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(54) Titre : INHIBITEURS DE PROTEINES KINASES ET LEURS UTILISATIONS

(54) Title: PROTEIN KINASE INHIBITORS AND USES THEREOF

(57) **Abrégé/Abstract:**

The present invention relates to a new class of 5-aryl-5H-pyrrolo[3,2-d]pyrimidin-4-amines which contain 6,7-fused cycloalkyl and heterocycloalkyl ring systems. Compounds of this class have been found to be effective inhibitors of protein kinases: including members of the SRC and Tec kinase families. These compounds demonstrate the requisite physiochemical properties for use as pharmaceutical agents for the treatment of various proliferative, inflammatory and autoimmune diseases such as, but not limited to, cancer, arthritis, MS and the like.

ABSTRACT

The present invention relates to a new class of 5-aryl-5H-pyrrolo[3,2-d]pyrimidin-4-amines which contain 6,7-fused cycloalkyl and heterocycloalkyl ring systems. Compounds of this class have been found to be effective inhibitors of protein

5 kinases: including members of the SRC and Tec kinase families. These compounds demonstrate the requisite physiochemical properties for use as pharmaceutical agents for the treatment of various proliferative, inflammatory and autoimmune diseases such as, but not limited to, cancer, arthritis, MS and the like.

PROTEIN KINASE INHIBITORS AND USES THEREOF

FIELD OF INVENTION

The present invention relates to inhibitors of protein kinases, compositions comprising those inhibitors, and uses of those inhibitors, including medical uses.

5 BACKGROUND OF THE INVENTION

Protein kinases are a large group of intracellular signaling proteins in eukaryotic cells. These enzymes are responsible for transfer of the terminal (gamma) phosphate from ATP to specific amino acid residues of target proteins. Protein kinases that catalyze phosphorylation of tyrosine residues are referred to as

10 tyrosine kinases, while those protein kinases which catalyze serine or threonine phosphorylation are referred to as serine/threonine kinases. Phosphorylation of target proteins can modulate their activity leading to profound changes in cellular signaling and metabolism. Kinases can be found in the cell membrane, cytosol and organelles such as the nucleus and are responsible for mediating multiple cellular

15 functions such as metabolism, cellular growth and division, cellular signaling, modulation of immune responses, and apoptosis. The receptor tyrosine kinases are a large family of cell surface receptors with protein tyrosine kinase activity that respond to extracellular cues and activate intracellular signaling cascades (Plowman et al. (1994) DN&P, 7(6):334-339).

20 Aberrant activation or excessive expression of various kinase families are implicated in the mechanism of multiple diseases and disorders characterized by benign and malignant proliferation, excess angiogenesis, as well as diseases resulting from dysregulation of the immune system. Thus inhibitors of select kinases or kinase families are expected to be useful in the treatment of diseases and disorders such

25 as: cancer, graft versus host disease, lupus erythematosus, psoriasis, colitis, ileitis, multiple sclerosis, uveitis, coronary artery vasculopathy, systemic sclerosis, atherosclerosis, asthma, transplant rejection, allergy, dermatomyositis, pemphigus and the like.

Examples of kinases that can be targeted to modulate disease include receptor tyrosine kinases such as members of the PDGFR and VEGFR families and intracellular proteins such as members of the Syk, SRC, and Tec families of kinases.

Tec kinases are non-receptor tyrosine kinases predominantly, but not exclusively, expressed in cells of hematopoietic origin (Bradshaw JM. Cell Signal. 2010,22:1175-84). The Tec family includes Tec, Bruton's tyrosine kinase (Btk), inducible T-cell kinase (Itk), resting lymphocyte kinase (Rlk/Txk), and bone marrow-expressed kinase (Bmx/Etk). Btk is a Tec family kinase which is important in B-cell receptor signaling. Btk is activated by Src-family kinases and phosphorylates PLC gamma leading to effects on B-cell function and survival. Additionally, Btk is important in signal transduction in response to immune complex recognition by macrophage, mast cells and neutrophils. Btk inhibition is also important in survival of lymphoma cells (Herman, SEM. Blood 2011, 117:6287-6289) suggesting that inhibition of Btk may be useful in the treatment of lymphomas. As such, inhibitors of Btk and related kinases are of great interest as anti-inflammatory as well as anti-cancer agents.

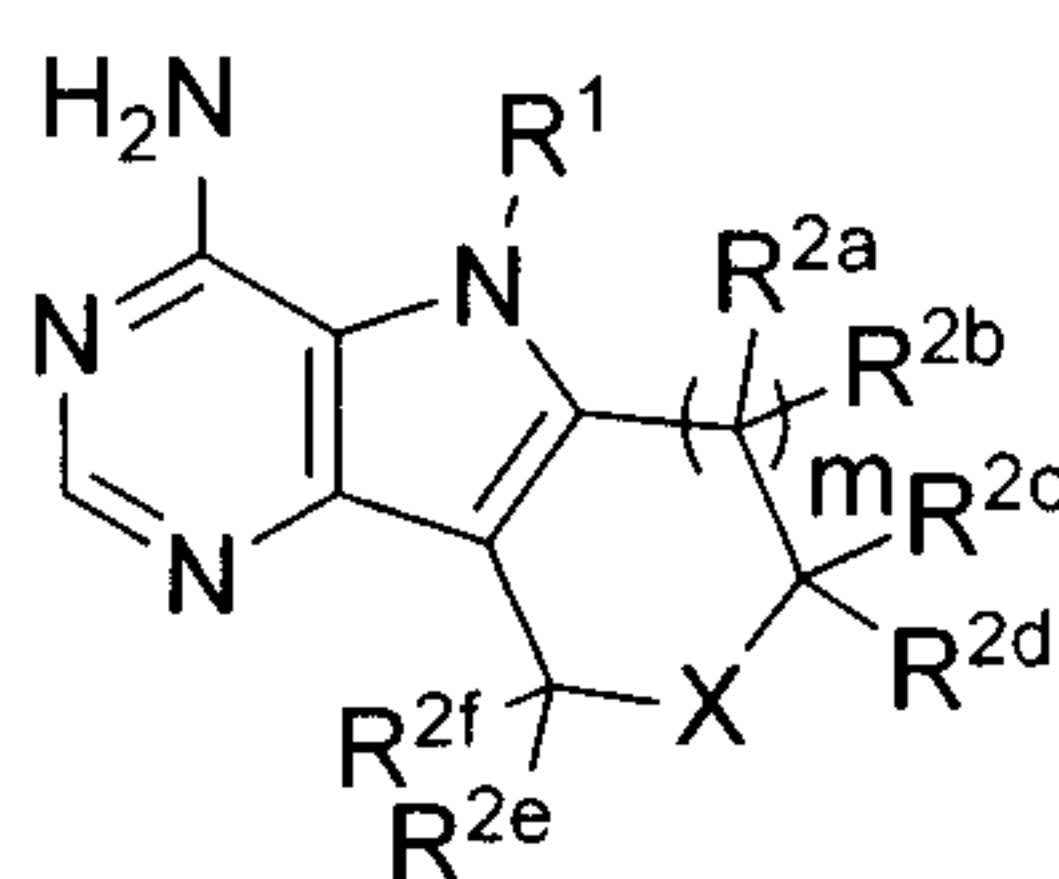
cSRC is the prototypical member of the SRC family of tyrosine kinases which includes Lyn, Fyn, Lck, Hck, Fgr, Blk, Syk, Yrk, and Yes. cSRC is critically involved in signaling pathways involved in cancer and is often over-expressed in human malignancies (Kim LC, Song L, Haura EB. Nat Rev Clin Oncol. 2009 6(10):587-9). The role of cSRC in cell adhesion, migration and bone remodeling strongly implicate this kinase in the development and progression of bone metastases. cSRC is also involved in signaling downstream of growth factor receptor tyrosine kinases and regulates cell cycle progression suggesting that cSRC inhibition would impact cancer cell proliferation. Additionally, inhibition of SRC family members may be useful in treatments designed to modulate immune function. SRC family members, including Lck, regulate T-cell receptor signal transduction which leads to gene regulation events resulting in cytokine release, survival and proliferation. Thus, inhibitors of Lck have been keenly sought as immunosuppressive agents with potential application in graft rejection and T-cell mediated autoimmune disease (Martin et al. Expert Opin Ther Pat. 2010, 20:1573-93).

Inhibition of kinases using small molecule inhibitors has successfully led to several approved therapeutic agents used in the treatment of human conditions. Herein, we disclose a novel family of kinase inhibitors. Further, we demonstrate that modifications in compound substitution can strongly influence kinase selectivity and therefore the biological function of that agent and disease state for which it may be useful as a therapeutic agent.

SUMMARY OF THE INVENTION

The present invention relates to a new class of 5-aryl-5H-pyrrolo[3,2-d]pyrimidin-4-amines which contain 6,7-fuse alkyl and heteroalkyl ring systems. Compounds of this class have been found to inhibit members of the Tec and Scr protein kinase families, more particularly Btk and Lck. These compounds demonstrate the requisite physiochemical properties that make them potentially suitable for use as pharmaceutical agents for the treatment of various proliferative, inflammatory and autoimmune diseases such as, but not limited to: cancer, graft versus host disease, lupus erythematosus, psoriasis, colitis, ileitis, multiple sclerosis, coronary artery vasculopathy, systemic sclerosis, atherosclerosis, asthma, transplant rejection, allergy, dermatomyositis, pemphigus and the like.

Provided herein is a compound of Formula 1:



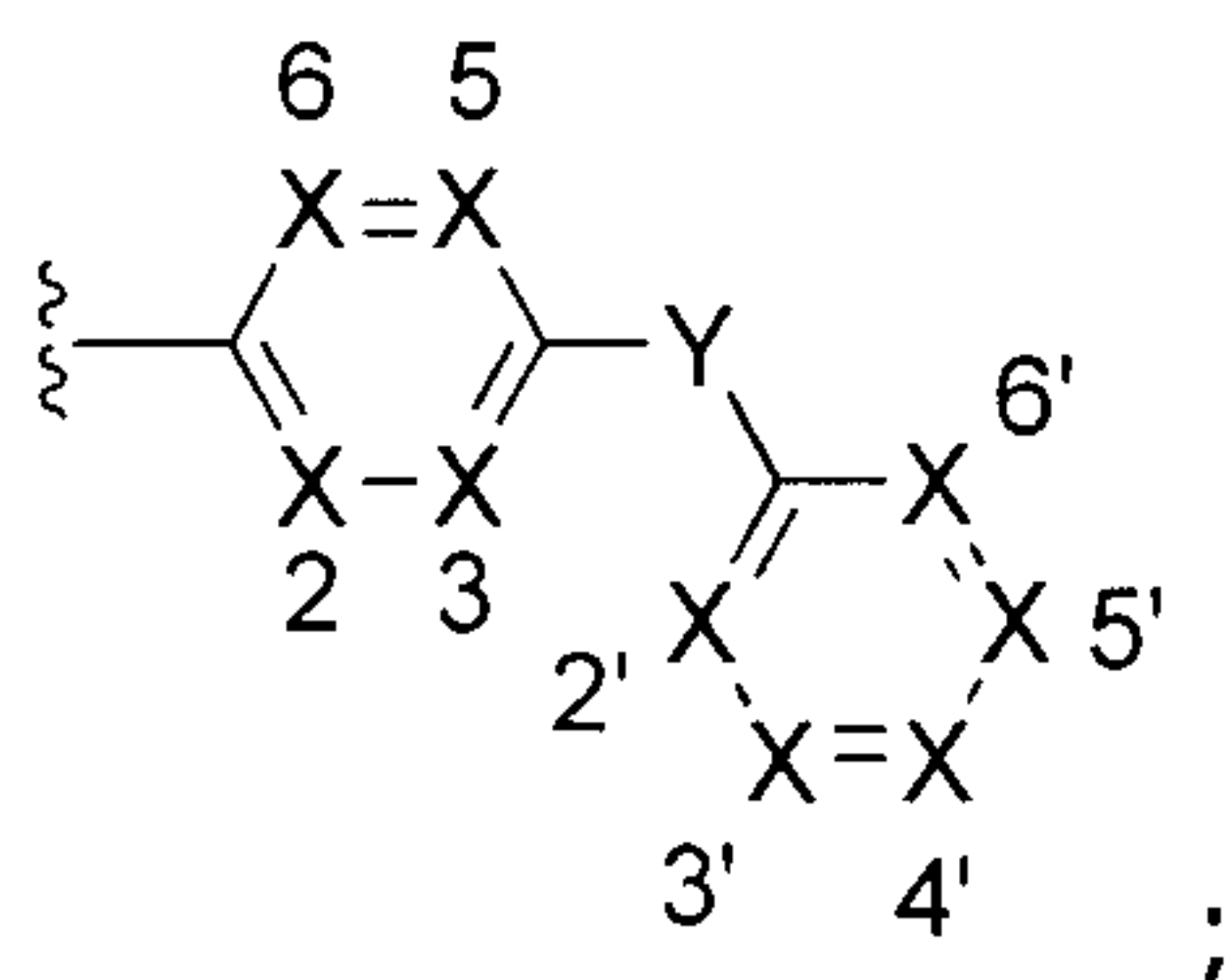
Formula 1

m is an integer from 0 to 1;

X is selected from CH₂, O, S(O)_n, NR⁶;

n is an integer for 0 to 2;

R¹ is



wherein Y is selected from O or CH₂;

wherein X², X³, X⁵, X⁶, X^{2'}, X^{3'}, X^{4'}, X^{5'}, X^{6'} are independently selected from CR and N;

each R is independently selected from hydrogen, halogen, -NO₂, -CN, alkyl, alkenyl, alkynyl, -OR³, -OC(O)R³, -OC(O)NR⁴R⁵, -NR⁴R⁵, -S(O)_nR³, -C(O)R³, -C(O)OR³, -C(O)NR⁴R⁵, -S(O)₂NR⁴R⁵, -NR²C(O)R³, -NR²S(O)_nR³, -NR²C(O)NR⁴R⁵, -NR²S(O)₂NR⁴R⁵, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

R² is selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl.

R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2f} are independently selected from hydrogen, alkyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl. R^{2a} and R^{2b}, R^{2c} and R^{2d} or R^{2e} and R^{2f} can be fused to form a 3 to 8 membered cycloalkyl or heterocyclyl ring system;

R³ is selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl;

R⁴ and R⁵ are independently selected from hydrogen, alkyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl or R⁴ and R⁵ can be fused to form a 3 to 8 membered heterocyclyl ring system;

R⁶ is selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, -C(O)R⁴, -C(O)OR⁴, -S(O)₂R⁴, -C(O)NR⁴R⁵, -S(O)₂NR⁴R⁵, -C(S)NR⁴R⁵;

The present invention encompasses all compounds described by Formula 1, racemic or diastereoisomeric mixtures, pharmaceutically acceptable salts, prodrugs and active metabolites thereof.

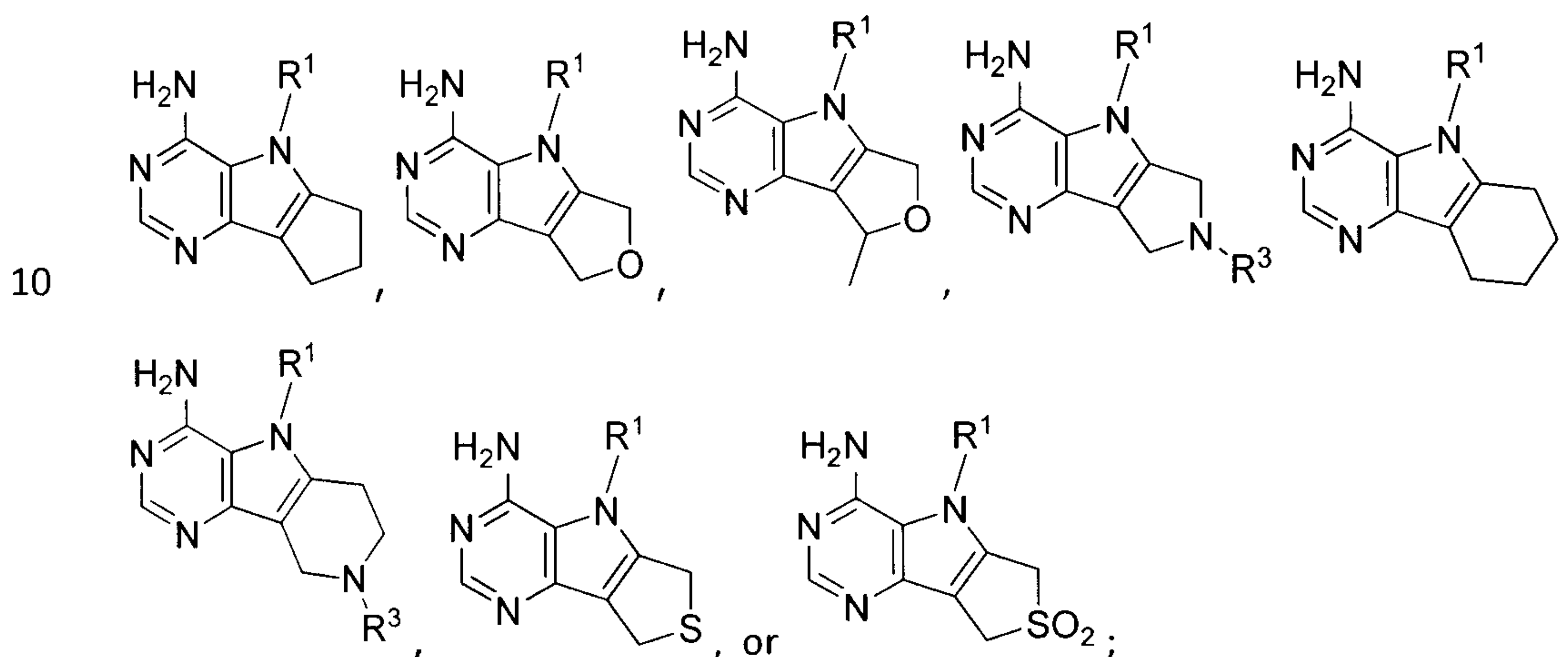
5 In certain embodiments, one or two occurrences of X are N;

In certain embodiments, each occurrence of X is independently CR;

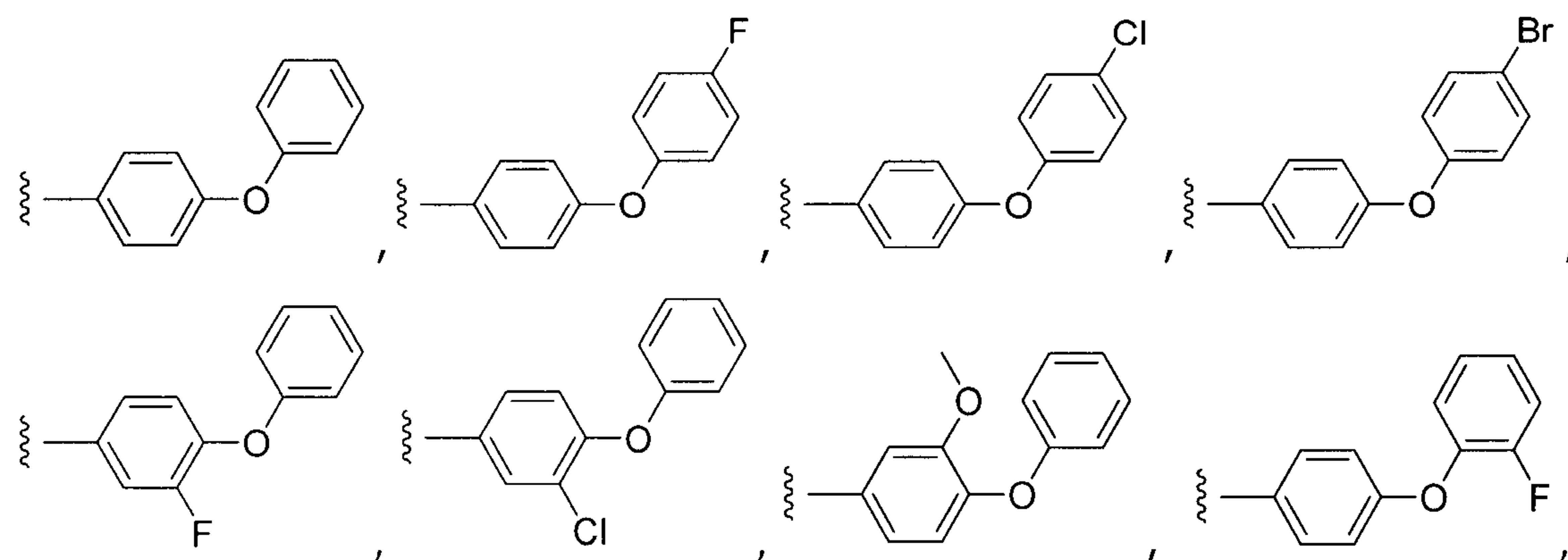
In certain preferred embodiments, R at 3' position is other than hydrogen;

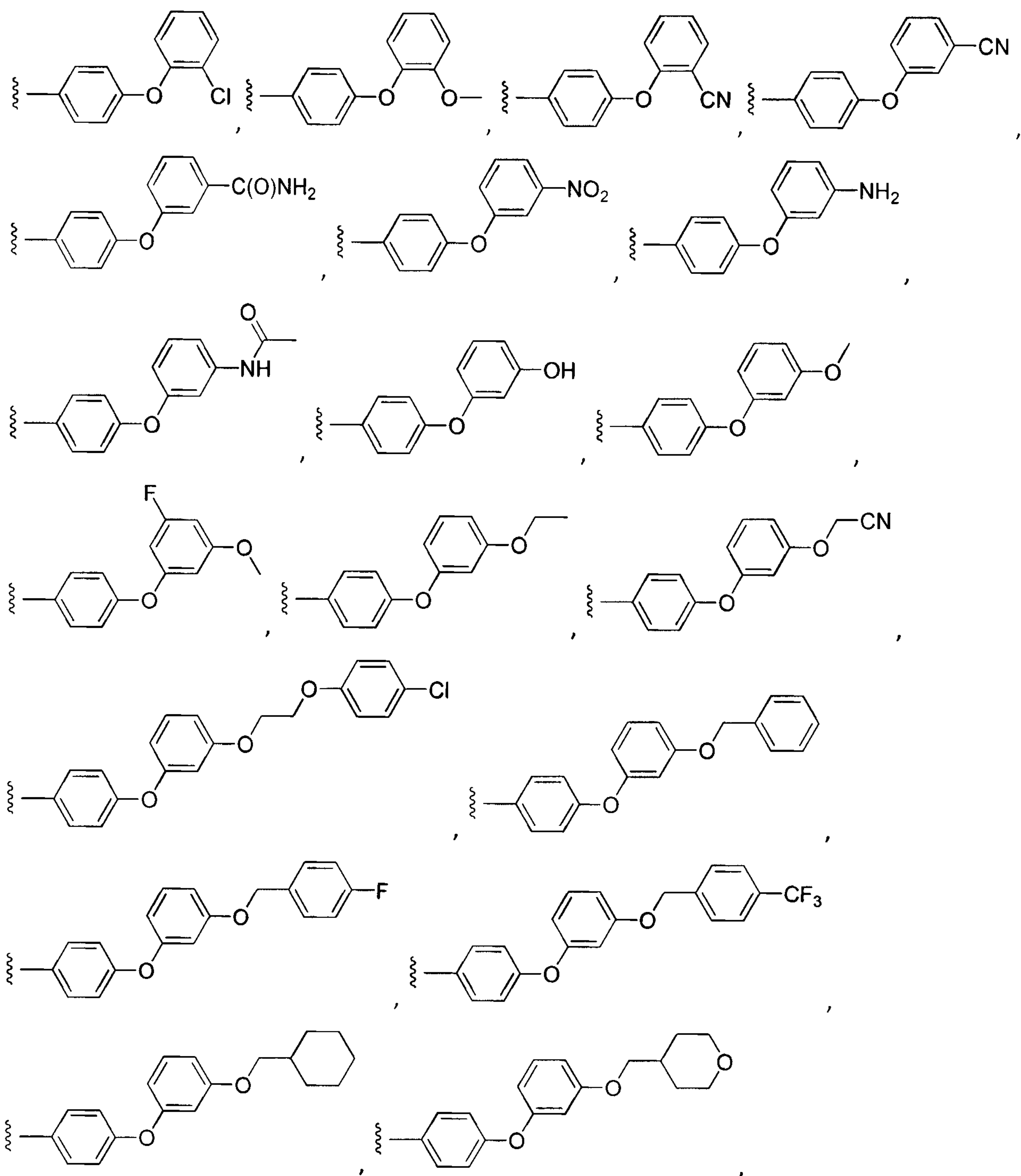
In certain preferred embodiments, R at 3' position is OR³;

In certain embodiments, compounds of Formula 1 may be further defined as:

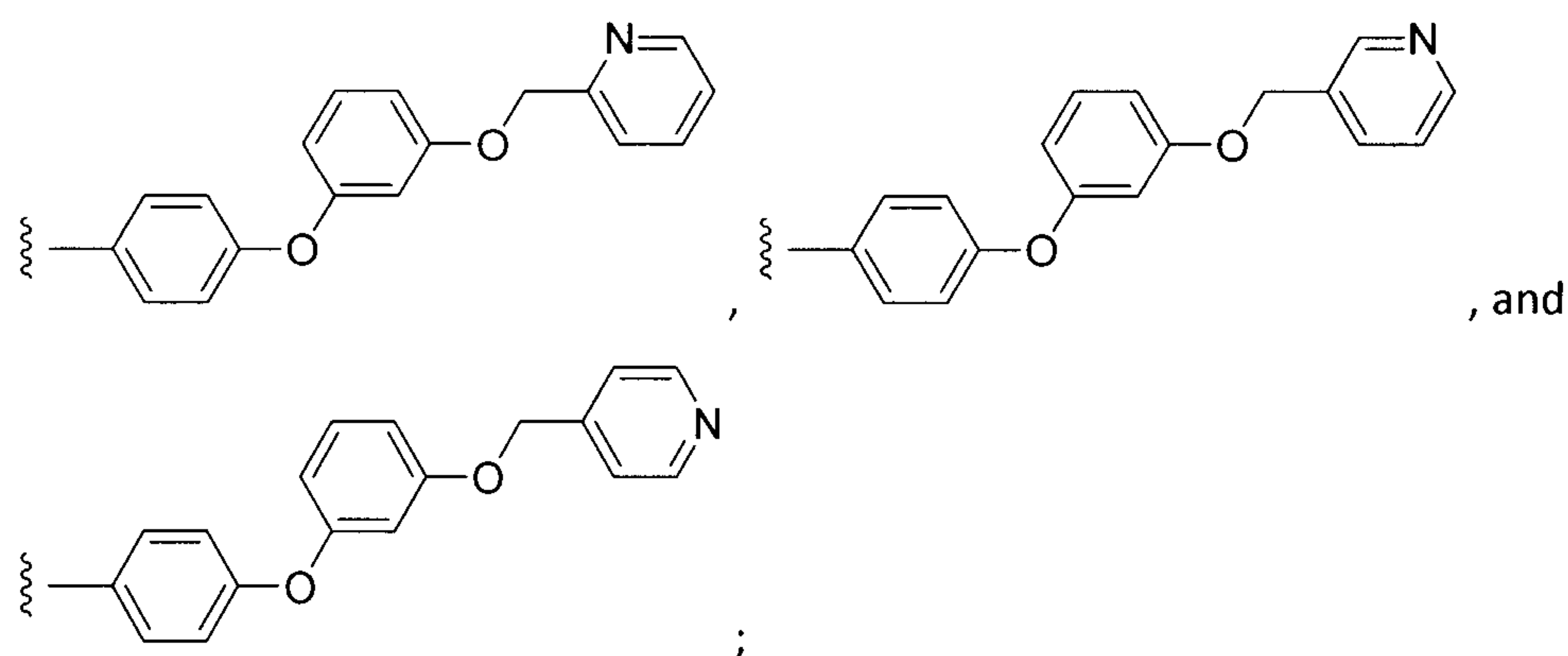


Wherein R¹ may be defined as:

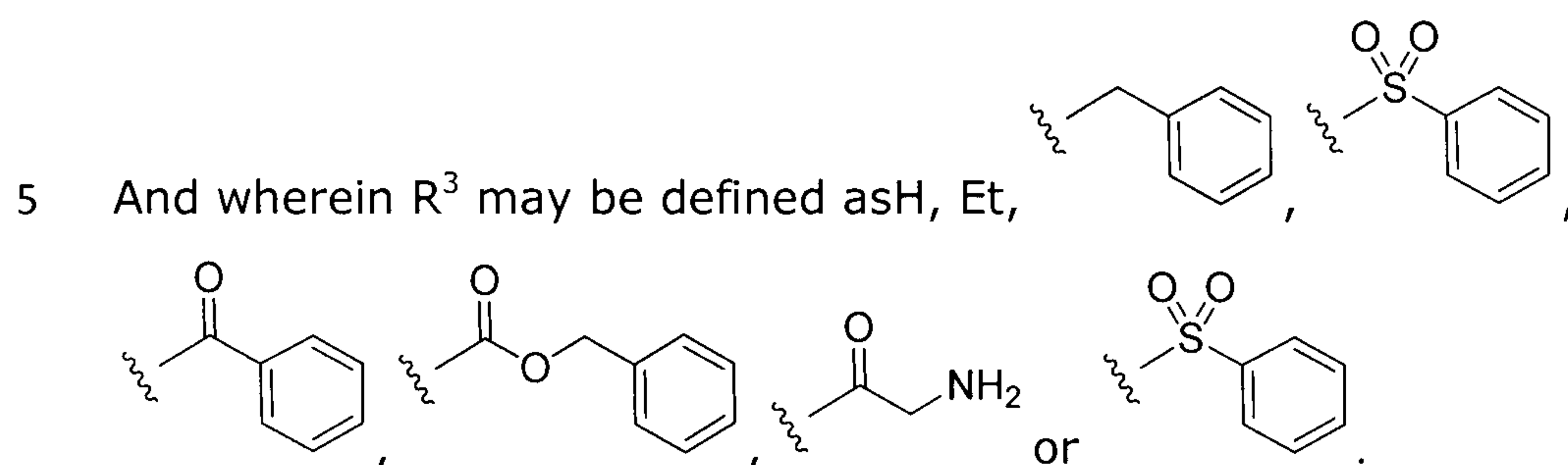




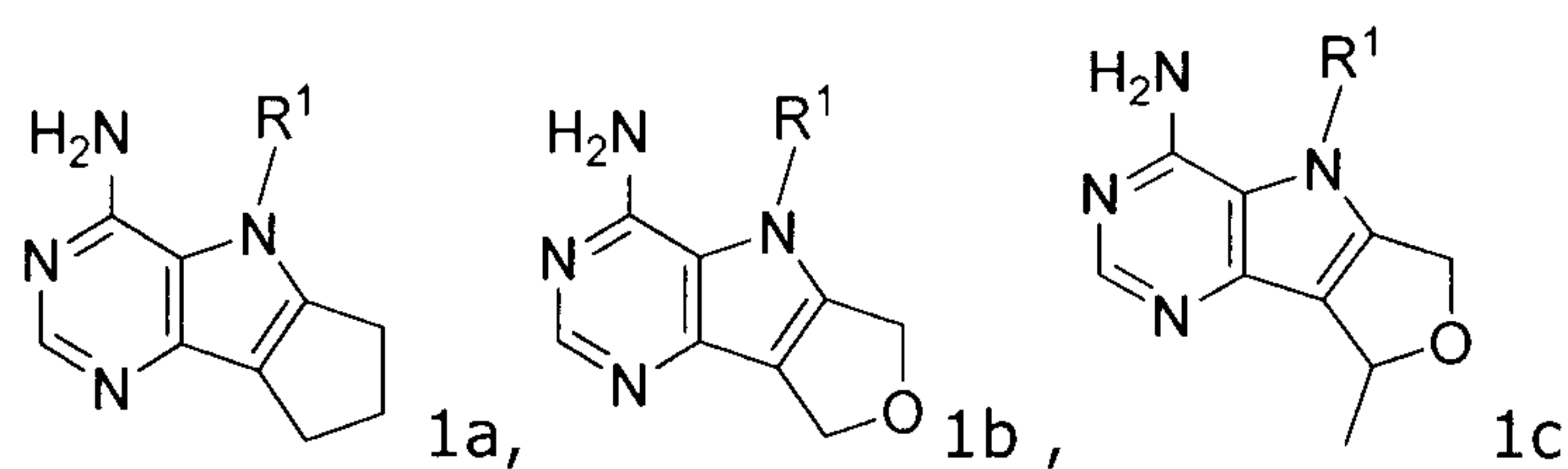
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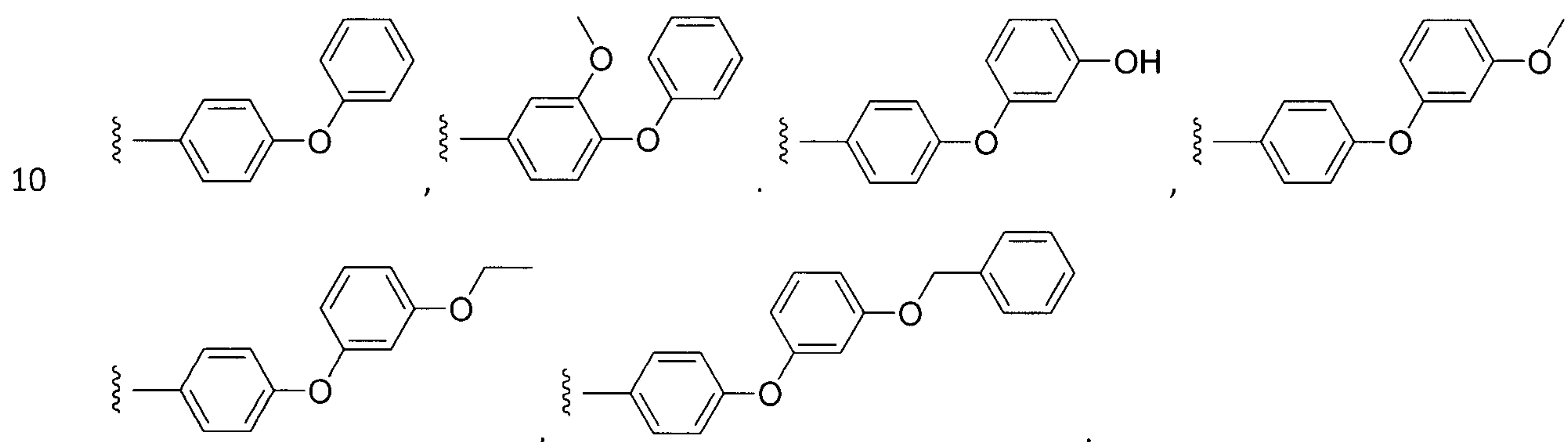
and wherein R^{2e} may be defined as H, Me, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OPh}$ or $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{Ph}$;

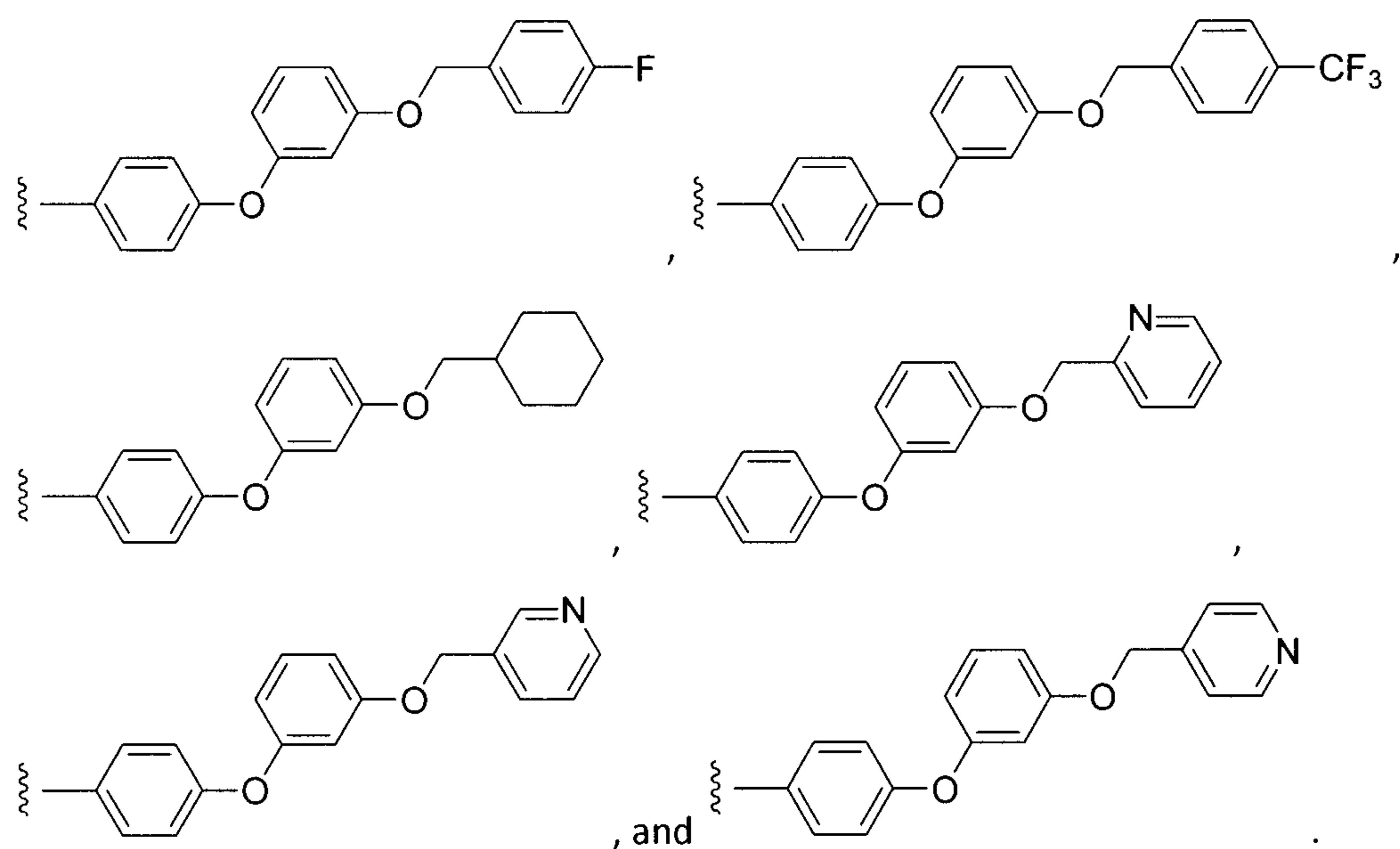


Preferred embodiments include compounds of formula 1a, 1b and 1c:

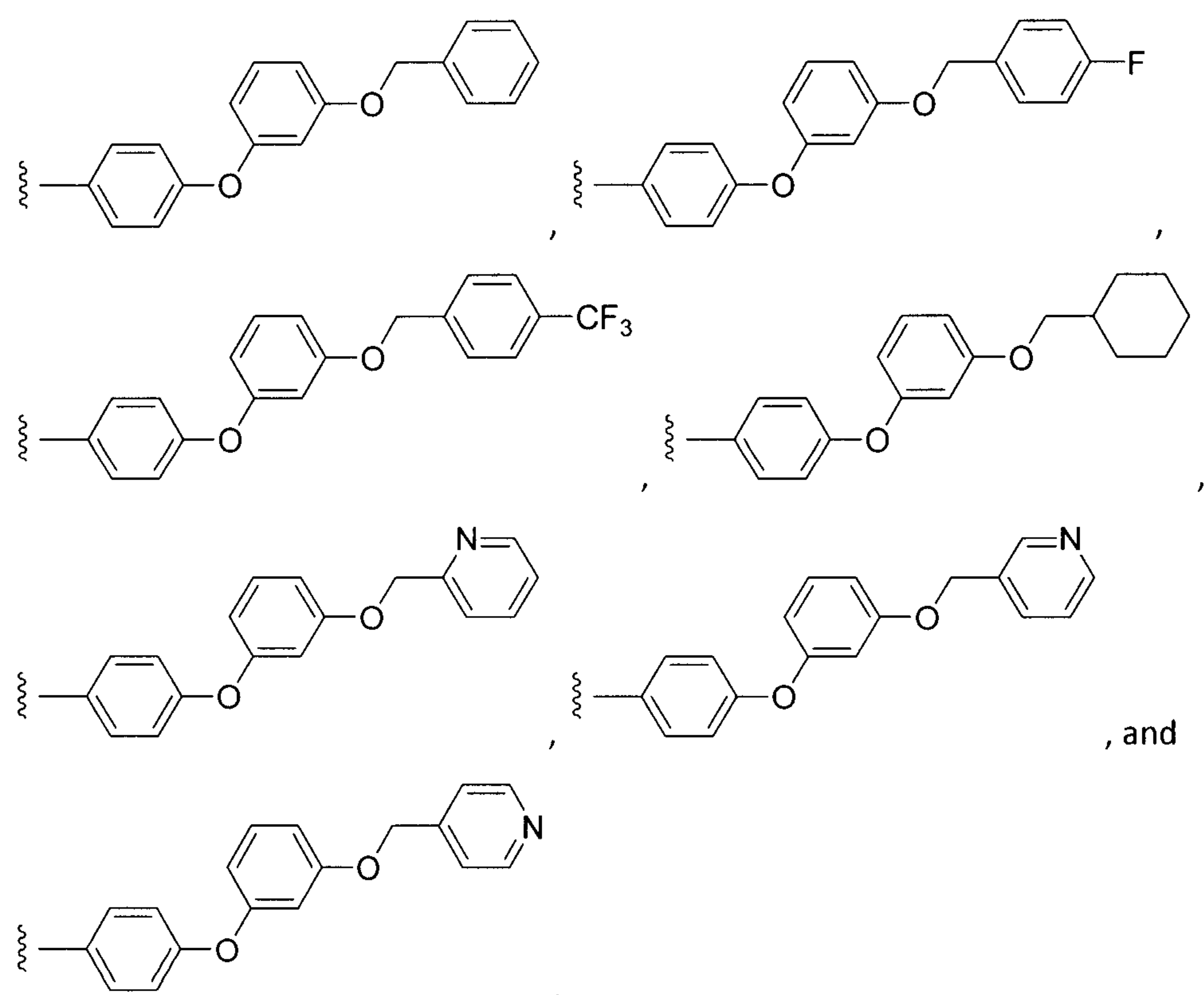


wherein R^1 is selected from the groups consisting of:





- 5 A more preferred embodiment includes compounds of Formula 1c where R¹ is selected from the group consisting of:



Another aspect of the present invention provides a pharmaceutical composition comprising a compound of Formula 1 and a pharmaceutically acceptable carrier, diluent or excipient.

5 Another aspect of the present invention provides a method of treating a malignant or non-malignant proliferative disorder or a disease state, or disorder or disease characterized by malignancy, inflammation, bone degradation, cartilage destruction, circulating autoantibodies, or cell proliferation, the method comprising administering to a subject in need thereof an amount of a compound or pharmaceutical composition as described above sufficient to treat the disorder or
10 disease state.

Another aspect of the present invention provides a method of modulating kinase function, the method comprising contacting a cell with a compound of the present invention in an amount sufficient to modulate the enzymatic activity of a given kinase or kinases, such as Btk, Lck, Blk or c-SRC, thereby modulating the kinase
15 function.

Another aspect of the present invention provides a method of modulating the target kinase function, the method comprising a) contacting a cell with a compound of the present invention in an amount sufficient to modulate the target kinase function, thereby b) modulating the target kinase activity and signaling.

20 Another aspect of the present invention provides a probe, the probe comprising a compound of Formula 1 labeled with a detectable label or an affinity tag. In other words, the probe comprises a residue of a compound of Formula 1 covalently conjugated to a detectable label. Such detectable labels include, but are not limited to, a fluorescent moiety, a chemiluminescent moiety, a paramagnetic contrast
25 agent, a metal chelate, a radioactive isotope-containing moiety, or biotin. As used herein, the term "affinity tag" means a ligand or group, linked either to a compound of the present invention or to the target kinase, that allows the conjugate to be extracted from a solution.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention relates to a new class of 5-aryl-5H-pyrrolo[3,2-d]pyrimidin-4-amines which contain 6,7-fused alkyl and heteroalkyl ring systems. Compounds of this class have been found to be effective inhibitors of protein kinases: including

5 members of the tyrosine kinases Aurora, SRC (more specifically Lck) and Tec (more specifically Btk) kinase families. These compounds are may potentially be suitable for use as pharmaceutical agents for the treatment of various proliferative, inflammatory and autoimmune diseases and disorders such as, cancer, graft versus

10 host disease, lupus erythematosus, psoriasis, colitis, ileitis, multiple sclerosis, coronary artery vasculopathy, systemic sclerosis, atherosclerosis, asthma, transplant rejection, allergy, dermatomyositis, or pemphigus and the like.

In certain embodiments, the invention relates to methods for the treatment of a disease or condition selected from autoimmune diseases and inflammation (e.g., arthritis, multiple sclerosis, lupus, and uveitis, asthma), cancer and

15 myeloproliferative disorders comprising administering a compound of Formula 1.

In certain embodiments, the invention relates to a method for treating cancer comprising administering a compound of Formula 1. The following table sets out examples of cancers (and the target tissues) that the compounds of Formula 1 have the potential to treat:

Tissue	Example
Adrenal gland	neuroblastoma
Bone	osteogenic sarcoma (osteosarcoma), fibrosarcoma, malignant fibrous histiocyoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulum cell sarcoma), multiple myeloma, malignant giant cell tumor chordoma, osteochronfroma (osteocartilaginous exostoses), benign chondroma, chondroblastoma, chondromyxofibroma, osteoid osteoma and giant cell

Tissue	Example
	tumors
Breast	ductal carcinoma, lobular carcinoma, infiltrating (invasive) ductal carcinoma (IDC) - infiltrating (invasive) lobular carcinoma (ILC) - inflammatory breast cancer (IBC), Paget's disease, tubular carcinoma, medullary carcinoma, mucinous carcinoma, papillary carcinoma, metaplastic carcinoma, phyllodes tumour, triple negative breast cancer, Her2 negative and Her2 positive carcinoma
Cardiac	sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma
Gastrointestinal	esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, lymphoma), stomach (carcinoma, lymphoma, leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma, glucagonoma, gastrinoma, carcinoid tumors, vipoma), small bowel (adenocarcinoma, lymphoma, carcinoid tumors, Karposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, fibroma), large bowel (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, leiomyoma)
Genitourinary tract	kidney (adenocarcinoma, Wilm's tumor [nephroblastoma], lymphoma, leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, adenocarcinoma), prostate (adenocarcinoma, sarcoma), testis (seminoma, teratoma, embryonal carcinoma, teratocarcinoma,

Tissue	Example
	choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumors, lipoma)
Gynecological	uterus (endometrial carcinoma), cervix (cervical carcinoma, pre-tumor cervical dysplasia), ovaries (ovarian carcinoma [serous cystadenocarcinoma, mucinous cystadenocarcinoma, unclassified carcinoma], granulosa-thecal cell tumors, Sertoli-Leydig cell tumors, dysgerminoma, malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonal rhabdomyosarcoma), fallopian tubes (carcinoma)
Hematologic	blood (myeloid leukemia [acute and chronic], acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma [malignant lymphoma]
Liver	hepatoma (hepatocellular carcinoma), cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, hemangioma
Lung	bronchogenic carcinoma (squamous cell, undifferentiated small cell, undifferentiated large cell, adenocarcinoma), alveolar (bronchiolar) carcinoma, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, mesothelioma
Nervous	skull (osteoma, hemangioma, granuloma, xanthoma,

Tissue	Example
system	osteitis deformans), meninges (meningioma, meningiosarcoma, gliomatosis), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germinoma [pinealoma], glioblastoma multiform, oligodendroglioma, schwannoma, retinoblastoma, congenital tumors), spinal cord neurofibroma, meningioma, glioma, sarcoma
Skin	malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, moles dysplastic nevi, lipoma, angioma, dermatofibroma, keloids

Compounds prepared as described herein can be administered in various forms, depending on the disorder to be treated and the age, condition, and body weight of the patient, as is well known in the art. For example, where the compounds are to

5 be administered orally, they may be formulated as tablets, capsules, granules, powders, or syrups; or for parenteral administration, they may be formulated as injections (intravenous, intramuscular, or subcutaneous), drop infusion preparations, or suppositories. For application by the ophthalmic mucous

10 membrane route, they may be formulated as eye drops or eye ointments. These formulations can be prepared by conventional means, and if desired, the active ingredient may be mixed with any conventional additive or excipient, such as a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, a suspension aid, an emulsifying agent, a coating agent, a cyclodextrin, and/or a buffer. Although the dosage will vary depending on the symptoms, age and body

15 weight of the patient, the nature and severity of the disorder to be treated or prevented, the route of administration and the form of the drug, in general, a daily dosage of from 0.01 to 2000 mg of the compound is recommended for an adult human patient, and this may be administered in a single dose or in divided doses. The amount of active ingredient which can be combined with a carrier material to

produce a single dosage form will generally be that amount of the compound which produces a therapeutic effect.

The precise time of administration and/or amount of the composition that will yield the most effective results in terms of efficacy of treatment in a given patient will
5 depend upon the activity, pharmacokinetics, and bioavailability of a particular compound, physiological condition of the patient (including age, sex, disease type and stage, general physical condition, responsiveness to a given dosage, and type of medication), route of administration, etc. However, the above guidelines can be used as the basis for fine-tuning the treatment, e.g., determining the optimum time
10 and/or amount of administration, which will require no more than routine experimentation consisting of monitoring the subject and adjusting the dosage and/or timing.

The phrase "pharmaceutically acceptable" is employed herein to refer to those ligands, materials, compositions, and/or dosage forms which are, within the scope
15 of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The phrase "pharmaceutically acceptable carrier" as used herein means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or
20 solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be acceptable in the sense of being compatible with the other ingredients of the formulation, including the active ingredient, and not injurious or harmful to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, and sucrose; (2)
25 starches, such as corn starch, potato starch, and substituted or unsubstituted β -cyclodextrin; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn
30 oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl

oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer's solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. In certain embodiments, pharmaceutical compositions of the present invention are non-pyrogenic, i.e., do not induce significant temperature elevations when administered to a patient.

The term "pharmaceutically acceptable salt" refers to the relatively non-toxic, inorganic and organic acid addition salts of the compound(s). These salts can be prepared *in situ* during the final isolation and purification of the compound(s), or by separately reacting a purified compound(s) in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, laurylsulphonate salts, and amino acid salts, and the like (See, for example, Berge et al. (1977) "Pharmaceutical Salts", *J. Pharm. Sci.* 66: 1-19).

In other cases, the compounds useful in the methods of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term "pharmaceutically acceptable salts" in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a compound(s). These salts can likewise be prepared *in situ* during the final isolation and purification of the compound(s), or by separately reacting the purified compound(s) in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine,

diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like (see, for example, Berge et al., *supra*).

Wetting agents, emulsifiers, and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, 5 sweetening, flavoring, and perfuming agents, preservatives and antioxidants can also be present in the compositions.

Examples of pharmaceutically acceptable antioxidants include: (1) water soluble antioxidants, such as ascorbic acid, cysteine hydrochloride, sodium bisulfate, sodium metabisulfite, sodium sulfite, and the like; (2) oil-soluble antioxidants, such 10 as ascorbyl palmitate, butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), lecithin, propyl gallate, alpha-tocopherol, and the like; and (3) metal chelating agents, such as citric acid, ethylenediamine tetraacetic acid (EDTA), sorbitol, tartaric acid, phosphoric acid, and the like.

Formulations suitable for oral administration may be in the form of capsules, 15 cachets, pills, tablets, lozenges (using a flavored basis, usually sucrose and acacia or tragacanth), powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert matrix, such as gelatin and glycerin, or sucrose and acacia) and/or as mouthwashes, and the like, each containing a 20 predetermined amount of a compound(s) as an active ingredient. A composition may also be administered as a bolus, electuary, or paste.

In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules, and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium 25 phosphate, and/or any of the following: (1) fillers or extenders, such as starches, cyclodextrins, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose, and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca 30 starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding

agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets, and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols, and the like.

A tablet may be made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared using binder (for example, gelatin or hydroxypropylmethyl cellulose), lubricant, inert diluent, preservative, disintegrant (for example, sodium starch glycolate or cross-linked sodium carboxymethyl cellulose), surface-active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound(s) moistened with an inert liquid diluent.

Tablets, and other solid dosage forms, such as dragees, capsules, pills, and granules, may optionally be scored or prepared with coatings and shells, such as enteric coatings and other coatings well known in the pharmaceutical-formulating art. They may also be formulated so as to provide slow or controlled release of the active ingredient therein using, for example, hydroxypropylmethyl cellulose in varying proportions to provide the desired release profile, other polymer matrices, liposomes, and/or microspheres. They may be sterilized by, for example, filtration through a bacteria-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved in sterile water, or some other sterile injectable medium immediately before use. These compositions may also optionally contain opacifying agents and may be of a composition that they release the active ingredient(s) only, or preferentially, in a certain portion of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The

active ingredient can also be in micro-encapsulated form, if appropriate, with one or more of the above-described excipients.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition
5 to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents, and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor,
10 and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols, and fatty acid esters of sorbitan, and mixtures thereof.

Besides inert diluents, the oral compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming, and preservative agents.

15 Suspensions, in addition to the active compound(s), may contain suspending agents as, for example, ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

Formulations for rectal or vaginal administration may be presented as a
20 suppository, which may be prepared by mixing one or more compound(s) with one or more suitable nonirritating excipients or carriers comprising, for example, cocoa butter, polyethylene glycol, a suppository wax or a salicylate, which is solid at room temperature, but liquid at body temperature and, therefore, will melt in the rectum or vaginal cavity and release the active agent.

25 Formulations which are suitable for vaginal administration also include pessaries, tampons, creams, gels, pastes, foams, or spray formulations containing such carriers as are known in the art to be appropriate.

Dosage forms for the topical or transdermal administration of a compound(s) include powders, sprays, ointments, pastes, creams, lotions, gels, solutions,

patches, and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required or beneficial.

5 The ointments, pastes, creams, and gels may contain, in addition to compound(s), excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc, and zinc oxide, or mixtures thereof.

10 Powders and sprays can contain, in addition to a compound(s), excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates, and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

15 The compound(s) can be alternatively administered by aerosol. This is accomplished by preparing an aqueous aerosol, liposomal preparation, or solid particles containing the composition. A nonaqueous (e.g., fluorocarbon propellant) suspension could be used. Sonic nebulizers are preferred because they minimize exposing the agent to shear, which can result in degradation of the compound.

20 Ordinarily, an aqueous aerosol is made by formulating an aqueous solution or suspension of the agent together with conventional pharmaceutically acceptable carriers and stabilizers. The carriers and stabilizers vary with the requirements of the particular composition, but typically include nonionic surfactants (Tweens, Pluronic, sorbitan esters, lecithin, Cremophors), pharmaceutically acceptable co-solvents such as polyethylene glycol, innocuous proteins like serum albumin, oleic acid, amino acids such as glycine, buffers, salts, sugars, or sugar alcohols.
25 Aerosols generally are prepared from isotonic solutions.

Transdermal patches have the added advantage of providing controlled delivery of a compound(s) to the body. Such dosage forms can be made by dissolving or dispersing the agent in the proper medium. Absorption enhancers can also be used to increase the flux of the compound(s) across the skin. The rate of such flux can

be controlled by either providing a rate controlling membrane or dispersing the compound(s) in a polymer matrix or gel.

Pharmaceutical compositions of this invention suitable for parenteral administration comprise one or more compound(s) in combination with one or more
5 pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions, or sterile powders which may be reconstituted into sterile injectable solutions or dispersions just prior to use, which may contain antioxidants, buffers, bacteriostats, solutes which render the formulation isotonic with the blood of the intended recipient or suspending or thickening agents.

10 Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof, vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of
15 coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and
20 antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include tonicity-adjusting agents, such as sugars, sodium chloride, and the like into the compositions. In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and
25 gelatin.

In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the drug from subcutaneous or intramuscular injection. For example, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms can be made by forming microencapsulated matrices of compound(s) in biodegradable polymers such as polylactide-polyglycolide.

Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other

5 biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

The preparations of agents may be given orally, parenterally, topically, or rectally.

10 They are, of course, given by forms suitable for each administration route. For example, they are administered in tablets or capsule form, by injection, inhalation, eye lotion, ointment, suppository, infusion; topically by lotion or ointment; and rectally by suppositories. Oral administration is preferred.

The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical

15 administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection, and infusion.

20 The phrases "systemic administration," "administered systemically," "peripheral administration" and "administered peripherally" as used herein mean the administration of a ligand, drug, or other material other than directly into the central nervous system, such that it enters the patient's system and thus, is subject to metabolism and other like processes, for example, subcutaneous administration.

25 These compound(s) may be administered to humans and other animals for therapy by any suitable route of administration, including orally, nasally, as by, for example, a spray, rectally, intravaginally, parenterally, intracisternally, and topically, as by powders, ointments or drops, including buccally and sublingually.

30 Regardless of the route of administration selected, the compound(s), which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the

present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

Actual dosage levels of the active ingredients in the pharmaceutical compositions of this invention may be varied so as to obtain an amount of the active ingredient
5 which is effective to achieve the desired therapeutic response for a particular patient, composition, and mode of administration, without being toxic to the patient.

The concentration of a disclosed compound in a pharmaceutically acceptable mixture will vary depending on several factors, including the dosage of the
10 compound to be administered, the pharmacokinetic characteristics of the compound(s) employed, and the route of administration. In general, the compositions of this invention may be provided in an aqueous solution containing about 0.1-10% w/v of a compound disclosed herein, among other substances, for parenteral administration. Typical dose ranges are from about 0.01 to about 50
15 mg/kg of body weight per day, given in 1-4 divided doses. Each divided dose may contain the same or different compounds of the invention. The dosage will be an effective amount depending on several factors including the overall health of a patient, and the formulation and route of administration of the selected compound(s).

20 *Definitions*

As used herein, the term "affinity tag" means a ligand or group, linked either to a compound of the present invention or to a protein kinase domain, that allows the conjugate to be extracted from a solution.

The term "alkyl" refers to substituted or unsubstituted saturated hydrocarbon
25 groups, including straight-chain alkyl and branched-chain alkyl groups, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc.

Representative alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, cyclopropylmethyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. The terms "alkenyl" and "alkynyl" refer to

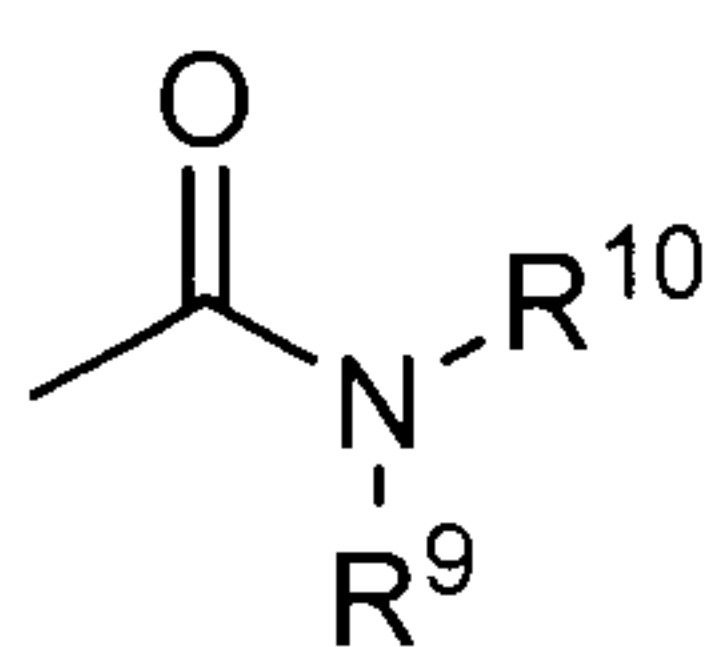
30 substituted or unsubstituted unsaturated aliphatic groups analogous in length and

possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively. Representative alkenyl groups include vinyl, propen-2-yl, crotyl, isopenten-2-yl, 1,3-butadien-2-yl), 2,4-pentadienyl, and 1,4-pentadien-3-yl. Representative alkynyl groups include ethynyl, 1- and 3-propynyl, and 3-butynyl. In certain preferred embodiments, alkyl substituents are lower alkyl groups, e.g., having from 1 to 6 carbon atoms. Similarly, alkenyl and alkynyl preferably refer to lower alkenyl and alkynyl groups, e.g., having from 2 to 6 carbon atoms. As used herein, "alkylene" refers to an alkyl group with two open valencies (rather than a single valency), such as $-(CH_2)_{1-10}-$ and substituted variants thereof.

The term "alkoxy" refers to an alkyl group having an oxygen attached thereto. Representative alkoxy groups include methoxy, ethoxy, propoxy, tert-butoxy and the like. An "ether" is two hydrocarbons covalently linked by an oxygen. Accordingly, the substituent of an alkyl that renders that alkyl an ether is or resembles an alkoxy.

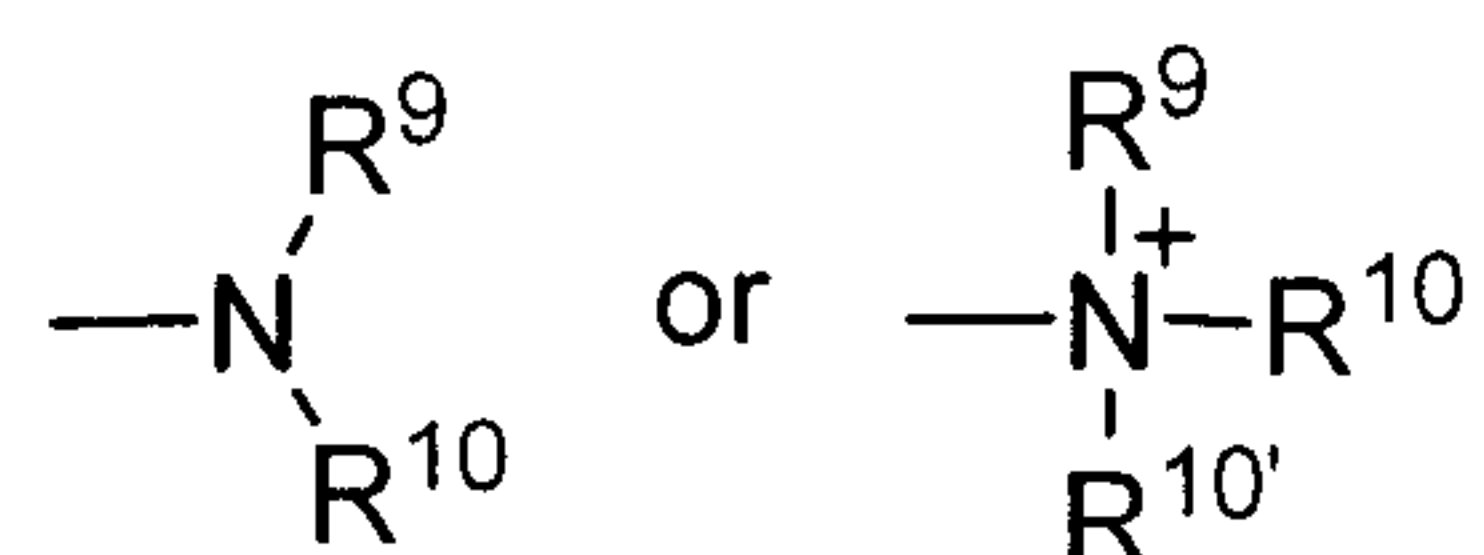
The term "alkoxyalkyl" refers to an alkyl group substituted with an alkoxy group, thereby forming an ether.

The terms "amide" and "amido" are art-recognized as an amino-substituted carbonyl and includes a moiety that can be represented by the general formula:



wherein R^9 , R^{10} are as defined above. Preferred embodiments of the amide will not include imides, which may be unstable.

The terms "amine" and "amino" are art-recognized and refer to both unsubstituted and substituted amines and salts thereof, e.g., a moiety that can be represented by the general formulae:



wherein R^9 , R^{10} and $\text{R}^{10'}$ each independently represent a hydrogen, an alkyl, an alkenyl, $-(\text{CH}_2)_m\text{-R}^8$, or R^9 and R^{10} 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^8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocyclyl or a polycyclyl; and
 5 m is zero or an integer from 1 to 8. In preferred embodiments, only one of R^9 or R^{10} can be a carbonyl, e.g., R^9 , R^{10} , and the nitrogen together do not form an imide. In even more preferred embodiments, R^9 and R^{10} (and optionally $\text{R}^{10'}$) each independently represent a hydrogen, an alkyl, an alkenyl, or $-(\text{CH}_2)_m\text{-R}^8$. In certain
 10 embodiments, the amino group is basic, meaning the protonated form has a $\text{pK}_a \geq 7.00$.

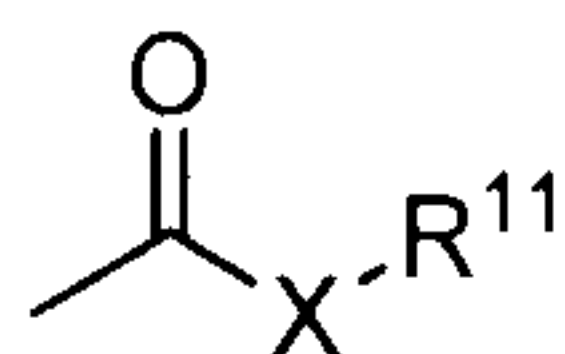
The term "aralkyl", as used herein, refers to an alkyl group substituted with an aryl group.

The term "aryl" as used herein includes 5-, 6-, and 7-membered substituted or
 15 unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. 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 wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups
 20 include benzene, naphthalene, phenanthrene, phenol, aniline, anthracene, and phenanthrene.

The terms "carbocycle" and "carbocyclyl", as used herein, refer to a non-aromatic substituted or unsubstituted ring in which each atom of the ring is carbon. The terms "carbocycle" and "carbocyclyl" also include polycyclic ring systems having
 25 two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is carbocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls.

Representative carbocyclic groups include cyclopentyl, cyclohexyl, 1-cyclohexenyl, and 3-cyclohexen-1-yl, cycloheptyl.

The term "carbonyl" is art-recognized and includes such moieties as can be represented by the general formula:



wherein X is a bond or represents an oxygen or a sulfur, and R¹¹ represents a hydrogen, an alkyl, an alkenyl, -(CH₂)_m-R⁸ or a pharmaceutically acceptable salt. Where X is an oxygen and R¹¹ is not hydrogen, the formula represents an "ester". Where X is an oxygen, and R¹¹ is a hydrogen, the formula represents a "carboxylic acid".

The terms "heteroaryl" includes substituted or unsubstituted aromatic 5- to 7-membered ring structures, more preferably 5- to 6-membered rings, whose ring structures include one to four heteroatoms. 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 wherein at least one of the rings is heteroaromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Heteroaryl groups include, for example, pyrrole, furan, thiophene, imidazole, isoxazole, oxazole, thiazole, triazole, pyrazole, pyridine, pyrazine, pyridazine and pyrimidine, and the like.

The term "heteroatom" as used herein means an atom of any element other than carbon or hydrogen. Preferred heteroatoms are nitrogen, oxygen, and sulfur.

The terms "heterocyclyl" or "heterocyclic group" refer to substituted or unsubstituted non-aromatic 3- to 10-membered ring structures, more preferably 3- to 7-membered rings, whose ring structures include one to four heteroatoms. The term terms "heterocyclyl" or "heterocyclic group" also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls,

and/or heterocyclyls. Heterocyclyl groups include, for example, tetrahydrofuran, tetrahydropyran, piperidine, piperazine, pyrrolidine, morpholine, lactones, and lactams.

The term "hydrocarbon", as used herein, refers to a group that is bonded through a carbon atom that does not have a =O or =S substituent, and typically has at least one carbon-hydrogen bond and a primarily carbon backbone, but may optionally include heteroatoms. Thus, groups like methyl, ethoxyethyl, 2-pyridyl, and trifluoromethyl are considered to be hydrocarbyl for the purposes of this application, but substituents such as acetyl (which has a =O substituent on the linking carbon) and ethoxy (which is linked through oxygen, not carbon) are not. Hydrocarbyl groups include, but are not limited to aryl, heteroaryl, carbocycle, heterocycle, alkyl, alkenyl, alkynyl, and combinations thereof.

The terms "polycyclyl" or "polycyclic" refer to two or more rings (e.g., cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls) in which two or more carbons are common to two adjoining rings, e.g., the rings are "fused rings". Each of the rings of the polycycle can be substituted or unsubstituted.

The term "preventing" is art-recognized, and when used in relation to a condition, such as a local recurrence (e.g., pain), a disease such as cancer, a syndrome complex such as heart failure or any other medical condition, is well understood in the art, and includes administration of a composition which reduces the frequency of, or delays the onset of, symptoms of a medical condition in a subject relative to a subject which does not receive the composition. Thus, prevention of cancer includes, for example, reducing the number of detectable cancerous growths in a population of patients receiving a prophylactic treatment relative to an untreated control population, and/or delaying the appearance of detectable cancerous growths in a treated population versus an untreated control population, e.g., by a statistically and/or clinically significant amount. Prevention of an infection includes, for example, reducing the number of diagnoses of the infection in a treated population versus an untreated control population, and/or delaying the onset of symptoms of the infection in a treated population versus an untreated control population. Prevention of pain includes, for example, reducing the magnitude of, or

alternatively delaying, pain sensations experienced by subjects in a treated population versus an untreated control population.

As used herein, the term "probe" means a compound of the invention which is labeled with either a detectable label or an affinity tag, and which is capable of binding, either covalently or non-covalently, to a protein kinase domain. When, for example, the probe is non-covalently bound, it may be displaced by a test compound. When, for example, the probe is bound covalently, it may be used to form cross-linked adducts, which may be quantified and inhibited by a test compound.

10 The term "substituted" refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. 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
15 spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term "substituted" is 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 non-aromatic substituents of organic
20 compounds. The permissible substituents can 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. Substituents can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl),
25 a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxyl, a phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an
30 aromatic or heteroaromatic moiety. It will be understood by those skilled in the art

that the moieties substituted on the hydrocarbon chain can themselves be substituted, if appropriate.

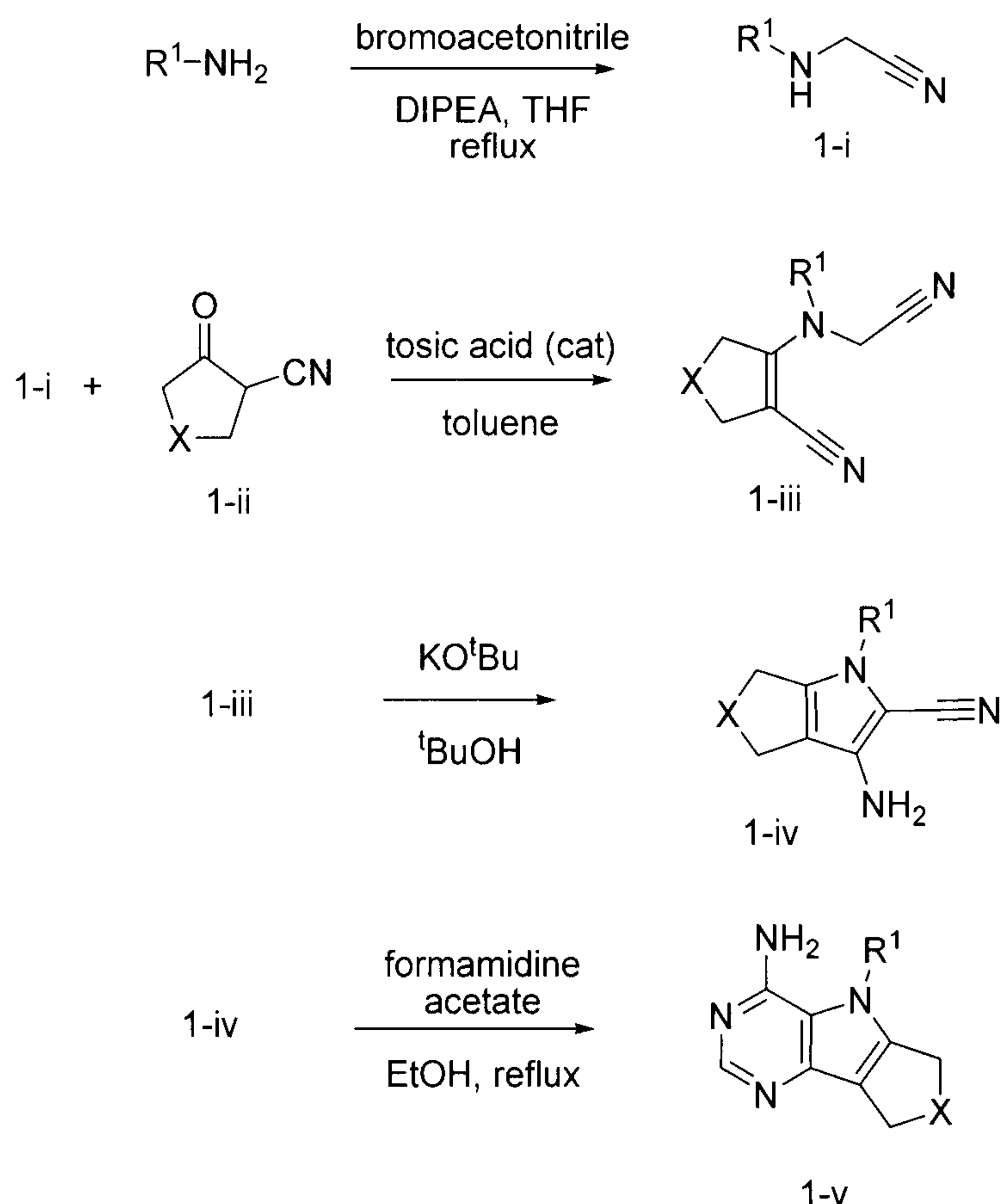
As used herein, the term "treating" or "treatment" includes reversing, reducing, or arresting the symptoms, clinical signs, and underlying pathology of a condition in
5 manner to improve or stabilize a subject's condition.

Compounds of the invention also include all isotopes of atoms present in the intermediates and/or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include deuterium and tritium.

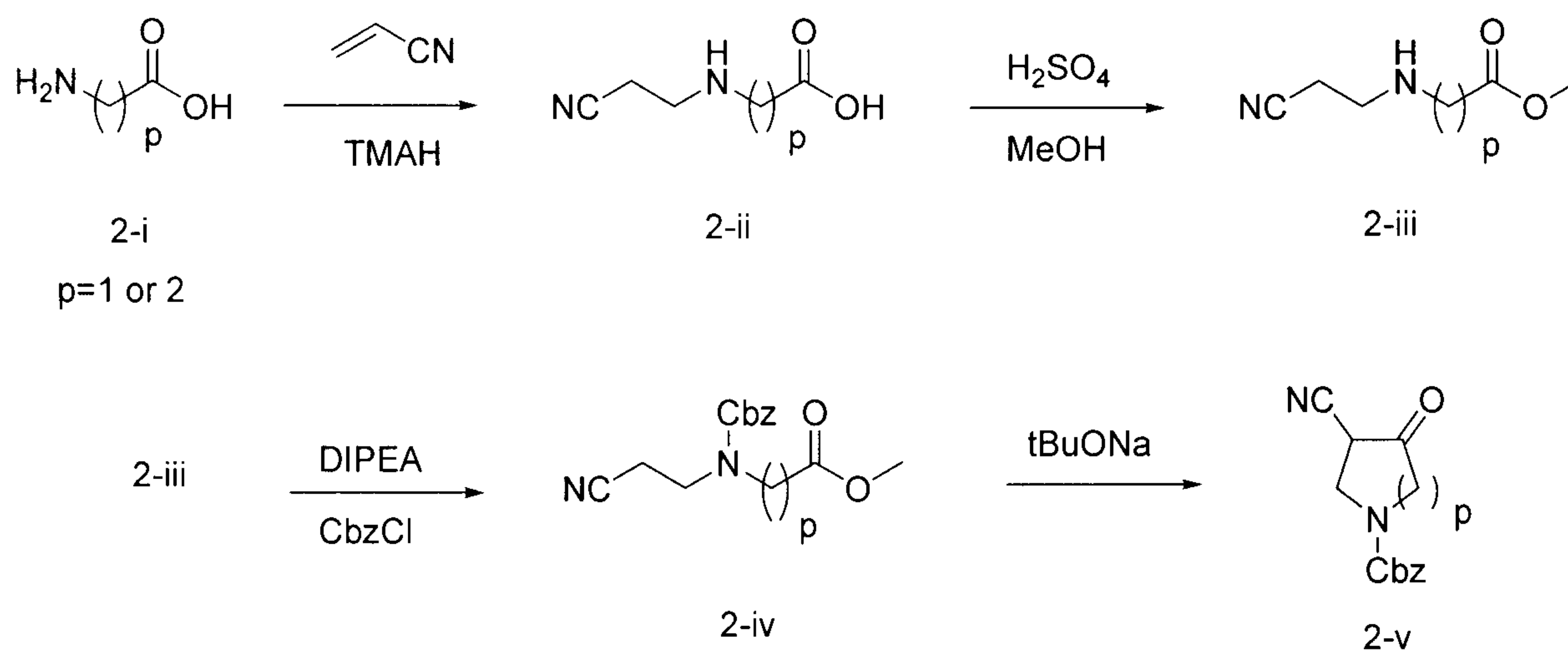
10 **General Synthetic Methods**

General Synthetic Method A:

Compounds of general Formula 1-v were prepared in a four step process which is summarized in Scheme 1. Alkylation of R^1NH_2 with bromoacetonitrile provided intermediate 1-i. Condensation of 1-i with 1-ii in the presence of an acid such as p-
15 toluenesulphonic acid, provided intermediate 1-iii. Treatment of intermediate 1-iii with a base such as tBuOK in t-BuOH provided intermediate 1-iv. Treatment of intermediate 1-iv with formamidine acetate in ethanol provided compounds of general formula 1-v.

**Scheme 1****General Procedure B:**

2-Cyanoketone intermediates such as intermediates 1-ii and 2-v were prepared by the use of General Procedure B as summarized in Scheme 2. For example, condensation of an amino acid derivative 2-i with acrylonitrile provided the N-alkyl amino acid 2-ii which was esterified in acidic methanol to provide amino ester 2-ii. Protection of the amino functionality using an appropriate protecting group such as Cbz provided intermediate such as 2-iv. Diekmann condensation of 2-iv in basic media provided intermediate 2-v.

**Scheme 2****Exemplification**

The following synthetic methods are intended to be representative of the chemistry used to prepare compounds of Formula 1 and are not intended to be limiting.

reduced pressure. Hexane was added to the residue, a precipitate formed, intermediate 3-a was collected by filtration as a beige solid.

Step 2: Intermediate 3-b

5 To a solution of intermediate 3-a (6.0 g, 26.8 mmol) in toluene (100 mL) were added 2-oxocyclopentanecarbonitrile (2.92 g, 26.8 mmol) and 4-methylbenzenesulfonic acid hydrate (509 mg, 2.68 mmol). The reaction was refluxed for 5 hours using a Dean-Stark and then cooled to room temperature. Saturated aqueous NaHCO₃ and ethyl acetate were added, the organic layer was
10 separated, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Diethyl ether was added to the residue, a precipitate formed, intermediate 3-b was collected by filtration as a beige solid.

Step 3: Intermediate 3-c

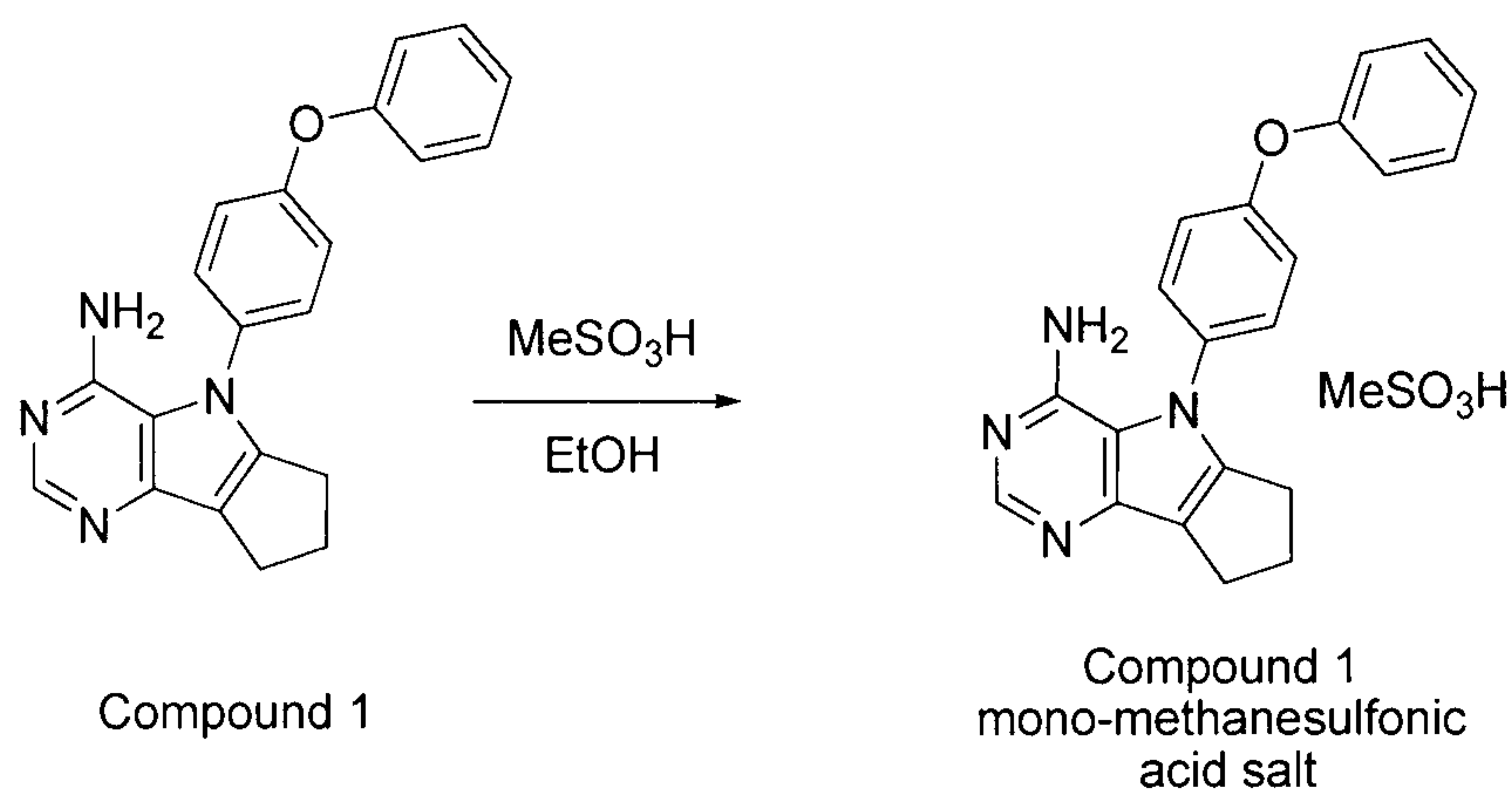
To a solution of intermediate 3-b (2.80 g, 8.88 mmol) in tert-butanol (20 mL) was
15 added sodium tert-butoxide (939 mg, 9.77 mmol). The resulting suspension was stirred at 80 °C for 2 hours and then cooled to room temperature. Saturated aqueous ammonium chloride and ethyl acetate were added, the organic layer was separated, the aqueous phase was extracted with ethyl acetate, the combined organic extracts were washed with brine, dried over MgSO₄, filtered and
20 concentrated under reduced pressure to provide intermediate 3-c as a beige solid.

Step 4: Compound 1

To a solution of intermediate 3-c (300 mg, 0.95 mmol) in EtOH was added formamidine acetate (792 mg, 7.61 mmol), the reaction was stirred at reflux for 1 hour and then cooled to room temperature. The reaction was concentrated in vacuo
25 to half volume. A precipitate formed and was collected by filtration, washed with methanol and diethyl ether to provide compound 1 as white solid. MS (m/z) M+H= 343.2

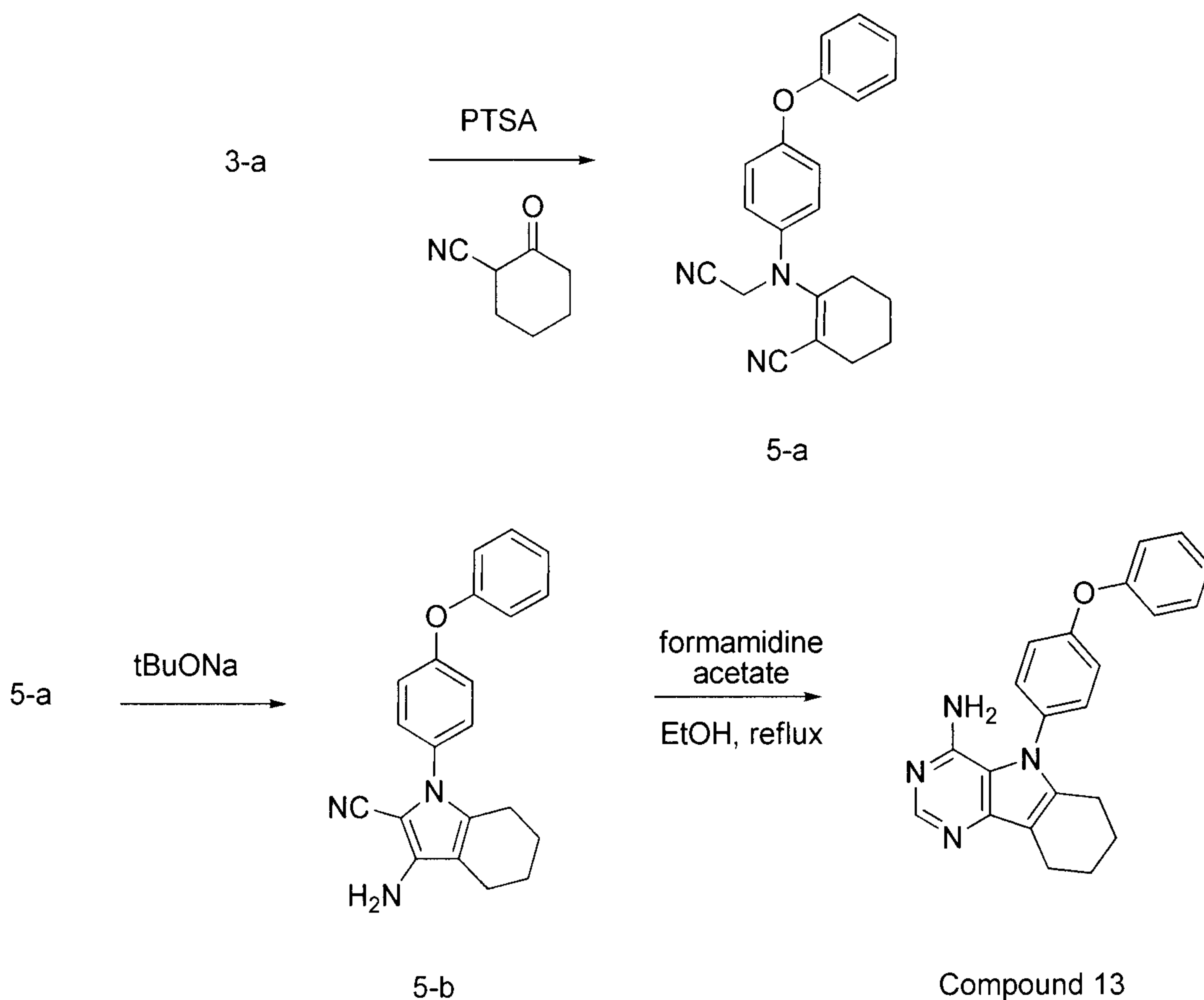
Compound 1 mono-methanesulfonic acid salt

Various medicinally acceptable addition salts of the compounds represented by Formula 1 may be prepared by the treatment of compounds of Formula 1 with an appropriate quantity of a medicinally acceptable acid. For example, as depicted in Scheme 3, the mono-methanesulfonic acid salt of compound 1 may be prepared by the treatment of compound 1 with 1 to 2 equivalence of methanesulfonic acid in an appropriate solvent to provide the mono-methanesulfonic acid salt of compound 1.



Scheme 4

10 Compound 1 (2.25 g, 6.57 mmol) was suspended in ethanol (250 ml) and treated with methanesulfonic acid (0.448 ml, 6.90 mmol). The suspension was stirred for 1 hour. Solvent was concentrated to approximately 50 mL and diethyl ether (200 mL) was added. The resulting white solid was filtered, washed with diethyl ether (2 X 20 mL) and dried in vacuo to provide Compound 1 mono-methanesulfonic acid
15 salt. MS (m/z) M+H= 343.2

Synthesis of Compound 13:**Scheme 5****Step 1 Intermediate 6-a**

- 5 To a solution of intermediate 3-a (1.82 g, 8.12 mmol) in toluene (32 mL) were added 2-oxocyclohexanecarbonitrile (1.0 g, 8.12 mmol) and 4-methylbenzenesulfonic acid hydrate (154 mg, 0.81 mmol). The reaction was refluxed overnight using a Dean-Stark and then cooled to room temperature. Saturated aqueous NaHCO_3 and ethyl acetate were added, the organic layer was
- 10 separated, washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. . Purification by silica gel chromatography provided intermediate 5-a as a yellow oil.

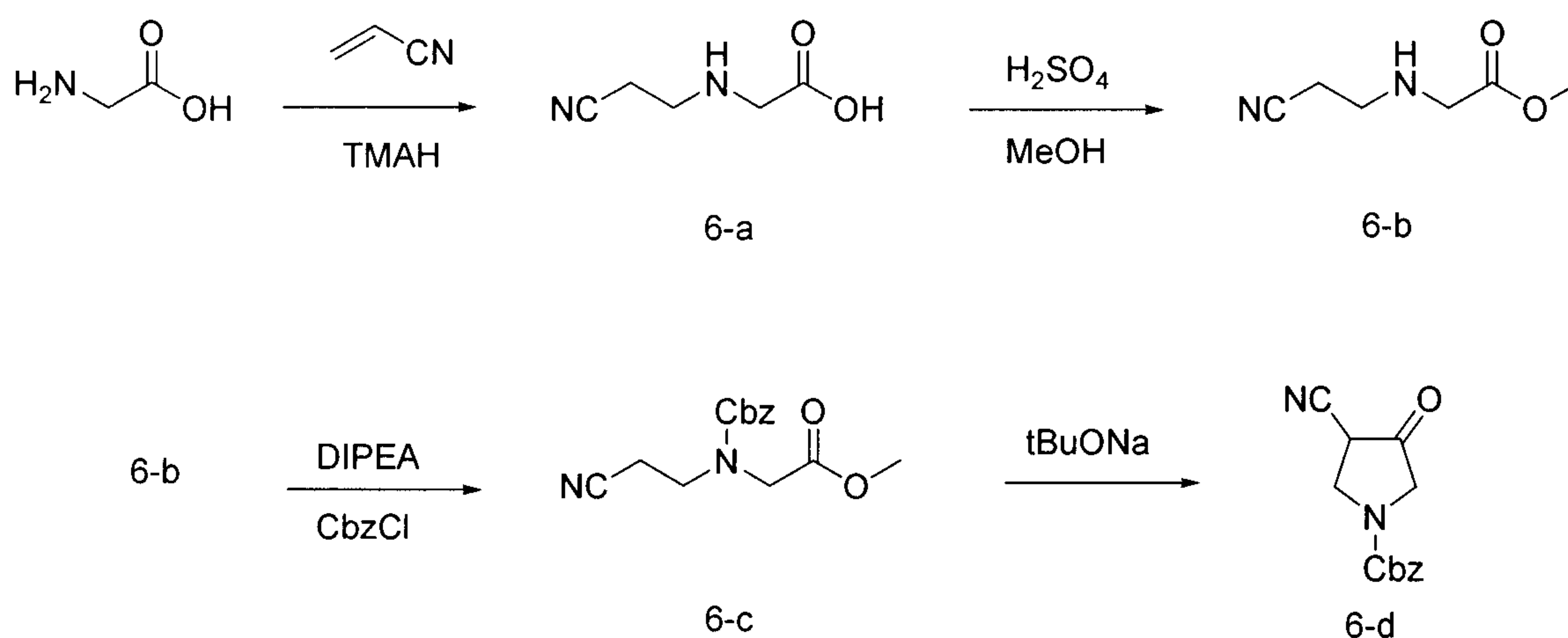
Step 2: Intermediate 5-b

To a solution of intermediate 5-a (600 mg, 1.82 mmol) in tert-butanol (20 mL) was added sodium tert-butoxide (193 mg, 2.0 mmol), the reaction was stirred at 100 °C for 1 hour and then cooled to room temperature. Saturated aqueous ammonium chloride and ethyl acetate were added, the organic layer was separated, the aqueous phase was extracted with ethyl acetate, the combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure to provide intermediate 5-b as beige solid.

Step 3: Compound 13

To a solution of intermediate 5-b (600 mg, 1.82 mmol) in EtOH was added formamidine acetate (1.52 g, 14.57 mmol), the reaction was stirred at reflux for 3 hours and then cooled to room temperature. The reaction was concentrated in vacuo to half volume; a precipitate formed and was collected by filtration, washed with methanol and diethyl ether to provide compound 13 as white solid. MS (m/z)

M+H= 357.2

Synthesis of intermediate 6-d

Scheme 6

Step 1: Intermediate 6-a

Glycine (15.0 g, 200 mmol) was suspended in water (30 mL) and TMAH 1.0 M in water (200 mL, 200 mmol) was added. The mixture was cooled to 10°C,
5 acrylonitrile (11.67 g, 220 mmol) was added and the reaction was stirred overnight and allowed to warm to room temperature slowly. The mixture was neutralized with concentrated HCl (15 mL) then concentrated to 50 mL and diluted with ethanol (100 mL). A precipitate formed and was collected by filtration, washed with ethanol to provide intermediate 6-a as a white solid.

10

Step 2: Intermediate 6-b

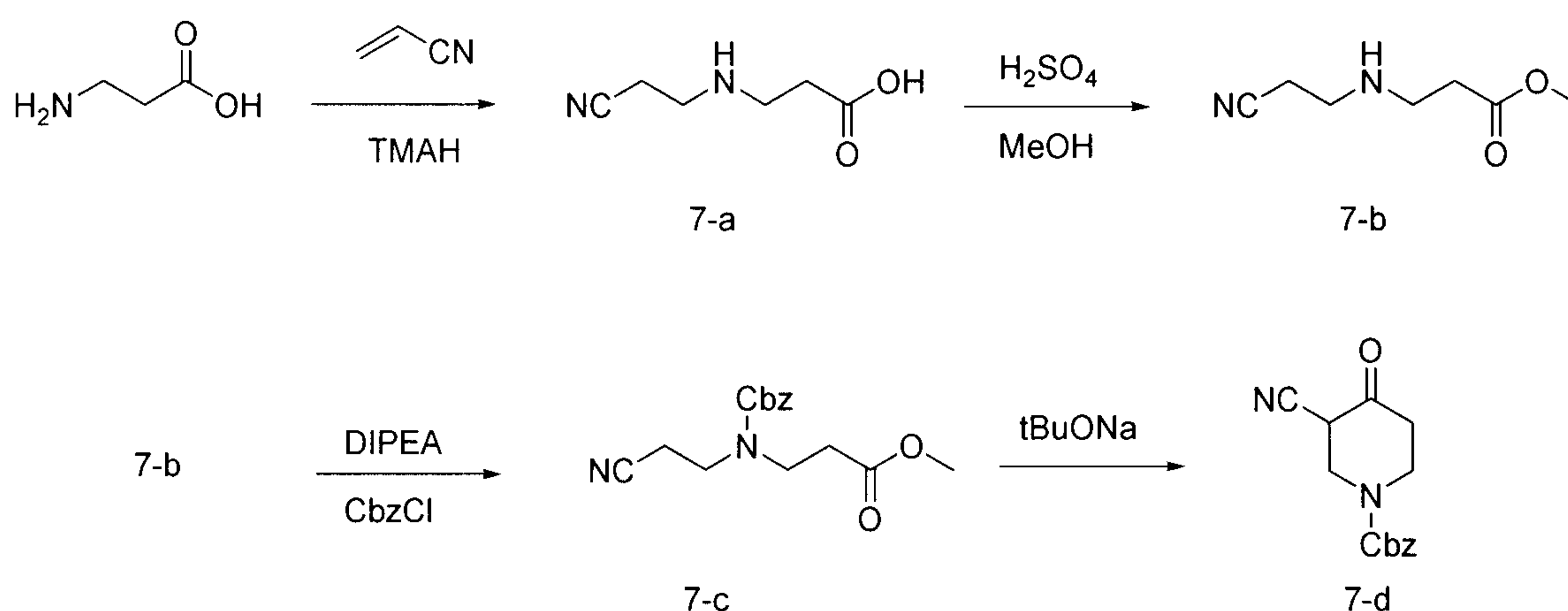
Sulfuric acid (10.2 mL) was added to a suspension of intermediate 6-a (16.2 g, 126 mmol) in MeOH (150 mL) and the reaction mixture was stirred at reflux overnight and then cooled to room temperature. The solvent was evaporated and the residue
15 was diluted with 20% sodium hydroxide until a pH of 8 was obtained. The aqueous layer was extracted three times with dichloromethane; the combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo to provide intermediate 6-b as colorless oil.

Step 3: Intermediate 6-c

20 To a solution of intermediate 6-b (12.7 g, 89 mmol) in dichloromethane (100 mL) cooled to 0°C, were added benzyl chloroformate (13.97 mL, 98 mmol) and DIPEA (17.16 mL, 98.0 mmol) and the reaction was stirred at room temperature for 18 hrs. The reaction mixture was concentrated to half volume. Water and ethyl acetate were added; the organic layer was separated, washed with 10% citric acid,
25 saturated aqueous NaHCO₃, and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 6-c as yellow oil.

Step 4: Intermediate 6-d

Sodium tert-butoxide (2.56 g, 26.7 mmol) was added to a solution of intermediate 7-c (6.7 g, 24.25 mmol) in toluene (80 mL), the reaction was stirred overnight at 80 °C and then cooled to room temperature. 1N HCl and ethyl acetate were added, the reaction was stirred for 15 minutes, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 6-d as a yellow oil.

Synthesis of Intermediate 7-d**Scheme 7****Step 1: Intermediate 7-a**

β- alanine (17.82 g, 200 mmol) was suspended in water (30 mL) and TMAH 1.0 M in water (200 mL, 200 mmol) was added. The mixture was cooled to 10 °C, acrylonitrile (11.67 g, 220 mmol) was added and the reaction was stirred overnight and allowed to warm to room temperature slowly. The mixture was neutralized with concentrated HCl (15 mL) then concentrated to 50 mL and diluted with ethanol (100 mL). A precipitate formed and was collected by filtration, washed with ethanol to provide intermediate 7-a as a white solid.

Step 2: Intermediate 7-b

Sulfuric acid (6.07 ml, 114 mmol) was added to a suspension of intermediate 7-a (16.2 g, 114 mmol) in MeOH (150 ml) and the reaction was stirred at reflux overnight and then cooled to room temperature. The solvent was evaporated and the residue was diluted with 20% sodium hydroxide until PH=8. The aqueous layer was extracted 3 times with dichloromethane; the combined organic extracts were dried over MgSO₄, filtered and concentrated in vacuo to provide intermediate 7-b as colorless oil.

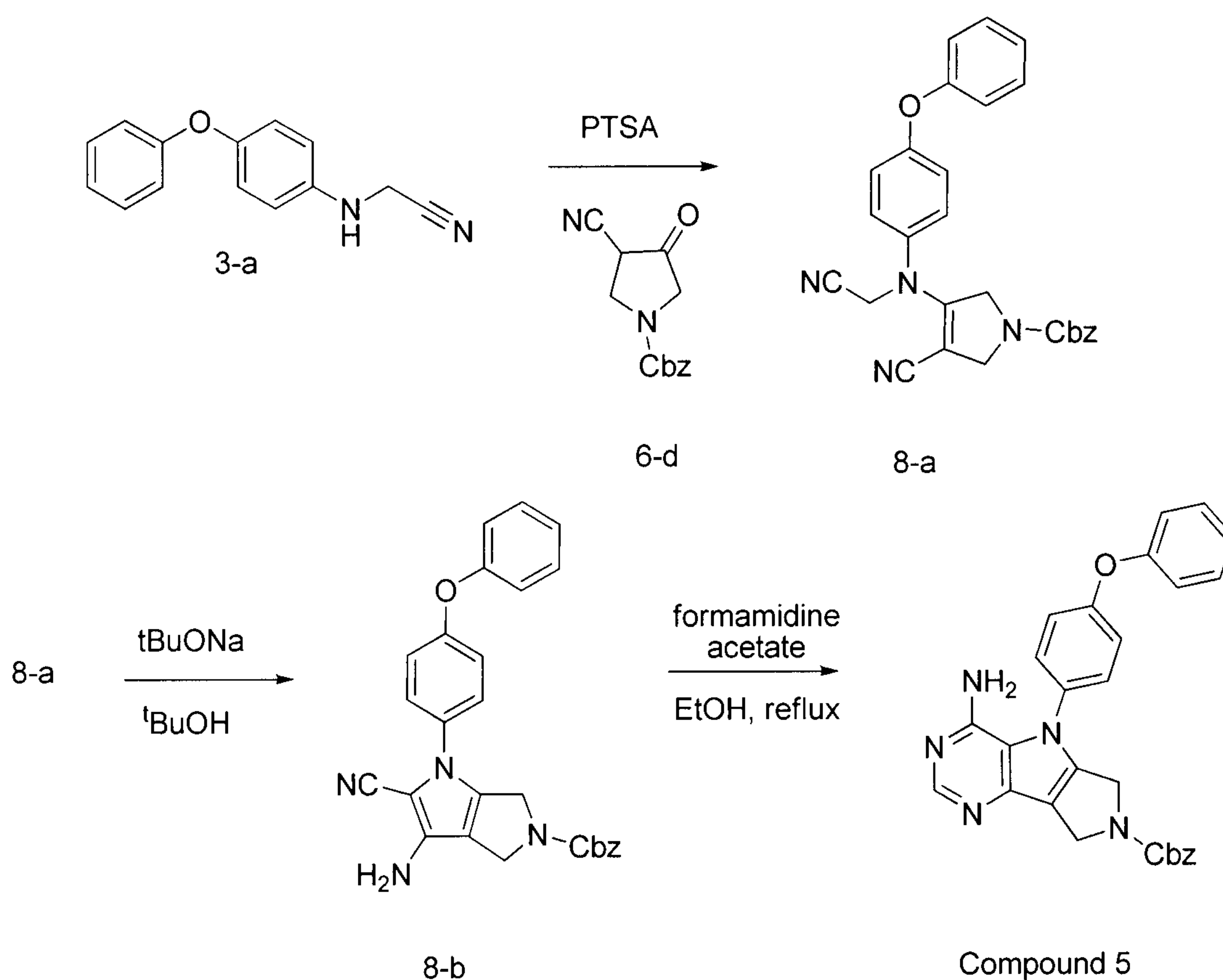
Step 3: Intermediate 7-c

To a solution of intermediate 7-b (3.4 g, 21.77 mmol) in dichloromethane, cooled to 0° C, were added benzyl chloroformate (3.40 ml, 23.95 mmol) and DIPEA (4.18 ml, 23.95 mmol) and the reaction was stirred at room temperature for 18 hours. The reaction was concentrated in vacuo to half volume. Water and ethyl acetate were added, the organic layer was separated, washed with 10% aqueous citric acid, saturated aqueous NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 7-c as a yellow oil.

Step 4: Intermediate 7-d

To a solution of intermediate 7-c (5.2 g, 17.91 mmol) in toluene (50 ml) was added sodium tert-butoxide (1.89 g, 19.70 mmol) and the reaction was stirred at 80°C for 18 hours and then cooled to room temperature. 1N HCl and ethyl acetate were added, the reaction was stirred for 15 minutes, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 7-d as a yellow oil.

