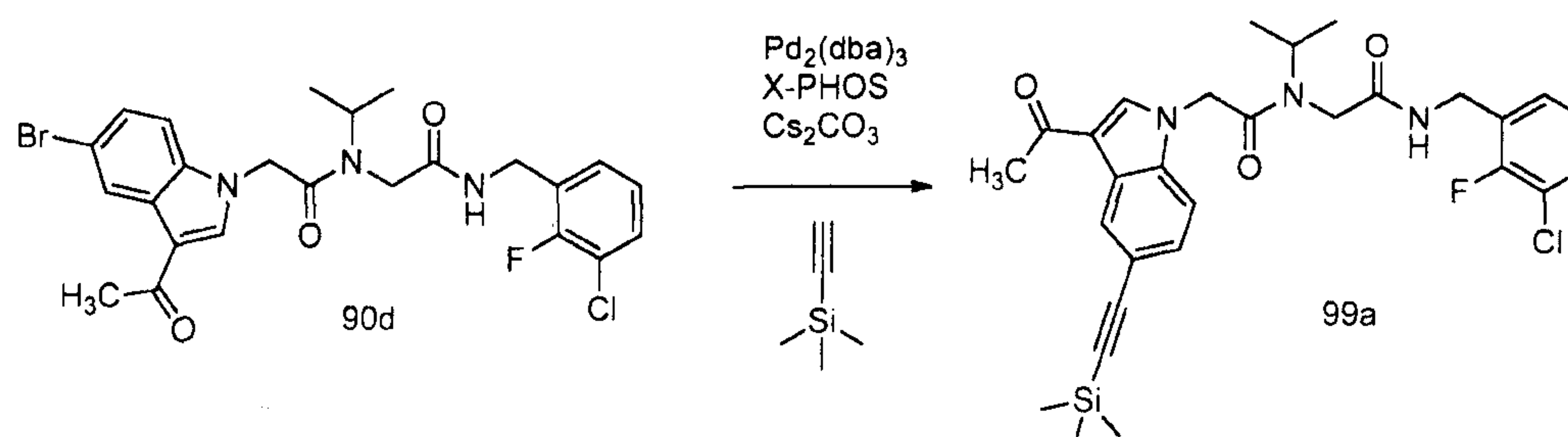
Reaction of 2-bromo-N-(3-chloro-2-fluorobenzyl)acetamide (**69b**) (307 mg, 1.09 mmol) with 1-cyclopropylethanamine (93 mg, 1.09 mmol) according to the procedure reported in step-2

- 10 of Scheme 35 gave after workup N-(3-chloro-2-fluorobenzyl)-2-((1-cyclopropylethyl)amino)acetamide (**98a**) as a yellow oil which was used as such without further purification; MS (ES⁺): 285.4 (M+1); MS (ES⁻): 283.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-cyclopropylethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**98b**)

- Reaction of N-(3-chloro-2-fluorobenzyl)-2-((1-cyclopropylethyl)amino)acetamide (**98a**) (312 mg, 1.1 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (288 mg, 1.32 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (40 g), eluting with MeOH in CHCl₃ 0 to 10%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-cyclopropylethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**98b**) (115 mg, 0.24 mmol, 22% yield) as a pale yellow solid as
- 20 a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.82 (t, *J* = 5.7 Hz) and 8.30 (t, *J* = 5.9 Hz) (2t, 1H), 8.22 – 8.13 (m, 1H), 7.74 and 7.70 (2s, 1H), 7.61 – 7.33 (m, 5H), 7.30 – 7.00 (m, 2H), 5.76 – 5.35 (m, 2H), 4.54 – 4.21 (m) and 3.96 (s) (4H), 3.80 – 3.46 (m, 1H), 1.27 (d, *J* = 6.4 Hz) and 1.02 (d, *J* = 6.8 Hz) (2d, 3H), 0.93 – 0.76 (m) and 0.64 – 0.37 (m) and 0.31 – 0.14 (m) and 0.13 – 0.02 (m) (5H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.19, -121.75; MS (ES⁺): 486.5 (M+1), 508.5 (M+Na); (ES⁻) 484.5 (M-1), 520.5 (M+Cl).
- 25

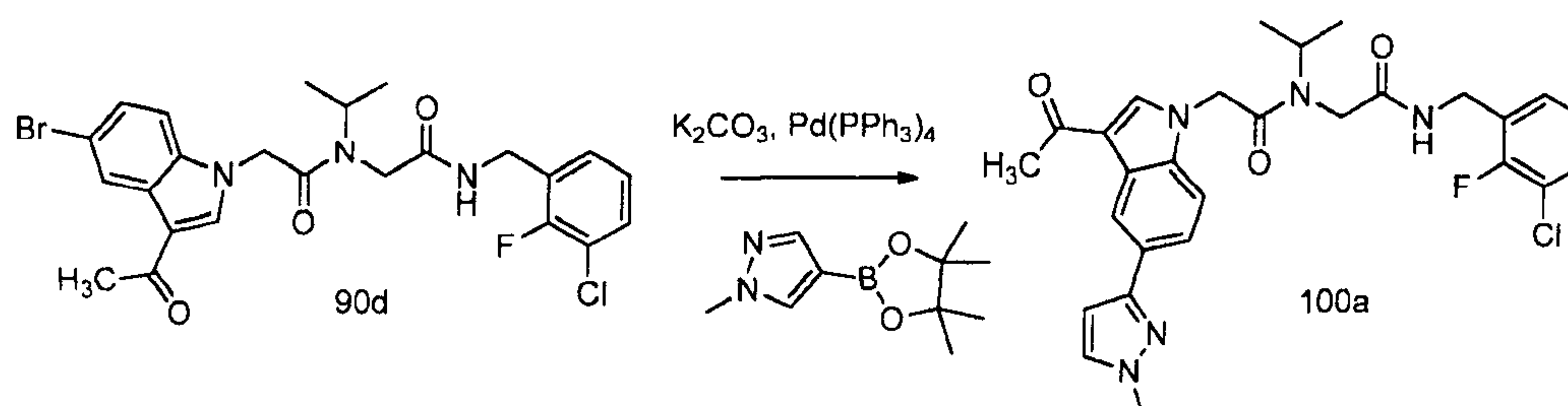
Scheme 99



Preparation of 2-(3-acetyl-5-((trimethylsilyl)ethynyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**99a**)

- 5 Reaction of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**) (504 mg, 0.94 mmol) with ethynyltrimethylsilane (0.13 mL, 0.94 mmol) according to the procedure reported in scheme 92 gave after workup and purification by flash column chromatography [silica gel (40 g), eluting with MeOH in CHCl₃ 0 to 100%; second column: silica gel (12 g), eluting with MeOH/EtOAc (9:1) in
- 10 hexanes 0 to 100%] 2-(3-acetyl-5-((trimethylsilyl)ethynyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**99a**) (21 mg, 0.038 mmol, 4% yield) as a yellow solid as a mixture of two rotamers; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.84 (t, *J* = 5.8 Hz) and 8.42 – 8.22 (m) (3H), 7.62 – 6.96 (m, 5H), 5.37 and 5.19 (2s, 2H), 4.65 – 4.52 and 4.26 – 4.21 (2m, 1H), 4.47 (d, *J* = 5.6 Hz) and 4.32 (d, *J* = 5.7 Hz) (2d, 2H), 4.17
- 15 and 3.84 (2s, 2H), 2.44 and 2.42 (2s, 3H), 1.25 (d, *J* = 6.4 Hz) and 0.99 (d, *J* = 6.8 Hz) (2d, 6H), 0.40 – 0.08 (m, 9H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.20, -121.77 (d, *J* = 4.0 Hz); MS (ES⁺): 554.6 & 556.6 (M+1), 576.6 & 578.7 (M+Na); MS (ES⁻): 588.5 & 590.6 (M+Cl).

Scheme 100

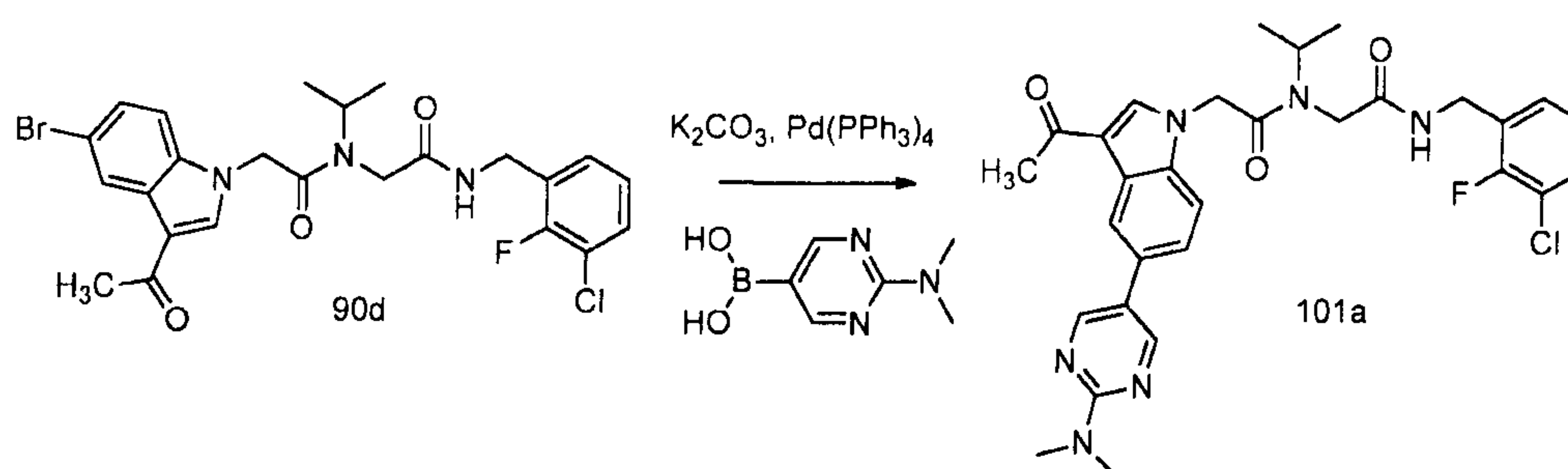


- 20 Preparation of 2-(3-acetyl-5-(1-methyl-1H-pyrazol-3-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**100a**)

To a degassed solution of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**) (150 mg, 0.28 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (70 mg, 0.335 mmol) in

dioxane (4 mL) was added a solution of K_2CO_3 (1.12 mL, 0.56 mmol) in water (1 mL) followed by tetrakis(triphenylphosphine) Palladium(0) (32 mg, 0.028 mmol) and heated at 80 °C for 4h. The mixture was cooled to room temperature and diluted with EtOAc (50 mL) and water (60 mL). The organic layer was separated washed with brine, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica gel (12 g), eluting with CMA80 in $CHCl_3$ 0 to 30%] to afford 2-(3-acetyl-5-(1-methyl-1H-pyrazol-3-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**100a**) (85 mg, 0.16 mmol, 57% yield) as a white solid; ^1H NMR (300 MHz, $DMSO-d_6$) (a mixture of two rotamers in 2:1 ratio) δ 8.83 and 8.35 (2t, J = 6.0 Hz, 1H), 8.31 – 8.27 (m, 1H), 8.24 and 8.19 (2s, 1H), 8.10 (s, 1H), 7.83 – 7.76 (m, 1H), 7.55 – 7.35 (m, 4H), 7.26 – 7.17 and 7.05 – 6.96 (2m, 1H), 5.34 and 5.16 (2s, 2H), 4.65 – 4.52 and 4.30 – 4.21 (2m, 1H), 4.48 and 4.34 (2d, J = 5.6 Hz, 2H), 4.18 and 3.85 (2s, 2H), 3.88 and 3.87 (2s, 3H), 2.44 and 2.42 (2s, 3H), 1.25 and 1.00 (2d, J = 6.4 Hz, 6H).; ^{19}F NMR (282 MHz, $DMSO-d_6$) (a mixture of two rotamers) δ -121.19 and -121.79; MS (ES+): 538.6 (M+1), 560.6 (M+Na); MS (ES): 536.6 (M-1).

Scheme 101

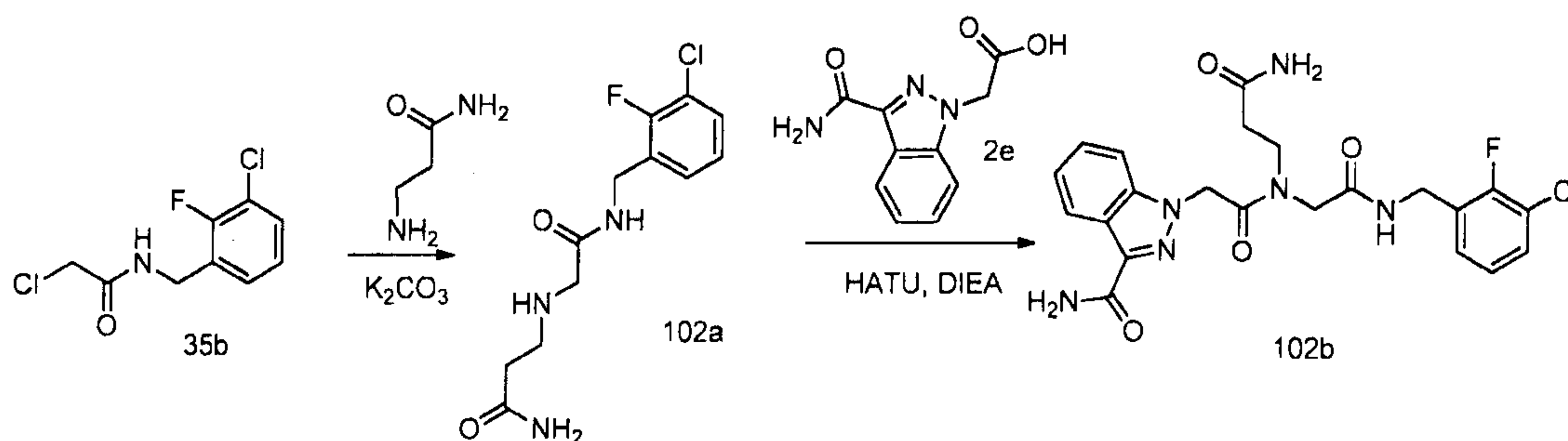


Preparation of 2-(3-acetyl-5-(2-(dimethylamino)pyrimidin-5-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**101a**)

Reaction of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**) (150 mg, 0.28 mmol) with (2-(dimethylamino)pyrimidin-5-yl)boronic acid (56 mg, 0.34 mmol) according the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in $CHCl_3$ 0 to 30%] 2-(3-acetyl-5-(2-(dimethylamino)pyrimidin-5-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**101a**) (26 mg, 0.045 mmol, 16% yield) as a white solid; ^1H NMR (300 MHz, $DMSO-d_6$) (mixture of rotamers) 8.83 and 8.35 (2t, J = 5.2 Hz, 1H), 8.65 and 8.646 (2s, 2H), 8.31 and 8.26 (2s, 1H), 7.60 – 7.47 (m, 2H), 7.47 – 7.36 (m, 2H), 7.28 –

7.16 and 7.07 – 6.95 (2m, 2H), 5.38 and 5.20 (2s, 2H), 4.65 – 4.53 and 4.29 – 4.22 (2m, 1H), 4.48 and 4.33 (2d, $J = 5.6$ Hz, 2H), 4.19 and 3.85 (2s, 2H), 3.25-3.10 (m, 6H), 2.45 and 2.44 (2s, 3H), 1.26 and 1.00 (d, $J = 6.8$ Hz, 6H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) (a mixture of two rotamers) δ -121.18 and -121.78; MS (ES⁺): 579.7 (M+1), 601.7 (M+Na), MS (ES⁻): 577.6 (M-1).

Scheme 102



Preparation of 1-(2-((3-amino-3-oxopropyl)(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**102b**)

Step-1: Preparation of 3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)propanamide (**102a**)

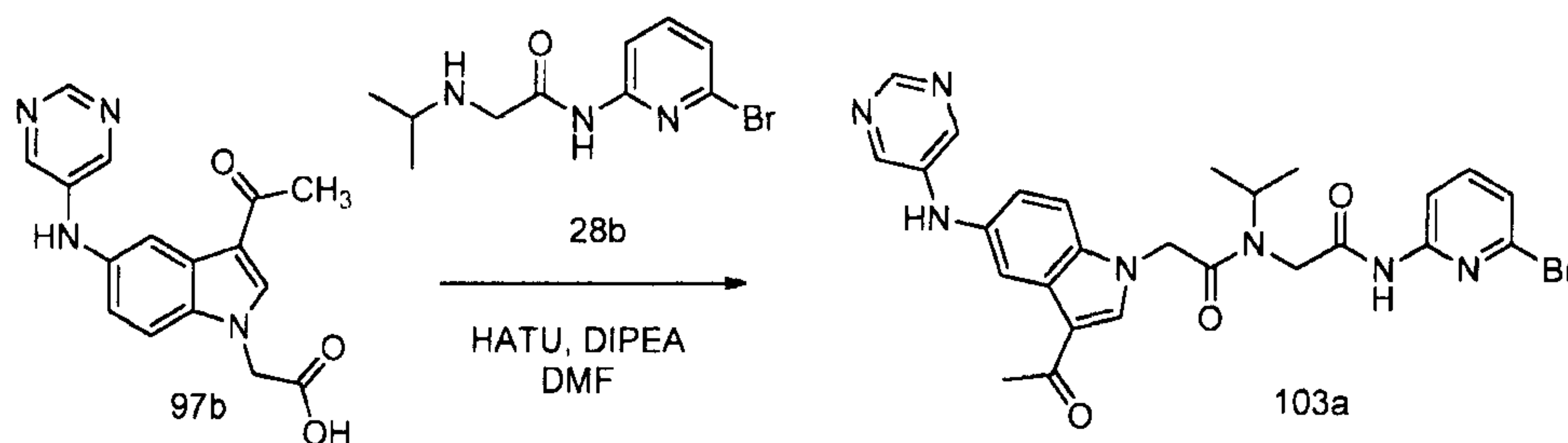
Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (350 mg, 1.48 mmol) with 3-aminopropanamide hydrochloride (462 mg, 3.71 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] 3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)propanamide (**102a**) (168 mg, 0.77 mmol, 52%) as a yellow oil; MS (ES⁺): 288.4 (M+1), 310.3 (M+Na); (ES⁻): 286.3 (M-1).

Step-2: Preparation of 1-(2-((3-amino-3-oxopropyl)(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**102b**)

Reaction of 3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)propanamide (**102a**) (168 mg, 0.77 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (200 mg, 0.7 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and trituration of crude residue with MeOH (5 mL) 1-(2-((3-amino-3-oxopropyl)(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**102b**) (158 mg, 0.32 mmol, 47% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 8.89 (t, $J = 5.5$ Hz) and 8.56 (t, $J = 5.8$ Hz) (2t, 1H), 8.24 – 8.08 (m, 1H), 7.78 – 7.65 (m, 1H), 7.64 – 6.85 (m, 9H), 5.70 and 5.41 2 (s, 2H), 4.47 (d, $J = 5.5$ Hz) and 4.38 – 4.24 (m) and 3.95 (s) (4H), 3.74 (t, $J = 6.3$ Hz) and 3.41 (t, $J = 7.0$ Hz) (2t, 2H), 2.28 (t, $J = 7.1$ Hz, 1H); ^{19}F NMR

(282 MHz, DMSO-*d*₆) δ -121.36, -121.65; MS (ES⁺) 489.5 (M+1); (ES⁻): 487.4 (M-1);
[based on NMR, this compound is a mixture of two rotamers 4:5 ratio].

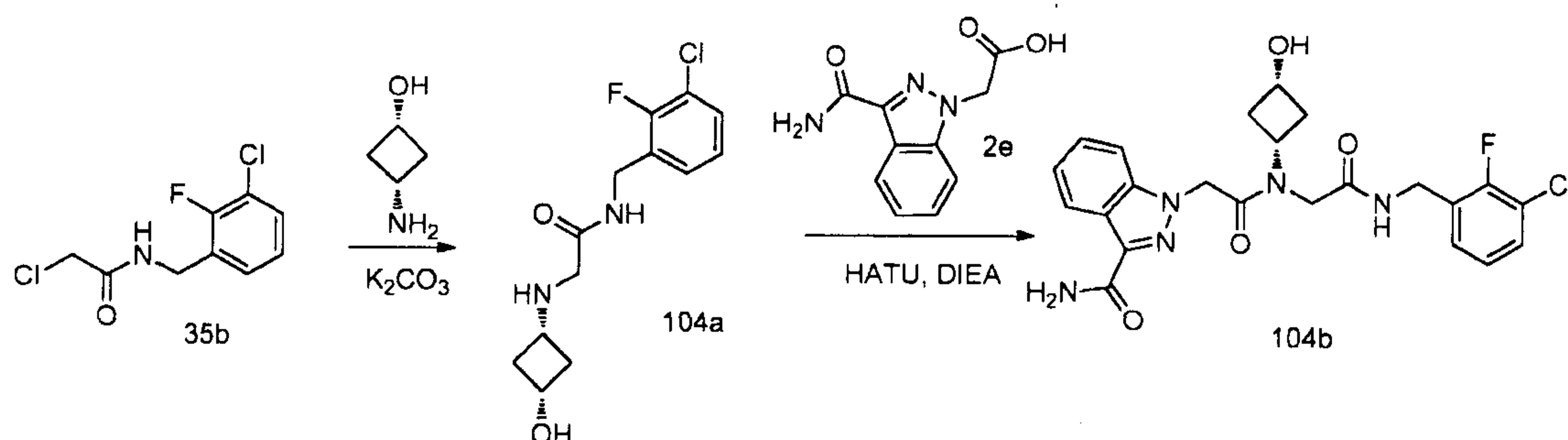
Scheme 103



5 Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**103a**)

Reaction of N-(6-bromopyridin-2-yl)-2-(isopropylamino)acetamide (**28b**) (61 mg, 0.23 mmol) with 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**97b**) (70 mg, 0.23 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and
10 purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 30%] 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**103a**) (45 mg, 0.080 mmol, 35% yield) as an off-white solid as a mixture of rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.20 and 10.83 (2s, 1H), 8.56 and 8.55 (2s, 1H), 8.50 and 8.49 (2s, 1H), 8.47 and 8.46 (2s, 2H), 8.25 and 8.24 (2s, 1H), 8.21 – 7.97 (m, 2H), 7.81 and 7.70 (2t, *J* = 8.0 Hz, 1H), 7.48 – 7.27 (m, 2H), 7.17 – 7.07 (m, 1H), 5.37 and 5.18 (2s, 2H), 4.71 – 4.59 and 4.36 – 4.23 (2m, 1H), 4.43 and 4.05 (2s, 2H), 2.42 and 2.40 (2s, 3H), 1.26 and 1.04 (2d, *J* = 6.8 Hz, 6H); MS (ES⁺): 564.5, 566.5 (M+1), MS (ES⁻): 562.5, 564.5 (M-1), 598.5, 600.5 (M+Cl).

Scheme 104



20

Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((*cis*)-3-hydroxycyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**104b**)

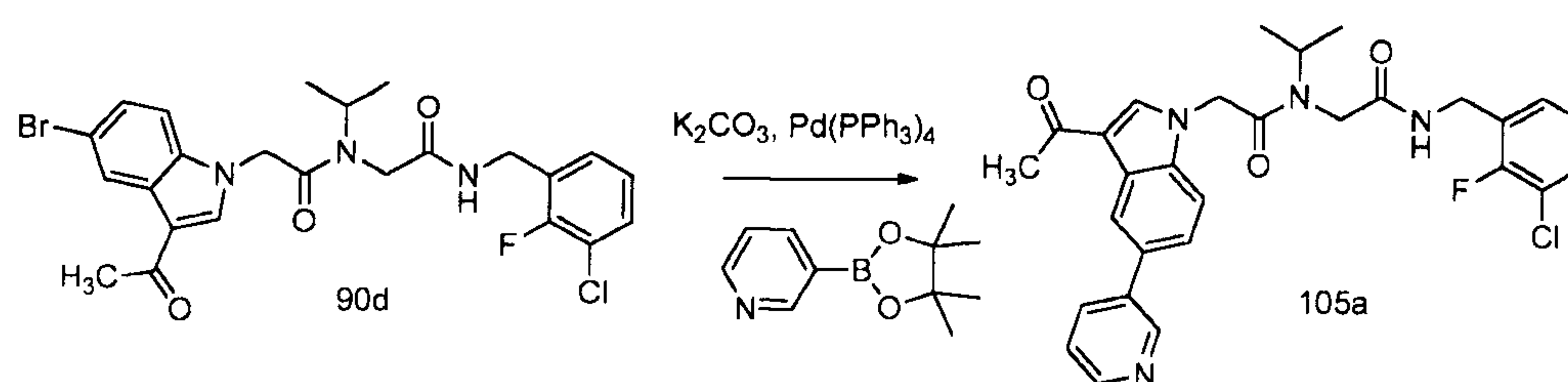
Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(((cis)-3-hydroxycyclobutyl)amino)acetamide (**104a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (350 mg, 1.48 mmol) with (cis)-3-aminocyclobutanol hydrochloride (458 mg, 3.71 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-(((cis)-3-hydroxycyclobutyl)amino)acetamide (**104a**) (250 mg, 0.87 mmol, 59%) as a yellow oil; MS (ES+): 287.3 (M+1); MS (ES-): 285.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((cis)-3-hydroxycyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**104b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(((cis)-3-hydroxycyclobutyl)amino)acetamide (**104a**) (250 mg, 0.87 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (210 mg, 0.96 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA-80 in CHCl₃ 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((cis)-3-hydroxycyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**104b**) (245 mg, 0.5 mmol, 58% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.88 (t, *J* = 5.7 Hz) and 8.44 (t, *J* = 5.9 Hz) (2t, 1H), 8.24-8.09 (m, 1H), 7.70 (s, 1H), 7.59 – 7.04 (m, 7H), 5.53 and 5.40 (2s, 2H), 5.20 – 5.06 (m, 1H), 4.47 (d, *J* = 5.5 Hz) and 4.34 (d, *J* = 5.7 Hz) (2d, 2H), 4.30 and 4.04 (2s, 2H), 4.19 – 4.05 (m, 1H), 3.88 – 3.68 (m, 1H), 2.70 – 2.55 (m, 1H), 2.39 – 2.25 (m, 1H), 2.13 – 1.90 (m, 1H), 1.85 – 1.70 (m, 1H).; ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.26, -121.59; MS (ES+); 488.5 (M+1); (ES-): 486.5 (M-1); [based on NMR, this compound is a mixture of rotamers 4:5 ratio]

Scheme 105

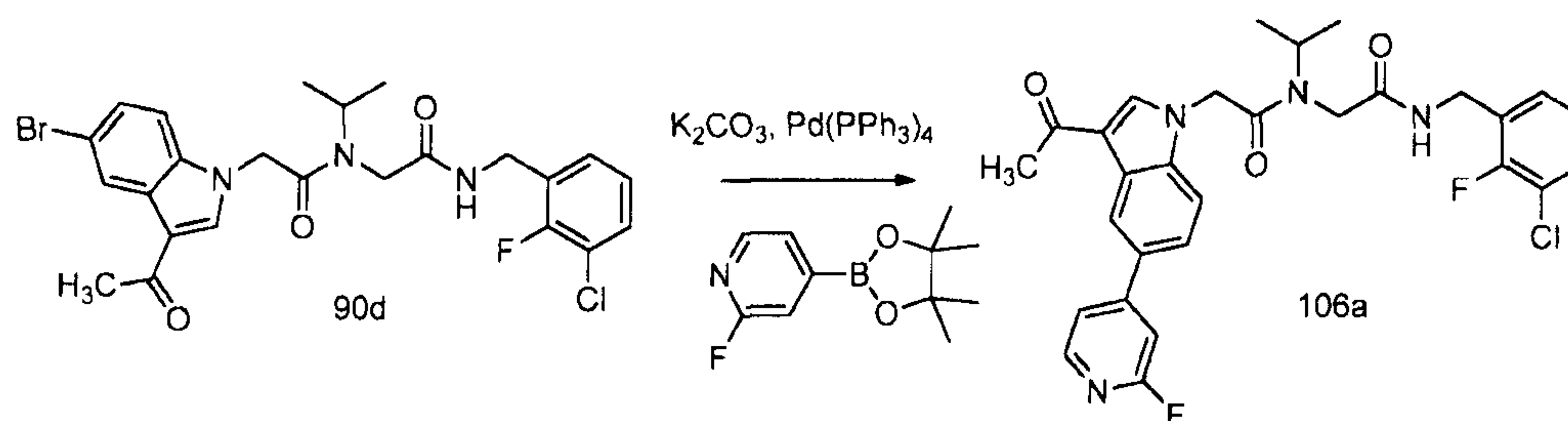


Preparation of 2-(3-acetyl-5-(pyridin-3-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**105a**)

Reaction of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**) (150 mg, 0.28 mmol) with pyridin-3-ylboronic acid

(34 mg, 0.28 mmol) according to the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl_3 0 to 30%] 2-(3-acetyl-5-(pyridin-3-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**105a**) (75 mg, 0.14 mmol, 50%
 5 yield) as a white solid as a mixture of rotamers in 2:1 ratio; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.91 - 8.87 (m, 1H), 8.84 (t, $J = 5.7$ Hz) and 8.39 - 8.27 (m) (2H), 8.61 - 8.53 (m, 1H), 8.45 (s, 1H), 8.14 - 8.05 (m, 1H), 7.67 - 7.57 (m, 2H), 7.57 - 7.47 (m, 2H), 7.46-7.36 (m, 1H), 7.26-6.94 (m, 1H), 5.41 and 5.22 (s, 2H), 4.66 - 4.53 and 4.32 - 4.21 (m, 1H), 4.49 and 4.34 (d, $J = 5.8$ Hz, 2H), 4.20 and 3.86 (s, 2H), 2.47 and 2.45 (s, 3H), 1.27 and 1.01 (2d, $J = 6.4$
 10 Hz, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.18, -121.77; MS (ES+) 535.6 (M+1), MS (ES-): 569.5, 571.5 (M+Cl).

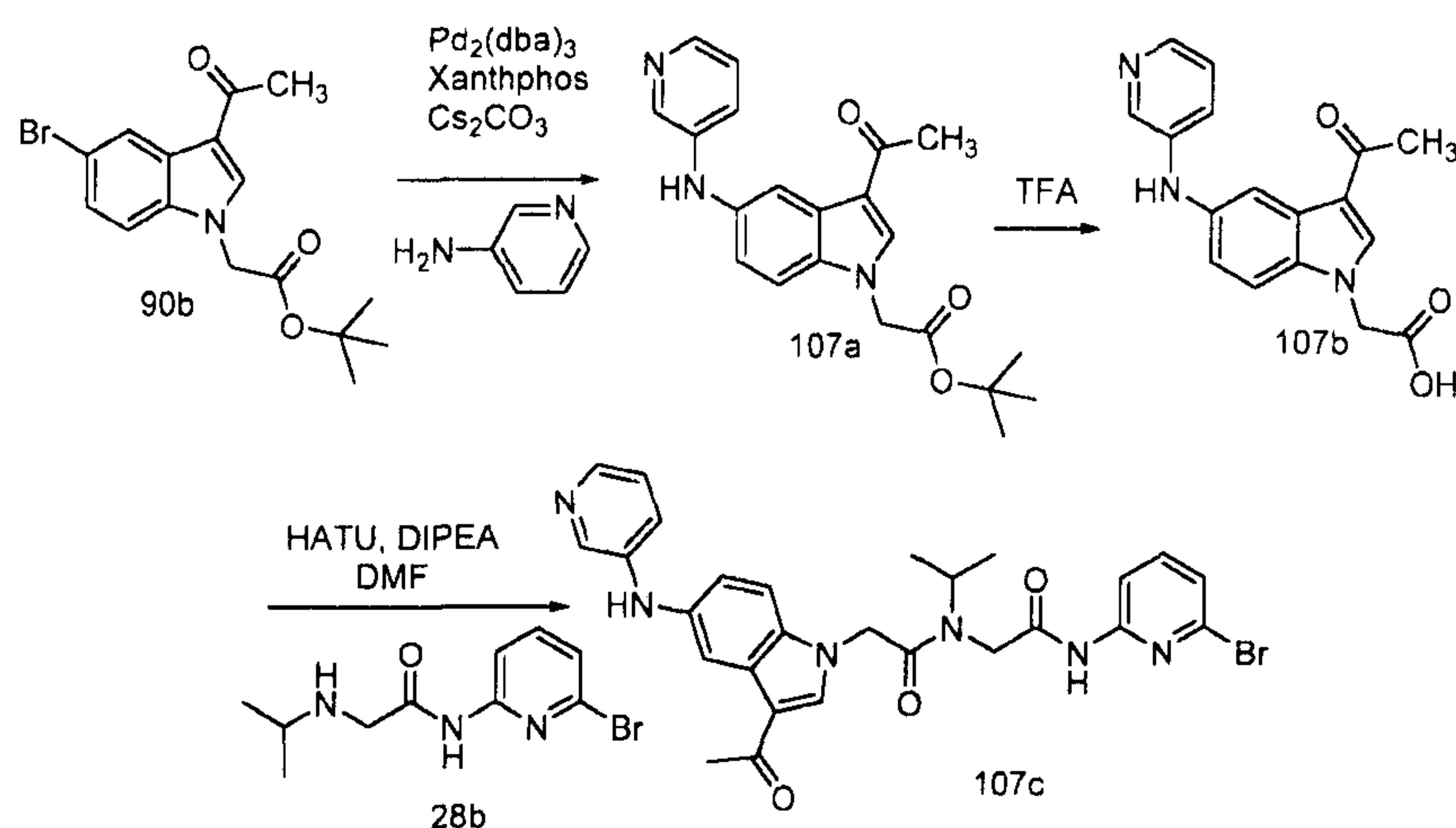
Scheme 106



Preparation of 2-(3-acetyl-5-(2-fluoropyridin-4-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**106a**)
 15

Reaction of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**) (150 mg, 0.28 mmol) with 2-fluoropyridin-4-ylboronic acid (39 mg, 0.28 mmol) according to the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with
 20 CMA80 in CHCl_3 0 to 30%] 2-(3-acetyl-5-(2-fluoropyridin-4-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**106a**) (52 mg, 0.094 mmol, 34% yield) as a white solid as a mixture of rotamers in 2:1 ratio; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.84 (t, $J = 5.7$ Hz) and 8.42 - 8.23 (m) (3H), 8.58 (bs, 1H), 7.81 - 6.89 (m, 7H), 5.42 and 5.23 (2s, 2H), 4.66 - 4.53 and 4.30 - 4.22 (m, 1H), 4.49 and 4.34 (2d, $J = 5.8$
 25 Hz, 2H), 4.20 and 3.86 (s, 2H), 2.48 and 2.46 (s, 3H), 1.27 and 1.00 (2d, $J = 6.8$ Hz, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -69.06, -69.09, -121.18, -121.77; MS (ES+): 553.6 (M+1), MS (ES-): 587.5 (M+Cl).

Scheme 107



Preparation of 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indol-1-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**107c**)

- 5 Step-1: Preparation of tert-butyl 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indol-1-yl)acetate (**107a**)

Reaction of tert-butyl 2-(3-acetyl-5-bromo-1H-indol-1-yl)acetate (**90b**) (1.05 g, 2.98 mmol) with pyridin-3-amine (310 mg, 3.28 mmol), according to the procedure reported in step-1 of Scheme 97 gave after workup and purification by column chromatography [silica gel (40 g),
10 eluting with CMA80 in CHCl₃ 0 to 20%] tert-butyl 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indol-1-yl)acetate (**107a**) (250 g, 0.7 mmol, 23% yield) as light yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.35 - 8.23 (m, 3H), 8.02 - 7.91 (m, 2H), 7.43 - 7.31 (m, 2H), 7.18 (dd, J = 8.3, 4.6 Hz, 1H), 7.07 (dd, J = 8.8, 2.2 Hz, 1H), 5.08 (s, 2H), 2.41 (s, 3H), 1.44 (s, 9H); MS (ES⁺): 366.5 (M+1), MS (ES⁻): 400.4 (M+Cl).

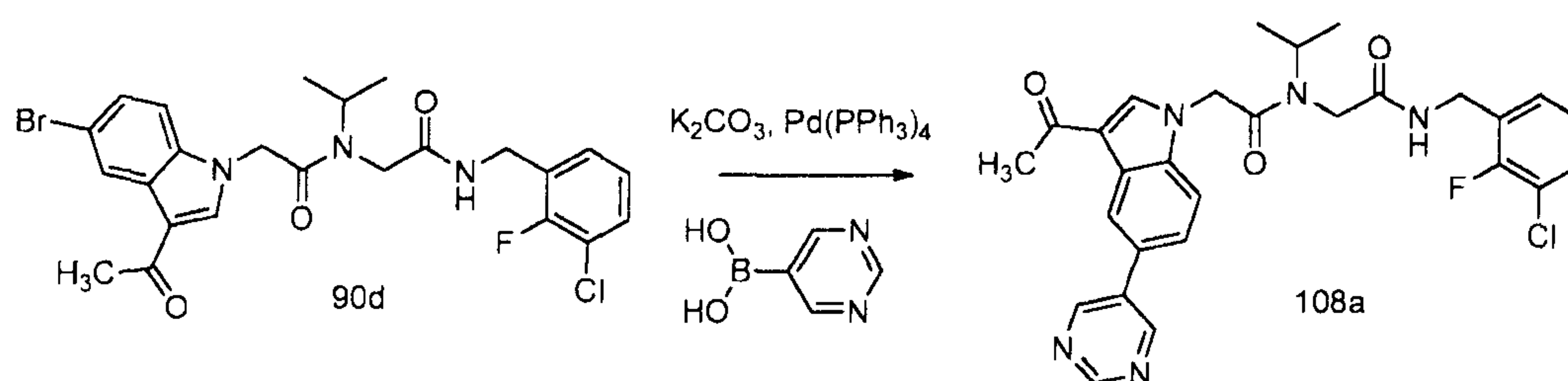
- 15 Step-2: Preparation of 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indol-1-yl)acetic acid (**107b**)

Reaction of tert-butyl 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indol-1-yl)acetate (**107a**) (250 mg, 0.68 mmol) with TFA (1.58 mL, 20.52 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and trituration of crude with EtOAc-hexane (10 mL) 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indol-1-yl)acetic acid (**107b**) (0.2 g, 0.647 mmol, 95%
20 yield) as light orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.31 (bs, 1H, D₂O exchangeable), 9.09 (s, 1H), 8.36 (s, 1H), 8.28 (s, 1H), 8.14 (s, 1H), 8.05 (s, 1H), 7.82 (s, 1H), 7.70 (s, 1H), 7.55 (d, J = 8.7 Hz, 1H), 7.18 (d, J = 8.6 Hz, 1H), 5.14 (s, 2H), 2.42 (s, 3H); MS (ES⁻): 308.3 (M-1).

- 25 Step-3: Preparation of 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indol-1-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**107c**)

Reaction of 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indol-1-yl)acetic acid (**107b**) (60 mg, 0.19 mmol) with N-(6-bromopyridin-2-yl)-2-(isopropylamino)acetamide (**28b**) (53 mg, 0.19 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (12 g), eluting with CMA-80 in CHCl₃ 0-100%] 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indol-1-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**107c**) (57 mg, 0.101 mmol, 52% yield) as a off-white solid as a mixture of rotamers in 2:1 ratio; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 11.20 and 10.82 (2s, 1H), 8.33 – 8.24 (m, 2H), 8.22 and 8.21 (2s, 1H), 8.05 – 7.91 (m, 3H), 7.81 and 7.70 (2t, *J* = 8.0 Hz, 1H), 7.44 – 7.28 (m, 3H), 7.23 – 7.11 (m, 1H), 7.12 – 7.01 (m, 1H), 5.35 and 5.16 (2s, 2H), 4.72 – 4.57 and 4.47 – 4.20 (2m, 1H), 4.43 and 4.05 (2s, 2H), 2.41 and 2.40 (2s, 3H), 1.26 and 1.04 (2d, *J* = 6.8 Hz, 6H); MS (ES⁺): 563.5, 565.5 (M+1); MS (ES⁻): 561.5, 563.5 (M-1), 597.5, 599.5 (M+Cl).

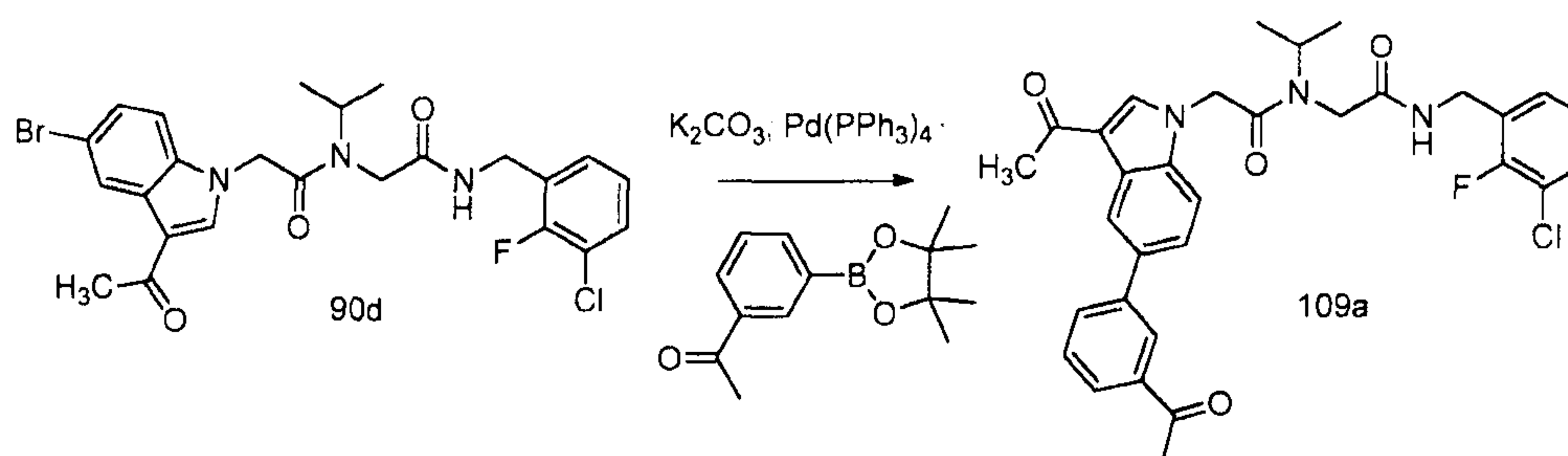
Scheme 108



Preparation of 2-(3-acetyl-5-(pyrimidin-5-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**108a**)

Reaction of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**) (150 mg, 0.28 mmol) with pyrimidin-5-ylboronic acid (35 mg, 0.28 mmol) according the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 30%] 2-(3-acetyl-5-(pyrimidin-5-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**108a**) (85 mg, 0.159 mmol, 57% yield) as a white solid; as a mixture of rotamers in 2:1 ratio; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 9.19 and 9.18 (2s, 1H), 9.12 and 9.11 (2s, 2H), 8.89 – 8.79 and 8.40 – 8.28 (2m, 2H), 8.48 (s, 1H), 7.71 – 6.95 (m, 5H), 5.42 and 5.23 (2s, 2H), 4.65 – 4.54 and 4.32 – 4.21 (2m, 1H), 4.49 and 4.34 (2d, *J* = 5.6 Hz, 2H), 4.20 and 3.86 (2s, 2H), 2.48 and 2.46 (2s, 3H), 1.27 and 1.01 (d, *J* = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ -121.18 and -121.79; MS (ES⁺): 536.5 (M+1), MS (ES⁻): 534.5 (M-1), 570.5 (M+Cl).

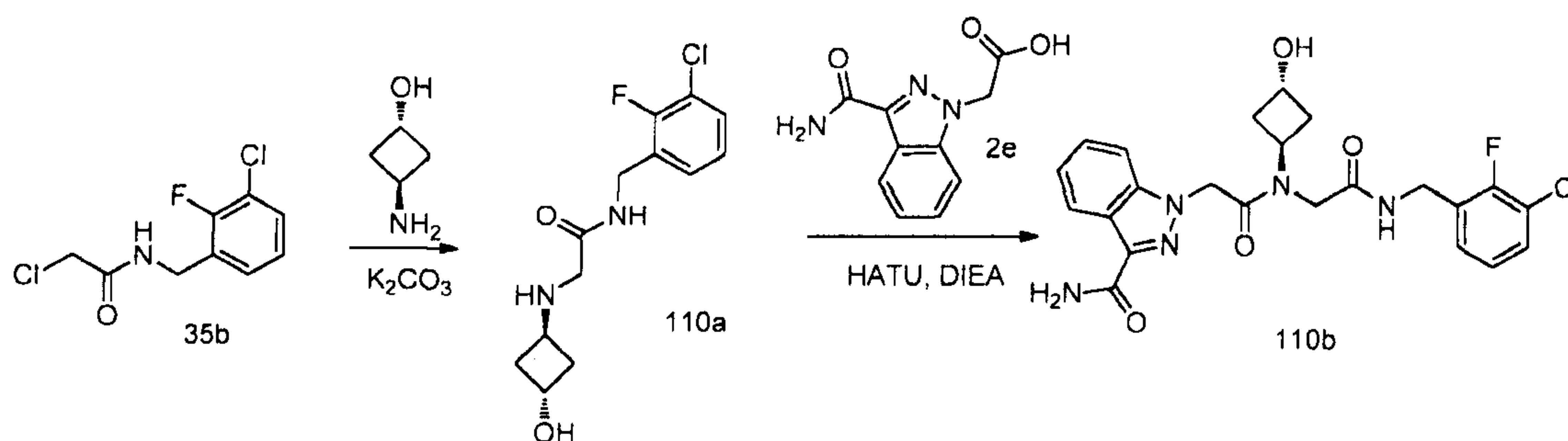
Scheme 109



Preparation of 2-(3-acetyl-5-(3-acetylphenyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**109a**)

- 5 Reaction of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**) (150 mg, 0.28 mmol) with 1-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)ethanone (70 mg, 0.28 mmol) according to the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 30%] 2-(3-acetyl-5-(3-acetylphenyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**109a**) (80 mg, 0.14 mmol, 50% yield) as a white solid as mixture of rotamers in 2:1 ratio; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.84 and 8.35 (2t, *J* = 5.7 Hz, 1H), 8.47 (bs, 1H), 8.35 and 8.34 (s, 1H), 8.21 – 8.13 (m, 1H), 8.01 – 7.88 (m, 2H), 7.70-6.95 (m, 6H), 5.41 and 5.22 (s, 2H), 4.68 – 4.51 and 4.32 – 4.20 (m, 1H), 4.49 and 4.34 (d, *J* = 5.8 Hz, 2H), 4.20 and 3.86 (s, 2H), 2.668 and 2.666 (2s, 3H), 2.47, 2.45 (s, 3H), 1.27 and 1.01 (2d, *J* = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.18, -121.76; MS (ES⁺): 576.6 (M+1), 598.6 (M+Na); MS (ES⁻): 574.6 (M-1).

Scheme 110



- 20 Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((trans)-3-hydroxycyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**110b**)

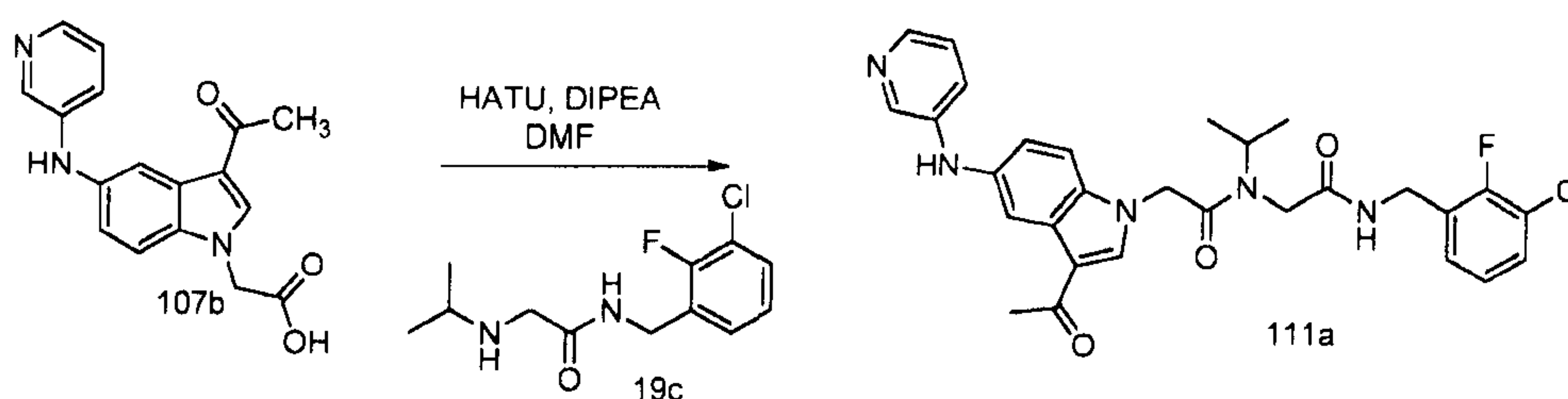
Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-hydroxycyclobutyl)amino)acetamide (**110a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (350 mg, 1.48 mmol) with (trans)-3-aminocyclobutanol hydrochloride (458 mg, 3.71 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-hydroxycyclobutyl)amino)acetamide (**110a**) (200 mg, 0.7 mmol, 47%) as a yellow oil; MS (ES⁺): 287.4 (M+1); (ES⁻): 285.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((trans)-3-hydroxycyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**110b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-hydroxycyclobutyl)amino)acetamide (**110a**) (200 mg, 0.7 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (168 mg, 0.77 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA-80 in CHCl₃ 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((trans)-3-hydroxycyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**110b**) (92mg, 27%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.86 (t, *J* = 5.5 Hz) and 8.43 (t, *J* = 5.7 Hz) (2t, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.78 – 7.64 (m, 1H), 7.63 – 7.00 (m, 7H), 5.53 and 5.42 (2s, 2H), 5.12 (d, *J* = 4.0 Hz) and 5.00 (d, *J* = 4.3 Hz) (2d, 1H), 4.96 – 4.79 (m, 1H), 4.47 (d, *J* = 5.2 Hz) and 4.33 (d, *J* = 5.5 Hz) (2d, 2H), 4.28 and 4.00 (2s, 2H), 4.23 – 4.05 (m, 1H), 2.46 – 2.30 (m, 1H), 2.28 – 2.09 (m, 2H), 2.02 – 1.85 (m, 1H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.23, -121.62; MS (ES⁺): 488.5 (M+1); (ES⁻): 486.5 (M-1); *[based on NMR, this compound is a mixture of rotamers 4:5 ratio]*.

Scheme 111



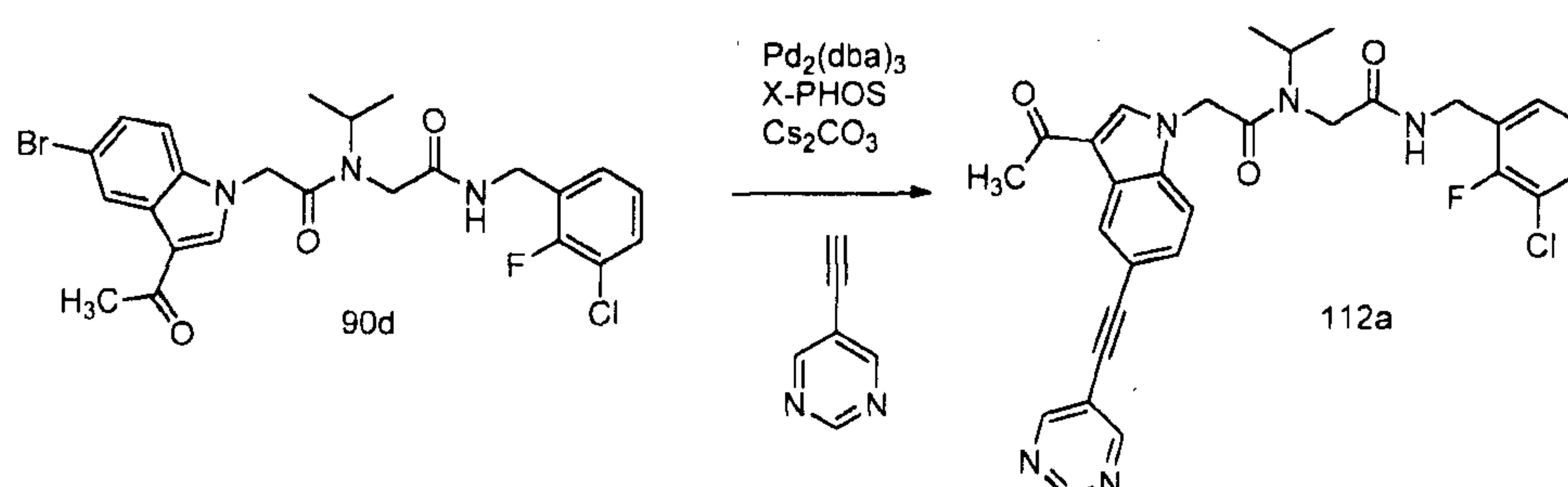
Preparation of 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**111a**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (50 mg, 0.19 mmol) with 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indol-1-yl)acetic acid (**107b**) (60 mg, 0.19 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in

CHCl₃ 0 to 30%] 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**111a**) (40 mg, 0.073 mmol, 38% yield) as an off-white solid as mixture of rotamers in 2:1 ratio; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 8.82 and 8.34 (2t, *J* = 5.7 Hz, 1H), 8.32 – 8.23 (m, 2H), 8.21 and 8.16 (2s, 1H), 7.98 (d, *J* = 2.2 Hz, 1H), 7.96 – 7.90 (m, 1H), 7.56 – 6.96 (m, 7H), 5.32 and 5.13 (2s, 2H), 4.67 – 4.51 and 4.31 – 4.18 (2m, 1H), 4.47 and 4.34 (2d, *J* = 5.8 Hz, 2H), 4.18 and 3.85 (2s, 2H), 2.40 and 2.39 (2s, 3H), 1.25 and 1.00 (2d, *J* = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ -121.18, -121.77; MS (ES⁺): 550.6 (M+1); MS (ES⁻): 584.6 (M+Cl).

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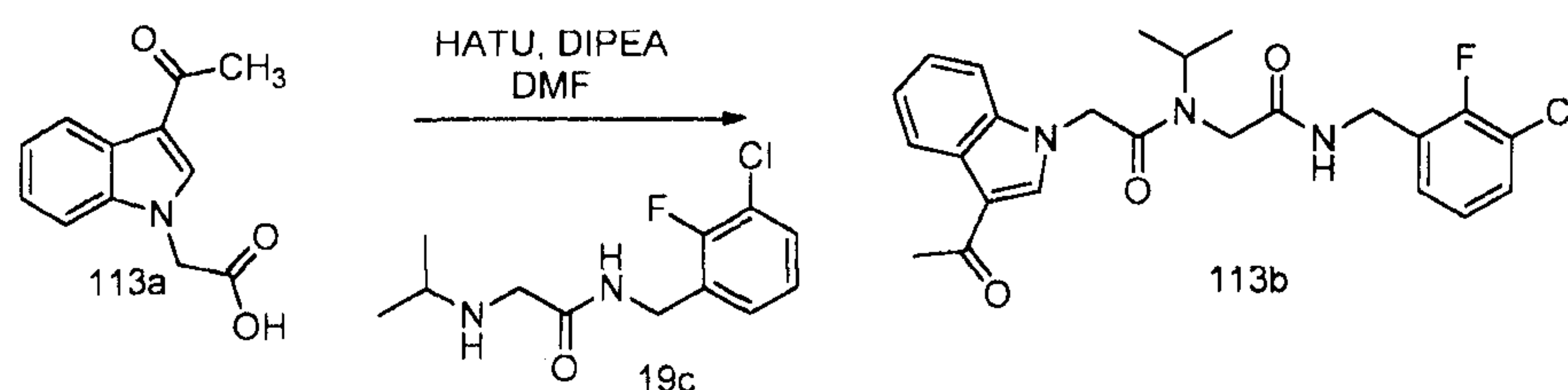
Scheme 112



Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylethynyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**112a**)

Reaction of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**) (300 mg, 0.56 mmol) with 5-ethynylpyrimidine (58 mg, 0.56 mmol) according to the procedure reported in Scheme 92 gave after workup and purification by flash column chromatography [First column: silica gel (24 g), eluting with MeOH in CHCl₃ 0 to 20%; Second column: silica gel (12 g), eluting with MeOH/EtOAc (9:1) in hexanes 0 to 100%] 2-(3-acetyl-5-(pyrimidin-5-ylethynyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**112a**) (13 mg, 0.023 mmol, 4% yield) as a yellow solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.183 and 9.180 (2s, 1H), 9.054 and 9.052 (2s, 2H), 8.84 (t, *J* = 5.8 Hz) and 8.36 (t) (2t, 1H), 8.45 (d, *J* = 1.5 Hz, 1H), 8.38 and 8.34 (2s, 1H), 7.68 – 6.93 (m, 5H), 5.41 and 5.22 (2s, 2H), 4.65 – 4.53 and 4.28 – 4.20 (2m, 1H), 4.52–4.30 (m, 2H), 4.19 and 3.85 (2s, 2H), 2.46 and 2.45 (2s, 3H), 1.26 (d, *J* = 6.5 Hz) and 1.00 (d, *J* = 6.8 Hz) (2t, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.18, -121.77; MS (ES⁺): 560.61 (M+1); MS (ES⁻): 594.5 & 596.5 (M+Cl).

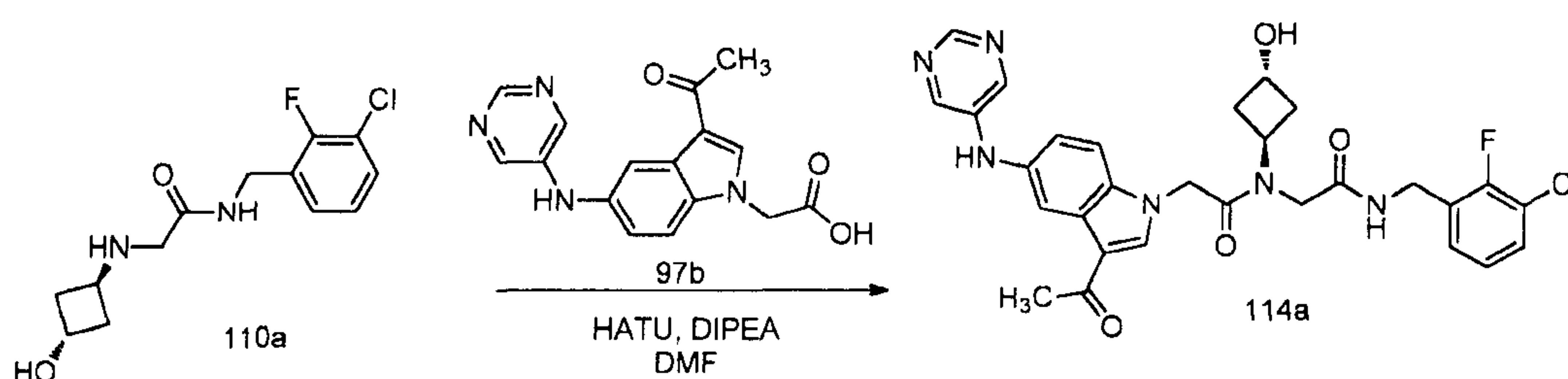
Scheme 113



Preparation of 2-(3-acetyl-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**113b**)

- 5 Reaction of N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (400 mg, 1.55 mmol) with 2-(3-acetyl-1H-indol-1-yl)acetic acid (**113a**) (403 mg, 1.86 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (24 g), eluting with CMA80 in CHCl₃ 0 to 10%] 2-(3-acetyl-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-
- 10 isopropylacetamide (**113b**) (279 mg, 0.609 mmol, 39% yield) as a pale yellow solid in the form of mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.82 and 8.35 (t, *J* = 5.4 Hz) (2t, 1H), 8.32 and 8.27 (2s, 1H), 8.22 (s, 1H), 8.18 (d, *J* = 7.0 Hz, 1H), 7.57 – 7.34 (m, 2H), 7.29 – 7.14 (m, 2H, another triplet was overlapped in this region), 7.00 (t, *J* = 7.9 Hz, 1H), 5.36 and 5.17 (2s, 2H), 4.65 – 4.52 and 4.30 – 4.22 (2m, 1H), 4.48 (d, *J* = 5.6 Hz) and
- 15 4.33 (d, *J* = 5.8 Hz) (2d, 2H), 4.19 (s) and 3.85 (2s, 2H), 2.43 and 2.42 (2s, 3H), 1.25 (d, *J* = 6.3 Hz) and 1.00 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.19, -121.82; MS (ES⁺): 458.5 (M+1), 480.5 (M+Na); MS (ES⁻): 456.5 (M-1), 492.5 (M+Cl).

Scheme 114



- 20 Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-((trans)-3-hydroxycyclobutyl)acetamide (**114a**)

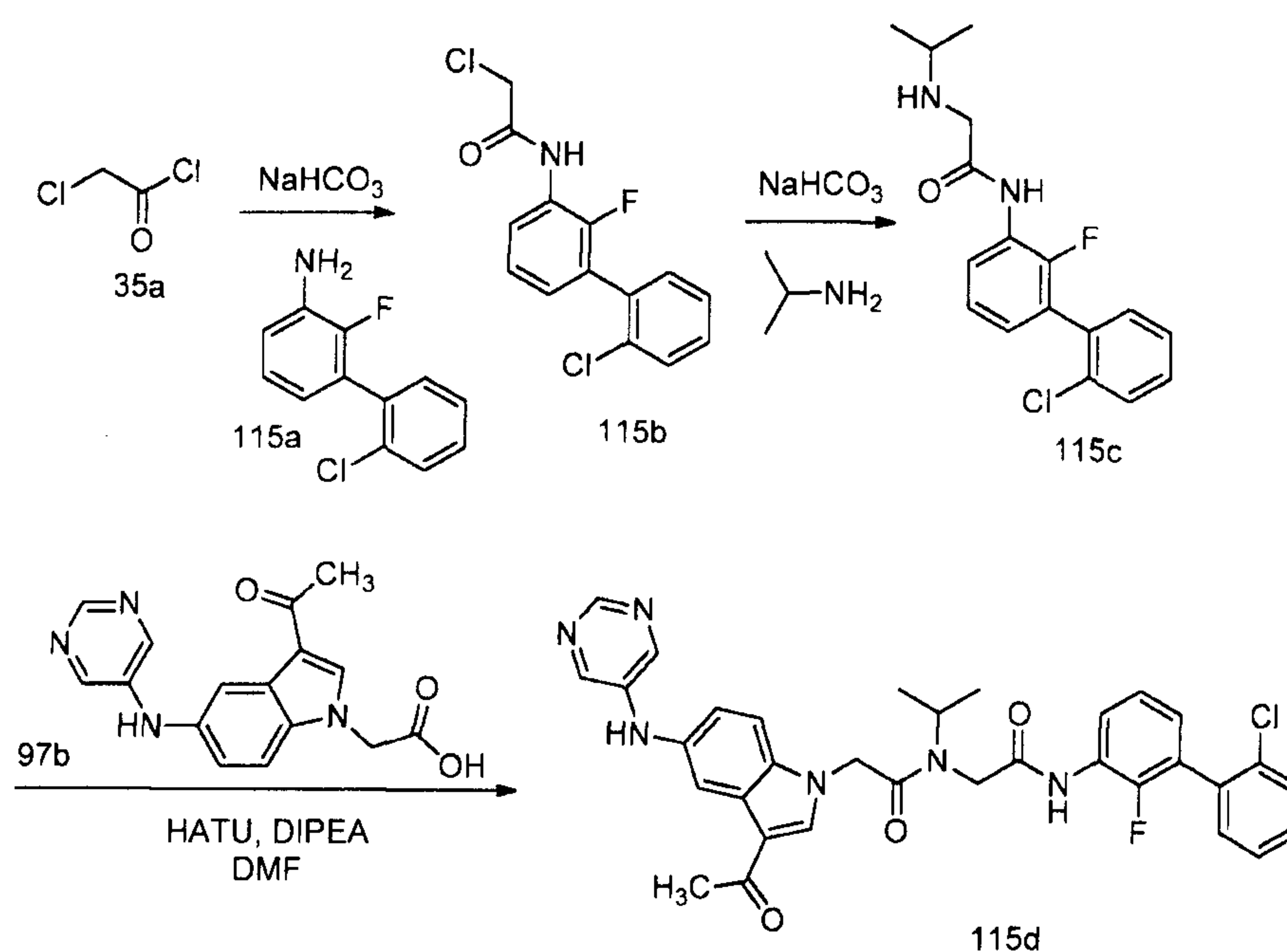
Reaction of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-hydroxycyclobutyl)amino)acetamide (**110a**) (55 mg, 0.19 mmol) with 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**97b**) (60 mg, 0.19 mmol) according to the procedure reported in step-3 of Scheme 2

- 25 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting

with CMA80 in CHCl_3 0 to 100%] 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-((trans)-3-hydroxycyclobutyl)acetamide (**114a**) (12 mg, 0.021 mmol, 11% yield) as a white solid as a mixture of rotamers in 2:1 ratio; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.85 and 8.42 (2t, $J = 5.6$ Hz, 1H), 8.563 and 8.559 (2s, 1H), 8.49 (s, 1H), 8.46 (s, 2H), 8.22 and 8.17 (2s, 1H), 8.004 and 7.997 (2s, 1H), 7.58 – 7.01 (m, 5H), 5.29 (s) and 5.17 – 4.79 (m) (s & m, 4H), 4.47 and 4.35 (2d, $J = 5.8$ Hz, 2H), 4.27 and 4.02 (2s, 2H), 4.24 – 4.09 (m, 1H), 2.41 and 2.40 (2s, 3H), 2.28 – 2.11 (m, 2H), 2.00 – 1.84 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.20, -121.62; MS (ES+): 579.6 (M+1), MS (ES-): 613.5, 615.5 (M+Cl).

10

Scheme 115



Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**115d**)

Step-1: Preparation of 2-chloro-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)acetamide (**115b**)

To a biphasic solution of 2'-chloro-2-fluorobiphenyl-3-amine (**115a**) (0.8 g, 3.61 mmol, prepared according to procedure reported by Altmann, Eva et al; in PCT Int. Appl., WO 2012/093101) in EtOAc (20 mL), Saturated aqueous NaHCO_3 (20 mL) was added 2-chloroacetyl chloride (**35a**) (0.58 mL, 7.22 mmol) and stirred at RT for 2 h. The layers were separated and aqueous layer was extracted with EtOAc (40 mL). The organic layers were combined washed with brine, dried, filtered and concentrated in vacuum to afford 2-chloro-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)acetamide (**115b**) (1 gm, 93% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.24 (s, 1H), 8.00 (t, $J = 7.9$ Hz, 1H), 7.64 – 7.57

(m, 1H), 7.53 – 7.39 (m, 3H), 7.28 (td, $J = 8.0, 1.0$ Hz, 1H), 7.19 – 7.07 (m, 1H), 4.37 (s, 2H); MS (ES+): 298.3, 300.3 (M+1), 320.3, 322.3 (M+Na); MS (ES-): 296.3, 298.3 (M-1).

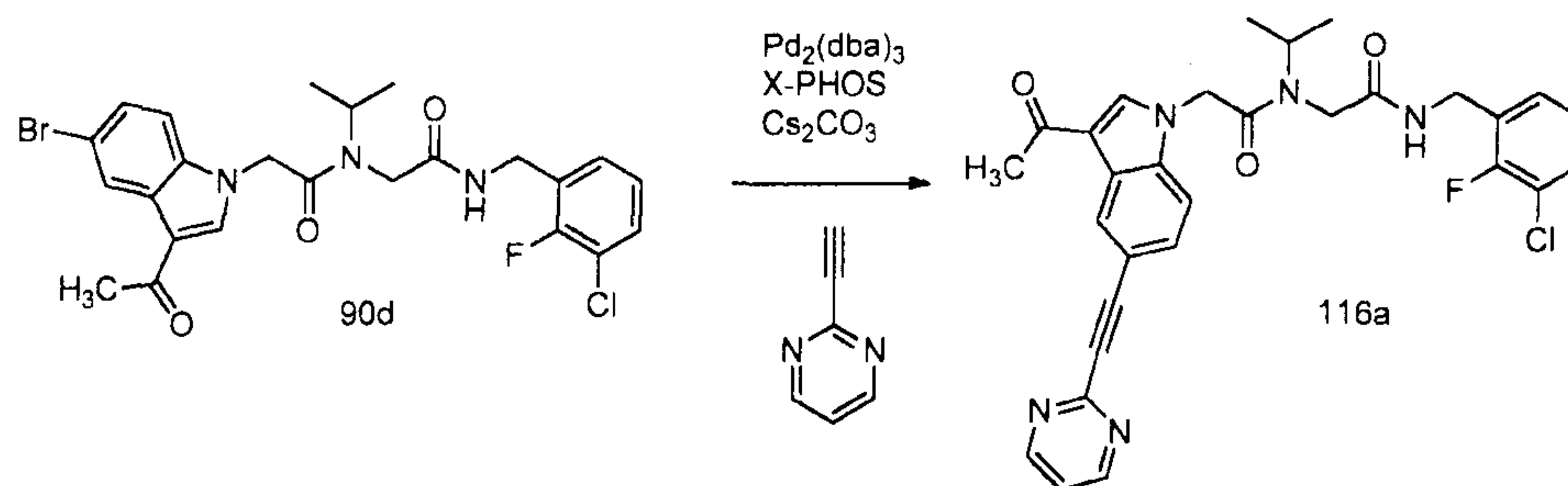
Step-2: Preparation of N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-2-(isopropylamino)acetamide (**115c**)

5 To a solution of 2-chloro-N-(2'-chloro-2-fluorobiphenyl-3-yl)acetamide (**115b**) (1.00 g, 3.35 mmol) in THF (30 mL) was added isopropylamine (0.86 mL, 10.06 mmol) and stirred at RT for 24h. Reaction mixture was poured into saturated aqueous NaHCO₃ solution (60 mL) and extracted with EtOAc (2 x 50 mL). The organics layers were combined washed with brine, dried, filtered, concentrated and purified by flash column chromatography [silica gel (24 g),
10 eluting with EtOAc in Hexane 0 to 100%] to afford N-(2'-chloro-2-fluorobiphenyl-3-yl)-2-(isopropylamino)acetamide (**115c**) (520 mg, 1.62 mmol, 48% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (major rotamer) δ 8.25 (td, $J = 7.8, 1.7$ Hz, 1H), 7.65 – 7.56 (m, 1H), 7.53 – 7.37 (m, 4H), 7.27 (td, $J = 8.0, 1.1$ Hz, 1H), 7.11 – 7.02 (m, 1H), 3.30 (s, 2H), 2.79 – 2.66 (m, 1H), 1.04 – 0.94 (m, 6H); MS (ES+) 321.4, 323.4 (M+1), MS (ES-): 355.3,
15 357.3 (M+Cl).

Step-3: Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**115d**)

Reaction of N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-2-(isopropylamino)acetamide (**115c**) (62 mg, 0.19 mmol) with 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid
20 (**97b**) (60 mg, 0.19 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 30%] 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**115d**) (21 mg, 0.034 mmol, 18% yield) as a white solid as a mixture of rotamers in 2:1 ratio; ¹H NMR
25 (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 10.25 and 9.74 (2s, 1H), 8.56 (s, 1H), 8.52 – 8.43 (m, 3H), 8.26 and 8.24 (s, 1H), 8.15 – 7.91 (m, 2H), 7.66 – 7.36 (m, 4H), 7.32 and 7.22 (2t, $J = 8.0$ Hz, 1H), 7.18 – 7.02 (m, 2H), 5.38 and 5.21 (2s, 2H), 4.75 – 4.59 and 4.38 – 4.23 (2m, 1H), 4.47 and 4.10 (2s, 2H), 2.42 and 2.40 (2s, 3H), 1.28 and 1.07 (2d, $J = 6.8$ Hz, 6H); MS (ES+); 613.5, 615.7 (M+1), MS (ES-); 611.6, 613.6 (M-1).

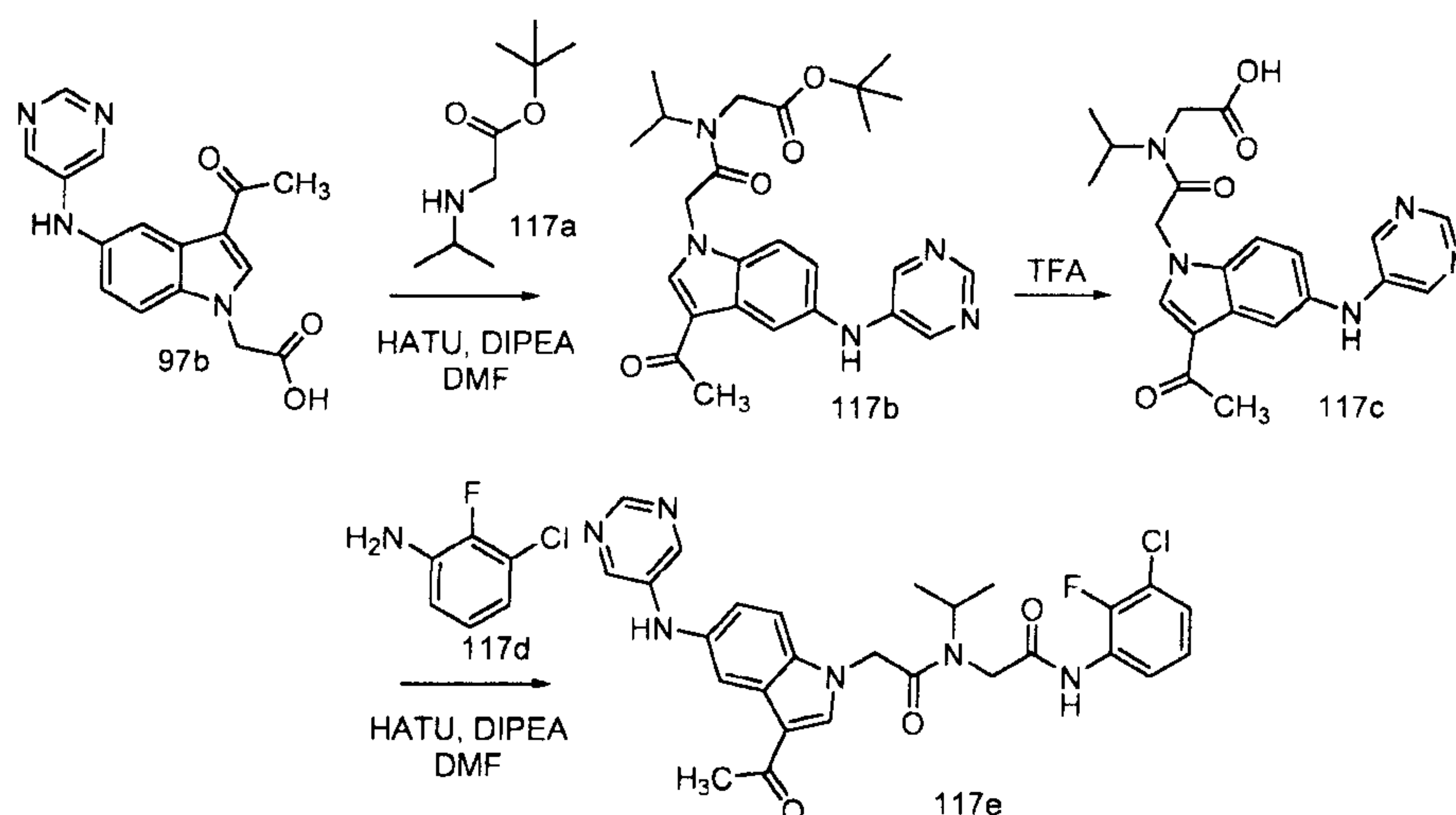
Scheme 116



Preparation of 2-(3-acetyl-5-(pyrimidin-2-ylethynyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**116a**)

Reaction of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**) (325 mg, 0.61 mmol) with 2-ethynylpyrimidine (63 mg, 0.61 mmol) according to the procedure reported in scheme 92 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with EtOAc/MeOH (9:1) in hexanes 0 to 100%] 2-(3-acetyl-5-(pyrimidin-2-ylethynyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**116a**) (14 mg, 0.025 mmol, 4% yield) as a dark-yellow solid in the form of mixture of two rotamers; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.92 – 8.80 (m, 2H), 8.59 (t, $J = 5.0$ Hz) and 8.42 – 8.29 (m) (t & m, 2H), 8.51 – 8.45 (m, 1H), 7.66-6.93 (m, 6H), 5.42 and 5.24 (2s, 2H), 4.67 – 4.55 and 4.29 – 4.24 (2m, 1H), 4.52 – 4.31 (m, 2H), 4.19 and 3.86 (2s, 2H), 2.47 and 2.46 (2s, 3H), 1.27 (d, $J = 6.4$ Hz) and 1.01 (d, $J = 6.8$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.17, -121.75; MS (ES+): 560.6 (M+1); MS (ES-): 558.5 & 560.6 (M-1).

Scheme 117



Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorophenyl)amino)-2-oxoethyl)-N-isopropylacetamide (**117e**)

Step-1: Preparation of tert-butyl 2-(2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-isopropylacetamido)acetate (**117b**)

- 5 Reaction of tert-butyl 2-(isopropylamino)acetate (**117a**) (134 mg, 0.77 mmol, prepared according to the procedure reported by Brotherton-Pleiss, Christine E. et al; in PCT Int. Appl., 2014049047) with 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**97b**) (160 mg, 0.52 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with
10 CMA80 in CHCl₃ 0 to 30%] tert-butyl 2-(2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-isopropylacetamido)acetate (**117b**) (120 mg, 0.26 mmol, 50% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.56 (d, J = 0.9 Hz, 1H), 8.49 (s, 1H), 8.47 (s, 1H), 8.46 (s, 1H), 8.24 (s, 1H), 8.01 (d, J = 2.1 Hz, 1H), 7.33 (t, J = 8.2 Hz, 1H), 7.16 - 7.06 (m, 1H), 5.36 and 5.05 (2s, 2H), 4.67 - 4.52 and 4.34 - 4.27 (m, 1H), 4.26 and 3.84 (2s, 2H), 2.42
15 and 2.41 (2s, 3H), 1.51 and 1.36 (2s, 9H), 1.22 and 1.04 (2d, J = 6.8 Hz, 6H); MS (ES-) 464.5 (M-1).

Step-2: Preparation of 2-(2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-isopropylacetamido)acetic acid (**117c**)

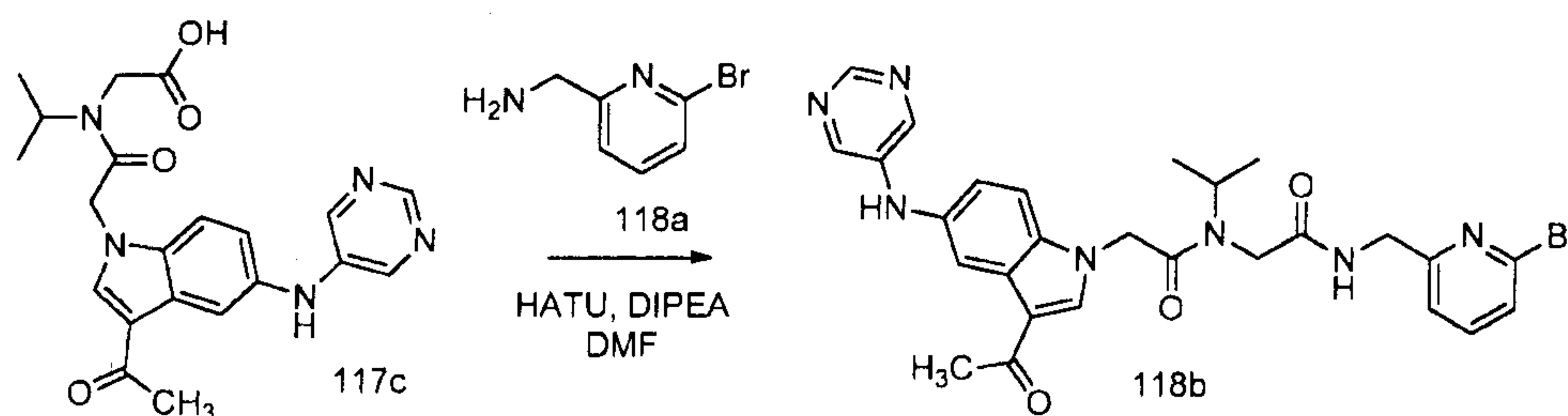
- Reaction of tert-butyl 2-(2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-isopropylacetamido)acetate (**117b**) (120 mg, 0.26 mmol) with TFA (0.4 mL, 5.16 mmol)
20 according to the procedure reported in step-2 of Scheme 2 gave after workup 2-(2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-isopropylacetamido)acetic acid (**117c**) (120 mg, 0.29 mmol, 114% yield) light orange gummy solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.57 (s, 1H), 8.48 (s, 2H), 8.25 (d, J = 1.3 Hz, 1H), 8.01 (t, J = 2.2 Hz, 1H), 7.36 and 7.34 (2s, 1H),
25 7.12 and 7.09 (2t, J = 1.9 Hz, 1H), 5.35 and 5.07 (s, 2H), 4.66 - 4.54 (m, 1H), 4.35 - 4.18 (m, 1H), 3.87 (s, 1H), 2.41 and 2.41 (2s, 3H), 1.23 and 1.04 (2d, J = 6.8 Hz, 6H); MS (ES+) 410.5 (M+1); MS (ES-) 408.5 (M-1).

Step-3: Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorophenyl)amino)-2-oxoethyl)-N-isopropylacetamide (**117e**)

- 30 Reaction of 2-(2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-isopropylacetamido)acetic acid (**117c**) (50 mg, 0.12 mmol) with 3-chloro-2-fluoroaniline (**117d**) (0.018 g, 0.122 mmol) according to the procedure reported in step-3 of Scheme 2 gave

after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 30%] 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorophenyl)amino)-2-oxoethyl)-N-isopropylacetamide (**117e**) (25 mg, 0.047 mmol, 38% yield) as an off-white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.33 and 9.84 (2s, 1H), 8.56 (s, 1H), 8.49 (s, 1H), 8.47 and 8.46 (2s, 2H), 8.25 and 8.23 (2s, 1H), 8.03 – 8.00 (m, 1H), 7.97 and 7.79 (2t, *J* = 7.6 Hz, 1H), 7.49 – 7.06 (m, 4H), 5.38 and 5.19 (2s, 2H), 4.75 – 4.58 and 4.37 – 4.25 (2m, 1H), 4.46 and 4.09 (2s, 2H), 2.42 and 2.41 (2s, 3H), 1.28 and 1.07 (2d, *J* = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ -126.50, -126.67; MS (ES⁺): 537.6 (M+1); MS (ES⁻): 535.5 (M-1).

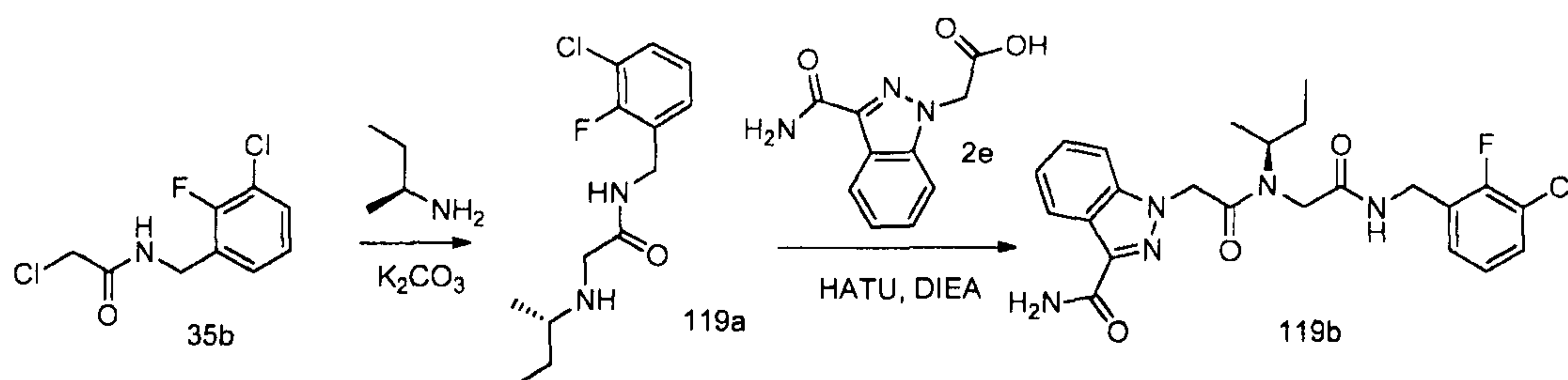
Scheme 118



Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((6-bromopyridin-2-yl)methyl)amino)-2-oxoethyl)-N-isopropylacetamide (**118b**)

Reaction of 2-(2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-isopropylacetamido)acetic acid (**117c**) (60 mg, 0.15 mmol) with (6-bromopyridin-2-yl)methanamine (**118a**) (27 mg, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 30%] 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((6-bromopyridin-2-yl)methyl)amino)-2-oxoethyl)-N-isopropylacetamide (**118b**) (5 mg, 0.086 mmol, 59% yield) as an off-white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.92 (t, *J* = 6.0 Hz, 1H), 8.56 and 8.55 (2s, 1H), 8.48 (s, 1H), 8.464 and 8.458 (2s, 2H), 8.24 and 8.19 (2s, 1H), 8.00 (t, 1H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.62 – 7.19 (m, 3H), 7.13 – 7.00 (m, 1H), 5.34 and 5.17 (2s, 2H), 4.67 – 4.54 and 4.28 – 4.24 (2m, 1H), 4.48 and 4.34 (2d, *J* = 6.0 Hz, 2H), 4.22 and 3.87 (2s, 2H), 2.40 and 2.39 (2s, 3H), 1.28 and 1.04 (d, *J* = 6.8 Hz, 6H); MS (ES⁺): 578.6, 580.6 (M+1); MS (ES⁻): 576.6, 578.5 (M-1).

Scheme 119



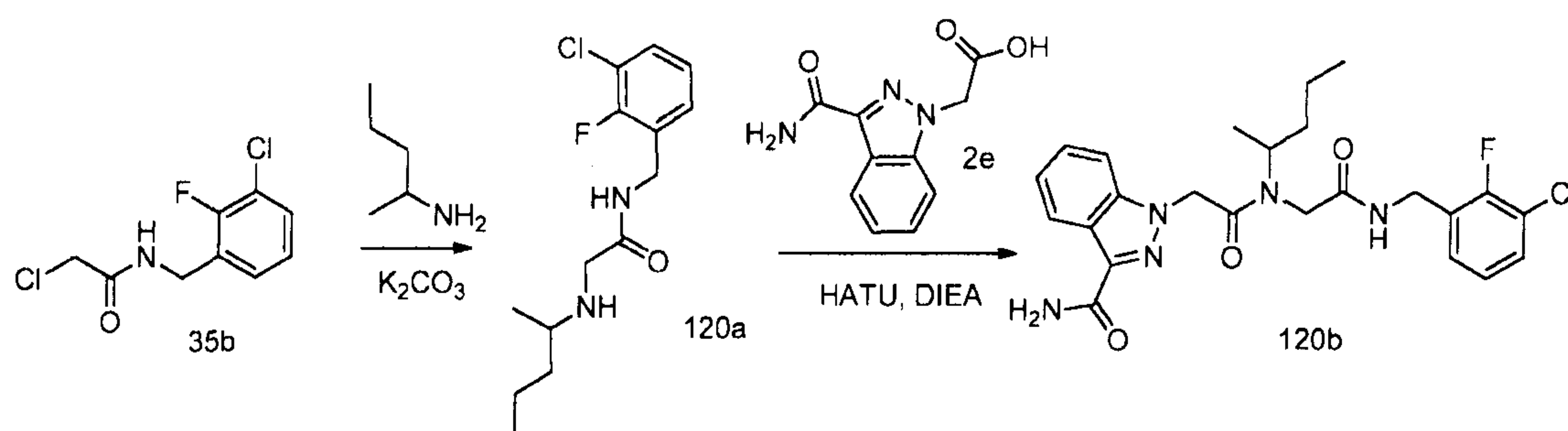
Preparation of (S)-1-(2-(sec-butyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**119b**)

- 5 Step-1: Preparation of (S)-2-(sec-butylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**119a**)
 Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (350 mg, 1.48 mmol) with
 (S)-butan-2-amine (271 mg, 3.71 mmol) according to the procedure reported in step-2 of
 Scheme 35 gave after workup (S)-2-(sec-butylamino)-N-(3-chloro-2-fluorobenzyl)acetamide
 (**119a**) (402 mg, 1.47 mmol, 99% yield) as a yellow oil, which was used in the next step
 10 without further purification; ^1H NMR (300 MHz, DMSO- d_6) δ 8.35 (t, J = 5.8 Hz, 1H), 7.52
 – 7.38 (m, 1H), 7.33 – 7.23 (m, 1H), 7.23 – 7.09 (m, 1H), 4.37 (d, J = 5.9 Hz, 2H), 3.13 (s,
 2H), 2.46 – 2.31 (m, 1H), 2.07 (s, 1H), 1.55 – 1.30 (m, 1H), 1.30 – 1.08 (m, 1H), 0.92 (d, J =
 6.3 Hz, 3H), 0.81 (t, J = 7.4 Hz, 3H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.65; MS (ES $^+$)
 273.4 (M+1); MS (ES $^-$) 271.3 (M-1);

- 15 Step-2: Preparation of (S)-1-(2-(sec-butyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**119b**)

Reaction of (S)-2-(sec-butylamino)-N-(3-chloro-2-fluorobenzyl)acetamide (**119a**) (180 mg,
 0.66 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (159 mg, 0.73 mmol)
 according to the procedure reported in step-3 of Scheme 2 gave after workup and purification
 20 by flash column chromatography [silica (12 g), eluting with CMA-80 in CHCl_3 0 to 60%]
 (S)-1-(2-(sec-butyl(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-
 indazole-3-carboxamide (**119b**) (220 mg, 0.46 mmol, 70% yield) as a white solid; ^1H NMR
 (300 MHz, DMSO- d_6) δ 8.82 (t, J = 5.7 Hz) and 8.35 (t, J = 5.9 Hz) (2t, 1H), 8.18 (d, J = 8.1
 Hz, 1H), 7.75 – 7.67 (m, 1H), 7.61 – 7.00 (m, 7H), 5.68 – 5.39 (m, 2H), 4.51 – 3.70 (m, 5H),
 25 1.63-0.50 (m, 8H); ^{19}F NMR (282 MHz, DMSO) δ -121.19, -121.76; MS (ES $^+$): 474.5
 (M+1), 496.5 (M+Na); (ES $^-$): 472.5 (M-1); 518.5 (M+Cl); [based on NMR, this compound is
 a mixture of two rotamers 2:1 ratio].

Scheme 120



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(pentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**120b**)

5 Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(pentan-2-ylamino)acetamide (**120a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (350 mg, 1.48 mmol) with pentan-2-amine (323 mg, 3.71 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup N-(3-chloro-2-fluorobenzyl)-2-(pentan-2-ylamino)acetamide (**120a**) (400 mg, 1.4 mmol, 94% yield) as a yellow oil, which was used in the next step

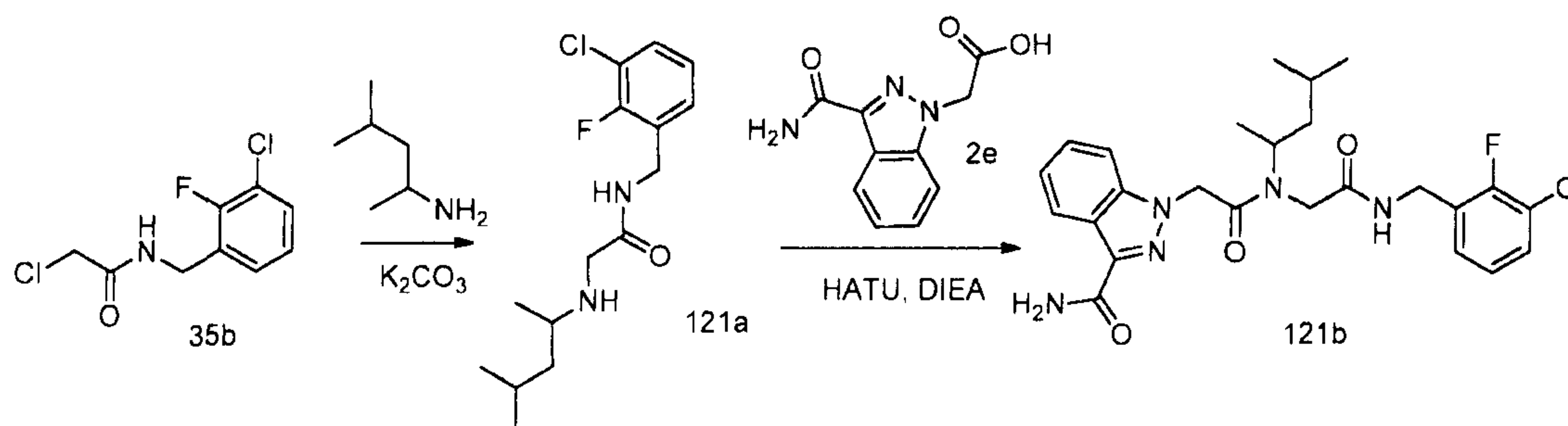
10 without further purification; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.36 (t, $J = 6.0$ Hz, 1H), 7.53 – 7.42 (m, 1H), 7.34 – 7.24 (m, 1H), 7.22 – 7.11 (m, 1H), 4.37 (d, $J = 5.8$ Hz, 2H), 3.14 (d, $J = 2.6$ Hz, 2H), 2.50 – 2.42 (m, 1H), 2.06 (s, 1H), 1.40 – 1.14 (m, 4H), 0.93 (d, $J = 6.3$ Hz, 3H), 0.84 (t, $J = 7.0$ Hz, 3H); ^{19}F NMR (282 MHz, DMSO) δ -121.65; MS (ES+) 287.4 (M+1); MS (ES-) 285.4 (M-1);

15 Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(pentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**120b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(pentan-2-ylamino)acetamide (**120a**) (146 mg, 0.51 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (123 mg, 0.56 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification

20 by flash column chromatography [silica (12 g), eluting with CMA-80 in CHCl_3 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(pentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**120b**) (174 mg, 0.36 mmol, 70% yield) as a white solid; ^1H NMR(300 MHz, $\text{DMSO}-d_6$) δ 8.81 (t, $J = 5.7$ Hz) and 8.35 (t, $J = 5.9$ Hz) (2t, 1H), 8.18 (d, $J = 8.1$ Hz, 1H), 7.71 (s, 1H), 7.57 – 7.10 (m, 7H), 5.66 – 5.35 (m, 2H), 4.63-3.67 (m, 5H), 1.45-0.69 (m, 10H); ^{19}F NMR (282 MHz, DMSO) δ -121.19, -121.75; MS (ES+): 488.5 (M+1), 510.5 (M+Na); (ES-): 486.5 (M-1). [based on NMR, this compound is a mixture of two rotamers with 3:1 ratio]

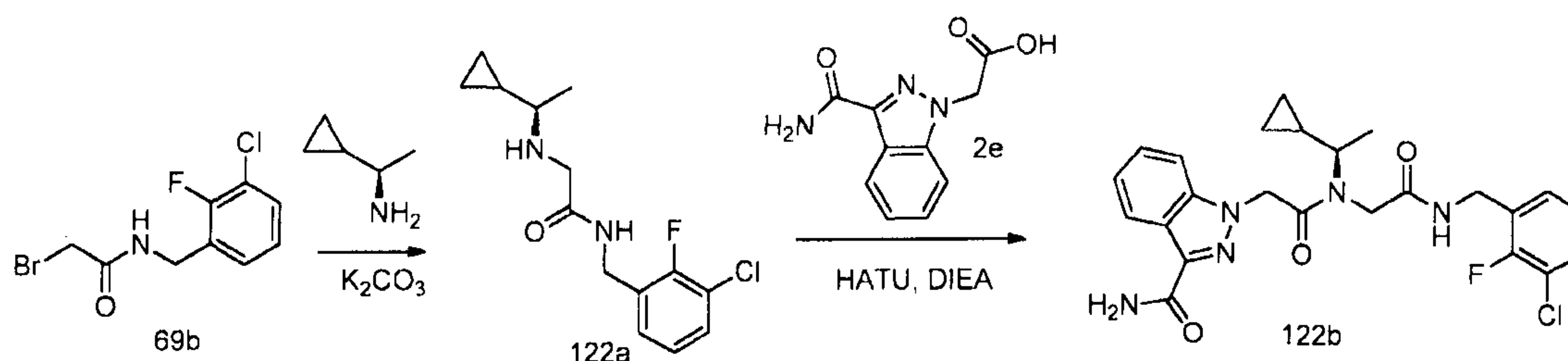
Scheme 121



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(4-methylpentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**121b**)

- 5 Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((4-methylpentan-2-yl)amino)acetamide (**121a**) Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (350 mg, 1.48 mmol) with 4-methylpentan-2-amine (375 mg, 3.71 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%]
- 10 to give N-(3-chloro-2-fluorobenzyl)-2-(4-methylpentan-2-ylamino)acetamide (**121a**) (235 mg, 0.78 mmol, 53% yield) as a yellow oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.35 (t, *J* = 6.0 Hz, 1H), 7.55 – 7.41 (m, 1H), 7.37 – 7.25 (m, 1H), 7.22 – 7.12 (m, 1H), 4.45 – 4.29 (m, 2H), 3.14 (d, *J* = 3.9 Hz, 2H), 2.54 – 2.49 (m, 1H), 2.06 (s, 1H), 1.75 – 1.51 (m, 1H), 1.35 – 1.13 (m, 1H), 1.13 – 0.98 (m, 1H), 0.92 (d, *J* = 6.2 Hz, 3H), 0.86 – 0.77 (m, 6H); ¹⁹F NMR (282
- 15 MHz, DMSO) δ -121.63; MS (ES⁺): 301.4 (M+1); MS (ES⁻): 299.4 (M-1);
- Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(4-methylpentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**121b**)
- Reaction of N-(3-chloro-2-fluorobenzyl)-2-(4-methylpentan-2-ylamino)acetamide (**121a**) (120 mg, 0.4 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (96 mg, 0.44
- 20 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA-80 in CHCl₃ 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(4-methylpentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**121b**) (142 mg, 0.28 mmol, 71% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.81 (t, *J* = 5.7 Hz) and 8.36 (t, *J* = 6.2 Hz) (2t, 1H),
- 25 8.25-8.11 (m, 1H), 7.72 (s, 1H), 7.57 – 7.17 (m, 7H), 5.78 – 5.25 (m, 2H), 4.66 – 4.02 (m, 5H), 1.56-0.63 (m, 12H); ¹⁹F NMR (282 MHz, DMSO) δ -121.17, -121.72; MS (ES⁺) 524.6 (M+Na); (ES⁻): 500.5 (M-1); [based on NMR, this compound is a mixture of two rotamers 4:1 ratio].

