



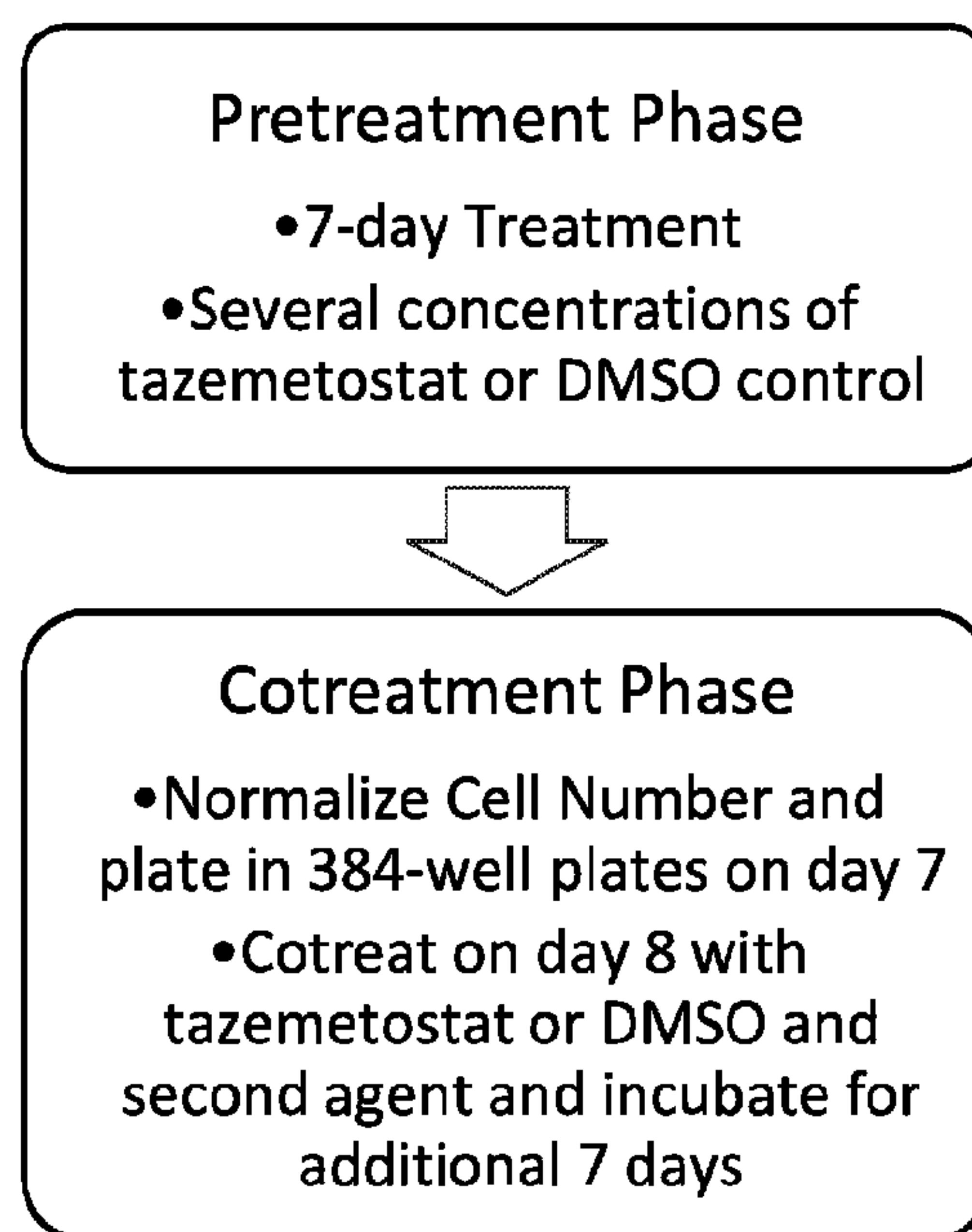
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(54) Titre : POLYTHERAPIE POUR LE TRAITEMENT DU CANCER
(54) Title: COMBINATION THERAPY FOR TREATING CANCER

FIGURE 1



(57) **Abrégé/Abstract:**

The disclosure relates to methods, compounds for use and medicaments for the treatment of cancer comprising administering to a subject in need thereof a first agent in a therapeutically effective amount and one or more second agents each in a therapeutically effective amount. In some embodiments, the first agent comprises an EZH2 inhibitor. In certain embodiments, the first agent is tazemetostat or a pharmaceutically acceptable salt thereof and the methods of the disclosure are used to treat lung cancer, e.g., non-small cell lung cancer.

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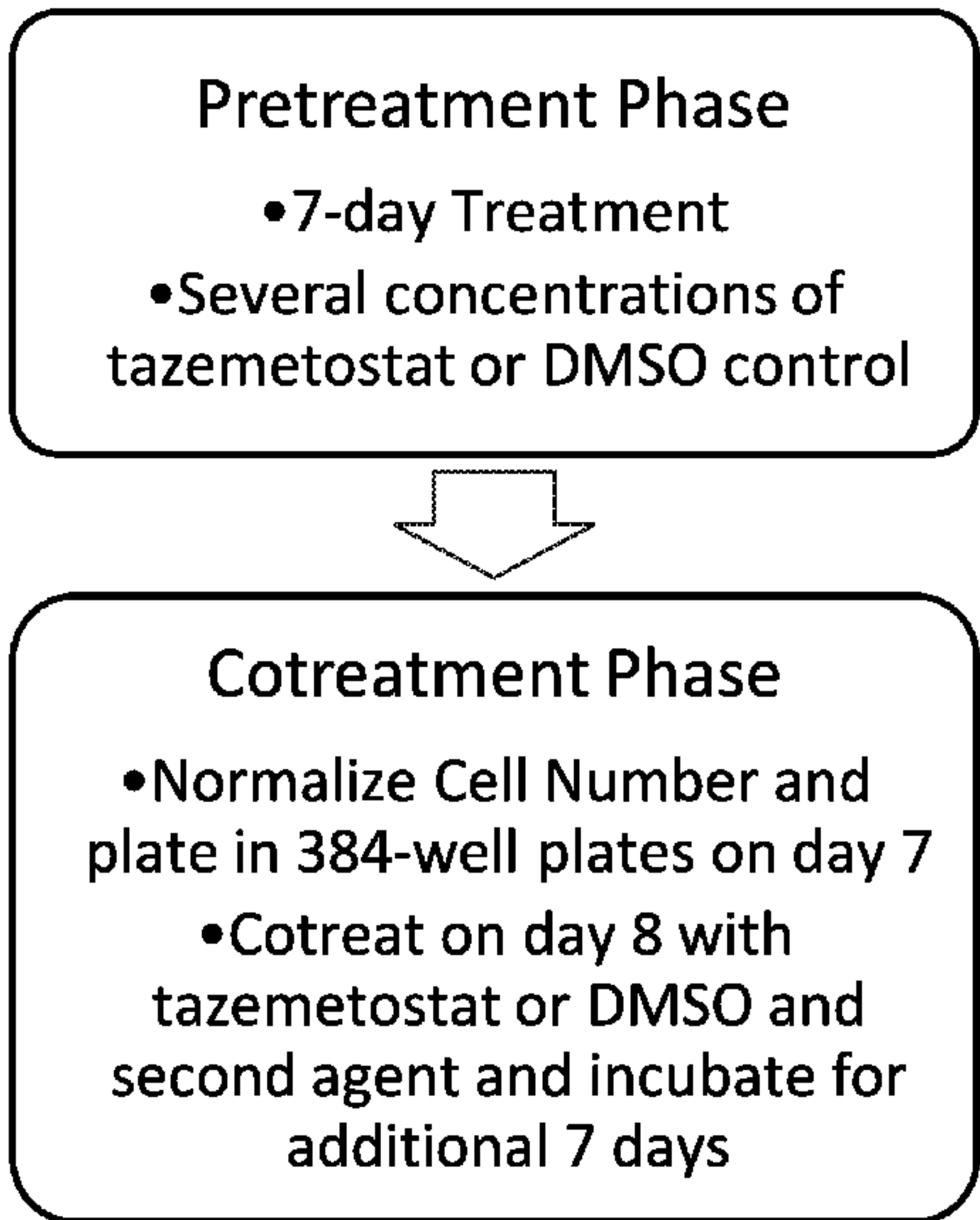
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(54) Title: COMBINATION THERAPY FOR TREATING CANCER

FIGURE 1



(57) Abstract: The disclosure relates to methods, compounds for use and medicaments for the treatment of cancer comprising administering to a subject in need thereof a first agent in a therapeutically effective amount and one or more second agents each in a therapeutically effective amount. In some embodiments, the first agent comprises an EZH2 inhibitor. In certain embodiments, the first agent is tazemetostat or a pharmaceutically acceptable salt thereof and the methods of the disclosure are used to treat lung cancer, e.g., non-small cell lung cancer.

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COMBINATION THERAPY FOR TREATING CANCER

RELATED APPLICATIONS

[001] This application claims priority to, and the benefit of, U.S. Provisional Application No. 62/554,484, filed September 5, 2017, the content of which is incorporated herein by reference in its entirety.

FIELD OF THE DISCLOSURE

[002] This invention relates to compositions comprising inhibitors of human histone methyltransferase EZH2, the catalytic subunit of the PRC2 complex which catalyzes the mono- through tri-methylation of lysine 27 on histone H3 (H3-K27), and one or more other therapeutic agents, particularly anticancer agents, and methods of combination therapy for treating cancer.

BACKGROUND

[003] Combination-therapy treatments for cancer have become more common, in part due to the perceived advantage of attacking the disease via multiple avenues. Although many effective combination-therapy treatments have been identified over the past few decades; in view of the continuing high number of deaths each year resulting from cancer, a continuing need exists to identify effective therapeutic regimens for use in anticancer treatment.

SUMMARY

[004] The disclosure is based upon the discovery that EZH2 histone methyltransferase inhibitors and other anti-cancer agents can be used in combination to treat certain tumors with superior results than those achieved by treating tumors with EZH2 histone methyltransferase inhibitors and the anti-cancer agents alone. Accordingly, the disclosure provides a composition comprising an EZH2 histone methyltransferase inhibitor and one or more other therapeutic agents, and methods for their use to treat diseases the course of which can be influenced by modulating the methylation status of histones or other proteins, e.g., cancer. In certain embodiments, the disclosure provides a composition comprising the EZH2 histone methyltransferase inhibitor tazemetostat or a pharmaceutically acceptable salt thereof and one or more second anti-cancer agents. In certain embodiments, the disclosure provides a composition comprising the EZH2 histone

methyltransferase inhibitor tazemetostat or a pharmaceutically acceptable salt thereof and a second anti-cancer agent for the treatment of lung cancer, e.g., of non-small cell lung cancer.

[005] Some aspects of this disclosure provide methods, strategies, treatment modalities, compositions, and combinations, for the treatment of cancer. In some embodiments, the disclosure provides methods comprising administering to a subject in need thereof (a) a first agent in a therapeutically effective amount, wherein the first agent comprises an EZH2 inhibitor, and (b) one or more second agents in a therapeutically effective amount. In some embodiments, the EZH2 inhibitor is an EZH2 inhibitor provided herein. For example, and without limitation, in some embodiments, the EZH2 inhibitor is a compound of Formula (I), (II), (III), (IVa), (IVb), (V), or (VIa), or a pharmaceutically acceptable salt thereof. In some exemplary embodiments, the EZH2 inhibitor is compound (A), (B), (C), (D), (E), (F), (G), (Ga), or (Gb), or a pharmaceutically acceptable salt thereof.

[006] In some embodiments, the disclosure provides methods for the treatment of cancer comprising administering to a subject in need thereof (a) a first agent in a therapeutically effective amount, wherein the first agent comprises compound (A), (B), (C), (D), (E), (F), (G), (Ga), or (Gb), or a pharmaceutically acceptable salt thereof, and (b) one or more second agents in a therapeutically effective amount. In certain embodiments the first agent and/or the second agent may comprise a pharmaceutically-acceptable carrier. In some embodiments, the pharmaceutically-acceptable carrier is the same for the first and second agents or are distinct between the first and second agents.

[007] In some embodiments, the disclosure provides methods for the treatment of cancer comprising administering to a subject in need thereof (a) a first agent in a therapeutically effective amount, wherein the first agent comprises tazemetostat or a pharmaceutically acceptable salt thereof, and (b) one or more second agents in a therapeutically effective amount. In certain embodiments the first agent and/or the second agent may comprise a pharmaceutically-acceptable carrier. In some embodiments, the pharmaceutically-acceptable carrier is the same for the first and second agents or is distinct between the first and second agents.

[008] In some embodiments, the one or more second agents comprise two or more second agents (e.g., two, three, four, or five, or more, different second agents). Typically, the second agent(s) comprise therapeutic agents, such as chemotherapeutic agents, immunooncology agents, and standard of care agents or combinations of such agents.

[009] Some aspects of the disclosure provide an EZH2 inhibitor for use in the treatment of cancer in a subject in need thereof, wherein the subject is also administered one or more second agents in a therapeutically effective amount.

[010] In some embodiments, the disclosure provides a compound of Formula (I), (II), (III), (IVa), (IVb), (V), or (VIa), or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a subject in need thereof, wherein the subject is also administered one or more second agents in a therapeutically effective amount.

[011] In some embodiments, the disclosure provides a compound (A), (B), (C), (D), (E), (F), (G), (Ga), or (Gb), or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a subject in need thereof, wherein the subject is also administered one or more second agents in a therapeutically effective amount.

[012] In some embodiments, the disclosure provides tazemetostat, or a pharmaceutically acceptable salt thereof, for use in the treatment of cancer in a subject in need thereof, wherein the subject is also administered one or more second agents in a therapeutically effective amount.

[013] Some aspects of the disclosure provide an EZH2 inhibitor for use as a medicament for the treatment of cancer in a subject in need thereof, wherein the subject is also administered one or more second agents in a therapeutically effective amount.

[014] In some embodiments, the disclosure provides a compound of Formula (I), (II), (III), (IVa), (IVb), (V), or (VIa), or a pharmaceutically acceptable salt thereof, for use as a medicament for the treatment of cancer in a subject in need thereof, wherein the subject is also administered one or more second agents in a therapeutically effective amount.

[015] In some embodiments, the disclosure provides a compound (A), (B), (C), (D), (E), (F), (G), (Ga), or (Gb), or a pharmaceutically acceptable salt thereof, for use as a medicament for the treatment of cancer in a subject in need thereof, wherein the subject is also administered one or more second agents in a therapeutically effective amount.

[016] In some embodiments, the disclosure provides tazemetostat, or a pharmaceutically acceptable salt thereof, for use as a medicament for the treatment of cancer in a subject in need thereof, wherein the subject is also administered one or more second agents in a therapeutically effective amount.

[017] Some aspects of the disclosure provide the use of an EZH2 inhibitor in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein the subject is also administered one or more second agents in a therapeutically effective amount.

[018] In some embodiments, the disclosure provides the use of a compound of Formula (I), (II), (III), (IVa), (IVb), (V), or (VIa), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein the subject is also administered one or more second agents in a therapeutically effective amount.

[019] In some embodiments, the disclosure provides the use of a compound (A), (B), (C), (D), (E), (F), (G), (Ga), or (Gb), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein the subject is also administered one or more second agents in a therapeutically effective amount.

[020] In some embodiments, the disclosure provides the use of tazemetostat, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer in a subject in need thereof, wherein the subject is also administered one or more second agents in a therapeutically effective amount.

[021] Some aspects of the disclosure provide an EZH2 inhibitor for use in combination with one or more second agents in a therapeutically effective amount, in the treatment of a cancer in a subject in need thereof.

[022] In some embodiments, the disclosure provides a compound of Formula (I), (II), (III), (IVa), (IVb), (V), or (VIa), or a pharmaceutically acceptable salt thereof, for use in combination with one or more second agents in a therapeutically effective amount, in the treatment of cancer in a subject in need thereof.

[023] In some embodiments, the disclosure provides a compound (A), (B), (C), (D), (E), (F), (G), (Ga), or (Gb), or a pharmaceutically acceptable salt thereof, for use in combination with one or more second agents in a therapeutically effective amount, in the treatment of cancer in a subject in need thereof.

[024] In some embodiments, the disclosure provides tazemetostat, or a pharmaceutically acceptable salt thereof, for use in combination with one or more second agents in a therapeutically effective amount, in the treatment of cancer in a subject in need thereof.

[025] Some aspects of the disclosure provide an EZH2 inhibitor for use as a medicament for combinational therapy with one or more second agents in a therapeutically effective amount, for treating a cancer in a subject in need thereof.

[026] In some embodiments, the disclosure provides a compound of Formula (I), (II), (III), (IVa), (IVb), (V), or (VIa), or a pharmaceutically acceptable salt thereof, for use as a medicament for combinational therapy with one or more second agents in a therapeutically effective amount, for treating a cancer in a subject in need thereof.

[027] In some embodiments, the disclosure provides the use of a compound (A), (B), (C), (D), (E), (F), (G), (Ga), or (Gb), or a pharmaceutically acceptable salt thereof, for use as a medicament for combinational therapy with one or more second agents in a therapeutically effective amount, for the treatment of a cancer in a subject in need thereof.

[028] In some embodiments, the disclosure provides the use of tazemetostat, or a pharmaceutically acceptable salt thereof, for use as a medicament for combinational therapy with one or more second agents in a therapeutically effective amount, for the treatment of a cancer in a subject in need thereof.

[029] Some aspects of the disclosure provide the use of an EZH2 inhibitor in the manufacture of a medicament for combinational therapy with one or more second agents in a therapeutically effective amount, for the treatment of a cancer in a subject in need thereof.

[030] In some embodiments, the disclosure provides the use of a compound of Formula (I), (II), (III), (IVa), (IVb), (V), or (VIa), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for combinational therapy with one or more second agents in a therapeutically effective amount, for the treatment of a cancer in a subject in need thereof.

[031] In some embodiments, the disclosure provides the use of a compound (A), (B), (C), (D), (E), (F), (G), (Ga), or (Gb), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for combinational therapy with one or more second agents in a therapeutically effective amount, for the treatment of a cancer in a subject in need thereof.

[032] In some embodiments, the disclosure provides the use of tazemetostat, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for combinational therapy with one or more second agents in a therapeutically effective amount, for the treatment of a cancer in a subject in need thereof.

[033] In some embodiments, a therapeutically effective amount of the EZH2 inhibitor is an amount between about 100 mg to about 1600 mg, inclusive of the endpoints. In certain embodiments, the therapeutically effective amount of the EZH2 inhibitor is about 100 mg, about 200 mg, about 400 mg, about 800 mg, or about 1600 mg. In certain embodiments, the therapeutically effective amount of the EZH2 inhibitor is about 800 mg.

[034] In some embodiments, a therapeutically effective amount of compound (A), (B), (C), (D), (E), (F), (G), (Ga), or (Gb), or a pharmaceutically acceptable salt thereof, is between about 100 mg to about 1600 mg, inclusive of the endpoints. In certain embodiments, the therapeutically effective amount of tazemetostat or a pharmaceutically acceptable salt thereof is about 100 mg, 200 mg, 400 mg, 800 mg, or about 1600 mg. In certain embodiments, the therapeutically effective amount of tazemetostat or a pharmaceutically acceptable salt thereof is about 800 mg.

[035] In some embodiments, a therapeutically effective amount of tazemetostat, or a pharmaceutically acceptable salt thereof, is between about 100 mg to about 1600 mg, inclusive of the endpoints. In certain embodiments, the therapeutically effective amount of tazemetostat, or a pharmaceutically acceptable salt thereof, is about 100 mg, 200 mg, 400 mg, 800 mg, or about 1600 mg. In certain embodiments, the therapeutically effective amount of tazemetostat or a pharmaceutically acceptable salt thereof is about 800 mg.

[036] In some embodiments, the therapeutically effective amount of the EZH2 inhibitor is administered as a single dose, or in multiple doses over a period of time, e.g., twice per day (BID), three times a day, etc. For example, and without limitation, in some embodiments, an EZH2 inhibitor provided herein is administered at a dose of between about 100 mg to about 1600 mg twice per day over a period between one week and six months.

[037] In some embodiments, the therapeutically effective amount of tazemetostat or a pharmaceutically acceptable salt thereof is administered twice per day (BID), e.g., at a dose of 800 mg or 1600 mg per administration.

[038] In some embodiments, the therapeutically effective amount of the EZH2 inhibitor is administered orally. For example, in some embodiments, the therapeutically effective amount of tazemetostat or a pharmaceutically acceptable salt thereof is administered as a capsule or tablet.

[039] In some embodiments, the therapeutically effective amount of the EZH2 inhibitor, e.g., of tazemetostat or a pharmaceutically acceptable salt thereof, is administered orally. For example, in some embodiments, the therapeutically effective amount of the EZH2 inhibitor, e.g., tazemetostat

or a pharmaceutically acceptable salt thereof, is administered orally as a capsule or tablet, or as a liquid suspension. In some embodiments, the therapeutically effective amount of the EZH2 inhibitor is administered parenterally, e.g., intravenously. For example, in some embodiments the therapeutically effective amount of the EZH2 inhibitor is administered parenterally as an injectable solution or suspension.

[040] Some embodiments of the methods provided herein include treating lung cancer, e.g., non-small cell lung cancer. Some embodiments of the methods provided herein include treating lung cancer, e.g., non-small cell lung cancer with an EZH2 inhibitor, e.g., tazemetostat or a pharmaceutically acceptable salt thereof, and with one or more second agents (e.g., one, two, three, four, or five different second agents). Some embodiments of the methods provided herein include treating lung cancer, e.g., non-small cell lung cancer with an EZH2 inhibitor, e.g., with tazemetostat or a pharmaceutically acceptable salt thereof and with two or more second agents (e.g., two, three, four, or five different second agents).

[041] Some embodiments of the compounds provided herein include compounds for use in the treatment of lung cancer, e.g., non-small cell lung cancer. Some embodiments of the compounds provided herein include tazemetostat, or a pharmaceutically acceptable salt thereof, and one or more second agents (e.g., one, two, three, four, or five different second agents) for use in the treatment of lung cancer, e.g., non-small cell lung cancer. Some embodiments of the compounds provided herein include tazemetostat, or a pharmaceutically acceptable salt thereof, and two or more second agents (e.g., two, three, four, or five different second agents) for use in the treatment of lung cancer, e.g., non-small cell lung cancer.

[042] Some embodiments of the compounds provided herein include compounds for use as a medicament for the treatment of lung cancer, e.g., non-small cell lung cancer. Some embodiments of the compounds provided herein include tazemetostat, or a pharmaceutically acceptable salt thereof, and one or more second agents (e.g., one, two, three, four, or five different second agents) for use as a medicament for the treatment of lung cancer, e.g., non-small cell lung cancer. Some embodiments of the compounds provided herein include tazemetostat, or a pharmaceutically acceptable salt thereof, and two or more second agents (e.g., two, three, four, or five different second agents) for use as a medicament for the treatment of lung cancer, e.g., non-small cell lung cancer.

[043] Some embodiments of the uses of compounds provided herein include the use of compounds in the manufacture of a medicament for the treatment of lung cancer, e.g., non-small cell lung cancer. Some embodiments of the uses of compounds provided herein include tazemetostat, or a pharmaceutically acceptable salt thereof, and one or more second agents (e.g., one, two, three, four, or five different second agents) in the manufacture of a medicament for the treatment of lung cancer, e.g., non-small cell lung cancer. Some embodiments the uses of compounds provided herein include the use of tazemetostat, or a pharmaceutically acceptable salt thereof, and two or more second agents (e.g., two, three, four, or five different second agents) in the manufacture of a medicament for the treatment of lung cancer, e.g., non-small cell lung cancer.

[044] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise an alkylating agent or an alkylating-like agent, an antineoplastic agent, a mitotic inhibitor, a tubulin polymerization inhibitor, an antimetabolite, a DNA methyltransferase (DNMT) inhibitor, a histone deacetylase (HDAC) inhibitor, a topoisomerase inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, an inhibitor of EGFR and ErbB2, an inhibitor of EGFR and human epidermal growth factor receptor 2 (Her2), an anaplastic lymphoma kinase (ALK) inhibitor, an inhibitor of ALK and ROS1, an inhibitor of ALK and EGFR, cyclin dependent kinase (CDK) 4/6 inhibitor, a mitogen-activated protein kinase (MEK) inhibitor, a BRAF inhibitor, a phosphoinositide 3-kinase (PI3K) inhibitor, a Wee1 inhibitor, a poly (ADP-ribose) polymerase (PARP) inhibitor, a glucocorticoid receptor agonist, a retinoic acid receptor agonist, a CBP/p300 inhibitor, or a combination thereof.

[045] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise an alkylating agent or an alkylating-like agent. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with an alkylating agent or an alkylating-like agent. Exemplary second agents that are alkylating agents or alkylating-like agents include, but are not limited to cisplatin.

[046] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise an antineoplastic agent. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor

(e.g., tazemetostat) is administered in combination with an antineoplastic agent. Exemplary second agents that are antineoplastic agents include, but are not limited to oxaliplatin.

[047] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is non-small cell lung cancer, the one or more second agents comprise a mitotic inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with a mitotic inhibitor. Exemplary second agents that are mitotic inhibitors include, but are not limited to paclitaxel, docetaxel, or vinblastine.

[048] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise a tubulin polymerization inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with a tubulin polymerization inhibitor. Exemplary second agents that are tubulin polymerization inhibitors include, but are not limited to vinorelbine.

[049] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is non-small cell lung cancer, the one or more second agents comprise an antimetabolite. In further embodiments, the one or more second agents comprise an antimetabolite of the folate type. Exemplary second agents that are antimetabolites include, but are not limited to gemcitabine. Exemplary second agents that are antimetabolites of the folate type include, but are not limited to methotrexate, pemetrexed or a combination thereof.

[050] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise a DNA methyltransferase (DNMT) inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with a DNA methyltransferase (DNMT) inhibitor. Exemplary second agents that are DNA methyltransferase (DNMT) inhibitors include, but are not limited to decitabine, azacitidine, or a combination thereof.

[051] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise a histone deacetylase (HDAC) inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with an HDAC inhibitor. Exemplary second agents that are HDAC inhibitors include, but are not limited to, vorinostat.

[052] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise a topoisomerase inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with a topoisomerase inhibitor. Exemplary second agents that are topoisomerase inhibitors include, but are not limited to irinotecan, etoposide, or a combination thereof.

[053] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise an epidermal growth factor receptor (EGFR) inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with an EGFR inhibitor. Exemplary second agents that are EGFR inhibitors include, but are not limited to erlotinib, gefitinib, AZD9291, or a combination thereof.

[054] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise an inhibitor of epidermal growth factor receptor (EGFR) and ErbB2. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with an inhibitor of EGFR and ErbB2. Exemplary second agents that are inhibitors of EGFR and ErbB2 include, but are not limited to lapatinib.

[055] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise an inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (Her2). Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with an inhibitor of EGFR and Her2. Exemplary second agents that are inhibitors of EGFR and Her2 include, but are not limited to afatinib.

[056] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise an anaplastic lymphoma kinase (ALK) inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with an ALK inhibitor. Exemplary second agents that are ALK inhibitors include, but are not limited to ceritinib.

[057] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise an inhibitor of anaplastic lymphoma kinase (ALK) and ROS1. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with an inhibitor of ALK and ROS1. Exemplary second agents that are inhibitors of ALK and ROS1 include, but are not limited to crizotinib.

[058] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise an inhibitor of anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR). Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with an inhibitor ALK and EGFR. Exemplary second agents that are inhibitors of ALK and EGFR include, but are not limited to brigatinib.

[059] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise a cyclin dependent kinase (CDK) 4/6 inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with cyclin dependent kinase (CDK) 4/6 inhibitor. Exemplary second agents that are cyclin dependent kinase (CDK) 4/6 inhibitors include, but are not limited to abemaciclib, palbociclib, ribociclib, or a combination thereof.

[060] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise a mitogen-activated protein kinase (MEK) inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with a MEK inhibitor. Exemplary second agents that are MEK inhibitors include, but are not limited to trametinib, selumetinib, or a combination thereof.

[061] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise a BRAF inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with a BRAF inhibitor. Exemplary second agents that are BRAF inhibitors include, but are not limited to vemurafenib.

[062] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise a phosphatidylinositol 3-kinase (PI3K) inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with a PI3K inhibitor. Exemplary second agents that are PI3K inhibitors include, but are not limited to, pictilisib or BKM-120.

[063] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise a Wee1 inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with a Wee1 inhibitor. Exemplary second agents that are Wee1 inhibitors include, but are not limited to MK-1775.

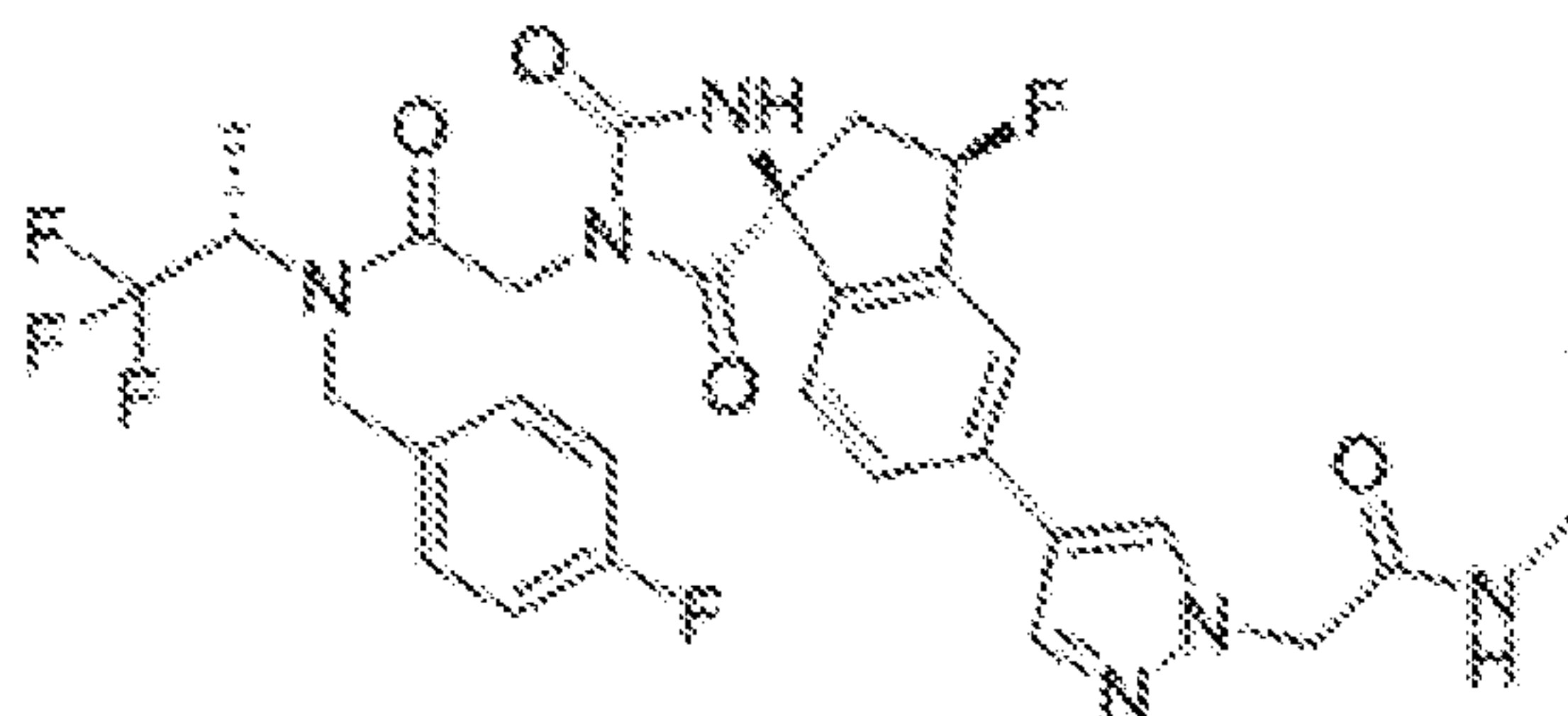
[064] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise a poly (ADP-ribose) polymerase (PARP) inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with a PARP inhibitor. Exemplary second agents that are PARP inhibitors include, but are not limited to veliparib.

[065] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise a glucocorticoid receptor agonist. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with a glucocorticoid receptor agonist. Exemplary second agents that are glucocorticoid receptor agonists include, but are not limited to prednisolone.

[066] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is lung cancer, e.g., non-small cell lung cancer, the one or more second agents comprise a retinoic acid receptor agonist. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with a retinoic acid receptor agonist. Exemplary second agents that are retinoic acid receptor agonists include, but are not limited to ATRA.

[067] In certain embodiments of the disclosure, and particularly those embodiments in which the cancer is non-small cell lung cancer, the one or more second agents may comprise a CBP/p300

inhibitor. Accordingly, in some embodiments of the disclosure, the EZH2 inhibitor (e.g., tazemetostat) is administered in combination with a CBP/p300 inhibitor. Exemplary second agents that are CBP/p300 inhibitor receptor agonists include, but are not limited to Compound H below.



(Compound H),

or a pharmaceutically acceptable salt thereof.

[068] Compound H, (N-(4-fluorobenzyl)-2-[(3'R,4S)-3'-fluoro-5'-{1-[2-(methylamino)-2-oxoethyl]-1H-pyrazol-4-yl}-2,5-dioxo-2',3'-dihydro-1H-spiro[imidazolidine-4,1'-inden]-1-yl]-N-[(2S)-1,1,1-trifluoropropan-2-yl]acetamide, is described in WO2016/044770, the entire contents of which is incorporated herein by reference.

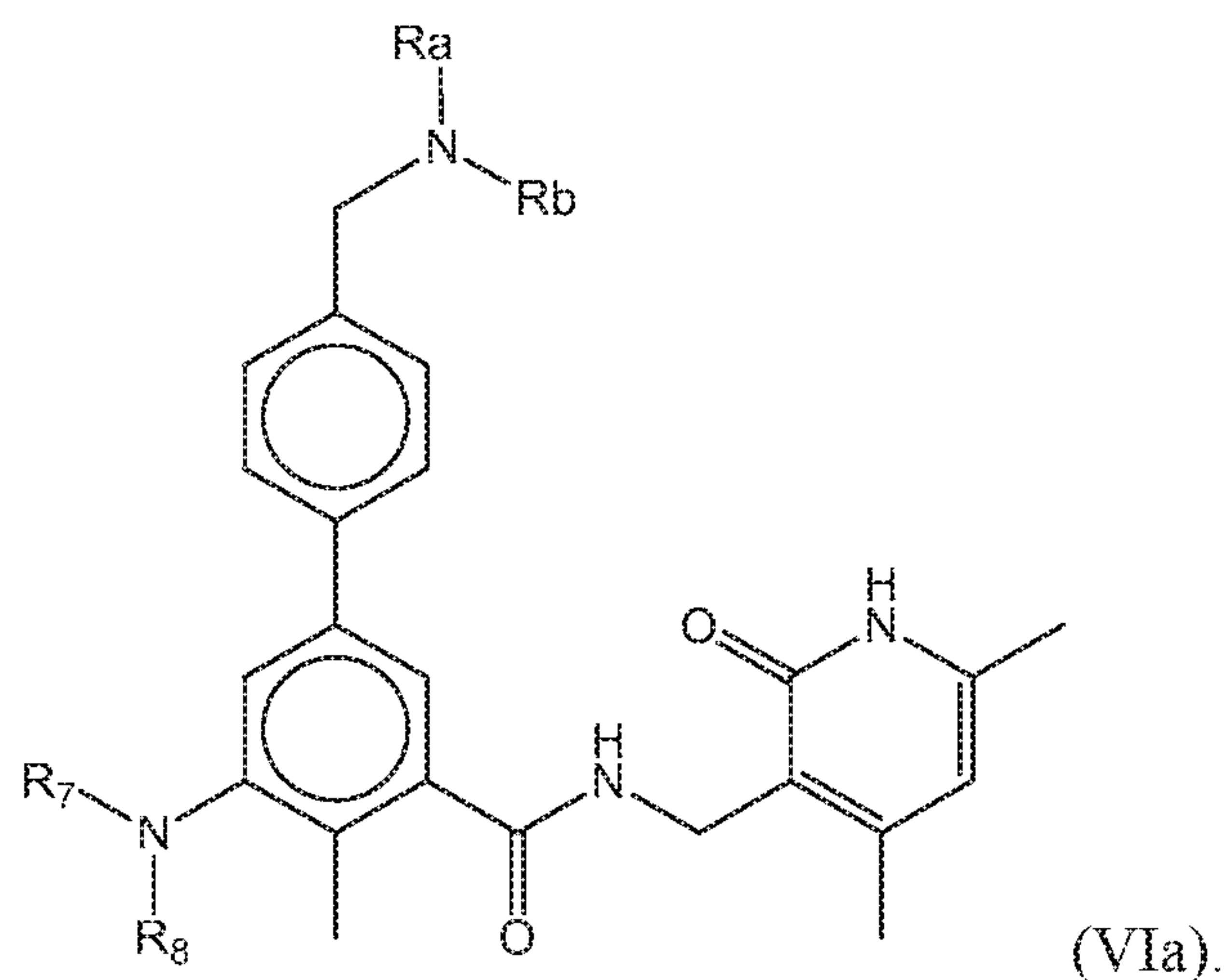
[069] In some embodiments, second anti-cancer agents of the disclosure are administered at a dosage of 0.01 mg/kg per day to about 1000 mg/kg per day.

[070] In some embodiments, the therapeutically effective amount of the EZH2 inhibitor and the second agent are administered simultaneously. Alternatively, the therapeutically effective amount of the EZH2 inhibitor and the one or more second agents are administered sequentially. In certain embodiments, the EZH2 inhibitor is administered prior to the one or more second agents. In certain embodiments, the one or more second agents are administered prior to the EZH2 inhibitor.

[071] In some embodiments where an EZH2 inhibitor (e.g., tazemetostat) and one or more second agents are administered in combination, the EZH2 inhibitor and the second agent are administered simultaneously. In some embodiments where an EZH2 inhibitor (e.g., tazemetostat) and one or more second agents are administered in combination, the EZH2 inhibitor and the second agent are administered sequentially. In some embodiments where an EZH2 inhibitor (e.g., tazemetostat) and one or more second agents are administered in combination, the EZH2 inhibitor is administered prior to the one or more second agents. In some embodiments where an EZH2 inhibitor (e.g., tazemetostat) and one or more second agents are administered in combination, the one or more second agents are administered prior to the EZH2 inhibitor.

[072] In some embodiments where an EZH2 inhibitor (e.g., tazemetostat) and one or more second agents are administered in combination, the therapeutically effective amount of the EZH2 inhibitor, e.g., of tazemetostat or a pharmaceutically acceptable salt thereof, and the second agent are administered simultaneously. Alternatively, the therapeutically effective amount of the EZH2 inhibitor, e.g., tazemetostat or a pharmaceutically acceptable salt thereof, and the one or more second agents are administered sequentially. In certain embodiments, the EZH2 inhibitor, e.g., tazemetostat or a pharmaceutically acceptable salt thereof, is administered prior to the one or more second agents. In certain embodiments, the one or more second agents are administered prior to the EZH2 inhibitor, e.g., tazemetostat or a pharmaceutically acceptable salt thereof.

[073] In certain embodiments of the disclosure, the EZH2 inhibitor is a compound of Formula (VIa) below.



[074] In some embodiments, compounds of Formula (VIa) can include one or more of the following features:

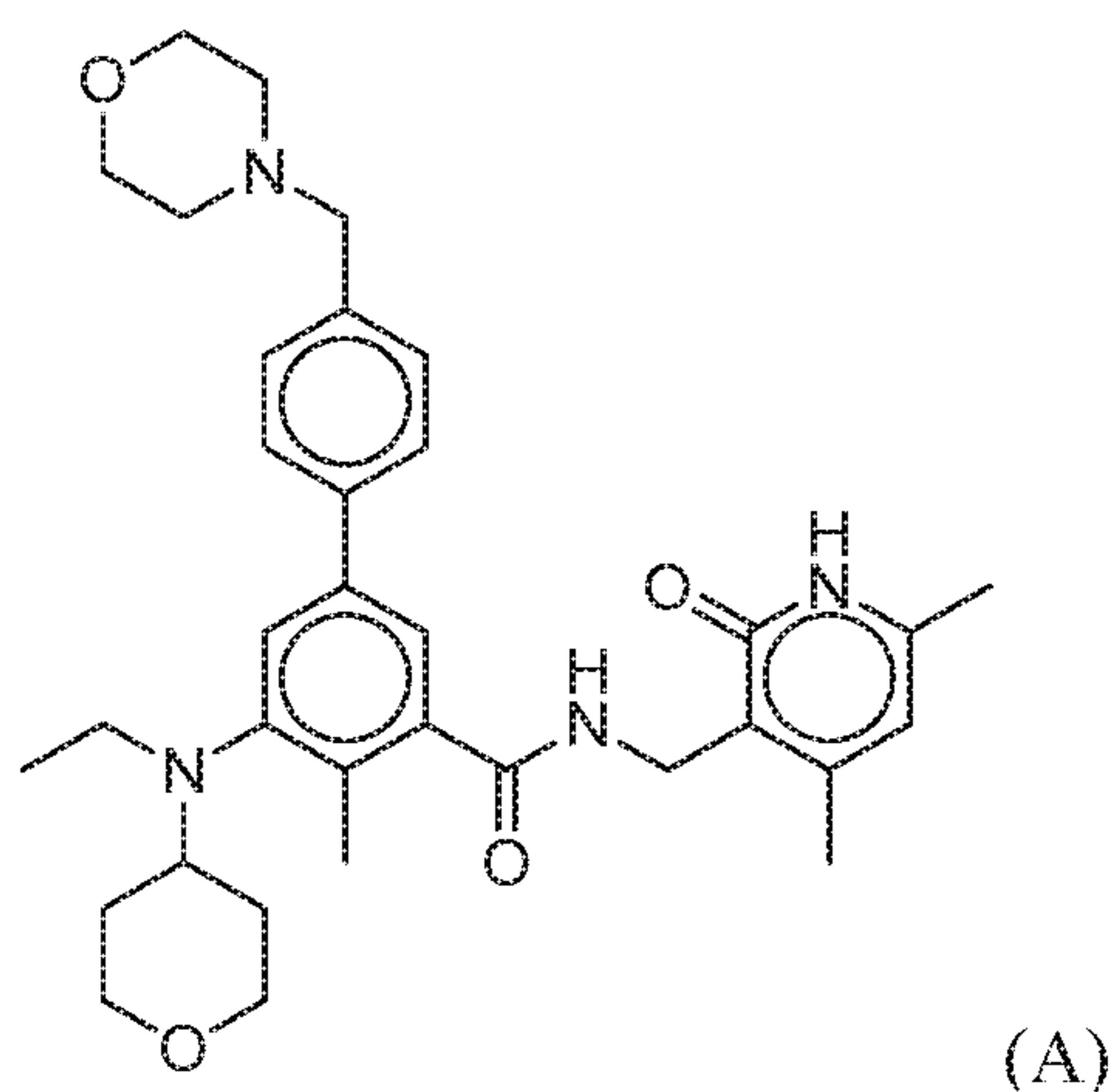
[075] Each of R_a and R_b , independently is H or C_1 - C_6 alkyl.

[076] R_a and R_b , together with the N atom to which they are attached, is a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatom, the C_1 - C_6 alkyl and the 4 to 12-membered (e.g., 4 to 7-membered) heterocycloalkyl ring being optionally substituted with one or more $-Q_3-T_3$.

[077] Q_3 is a bond or unsubstituted or substituted C_1 - C_3 alkyl linker.

[078] T_3 is H, halo, 4 to 7-membered heterocycloalkyl, C_1 - C_3 alkyl, OR_d , $COOR_d$, $-S(O)_2R_d$, or $-NR_dR_e$, each of R_d and R_e independently being H or C_1 - C_6 alkyl.

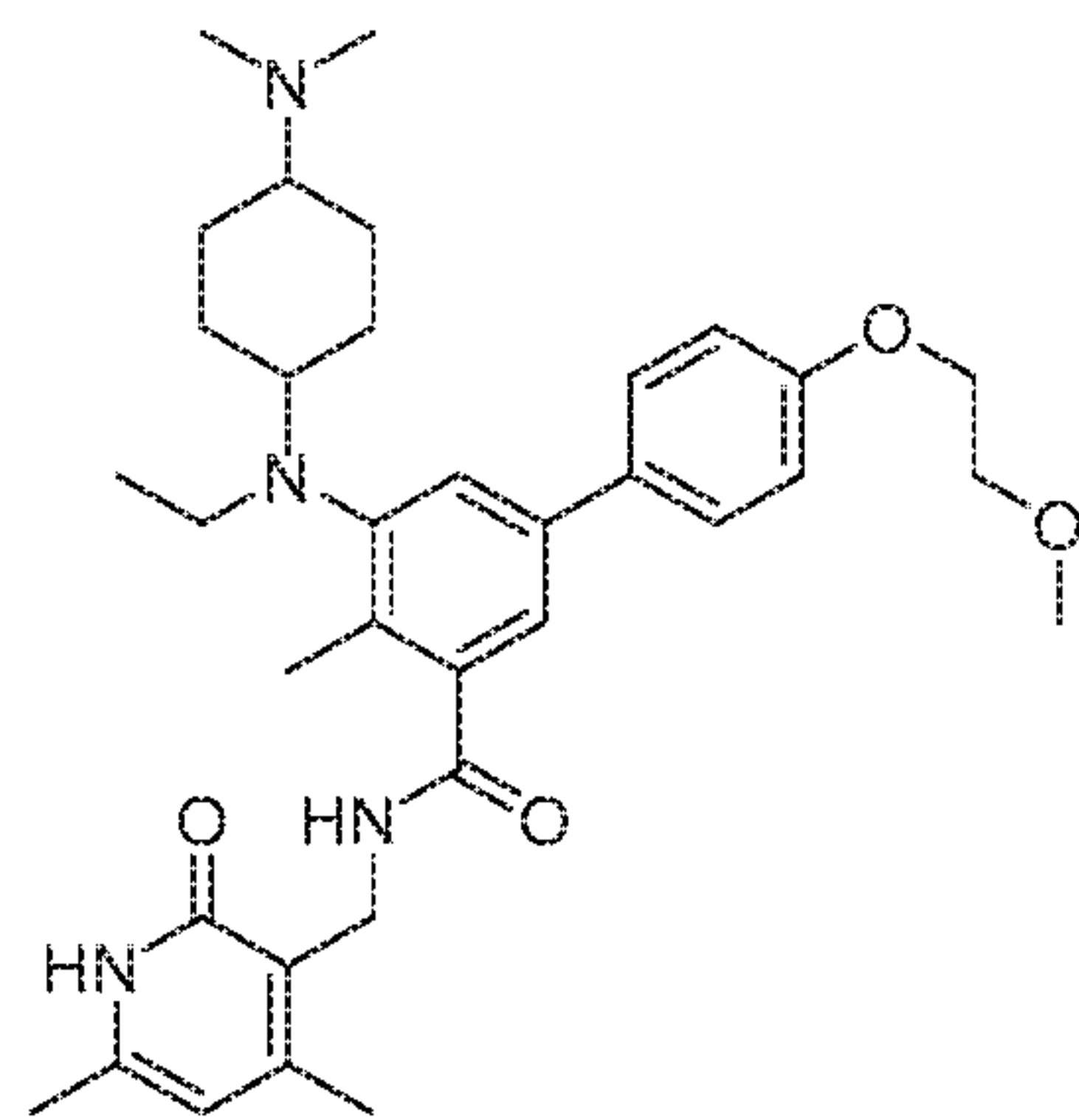
- [079] R₇ is C₁-C₆ alkyl, C₃-C₈ cycloalkyl or 4 to 12-membered (e.g., 4 to 7-membered) heterocycloalkyl, each optionally substituted with one or more -Q₅-T₅. For example, R₇ is not H.
- [080] R₇ is 4 to 7-membered heterocycloalkyl optionally substituted with one or more -Q₅-T₅.
- [081] R₇ is piperidinyl, tetrahydropyran, cyclopentyl, or cyclohexyl, each optionally substituted with one -Q₅-T₅.
- [082] T₅ is H, halo, C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, C₆-C₁₀ aryl, or 4 to 12-membered (e.g., 4 to 7-membered) heterocycloalkyl.
- [083] Q₅ is a bond and T₅ is C₁-C₆ alkyl, C₃-C₈ cycloalkyl, or 4 to 12-membered (e.g., 4 to 7-membered) heterocycloalkyl.
- [084] Q₅ is CO, S(O)₂, or NHC(O); and T₅ is C₁-C₆ alkyl, C₁-C₆ alkoxy, C₃-C₈ cycloalkyl, or 4 to 12-membered (e.g., 4 to 7-membered) heterocycloalkyl.
- [085] Q₅ is C₁-C₃ alkyl linker and T₅ is H or C₆-C₁₀ aryl.
- [086] Q₅ is C₁-C₃ alkyl linker and T₅ is C₃-C₈ cycloalkyl, 4 to 7-membered heterocycloalkyl, or S(O)_qR_q.
- [087] R₇ is cyclopentyl or cyclohexyl, each optionally substituted with one -Q₅-T₅.
- [088] Q₅ is NHC(O) and T₅ is C₁-C₆ alkyl or C₁-C₆ alkoxy.
- [089] R₇ is isopropyl.
- [090] Each of R₂ and R₄, independently is H or C₁-C₆ alkyl optionally substituted with amino, mono-C₁-C₆ alkylamino, di-C₁-C₆ alkylamino, or C₆-C₁₀ aryl.
- [091] R₈ is H, methyl, or ethyl.
- [092] R₈ is methyl.
- [093] R₈ is ethyl.
- [094] R₈ is 4 to 7-heterocycloalkyl, e.g., tetrahydropyran.
- [095] In certain embodiments of the disclosure, the compound of Formula (VIa) is tazemetostat (also referred to herein as compound (A), and also known as Compound 44, EPZ-6438, and E7438) having the following formula:



(A)

or a pharmaceutically acceptable salt or solvate thereof.

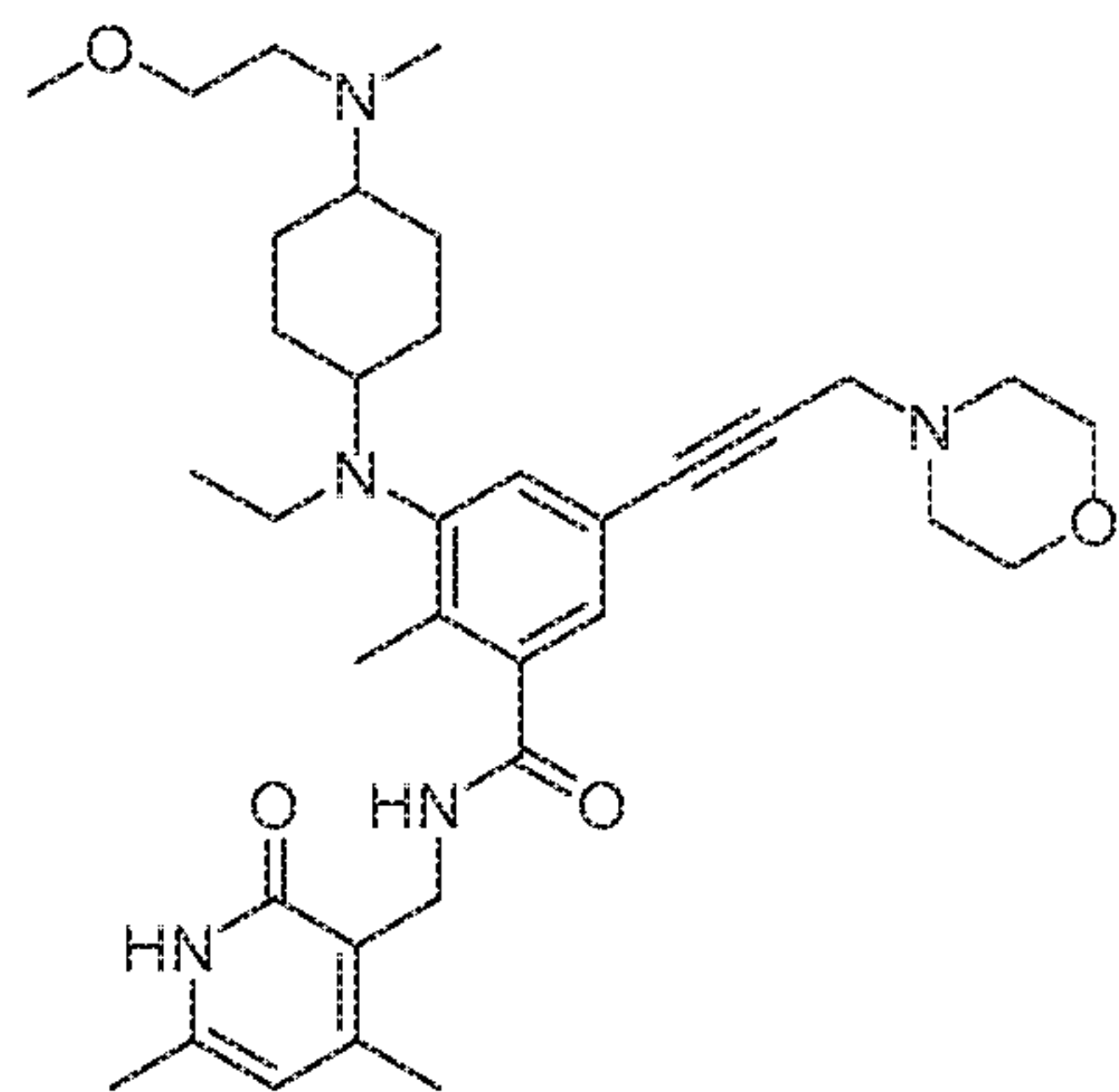
[096] In certain embodiments of the methods of the disclosure, the EZH2 inhibitor is Compound B having the following formula:



(B), stereoisomers thereof, or pharmaceutically acceptable salts or

solvates thereof.

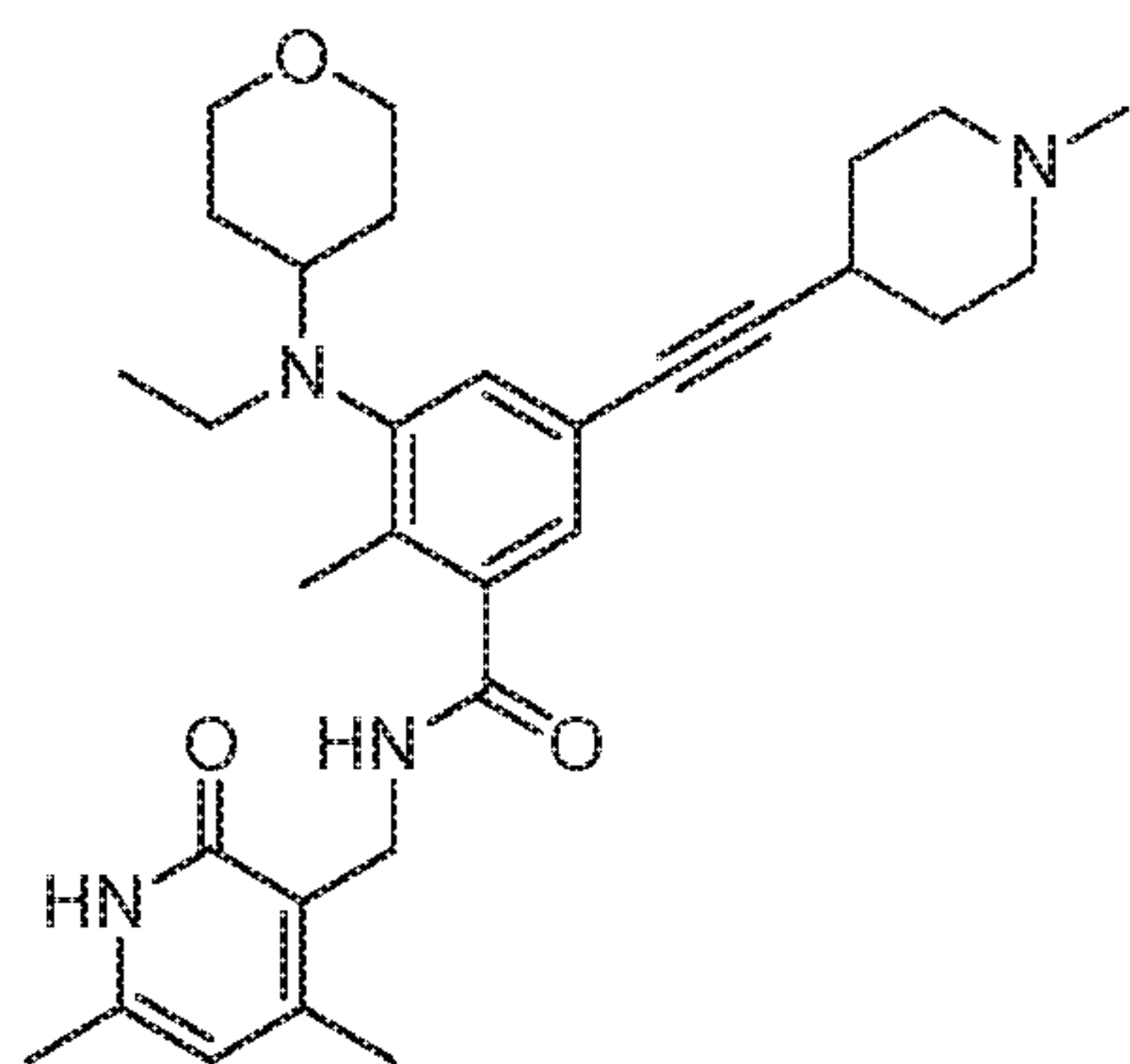
[097] In certain embodiments of the disclosure, the EZH2 inhibitor is Compound C (also known as EPZ011989) having the following formula:



(C), stereoisomers thereof, or pharmaceutically acceptable salts or

solvates thereof.

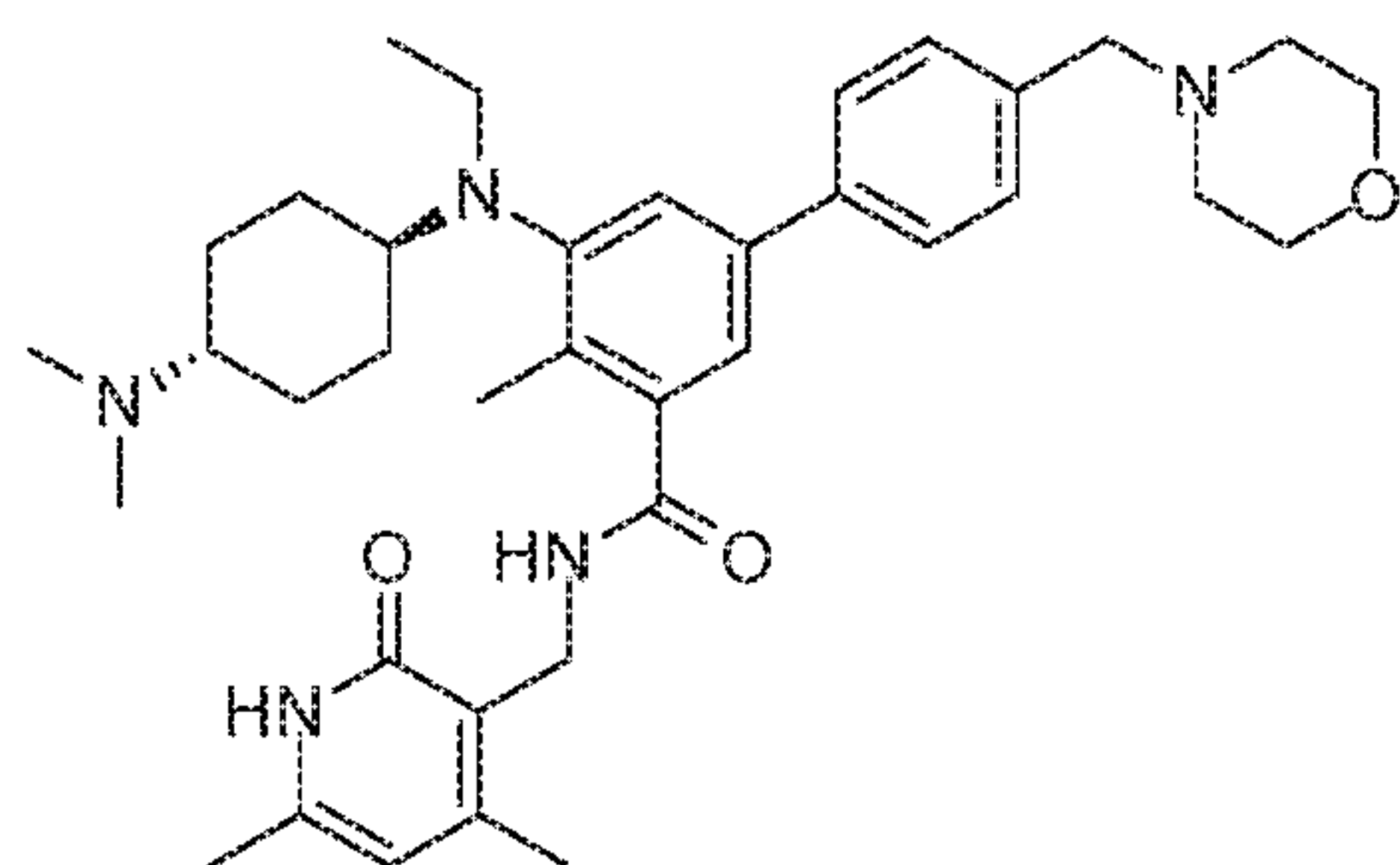
[098] In certain embodiments of the disclosure, the EZH2 inhibitor is Compound D having the following formula:



(D), stereoisomers thereof, or pharmaceutically acceptable salts or

solvates thereof.

[099] In certain embodiments of the disclosure, the EZH2 inhibitor is Compound E having the following formula:



(E), stereoisomers thereof, or pharmaceutically acceptable salts

or solvates thereof.

[0100] Therapeutic agents of the disclosure (including a first and/or one or more second agents) may be administered by any appropriate route including, but not limited to, enteral routes, and parenteral routes, e.g., oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes.

[0101] The methods of, or compounds or medicaments for use in, combination therapy featured in the disclosure may result in a synergistic effect, wherein the effect of a combination of therapeutic agents (e.g., an EZH2 inhibitor, e.g., tazemetostat or a pharmaceutically acceptable salt thereof, and one or more second anti-cancer agents) is greater than the sum of the effects resulting from administration of any of the therapeutic agents as single agents. A synergistic effect may also be an effect that cannot be achieved by administration of any of the therapeutic agents as single agents. The synergistic effect may include, but is not limited to, an effect of treating cancer, e.g., non-small cell lung cancer, by reducing tumor size, reducing the number or frequency of malignant cells in a subject or a sample obtained from a subject, inhibiting tumor growth, inhibiting growth, survival, or proliferation of malignant cells, or increasing survival of the

subject. The synergistic effect may also include reducing cancer cell viability, inducing cancer cell death, and inhibiting or delaying cancer cell growth.

[0102] In some embodiments, a subject as provided by the disclosure has cancer, including, but not limited to, non-small cell lung cancer. The subject may be of any species; however, subjects are preferably human. In some embodiments, the subject may have cancer characterized by any stage, including, but not limited to, stage 0, I, II, III, and IV. In some embodiments, the subject's cancer is a primary or secondary tumor. The subject's cancer may be metastatic. The subject's cancer may have metastasized to a secondary location from another primary location. In some embodiments, the subject's non-small cell lung cancer may migrate, or may have migrated, from one region of the bone marrow to another.

[0103] In some embodiments, a subject as provided herein, e.g., a subject having non-small cell lung cancer, may express a wild type EZH2.

[0104] In some embodiments, a subject as provided herein, e.g., a subject having non-small cell lung cancer, may express a mutant EZH2. For example, a mutant EZH2 comprises one or more mutations, wherein the mutation is a substitution, a point mutation, a nonsense mutation, a missense mutation, a deletion, or an insertion. A mutant EZH2 of the disclosure may comprise a mutation in the substrate pocket domain. A mutant EZH2 may have a substitution at amino acid Y641. In some embodiments, the mutant EZH2 has one of the following mutations: substitution of phenylalanine (F) for the wild type residue tyrosine (Y) at amino acid position 641 (Y641F); a substitution of histidine (H) for the wild type residue tyrosine (Y) at amino acid position 641 (Y641H); a substitution of asparagine (N) for the wild type residue tyrosine (Y) at amino acid position 641 (Y641N); a substitution of serine (S) for the wild type residue tyrosine (Y) at amino acid position 641 (Y641S); and a substitution of cysteine (C) for the wild type residue tyrosine (Y) at amino acid position 641 (Y641C).

[0105] In some embodiments, of the EZH2 mutation may include, but is not limited to: a substitution of glycine (G) for the wild type residue alanine (A) at amino acid position 677 (A677G); a substitution of valine (V) for the wild type residue alanine (A) at amino acid position 687 (A687V); a substitution of methionine (M) for the wild type residue valine (V) at amino acid position 674 (V674M); a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 685 (R685H); a substitution of cysteine (C) for the wild type residue arginine (R) at amino acid position 685 (R685C); a substitution of serine (S) for the wild type residue

asparagine (N) at amino acid position 322 (N322S), a substitution of glutamine (Q) for the wild type residue arginine (R) at amino acid position 288 (R288Q), a substitution of isoleucine (I) for the wild type residue threonine (T) at amino acid position 573 (T573I), a substitution of glutamic acid (E) for the wild type residue aspartic acid (D) at amino acid position 664 (D664E), a substitution of glutamine (Q) for the wild type residue arginine (R) at amino acid position 458 (R458Q), a substitution of lysine (K) for the wild type residue glutamic acid (E) at amino acid position 249 (E249K), a substitution of cysteine (C) for the wild type residue arginine (R) at amino acid position 684 (R684C), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 628 (R628H), a substitution of histidine (H) for the wild type residue glutamine (Q) at amino acid position 501 (Q501H), a substitution of asparagine (N) for the wild type residue aspartic acid (D) at amino acid position 192 (D192N), a substitution of valine (V) for the wild type residue aspartic acid (D) at amino acid position 664 (D664V), a substitution of leucine (L) for the wild type residue valine (V) at amino acid position 704 (V704L), a substitution of serine (S) for the wild type residue proline (P) at amino acid position 132 (P132S), a substitution of lysine (K) for the wild type residue glutamic acid (E) at amino acid position 669 (E669K), a substitution of threonine (T) for the wild type residue alanine (A) at amino acid position 255 (A255T), a substitution of valine (V) for the wild type residue glutamic acid (E) at amino acid position 726 (E726V), a substitution of tyrosine (Y) for the wild type residue cysteine (C) at amino acid position 571 (C571Y), a substitution of cysteine (C) for the wild type residue phenylalanine (F) at amino acid position 145 (F145C), a substitution of threonine (T) for the wild type residue asparagine (N) at amino acid position 693 (N693T), a substitution of serine (S) for the wild type residue phenylalanine (F) at amino acid position 145 (F145S), a substitution of histidine (H) for the wild type residue glutamine (Q) at amino acid position 109 (Q109H), a substitution of cysteine (C) for the wild type residue phenylalanine (F) at amino acid position 622 (F622C), a substitution of arginine (R) for the wild type residue glycine (G) at amino acid position 135 (G135R), a substitution of glutamine (Q) for the wild type residue arginine (R) at amino acid position 168 (R168Q), a substitution of arginine (R) for the wild type residue glycine (G) at amino acid position 159 (G159R), a substitution of cysteine (C) for the wild type residue arginine (R) at amino acid position 310 (R310C), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 561 (R561H), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 634 (R634H), a substitution of arginine (R) for the wild type

residue glycine (G) at amino acid position 660 (G660R), a substitution of cysteine (C) for the wild type residue tyrosine (Y) at amino acid position 181 (Y181C), a substitution of arginine (R) for the wild type residue histidine (H) at amino acid position 297 (H297R), a substitution of serine (S) for the wild type residue cysteine (C) at amino acid position 612 (C612S), a substitution of tyrosine (Y) for the wild type residue histidine (H) at amino acid position 694 (H694Y), a substitution of alanine (A) for the wild type residue aspartic acid (D) at amino acid position 664 (D664A), a substitution of threonine (T) for the wild type residue isoleucine (I) at amino acid position 150 (I150T), a substitution of arginine (R) for the wild type residue isoleucine (I) at amino acid position 264 (I264R), a substitution of leucine (L) for the wild type residue proline (P) at amino acid position 636 (P636L), a substitution of threonine (T) for the wild type residue isoleucine (I) at amino acid position 713 (I713T), a substitution of proline (P) for the wild type residue glutamine (Q) at amino acid position 501 (Q501P), a substitution of glutamine (Q) for the wild type residue lysine (K) at amino acid position 243 (K243Q), a substitution of aspartic acid (D) for the wild type residue glutamic acid (E) at amino acid position 130 (E130D), a substitution of glycine (G) for the wild type residue arginine (R) at amino acid position 509 (R509G), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 566 (R566H), a substitution of histidine (H) for the wild type residue aspartic acid (D) at amino acid position 677 (D677H), a substitution of asparagine (N) for the wild type residue lysine (K) at amino acid position 466 (K466N), a substitution of histidine (H) for the wild type residue arginine (R) at amino acid position 78 (R78H), a substitution of methionine (M) for the wild type residue lysine (K) at amino acid position 1 (K6M), a substitution of leucine (L) for the wild type residue serine (S) at amino acid position 538 (S538L), a substitution of glutamine (Q) for the wild type residue leucine (L) at amino acid position 149 (L149Q), a substitution of valine (V) for the wild type residue leucine (L) at amino acid position 252 (L252V), a substitution of valine (V) for the wild type residue leucine (L) at amino acid position 674 (L674V), a substitution of valine (V) for the wild type residue alanine (A) at amino acid position 656 (A656V), a substitution of aspartic acid (D) for the wild type residue alanine (A) at amino acid position 731 (Y731D), a substitution of threonine (T) for the wild type residue alanine (A) at amino acid position 345 (A345T), a substitution of aspartic acid (D) for the wild type residue alanine (A) at amino acid position 244 (Y244D), a substitution of tryptophan (W) for the wild type residue cysteine (C) at amino acid position 576 (C576W), a substitution of lysine (K) for the wild type residue asparagine (N) at

amino acid position 640 (N640K), a substitution of lysine (K) for the wild type residue asparagine (N) at amino acid position 675 (N675K), a substitution of tyrosine (Y) for the wild type residue aspartic acid (D) at amino acid position 579 (D579Y), a substitution of isoleucine (I) for the wild type residue asparagine (N) at amino acid position 693 (N693I), and/or a substitution of lysine (K) for the wild type residue asparagine (N) at amino acid position 693 (N693K).

[0106] Other mutations of EZH2 can include: a frameshift at amino acid position 730, 391, 461, 441, 235, 254, 564, 662, 715, 405, 685, 64, 73, 656, 718, 374, 592, 505, 730, or 363 or the corresponding nucleotide position of the nucleic acid sequence; a deletion of glutamic acid (E) and leucine (L) at amino acid positions 148 and 149 or a nonsense mutation at amino acid position 733, 25, 317, 62, 553, 328, 58, 207, 123, 63, 137, or 60.

[0107] Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. In the specification, the singular forms also include the plural unless the context clearly dictates otherwise. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the disclosure, some exemplary, non-limiting suitable methods and materials are described below. All publications, patent applications, patents and other references mentioned herein are incorporated by reference. The references cited herein are not admitted to be prior art to the claimed invention. In the case of conflict, the present specification, including definitions, will control. In addition, the materials, methods and examples are illustrative only and are not intended to be limiting.

[0108] Other features and advantages of the invention will be apparent from the following detailed description and claims.

BRIEF DESCRIPTIONS OF FIGURES

[0109] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication with color drawing(s) will be provided by the Office upon request and payment of the necessary fee.

[0110] The above and further features will be more clearly appreciated from the following detailed description when taken in conjunction with the accompanying drawings.

[0111] **Figure 1** is a schematic diagram outlining the experimental procedure of Example 1.

[0112] **Figure 2** is a set of graphs illustrating synergy of decitabine with an EZH2 inhibitor (tazemetostat) in A427 cells. Panel A is the dose matrix for the in vitro assay. Panel B shows the Loewe excess matrix for the combination of tazemetostat with decitabine. Panel C shows the isobologram for the combination of tazemetostat with decitabine.

[0113] **Figure 3** is a set of graphs illustrating synergy of trametinib with an EZH2 inhibitor (tazemetostat) in A427 cells. Panel A is the dose matrix for the in vitro assay. Panel B shows the Loewe excess matrix for the combination of tazemetostat with trametinib. Panel C shows the isobologram for the combination of tazemetostat with trametinib.

[0114] **Figure 4** is a set of graphs illustrating synergy of palbociclib with an EZH2 inhibitor (tazemetostat) in A427 cells. Panel A is the dose matrix for the in vitro assay. Panel B shows the Loewe excess matrix for the combination of tazemetostat with palbociclib. Panel C shows the isobologram for the combination of tazemetostat with palbociclib.

[0115] **Figure 5** is a set of graphs illustrating synergy of ceritinib with an EZH2 inhibitor (tazemetostat) in A427 cells. Panel A is the dose matrix for the in vitro assay. Panel B shows the Loewe excess matrix for the combination of tazemetostat with ceritinib. Panel C shows the isobologram for the combination of tazemetostat with ceritinib.

[0116] **Figure 6** is an illustration of the EZH2 protein structure.

DETAILED DESCRIPTION

[0117] Some aspects of this disclosure provide methods, strategies, compositions, and combinations for combination therapy for the treatment of cancer, e.g., non-small cell lung cancer, in a subject, comprising administering an EZH2 inhibitor and a second anti-cancer agent to the subject. In some embodiments, the EZH2 inhibitor is a compound provided herein. In some embodiments, the EZH2 inhibitor is tazemetostat or a pharmaceutically acceptable salt thereof. In some embodiments, the combination of the EZH2 inhibitor synergizes with the second anti-cancer agent to achieve a desired clinical effect.

EZH2

[0118] EZH2 is a histone methyltransferase that is the catalytic subunit of the PRC2 complex which catalyzes the mono- through tri-methylation of lysine 27 on histone H3 (H3-K27). Histone H3-K27 trimethylation is a mechanism for suppressing transcription of specific genes that are

proximal to the site of histone modification. This trimethylation is known to be a cancer marker with altered expression in cancer, such as prostate cancer (see, e.g., U.S. Patent Application Publication No. 2003/0175736; incorporated herein by reference in its entirety). Other studies provided evidence for a functional link between dysregulated EZH2 expression, transcriptional repression, and neoplastic transformation. Varambally et al. (2002) *Nature* 419(6907):624-9 Klee et al. (2003) *Proc Natl Acad Sci USA* 100(20):11606-11.

[0119] Human EZH2 nucleic acids and polypeptides have previously been described. See, e.g., Chen et al. (1996) *Genomics* 38:30-7 [746 amino acids]; Swiss-Prot Accession No. Q15910 [746 amino acids]; GenBank Accession Nos. NM_004456 and NP_004447 (isoform a [751 amino acids]); and GenBank Accession Nos. NM_152998 and NP_694543 (isoform b [707 amino acids]), each of which is incorporated herein by reference in its entirety.

[0120] Also for purposes of this application, a Y641 mutant of human EZH2, and, equivalently, a Y641 mutant of EZH2, is to be understood to refer to a human EZH2 in which the amino acid residue corresponding to Y641 of wild-type human EZH2 is substituted by an amino acid residue other than tyrosine.

[0121] In some embodiments the amino acid sequence of a Y641 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of a single amino acid residue corresponding to Y641 of wild-type human EZH2 by an amino acid residue other than tyrosine.

[0122] In some embodiments the amino acid sequence of a Y641 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of phenylalanine (F) for the single amino acid residue corresponding to Y641 of wild-type human EZH2. The Y641 mutant of EZH2 according to these embodiments is referred to herein as a Y641F mutant or, equivalently, Y641F.

[0123] In some embodiments the amino acid sequence of a Y641 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of histidine (H) for the single amino acid residue corresponding to Y641 of wild-type human EZH2. The Y641 mutant of EZH2 according to these embodiments is referred to herein as a Y641H mutant or, equivalently, Y641H.

[0124] In some embodiments the amino acid sequence of a Y641 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of asparagine (N) for the single amino acid residue corresponding to Y641 of wild-type human EZH2. The Y641 mutant of EZH2 according to these embodiments is referred to herein as a Y641N mutant or, equivalently,

Y641N.

[0125] In some embodiments the amino acid sequence of a Y641 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of serine (S) for the single amino acid residue corresponding to Y641 of wild-type human EZH2. The Y641 mutant of EZH2 according to these embodiments is referred to herein as a Y641S mutant or, equivalently, Y641S.

[0126] In some embodiments the amino acid sequence of a Y641 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of cysteine (C) for the single amino acid residue corresponding to Y641 of wild-type human EZH2. The Y641 mutant of EZH2 according to these embodiments is referred to herein as a Y641C mutant or, equivalently, Y641C.

[0127] In some embodiments the amino acid sequence of a A677 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of a non-alanine amino acid, preferably glycine (G) for the single amino acid residue corresponding to A677 of wild-type human EZH2. The A677 mutant of EZH2 according to these embodiments is referred to herein as an A677 mutant, and preferably an A677G mutant or, equivalently, A677G.

[0128] In some embodiments the amino acid sequence of a A687 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of a non-alanine amino acid, preferably valine (V) for the single amino acid residue corresponding to A687 of wild-type human EZH2. The A687 mutant of EZH2 according to these embodiments is referred to herein as an A687 mutant and preferably an A687V mutant or, equivalently, A687V.

[0129] In some embodiments the amino acid sequence of a R685 mutant of EZH2 differs from the amino acid sequence of wild-type human EZH2 only by substitution of a non-arginine amino acid, preferably histidine (H) or cysteine (C) for the single amino acid residue corresponding to R685 of wild-type human EZH2. The R685 mutant of EZH2 according to these embodiments is referred to herein as an R685 mutant and preferably an R685C mutant or an R685H mutant or, equivalently, R685H or R685C.

[0130] Cells heterozygous for EZH2 would be expected to display a malignant phenotype due to the efficient formation of H3-K27me1 by the WT enzyme and the efficient, subsequent transition of this progenitor species to H3-K27me2, and, especially, H3-K27me3, by the mutant enzyme form(s).

[0131] Previous results point to dependency on enzymatic coupling between enzymes that perform H3-K27 mono-methylation and certain mutant forms of EZH2 for pathogenesis in

follicular lymphoma and diffuse large B-cell lymphoma. For example, cells expressing Y641 mutant EZH2 may be more sensitive to small molecule EZH2 inhibitors than cells expressing WT EZH2. Specifically, cells expressing Y641 mutant EZH2 show reduced growing, dividing or proliferation, or even undergo apoptosis or necrosis after the treatment of EZH2 inhibitors. In contrast, cells expressing WT EZH2 are not responsive to the anti-proliferative effect of the EZH2 inhibitors (U.S. Patent Application No. 13/230,703 (now U.S. Pat. 8,895,245); incorporated herein by reference in its entirety.)

[0132] Some aspects of the disclosure relate to treating or alleviating a symptom of cancer or precancerous condition in a subject by administering to a subject expressing either a wild type or a mutant EZH2 a therapeutically effective amount of an EZH2 inhibitor as described herein, e.g., a compound of Formulae (I)-(VIa) (preferably tazemetostat) in combination with a second anti-cancer agent suitable to be administered together simultaneously, sequentially, or in alternation.

[0133] Some aspects of the invention relate to inhibiting in a subject conversion of H3-K27 to trimethylated H3-K27. The inhibition can involve inhibiting in a subject conversion of unmethylated H3-K27 to monomethylated H3-K27, conversion of monomethylated H3-K27 to dimethylated H3-K27, conversion of dimethylated H3-K27 to trimethylated H3-K27, or any combination thereof, including, for example, conversion of monomethylated H3-K27 to dimethylated H3-K27 and conversion of dimethylated H3-K27 to trimethylated H3-K27. As used herein, unmethylated H3-K27 refers to histone H3 with no methyl group covalently linked to the amino group of lysine 27. As used herein, monomethylated H3-K27 refers to histone H3 with a single methyl group covalently linked to the amino group of lysine 27. Monomethylated H3-K27 is also referred to herein as H3-K27me1. As used herein, dimethylated H3-K27 refers to histone H3 with two methyl groups covalently linked to the amino group of lysine 27. Dimethylated H3-K27 is also referred to herein as H3-K27me2. As used herein, trimethylated H3-K27 refers to histone H3 with three methyl groups covalently linked to the amino group of lysine 27. Trimethylated H3-K27 is also referred to herein as H3-K27me3.