Synthesis of Compound 5



Scheme 8

Step 1: Intermediate 8-a

- 5 To a solution of intermediate 3-a (2.45 g, 10.92 mmol), in toluene (50 mL), were added intermediate 6-d (3.2 g, 13.10 mmol) and 4-methylbenzenesulfonic acid hydrate (208 mg, 1.09 mmol), the reaction was refluxed for 5 hours using a Dean-Stark and then cooled to room temperature. Saturated aqueous NaHCO_3 and ethyl acetate were added, the organic layer was separated, washed with brine, dried over
- 10 MgSO_4 , filtered and concentrated under reduced pressure. Methanol was added to the residue, a precipitate formed, intermediate 8-a was collected by filtration as off-white solid.

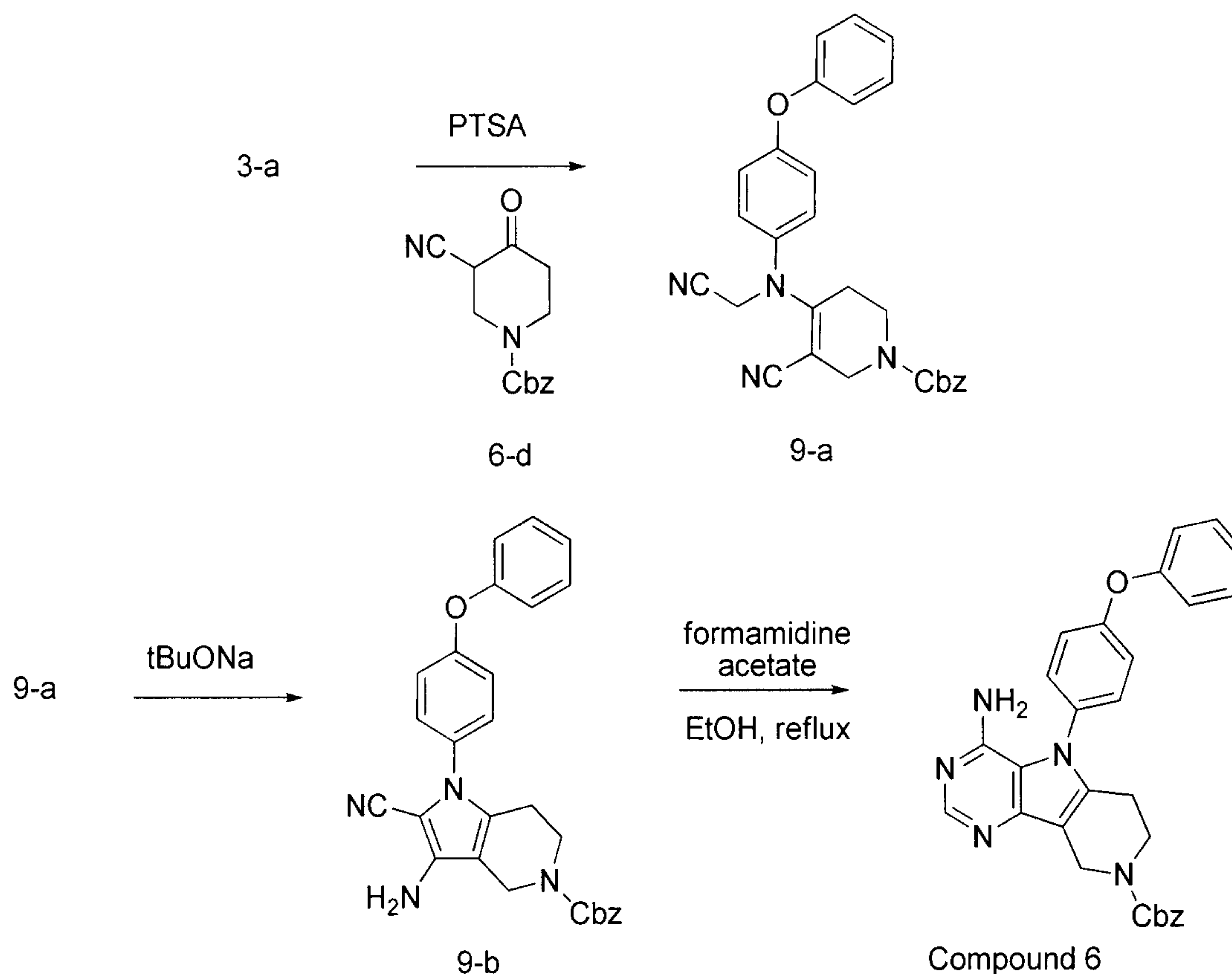
Step 2: Intermediate 8-b

To a solution of intermediate 8-a (3.0 g, 6.66 mmol) in tert-butanol (20 mL) was added sodium tert-butoxide (704 mg, 7.33 mmol), the reaction was stirred at 100 °C for 1 hour and then cooled to room temperature. Water was added and pH was
5 adjusted to 7 with 1N HCl. Ethyl acetate was then added, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated in vacuo to provide intermediate 8-b as beige solid.

Step 3: Compound 5

To a solution of intermediate 8-b (2.60 g, 5.77 mmol) in ethanol was added
10 formamidine acetate (4.81 g, 46.5 mmol) and the reaction was stirred at reflux for 3 hours. The reaction was concentrated to half volume; water was added, a precipitate formed and was collected by filtration. Purification by silica gel chromatography provided compound 5 as an off-white solid. MS (m/z) M+H= 478.1

Synthesis of Compound 6



Scheme 9

Step 1: Intermediate 9-a

- 5 To a solution of intermediate 3-a (7.24 g, 32.3 mmol) in toluene (160 mL) were added intermediate 6-d (10.0 g, 38.7 mmol) and 4-methylbenzenesulfonic acid hydrate (614 mg, 3.23 mmol), the reaction was refluxed for 3 hours using a Dean-Stark and then cooled to room temperature. Saturated aqueous NaHCO₃ and ethyl acetate were added, the organic layer was separated, washed with brine, dried over
- 10 MgSO₄, filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 9-a as a beige foam.

Step 2: Intermediate 9-b

To a solution of intermediate 9-a (4.2 g, 9.04 mmol) in tert-butanol (50 mL) was added sodium tert-butoxide (956 mg, 9.95 mmol), the reaction was stirred at 100

5 To a solution of intermediate 9-b (4.25 g, 9.15 mmol) in ethanol was added
formamidine acetate (7.62 g, 73.2 mmol), the reaction was stirred at reflux for 3
hours and then cooled to room temperature. The reaction was concentrated in
vacuo to half volume; water was added, a precipitate formed and was collected by
filtration, washed with ethyl acetate to provide compound 6 as beige solid. MS
10 (m/z) M+H= 492.2

Chemical reaction scheme showing the hydrogenation of Compound 5 to Compound 7.

Compound 5 (left) is a tricyclic molecule consisting of a pyrimidine ring fused to an indole-like system, which is further fused to a pyrrolidine ring. It features a benzyl group (Cbz) attached to the nitrogen of the pyrrolidine ring and a 4-benzyloxyphenyl group attached to the nitrogen of the indole-like system.

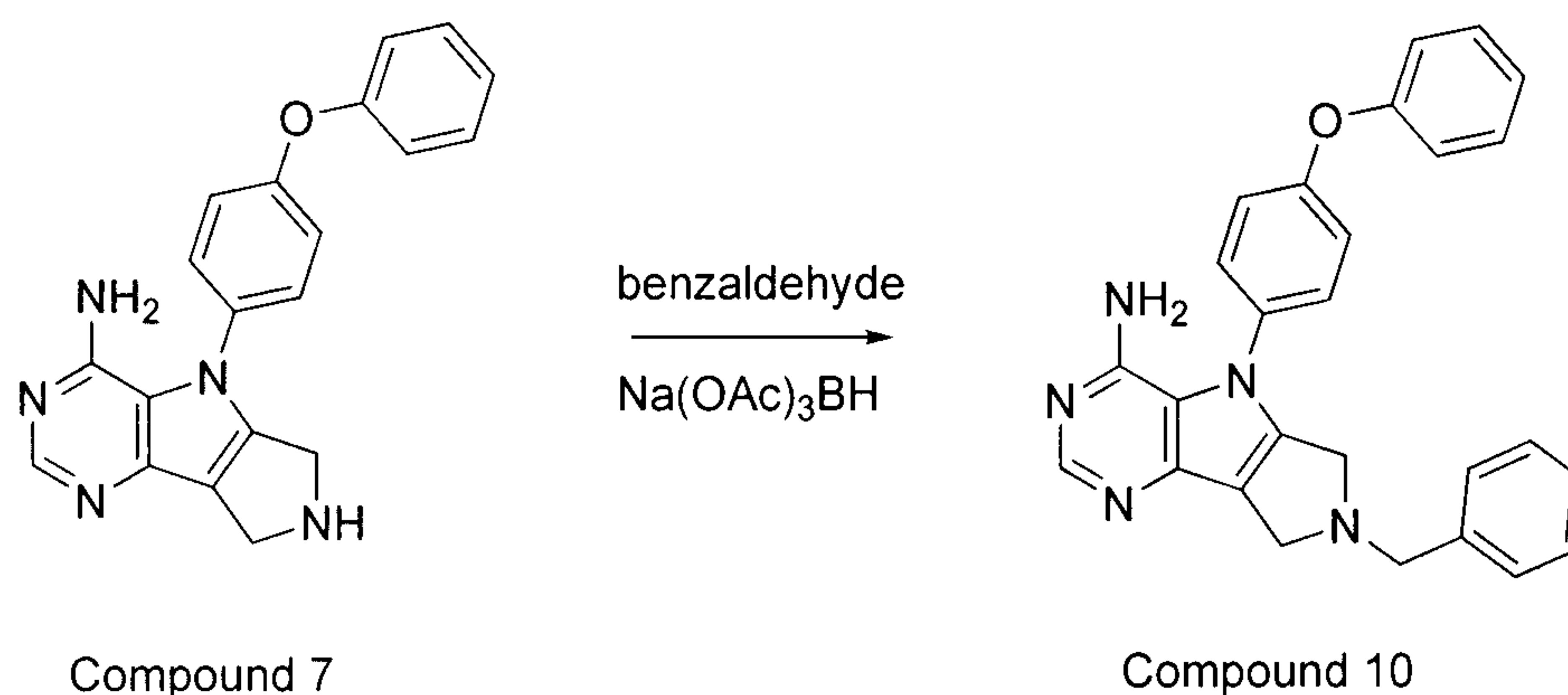
The reaction conditions are H_2 , Pd/C, indicated by the arrow.

Compound 7 (right) is the product of the hydrogenation, where the pyrrolidine ring has been reduced to a pyrrole ring, resulting in a tricyclic structure with a pyrimidine ring fused to an indole-like system, which is further fused to a pyrrole ring. It retains the benzyl group (Cbz) and the 4-benzyloxyphenyl group.

Scheme 10

To a solution of compound 5 (1.5 g, 3.14 mmol) in methanol and stirred under nitrogen was added 10% Pd/C (669 mg, 3.14 mmol) and formic acid (1.0 ml, 26.1 mmol). The reaction mixture was purged with H₂ and stirred for 24 hours. The reaction was then filtered through celite and the filtrate was concentrated in vacuo. 1N HCl in diethyl ether was added to the residue and compound 7·2HCl was collected by filtration as an off-white solid. MS (m/z) M+H= 344.2

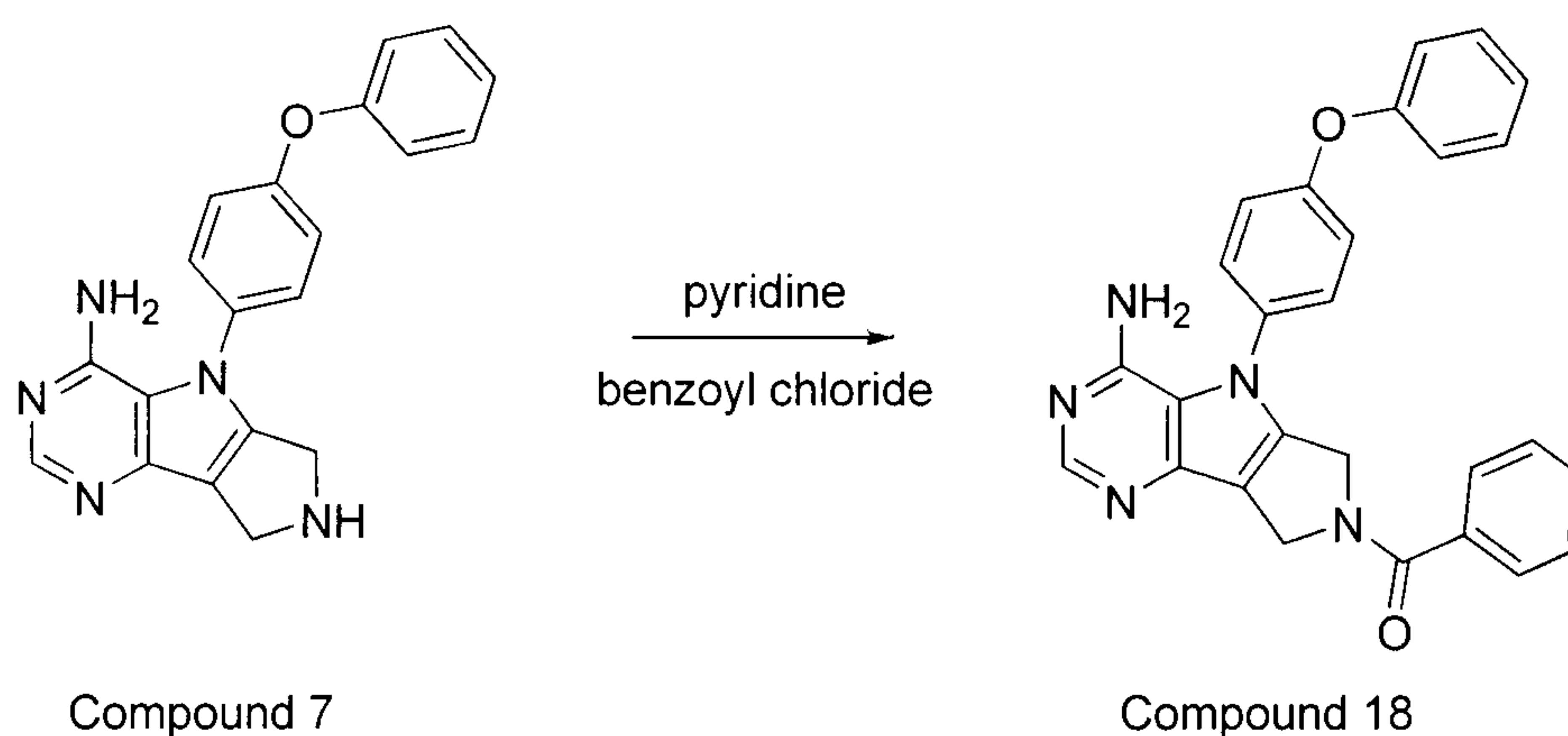
Synthesis of Compound 10



Scheme 11

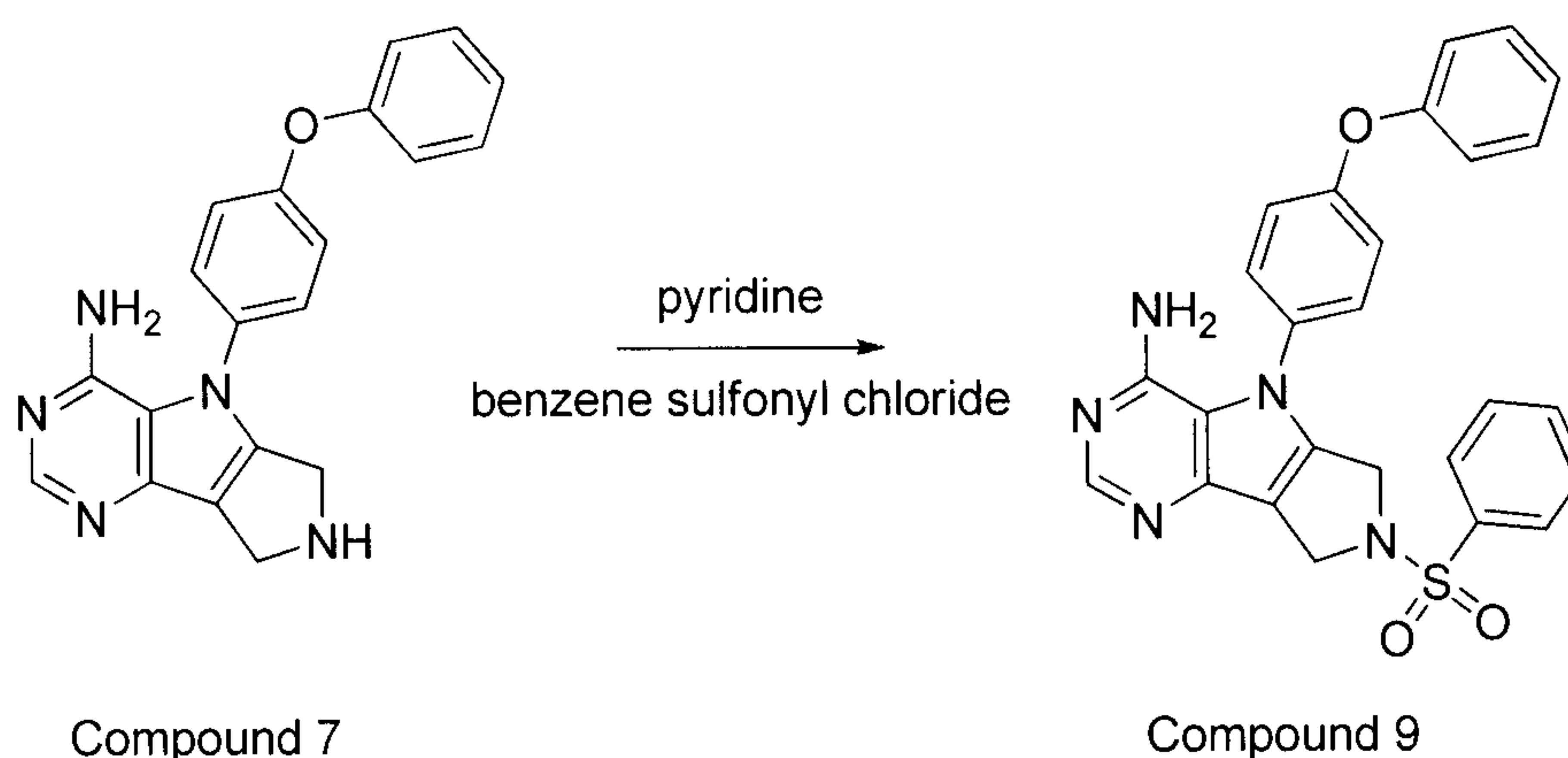
- 5 To a solution of compound 7 (200 mg, 0.58 mmol) in THF (10 ml) were sequentially added benzaldehyde (59 μl , 0.582 mmol), acetic acid (3.3 μl , 0.058 mmol) and sodium triacetoxyborohydride (370 mg, 1.747 mmol) and the suspension was stirred at room temperature overnight. Saturated aqueous NaHCO_3 and ethyl acetate were added, the organic layer was separated, washed with brine,
- 10 dried over MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 10 as a white solid. MS (m/z) $\text{M}+\text{H}^+$ = 434.2

Synthesis of Compound 25

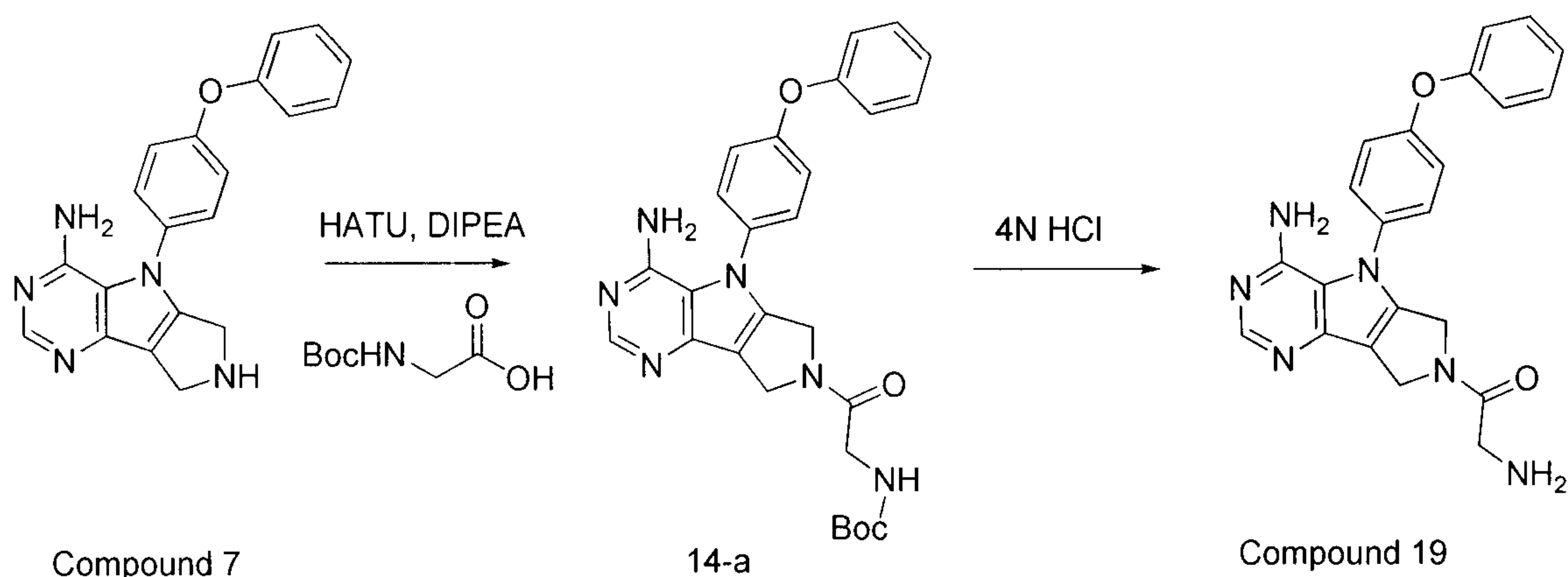


Scheme 12

To a solution of compound 7 (300 mg, 0.58 mmol) in THF (5 mL) and pyridine (5 mL) were sequentially added benzoyl chloride (152 μ L, 1.31 mmol) and DMAP (21 mg, 0.17 mmol). The reaction was stirred at 80 °C overnight and then cooled to room temperature. A saturated aqueous solution of ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 18 as white solid. MS (m/z) $\text{M}+\text{H}^+= 448.3$

Synthesis of Compound 9**Scheme 13**

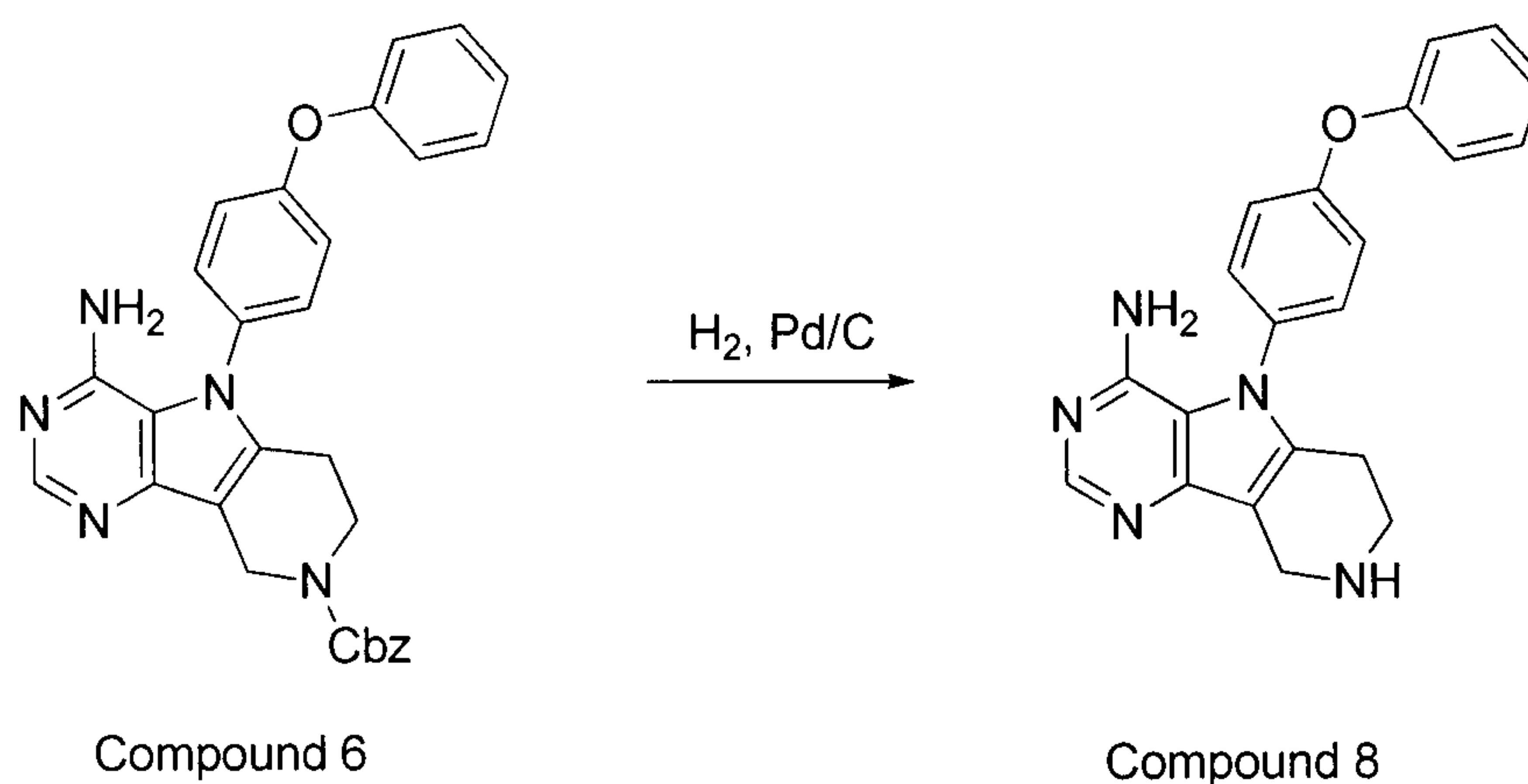
To a solution of compound 7 (200 mg, 0.58 mmol) in THF (5 mL) and pyridine (5 mL) were sequentially added benzenesulfonyl chloride (350 mg, 1.97 mmol) and DMAP (71 mg, 0.58 mmol). The reaction was stirred at 80 °C for 3 days and then cooled to room temperature. A saturated aqueous solution of ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 9 as a yellow solid. MS (m/z) $\text{M}+\text{H}^+= 484.1$

Synthesis of Compound 19**Scheme 14****Step 1: Intermediate 14-a**

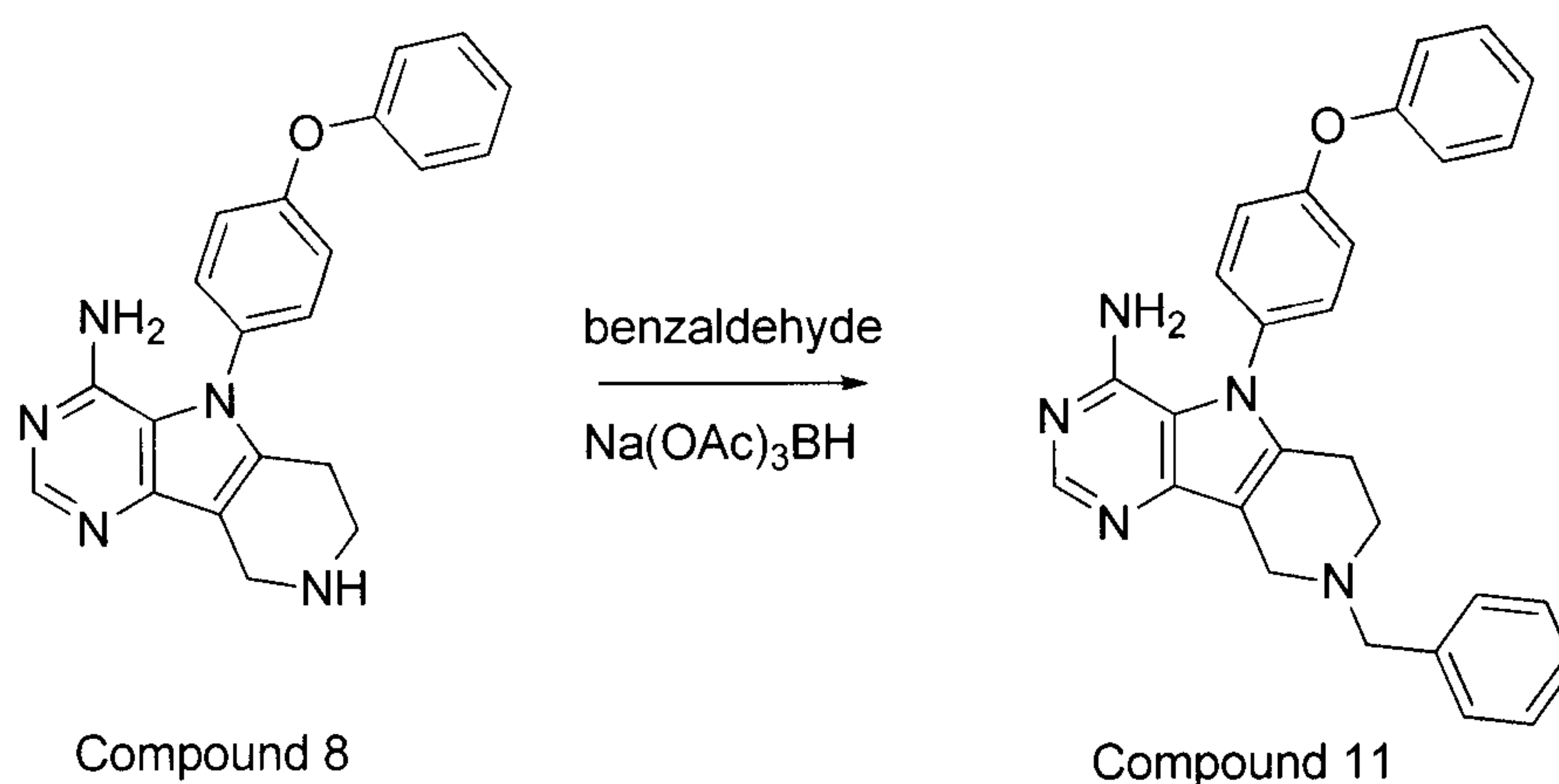
- 5 To a solution of compound 7 (300 mg, 0.87 mmol) and Boc-Gly-OH (168 mg, 0.96 mmol) in DMF were added HATU (332 mg, 0.87 mmol) and DIPEA (304 μ L, 1.74 mmol) and the reaction was then stirred at room temperature for 1 hour. Water was added; a precipitate formed and was collected by filtration to provide intermediate 14-a as a beige solid.

10 **Step 2: Compound 19**

- 4N HCl (5 ml, 20.0 mmol) in 1,4-dioxane was added to intermediate 14-a (400 mg, 0.79 mmol) in methanol (5 ml) and the suspension was stirred at room temperature for 1 hour. Volatiles were removed under reduced pressure, ethyl acetate was added to the residue, a precipitate formed and was collected by
- 15 filtration to provide compound 19 $\cdot$ 2HCl as a white solid. MS (m/z) M+H= 401.2

Synthesis of Compound 8**Scheme 15**

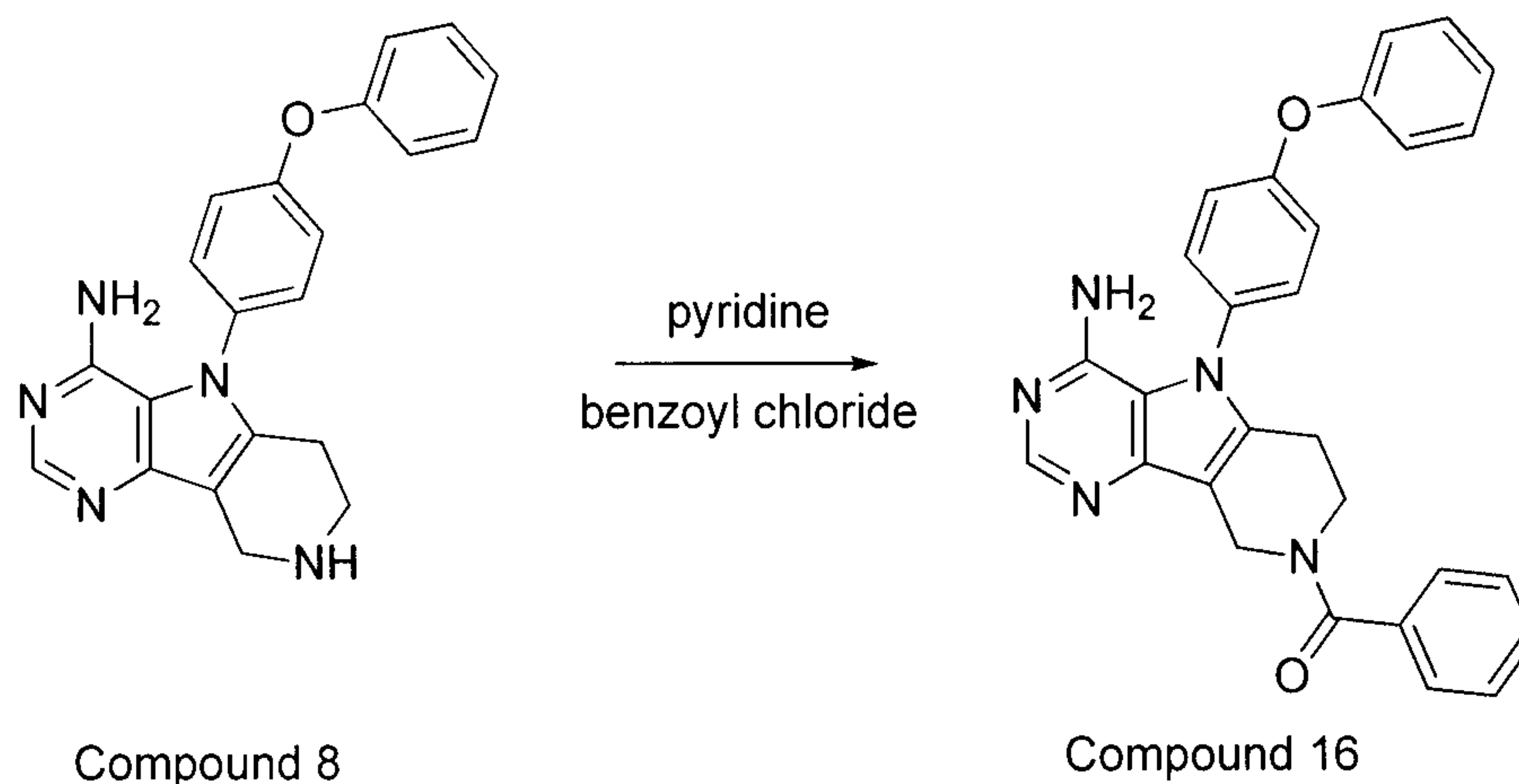
To a solution of compound 6 (1.20 g, 2.44 mmol) in methanol and stirred under nitrogen was added 10% Pd/C (52 mg, 0.24 mmol). The reaction mixture was purged with H₂ and stirred at room temperature for 24 hours. The reaction was then filtered through celite and the filtrate was concentrated in vacuo. 1N HCl in diethyl ether was added to the residue and compound 8·2HCl was collected by filtration as an off-white solid. MS (m/z) M+H= 358.2

10 Synthesis of Compound 11**Scheme 16**

To a solution of compound 8 (200 mg, 0.58 mmol) in THF (10 ml) were sequentially added benzaldehyde (57 μl, 0.56 mmol) and sodium

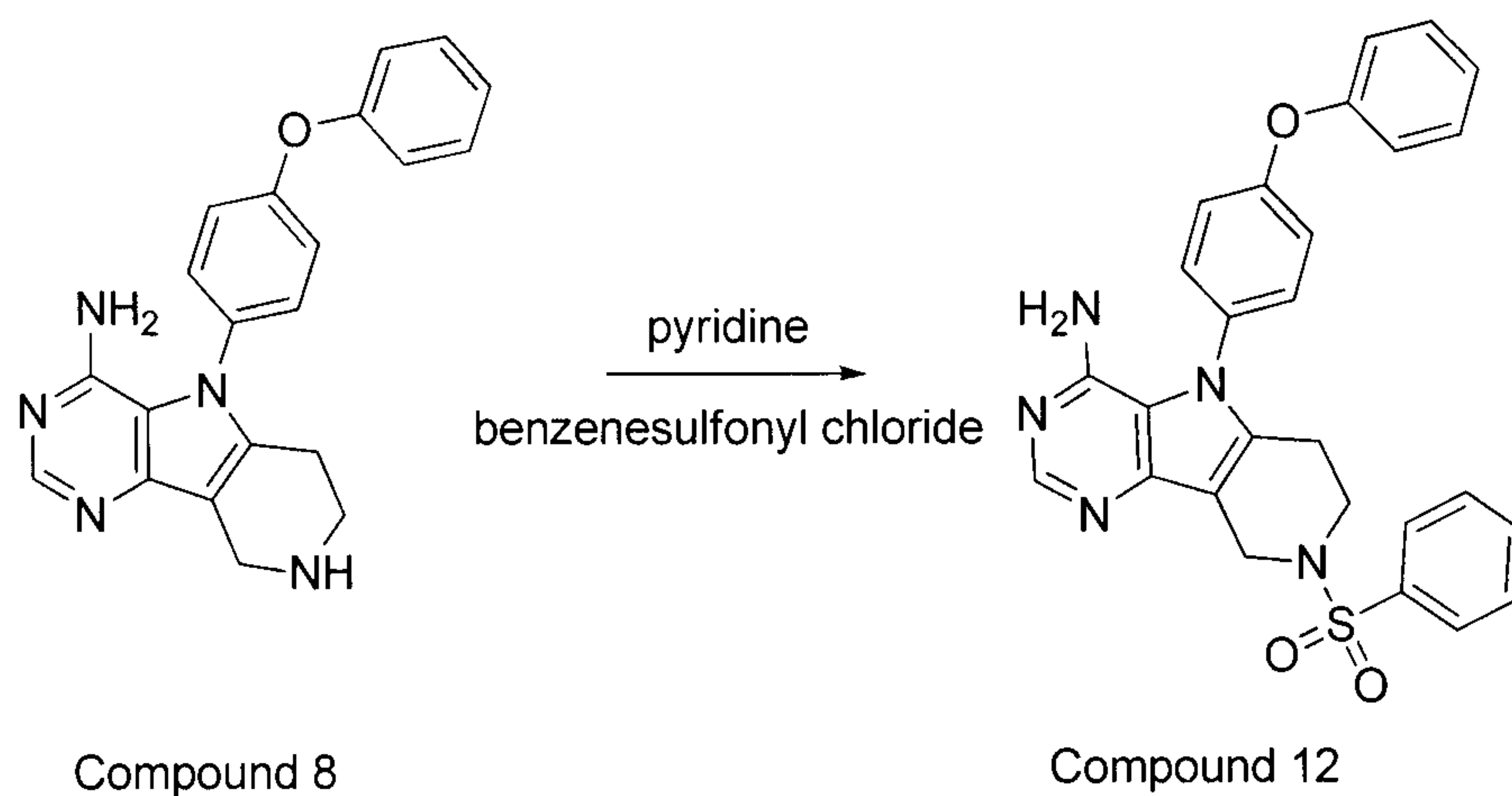
triacetoxyborohydride (356 mg, 1.68 mmol) and the suspension was stirred at room temperature overnight. Saturated aqueous NaHCO_3 and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 11 as a yellow solid. MS (m/z) $\text{M}+\text{H}^+= 448.2$

Synthesis of compound 16

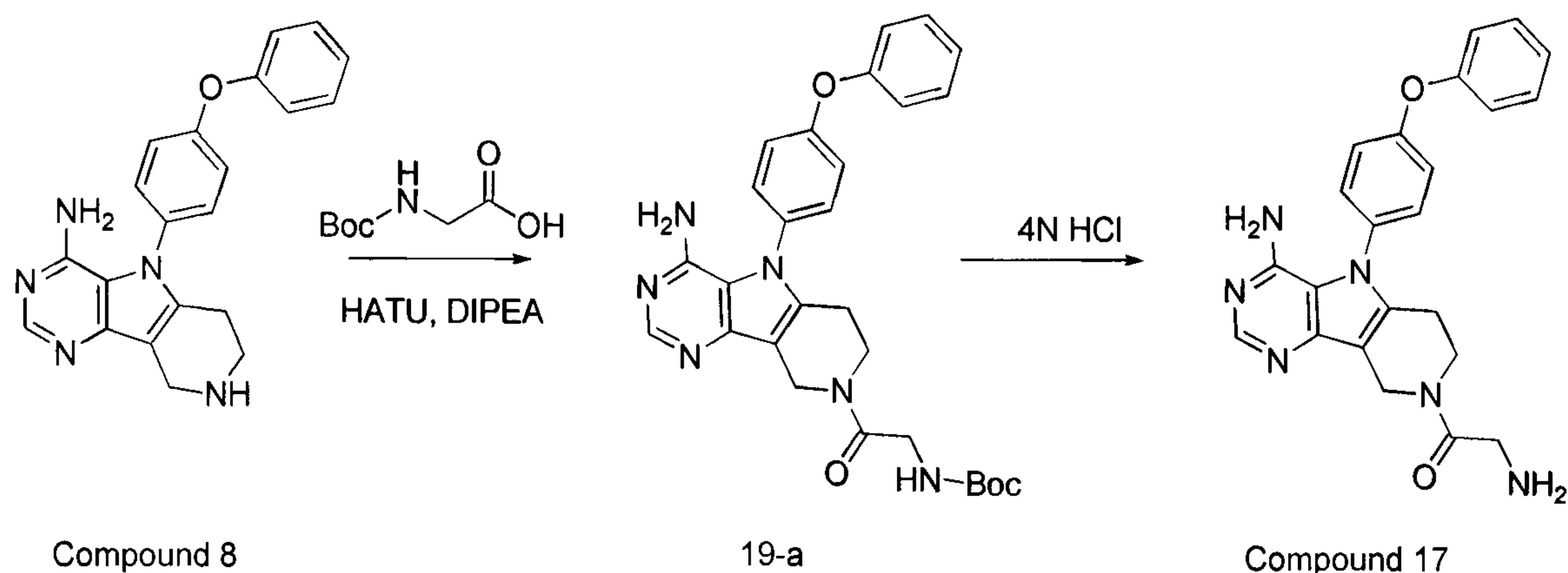


Scheme 17

To a solution of compound 8 (300 mg, 0.84 mmol) in THF (5 mL) and pyridine (5 mL) were sequentially added benzoyl chloride (146 μL , 1.25 mmol) and DMAP (21 mg, 0.17 mmol). The reaction was stirred at 80°C overnight and then cooled to room temperature. A saturated aqueous solution of ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 16 as a white solid. MS (m/z) $\text{M}+\text{H}^+= 462.1$

Synthesis of compound 12**Scheme 18**

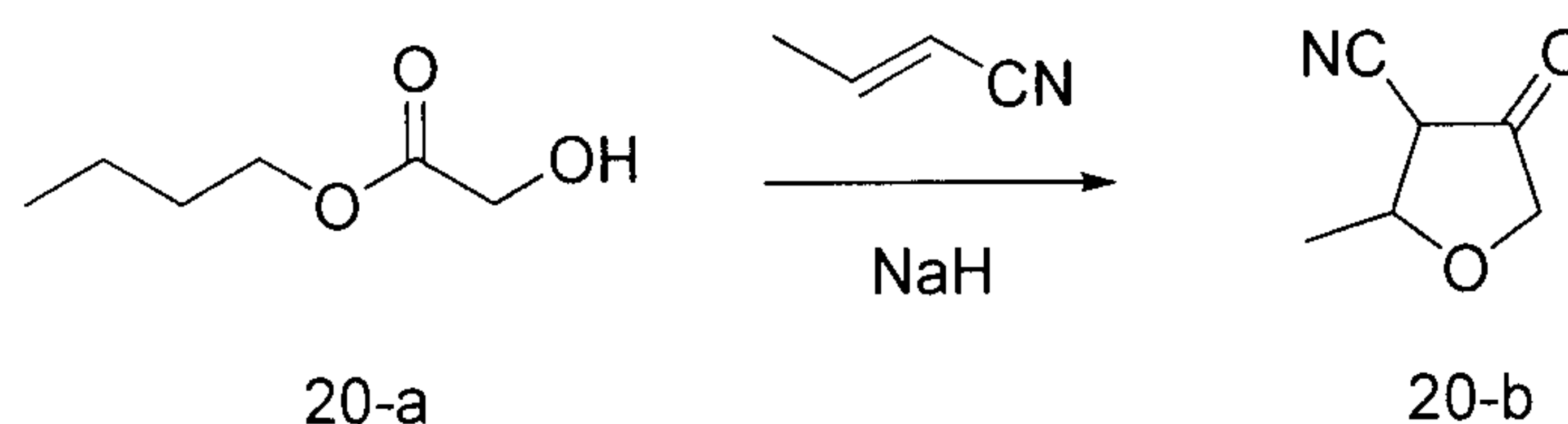
To a solution of compound 8 (200 mg, 0.56 mmol) in THF (5 mL) and pyridine (5
5 mL) were sequentially added benzenesulfonyl chloride (260 mg, 1.47 mmol) and
DMAP (14 mg, 0.11 mmol). The reaction was stirred at 80 °C overnight and then
cooled to room temperature. A saturated aqueous solution of ammonium chloride
and ethyl acetate were added, the organic layer was separated, washed with brine,
dried over MgSO₄, filtered and concentrated in vacuo. Purification by silica gel
10 chromatography provided compound 12 as a yellow solid. MS (m/z) M+H= 498.1

Synthesis of compound 17**Scheme 19****5 Step 1: Intermediate 19-a**

To a solution of compound 8 (300 mg, 0.83 mmol) and Boc-Gly-OH (162 mg, 0.92 mmol) in DMF were added HATU (319 mg, 0.83 mmol) and DIPEA (292 μ L, 1.67 mmol) and the reaction was then stirred at room temperature for 1 hour. Water was added; a precipitate formed and was collected by filtration to provide intermediate 19-a as a beige solid.

Step 2: Compound 24

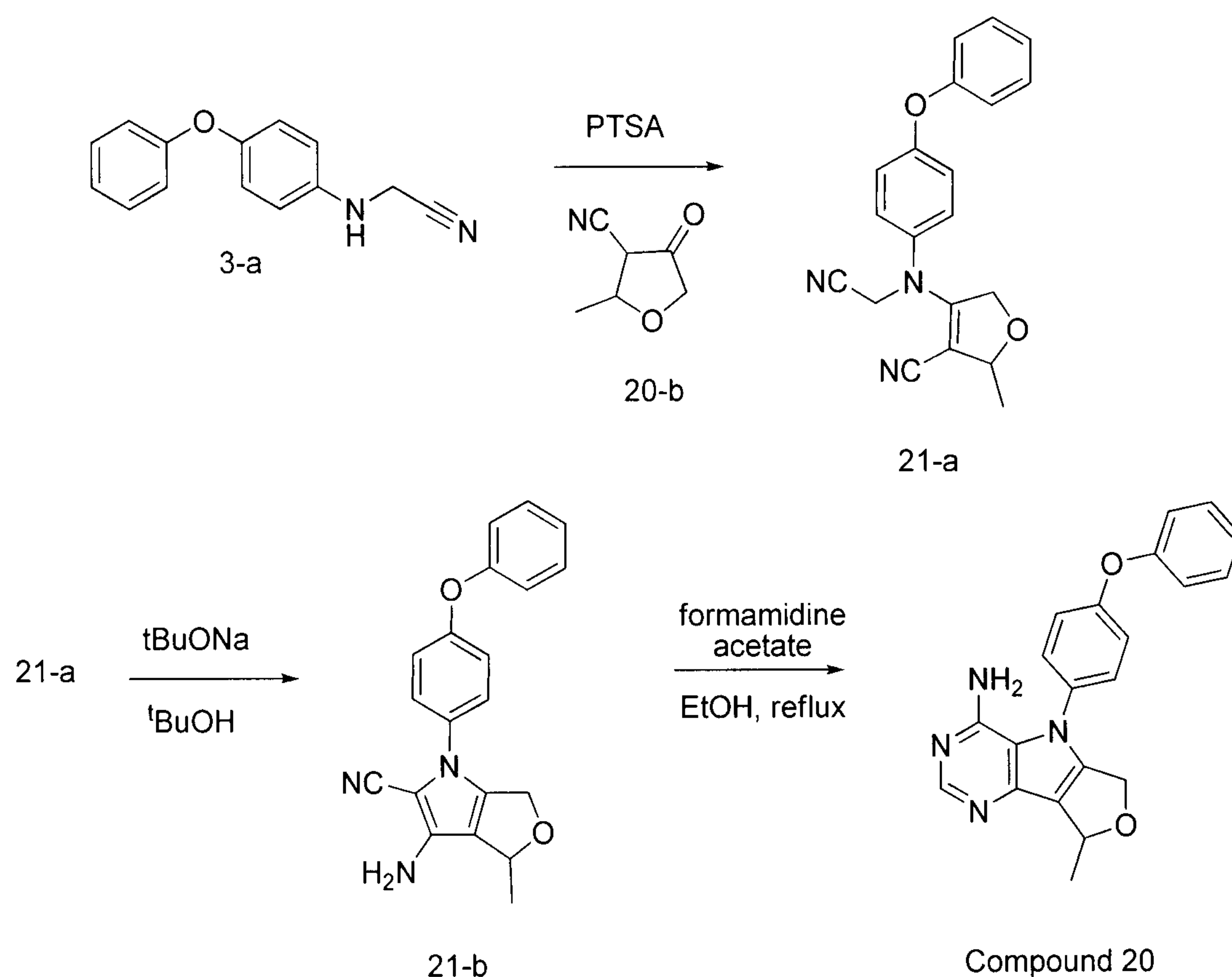
4N HCl (5 ml, 20.00 mmol) in 1,4-dioxane was added to intermediate 19-a (130 mg, 0.253 mmol) in MeOH (5 ml) and the suspension was stirred at room temperature for 1 hour. Volatiles were removed under reduced pressure, ethyl acetate was added to the residue, a precipitate formed and was collected by filtration to provide compound 17·2HCl as a white solid. MS (m/z) M+H= 415.1

Synthesis of Intermediate 20-b**Scheme 20**

A solution of butyl 2-hydroxyacetate 20-a (47.2 g, 357 mmol) in THF (50 mL) was
 5 added dropwise to a suspension of sodium hydride (14.28 g, 357 mmol) in THF
 (250 mL). The mixture is treated at reflux with a solution of crotonitrile (23.96 g,
 357 mmol) in THF (50 mL) and the mixture is held at reflux for 2 hours then cooled
 to room temperature. The solvent was evaporated; 2N NaOH (200 mL) and diethyl
 ether (200 mL) were added to the residue. The organic layer was separated; the
 10 aqueous phase was extracted twice with diethyl ether and then acidified to pH 1
 with concentrated HCl (75 mL). The aqueous phase was then extracted with 3
 times with dichloromethane; the combined organic extracts were dried over
 MgSO₄, filtered and concentrated under vacuum to provide intermediate 20-b as
 beige oil.

15

Synthesis of compound 20



Scheme 21

Step 1: Intermediate 21-a

- 5 To a solution of intermediate 3-a (14.34 g, 63.9 mmol) in toluene (250 mL) were added intermediate 20-b (10.0 g, 80.0 mmol) and 4-methylbenzenesulfonic acid hydrate (1.21 g, 6.39 mmol), the reaction was refluxed for 3 hours using a Dean-Stark and then cooled to room temperature. Saturated aqueous NaHCO₃ and ethyl acetate were added, the organic layer was separated, washed with brine, dried over
- 10 MgSO₄, filtered and concentrated under reduced pressure to provide intermediate 21-a as a beige solid.

Step 2: Intermediate 21-b

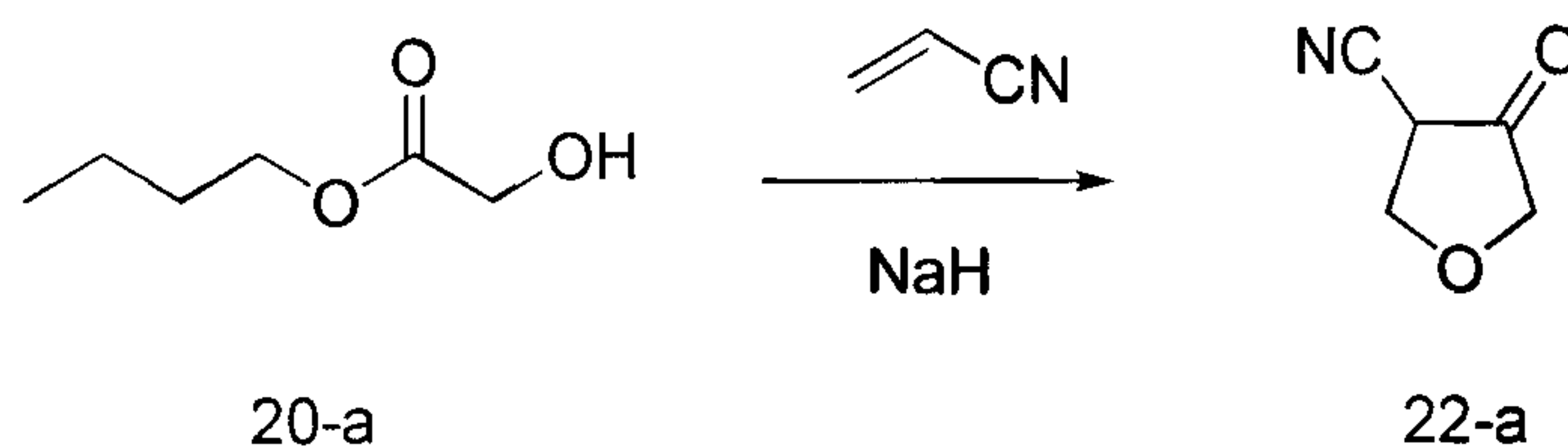
- To a solution of intermediate 21-a (22.0 g, 66.4 mmol) in tert-butanol (330 mL) was added sodium tert-butoxide (7.02 g, 73.0 mmol), the reaction was stirred at
- 15 80 °C for 15 minutes and then cooled to room temperature. 1 N HCl and ethyl

acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated in vacuo. Diethyl ether was added to the residue; a precipitate formed and was collected by filtration to provide intermediate 21-b as beige solid.

5 Step 3: Compound 20

To a solution of intermediate 21-b (22.0 g, 66.4 mmol) in ethanol was added formamidine acetate (27.6 g, 266.0 mmol), the reaction was stirred at reflux for 1.5 hour and then cooled to room temperature. The reaction was concentrated in vacuo to half volume; water was added, a precipitate formed and was collected by
10 filtration. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 20·HCl as a white solid. MS (m/z) $M+H= 359.2$

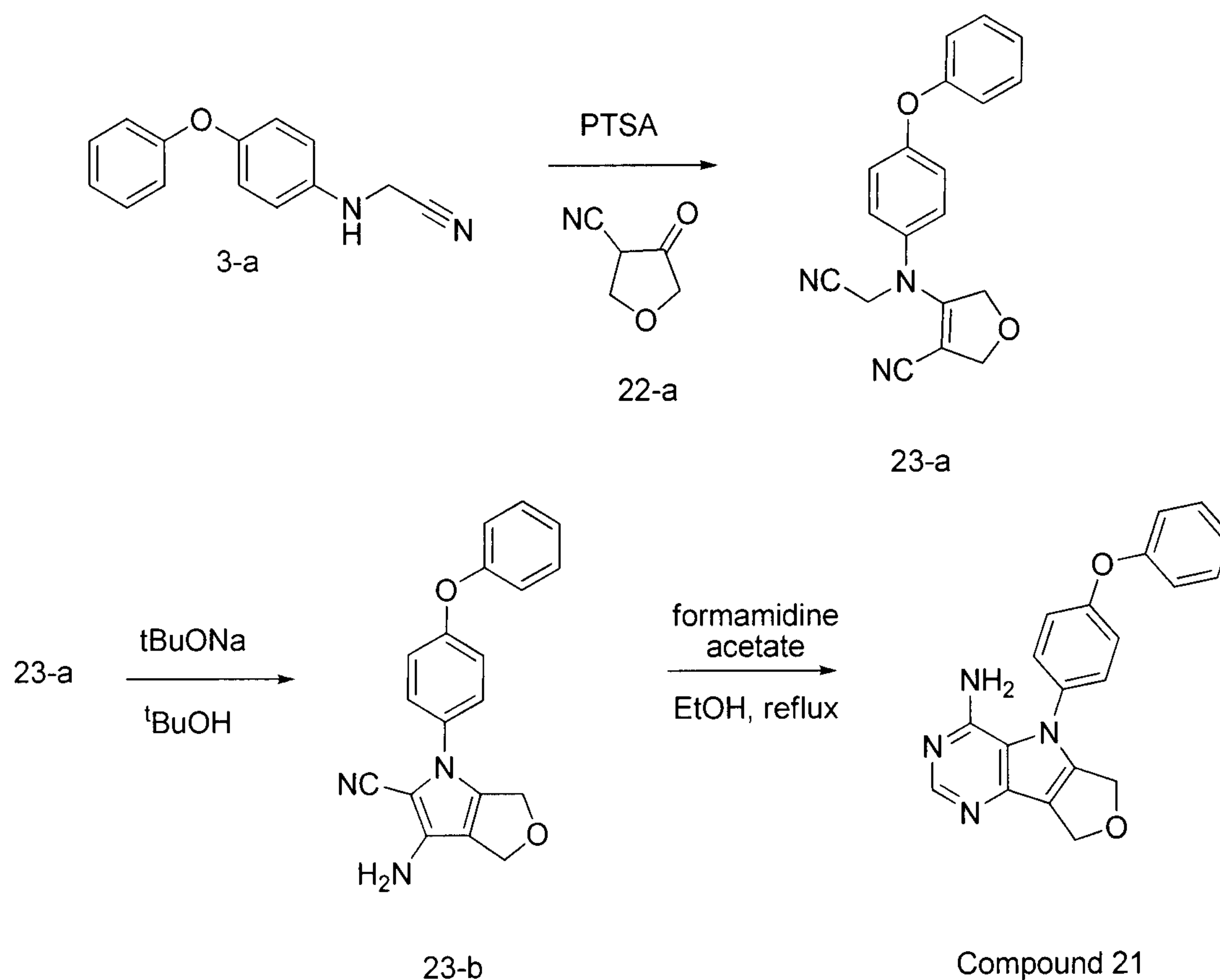
Synthesis of Intermediate 22-a



15 Scheme 22

A solution of butyl 2-hydroxyacetate 20-a (36.3 g, 275 mmol) in THF (50 mL) was added dropwise to a suspension of sodium hydride (10.99 g, 275 mmol) in THF (250 mL). The mixture is treated at reflux with a solution of acrylonitrile (14.57 g, 275.0 mmol) in THF (50 mL) and the mixture is held at reflux for 1.5 hour then cooled to room temperature. A saturated aqueous solution of NaHCO_3 (250 mL) and diethyl ether were added, the organic layer was separated, the aqueous phase was extracted with diethyl ether and acidified to PH 1 with hydrochloric acid and extracted 3 times with diethyl ether. The combined organic extract were dried over
20
25 MgSO_4 and concentrated in vacuo to provide intermediate 22-a as beige solid.

Synthesis of compound 21



Scheme 23

5 Step 1: Intermediate 23-a

To a solution of intermediate 3-a (2.5 g, 11.1 mmol) in toluene (55 mL) were added intermediate 22.a (1.85 g, 16.7 mmol) and 4-methylbenzenesulfonic acid hydrate (212 mg, 1.11 mmol), the reaction was refluxed for 3 hours using a Dean-Stark and then cooled to room temperature. Saturated aqueous NaHCO₃ and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 23-a as a beige solid.

Step 2: Intermediate 23-b

To a solution of intermediate 23-a (3.0 g, 9.45 mmol) in tert-butanol (80 mL) was added sodium tert-butoxide (909 mg, 9.45 mmol), the reaction was stirred at 100

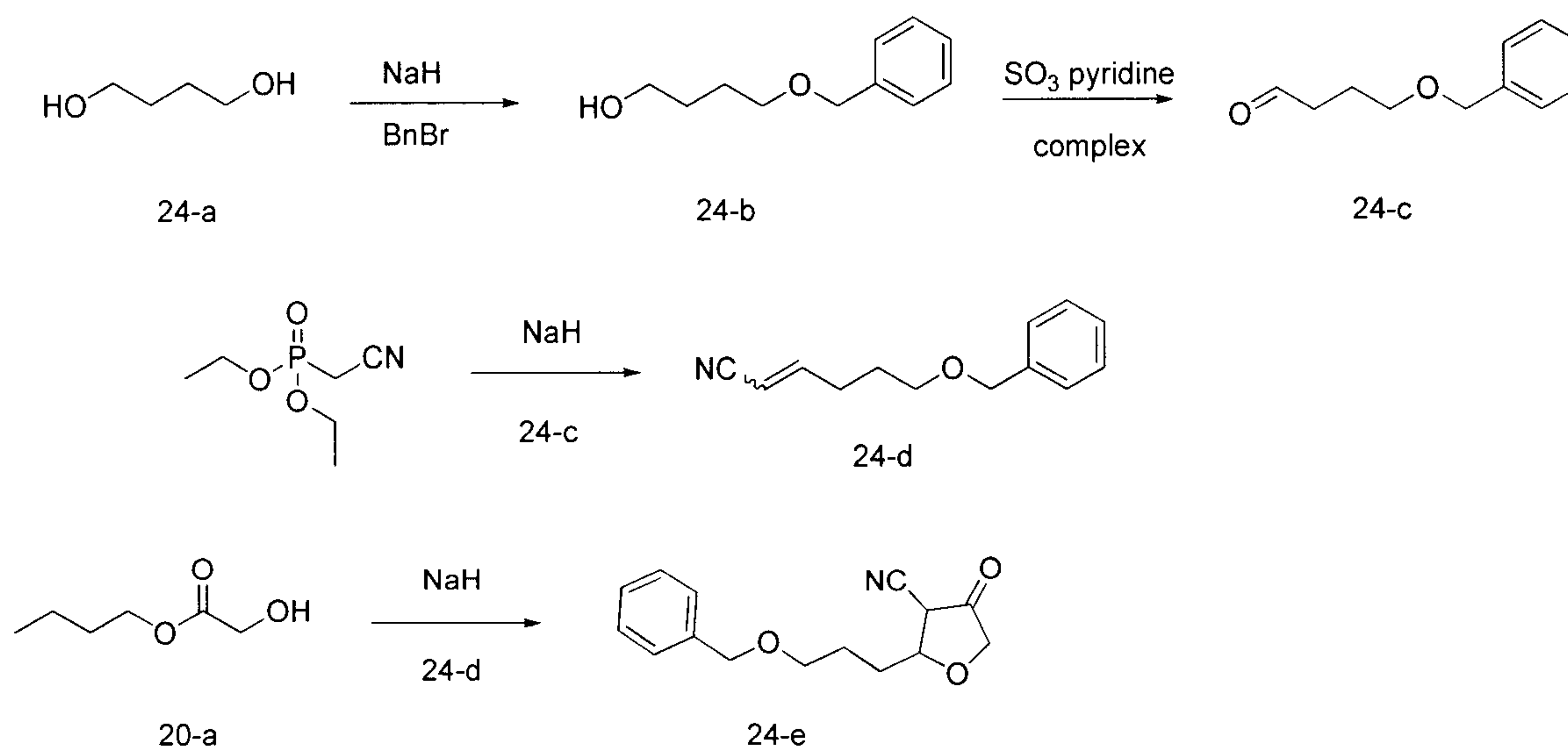
°C for 1 hour and then cooled to room temperature. 1N HCl and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated in vacuo to provide intermediate 23-b as beige solid. MS (m/z) M+H= 318.3

5 Step 3: Compound 21

To a solution of intermediate 23-b (2.8 g, 8.82 mmol) in ethanol was added formamidine acetate (4.59 g, 44.1 mmol), the reaction was stirred at reflux for 3 hours and then cooled to room temperature. The reaction was concentrated to half volume; water was added, a precipitate formed and was collected by filtration.

10 Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 21·HCl as a white solid. MS (m/z) M+H= 345.2

Synthesis of Intermediate 24-e



Scheme 24

Step 1: Intermediate 24-b

To a suspension of sodium hydride (8.86 g, 222 mmol) in THF (500 ml) cooled to 0°C, were added butane-1,4-diol 24-a (19.63 ml, 222 mmol) dropwise over a

period of 15 minutes and the reaction was stirred at 0 °C for 30 minutes. (bromomethyl)benzene (23.71 ml, 199 mmol) was added dropwise over a period of 15 minutes followed by tetrabutylammonium bromide (7.14 g, 22.15 mmol). The reaction was allowed to warm to room temperature and stirred overnight. The reaction mixture was then added to 5% HCl at 0 °C with vigorous stirring, diethyl ether was added, The organic layer was separated, the aqueous phase was extracted twice with diethyl ether, the combined organic extracts were dried over anhydrous MgSO_4 , filtered and concentrated in vacuo to provide intermediate 24-b as yellow oil.

Step 2: Intermediate 24-c

To a solution of intermediate 24-b (10.0 g, 55.5 mmol) in dichloromethane (200 mL) cooled to 0 °C was added DMSO (15.76 ml, 222 mmol) and DIPEA (33.8 ml, 194 mmol). SO_3 pyridine complex (17.66 g, 111 mmol) in DMSO (15 mL) was then added and the mixture was stirred for 2 hours at 0°C. Water and ethyl acetate were added; the organic layer was separated, washed with water, saturated aqueous NaHCO_3 and brine, dried over MgSO_4 , filtered and concentrated under reduced pressure to provide intermediate 24-c as yellow oil.

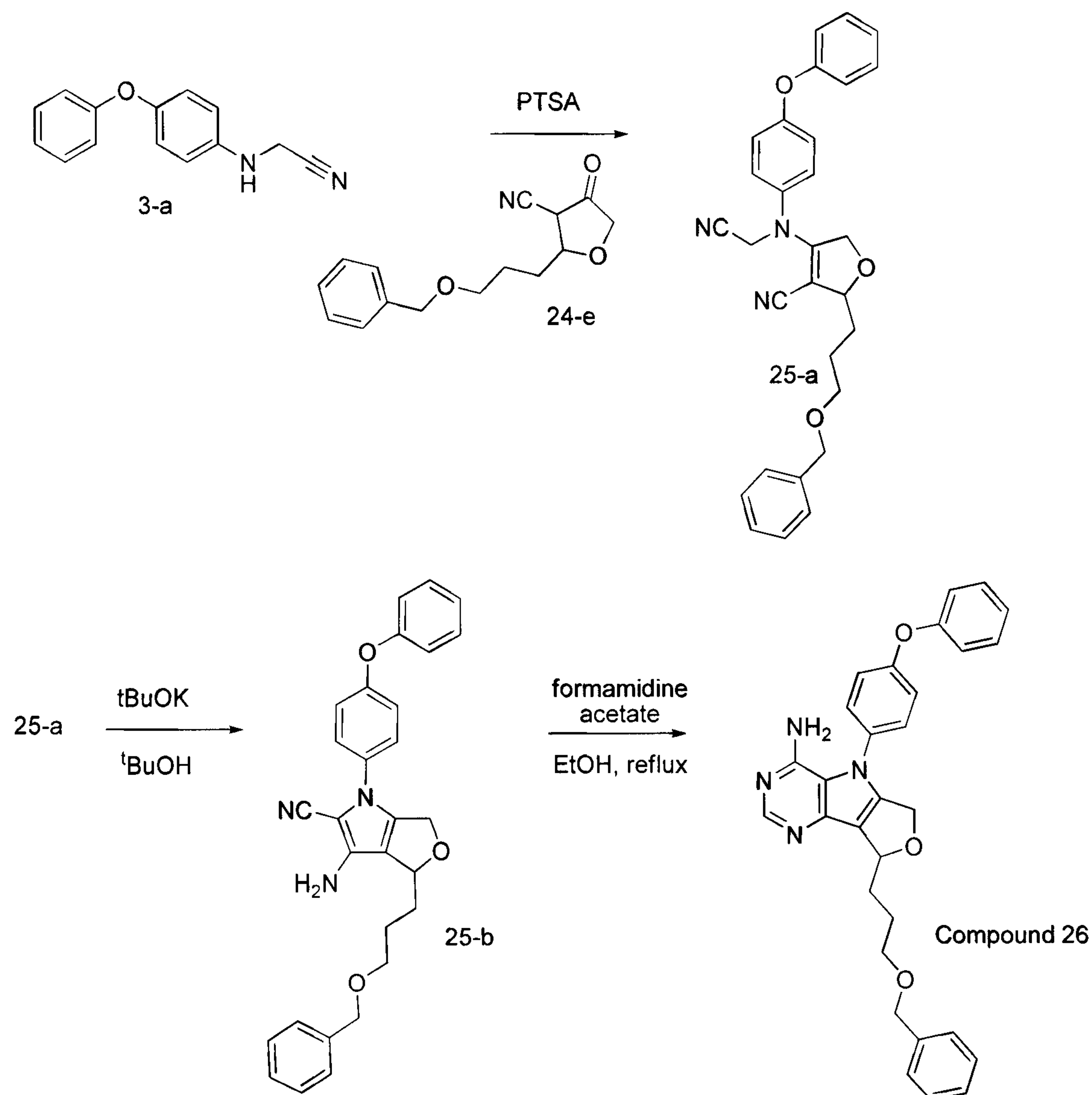
Step 3: Intermediate 24-d

To a suspension of sodium hydride (2.22 g, 55.5 mmol) in THF (50 ml) cooled to 0°C, was added dropwise a solution of diethyl cyanomethylphosphonate (9.84 g, 55.5 mmol) in THF (50 mL), after stirring for 15 minutes a solution of intermediate 24-c (9.9 g, 55.5 mmol) in THF (50 mL) was then added dropwise, the reaction mixture was then allowed to warm to room temperature and stirred overnight. Water and diethyl ether were added, the organic layer was separated, the aqueous phase was extracted with diethyl ether, and the combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 24-d as yellow oil.

Step 3: Intermediate 24-e

A solution of butyl 2-hydroxyacetate 20-a (5.12 g, 38.8 mmol) in THF (25 mL) was added dropwise to a suspension of sodium hydride (1.55 g, 38.8 mmol) in THF (50 mL). The mixture is treated at reflux with intermediate 24-d (7.8 g, 38.8 mmol) in THF (25 mL) and the mixture is held at reflux for 3 hours then cooled to room temperature. The solvent was evaporated; 2N NaOH (100 mL) and diethyl ether (100 mL) were added to the residue. The organic layer was separated, the aqueous phase was extracted twice with diethyl ether and then acidified to pH 1 with concentrated HCl . The aqueous layer was then extracted with 3 times with dichloromethane; the combined organic extracts were dried over MgSO_4 , filtered and concentrated under reduced pressure to provide intermediate 24-e as beige oil.

Synthesis of compound 26



Scheme 25

5

Step 1: Intermediate 25-a

To a solution of intermediate 3-a (692 mg, 3.10 mmol) in toluene (20 mL) were added intermediate 24-e (1.20 g, 4.63 mmol) and 4-methylbenzenesulfonic acid hydrate (59 mg, 0.30 mmol), the reaction was refluxed overnight using a Dean-

Stark and then cooled to room temperature. Saturated aqueous NaHCO_3 and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure to provide intermediate 25-a as brown oil.

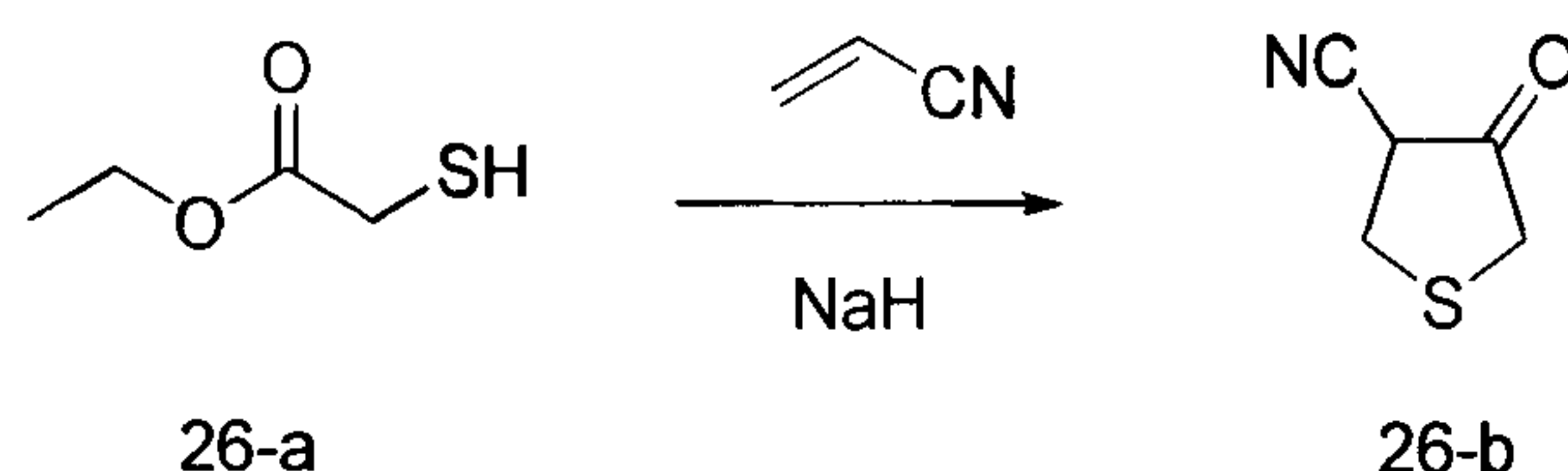
5 **Step 2: Intermediate 25-b**

To a solution of intermediate 25-a (1.5 g, 3.22 mmol) in tert-butanol (16 mL) was added a 1.0 M solution of potassium tert-butoxide in THF (3.54 mL, 3.54 mmol), the reaction was stirred at 80 °C for 30 minutes and then cooled to room temperature. 1N HCl and ethyl acetate were added, the organic layer was
 10 separated, washed with brine, dried over MgSO_4 , filtered and concentrated in vacuo to provide intermediate 25-b as beige solid.

Step 3: Compound 26

To a solution of intermediate 25-b (1.5 g, 3.22 mmol) in ethanol was added formamidine acetate (2.68 g, 25.8 mmol), the reaction was stirred at reflux for 3
 15 hours and then cooled to room temperature. The reaction was concentrated in vacuo to half volume; water and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound
 20 26·HCl as a white solid. MS (m/z) $\text{M}+\text{H}^+$ = 493.3

Synthesis of Intermediate 26-b

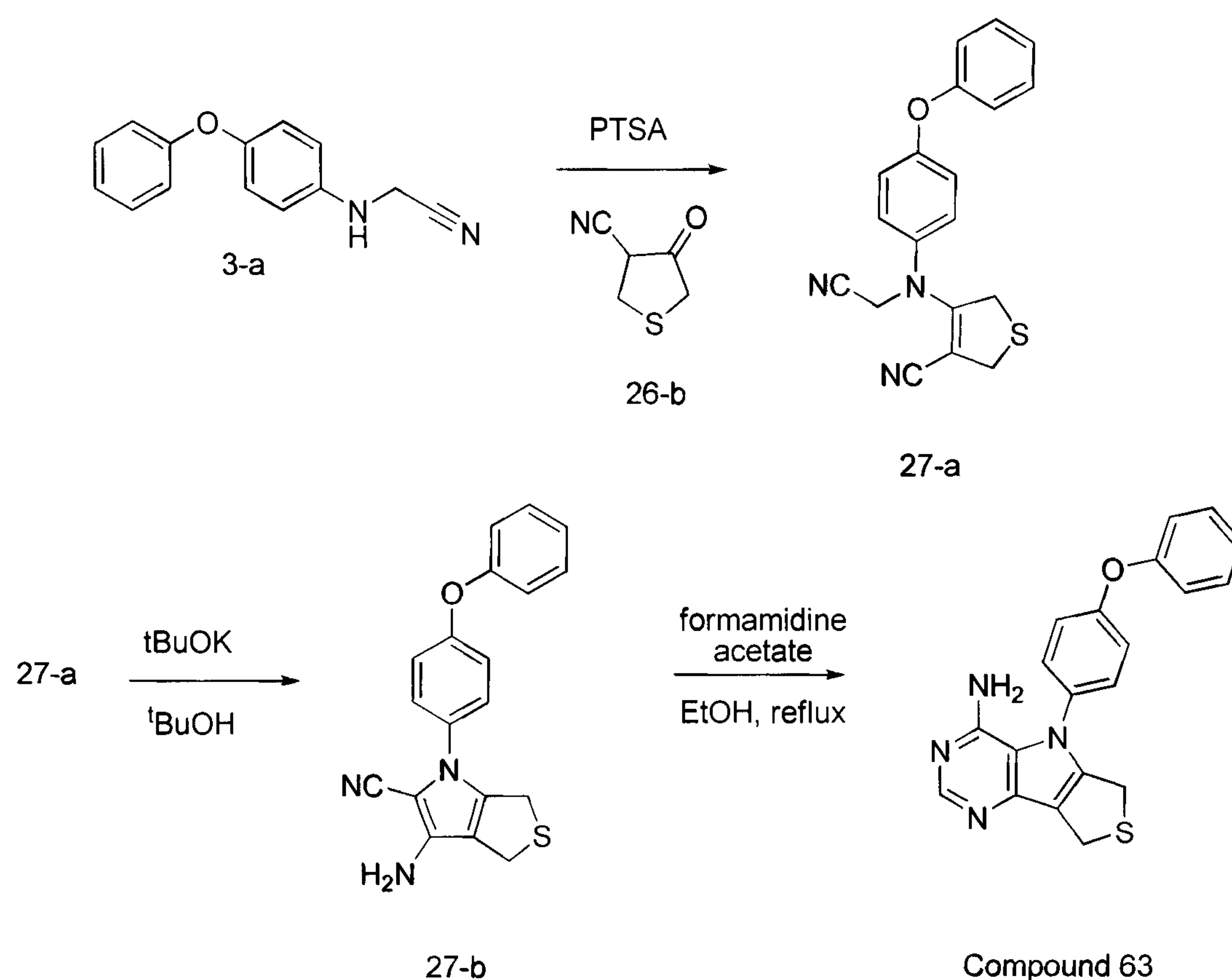


Scheme 26

25 To a 25% solution of sodium methoxide in methanol (37.7 mL, 165 mmol) cooled to 0°C was sequentially added dropwise ethyl 2-mercaptoacetate (13 mL, 118 mmol)

and acrylonitrile (7.76 ml, 118 mmol) and the reaction was stirred at reflux for 1 hour. The solvent was evaporated; water and diethyl ether were added to the residue. The organic layer was separated; the aqueous phase was acidified to PH=1 with concentrated HCl. The aqueous phase was then extracted 3 times with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure to provide intermediate 26-b as beige oil.

Synthesis of compound 63



Scheme 27

Step 1: Intermediate 27-a

To a solution of intermediate 3-a (5.29 g, 23.59 mmol) in toluene (100 mL) were added intermediate 26-b (3.0 g, 23.59 mmol) and 4-methylbenzenesulfonic acid hydrate (449 mg, 2.35 mmol), the reaction was refluxed for 4 hours using a Dean-Stark and then cooled to room temperature. Saturated aqueous NaHCO_3 and ethyl

acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 27-a as beige solid.

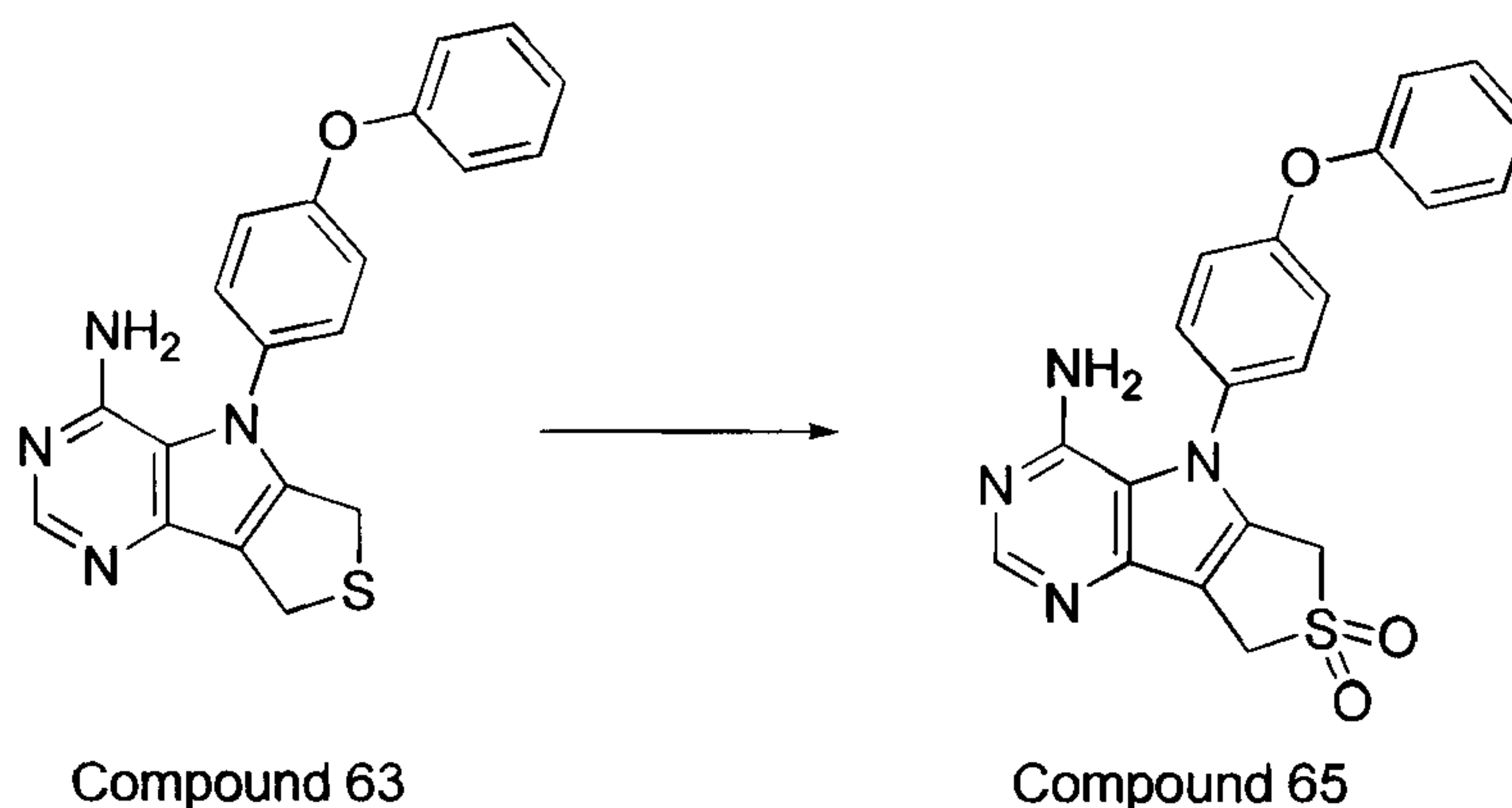
Step 2: Intermediate 27-b

5 To a solution of intermediate 27-a (8.0 g, 24.0 mmol) in tert-butanol (100 mL) was added a 1.0 M solution of potassium tert-butoxide in THF (23.99 mL, 23.99 mmol), the reaction was stirred at 90 °C for 2 hours and then cooled to room temperature. Water and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated in vacuo to provide intermediate
10 27-b as beige solid.

Step 3: Compound 63

To a solution of intermediate 27-b (8.0 g, 23.99 mmol) in ethanol was added formamidine acetate (19.98 g, 192 mmol), the reaction was stirred at reflux overnight and then cooled to room temperature. The reaction was concentrated in
15 vacuo to half volume; water and ethyl acetate were added, the organic layer was separated, washed with saturated aqueous NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided compound 63 as beige solid. MS (m/z) $\text{M}+\text{H}=361.2$

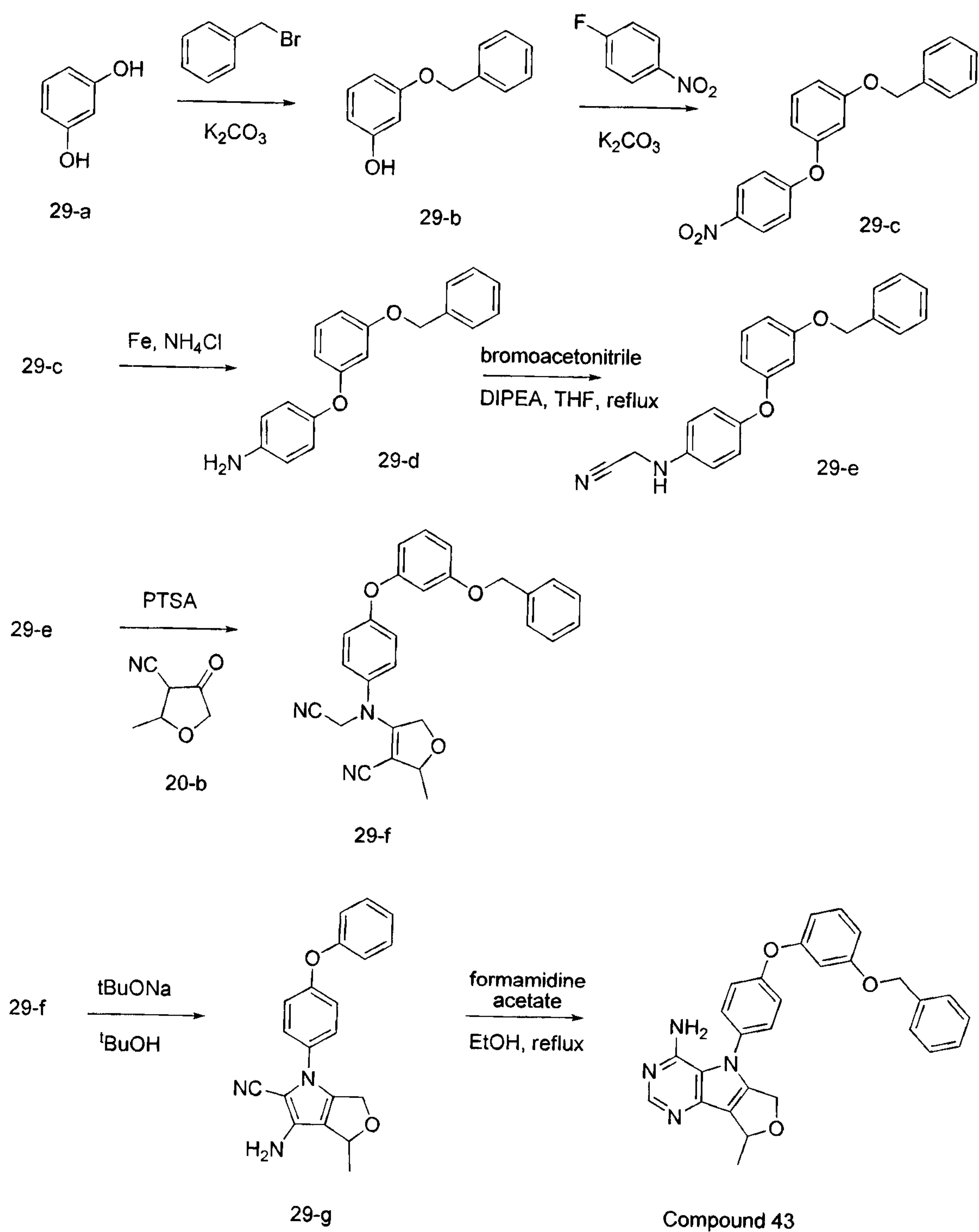
20 Synthesis of compound 65



Scheme 28

To a solution of compound 63 (1 g, 2.77 mmol) in a 1:1:1 mixture of tetrahydrofuran/methanol/water was added oxone (1.70 g, 2.77 mmol) and the
5 solution was stirred at room temperature for 1 hour. Water and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided compound 65 as white solid. MS (m/z) $\text{M}+\text{H}^+$ = 393.2

Synthesis of compound 43



Scheme 29**Step 1: Intermediate 29-b**

Benzyl bromide (27.0 ml, 227 mmol) was added dropwise to a stirred suspension of resorcinol (25 g, 227 mmol) and potassium carbonate (31.4 g, 227 mmol) in acetone (150 ml) and the reaction was heated under reflux overnight. Volatiles were removed under reduced pressure. Water and ethylacetate were added, the organic layer was separated, washed with brine dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 29-b as beige oil.

Step 2: Intermediate 29-c

To a solution of 1-fluoro-4-nitrobenzene (12.17 g, 86 mmol) in DMSO (150 ml) were added intermediate 29-b (19.0 g, 95 mmol), K₂CO₃ (13.11 g, 95 mmol) and the reaction was stirred at 150 °C for 18 hours. A saturated aqueous solution of ammonium chloride and diethyl ether were added, the organic layer was separated, the aqueous layer was extracted with diethyl ether, the combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to provide intermediate 29-c as brown solid.

Step 3: Intermediate 29-d

To a solution of intermediate 29-c (14.1 g, 43.9 mmol) in ethanol (150 ml) and water (50 ml) were sequentially added ammonium chloride (11.74 g, 219 mmol), iron (9.80 g, 176 mmol) and the reaction mixture was stirred at reflux overnight and then cooled to room temperature. Volatiles were removed in vacuo. Water and ethylacetate were added; the organic layer was separated, washed with saturated aqueous NaHCO₃ and brine, dried over MgSO₄, filtered and concentrated under reduced pressure to provide intermediate 29-d as beige solid.

Step 4: Intermediate 29-e

To a solution of intermediate 29-d (10.8 g, 37.1 mmol) and 2-bromoacetonitrile (5.34 g, 44.5 mmol) in THF (100 mL) was added DIPEA (7.77 ml, 44.5 mmol) at room temperature and the reaction was stirred at 80°C overnight. A Saturated aqueous solution of ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with a saturated aqueous solution of ammonium chloride and brine, dried over MgSO_4 , filtered and concentrated under reduced pressure to provide intermediate 29-e as brown oil.

Step 5: Intermediate 29-f

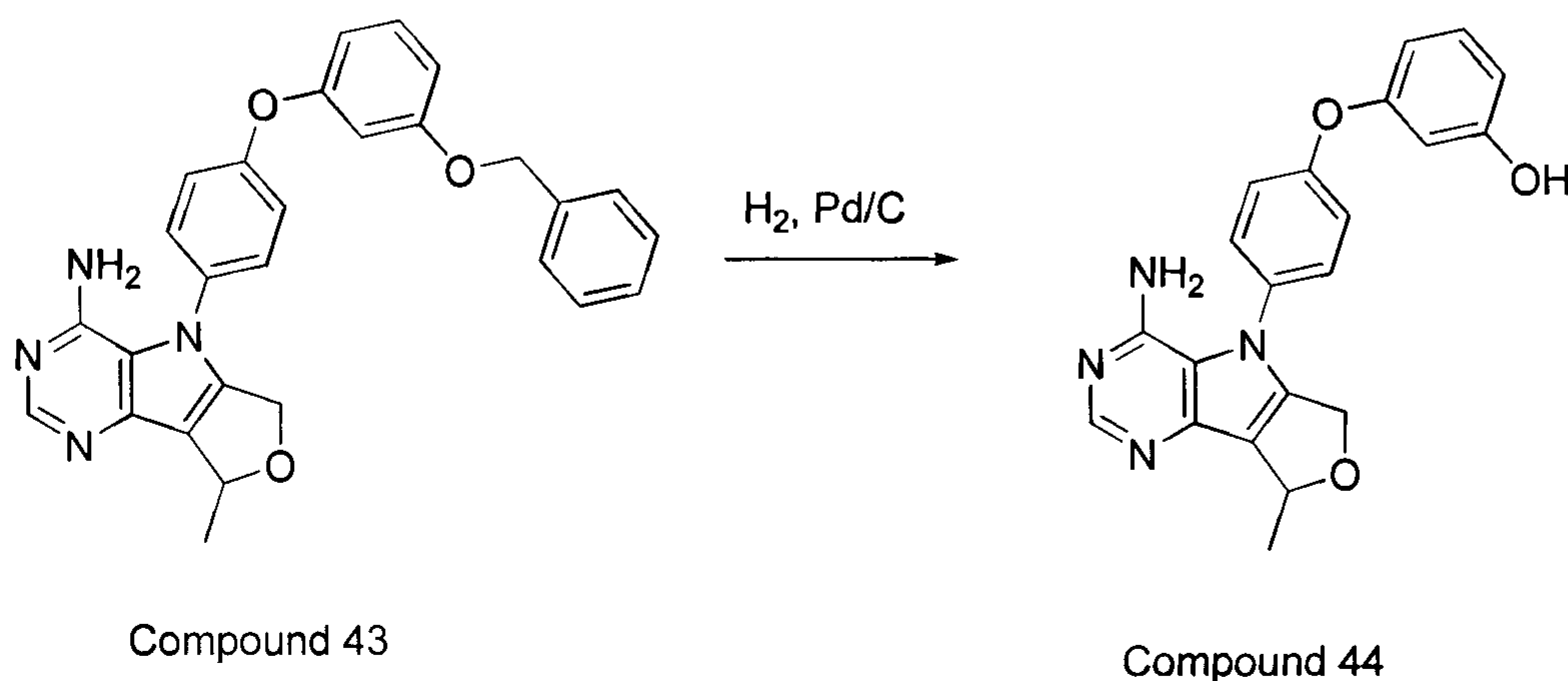
To a solution of intermediate 29-e (12.5 g, 37.8 mmol) in toluene (50 ml) were added intermediate 20-b (7.10 g, 56.8 mmol) and 4-methylbenzenesulfonic acid hydrate (720 mg, 3.78 mmol). The reaction was refluxed for 6 hours using a dean-stark and then cooled to room temperature. A saturated aqueous solution of NaHCO_3 and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 29-f as a beige foam.

Step 6: Intermediate 29-g

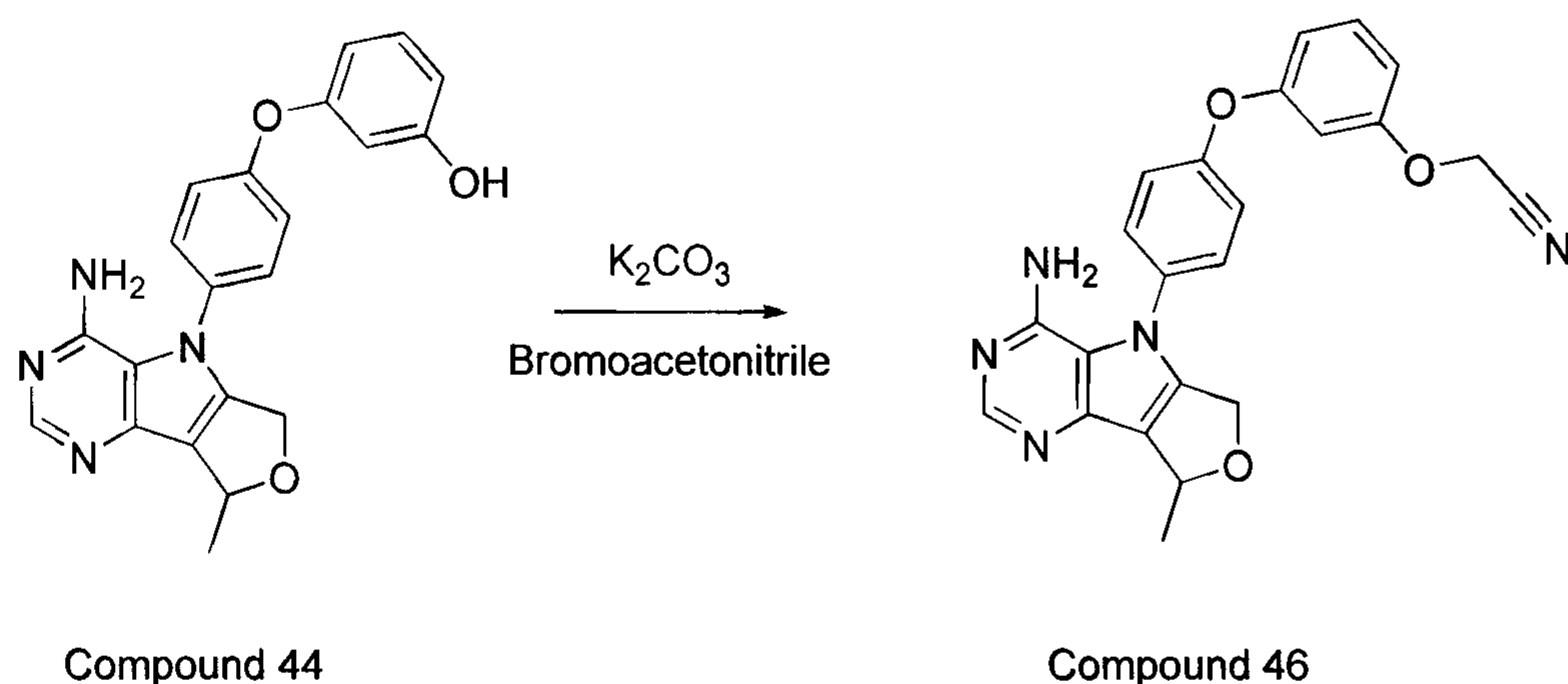
To a solution of intermediate 29-f (8.2 g, 18.74 mmol) in tert-butanol (50.0 ml) was added potassium tert-butoxide (2.31 g, 20.62 mmol) and the reaction was stirred at 80 °C for 1 hour and then cooled to room temperature. A Saturated aqueous solution of ammonium chloride and ethyl acetate were added, the organic layer was separated, the aqueous phase was extracted with ethyl acetate, the combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure to provide intermediate 29-g as beige solid.