Scheme 122



Preparation of (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-cyclopropylethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**122b**)

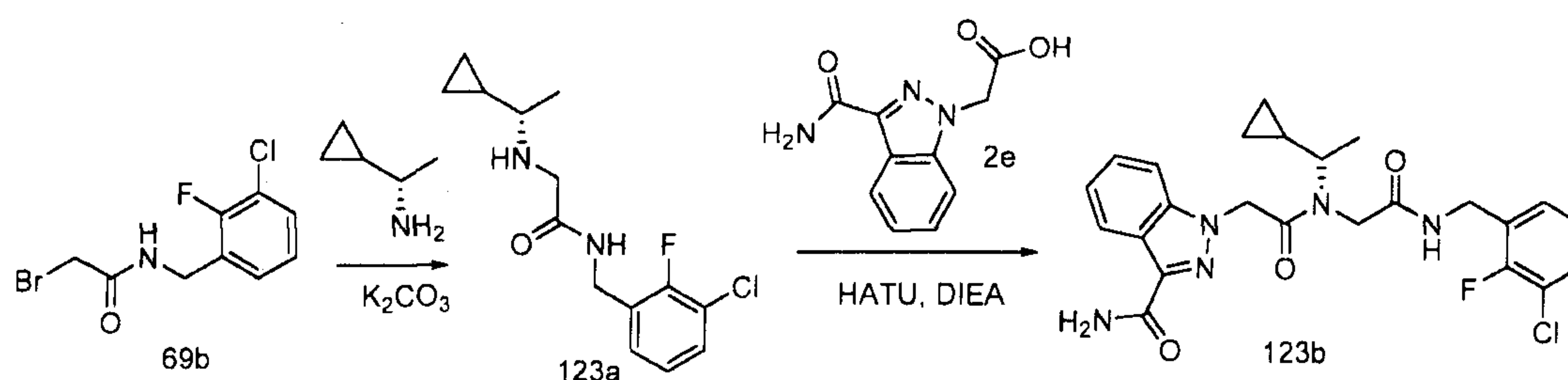
5 Step-1: Preparation of (R)-N-(3-chloro-2-fluorobenzyl)-2-((1-cyclopropylethyl)amino)acetamide (**122a**)

Reaction of 2-bromo-N-(3-chloro-2-fluorobenzyl)acetamide (**69b**) (323 mg, 1.16 mmol) with (R)-1-cyclopropylethanamine (99 mg, 1.16 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup (R)-N-(3-chloro-2-fluorobenzyl)-2-((1-cyclopropylethyl)amino)acetamide (**122a**) (310 mg, 1.09 mmol, 94% yield) as a yellow oil which was used as such without further purification; MS (ES⁺): 285.4 (M+1).

Step-2: Preparation of (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-cyclopropylethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**122b**)

Reaction of (R)-N-(3-chloro-2-fluorobenzyl)-2-((1-cyclopropylethyl)amino)acetamide (**122a**) (310 mg, 1.09 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (286 mg, 1.31 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (40 g), eluting with MeOH in CHCl₃ 0 to 10%] (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-cyclopropylethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**122b**) (0.251 g, 0.517 mmol, 47.4% yield) as a white solid as a mixture two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.82 (t, *J* = 5.7 Hz) and 8.29 (t, *J* = 5.9 Hz) (2t, 1H), 8.23 – 8.12 (m, 1H), 7.73 and 7.69 (2s, 1H), 7.59 – 6.96 (m, 7H), 5.68 – 5.39 (m, 2H), 4.46 (d, *J* = 5.5 Hz) and 4.39 – 4.26 (m) and 3.96 (s) (d & m & s, 4H), 3.80 – 3.62 and 3.60 – 3.46 (2m, 1H), 1.27 (d, *J* = 6.4 Hz) and 1.03 (d, *J* = 6.8 Hz) (2d, 3H), 1.15 – 0.79 (m, 1H), 0.61-0.00 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.19, -121.75; MS (ES⁺): 486.5, 488.5 (M+1), 508.5, 510.5 (M+Na); MS (ES⁻): 484.5 (M-1), 520.5, 522.5 (M+Cl).

Scheme 123



Preparation of (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-cyclopropylethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**123b**)

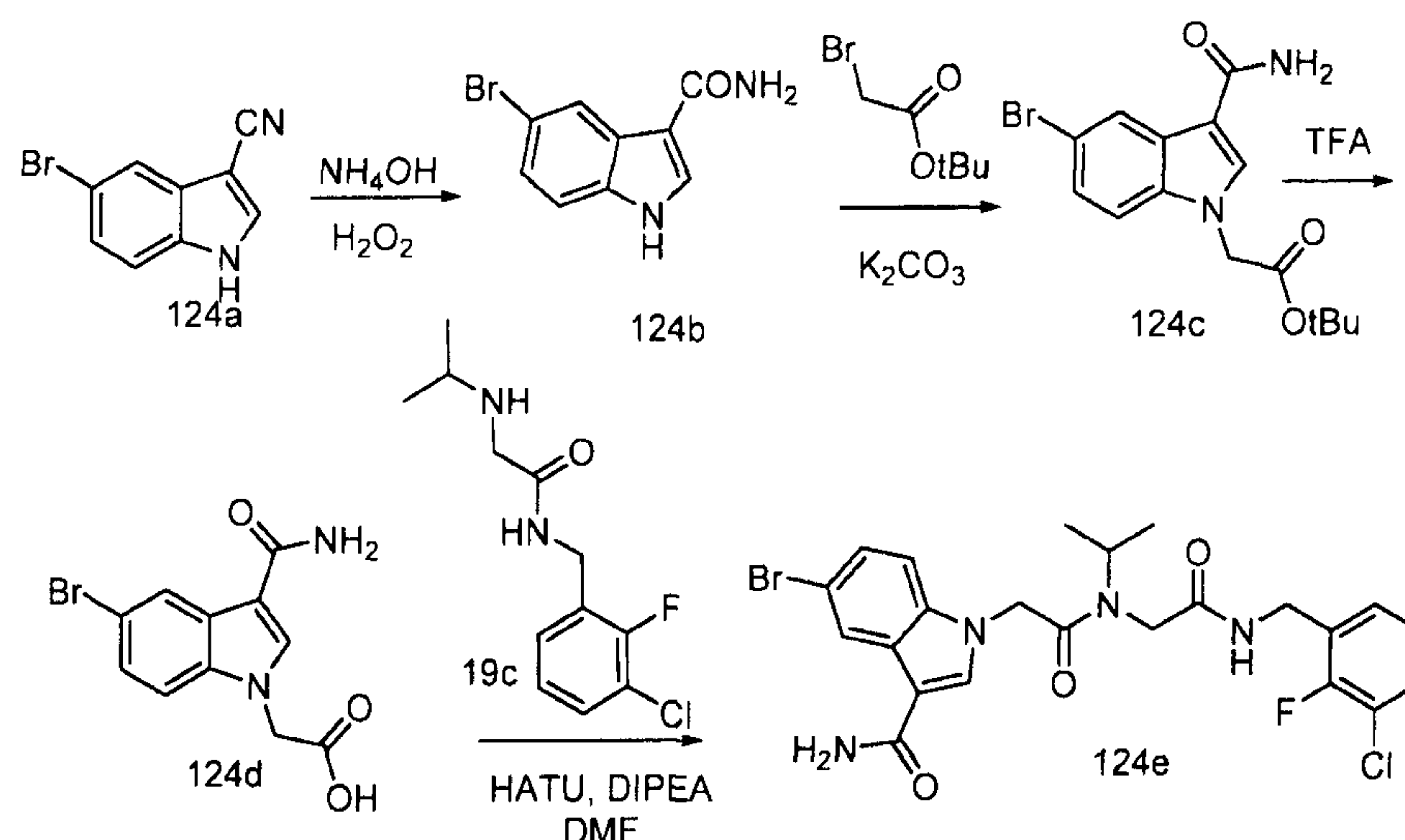
- 5 Step-1: Preparation of (S)-N-(3-chloro-2-fluorobenzyl)-2-((1-cyclopropylethyl)amino)acetamide (**123a**)

Reaction of 2-bromo-N-(3-chloro-2-fluorobenzyl)acetamide (**69b**) (355 mg, 1.27 mmol) with (S)-1-cyclopropylethanamine (108 mg, 1.27 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup (S)-N-(3-chloro-2-fluorobenzyl)-2-((1-cyclopropylethyl)amino)acetamide (**123a**) (354 mg, 1.24 mmol, 98% yield) as a thick yellow oil which was used as such in the next step; MS (ES⁺): 285.4 (M+1); MS (ES⁻): 319.3 (M+Cl)

Step-2: Preparation of (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-cyclopropylethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**123b**)

- 15 Reaction of (S)-N-(3-chloro-2-fluorobenzyl)-2-((1-cyclopropylethyl)amino)acetamide (**123a**) (350 mg, 1.23 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (323 mg, 1.48 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [First column: Silica gel, (24 g) eluting with MeOH in DCM from 0-20%; Second column silica gel, (24 g) eluting with MeOH in CHCl₃ from 0-10%] (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-cyclopropylethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**123b**) (0.079 g, 0.163 mmol, 13% yield) as a white solid in the form of mixture two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.83 (t, *J* = 5.7 Hz) and 8.30 (t, *J* = 5.9 Hz) (2t, 1H), 8.21 – 8.15 (m, 1H), 7.73 and 7.70 (2s, 1H), 7.62-6.96 (m, 7H), 5.70 – 5.36 (m, 2H), 4.46 (d, *J* = 5.5 Hz) and 4.36 – 4.26 (m) and 3.97 (s) (d & m & s, 4H), 3.80 – 3.63 and 3.59 – 3.45 (2m, 1H), 1.28 (d, *J* = 6.5 Hz) and 1.03 (d, *J* = 6.8 Hz) (2d, 3H), 1.15 – 0.79 (m, 1H), 0.60 to -0.02 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.19, -121.75. MS (ES⁺): 486.5 (M+1), 508.5 (M+Na); MS (ES⁻): 484.5 & 486.5 (M-1), 520.5 (M+Cl).

Scheme 124



Preparation of 5-bromo-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-3-carboxamide (**124e**)

5 Step-1: Preparation of 5-bromo-1H-indole-3-carboxamide (**124b**)

Reaction of 5-bromo-1H-indole-3-carbonitrile (**124a**) (1.38 g, 6.22 mmol) with ammonium hydroxide (4.85 mL, 124 mmol) and hydrogen peroxide (1.9 mL, 62.2 mmol) according to the procedure reported Scheme 65 gave after workup 5-bromo-1H-indole-3-carboxamide (**124b**) (1.2 g, 5.02 mmol, 81% yield) as an off-white solid; MS (ES⁺): 239.2, 241.2 (M+2),
 10 MS (ES⁻): 237.1, 239.1 (M-2).

Step-2: Preparation of tert-butyl 2-(5-bromo-3-carbamoyl-1H-indol-1-yl)acetate (**124c**)

Reaction of 5-bromo-1H-indole-3-carboxamide (**124b**) (1.2 g, 5.02 mmol) with tert-butyl 2-bromoacetate (1.11 mL, 7.53 mmol) using potassium carbonate (1.39 g, 10.04 mmol) as base according to the procedure reported step-1 of Scheme 45 gave after workup and purification
 15 by flash column chromatography [silica gel (40 g), eluting with CMA80 in CHCl₃ 0 to 15%] tert-butyl 2-(5-bromo-3-carbamoyl-1H-indol-1-yl)acetate (**124c**) (970 mg, 2.75 mmol, 55% yield) as off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.36 - 8.27 (m, 1H), 8.00 (s, 1H), 7.54 (brs, 1H), 7.43 (dd, J = 8.8, 0.6 Hz, 1H), 7.33 (dd, J = 8.7, 2.0 Hz, 1H), 6.96 (brs, 1H), 5.10 (s, 2H), 1.42 (s, 9H); MS (ES⁺): 353.4, 355.4 (M+2), MS (ES⁻): 351.3, 353.3 (M-1).

20 Step-3: Preparation of 2-(5-bromo-3-carbamoyl-1H-indol-1-yl)acetic acid (**124d**)

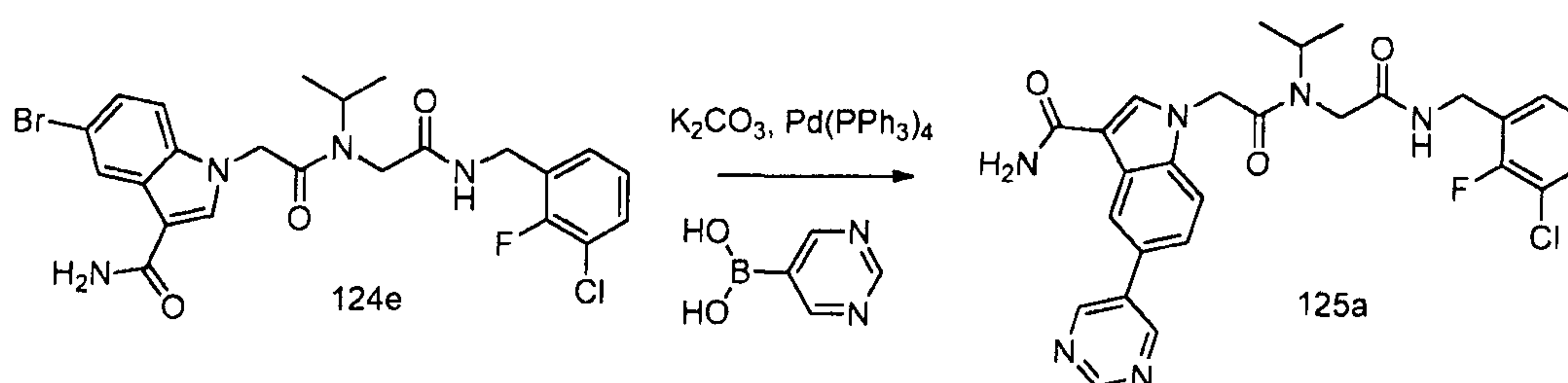
Reaction of tert-butyl 2-(5-bromo-3-carbamoyl-1H-indol-1-yl)acetate (**124c**) (500 mg, 1.42 mmol) with TFA (2.18 mL, 28.3 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and trituration of crude product with 30% EtOAc-hexane (10

mL) 2-(5-bromo-3-carbamoyl-1H-indol-1-yl)acetic acid (**124d**) (420 mg, 1.41 mmol, 100% yield) as light orange solid; ^1H NMR (300 MHz, DMSO- d_6) δ 13.24 (bs, 1H), 8.31 (d, $J = 1.9$ Hz, 1H), 8.01 (s, 1H), 7.65 - 7.38 (m, 2H), 7.32 (dd, $J = 8.7, 2.0$ Hz, 1H), 6.97 (s, 1H), 5.10 (s, 2H); MS (ES $^+$): 297.2, 299.3 (M+2); MS (ES $^-$): 295.2, 297.2 (M-2).

5 Step-4: Preparation of 5-bromo-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-3-carboxamide (**124e**)

Reaction of 2-(5-bromo-3-carbamoyl-1H-indol-1-yl)acetic acid (**124d**) (400 mg, 1.35 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (348 mg, 1.35 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup 5-bromo-1-(2-
10 ((2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-3-carboxamide (**124e**) (0.52 g, 0.967 mmol, 71.8% yield) as a white solid as a mixture of two rotamers; ^1H NMR (300 MHz, DMSO- d_6) (a mixture of two rotamers) δ 8.81 (t, $J = 5.7$ Hz) and 8.34 - 8.27 (m) (t & m, 2H), 7.97 (s, 1H), 7.59 - 6.76 (m, 7H), 5.32 and 5.14 (2s, 2H), 4.62 - 4.51 and 4.28 - 4.21 (2m, 1H), 4.46 and 4.32 (2d, $J = 5.6$ Hz, 2H), 4.15 and 3.83 (2s, 2H), 1.23 and 0.98 (2d, $J = 6.8$ Hz, 6H); ^{19}F NMR (282 MHz, DMSO- d_6) (a mixture of two
15 rotamers) δ -121.22 and -121.76; MS (ES $^+$): 561.4 (M+23), MS (ES $^-$): 571.4, 573.3 (M+Cl).

Scheme 125



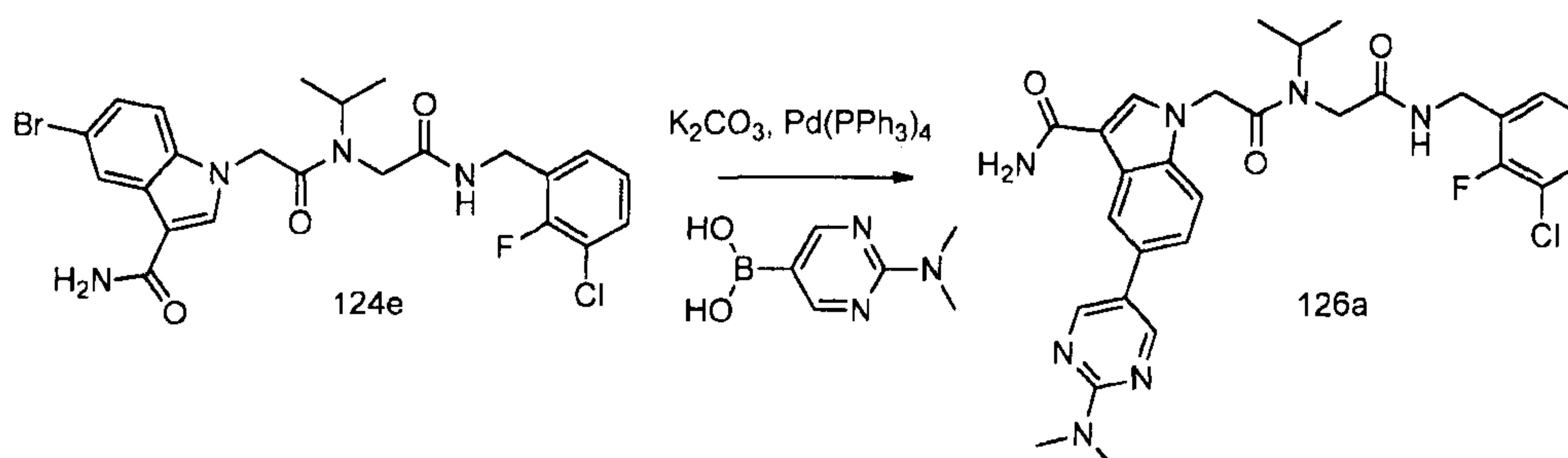
20 Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(pyrimidin-5-yl)-1H-indole-3-carboxamide (**125a**)

Reaction of 5-bromo-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-3-carboxamide (**124e**) (120 mg, 0.22 mmol) with pyrimidin-5-ylboronic acid (33 mg, 0.27 mmol) according the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica
25 gel (12 g), eluting with CMA80 in CHCl_3 0 to 30%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(pyrimidin-5-yl)-1H-indole-3-carboxamide (**125a**) as a white solid as a mixture of rotamers in 2:1 ratio; ^1H NMR (300 MHz, DMSO- d_6) δ 9.167 and 9.161 (2s, 1H), 9.138 and 9.131 (2s, 2H), 8.83 and 8.33

(2t, $J = 5.7$ Hz, 1H), 8.45 (s, 1H), 8.01 and 7.99 (2s, 1H), 7.74 – 6.80 (m, 7H), 5.37 and 5.19 (2s, 2H), 4.65 – 4.53 and 4.31 – 4.20 (2m, 1H), 4.48 and 4.33 (2d, $J = 5.6$ Hz, 2H), 4.18 and 3.85 (2s, 2H), 1.25 and 1.00 (2d, $J = 6.6$ Hz, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.21 and -121.79; MS (ES+) 537.5 (M+1), 559.5 (M+23), MS (ES-) 571.5 (M+Cl).

5

Scheme 126



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(2-(dimethylamino)pyrimidin-5-yl)-1H-indole-3-carboxamide (**126a**)

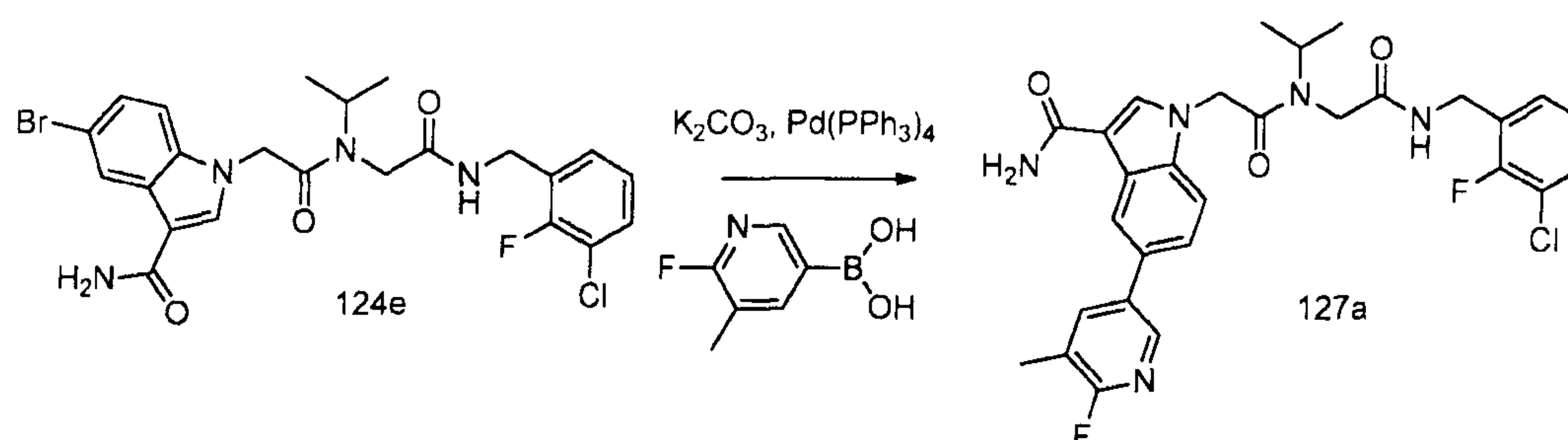
Reaction of 5-bromo-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-

10 oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-3-carboxamide (**124e**) (120 mg, 0.22 mmol) with 2-(dimethylamino)pyrimidin-5-ylboronic acid (45 mg, 0.27 mmol) according the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl_3 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(2-

15 (dimethylamino)pyrimidin-5-yl)-1H-indole-3-carboxamide (**126a**) (85 mg, 0.15 mmol, 66% yield) as a white solid as a mixture of rotamers in 2:1 ratio; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.82 (t, $J = 5.8$ Hz, 1H), 8.66 (s, 2H), 8.37 - 8.23 (m, 1H), 7.99 - 7.90 (m, 2H), 7.66 – 6.72 (m, 6H), 5.33 and 5.15 (2s, 2H), 4.64 - 4.51 and 4.28 - 4.22 (2m, 1H), 4.48 and 4.32 (2d, $J = 5.8$ Hz, 2H), 4.17 and 3.84 (2s, 2H), 3.178 and 3.172 (2s, 6H), 1.24 and 0.99 (2d, $J = 6.8$ Hz,

20 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.21 and -121.77; MS (ES+): 580.6 (M+1); MS (ES-): 614.6 (M+Cl).

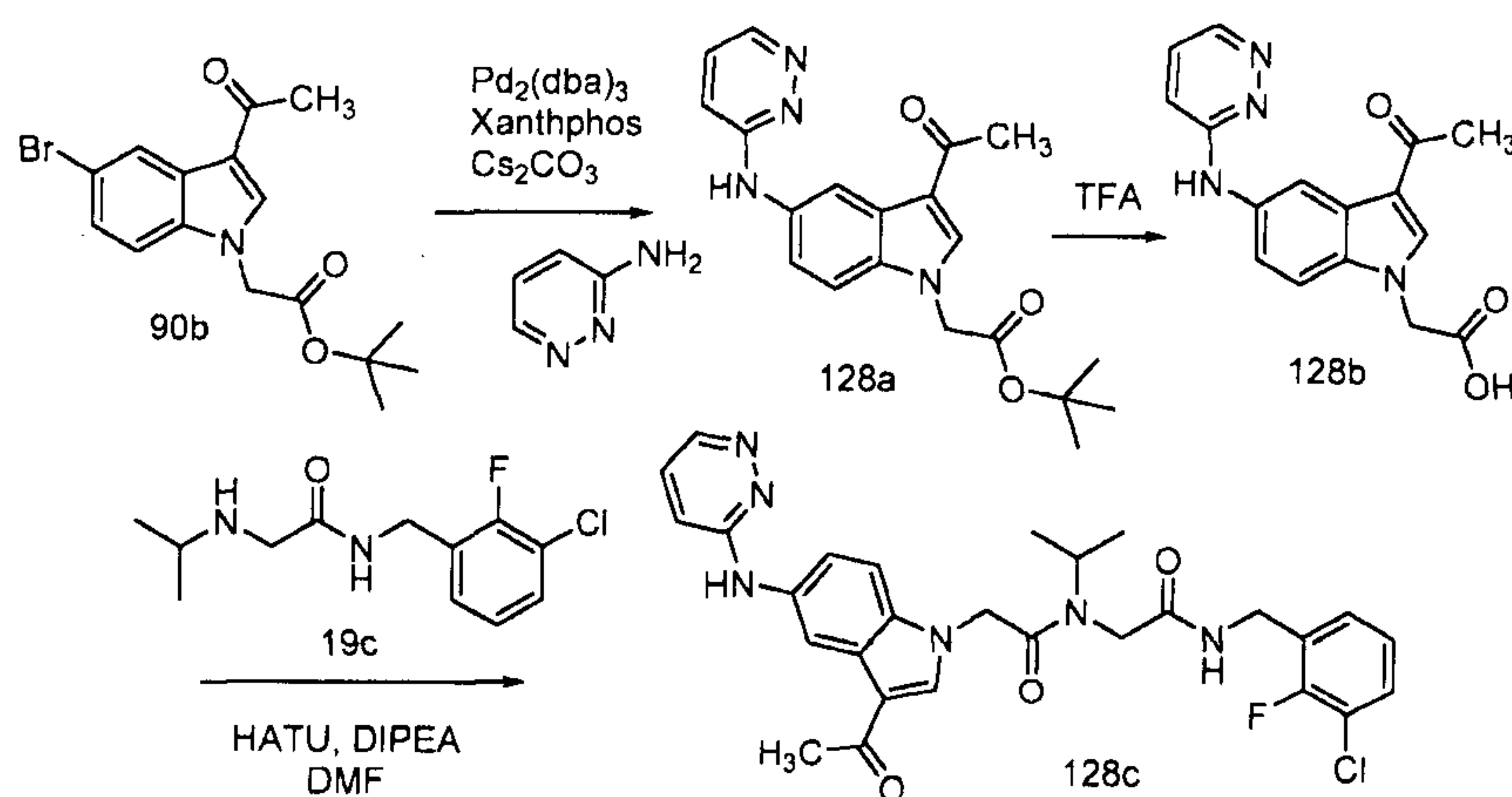
Scheme 127



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(6-fluoro-5-methylpyridin-3-yl)-1H-indole-3-carboxamide (**127a**)

Reaction of 5-bromo-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-3-carboxamide (**124e**) (120 mg, 0.22 mmol) with 6-fluoro-5-methylpyridin-3-ylboronic acid (0.041 g, 0.268 mmol) according the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 30%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(6-fluoro-5-methylpyridin-3-yl)-1H-indole-3-carboxamide (**127a**) (95 mg, 0.17 mmol, 75% yield) as a white solid as a mixture of rotamers in 2:1 ratio; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.83 (t, *J* = 5.7 Hz, 1H), 8.40 – 8.29 (m, 2H), 8.17 – 8.08 (m, 1H), 7.98 and 7.97 (2s, 1H), 7.61 – 7.34 (m, 5H), 7.22 and 7.03 (2t, *J* = 7.8 Hz, 1H), 6.94 (bs, 1H), 5.35 and 5.18 (2s, 2H), 4.66 – 4.52 and 4.30 – 4.22 (2m, 1H), 4.48 and 4.33 (d, *J* = 5.6 Hz, 2H), 4.18 and 3.85 (2s, 2H), 2.34 (s, 3H), 1.24 and 1.00 (d, *J* = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ -76.98, -121.21 and -121.78; MS (ES⁺): 568.6 (M+1), 590.5 (M+23), MS (ES⁻): 602.5 (M+Cl).

Scheme 128



Preparation of 2-(3-acetyl-5-(pyridazin-3-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**128c**)

Step-1: Preparation of tert-butyl 2-(3-acetyl-5-(pyridazin-3-ylamino)-1H-indol-1-yl)acetate (**128a**)

Reaction of tert-butyl 2-(3-acetyl-5-bromo-1H-indol-1-yl)acetate (**90b**) (1.0 g, 2.84 mmol) with pyridazin-3-amine (0.41 g, 4.26 mmol) according to the procedure reported in step-1 of Scheme 97 gave after workup and purification by flash column chromatography [silica gel

(40 g), eluting with CMA80 in CHCl₃ 0 to 20%] tert-butyl 2-(3-acetyl-5-(pyridazin-3-ylamino)-1H-indol-1-yl)acetate (**128a**) (180 mg, 0.49 mmol, 17% yield) as light yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.22 (s, 1H), 8.61 (d, J = 4.6 Hz, 1H), 8.45 - 8.35 (m, 1H), 8.27 (s, 1H), 7.73 (dd, J = 8.9, 2.1 Hz, 1H), 7.47 - 7.32 (m, 2H), 7.12 - 7.02 (m, 1H), 5.09 (s, 2H), 2.43 (s, 3H), 1.44 (s, 9H); MS (ES⁺): 367.5 (M+1); 389.5 (M+Na); (ES⁻): 365.4 (M-1).

Step-2: Preparation of 2-(3-acetyl-5-(pyridazin-3-ylamino)-1H-indol-1-yl)acetic acid (**128b**)

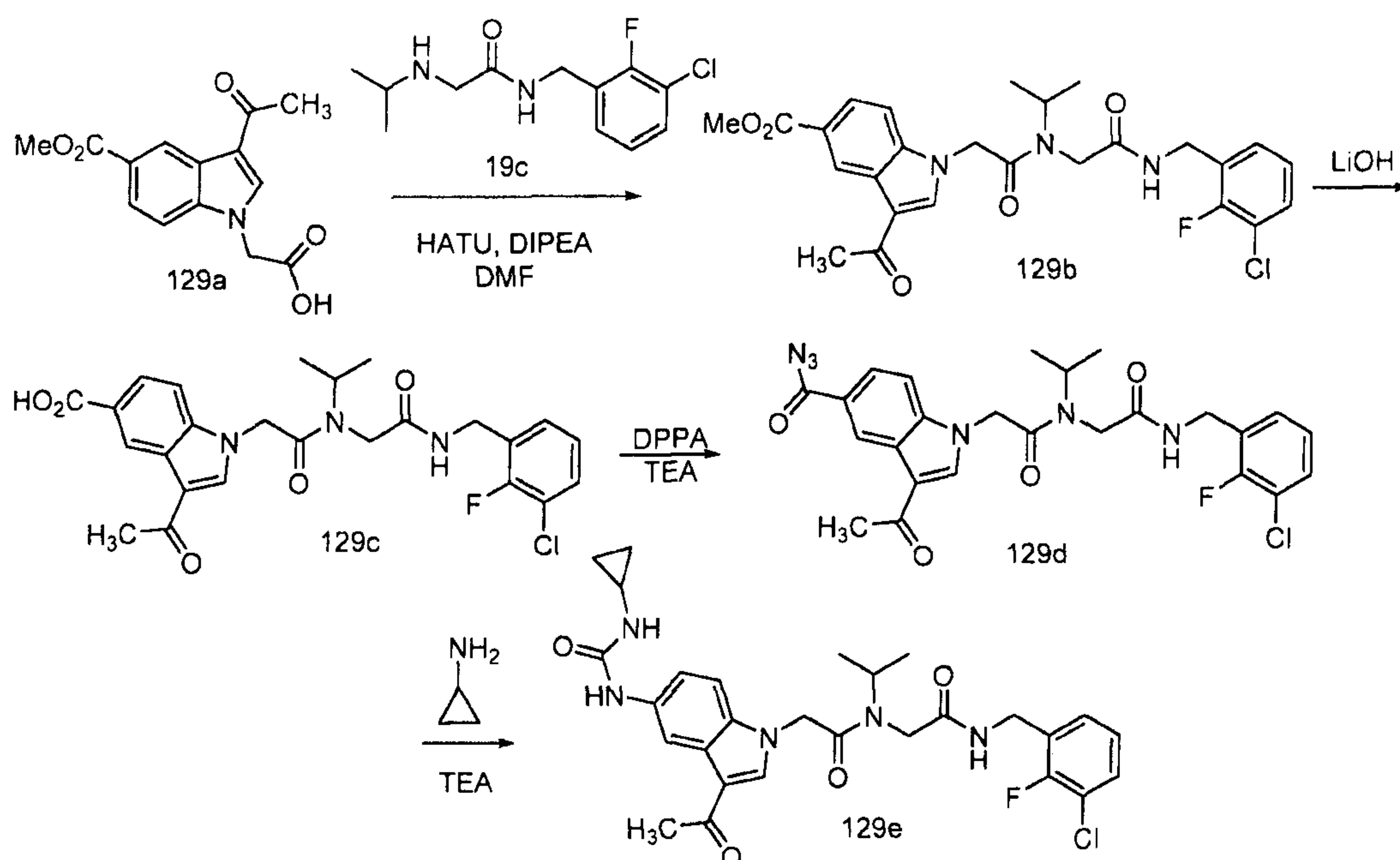
Reaction of tert-butyl 2-(3-acetyl-5-(pyridazin-3-ylamino)-1H-indol-1-yl)acetate (**128a**) (120 mg, 0.33 mmol) with TFA (0.63 mL, 8.19 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup 2-(3-acetyl-5-(pyridazin-3-ylamino)-1H-indol-1-yl)acetic

acid (**128b**) (0.12 g, 0.28 mmol, 88% yield) as light orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.45 (brs, 1H), 10.24 (s, 1H), 8.76 (d, J = 4.7 Hz, 1H), 8.38 (d, J = 2.3 Hz, 2H), 7.81 (dd, J = 9.3, 4.5 Hz, 1H), 7.62 - 7.43 (m, 2H), 7.32 - 7.10 (m, 1H), 5.15 (s, 2H), 2.44 (s, 3H); MS (ES⁺): 311.4 (M+1); (ES⁻): 309.4 (M-1).

Step-3: Preparation of 2-(3-acetyl-5-(pyridazin-3-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**128c**)

Reaction of 2-(3-acetyl-5-(pyridazin-3-ylamino)-1H-indol-1-yl)acetic acid (**128b**) (60 mg, 0.19 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (50 mg, 0.19 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (12 g), eluting with CMA-80 in CHCl₃ 0-100%] 2-(3-acetyl-5-(pyridazin-3-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**128c**) (54 mg, 0.098 mmol, 51% yield) as an off-white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.20 (s, 1H), 8.82 and 8.34 (2t, J = 5.7 Hz, 1H), 8.65 - 8.55 (m, 1H), 8.40 (m, 1H), 8.23 and 8.17 (2s, 1H), 7.65 (dd, J = 8.8, 2.2 Hz, 1H), 7.57 - 7.34 (m, 4H), 7.27 - 7.17 (m, 1H), 7.12 - 7.02 (m, 1H), 5.33 and 5.15 (2s, 2H), 4.65 - 4.53 and 4.31 - 4.21 (2m, 1H), 4.48 and 4.35 (2d, J = 5.8 Hz, 2H), 4.19 and 3.86 (2s, 2H), 2.42 and 2.41 (2s, 3H), 1.26 and 1.00 (2d, J = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.18 and -121.86; MS (ES⁺): 551.6 (M+1), MS (ES⁻): 585.5 (M+Cl).

Scheme 129



Preparation of 2-(3-acetyl-5-(3-cyclopropylureido)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**129e**)

- 5 Step-1: Preparation of methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylate (**129b**)

Reaction of 2-(3-acetyl-5-(methoxycarbonyl)-1H-indol-1-yl)acetic acid (**129a**) (154 mg, 0.56 mmol, prepared according to the procedure reported by Altmann, Eva et al, in PCT Int. Appl., WO 2012/093101) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**)

- 10 (174 mg, 0.67 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (12 g), eluting with MeOH in CHCl₃ 0-10%] methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylate (**129b**) (261 mg, 0.51 mmol, 90% yield) as a light brown gum; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.87 (d, *J* = 0.6 Hz) and 8.86 (d, *J* = 0.6 Hz) (2d, 1H), 8.82 (t, *J* = 5.7 Hz) and 8.34 (2t, 1H), 8.40 and 8.36 (2s, 1H), 7.85 (dd, *J* = 8.7, 1.7 Hz) and 7.79 (dd, *J* = 8.7, 1.7 Hz) (2dd, 1H), 7.63 – 6.93 (m, 4H), 5.42 and 5.23 (2s, 2H), 4.68 – 4.51 and 4.28-4.18 (2m, 1H), 4.33 (d, *J* = 6.1 Hz) and 4.25 (d, *J* = 6.3 Hz) (2d, 2H), 4.19 and 3.85 (2s, 2H), 3.884 and 3.878 (2s, 3H), 2.47 and 2.45 (2s, 3H), 1.27 (d, *J* = 6.4 Hz) and 1.00 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.19, -121.76; MS (ES⁺): 516.5 (M+1), MS (ES⁻): 514.5 (M-1).
- 20

Step-2: Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**129c**)

To a solution of methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylate (**129b**) (560 mg, 1.09 mmol) in THF (8 mL) and MeOH (8 mL) was added a solution of lithium hydroxide hydrate (279 mg, 6.51 mmol) in water (8 mL) and stirred at room temperature for 3 days. The reaction mixture was concentrated to remove THF and MeOH, diluted with water (4 mL), acidified with 4 N HCl and solid obtained was collected by filtration, dried under vacuum to give 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**129c**) (360 mg, 0.72 mmol, 66% yield) as a yellow solid, which was used in the next step without further purification; ¹H NMR (300 MHz, DMSO-*d*₆, a mixture of two rotamers) δ 8.88 – 8.79 and 8.40 – 8.31 (2m, 3H), 7.82 (dd, *J* = 8.6, 1.7 Hz,) and 7.78 (dd, *J* = 8.6, 1.7 Hz) (2dd, 1H), 7.62 – 6.88 (m, 4H), 5.41 and 5.22 (2s, 2H), 4.64 – 4.51 and 4.29 – 4.20 (2m, 1H), 4.47 (d, *J* = 5.5 Hz) and 4.33 (d, *J* = 6.0 Hz) (2d, 2H), 4.19 and 3.85 (2s, 2H), 2.46 and 2.44 (2s, 3H), 1.26 (d, *J* = 6.4 Hz) and 1.00 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.19, -121.76; MS (ES⁺): 524.5 & 526.5 (M+Na); MS (ES⁻): 536.5 & 538.5 (M+Cl).

Step-3: Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carbonyl azide (**129d**)

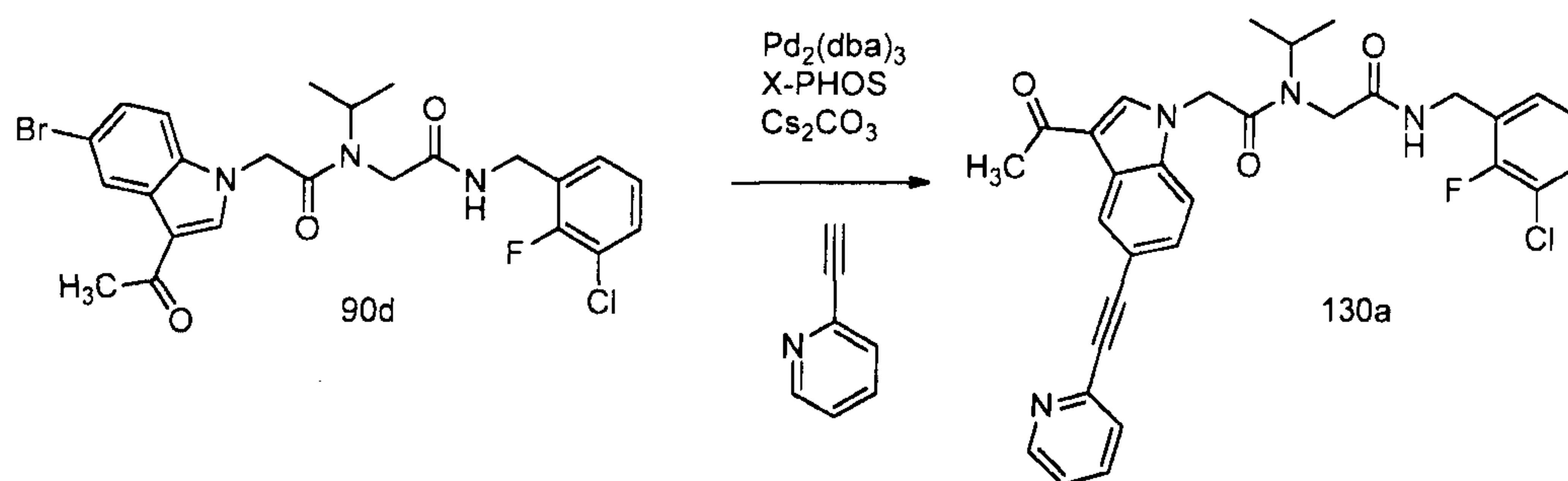
A suspension of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**129c**) (139 mg, 0.28 mmol) in THF (10 mL) was treated with triethylamine (0.039 μL, 0.28 mmol) and stirred at room temperature for 15 min. The mixture was then treated with diphenyl phosphorazidate (0.062 mL, 0.277 mmol) and stirred at room temperature for 15 h. The reaction mixture was concentrated in vacuum to dryness, solid obtained was triturated with DCM, collected by filtration, dried under vacuum to afford 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carbonyl azide (**129d**); MS (ES⁻): 525.5 (M-1)

Step-4: Preparation of 2-(3-acetyl-5-(3-cyclopropylureido)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**129e**)

A suspension of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carbonyl azide (**129d**) (75 mg, 0.14 mmol) in THF/Tol (24 mL, Ratio: 1:2) was heated at reflux for 4h, cooled to room temperature and concentrated in vacuum to dryness. The residue obtained was dissolved in THF (20 mL) and ACN (10 mL) followed by the addition of cyclopropanamine (16.25 mg,

0.29 mmol) and triethylamine (0.060 μ L, 0.427 mmol). The reaction mixture was stirred at room temperature overnight, diluted with EtOAc (100 mL), washed with water (3x), dried, filtered and concentrated in vacuum. The residue was purified by column chromatography [silica (12 g), eluting with CMA80 in CHCl_3 0 to 40%] followed by preparative HPLC with water/ACN to give 2-(3-acetyl-5-(3-cyclopropylureido)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**129e**) (6 mg, 10.79 μ mol, 6% yield) as a white solid after lyophilization; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) (a mixture of two rotamers) δ 8.84 – 8.13 (m, 4H), 7.60 – 6.90 (m, 5H), 6.27 (d, J = 2.3 Hz, 1H), 5.29 and 5.11 (2s, 2H), 4.66 – 4.50 and 4.28-4.20 (2m, 1H), 4.47 (d, J = 5.4 Hz) and 4.34 (d, J = 5.8 Hz) (2d, 2H), 4.17 and 3.84 (2s, 2H), 2.40 and 2.39 (2s, 3H), 1.24 (d, J = 6.3 Hz) and 1.00 (d, J = 6.8 Hz) (2d, 6H), 0.71 – 0.55 (m, 2H), 0.50 – 0.31 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -73.45 (TFA peak), -121.20, -121.82; MS (ES⁺); 578.5 (M+Na); MS (ES⁻): 554.5 (M-1).

Scheme 130



Preparation of 2-(3-acetyl-5-(pyridin-2-ylethynyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**130a**)

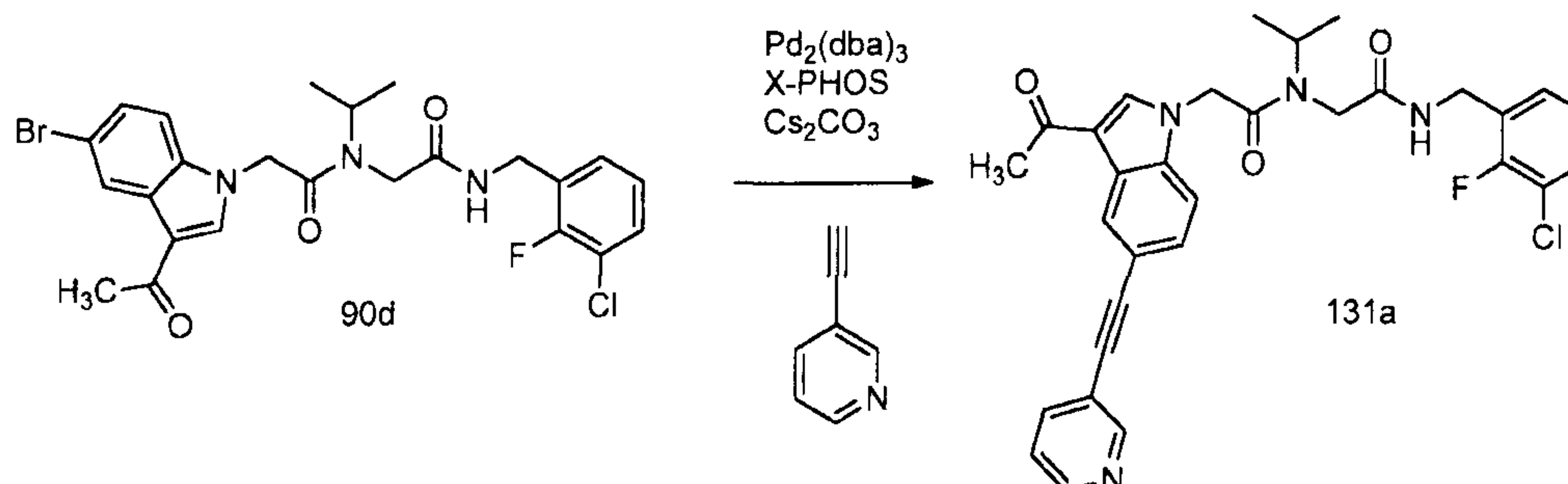
Reaction of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**) (301 mg, 0.56 mmol) with 2-ethynylpyridine (58 mg, 0.56 mmol) according to the procedure reported in scheme 92 gave after workup and purification by flash column chromatography [silica gel 12 g, eluting with EtOAc/MeOH (9:1) in hexanes 0 to 100%] 2-(3-acetyl-5-(pyridin-2-ylethynyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**130a**) (17 mg, 0.030 mmol, 5% yield) as a dark-yellow solid as a mixture of two rotamers; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.84 (t, J = 5.8 Hz, D_2O exchangeable) and 8.39 – 8.31 (m) (2H), , 8.65 – 8.57 (m, 1H), 8.43 (d, J = 1.5 Hz, 1H), 7.92-7.81 (m, 1H), 7.69 and 7.67 (2s, 1H), 7.63-6.94 (m, 6H), 5.41 and 5.23 (2s, 2H), 4.65 – 4.55 and 4.29 – 4.24 (2m, 1H), 4.52 – 4.30 (m, 2H), 4.19 and 3.86 (2s, 2H), 2.47 and 2.45 (2s, 3H), 1.27 (d, J = 6.4 Hz) and 1.01 (d, J = 6.7 Hz) (2d,

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6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.17, -121.76; MS (ES⁺): 559.5, 561.6 (M+1); MS (ES⁻): 558.5, 557.5 (M-1), 593.5 (M+Cl).

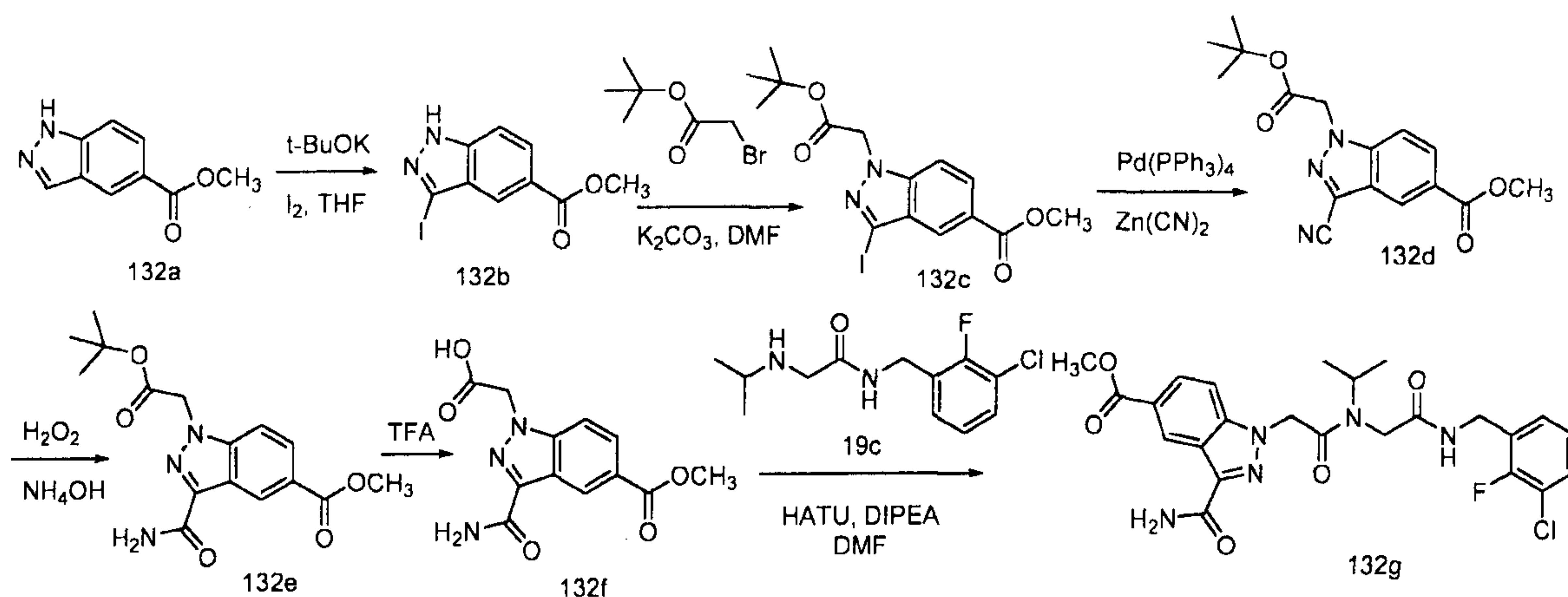
Scheme 131



5 Preparation of 2-(3-acetyl-5-(pyridin-3-ylethynyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**131a**)

Reaction of 2-(3-acetyl-5-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**90d**) (301 mg, 0.56 mmol) with 3-ethynylpyridine (58 mg, 0.56 mmol) according to the procedure reported in scheme 92 gave after workup and
 10 purification by flash column chromatography [silica gel 12 g, eluting with MeOH in CHCl_3 0 to 20%] 2-(3-acetyl-5-(pyridin-3-ylethynyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**131a**) (14 mg, 0.025 mmol, 5% yield) as a dark-yellow solid as a mixture of two rotamers; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.84 (t, J = 5.7 Hz) and 8.44-8.32 (t & m, 3H), 8.81 – 8.78 (m, 1H), 8.60 – 8.55 (m, 1H), 8.02
 15 (dt, J = 7.9, 1.9 Hz, 1H), 7.66-6.94 (m, 6H), 5.41 and 5.22 (2s, 2H), 4.68 – 4.54 and 4.30 – 4.22 (2m, 1H), 4.48 (d, J = 5.6 Hz) and 4.34 (d, J = 6.5 Hz) (2d, 2H), 4.19 and 3.86 (2s, 2H), 2.46 and 2.45 (2s, 3H), 1.27 (d, J = 6.4 Hz) and 1.01 (d, J = 6.8 Hz) (2d, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.18, -121.77; MS (ES⁺): 559.61, 561.58 (M+1); MS (ES⁻): 559.5, 557.5 (M-1), 593.5 (M+Cl).

Scheme 132



Preparation of methyl 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**132g**)

Step-1: Preparation of methyl 3-iodo-1H-indazole-5-carboxylate (**132b**)

To a solution of methyl 1H-indazole-5-carboxylate (**132a**) (5 g, 28.4 mmol) in THF (40 mL) was added I₂ (10.81 g, 42.6 mmol) and KOtBu (7.96 g, 71.0 mmol) at 0 °C, the resulting mixture was stirred for 3h at room temperature. The reaction mixture was diluted with 10% aqueous sodium thiosulfate and extracted with EtOAc (3 x 40 mL). The combined organic layers were washed with water, brine, dried and concentrated in vacuum. The obtained solid was washed with MeOH (20 mL) to give methyl 3-iodo-1H-indazole-5-carboxylate (**132b**) (5.6 g, 18.54 mmol, 65% yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.87 (s, 1H), 8.08 – 8.03 (m, 1H), 7.97 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.65 (dd, *J* = 8.8, 0.7 Hz, 1H), 3.88 (s, 3H); MS (ES⁺): 303.2 (M+1); MS (ES⁻): 301.2 (M-1).

Step-2: Preparation of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-iodo-1H-indazole-5-carboxylate (**132c**)

Reaction of methyl 3-iodo-1H-indazole-5-carboxylate (**132b**) (5 g, 16.55 mmol) with *tert*-butyl 2-bromoacetate (4.84 g, 24.83 mmol) according to the procedure reported in step-1 of Scheme 56 gave after workup and trituration of solid with hexane (50 mL) methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-iodo-1H-indazole-5-carboxylate (**132c**) (5.74 g, 13.79 mmol, 83% yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.16 – 7.92 (m, 2H), 7.89 – 7.67 (m, 1H), 5.37 (s, 2H), 3.90 (s, 3H), 1.40 (s, 9H); MS (ES⁺): 439.4 (M+Na).

Step-3: Preparation of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-cyano-1H-indazole-5-carboxylate (**132d**)

A mixture of Pd(Ph₃P)₄ (83 mg, 0.072 mmol), methyl 1-(2-tert-butoxy-2-oxoethyl)-3-iodo-1*H*-indazole-5-carboxylate (**132c**) (300 mg, 0.72 mmol), zinc cyanide (110 mg, 0.94 mmol) in DMF (5 mL) was heated at 120 °C for 30 min on microwave under argon atmosphere. The reaction was cooled to room temperature diluted with EtOAc (100 mL), washed with water, brine, dried, filtered and concentrated in vacuum. The residue was purified by column chromatography [silica (12 g), eluting with EtOAc in hexane 0 to 30%] to give methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-cyano-1*H*-indazole-5-carboxylate (**132d**) (125 mg, 0.4 mmol, 55% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.49 (s, 1H), 8.20 – 8.10 (m, 1H), 8.07 – 7.99 (m, 1H), 5.58 (s, 2H), 3.92 (s, 3H), 1.41 (s, 9H); MS (ES⁺): 316.4 (M+1); 338.4 (M+Na); MS (ES⁻): 314.4 (M-1).

Step-4: Preparation of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-carbamoyl-1*H*-indazole-5-carboxylate (**132e**)

Reaction of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-cyano-1*H*-indazole-5-carboxylate (**132d**) (795 mg, 2.52 mmol) in ethanol (16 mL) using conc. NH₄OH (8 mL, 54.4 mmol) and H₂O₂ (aq. 35%, 1.56 mL, 15.13 mmol) according to the procedure reported in Scheme 65 gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM 0 to 50%] methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-carbamoyl-1*H*-indazole-5-carboxylate (**132e**) (302 mg, 0.91 mmol, 36% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.93 – 8.83 (m, 1H), 8.03 (dd, *J* = 8.9, 1.6 Hz, 1H), 7.92 (s, 1H), 7.89 – 7.79 (m, 1H), 7.61 (s, 1H), 5.41 (s, 2H), 3.91 (s, 3H), 1.41 (s, 9H); MS (ES⁺): 334.4 (M+1); 356.4 (M+Na); MS (ES⁻): 332.3 (M-1).

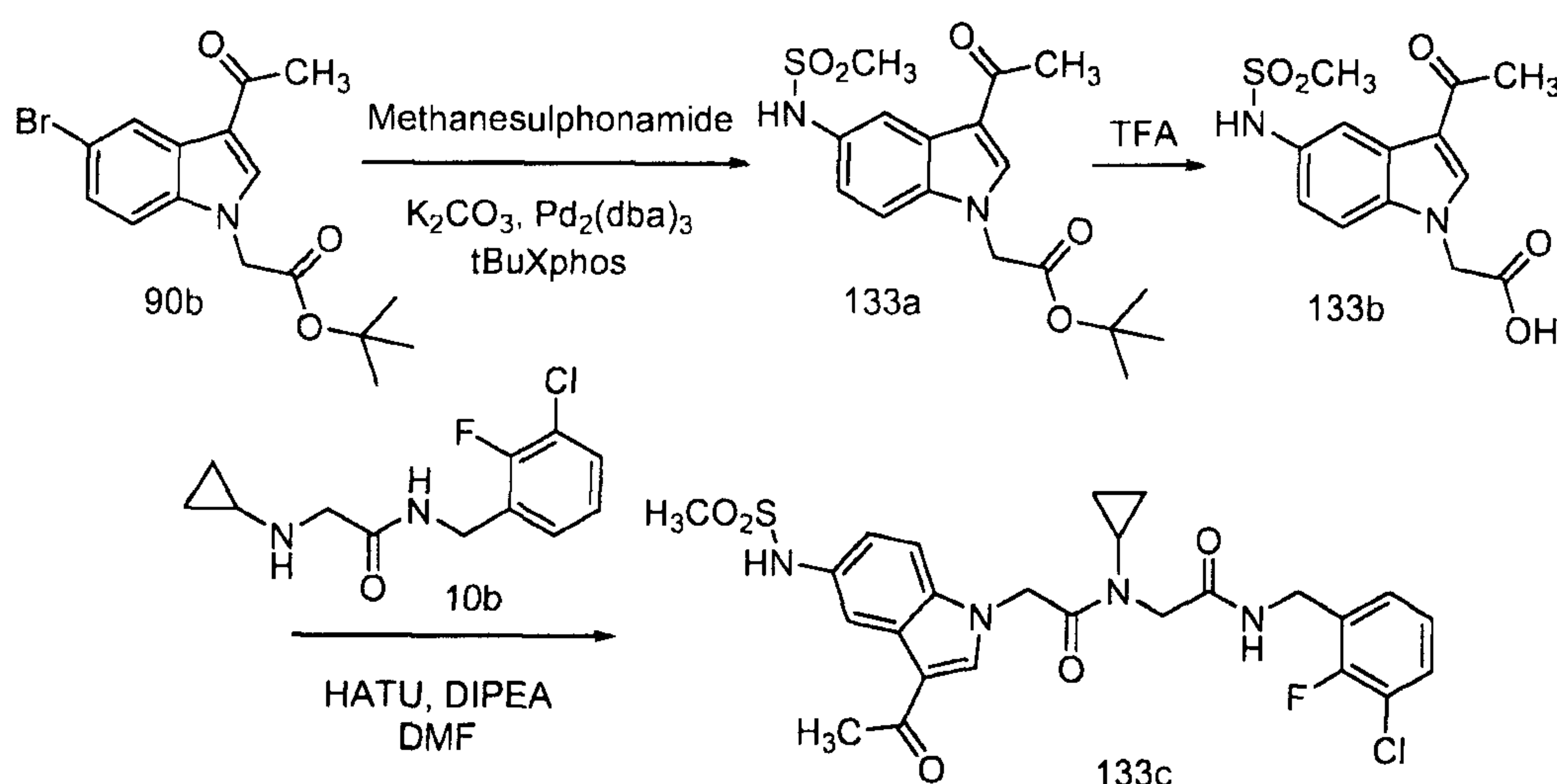
Step-5: Preparation of 2-(3-carbamoyl-5-(methoxycarbonyl)-1*H*-indazol-1-yl)acetic acid (**132f**)

Reaction of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-carbamoyl-1*H*-indazole-5-carboxylate (**132e**) (3.05 g, 9.15 mmol) with TFA (7.05 mL, 91 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup 2-(3-carbamoyl-5-(methoxycarbonyl)-1*H*-indazol-1-yl)acetic acid (**132f**) (2.7 g, 6.9 mmol, 75% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.93 – 8.82 (m, 1H), 8.01 (dd, *J* = 8.9, 1.6 Hz, 1H), 7.91 (s, 1H), 7.86 (dd, *J* = 8.9, 0.7 Hz, 1H), 7.59 (s, 1H), 5.41 (s, 2H), 3.90 (s, 3H); MS (ES⁺): 278.3 (M+1).

Step-5: Preparation of methyl 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1*H*-indazole-5-carboxylate (**132g**)

Reaction of 2-(3-carbamoyl-5-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid (**132f**) (100 mg, 0.26 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (66 mg, 0.26 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (12 g), eluting with DMA80 in DCM 0 to 50%] to
 5 give methyl 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**132g**) (62 mg, 0.12 mmol, 47% yield) as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.91 – 8.86 (m, 1H), 8.83 (t, *J* = 5.7 Hz) and 8.36 (t, *J* = 5.9 Hz) (2t, 1H), 8.06 – 6.97 (m, 7H), 5.65 and 5.52 (2s, 2H), 4.61 – 4.49 and 4.28 – 4.21 (2m, 1H), 4.46 (d, *J* = 5.4 Hz) and 4.31 (d, *J* = 5.6 Hz)
 10 (2d, 2H), 4.18 and 3.84 (2s, 2H), 3.91 and 3.9 (2s, 3H), 1.24 (d, *J* = 6.4 Hz) and 0.99 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.22, -121.71; MS (ES⁺): 518.5 (M+1); MS (ES⁻): 516.5 (M-1).

Scheme 133



15 Preparation of 2-(3-acetyl-5-(methylsulfonamido)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**133c**)

Step-1: Preparation of tert-butyl 2-(3-acetyl-5-(methylsulfonamido)-1H-indol-1-yl)acetate (**133a**)

To degassed Dioxane (4 mL) in a sealed reactor were added tert-butyl 2-(3-acetyl-5-bromo-1H-indol-1-yl)acetate (**90b**) (500 mg, 1.42 mmol), methanesulfonamide (162 mg, 1.70
 20 mmol), potassium carbonate (392 mg, 2.84 mmol), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (tBuXphos, 30 mg, 0.071 mmol), Pd₂(dba)₃ (32 mg, 0.035 mmol) and heated at 90 °C for 16 h. Mixture was cooled to room temperature, filtered over Celite pad and pad was washed with EtOAc (2 x 10 mL). The combined filtrate was washed water (2 x 30 mL),

dried, filtered and concentrated in vacuum. The residue obtained was purified by column chromatography [silica gel (24 g), eluting with MeOH-EtOAc (1:9) in hexane 0 to 80%] to afford tert-butyl 2-(3-acetyl-5-(methylsulfonamido)-1H-indol-1-yl)acetate (**133a**) (220 mg, 0.6 mmol, 42% yield) as an orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.49 (s, 1H), 8.32 (s, 1H), 8.10 (d, J = 2.1 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.16 (dd, J = 8.8, 2.2 Hz, 1H), 5.10 (s, 2H), 2.88 (s, 3H), 2.42 (s, 3H), 1.44 (s, 9H).

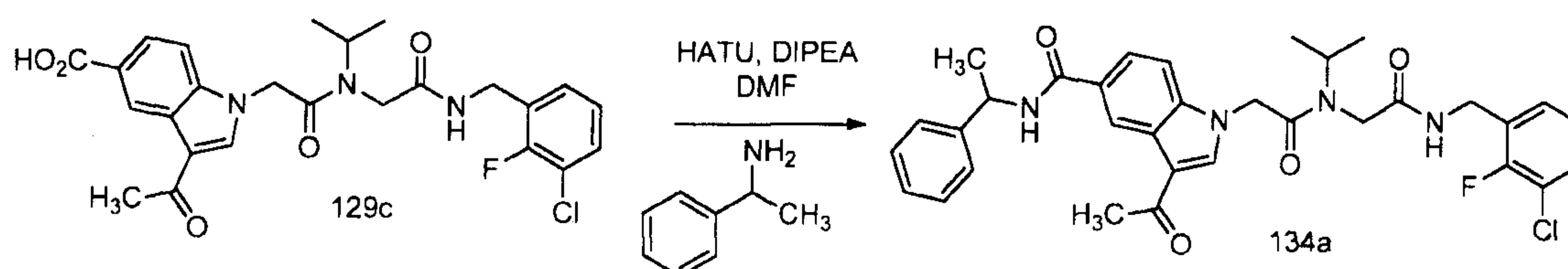
Step-2: Preparation of 2-(3-acetyl-5-(methylsulfonamido)-1H-indol-1-yl)acetic acid (**133b**)

Reaction of tert-butyl 2-(3-acetyl-5-(methylsulfonamido)-1H-indol-1-yl)acetate (**133a**) (220 mg, 0.6 mmol) with TFA (0.93 mL, 12.01 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup, trituration of residue with toluene (2 x 30 mL) and 30% EtOAc-hexane (10 mL) 2-(3-acetyl-5-(methylsulfonamido)-1H-indol-1-yl)acetic acid (**133b**) (230 mg, 0.74 mmol, 90% yield) as light orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.26 (s, 1H D₂O exchangeable), 9.49 (s, 1H), 8.34 (s, 1H), 8.10 (d, J = 2.1 Hz, 1H), 7.49 (d, J = 8.9 Hz, 1H), 7.16 (dd, J = 8.8, 2.2 Hz, 1H), 5.11 (s, 2H), 2.88 (s, 3H), 2.42 (s, 3H); MS (ES⁺): 311.3 (M+1), MS (ES⁻): 309.3 (M-1).

Step-3: Preparation of 2-(3-acetyl-5-(methylsulfonamido)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**133c**)

Reaction of 2-(3-acetyl-5-(methylsulfonamido)-1H-indol-1-yl)acetic acid (**133b**) (60 mg, 0.19 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (60 mg, 0.23 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 30%] 2-(3-acetyl-5-(methylsulfonamido)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**133c**) (46 mg, 0.084 mmol, 43% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.47 (s, 1H), 8.47 (t, J = 5.9 Hz, 1H), 8.29 (s, 1H), 8.10 (d, J = 2.1 Hz, 1H), 7.52 - 7.36 (m, 2H), 7.23 (t, J = 7.1 Hz, 1H), 7.17 - 7.04 (m, 2H), 5.42 (s, 2H), 4.35 (d, J = 5.7 Hz, 2H), 3.99 (s, 2H), 3.08 (d, J = 4.4 Hz, 1H), 2.89 (s, 3H), 2.41 (s, 3H), 1.08 - 0.94 (m, 2H), 0.95 - 0.82 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.61; MS (ES⁺): 549.5 (M+1), MS (ES⁻): 547.5 (M-1), 583.5 (M+Cl).

Scheme 134



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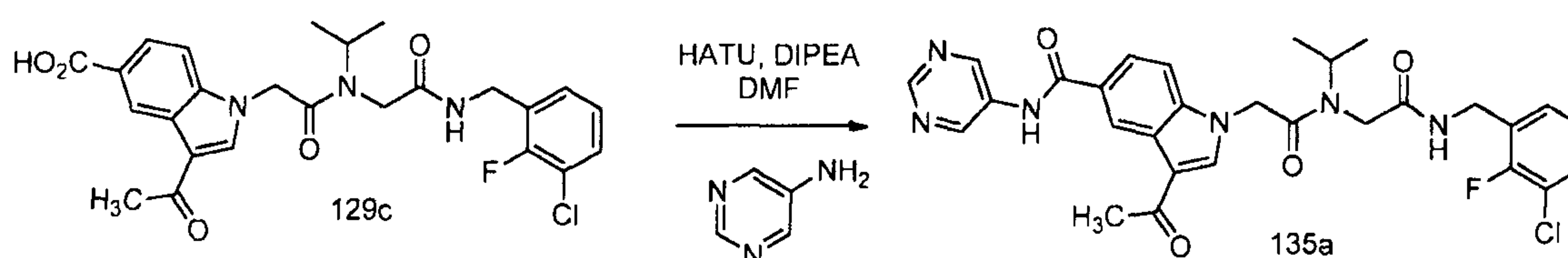
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Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N-(1-phenylethyl)-1H-indole-5-carboxamide (**134a**)

Reaction of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**129c**) (50 mg, 0.1

5 mmol) with 1-phenylethylamine (20 mg, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (4 g), eluting with MeOH in CHCl₃ 0 to 10%] 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N-(1-phenylethyl)-1H-indole-5-carboxamide (**134a**) (34 mg, 56%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 8.87 – 8.78 and 8.38-8.27 (2m, 2H), 8.72 (d, *J* = 1.7 Hz) and 8.71 (2d, 1H), 8.35 and 8.30 (2s, 1H), 7.77 (dd, *J* = 8.6, 1.8 Hz), and 7.72 (2dd, 1H), 7.56-6.92 (m, 9H), 5.39 and 5.20 (2s, 2H), 5.27-5.12 (m, 1H), 4.65 – 4.51 and 4.29 – 4.20 2(m, 1H),, 4.48 (d, *J* = 5.5 Hz) and 4.33 (d, *J* = 5.8 Hz) (2d, 2H), 4.19 and 3.85 (2s, 2H), 2.46 and 2.45 2(s, 3H), 1.51 (d, *J* = 3.0 Hz) and 1.49 (d, *J* = 3.1 Hz) (2d, 3H), 1.26 (d, *J* = 6.5 Hz) and 1.00 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.20 , -121.79; MS (ES⁺): 627.6 & 629.6 (M+Na); MS (ES⁻): 639.6 & 641.5 (M+Cl).

Scheme 135



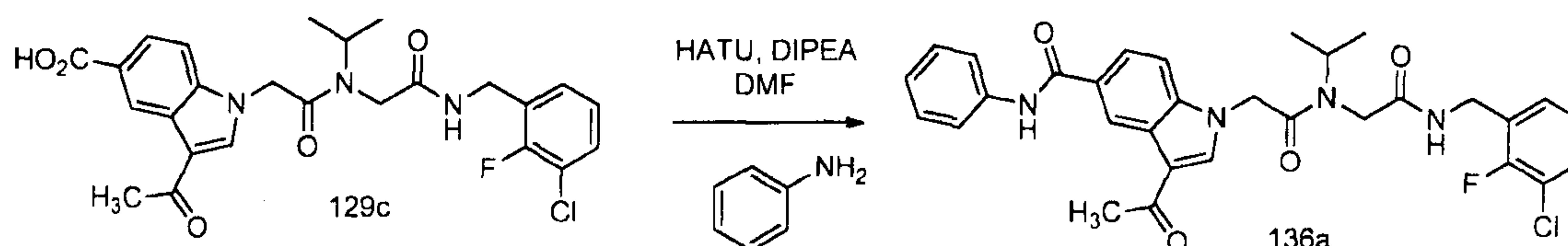
Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N-(pyrimidin-5-yl)-1H-indole-5-carboxamide (**135a**)

Reaction of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**129c**) (50 mg, 0.1

25 mmol) with pyrimidin-5-amine (14.80 mg, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (4 g), eluting with MeOH in CHCl₃ 0 to 10%] 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N-(pyrimidin-5-yl)-1H-indole-5-carboxamide (**135a**) (31 mg, 54%); ¹H NMR(300 MHz, DMSO-*d*₆) δ 9.20 – 9.17 (m, 1H), 8.91 – 8.82 and 8.40 – 8.33 (2m, 2H), 8.79 (t, *J* = 1.4 Hz) and 8.77 (t, *J* = 1.5 Hz) (2t, 1H), 8.55 and 8.52 (2s, 1H), 8.13 (dd, *J* = 8.8, 1.8 Hz) and 8.04 (dd, *J* = 8.8, 1.8 Hz) (2dd, 1H), 7.82 (d, *J* = 8.8 Hz)

and 7.77 (d, $J = 8.8$ Hz) (2d, 1H), 7.70 (dd, $J = 4.5, 1.8$ Hz) and 7.68 (dd, $J = 4.5, 1.8$ Hz) (2dd, 1H), 7.59 – 6.91 (m, 4H), 5.52 (s) and 5.46 – 5.17 (m) (2H), 4.67 – 4.51 and 4.30–4.15 (2m, 1H), 4.49 (d, $J = 5.4$ Hz) and 4.34 (d, $J = 5.7$ Hz) (2d, 2H), 4.21 and 3.87 (2s, 2H), 1.29 (d, $J = 6.5$ Hz) and 1.01 (d, $J = 6.7$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.18, -121.75.

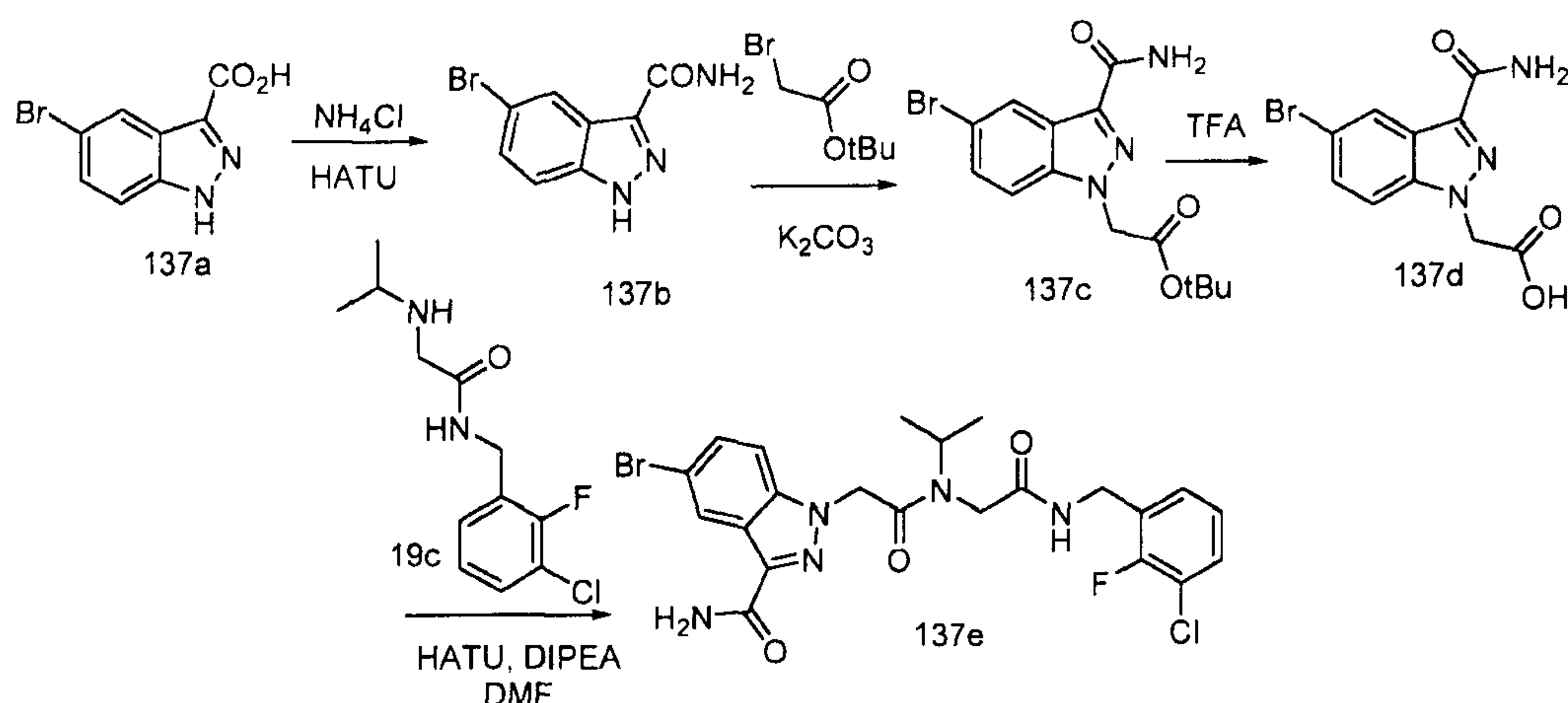
Scheme 136



Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N-phenyl-1H-indole-5-carboxamide (**136a**)

- Reaction of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**129c**) (50 mg, 0.1 mmol) with aniline (0.014 mL, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (4 g), eluting with MeOH in CHCl_3 0 to 10%] 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N-phenyl-1H-indole-5-carboxamide (**136a**) (33 mg, 57%) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.30 and 10.27 (2s, 1H), 8.84 (t, $J = 5.8$ Hz) and 8.35 (2t, 1H), 8.80 – 8.77 (m, 1H), 8.39 and 8.35 (2s, 1H), 7.86 – 7.77 (m, 3H), 7.60 (d, $J = 3.7$ Hz) and 7.57 (d, $J = 3.7$ Hz) (2d, 1H), 7.55 – 6.97 (m, 6H), 5.42 and 5.24 (2s, 2H), 4.65 – 4.51 and 4.30 – 4.22 (2m, 1H), 4.49 (d, $J = 5.6$ Hz) and 4.34 (d, $J = 5.8$ Hz) (2d, 2H), 4.20 and 3.86 (2s, 2H), 1.27 (d, $J = 6.4$ Hz) and 1.01 (d, $J = 6.8$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.18, -121.75; MS (ES⁻): 611.5 & 613.5 (M+Cl).

Scheme 137



Preparation of 5-bromo-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**137e**)

5 Step-1: Preparation of 5-bromo-1H-indazole-3-carboxamide (**137b**)

To a solution of 5-bromo-1H-indazole-3-carboxylic acid (**137a**) (3.00 g, 12.45 mmol, prepared according to the procedure reported by Hood, John and Sunil Kumar in PCT Int. Appl., 2013040215) in DMF (60 mL) was added ammonium chloride (1.997 g, 37.3 mmol), HATU (7.10 g, 18.67 mmol) followed by the drop-wise addition of DIPEA (21.74 mL, 124 mmol). The reaction mixture was stirred at room temperature for 3 h, quenched with water (100 mL) and extracted with EtOAc (2 x 100 mL). The organic layers were combined washed with brine (50 mL), dried, filtered and evaporated to dryness. The solid obtained was washed with MeOH (3 x 10 mL) and dried to afford 5-bromo-1H-indazole-3-carboxamide (**137b**) (1.33 g, 5.54 mmol, 44% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.77 (s, 1H, D₂O exchangeable), 8.31 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.84 (s, 1H), 7.64 - 7.58 (m, 1H), 7.53 (dd, *J* = 8.8, 1.9 Hz, 1H), 7.46 (s, 1H); MS (ES⁻): 240.1, 238.1 (M-2).

Step-2: Preparation of tert-butyl 2-(5-bromo-3-carbamoyl-1H-indazol-1-yl)acetate (**137c**)

Reaction of 5-bromo-1H-indazole-3-carboxamide (**137b**) (1.2 g, 5.0 mmol) with tert-butyl 2-bromoacetate (0.89 mL, 6.0 mmol) using potassium carbonate (1.73 g, 12.5 mmol) as base according to the procedure reported step-1 of Scheme 45 gave after workup tert-butyl 2-(5-bromo-3-carbamoyl-1H-indazol-1-yl)acetate (**137c**) (1.55 g, 4.38 mmol, 88% yield) as a light green solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.33 (dd, *J* = 1.9, 0.7 Hz, 1H), 7.84 (s, 1H, D₂O exchangeable), 7.75 (dd, *J* = 9.0, 0.7 Hz, 1H), 7.65 - 7.59 (m, 1H), 7.53 (s, 1H, D₂O exchangeable), 5.37 (s, 2H), 1.41 (s, 9H); MS (ES⁺): 376.3, 378.3 (M+Na); MS (ES⁻): 354.3, 352.2 (M-2).

Step-3: Preparation of 2-(5-bromo-3-carbamoyl-1H-indazol-1-yl)acetic acid (**137d**)

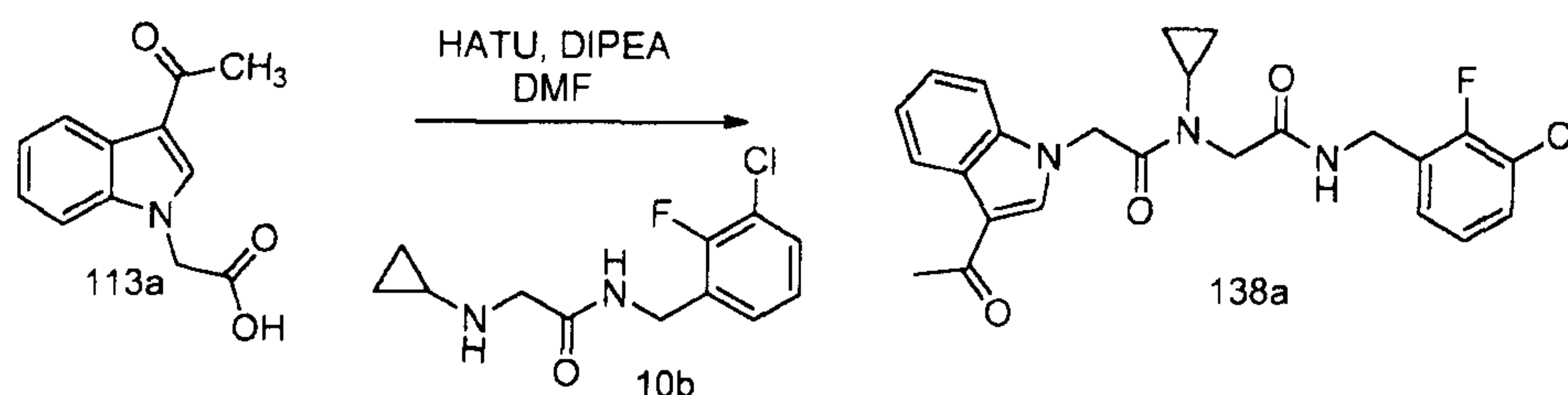
Reaction of tert-butyl 2-(5-bromo-3-carbamoyl-1H-indazol-1-yl)acetate (**137c**) (1.0 g, 2.82 mmol) with TFA (4.35 mL, 56.5 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup

2-(5-bromo-3-carbamoyl-1H-indazol-1-yl)acetic acid (**137d**) (806 mg, 2.70 mmol, 96% yield) as a yellow solid in the form of TFA adduct; ^1H NMR (300 MHz, DMSO- d_6) δ 13.34 (s, 1H, D₂O exchangeable), 8.33 (d, J = 1.8 Hz, 1H), 7.84 (s, 1H), 7.78 (d, J = 8.9 Hz, 1H), 7.61 (dd, J = 9.0, 1.9 Hz, 1H), 7.52 (s, 1H), 5.37 (s, 2H); MS (ES⁺): 298.3, 300.2 (M+2); MS (ES⁻): 595.3, 597.3 (2M-1).

Step-4: Preparation of 5-bromo-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**137e**)

Reaction of 2-(5-bromo-3-carbamoyl-1H-indazol-1-yl)acetic acid (**137d**) (100 mg, 0.34 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (104 mg, 0.4 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [Silica gel, (24 g) eluting with MeOH in DCM 0-30%], 5-bromo-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**137e**) (34 mg, 0.063 mmol, 19% yield) as a white solid as a mixture two rotamers; ^1H NMR (300 MHz, DMSO- d_6) δ 8.83 and 8.36 (J = 5.7 Hz, 1H) (2t, 1H), 8.32 (dd, J = 1.8, 0.8 Hz, 1H), 7.82 and 7.79 (2s, 1H), 7.68 – 6.95 (m, 6H), 5.61 and 5.47 (2s, 2H), 4.62 – 4.48 and 4.28 – 4.21 (2m, 1H), 4.46 (d, J = 5.6 Hz) and 4.31 (d, J = 5.9 Hz) (2d, 2H), 4.17 and 3.83 (2s, 2H), 1.23 (d, J = 6.4 Hz) and 0.98 (d, J = 6.8 Hz) (2d, 6H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.22, -121.71; MS (ES⁺): 538.5 & 540.5 (M+1); MS (ES⁻): 538.4 & 536.4 (M-1).

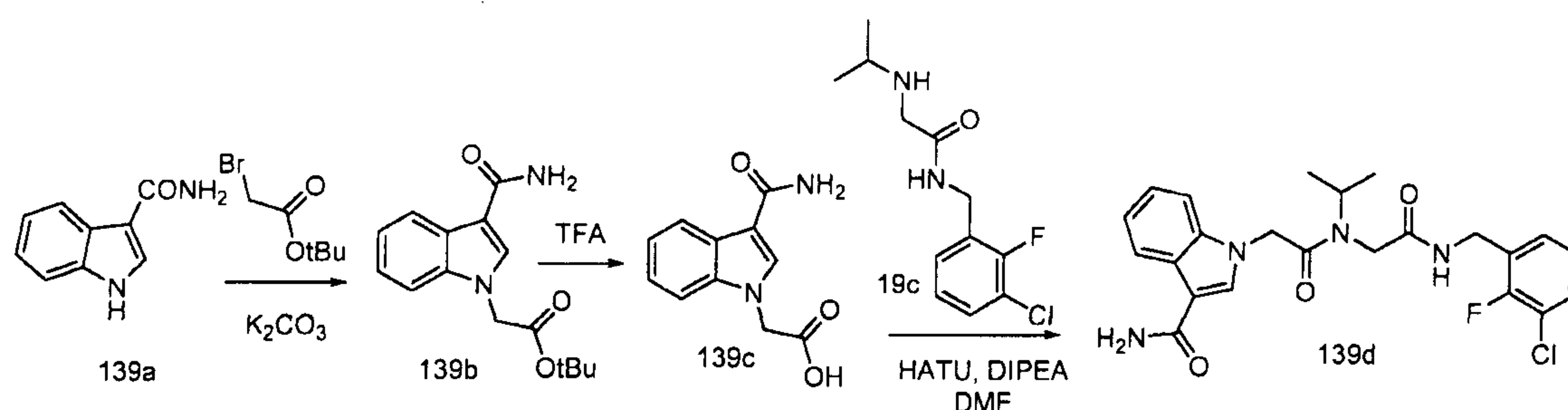
Scheme 138



Preparation of 2-(3-acetyl-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**138a**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (100 mg, 0.39 mmol) with 2-(3-acetyl-1H-indol-1-yl)acetic acid (**113a**) (85 mg, 0.39 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (24 g), eluting with CMA80 in CHCl₃ 0 to 20%] 2-(3-acetyl-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**138a**) (115 mg, 0.25 mmol, 65% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.46 (t, *J* = 5.8 Hz, 1H), 8.28 (s, 1H), 8.21 - 8.14 (m, 1H), 7.52 - 7.40 (m, 2H), 7.28 - 7.16 (m, 3H), 7.10 (t, *J* = 7.9 Hz, 1H), 5.44 (s, 2H), 4.34 (d, *J* = 5.8 Hz, 2H), 3.99 (s, 2H), 3.16 - 3.02 (m, 1H), 2.43 (s, 3H), 1.04 - 0.96 (m, 2H), 0.96 - 0.87 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.62; MS (ES⁺): 456.5 (M+1), 478.5 (M+Na), MS (ES⁻): 454.4 (M-1), 490.4 (M+Cl).

Scheme 139



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-3-carboxamide (**139d**)

Step-1: Preparation of tert-butyl 2-(3-carbamoyl-1H-indol-1-yl)acetate (**139b**)

Reaction of 1H-indole-3-carboxamide (**139a**) (1.0 g, 6.24 mmol) with tert-butyl 2-bromoacetate (1.11 mL, 7.49 mmol) using potassium carbonate (2.16 g, 15.61 mmol) as base according to the procedure reported step-1 of Scheme 45 gave after workup tert-butyl 2-(3-carbamoyl-1H-indol-1-yl)acetate (**139b**) (1.55 g, 5.65 mmol, 91% yield) as a yellow white solid; MS (ES⁺): 275.4 (M+1), 294.7 (M+Na); MS (ES⁻): 273.3 (M-1)

Step-2: Preparation of 2-(3-carbamoyl-1H-indol-1-yl)acetic acid (**139c**)

Reaction of tert-butyl 2-(3-carbamoyl-1H-indol-1-yl)acetate (**139b**) (1.12 g, 4.08 mmol) with TFA (6.29 mL, 82 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup

2-(3-carbamoyl-1H-indol-1-yl)acetic acid (**139c**) (1.18 g, 3.55 mmol, 87% yield) as a yellow solid in the form of TFA adduct; MS (ES⁺): 219.3 (M+1).

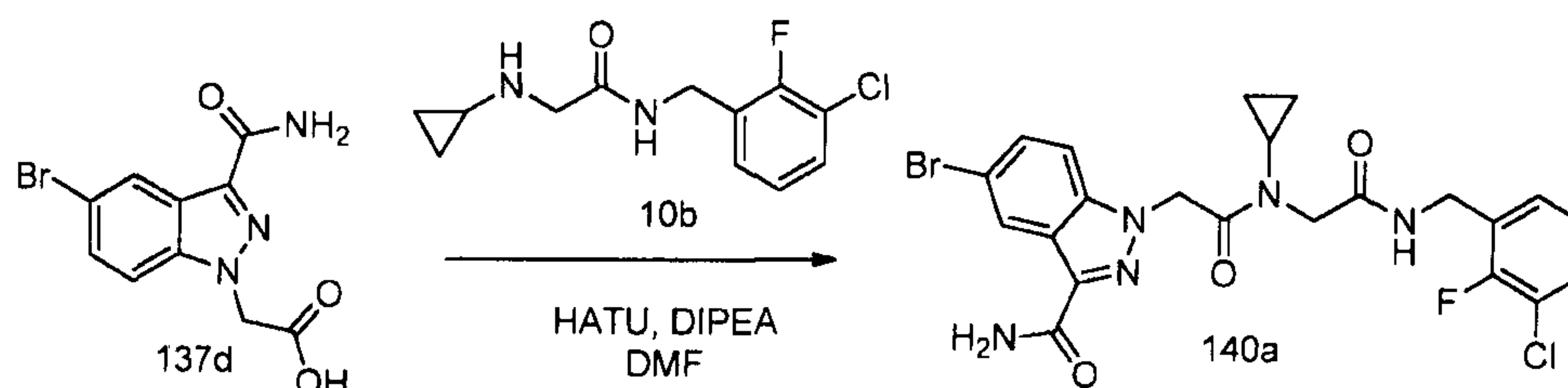
Step-3: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-3-carboxamide (**139d**)

Reaction of 2-(3-carbamoyl-1H-indol-1-yl)acetic acid (**139c**) (150 mg, 0.69 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (213 mg, 0.83 mmol)

5 according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [Silica gel, (24 g) eluting with MeOH in DCM 0-30%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-3-carboxamide (**139d**) (43 mg, 0.094 mmol, 14% yield) as a white solid as a mixture two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.81 (t, *J* = 5.7 Hz) and 8.34 (t, *J* = 5.9 Hz) (2t, 1H), 8.20 – 8.11 (m, 1H), 7.93 and 7.92 (2s, 1H), 7.59-6.63 (m, 8H), 5.30 and 5.13 (2s, 2H), 4.68 – 4.52 and 4.30 – 4.23 (2m, 1H), 4.47 (d, *J* = 5.6 Hz) and 4.33 (d, *J* = 5.9 Hz) (2d, 2H), 4.17 and 3.84 (2s, 2H), 1.23 (d, *J* = 6.5 Hz) and 0.99 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.22, -121.81; MS (ES⁺): 481.5, 483.5 (M+Na), 939.9, 941.9 (2M+Na); (ES⁻): 457.5 (M-1), 493.4, 495.5 (M+Cl).

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Scheme 140

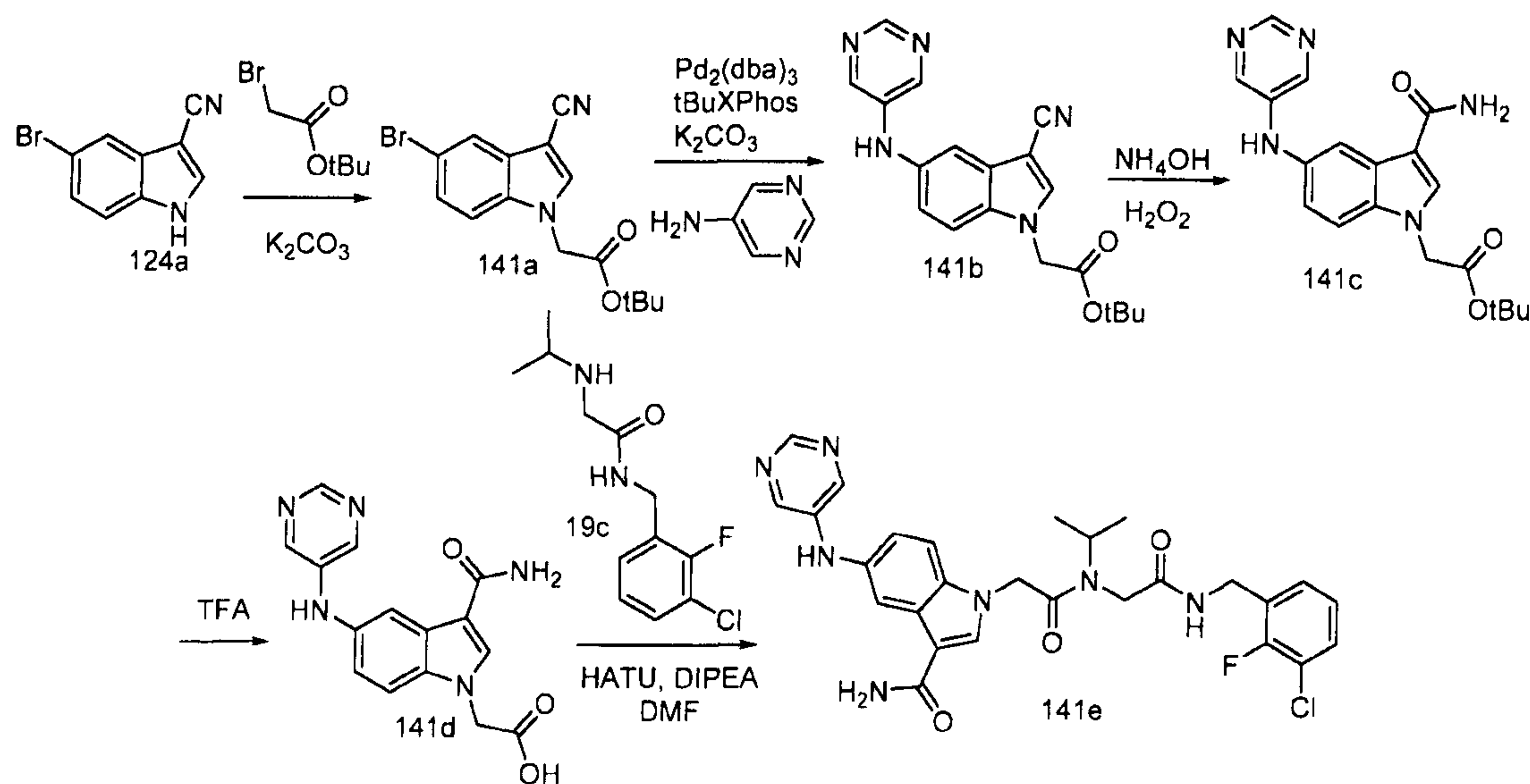


Preparation of 5-bromo-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**140a**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (517 mg, 2.01 mmol) with 2-(5-bromo-3-carbamoyl-1H-indazol-1-yl)acetic acid (**137d**) (500 mg, 1.68 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (40 g), eluting with MeOH in DCM 0 to 30%] 5-bromo-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**140a**) (329 mg, 0.613 mmol, 37% yield) as a light brown solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.50 (t, *J* = 5.8 Hz, 1H), 8.32 (dd, *J* = 1.9, 0.7 Hz, 1H), 7.83 (s, 1H), 7.72 – 7.64 (m, 1H), 7.56 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.28 – 7.18 (m, 1H), 7.17 – 7.06 (m, 1H), 5.68 (s, 2H), 4.33 (d, *J* = 5.7 Hz, 2H), 3.98 (s, 2H), 3.13 – 3.00 (m, 1H), 1.03 – 0.95 (m, 2H), 0.95 – 0.86

(m, 2H). ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.56; MS (ES⁺): 560.4, 558.4 (M+Na); MS (ES⁻): 534.3, 536.4 (M-1).

Scheme 141



- 5 Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(pyrimidin-5-ylamino)-1H-indole-3-carboxamide (**141e**)

Step-1: Preparation of tert-butyl 2-(5-bromo-3-cyano-1H-indol-1-yl)acetate (**141a**)

Reaction of 5-bromo-1H-indole-3-carbonitrile (**124a**) (2.2 g, 9.95 mmol) with tert-butylbromoacetate (2.06 mL, 13.93 mmol) in acetonitrile (50 mL) using potassium carbonate (2.75 g, 19.90 mmol) as base, according to the procedure reported in step-1 of Scheme 43 gave after workup and purification by column chromatography [silica gel (40 g), eluting with EtOAc in hexane 0 to 80 %] tert-butyl 2-(5-bromo-3-cyano-1H-indol-1-yl)acetate (**141a**) (1.4 g, 4.18 mmol, 42% yield) as an off-white solid; MS (ES⁺): 335.3, 337.3 (M+2), MS (ES⁻): 369.2, 371.2 (M+Cl).

- 15 Step-2: Preparation of 2-(3-carbamoyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**141b**)

Reaction of tert-butyl 2-(5-bromo-3-cyano-1H-indol-1-yl)acetate (**141a**) (1.3 g, 3.88 mmol), with pyrimidin-5-amine (369 mg, 3.88 mmol) using potassium carbonate (1.07 g, 7.76 mmol), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (165 mg, 0.389 mmol), Pd₂(dba)₃ (178 mg, 0.19 mmol) according to the procedure reported in step-1 of Scheme 97 gave after workup and purification by flash column chromatography [silica gel (40 g), eluting with MeOH/EtOAc (1:9) in Hexane 0 to 100%] 2-(3-carbamoyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**141b**) (320 mg, 0.92 mmol, 24% yield) as light colorless foam; ^1H

NMR (300 MHz, DMSO-*d*₆) δ 8.61 (s, 1H), 8.54 (s, 1H), 8.51 (s, 2H), 8.19 (s, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.35 (d, *J* = 2.0 Hz, 1H), 7.19 (dd, *J* = 8.8, 2.1 Hz, 1H), 5.13 (s, 2H), 1.43 (s, 9H); MS (ES⁺): 350.4 (M+1), MS (ES⁻): 348.3 (M-1), 384.4 (M+Cl).

Step-3: Preparation of tert-butyl 2-(3-carbamoyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetate (**141c**)

Reaction of 2-(3-carbamoyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**141b**) (320 mg, 0.92 mmol) in EtOH (10 mL) with conc. NH₄OH (0.71 mL, 18.32 mmol) and Hydrogen peroxide (35% aqueous, 0.42 mL, 13.74 mmol) according to the procedure reported in step-1 of Scheme 97 gave after workup tert-butyl 2-(3-carbamoyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetate (**141c**) (300 mg, 0.82 mmol, 89% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.22 (s, 1H), 8.54 (s, 1H), 8.44 (s, 2H), 7.99 (d, *J* = 2.2 Hz, 1H), 7.94 (s, 1H), 7.40 (d, *J* = 8.8 Hz, 1H), 7.06 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.85 (brs, 1H), 5.06 (s, 2H), 1.43 (d, *J* = 2.6 Hz, 9H); MS (ES⁺): 368.5 (M+1), 390.5 (M+Na); MS (ES⁻): 366.4 (M-1), 402.4 (M+Cl).