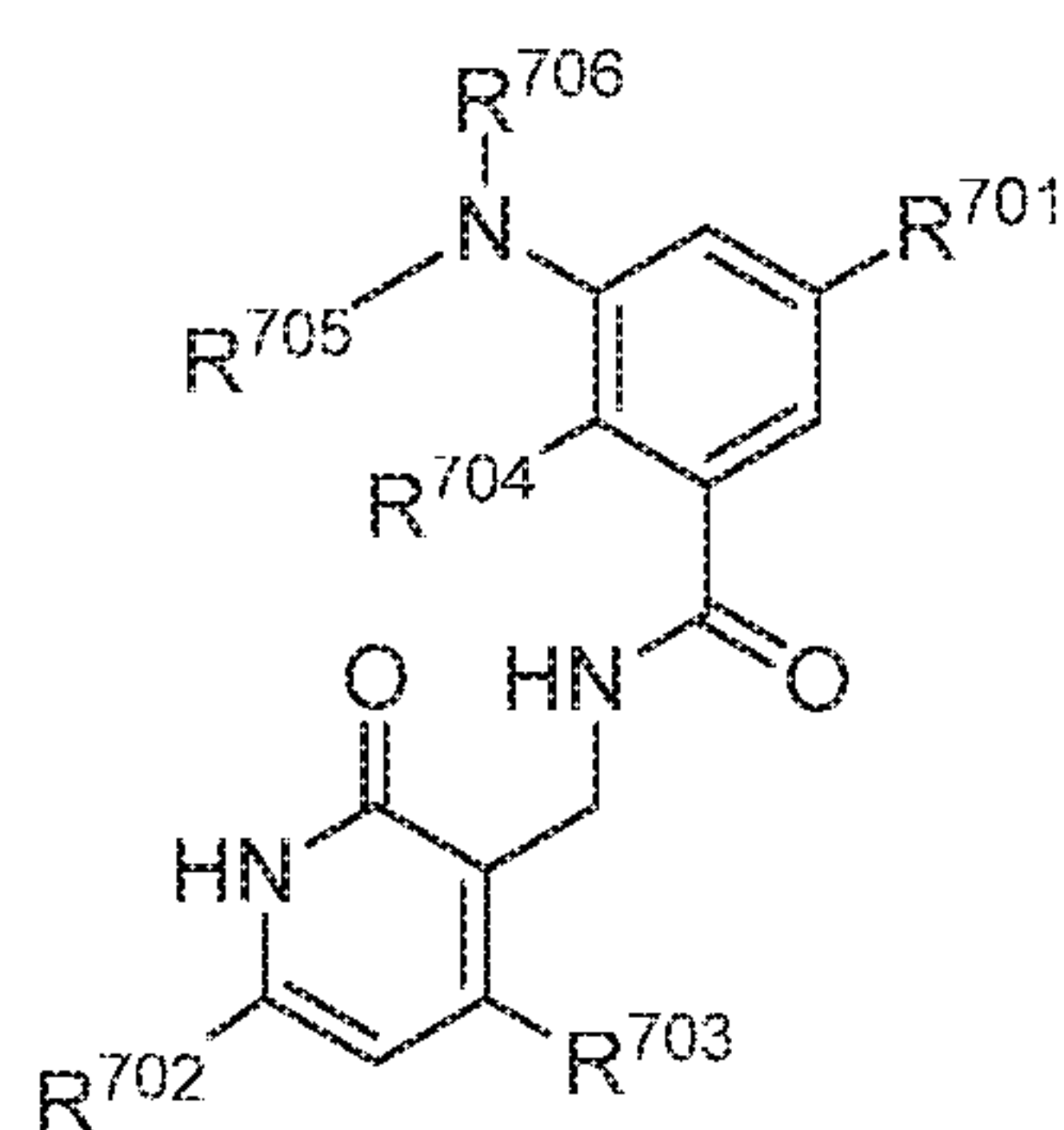
[0134] Histone H3 is a 136 amino acid long protein, the sequence of which is known. See, for example, GenBank Accession No. CAB02546, the content of which is incorporated herein by reference. As disclosed further herein, in addition to full-length histone H3, peptide fragments of histone H3 comprising the lysine residue corresponding to K27 of full-length histone H3 can be used as substrate for EZH2 (and likewise for mutant forms of EZH2) to assess conversion of H3-

K27m1 to H3-K27m2 and conversion of H3-K27m2 to H3-K27m3. In some embodiments, such peptide fragment corresponds to amino acid residues 21-44 of histone H3.

EZH2 Inhibitors

[0135] Exemplary EZH2 inhibitors suitable for use according to the disclosure include compounds of Formulae (I)-(VIa). Other compounds of Formulae (I)-(VIa) suitable for the methods of the disclosure are described in U.S. Publication 20120264734, the contents of which are hereby incorporated by reference in their entireties.

[0136] In some embodiments, an EZH2 inhibitor of the disclosure may have the following Formula I:



(I) or a pharmaceutically acceptable salt thereof; wherein

R^{701} is H, F, OR^{707} , NHR^{707} , $-(C\equiv C)-(CH_2)_n-R^{708}$, phenyl, 5- or 6-membered heteroaryl, C_{3-8} cycloalkyl, or 4-7 membered heterocycloalkyl containing 1-3 heteroatoms, wherein the phenyl, 5- or 6-membered heteroaryl, C_{3-8} cycloalkyl or 4-7 membered heterocycloalkyl each independently is optionally substituted with one or more groups selected from halo, C_{1-3} alkyl, OH, $O-C_{1-6}$ alkyl, $NH-C_{1-6}$ alkyl, and, C_{1-3} alkyl substituted with C_{3-8} cycloalkyl or 4-7 membered heterocycloalkyl containing 1-3 heteroatoms, wherein each of the $O-C_{1-6}$ alkyl and $NH-C_{1-6}$ alkyl is optionally substituted with hydroxyl, $O-C_{1-3}$ alkyl or $NH-C_{1-3}$ alkyl, each of the $O-C_{1-3}$ alkyl and $NH-C_{1-3}$ alkyl being optionally further substituted with $O-C_{1-3}$ alkyl or $NH-C_{1-3}$ alkyl;

each of R^{702} and R^{703} , independently is H, halo, C_{1-4} alkyl, C_{1-6} alkoxy or C_6-C_{10} aryloxy, each optionally substituted with one or more halo;

each of R^{704} and R^{705} , independently is C_{1-4} alkyl;

R^{706} is cyclohexyl substituted by $N(C_{1-4} \text{ alkyl})_2$ wherein one or both of the C_{1-4} alkyl is substituted with C_{1-6} alkoxy; or R^{706} is tetrahydropyranyl;

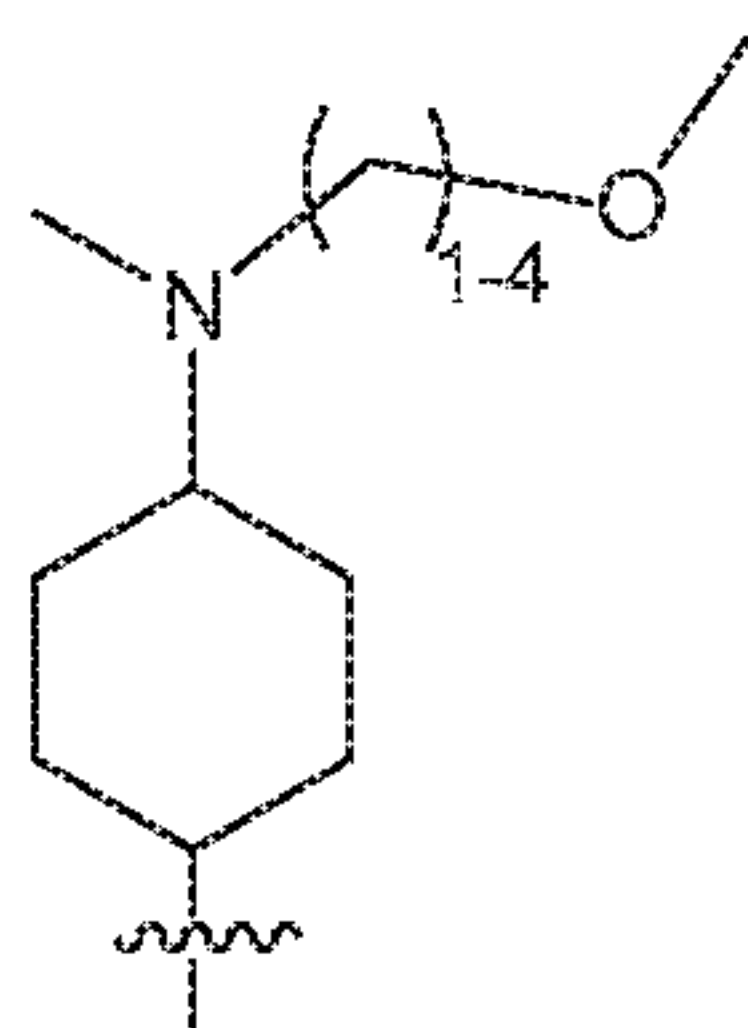
R^{707} is C_{1-4} alkyl optionally substituted with one or more groups selected from hydroxyl, C_{1-4} alkoxy, amino, mono- or di- C_{1-4} alkylamino, C_{3-8} cycloalkyl, and 4-7 membered

heterocycloalkyl containing 1-3 heteroatoms, wherein the C₃₋₈ cycloalkyl or 4-7 membered heterocycloalkyl each independently is further optionally substituted with C₁₋₃ alkyl;

R⁷⁰⁸ is C₁₋₄ alkyl optionally substituted with one or more groups selected from OH, halo, and C₁₋₄ alkoxy, 4-7 membered heterocycloalkyl containing 1-3 heteroatoms, or O-C₁₋₆ alkyl, wherein the 4-7 membered heterocycloalkyl can be optionally further substituted with OH or C₁₋₆ alkyl; and

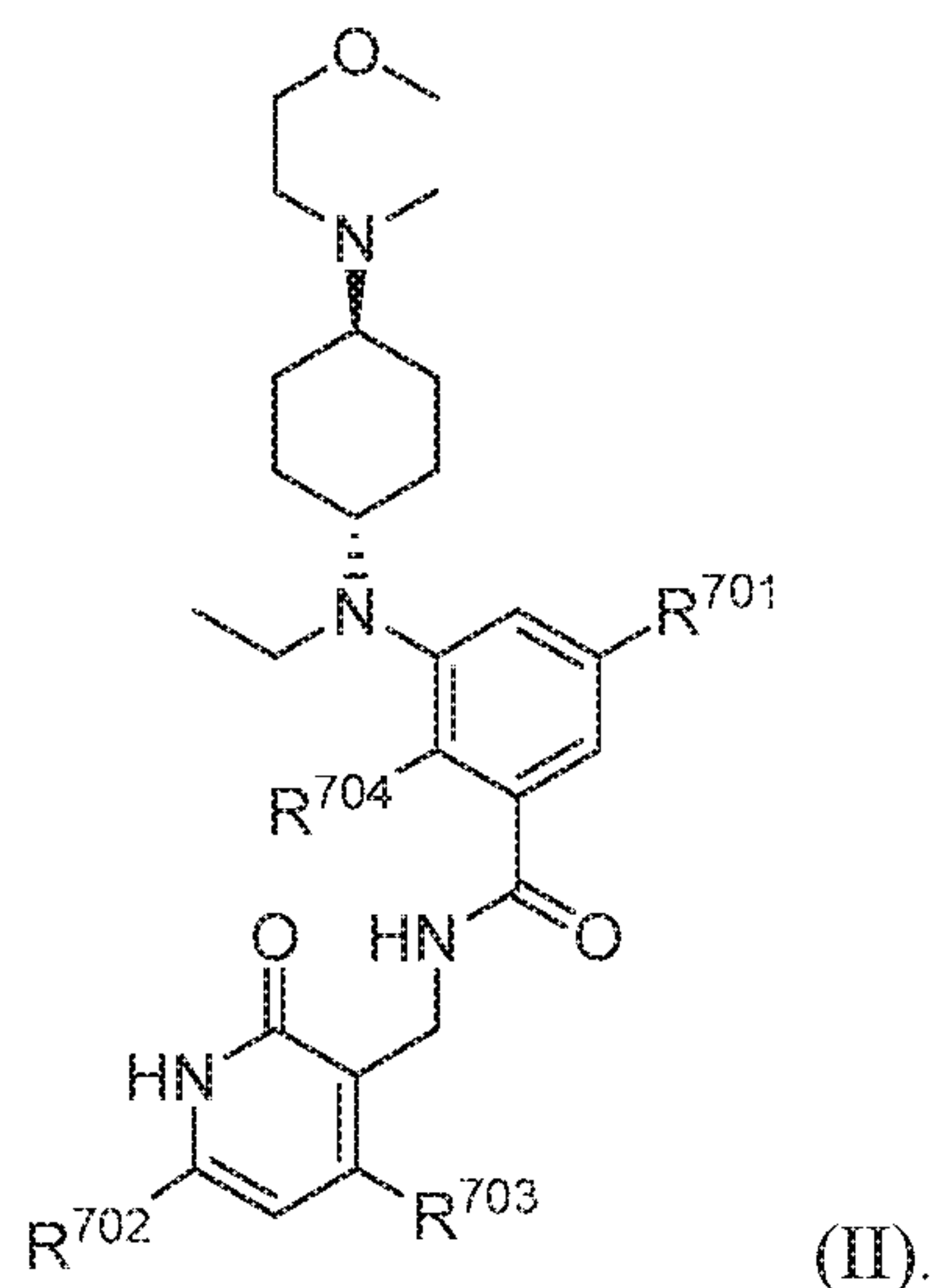
n₇ is 0, 1 or 2.

[0137] For example, R⁷⁰⁶ is cyclohexyl substituted by N(C₁₋₄ alkyl)₂ wherein one of the C₁₋₄ alkyl is unsubstituted and the other is substituted with methoxy.



[0138] For example, R⁷⁰⁶ is

[0139] In some embodiments, an EZH2inhibitor of the disclosure may have the following Formula II:



[0140] For example, R⁷⁰² is methyl or isopropyl and R⁷⁰³ is methyl or methoxyl.

[0141] For example, R⁷⁰⁴ is methyl.

[0142] For example, R⁷⁰¹ is OR⁷⁰⁷ and R⁷⁰⁷ is C₁₋₃ alkyl optionally substituted with OCH₃ or morpholine.

[0143] For example, R⁷⁰¹ is H or F.

[0144] For example, R⁷⁰¹ is tetrahydropyranyl, phenyl, pyridyl, pyrimidyl, pyrazinyl, imidazolyl, or pyrazolyl, each of which is optionally substituted with methyl, methoxy, ethyl substituted with morpholine, or -OCH₂CH₂OCH₃.

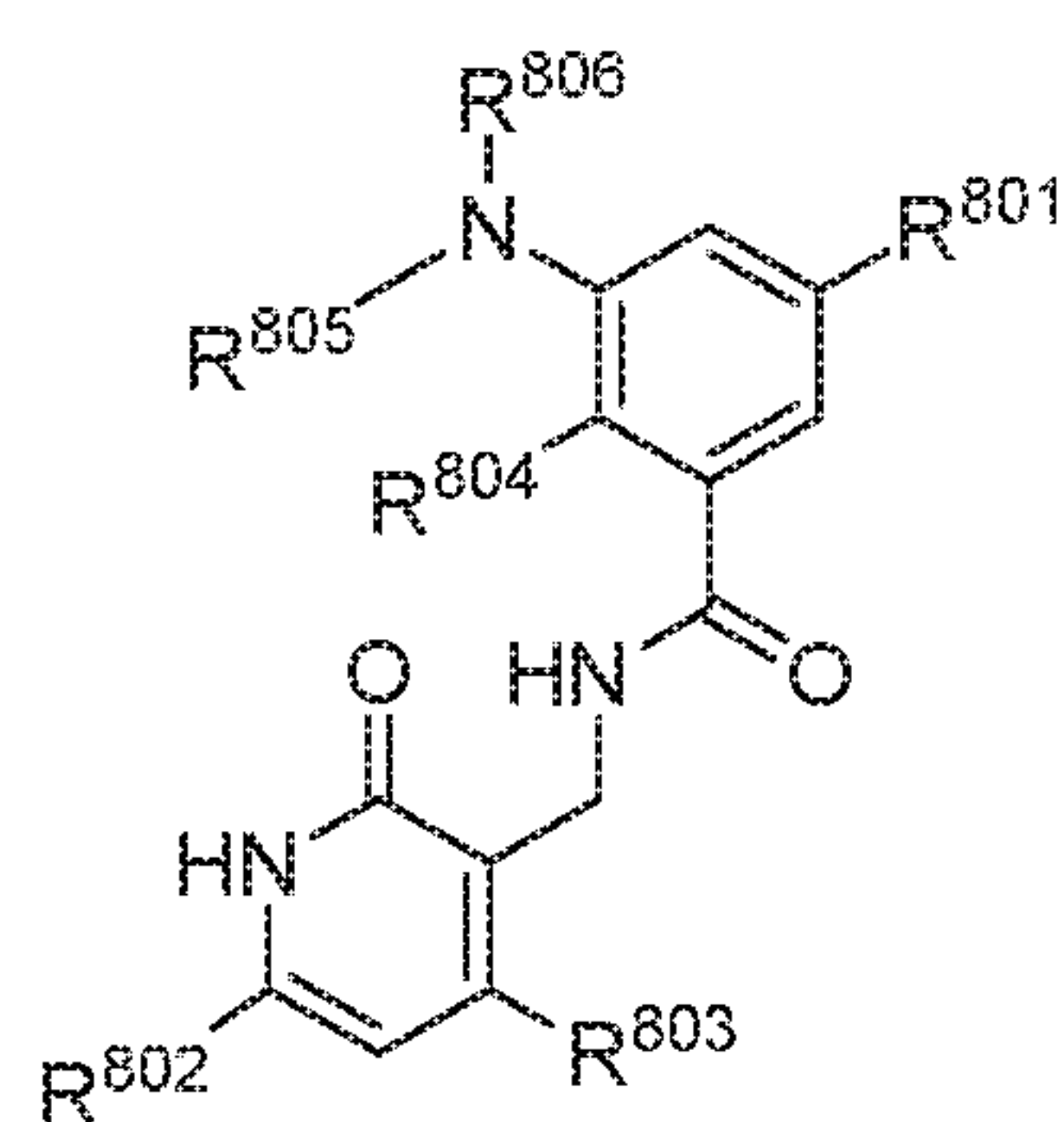
[0145] For example, R⁷⁰⁸ is morpholine, piperidine, piperazine, pyrrolidine, diazepane, or azetidine, each of which is optionally substituted with OH or C₁₋₆ alkyl.

[0146] For example, R⁷⁰⁸ is morpholine

[0147] For example, R⁷⁰⁸ is piperazine substituted with C₁₋₆ alkyl.

[0148] For example, R⁷⁰⁸ is methyl, t-butyl or C(CH₃)₂OH.

[0149] In some embodiments, an EZH2 inhibitor of the disclosure may have the following Formula III:



(III) or a pharmaceutically acceptable salt thereof.

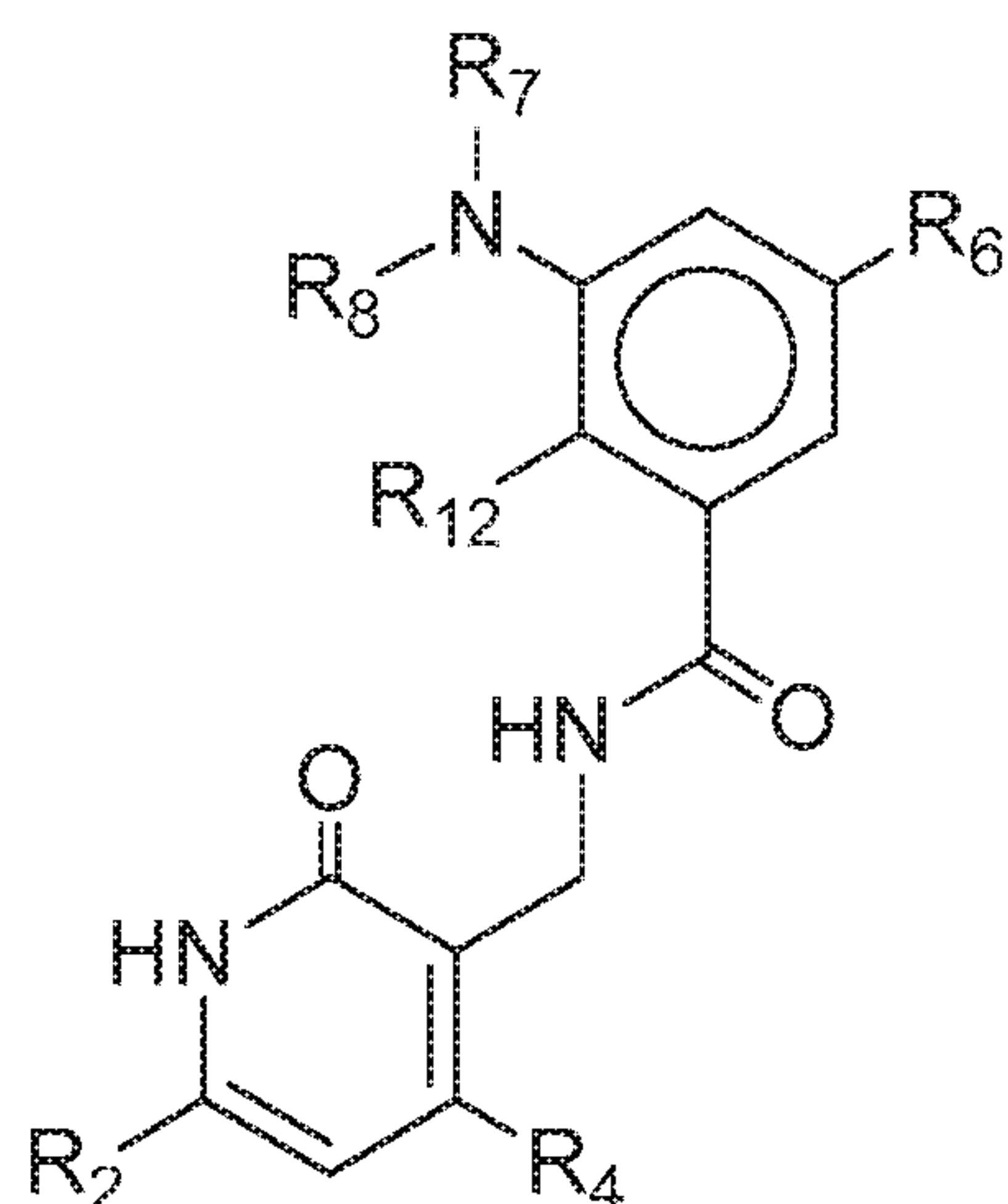
[0150] In this formula:

R⁸⁰¹ is C₁₋₆ alkyl, C₂₋₆ alkenyl, C₂₋₆ alkynyl, C₃₋₈ cycloalkyl, 4-7 membered heterocycloalkyl containing 1-3 heteroatoms, phenyl or 5- or 6-membered heteroaryl, each of which is substituted with O-C₁₋₆ alkyl-R_x or NH-C₁₋₆ alkyl-R_x, wherein R_x is hydroxyl, O-C₁₋₃ alkyl or NH-C₁₋₃ alkyl, and R_x is optionally further substituted with O-C₁₋₃ alkyl or NH-C₁₋₃ alkyl except when R_x is hydroxyl; or R⁸⁰¹ is phenyl substituted with -Q₂-T₂, wherein Q₂ is a bond or C₁₋₃ alkyl linker optionally substituted with halo, cyano, hydroxyl or C₁₋₆ alkoxy, and T₂ is optionally substituted 4- to 12-membered heterocycloalkyl; and R⁸⁰¹ is optionally further substituted;

each of R⁸⁰² and R⁸⁰³, independently is H, halo, C₁₋₄ alkyl, C₁₋₆ alkoxy or C₆₋₁₀ aryloxy, each optionally substituted with one or more halo;

each of R⁸⁰⁴ and R⁸⁰⁵, independently is C₁₋₄ alkyl; and

R⁸⁰⁶ is -Q_x-T_x, wherein Q_x is a bond or C₁₋₄ alkyl linker, T_x is H, optionally substituted C₁₋₄ alkyl, optionally substituted C₃₋₈ cycloalkyl or optionally substituted 4- to 14-membered heterocycloalkyl.



(V), or a pharmaceutically acceptable salt or ester thereof.

[0160] In this formula:

R₂, R₄ and R₁₂ are each, independently C₁₋₆ alkyl;

R₆ is C₆₋₁₀ aryl or 5- or 6-membered heteroaryl, each of which is optionally substituted with one or more -Q₂-T₂, wherein Q₂ is a bond or C₁₋₃ alkyl linker optionally substituted with halo, cyano, hydroxyl or C₁₋₆ alkoxy, and T₂ is H, halo, cyano, -OR_a, -NR_aR_b, -(NR_aR_bR_c)⁺A⁻, -C(O)R_a, -C(O)OR_a, -C(O)NR_aR_b, -NR_bC(O)R_a, -NR_bC(O)OR_a, -S(O)₂R_a, -S(O)₂NR_aR_b, or R_{S2}, in which each of R_a, R_b, and R_c, independently is H or R_{S3}, A⁻ is a pharmaceutically acceptable anion, each of R_{S2} and R_{S3}, independently, is C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, or R_a and R_b, together with the N atom to which they are attached, form a 4 to 12-membered heterocycloalkyl ring having 0 or 1 additional heteroatom, and each of R_{S2}, R_{S3}, and the 4 to 12-membered heterocycloalkyl ring formed by R_a and R_b, is optionally substituted with one or more -Q₃-T₃, wherein Q₃ is a bond or C₁₋₃ alkyl linker each optionally substituted with halo, cyano, hydroxyl or C₁₋₆ alkoxy, and T₃ is selected from the group consisting of halo, cyano, C₁₋₆ alkyl, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, OR_d, COOR_d, -S(O)₂R_d, -NR_dR_e, and -C(O)NR_dR_e, each of R_d and R_e independently being H or C₁₋₆ alkyl, or -Q₃-T₃ is oxo; or any two neighboring -Q₂-T₂, together with the atoms to which they are attached form a 5- or 6-membered ring optionally containing 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C₁₋₆ alkyl, cyano, C₁₋₆ alkoxy, amino, mono-C₁₋₆ alkylamino, di-C₁₋₆ alkylamino, C₃₋₈ cycloalkyl, C₆₋₁₀ aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl;

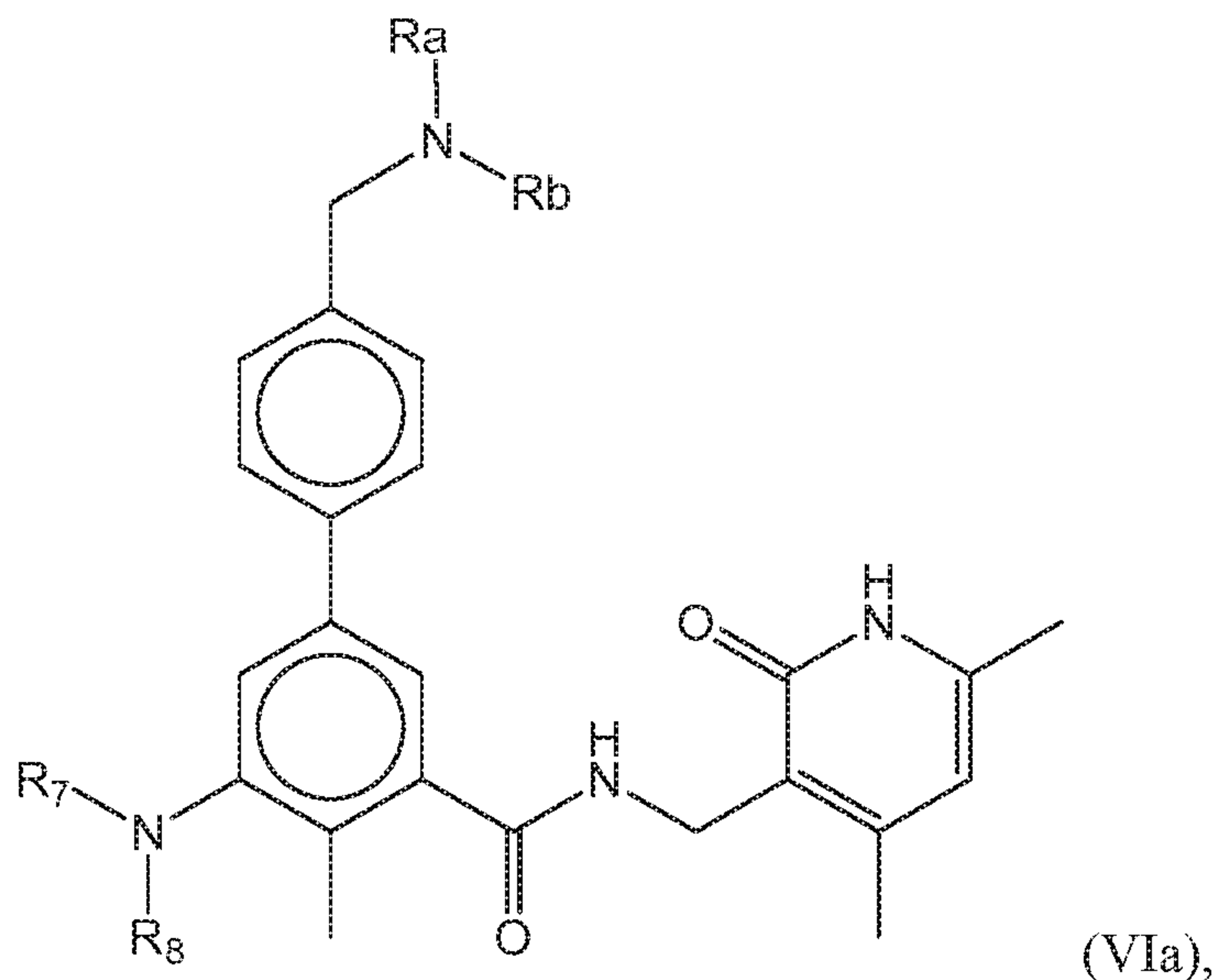
R₇ is -Q₄-T₄, in which Q₄ is a bond, C₁-C₄ alkyl linker, or C₂-C₄ alkenyl linker, each linker optionally substituted with halo, cyano, hydroxyl or C₁-C₆ alkoxy, and T₄ is H, halo, cyano, NR_fR_g, -OR_f, -C(O)R_f, -C(O)OR_f, -C(O)NR_fR_g, -C(O)NR_fOR_g, -NR_fC(O)R_g, -S(O)₂R_f, or R_{S4}, in which each of R_f and R_g, independently is H or R_{S5}, each of R_{S4} and R_{S5}, independently is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, C₆-C₁₀ aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and each of R_{S4} and R_{S5} is optionally substituted with one or more -Q₅-T₅, wherein Q₅ is a bond, C(O), C(O)NR_k, NR_kC(O), S(O)₂, or C₁-C₃ alkyl linker, R_k being H or C₁-C₆ alkyl, and T₅ is H, halo, C₁-C₆ alkyl, hydroxyl, cyano, C₁-C₆ alkoxy, amino, mono-C₁-C₆ alkylamino, di-C₁-C₆ alkylamino, C₃-C₈ cycloalkyl, C₆-C₁₀ aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or S(O)_qR_q in which q is 0, 1, or 2 and R_q is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, C₆-C₁₀ aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T₅ is optionally substituted with one or more substituents selected from the group consisting of halo, C₁-C₆ alkyl, hydroxyl, cyano, C₁-C₆ alkoxy, amino, mono-C₁-C₆ alkylamino, di-C₁-C₆ alkylamino, C₃-C₈ cycloalkyl, C₆-C₁₀ aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T₅ is H, halo, hydroxyl, or cyano; or -Q₅-T₅ is oxo; and

R₈ is H, halo, hydroxyl, COOH, cyano, R_{S6}, OR_{S6}, or COOR_{S6}, in which R_{S6} is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, 4 to 12-membered heterocycloalkyl, amino, mono-C₁-C₆ alkylamino, or di-C₁-C₆ alkylamino, and R_{S6} is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, COOH, C(O)O-C₁-C₆ alkyl, cyano, C₁-C₆ alkoxy, amino, mono-C₁-C₆ alkylamino, and di-C₁-C₆ alkylamino; or R₇ and R₈, together with the N atom to which they are attached, form a 4 to 11-membered heterocycloalkyl ring having 0 to 2 additional heteroatoms, and the 4 to 11-membered heterocycloalkyl ring formed by R₇ and R₈ is optionally substituted with one or more -Q₆-T₆, wherein Q₆ is a bond, C(O), C(O)NR_m, NR_mC(O), S(O)₂, or C₁-C₃ alkyl linker, R_m being H or C₁-C₆ alkyl, and T₆ is H, halo, C₁-C₆ alkyl, hydroxyl, cyano, C₁-C₆ alkoxy, amino, mono-C₁-C₆ alkylamino, di-C₁-C₆ alkylamino, C₃-C₈ cycloalkyl, C₆-C₁₀ aryl, 4 to 12-membered heterocycloalkyl, 5- or 6-membered heteroaryl, or S(O)_pR_p in which p is 0, 1, or 2 and R_p is C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₈ cycloalkyl, C₆-C₁₀ aryl, 4 to 12-membered heterocycloalkyl, or 5- or 6-membered heteroaryl, and T₆ is optionally substituted with one or more substituents selected from the group consisting of halo, C₁-C₆ alkyl, hydroxyl, cyano, C₁-C₆

alkoxyl, amino, mono-C₁-C₆ alkylamino, di-C₁-C₆ alkylamino, C₃-C₈ cycloalkyl, C₆-C₁₀ aryl, 4 to 12-membered heterocycloalkyl, and 5- or 6-membered heteroaryl except when T₆ is H, halo, hydroxyl, or cyano; or -Q₆-T₆ is oxo.

[0161] For example, R₆ is C₆-C₁₀ aryl or 5- or 6-membered heteroaryl, each of which is optionally, independently substituted with one or more -Q₂-T₂, wherein Q₂ is a bond or C₁-C₃ alkyl linker, and T₂ is H, halo, cyano, -OR_a, -NR_aR_b, -(NR_aR_bR_c)⁺A⁻, -C(O)NR_aR_b, -NR_bC(O)R_a, -S(O)₂R_a, or R_{S2}, in which each of R_a and R_b, independently is H or R_{S3}, each of R_{S2} and R_{S3}, independently, is C₁-C₆ alkyl, or R_a and R_b, together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatom, and each of R_{S2}, R_{S3}, and the 4 to 7-membered heterocycloalkyl ring formed by R_a and R_b, is optionally, independently substituted with one or more -Q₃-T₃, wherein Q₃ is a bond or C₁-C₃ alkyl linker and T₃ is selected from the group consisting of halo, C₁-C₆ alkyl, 4 to 7-membered heterocycloalkyl, OR_d, -S(O)₂R_d, and -NR_dR_e, each of R_d and R_e independently being H or C₁-C₆ alkyl, or -Q₃-T₃ is oxo; or any two neighboring -Q₂-T₂, together with the atoms to which they are attached form a 5- or 6-membered ring optionally containing 1-4 heteroatoms selected from N, O and S.

[0162] In some embodiments, an EZH2 inhibitor of the disclosure may have the following Formula (VIa):



or a pharmaceutically acceptable salts or esters thereof, wherein R₇, R₈, R_a, and R_b are defined herein.

[0163] The compounds of Formula (VIa) can include one or more of the following features:

[0164] For example, each of R_a and R_b independently is H or C_1 - C_6 alkyl optionally substituted with one or more $-Q_3-T_3$.

[0165] For example, one of R_a and R_b is H.

[0166] For example, R_a and R_b , together with the N atom to which they are attached, form a 4 to 7-membered heterocycloalkyl ring having 0 or 1 additional heteroatoms to the N atom (e.g., azetidiny, pyrrolidiny, imidazolidiny, pyrazolidiny, oxazolidiny, isoxazolidiny, triazolidiny, piperidiny, 1,2,3,6-tetrahydropyridiny, piperaziny, morpholiny, 1,4-diazepany, 1,4-oxazepany, 2-oxa-5-azabicyclo[2.2.1]heptany, 2,5-diazabicyclo[2.2.1]heptany, and the like) and the ring is optionally substituted with one or more $-Q_3-T_3$.

[0167] For example, R_a and R_b , together with the N atom to which they are attached, form azetidiny, pyrrolidiny, imidazolidiny, pyrazolidiny, oxazolidiny, isoxazolidiny, triazolidiny, tetrahydrofurany, piperidiny, 1,2,3,6-tetrahydropyridiny, piperaziny, or morpholiny, and the ring is optionally substituted with one or more $-Q_3-T_3$.

[0168] For example, one or more $-Q_3-T_3$ are oxo.

[0169] For example, Q_3 is a bond or unsubstituted or substituted C_1 - C_3 alkyl linker.

[0170] For example, T_3 is H, halo, 4 to 7-membered heterocycloalkyl, C_1 - C_3 alkyl, OR_d , $COOR_d$, $S(O)_2R_d$, or $-NR_dR_e$.

[0171] For example, each of R_d and R_e independently being H or C_1 - C_6 alkyl.

[0172] For example, R_7 is C_3 - C_8 cycloalkyl or 4 to 7-membered heterocycloalkyl, each optionally substituted with one or more $-Q_5-T_5$.

[0173] For example, R_7 is piperidiny, tetrahydropyran, tetrahydro-2H-thiopyrany, cyclopentyl, cyclohexyl, pyrrolidiny, or cycloheptyl, each optionally substituted with one or more $-Q_5-T_5$.

[0174] For example, R_7 is cyclopentyl cyclohexyl or tetrahydro-2H-thiopyrany, each of which is optionally substituted with one or more $-Q_5-T_5$.

[0175] For example, Q_5 is $NHC(O)$ and T_5 is C_1 - C_6 alkyl or C_1 - C_6 alkoxy, each

[0176] For example, one or more $-Q_5-T_5$ are oxo.

[0177] For example, R_7 is 1-oxide-tetrahydro-2H-thiopyrany or 1,1-dioxide-tetrahydro-2H-thiopyrany.

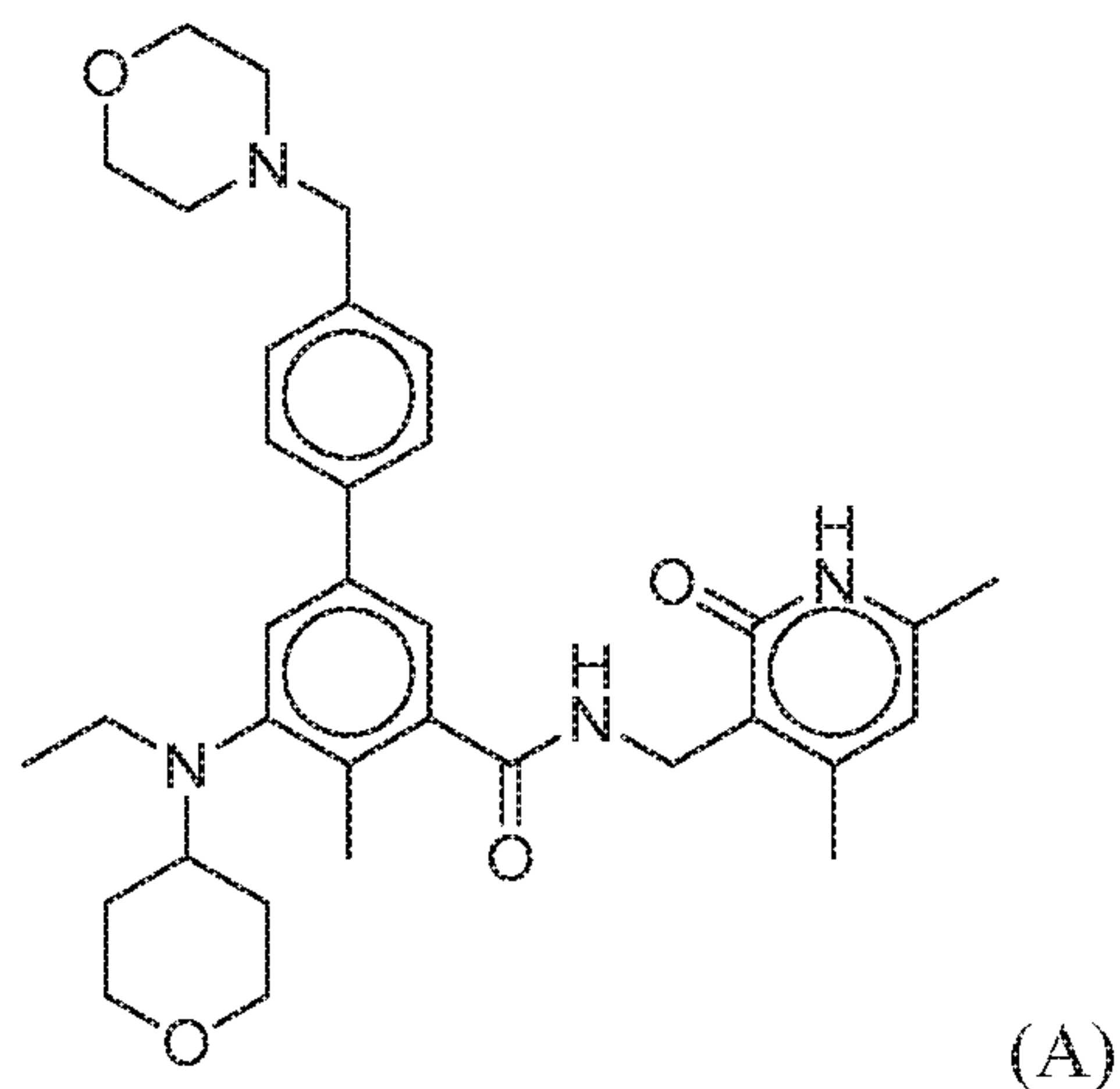
[0178] For example, Q_5 is a bond and T_5 is amino, mono- C_1 - C_6 alkylamino, di- C_1 - C_6 alkylamino.

[0179] For example, Q_5 is CO, $S(O)_2$, or $NHC(O)$; and T_5 is C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_3 - C_8 cycloalkyl, or 4 to 7-membered heterocycloalkyl.

[0180] For example, R_8 is H or C_1 - C_6 alkyl which is optionally substituted with one or more substituents selected from the group consisting of halo, hydroxyl, $COOH$, $C(O)O$ - C_1 - C_6 alkyl, cyano, C_1 - C_6 alkoxy, amino, mono- C_1 - C_6 alkylamino, and di- C_1 - C_6 alkylamino.

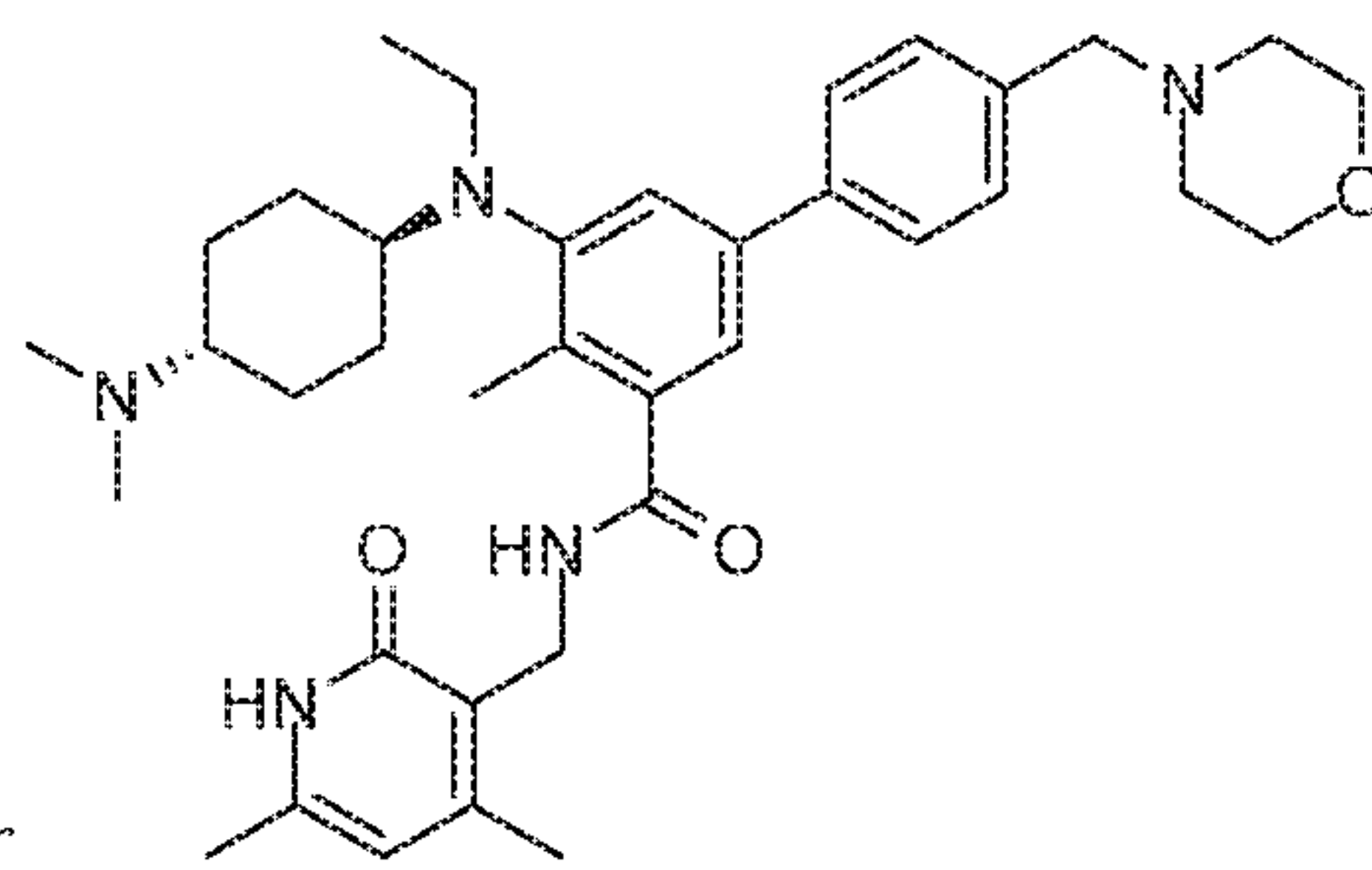
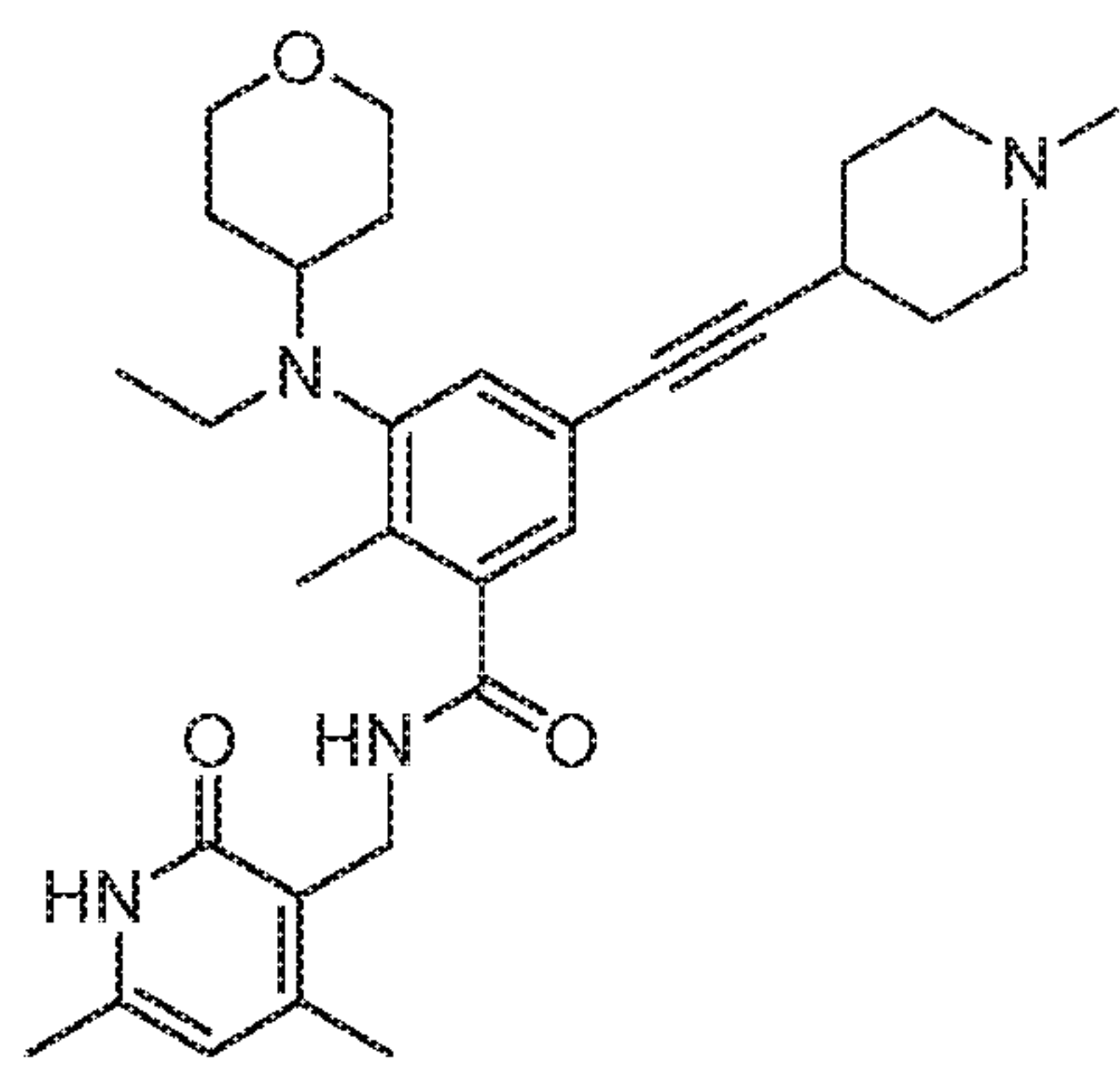
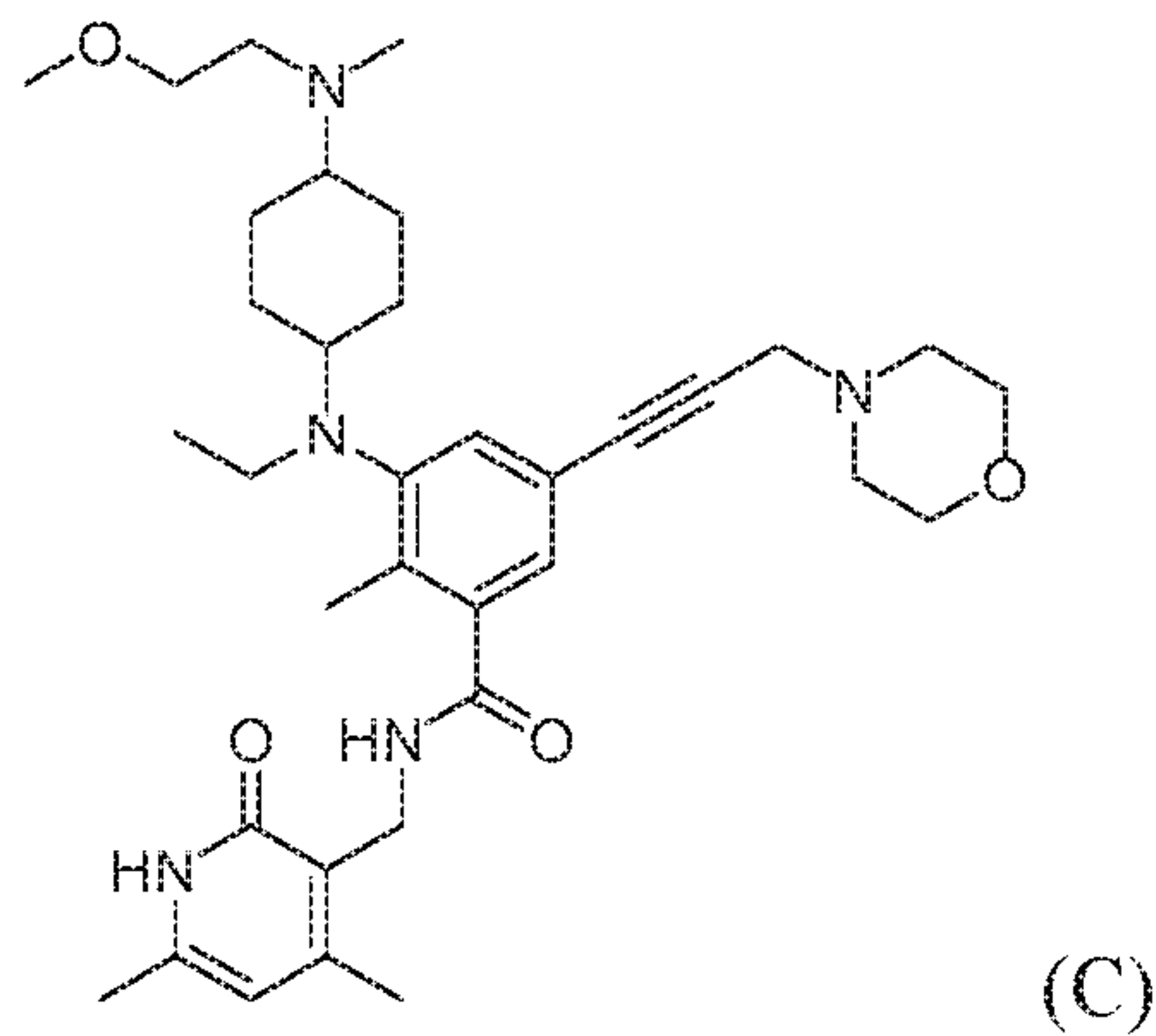
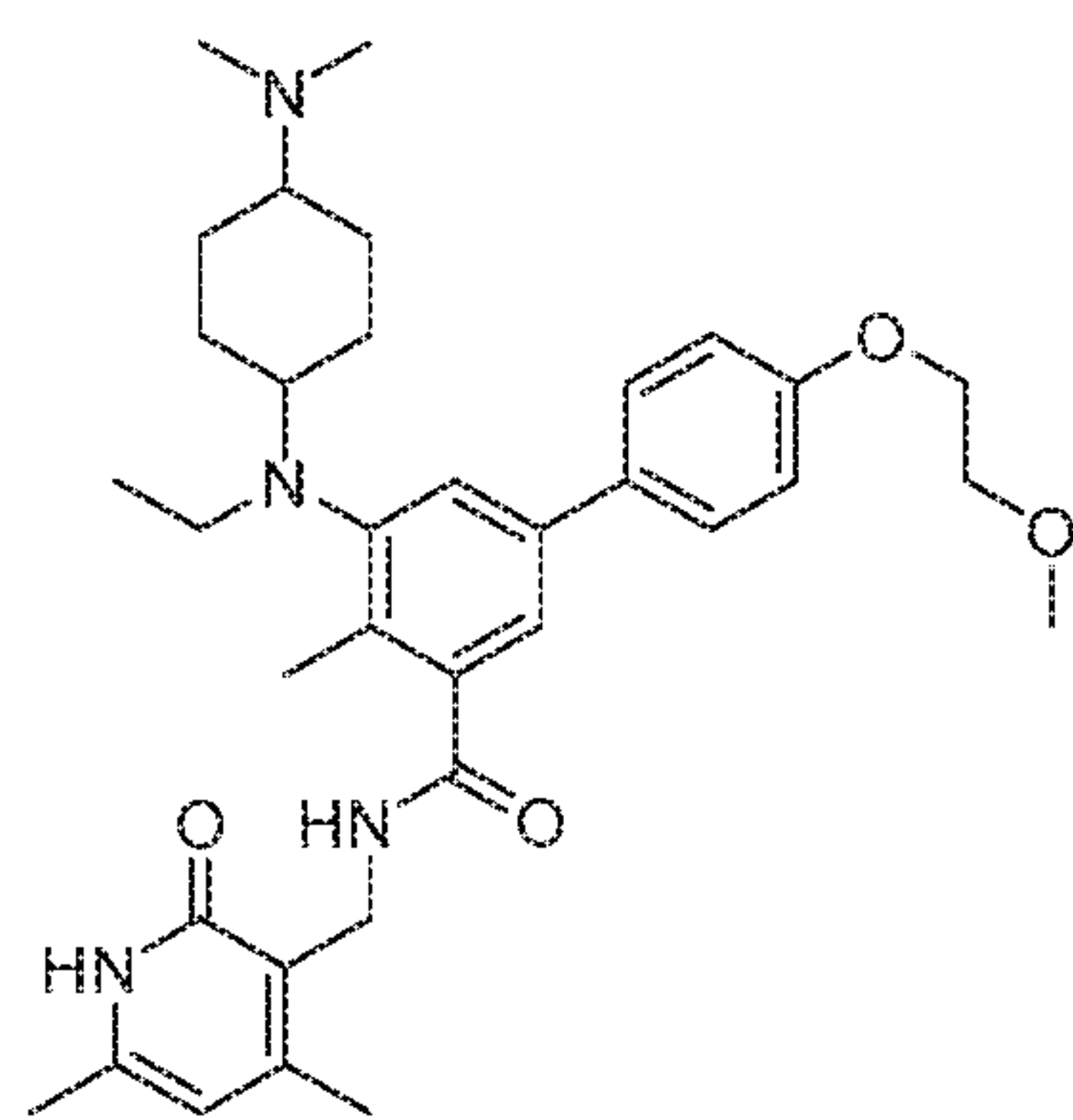
[0181] For example, R_8 is H, methyl, or ethyl.

[0182] In some embodiments, the EZH2 inhibitor is tazemetostat (also referred to herein as Compound 44 or Compound (A)):



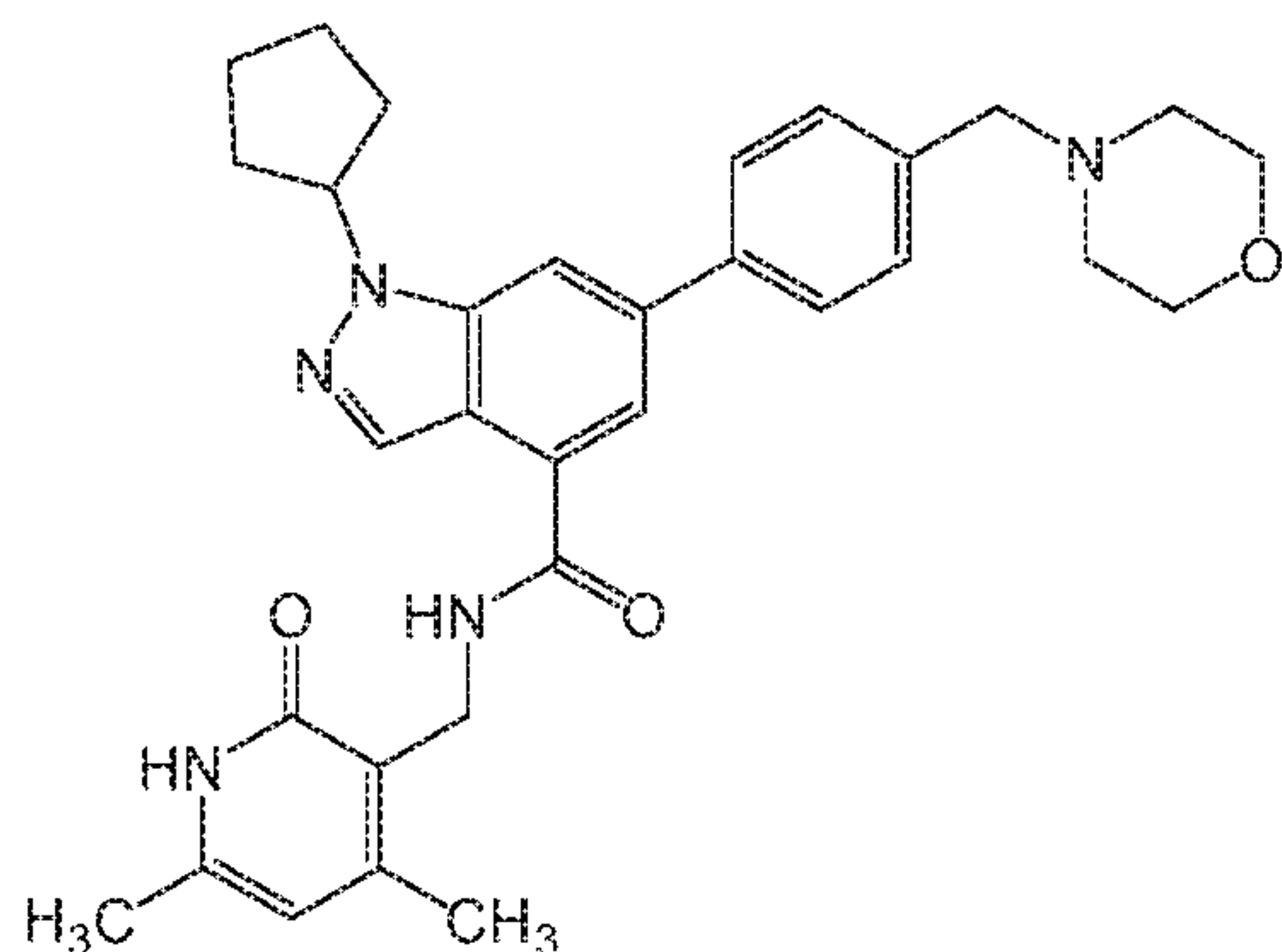
or a stereoisomer, solvate, or pharmaceutically acceptable salt thereof.

[0183] In some embodiments, the EZH2 inhibitor is:



solvates, or pharmaceutically acceptable salts thereof.

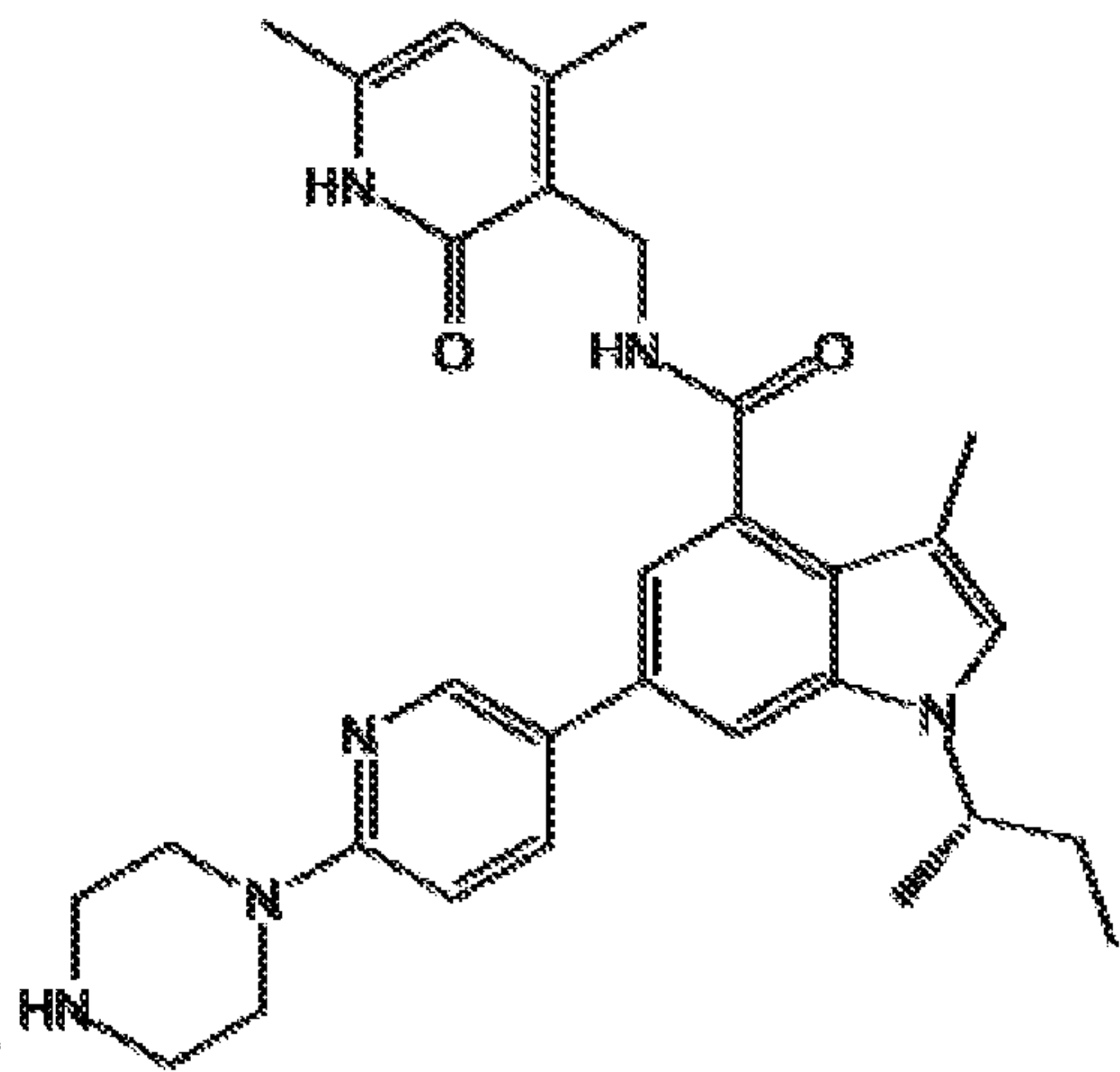
[0184] In certain embodiments, the EZH2 inhibitor is Compound F:



(F) or stereoisomers, solvates, or pharmaceutically

acceptable salts thereof.

[0185] In some embodiments, the EZH2 inhibitor is GSK-126 having the following

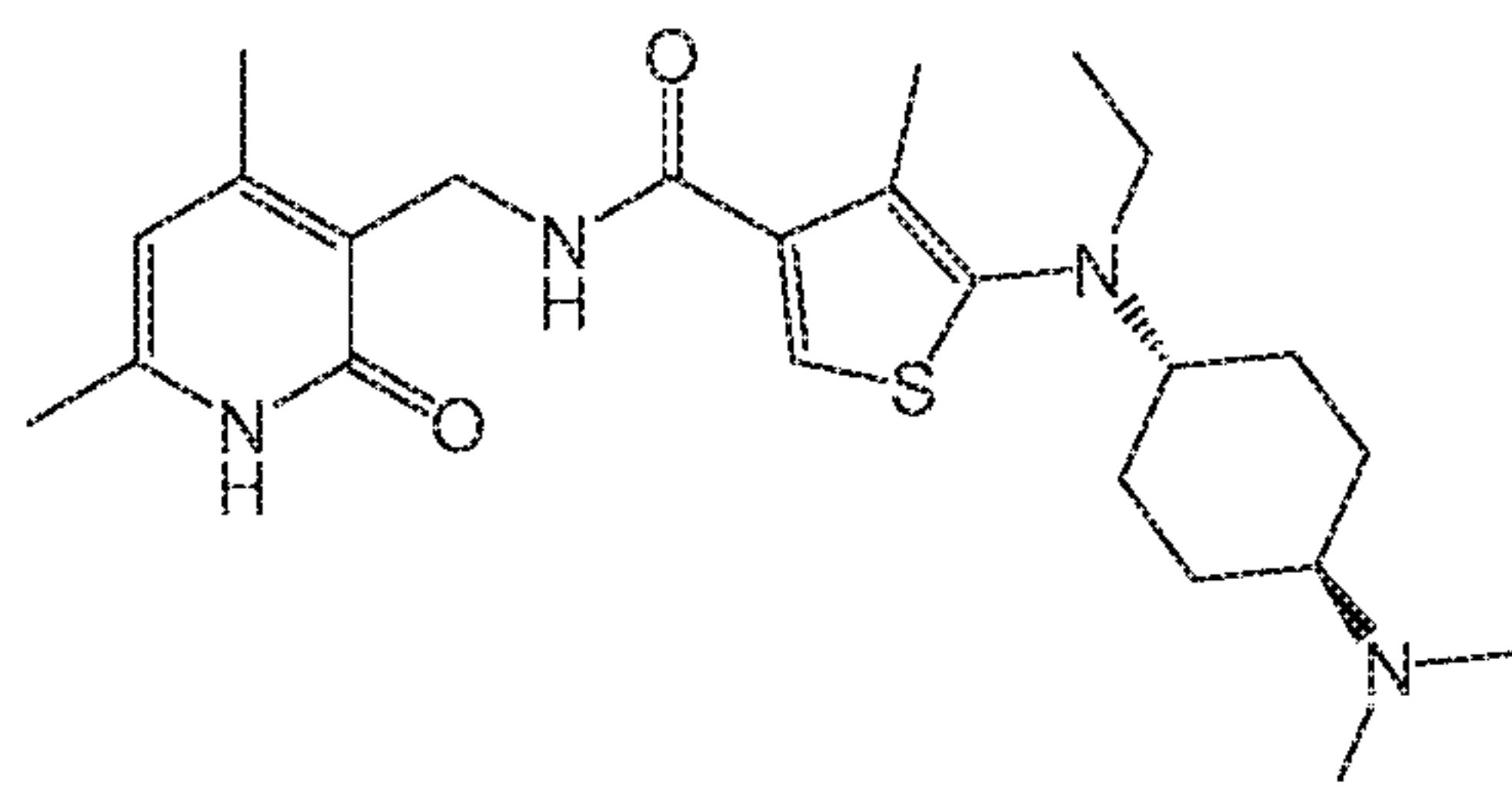


formula:

, stereoisomers thereof, or pharmaceutically

acceptable salts or solvates thereof.

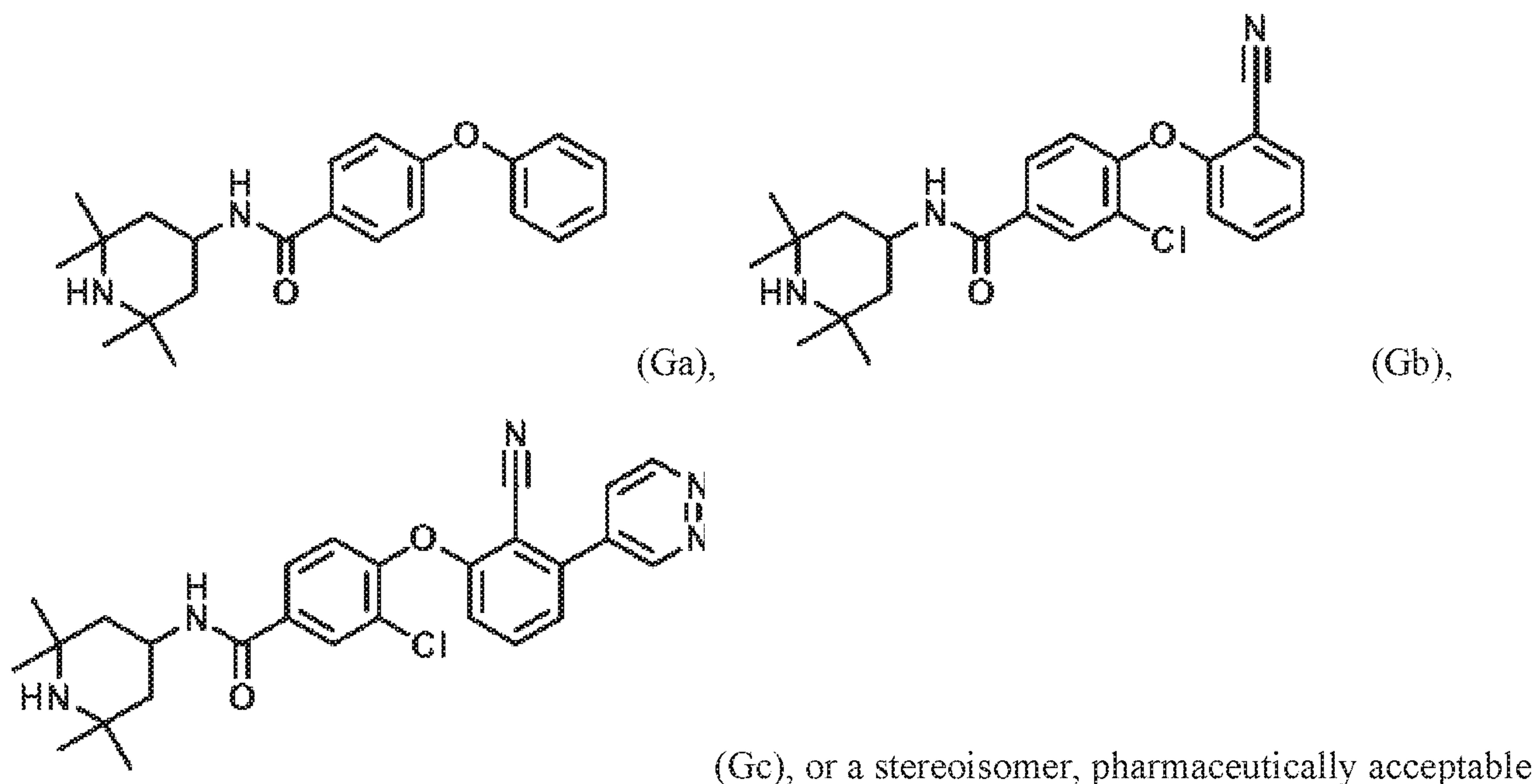
[0186] In certain embodiments, the EZH2 inhibitor is Compound G:



(G), or stereoisomers thereof or pharmaceutically acceptable

salts and solvates thereof.

[0187] In certain embodiments, a compound (e.g., EZH2 inhibitor) that can be used in any methods presented here is any of Compounds Ga-Gc:



salt, or solvate thereof.

[0188] In some embodiments, the EZH2 inhibitor may comprise, consist essentially of or consist of CPI-1205 or GSK343.

[0189] Additional suitable EZH2 inhibitors for use in the methods, strategies, compositions, and/or combinations provided herein will be apparent to those skilled in the art. In some embodiments of the strategies, treatment modalities, methods, combinations, and compositions provided herein, the EZH2 inhibitor is an EZH2 inhibitor described in US 8,536,179 (describing GSK-126 among other compounds and corresponding to WO 2011/140324), the entire contents of each of which are incorporated herein by reference.

[0190] In some embodiments of the strategies, treatment modalities, methods, combinations, and compositions provided herein, the EZH2 inhibitor is an EZH2 inhibitor described in PCT/US2014/015706, published as WO 2014/124418, in PCT/US2013/025639, published as WO 2013/120104, and in US 14/839,273, published as US 2015/0368229, the entire contents of each of which are incorporated herein by reference.

[0191] In some embodiments, the compound of the disclosure is the compound itself, i.e., the free base or “naked” molecule. In some embodiments, the compound is a salt thereof, e.g., a pharmaceutically acceptable salt, for example, a mono-HCl or tri-HCl salt, mono-HBr or tri-HBr salt of the naked molecule. Pharmaceutically acceptable salts of the compounds provided herein

will be apparent to those of skill in the art based on the present disclosure and the knowledge in the art. The disclosure is not limited in this respect.

[0192] Representative compounds of Formula VIa of the disclosure include compounds listed in Table 1.