Step 8: Compound 43

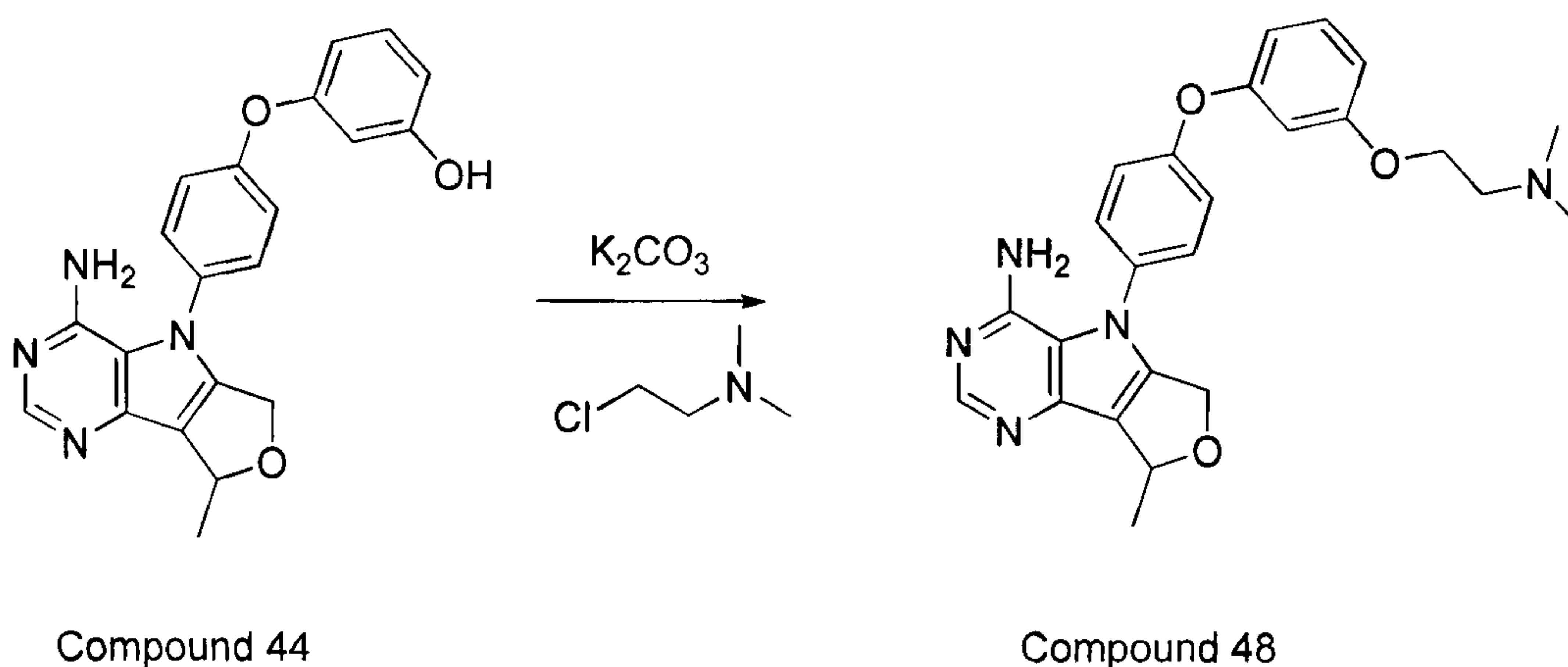
To a solution of intermediate 29-g (8.20 g, 18.74 mmol) in ethanol (75 ml) was added formamidine acetate (15.61 g, 150.0 mmol) and the reaction was stirred at 80 °C for 3 hours and then cooled to room temperature. Volatiles were removed in vacuo. A saturated aqueous solution of NaHCO₃ and ethyl acetate were added to the residue, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 43·HCl as a white solid. MS (m/z) M+H= 465.2

Synthesis of compound 44**Scheme 30**

To a solution of compound 43 (3.85 g, 8.29 mmol) in methanol and stirred under nitrogen was added 10% Pd/C (882 mg, 8.29 mmol). The reaction mixture was purged with H₂ and stirred at room temperature for 3 hours. The reaction was then filtered through celite and the filtrate was concentrated in vacuo. Ethyl acetate was added to the residue; a precipitate formed and was collected by filtration to provide compound 44 as a white solid. MS (m/z) M+H= 375.2

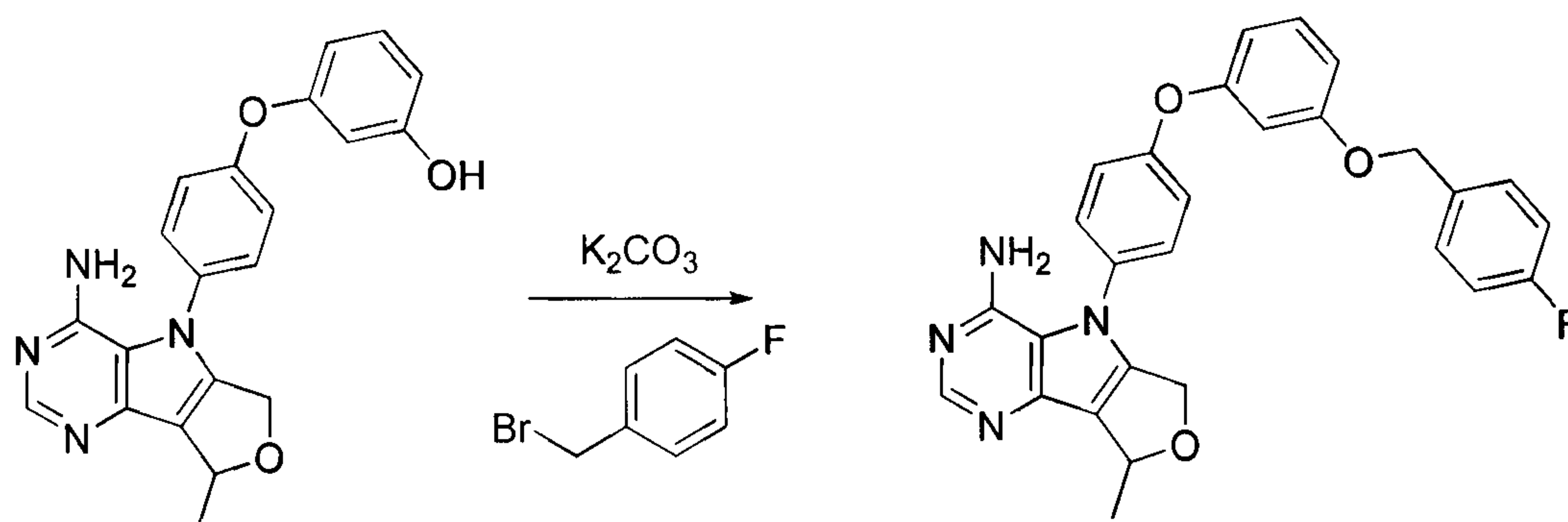
Synthesis of compound 46**Scheme 31**

- 5 To a solution of compound 44 (129 mg, 0.345 mmol) in DMF (3 ml) were sequentially added potassium carbonate (99 mg, 0.718 mmol), bromoacetonitrile (30 μ l, 0.43 mmol) and the solution was stirred at 90 °C overnight. Water and ethyl acetate were added, the organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by
- 10 reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 46·HCl as a white solid. MS (m/z) M+H= 414.2

Synthesis of compound 48

Scheme 32

To a solution of compound 44 (200 mg, 0.53 mmol) in DMF (3 ml) were sequentially added potassium carbonate (221 mg, 1.60 mmol), tetrabutylammonium bromide (9.87 mg, 0.027 mmol) and 2-chloro-N,N-dimethylethanamine hydrochloride salt (85 mg, 0.588 mmol) and the solution was stirred at room temperature for 3 hours. Water and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 48·2HCl as a white solid. MS (m/z) $\text{M}+\text{H}^+=446.4$

Synthesis of compound 49

15 Compound 44

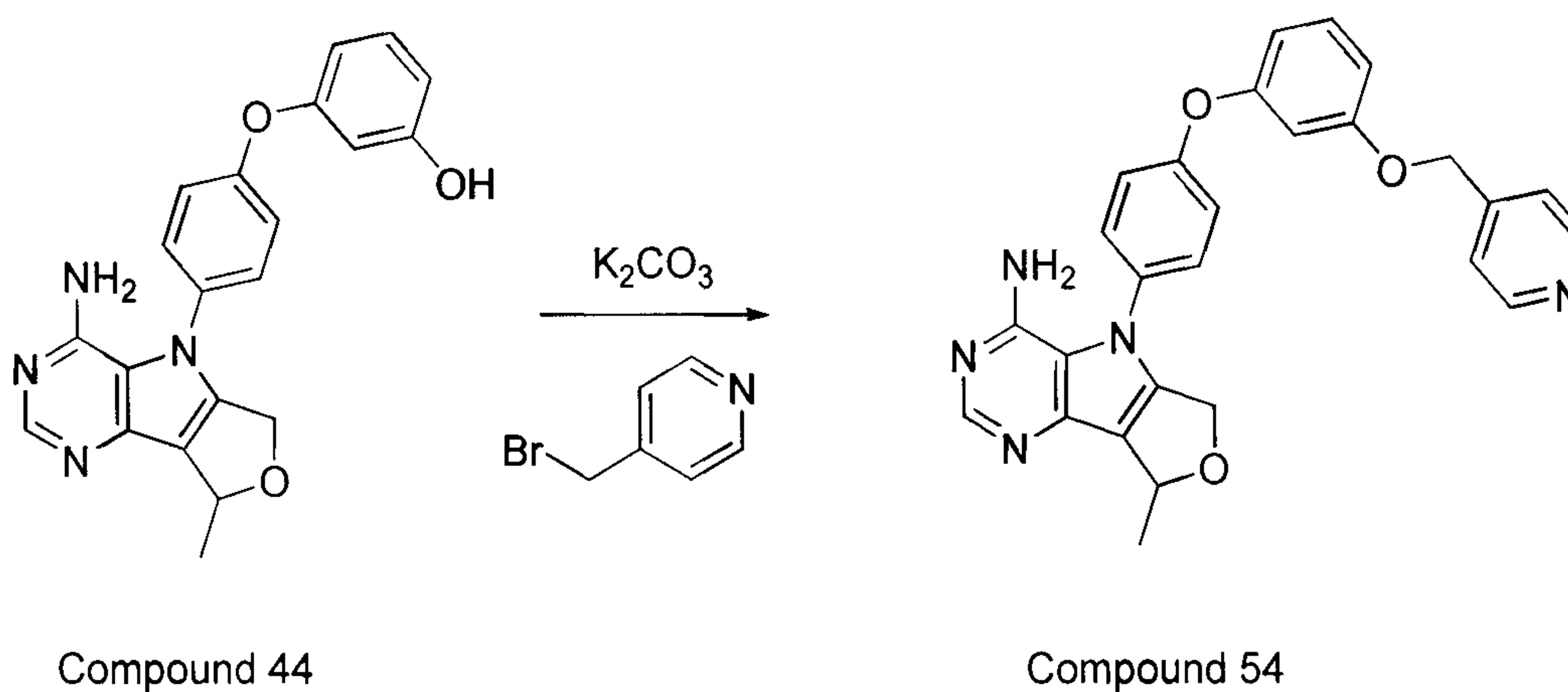
Compound 49

Scheme 33

To a solution of compound 44 (200 mg, 0.53 mmol) in DMF (3 ml) were sequentially added potassium carbonate (200 mg, 1.44 mmol), 4-Fluorobenzyl bromide (111 mg, 0.58 mmol) and the reaction was stirred for 4 hours at room temperature. Water and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated under reduced

pressure. Purification by silica gel chromatography provided compound 49 as a white solid. MS (m/z) M+H= 483.2

Synthesis of compound 54

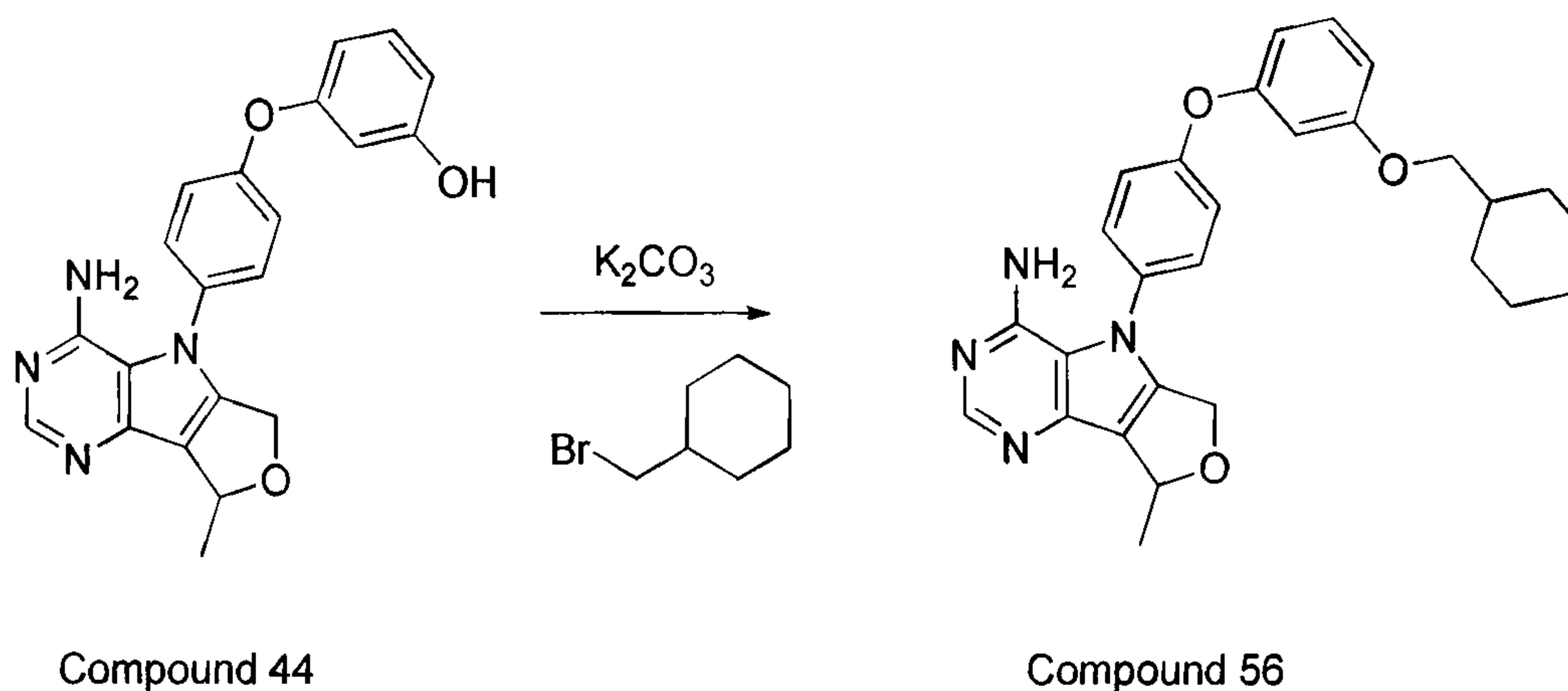


Scheme 34

To a solution of compound 44 (200 mg, 0.53 mmol) in DMF (3 ml) were sequentially added potassium carbonate (200 mg, 1.447 mmol), 4-(bromomethyl)pyridine, HBr salt (149 mg, 0.58 mmol) and the reaction was stirred at room temperature for 4 hours. Water and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 54·2HCl as a white solid. MS (m/z) M+H= 466.2

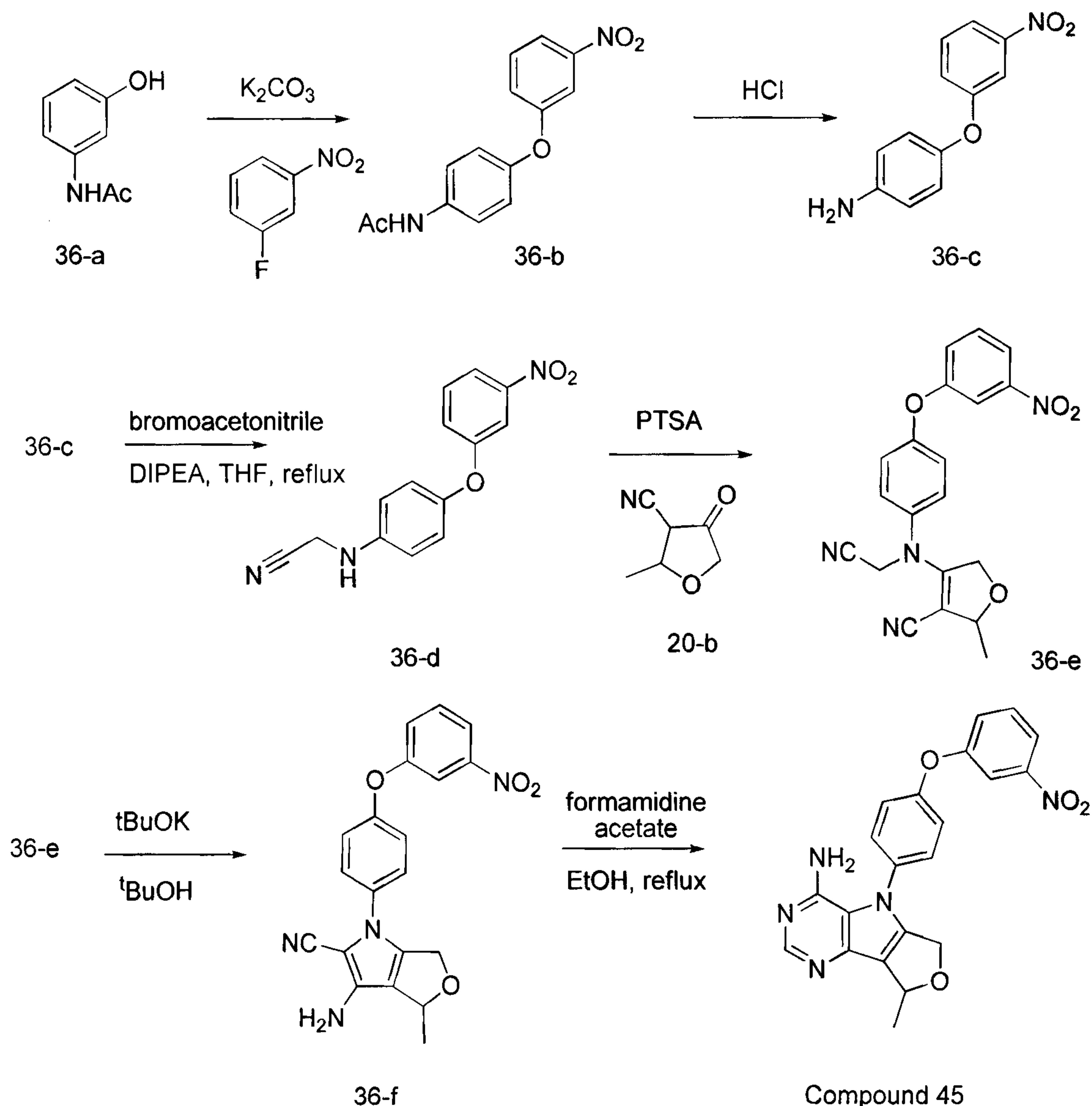
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15

Synthesis of compound 56**Scheme 35**

- 5 To a solution of compound 44 (200 mg, 0.53 mmol) in DMF (3 mL) were sequentially added potassium carbonate (148 mg, 1.068 mmol), (bromomethyl)cyclohexane (104 mg, 0.588 mmol) and the solution was stirred at 90 °C for 18 hours. Water and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated under
- 10 reduced pressure. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 56·HCl as a white solid. MS (m/z) $M+H= 471.3$

Synthesis of compound 45



Scheme 36

Step 1: Intermediate 36-b

- To a solution of N-(4-hydroxyphenyl)acetamide 36-a (10 g, 66.2 mmol) and 1-fluoro-3-nitrobenzene (8.49 g, 60.1 mmol) in DMF (100 ml) was added potassium carbonate (9.14 g, 66.2 mmol) and the reaction was heated at 150 °C overnight and then cooled to room temperature. The reaction was poured into one liter of ice-cold water and stirred for 30 minutes. A precipitate formed and was collected by

filtration, washed with water and dried under vacuo to provide intermediate 36-b as a yellow solid.

Step 2: Intermediate 36-c

5 Intermediate 36-b (11.9 g, 43.7 mmol) was heated to 95 °C in 70 mL of 12N HCl for 48 hours. After cooling to room temperature, a precipitate formed and was collected by filtration, washed with diethyl ether to provide intermediate 36-c as beige solid.

10 **Step 3: Intermediate 36-d**

To a solution of intermediate 36-c (7.20 g, 27.0 mmol) and 2-bromoacetonitrile (4.21 g, 35.1 mmol) in THF (50 mL) was added DIPEA (14.15 ml, 81.0 mmol) at room temperature and the reaction was stirred at 80°C overnight. A Saturated aqueous solution of ammonium chloride and ethyl acetate were added, the organic
15 layer was separated, washed with a saturated aqueous solution of ammonium chloride and brine, dried over MgSO₄, filtered and concentrated under reduced pressure to provide intermediate 36-d as beige solid.

Step 4: Intermediate 36-e

20 To a solution of intermediate 36-d (3.0 g, 11.14 mmol) in toluene (50 ml) were added intermediate 20-b (2.79 g, 22.28 mmol) and 4-methylbenzenesulfonic acid hydrate (212 mg, 1.11 mmol). The reaction was refluxed for 3 hours using a dean-stark and then cooled to room temperature. A saturated aqueous solution of NaHCO₃ and ethyl acetate were added, the organic layer was separated, washed
25 with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 36-e as a yellow oil.

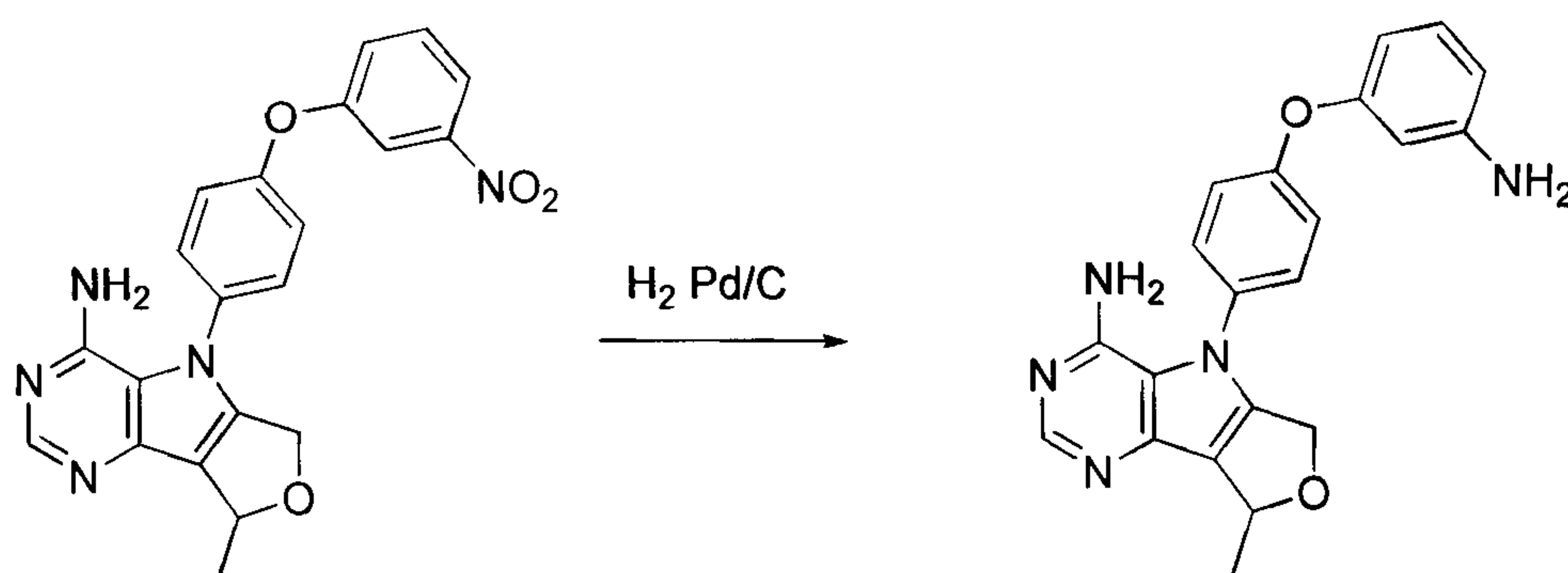
Step 5: Intermediate 36-f

To a solution of intermediate 36-e (1.0 g, 2.66 mmol) in tert-butanol (13 mL) was added a 1.0 M solution of potassium tert-butoxide in THF (2.92 mL, 2.92 mmol), the reaction was stirred at 50 °C for 30 minutes and then cooled to room

- 5 temperature. A saturated aqueous solution of ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure to provide intermediate 36-f as beige solid.

Step 8: Compound 45

- 10 To a solution of intermediate 36-f (1.0 g, 2.66 mmol) in ethanol (33 ml) was added formamidine acetate (2.21 g, 21.26 mmol) and the reaction was stirred at 80 °C for 2 hours and then cooled to room temperature. Volatiles were removed in vacuo. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the residue, the organic layer was separated, washed with brine, dried over MgSO_4 ,
 15 filtered and concentrated under reduced pressure. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 45·HCl as a white solid. MS (m/z) $\text{M}+\text{H}=404.2$

Synthesis of compound 47

Compound 45

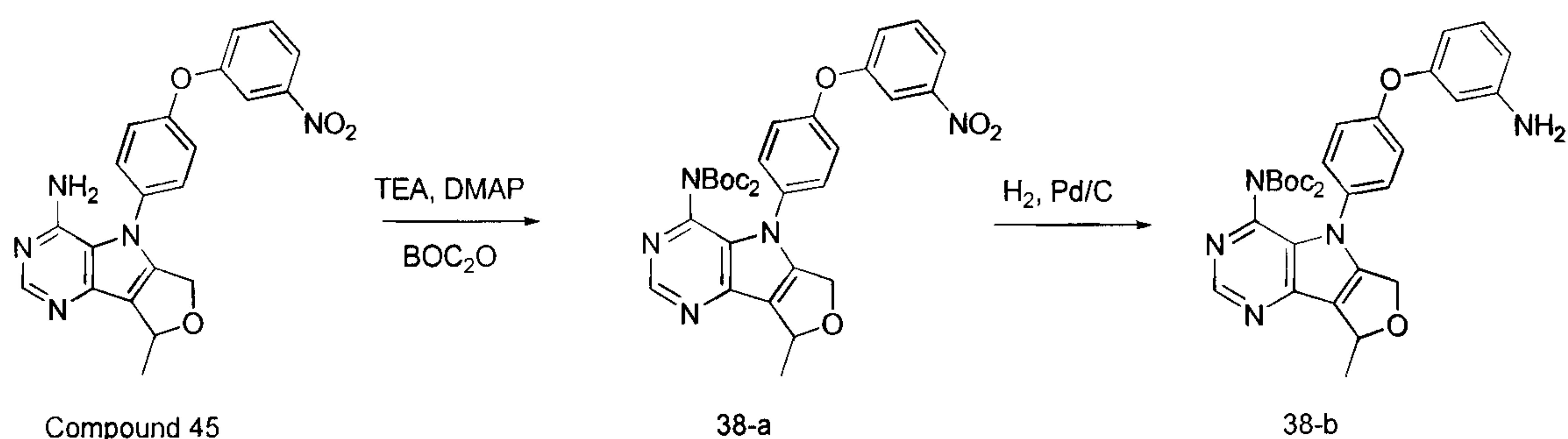
Compound 47

Scheme 37

To a solution of compound 45 (55 mg, 0.14 mmol) in methanol and stirred under nitrogen was added 10% Pd/C (51 mg, 0.05 mmol). The reaction mixture was purged with H₂ and stirred at room temperature overnight. The reaction was then
 5 filtered through celite and the filtrate was concentrated in vacuo. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 47·2HCl as yellow solid. MS (m/z) M+H= 374.2

Synthesis of intermediate 38-b

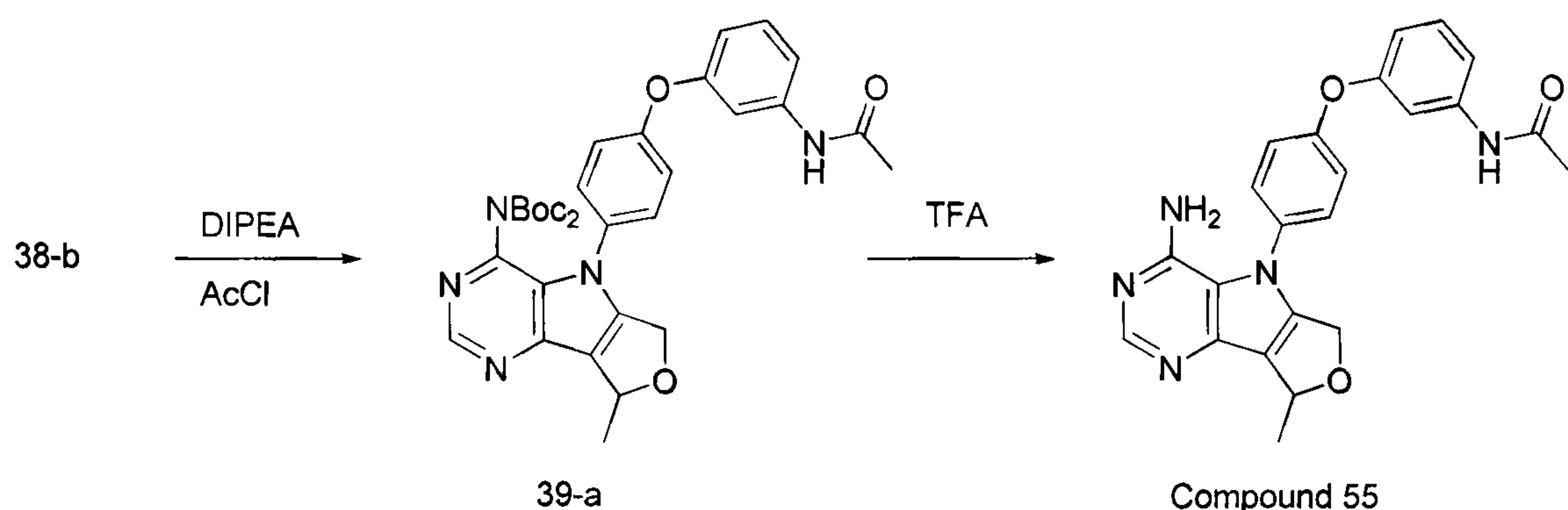
10

**Scheme 38****Step 1: Intermediate 38-a**

15 To a solution of compound 45 (570 mg, 1.413 mmol) in THF (14.0 ml) were sequentially added BOC₂O (1.96 ml, 8.48 mmol), DMAP (3.5 mg, 0.283 mmol) and DIPEA (740 μ l, 4.24 mmol) and the reaction was stirred for 5 days at room temperature. A saturated aqueous solution of ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO₄,
 20 filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 38-a as a brown solid.

Step 2: Intermediate 38-b

To a solution of intermediate 38-a (190 mg, 0.31 mmol) in ethyl acetate and stirred under nitrogen was added 10% Pd/C (117 mg, 0.11 mmol). The reaction mixture was purged with H₂ and stirred at room temperature overnight. The reaction was then filtered through celite and the filtrate was concentrated in vacuo. Purification by reverse phase chromatography provided intermediate 38-b as brown solid.

Synthesis of Compound 55**Sche**

10

me 39**Step 1: Intermediate 39-a**

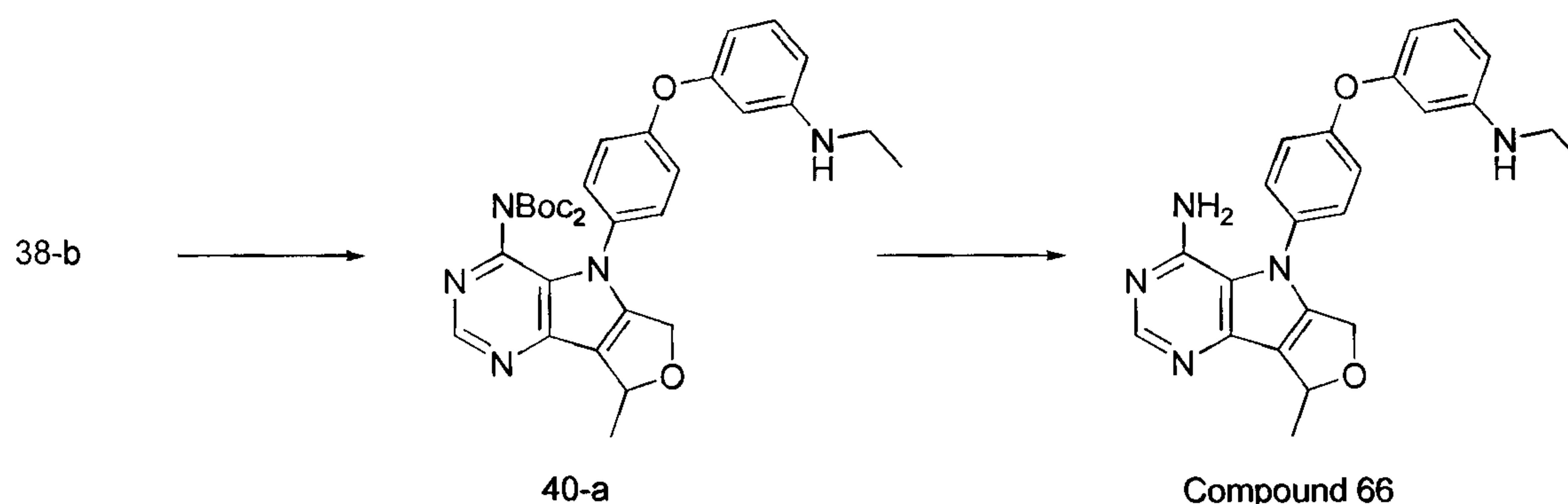
To a solution of intermediate 38-b (105 mg, 0.183 mmol) in THF (3.05 ml) were sequentially added DIPEA (64 μ l, 0.36 mmol), acetyl chloride (14 μ l, 0.201 mmol) and the reaction was stirred at room temperature for 2 hours. A saturated aqueous solution of ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 39-a as a yellow solid.

20 Step 2: Compound 55

To a solution of intermediate 39-a (57 mg, 0.09 mmol) in dichloromethane (1.0 ml) cooled to 0°C was added TFA (1.07 ml, 13.89 mmol) and the reaction was then

stirred at room temperature for 1 hour. Volatiles were removed in vacuo. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 55·HCl as white solid. MS (m/z) M+H= 416.3

5 Synthesis of Compound 66



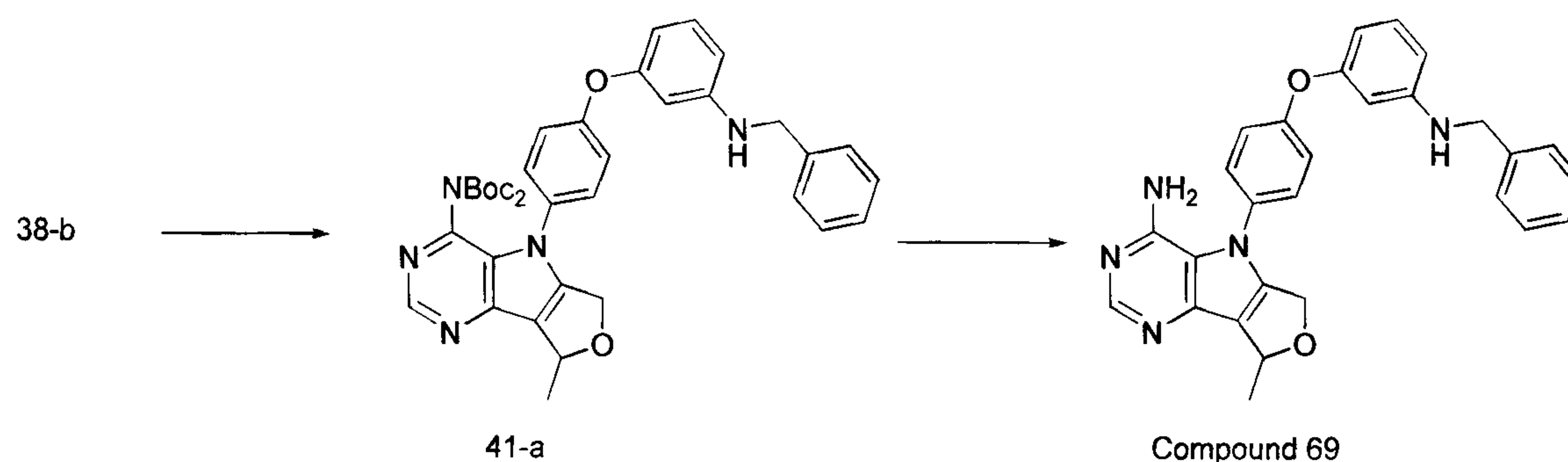
Scheme 40

Step 1: Intermediate 40-a

To a solution of intermediate 38-b (80 mg, 0.13 mmol) and acetaldehyde (94 μ l, 0.14 mmol) in methanol (0.5 ml) was added sodium cyanoborohydride (53 mg, 0.84 mmol) and the reaction was stirred at room temperature for 24 hours. A saturated aqueous solution of NaHCO₃ and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 40-a as a yellow foam.

Step 2: Compound 66

To a solution of intermediate 40-a (60 mg, 0.10 mmol) in dichloromethane (0.5 ml) cooled to 0°C was added TFA (499 μ l, 6.48 mmol) and the reaction was then stirred at room temperature for 1 hour. Volatiles were removed in vacuo. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 66·2HCl as yellow solid. MS (m/z) M+H= 402.2

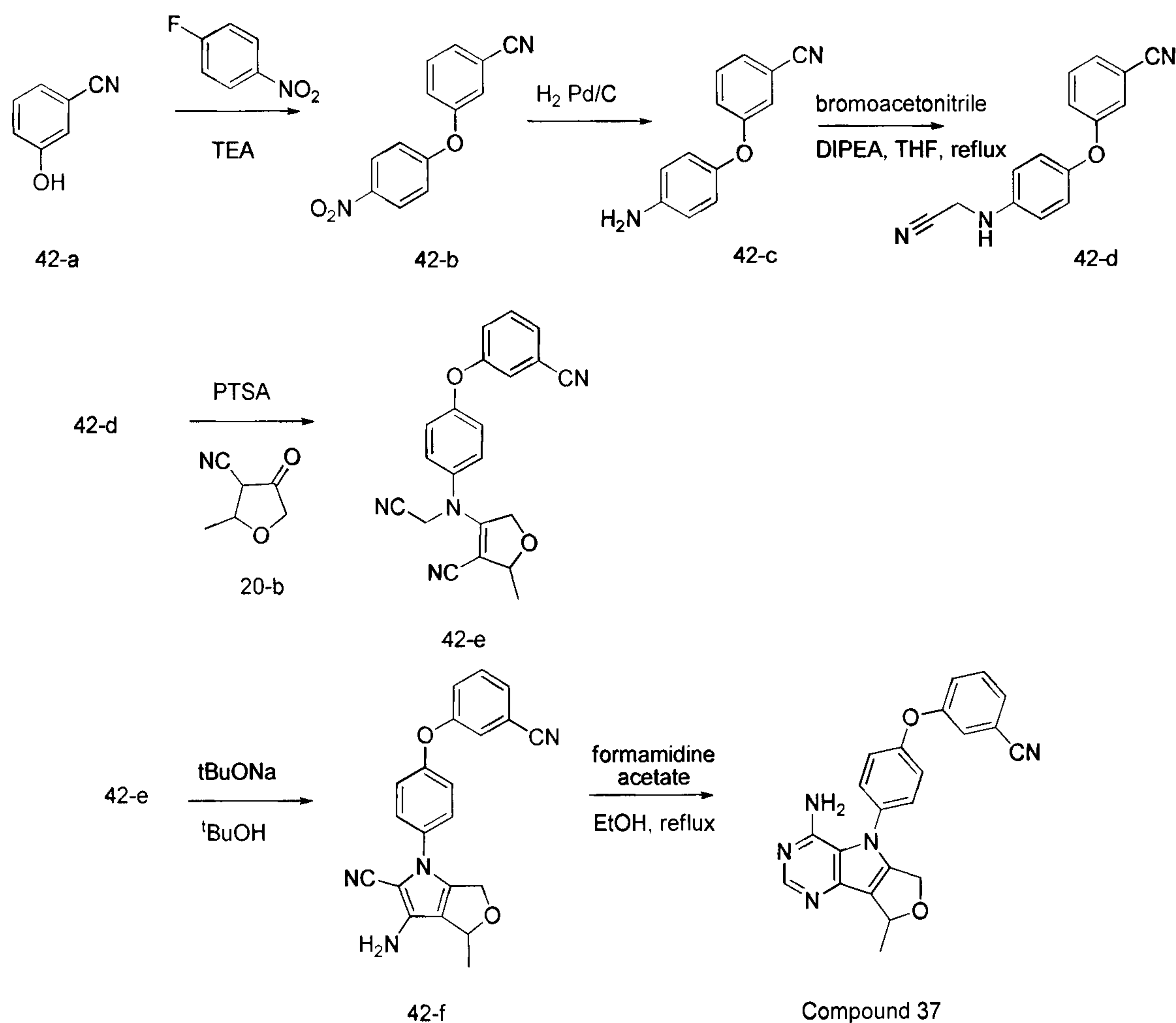
Synthesis of Compound 69**Scheme 41****5 Step 1: Intermediate 41-a**

To a solution of intermediate 38-b (110 mg, 0.192 mmol) and benzaldehyde (41 mg, 0.38 mmol) in methanol (2.0 ml) was added sodium cyanoborohydride (24 mg, 0.38 mmol) and the reaction was stirred at room temperature for 24 hours. A saturated aqueous solution of NaHCO₃ and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 41-a as a yellow oil.

Step 2: Compound 69

To a solution of intermediate 41-a (110 mg, 0.16 mmol) in dichloromethane (0.5 ml) cooled to 0°C was added TFA (830 µl, 10.8 mmol) and the reaction was then stirred at room temperature for 1 hour. Volatiles were removed in vacuo. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 69·2HCl as yellow solid. MS (m/z) M+H= 464.2

Synthesis of Compound 37



Scheme 42

Step 1: Intermediate 42-b

- 5 To a solution of 1-fluoro-4-nitrobenzene (1.50 ml, 14.17 mmol) in DMSO (70 ml) were added 3-hydroxybenzonitrile (1.85 g, 15.60 mmol) and TEA (7.90 ml, 56.7 mmol) and the reaction was heated at 150 °C overnight and then cooled to room temperature. A saturated aqueous solution of ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO₄,
- 10 filtered and concentrated under reduced pressure to provide intermediate 42-b as brown oil.

Step 2: Intermediate 42-c

To a solution of intermediate 42-b (3.3 g, 13.74 mmol) in methanol and stirred under nitrogen was added 10% Pd/C (1.46 g, 0.68 mmol). The reaction mixture was purged with H₂ and stirred at room temperature overnight. The reaction was
5 then filtered through celite and the filtrate was concentrated in vacuo to provide intermediate 42-c as brown oil.

Step 3: Intermediate 42-d

To a solution of intermediate 42-c (3.0 g, 14.27 mmol) and 2-bromoacetonitrile (1.98 ml, 28.5 mmol) in THF (30 mL) was added DIPEA (5.23 ml, 30.0 mmol) at
10 room temperature and the reaction was stirred at 80°C overnight. A Saturated aqueous solution of ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with a saturated aqueous solution of ammonium chloride and brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 42-d as a
15 beige solid.

Step 4: Intermediate 42-e

To a solution of intermediate 42-d (2.0 g, 8.02 mmol) in toluene (25 ml) were
20 added intermediate 20-b (1.51 g, 12.04 mmol) and 4-methylbenzenesulfonic acid hydrate (153 mg, 0.80 mmol). The reaction was refluxed for 3 hours using a dean-stark and then cooled to room temperature. A saturated aqueous solution of NaHCO₃ and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to
25 provide intermediate 42-e as brown solid.

Step 5: Intermediate 42-f

To a solution of intermediate 42-e (2.9 g, 8.14 mmol) in tert-butanol (40 mL) was added a 1.0 M solution of potassium tert-butoxide in THF (8.95 mL, 8.95 mmol),
30 the reaction was stirred at 80 °C for 30 minutes and then cooled to room

To a solution of intermediate 42-f (600 mg, 1.68 mmol) in ethanol (7.0 ml) was added formamidine acetate (1.20 g, 11.53 mmol) and the reaction was stirred at 80 °C for 2 hours and then cooled to room temperature. Volatiles were removed in vacuo. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the residue, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 37·HCl as a beige solid. MS (m/z) M+H= 384.3

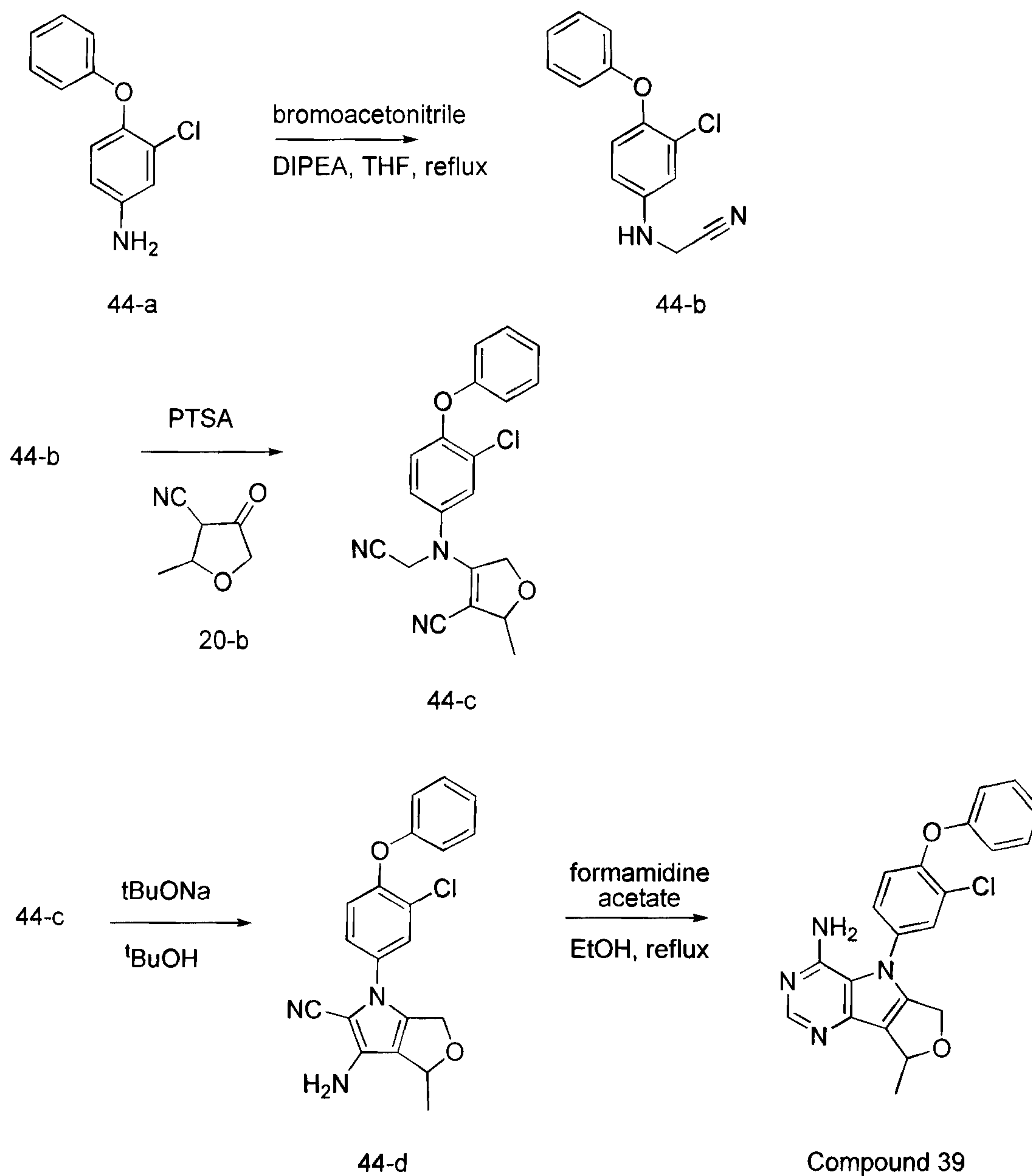
 Compound 37 $\xrightarrow{\text{NaOH, H}_2\text{O}_2}$ Compound 38

To a solution of compound 37 (250 mg, 0.65 mmol) in DMSO (13.0 ml) were sequentially added 1N sodium hydroxide (652 μ l, 0.65 mmol), H₂O₂ (100 μ l, 0.97 mmol) and the mixture was stirred at room temperature for 15 minutes.

Water was added; a precipitate formed and was collected by filtration, washed with diethyl ether to provide compound 38 as white solid. MS (m/z) M+H= 402.2

Synthesis of Compound 39

5



Scheme 44**Step 1: Intermediate 44-b**

To a solution of intermediate 44-a (3.0 g, 11.71 mmol) and 2-bromoacetonitrile (2.44 ml, 35.1 mmol) in THF (110 mL) was added DIPEA (8.77 ml, 50.4 mmol) at room temperature and the reaction was stirred at 80°C overnight. A Saturated aqueous solution of ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with a saturated aqueous solution of ammonium chloride and brine, dried over MgSO_4 , filtered and concentrated under reduced pressure to provide intermediate 44-b as brown oil.

Step 2: Intermediate 44-c

To a solution of intermediate 44-b (3.02 g, 11.67 mmol) in toluene (110 ml) were added intermediate 20-b (1.75 g, 14.01 mmol) and 4-methylbenzenesulfonic acid hydrate (222 mg, 1.16 mmol). The reaction was refluxed for 18 hours using a dean-stark and then cooled to room temperature. A saturated aqueous solution of NaHCO_3 and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 44-c as a yellow oil.

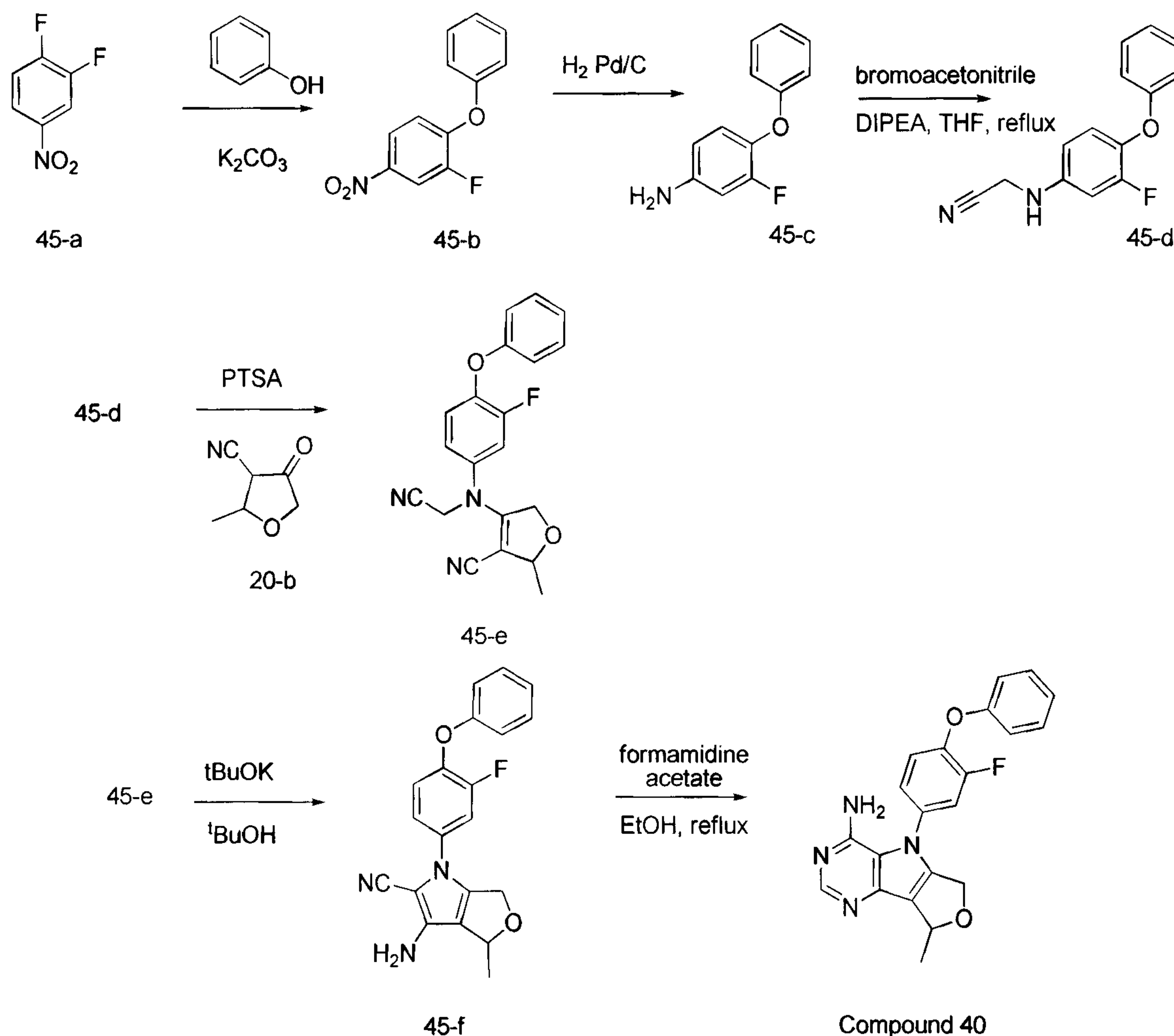
Step 3: Intermediate 44-d

To a solution of intermediate 44-c (3.04 g, 8.31 mmol) in tert-butanol (80 mL) was added a 1.0 M solution of potassium tert-butoxide in THF (9.14 mL, 9.14 mmol), the reaction was stirred at 80 °C for 18 hours and then cooled to room temperature. 10% aqueous HCl and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure to provide intermediate 44-d as brown solid. MS (m/z) $\text{M}+\text{H}= 366.3$

Step 4: Compound 39

To a solution of intermediate 44-d (3.03 g, 8.28 mmol) in ethanol (83.0 ml) was added formamidine acetate (6.90 g, 66.30 mmol) and the reaction was stirred at 80 °C for 18 hours and then cooled to room temperature. Volatiles were removed in vacuo. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the residue, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 39·HCl as a pale yellow solid.

MS (m/z) M+H= 393.6

Synthesis of Compound 40

Scheme 45**Step 1: Intermediate 45-b**

To a solution of intermediate 1,2-difluoro-4-nitrobenzene 45-a (2.08 ml, 18.86
5 mmol) in DMF (37 ml) were sequentially added phenol (1.95 g, 20.74 mmol),
potassium carbonate (2.87 g, 20.74 mmol) and the reaction was stirred at 150°C
overnight and then cooled to room temperature. Volatiles were removed in vacuo.
Water and ethyl acetate were added, the organic layer was separated, washed with
10 brine, dried over MgSO₄, filtered and concentrated under reduced pressure to
provide intermediate 45-b as brown oil.

Step 2: Intermediate 45-c

To a solution of intermediate 45-b (4.4 g, 18.87 mmol) in methanol (90 ml) and
stirred under nitrogen was added 10% Pd/C (1.00 g, 94.3 mmol). The reaction
15 mixture was purged with H₂ and stirred at room temperature overnight. The
reaction was then filtered through celite and the filtrate was concentrated in vacuo
to provide intermediate 45-c as brown oil. MS (m/z) M+H= 204.1

Step 3: Intermediate 45-d

To a solution of intermediate 45-c (3.83 g, 18.85 mmol) and 2-bromoacetonitrile
20 (3.94 ml, 56.5 mmol) in THF (95 mL) was added DIPEA (10.83 ml, 62.2 mmol) at
room temperature and the reaction was stirred at 80°C overnight. A saturated
aqueous solution of ammonium chloride and ethyl acetate were added, the organic
layer was separated, washed with a saturated aqueous solution of ammonium
chloride and brine, dried over MgSO₄, filtered and concentrated under reduced
25 pressure. Purification by silica gel chromatography provided intermediate 45-d as a
brown oil.

Step 4: Intermediate 45-e

To a solution of intermediate 45-d (4.50 g, 18.58 mmol) in toluene (190 ml) were added intermediate 20-b (3.25 g, 26.0 mmol) and 4-methylbenzenesulfonic acid hydrate (707 mg, 3.72 mmol). The reaction was refluxed for 18 hours using a dean-stark and then cooled to room temperature. A saturated aqueous solution of NaHCO₃ and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by silica gel chromatography provided intermediate 45-e as a yellow oil.

Step 5: Intermediate 45-f

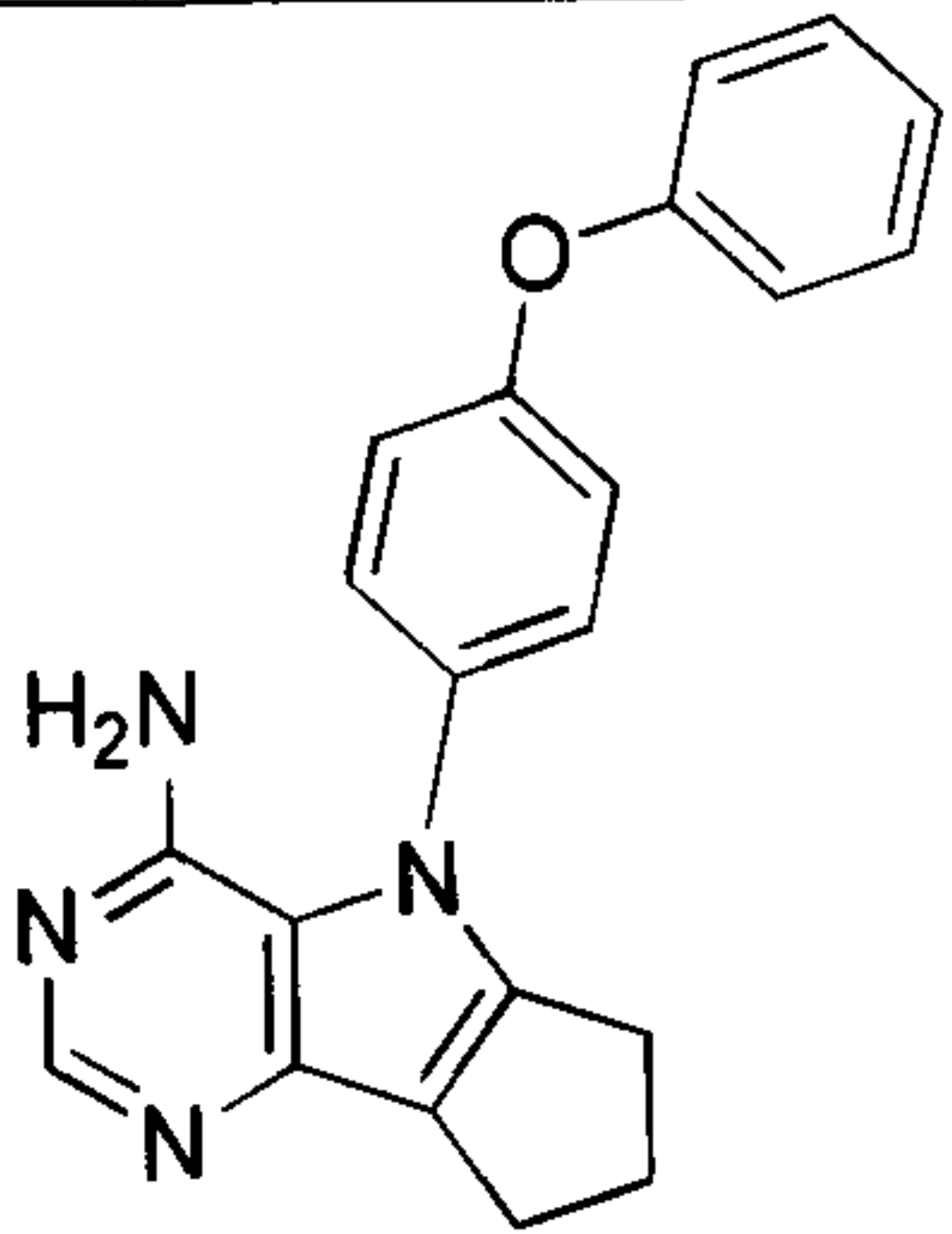
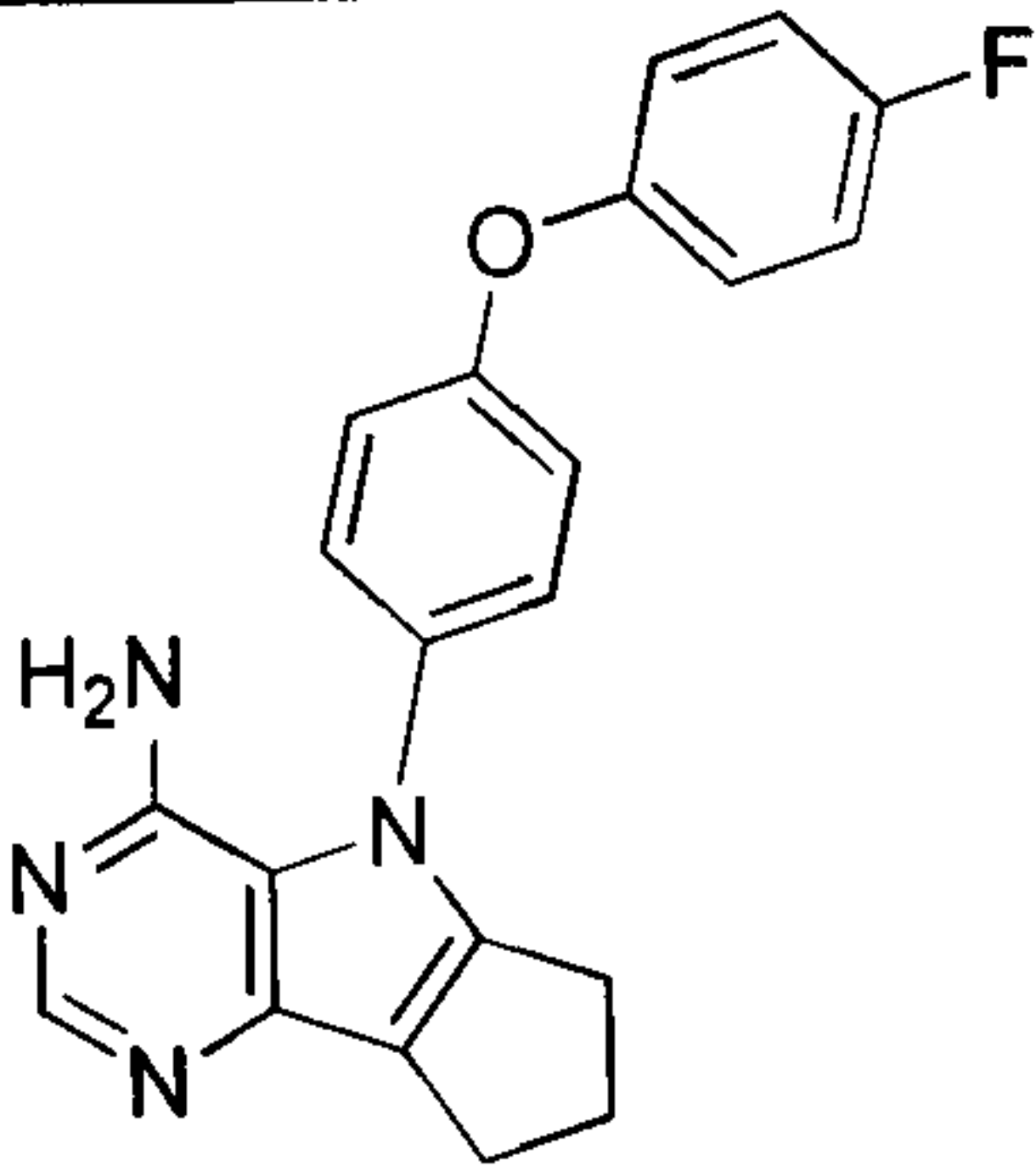
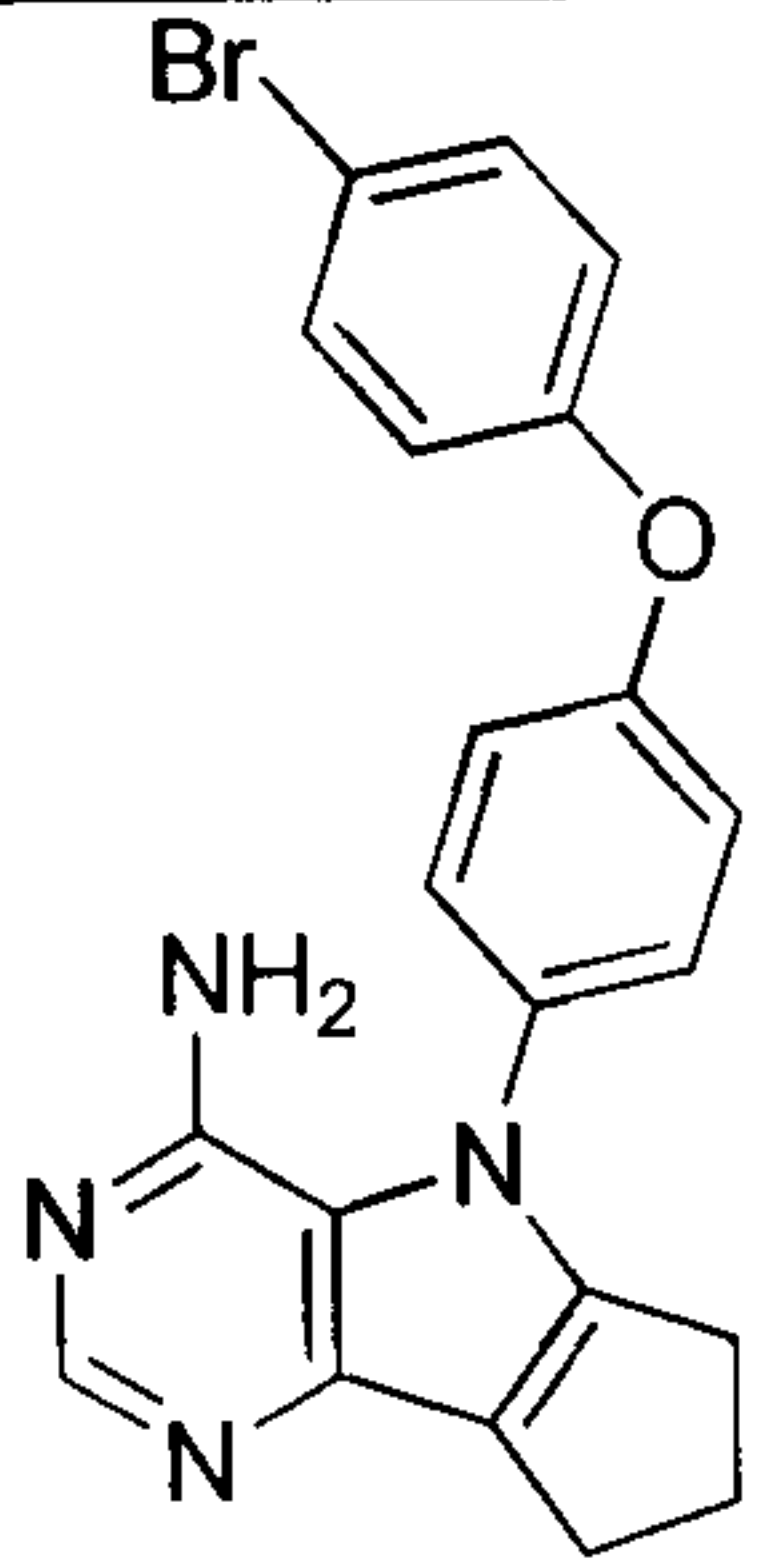
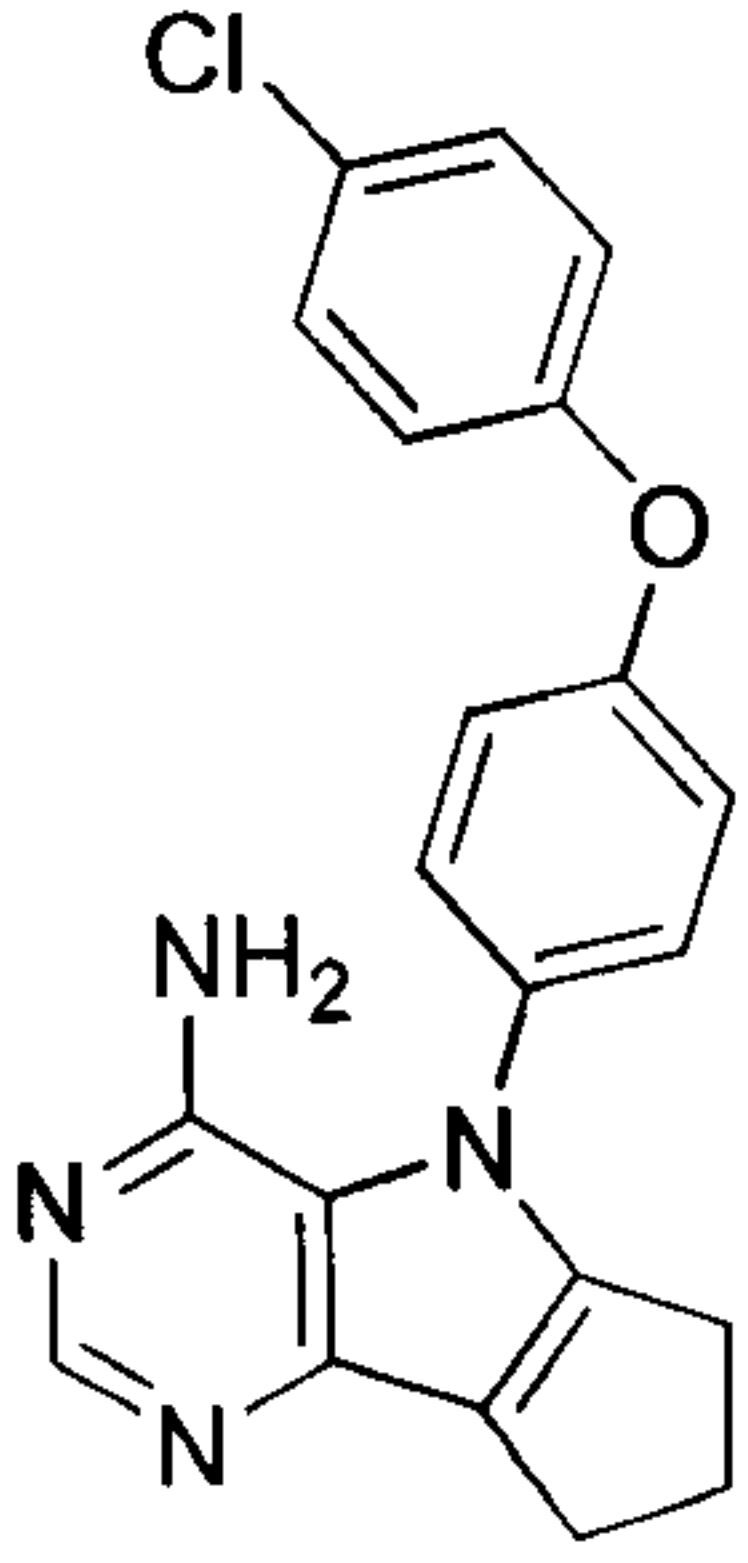
To a solution of intermediate 45-e (3.31 g, 9.47 mmol) in tert-butanol (95 mL) was added a 1.0 M solution of potassium tert-butoxide in THF (10.42 mL, 10.42 mmol), the reaction was stirred at 80 °C for 18 hours and then cooled to room temperature. 10% aqueous HCl and ethyl acetate were added, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure to provide intermediate 45-f as brown solid. MS (m/z) M+H= 350.4

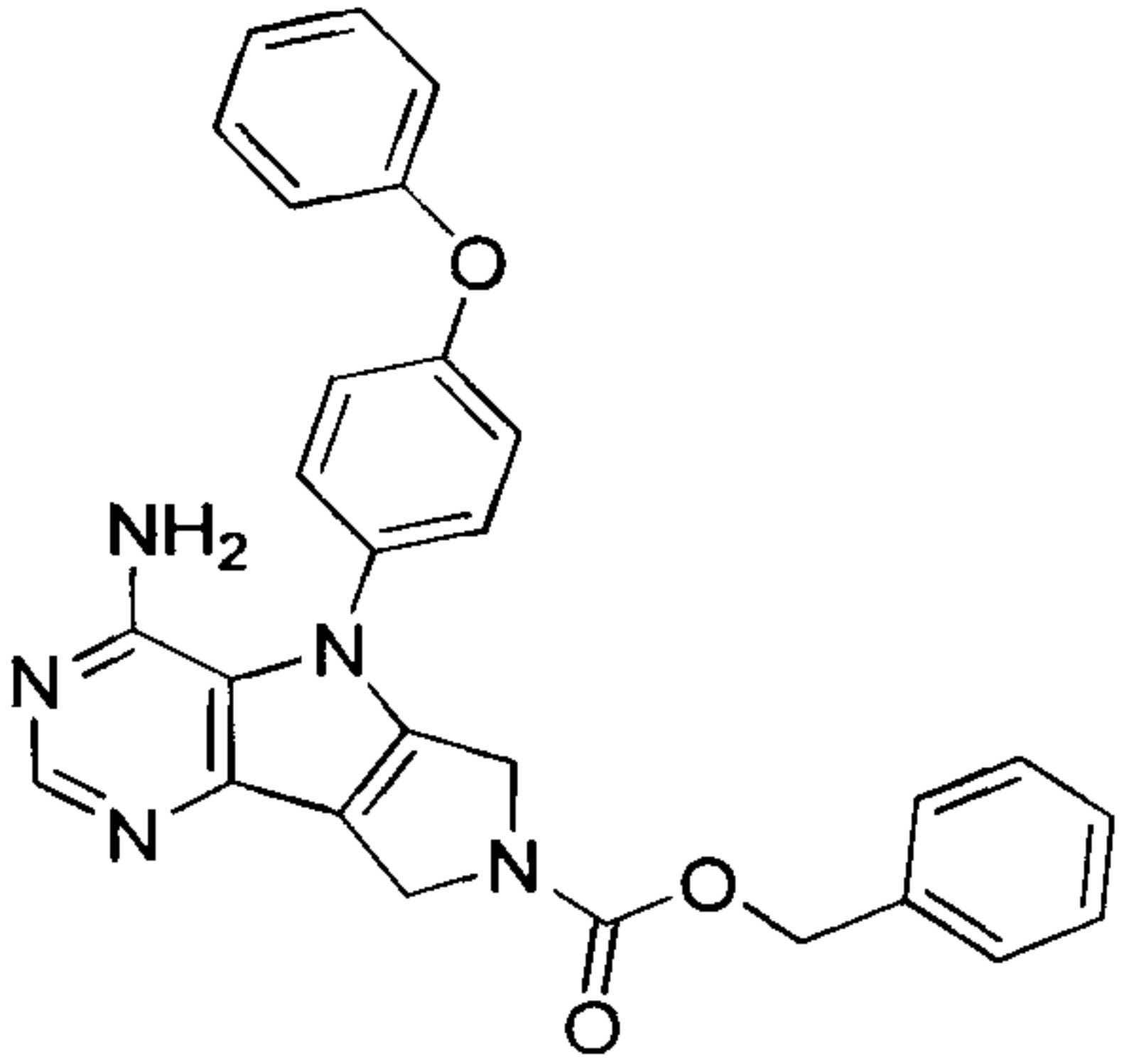
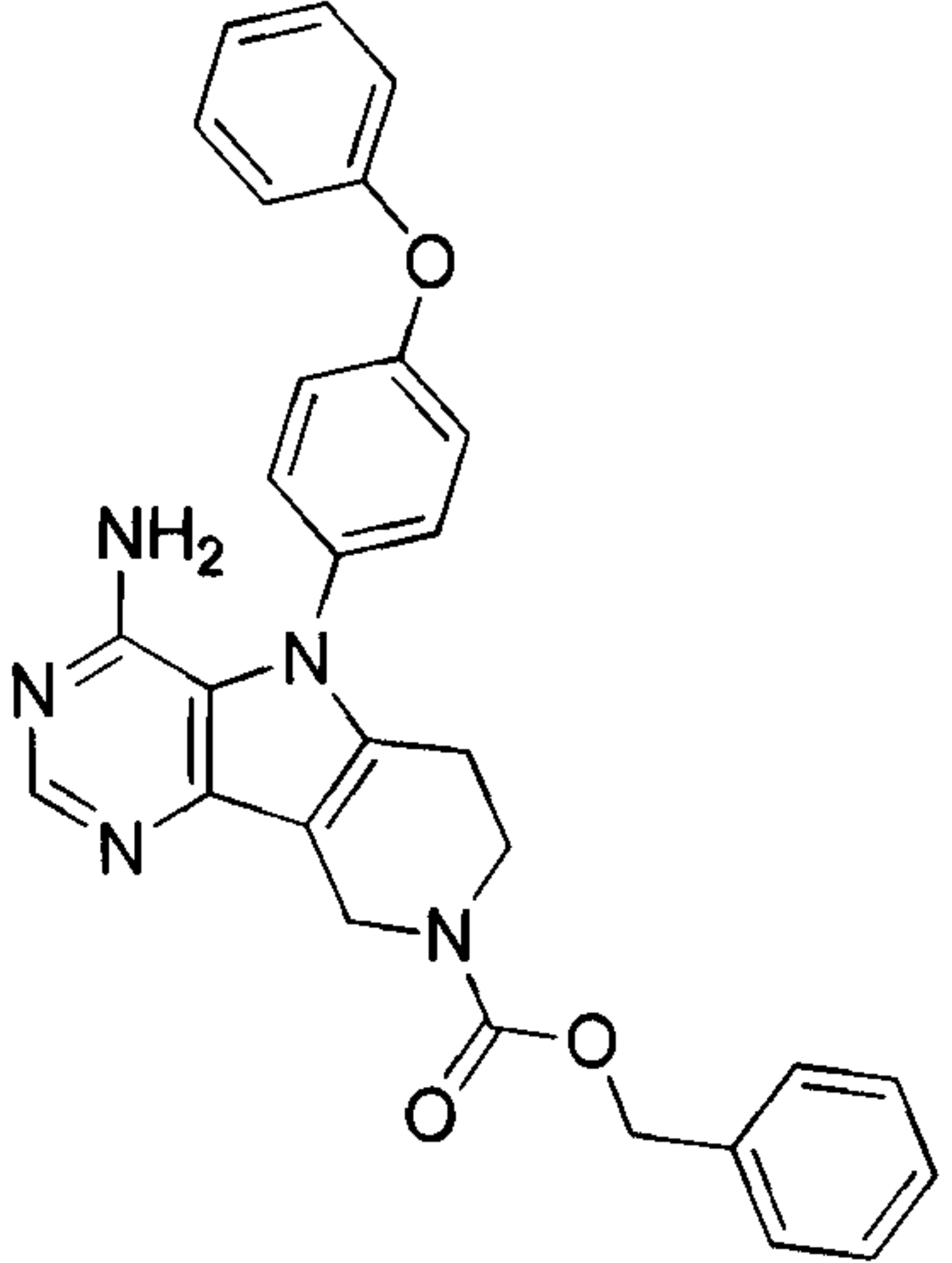
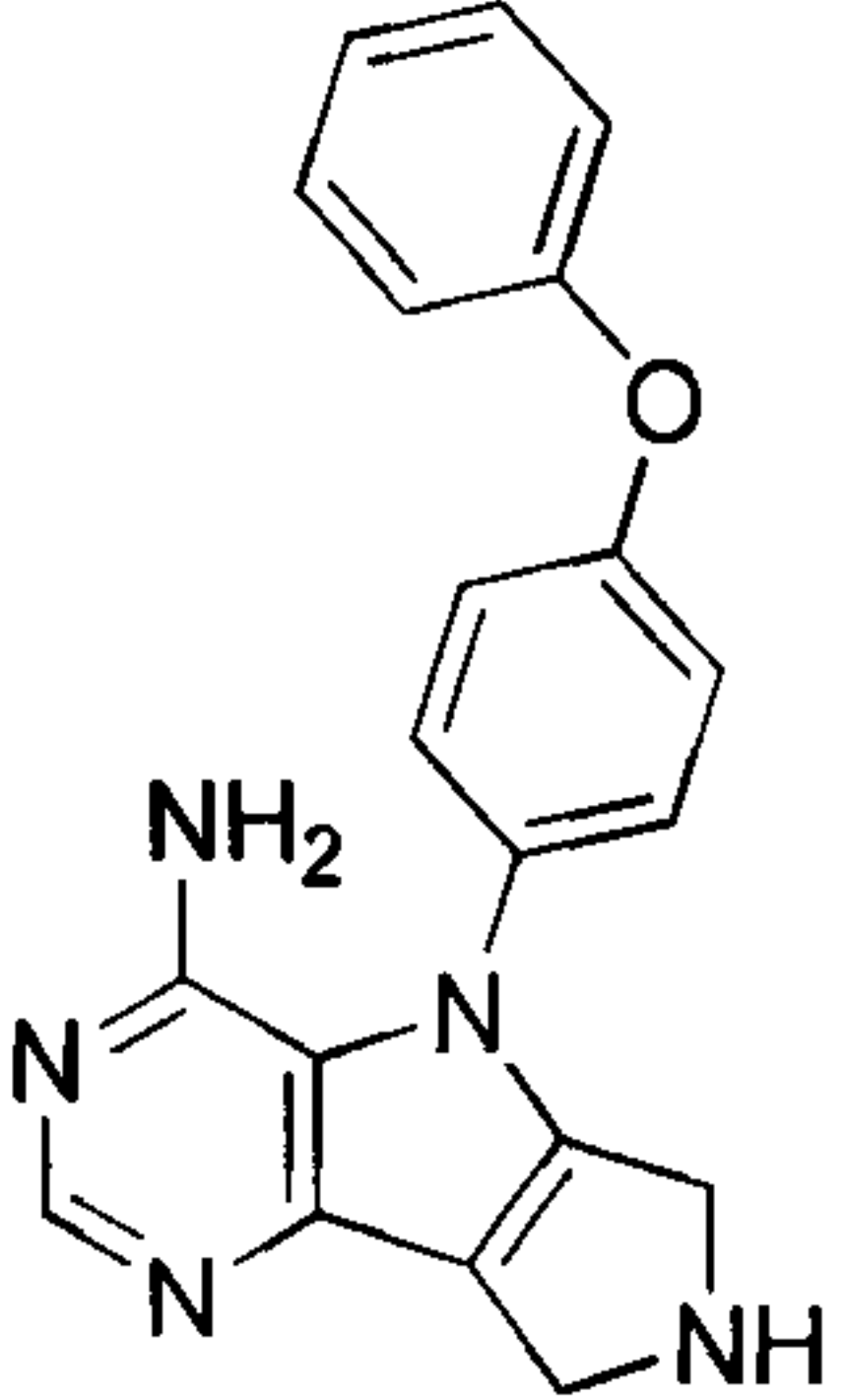
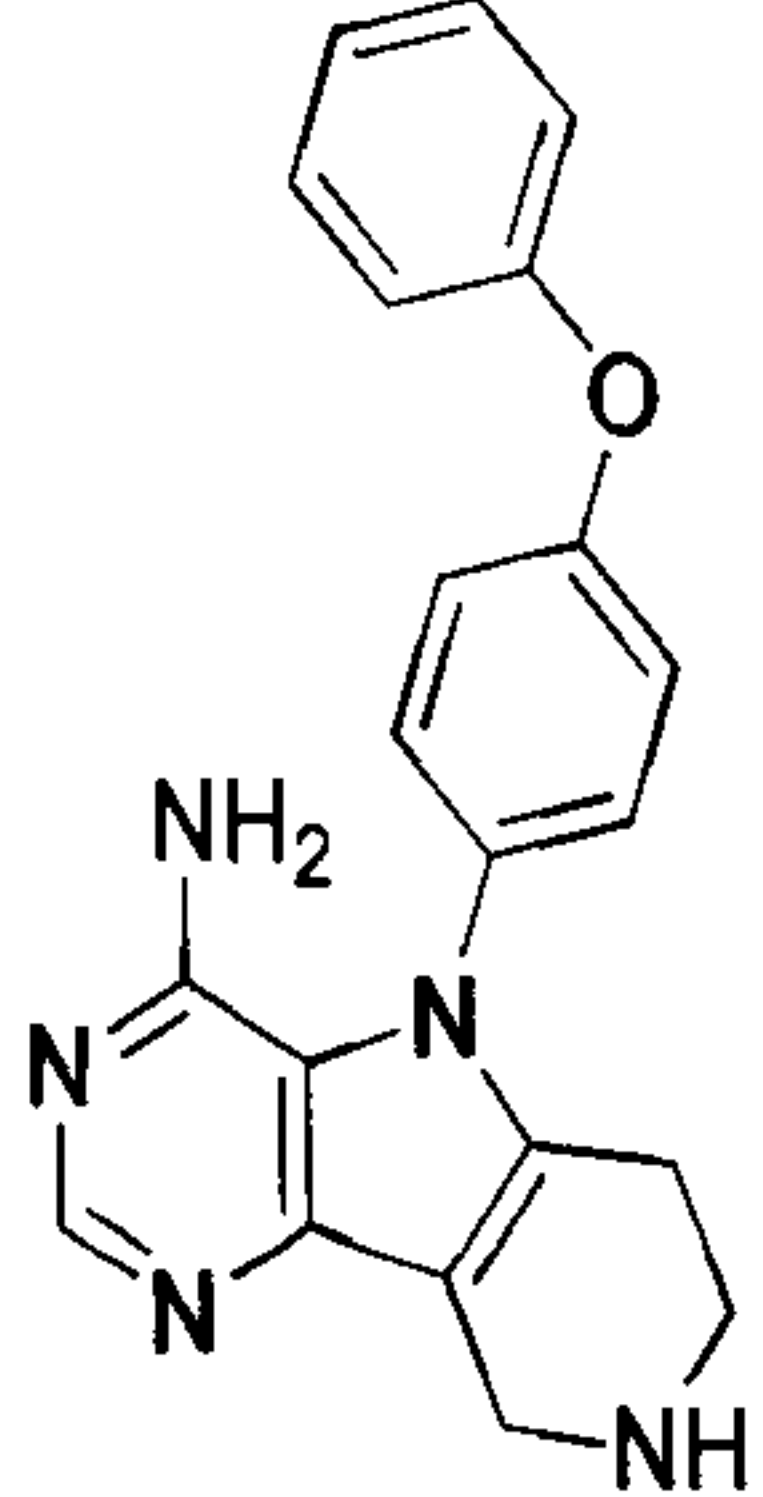
Step 6: Compound 40

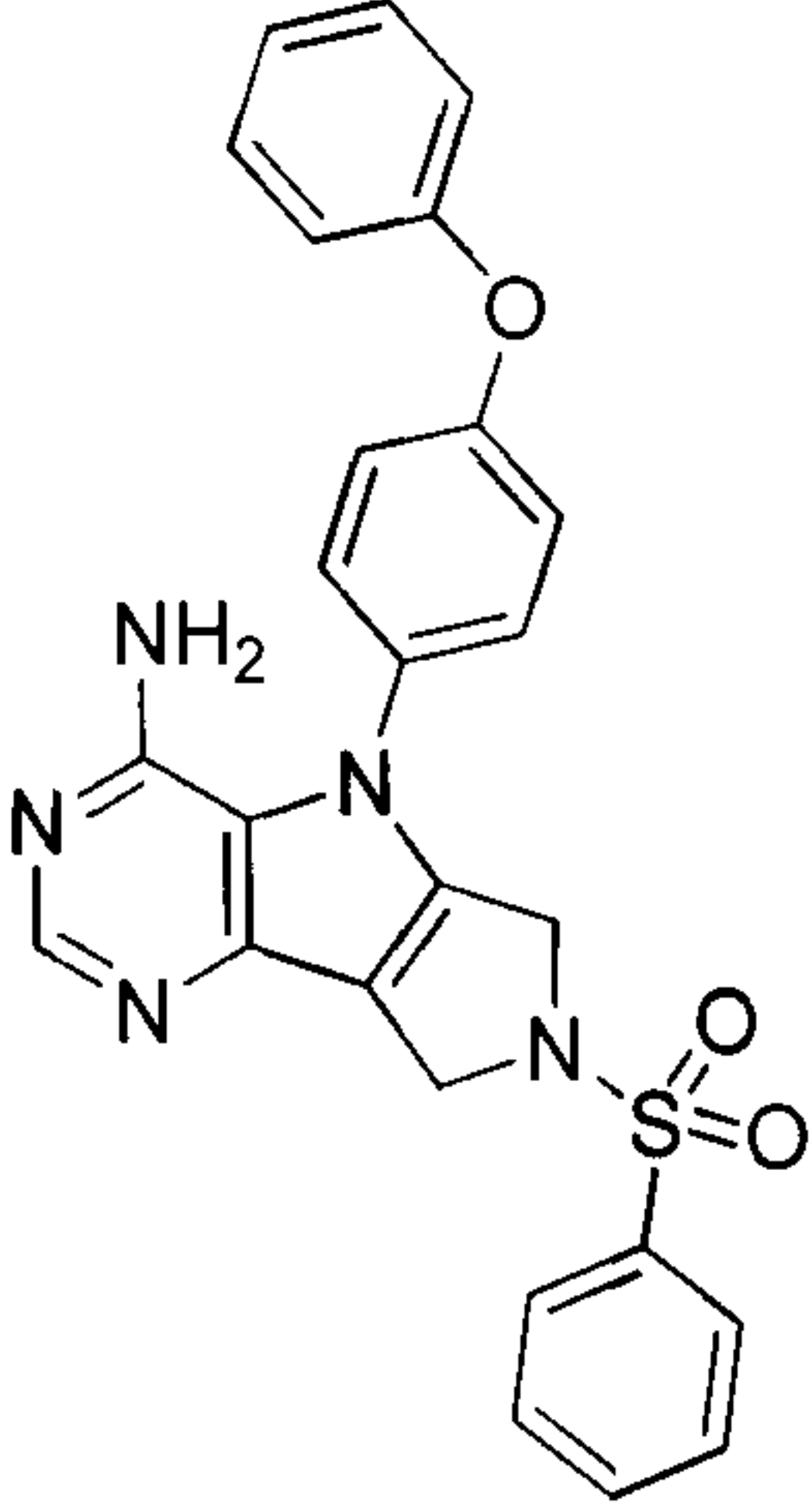
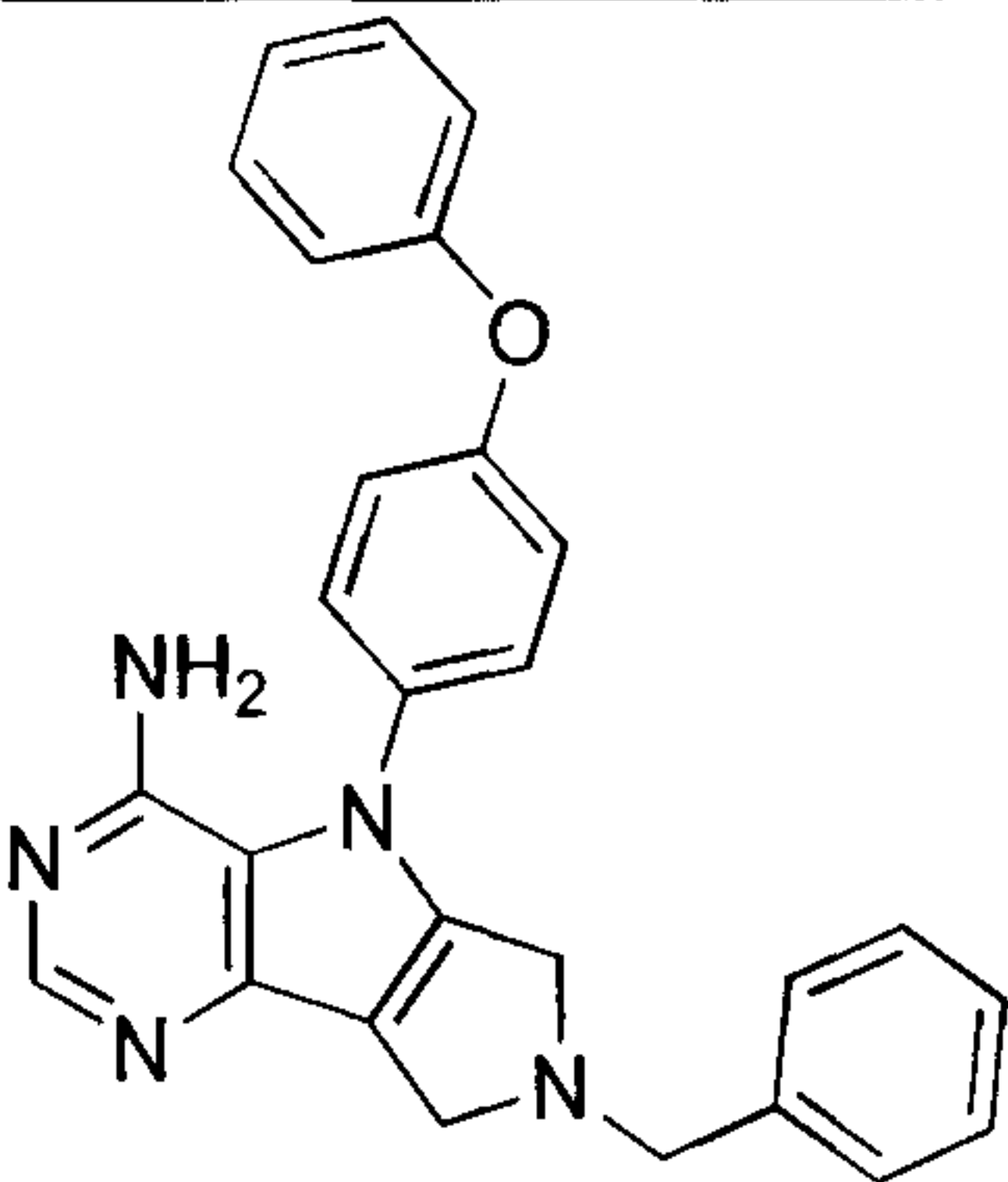
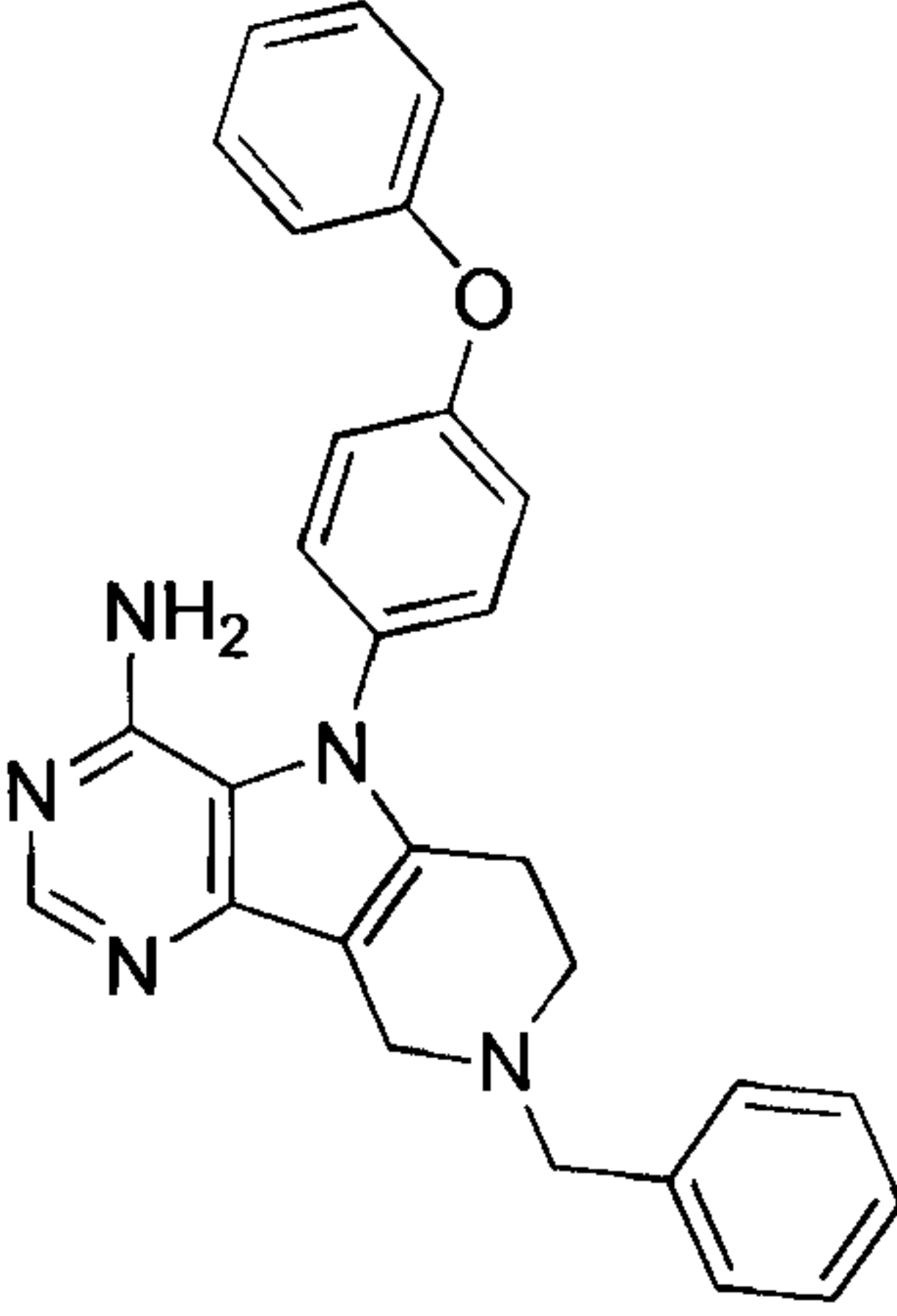
To a solution of intermediate 45-f (3.30 g, 9.45 mmol) in ethanol (95.0 ml) was added formamidine acetate (7.87 g, 76.0 mmol) and the reaction was stirred at 80 °C for 18 hours and then cooled to room temperature. Volatiles were removed in vacuo. A saturated aqueous solution of ammonium chloride and ethyl acetate were added to the residue, the organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by reverse phase chromatography eluting with a 10% methanol in 0.1% HCl to 40% methanol in 0.1% HCl gradient provided compound 40·HCl as a white solid. MS (m/z) M+H= 377.2

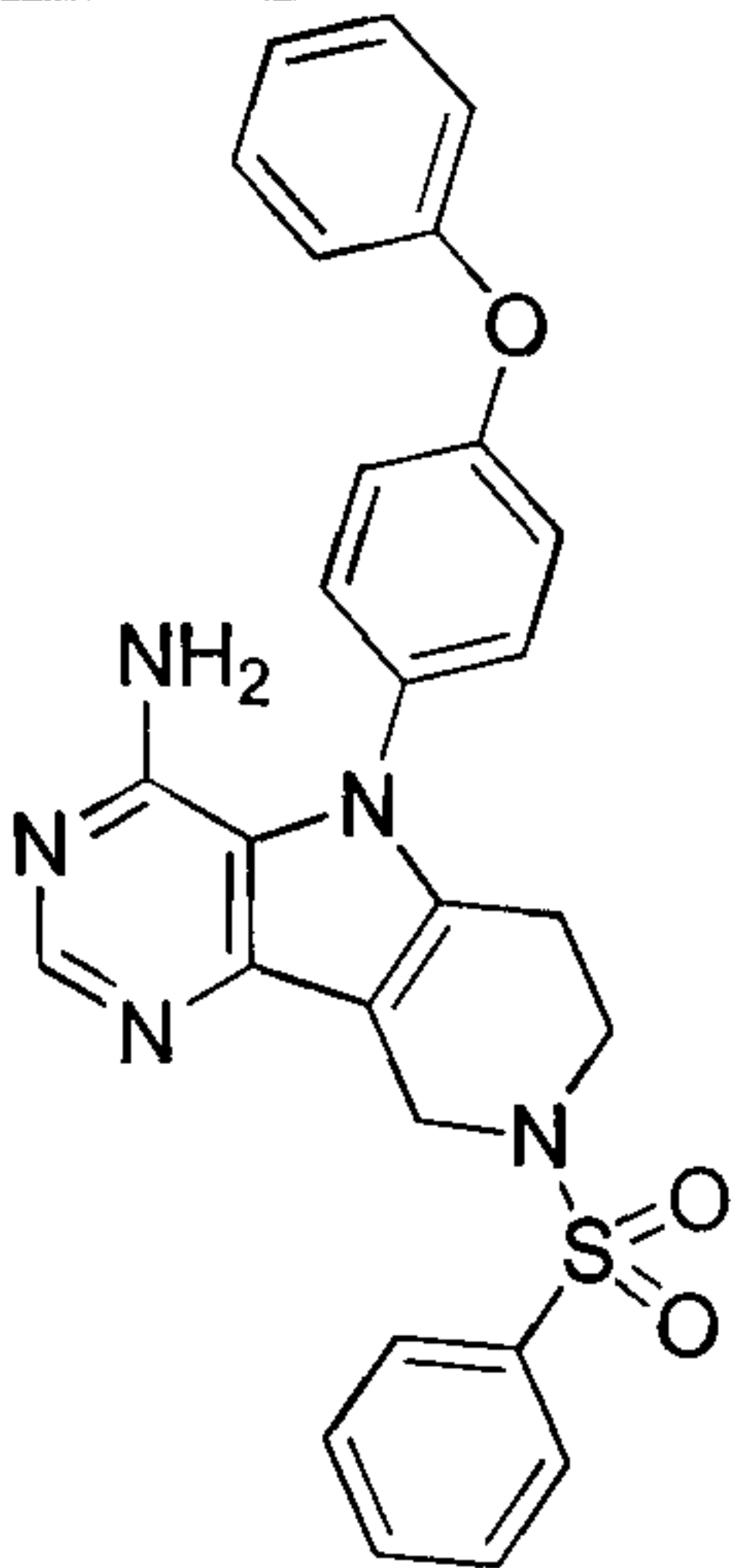
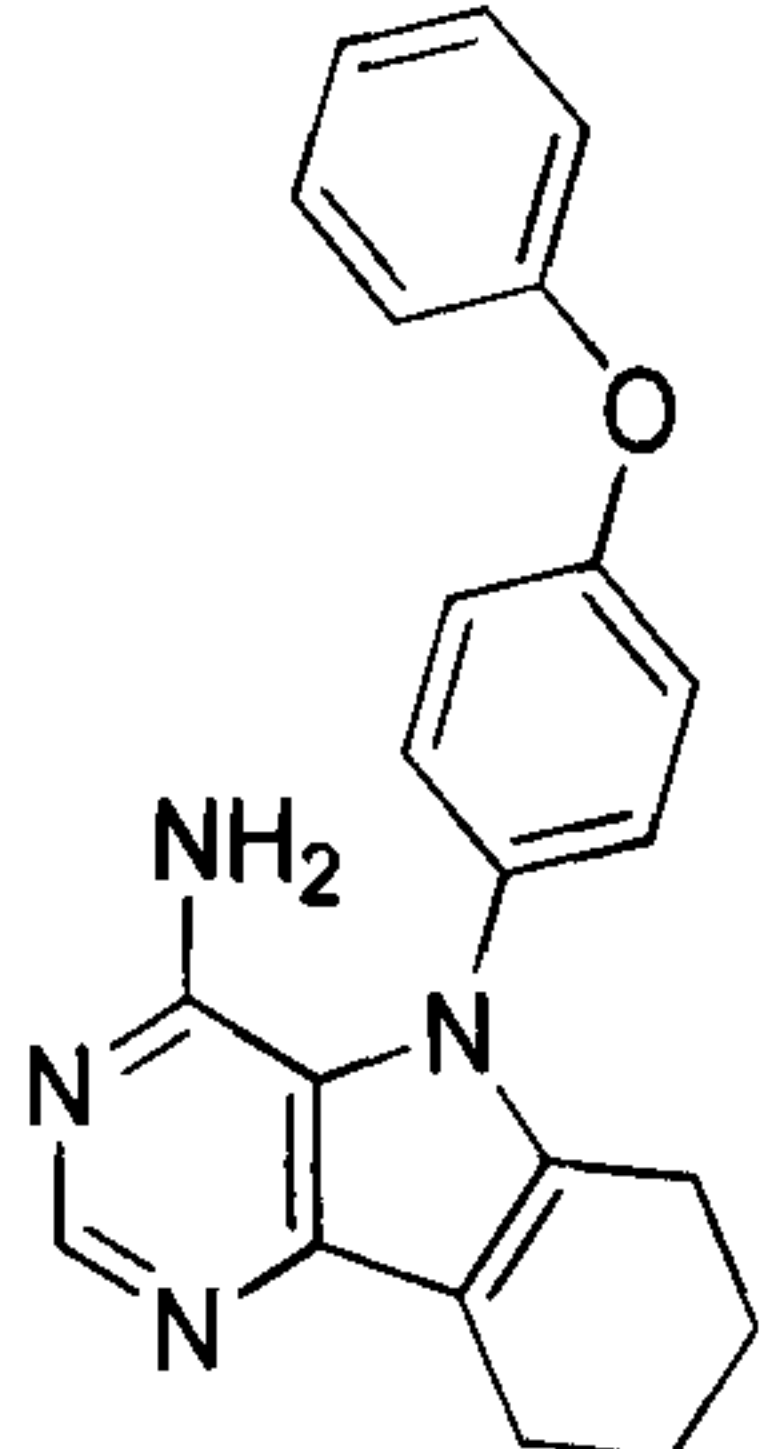
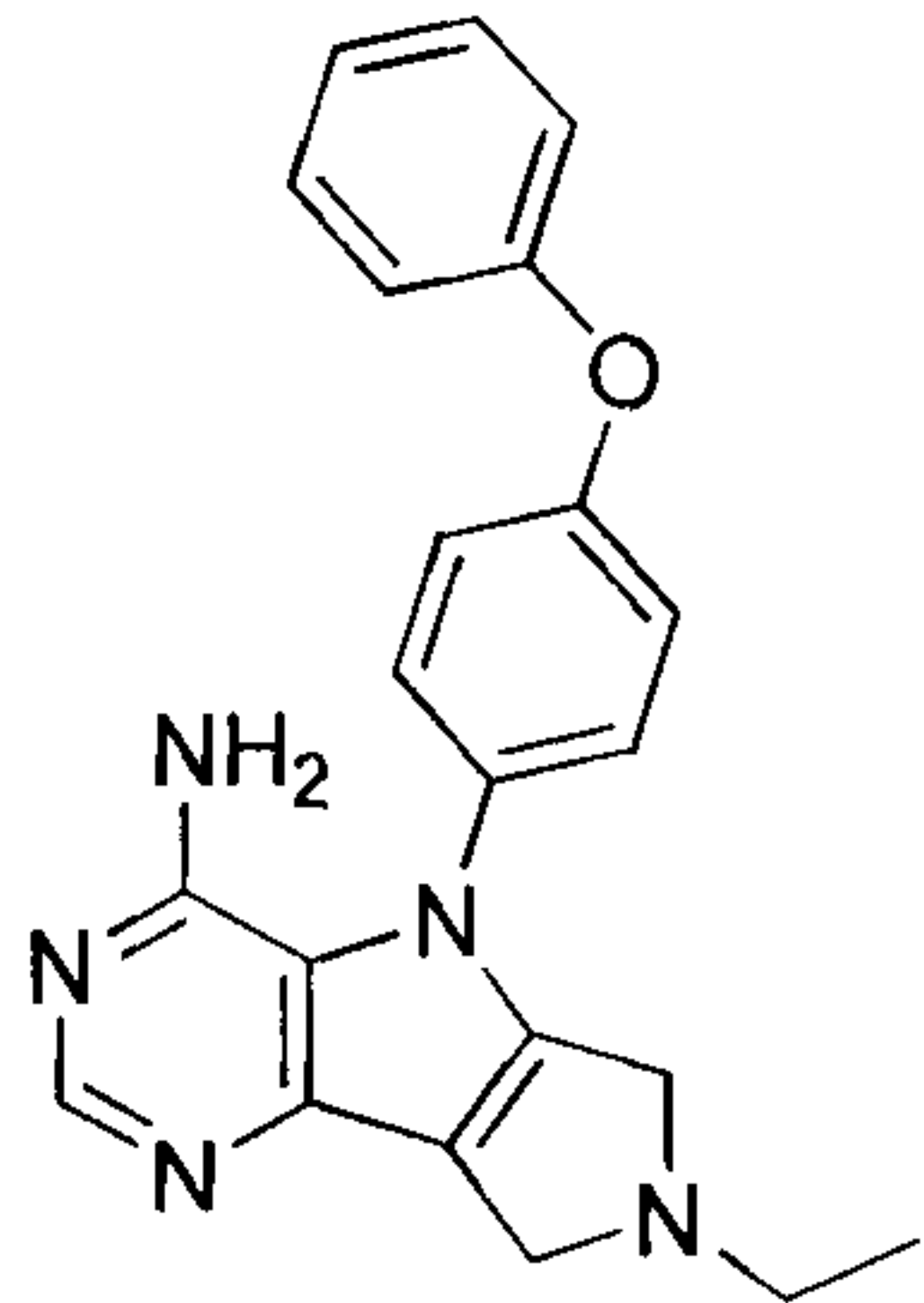
Table 1 summarizes representative compound of Formula 1.