Step-4: Preparation of 2-(3-carbamoyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**141d**)

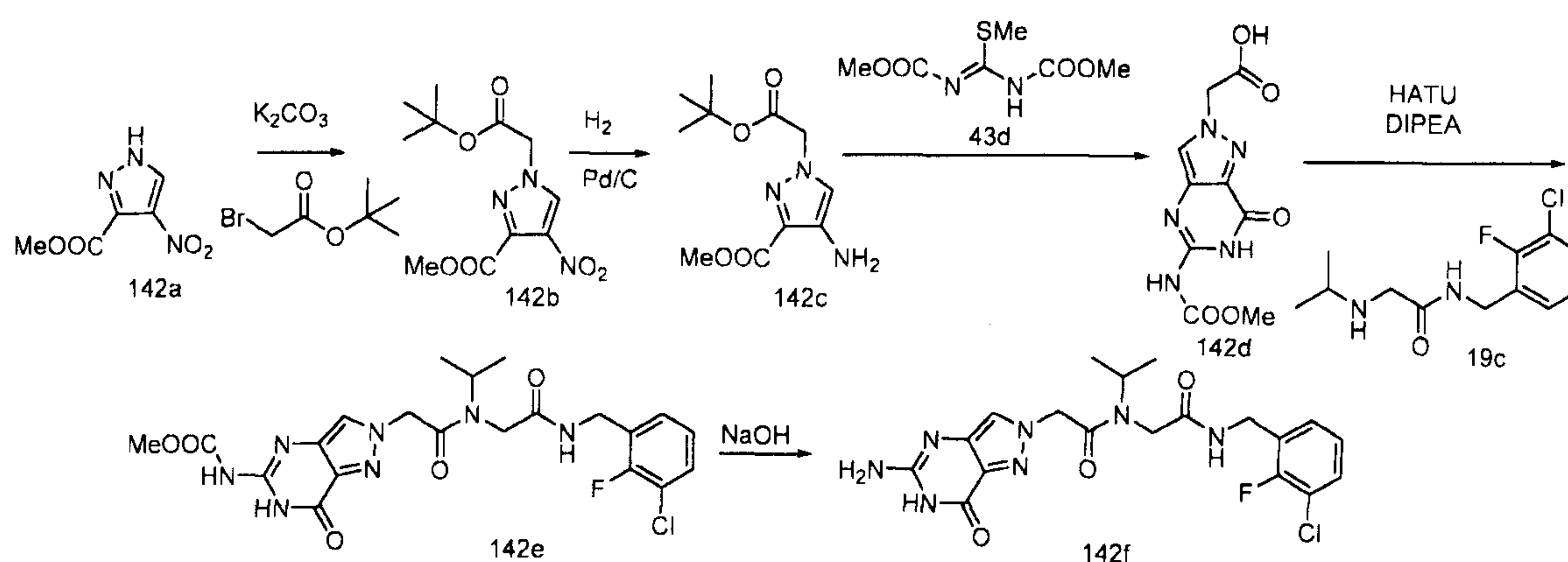
Reaction of tert-butyl 2-(3-carbamoyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetate (**141c**) (300 mg, 0.82 mmol) with TFA (1.26 mL, 16.33 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and trituration of crude with toluene (2 x 30 mL) and 30% EtOAc-hexane (10 mL), 2-(3-carbamoyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**141d**) (250 mg, 0.8 mmol, 98% yield) as light orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.54 (brs, 1H, D₂O exchangeable), 8.54 (s, 1H), 8.45 (s, 2H), 8.00 (d, *J* = 2.2 Hz, 1H), 7.96 (s, 1H), 7.43 (d, *J* = 8.8 Hz, 1H), 7.11 – 7.01 (m, 1H), 5.07 (s, 2H); MS (ES⁺): 312.4 (M+1); MS (ES⁻): 310.3 (M-1).

Step-5: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(pyrimidin-5-ylamino)-1H-indole-3-carboxamide (**141e**)

Reaction of 2-(3-carbamoyl-5-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**141d**) (70 mg, 0.23 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (64 mg, 0.25 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (12 g), eluting with CMA-80 in CHCl₃ 0-50%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(pyrimidin-5-ylamino)-1H-indole-3-carboxamide (**141e**) (33 mg, 0.06 mmol, 27% yield) as a

white solid as a mixture of rotamers in 2:1; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.82 and 8.34 (2t, $J = 5.9$ Hz, 1H), 8.531 and 8.538 (2s, 1H), 8.44 (s, 2H), 8.39 (s, 1H), 8.00 and 7.99 (2s, 1H), 7.91 (s, 1H), 7.62 – 6.65 (m, 6H), 5.29 and 5.12 (2s, 2H), 4.67 - 4.52 and 4.30 - 4.18 (m, 1H), 4.47 and 4.33 (2d, $J = 5.6$ Hz, 2H), 4.16 and 3.85 (2s, 2H), 1.23 and 0.99 (2d, $J = 6.8$ Hz, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.20 and -121.77; MS (ES⁺): 552.6 (M+1), 574.6 (M+Na); MS (ES⁻): 586.5 (M+Cl).

Scheme 142



Preparation of 2-(5-amino-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**142f**)

Step-1: Preparation of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-4-nitro-1H-pyrazole-3-carboxylate (**142b**)

Reaction of methyl 4-nitro-1H-pyrazole-3-carboxylate (**142a**) (3 g, 17.53 mmol) and tert-butyl 2-bromoacetate (3.11 mL, 21.04 mmol) in DMF (10 mL) using potassium carbonate (3.63 g, 26.3 mmol) according to the procedure reported in step-1 of Scheme 43 gave after workup and purification by flash column chromatography [silica gel eluting with hexanes/EtOAc (1:0 to 4:1)] methyl 1-(2-(tert-butoxy)-2-oxoethyl)-4-nitro-1H-pyrazole-3-carboxylate (**142b**) (3.35 g, 67%) as a colorless gum; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.98 (s, 1H), 5.14 (s, 2H), 3.89 (s, 3H), 1.44 (s, 9H); MS (ES⁺): 308.3 (M+Na).

Step-2: Preparation of methyl 4-amino-1-(2-(tert-butoxy)-2-oxoethyl)-1H-pyrazole-3-carboxylate (**142c**)

Hydrogenation of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-4-nitro-1H-pyrazole-3-carboxylate (**142b**) (3.19 g, 11.18 mmol) in MeOH (100 mL) using palladium (0.595 g, 0.559 mmol) (Pd/C, 10%) as catalyst according to procedure reported in Scheme 79 gave after workup 4-amino-1-(2-(tert-butoxy)-2-oxoethyl)-1H-pyrazole-3-carboxylate (**142c**) (2.65 g, 93%) as an

off white solid which was used as such in next step without further purification; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.17 (s, 1H), 4.87 (s, 2H), 4.71 (s, 2H), 3.75 (s, 3H), 1.42 (s, 9H); MS (ES⁺): 278.4 (M+Na).

Step-3: Preparation of 2-(5-((methoxycarbonyl)amino)-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)acetic acid (**142d**)

Reaction of methyl 4-amino-1-(2-(tert-butoxy)-2-oxoethyl)-1H-pyrazole-3-carboxylate (**142c**) (530 mg, 2.08 mmol) with (methoxycarbonylamino)(methylthio)methylenecarbamic acid methyl ester (**43d**) (646 mg) in acetic acid according to the procedure reported in step-2 of Scheme 43 gave after workup and trituration with CHCl_3 2-(5-((methoxycarbonyl)amino)-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)acetic acid (**142d**) (223 mg, 40%) as an off-white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 13.35 (bs, 1H), 11.29 (s, 1H), 11.05 (s, 1H), 8.14 (s, 1H), 5.18 (s, 2H), 3.74 (s, 3H); MS (ES⁻): 266.3 (M-1).

Step-4: Preparation of methyl (2-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-5-yl)carbamate (**142e**)

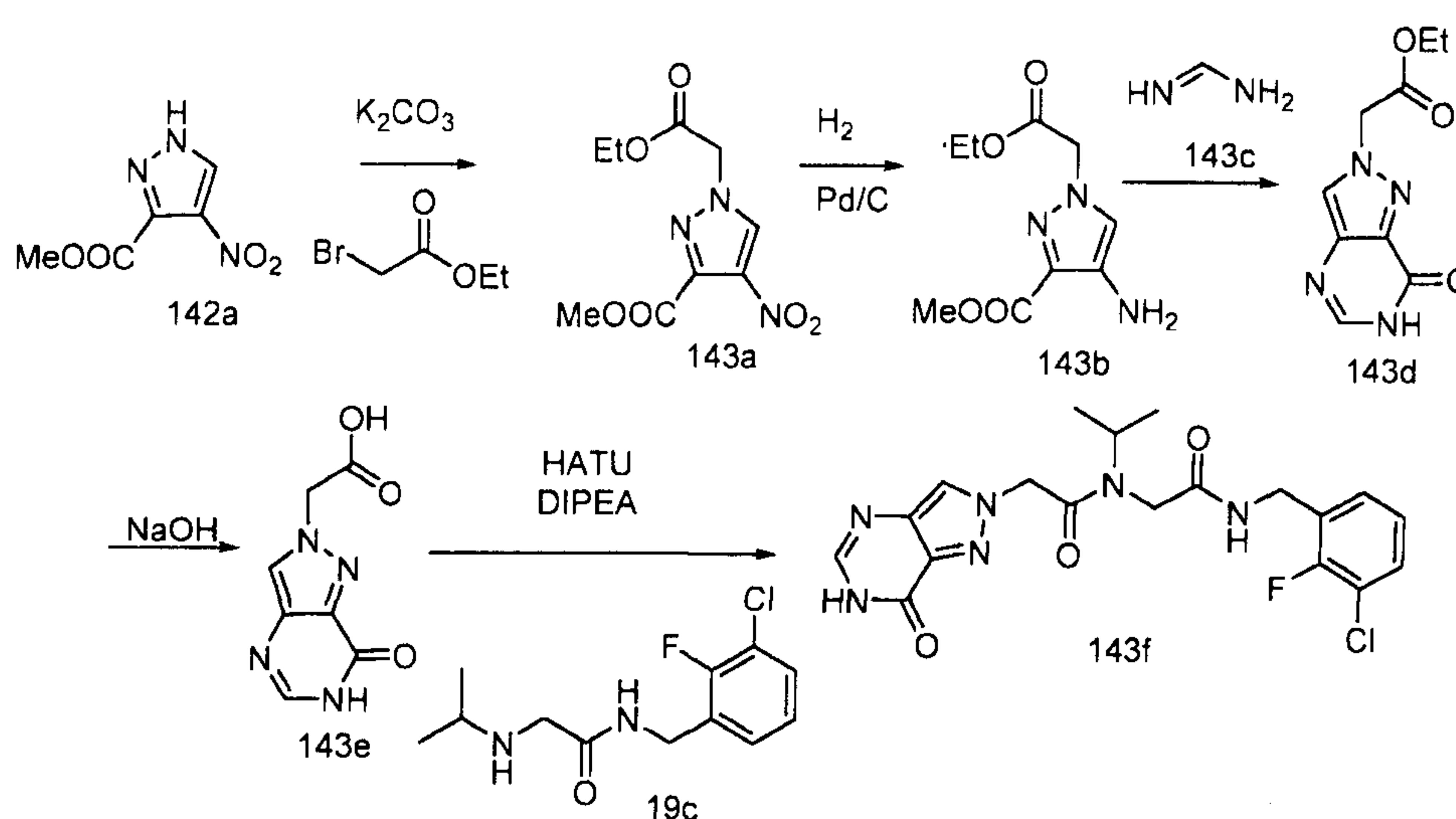
Reaction of 2-(5-((methoxycarbonyl)amino)-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)acetic acid (**142d**) (36 mg, 0.14 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (35 mg, 0.14 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (12 g), eluting with $\text{CHCl}_3/\text{MeOH}$ (1:0 to 9:1)] methyl (2-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-5-yl)carbamate (**142e**) (35 mg, 61% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.29 (s, 1H), 11.08 (s, 1H), 8.77 (t, $J = 5.8$ Hz) and 8.36 (t, $J = 5.9$ Hz) (2t, 1H), 8.05 and 8.04 (2s, 1H), 7.56 – 7.08 (m, 3H), 5.44 and 5.27 (2s, 2H), 4.64 – 4.49 and 4.20-4.08 (2m, 1H), 4.42 (d, $J = 5.6$ Hz) and 4.33 (d, $J = 5.9$ Hz) (2d, 2H), 4.12 and 3.84 (2s, 2H), 3.73 (s, 3H), 1.18 (d, $J = 6.4$ Hz) and 0.98 (d, $J = 6.8$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.32, -121.72; MS (ES⁺): 508.6 (M+1) and 530.5 (M+Na).

Step-5: Preparation of 2-(5-amino-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**142f**)

Reaction of methyl (2-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-5-yl)carbamate (**142e**) (32 mg, 0.063 mmol) with 2 N aqueous sodium hydroxide (0.32 mL, 0.63 mmol) in MeOH according to the procedure reported in step-4 of scheme 43 gave after

workup and purification by flash column [silica gel (12 g), eluting with CHCl₃/CMA80 (1:0 to 0:1)] 2-(5-amino-7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**142f**) (6 mg, 32%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.76 (t, *J* = 5.8 Hz) & 8.36 (t, *J* = 5.9 Hz) (2t, 1H), 7.67 & 7.63 (2s, 1H), 7.55 – 7.08 (m, 3H), 5.93 (bs, 2H), 5.33 & 5.16 (2s, 2H), 4.41 (d, *J* = 5.6 Hz) & 4.34 (d, *J* = 6.0 Hz) (2d, 2H), 4.63 – 4.52 & 4.19 – 4.04 (2m, 1H), 4.10 & 3.83 (s) (2s, 2H), 1.15 (d, *J* = 6.4 Hz) & 0.98 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.34, -121.74; MS (ES⁺): 472.5 (M+Na).

Scheme 143



Preparation of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropyl-2-(7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)acetamide (**143f**)

Step-1: Preparation of methyl 1-(2-ethoxy-2-oxoethyl)-4-nitro-1H-pyrazole-3-carboxylate (**143a**)

Reaction of methyl 4-nitro-1H-pyrazole-3-carboxylate (**142a**) (1.9 g, 11.1 mmol) and 2-bromoacetate (1.508 mL, 13.32 mmol) in DMF (7 mL) using potassium carbonate (2.3 g, 16.66 mmol) according to the procedure reported in step-1 of Scheme 43 gave after workup and purification by flash column chromatography [silica gel eluting with hexanes/EtOAc (1:0 to 2:1)] methyl 1-(2-ethoxy-2-oxoethyl)-4-nitro-1H-pyrazole-3-carboxylate (**143a**) (2.28 g, 80%) as a yellow oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.99 (s, 1H), 5.26 (s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 3.89 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 258.3 (M+Na).

Step-2: Preparation of methyl 4-amino-1-(2-ethoxy-2-oxoethyl)-1H-pyrazole-3-carboxylate (**143b**)

Hydrogenation of methyl 1-(2-ethoxy-2-oxoethyl)-4-nitro-1H-pyrazole-3-carboxylate (**143a**) (2.19 g, 8.5 mmol) in MeOH (80 mL) using palladium (0.45 g, Pd/C, 10%) as catalyst according to procedure reported in Scheme 79 gave after workup methyl 4-amino-1-(2-ethoxy-2-oxoethyl)-1H-pyrazole-3-carboxylate (**143b**) as an off white solid which was used
 5 as such in next step without further purification; MS (ES⁺): 228.3 (M+Na).

Step-3: Preparation of ethyl 2-(7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)acetate (**143d**)

A mixture of methyl 4-amino-1-(2-ethoxy-2-oxoethyl)-1H-pyrazole-3-carboxylate (**143b**) (1.75 g of the above crude product from step-2) and formimidamide acetate (**143c**) (8.08 g, 77 mmol) in ethanol (75 mL) was refluxed for 12 h. The reaction mixture was cooled to room
 10 temperature and solid obtained was collected by filtration, washed with ethanol, and dried under vacuum to give ethyl 2-(7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)acetate (**143d**) (1.49 g, 82% for two steps) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.92 (s, 1H), 8.36 (s, 1H), 7.79 (d, *J* = 2.6 Hz, 1H), 5.34 (s, 2H), 4.18 (d, *J* = 7.1 Hz, 2H),
 15 1.22 (t, *J* = 7.1 Hz, 3H); MS (ES⁺): 245.3 (M+Na).

Step-4: Preparation of 2-(7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)acetic acid (**143e**)

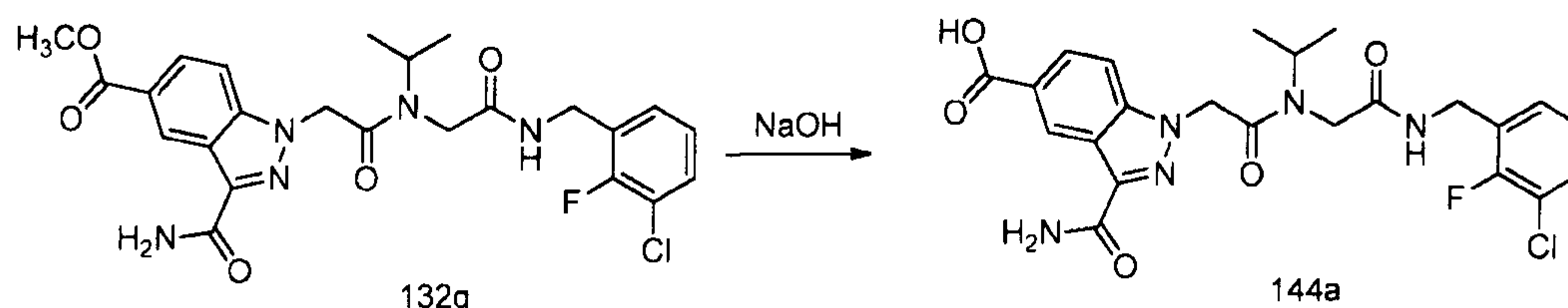
Reaction of ethyl 2-(7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)acetate (**143d**) (200 mg, 0.9 mmol) with 2 N aqueous sodium hydroxide (2.7 mL, 5.4 mmol) in MeOH
 20 according to the procedure reported in step-4 of scheme 43 gave after workup 2-(7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)acetic acid (**143e**) (165 mg, 94%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.40 (s, 1H), 11.90 (s, 1H), 8.34 (s, 1H), 7.79 (d, *J* = 3.4 Hz, 1H), 5.22 (s, 2H); MS (ES⁻): 193.1 (M-1),

Step-5: Preparation of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropyl-2-(7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)acetamide (**143f**)
 25

Reaction of 2-(7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)acetic acid (**143e**) (70 mg, 0.36 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (112 mg, 0.43 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (4 g), eluting with CHCl₃/MeOH (1:0 to 9:1)] N-
 30 (2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropyl-2-(7-oxo-6,7-dihydro-2H-pyrazolo[4,3-d]pyrimidin-2-yl)acetamide (**143f**) (85 mg, 54% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.86 (bs, 1H), 8.77 (t, *J* = 5.7 Hz) & 8.35 (2t, 1H), 8.25 & 8.24 (2s, 1H), 7.78 (t, *J* = 3.1 Hz, 1H), 7.55 – 7.09 (m, 3H), 5.48 & 5.31 (2s, 2H), 4.68 – 4.48

& 4.22 – 4.10 (2m, 1H), 4.42 (d, $J = 5.6$ Hz) & 4.33 (d, $J = 5.7$ Hz) (2d, 2H), 4.13 & 3.85 (2s, 2H), 1.19 (d, $J = 6.4$ Hz) & 0.99 (d, $J = 6.8$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.32, -121.71; MS (ES⁺): 435.4 (M+1).

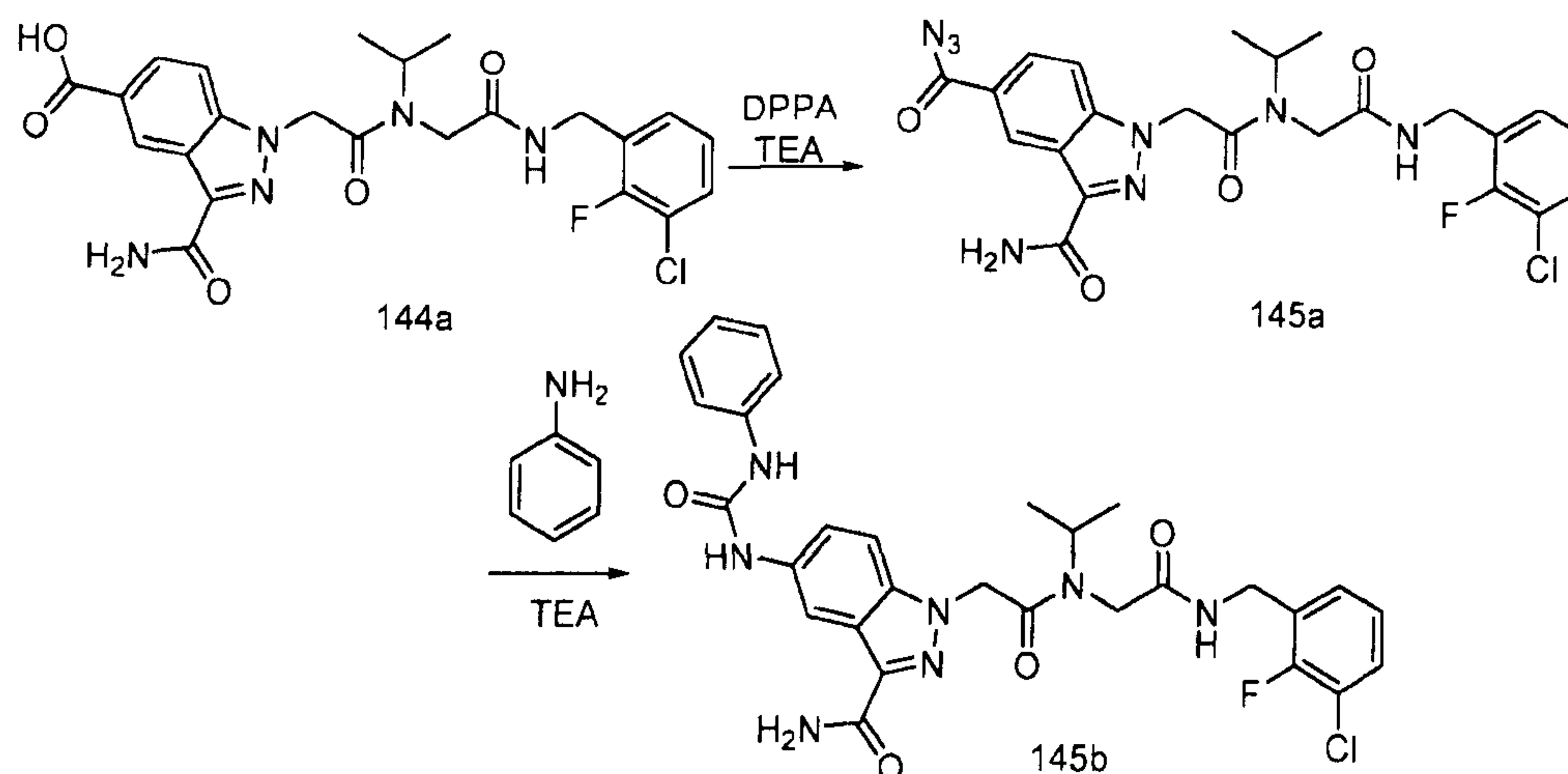
Scheme 144



Preparation of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**144a**)

Reaction of methyl 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**132g**) (3.2 g, 6.18 mmol) in MeOH/water (50 mL, 5:2, v/v) using NaOH (1.24 g, 30.9 mmol) in water (10 mL), according to the procedure reported in step-4 of scheme 43 gave after workup 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**144a**) (3.04 g, 6.03 mmol, 98% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 12.95 (s, 1H), 8.96 – 8.30 (m, 2H), 7.98 (dd, $J = 8.9, 1.5$ Hz) and 7.93 (dd, $J = 8.9, 1.5$ Hz) (2dd, 1H), 7.86 and 7.84 (2s, 1H), 7.69 (d, $J = 9.0$ Hz) and 7.61 (d, $J = 8.9$ Hz) (2d, 1H), 7.57 – 6.92 (m, 4H), 5.64 and 5.51 (2s, 2H), 4.63 – 4.49 and 4.27-4.20 (2m, 1H), 4.46 (d, $J = 5.4$ Hz) and 4.31 (d, $J = 5.7$ Hz) (2d, 2H), 4.18 and 3.83 (2s, 2H), 1.23 (d, $J = 6.4$ Hz) and 0.99 (d, $J = 6.8$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.22, -121.70; MS (ES⁺): 504.5 (M+1), 526.5 (M+Na); MS (ES⁻): 502.5 (M-1).

Scheme 145



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3-phenylureido)-1H-indazole-3-carboxamide (**145b**)

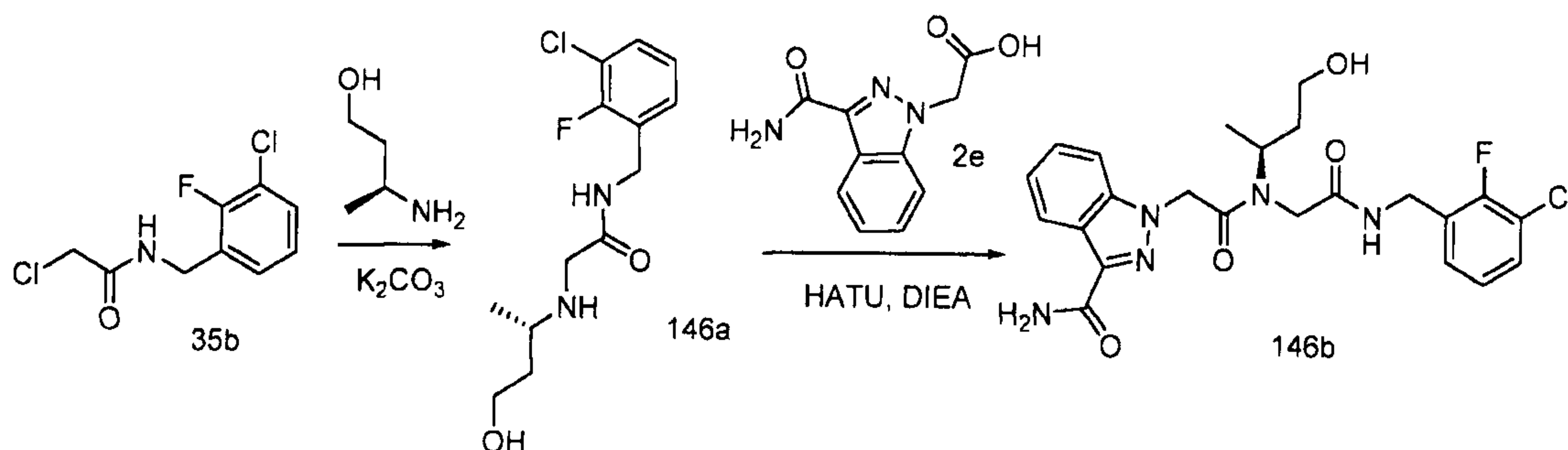
Step-1: Preparation of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**145a**)

5 Reaction of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**144a**) (800 mg, 1.588 mmol) according to the procedure reported in step-3 of Scheme 129 gave after workup 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**145a**) (1.32 g, 2.5 mmol), which was used directly
10 in the next step without further purification.

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3-phenylureido)-1H-indazole-3-carboxamide (**145b**)

Reaction of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**145a**) (112 mg, 0.212 mmol) in toluene (15 mL) with aniline (39.4 mg, 0.424 mmol) using TEA (0.059 mL, 0.424 mmol) as base according to the procedure reported in step-4 of Scheme 129 gave after workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3-phenylureido)-1H-indazole-3-carboxamide (**145b**) (9 mg, 0.015 mmol, 7%
20 yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 8.83 – 8.77 and 8.42-8.28 (2m, 3H), 8.63 (s, 1H), 7.65 – 6.91 (m, 12H), 5.55 and 5.41 (2s, 2H), 4.62 – 4.50 and 4.30 – 4.21 (2m, 1H), 4.46 (d, *J* = 4.9 Hz) and 4.32 (d, *J* = 5.2 Hz) (2d, 2H), 4.18 and 3.83 (2s, 2H), 1.22 (d, *J* = 6.4 Hz) and 0.99 (d, *J* = 6.7 Hz) (2d, 6H); ¹⁹F NMR (282
25 MHz, DMSO-*d*₆) δ -121.22, -121.74; MS (ES⁺): 594.6 (M+1) MS (ES⁻): 628.6 (M+Cl).

Scheme 146



Preparation of (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(4-hydroxybutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**146b**)

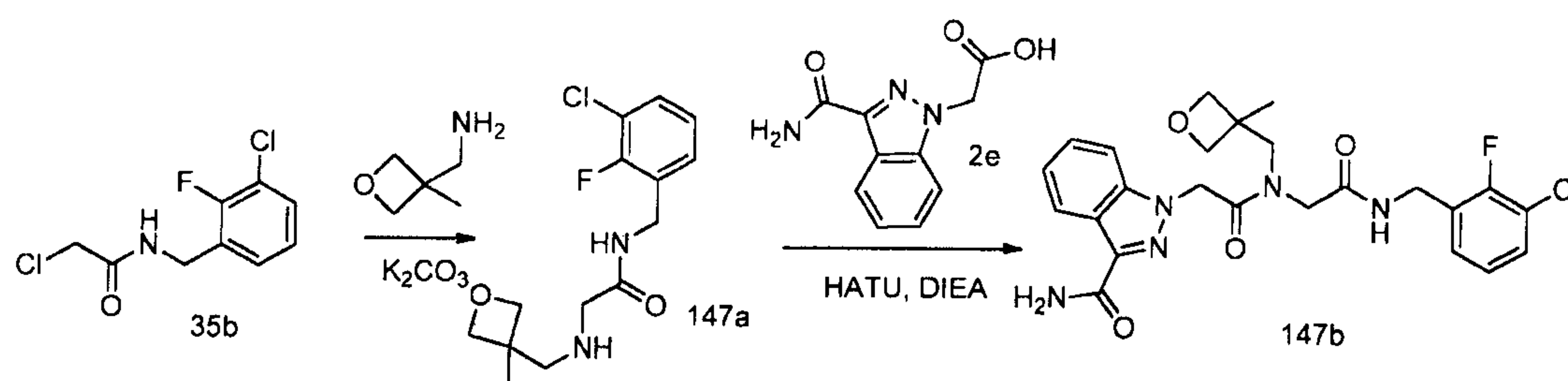
Step-1: Preparation of (S)-N-(3-chloro-2-fluorobenzyl)-2-((4-hydroxybutan-2-yl)amino)acetamide (**146a**)

- 5 Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (350 mg, 1.48 mmol) with (S)-3-aminobutan-1-ol (264 mg, 2.97 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup (S)-N-(3-chloro-2-fluorobenzyl)-2-((4-hydroxybutan-2-yl)amino)acetamide (**146a**) (112, 26%) as a yellow oil, which was used in the next step without further purification; MS (ES⁺): 289.4 (M+1); MS (ES⁻): 287.3 (M-1).

- 10 Step-2: Preparation of (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(4-hydroxybutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**146b**)

- Reaction of (S)-N-(3-chloro-2-fluorobenzyl)-2-((4-hydroxybutan-2-yl)amino)acetamide (**146a**) (112 mg, 0.39 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (94 mg, 0.43 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and
 15 purification by flash column chromatography [silica (12 g), eluting with DMA-80 in DCM 0 to 40%] (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(4-hydroxybutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**146b**) (40 mg, 0.082 mmol, 21% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.83 (t, *J* = 5.7 Hz) and 8.40 (t, *J* = 5.9 Hz) (2t, 1H), 8.24 – 8.12 (m, 1H), 7.71 (d, *J* = 6.3 Hz, 1H), 7.56 – 6.99 (m, 7H), 5.83 – 5.35
 20 (m, 2H), 4.95-3.65 (m, 6H), 3.62-3.19 (m, 2H), 1.83 – 1.38 (m, 2H), 1.25 (d, *J* = 6.5 Hz) and 0.98 (d, *J* = 6.8 Hz) (2d, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.25, -121.76; MS (ES⁺): 490.5 (M+1), 512.5 (M+Na); MS (ES⁻): 488.5 (M-1); [based on NMR, this compound is a mixture of rotamer 1:1 ratio].

Scheme 147



Preparation of (1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((3-methyloxetan-3-yl)methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**147b**)

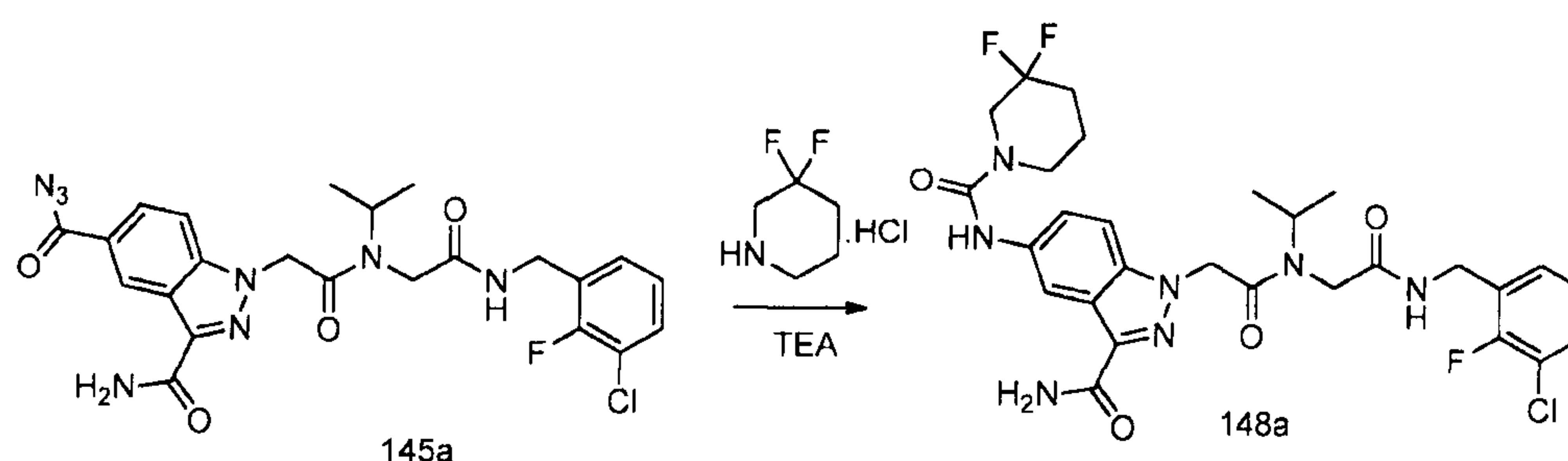
Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((2-(3-methyloxetan-3-yl)ethyl)amino)acetamide (**147a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (292 mg, 1.24 mmol) with (3-methyloxetan-3-yl)methanamine (250 mg, 2.47 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-((2-(3-methyloxetan-3-yl)ethyl)amino)acetamide (**147a**) (113 mg, 30%) as a colorless oil; MS (ES⁺): 301.3 (M+1), 323.3 (M+Na); MS (ES⁻): 299.3 (M-1).

Step-2: Preparation of (1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((3-methyloxetan-3-yl)methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**147b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-((2-(3-methyloxetan-3-yl)ethyl)amino)acetamide (**147a**) (113 mg, 0.38 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (91 mg, 0.4 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA-80 in DCM 0 to 40%] (1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((3-methyloxetan-3-yl)methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**147b**) (76 mg, 0.15 mmol, 40% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.83 (t, *J* = 5.6 Hz) and 8.50 (t, *J* = 5.8 Hz) (2t, 1H), 8.19 (d, *J* = 8.1 Hz, 1H), 7.82 – 7.65 (m, 1H), 7.57 – 7.10 (m, 7H), 5.54 and 5.49 (2s, 2H), 4.54-3.03 (m, 10H), 1.24 and 1.22 (2s, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.16, -121.55; MS (ES⁺): 524.5 (M+Na); [based on NMR, this compound is a mixture of two rotamers 4:1 ratio].

Scheme 148



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropiperidin-1-carboxamido)-1H-indazole-3-carboxamide (**148a**)

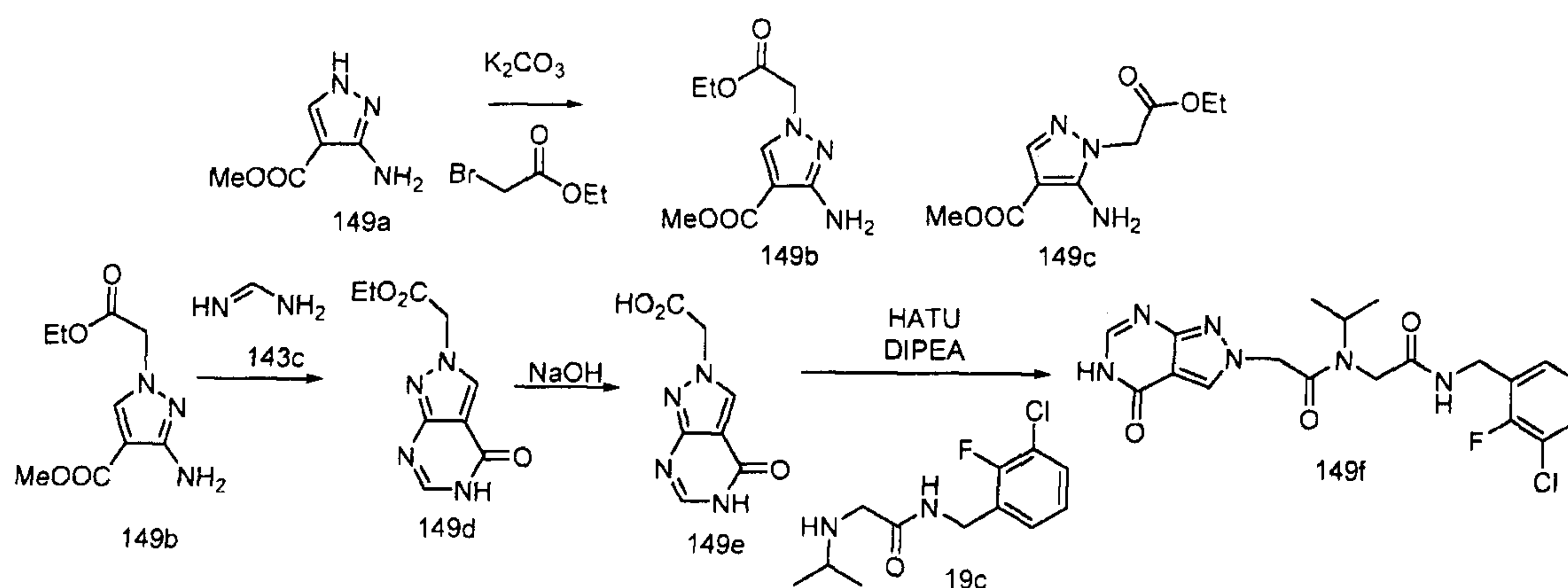
Reaction of 3-carbamoyl-1-(2-((2-(3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**145a**) (200 mg, 0.38 mmol) in toluene (15 mL) with 3,3-difluoropiperidine hydrochloride (119 mg, 0.756 mmol)

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using TEA (0.21 mL, 1.51 mmol) as base according to the procedure reported in step-4 of Scheme 129 gave after workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropiperidine-1-carboxamido)-1H-indazole-3-carboxamide (**148a**) (36 mg, 0.058 mmol, 15% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (as a mixture of two rotamers) δ 8.82 (t, *J* = 5.8 Hz) and 8.36 (t, *J* = 5.8 Hz) (2t, 1H), 8.78 (s, 1H), 8.19 (s, 1H), 7.71 – 7.04 (m, 7H), 5.54 and 5.41 (2s, 2H), 4.65 – 4.50 and 4.29-4.21 (2m, 1H), 4.46 (d, *J* = 5.3 Hz) and 4.32 (d, *J* = 5.6 Hz) (2d, 2H), 4.21 – 3.70 (m, 4H), 3.52 (t, 2H), 2.17 – 1.95 (m, 2H), 1.82 – 1.60 (m, 2H), 1.22 (d, *J* = 6.4 Hz) and 0.99 (d, *J* = 6.8 Hz)(2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -101.17, -121.22, -121.78; MS (ES⁺): 622.6 (M+1), 644.6 (M+Na); MS (ES⁻): 620.5 (M-1).

Scheme 149



Preparation of N-(2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)-N-isopropyl-2-(4-oxo-4,5-dihydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)acetamide (**149f**)

Step-1: Preparation of methyl 3-amino-1-(2-ethoxy-2-oxoethyl)-1H-pyrazole-4-carboxylate (**149b**)

Reaction of methyl 3-amino-1H-pyrazole-4-carboxylate (**149a**) (4.9 g, 33.0 mmol) and 2-bromoacetate (4.48 mL, 39.6 mmol) in DMF (20 mL) using potassium carbonate (6.91 g, 49.5 mmol) according to the procedure reported in step-1 of Scheme-43 gave after workup and purification by flash column chromatography [silica gel eluting with hexanes/EtOAc (1:0 to 1:1)] methyl 5-amino-1-(2-ethoxy-2-oxoethyl)-1H-pyrazole-4-carboxylate (**149b**) (3.98 g, 53%) as a yellow oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.97 (s, 1H), 5.41 (s, 2H), 4.82 (s, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.70 (s, 3H), 1.20 (t, *J* = 7.2 Hz, 3H); MS (ES⁺): 228.3 (M+1); and methyl 5-amino-1-(2-ethoxy-2-oxoethyl)-1H-pyrazole-4-carboxylate (**149c**) (2.73 g,

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36%) as a yellow solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 7.48 (s, 1H), 6.42 (s, 2H), 4.82 (s, 2H), 4.13 (q, $J = 7.1$ Hz, 2H), 3.68 (s, 3H), 1.20 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 228.3 (M+1).

Step-2: Preparation of ethyl 2-(4-oxo-4,5-dihydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)acetate (**149d**)

5 Reaction of methyl 3-amino-1-(2-ethoxy-2-oxoethyl)-1H-pyrazole-4-carboxylate (**149b**) (3.44 g, 15.15 mL) with formimidamide acetate (**143c**) (15.93 g, 151 mmol) in ethanol (120 mL) according to the procedure reported in step-3 of Scheme-143 gave after workup and purification by flash column chromatography [silica gel eluting with $\text{CHCl}_3/\text{MeOH}$ (1:0 to 9:1)] ethyl 2-(4-oxo-4,5-dihydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)acetate (**149d**) (979 mg, 29%) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.80 (s, 1H), 8.53 (s, 1H), 7.95 (s, 1H), 5.25 (s, 2H), 4.18 (q, $J = 7.1$ Hz, 2H), 1.22 (t, $J = 7.1$ Hz, 3H); MS (ES⁺): 223.3 (M+1).

Step-3: Preparation of 2-(4-oxo-4,5-dihydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)acetic acid (**149e**)

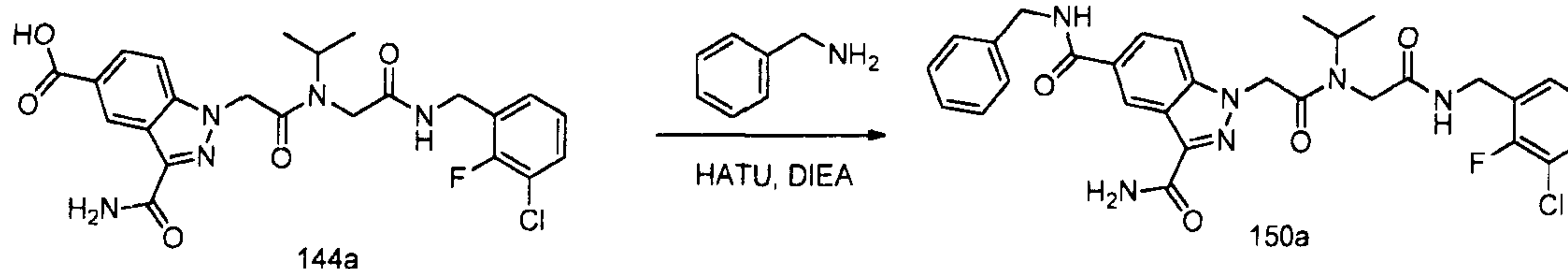
15 Reaction of ethyl 2-(4-oxo-4,5-dihydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)acetate (**149d**) (200 mg, 0.9 mmol) with 2 N aqueous sodium hydroxide (2.7 mL, 5.4 mmol) in MeOH according to the procedure reported in step-4 of scheme 43 gave after workup 2-(4-oxo-4,5-dihydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)acetic acid (**149e**) (162 mg, 93%) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 13.40 (s, 1H), 11.77 (s, 1H), 8.51 (s, 1H), 7.94 (d, $J = 3.7$ Hz, 1H), 5.13 (s, 2H); MS (ES⁺): 193.1 (M-1).

Step-4: Preparation of N-(2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)-N-isopropyl-2-(4-oxo-4,5-dihydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)acetamide (**149f**)

Reaction of 2-(4-oxo-4,5-dihydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)acetic acid (**149e**) (70 mg, 0.36 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (112 mg, 0.43 mmol) according to the procedure reported in step-3 of Scheme-2 gave after workup and purification by flash column [silica gel (4 g), eluting with $\text{CHCl}_3/\text{MeOH}$ (1:0 to 9:1)] N-(2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)-N-isopropyl-2-(4-oxo-4,5-dihydro-2H-pyrazolo[3,4-d]pyrimidin-2-yl)acetamide (**149f**) (81 mg, 52% yield) as an off-white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 11.74 (bs, 1H), 8.76 (t, $J = 5.8$ Hz) & 8.36 (t, $J = 5.9$ Hz) (2t, 1H) 8.43 & 8.42 (2s, 1H), 7.93 (t, $J = 2.7$ Hz, 1H), 7.54 – 7.10 (m, 3H), 5.40 & 5.23 (2s, 2H), 4.65 – 4.49 & 4.23 – 4.10 (2m, 1H), , 4.42 (d, $J = 5.8$ Hz) & 4.32 (d, $J = 5.8$ Hz) (2d, 2H), 4.13 & 3.84 (2s, 2H), 1.18 (d, $J = 6.5$ Hz) & 0.98 (d, $J = 6.8$ Hz) (2d, 6H); ^{19}F NMR(282

MHz, DMSO-*d*₆) δ -121.32, -121.71; MS (ES⁻): 433.5 & 435.3 (M-1); 469.5 & 471.5 (M+Cl).

Scheme 150

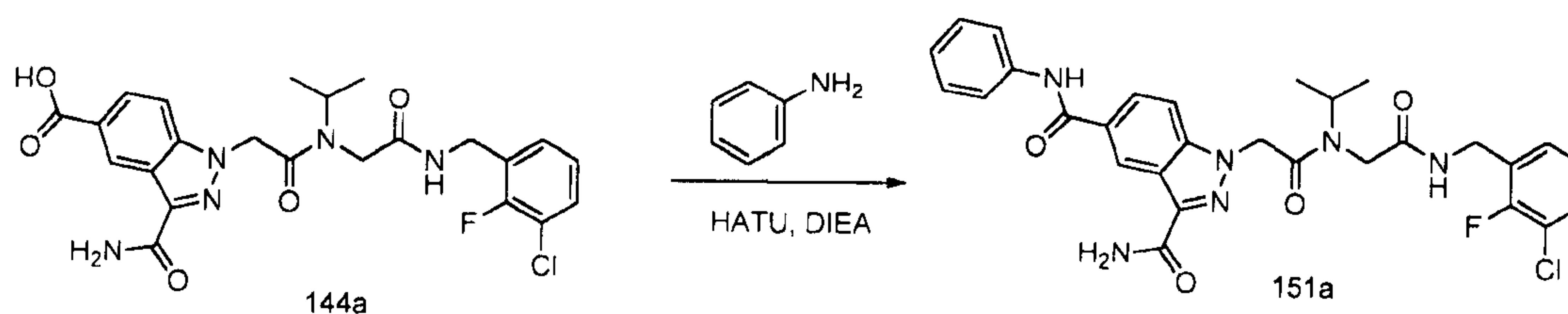


- 5 Preparation of N5-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3,5-dicarboxamide (**150a**)

Reaction of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**144a**) (50 mg, 0.1 mmol) with phenylmethanamine (0.016 mL, 0.149 mmol) according to the procedure
 10 reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (4 g), eluting with MeOH in DCM (1:0 to 19:1)] N5-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3,5-dicarboxamide (**150a**) (25 mg, 43%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.20 (t, *J* = 6.0 Hz) and 8.88 – 8.68 (m) and 8.36 (t, *J* = 5.8 Hz) (3H), 7.98 – 7.88 (m, 1H),
 15 7.81 and 7.79 (2s, 1H), 7.67 (d, *J* = 8.9 Hz) and 7.60 (dd, *J* = 8.9, 0.8 Hz) (d & dd, 1H), 7.55 – 6.96 (m, 9H), 5.63 and 5.49 (2s, 2H), 4.60 – 4.48 and 4.28 – 4.21 (2m, 3H), 4.46 (d, *J* = 5.7 Hz) and 4.31 (d, *J* = 5.8 Hz) (2d, 2H), 4.18 and 3.83 (2s, 2H), 1.23 (d) and 0.99 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.22, -121.73; MS (ES⁺): 615.6 & 617.6 (M+Na); MS (ES⁻): 627.5 & 629.5 (M+Cl).

20

Scheme 151



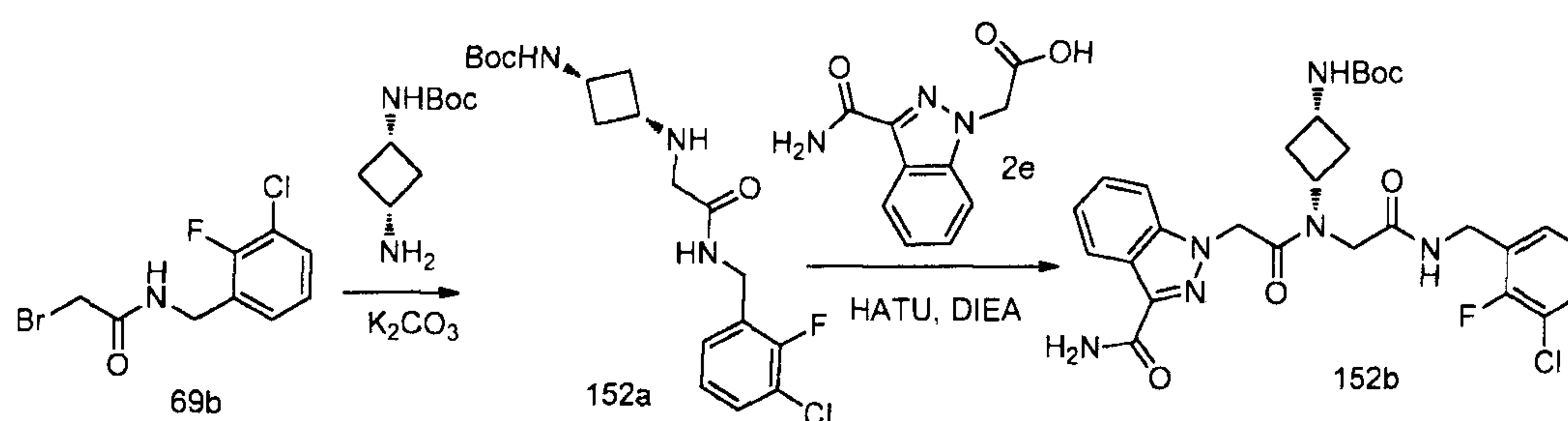
Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-phenyl-1H-indazole-3,5-dicarboxamide (**151a**)

Reaction of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**144a**) (50 mg, 0.1 mmol) with aniline (0.016 mL, 0.18 mmol) according to the procedure reported in step-3 of
 25

Scheme 2 gave after workup and purification by flash column chromatography [silica (4 g), eluting with MeOH in DCM (1:0 to 19:1)] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-phenyl-1H-indazole-3,5-dicarboxamide (**151a**) (17 mg, 30%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.44 and 10.43 (2s, 1H), 8.89 – 8.79 (m) and 8.38 (t, *J* = 5.9 Hz) (2H), 8.02 – 7.92 (m, 1H), 7.87 – 7.77 (m, 3H), 7.75 – 7.64 (m, 1H), 7.57 – 6.98 (m, 7H), 5.65 and 5.52 2(s, 2H), 4.61 – 4.50 and 4.31 – 4.21 (2m, 1H), 4.47 (d, *J* = 5.5 Hz) and 4.32 (d, *J* = 6.0 Hz (2d, 2H), 4.19 and 3.85 (2s, 2H), 1.24 (d, *J* = 6.2 Hz) and 1.00 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.21, -121.70; MS (ES⁺): 601.6 & 603.6 (M+Na).

10

Scheme 152



Preparation of tert-butyl ((cis)-3-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)cyclobutyl)carbamate (**152b**)

Step-1: Preparation of tert-butyl ((cis)-3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)cyclobutyl)carbamate (**152a**)

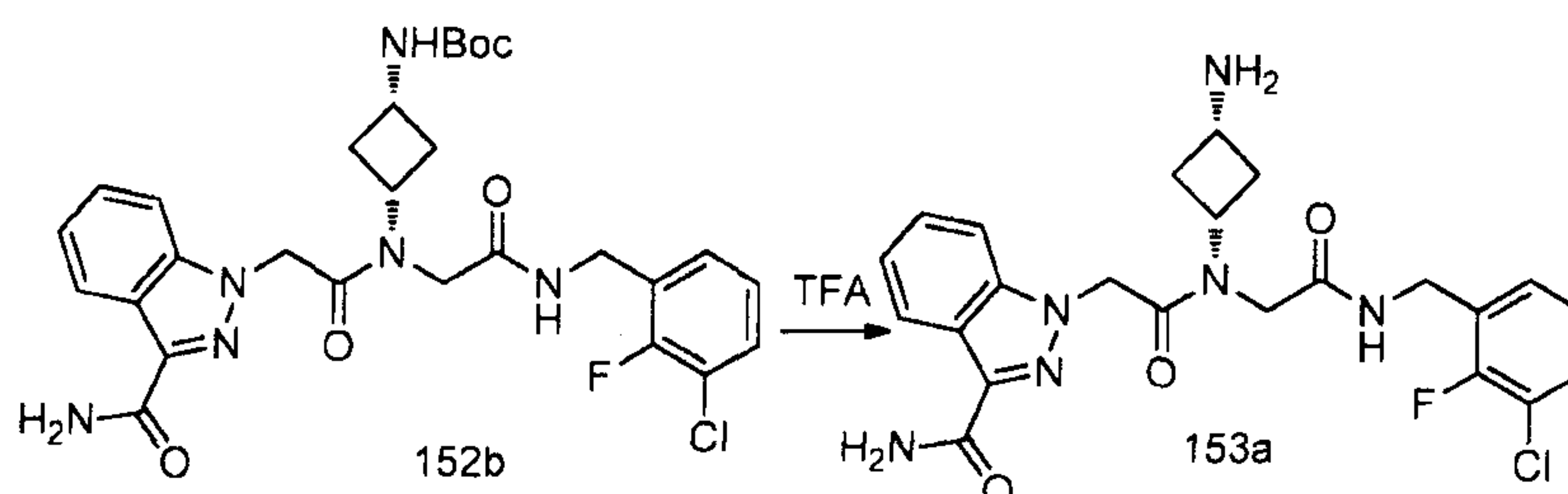
Reaction of 2-bromo-N-(3-chloro-2-fluorobenzyl)acetamide (**69b**) (250 mg, 0.89 mmol) with tert-butyl (cis)-3-aminocyclobutylcarbamate (250 mg, 1.34 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica gel 12 g, eluting with MeOH in DCM 0 to 50%] tert-butyl ((cis)-3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)cyclobutyl)carbamate (**152a**) (243 mg, 0.63 mmol, 71% yield) as a thick yellow oil. MS (ES⁺): 386.5 (M+1); MS (ES⁻): 384.4 (M-1).

Step-2: Preparation of tert-butyl ((cis)-3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)cyclobutyl)carbamate (**152a**)

Reaction of tert-butyl ((cis)-3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)cyclobutyl)carbamate (**152a**) (114 mg, 0.3 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (78 mg, 0.36 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [Silica

gel, (12 g) eluting with MeOH in DCM from 0-20%] tert-butyl ((cis)-3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)cyclobutyl)carbamate (**152a**) (122 mg, 0.21 mmol, 70% yield) as a white solid as a mixture two rotamers; ^1H NMR (300 MHz, DMSO- d_6) δ 8.80 and 8.40 (2t, $J = 5.9$ Hz, 1H), 8.20 – 8.15 (m, 1H), 7.69 (bs, 1H), 7.59 and 7.57 (2s, 1H),
 5 7.53-6.99 (m, 6H), 5.56 and 5.36 (2s, 2H), 4.47 (d, $J = 5.6$ Hz) and 4.37 – 4.25 (m) and 4.04 (s) (5H), 3.82 – 3.55 (m, 1H), 2.60 – 2.53 and 2.36 – 1.82 (2m, 4H), 1.38 and 1.37 (2s, 9H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.25, -121.60. MS (ES-): 621.5, 623.5 (M+Cl).

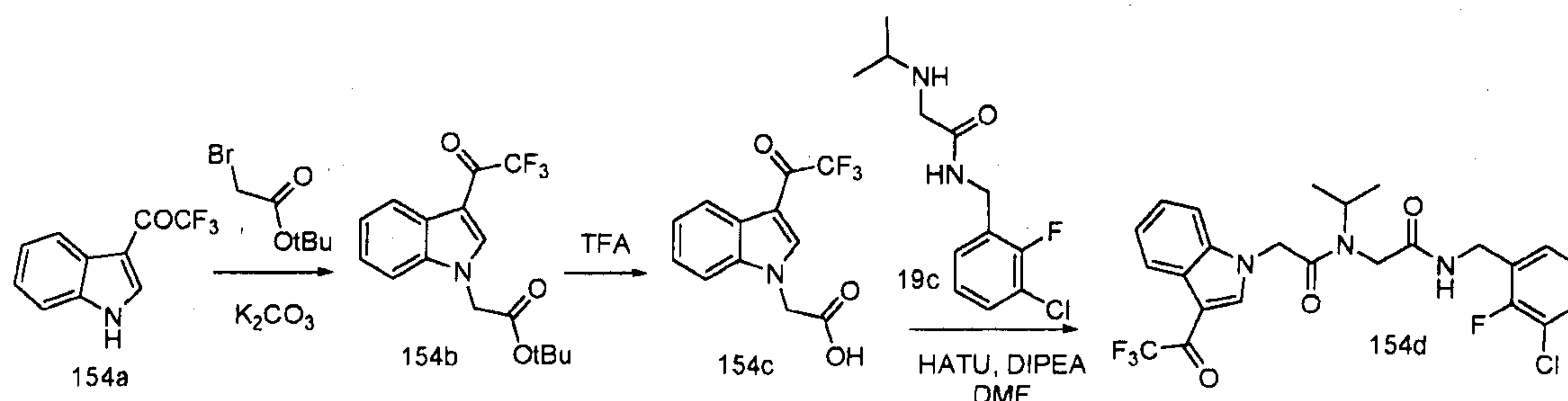
Scheme 153



10 Preparation of 1-(2-(((cis)-3-aminocyclobutyl)(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**153a**)

Reaction of tert-butyl ((cis)-3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)cyclobutyl)carbamate (**152a**) (109 mg, 0.19 mmol) with TFA (0.286 mL, 3.71 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and
 15 purification by flash column chromatography [Silica gel, (8 g) eluting with DMA80 in DCM 0-30%] 1-(2-(((cis)-3-aminocyclobutyl)(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**153a**) (15 mg, 0.031 mmol, 17% yield) as a white solid as a mixture of two rotamers; ^1H NMR (300 MHz, DMSO- d_6) δ 8.96 – 8.89 and 8.41 (t, $J = 6.0$ Hz), (m & t, 1H, D $_2$ O exchangeable), 8.21 – 8.13 (m, 1H), 7.68 (s, 1H, D $_2$ O exchangeable), 7.61-7.00 (m, 7H), 5.53 and 5.40 (2s, 2H), 4.47 (d, $J = 5.6$ Hz) and
 20 4.38 – 3.97 (m) (5 H), 3.03 – 2.85 (m, 1H), 2.32 – 1.47 (m, 4H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.23, -121.62; MS (ES+): 487.5 (M+1); MS (ES-): 485.5 (M-1), 521.4, 523.4 (M+Cl).

Scheme 154



Preparation of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropyl-2-(3-(2,2,2-trifluoroacetyl)-1H-indol-1-yl)acetamide (**154d**)

Step-1: Preparation of tert-butyl 2-(3-(2,2,2-trifluoroacetyl)-1H-indol-1-yl)acetate (**154b**)

5 Reaction of 2,2,2-trifluoro-1-(1H-indol-3-yl)ethanone (**154a**) (800 mg, 3.75 mmol) with tert-butyl 2-bromoacetate (1.46 g, 7.51 mmol) using Potassium carbonate (1.03 g, 7.51 mmol) as base in acetonitrile (50 mL) according to the procedure reported step-1 of Scheme 43 gave after workup and purification by flash column chromatography [silica gel (24 g), eluting with EtOAc-hexane 0 to 60%] tert-butyl 2-(3-(2,2,2-trifluoroacetyl)-1H-indol-1-yl)acetate (**154b**)
 10 (1.15 g, 3.51 mmol, 94% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.60 (q, J = 1.9 Hz, 1H), 8.23 - 8.17 (m, 1H), 7.63 - 7.57 (m, 1H), 7.44 - 7.35 (m, 2H), 5.27 (s, 2H), 1.43 (s, 9H); MS (ES⁺) 328.4 (M+1), MS (ES⁻): 326.4, (M-1), 362.3 (M+Cl).

Step-2: Preparation of 2-(3-(2,2,2-trifluoroacetyl)-1H-indol-1-yl)acetic acid (**154c**)

15 Reaction of tert-butyl 2-(3-(2,2,2-trifluoroacetyl)-1H-indol-1-yl)acetate (**154b**) (1.1 g, 3.36 mmol) with TFA (3.88 mL, 50.4 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and trituration of crude product with 30% EtOAc-hexane (10 mL) 2-(3-(2,2,2-trifluoroacetyl)-1H-indol-1-yl)acetic acid (**154c**) (650 mg, 2.4 mmol, 71% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.38 (s, 1H, D₂O exchangeable), 8.64 - 8.55 (m, 1H), 8.26 - 8.14 (m, 1H), 7.70 - 7.58 (m, 1H), 7.44 - 7.30 (m, 2H), 5.28 (s,
 20 2H); MS (ES⁺) 272.3 (M+1), 294.3 (M+Na), MS (ES⁻): 270.2, (M-1).

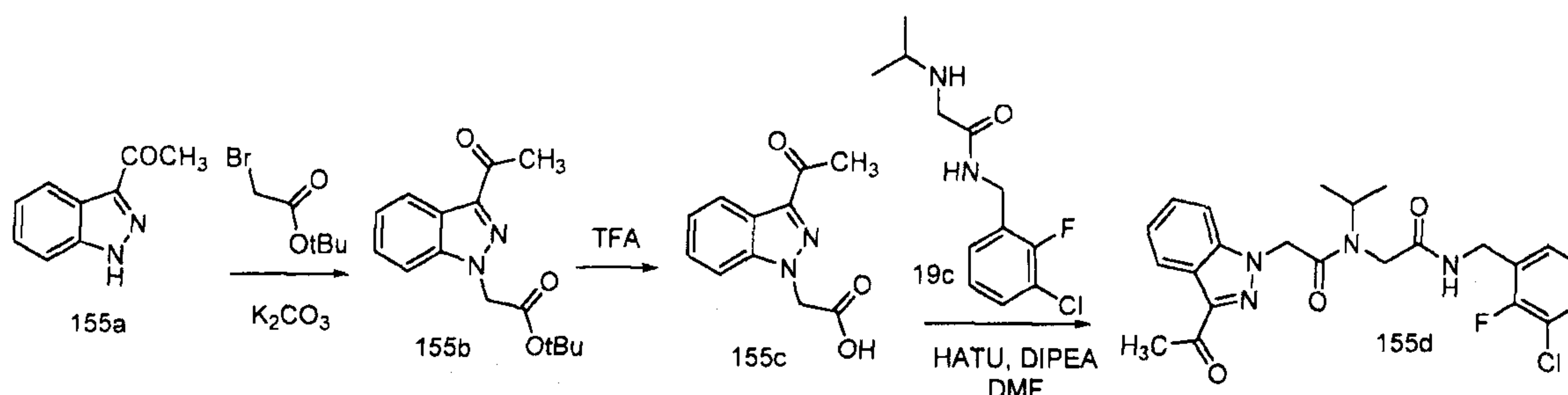
Step-3: Preparation of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropyl-2-(3-(2,2,2-trifluoroacetyl)-1H-indol-1-yl)acetamide (**154d**)

Reaction of 2-(3-(2,2,2-trifluoroacetyl)-1H-indol-1-yl)acetic acid (**154c**) (80 mg, 0.3 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (76 mg, 0.3 mmol)
 25 according to the procedure reported in step-3 of Scheme 2 gave after workup and purification

by flash column chromatography [silica gel (12 g), eluting with DMA80 - DCM 0 to 20%] N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropyl-2-(3-(2,2,2-trifluoroacetyl)-1H-indol-1-yl)acetamide (**154d**) (115 mg, 0.23 mmol, 76% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 8.83 and 8.34 (2t, J = 5.7 Hz, 1H), 8.56 and 8.47 (2d, J = 2.0 Hz, 1H), 8.23 – 8.17 (m, 1H), 7.67 – 6.92 (m, 6H), 5.51 and 5.30 (2s, 2H), 4.64 - 4.54 and 4.29 - 4.19 (2m, 1H), 4.48 and 4.33 (2d, J = 5.6 Hz, 2H), 4.18 and 3.85 (2s, 2H), 1.27 and 1.00 (2d, J = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ -71.30 and -71.33, -121.19 and -121.86; MS (ES+) 512.5 (M+1), 534.5 (M+Na), MS (ES-): 510.5 (M-1), 546.5 (M+Cl).

10

Scheme 155



Preparation of 2-(3-acetyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**155d**)

Step-1: Preparation of tert-butyl 2-(3-acetyl-1H-indazol-1-yl)acetate (**155b**)

Reaction of 1-(1H-indazol-3-yl)ethanone (**155a**) (800 mg, 5.0 mmol) with tert-butyl 2-bromoacetate (1.47 g, 10 mmol) using Potassium carbonate (1.38 g, 10 mmol) as base in acetonitrile (50 mL) according to the procedure reported step-1 of Scheme 43 gave after workup and purification by flash column chromatography [silica gel (24 g), eluting with EtOAc-hexane 0 to 60%] tert-butyl 2-(3-acetyl-1H-indazol-1-yl)acetate (**155b**) (1.3 g, 4.74 mmol, 95 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.19 (dt, J = 8.1, 1.0 Hz, 1H), 7.75 (dt, J = 8.5, 0.9 Hz, 1H), 7.51 (ddd, J = 8.4, 6.9, 1.2 Hz, 1H), 7.36 (ddd, J = 7.9, 6.9, 0.9 Hz, 1H), 5.45 (s, 2H), 2.62 (s, 3H), 1.42 (s, 9H); MS (ES+) 297.4 (M+Na); MS (ES-): 273.4 (M-1).

Step-2: Preparation of 2-(3-acetyl-1H-indazol-1-yl)acetic acid (**155c**)

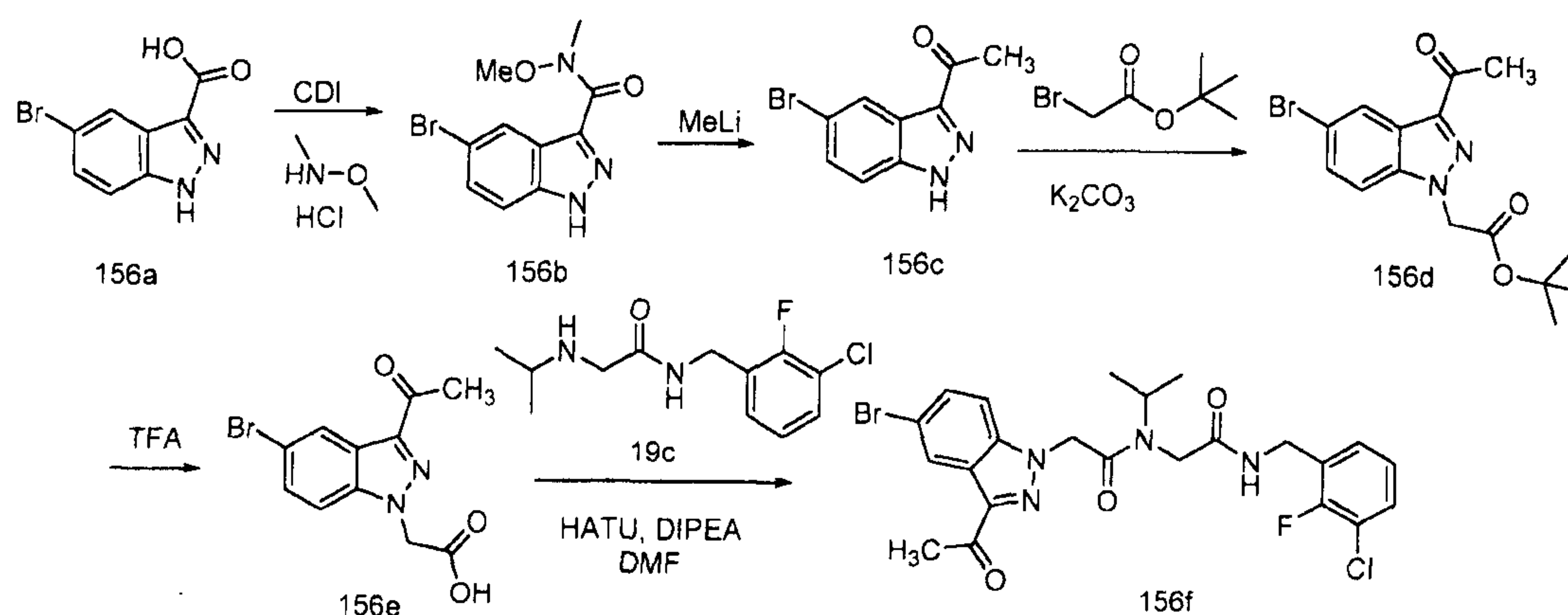
Reaction of tert-butyl 2-(3-acetyl-1H-indazol-1-yl)acetate (**155b**) (1 g, 3.65 mmol) with TFA (5.62 mL, 72.9 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and trituration of crude product with 30% EtOAc-hexane (10 mL) 2-(3-acetyl-1H-

indazol-1-yl)acetic acid (**155c**) (800 mg, 3.67 mmol, 101 % yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 13.35 (s, 1H), 8.19 (dt, J = 8.1, 1.0 Hz, 1H), 7.79 (dt, J = 8.5, 0.9 Hz, 1H), 7.50 (ddd, J = 8.4, 6.9, 1.2 Hz, 1H), 7.36 (ddd, J = 8.0, 6.9, 0.9 Hz, 1H), 5.46 (s, 2H), 2.62 (s, 3H); MS (ES+) 219.3 (M+1), 241.3 (M+Na), MS (ES-): 217.2 (M-1).

5 Step-3: Preparation of 2-(3-acetyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**155d**)

Reaction of 2-(3-acetyl-1H-indazol-1-yl)acetic acid (**155c**) (65 mg, 0.3 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (77 mg, 0.3 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash
10 column chromatography [silica gel (12 g), eluting with DMA80 – DCM; 0 to 20%] 2-(3-acetyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**155d**) (120 mg, 0.26 mmol, 88% yield) as a white solid as a mixture of two rotamers; ^1H NMR (300 MHz, DMSO- d_6) δ 8.83 and 8.34 (t, J = 5.7 Hz) (2t, 1H), 8.21 – 8.16 (m, 1H), 7.72 – 6.96 (m, 6H), 5.70 and 5.53 (2s, 2H), 4.62 – 4.50 and 4.32 – 4.19 (2m, 1H), 4.47 and 4.32 (2d, J = 5.6 Hz, 2H), 4.18 and 3.84 (s, 2H), 2.69 and 2.61 (2s, 3H), 1.25
15 and 1.00 (d, J = 6.8 Hz, 6H). ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.21, -121.76; MS (ES+) 458.4, 459.5 (M+1), 481.5 (M+Na), MS (ES-): 493.4 (M+Cl).

Scheme 156



20 Preparation of 2-(3-acetyl-5-bromo-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**156f**)

Step-1: Preparation of 5-bromo-N-methoxy-N-methyl-1H-indazole-3-carboxamide (**156b**)

To a solution of 5-bromo-1H-indazole-3-carboxylic acid (**156a**) (1 g, 4.15 mmol) in DMF (20 mL) was added CDI (0.81 g, 4.98 mmol) and stirred at 65 °C for 15 min. The resultant clear
25 solution was cooled to RT, added N,O-dimethylhydroxylamine hydrochloride (0.49 g, 5

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mmol) and continued stirring at 65 °C for 3h. Mixture was cooled to RT, concentrated under vacuum and resultant solution was diluted with water (100 mL) and stirred for 10 min. The solid obtained was collected by filtration, washed with water (3 x 5 mL) and dried to afford 5-bromo-N-methoxy-N-methyl-1H-indazole-3-carboxamide (**156b**) (830 mg, 2.92 mmol, 70% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.85 (s, 1H), 8.18 (d, J = 1.8 Hz, 1H), 7.69 - 7.49 (m, 2H), 3.78 (s, 3H), 3.45 (s, 3H); MS (ES+) 284.3, 286.2 (M+2), 306.3, 308.3 (M+Na); MS (ES-): 318.2, 320.2 (M+Cl).

Step-2: Preparation of 1-(5-bromo-1H-indazol-3-yl)ethanone (**156c**)

To a solution of 5-bromo-N-methoxy-N-methyl-1H-indazole-3-carboxamide (**156b**) (820 mg, 2.89 mmol) in THF (30 mL) at 0 °C under argon atmosphere was added MeLi (8.66 mL, 8.66 mmol). The mixture was slowly warmed to RT and continued to stir for 3h at RT. Mixture was poured into 1 N aqueous KHSO₄ solution (50 mL) and then diluted with EtOAc (40 mL). Layers were separated, aqueous layer was extracted with EtOAc (1x40 mL) and the combined organics were washed with brine, dried, filtered and concentrated to afford crude product as a dark green solid. This solid was suspended in 30% EtOAc-hexane (10 mL) and sonicated for few minutes. The solid obtained was collected by filtration, washed with 30% EtOAc-hexane (2 x 2 mL) to afford 1-(5-bromo-1H-indazol-3-yl)ethanone (**156c**) (470 mg, 1.97 mmol, 68% yield) as light green solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 14.06 (s, 1H), 8.30 (dd, J = 1.8, 0.8 Hz, 1H), 7.68 (dd, J = 8.8, 0.7 Hz, 1H), 7.58 (dd, J = 8.9, 1.9 Hz, 1H), 2.63 (s, 3H); MS (ES+) 239.2, 241.2 (M+2), MS (ES-): 237.1, 239.1 (M-2), 273.2, 275.1 (M+Cl).

Step-3: Preparation of tert-butyl 2-(3-acetyl-5-bromo-1H-indazol-1-yl)acetate (**156d**)

Reaction of 1-(5-bromo-1H-indazol-3-yl)ethanone (**156c**) (400 mg, 1.67 mmol) with tert-butyl 2-bromoacetate (0.49 mL, 3.35 mmol) using Potassium carbonate (0.46 g, 3.35 mmol) as base in acetonitrile (20 mL) according to the procedure reported step-1 of Scheme 43 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with EtOAc-hexane 0 to 100%] tert-butyl 2-(3-acetyl-5-bromo-1H-indazol-1-yl)acetate (**156d**) (480 mg, 1.36 mmol, 81% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.32 (dd, J = 1.9, 0.7 Hz, 1H), 7.79 (dd, J = 9.0, 0.7 Hz, 1H), 7.67 (dd, J = 8.9, 1.9 Hz, 1H), 5.48 (s, 2H), 2.62 (s, 3H), 1.42 (s, 9H); MS (ES+) 375.3, 377.3 (M+2), MS (ES-): 387.3, 389.3 (M+Cl).

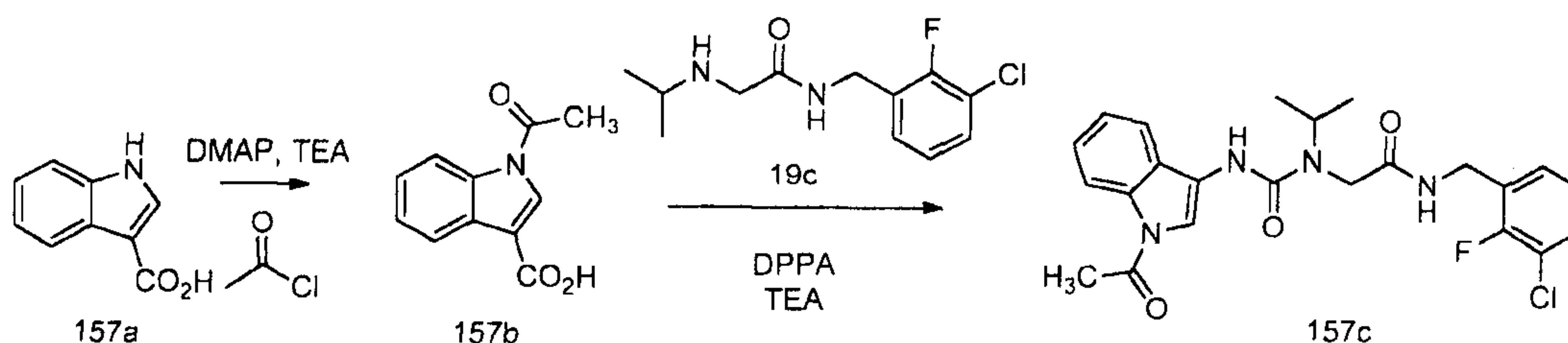
Step-4: Preparation of 2-(3-acetyl-5-bromo-1H-indazol-1-yl)acetic acid (**156e**)

Reaction of tert-butyl 2-(3-acetyl-5-bromo-1H-indazol-1-yl)acetate (**156d**) (480 mg, 1.36 mmol) with TFA (2.09 mL, 27.2 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and trituration of crude product with 20% EtOAc-hexane (10 mL) 2-(3-acetyl-5-bromo-1H-indazol-1-yl)acetic acid (**156e**) (400 mg, 1.35 mmol, 99%
 5 yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.42 (s, 1H), 8.32 (d, J = 1.9, 0.7 Hz, 1H), 7.82 (dd, J = 9.0, 0.7 Hz, 1H), 7.66 (dd, J = 9.0, 1.9 Hz, 1H), 5.48 (s, 2H), 2.62 (s, 3H); MS (ES⁺): 297.2, 299.2 (M+2), 319.2, 321.2 (M+Na); MS (ES⁻): 295.2, 297.2 (M-2).

Step-5: Preparation of 2-(3-acetyl-5-bromo-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**156f**)
 10

Reaction of 2-(3-acetyl-5-bromo-1H-indazol-1-yl)acetic acid (**156e**) (70 mg, 0.24 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (61 mg, 0.24 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with DMA80 – DCM; 0 to 20%]
 15 2-(3-acetyl-5-bromo-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**156f**) (93 mg, 0.173 mmol, 73% yield) as a white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.83 and 8.34 (2t, J = 5.7 Hz, 1H), 8.32 - 8.30 (m, 1H), 7.74 – 6.91 (m, 5H), 5.72 and 5.55 (2s, 2H), 4.62 - 4.50 and 4.30 - 4.19 (2m, 1H), 4.46 and 4.31 (2d, J = 5.6 Hz, 2H), 4.17 and 3.84 (2s, 2H), 2.69 and 2.61 (2s, 3H), 1.24
 20 and 0.99 (2d, J = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO- *d*₆) δ -121.22 , -121.72; MS(ES⁻) 535.4, 537.4 (M-2), 571.4, 573.4; (M+Cl).

Scheme 157



Preparation of 2-(3-(1-acetyl-1H-indol-3-yl)-1-isopropylureido)-N-(3-chloro-2-fluorobenzyl)acetamide (**157c**)
 25

Step-1: Preparation of 1-acetyl-1H-indole-3-carboxylic acid (**157b**)

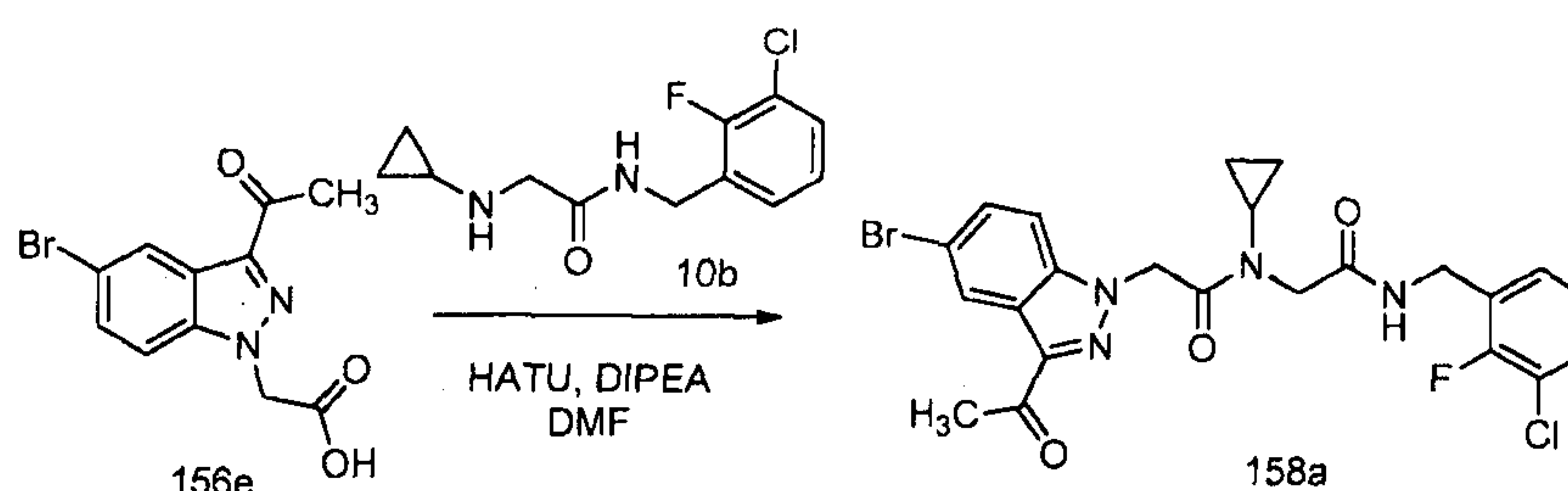
To a solution of 1H-indole-3-carboxylic acid (**157a**) (10 g, 62.1 mmol), TEA (19.03 mL, 137 mmol) and DMAP (1.516 g, 12.41 mmol) in DCM (100 mL) cooled to 0 °C was added drop-

wise acetyl chloride (4.41 mL, 62.1 mmol) and stirred for 3h at RT. The reaction mixture was poured into an aqueous 1 N HCl solution, the solid obtained was collected by filtration, washed with water, MeOH and dried to give 1-acetyl-1H-indole-3-carboxylic acid (**157b**) (10.2 g, 50.2 mmol, 81 % yield) as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.83 (s, 1H), 8.44 (s, 1H), 8.39 – 8.31 (m, 1H), 8.13 – 8.05 (m, 1H), 7.43 – 7.32 (m, 2H), 2.74 (s, 3H); MS (ES⁺): 204.2 (M+1); (ES⁻) 202.2 (M-1).

Step-2: Preparation of 2-(3-(1-acetyl-1H-indol-3-yl)-1-isopropylureido)-N-(3-chloro-2-fluorobenzyl)acetamide (**157c**)

To a solution of 1-acetyl-1H-indole-3-carboxylic acid (**157b**) (0.1 g, 0.49 mmol) in dioxane (10 mL) was added triethylamine (0.2 mL, 1.4 mmol), diphenylphosphoryl azide (0.21 mL, 0.984 mmol) and stirred at RT for 2 h. To the mixture added N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (127 mg, 0.49 mmol) and mixture was heated at 90 °C for 4h. Mixture was cooled to RT, partitioned between saturated aqueous NaHCO₃ (60 mL) and EtOAc (60 mL). Layers were separated and aqueous layer was extracted with EtOAc (50 mL). The combined organics were washed with brine, dried, filtered, concentrated in vacuum and the residue obtained was purified by flash column chromatography [silica gel, (12 g) eluting with EtOAc in hexanes 0 to 100%] to afford 2-(3-(1-acetyl-1H-indol-3-yl)-1-isopropylureido)-N-(3-chloro-2-fluorobenzyl)acetamide (**157c**) (95 mg, 0.21 mmol, 42% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.10 (s, 1H), 8.78 (t, J = 5.8 Hz, 1H), 8.33 (d, J = 8.1 Hz, 1H), 7.84 (s, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.54 - 7.44 (m, 1H), 7.42 - 7.23 (m, 3H), 7.18 - 7.10 (m, 1H), 4.56 - 4.34 (m, 3H), 3.98 (s, 2H), 2.58 (s, 3H), 1.10 (d, J = 6.7 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.32; MS (ES⁺): 459.5 (M+1), 481.5 (M+Na); MS (ES⁻): 457.5 (M-1), 493.4 (M+Cl).

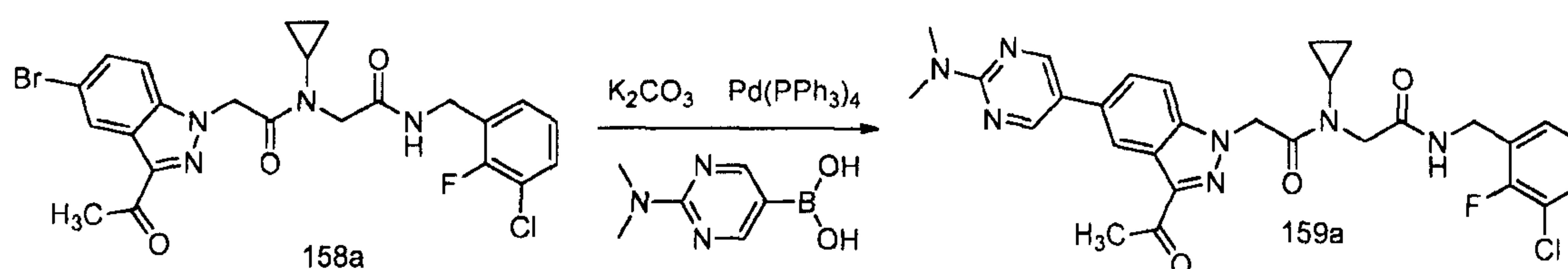
Scheme 158



Preparation of 2-(3-acetyl-5-bromo-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**158a**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (332 mg, 1.29 mmol) with 2-(3-acetyl-5-bromo-1H-indazol-1-yl)acetic acid (**156e**) (320 mg, 1.06 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by [silica (12 g), eluting with DMA80 in DCM from 0 to 20%] 2-(3-acetyl-5-bromo-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**158a**) (0.48 g, 0.9 mmol, 83% yield) as a colorless foam; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.48 (t, *J* = 5.9 Hz, 1H), 8.31 (dd, *J* = 1.8, 0.7 Hz, 1H), 7.73 (dd, *J* = 9.0, 0.7 Hz, 1H), 7.60 (dd, *J* = 8.9, 1.9 Hz, 1H), 7.51 – 7.41 (m, 1H), 7.26-7.18 (m, 1H), 7.14 – 7.05 (m, 1H), 5.77 (s, 2H), 4.33 (d, *J* = 5.8 Hz, 2H), 3.98 (s, 2H), 3.18 – 3.02 (m, 1H), 2.62 (s, 3H), 1.09 – 0.95 (m, 2H), 0.95 – 0.79 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.57; MS (ES⁺): 535.4 (M+1), 557.5 (M+Na), MS (ES⁻): 533.4 (M-1), 569.4 (M+Cl).

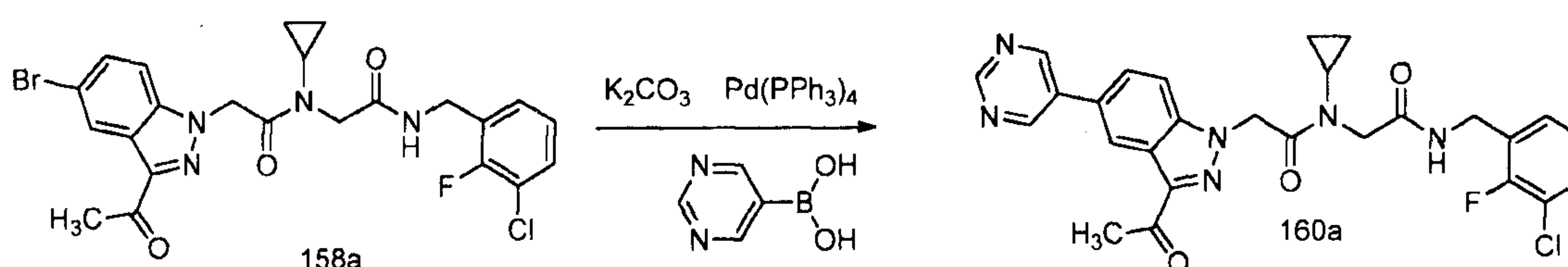
Scheme 159



Preparation of 2-(3-acetyl-5-(2-(dimethylamino)pyrimidin-5-yl)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**159a**)

Reaction of 2-(3-acetyl-5-bromo-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**158a**) (125 mg, 0.23 mmol) with 2-(dimethylamino)pyrimidin-5-ylboronic acid (0.047 g, 0.280 mmol) according to the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 20%] 2-(3-acetyl-5-(2-(dimethylamino)pyrimidin-5-yl)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**159a**) (93 mg, 0.16 mmol, 69% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.71 (s, 2H), 8.48 (t, *J* = 5.9 Hz, 1H), 8.29 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.79 (dd, *J* = 8.8, 0.9 Hz, 1H), 7.72 (dd, *J* = 8.8, 1.7 Hz, 1H), 7.50 – 7.41 (m, 1H), 7.28-7.18 (m, 1H), 7.15 – 7.06 (m, 1H), 5.78 (s, 2H), 4.34 (d, *J* = 5.7 Hz, 2H), 4.00 (s, 2H), 3.19 (s, 6H), 3.16 – 3.08 (m, 1H), 2.63 (s, 3H), 1.09 – 0.99 (m, 2H), 0.96 – 0.88 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.58; MS (ES⁺): 578.7 (M+1), 600.6 (M+Na); MS (ES⁻): 576.5 (M-1), 612.5 (M+Cl).

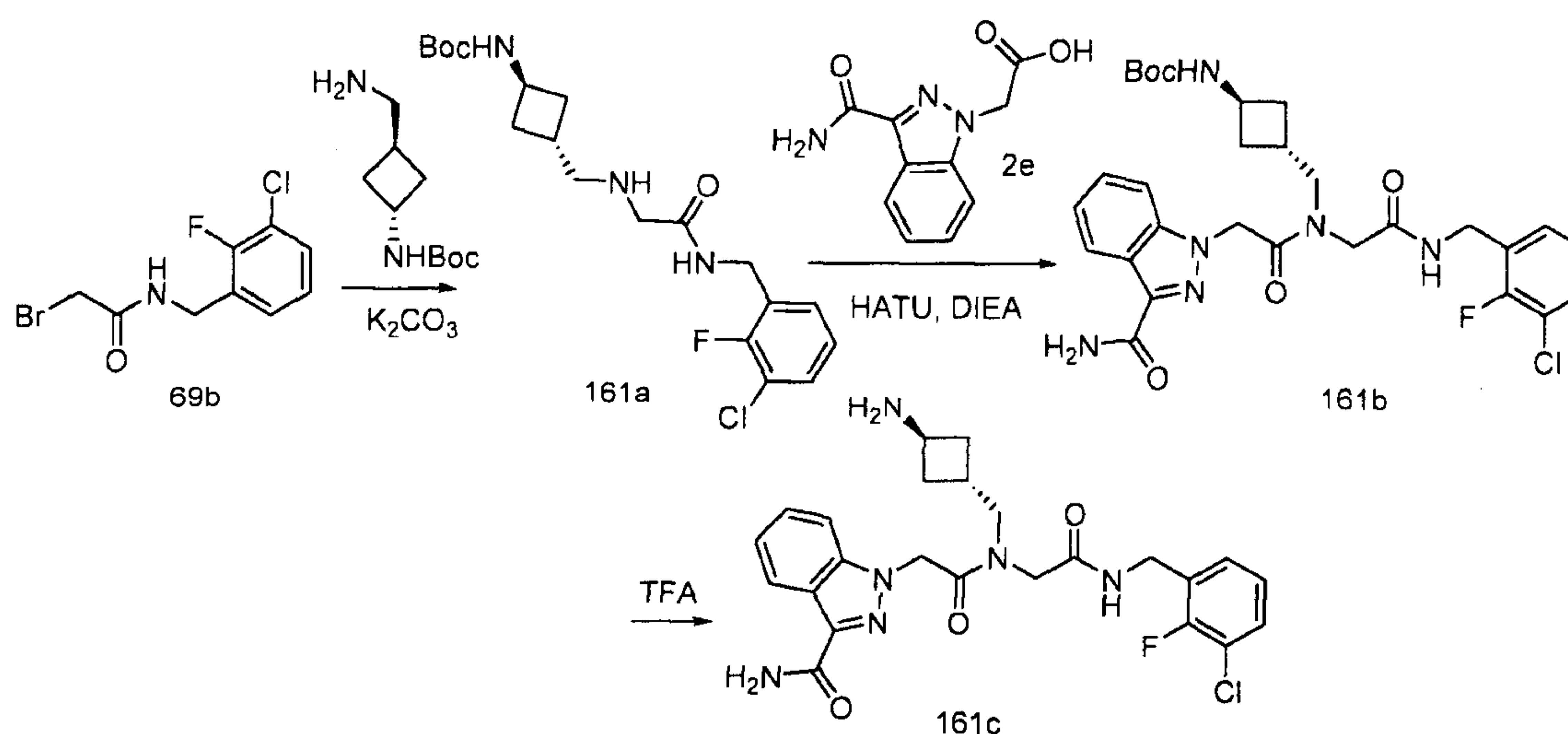
Scheme 160



Preparation of 2-(3-acetyl-5-(pyrimidin-5-yl)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**160a**)

- 5 Reaction of 2-(3-acetyl-5-bromo-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**158a**) (125 mg, 0.23 mmol) with pyrimidin-5-ylboronic acid (0.035 g, 0.280 mmol) according to the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 20%] 2-(3-acetyl-5-(pyrimidin-5-yl)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**160a**) (96 mg, 0.18 mmol, 77% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.22 (s, 1H), 9.19 (s, 2H), 8.52 – 8.43 (m, 2H), 7.89 (bs, 2H), 7.51 – 7.39 (m, 1H), 7.29-7.18 (m, 1H), 7.16 – 7.06 (m, 1H), 5.82 (s, 2H), 4.35 (d, *J* = 5.8 Hz, 2H), 4.00 (s, 2H), 3.20 – 3.09 (m, 1H), 2.66 (s, 3H), 1.10 – 1.00 (m, 2H), 0.97 – 0.88 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.58; MS (ES⁺): 535.6 (M+1), 557.6 (M+Na); MS (ES⁻): 569.5 (M+Cl).

Scheme 161



Preparation of 1-(2-((((trans)-3-aminocyclobutyl)methyl)(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**161c**)

- 20 Step-1: Preparation of tert-butyl (trans-3-((((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)methyl)cyclobutyl)carbamate (**161a**)

Reaction of 2-bromo-N-(3-chloro-2-fluorobenzyl)acetamide (**69b**) (250 mg, 0.89 mmol) tert-butyl (trans)-3-(aminomethyl)cyclobutylcarbamate (268 mg, 1.34 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica gel 12 g, eluting with MeOH in DCM 0 to 20%] tert-butyl
 5 ((trans)-3-(((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)methyl)cyclobutyl)carbamate (**161a**) (152 mg, 0.38 mmol, 43% yield) as a white solid; MS (ES+): 400.5 (M+1), 799.8 (2M+1), 422.5 (M+Na); MS (ES-): 434.5 (M+Cl).

Step-2: Preparation of tert-butyl ((trans)-3-((2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)methyl)cyclobutyl)carbamate (**161b**)
 10

Reaction tert-butyl ((trans)-3-(((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)methyl)cyclobutyl)carbamate (**161a**) (85 mg, 0.21 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (56 mg, 0.26 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column
 15 chromatography [Silica gel, (24 g) eluting with MeOH in CHCl₃ 0-10%] tert-butyl ((trans)-3-((2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)methyl)cyclobutyl)carbamate (**161b**) (59 mg, 0.1 mmol, 46% yield) as a white solid as a mixture two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.81 & 8.48 (t, *J* = 5.6 Hz) (2t, 1H), 8.19 & 8.17 (2s, 1H), 7.73 (bs, 1H), 7.64 – 7.00 (m, 7H), 5.59 & 5.46 (s, 2H), 4.46 (d, *J* = 5.6 Hz) & 4.32 (d, *J* = 5.8 Hz) (2d, 2H), 4.29 – 3.88 (m, 3H), 3.62 (d, *J* = 7.7 Hz, 1H), 2.27 (s, 1H), 2.05 (t, *J* = 7.0 Hz, 1H), 1.97 – 1.75 (m, 3H), 1.38 & 1.35 (2s, 9H);
 20 ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.30, -121.67; MS (ES+): 601.7 (M+1), 623.7, 625.7 (M+Na); MS (ES-): 600.6 (M-1), 635.7, 637.6 (M+Cl).