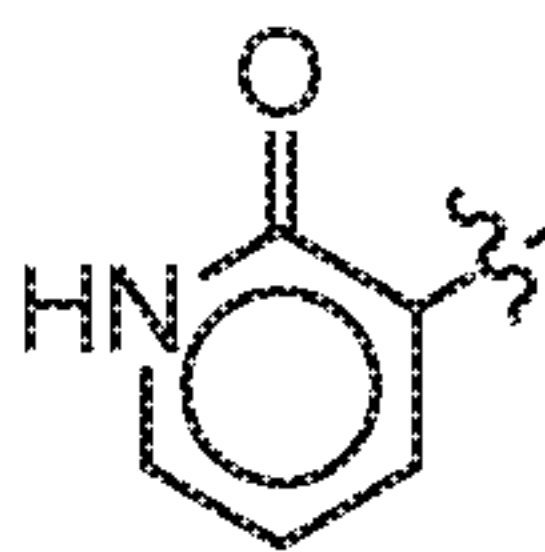
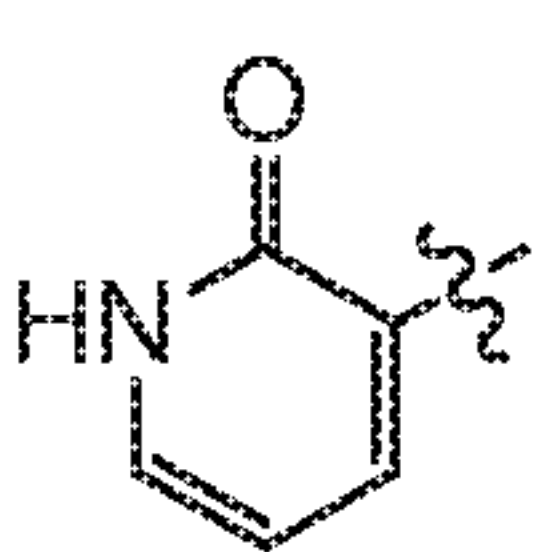
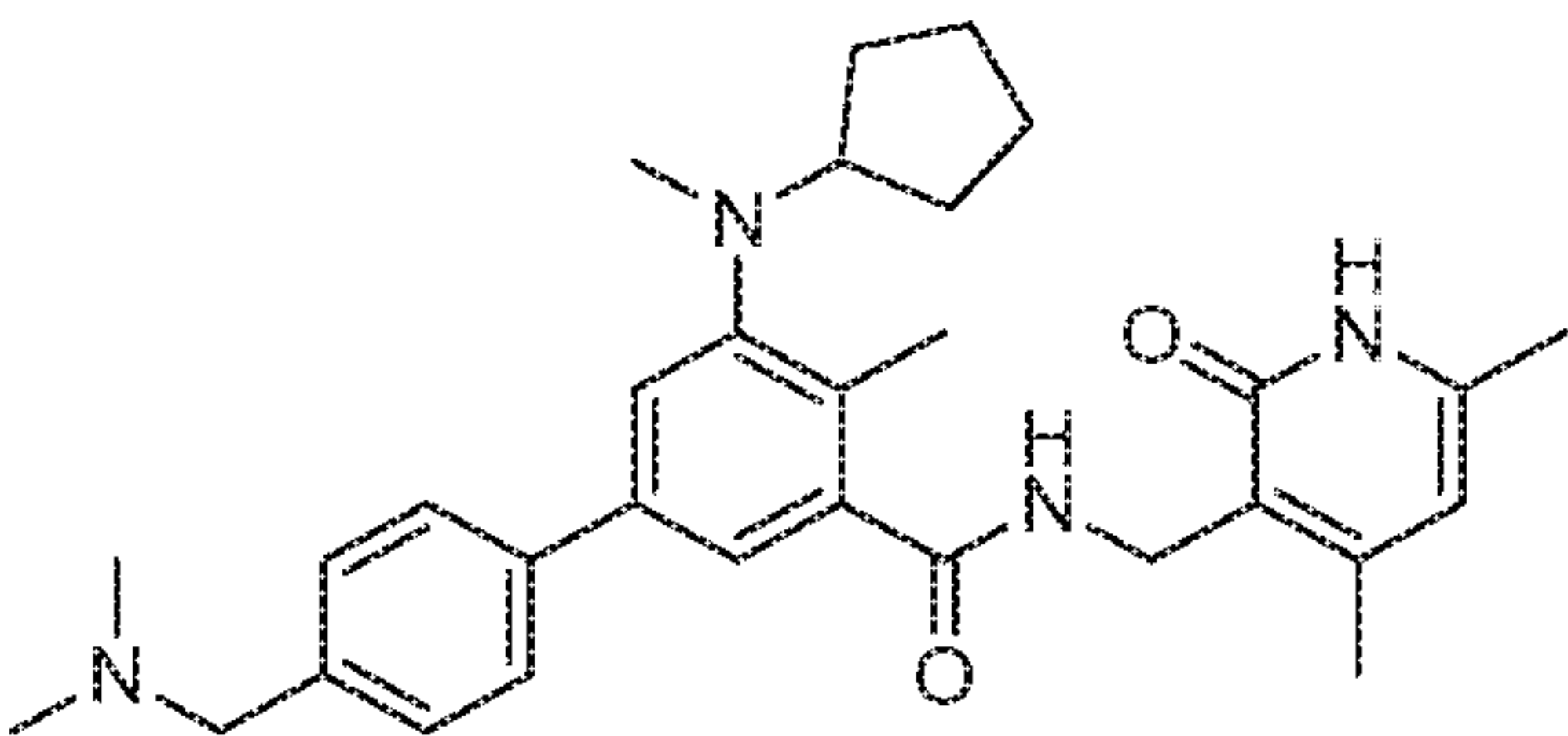
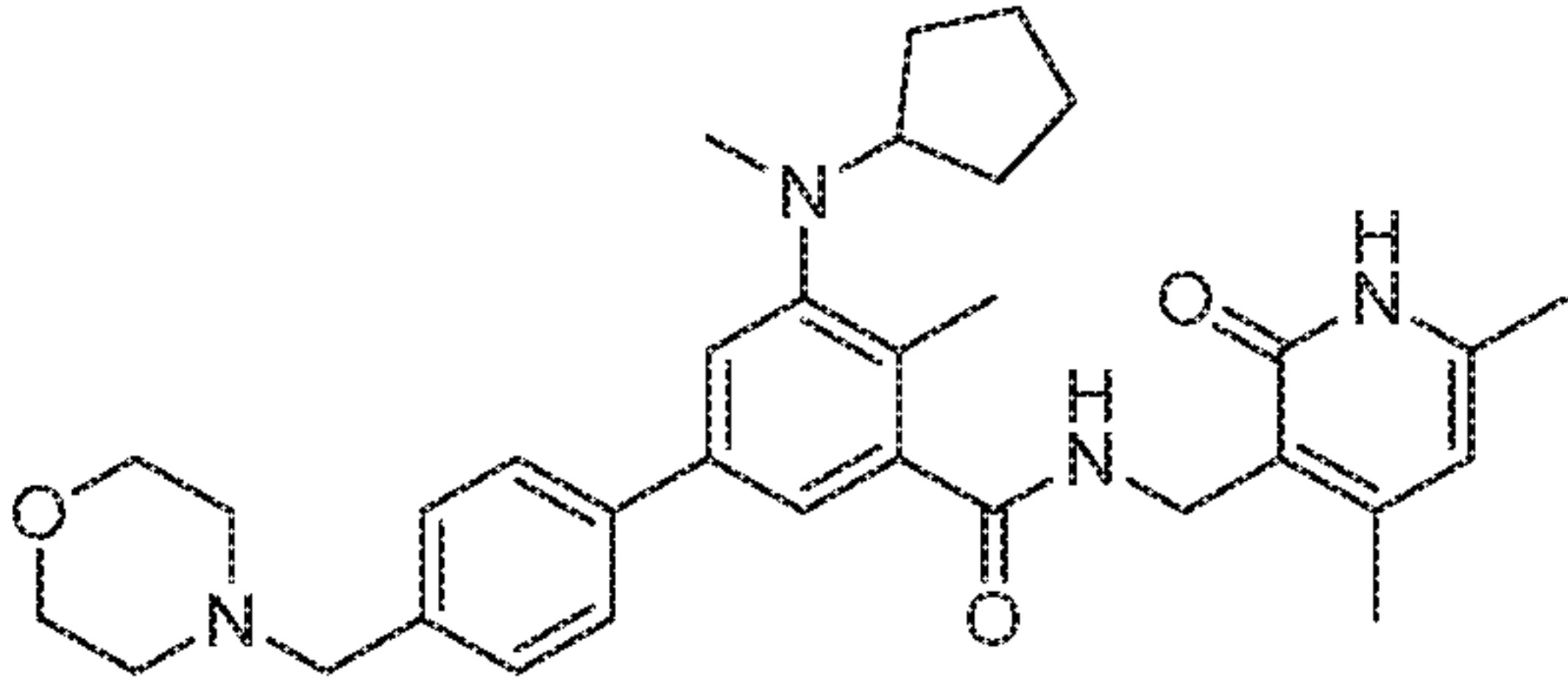
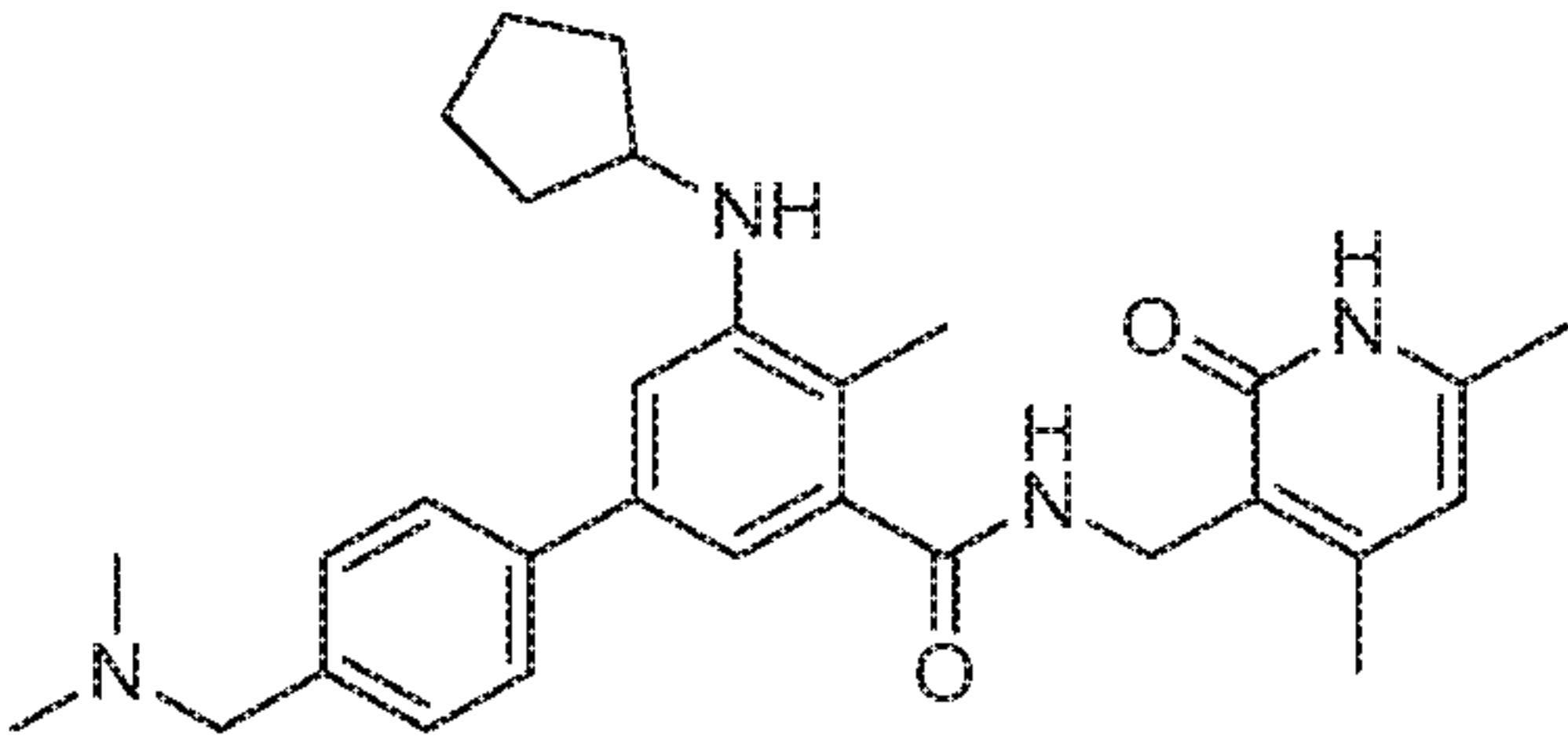
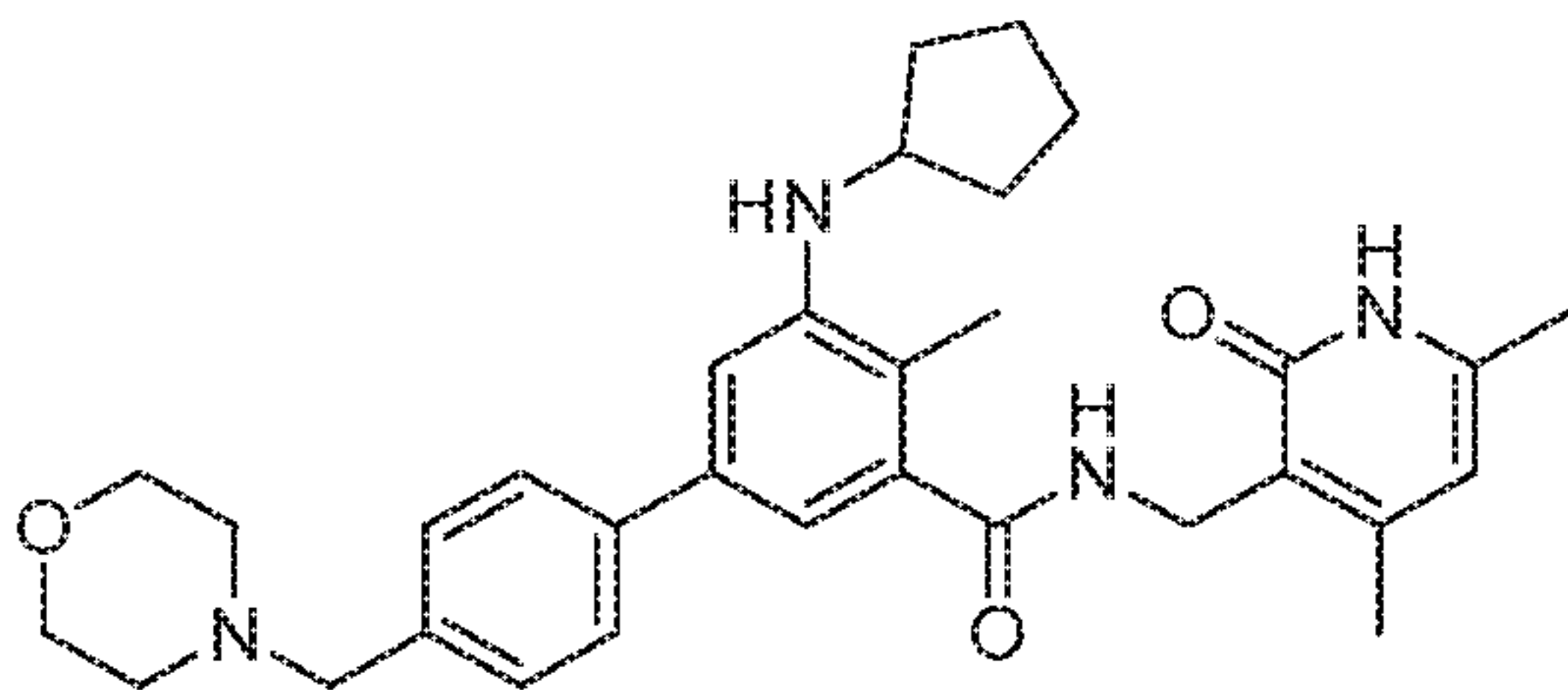
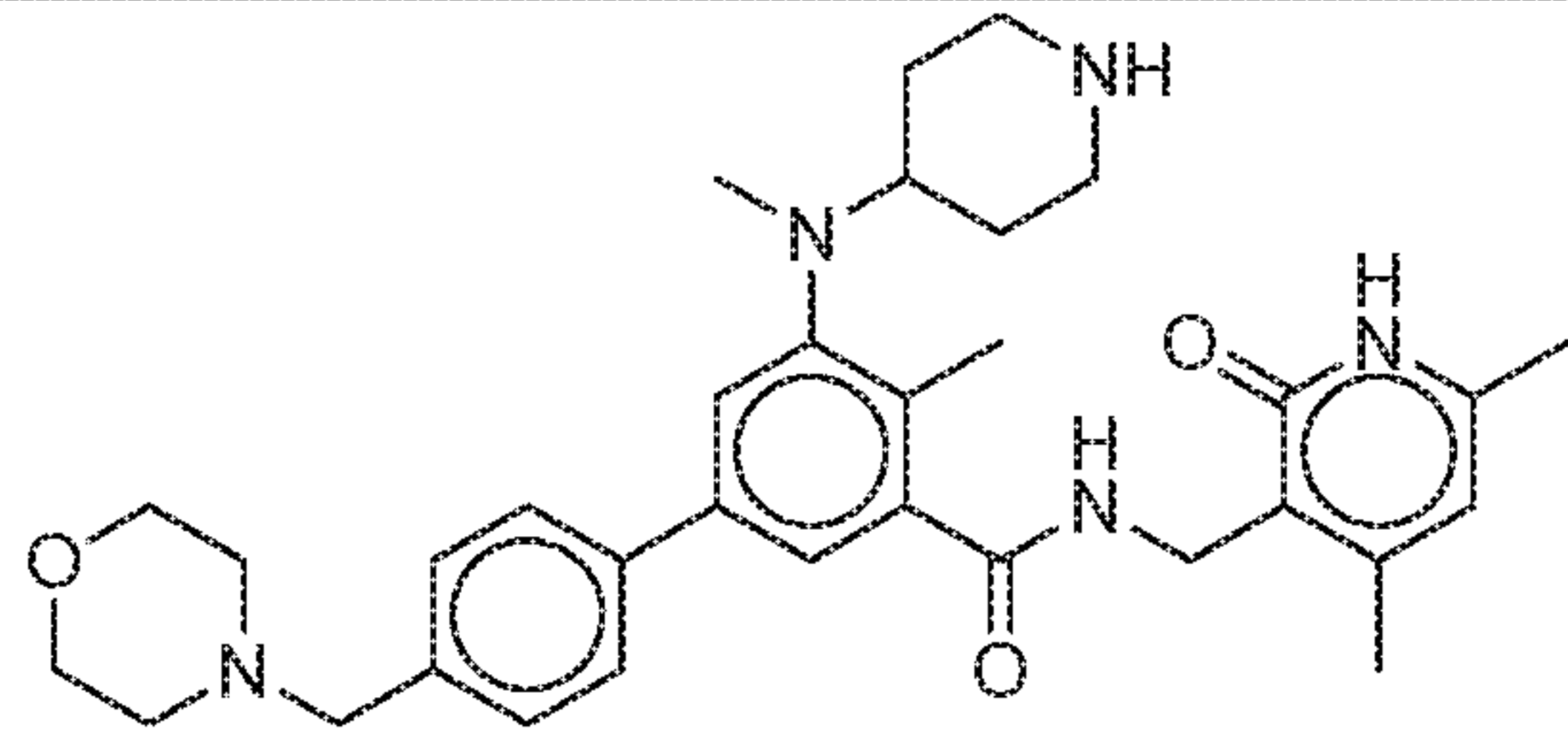
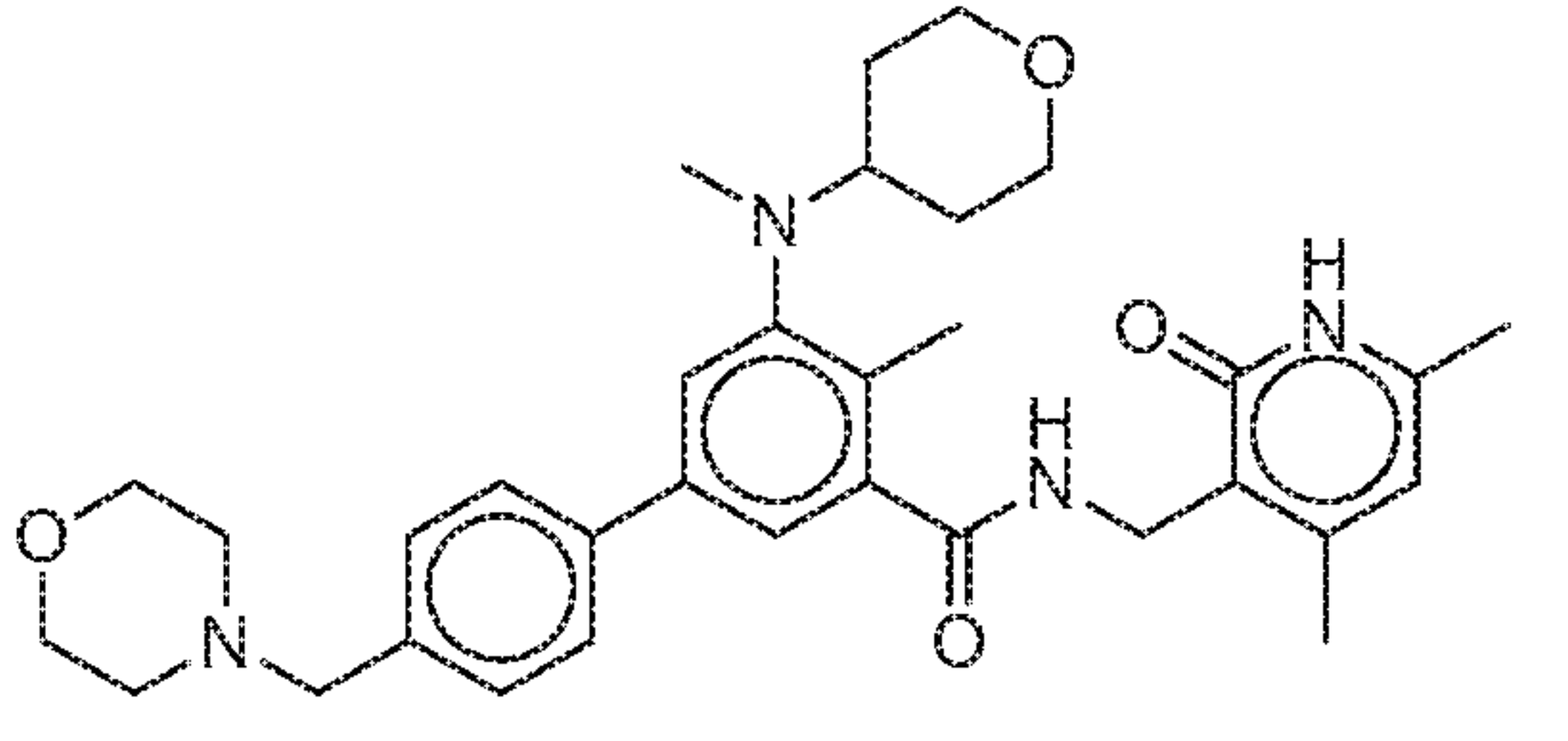
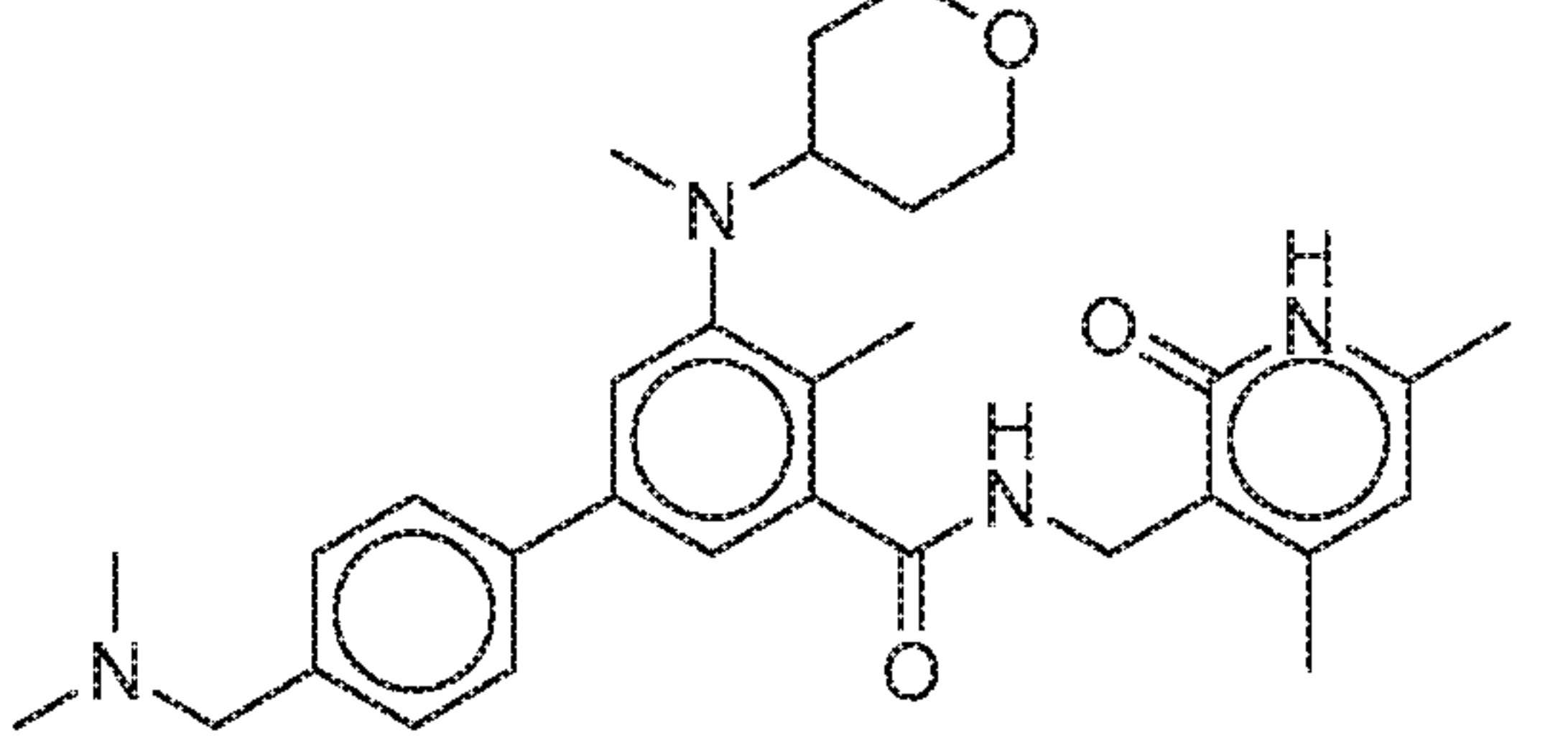
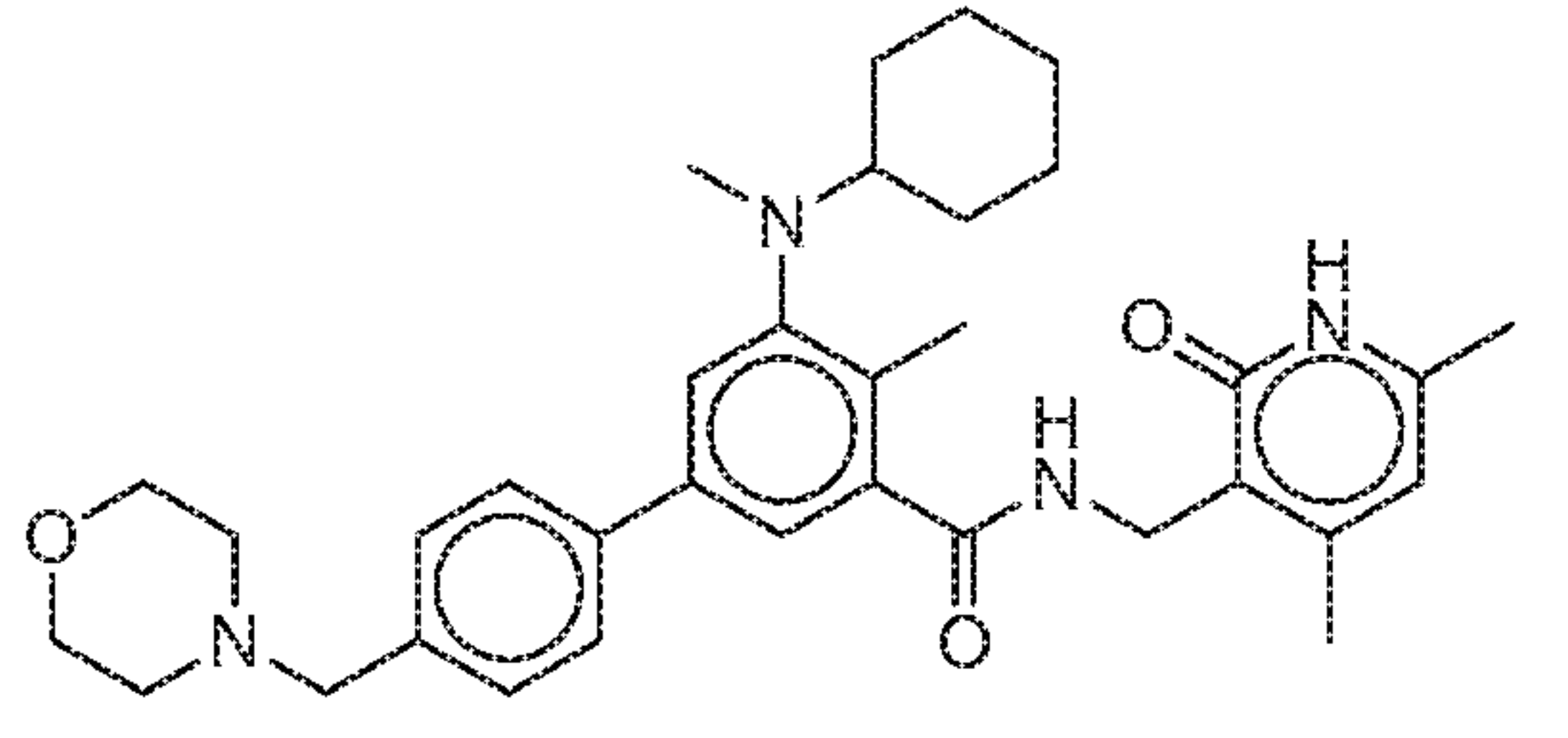
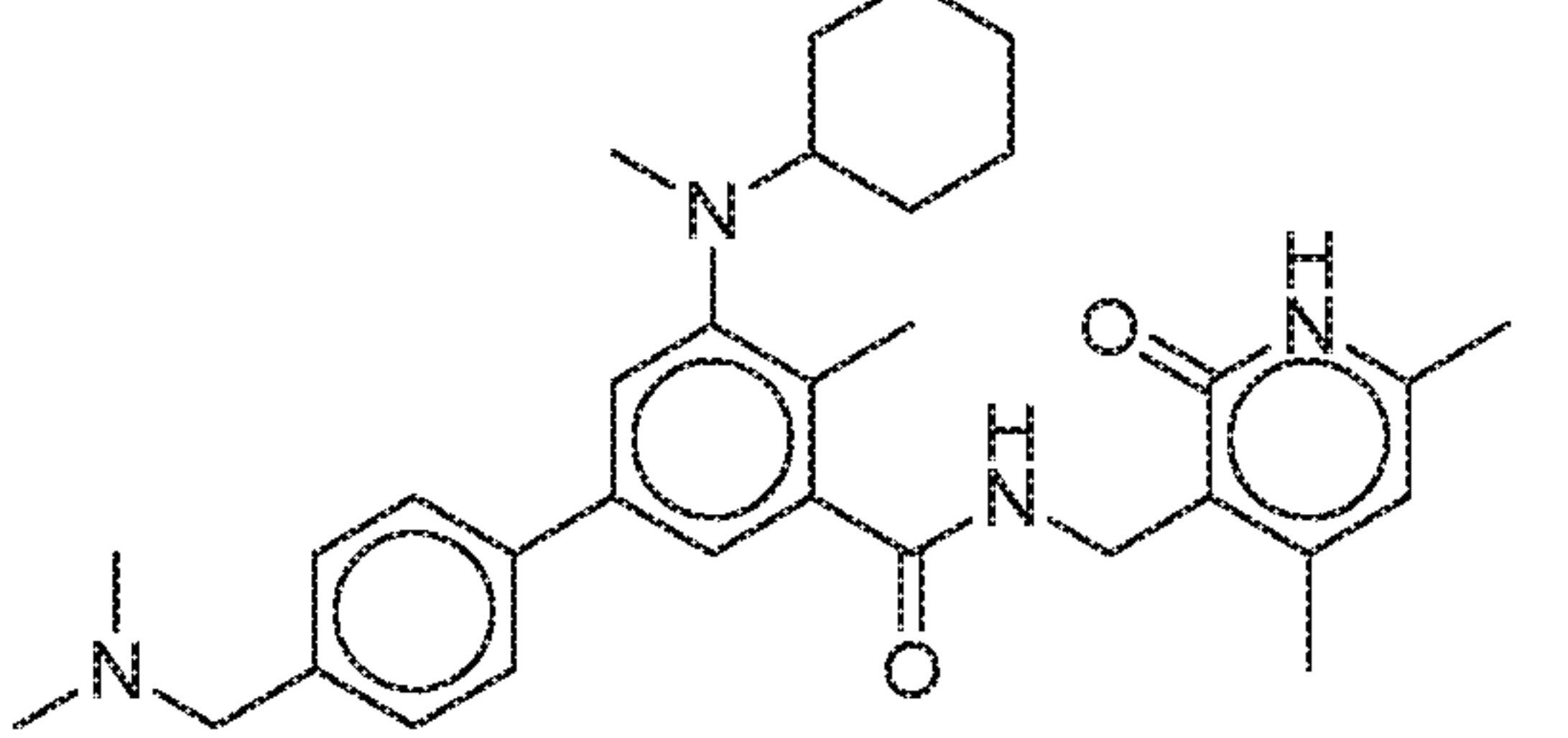
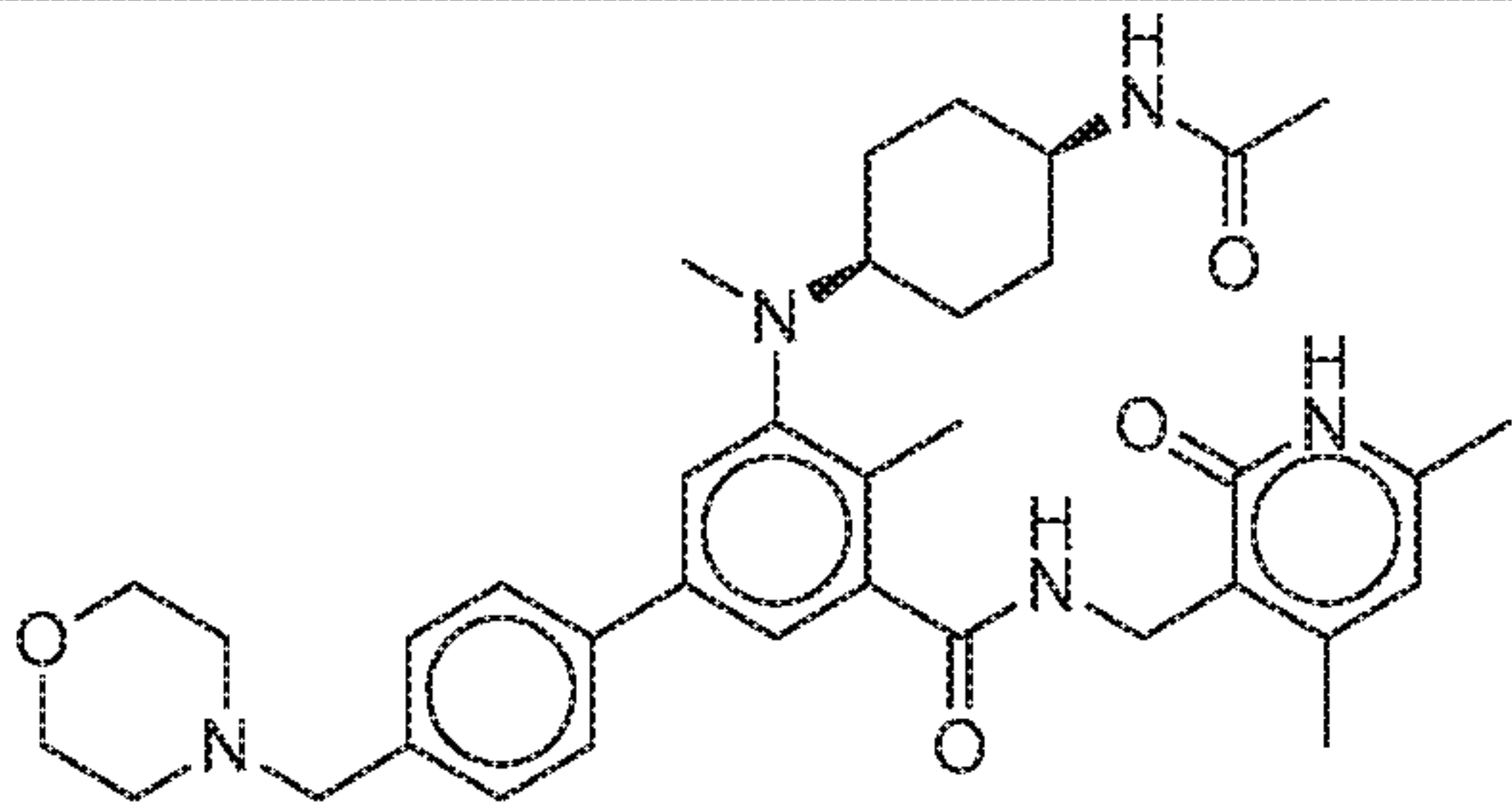
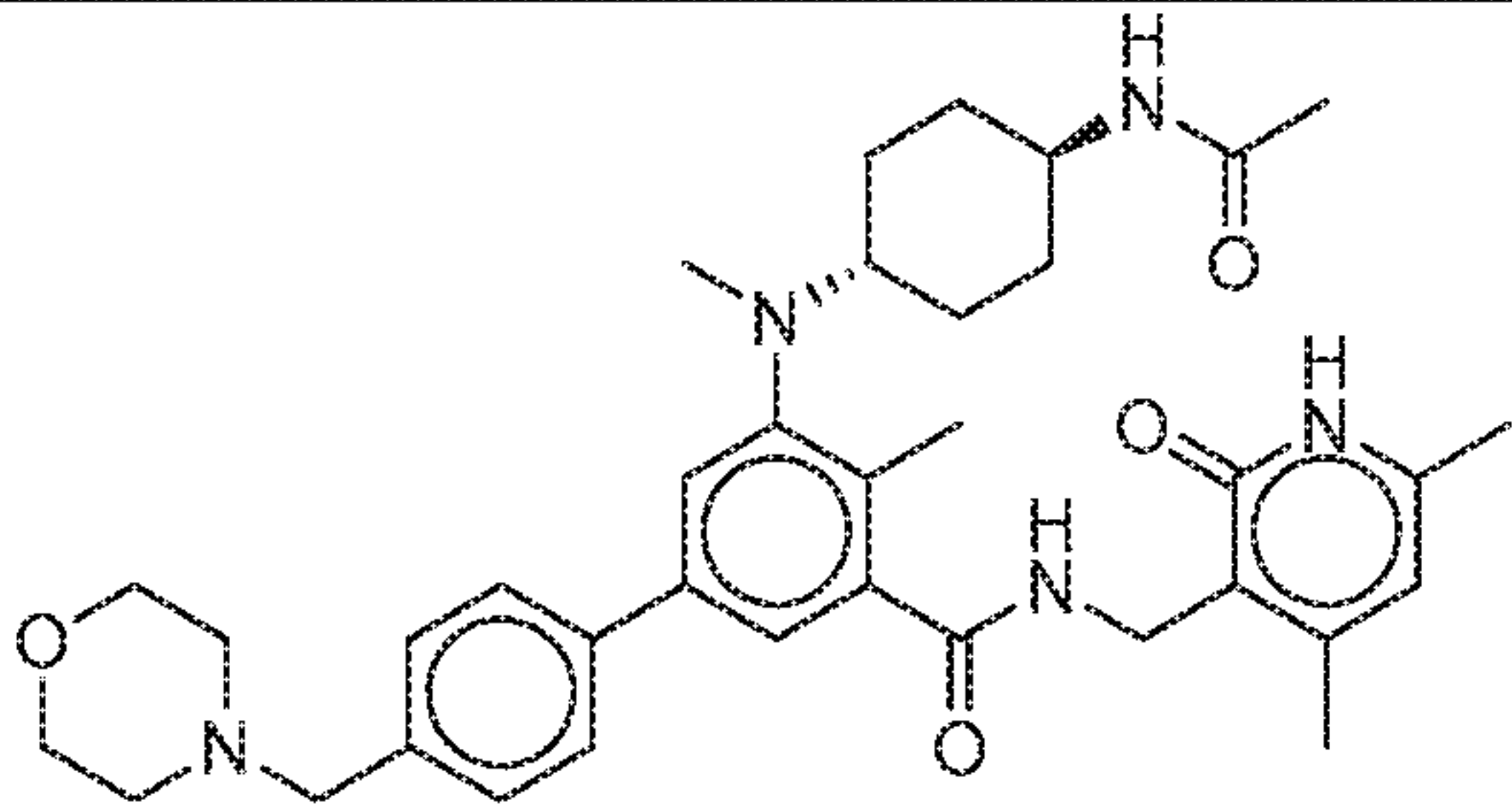
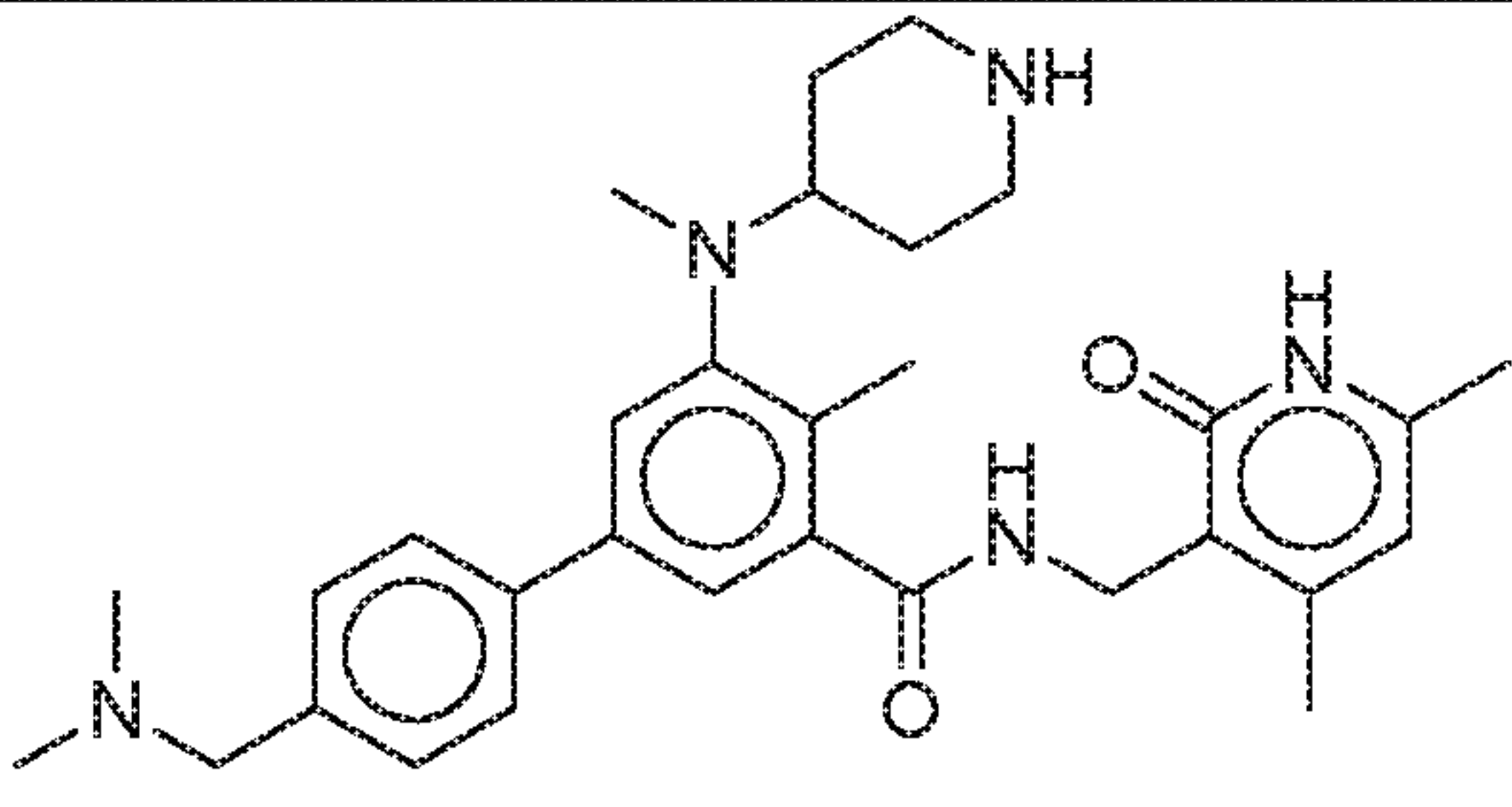
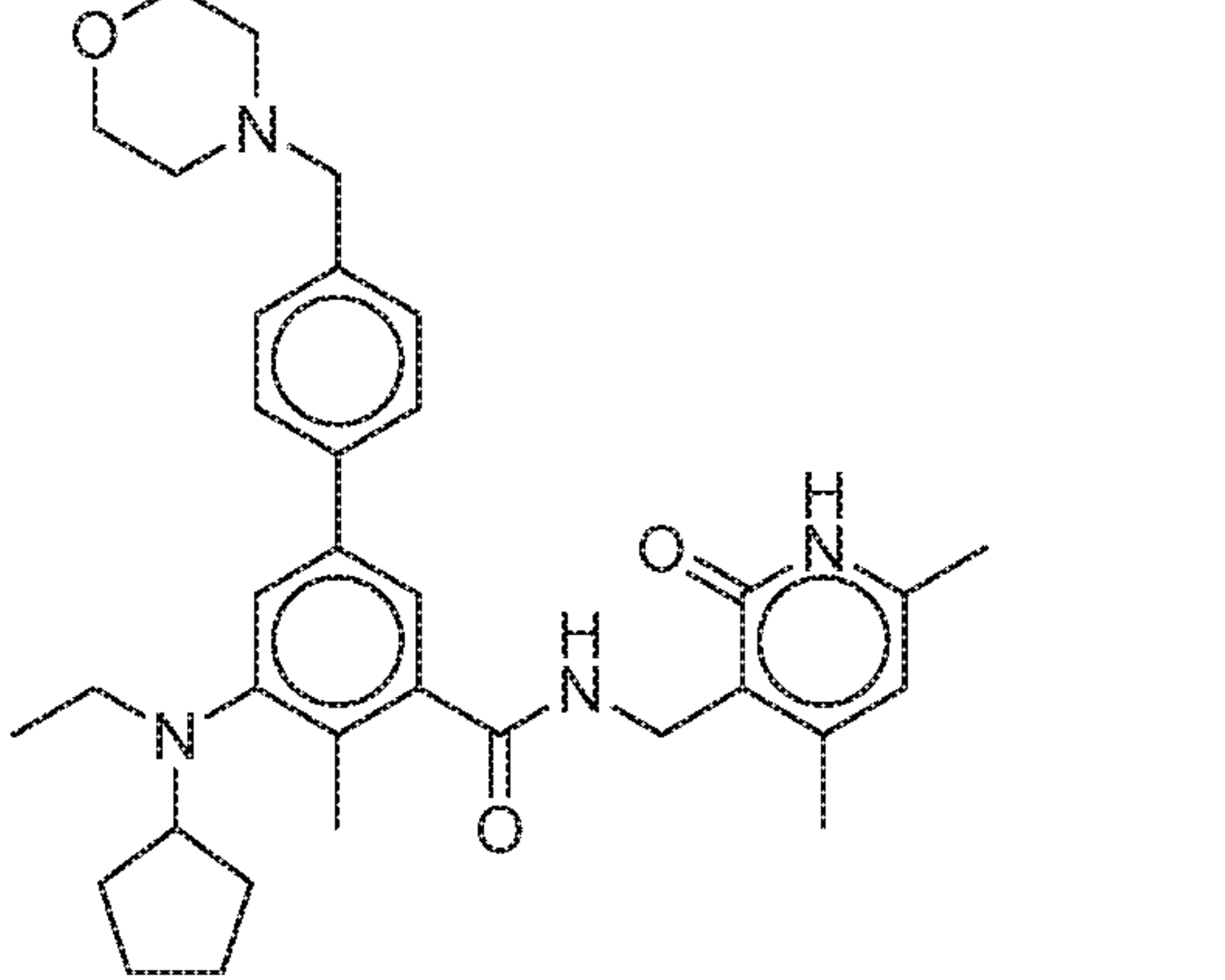
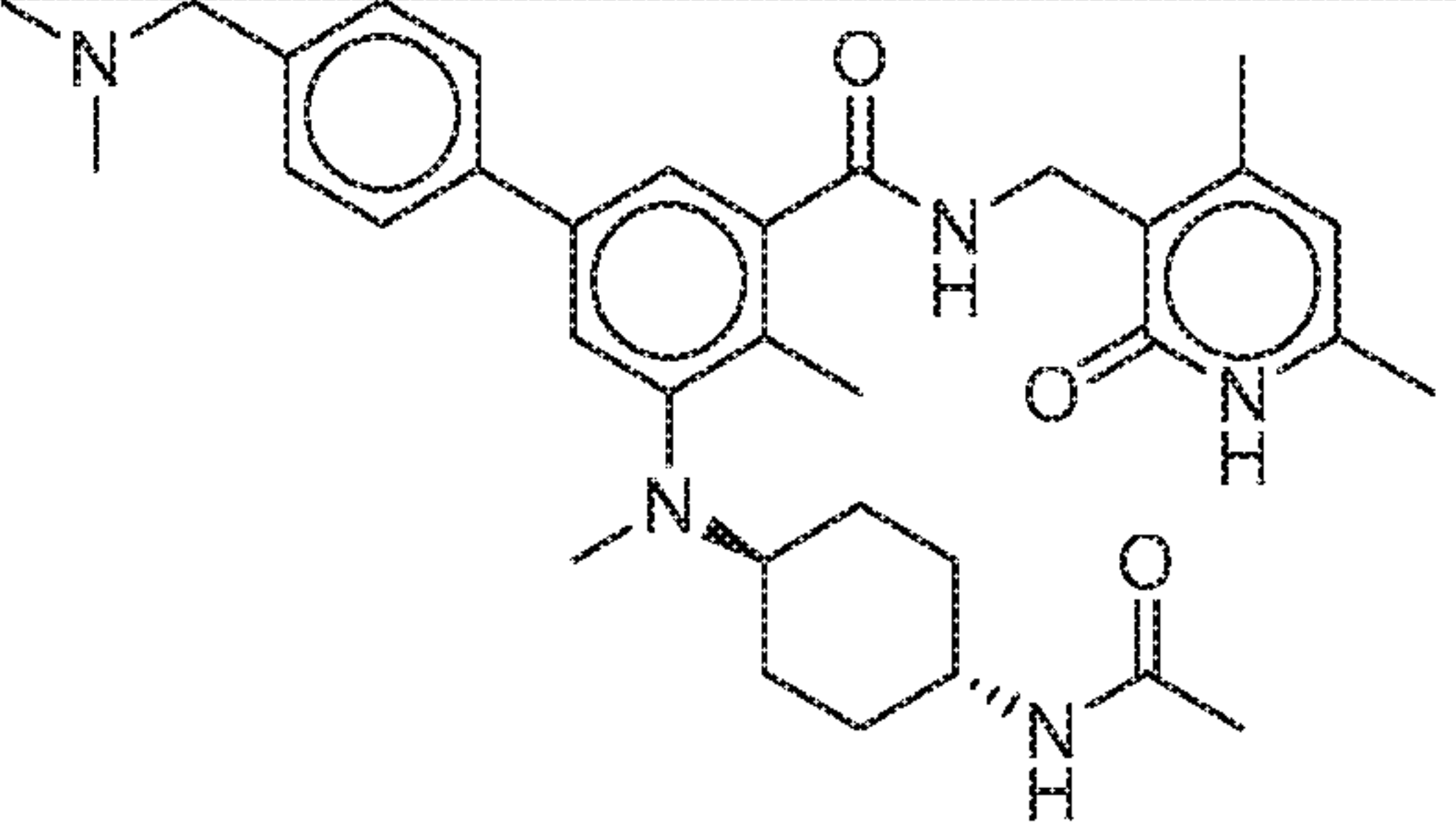
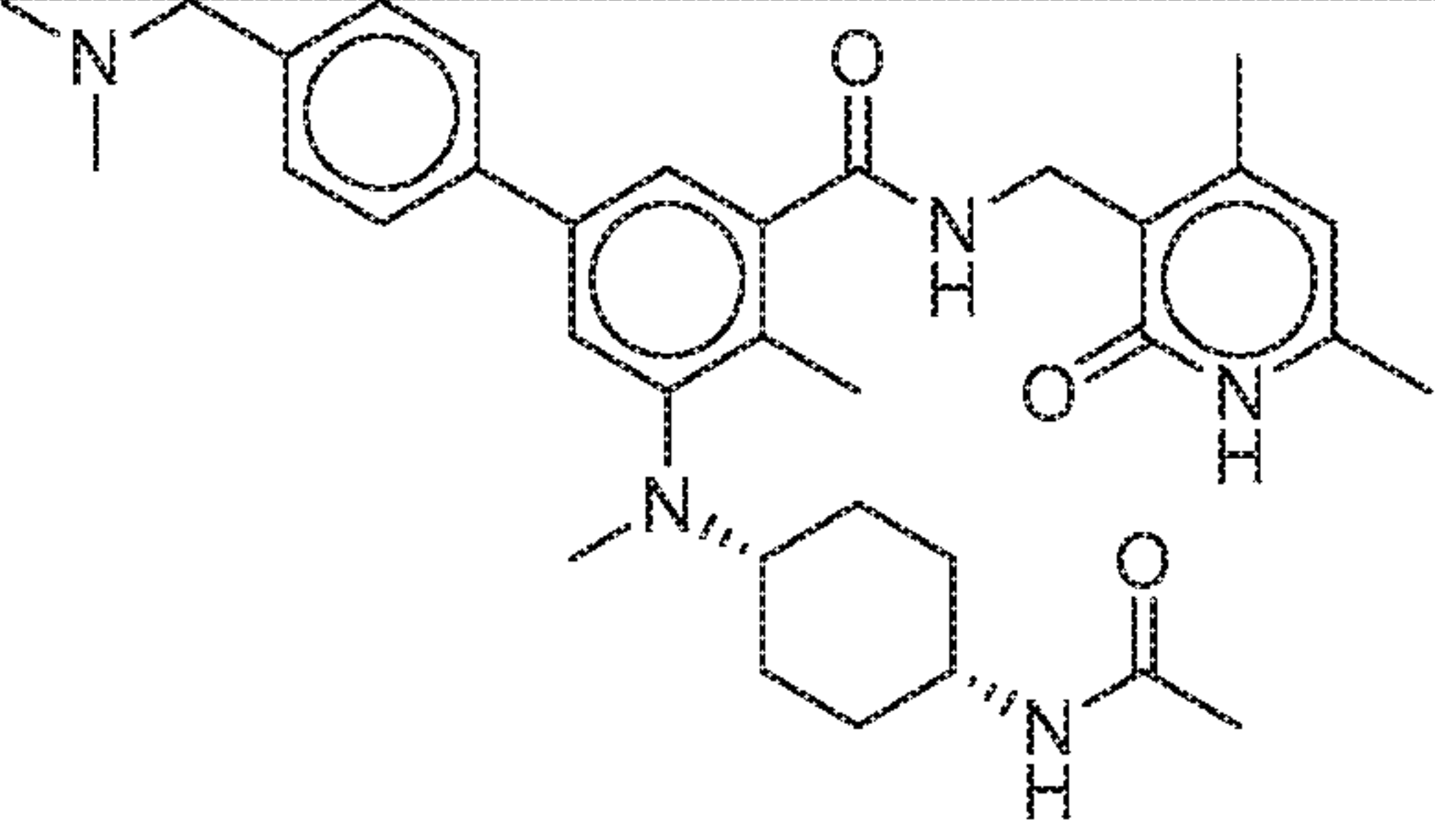
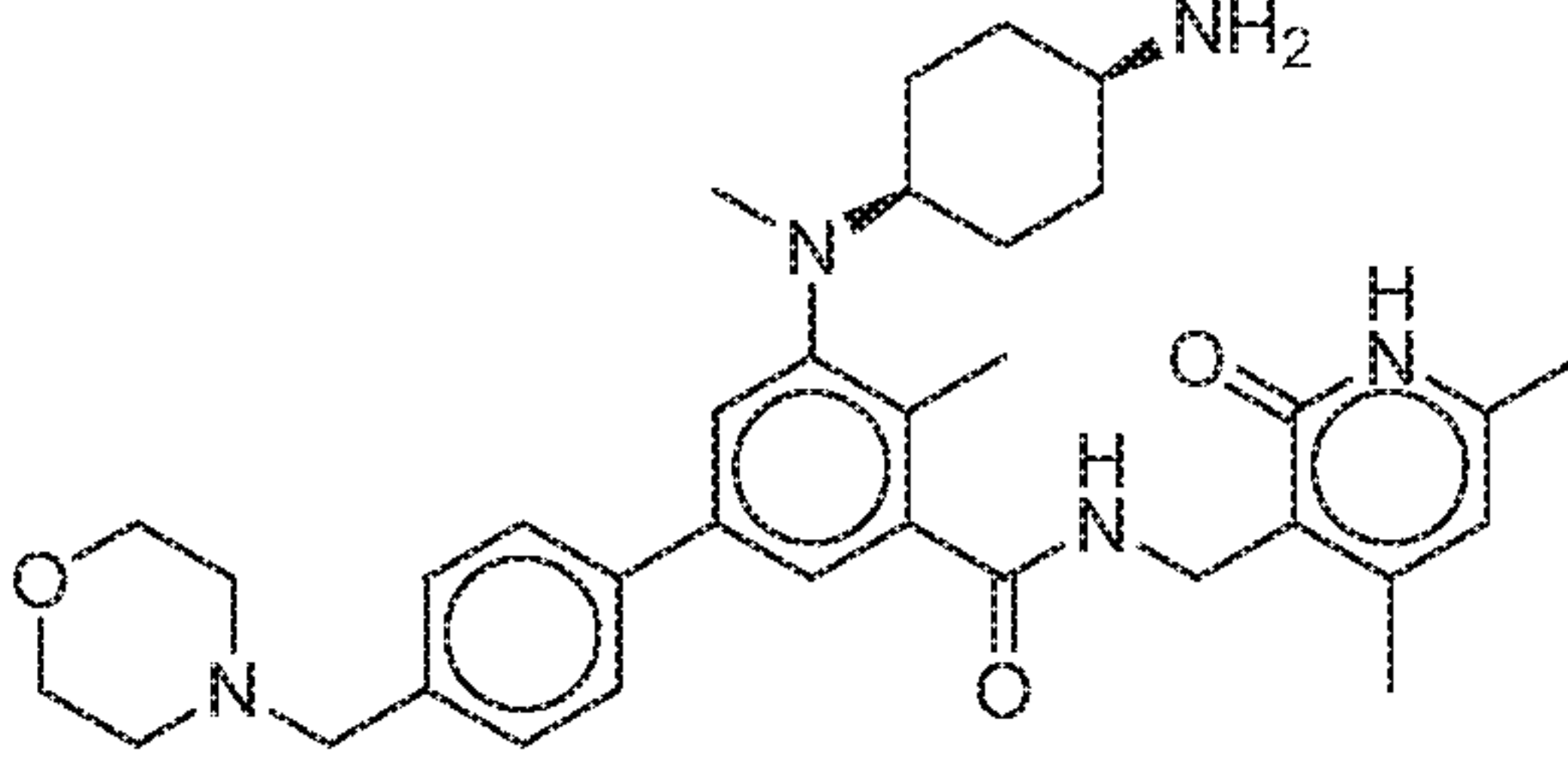
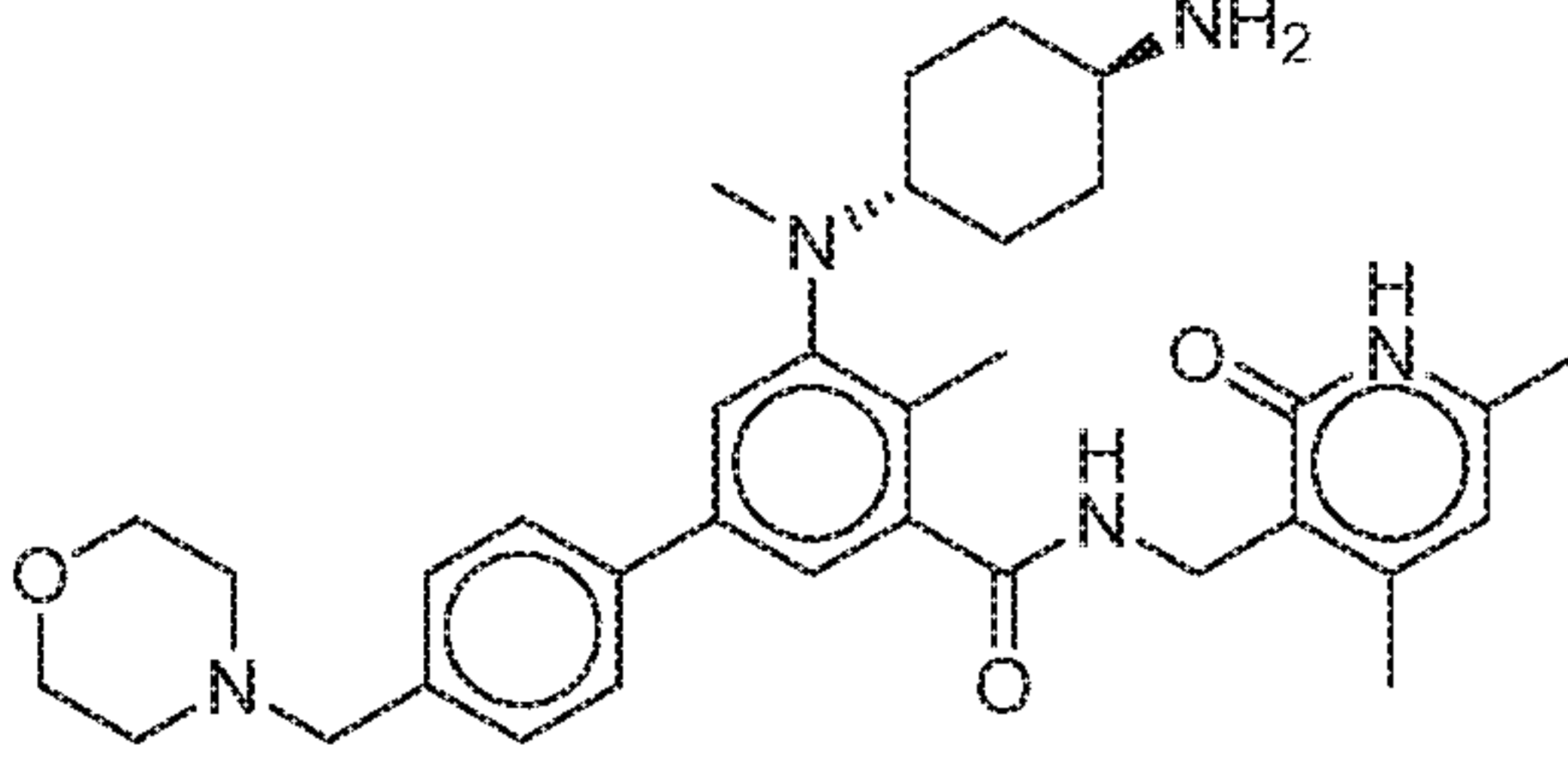
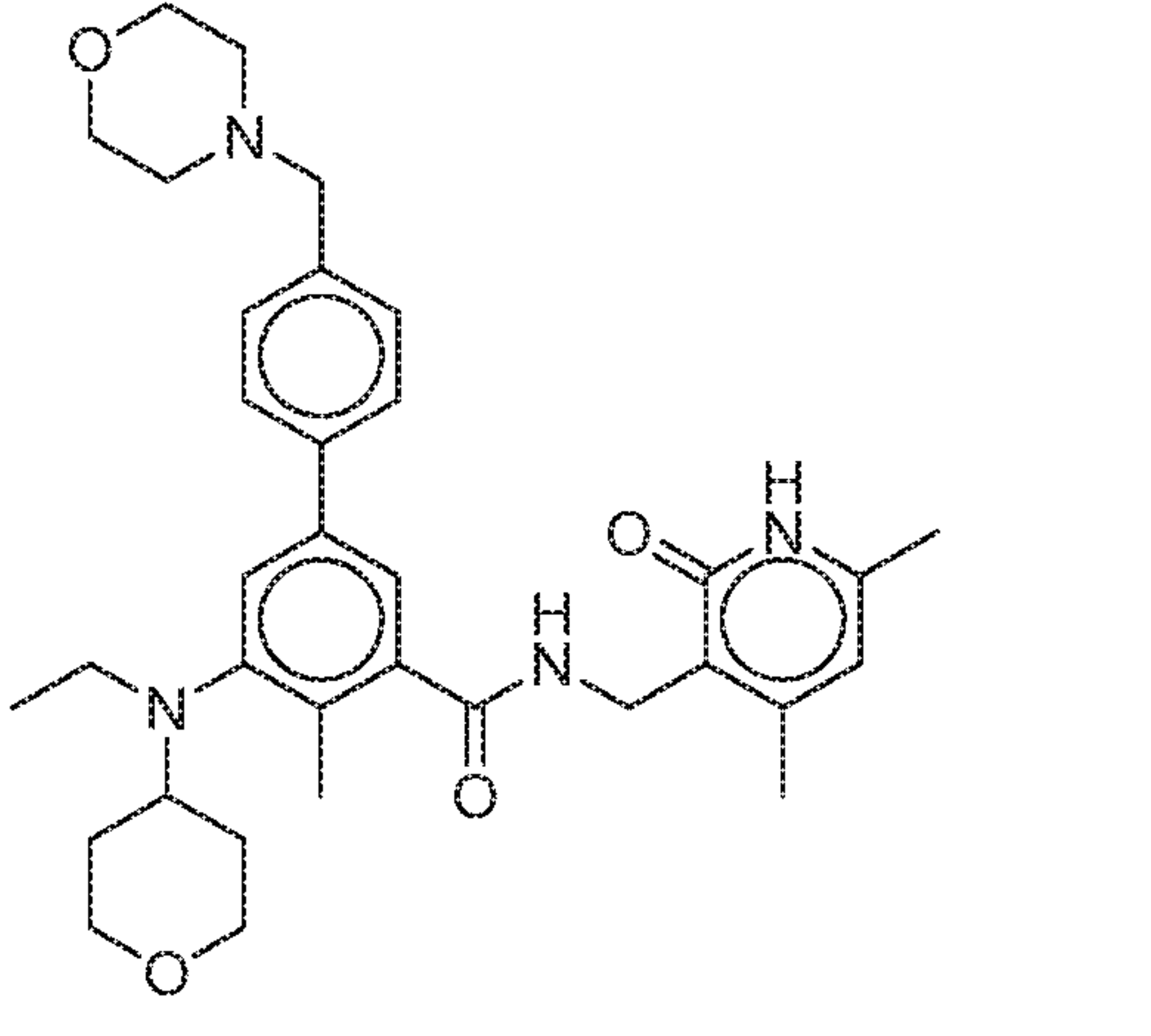
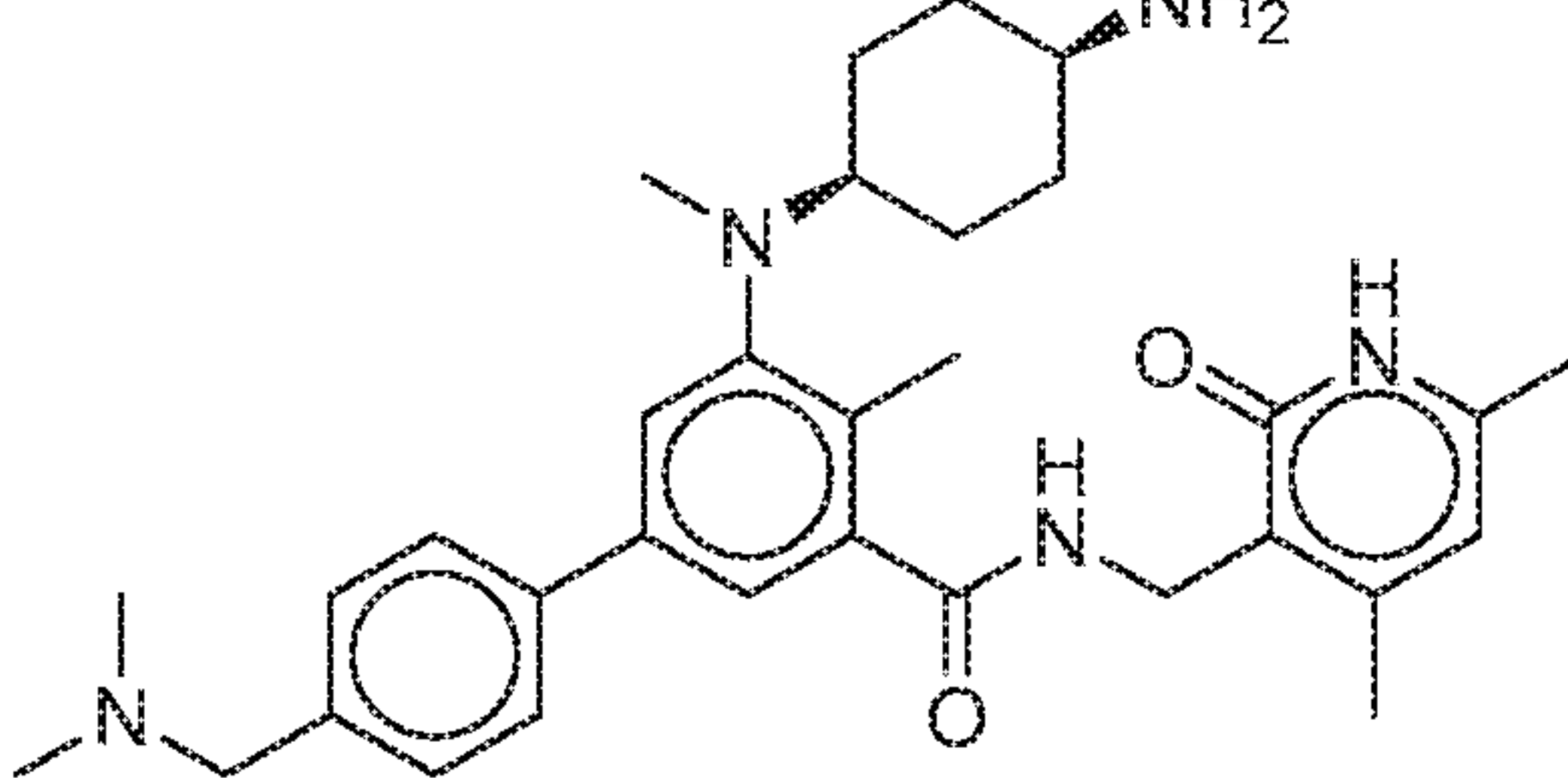
[0193] In Table 1, each occurrence of  should be construed as .

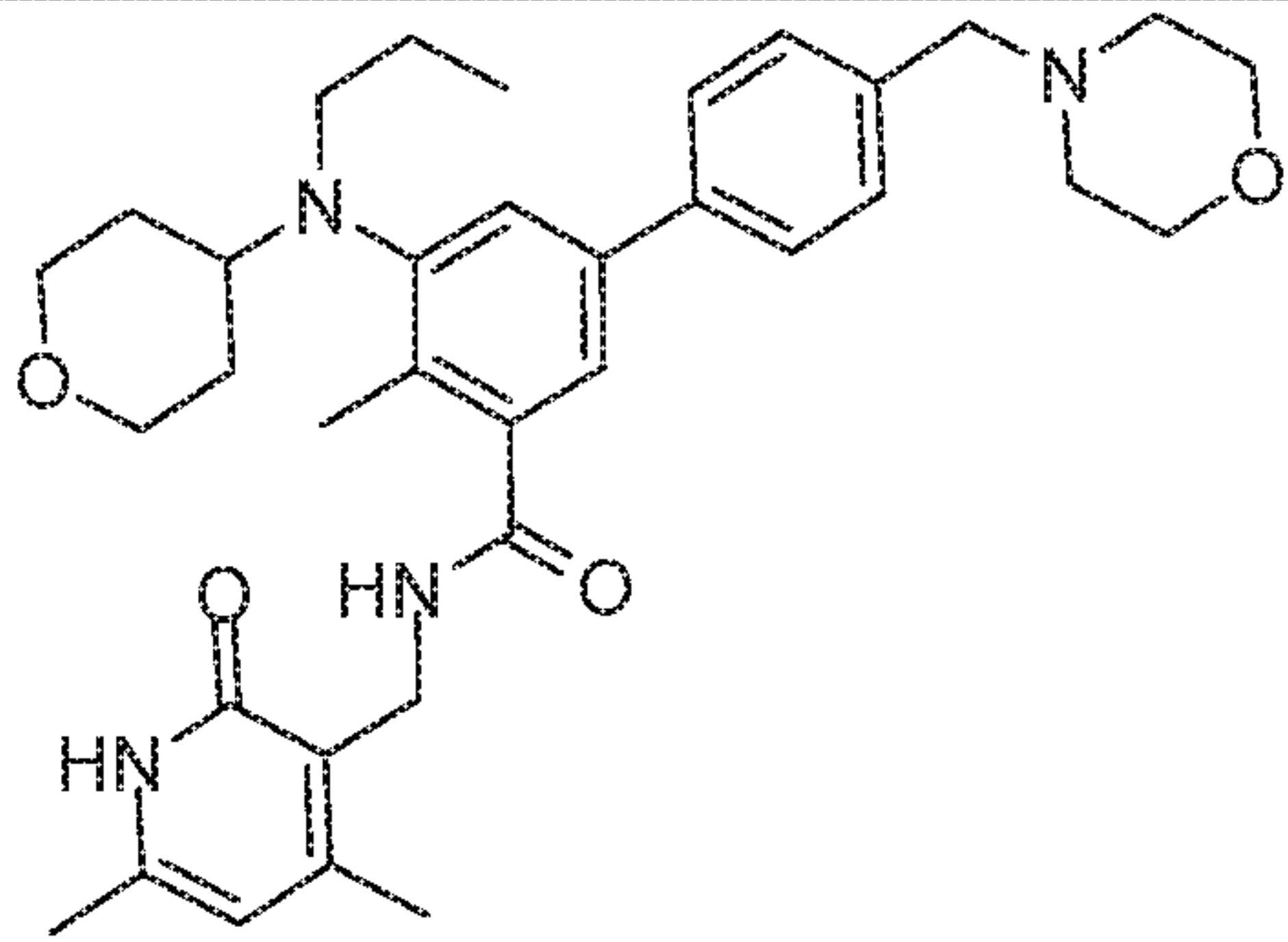
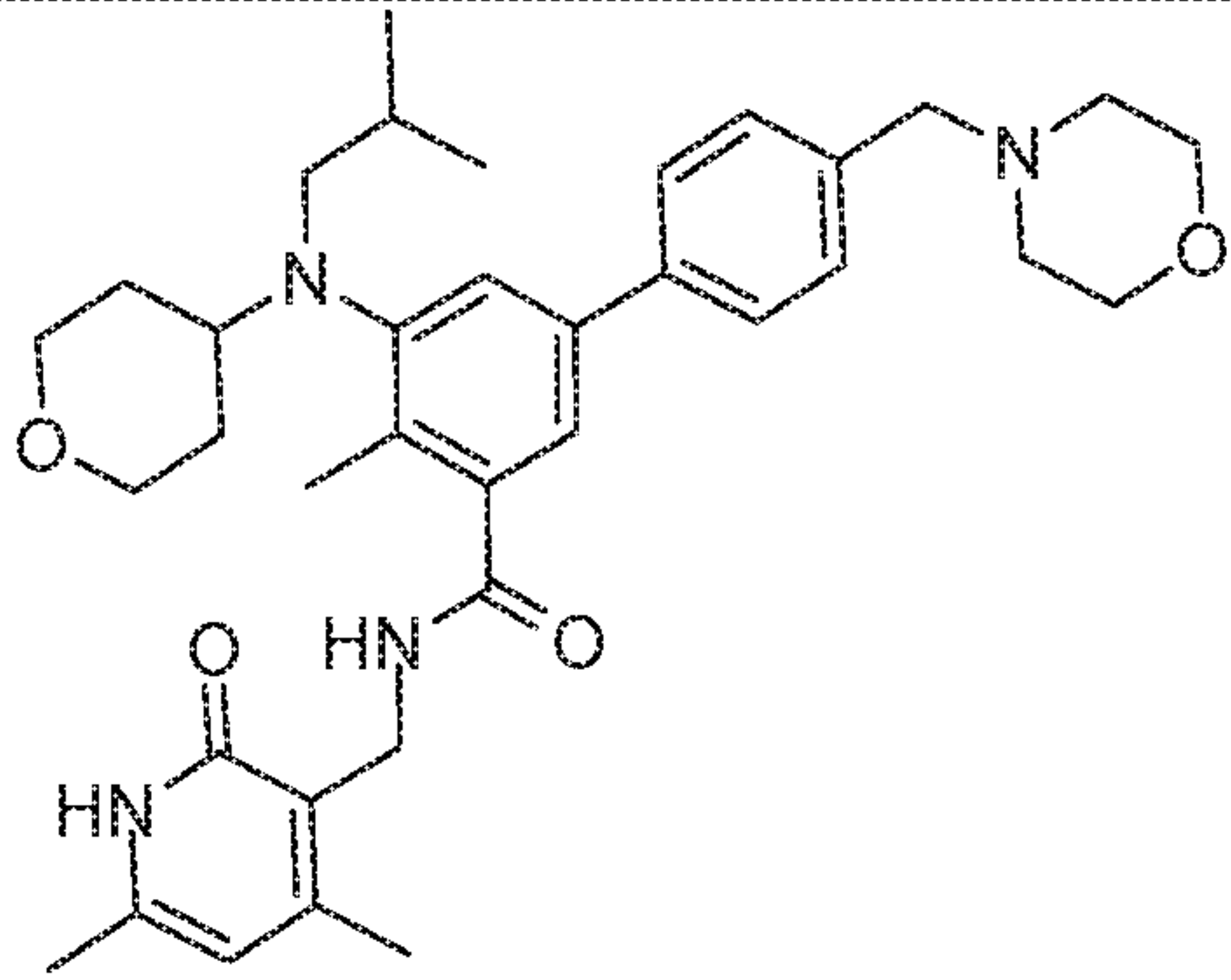
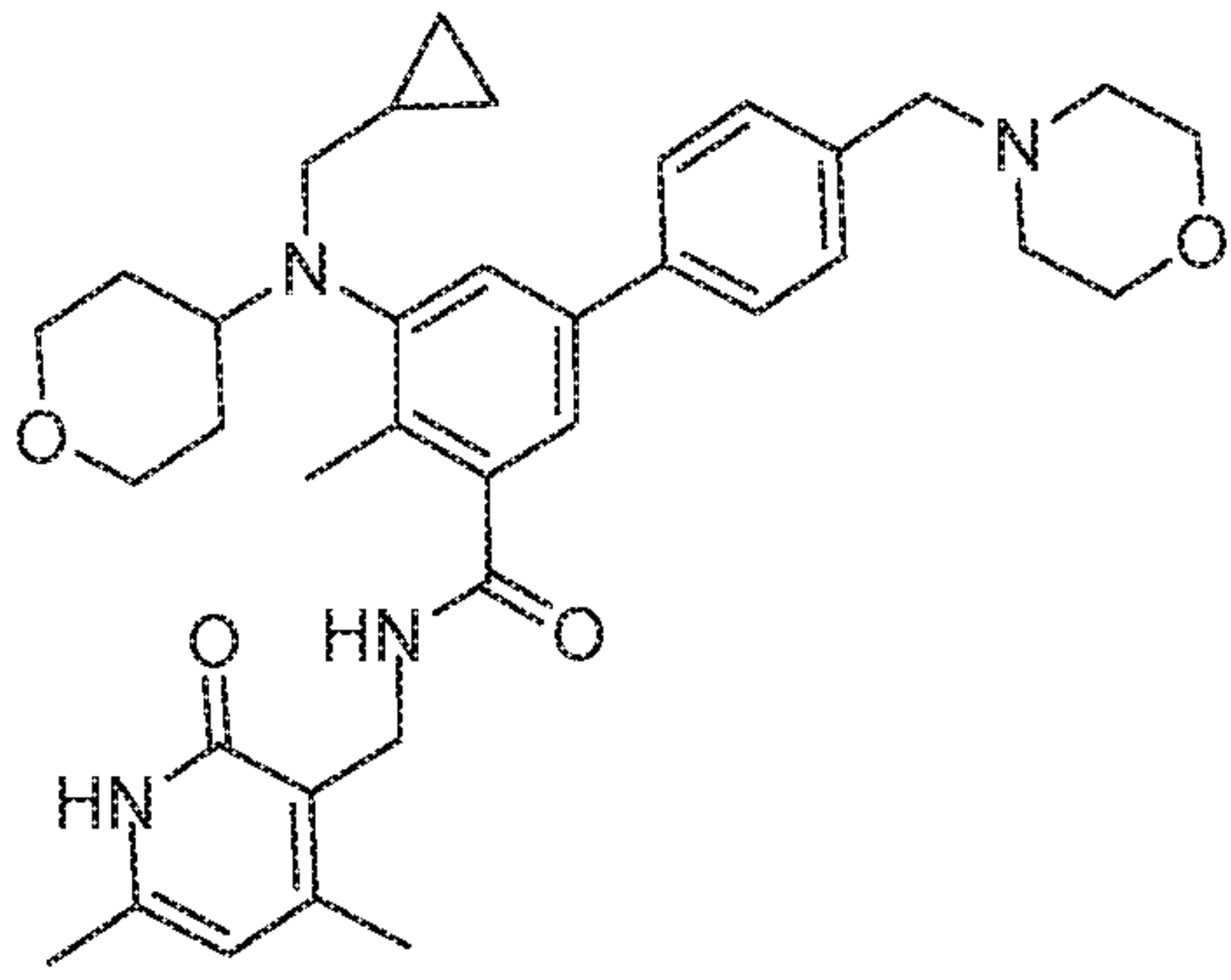
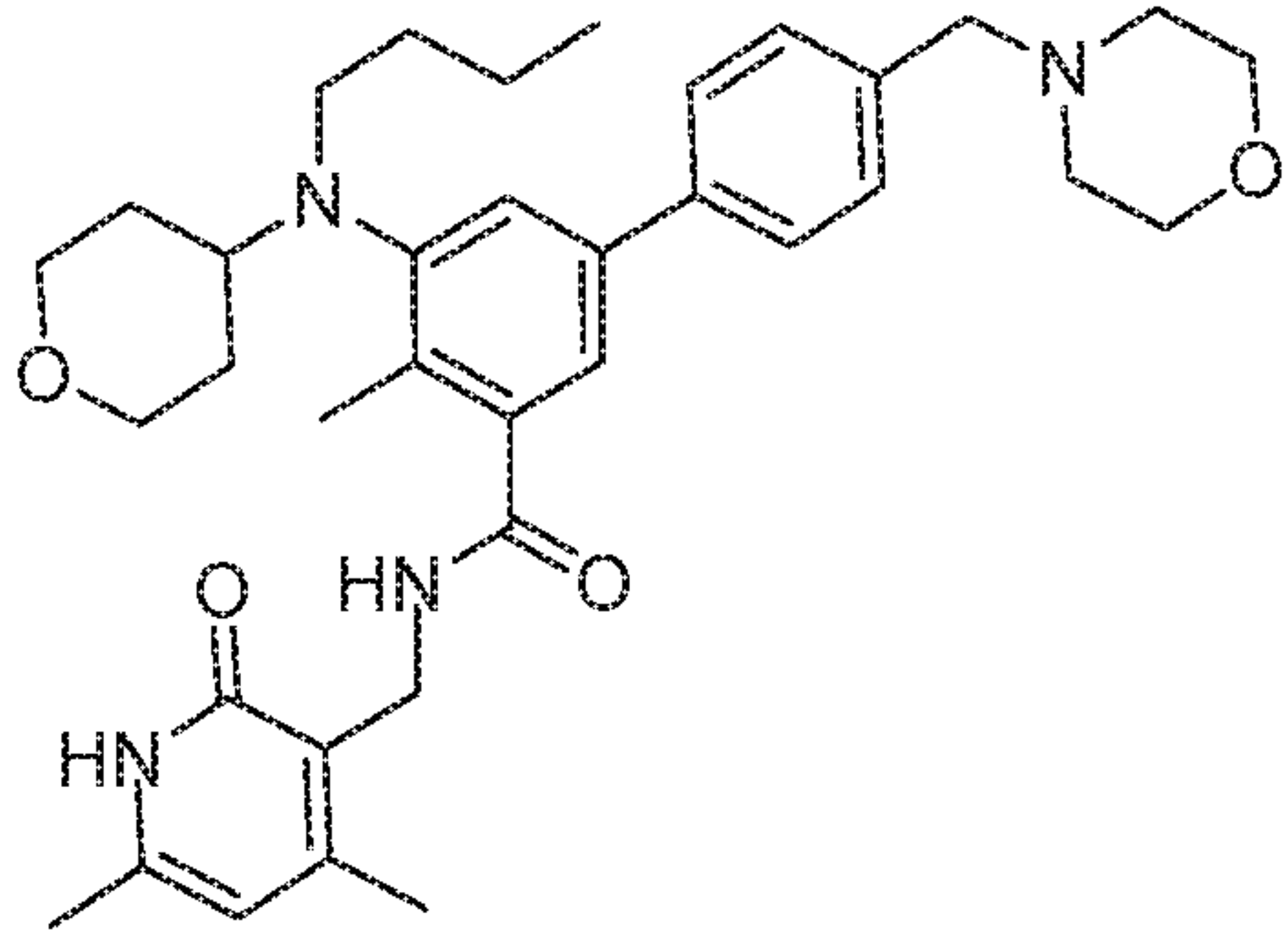
Table 1

Compound Number	Structure	MS (M+1) ⁺
1		501.39
2		543.22
3		486.21
4		529.30

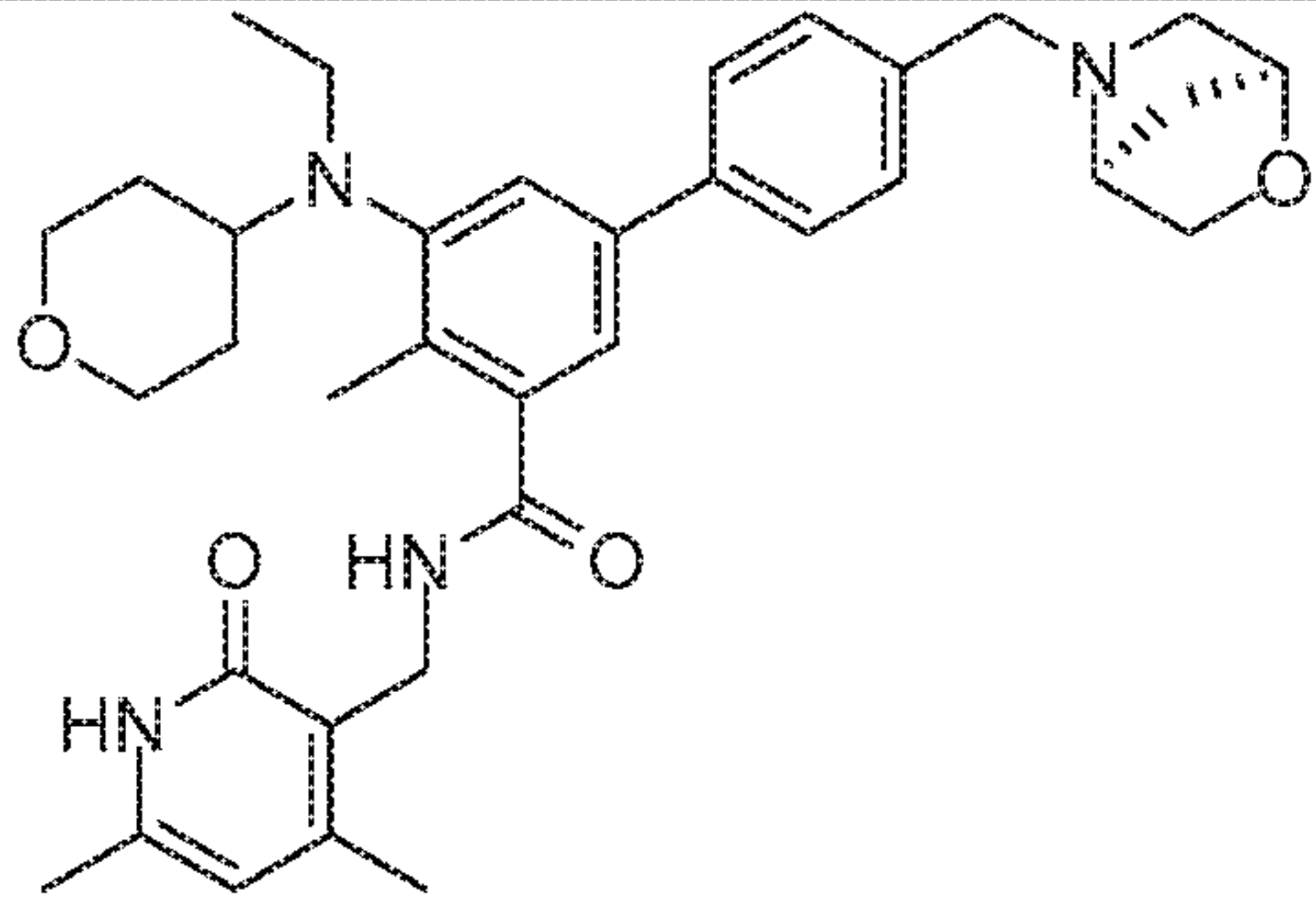
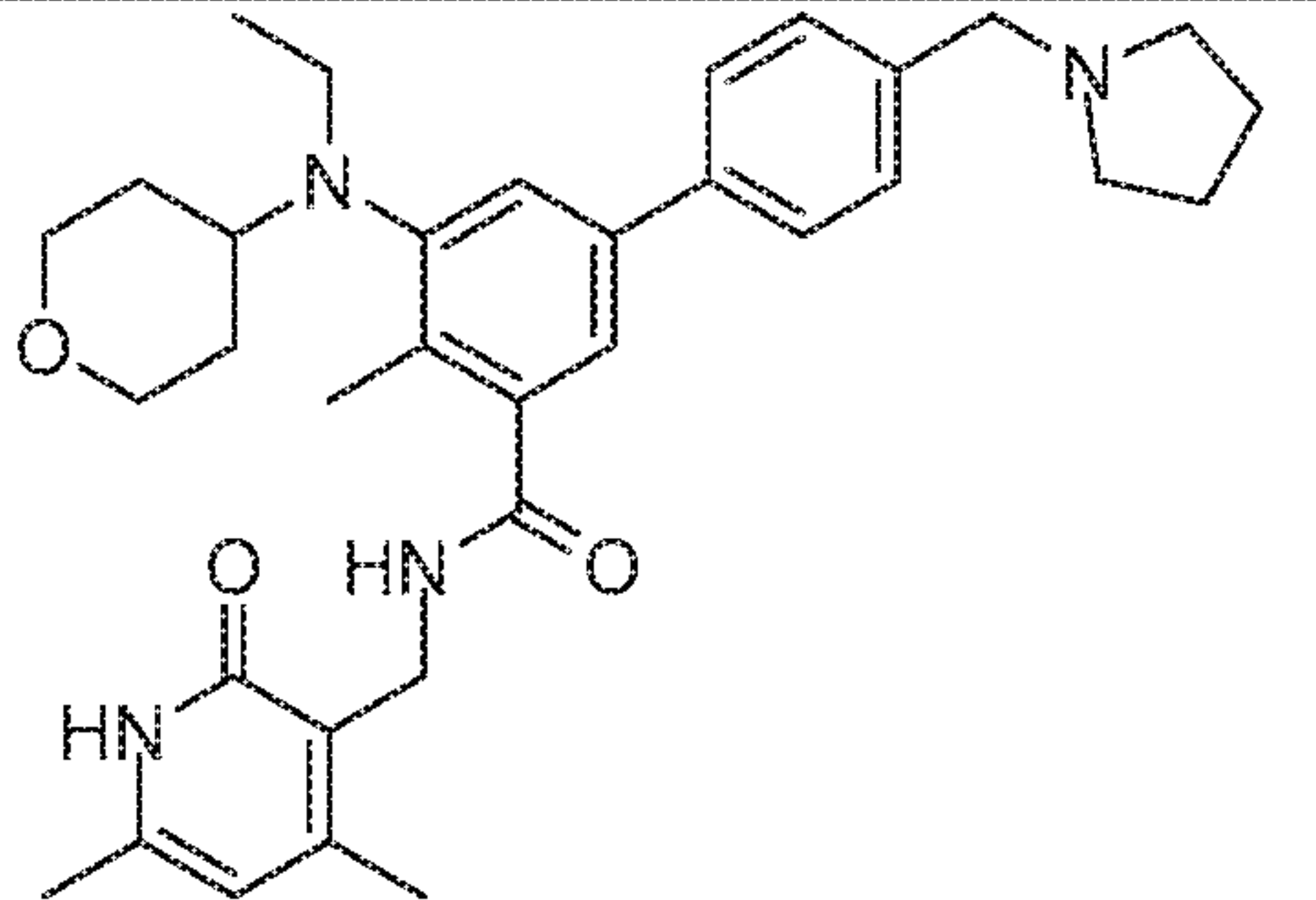
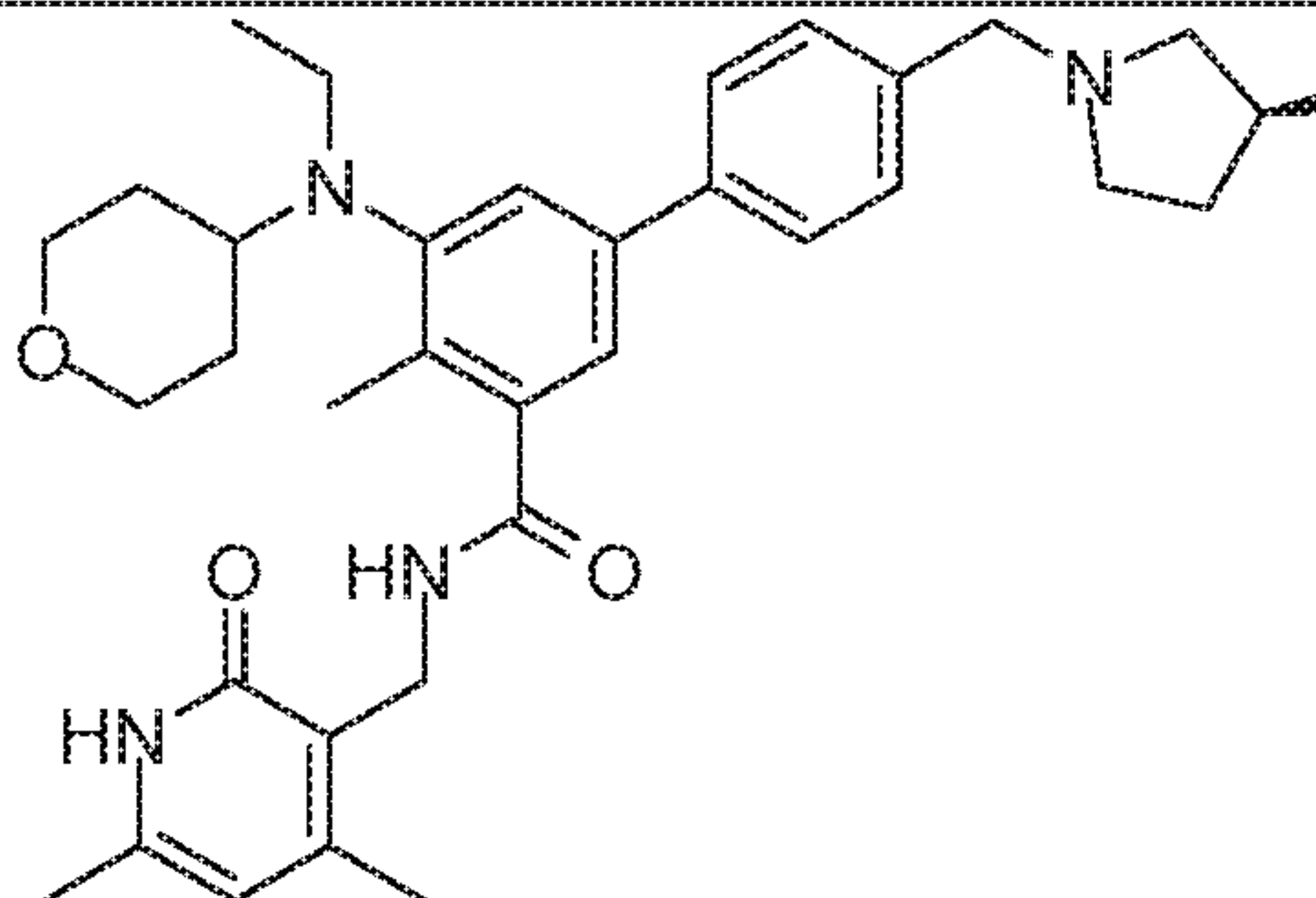
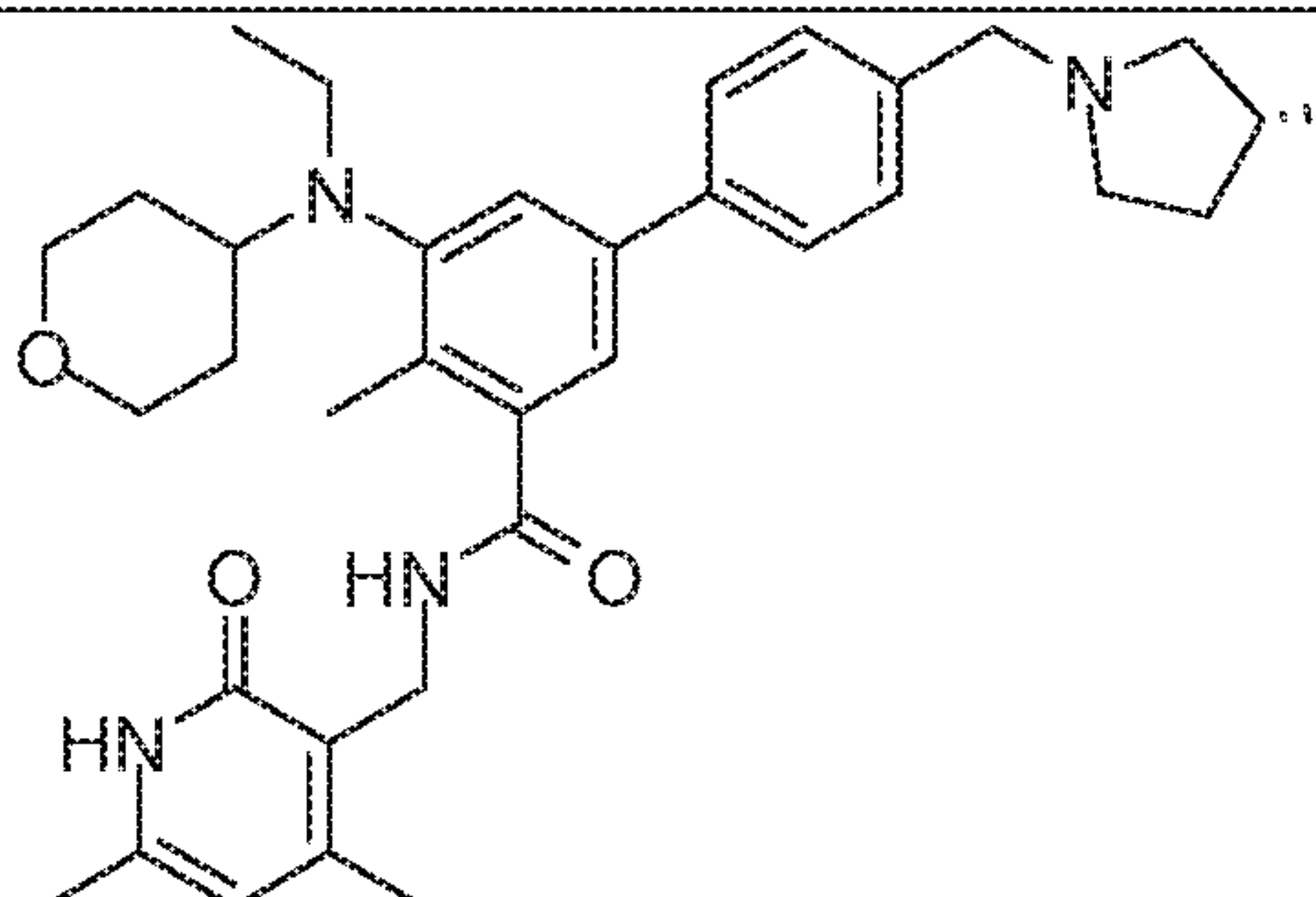
Compound Number	Structure	MS (M+1) ⁺
11		558.45
12		559.35
13		517.3
14		557.4
16		515.4

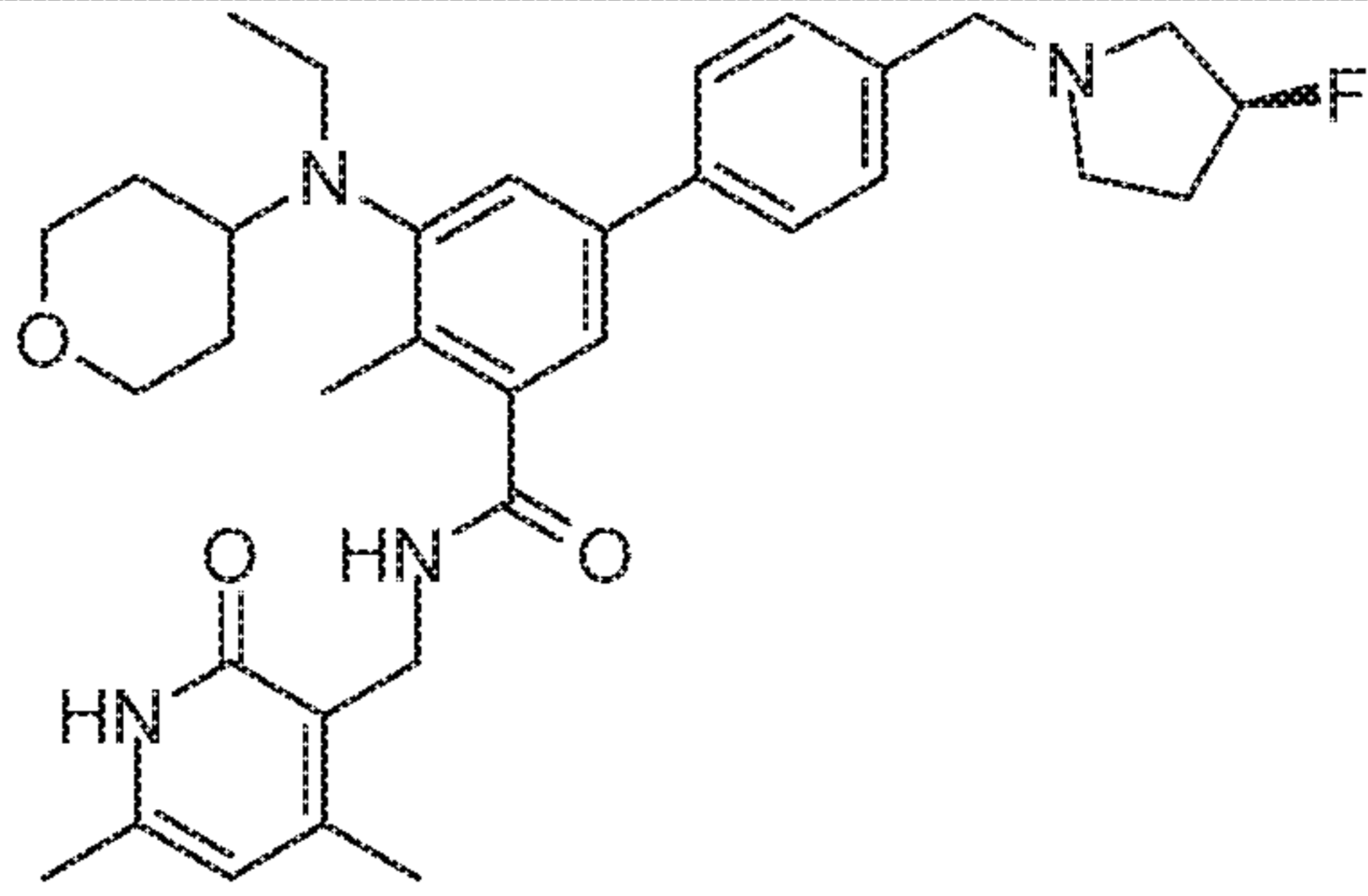
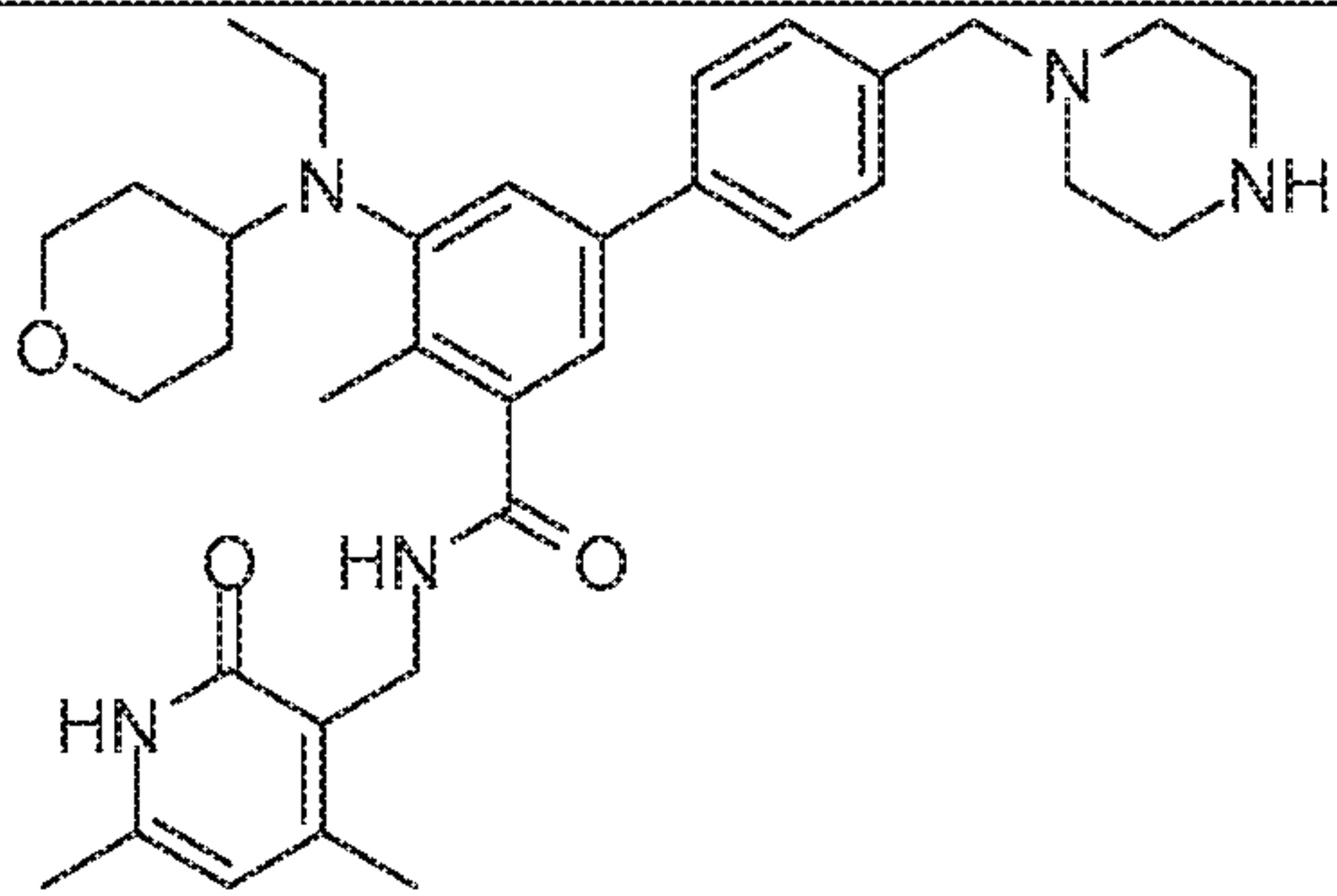
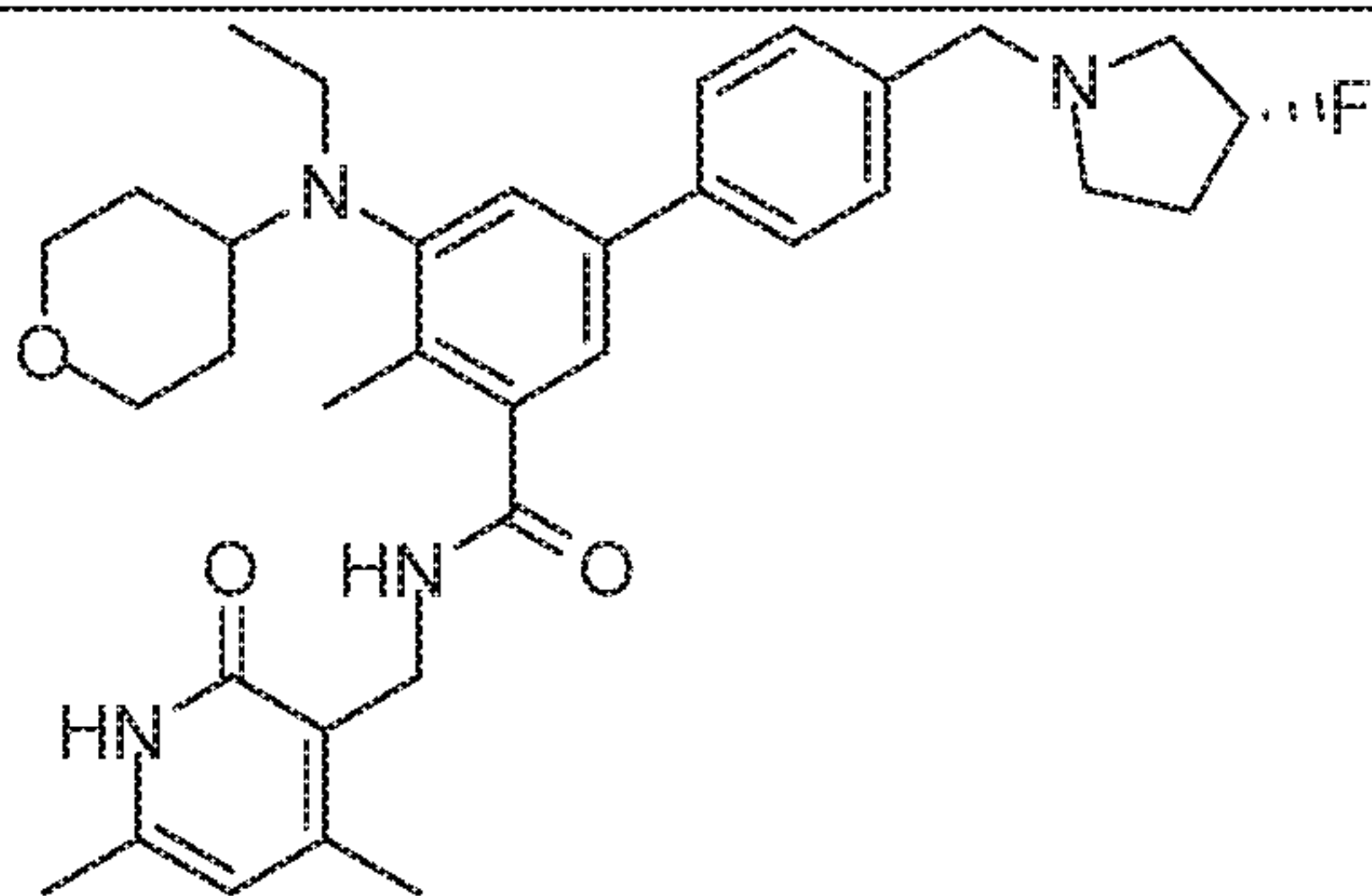
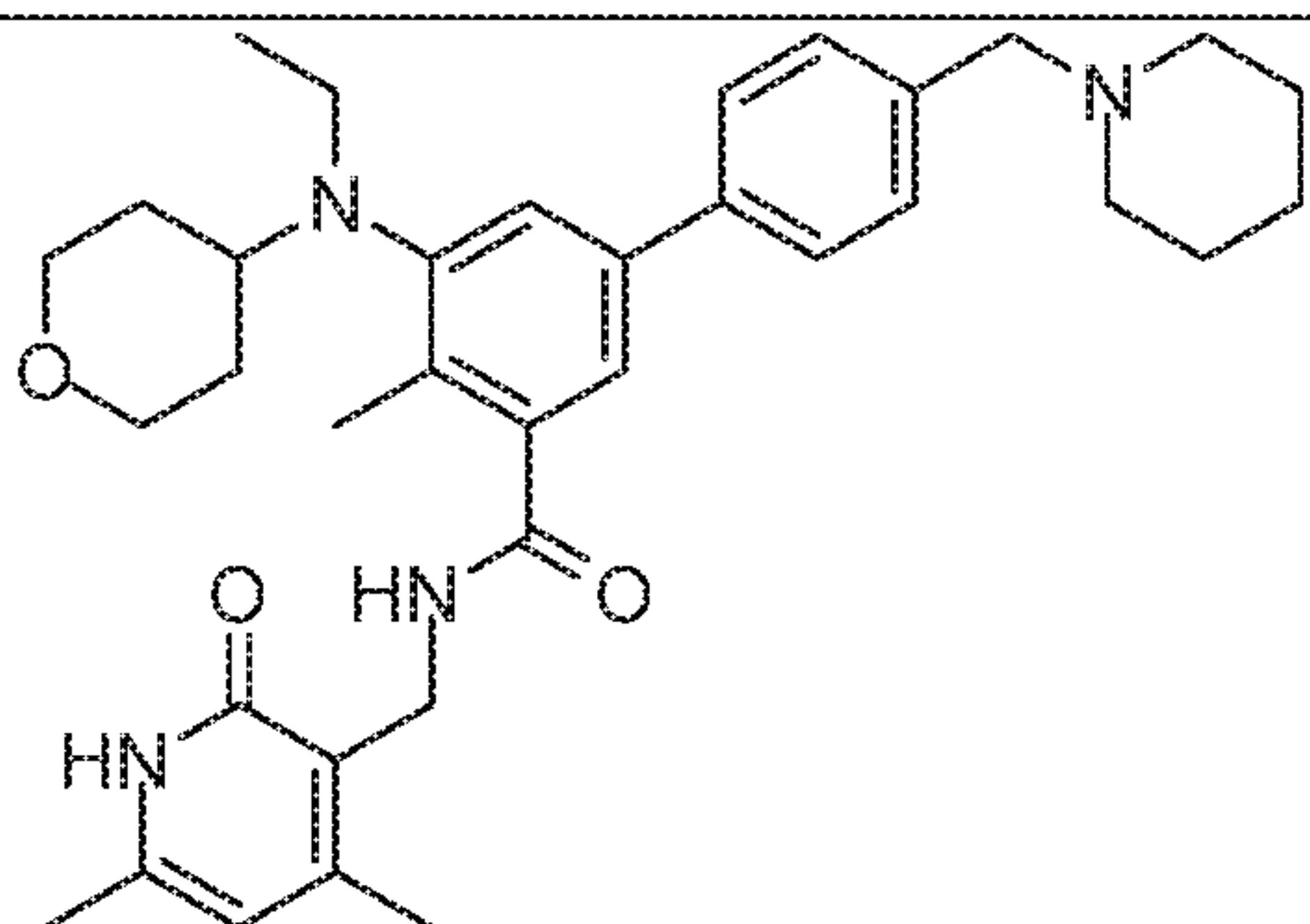
Compound Number	Structure	MS (M+1) ⁺
20		614.4
21		614.4
27		516.35
36		557.35
39		572.35

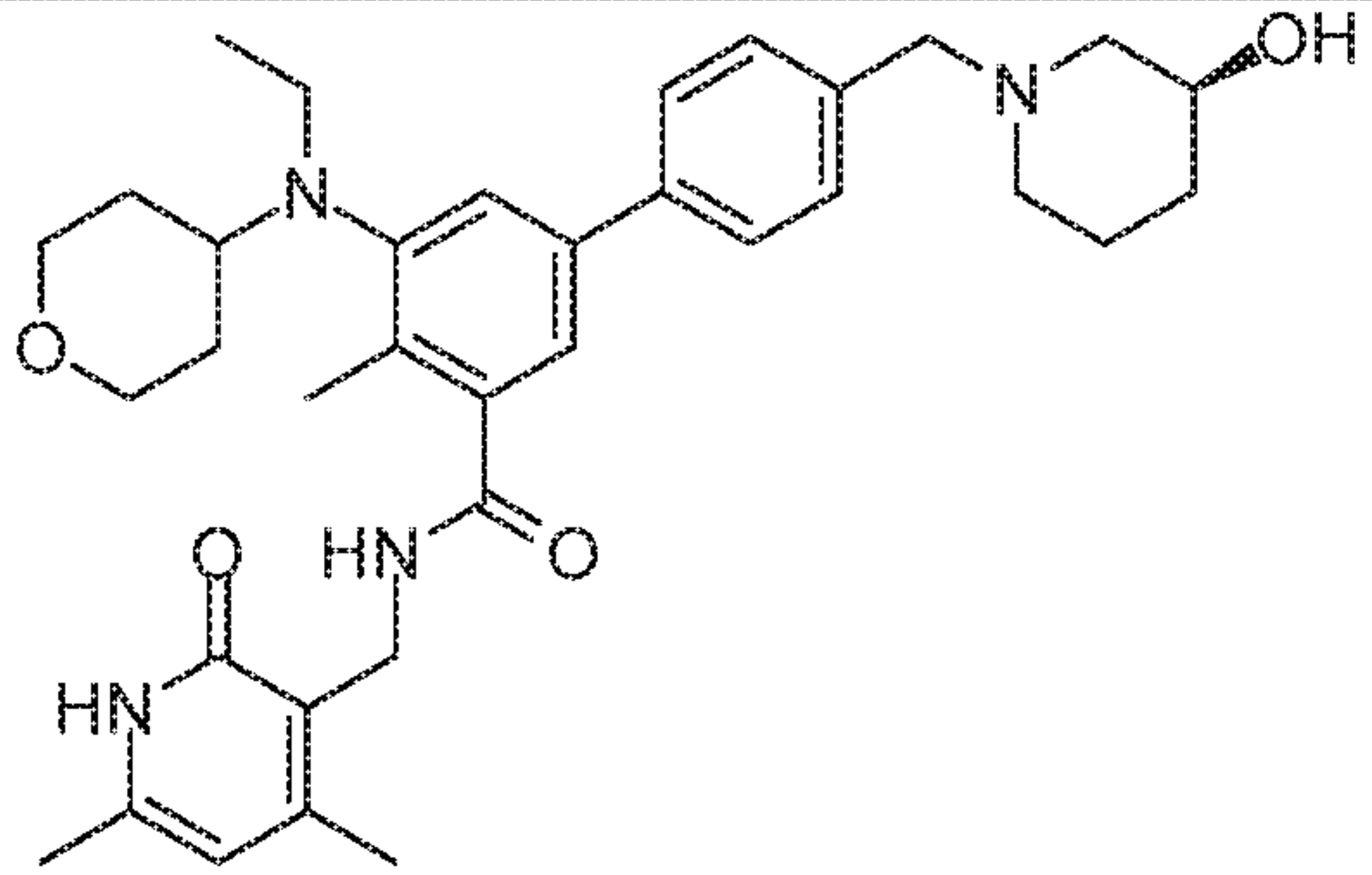
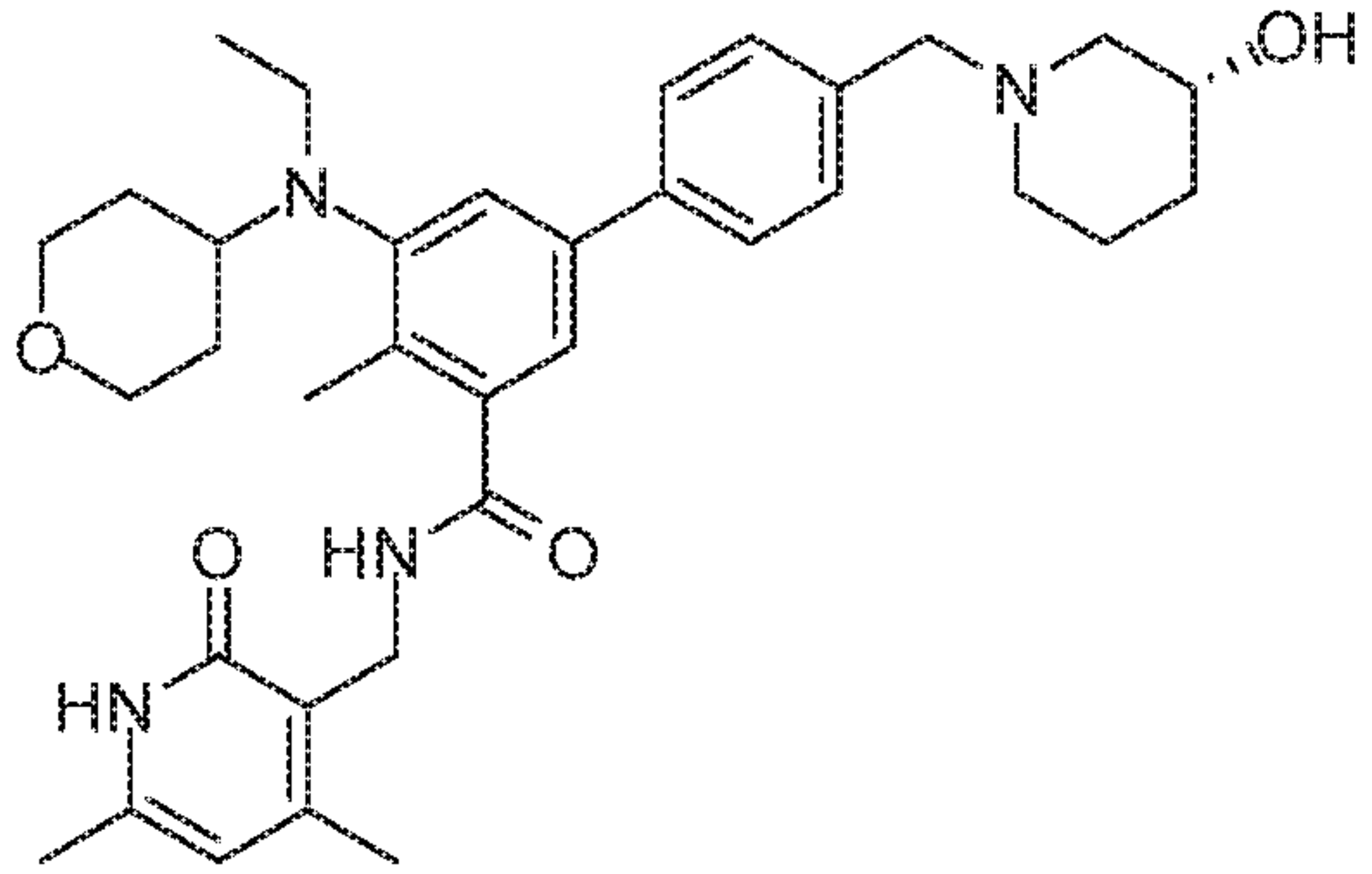
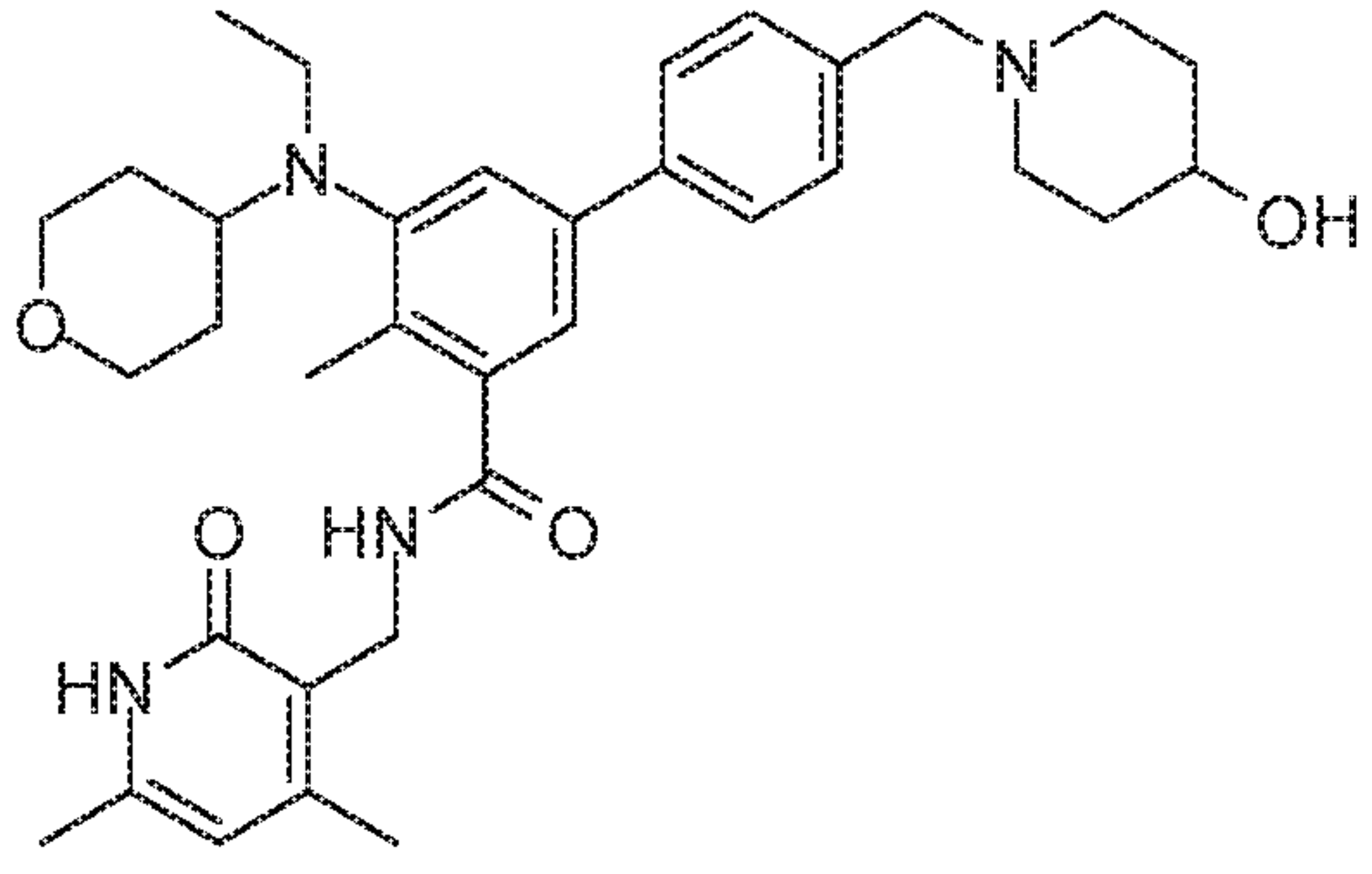
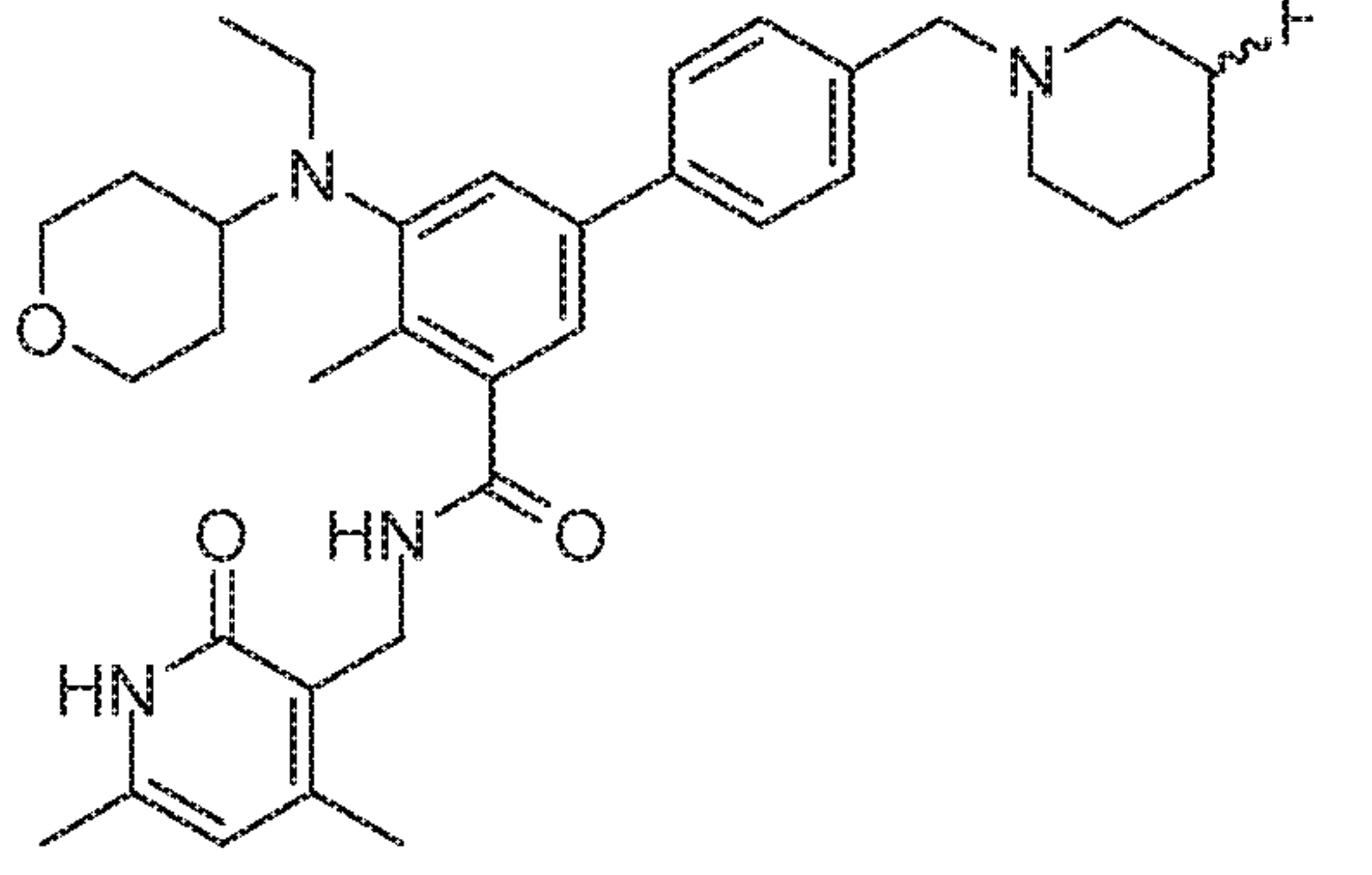
Compound Number	Structure	MS (M+1) ⁺
40		572.35
42		572.4
43		572.6
44		573.40
47		530.35

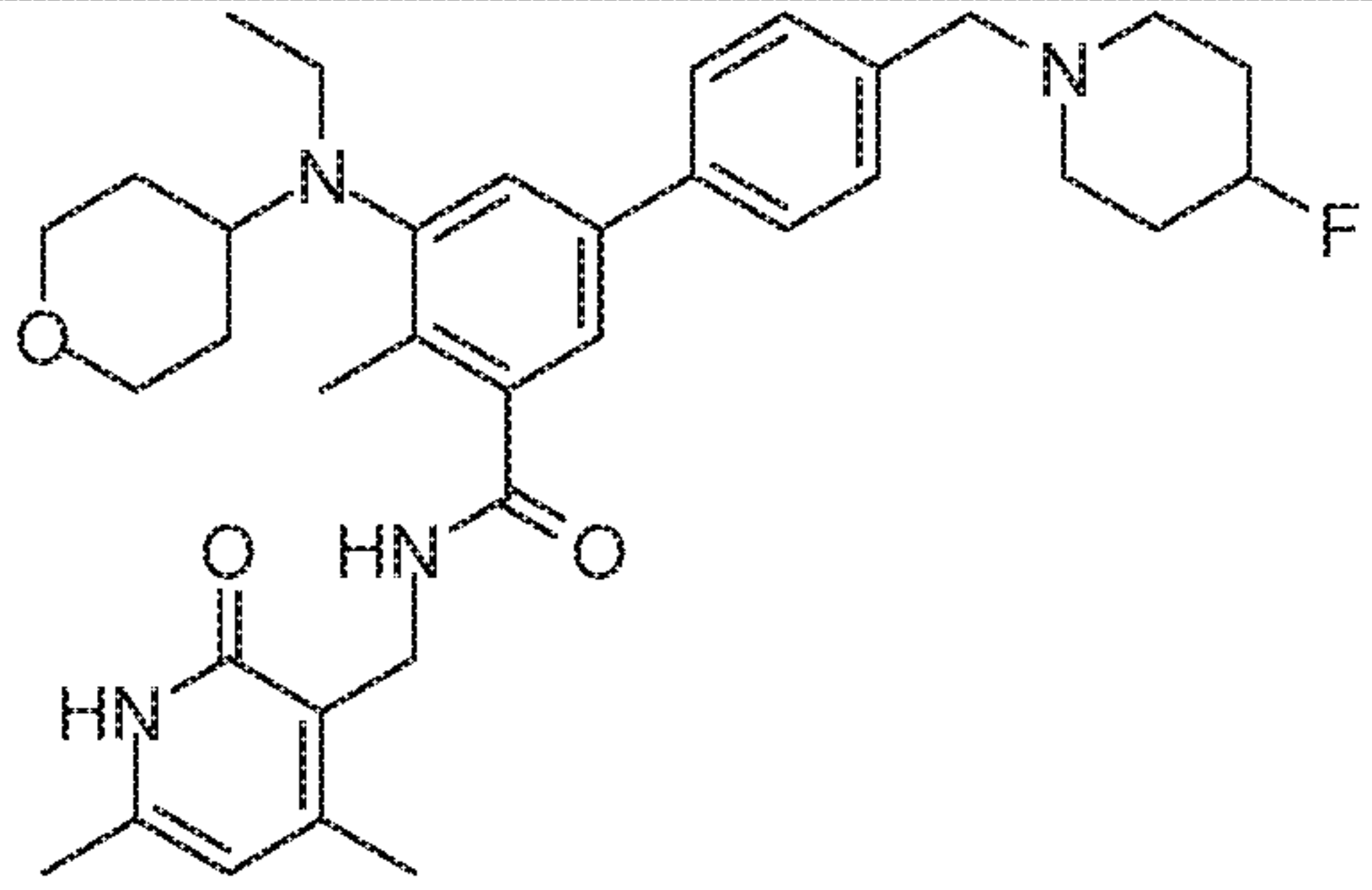
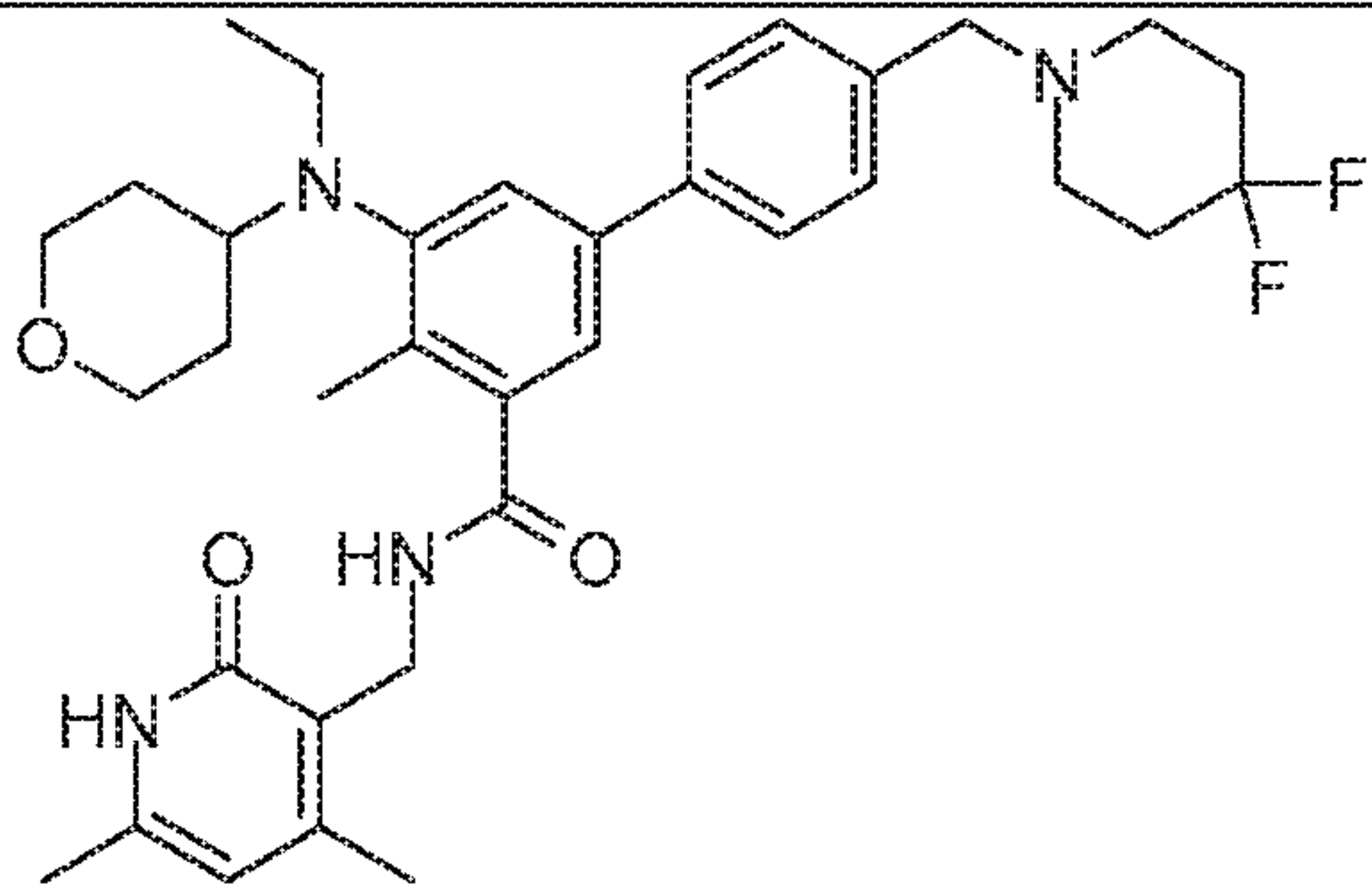
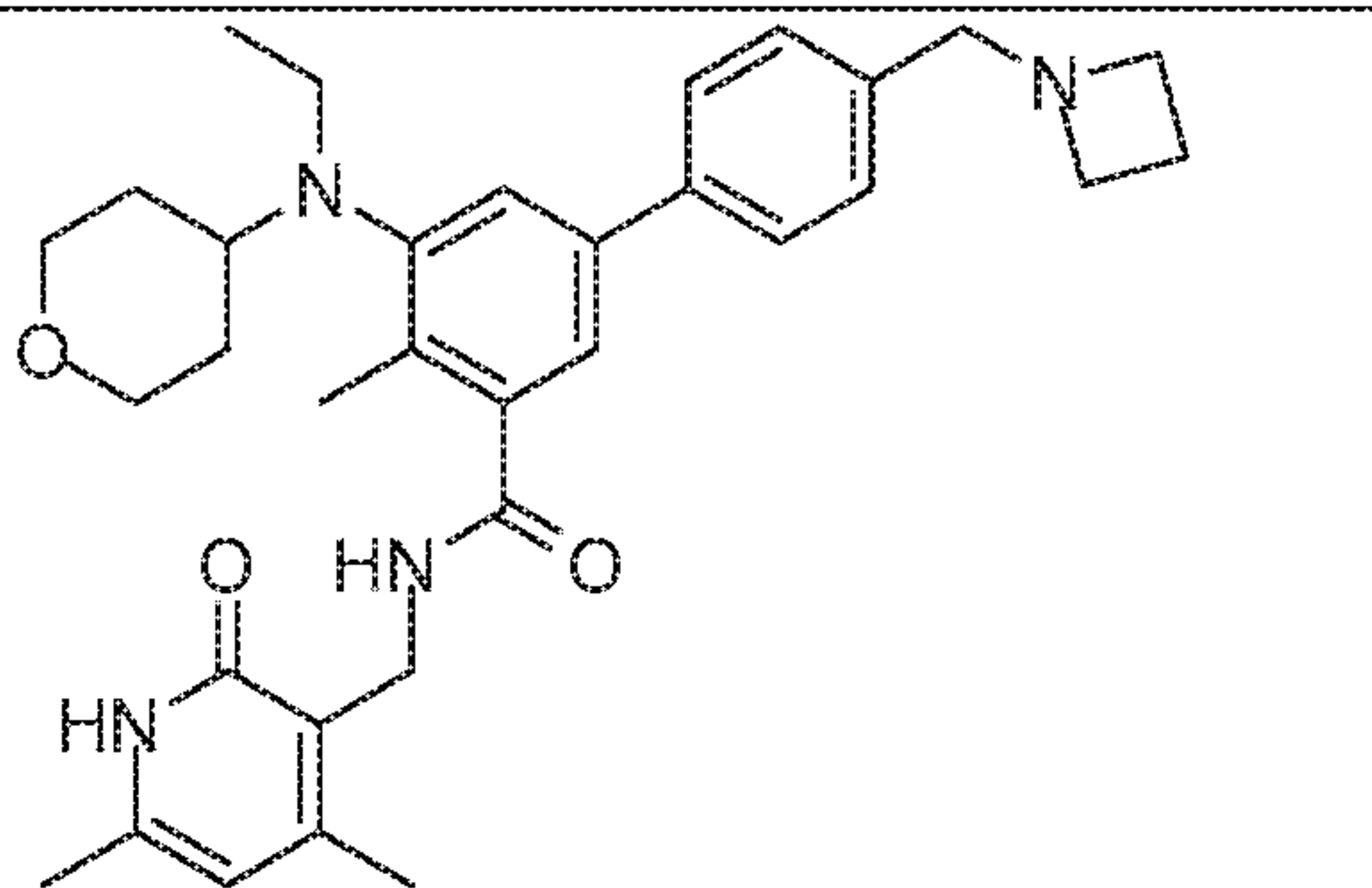
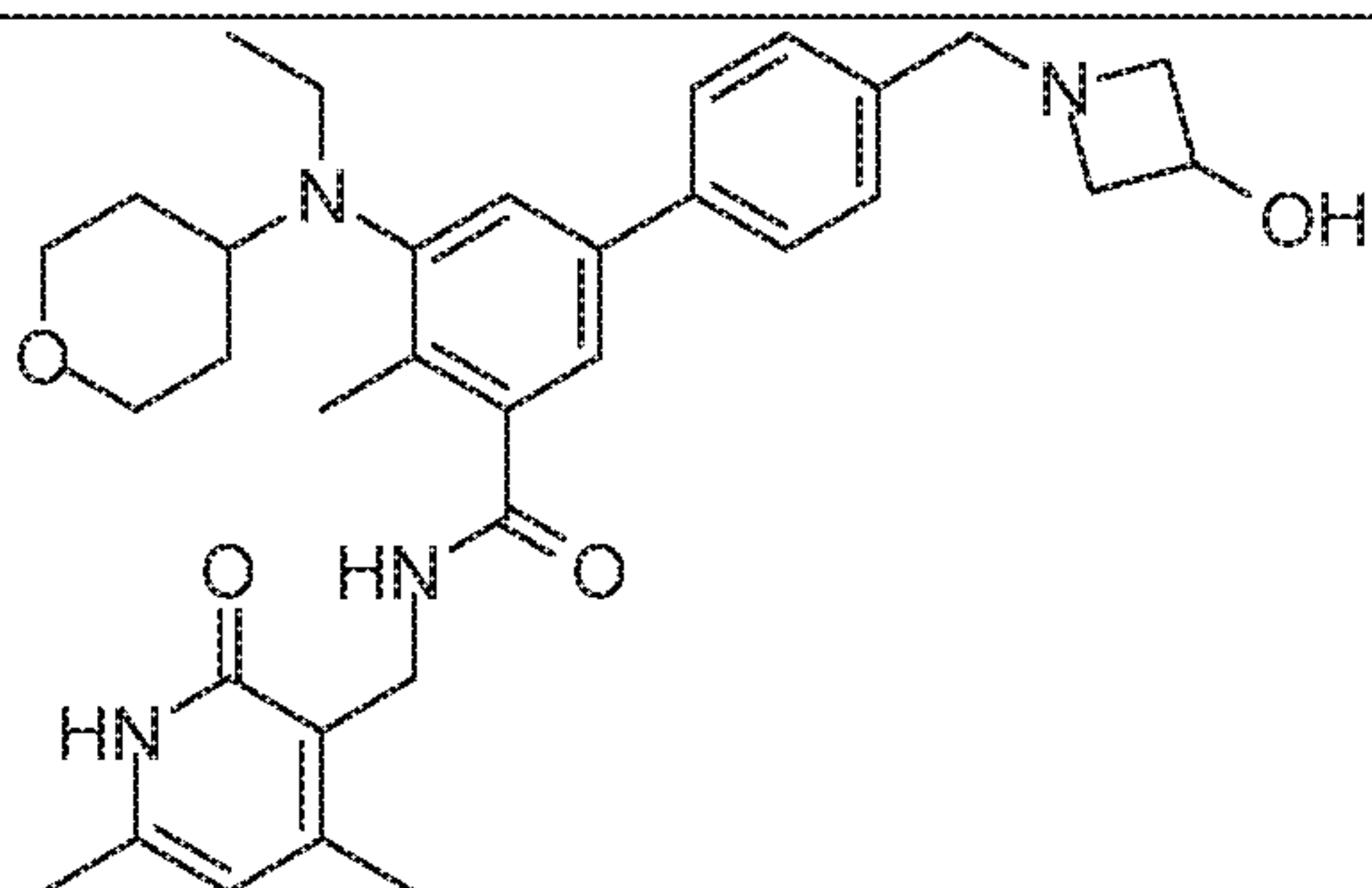
Compound Number	Structure	MS (M+1) ⁺
59		587.40
60		601.30
61		599.35
62		601.35

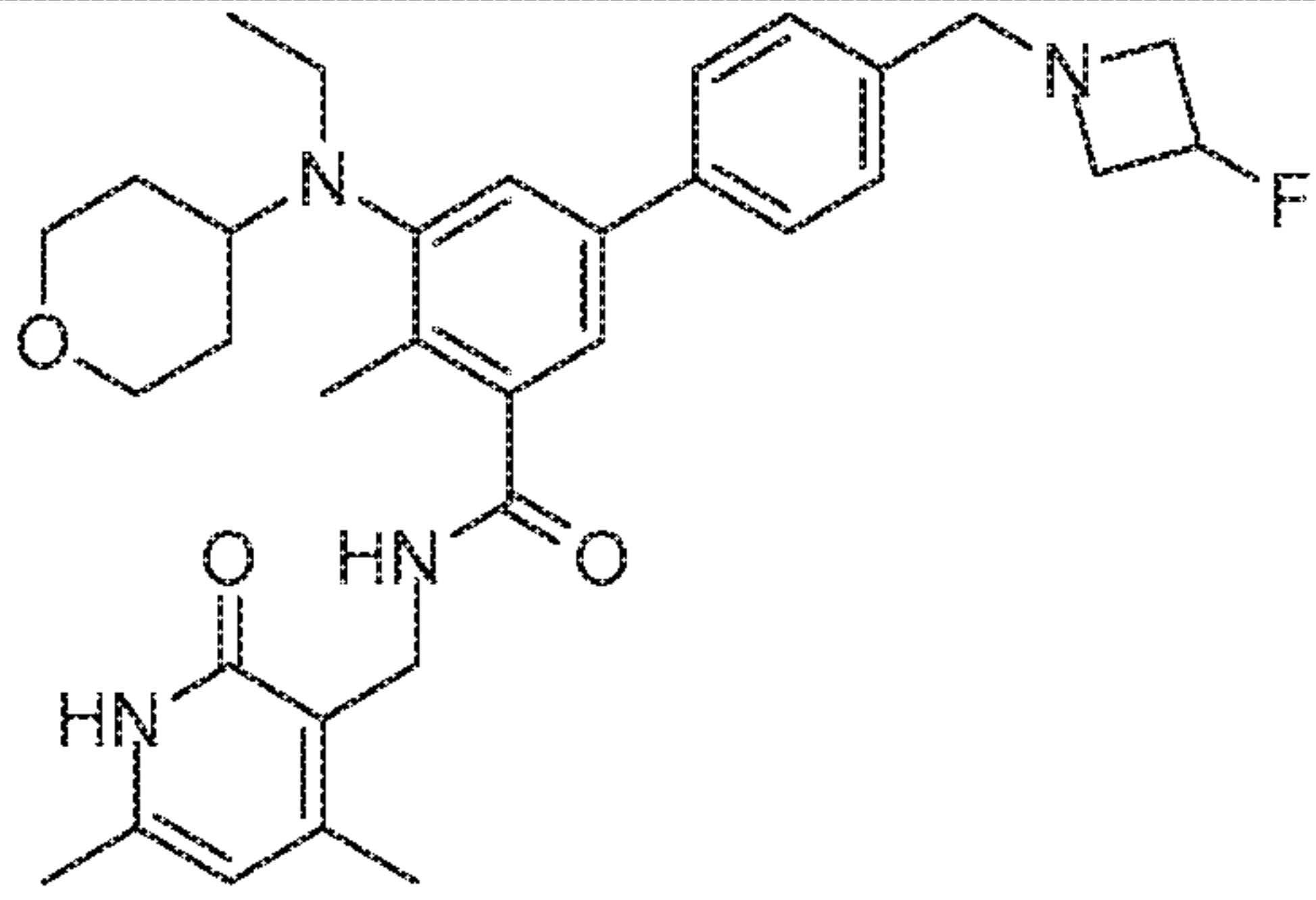
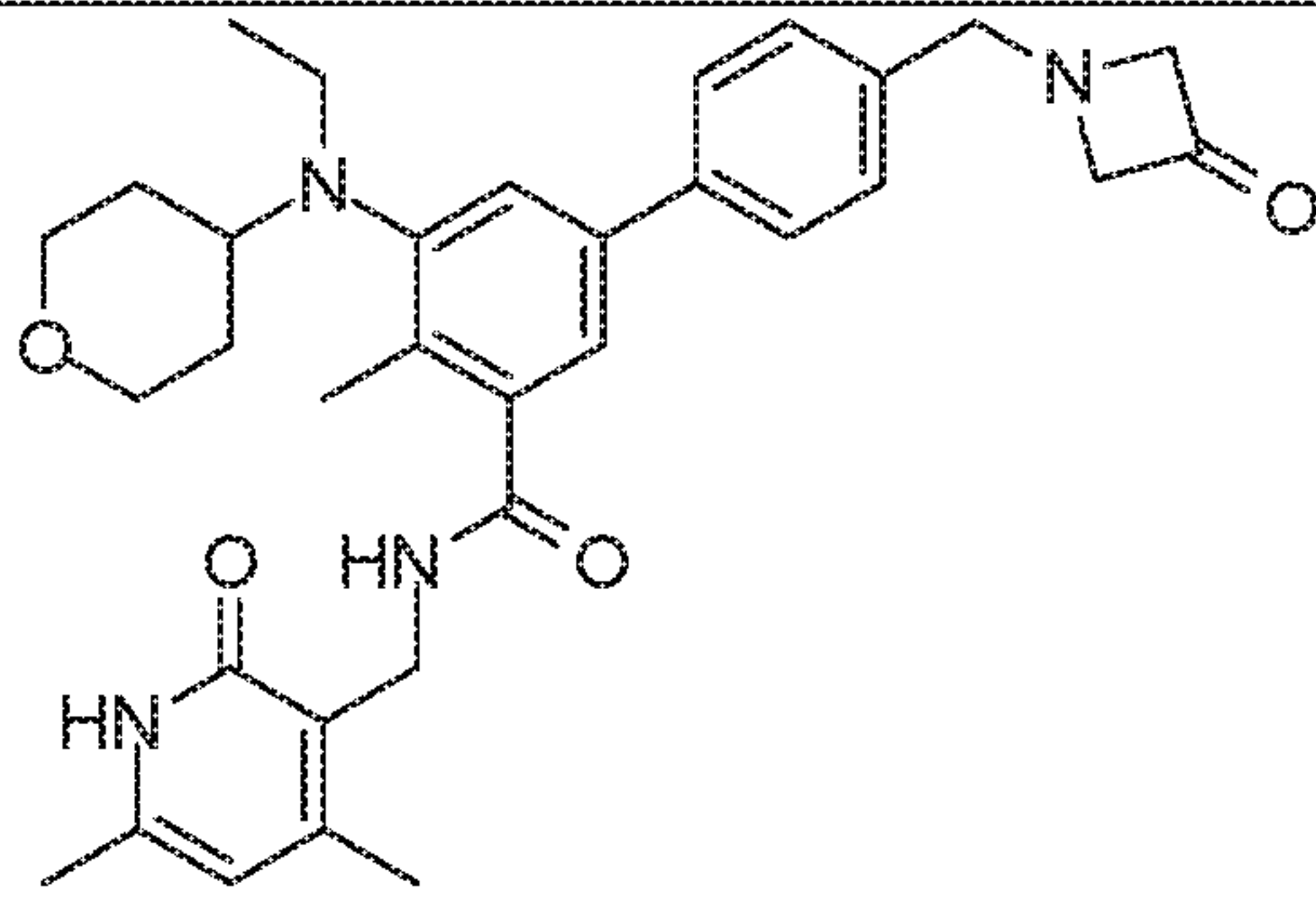
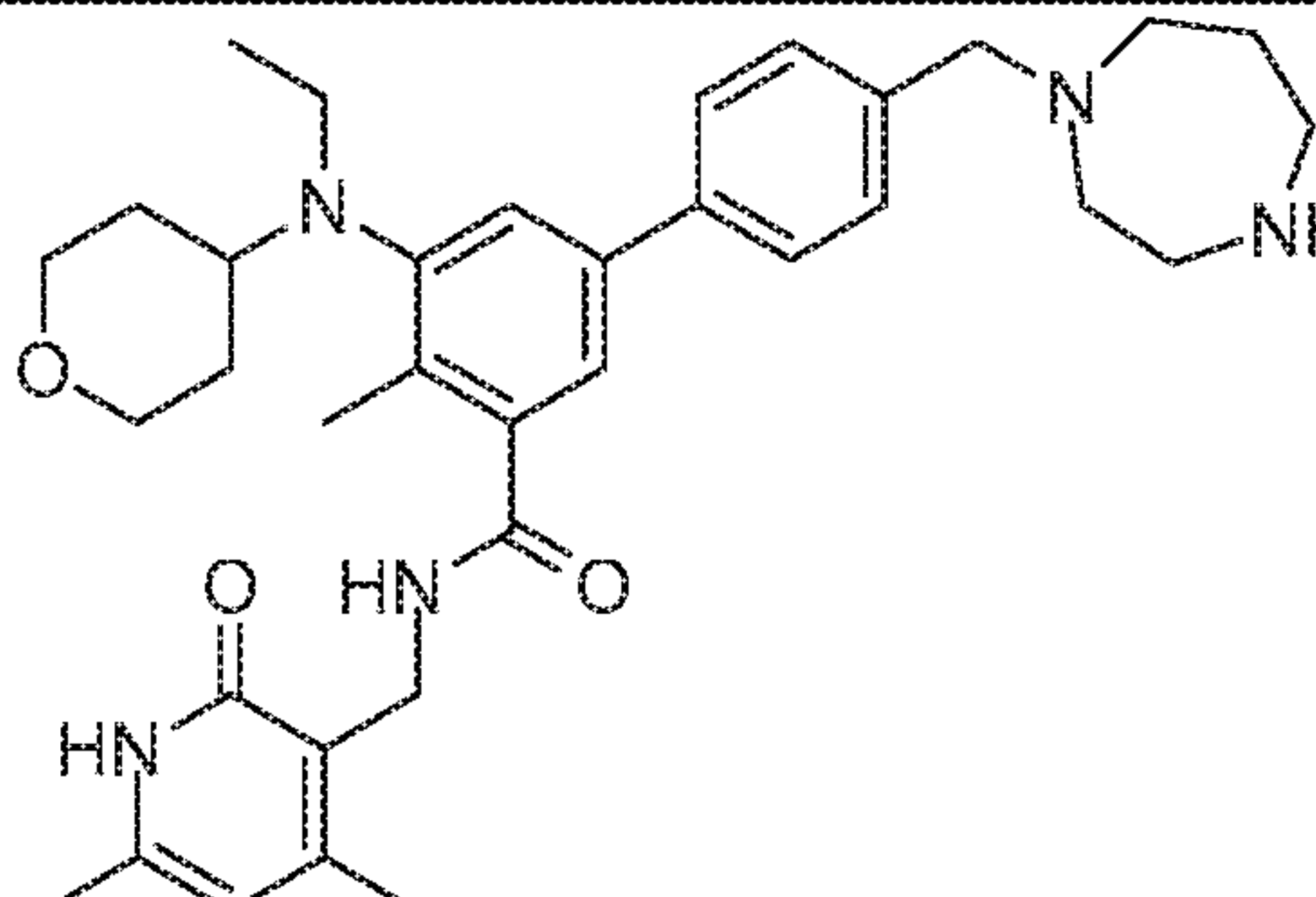
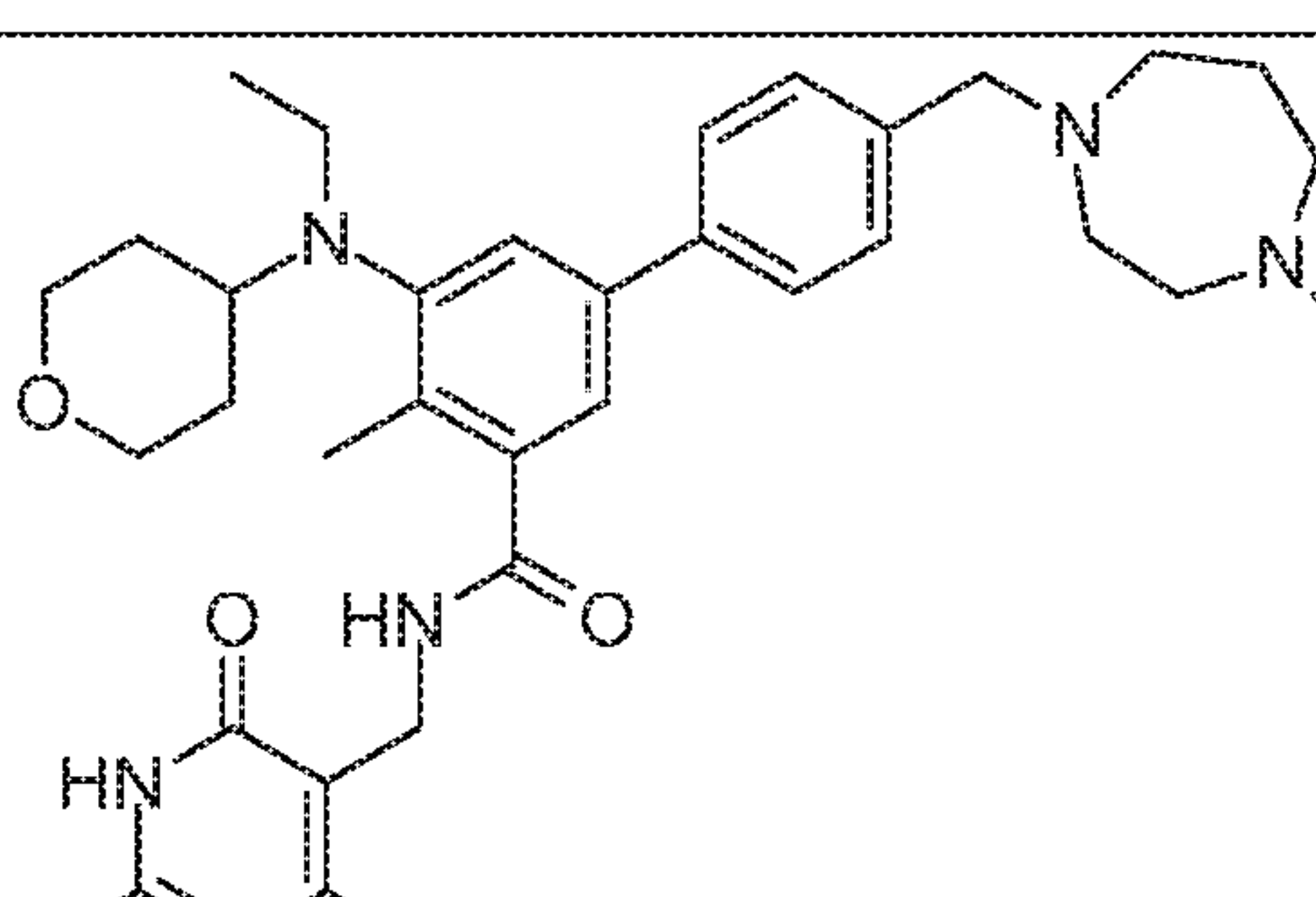
Compound Number	Structure	MS (M+1) ⁺
63		613.35
65		531.30
66		586.40
67		585.25

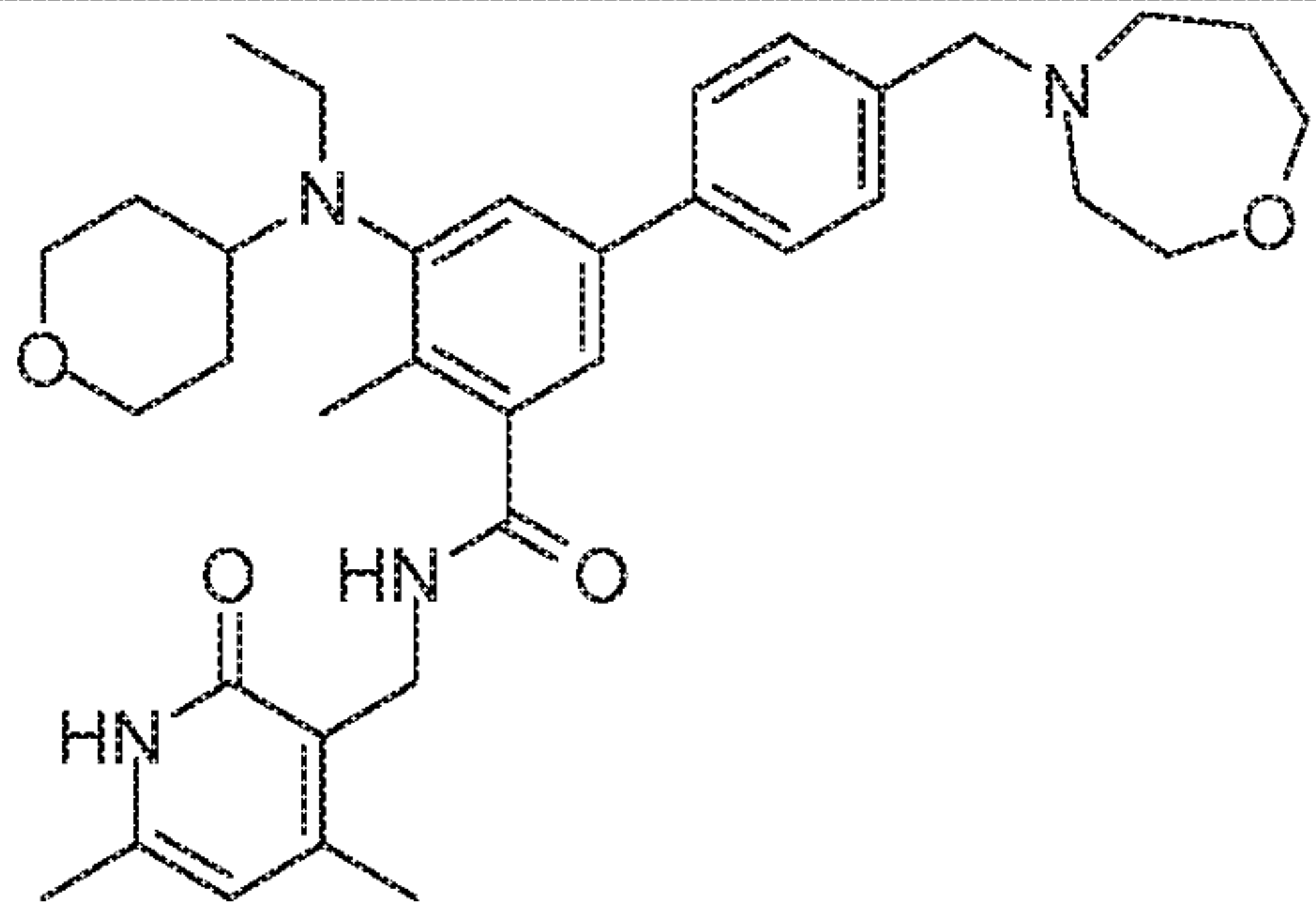
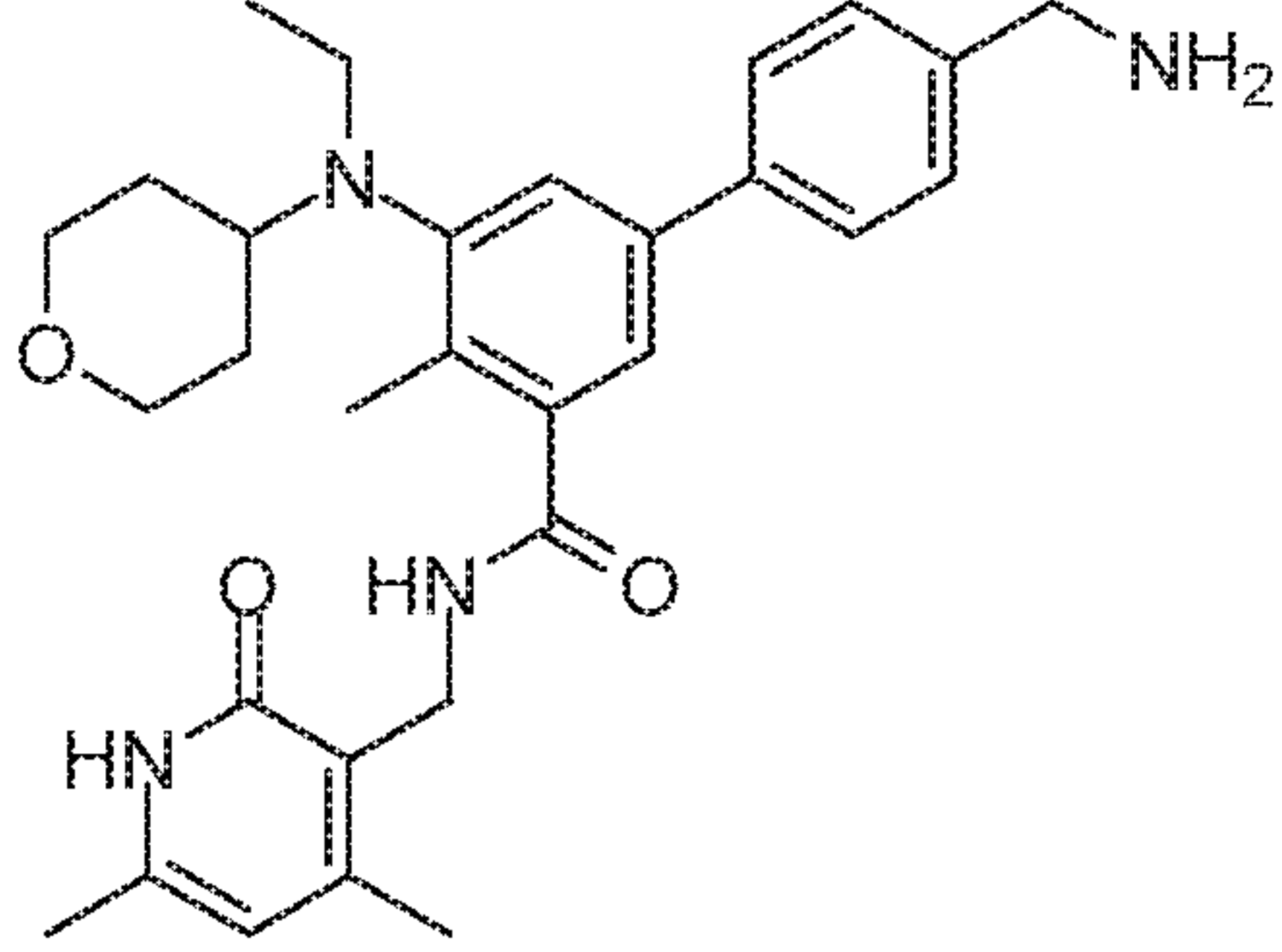
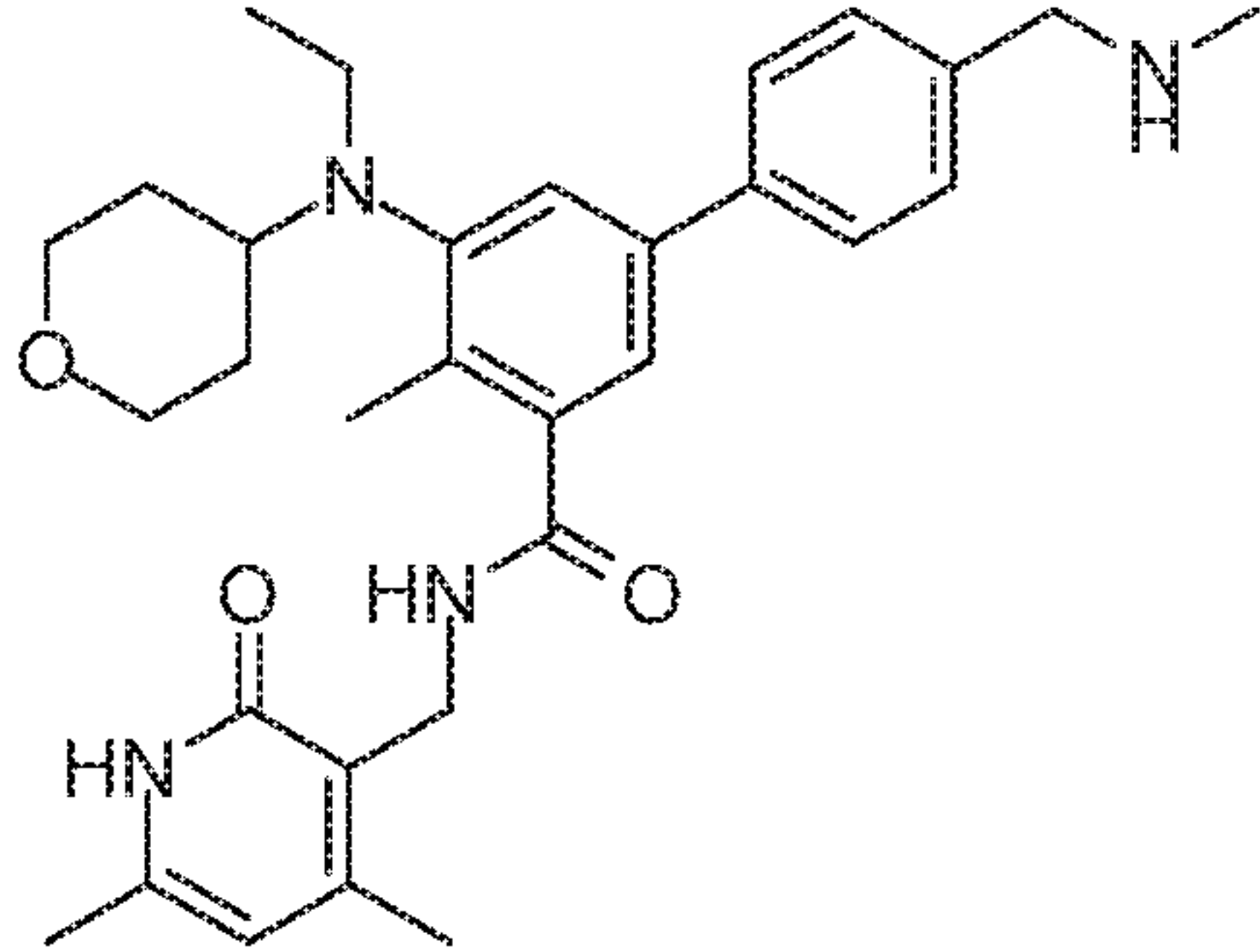
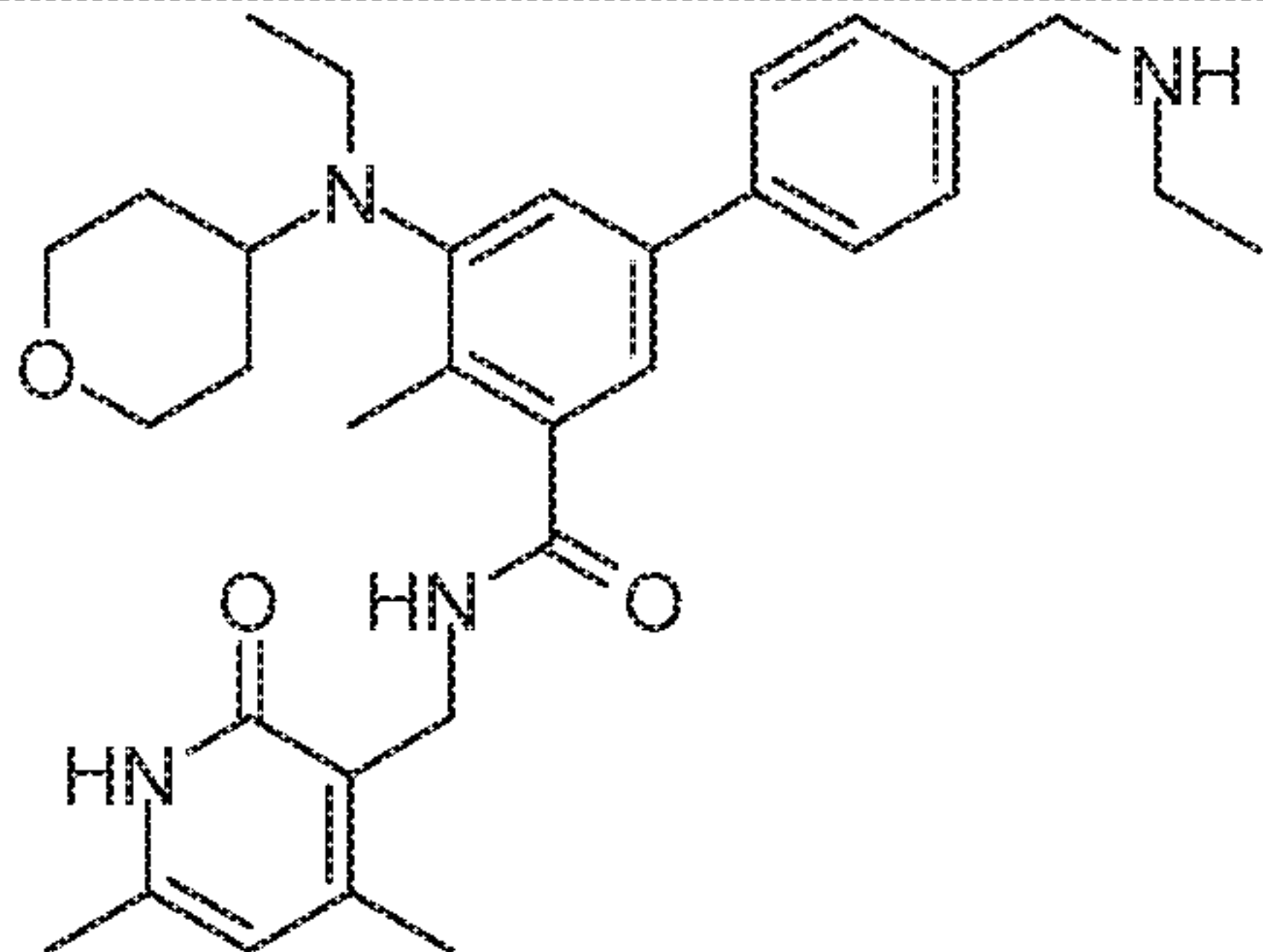
Compound Number	Structure	MS (M+1) ⁺
68		585.35
69		557.25
70		573.40
71		573.40

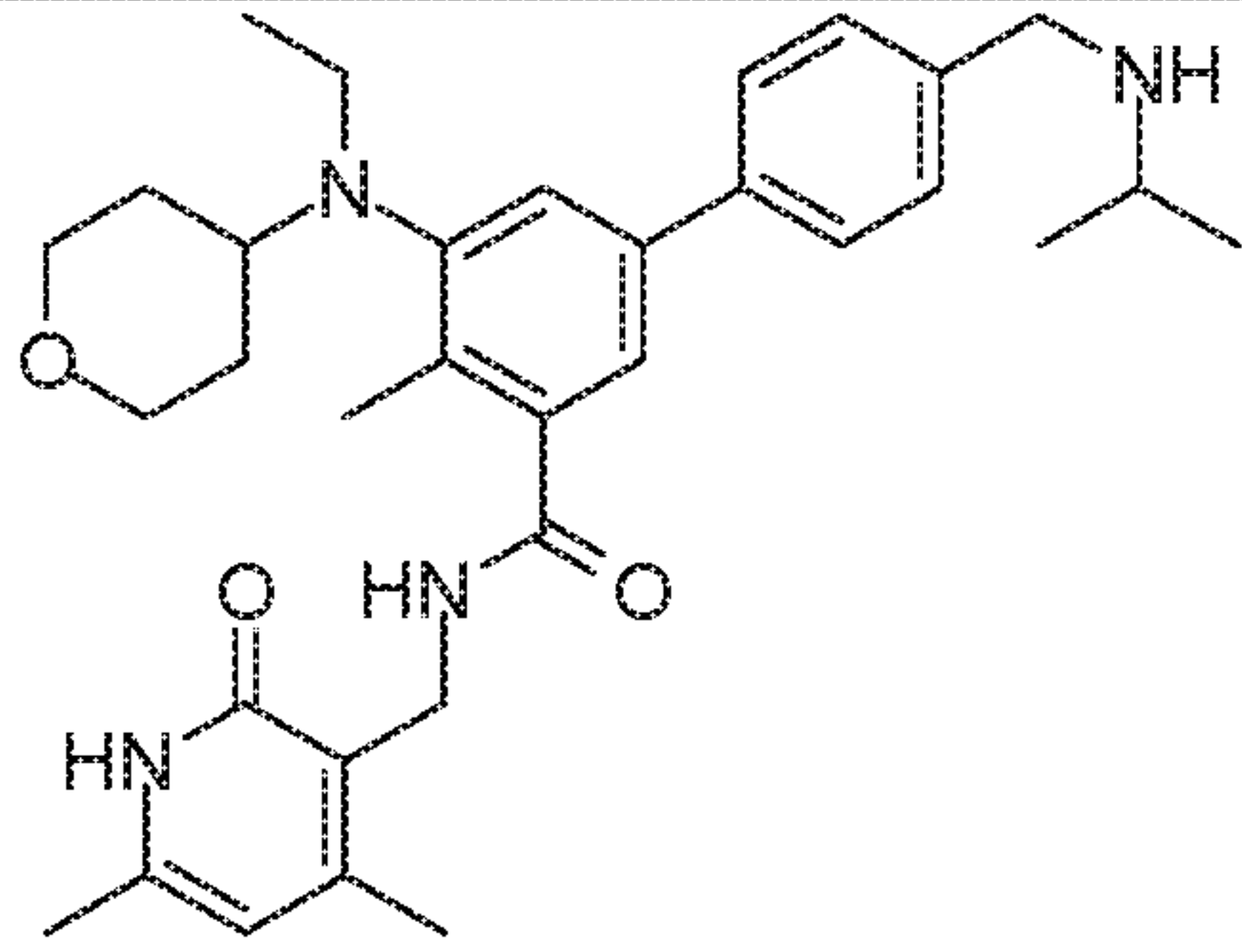
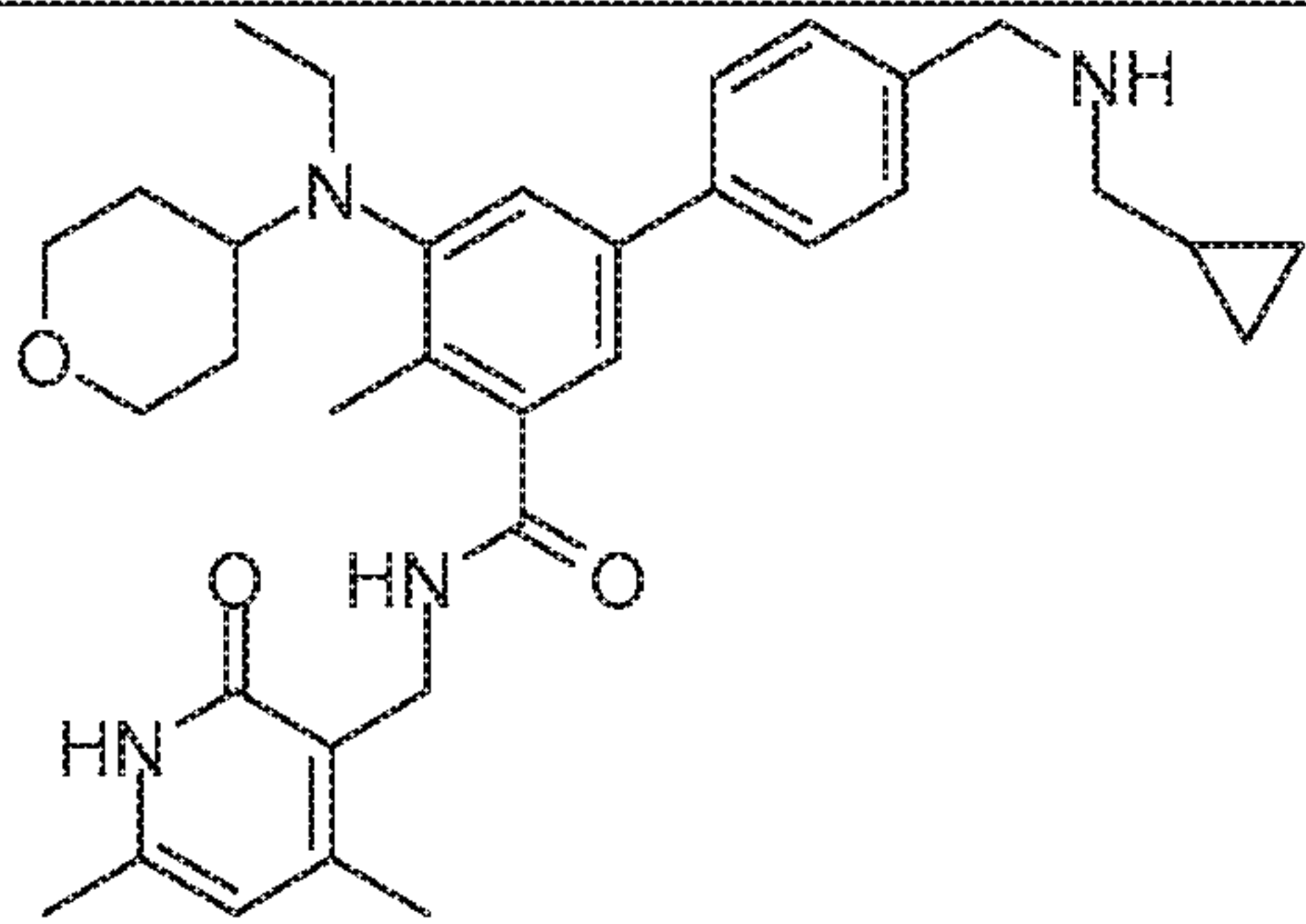
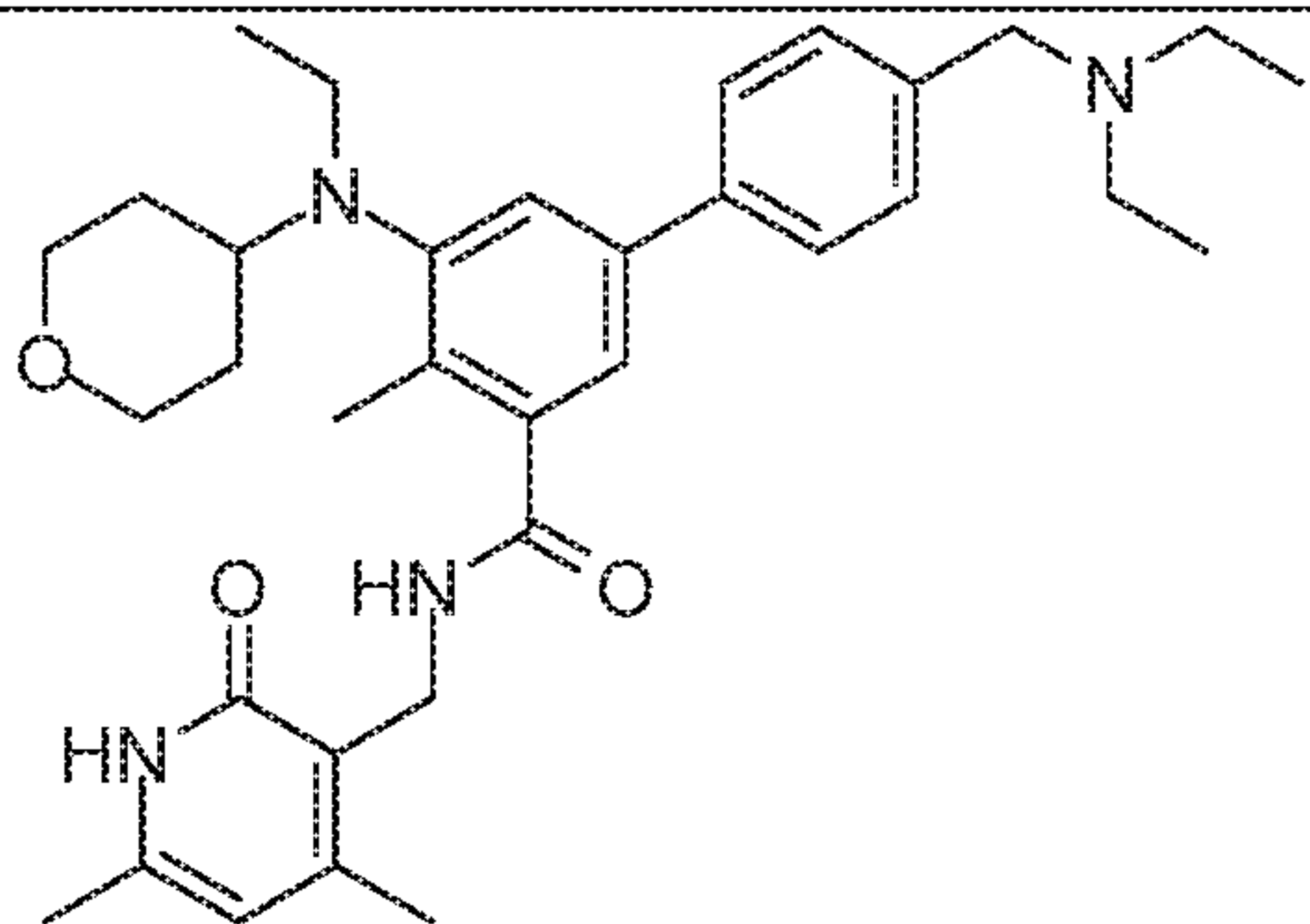
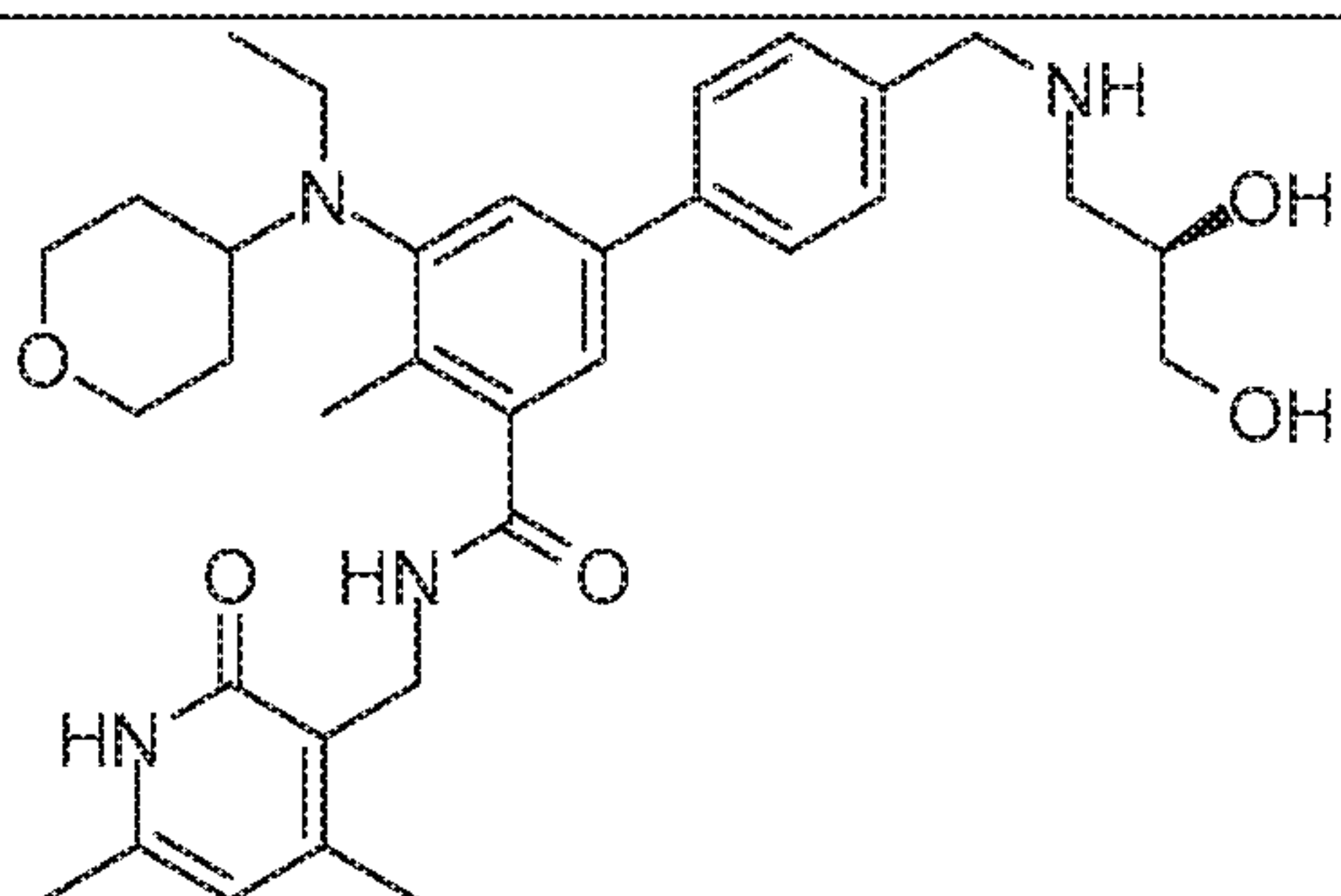
Compound Number	Structure	MS (M+1) ⁺
72		575.35
73		572.10
74		575.35
75		571.25

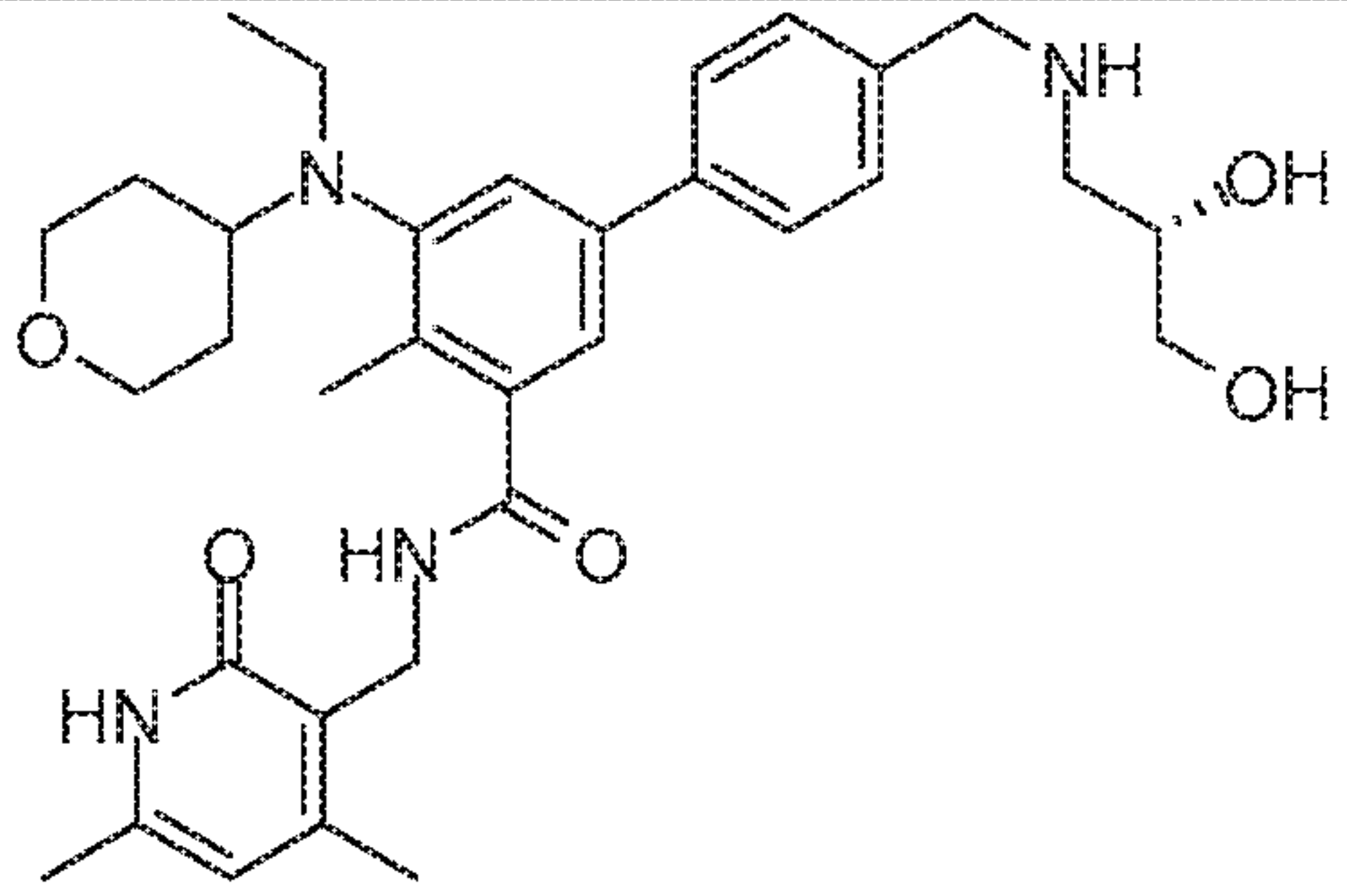
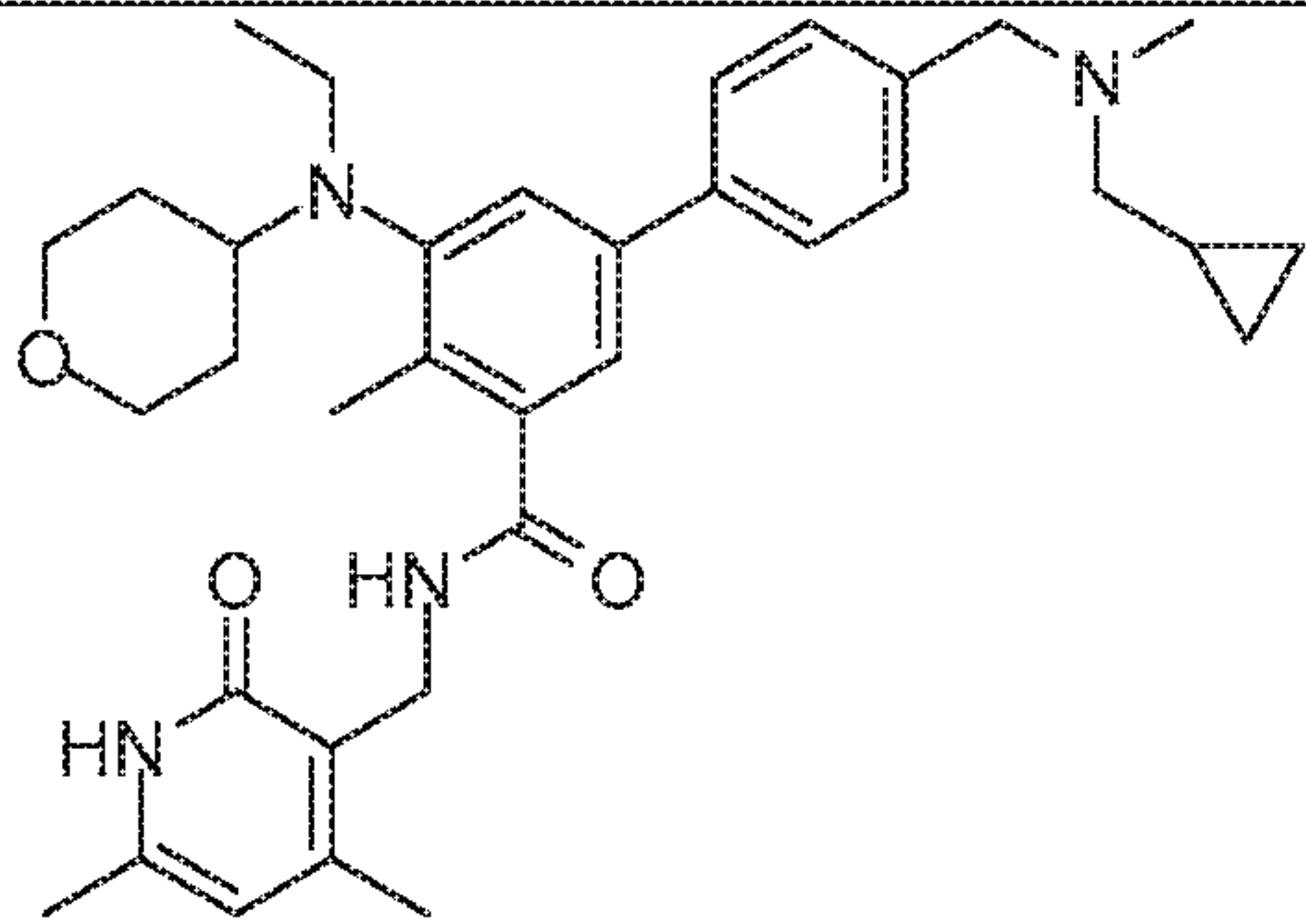
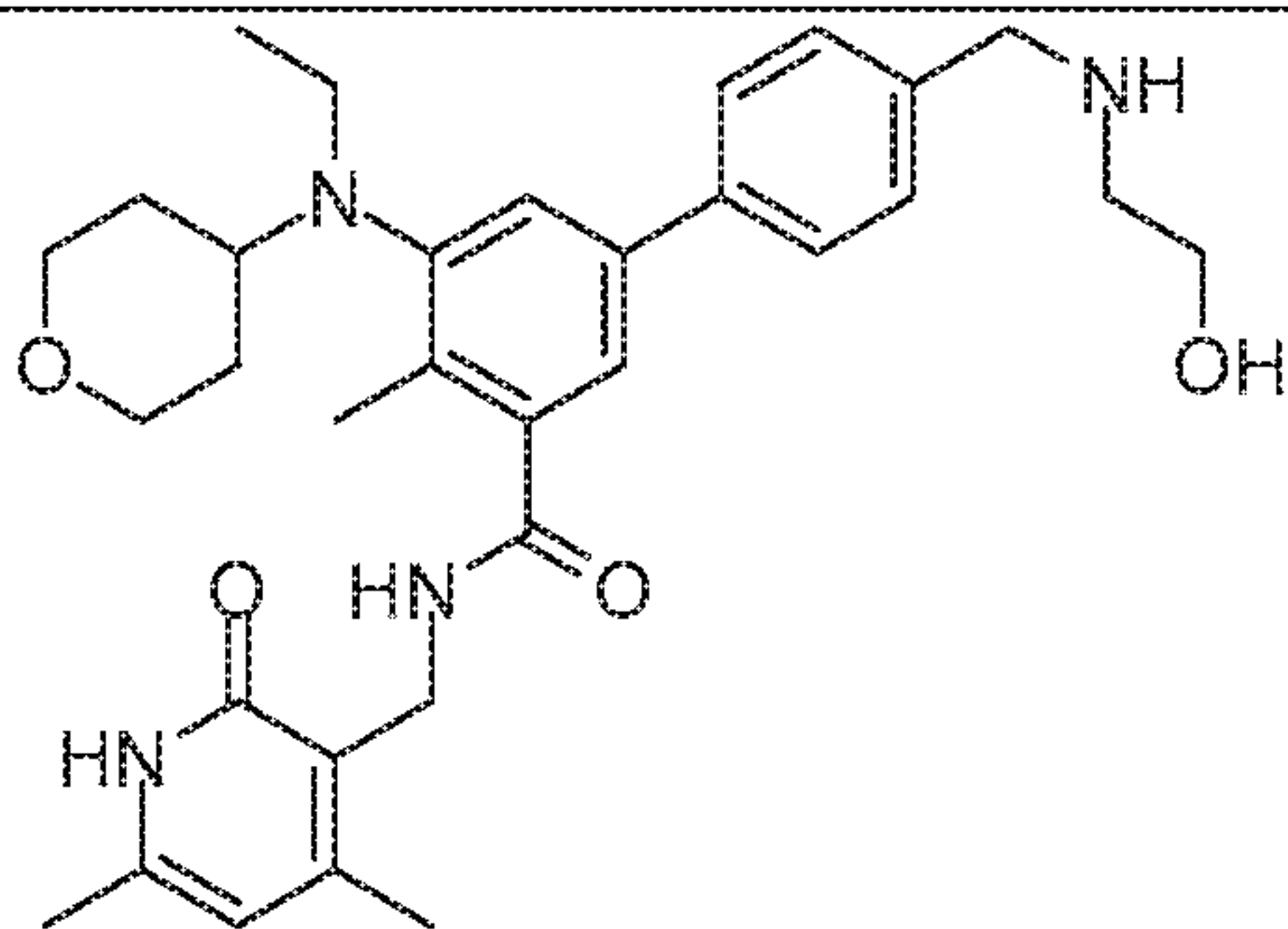
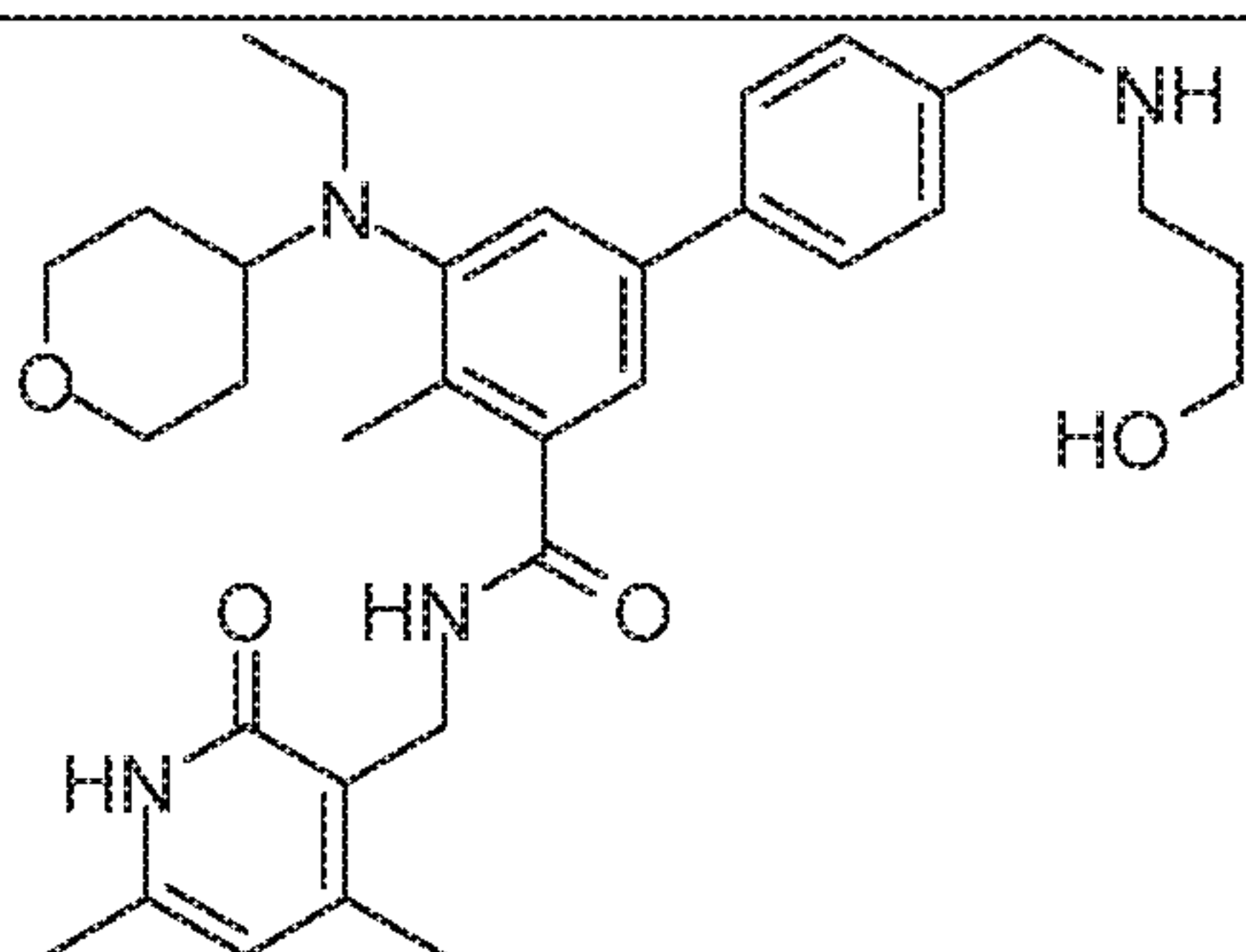
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76		587.40
77		587.45
78		587.20
79		589.35

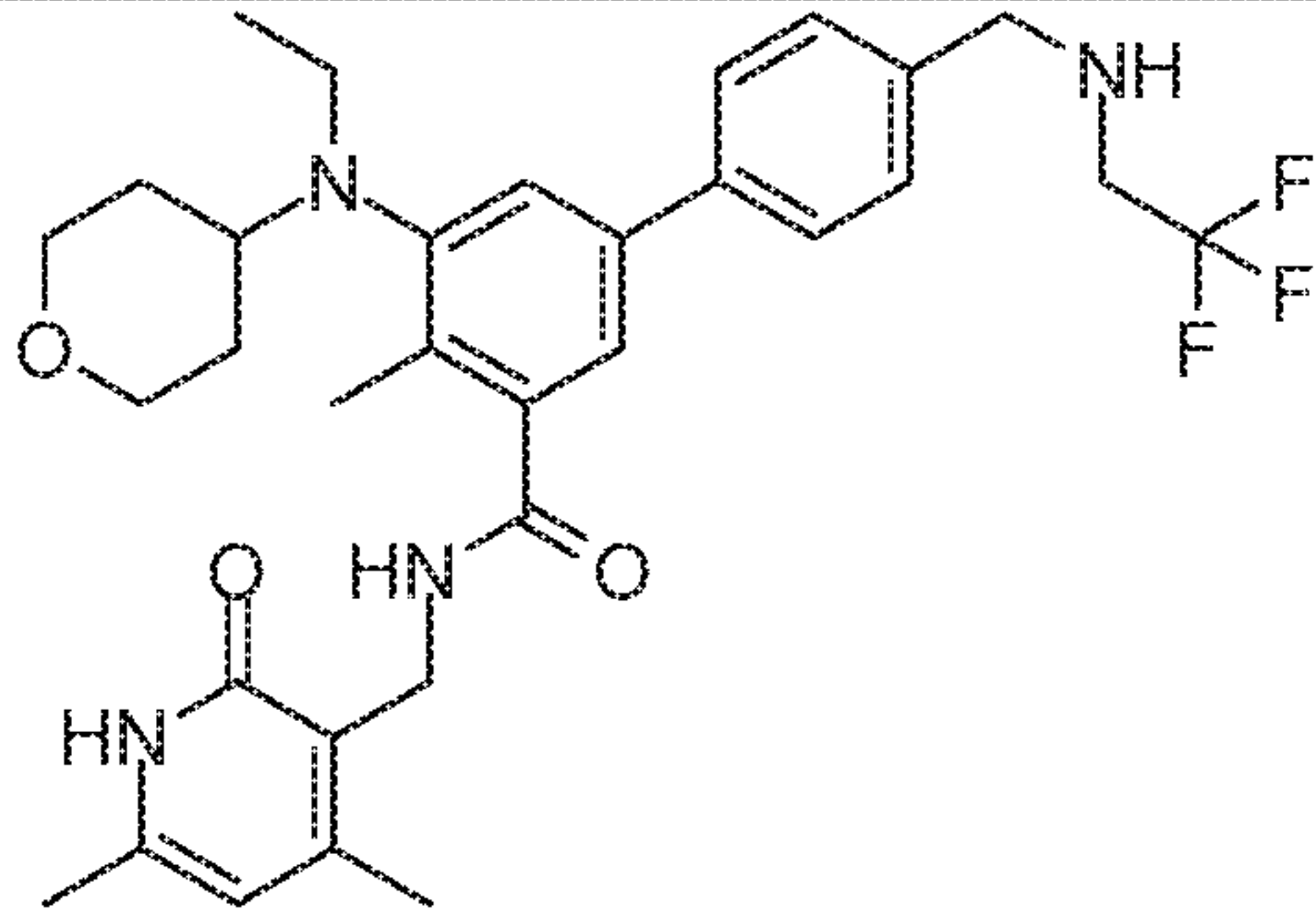
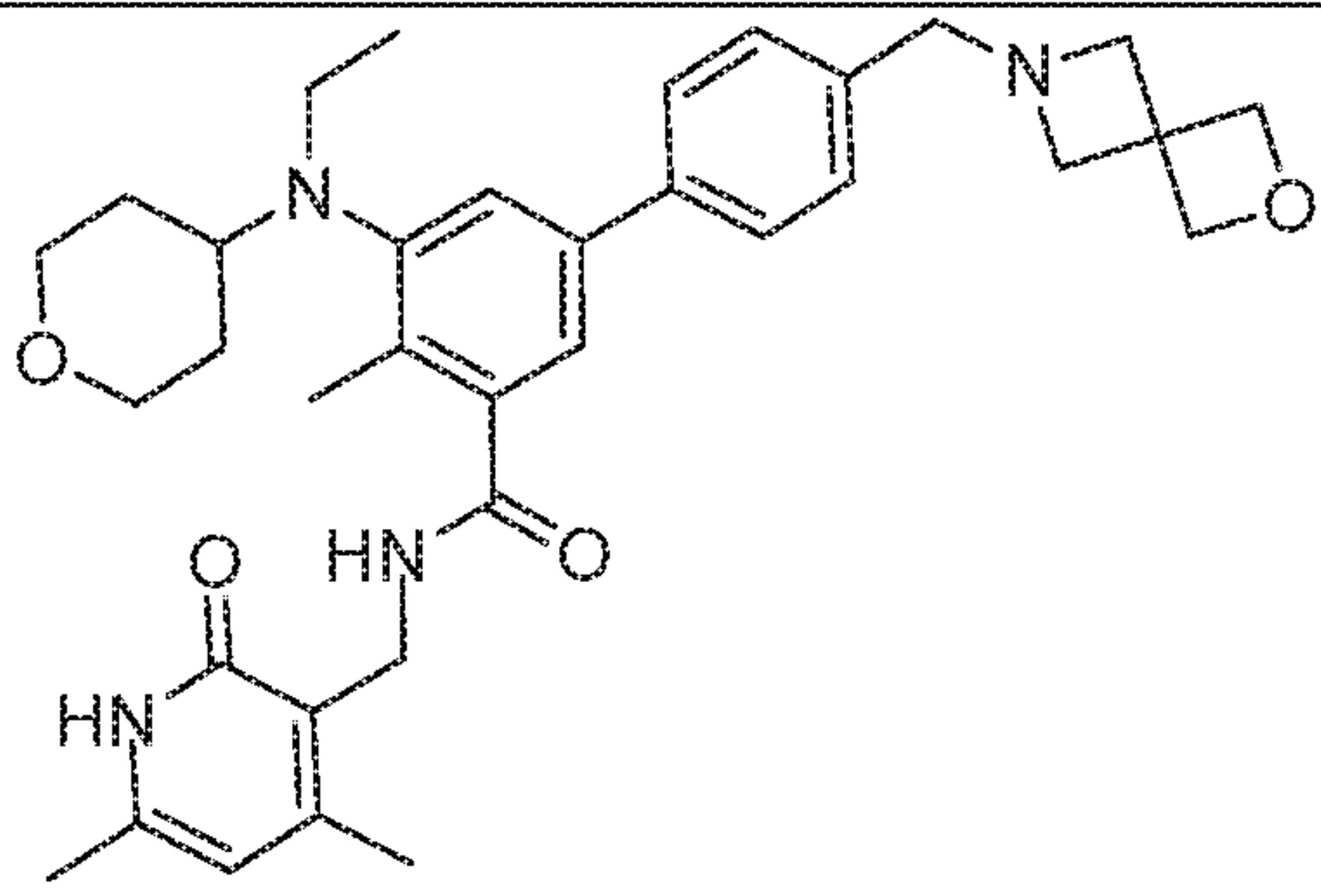
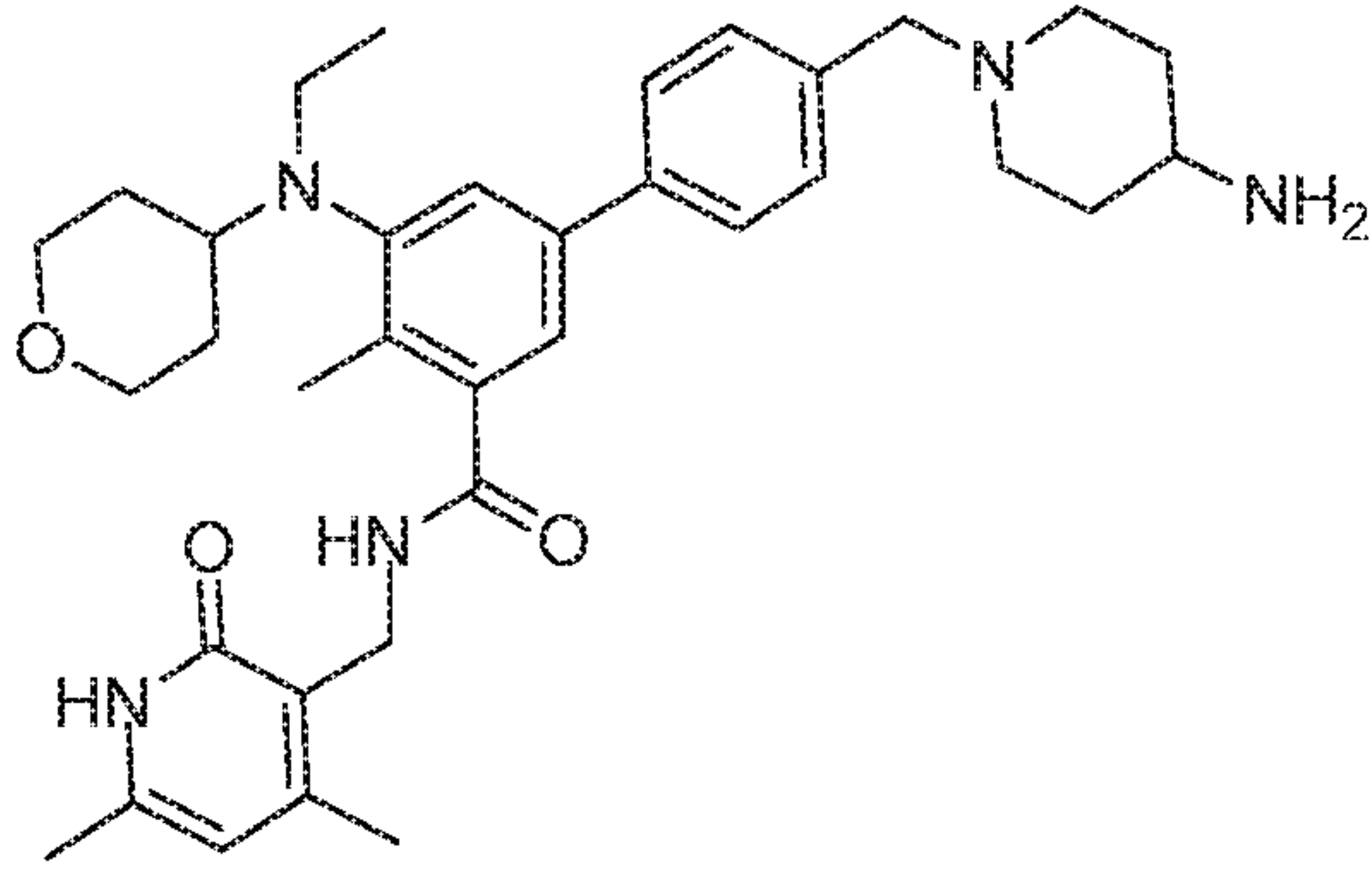
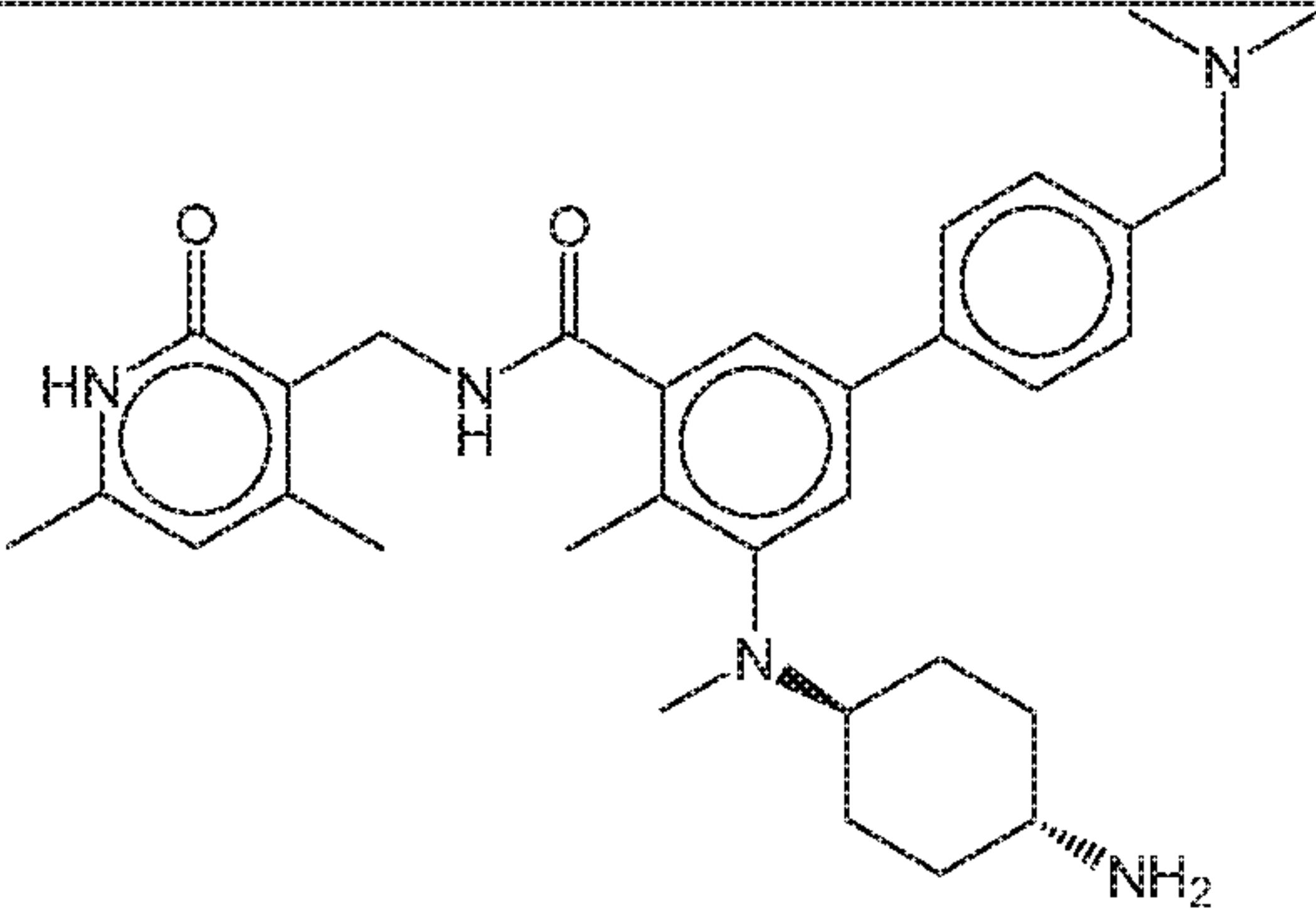
Compound Number	Structure	MS (M+1) ⁺
80		589.30
81		607.35
82		543.40
83		559.80

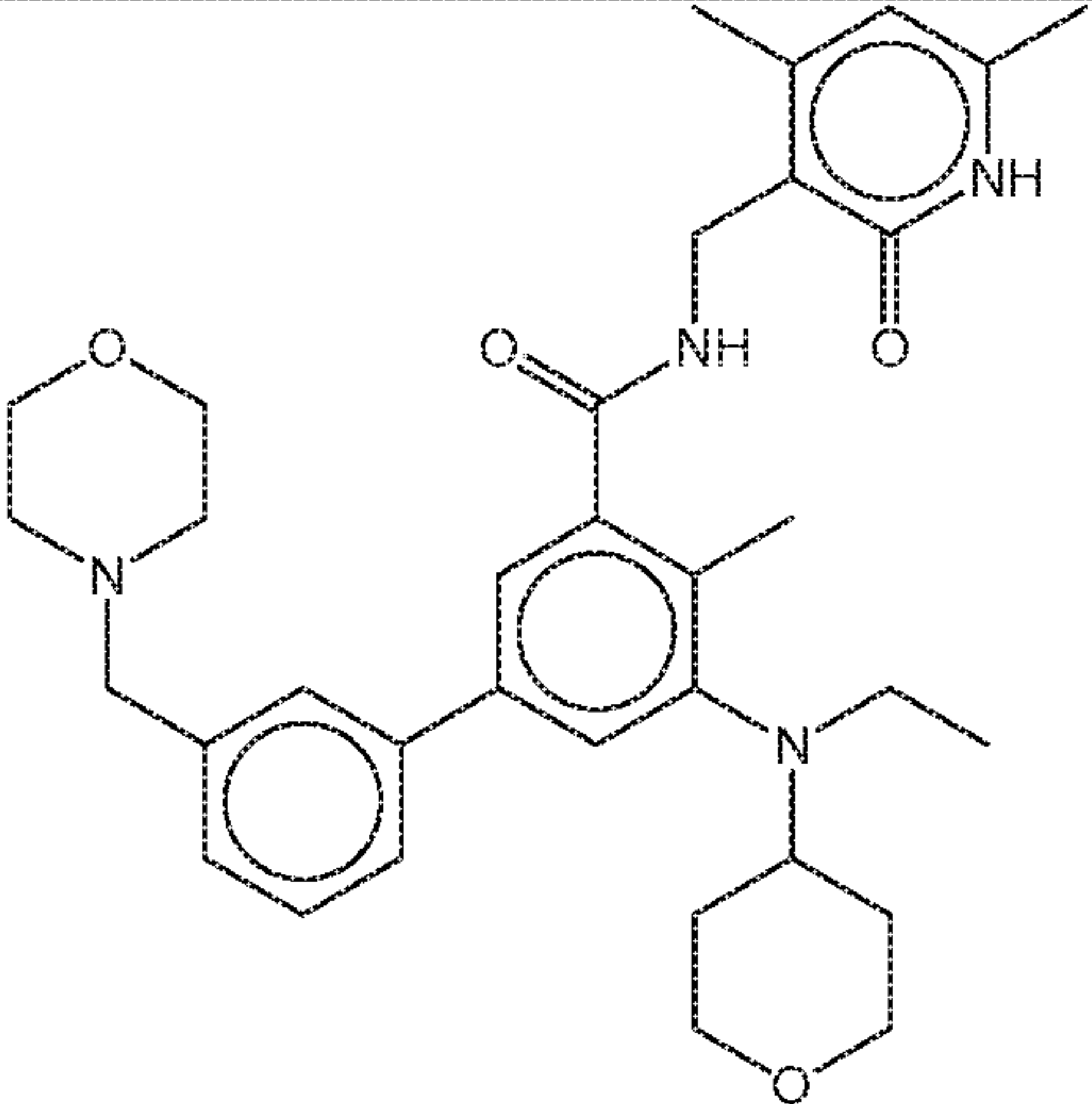
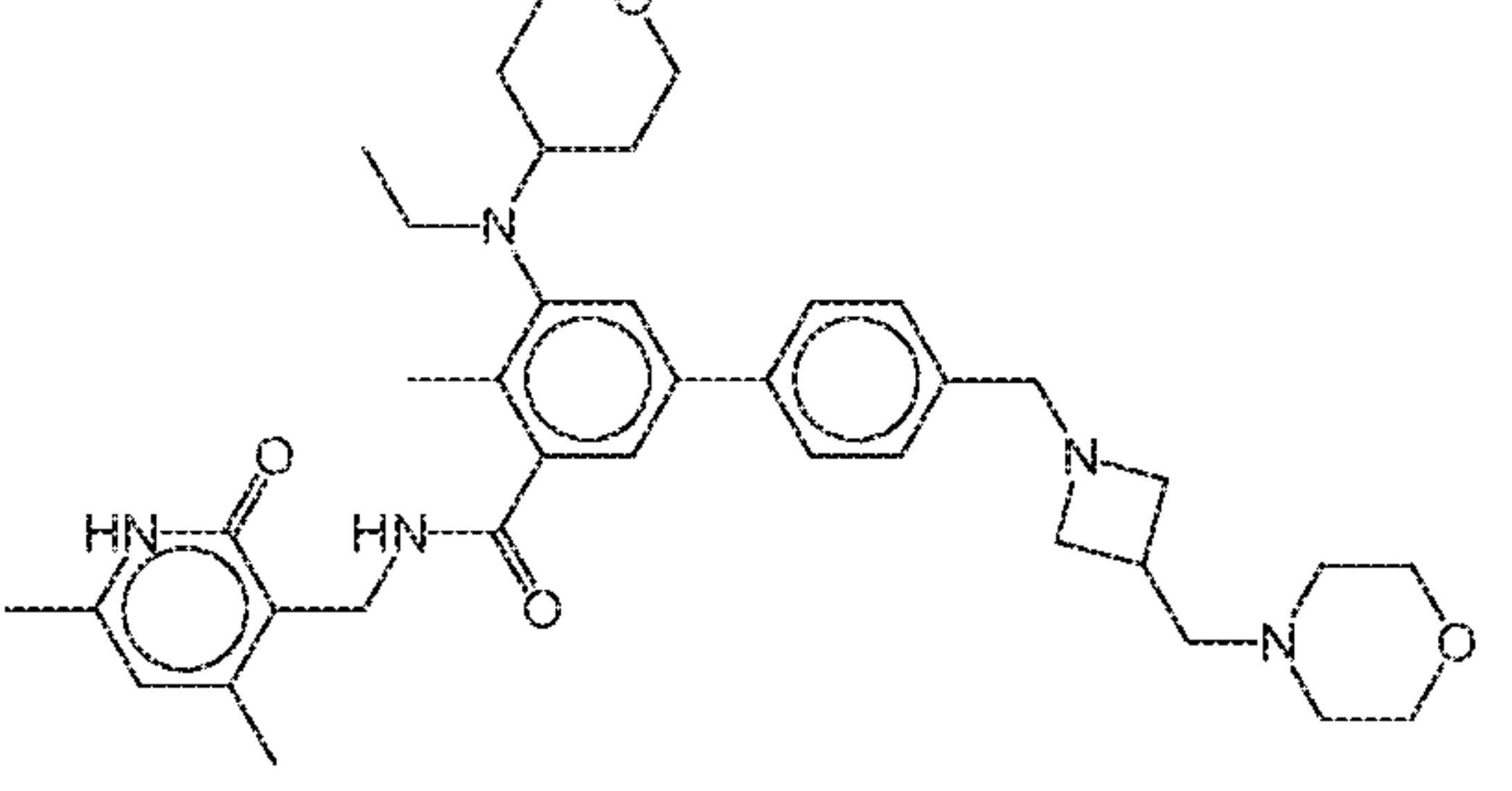
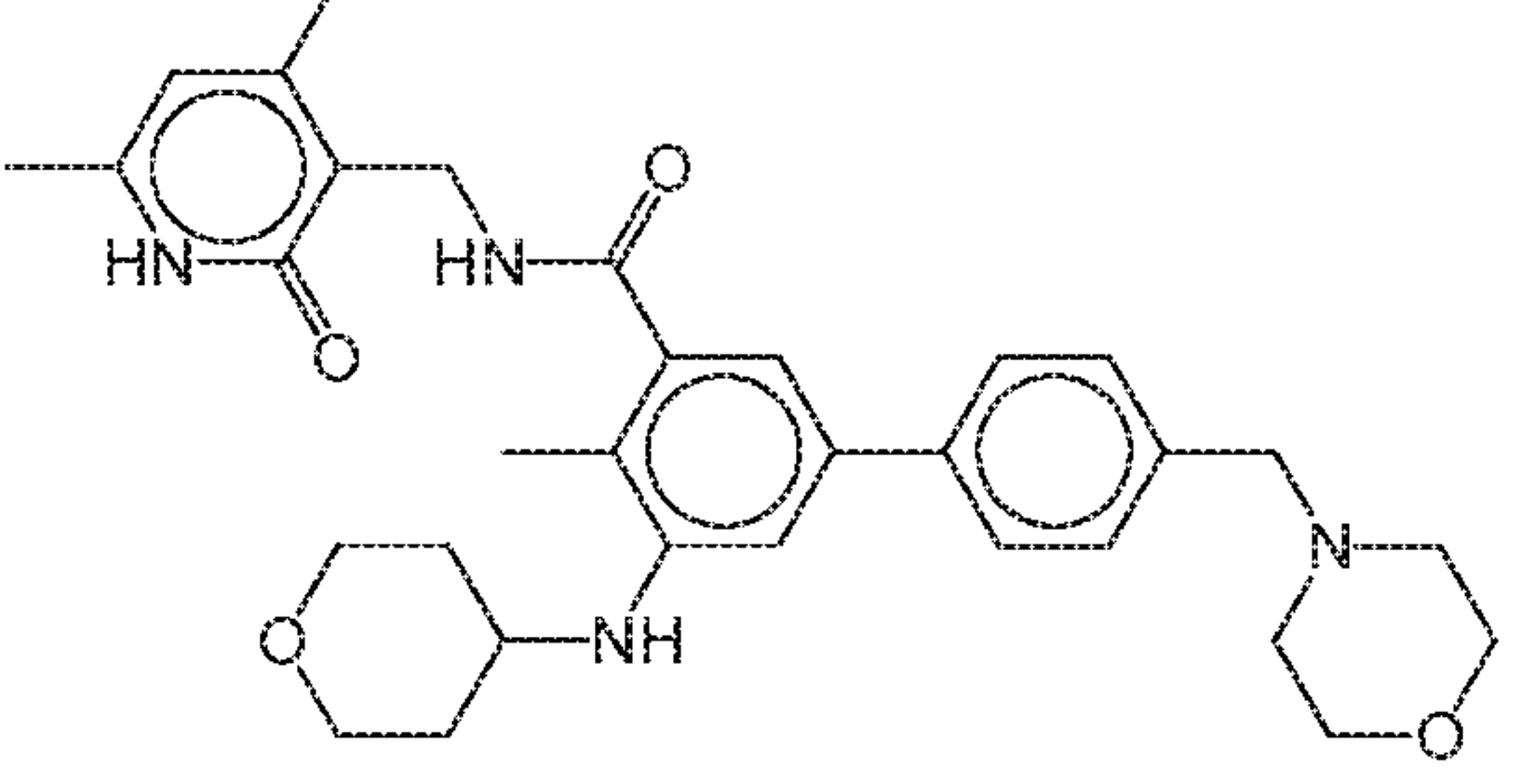
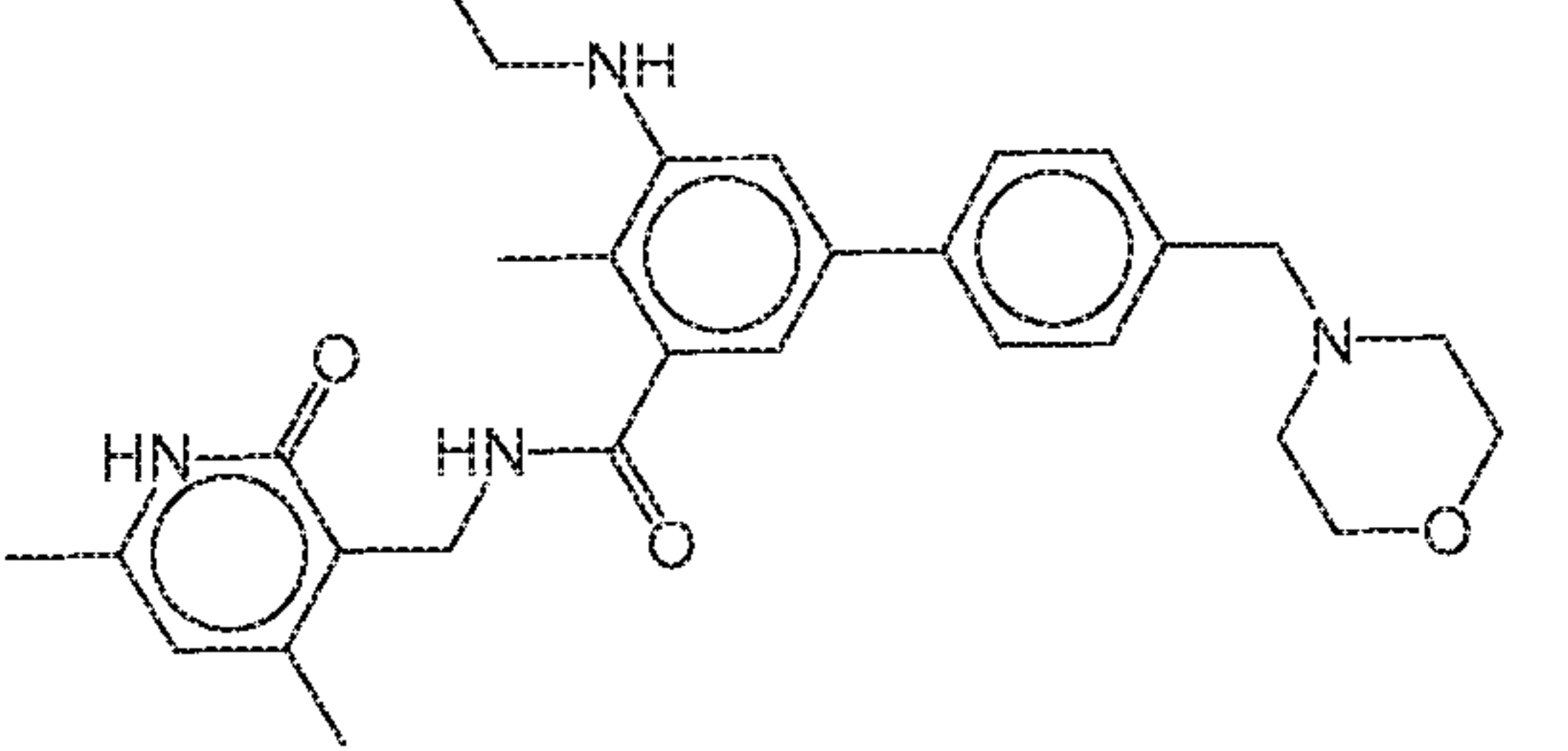
Compound Number	Structure	MS (M+1) ⁺
84		561.25
85		
86		585.37
87		600.30

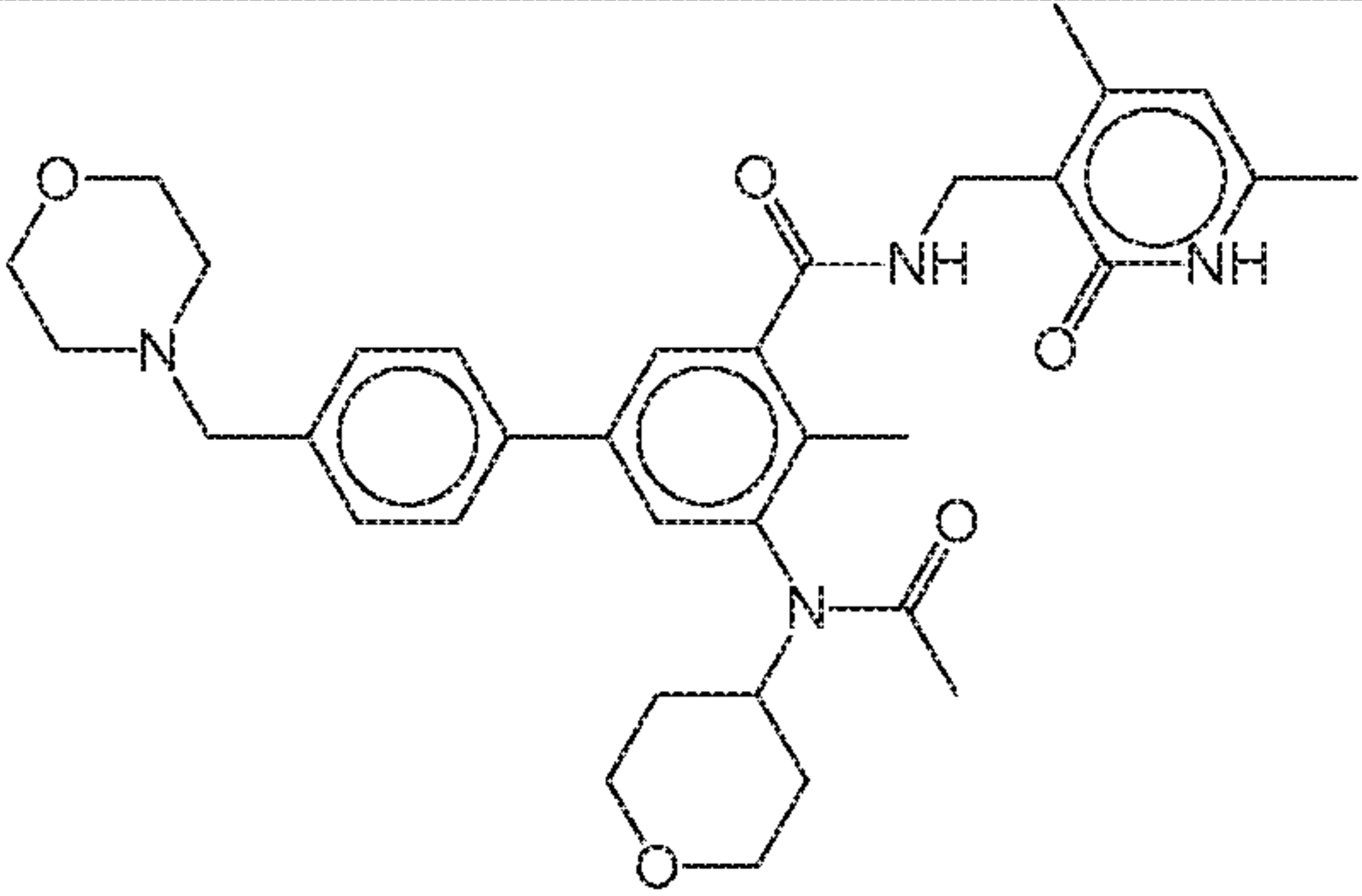
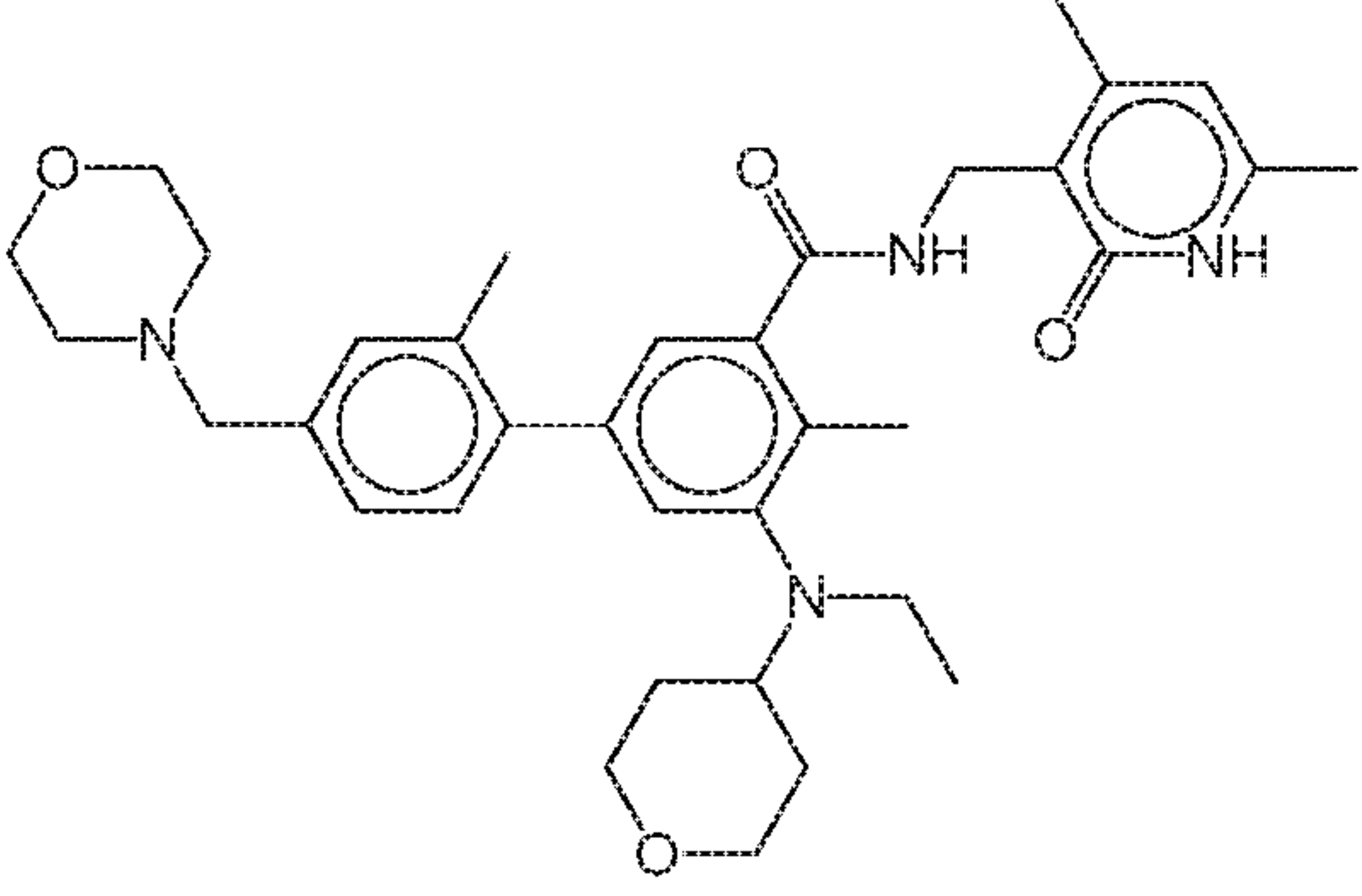
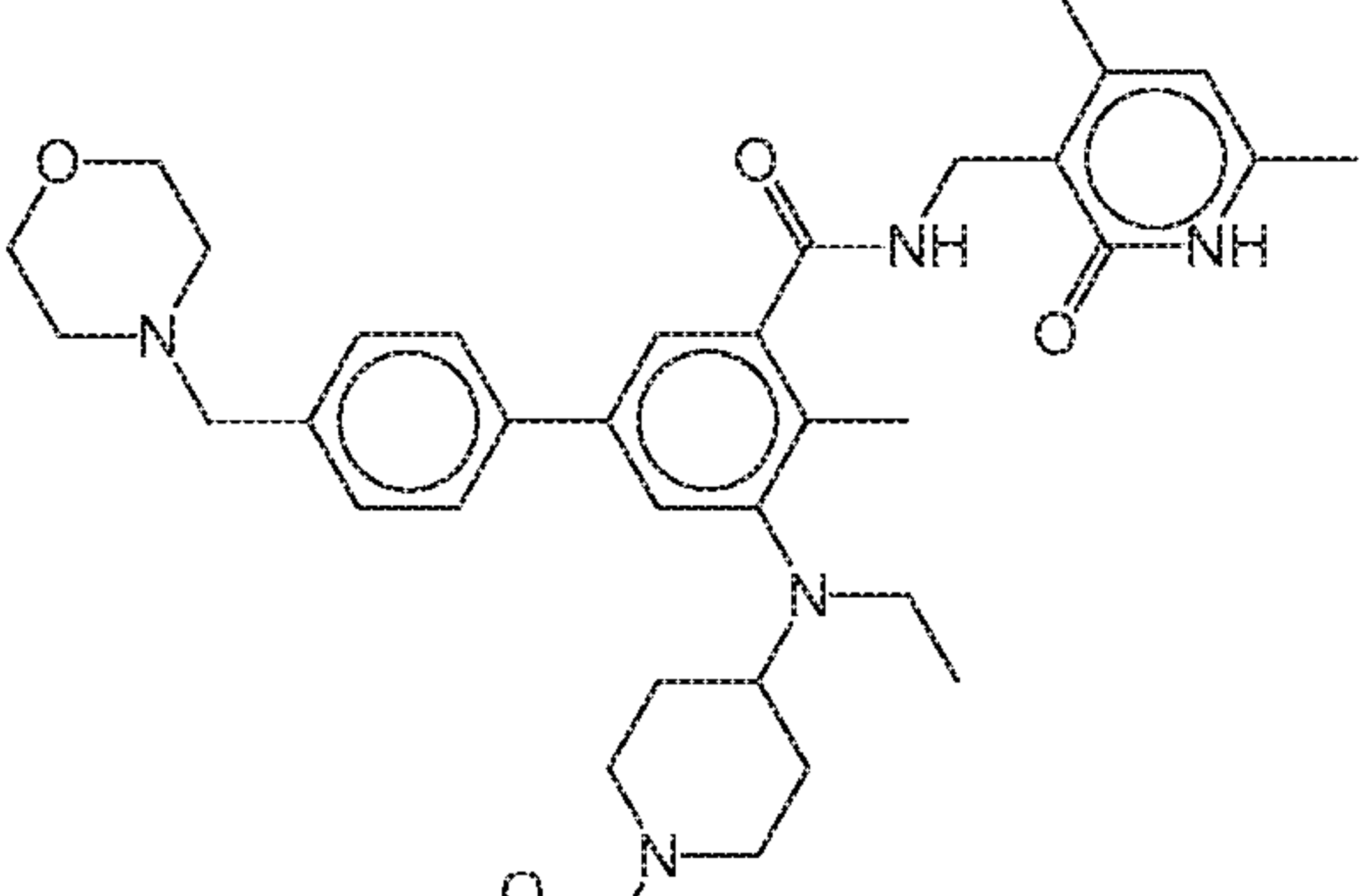
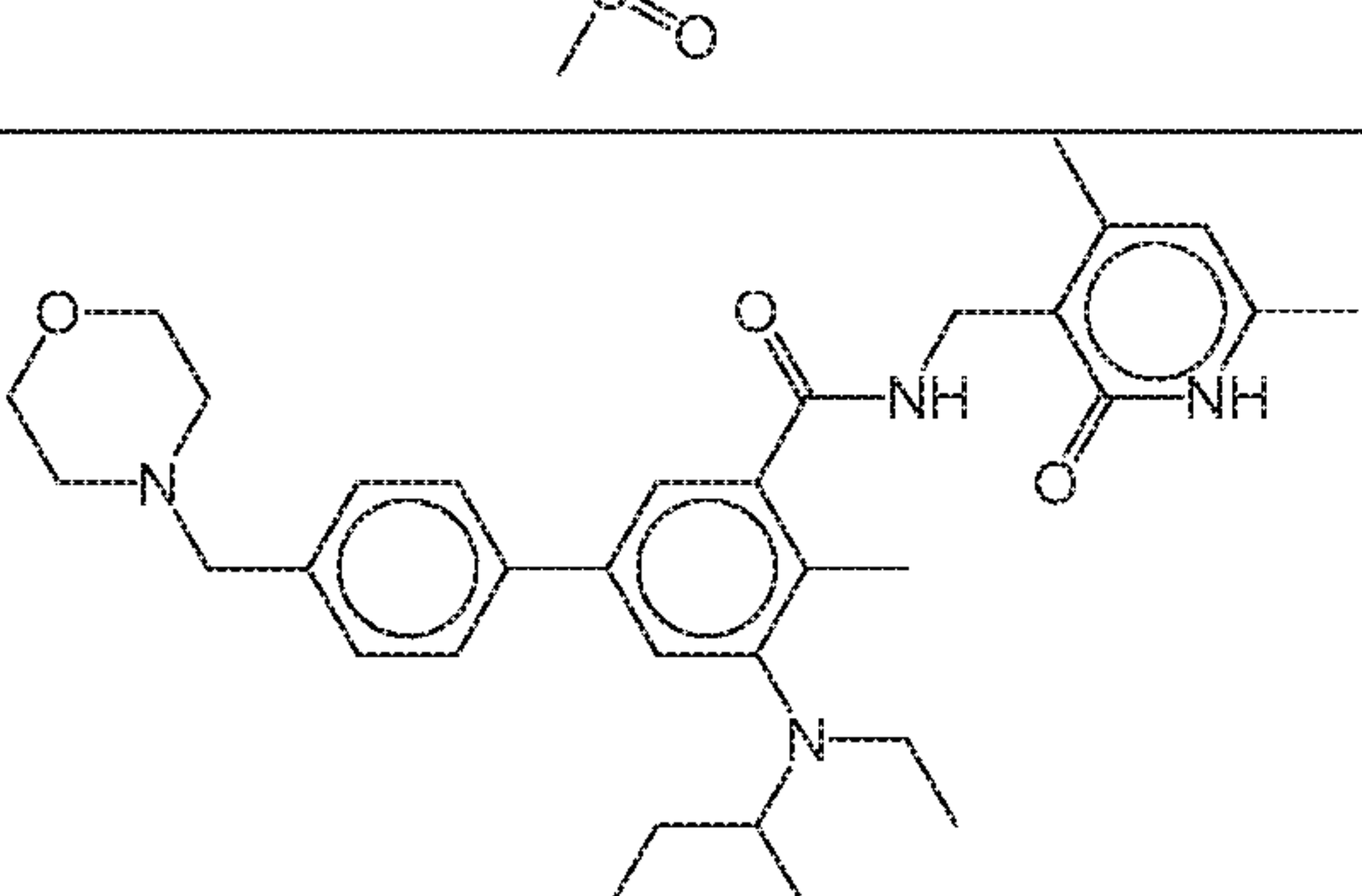
Compound Number	Structure	MS (M+1) ⁺
88		587.40
89		503.40
90		517.30
91		531.35

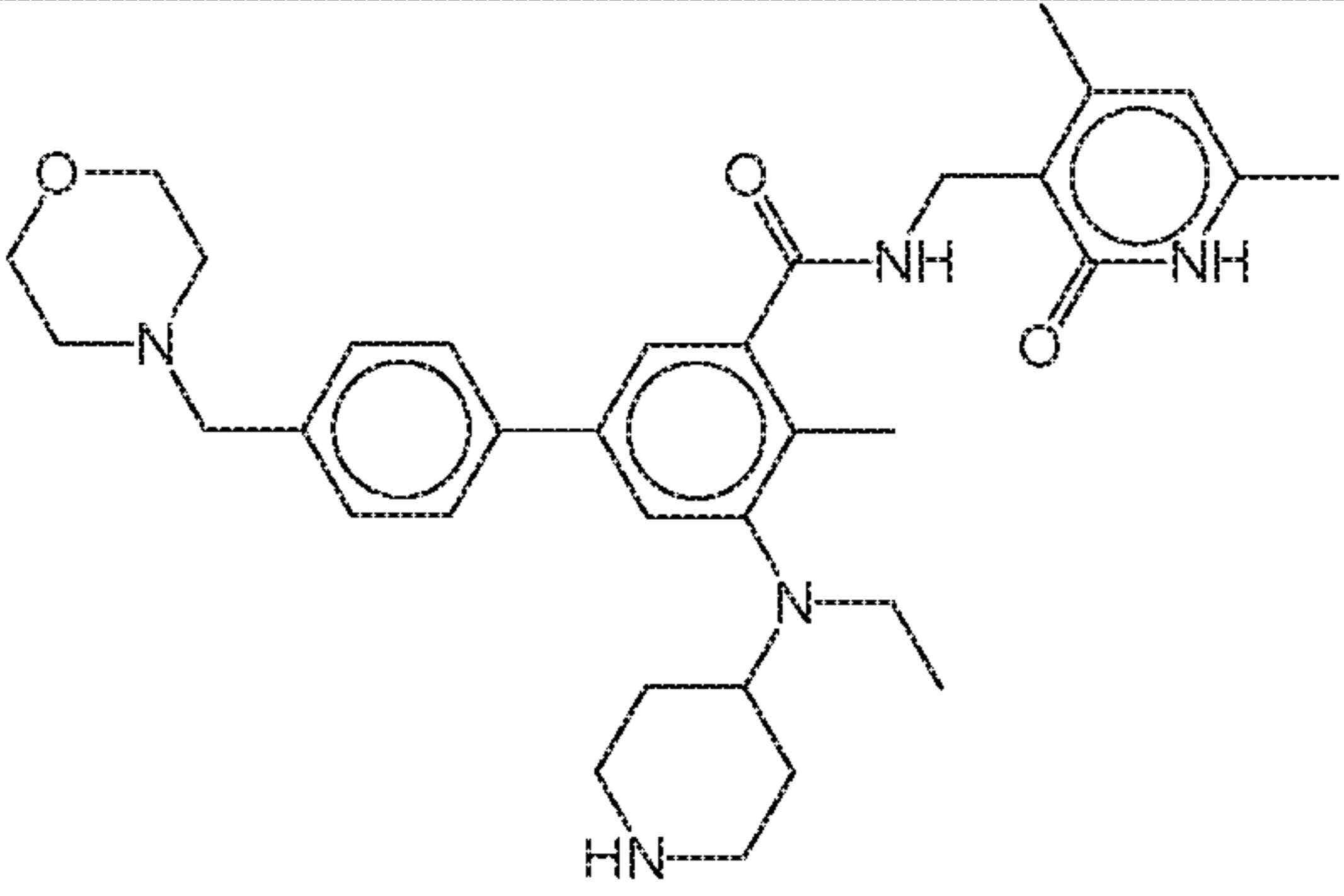
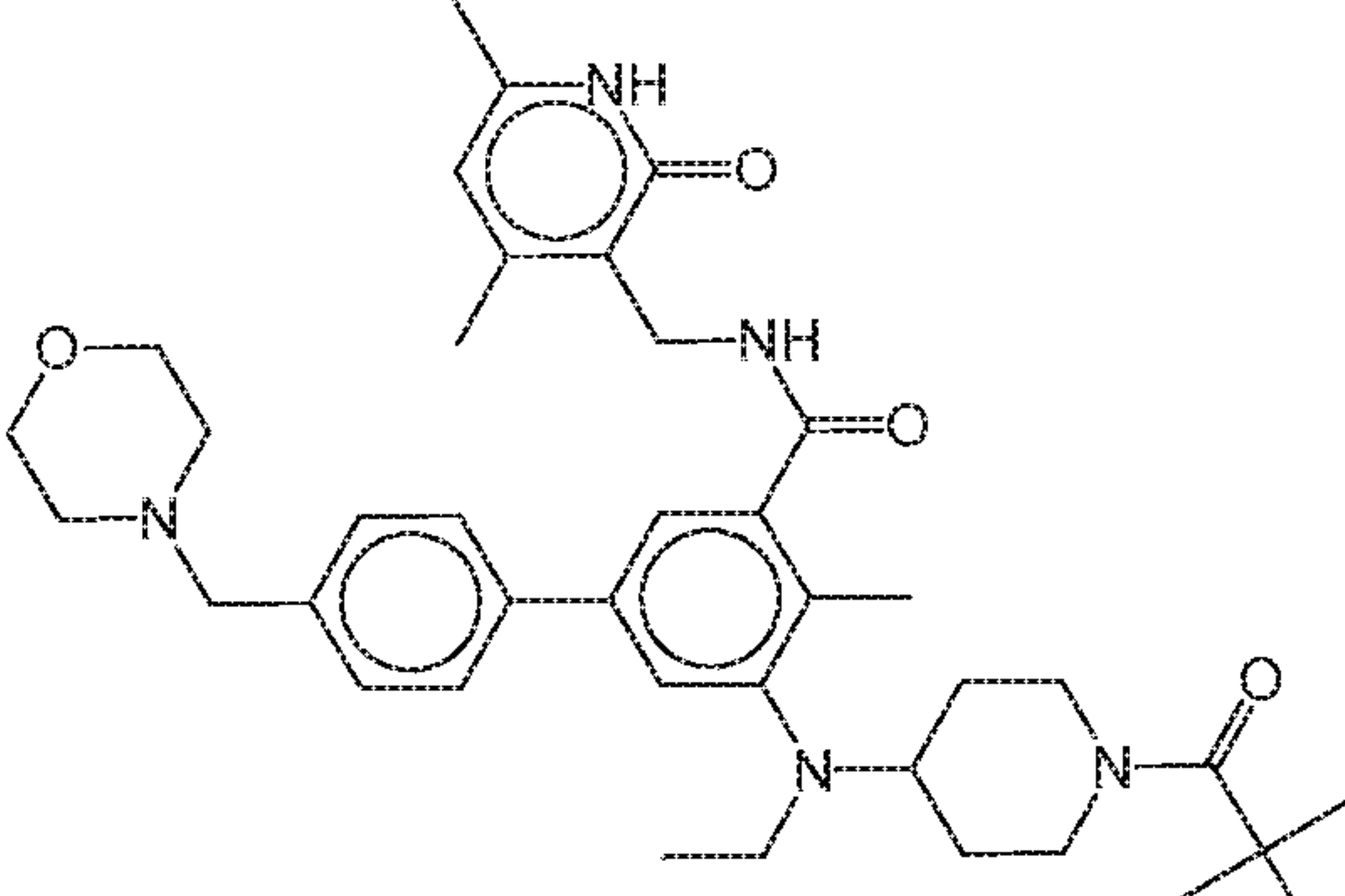
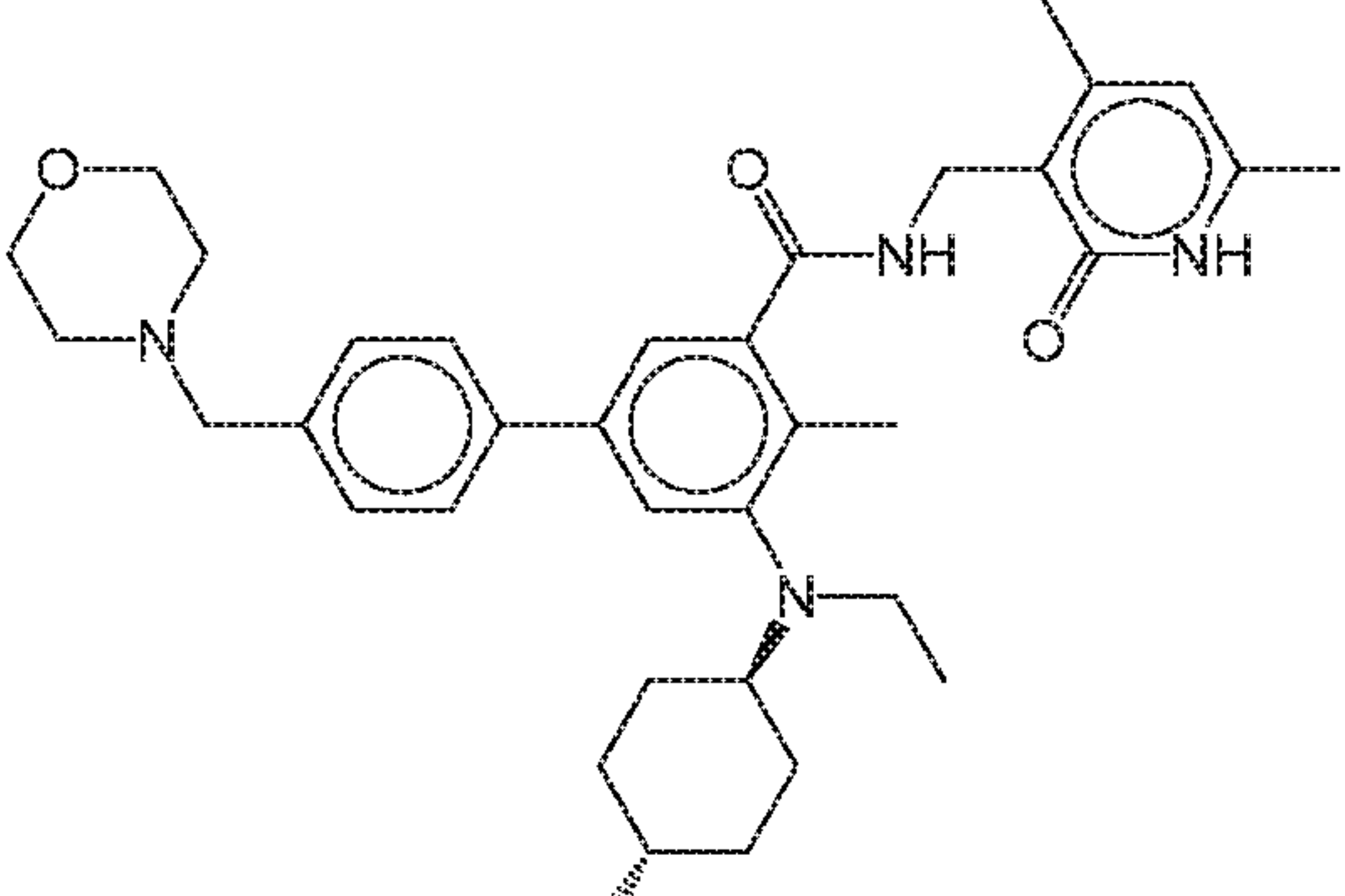
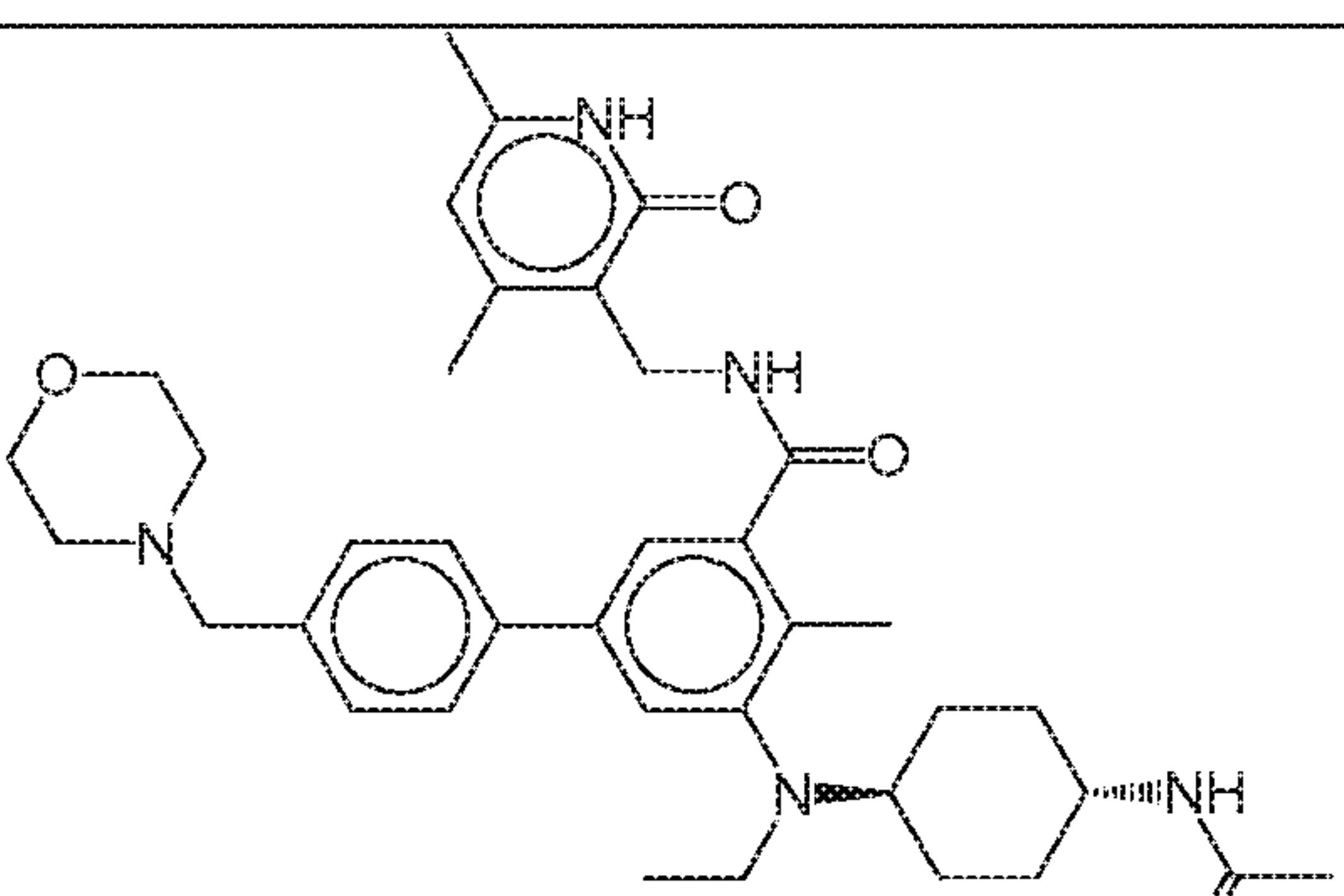
Compound Number	Structure	MS (M+1) ⁺
92		545.40
93		557.35
94		559.20
95		599.35 (M+Na)

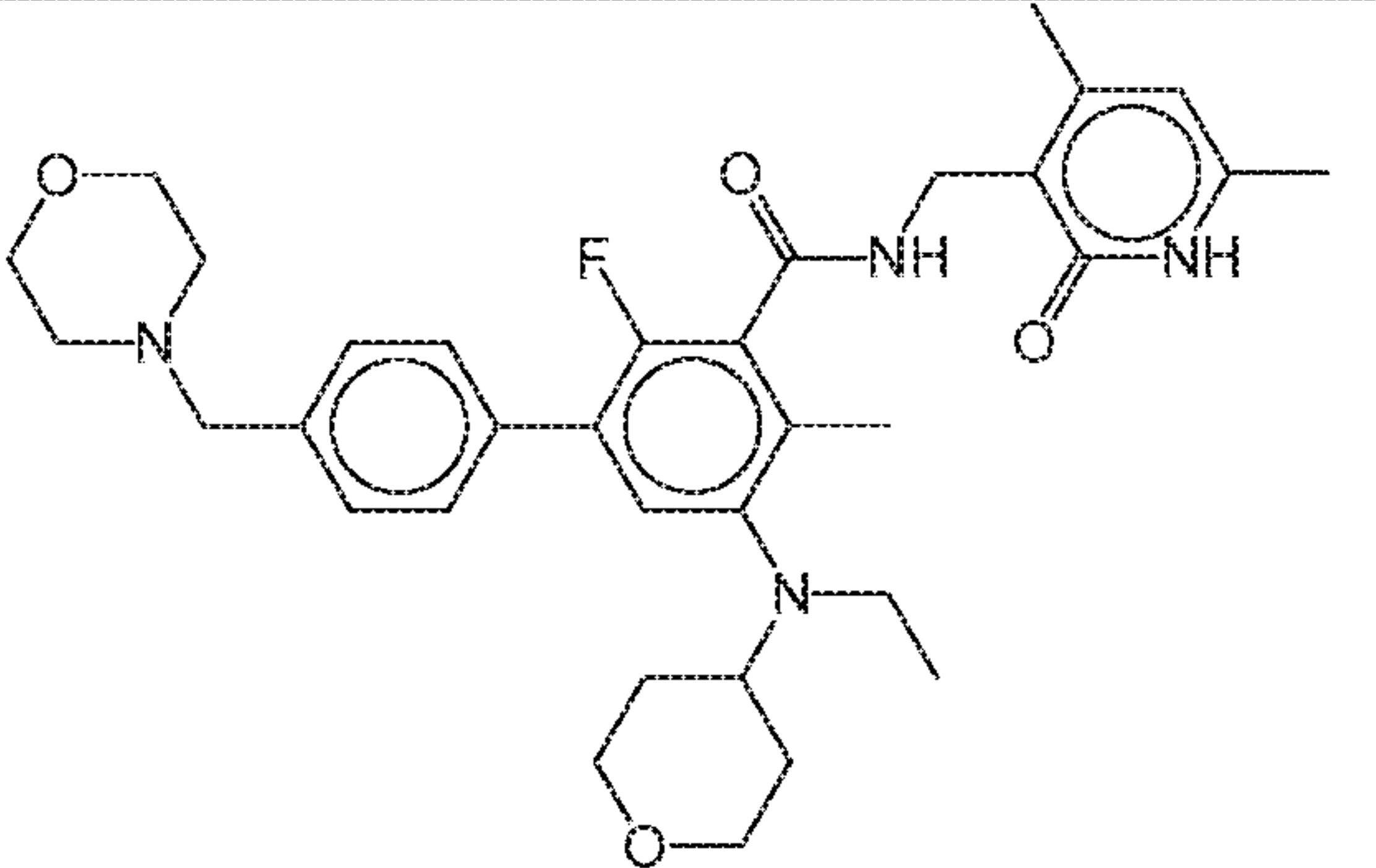
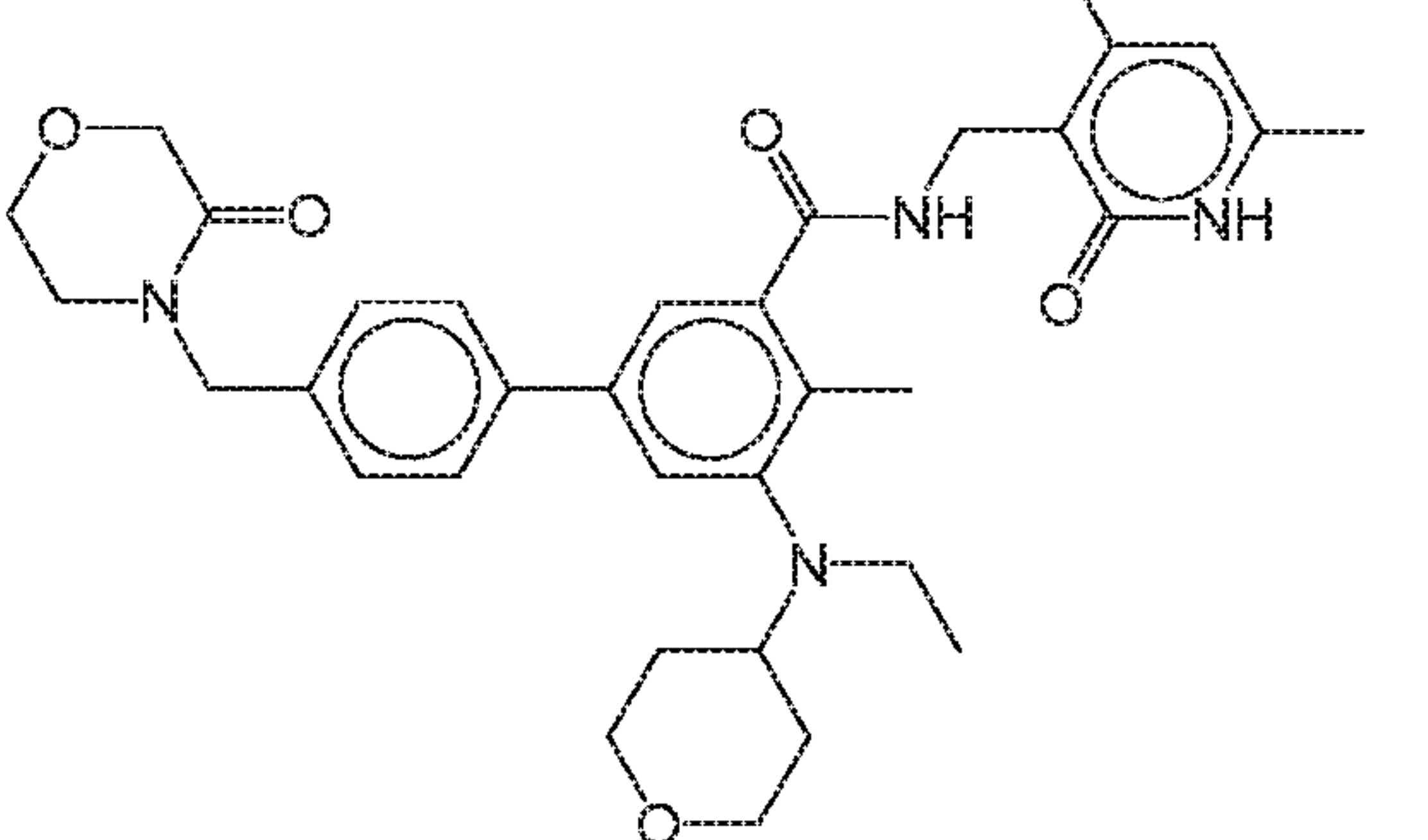
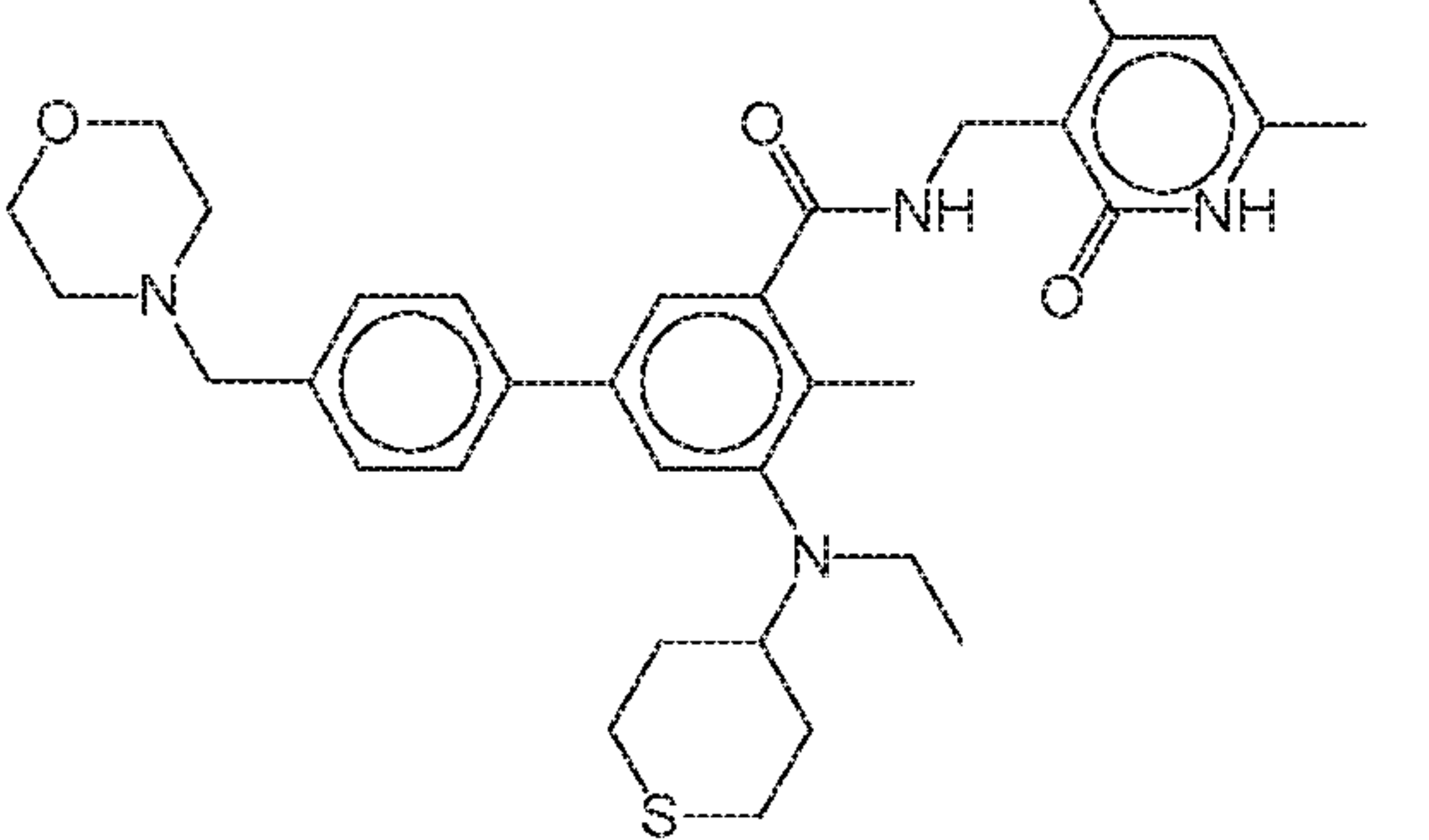
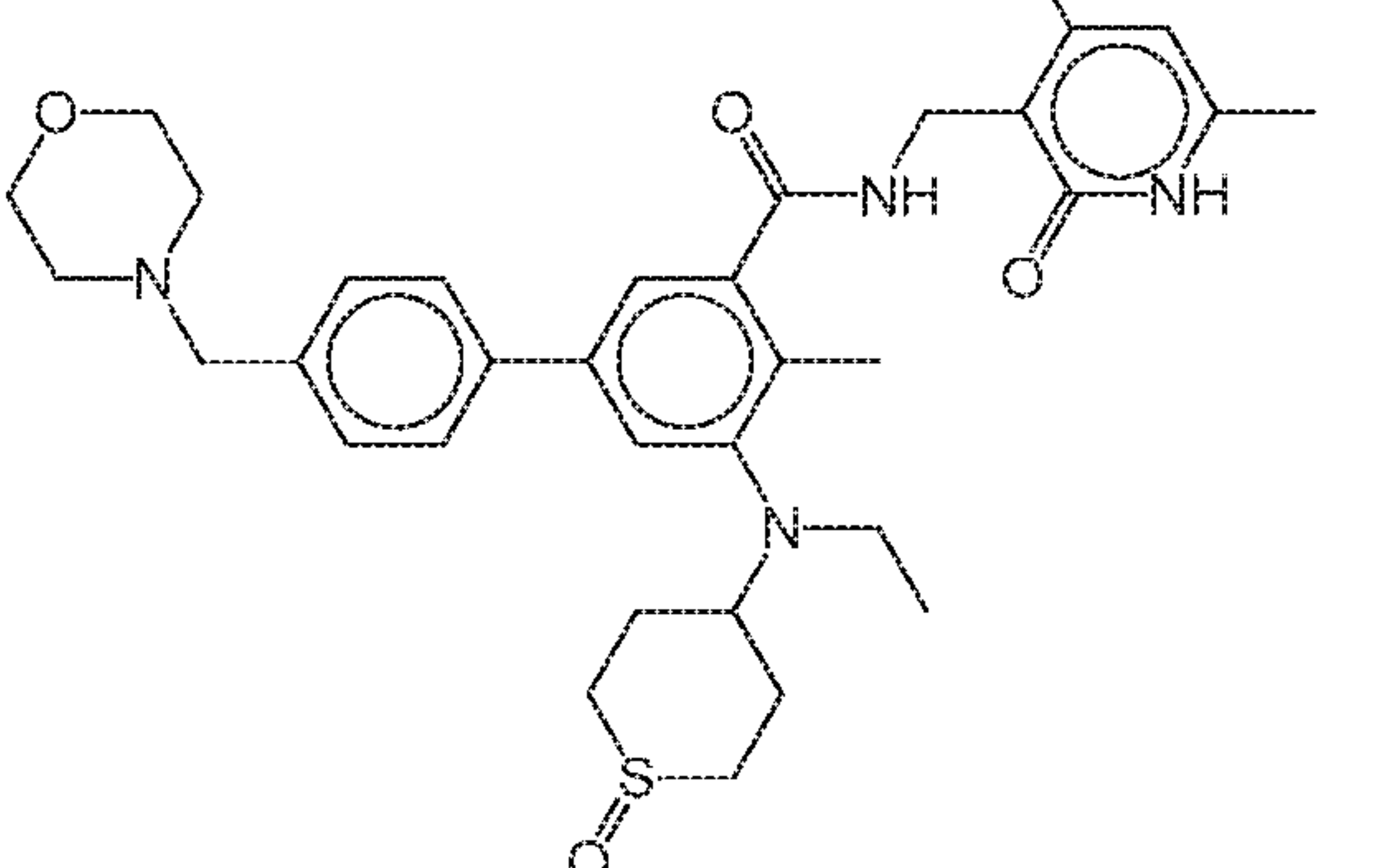
Compound Number	Structure	MS (M+1) ⁺
96		577.25
97		571.40
98		547.35
99		561.30

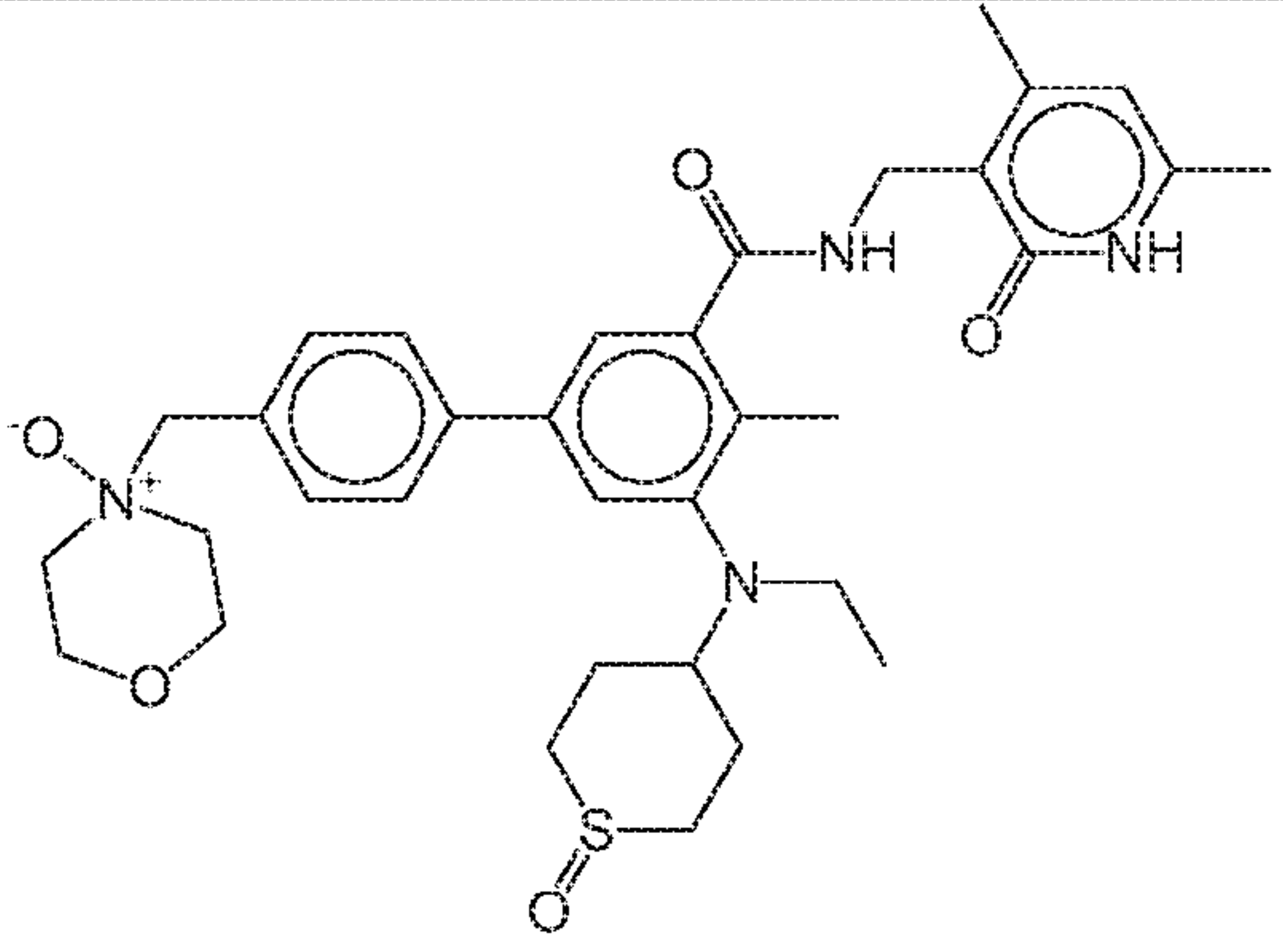
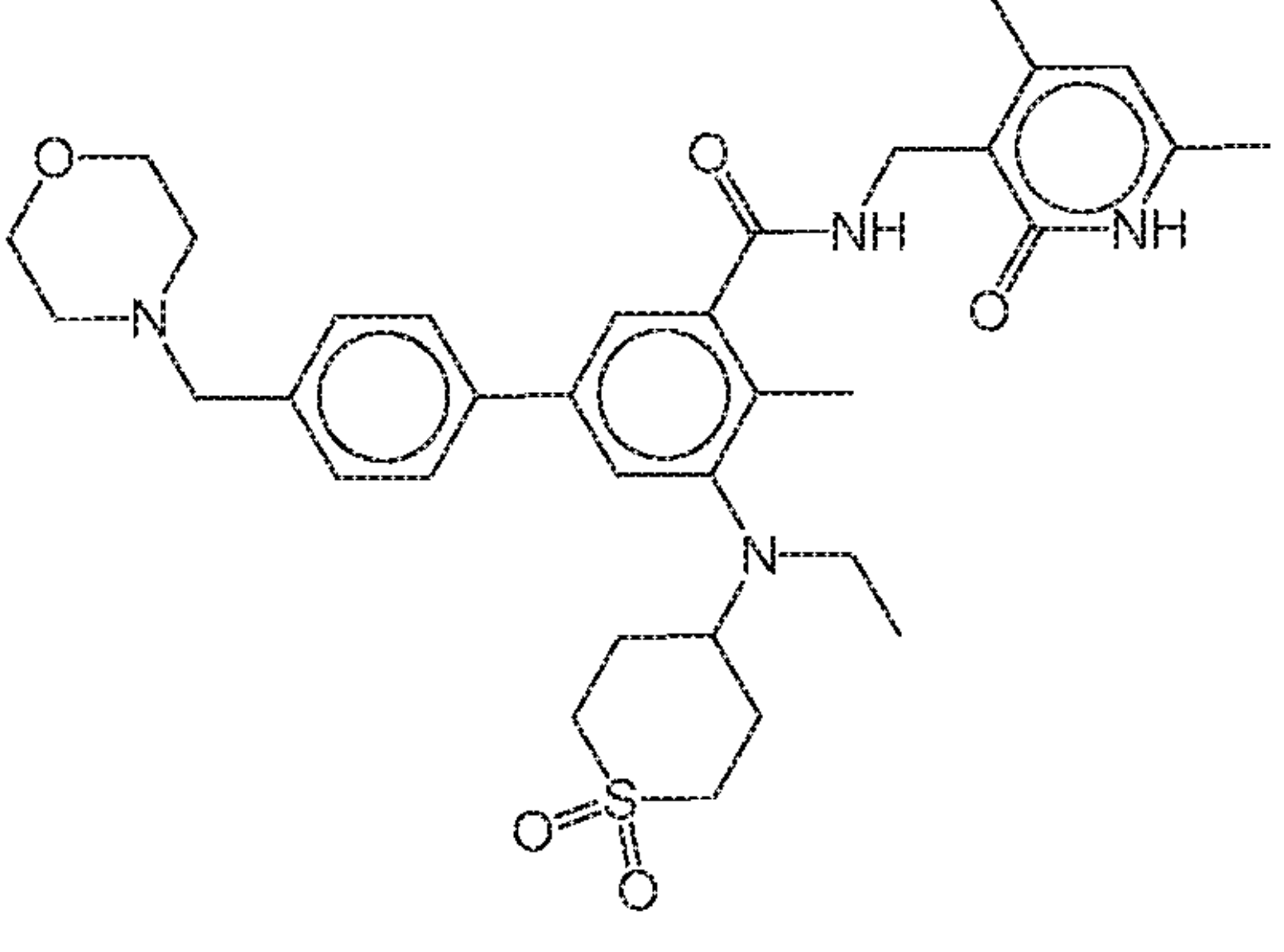
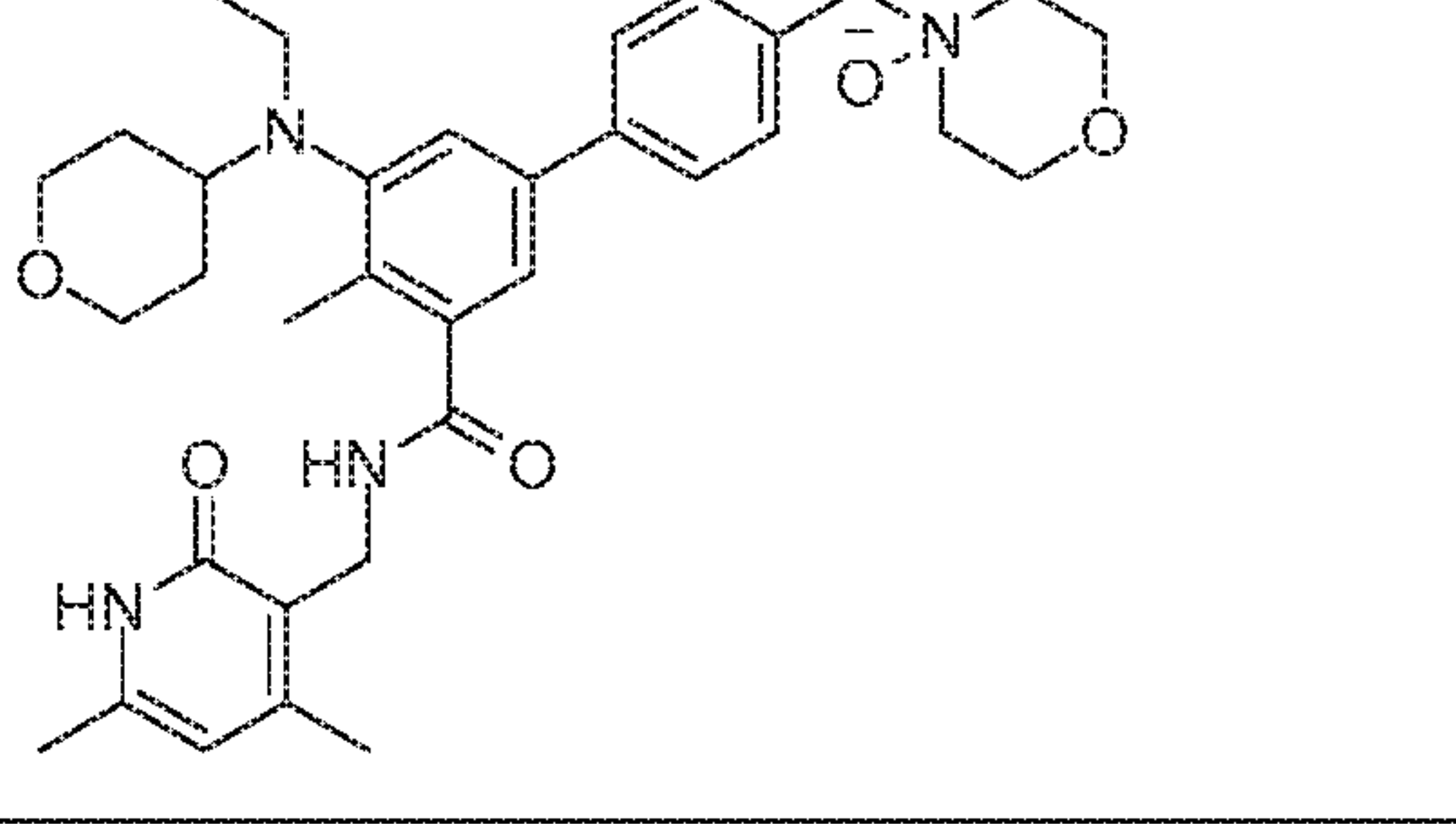
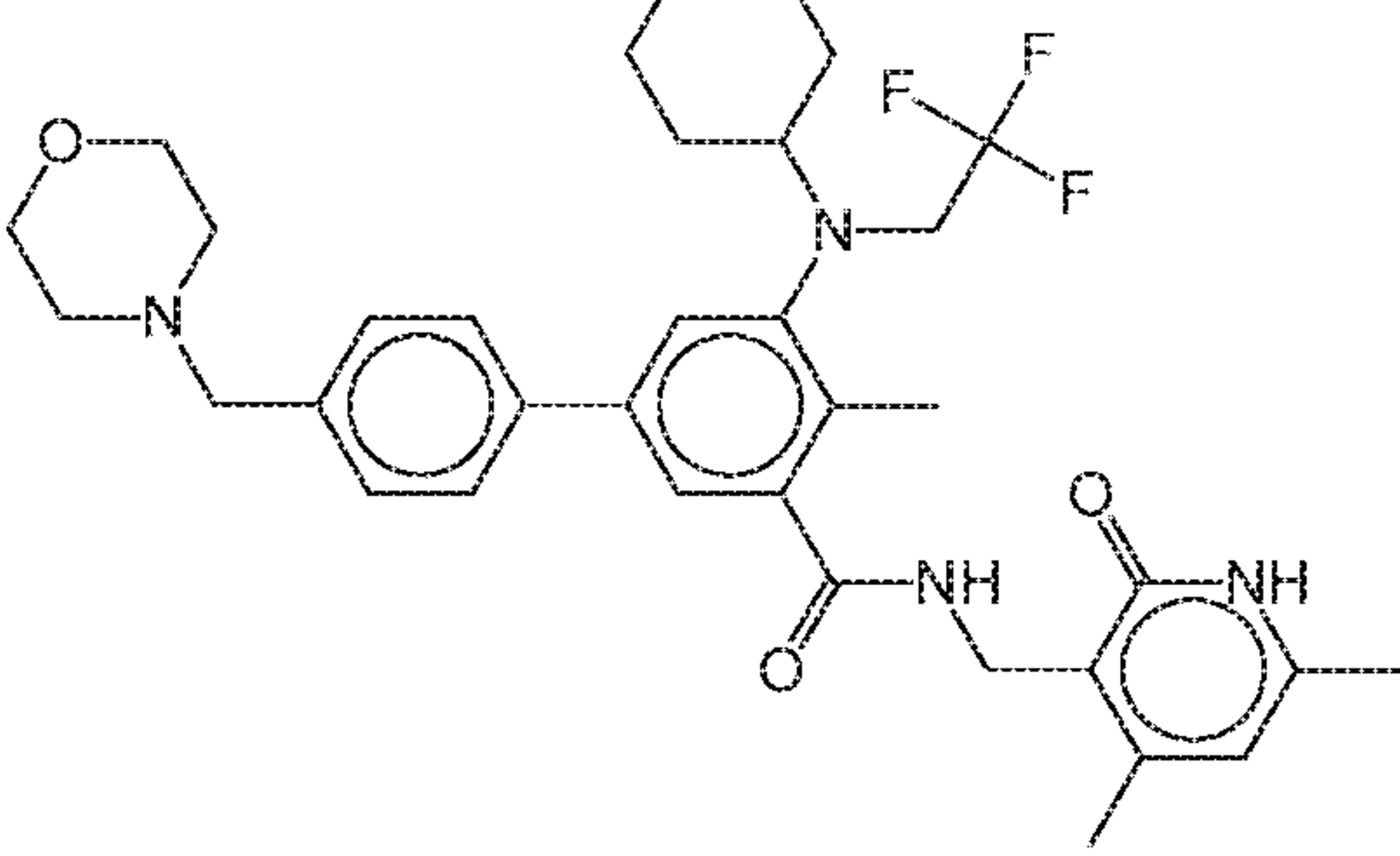
Compound Number	Structure	MS (M+1) ⁺
104		585.25
105		585.40
107		
108		530.35

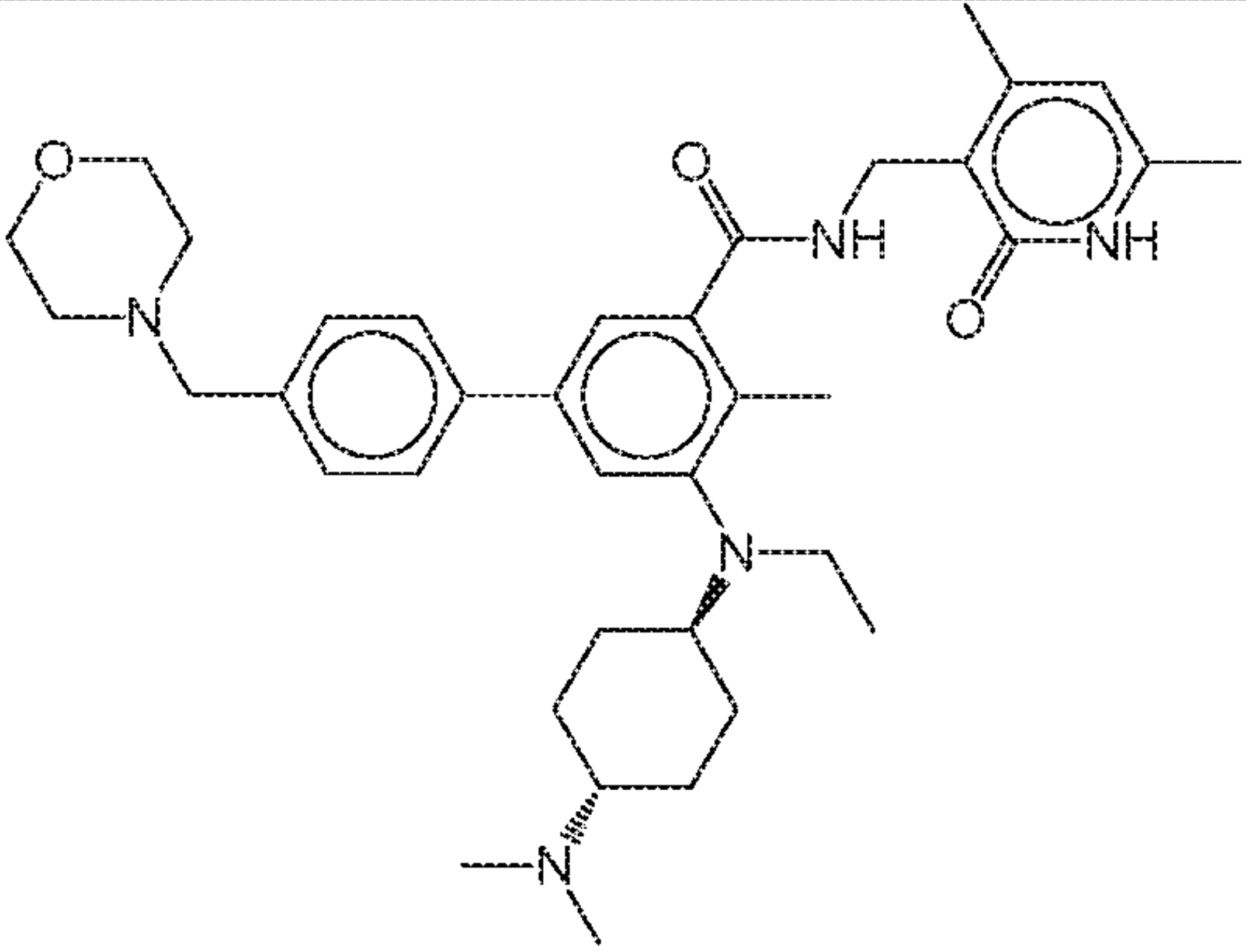
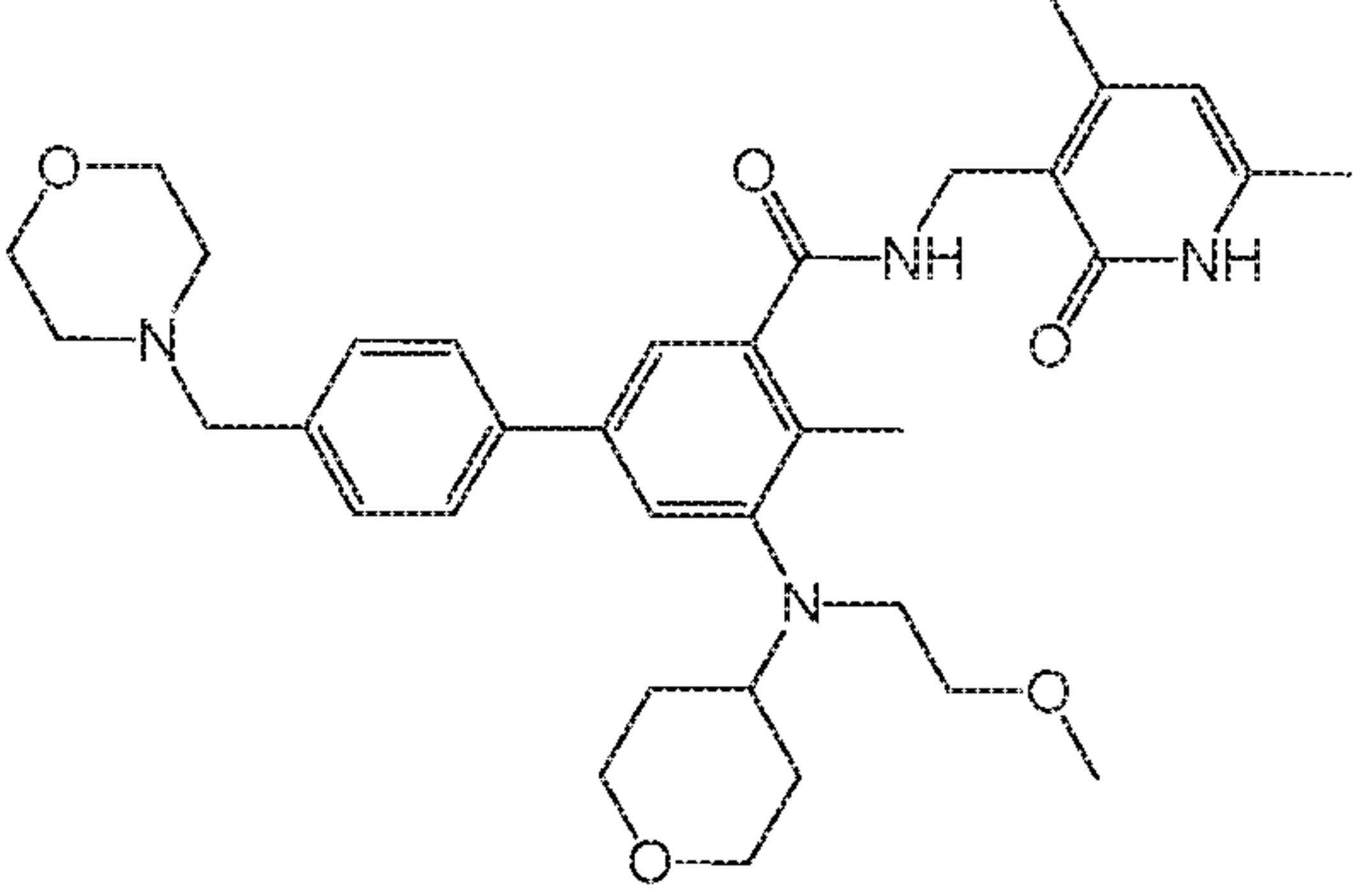
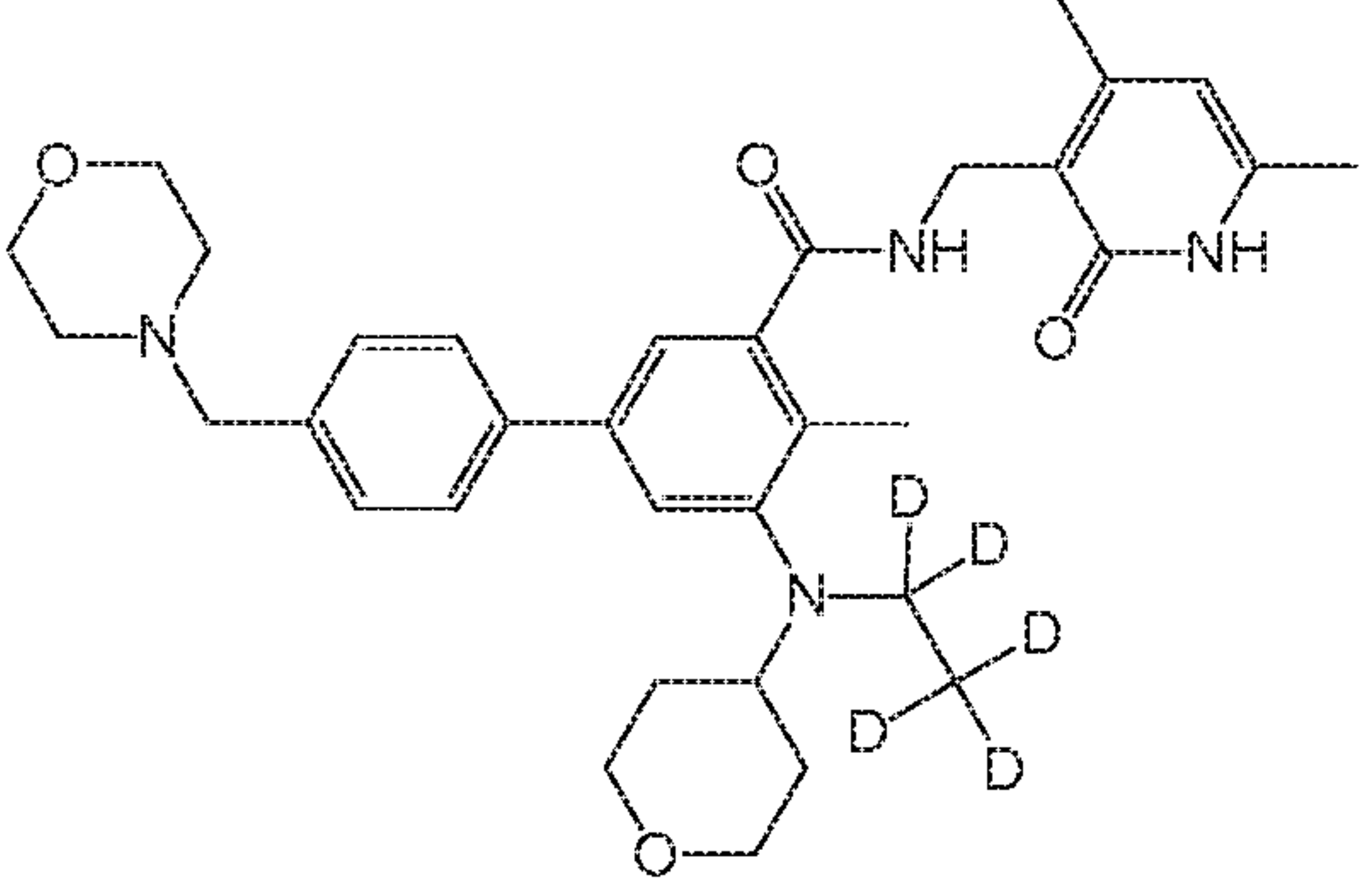
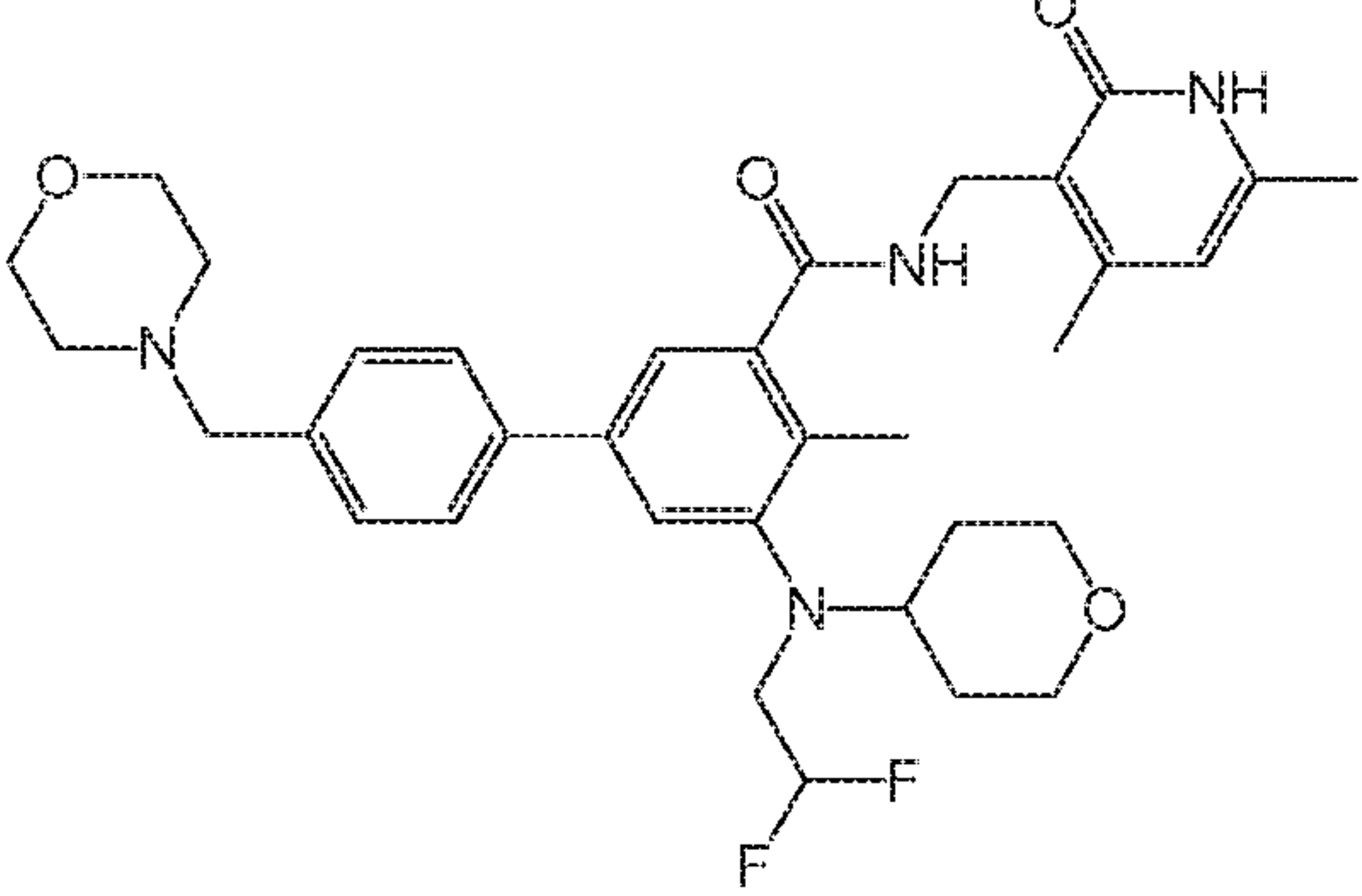
Compound Number	Structure	MS (M+1) ⁺
114		573.25
115		642.45
116		545.15
117		489.20

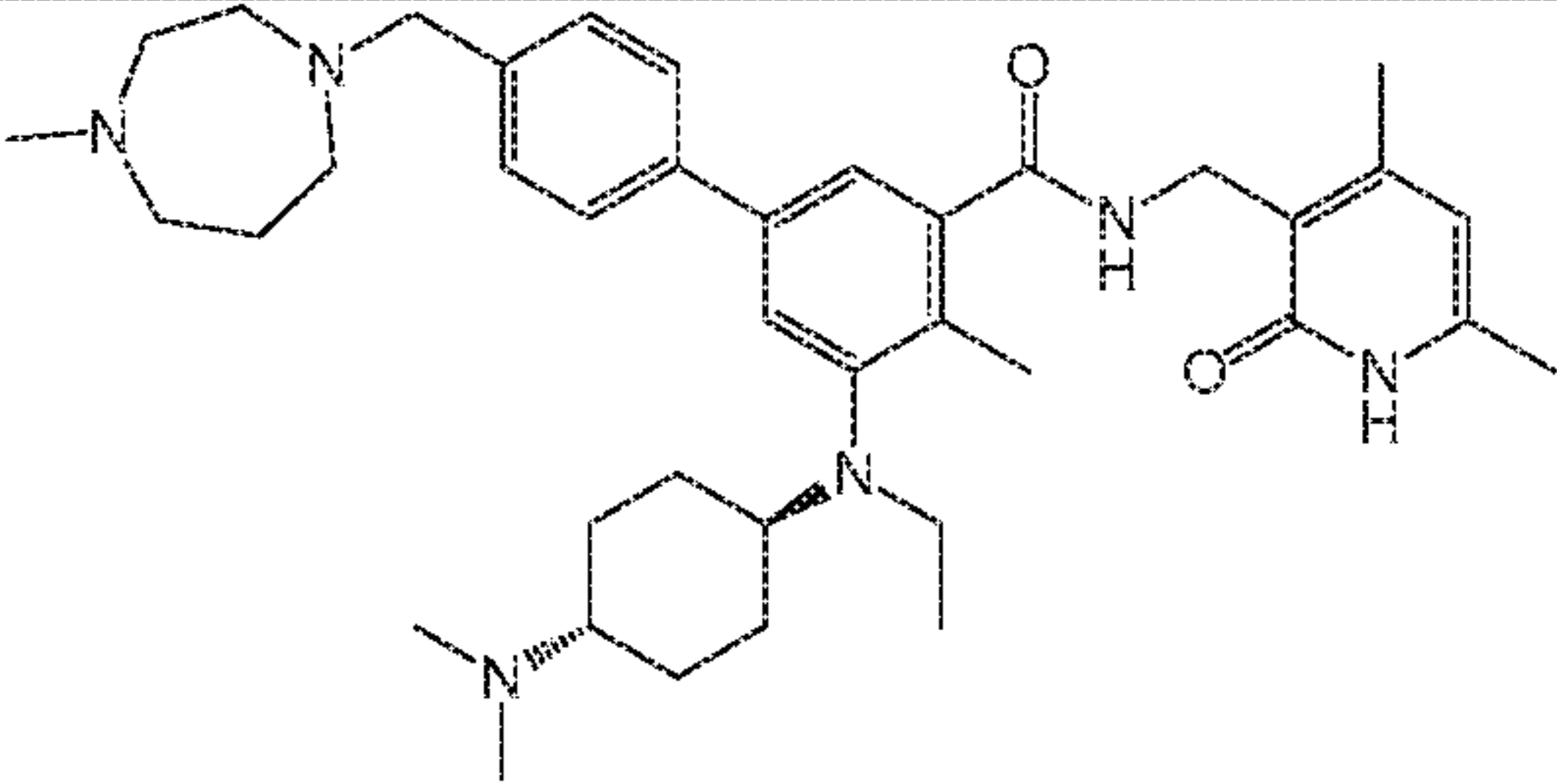
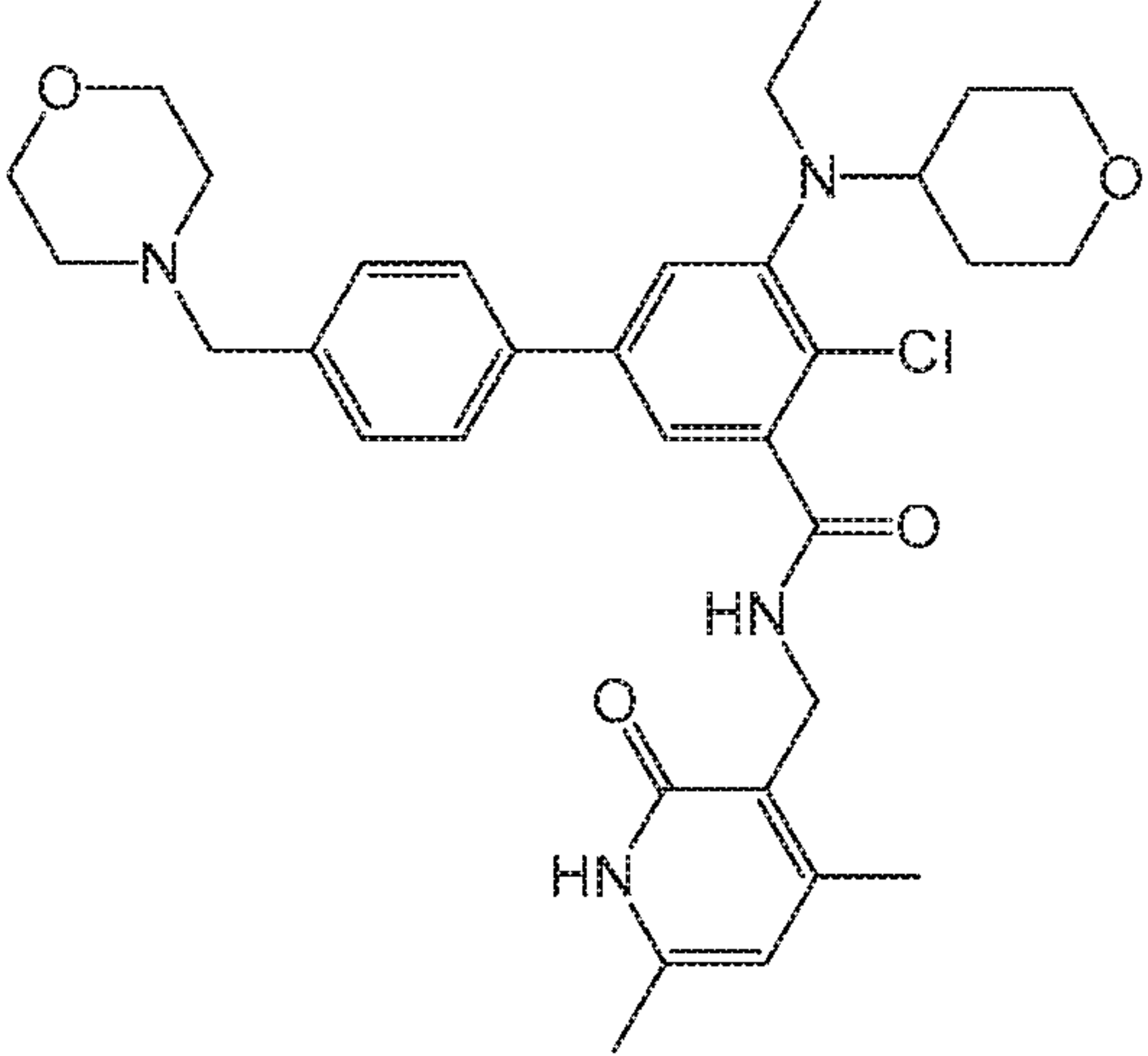
Compound Number	Structure	MS (M+1) ⁺
119		609.35
122		587.55
124		650.85
125		614.75

Compound Number	Structure	MS (M+1) ⁺
126		572.35
127		656.65
128		586.45
129		628.35

Compound Number	Structure	MS (M+1) ⁺
130		591.2
131		587.35
132		589.25
133		605.25

Compound Number	Structure	MS (M+1) ⁺
135		621.40
136		621.45
137		589.35
138		627.5

Compound Number	Structure	MS (M+1) ⁺
141		614.65
142		603.45
143		578.35
144		609.15

Compound Number	Structure	MS (M+1) ⁺
146		641.50
178		593.60

[0194] As used herein, “alkyl”, “C₁, C₂, C₃, C₄, C₅ or C₆ alkyl” or “C₁-C₆ alkyl” is intended to include C₁, C₂, C₃, C₄, C₅ or C₆ straight chain (linear) saturated aliphatic hydrocarbon groups and C₃, C₄, C₅ or C₆ branched saturated aliphatic hydrocarbon groups. For example, C₁-C₆ alkyl is intended to include C₁, C₂, C₃, C₄, C₅ and C₆ alkyl groups. Examples of alkyl include, moieties having from one to six carbon atoms, such as, but not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, s-pentyl or n-hexyl.

[0195] In some embodiments, a straight chain or branched alkyl has six or fewer carbon atoms (e.g., C₁-C₆ for straight chain, C₃-C₆ for branched chain), and in some embodiments, a straight chain or branched alkyl has four or fewer carbon atoms.

[0196] As used herein, the term “cycloalkyl” refers to a saturated or unsaturated nonaromatic hydrocarbon mono-or multi-ring (e.g., fused, bridged, or spiro rings) system having 3 to 30 carbon atoms (e.g., C₃-C₁₀). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, and adamantyl. The term “heterocycloalkyl” refers to a saturated or unsaturated

nonaromatic 3-8 membered monocyclic, 7-12 membered bicyclic (fused, bridged, or spiro rings), or 11-14 membered tricyclic ring system (fused, bridged, or spiro rings) having one or more heteroatoms (such as O, N, S, or Se), unless specified otherwise. Examples of heterocycloalkyl groups include, but are not limited to, piperidinyl, piperazinyl, pyrrolidinyl, dioxanyl, tetrahydrofuranyl, isoindolinyl, indolinyl, imidazolidinyl, pyrazolidinyl, oxazolidinyl, isoxazolidinyl, triazolidinyl, tetrahydrofuranyl, oxiranyl, azetidiny, oxetanyl, thietanyl, 1,2,3,6-tetrahydropyridinyl, tetrahydropyranyl, dihydropyranyl, pyranyl, morpholinyl, 1,4-diazepanyl, 1,4-oxazepanyl, 2-oxa-5-azabicyclo[2.2.1]heptanyl, 2,5-diazabicyclo[2.2.1]heptanyl, 2-oxa-6-azaspiro[3.3]heptanyl, 2,6-diazaspiro[3.3]heptanyl, 1,4-dioxa-8-azaspiro[4.5]decanyl and the like.

[0197] The term “optionally substituted alkyl” refers to unsubstituted alkyl or alkyl having designated substituents replacing one or more hydrogen atoms on one or more carbons of the hydrocarbon backbone. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0198] An “arylalkyl” or an “aralkyl” moiety is an alkyl substituted with an aryl (*e.g.*, phenylmethyl (benzyl)). An “alkylaryl” moiety is an aryl substituted with an alkyl (*e.g.*, methylphenyl).

[0199] As used herein, “alkyl linker” is intended to include C₁, C₂, C₃, C₄, C₅ or C₆ straight chain (linear) saturated divalent aliphatic hydrocarbon groups and C₃, C₄, C₅ or C₆ branched saturated aliphatic hydrocarbon groups. For example, C₁-C₆ alkyl linker is intended to include C₁, C₂, C₃, C₄, C₅ and C₆ alkyl linker groups. Examples of alkyl linker include, moieties having from one to six carbon atoms, such as, but not limited to, methyl (-CH₂-), ethyl (-CH₂CH₂-), n-propyl (-CH₂CH₂CH₂-), i-propyl (-CHCH₃CH₂-), n-butyl (-CH₂CH₂CH₂CH₂-), s-butyl (-CHCH₃CH₂CH₂-), i-butyl (-C(CH₃)₂CH₂-), n-pentyl (-CH₂CH₂CH₂CH₂CH₂-), s-pentyl (-CHCH₃CH₂CH₂CH₂-) or n-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₂-).

[0200] “Alkenyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double bond. For example, the term “alkenyl” includes straight chain alkenyl groups (*e.g.*, ethenyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl, decenyl), and branched alkenyl groups. In certain embodiments, a straight chain or branched alkenyl group has six or fewer carbon atoms in its backbone (*e.g.*, C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term “C₂-C₆” includes alkenyl groups containing two to six carbon atoms. The term “C₃-C₆” includes alkenyl groups containing three to six carbon atoms.

[0201] The term “optionally substituted alkenyl” refers to unsubstituted alkenyl or alkenyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0202] “Alkynyl” includes unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but which contain at least one triple bond. For example, “alkynyl” includes straight chain alkynyl groups (*e.g.*, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl, octynyl, nonynyl, decynyl), and branched alkynyl groups. In certain embodiments, a straight chain or branched alkynyl group has six or fewer carbon atoms in its backbone (*e.g.*, C₂-C₆ for straight chain, C₃-C₆ for branched chain). The term “C₂-C₆” includes alkynyl groups containing two to six carbon atoms. The term “C₃-C₆” includes alkynyl groups containing three to six carbon atoms.

[0203] The term “optionally substituted alkynyl” refers to unsubstituted alkynyl or alkynyl having designated substituents replacing one or more hydrogen atoms on one or more hydrocarbon backbone carbon atoms. Such substituents can include, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy,

carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0204] Other optionally substituted moieties (such as optionally substituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl) include both the unsubstituted moieties and the moieties having one or more of the designated substituents. For example, substituted heterocycloalkyl includes those substituted with one or more alkyl groups, such as 2,2,6,6-tetramethyl-piperidinyl and 2,2,6,6-tetramethyl-1,2,3,6-tetrahydropyridinyl.

[0205] “Aryl” includes groups with aromaticity, including “conjugated,” or polycyclic systems with at least one aromatic ring and do not contain any heteroatom in the ring structure. Examples include phenyl, benzyl, 1,2,3,4-tetrahydronaphthalenyl, etc.

[0206] “Heteroaryl” groups are aryl groups, as defined above, except having from one to four heteroatoms in the ring structure, and may also be referred to as “aryl heterocycles” or “heteroaromatics.” As used herein, the term “heteroaryl” is intended to include a stable 5-, 6-, or 7-membered monocyclic or 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms and one or more heteroatoms, *e.g.*, 1 or 1-2 or 1-3 or 1-4 or 1-5 or 1-6 heteroatoms, or *e.g.*, 1, 2, 3, 4, 5, or 6 heteroatoms, independently selected from the group consisting of nitrogen, oxygen and sulfur. The nitrogen atom may be substituted or unsubstituted (*i.e.*, N or NR wherein R is H or other substituents, as defined). The nitrogen and sulfur heteroatoms may optionally be oxidized (*i.e.*, N→O and S(O)_p, where p = 1 or 2). It is to be noted that total number of S and O atoms in the aromatic heterocycle is not more than 1.

[0207] Examples of heteroaryl groups include pyrrole, furan, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like.

[0208] Furthermore, the terms “aryl” and “heteroaryl” include polycyclic aryl and heteroaryl groups, *e.g.*, tricyclic, bicyclic, *e.g.*, naphthalene, benzoxazole, benzodioxazole, benzothiazole,

benzoimidazole, benzothiophene, methylenedioxyphenyl, quinoline, isoquinoline, naphthrydine, indole, benzofuran, purine, benzofuran, deazapurine, indolizine.

[0209] In the case of multicyclic aromatic rings, only one of the rings needs to be aromatic (*e.g.*, 2,3-dihydroindole), although all of the rings may be aromatic (*e.g.*, quinoline). The second ring can also be fused or bridged.

[0210] The cycloalkyl, heterocycloalkyl, aryl, or heteroaryl ring can be substituted at one or more ring positions (*e.g.*, the ring-forming carbon or heteroatom such as N) with such substituents as described above, for example, alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkoxy, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy, carboxylate, alkylcarbonyl, alkylaminocarbonyl, aralkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, alkenylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylthiocarbonyl, phosphate, phosphonate, phosphinate, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety. Aryl and heteroaryl groups can also be fused or bridged with alicyclic or heterocyclic rings, which are not aromatic so as to form a multicyclic system (*e.g.*, tetralin, methylenedioxyphenyl).

[0211] As used herein, “carbocycle” or “carbocyclic ring” is intended to include any stable monocyclic, bicyclic or tricyclic ring having the specified number of carbons, any of which may be saturated, unsaturated, or aromatic. Carbocycle includes cycloalkyl and aryl. For example, a C₃-C₁₄ carbocycle is intended to include a monocyclic, bicyclic or tricyclic ring having 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 carbon atoms. Examples of carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclobutenyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloheptenyl, cycloheptyl, cycloheptenyl, adamantyl, cyclooctyl, cyclooctenyl, cyclooctadienyl, fluorenyl, phenyl, naphthyl, indanyl, adamantyl and tetrahydronaphthyl. Bridged rings are also included in the definition of carbocycle, including, for example, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane and [2.2.2]bicyclooctane. A bridged ring occurs when one or more carbon atoms link two non-adjacent carbon atoms. In some embodiments, bridge rings are one or two carbon atoms. It is noted that a bridge always converts a monocyclic ring into a tricyclic ring.

When a ring is bridged, the substituents recited for the ring may also be present on the bridge. Fused (*e.g.*, naphthyl, tetrahydronaphthyl) and spiro rings are also included.

[0212] As used herein, “heterocycle” or “heterocyclic group” includes any ring structure (saturated, unsaturated, or aromatic) which contains at least one ring heteroatom (*e.g.*, N, O or S). Heterocycle includes heterocycloalkyl and heteroaryl. Examples of heterocycles include, but are not limited to, morpholine, pyrrolidine, tetrahydrothiophene, piperidine, piperazine, oxetane, pyran, tetrahydropyran, azetidine, and tetrahydrofuran.

[0213] Examples of heterocyclic groups include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzoxazoliny, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazoliny, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazoliny, imidazolyl, 1*H*-indazolyl, indolenyl, indoliny, indoliziny, indolyl, 3*H*-indolyl, isatinoyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindoliny, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,4-oxadiazol5(4*H*)-one, oxazolidinyl, oxazolyl, oxindolyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidonyl, 4-piperidonyl, piperonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrroliny, 2*H*-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinoliziny, quinoxaliny, quinuclidiny, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl and xanthenyl.

[0214] The term “substituted,” as used herein, means that any one or more hydrogen atoms on the designated atom is replaced with a selection from the indicated groups, provided that the designated atom’s normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is oxo or keto (*i.e.*, =O), then 2 hydrogen atoms on the atom are replaced. Keto substituents are not present on aromatic moieties. Ring double bonds, as used

herein, are double bonds that are formed between two adjacent ring atoms (*e.g.*, C=C, C=N or N=N). “Stable compound” and “stable structure” are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

[0215] When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom in the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such formula. Combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0216] When any variable (*e.g.*, R₁) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to be substituted with 0-2 R₁ moieties, then the group may optionally be substituted with up to two R₁ moieties and R₁ at each occurrence is selected independently from the definition of R₁. Also, combinations of substituents and/or variables are permissible, but only if such combinations result in stable compounds.

[0217] The term “hydroxy” or “hydroxyl” includes groups with an -OH or -O[•].

[0218] As used herein, “halo” or “halogen” refers to fluoro, chloro, bromo and iodo. The term “perhalogenated” generally refers to a moiety wherein all hydrogen atoms are replaced by halogen atoms. The term “haloalkyl” or “haloalkoxy” refers to an alkyl or alkoxy substituted with one or more halogen atoms.

[0219] The term “carbonyl” includes compounds and moieties which contain a carbon connected with a double bond to an oxygen atom. Examples of moieties containing a carbonyl include, but are not limited to, aldehydes, ketones, carboxylic acids, amides, esters, anhydrides, etc.

[0220] The term “carboxyl” refers to -COOH or its C₁-C₆ alkyl ester.

[0221] “Acyl” includes moieties that contain the acyl radical (R-C(O)-) or a carbonyl group.

“Substituted acyl” includes acyl groups where one or more of the hydrogen atoms are replaced by, for example, alkyl groups, alkynyl groups, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino,

arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moiety.

[0222] “Aroyl” includes moieties with an aryl or heteroaromatic moiety bound to a carbonyl group. Examples of aroyl groups include phenylcarboxy, naphthyl carboxy, etc.

[0223] “Alkoxyalkyl,” “alkylaminoalkyl,” and “thioalkoxyalkyl” include alkyl groups, as described above, wherein oxygen, nitrogen, or sulfur atoms replace one or more hydrocarbon backbone carbon atoms.

[0224] The term “alkoxy” or “alkoxyl” includes substituted and unsubstituted alkyl, alkenyl and alkynyl groups covalently linked to an oxygen atom. Examples of alkoxy groups or alkoxyl radicals include, but are not limited to, methoxy, ethoxy, isopropoxy, propoxy, butoxy and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxycarbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

[0225] The term “ether” or “alkoxy” includes compounds or moieties which contain an oxygen bonded to two carbon atoms or heteroatoms. For example, the term includes “alkoxyalkyl,” which refers to an alkyl, alkenyl, or alkynyl group covalently bonded to an oxygen atom which is covalently bonded to an alkyl group.

[0226] The term “ester” includes compounds or moieties which contain a carbon or a heteroatom bound to an oxygen atom which is bonded to the carbon of a carbonyl group. The term “ester”

includes alkoxy-carboxy groups such as methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, pentoxycarbonyl, etc.

[0227] The term “thioalkyl” includes compounds or moieties which contain an alkyl group connected with a sulfur atom. The thioalkyl groups can be substituted with groups such as alkyl, alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy-carbonyloxy, aryloxy-carbonyloxy, carboxylate, carboxylic acid, alkylcarbonyl, arylcarbonyl, alkoxy-carbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl-amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocycl-yl, alkylaryl, or an aromatic or heteroaromatic moieties.

[0228] The term “thiocarbonyl” or “thiocarboxy” includes compounds and moieties which contain a carbon connected with a double bond to a sulfur atom.

[0229] The term “thioether” includes moieties which contain a sulfur atom bonded to two carbon atoms or heteroatoms. Examples of thioethers include, but are not limited to alkthioalkyls, alkthioalkenyls, and alkthioalkynyls. The term “alkthioalkyls” include moieties with an alkyl, alkenyl, or alkynyl group bonded to a sulfur atom which is bonded to an alkyl group. Similarly, the term “alkthioalkenyls” refers to moieties wherein an alkyl, alkenyl or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkenyl group; and alkthioalkynyls” refers to moieties wherein an alkyl, alkenyl or alkynyl group is bonded to a sulfur atom which is covalently bonded to an alkynyl group.

[0230] As used herein, “amine” or “amino” refers to unsubstituted or substituted -NH₂.

“Alkylamino” includes groups of compounds wherein nitrogen of -NH₂ is bound to at least one alkyl group. Examples of alkylamino groups include benzylamino, methylamino, ethylamino, phenethylamino, etc. “Dialkylamino” includes groups wherein the nitrogen of -NH₂ is bound to at least two additional alkyl groups. Examples of dialkylamino groups include, but are not limited to, dimethylamino and diethylamino. “Arylamino” and “diarylamino” include groups wherein the nitrogen is bound to at least one or two aryl groups, respectively. “Aminoaryl” and “aminoaryloxy” refer to aryl and aryloxy substituted with amino. “Alkylaryl-amino,” “alkylaminoaryl” or “arylaminoalkyl” refers to an amino group which is bound to at least one

alkyl group and at least one aryl group. “Alkaminoalkyl” refers to an alkyl, alkenyl, or alkynyl group bound to a nitrogen atom which is also bound to an alkyl group. “Acylamino” includes groups wherein nitrogen is bound to an acyl group. Examples of acylamino include, but are not limited to, alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido groups.

[0231] The term “amide” or “aminocarboxy” includes compounds or moieties that contain a nitrogen atom that is bound to the carbon of a carbonyl or a thiocarbonyl group. The term includes “alkaminocarboxy” groups that include alkyl, alkenyl or alkynyl groups bound to an amino group which is bound to the carbon of a carbonyl or thiocarbonyl group. It also includes “arylaminocarboxy” groups that include aryl or heteroaryl moieties bound to an amino group that is bound to the carbon of a carbonyl or thiocarbonyl group. The terms “alkylaminocarboxy”, “alkenylaminocarboxy”, “alkynylaminocarboxy” and “arylaminocarboxy” include moieties wherein alkyl, alkenyl, alkynyl and aryl moieties, respectively, are bound to a nitrogen atom which is in turn bound to the carbon of a carbonyl group. Amides can be substituted with substituents such as straight chain alkyl, branched alkyl, cycloalkyl, aryl, heteroaryl or heterocycle. Substituents on amide groups may be further substituted.

[0232] Compounds of the disclosure that contain nitrogens can be converted to N-oxides by treatment with an oxidizing agent (*e.g.*, 3-chloroperoxybenzoic acid (*m*CPBA) and/or hydrogen peroxides) to afford other compounds of the disclosure. Thus, all shown and claimed nitrogen-containing compounds are considered, when allowed by valency and structure, to include both the compound as shown and its N-oxide derivative (which can be designated as N→O or N⁺-O⁻). Furthermore, in other instances, the nitrogens in the compounds of the disclosure can be converted to N-hydroxy or N-alkoxy compounds. For example, N-hydroxy compounds can be prepared by oxidation of the parent amine by an oxidizing agent such as *m*-CPBA. All shown and claimed nitrogen-containing compounds are also considered, when allowed by valency and structure, to cover both the compound as shown and its N-hydroxy (*i.e.*, N-OH) and N-alkoxy (*i.e.*, N-OR, wherein R is substituted or unsubstituted C₁-C₆ alkyl, C₁-C₆ alkenyl, C₁-C₆ alkynyl, 3-14-membered carbocycle or 3-14-membered heterocycle) derivatives.

[0233] “Isomerism” means compounds that have identical molecular formulae but differ in the sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed “stereoisomers.” Stereoisomers that are not mirror images of one another are termed “diastereoisomers,” and stereoisomers that are

non-superimposable mirror images of each other are termed “enantiomers” or sometimes optical isomers. A mixture containing equal amounts of individual enantiomeric forms of opposite chirality is termed a “racemic mixture.”

[0234] A carbon atom bonded to four nonidentical substituents is termed a “chiral center.”

[0235] “Chiral isomer” means a compound with at least one chiral center. Compounds with more than one chiral center may exist either as an individual diastereomer or as a mixture of diastereomers, termed “diastereomeric mixture.” When one chiral center is present, a stereoisomer may be characterized by the absolute configuration (R or S) of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. The substituents attached to the chiral center under consideration are ranked in accordance with the *Sequence Rule* of Cahn, Ingold and Prelog. (Cahn *et al.*, *Angew. Chem. Inter. Edit.* 1966, 5, 385; errata 511; Cahn *et al.*, *Angew. Chem.* 1966, 78, 413; Cahn and Ingold, *J. Chem. Soc.* 1951 (London), 612; Cahn *et al.*, *Experientia* 1956, 12, 81; Cahn, *J. Chem. Educ.* 1964, 41, 116).

[0236] “Geometric isomer” means the diastereomers that owe their existence to hindered rotation about double bonds or a cycloalkyl linker (e.g., 1,3-cyclobutyl). These configurations are differentiated in their names by the prefixes cis and trans, or Z and E, which indicate that the groups are on the same or opposite side of the double bond in the molecule according to the Cahn-Ingold-Prelog rules.

[0237] It is to be understood that the compounds of the disclosure may be depicted as different chiral isomers or geometric isomers. It should also be understood that when compounds have chiral isomeric or geometric isomeric forms, all isomeric forms are intended to be included in the scope of the disclosure, and the naming of the compounds does not exclude any isomeric forms.

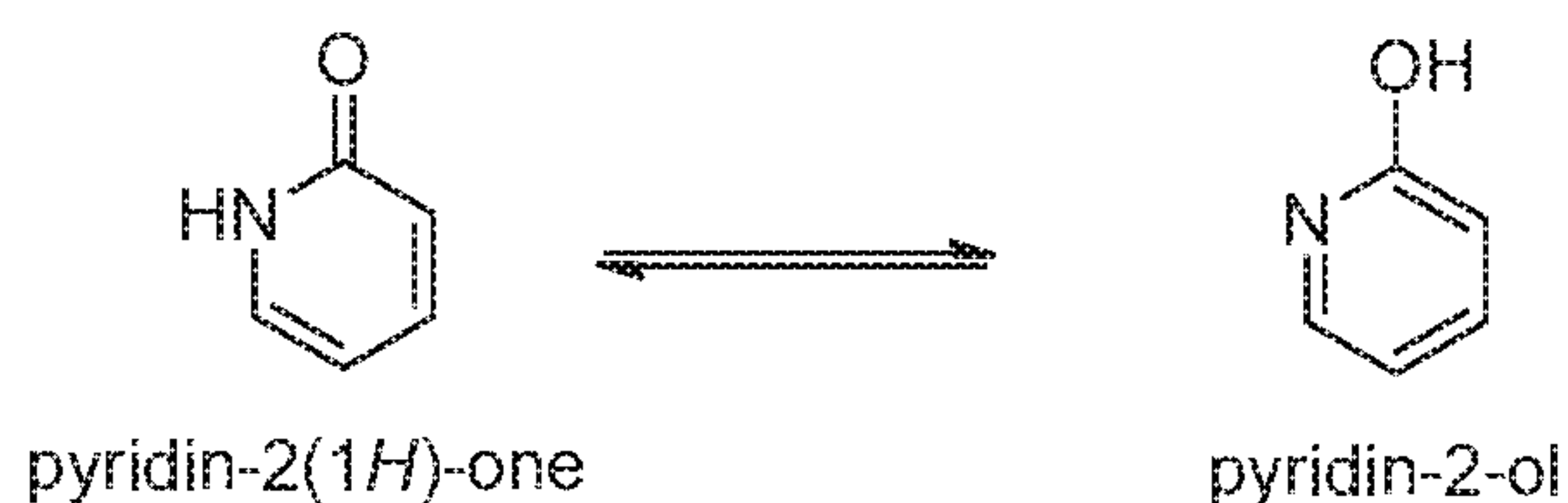
[0238] Furthermore, the structures and other compounds discussed in this invention include all atropic isomers thereof. “Atropic isomers” are a type of stereoisomer in which the atoms of two isomers are arranged differently in space. Atropic isomers owe their existence to a restricted rotation caused by hindrance of rotation of large groups about a central bond. Such atropic isomers typically exist as a mixture, however as a result of recent advances in chromatography techniques, it has been possible to separate mixtures of two atropic isomers in select cases.

[0239] “Tautomer” is one of two or more structural isomers that exist in equilibrium and is readily converted from one isomeric form to another. This conversion results in the formal migration of a hydrogen atom accompanied by a switch of adjacent conjugated double bonds. Tautomers exist as

a mixture of a tautomeric set in solution. In solutions where tautomerization is possible, a chemical equilibrium of the tautomers will be reached. The exact ratio of the tautomers depends on several factors, including temperature, solvent and pH. The concept of tautomers that are interconvertible by tautomerization is called tautomerism.

[0240] Of the various types of tautomerism that are possible, two are commonly observed. In keto-enol tautomerism a simultaneous shift of electrons and a hydrogen atom occurs. Ring-chain tautomerism arises as a result of the aldehyde group (-CHO) in a sugar chain molecule reacting with one of the hydroxy groups (-OH) in the same molecule to give it a cyclic (ring-shaped) form as exhibited by glucose.

[0241] Common tautomeric pairs are: ketone-enol, amide-nitrile, lactam-lactim, amide-imidic acid tautomerism in heterocyclic rings (*e.g.*, in nucleobases such as guanine, thymine and cytosine), imine-enamine and enamine-enamine. An example of keto-enol equilibria is between pyridin-2(1H)-ones and the corresponding pyridin-2-ols, as shown below.



[0242] It is to be understood that the compounds of the disclosure may be depicted as different tautomers. It should also be understood that when compounds have tautomeric forms, all tautomeric forms are intended to be included in the scope of the disclosure, and the naming of the compounds does not exclude any tautomer form.

[0243] The compounds of Formulae (I)-(VIa) disclosed herein include the compounds themselves, as well as their salts and their solvates, if applicable. A salt, for example, can be formed between an anion and a positively charged group (*e.g.*, amino) on an aryl- or heteroaryl-substituted benzene compound. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate (*e.g.*, trifluoroacetate). The term “pharmaceutically acceptable anion” refers to an anion suitable for forming a pharmaceutically acceptable salt. Likewise, a salt can also be formed between a cation and a negatively charged group (*e.g.*, carboxylate) on an aryl- or heteroaryl-

substituted benzene compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The aryl- or heteroaryl-substituted benzene compounds also include those salts containing quaternary nitrogen atoms. In the salt form, it is understood that the ratio of the compound to the cation or anion of the salt can be 1:1, or any ration other than 1:1, e.g., 3:1, 2:1, 1:2, or 1:3.

[0244] Additionally, the compounds of the disclosure, for example, the salts of the compounds, can exist in either hydrated or unhydrated (the anhydrous) form or as solvates with other solvent molecules. Nonlimiting examples of hydrates include monohydrates, dihydrates, etc. Nonlimiting examples of solvates include ethanol solvates, acetone solvates, etc.

[0245] “Solvate” means solvent addition forms that contain either stoichiometric or non stoichiometric amounts of solvent. Some compounds have a tendency to trap a fixed molar ratio of solvent molecules in the crystalline solid state, thus forming a solvate. If the solvent is water the solvate formed is a hydrate; and if the solvent is alcohol, the solvate formed is an alcoholate. Hydrates are formed by the combination of one or more molecules of water with one molecule of the substance in which the water retains its molecular state as H₂O.

[0246] As used herein, the term “analog” refers to a chemical compound that is structurally similar to another but differs slightly in composition (as in the replacement of one atom by an atom of a different element or in the presence of a particular functional group, or the replacement of one functional group by another functional group). Thus, an analog is a compound that is similar or comparable in function and appearance, but not in structure or origin to the reference compound.

[0247] As defined herein, the term “derivative” refers to compounds that have a common core structure, and are substituted with various groups as described herein. For example, all of the compounds represented by Formula (I) are aryl- or heteroaryl-substituted benzene compounds, and have Formula (I) as a common core.

[0248] The term “bioisostere” refers to a compound resulting from the exchange of an atom or of a group of atoms with another, broadly similar, atom or group of atoms. The objective of a bioisosteric replacement is to create a new compound with similar biological properties to the parent compound. The bioisosteric replacement may be physicochemically or topologically based. Examples of carboxylic acid bioisosteres include, but are not limited to, acyl sulfonimides,

tetrazoles, sulfonates and phosphonates. See, *e.g.*, Patani and LaVoie, *Chem. Rev.* 96, 3147-3176, 1996.

[0249] The disclosure is intended to include all isotopes of atoms occurring in the present compounds. Isotopes include those atoms having the same atomic number but different mass numbers. By way of general example and without limitation, isotopes of hydrogen include tritium and deuterium, and isotopes of carbon include C-13 and C-14.

[0250] Any compound of Formulae (I)-(VIa) of the disclosure, as described herein, may be an EZH2 inhibitor.

[0251] In certain aspects of the invention an inhibitor of EZH2 “selectively inhibits” histone methyltransferase activity of the mutant EZH2 when it inhibits histone methyltransferase activity of the mutant EZH2 more effectively than it inhibits histone methyltransferase activity of wild-type EZH2. For example, in some embodiments the selective inhibitor has an IC50 for the mutant EZH2 that is at least 40 percent lower than the IC50 for wild-type EZH2. In some embodiments the selective inhibitor has an IC50 for the mutant EZH2 that is at least 50 percent lower than the IC50 for wild-type EZH2. In some embodiments the selective inhibitor has an IC50 for the mutant EZH2 that is at least 60 percent lower than the IC50 for wild-type EZH2. In some embodiments the selective inhibitor has an IC50 for the mutant EZH2 that is at least 70 percent lower than the IC50 for wild-type EZH2. In some embodiments the selective inhibitor has an IC50 for the mutant EZH2 that is at least 80 percent lower than the IC50 for wild-type EZH2. In some embodiments the selective inhibitor has an IC50 for the mutant EZH2 that is at least 90 percent lower than the IC50 for wild-type EZH2.

[0252] In some embodiments, the selective inhibitor of a mutant EZH2 exerts essentially no inhibitory effect on wild-type EZH2.

[0253] In certain aspects of the invention the inhibitor (*e.g.* compound disclosed herein) inhibits conversion of H3-K27me2 to H3-K27me3. In some embodiments the inhibitor is said to inhibit trimethylation of H3-K27. Since conversion of H3-K27me1 to H3-K27me2 precedes conversion of H3-K27me2 to H3-K27me3, an inhibitor of conversion of H3-K27me1 to H3-K27me2 naturally also inhibits conversion of H3-K27me2 to H3-K27me3, *i.e.*, it inhibits trimethylation of H3-K27. It is also possible to inhibit conversion of H3-K27me2 to H3-K27me3 without inhibition of conversion of H3-K27me1 to H3-K27me2. Inhibition of this type would also result in inhibition of trimethylation of H3-K27, albeit without inhibition of dimethylation of H3-K27.

[0254] In some embodiments the inhibitor (e.g. compound disclosed herein) inhibits conversion of H3-K27me1 to H3-K27me2 and the conversion of H3-K27me2 to H3-K27me3. Such inhibitor may directly inhibit the conversion of H3-K27me1 to H3-K27me2 alone. Alternatively, such inhibitor may directly inhibit both the conversion of H3-K27me1 to H3-K27me2 and the conversion of H3-K27me2 to H3-K27me3.

[0255] In certain aspects of the invention, the EZH2 inhibitor (e.g. compound disclosed herein) inhibits histone methyltransferase activity. Inhibition of histone methyltransferase activity can be detected using any suitable method. The inhibition can be measured, for example, either in terms of rate of histone methyltransferase activity or as product of histone methyltransferase activity.

[0256] The inhibition is a measurable inhibition compared to a suitable control. In some embodiments, inhibition is at least 10 percent inhibition compared to a suitable control. That is, the rate of enzymatic activity or the amount of product with the inhibitor is less than or equal to 90 percent of the corresponding rate or amount made without the inhibitor. In various other embodiments, inhibition is at least 20, 25, 30, 40, 50, 60, 70, 75, 80, 90, or 95 percent inhibition compared to a suitable control. In some embodiments, inhibition is at least 99 percent inhibition compared to a suitable control. That is, the rate of enzymatic activity or the amount of product with the inhibitor is less than or equal to 1 percent of the corresponding rate or amount made without the inhibitor.

[0257] A composition of the disclosure may comprise a compound of Formulae (I)-(VIa), or a pharmaceutically acceptable salt thereof, and one or more other therapeutic agents, or a pharmaceutically acceptable salt thereof. The disclosure provides for the administration of a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, and one or more therapeutic agents or a pharmaceutically acceptable salt thereof, as a co-formulation or separate formulations, wherein the administration of formulations is simultaneous, sequential, or in alternation. In certain embodiments, the other therapeutic agents can be an agent that is recognized in the art as being useful to treat the disease or condition being treated by the composition of the disclosure. In some embodiments, the other therapeutic agent can be an agent that is not recognized in the art as being useful to treat the disease or condition being treated by the composition of the disclosure. In some aspects, the other therapeutic agents can be an agent that imparts a beneficial attribute to the composition of the disclosure (e.g., an agent that affects the viscosity of the composition). The beneficial attribute to the composition of the disclosure

includes, but is not limited to, pharmacokinetic or pharmacodynamic co-action resulting from the combination of a compound of Formulae (I)-(VIa) and one or more other therapeutic agents.

[0258] The therapeutic agents set forth below are for illustrative purposes and not intended to be limiting. The disclosure includes at least one other therapeutic agent selected from the lists below. The disclosure can include more than one other therapeutic agent, e.g., two, three, four, or five other therapeutic agents such that the composition of the disclosure can perform its intended function.

[0259] In some embodiments, the other therapeutic agent is an anticancer agent. In some embodiments, the anticancer agent is a compound that affects histone modifications, such as an HDAC inhibitor (such as Zolinza® or Farydak®). In certain embodiments, an anticancer agent is selected from the group consisting of chemotherapeutics (such as 2CdA, 5-FU, 6-Mercaptopurine, 6-TG, Abraxane™, Accutane®, Actinomycin-D, Adriamycin®, Alimta®, Alkeran®, all-trans retinoic acid, amethopterin, Ara-C, Azacitadine, BCNU, Blenoxane®, Camptosar®, CeeNU®, Clofarabine, Clolar™, Cytosan®, daunorubicin hydrochloride, DaunoXome®, Dacogen®, DIC, Doxil®, Ellence®, Eloxatin®, Emcyt®, etoposide phosphate, Etopophos®, Fludara®, FUDR®, Gemzar®, Gleevec®, hexamethylmelamine, Hycamtin®, Hydrea®, Idamycin®, Ifex®, Imbruvica®, ixabepilone, Ixempra®, L-asparaginase, Leukeran®, liposomal Ara-C, L-PAM, Lysodren, mafosfamide, Marqibo®, Matulane®, mithracin, Mitomycin-C, Myleran®, Navelbine®, Neutrexin®, nilotinib, Nipent®, Nitrogen Mustard, Novantrone®, Oncaspar®, Panretin®, Paraplatin®, Platinol®, prolifeoprospan 20 with carmustine implant, Sandostatin®, Targretin®, Tasigna®, Taxotere®, Temodar®, TESPAs, Toposar®, Treanda®, Trisenox®, Valstar®, Velban®, Vidaza™, vincristine sulfate, VM 26, Xeloda® and Zanosar®); biologics (such as Alpha Interferon, Bacillus Calmette-Guerin, Bexxar®, Campath®, Ergamisol®, Erlotinib, Herceptin®, Interleukin-2, Iressa®, lenalidomide, Mylotarg®, Ontak®, Pegasys®, Revlimid®, Rituxan®, Tarceva™, Thalomid®, Tykerb®, Velcade® and Zevalin™); corticosteroids, (such as dexamethasone sodium phosphate, DeltaSone® and Delta-Cortef®); glucocorticoid receptor agonists (such as Baycadron®, Maxidex®, Ozurdex®, Econopred®, Omnipred®, or Millipred®); hormonal therapies (such as Arimidex®, Aromasin®, Casodex®, Cytadren®, Eligard®, Eulexin®, Evista®, Faslodex®, Femara®, Halotestin®, Megace®, Nilandron®, Nolvadex®, Plenaxis™ and Zoladex®); and radiopharmaceuticals (such as Iodotope®, Metastron®, Phosphocol® and Samarium SM-153); immunomodulatory drugs (such

as Pomalyst®, Revlimid® and Thalidomid®); proteasome inhibitors (such as Kyprolis®, Ninlaro® and Velcade®); bcl-2 inhibitors (such as Venclexta®).

[0260] Exemplary glucocorticoid receptor agonists include but are not limited to, dexamethasone (Baycadron®, Maxidex®, Ozurdex®), methylprednisolone (Depo-Medrol®, Solu-Medrol®), or prednisolone (Econopred®, Omnipred®, Millipred®).

[0261] Exemplary immunomodulatory drugs include, but are not limited to, lenalidomide (Revlimid®), pomalidomide (Pomalyst®) and thalidomide (Thalidomid®);

[0262] Exemplary proteasome inhibitors, include but are not limited to, bortezomib (Velcade®), carfilzomib (Kyprolis®) and ixazomib (Ninlaro®),

[0263] Exemplary Bcl-2 inhibitors include, but are not limited to, venetoclax (Venclexta®).

[0264] In some embodiments, the other therapeutic agent is a chemotherapeutic agent (also referred to as an anti-neoplastic agent or anti-proliferative agent), selected from the group including an alkylating agent; an antibiotic; an anti-metabolite; a detoxifying agent; an interferon; a polyclonal or monoclonal antibody; an EGFR inhibitor; a HER2 inhibitor; a histone deacetylase inhibitor; a hormone; a mitotic inhibitor; an MTOR inhibitor; a multi-kinase inhibitor; a serine/threonine kinase inhibitor; a tyrosine kinase inhibitors; a VEGF/VEGFR inhibitor; a taxane or taxane derivative, an aromatase inhibitor, an anthracycline, a microtubule targeting drug, a topoisomerase poison drug, an inhibitor of a molecular target or enzyme (e.g., a kinase or a protein methyltransferase), a cytidine analogue drug or any chemotherapeutic, anti-neoplastic or anti-proliferative agent listed in www.cancer.org/docroot/cdg/cdg_0.asp.

[0265] Exemplary alkylating agents or alkylating-like agents include, but are not limited to, cyclophosphamide (Cytoxan®, Neosar®); chlorambucil (Leukeran®); melphalan (Alkeran®); carmustine (BiCNU®); busulfan (Busulfex®); lomustine (CeeNU®); dacarbazine (DTIC-Dome®); oxaliplatin (Eloxatin®); carmustine (Gliadel®); ifosfamide (Ifex®); mechlorethamine (Mustargen); busulfan (Myleran®); carboplatin (Paraplatin®); cisplatin (CDDP®, Platinol®); temozolomide (Temodar®); thiotepa (Thioplex®); bendamustine (Treanda®); or streptozocin (Zanosar®).

[0266] Exemplary antibiotics include, but are not limited to, doxorubicin (Adriamycin®); doxorubicin liposomal (Doxil®); mitoxantrone (Novantrone®); bleomycin (Blenoxane®); daunorubicin (Cerubidine®); daunorubicin liposomal (DaunoXome®); dactinomycin

(Cosmegen®); epirubicin (Ellence®); idarubicin (Idamycin®); plicamycin (Mithracin®); mitomycin (Mutamycin®); pentostatin (Nipent®); or valrubicin (Valstar®).

[0267] Exemplary anti-metabolites include, but are not limited to, fluorouracil (Adrucil®); capecitabine (Xeloda®); hydroxyurea (Hydrea®); mercaptopurine (Purinethol®); pemetrexed (Alimta); fludarabine (Fludara®); nelarabine (Arranon®); cladribine (Cladribine Novaplus®); clofarabine (Clolar®); cytarabine (Cytosar-U®); decitabine (Dacogen®); cytarabine liposomal (DepoCyt®); hydroxyurea (Droxia®); pralatrexate (Folotyn®); floxuridine (FUDR®); gemcitabine (Gemzar®); cladribine (Leustatin®); fludarabine (Oforta®); methotrexate (MTX®; Rheumatrex®); methotrexate (Trexall®); thioguanine (Tabloid®); TS-1 or cytarabine (Tarabine PFS®).

[0268] Exemplary antimetabolites, including antimetabolites of the folate type, include, but are not limited to, gemcitabine methotrexate, and pemetrexed.

[0269] Exemplary detoxifying agents include, but are not limited to, amifostine (Ethyol®) or mesna (Mesnex®).

[0270] Exemplary interferons include, but are not limited to, interferon alfa-2b (Intron A®) or interferon alfa-2a (Roferon-A®).

[0271] Exemplary polyclonal or monoclonal antibodies include, but are not limited to, trastuzumab (Herceptin®); ofatumumab (Arzerra®); bevacizumab (Avastin®); rituximab (Rituxan®); cetuximab (Erbix®); panitumumab (Vectibix®); tositumomab/iodine131 tositumomab (Bexxar®); alemtuzumab (Campath®); ibritumomab (Zevalin®; In-111®; Y-90 Zevalin®); gemtuzumab (Mylotarg®); eculizumab (Soliris®) ordenosumab.

[0272] Exemplary EGFR inhibitors include, but are not limited to, gefitinib (Iressa); lapatinib (Tykerb®); cetuximab (Erbix®); erlotinib (Tarceva®); panitumumab (Vectibix®); PKI-166; canertinib (CI-1033); matuzumab (Emd7200) or EKB-569.

[0273] Exemplary HER2 inhibitors include, but are not limited to, trastuzumab (Herceptin®); lapatinib (Tykerb®) or AC-480.

[0274] Histone Deacetylase Inhibitors include, but are not limited to, vorinostat (Zolinza®) and panobinostat (Farydak®).

[0275] Exemplary hormones include, but are not limited to, tamoxifen (Soltamox; Nolvadex®); raloxifene (Evista®); megestrol (Megace®); leuprolide (Lupron®; Lupron Depot®; Eligard®; Viadur®); fulvestrant (Faslodex®); letrozole (Femara®); triptorelin (Trelstar LA®; Trelstar

Depot®); exemestane (Aromasin®); goserelin (Zoladex®); bicalutamide (Casodex®); anastrozole (Arimidex®); fluoxymesterone (Androxy®; Halotestin®); medroxyprogesterone (Provera®; Depo-Provera®); estramustine (Emcyt®); flutamide (Eulexin®); toremifene (Fareston®); degarelix (Firmagon®); nilutamide (Nilandron®); abarelix (Plenaxis®); or testolactone (Teslac®).

[0276] Exemplary mitotic inhibitors include, but are not limited to, paclitaxel (Taxol®; Onxol®, Abraxane®); docetaxel (Taxotere®); vincristine (Oncovin®; Vincasar PFS®); vinblastine (Velban®); etoposide (Toposar®, Etopophos®, VePesid®); teniposide (Vumon®); ixabepilone (Ixempra®); nocodazole; epothilone; vinorelbine (Navelbine®); camptothecin (CPT); irinotecan (Camptosar®); topotecan (Hycamtin®); amsacrine or lamellarin D (LAM-D).

[0277] Exemplary MTOR inhibitors include, but are not limited to, everolimus (Afinitor®) or temsirolimus (Torisel®); rapamune, ridaforolimus; or AP23573.

[0278] Exemplary VEGF/VEGFR inhibitors include, but are not limited to, bevacizumab (Avastin®); sorafenib (Nexavar®); sunitinib (Sutent®); ranibizumab; pegaptanib; or vandetanib.

[0279] Exemplary microtubule targeting drugs include, but are not limited to, paclitaxel, docetaxel, vincristine, vinblastin, nocodazole, epothilones and navelbine.

[0280] Exemplary topoisomerase poison drugs/topoisomerase inhibitors include, but are not limited to, irinotecan, teniposide, etoposide, adriamycin, camptothecin, daunorubicin, dactinomycin, mitoxantrone, amsacrine, epirubicin and idarubicin.

[0281] Exemplary taxanes or taxane derivatives include, but are not limited to, paclitaxel and docetaxol.

[0282] Exemplary general chemotherapeutic, anti-neoplastic, anti-proliferative agents include, but are not limited to, altretamine (Hexalen); isotretinoin (Accutane; Amnesteem; Claravis; Sotret); tretinoin (Vesanoid®); azacitidine (Vidaza®); bortezomib (Velcade®) asparaginase (Elspar®); ibrutinib (Imbruvica®); levamisole (Ergamisol®); mitotane (Lysodren®); procarbazine (Matulane); pegaspargase (Oncaspar®); denileukin diftitox (Ontak®); porfimer (Photofrin®); aldesleukin (Proleukin®); lenalidomide (Revlimid®); bexarotene (Targretin®); thalidomide (Thalomid®); temsirolimus (Torisel®); arsenic trioxide (Trisenox®); verteporfin (Visudyne®); mimosine (Leucenol®); (1M tegafur - 0.4 M 5-chloro-2,4-dihydroxypyrimidine - 1 M potassium oxonate), or lovastatin.

[0283] In some aspects, the other therapeutic agent is a chemotherapeutic agent or a cytokine such as G-CSF (granulocyte colony stimulating factor).

[0284] In further aspects, the other therapeutic agents can be standard chemotherapy combinations such as, but not restricted to, CMF (cyclophosphamide, methotrexate and 5-fluorouracil), CAF (cyclophosphamide, adriamycin and 5-fluorouracil), AC (adriamycin and cyclophosphamide), FEC (5-fluorouracil, epirubicin, and cyclophosphamide), ACT or ATC (adriamycin, cyclophosphamide, and paclitaxel), rituximab, Xeloda (capecitabine), Cisplatin (CDDP), Carboplatin, TS-1 (tegafur, gimestat and otastat potassium at a molar ratio of 1:0.4:1), Camptothecin-11 (CPT-11, Irinotecan or Camptosar™), CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone or prednisolone), R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone or prednisolone), CVP (cyclophosphamide, vincristine, and prednisone), hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and prednisone), or CMFP (cyclophosphamide, methotrexate, 5-fluorouracil and prednisone).

[0285] In other aspects, the other therapeutic agents can be an inhibitor of an enzyme, such as a receptor or non-receptor kinase. Receptor and non-receptor kinases are, for example, tyrosine kinases or serine/threonine kinases. Kinase inhibitors described herein are small molecules, polynucleic acids, polypeptides, or antibodies.

[0286] Exemplary kinase inhibitors include, but are not limited to, afatinib (targets EFGR/Her2), Bevacizumab (targets VEGF), BIBW 2992 (targets EGFR and ErbB2), brigatinib (targets ALK and EFGR), ceritinib (targets ALK), crizotinib (targets ALK and ROS1), Cetuximab/Erbitux (targets ErbB1), Imatinib/Gleevec (targets Bcr-Abl), Trastuzumab (targets ErbB2), Gefitinib/Iressa (targets EGFR), Ranibizumab (targets VEGF), Pegaptanib (targets VEGF), Erlotinib/Tarceva (targets ErbB1), Nilotinib (targets Bcr-Abl), Lapatinib (targets ErbB1 and ErbB2/Her2), GW-572016/lapatinib ditosylate (targets HER2/ErbB2), Panitumumab/Vectibix (targets EGFR), Vandetinib (targets RET/VEGFR), E7080 (multiple targets including RET and VEGFR), Herceptin (targets HER2/ErbB2), PKI-166 (targets EGFR), Canertinib/CI-1033 (targets EGFR), Sunitinib/SU-11464/Sutent (targets EGFR and FLT3), Matuzumab/Emd7200 (targets EGFR), EKB-569 (targets EGFR), Zd6474 (targets EGFR and VEGFR), PKC-412 (targets VEGFR and FLT3), Vatalanib/Ptk787/ZK222584 (targets VEGFR), CEP-701 (targets FLT3), SU5614 (targets FLT3), MLN518 (targets FLT3), XL999 (targets FLT3), VX-322 (targets FLT3), Azd0530

(targets SRC), BMS-354825 (targets SRC), SKI-606 (targets SRC), CP-690 (targets JAK), AG-490 (targets JAK), WHI-P154 (targets JAK), WHI-P131 (targets JAK), sorafenib/Nexavar (targets RAF kinase, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR- β , KIT, FLT-3, and RET), Dasatinib/Sprycel (BCR/ABL and Src), AC-220 (targets Flt3), AC-480 (targets all HER proteins, “panHER”), Motesanib diphosphate (targets VEGF1-3, PDGFR, and c-kit), Denosumab (targets RANKL, inhibits SRC), AMG888 (targets HER3), and AP24534 (multiple targets including Flt3).

[0287] Exemplary serine/threonine kinase inhibitors include, but are not limited to, Rapamune (targets mTOR/FRAP1), Deforolimus (targets mTOR), Certican/Everolimus (targets mTOR/FRAP1), AP23573 (targets mTOR/FRAP1), Eril/Fasudil hydrochloride (targets RHO), abemaciclib (targets CDK), palbociclib (targets CDK), ribociclib (targets CDK), Flavopiridol (targets CDK), Seliciclib/CYC202/Roscovitine (targets CDK), SNS-032/BMS-387032 (targets CDK), Ruboxistaurin (targets PKC), Pkc412 (targets PKC), Bryostatin (targets PKC), KAI-9803 (targets PKC), SF1126 (targets PI3K), pictilisib (targets PI3K), BKM-120 (targets PI3K), VX-680 (targets Aurora kinase), Azd1152 (targets Aurora kinase), Arry-142886/AZD-6244 (targets MAP/MEK), AZD9291 (targets EGFR), SCIO-469 (targets MAP/MEK), GW681323 (targets MAP/MEK), CC-401 (targets JNK), CEP-1347 (targets JNK), MK-1775 (targets Wee), veliparib (targets PARP), decitabine (targets DNMT), azacitidine (targets DNMT), and PD 332991 (targets CDK).

[0288] Exemplary tyrosine kinase inhibitors include, but are not limited to, erlotinib (Tarceva); gefitinib (Iressa); imatinib (Gleevec); sorafenib (Nexavar); sunitinib (Sutent); trastuzumab (Herceptin); bevacizumab (Avastin); rituximab (Rituxan); lapatinib (Tykerb); cetuximab (Erbix); panitumumab (Vectibix); everolimus (Afinitor); alemtuzumab (Campath); gemtuzumab (Mylotarg); temsirolimus (Torisel); pazopanib (Votrient); dasatinib (Sprycel); nilotinib (Tasigna); vatalanib (Ptk787; ZK222584); CEP-701; SU5614; MLN518; XL999; VX-322; Azd0530; BMS-354825; SKI-606 CP-690; AG-490; WHI-P154; WHI-P131; AC-220; or AMG888. More examples of the other therapeutic agents suitable to be used in combination with compounds of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof are disclosed in co-pending U.S. Application No. 61/992,881 filed May 13, 2014 and International Application No. PCT/US2014/069167 filed December 8, 2014, the contents of each of which are incorporated herein by reference in their entireties.

[0289] Exemplary tubulin polymerization inhibitors include, but are not limited to, vinorelbine.

[0290] Exemplary mitogen-activated protein kinase (MEK) inhibitors include, but are not limited to, trametinib, and selumetinib.

[0291] Exemplary BRAF inhibitors include, but are not limited to, Vemurafenib.

[0292] Exemplary second agents that may be a retinoic acid receptor agonist include, but are not limited to ATRA.

[0293] Exemplary second agents that may be a CBP/p300 inhibitor receptor agonist include, but are not limited to Compound H, or a pharmaceutically acceptable salt thereof.

[0294] In some embodiments, the other therapeutic agent is a pleiotropic pathway modifier. Exemplary pleiotropic pathway modifiers include, but are not limited to, CC-122.

[0295] The disclosure provides methods for combination therapy in which a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, and one or more other therapeutic agents are administered to a subject in need for treatment of a disease or cancer. The disclosure also provides compositions for use as a medicament for combination therapy in which the composition comprises a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, and is administered to a subject in need for treatment of a disease or cancer in combination with one or more other therapeutic agents. The disclosure further provides the use of a composition in the manufacture of a medicament for combination therapy in which the composition comprises a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, and is administered to a subject in need for treatment of a disease or cancer in combination with one or more other therapeutic agents. The combination therapy can also be administered to cancer cells to inhibit proliferation or induce cell death. In some aspects, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof is administered subsequent to administration of the composition of the disclosure comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, and one or more other therapeutic agents. In some aspects, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof is administered prior to administration of the composition of the disclosure comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, and one or more other therapeutic agents. In some aspects, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof is administered subsequent to administration of one or more therapeutic agents, such that the other therapeutic agents are administered either in a single composition or in two or more compositions, e.g., administered simultaneously, sequentially, or in

alternation. In some aspects, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof is administered prior to administration of one or more therapeutic agents, such that the other therapeutic agents are administered either in a single composition or in two or more compositions, e.g., administered simultaneously, sequentially, or in alternation.

[0296] In some aspects, tazemetostat or a pharmaceutically acceptable salt thereof is administered subsequent to administration of the composition of the disclosure comprising tazemetostat or a pharmaceutically acceptable salt thereof, and one or more other therapeutic agents. In some aspects, tazemetostat or a pharmaceutically acceptable salt thereof is administered prior to administration of the composition of the disclosure comprising tazemetostat or a pharmaceutically acceptable salt thereof, and one or more other therapeutic agents. In some aspects, tazemetostat or a pharmaceutically acceptable salt thereof is administered subsequent to administration of one or more therapeutic agents, such that the other therapeutic agents are administered either in a single composition or in two or more compositions, e.g. administered simultaneously, sequentially, or in alternation. In some aspects, tazemetostat or a pharmaceutically acceptable salt thereof is administered prior to administration of one or more therapeutic agents, such that the other therapeutic agents are administered either in a single composition or in two or more compositions, e.g. administered simultaneously, sequentially, or in alternation.

[0297] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with an alkylating-like agent, an antineoplastic agent, a mitotic inhibitor, a tubulin polymerization inhibitor, an antimetabolite, a DNA methyltransferase (DNMT) inhibitor, a histone deacetylase (HDAC) inhibitor, a topoisomerase inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, an inhibitor of EGFR and ErbB2, an inhibitor of EGFR and human epidermal growth factor receptor 2 (Her2), an anaplastic lymphoma kinase (ALK) inhibitor, an inhibitor of ALK and ROS1, an inhibitor of ALK and EGFR, cyclin dependent kinase (CDK) 4/6 inhibitor, a mitogen-activated protein kinase (MEK) inhibitor, a BRAF inhibitor, a phosphoinositide 3-kinase (PI3K) inhibitor, a Wee1 inhibitor, a poly (ADP-ribose) polymerase (PARP) inhibitor, a glucocorticoid receptor agonist, a retinoic acid receptor agonist, a CBP/p300 inhibitor, or a combination thereof.

[0298] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is

administered in combination with an alkylating-like agent, an antineoplastic agent, a mitotic inhibitor, a tubulin polymerization inhibitor, an antimetabolite, a DNA methyltransferase (DNMT) inhibitor, a histone deacetylase (HDAC) inhibitor, a topoisomerase inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, an inhibitor of EGFR and ErbB2, an inhibitor of EGFR and human epidermal growth factor receptor 2 (Her2), an anaplastic lymphoma kinase (ALK) inhibitor, an inhibitor of ALK and ROS1, an inhibitor of ALK and EGFR, cyclin dependent kinase (CDK) 4/6 inhibitor, a mitogen-activated protein kinase (MEK) inhibitor, a BRAF inhibitor, a phosphoinositide 3-kinase (PI3K) inhibitor, a Wee1 inhibitor, a poly (ADP-ribose) polymerase (PARP) inhibitor, a glucocorticoid receptor agonist, a retinoic acid receptor agonist, a CBP/p300 inhibitor, or a combination thereof.

[0299] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with cisplatin, oxaliplatin, paclitaxel, docetaxel, vinorelbine, gemcitabine, decitabine, azacitidine, vorinostat, irinotecan, etoposide, vinblastine, erlotinib, gefitinib, lapatinib, afatinib, AZD9291, crizotinib, ceritinib, brigatinib, abemaciclib, palbociclib, ribociclib, methotrexate, perimetrexed, trametinib, selumetinib, vemurafenib, pictilisib, BKM-120, MK-1775, veliparib, prednisolone, ATRA, Compound H or a pharmaceutically acceptable salt thereof, or a combination thereof.

[0300] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with cisplatin, oxaliplatin, paclitaxel, docetaxel, vinorelbine, gemcitabine, decitabine, azacitidine, vorinostat, irinotecan, etoposide, vinblastine, erlotinib, gefitinib, lapatinib, afatinib, AZD9291, crizotinib, ceritinib, brigatinib, abemaciclib, palbociclib, ribociclib, methotrexate, perimetrexed, trametinib, selumetinib, vemurafenib, pictilisib, BKM-120, MK-1775, veliparib, prednisolone, ATRA, Compound H or a pharmaceutically acceptable salt thereof, or a combination thereof.

[0301] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with an alkylating agent or an alkylating-like agent. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt

thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with cisplatin.

[0302] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with an alkylating agent or an alkylating-like agent agonist. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with cisplatin.

[0303] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with an antineoplastic agent. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with oxaliplatin.

[0304] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with an antineoplastic agent. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with oxaliplatin.

[0305] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a mitotic inhibitor. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with paclitaxel, docetaxel, vinblastine, or a combination thereof.

[0306] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a mitotic inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with paclitaxel, docetaxel, vinblastine, or a combination thereof.

[0307] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a tubulin polymerization inhibitor.

For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with vinorelbine.

[0308] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a tubulin polymerization inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with vinorelbine.

[0309] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with an antimetabolite. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with gemcitabine.

[0310] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with an antimetabolite. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with gemcitabine.

[0311] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with an antimetabolite of the folate type. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with methotrexate, pemetrexed, or a combination thereof.

[0312] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with an antimetabolite of the folate type. For example, tazemetostat

or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with methotrexate, pemetrexed, or a combination thereof.

[0313] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a DNA methyltransferase (DNMT) inhibitor. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with decitabine, azacitidine, or a combination thereof.

[0314] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a DNA methyltransferase (DNMT) inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with decitabine, azacitidine, or a combination thereof.

[0315] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a histone deacetylase (HDAC) inhibitor. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with vorinostat.

[0316] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a histone deacetylase (HDAC) inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with vorinostat.

[0317] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a topoisomerase inhibitor. For

example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with irinotecan, etoposide, or a combination thereof.

[0318] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a topoisomerase inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with irinotecan, etoposide, or a combination thereof.

[0319] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with an epidermal growth factor receptor (EGFR) inhibitor. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with erlotinib, gefitinib, AZD9291, or a combination thereof.

[0320] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with an epidermal growth factor receptor (EGFR) inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with erlotinib, gefitinib, AZD9291, or a combination thereof.

[0321] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with an inhibitor of epidermal growth factor receptor (EGFR) and ErbB2. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with lapatinib.

[0322] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is

administered in combination with an inhibitor of epidermal growth factor receptor (EGFR) and ErbB2. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with lapatinib.

[0323] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with an inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (Her2). For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with afatinib.

[0324] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with an inhibitor of epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (Her2). For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with afatinib.

[0325] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with an anaplastic lymphoma kinase (ALK) inhibitor. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with ceritinib.

[0326] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with an anaplastic lymphoma kinase (ALK) inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with ceritinib.

[0327] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically

acceptable salt thereof, is administered in combination with an inhibitor of anaplastic lymphoma kinase (ALK) inhibitor and ROS1. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with crizotinib.

[0328] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with an inhibitor of anaplastic lymphoma kinase (ALK) inhibitor and ROS1. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with crizotinib.

[0329] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with an inhibitor of anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR). For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with brigatinib.

[0330] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with an inhibitor of anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR). For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with brigatinib.

[0331] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with an cyclin dependent kinase (CDK) 4/6 inhibitor. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with abemaciclib, palbociclib, ribociclib, or a combination thereof.

[0332] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with an cyclin dependent kinase (CDK) 4/6 inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with abemaciclib, palbociclib, ribociclib, or a combination thereof.

[0333] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a mitogen-activated protein kinase (MEK) inhibitor. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with trametinib, selumetinib, or a combination thereof.

[0334] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a mitogen-activated protein kinase (MEK) inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with trametinib, selumetinib, or a combination thereof.

[0335] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a BRAF inhibitor. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with vemurafenib.

[0336] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a BRAF inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with vemurafenib.

[0337] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a phosphoinositide 3-kinase (PI3K) inhibitor. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with pictilisib, BKM-120, or a combination thereof.

[0338] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a phosphoinositide 3-kinase (PI3K) inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with pictilisib, BKM-120, or a combination thereof.

[0339] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a Wee1 inhibitor. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with MK-1775.

[0340] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a Wee1 inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with MK-1775.

[0341] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a poly (ADP-ribose) polymerase (PARP) inhibitor. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with veliparib.

[0342] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a poly (ADP-ribose) polymerase (PARP) inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with veliparib.

[0343] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a poly (ADP-ribose) polymerase (PARP) inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with veliparib.

[0344] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a glucocorticoid receptor agonist. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with prednisolone.

[0345] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a glucocorticoid receptor agonist. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with prednisolone.

[0346] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a retinoic acid receptor agonist. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with ATRA.

[0347] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is

administered in combination with a retinoic acid receptor agonist. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with ATRA.

[0348] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a CBP/p300 inhibitor. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with Compound H.

[0349] In some embodiments, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a CBP/p300 inhibitor. For example, a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, or a composition comprising a compound of Formulae (I)-(VIa) or a pharmaceutically acceptable salt thereof, is administered in combination with a pharmaceutically acceptable salt of Compound H.

[0350] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a CBP/p300 inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with Compound H.

[0351] In some embodiments, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a CBP/p300 inhibitor. For example, tazemetostat or a pharmaceutically acceptable salt thereof, or a composition comprising tazemetostat or a pharmaceutically acceptable salt thereof, is administered in combination with a pharmaceutically acceptable salt of Compound H.

[0352] In certain embodiments, “combination therapy” is intended to embrace administration of these therapeutic agents in a sequential manner, wherein each therapeutic agent is administered at a different time, as well as administration of these therapeutic agents, or at least two of the therapeutic agents concurrently, or in a substantially simultaneous manner. Simultaneous administration can be accomplished, for example, by administering to the subject a single capsule

having a fixed ratio of each therapeutic agent or in multiple, single capsules for each of the therapeutic agents. Sequential or substantially simultaneous administration of each therapeutic agent can be effected by any appropriate route including, but not limited to, oral routes, intravenous routes, intramuscular routes, and direct absorption through mucous membrane tissues. The therapeutic agents can be administered by the same route or by different routes. For example, a first therapeutic agent of the combination selected may be administered by intravenous injection while the other therapeutic agents of the combination may be administered orally. Alternatively, for example, all therapeutic agents may be administered orally or all therapeutic agents may be administered by intravenous injection. Therapeutic agents may also be administered in alternation.

[0353] In certain aspects of the invention, the combination therapies featured in the disclosure can result in a synergistic effect in the treatment of a disease or cancer. A “synergistic effect” is defined as where the efficacy of a combination of therapeutic agents is greater than the sum of the effects of any of the agents given alone. A synergistic effect may also be an effect that cannot be achieved by administration of any of the compounds or other therapeutic agents as single agents. The synergistic effect may include, but is not limited to, an effect of treating cancer by reducing tumor size, inhibiting tumor growth, or increasing survival of the subject. The synergistic effect may also include reducing cancer cell viability, inducing cancer cell death, and inhibiting or delaying cancer cell growth.

[0354] In certain aspects of the invention “combination therapy” also embraces the administration of the therapeutic agents as described above in further combination with other biologically active ingredients and non-drug therapies (*e.g.*, surgery or radiation treatment). Where the combination therapy further comprises a non-drug treatment, the non-drug treatment may be conducted at any suitable time so long as a beneficial effect from the co-action of the combination of the therapeutic agents and non-drug treatment is achieved. For example, in appropriate cases, the beneficial effect is still achieved when the non-drug treatment is temporally removed from the administration of the therapeutic agents, perhaps by days or even weeks.

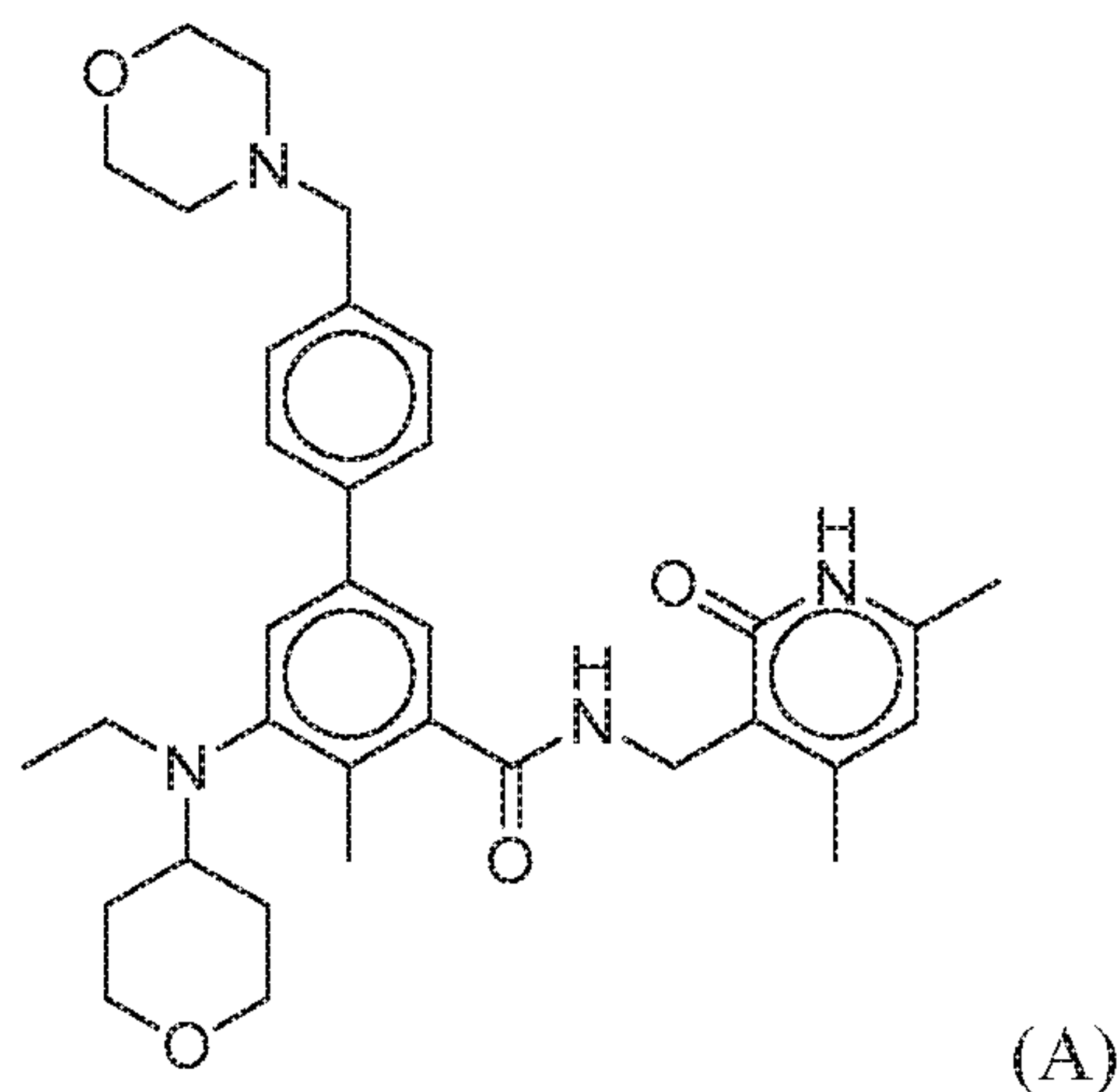
[0355] In other aspects, a composition of the disclosure, or a pharmaceutically acceptable salt, solvate, analog or derivative thereof, may be administered in combination with radiation therapy. Radiation therapy can also be administered in combination with a composition of the disclosure and another chemotherapeutic agent described herein as part of a multiple agent therapy.

[0356] In some embodiments, combination therapy is achieved by administering two or more agents, e.g., a compound of Formulae (I)-(VIa) and one or more other therapeutic agents as described herein, wherein the compound of Formulae (I)-(VIa) is formulated and administered separately from the one or more other therapeutic agents. In some embodiments, combination treatment is achieved by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While, in some embodiments, the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of one or more second agents (e.g., a combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

[0357] In some embodiments, the administration schedules of the two or more agents, e.g., a compound of Formulae (I)-(VIa) and one or more other therapeutic agents as described herein, differs. For example, in some embodiments, the first agent, e.g., an EZH2 inhibitor as provided herein, is administered daily, e.g., twice daily at a dose between 100 mg and 1600 mg, and one or more second agents, e.g., an anti-cancer agent provided herein is/are administered once per week, once every two weeks, once every three weeks, or once every four weeks. In some embodiments, one agent, e.g., the EZH2 inhibitor is administered continuously over a treatment period, e.g., daily (e.g., BID), for a period of one month, two months, three months, four months, etc., while one or more second agents, e.g., an anti-cancer agent provided herein, is/are administered during this time period in sequential treatment periods with intermittent non-treatment periods, e.g., two weeks of treatment followed by one week of non-treatment. Combination treatment can be achieved in such embodiments, by having at least one treatment period of one agent overlap with at least one treatment period of the other agent.

[0358] The disclosure also provides pharmaceutical compositions comprising a compound of Formulae (I)-(VIa) or pharmaceutically acceptable salts thereof, and one or more other therapeutic

agents disclosed herein, mixed with pharmaceutically suitable carriers or excipient(s) at doses to treat or prevent a disease or condition as described herein. In some aspects, the disclosure also provides pharmaceutical compositions comprising any compound of Table I or pharmaceutically acceptable salts thereof, and one or more therapeutic agents, mixed with pharmaceutically suitable carriers or excipient (s) at doses to treat or prevent a disease or condition as described herein. In other aspects, the disclosure also provides pharmaceutical compositions comprising tazemetostat



(A)

or pharmaceutically acceptable salts thereof, and one or more therapeutic agents, mixed with pharmaceutically suitable carriers or excipient(s) at doses to treat or prevent a disease or condition as described herein. The pharmaceutical compositions of the disclosure can also be administered in combination with other therapeutic agents or therapeutic modalities simultaneously, sequentially, or in alternation.

[0359] Mixtures of compositions of the disclosure can also be administered to the patient as a simple mixture or in suitable formulated pharmaceutical compositions. For example, some aspects of the invention relate to a pharmaceutical composition comprising a therapeutically effective dose of an EZH2 inhibitor of Formulae (I)-(VIa), or a pharmaceutically acceptable salt, hydrate, enantiomer or stereoisomer thereof; one or more other therapeutic agents, and a pharmaceutically acceptable diluent or carrier.

[0360] A “pharmaceutical composition” is a formulation containing the compounds of the disclosure in a form suitable for administration to a subject. A compound of Formulae (I)-(VIa) (e.g., tazemetostat) and one or more other therapeutic agents described herein each can be formulated individually or in multiple pharmaceutical compositions in any combinations of the active ingredients. Accordingly, one or more administration routes can be properly elected based on the dosage form of each pharmaceutical composition. Alternatively, a compound of Formulae

(D)-(VIa) (e.g., tazemetostat) and one or more other therapeutic agents described herein can be formulated as one pharmaceutical composition.

[0361] In some embodiments, a pharmaceutical composition useful for the methods, strategies, treatment modalities, compositions, or combinations provided herein, is in bulk or in unit dosage form. The unit dosage form may be any of a variety of forms, including, for example, a capsule, a sachet, an IV bag, a tablet, a single pump on an aerosol inhaler, or a vial or ampoule. The quantity of active ingredient (*e.g.*, a formulation of a disclosed compound or salt, hydrate, solvate or isomer thereof, or a combination of such compounds) in a unit dose of composition is an effective amount and is varied according to the particular treatment involved. One skilled in the art will appreciate that it is sometimes necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration. A variety of routes are contemplated, including oral, pulmonary, rectal, parenteral, transdermal, subcutaneous, intravenous, intramuscular, intraperitoneal, inhalational, buccal, sublingual, intrapleural, intrathecal, intranasal, and the like. Dosage forms for the topical or transdermal administration of a compound of this invention include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches and inhalants. In some embodiments, the active compound is mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants that are required.

[0362] As used herein, the phrase “pharmaceutically acceptable” refers to those compounds, anions, cations, materials, compositions, carriers, and/or dosage forms which are, within the scope 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.

[0363] “Pharmaceutically acceptable excipient” means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes excipient that is acceptable for veterinary use as well as human pharmaceutical use. A “pharmaceutically acceptable excipient” as used in the specification and claims includes both one and more than one such excipient.

[0364] A pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, *e.g.*, intravenous, intradermal, subcutaneous, oral (*e.g.*, inhalation), transdermal (topical), and

transmucosal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0365] A composition of the invention can be administered to a subject in many of the well-known methods currently used for chemotherapeutic treatment. For example, for treatment of cancers, a compound of the invention may be injected directly into tumors, injected into the blood stream or body cavities or taken orally or applied through the skin with patches. The dose chosen should be sufficient to constitute effective treatment but not so high as to cause unacceptable side effects. The state of the disease condition (*e.g.*, cancer, precancer, and the like) and the health of the patient should preferably be closely monitored during and for a reasonable period after treatment.

[0366] The term “therapeutically effective amount”, as used herein, refers to an amount of a pharmaceutical agent to treat, ameliorate, or prevent an identified disease or condition, or to exhibit a detectable therapeutic or inhibitory effect. The effect can be detected by any assay method known in the art. The precise effective amount for a subject will depend upon the subject’s body weight, size, and health; the nature and extent of the condition; and the therapeutic or combination of therapeutics selected for administration. Therapeutically effective amounts for a given situation can be determined by routine experimentation that is within the skill and judgment of the clinician. In some aspects, the disease or condition to be treated is cancer. In other aspects, the disease or condition to be treated is a cell proliferative disorder.

[0367] In certain embodiments the therapeutically effective amount of each pharmaceutical agent used in combination will be lower when used in combination in comparison to monotherapy with each agent alone. Such lower therapeutically effective amount could afford for lower toxicity of the therapeutic regimen.

[0368] For any compound, the therapeutically effective amount can be estimated initially either in cell culture assays, *e.g.*, of neoplastic cells, or in animal models, usually rats, mice, rabbits, dogs, or pigs. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans. Therapeutic/prophylactic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population). The dose ratio between toxic and therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD₅₀/ED₅₀. Pharmaceutical compositions that exhibit large therapeutic indices are preferred. The dosage may vary within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

[0369] Dosage and administration are adjusted to provide sufficient levels of the active agent(s) or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or once every two weeks depending on half-life and clearance rate of the particular formulation.

[0370] The pharmaceutical compositions containing active compounds of the disclosure may be manufactured in a manner that is generally known, *e.g.*, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. Pharmaceutical compositions may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers comprising excipients and/or auxiliaries that facilitate processing of the active compounds into preparations that can be used pharmaceutically. Of course, the appropriate formulation is dependent upon the route of administration chosen.

[0371] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the

extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol and sorbitol, and sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent which delays absorption, for example, aluminum monostearate and gelatin.

[0372] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

[0373] Oral compositions generally include an inert diluent or an edible pharmaceutically acceptable carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a

lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

[0374] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser, which contains a suitable propellant, *e.g.*, a gas such as carbon dioxide, or a nebulizer.

[0375] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0376] The active compounds can be prepared with pharmaceutically acceptable carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0377] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved.

[0378] In therapeutic applications, the dosages of the EZH2 inhibitors described herein, other therapeutic agents described herein, compositions comprising a compound of Formulae (I)-(VIa) and one or more other therapeutic agents, or the pharmaceutical compositions used in accordance with the invention vary depending on the agent, the age, weight, and clinical condition of the recipient patient, and the experience and judgment of the clinician or practitioner administering the therapy, among other factors affecting the selected dosage. Generally, the dose should be sufficient to result in slowing, and preferably regressing, the growth of the tumors and also preferably causing complete regression of the cancer. Dosages can range from about 0.01 mg/kg per day to about 5000 mg/kg per day. In some aspects, dosages can range from about 1 mg/kg per day to about 1000 mg/kg per day. In some aspects, the dose will be in the range of about 0.1 mg/day to about 50 g/day; about 0.1 mg/day to about 25 g/day; about 0.1 mg/day to about 10 g/day; about 0.1 mg to about 3 g/day; or about 0.1 mg to about 1 g/day, in single, divided, or continuous doses (which dose may be adjusted for the patient's weight in kg, body surface area in m², and age in years). An effective amount of a pharmaceutical agent is that which provides an objectively identifiable improvement as noted by the clinician or other qualified observer. For example, regression of a tumor in a patient may be measured with reference to the diameter of a tumor. Decrease in the diameter of a tumor indicates regression. Regression is also indicated by failure of tumors to reoccur after treatment has stopped. As used herein, the term "dosage effective manner" refers to amount of an active compound to produce the desired biological effect in a subject or cell.

[0379] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0380] The composition of the disclosure is capable of further forming salts. The composition of the disclosure is capable of forming more than one salt per molecule, e.g., mono-, di-, tri-. All of these forms are also contemplated within the scope of the claimed invention.

[0381] As used herein, "pharmaceutically acceptable salts" refer to derivatives of the compounds of the disclosure wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines, alkali or organic salts of acidic residues such as carboxylic acids, and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example,

from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include, but are not limited to, those derived from inorganic and organic acids selected from 2-acetoxybenzoic, 2-hydroxyethane sulfonic, acetic, ascorbic, benzene sulfonic, benzoic, bicarbonic, carbonic, citric, edetic, ethane disulfonic, 1,2-ethane sulfonic, fumaric, glucoheptonic, gluconic, glutamic, glycolic, glycollyarsanilic, hexylresorcinic, hydrabamic, hydrobromic, hydrochloric, hydroiodic, hydroxymaleic, hydroxynaphthoic, isethionic, lactic, lactobionic, lauryl sulfonic, maleic, malic, mandelic, methane sulfonic, napsylic, nitric, oxalic, pamoic, pantothenic, phenylacetic, phosphoric, polygalacturonic, propionic, salicylic, stearic, subacetic, succinic, sulfamic, sulfanilic, sulfuric, tannic, tartaric, toluene sulfonic, and the commonly occurring amine acids, *e.g.*, glycine, alanine, phenylalanine, arginine, etc.

[0382] Other examples of pharmaceutically acceptable salts include hexanoic acid, cyclopentane propionic acid, pyruvic acid, malonic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, 4-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo-[2.2.2]-oct-2-ene-1-carboxylic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, muconic acid, and the like. The disclosure also encompasses salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, *e.g.*, an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

[0383] It should be understood that all references to pharmaceutically acceptable salts include solvent addition forms (solvates), of the same salt.

[0384] The composition of the disclosure may also be prepared as esters, for example, pharmaceutically acceptable esters. For example, a carboxylic acid function group in a compound can be converted to its corresponding ester, *e.g.*, a methyl, ethyl or other ester. Also, an alcohol group in a compound can be converted to its corresponding ester, *e.g.*, acetate, propionate or other ester.

[0385] The composition, or pharmaceutically acceptable salts or solvates thereof, are administered orally, nasally, transdermally, pulmonary, inhalationally, buccally, sublingually, intraperitoneally, subcutaneously, intramuscularly, intravenously, rectally, intrapleurally, intrathecally and parenterally. In some embodiments, the compound is administered orally. One skilled in the art will recognize the advantages of certain routes of administration.

[0386] The dosage regimen utilizing the compounds is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

[0387] Techniques for formulation and administration of the disclosed compounds of the invention can be found in *Remington: the Science and Practice of Pharmacy*, 19th edition, Mack Publishing Co., Easton, PA (1995). In some embodiments, the compounds described herein, and the pharmaceutically acceptable salts thereof, are used in pharmaceutical preparations in combination with a pharmaceutically acceptable carrier or diluent. Suitable pharmaceutically acceptable carriers include inert solid fillers or diluents and sterile aqueous or organic solutions. The compounds will be present in such pharmaceutical compositions in amounts sufficient to provide the desired dosage amount in the range described herein.

[0388] All percentages and ratios used herein, unless otherwise indicated, are by weight. Other features and advantages of the disclosure are apparent from the different examples. The provided examples illustrate different components and methodology useful in practicing the disclosure. The examples do not limit the claimed invention. Based on the present disclosure the skilled artisan can identify and employ other components and methodology useful for practicing the disclosure.

[0389] As used herein, a “subject in need thereof” is a subject having a disorder in which EZH2-mediated protein methylation plays a part, or a subject having an increased risk of developing such disorder relative to the population at large. In some embodiments, a subject in need thereof has cancer. A “subject” includes a mammal. The mammal can be *e.g.*, any mammal, *e.g.*, a human, primate, bird, mouse, rat, fowl, dog, cat, cow, horse, goat, camel, sheep or a pig. In some embodiments, the mammal is a human.

[0390] The subject of the disclosure includes any human subject who has been diagnosed with, has symptoms of, or is at risk of developing a cancer or a precancerous condition. The subject of the disclosure includes any human subject expressing a mutant EZH2. For example, a mutant EZH2 comprises one or more mutations, wherein the mutation is a substitution, a point mutation, a nonsense mutation, a missense mutation, a deletion, or an insertion or any other EZH2 mutation described herein.

[0391] A subject in need thereof may have refractory or resistant cancer. “Refractory or resistant cancer” means cancer that does not respond to treatment. The cancer may be resistant at the beginning of treatment or it may become resistant during treatment. In some embodiments, the subject in need thereof has cancer recurrence following remission on most recent therapy. In some embodiments, the subject in need thereof received and failed all known effective therapies for cancer treatment. In some embodiments, the subject in need thereof received at least one prior therapy. In certain embodiments the prior therapy is monotherapy. In certain embodiments the prior therapy is combination therapy.

[0392] In some embodiments, a subject in need thereof may have a secondary cancer as a result of a previous therapy. “Secondary cancer” means cancer that arises due to or as a result from previous carcinogenic therapies, such as chemotherapy.

[0393] The subject may also exhibit resistance to EZH2 histone methyltransferase inhibitors or any other therapeutic agent.

[0394] As used herein, the term “responsiveness” is interchangeable with terms “responsive”, “sensitive”, and “sensitivity”, and it is meant that a subject is showing therapeutic responses when administered a composition of the invention, *e.g.*, tumor cells or tumor tissues of the subject undergo apoptosis and/or necrosis, and/or display reduced growing, dividing, or proliferation. This term is also meant that a subject will or has a higher probability, relative to the population at large, of showing therapeutic responses when administered a composition of the invention, *e.g.*, tumor cells or tumor tissues of the subject undergo apoptosis and/or necrosis, and/or display reduced growing, dividing, or proliferation.

[0395] By “sample” it means any biological sample derived from the subject, includes but is not limited to, cells, tissues samples, body fluids (including, but not limited to, mucus, blood, plasma, serum, urine, saliva, and semen), tumor cells, and tumor tissues. In some embodiments, the sample is selected from bone marrow, peripheral blood cells, blood, plasma and serum. Samples can be provided by the subject under treatment or testing. Alternatively samples can be obtained by the physician according to routine practice in the art.

[0396] As used herein, a “normal cell” is a cell that cannot be classified as part of a “cell proliferative disorder”. A normal cell lacks unregulated or abnormal growth, or both, that can lead to the development of an unwanted condition or disease. In some embodiments, a normal cell possesses normally functioning cell cycle checkpoint control mechanisms.

[0397] As used herein, “contacting a cell” refers to a condition in which a compound or other composition of matter is in direct contact with a cell, or is close enough to induce a desired biological effect in a cell.

[0398] As used herein, “candidate compound” refers to a compound of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, that has been or will be tested in one or more *in vitro* or *in vivo* biological assays, in order to determine if that compound is likely to elicit a desired biological or medical response in a cell, tissue, system, animal or human that is being sought by a researcher or clinician. A candidate compound is a compound of the disclosure, or a pharmaceutically acceptable salt or solvate thereof. The biological or medical response can be the treatment of cancer. The biological or medical response can be treatment or prevention of a cell proliferative disorder. *In vitro* or *in vivo* biological assays can include, but are not limited to, enzymatic activity assays, electrophoretic mobility shift assays, reporter gene assays, *in vitro* cell viability assays, and the assays described herein.

[0399] As used herein, “treating” or “treat” describes the management and care of a patient for the purpose of combating a disease, condition, or disorder and includes the administration of a compound of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, to alleviate the symptoms or complications of a disease, condition or disorder, or to eliminate the disease, condition or disorder.

[0400] A composition of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, can also be used to prevent a disease, condition or disorder. As used herein, “preventing” or “prevent” describes reducing or eliminating the onset of the symptoms or complications of the disease, condition or disorder.

[0401] As used herein, the term “alleviate” is meant to describe a process by which the severity of a sign or symptom of a disorder is decreased. Importantly, a sign or symptom can be alleviated without being eliminated. In some embodiments, the administration of pharmaceutical compositions of the invention leads to the elimination of a sign or symptom, however, elimination is not required. Effective dosages are expected to decrease the severity of a sign or symptom. For instance, a sign or symptom of a disorder such as cancer, which can occur in multiple locations, is alleviated if the severity of the cancer is decreased within at least one of multiple locations.

[0402] As used herein, the term "severity" is meant to describe the potential of cancer to transform from a precancerous, or benign, state into a malignant state. Alternatively, or in addition, severity is meant to describe a cancer stage, for example, according to the TNM system (accepted by the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC)) or by other art-recognized methods. Cancer stage refers to the extent or severity of the cancer, based on factors such as the location of the primary tumor, tumor size, number of tumors, and lymph node involvement (spread of cancer into lymph nodes). Alternatively, or in addition, severity is meant to describe the tumor grade by art-recognized methods (see, National Cancer Institute, www.cancer.gov). Tumor grade is a system used to classify cancer cells in terms of how abnormal they look under a microscope and how quickly the tumor is likely to grow and spread. Many factors are considered when determining tumor grade, including the structure and growth pattern of the cells. The specific factors used to determine tumor grade vary with each type of cancer. Severity also describes a histologic grade, also called differentiation, which refers to how much the tumor cells resemble normal cells of the same tissue type (see, National Cancer Institute, www.cancer.gov). Furthermore, severity describes a nuclear grade, which refers to the size and shape of the nucleus in tumor cells and the percentage of tumor cells that are dividing (see, National Cancer Institute, www.cancer.gov).

[0403] In other aspects of the invention, severity describes the degree to which a tumor has secreted growth factors, degraded the extracellular matrix, become vascularized, lost adhesion to juxtaposed tissues, or metastasized. Moreover, severity describes the number of locations to which a primary tumor has metastasized. Finally, severity includes the difficulty of treating tumors of varying types and locations. For example, inoperable tumors, those cancers which have greater access to multiple body systems (hematological and immunological tumors), and those which are the most resistant to traditional treatments are considered most severe. In these situations, prolonging the life expectancy of the subject and/or reducing pain, decreasing the proportion of cancerous cells or restricting cells to one system, and improving cancer stage/tumor grade/histological grade/nuclear grade are considered alleviating a sign or symptom of the cancer.

[0404] As used herein the term "symptom" is defined as an indication of disease, illness, injury, or that something is not right in the body. Symptoms are felt or noticed by the individual experiencing the symptom, but may not easily be noticed by others. Others are defined as non-health-care professionals.

[0405] As used herein the term "sign" is also defined as an indication that something is not right in the body. But signs are defined as things that can be seen by a doctor, nurse, or other health care professional.

Non-Small Cell Lung Cancer

[0406] Lung cancer is the second most common form of cancer and is the leading cause of cancer-related mortality. Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for about 85% of all lung cancer cases. Most patients present with advanced stage III or IV NSCLC with a 5-year survival of 24% and 4% respectively. Because of the advanced nature of disease on presentation, surgical resection is often not an option. For the majority of patients therapy involves chemotherapy and/or radiation treatment. The selection of chemotherapy is highly variable based on disease stage, patient performance criteria and geographical regional preference. In most cases chemotherapy is based on a doublet that includes a platinating agent such as cisplatin or carboplatin, and a second cytotoxic drug such as gemcitabine, etoposide or taxotere. For a small number of patients, therapy can include treatment with agents that target specific proteins that are mutated or dysregulated such as ALK and EGFR (e.g., crizotinib, gefitinib and erlotinib). Patients are selected for these targeted treatments based on genetic or proteomic markers. A great number of agents have been assessed in late stage NSCLC clinical studies, however most have shown very little benefit over chemotherapy based treatments, with median overall survival typically less than 11 months. Accordingly, there is a tremendous need for new strategies to improve non-small cell lung cancer treatments.

Cancer

[0407] A "cancer cell" or "cancerous cell" is a cell manifesting a cell proliferative disorder that is a cancer. Any reproducible means of measurement may be used to identify cancer cells or precancerous cells. Cancer cells or precancerous cells can be identified by histological typing or grading of a tissue sample (e.g., a biopsy sample). Cancer cells or precancerous cells can be identified through the use of appropriate molecular markers.

[0408] Exemplary cancers include, but are not limited to, adrenocortical carcinoma, AIDS-related cancers, AIDS-related lymphoma, anal cancer, anorectal cancer, cancer of the anal canal, appendix

cancer, childhood cerebellar astrocytoma, childhood cerebral astrocytoma, basal cell carcinoma, skin cancer (non-melanoma), biliary cancer, extrahepatic bile duct cancer, intrahepatic bile duct cancer, bladder cancer, urinary bladder cancer, bone and joint cancer, osteosarcoma and malignant fibrous histiocytoma, brain cancer, brain tumor, brain stem glioma, cerebellar astrocytoma, cerebral astrocytoma/malignant glioma, ependymoma, medulloblastoma, supratentorial primitive neuroectodermal tumors, visual pathway and hypothalamic glioma, breast cancer, bronchial adenomas/carcinoids, carcinoid tumor, gastrointestinal, nervous system cancer, nervous system lymphoma, central nervous system cancer, central nervous system lymphoma, cervical cancer, childhood cancers, chronic lymphocytic leukemia, chronic myelogenous leukemia, chronic myeloproliferative disorders, colon cancer, colorectal cancer, cutaneous T-cell lymphoma, lymphoid neoplasm, mycosis fungoides, Sezary Syndrome, endometrial cancer, esophageal cancer, extracranial germ cell tumor, extragonadal germ cell tumor, extrahepatic bile duct cancer, eye cancer, intraocular melanoma, retinoblastoma, gallbladder cancer, gastric (stomach) cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumor (GIST), germ cell tumor, ovarian germ cell tumor, gestational trophoblastic tumor glioma, head and neck cancer, hepatocellular (liver) cancer, Hodgkin lymphoma, hypopharyngeal cancer, intraocular melanoma, ocular cancer, islet cell tumors (endocrine pancreas), Kaposi Sarcoma, kidney cancer, renal cancer, kidney cancer, laryngeal cancer, acute lymphoblastic leukemia, acute myeloid leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, hairy cell leukemia, lip and oral cavity cancer, liver cancer, lung cancer, non-small cell lung cancer, small cell lung cancer, AIDS-related lymphoma, non-Hodgkin lymphoma, primary central nervous system lymphoma, mantle cell lymphoma, Waldenström macroglobulinemia, medulloblastoma, melanoma, intraocular (eye) melanoma, merkel cell carcinoma, mesothelioma malignant, mesothelioma, metastatic squamous neck cancer, mouth cancer, cancer of the tongue, multiple endocrine neoplasia syndrome, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/ myeloproliferative diseases, chronic myelogenous leukemia, acute myeloid leukemia, multiple myeloma, chronic myeloproliferative disorders, nasopharyngeal cancer, neuroblastoma, oral cancer, oral cavity cancer, oropharyngeal cancer, ovarian cancer, ovarian epithelial cancer, ovarian low malignant potential tumor, pancreatic cancer, islet cell pancreatic cancer, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal cancer, pheochromocytoma, pineoblastoma and supratentorial primitive neuroectodermal tumors, pituitary tumor, plasma cell neoplasm/multiple myeloma,

pleuropulmonary blastoma, prostate cancer, rectal cancer, renal pelvis and ureter, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, ewing family of sarcoma tumors, Kaposi Sarcoma, soft tissue sarcoma, uterine cancer, uterine sarcoma, skin cancer (non-melanoma), skin cancer (melanoma), merkel cell skin carcinoma, small intestine cancer, soft tissue sarcoma, squamous cell carcinoma, stomach (gastric) cancer, supratentorial primitive neuroectodermal tumors, testicular cancer, throat cancer, thymoma, thymoma and thymic carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter and other urinary organs, gestational trophoblastic tumor, urethral cancer, endometrial uterine cancer, uterine sarcoma, uterine corpus cancer, vaginal cancer, vulvar cancer, and Wilm's Tumor.

[0409] A “cell proliferative disorder of the hematologic system” is a cell proliferative disorder involving cells of the hematologic system. A cell proliferative disorder of the hematologic system can include lymphoma, leukemia, myeloid neoplasms, mast cell neoplasms, myelodysplasia, benign monoclonal gammopathy, lymphomatoid granulomatosis, lymphomatoid papulosis, polycythemia vera, chronic myelocytic leukemia, agnogenic myeloid metaplasia, and essential thrombocythemia. A cell proliferative disorder of the hematologic system can include hyperplasia, dysplasia, and metaplasia of cells of the hematologic system. In some embodiments, compositions of the disclosure may be used to treat a cancer selected from the group consisting of a hematologic cancer of the disclosure or a hematologic cell proliferative disorder of the disclosure. A hematologic cancer of the disclosure can include multiple myeloma, lymphoma (including Hodgkin's lymphoma, non-Hodgkin's lymphoma, e.g., mantle cell lymphoma, childhood lymphomas, and lymphomas of lymphocytic and cutaneous origin), leukemia (including childhood leukemia, hairy-cell leukemia, acute lymphocytic leukemia, acute myelocytic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, chronic myelogenous leukemia, and mast cell leukemia), myeloid neoplasms and mast cell neoplasms.

[0410] A “cell proliferative disorder of the lung” is a cell proliferative disorder involving cells of the lung. Cell proliferative disorders of the lung can include all forms of cell proliferative disorders affecting lung cells. Cell proliferative disorders of the lung can include lung cancer, a precancer or precancerous condition of the lung, benign growths or lesions of the lung, and malignant growths or lesions of the lung, and metastatic lesions in tissue and organs in the body other than the lung. In some embodiments, compositions of the disclosure are used to treat lung cancer or cell proliferative disorders of the lung. Lung cancer can include all forms of cancer of

the lung. Lung cancer can include malignant lung neoplasms, carcinoma *in situ*, typical carcinoid tumors, and atypical carcinoid tumors. Lung cancer can include small cell lung cancer (“SCLC”), non-small cell lung cancer (“NSCLC”), squamous cell carcinoma, adenocarcinoma, small cell carcinoma, large cell carcinoma, adenosquamous cell carcinoma, and mesothelioma. Lung cancer can include “scar carcinoma,” bronchioalveolar carcinoma, giant cell carcinoma, spindle cell carcinoma, and large cell neuroendocrine carcinoma. Lung cancer can include lung neoplasms having histologic and ultrastructural heterogeneity (*e.g.*, mixed cell types).

[0411] Cell proliferative disorders of the lung can include all forms of cell proliferative disorders affecting lung cells. Cell proliferative disorders of the lung can include lung cancer, precancerous conditions of the lung. Cell proliferative disorders of the lung can include hyperplasia, metaplasia, and dysplasia of the lung. Cell proliferative disorders of the lung can include asbestos-induced hyperplasia, squamous metaplasia, and benign reactive mesothelial metaplasia. Cell proliferative disorders of the lung can include replacement of columnar epithelium with stratified squamous epithelium, and mucosal dysplasia. Individuals exposed to inhaled injurious environmental agents such as cigarette smoke and asbestos may be at increased risk for developing cell proliferative disorders of the lung. Prior lung diseases that may predispose individuals to development of cell proliferative disorders of the lung can include chronic interstitial lung disease, necrotizing pulmonary disease, scleroderma, rheumatoid disease, sarcoidosis, interstitial pneumonitis, tuberculosis, repeated pneumonias, idiopathic pulmonary fibrosis, granulomata, asbestosis, fibrosing alveolitis, and Hodgkin's disease.

[0412] A “cell proliferative disorder of the colon” is a cell proliferative disorder involving cells of the colon. In some embodiments, the cell proliferative disorder of the colon is colon cancer. In some embodiments, compositions of the disclosure are used to treat colon cancer or cell proliferative disorders of the colon. Colon cancer can include all forms of cancer of the colon. Colon cancer can include sporadic and hereditary colon cancers. Colon cancer can include malignant colon neoplasms, carcinoma *in situ*, typical carcinoid tumors, and atypical carcinoid tumors. Colon cancer can include adenocarcinoma, squamous cell carcinoma, and adenosquamous cell carcinoma. Colon cancer can be associated with a hereditary syndrome selected from the group consisting of hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, Gardner's syndrome, Peutz-Jeghers syndrome, Turcot's syndrome and juvenile polyposis. Colon cancer can be caused by a hereditary syndrome selected from the group

consisting of hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, Gardner's syndrome, Peutz-Jeghers syndrome, Turcot's syndrome and juvenile polyposis.

[0413] Cell proliferative disorders of the colon can include all forms of cell proliferative disorders affecting colon cells. Cell proliferative disorders of the colon can include colon cancer, precancerous conditions of the colon, adenomatous polyps of the colon and metachronous lesions of the colon. A cell proliferative disorder of the colon can include adenoma. Cell proliferative disorders of the colon can be characterized by hyperplasia, metaplasia, and dysplasia of the colon. Prior colon diseases that may predispose individuals to development of cell proliferative disorders of the colon can include prior colon cancer. Current disease that may predispose individuals to development of cell proliferative disorders of the colon can include Crohn's disease and ulcerative colitis. A cell proliferative disorder of the colon can be associated with a mutation in a gene selected from the group consisting of *p53*, *ras*, *FAP* and *DCC*. An individual can have an elevated risk of developing a cell proliferative disorder of the colon due to the presence of a mutation in a gene selected from the group consisting of *p53*, *ras*, *FAP* and *DCC*.

[0414] A "cell proliferative disorder of the pancreas" is a cell proliferative disorder involving cells of the pancreas. Cell proliferative disorders of the pancreas can include all forms of cell proliferative disorders affecting pancreatic cells. Cell proliferative disorders of the pancreas can include pancreas cancer, a precancer or precancerous condition of the pancreas, hyperplasia of the pancreas, and dysaplasia of the pancreas, benign growths or lesions of the pancreas, and malignant growths or lesions of the pancreas, and metastatic lesions in tissue and organs in the body other than the pancreas. Pancreatic cancer includes all forms of cancer of the pancreas. Pancreatic cancer can include ductal adenocarcinoma, adenosquamous carcinoma, pleomorphic giant cell carcinoma, mucinous adenocarcinoma, osteoclast-like giant cell carcinoma, mucinous cystadenocarcinoma, acinar carcinoma, unclassified large cell carcinoma, small cell carcinoma, pancreatoblastoma, papillary neoplasm, mucinous cystadenoma, papillary cystic neoplasm, and serous cystadenoma. Pancreatic cancer can also include pancreatic neoplasms having histologic and ultrastructural heterogeneity (*e.g.*, mixed cell types).

[0415] A "cell proliferative disorder of the prostate" is a cell proliferative disorder involving cells of the prostate. Cell proliferative disorders of the prostate can include all forms of cell proliferative disorders affecting prostate cells. Cell proliferative disorders of the prostate can include prostate cancer, a precancer or precancerous condition of the prostate, benign growths or

lesions of the prostate, malignant growths or lesions of the prostate and metastatic lesions in tissue and organs in the body other than the prostate. Cell proliferative disorders of the prostate can include hyperplasia, metaplasia, and dysplasia of the prostate.

[0416] A “cell proliferative disorder of the skin” is a cell proliferative disorder involving cells of the skin. Cell proliferative disorders of the skin can include all forms of cell proliferative disorders affecting skin cells. Cell proliferative disorders of the skin can include a precancer or precancerous condition of the skin, benign growths or lesions of the skin, melanoma, malignant melanoma and other malignant growths or lesions of the skin, and metastatic lesions in tissue and organs in the body other than the skin. Cell proliferative disorders of the skin can include hyperplasia, metaplasia, and dysplasia of the skin.

[0417] A “cell proliferative disorder of the ovary” is a cell proliferative disorder involving cells of the ovary. Cell proliferative disorders of the ovary can include all forms of cell proliferative disorders affecting cells of the ovary. Cell proliferative disorders of the ovary can include a precancer or precancerous condition of the ovary, benign growths or lesions of the ovary, ovarian cancer, malignant growths or lesions of the ovary, and metastatic lesions in tissue and organs in the body other than the ovary. Cell proliferative disorders of the skin can include hyperplasia, metaplasia, and dysplasia of cells of the ovary.

[0418] A “cell proliferative disorder of the breast” is a cell proliferative disorder involving cells of the breast. Cell proliferative disorders of the breast can include all forms of cell proliferative disorders affecting breast cells. Cell proliferative disorders of the breast can include breast cancer, a precancer or precancerous condition of the breast, benign growths or lesions of the breast, and malignant growths or lesions of the breast, and metastatic lesions in tissue and organs in the body other than the breast. Cell proliferative disorders of the breast can include hyperplasia, metaplasia, and dysplasia of the breast.

[0419] A cell proliferative disorder of the breast can be a precancerous condition of the breast. In some embodiments, compositions of the disclosure are used to treat a precancerous condition of the breast. A precancerous condition of the breast can include atypical hyperplasia of the breast, ductal carcinoma *in situ* (DCIS), intraductal carcinoma, lobular carcinoma *in situ* (LCIS), lobular neoplasia, and stage 0 or grade 0 growth or lesion of the breast (*e.g.*, stage 0 or grade 0 breast cancer, or carcinoma *in situ*). A precancerous condition of the breast can be staged according to the TNM classification scheme as accepted by the American Joint Committee on Cancer (AJCC),

where the primary tumor (T) has been assigned a stage of T0 or Tis; and where the regional lymph nodes (N) have been assigned a stage of N0; and where distant metastasis (M) has been assigned a stage of M0.

[0420] The cell proliferative disorder of the breast can be breast cancer. In some embodiments, compositions of the disclosure are used to treat breast cancer. Breast cancer includes all forms of cancer of the breast. Breast cancer can include primary epithelial breast cancers. Breast cancer can include cancers in which the breast is involved by other tumors such as lymphoma, sarcoma or melanoma. Breast cancer can include carcinoma of the breast, ductal carcinoma of the breast, lobular carcinoma of the breast, undifferentiated carcinoma of the breast, cystosarcoma phyllodes of the breast, angiosarcoma of the breast, and primary lymphoma of the breast. Breast cancer can include Stage I, II, IIIA, IIIB, IIIC and IV breast cancer. Ductal carcinoma of the breast can include invasive carcinoma, invasive carcinoma *in situ* with predominant intraductal component, inflammatory breast cancer, and a ductal carcinoma of the breast with a histologic type selected from the group consisting of comedo, mucinous (colloid), medullary, medullary with lymphocytic infiltrate, papillary, scirrhous, and tubular. Lobular carcinoma of the breast can include invasive lobular carcinoma with predominant *in situ* component, invasive lobular carcinoma, and infiltrating lobular carcinoma. Breast cancer can include Paget's disease, Paget's disease with intraductal carcinoma, and Paget's disease with invasive ductal carcinoma. Breast cancer can include breast neoplasms having histologic and ultrastructural heterogeneity (*e.g.*, mixed cell types).

[0421] A cancer that is to be treated can be staged according to the American Joint Committee on Cancer (AJCC) TNM classification system, where the tumor (T) has been assigned a stage of TX, T1, T1mic, T1a, T1b, T1c, T2, T3, T4, T4a, T4b, T4c, or T4d; and where the regional lymph nodes (N) have been assigned a stage of NX, N0, N1, N2, N2a, N2b, N3, N3a, N3b, or N3c; and where distant metastasis (M) can be assigned a stage of MX, M0, or M1. A cancer that is to be treated can be staged according to an American Joint Committee on Cancer (AJCC) classification as Stage I, Stage IIA, Stage IIB, Stage IIIA, Stage IIIB, Stage IIIC, or Stage IV. A cancer that is to be treated can be assigned a grade according to an AJCC classification as Grade GX (*e.g.*, grade cannot be assessed), Grade 1, Grade 2, Grade 3 or Grade 4. A cancer that is to be treated can be staged according to an AJCC pathologic classification (pN) of pNX, pN0, PN0 (I-), PN0 (I+), PN0

(mol-), PN0 (mol+), PN1, PN1(mi), PN1a, PN1b, PN1c, pN2, pN2a, pN2b, pN3, pN3a, pN3b, or pN3c.

[0422] A cancer that is to be treated can include a tumor that has been determined to be less than or equal to about 2 centimeters in diameter. A cancer that is to be treated can include a tumor that has been determined to be from about 2 to about 5 centimeters in diameter. A cancer that is to be treated can include a tumor that has been determined to be greater than or equal to about 3 centimeters in diameter. A cancer that is to be treated can include a tumor that has been determined to be greater than 5 centimeters in diameter. A cancer that is to be treated can be classified by microscopic appearance as well differentiated, moderately differentiated, poorly differentiated, or undifferentiated. A cancer that is to be treated can be classified by microscopic appearance with respect to mitosis count (*e.g.*, amount of cell division) or nuclear pleiomorphism (*e.g.*, change in cells). A cancer that is to be treated can be classified by microscopic appearance as being associated with areas of necrosis (*e.g.*, areas of dying or degenerating cells). A cancer that is to be treated can be classified as having an abnormal karyotype, having an abnormal number of chromosomes, or having one or more chromosomes that are abnormal in appearance. A cancer that is to be treated can be classified as being aneuploid, triploid, tetraploid, or as having an altered ploidy. A cancer that is to be treated can be classified as having a chromosomal translocation, or a deletion or duplication of an entire chromosome, or a region of deletion, duplication or amplification of a portion of a chromosome.

[0423] A cancer that is to be treated can be evaluated by DNA cytometry, flow cytometry, or image cytometry. A cancer that is to be treated can be typed as having 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of cells in the synthesis stage of cell division (*e.g.*, in S phase of cell division). A cancer that is to be treated can be typed as having a low S-phase fraction or a high S-phase fraction.

[0424] Cancer is a group of diseases that may cause almost any sign or symptom. The signs and symptoms will depend on where the cancer is, the size of the cancer, and how much it affects the nearby organs or structures. If a cancer spreads (metastasizes), then symptoms may appear in different parts of the body.

[0425] The disorder in which EZH2-mediated protein methylation plays a part can be a neurological disease. The compound of this invention can thus also be used for treating neurologic diseases such as epilepsy, schizophrenia, bipolar disorder or other psychological and/or

psychiatric disorders, neuropathies, skeletal muscle atrophy, and neurodegenerative diseases, e.g., a neurodegenerative disease. Exemplary neurodegenerative diseases include: Alzheimer's, Amyotrophic Lateral Sclerosis (ALS), and Parkinson's disease. Another class of neurodegenerative diseases includes diseases caused at least in part by aggregation of poly-glutamine. Diseases of this class include: Huntington's Diseases, Spinalbulbar Muscular Atrophy (SBMA or Kennedy's Disease) Dentatorubropallidoluysian Atrophy (DRPLA), Spinocerebellar Ataxia 1 (SCA1), Spinocerebellar Ataxia 2 (SCA2), Machado-Joseph Disease (MJD; SCA3), Spinocerebellar Ataxia 6 (SCA6), Spinocerebellar Ataxia 7 (SCA7), and Spinocerebellar Ataxia 12 (SCA12).

[0426] Any other disease in which epigenetic methylation, which is mediated by EZH2, plays a role may be treatable or preventable using compositions and methods described herein.

[0427] Treating cancer can result in a reduction in size of a tumor. A reduction in size of a tumor may also be referred to as “tumor regression”. In some embodiments, after treatment, tumor size is reduced by 5% or greater relative to its size prior to treatment; in some embodiments, tumor size is reduced by 10% or greater; reduced by 20% or greater; reduced by 30% or greater; reduced by 40% or greater; reduced by 50% or greater; or reduced by 75% or greater. Size of a tumor may be measured by any reproducible means of measurement. The size of a tumor may be measured as a diameter of the tumor.

[0428] Treating cancer can result in a reduction in tumor volume. In some embodiments, after treatment, tumor volume is reduced by 5% or greater relative to its size prior to treatment; in some embodiments, tumor volume is reduced by 10% or greater; reduced by 20% or greater; reduced by 30% or greater; reduced by 40% or greater; even reduced by 50% or greater; and most preferably, reduced by greater than 75% or greater. Tumor volume may be measured by any reproducible means of measurement.

[0429] Treating cancer results in a decrease in number of tumors. In some embodiments, after treatment, tumor number is reduced by 5% or greater relative to number prior to treatment; in some embodiments, tumor number is reduced by 10% or greater; reduced by 20% or greater; reduced by 30% or greater; reduced by 40% or greater; even reduced by 50% or greater; and most preferably, reduced by greater than 75%. Number of tumors may be measured by any reproducible means of measurement. The number of tumors may be measured by counting tumors

visible to the naked eye or at a specified magnification. In some embodiments, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

[0430] Treating cancer can result in a decrease in number of metastatic lesions in other tissues or organs distant from the primary tumor site. In some embodiments, after treatment, the number of metastatic lesions is reduced by 5% or greater relative to number prior to treatment; in some embodiments, the number of metastatic lesions is reduced by 10% or greater; reduced by 20% or greater; reduced by 30% or greater; reduced by 40% or greater; reduced by 50% or greater; and most preferably, reduced by greater than 75%. The number of metastatic lesions may be measured by any reproducible means of measurement. The number of metastatic lesions may be measured by counting metastatic lesions visible to the naked eye or at a specified magnification. In some embodiments, the specified magnification is 2x, 3x, 4x, 5x, 10x, or 50x.

[0431] Treating cancer can result in an increase in average survival time of a population of treated subjects in comparison to a population receiving carrier alone. In some embodiments, the average survival time is increased by more than 30 days; by more than 60 days; by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0432] Treating cancer can result in an increase in average survival time of a population of treated subjects in comparison to a population of untreated subjects. In some embodiments, the average survival time is increased by more than 30 days; by more than 60 days; by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0433] Treating cancer can result in increase in average survival time of a population of treated subjects in comparison to a population receiving monotherapy with a drug that is not a compound

of the disclosure, or a pharmaceutically acceptable salt, solvate, analog or derivative thereof. In some embodiments, the average survival time is increased by more than 30 days; by more than 60 days; by more than 90 days; and most preferably, by more than 120 days. An increase in average survival time of a population may be measured by any reproducible means. An increase in average survival time of a population may be measured, for example, by calculating for a population the average length of survival following initiation of treatment with an active compound. An increase in average survival time of a population may also be measured, for example, by calculating for a population the average length of survival following completion of a first round of treatment with an active compound.

[0434] Treating cancer can result in a decrease in the mortality rate of a population of treated subjects in comparison to a population receiving carrier alone. Treating cancer can result in a decrease in the mortality rate of a population of treated subjects in comparison to an untreated population. Treating cancer can result in a decrease in the mortality rate of a population of treated subjects in comparison to a population receiving monotherapy with a drug that is not a compound of the disclosure, or a pharmaceutically acceptable salt, solvate, analog or derivative thereof. In some embodiments, the mortality rate is decreased by more than 2%; by more than 5%; by more than 10%; and most preferably, by more than 25%. A decrease in the mortality rate of a population of treated subjects may be measured by any reproducible means. A decrease in the mortality rate of a population may be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following initiation of treatment with an active compound. A decrease in the mortality rate of a population may also be measured, for example, by calculating for a population the average number of disease-related deaths per unit time following completion of a first round of treatment with an active compound.

[0435] Treating cancer can result in a decrease in tumor growth rate. In some embodiments, after treatment, tumor growth rate is reduced by at least 5% relative to number prior to treatment; in some embodiments, tumor growth rate is reduced by at least 10%; reduced by at least 20%; reduced by at least 30%; reduced by at least 40%; reduced by at least 50%; reduced by at least 50%; and most preferably, reduced by at least 75%. Tumor growth rate may be measured by any reproducible means of measurement. Tumor growth rate can be measured according to a change in tumor diameter per unit time.

[0436] Treating cancer can result in a decrease in tumor regrowth. In some embodiments, after treatment, tumor regrowth is less than 5%; in some embodiments, tumor regrowth is less than 10%; less than 20%; less than 30%; less than 40%; less than 50%; less than 50%; and most preferably, less than 75%. Tumor regrowth may be measured by any reproducible means of measurement. Tumor regrowth is measured, for example, by measuring an increase in the diameter of a tumor after a prior tumor shrinkage that followed treatment. A decrease in tumor regrowth is indicated by failure of tumors to reoccur after treatment has stopped.

[0437] Treating or preventing a cell proliferative disorder can result in a reduction in the rate of cellular proliferation. In some embodiments, after treatment, the rate of cellular proliferation is reduced by at least 5%; by at least 10%; by at least 20%; by at least 30%; by at least 40%; by at least 50%; even by at least 50%; and most preferably, by at least 75%. The rate of cellular proliferation may be measured by any reproducible means of measurement. The rate of cellular proliferation is measured, for example, by measuring the number of dividing cells in a tissue sample per unit time.

[0438] Treating or preventing a cell proliferative disorder can result in a reduction in the proportion of proliferating cells. In some embodiments, after treatment, the proportion of proliferating cells is reduced by at least 5%; by at least 10%; by at least 20%; by at least 30%; by at least 40%; by at least 50%; by at least 50%; and most preferably, by at least 75%. The proportion of proliferating cells may be measured by any reproducible means of measurement. In some embodiments, the proportion of proliferating cells is measured, for example, by quantifying the number of dividing cells relative to the number of nondividing cells in a tissue sample.

[0439] The proportion of proliferating cells can be equivalent to the mitotic index.

[0440] Treating or preventing a cell proliferative disorder can result in a decrease in size of an area or zone of cellular proliferation. In some embodiments, after treatment, size of an area or zone of cellular proliferation is reduced by at least 5% relative to its size prior to treatment; reduced by at least 10%; reduced by at least 20%; reduced by at least 30%; reduced by at least 40%; reduced by at least 50%; reduced by at least 50%; and most preferably, reduced by at least 75%. Size of an area or zone of cellular proliferation may be measured by any reproducible means of measurement. The size of an area or zone of cellular proliferation may be measured as a diameter or width of an area or zone of cellular proliferation.

[0441] Treating or preventing a cell proliferative disorder can result in a decrease in survival or viability of proliferating cells, e.g., of malignant cells. In some embodiments, after treatment, survival or viability of proliferating cells is reduced by at least 5% relative to the rate of survival or viability prior to treatment; reduced by at least 10%; reduced by at least 20%; reduced by at least 30%; reduced by at least 40%; reduced by at least 50%; reduced by at least 50%; and reduced by at least 75%, reduced by at least 80%, reduced by at least 90%, reduced by at least 95%, reduced by at least 99%. The rate of survival or viability of proliferating cells may be measured by any reproducible means of measurement. Some exemplary suitable assays for measuring cell viability, survival, and proliferation rate are described herein, and additional suitable assays will be apparent to the skilled artisan based on the present disclosure and the knowledge in the art. In some exemplary embodiments, the rate of survival of proliferating cells is measured, for example, by quantifying the number of remaining cells after a certain time of treatment relative to the initial number of cells. In some embodiments, cell viability is measured, for example, in an *in vitro* cell viability assay.

[0442] Treating or preventing a cell proliferative disorder can result in a decrease in the number or proportion of cells having an abnormal appearance or morphology. In some embodiments, after treatment, the number of cells having an abnormal morphology is reduced by at least 5% relative to its size prior to treatment; reduced by at least 10%; reduced by at least 20%; reduced by at least 30%; reduced by at least 40%; reduced by at least 50%; reduced by at least 50%; and most preferably, reduced by at least 75%. An abnormal cellular appearance or morphology may be measured by any reproducible means of measurement. An abnormal cellular morphology can be measured by microscopy, e.g., using an inverted tissue culture microscope. An abnormal cellular morphology can take the form of nuclear pleiomorphism.

[0443] As used herein, the term “selectively” means tending to occur at a higher frequency in one population than in another population. The compared populations can be cell populations. In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, acts selectively on a cancer or precancerous cell but not on a normal cell. In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, acts selectively to modulate one molecular target (e.g., a target protein methyltransferase) but does not significantly modulate another molecular target (e.g., a non-target protein methyltransferase). The invention also provides a method for selectively inhibiting the activity of

an enzyme, such as a protein methyltransferase. In some embodiments, an event occurs selectively in population A relative to population B if it occurs greater than two times more frequently in population A as compared to population B. An event occurs selectively if it occurs greater than five times more frequently in population A. An event occurs selectively if it occurs greater than ten times more frequently in population A; greater than fifty times; greater than 100 times; and most preferably, greater than 1000 times more frequently in population A as compared to population B. For example, cell death would be said to occur selectively in cancer cells if it occurred greater than twice as frequently in cancer cells as compared to normal cells.

[0444] A composition of the disclosure, e.g., a composition comprising any compound of Formulae (I)-(VIa) or pharmaceutically acceptable salt thereof, and one or more other therapeutic agents, such as prednisone, can modulate the activity of a molecular target (e.g., a target protein methyltransferase). Modulating refers to stimulating or inhibiting an activity of a molecular target. In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, modulates the activity of a molecular target if it stimulates or inhibits the activity of the molecular target by at least 2-fold relative to the activity of the molecular target under the same conditions but lacking only the presence of said compound. In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, modulates the activity of a molecular target if it stimulates or inhibits the activity of the molecular target by at least 5-fold, at least 10-fold, at least 20-fold, at least 50-fold, at least 100-fold relative to the activity of the molecular target under the same conditions but lacking only the presence of said compound. The activity of a molecular target may be measured by any reproducible means. The activity of a molecular target may be measured *in vitro* or *in vivo*. For example, the activity of a molecular target may be measured *in vitro* by an enzymatic activity assay or a DNA binding assay, or the activity of a molecular target may be measured *in vivo* by assaying for expression of a reporter gene.

[0445] A composition of the disclosure does not significantly modulate the activity of a molecular target if the addition of the compound does not stimulate or inhibit the activity of the molecular target by greater than 10% relative to the activity of the molecular target under the same conditions but lacking only the presence of said compound.

[0446] As used herein, the term “isozyme selective” means preferential inhibition or stimulation of a first isoform of an enzyme in comparison to a second isoform of an enzyme (e.g., preferential

inhibition or stimulation of a protein methyltransferase isozyme alpha in comparison to a protein methyltransferase isozyme beta). In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, demonstrates a minimum of a fourfold differential, preferably a tenfold differential, more preferably a fifty fold differential, in the dosage required to achieve a biological effect. In some embodiments, a compound of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, demonstrates this differential across the range of inhibition, and the differential is exemplified at the IC_{50} , *i.e.*, a 50% inhibition, for a molecular target of interest.

[0447] Administering a composition of the disclosure to a cell or a subject in need thereof can result in modulation (*i.e.*, stimulation or inhibition) of an activity of a protein methyltransferase of interest.

[0448] Administering a compound of the disclosure, *e.g.*, a composition comprising any compound of Formulae (I)-(VIa) or pharmaceutically acceptable salt thereof, and one or more other therapeutic agents, such as prednisone, to a cell or a subject in need thereof results in modulation (*i.e.*, stimulation or inhibition) of an activity of an intracellular target (*e.g.*, substrate). Several intracellular targets can be modulated with the compounds of the disclosure, including, but not limited to, protein methyltransferase.

[0449] Activating refers to placing a composition of matter (*e.g.*, protein or nucleic acid) in a state suitable for carrying out a desired biological function. A composition of matter capable of being activated also has an unactivated state. An activated composition of matter may have an inhibitory or stimulatory biological function, or both.

[0450] Elevation refers to an increase in a desired biological activity of a composition of matter (*e.g.*, a protein or a nucleic acid). Elevation may occur through an increase in concentration of a composition of matter.

[0451] Treating cancer or a cell proliferative disorder can result in cell death, and preferably, cell death results in a decrease of at least 10% in number of cells in a population. In some embodiments, cell death means a decrease of at least 20%; a decrease of at least 30%; a decrease of at least 40%; a decrease of at least 50%; most preferably, a decrease of at least 75%. Number of cells in a population may be measured by any reproducible means. A number of cells in a population can be measured by fluorescence activated cell sorting (FACS), immunofluorescence

microscopy and light microscopy. Methods of measuring cell death are as shown in Li *et al.*, *Proc Natl Acad Sci U S A.* 100(5): 2674-8, 2003. In some aspects, cell death occurs by apoptosis.

[0452] In some embodiments, an effective amount of a composition of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, is not significantly cytotoxic to normal cells. A therapeutically effective amount of a compound is not significantly cytotoxic to normal cells if administration of the compound in a therapeutically effective amount does not induce cell death in greater than 10% of normal cells. A therapeutically effective amount of a compound does not significantly affect the viability of normal cells if administration of the compound in a therapeutically effective amount does not induce cell death in greater than 10% of normal cells. In some aspects, cell death occurs by apoptosis.

[0453] Contacting a cell with a composition of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, can induce or activate cell death selectively in cancer cells. Administering to a subject in need thereof a compound of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, can induce or activate cell death selectively in cancer cells. Contacting a cell with a composition of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, can induce cell death selectively in one or more cells affected by a cell proliferative disorder. In some embodiments, administering to a subject in need thereof a composition of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, induces cell death selectively in one or more cells affected by a cell proliferative disorder.

[0454] The disclosure relates to methods of treating or preventing cancer by administering a composition of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, to a subject in need thereof, where administration of the composition of the disclosure, or a pharmaceutically acceptable salt or solvate thereof, results in one or more of the following: prevention of cancer cell proliferation by accumulation of cells in one or more phases of the cell cycle (e.g. G1, G1/S, G2/M), or induction of cell senescence, or promotion of tumor cell differentiation; promotion of cell death in cancer cells via cytotoxicity, necrosis or apoptosis, without a significant amount of cell death in normal cells, antitumor activity in animals with a therapeutic index of at least 2. As used herein, “therapeutic index” is the maximum tolerated dose divided by the efficacious dose.

[0455] One skilled in the art may refer to general reference texts for detailed descriptions of known techniques discussed herein or equivalent techniques. These texts include Ausubel *et al.*, *Current Protocols in Molecular Biology*, John Wiley and Sons, Inc. (2005); Sambrook *et al.*,

Molecular Cloning, A Laboratory Manual (3rd edition), Cold Spring Harbor Press, Cold Spring Harbor, New York (2000); Coligan *et al.*, *Current Protocols in Immunology*, John Wiley & Sons, N.Y.; Enna *et al.*, *Current Protocols in Pharmacology*, John Wiley & Sons, N.Y.; Fingl *et al.*, *The Pharmacological Basis of Therapeutics* (1975), *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, PA, 18th edition (1990). These texts can, of course, also be referred to in making or using an aspect of the invention.

Example 1: EZH2 Non-Small Cell Lung Cancer in Vitro Combination Studies

[0456] Methods: Studies were performed using breast cancer cell lines in vitro to evaluate the anti-proliferative effect of combinations of tazemetostat and a second agent. Initial proliferation studies were performed to determine the IC₅₀ of tazemetostat in each cell line. For the screen, tazemetostat was used at concentrations bracketed around the IC₅₀ value. If 50% inhibitory concentration was not reached then tazemetostat was tested starting at 10 μ M.

[0457] In order to study the effect of dual combination of tazemetostat and a second agent on cell proliferation, cells in log-linear phase growth rate were pre-treated with various concentrations of tazemetostat or DMSO for 7 days in flasks, plated in 384-well plates in the absence of compounds and co-treated on day 8 with tazemetostat or DMSO and the second agent serially diluted for additional 6 days (as depicted in Figure 1). On day 15, plates were developed for endpoint analysis using Cell Titer Glo to measure ATP content, which was used as an indicator of cell viability. DMSO concentration was kept constant throughout the assay at 0.15% v/v.

[0458] Cell lines: All cell lines were obtained from American Type Culture Collection (ATCC; Rockville, MD). NCI-H1573 was cultured in DMEM: F12 Medium containing the following components: 0.02 mg/ml insulin, 0.01 mg/ml transferrin, 25 nM sodium selenite, 50 nM Hydrocortisone, 1 ng/ml Epidermal Growth Factor, 0.01 mM ethanolamine, 0.01 mM phosphorylethanolamine, 100 pM triiodothyronine, 0.5% (w/v) bovine serum albumin, 0.5 mM sodium pyruvate, 4.5mM L-glutamine and 1% v/v Pen/Strep. A427, Calu-3, Calu-6 cell lines were cultured in EMEM + 10% Fetal bovine serum (FBS) + 1% v/v Penicillin/Streptomycin (P/S). A549 cell lines was cultured in F-12K + 10% FBS + 1% v/v P/S. NCI-H1793 was cultured in HITES + 5% FBS + 1% v/v P/S. HCC827, NCI-H838, NCI-H460, NCI-H661, NCI-H23, NCI-H1299, NCI-H1703, NCI-H1993, NCI-H2030, NCI-H2122 and NCI-H522 cell lines were cultured in RPMI-1640 + 10%FBS.

[0459] Analysis of Synergy: Analysis of combinatorial effects and synergy quantification was performed using CHALICE software (Horizon Discovery, Cambridge, UK) was used to determine synergy using the Loewe method (Lehar et al, Mol Syst Biol 2007;3:80). Loewe volumes greater than 1 denoted “synergy” and volumes ≤ -1 denoted “antagonism”. A value between -1 and 1 denoted “additivity”. If neither single agent nor their combination reached 50% inhibitory concentration it was deemed as “no effect”.

[0460] The results of analyses of combinatorial effects between tazemetostat and several standard of care drugs and targeted therapies are shown in Table 2.

Table 2: In vitro combination studies in non-small cell lung cancer cell lines: Summary of combinatorial effects

		Cellline																	
Drug	Modality	A427	A549	NCI- H1299	NCI- H1573	NCI- H1703	NCI- H1793	NCI- H1993	NCI- H2030	NCI- H2110	NCI- H2122	NCI- H23	NCI- H460	NCI- RS22	NCI- H661	NCI- H838	Calu-3	Calu-6	HCC827
Cisplatin	DNA adduct forming	Syn.	Syn.	No eff.	Add.	No eff.	No eff.	Syn.	Syn.	Add.	Anta.	Add.	Add.	Anta.	Syn.	Add.	Syn.	Add.	Add.
Oxaliplatin		Syn.	Anta.	Anta.	NT	Anta.	NT	Add.	NT	NT	Add.	Anta.	NT	Anta.	Syn.	Add.	NT	NT	NT
Paclitaxel	Binds microtubules	Add.	Add.	Syn.	Add.	Add.	Add.	Add.	Syn.	Add.	Add.	Add.	Add.	Add.	Syn.	Add.	Syn.	Add.	Add.
Docetaxel		Syn.	Add.	Syn.	Add.	Add.	Syn.	Syn.	Syn.	Syn.	Add.	Add.	Add.	Syn.	Add.	Syn.	Syn.	Add.	Add.
Vinorelbine	Tubulin polymerization inhibitor	Syn.	Add.	Syn.	Add.	Add.	Add.	Add.	Add.	Add.	Syn.	Add.	Add.	Anta.	Syn.	Add.	Syn.	Syn.	Add.
Gemcitabine	Antimetabolite	Syn.	Add.	Add.	Add.	Add.	Add.	Add.	Add.	Anta.	Add.	Add.	Add.	Anta.	Syn.	Add.	Add.	Add.	Add.
Decitabine	DNMT inhibitor	Syn.	Syn.	Syn.	No eff.	Syn.	Syn.	Syn.	Syn.	Add.	Syn.	Add.	Syn.	Anta.	Syn.	Syn.	Syn.	Syn.	Syn.
Azacitidine		Syn.	Add.	Syn.	Add.	Syn.	Add.	Add.	Syn.	Syn.	Add.	Syn.	Add.	Syn.	No eff.	Add.	Syn.	Syn.	Syn.
Vorinostat	HDACi	Syn.	Add.	Add.	Syn.	Syn.	Syn.	Add.	Syn.	Add.	Add.	Syn.	Syn.	Syn.	Add.	Add.	Add.	Syn.	Add.
Irinotecan	Topo inhibitor	Syn.	Add.	Syn.	Add.	Add.	Syn.	Syn.	Syn.	Add.	Anta.	Add.	Syn.	Add.	Syn.	Add.	Syn.	Syn.	Add.
Etoposide		Syn.	Add.	Syn.	Add.	Add.	Add.	Add.	Syn.	Syn.	Add.	Add.	Add.	Add.	Syn.	Syn.	Add.	Syn.	Add.
Vinblastine	Mitosis inhibitor	Syn.	Add.	Syn.	Add.	Add.	Syn.	Add.	Add.	Add.	Add.	Add.	Add.	Add.	Add.	Add.	Syn.	Add.	Add.
Erlotinib	EGFR inhibitor	NT	Anta.	Syn.	Syn.	Syn.	Syn.	Syn.	Add.	Syn.	Syn.	No eff.	No eff.	Syn.	Syn.	Syn.	Syn.	No eff.	Syn.
Gefitinib		Syn.	Anta.	No eff.	Syn.	Anta.	Syn.	Syn.	No eff.	Anta.	Syn.	Anta.	No eff.	No eff.	Syn.	Anta.	Syn.	Syn.	Syn.
Lapatinib	EGFRi and Erb2 i	NT	Add.	Add.	Syn.	Syn.	Syn.	No eff.	Anta.	Syn.	Anta.	Add.	Syn.	Syn.	Anta.	Syn.	Syn.	No eff.	Add.
Afatinib		Syn.	Anta.	Add.	Add.	Add.	Add.	Syn.	Add.	Syn.	Add.	Add.	Add.	Syn.	Syn.	Add.	Syn.	Add.	Add.
AZD9291	EGFRi	Anta.	Add.	Add.	Add.	Add.	Syn.	Add.	Add.	Syn.	Anta.	Add.	Add.	Syn.	Anta.	Syn.	Syn.	NT	Add.
Crizotinib	ALKi and ROSi	Syn.	Add.	Add.	Syn.	Anta.	Syn.	Add.	Syn.	Add.	Add.	Add.	Add.	Add.	Syn.	Add.	Add.	Add.	Add.
Certinib		Syn.	Add.	Add.	Syn.	Add.	Add.	Add.	Syn.	Add.	Anta.	Anta.	Add.	Add.	Add.	Syn.	Add.	Add.	Add.
Brigatinib	ALKi and EGFRi	Syn.	Syn.	Add.	Syn.	Syn.	Syn.	Syn.	Syn.	Syn.	Add.	Syn.	Syn.	Syn.	Add.	Syn.	Syn.	Add.	Add.
Abemaciclib		Syn.	Add.	Syn.	Syn.	Add.	Add.	Syn.	Syn.	Syn.	Add.	Anta.	Add.	Add.	Syn.	Anta.	Syn.	Add.	Add.
Palbociclib	CDK4/6 inhibitor	Syn.	Add.	Add.	Syn.	Anta.	Syn.	Add.	Syn.	Add.	Add.	Add.	Add.	Add.	Syn.	Add.	Add.	Add.	Add.
Ribociclib		Syn.	Add.	Add.	Syn.	Add.	Add.	Add.	Syn.	Add.	Anta.	Anta.	No eff.	No eff.	Syn.	Syn.	Syn.	No eff.	Add.
Methotrexate	Folate antimetabolite	Add.	Anta.	Anta.	NT	Anta.	NT	NT	Anta.	NT	Anta.	Anta.	NT	Anta.	NT	Anta.	NT	NT	NT
Permetrexed		NT	Anta.	Anta.	NT	NT	Anta.	NT	NT	Anta.	NT	Anta.	Anta.	NT	Anta.	No eff.	Anta.	NT	NT
Trametinib	MEKi	Syn.	Anta.	Syn.	Syn.	Syn.	Syn.	Syn.	Syn.	Syn.	Anta.	Add.	Anta.	Syn.	Add.	Syn.	Syn.	Add.	Syn.
Selumetinib		Syn.	Add.	Add.	Syn.	Syn.	Syn.	Syn.	Syn.	Add.	Syn.	Anta.	Add.	Anta.	Syn.	Syn.	Syn.	Syn.	Syn.
Vemurafenib	BRAF i	No eff.	No eff.	Anta.	Anta.	Add.	No eff.	No eff.	Syn.	No eff.	No eff.	No eff.	No eff.	No eff.	No eff.	No eff.	Add.	No eff.	No eff.
Pictilisib		Syn.	Add.	Add.	Syn.	Add.	Add.	Syn.	Add.	Add.	Anta.	Anta.	Add.	Add.	Syn.	Syn.	Add.	Anta.	Anta.
BKM-120	PI3Ki	Syn.	Add.	Add.	Add.	Add.	Syn.	Syn.	Add.	Add.	Add.	Syn.	Add.	Add.	Syn.	Syn.	Add.	Add.	Add.
MK-1775		Syn.	Add.	Add.	Syn.	Syn.	Syn.	Syn.	Syn.	Add.	Add.	Add.	Syn.	Add.	Syn.	Syn.	Add.	Syn.	Add.
Velparib	Wee1 inhibitor	Syn.	Add.	Add.	Syn.	Syn.	Syn.	Add.	Syn.	Add.	Add.	Syn.	Add.	Syn.	Syn.	Add.	Add.	Syn.	Add.
Prednisolone	PARPi	Syn.	No eff.	NT	Syn.	No eff.	No eff.	No eff.	No eff.	No eff.	Anta.	No eff.	Add.	No eff.	No eff.	No eff.	No eff.	No eff.	Syn.
ATRA	CR agonist	Add.	Add.	NT	Syn.	No eff.	Syn.	No eff.	No eff.	No eff.	Anta.	No eff.	Add.	No eff.	No eff.	No eff.	No eff.	Syn.	Anta.
Cmpd H	CREBBPi	Syn.	NT	NT	Anta.	NT	Syn.	Syn.	NT	Add.	Add.	Anta.	Syn.	NT	Anta.	Add.	Syn.	Add.	Add.

EXEMPLARY EMBODIMENTS

[0461] Embodiment 1. A method for treatment of non-small cell lung cancer (NSCLC) comprising administering to a subject in need thereof

(a) a first agent in a therapeutically effective amount, wherein the first agent comprises an EZH2 inhibitor, and

(b) one or more second agents in a therapeutically effective amount.

[0462] Embodiment 2. The method of Embodiment 1, wherein the EZH2 inhibitor is tazemetostat or a pharmaceutically acceptable salt thereof.

[0463] Embodiment 3. The method of Embodiment 1, wherein the therapeutically effective amount of the EZH2 inhibitor is between about 100 mg and about 1600 mg, inclusive of the endpoints.

[0464] Embodiment 4. The method of Embodiment 3, wherein the therapeutically effective amount of the EZH2 inhibitor is about 100 mg, about 200 mg, about 400 mg, about 800 mg, or about 1600 mg.

[0465] Embodiment 5. The method of Embodiment 4, wherein the therapeutically effective amount of the EZH2 inhibitor is about 800 mg.

[0466] Embodiment 6. The method of Embodiment 2, wherein the therapeutically effective amount of tazemetostat or a pharmaceutically acceptable salt thereof is between about 100 mg and about 1600 mg, inclusive of the endpoints.

[0467] Embodiment 7. The method of Embodiment 6, wherein the therapeutically effective amount of tazemetostat or a pharmaceutically acceptable salt thereof is about 100 mg, about 200 mg, about 400 mg, about 800 mg, or about 1600 mg.

[0468] Embodiment 8. The method of Embodiment 7, wherein the therapeutically effective amount of tazemetostat or a pharmaceutically acceptable salt thereof is about 800 mg.

[0469] Embodiment 9. The method of any one of the preceding Embodiments, wherein the therapeutically effective amount of the EZH2 inhibitor is administered twice per day (BID).

[0470] Embodiment 10. The method of any one of the preceding Embodiments, wherein the therapeutically effective amount of the EZH2 inhibitor is administered orally.

[0471] Embodiment 11. The method of Embodiment 10, wherein the therapeutically effective amount of the EZH2 inhibitor is administered as a capsule or tablet.

[0472] Embodiment 12. A method of inhibiting or decreasing growth, viability, survival, or proliferation of a cancer cell comprising contacting the cell with

- (a) an effective amount of EZH2 inhibitor, and
- (b) one or more second agents.

[0473] Embodiment 13. The method of Embodiment 12, wherein the cancer cell is a non-small cell lung cancer (NSCLC) cell.

[0474] Embodiment 14. The method of Embodiment 12 or 13, wherein the EZH2 inhibitor is tazemetostat or a pharmaceutically acceptable salt thereof.

[0475] Embodiment 15. The method of any one of Embodiments 12-14, wherein the effective amount of the EZH2 inhibitor is an amount sufficient to inhibit or decrease growth, viability, survival, or proliferation of the non-small cell lung cancer cell by at least 50%.

[0476] Embodiment 16. The method of any one of Embodiments 12-14, wherein the effective amount of the EZH2 inhibitor is an amount sufficient to inhibit or decrease growth, viability, survival, or proliferation of the non-small cell lung cancer cell by at least 70%.

[0477] Embodiment 17. The method of any one of Embodiments 12-14, wherein the effective amount of the EZH2 inhibitor is an amount sufficient to inhibit or decrease growth, viability, survival, or proliferation of the non-small cell lung cancer cell by at least 90%.

[0478] Embodiment 18. The method of any one of Embodiments 12-14, wherein the contacting is in vitro or ex vivo.

[0479] Embodiment 19. The method of any one of Embodiments 12-14, wherein the contacting is in vivo by administering the EZH2 inhibitor and the one or more second agents to a subject harboring the cancer cell.

[0480] Embodiment 20. The method of any one of Embodiments 1-19, wherein the one or more second agents comprise a standard of care agent.

[0481] Embodiment 21. The method of any one of Embodiments 1-19, wherein the one or more second agents comprise an alkylating agent or an alkylating-like agent, an antineoplastic agent, a mitotic inhibitor, a tubulin polymerization inhibitor, an antimetabolite, a DNA methyltransferase (DNMT) inhibitor, a histone deacetylase (HDAC) inhibitor, a topoisomerase inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, an inhibitor of EGFR and ErbB2, an inhibitor of EGFR and human epidermal growth factor receptor 2 (Her2), an anaplastic lymphoma kinase (ALK) inhibitor, an inhibitor of ALK and ROS1, an inhibitor of ALK and EGFR, cyclin dependent kinase (CDK) 4/6 inhibitor, a mitogen-activated protein kinase (MEK) inhibitor, a BRAF inhibitor, a phosphoinositide 3-kinase (PI3K) inhibitor, a Wee1 inhibitor, a poly

(ADP-ribose) polymerase (PARP) inhibitor, a glucocorticoid receptor agonist, a retinoic acid receptor agonist, a CBP/p300 inhibitor, or a combination thereof.

[0482] Embodiment 22. The method of Embodiment 21, wherein the one or more second agents comprise an alkylating agent or an alkylating-like agent.

[0483] Embodiment 23. The method of Embodiment 22, wherein the one or more second agents comprise cisplatin.

[0484] Embodiment 24. The method of Embodiment 21, wherein the one or more second agents comprise an antineoplastic agent.

[0485] Embodiment 25. The method of Embodiment 24, wherein the one or more second agents comprise oxaliplatin.

[0486] Embodiment 26. The method of Embodiment 21, wherein the one or more second agents comprise an mitotic inhibitor.

[0487] Embodiment 27. The method of Embodiment 26, wherein the one or more second agents comprise paclitaxel, docetaxel, vinblastine, or a combination thereof.

[0488] Embodiment 28. The method of Embodiment 21, wherein the one or more second agents comprise a tubulin polymerization inhibitor.

[0489] Embodiment 29. The method of Embodiment 28, wherein the one or more second agents comprise vinorelbine.

[0490] Embodiment 30. The method of Embodiment 21, wherein the one or more second agents comprise an antimetabolite.

[0491] Embodiment 31. The method of Embodiment 30, wherein the one or more second agents comprise gemcitabine.

[0492] Embodiment 32. The method of Embodiment 30, wherein the one or more second agents comprise an antimetabolite of the folate type.

[0493] Embodiment 33. The method of Embodiment 32, wherein the one or more second agents comprise methotrexate, pemetrexed, or a combination thereof.

[0494] Embodiment 34. The method of Embodiment 21, wherein the one or more second agents comprise a DNA methyltransferase (DNMT) inhibitor.

[0495] Embodiment 35. The method of Embodiment 34, wherein the one or more second agents comprise decitabine, azacitidine, or a combination thereof.

- [0496] Embodiment 36. The method of Embodiment 21, wherein the one or more second agents comprise a histone deacetylase (HDAC) inhibitor.
- [0497] Embodiment 37. The method of Embodiment 36, wherein the one or more second agents comprise vorinostat.
- [0498] Embodiment 38. The method of Embodiment 21, wherein the one or more second agents comprise a topoisomerase inhibitor.
- [0499] Embodiment 39. The method of Embodiment 38, wherein the one or more second agents comprise irinotecan, etoposide, or a combination thereof.
- [0500] Embodiment 40. The method of Embodiment 21, wherein the one or more second agents comprise an epidermal growth factor receptor (EGFR) inhibitor.
- [0501] Embodiment 41. The method of Embodiment 40, wherein the one or more second agents comprise erlotinib, gefitinib, AZD9291, or a combination thereof.
- [0502] Embodiment 42. The method of Embodiment 21, wherein the one or more second agents comprise an inhibitor of EGFR and ErbB2.
- [0503] Embodiment 43. The method of Embodiment 42, wherein the one or more second agents comprise lapatinib.
- [0504] Embodiment 44. The method of Embodiment 21, wherein the one or more second agents comprise an inhibitor of EGFR and human epidermal growth factor receptor 2 (Her2).
- [0505] Embodiment 45. The method of Embodiment 44, wherein the one or more second agents comprise afatinib.
- [0506] Embodiment 46. The method of Embodiment 21, wherein the one or more second agents comprise an anaplastic lymphoma kinase (ALK) inhibitor.
- [0507] Embodiment 47. The method of Embodiment 46, wherein the one or more second agents comprise ceritinib.
- [0508] Embodiment 48. The method of Embodiment 21, wherein the one or more second agents comprise an inhibitor of ALK and ROS1.
- [0509] Embodiment 49. The method of Embodiment 48, wherein the one or more second agents comprise crizotinib.
- [0510] Embodiment 50. The method of Embodiment 21, wherein the one or more second agents comprise an inhibitor of ALK and EGFR.

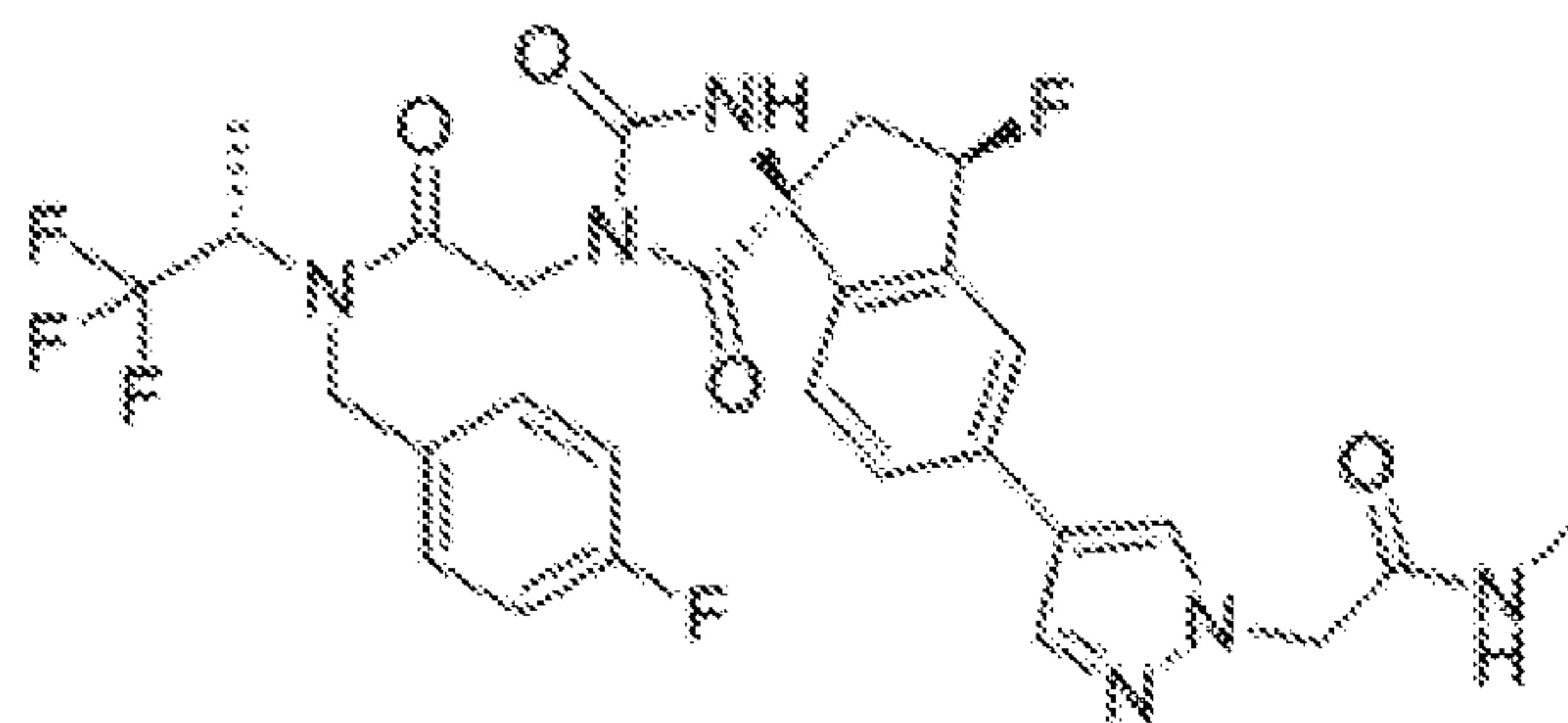
- [0511] Embodiment 51. The method of Embodiment 50, wherein the one or more second agents comprise brigatinib.
- [0512] Embodiment 52. The method of Embodiment 21, wherein the one or more second agents comprise a cyclin dependent kinase (CDK) 4/6 inhibitor.
- [0513] Embodiment 53. The method of Embodiment 52, wherein the one or more second agents comprise abemaciclib, palbociclib, ribociclib, or a combination thereof.
- [0514] Embodiment 54. The method of Embodiment 21, wherein the one or more second agents comprise a mitogen-activated protein kinase (MEK) inhibitor.
- [0515] Embodiment 55. The method of Embodiment 54, wherein the one or more second agents comprise trametinib, selumetinib, or a combination thereof.
- [0516] Embodiment 56. The method of Embodiment 21, wherein the one or more second agents comprise a BRAF inhibitor.
- [0517] Embodiment 57. The method of Embodiment 56, wherein the one or more second agents comprise vemurafenib.
- [0518] Embodiment 58. The method of Embodiment 21, wherein the one or more second agents comprise a phosphoinositide 3-kinase (PI3K) inhibitor.
- [0519] Embodiment 59. The method of Embodiment 58, wherein the one or more second agents comprise pictilisib, BKM-120, or a combination thereof.
- [0520] Embodiment 60. The method of Embodiment 21, wherein the one or more second agents comprise a Wee1 inhibitor.
- [0521] Embodiment 61. The method of Embodiment 60, wherein the one or more second agents comprise MK-1775.
- [0522] Embodiment 62. The method of Embodiment 21, wherein the one or more second agents comprise a poly (ADP-ribose) polymerase (PARP) inhibitor.
- [0523] Embodiment 63. The method of Embodiment 62, wherein the one or more second agents comprise veliparib.
- [0524] Embodiment 64. The method of Embodiment 21, wherein the one or more second agents comprise a glucocorticoid receptor agonist.
- [0525] Embodiment 65. The method of Embodiment 64, wherein the one or more second agents comprise prednisolone.

[0526] Embodiment 66. The method of Embodiment 21, wherein the one or more second agents comprise a retinoic acid receptor agonist.

[0527] Embodiment 67. The method of Embodiment 66, wherein the one or more second agents comprise ATRA.

[0528] Embodiment 68. The method of Embodiment 21, wherein the one or more second agents comprise a CBP/p300 inhibitor.

[0529] Embodiment 69. The method of Embodiment 68, wherein the one or more second agents comprise Compound H:



(Compound H),

or a pharmaceutically acceptable salt thereof.

[0530] Embodiment 70. The method of any one of the preceding Embodiments, wherein the EZH2 inhibitor and the one or more second agents are administered sequentially.

[0531] Embodiment 71. The method of any one of the preceding Embodiments, wherein the EZH2 inhibitor is administered prior to the one or more second agents.

[0532] Embodiment 72. The method of any one of the preceding Embodiments, wherein the one or more second agents are administered prior to the EZH2 inhibitor.

[0533] Embodiment 73. The method of any one of the preceding Embodiments, wherein the EZH2 inhibitor is a pharmaceutically acceptable salt of tazemetostat.

[0534] All publications and patent documents cited herein are incorporated herein by reference as if each such publication or document was specifically and individually indicated to be incorporated herein by reference. Citation of publications and patent documents is not intended as an admission that any is pertinent prior art, nor does it constitute any admission as to the contents or date of the same. The invention having now been described by way of written description, those of skill in the art will recognize that the invention can be practiced in a variety of embodiments and that the foregoing description and examples below are for purposes of illustration and not limitation of the claims that follow. Where names of cell lines or genes are used, abbreviations and names conform to the nomenclature of the American Type Culture Collection (ATCC) or the National Center for Biotechnology Information (NCBI), unless otherwise noted or evident from the context.

[0535] The invention can be embodied in other specific forms without departing from the spirit or essential characteristics thereof. The foregoing embodiments are therefore to be considered in all respects illustrative rather than limiting on the invention described herein. Scope of the invention is thus indicated by the appended claims rather than by the foregoing description, and all changes that come within the meaning and range of equivalency of the claims are intended to be embraced therein.

CLAIMS

1. A method for treatment of non-small cell lung cancer (NSCLC) comprising administering to a subject in need thereof
 - (a) a first agent in a therapeutically effective amount, wherein the first agent comprises an EZH2 inhibitor, and
 - (b) one or more second agents in a therapeutically effective amount.
2. The method of claim 1, wherein the EZH2 inhibitor is tazemetostat or a pharmaceutically acceptable salt thereof.
3. The method of claim 1, wherein the therapeutically effective amount of the EZH2 inhibitor is between about 100 mg and about 1600 mg, inclusive of the endpoints.
4. The method of claim 3, wherein the therapeutically effective amount of the EZH2 inhibitor is about 100 mg, about 200 mg, about 400 mg, about 800 mg, or about 1600 mg.
5. The method of claim 4, wherein the therapeutically effective amount of the EZH2 inhibitor is about 800 mg.
6. The method of claim 2, wherein the therapeutically effective amount of tazemetostat or a pharmaceutically acceptable salt thereof is between about 100 mg and about 1600 mg, inclusive of the endpoints.
7. The method of claim 6, wherein the therapeutically effective amount of tazemetostat or a pharmaceutically acceptable salt thereof is about 100 mg, about 200 mg, about 400 mg, about 800 mg, or about 1600 mg.
8. The method of claim 7, wherein the therapeutically effective amount of tazemetostat or a pharmaceutically acceptable salt thereof is about 800 mg.

9. The method of any one of the preceding claims, wherein the therapeutically effective amount of the EZH2 inhibitor is administered twice per day (BID).
10. The method of any one of the preceding claims, wherein the therapeutically effective amount of the EZH2 inhibitor is administered orally.
11. The method of claim 10, wherein the therapeutically effective amount of the EZH2 inhibitor is administered as a capsule or tablet.
12. A method of inhibiting or decreasing growth, viability, survival, or proliferation of a cancer cell comprising contacting the cell with
 - (a) an effective amount of EZH2 inhibitor, and
 - (b) one or more second agents.
13. The method of claim 12, wherein the cancer cell is a non-small cell lung cancer (NSCLC) cell.
14. The method of claim 12 or 13, wherein the EZH2 inhibitor is tazemetostat or a pharmaceutically acceptable salt thereof.
15. The method of any one of claims 12-14, wherein the effective amount of the EZH2 inhibitor is an amount sufficient to inhibit or decrease growth, viability, survival, or proliferation of the non-small cell lung cancer cell by at least 50%.
16. The method of any one of claims 12-14, wherein the effective amount of the EZH2 inhibitor is an amount sufficient to inhibit or decrease growth, viability, survival, or proliferation of the non-small cell lung cancer cell by at least 70%.
17. The method of any one of claims 12-14, wherein the effective amount of the EZH2 inhibitor is an amount sufficient to inhibit or decrease growth, viability, survival, or proliferation of the non-small cell lung cancer cell by at least 90%.

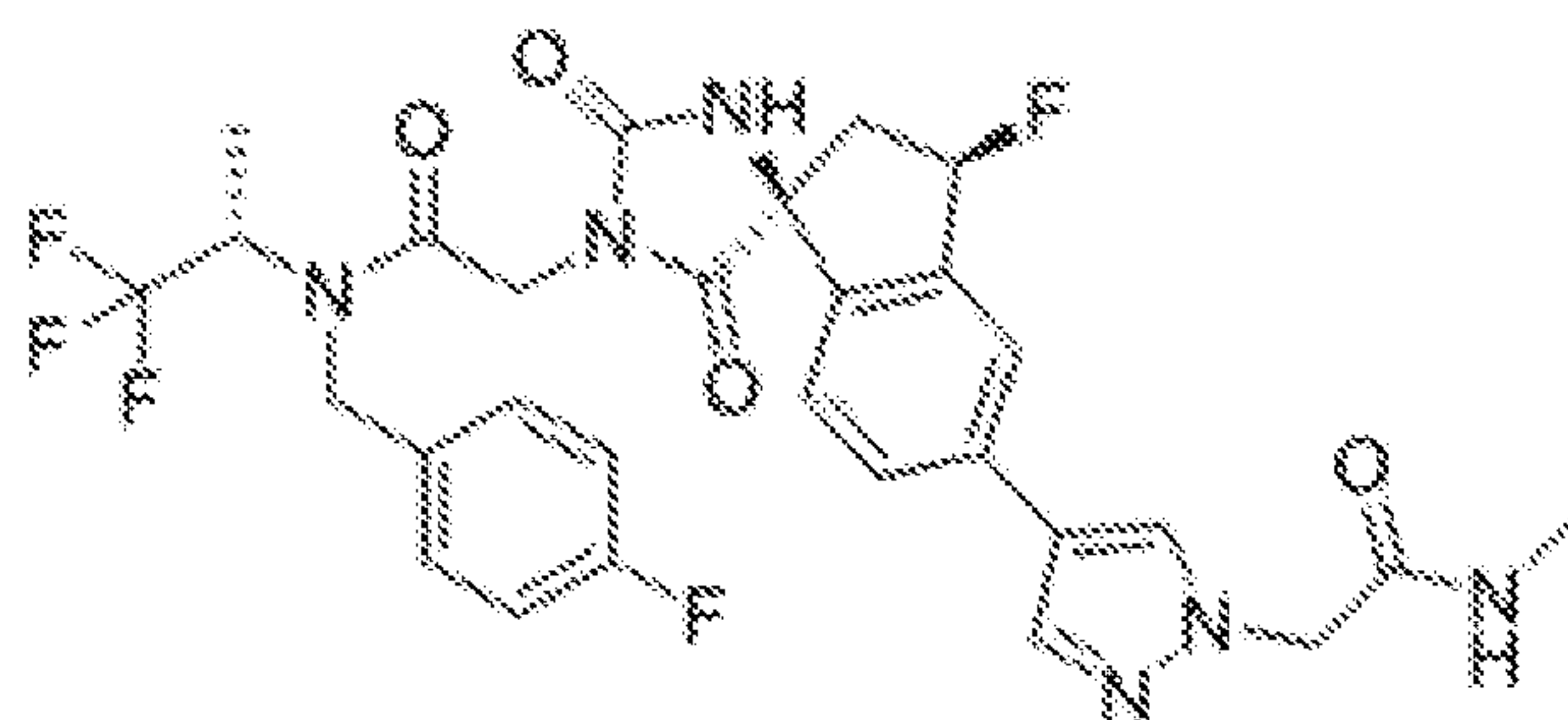
18. The method of any one of claims 12-14, wherein the contacting is in vitro or ex vivo.
19. The method of any one of claims 12-14, wherein the contacting is in vivo by administering the EZH2 inhibitor and the one or more second agents to a subject harboring the cancer cell.
20. The method of any one of claims 1-19, wherein the one or more second agents comprise a standard of care agent.
21. The method of any one of claims 1-19, wherein the one or more second agents comprise an alkylating agent or an alkylating-like agent, an antineoplastic agent, a mitotic inhibitor, a tubulin polymerization inhibitor, an antimetabolite, a DNA methyltransferase (DNMT) inhibitor, a histone deacetylase (HDAC) inhibitor, a topoisomerase inhibitor, an epidermal growth factor receptor (EGFR) inhibitor, an inhibitor of EGFR and ErbB2, an inhibitor of EGFR and human epidermal growth factor receptor 2 (Her2), an anaplastic lymphoma kinase (ALK) inhibitor, an inhibitor of ALK and ROS1, an inhibitor of ALK and EGFR, cyclin dependent kinase (CDK) 4/6 inhibitor, a mitogen-activated protein kinase (MEK) inhibitor, a BRAF inhibitor, a phosphoinositide 3-kinase (PI3K) inhibitor, a Wee1 inhibitor, a poly (ADP-ribose) polymerase (PARP) inhibitor, a glucocorticoid receptor agonist, a retinoic acid receptor agonist, a CBP/p300 inhibitor, or a combination thereof.
22. The method of claim 21, wherein the one or more second agents comprise an alkylating agent or an alkylating-like agent.
23. The method of claim 22, wherein the one or more second agents comprise cisplatin.
24. The method of claim 21, wherein the one or more second agents comprise an antineoplastic agent.
25. The method of claim 24, wherein the one or more second agents comprise oxaliplatin.

26. The method of claim 21, wherein the one or more second agents comprise an mitotic inhibitor.
27. The method of claim 26, wherein the one or more second agents comprise paclitaxel, docetaxel, vinblastine, or a combination thereof.
28. The method of claim 21, wherein the one or more second agents comprise a tubulin polymerization inhibitor.
29. The method of claim 28, wherein the one or more second agents comprise vinorelbine.
30. The method of claim 21, wherein the one or more second agents comprise an antimetabolite.
31. The method of claim 30, wherein the one or more second agents comprise gemcitabine.
32. The method of claim 30, wherein the one or more second agents comprise an antimetabolite of the folate type.
33. The method of claim 32, wherein the one or more second agents comprise methotrexate, pemetrexed, or a combination thereof.
34. The method of claim 21, wherein the one or more second agents comprise a DNA methyltransferase (DNMT) inhibitor.
35. The method of claim 34, wherein the one or more second agents comprise decitabine, azacitidine, or a combination thereof.
36. The method of claim 21, wherein the one or more second agents comprise a histone deacetylase (HDAC) inhibitor.

37. The method of claim 36, wherein the one or more second agents comprise vorinostat.
38. The method of claim 21, wherein the one or more second agents comprise a topoisomerase inhibitor.
39. The method of claim 38, wherein the one or more second agents comprise irinotecan, etoposide, or a combination thereof.
40. The method of claim 21, wherein the one or more second agents comprise an epidermal growth factor receptor (EGFR) inhibitor.
41. The method of claim 40, wherein the one or more second agents comprise erlotinib, gefitinib, AZD9291, or a combination thereof.
42. The method of claim 21, wherein the one or more second agents comprise an inhibitor of EGFR and ErbB2.
43. The method of claim 42, wherein the one or more second agents comprise lapatinib.
44. The method of claim 21, wherein the one or more second agents comprise an inhibitor of EGFR and human epidermal growth factor receptor 2 (Her2).
45. The method of claim 44, wherein the one or more second agents comprise afatinib.
46. The method of claim 21, wherein the one or more second agents comprise an anaplastic lymphoma kinase (ALK) inhibitor.
47. The method of claim 46, wherein the one or more second agents comprise ceritinib.
48. The method of claim 21, wherein the one or more second agents comprise an inhibitor of ALK and ROS1.

49. The method of claim 48, wherein the one or more second agents comprise crizotinib.
50. The method of claim 21, wherein the one or more second agents comprise an inhibitor of ALK and EGFR.
51. The method of claim 50, wherein the one or more second agents comprise brigatinib.
52. The method of claim 21, wherein the one or more second agents comprise a cyclin dependent kinase (CDK) 4/6 inhibitor.
53. The method of claim 52, wherein the one or more second agents comprise abemaciclib, palbociclib, ribociclib, or a combination thereof.
54. The method of claim 21, wherein the one or more second agents comprise a mitogen-activated protein kinase (MEK) inhibitor.
55. The method of claim 54, wherein the one or more second agents comprise trametinib, selumetinib, or a combination thereof.
56. The method of claim 21, wherein the one or more second agents comprise a BRAF inhibitor.
57. The method of claim 56, wherein the one or more second agents comprise vemurafenib.
58. The method of claim 21, wherein the one or more second agents comprise a phosphoinositide 3-kinase (PI3K) inhibitor.
59. The method of claim 58, wherein the one or more second agents comprise pictilisib, BKM-120, or a combination thereof.

60. The method of claim 21, wherein the one or more second agents comprise a Wee1 inhibitor.
61. The method of claim 60, wherein the one or more second agents comprise MK-1775.
62. The method of claim 21, wherein the one or more second agents comprise a poly (ADP-ribose) polymerase (PARP) inhibitor.
63. The method of claim 62, wherein the one or more second agents comprise veliparib.
64. The method of claim 21, wherein the one or more second agents comprise a glucocorticoid receptor agonist.
65. The method of claim 64, wherein the one or more second agents comprise prednisolone.
66. The method of claim 21, wherein the one or more second agents comprise a retinoic acid receptor agonist.
67. The method of claim 66, wherein the one or more second agents comprise ATRA.
68. The method of claim 21, wherein the one or more second agents comprise a CBP/p300 inhibitor.
69. The method of claim 68, wherein the one or more second agents comprise Compound H:



(Compound H),

or a pharmaceutically acceptable salt thereof.

70. The method of any one of the preceding claims, wherein the EZH2 inhibitor and the one or more second agents are administered sequentially.
71. The method of any one of the preceding claims, wherein the EZH2 inhibitor is administered prior to the one or more second agents.
72. The method of any one of the preceding claims, wherein the one or more second agents are administered prior to the EZH2 inhibitor.
73. The method of any one of the preceding claims, wherein the EZH2 inhibitor is a pharmaceutically acceptable salt of tazemetostat.

FIGURE 1

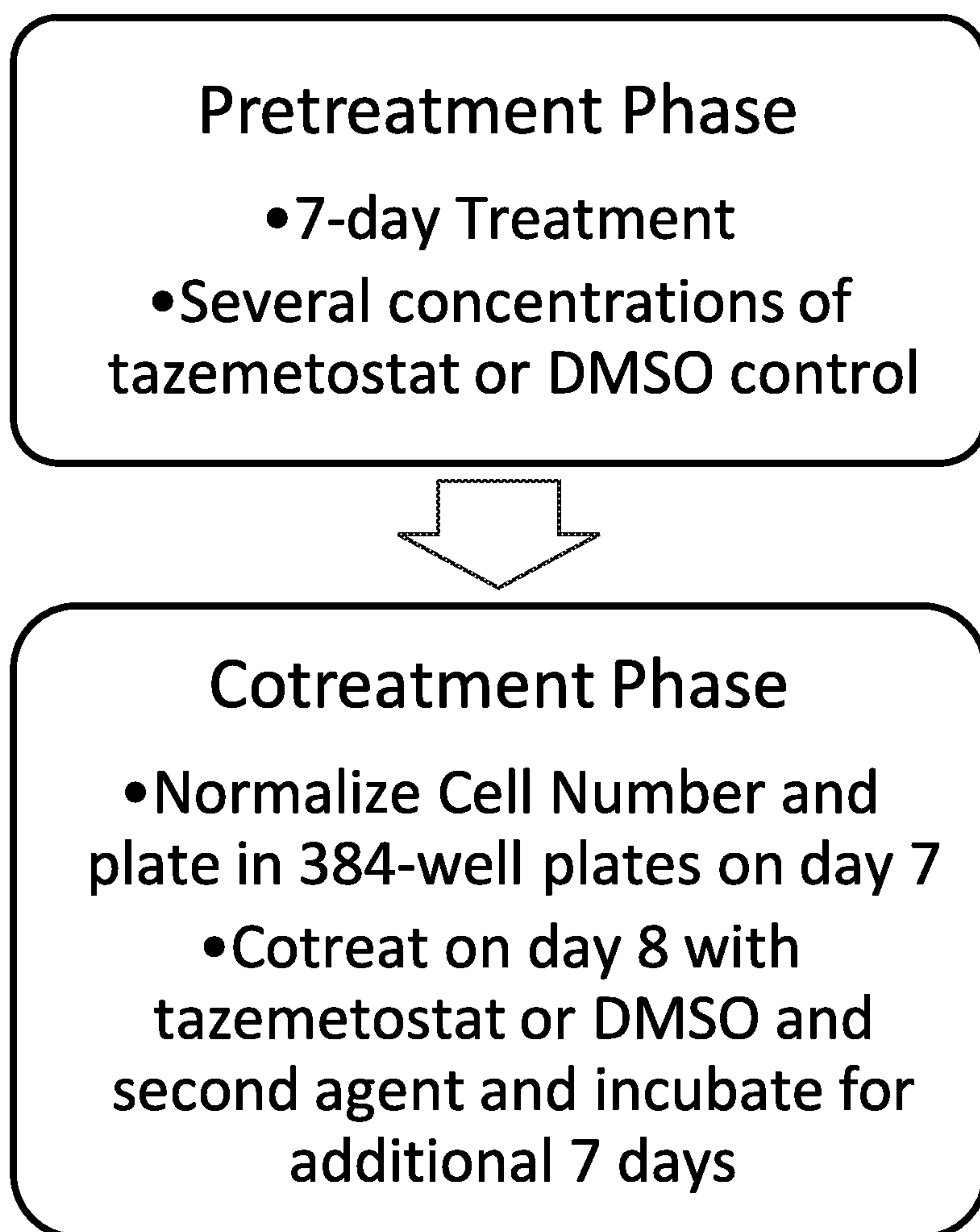
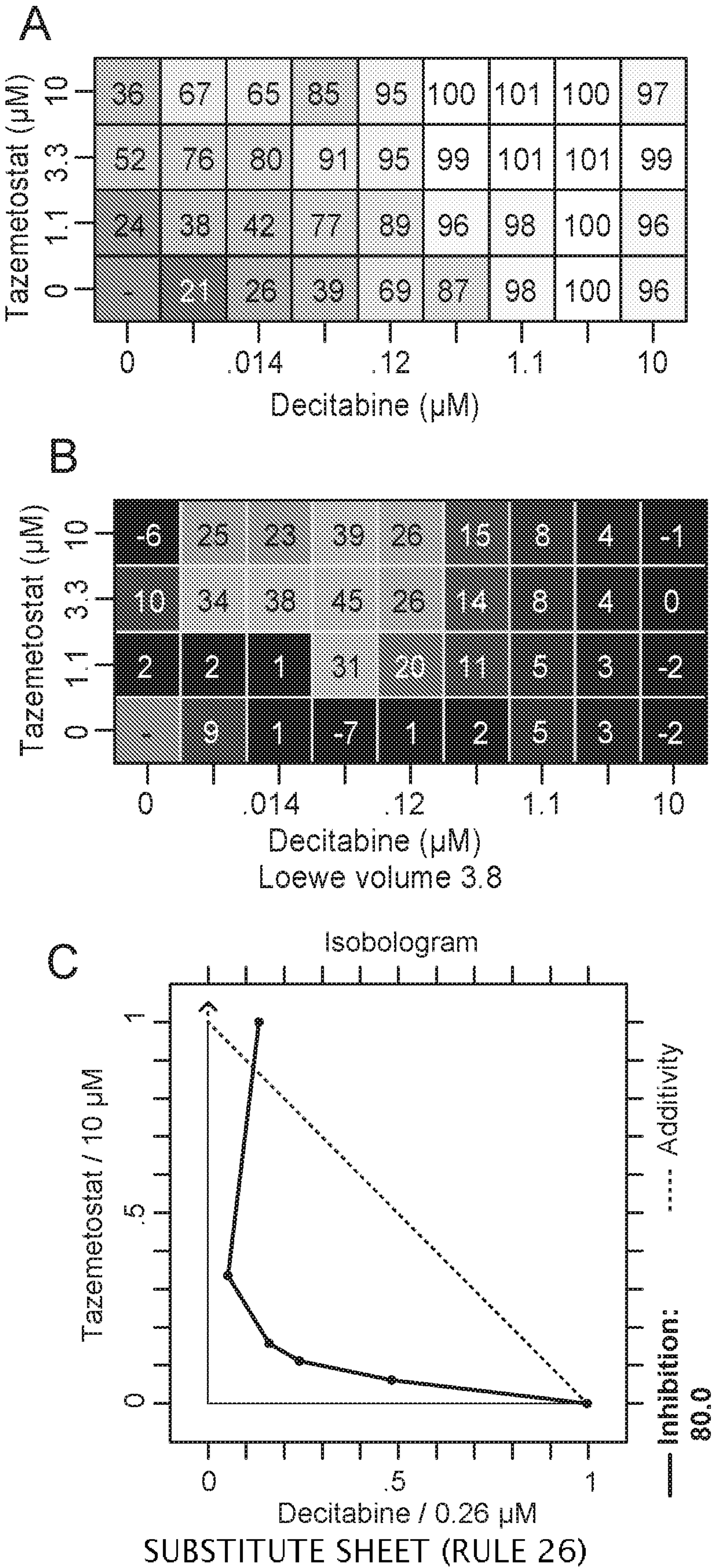
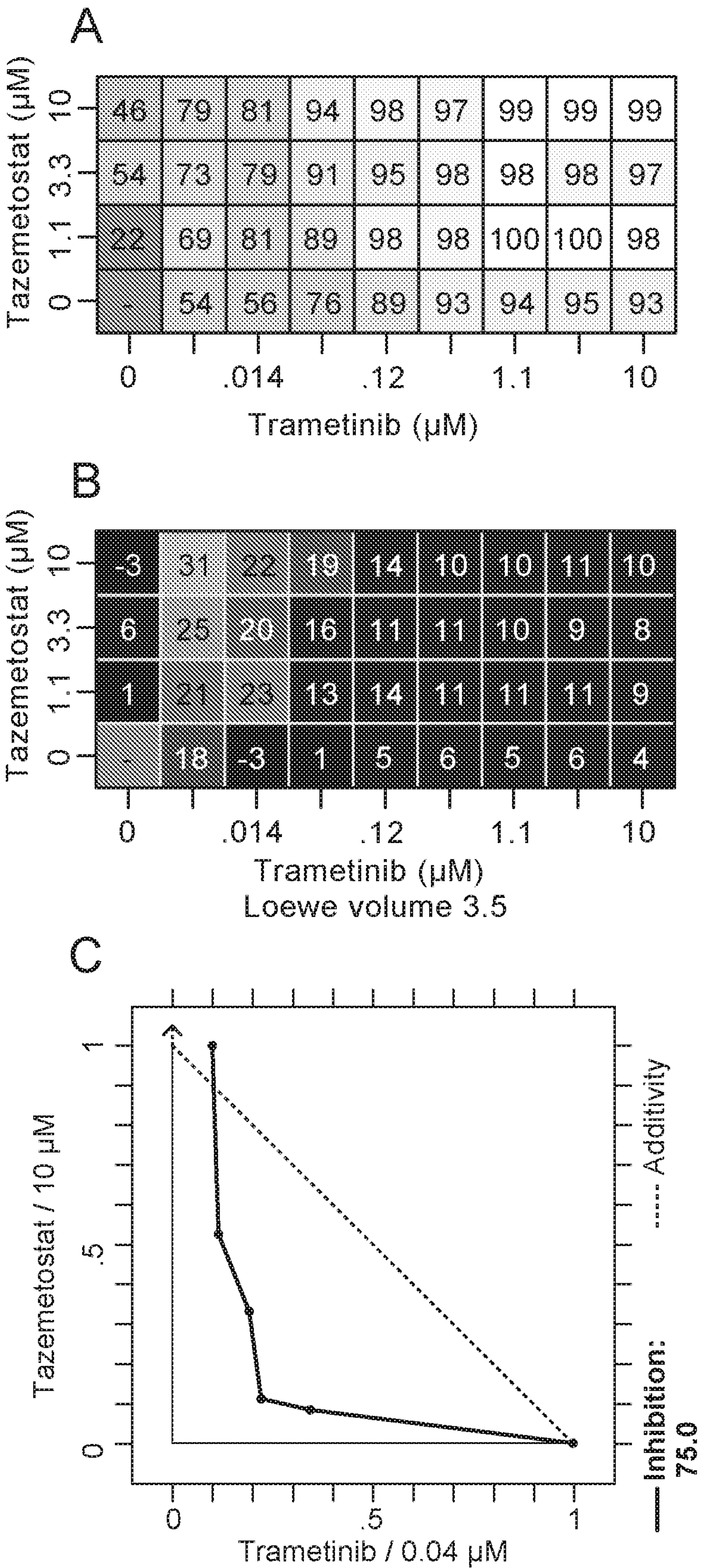


FIGURE 2



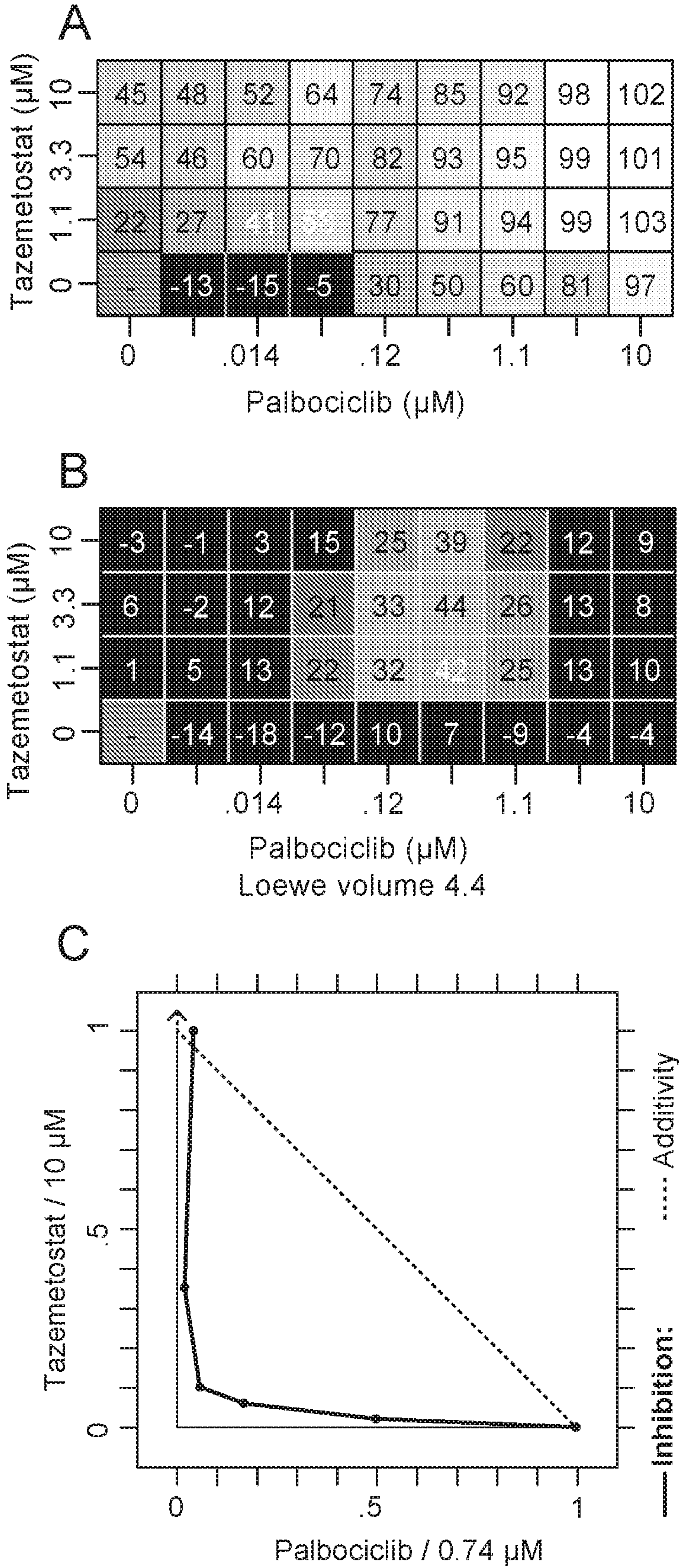
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FIGURE 3



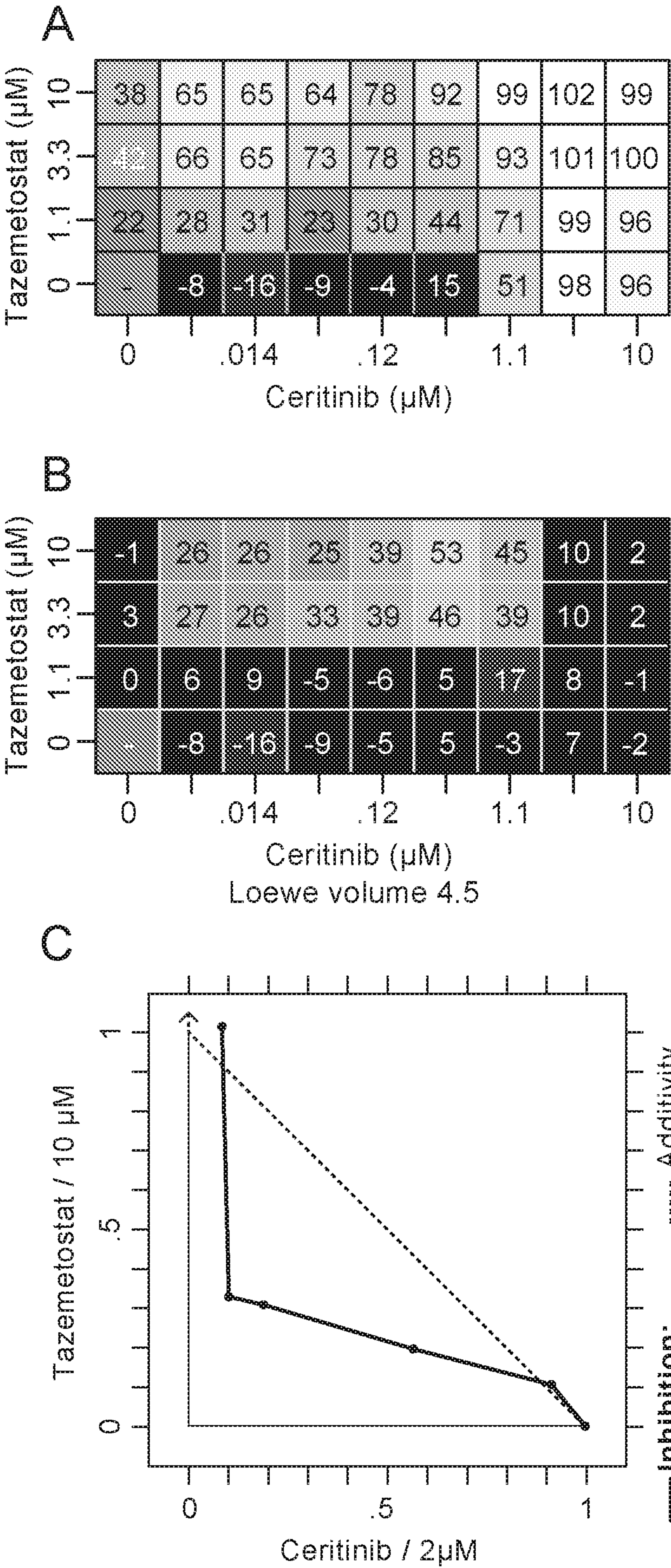
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FIGURE 4



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FIGURE 5



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FIGURE 6

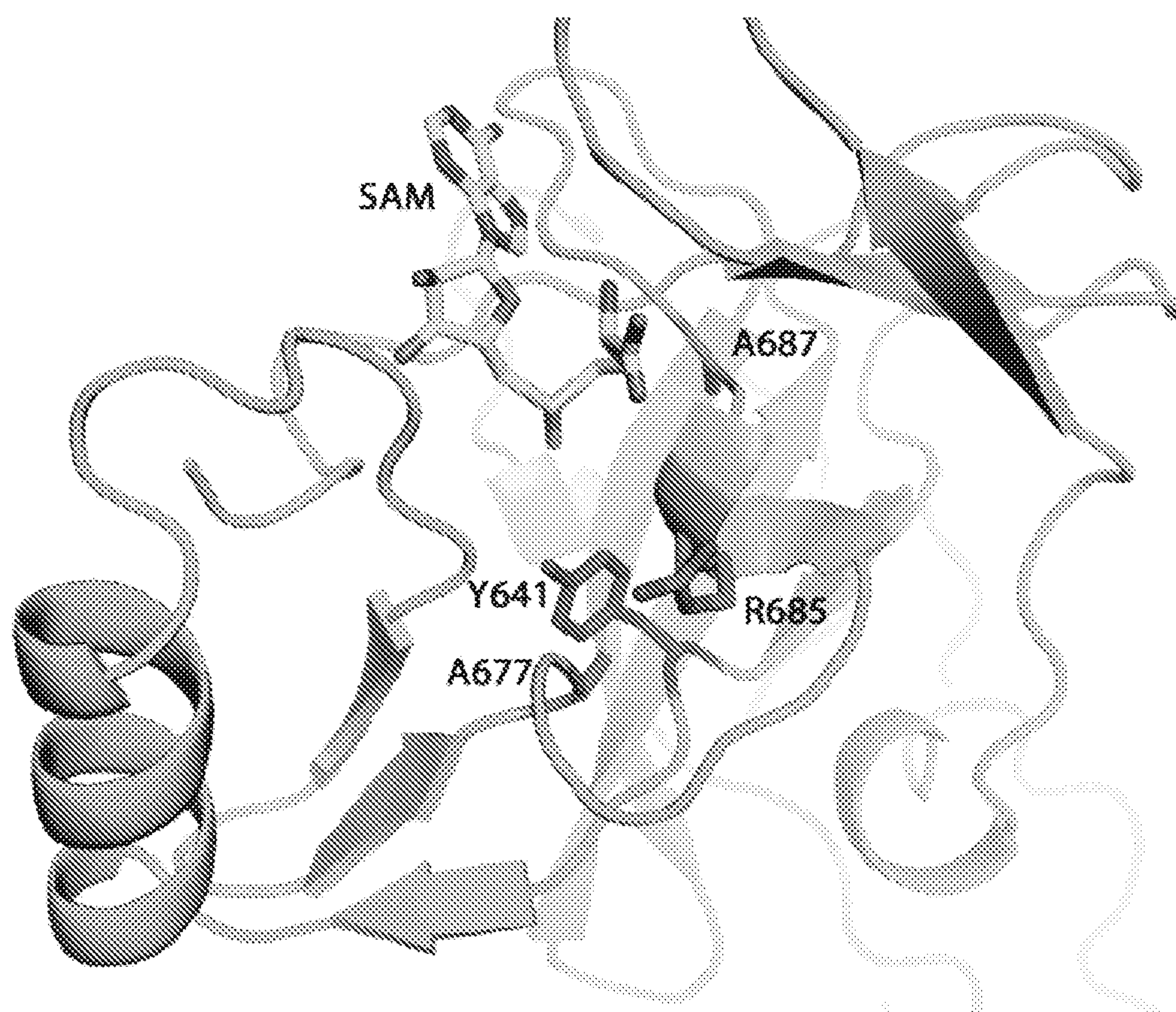
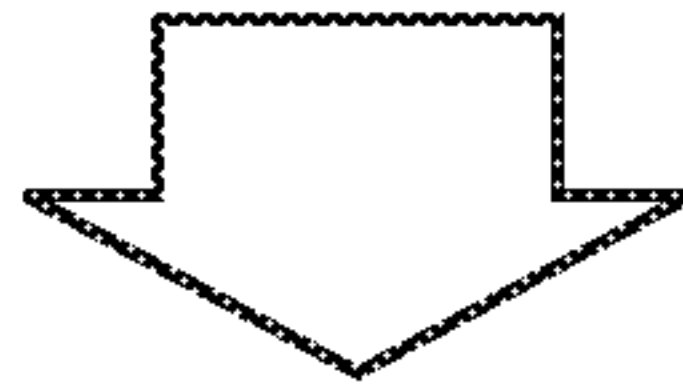


FIGURE 1

Pretreatment Phase

- 7-day Treatment
- Several concentrations of tazemetostat or DMSO control



Cotreatment Phase

- Normalize Cell Number and plate in 384-well plates on day 7
- Cotreat on day 8 with tazemetostat or DMSO and second agent and incubate for additional 7 days