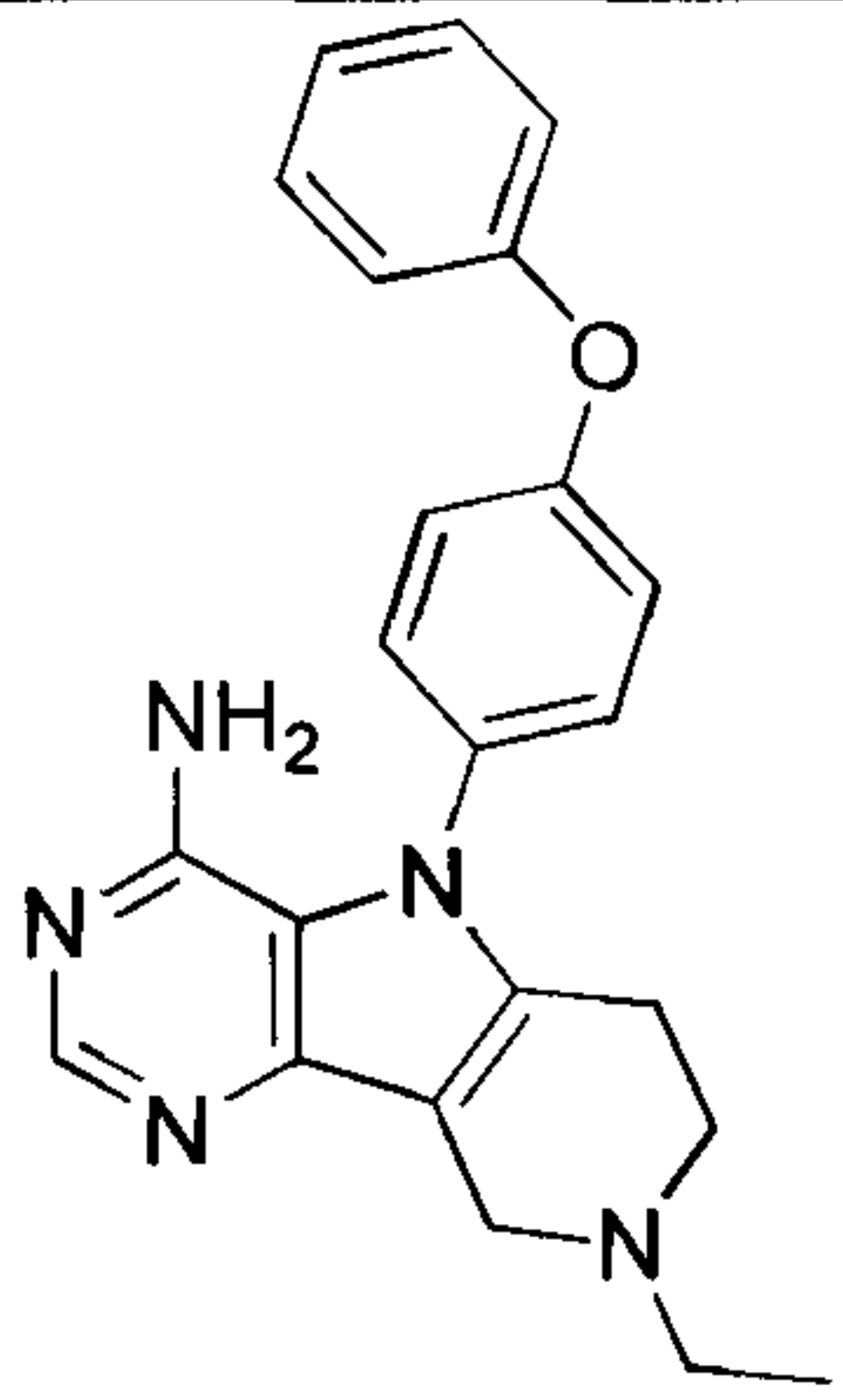
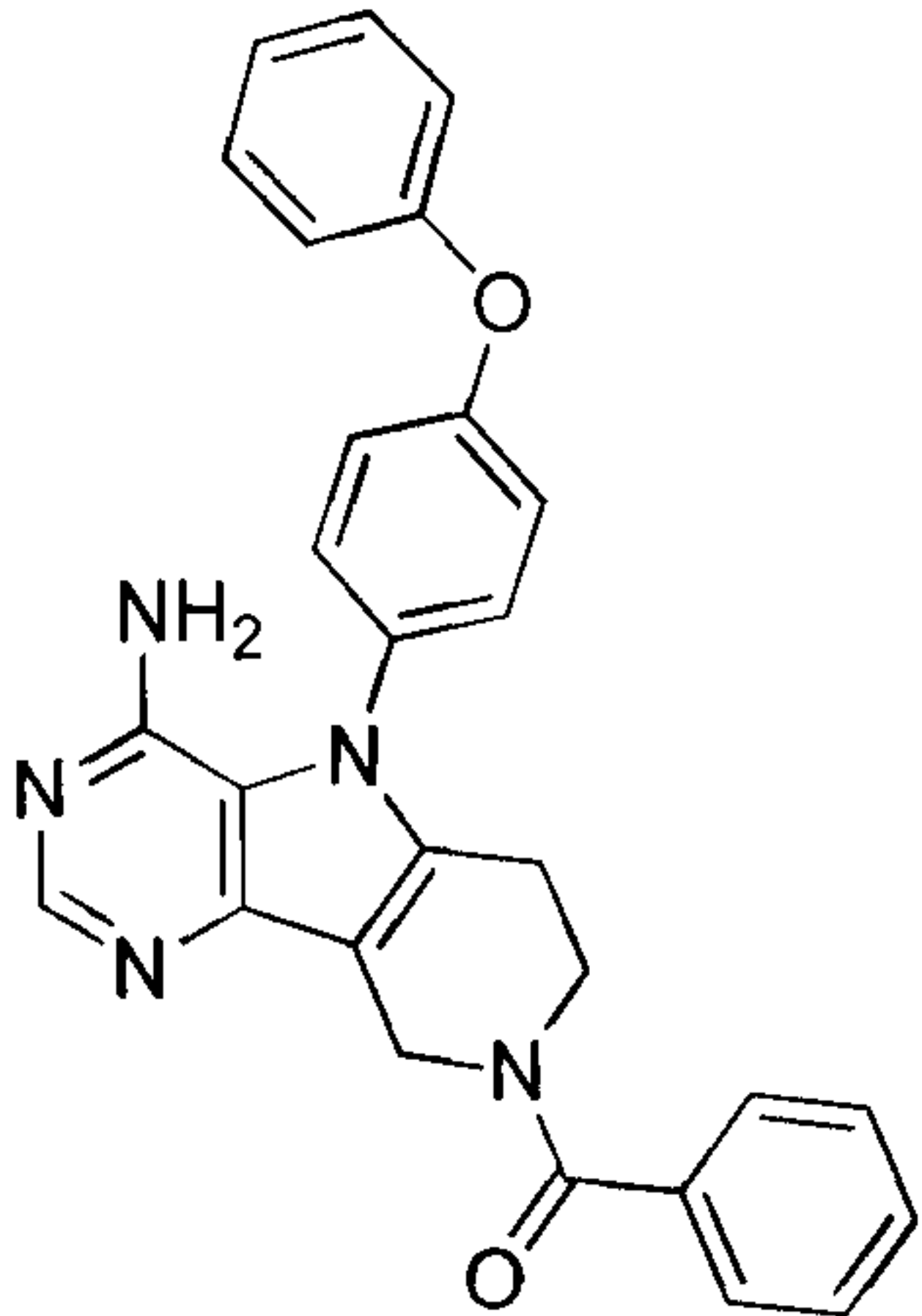
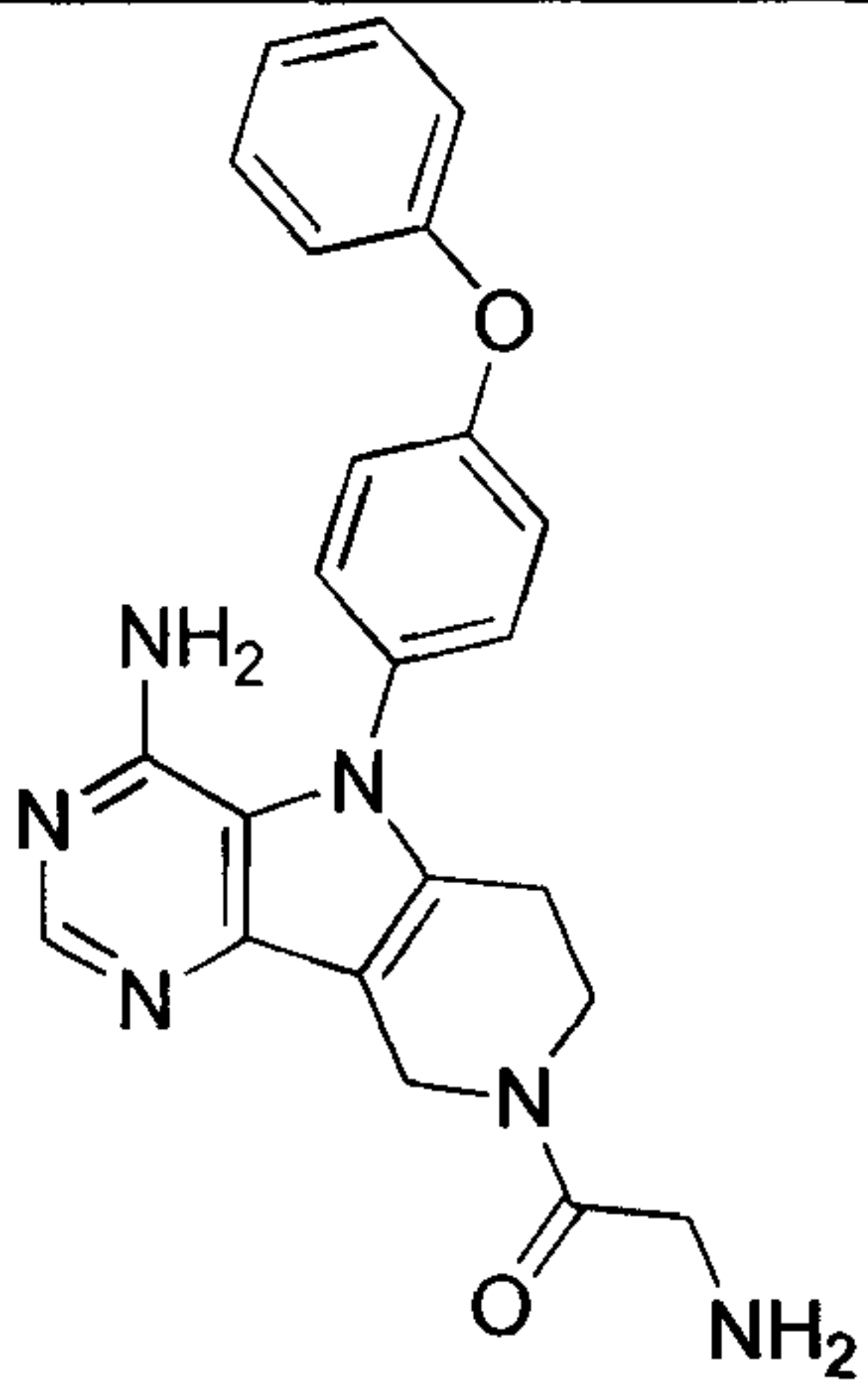
Table 1: Example Compounds of Formula 1

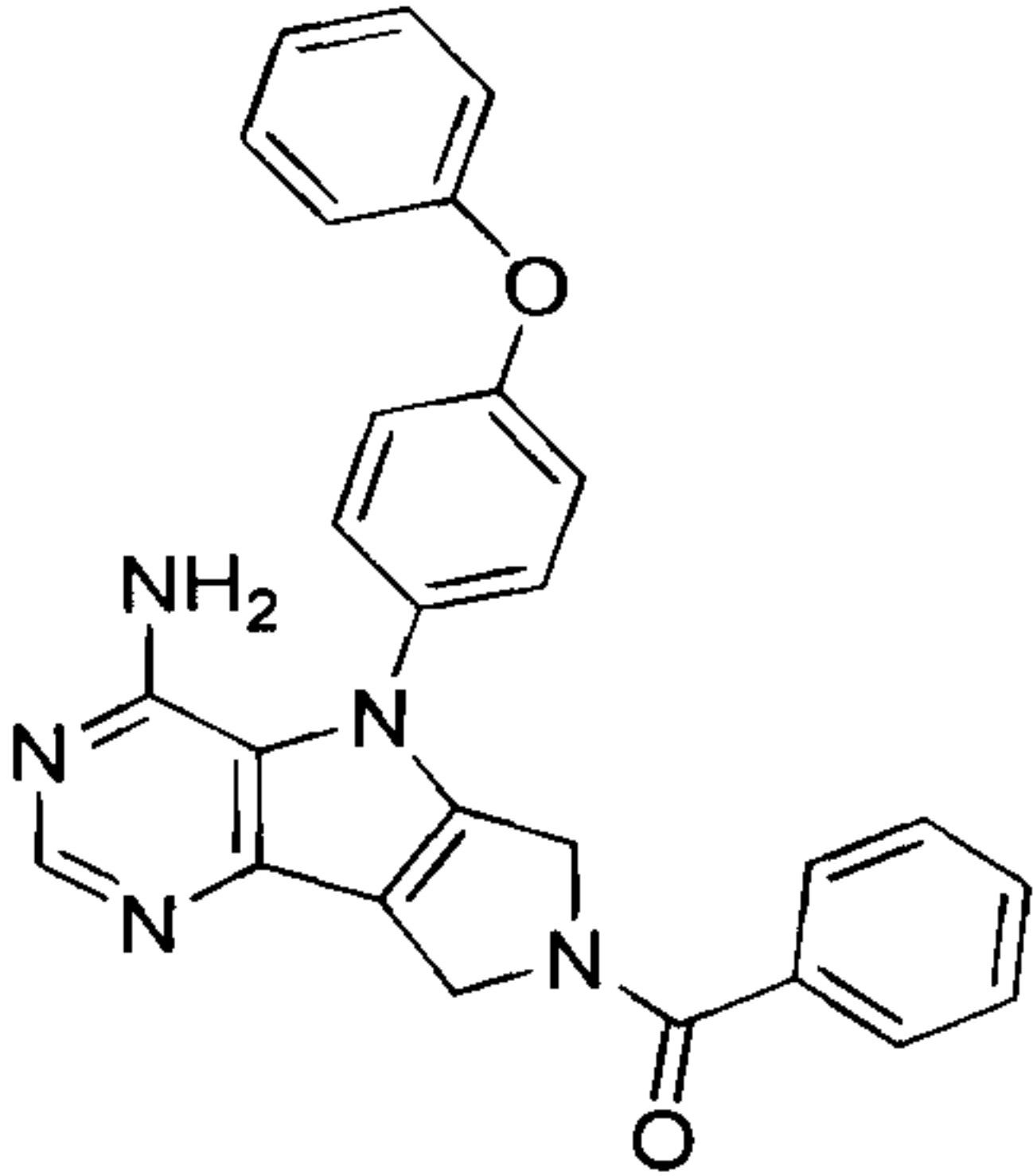
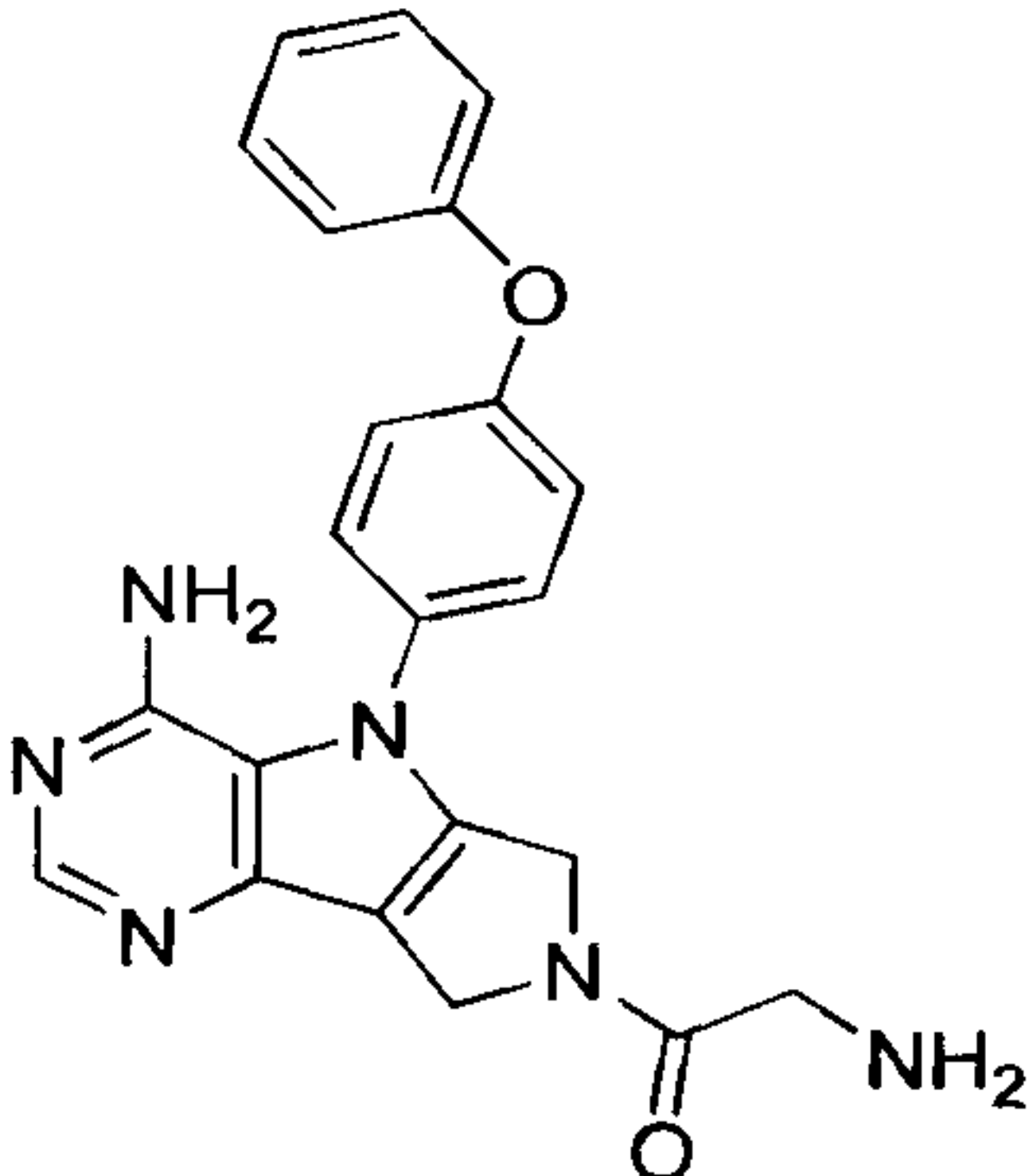
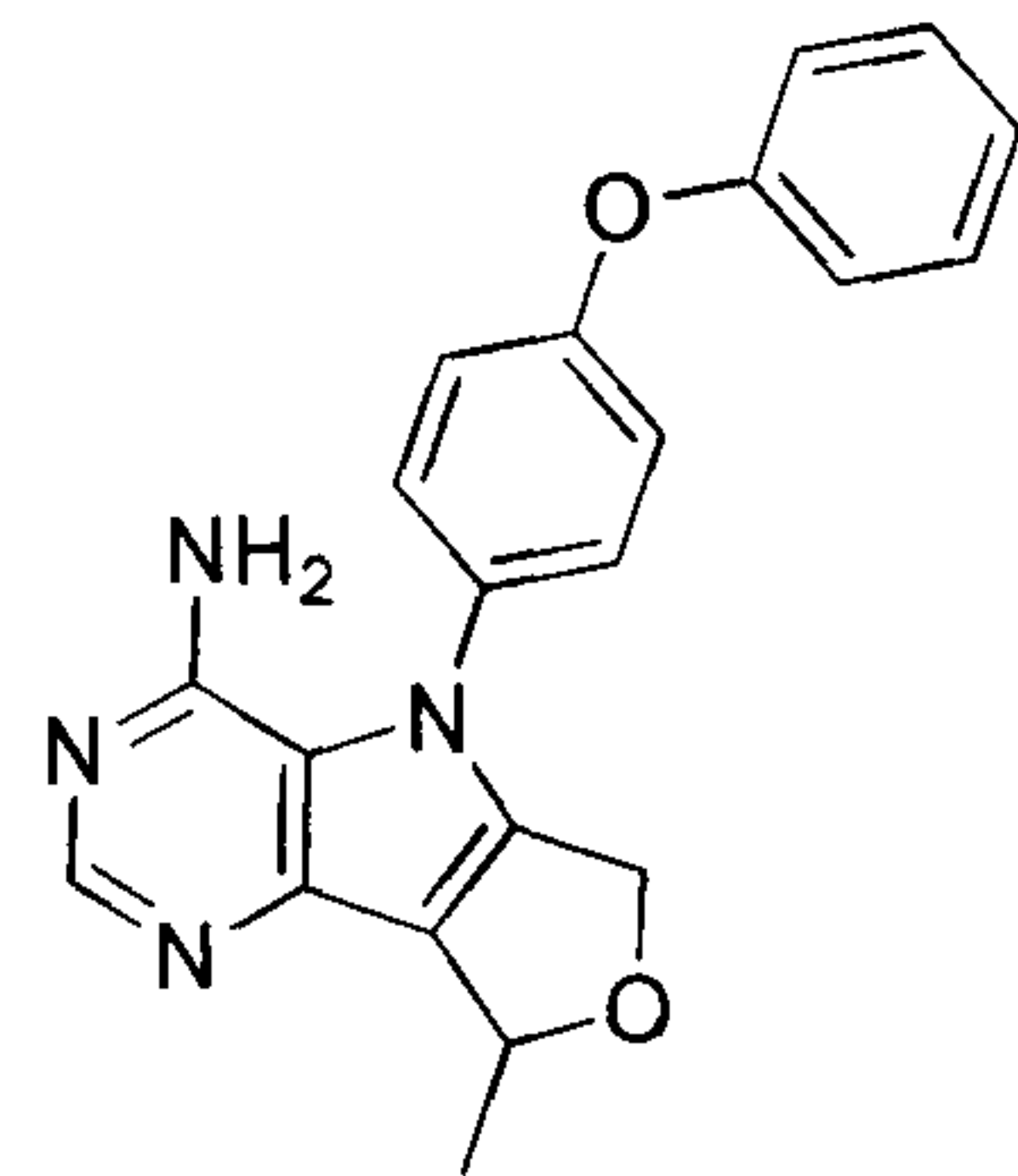
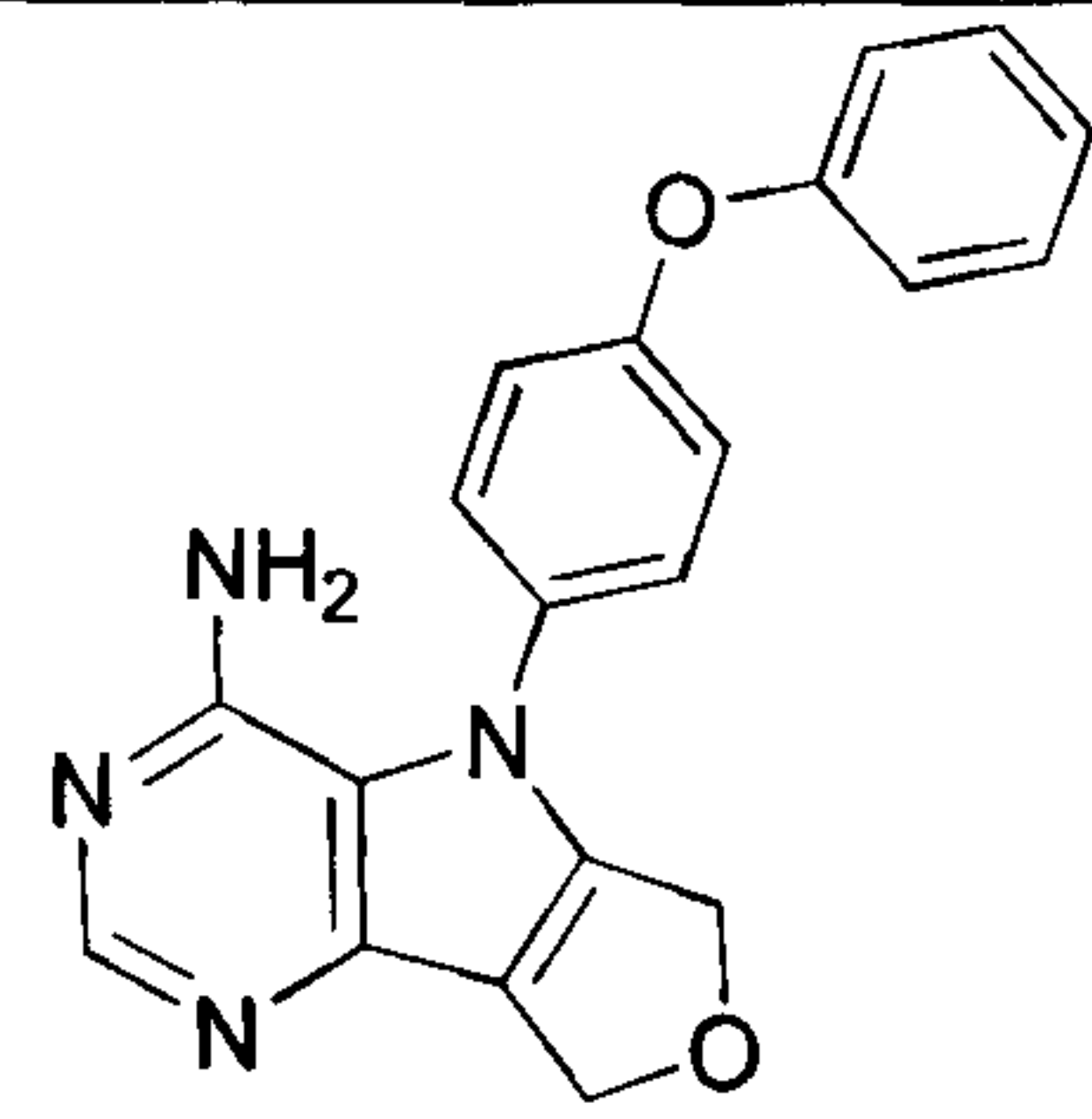
Compound	Structure	MS (m/z)
1		$[M+H]^+ = 343.2$
2		$[M+H]^+ = 361.2$
3		$[M+H]^+ = 421.6$
4		$[M+H]^+ = 377.2$

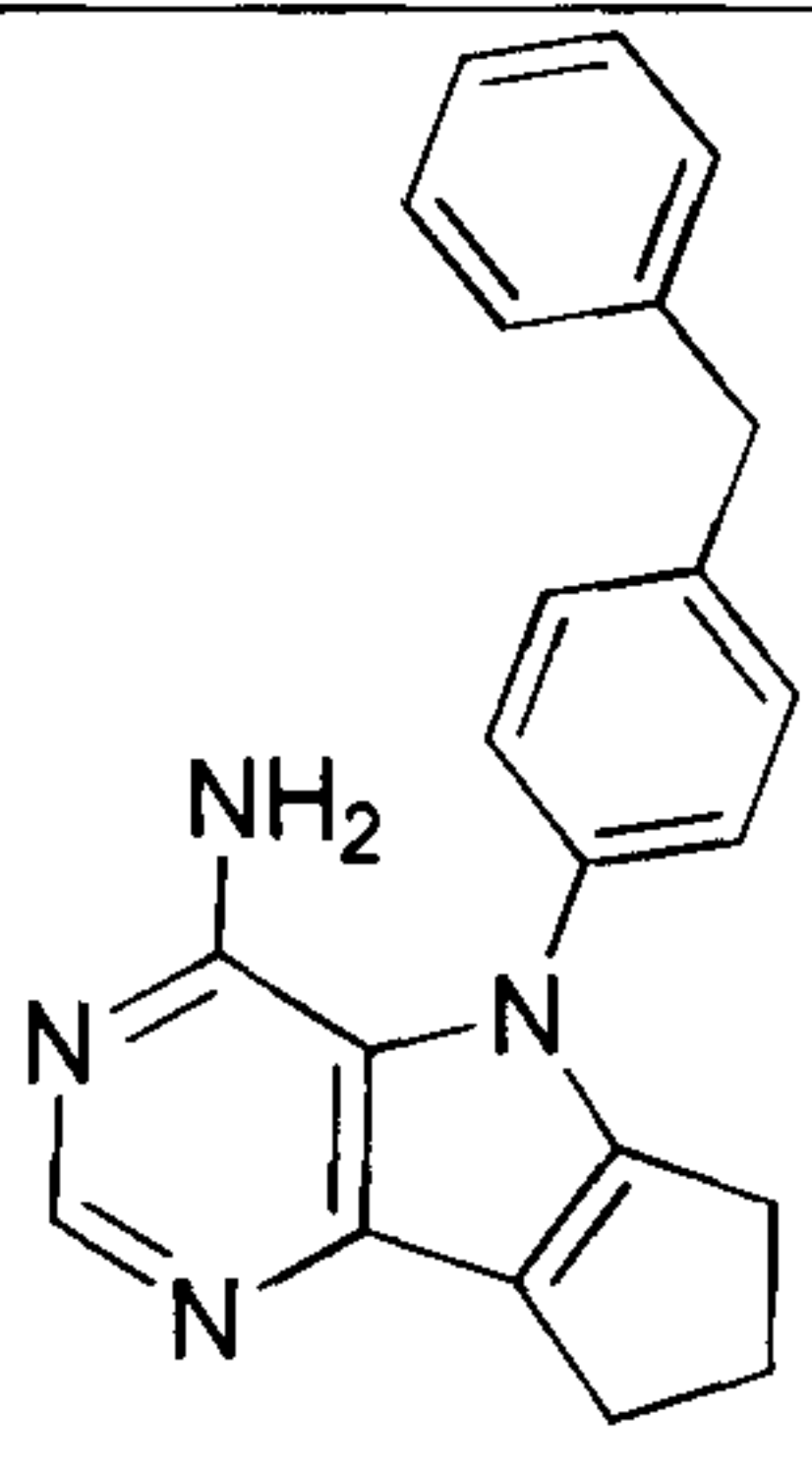
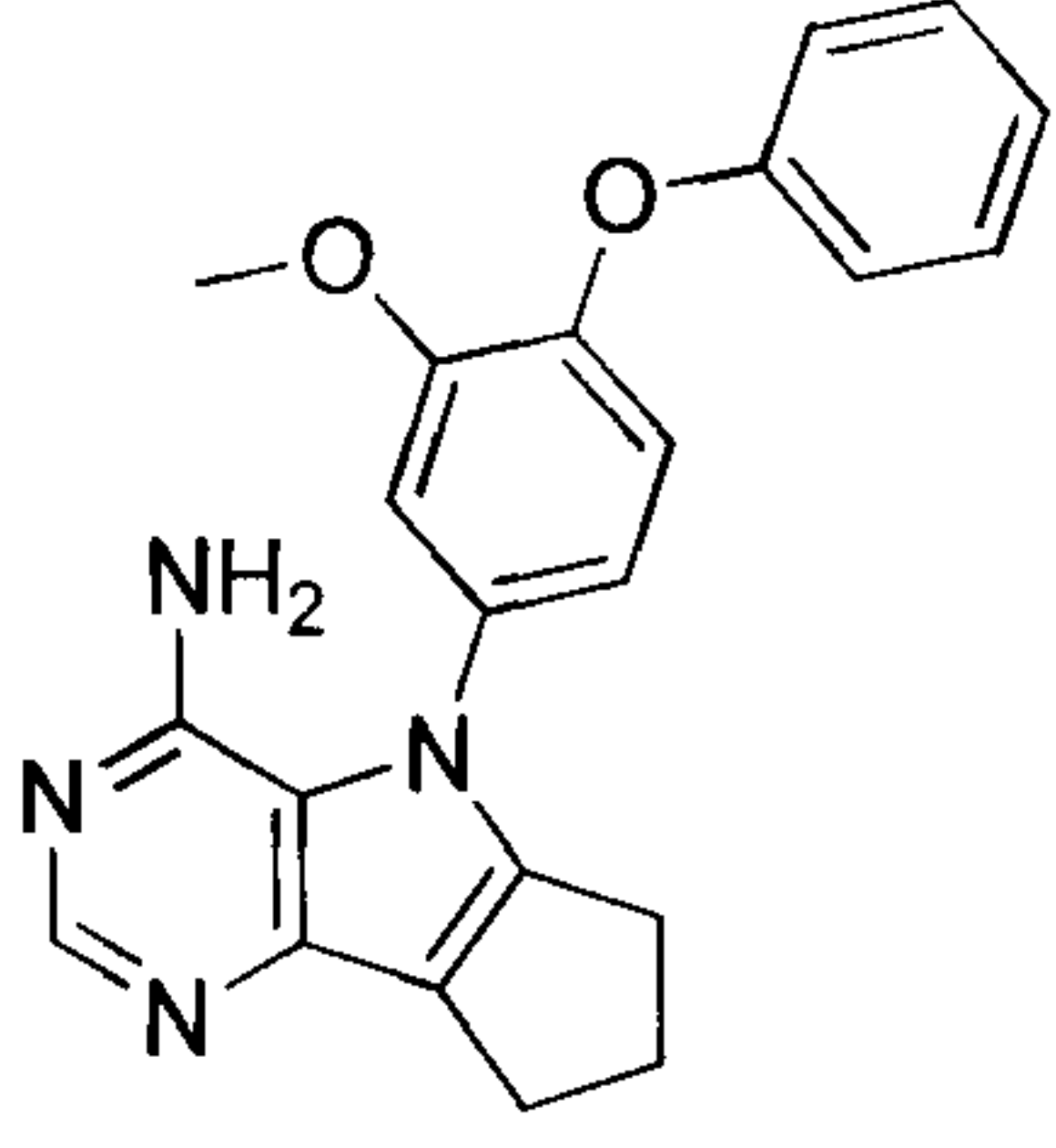
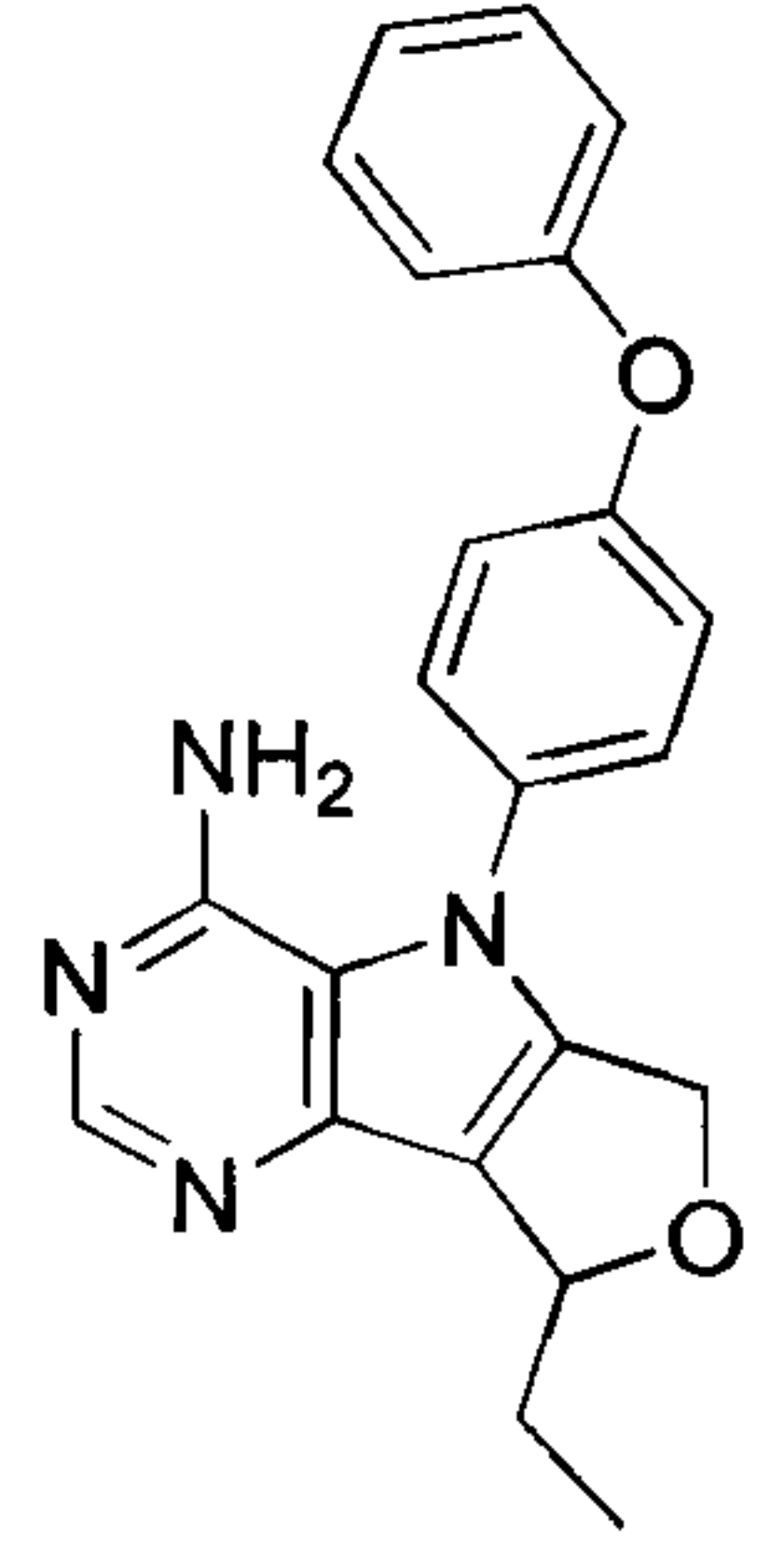
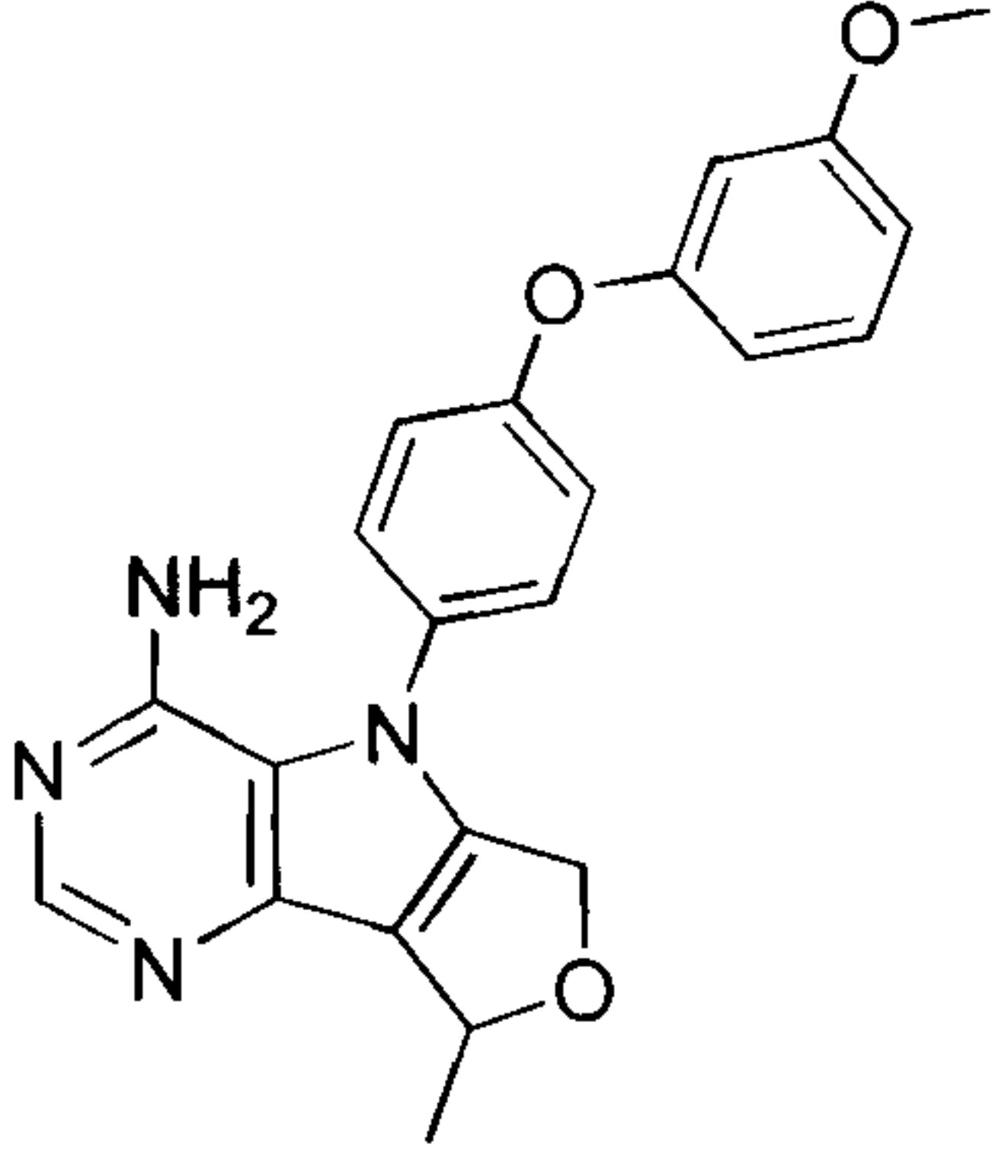
5		$[M+H]^+ = 478.1$
6		$[M+H]^+ = 492.1$
7		$[M+H]^+ = 344.2$
8		$[M+H]^+ = 358.2$

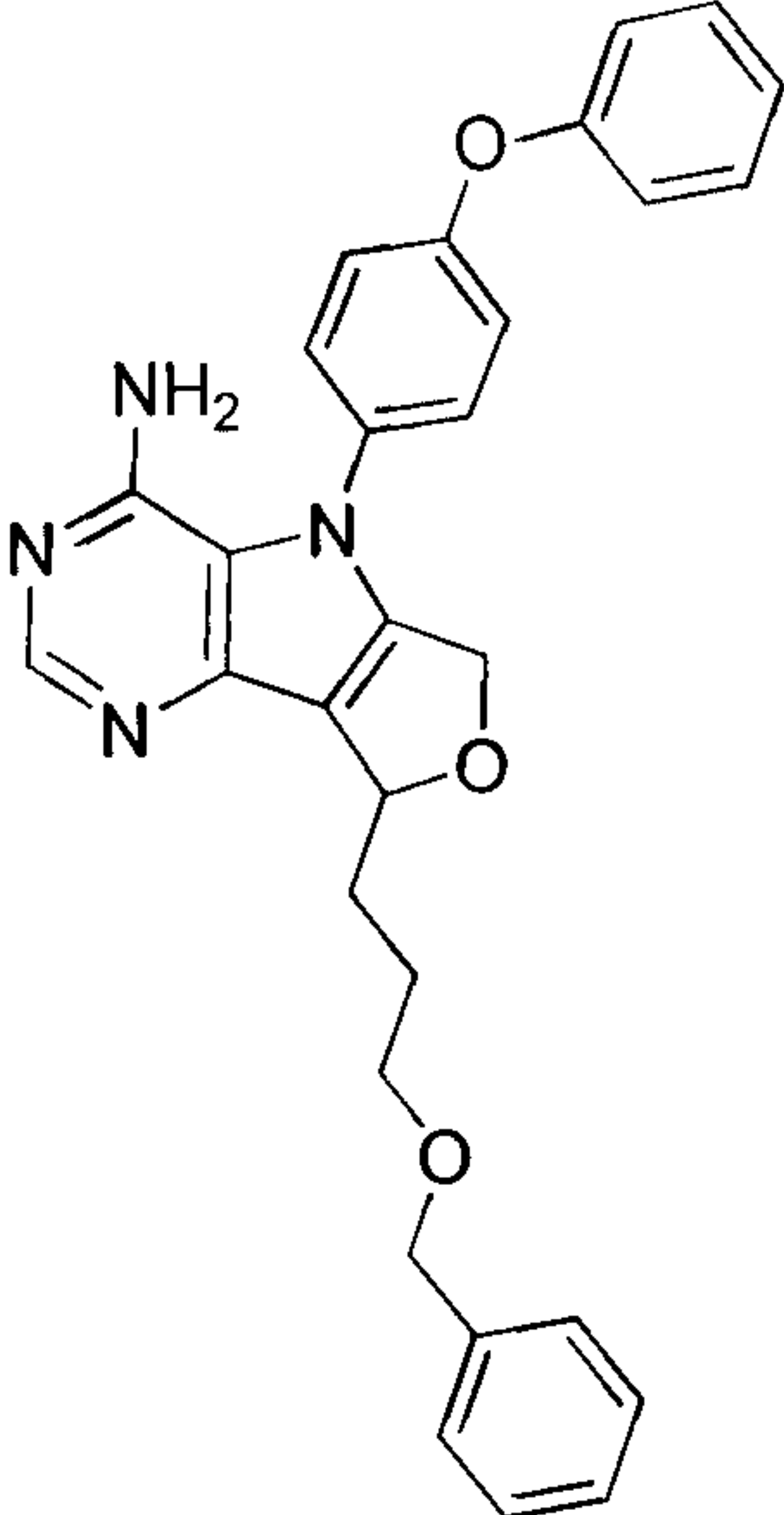
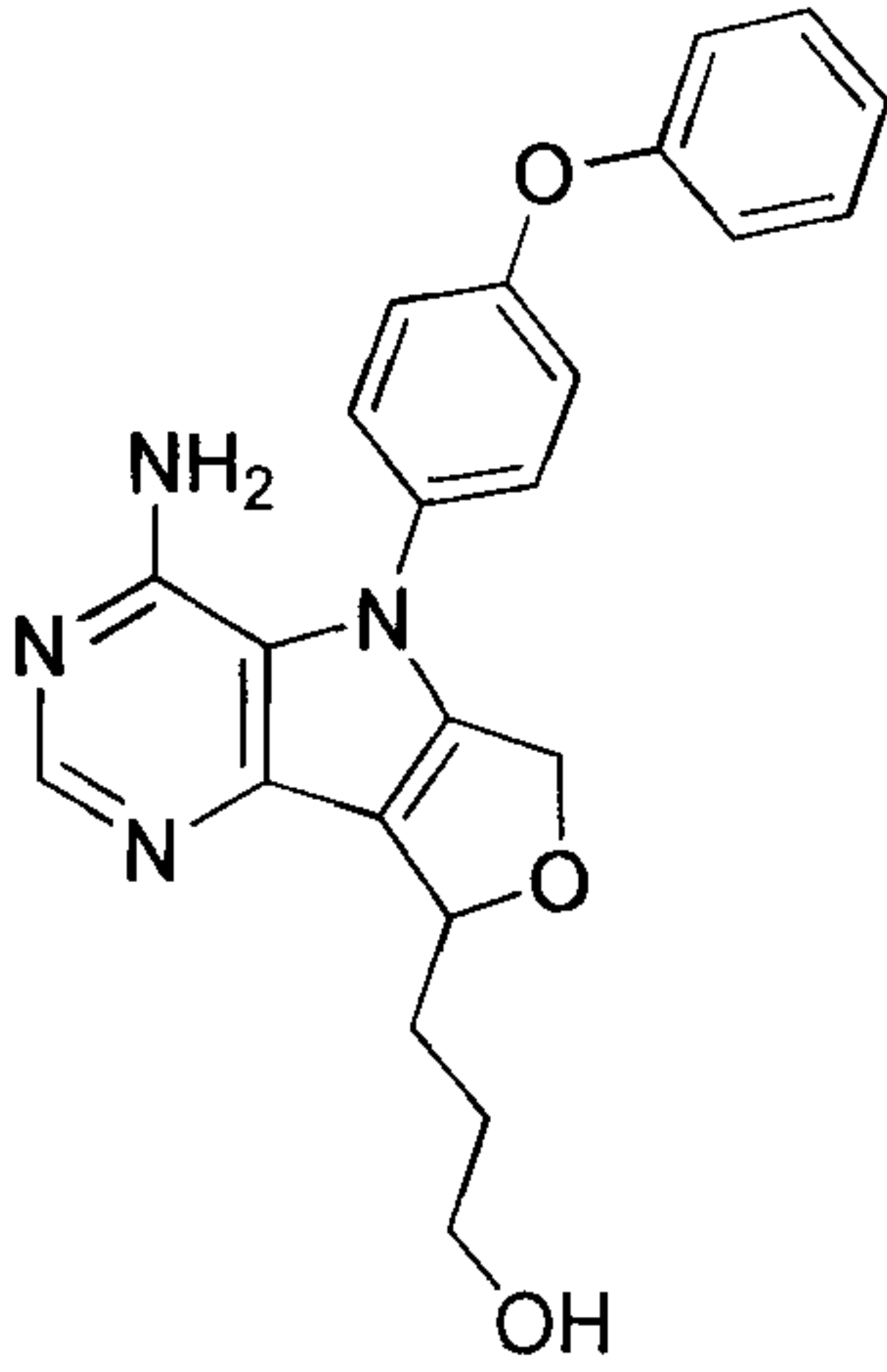
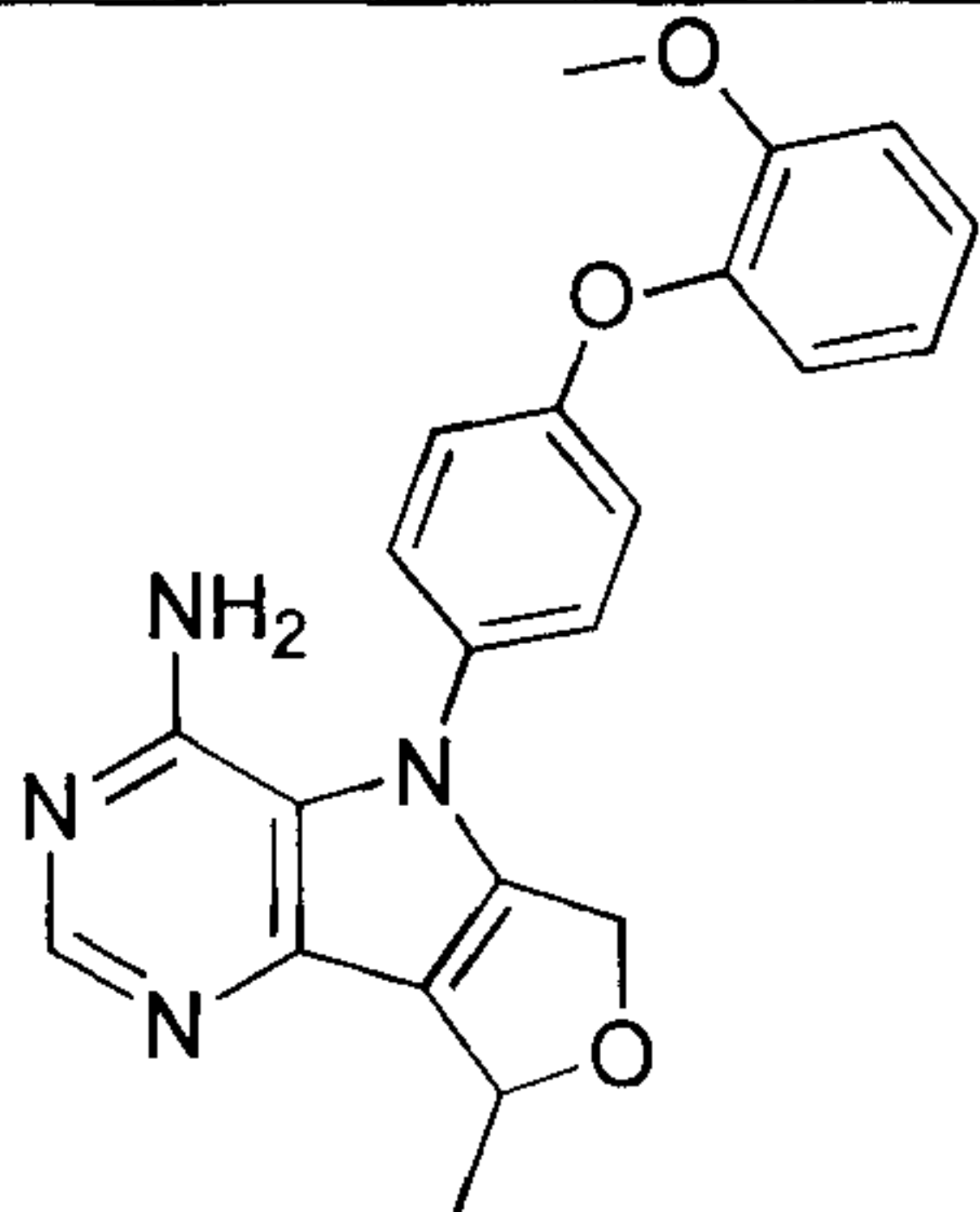
9		$[M+H]^+=484.1$
10		$[M+H]^+=434.2$
11		$[M+H]^+=448.2$

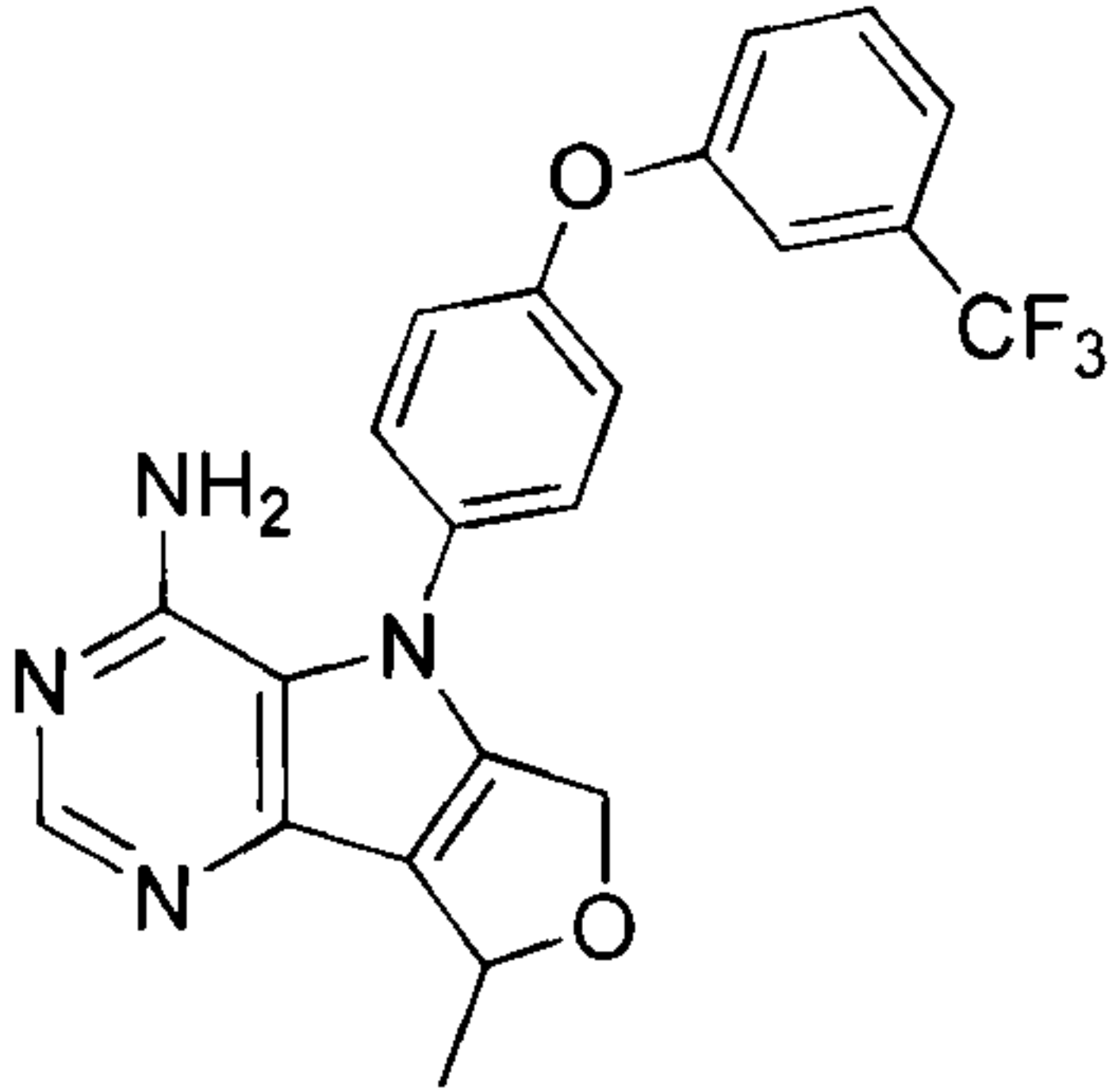
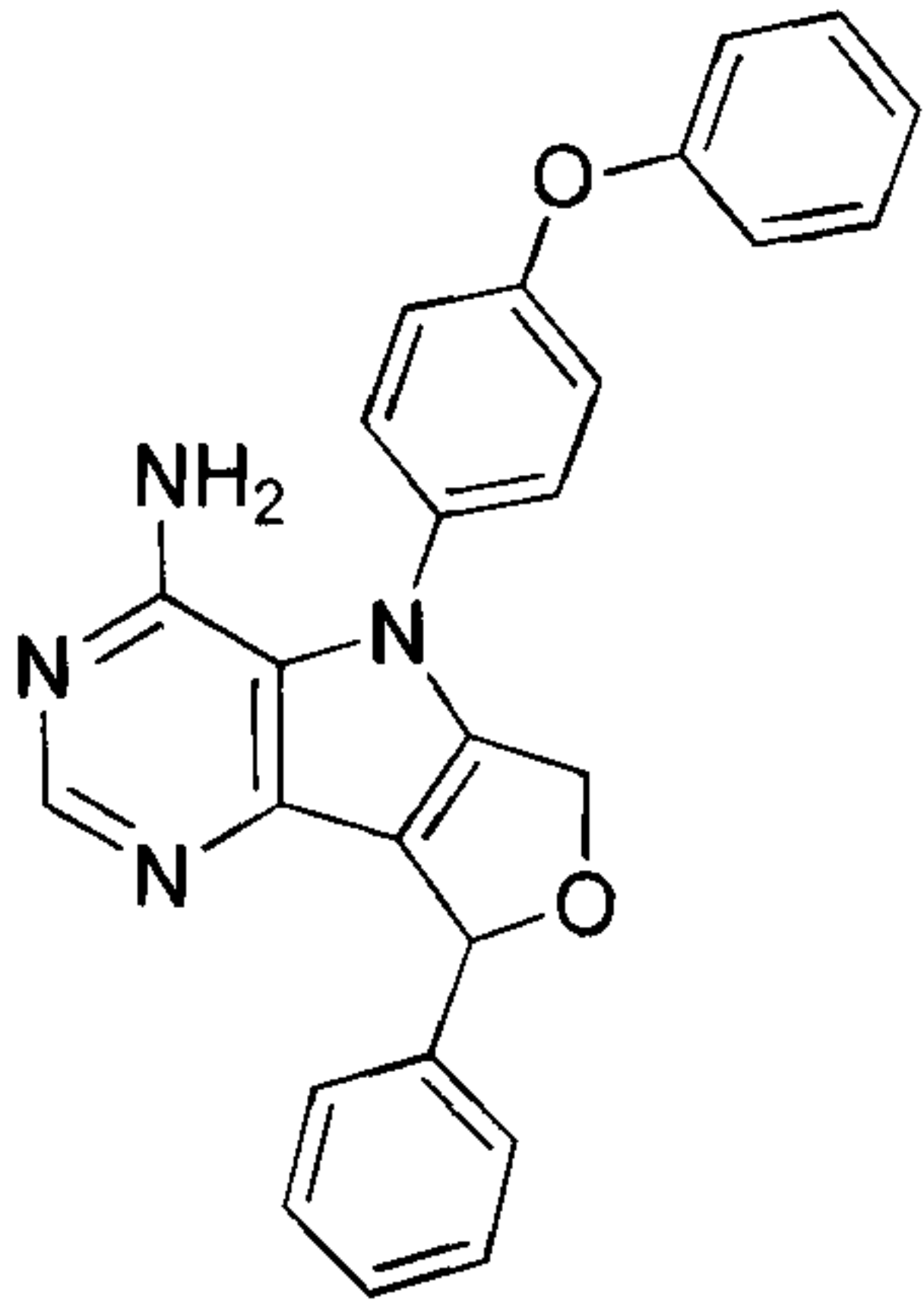
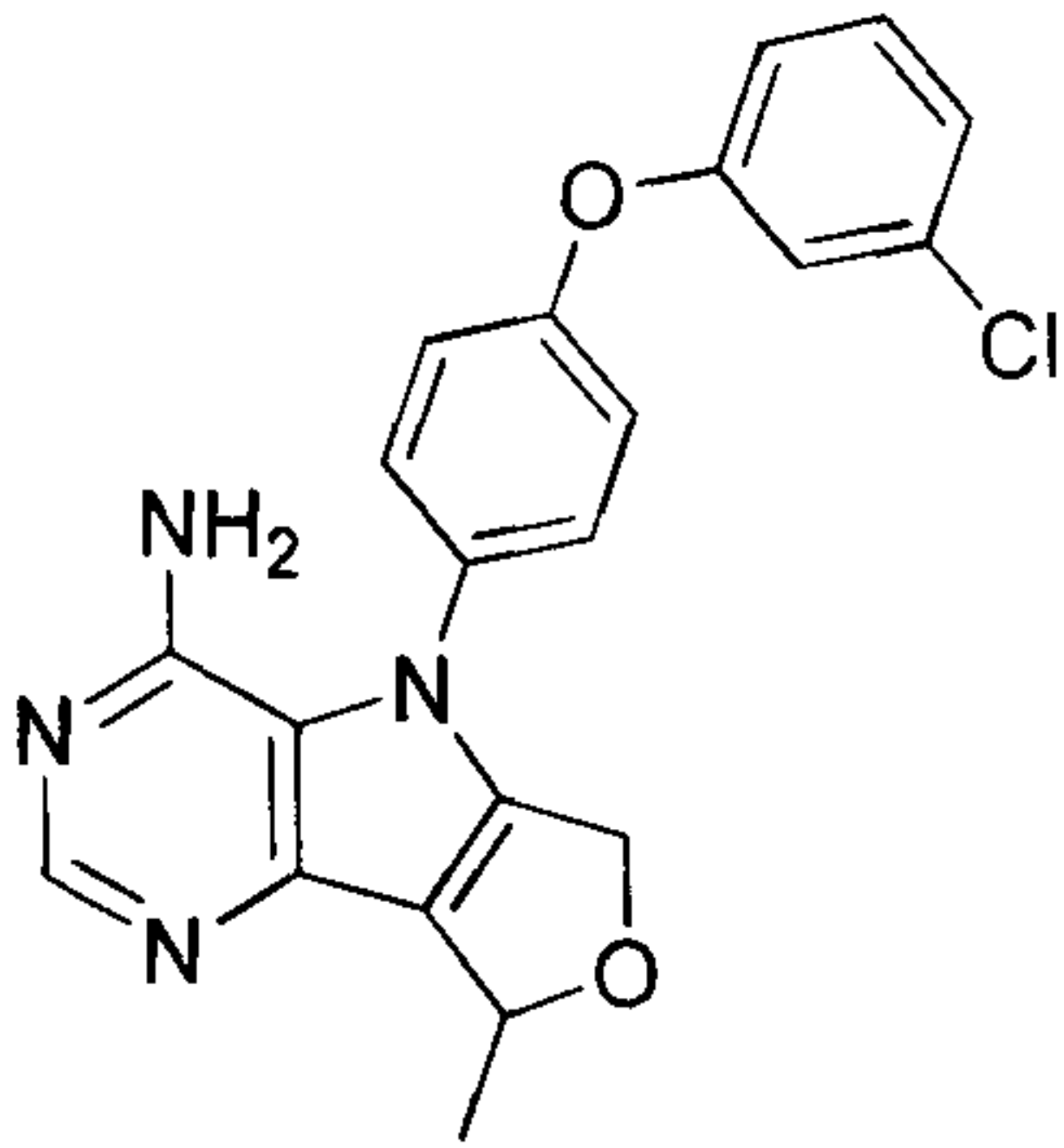
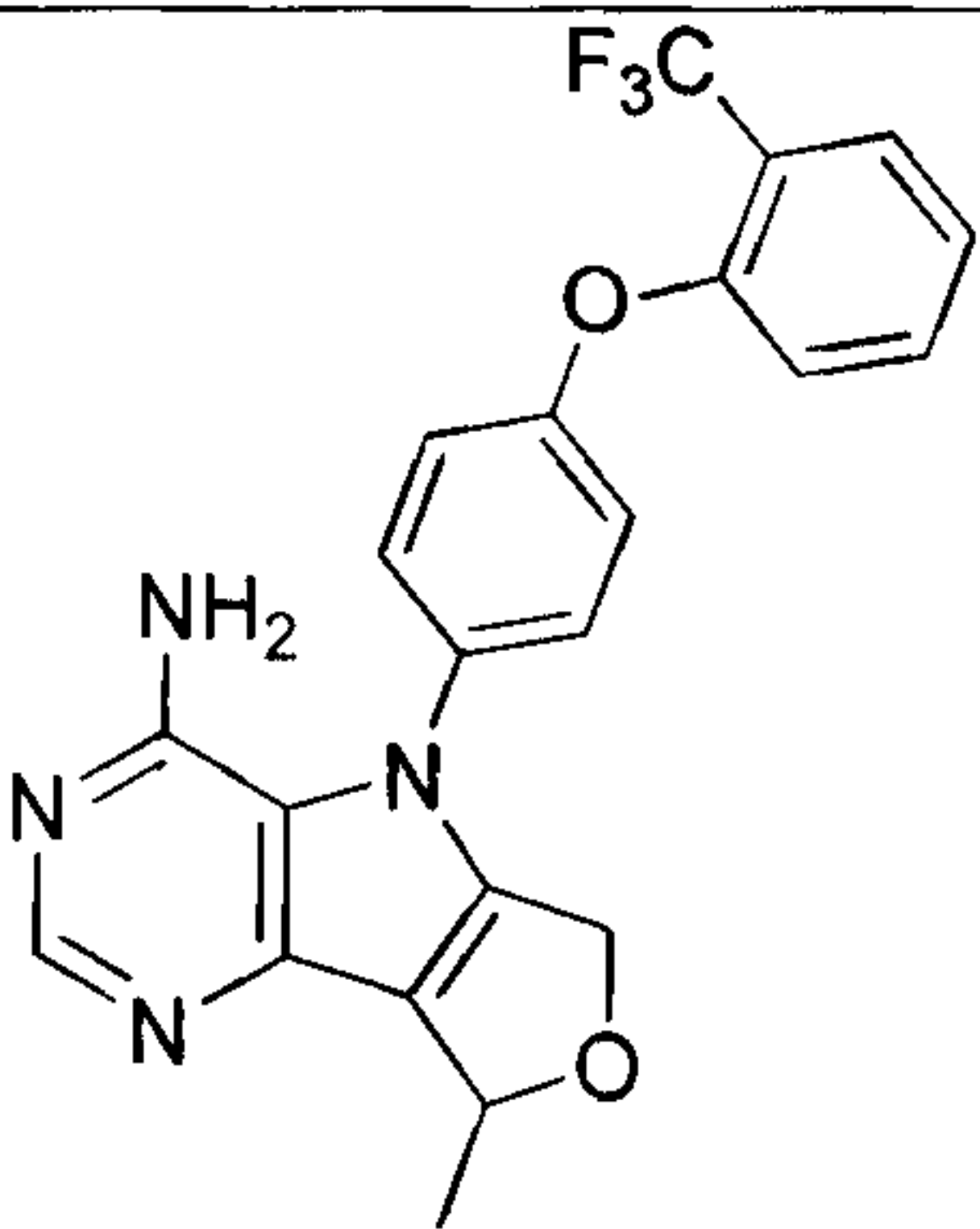
12		$[M+H]^+ = 498.1$
13		$[M+H]^+ = 357.2$
14		$[M+H]^+ = 372.2$

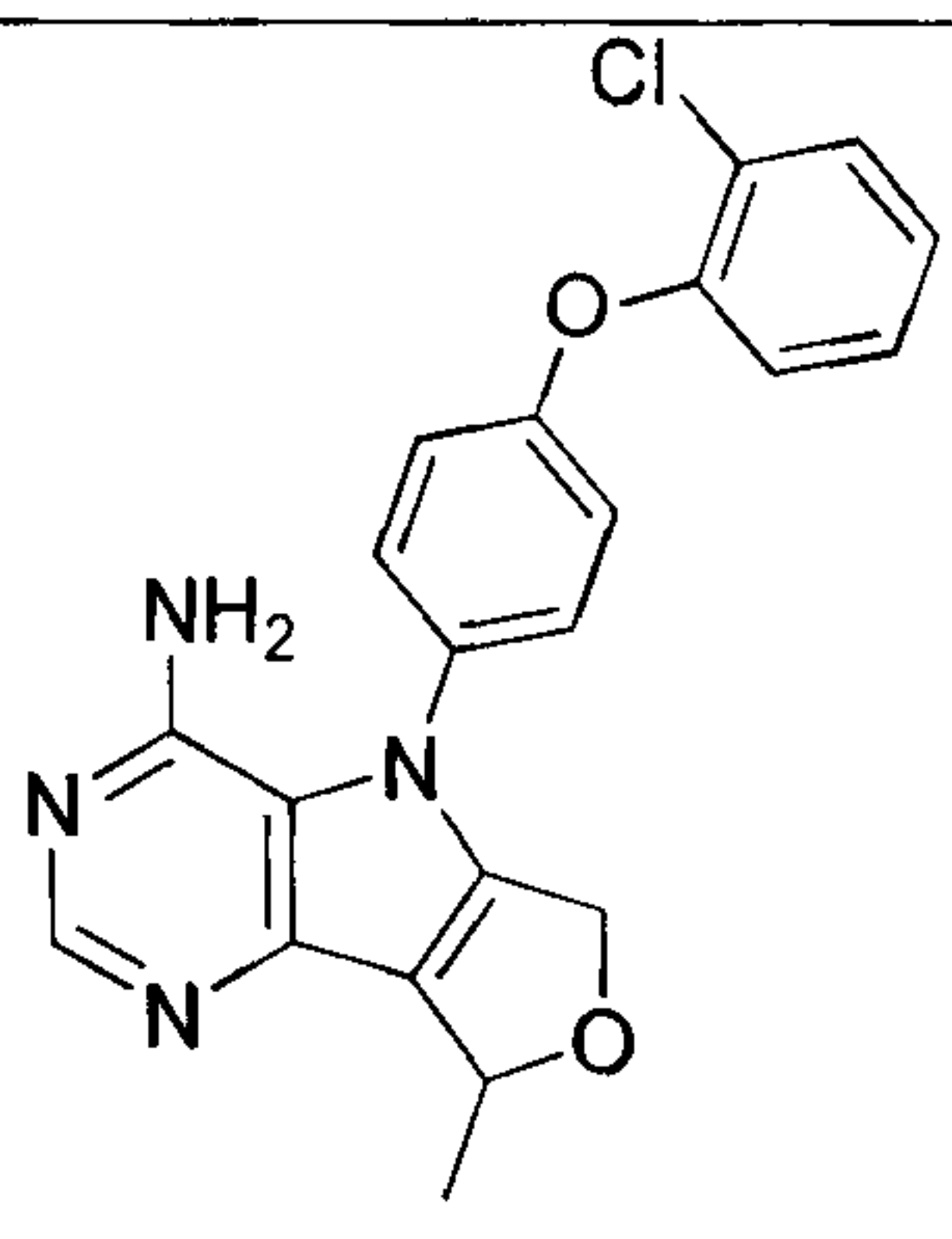
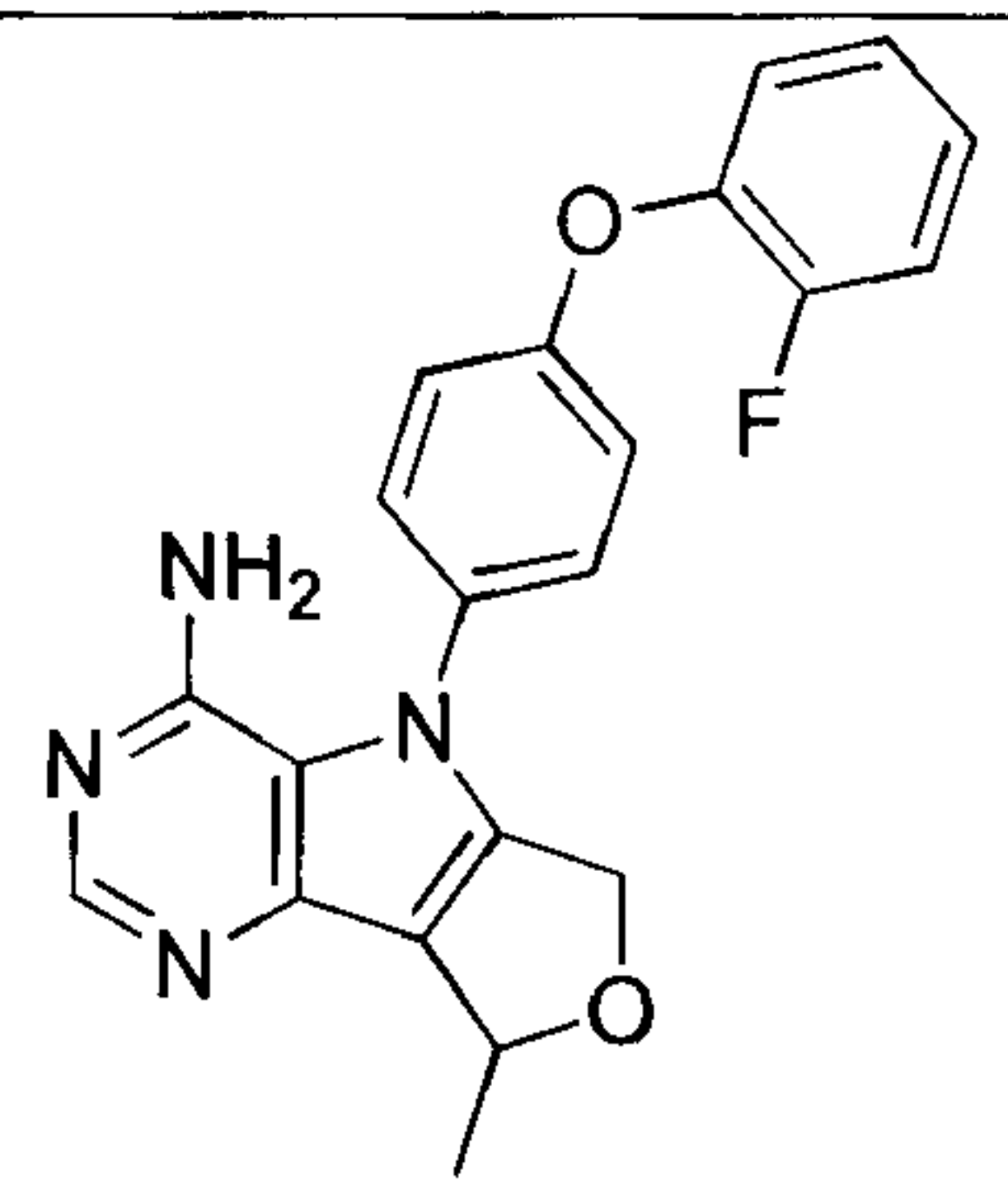
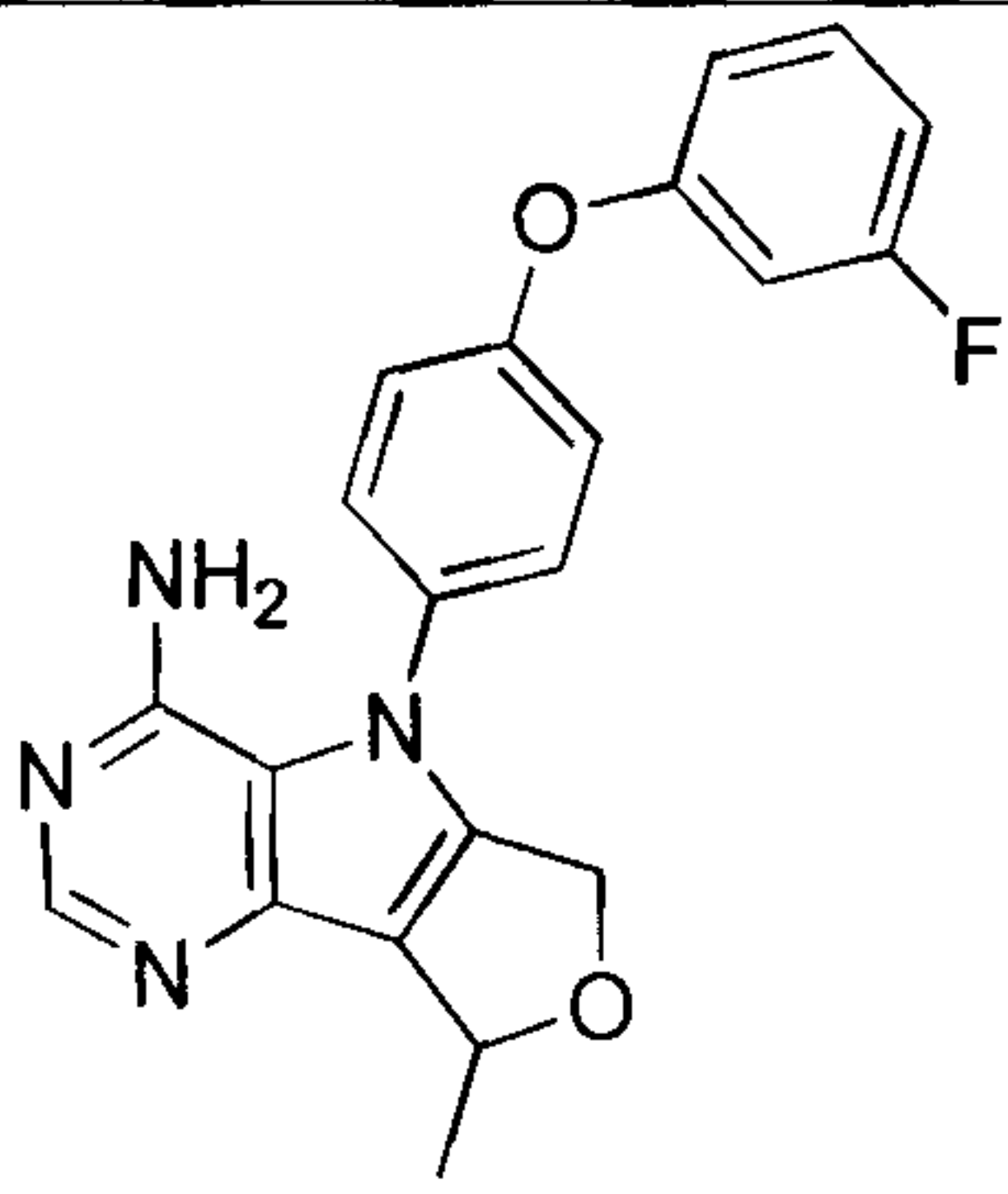
15		$[M+H]^+ = 386.3$
16		$[M+H]^+ = 462.1$
17		$[M+H]^+ = 415.1$

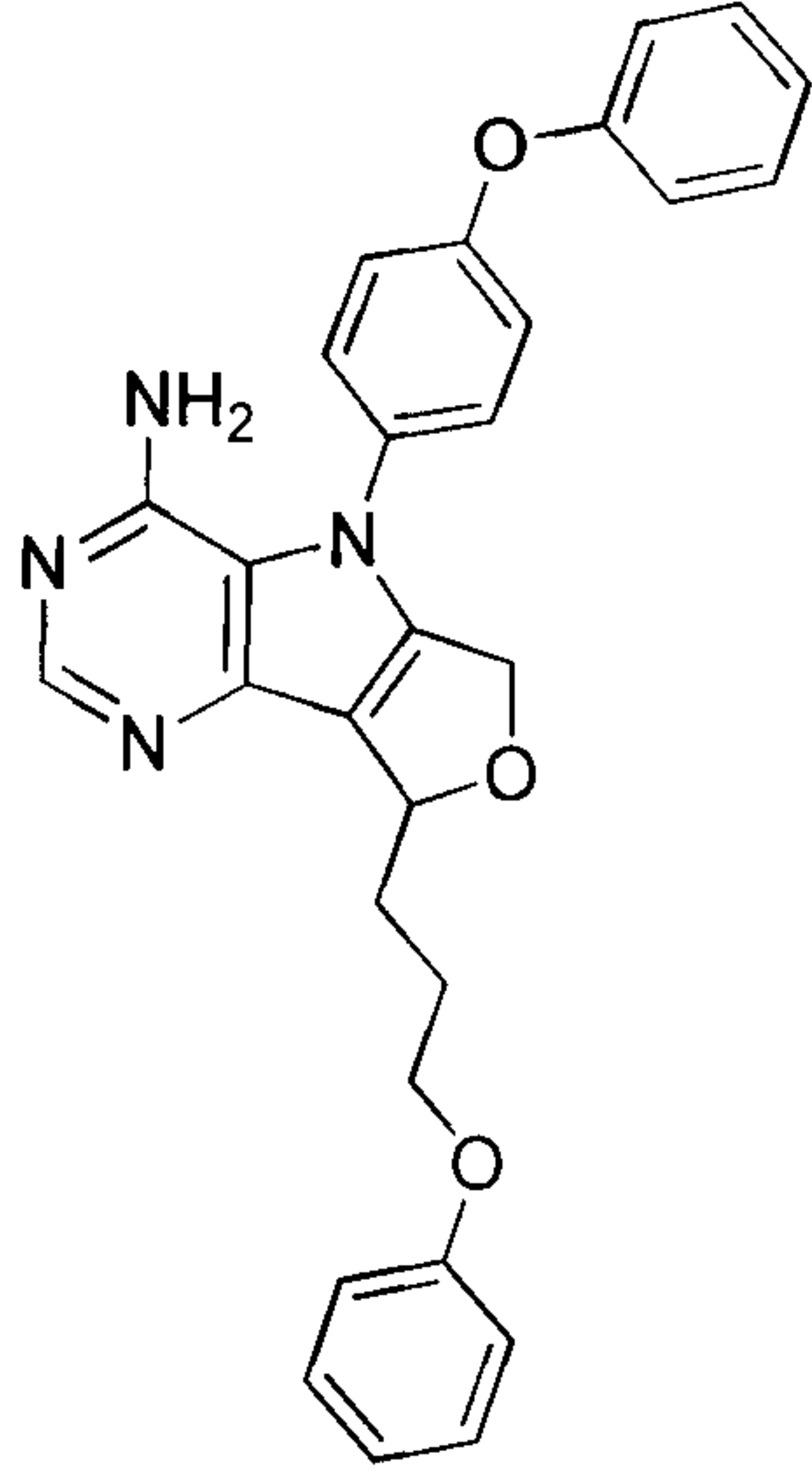
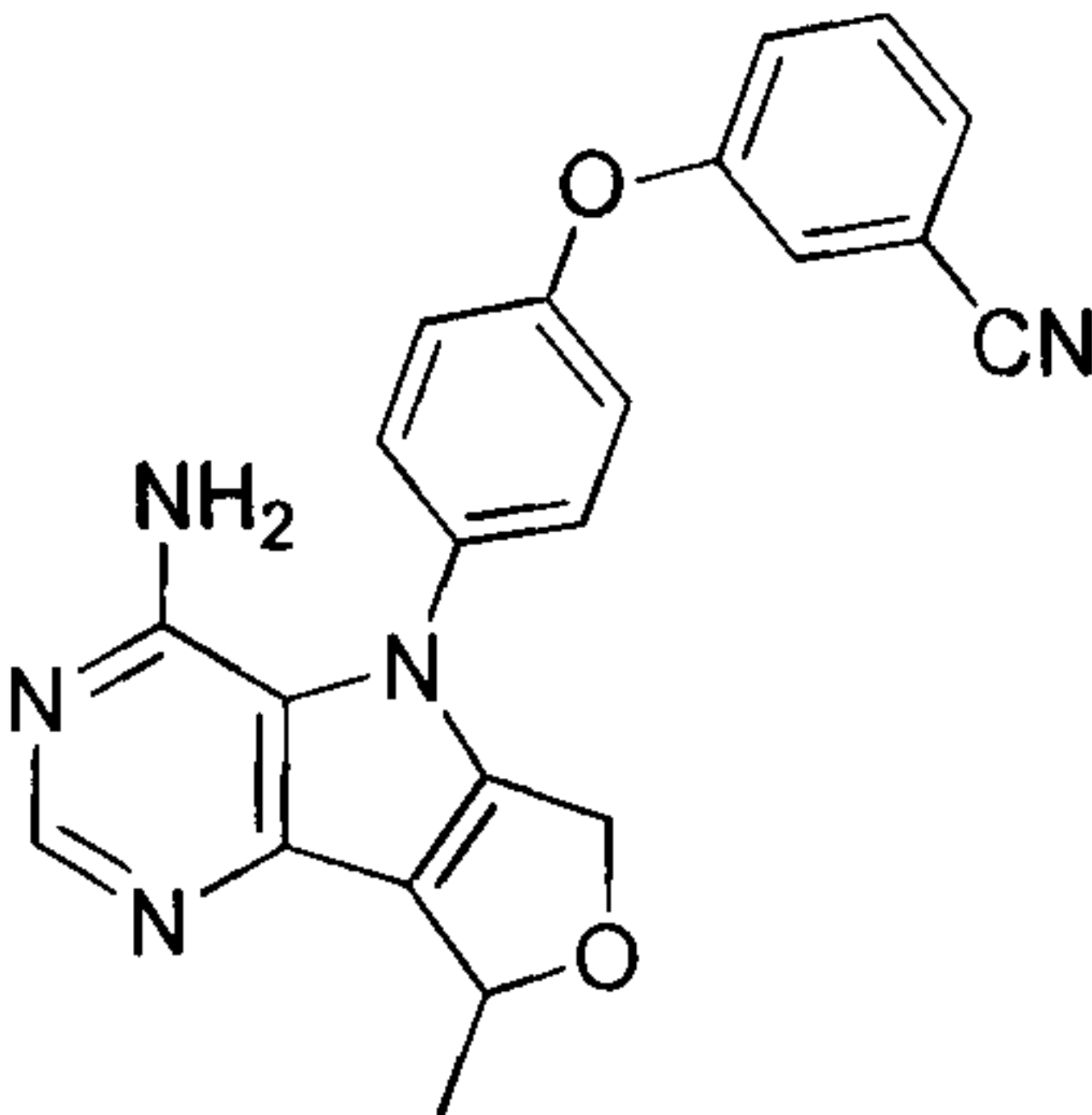
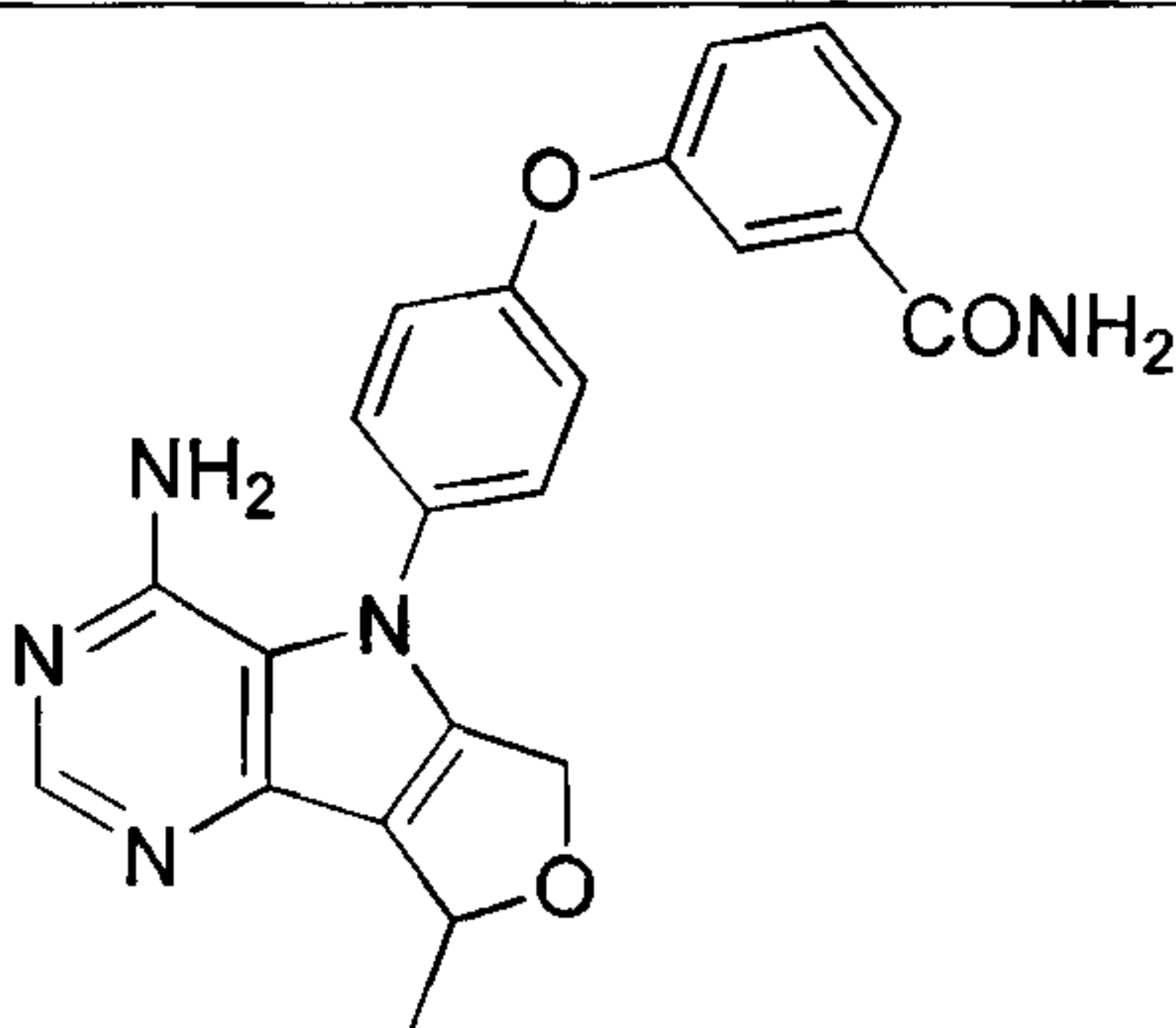
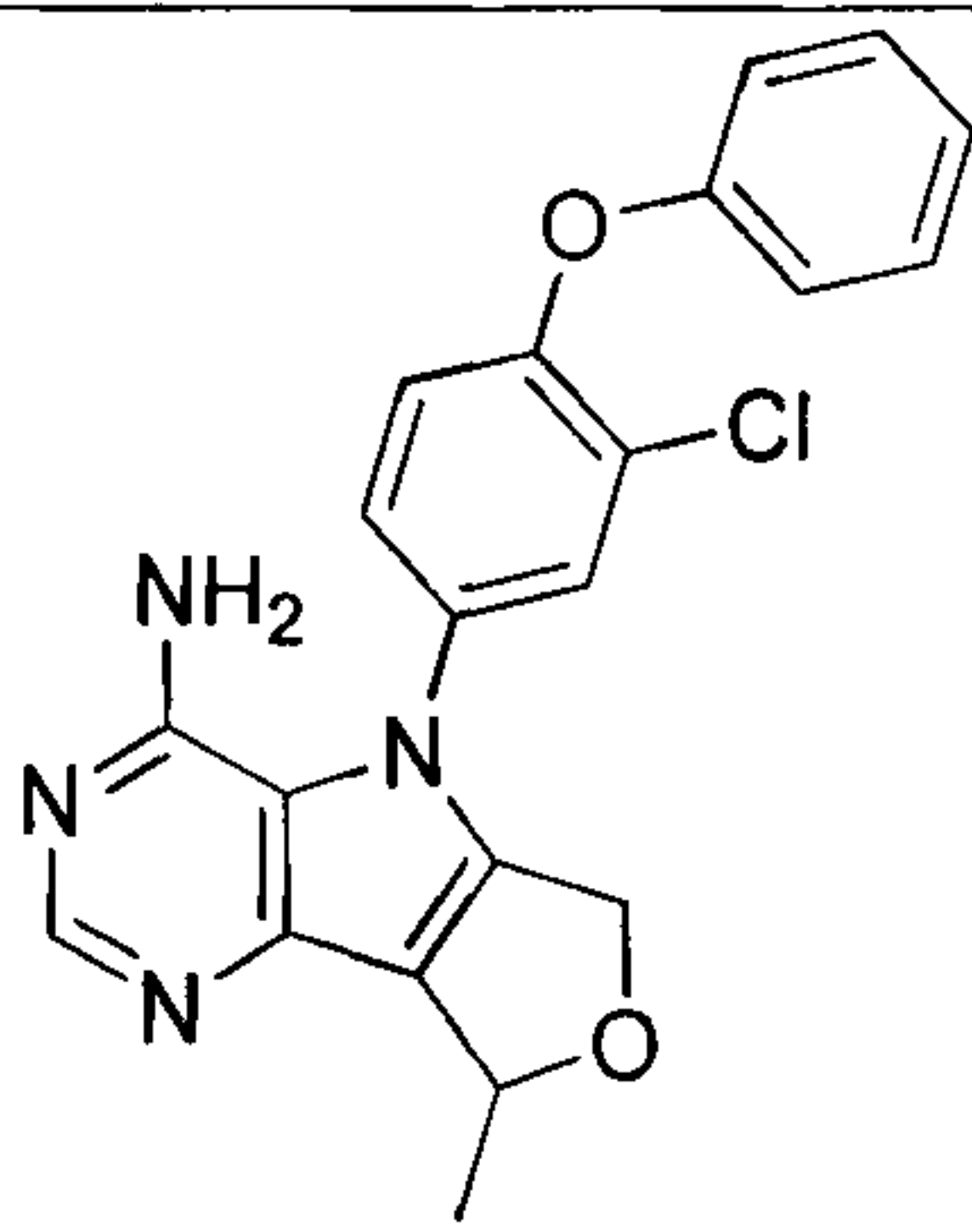
18		$[M+H]^+ = 448.3$
19		$[M+H]^+ = 401.2$
20		$[M+H]^+ = 359.2$
21		$[M+H]^+ = 345.2$

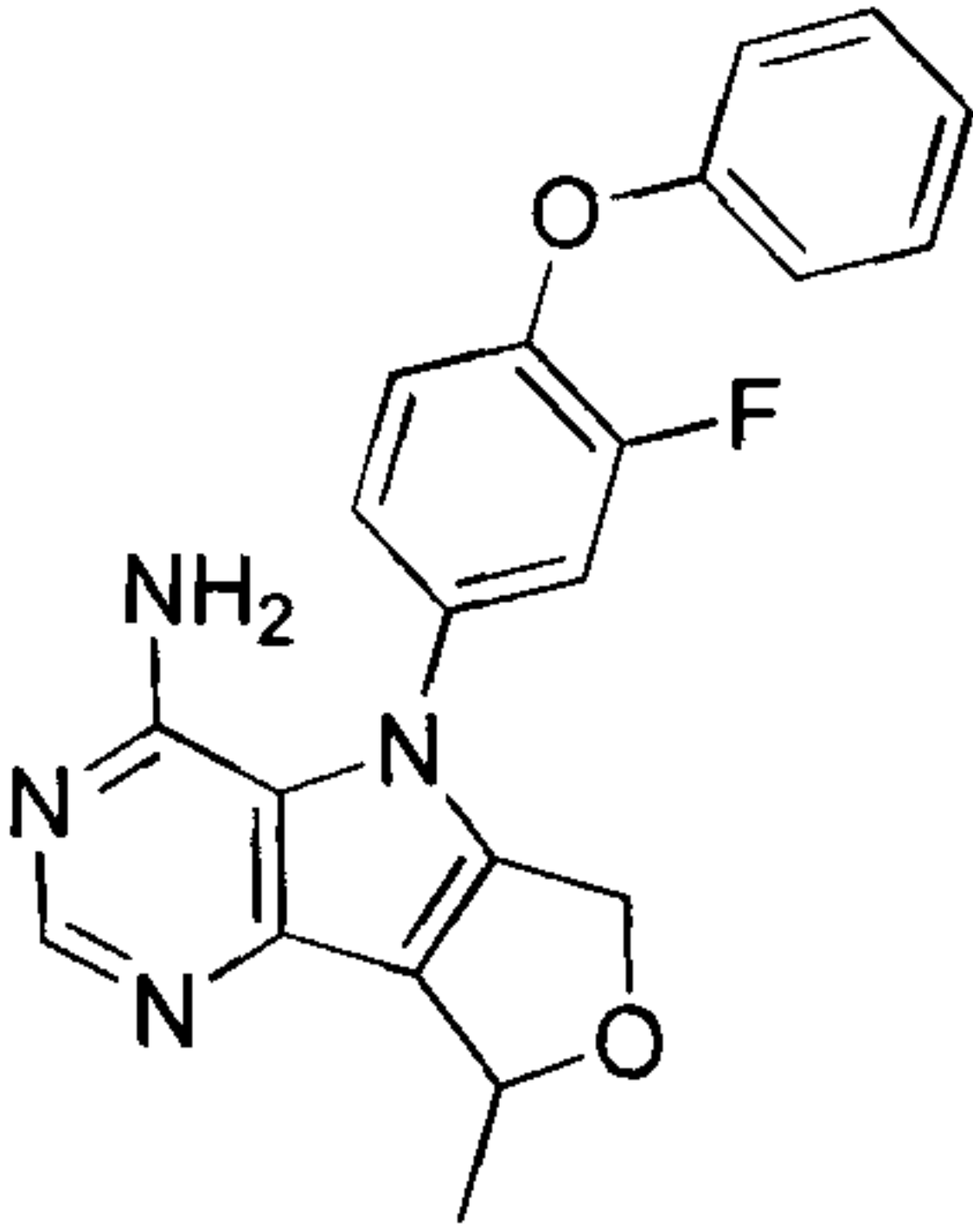
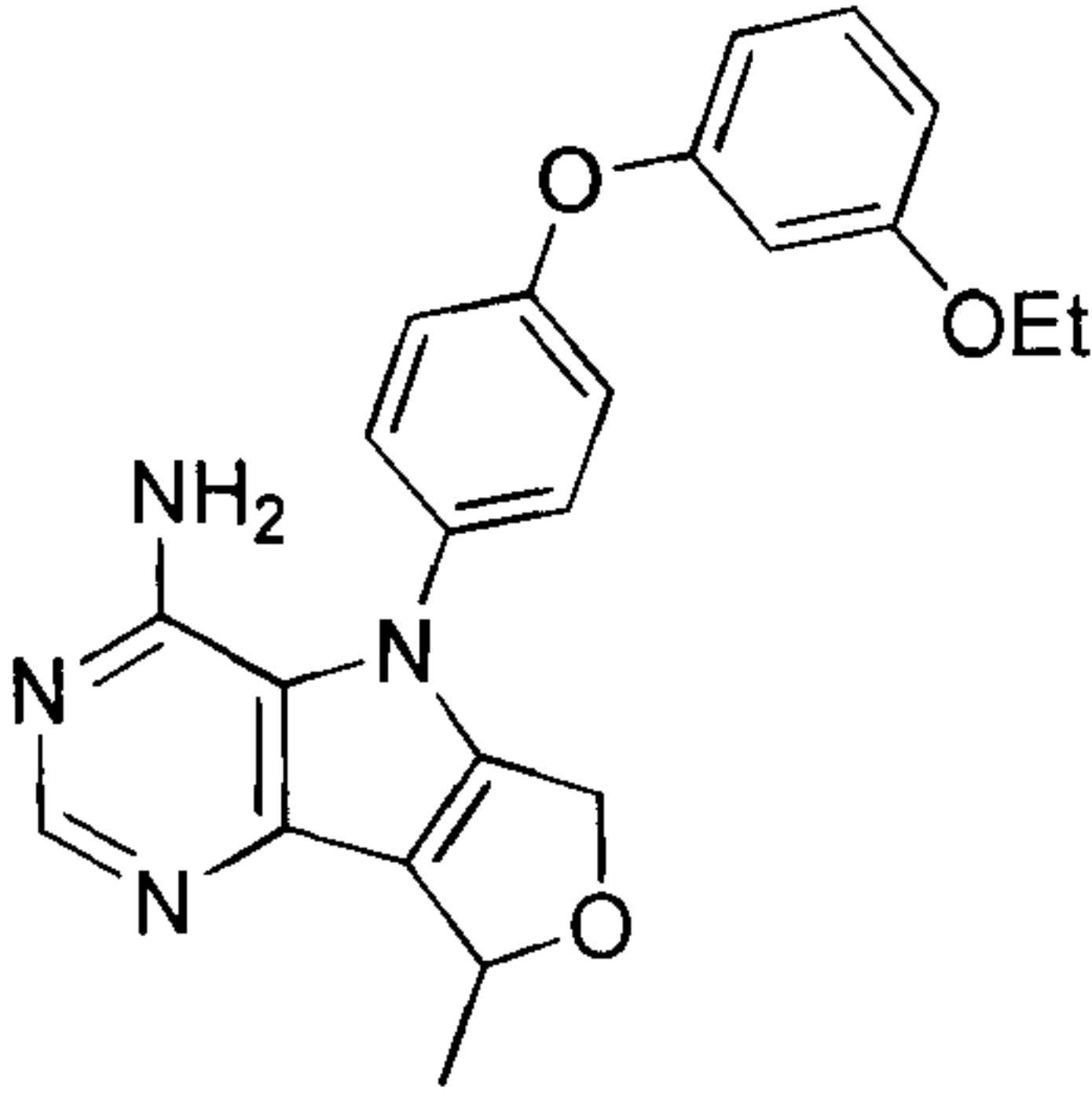
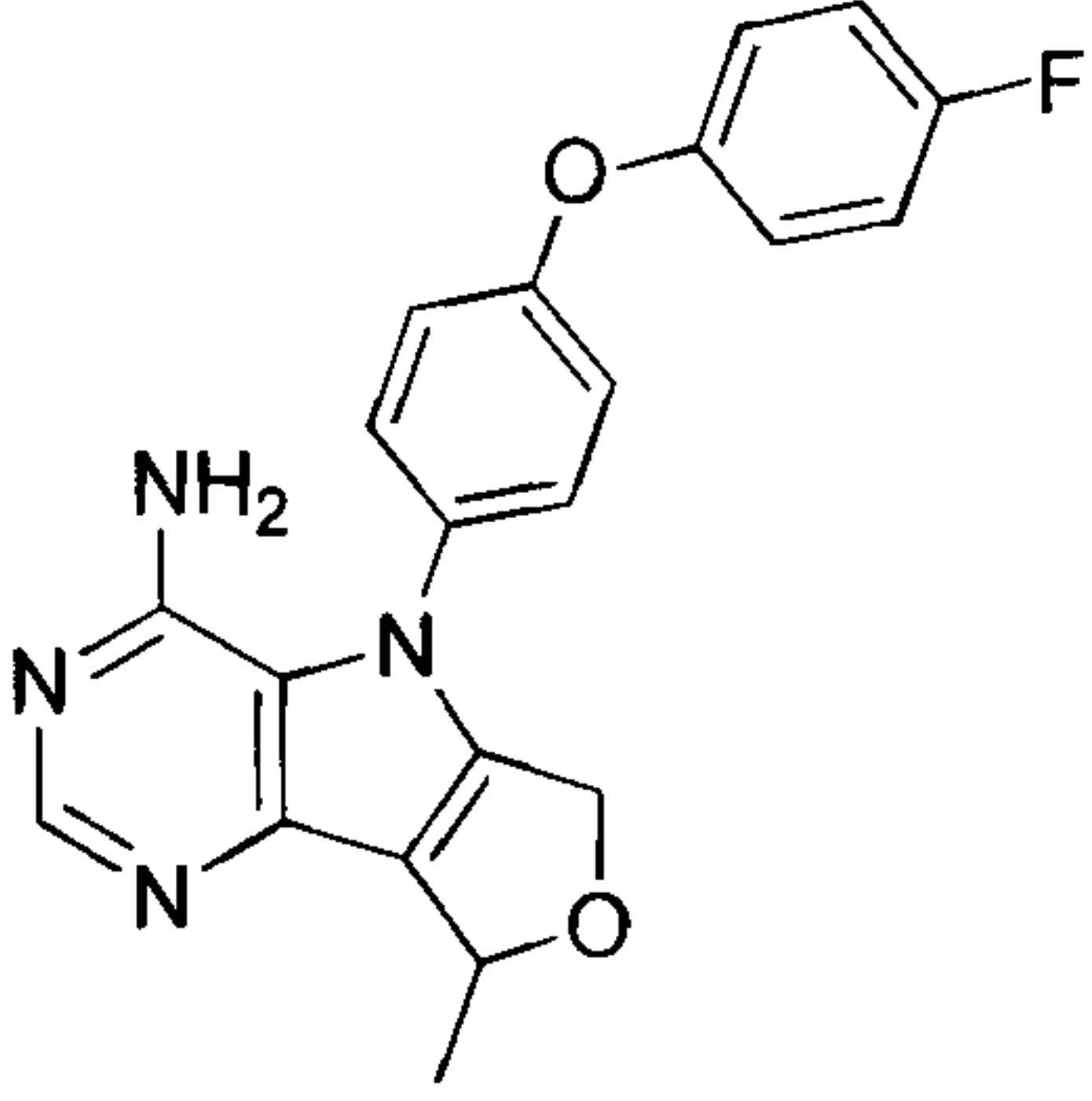
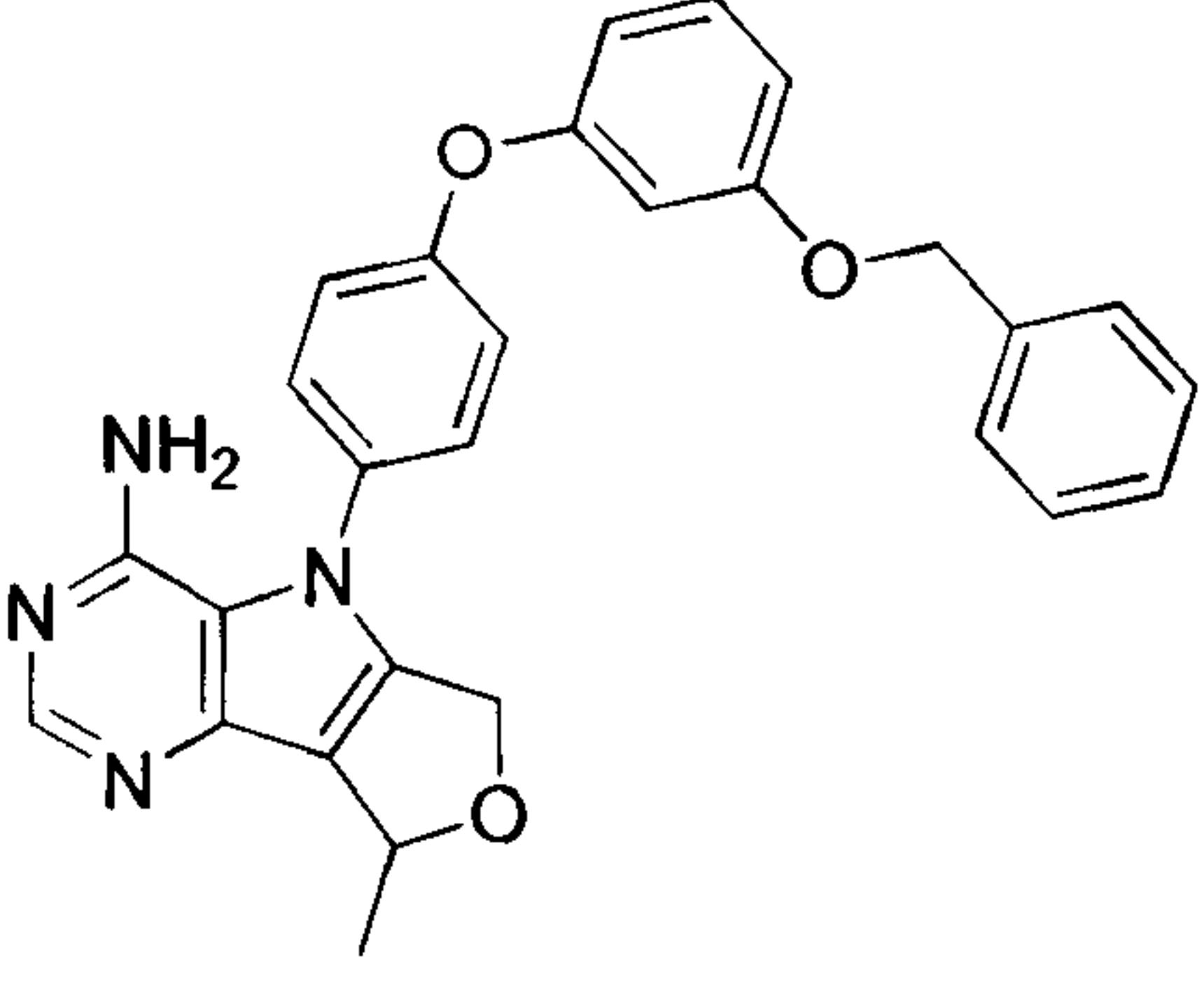
22		$[M+H]^+ = 341.3$
23		$[M+H]^+ = 373.2$
24		$[M+H]^+ = 373.3$
25		$[M+H]^+ = 389.2$