Step-3: Preparation of 1-(2-((((trans)-3-aminocyclobutyl)methyl)(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**161c**)
 25

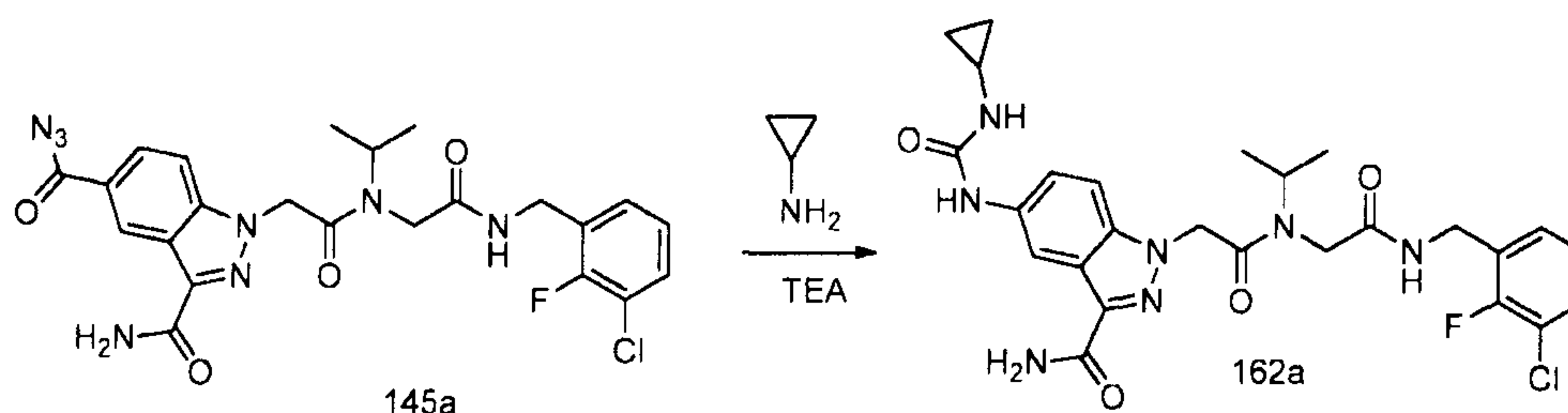
Reaction of tert-butyl ((trans)-3-((2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)methyl)cyclobutyl)carbamate (**161b**) (56 mg, 0.09 mmol) with TFA (0.144 mL, 1.863 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and purification by flash column chromatography [Silica gel, (8 g) eluting with CMA50 in DCM 0-100%] 1-(2-((((trans)-3-aminocyclobutyl)methyl)(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide
 30 (**161c**) (24 mg, 0.048 mmol, 51% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.81 (t, *J* = 5.7 Hz) and 8.45 (t, *J* = 5.8 Hz) (2t, 1H), 8.21 – 8.15 (m, 1H), 7.73 (s, 1H),

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7.60 – 7.00 (m, 7H), 5.57 and 5.47 (2s, 2H), 4.45 (d, $J = 5.5$ Hz) and 4.32 (d, $J = 5.7$ Hz) (2d, 2H), 4.22 and 3.93 (2s, 2H), 2.36-1.44 (m, 5H); ^1H NMR (300 MHz, DMSO- d_6 , D $_2$ O exchange) δ 8.22 – 8.14 (m, 1H), 7.61-7.01 (m, 7H), 5.59 & 5.45 (2s, 2H), 4.46 and 4.34 and 4.23 (3s, 3H), 3.67-3.20 (m, 3H), 2.40-1.56 (m, 5H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.24, -121.64; MS (ES $^+$): 501.6 (M+1), 523.6 (M+Na); MS (ES $^-$): 499.5 (M-1), 535.5 (M+Cl).

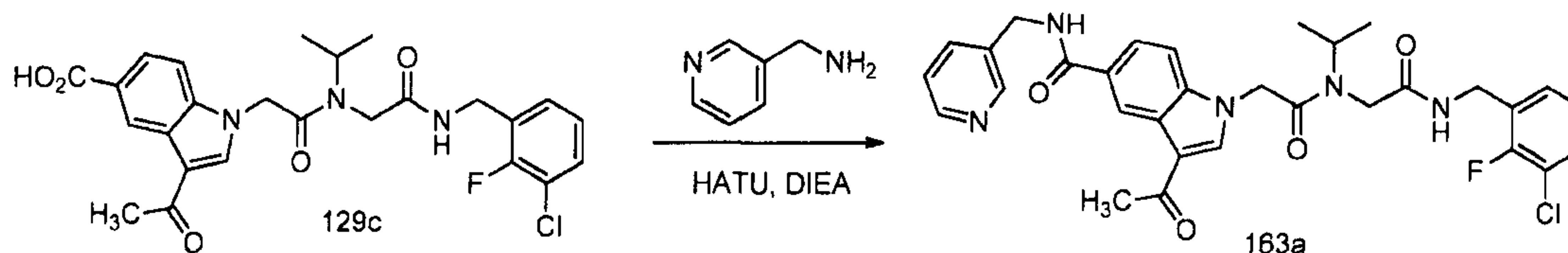
Scheme 162



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3-cyclopropylureido)-1H-indazole-3-carboxamide (**162a**)

Reaction of 3-carbamoyl-1-(2-((2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**145a**) (270 mg, 0.51 mmol) in toluene (15 mL) with cyclopropanamine (58.3 mg, 1.02 mmol) using TEA (0.29 mL, 2.04 mmol) as base according to the procedure reported in step-4 of Scheme 129 gave after workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3-cyclopropylureido)-1H-indazole-3-carboxamide (**162a**) (29 mg, 0.052 mmol, 11% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) (a mixture of two rotamers) δ 8.82 (t, $J = 5.7$ Hz) and 8.36 (t, $J = 6.0$ Hz) (2t, 1H), 8.46 and 8.45 (2s, 1H), 8.23 – 8.17 (m, 1H), 7.67 – 7.03 (m, 7H), 6.44 – 6.30 (m, 1H), 5.52 and 5.38 (2s, 2H), 4.62 – 4.22 (m, 3H), 4.17 and 3.83 (2s, 2H), 2.59 – 2.53 (m, 1H), 1.21 (d, $J = 6.8$ Hz) and 0.98 (d, $J = 6.8$ Hz) (2d, 6H), 0.68 – 0.59 (m, 2H), 0.47 – 0.37 (m, 2H); ^{19}F NMR (282 MHz, DMSO) δ -121.22, -121.76; MS (ES $^+$): 580.6 (M+Na); MS (ES $^-$): 558.5 (M-1).

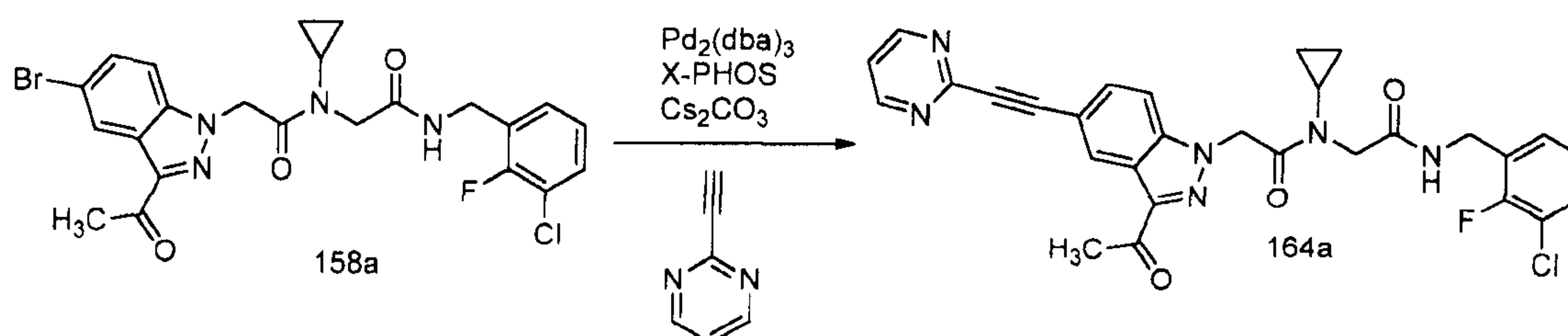
Scheme 163



Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N-(pyridin-3-ylmethyl)-1H-indole-5-carboxamide (163a)

Reaction of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**129c**) (50 mg, 0.1 mmol) with pyridin-3-ylmethanamine (0.015 mL, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (4 g), eluting with MeOH in DCM (1:0 to 19:1)] 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N-(pyridin-3-ylmethyl)-1H-indole-5-carboxamide (**163a**) (42 mg, 71%) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) (a mixture of two rotamers) δ 9.16 – 9.06 (m, 1H), 8.83 (t, J = 5.7 Hz) and 8.34 (t) (2t, 1H), 8.78 – 8.71 (m, 1H), 8.57 (bs, 1H), 8.49 – 8.43 (m, 1H), 8.35 and 8.31 (2s, 1H), 7.83 – 6.91 (m, 7H), 5.40 and 5.21 (2s, 2H), 4.63 – 4.54 and 4.29 – 4.21 (2m, 1H), 4.53 and 4.51 (2s, 2H), 4.47 (d, J = 5.3 Hz) and 4.33 (d, J = 5.8 Hz) (2d, 2H), 4.19 and 3.85 (2s, 2H), 2.46 and 2.45 (2s, 3H), 1.26 (d, J = 6.4 Hz) and 1.00 (d, J = 6.7 Hz) (2d, 6H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.19, -121.79; MS (ES $^+$): 592.6 & 594.6 ($M + 1$).

Scheme 164



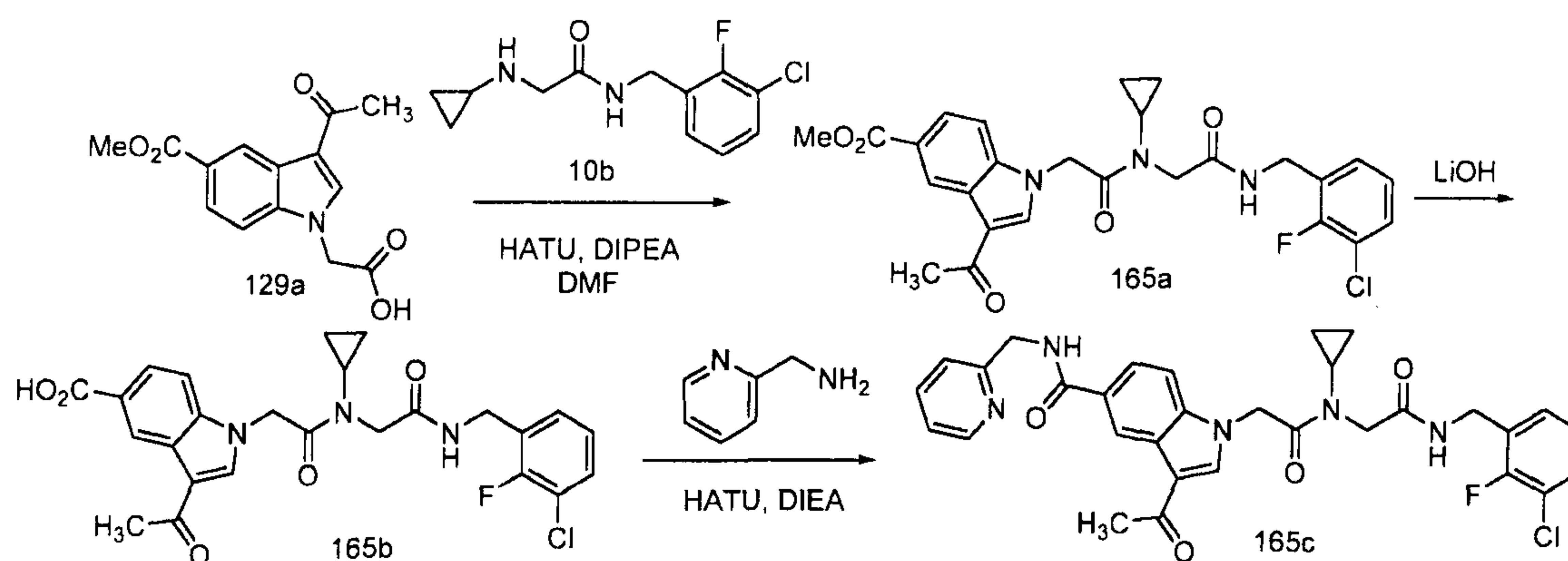
Preparation of 2-(3-acetyl-5-(pyrimidin-2-ylethynyl)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**164a**)

Reaction of 2-(3-acetyl-5-bromo-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**158a**) (300 mg, 0.56 mmol) using Cs_2CO_3 (365 mg, 1.12 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (X-PHOS, 53 mg, 0.112 mmol), $\text{Pd}_2(\text{dba})_3$ (51 mg, 0.056 mmol) according to procedure reported in Scheme 92 gave

after workup and purification by flash column chromatography [silica gel (8 g), eluting with MeOH in DCM from 0 to 30%] 2-(3-acetyl-5-(pyrimidin-2-ylethynyl)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**164a**) (21 mg, 0.038 mmol, 7% yield) as a dark-yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.87 (d, *J* = 4.9 Hz, 2H), 8.49 (t, *J* = 6.0 Hz, 1H), 8.46 – 8.43 (m, 1H), 7.89 – 7.80 (m, 1H), 7.70 (dd, *J* = 8.8, 1.5 Hz, 1H), 7.54 (t, *J* = 5.0 Hz, 1H), 7.46 (td, *J* = 7.6, 1.7 Hz, 1H), 7.27–7.19 (m, 1H), 7.14 – 7.07 (m, 1H), 5.81 (s, 2H), 4.34 (d, *J* = 5.8 Hz, 2H), 4.00 (s, 2H), 3.21 – 3.05 (m, 1H), 2.65 (s, 3H), 1.09 – 0.83 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.57; MS (ES⁺): 581.6, 583.6 (M+Na); MS (ES⁻): 593.5, 595.6 (M+Cl).

10

Scheme 165



Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-N-(pyridin-2-ylmethyl)-1H-indole-5-carboxamide (**165c**)

15 Step-1: Preparation of methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylate (**165a**)

Reaction of 2-(3-acetyl-5-(methoxycarbonyl)-1H-indol-1-yl)acetic acid (**129a**) (5.91 mmol, prepared according to the procedure reported by Altmann, Eva et al, in PCT Int. Appl., WO 2012/093101) with N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (1.82 g, 7.09 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel, eluting with hexanes/10% MeOH in EtOAc (1:0 to 1:2)] methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylate (**165a**) (1.89 g, 62%) as a light brown solid. ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.87 (dd, *J* = 1.7, 0.6 Hz, 1H), 8.47 (t, *J* = 5.9 Hz, 1H), 8.42 (s, 1H), 7.81 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.58 (dd, *J* = 8.7, 0.7 Hz, 1H), 7.49 – 7.41 (m, 1H), 7.26 – 7.18 (m, 1H), 7.12 – 7.05 (m, 1H), 5.50 (s, 2H), 4.34 (d, *J* = 5.8

25

Hz, 2H), 3.99 (s, 2H), 3.88 (s, 3H), 3.16 – 3.04 (m, 1H), 2.46 (s, 3H), 1.05 – 0.85 (m, 4H);

^{19}F NMR (282 MHz, DMSO- d_6) δ -121.59; MS (ES+): 536.5 & 538.5 (M+Na).

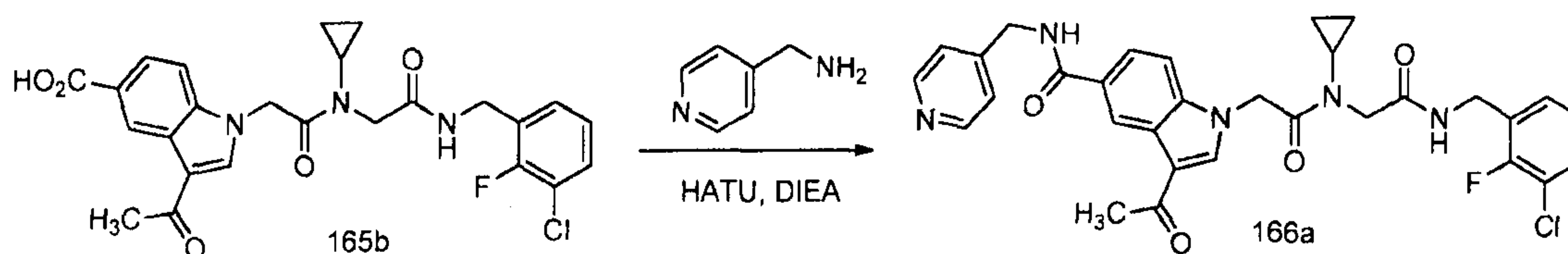
Step-2: Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**165b**)

5 Reaction of methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylate (**165a**) (1.83 g, 3.56 mmol) in THF (30 mL) and MeOH (30 mL) was added a solution of lithium hydroxide hydrate (911 mg, 21.28 mmol) in water (30 mL) according to the procedure reported in step-2 of Scheme 129 gave after workup 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**165b**) (1.51 g, 85%)
10 as a light brown solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.83 (d, J = 1.6 Hz, 1H), 8.48 (t, J = 5.9 Hz, 1H), 8.38 (s, 1H), 7.80 (dd, J = 8.6, 1.7 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 7.45 (td, J = 7.6, 1.7 Hz, 1H), 7.27 – 7.18 (m, 1H), 7.12 – 7.05 (m, 1H), 5.48 (s, 2H), 4.34 (d, J = 5.7 Hz, 2H), 3.99 (s, 2H), 3.15 – 3.03 (m, 1H), 2.45 (s, 3H), 1.06 – 0.82 (m, 4H); ^{19}F NMR (282
15 MHz, DMSO- d_6) δ -121.59; MS (ES+): 522.5 (M+Na); MS (ES-): 534.5 & 536.5 (M+Cl).

Step-3: Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-N-(pyridin-2-ylmethyl)-1H-indole-5-carboxamide (**165c**)

Reaction of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**165b**) (50 mg, 0.1
20 mmol) with pyridin-2-ylmethanamine (0.015 mL, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (4 g), eluting with MeOH in DCM (1:0 to 19:1)] 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-N-(pyridin-2-ylmethyl)-1H-indole-5-carboxamide (**165c**) (45 mg, 76%) as a light yellow solid; ^1H NMR
25 (300 MHz, DMSO- d_6) (a mixture of two rotamers) δ 9.13 (t, J = 5.9 Hz, 1H), 8.80 – 8.78 (m, 1H), 8.53 – 8.50 (m, 1H), 8.47 (t, J = 5.9 Hz, 1H), 8.38 (s, 1H), 7.83 – 7.70 (m, 2H), 7.54 (d, J = 8.7 Hz, 1H), 7.48 – 7.41 (m, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.29 – 7.19 (m, 2H), 7.09 (t, J = 7.9 Hz, 1H), 5.49 (s, 2H), 4.59 (d, J = 5.8 Hz, 2H), 4.35 (d, J = 5.7 Hz, 2H), 4.00 (s, 2H),
30 3.15 – 3.06 (m, 1H), 2.46 (s, 3H), 1.05 – 0.88 (m, 4H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.60; MS (ES+): 590.6 (M+1) & 612.6 (M+Na).

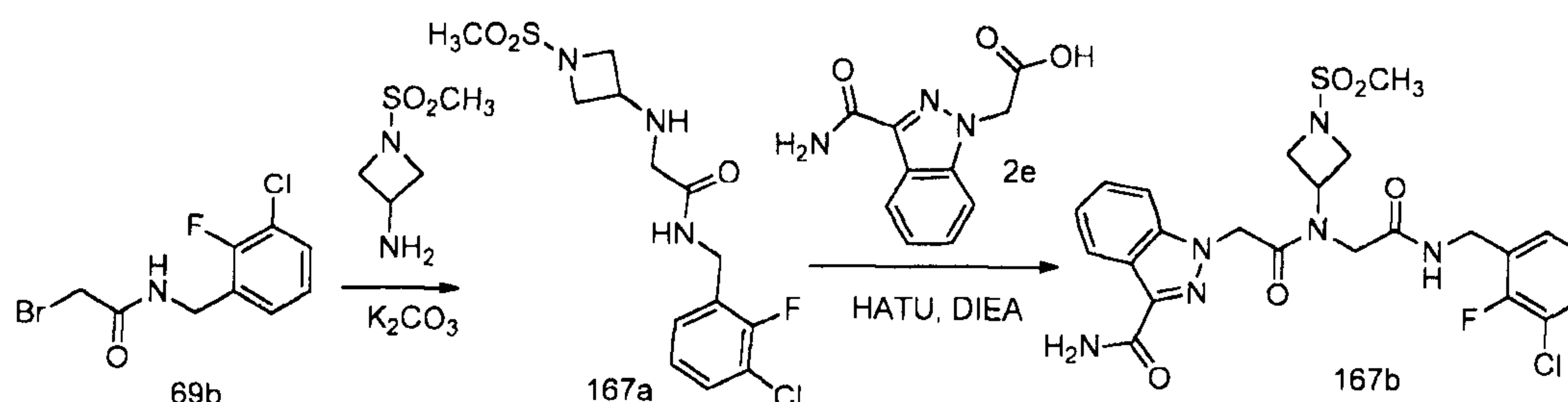
Scheme 166



Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-N-(pyridin-4-ylmethyl)-1H-indole-5-carboxamide (166a)

Reaction of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**165b**) (50 mg, 0.1 mmol) with pyridin-4-ylmethanamine (0.016 mL, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (4 g), eluting with MeOH in DCM (1:0 to 19:1)] 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-N-(pyridin-4-ylmethyl)-1H-indole-5-carboxamide (**166a**) (27 mg, 46%) as an off-white solid; ^1H NMR (300 MHz, DMSO- d_6) (a mixture of two rotamers) δ 9.15 (t, J = 5.9 Hz, 1H), 8.79 – 8.77 (m, 1H), 8.54 – 8.43 (m, 3H), 8.38 (s, 1H), 7.78 (dd, J = 8.7, 1.8 Hz, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.49 – 7.41 (m, 1H), 7.34 – 7.29 (m, 2H), 7.27 – 7.18 (m, 1H), 7.14 – 7.02 (m, 1H), 5.49 (s, 2H), 4.52 (d, J = 5.9 Hz, 2H), 4.35 (d, J = 5.8 Hz, 2H), 4.00 (s, 2H), 3.17 – 3.03 (m, 1H), 2.46 (s, 3H), 1.08 – 0.74 (m, 4H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.59; MS (ES $^+$): 590.7 & 592.7 (M+1).

Scheme 167



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-(methylsulfonyl)azetidin-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**167b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((1-(methylsulfonyl)azetidin-3-yl)amino)acetamide (**167a**)

Reaction of 2-bromo-N-(3-chloro-2-fluorobenzyl)acetamide (**69b**) (250 mg, 0.89 mmol) with 1-(methylsulfonyl)azetidin-3-amine (241 mg, 1.60 mmol) according to the procedure

reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [Silica gel, (12 g) eluting with MeOH in DCM, 0-30%) to afford N-(3-chloro-2-fluorobenzyl)-2-((1-(methylsulfonyl)azetidin-3-yl)amino)acetamide (**167a**) (68 mg, 0.194 mmol, 22% yield) as a thick yellow oil which was used as such in the next step; MS (ES+): 350.4 (M+1), 372.4 (M+Na); MS (ES-): 348.3 (M-1), 384.3, 386.3 (M+Cl)

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-(methylsulfonyl)azetidin-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**167b**)

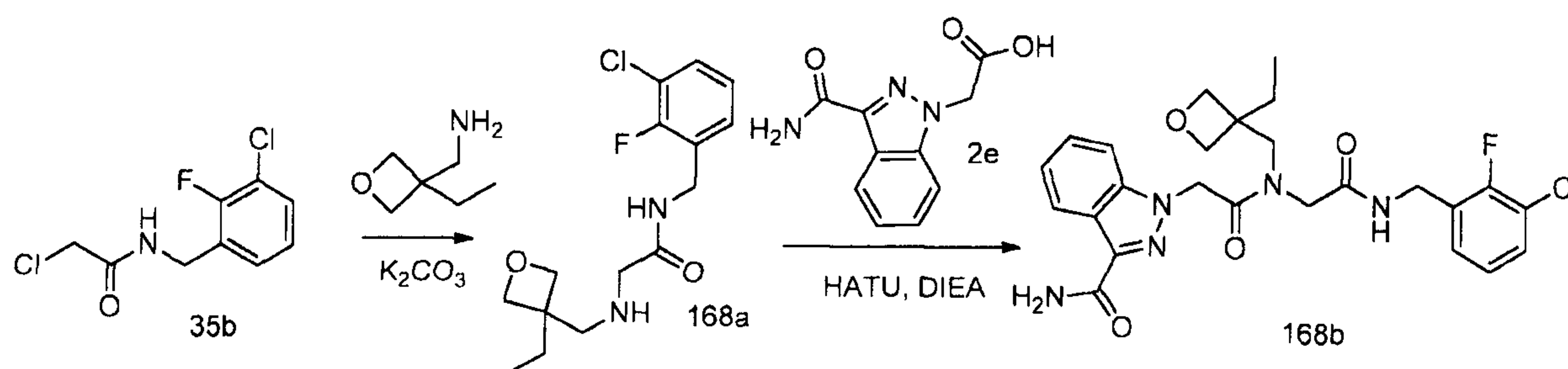
Reaction of N-(3-chloro-2-fluorobenzyl)-2-((1-(methylsulfonyl)azetidin-3-

yl)amino)acetamide (**167a**) (30 mg, 0.086 mmol) with 2-(3-carbamoyl-1H-indazol-1-

yl)acetic acid (**2e**) (19 mg, 0.086 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [Silica gel, (8 g) eluting with MeOH in DCM from 0-30%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-(methylsulfonyl)azetidin-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**167b**) (8 mg, 0.015 mmol, 17 % yield) as a white solid as a mixture of two rotamers; ¹H

NMR (300 MHz, DMSO-*d*₆) δ 8.99 (t, *J* = 5.7 Hz) & 8.64 (t, *J* = 5.8 Hz) (2t, 1H), 8.22 – 8.12 (m, 1H), 7.74 – 7.66 (m, 2H), 7.62-6.95 (m, 6H), 5.64 & 5.42 (s, 2H), 5.19 – 4.76 (m, 1H), 4.49 (d, *J* = 5.6 Hz) & 4.34 (d, *J* = 5.8 Hz) (2d, 2H), 4.42 (s) and 4.23-3.78 (m) (6H), 3.08 & 2.99 (s, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.32, -121.65; MS (ES+): 551.52 (M+1), 573.5 (M+Na); MS (ES-): 549.5 (M-1), 585.3 (M+Cl).

Scheme 168



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((3-ethyloxetan-3-yl)methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**168b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((2-(3-ethyloxetan-3-yl)methyl)amino)acetamide (**168a**)

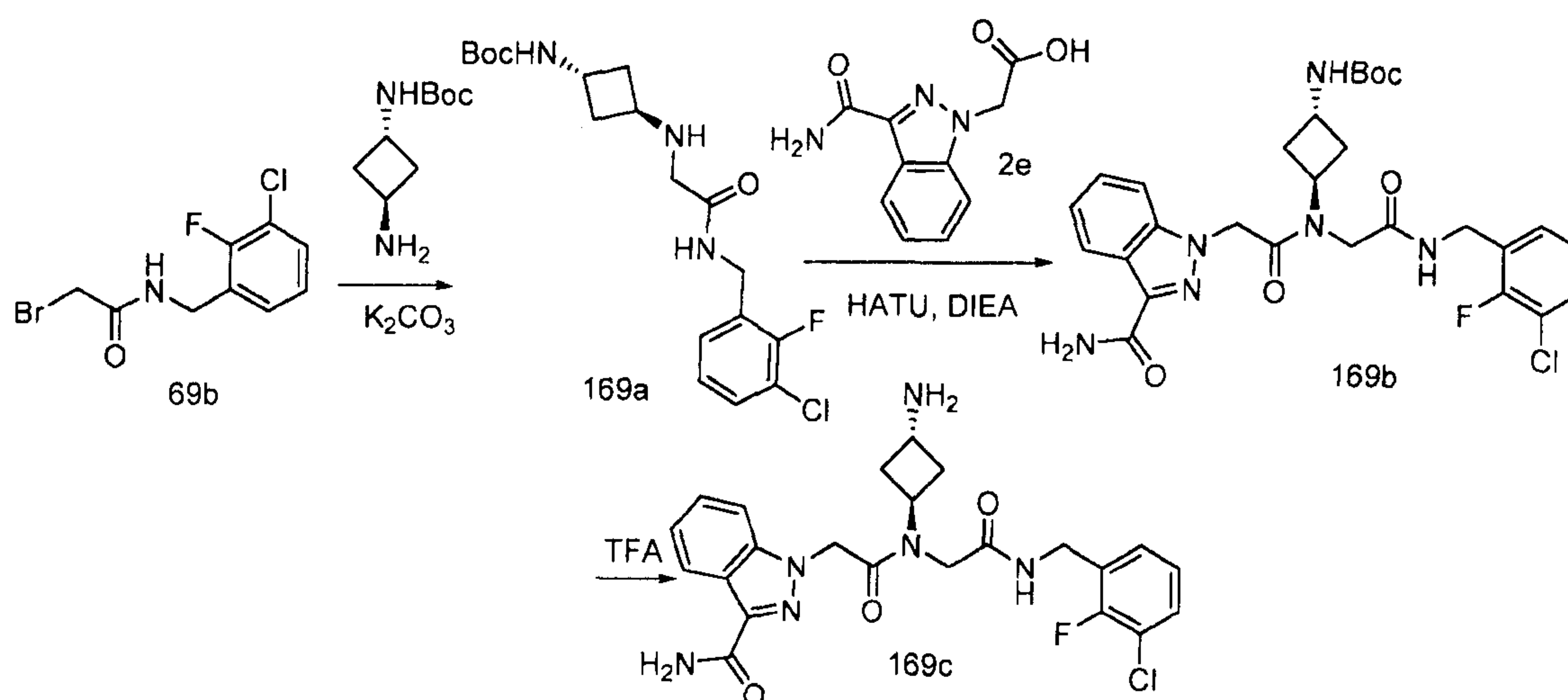
Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (205 mg, 0.87 mmol) with (3-ethyloxetan-3-yl)methanamine (250 mg, 2.47 mmol) according to the procedure reported

in step-2 of Scheme 35 gave after workup N-(3-chloro-2-fluorobenzyl)-2-((2-(3-ethyloxetan-3-yl)methyl)amino)acetamide (**168a**) as a colorless oil which was used in the next step without further purification; MS (ES+) 315.4 (M+1); (ES-) 313.4 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((3-ethyloxetan-3-yl)methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**168b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-((2-(3-ethyloxetan-3-yl)methyl)amino)acetamide (**168a**) (51 mg, 0.162 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (43 mg, 0.19 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA-80 in DCM 0 to 100%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((3-ethyloxetan-3-yl)methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**168b**) (26 mg, 0.05 mmol, 31% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.84 (t, *J* = 5.7 Hz) and 8.51 (t (1H), 8.18 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.79-7.00 (m, 8H), 5.51 and 5.50 (2s, 2H), 4.47 (d, *J* = 5.5 Hz) and 4.40-3.73 (m) (8H), 1.74 (q) and 1.61 (q, *J* = 7.3 Hz, 2H), 1.09 (t, *J* = 7.3 Hz) and 0.84 (t, *J* = 7.4 Hz) (3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.17, -121.55; MS (ES+): 516.5 (M+1); MS (ES-): 514.5 (M-1).

Scheme 169



Preparation of 1-(2-(((trans)-3-aminocyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**169c**)

Step-1: Preparation of tert-butyl ((trans)-3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)cyclobutyl)carbamate (**169a**)

Reaction of 2-bromo-N-(3-chloro-2-fluorobenzyl)acetamide (**69b**) (250 mg, 0.89 mmol) with tert-butyl (trans)-3-aminocyclobutylcarbamate (250 mg, 1.34 mmol) according to the

procedure reported in step-2 of Scheme 35 gave tert-butyl ((trans)-3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)cyclobutyl)carbamate (**169a**) (173 mg, 0.45 mmol, 50% yield) as a thick yellow oil; MS (ES+): 386.5 (M+1), 408.5 (M+Na); MS (ES-): 384.4 (M-1), 420.4, 422.4 (M+Cl).

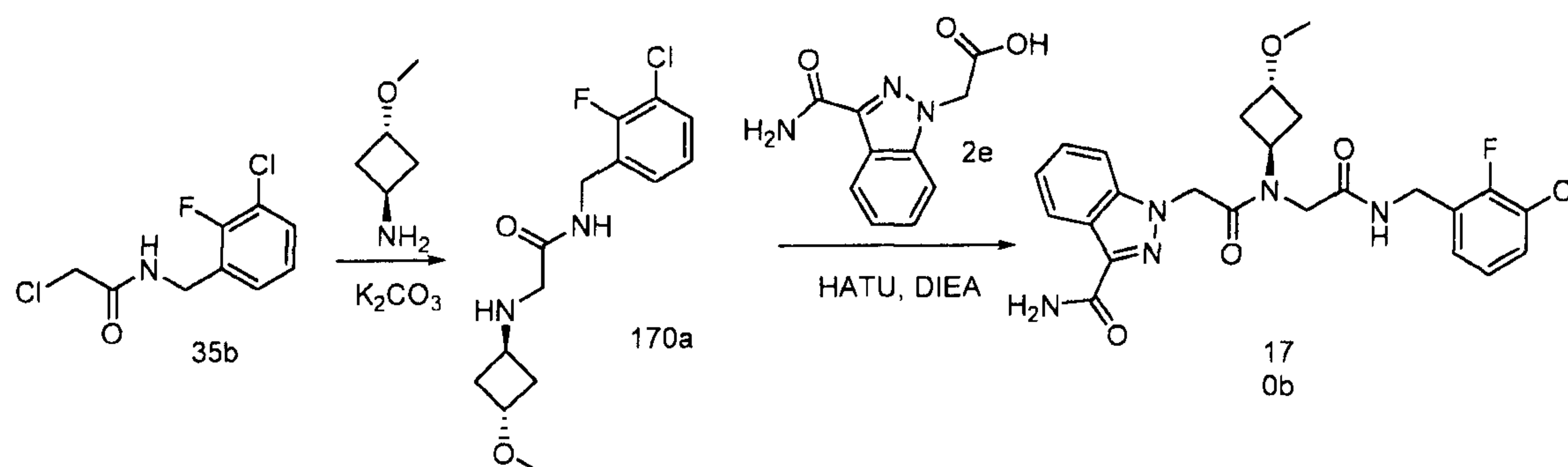
- 5 Step-2: Preparation of tert-butyl ((trans)-3-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)cyclobutyl)carbamate (**169b**)

Reaction of tert-butyl ((trans)-3-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)cyclobutyl)carbamate (**169a**) (108 mg, 0.28 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (74 mg, 0.34 mmol) according to the procedure reported in step-
 10 3 of Scheme 2 gave after workup and purification by flash column chromatography [Silica gel, (24 g) eluting with MeOH in CHCl₃ 0-10%] tert-butyl ((trans)-3-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)cyclobutyl)carbamate (**169b**) (0.101 g, 0.172 mmol, 61.5 % yield) as an off-white solid in the form of mixture two rotamers; MS (ES+): 587.6 (M+1), 609.6, 611.6
 15 (M+Na); MS (ES-): 585.6 (M-1), 621.6, 623.6 (M+Cl).

Step-3: Preparation of 1-(2-(((trans)-3-aminocyclobutyl)(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**169c**)

Reaction of tert-butyl ((trans)-3-(2-(3-carbamoyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)acetamido)cyclobutyl)carbamate (**169b**) (91 mg, 0.16
 20 mmol) with TFA (0.24 mL, 3.1 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and purification by flash column chromatography [Silica gel, (12 g) eluting with DMA80 in DCM 0-100%] 1-(2-(((trans)-3-aminocyclobutyl)(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**169c**) (17 mg, 22 % yield) as a white solid as a mixture of two isomers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.88 (t, *J* = 5.8 Hz) & 8.43 (t, *J* = 5.9 Hz) (2t, 1H, D₂O exchangeable), 8.21-8.14 (m, 1H), 7.72 (s, 1H), 7.63 – 7.02 (m, 7H), 5.53 & 5.42 (2s, 2H), 5.06 – 4.81 (m, 1H), 4.47 (d, *J* = 5.6 Hz) & 4.33 (d, *J* = 5.8 Hz) (2d, 2H), 4.29 & 4.01 (2s, 2H), 2.42 – 1.69 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.25, -121.64; MS (ES+): 487.5 (M+1), 509.5 (M+Na); MS (ES-): 485.5 (M-1), 521.43 (M+Cl).

Scheme 170



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((trans)-3-methoxycyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**170b**)

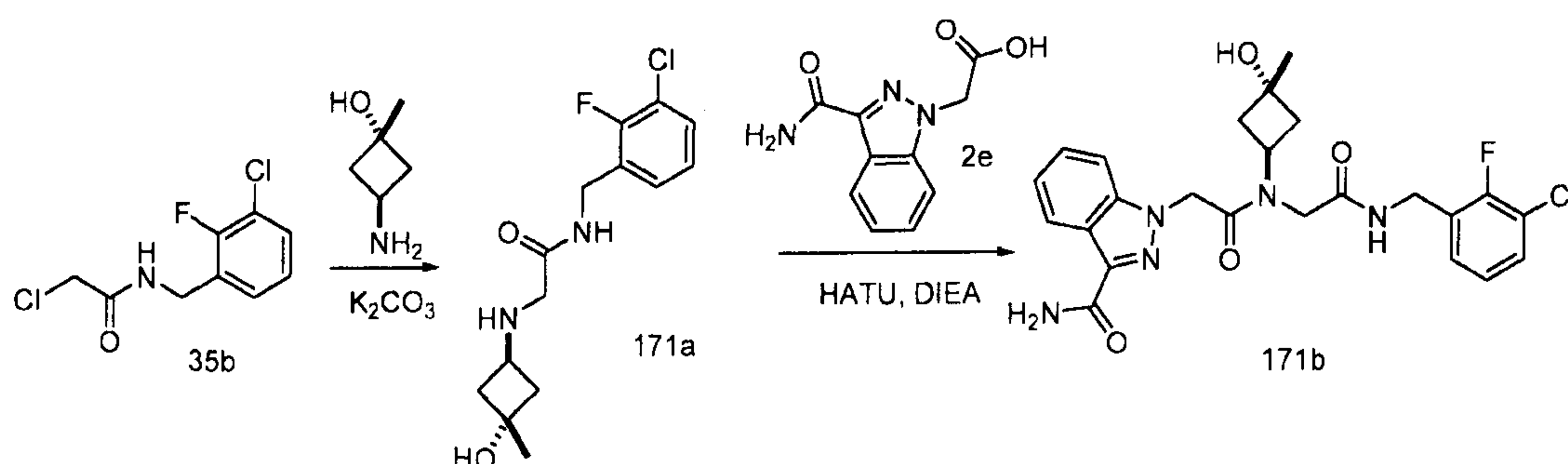
Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-methoxycyclobutyl)amino)acetamide (**170a**)

- 5 Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (195 mg, 0.826 mmol) with trans-3-methoxycyclobutanamine hydrochloride (250 mg, 1.82 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-methoxycyclobutyl)amino)acetamide (**170a**) (122 mg, 0.41 mmol, 50%) as a colorless oil; MS (ES⁺) 301.4 (M+1); MS (ES⁻): 299.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((trans)-3-methoxycyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**170b**)

- Reaction of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-methoxycyclobutyl)amino)acetamide (**170a**) (122 mg, 0.41 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (122 mg, 0.41 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA-80 in CHCl₃ 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((trans)-3-methoxycyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**170b**) (137 mg, 0.27 mmol, 67% yield) as an off white solid; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.87 (t, *J* = 5.7 Hz) and 8.44 (t, *J* = 5.9 Hz) (2t, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 7.72-7.01 (m, 8H), 5.55 and 5.42 (2s, 2H), 4.85 – 4.69 (m, 1H), 4.47 (d, *J* = 5.6 Hz) and 4.33 (d, *J* = 5.7 Hz) (2d, 2H), 4.29 and, 4.02 (2s, 2H), 3.92 – 3.78 (m, 1H), 3.17 and 3.10 (2s, 3H), 2.43-1.93 (m, 4H); ¹⁹F NMR (282 MHz, DMSO) δ -121.18, -121.60; MS (ES⁺) 502.5 (M+1); 524.5 (M+Na); (ES⁻) 500.5 (M-1); (Based on NMR, this compound is a mixture of rotamers 4:5 ratio).

Scheme 171



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((trans)-3-hydroxy-3-(cis)-methylcyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**171b**)

5 Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-hydroxy-3-(cis)-methylcyclobutyl)amino)acetamide (**171a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (195 mg, 0.83 mmol) with (trans)-3-amino-1-methylcyclobutanol hydrochloride (250 mg, 1.82 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash

10 column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-hydroxy-3-(cis)-

methylcyclobutyl)amino)acetamide (**171a**) (108 mg, 0.36 mmol, 43%) as a colorless oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.33 (t, *J* = 6.1 Hz, 1H), 7.48 (td, *J* = 7.6, 1.9 Hz, 1H), 7.31 – 7.24 (m, 1H), 7.23 – 7.15 (m, 1H), 4.69 (s, 1H), 4.36 (d, *J* = 5.9 Hz, 2H), 3.17 (d, *J* = 4.7 Hz,

15 2H), 3.03 (s, 2H), 2.14 – 2.03 (m, 2H), 1.70 – 1.58 (m, 2H), 1.23 (s, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.65; MS (ES+) 3001.4 (M+1), 323.4 (M+Na); (ES-) 299.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((trans)-3-hydroxy-3-(cis)-methylcyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**171b**)

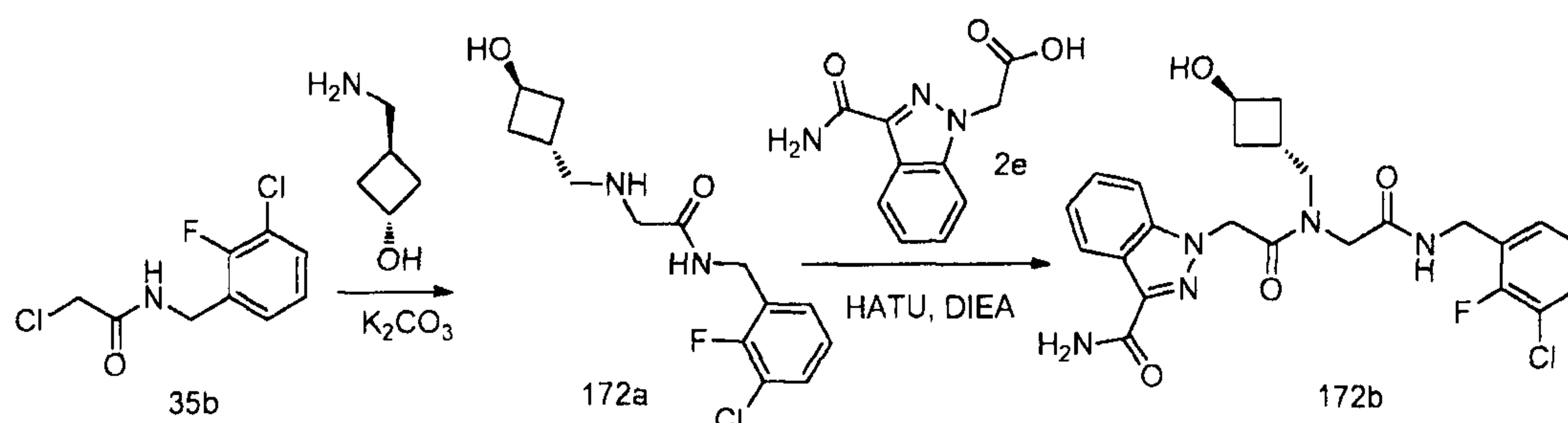
Reaction of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-hydroxy-3-(cis)-

20 methylcyclobutyl)amino)acetamide (**171a**) (108 mg, 0.36 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (87 mg, 0.4 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA-80 in CHCl₃ 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-

25 oxoethyl)((trans)-3-hydroxy-3-(cis)-methylcyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**171b**) (65 mg, 0.13 mmol, 36% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.88 (t, *J* = 5.7 Hz) and 8.42 (t, *J* = 5.9 Hz) (2t, 1H), 8.17 (m, 1H), 7.69 (m, 1H), 7.31 – 7.01 (m, 7H), 5.53 and 5.42 (2s, 2H), 5.01 – 4.67 (m, 2H), 4.46 (d, *J* = 5.5 Hz) and 4.33 (d, *J* = 5.8 Hz) (2d, 2H), 4.24 and 3.99 (2s, 2H), 2.32-1.83 (m, 4H), 1.26 and 1.17 (2s,

3H); ^{19}F NMR (282 MHz, DMSO) δ -121.09, -121.56; MS (ES⁺) 524.5 (M+Na); (ES⁻): 500.5 (M-1); (Based on NMR, this compound is a mixture of rotamers 1:1 ratio).

Scheme 172



5 Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(((trans)-3-hydroxycyclobutyl)methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**172b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-hydroxycyclobutyl)methyl)amino)acetamide (**172a**)

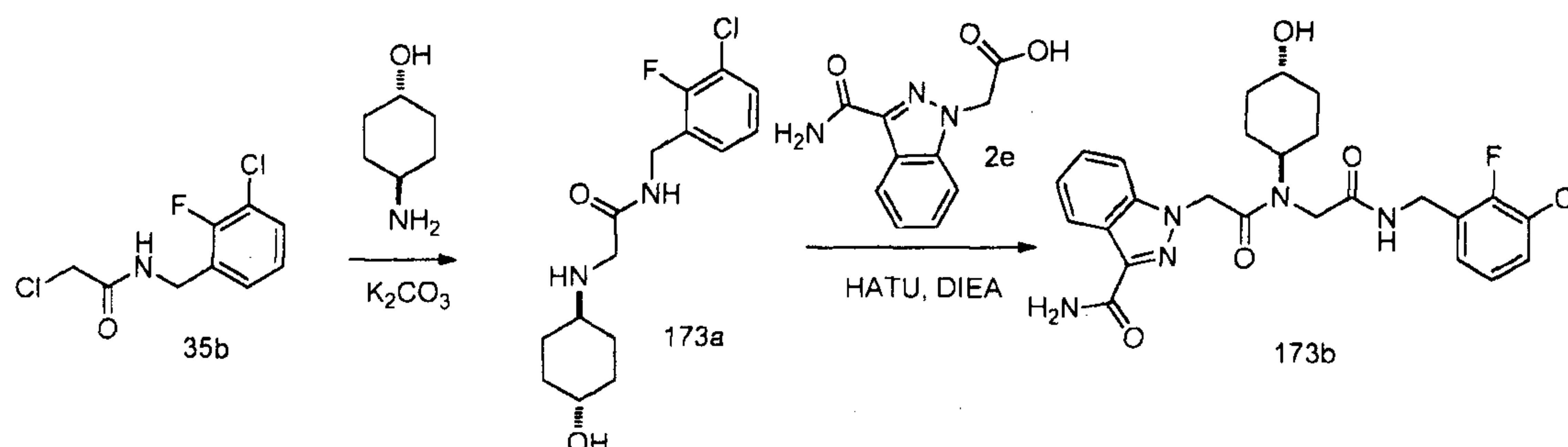
Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (254 mg, 1.08 mmol) with
 10 (trans)-3-(aminomethyl)cyclobutanol hydrochloride (370 mg, 2.69 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%]
 of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-hydroxycyclobutyl)methyl)amino)acetamide (**172a**) (130 mg, 0.43 mmol, 40%) as a colorless oil; MS (ES⁺): 301.4, 303.4 (M+1, M+2),
 15 323.3 (M+Na); MS (ES⁻) 299.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(((trans)-3-hydroxycyclobutyl)methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**172b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-hydroxycyclobutyl)methyl)amino)acetamide (**172a**) (130 mg, 0.43 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (104 mg, 0.48 mmol) according to the procedure
 20 reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA-80 in CHCl₃ 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(((trans)-3-hydroxycyclobutyl)methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**172b**) (32 mg, 0.064 mmol, 15 % yield) as a white
 25 solid; ^1H NMR (300 MHz, DMSO-*d*₆) δ 8.81 (t, J = 5.8 Hz) and 8.45 (t, J = 6.0 Hz) (2t, 1H), 8.21 – 8.13 (m, 1H), 7.73 (bs, 1H), 7.58 – 7.07 (m, 7H), 5.57 and 5.47 (2s, 2H), 5.05 (d, J = 6.1 Hz) and 4.93 (d, J = 6.0 Hz) (2d, 1H), 4.45 (d, J = 5.5 Hz) and 4.32 (d, J = 6.0 Hz) (2d, 2H), 4.23 and 3.93 (2s, 2H), 4.41-4.25 and 4.19 – 4.07 (2m, 1H), 3.56 (d, J = 8.0 Hz) and

3.31 (d, $J = 7.9$ Hz) (2d, 2H), 2.32 – 1.76 (m, 5H); ^{19}F NMR (282 MHz, DMSO) δ -121.27, -121.65; MS (ES+) 524.5 (M+Na); (ES-) 500.5 (M-1). (Based on NMR, this compound is a mixture of rotamers 2:1 ratio)

Scheme 173



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((trans)-4-hydroxycyclohexyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**173b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-4-hydroxycyclohexyl)amino)acetamide (**173a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (342 mg, 1.45 mmol) with (trans)-4-aminocyclohexanol (500 mg, 4.34 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-4-hydroxycyclohexyl)amino)acetamide (**173a**) (445 mg, 1.41 mmol, 98%) as a colorless oil; MS (ES+): 315.4, 317.4 (M+1, M+3); (ES-): 313.3.

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((trans)-4-hydroxycyclohexyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**173b**)

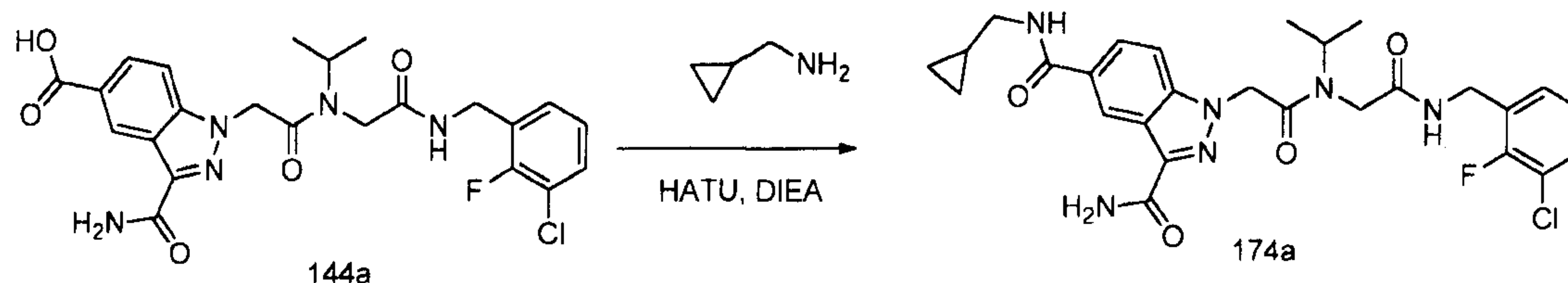
Reaction of N-(3-chloro-2-fluorobenzyl)-2-(((trans)-4-hydroxycyclohexyl)amino)acetamide (**173a**) (320 mg, 1.02 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (245 mg, 1.12 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl_3 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((trans)-4-hydroxycyclohexyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**173b**) (110 mg, 0.21 mmol, 21% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.80 (t, $J = 5.7$ Hz) and 8.33 (t, $J = 6.0$ Hz) (2t, 1H), 8.21 – 8.14 (m, 1H), 7.75 – 7.64 (m, 1H), 7.63 – 7.00 (m, 7H), 5.61 and 5.45 (2s, 2H), 4.60 (d, $J = 4.2$ Hz) and 4.55 (d, $J = 4.6$ Hz) (2d, 1H), 4.45 (d, $J = 5.6$ Hz) and 4.31 (d, $J = 5.8$ Hz) (2d, 2H), 4.24 – 3.72 (m, 3H), 3.45 – 3.19 (m, 1H), 1.94-0.98 (m, 8H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.13, -121.69; MS (ES+): 516.5 (M+1), 538.5

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(M+Na); (ES-): 514.5 (M-1), 550.5 (M+Cl); (Based on NMR, this compound is a mixture of rotamers 3:2 ratio).

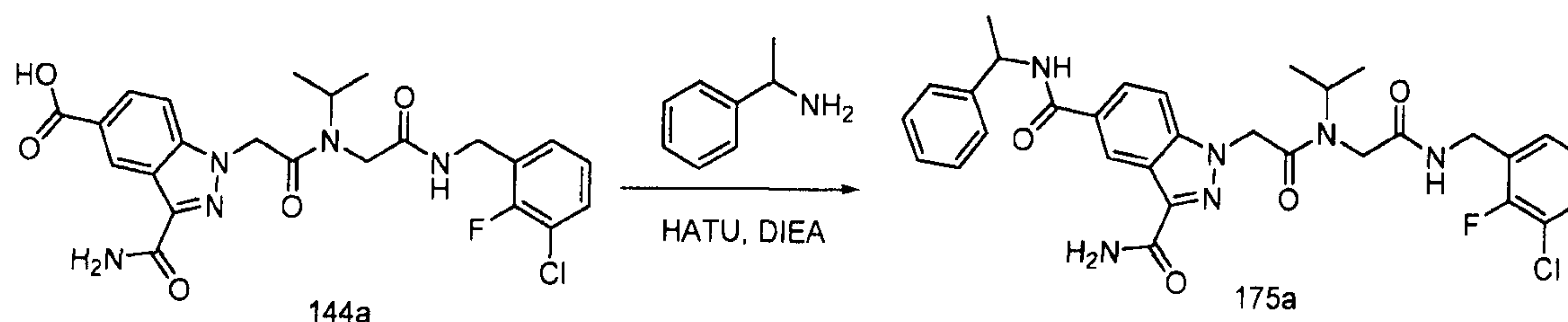
Scheme 174



- 5 Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-(cyclopropylmethyl)-1H-indazole-3,5-dicarboxamide (174a)

Reaction of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**144a**) (50 mg, 0.1 mmol) with cyclopropylmethanamine (0.013 mL, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (4 g), eluting with MeOH in DCM (1:0 to 19:1)] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-(cyclopropylmethyl)-1H-indazole-3,5-dicarboxamide (174a) (31 mg, 56%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 8.83 (t, *J* = 5.7 Hz) and 8.37 (t, *J* = 5.9 Hz) (2t, 1H), 8.77 – 8.62 (m, 2H), 7.93 – 6.94 (m, 7H), 5.62 and 5.48 (2s, 2H), 4.61 – 4.48 and 4.29 – 4.20 2(m, 1H), 4.46 (d, *J* = 5.6 Hz) and 4.31 (d, *J* = 5.8 Hz) (2d, 2H), 4.18 and 3.83 (2s, 2H), 3.17 (t, *J* = 6.3 Hz, 2H), 1.23 (d, *J* = 6.3 Hz) and 0.99 (d, *J* = 6.8 Hz) (2d, 6H), 1.13 – 1.01 (m, 1H), 0.51 – 0.37 (m, 2H), 0.32 – 0.18 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.22, -121.73; MS (ES+): 557.6 (M+1) & 579.6 (M+Na); MS (ES-): 591.5 & 593.5 (M+Cl).

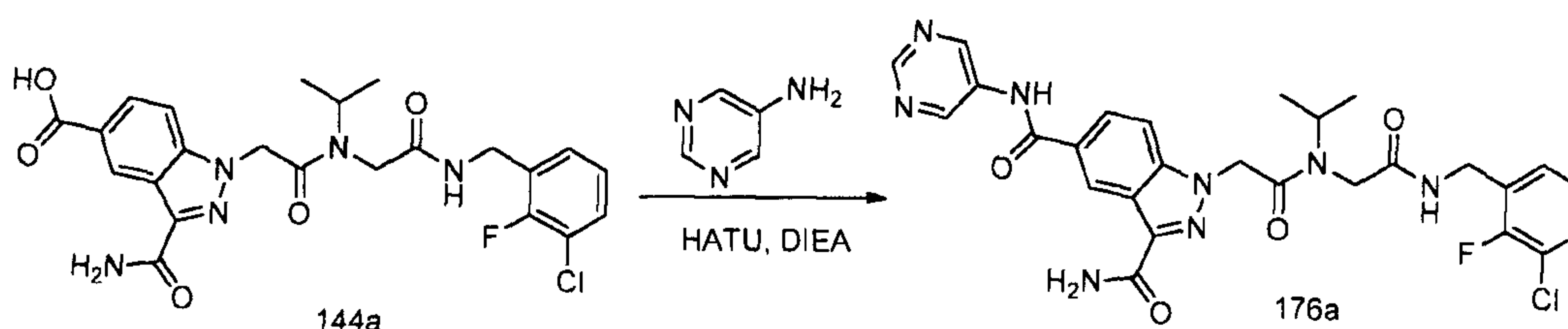
Scheme 175



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-(1-phenylethyl)-1H-indazole-3,5-dicarboxamide (**175a**)

Reaction of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**144a**) (50 mg, 0.1 mmol) with 1-phenylethanamine (0.02 mL, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (4 g), eluting with MeOH in DCM (1:0 to 19:1)] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-(1-phenylethyl)-1H-indazole-3,5-dicarboxamide (**175a**) (49 mg, 81%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 9.02 (d, *J* = 3.6 Hz) and 8.99 (d, *J* = 3.8 Hz) (2d, 1H), 8.83 (t, *J* = 5.7 Hz) and 8.36 (t, *J* = 5.9 Hz) (2t, 1H), 8.77 – 8.71 (m, 1H), 7.97 – 6.94 (m, 12H), 5.62 and 5.48 (2s, 2H), 5.29 – 5.09 (m, 1H), 4.62 – 4.49 and 4.28 – 4.21 (2m, 1H), 4.46 (d, *J* = 5.6 Hz) and 4.31 (d, *J* = 5.9 Hz) (2d, 2H), 4.18 and 3.83 (2s, 2H), 1.55 – 1.46 (m, 3H), 1.23 (d, *J* = 6.3 Hz) and 0.99 (d, *J* = 6.9 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.22, -121.73; MS (ES⁺): 607.7 (M+1) & 629.7 (M+Na); MS (ES⁻): 641.6 & 643.6 (M+Cl).

Scheme 176

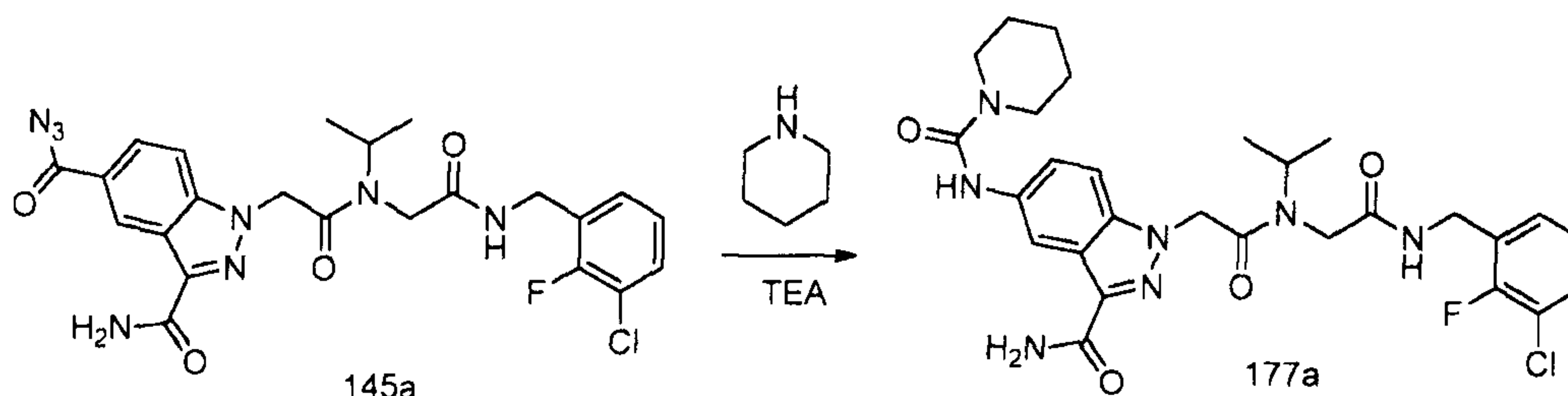


Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-(pyrimidin-5-yl)-1H-indazole-3,5-dicarboxamide (**176a**)

Reaction of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**144a**) (50 mg, 0.1 mmol) with pyrimidin-5-amine (15 mg, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (4 g), eluting with MeOH in DCM (1:0 to 9:1)] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-(pyrimidin-5-yl)-1H-indazole-3,5-dicarboxamide (**176a**) (10 mg, 17%) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 10.863 and 10.857 (2s, 1H), 9.213 and 9.209 (2s, 2H), 8.941 and 8.938 (2s, 1H), 8.93 – 8.82 (m, 2H), 8.49 – 6.91 (m, 7H), 5.67 and 5.53 (2s, 2H).

2H), 4.66 – 4.50 and 4.29-4.22 (2m, 1H), 4.47 (d, $J = 5.5$ Hz) and 4.32 (d, $J = 6.0$ Hz) (2d, 2H), 4.20 and 3.85 (2s, 2H), 1.24 (d, $J = 6.6$ Hz) and 1.00 (d, $J = 6.8$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.21, -121.70; MS (ES+): 581.6 (M+1); 603.6 (M+Na) .

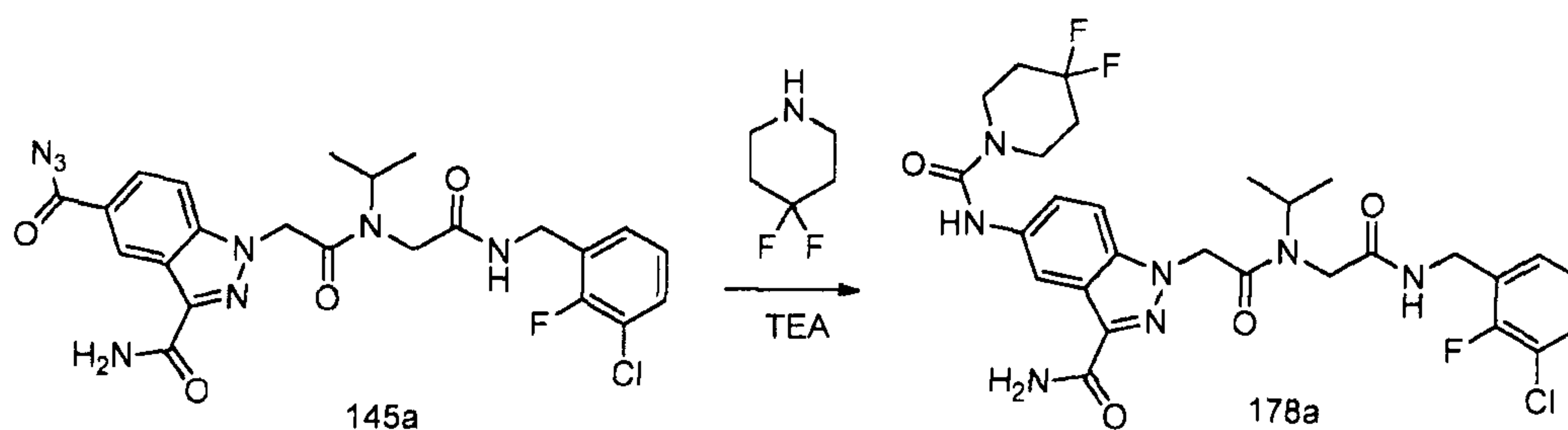
Scheme 177



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(piperidine-1-carboxamido)-1H-indazole-3-carboxamide (**177a**)

Reaction of 3-carbamoyl-1-(2-((2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**145a**) (420 mg, 0.79 mmol) in toluene (15 mL) with piperidine (135 mg, 1.59 mmol) using TEA (0.44 mL, 3.18 mmol) as base according to the procedure reported in step-4 of Scheme 129 gave after workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(piperidine-1-carboxamido)-1H-indazole-3-carboxamide (**177a**) (179 mg, 0.31 mmol, 39% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.82 (t, $J = 5.7$ Hz) and 8.37 (t, $J = 5.9$ Hz) (2t, 1H), 8.58 (s, 1H), 8.22 – 8.15 (m, 1H), 7.66 – 7.06 (m, 7H), 5.53 and 5.40 (2s, 2H), 4.63 – 4.23 (m, 3H), 4.17 and, 3.83 (2s, 2H), 3.48 – 3.39 (m, 4H), 1.65 – 1.42 (m, 6H), 1.21 (d, $J = 6.5$ Hz) and 0.99 (d, $J = 6.8$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.22, -121.78; MS (ES+) 586.6 (M+1); MS (ES-) 584.5 (M-1).

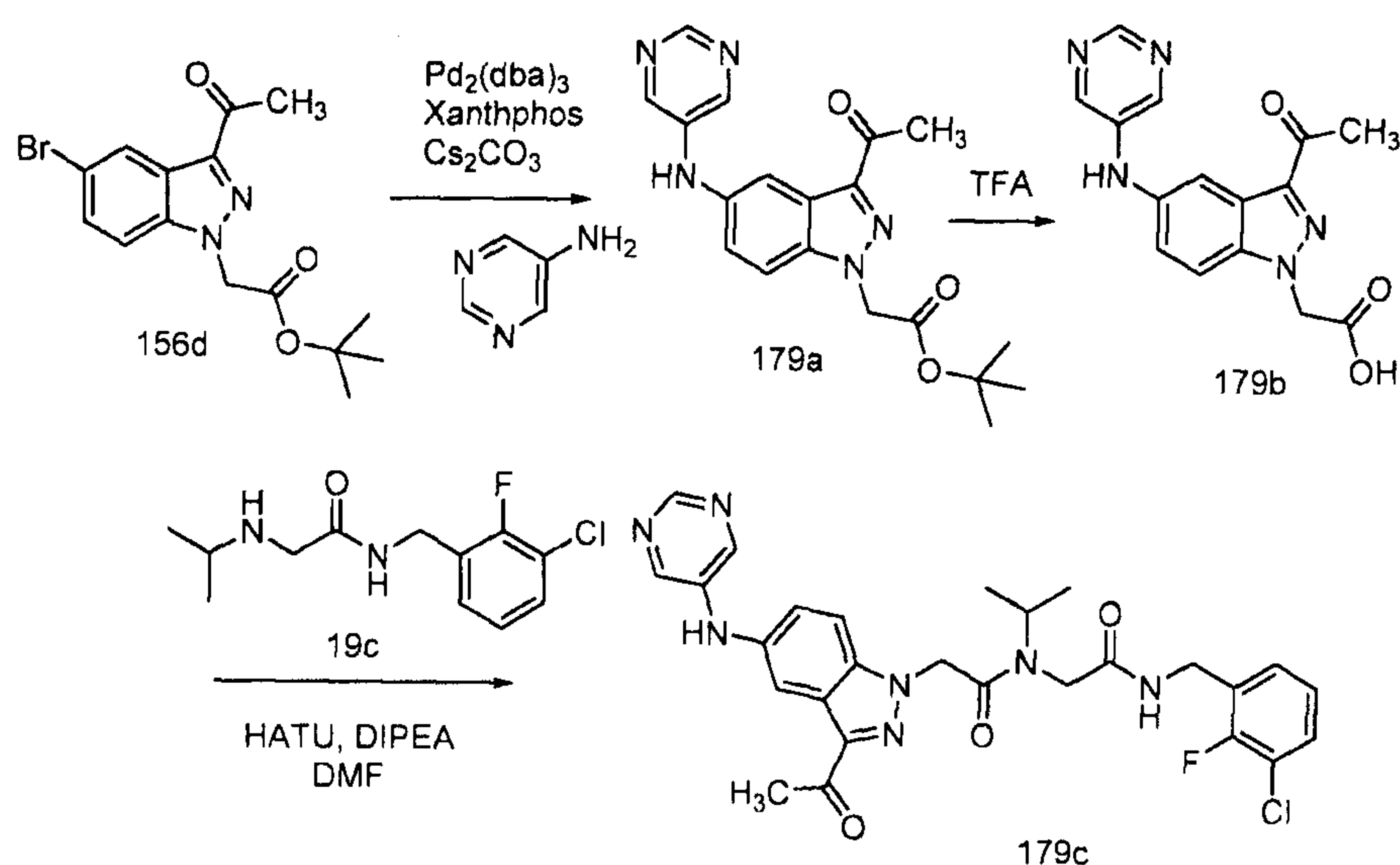
Scheme 178



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(4,4-difluoropiperidine-1-carboxamido)-1H-indazole-3-carboxamide (**178a**)

Reaction of 3-carbamoyl-1-(2-((2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**145a**) (150 mg, 0.28 mmol) in toluene (10 mL) with 4,4-difluoropiperidine hydrochloride (134 mg, 0.85 mmol) using TEA (0.16 mL, 1.13 mmol) as base according to the procedure reported in step-4 of Scheme 129 gave after workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzylamino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(4,4-difluoropiperidine-1-carboxamido)-1H-indazole-3-carboxamide (**178a**) (43 mg, 0.069 mmol, 24% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.91 – 8.32 (m, 2H), 8.23 – 8.14 (m, 1H), 7.66 – 7.06 (m, 7H), 5.53 and 5.40 (2s, 2H), 4.62 – 4.23 (m, 3H), 4.17 and 3.83 (2s, 2H), 3.66 – 3.56 (m, 4H), 2.09 – 1.87 (m, 4H), 1.21 (d, *J* = 6.5 Hz) and 0.99 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -95.19, -121.22, -121.78; MS (ES⁺): 622.6 (M+1); MS (ES⁻): 620.5 (M-1).

Scheme 179



Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzylamino)-2-oxoethyl)-N-isopropylacetamide (**179c**)

Step-1: Preparation of tert-butyl 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)acetate (**179a**) Reaction of tert-butyl 2-(3-acetyl-5-bromo-1H-indazol-1-yl)acetate (**156d**) (1.0 g, 2.83 mmol) with pyrimidin-5-amine (0.539 g, 5.66 mmol) according to the procedure reported in step-1 of Scheme 97 gave after workup and purification by flash column chromatography [silica gel (40 g), eluting with DMA80 in DCM 0 to 20%] tert-butyl 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)acetate (**179a**) (720 mg, 1.96 mmol, 69% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.73 (s, 1H), 8.65 (s, 1H), 8.56

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(s, 2H), 7.93 - 7.88 (m, 1H), 7.72 (dd, $J = 9.0, 0.7$ Hz, 1H), 7.37 (dd, $J = 9.1, 2.2$ Hz, 1H), 5.42 (s, 2H), 2.59 (s, 3H), 1.44 (s, 9H); MS (ES⁺): 368.5 (M+1), 390.5 (M+Na); MS (ES⁻): 366.5 (M-1), 402.4 (M+Cl).

Step-2: Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)acetic acid

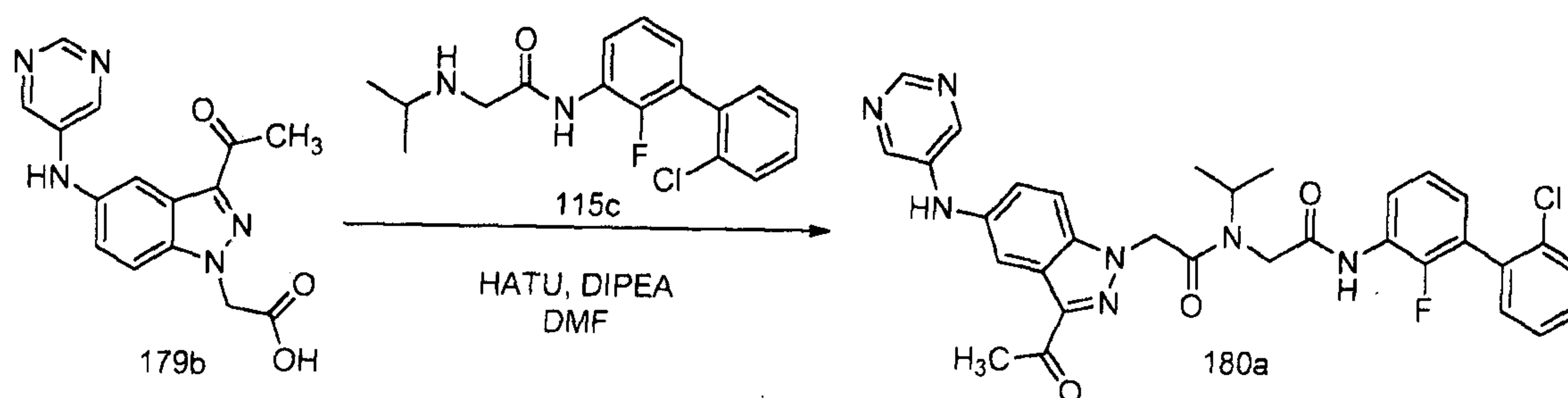
5 (179b)

Reaction of tert-butyl 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)acetate (179a) (700 mg, 1.91 mmol) with TFA (1.47 mL, 19.05 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and trituration with 30% EtOAc-hexane (10 mL) 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)acetic acid (179b) (400 mg, 1.35 mmol, 10 99 % yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.37 (s, 1H, D₂O exchangeable), 8.74 (s, 1H), 8.66 (s, 1H), 8.56 (s, 2H), 7.90 (dd, $J = 2.2, 0.7$ Hz, 1H), 7.76 (dd, $J = 9.0, 0.7$ Hz, 1H), 7.36 (dd, $J = 9.0, 2.2$ Hz, 1H), 5.43 (s, 2H), 2.59 (s, 3H); MS (ES⁺): 312.4 (M+1), 334.4 (M+Na), MS (ES⁻): 310.4 (M-1).

Step-3: Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (179c)

Reaction of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)acetic acid (179b) (70 mg, 0.23 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (19c) (58 mg, 0.23 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (12 g), eluting with DMA-80 in DCM 0-20%] 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (179c) (105 mg, 0.19 mmol, 85 % yield) as a very light orange solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.84 and 8.36 (2t, $J = 5.6$ Hz, 1H), 8.72 (s, 1H), 8.65 and 8.64 (2s, 1H), 8.55 (s, 2H), 7.908 and 7.902 (2s, 1H), 7.70 - 7.00 (m, 5H), 5.67 and 5.51 (2s, 2H), 4.63 - 4.52 and 4.33 - 4.20 (2m, 1H), 4.47 and 4.33 (2d, $J = 6.0$ Hz, 2H), 4.18 and 3.85 (2s, 2H), 2.59 (s, 3H), 1.25 and 1.00 (2d, $J = 6.8$ Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.21, -121.72; MS (ES⁺): 552.6 (M+1); MS (ES⁻): 586.5, 588.5 (M+Cl).

Scheme 180



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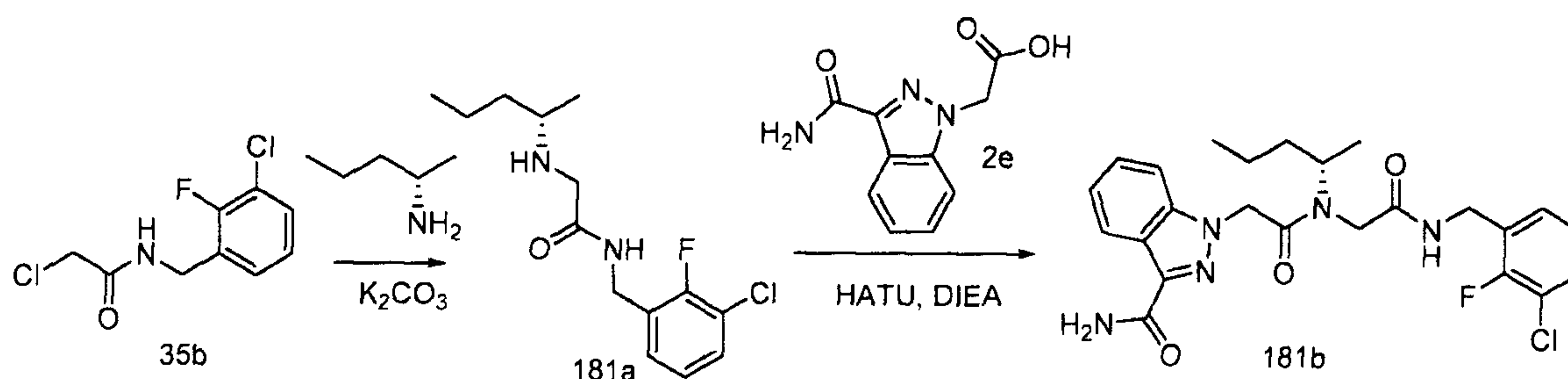
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Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)-N-(2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**180a**)

Reaction of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)acetic acid (**179b**) (70 mg, 0.23 mmol) with N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)-2-(isopropylamino)acetamide (**115c**) (72 mg, 0.23 mmol) according to the procedure reported in step-3 of scheme-2 gave after workup and purification by flash column [silica gel (12 g), eluting with DMA-80 in DCM 0-20%] 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)-N-(2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**180a**) (61 mg, 0.099 mmol, 44% yield) as an off-white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.27 and 9.76 (2s, 1H), 8.73 and 8.72 (2s, 1H), 8.65 (s, 1H), 8.55 and 8.54 (2s, 2H), 8.11 and 7.95 (2t, *J* = 7.4 Hz, 1H), 7.90 and 7.89 (2d, *J* = 2.1 Hz, 1H), 7.68 – 7.00 (m, 6H), 5.73 and 5.55 (2s, 2H), 4.73 - 4.57 and 4.40 - 4.26 (2m, 1H), 4.47 and 4.09 (2s, 2H), 2.59 and 2.58 (2s, 3H), 1.28 and 1.07 (2d, *J* = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -126.81, -126.96; MS (ES⁺): 614.6 (M+1); MS (ES⁻): 648.6 (M+Cl).

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Scheme 181



Preparation of (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(pentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**181b**)

Step-1: Preparation of (S)-N-(3-chloro-2-fluorobenzyl)-2-(pentan-2-ylamino)acetamide (**181a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (267 mg, 1.13 mmol) with (S)-pentan-2-amine hydrochloride (350 mg, 2.83 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] (S)-N-(3-chloro-2-fluorobenzyl)-2-(pentan-2-ylamino)acetamide (**181a**) (112 mg, 0.39 mmol, 35%) as a colorless oil; MS (ES⁺): 287.4, 289.4 (M+1, M+3); (ES⁻): 285.4.

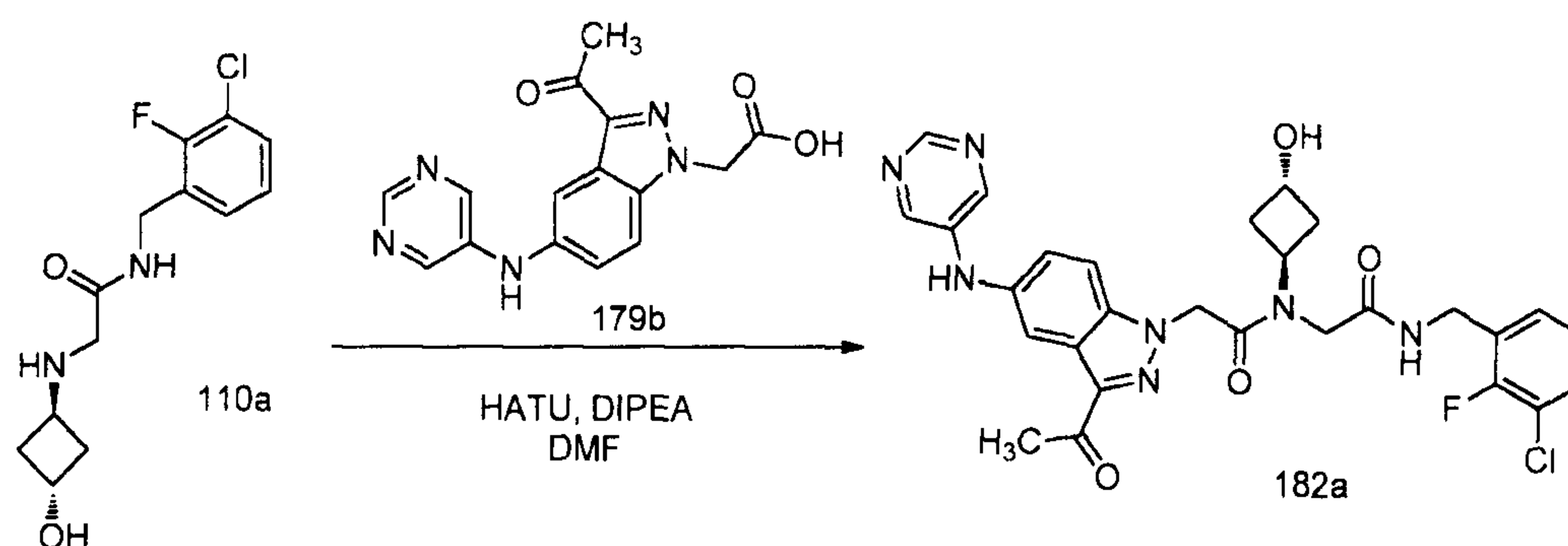
Step-2: Preparation of (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(pentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**181b**)

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Reaction of (S)-N-(3-chloro-2-fluorobenzyl)-2-(pentan-2-ylamino)acetamide (**181a**) (112 mg, 0.39 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (94 mg, 0.43 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM 0 to 60%] (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(pentan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**181b**) (141 mg, 0.29 mmol, 74% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 8.81 (t, *J* = 5.6 Hz) and 8.34 (t, *J* = 6.2 Hz) (2t, 1H), 8.22 – 8.13 (m, 1H), 7.70 (bs, 1H), 7.59 – 7.04 (m, 7H), 5.63 – 5.40 (m, 2H), 4.56-3.70 (m, 5H), 1.62-0.58 (m, 10H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.19, -121.73; MS (ES⁺): 488.5 (M+1); MS (ES⁻): 486.5 (M-1).

Scheme 182

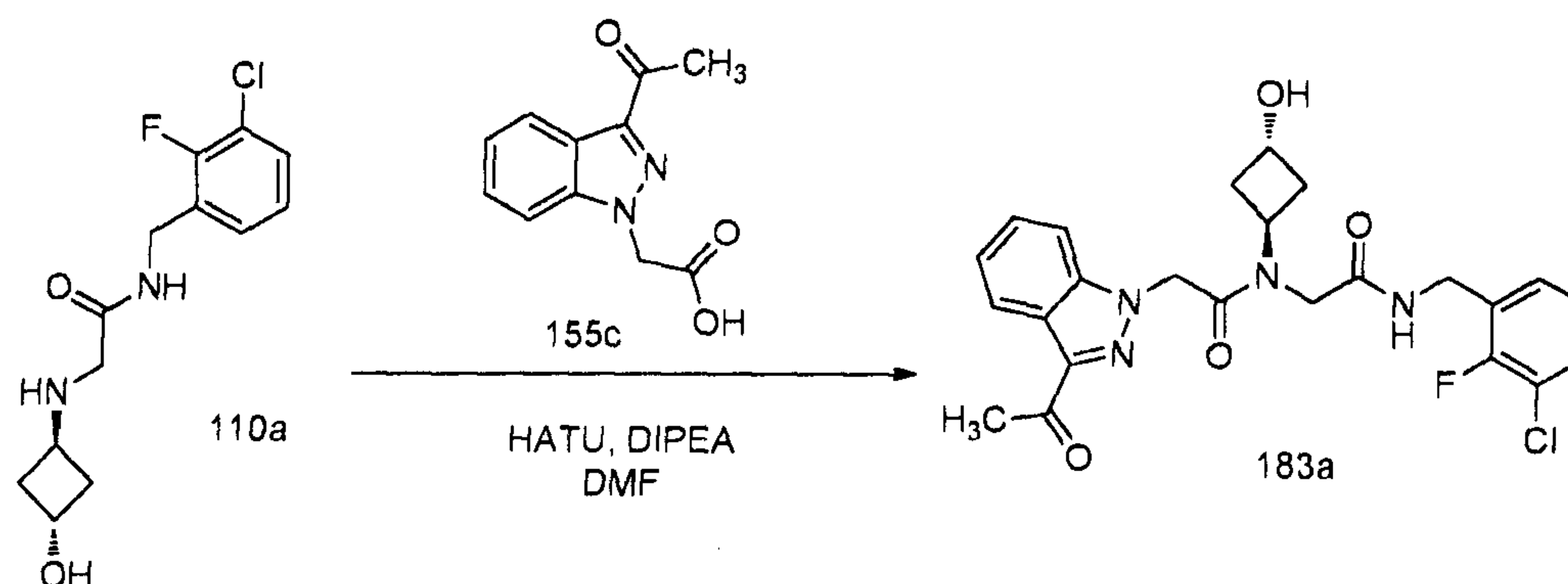


Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-(trans-3-hydroxycyclobutyl)acetamide (**182a**)

Reaction of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)acetic acid (**179b**) (70 mg, 0.23 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-hydroxycyclobutyl)amino)acetamide (**110a**) (64 mg, 0.23 mmol) according to the procedure reported in step-3 of scheme-2 gave after workup and purification by flash column [silica gel (12 g), eluting with DMA-80 in DCM 0-50%] 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-(trans-3-hydroxycyclobutyl)acetamide (**182a**) (65 mg, 0.11 mmol, 50% yield) as a off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 8.87 and 8.43 (2t, *J* = 5.7 Hz, 1H), 8.728 and 8.72 (2s, 1H), 8.657 and 8.65 (2s, 1H), 8.55 (s, 2H), 7.90 and 7.89 (2s, 1H), 7.67 – 7.03 (m, 5H), 5.61 and 5.48 (2s, 2H), 5.10 and 5.02 (2d, *J* = 4.0 Hz, 1H), 4.96 and 4.86 (2t, *J* = 8.2 Hz, 1H), 4.47 and 4.34 (2d, *J* = 5.6 Hz, 2H), 4.27 and 4.02 (2s, 2H), 4.24 - 4.09 (m, 1H), 2.587 and 2.58 (2s, 3H), 2.46 - 2.33 (m, 1H), 2.29 - 2.12 (m, 2H), 2.02 - 1.88 (m, 1H);

^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) (a mixture of two rotamers) δ -121.22 , -121.59; MS (ES⁺): 580.6 (M+1), 602.5 (M+Na); MS (ES⁻): 614.5 (M+Cl).

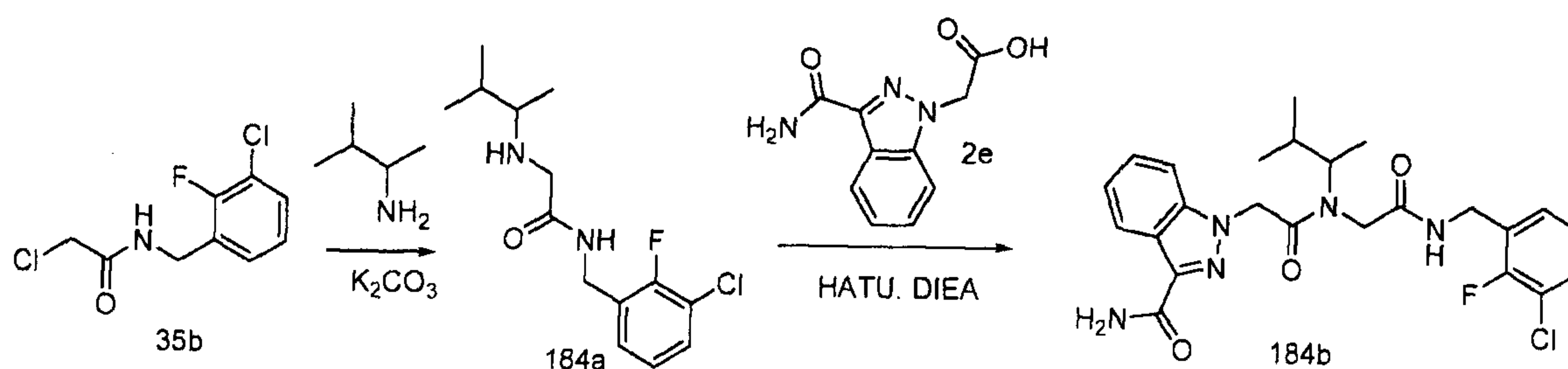
Scheme 183



- 5 Preparation of 2-(3-acetyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-(trans-3-hydroxycyclobutyl)acetamide (**183a**)

Reaction of 2-(3-acetyl-1H-indazol-1-yl)acetic acid (**155c**) (70 mg, 0.32 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(((trans)-3-hydroxycyclobutyl)amino)acetamide (**110a**) (92 mg, 0.32 mmol) according to the procedure reported in step-3 of scheme-2 gave after workup and
 10 purification by flash column [silica gel (12 g), eluting with DMA-80 in DCM 0-40%] 2-(3-acetyl-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-(trans-3-hydroxycyclobutyl)acetamide (**183a**) (70 mg, 0.14 mmol, 45% yield) as a off-white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) (mixture of two rotamers) δ 8.87 and 8.42 (2t, J = 5.9 Hz, 1H), 8.20 and 8.17 (2d, J = 1.0 Hz, 1H), 7.72 – 6.99 (m, 6H), 5.63 and 5.50 (2s, 2H), 5.10 and 5.01
 15 (2d, J = 4.4 Hz, 1H), 4.98 - 4.80 (m, 1H), 4.47 and 4.33 (2d, J = 5.8 Hz, 2H), 4.28 and 4.01 (2s, 2H) 4.24 - 4.09 (m, 1H), 2.61 (s, 3H), 2.46 - 2.34 (m, 1H), 2.29 - 2.13 (m, 2H), 2.00 - 1.88 (m, 1H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) (mixture of two rotamers) δ -121.23 , -121.63; MS (ES⁺): 487.5 (M+1); MS (ES⁻): 521.4 (M+Cl).

Scheme 184



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(3-methylbutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**184b**)

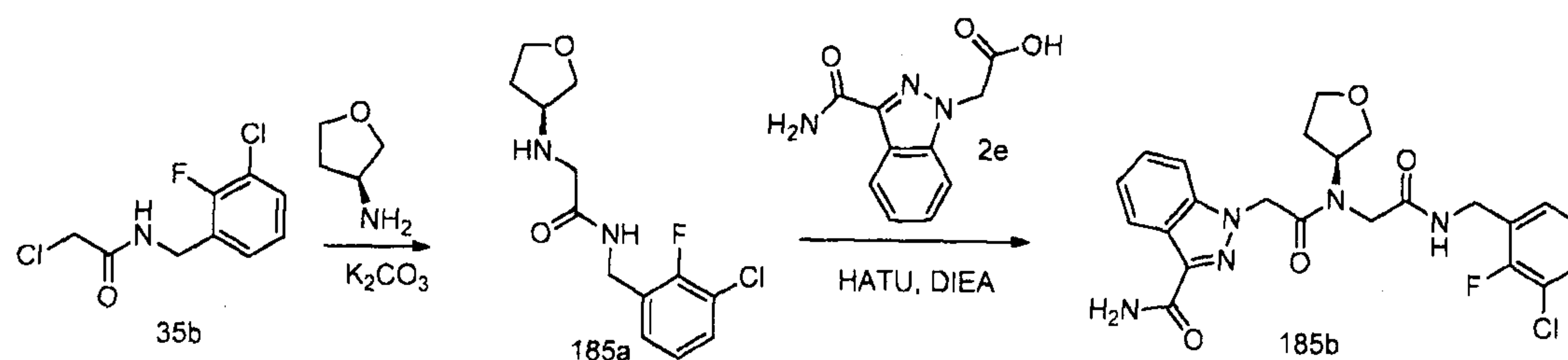
Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((3-methylbutan-2-yl)amino)acetamide (**184a**)

- 5 Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (316 mg, 1.34 mmol) with 3-methylbutan-2-amine (350 mg, 4.02 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-chloro-2-fluorobenzyl)-2-((3-methylbutan-2-yl)amino)acetamide (**184a**) (145 mg, 0.51 mmol, 38%) as a colorless oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.32 (t, *J* = 6.1 Hz, 1H), 7.46 (ddd, *J* = 7.9, 7.2, 1.8 Hz, 1H), 7.32 – 7.23 (m, 1H), 7.22 – 7.12 (m, 1H), 4.48 – 4.29 (m, 2H), 3.22 – 3.05 (m, 2H), 2.40 – 2.24 (m, 1H), 1.99 (s, 1H), 1.68 – 1.53 (m, 1H), 0.86 – 0.77 (m, 9H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.62; MS (ES⁺): 287.4 (M+1); MS (ES⁻): 285.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(3-methylbutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**184b**)

- Reaction of N-(3-chloro-2-fluorobenzyl)-2-((3-methylbutan-2-yl)amino)acetamide (**184a**) (145 mg, 0.51 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (122 mg, 0.56 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM 0 to 60%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(3-methylbutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**184b**) (113 mg, 0.23 mmol, 46% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (mixture of two rotamers) δ 8.81 (t, *J* = 5.7 Hz) and 8.34 (t, *J* = 6.0 Hz) (2t, 1H), 8.23 – 8.13 (m, 1H), 7.77 – 7.66 (m, 1H), 7.58 – 7.15 (m, 7H), 5.72 – 5.36 (m, 2H), 4.54 – 3.63 (m, 5H), 1.82 – 1.55 (m, 1H), 1.26 (d, *J* = 6.4 Hz) and 1.01 – 0.93 (m) and 0.84 (d, *J* = 6.5 Hz) and 0.74 (d, *J* = 6.5 Hz (9H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.20, -121.80; MS (ES⁺) 488.5 (M+1); MS (ES⁻) 486.5 (M-1).

Scheme 185



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PCT/US2017/015953

Preparation of (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(tetrahydrofuran-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**185b**)

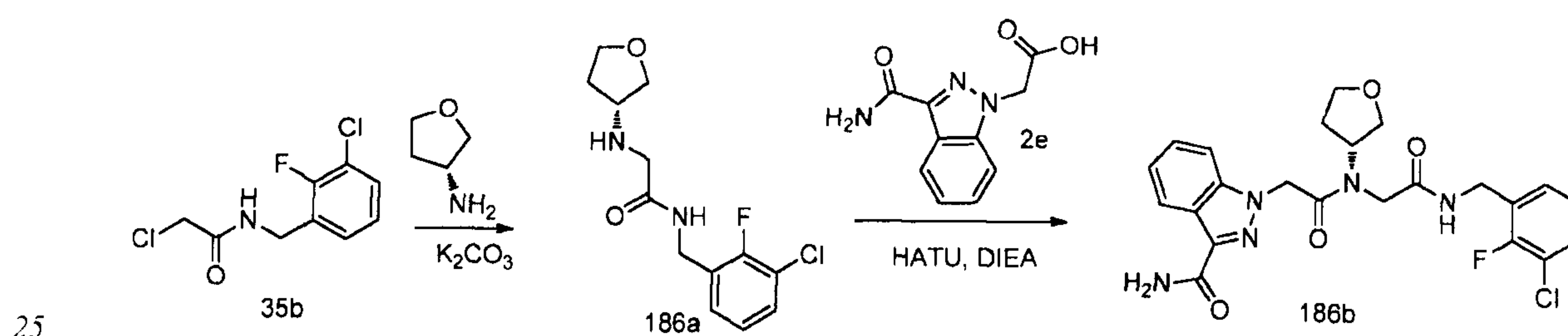
Step-1: Preparation of (S)-N-(3-chloro-2-fluorobenzyl)-2-((tetrahydrofuran-3-yl)amino)acetamide (**185a**)

- 5 Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (325 mg, 1.38 mmol) with (S)-tetrahydrofuran-3-amine (300 mg, 3.44 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] (S)-N-(3-chloro-2-fluorobenzyl)-2-((tetrahydrofuran-3-yl)amino)acetamide (**185a**) (112 mg, 0.39 mmol, 28%)
10 as a colorless oil; MS (ES⁺): 287.4 (M+1), 309.3 (M+Na); MS (ES⁻): 285.3

Step-2: Preparation of (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(tetrahydrofuran-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**185b**)

- Reaction of (S)-N-(3-chloro-2-fluorobenzyl)-2-((tetrahydrofuran-3-yl)amino)acetamide (**185a**) (112 mg, 0.39 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (94 mg, 0.43 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM 0 to 60%] (S)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(tetrahydrofuran-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**185b**) (103 mg, 0.21 mmol, 54% yield)
15 as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (mixture of two rotamers) δ 8.89 (t, *J* = 5.8 Hz and, 8.49 (t, *J* = 5.9 Hz) (2t, 1H), 8.22 – 8.13 (m, 1H), 7.74 – 7.64 (m, 1H), 7.63 – 7.00 (m, 7H), 5.81-5.29 (m, 2H), 4.97 – 4.74 (m, 1H), 4.47 (d, *J* = 5.6 Hz) and 4.31 (d, *J* = 5.9 Hz) (2d, 2H), 4.25 (s) and 4.00 – 3.43 (m) (s & m, 6H), 2.42-1.54 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.27, -121.73; MS (ES⁺): 488.5 (M+1); MS (ES⁻): 486.5 (M-1).

Scheme 186



Preparation of (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(tetrahydrofuran-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**186b**)

Step-1: Preparation of (R)-N-(3-chloro-2-fluorobenzyl)-2-((tetrahydrofuran-3-yl)amino)acetamide (**186a**)

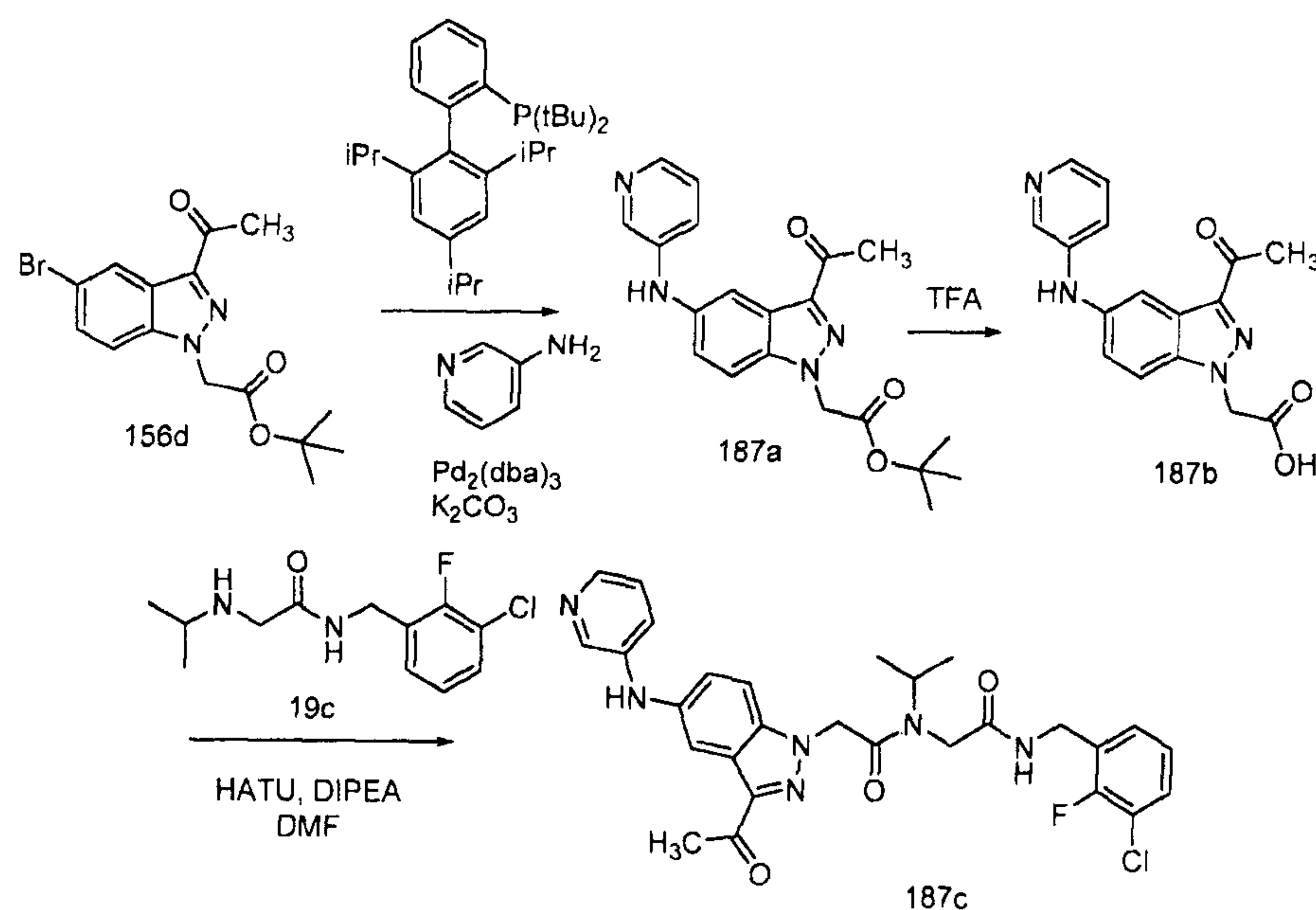
Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (339 mg, 1.44 mmol) with (R)-tetrahydrofuran-3-amine (250 mg, 2.87 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] (R)-N-(3-chloro-2-fluorobenzyl)-2-((tetrahydrofuran-3-yl)amino)acetamide (**186a**) (109 mg, 0.38 mmol, 27%) as a colorless oil; MS (ES⁺): 287.4 (M+1), 309.3 (M+Na); MS (ES⁻): 285.3

Step-2: Preparation of (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(tetrahydrofuran-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**186b**)

Reaction of (R)-N-(3-chloro-2-fluorobenzyl)-2-((tetrahydrofuran-3-yl)amino)acetamide (**186a**) (109 mg, 0.38 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (92 mg, 0.42 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM 0 to 60%] (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(tetrahydrofuran-3-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**186b**) (23 mg, 0.047 mmol, 12% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.95 – 8.43 (m, 1H), 8.23 – 8.13 (m, 1H), 7.74 – 7.64 (m, 1H), 7.63-6.95 (m, 7H), 5.76 – 5.54 (m) and 5.40 (s) (2H), 5.00 – 4.73 (m, 1H), 4.47 (d, *J* = 5.5 Hz) and 4.32 (d, *J* = 5.9 Hz) (2d, 2H), 4.25 (s) and 4.02 – 3.51 (m) (6H), 2.16 – 1.61 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.28, -121.74; MS (ES⁺): 488.5 (M+1); MS (ES⁻): 486.5 (M-1).

20

Scheme 187



Preparation of 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**187c**)

Step-1: Preparation of tert-butyl 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indazol-1-yl)acetate (**187a**) Reaction of tert-butyl 2-(3-acetyl-5-bromo-1H-indazol-1-yl)acetate (**156d**) (935 mg, 2.65 mmol) with pyridin-3-amine (0.498 g, 5.29 mmol), using potassium carbonate (732 mg, 5.29 mmol), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (135 mg, 0.32 mmol), Pd₂(dba)₃ (145 mg, 0.16 mmol) according to the procedure reported in step-1 of Scheme 97 gave after workup and purification by flash column chromatography [silica gel (40 g), eluting with DMA80 in DCM 0 to 50] tert-butyl 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indazol-1-yl)acetate (**187a**) (722 mg, 1.97 mmol, 74% yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.54 (s, 1H), 8.37 (d, *J* = 2.8 Hz, 1H), 8.05 (dd, *J* = 4.6, 1.4 Hz, 1H), 7.88 (d, *J* = 2.1 Hz, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 7.56 – 7.41 (m, 1H), 7.38 – 7.22 (m, 2H), 5.41 (s, 2H), 2.59 (s, 3H), 1.44 (s, 9H); MS (ES⁺): 367.5 (M+1), 389.5 (M+Na); MS (ES⁻): 365.4 (M-1).

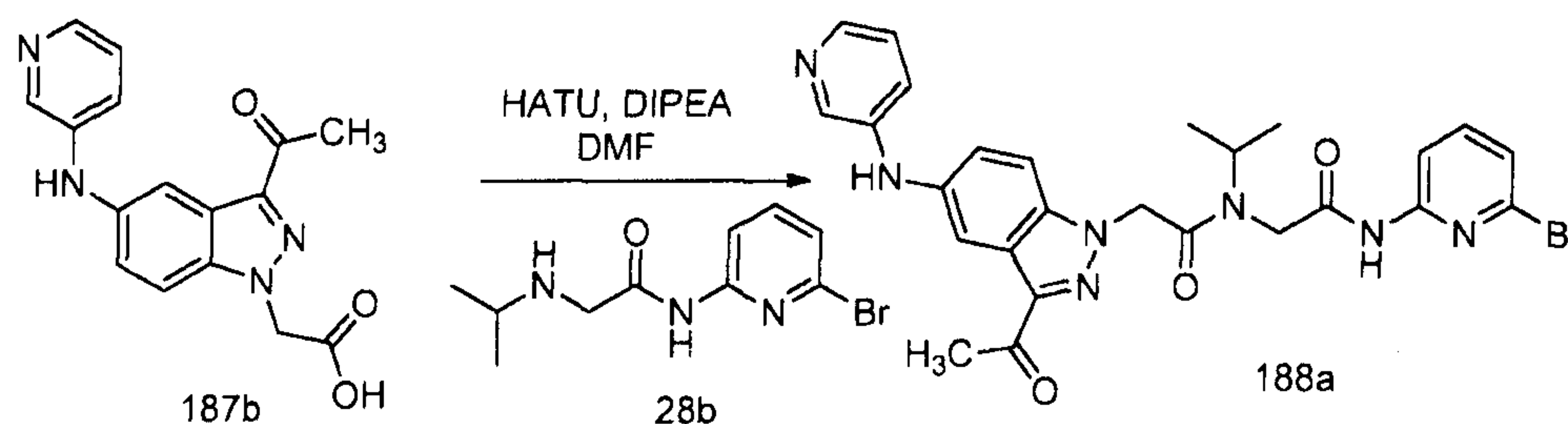
Step-2: Preparation of 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indazol-1-yl)acetic acid (**187b**) Reaction of tert-butyl 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indazol-1-yl)acetate (**187a**) (115 mg, 0.31 mmol) with TFA (0.73 mL, 9.42 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and trituration with hexane (10 mL) 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indazol-1-yl)acetic acid (**187b**) (129 mg, 0.3 mmol, 97 % yield) as a yellow solid in the form of TFA adduct; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.44 (bs, 1H, D₂O exchangeable), 9.34 (s, 1H, D₂O exchangeable), 8.41 (s, 1H), 8.24 (d, *J* = 5.3 Hz, 1H), 8.05 – 7.92 (m, 2H), 7.85 (d, *J* = 9.0 Hz, 1H), 7.78 (dd, *J* = 8.7, 5.2 Hz, 1H), 7.44 (dd, *J* = 9.0, 2.1 Hz, 1H), 5.47 (s, 2H), 2.61 (s, 3H); MS (ES⁺): 311.4 (M+1); MS (ES⁻): 619.5 (2M-1).

Step-3: Preparation of 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**187c**)

Reaction of 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indazol-1-yl)acetic acid (**187b**) (234 mg, 0.754 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (234 mg, 0.91 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (12 g), eluting with DMA-80 in DCM 0-100%] 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**187c**) (38 mg, 0.069 mmol, 9% yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.84 (t, *J* = 5.8 Hz) and 8.42 – 8.29 (m) (t & m, 2H), 8.52 (s, 1H), 8.10 – 8.00 (m, 1H), 7.88 (d, *J* = 2.0 Hz, 1H), 7.63 – 6.99 (m, 6H), 5.66 & 5.49 (2s, 2H), 4.66 – 4.52 & 4.30 – 4.22 (2m, 1H), 4.47 (d, *J* = 5.6 Hz) and 4.33 (d, *J* = 5.9 Hz) (2d, 2H),

4.18 & 3.86 (2s, 2H), 2.58 (s, 3H), 1.25 (d, $J = 6.5$ Hz) & 1.01 (d, $J = 6.8$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -121.21, -121.72; MS (ES+): 573.5, 575.5 ($\text{M}+\text{Na}$); MS (ES-): 549.4 ($\text{M}-1$);

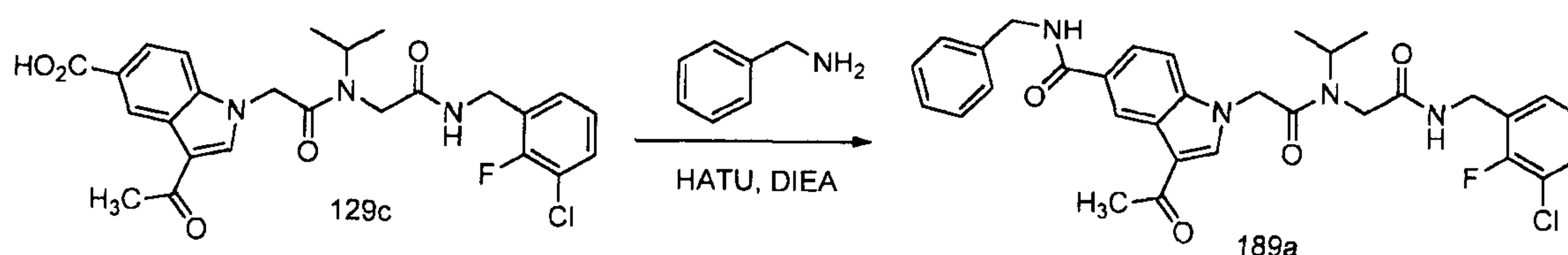
Scheme 188



Preparation of 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indazol-1-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**188a**)

Reaction of 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indazol-1-yl)acetic acid (**187b**) (210 mg, 0.68 mmol) with N-(6-bromopyridin-2-yl)-2-(isopropylamino)acetamide (**28b**) (221 mg, 0.81 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (24 g), eluting with DMA-80 in DCM 0-100%] 2-(3-acetyl-5-(pyridin-3-ylamino)-1H-indazol-1-yl)-N-(2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**188a**) (139 mg, 0.25 mmol, 36% yield) as a light green solid as a mixture of two rotamers; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 11.21 & 10.82 (2s, 1H, D_2O exchangeable), 8.53 & 8.51 (2s, 1H), 8.36 (t, $J = 3.3$ Hz, 1H), 8.23 – 7.97 (m, 2H), 7.88 (d, $J = 2.0$ Hz) & 7.86 (d, $J = 2.1$ Hz) (2d, 1H), 7.81 (t, $J = 8.0$ Hz) & 7.70 (t, $J = 8.0$ Hz) (2t, 1H), 7.61 (d, $J = 3.4$ Hz) & 7.58 (d, $J = 3.4$ Hz) (2d, 1H), 7.50- 7.21 (m, 4H), 5.70 & 5.51 (2s, 2H), 4.71 – 4.57 & 4.38 – 4.26 (2m, 1H), 4.43 & 4.05 (2s, 2H), 2.59 & 2.58 (2s, 3H), 1.26 (d, $J = 6.4$ Hz) & 1.05 (d, $J = 6.8$ Hz) (2d, 6H); MS (ES+): 564.5 & 566.5 ($\text{M}+1$), 586.5 & 588.5 ($\text{M}+\text{Na}$); MS (ES-): 562.4 & 564.4 ($\text{M}-1$).

Scheme 189

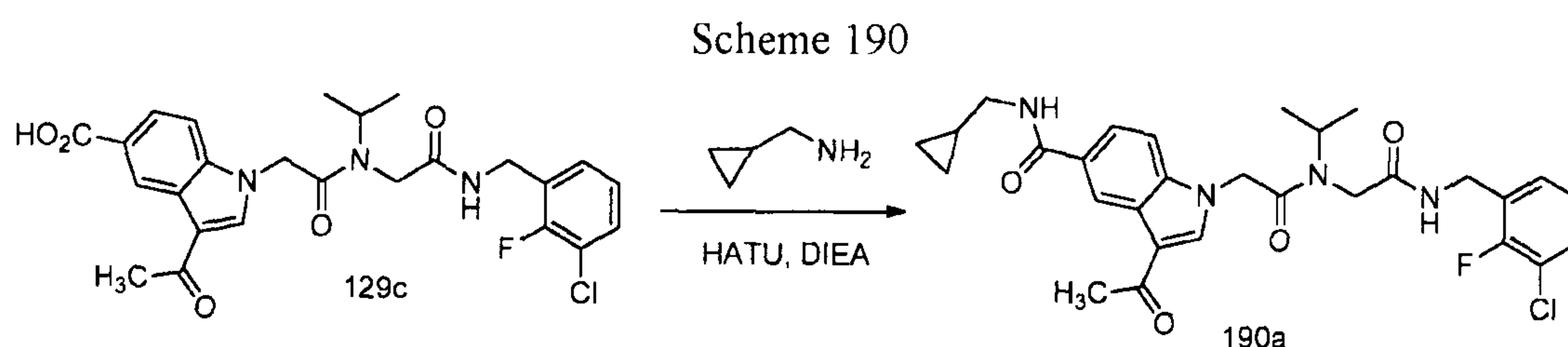


Preparation of 3-acetyl-N-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxamide (**189a**)

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Reaction of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**129c**) (50 mg, 0.1 mmol) with phenylmethanamine (0.016 mL, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (4 g), eluting with CHCl₃/MeOH (1:0 to 19:1)] 3-acetyl-N-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxamide (**189a**) (47 mg, 80%) as a light brown solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.09 – 8.79 (m, 1H), 8.77 – 8.73 (m, 1H), 8.35 and 8.31 (2s, 1H), 7.82 – 6.93 (m, 11H), 5.40 and 5.21 (2s, 2H), 4.62 – 4.21 (m, 5H), 4.19 and 3.85 (2s, 2H), 2.46 and 2.45 (2s, 3H), 1.26 (d, *J* = 6.5 Hz) and 1.00 (d, *J* = 6.8 Hz (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.19, -121.80; MS (ES⁻): 589.9 & 591.6 (M-1), 625.5 & 627.6 (M+Cl).



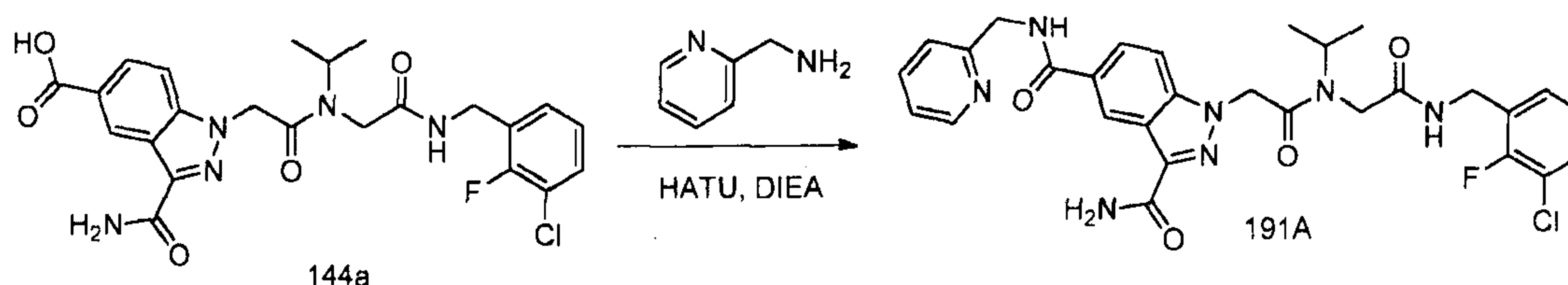
Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N-(cyclopropylmethyl)-1H-indole-5-carboxamide (**190a**)

Reaction of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**129c**) (50 mg, 0.1 mmol) with cyclopropylmethanamine (0.013 mL, 0.149 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica gel (4 g), eluting with CHCl₃/MeOH (1:0 to 19:1)] 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N-(cyclopropylmethyl)-1H-indole-5-carboxamide (**190a**) (39 mg, 71%) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (mixture of two rotamers) δ 8.89 – 8.48 (m, 2H), 8.34 and 8.30 (2s, 1H), 7.79 – 6.91 (m, 6H), 5.39 and 5.20 (2s, 2H), 4.65 – 4.51 and 4.29 – 4.20 (2m, 1H), 4.48 (d, *J* = 5.5 Hz) and 4.33 (d, *J* = 5.8 Hz) (2d, 2H), 4.19 and 3.85 (2s, 2H), 3.16 (t, *J* = 6.1 Hz, 2H), 2.46 and 2.45 (2s, 3H), 1.26 (d, *J* = 6.5 Hz) and 1.00 (d, *J* = 6.8 Hz) (2d, 6H), 1.12 – 1.01 (m, 1H), 0.48 – 0.38 (m, 2H), 0.29 – 0.19 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.19, -121.79; MS (ES⁺): 555.6 (M+1) and 577.6 (M+Na), MS (ES⁻): 589.6 & 591.5 (M+Cl).

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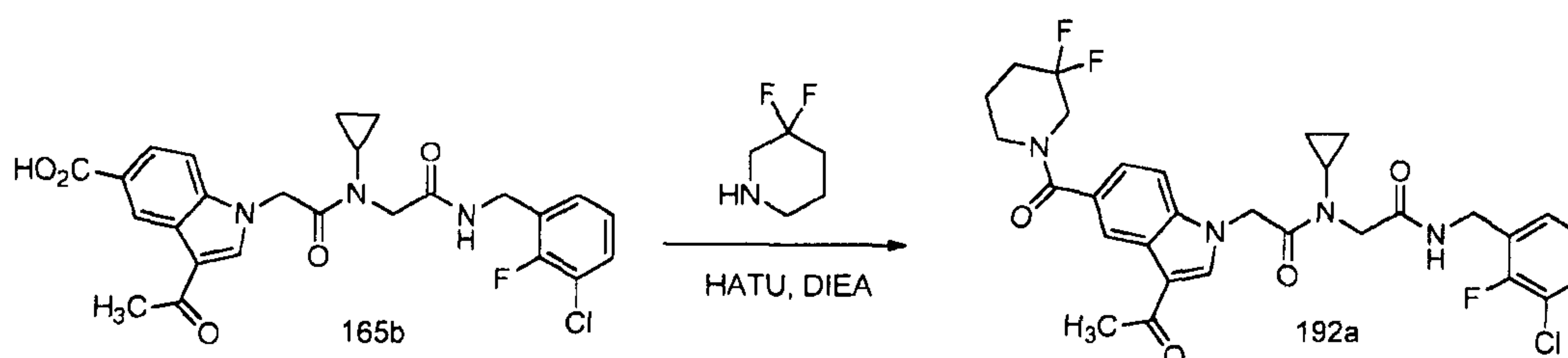
Scheme 191



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-(pyridin-2-ylmethyl)-1H-indazole-3,5-dicarboxamide (**191a**)

Reaction of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**144a**) (50 mg, 0.1 mmol) with pyridin-2-ylmethanamine (0.015 mL, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (4 g), eluting with MeOH in DCM (1:0 to 9:1)] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-(pyridin-2-ylmethyl)-1H-indazole-3,5-dicarboxamide (**191a**) (27 mg, 46%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (mixture of two rotamers) δ 9.28 (t, *J* = 5.8 Hz, 1H), 8.84 (t, *J* = 5.7 Hz) and 8.37 (t, *J* = 5.9 Hz)(2t, 1H), 8.81 – 8.78 (m, 1H), 8.55 – 8.50 (m, 1H), 8.01 – 7.90 (m, 1H), 7.86 – 7.73 (m, 2H), 7.69 (d, *J* = 8.9 Hz) and 7.62 (d, *J* = 8.8 Hz) (2d, 1H), 7.55 – 6.94 (m, 6H), 5.64 and 5.50 (2s, 2H), 4.60 (d, *J* = 5.8 Hz, 2H), 4.58 – 4.49 and 4.29 – 4.21 (2m, 1H), 4.46 (d, *J* = 5.6 Hz) and 4.31 (d, *J* = 5.8 Hz) (2d, 2H), 4.19 and 3.84 (2s, 2H), 1.23 (d, *J* = 6.3 Hz) and 0.99 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR(282 MHz, DMSO-*d*₆) δ -121.22, -121.73; MS (ES⁺): 594.6 & 596.6 (M+1); 628.5 & 630.6 (M+Na).

Scheme 192

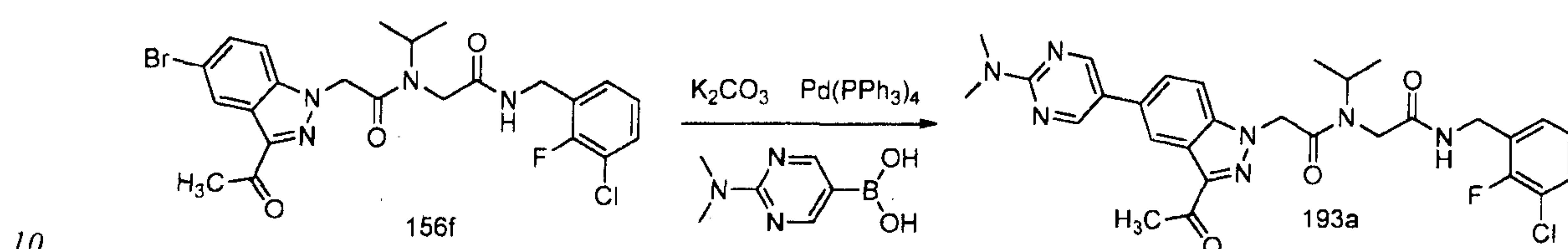


Preparation of 2-(3-acetyl-5-(3,3-difluoropiperidine-1-carbonyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**192a**)

Reaction of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**165b**) (50 mg, 0.1 mmol) with 3,3-difluoropiperidine hydrochloride (24 mg, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column

chromatography [silica (4 g), eluting with MeOH in DCM (1:0 to 19:1)] 2-(3-acetyl-5-(3,3-difluoropiperidine-1-carbonyl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**192a**) (39 mg, 65%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.47 (t, *J* = 5.8 Hz, 1H), 8.39 (s, 1H), 8.22 (d, *J* = 1.6 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.45 (td, *J* = 7.7, 1.7 Hz, 1H), 7.28 – 7.16 (m, 2H), 7.09 (td, *J* = 7.9, 1.0 Hz, 1H), 5.48 (s, 2H), 4.34 (d, *J* = 5.7 Hz, 2H), 4.00 (s, 2H), 3.96 – 3.42 (m, 4H), 3.17 – 3.04 (m, 1H), 2.44 (s, 3H), 2.20 – 1.98 (m, 2H), 1.70 (bs, 2H), 1.05 – 0.82 (m, 4H); MS (ES⁺): 603.6 (M+1); MS (ES⁻): 601.6 (M-1), 637.6, 639.6 (M+Cl).

Scheme 193



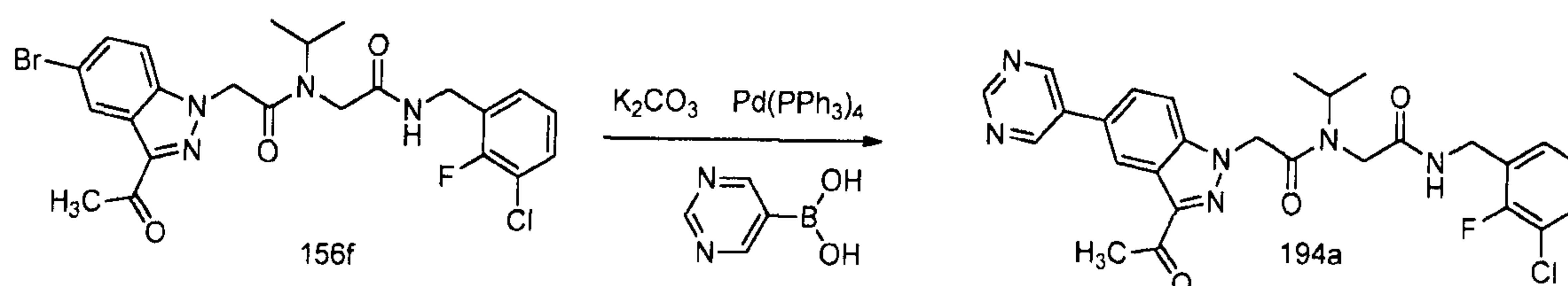
Preparation of 2-(3-acetyl-5-(2-(dimethylamino)pyrimidin-5-yl)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**193a**)

Reaction of 2-(3-acetyl-5-bromo-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**156f**) (150 mg, 0.28 mmol) with 2-

15 (dimethylamino)pyrimidin-5-ylboronic acid (47 mg, 0.28 mmol) according to the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 20%] 2-(3-acetyl-5-(2-(dimethylamino)pyrimidin-5-yl)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**193a**) (50 mg, 0.093 mmol, 33% yield) as a white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) (mixture of two rotamers) δ 8.84 and 8.36 (2t, *J* = 5.8 Hz, 1H), 8.71 (s, 2H), 8.31 - 8.26 (m, 1H), 7.82 – 6.92 (m, 5H), 5.73 and 5.55 (2s, 2H), 4.64 - 4.51 and 4.30 - 4.22 (2m, 1H), 4.48 and 4.32 (2d, *J* = 5.6 Hz, 2H), 4.19 and 3.85 (2s, 2H), 3.199 and 3.19 (2s, 6H), 2.63 (s, 3H), 1.25 and 1.00 (2d, *J* = 6.7 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) (mixture of two rotamers) δ -121.20, -121.74; MS (ES⁺): 580.6 (M+1), MS (ES⁻): 614.5 (M+Cl).

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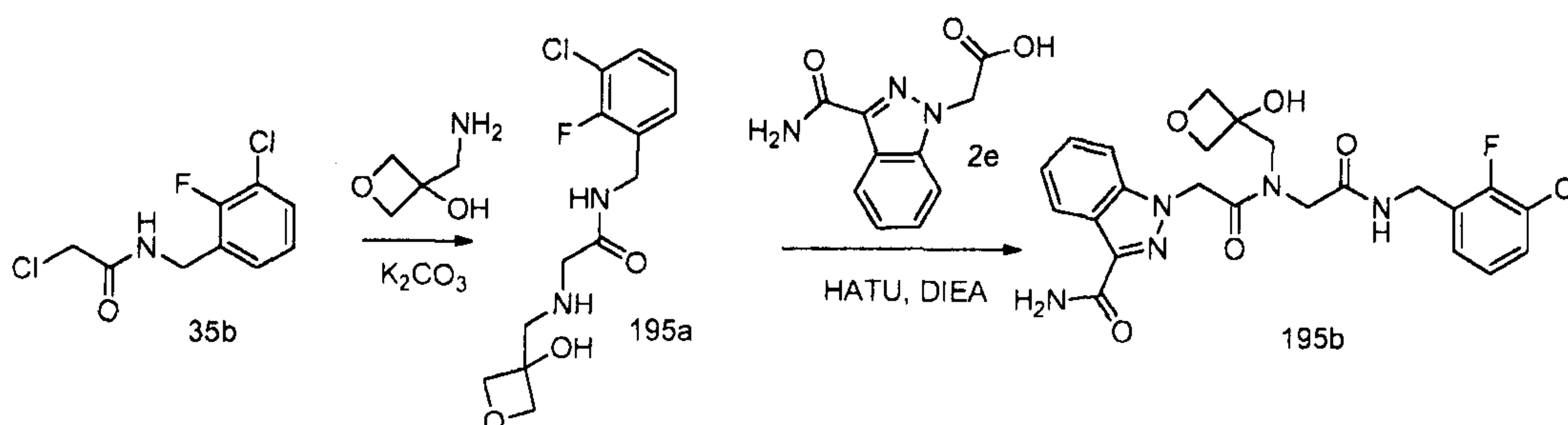
Scheme 194



Preparation of 2-(3-acetyl-5-(pyrimidin-5-yl)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**194a**)

Reaction of 2-(3-acetyl-5-bromo-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**156f**) (150 mg, 0.28 mmol) with pyrimidin-5ylboronic acid (0.035 g, 0.28 mmol) according the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 20%] 2-(3-acetyl-5-(pyrimidin-5-yl)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**194a**) (98 mg, 0.18 mmol, 65% yield) as a white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 9.228 and 9.22 (2s, 1H), 9.187 and 9.18 (2s, 2H), 8.85 and 8.36 (2t, J = 5.6 Hz, 1H), 8.51 - 8.44 (m, 1H), 7.97 - 7.75 (m, 2H), 7.57 - 6.96 (m, 3H), 5.77 and 5.59 (2s, 2H), 4.65 - 4.52 and 4.30 - 4.17 (2m, 1H), 4.48 and 4.32 (2d, J = 5.8 Hz, 2H), 4.20 and 3.86 (2s, 2H), 2.65 (s, 3H), 1.27 and 1.01 (2d, J = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) (mixture of two rotamers) δ -121.20, -121.74; MS (ES⁺): 537.5 (M+1), 559.6 (M+Na); MS (ES⁻): 571.5 (M+Cl).

Scheme 195



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((3-hydroxyoxetan-3-yl)methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**195b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((2-(3-hydroxyoxetan-3-yl)ethyl)amino)acetamide (**195a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (410 mg, 1.74 mmol) with 3-(aminomethyl)oxetan-3-ol (269 mg, 2.61 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup N-(3-chloro-2-fluorobenzyl)-2-((3-hydroxyoxetan-3-yl)methylamino)acetamide (**195a**) (250 mg, 0.83 mmol, 48%) as an oil which was used in the next step without further purification; MS (ES⁺) 303.4 (M+1); (ES⁻) 301.3 (M-1).

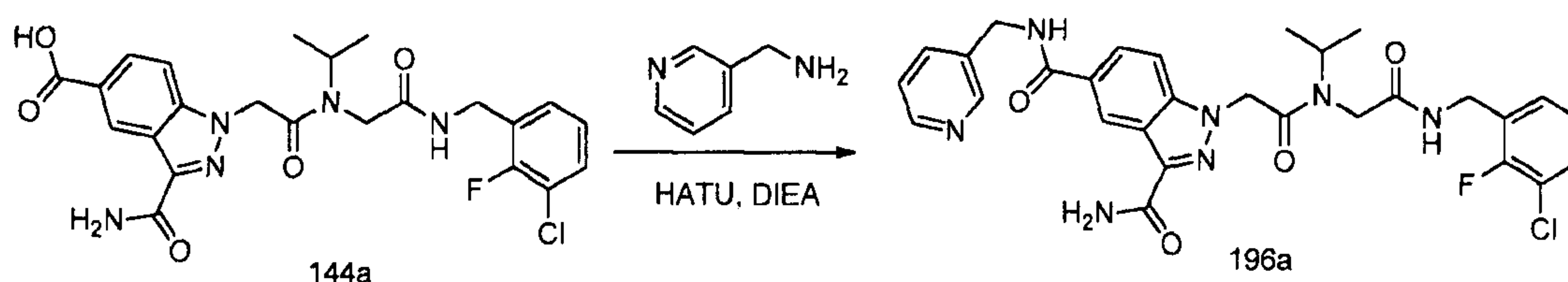
Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((3-hydroxyoxetan-3-yl)methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**195b**)

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Reaction of N-(3-chloro-2-fluorobenzyl)-2-((2-(3-hydroxyoxetan-3-yl)ethyl)amino)acetamide (195a) (250 mg, 0.83 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (2e) (181 mg, 0.83 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with MeOH in DCM 0 to 50%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((3-hydroxyoxetan-3-yl)methyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (195b) (85 mg, 0.17 mmol, 20% yield) as a white solid as a mixture as a rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.81 (t, *J* = 5.7 Hz) & 8.58 (t, *J* = 5.8 Hz) (2t, 1H, D₂O exchangeable), 8.21 – 8.16 (m, 1H), 7.74 & 7.71 (2s, 1H), 7.59 – 7.02 (m, 7H), 6.52 & 6.05 (2s, 1H, D₂O exchangeable), 5.63 & 5.45 (2s, 2H), 4.61 – 4.29 (m, 8H), 4.04 & 3.94 (2s, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.39, -121.56; MS (ES⁺): 526.5 (M+Na); MS (ES⁻): 502.4 (M-1).

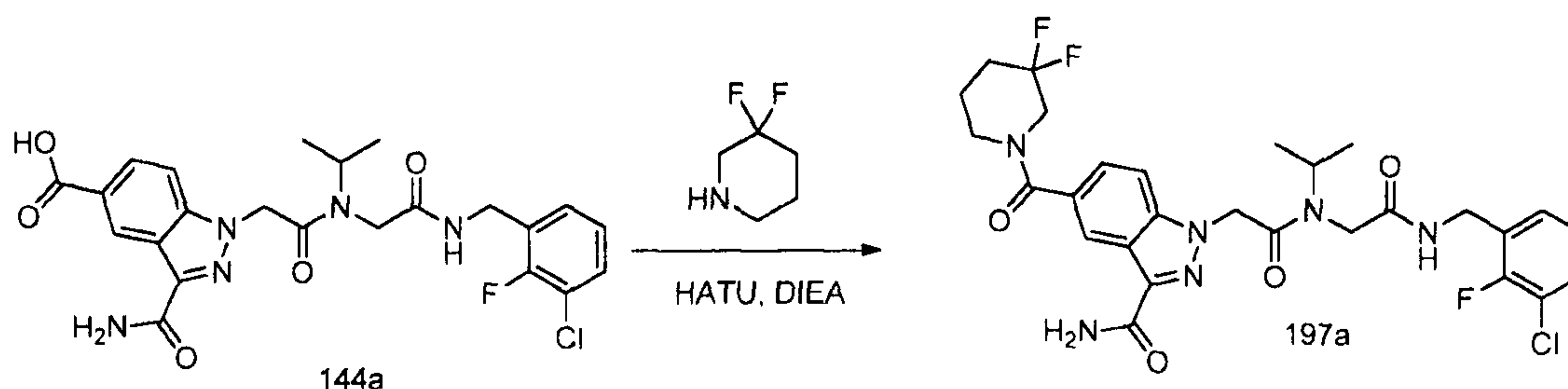
Scheme 196



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-(pyridin-3-ylmethyl)-1H-indazole-3,5-dicarboxamide (196a)

Reaction of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (144a) (50 mg, 0.1 mmol) with pyridin-3-ylmethanamine (0.015 mL, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (4 g), eluting with MeOH in DCM (1:0 to 9:1)] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-(pyridin-3-ylmethyl)-1H-indazole-3,5-dicarboxamide (196a) (32 mg, 54%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (mixture of two rotamers) δ 9.30 – 9.21 (m, 1H), 8.83 (t, *J* = 5.7 Hz) and 8.36 (t, *J* = 6.0 Hz) (2t, 1H) 8.78 – 8.74 (m, 1H), 8.61 – 8.55 (m, 1H), 8.46 (dt, *J* = 4.8, 1.6 Hz, 1H), 7.98 – 6.94 (m, 9H), 5.63 and 5.49 (2s, 2H), 4.60-4.45 and 4.30-4.20 (2m, 1H), 4.53 (d, *J* = 6.0 Hz, 2H), 4.46 (d, *J* = 5.6 Hz) and 4.31 (d, *J* = 5.9 Hz) (2d, 2H), 4.18 and 3.83 (2s, 2H), 1.23 (d, *J* = 6.3 Hz) and 0.99 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.22, -121.73; MS (ES⁺): 594.6 (M+1); MS (ES⁻): 628.6 & 630.6 (M+Cl).

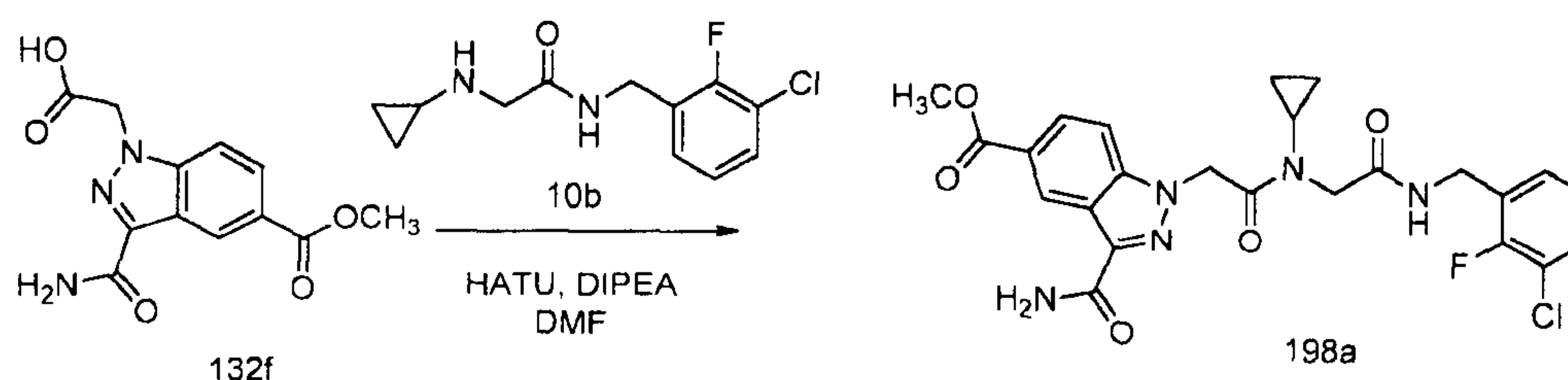
Scheme 197



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropiperidine-1-carbonyl)-1H-indazole-3-carboxamide (**197a**)

- 5 Reaction of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**144a**) (50 mg, 0.1 mmol) with 3,3-difluoropiperidine hydrochloride (24 mg, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (8 g), eluting with MeOH in DCM (1:0 to 19:1)] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropiperidine-1-carbonyl)-1H-indazole-3-carboxamide (**197a**) (43 mg, 71%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.84 (t, *J* = 5.8 Hz) and 8.37 (t, *J* = 5.9 Hz) (2t, 1H), 8.21 (bs, 1H), 7.82 and 7.80 (2s, 1H), 7.74 – 7.58 (m, 1H), 7.55 – 6.96 (m, 5H), 5.64 and 5.50 (2s, 2H), 4.63 – 4.49 and 4.29 – 4.21 2(m, 1H), , 4.46 (d, *J* = 5.6 Hz) and 4.31 (d, *J* = 5.8 Hz) (2d, 2H), 4.18 and 3.84 (2s, 2H), 4.10 - 3.20 (m, 4H), 2.21 – 2.02 (m, 2H), 1.71 (bs, 2H), 1.24 (d, *J* = 6.4 Hz) and 0.99 (d, *J* = 6.8 Hz) (2d, 6H); MS (ES⁺): 607.6 & 609.6 (M+1).
- 10
- 15

Scheme 198

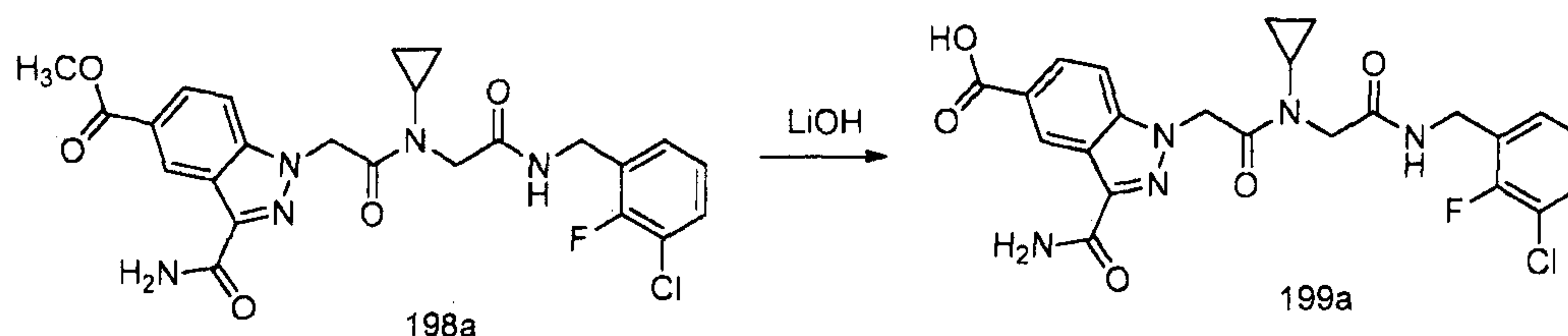


- Preparation of methyl 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**198a**)
- 20

- Reaction of 2-(3-carbamoyl-5-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid, TFA adduct (**132f**) (4.38 g, 11.19 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (3.22 g, 12.54 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (40 g), eluting with DMA80 in DCM 0 to 30%] methyl 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-
- 25

oxoethyl)(cyclopropylamino)-2-oxoethyl)-1H-indazole-5-carboxylate (**198a**) (4.23 g, 8.20 mmol, 73% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.91 – 8.84 (m, 1H), 8.50 (t, $J = 5.8$ Hz, 1H), 7.97 (dd, $J = 8.9, 1.6$ Hz, 1H), 7.90 (s, 1H), 7.80 – 7.73 (m, 1H), 7.60 – 7.53 (m, 1H), 7.50 – 7.41 (m, 1H), 7.26 – 7.17 (m, 1H), 7.15 – 7.05 (m, 1H), 5.72 (s, 2H), 4.33 (d, $J = 5.7$ Hz, 2H), 3.98 (s, 2H), 3.90 (s, 3H), 3.14 – 3.01 (m, 1H), 1.06 – 0.97 (m, 2H), 0.96 – 0.86 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.56; MS (ES+) 516.4 (M+1); (ES-) 514.3 (M-1).

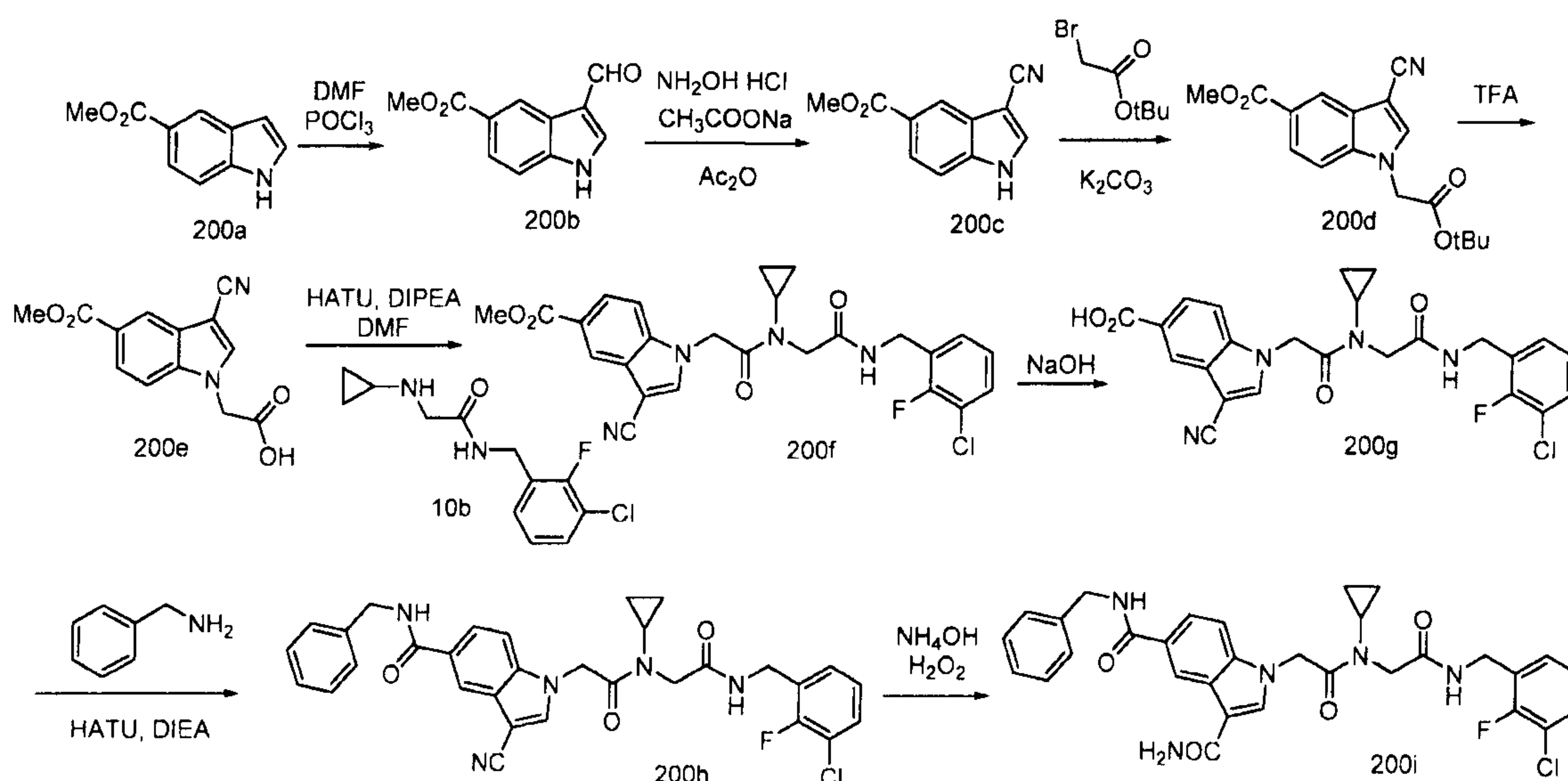
Scheme 199



10 Preparation of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**199a**)

Reaction of methyl 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**198a**) (4.17 g, 8.08 mmol) in THF (50 mL) and water (50 mL) using a solution of lithium hydroxide hydrate
 15 (2.37 g, 56.6 mmol) in water (20 mL) according to the procedure reported in step-2 of Scheme 29 gave after workup 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**199a**) (4.06 g, 8.09 mmol, 100 % yield) as a white solid, which was used in the next step without further purification; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.84 (s, 1H), 8.89 – 8.81 (m, 1H), 8.56 (t, $J =$
 20 5.9 Hz, 1H), 8.01 – 7.91 (m, 1H), 7.87 (s, 1H), 7.79 – 7.70 (m, 1H), 7.53 (s, 1H), 7.50 – 7.41 (m, 1H), 7.28 – 7.19 (m, 1H), 7.14 – 7.05 (m, 1H), 5.72 (s, 2H), 4.33 (d, $J = 5.7$ Hz, 2H), 3.99 (s, 2H), 3.12 – 2.99 (m, 1H), 1.11 – 0.98 (m, 2H), 0.98 – 0.84 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.58; MS (ES+): 502.5 (M+1); (ES-): 501.5 (M-1).

Scheme 200



Preparation of N-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-3-cyano-1H-indole-5-carboxamide (**200i**)

5 Step-1: Preparation of methyl 3-formyl-1H-indole-5-carboxylate (**200b**)

To a solution of methyl 1H-indole-5-carboxylate (**200a**) (4 g, 22.83 mmol) in DMF (36 mL) cooled to 0 °C was added phosphoryl trichloride (2.87 mL, 31.1 mmol) and stirred at RT for 2 h. The reaction mixture was quenched with water (130 mL) refluxed for 15 min, cooled to RT and solid obtained was collected by filtration, washed with water, hexanes, dried under vacuum to give methyl 3-formyl-1H-indole-5-carboxylate (**200b**) (4.38 g, 94%) as a light brown solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.45 (s, 1H), 9.98 (s, 1H), 8.77 (dd, *J* = 1.7, 0.7 Hz, 1H), 8.45 (s, 1H), 7.88 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.61 (dd, *J* = 8.6, 0.7 Hz, 1H), 3.87 (s, 3H); MS (ES⁺): 204.2 (M+1).

Step-2: Preparation of methyl 3-cyano-1H-indole-5-carboxylate (**200c**)

15 To a solution of methyl 3-formyl-1H-indole-5-carboxylate (**200b**) (1.02 g, 5 mmol), hydroxylamine hydrochloride (556 mg, 8 mmol), and sodium acetate (451 mg, 5.5 mmol) in acetic acid (7.5 mL) was added acetic anhydride (1.0 mL, 10.6 mmol) and heated at reflux for 6.5 h. The reaction mixture was diluted with ice-water, solid separated was collected by filtration, washed with water, dried under vacuum to give methyl 3-cyano-1H-indole-5-carboxylate (**200c**) (856 mg, 86%) as a brown solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.57 (s, 1H), 8.42 (s, 1H), 8.25 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.89 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.66 (dd, *J* = 8.6, 0.7 Hz, 1H), 3.88 (s, 3H); MS (ES⁺): 223.3 (M+Na).

Step-3: Preparation of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-cyano-1H-indole-5-carboxylate (**200d**)

Reaction of methyl 3-cyano-1H-indole-5-carboxylate (**200c**) (800 mg, 4.0 mmol) with *tert*-butyl 2-bromoacetate (0.89 mL, 5.99 mmol) according to the procedure reported in step-1 of Scheme 56 gave after workup methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-cyano-1H-indole-5-carboxylate (**200d**) (1.29 g, 4 mmol) which was used as such for next step; MS (ES⁺): 337.4 (M+Na).

Step-4: Preparation of 2-(3-cyano-5-(methoxycarbonyl)-1H-indol-1-yl)acetic acid (**200e**)

Reaction of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-cyano-1H-indole-5-carboxylate (**200d**) from above (1.27 g) with TFA (4.55 mL, 59.1 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup 2-(3-cyano-5-(methoxycarbonyl)-1H-indol-1-yl)acetic acid (**200e**) which was used as such in next step; MS (ES⁺): 281.3 (M+Na).

Step-5: Preparation of methyl 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-3-cyano-1H-indole-5-carboxylate (**200f**)

Reaction of 2-(3-cyano-5-(methoxycarbonyl)-1H-indol-1-yl)acetic acid (**200e**) (crude from above, 4 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (1.21 g, 4.73 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (12 g), eluting with hexanes/10% MeOH in EtOAc (1:0 to 1:1)] methyl 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-3-cyano-1H-indole-5-carboxylate (**200f**) (446 mg, 23% yield for three steps) as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.46 (t, *J* = 5.8 Hz, 1H), 8.34 (s, 1H), 8.26 – 8.23 (m, 1H), 7.87 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.50 – 7.41 (m, 1H), 7.25 – 7.18 (m, 1H), 7.12 – 7.04 (m, 1H), 5.53 (s, 2H), 4.34 (d, *J* = 5.7 Hz, 2H), 3.98 (s, 2H), 3.89 (s, 3H), 3.18 – 3.00 (m, 1H), 1.03 – 0.85 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.57; MS (ES⁺): 497.5 (M+1); MS (ES⁻): 495.5 & 497.5 (M-1).

Step-6: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-3-cyano-1H-indole-5-carboxylic acid (**200g**)

Reaction of methyl 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-3-cyano-1H-indole-5-carboxylate (**200f**) (429 mg, 0.863 mmol) in MeOH (30 mL) using 2 N aqueous NaOH (2.59 mL, 5.18 mmol) according to the procedure reported in step-4 of scheme 43 gave after workup 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-3-cyano-1H-indole-5-

carboxylic acid (**200g**) (371 mg, 89% yield) as an off-white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.46 (t, $J = 5.8$ Hz, 1H), 8.31 (s, 1H), 8.24 – 8.21 (m, 1H), 7.86 (dd, $J = 8.7$, 1.6 Hz, 1H), 7.67 (d, $J = 8.7$ Hz, 1H), 7.45 (td, $J = 7.6$, 1.8 Hz, 1H), 7.27 – 7.17 (m, 1H), 7.09 (td, $J = 7.9$, 1.0 Hz, 1H), 5.52 (s, 2H), 4.34 (d, $J = 5.7$ Hz, 2H), 3.98 (s, 2H), 3.18 – 3.00 (m, 1H), 1.09 – 0.79 (m, 4H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.56; MS (ES-): 517.4 & 519.5 (M+Cl).

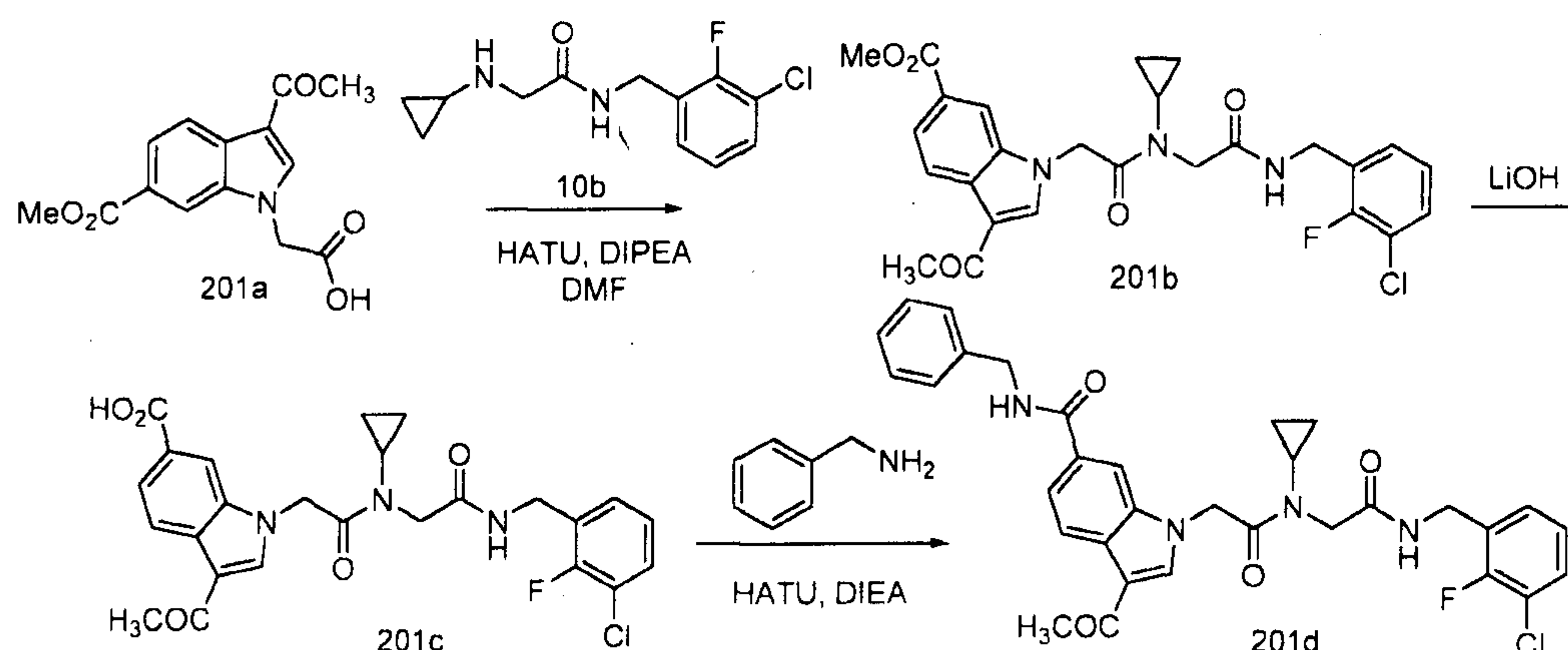
Step-7: Preparation of N-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-3-cyano-1H-indole-5-carboxamide (**200h**)

Reaction of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-3-cyano-1H-indole-5-carboxylic acid (**200g**) (100 mg, 0.21 mmol) with phenylmethanamine (0.034 mL, 0.31 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (12 g), eluting DCM/MeOH (1:0 to 19:1)] N-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-3-cyano-1H-indole-5-carboxamide (**200h**) as a light brown gum; MS (ES-): 606.6 (M+Cl).

Step-8: Preparation of N-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-3-cyano-1H-indole-5-carboxamide (**200i**)

Reaction of N-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-3-cyano-1H-indole-5-carboxamide (**200h**) (132 mg) in ethanol (4 mL) using conc. NH_4OH (1.5 mL) and H_2O_2 (aq. 35%, 0.066 mL, 0.74 mmol) according to the procedure reported in Scheme 65 gave after workup and purification by flash column chromatography [silica (4 g), eluting with DCM/MeOH (1:0 to 19:1)] N-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-3-cyano-1H-indole-5-carboxamide (**200i**) (56 mg, 51% for two steps) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.99 (t, $J = 6.0$ Hz, 1H), 8.71 (d, $J = 1.8$ Hz, 1H), 8.47 (t, $J = 5.8$ Hz, 1H), 8.01 (s, 1H), 7.71 (dd, $J = 8.7$, 1.7 Hz, 1H), 7.54 – 6.87 (m, 11H), 5.42 (s, 2H), 4.50 (d, $J = 6.0$ Hz, 2H), 4.34 (d, $J = 5.7$ Hz, 2H), 3.99 (s, 2H), 3.15 – 3.02 (m, 1H), 1.06 – 0.82 (m, 4H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.61; MS (ES+): 590.7 & 592.6 (M+1); MS (ES-): 624.5 & 626.6 (M+Cl).

Scheme 201



Preparation of 3-acetyl-N-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-6-carboxamide (**201d**)

Step-1: Preparation of methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-6-carboxylate (**201b**)

- 5 Reaction of 2-(3-acetyl-6-(methoxycarbonyl)-1H-indol-1-yl)acetic acid (**201a**) TFA adduct (10.77 g, 27.7 mmol, Prepared according to the procedure reported by Altmann, Eva et al; in PCT Int. Appl., WO 2012/093101) with N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (7.10 g, 27.7 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and trituration of crude with EtOAc, methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-6-carboxylate (**201b**) (8.17 g, 57%) as an off-white; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.55 – 8.43 (m, 2H), 8.27 (dd, *J* = 8.4, 0.7 Hz, 1H), 8.15 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.82 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.48 – 7.36 (m, 1H), 7.26 – 7.16 (m, 1H), 7.04 (td, *J* = 7.9, 1.1 Hz, 1H), 5.57 (s, 2H), 4.35 (d, *J* = 5.8 Hz, 2H), 3.99 (s, 2H), 3.82 (s, 3H), 3.20 – 3.05 (m, 1H), 2.45 (s, 3H), 1.08 – 0.80 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.72; MS (ES⁺): 514.5 & 516.5 (M+1).

Step-2: Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-6-carboxylic acid (**201c**)

- 20 Reaction of methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-6-carboxylate (**201b**) (8 g, 15.57 mmol) in THF (100 mL) and MeOH (100 mL) using a solution of lithium hydroxide hydrate (4 g, 93 mmol) in water (100 mL) according to the procedure reported in step-2 of Scheme 129 gave after workup 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-6-carboxylic acid (**201c**) (8.012 g) as a

light brown solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.80 (s, 1H), 8.53 – 8.41 (m, 2H), 8.24 (dd, $J = 8.4, 0.6$ Hz, 1H), 8.15 – 8.11 (m, 1H), 7.81 (dd, $J = 8.3, 1.4$ Hz, 1H), 7.45 (td, $J = 7.7, 7.2, 1.7$ Hz, 1H), 7.27 – 7.17 (m, 1H), 7.08 (td, $J = 7.9, 1.0$ Hz, 1H), 5.55 (s, 2H), 4.34 (d, $J = 5.8$ Hz, 2H), 3.99 (s, 2H), 3.20 – 3.06 (m, 1H), 2.45 (s, 3H), 1.08 – 0.82 (m, 4H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.66; MS (ES⁺): 522.5 & 524.5 (M+Na).

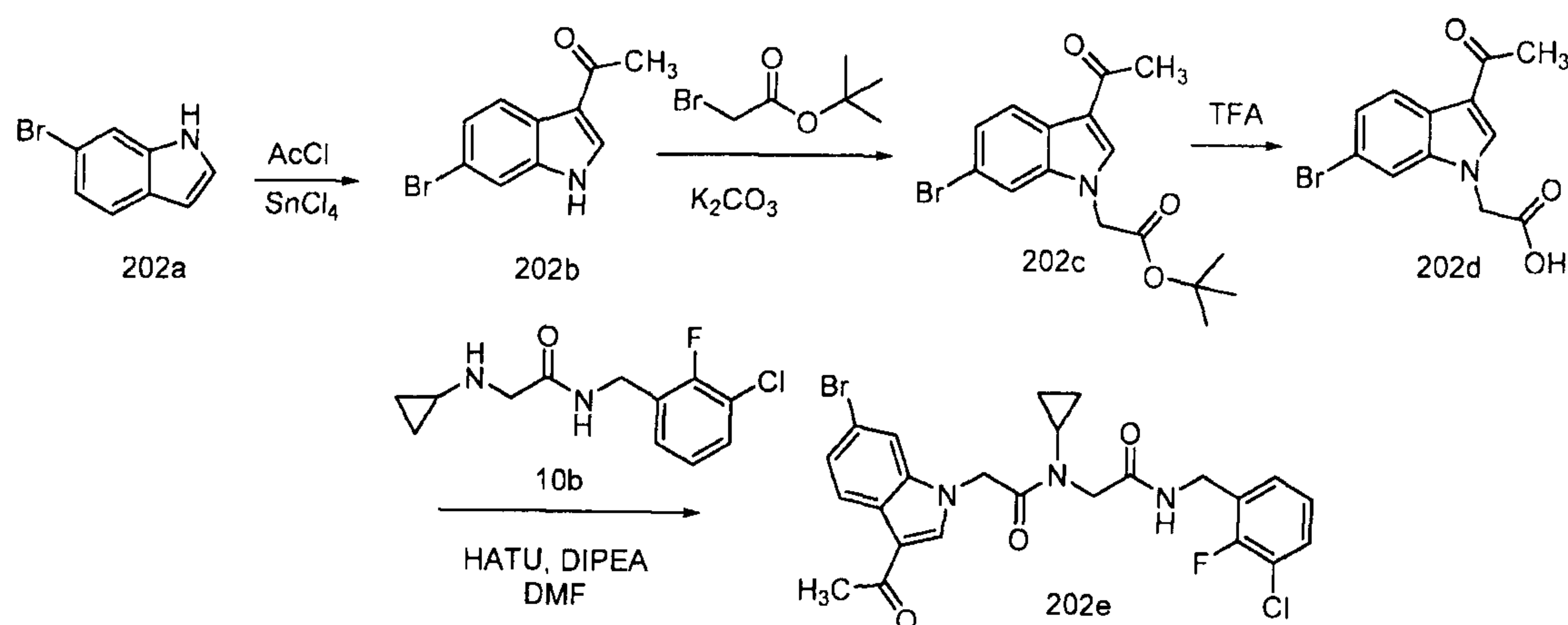
Step-3: Preparation of 3-acetyl-N-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-6-carboxamide (**201d**)

Reaction of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-6-carboxylic acid (**201c**) (50 mg, 0.1

mmol) with phenylmethanamine (0.017 mL, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (4 g), eluting DCM/MeOH (1:0 to 19:1)] 3-acetyl-N-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-6-carboxamide (**201d**) (31 mg, 53%) as a light yellow solid. ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.96 (t, $J = 6.0$ Hz, 1H), 8.54 (t, $J = 5.8$ Hz, 1H), 8.42 (s, 1H), 8.22 (d, $J = 8.3$ Hz, 1H), 8.02 (s, 1H), 7.78 (dd, $J = 8.4, 1.4$ Hz, 1H), 7.47 – 7.39 (m, 1H), 7.34 – 7.15 (m, 6H), 7.04 (t, $J = 7.9$ Hz, 1H), 5.52 (s, 2H), 4.50 (d, $J = 5.9$ Hz, 2H), 4.30 (d, $J = 5.8$ Hz, 2H), 4.01 (s, 2H), 3.22-3.02 (m, 1H), 2.45 (s, 3H), 1.05 – 0.80 (m, 4H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.58; MS (ES⁺): 589.6 (M+1); MS (ES⁻): 623.5 & 625.5 (M+Cl).

20

Scheme 202



Preparation of 2-(3-acetyl-6-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**202e**)

Step-1: Preparation of 1-(6-bromo-1H-indol-3-yl)ethanone (**202b**)

WO 2017/136395

PCT/US2017/015953

To a solution of 6-bromo-1H-indole (**202a**) (5 g, 25.5 mmol) in toluene (80 mL) at 0 °C under inert atmosphere was added acetyl chloride (2.72 mL, 38.3 mmol), stirred for 10 mins followed by dropwise addition of Tin(IV) chloride (4.49 mL, 38.3 mmol) in toluene (20 mL). The reaction mixture was stirred at 0 °C for 3h in ice-water bath and the pink fine suspension
 5 was poured into a bi-phasic layer of aqueous saturated NaHCO₃ (600 mL) and EtOAc (400 mL). The mixture was stirred vigorously for 15 min and filtered over Celite pad to remove inorganic impurities. The organic layer was separated washed with brine, dried, filtered and concentrated in vacuum to afford 1-(6-bromo-1H-indol-3-yl)ethanone (**202b**) (4.15 g, 17.43 mmol, 68% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.04 (s, 1H), 8.34 (d, J = 1.6 Hz, 1H), 8.10 (dd, J = 8.5, 0.6 Hz, 1H), 7.65 (dd, J = 1.8, 0.6 Hz, 1H), 7.31 (dd, J = 8.5, 1.8 Hz, 1H), 2.44 (s, 3H); MS (ES⁺): 238.2, 240.2 (M+2); MS (ES⁻): 236.1, 238.1 (M-2).

Step-2: Preparation of tert-butyl 2-(3-acetyl-6-bromo-1H-indol-1-yl)acetate (**202c**)

Reaction of 1-(6-bromo-1H-indol-3-yl)ethanone (**202b**) (4 g, 16.8 mmol) with *tert*-butyl 2-bromoacetate (4.97 mL, 33.6 mmol) according to the procedure reported in step-1 of Scheme
 15 56 gave after workup and trituration of crude with 20% EtOAc-hexane (40 mL), tert-butyl 2-(3-acetyl-6-bromo-1H-indol-1-yl)acetate (**202c**) (4.49 g, 12.75 mmol, 76% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.34 (s, 1H), 8.11 (dd, J = 8.5, 0.5 Hz, 1H), 7.82 (dd, J = 1.8, 0.5 Hz, 1H), 7.36 (dd, J = 8.5, 1.7 Hz, 1H), 5.14 (s, 2H), 2.43 (s, 3H), 1.44 (s, 9H); MS (ES⁺): 352.3, 354.3 (M+2), MS (ES⁻): 386.2, 388.2 (M+Cl).

20 Step-3: Preparation of 2-(3-acetyl-6-bromo-1H-indol-1-yl)acetic acid (**202d**)

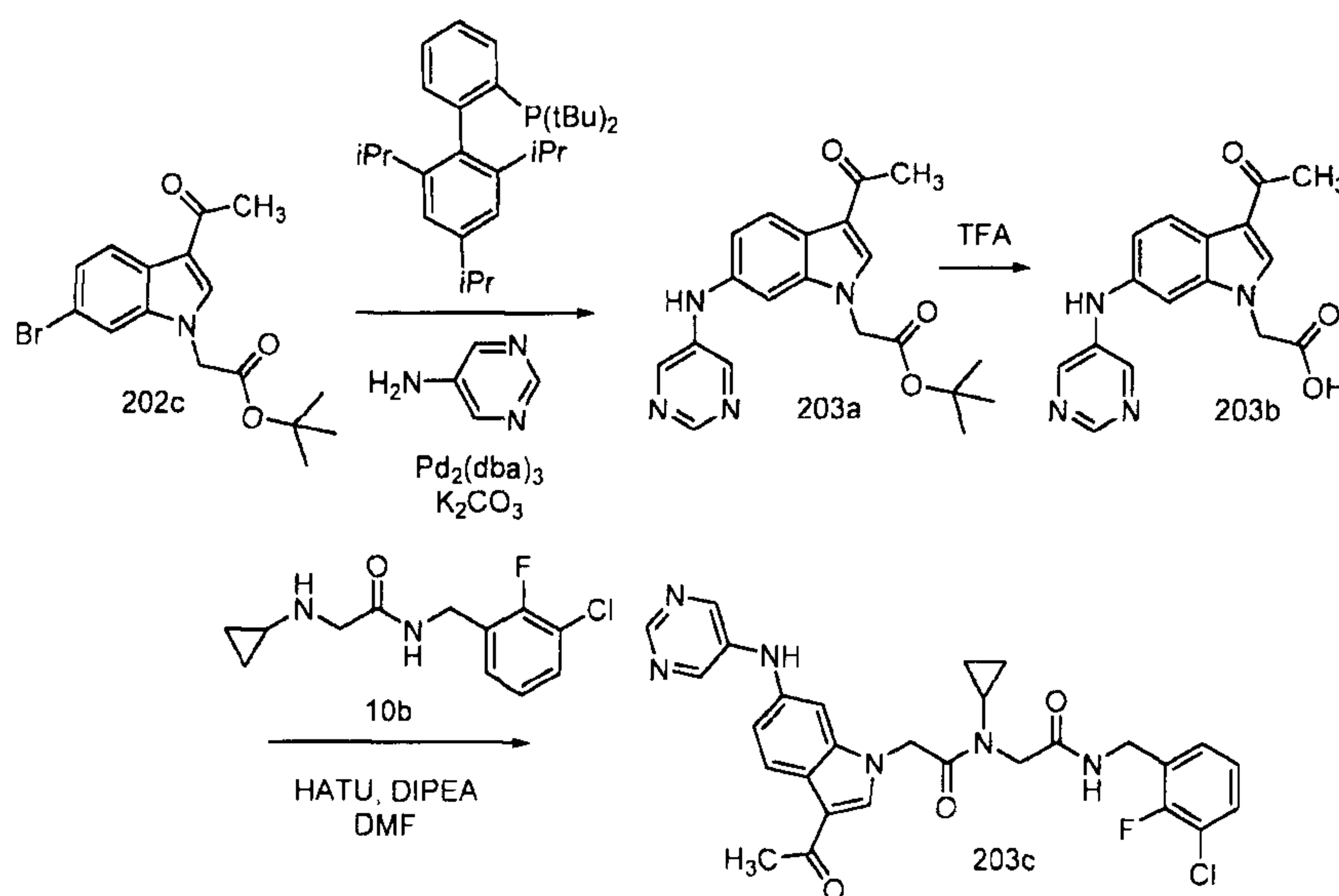
Reaction of tert-butyl 2-(3-acetyl-6-bromo-1H-indol-1-yl)acetate (**202c**) (1.5 g, 4.26 mmol) with TFA (6.56 mL, 85 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and trituration of crude with 20% EtOAc-hexane (10 mL), 2-(3-acetyl-6-bromo-1H-indol-1-yl)acetic acid (**202d**) TFA adduct (1.25 g, 4.22 mmol, 99 % yield) as an
 25 off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.26 (s, 1H, D₂O exchangeable), 8.36 (s, 1H), 8.10 (dd, J = 8.5, 0.5 Hz, 1H), 7.86 (dd, J = 1.8, 0.5 Hz, 1H), 7.36 (dd, J = 8.5, 1.7 Hz, 1H), 5.15 (s, 2H), 2.43 (s, 3H); MS (ES⁺): 296.2, 298.3 (M+2); MS (ES⁻): 294.2, 296.2 (M-2).

Step-4: Preparation of 2-(3-acetyl-6-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**202e**)
 30

Reaction of 2-(3-acetyl-6-bromo-1H-indol-1-yl)acetic acid (**202d**) (600 mg, 2.03 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (572 mg, 2.23 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification

by flash column [silica gel (24 g), eluting with DMA80 - DCM 0 to 20%] 2-(3-acetyl-6-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**202e**) (0.78 g, 1.46 mmol, 72% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.47 (t, J = 5.9 Hz, 1H), 8.30 (s, 1H), 8.10 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 1.7 Hz, 1H), 7.49 - 7.41 (m, 1H), 7.34 (dd, J = 8.5, 1.7 Hz, 1H), 7.28 - 7.19 (m, 1H), 7.09 (td, J = 7.9, 1.1 Hz, 1H), 5.45 (s, 2H), 4.35 (d, J = 5.8 Hz, 2H), 3.99 (s, 2H), 3.16 - 3.04 (m, 1H), 2.42 (s, 3H), 1.05 - 0.96 (m, 2H), 0.95 - 0.85 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.66; MS (ES⁺) 534.4, 536.4 (M+1); MS (ES⁻): 570.3 (M+Cl).

Scheme 203



Preparation of 2-(3-acetyl-6-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**203c**)

Step-1: Preparation of tert-butyl 2-(3-acetyl-6-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetate (**203a**)

Reaction of tert-butyl 2-(3-acetyl-6-bromo-1H-indol-1-yl)acetate (**202c**) (1.0 g, 2.84 mmol) with pyrimidin-5-amine (351 mg, 3.69 mmol) using potassium carbonate (785 mg, 5.68 mmol), di-tert-butyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (169 mg, 0.4 mmol), $\text{Pd}_2(\text{dba})_3$ (182 mg, 0.2 mmol) according to the procedure reported in step-1 of Scheme 97 gave after workup and purification by flash column [silica gel (40 g), eluting with DMA80 - DCM 0 to 20%] tert-butyl 2-(3-acetyl-6-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetate (**203a**) (72 mg, 1.96 mmol, 69% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.60 (s, 1H), 8.59 (s, 1H), 8.55 (s, 2H), 8.21 (s, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.26 (d, J = 1.9 Hz,

1H), 7.02 (dd, $J = 8.5, 1.9$ Hz, 1H), 5.76 (s, 1H), 5.10 (s, 2H), 2.42 (s, 3H), 1.43 (s, 9H); MS (ES+) 367.5 (M+1); MS (ES-): 365.4 (M-1).

Step-2: Preparation of 2-(3-acetyl-6-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**203b**)

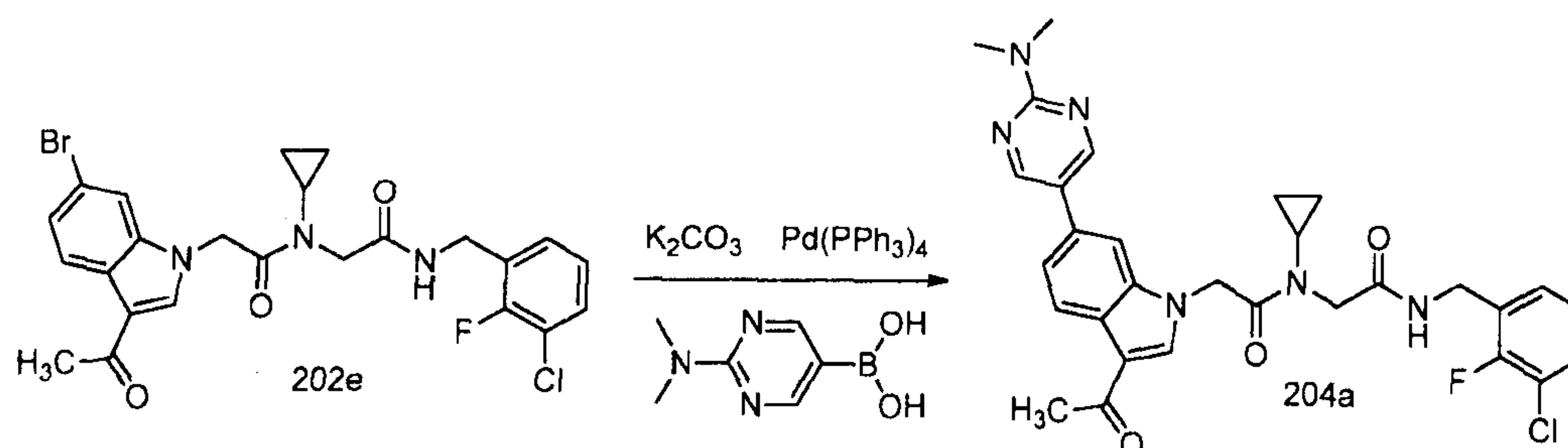
Reaction of tert-butyl 2-(3-acetyl-6-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetate (**203a**) (530 mg, 1.45 mmol) with TFA (1.47 mL, 19.05 mmol) according to the procedure reported in step-2 of Scheme 2 gave after workup and trituration of crude with 30% EtOAc-hexane (10 mL), 2-(3-acetyl-6-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**203b**) TFA adduct (470 mg, 1.11 mmol, 77% yield) as an orange solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.60 (s, 1H), 8.55 (s, 2H), 8.23 (s, 1H), 8.09 (d, $J = 8.5$ Hz, 1H), 7.30 (d, $J = 1.9$ Hz, 1H), 7.03 (dd, $J = 8.5, 2.0$ Hz, 1H), 5.11 (s, 2H), 2.42 (s, 3H).

Step-3: Preparation of 2-(3-acetyl-6-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**203c**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (66 mg, 0.26 mmol) with 2-(3-acetyl-6-(pyrimidin-5-ylamino)-1H-indol-1-yl)acetic acid (**203b**) (80 mg, 0.26 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with DMA80 - DCM 0 to 30%] 2-(3-acetyl-6-(pyrimidin-5-ylamino)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**203c**) (65 mg, 0.12 mmol, 46% yield) as an off-white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.56 (s, 1H), 8.53 (s, 1H), 8.51 (s, 2H), 8.44 (t, $J = 5.9$ Hz, 1H), 8.21 (s, 1H), 8.09 (d, $J = 8.5$ Hz, 1H), 7.43 (td, $J = 7.7, 7.2, 1.7$ Hz, 1H), 7.27 – 7.17 (m, 2H), 7.14 – 6.98 (m, 2H), 5.41 (s, 2H), 4.31 (d, $J = 5.7$ Hz, 2H), 3.98 (s, 2H), 3.12 – 2.98 (m, 1H), 2.41 (s, 3H), 1.01 – 0.94 (m, 2H), 0.94 – 0.86 (m, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.62; MS (ES+): 549.5 (M+1), 571.5 (M+Na), MS (ES-): 547.5 (M-1).

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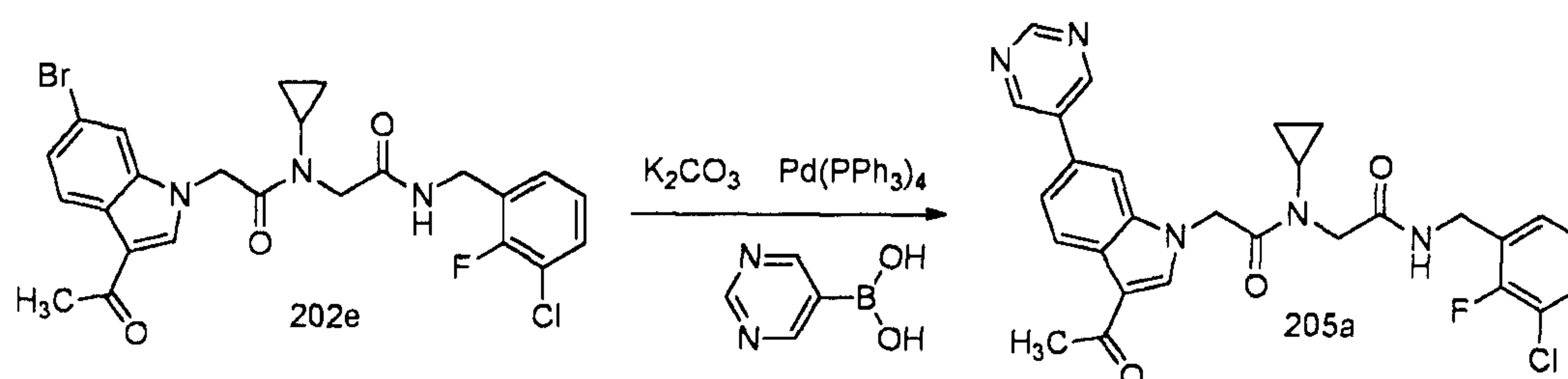
Scheme 204



Preparation of 2-(3-acetyl-6-(2-(dimethylamino)pyrimidin-5-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**204a**)

Reaction of 2-(3-acetyl-6-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**202e**) (150 mg, 0.28 mmol) with 2-(dimethylamino)pyrimidin-5-ylboronic acid (56 mg, 0.34 mmol) according to the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 20%] 2-(3-acetyl-6-(2-(dimethylamino)pyrimidin-5-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**204a**) (85 mg, 0.15 mmol, 53% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.73 (s, 2H), 8.51 (t, *J* = 5.9 Hz, 1H), 8.29 (s, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 7.69 (bs, 1H), 7.49 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.24-7.16 (m, 1H), 6.97-6.86 (m, 1H), 5.49 (s, 2H), 4.36 (d, *J* = 5.8 Hz, 2H), 4.01 (s, 2H), 3.19 – 3.11 (m, 7H), 2.44 (s, 3H), 1.03 – 0.96 (m, 2H), 0.96 – 0.88 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.72; MS (ES⁺): 577.5 (M+1); MS (ES⁻): 611.4 (M+Cl).

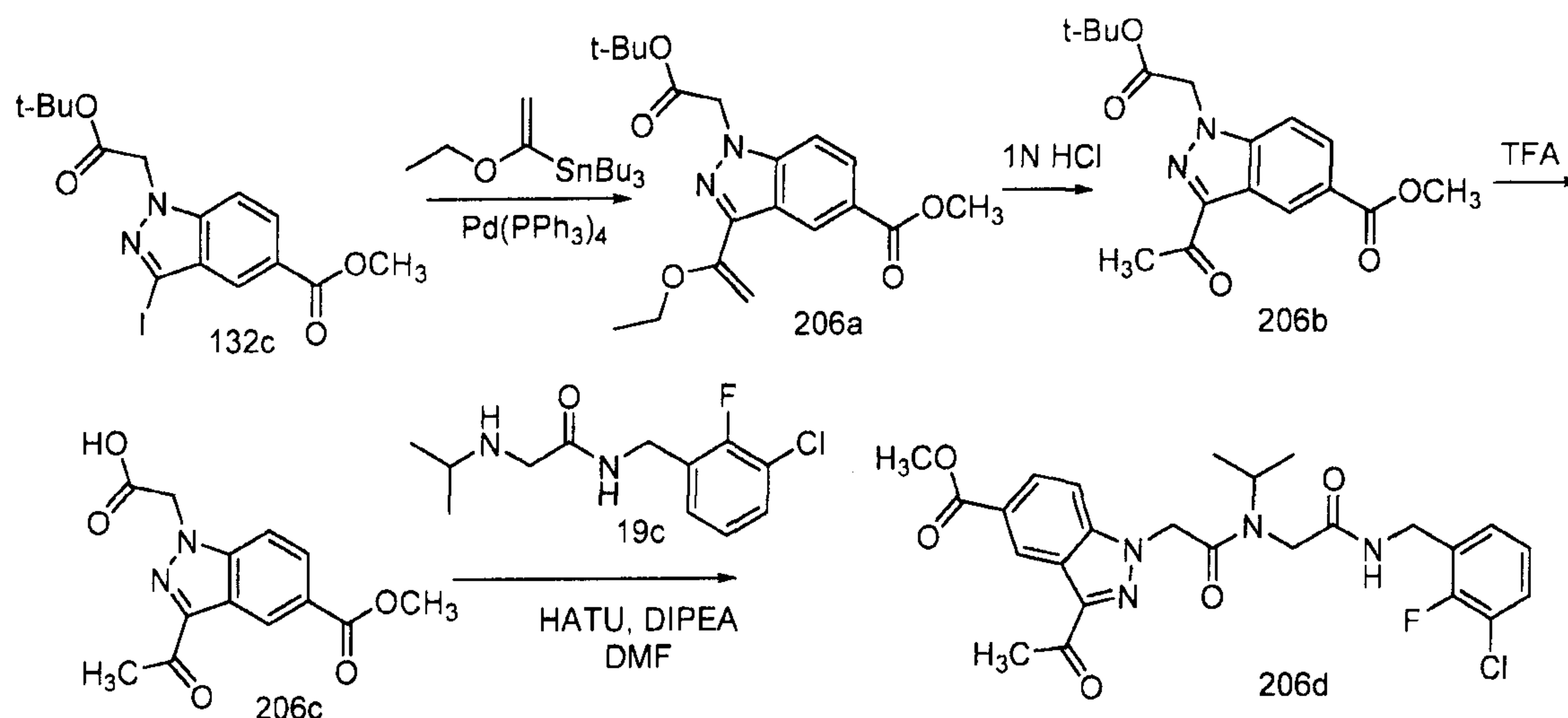
Scheme 205



Preparation of 2-(3-acetyl-6-(pyrimidin-5-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**205a**)

Reaction of 2-(3-acetyl-6-bromo-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**202e**) (150 mg, 0.28 mmol) with pyrimidin-5-ylboronic acid (42 mg, 0.34 mmol) according to the procedure reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with CMA80 in CHCl₃ 0 to 20%] 2-(3-acetyl-6-(pyrimidin-5-yl)-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**205a**) (60 mg, 0.11 mmol, 40% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.18 (s, 2H), 9.12 (s, 1H), 8.51 (t, *J* = 5.9 Hz, 1H), 8.38 (s, 1H), 8.29 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 1.6 Hz, 1H), 7.67 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.34 (td, *J* = 7.7, 7.2, 1.7 Hz, 1H), 7.21 – 7.12 (m, 1H), 6.88 (td, *J* = 7.9, 1.1 Hz, 1H), 5.54 (s, 2H), 4.35 (d, *J* = 5.7 Hz, 2H), 4.01 (s, 2H), 3.23 – 3.11 (m, 1H), 2.46 (s, 3H), 1.05 – 0.97 (m, 2H), 0.97 – 0.90 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.60; MS (ES⁺): 534.5 (M+1), MS (ES⁻): 532.4 (M-1), 568.4 (M+Cl).

Scheme 206



Preparation of methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**206d**)

5 Step-1: Preparation of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-(1-ethoxyvinyl)-1H-indazole-5-carboxylate (**206a**)

To a solution of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-iodo-1H-indazole-5-carboxylate (**132c**) (9.2 g, 22.10 mmol) in toluene (75 mL) under Argon atmosphere was added tributyl(1-ethoxyvinyl)stannane (9.98 g, 27.6 mmol), Pd(Ph₃P)₄ (2.55 g, 2.210 mmol) and
 10 heated at 120 °C for 15h. The reaction mixture was cooled to room temperature, diluted with EtOAc (200 mL), filtered through a Celite pad. The filtrate was washed with water, brine, dried and concentrated in vacuum. The residue obtained was purified by chromatography [silica (40 g), eluting with EtOAc in hexane 0 to 40%] to afford methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-(1-ethoxyvinyl)-1H-indazole-5-carboxylate (**206a**) (7.5 g, 19.31 mmol, 87 %
 15 yield) as a yellow oil; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.67 (dd, *J* = 1.6, 0.8 Hz, 1H), 7.97 (dd, *J* = 8.9, 1.6 Hz, 1H), 7.73 (dd, *J* = 8.9, 0.8 Hz, 1H), 5.34 (s, 2H), 4.97 (d, *J* = 2.3 Hz, 1H), 4.46 (d, *J* = 2.3 Hz, 1H), 4.03 (q, *J* = 6.9 Hz, 2H), 3.88 (s, 3H), 1.45 (m, 3H), 1.40 (s, 9H), 0.85 (t, *J* = 7.2 Hz, 3H); MS (ES⁺): 361.5 (M+1), 383.5 (M+Na); MS (ES⁻): 359.3 (M-1).

20 Step-2: Preparation of methyl 3-acetyl-1-(2-(tert-butoxy)-2-oxoethyl)-1H-indazole-5-carboxylate (**206b**)

To a solution of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-(1-ethoxyvinyl)-1H-indazole-5-carboxylate (**206a**) from step-1 in EtOAc (200 mL) was added HCl (1 N, 120 mL) and sonicated for 10 min. The organic phase was separated, dried, concentrated in vacuum to

afford methyl 3-acetyl-1-(2-(tert-butoxy)-2-oxoethyl)-1H-indazole-5-carboxylate (**206b**) (6.2 g, 18.65 mmol, 84 % yield over 2 steps) as a white solid, which was used in the next step without further purification; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.84 (dd, $J = 1.6, 0.8$ Hz, 1H), 8.06 (dd, $J = 8.9, 1.6$ Hz, 1H), 7.89 (dd, $J = 8.9, 0.9$ Hz, 1H), 5.51 (s, 2H), 3.91 (s, 3H), 2.65 (s, 3H), 1.42 (s, 9H); MS (ES^+), 355.4 ($\text{M}+\text{Na}$); 331.4 ($\text{M}-1$).

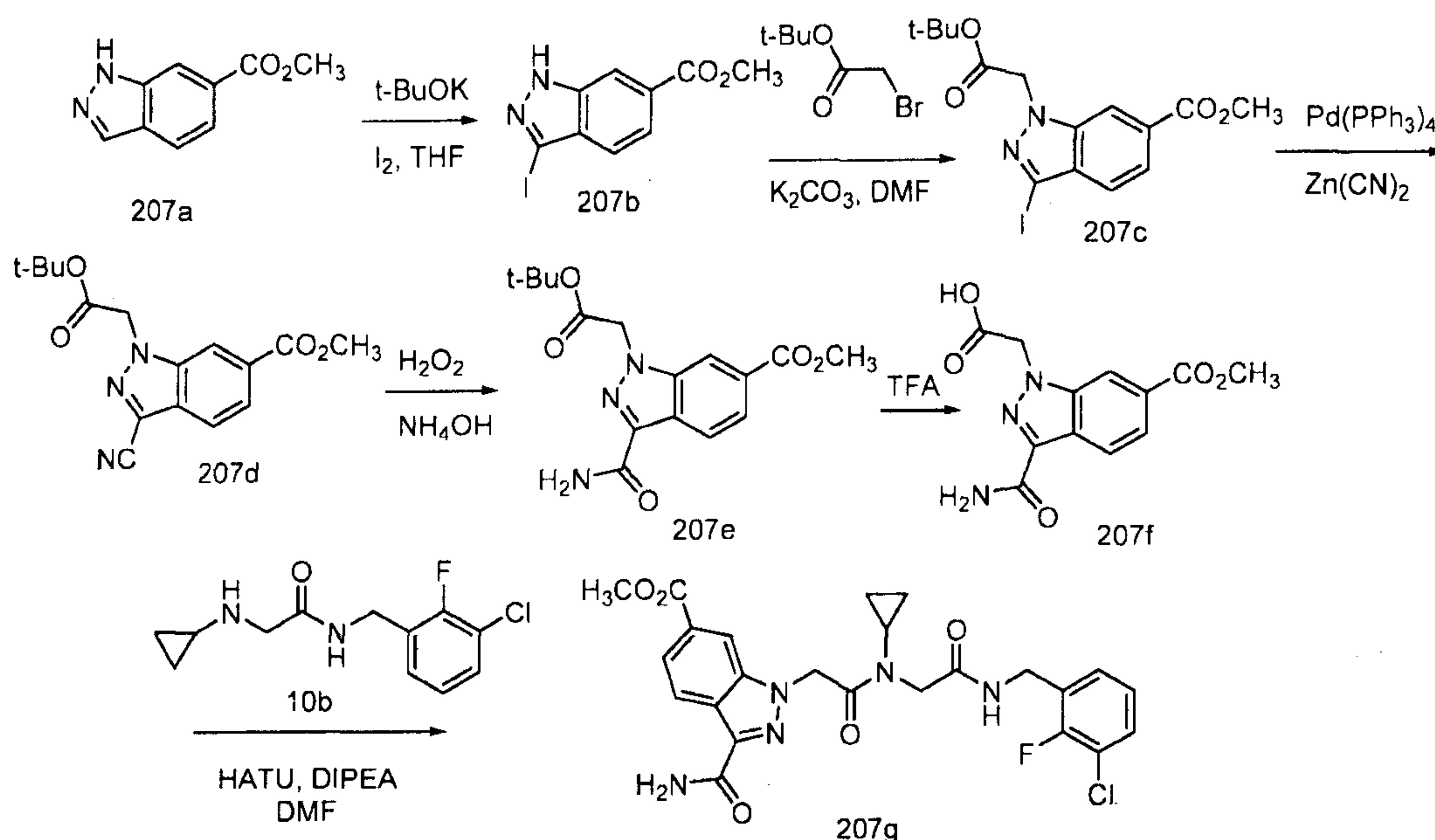
Step-3: Preparation of 2-(3-acetyl-5-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid (**206c**)

Reaction of methyl 3-acetyl-1-(2-(tert-butoxy)-2-oxoethyl)-1H-indazole-5-carboxylate (**206b**) (6.1 g, 18.35 mmol) with TFA (7.07 mL, 92 mmol) in DCM (50 mL) according to the procedure reported in step-2 of Scheme 2 gave after workup 2-(3-acetyl-5-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid (**206c**) (5.8 g, 14.86 mmol, 81 % yield) TFA salt as an off white solid, which was used in the next step without further purification; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 13.00 (s, 1H), 8.83 (dd, $J = 1.7, 0.8$ Hz, 1H), 8.08 – 7.99 (m, 1H), 7.91 (dd, $J = 8.9, 0.8$ Hz, 1H), 5.51 (s, 2H), 3.91 (s, 3H), 2.65 (s, 3H); MS (ES^-): 275.3 ($\text{M}-1$)

Step-4: Preparation of methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**206d**)

Reaction of 2-(3-acetyl-5-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid (**206c**) TFA adduct (1.9 g, 4.87 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (1.51 g, 5.84 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (12 g), eluting with DMA80 in DCM 0 to 40%] methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**206d**) (2.24 g, 4.33 mmol, 89 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.89 – 8.29 (m, 2H), 8.04 (dd, $J = 8.9, 1.7$ Hz) and 7.97 (dd, $J = 8.9, 1.7$ Hz) (2dd, 1H), 7.77 (dd, $J = 8.9, 0.8$ Hz) and 7.70 (dd, $J = 8.9, 0.8$ Hz) (2dd, 1H), 7.56 – 6.95 (m, 3H), 5.76 and 5.59 (2s, 2H), 4.69 – 4.23 (m, 3H), 4.18 and 3.85 (2s, 2H), 3.913 and 3.908 (2s, 3H), 2.64 (s, 3H), 1.26 (d, $J = 6.7$ Hz) and 1.00 (d, $J = 6.8$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, DMSO) δ -121.21, -121.72; MS (ES^+): 517.5 ($\text{M}+1$), 539.5 ($\text{M}+\text{Na}$); MS (ES^-): 515.5 ($\text{M}-1$).

Scheme 207



Preparation of methyl 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-6-carboxylate (**207g**)

5 Step-1: Preparation of methyl 3-iodo-1H-indazole-6-carboxylate (**207b**)

Compound methyl 3-iodo-1H-indazole-6-carboxylate (**207b**) was prepared from methyl 1H-indazole-6-carboxylate (15 g, 85 mmol) according to the procedure reported in step-1 of Scheme 132 to furnish product (22 g, 72.8 mmol, 86% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 13.82 (s, 1H, D_2O exchangeable), 8.16 – 8.08 (m, 1H), 7.71 (dd, $J = 8.6$, 1.4 Hz, 1H), 7.53 (dd, $J = 8.6$, 0.8 Hz, 1H), 3.88 (s, 3H); MS (ES+); 303.2 ($\text{M}+1$); MS (ES-): 301.2 ($\text{M}-1$).

Step-2: Preparation of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-iodo-1H-indazole-6-carboxylate (**207c**)

Reaction of methyl 3-iodo-1H-indazole-6-carboxylate (**207b**) (12 g, 39.7 mmol) with *tert*-butyl 2-bromoacetate (11.62 g, 59.6 mmol) according to the procedure reported in step-1 of Scheme 56 gave after workup methyl 1-(2-*tert*-butoxy-2-oxoethyl)-3-iodo-1H-indazole-6-carboxylate (**207c**) (11.7 g, 28.1 mmol, 71% yield) as an off white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.37 (t, $J = 1.1$ Hz, 1H), 7.78 (dd, $J = 8.5$, 1.3 Hz, 1H), 7.56 (dd, $J = 8.5$, 0.8 Hz, 1H), 5.44 (s, 2H), 3.91 (s, 3H), 1.40 (s, 9H); MS (ES+): 439.4 ($\text{M}+\text{Na}$).

20 Step-3: Preparation of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-cyano-1H-indazole-6-carboxylate (**207d**)

A mixture of methyl 1-(2-tert-butoxy-2-oxoethyl)-3-iodo-1H-indazole-6-carboxylate (**207c**) (10.7 g, 25.7 mmol), zinc (0.336 g, 5.14 mmol), zinc cyanide (3.62 g, 30.8 mmol), Pd₂(dba)₃, (1.883 g, 2.06 mmol), Xantphos (1.488 g, 2.57 mmol), TMEDA (0.776 mL, 5.14 mmol) in DMF (75 mL) was purged with Argon for 5 mins and heated at 100°C for 6 h. The reaction
 5 mixture was cooled to room temperature, diluted with EtOAc (250 mL), and filtered through Celite, rinsing with EtOAc (2 x 100 mL). The filtrate was concentrated to dryness and the residue was triturated with MeOH (10 mL). The solid obtained was collected by filtration washed with MeOH (2 x 3 mL), dried to give methyl 1-(2-tert-butoxy-2-oxoethyl)-3-cyano-1H-indazole-6-carboxylate (**207d**) (5.28 g, 16.74 mmol, 65.1 % yield) as a white solid; ¹H
 10 NMR (300 MHz, DMSO-*d*₆) δ 8.61 (t, *J* = 1.1 Hz, 1H), 8.05 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.95 (dd, *J* = 8.6, 1.3 Hz, 1H), 5.65 (s, 2H), 3.93 (s, 3H), 1.41 (s, 9H); MS (ES⁺): 338.4 (M+Na); MS (ES⁻): 314.3 (M-1).

Step-4: Preparation of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-carbamoyl-1H-indazole-6-carboxylate (**207e**)

15 Reaction of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-cyano-1H-indazole-6-carboxylate (**207d**) (5.18 g, 16.42 mmol) in ethanol (50 mL) using conc. NH₄OH (30 mL) and H₂O₂ (aq. 35%, 10.16 mL, 99 mmol) according to the procedure reported in Scheme 65 gave after workup methyl 1-(2-tert-butoxy-2-oxoethyl)-3-carbamoyl-1H-indazole-6-carboxylate (**207e**) (3.4 g, 10.18 mmol, 62% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.43 (t, *J* = 1.1 Hz, 1H), 8.30 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.90 – 7.81 (m, 2H), 7.54 (s, 1H), 5.49 (s, 2H),
 20 3.92 (s, 3H), 1.41 (s, 9H); MS (ES⁺): 333.4 (M+1)

Step-5: Preparation of 2-(3-carbamoyl-6-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid (**207f**)

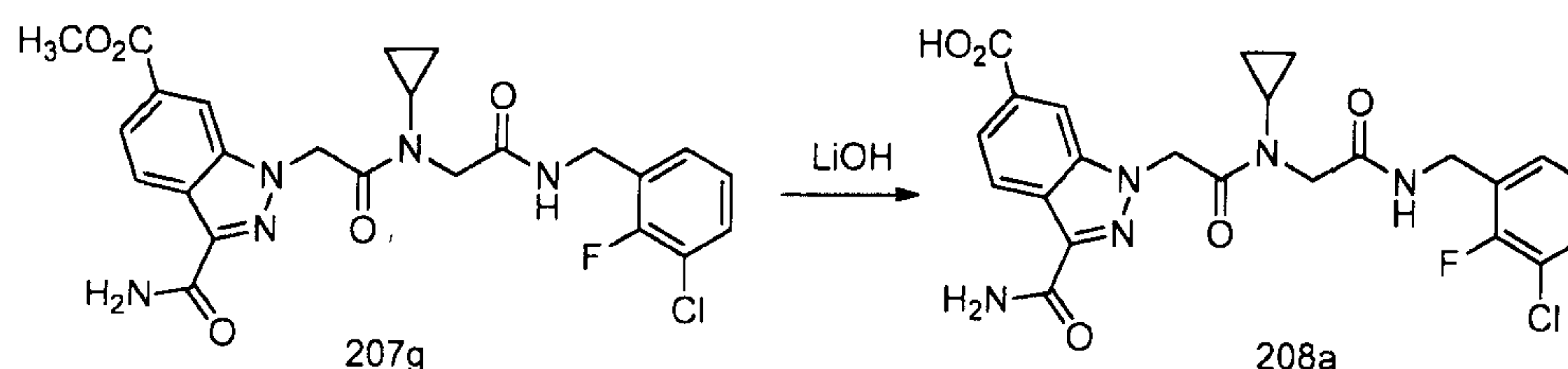
Reaction of methyl 1-(2-(tert-butoxy)-2-oxoethyl)-3-carbamoyl-1H-indazole-5-carboxylate
 25 (**207e**) (3.3 g, 9.9 mmol) with TFA (3.81 mL, 49.5 mmol) in DCM (50 mL) according to the procedure reported in step-2 of Scheme 2 gave after workup 2-(3-carbamoyl-6-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid (**207f**) TFA salt (2.8 g, 7.16 mmol, 72% yield) as a white solid, which was used in the next step without further purification; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.37 (s, 1H), 8.47 – 8.41 (m, 1H), 8.35 – 8.24 (m, 1H), 7.90 – 7.80
 30 (m, 2H), 7.54 (s, 1H), 5.50 (s, 2H), 3.91 (s, 3H); MS (ES⁺): 278.3 (M+1); MS (ES⁻): 276.2 (M-1).