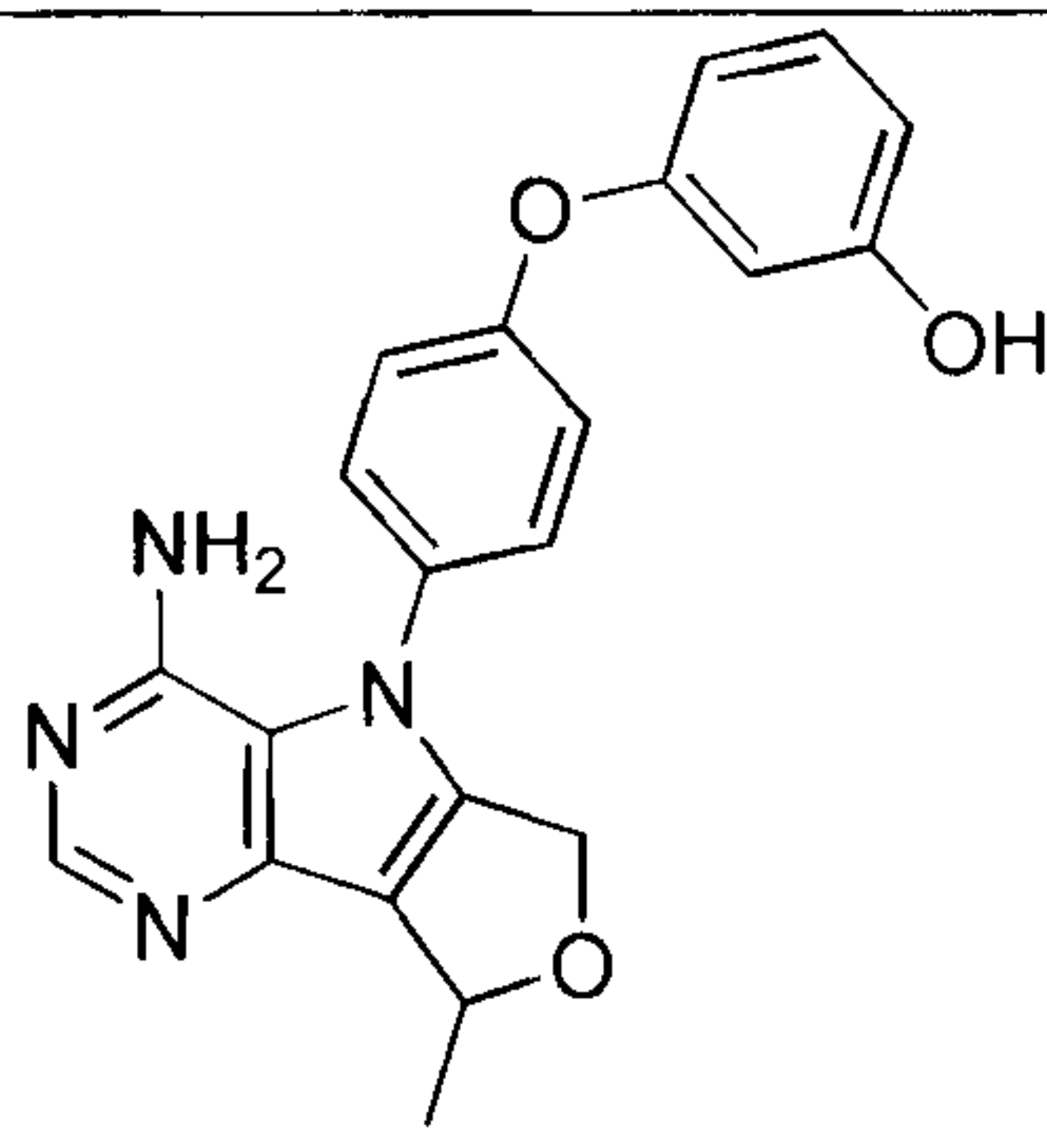
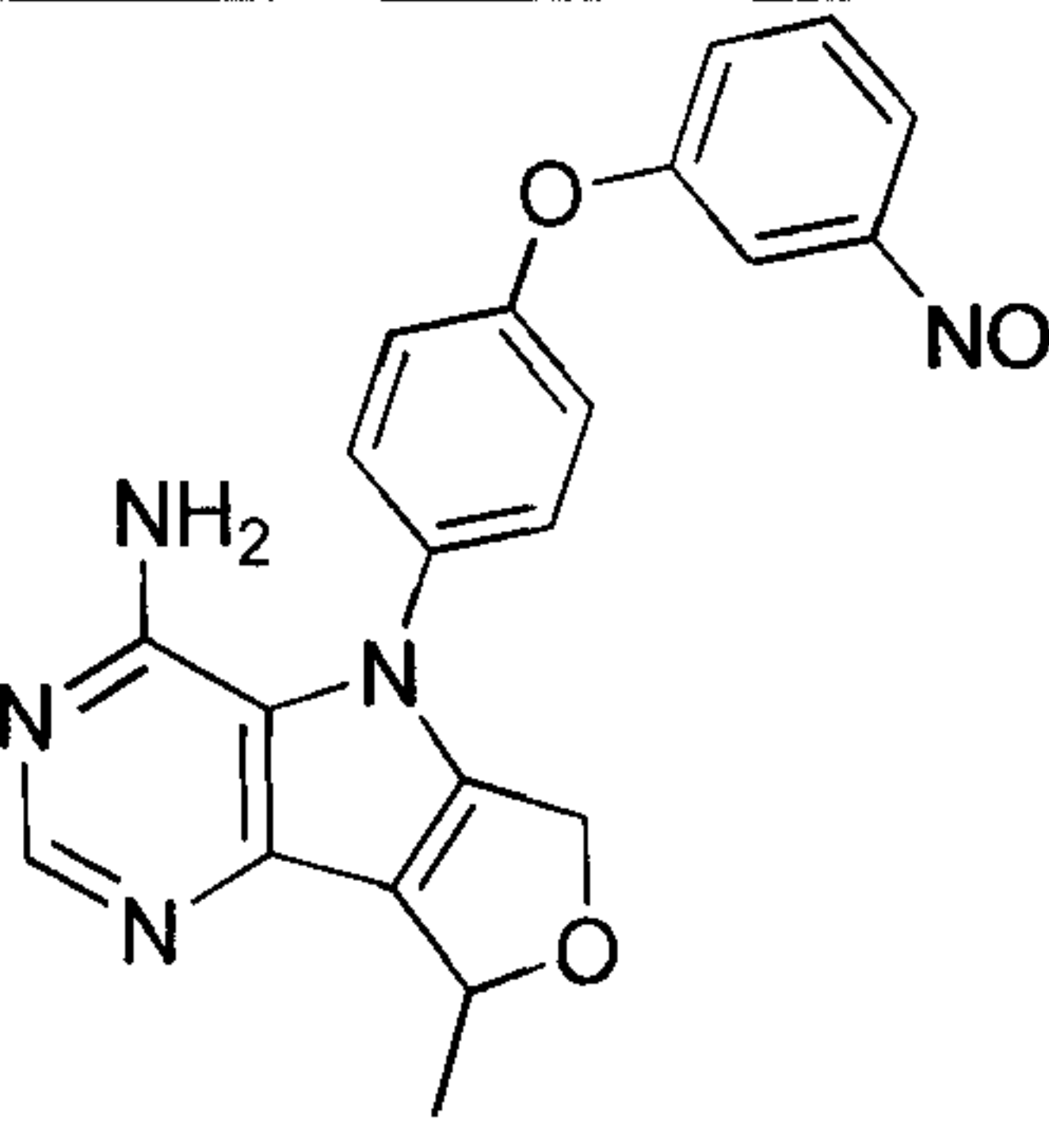
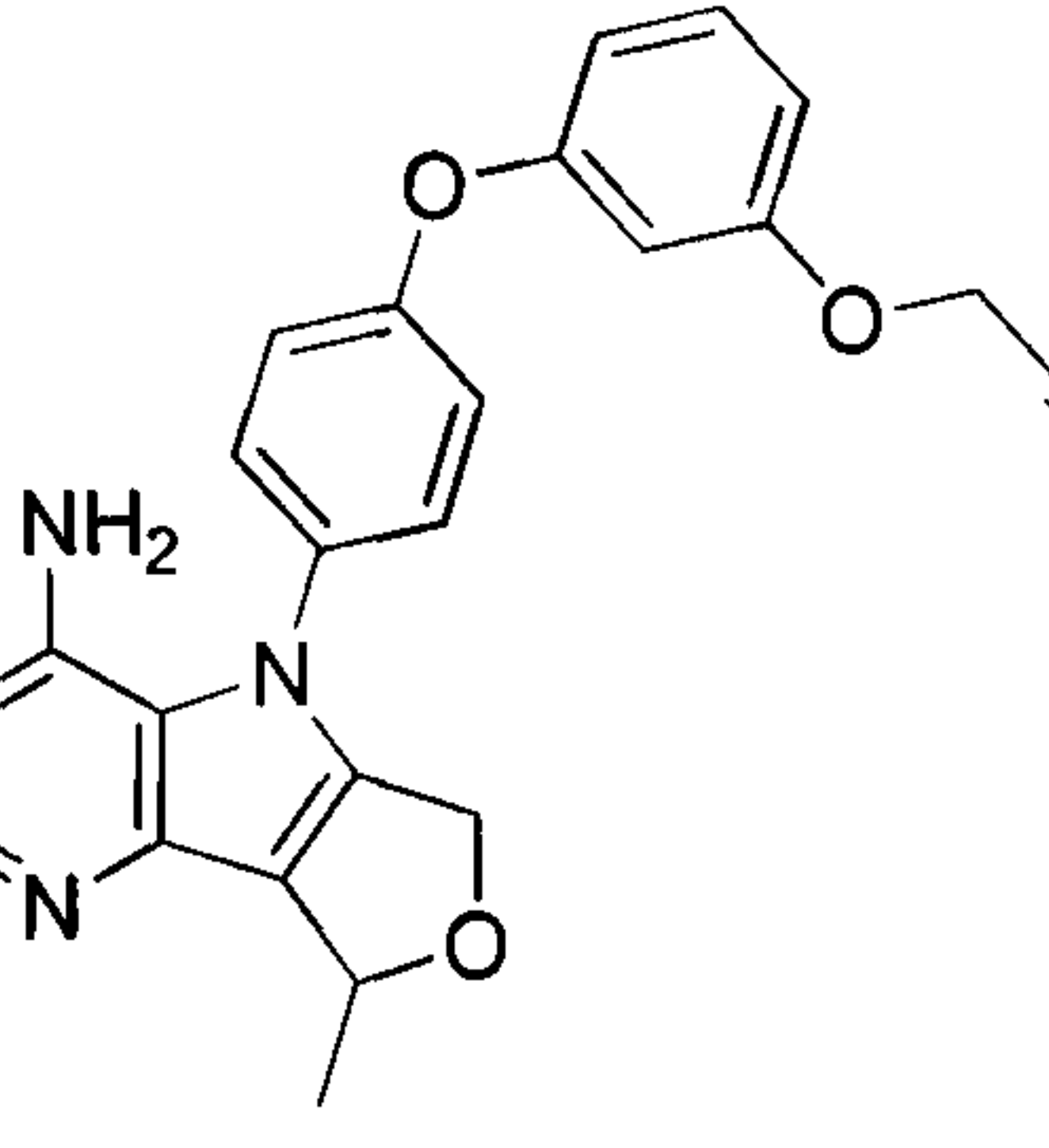
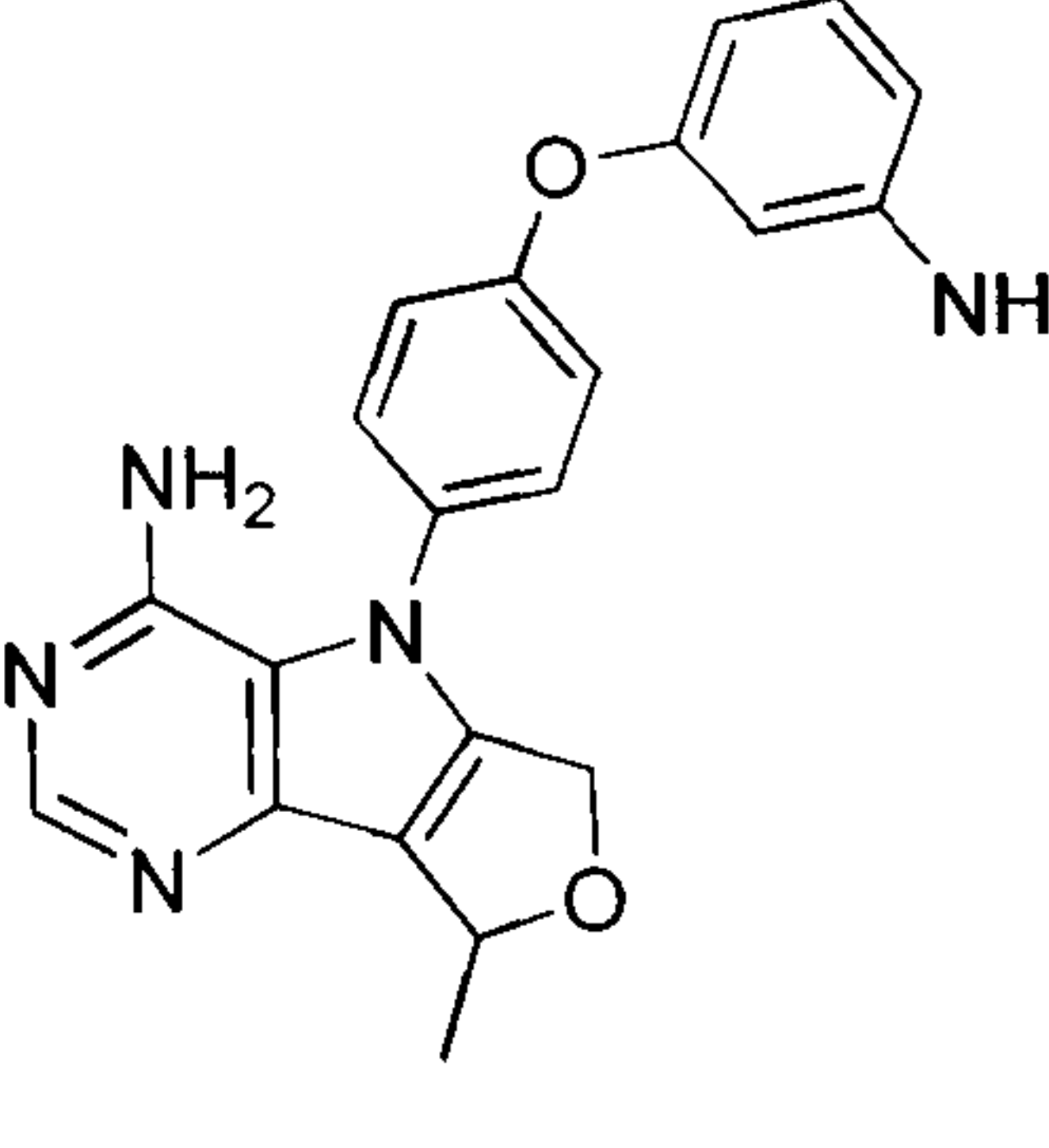
26		$[M+H]^+=493.3$
27		$[M+H]^+=403.3$
28		$[M+H]^+=389.3$

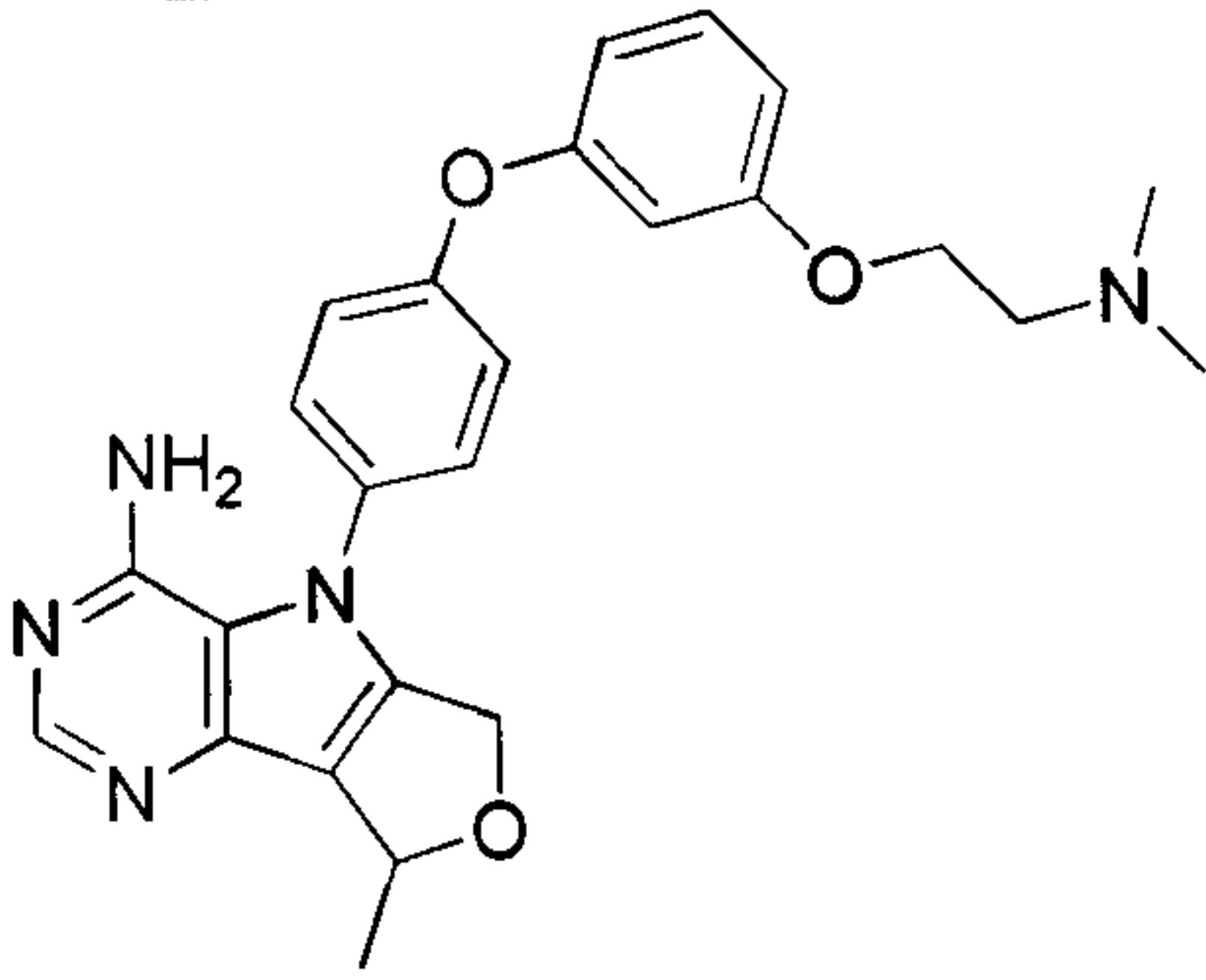
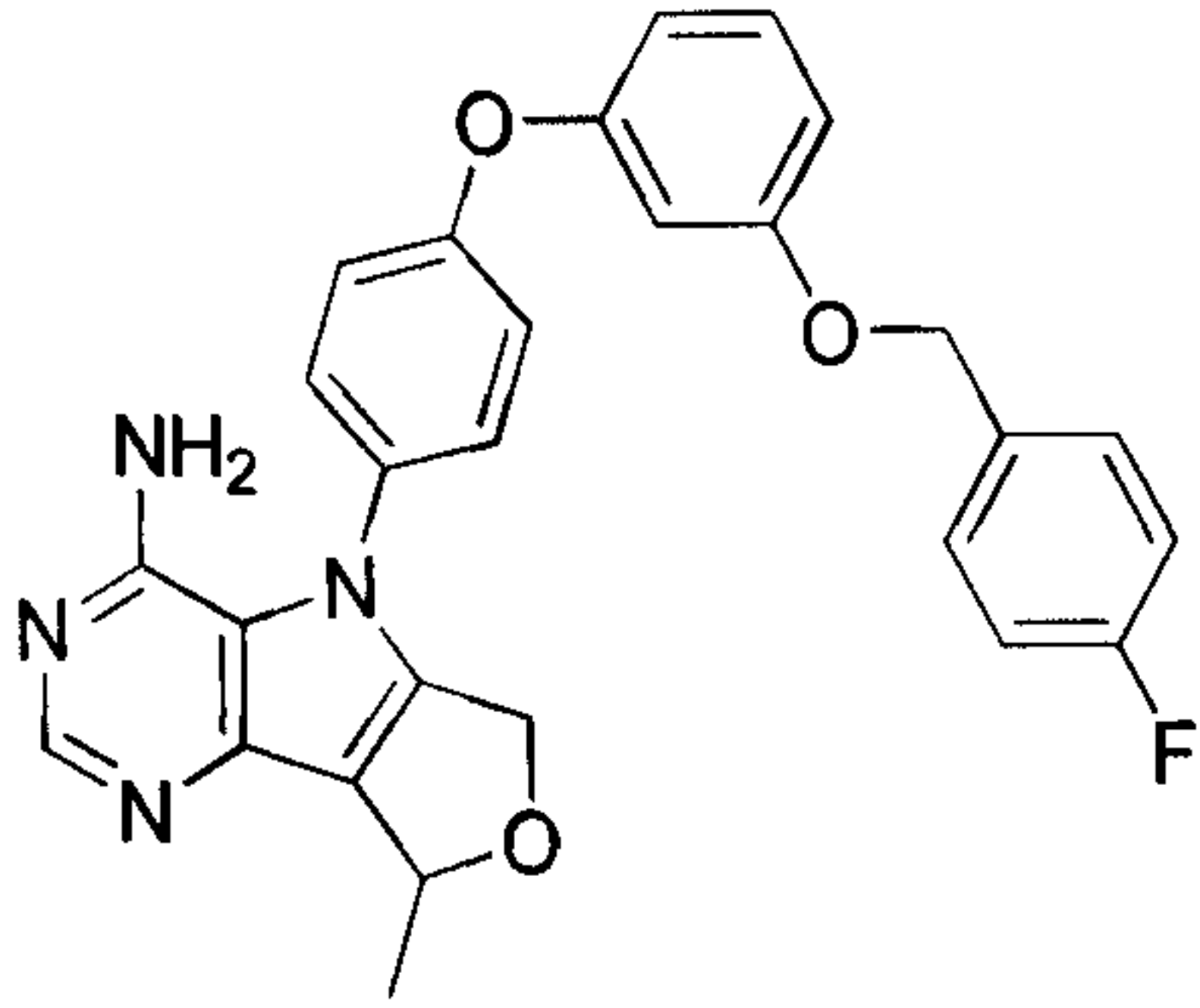
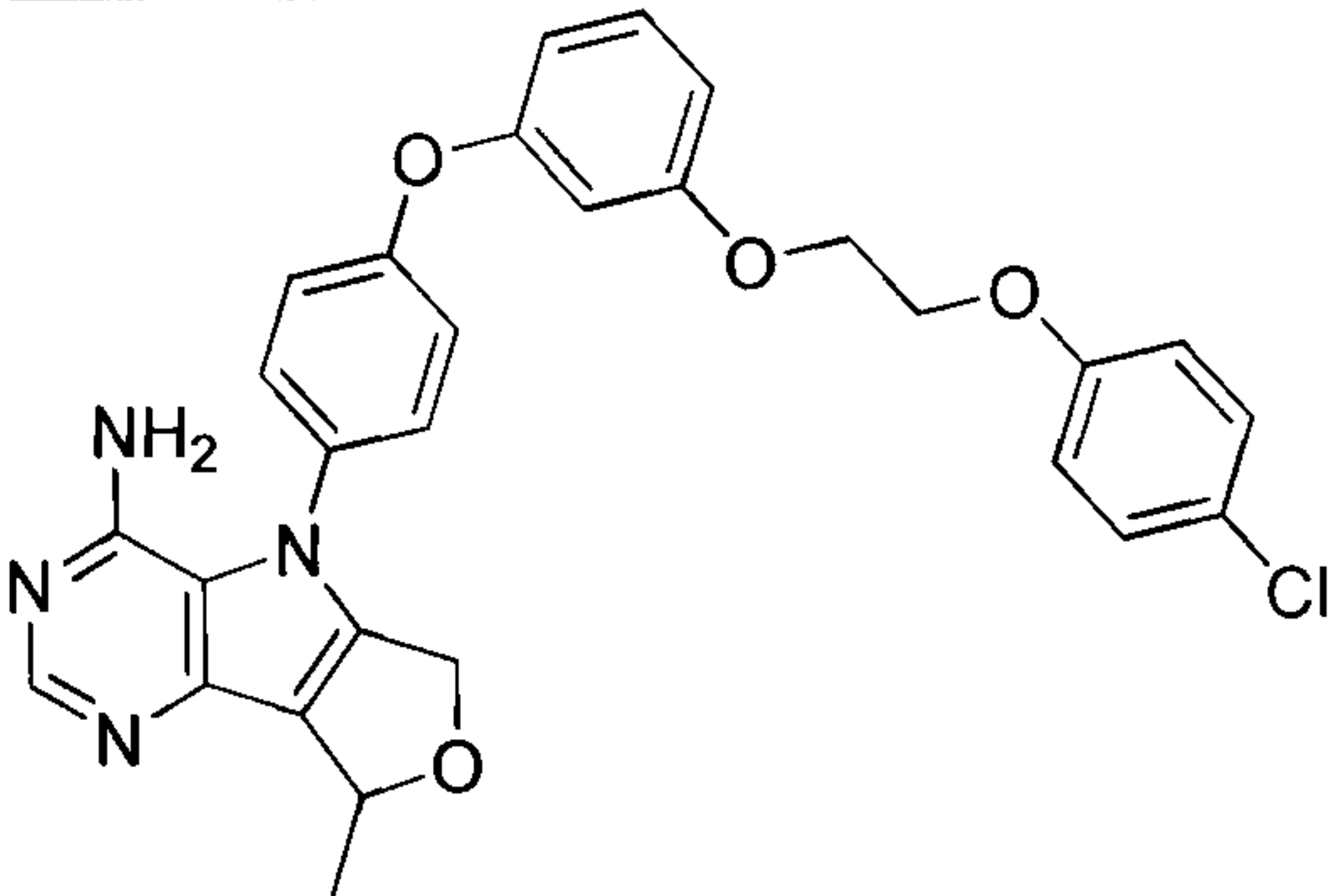
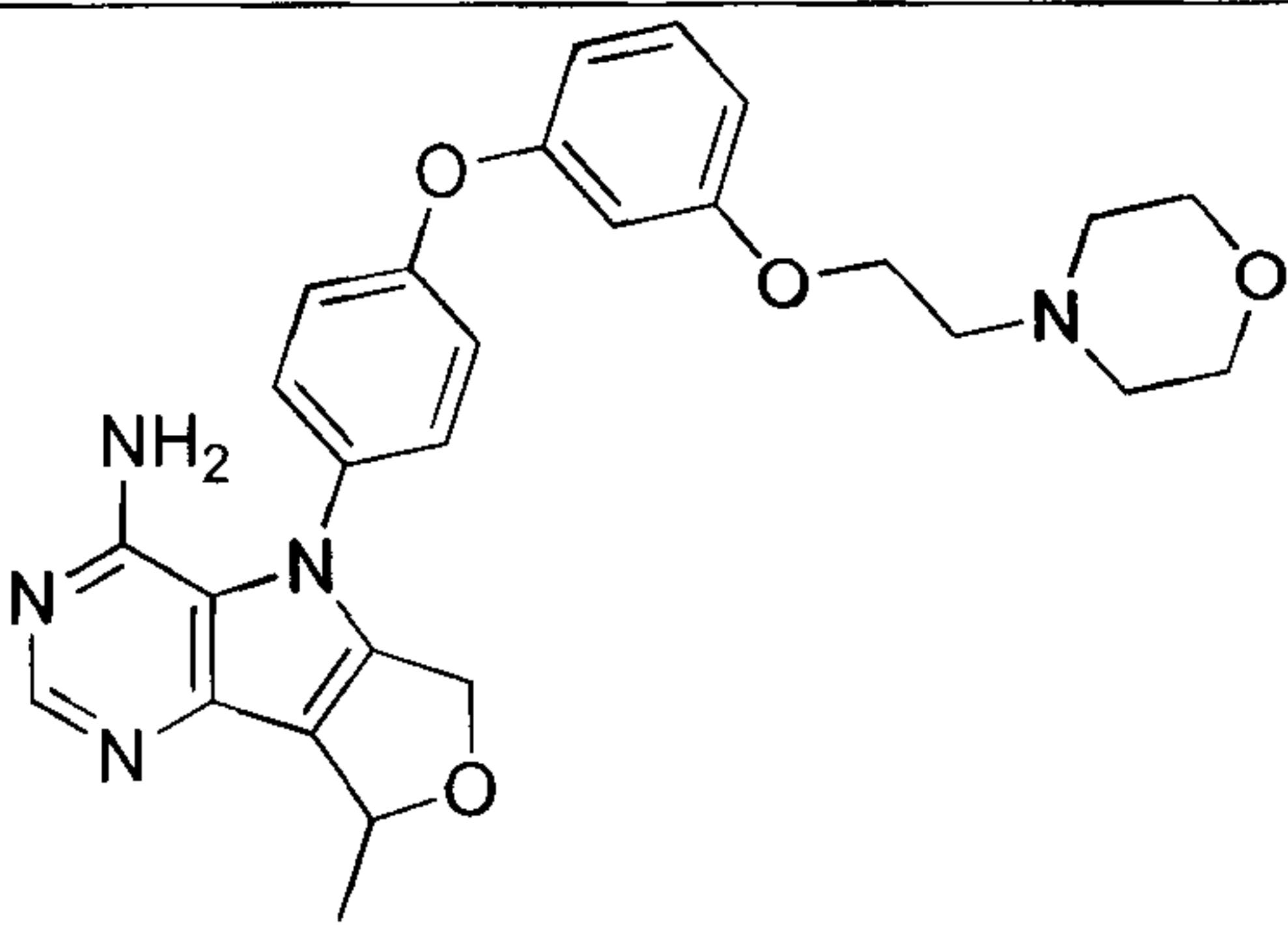
29		$[M+H]^+ = 427.2$
30		$[M+H]^+ = 421.2$
31		$[M+H]^+ = 393.4$
32		$[M+H]^+ = 427.2$

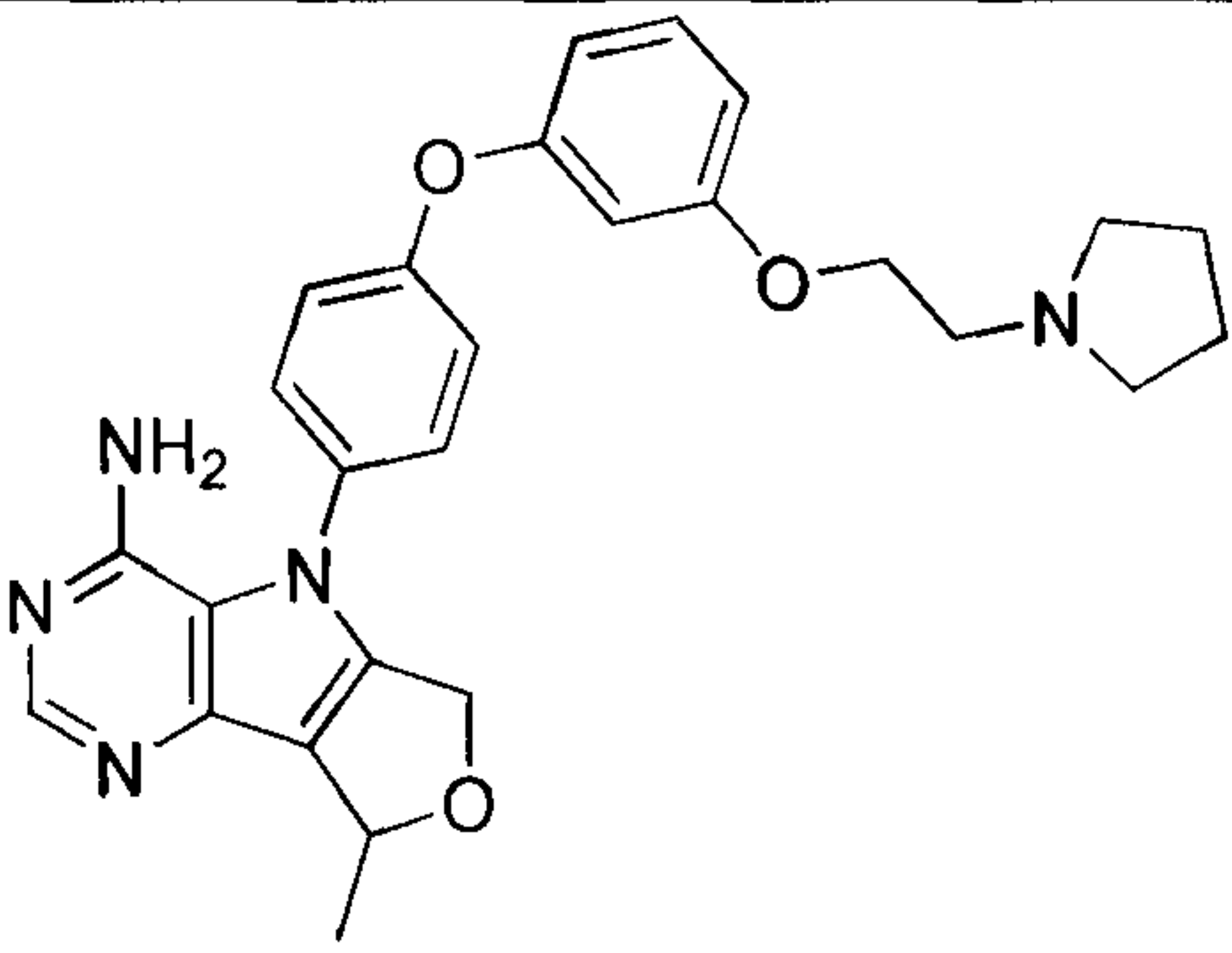
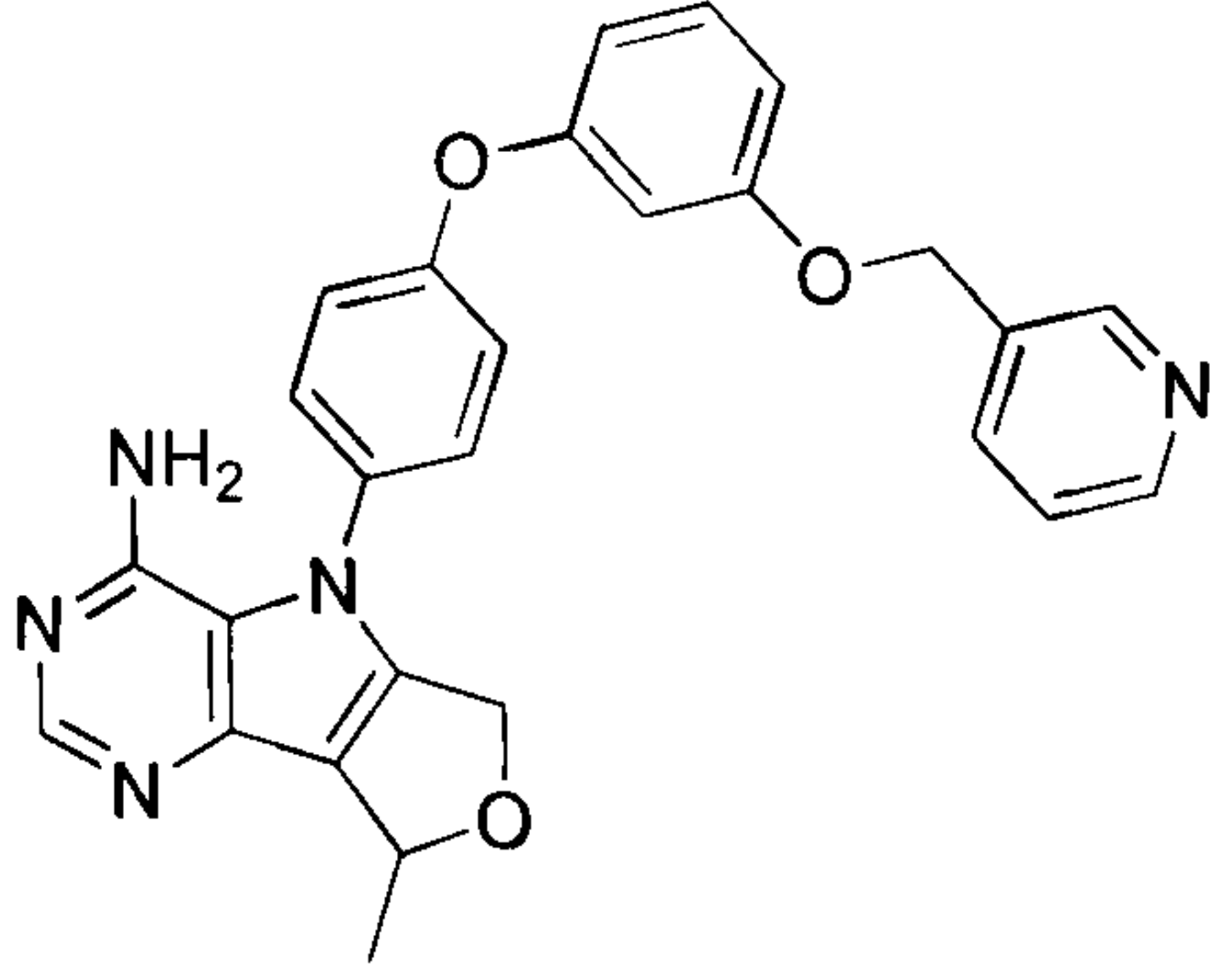
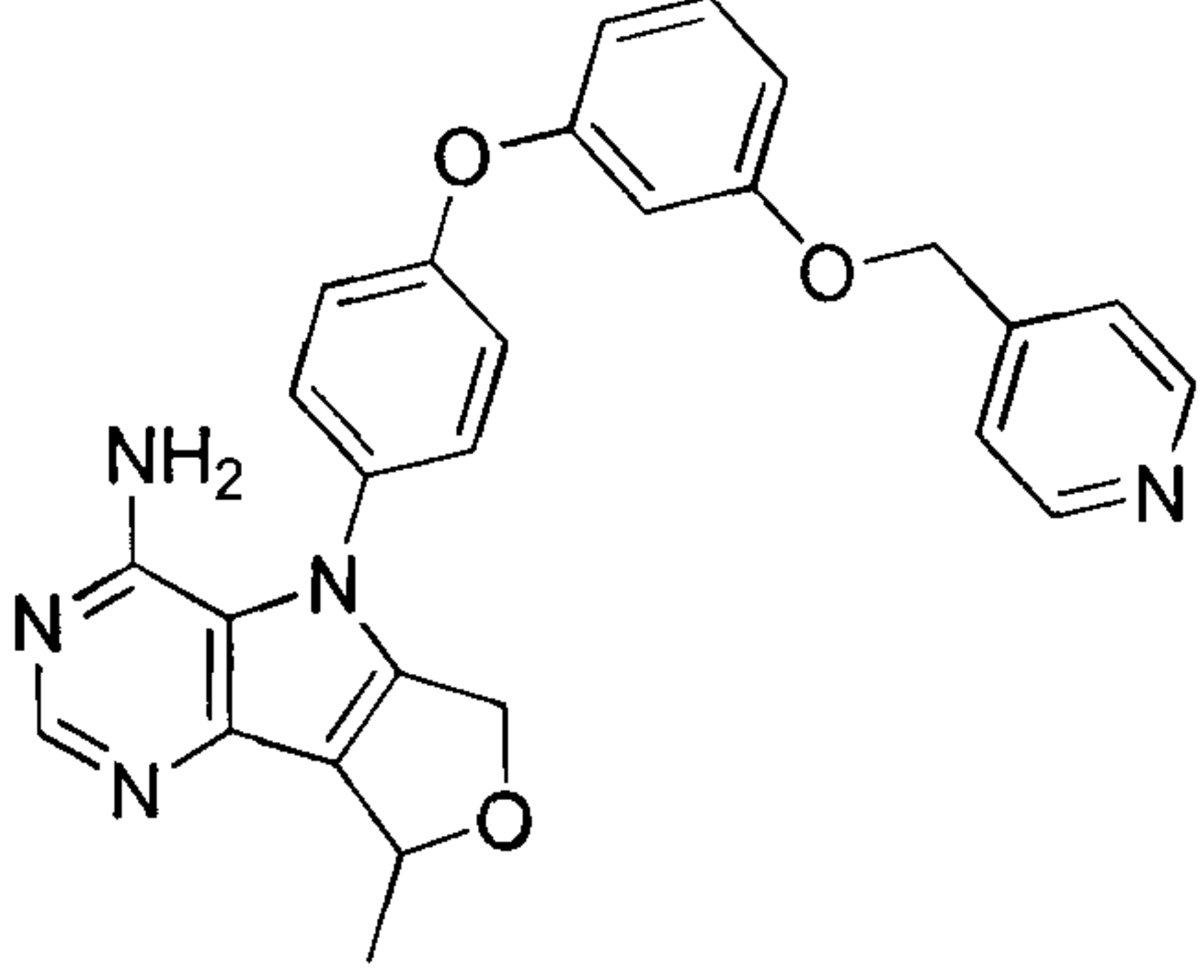
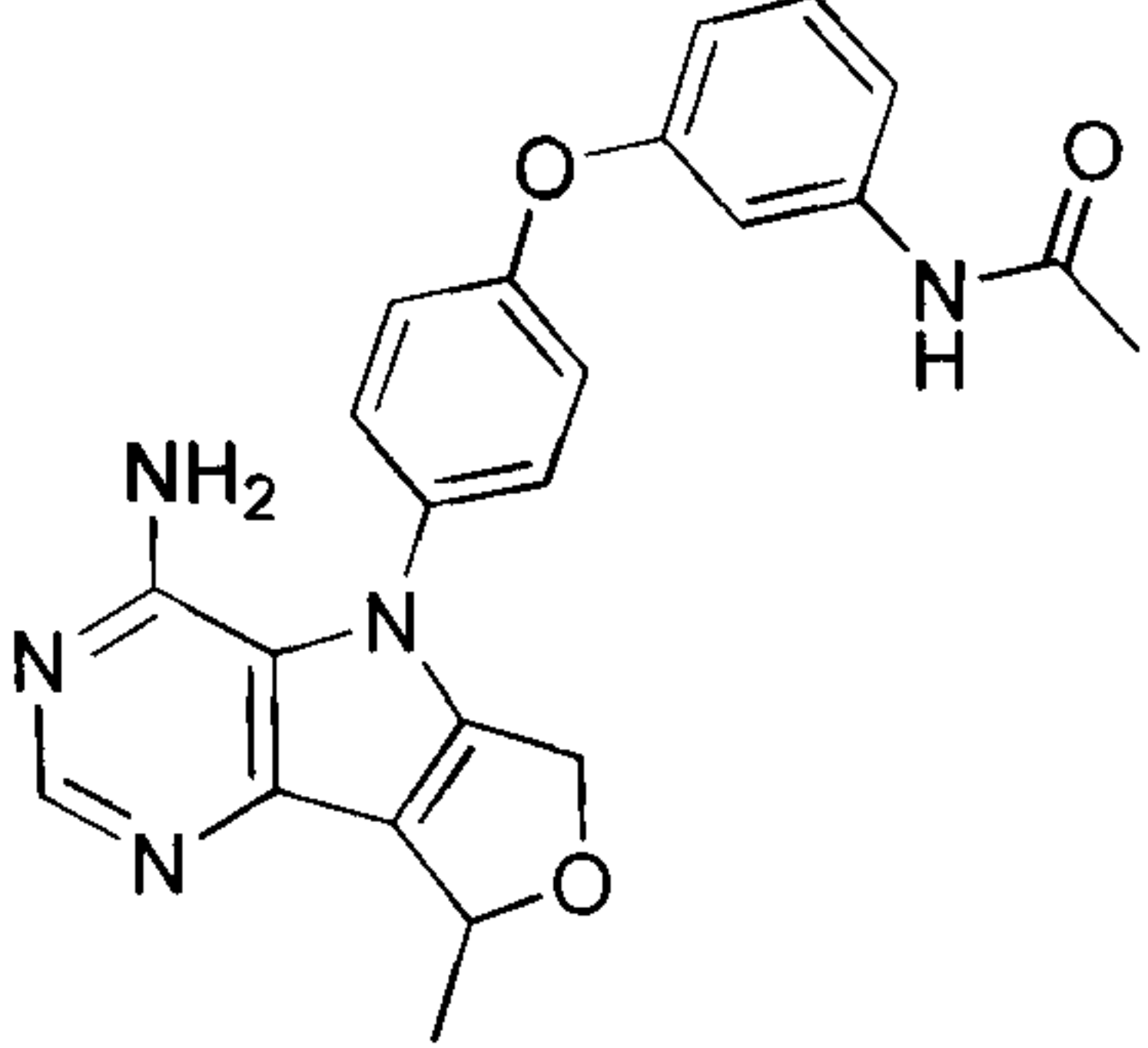
33		$[M+H]^+=393.4$
34		$[M+H]^+=377.2$
35		$[M+H]^+=377.4$

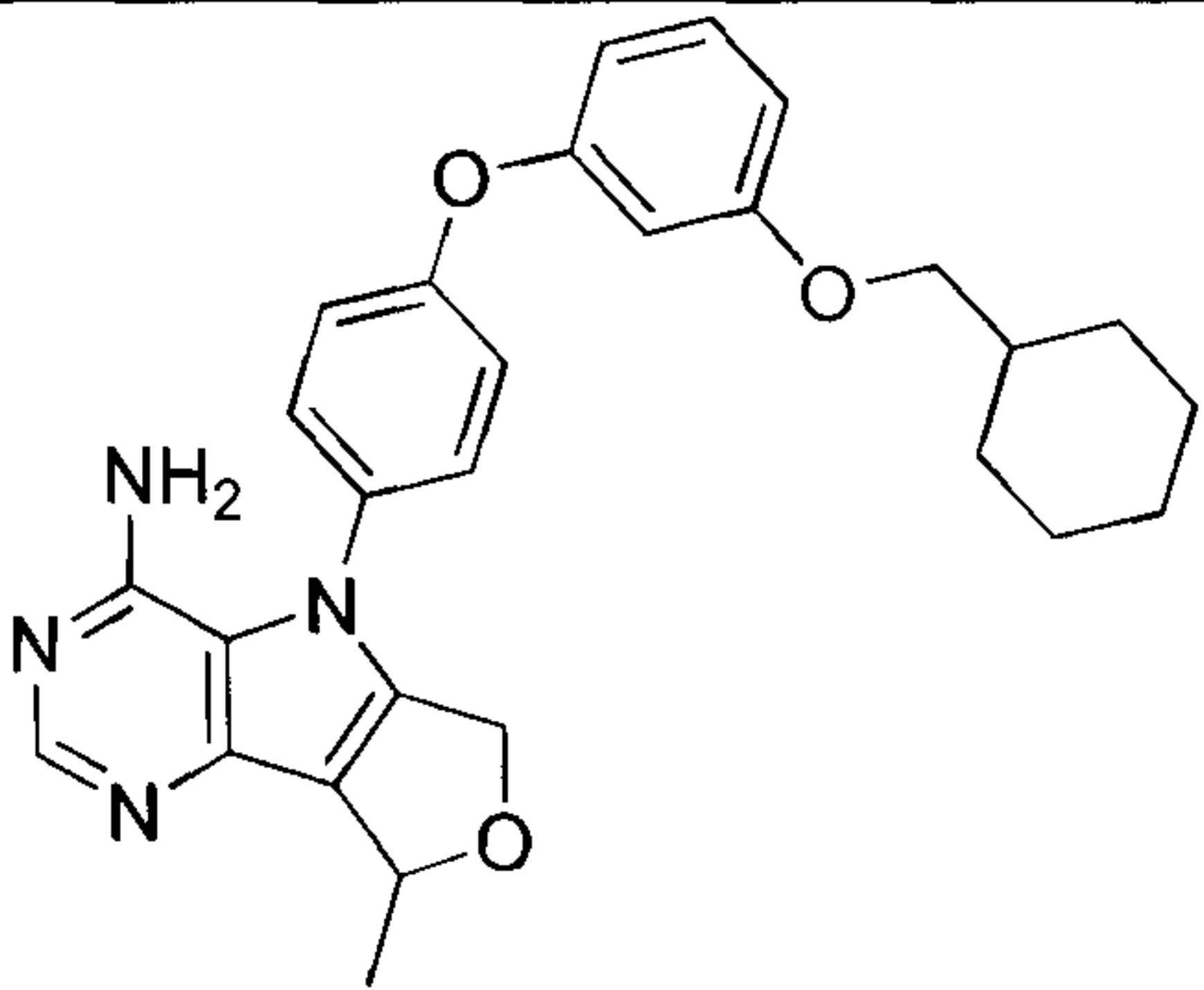
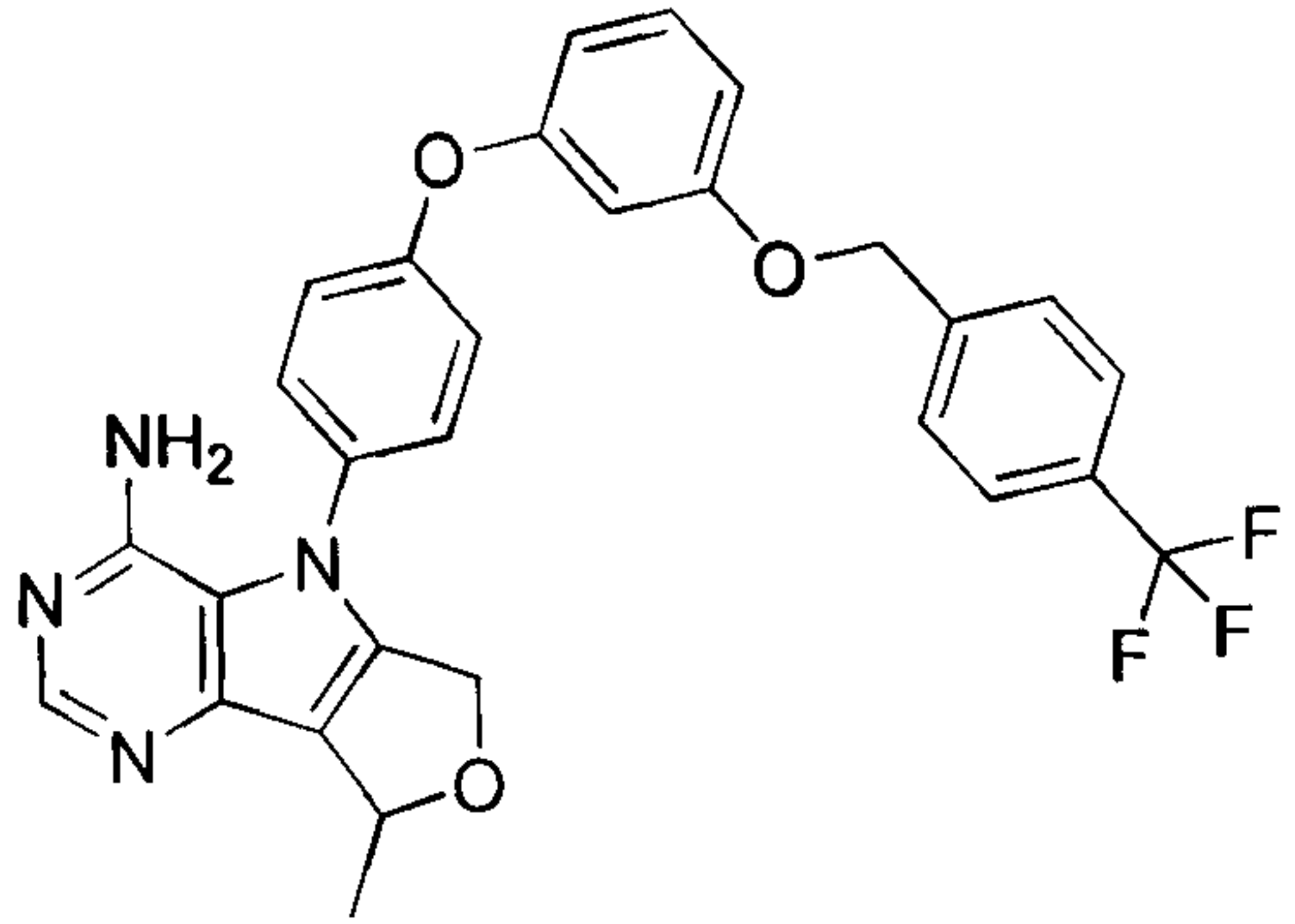
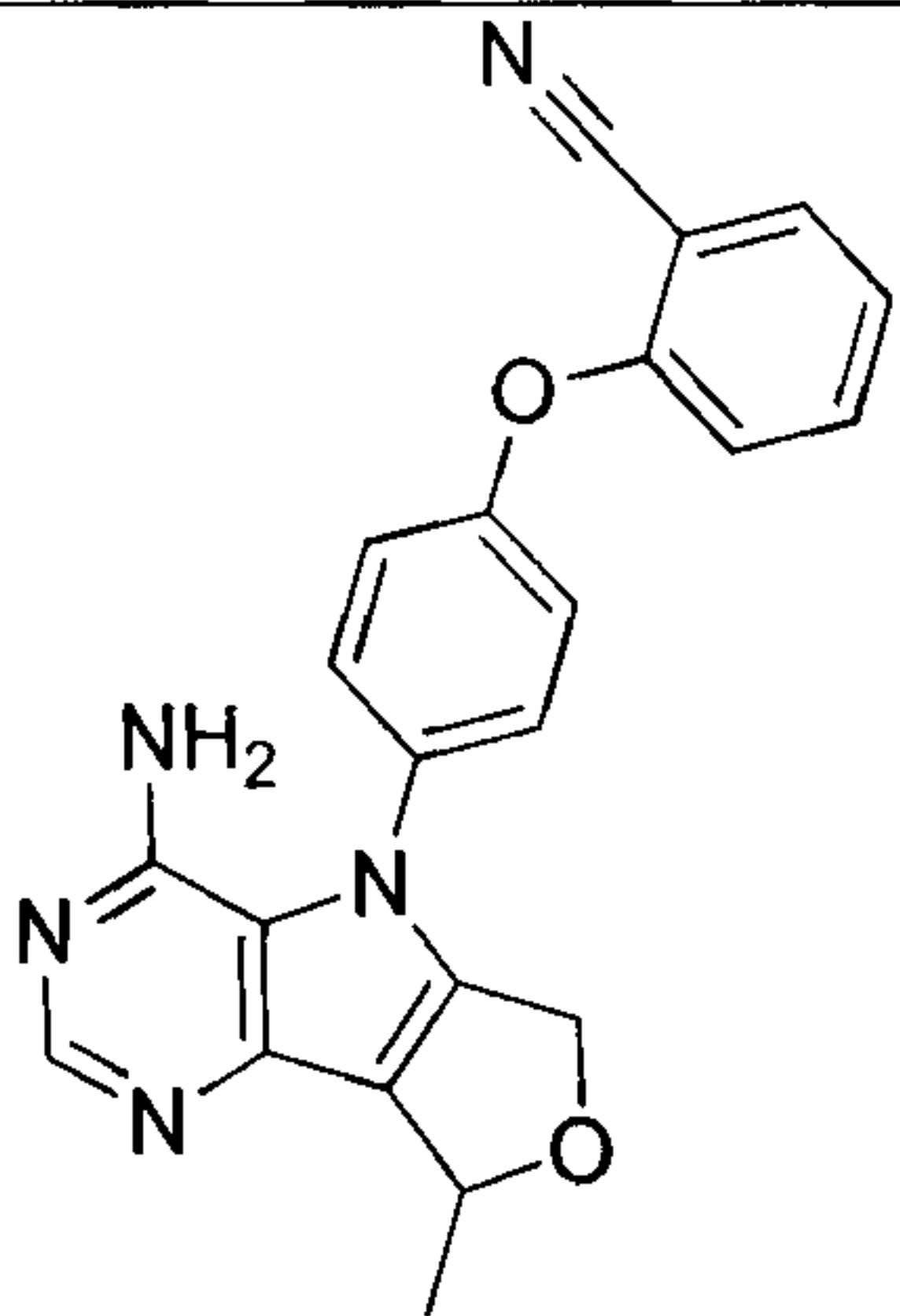
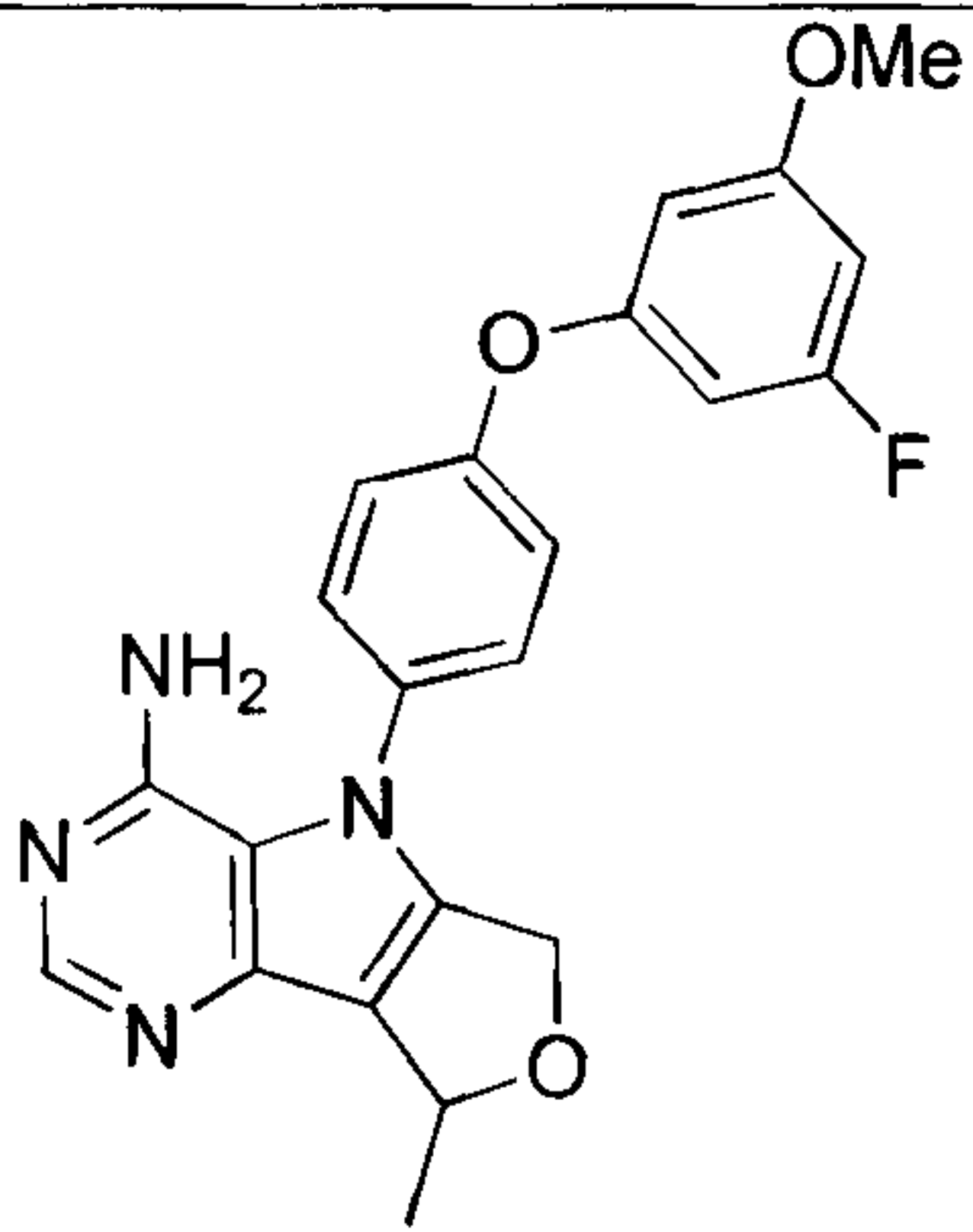
36		$[M+H]^+=479.3$
37		$[M+H]^+=384.3$
38		$[M+H]^+=402.2$
39		$[M+H]^+=393.6$

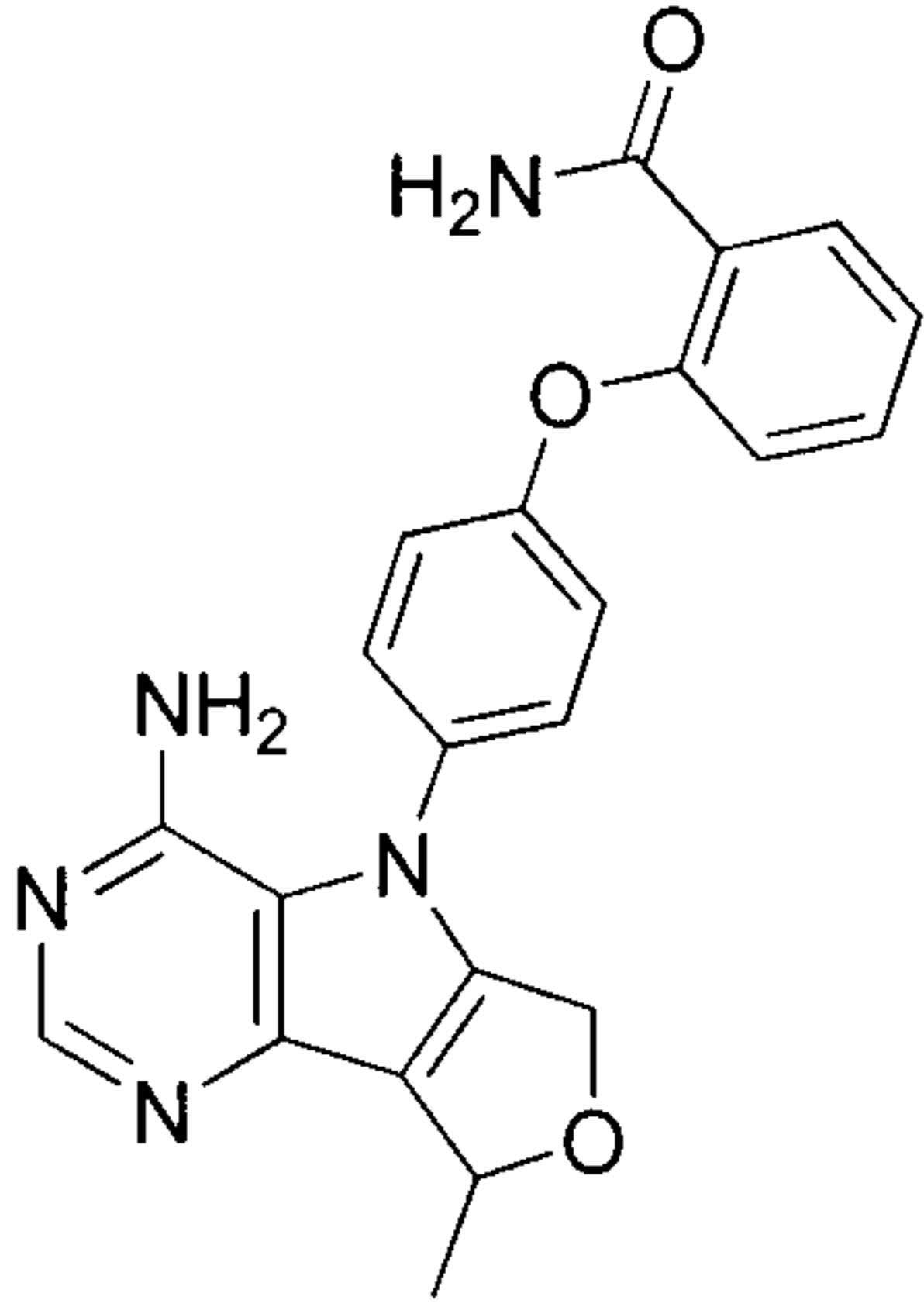
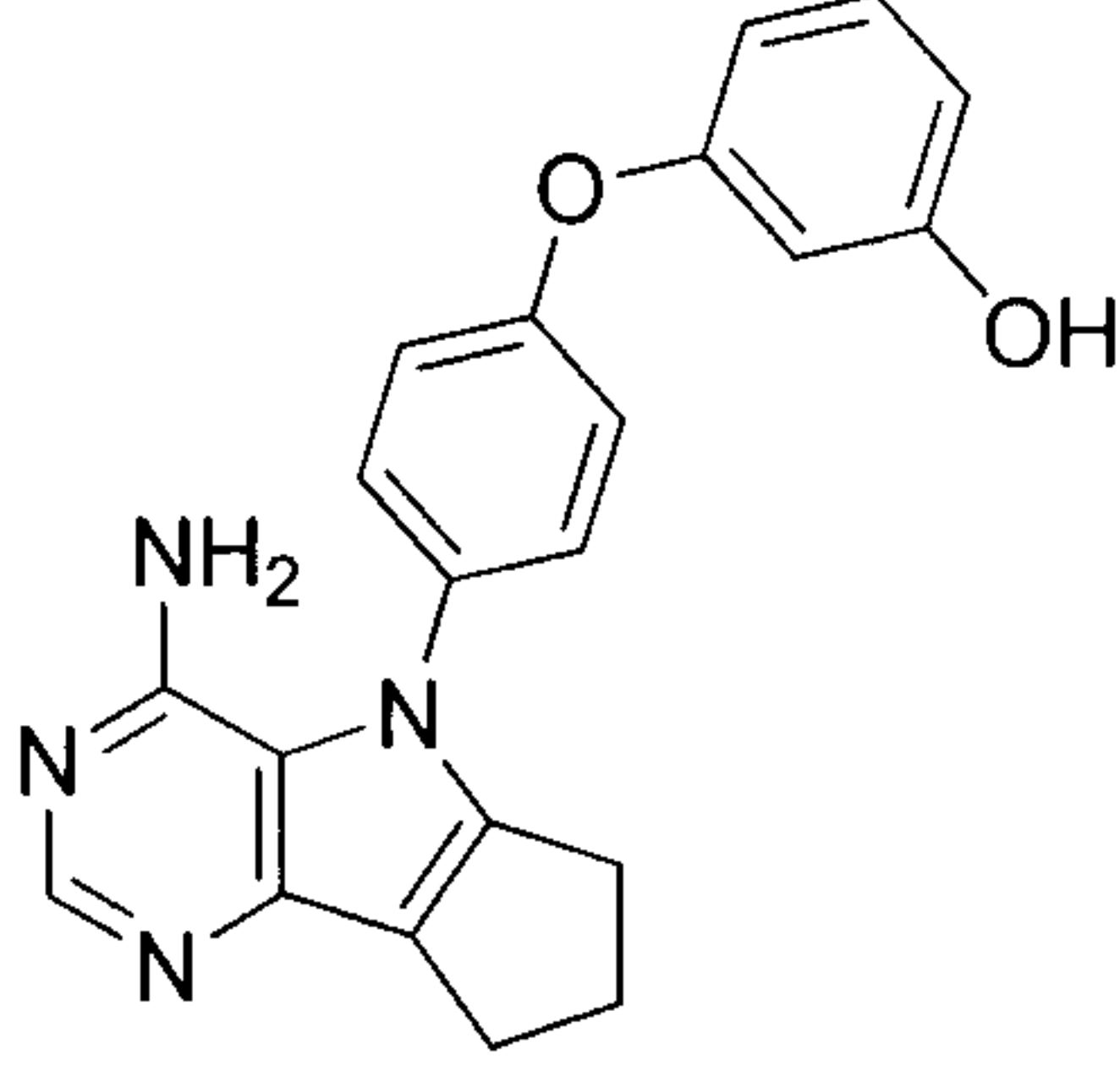
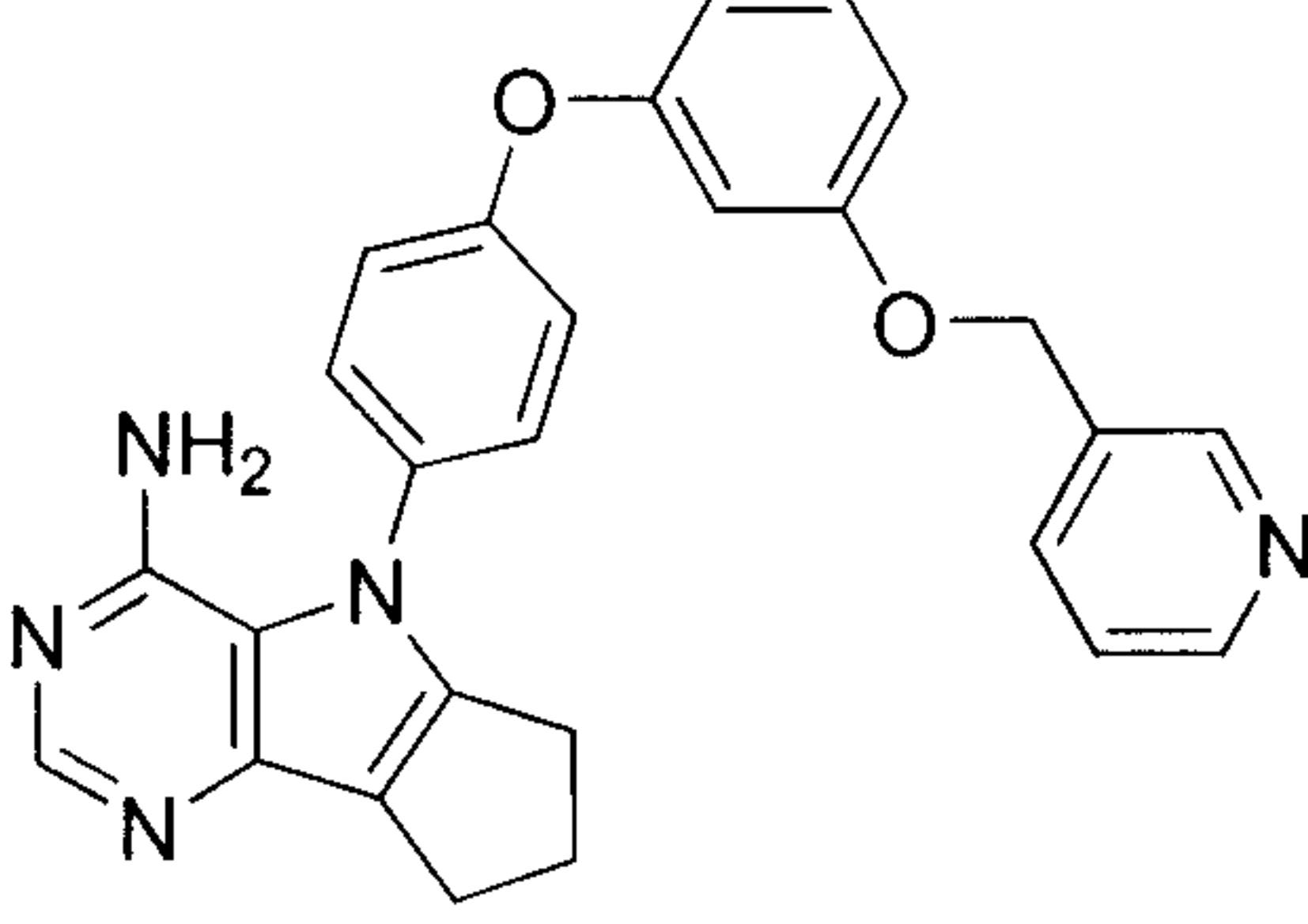
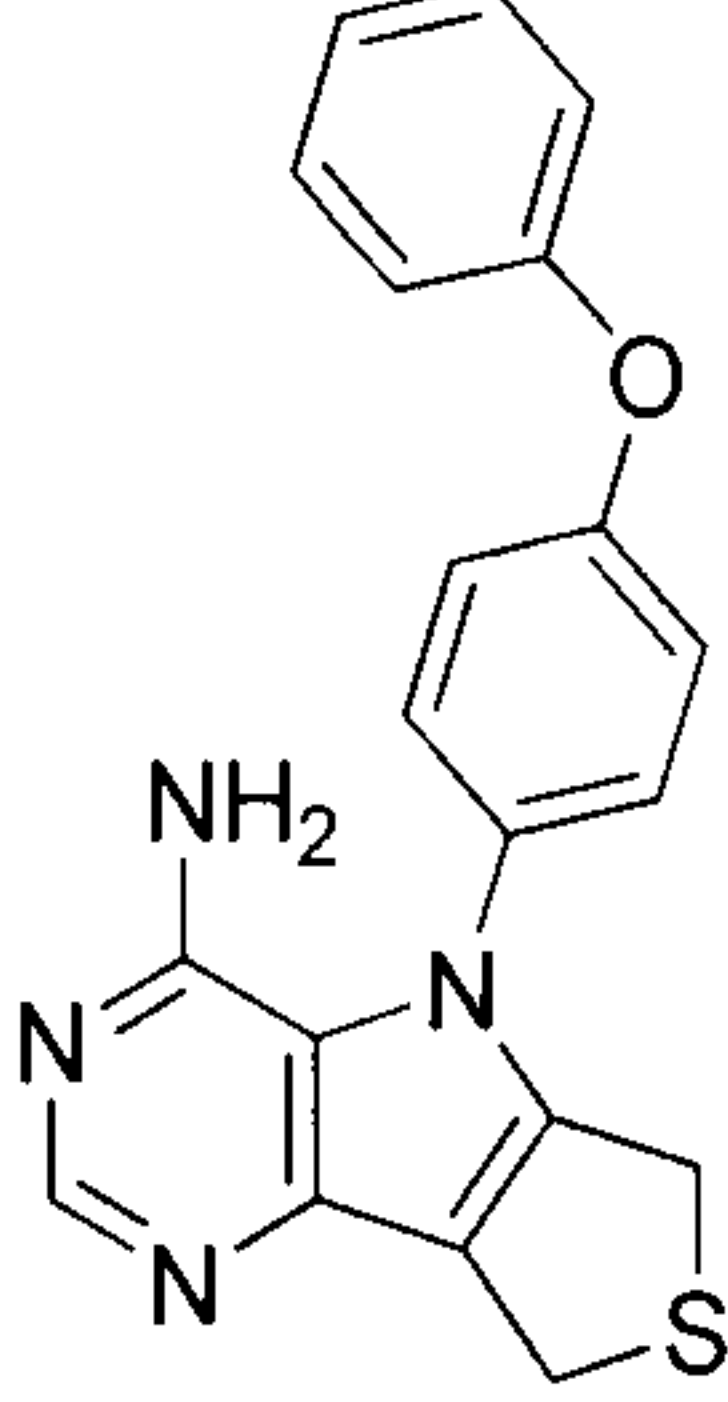
40		$[M+H]^+=377.2$
41		$[M+H]^+=403.3$
42		$[M+H]^+=377.2$
43		$[M+H]^+=465.2$

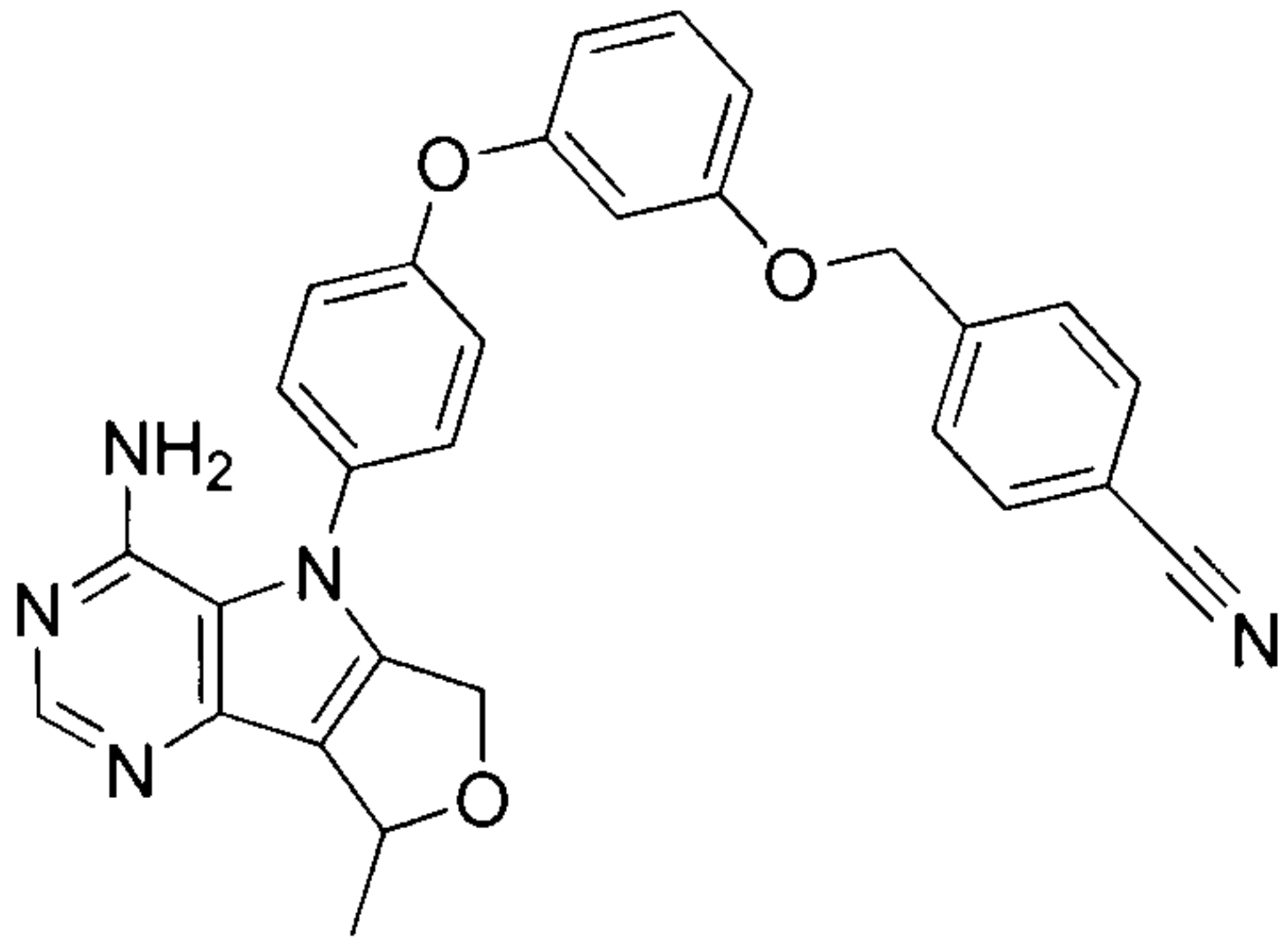
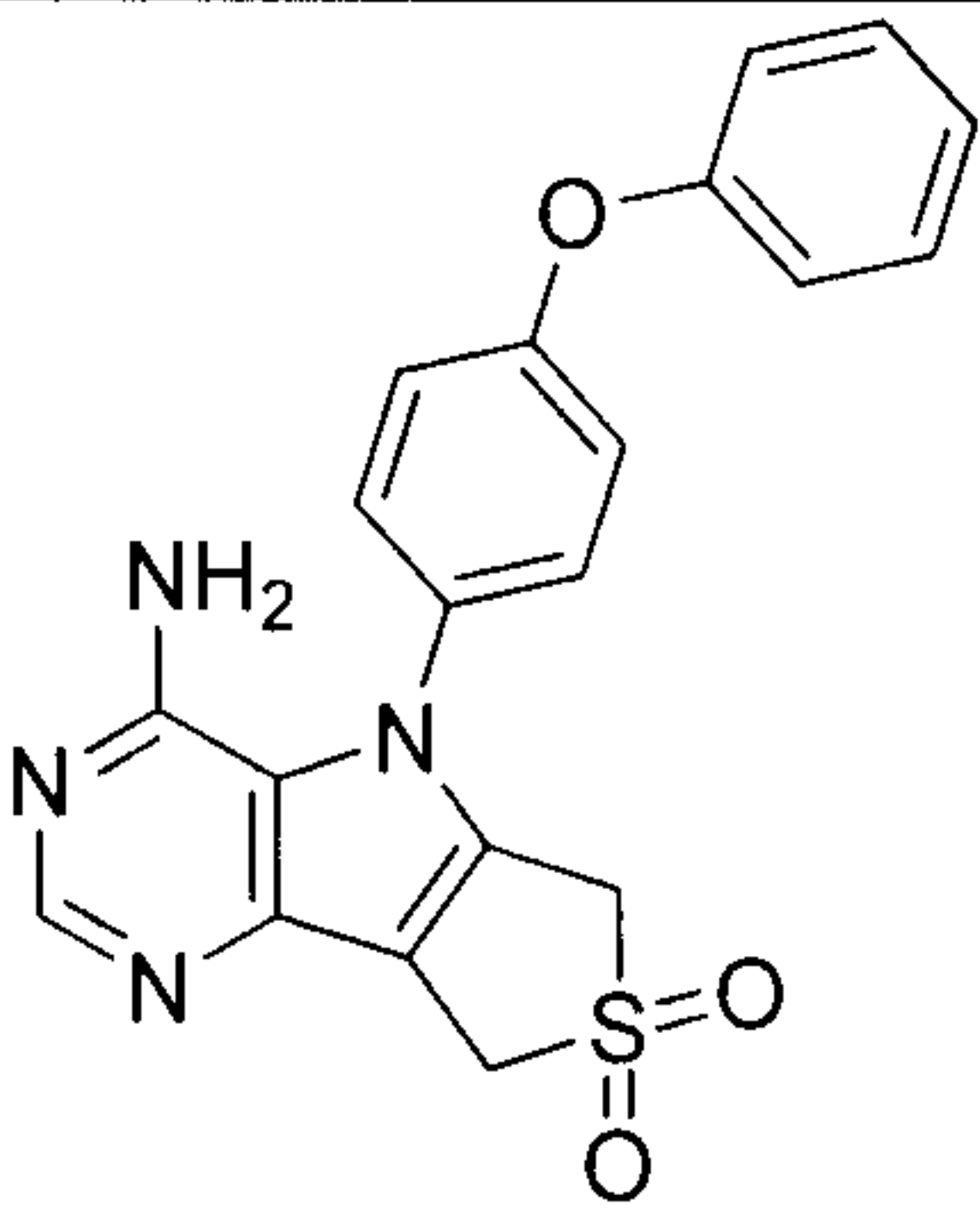
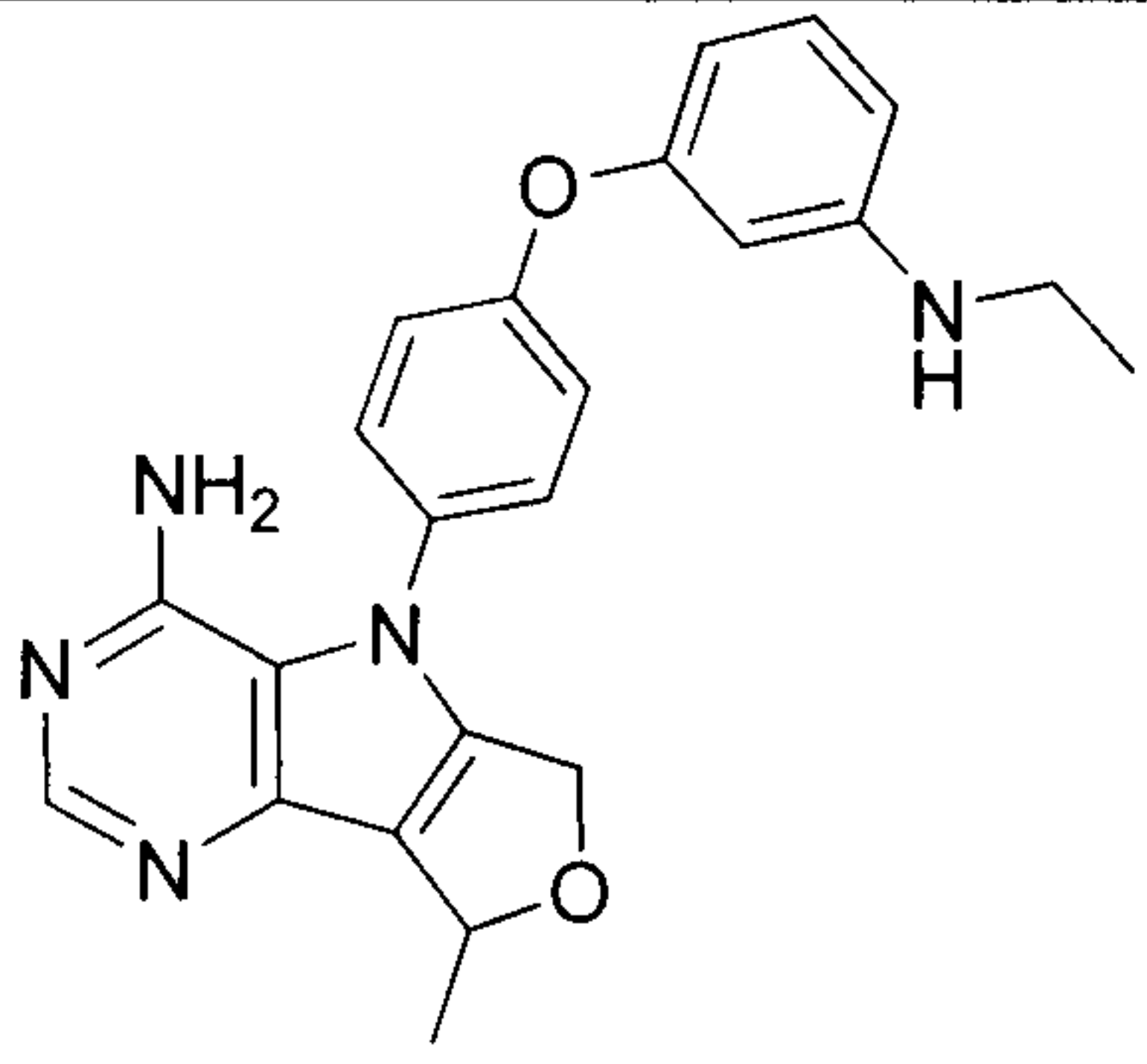
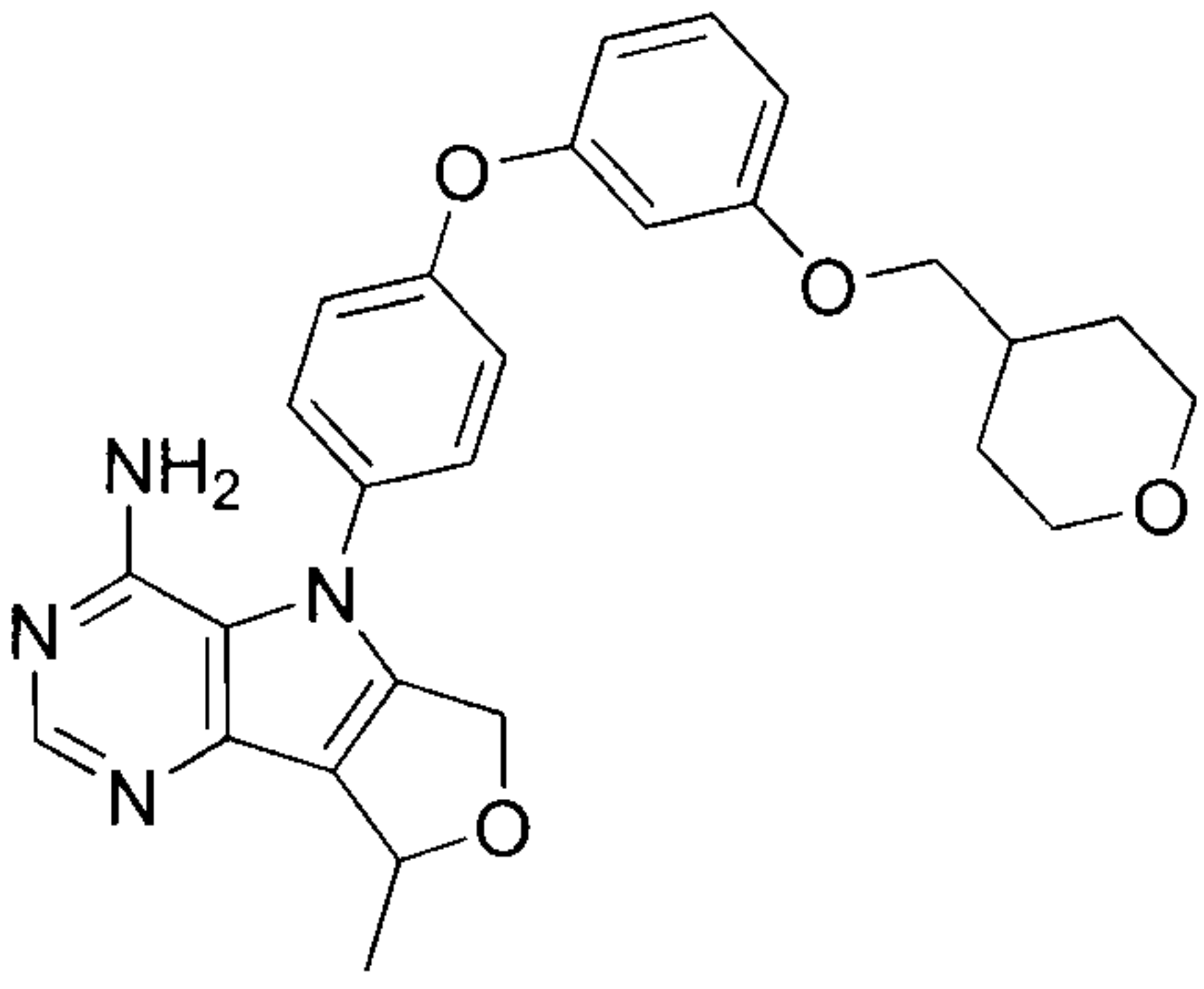
44		$[M+H]^+ = 375.2$
45		$[M+H]^+ = 404.2$
46		$[M+H]^+ = 414.2$
47		$[M+H]^+ = 374.2$

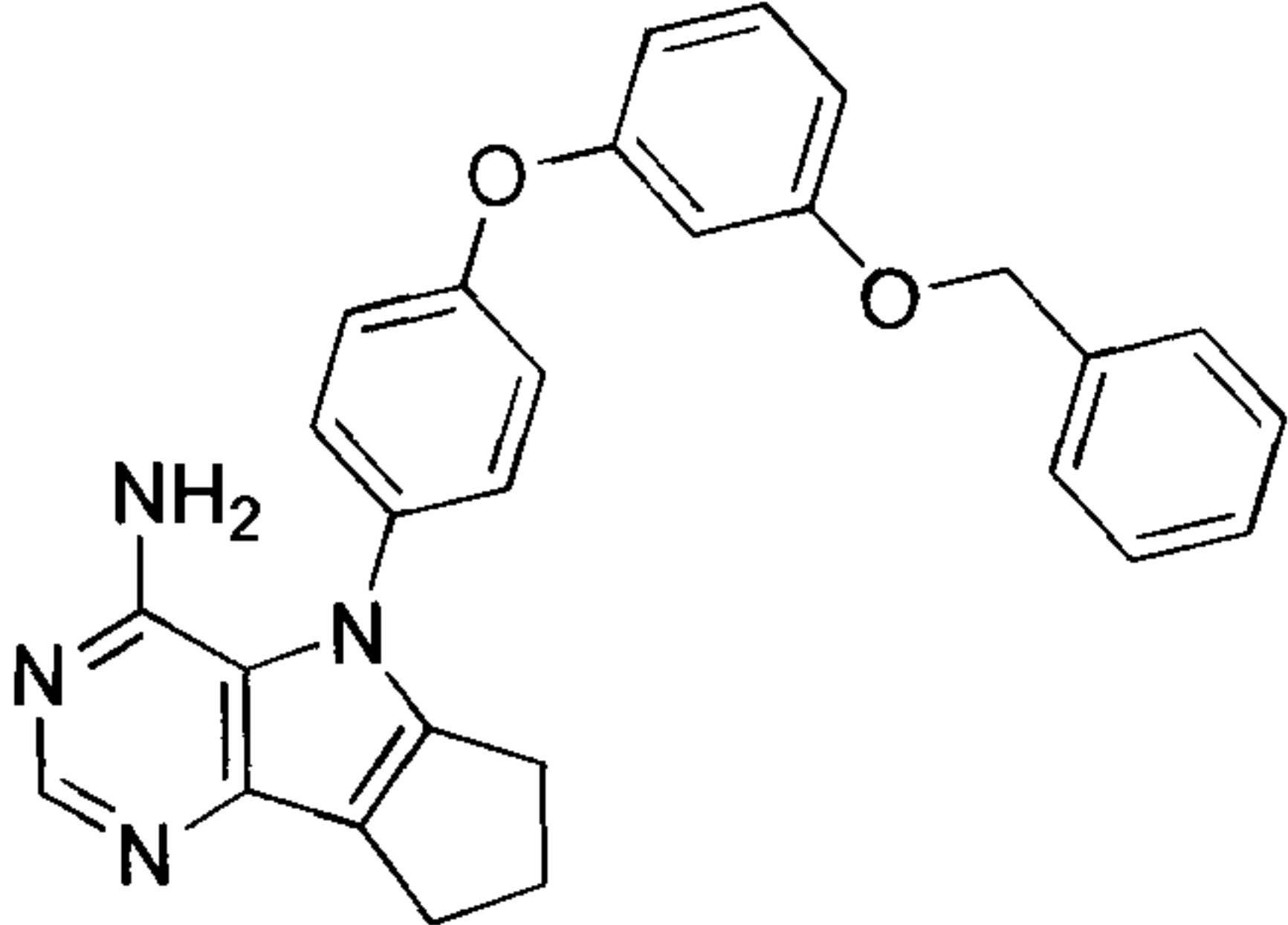
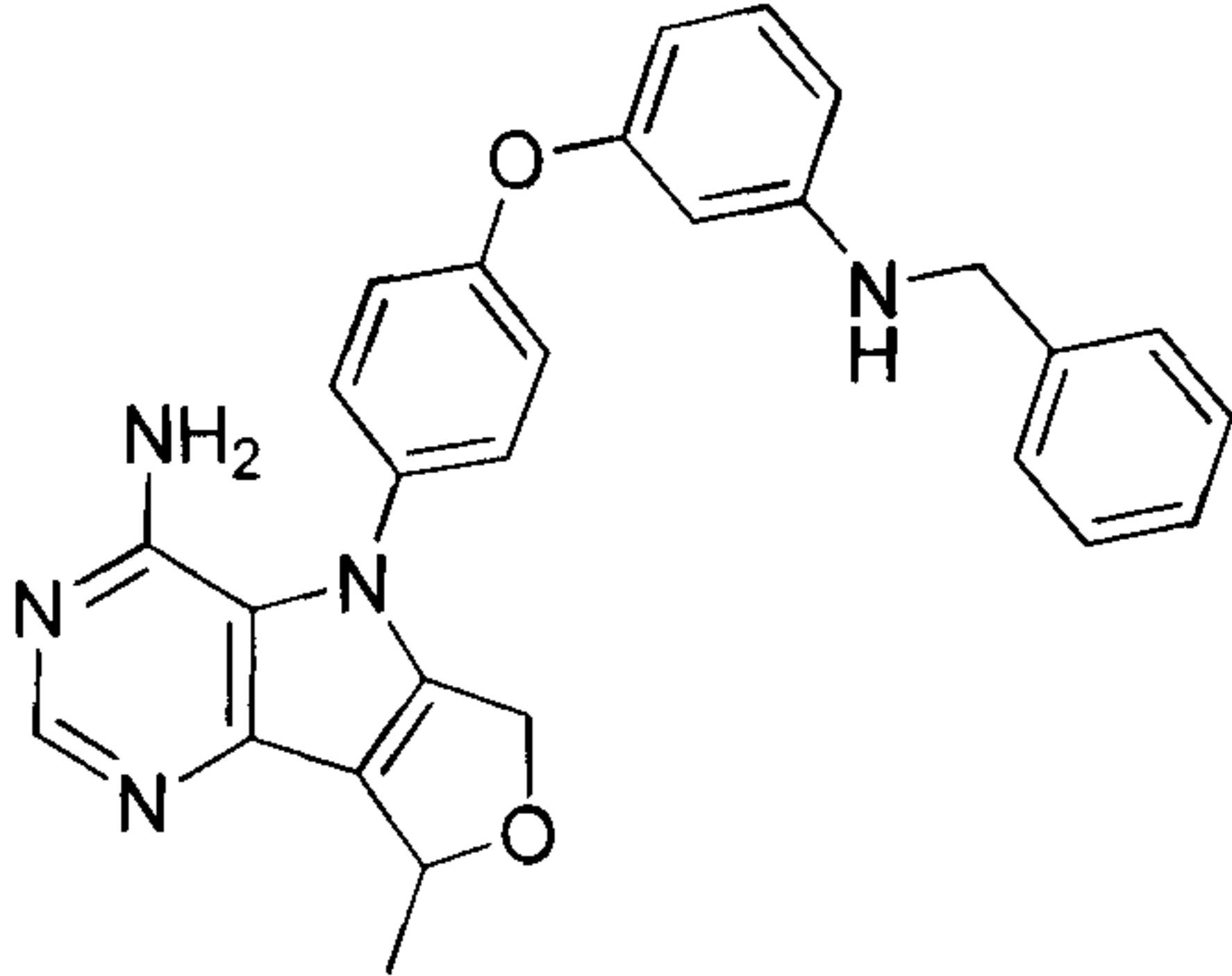
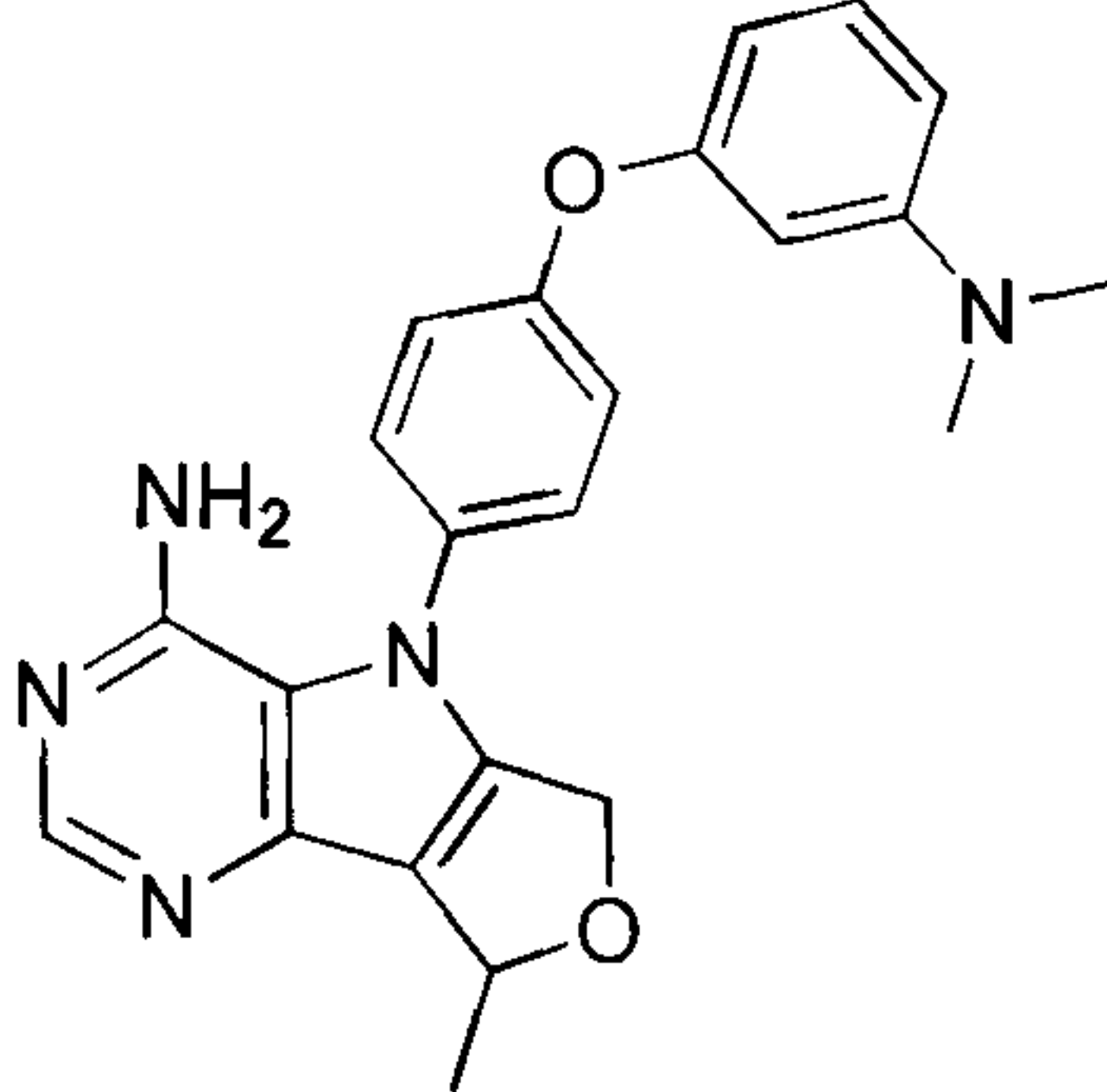
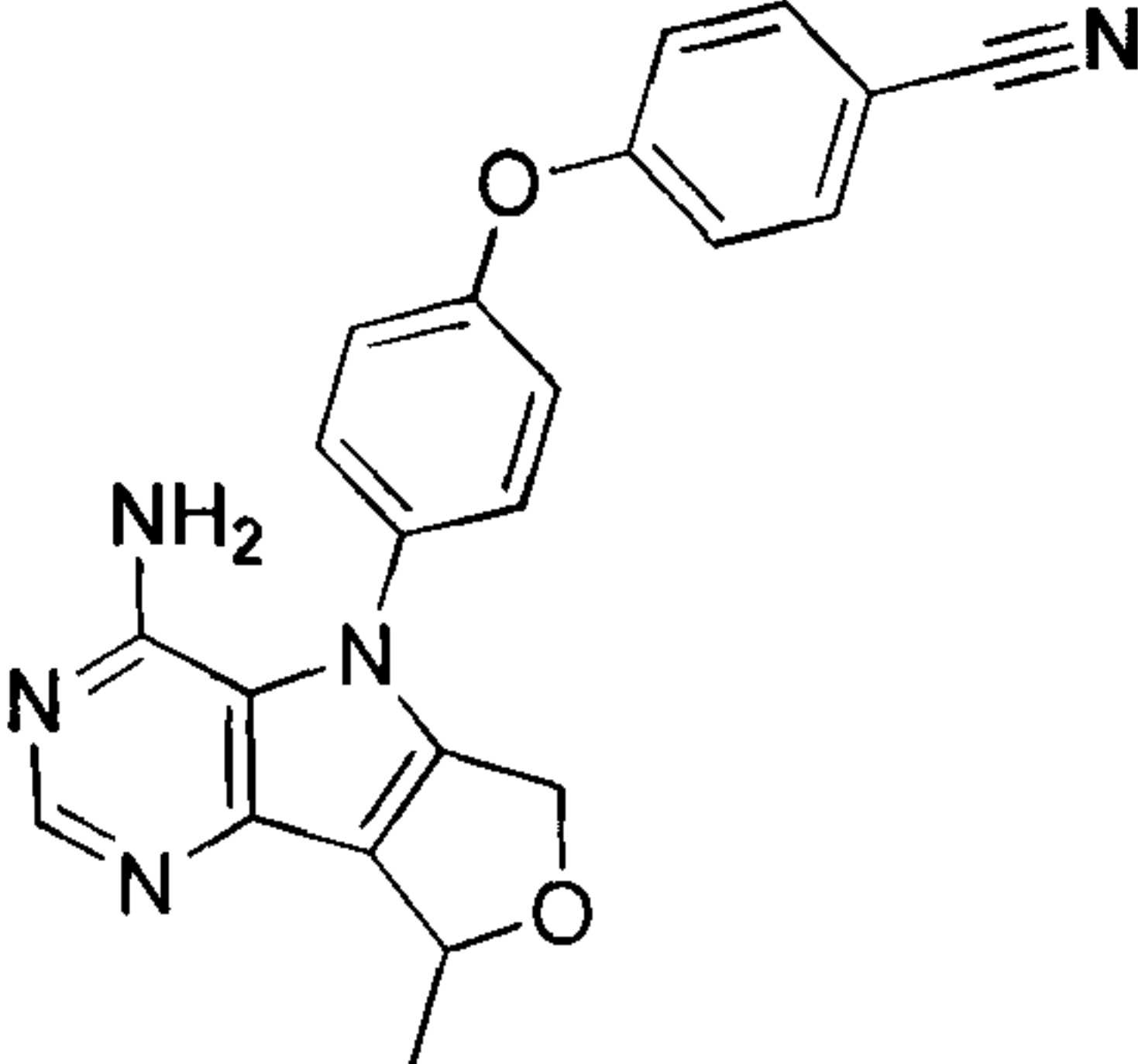
48		$[M+H]^+ = 446.4$
49		$[M+H]^+ = 483.2$
50		$[M+H]^+ = 529.3$
51		$[M+H]^+ = 488.2$

52		$[M+H]^+ = 472.3$
53		$[M+H]^+ = 466.2$
54		$[M+H]^+ = 466.2$
55		$[M+H]^+ = 416.3$

56		$[M+H]^+ = 471.3$
57		$[M+H]^+ = 533.1$
58		$[M+H]^+ = 384.4$
59		$[M+H]^+ = 407.4$

60		$[M+H]^+=402.2$
61		$[M+H]^+=359.2$
62		$[M+H]^+=450.2$
63		$[M+H]^+=361.2$

64		$[M+H]^+=490.2$
65		$[M+H]^+=393.2$
66		$[M+H]^+=402.2$
67		$[M+H]^+=473.3$

68		$[M+H]^+ = 449.2$
69		$[M+H]^+ = 464.2$
70		$[M+H]^+ = 402.3$
71		$[M+H]^+ = 384.2$

Kinase Binding

Btk and Lck Kinase Inhibition Assay

Fluorescence polarization-based kinase assays were performed in 384 well-plate format using histidine tagged recombinant human full-length Bruton Agammaglobulinemia Tyrosine Kinase (Btk) or histidine tagged recombinant Human Lymphocyte-Specific Protein Tyrosine Kinase (Lck) and a modified protocol of the KinEASE™ FP Fluorescein Green Assay supplied from Millipore. Kinase reaction were performed at room temperature for 60 minutes in presence of 250 μ M substrate, 10 μ M ATP and variable test article concentrations. The reaction was stopped with EDTA/kinease detection reagents and the polarization measured on a Tecan 500 instrument. From the dose-response curve obtained, the IC₅₀ was calculated using Graph pad prisms® using a non linear fit curve. The Km for ATP on each enzyme was experimentally determined and the Ki values calculated using the Cheng-Prusoff equation (see: Cheng Y, Prusoff WH. (1973) Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50 per cent inhibition (I₅₀) of an enzymatic reaction". *Biochem Pharmacol* **22** (23): 3099–108).

k_i values are reported in Tables 2 and 3:

a - Less than 100 nM; b - less than 1000 nM, c – more than 1000 nM

Table 2: Inhibition of Btk

Compound	k _i Btk (nM)	Compound	k _i Btk (nM)
1	b	41	a
2	c	42	c
3	b	43	a
4	b	44	b
5	-	45	b
6	-	46	a
7	c	47	b
8	b	48	c
9	c	49	a
10	-	50	a

11	-	51	c
12	-	52	c
13	b	53	a
14	c	54	a
15	c	55	b
16	-	56	a
17	-	57	a
18	c	58	-
19	-	59	-
20	a	60	-
21	b	61	-
22	b	62	-
23	b	63	-
24	b	64	-
25	a	65	-
26	c	66	-
27	b	67	-
28	b	68	-
29	b	69	-
30	c	70	-
31	b	71	-
32	b	72	-
33	b		
34	a		
35	b		
36	a		

37	a		
38	c		
39	b		
40	b		

Table 3: Inhibition of Lck

Compound	k _i Lck (nM)	Compound	k _i Lck (nM)
1	a	41	a
2	c	42	b
3	b	43	a
4	b	44	a
5	-	45	b
6	-	46	a
7	b	47	-
8	b	48	-
9	b	49	a
10	-	50	a
11	-	51	-
12	-	52	-
13	b	53	a
14	b	54	a
15	a	55	-
16	-	56	a
17	-	57	a
18	b	58	a
19	-	59	a

20	a	60	b
21	a	61	39 - a
22	a	62	-
23	a	63	-
24	a	64	-
25	a	65	-
26	b	66	-
27	a	67	-
28	b	68	-
29	b	69	-
30	b	70	-
31	a	71	-
32	b	72	-
33	a		
34	a		
35	b		
36	b		
37	c		
38	c		
39	a		
40	a		

Splenic B Cell Proliferation Assay

5 Splenocytes were obtained from 6 week old male CD1 mice (Charles River Laboratories Inc.). Mouse spleens were manually disrupted in PBS and filtered using a 70um cell strainer followed by ammonium chloride red blood cell lysis. Cells were washed, resuspended in Splenocyte Medium (HyClone RPMI supplemented with 10% heat-inactivated FBS, 0.5X non-essential amino acids, 10mM HEPES, 50uM

beta mercaptoethanol) and incubated at 37°C, 5% CO₂ for 2h to remove adherent cells. Suspension cells were seeded in 96 well plates at 50,000 cells per well and incubated at 37°C, 5% CO₂ for 1h. Splenocytes were pre-treated in triplicate with 10,000 nM curves of Formula 1 compounds for 1h, followed by stimulation of B cell proliferation with 2.5ug/ml anti-IgM F(ab')₂ (Jackson ImmunoResearch) for 72h. Cell proliferation was measured by Cell Titer-Glo Luminescent Assay (Promega). EC₅₀ values (50% proliferation in the presence of compound as compared to vehicle treated controls) were calculated from dose response compound curves using GraphPad Prism Software.

10 EC₅₀ values are reported in Table 4:

a - Less than 100 nM; b - less than 1000 nM, c – more than 1000 nM

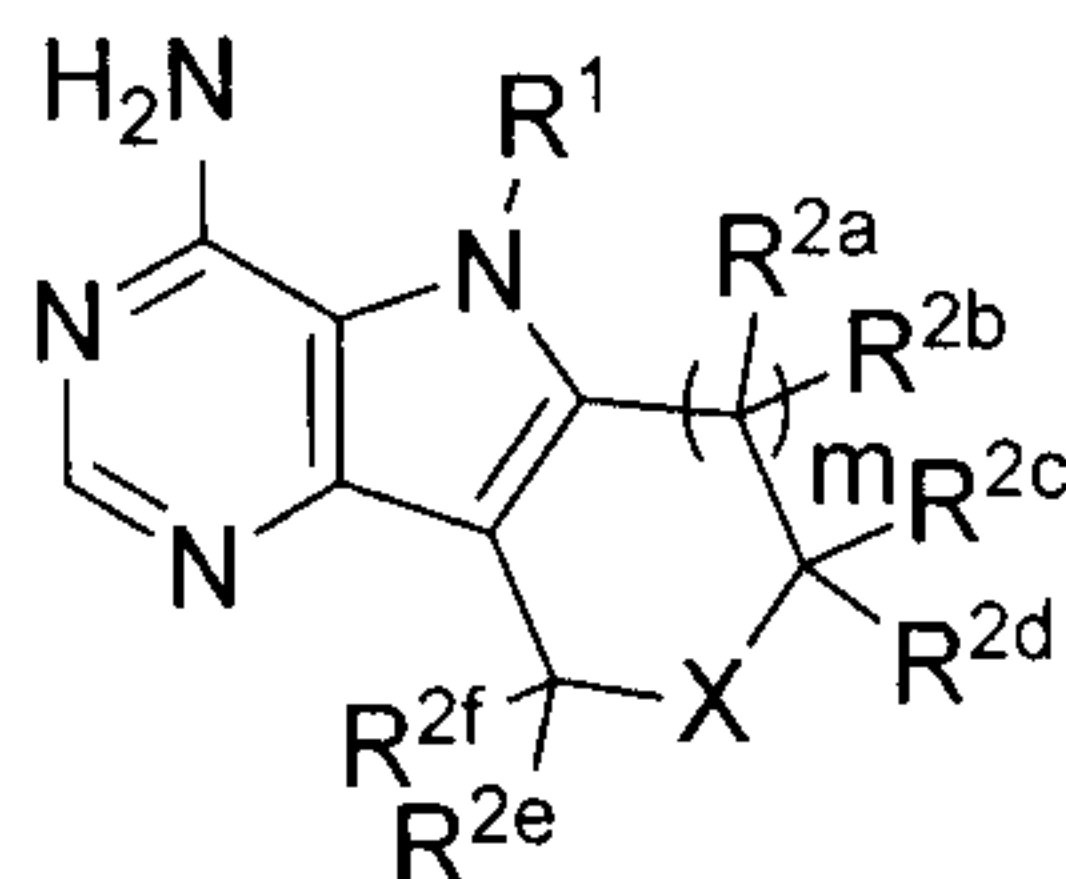
Table 4: Inhibition of splenic B cell proliferation

Compound	EC ₅₀ (nM)	Compound	EC ₅₀ (nM)
1	c	41	c
2	c	42	c
3	c	43	-
4	c	44	c
5	-	45	c
6	-	46	b
7	c	47	-
8	-	48	-
9	-	49	-
10	-	50	c
11	-	51	-
12	-	52	-
13	c	53	b
14	c	54	-
15	-	55	-

16	-	56	-
17	-	57	-
18	-	58	b
19	-	59	b
20	b	60	c
21	c	61	c
22	-	62	b
23	c	63	-
24	b	64	-
25	b	65	-
26	c	66	-
27	c	67	-
28	c	68	-
29	b	69	-
30	c	70	-
31	b	71	-
32	b	72	-
33	b		
34	c		
35	c		
36	c		
37	c		
38	c		
39	c		
40	b		

We claim:

1. A compound of Formula 1:



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Formula 1

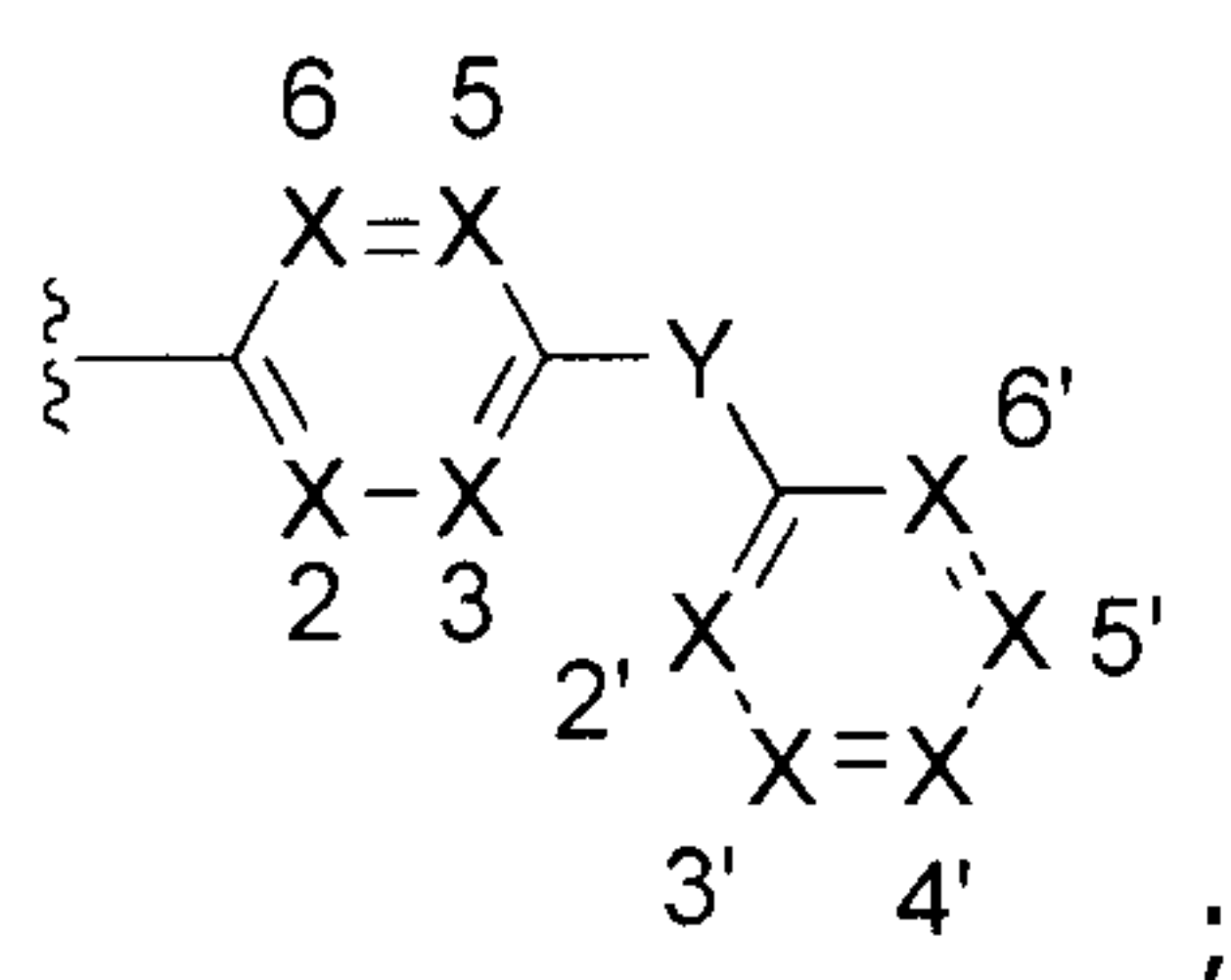
an isomer, enantiomer, diastereomer or tautomer thereof,

m is an integer from 0 to 1;

X is selected from CH₂, O, S(O)_n, NR⁶;

10 n is an integer for 0 to 2;

R¹ is



wherein Y is selected from O or CH₂;

wherein X², X³, X⁵, X⁶, X^{2'}, X^{3'}, X^{4'}, X^{5'}, X^{6'} are independently selected from CR and

15 N;

each R is independently selected from hydrogen, halogen, -NO₂, -CN, alkyl, alkenyl, alkynyl, -OR³, -OC(O)R³, -OC(O)NR⁴R⁵, -NR⁴R⁵, -S(O)_nR³, -C(O)R³, -C(O)OR³, -C(O)NR⁴R⁵, -S(O)₂NR⁴R⁵, -NR²C(O)R³, -NR²S(O)_nR³, -NR²C(O)NR⁴R⁵, -NR²S(O)₂NR⁴R⁵, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

R^2 is selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl.

$R^{2a}, R^{2b}, R^{2c}, R^{2d}, R^{2e}, R^{2f}$ are independently selected from hydrogen, alkyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, or heteroaryl. R^{2a} and R^{2b} , R^{2c} and R^{2d} or R^{2e} and R^{2f} can be fused to form a 3 to 8 membered cycloalkyl or heterocyclyl ring system;

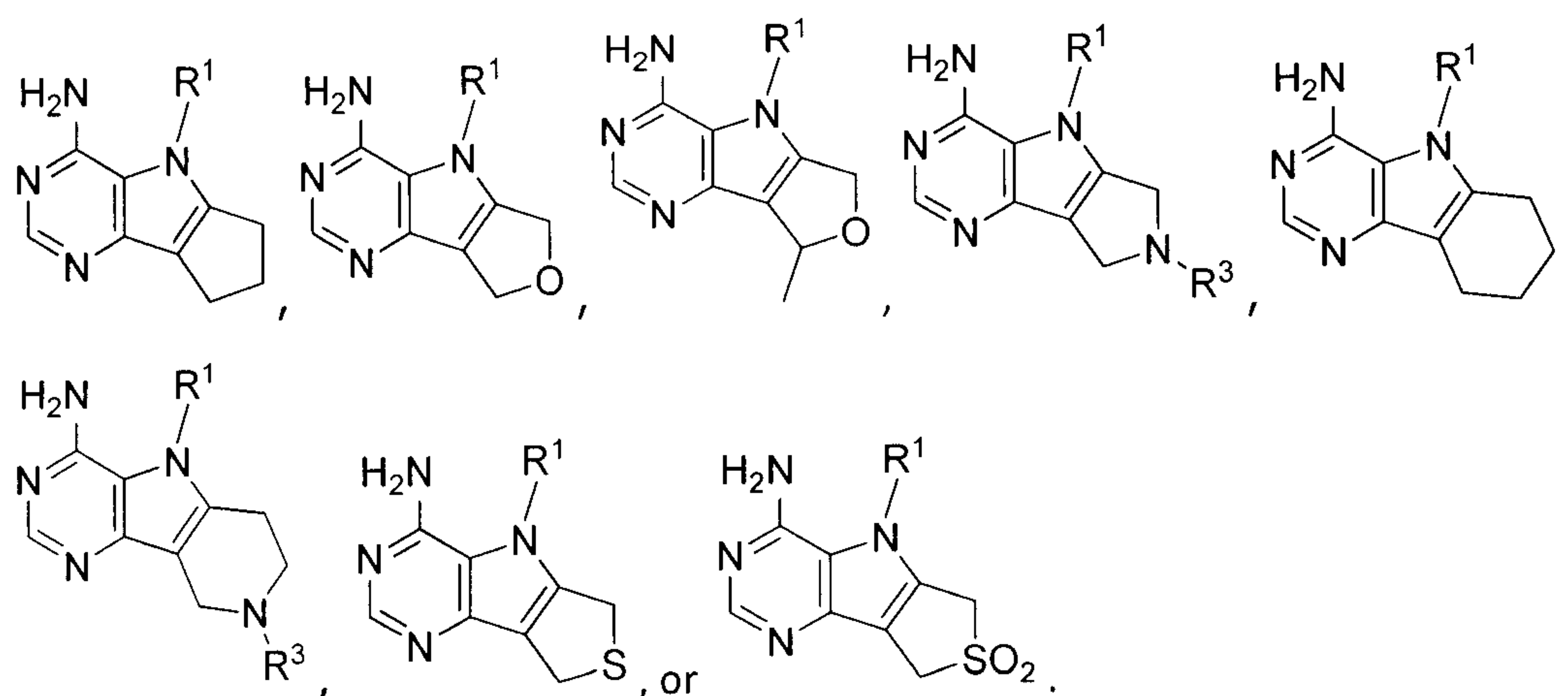
R^3 is selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl;

R^4 and R^5 are independently selected from hydrogen, alkyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl or R^4 and R^5 can be fused to form a 3 to 8 membered heterocyclyl ring system;

R^6 is selected from hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, carbocyclyl, heterocyclyl, aryl, heteroaryl, $-C(O)R^4$, $-C(O)OR^4$, $-S(O)_2R^4$, $-C(O)NR^4R^5$, $-S(O)_2NR^4R^5$, $-C(S)NR^4R^5$;

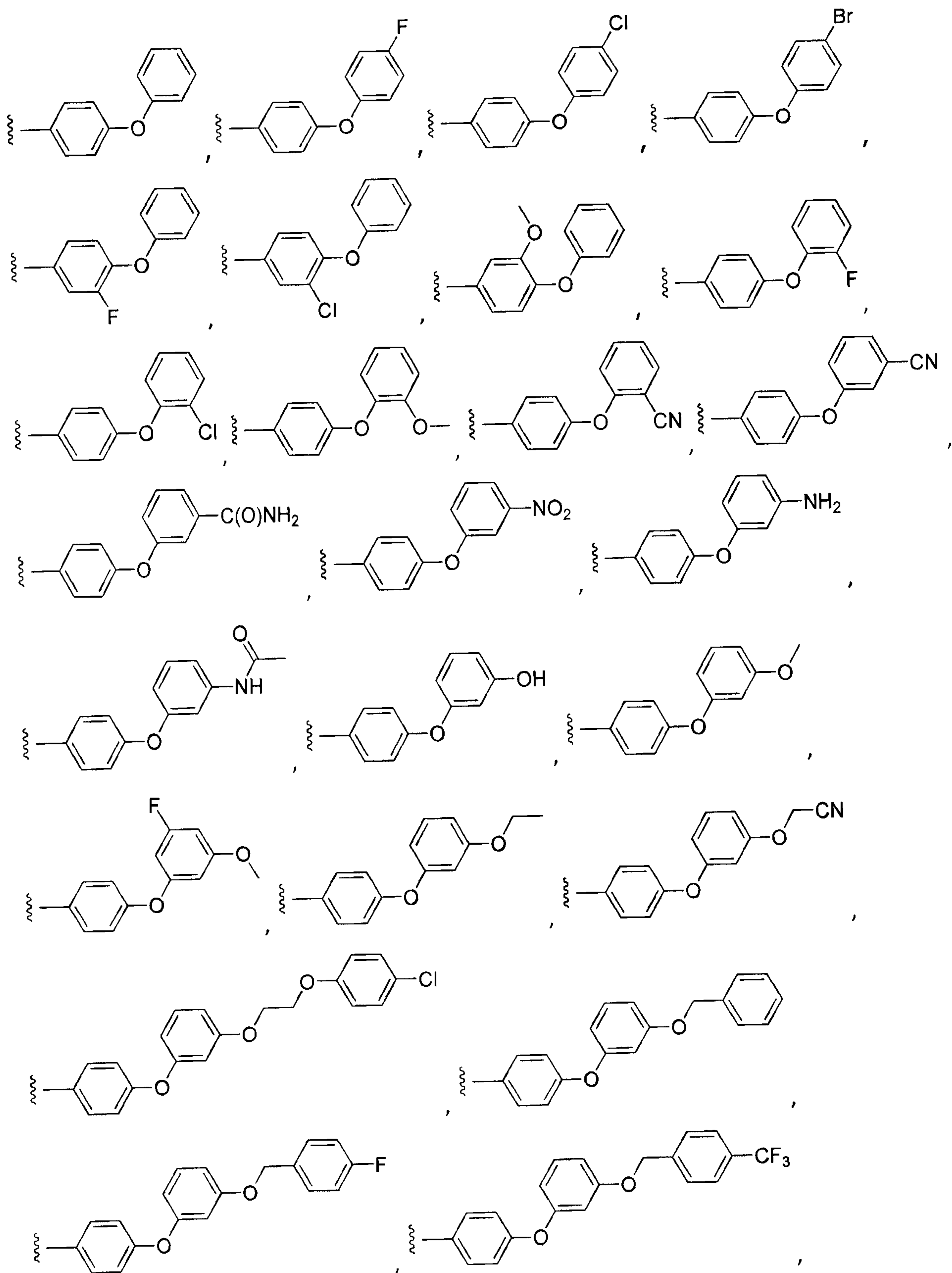
racemic or diastereoisomeric mixtures, pharmaceutically acceptable salts, prodrugs and active metabolites thereof.

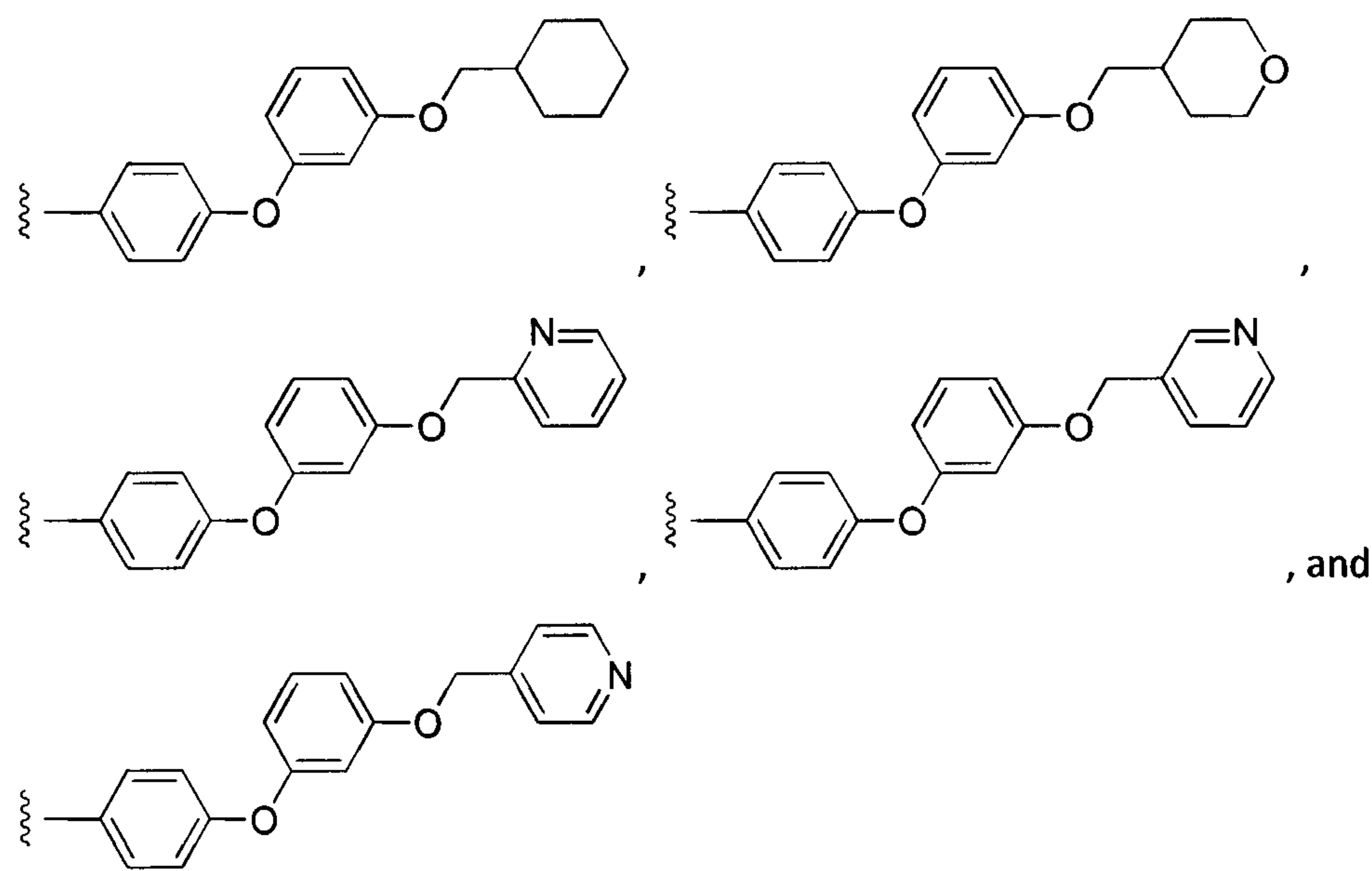
2. A compound of claim 1 wherein Formula I is selected from:



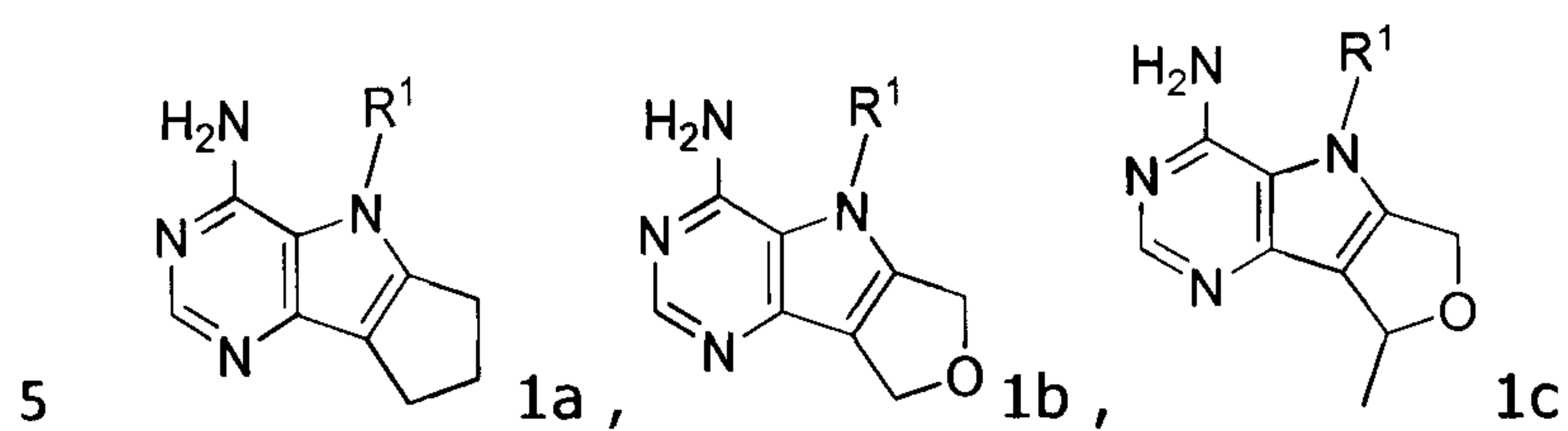
3. A compound of claims 1 or 2 wherein R^1 is selected from:

5

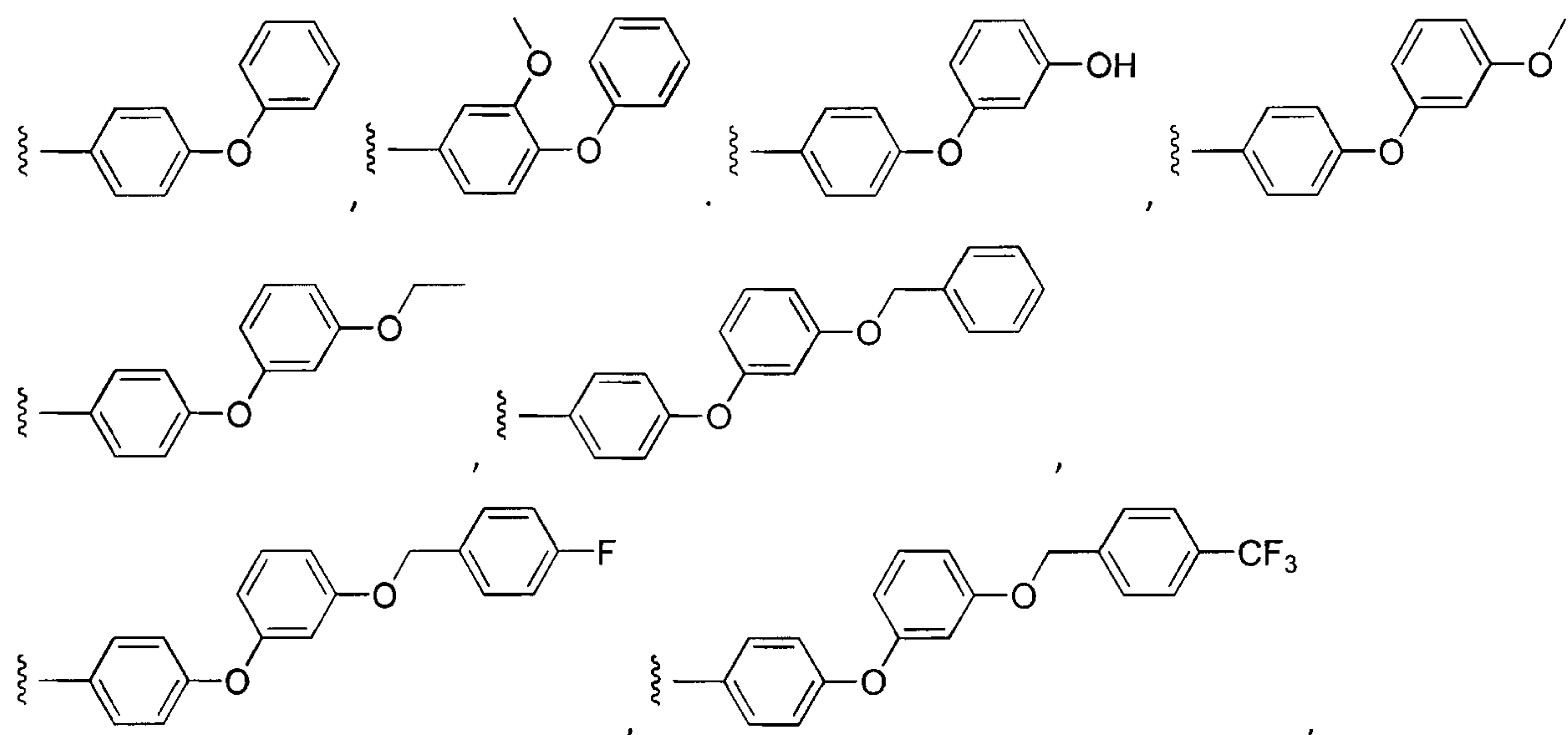


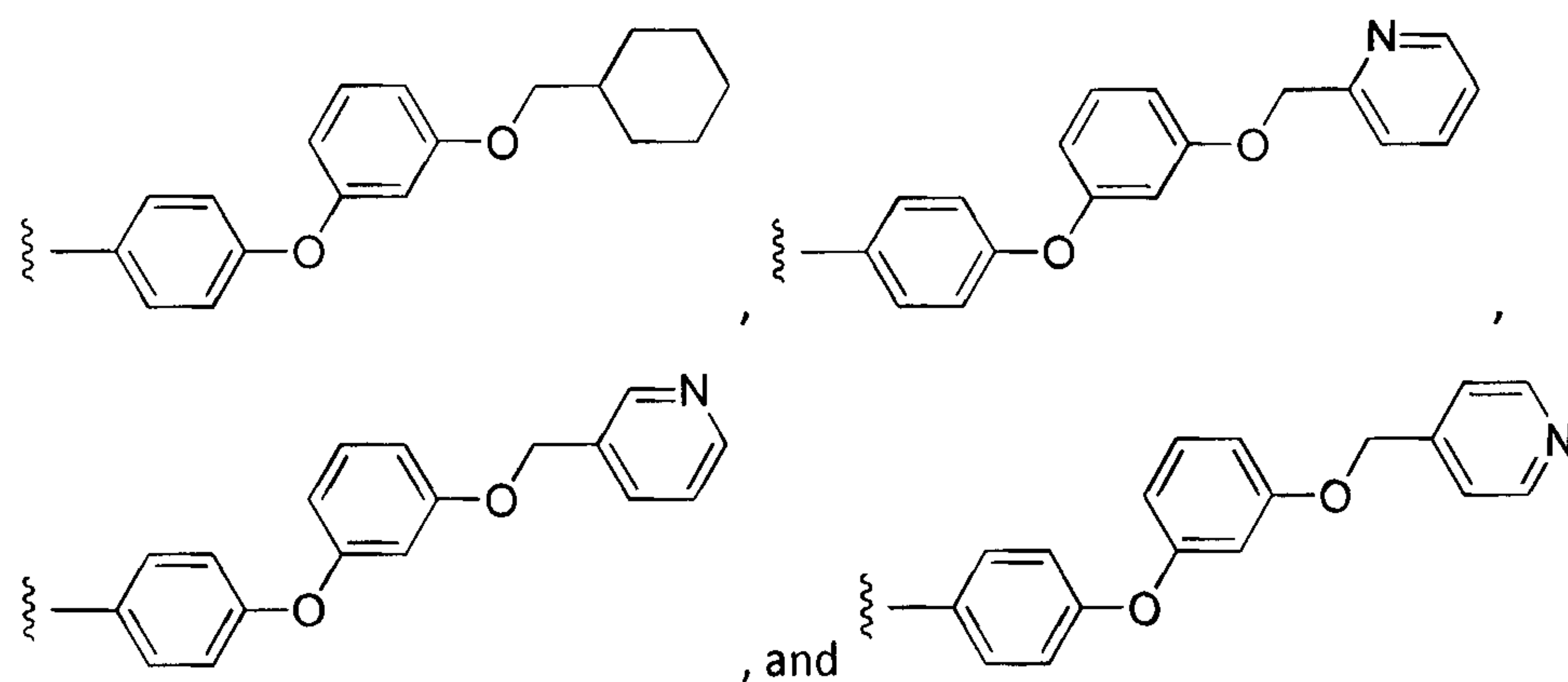


4. A compound of claims 1 to 3 represented by formulas 1a, 1b and c:



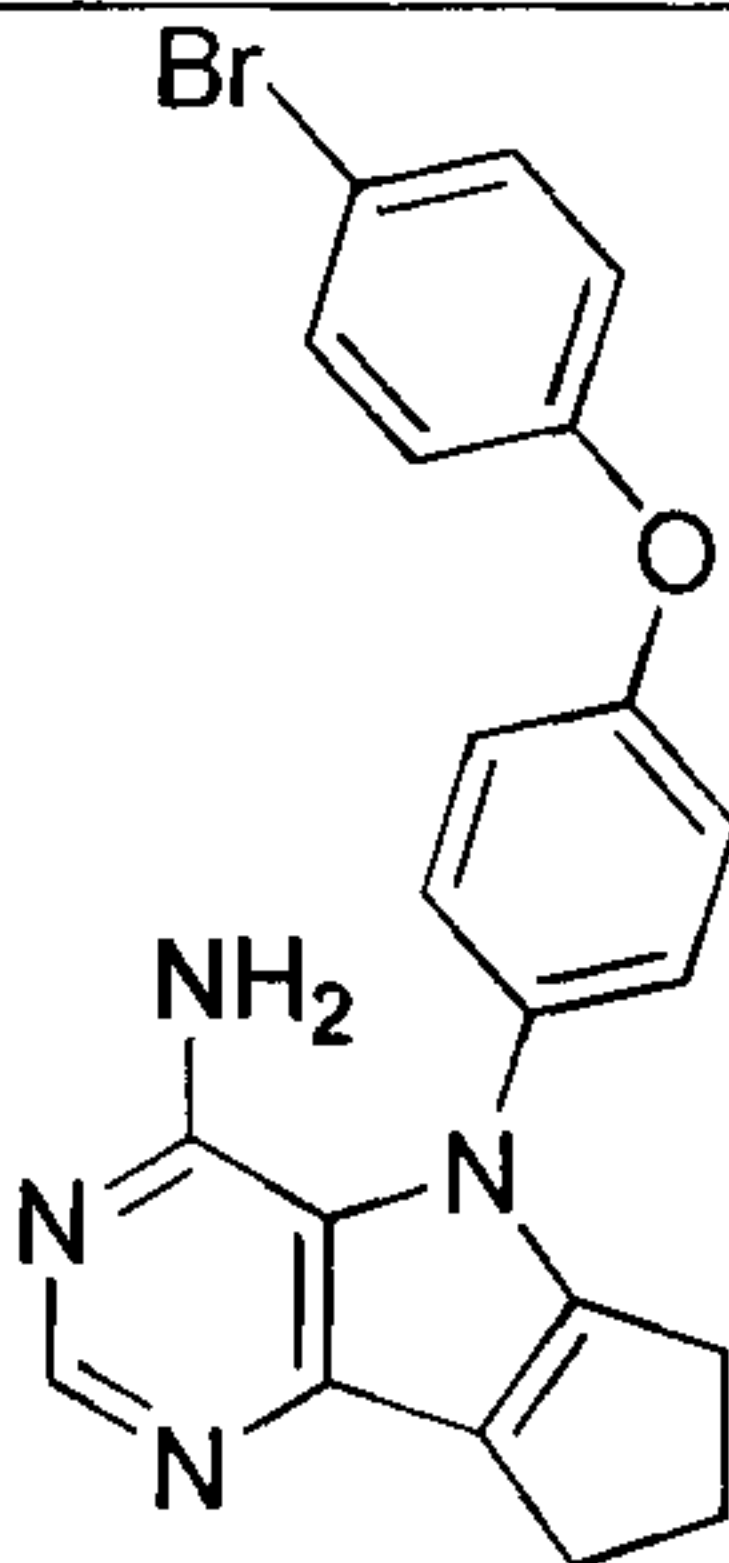
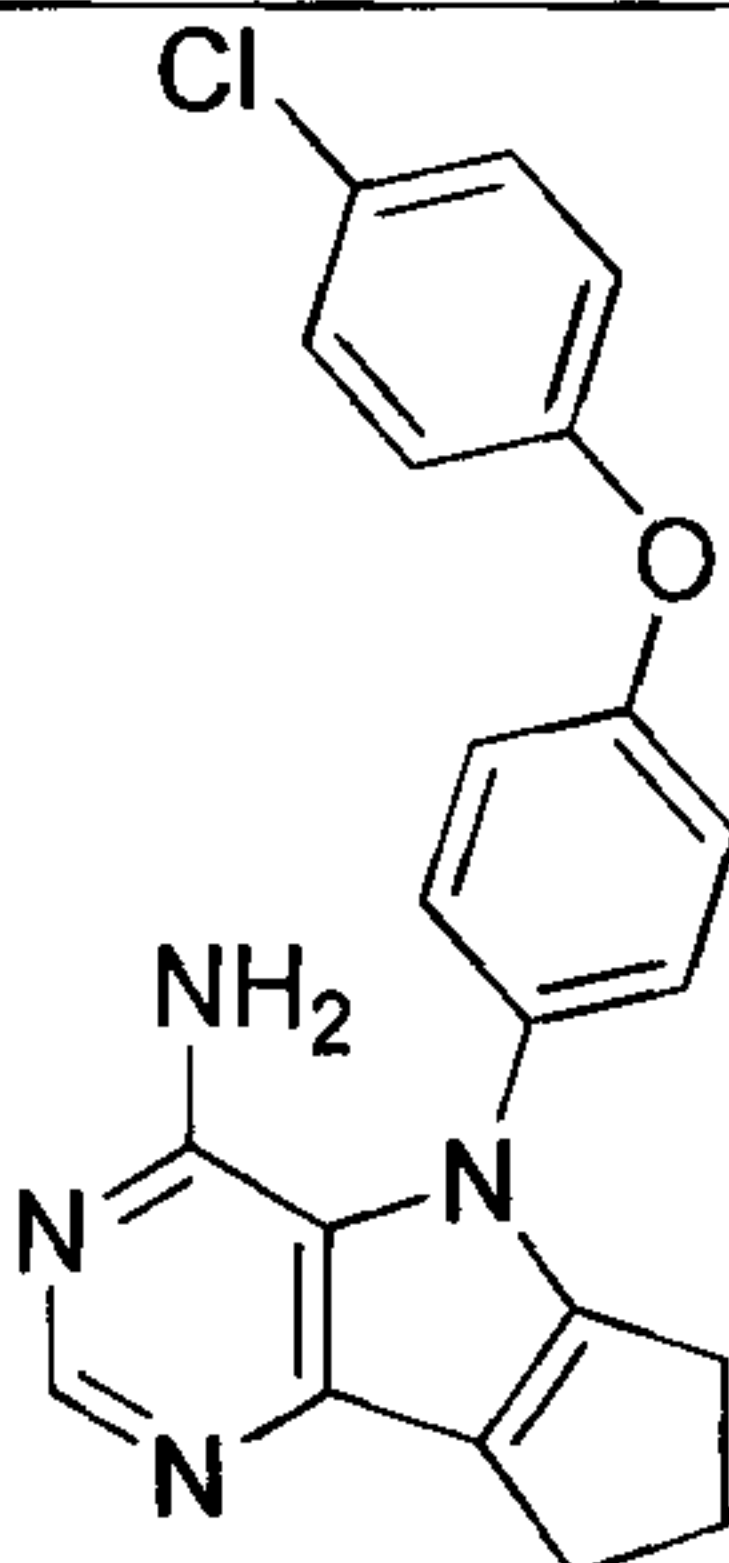
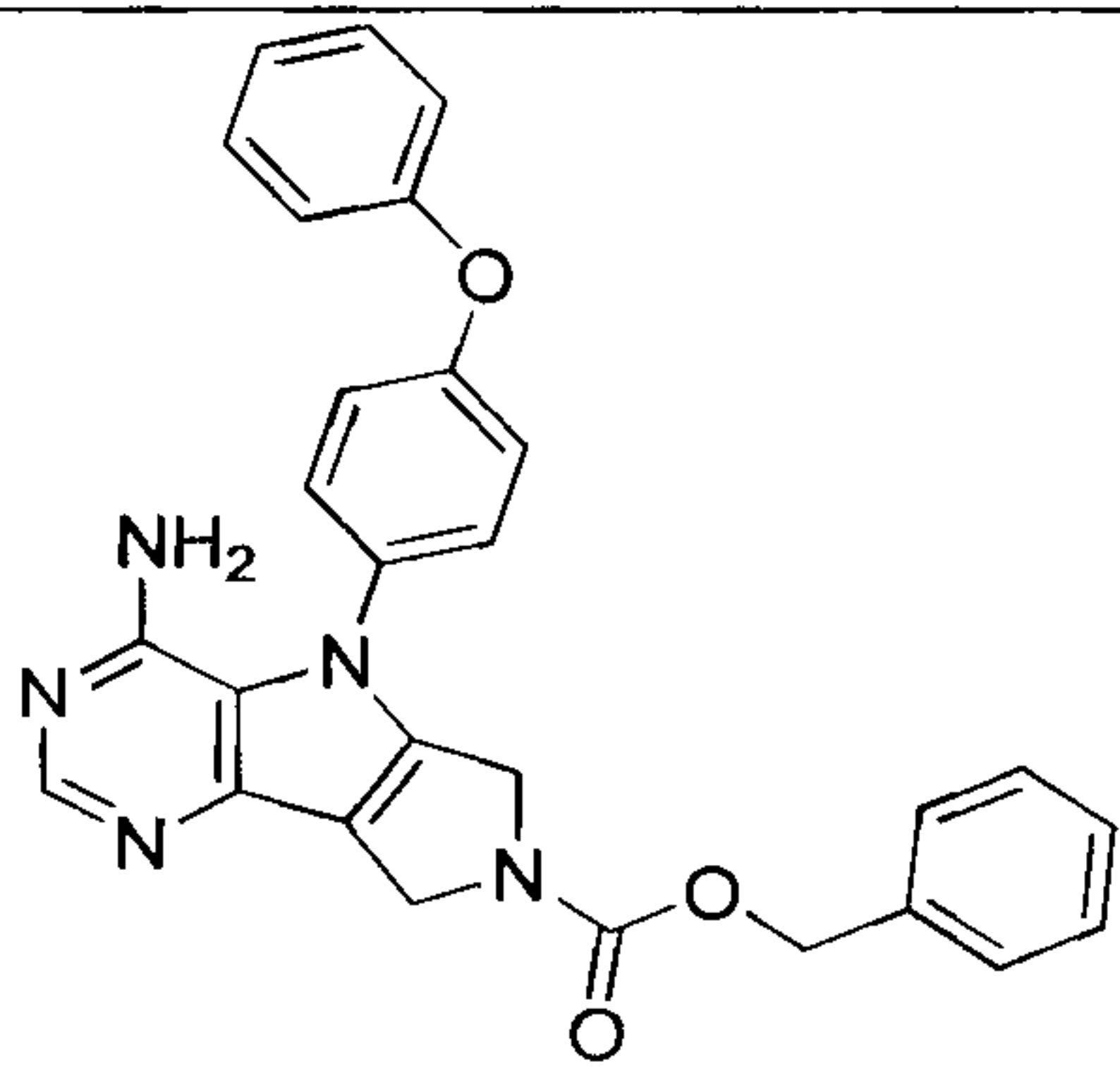
wherein R^1 is selected from the groups consisting of:

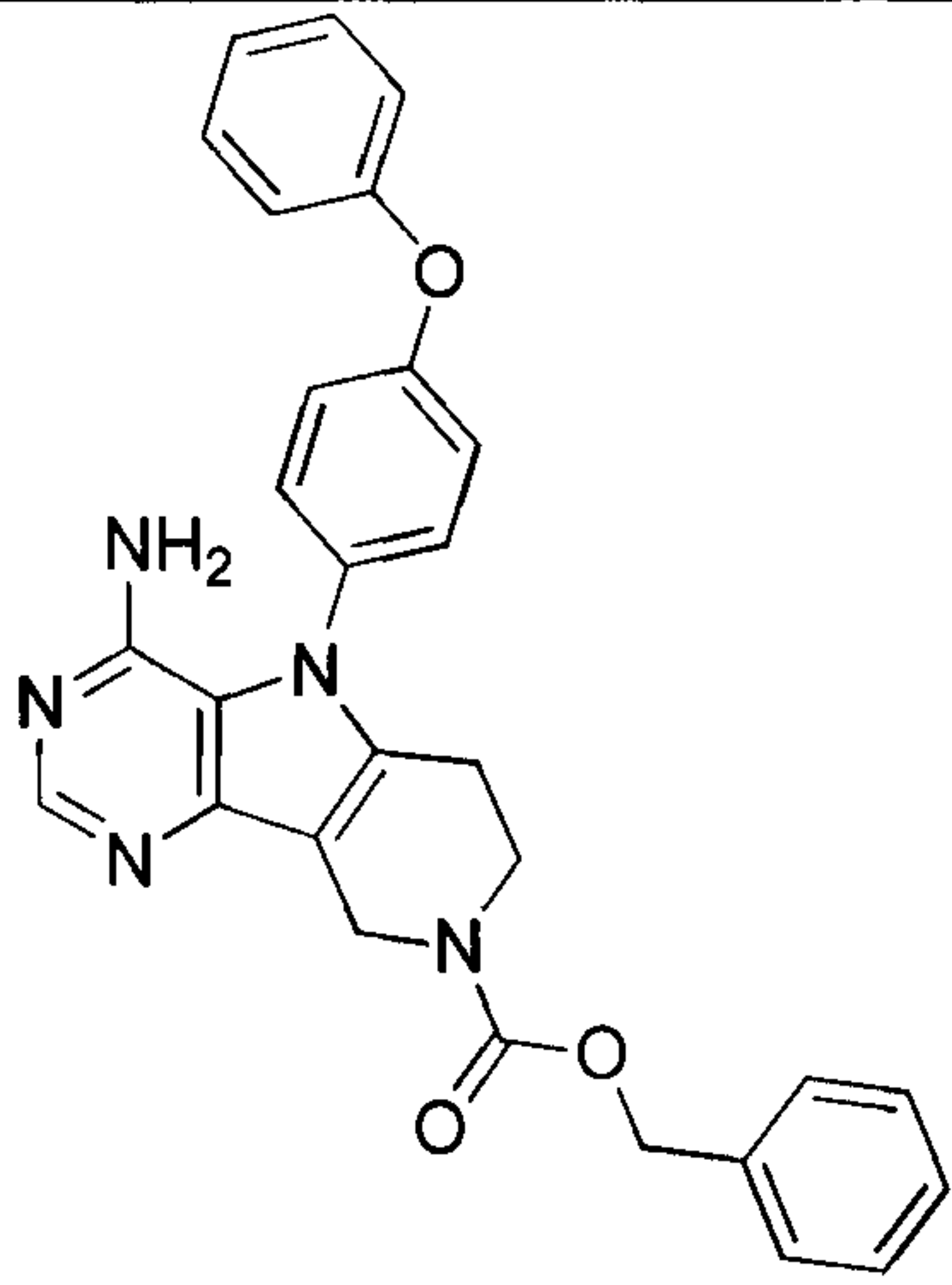
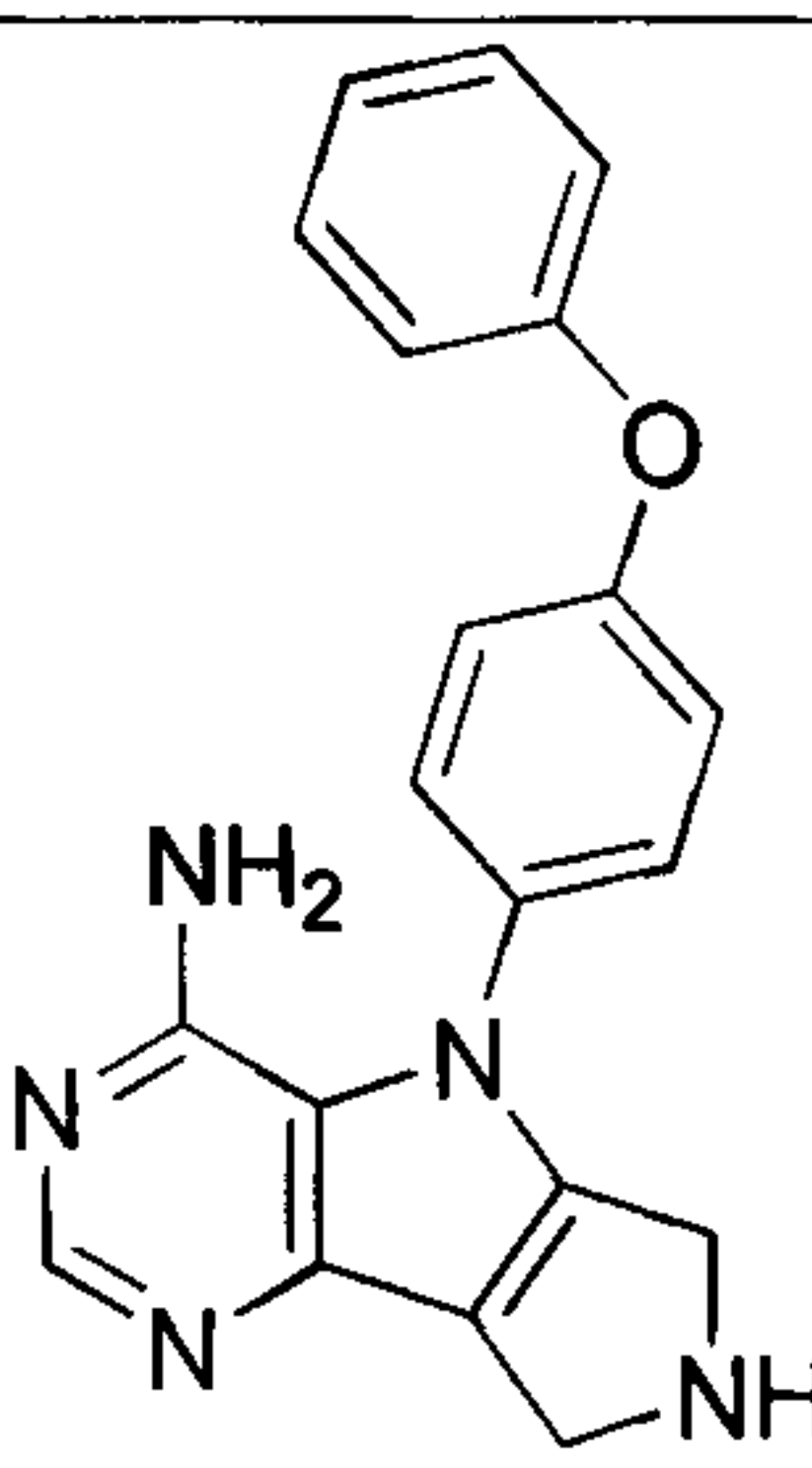
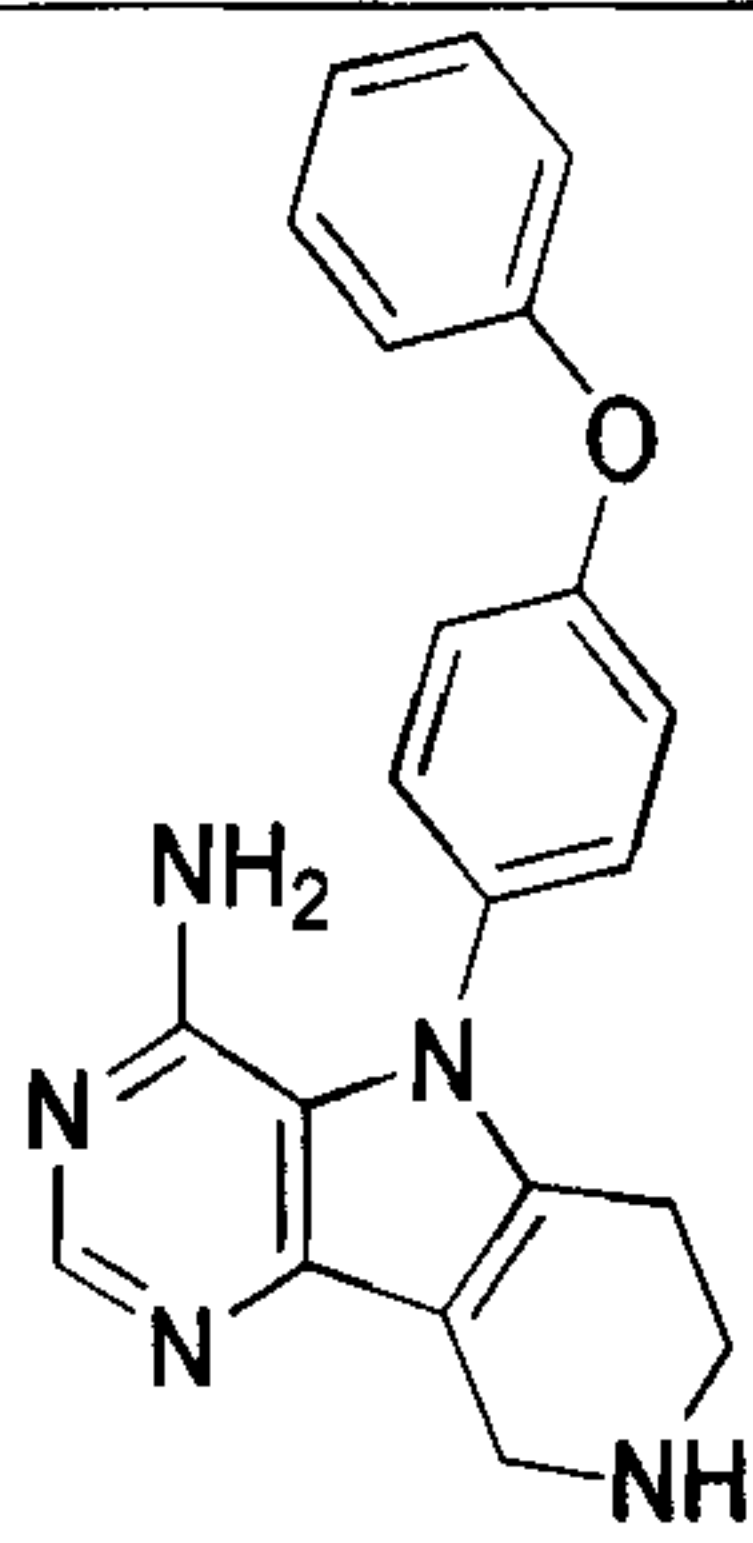


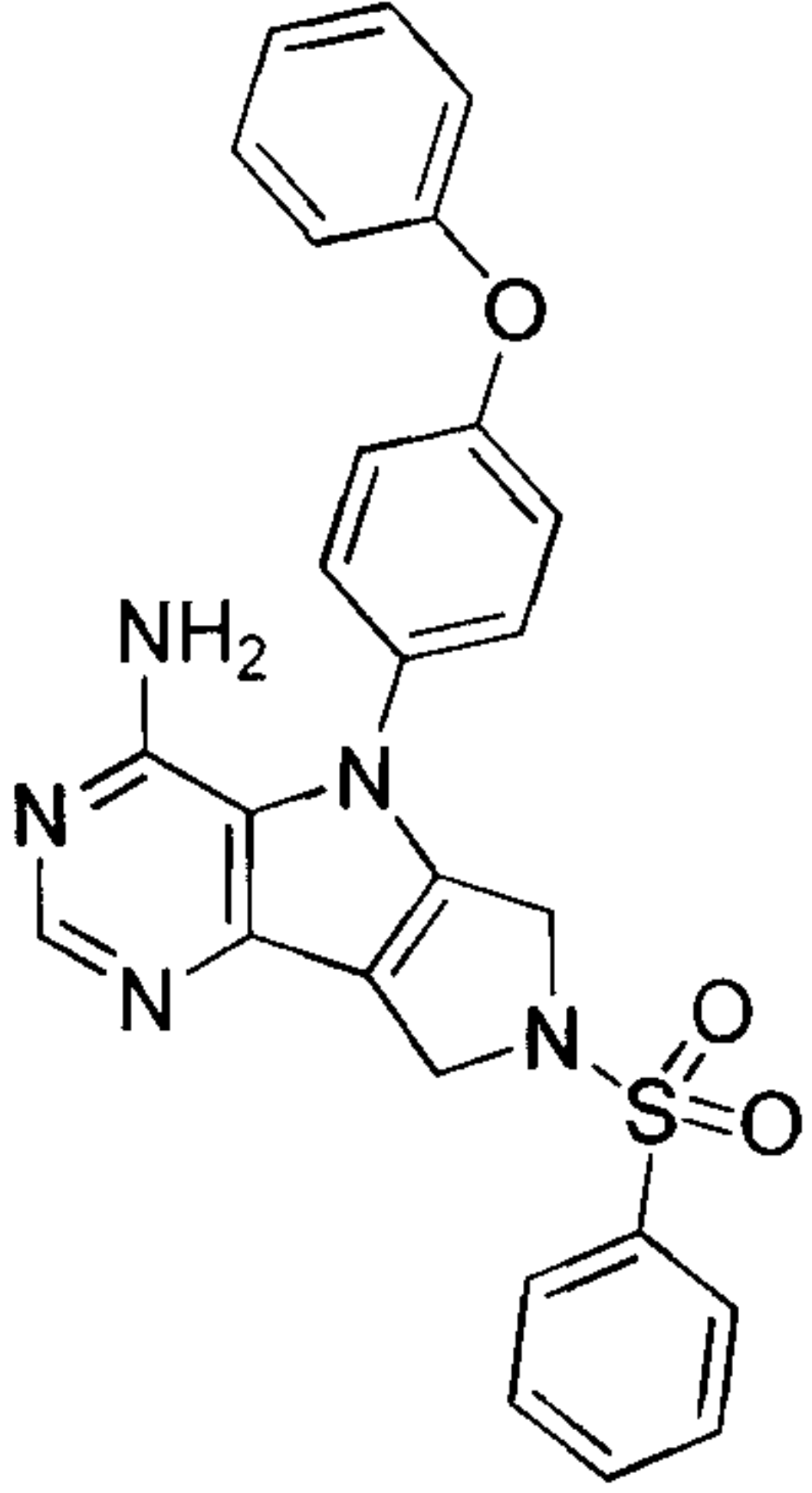
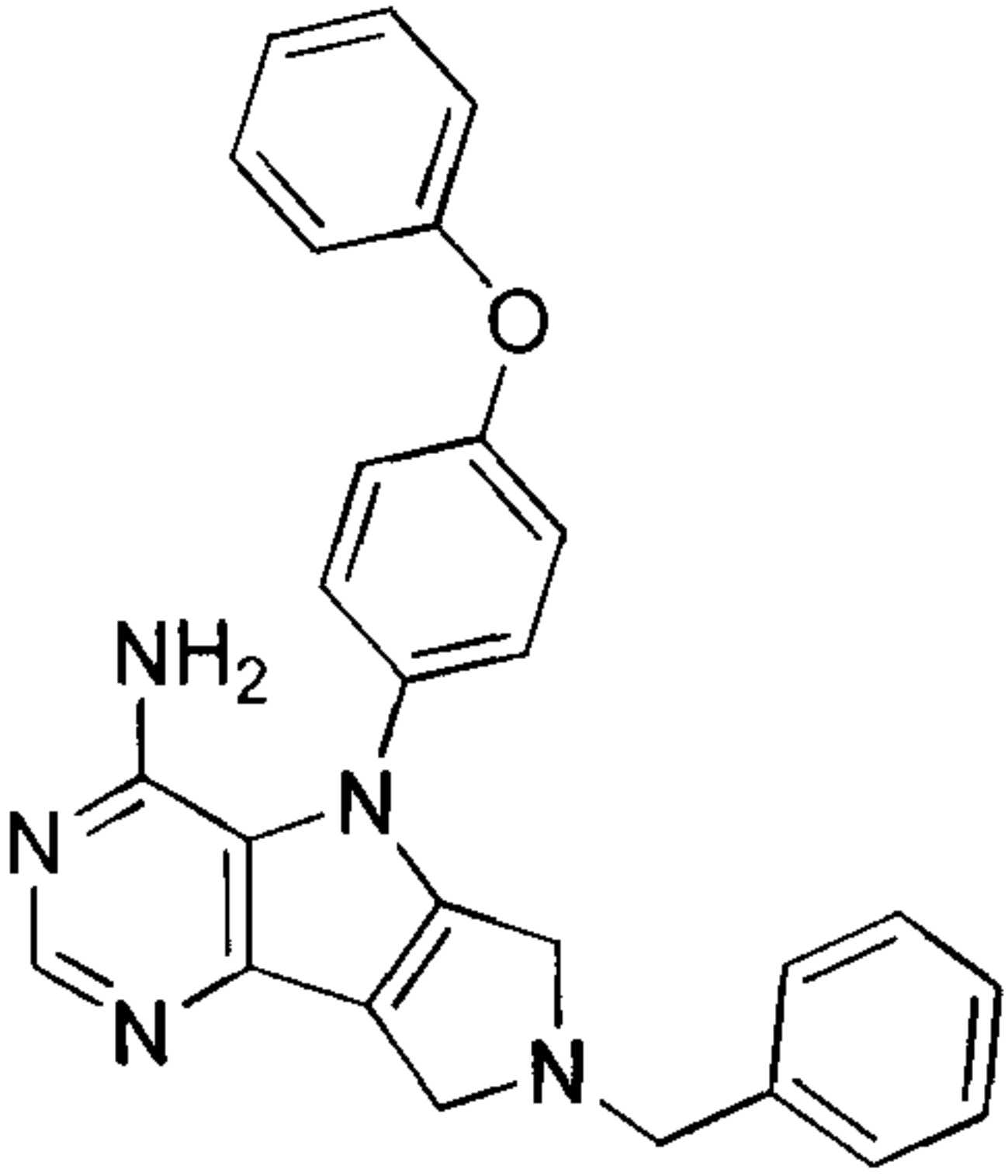
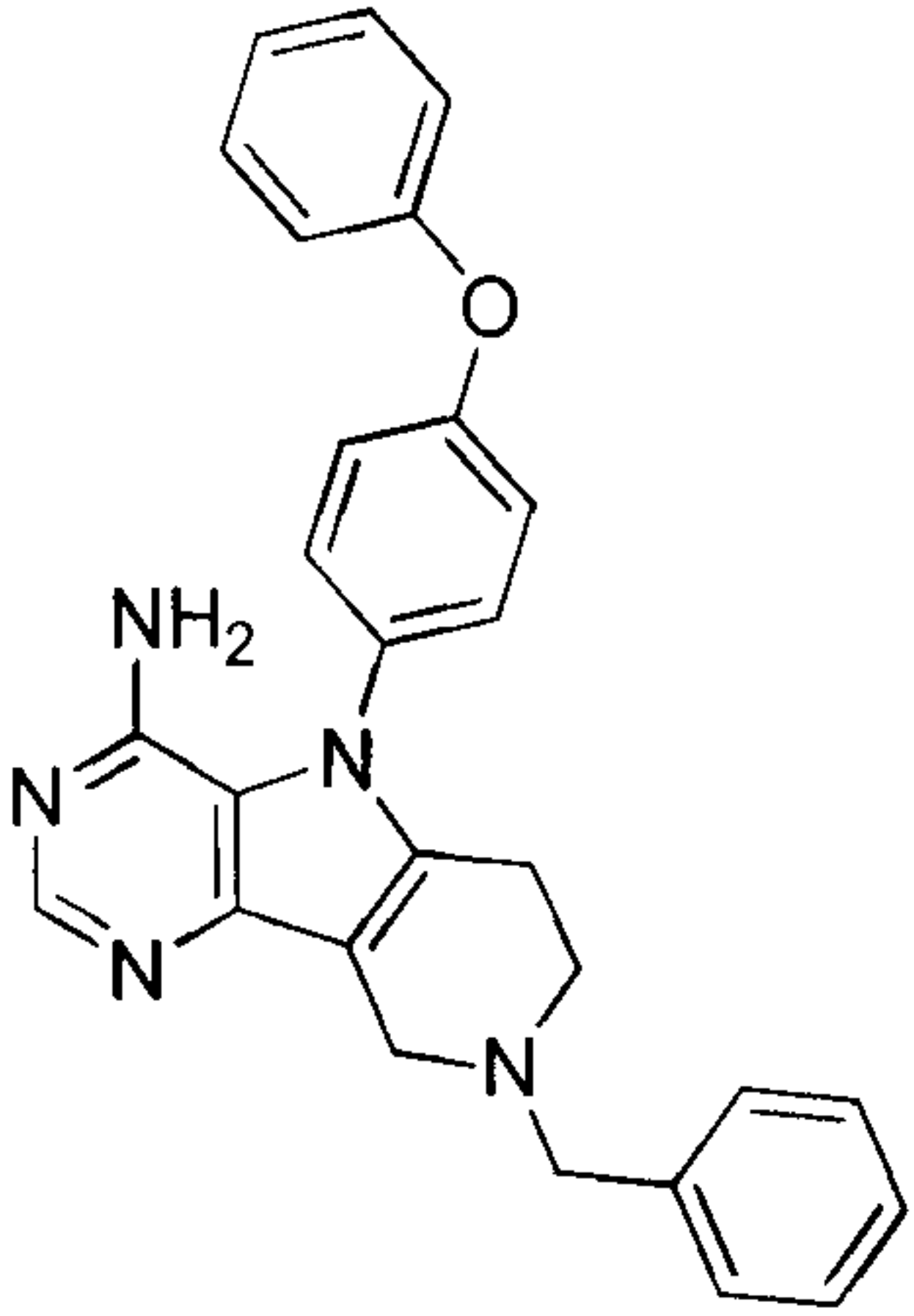


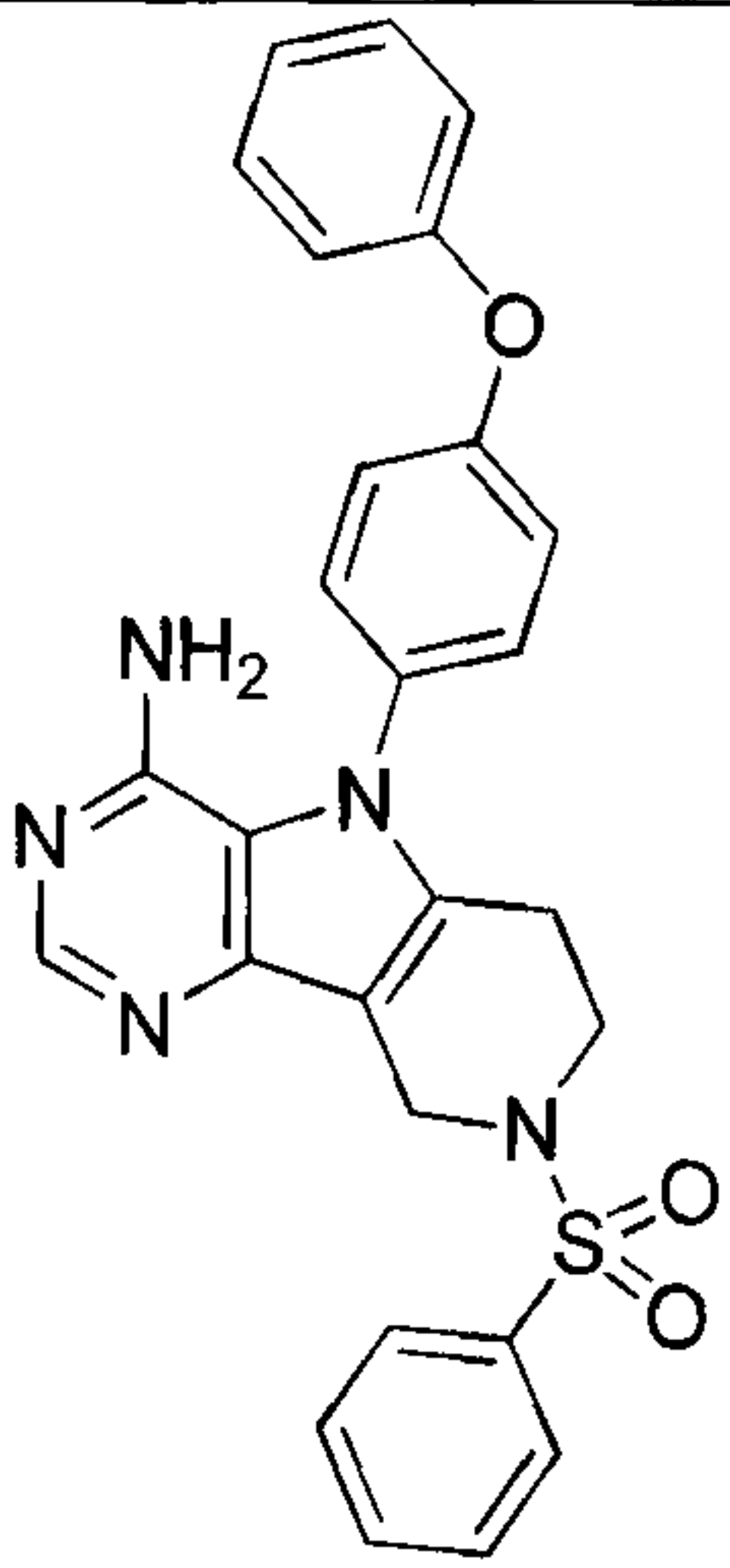
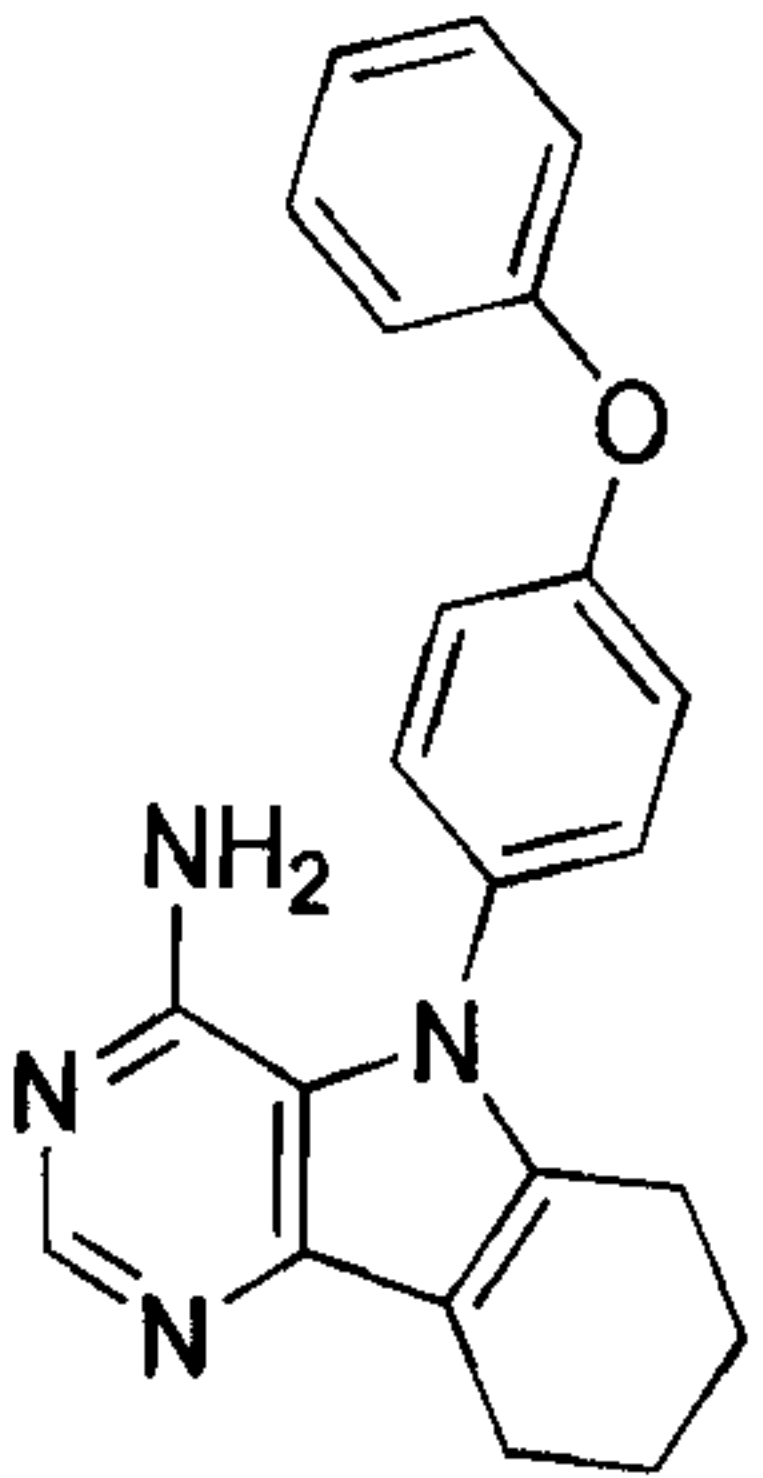
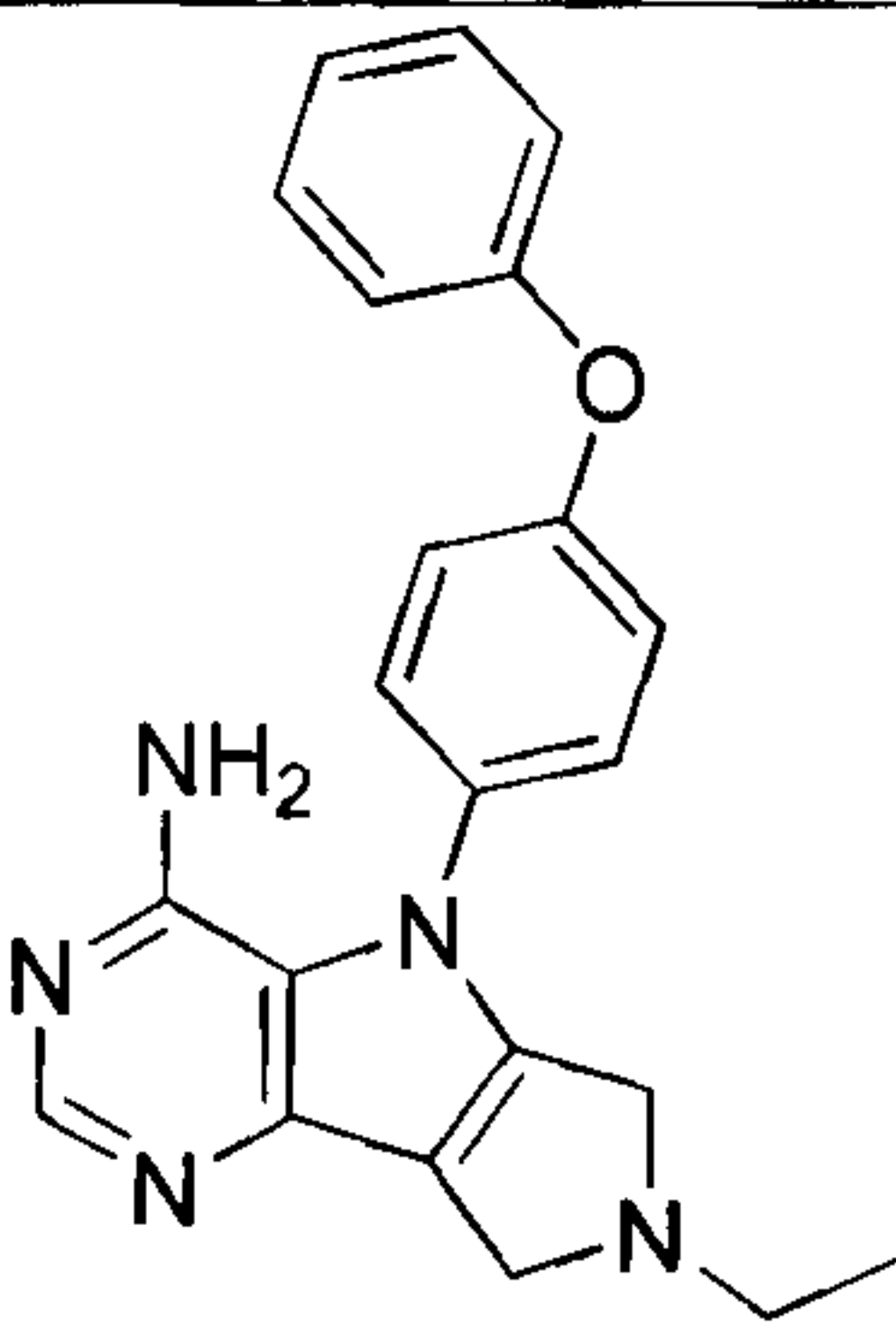
5. A compound selected from the group consisting of:

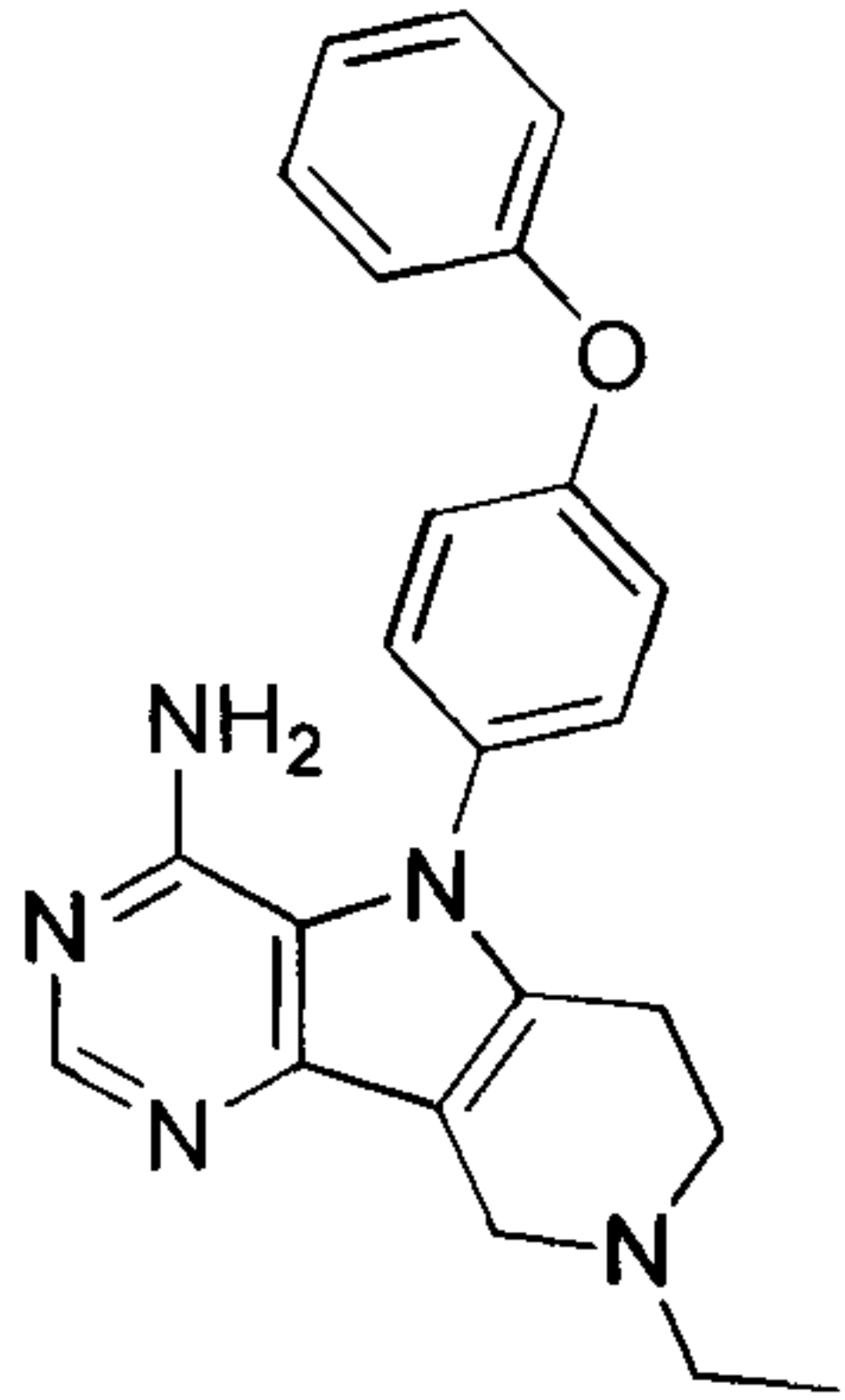
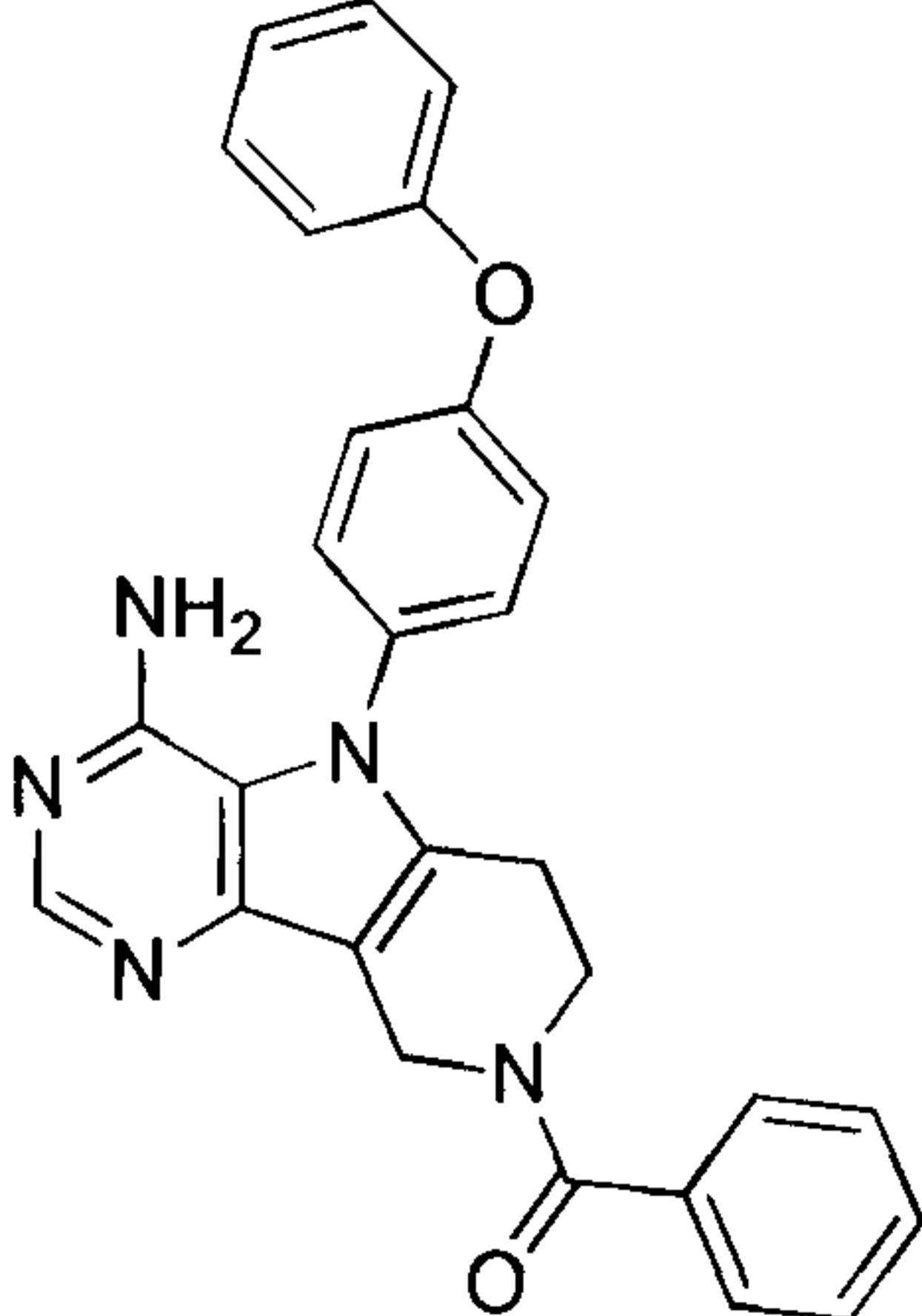
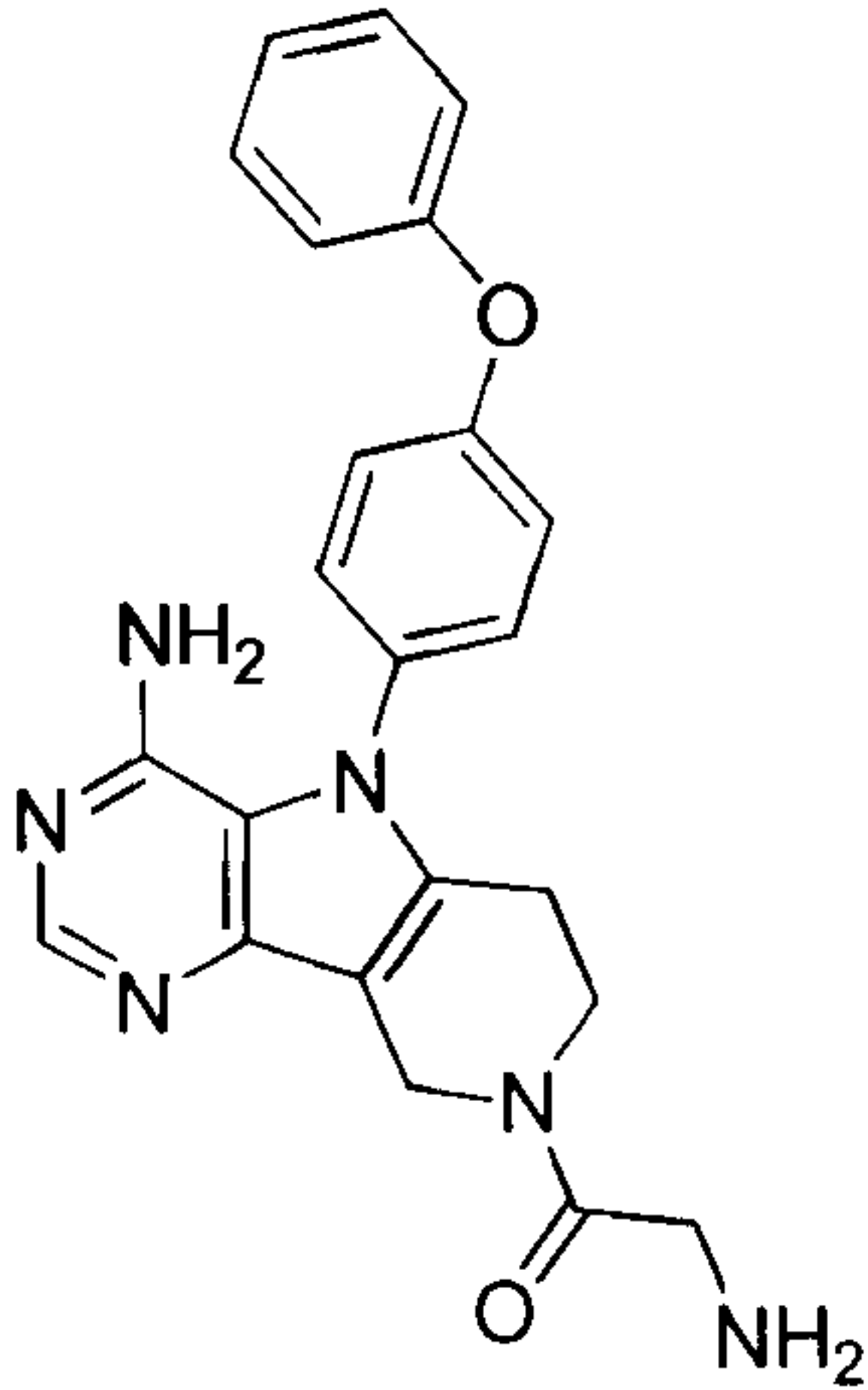
Compound	Structure	MS (m/z)
1		$[M+H]^+ = 343.2$
2		$[M+H]^+ = 361.2$

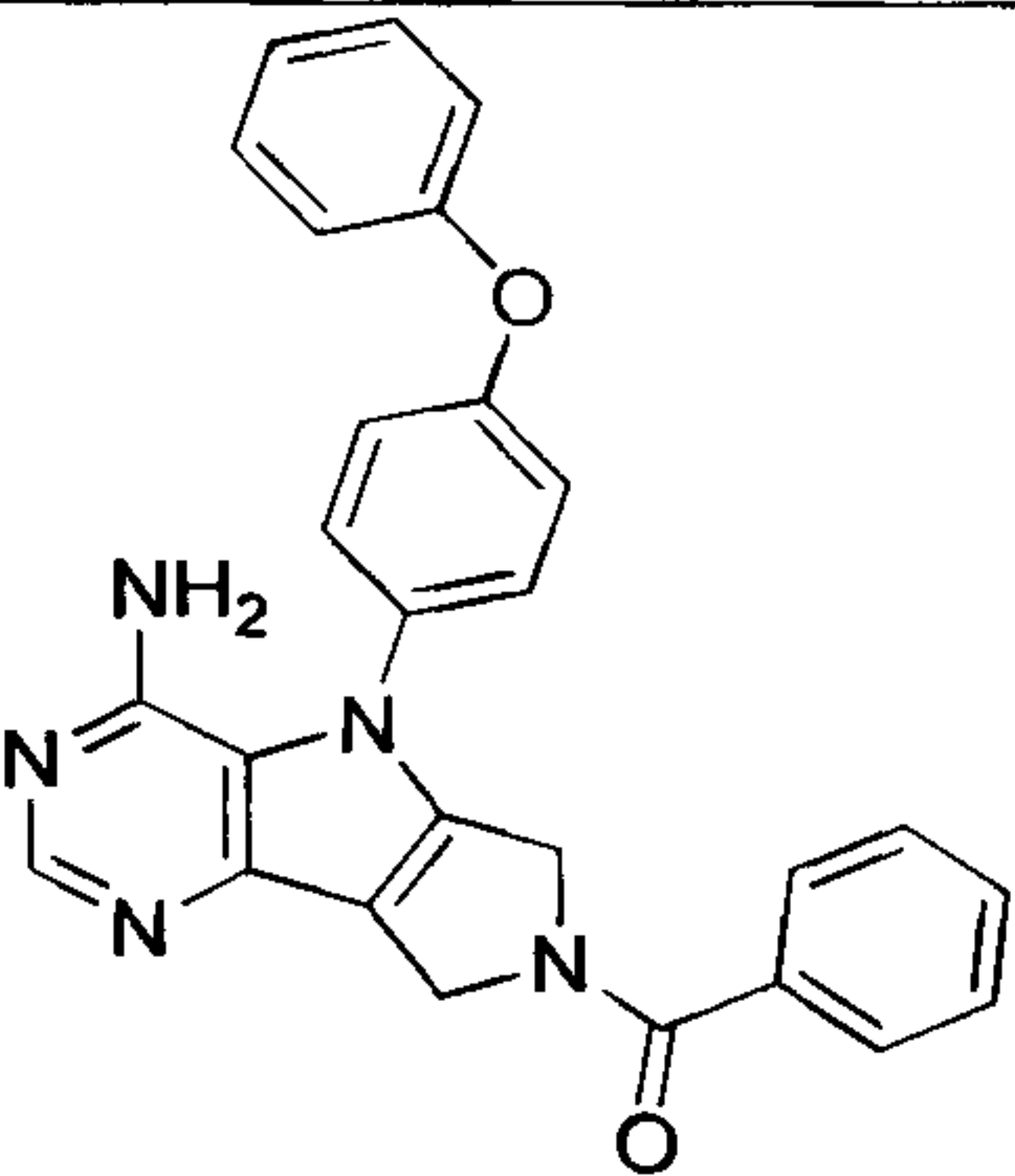
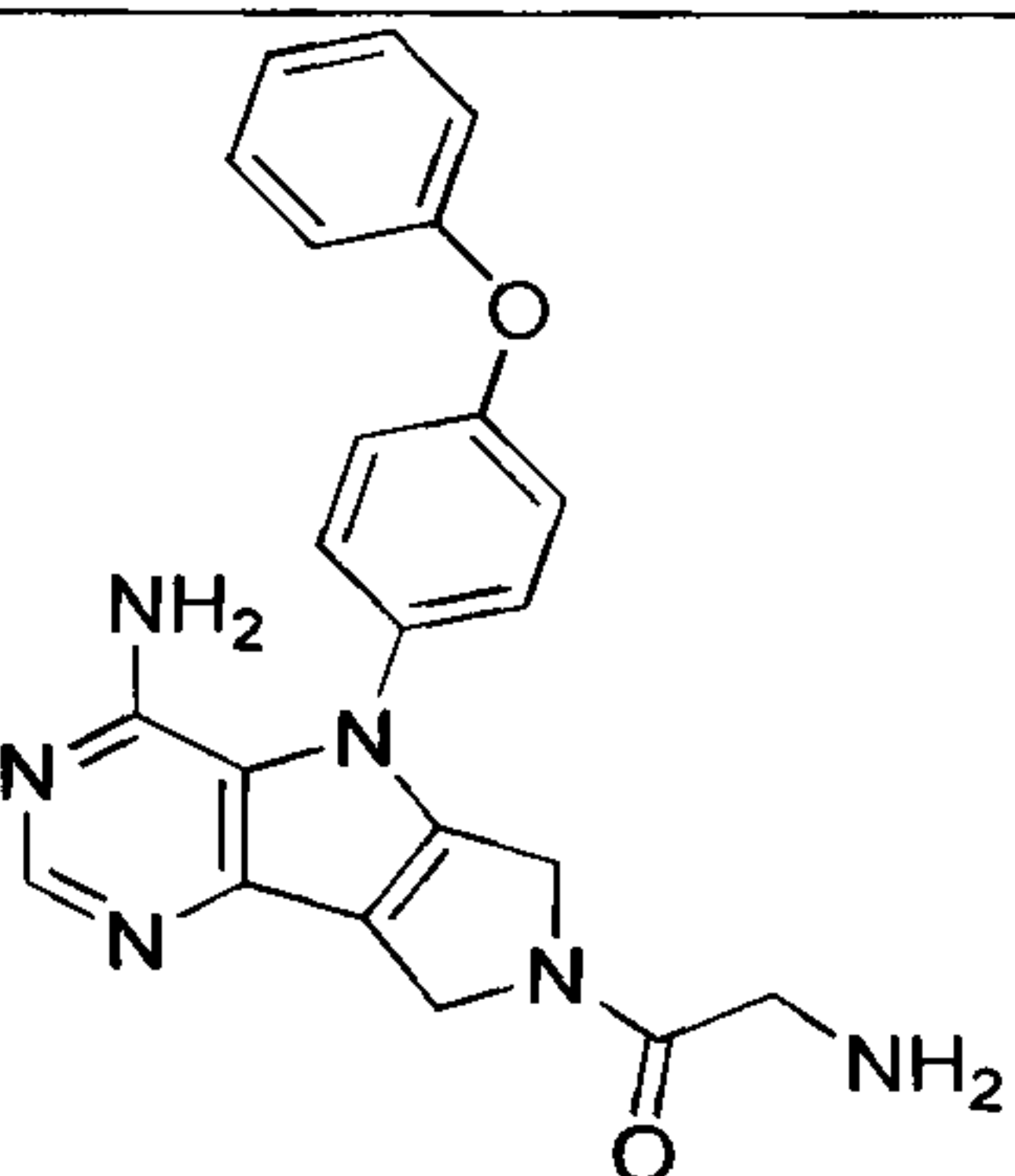
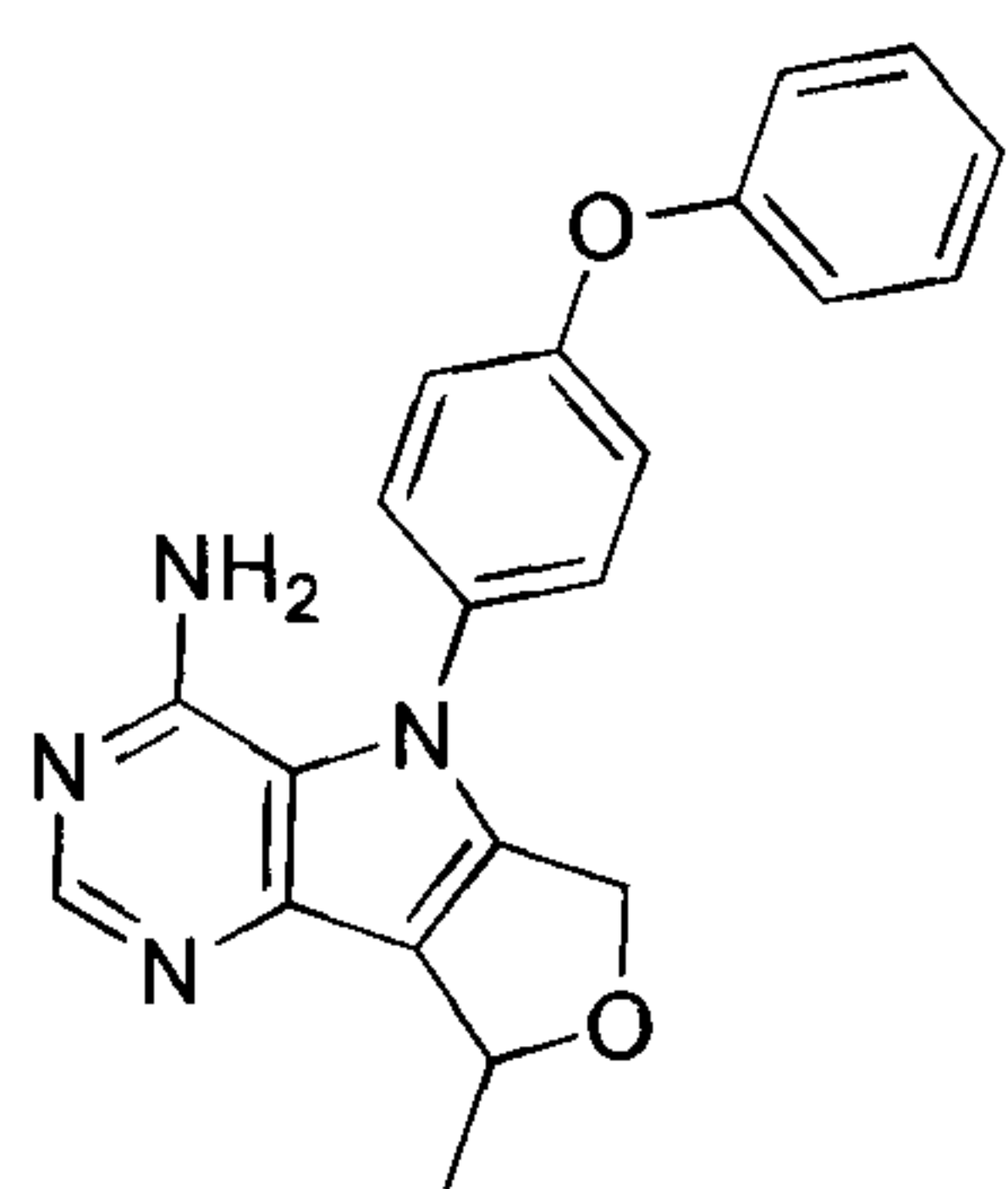
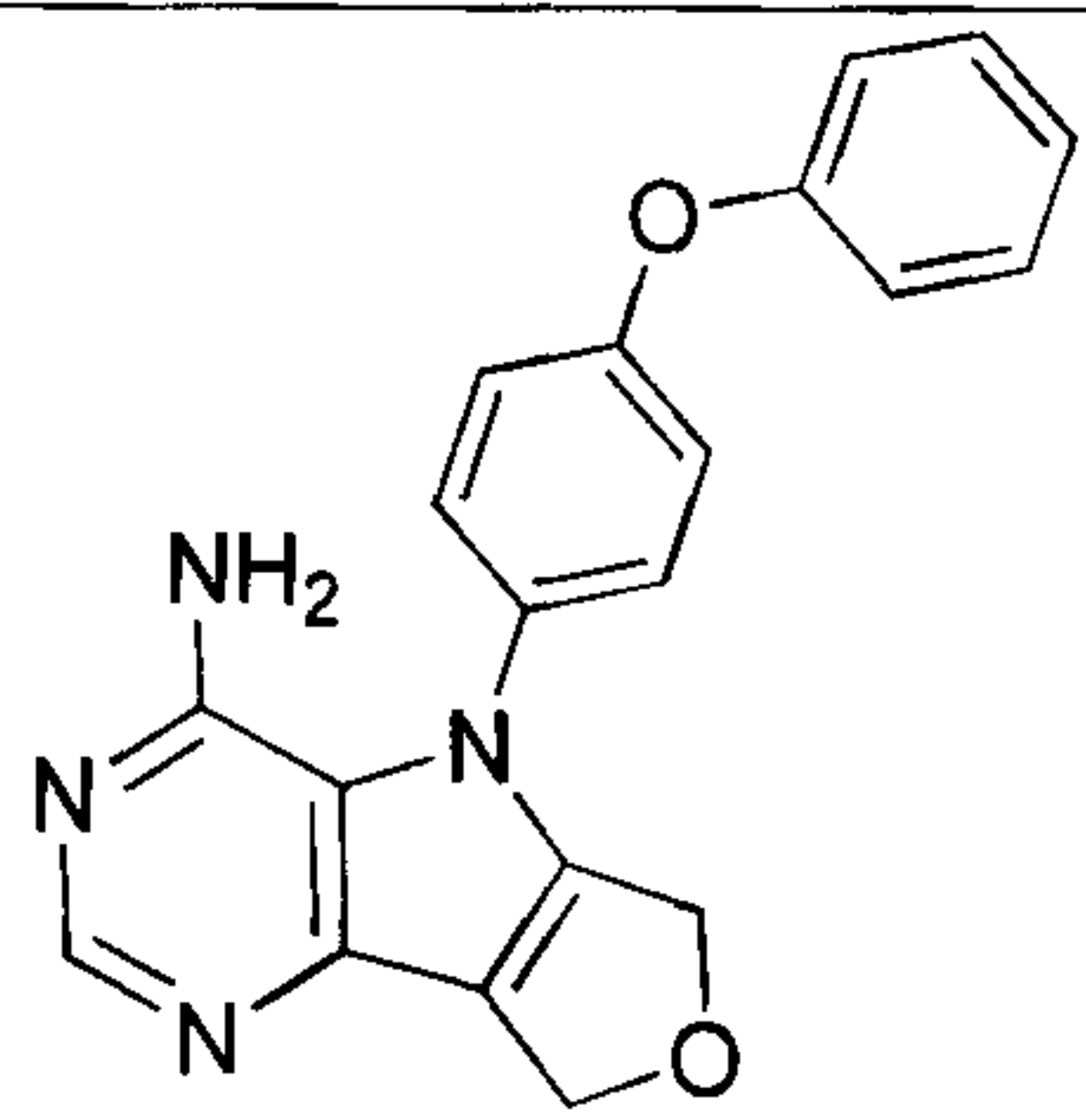
3		$[M+H]^+ = 421.6$
4		$[M+H]^+ = 377.2$
5		$[M+H]^+ = 478.1$