Step-6: Preparation of methyl 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-6-carboxylate (**207g**)

Reaction of 2-(3-carbamoyl-6-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid (**207f**) TFA adduct (1.82 g, 4.65 mmol) with N-(3-chloro-2-fluorobenzyl)-2-

- 5 (cyclopropylamino)acetamide (**10b**) (1.43 g, 5.58 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (40 g), eluting with DMA80 in DCM 0 to 40%] methyl 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-6-carboxylate (**207g**) (1.6 g, 3.10 mmol, 67% yield) as a yellow solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.52 (t, *J* = 5.9 Hz, 1H), 8.38 (t, *J* = 1.1 Hz, 1H), 8.29 (dd, *J* = 8.5, 0.8 Hz, 1H), 7.87 (s, 1H), 7.83 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.50 (s, 1H), 7.44 (ddd, *J* = 8.8, 7.3, 1.7 Hz, 1H), 7.21 (td, *J* = 7.3, 6.8, 1.7 Hz, 1H), 7.06 (td, *J* = 7.9, 1.1 Hz, 1H), 5.80 (s, 2H), 4.33 (d, *J* = 5.7 Hz, 2H), 3.99 (s, 2H), 3.88 (s, 3H), 3.17 – 3.04 (m, 1H), 1.07 – 0.99 (m, 2H), 0.97 – 0.88 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.65; MS (ES⁺): 538.5 (M+Na); (ES⁻): 514.4 (M-1).

Scheme 208



Preparation of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-6-carboxylic acid (**208a**)

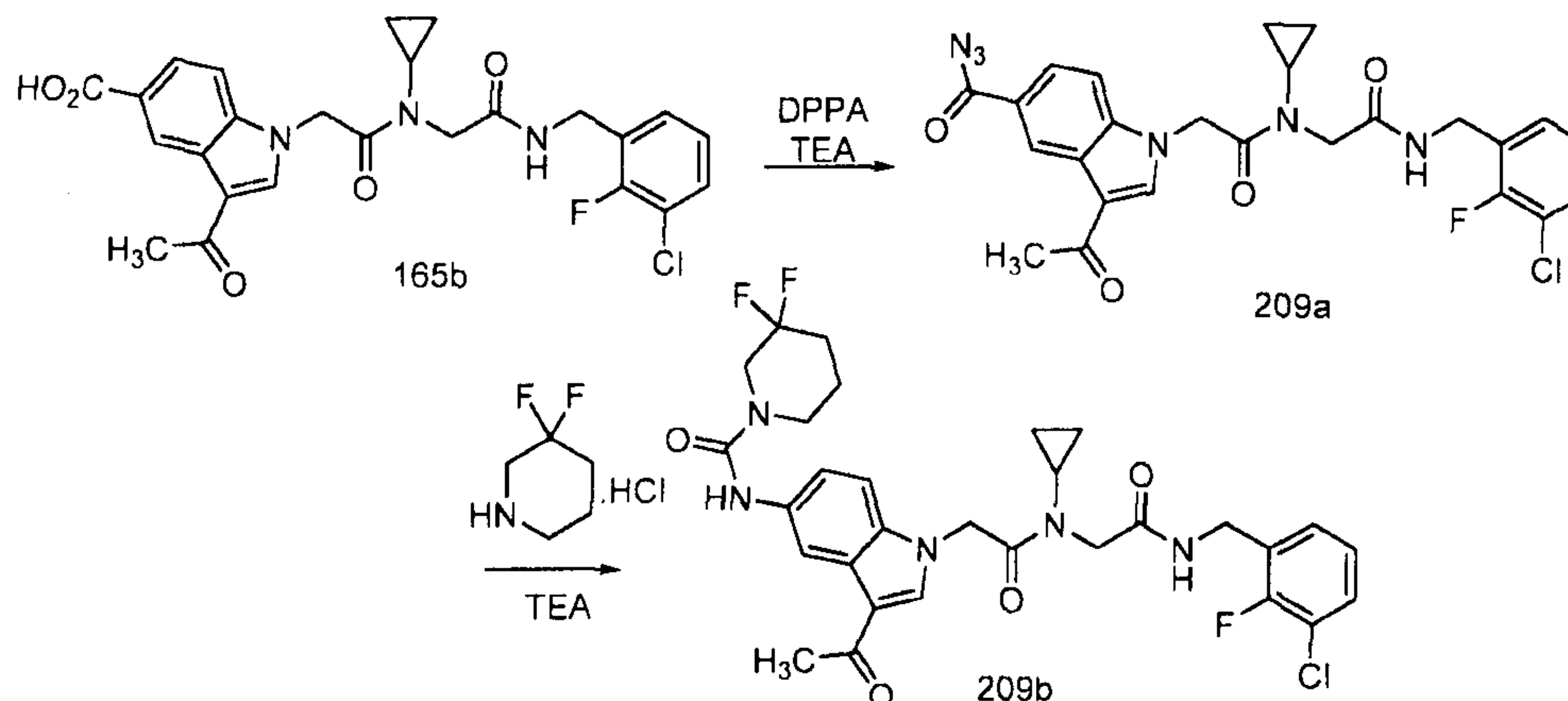
- 20 Reaction of methyl 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-6-carboxylate (**207g**) (1.6 g, 3.10 mmol) in MeOH (25 mL) and water (25 mL) with lithium hydroxide hydrate (0.78 g, 18.61 mmol) according to the procedure reported in step-2 of Scheme 129 gave after workup 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-6-carboxylic acid (**208a**) (1.3 g, 2.59 mmol, 84 % yield) as an off
- 25 white solid, which was used in the next step without further purification; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.18 (s, 1H), 8.52 (t, *J* = 5.8 Hz, 1H), 8.36 (s, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 7.95 – 7.76 (m, 2H), 7.58 – 7.39 (m, 2H), 7.34 – 7.18 (m, 1H), 7.09 (t, *J* = 7.9 Hz, 1H), 5.79 (s, 2H), 4.33 (d, *J* = 5.7 Hz, 2H), 3.99 (s, 2H), 3.14 – 2.98 (m, 1H), 1.09 – 0.97 (m, 2H), 0.97

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– 0.83 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.60; MS (ES+): 502.4 (M+1); MS (ES-) 500.4 (M-1).

Scheme 209



- 5 Preparation of N-(3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indol-5-yl)-3,3-difluoropiperidine-1-carboxamide (**209b**)

Step-1: Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carbonyl azide (**209a**)

- 10 Compound 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carbonyl azide (**209a**) was prepared from 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**165b**) (1.8 g, 3.60 mmol) according to the procedure reported in step-3 of Scheme 129 to afford product; MS (ES-): 523.4 (M-1).

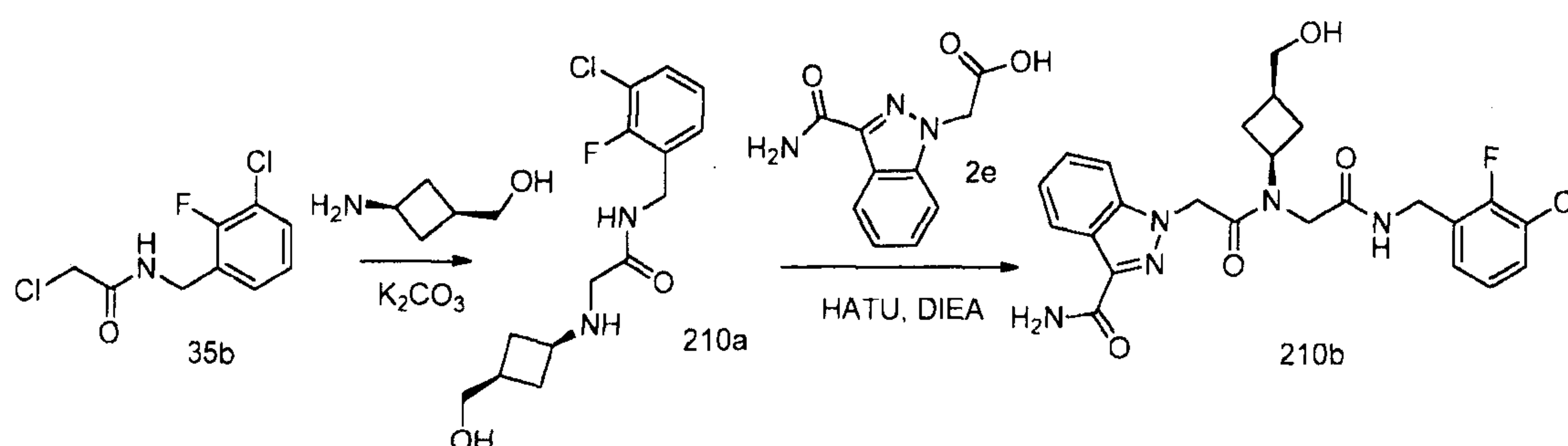
- 15 Step-2: Preparation of N-(3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indol-5-yl)-3,3-difluoropiperidine-1-carboxamide (**209b**)

- Compound (**209b**) was prepared from 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carbonyl azide (**209a**) (200 mg, 0.38 mmol) and 3,3-difluoropiperidine hydrochloride (120 mg, 0.76 mmol) using TEA (0.21 mL, 1.51 mmol) as base according to the procedure reported in step-4 of Scheme 129 to afford after workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] (45 mg, 0.073 mmol, 19%) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.65 (s, 1H), 8.47 (t, J = 5.8 Hz, 1H), 8.21 (s, 1H), 8.19 (s, 1H), 7.45 (t, J = 7.6 Hz, 1H), 7.41 – 7.28 (m, 2H), 7.24 (t, J = 7.1 Hz, 1H), 7.12 (t, J = 7.9 Hz, 1H), 5.39 (s, 2H),
- 20
- 25

4.35 (d, $J = 5.7$ Hz, 2H), 4.00 (s, 2H), 3.81 (t, $J = 12.1$ Hz, 2H), 3.52 (t, $J = 5.3$ Hz, 2H), 3.17 – 2.97 (m, 1H), 2.41 (s, 3H), 2.16 – 1.94 (m, 2H), 1.79 – 1.59 (m, 2H), 1.04 – 0.88 (m, 4H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -101.12, -121.63; MS (ES+): 618.6 (M+1); MS (ES-): 616.5 (M-1).

5

Scheme 210



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((cis)-3-(hydroxymethyl)cyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**210b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(((cis)-3-(hydroxymethyl)cyclobutyl)amino)acetamide (**210a**)

10 Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (300 mg, 1.27 mmol) with ((cis)-3-aminocyclobutyl)methanol hydrochloride (262 mg, 1.91 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup N-(3-chloro-2-fluorobenzyl)-2-(((cis)-3-(hydroxymethyl)cyclobutyl)amino)acetamide (**210a**) as an oil which was used in the next step without further purification; MS (ES+): 301.4 (M+1); MS (ES-): 299.4 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((cis)-3-(hydroxymethyl)cyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**210b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(((cis)-3-

(hydroxymethyl)cyclobutyl)amino)acetamide (**210a**) (169 mg, 0.56 mmol) with 2-(3-

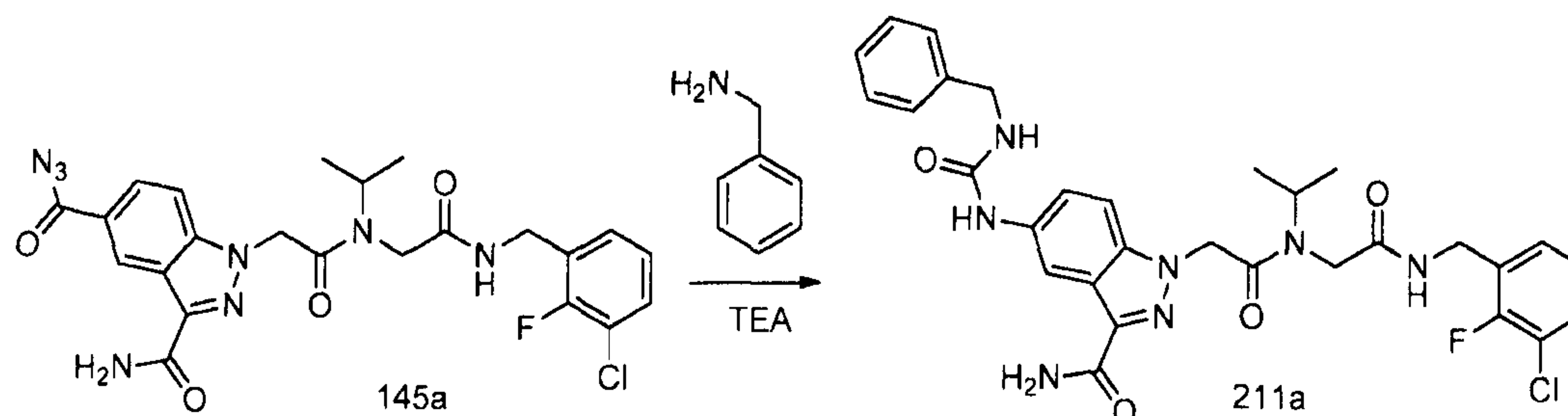
20 carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (123 mg, 0.56 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column

chromatography [silica (12 g), eluting with MeOH in DCM 0 to 30%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((cis)-3-(hydroxymethyl)cyclobutyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**210b**) (53 mg, 0.11 mmol, 19 % yield) as a white solid as a mixture

25 of two rotamers; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.89 (t, $J = 5.8$ Hz) & 8.42 (t, $J = 5.9$ Hz) (2t, 1H), 8.23 – 8.13 (m, 1H), 7.70 (s, 1H), 7.62 – 7.00 (m, 7H), 5.56 & 5.40 (2s, 2H), 4.59 & 4.52 (t, $J = 5.2$ Hz) (2t, 1H, D_2O exchangeable), 4.55-4.37 (m, 1H), 4.47 (d, $J = 6.2$ Hz) & 4.34 (d, $J = 5.9$ Hz) (2d, 2H), 4.28 & 4.01 (2s, 2H), 3.43-3.28 (m, 2H), 2.34-1.66 (m, 5H); ^{19}F

NMR (282 MHz, DMSO-*d*₆) δ -121.25, -121.66; MS (ES⁺): 502.5 (M+1), 524.5, 526.5 (M+Na); MS (ES⁻): 500.4 (M-1), 536.4 (M+Cl).

Scheme 211

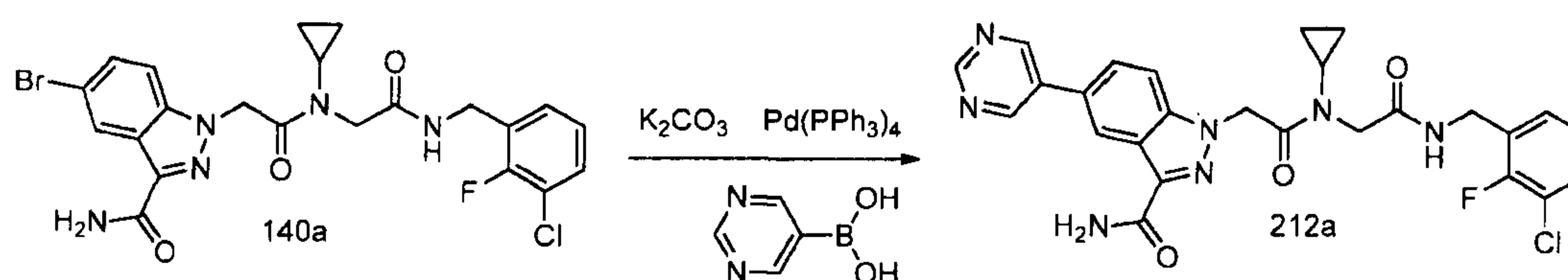


- 5 Preparation of 5-(3-benzylureido)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**211a**)

Reaction of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**145a**) (150 mg, 0.284 mmol) in toluene (15 mL) with phenylmethanamine (60.8 mg, 0.567 mmol) using TEA (0.16 mL, 1.13 mmol) as base according to the procedure reported in step-4 of Scheme 129 gave after workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] 5-(3-benzylureido)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**211a**) (11 mg, 0.018 mmol, 6% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 8.81 (t, *J* = 5.7 Hz) and 8.36 (t, *J* = 5.9 Hz) (2t, 1H), 8.74 – 8.64 (m, 1H), 8.24 and 8.20 (2s, 1H), 7.63 – 7.54 (m, 1H), 7.52 – 6.99 (m, 11H), 6.58 (t, *J* = 5.7 Hz, 1H), 5.52 and 5.39 (2s, 2H), 4.61 – 4.23 (m, 5H), 4.17 and 3.83 (2s, 2H), 1.21 (d, *J* = 6.5 Hz) and 0.98 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.23, -121.76; MS (ES⁺): 608.6 (M+1); MS (ES⁻): 606.6 (M-1).

20

Scheme 212



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(pyrimidin-5-yl)-1H-indazole-3-carboxamide (**212a**)

Reaction of 5-bromo-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**140a**) (125 mg, 0.23 mmol) with pyrimidin-5-ylboronic acid (32 mg, 0.256 mmol) according the procedure

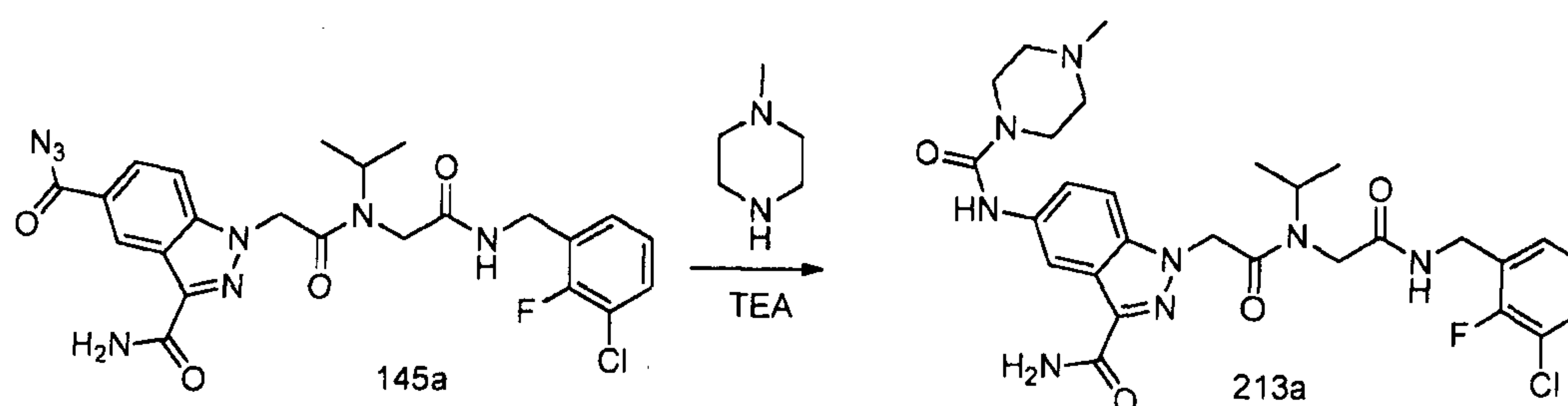
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reported in Scheme 100 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with DMA80 - DCM 0 to 30%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(pyrimidin-5-yl)-1H-indazole-3-carboxamide (**212a**) (69 mg, 0.13 mmol, 55% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.21 (s, 1H), 9.17 (s, 2H), 8.56 – 8.44 (m, 2H), 7.89 – 7.78 (m, 3H), 7.54 – 7.39 (m, 2H), 7.27-7.19 (m, 1H), 7.17 – 7.07 (m, 1H), 5.73 (s, 2H), 4.34 (d, *J* = 5.7 Hz, 2H), 4.00 (s, 2H), 3.15 – 3.02 (m, 1H), 1.08 – 0.96 (m, 2H), 0.99 – 0.86 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.57; MS (ES⁺): 536.6 (M+1), 558.5 (M+Na); MS (ES⁻): 534.5 (M-1), 570.5 (M+Cl).

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Scheme 213

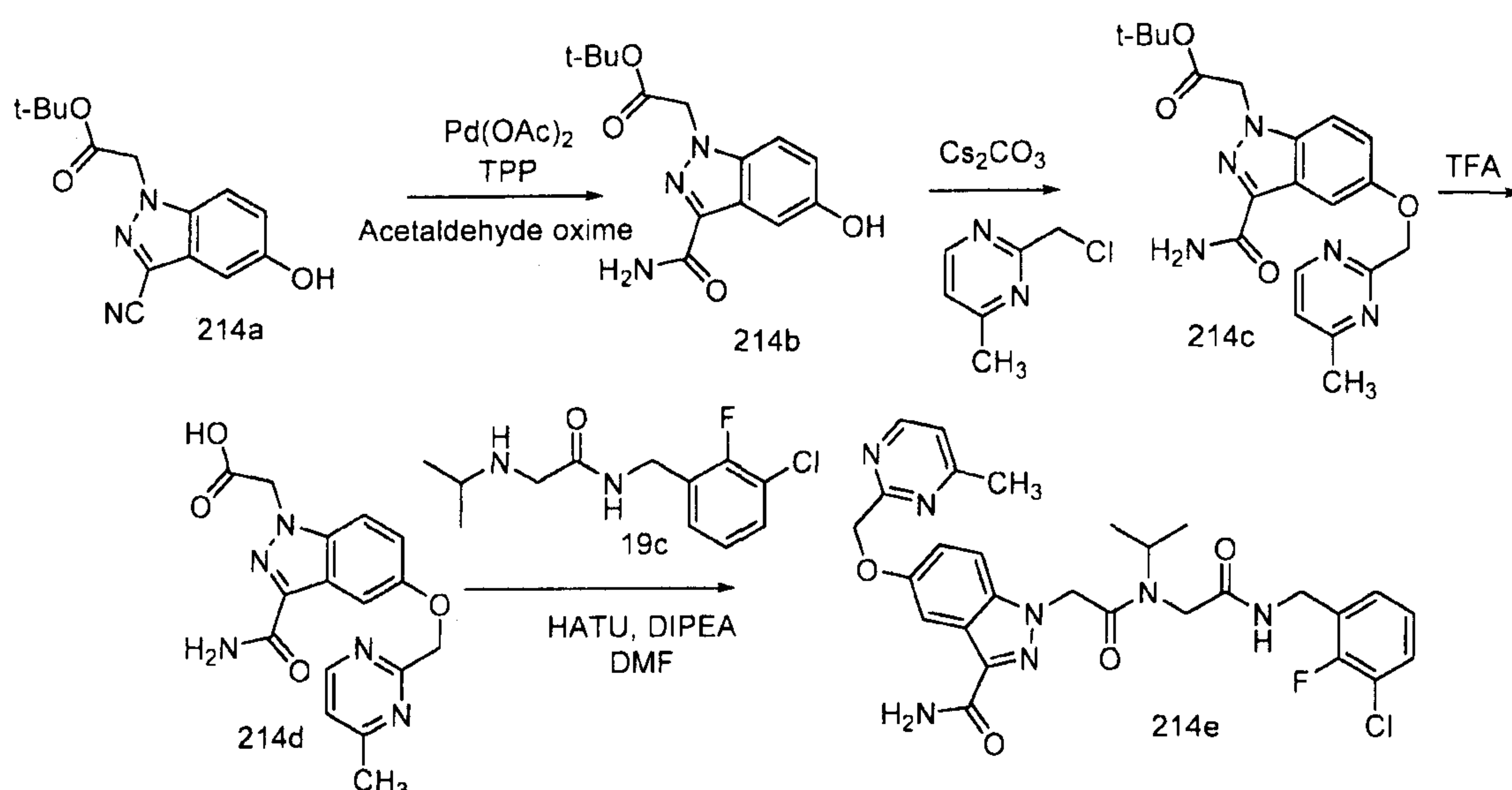


Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(4-methylpiperazine-1-carboxamido)-1H-indazole-3-carboxamide (**213a**)

Reaction of 3-carbamoyl-1-(2-((2-(3-chloro-2-fluorobenzyl)amino)-2-

15 oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**145a**) (150 mg, 0.284 mmol) in toluene (15 mL) with 1-methylpiperazine (56.8 mg, 0.567 mmol) using TEA (0.16 mL, 1.13 mmol) as base according to the procedure reported in step-4 of Scheme 129 gave after workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(4-methylpiperazine-1-carboxamido)-1H-indazole-3-carboxamide (**213a**) (31 mg, 0.052 mmol, 18% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (mixture of two rotamers) δ 8.82 (t, *J* = 5.7 Hz) and 8.36 (t, *J* = 5.8 Hz) (2t, 1H), , 8.65 (s, 1H), 8.19 – 8.15 (m, 1H), 7.64-7.01 (m, 7H), 5.53 and 5.39 (2s, 2H), 4.60 – 4.25 (m, 3H), 4.17 and 3.83 (2s, 2H), 3.50 – 3.43 (m, 4H), 2.39 – 2.31 (m, 4H), 2.23 (s, 3H), 1.21 (d, *J* = 6.6 Hz) and 0.98 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.22, -121.79; MS (ES⁺): 601.5 (M+1); MS (ES⁻): 599.5 (M-1).

Scheme 214



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-((4-methylpyrimidin-2-yl)methoxy)-1H-indazole-3-carboxamide (**214e**)

Step-1: Preparation of tert-butyl 2-(3-carbamoyl-5-hydroxy-1H-indazol-1-yl)acetate (**214b**)

5 A mixture of *tert*-butyl 2-(3-cyano-5-hydroxy-1H-indazol-1-yl)acetate (**214a**) (Prepared according to the procedure reported by Altmann, Eva et al; in PCT Int. Appl., WO 2014/002053, 360 mg, 1.32 mmol), palladium(II) acetate (30 mg, 0.13 mmol), triphenylphosphine (69 mg, 0.26 mmol) acetaldehyde oxime (0.16 mL, 2.63 mmol) in ethanol (8 mL) and water (2 mL) was heated to 90 °C for 2 h. The reaction mixture was cooled to
 10 room temperature, diluted with EtOAc (50 mL), filtered through a Celite pad and evaporated to dryness. The residue obtained was purified by flash column chromatography [Silica gel, (12 g) eluting with EtOAc in hexanes 0-100%] to afford tert-butyl 2-(3-carbamoyl-5-hydroxy-1H-indazol-1-yl)acetate (**214b**) (351 mg, 1.21 mmol, 91 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.41 (s, 1H), 7.67 – 7.47 (m, 3H), 7.28 (s, 1H), 6.97 (dd, *J* = 8.9, 2.4 Hz, 1H), 5.26 (s, 2H), 1.41 (s, 9H); MS (ES⁺): 292.1 (M+1), MS (ES⁻): 290.3 (M-1).
 15

Step-2: Preparation of tert-butyl 2-(3-carbamoyl-5-((4-methylpyrimidin-2-yl)methoxy)-1H-indazol-1-yl)acetate (**214c**)

To a solution of *tert*-butyl 2-(3-carbamoyl-5-hydroxy-1H-indazol-1-yl)acetate (**214b**) (201 mg, 0.69 mmol) in DMF (5 mL) was added cesium carbonate (0.28 g, 0.863 mmol) and 2-(chloromethyl)-4-methylpyrimidine (108 mg, 0.759 mmol). The reaction mixture was stirred at room temperature for 13 h and quenched with cold water (50 mL). The solid obtained was collected by filtration, washed with water (2 x 25 mL), dried under reduced pressure over
 20

P₂O₅ to furnish tert-butyl 2-(3-carbamoyl-5-((4-methylpyrimidin-2-yl)methoxy)-1H-indazol-1-yl)acetate (**214c**) (152 mg, 0.38 mmol, 55% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.66 (d, *J* = 5.1 Hz, 1H), 7.67 – 7.60 (m, 2H), 7.59 (d, *J* = 2.4 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.20 (dd, *J* = 9.1, 2.4 Hz, 1H), 5.30 (s, 2H), 5.25 (s, 2H), 2.49 (s, 3H), 1.41 (s, 9H); MS (ES⁺): 398.5 (M+1), 795.9 (2M+1); MS (ES⁻): 396.4 (M-1).

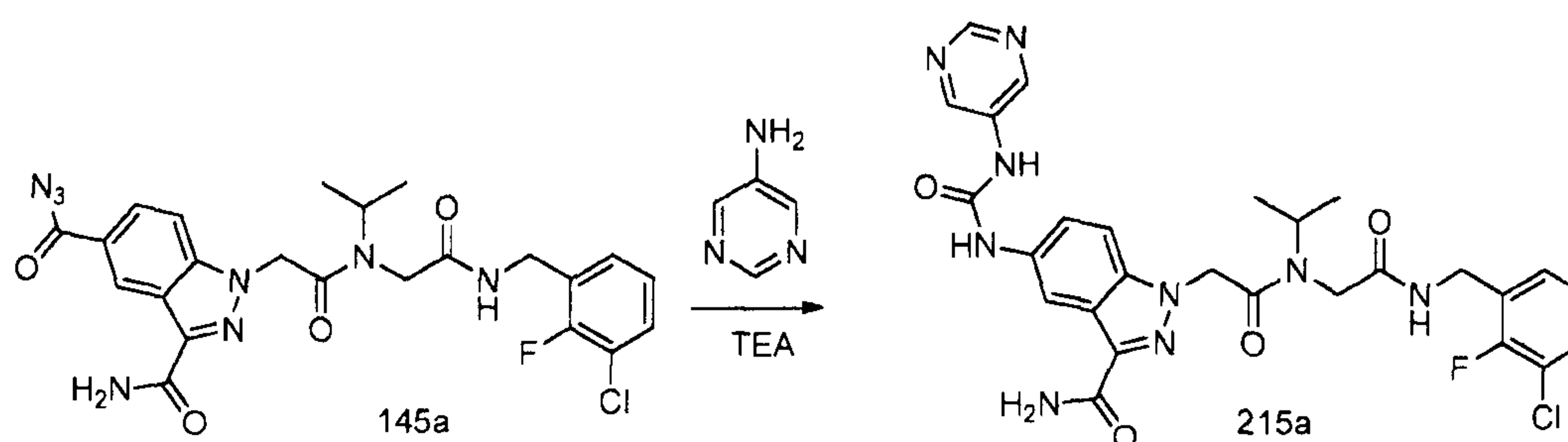
Step-3: Preparation of 2-(3-carbamoyl-5-((4-methylpyrimidin-2-yl)methoxy)-1H-indazol-1-yl)acetic acid (**214d**)

Reaction of tert-butyl 2-(3-carbamoyl-5-((4-methylpyrimidin-2-yl)methoxy)-1H-indazol-1-yl)acetate (**214c**) (138 mg, 0.35 mmol) with TFA (0.54 mL, 6.94 mmol) in DCM (10 mL) according to the procedure reported in step-2 of Scheme 2 gave after workup and trituration with hexanes, 2-(3-carbamoyl-5-((4-methylpyrimidin-2-yl)methoxy)-1H-indazol-1-yl)acetic acid (**214d**) (148 mg, 0.33 mmol, 94% yield) TFA salt as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.4 (bs, 1H), 8.67 (d, *J* = 5.1 Hz, 1H), 7.68 – 7.62 (m, 2H), 7.58 (d, *J* = 2.4 Hz, 1H), 7.39 – 7.29 (m, 2H), 7.19 (dd, *J* = 9.1, 2.4 Hz, 1H), 5.31 (s, 2H), 5.26 (s, 2H), 2.49 (s, 3H); MS (ES⁺): 342.4 (M+1).

Step-4: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-((4-methylpyrimidin-2-yl)methoxy)-1H-indazole-3-carboxamide (**214e**)

Reaction of 2-(3-carbamoyl-5-((4-methylpyrimidin-2-yl)methoxy)-1H-indazol-1-yl)acetic acid (**214d**) TFA (103 mg, 0.23 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (70 mg, 0.27 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (12 g), eluting with DMA80 in DCM, 0 to 100%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-((4-methylpyrimidin-2-yl)methoxy)-1H-indazole-3-carboxamide (**214e**) (94 mg, 0.16 mmol, 71% yield) as an off-white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.82 (t, *J* = 5.7 Hz) & 8.36 (t, *J* = 6.1 Hz) (2t, 1H), 8.67 (d, *J* = 5.1 Hz, 1H), 7.61-6.98 (m, 9H), 5.54 & 5.40 (2s, 2H), 5.26 & 5.25 (2s, 2H), 4.60 – 4.49 & 4.28 – 4.22 (2m, 1H), 4.46 (d, *J* = 5.5 Hz) & 4.32 (d, *J* = 5.8 Hz) (2d, 2H), 4.16 & 3.83 (2s, 2H), 2.49 (s, 3H), 1.25 (d) & 0.98 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.22, -121.76; MS (ES⁺): 582.6 & 584.6 (M+1), 604.6, 606.6 (M+Na); MS (ES⁻): 580.5 (M-1).

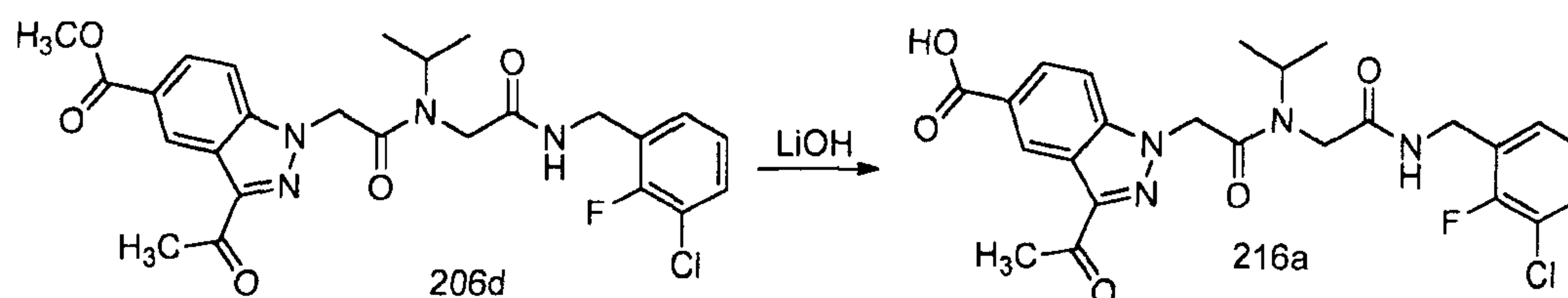
Scheme 215



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3-(pyrimidin-5-yl)ureido)-1H-indazole-3-carboxamide (**215a**)

- 5 Reaction of 3-carbamoyl-1-(2-((2-(3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxyl azide (**145a**) (150 mg, 0.284 mmol) in toluene (15 mL) with pyrimidin-5-amine (54 mg, 0.57 mmol) using TEA (0.16 mL, 1.13 mmol) as base according to the procedure reported in step-4 of Scheme 129 gave after workup and purification by column chromatography [silica gel (12 g), eluting with
- 10 DMA80 in DCM 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3-(pyrimidin-5-yl)ureido)-1H-indazole-3-carboxamide (**215a**) (14 mg, 0.023 mmol, 8% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 9.36-9.09 (m, 2H), 8.044 and 8.935 (2s, 2H), 8.88 – 8.29 (m, 3H), 7.71 – 7.59 (m, 1H), 7.57 – 6.99 (m, 6H), 5.56 and 5.42 (2s, 2H), 4.64 – 4.25 (m, 3H), 4.18 and 3.84 (2s,
- 15 2H), 1.22 (d, $J = 6.3$ Hz) and 0.99 (d, $J = 6.7$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.22, -121-75; MS (ES+) 596.6 (M+1); (ES-) 594.5 (M-1).

Scheme 216

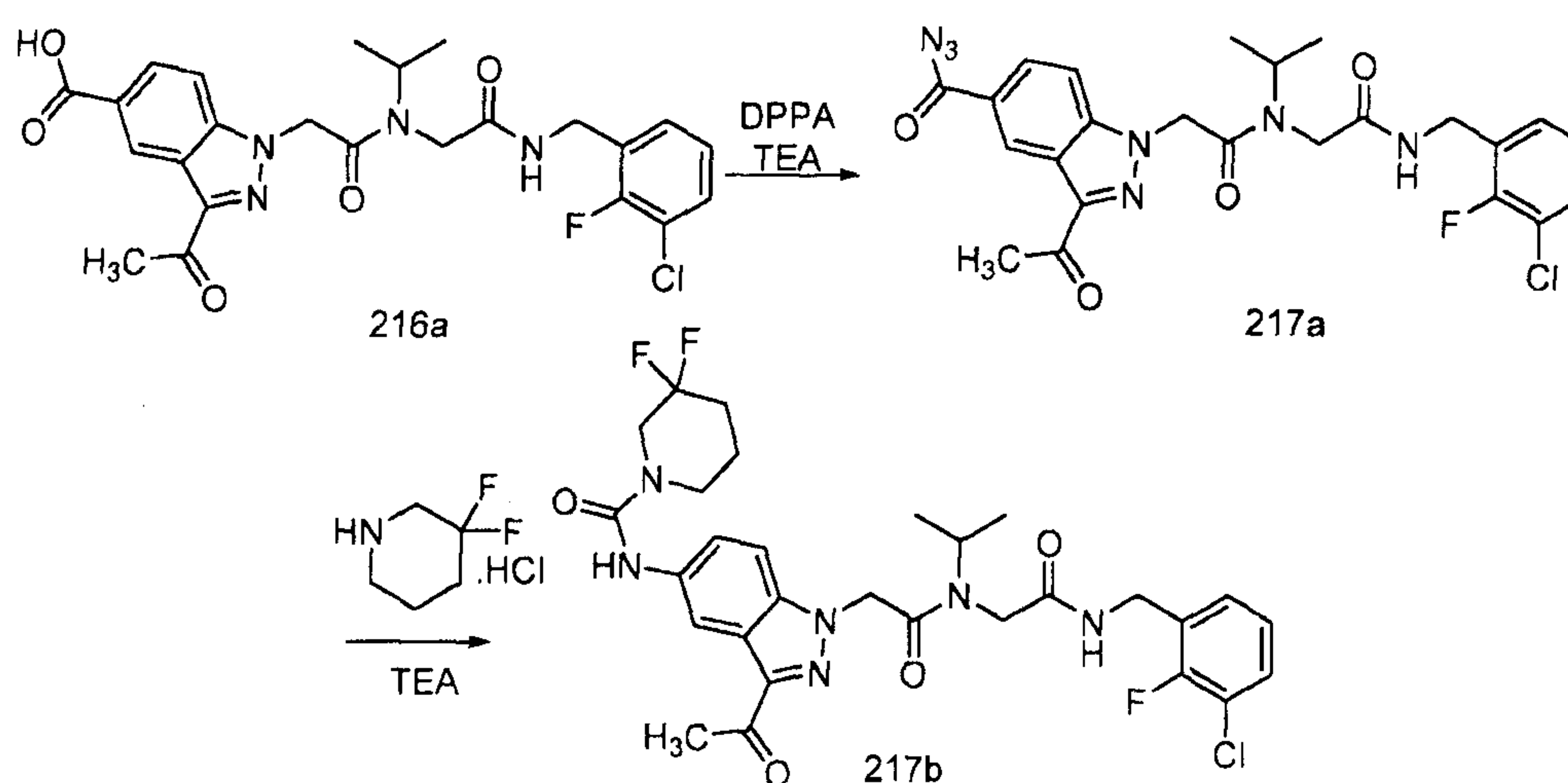


- Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**216a**)
- 20

- Reaction of methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**206d**) (2.24 g, 4.33 mmol) in MeOH (25 mL) and water (25 mL) with lithium hydroxide hydrate (1.091 g, 26.0 mmol) according to the procedure reported in step-2 of Scheme 129 gave after workup 3-
- 25 acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-

1H-indazole-5-carboxylic acid (**216a**) (2.1 g, 4.18 mmol, 96% yield) as an off white solid, which was used in the next step without further purification; ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 13.07 (s, 1H), 9.21 (t, *J* = 5.8 Hz) and 8.62 (t, *J* = 6.0 Hz) (2t, 1H), 8.86 – 8.77 (m, 1H), 8.05 – 7.64 (m, 2H), 7.55 – 6.88 (m, 3H), 5.81 and 5.60 (2s, 2H), 4.64 – 4.20 (m, 3H), 4.26 and 3.84 (2s, 2H), 2.64 and 2.29 (2s, 3H), 1.26 (d, *J* = 6.4 Hz) and 1.00 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.29, -121.81; MS (ES⁺): 502.4 (M+1); (ES⁻): 500.4 (M-1).

Scheme 217



Preparation of N-(3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)-3,3-difluoropiperidine-1-carboxamide (**217b**)

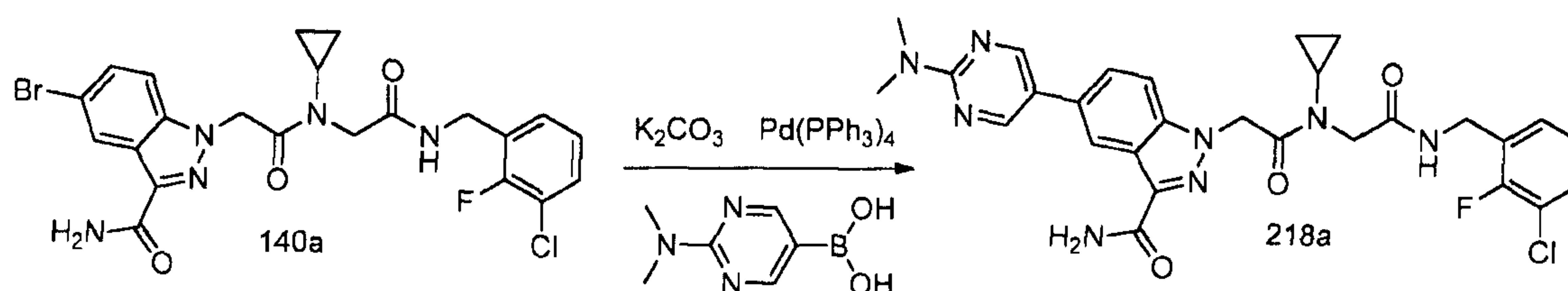
Step-1: Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**217a**)

Compound 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**217a**) was prepared from 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**216a**) (950 mg, 1.889 mmol) according to the procedure reported in step-3 of Scheme 129 to afford product (1.4 g, 2.65 mmol, 140 % yield), which was used in the next step without further purification. MS (ES⁺): 528.5 (M+1).

Step-2: Preparation of N-(3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)-3,3-difluoropiperidine-1-carboxamide (**217b**)

Compound (**217b**) was prepared from 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**217a**) (220 mg, 0.42 mmol) and 3,3-difluoropiperidine hydrochloride (131 mg, 0.83 mmol) using TEA (0.23 mL, 1.67 mmol) as base according to the procedure reported in step-4 of Scheme 129 to afford
 5 after workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] (32 mg, 0.052 mmol, 12.36 % yield) product as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (mixture of two rotamers) δ 8.93 – 8.31 (m, 2H), 8.24 (bs, 1H), 7.65 – 7.00 (m, 5H), 5.64 and 5.48 (2s, 2H), 4.66 – 4.23 (m, 3H), 4.17 and 3.78 (2s, 2H), 3.88-3.80 (m, 2H), 3.61 – 3.47 (m, 2H), 2.59 (s, 3H), 2.19 – 1.95 (m, 2H), 1.84 – 1.60 (m,
 10 2H), 1.24 (d, *J* = 6.4 Hz) and 1.00 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -101.15, -121.22, -121.78; MS (ES⁺): 621.7 (M+1); (ES⁻): 619.6 (M-1).

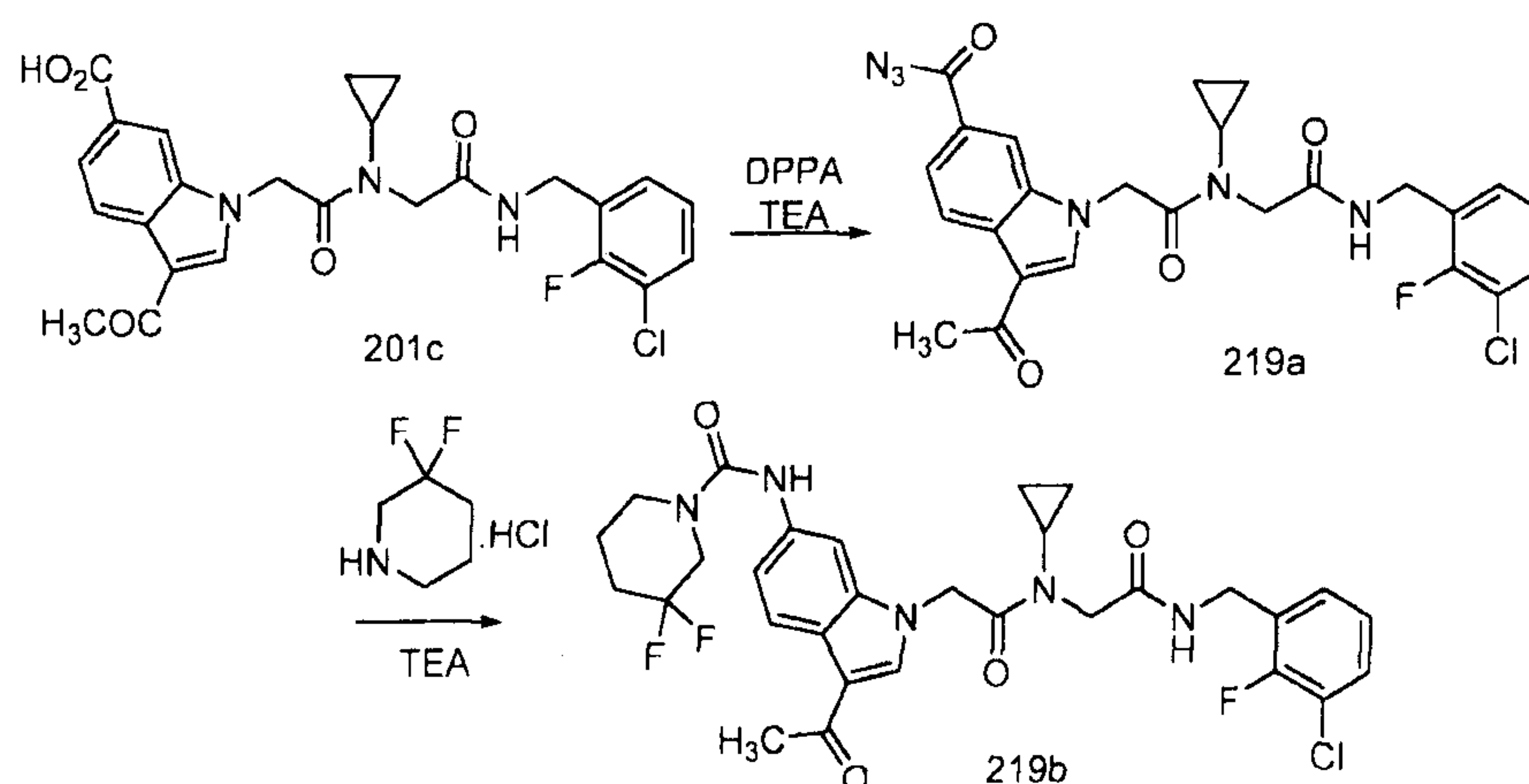
Scheme 218



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(2-(dimethylamino)pyrimidin-5-yl)-1H-indazole-3-carboxamide (**218a**)
 15

Reaction of 5-bromo-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**140a**) (125 mg, 0.23 mmol) with 2-(dimethylamino)pyrimidin-5-ylboronic acid (43 mg, 0.26 mmol) according the procedure reported in Scheme 100 gave after workup and purification by flash column
 20 chromatography [silica gel (12 g), eluting with DMA80 - DCM 0 to 30%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(2-(dimethylamino)pyrimidin-5-yl)-1H-indazole-3-carboxamide (**218a**) (42 mg, 0.073 mmol, 31% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.69 (s, 2H), 8.50 (t, *J* = 5.9 Hz, 1H), 8.28 (dd, *J* = 1.7, 0.9 Hz, 1H), 7.80 – 7.62 (m, 3H), 7.51 – 7.39 (m, 2H), 7.28 – 7.19 (m, 1H), 7.12 (td, *J* = 7.9, 1.0 Hz, 1H), 5.69 (s, 2H), 4.33 (d, *J* = 5.7 Hz, 2H), 3.99 (s, 2H),
 25 3.18 (s, 6H), 3.13 – 3.02 (m, 1H), 1.05 – 0.96 (m, 2H), 0.97 – 0.86 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.57; MS (ES⁺): 579.6 (M+1), 601.6 (M+Na); MS (ES⁻): 577.5 (M-1), 613.6 (M+Cl).

Scheme 219



Preparation of N-(3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indol-6-yl)-3,3-difluoropiperidine-1-carboxamide (**219b**)

Step-1: Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-6-carbonyl azide (**219a**)

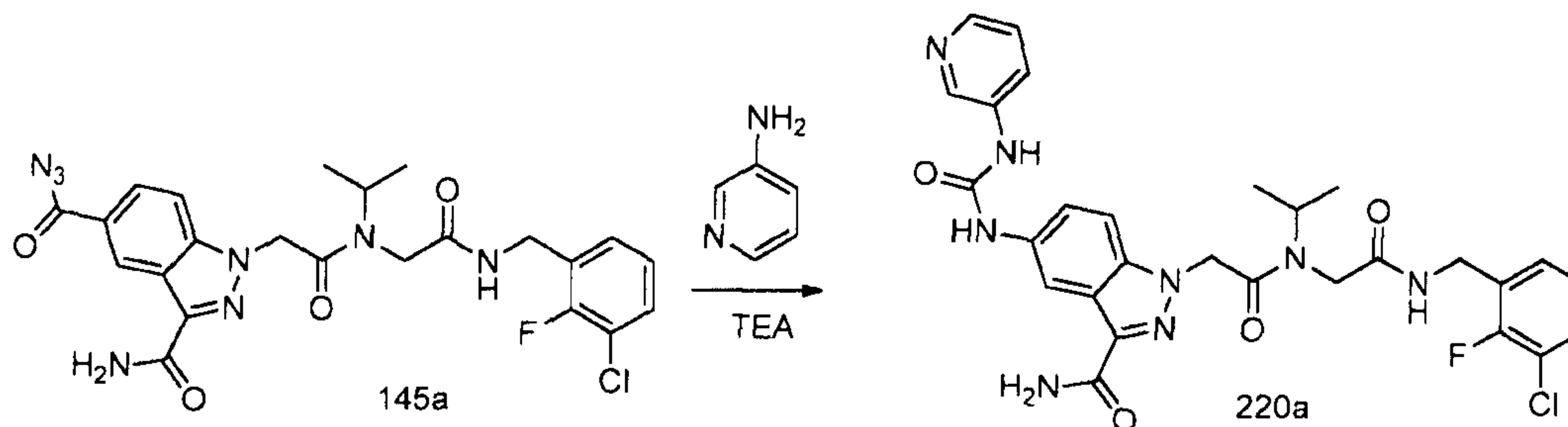
Compound (**219a**) was prepared from 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-6-carboxylic acid (**201a**) (1.98 g, 3.96 mmol) according to the procedure reported in step-3 of Scheme 129 to afford product (**219a**) (2.2 g, 4.19 mmol, 106 % yield) which was used in the next step without further purification; MS (ES⁻): 523.5 (M-1).

Step-2: Preparation of N-(3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indol-6-yl)-3,3-difluoropiperidine-1-carboxamide (**219b**)

Compound (**219b**) was prepared from 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-6-carbonyl azide (**219a**) (200 mg, 0.38 mmol) and 3,3-difluoropiperidine hydrochloride (120 mg, 0.76 mmol) using TEA (0.21 mL, 1.51 mmol) as base according to the procedure reported in step-4 of Scheme 129 to afford after workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] (17 mg, 0.028 mmol, 7% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.66 (s, 1H), 8.47 (t, *J* = 5.8 Hz, 1H), 8.19 (s, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.58 (d, *J* = 1.8 Hz, 1H), 7.50 – 7.41 (m, 1H), 7.28 – 7.20 (m, 2H), 7.17 – 7.09 (m, 1H), 5.35 (s, 2H), 4.34 (d, *J* = 5.7 Hz, 2H), 4.00 (s, 2H), 3.79 (t, *J* = 12.1 Hz, 2H), 3.56 – 3.46 (m, 2H), 3.13 – 3.01 (m, 1H), 2.40 (s, 3H), 2.16 – 1.95 (m, 2H), 1.78 – 1.59 (m, 2H), 1.02 – 0.98

(m, 2H), 0.97 – 0.90 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -101.11, -121.65; MS (ES+): 618.6 (M+1); MS (ES-): 616.6 (M-1).

Scheme 220

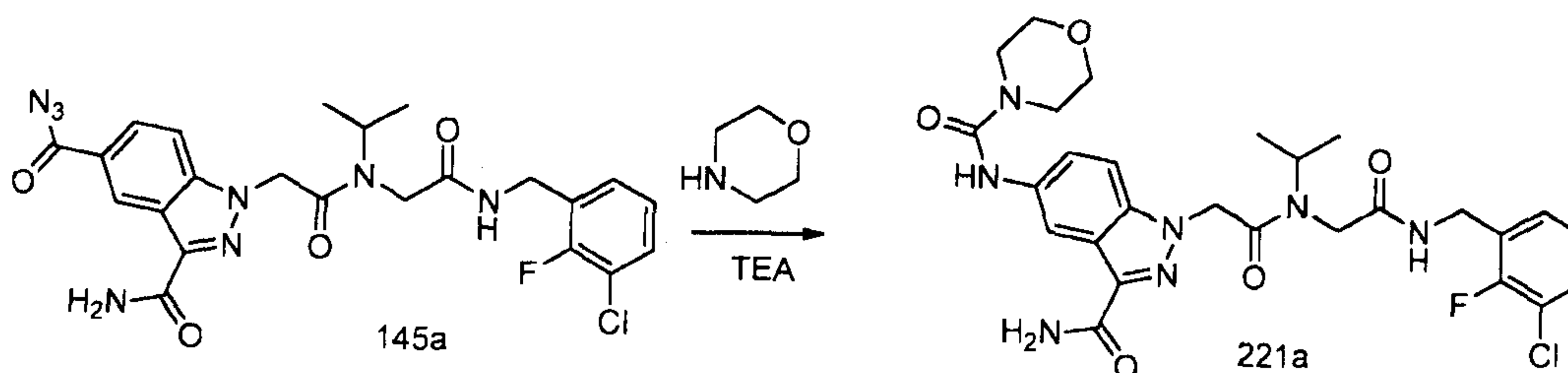


5 Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3-(pyridin-3-yl)ureido)-1H-indazole-3-carboxamide (**220a**)

Reaction of 3-carbamoyl-1-(2-((2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**145a**) (150 mg, 0.28 mmol) in toluene (15 mL) with pyridin-3-amine (53 mg, 0.57 mmol) using TEA (0.16 mL, 1.13 mmol) as base according to the procedure reported in step-4 of Scheme 129 gave after
 10 workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3-(pyridin-3-yl)ureido)-1H-indazole-3-carboxamide (**220a**) (22 mg, 0.037 mmol, 13.04 % yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) (mixture of two
 15 rotamers) δ 8.98 and 8.96 (2s, 1H), 8.90 – 8.77 and 8.41 – 8.30 (2m, 3H), 8.66 – 8.56 (m, 1H), 8.22 – 8.13 (m, 1H), 8.02 – 7.91 (m, 1H), 7.67-6.99 (m, 8H), 5.55 and 5.42 (2s, 2H), 4.64 – 4.23 (m, 3H), 4.18 and 3.83 (2s, 2H), 1.22 (d, J = 6.3 Hz) and 0.99 (d, J = 6.7 Hz) (2d, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.21, -121.74; MS (ES+): 595.6 (M+1); (ES-): 593.5 (M-1)

20

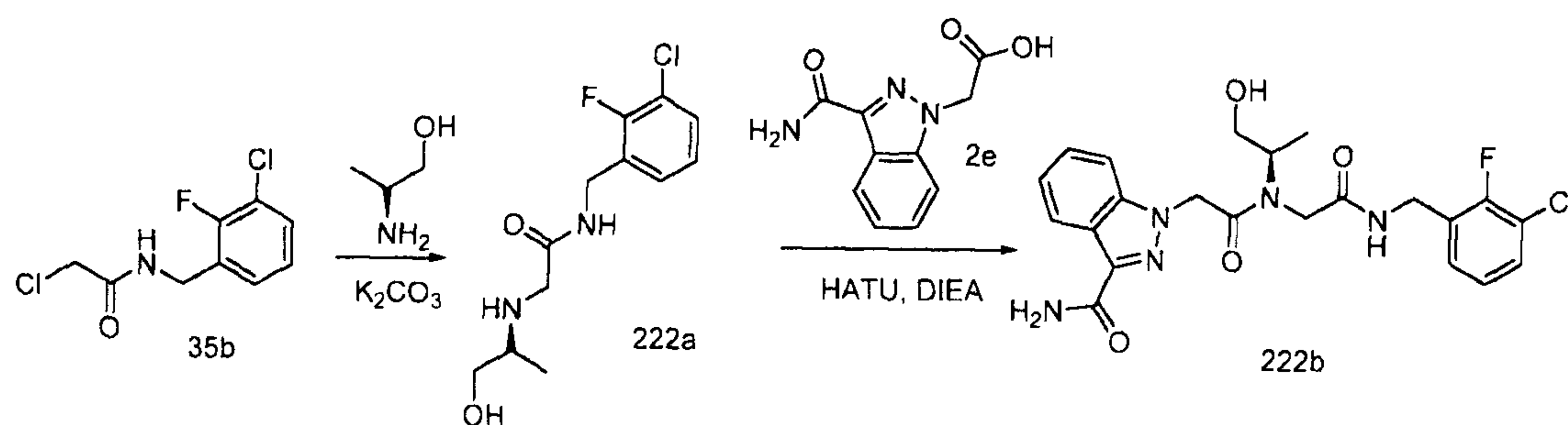
Scheme 221



Preparation of N-(3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)morpholine-4-carboxamide (**221a**)

Reaction of 3-carbamoyl-1-(2-((2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**145a**) (150 mg, 0.28 mmol) in toluene (15 mL) with morpholine (49.4 mg, 0.57 mmol) using TEA (0.16 mL, 1.13 mmol) as base according to the procedure reported in step-4 of Scheme 129 gave after
 5 workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] N-(3-carbamoyl-1-(2-((2-(3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)morpholine-4-carboxamide (**221a**) (33 mg, 0.056 mmol, 20% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.81 and 8.36 (2t, *J* = 5.7 Hz, 1H), 8.67 (s, 1H), 8.22 – 8.15 (m, 1H), 7.65 – 7.00 (m, 7H), 5.53 and
 10 5.40 (2s, 2H), 4.61 – 4.23 (m, 3H), 4.17 and 3.83 (2s, 2H), 3.66 – 3.56 (m, 4H), 3.47 – 3.39 (m, 4H), 1.21 (d, *J* = 6.6 Hz) and 0.98 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO) δ -121.22, -121.78; MS (ES⁺): 588.6 (M+1); MS (ES⁻): 586.5 (M-1).

Scheme 222



15 Preparation of (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-hydroxypropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**222b**)

Step-1: Preparation of (R)-N-(3-chloro-2-fluorobenzyl)-2-((1-hydroxypropan-2-yl)amino)acetamide (**222a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 2.12 mmol) with
 20 (R)-2-aminopropan-1-ol (318 mg, 4.24 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup (R)-N-(3-chloro-2-fluorobenzyl)-2-((1-hydroxypropan-2-yl)amino)acetamide (**222a**) (582 mg, 2.12 mmol, 100%) which was used as such in the next step; MS (ES⁺): 275.3 (M+1); MS (ES⁻): 273.3 (M-1).

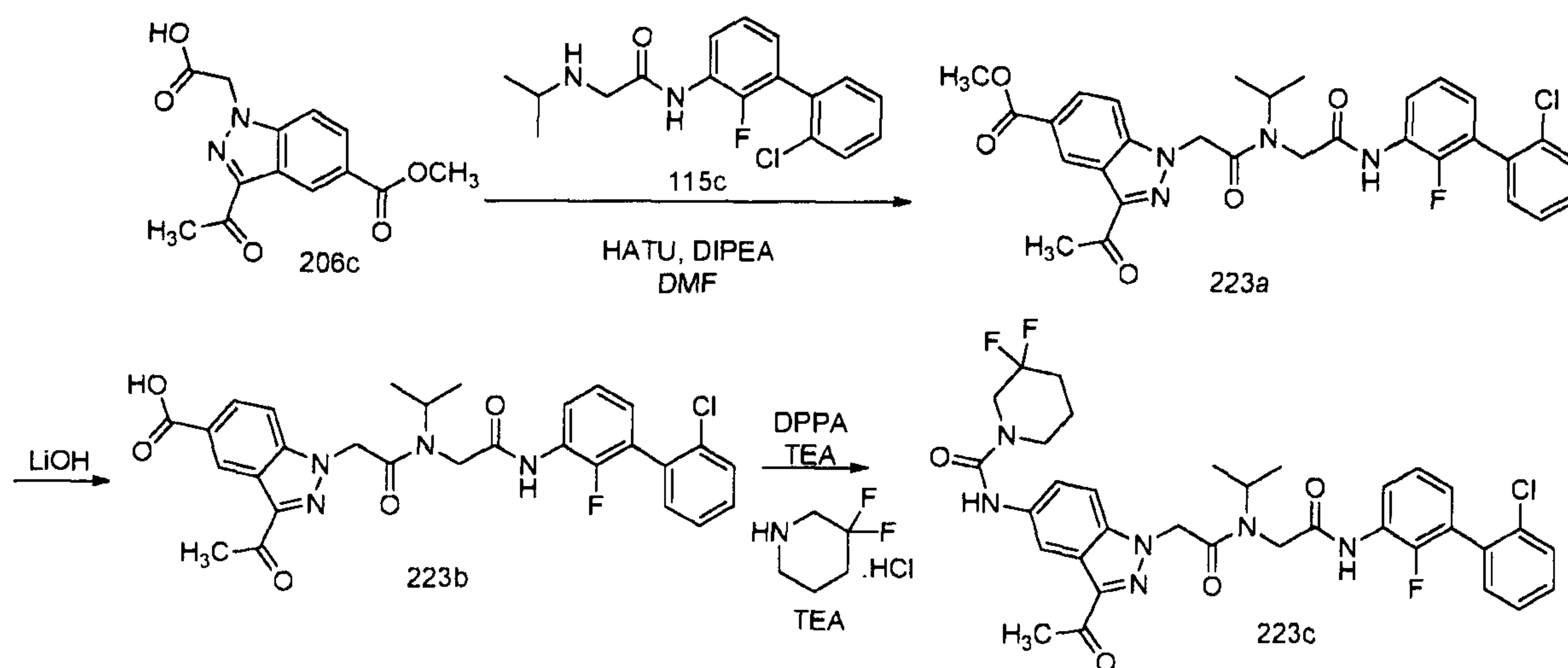
Step-2: Preparation of (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-hydroxypropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**222b**)
 25

Reaction of (R)-N-(3-chloro-2-fluorobenzyl)-2-((1-hydroxypropan-2-yl)amino)acetamide (**222a**) (200 mg, 0.73 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (251 mg, 0.91 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and

purification by flash column chromatography [silica (12 g), eluting with CMA80 in CHCl₃ 0 to 60%] (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-hydroxypropan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**222b**) (39 mg, 0.082 mmol, 9% yield) as an off-white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.88 (t, *J* = 5.7 Hz) & 8.61 (t, *J* = 5.9 Hz) (2t, 1H, D₂O exchangeable), 8.24 – 8.13 (m, 1H), 7.71 (s, 1H), 7.60 – 6.94 (m, 7H), 5.63 (d, *J* = 3.6 Hz) & 5.42 (d, *J* = 2.9 Hz) (2d, 2H), 5.51 (t, *J* = 6.0 Hz) & 4.81 (t, *J* = 5.7 Hz) (2t, 1H, D₂O exchangeable), 4.59 – 3.74 (m, 5H), 3.55 – 3.24 (m, 2H), 1.15 (d, *J* = 6.6 Hz) & 0.96 (d, *J* = 6.9 Hz) (2d, 3H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.26, -121.65; MS (ES⁺): 498.5 (M+Na); MS (ES⁻): 474.4 (M-1), 510.4 (M+Cl).

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Scheme 223



Preparation of N-(3-acetyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)-3,3-difluoropiperidine-1-carboxamide (**223c**)

Step-1: Preparation of methyl 3-acetyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**223a**)
 Reaction of 2-(3-acetyl-5-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid (**206c**) TFA adduct (237 g, 0.86 mmol) with N-(2'-chloro-2-fluorobiphenyl-3-yl)-2-(isopropylamino)acetamide (**115c**) (250 mg, 0.78 mmol) according to the procedure reported in step-3 of scheme-2 gave after workup and purification by flash column [silica (24g), eluting with DMA80 in DCM 0 to 20%] methyl 3-acetyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**223a**) (280 mg, 0.48 mmol, 62% yield) as a off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (mixture of two

rotamers) δ 10.27 and 9.74 (2s, 1H), 8.85 and 8.83 (dd, $J = 1.6, 0.8$ Hz, 1H), 8.18-6.97 (m, 9H), 5.83 and 5.64 (2s, 2H), 4.69 – 4.57 and 4.38 – 4.26 (2m, 1H), 4.47 and 4.09 (2s, 2H), 3.918 and 3.91 (s, 3H), 2.657 and 2.65 (2s, 3H), 1.29 and 1.07 (2d, $J = 6.8$ Hz, 6H); MS (ES+): 579.6 (M+1), 601.6 (M+Na); MS (ES-): 577.5 (M-1), 613.5 (M+Cl).

5 Step-2: Preparation 3-acetyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**223b**)

Reaction of methyl 3-acetyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**223a**) (280 mg, 0.48 mmol) in THF (25 mL) with a solution of lithium hydroxide hydrate (23 mg, 0.97 mmol) in
10 water (1 mL) according to the procedure reported in step-2 of scheme-29 gave after workup 3-acetyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**223b**) (250 mg, 0.44 mmol, 92% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) (mixture of two rotamers) δ 13.01 (s, 1H), 10.27 and 9.74 (2s, 1H), 8.83 and 8.82 (2s, 1H), 8.19-6.97 (m, 9H),
15 5.81 and 5.63 (2s, 2H), 4.70 – 4.57 and 4.38 – 4.27 (2m, 1H), 4.47 and 4.09 (s, 2H), 2.65 and 2.64 (2s, 3H), 1.29 and 1.07 (2d, $J = 6.7$ Hz, 6H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -126.85, -126.96; MS (ES-): 563.6 & 565.4 (M-1).

Step-3: Preparation of N-(3-acetyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)-3,3-difluoropiperidine-1-
20 carboxamide (**223c**)

To a solution of 3-acetyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**223b**) (150 mg, 0.27 mmol) in toluene (4 mL) was added triethylamine (0.19 mL, 1.33 mmol), diphenyl phosphorazidate (110 mg, 0.4 mmol) and stirred at RT for 2h. Dioxane (2 ml) was added to
25 the reaction mixture and heated at 90 °C for 2h. The reaction mixture was cooled to RT, added 3,3-difluoropiperidine hydrochloride (84 mg, 0.53 mmol) and continued stirring at 90 °C for 20h. The reaction mixture was cooled to RT, partitioned between 0.5 M aq. HCl (40 ml) and EtOAc (50 ml). The aqueous layer was separated and extracted with EtOAc (40 ml). The organic layers were combined washed with saturated aqueous NaHCO₃ solution (40 ml),
30 brine, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica gel (12 g), eluting with MeOH:EtOAc (9:1) in hexanes 0 to 70%] to afford N-(3-acetyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)-3,3-difluoropiperidine-1-carboxamide (**223c**) (32 mg, 0.047 mmol, 18% yield) as white solid; ^1H NMR (300 MHz,

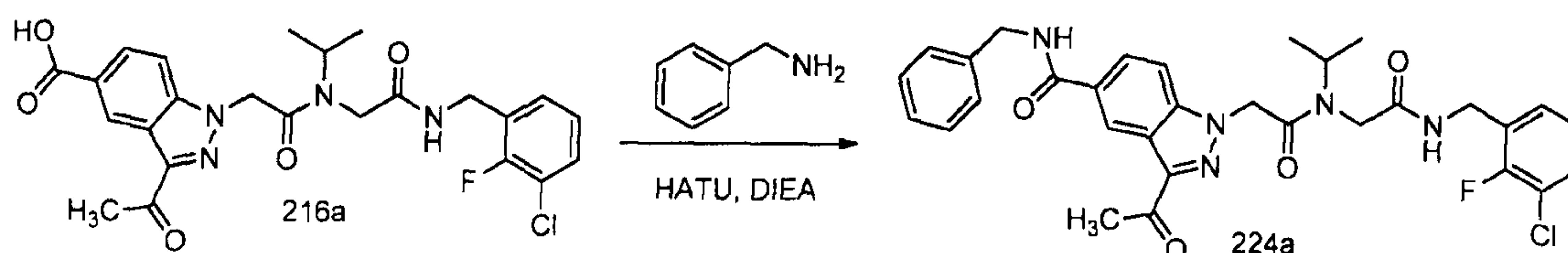
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DMSO-*d*₆) (mixture of two rotamers) δ 10.26 and 9.75(2s, 1H), 8.84 and 8.82 (2s, 1H), 8.24 and 8.23 (2s, 1H), 8.11 and 7.95 (2t, J = 7.8 Hz, 1H), 7.67 – 7.01 (m, 8H), 5.69 and 5.53 (2s, 2H), 4.72 – 4.56 and 4.38 – 4.27 (2m, 1H), 4.46 and 4.09 (2s, 2H), 3.82 (t, J = 12.0 Hz, 2H), 3.58-3.48 (m, 2H), 2.595 and 2.588 (2s, 3H), 2.17 – 1.95 (m, 2H), 1.78 – 1.64 (m, 2H), 1.27 and 1.07 (2d, J = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) (mixture of two rotamers) δ -101.15, -126.86 and -126.99; MS (ES⁺): 683.7 (M+1), 705.7 (M+Na), MS (ES⁻): 717.6 (M+Cl).

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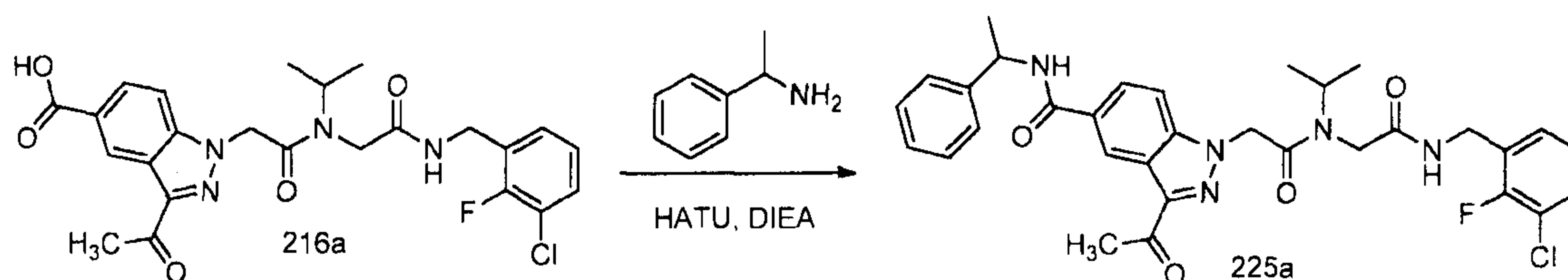
Scheme 224



Preparation of 3-acetyl-N-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxamide (**224a**)

Reaction of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**216a**) (50 mg, 0.1 mmol) with phenylmethanamine (0.017 mL, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (8 g), eluting DCM/MeOH (1:0 to 19:1)] 3-acetyl-N-benzyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxamide (**224a**) (35 mg, 60%) as a white solid as mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.25 (t, J = 5.9 Hz, 1H), 8.85 (t, J = 5.6 Hz) and 8.36 (t, J = 5.9 Hz) (2t, 1H), 8.79 – 8.75 (m, 1H), 8.00 (dd, J = 8.9, 1.6 Hz,) and 7.95 (dd, J = 8.9, 1.6 Hz) (2dd, 1H), 7.72 (d) and 7.66 (d, J = 8.9 Hz) (2d, 1H), 7.58 – 6.86 (m, 8H), 5.74 and 5.57 (2s, 2H), 4.64 – 4.22 (m, 5H), 4.19 and 3.85 (2s, 2H), 2.69 and 2.64 (s, 3H), 1.26 (d, J = 6.5 Hz) and 1.00 (d, J = 6.7 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.21, -121.74; MS (ES⁺): 614.7 (M+Na); MS (ES⁻): 590.6 (M-1), 626.5 (M+Cl).

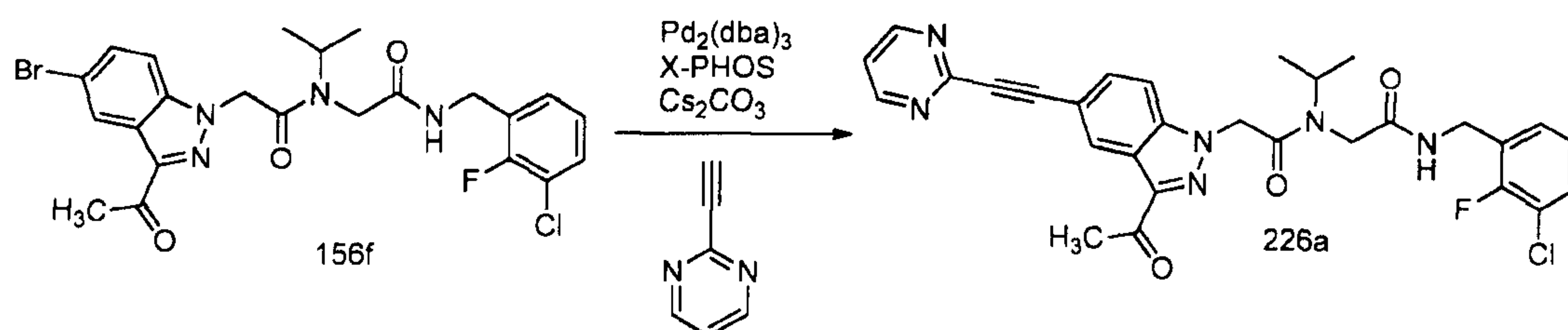
Scheme 225



Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N-(1-phenylethyl)-1H-indazole-5-carboxamide (225a)

Reaction of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**216a**) (50 mg, 0.1 mmol) with 1-phenylethanamine (0.02 mL, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (8 g), eluting EtOAc/MeOH (1:0 to 19:1)] 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N-(1-phenylethyl)-1H-indazole-5-carboxamide (**225a**) (37 mg, 61%) as a white solid as mixture of two rotamers; ^1H NMR(300 MHz, DMSO- d_6) δ 9.08 – 9.00 (m, 1H), 8.85 (t, J = 5.8 Hz) and 8.36 (t, J = 5.9 Hz) (2t, 1H), 8.77 – 8.72 (m, 1H), 7.98 (dd, J = 8.9, 1.6 Hz) and 7.92 (dd, J = 8.9, 1.6 Hz) (2dd, 1H), 7.70 (d) and 7.66 (d, J = 8.9 Hz) (2d, 1H), 7.55 – 6.90 (m, 8H), 5.73 and 5.56 (2s, 2H), 5.30 – 5.12 (m, 1H), 4.64 – 4.50 and 4.29 – 4.21 (2m, 1H), 4.47 (d, J = 5.6 Hz) and 4.32 (d, J = 5.9 Hz) (2d, 2H), 4.19 and 3.85 (2s, 2H), 2.69 and 2.64 (2s, 3H), 1.55 – 1.46 (m, 3H), 1.25 (d, J = 6.6 Hz) and 1.00 (d, J = 6.7 Hz) (2d, 6H); ^{19}F NMR(282 MHz, DMSO- d_6) δ -121.22, -121.73; MS (ES-): 604.2 (M-1).

Scheme 226



Preparation of 2-(3-acetyl-5-(pyrimidin-2-ylethynyl)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**226a**)

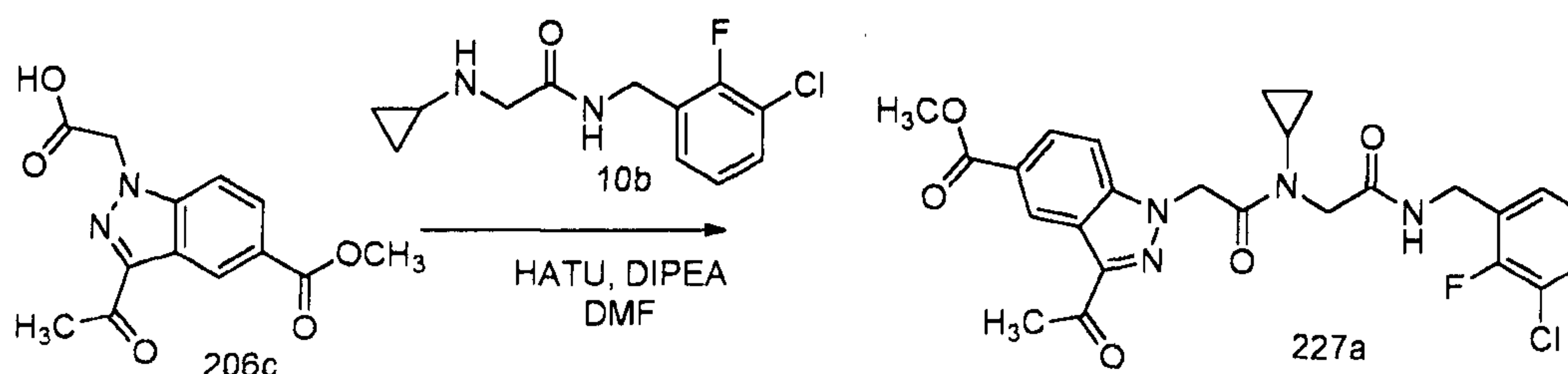
Reaction of 2-(3-acetyl-5-bromo-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**156f**) (300 mg, 0.56 mmol) using Cs_2CO_3 (365 mg, 1.12 mmol), dicyclohexyl(2',4',6'-triisopropylbiphenyl-2-yl)phosphine (X-PHOS, 53 mg, 0.112

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mmol), Pd₂(dba)₃ (51 mg, 0.056 mmol) according to procedure reported in Scheme 92 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with MeOH in DCM from 0 to 100%] 2-(3-acetyl-5-(pyrimidin-2-ylethynyl)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**226a**) (16 mg, 0.029 mmol, 5 % yield) as a dark-yellow solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.93 – 8.80 (m) and 8.36 (t, *J* = 5.8 Hz) (3H), 8.49 – 8.42 (m, 1H), 7.82 – 6.98 (m, 6H), 5.76 & 5.59 (2s, 2H), 4.64 – 4.52 & 4.29 – 4.21 (2m, 1H), 4.48 (d, *J* = 5.6 Hz) & 4.32 (d, *J* = 5.8 Hz) (2d, 2H), 4.19 & 3.85 (2s, 2H), 2.64 (s, 3H), 1.26 (d, *J* = 6.4 Hz) & 1.00 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.20, -121.71; MS (ES⁺): 561.5 (M+1), 583.5 (M+Na); MS (ES⁻): 559.4 (M-1), 595.4 (M+Cl).

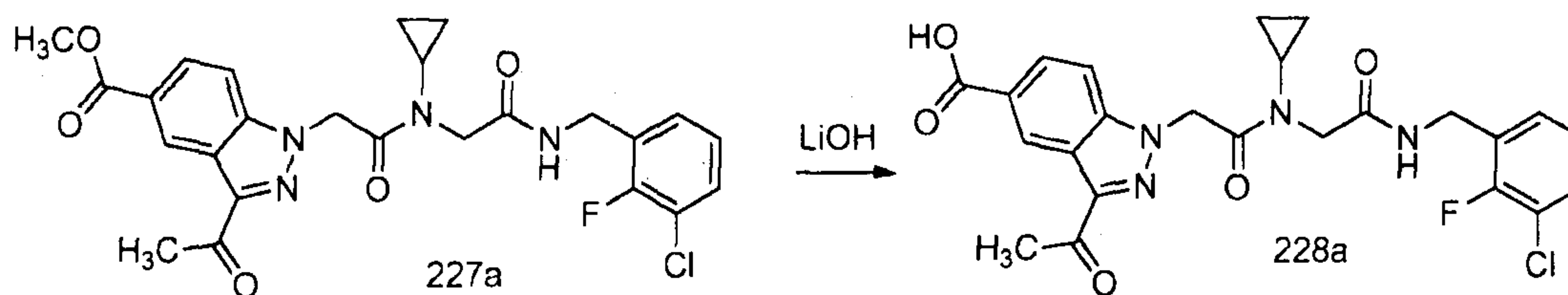
Scheme 227



Preparation of methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**227a**)

Reaction of 2-(3-acetyl-5-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid (**206c**) TFA adduct (2.09 g, 5.36 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (1.65 g, 6.43 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (40 g), eluting with DMA80 in DCM 0 to 40%] methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**227a**) (2.3 g, 4.47 mmol, 83% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.87 – 8.81 (m, 1H), 8.48 (t, *J* = 5.9 Hz, 1H), 7.99 (dd, *J* = 8.9, 1.6 Hz, 1H), 7.88 – 7.77 (m, 1H), 7.50 – 7.39 (m, 1H), 7.28 – 7.18 (m, 1H), 7.14 – 7.03 (m, 1H), 5.80 (s, 2H), 4.34 (d, *J* = 5.7 Hz, 2H), 3.99 (s, 2H), 3.91 (s, 3H), 3.20 – 3.05 (m, 1H), 2.65 (s, 3H), 1.10 – 0.99 (m, 2H), 0.96 – 0.82 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.57; MS (ES⁺): 515.5 (M+1); MS (ES⁻): 513.4 (M-1).

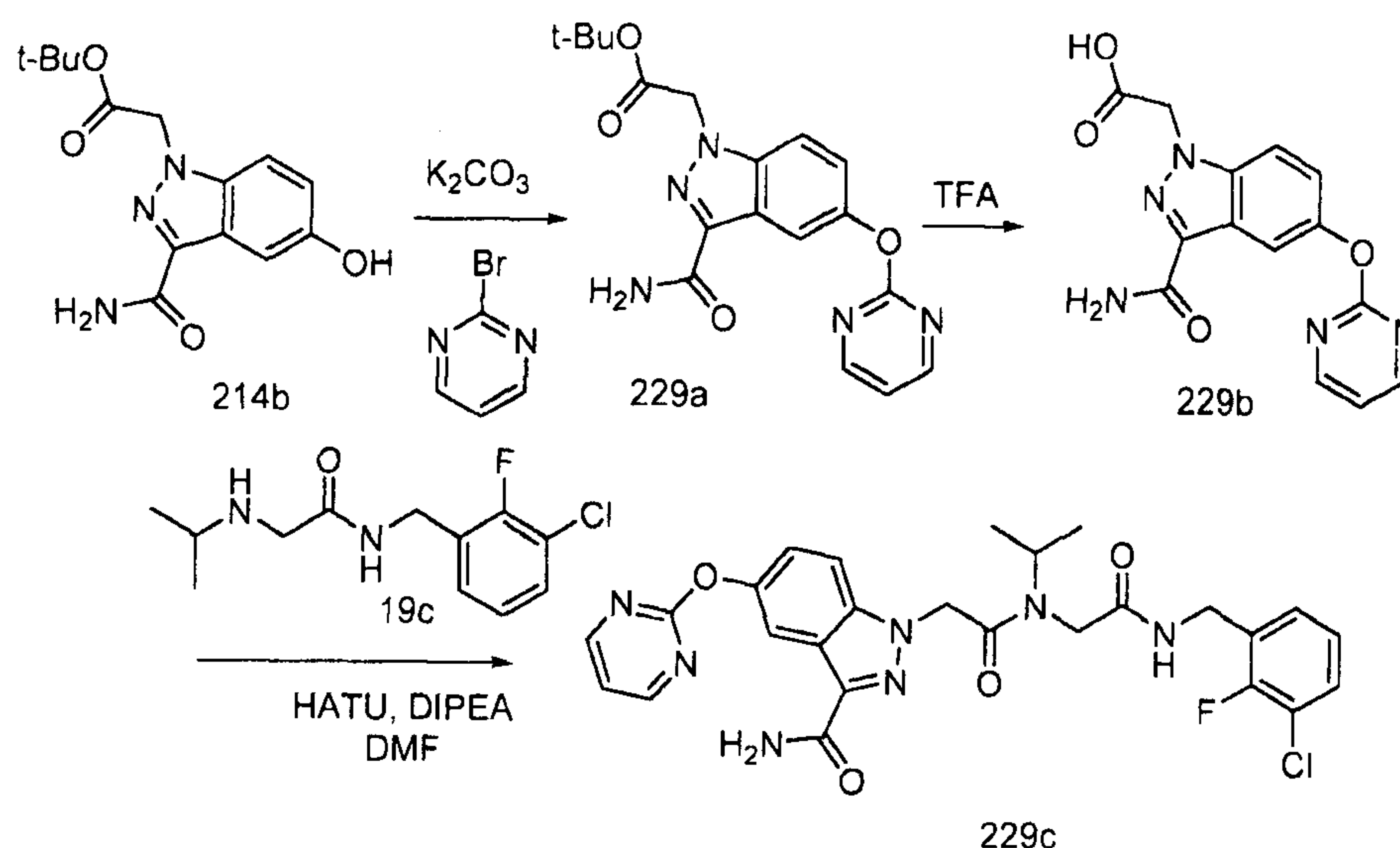
Scheme 228



Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**228a**)

- 5 Reaction of methyl 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**227a**) (2.3 g, 4.47 mmol) in MeOH (25 mL) and water (25 mL) with a solution of lithium hydroxide hydrate (1.31 g, 31.3 mmol) in water (10 mL) according to the procedure reported in step-2 of Scheme 129 gave after workup 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**228a**) (2.2 g, 4.39 mmol, 98% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.05 (s, 1H), 8.88 – 8.80 (m, 1H), 8.50 (t, *J* = 5.9 Hz, 1H), 8.04 – 7.95 (m, 1H), 7.84 – 7.75 (m, 1H), 7.51 – 7.40 (m, 1H), 7.29 – 7.19 (m, 1H), 7.14 – 7.04 (m, 1H), 5.80 (s, 2H), 4.34 (d, *J* = 5.7 Hz, 2H), 4.00 (s, 2H), 3.20 – 3.07 (m, 1H), 2.65 (s, 3H), 1.09 – 0.99 (m, 2H), 0.98 – 0.83 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.57; MS (ES⁺): 501.5 (M+1); (ES⁻): 499.4 (M-1).
- 10
- 15

Scheme 229



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(pyrimidin-2-yloxy)-1H-indazole-3-carboxamide (**229c**)

Step-1: Preparation of tert-butyl 2-(3-carbamoyl-5-(pyrimidin-2-yloxy)-1H-indazol-1-yl)acetate (**229a**)

To a solution of tert-butyl 2-(3-carbamoyl-5-hydroxy-1H-indazol-1-yl)acetate (**214b**) (115 mg, 0.4 mmol) in acetonitrile (5 mL) was added 2-bromopyrimidine (78 mg, 0.49 mmol),
 5 potassium carbonate (164 mg, 1.18 mmol) and heated at reflux for 16 h. The reaction mixture was concentrated in vacuum and residue was suspended in brine (50 mL) and extracted with EtOAc (2 x 50 mL). The organic layers were combined dried, filtered and evaporated to dryness. The residue was purified by flash column chromatography [silica gel (12 g), eluting with EtOAc/MeOH (9:1) in hexanes from 0 to 100%] to afford tert-butyl 2-(3-carbamoyl-5-
 10 (pyrimidin-2-yloxy)-1H-indazol-1-yl)acetate (**229a**) (130 mg, 0.35 mmol, 89 %yield) as an orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.65 (s, 1H), 8.64 (s, 1H), 7.86 (dd, *J* = 2.3, 0.7 Hz, 1H), 7.81 – 7.75 (m, 2H), 7.46 (s, 1H), 7.34 (dd, *J* = 9.0, 2.3 Hz, 1H), 7.28 (t, *J* = 4.8 Hz, 1H), 5.39 (s, 2H), 1.44 (s, 9H); MS (ES⁺): 370.4 (M+1), 739.7 (2M+1), 392.4 (M+Na); MS (ES⁻): 368.4 (M-1).

15 Step-2: Preparation of 2-(3-carbamoyl-5-(pyrimidin-2-yloxy)-1H-indazol-1-yl)acetic acid (**229b**)

Reaction of tert-butyl 2-(3-carbamoyl-5-(pyrimidin-2-yloxy)-1H-indazol-1-yl)acetate (**229a**) (118 mg, 0.32 mmol) with TFA (0.74 mL, 9.58 mmol) in DCM (5 mL) according to the procedure reported in step-2 of Scheme 2 gave after workup and trituration with hexanes, 2-
 20 (3-carbamoyl-5-(pyrimidin-2-yloxy)-1H-indazol-1-yl)acetic acid (**229b**) (0.129 g, 0.302 mmol, 95 % yield) as a yellow solid in the form of TFA adduct; MS (ES⁺): 314.3 (M+1).

Step-3: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(pyrimidin-2-yloxy)-1H-indazole-3-carboxamide (**229c**)

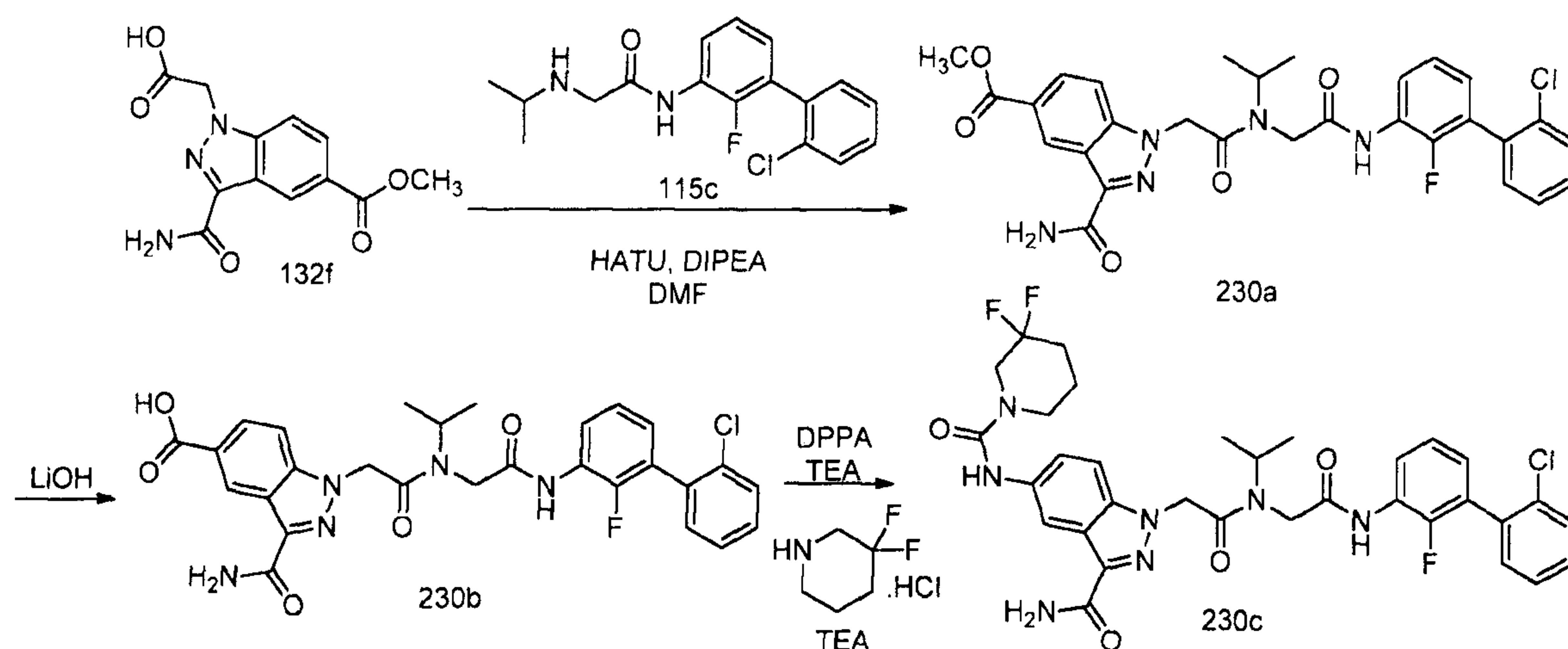
25 Reaction of 2-(3-carbamoyl-5-(pyrimidin-2-yloxy)-1H-indazol-1-yl)acetic acid (**229b**) TFA adduct (119mg, 0.38 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (118 mg, 0.46 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (12 g), eluting with MeOH in DCM, 0 to 50%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-
 30 oxoethyl)-5-(pyrimidin-2-yloxy)-1H-indazole-3-carboxamide (**229c**) (85 mg, 0.15 mmol, 40% yield) as an off-white solid as a mixture of two rotamers; ¹H NMR(300 MHz, DMSO-*d*₆) δ 8.83 (t, *J* = 5.7 Hz) & 8.38 (t, *J* = 5.9 Hz) (2t, 1H), 8.67 – 8.62 (m, 2H), 7.88 – 7.83 (m, 1H), 7.75 and 7.73 (2s, 1H), 7.68 (dd, *J* = 9.1, 0.7 Hz) and 7.62 (dd, *J* = 9.1, 0.7 Hz) (2dd, 1H), 7.55 – 7.01 (m, 6H), 5.63 & 5.49 (2s, 2H), 4.65 – 4.50 & 4.39 – 4.24 (2m, 1H), 4.46 (d,

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$J = 5.6$ Hz) & 4.32 (d, $J = 5.8$ Hz) (2d, 2H), 4.19 & 3.85 (2s, 2H), 1.24 (d, $J = 6.4$ Hz) & 1.00 (d, $J = 6.7$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.21, -121.77; MS (ES+): 554.5 (M+1), 576.5 (M+Na); MS (ES-): 588.4 (M+Cl).

Scheme 230



Preparation of 1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropiperidine-1-carboxamido)-1H-indazole-3-carboxamide (**230c**)

- Step-1: Preparation of methyl 3-carbamoyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**230a**)
- Reaction of 2-(3-carbamoyl-5-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid (**132f**) TFA adduct (300 g, 0.94 mmol) with N-(2'-chloro-2-fluorobiphenyl-3-yl)-2-(isopropylamino)acetamide (**115c**) (300 mg, 0.94 mmol) according to the procedure reported in step-3 of scheme-2 gave after workup and purification by flash column [silica (24g), eluting with DMA80 in DCM 0 to 20%] methyl 3-carbamoyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**230a**) (310 mg, 0.53 mmol, 57% yield) as an off-white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) (mixture of two rotamers) δ 10.27 and 9.76 (2s, 1H), 8.91-8.86 (m, 1H), 8.16-6.96 (m, 11H), 5.71 and 5.56 (2s, 2H), 4.68 – 4.55 and 4.38 – 4.26 (2m, 1H), 4.47 and 4.08 (2s, 2H), 3.909 and 3.90 (2s, 3H), 1.27 and 1.06 (2d, $J = 6.8$ Hz, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -126.77, -126.94; MS (ES+): 580.5 (M+1), 602.5 (M+Na), MS (ES-): 578.5 (M-1), 614.6 (M+Cl).

- Step-2: Preparation 3-carbamoyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**230b**)

Reaction of methyl 3-carbamoyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylate (**230a**) (300 mg, 0.52 mmol) in THF (5 mL) with a solution of lithium hydroxide hydrate (25 mg, 1.03 mmol) in water (1 mL) according to the procedure reported in step-2 of scheme-29 gave after workup

5 3-carbamoyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**230b**) (270 mg, 0.48 mmol, 92% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (mixture of two rotamers) δ 12.94 (s, 1H), 10.26 and 9.76 (2s, 1H), 8.86 and 8.85 (2dd, *J* = 1.6, 0.8 Hz, 1H), 8.16-6.96 (m, 11H), 5.69 and 5.55 (2s, 2H), 4.68 – 4.56 and 4.37 – 4.28 (m, 1H), 4.47 and

10 4.08 (2s, 2H), 1.27 and 1.06 (2d, *J* = 6.8 Hz, 6H); MS (ES⁻): 564.4 & 566.4 (M-1).

Step-3: Preparation of 1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropiperidine-1-carboxamido)-1H-indazole-3-carboxamide (**230c**)

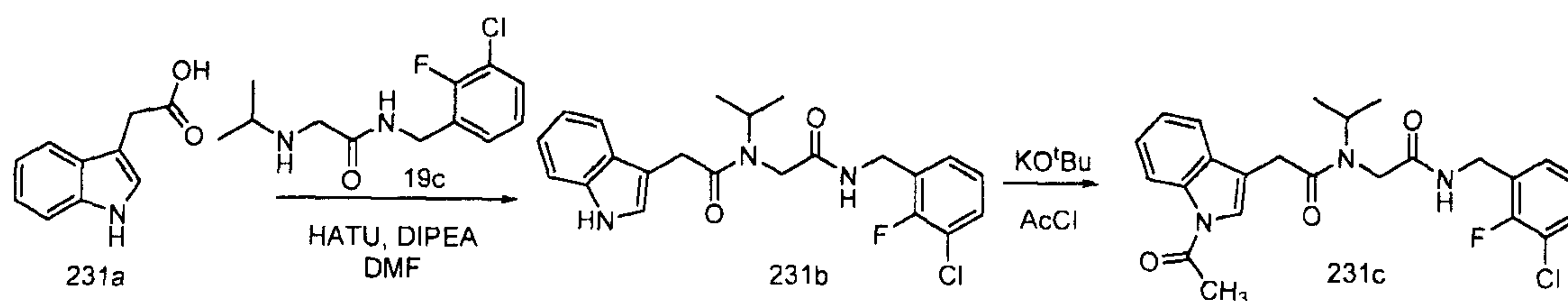
Compound **230c** was prepared from 3-carbamoyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-

15 biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**230b**) (150 mg, 0.27 mmol) according to the procedure reported in step-3 of scheme-223. This gave after work up and purification by flash column chromatography [silica gel (12 g), eluting with MeOH:EtOAc (9:1) in hexanes 0 to 70%] (120 mg, 0.18 mmol, 66% yield) of compound **230c** as white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (mixture of two rotamers) δ

20 10.25 and 9.77 (2s, 1H), 8.78 and 8.77 (2s, 1H), 8.188 and 8.183 (2s, 1H), 8.19 - 8.05 and 7.99- 7.90 (2m, 1H), 7.69-6.99 (m, 10H), 5.58 and 5.45 (2s, 2H), 4.70 – 4.56 and 4.38 – 4.27 (2m, 1H), 4.46 and 4.08 (2s, 2H), 3.81 (t, *J* = 12.1 Hz, 2H), 3.58-3.47 (m, 2H), 2.18 – 1.95 (m, 2H), 1.79 – 1.64 (m, 2H), 1.25 and 1.06 (2d, *J* = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) (mixture of two rotamers) δ -101.16, -126.79 and -126.98; MS (ES⁺): 684.6

25 (M+1).

Scheme 231



Preparation of 2-(1-acetyl-1H-indol-3-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**231c**)

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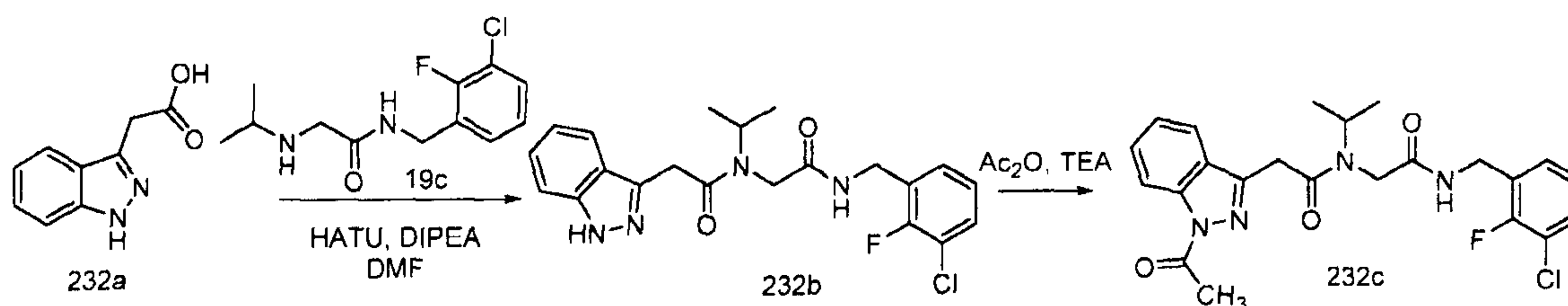
Step-1: Preparation of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-(1H-indol-3-yl)-N-isopropylacetamide (**231b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (795 mg, 3.07 mmol) with 2-(1H-indol-3-yl)acetic acid (**231a**) (359 mg, 2.05 mmol) according to the
 5 procedure reported in step-3 of Scheme 2 gave after workup and trituration of crude with EtOAc N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-(1H-indol-3-yl)-N-isopropylacetamide (**231b**) (583 mg, 1.40 mmol, 68% yield) as a white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.89 (s, 1H), 8.63 (t, *J* = 5.7 Hz) & 8.32 (t, *J* = 5.9 Hz) (2t, 1H), 7.58 – 6.90 (m, 8H), 4.73 – 4.57 & 4.29 – 4.16 (2m, 1H), 4.41 (d, *J* =
 10 5.7 Hz) & 4.34 (d, *J* = 5.9 Hz) (2d, 2H), 3.94 & 3.60 (2s, 2H), 3.81 & 3.80 (2s, 2H), 1.00 (d, *J* = 6.5 Hz) & 0.96 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.31, -121.81; MS (ES⁺): 416.5 (M+1), 438.5 (M+Na); MS (ES⁻): 414.4 (M-1), 450.4 (M+Cl).

Step-2: Preparation of 2-(1-acetyl-1H-indol-3-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**231c**)

15 To a solution of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-(1H-indol-3-yl)-N-isopropylacetamide (**231b**) (0.15 g, 0.360 mmol) in THF (5 mL) at 0 °C under Argon atmosphere was added potassium tert-butoxide (40 mg, 0.361 mmol) and stirred for 10 mins. To the resulting suspension was added acetyl chloride (0.023 mL, 0.325 mmol) and stirred at 0 °C for 30 mins. The reaction mixture quenched with saturated aqueous NH₄Cl solution (30
 20 mL) and extracted with EtOAc (2 x 30 mL). The combined organic layers were washed with brine, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica gel (12 g), eluting with EtOAc in hexanes 0 to 100%] to afford 2-(1-acetyl-1H-indol-3-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**231c**) (42 mg, 0.092 mmol, 25% yield) as a white solid; ¹H NMR (300
 25 MHz, DMSO-*d*₆) (mixture of two rotamers) δ 8.70 and 8.40 (2t, *J* = 5.9 Hz, 1H), 8.33-8.27 (m, 1H), 7.90 and 7.63 (2s, 1H), 7.61 - 7.09 (m, 6H), 4.71 – 4.59 and 4.29 – 4.18 (2m, 1H), 4.42 and 4.35 (2d, *J* = 5.8 Hz, 2H), 4.09 and 3.69 (2s, 2H), 3.85 (s, 2H), 2.60 and 2.59 (2s, 3H), 1.10 (d, *J* = 6.5 Hz) and 0.99 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ -121.29, -121.75; MS (ES⁺) 480.4 & 482.5 (M+Na); MS (ES⁻):
 30 456.4 & 458.4 (M-1).

Scheme 232



Preparation of 2-(1-acetyl-1H-indazol-3-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**232c**)

- 5 Step-1: Preparation of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-(1H-indazol-3-yl)-N-isopropylacetamide (**232b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (257 mg, 0.99 mmol) with 2-(1H-indazol-3-yl)acetic acid (**232a**) (175 mg, 0.99 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column
10 chromatography [silica gel (12 g), eluting with EtOAc in hexane 0 to 100%] N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-(1H-indazol-3-yl)-N-isopropylacetamide (**232b**) (310 mg, 0.74 mmol, 75% yield); ¹H NMR (300 MHz, DMSO-*d*₆) (a mixture of two rotamers) δ 12.85 and 12.76 (2s, 1H), 8.70 and 8.48 (2t, *J* = 6.0 Hz, 1H), 7.70 and 7.65 (2d, *J* = 8.1 Hz, 1H), 7.54-6.99 (m, 6H), 4.68 – 4.57 and 4.33 – 4.23 (2m, 1H), 4.42 and 4.37 (2d, *J* = 6.0 Hz, 2H), 4.11 and 4.09 (2s, 2H), 3.90 and 3.81 (2s, 2H), 1.03 and 0.95 (2d, *J* = 6.8 Hz, 6H); MS
15 (ES⁺): 417.4 (M+1), 439.4 (M+Na); MS (ES⁻): 415.3 (M-1).

Step-2: Preparation of 2-(1-acetyl-1H-indazol-3-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**232c**)

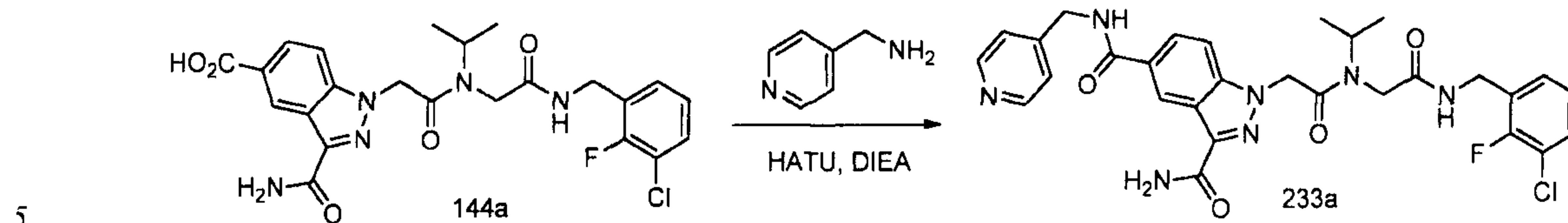
To a solution of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-(1H-indazol-3-yl)-N-isopropylacetamide (**232b**) (150 mg, 0.36 mmol) in DCM (5 mL) was added at room
20 temperature triethylamine (0.15 mL, 1.08 mmol), DMAP (8.79 mg, 0.072 mmol), acetic anhydride (0.068 mL, 0.72 mmol) and stirred at RT for 48h. The reaction mixture was concentrated to dryness and purified by flash column chromatography [silica gel (12 g), eluting with EtOAc in hexane 0 to 100%] to afford 2-(1-acetyl-1H-indazol-3-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**232c**) (82 mg, 0.18 mmol, 50% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) (mixture of two rotamers) δ 8.75 and 8.34 (2t, *J* = 5.7 Hz, 1H), 8.30 and 8.27 (2dt, *J* = 2.7, 0.9 Hz, 1H), 7.82 - 7.74 (m, 1H), 7.64 - 7.57 (m, 1H), 7.52 - 7.02 (m, 4H), 4.69 - 4.57 and 4.40 - 4.36 (2m, 1H), 4.43 and 4.33 (2d, *J* = 6.0 Hz, 2H), 4.24 and 4.15 (2s, 2H), 4.05 and 3.83 (2s, 2H), 2.68 and 2.67 (2s, 3H),

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1.17 and 1.00 (2d, $J = 6.8$ Hz, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) (a mixture of two rotamers) δ -121.28, -121.81; MS (ES+) 459.5 (M+1), 481.4 (M+23), MS (ES-) 493.4 (M+Cl).

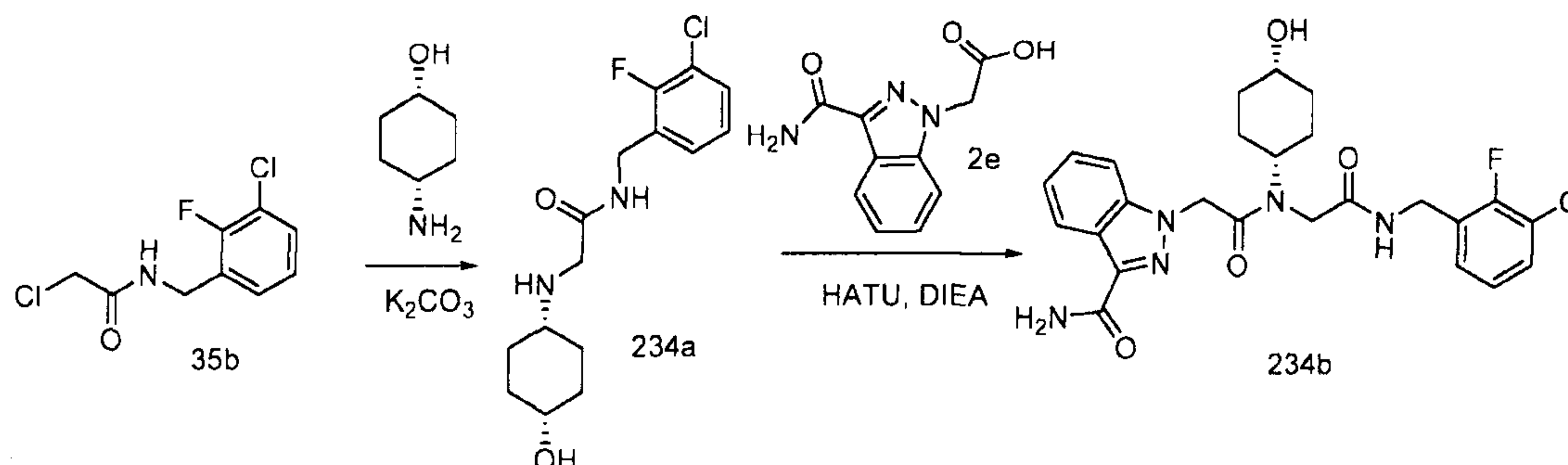
Scheme 233



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-(pyridin-4-ylmethyl)-1H-indazole-3,5-dicarboxamide (**233a**)

Reaction of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**144a**) (50 mg, 0.1 mmol) with pyridin-4-ylmethanamine (0.015 mL, 0.15 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (4 g), eluting with MeOH in DCM (1:0 to 9:1)] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-N5-(pyridin-4-ylmethyl)-1H-indazole-3,5-dicarboxamide (**233a**) (26 mg, 44%) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) (mixture of two rotamers) δ 9.32 – 9.26 (m, 1H), 8.83 (t, $J = 5.9$ Hz) and 8.36 (t, $J = 5.9$ Hz) (2t, 1H), 8.80 – 8.77 (m, 1H), 8.53 – 8.47 (m, 2H), 7.94 (ddd, $J = 10.8, 8.9, 1.7$ Hz, 1H), 7.83 and 7.80 (2s, 1H), 7.72 – 7.60 (m, 1H), 7.56 – 6.95 (m, 6H), 5.64 and 5.50 (2s, 2H), 4.62 – 4.22 (m, 5H), 4.19 and 3.84 (2s, 2H), 1.23 (d, $J = 6.4$ Hz) and 0.99 (d, $J = 6.8$ Hz) (2d, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.22, -121.72; MS (ES+): 594.6 & 596.6 (M+1); MS (ES-): 628.6 & 630.5 (M+Cl).

Scheme 234



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((1S,4S)-4-hydroxycyclohexyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**234b**)

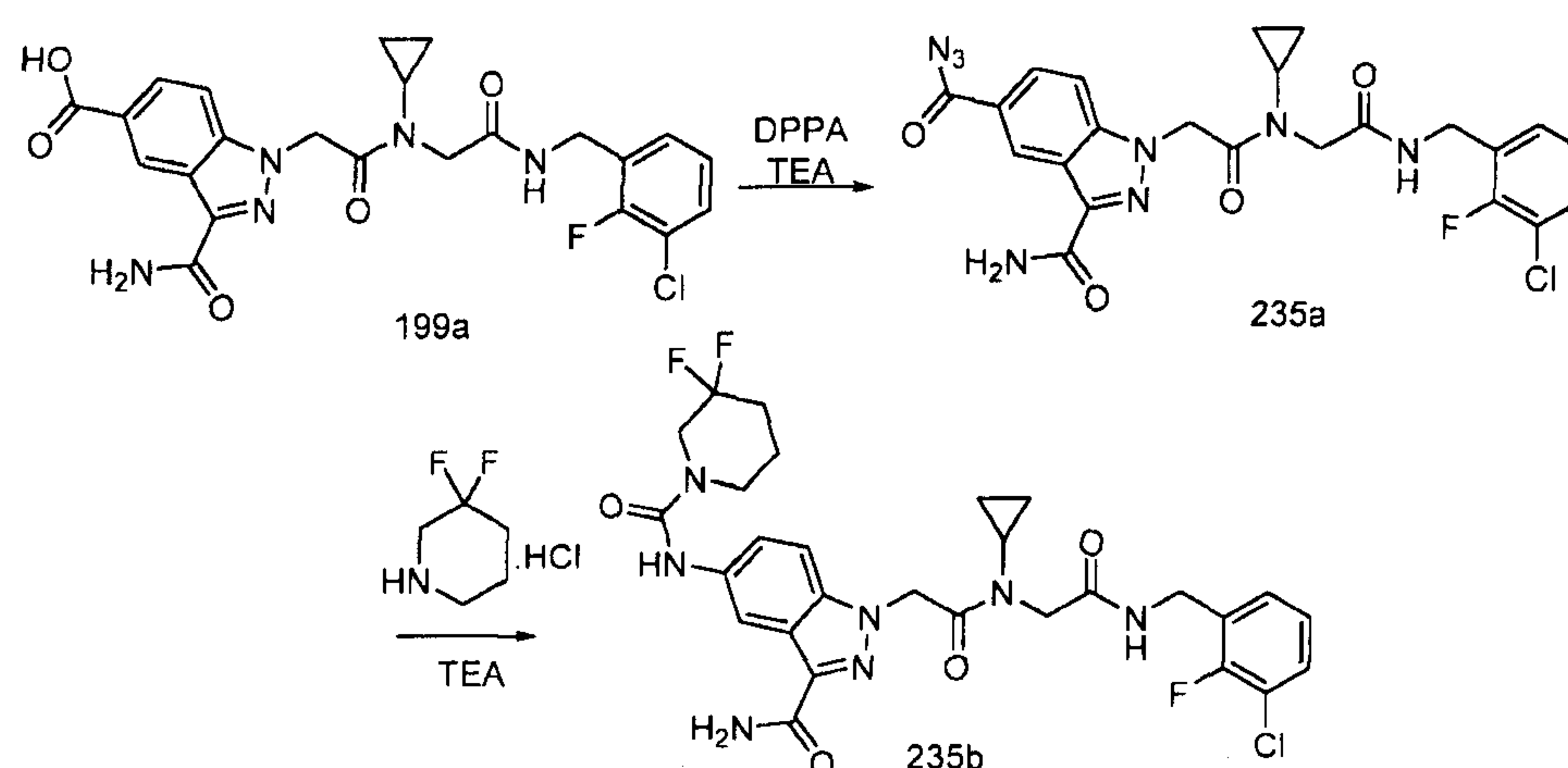
Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-(((cis)-4-hydroxycyclohexyl)amino)acetamide (**234a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 2.12 mmol) with (1s,4s)-4-aminocyclohexanol (244 mg, 2.12 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup N-(3-chloro-2-fluorobenzyl)-2-(((cis)-4-hydroxycyclohexyl)amino)acetamide (**234a**) as a colorless oil which was used as such in the next step; MS (ES⁺): 315.4 (M+1); MS (ES⁻): 313.4 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((cis)-4-hydroxycyclohexyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**234b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-(((1s,4s)-4-hydroxycyclohexyl)amino)acetamide (**234a**) (360 mg, 1.14 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (301 mg, 1.37 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)((cis)-4-hydroxycyclohexyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**234b**) (163 mg, 0.32 mmol, 28% yield) as a white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.89 (t, *J* = 5.7 Hz) & 8.36 (t, *J* = 6.0 Hz) (2t, 1H), 8.23 – 8.11 (m, 1H), 7.79 – 6.98 (m, 8H), 5.61 & 5.45 (2s, 2H), 4.52 – 3.73 (m, 7H), 1.88 – 1.13 (m, 8H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.25, -121.69; MS (ES⁺): 516.5 (M+1), 538.4 (M+Na); MS (ES⁻): 514.4 (M-1), 550.5 (M+Cl).

Scheme 235



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropiperidine-1-carboxamido)-1H-indazole-3-carboxamide (**235b**)

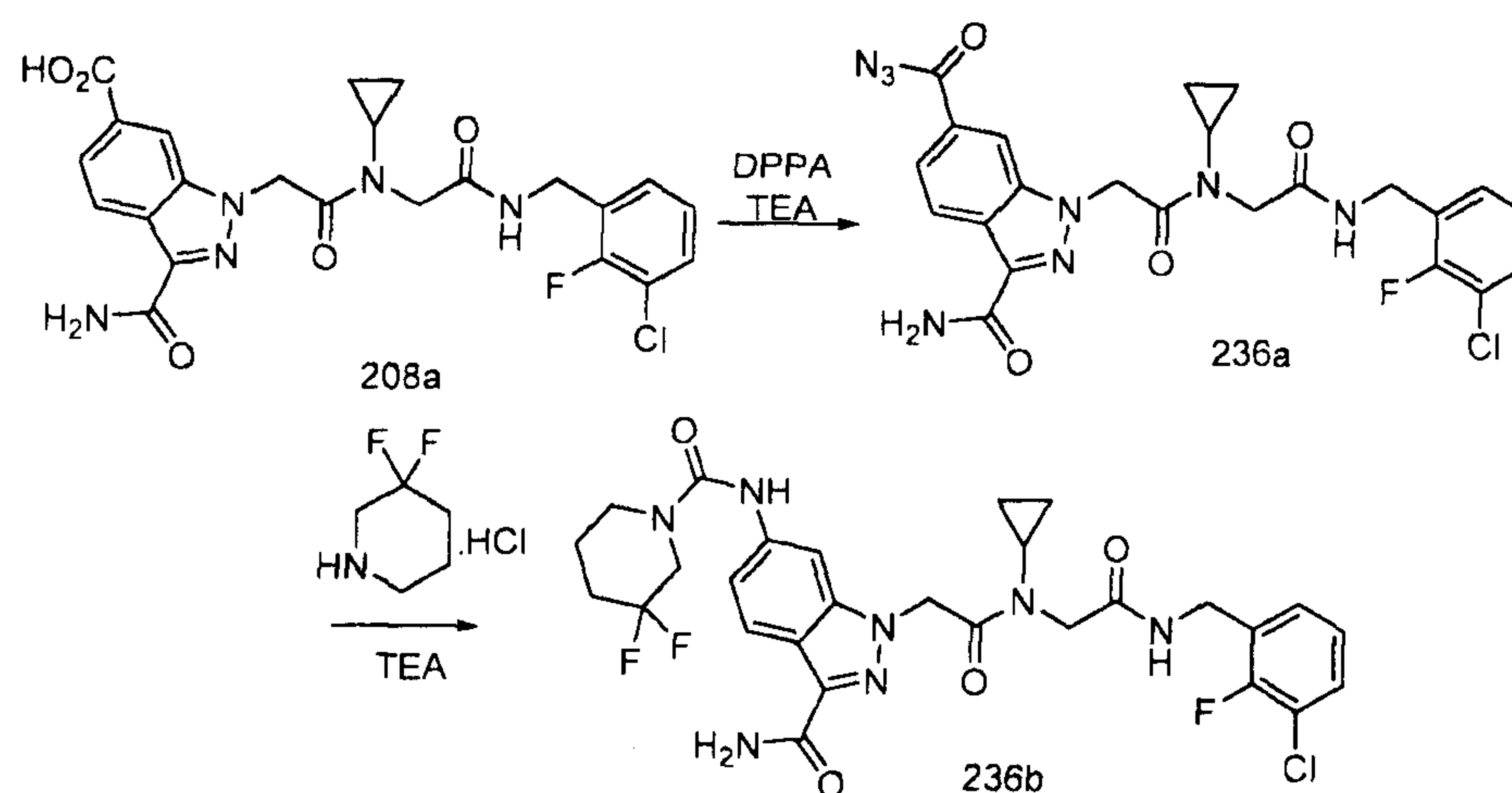
Step-1: Preparation of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**235a**)

Compound **235a** was prepared from 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**199a**) (4 g, 7.97 mmol) according to the procedure reported in step-3 of Scheme 129 to afford product as a white solid (6.6 g, 12.53 mmol, 157 % yield), which was used in the next step without further purification; MS (ES⁻): 525.4 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropiperidine-1-carboxamido)-1H-indazole-3-carboxamide (**235b**)

Compound **235b** was prepared from 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**235a**) (500 mg, 0.47 mmol) and 3,3-difluoropiperidine hydrochloride (150 mg, 0.95 mmol) using TEA (0.27 mL, 1.9 mmol) as base according to the procedure reported in step-4 of Scheme 129 to afford after workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropiperidine-1-carboxamido)-1H-indazole-3-carboxamide (**235b**) (86 mg, 0.14 mmol, 29% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.78 (s, 1H), 8.50 (t, *J* = 5.8 Hz, 1H), 8.25 – 8.13 (m, 1H), 7.65 (s, 1H), 7.59 – 7.42 (m, 3H), 7.33 (s, 1H), 7.28 – 7.19 (m, 1H), 7.17 – 7.08 (m, 1H), 5.61 (s, 2H), 4.33 (d, *J* = 5.7 Hz, 2H), 3.99 (s, 2H), 3.82 (t, *J* = 12.0 Hz, 2H), 3.60 – 3.46 (m, 2H), 3.13 – 2.94 (m, 1H), 2.18 – 1.96 (m, 2H), 1.81 – 1.63 (m, 2H), 1.04 – 0.84 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -101.17, -121.60; MS (ES⁺): 620.6 (M+1); MS (ES⁻): 618.5 (M-1).

Scheme 236



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-6-(3,3-difluoropiperidine-1-carboxamido)-1H-indazole-3-carboxamide (**236b**)

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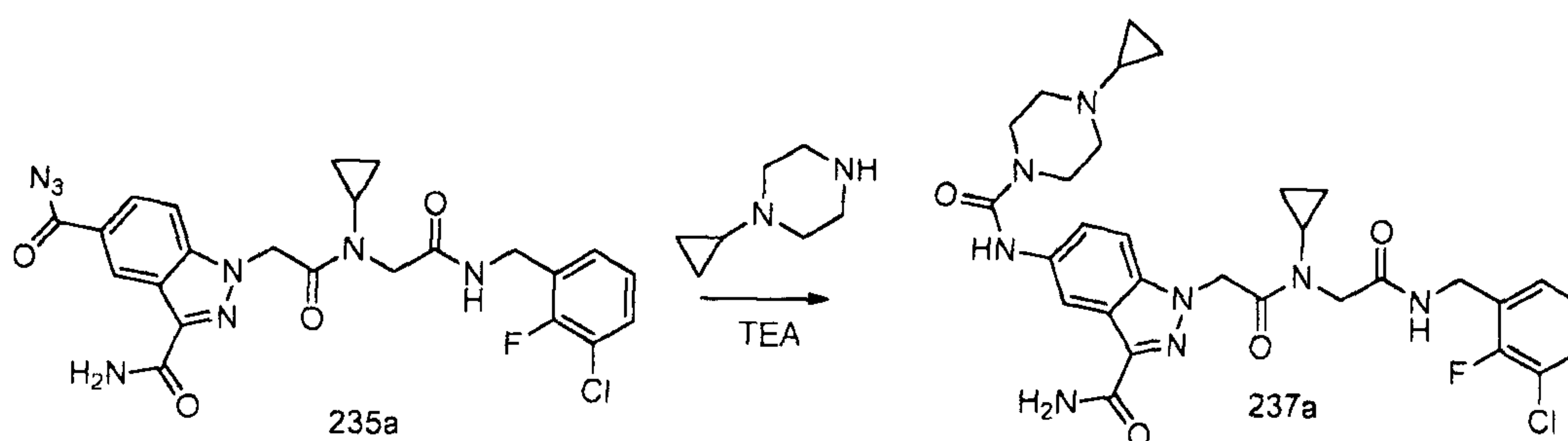
Step-1: Preparation of 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-6-carbonyl azide (**236a**)

Compound **236a** was prepared from 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-6-carboxylic acid (**208a**) (800 mg, 1.6 mmol) according to the procedure reported in step-3 of Scheme 129 to afford product; MS (ES⁺) 549.5 (M+Na).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-6-(3,3-difluoropiperidine-1-carboxamido)-1H-indazole-3-carboxamide (**236b**)

Compound **236b** was prepared from 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-6-carbonyl azide (**236a**) (200 mg, 0.38 mmol) and 3,3-difluoropiperidine hydrochloride (120 mg, 0.76 mmol) using TEA (0.21 mL, 1.51 mmol) as base according to the procedure reported in step-4 of Scheme 129 to afford after workup and purification by column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] (26 mg, 0.042 mmol, 11.05 % yield) product as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.93 (s, 1H), 8.58 (t, *J* = 5.8 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.77 (s, 1H), 7.74 – 7.61 (m, 1H), 7.49 – 7.43 (m, 1H), 7.36 – 7.31 (m, 2H), 7.27 – 7.21 (m, 1H), 7.17 – 7.12 (m, 1H), 5.57 (s, 2H), 4.33 (d, *J* = 5.5 Hz, 2H), 4.00 (s, 2H), 3.82 (t, *J* = 11.9 Hz, 2H), 3.55 – 3.51 (m, 2H), 3.15 – 2.97 (m, 1H), 2.13 – 1.97 (m, 2H), 1.81 – 1.64 (m, 2H), 1.34 – 1.20 (m, 2H), 1.00 – 0.92 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -101.18, -121.66; MS (ES⁺) 620.6 (M+1); MS (ES⁻): 654.5, 656.5 (M+Cl).

Scheme 237



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(4-cyclopropylpiperazine-1-carboxamido)-1H-indazole-3-carboxamide (**237a**)

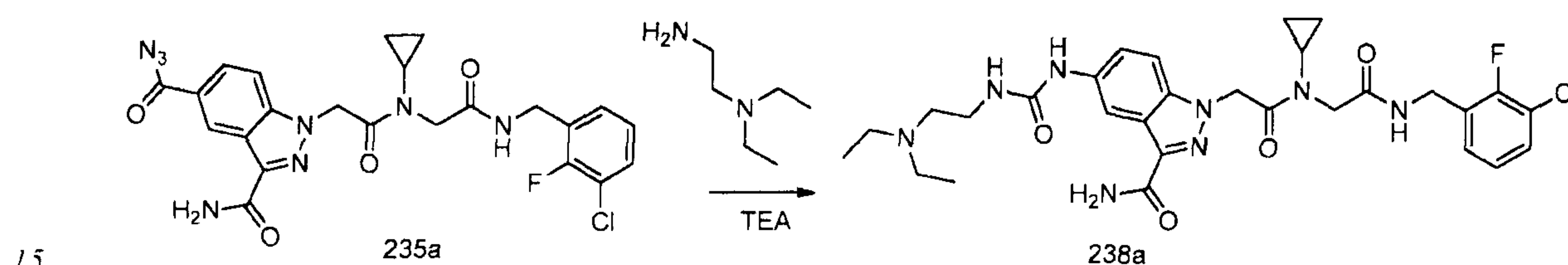
Compound **237a** was prepared from 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**235a**) (200 mg,

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0.19 mmol) and 1-cyclopropylpiperazine (48 mg, 0.38 mmol) using TEA (0.11 mL, 0.76 mmol) as base according to the procedure reported in step-4 of Scheme 129. This gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(4-cyclopropylpiperazine-1-carboxamido)-1H-indazole-3-carboxamide (**237a**) (30 mg, 0.048 mmol, 25% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.65 (s, 1H), 8.50 (t, *J* = 5.9 Hz, 1H), 8.21 – 8.15 (m, 1H), 7.67 – 7.60 (m, 1H), 7.60 – 7.42 (m, 3H), 7.35 – 7.28 (m, 1H), 7.27 – 7.20 (m, 1H), 7.18 – 7.09 (m, 1H), 5.61 (s, 2H), 4.33 (d, *J* = 5.7 Hz, 2H), 3.99 (s, 2H), 3.42 (t, *J* = 4.9 Hz, 4H), 3.10 – 3.01 (m, 1H), 2.58 – 2.52 (m, 4H), 1.71 – 1.61 (m, 1H), 1.02 – 0.96 (m, 2H), 0.95 – 0.89 (m, 2H), 0.46 – 0.40 (m, 2H), 0.38 – 0.33 (m, 2H); ¹⁹F NMR (282 MHz, DMSO) δ -121.60; MS (ES+) 625.7 (M+1), 647.7 (M+Na); (ES-) 623.6 (M-1).

Scheme 238

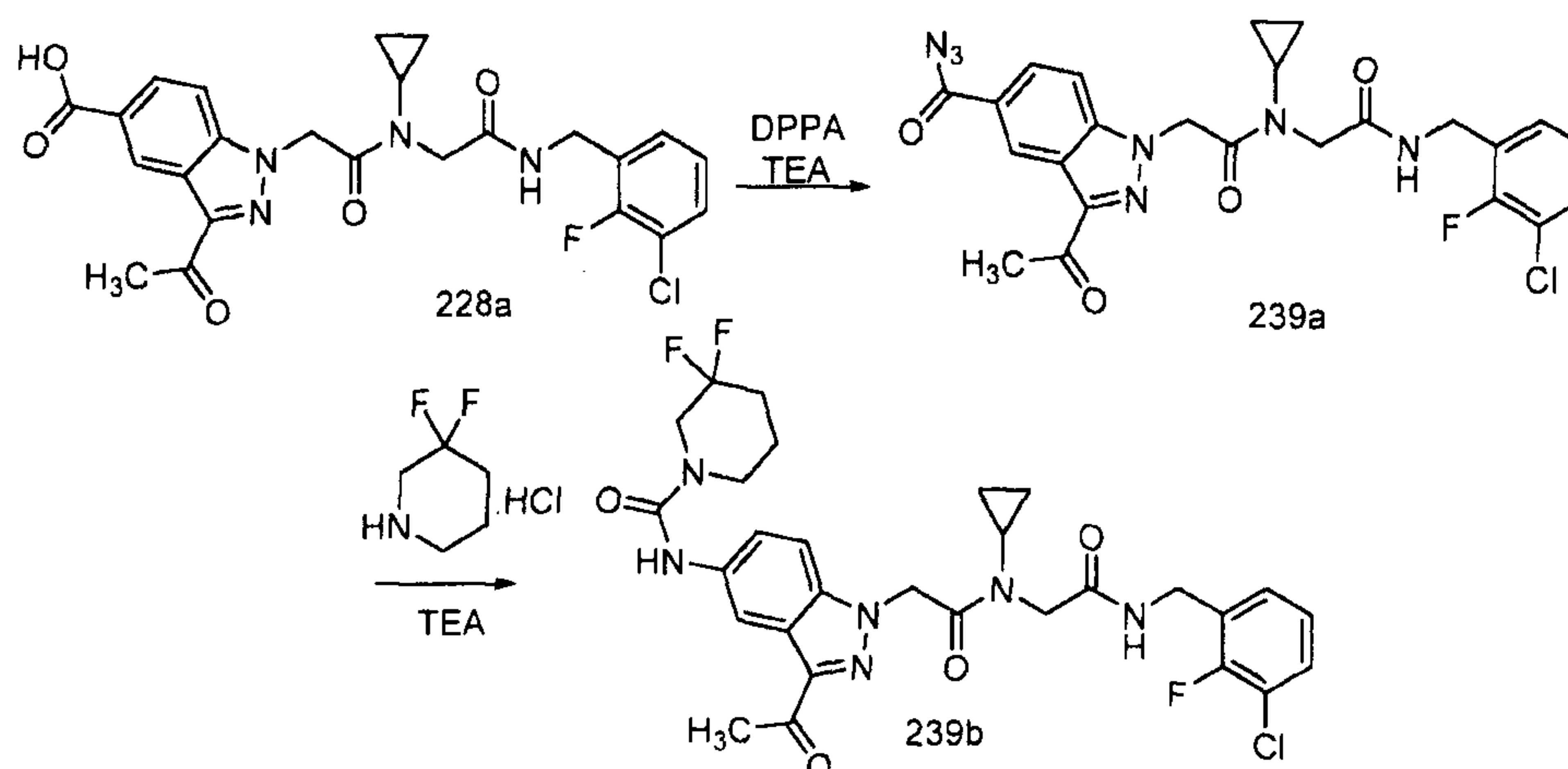


Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3-(2-(diethylamino)ethyl)ureido)-1H-indazole-3-carboxamide (**238a**)

Compound **238a** was prepared from 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**235a**) (150 mg, 0.14 mmol) and *N,N'*-diethylethane-1,2-diamine (33 mg, 0.29 mmol) using TEA (0.08 mL, 0.57 mmol) as base according to the procedure reported in step-4 of Scheme 129. This gave after workup, purification by flash column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] and prep-HPLC [eluting with CH₃CN in water (contains 0.1% TFA) from 0-100%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3-(2-(diethylamino)ethyl)ureido)-1H-indazole-3-carboxamide (**238a**) (16 mg, 0.026 mmol, 18% yield) as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.81 (s, 1H), 8.50 (t, *J* = 5.9 Hz, 1H), 8.24 – 8.13 (m, 1H), 7.60 (s, 1H), 7.53 – 7.41 (m, 3H), 7.33 – 7.27 (m, 1H), 7.27 – 7.19 (m, 1H), 7.17 – 7.07 (m, 1H), 6.00 (t, *J* = 5.4 Hz, 1H), 5.60 (s, 2H), 4.33 (d, *J* = 5.7 Hz, 2H), 3.98 (s, 2H), 3.16 (q, *J* = 6.2 Hz, 2H),

3.09 – 2.95 (m, 1H), 2.57 – 2.50 (m, 6H), 1.07 – 0.83 (m, 10H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -73.45 (TFA peak), -121.60; MS (ES+) 615.7 (M+1); MS (ES-): 614.6 (M-1).

Scheme 239



5

Preparation of N-(3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)-3,3-difluoropiperidine-1-carboxamide (**239b**)

Step-1: Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**239a**)

Compound **235a** was prepared from 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**228a**) (630 mg, 1.26 mmol) according to the procedure reported in step-3 of Scheme 129 to afford product as a white solid (750 mg, 1.426 mmol, 113 % yield), which was used in the next step without further purification; MS (ES+): 526.5 (M+1).

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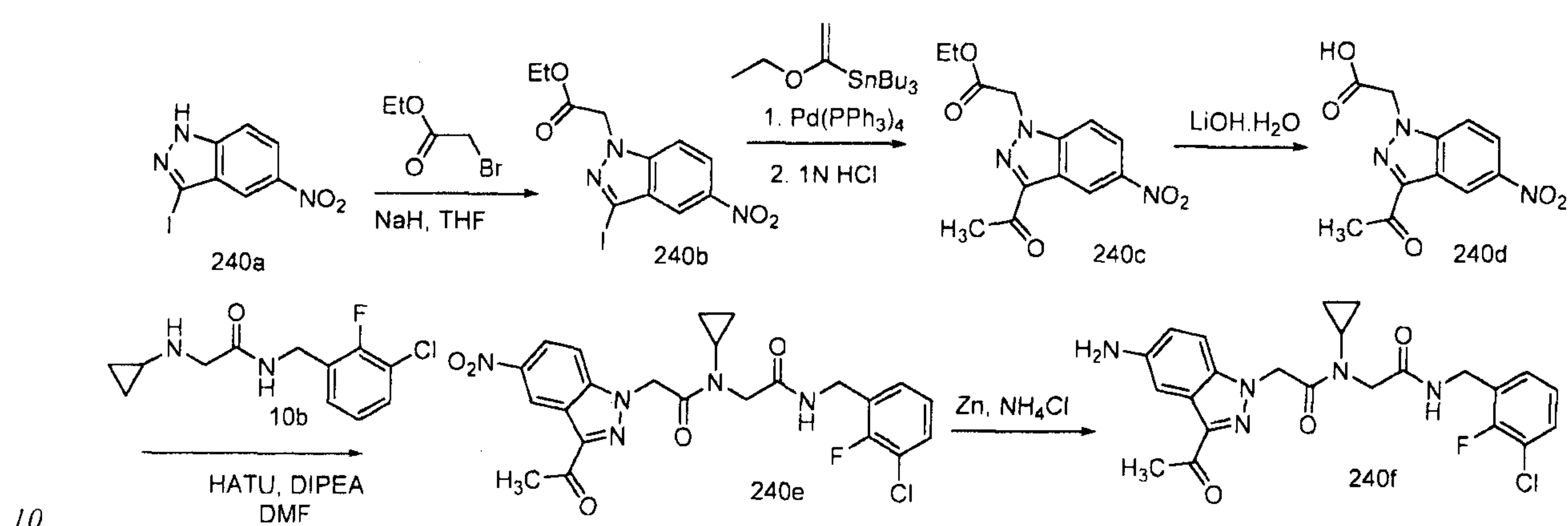
Step-2: Preparation of N-(3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)-3,3-difluoropiperidine-1-carboxamide (**239b**)

Compound **239b** was prepared from 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**239a**) (350 mg, 0.67 mmol) and 3,3-difluoropiperidine hydrochloride (210 mg, 1.33 mmol) using TEA (0.37 mL, 2.66 mmol) as base according to the procedure reported in step-4 of Scheme 129. This gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] N-(3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)-3,3-difluoropiperidine-1-

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carboxamide (**239b**) (190 mg, 0.31 mmol, 46% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.83 (s, 1H), 8.48 (t, $J = 5.8$ Hz, 1H), 8.28 – 8.19 (m, 1H), 7.63 – 7.52 (m, 2H), 7.45 (td, $J = 7.6, 1.7$ Hz, 1H), 7.23 (td, $J = 7.3, 6.8, 1.7$ Hz, 1H), 7.15 – 7.07 (m, 1H), 5.70 (s, 2H), 4.34 (d, $J = 5.7$ Hz, 2H), 3.99 (s, 2H), 3.82 (t, $J = 12.0$ Hz, 2H), 3.61–3.47 (m, 2H), 3.19 – 3.01 (m, 1H), 2.60 (s, 3H), 2.17 – 1.97 (m, 2H), 1.80 – 1.64 (m, 2H), 1.07 – 0.96 (m, 2H), 0.96 – 0.80 (m, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -101.17, -121.61; MS (ES+) 619.7 (M+1); (ES-): 617.6 (M-1).

Scheme 240



Preparation of 2-(3-acetyl-5-amino-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**240f**)

Step-1: Preparation of ethyl 2-(3-iodo-5-nitro-1H-indazol-1-yl)acetate (**240b**)

Reaction of 3-iodo-5-nitro-1H-indazole (**240a**) (3 g, 10.38 mmol) with ethyl 2-bromoacetate (1.38 mL, 12.46 mmol) using sodium hydride (0.46 g, 11.42 mmol) as base according to the procedure reported in step-1 of Scheme 57 gave after workup and purification by flash column chromatography [silica (40 g), eluting with EtOAc in hexane 0 to 30%] ethyl 2-(3-iodo-5-nitro-1H-indazol-1-yl)acetate (**240b**) (2.52 g, 6.72 mmol, 64.7 % yield) as an orange solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.38 – 8.30 (m, 2H), 7.95 (d, $J = 9.9$ Hz, 1H), 5.56 (s, 2H), 4.16 (q, $J = 7.1$ Hz, 2H), 1.21 (t, $J = 7.1$ Hz, 3H); MS (ES+): 376.3 (M+1), 398.3 (M+Na).

Step-2: Preparation of ethyl 2-(3-acetyl-5-nitro-1H-indazol-1-yl)acetate (**240c**)

Reaction of ethyl 2-(3-iodo-5-nitro-1H-indazol-1-yl)acetate (**240b**) (1.5 g, 4.00 mmol) in Toluene (40 mL) using tributyl(1-ethoxyvinyl)stannane (1.62 mL, 4.80 mmol) and $\text{Pd}(\text{PPh}_3)_4$ according to the procedure reported in step-1 and step-2 of Scheme 206 gave after workup

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and purification by flash column chromatography [silica gel (24 g), eluting with EtOAc in DCM 0 to 20%] ethyl 2-(3-acetyl-5-nitro-1H-indazol-1-yl)acetate (**240c**) (0.83 g, 2.85 mmol, 71% yield) as dark orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.01 (dd, J = 2.3, 0.7 Hz, 1H), 8.37 (dd, J = 9.3, 2.2 Hz, 1H), 8.06 (dd, J = 9.3, 0.7 Hz, 1H), 5.70 (s, 2H), 4.19 (q, J = 7.1 Hz, 2H), 2.67 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H); MS (ES⁺): 292.3 (M+1), MS (ES⁻): 326.3 (M+Cl).

Step-3: Preparation of 2-(3-acetyl-5-nitro-1H-indazol-1-yl)acetic acid (**240d**)

Reaction of ethyl 2-(3-acetyl-5-nitro-1H-indazol-1-yl)acetate (**240c**) (0.8 g, 2.75 mmol) in THF (20 mL) using a solution of lithium hydroxide hydrate (0.13 g, 5.49 mmol) in water (5 mL) according to the procedure reported in step-2 of Scheme 129 gave after workup 2-(3-acetyl-5-nitro-1H-indazol-1-yl)acetic acid (**240d**) (0.71 g, 2.7 mmol, 98 % yield) as off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.52 (s, 1H), 9.00 (dd, J = 2.2, 0.6 Hz, 1H), 8.36 (dd, J = 9.3, 2.2 Hz, 1H), 8.06 (dd, J = 9.4, 0.7 Hz, 1H), 5.58 (s, 2H), 2.67 (s, 3H); MS (ES⁺): 264.3 (M+1); MS (ES⁻): 262.2 (M-1).

Step-4: Preparation of 2-(3-acetyl-5-nitro-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**240e**)

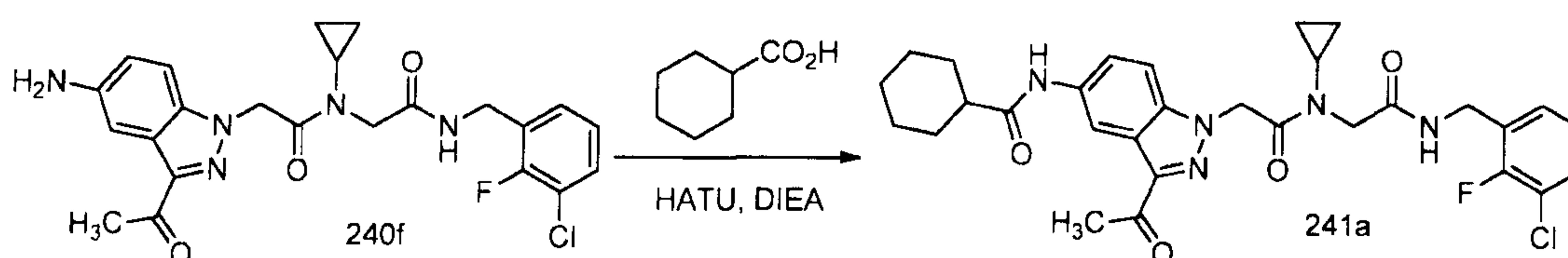
Reaction of 2-(3-acetyl-5-nitro-1H-indazol-1-yl)acetic acid (**240d**) (0.65 g, 2.47 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (0.7 g, 2.72 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (12 g), eluting with DMA80 in DCM 0 to 40%] 2-(3-acetyl-5-nitro-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**240e**) (820 mg, 1.63 mmol, 66% yield) as a light orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.00 (dd, J = 2.3, 0.6 Hz, 1H), 8.49 (t, J = 5.9 Hz, 1H), 8.30 (dd, J = 9.3, 2.2 Hz, 1H), 7.95 (dd, J = 9.3, 0.7 Hz, 1H), 7.45 (td, J = 7.6, 1.7 Hz, 1H), 7.26 - 7.17 (m, 1H), 7.09 (td, J = 7.9, 1.0 Hz, 1H), 5.87 (s, 2H), 4.34 (d, J = 5.7 Hz, 2H), 3.99 (s, 2H), 3.19 - 3.07 (m, 1H), 2.67 (s, 3H), 1.09 - 0.99 (m, 2H), 0.96 - 0.86 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.56; MS (ES⁺): 524.4 (M+Na), MS (ES⁻): 536.3 (M+Cl).

Step-5: Preparation of 2-(3-acetyl-5-amino-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**240f**)

To a solution of 2-(3-acetyl-5-nitro-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**240e**) (800 mg, 1.59 mmol) in THF (20 mL) and MeOH (5 mL) was added NH₄Cl (1.71 g, 31.9 mmol), Zinc (1.04 g, 15.94 mmol) and stirred

at RT for 3 h. The reaction mixture was filtered over a Celite pad, washed with 20% MeOH in EtOAc (2 x 8 mL). The filtrate was concentrated in vacuum to dryness and the resultant residue was suspended in brine (60 mL) and EtOAc (80 mL). The organic layer was separated, dried, filtered and concentrated in vacuum to afford 2-(3-acetyl-5-amino-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**240f**) (650 mg, 1.378 mmol, 86% yield) as a light orange solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.47 (t, *J* = 5.4 Hz, 1H), 7.53-7.41 (m, 1H), 7.35 (d, *J* = 8.9 Hz, 1H), 7.30 – 7.07 (m, 3H), 6.81 (dd, *J* = 8.9, 2.1 Hz, 1H), 5.60 (s, 2H), 5.21 (s, 2H), 4.34 (d, *J* = 5.8 Hz, 2H), 3.98 (s, 2H), 3.14 – 3.03 (m, 1H), 2.53 (s, 3H), 1.04 – 0.95 (m, 2H), 0.93 – 0.84 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.62; MS (ES⁺): 472.4 (M+1), 494.4 (M+Na), MS (ES⁻): 506.4 (M+Cl).

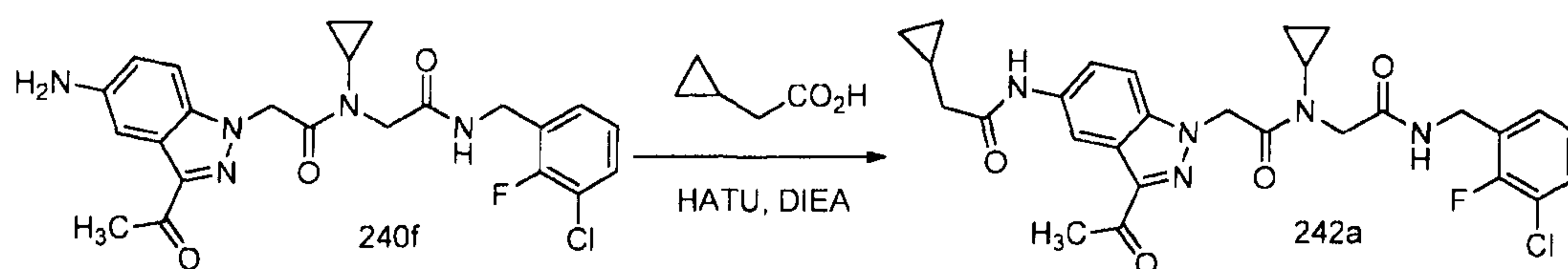
Scheme 241



Preparation of N-(3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)cyclohexanecarboxamide (**241a**)

Reaction of 2-(3-acetyl-5-amino-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**240f**) (100 mg, 0.21 mmol) with cyclohexanecarboxylic acid (33 mg, 0.25 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane 0 to 100%] N-(3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)cyclohexanecarboxamide (**241a**) (85 mg, 0.15 mmol, 69 % yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.97 (s, 1H), 8.54-8.51 (m, 1H), 8.48 (t, *J* = 5.9 Hz, 1H), 7.67 – 7.56 (m, 2H), 7.50 – 7.42 (m, 1H), 7.27-7.17 (m, 1H), 7.10 (td, *J* = 7.9, 1.0 Hz, 1H), 5.71 (s, 2H), 4.34 (d, *J* = 5.8 Hz, 2H), 3.98 (s, 2H), 3.18 – 3.04 (m, 1H), 2.60 (s, 3H), 2.41 – 2.28 (m, 1H), 1.91 – 1.58 (m, 6H), 1.52 – 1.14 (m, 4H), 1.07 – 0.97 (m, 2H), 0.95 – 0.84 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.60; MS (ES⁺): 604.6 (M+Na); MS (ES⁻): 580.5 (M-1), 616.5 (M+Cl).

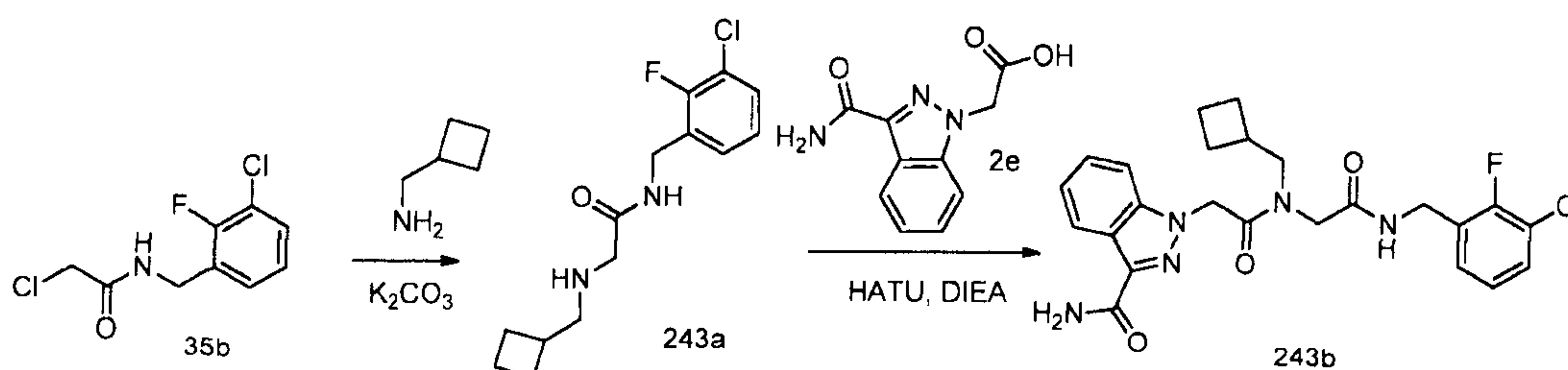
Scheme 242



Preparation of 2-(3-acetyl-5-(2-cyclopropylacetamido)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**242a**)

- 5 Reaction of 2-(3-acetyl-5-amino-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**240f**) (100 mg, 0.21 mmol) with 2-cyclopropylacetic acid (25 mg, 0.25 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc in hexane 0 to 100%] 2-(3-acetyl-5-(2-cyclopropylacetamido)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**242a**) (80 g, 0.14 mmol, 68% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.98 (s, 1H), 8.56 – 8.43 (m, 2H), 7.68 – 7.57 (m, 2H), 7.50 – 7.42 (m, 1H), 7.10 (td, *J* = 7.9, 1.0 Hz, 1H), 7.15 – 7.06 (m, 1H), 5.72 (s, 2H), 4.34 (d, *J* = 5.8 Hz, 2H), 3.99 (s, 2H), 3.17 – 3.05 (m, 1H), 2.60 (s, 3H), 2.23 (d, *J* = 7.0 Hz, 2H), 1.14 – 0.97 (m, 3H), 0.96 – 0.85 (m, 2H), 0.55 – 0.44 (m, 2H), 0.26 – 0.16 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.60; MS (ES⁺): 576.6 (M+Na); MS (ES⁻): 588.5 (M+Cl).

Scheme 243



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclobutylmethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**243b**)

Step-1: Preparation of N-(3-chloro-2-fluorobenzyl)-2-((cyclobutylmethyl)amino)acetamide (**243a**)

- Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (243 mg, 1.03 mmol) with cyclobutylmethanamine hydrochloride (250 mg, 2.056 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup and purification by flash column chromatography [silica (12 g), eluting with EtOAc/MeOH (9:1) in hexane 0 to 60%] N-(3-

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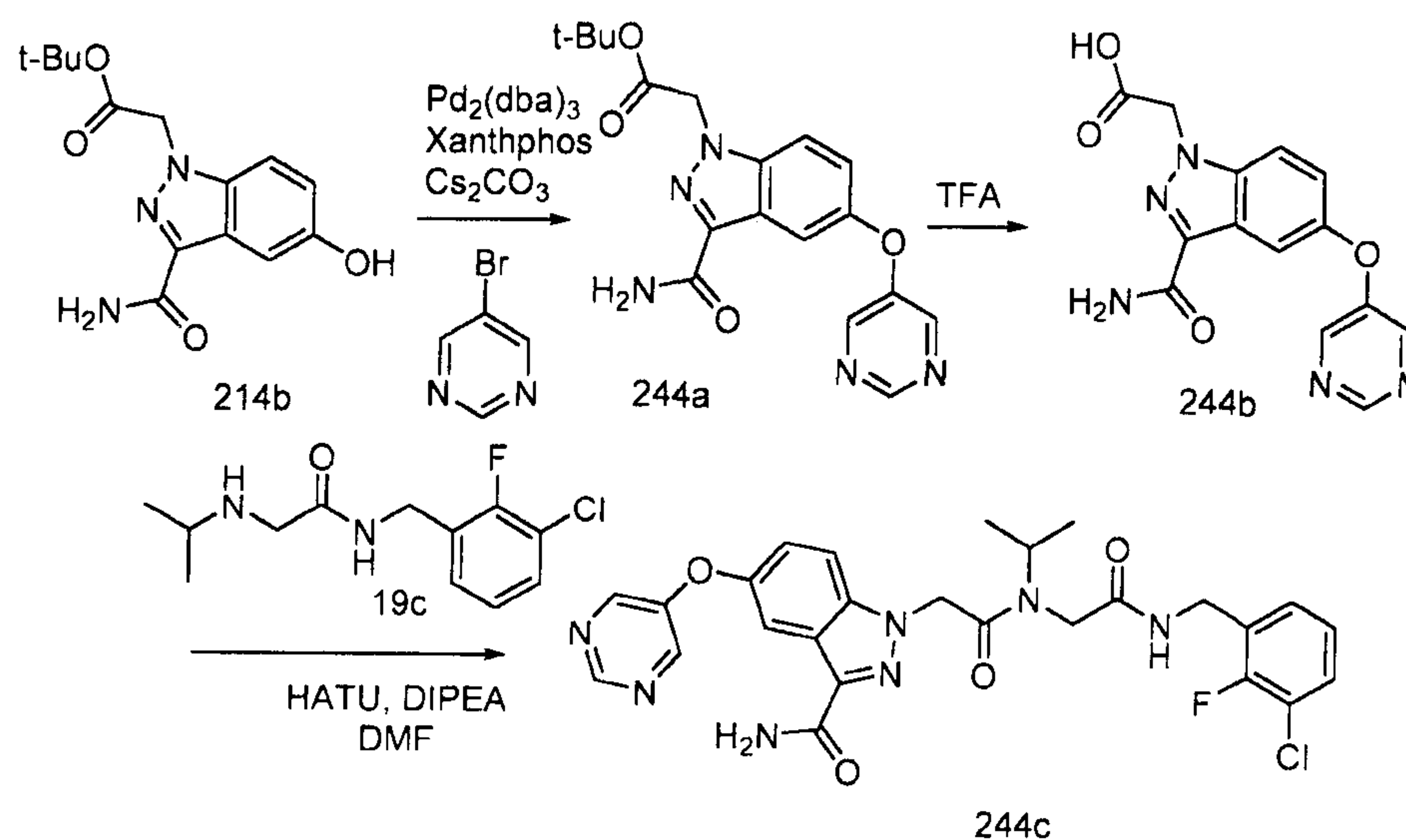
chloro-2-fluorobenzyl)-2-((cyclobutylmethyl)amino)acetamide (**243a**) (203 mg, 0.71 mmol, 69% yield) as a clear oil which was used as such in the next step; MS (ES⁺) 285.4 (M+1); (ES⁻) 283.3 (M-1).

Step-2: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-

5 oxoethyl)(cyclobutylmethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**243b**)

Reaction of N-(3-chloro-2-fluorobenzyl)-2-((cyclobutylmethyl)amino)acetamide (**243a**) (109 mg, 0.38 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (92 mg, 0.42 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-
10 ((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclobutylmethyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**243b**) (48 mg, 0.1 mmol, 26% yield) as a white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.83 (t, *J* = 5.7 Hz) and 8.46 (t, *J* = 5.8 Hz) (2t, 1H), 8.18 (d, *J* = 8.1 Hz, 1H), 7.79 – 7.65 (m, 1H), 7.58 – 7.05 (m, 7H), 5.57 and 5.46 2(s, 2H), 4.45 (d, *J* = 5.5 Hz) and 4.33 (d, *J* = 5.7 Hz) (2d, 2H), 4.22 and 3.92 (2s, 2H),
15 3.53 and, 3.29 (2d, *J* = 7.2 Hz, 2H), 2.73 – 2.60 and 2.47 – 2.32 (m, 1H), 2.07 – 1.50 (m, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.18, -121.60; MS (ES⁺) 486.5 (M+1); (ES⁻) 484.5 (M-1).

Scheme 244



20 Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(pyrimidin-5-yloxy)-1H-indazole-3-carboxamide (**244c**)

Step-1: Preparation of tert-butyl 2-(3-carbamoyl-5-(pyrimidin-5-yloxy)-1H-indazol-1-yl)acetate (**229a**)

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Reaction of tert-butyl 2-(3-carbamoyl-5-hydroxy-1H-indazol-1-yl)acetate (**214b**) (164 mg, 0.56 mmol) with 5-bromopyrimidine (107 mg, 0.68 mmol) using cesium carbonate (367 mg, 1.13 mmol), Pd₂(dba)₃ (26 mg, 0.03 mmol) and (9,9-dimethyl-9H-xanthene-4,5-diyl)bis(diphenylphosphine) (Xantphos, 33 mg, 0.06 mmol) according to the procedure
 5 reported in step-1 of Scheme 97 gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with methanol in DCM 0 to 100%] tert-butyl 2-(3-carbamoyl-5-(pyrimidin-5-yloxy)-1H-indazol-1-yl)acetate (**229a**) (39 mg, 0.11 mmol, 19 %yield) as an off-white solid; MS (ES⁺): 370.4 (M+1); MS (ES⁻): 368.3 (M-1).

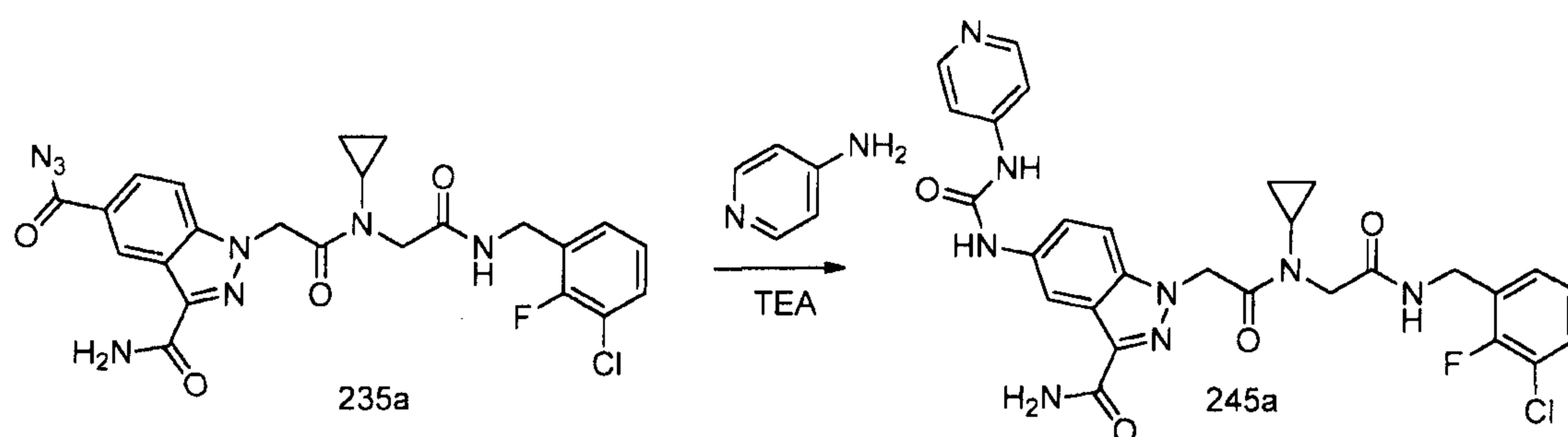
Step-2: Preparation 2-(3-carbamoyl-5-(pyrimidin-5-yloxy)-1H-indazol-1-yl)acetic acid
 10 (**244b**)

Reaction of tert-butyl 2-(3-carbamoyl-5-(pyrimidin-5-yloxy)-1H-indazol-1-yl)acetate (**244a**) (39 mg, 0.11 mmol) with TFA (0.24 mL, 3.17 mmol) in DCM (10 mL) according to the procedure reported in step-2 of Scheme 2 gave after workup 2-(3-carbamoyl-5-(pyrimidin-5-yloxy)-1H-indazol-1-yl)acetic acid (**244b**) (33 mg, 0.11 mmol, 100 % yield) as a yellow solid
 15 in the form of TFA adduct; MS (ES⁺): 314.3 (M+1); MS (ES⁻): 312.3 (M-1).

Step-3: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(pyrimidin-5-yloxy)-1H-indazole-3-carboxamide (**244c**)

Reaction of 2-(3-carbamoyl-5-(pyrimidin-5-yloxy)-1H-indazol-1-yl)acetic acid (**244b**) TFA
 20 adduct (33 mg, 0.11 mmol) with N-(3-chloro-2-fluorobenzyl)-2-(isopropylamino)acetamide (**19c**) (33 mg, 0.13 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (12 g), eluting with DMA-80 in DCM, 0 to 100%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(pyrimidin-5-yloxy)-1H-indazole-3-carboxamide (**244c**) (8 mg, 0.014 mmol,
 25 14% yield) as an off-white solid as a mixture of two rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.83 & 10.78 (2s, 1H), 9.57 & 9.56 (2s, 1H), 9.29 & 9.28 (2s, 2H), 8.91 & 8.90 (2s, 1H), 8.85 (t, *J* = 5.8 Hz) & 8.40 (t, *J* = 5.9 Hz) (2t, 1H), 7.60 – 6.94 (m, 6H), 5.62 & 5.50 (2s, 2H), 4.63 – 3.78 (m, 5H), 1.23 (d, *J* = 6.1 Hz) & 0.99 (d, *J* = 6.8 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.20, -121.69; MS (ES⁺): 554.5 (M+1), 576.5 (M+Na); MS (ES⁻):
 30 552.5 (M-1), 588.5 (M+Cl).

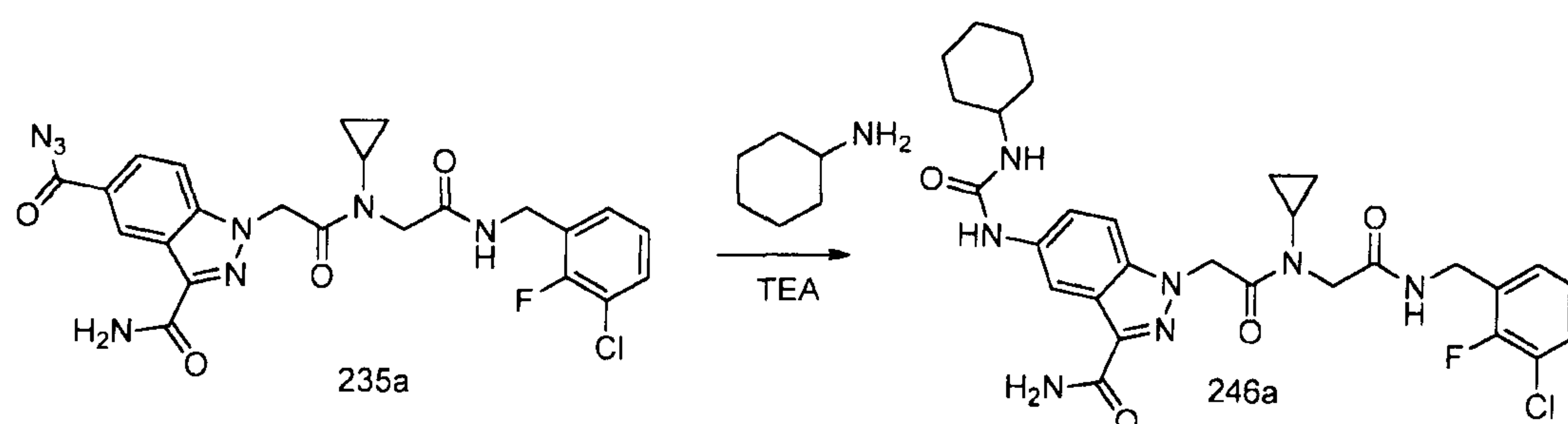
Scheme 245



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3-(pyridin-4-yl)ureido)-1H-indazole-3-carboxamide (**245a**)

- 5 Compound **245a** was prepared from 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**235a**) (300 mg, 0.29 mmol) and pyridin-4-amine (53.6 mg, 0.569 mmol) using TEA (0.16 mL, 1.14 mmol) as base according to the procedure reported in step-4 of Scheme 129. This gave after workup, purification by flash column chromatography [silica gel (12 g), eluting with DMA80 in DCM
- 10 0 to 40%] and prep-HPLC [eluting with CH₃CN in water (contains 0.1% TFA) from 0-100%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3-(pyridin-4-yl)ureido)-1H-indazole-3-carboxamide (**245a**) (9 mg, 0.015 mmol, 5% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.75 (s, 1H), 9.87 (s, 1H), 8.60 (d, *J* = 6.8 Hz, 2H), 8.51 (t, *J* = 5.9 Hz, 1H), 8.44 (d, *J* = 1.9 Hz, 1H), 7.94 (d, *J* = 6.6 Hz, 2H), 7.73 – 7.68
- 15 (m, 1H), 7.62 (d, *J* = 9.0 Hz, 1H), 7.51 – 7.41 (m, 2H), 7.40 – 7.31 (m, 1H), 7.30 – 7.19 (m, 1H), 7.18 – 7.06 (m, 1H), 5.65 (s, 2H), 4.33 (d, *J* = 5.7 Hz, 2H), 3.99 (s, 2H), 3.13 – 2.97 (m, 1H), 1.08 – 0.95 (m, 2H), 0.95 – 0.82 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -73.66 (TFA peak), -121.58; MS (ES⁺): 593.5 (M+1).

Scheme 246

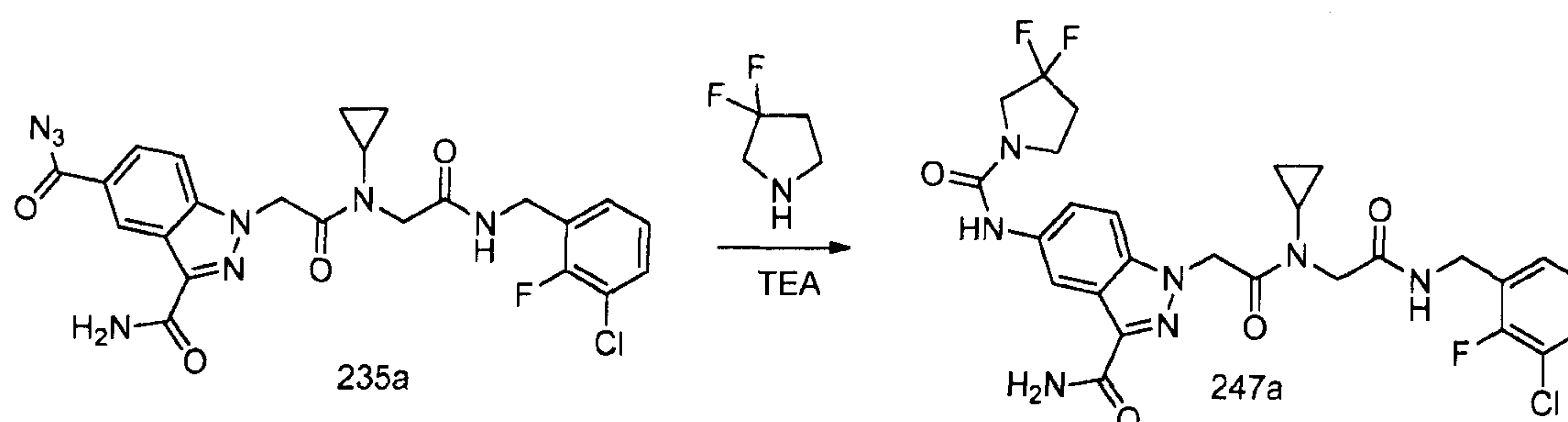


Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3-cyclohexylureido)-1H-indazole-3-carboxamide (**246a**)

Compound **246a** was prepared from 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**235a**) (300 mg, 0.29 mmol) and cyclohexanamine (57 mg, 0.57 mmol) using TEA (0.16 mL, 1.14 mmol) as base according to the procedure reported in step-4 of Scheme 129. This gave after workup, purification by flash column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3-cyclohexylureido)-1H-indazole-3-carboxamide (**246a**) (15 mg, 0.025 mmol, 9% yield) as a white solid; ^1H NMR(300 MHz, DMSO- d_6) δ 8.50 (t, J = 6.0 Hz, 1H), 8.42 (s, 1H), 8.24 – 8.12 (m, 1H), 7.60 (s, 1H), 7.55 – 7.37 (m, 3H), 7.30 (s, 1H), 7.26 – 7.18 (m, 1H), 7.12 (t, J = 7.8 Hz, 1H), 5.99 (d, J = 7.8 Hz, 1H), 5.60 (s, 2H), 4.33 (d, J = 5.8 Hz, 2H), 3.98 (s, 2H), 3.58 – 3.42 (m, 1H), 3.14 – 2.97 (m, 1H), 1.93 – 1.75 (m, 2H), 1.75 – 1.61 (m, 2H), 1.61 – 1.44 (m, 1H), 1.36 – 1.13 (m, 5H), 1.03 – 0.95 (m, 2H), 0.95 – 0.84 (m, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.59; MS (ES+): 598.6 (M+1).

15

Scheme 247



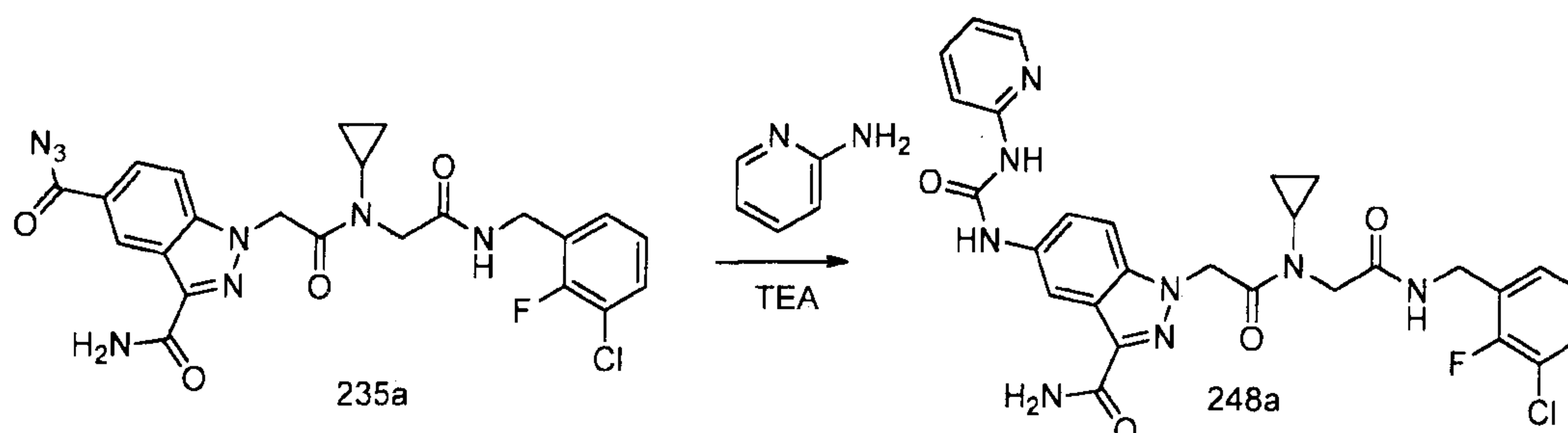
Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropyrrolidine-1-carboxamido)-1H-indazole-3-carboxamide (**247a**)

Compound **247a** was prepared from 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**235a**) (300 mg, 0.29 mmol) and 3,3-difluoropyrrolidine hydrochloride (102 mg, 0.712 mmol) using TEA (0.16 mL, 1.14 mmol) as base according to the procedure reported in step-4 of Scheme 129. This gave after workup, purification by flash column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropyrrolidine-1-carboxamido)-1H-indazole-3-carboxamide (**247a**) (26 mg, 0.043 mmol, 15% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.58 – 8.45 (m, 2H), 8.25 – 8.20 (m, 1H), 7.69 – 7.63 (m, 1H), 7.61 (d, J = 2.0 Hz, 1H), 7.56 – 7.42 (m, 2H), 7.36 – 7.30 (m, 1H), 7.26 – 7.18 (m, 1H), 7.13 (td, J

= 7.8, 1.0 Hz, 1H), 5.62 (s, 2H), 4.33 (d, $J = 5.8$ Hz, 2H), 3.99 (s, 2H), 3.84 (t, $J = 13.3$ Hz, 2H), 3.65 (t, $J = 7.4$ Hz, 2H), 3.14 – 2.96 (m, 1H), 2.49 – 2.38 (m, 2H), 1.06 – 0.96 (m, 2H), 0.93 – 0.83 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -100.42, -121.60; MS (ES+) 606.5 (M+1).

5

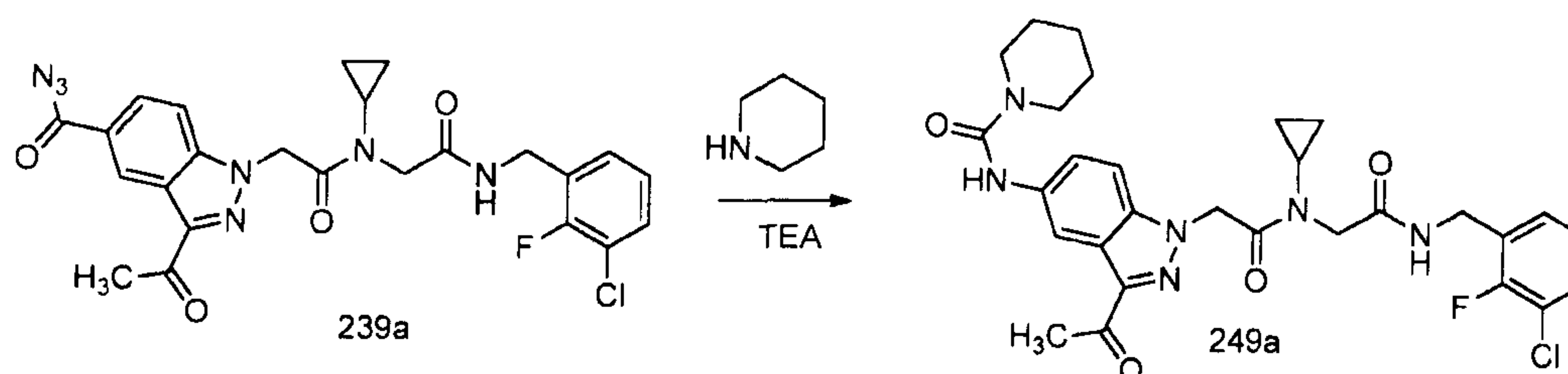
Scheme 248



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3-(pyridin-2-yl)ureido)-1H-indazole-3-carboxamide (**248a**)

Compound **248a** was prepared from 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**235a**) (286 mg, 0.27 mmol) and pyridin-2-amine (51 mg, 0.54 mmol) using TEA (0.15 mL, 1.11 mmol) as base according to the procedure reported in step-4 of Scheme 129. This gave after workup, purification by flash column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3-(pyridin-2-yl)ureido)-1H-indazole-3-carboxamide (**248a**) (11 mg, 0.02 mmol, 7% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 10.61 (s, 1H), 9.45 (s, 1H), 8.51 (t, $J = 5.9$ Hz, 1H), 8.40 (d, $J = 2.0$ Hz, 1H), 8.34 – 8.24 (m, 1H), 7.80 – 7.71 (m, 1H), 7.70 – 7.64 (m, 1H), 7.60 (d, $J = 9.0$ Hz, 1H), 7.55 – 7.42 (m, 3H), 7.36 (s, 1H), 7.27 – 7.19 (m, 1H), 7.16 – 7.08 (m, 1H), 7.05 – 6.97 (m, 1H), 5.64 (s, 2H), 4.34 (d, $J = 5.7$ Hz, 2H), 3.99 (s, 2H), 3.13 – 2.97 (m, 1H), 1.05 – 0.97 (m, 2H), 0.96 – 0.83 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.58; MS (ES+); 593.5 (M+1); (ES-): 591.5 (M-1).

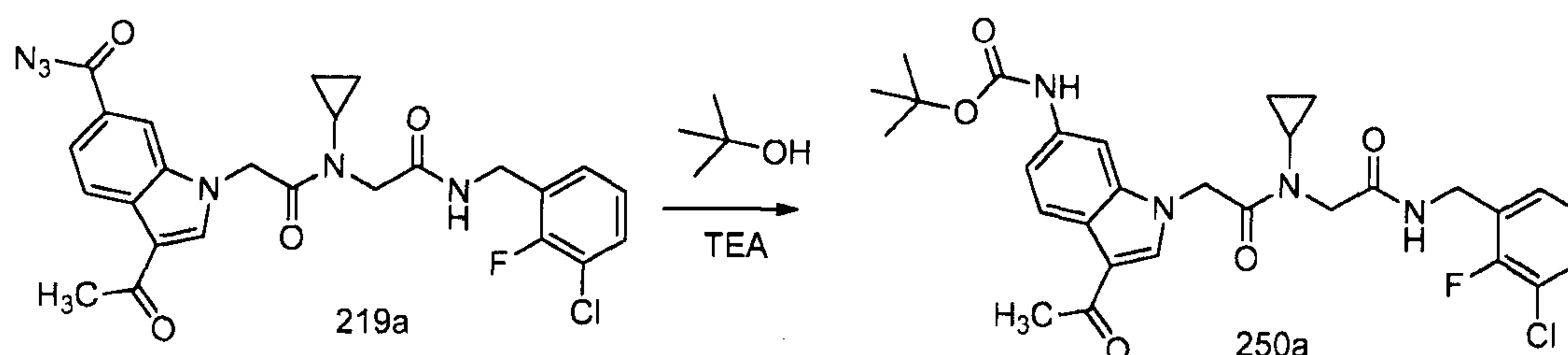
Scheme 249



Preparation of N-(3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)piperidine-1-carboxamide (**249a**)

Compound **249a** was prepared from 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**239a**) (300 mg, 0.57 mmol) and piperidine (97 mg, 1.14 mmol) using TEA (0.32 mL, 2.28 mmol) as base according to the procedure reported in step-4 of Scheme 129. This gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] N-(3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)piperidine-1-carboxamide (**249a**) (42 mg, 0.07 mmol, 13% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.63 (s, 1H), 8.48 (t, *J* = 5.9 Hz, 1H), 8.25 (d, *J* = 1.8 Hz, 1H), 7.67 – 7.50 (m, 2H), 7.50 – 7.40 (m, 1H), 7.28 – 7.16 (m, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 5.69 (s, 2H), 4.35 (d, *J* = 5.6 Hz, 2H), 4.00 (s, 2H), 3.56 – 3.40 (m, 4H), 3.21 – 3.03 (m, 1H), 2.59 (s, 3H), 1.66 – 1.43 (m, 6H), 1.09 – 0.98 (m, 2H), 0.97 – 0.80 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.61; MS (ES⁺): 583.6 (M+1); (ES⁻): 581.6 (M-1).

Scheme 250

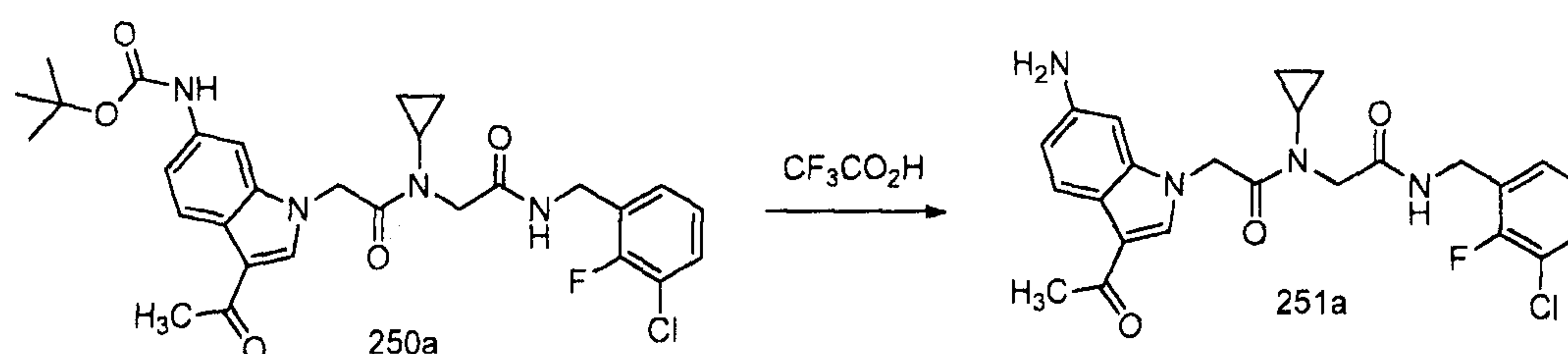


Preparation of tert-butyl (3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indol-6-yl)carbamate (**250a**)

Compound (**250a**) was prepared from 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-6-carbonyl azide (**219a**) (210 mg, 0.4 mmol) and 2-methylpropan-2-ol (0.23 mL, 2.4 mmol) using TEA (0.11 mL, 0.8 mmol) as base according to the procedure reported in step-4 of Scheme 129 to afford after workup and purification by column chromatography [silica gel, eluting with dichloromethane/methanol (1:0 to 9:1)] tert-butyl (3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indol-6-yl)carbamate (**250a**) (55 mg, 24% for two steps) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.32 (s, 1H), 8.48 (t, *J* = 5.8 Hz, 1H), 8.19 (s, 1H), 7.99 (d, *J* = 8.6 Hz, 1H), 7.57 (s, 1H), 7.51 – 7.39 (m, 1H), 7.27 – 7.18 (m, 2H), 7.17 – 7.05 (m, 1H), 5.35 (s, 2H), 4.34 (d, *J* = 5.8 Hz, 2H), 4.00 (s, 2H), 3.11 – 2.99

(m, 1H), 2.40 (s, 3H), 1.47 (s, 9H), 1.09 – 0.85 (m, 4H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.67; MS (ES⁺): 593.5 & 595.5 (M+Na).

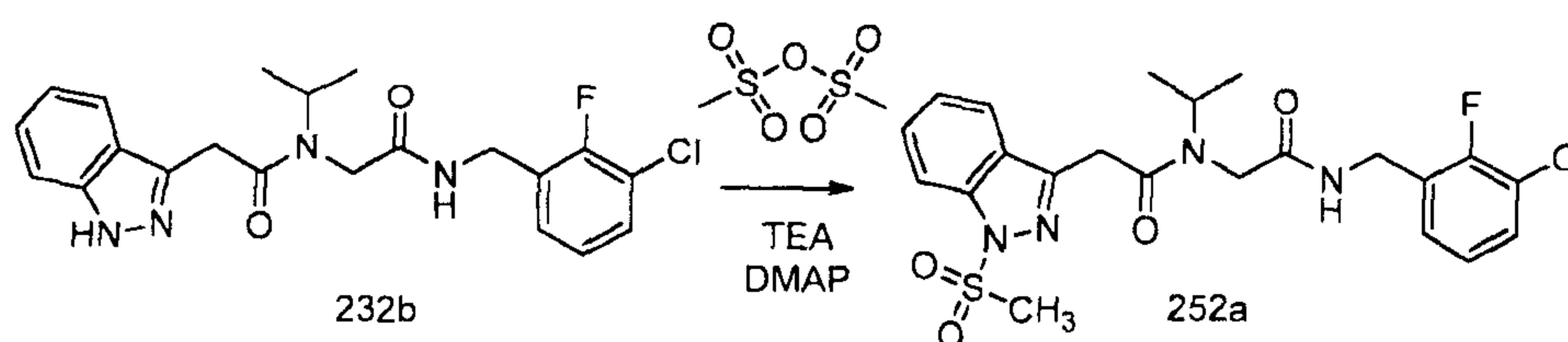
Scheme 251



- 5 Preparation of 2-(3-acetyl-6-amino-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**251a**)

Compound (**251a**) was prepared by hydrolysis of Boc protecting group of tert-butyl (3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indol-6-yl)carbamate (**250a**) (47 mg, 0.08 mmol) using 2,2,2-trifluoroacetic acid (0.127 mL, 1.646 mmol) in DCM (10 mL). This gave after workup and purification by flash column chromatography [silica gel, eluting with dichloromethane/DMA 80 (1:0 to 3:1)] 2-(3-acetyl-6-amino-1H-indol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**251a**) (26 mg, 67%) as a light brown solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.48 (t, J = 5.8 Hz, 1H), 7.95 (s, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.47 (td, J = 7.6, 1.8 Hz, 1H), 7.25 (td, J = 7.3, 6.8, 1.8 Hz, 1H), 7.15 (td, J = 7.9, 1.0 Hz, 1H), 6.54 (dd, J = 8.4, 1.9 Hz, 1H), 6.46 (d, J = 1.8 Hz, 1H), 5.23 (s, 2H), 4.94 (s, 2H), 4.34 (d, J = 5.7 Hz, 2H), 4.00 (s, 2H), 3.10 – 2.97 (m, 1H), 2.35 (s, 3H), 1.04 – 0.88 (m, 4H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.61; MS (ES⁺): 493.5 & 495.5 (M+Na); MS (ES⁻): 505.4 & 507.4 (M+Cl).

Scheme 252



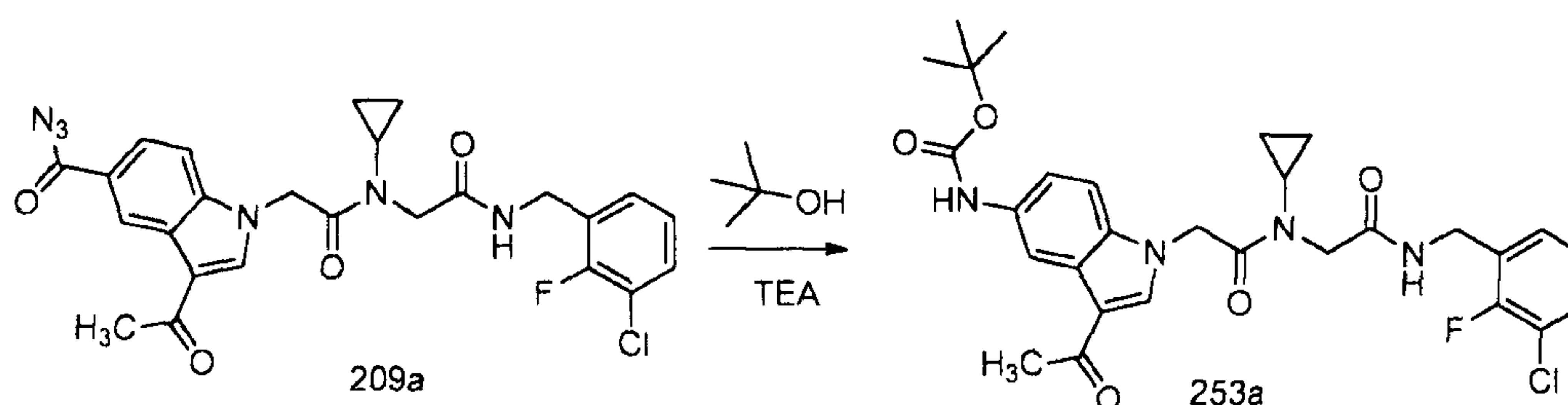
- 20 Preparation of N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropyl-2-(1-(methanesulfonyl)-1H-indazol-3-yl)acetamide (**252a**)

Compound (**252a**) was prepared from N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-2-(1H-indazol-3-yl)-N-isopropylacetamide (**232b**) (100 mg, 0.24 mmol) using methanesulphonic anhydride (84 mg, 0.48 mmol), triethylamine (0.1 mL, 0.72 mmol), DMAP (6 mg, 0.048 mmol) according to the procedure reported in step-2 of Scheme 232.

This gave after workup and purification by flash column chromatography [silica gel (12 g), eluting with EtOAc in hexane 0 to 100%] N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropyl-2-(1-(methylsulfonyl)-1H-indazol-3-yl)acetamide (**252a**) (21 mg, 0.042 mmol, 18 % yield) as a white solid as a mixture of rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.70 and 8.48 (2t, *J* = 5.7 Hz, 1H), 7.74-7.68 and 7.68-7.61 (2m, 1H), 7.53-7.00 (m, 6H), 4.69 – 4.57 and 4.34 – 4.24 (2m, 1H), 4.42 and 4.37 (2d, *J* = 5.9 Hz, 2H), 4.12 and 4.09 (2s, 2H), 3.91 and 3.81 (2s, 2H), 2.37 (s, 3H), 1.03 and 0.95 (2d, *J* = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.35 and -121.77; MS (ES⁻): 529.5 (M+Cl).

10

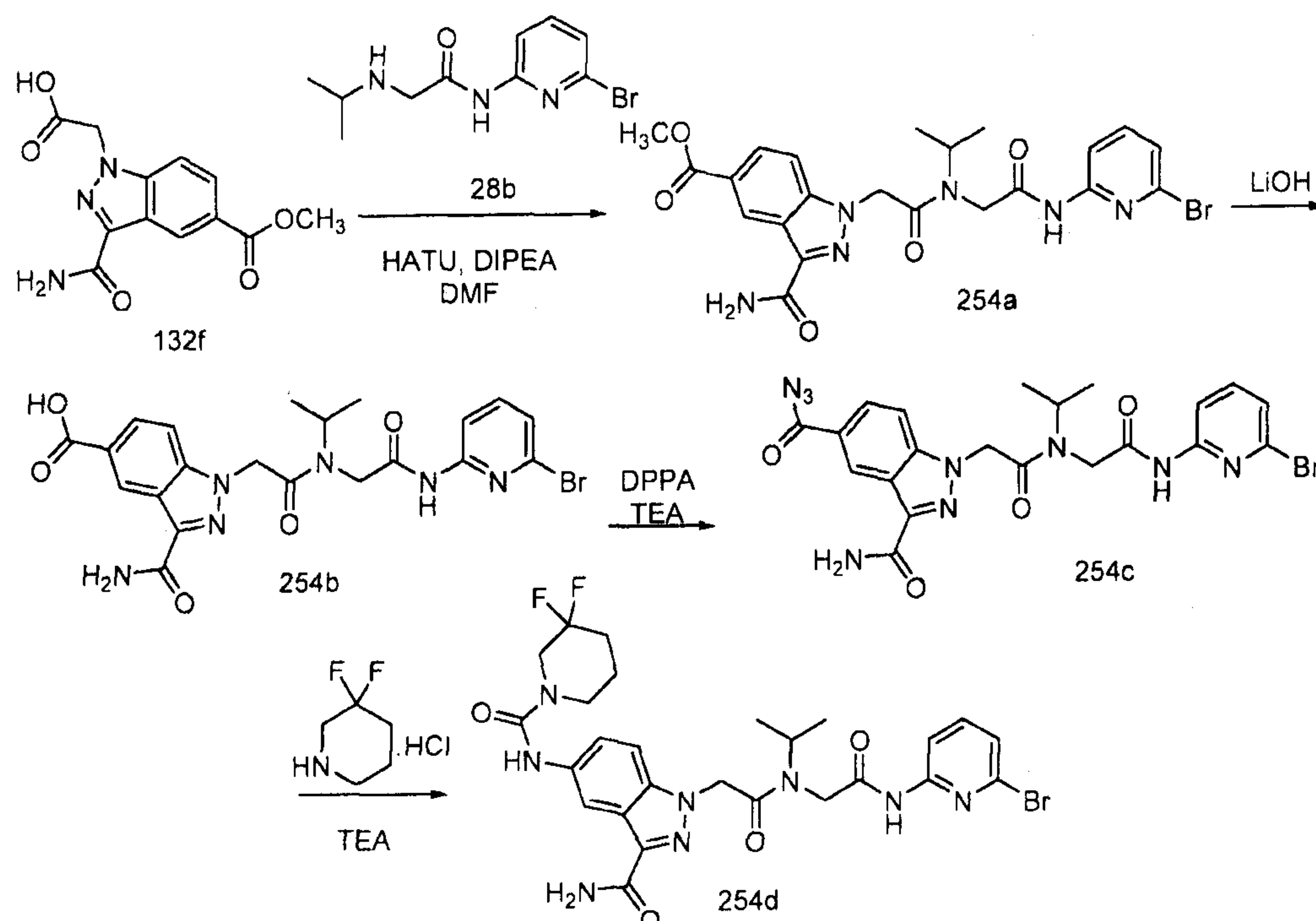
Scheme 253



Preparation of tert-butyl (3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indol-5-yl)carbamate (**253a**)

Compound (**253a**) was prepared from 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carbonyl azide (**209a**) (210 mg, 0.4 mmol) and 2-methylpropan-2-ol (0.23 mL, 2.4 mmol) using TEA (0.11 mL, 0.8 mmol) as base according to the procedure reported in step-4 of Scheme 129 to afford after workup and purification by column chromatography [silica gel, eluting with hexanes/10% methanol in ethyl acetate (1:0 to 1:1)] tert-butyl (3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indol-5-yl)carbamate (**253a**) (42 mg, 18%) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.22 (s, 1H), 8.47 (t, *J* = 5.9 Hz, 1H), 8.35 (d, *J* = 1.9 Hz, 1H), 8.20 (s, 1H), 7.49 – 7.42 (m, 1H), 7.33 – 7.18 (m, 3H), 7.11 (td, *J* = 7.9, 1.0 Hz, 1H), 5.38 (s, 2H), 4.35 (d, *J* = 5.7 Hz, 2H), 3.99 (s, 2H), 3.14 – 2.97 (m, 1H), 2.40 (s, 3H), 1.49 (s, 9H), 1.03 – 0.81 (m, 4H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.63; MS (ES⁺): 593.6 & 595.6 (M+Na); MS (ES⁻): 569.6 & 571.5 (M-1).

Scheme 254



Preparation of 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropiperidine-1-carboxamido)-1H-indazole-3-carboxamide (**254d**)

5 Step-1: Preparation of methyl 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-3-carbamoyl-1H-indazole-5-carboxylate (**254a**)

Reaction of 2-(3-carbamoyl-5-(methoxycarbonyl)-1H-indazol-1-yl)acetic acid (**132f**) TFA adduct (719 mg, 1.84 mmol) with N-(6-bromopyridin-2-yl)-2-(isopropylamino)acetamide (**28b**) (500 mg, 1.84 mmol) according to the procedure reported in step-3 of Scheme 2 gave
 10 after workup and purification by flash column [silica (12 g), eluting with DMA80 in DCM 0 to 30%] methyl 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-3-carbamoyl-1H-indazole-5-carboxylate (**254a**) (865 mg, 1.63 mmol, 89 % yield) as an off white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.21 and 10.82 (2s, 1H), 8.94 – 8.84 (m, 1H), 8.19 – 7.28 (m, 7H), 5.70 and, 5.52 (2s, 2H), 4.67 – 4.54 and 4.37 – 4.27 (2m, 1H),
 15 4.43 and 4.03 (s, 1H), 3.90 (d, *J* = 3.3 Hz, 3H), 1.26 (d, *J* = 6.4 Hz) and 1.03 (d, *J* = 6.8 Hz) (2d, 6H); MS (ES⁺) 533.4 (M+2); 529.4 (M-1).

Step-2: Preparation of 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-3-carbamoyl-1H-indazole-5-carboxylic acid (**254b**)

Reaction of methyl 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-3-carbamoyl-1H-indazole-5-carboxylate (**254a**) (860 mg, 1.62 mmol) in
 20 MeOH/water (50 mL) with a solution of lithium hydroxide hydrate (679 mg, 16.18 mmol) in

water (10 mL) according to the procedure reported in step-2 of Scheme 129 gave after workup 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-3-carbamoyl-1H-indazole-5-carboxylic acid (**254b**) (736 g, 1.43 mmol, 88% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 12.95 (s, 1H), 11.21 and 10.82 (2s, 1H), 8.93 – 8.78 (m, 1H), 8.26 – 7.16 (m, 7H), 5.67 and 5.51 (2s, 2H), 4.73 – 4.54 and 4.34 – 4.25 (2m, 1H), 4.43 and 4.03 (2s, 2H), 1.25 (d, *J* = 6.6 Hz) and 1.03 (d, *J* = 6.7 Hz) (2d, 6H); MS (ES⁺) 515.3 (M-1).

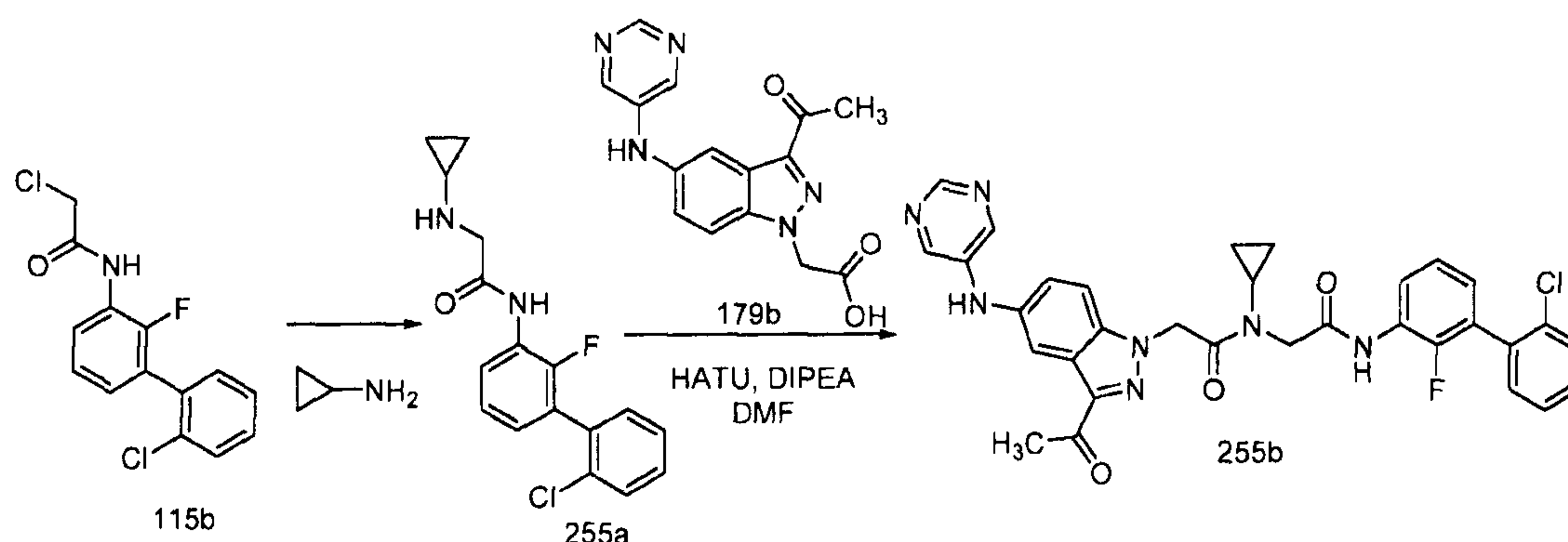
Step-3: Preparation of 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-3-carbamoyl-1H-indazole-5-carbonyl azide (**254c**)

10 Compound **254c** was prepared from 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-3-carbamoyl-1H-indazole-5-carboxylic acid (**254b**) (400 mg, 0.77 mmol) according to the procedure reported in step-3 of Scheme 129 to afford product (600 mg, 143 % yield), which was used in the next step without further purification.

Step-4: Preparation of 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropiperidine-1-carboxamido)-1H-indazole-3-carboxamide (**254d**)

Compound (**254d**) was prepared from 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-3-carbamoyl-1H-indazole-5-carbonyl azide (**254c**) (300 mg, 0.55 mmol) and 3,3-difluoropiperidine hydrochloride (174 mg, 1.106 mmol) using TEA (0.31 mL, 2.2 mmol) as base according to the procedure reported in step-4 of Scheme 129 to afford after workup and purification by column chromatography [silica (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3,3-difluoropiperidine-1-carboxamido)-1H-indazole-3-carboxamide (**254d**) (32 mg, 0.05 mmol, 9% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.20 and 10.83 (2s, 1H), 8.78 (d, *J* = 5.6 Hz, 1H), 8.28 – 7.95 (m, 2H), 7.86 – 7.23 (m, 6H), 5.57 and 5.41 (2s, 2H), 4.71 – 4.52 and 4.38-4.20 (m, 1H), 4.42 and 4.03 (2s, 2H), 3.81 (t, *J* = 11.6 Hz, 2H), 3.52 (bs, 2H), 2.16 – 1.91 (m, 2H), 1.71 (bs, 2H), 1.24 (d, *J* = 6.3 Hz) and 1.03 (d, *J* = 6.7 Hz) (2d, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -101.17; MS (ES⁺): 635.6 (M+1); (ES⁻): 633.5 (M-1).

Scheme 255



Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)-N-(2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**255b**)

5 Step-1: Preparation of N-(2'-chloro-2-fluorobiphenyl-3-yl)-2-(cyclopropylamino)acetamide (**255a**)

Compound (**255a**) was prepared from 2-chloro-N-(2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)acetamide (**115b**) (2 g, 6.71 mmol) and cyclopropylamine (1.18 mL, 16.77 mmol)

according to the procedure reported in step-2 of scheme-115. This gave after workup and

10 purification by flash column chromatography [silica gel 24 g, eluting with EtOAc-Hexane 10 to 100%] N-(2'-chloro-2-fluorobiphenyl-3-yl)-2-(cyclopropylamino)acetamide (**255a**) (1.8 g, 5.65 mmol, 84% yield) as a thick syrup; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.73 (s, 1H), 8.20 – 8.10 (m, 1H), 7.64 – 7.57 (m, 1H), 7.53 – 7.38 (m, 3H), 7.26 (td, *J* = 7.9, 1.0 Hz, 1H), 7.11 – 7.04 (m, 1H), 3.38 (bs, 2H), 3.11 (bs, 1H), 2.24 – 2.12 (m, 1H), 0.43 – 0.34 (m, 2H), 0.32 – 0.23 (m, 2H); MS (ES⁺): 319.4 (M+1), MS (ES⁻): 353.3 (M+Cl).

Step-2: Preparation of 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)-N-(2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**255b**)

Reaction of N-(2'-chloro-2-fluorobiphenyl-3-yl)-2-(cyclopropylamino)acetamide (**255a**) (70 mg, 0.22 mmol) with 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)acetic acid

20 (**179b**) (68 mg, 0.22 mmol) according to the procedure reported in step-3 of scheme-2 gave after workup and purification by flash column [silica gel (12 g), eluting with DMA-80 in

DCM 0-40%] 2-(3-acetyl-5-(pyrimidin-5-ylamino)-1H-indazol-1-yl)-N-(2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**255b**) (90 mg, 0.15

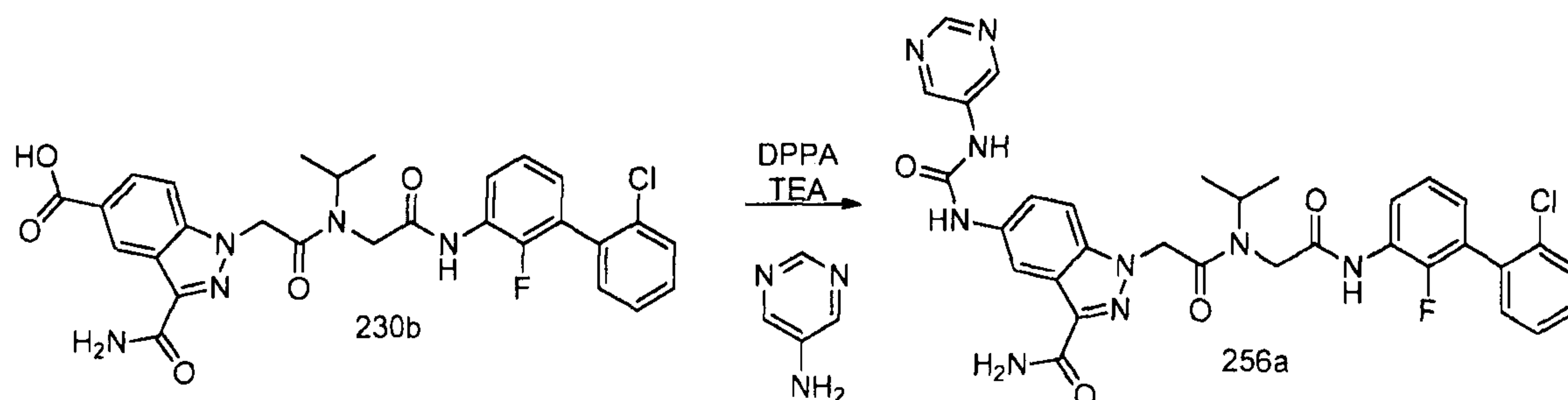
mmol, 67% yield) as an off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.94 (s, 1H), 8.72 (s, 1H), 8.65 (s, 1H), 8.55 (s, 2H), 7.98 (t, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 2.1 Hz, 1H), 7.69 (d, *J* = 8.9 Hz, 1H), 7.63 – 7.54 (m, 1H), 7.52 – 7.30 (m, 4H), 7.24 (t, *J* = 7.9 Hz, 1H), 7.14 – 7.03

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(m, 1H), 5.77 (s, 2H), 4.24 (s, 2H), 3.22 – 3.10 (m, 1H), 2.60 (s, 3H), 1.12 – 1.01 (m, 2H), 1.00 – 0.90 (m, 2H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -126.70; MS (ES+): 612.6 (M+1); MS (ES-): 610.6 (M-1).

Scheme 256

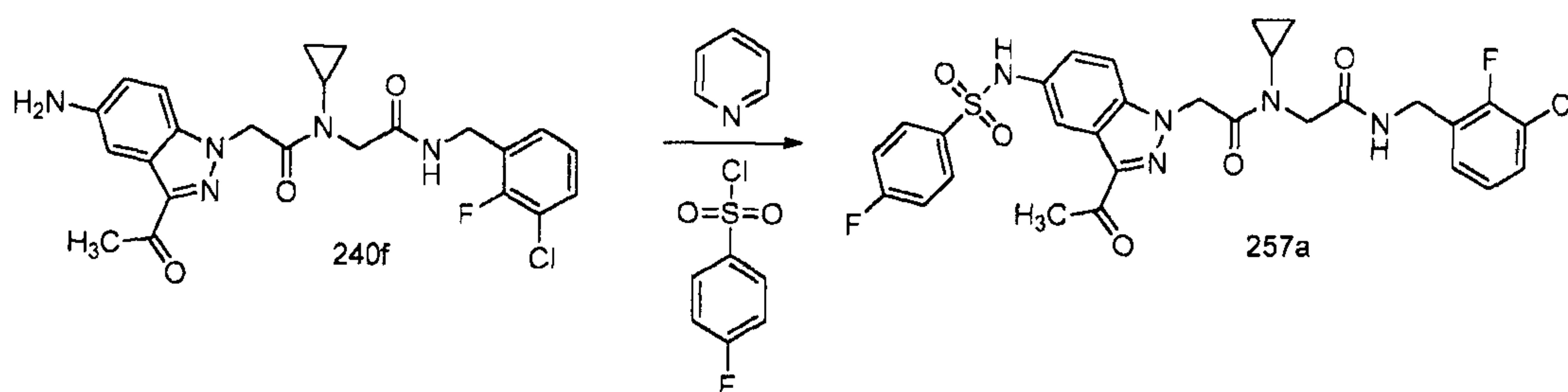


Preparation of 1-(2-((2-((2'-(2-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3-(pyrimidin-5-yl)ureido)-1H-indazole-3-carboxamide (**256a**)

Compound (**256a**) was prepared from 3-carbamoyl-1-(2-((2-((2'-(2-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**230b**) (85 mg, 0.15 mmol) and pyrimidin-5-amine (29 mg, 0.3 mmol) according to the procedure reported in step-3 of scheme-223 to afford after workup and purification by column chromatography [silica gel, (4 g) eluting with DMA80 in DCM 0 to 50%] 1-(2-((2-((2'-(2-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(3-(pyrimidin-5-yl)ureido)-1H-indazole-3-carboxamide (**256a**)

(27 mg, 0.041 mmol, 27% yield) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) (as a mixture of two rotamers) δ 10.26 and 9.77 (2s, 1H), 9.15 (s, 1H), 8.99 and 8.97 (2s, 1H), 8.94 and 8.93 (2s, 2H), 8.810 and 8.808 (2s, 1H), 8.35 and 8.32 (2d, $J = 1.4$ Hz, 1H), 8.10 and 7.95 (2t, $J = 7.8$ Hz, 1H), 7.76 – 7.00 (m, 10H), 5.61 and 5.47 (2s, 2H), 4.72 – 4.57 and 4.41 – 4.26 (2m, 1H), 4.47 and 4.08 (2s, 2H) 1.26 and 1.06 (2d, $J = 6.7$ Hz, 6H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -126.77 and -126.97; MS (ES-): 692.5 & 694.5 (M+Cl).

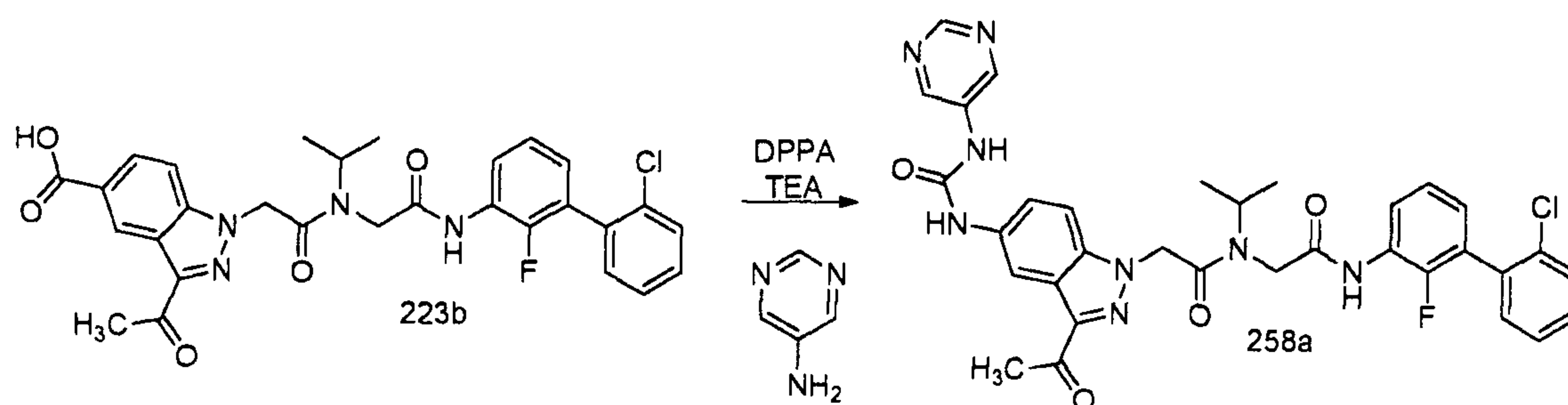
Scheme 257



Preparation of 2-(3-acetyl-5-(4-fluorophenylsulfonamido)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**257a**)

To a solution of 2-(3-acetyl-5-amino-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**240f**) (8 mg, 0.17 mmol) in DCM
 5 (3 mL) was added Pyridine (0.069 mL, 0.85 mmol), 4-fluorobenzene-1-sulfonyl chloride (49 mg, 0.25 mmol) and stirred at RT for 3h. The reaction mixture was quenched with methanol (0.5 mL), concentrated in vacuum to dryness and the residue was purified by flash column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 20%] to afford 2-(3-acetyl-5-(4-fluorophenylsulfonamido)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-cyclopropylacetamide (**257a**) (70 mg, 0.11 mmol, 66%
 10 yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.36 (s, 1H), 8.46 (t, J = 5.9 Hz, 1H), 7.90 - 7.85 (m, 1H), 7.82 - 7.74 (m, 2H), 7.58 (d, J = 8.9 Hz, 1H), 7.52 - 7.31 (m, 3H), 7.27 - 7.16 (m, 2H), 7.14 - 7.02 (m, 1H), 5.69 (s, 2H), 4.33 (d, J = 5.7 Hz, 2H), 3.96 (s, 2H), 3.15 - 3.01 (m, 1H), 2.56 (s, 3H), 1.07 - 0.95 (m, 2H), 0.94 - 0.82 (m, 2H); ¹⁹F NMR (282
 15 MHz, DMSO-*d*₆) δ -105.97, -121.58; MS (ES⁺): 630.5 (M+1), 652.6 (M+Na); MS (ES⁻): 628.5 (M-1), 664.5 (M+Cl).

Scheme 258

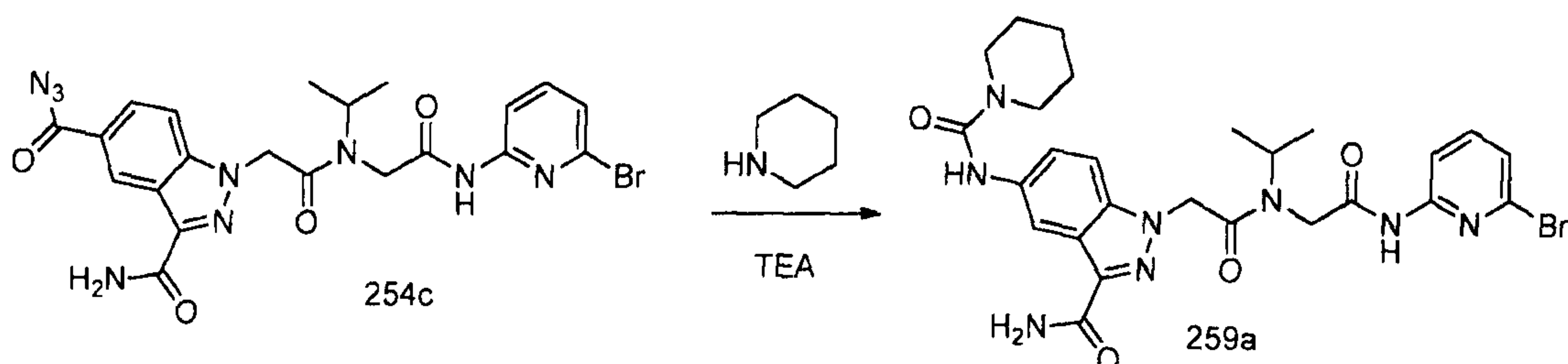


Preparation of 2-(3-acetyl-5-(3-(pyrimidin-5-yl)ureido)-1H-indazol-1-yl)-N-(2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**258a**)
 20

Compound (**256a**) was prepared from 3-acetyl-1-(2-((2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carboxylic acid (**223b**) (110 mg, 0.2 mmol) and pyrimidin-5-amine (37 mg, 0.4 mmol) according to the procedure reported in step-3 of scheme-223 to afford after workup and purification by column chromatography [silica gel, (4 g) eluting with DMA80 in DCM 0 to 30%] 2-(3-acetyl-5-(3-(pyrimidin-5-yl)ureido)-1H-indazol-1-yl)-N-(2-((2'-chloro-2-fluoro-[1,1'-biphenyl]-3-yl)amino)-2-oxoethyl)-N-isopropylacetamide (**258a**) (26 mg, 0.04 mmol, 20% yield) as a white solid as a mixture of rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 10.27 and 9.76 (2s,
 25

1H), 9.23 (s, 1H), 9.02 and 9.01 (2s, 1H), 8.94 (s, 2H), 8.82 (s, 1H), 8.41 and 8.37 (2s, 1H), 8.12 and 7.96 (2t, J = 8.0 Hz, 1H), 7.71 - 6.99 (m, 8H), 5.72 and 5.55 (2s, 2H), 4.72 - 4.57 and 4.41 - 4.26 (2m, 1H), 4.47 and 4.09 (2s, 2H), 2.61 and 2.60 (2s, 3H), 1.28 and 1.07 (2d, J = 6.8 Hz, 6H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -126.85 and -126.99; MS (ES⁺): 657.5 (M+1), MS (ES⁻): 655.5 (M-1), 691.5 (M+Cl).

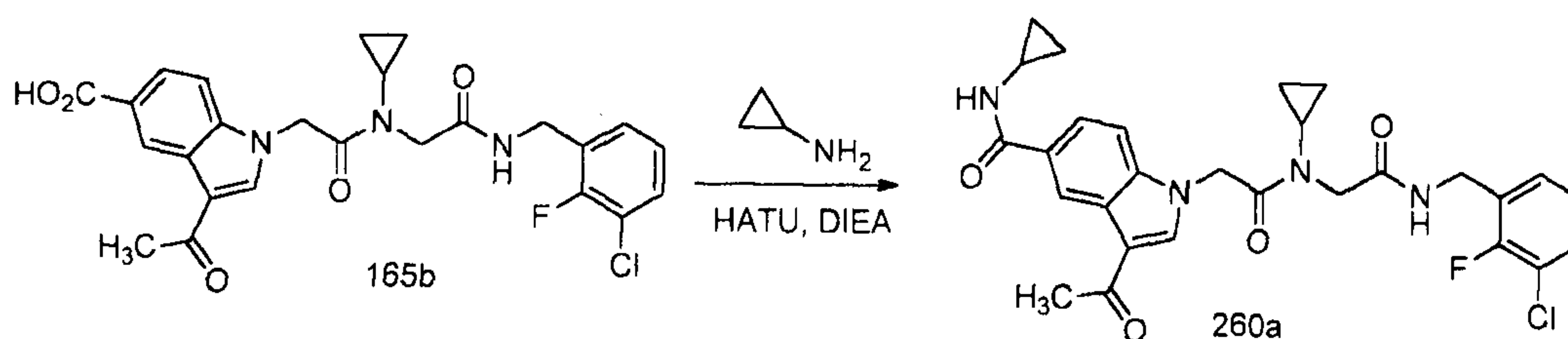
Scheme 259



Preparation of 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(piperidine-1-carboxamido)-1H-indazole-3-carboxamide (**259a**)

Compound (**259a**) was prepared from 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-3-carbamoyl-1H-indazole-5-carbonyl azide (**254c**) (300 mg, 0.55 mmol) and piperidine (94 mg, 1.11 mmol) using TEA (0.31 mL, 2.2 mmol) as base according to the procedure reported in step-4 of Scheme 129 to afford after workup and purification by column chromatography [silica (12 g), eluting with DMA80 in DCM 0 to 40%] 1-(2-((2-((6-bromopyridin-2-yl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-5-(piperidine-1-carboxamido)-1H-indazole-3-carboxamide (**259a**) (61 mg, 0.1 mmol, 18% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 11.20 and 10.82 (2s, 1H), 8.57 (d, J = 5.1 Hz, 1H), 8.24 - 7.94 (m, 2H), 7.86 - 7.27 (m, 6H), 5.56 and 5.40 (2s, 2H), 4.66 - 4.52 and 4.35 - 4.26 (2m, 1H), 4.42 and 4.02 (2s, 2H), 3.52 - 3.38 (m, 4H), 1.62 - 1.46 (m, 6H), 1.23 (d, J = 6.4 Hz) and 1.03 (d, J = 6.7 Hz) (2d, 6H); MS (ES⁺): 599.6 (M+1); (ES⁻): 597.5 (M-1).

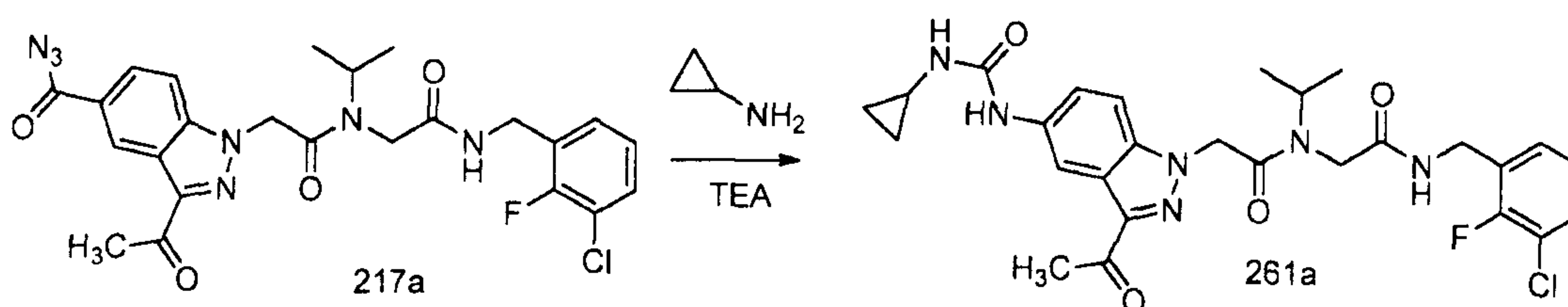
Scheme 260



Preparation of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-N-cyclopropyl-1H-indole-5-carboxamide (**260a**)

Reaction of 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indole-5-carboxylic acid (**165b**) (50 mg, 0.1 mmol) with cyclopropanamine (10.40 μ L, 0.150 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column [silica (8 g),
 5 eluting dichloromethane/methanol (1:0 to 19:1)] 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-N-cyclopropyl-1H-indole-5-carboxamide (**260a**) (30 mg, 56%) as a white solid; ^1H NMR (300 MHz, DMSO- d_6) δ 8.67 – 8.64 (m, 1H), 8.50 – 8.41 (m, 2H), 8.35 (s, 1H), 7.67 (dd, J = 8.7, 1.8 Hz, 1H), 7.52 – 7.41 (m, 2H), 7.27 – 7.19 (m, 1H), 7.09 (td, J = 7.8, 1.0 Hz, 1H), 5.47 (s, 2H), 4.34 (d, J = 5.7 Hz,
 10 2H), 3.99 (s, 2H), 3.17 – 3.03 (m, 1H), 2.96 – 2.79 (m, 1H), 2.45 (s, 3H), 1.05 – 0.82 (m, 4H), 0.75 – 0.55 (m, 4H); ^{19}F NMR (282 MHz, DMSO- d_6) δ -121.59; MS (ES $^+$): 539.5 & 541.5 (M+1).

Scheme 261



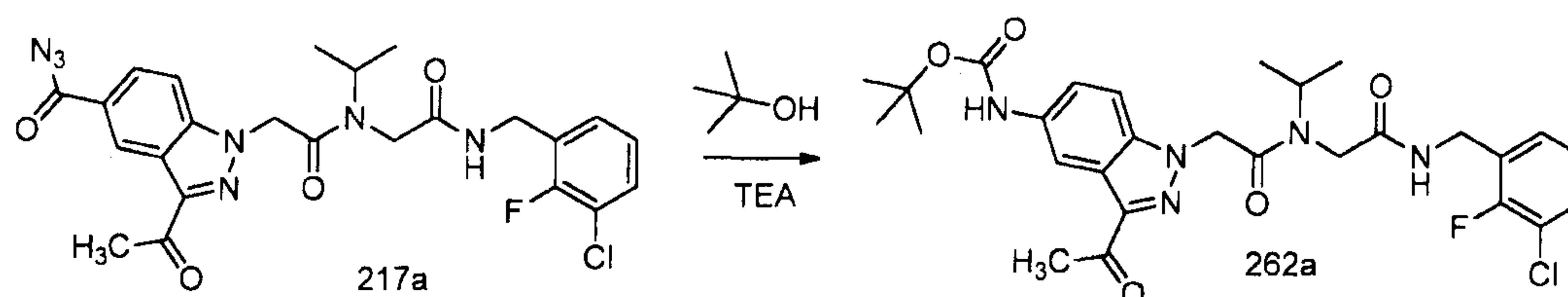
15 Preparation of 2-(3-acetyl-5-(3-cyclopropylureido)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**261a**)

Compound (**261a**) was prepared from 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**217a**) (105 mg, 0.2 mmol) and cyclopropanamine (0.028 mL, 0.4 mmol) using TEA (0.055 mL, 0.4 mmol) as
 20 base according to the procedure reported in step-4 of Scheme 129 to afford after workup and purification by column chromatography [silica gel (8 g), eluting with dichloromethane/methanol (1:0 to 19:1)] 2-(3-acetyl-5-(3-cyclopropylureido)-1H-indazol-1-yl)-N-(2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)-N-isopropylacetamide (**261a**) (16 mg, 14%) as an off-white solid; ^1H NMR(300 MHz, DMSO- d_6) δ 8.83 (t, J = 5.9 Hz) and
 25 8.39 – 8.09 (m) (2H), 8.60 and 8.58 (2s, 1H), 7.58 – 6.94 (m, 5H), 6.49 – 6.30 (m, 1H), 5.63 and 5.46 (2s, 2H), 4.64 – 4.50 and 4.29 – 4.20 (2m, 1H), 4.46 (d, J = 5.5 Hz) and 4.32 (d, J = 6.0 Hz (2d, 2H), 4.17 and 3.84 (2s, 2H), 2.58 and 2.41 (2s, 3H), 1.23 (d, J = 6.5 Hz) and 0.99 (d, J = 6.8 Hz) (2d, 6H), 0.71 – 0.55 (m, 2H), 0.49 – 0.34 (m, 2H); MS (ES $^-$): 591.5 & 593.5 (M+Cl).

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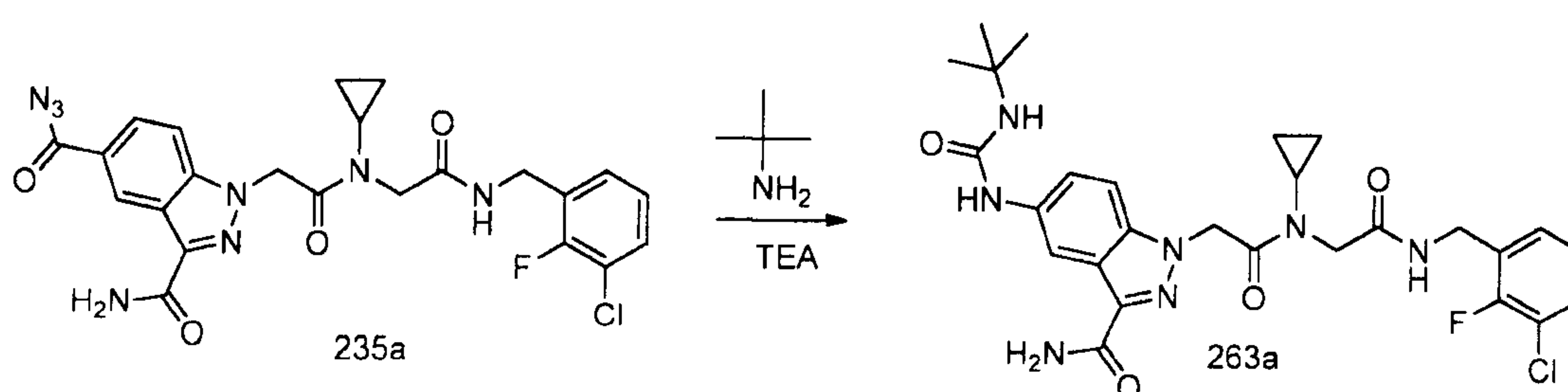
Scheme 262



Preparation of tert-butyl (3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)carbamate (**262a**)

- Compound (**262a**) was prepared from 3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**217a**) (105 mg, 0.2 mmol) and 2-methylpropan-2-ol (0.114 mL, 1.19 mmol) using TEA (0.055 mL, 0.4 mmol) as base according to the procedure reported in step-4 of Scheme 129 to afford after workup and purification by column chromatography [silica gel, eluting with dichloromethane/methanol (1:0 to 19:1)] tert-butyl (3-acetyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(isopropyl)amino)-2-oxoethyl)-1H-indazol-5-yl)carbamate (**262a**) (8 mg, 7%) as an off-white solid as a mixture of rotamers; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.47 (s, 1H), 8.83 and 8.35 (2t, 1H), 8.42 (s, 1H), 7.58 – 6.67 (m, 5H), 5.63 and 5.46 (2s, 2H), 4.62 – 4.22 (m, 3H), 4.16 and 3.84 (2s, 2H), 2.58 and 2.53 (2s, 3H), 1.50 and 1.49 (2s, 9H), 1.23 and 0.99 (2d, *J* = 6.8 Hz, 6H); MS (ES⁻): 608.6 & 610.6 (M+Cl).

Scheme 263

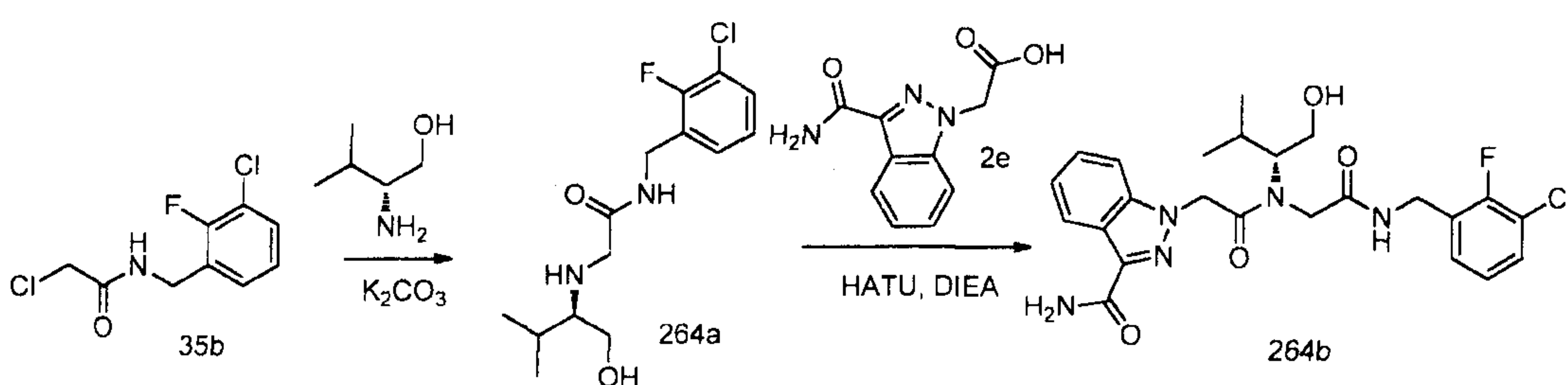


- Preparation of 5-(3-tert-butylureido)-1-(2-((2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**263a**)

- Compound **263a** was prepared from 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**235a**) (300 mg, 0.29 mmol) and 3,3-difluoropyrrolidine hydrochloride (102 mg, 0.712 mmol) using TEA (0.16 mL, 1.14 mmol) as base according to the procedure reported in step-4 of Scheme 129. This gave after workup, purification by flash column chromatography [silica gel (12 g),

eluting with DMA80 in DCM 0 to 40%] 5-(3-tert-butylureido)-1-(2-((2-(3-chloro-2-fluorobenzylamino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**263a**) (30 mg, 0.052 mmol, 14% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.46 (t, *J* = 5.8 Hz, 1H), 8.33 (s, 1H), 8.23 – 8.18 (m, 1H), 7.54 (s, 1H), 7.51 – 7.41 (m, 2H), 7.33 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.30 – 7.19 (m, 2H), 7.17 – 7.07 (m, 1H), 5.88 (s, 1H), 5.59 (s, 2H), 4.33 (d, *J* = 5.7 Hz, 2H), 3.98 (s, 2H), 3.14 – 2.97 (m, 1H), 1.31 (s, 9H), 1.02 – 0.95 (m, 2H), 0.95 – 0.85 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -121.59; MS (ES-) 570.4 (M-1).

Scheme 264



Preparation of (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-hydroxy-3-methylbutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**264b**)

Step-1: Preparation of (R)-N-(3-chloro-2-fluorobenzyl)-2-((1-hydroxy-3-methylbutan-2-yl)amino)acetamide (**264a**)

Reaction of 2-chloro-N-(3-chloro-2-fluorobenzyl)acetamide (**35b**) (500 mg, 2.12 mmol) with (R)-2-amino-3-methylbutan-1-ol (437 mg, 4.24 mmol) according to the procedure reported in step-2 of Scheme 35 gave after workup (R)-N-(3-chloro-2-fluorobenzyl)-2-((1-hydroxy-3-methylbutan-2-yl)amino)acetamide (**264a**) (641 mg, 2.12 mmol, 100 % yield) which was used as such in the next step; MS (ES+): 303.4 (M+1), 325.4 (M+Na); MS (ES-): 337.3 (M+Cl).

Step-2: Preparation of (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-hydroxy-3-methylbutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**264b**)

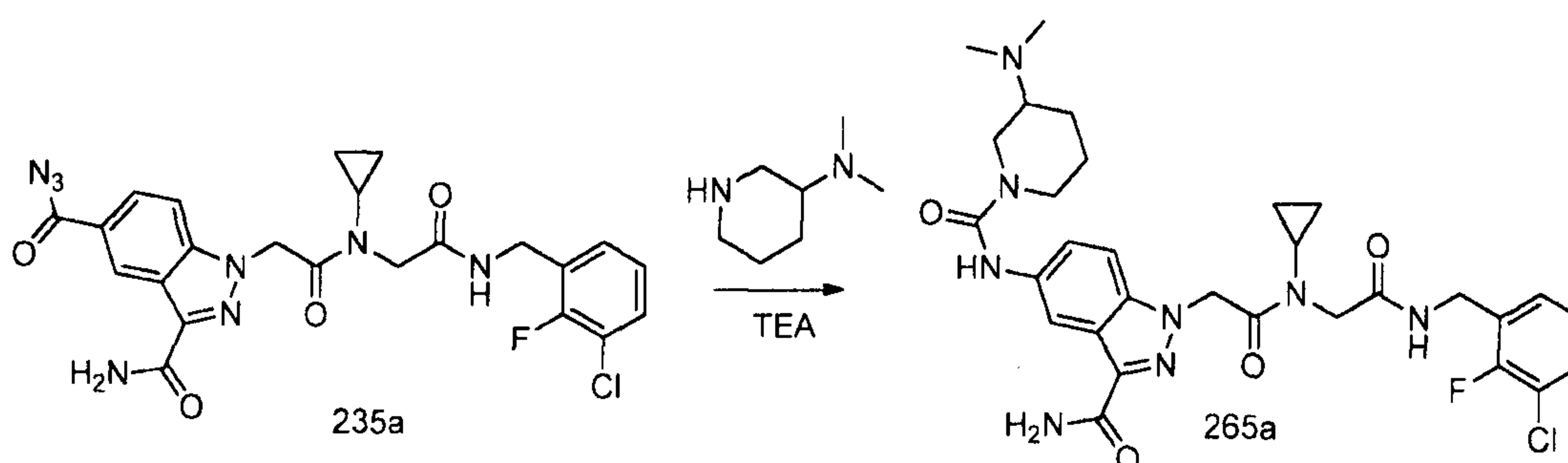
Reaction of (R)-N-(3-chloro-2-fluorobenzyl)-2-((1-hydroxy-3-methylbutan-2-yl)amino)acetamide (**264a**) (360 mg, 1.19 mmol) with 2-(3-carbamoyl-1H-indazol-1-yl)acetic acid (**2e**) (261 mg, 1.19 mmol) according to the procedure reported in step-3 of Scheme 2 gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM 0 to 50%] (R)-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(1-hydroxy-3-methylbutan-2-yl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**264b**) (0.016 g, 0.032 mmol, 3% yield) as a white solid in the form of mixture of rotamers.

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^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.95 (t, $J = 5.7$ Hz) & 8.82 (t, $J = 5.8$ Hz) (2t, 1H), 8.27 – 8.12 (m, 1H), 7.79 and 7.71 (2s, 1H), 7.67 – 6.85 (m, 7H), 5.75 (bs, 1H, D_2O exchangeable), 5.70 – 5.39 (m, 2H), 4.59–3.37 (m, 7H), 1.92 – 1.65 (m, 1H), 1.00 (d, $J = 6.4$ Hz) and 0.94 (d, $J = 6.5$ Hz) and 0.87 (d, $J = 6.5$ Hz) and 0.76 (d, $J = 6.6$ Hz) (4d, 6H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.32, -121.55; MS (ES⁺): 504.5 (M+1), 526.5 (M+Na); MS (ES⁻): 502.5 (M-1).

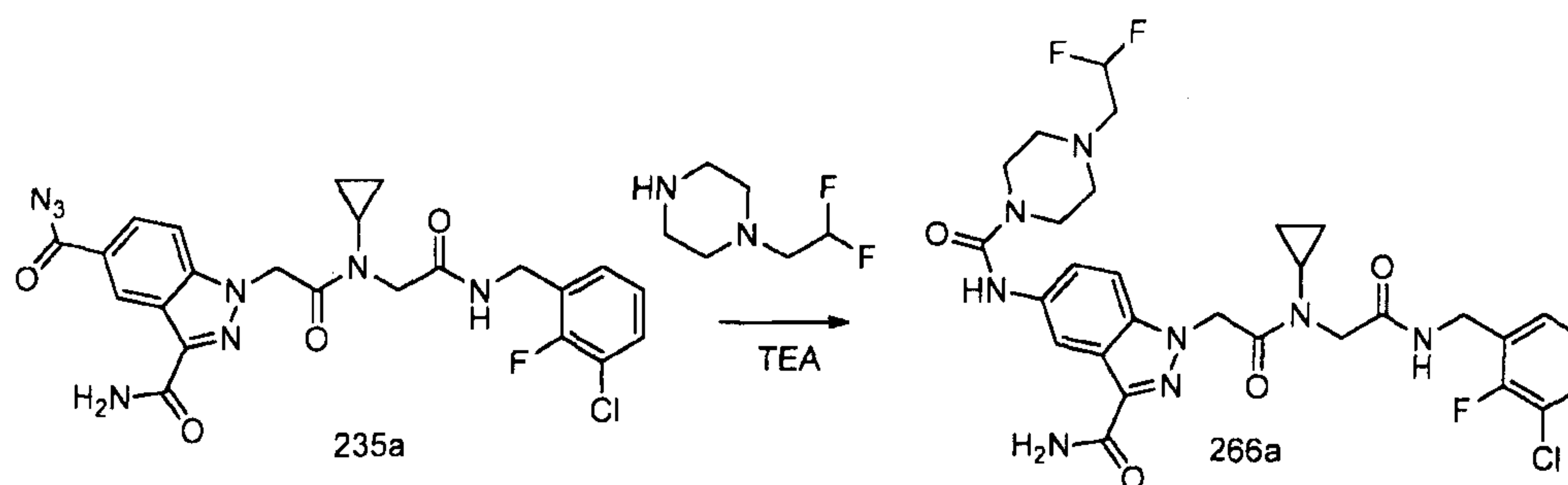
Scheme 265



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3-(dimethylamino)piperidine-1-carboxamido)-1H-indazole-3-carboxamide (265a)

Compound **265a** was prepared from 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**235a**) (400 mg, 0.38 mmol) and N,N-dimethylpiperidin-3-amine (97 mg, 0.76 mmol) using TEA (0.21 mL, 1.52 mmol) as base according to the procedure reported in step-4 of Scheme 129. This gave after workup, purification by flash column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] followed by preparative HPLC [C_{18} column, eluting with CH_3CN in water (containing 0.1% TFA) 0-100%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(3-(dimethylamino)piperidine-1-carboxamido)-1H-indazole-3-carboxamide (**265a**) (32 mg, 0.051 mmol, 13 % yield) white solid as a TFA salt; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.60 – 9.46 (m, 1H), 8.77 (s, 1H), 8.50 (t, $J = 5.8$ Hz, 1H), 8.25 – 8.18 (m, 1H), 7.66 (s, 1H), 7.56 – 7.50 (m, 2H), 7.50 – 7.42 (m, 1H), 7.32 (s, 1H), 7.27 – 7.19 (m, 1H), 7.19 – 7.08 (m, 1H), 5.61 (s, 2H), 4.33 (d, $J = 5.7$ Hz, 2H), 4.24 (d, $J = 13.0$ Hz, 2H), 3.98 (s, 2H), 3.94 – 3.88 (m, 1H), 3.33 – 3.22 (m, 1H), 3.10 – 2.97 (m, 2H), 2.86 and 2.85 and 2.82 and 2.81 (4s, 6H), 2.13 – 2.03 (m, 1H), 1.86 – 1.65 (m, 2H), 1.61 – 1.39 (m, 1H), 1.03 – 0.95 (m, 2H), 0.95 – 0.85 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -73.92 (TFA peak), -121.58; MS (ES⁺): 627.5 (M+1).

Scheme 266

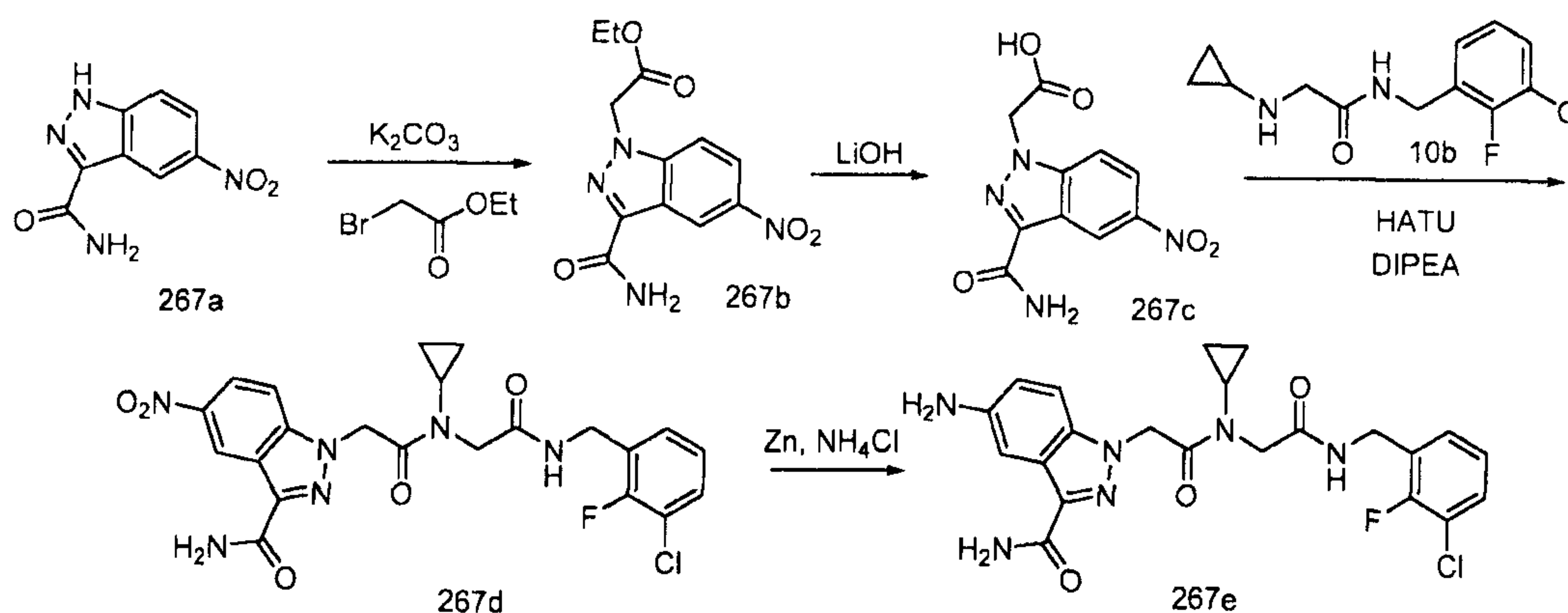


Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(4-(2,2-difluoroethyl)piperazine-1-carboxamido)-1H-indazole-3-carboxamide
 5 (266a)

Compound **266a** was prepared from 3-carbamoyl-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-5-carbonyl azide (**235a**) (400 mg, 0.38 mmol) and 1-(2,2-difluoroethyl)piperazine hydrochloride (163 mg, 0.87 mmol) using TEA (0.24 mL, 1.75 mmol) as base according to the procedure reported in step-4 of Scheme
 10 129. This gave after workup, purification by flash column chromatography [silica gel (12 g), eluting with DMA80 in DCM 0 to 40%] followed by preparative HPLC [C₁₈ column, eluting with CH₃CN in water (containing 0.1% TFA) 0-100%] 1-(2-((2-((3-chloro-2-
 fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(4-(2,2-
 difluoroethyl)piperazine-1-carboxamido)-1H-indazole-3-carboxamide (**266a**) (32 mg, 0.042
 15 mmol, 10 % yield) white solid as a TFA salt; ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.80 (s, 1H), 8.50 (t, *J* = 5.9 Hz, 1H), 8.21 – 8.15 (m, 1H), 7.65 (s, 1H), 7.58 – 7.43 (m, 3H), 7.36 – 7.29 (m, 1H), 7.28 – 7.20 (m, 1H), 7.19 – 7.07 (m, 2H), 5.61 (s, 2H), 4.33 (d, *J* = 5.6 Hz, 2H), 3.98 (s, 2H), 3.78-2.71 (m, 12H), 1.03 – 0.95 (m, 2H), 0.95 – 0.86 (m, 2H); ¹⁹F NMR (282 MHz, DMSO-*d*₆) δ -74.40 (TFA peak), -119.35, -121.59; MS (ES⁺) 649.5 (M+1).

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Scheme 267



Preparation of 5-amino-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**267e**)

Step-1: Preparation of ethyl 2-(3-carbamoyl-5-nitro-1H-indazol-1-yl)acetate (**267b**)

Compound **267b** was prepared from 5-nitro-1H-indazole-3-carboxamide (**267a**) (1.85 g, 8.97 mmol, prepared according to the procedure reported by Ochs, Raymond S. and Talele, Tanaji T; in U.S. Pat. Appl. Publ., 20120130078) and ethyl 2-bromoacetate (1.985 mL, 17.95 mmol), using Potassium carbonate (2.480 g, 17.95 mmol) as base according to the procedure reported in step-1 of Scheme 56. This gave after workup ethyl 2-(3-carbamoyl-5-nitro-1H-indazol-1-yl)acetate (**267b**) (2 g, 6.84 mmol, 76% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.06 (dd, *J* = 2.3, 0.7 Hz, 1H), 8.33 (dd, *J* = 9.3, 2.3 Hz, 1H), 8.09 - 7.97 (m, 2H), 7.73 (s, 1H), 5.60 (s, 2H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 3H); MS (ES+) 293.4 (M+1), MS (ES-): 327.3 (M+Cl).

Step-2: Preparation of 2-(3-carbamoyl-5-nitro-1H-indazol-1-yl)acetic acid (**267c**)

Compound **267c** was prepared from ethyl 2-(3-carbamoyl-5-nitro-1H-indazol-1-yl)acetate (**267b**) (2 g, 6.84 mmol) using a solution of LiOH (0.49 g, 20.53 mmol) in Water (10 mL) as base, according to the procedure reported in step-2 of Scheme 129. This gave after workup 2-(3-carbamoyl-5-nitro-1H-indazol-1-yl)acetic acid (**267c**) (1.6 g, 6.06 mmol, 88% yield) as a white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 13.48 (s, 1H), 9.05 (dd, *J* = 2.3, 0.7 Hz, 1H), 8.32 (dd, *J* = 9.3, 2.3 Hz, 1H), 8.04 (s, 1H), 8.01 (dd, *J* = 9.3, 0.7 Hz, 1H), 7.72 (s, 1H), 5.48 (s, 2H); MS (ES-): 263.2 (M-1).

Step-3: Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-nitro-1H-indazole-3-carboxamide (**267d**)

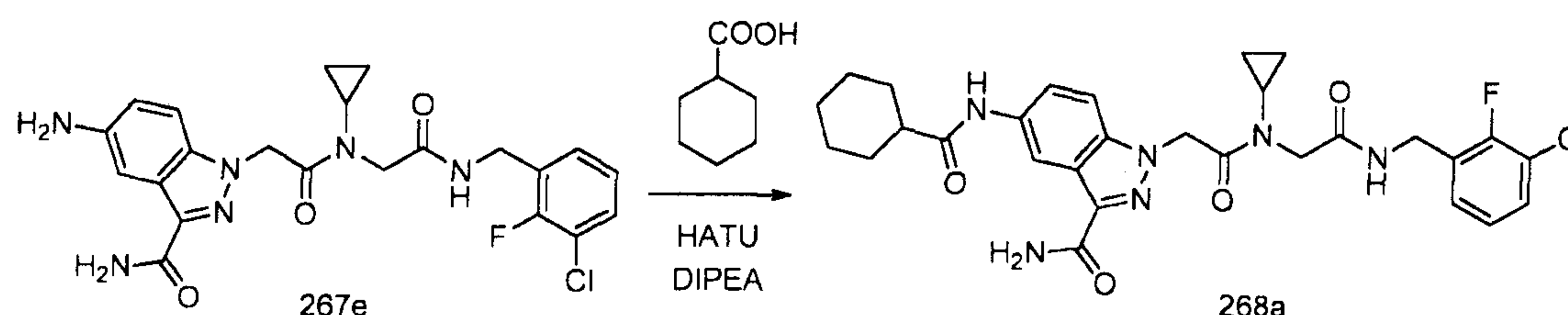
Compound **267d** was prepared from 2-(3-carbamoyl-5-nitro-1H-indazol-1-yl)acetic acid (**267c**) (800 mg, 3.03 mmol) and N-(3-chloro-2-fluorobenzyl)-2-(cyclopropylamino)acetamide (**10b**) (933 mg, 3.63 mmol) according to the procedure reported in step-3 of Scheme 2. This gave after workup and trituration with ethyl acetate/hexanes (20 mL, 1:1) 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-nitro-1H-indazole-3-carboxamide (**267d**) (1.3 g, 2.59 mmol, 85 % yield) as a off-white solid; ¹H NMR (300 MHz, DMSO-*d*₆) δ 9.05 (dd, *J* = 2.3, 0.6 Hz, 1H), 8.52 (t, *J* = 5.8 Hz, 1H), 8.27 (dd, *J* = 9.3, 2.3 Hz, 1H), 8.04 (s, 1H), 7.91 (dd, *J* = 9.3, 0.7 Hz, 1H), 7.69 (s, 1H), 7.50 - 7.42 (m, 1H), 7.27 - 7.18 (m, 1H), 7.14 - 7.07 (m, 1H), 5.78 (s, 2H), 4.33 (d, *J* = 5.7 Hz, 2H), 3.99 (s, 2H), 3.14 - 3.01 (m, 1H), 1.05 - 0.96

(m, 2H), 0.96 – 0.87 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.55; MS (ES⁺): 525.5 (M+Na), MS (ES⁻): 537.4 (M+Cl).

Step-4: Preparation of 5-amino-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**267e**)

To a solution of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-nitro-1H-indazole-3-carboxamide (**267d**) (1.2 g, 2.39 mmol) in THF/methanol (80 mL, 1:1) was added ammonium Chloride (2.55 g, 47.7 mmol), Zinc (1.56 g, 23.86 mmol) and stirred at RT for 3h. The mixture was filtered over a Celite pad, pad was washed with 20% methanol in EtOAc (2 x 10 mL) and concentrated partially in vacuum. The resultant residue was partitioned between brine (60 mL) and EtOAc (80 mL). The organic layer was separated, dried, filtered and concentrated in vacuum. The residue obtained was purified by flash column chromatography [silica gel (24 g), eluting with DMA80 in DCM, 0 to 25%] to afford 5-amino-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**267e**) (1.05 g, 2.22 mmol, 93% yield) as light orange solid; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.49 (t, J = 5.8 Hz, 1H), 7.52 - 7.41 (m, 2H), 7.35 - 7.07 (m, 5H), 6.79 (dd, J = 8.9, 2.1 Hz, 1H), 5.52 (s, 2H), 5.04 (s, 2H), 4.33 (d, J = 5.7 Hz, 2H), 3.97 (s, 2H), 3.09 - 2.98 (m, 1H), 1.02 - 0.93 (m, 2H), 0.93 - 0.85 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO}-d_6$) δ -121.61; MS (ES⁺): 473.5 (M+1), 495.4 (M+Na); MS (ES⁻): 507.4 (M+Cl).

Scheme 268



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(cyclohexanecarboxamido)-1H-indazole-3-carboxamide (**268a**)

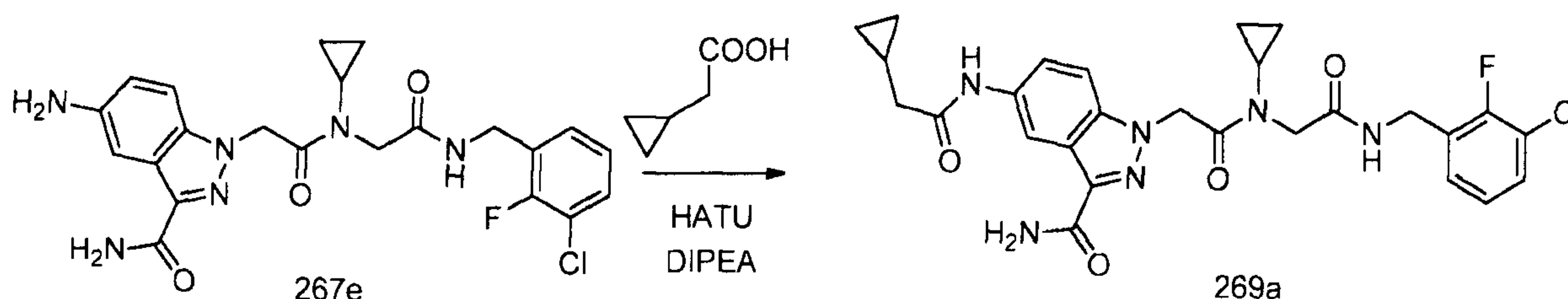
Compound **268a** was prepared from 5-amino-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**267e**) (120 mg, 0.25 mmol) and cyclohexanecarboxylic acid (33 mg, 0.25 mmol) according to the procedure reported in step-3 of Scheme 2. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM 0 to 30%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(cyclohexanecarboxamido)-1H-indazole-3-carboxamide (**268a**) (70 mg, 0.12 mmol, 47%)

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yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 9.91 (s, 1H), 8.50 (t, $J = 6.0$ Hz, 1H), 8.45 (s, 1H), 7.71 – 7.51 (m, 3H), 7.46 (td, $J = 7.6, 1.7$ Hz, 1H), 7.35 (s, 1H), 7.28–7.18 (m, 1H), 7.12 (t, $J = 7.9$ Hz, 1H), 5.62 (s, 2H), 4.33 (d, $J = 5.7$ Hz, 2H), 3.98 (s, 2H), 3.12 – 2.99 (m, 1H), 2.34 (t, $J = 11.4$ Hz, 1H), 1.91 – 1.11 (m, 10H), 1.04 – 0.94 (m, 2H), 0.94 – 0.85 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -121.59; MS (ES⁺): 584.5 (M+1), MS (ES⁻): 617.5 (M+Cl).

Scheme 269



Preparation of 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(2-cyclopropylacetamido)-1H-indazole-3-carboxamide (**269a**)

Compound **269a** was prepared from 5-amino-1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-1H-indazole-3-carboxamide (**267e**) (120 mg, 0.25 mmol) and 2-cyclopropylacetic acid (25 mg, 0.25 mmol) according to the procedure reported in step-3 of Scheme 2. This gave after workup and purification by flash column chromatography [silica (12 g), eluting with DMA80 in DCM 0 to 30%] 1-(2-((2-((3-chloro-2-fluorobenzyl)amino)-2-oxoethyl)(cyclopropyl)amino)-2-oxoethyl)-5-(2-cyclopropylacetamido)-1H-indazole-3-carboxamide (**269a**) (95 mg, 0.17 mmol, 68% yield) as a white solid; ^1H NMR (300 MHz, $\text{DMSO-}d_6$) δ 9.92 (s, 1H), 8.50 (t, $J = 5.8$ Hz, 1H), 8.44 (d, $J = 1.8$ Hz, 1H), 7.72 – 7.52 (m, 3H), 7.51 – 7.41 (m, 1H), 7.35 (s, 1H), 7.28–7.17 (m, 1H), 7.12 (t, $J = 7.8$ Hz, 1H), 5.63 (s, 2H), 4.33 (d, $J = 5.7$ Hz, 2H), 3.98 (s, 2H), 3.13 – 2.99 (m, 1H), 2.22 (d, $J = 7.0$ Hz, 2H), 1.15 – 0.84 (m, 5H), 0.55 – 0.43 (m, 2H), 0.26 – 0.16 (m, 2H); ^{19}F NMR (282 MHz, $\text{DMSO-}d_6$) δ -121.59; MS (ES⁺): 555.5 (M+1), 577.4 (M+Na); MS (ES⁻): 589.4 (M+Cl).

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CECI EST LE TOME 1 DE 2
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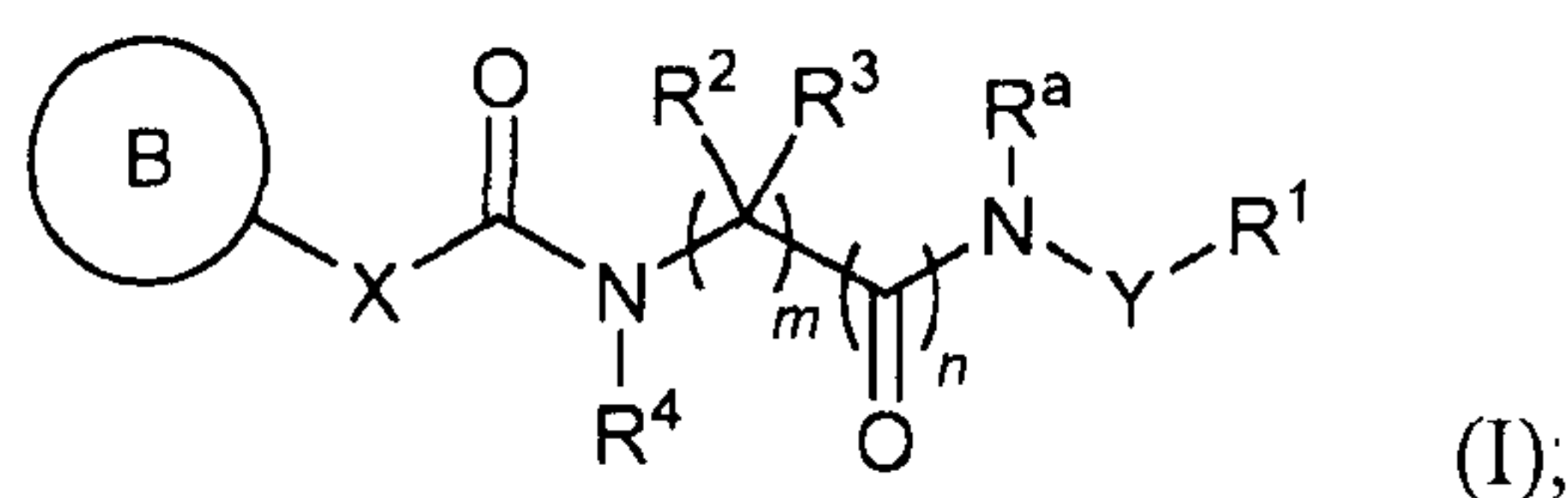
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CLAIMS

What is claimed is:

1. A compound represented by Formula (I), or a pharmaceutically acceptable salt thereof:



wherein, independently for each occurrence:

R^1 represents optionally substituted aryl, heteroaryl, cycloalkyl, heterocycloalkyl, alkyl, or alkenyl;

R^2 and R^3 each independently represent H, F, or optionally substituted alkyl, alkenyl, alkynyl, alkoxyalkyl, haloalkyl, hydroxyalkyl, (alkylthio)alkyl, aralkyl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl;

or R^2 and R^3 , taken together with the carbon atom to which they are bonded, form an optionally substituted cycloalkyl or heterocycloalkyl ring;

R^4 represents H or optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, (heterocycloalkyl)alkyl, aralkyl, heteroaralkyl, hydroxyalkyl, or haloalkyl;

X represents NH, CH₂, CHF, CF₂, CH(C₁-C₆)alkyl, or C((C₁-C₆)alkyl)₂;

Y is absent or represents CH₂, C(O), CR¹⁵R¹⁶, S(O)₂, or optionally substituted (C₃-C₇)cycloalkylene, arylene, or heteroarylene;

R^a represents H or optionally substituted (C₁-C₆)alkyl, (heterocycloalkyl)alkyl, or (C₃-C₇)cycloalkyl;

m is an integer from 1-6;

n is 0 or 1;

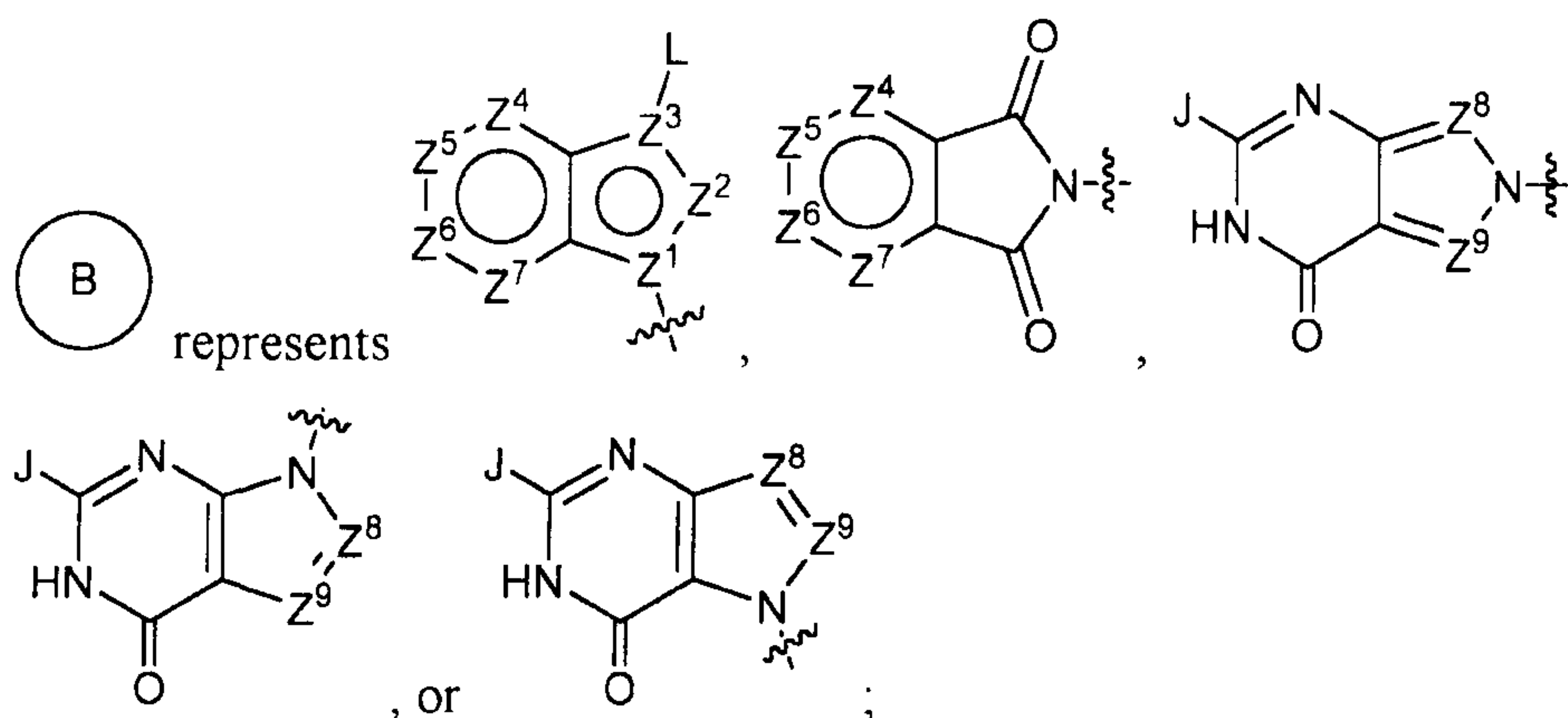
R^{15} and R^{16} are each independently selected from the group consisting of H, hydroxy, halogen, -C(O)OR¹⁷, -OR¹⁷, -C(O)NR¹⁷R¹⁸, -NR¹⁷R¹⁸, alkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl,

(cycloalkyl)alkyl, heterocycloalkyl, and (heterocycloalkyl)alkyl, wherein alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, and (heterocycloalkyl)alkyl are optionally substituted with one or more substituents selected from the group consisting of $-\text{CN}$, $-\text{OR}^{17}$, $-\text{NR}^{17}\text{R}^{18}$, halo, and alkyl;

or R^{15} and R^{16} may be taken together with the intervening atom to form an optionally substituted carbocyclic or heterocyclic ring;

R^{17} and R^{18} are each independently selected from the group consisting of H, alkyl, haloalkyl, hydroxyalkyl, alkoxyalkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, and (heterocycloalkyl)alkyl;

or R^{17} and R^{18} , when attached to the same atom, may be taken together with the intervening atom to form an optionally substituted heterocyclic ring;



Z^1 and Z^3 each independently represent C or N;

Z^2 represents N, CH, or CF;

Z^4 represents N or CR^8 ;

Z^5 represents N or CR^5 ;

Z^6 represents N or CR^6 ;

Z^7 represents N or CR^9 ;

Z^8 and Z^9 each independently represent N or CR^{19} ;

R^5 and R^6 each independently represent H, halogen, $-\text{CN}$, $-\text{NO}_2$, $-\text{OR}^{13}$, $-\text{NR}^{13}\text{R}^{14}$, $-\text{C}(\text{O})\text{R}^{13}$, $-\text{C}(\text{O})\text{OR}^{13}$, $-\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $-\text{OC}(\text{O})\text{R}^{13}$, $-\text{NR}^{13}\text{C}(\text{O})\text{R}^{14}$, $-\text{OC}(\text{O})\text{NR}^{13}\text{R}^{14}$, $-\text{OC}(\text{O})\text{OR}^{13}$, $-\text{NR}^{13}\text{C}(\text{O})\text{OR}^{14}$, $-\text{NR}^{13}\text{C}(\text{O})\text{NR}^{13}\text{R}^{14}$, $-\text{OS}(\text{O})_p(\text{R}^{13})$, $-\text{NR}^{13}\text{S}(\text{O})_p(\text{R}^{14})$, or optionally substituted alkyl, alkenyl,

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alkynyl, haloalkyl, aralkyl, heteroaralkyl, heteroaryl, aryl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl;

L represents $-H$, $-CN$, $-C(O)R^7$, $-CH(OH)R^7$, or $-S(O)_p(alkyl)$;

R^7 , independently for each occurrence, represents H , NH_2 , CH_3 , OH , CF_3 , CH_2OH , $(C_1-C_6)alkyl$, hydroxy $(C_1-C_6)alkyl$, $(C_1-C_6)alkoxy(C_1-C_6)alkyl$, halo $(C_1-C_6)alkyl$, $NH(C_1-C_6)alkyl$, $N((C_1-C_6)alkyl)_2$;

R^8 and R^9 each independently represent H , halogen, $-OR^{13}$, $-NR^{13}R^{14}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NR^{13}R^{14}$, $-OC(O)R^{13}$, $-NR^{13}C(O)R^{14}$, $-OC(O)NR^{13}R^{14}$, $-OC(O)OR^{13}$, $-NR^{13}C(O)OR^{14}$, $-NR^{13}C(O)NR^{13}R^{14}$, $-OS(O)_p(R^{13})$, $-NR^{13}S(O)_p(R^{14})$, or optionally substituted alkyl, alkenyl, alkynyl, haloalkyl, aralkyl, heteroaralkyl, heteroaryl, or aryl;

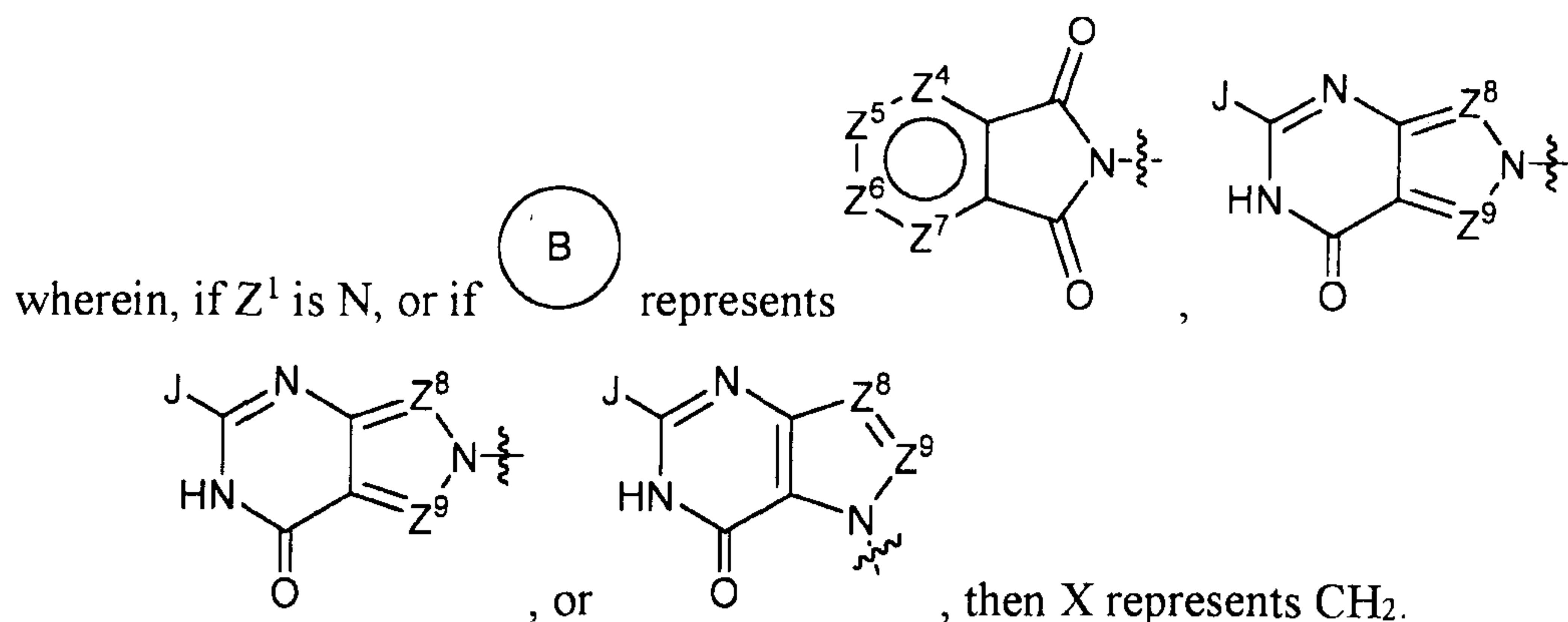
or R^5 and R^8 , or R^5 and R^6 , or R^6 and R^9 may be taken together with the intervening atoms to form an optionally substituted heterocyclic or carbocyclic ring;

R^{13} and R^{14} , independently for each occurrence, represent H or optionally substituted alkyl, alkenyl, alkynyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, or (heterocycloalkyl)alkyl; or, when R^{13} and R^{14} are attached to the same atom, R^{13} and R^{14} taken together with the atom may form an optionally substituted heterocyclic ring;

R^{19} , independently for each occurrence, represents H , F , CN , $-C(O)R^7$, $-CH(OH)R^7$, or $-S(O)_p(alkyl)$;

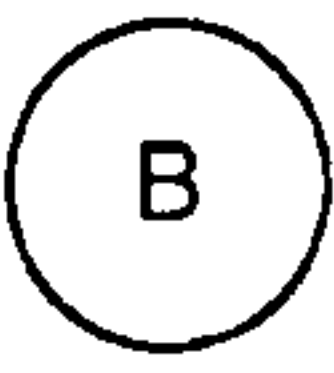
J represents H or NH_2 ; and

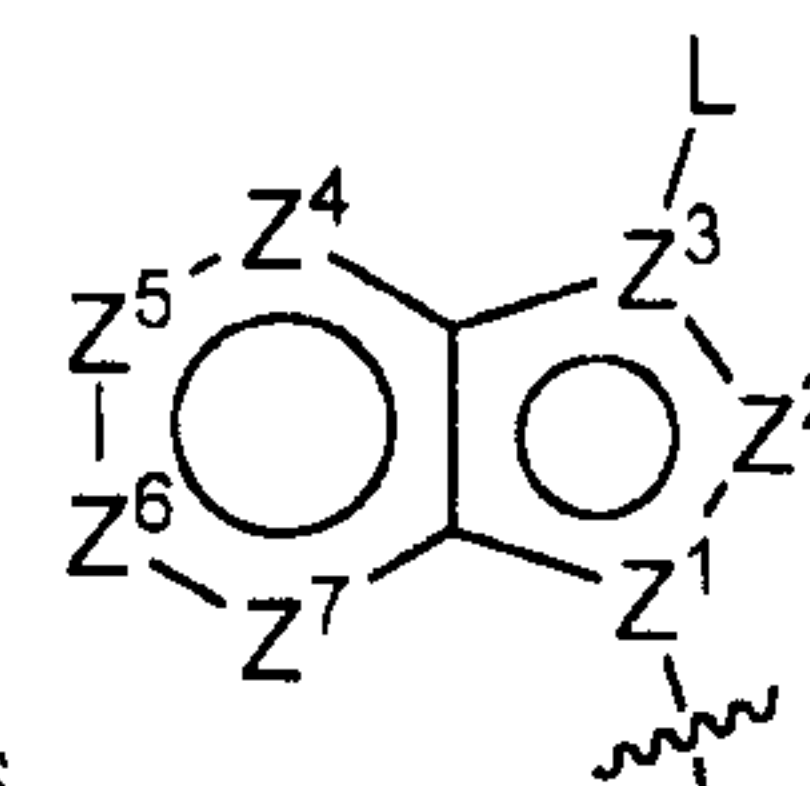
p is 0, 1, or 2;

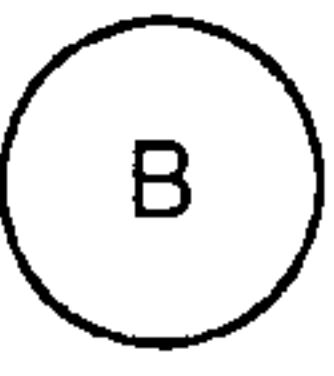


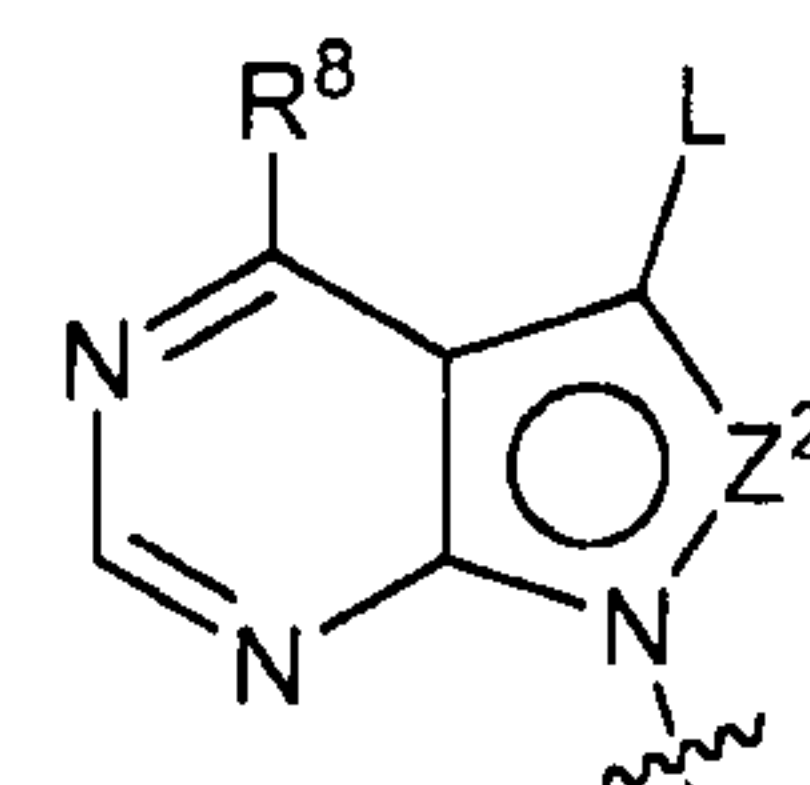
2. The compound of claim 1, wherein n is 1.
3. The compound of claim 1 or 2, wherein R^1 represents aryl or heteroaryl, optionally substituted by one or more substituents independently selected from the group consisting of halogen, $-CN$, alkoxy, haloalkoxy, alkyl, haloalkyl, alkenyl, dialkylamino, heterocycloalkyl, aryl, and heteroaryl.
4. The compound of any one of claims 1-3, wherein R^1 represents aryl or heteroaryl, substituted by one or more substituents, at least one of which is halogen.
5. The compound of any one of claims 1-4, wherein Y is absent.
6. The compound of any one of claims 1-4, wherein Y is CH_2 .
7. The compound of any one of claims 1-4, wherein Y is $CR^{15}R^{16}$.
8. The compound of claim 7, wherein R^{15} and R^{16} are selected from the group consisting of H, alkyl, hydroxyalkyl, haloalkyl, alkoxyalkyl, aralkyl, heteroaralkyl, (cycloalkyl)alkyl, and (heterocycloalkyl)alkyl;
wherein alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, and (heterocycloalkyl)alkyl are optionally substituted with one or more substituents selected from the group consisting of $-CN$, $-OR^{17}$, $-NR^{17}R^{18}$, halo, and alkyl; and
further wherein R^{17} and R^{18} are each independently selected from the group consisting of H and alkyl.
9. The compound of any one of claims 1-8, wherein R^2 is H; and R^3 represents H or optionally substituted alkyl, alkoxyalkyl, hydroxyalkyl, (alkylthio)alkyl, aralkyl, heteroaralkyl, cycloalkyl, or (cycloalkyl)alkyl.
10. The compound of any one of claims 1-9, wherein R^4 represents H or optionally substituted alkyl, cycloalkyl, (cycloalkyl)alkyl, heterocycloalkyl, aralkyl, hydroxyalkyl, or haloalkyl.
11. The compound of any one of claims 1-10, wherein R^4 represents H or optionally substituted alkyl or cycloalkyl.
12. The compound of any one of claims 1-11, wherein R^a is H.

13. The compound of any one of claims 1-12, wherein m is 1.

14. The compound of any one of claims 1-13, wherein  represents



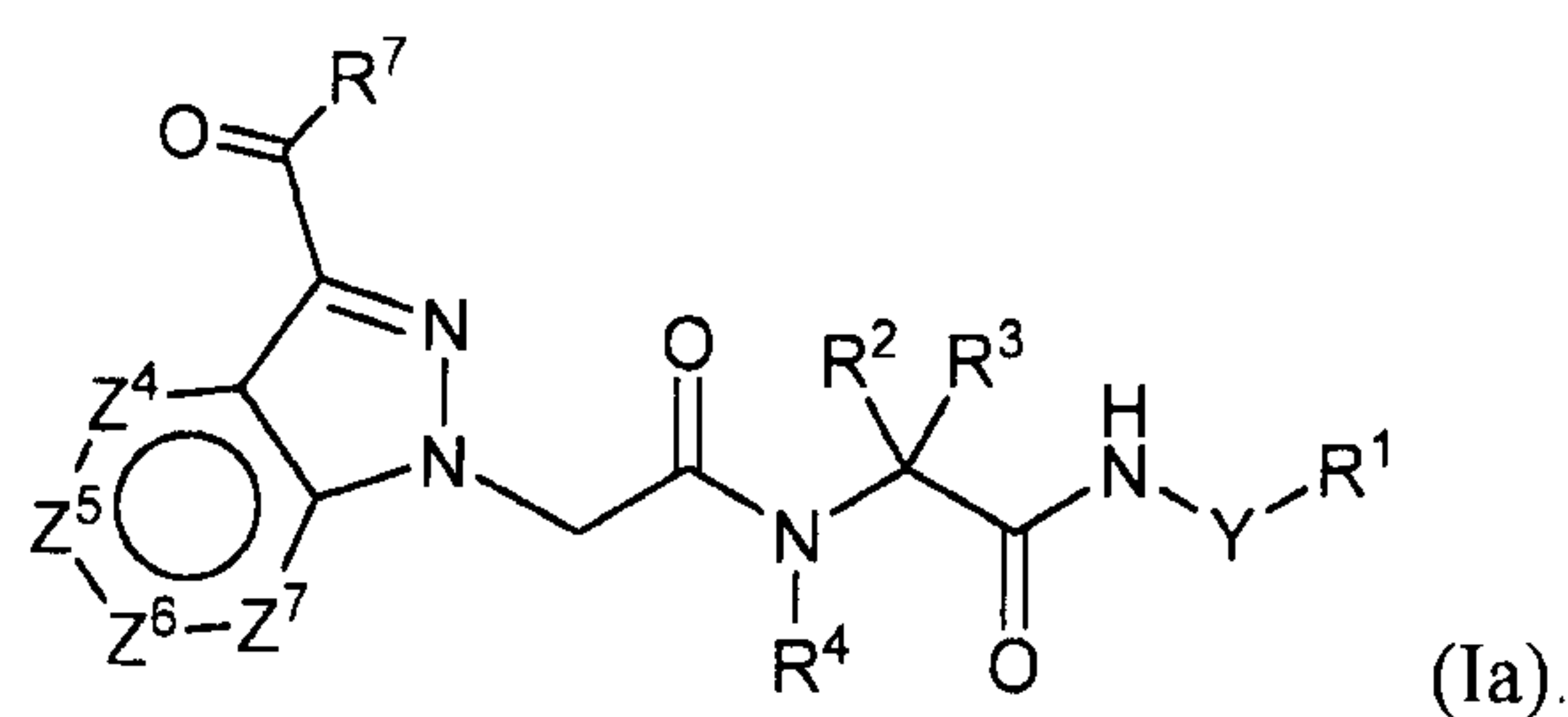
15. The compound of any one of claims 1-14, wherein  represents



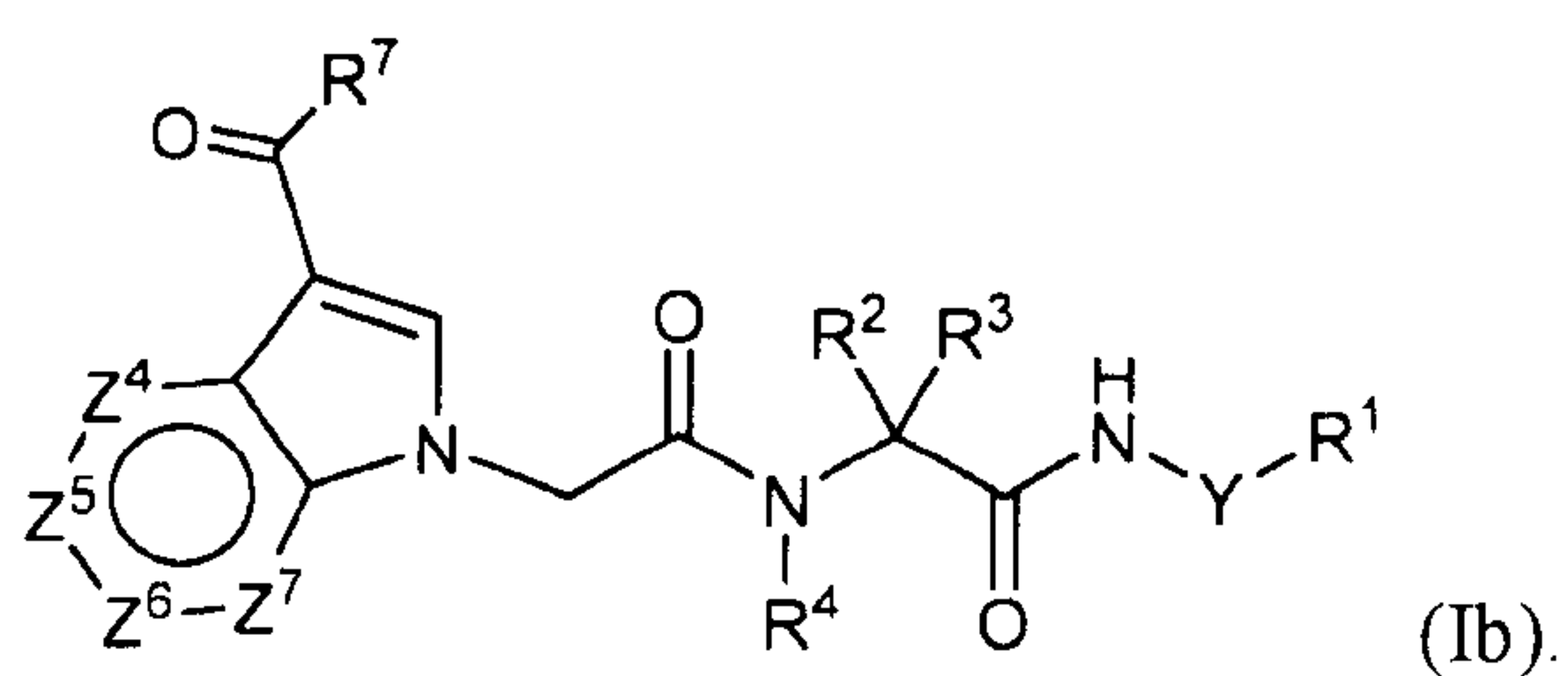
16. The compound of any one of claims 1-15, wherein L represents $-\text{C}(\text{O})\text{R}^7$.

17. The compound of any one of claims 1-16, wherein X represents NH or CH_2 .

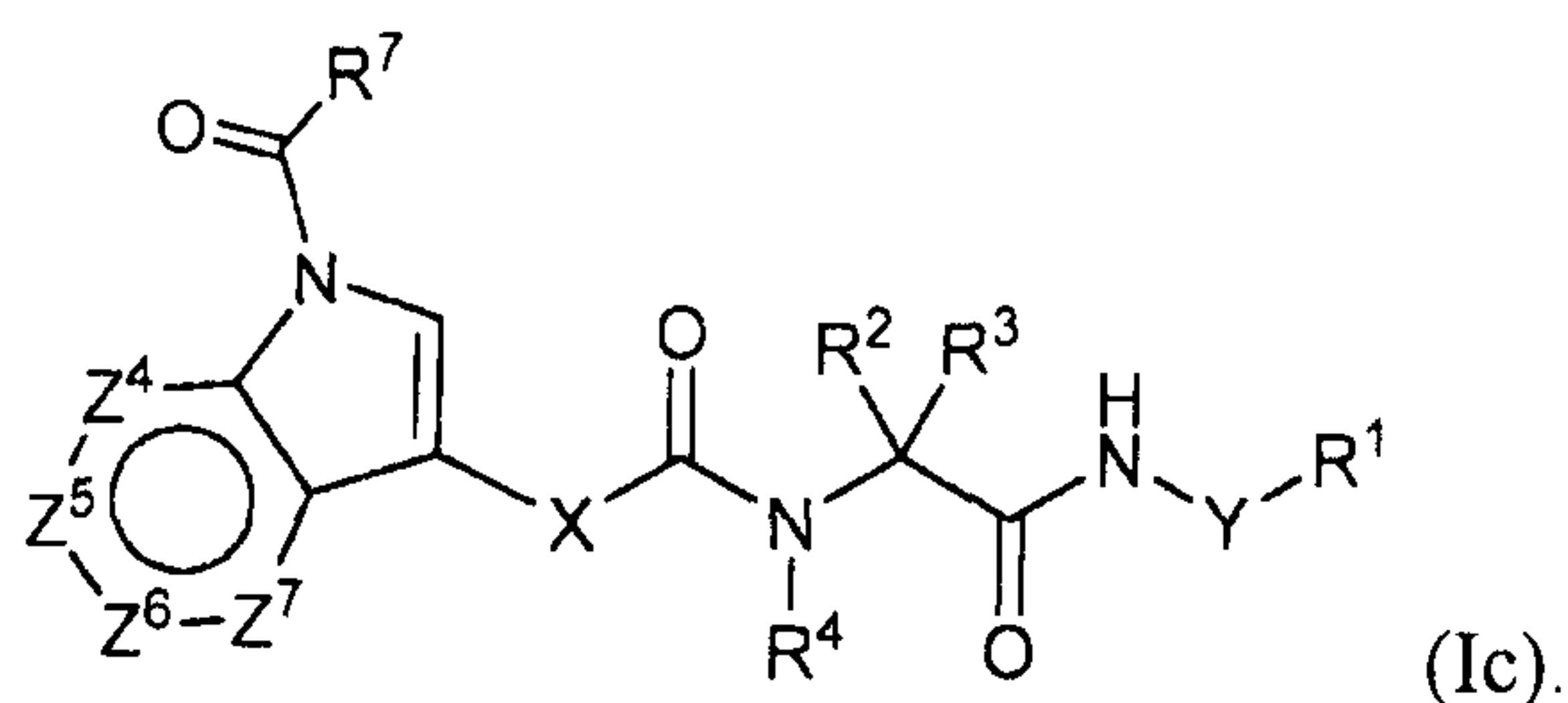
18. The compound of any one of claims 1-17, having the structure of Formula (Ia):



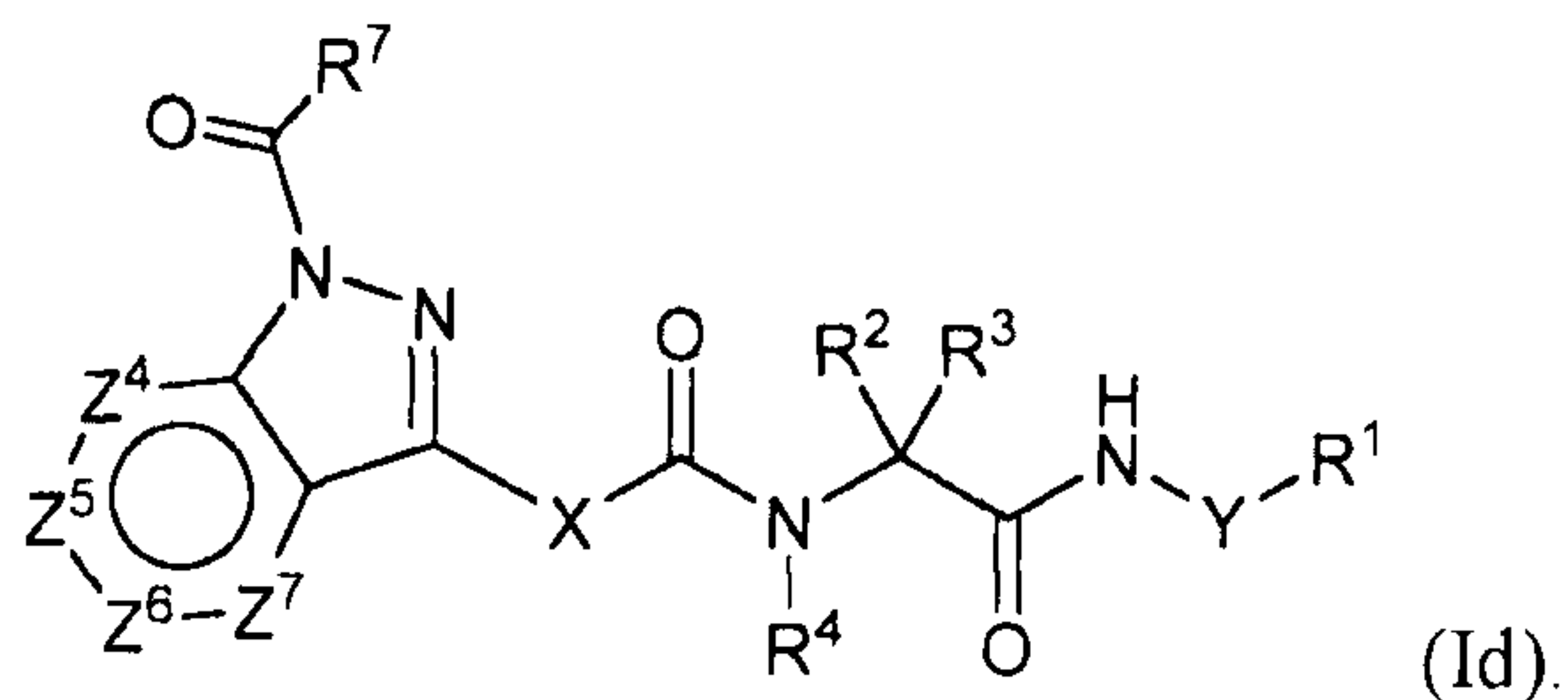
19. The compound of any one of claims 1-17, having the structure of Formula (Ib):



20. The compound of any one of claims 1-17, having the structure of Formula (Ic):



21. The compound of any one of claims 1-17, having the structure of Formula (Id):



22. The compound of claim 20 or 21, wherein X is NH.
23. The compound of any one of claims 18-22, wherein:
 Z^4 represents CR^8 ;
 Z^5 represents CR^5 ;
 Z^6 represents CR^6 ; and
 Z^7 represents CR^9 .
24. The compound of any one of claims 18-23, wherein Z^4 and Z^7 each represent CH.
25. The compound of any one of claims 18-24, wherein Z^5 represents CR^5 ; and Z^6 represents CR^6 ; and
 R^5 and R^6 each independently represent H, halogen, $-NR^{13}R^{14}$, $-C(O)R^{13}$, $-C(O)OR^{13}$, $-C(O)NHR^{14}$, $-NHC(O)NR^{13}R^{14}$, $-NHS(O)_2(R^{14})$, or optionally substituted alkyl, alkenyl, alkynyl, heteroaryl, or aryl.
26. The compound of claim 25, wherein R^5 and R^6 each independently represent H or alkyl, alkenyl, alkynyl, heteroaryl, or aryl, optionally substituted with one or more substituents selected from the group consisting of aryl, heteroaryl, silyl, alkyl, amino, alkylamino, dialkylamino, $-C(O)(alkyl)$, and halogen.

27. The compound of claim 25, wherein R^{13} and R^{14} , independently for each occurrence, represent H or optionally substituted aryl, aralkyl, heteroaryl, heteroaralkyl, cycloalkyl, or (cycloalkyl)alkyl.
28. The compound of any one of claims 16-27, wherein R^7 represents NH_2 , CH_3 , or CF_3 .
29. The compound of any one of claims 16-28, wherein R^7 represents NH_2 .
30. A pharmaceutical composition, comprising a compound of any one of claims 1-29; and a pharmaceutically acceptable carrier.
31. A method of treating or preventing a disease or condition characterized by aberrant complement system activity, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-29.
32. The method of claim 31, wherein the disease or condition characterized by aberrant complement system activity is an immunological disorder.
33. The method of claim 31, wherein the disease or condition characterized by aberrant complement system activity is a disease of the central nervous system.
34. The method of claim 31, wherein the disease or condition characterized by aberrant complement system activity is a neurodegenerative disease or neurological disease.
35. The method of claim 31, wherein the disease or condition characterized by aberrant complement system activity is a renal disease.
36. The method of claim 31, wherein the disease or condition characterized by aberrant complement system activity is a cardiovascular disease.
37. The method of claim 31, wherein the disease or condition characterized by aberrant complement system activity is selected from the group consisting of paroxysmal nocturnal hemoglobinuria, atypical hemolytic uremic syndrome, organ transplant rejection, myasthenia gravis, neuromyelitis optica, membranoproliferative glomerulonephritis, dense-deposit disease, cold agglutinin disease, and catastrophic antiphospholipid syndrome.