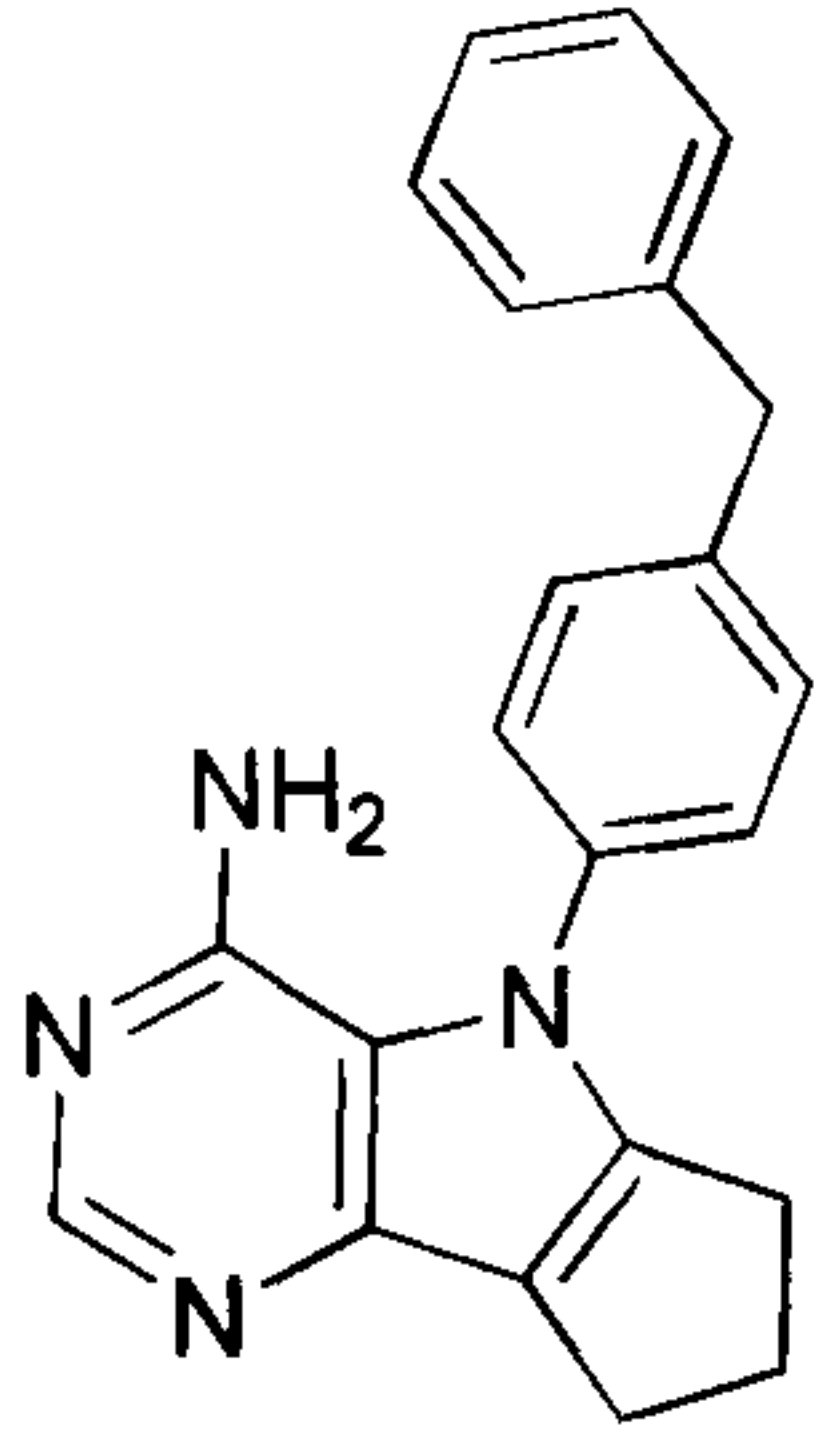
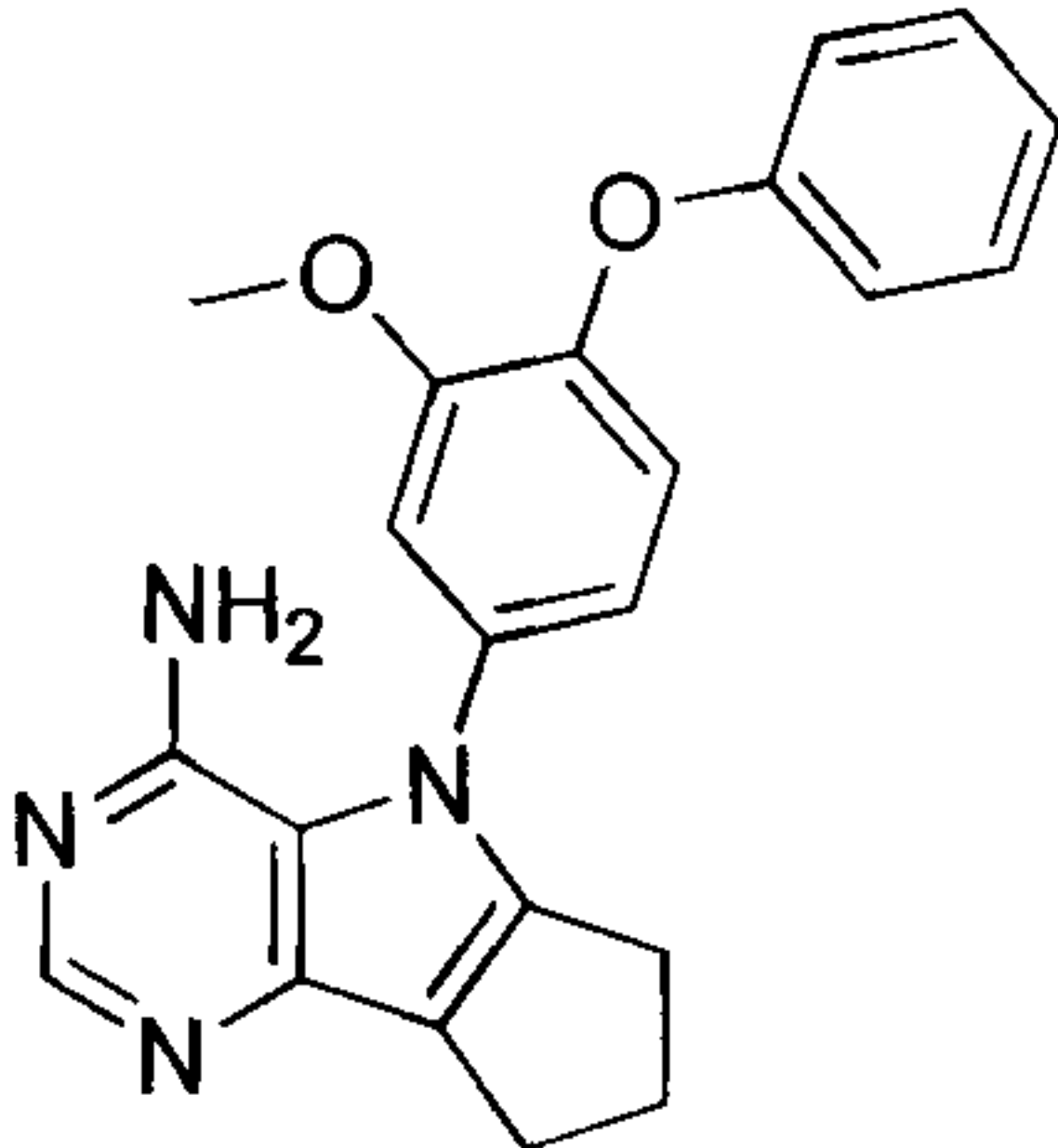
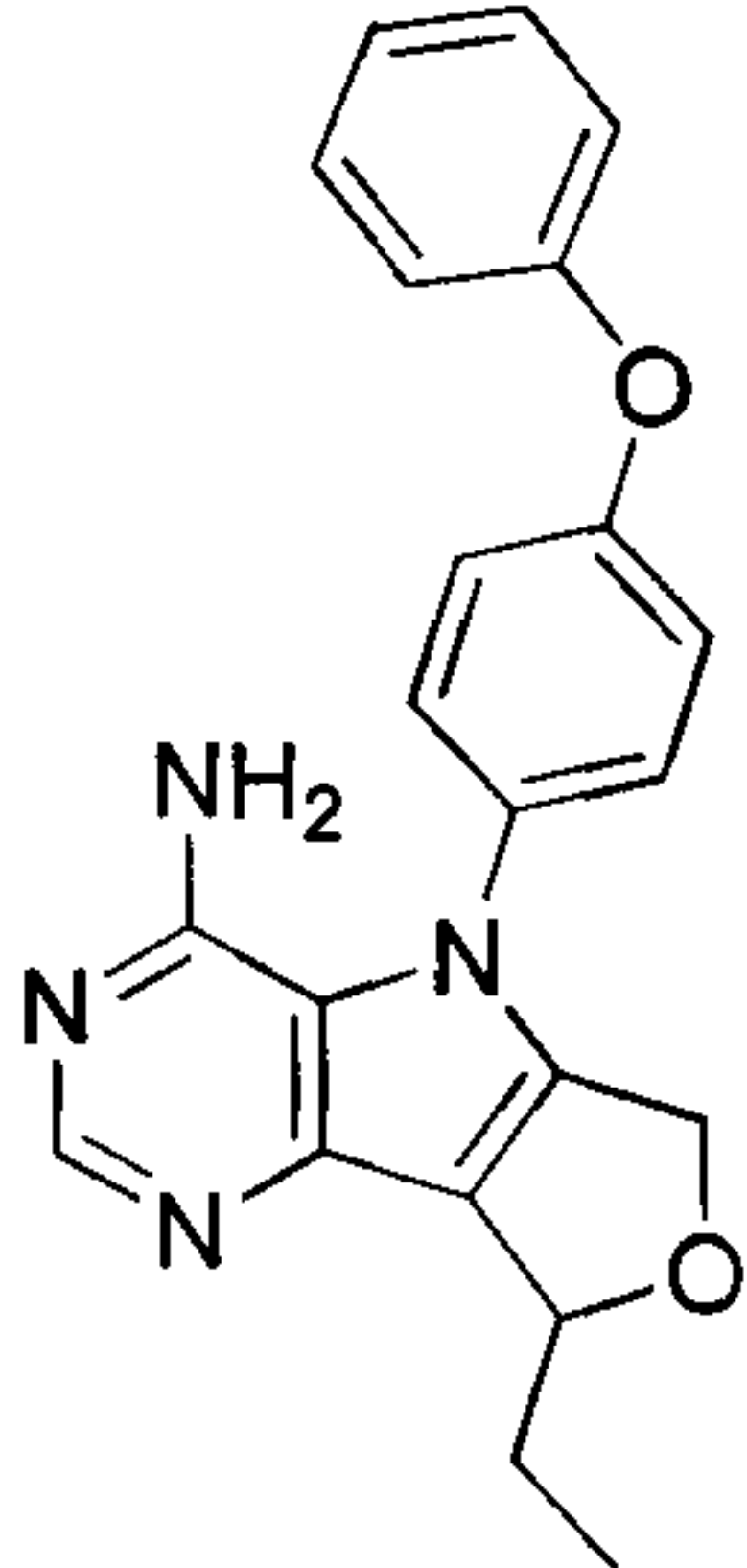
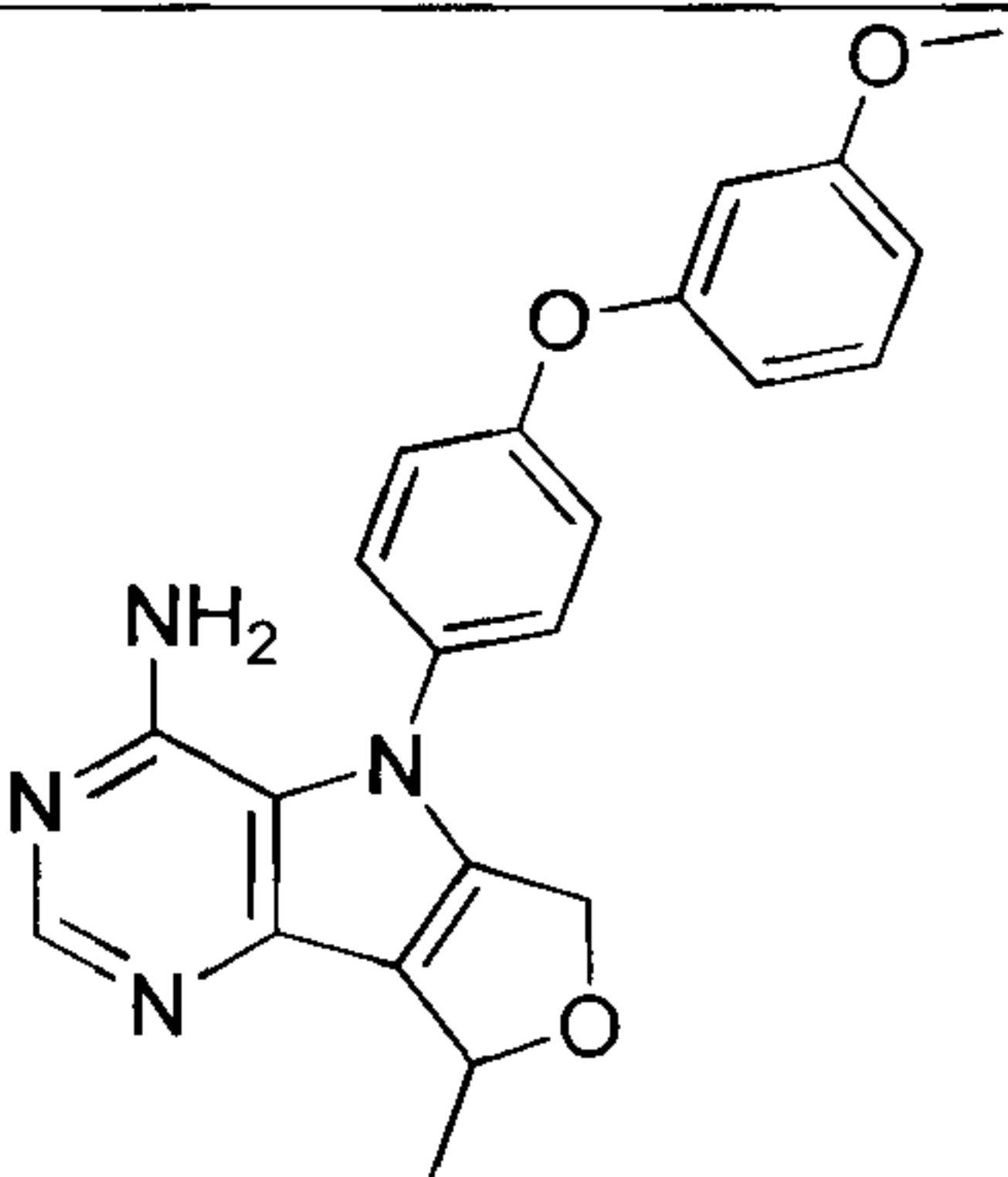
6	 <chem>O=C(OCc1ccccc1)NCCc2c3c(ncn23)Nc4ccc(Oc5ccccc5)cc4</chem>	$[M+H]^+=492.1$
7	 <chem>Nc1nc2c(ncn12)c3c[nH]c3Nc4ccc(Oc5ccccc5)cc4</chem>	$[M+H]^+=344.2$
8	 <chem>Nc1nc2c(ncn12)c3c[nH]c3Nc4ccc(Oc5ccccc5)cc4</chem>	$[M+H]^+=358.2$

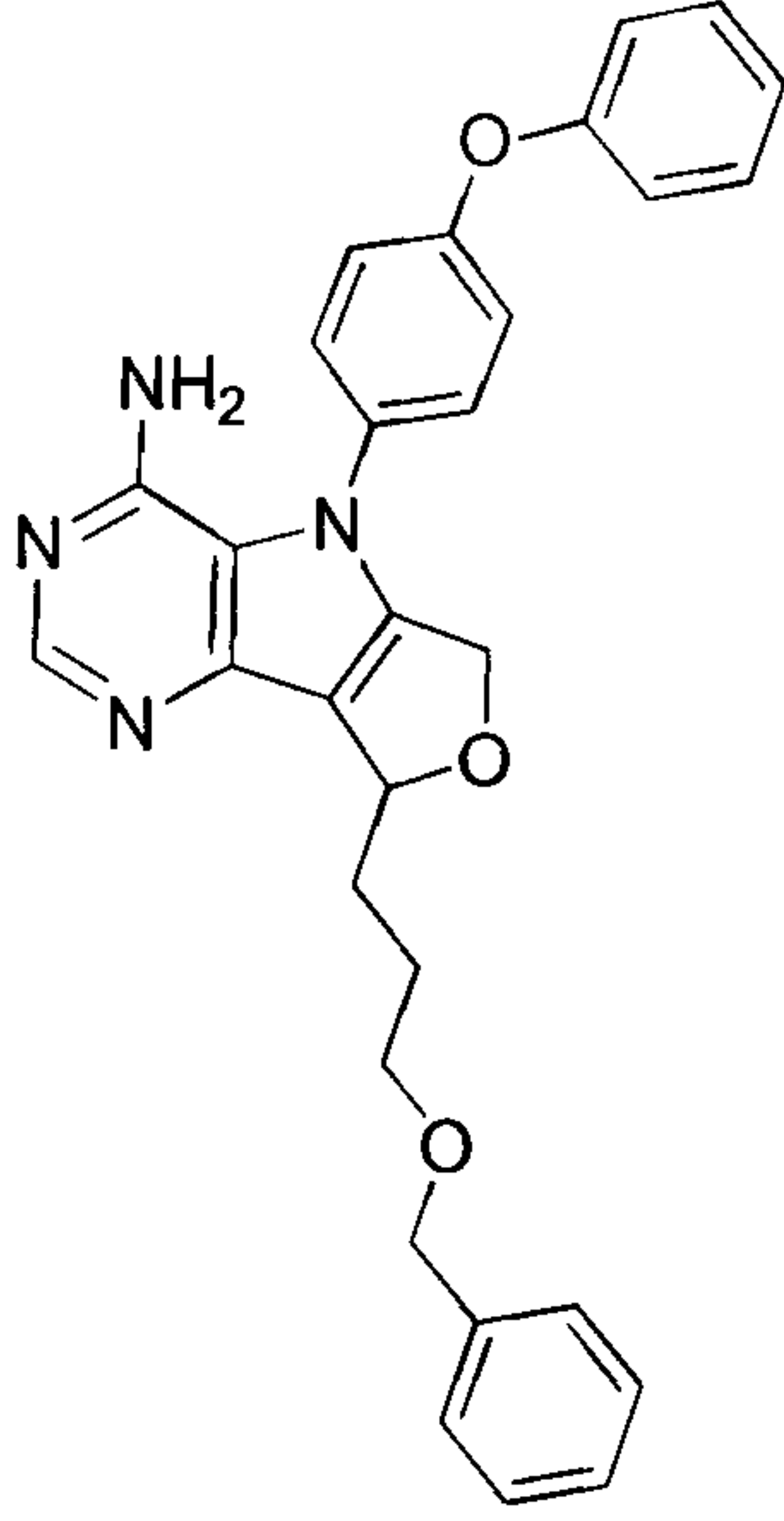
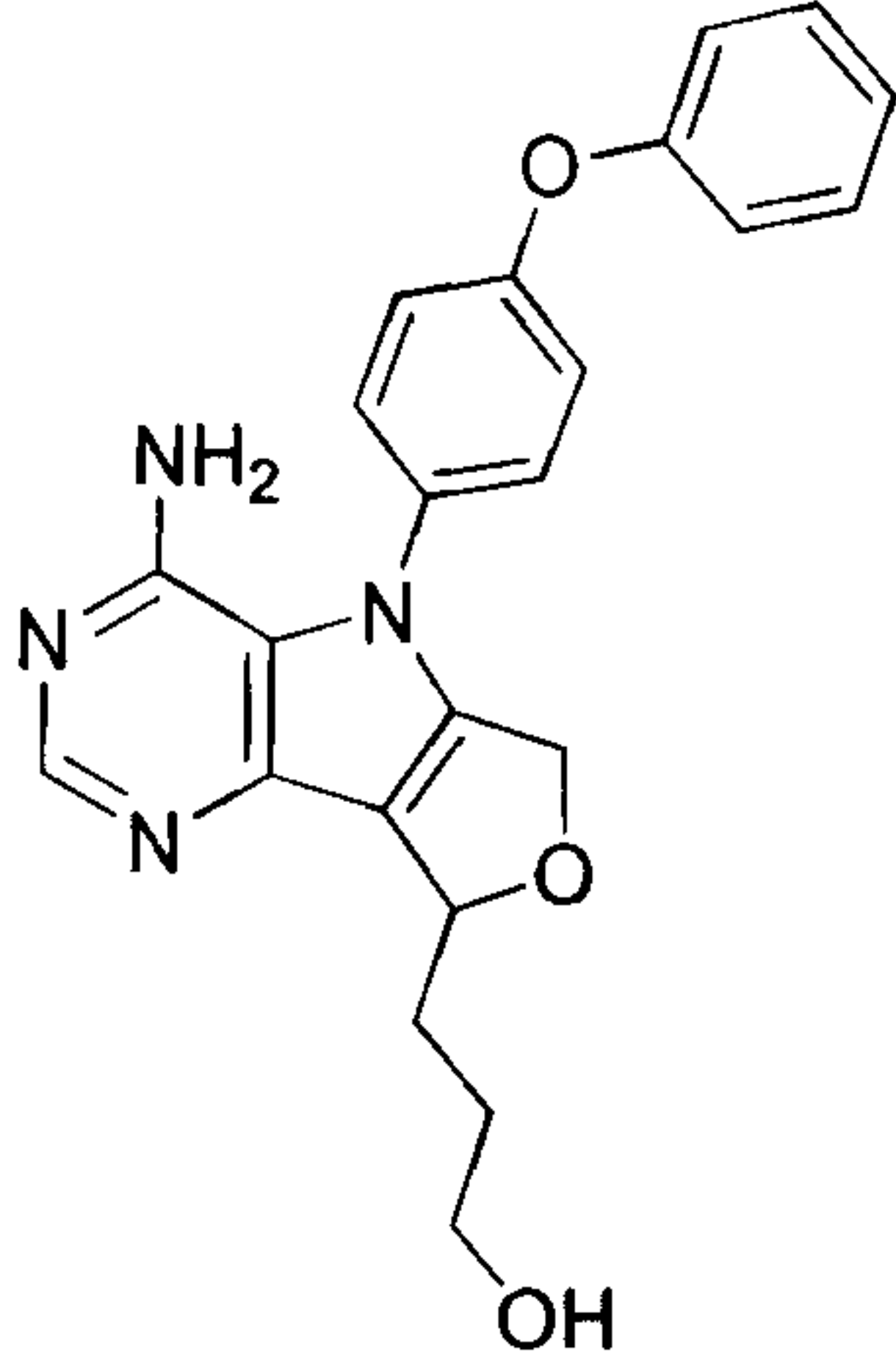
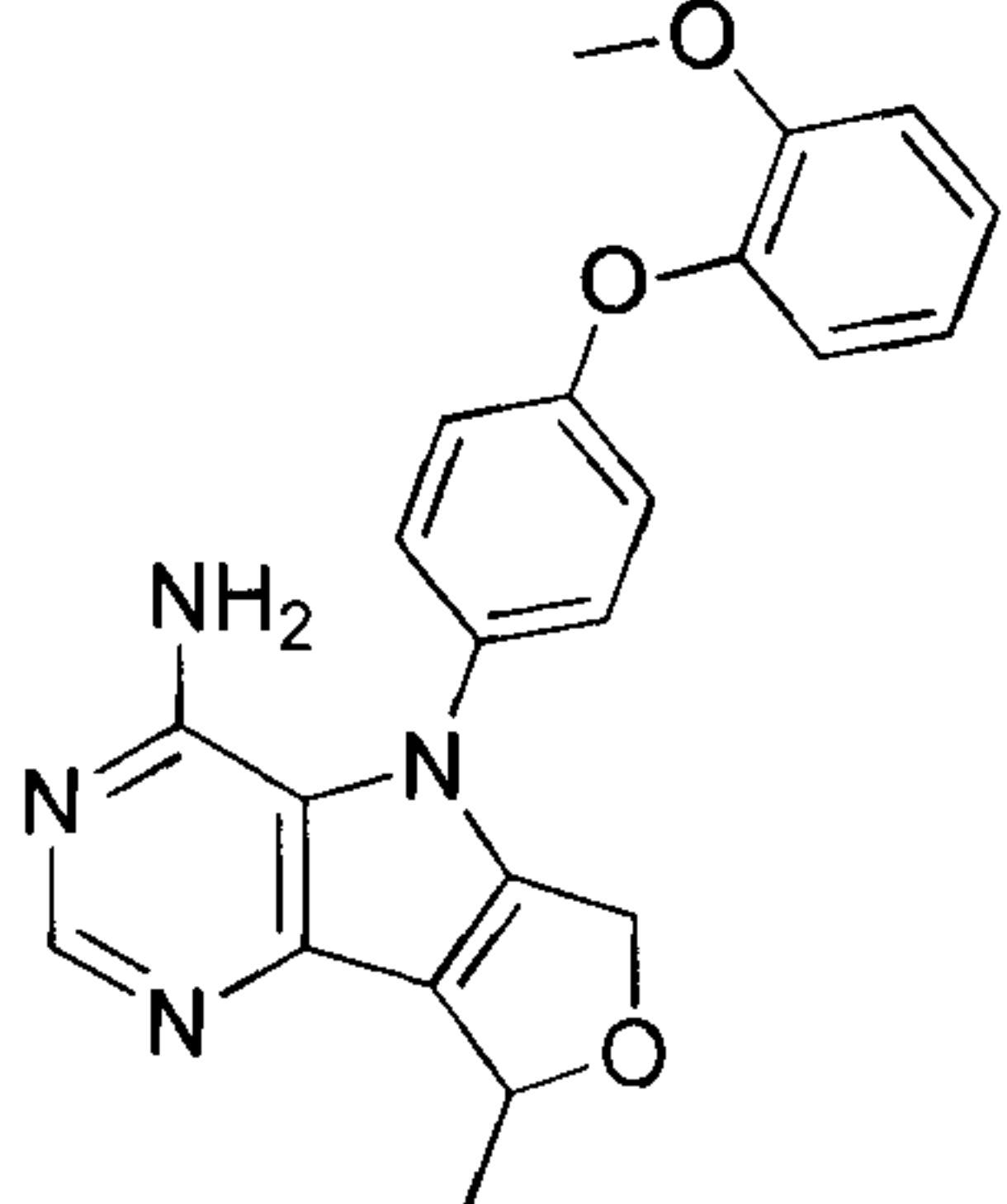
9		$[M+H]^+ = 484.1$
10		$[M+H]^+ = 434.2$
11		$[M+H]^+ = 448.2$

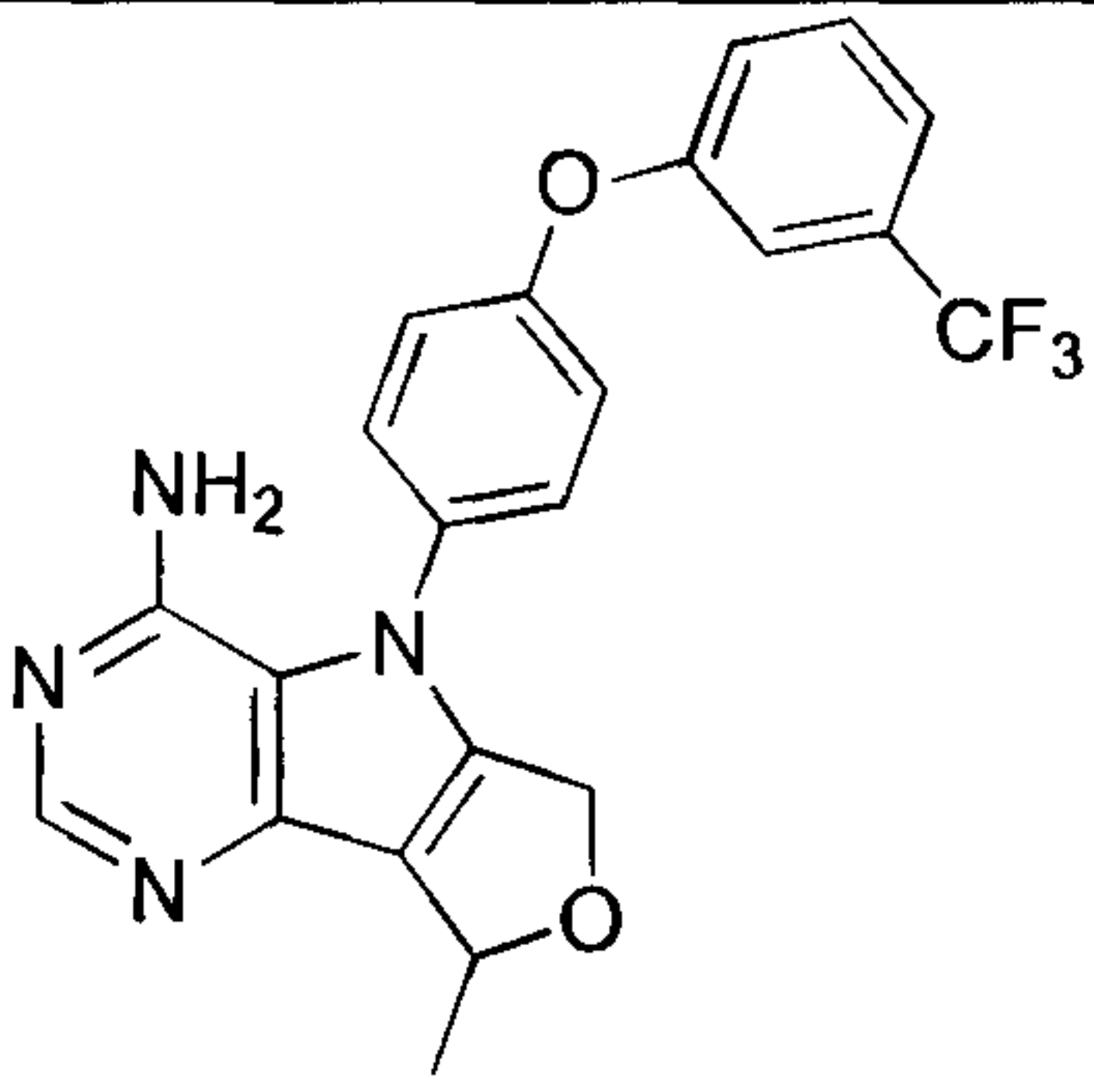
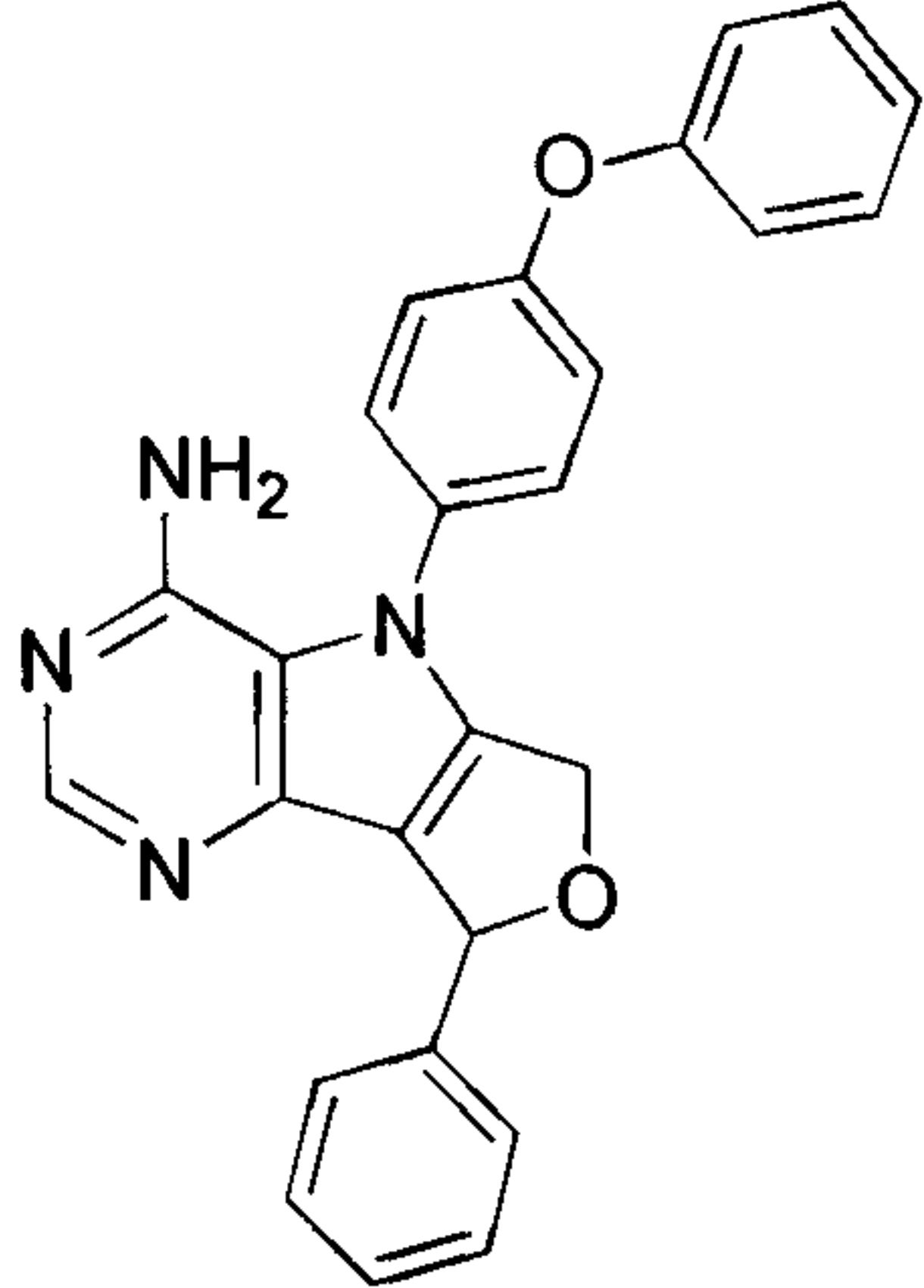
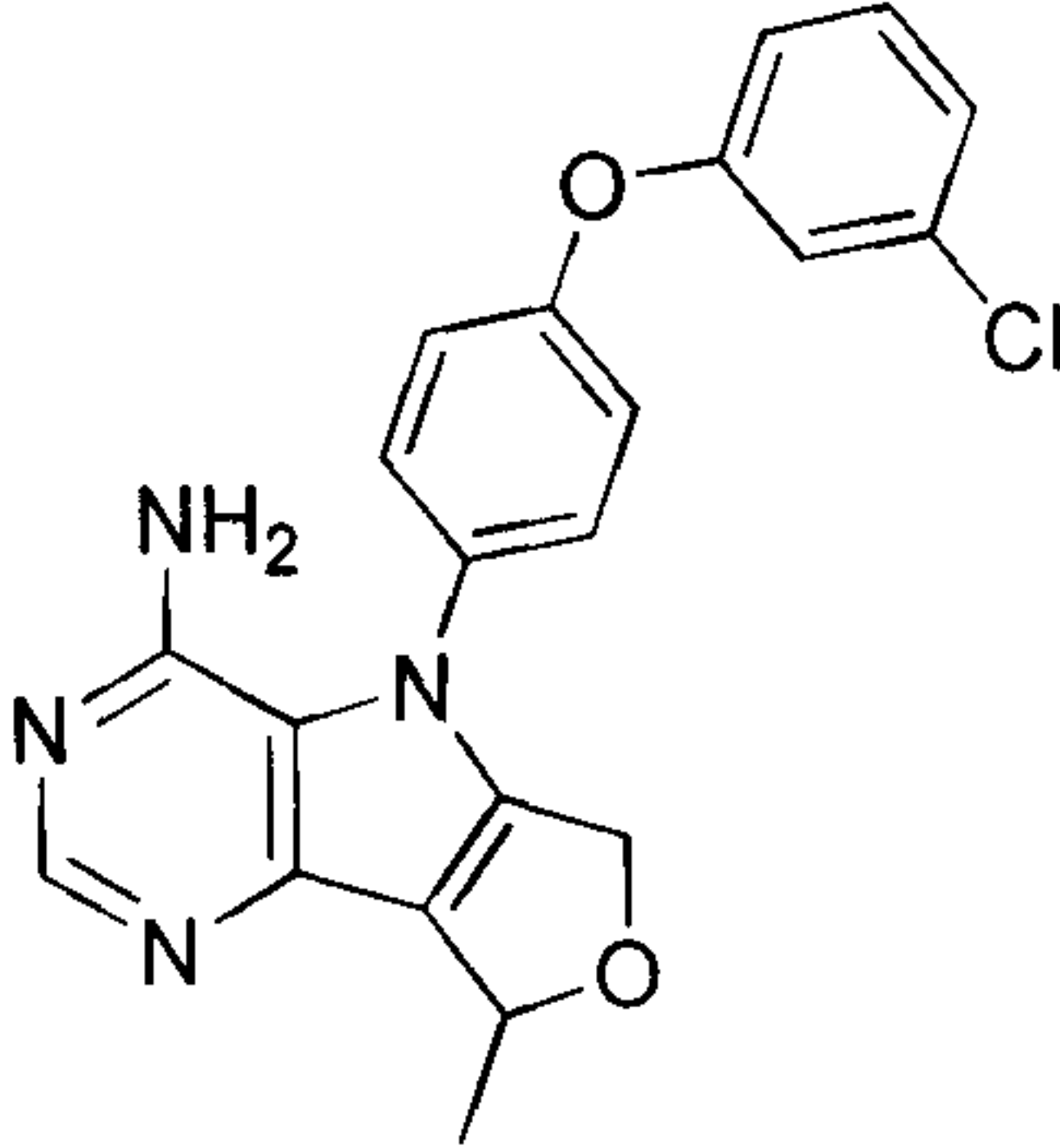
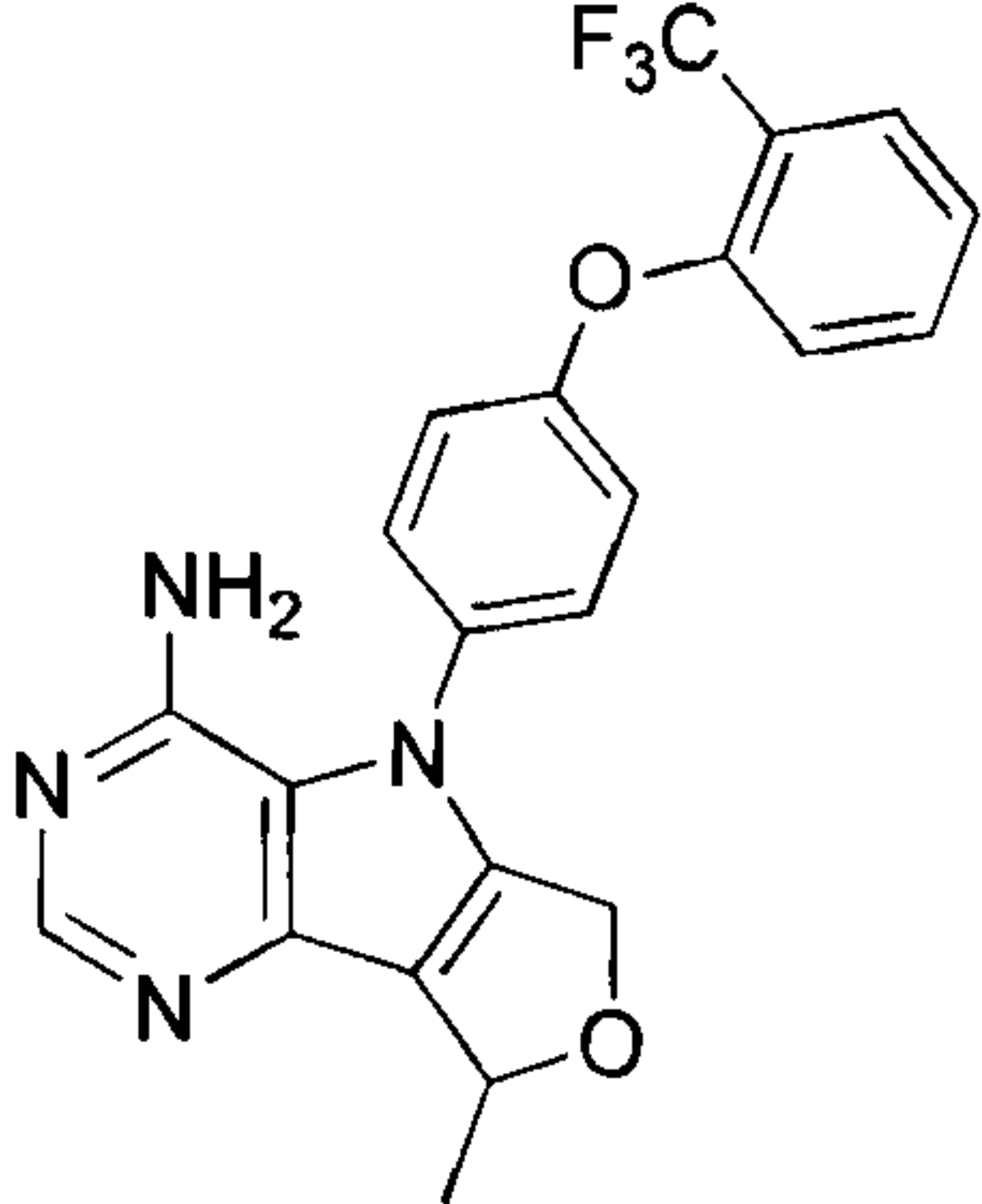
12		$[M+H]^+ = 498.1$
13		$[M+H]^+ = 357.2$
14		$[M+H]^+ = 372.2$

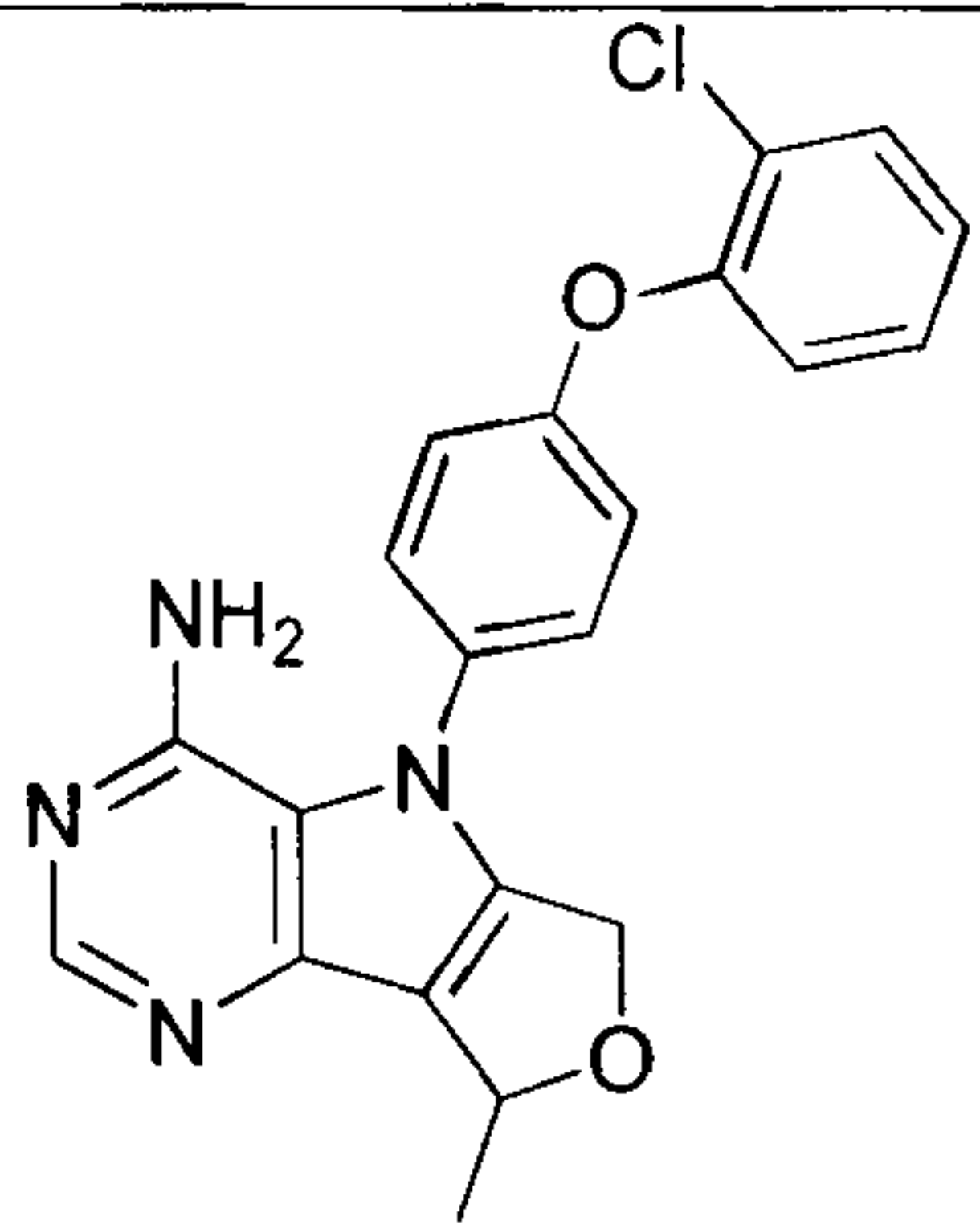
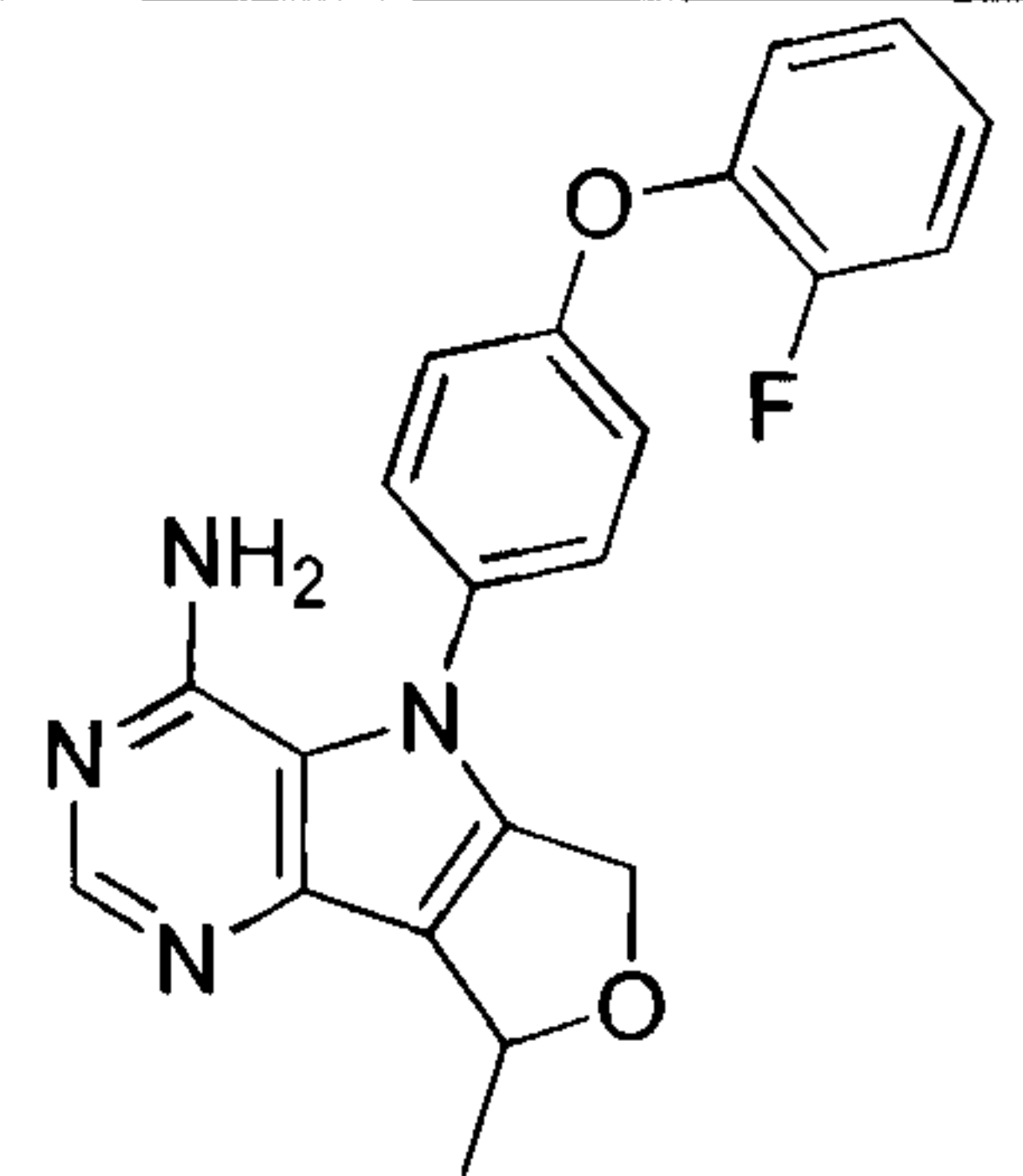
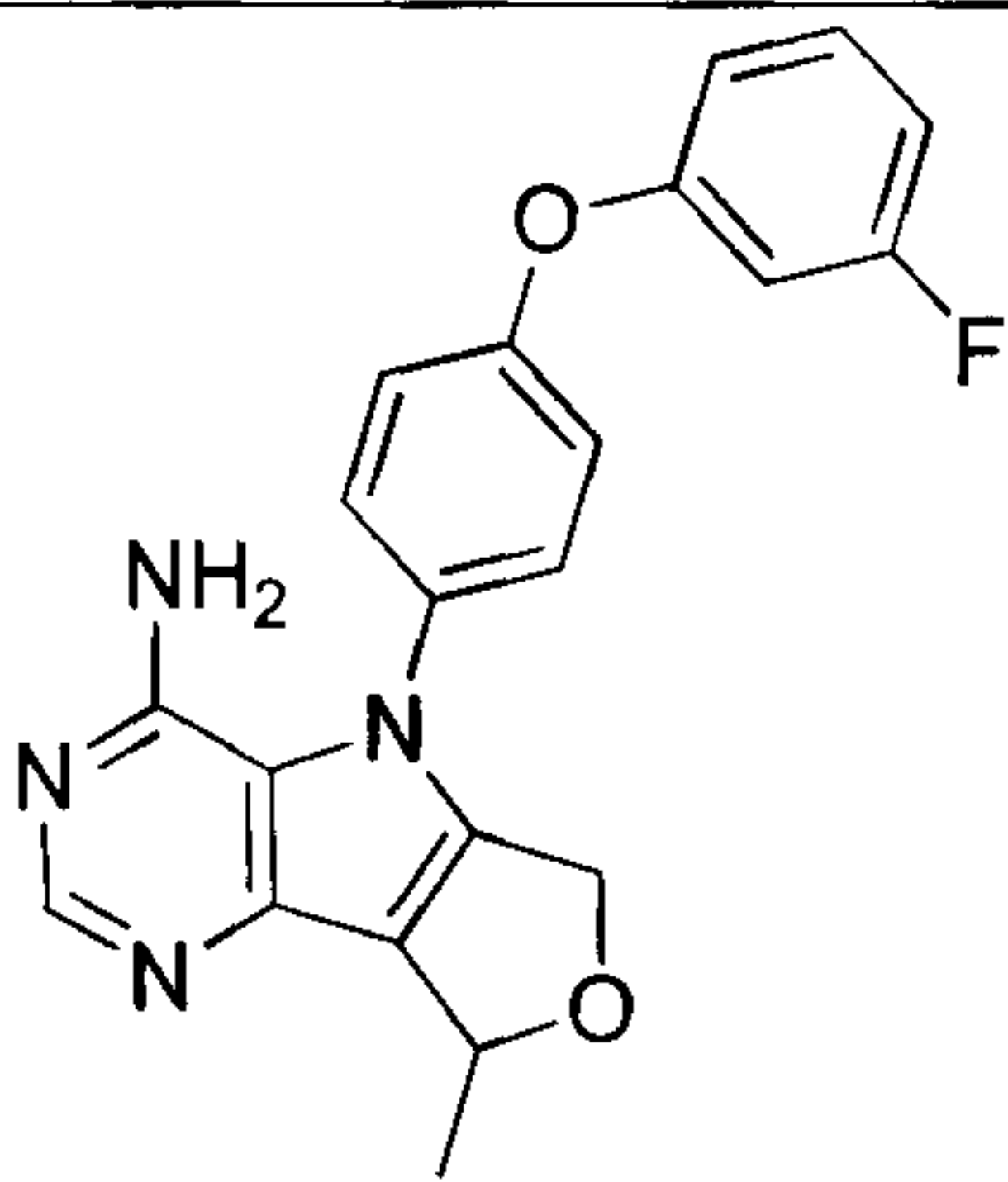
15		$[M+H]^+ = 386.3$
16		$[M+H]^+ = 462.1$
17		$[M+H]^+ = 415.1$

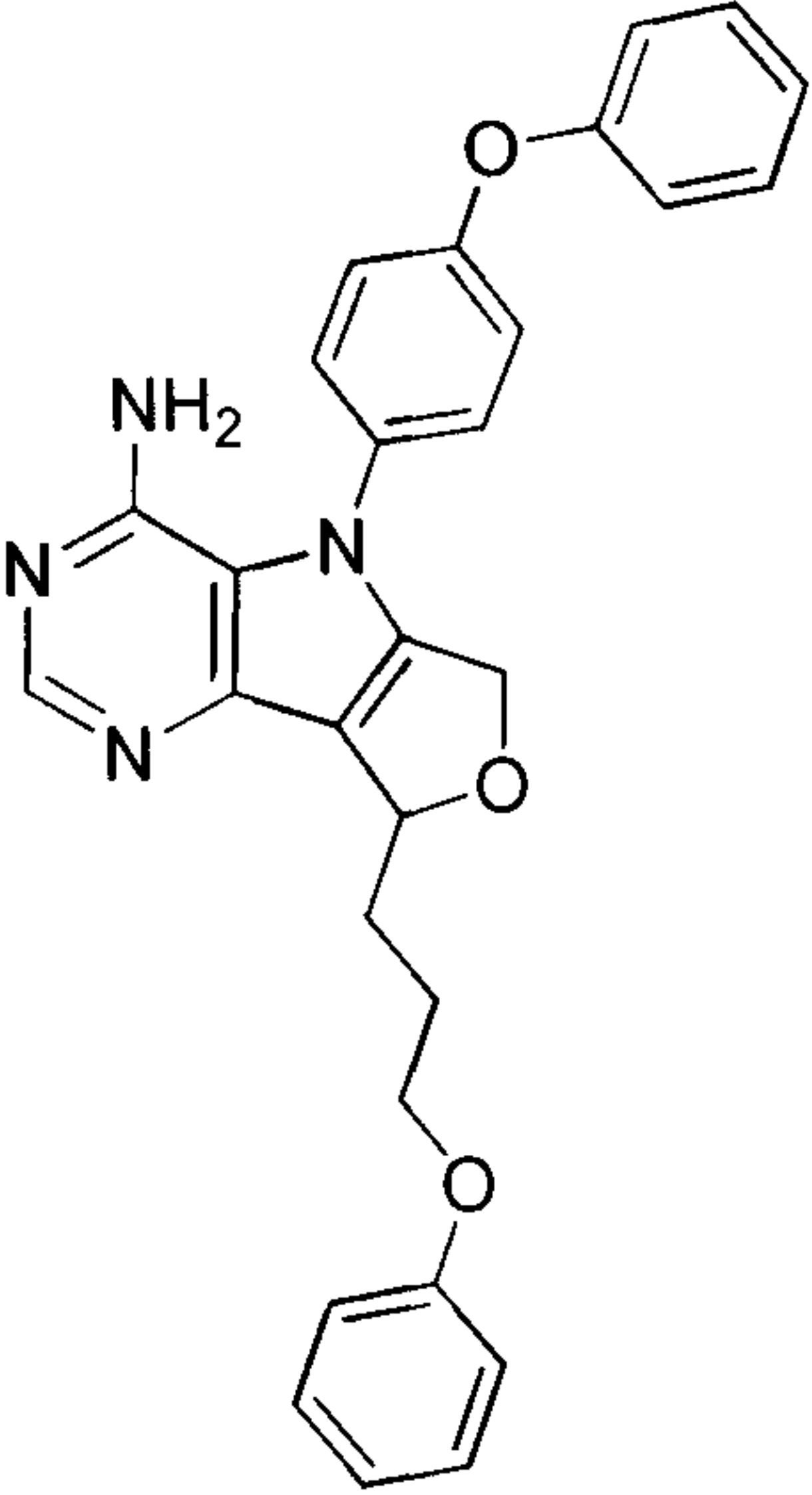
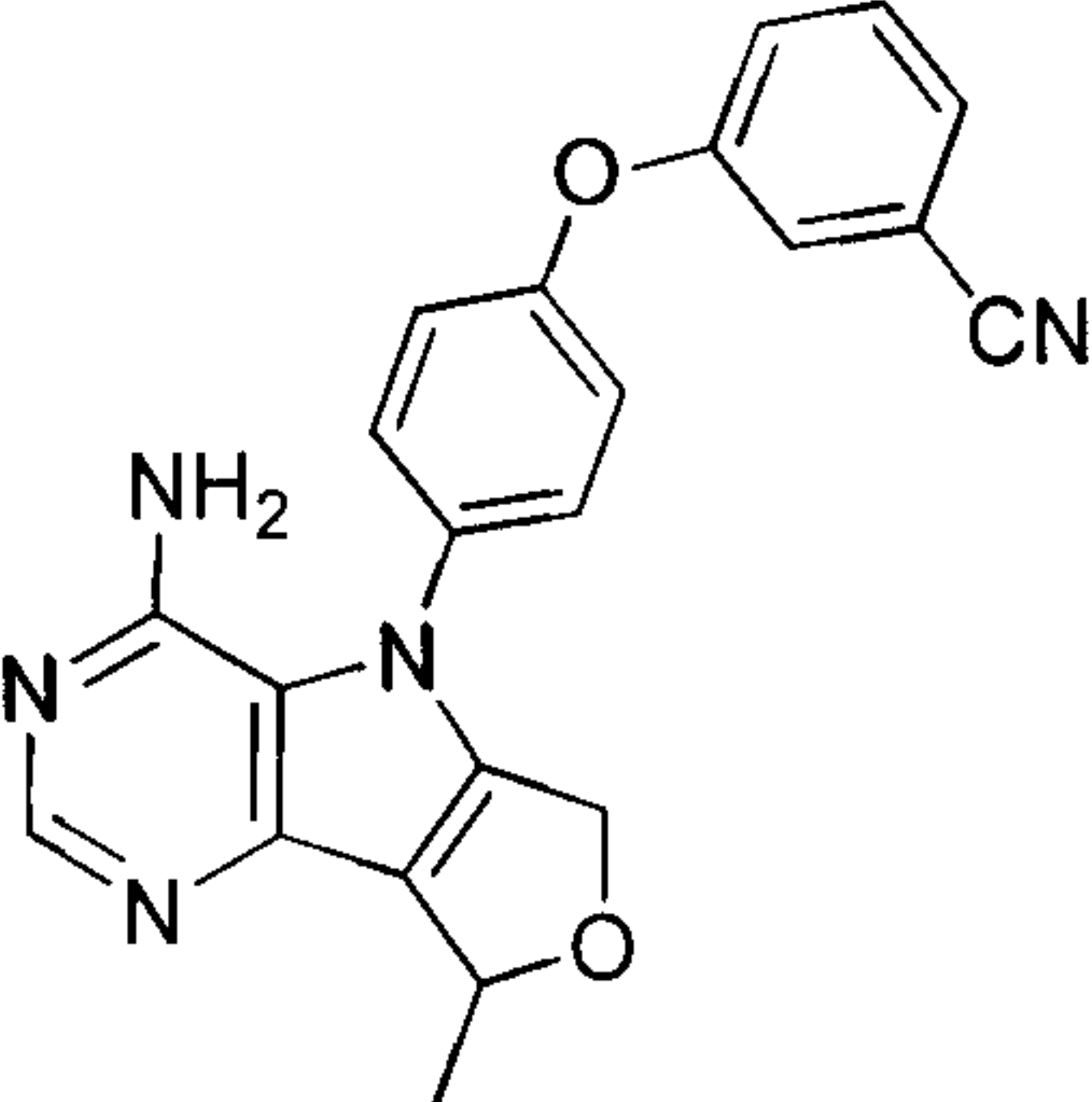
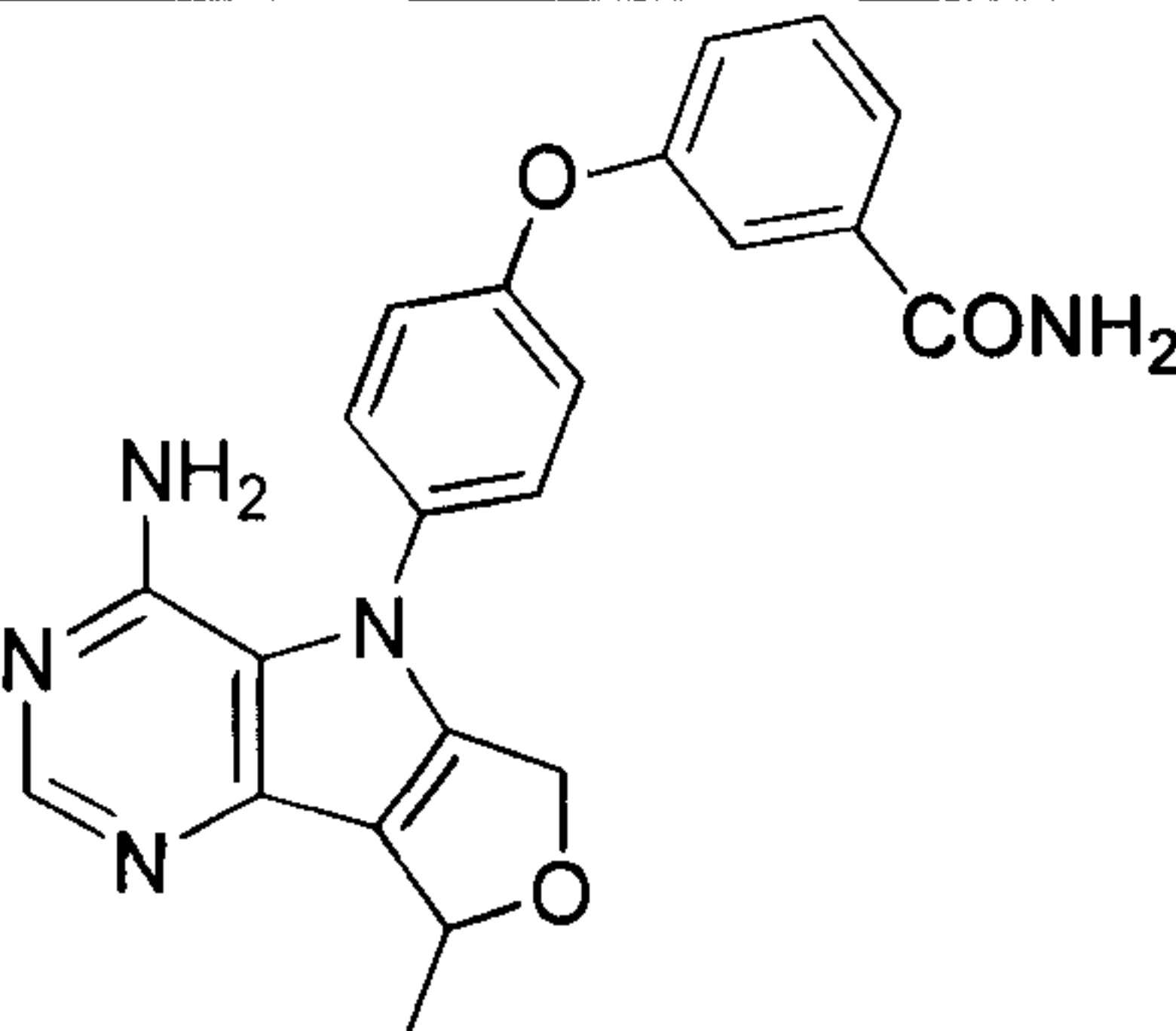
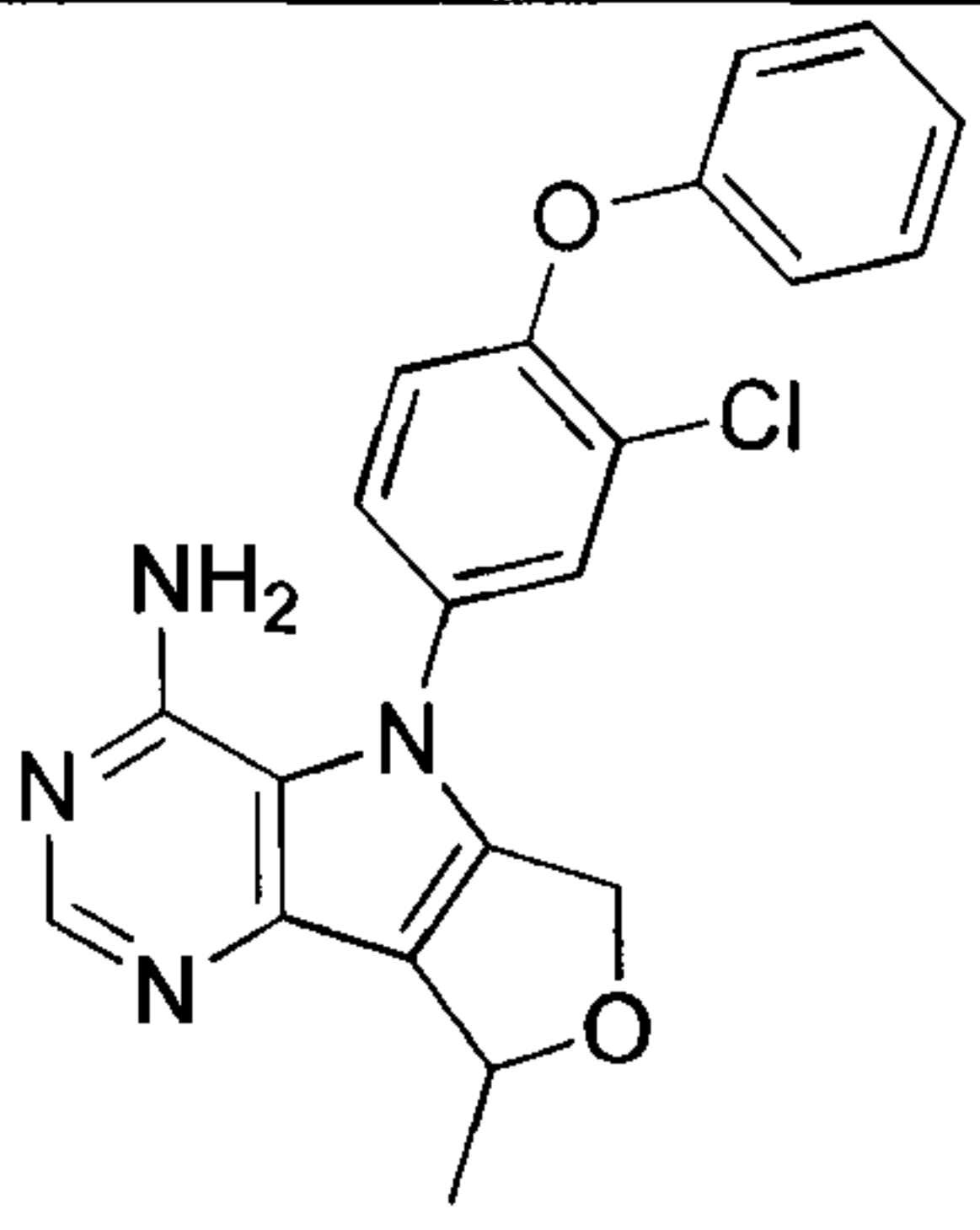
18		$[M+H]^+=448.3$
19		$[M+H]^+=401.2$
20		$[M+H]^+=359.2$
21		$[M+H]^+=345.2$

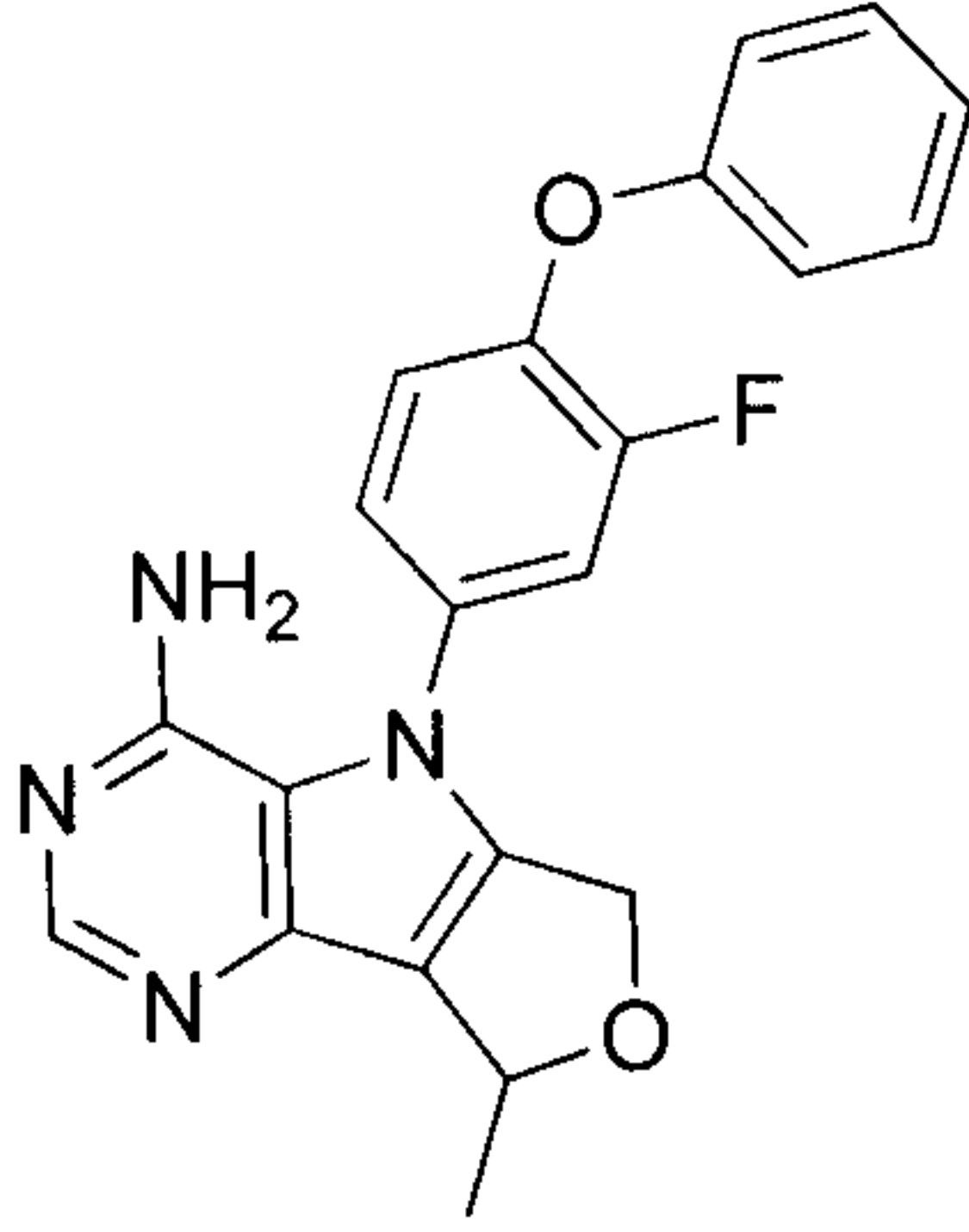
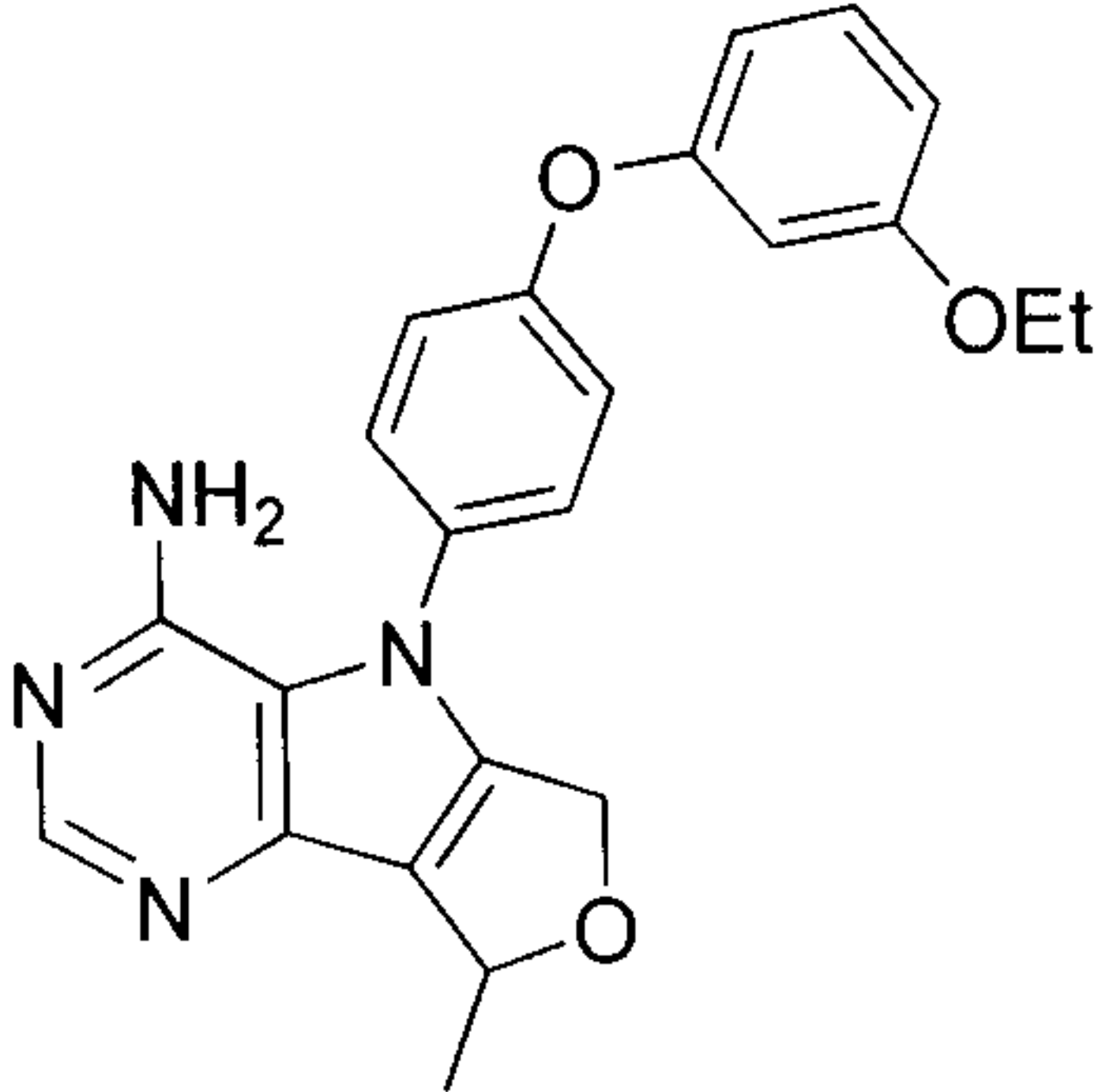
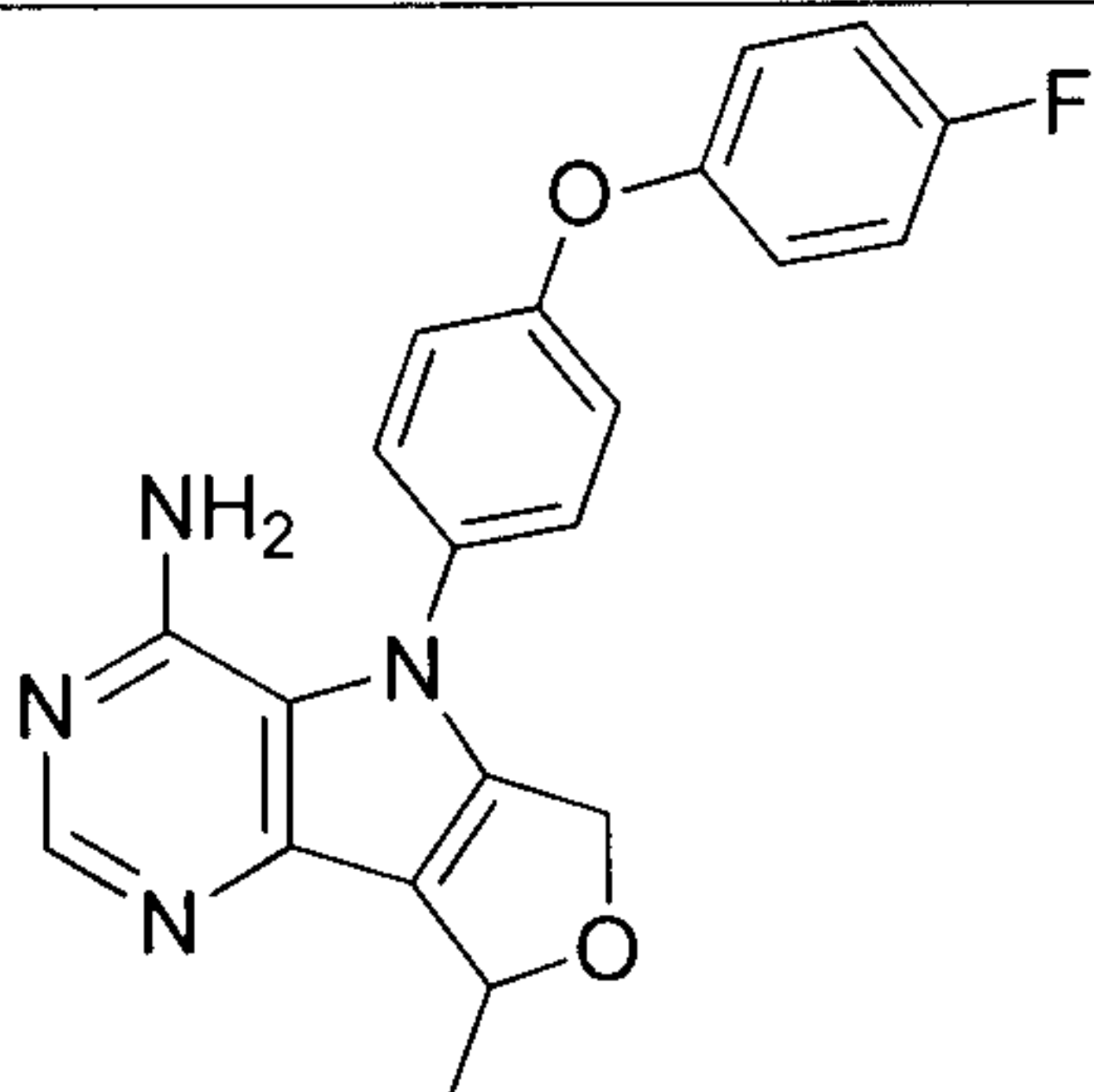
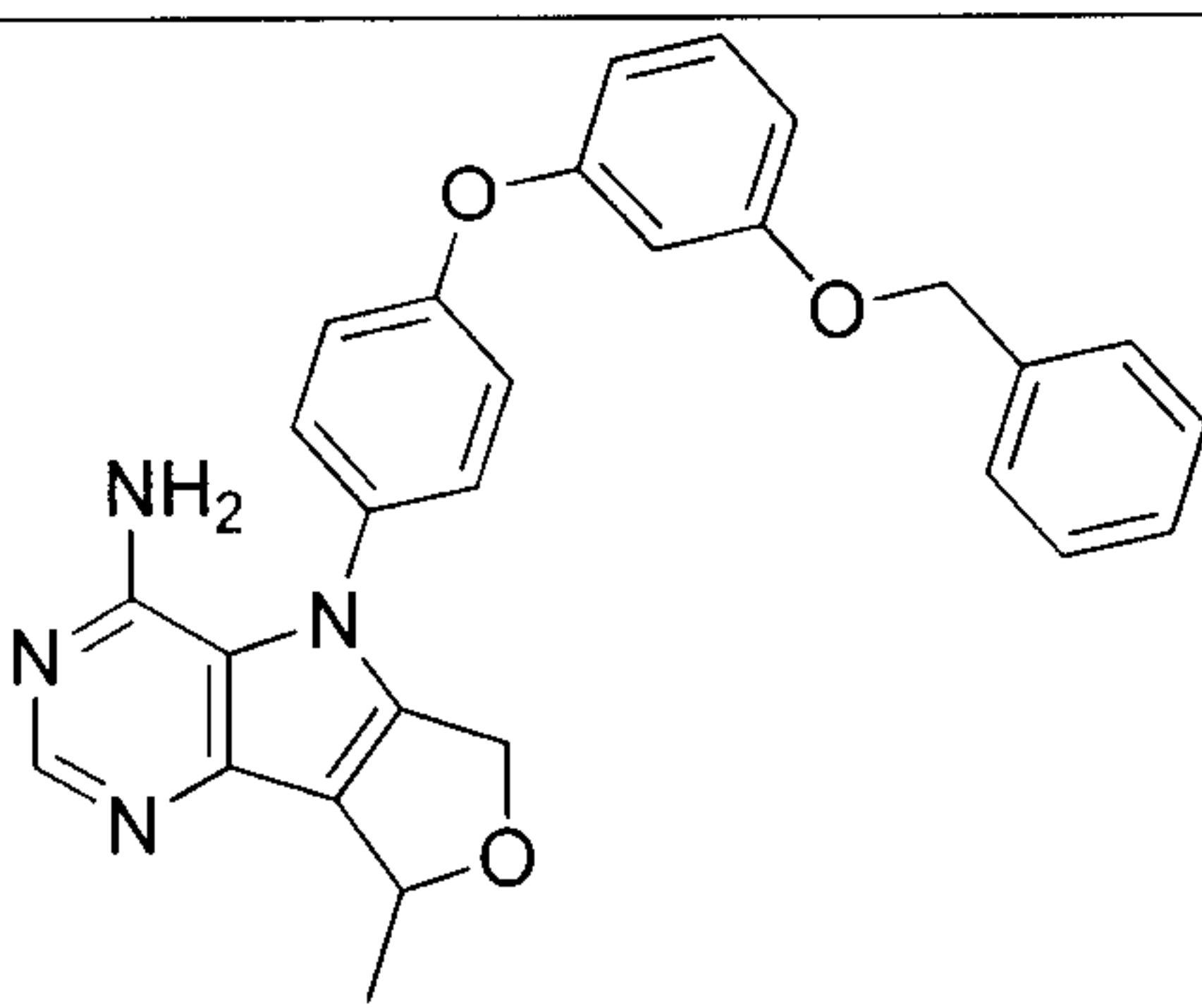
22		$[M+H]^+ = 341.3$
23		$[M+H]^+ = 373.2$
24		$[M+H]^+ = 373.3$
25		$[M+H]^+ = 389.2$

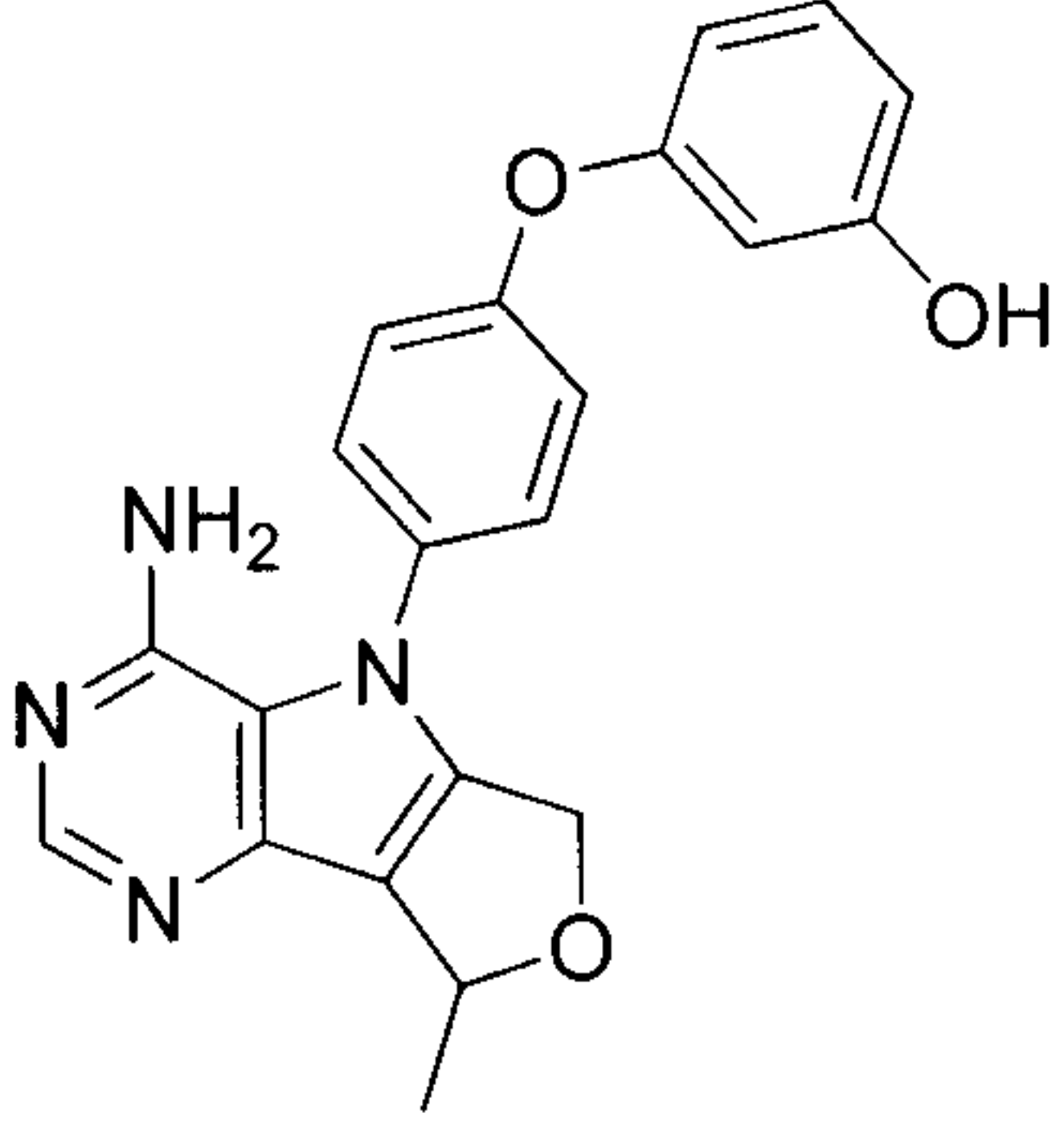
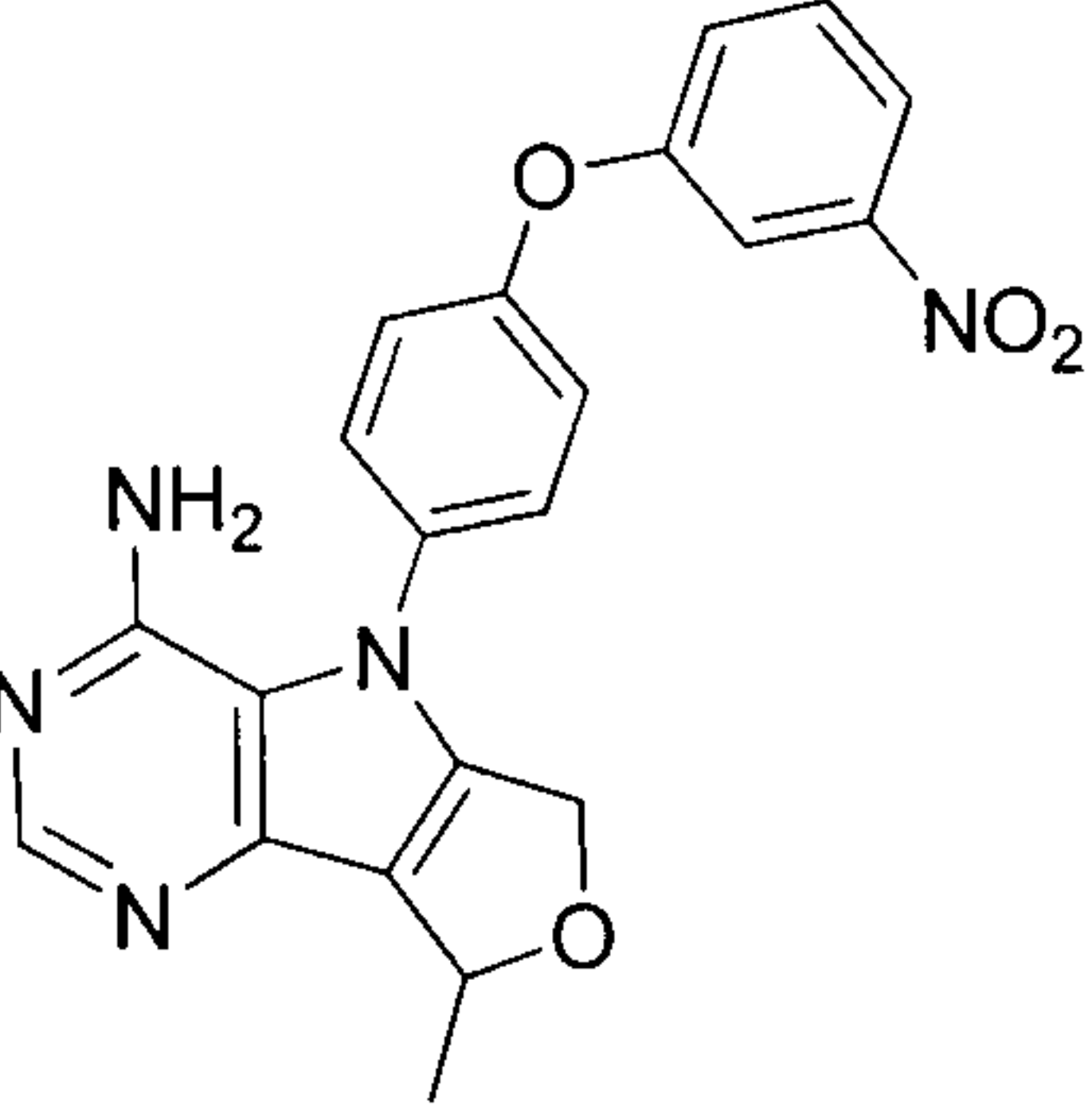
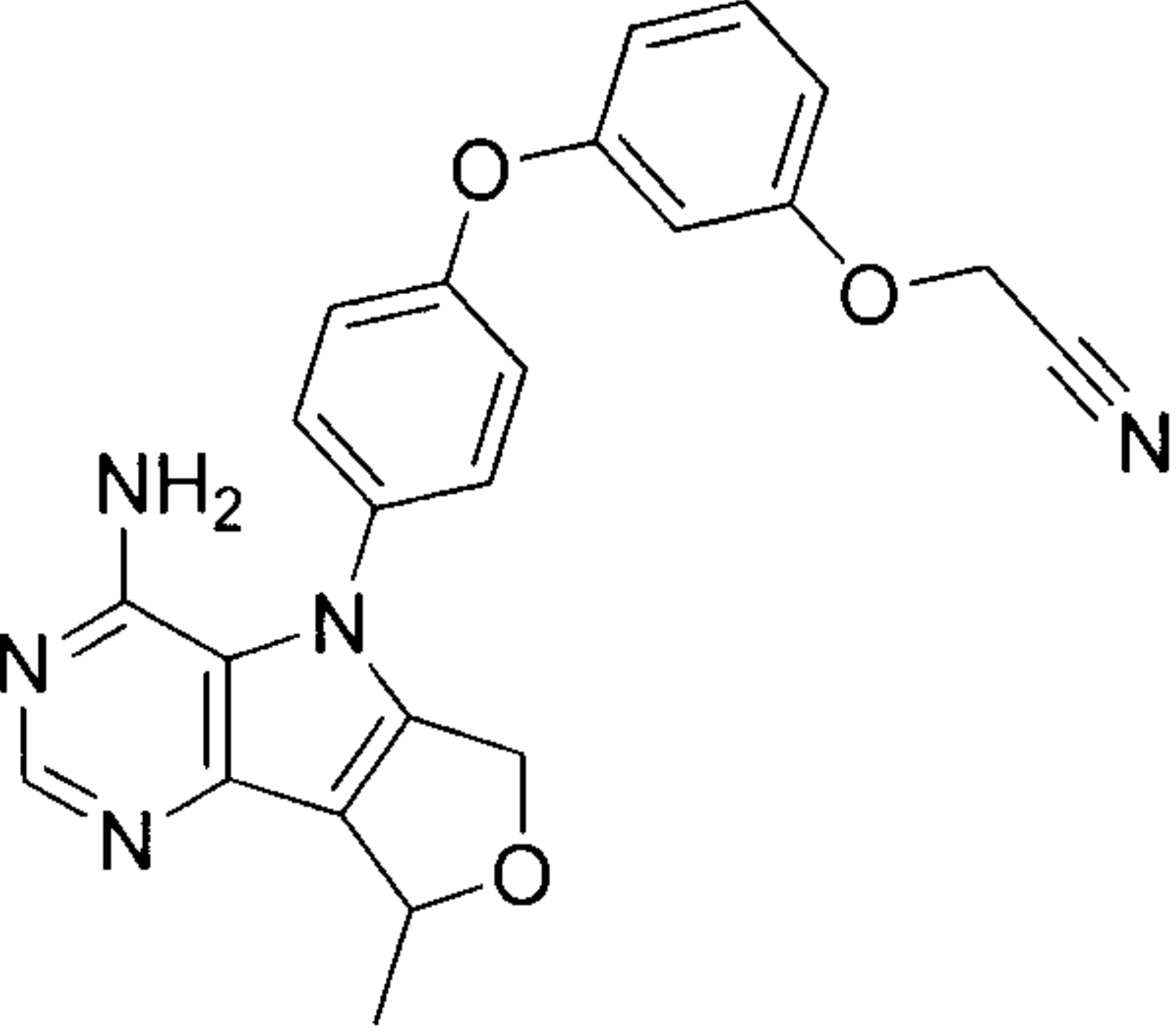
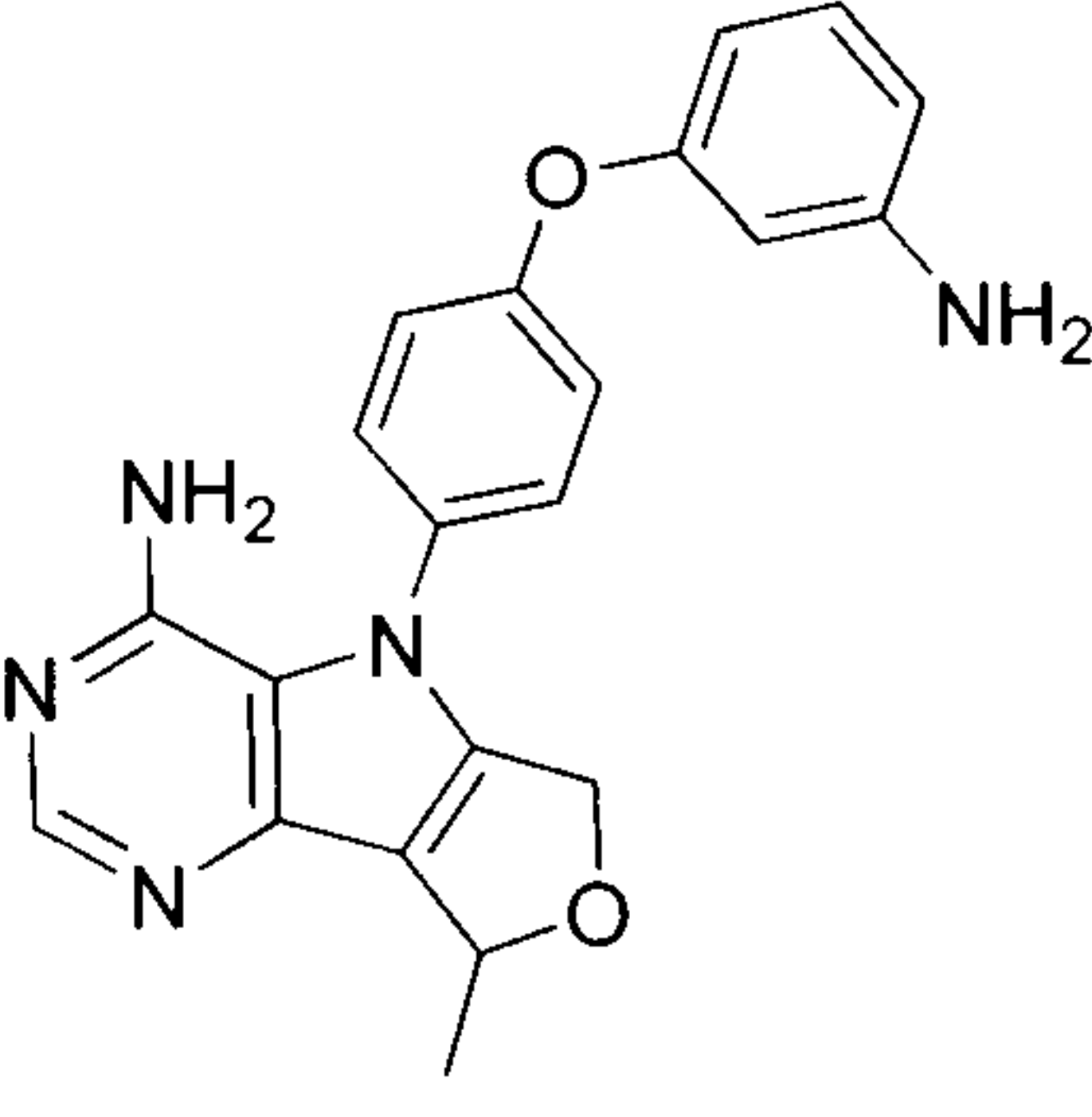
26		$[M+H]^+=493.3$
27		$[M+H]^+=403.3$
28		$[M+H]^+=389.3$

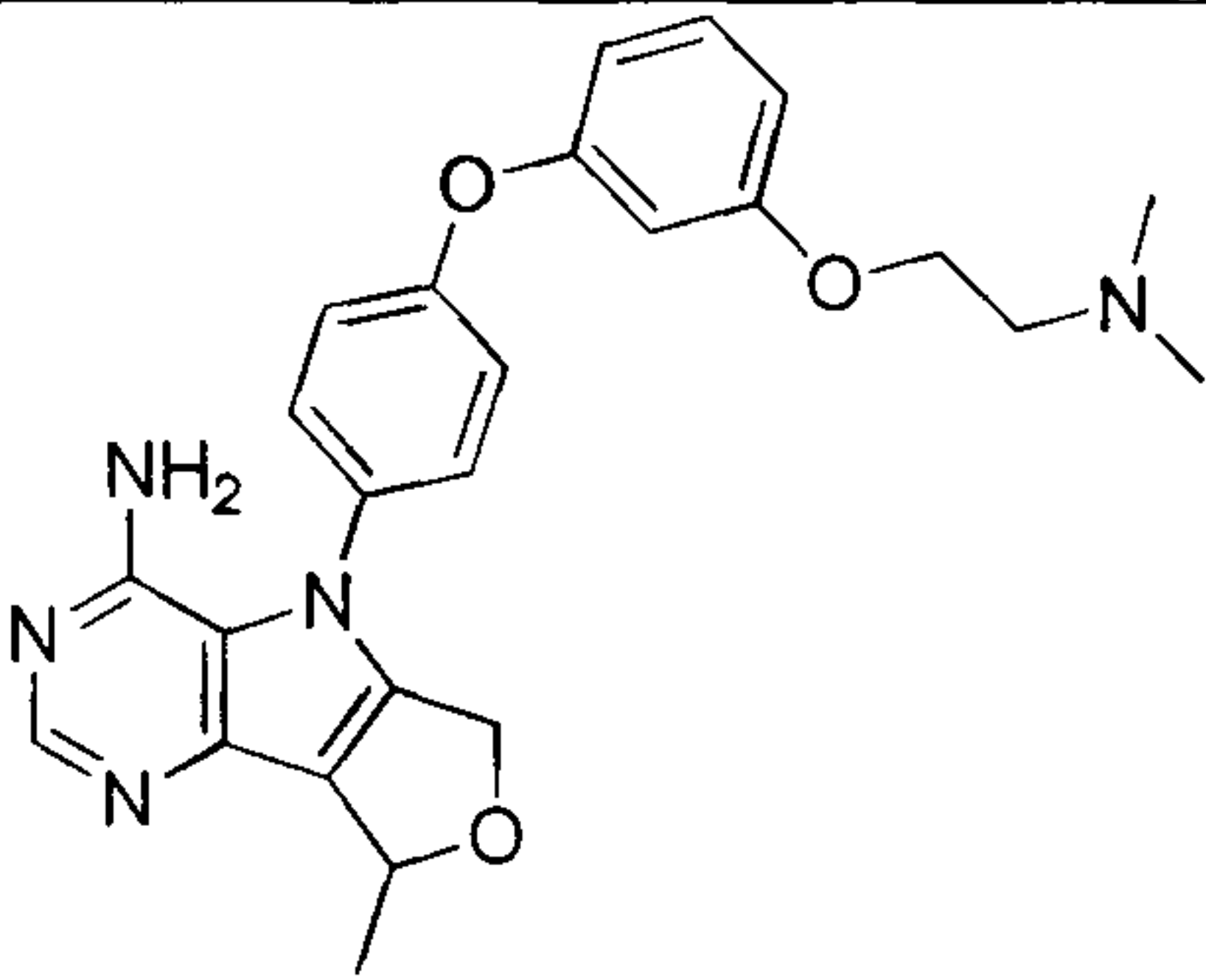
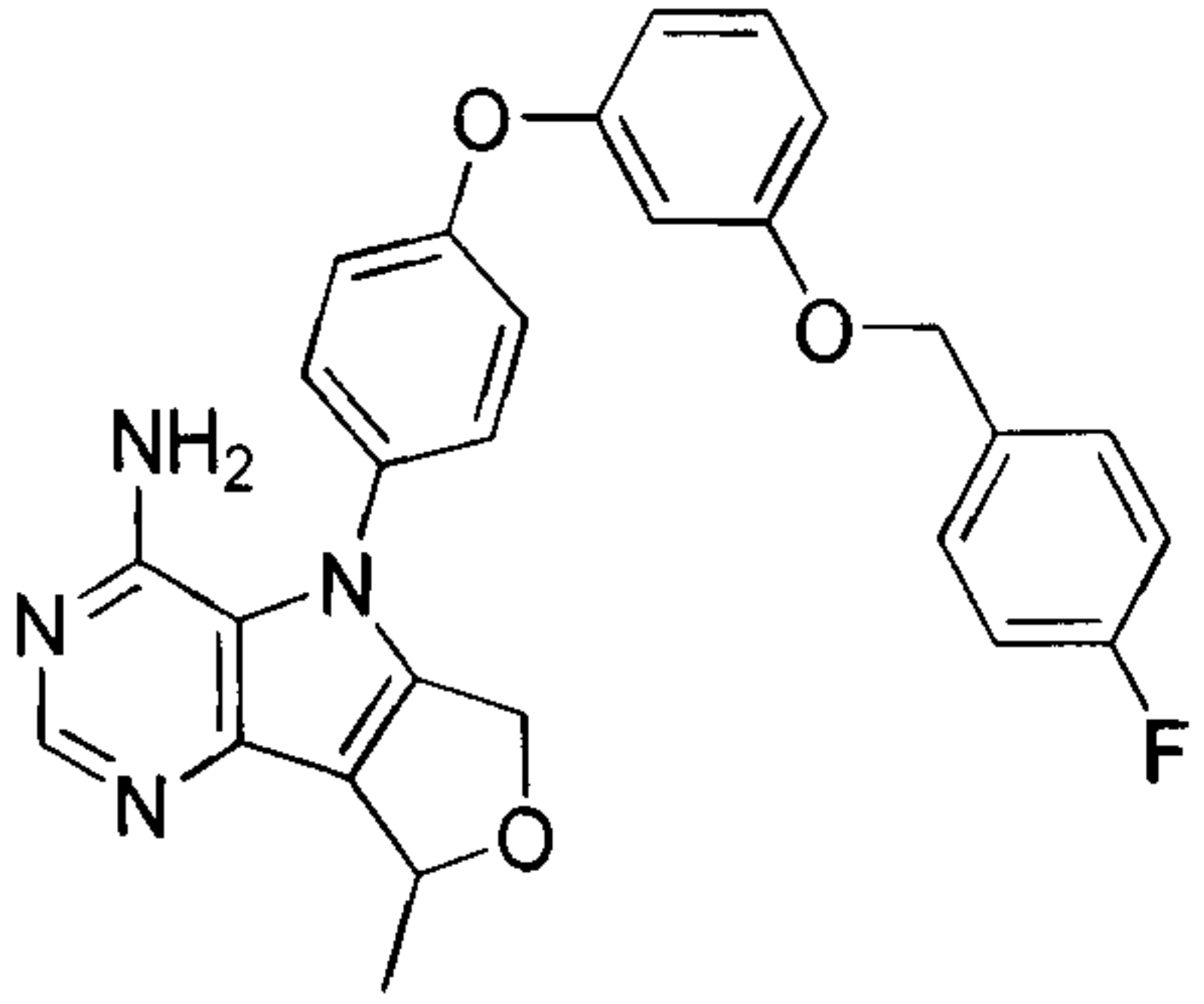
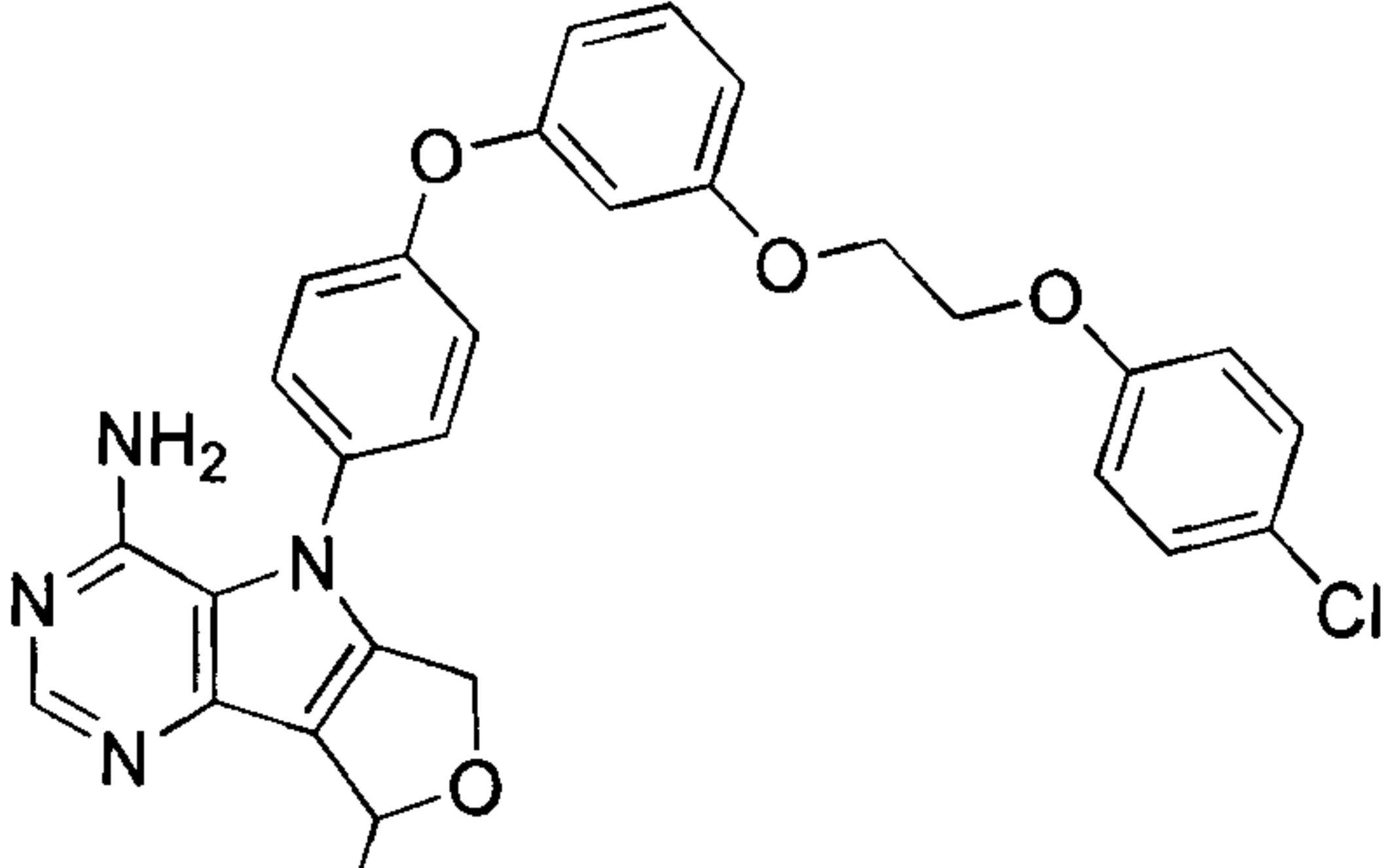
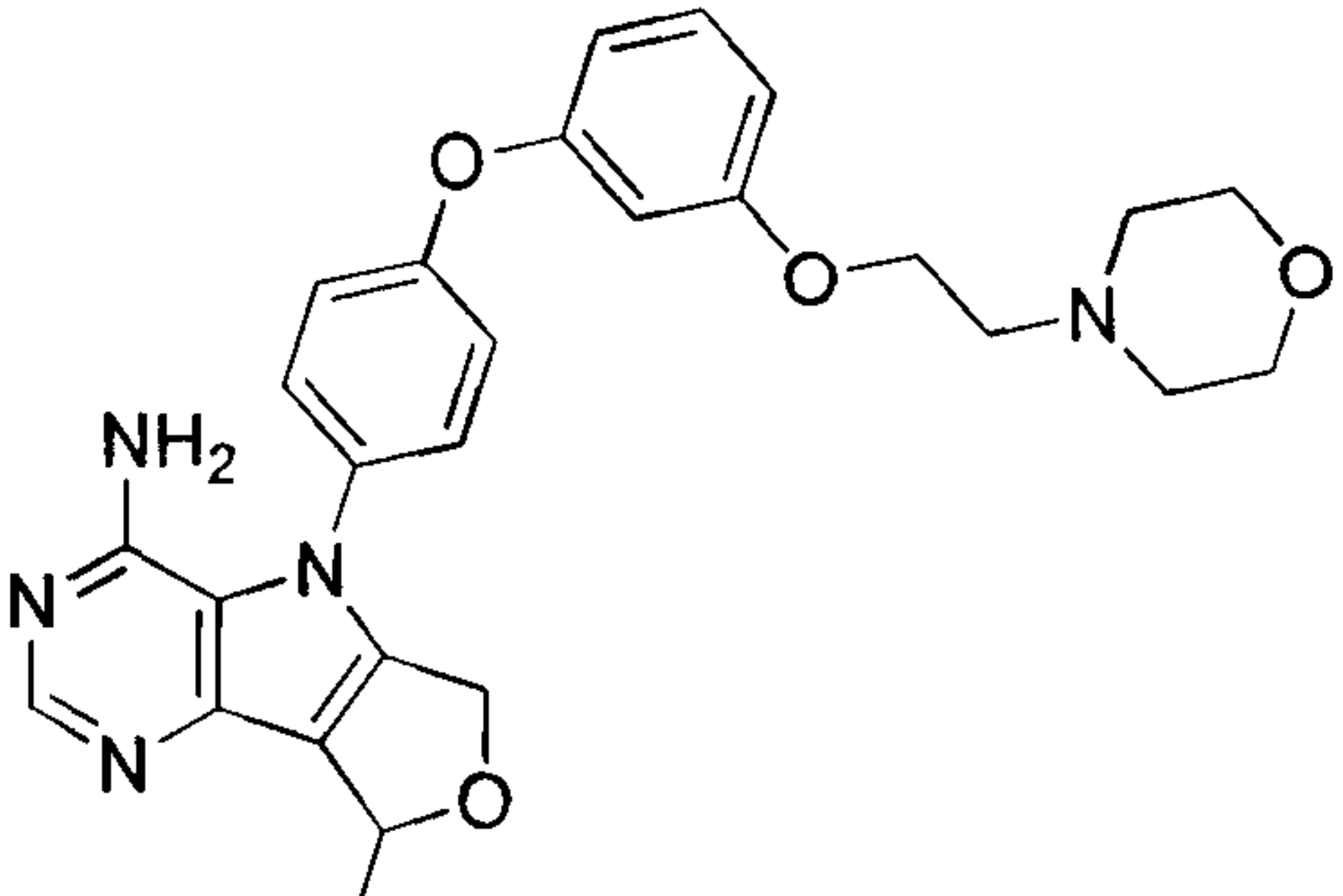
29		$[M+H]^+=427.2$
30		$[M+H]^+=421.2$
31		$[M+H]^+=393.4$
32		$[M+H]^+=427.2$

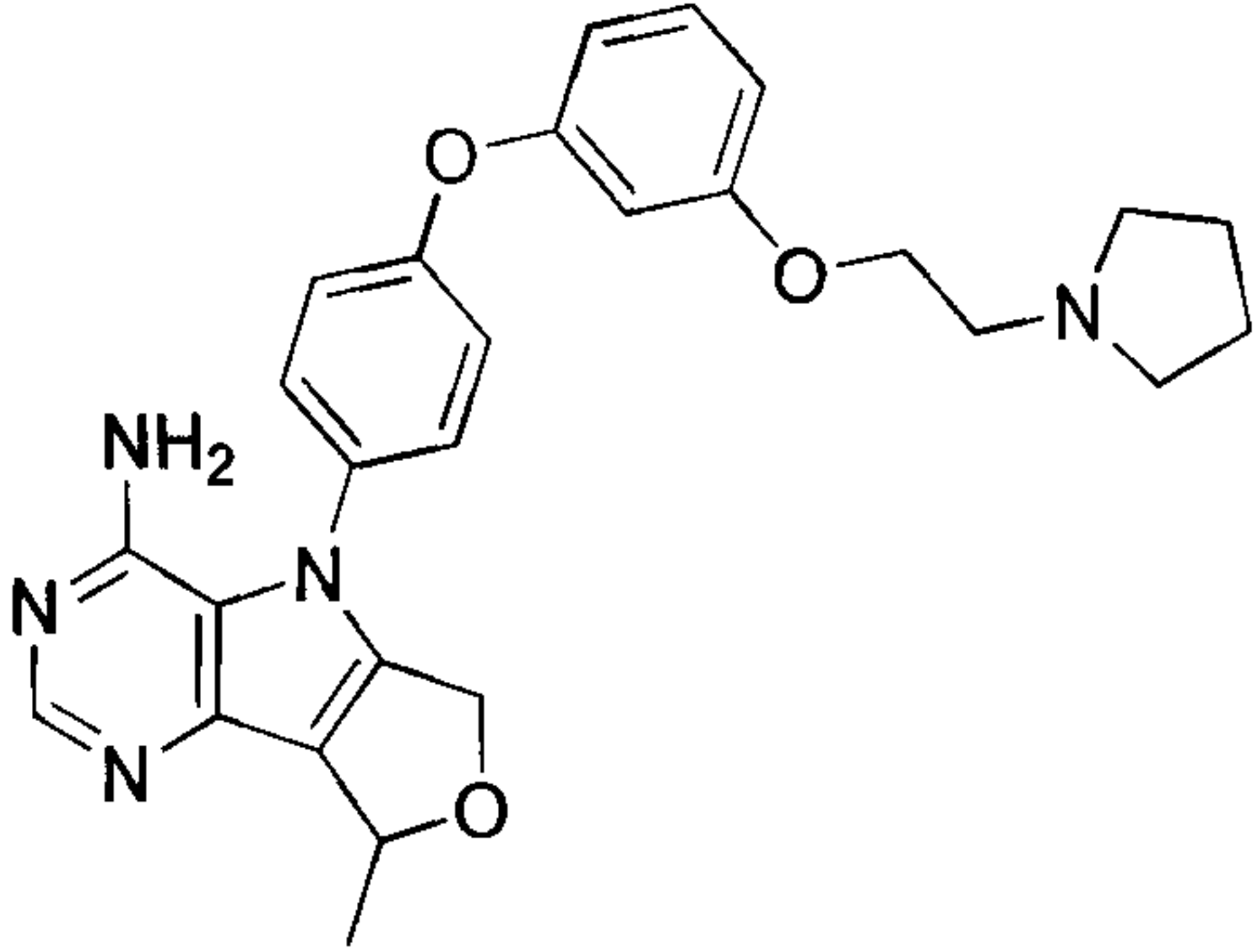
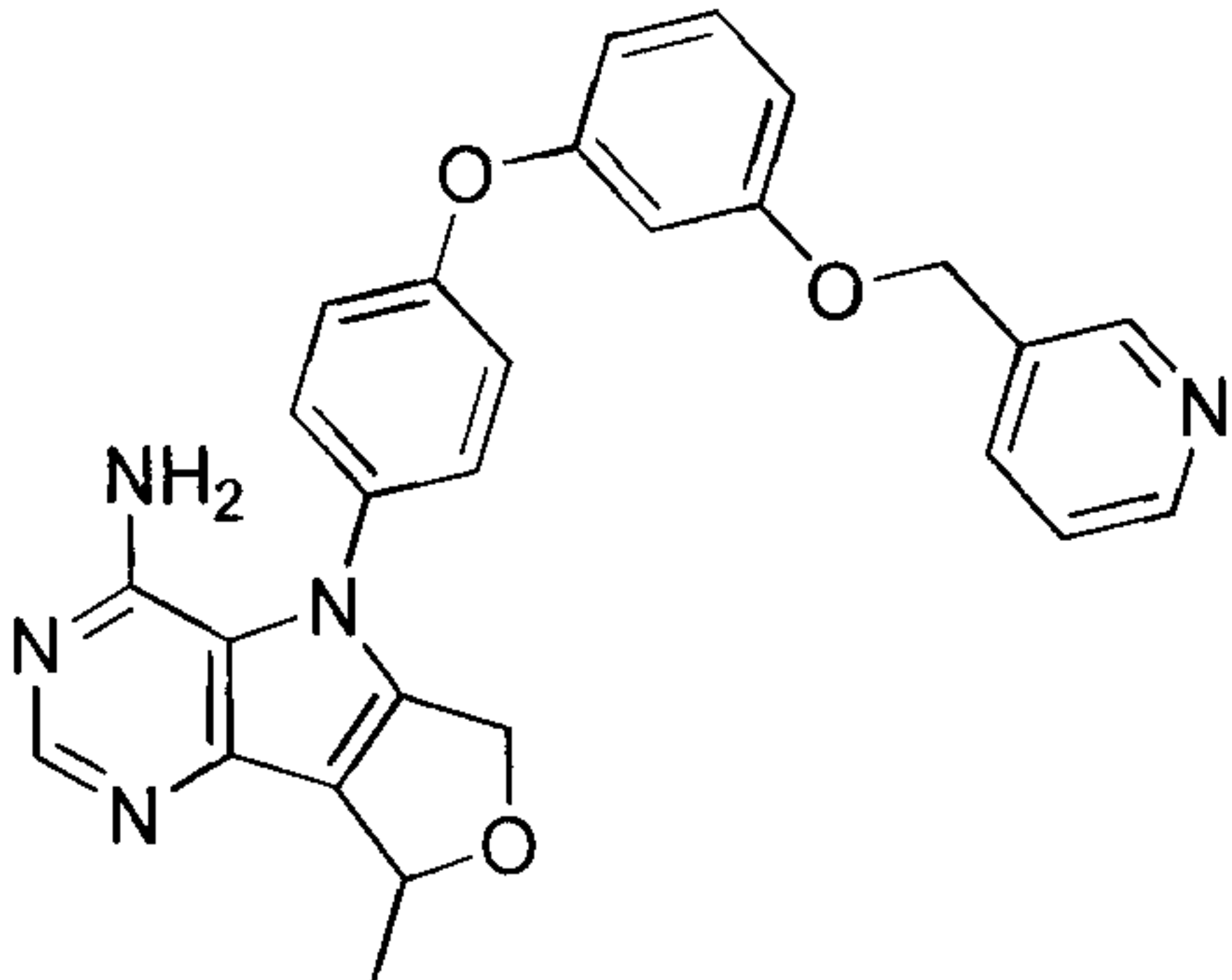
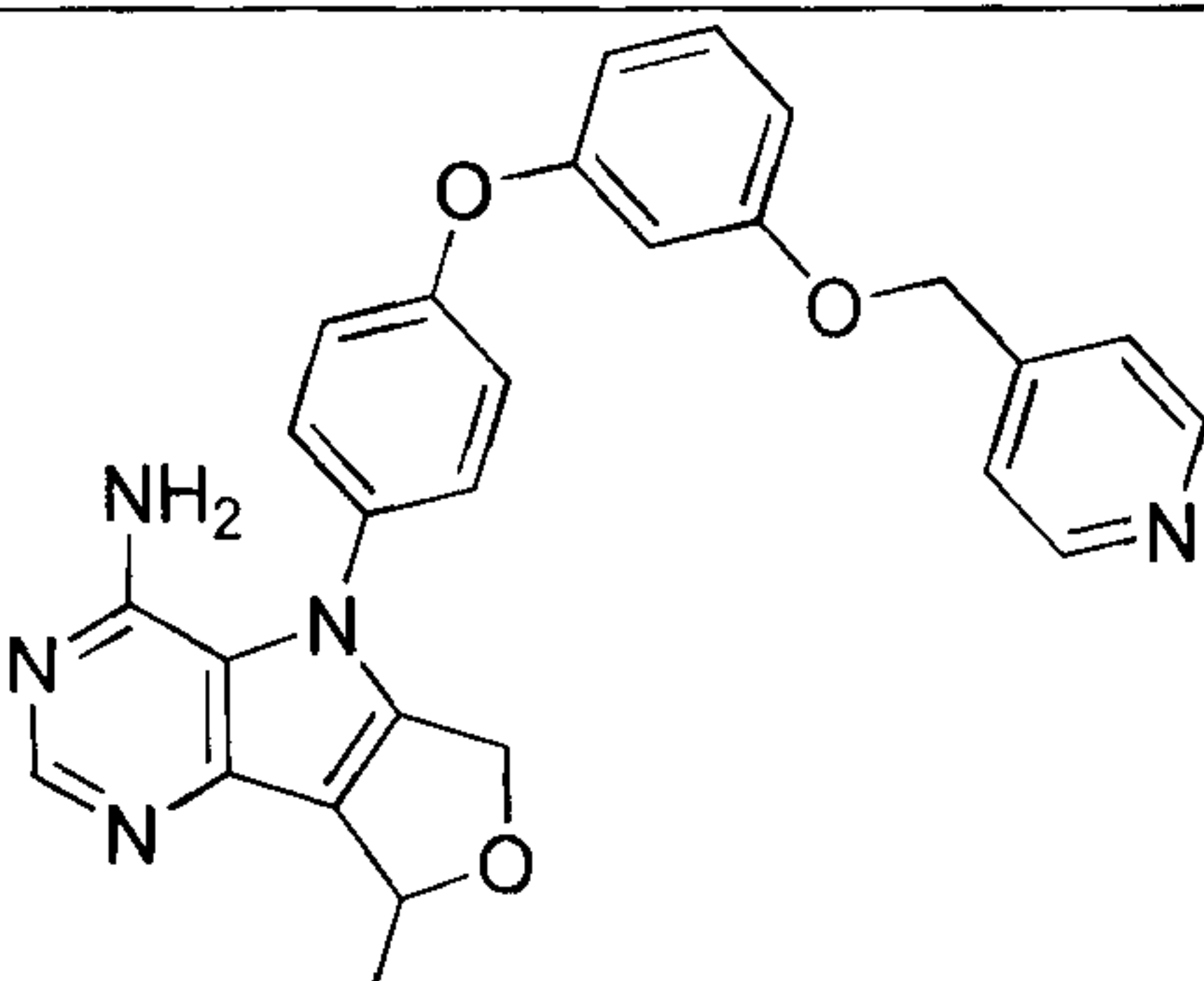
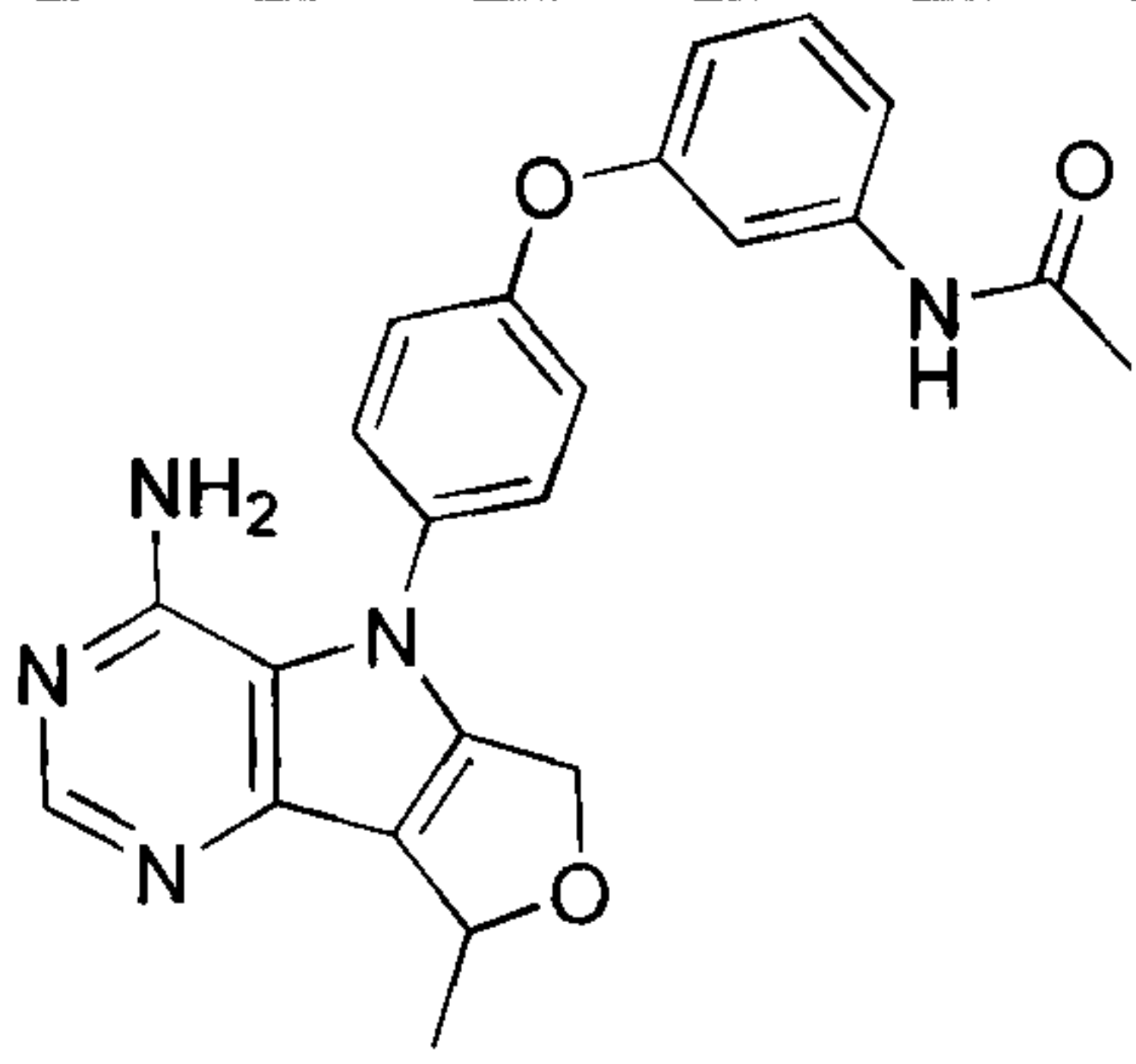
33		$[M+H]^+ = 393.4$
34		$[M+H]^+ = 377.2$
35		$[M+H]^+ = 377.4$

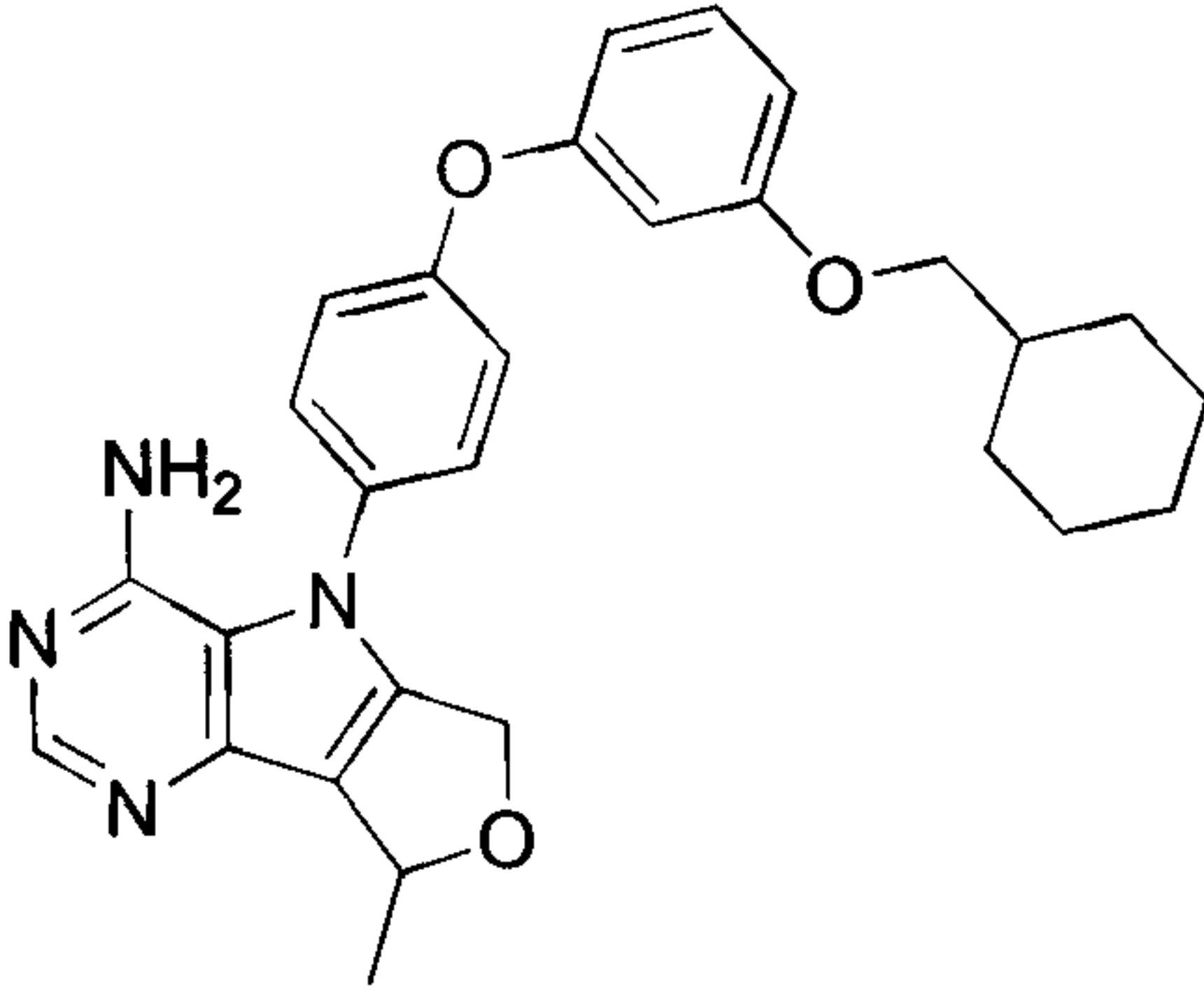
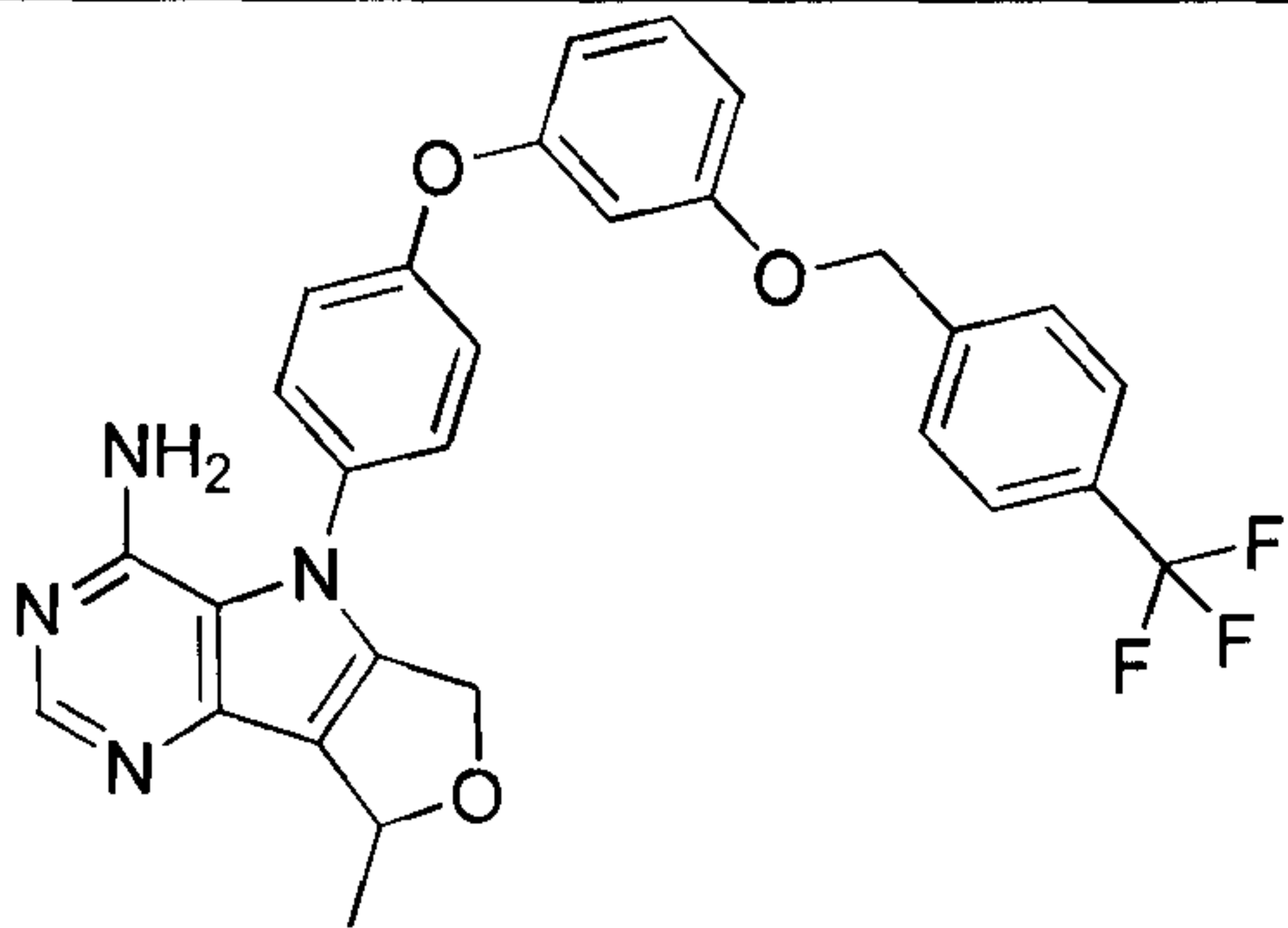
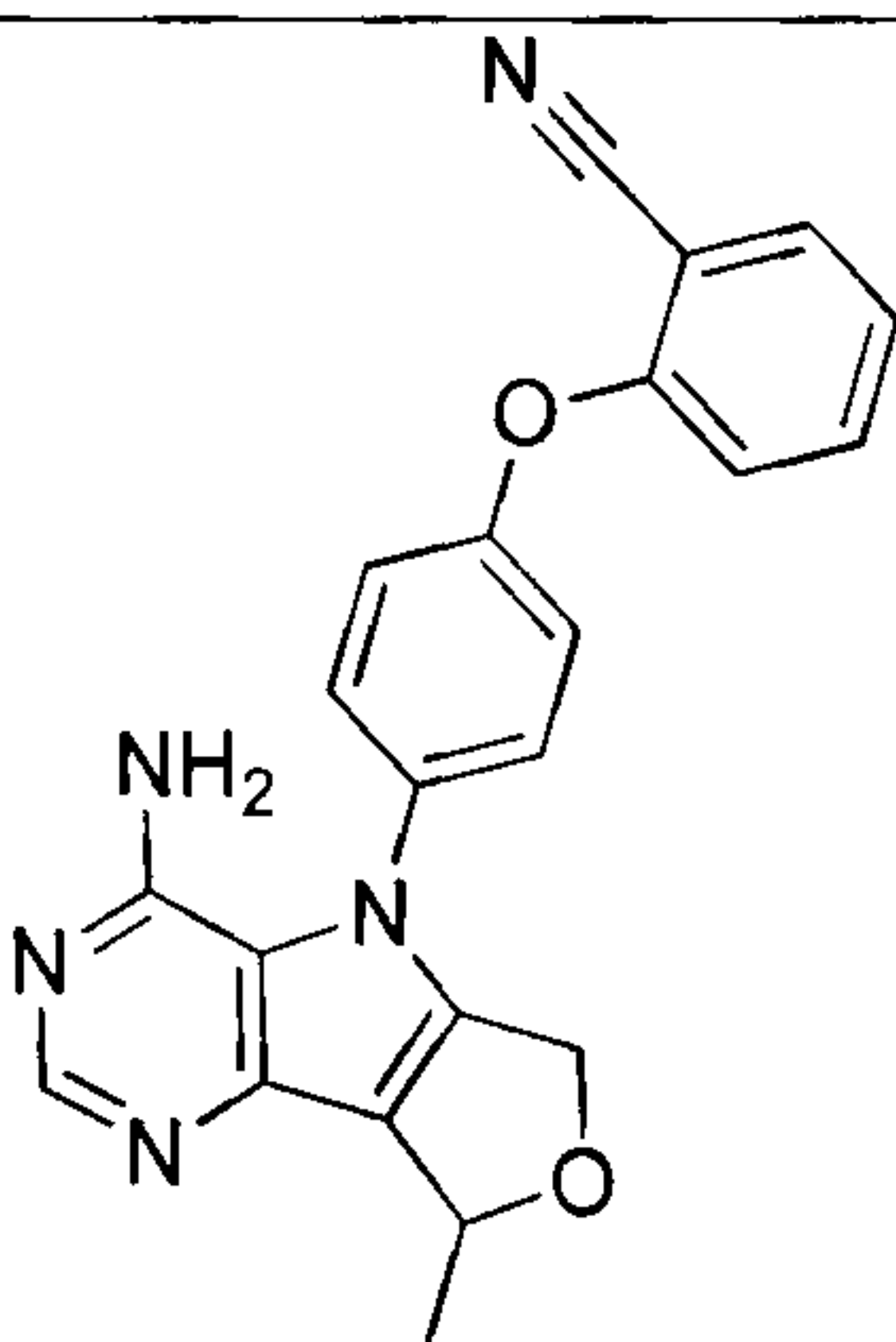
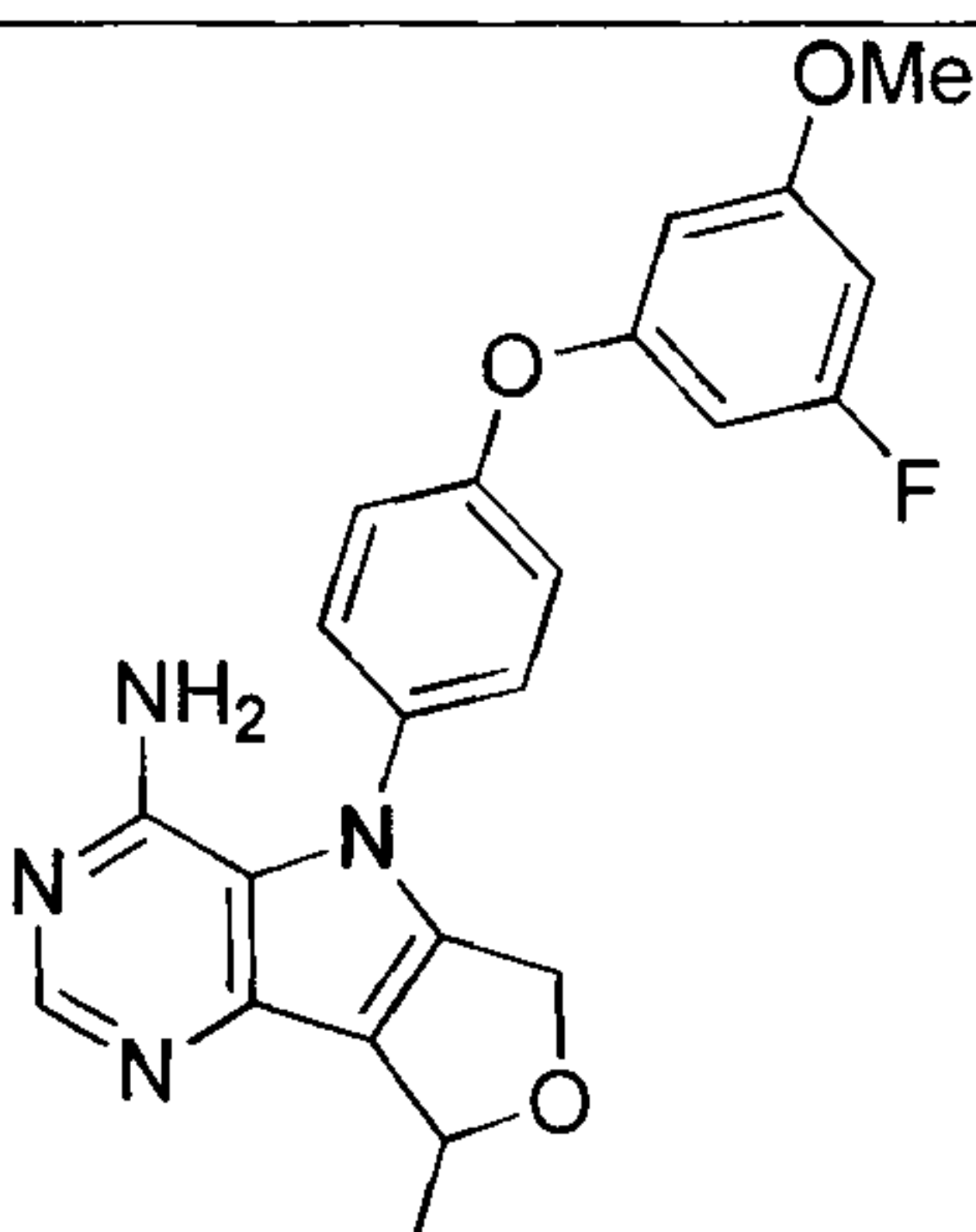
36		$[M+H]^+=479.3$
37		$[M+H]^+=384.3$
38		$[M+H]^+=402.2$
39		$[M+H]^+=393.6$

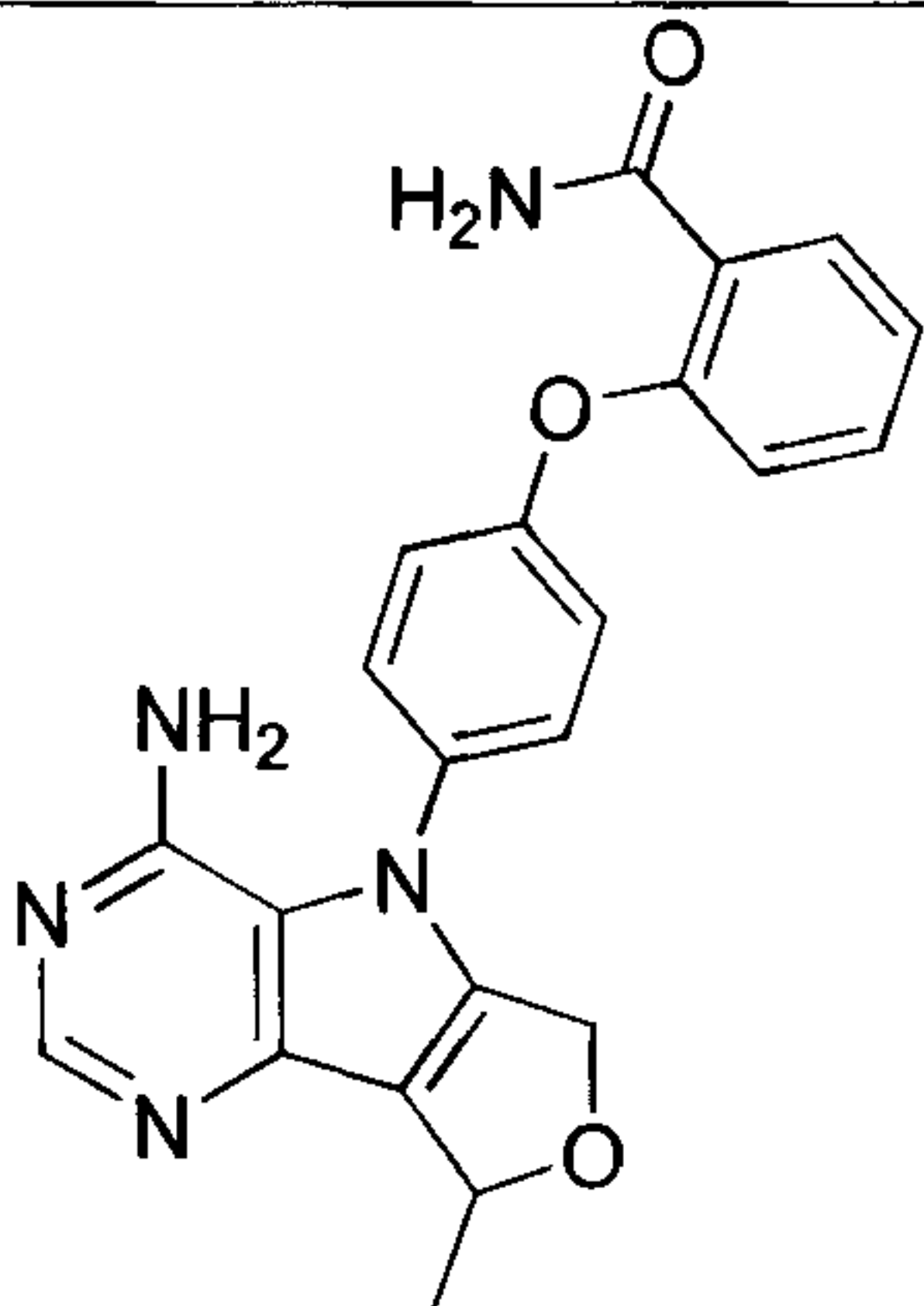
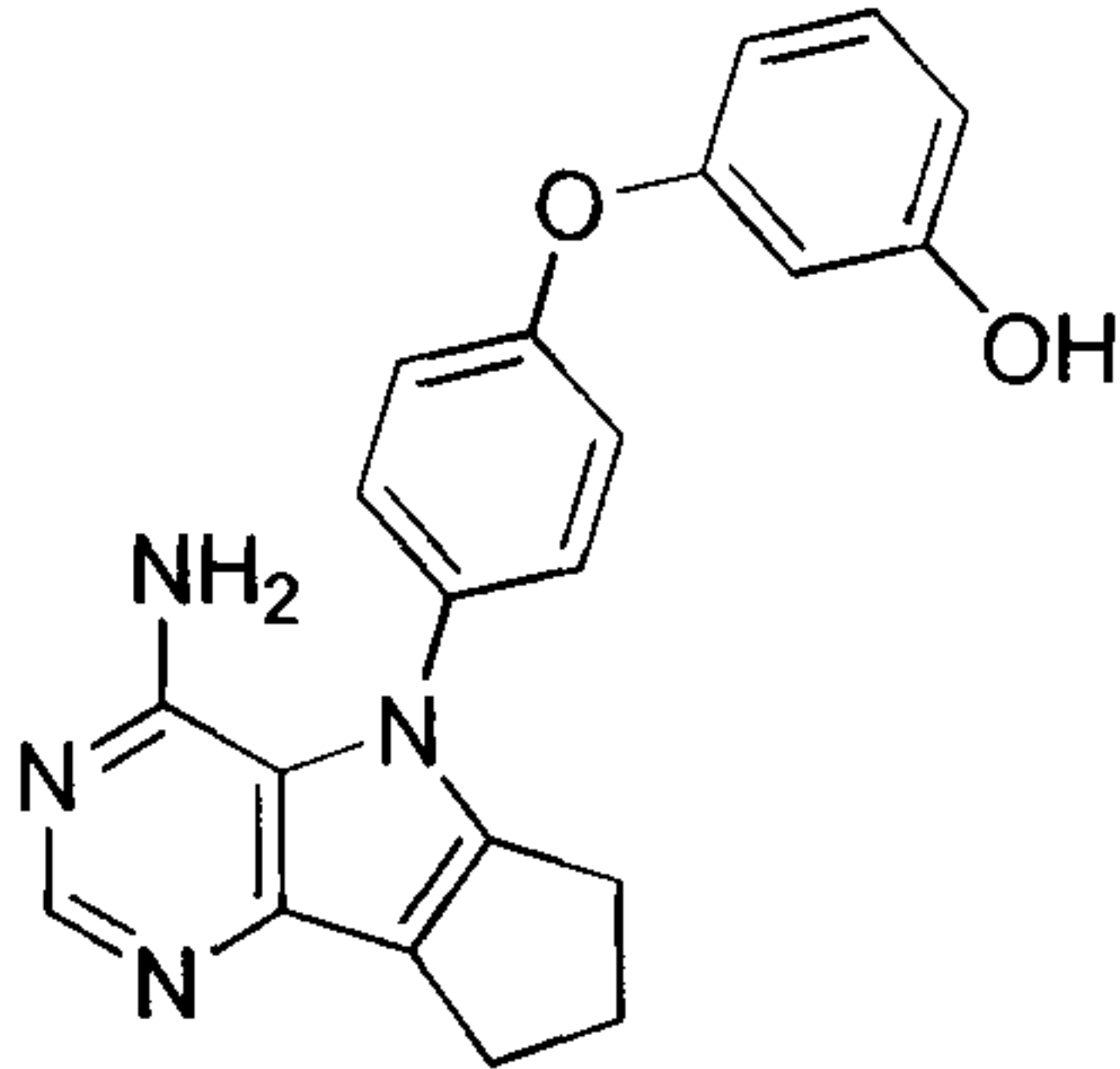
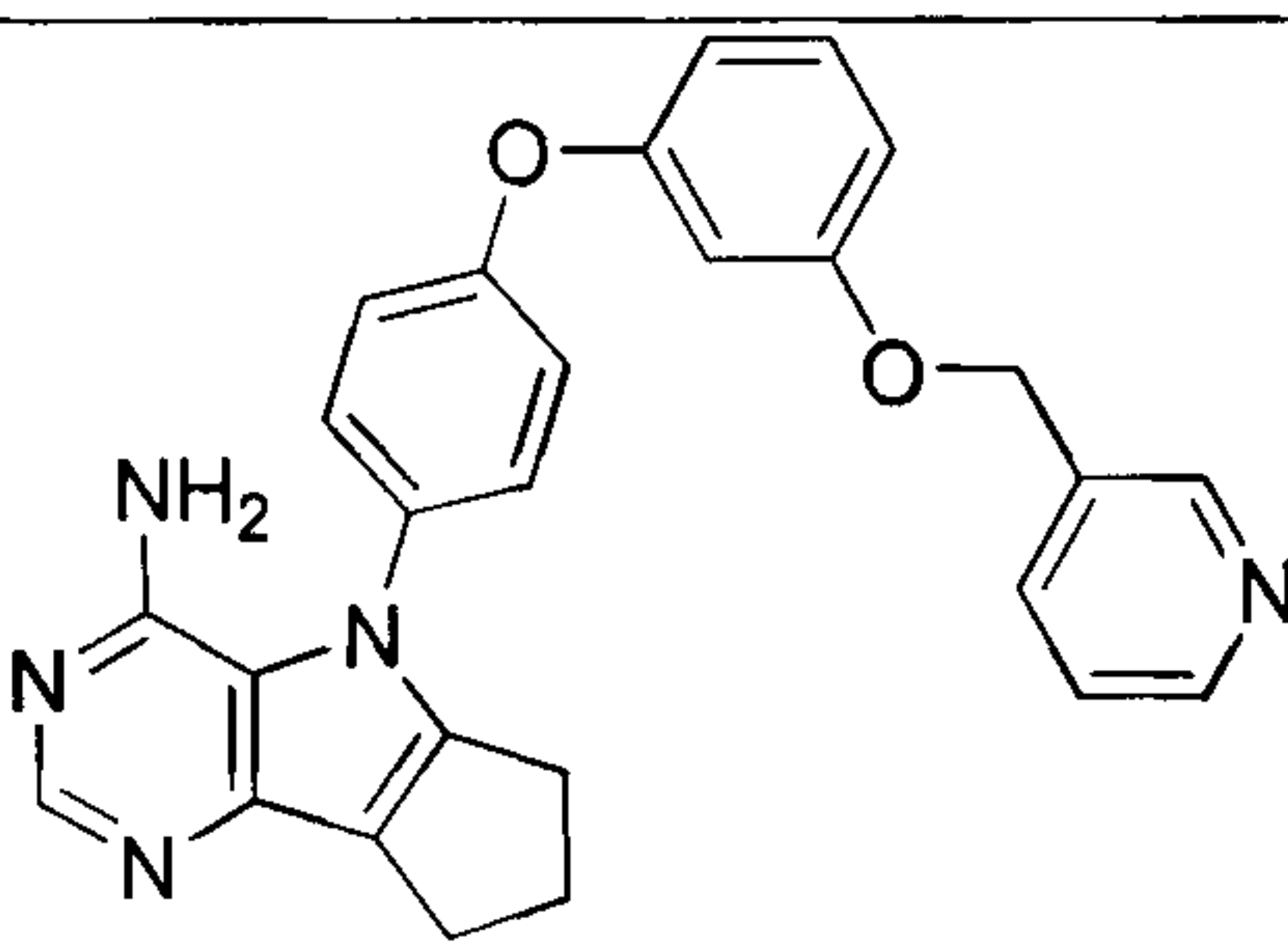
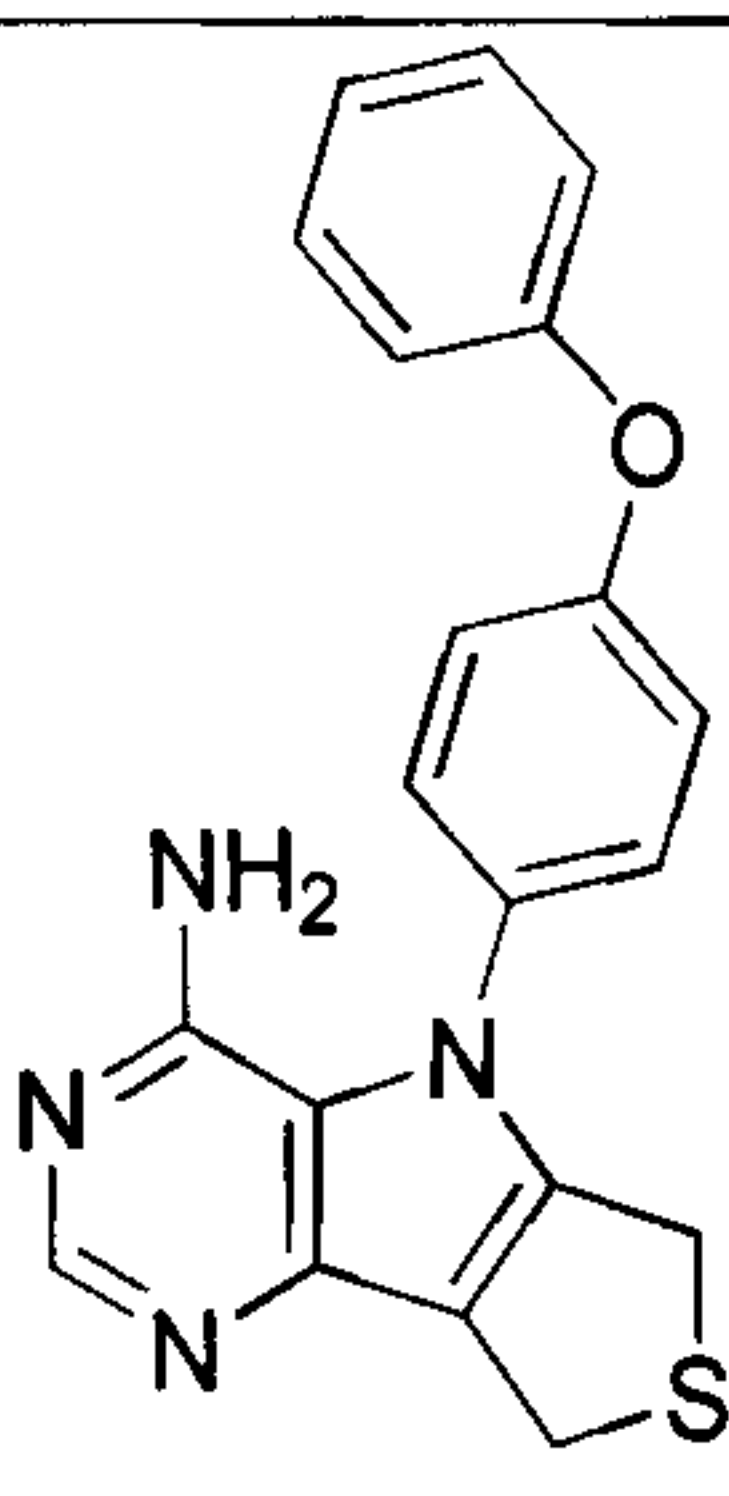
40		$[M+H]^+ = 377.2$
41		$[M+H]^+ = 403.3$
42		$[M+H]^+ = 377.2$
43		$[M+H]^+ = 465.2$

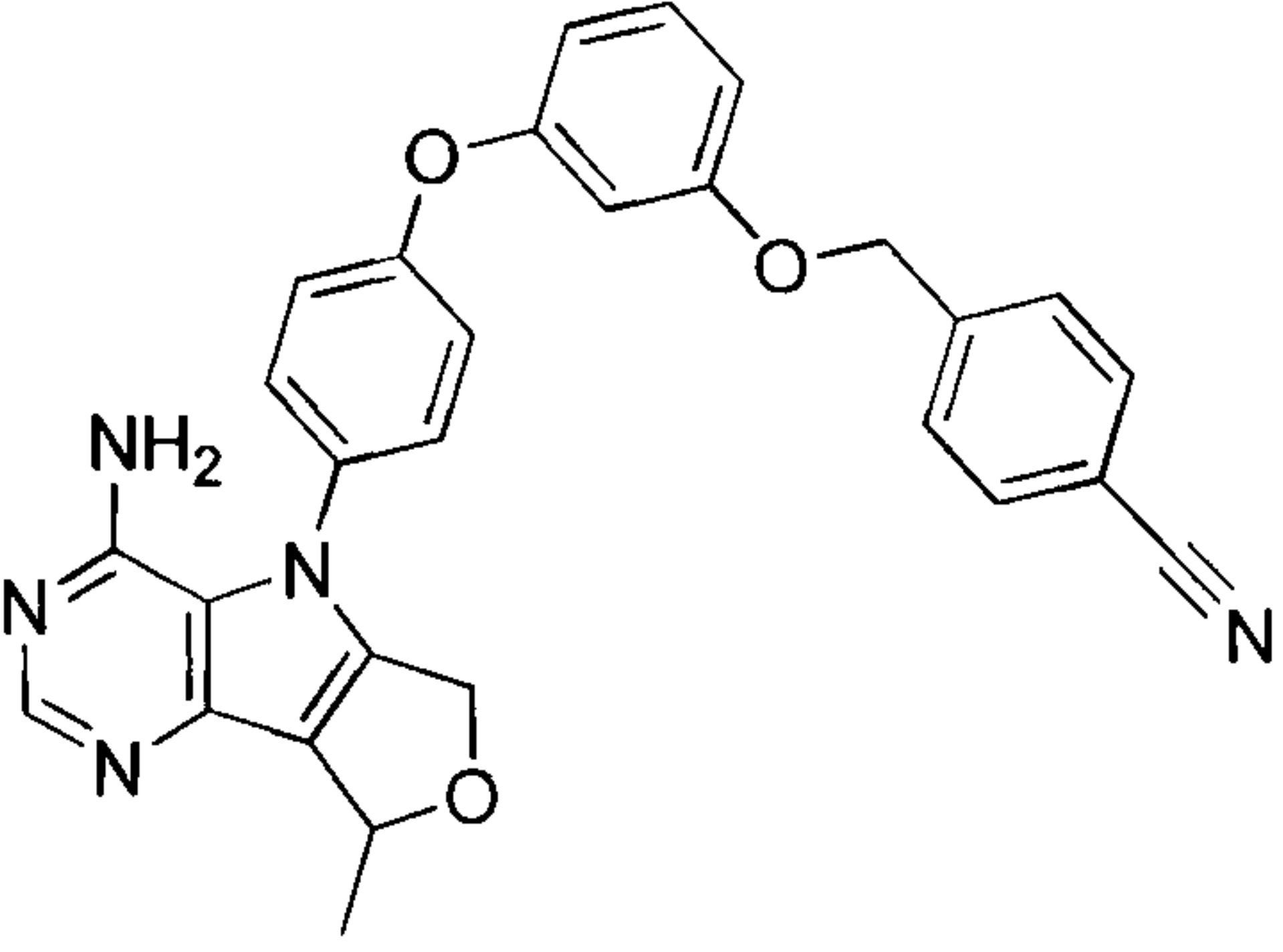
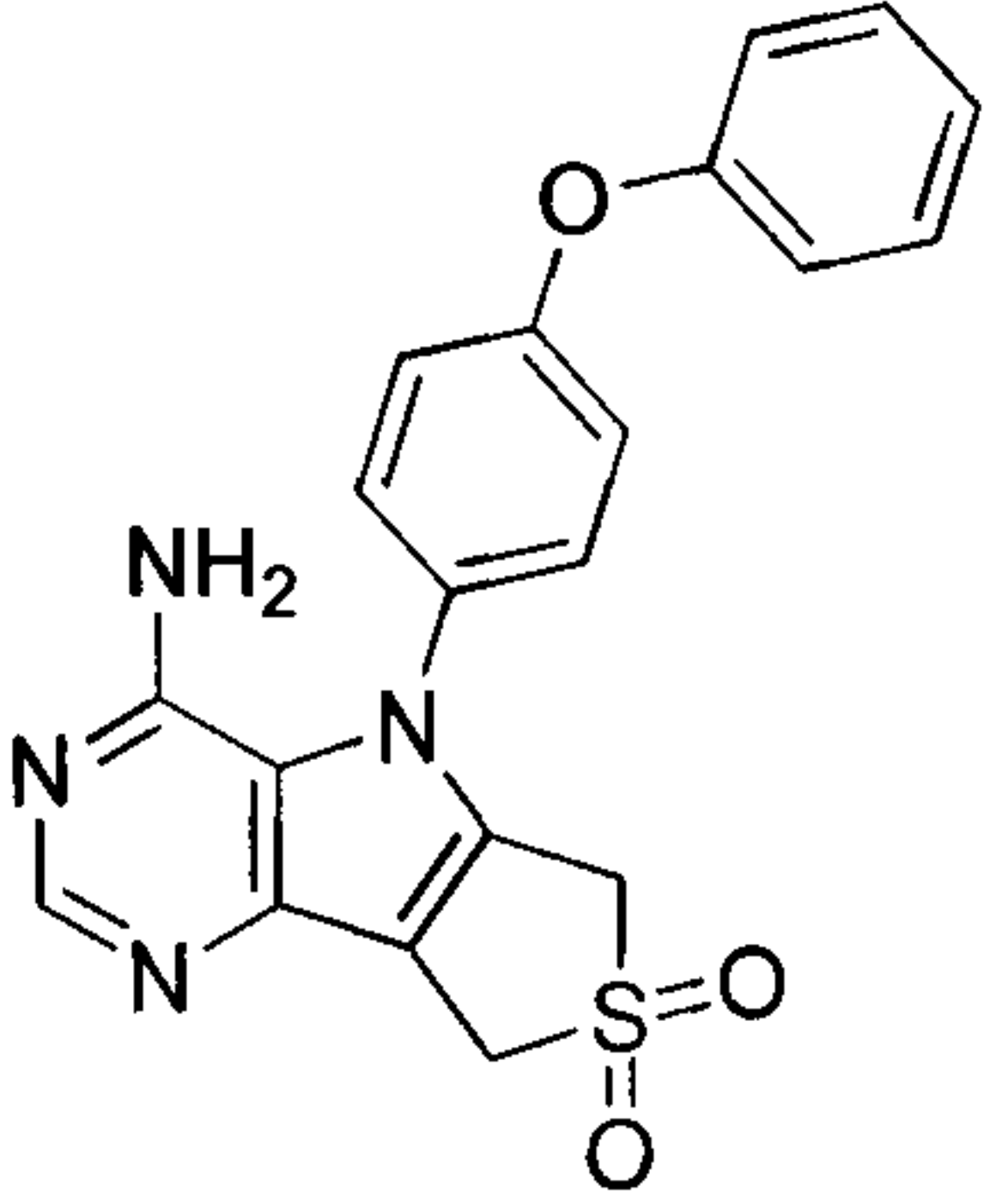
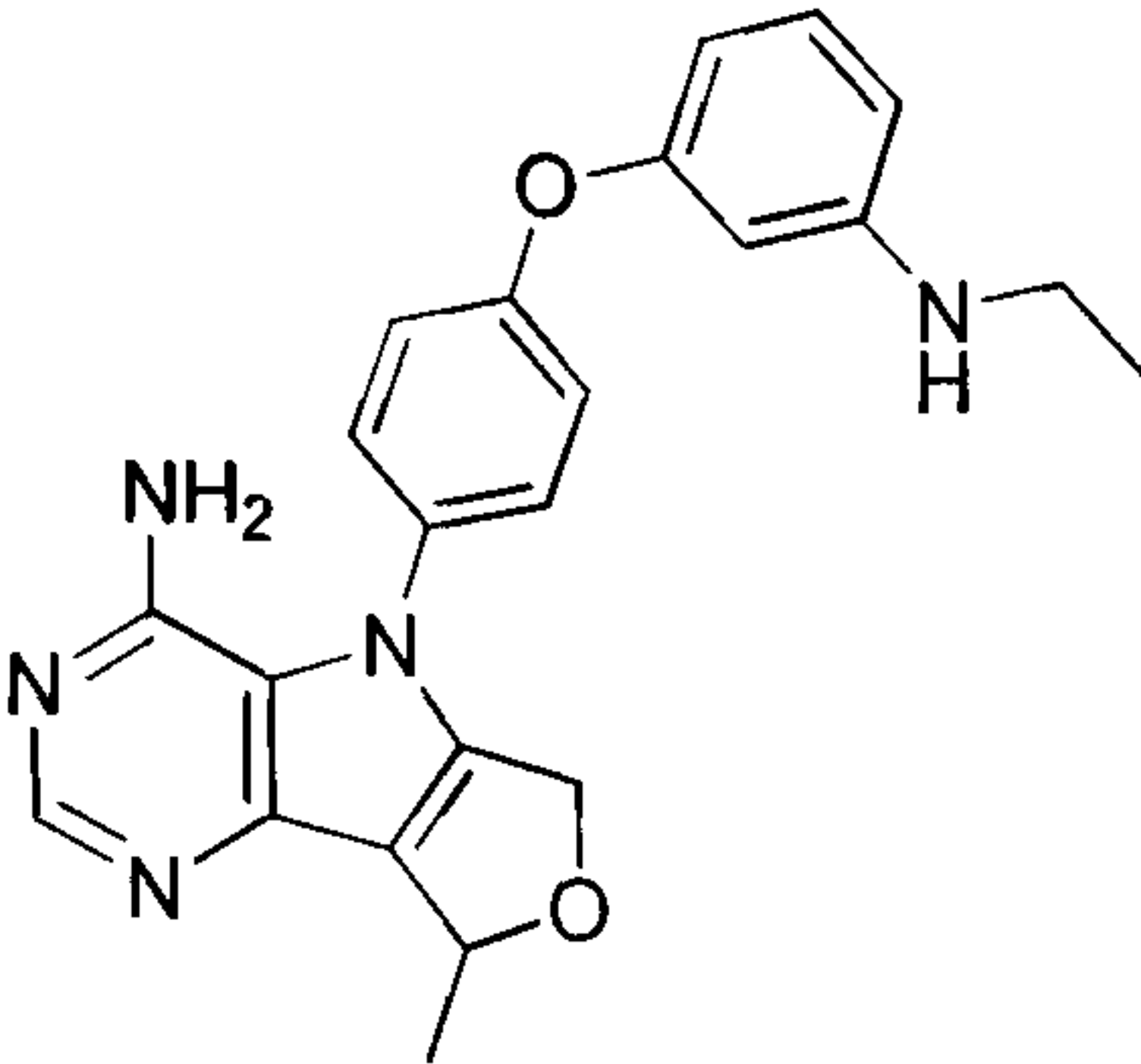
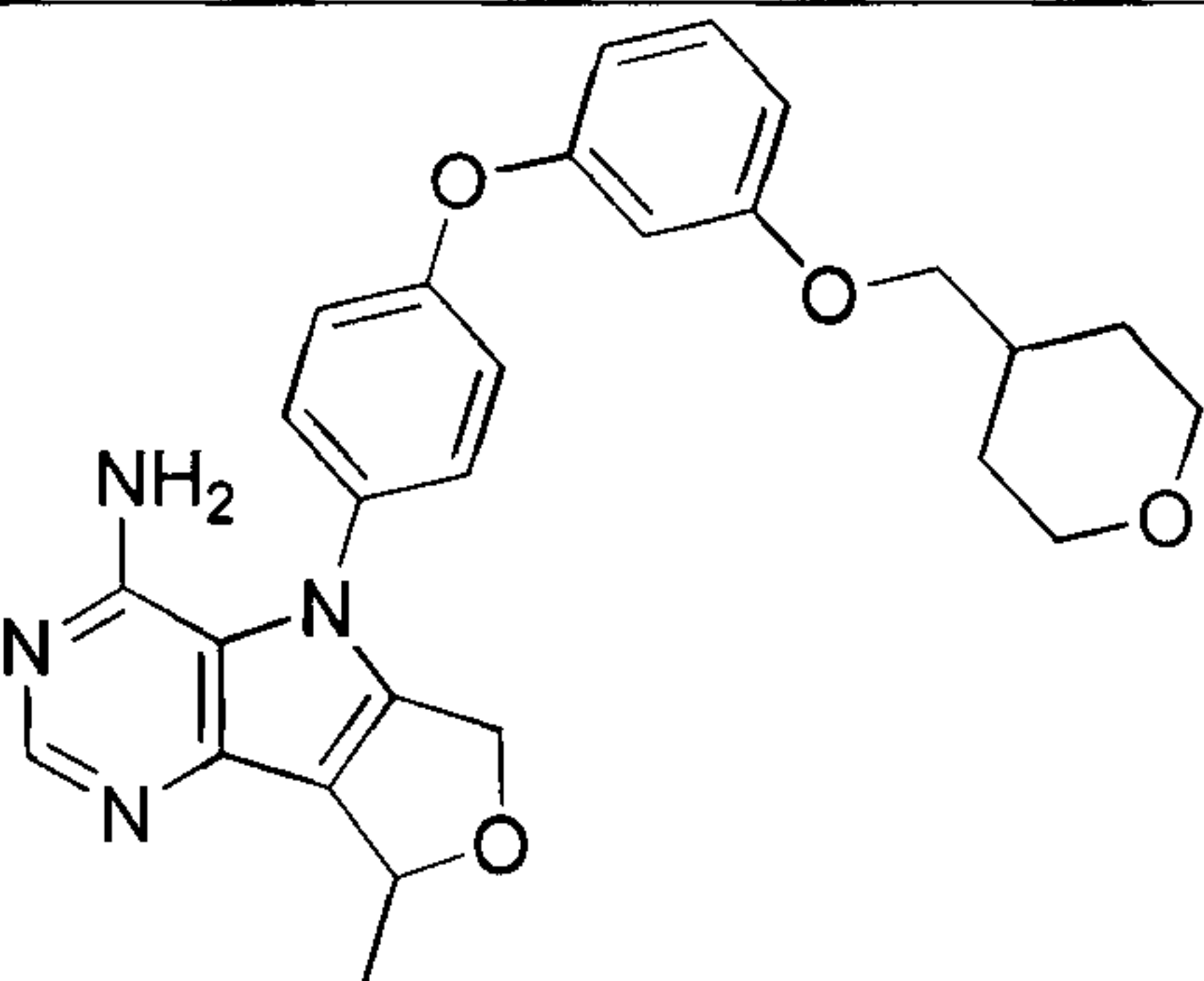
44		$[M+H]^+ = 375.2$
45		$[M+H]^+ = 404.2$
46		$[M+H]^+ = 414.2$
47		$[M+H]^+ = 374.2$

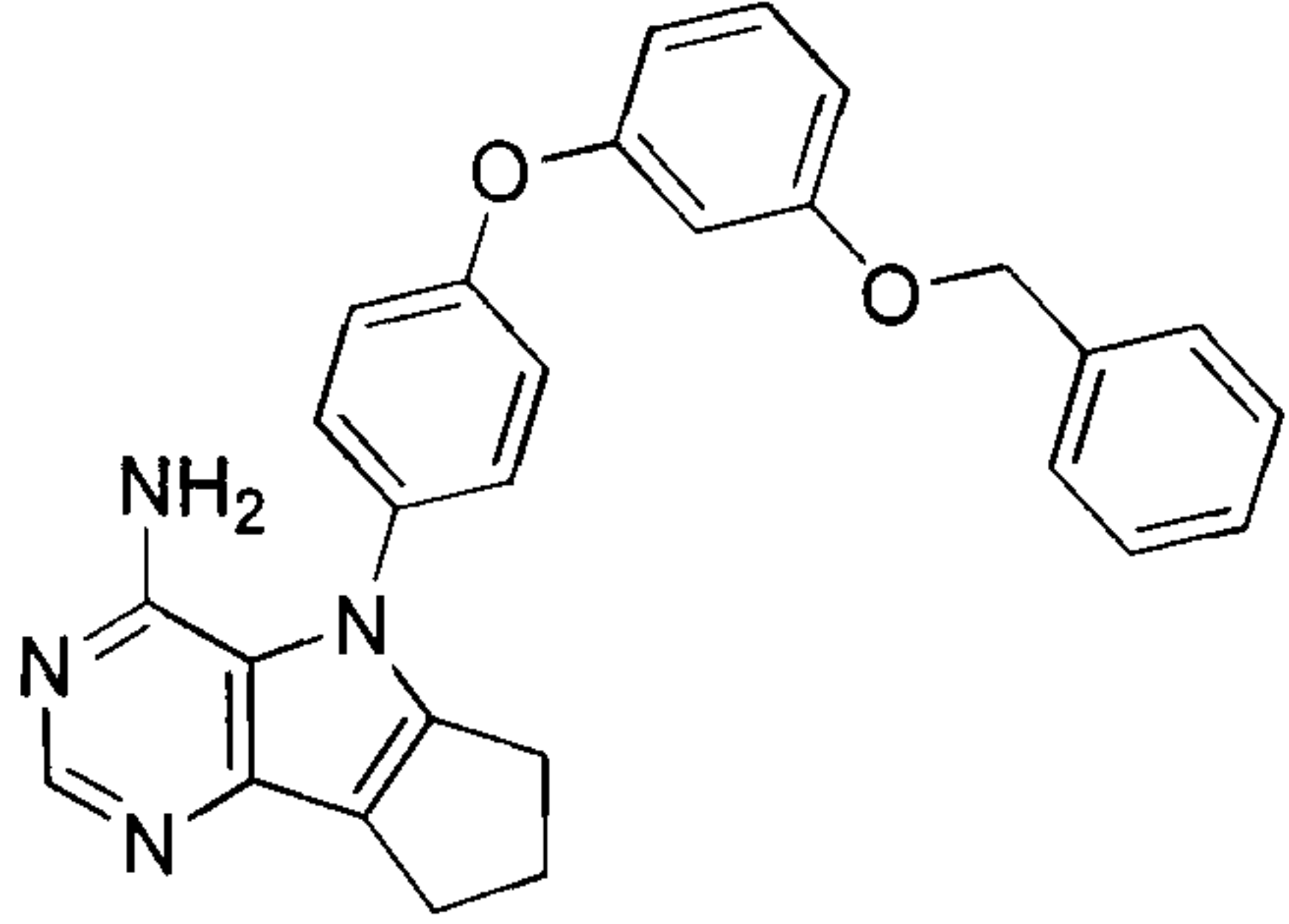
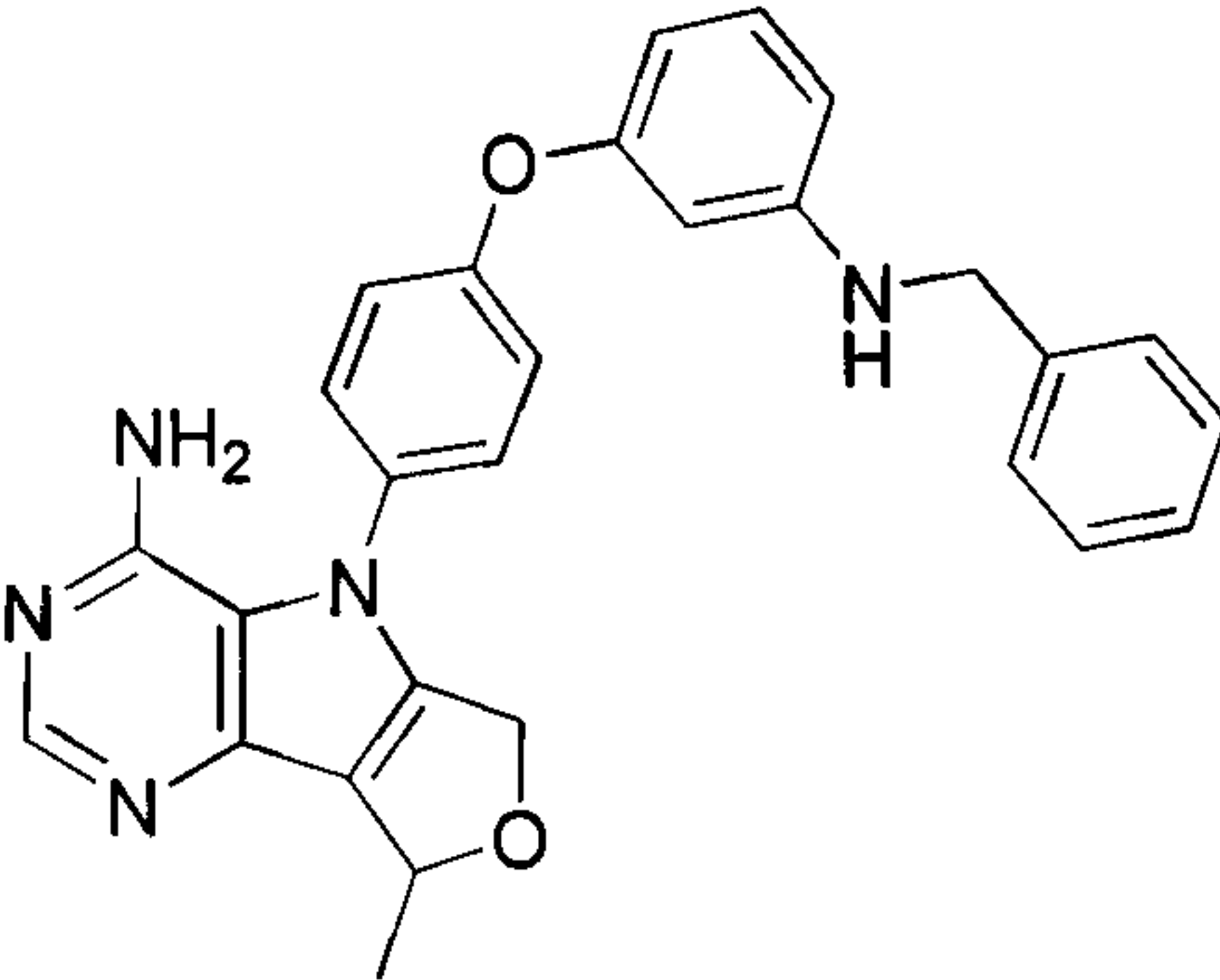
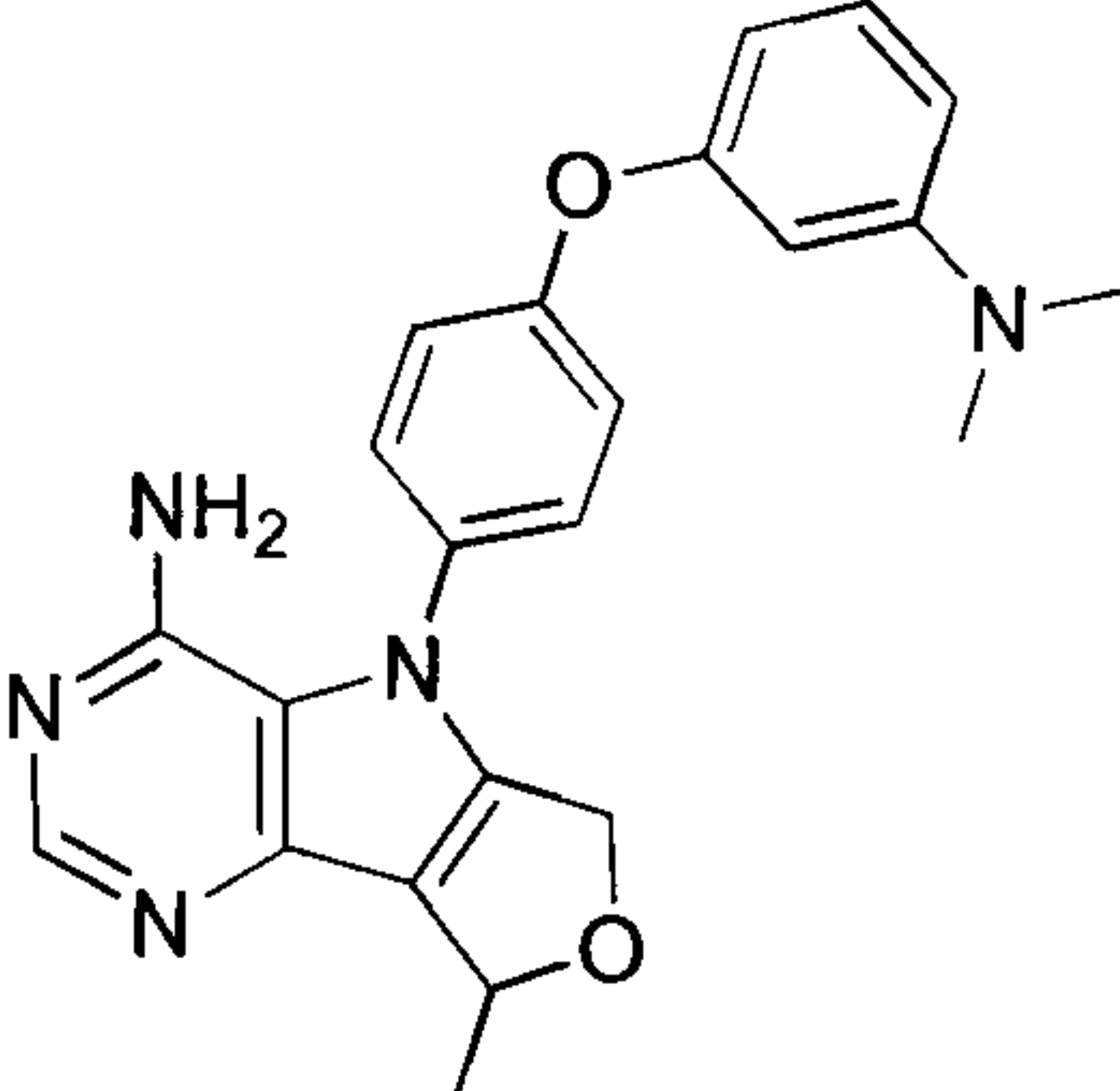
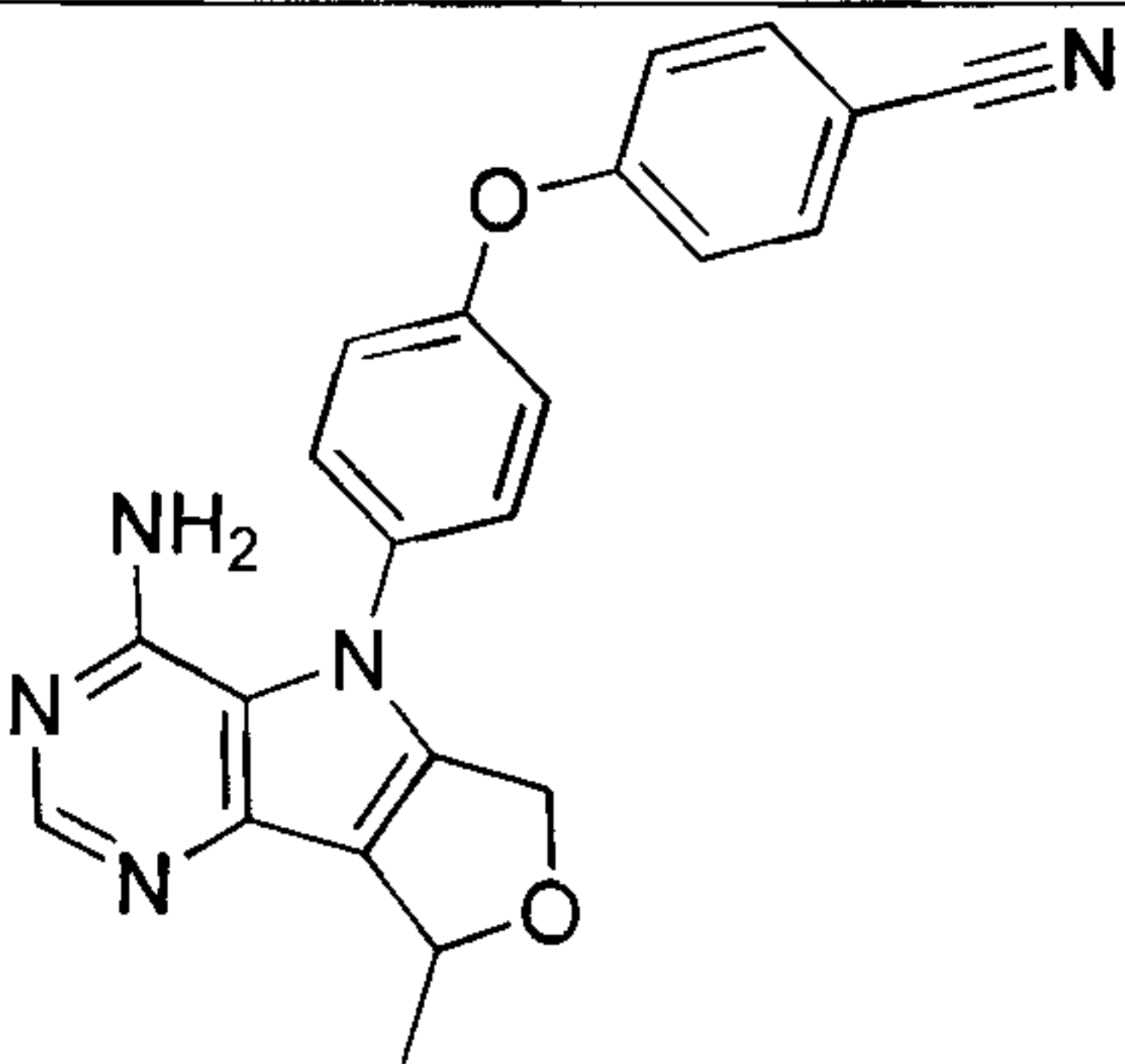
48		$[M+H]^+ = 446.4$
49		$[M+H]^+ = 483.2$
50		$[M+H]^+ = 529.3$
51		$[M+H]^+ = 488.2$

52		$[M+H]^+ = 472.3$
53		$[M+H]^+ = 466.2$
54		$[M+H]^+ = 466.2$
55		$[M+H]^+ = 416.3$

56		$[M+H]^+ = 471.3$
57		$[M+H]^+ = 533.1$
58		$[M+H]^+ = 384.4$
59		$[M+H]^+ = 407.4$

60		$[M+H]^+ = 402.2$
61		$[M+H]^+ = 359.2$
62		$[M+H]^+ = 450.2$
63		$[M+H]^+ = 361.2$

64		$[M+H]^+ = 490.2$
65		$[M+H]^+ = 393.2$
66		$[M+H]^+ = 402.2$
67		$[M+H]^+ = 473.3$

68		$[M+H]^+ = 449.2$
69		$[M+H]^+ = 464.2$
70		$[M+H]^+ = 402.3$
71		$[M+H]^+ = 384.2$

6. A compound of claim 5, selected from compound 1, 13, 23, 62, and 68.

7. A compound of claim 5, selected from compound 20, 21, 23, 24, 28, 29, 31, 32, 33, 34, 35, 37, 39, 45, and 47.
8. A compound of claim 5, selected from compound 25, 41 43, 44, 46, and 49.
9. A compound of claim 5, selected from compound 50, 53, 54, 56, 62, 57, and
5 67.
10. A pharmaceutical composition comprising a compound of any one of claims 1 to 9 and a pharmaceutically acceptable carrier or diluent.
11. A pharmaceutical composition of claim 10 for treating a disorder or disease
10 state characterized by one or more of proliferation, angiogenesis, or bone resorption.
12. A method for treating or preventing autoimmune disease comprising administering a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10.
13. A method for treating or preventing autoimmune disease comprising
15 administering a compound of any one of claims claims 7, 8 or 9 or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9.
14. A method for treating or preventing inflammation comprising administering a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10.
15. A method for treating or preventing inflammation comprising administering a
20 compound of any one of claims claims 7, 8 or 9 or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9.
16. A method for treating or preventing cancer comprising administering a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10.

17. A method for treating or preventing cancer comprising administering a compound of any one of claims 7, 8 or 9 or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9.

18. A method for treating or preventing arthritis comprising administering a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10.

19. A method for treating or preventing arthritis comprising administering a compound of any one of claims 7, 8 or 9 or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9.

20. A method for treating or preventing lymphoma or leukemia comprising administering a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10.

21. A method for treating or preventing lymphoma or leukemia comprising administering a compound of any one of claims 7, 8 or 9 or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9.

22. A method for treating or preventing graft versus host disease, lupus erythematosus, psoriasis, colitis, ileitis, multiple sclerosis, uveitis, coronary artery vasculopathy, systemic sclerosis, atherosclerosis, asthma, transplant rejection, allergy, dermatomyositis, or pemphigus comprising administering a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10.

23. A method for treating or preventing graft versus host disease, lupus erythematosus, psoriasis, colitis, ileitis, multiple sclerosis, uveitis, coronary artery vasculopathy, systemic sclerosis, atherosclerosis, asthma, transplant rejection, allergy, dermatomyositis, or pemphigus comprising administering a compound of any one of claims 7, 8 or 9 or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9.

24. A method for treating or preventing a disorder or disease state characterized by one or more of malignancy, inflammation, bone degradation, cartilage destruction, circulating autoantibodies, cell proliferation comprising administering a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10.
- 5 25. A method for treating or preventing a disorder or disease state characterized by one or more of malignancy, inflammation, bone degradation, cartilage destruction, circulating autoantibodies, cell proliferation comprising administering a compound of any one of claims claims 7, 8 or 9 or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9.
- 10 26. Use of a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10 for the preparation of a medicament for treating or preventing autoimmune disease.
- 15 27. Use of a compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing autoimmune disease.
28. Use of a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10 for the preparation of a medicament for treating or preventing inflammation.
- 20 29. Use of a compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing inflammation.
30. Use of a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10 for the preparation of a medicament for treating or preventing cancer.

31. Use of a compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing cancer.

32. Use of a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10 for the preparation of a medicament for treating or preventing arthritis.

33. Use of a compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing arthritis.

34. Use of a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10 for the preparation of a medicament for treating or preventing lymphoma or leukemia.

35. Use of a compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing lymphoma or leukemia.

36. Use of a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10 for the preparation of a medicament for treating or graft versus host disease, lupus erythematosus, psoriasis, colitis, ileitis, multiple sclerosis, uveitis, coronary artery vasculopathy, systemic sclerosis, atherosclerosis, asthma, transplant rejection, allergy, dermatomyositis, or pemphigus.

37. Use of a compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing graft versus host disease, lupus erythematosus, psoriasis, colitis, ileitis, multiple sclerosis, uveitis, coronary artery vasculopathy, systemic sclerosis, atherosclerosis, asthma, transplant rejection, allergy, dermatomyositis, or pemphigus.

38. Use of a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10 for the preparation of a medicament for treating or preventing a disorder or disease state characterized by one or more of malignancy, inflammation, bone degradation, cartilage destruction, circulating autoantibodies, or cell proliferation.
39. Use of a compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing a disorder or disease state characterized by one or more of malignancy, inflammation, bone degradation, cartilage destruction, circulating autoantibodies, or cell proliferation.
40. A compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10 for the preparation of a medicament for treating or preventing autoimmune disease.
41. A compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing autoimmune disease.
42. A compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10 for the preparation of a medicament for treating or preventing inflammation.
43. A compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing inflammation.
44. A compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10 for the preparation of a medicament for treating or preventing cancer.

45. A compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing cancer.

46. A compound of any one of claims 1 to 9 or a pharmaceutical composition of
5 claim 10 for the preparation of a medicament for treating or preventing arthritis.

47. A compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing arthritis.

48. A compound of any one of claims 1 to 9 or a pharmaceutical composition of
10 claim 10 for the preparation of a medicament for treating or preventing lymphoma or leukemia.

49. A compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing lymphoma or leukemia.

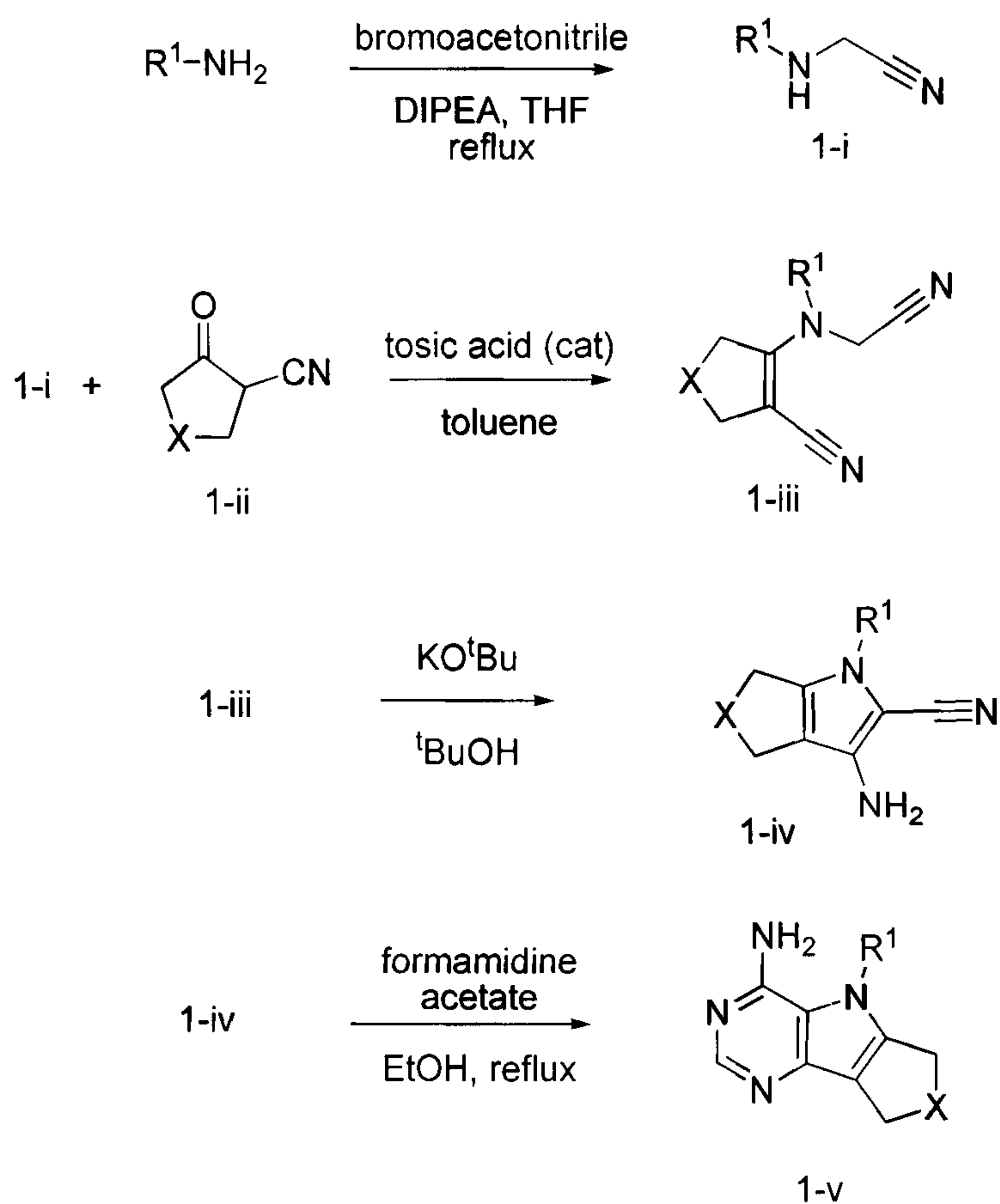
15 50. A compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10 for the preparation of a medicament for treating or preventing graft versus host disease, lupus erythematosus, psoriasis, colitis, illeitis, multiple sclerosis, uveitis, coronary artery vasculopathy, systemic sclerosis, atherosclerosis, asthma, transplant rejection, allergy, dermatomyositis, or pemphigus.

20 51. A compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing graft versus host disease, lupus erythematosus, psoriasis, colitis, illeitis, multiple sclerosis, uveitis, coronary artery vasculopathy, systemic sclerosis, atherosclerosis, asthma, transplant rejection,
25 allergy, dermatomyositis, or pemphigus.

52. A compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10 for the preparation of a medicament for treating or preventing a disorder or disease state characterized by one or more of malignancy, inflammation, bone degradation, cartilage destruction, circulating autoantibodies, or cell proliferation.
- 5 53. A compound of any one of claims 7, 8, or 9, or a pharmaceutical composition comprising the compound of any one of claims 7, 8, or 9, for the preparation of a medicament for treating or preventing a disorder or disease state characterized by one or more of malignancy, inflammation, bone degradation, cartilage destruction, circulating autoantibodies, or cell proliferation.
- 10 54. A method of modulating the target kinase function comprising administering a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10.
55. Use of a compound of any one of claims 1 to 9 or a pharmaceutical composition of claim 10 for the preparation of a medicament for modulating the
15 target kinase function.
56. A use of claim 55 or a method of claim 54, wherein said target kinase function is a function of kinase selected from the Tec, Syk, or Src kinase families, more specifically Btk and Lck.
57. A probe comprising a compound of any one of claims 1 to 9 and a detectable
20 label or affinity tag for said compound.
58. A probe as claimed in claim 57, wherein the detectable label is selected from a fluorescent moiety, a chemiluminescent moiety, a paramagnetic contrast agent, a metal chelate, a radioactive isotope-containing moiety, and biotin.
- 25 59. A process for preparing a compound of Formula 1-v, comprising the steps of:

- a) alkylation of R^1NH_2 with bromoacetonitrile to provide intermediate 1-i;
- b) condensation of 1-i with 1-ii in the presence of an acid to provide intermediate 1-iii.;
- 5 c) treatment of intermediate 1-iii with a base to provide intermediate 1-iv;
- d) treatment of intermediate 1-iv with formamidine acetate in an alcohol to provide a compound of formula 1-v.

10 60. A process of claim 59, comprising:



61. An intermediate compound represented by:

