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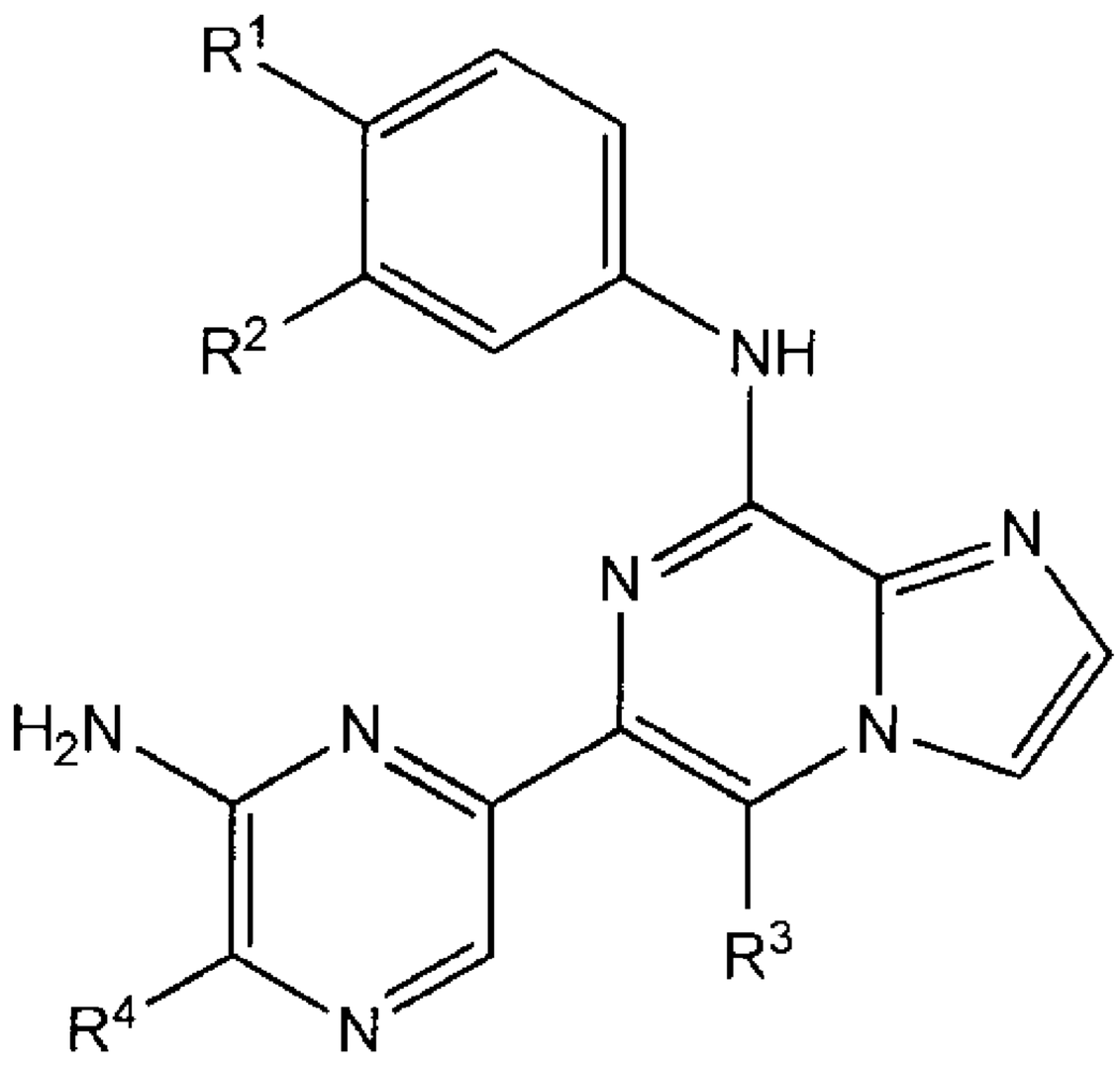
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(54) Title: SYK INHIBITORS



Formula I

(57) Abrégé/Abstract:
The present disclosure relates to compounds that are Syk inhibitors. In particular embodiments, the structure of the compounds is given by Formula I: (see formula I) wherein R^1, R^2, R^3, and R^4 are as described herein. The present disclosure further provides pharmaceutical compositions that include a compound of Formula I, or pharmaceutically acceptable salts thereof, and methods of using these compounds and compositions for Syk inhibition.

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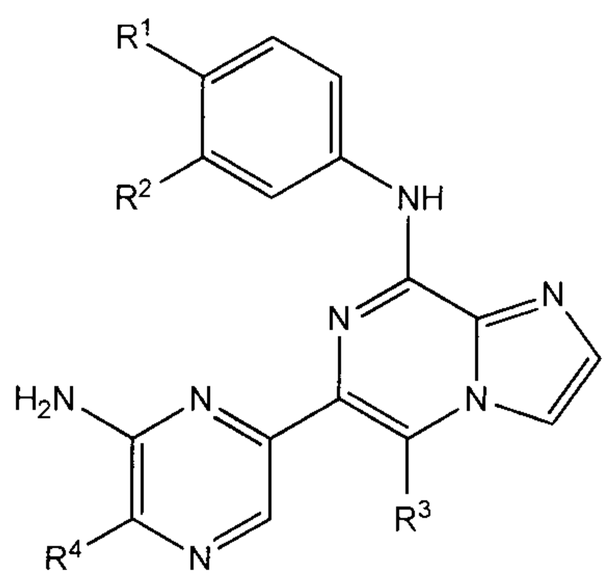
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ABSTRACT

The present disclosure relates to compounds that are Syk inhibitors. In particular embodiments, the structure of the compounds is given by Formula I:



Formula I

wherein R^1, R^2, R^3, and R^4 are as described herein. The present disclosure further provides pharmaceutical compositions that include a compound of Formula I, or pharmaceutically acceptable salts thereof, and methods of using these compounds and compositions for Syk inhibition.

SYK INHIBITORS

FIELD

The present disclosure relates to compounds that are SYK inhibitors. The disclosure also relates to methods for preparation of the compounds and to pharmaceutical compositions comprising such compounds.

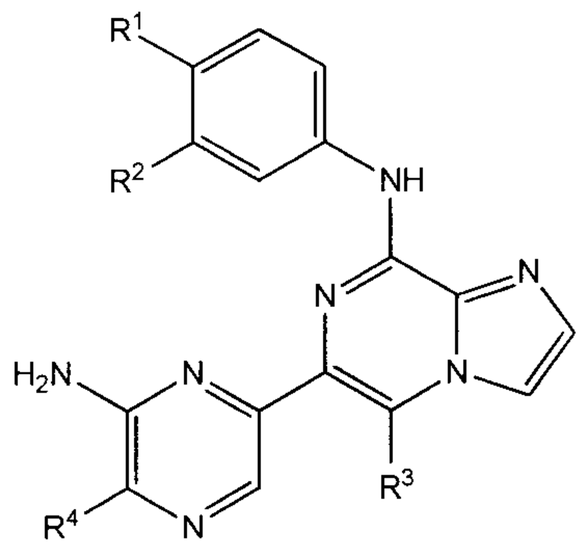
BACKGROUND

Protein kinases, the largest family of human enzymes, encompass well over 500 proteins. Spleen Tyrosine Kinase (Syk) is a member of the Syk family of tyrosine kinases, and is a regulator of early B-cell development as well as mature B-cell activation, signaling, and survival.

The inhibition of Syk activity may be useful for the treatment of allergic disorders, autoimmune diseases and inflammatory diseases such as: SLE, rheumatoid arthritis, multiple vasculitides, idiopathic thrombocytopenic purpura (ITP), myasthenia gravis, allergic rhinitis, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDs) and asthma. In addition, Syk has been reported to play an important role in ligand-independent tonic signaling through the B-cell receptor, known to be an important survival signal in B-cells. Thus, inhibition of Syk activity may also be useful in treating certain types of cancer, including B-cell lymphoma and leukemia. U.S. Patent Numbers 8,455,493 and 8,440,667 disclose Syk inhibitors, the disclosures of which are hereby incorporated by reference in their entirety. Syk is also a known inhibitor of apoptosis in lymphoma B-cells. Defective apoptosis contributes to the pathogenesis and drug resistance of human leukemias and lymphomas. There is a continued need to provide compounds that are effective Syk inhibitors, including compounds having desirable pharmacokinetic properties, and which may therefore be useful as therapeutics for potentially treating cancers and other diseases.

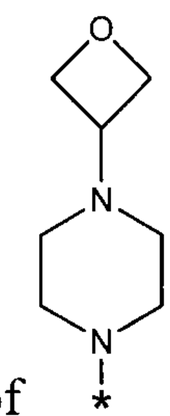
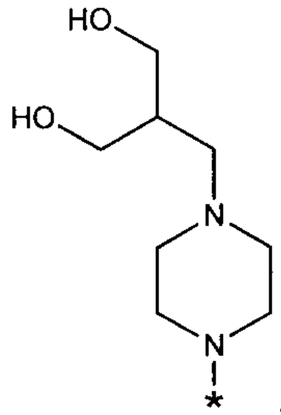
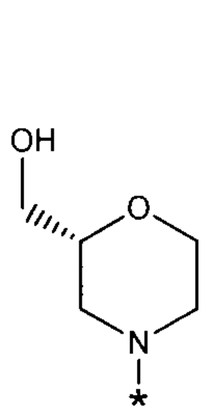
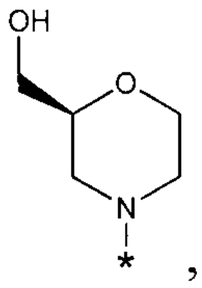
SUMMARY

Accordingly, the present disclosure provides compounds that function as Syk inhibitors. In one embodiment, the disclosure provides a compound of Formula I:



Formula I

or a pharmaceutically acceptable salt, pharmaceutically acceptable co-crystal, pharmaceutically acceptable ester, stereoisomer, mixture of stereoisomers or tautomer thereof, wherein:

R^1 is selected from the group consisting of  ,  ,  , and  , wherein * indicates the carbon atom of the indicated phenyl ring of Formula I to which R^1 is attached;

R^2 is H or 2-hydroxyethoxyl;

R^3 is H or methyl; and

R^4 is H or methyl.

Within each of the embodiments described herein comprising a compound of Formula I, there is a further embodiment wherein each of R^2, R^3, and R^4 is H. Within each of the embodiments described herein comprising a compound of Formula I, there is a another embodiment wherein R^2 is H, R^3 is methyl, and R^4 is H. Within each of the embodiments described herein comprising a compound of Formula I, there is also another embodiment wherein R^2 is H, R^3 is H, and R^4 is methyl.

Within each of the embodiments described herein comprising a compound of Formula I, there is still another embodiment wherein R^2 is 2-hydroxyethoxyl, R^3 is methyl, and R^4 is H. Within each of the embodiments described herein comprising a compound of Formula I, there is still another embodiment wherein R^2 is 2-hydroxyethoxyl, R^3 is methyl, and R^4 is H. Within each of the embodiments described herein comprising a compound of Formula I, there is still further embodiment wherein R^2 is 2-hydroxyethoxyl, R^3 is H, and R^4 is methyl.

In some embodiments, the disclosure provides pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, and a pharmaceutically acceptable vehicle. In some embodiments, the disclosure provides pharmaceutical compositions comprising a compound of Formula II, or a pharmaceutically acceptable salt or co-crystal thereof, and a pharmaceutically acceptable vehicle.

In some embodiments, the disclosure provides pharmaceutical compositions comprising a compound of Formula I, or a pharmaceutically acceptable salt, pharmaceutically acceptable co-crystal, pharmaceutically acceptable ester, stereoisomer, mixture of stereoisomers or tautomer thereof, and at least one pharmaceutically acceptable vehicle. In other embodiments, the disclosure provides pharmaceutical compositions comprising a compound of Formula II, shown below, or a pharmaceutically acceptable salt, pharmaceutically acceptable co-crystal, pharmaceutically acceptable ester, stereoisomer, mixture of stereoisomers or tautomer thereof, and at least one pharmaceutically acceptable vehicle. Examples of pharmaceutically acceptable vehicle may be selected from carriers and other excipients, adjuvants and the like.

Also provided is a method of inhibiting kinase activity of a Syk kinase polypeptide. In some embodiments, this comprises contacting the polypeptide with a compound of Formula I or a pharmaceutically acceptable salt, pharmaceutically acceptable co-crystal, pharmaceutically acceptable ester, stereoisomer, mixture of stereoisomers or tautomer thereof. In other embodiments, this comprises contacting the polypeptide with a compound of Formula II or a pharmaceutically acceptable salt, pharmaceutically acceptable co-crystal, pharmaceutically acceptable ester, stereoisomer, mixture of stereoisomers or tautomer thereof. In one aspect is provided a method of inhibiting kinase activity of a Syk kinase

polypeptide by contacting the polypeptide with a compound of Formula I or a pharmaceutically acceptable salt or co-crystal thereof. In another aspect is provided a method of inhibiting kinase activity of a Syk kinase polypeptide by contacting the polypeptide with a compound of Formula II or a pharmaceutically acceptable salt or co-crystal thereof.

Additional aspects and embodiments of this disclosure are described throughout.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is an XRPD Analysis of Mono MSA Salt Form I of the compound of Example 2.

FIG. 2 is an NMR Analysis of Mono MSA Salt Form I of the compound of Example 2.

FIG. 3 is a DSC Analysis of Mono MSA Salt Form I of the compound of Example 2.

FIG. 4 is a TGA Analysis of Mono MSA Salt Form I of the compound of Example 2.

FIG. 5 is an XRPD Analysis Mono MSA Salt Form II of the compound of Example 2.

FIG. 6 is an NMR Analysis Mono MSA Salt Form II of the compound of Example 2.

FIG. 7 is a DSC Analysis of Mono MSA Salt Form II of the compound of Example 2.

FIG. 8 is a TGA Analysis of Mono MSA Salt Form II of the compound of Example 2.

FIG. 9 is an XRPD Analysis of Succinate Form I of the compound of Example 2.

FIG. 10 is an NMR Analysis of Succinate Form I of the compound of Example 2.

FIG. 11 is a DSC Analysis of Succinate Form I of the compound of Example 2.

FIG. 12 is a TGA Analysis of Succinate Form I of the compound of Example 2.

FIG. 13 is an XRPD Analysis of Succinate Form II of the compound of Example 2.

FIG. 14 is an NMR Analysis of Succinate Form II of the compound of Example 2.

FIG. 15 is a DSC Analysis of Succinate Form II of the compound of Example 2.

FIG. 16 is a TGA Analysis of Succinate Form II of the compound of Example 2.

DETAILED DESCRIPTION

It has surprisingly been discovered that compounds of Formula I and Formula II, or pharmaceutically acceptable salts thereof, possess advantageous properties, making them attractive compounds for use as described herein. The compounds, in addition to being Syk inhibitors, possess desirable solubility and pharmacokinetic properties. These findings are particularly striking in view of the properties of comparable parameters of compounds of similar base structure.

The following description sets forth exemplary methods, parameters and the like. It should be recognized, however, that such description is not intended as a limitation on the scope of the present disclosure but is instead provided as a description of exemplary embodiments.

Also described for a compound of Formula I and a compound of Formula II are the pharmaceutically acceptable salts, pharmaceutically acceptable esters, pharmaceutically acceptable solvates, hydrates, isomers (including optical isomers, racemates, or other mixtures thereof), tautomers, isotopes, polymorphs, and pharmaceutically acceptable prodrugs of such compounds.

The compounds of the disclosure may possess an asymmetric center, and can be produced as a racemic mixture or as individual enantiomers. The individual enantiomers may be obtained by asymmetric synthesis or by resolving a racemic or non-racemic mixture of an intermediate at some appropriate stage of the synthesis. The individual enantiomers may also be obtained by resolution of the compound by conventional means, such as crystallization in the presence of a resolving agent, or chromatography, using, for example a chiral high pressure liquid chromatography (HPLC) column. The individual enantiomers as

well as racemic and non-racemic mixtures of enantiomers are within the scope of the present disclosure, all of which are intended to be included within the structures depicted in this specification unless otherwise specifically indicated.

Definitions

As used in the present disclosure, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

"Isomers" are different compounds that have the same molecular formula. Isomers include stereoisomers, enantiomers and diastereomers.

"Stereoisomers" are isomers that differ only in the way the atoms are arranged in space.

"Enantiomers" are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic" mixture. The term "(±)" is used to designate a racemic mixture where appropriate.

The absolute stereochemistry is specified according to the Cahn Ingold Prelog R S system. When the compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either R or S. Resolved compounds whose absolute configuration is unknown are designated (+) or (-) depending on the direction (dextro- or laevorotary) that they rotate the plane of polarized light at the wavelength of the sodium D line.

The term "polymorph" refers to different crystal structures of a crystalline compound. The different polymorphs may result from differences in crystal packing (packing polymorphism) or differences in packing between different conformers of the same molecule (conformational polymorphism). It is understood that any polymorph of a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, if used in a subject, while possibly providing varied properties, including pharmacokinetic properties, once absorbed into the subject, results in the compound of Formula I, such that the use of a compound of Formula I encompasses the use of any polymorph of a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof.

The term "solvate" refers to a complex formed by the combining of a compound of Formula I and a solvent. It is understood that any solvate of a compound of Formula I, if used in a subject, while possibly providing varied properties, including pharmacokinetic properties, once absorbed into the subject, results in the compound of Formula I, such that the use of a compound of Formula I encompasses the use of any solvate of a compound of Formula I.

The term "hydrate" refers to the complex formed by the combining of a compound of Formula I and water. It is understood that any hydrate of a compound of Formula I, if used in a subject, while possibly providing varied properties, including pharmacokinetic properties, once absorbed into the subject, results in the compound of Formula I, such that the use of a compound of Formula I encompasses the use of any hydrate of a compound of Formula I.

The term "prodrug" refers to a compound derived from or readily converted to a compound of Formula I that include chemical groups which, *in vivo*, can be converted and/or can be split off from the remainder of the molecule to provide a compound of Formula I or active moiety of the drug, or a pharmaceutically acceptable salt or co-crystal thereof or a biologically active metabolite thereof. It is understood that any prodrug of a compound of Formula I, if used in a subject, while possibly providing varied properties, including pharmacokinetic properties, once absorbed into the subject, results in the compound of Formula I, such that the use of a compound of Formula I encompasses the use of any prodrug of a compound of Formula I.

Also provided herein are isotopically labeled forms of compounds detailed herein. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as, but not limited to ^{2}H (deuterium, D), ^{3}H (tritium), ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F, ^{31}P, ^{32}P, ^{35}S, ^{36}Cl and ^{125}I. Various isotopically labeled compounds of the present disclosure, for example those into which radioactive isotopes such as ^{3}H, ^{13}C and ^{14}C are incorporated, are provided. Such isotopically labeled compounds may be useful in

metabolic studies, reaction kinetic studies, detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays or potentially in radioactive treatment of subjects. Also provided for isotopically labeled compounds described herein are any pharmaceutically acceptable salts, pharmaceutically acceptable esters, pharmaceutically acceptable solvates, hydrates, enantiomers, mixture of enantiomers, tautomers, polymorphs, and pharmaceutically acceptable prodrugs thereof.

The disclosure also includes the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, in which from 1 to n hydrogens attached to a carbon atom is/are replaced by deuterium, in which n is the number of hydrogens in the molecule. Such compounds may exhibit increased resistance to metabolism and may thus be useful for increasing the half life of the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, when administered to a mammal. See, for example, Foster, "Deuterium Isotope Effects in Studies of Drug Metabolism", Trends Pharmacol. Sci. 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogens have been replaced by deuterium.

Deuterium labeled or substituted compounds of the disclosure may have improved DMPK (drug metabolism and pharmacokinetics) properties, relating to distribution, metabolism and excretion (ADME). Substitution with heavier isotopes such as deuterium may afford certain advantages resulting from greater metabolic stability, for example increased *in vivo* half-life, reduced dosage requirements and/or a potential improvement in therapeutic index. An ^{18}F labeled compound may be useful for PET or SPECT studies. Isotopically labeled compounds of this disclosure and prodrugs thereof can generally be prepared by carrying out the procedures disclosed in the schemes or in the examples and preparations described below by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent. It is understood that deuterium in this context is regarded as a substituent in the compound of Formula I.

The concentration of such a heavier isotope, specifically deuterium, may be defined by an isotopic enrichment factor. In the compounds of this disclosure any atom not

specifically designated as a particular isotope is meant to represent any stable isotope of that atom. Unless otherwise stated, when a position is designated specifically as "H" or "hydrogen", the position is understood to have hydrogen at its natural abundance isotopic composition. Accordingly, in the compounds of this disclosure any atom specifically designated as a deuterium (D) is meant to represent deuterium.

The term "inhibition" indicates a decrease, such as a significant decrease, in the baseline activity of a biological activity or process. "Inhibition of Syk activity" refers to a decrease in Syk activity as a direct or indirect response to the presence of a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, relative to the activity of Syk in the absence of such compound or a pharmaceutically acceptable salt or co-crystal thereof. The decrease in activity may be due to the direct interaction of the compound with Syk, or due to the interaction of the compound(s) described herein with one or more other factors that in turn affect Syk activity. For example, the presence of the compound(s) may decrease Syk activity by directly binding to the Syk, by causing (directly or indirectly) another factor to decrease Syk activity, or by (directly or indirectly) decreasing the amount of Syk present in the cell or organism. In some embodiments, the inhibition of Syk activity may be compared in the same subject prior to use of a compound described hereine, or other subjects not receiving the compound.

Inhibition of Syk activity also refers to observable inhibition of Syk activity in a standard biochemical assay for Syk activity, such as the ATP hydrolysis assay described in Example 12 below.

In some embodiments, the compound described herein, e.g. a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, may inhibit Syk kinase activity with an IC_{50} value less than or equal to 1 micromolar, such as 0.1 nM to 1 μM or 1 nM to 1 μM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have an IC_{50} value less than or equal to less than 500 nanomolar, such as 0.1 nM to 500 nM or 1 nM to 500 nM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have an IC_{50} value less than or equal to less than 200 nanomolar, such as 0.1 nM to 200 nM or 1 nM to 200 nM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may

have an IC_{50} value less than or equal to less than 100 nanomolar, such as 0.1 nM to 100 nM or 1 nM to 100 nM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have an IC_{50} value less than or equal to 50 nanomola, such as 0.1 nM to 50 nM or 1 nM to 50 nM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have an IC_{50} value less than or equal to 20 nanomolar, such as 0.1 nM to 20 nM or 1 nM to 20 nM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have an IC_{50} value less than or equal to 10 nanomolar, such as 0.1 nM to 10 nM or 1 nM to 10 nM. In some embodiments, the IC_{50} value is measured as described in the assay of Example 12.

The "reduction in basophil activation" refers to the ability of compounds as described herein to reduce the activation of basophils. Basophil activation is involved, for example, in inflammatory and autoimmune diseases, and the reduction of activation of basophils is therefore desired. The activation of basophils in compounds as described herein, e.g. a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereor, can be assessed by the measurement of CD63 expression by basophils, such as by a CD63 human whole blood basophil cellular assay (25% blood), e.g. such as the assay described in Example 9 below.

In some embodiments, the compound described herein e.g. a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, may have an EC_{50} value in a suitable CD63 assay of less than or equal to 10 micromolar, such as 1 nM to 10 μM or 10 nM to 10 μM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof, may have an EC_{50} value less than or equal to less than 1 micromolar, such as 1 nM to 1 μM or 10 nM to 1 μM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have an EC_{50} value less than or equal to 500 nanomolar, such as 1 nM to 500 nM or 10 nM to 500 nM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have an EC_{50} value less than or equal to 200 nanomolar, such as 1 nM to 200 nM or 10 nM to 200 nM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have an EC_{50} value less than or equal to 150 nanomolar, such as 1 nM to 150 nM or 10 nM to 150 nM. In some embodiments, the compound or a

pharmaceutically acceptable salt or co-crystal thereof may have an IC_{50} value less than or equal to 100 nanomolar, such as 1 nM to 100 nM or 10 nM to 100 nM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have an EC_{50} value less than or equal to 75 nanomolar, such as 1 nM to 75 nM or 10 nM to 75 nM. In some embodiments, the EC_{50} value is measured as described in the assay of Example 9.

The "kinetic solubility" refers to an assessment of the solubility of a compound in a suitable buffer, such as phosphate buffer at pH 7.4, at a given temperature, for example at 37 °C. In on instance, kinetic solubility is measured at 37 °C in phosphate buffer at pH 7.4, such as by the assay as described in Example 10.

In some embodiments, the compounds described herein, e.g. a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, may have a kinetic solubility at 37 °C in phosphate buffer at pH 7.4 of greater than or equal to 10 μM, such as 10 μM to 500 μM or 10 μM to 250 μM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have a kinetic solubility at 37 °C in phosphate buffer at pH 7.4 of greater than or equal to 20 μM, such as 20 μM to 500 μM or 20 μM to 250 μM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have a kinetic solubility at 37 °C in phosphate buffer at pH 7.4 of greater than or equal to 30 μM, such as 30 μM to 500 μM or 30 μM to 250 μM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have a kinetic solubility at 37 °C in phosphate buffer at pH 7.4 of greater than or equal to 40 μM, such as 40 μM to 500 μM or 40 μM to 250 μM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have a kinetic solubility at at 37 °C in phosphate buffer pH 7.4 of greater than or equal to 50 μM, such as 50 μM to 500 μM or 50 μM to 250 μM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have a kinetic solubility at 37 °C in phosphate buffer at pH 7.4 of greater than or equal to 60 μM, such as 60 μM to 500 μM or 60 μM to 250 μM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have a kinetic solubility at 37 °C in phosphate buffer at pH 7.4 of greater than or equal to 70 μM, such as 70 μM to 500 μM or 70 μM to 250 μM. In some

embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have a kinetic solubility at 37 °C in phosphate buffer at pH 7.4 of greater than or equal to 80 μM, such as 80 μM to 500 μM or 80 μM to 250 μM. In some embodiments, the compound or a pharmaceutically acceptable salt or co-crystal thereof may have a kinetic solubility at 37 °C in phosphate buffer at pH 7.4 of greater than or equal to 90 μM, such as 90 μM to 500 μM or 90 μM to 250 μM. In some embodiments, the kinetic solubility is measured by the assay as described in Example 10.

The "human hepatocyte stability" is a measure of the stability of compounds to metabolism by human hepatocytes, and is assessed as the predicted hepatic plasma clearance of the compounds in L/hr/kg. The predicted hepatocyte clearance can be measured, for example, by the assay described in Example 11.

In some embodiments, the compounds described herein, e.g. a compound of Formula I may have a predicted hepatic plasma clearance of less than or equal to 0.50 L/hr/kg, such as 0.005 L/hr/kg to 0.50 L/hr/kg or 0.01 L/hr/kg to 0.50 L/hr/kg. In some embodiments, the compound may have a predicted hepatic plasma clearance of less than or equal to 0.40 L/hr/kg, such as 0.005 L/hr/kg to 0.40 L/hr/kg or 0.01 L/hr/kg to 0.40 L/hr/kg. In some embodiments, the compound may have a predicted hepatic plasma clearance of less than or equal to 0.30 L/hr/kg, such as 0.005 L/hr/kg to 0.30 L/hr/kg or 0.01 L/hr/kg to 0.30 L/hr/kg. In some embodiments, the compound may have a predicted hepatic plasma clearance of less than or equal to 0.20 L/hr/kg, such as 0.005 L/hr/kg to 0.20 L/hr/kg or 0.01 L/hr/kg to 0.20 L/hr/kg. In some embodiments, the compound may have a predicted hepatic plasma clearance of less than or equal to 0.10 L/hr/kg, such as 0.005 L/hr/kg to 0.10 L/hr/kg or 0.01 L/hr/kg to 0.10 L/hr/kg. In some embodiments, the compound may have a predicted hepatic plasma clearance of less than or equal to 0.09 L/hr/kg, such as 0.005 L/hr/kg to 0.09 L/hr/kg or 0.01 L/hr/kg to 0.09 L/hr/kg. In some embodiments, the compound may have a predicted hepatic plasma clearance of less than or equal to 0.08 L/hr/kg, such as 0.005 L/hr/kg to 0.08 L/hr/kg or 0.01 L/hr/kg to 0.08 L/hr/kg. In some embodiments, the compound may have a predicted hepatic plasma clearance of less than or equal to 0.07 L/hr/kg, such as 0.005 L/hr/kg to 0.07 L/hr/kg or 0.01 L/hr/kg to 0.07 L/hr/kg. In some embodiments, the compound may have a predicted hepatic plasma clearance of or less than or equal to 0.06

L/hr/kg, such as 0.005 L/hr/kg to 0.06 L/hr/kg or 0.01 L/hr/kg to 0.06 L/hr/kg. In some embodiments, the predicted hepatocyte clearance is measured by the assay described in Example 11.

By "significant" is meant any detectable change that is statistically significant in a standard parametric test of statistical significance such as Student's T-test, where $p < 0.05$.

"Subject" refers to an animal, such as a mammal, that has been or will be the object of potential treatment, observation or experiment. In some embodiments, the subject may be a mammal; in some embodiments the subject may be human; and in some embodiments the subject may be chosen from cats and dogs.

In many cases, the compounds of this disclosure are capable of forming acid and/or base salts by virtue of the presence of amino and/or carboxyl groups or groups similar thereto.

"Pharmaceutically acceptable salts" include, for example, salts with inorganic acids and salts with an organic acid. Examples of salts may include hydrochloride, phosphate, diphosphate, hydrobromide, sulfate, sulfinate, nitrate, malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate (mesylate), benzenesuflonate (besylate), p-toluenesulfonate (tosylate), 2-hydroxyethylsulfonate, benzoate, salicylate, stearate, and alkanoate (such as acetate, HOOC-$(CH_2)_n$-COOH where n is 0-4). In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare nontoxic pharmaceutically acceptable addition salts.

The compound of Formula I can also be a pharmaceutically acceptable co-crystal or a co-crystal salt. The "co-crystal" or "co-crystal salt" as used herein means a crystalline material composed of two or more unique solids at room temperature, each of which has distinctive physical characteristics such as structure, melting point, and heats of fusion,

hygroscopicity, solubility, and stability. A co-crystal or a co-crystal salt can be produced according to a per se known co-crystallization method. The terms co-crystal (or cocrystal) or co-crystal salt also refer to a multicomponent system in which there exists a host API (active pharmaceutical ingredient) molecule or molecules, such as a compound of Formula I, and a guest (or co-former) molecule or molecules. In particular embodiments said pharmaceutically acceptable co-crystal of the compound of Formula I with a co-former molecule is in a crystalline form selected from a malonic acid co-crystal , a succinic acid co-crystal, a decanoic acid co-crystal, a salicylic acid co-crystal, a vanillic acid co-crystal, a maltol co-crystal, or a glycolic acid co-crystal. Co-crystals may have improved properties as compared to the parent form (i.e., the free molecule, zwitter ion, etc.) or a salt of the parent compound. Improved properties may include increased solubility, increased dissolution, increased bioavailability, increased dose response, decreased hygroscopicity, a crystalline form of a normally amorphous compound, a crystalline form of a difficult to salt or unsaltable compound, decreased form diversity, more desired morphology, and the like.

The term "crystal forms" and related terms herein refer to the various crystalline modifications of a given substance, including, but not limited to, polymorphs, solvates, hydrates, co-crystals, and other molecular complexes, as well as salts, solvates of salts, hydrates of salts, other molecular complexes of salts, and polymorphs thereof. Crystal forms of a substance can be obtained by a number of methods, as known in the art. Such methods include, but are not limited to, melt recrystallization, melt cooling, solvent recrystallization, recrystallization in confined spaces such as, e.g., in nanopores or capillaries, recrystallization on surfaces or templates, such as, e.g., on polymers, recrystallization in the presence of additives, such as, e.g., co-crystal counter-molecules, desolvation, dehydration, rapid evaporation, rapid cooling, slow cooling, vapor diffusion, sublimation, grinding and solvent-drop grinding.

As used herein, “pharmaceutically acceptable excipient” is a pharmaceutically acceptable vehicle that includes, without limitation, any and all carriers, solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is

well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in potential therapeutic compositions is contemplated. Supplementary active ingredients can also be incorporated into the compositions.

The term "carrier" refers to an excipient or vehicle that includes without limitation diluents, disintegrants, precipitation inhibitors, surfactants, glidants, binders, lubricants, and the like with which the compound is administered. Carriers are generally described herein and also in "Remington's Pharmaceutical Sciences" by E.W. Martin. Examples of carriers include, but are not limited to, aluminum monostearate, aluminum stearate, carboxymethylcellulose, carboxymethylcellulose sodium, crospovidone, glyceryl isostearate, glyceryl monostearate, hydroxyethyl cellulose, hydroxyethyl cellulose, hydroxymethyl cellulose, hydroxyoctacosanyl hydroxystearate, hydroxypropyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, poloxamer 124, poloxamer 181, poloxamer 182, poloxamer 188, poloxamer 237, poloxamer 407, povidone, silicon dioxide, colloidal silicon dioxide, silicone, silicone adhesive 4102, and silicone emulsion. It should be understood, however, that the carriers selected for the pharmaceutical compositions, and the amounts of such carriers in the composition, may vary depending on the method of formulation (*e.g.*, dry granulation formulation, solid dispersion formulation).

The term "diluent" generally refers to a substance that is used to dilute the compound of interest prior to delivery. Diluents can also serve to stabilize compounds. Examples of diluents may include starch, saccharides, disaccharides, sucrose, lactose, polysaccharides, cellulose, cellulose ethers, hydroxypropyl cellulose, sugar alcohols, xylitol, sorbitol, maltitol, microcrystalline cellulose, calcium or sodium carbonate, lactose, lactose monohydrate, dicalcium phosphate, cellulose, compressible sugars, dibasic calcium phosphate dehydrate, mannitol, microcrystalline cellulose, and tribasic calcium phosphate.

The term "disintegrant" generally refers to a substance which, upon addition to a solid preparation, facilitates its break-up or disintegration after administration and permits the release of an active ingredient as efficiently as possible to allow for its rapid dissolution. Examples of disintegrants may include maize starch, sodium starch glycolate,

croscarmellose sodium, crospovidone, microcrystalline cellulose, modified corn starch, sodium carboxymethyl starch, povidone, pregelatinized starch, and alginic acid.

The term "precipitation inhibitors" generally refers to a substance that prevents or inhibits precipitation of the active agent from a supersaturated solution. One example of a precipitation inhibitor includes hydroxypropylmethylcellulose (HPMC).

The term "surfactants" generally refers to a substance that lowers the surface tension between a liquid and a solid that could improve the wetting of the active agent or improve the solubility of the active agent. Examples of surfactants include poloxamer and sodium lauryl sulfate.

The term "glidant" generally refers to substances used in tablet and capsule formulations to improve flow-properties during tablet compression and to produce an anti-caking effect. Examples of glidants may include colloidal silicon dioxide, talc, fumed silica, starch, starch derivatives, and bentonite.

The term "binder" generally refers to any pharmaceutically acceptable film which can be used to bind together the active and inert components of the carrier together to maintain cohesive and discrete portions. Examples of binders may include hydroxypropylcellulose, hydroxypropylmethylcellulose, povidone, copovidone, and ethyl cellulose.

The term "lubricant" generally refers to a substance that is added to a powder blend to prevent the compacted powder mass from sticking to the equipment during the tableting or encapsulation process. A lubricant can aid the ejection of the tablet form the dies, and can improve powder flow. Examples of lubricants may include magnesium stearate, stearic acid, silica, fats, calcium stearate, polyethylene glycol, sodium stearyl fumarate, or talc; and solubilizers such as fatty acids including lauric acid, oleic acid, and C_8/C_{10} fatty acid.

Compounds

Compounds are provided here and elsewhere throughout, such as in the Summary and in the Examples.

The compounds provided herein are named using ChemBioDraw Ultra 12.0, and one skilled in the art understands that the compound structure may be named or identified using other commonly recognized nomenclature systems and symbols including CAS and IUPAC.

In some embodiments of the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, R^2 is H. In some embodiments of the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, R^2 is 2-hydroxyethoxyl.

In some embodiments of the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, R^3 is H. In some embodiments of the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, R^3 is methyl.

In some embodiments of the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, R^4 is H or methyl. In some embodiments of the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, R^4 is H. In some embodiments of the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, R^4 is methyl.

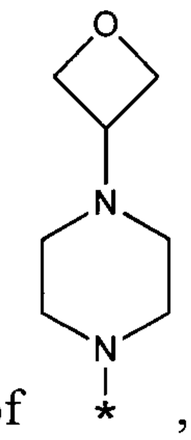
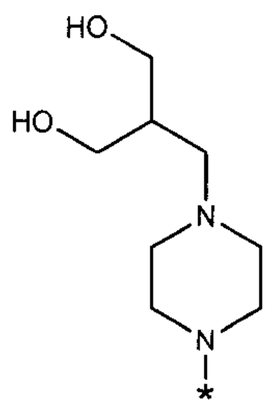
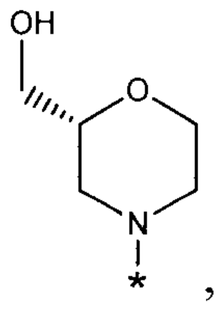
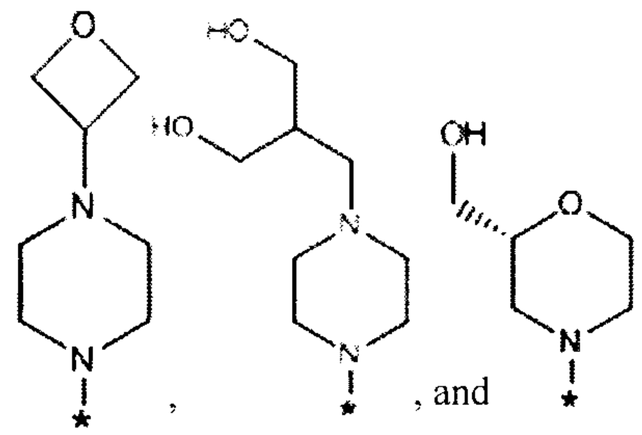
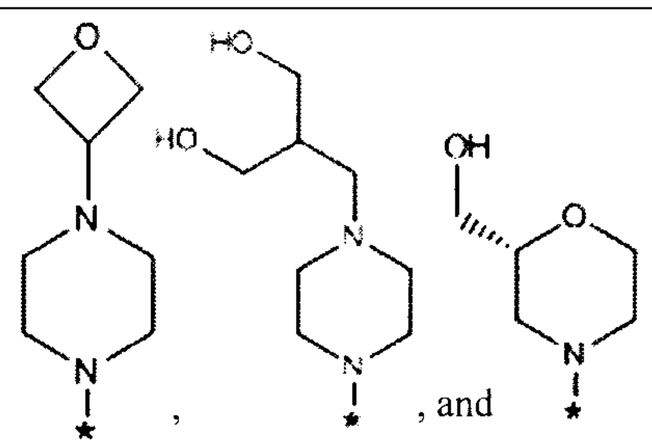
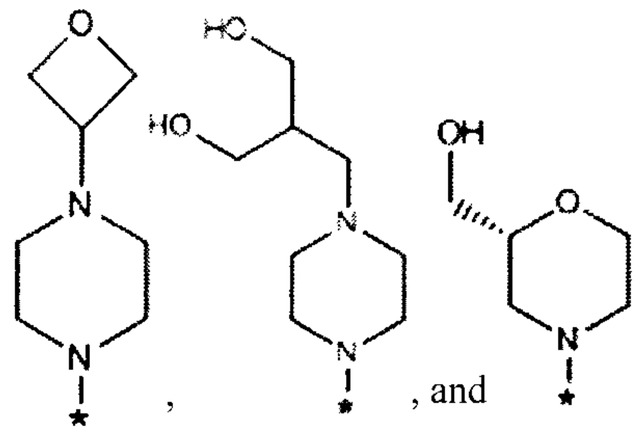
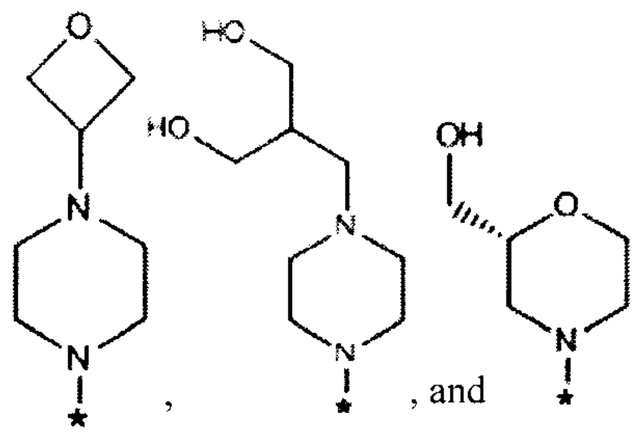
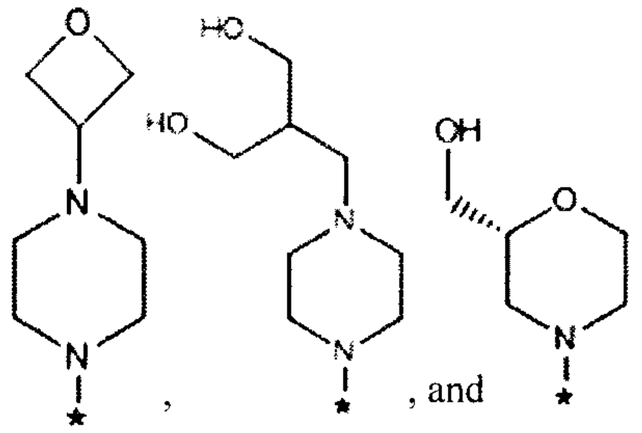
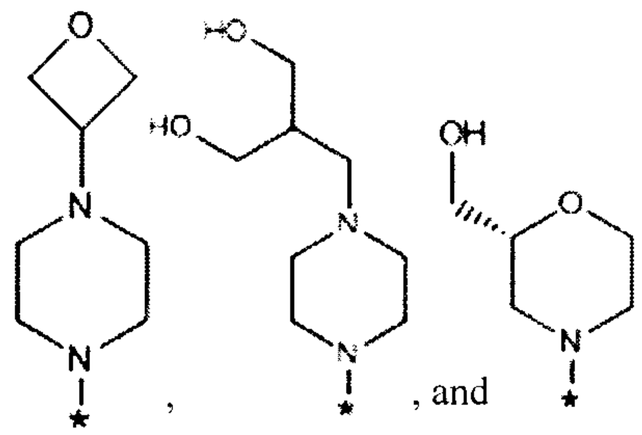
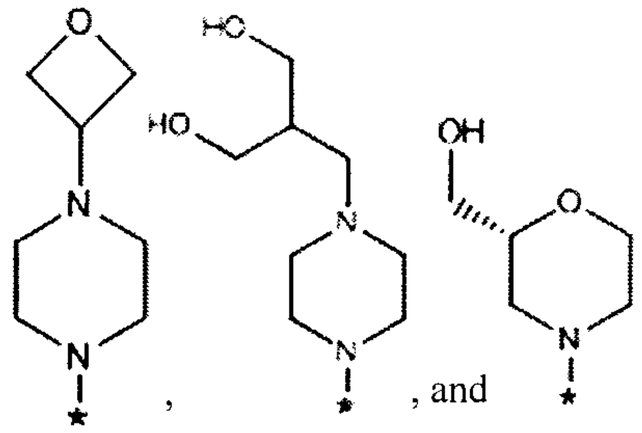
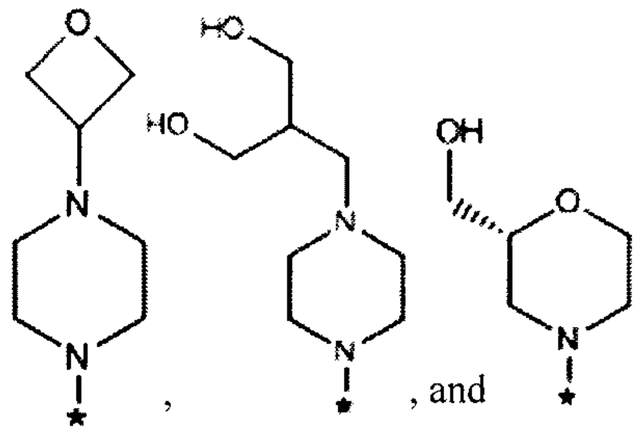
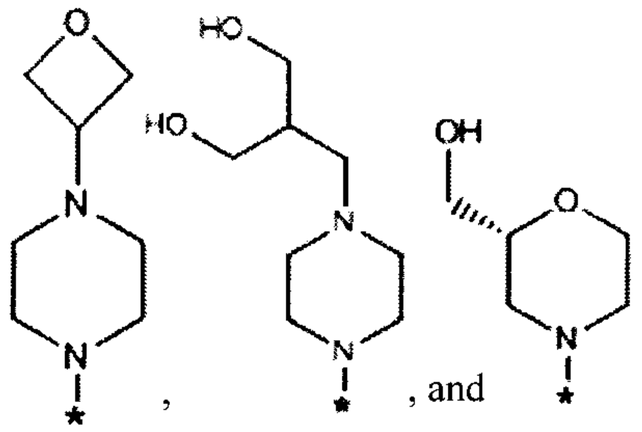
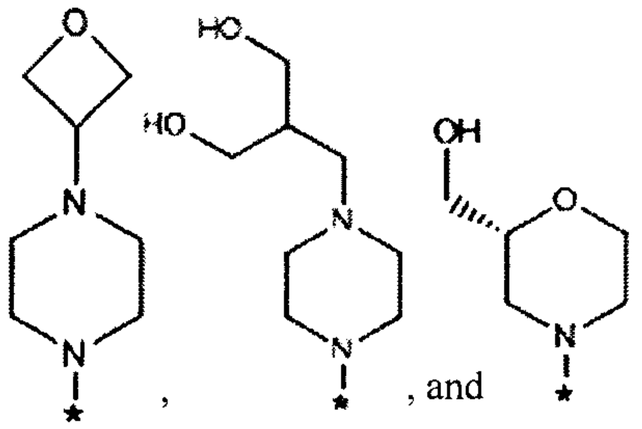
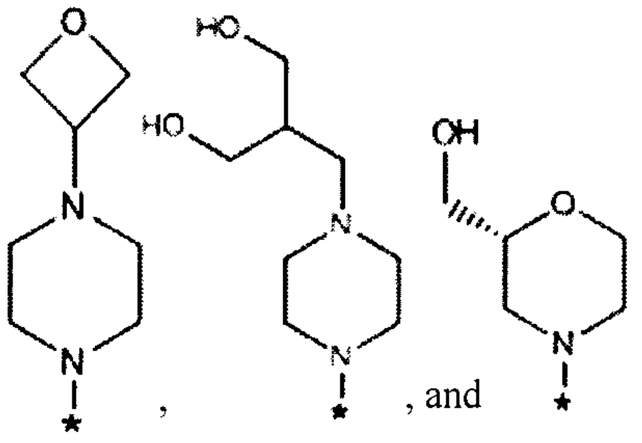
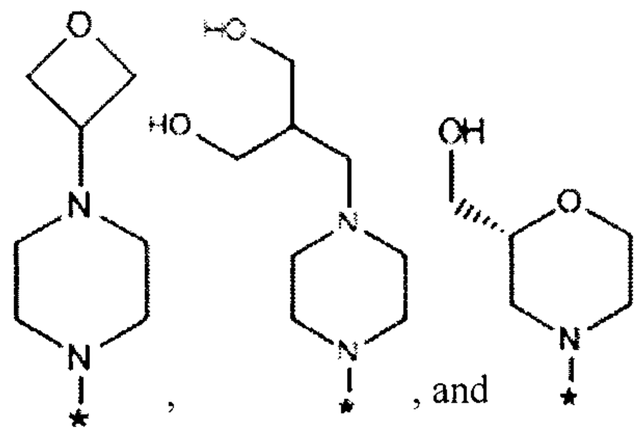
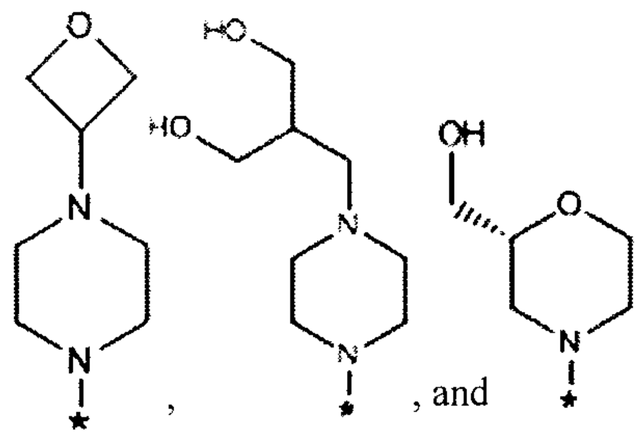
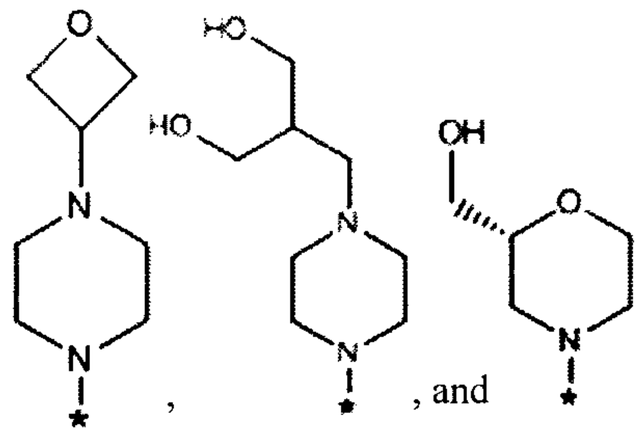
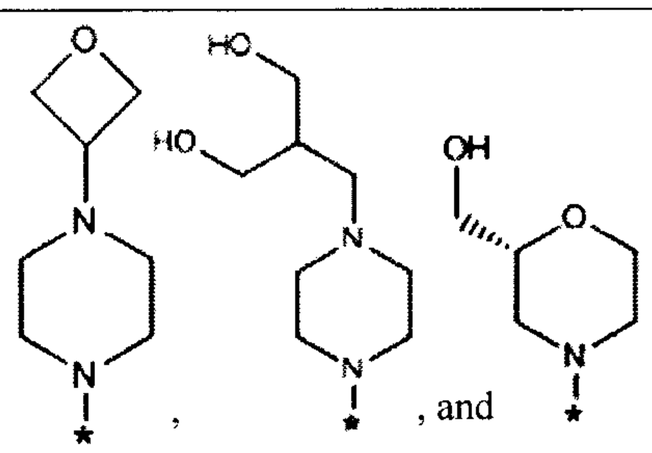
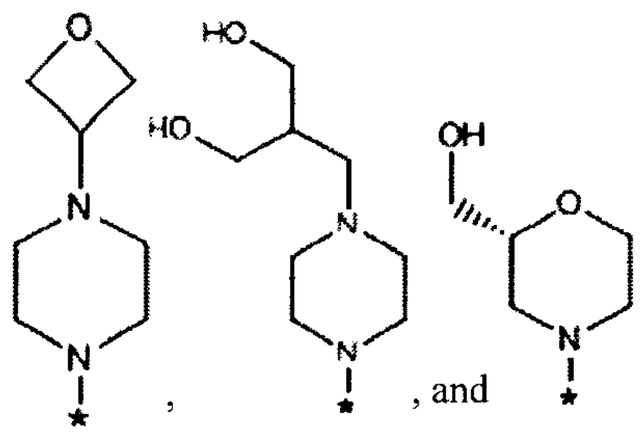
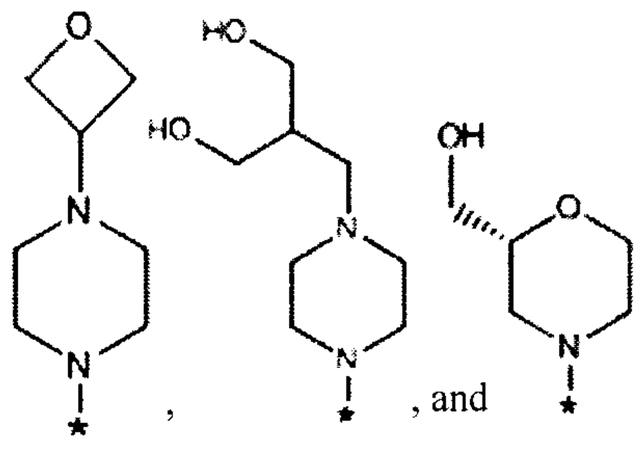
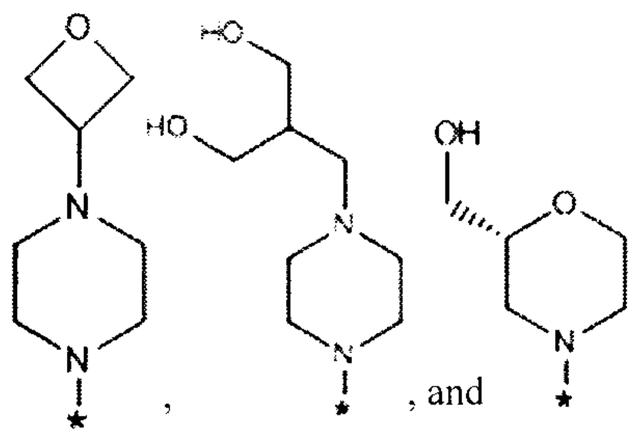
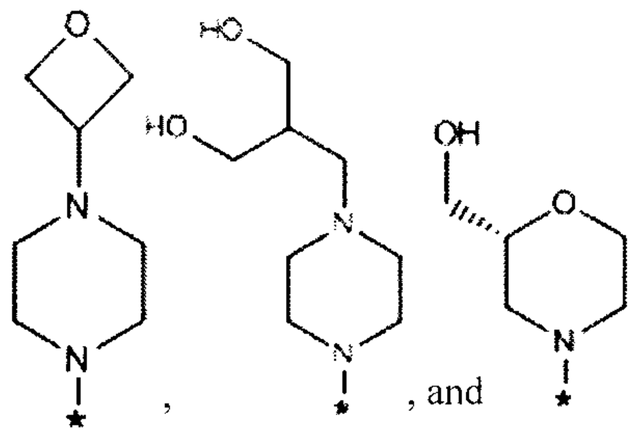
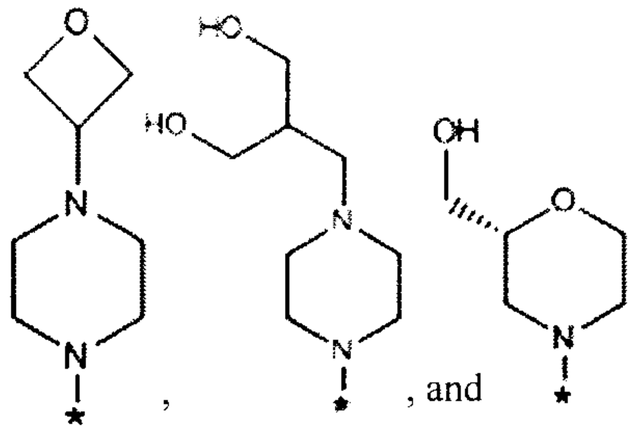
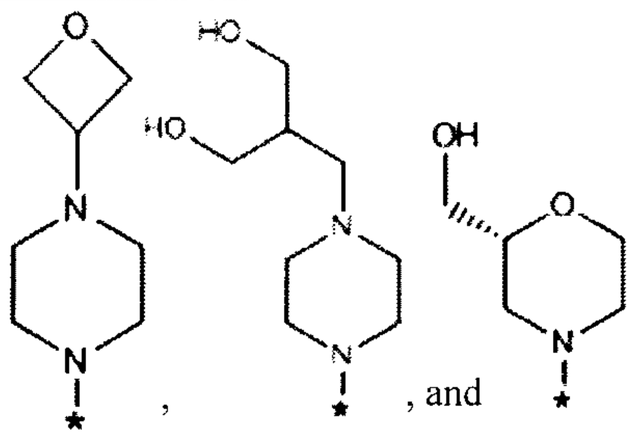
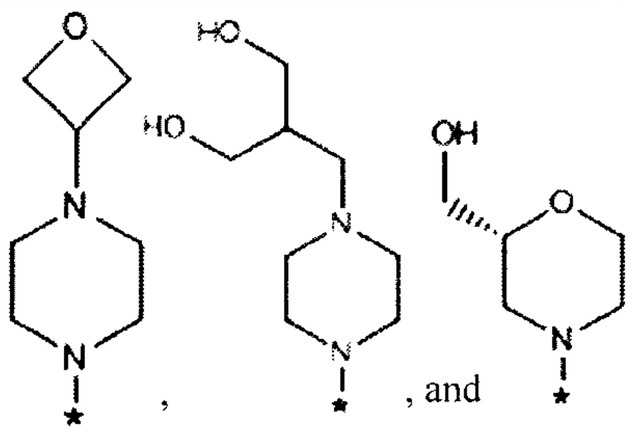
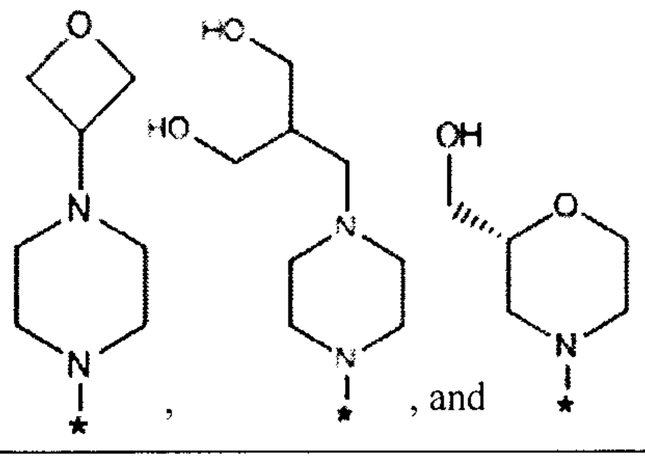
Separate embodiments herein, each providing a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, in which R^1 is selected from the group consisting of , , and , include embodiments A-1 through A-27 wherein R^2, R^3, and R^4 are as defined in Table A for each of the embodiments.

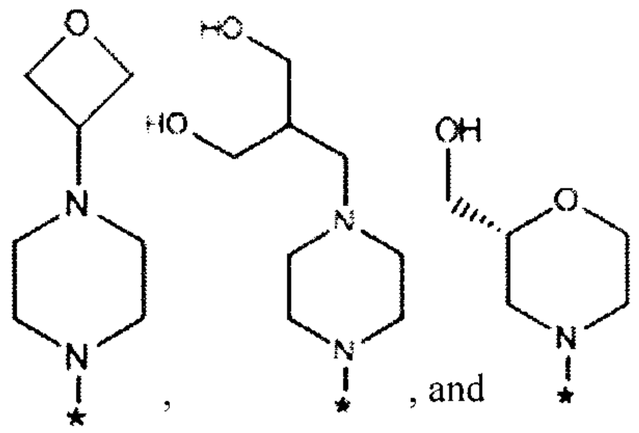
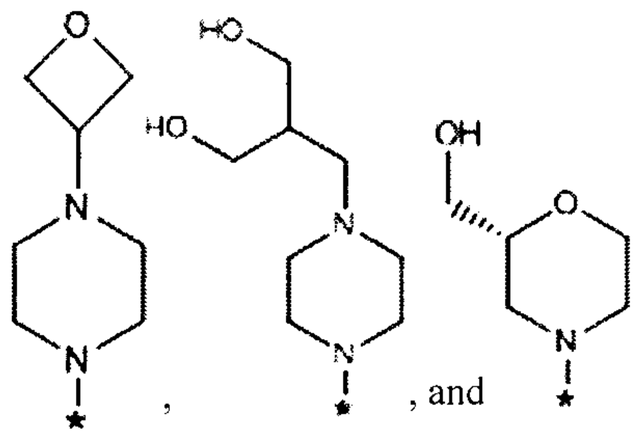
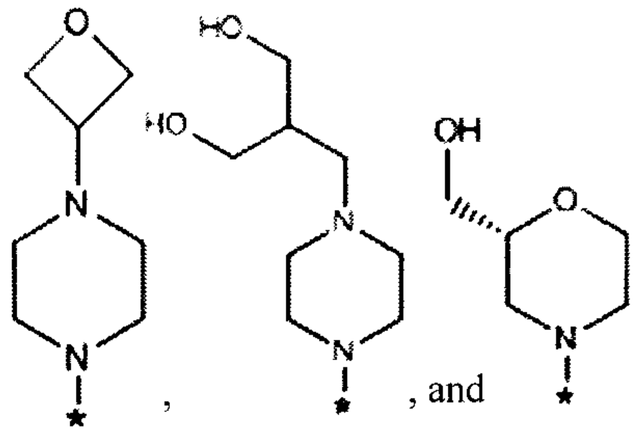
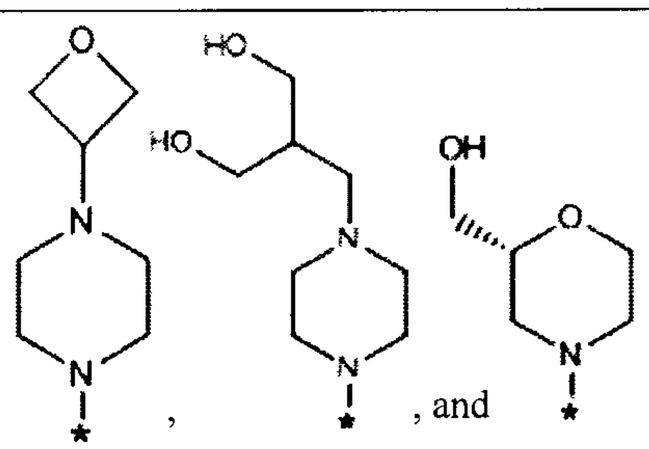
Table A

Embodiment No.	R^1 selected from	R^2	R^3	R^4
A-1	 , , and	H or 2-hydroxyethoxyl	H or methyl	H or methyl
A-2	 , , and	H or 2-hydroxyethoxyl	H	H or methyl
A-3	 , , and	H or 2-hydroxyethoxyl	methyl	H or methyl
A-4	 , , and	H or 2-hydroxyethoxyl	H or methyl	H
A-5	 , , and	H or 2-hydroxyethoxyl	H or methyl	Methyl

A-6	 , and	H or 2-hydroxyethoxyl	H	H
A-7	 , and	H or 2-hydroxyethoxyl	H	methyl
A-8	 , and	H or 2-hydroxyethoxyl	methyl	H
A-9	 , and	H or 2-hydroxyethoxyl	methyl	methyl
A-10	 , and	H	H or methyl	H or methyl
A-11	 , and	H	H	H or methyl

A-12	 , and	H	methyl	H or methyl
A-13	 , and	H	H or methyl	H
A-14	 , and	H	H or methyl	methyl
A-15	 , and	H	H	H
A-16	 , and	H	methyl	H
A-17	 , and	H	H	methyl

A-18	 , and	H	methyl	methyl
A-19	 , and	2-hydroxyethoxyl	H or methyl	H or methyl
A-20	 , and	2-hydroxyethoxyl	H	H or methyl
A-21	 , and	2-hydroxyethoxyl	methyl	H or methyl
A-22	 , and	2-hydroxyethoxyl	H or methyl	H
A-23	 , and	2-hydroxyethoxyl	H or methyl	methyl

A-24	 , and	2-hydroxyethoxyl	H	H
A-25	 , and	2-hydroxyethoxyl	methyl	H
A-26	 , and	2-hydroxyethoxyl	H	methyl
A-27	 , and	2-hydroxyethoxyl	methyl	methyl

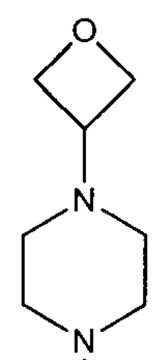
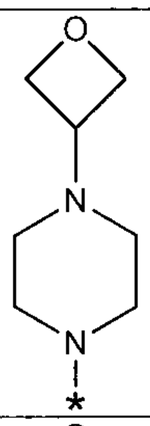
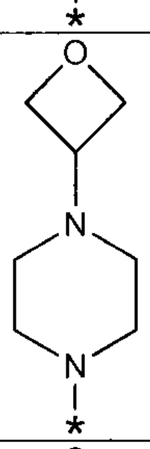
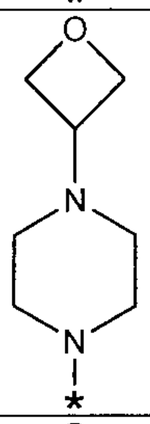
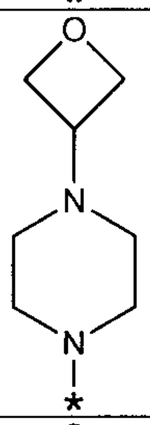
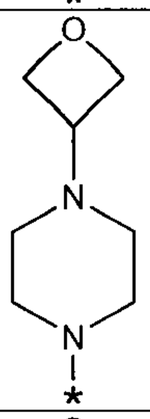
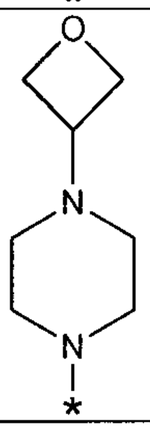
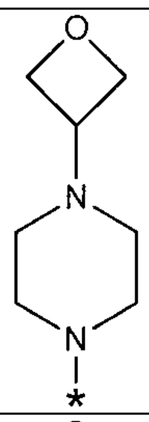
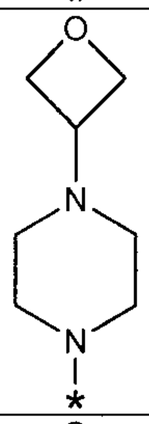
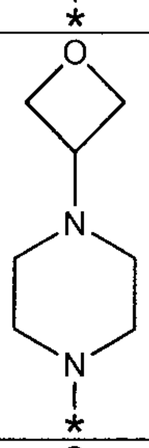
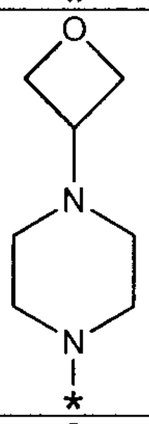
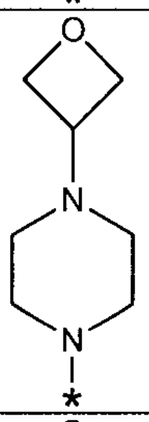
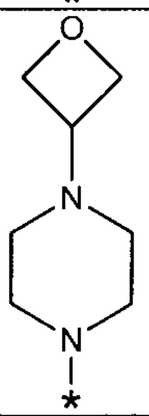
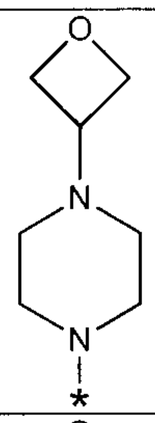
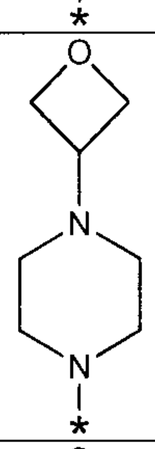
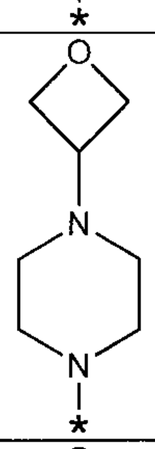
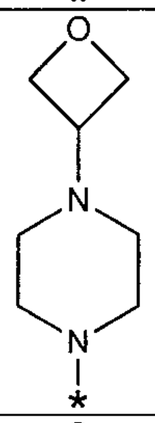
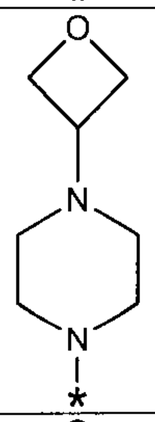
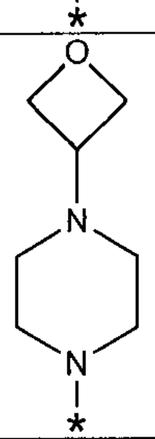
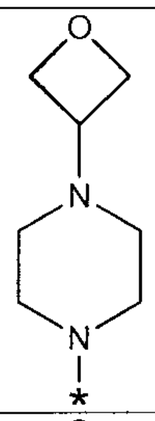
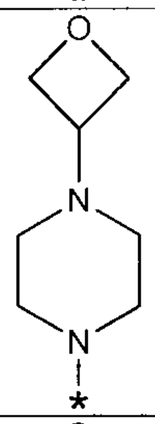
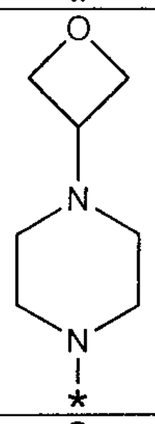
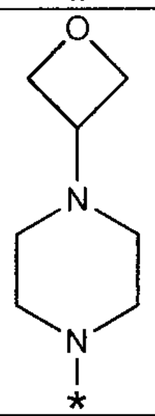
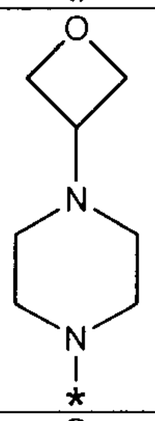
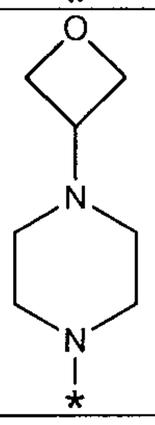
Separate embodiments herein, each providing a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, in which R^1 is  , include embodiments B-1 through B-27 wherein R^2, R^3, and R^4 are as defined in Table B for each of the embodiments.

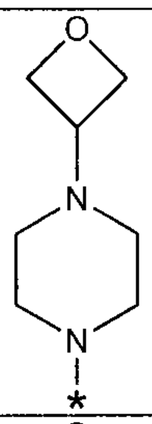
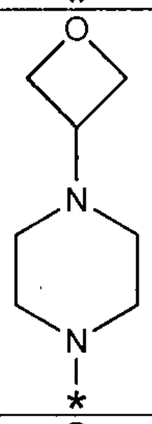
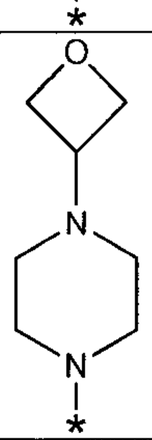
Table B

Embodiment No.	R^1	R^2	R^3	R^4
B-1		H or 2-hydroxyethoxyl	H or methyl	H or methyl
B-2		H or 2-hydroxyethoxyl	H	H or methyl
B-3		H or 2-hydroxyethoxyl	methyl	H or methyl
B-4		H or 2-hydroxyethoxyl	H or methyl	H
B-5		H or 2-hydroxyethoxyl	H or methyl	Methyl
B-6		H or 2-hydroxyethoxyl	H	H

B-7		H or 2-hydroxyethoxyl	H	methyl
B-8		H or 2-hydroxyethoxyl	methyl	H
B-9		H or 2-hydroxyethoxyl	methyl	methyl
B-10		H	H or methyl	H or methyl
B-11		H	H	H or methyl
B-12		H	methyl	H or methyl

B-13		H	H or methyl	H
B-14		H	H or methyl	methyl
B-15		H	H	H
B-16		H	methyl	H
B-17		H	H	methyl
B-18		H	methyl	methyl

B-19		2-hydroxyethoxyl	H or methyl	H or methyl
B-20		2-hydroxyethoxyl	H	H or methyl
B-21		2-hydroxyethoxyl	methyl	H or methyl
B-22		2-hydroxyethoxyl	H or methyl	H
B-23		2-hydroxyethoxyl	H or methyl	methyl
B-24		2-hydroxyethoxyl	H	H

B-25		2-hydroxyethoxyl	methyl	H
B-26		2-hydroxyethoxyl	H	methyl
B-27		2-hydroxyethoxyl	methyl	methyl

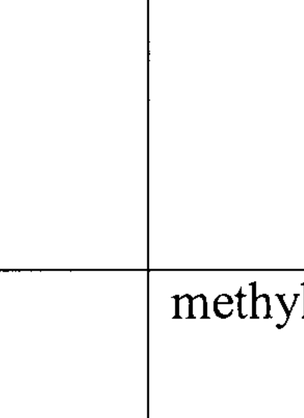
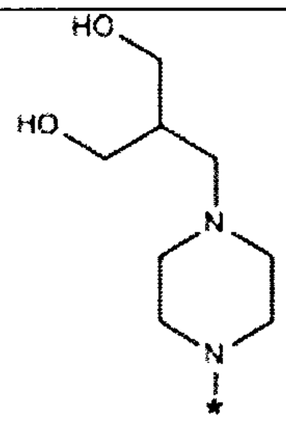
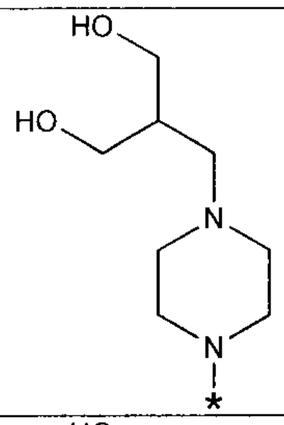
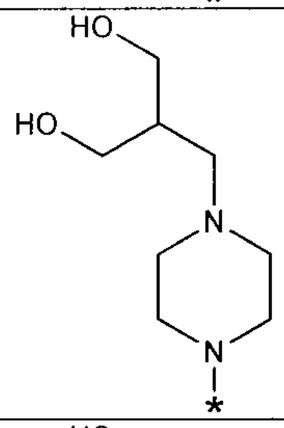
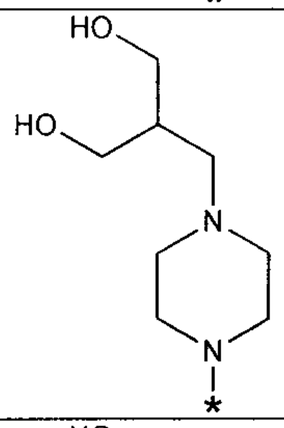
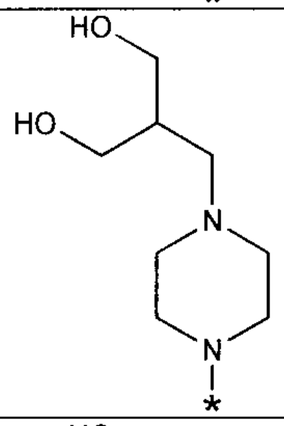
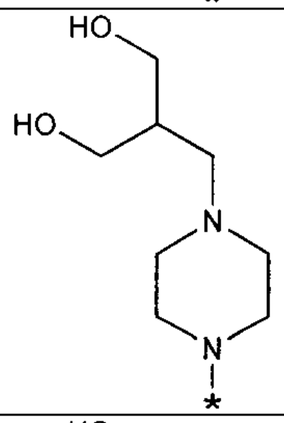
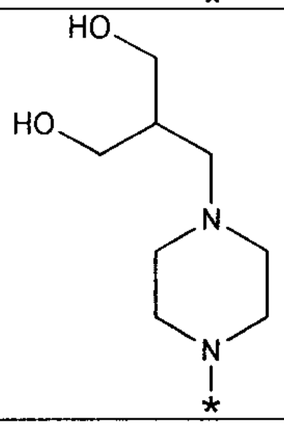
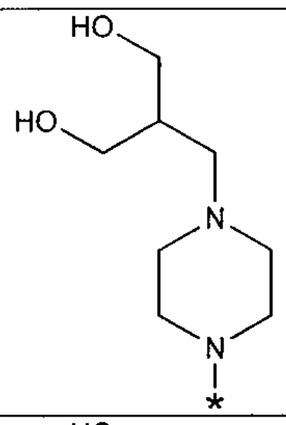
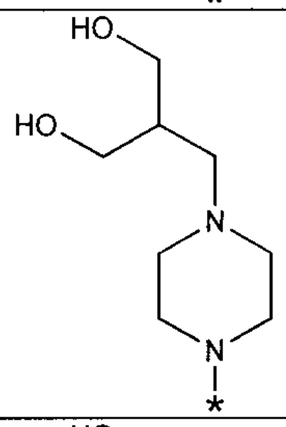
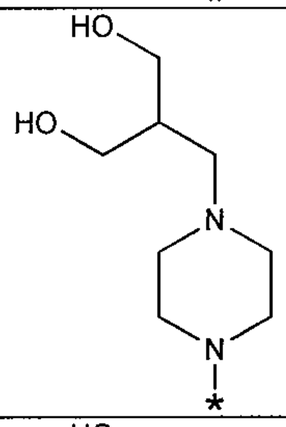
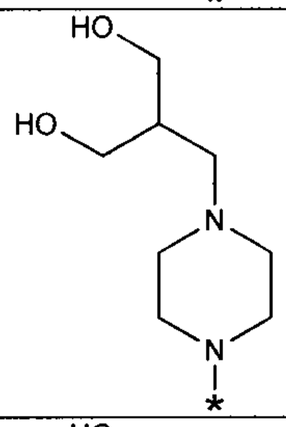
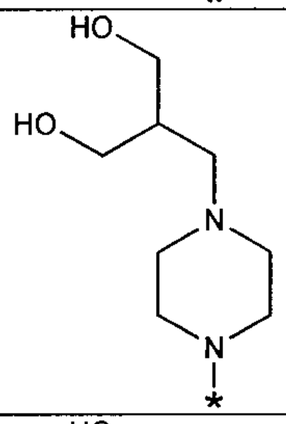
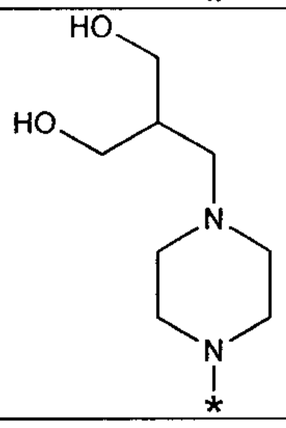
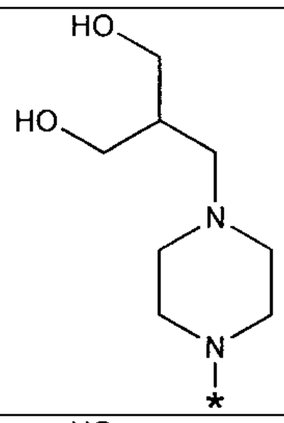
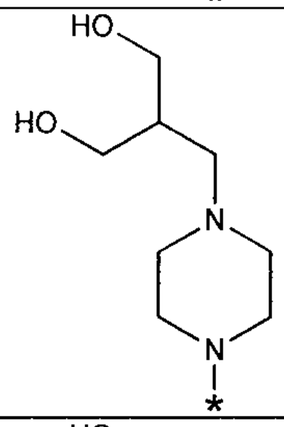
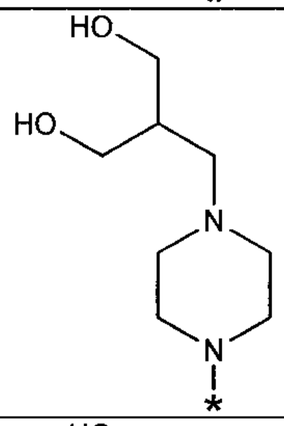
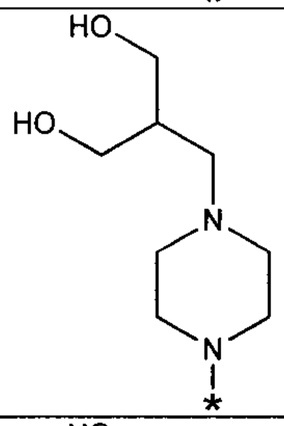
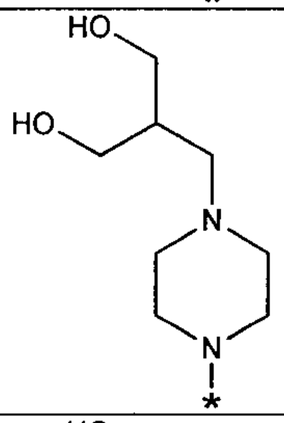
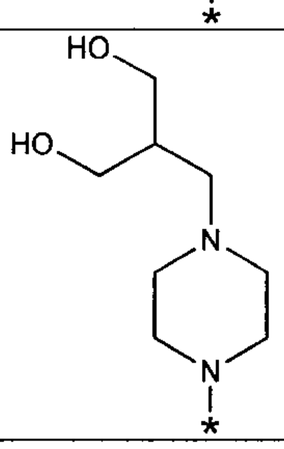
Separate embodiments herein, each providing a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, in which R^1 is , include embodiments C-1 through C-27 wherein R^2, R^3, and ^{R4} are as defined in Table C for each of the embodiments.

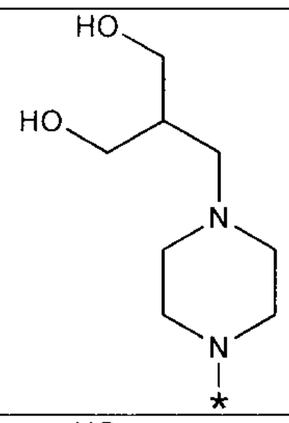
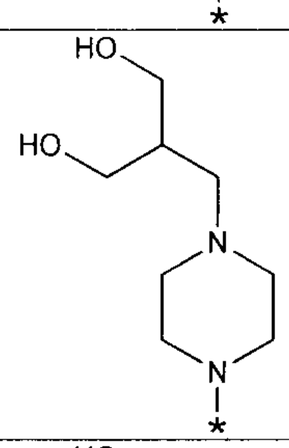
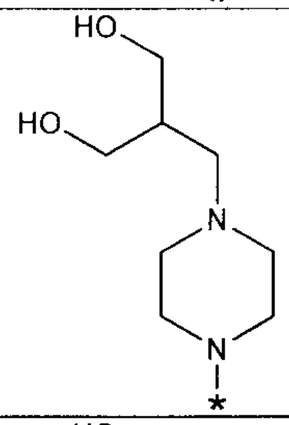
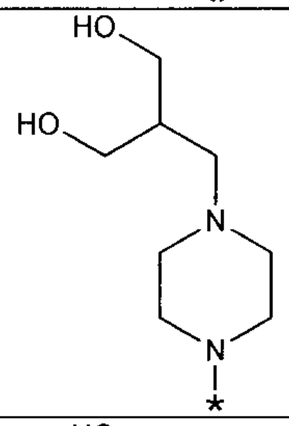
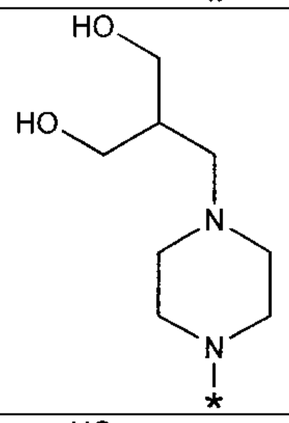
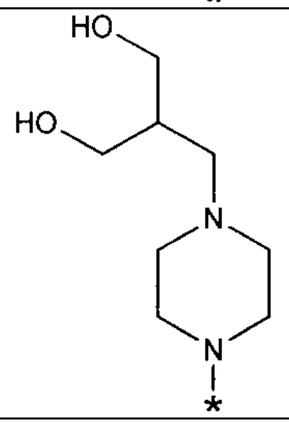
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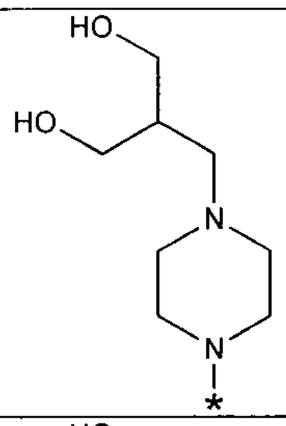
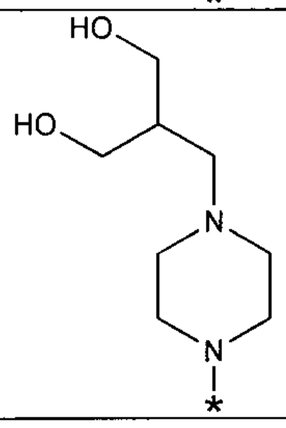
Embodiment No.	**R^1**	**R^2**	**R^3**	**R^4**
C-1		H or 2-hydroxyethoxyl	H or methyl	H or methyl

C-2		H or 2-hydroxyethoxyl	H	H or methyl
C-3		H or 2-hydroxyethoxyl	methyl	H or methyl
C-4		H or 2-hydroxyethoxyl	H or methyl	H
C-5		H or 2-hydroxyethoxyl	H or methyl	Methyl
C-6		H or 2-hydroxyethoxyl	H	H
C-7		H or 2-hydroxyethoxyl	H	methyl

C-8		H or 2-hydroxyethoxyl	methyl	H
C-9		H or 2-hydroxyethoxyl	methyl	methyl
C-10		H	H or methyl	H or methyl
C-11		H	H	H or methyl
C-12		H	methyl	H or methyl
C-13		H	H or methyl	H

C-14		H	H or methyl	methyl
C-15		H	H	H
C-16		H	methyl	H
C-17		H	H	methyl
C-18		H	methyl	methyl
C-19		2-hydroxyethoxyl	H or methyl	H or methyl

C-20		2-hydroxyethoxyl	H	H or methyl
C-21		2-hydroxyethoxyl	methyl	H or methyl
C-22		2-hydroxyethoxyl	H or methyl	H
C-23		2-hydroxyethoxyl	H or methyl	methyl
C-24		2-hydroxyethoxyl	H	H
C-25		2-hydroxyethoxyl	methyl	H

C-26		2-hydroxyethoxyl	H	methyl
C-27		2-hydroxyethoxyl	methyl	methyl

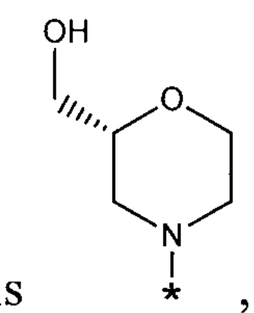
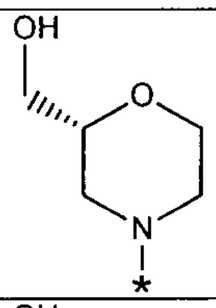
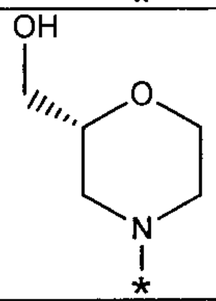
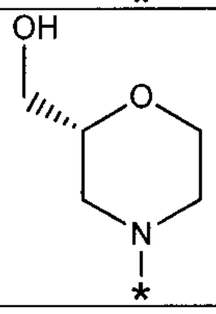
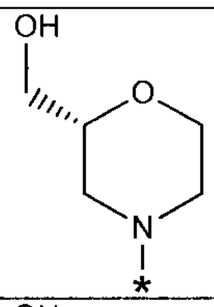
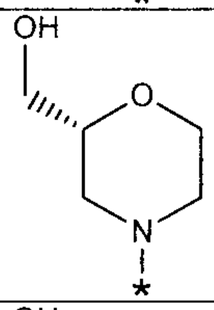
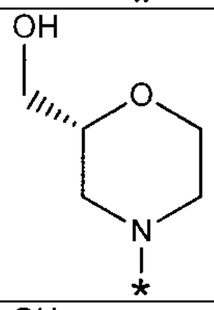
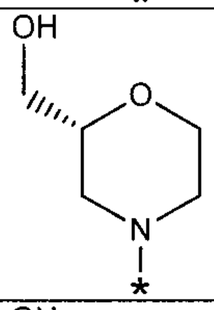
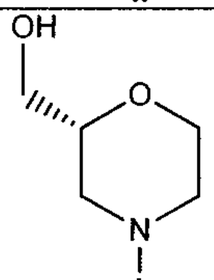
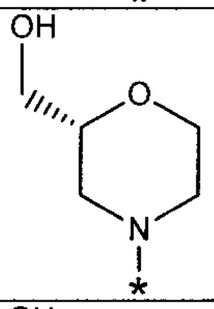
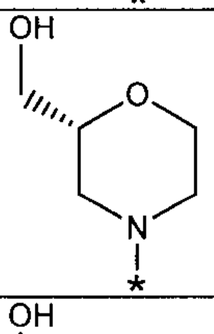
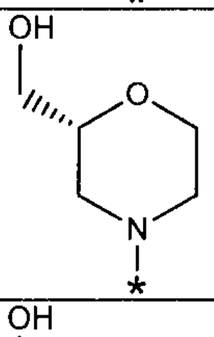
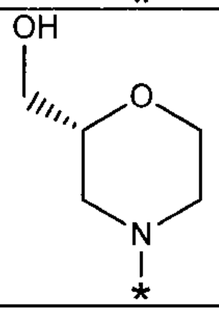
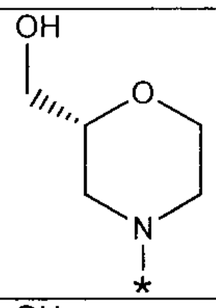
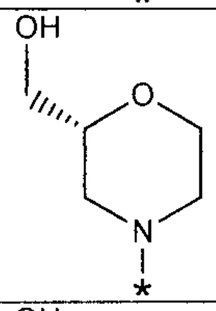
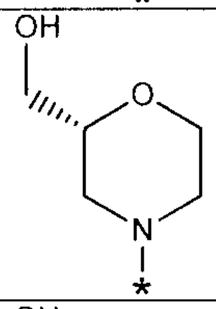
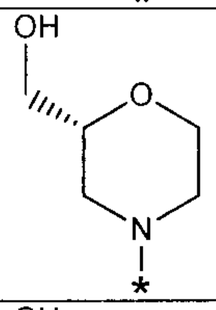
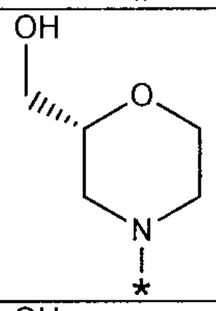
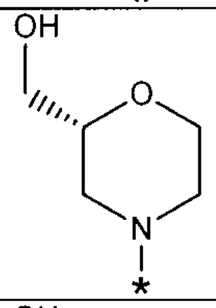
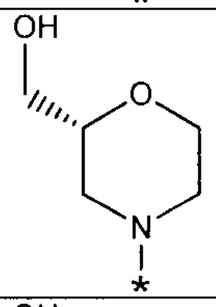
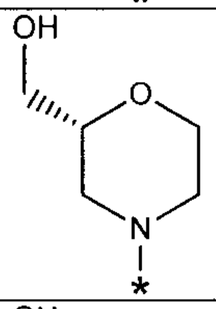
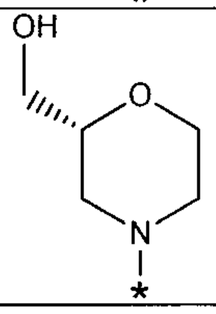
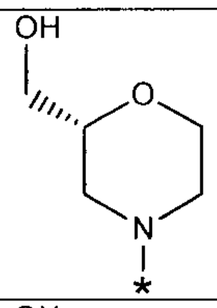
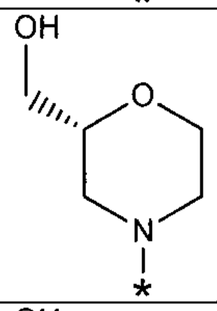
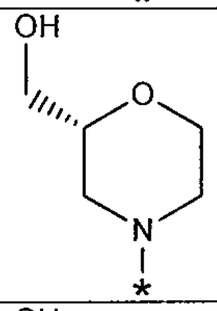
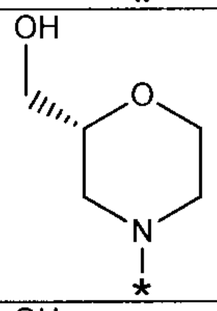
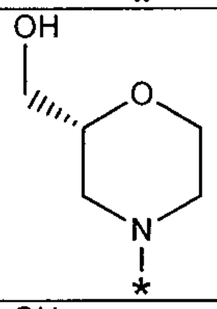
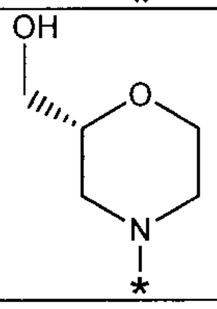
Separate embodiments herein, each providing a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, in which R^1 is , include embodiments D-1 through D-27 wherein R^2, R^3, and ^{R4} are as defined in Table D for each of the embodiments.

Table D

Embodiment No.	**R^1**	**R^2**	**R^3**	**R^4**
D-1		H or 2-hydroxyethoxyl	H or methyl	H or methyl
D-2		H or 2-hydroxyethoxyl	H	H or methyl
D-3		H or 2-hydroxyethoxyl	methyl	H or methyl

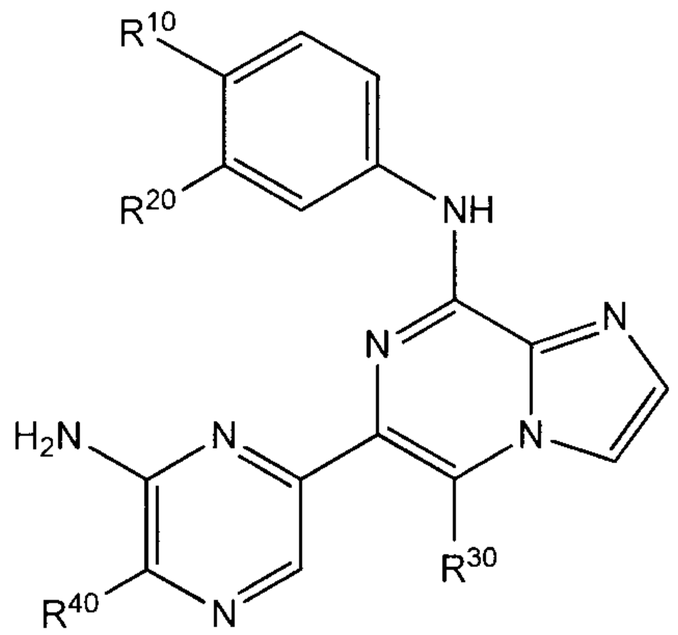
D-4		H or 2-hydroxyethoxyl	H or methyl	H
D-5		H or 2-hydroxyethoxyl	H or methyl	Methyl
D-6		H or 2-hydroxyethoxyl	H	H
D-7		H or 2-hydroxyethoxyl	H	methyl
D-8		H or 2-hydroxyethoxyl	methyl	H
D-9		H or 2-hydroxyethoxyl	methyl	methyl
D-10		H	H or methyl	H or methyl
D-11		H	H	H or methyl
D-12		H	methyl	H or methyl

D-13		H	H or methyl	H
D-14		H	H or methyl	methyl
D-15		H	H	H
D-16		H	methyl	H
D-17		H	H	methyl
D-18		H	methyl	methyl
D-19		2-hydroxyethoxyl	H or methyl	H or methyl
D-20		2-hydroxyethoxyl	H	H or methyl
D-21		2-hydroxyethoxyl	methyl	H or methyl

D-22		2-hydroxyethoxyl	H or methyl	H
D-23		2-hydroxyethoxyl	H or methyl	methyl
D-24		2-hydroxyethoxyl	H	H
D-25		2-hydroxyethoxyl	methyl	H
D-26		2-hydroxyethoxyl	H	methyl
D-27		2-hydroxyethoxyl	methyl	methyl

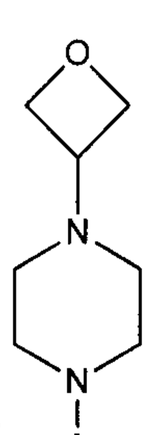
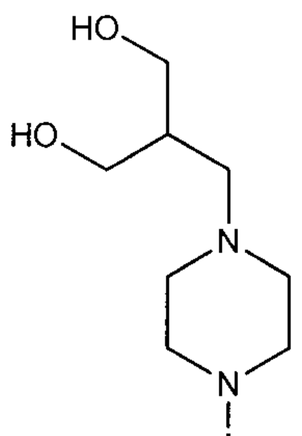
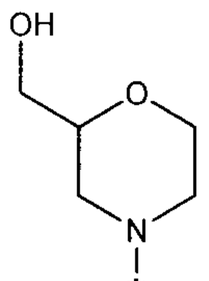
Embodiments herein that refer to the compound of Formula I in one aspect also refer to a pharmaceutically acceptable salt of the compound of Formula I, even if not explicity stated as such.

Also provided herein is a compound of Formula II:



Formula II

or a pharmaceutically acceptable salt or co-crystal thereof, wherein:

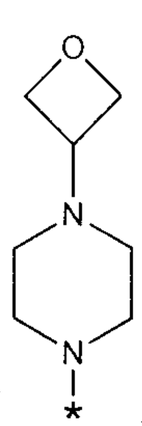
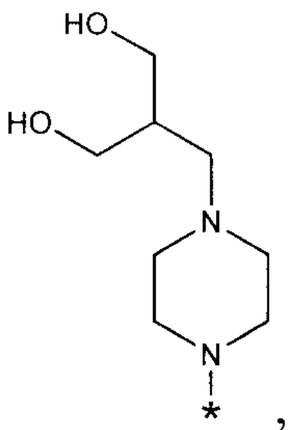
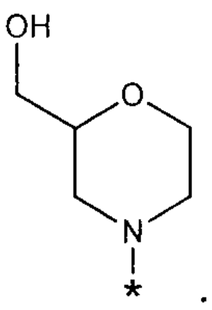
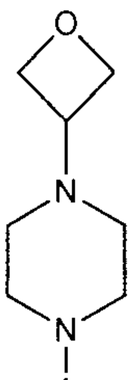
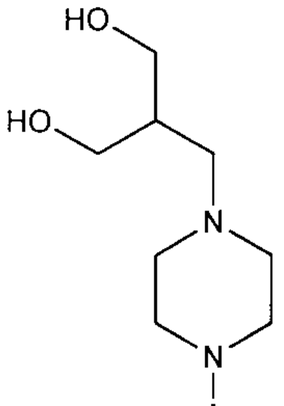
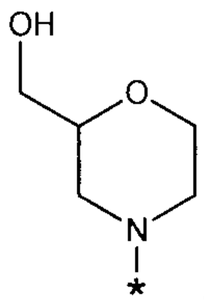
R^{10} is selected from the group consisting of  ,  , and  ,

wherein * indicates the carbon atom of the indicated phenyl ring of Formula II to which R^1 is attached;

R^{20} is H or 2-hydroxyethoxyl;

R^{30} is H or methyl; and

R^{40} is H, halogen (i.e. F, Cl, Br, or I), methyl, or halo substituted methyl (i.e. methyl wherein 1 to 3 hydrogen atoms are substituted by 1 to 3 halogen atoms, which may be the same or different, e.g. fluoromethyl, chloromethyl, difluoromethyl, dichloromethyl, chlorofluoromethyl, trifluoromethyl, and the like).

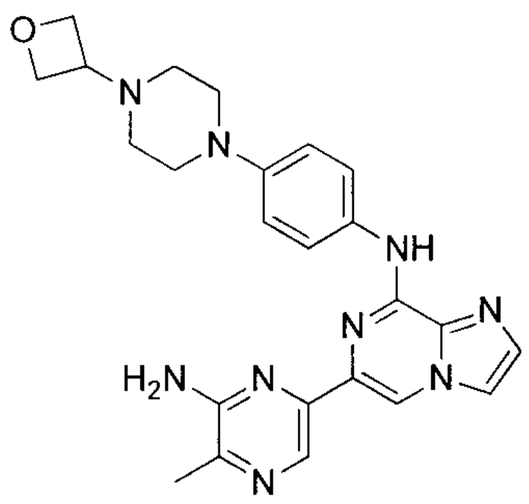
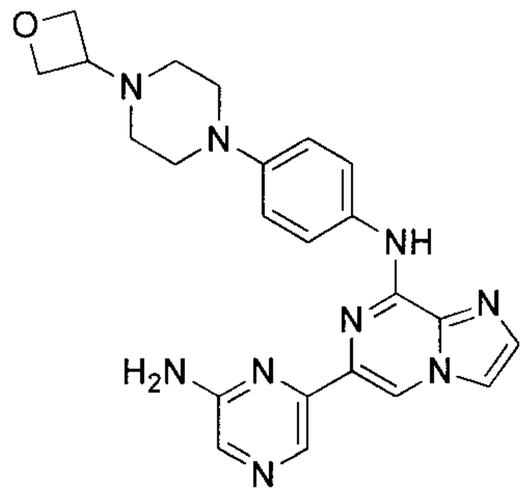
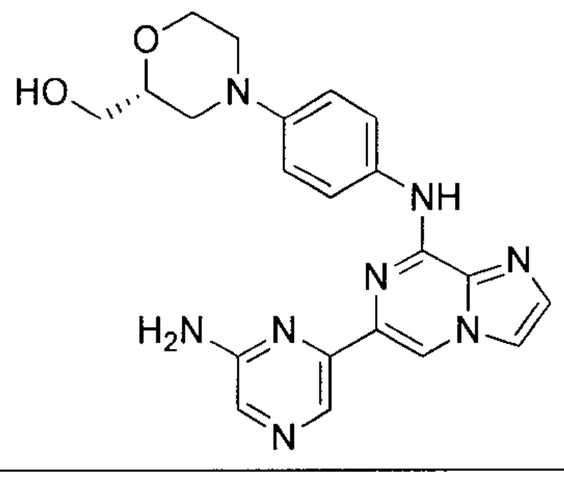
In some embodiments of the compound of Formula II, or a pharmaceutically acceptable salt thereof, R^{10} is selected from the group consisting of , , and . In some embodiments, R^{10} is . In some embodiments, R^{10} is . In some embodiments, R^{10} is . Within each of the embodiments described herein comprising a compound of Formula II, there is a further embodiment wherein each of R^{20}, R^{30}, and R^{40} is H. Within each of the embodiments described herein comprising a compound of Formula II, there is a another embodiment wherein R^{20} is H, R^{30} is methyl, and R^{40} is H. Within each of the embodiments described herein comprising a compound of Formula II, there is also another embodiment wherein R^{20} is H, R^{30} is H, and R^{40} is methyl.

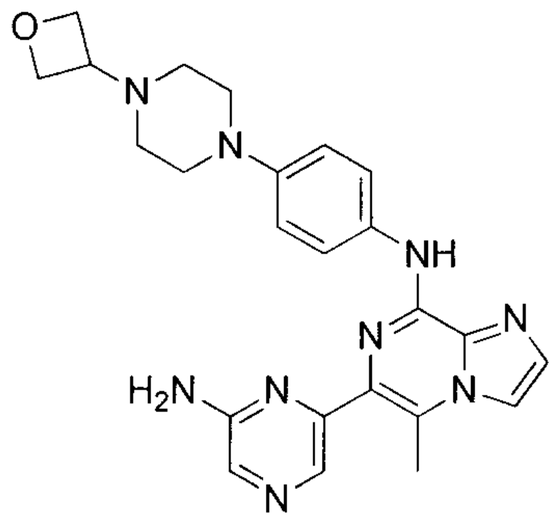
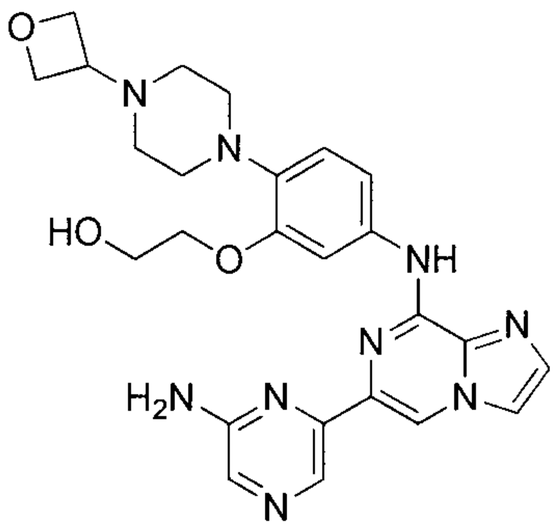
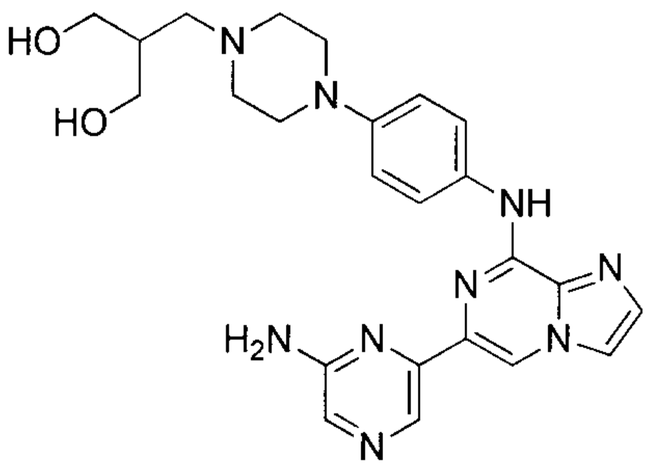
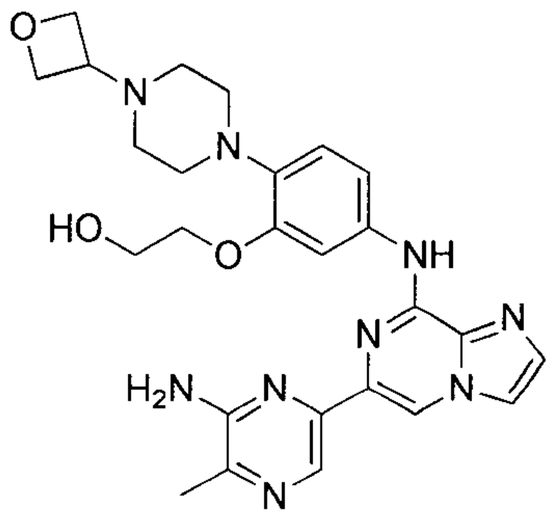
Within each of the embodiments described herein comprising a compound of Formula II, there is still another embodiment wherein R^{20} is 2-hydroxyethoxyl, R^{30} is methyl, and R^{40} is H. Within each of the embodiments described herein comprising a compound of Formula II, there is still another embodiment wherein R^{20} is 2-hydroxyethoxyl, R^{30} is methyl, and R^{40} is H. Within each of the embodiments described herein comprising a compound of Formula II, there is still further embodiment wherein R^{20} is 2-hydroxyethoxyl, R^{30} is H, and R^{40} is methyl.

Representative compounds of the invention are listed in Table A below. The compounds in Table A are named using ChemBioDraw Ultra 12.0 and it should be understood that other names be used to identify compounds of the same structure. Other

compounds or radicals may be named with common names, or systematic or non-systematic names. The compounds may also be named using other nomenclature systems and symbols that are commonly recognized in the art of chemistry including, for example, Chemical Abstract Service (CAS) and International Union of Pure and Applied Chemistry (IUPAC). Any ambiguity in naming of compounds can be resolved by deferring to the structure, where provided.

Table A. Representative Compounds

Structure	Name
	6-(6-amino-5-methylpyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine
	6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine
	(R)-(4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)morpholin-2-yl)methanol

	6-(6-aminopyrazin-2-yl)-5-methyl-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine
	2-(5-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol
	2-((4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)piperazin-1-yl)methyl)propane-1,3-diol
	2-(5-((6-(6-amino-5-methylpyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol

The compounds described herein, e.g. a compound of Formula I, or a pharmaceutically acceptable salt therof, provide distinct advantages as Syk inhibitors. The compounds described herein are inhibitors of Syk kinase activity, as measured, for example, as the inhibition of Syk kinase activity in a biochemical assay or as the reduction in basophil activation as measured by CD63 expression, as described in the Examples. The compounds

described herein may also have desirable properties for use as a potential pharmaceutical, including kinetic solubility at 37 °C in phosphate buffer at pH 7.4 and low levels of hepatocyte clearance. These features result in Syk inhibitors that may be useful for potential treatment of disease with pharmacokinetic characteristics that may provide a therapeutic window such that the compounds may be effective in smaller doses than currently known compounds. As such, the compounds may provide effective doses with minimal off target activity, which may reduce unwanted side effects, lessen the chance of drug-drug interactions, and increase a subject's compliance with a given potential therapeutic regimen.

In some embodiments, the compounds described herein, e.g. a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, may be effective in one or more of Syk kinase activity inhibition or reduction of basophil activation as measured by CD63 expression, for example, the compound may inhibit Syk kinase activity with an IC_{50} value less than or equal to 1 micromolar, less than or equal to 500 nanomolar, less than or equal to 200 nanomolar, less than or equal to 100 nanomolar, less than or equal to 50 nanomolar, less than or equal to 20 nanomolar, or less than or equal to 10 nanomolar, as demonstrated by a suitable assay for Syk kinase activity, such as the assay as described in Example 12; and/or reduces CD63 expression activity with an EC_{50} value potentially less than or equal to 1 micromolar, less than or equal to 500 nanomolar, less than or equal to 200 nanomolar, less than or equal to 150 nanomolar, less than or equal to 100 nanomolar, or less than or equal to 75 nanomolar, as demonstrated by a suitable assay for the measurement of CD63 expression in basophils, such as the assay as described in Example 9.

In some embodiments, the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, may be effective in both of Syk kinase inhibition and reduction of CD63 expression, for example, the compound may have Syk kinase activity with an IC_{50} value less than or equal to 1 micromolar, less than or equal to 500 nanomolar, less than or equal to 200 nanomolar, less than or equal to 100 nanomolar, less than or equal to 50 nanomolar, less than or equal to 20 nanomolar, or less than or equal to 10 nanomolar, as demonstrated by a suitable assay for Syk kinase activity, such as the assay as described in Example 12; and may have reduction in CD63 expression with an EC_{50} value less than or equal to 1 micromolar, less than or equal to 500 nanomolar, less than or equal to 200

nanomolar, less than or equal to 150 nanomolar, less than or equal to 100 nanomolar, or less than or equal to 75 nanomolar, as demonstrated by a suitable assay for the measurement of CD63 expression in basophils, such as the assay as described in Example 9.

In some embodiments, in addition to having the property of one or more of Syk kinase inhibition or reduction of basophil activation as measured by CD63 expression, including having both of the properties of Syk kinase inhibition and reduction of basophil activation as measured by CD63 expression, the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, may have desirable properties for potential use as a pharmaceutical, including one or more of kinetic solubility and low levels of hepatocyte clearance. In some embodiments, the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, may have a desirable property of one or more of kinetic solubility and low levels of hepatocyte clearance, including kinetic solubility at 37 °C in phosphate buffer at pH 7.4 of greater than or equal to 10 μM, greater than or equal to 20 μM, greater than or equal to 30 μM, greater than or equal to 40 μM, greater than or equal to 50 μM, greater than or equal to 60 μM, greater than or equal to 70 μM, greater than or equal to 80 μM, or greater than or equal to 90 μM, as demonstrated by a suitable measure of kinetic solubility, such as the assay as described in Example 10; and/or may have a predicted hepatocyte clearance of less than or equal to 0.50 L/hr/kg, less than or equal to 0.40 L/hr/kg, less than or equal to 0.30 L/hr/kg, less than or equal to 0.20 L/hr/kg, less than or equal to 0.10 L/hr/kg, less than or equal to 0.09 L/hr/kg, less than or equal to 0.08 L/hr/kg, less than or equal to 0.07 L/hr/kg, or less than or equal to 0.06 L/hr/kg, as demonstrated by a suitable measure of predicted hepatocyte clearance, such as the assay as described in Example 11.

In some embodiments, the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, may have a desirable property of kinetic solubility, and low levels of hepatocyte clearance, including kinetic solubility at 37 °C in phosphate buffer at pH 7.4 of greater than or equal to 10 μM, greater than or equal to 20 μM, greater than or equal to 30 μM, greater than or equal to 40 μM, greater than or equal to 50 μM, greater than or equal to 60 μM, greater than or equal to 70 μM, greater than or equal to 80 μM, or greater than or equal to 90 μM, as demonstrated by a suitable measure of kinetic solubility, such as the

assay as described in Example 10; and may have a predicted hepatocyte clearance of less than or equal to 0.50 L/hr/kg, less than or equal to 0.40 L/hr/kg, less than or equal to 0.30 L/hr/kg, less than or equal to 0.20 L/hr/kg, less than or equal to 0.10 L/hr/kg, less than or equal to 0.09 L/hr/kg, less than or equal to 0.08 L/hr/kg, less than or equal to 0.07 L/hr/kg, or less than or equal to 0.06 L/hr/kg, as demonstrated by a suitable measure of predicted hepatocyte clearance, such as the assay as described in Example 11.

In some embodiments, the compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, may be effective in both of Syk kinase inhibition and reduction of CD63 expression, and may have a desirable property of kinetic solubility, and low levels of hepatocyte clearance, for example, the compound may have Syk kinase activity with an IC_{50} value less than or equal to 1 micromolar, less than or equal to 500 nanomolar, less than or equal to 200 nanomolar, less than or equal to 100 nanomolar, less than or equal to 50 nanomolar, less than or equal to 20 nanomolar, or less than or equal to 10 nanomolar, as demonstrated by a suitable assay for Syk kinase activity, such as the assay as described in Example 12; and may have reduced CD63 expression with an EC_{50} value less than or equal to 1 micromolar, less than or equal to 500 nanomolar, less than or equal to 200 nanomolar, less than or equal to 150 nanomolar, less than or equal to 100 nanomolar, or less than or equal to 75 nanomolar, as demonstrated by a suitable assay for the measurement of CD63 expression in basophils, such as the assay as described in Example 10; and may have kinetic solubility at 37 ^{o}C in phosphate buffer at pH 7.4 of greater than or equal to 10 μM, greater than or equal to 20 μM, greater than or equal to 30 μM, greater than or equal to 40 μM, greater than or equal to 50 μM, greater than or equal to 60 μM, greater than or equal to 70 μM, greater than or equal to 80 μM, or greater than or equal to 90 μM, as demonstrated by a suitable measure of kinetic solubility, such as the assay as described in Example 10; and may have a predicted hepatocyte clearance of less than or equal to 0.50 L/hr/kg, less than or equal to 0.40 L/hr/kg, less than or equal to 0.30 L/hr/kg, less than or equal to 0.20 L/hr/kg, less than or equal to 0.10 L/hr/kg, less than or equal to 0.09 L/hr/kg, less than or equal to 0.08 L/hr/kg, less than or equal to 0.07 L/hr/kg, or less than or equal to 0.06 L/hr/kg, as demonstrated by a suitable measure of predicted hepatocyte clearance, such as the assay as described in Example 11.

Methods of Use

Provided is a method of inhibiting Syk activing in a subject, comprising administrating to the subject an effective amount of a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof. In one aspect, the subject is administered a pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, and a pharmaceutically acceptable vehicle.

Methods of use may also include inhibiting Syk activity and/ or inhibiting B-cell activity, by inhibiting ATP binding or hydrolysis by Syk or by some other mechanism, *in vivo*, by administering an effective concentration of a compound of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof. An example of an effective concentration would be that concentration sufficient to inhibit Syk activity *in vitro*. An effective concentration may be ascertained experimentally, for example by assaying blood concentration of the compound following administration to a subject, or theoretically, by calculating bioavailability.

Pharmaceutical Compositions

Compounds of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, may be provided in the form of pharmaceutical compositions. This disclosure therefore provides pharmaceutical compositions that contain, as the active ingredient, one or more of the compounds described, or a pharmaceutically acceptable salt or pharmaceutically acceptable ester thereof, and one or more pharmaceutically acceptable vehicle, such as excipients, carriers, including inert solid diluents and fillers, diluents, including sterile aqueous solution and various organic solvents, permeation enhancers, solubilizers and adjuvants. Such compositions are prepared in a manner well known in the pharmaceutical art (see, e.g., Remington's Pharmaceutical Sciences, Mace Publishing Co., Philadelphia, PA 17th Ed. (1985); and Modern Pharmaceutics, Marcel Dekker, Inc. 3rd Ed. (G.S. Banker & C.T. Rhodes, Eds.)

Synthesis

The compounds of the disclosure may be prepared using methods disclosed herein and routine modifications thereof which will be apparent given the disclosure herein and methods well known in the art. Conventional and well-known synthetic methods may be used in addition to the teachings herein. The synthesis of typical compounds of Formula I, or a pharmaceutically acceptable salt or co-crystal thereof, may be accomplished as described in the following examples. If available, reagents may be purchased commercially, e.g. from Sigma Aldrich or other chemical suppliers.

General Syntheses

Typical embodiments of compounds in accordance with the present disclosure may be synthesized using the general reaction schemes described below. It will be apparent given the description herein that the general schemes may be altered by substitution of the starting materials with other materials having similar structures to result in products that are correspondingly different. Descriptions of syntheses follow to provide numerous examples of how the starting materials may vary to provide corresponding products. Given a desired product for which the substituent groups are defined, the necessary starting materials generally may be determined by inspection. Starting materials are typically obtained from commercial sources or synthesized using published methods.For synthesizing compounds which are embodiments of the present disclosure, inspection of the structure of the compound to be synthesized will provide the identity of each substituent group. The identity of the final product will generally render apparent the identity of the necessary starting materials by a simple process of inspection, given the examples herein.

Synthetic Reaction Parameters

The compounds of this disclosure can be prepared from readily available starting materials using, for example, the following general methods and procedures. It will be appreciated that where typical or preferred process conditions (i.e., reaction temperatures, times, mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. Optimum reaction conditions may vary with the

particular reactants or solvent used, but such conditions can be determined by one skilled in the art by routine optimization procedures.

Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary to prevent certain functional groups from undergoing undesired reactions. Suitable protecting groups for various functional groups as well as suitable conditions for protecting and deprotecting particular functional groups are well known in the art. For example, numerous protecting groups are described in T. W. Greene and G. M. Wuts (1999) *Protecting Groups in Organic Synthesis*, 3rd Edition, Wiley, New York, and references cited therein.

Furthermore, the compounds of this disclosure may contain a chiral center. Accordingly, if desired, such compounds can be prepared or isolated as pure stereoisomers, i.e., as individual enantiomers or as stereoisomer-enriched mixtures. All such stereoisomers (and enriched mixtures) are included within the scope of this disclosure, unless otherwise indicated. Pure stereoisomers (or enriched mixtures) may be prepared using, for example, optically active starting materials or stereoselective reagents well-known in the art. Alternatively, racemic mixtures of such compounds can be separated using, for example, chiral column chromatography, chiral resolving agents, and the like.

The starting materials for the following reactions are generally known compounds or can be prepared by known procedures or obvious modifications thereof. For example, many of the starting materials are available from commercial suppliers such as Aldrich Chemical Co. (Milwaukee, Wisconsin, USA). Others may be prepared by procedures or obvious modifications thereof, described in standard reference texts such as Fieser and Fieser's Reagents for Organic Synthesis, Volumes 1-15 (John Wiley, and Sons, 1991), Rodd's Chemistry of Carbon Compounds, Volumes 1-5, and Supplementals (Elsevier Science Publishers, 1989) organic Reactions, Volumes 1-40 (John Wiley, and Sons, 1991), March's Advanced Organic Chemistry, (John Wiley, and Sons, 5th Edition, 2001), and Larock's Comprehensive Organic Transformations (VCH Publishers Inc., 1989).

The terms "solvent," "inert organic solvent" or "inert solvent" refer to a solvent inert under the conditions of the reaction being described in conjunction therewith (including, for

example, benzene, toluene, acetonitrile, tetrahydrofuran ("THF"), dimethylformamide ("DMF"), chloroform, methylene chloride (or dichloromethane), diethyl ether, methanol, pyridine and the like). Unless specified to the contrary, the solvents used in the reactions of the present disclosure are inert organic solvents, and the reactions are carried out under an inert gas, preferably nitrogen.

The term "q.s." means adding a quantity sufficient to achieve a stated function, e.g., to bring a solution to the desired volume (i.e., 100%).

The following examples are included to demonstrate preferred embodiments of the disclosure. It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the disclosure, and thus can be considered to constitute preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed and still obtain a like or similar result without departing from the spirit and scope of the disclosure.

List of abbreviations and acronyms.

Abbreviation	**Meaning**
°C	Degree Celcius
anal	Analytical
ATP	Adenosine-5'-triphosphate
ATX II	Anemonia sulcata toxin
AcOH	Acetic acid
ACN	Acetonitrile
CAN	Ceric ammonium nitrate
CDI	1,1'-carbonyldiimidazole
CHO	Chinese hamster ovary
conc.	Concentrated
D	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DAST	(Diethylamino)sulfur trifluoride

Abbreviation	Meaning
Dd	Doublet of doublets
DCE	1,2-dichloroethane
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIPEA	N,N-diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
dppf	1,1'-Bis(diphenylphosphino)ferrocene
EA	Ethyl alcohol
ECF	Extracellular fluid
EDTA	Ethylenediaminetetraacetic acid
EGTA	Ethylene glycol tetraacetic acid
equiv/eq	Equivalents
ESI	Electrospray ionization
Ac	Acetate
Et	Ethyl
EtOAc	Ethyl Acetate
G	Grams
HEPES	(4-(2-Hydroxyethyl)-1-piperazineethanesulfonic acid)
HATU	2-(7-Aza-1H-Benzotriazole -1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
hERG	human Ether-à-go-go Related Gene
HMDS	hexamethyldisilazane(azide)
HPLC	High-performance liquid chromatography
H	Hours
Hz	Hertz
IPA	Isopropyl alcohol
IC_{50}	The half maximal inhibitory concentration
IMR-32	Human neuroblastoma cell line

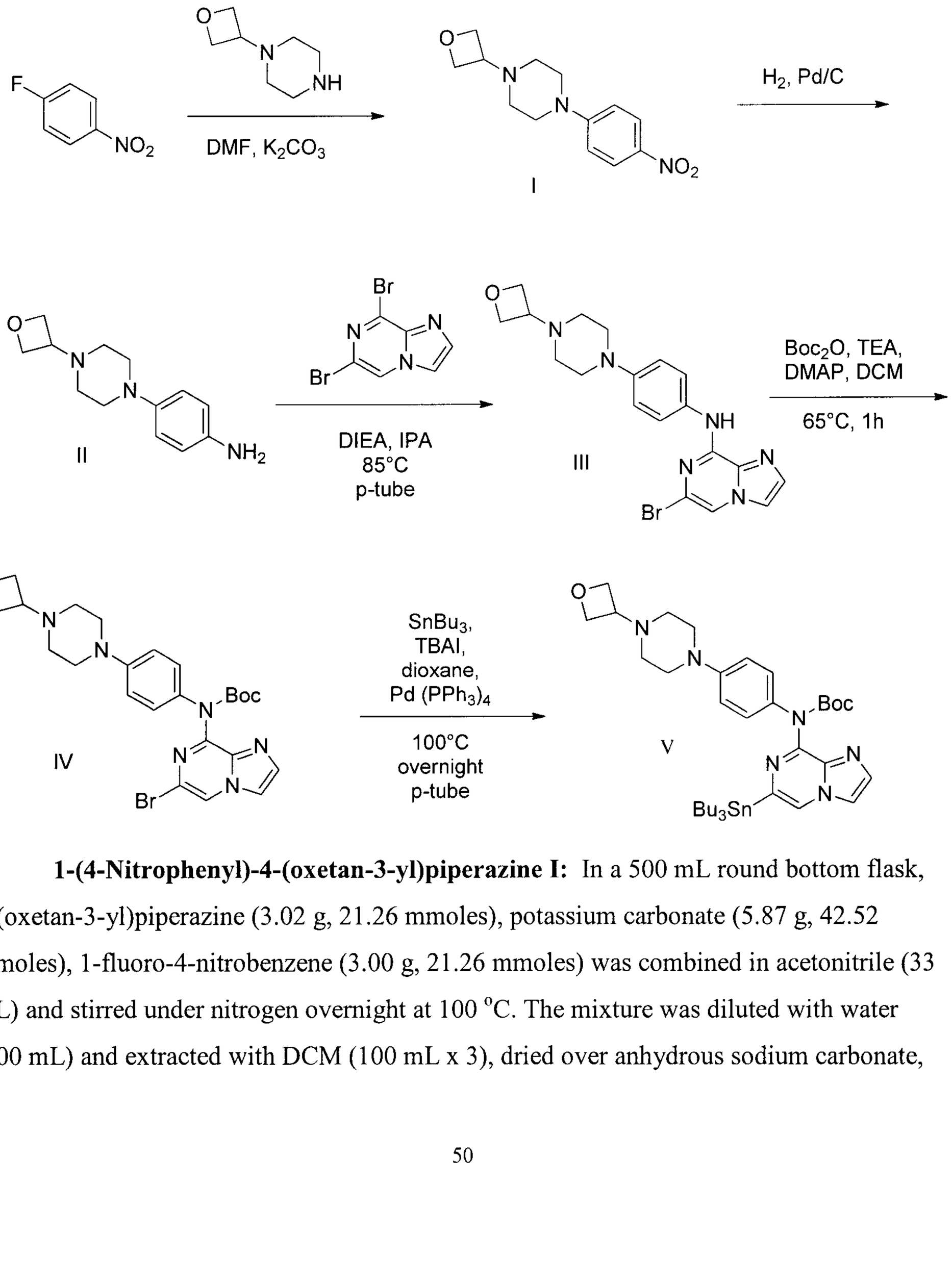
Abbreviation	Meaning
J	Coupling constant
Kg	Kilogram
kHz	Kilohertz
LAH	Lithium ammonium hydride
LCMS/LC-MS	Liquid chromatography–mass spectrometry
M	Molar
M	multiplet
m/z	mass-to-charge ratio
M+	Mass peak
M+H	Mass peak plus hydrogen
mCPBA	3-chloroperoxybenzoic acid
Me	Methyl
MeOH	Methanol
mg	Milligram
MHz	Megahertz
min/m	Minute
ml/mL	Milliliter
mM	Millimolar
mmol	Millimole
nmol	Nanomole
mOsmol	Milliosmole
MRM	Magnetic Resonance Microscopy
MS	Mass spectroscopy
ms	Millisecond
mV	Millivolt
mw	Microwave
N	Normal
mol	Mole
NMP	*N*-methylpyrrolidinone
NMR	Nuclear magnetic resonance

Abbreviation	Meaning
pA	Picoamps
Ph	Phenyl
ppm	Parts per million
prep	Preparative
q.s.	Quantity sufficient to achieve a stated function
Rf	Retention factor
RP	Reverse phase
RT/rt	Room temperature
S	Second
S	Singlet
SEM	2-(Trimethylsilyl)ethoxymethyl
T	Triplet
TB	Tonic Block
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	trimethylsilyl
TTX	Tetrodotoxin
UDB	Use Dependent Block
WT	Wild type
Δ	Chemical shift
Mg	Microgram
µL/ µl	Microliter
µM	Micromolar
µm	Micrometer
µmol	Micromole

EXAMPLES

Preparation of Common Intermediates

Intermediate 1.01. Preparation of tert-Butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate IV and tert-butyl 4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl(6-(tributylstannyl)imidazo[1,2-a]pyrazin-8-yl)carbamate V



1-(4-Nitrophenyl)-4-(oxetan-3-yl)piperazine I: In a 500 mL round bottom flask, 1-(oxetan-3-yl)piperazine (3.02 g, 21.26 mmoles), potassium carbonate (5.87 g, 42.52 mmoles), 1-fluoro-4-nitrobenzene (3.00 g, 21.26 mmoles) was combined in acetonitrile (33 mL) and stirred under nitrogen overnight at 100 °C. The mixture was diluted with water (100 mL) and extracted with DCM (100 mL x 3), dried over anhydrous sodium carbonate,

filtered and the filtrate was concentrated. The residue was dissolved in minimal DCM using a sonicator and crashed out with hexane. The precipitate was filtered, washed with hexane and dried to provide the title compound I .

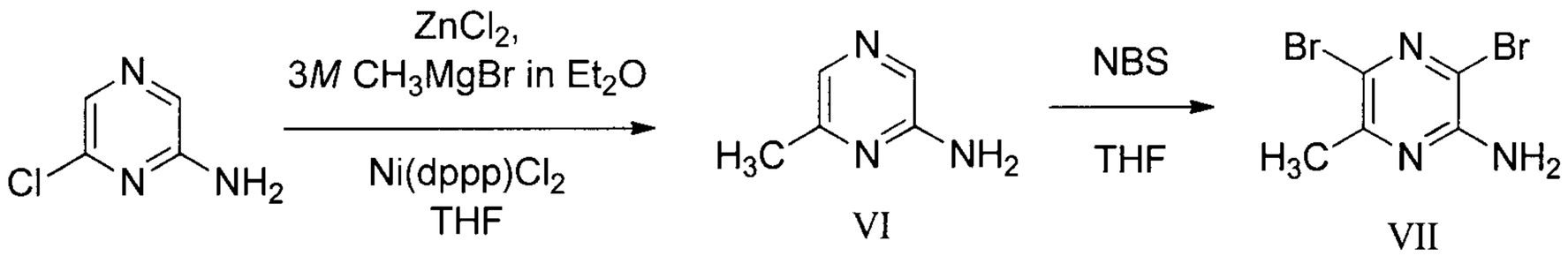
4-(4-(Oxetan-3-yl)piperazin-1-yl)aniline II: In a hydrogenation vessel, 1-(4-nitrophenyl)-4-(oxetan-3-yl)piperazine I (4.70 g, 17.85 mmoles) was dissolved as much as possible in MeOH (26 mL) and DCM (5 mL). Pd/C (10%) (2.85 g, 2.68 mmoles) was added and the reaction was stored under nitrogen. The reaction was shaken on the Parr hydrogenator at 45 PSI. After 15 minutes, the reaction was fully recharged to 45 PSI and shaken for an additional hour. The material was filtered over celite, washed with 25% MeOH/DCM and concentrated to provide the title compound II.

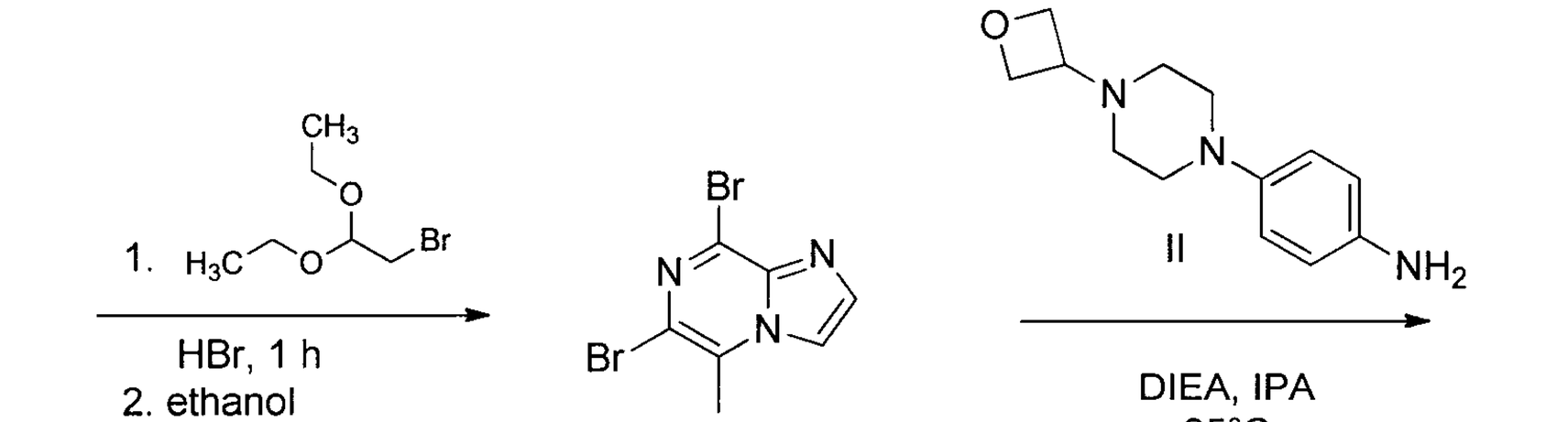
6-Bromo-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine III: To 4-(4-(oxetan-3-yl)piperazin-1-yl)aniline II (2.00 g, 8.57 mmoles), hunig's base (3.29 mL) and 6,8-dibromoimidazo[1,2-a]pyrazine (2.37 g, 8.57 mmoles) was added in DMF (43 mL). The reaction was stirred at 85 °C in a pressure tube for overnight. The material was quenched with saturated sodium bicarbonate, extracted with DCM (120 mL x 3) and the organic layers were combined and washed with water (120 mL x 3), dried over anhydrous sodium carbonate and concentrated. The crude material was purified using a 120 g Isco column and eluted off using a stepwise gradient of 0-60% (10% MeOH/DCM). The desired fractions were combined and concentrated to provide the title compound III.

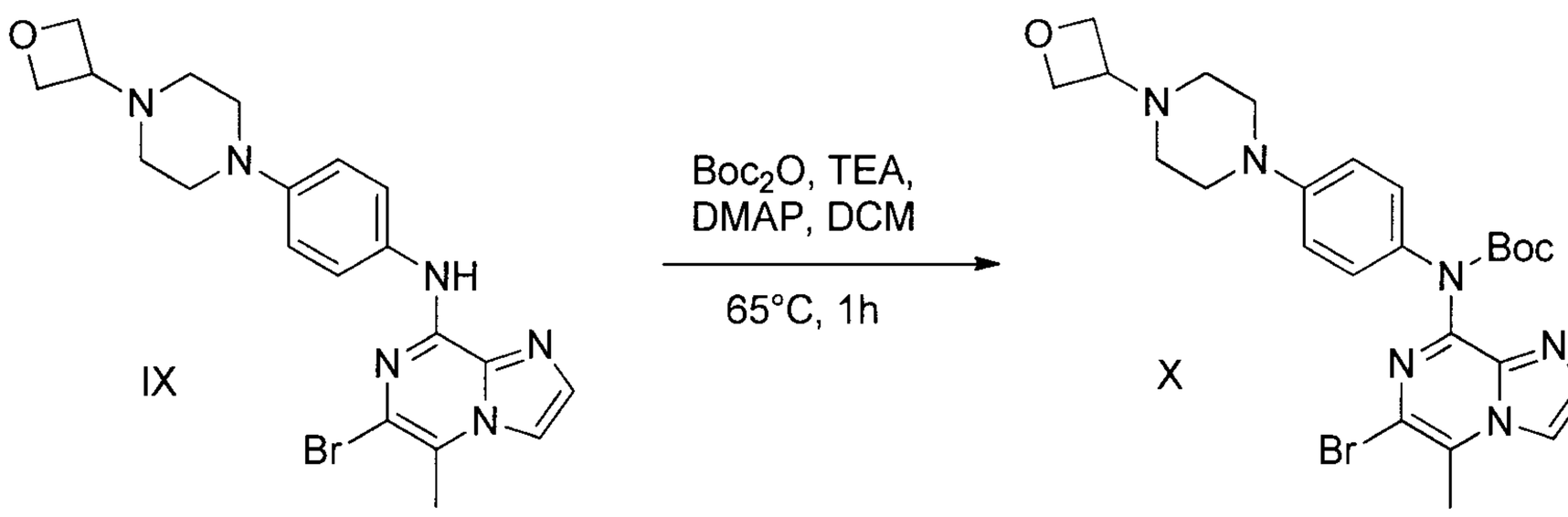
tert-Butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate IV: 6-bromo-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine III (1000 mg, 2.33 mmol), di-tert-butyl dicarbonate (1016.72 mg, 4.66 mmol) and N,N-dimethylpyridin-4-amine (21.34 mg, 0.17 mmol) were stirred in DCM (1.01 ml) and refluxed at 65 °C for 3h. The reaction was diluted with 100 mL of DCM, washed with H2O (x3), dried, filtered and concentrated. The crude material was dissolved in minimal DCM, loaded onto a preloaded silica loader and eluted off a 40 g column using 0-30% MeOH/DCM over 20 column volumes. The desired fractions were combined and concentrated to provide the title compound IV (1.2 g, 97%). This compound is used in Example 2.

tert-Butyl 4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl(6-(tributylstannyl)imidazo[1,2-a]pyrazin-8-yl)carbamate V: In a 350 mL p-tube, tert-butyl 6-bromoimidazo[1,2-a]pyrazin-8-yl(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate IV (8150 mg, 15.39 mmol), 1,1,1,2,2,2-hexabutyldistannane (11.67 ml, 23.09 mmol), tetrakis(triphenylphosphine)palladium (889.43 mg, 0.77 mmol), and tetrabutylammonium iodide (5686.03 mg, 15.39 mmol) were combined in dioxane (62 ml) and heated to 110 °C overnight. According to LCMS, no starting material remained. The reaction was absorbed onto celite and eluted off a 160 g alumina column using a 0-10-20-30-100% (50% EtOAc/Hex-Hex) gradient holding at 50% for 10-15 column volumes over 50-60 column volumes to provide the title compound V. This compound is used in Examples 1 and 2.

Intermediate 1.02. Preparation tert-butyl (6-bromo-5-methylimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate X







6-Methylpyrazin-2-amine VI: To a solution of anhydrous zinc(II) chloride (26.3 g, 193 mmol) in THF (150 mL) at 0 °C, was added 3M methyl magnesium bromide in diethyl ether (129 mL) drop wise over a period of 1 h. [1,3-bis(diphenylphosphino)propane]nickel(II) chloride (2.08 g, 3.85 mmol) was then added and the mixture allowed to warm to room temperature. To the above mixture, a solution of 6-chloro-2-aminopyrazine (5.00 g, 38.6 mmol) in anhydrous THF (25 mL) was added and the reaction stirred, under a nitrogen atmosphere, at reflux for 6 h. After this time, the mixture was cooled to room temperature, then to 0 °C and carefully quenched with saturated aqueous ammonium chloride (50 mL). The organic layer was separated and dried over sodium sulfate. The drying agent was filtered and the filtrate concentrated under reduced pressure to provide crude 6-methylpyrazin-2-amine VI (2.60 g, 62%) as a light yellow solid which was used in the next step without purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.63 (s, 1H), 7.53 (s, 1H), 4.96 (bs, 2H), 2.16 (s, 3H).

3,5-Dibromo-6-methylpyrazin-2-amine VII: To a solution of 6-methylpyrazin-2-amine VI (2.00 g, 18.3 mmol) in THF (40 mL) at 10 °C, was added *N*-bromosuccinimide (6.70 g, 37.6 mmol) portion wise over 15 min and the mixture allowed to warm to room temperature while stirring. After 2 h, the reaction was concentrated under reduced pressure and the resulting residue was purified by column chromatography (silica, gradient, hexanes to EtOAc) to provide 3,5-dibromo-6-methylpyrazin-2-amine VII: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.93 (bs, 2H), 2.38 (s, 3H).

6,8-Dibromo-5-methylimidazo[1,2-*a*]pyrazine VIII: A mixture of 2-bromo-1,1-diethoxyethane (3.21 mL, 20.7 mmol) and 48% aqueous hydrobromic acid (1.0 mL) was stirred at reflux for 2 h. The reaction was then cooled to room temperature and treated with sodium bicarbonate until gas evolution ceased. The mixture was filtered and the filtrate diluted with ethanol (15 mL). To this mixture, 3,5-dibromo-6-methylpyrazin-2-amine VII (3.00 g, 11.2 mmol) was added and the reaction stirred at reflux for 16 h. After this time, the reaction was cooled to room temperature and concentrated under reduced pressure to a volume of approximately 10 mL. The suspension was filtered and the filter cake washed with cold ethanol (5 mL). The filter cake was then taken into water (50 mL) and the pH was adjusted to ~ 8 with potassium carbonate. The resulting suspension was filtered and the

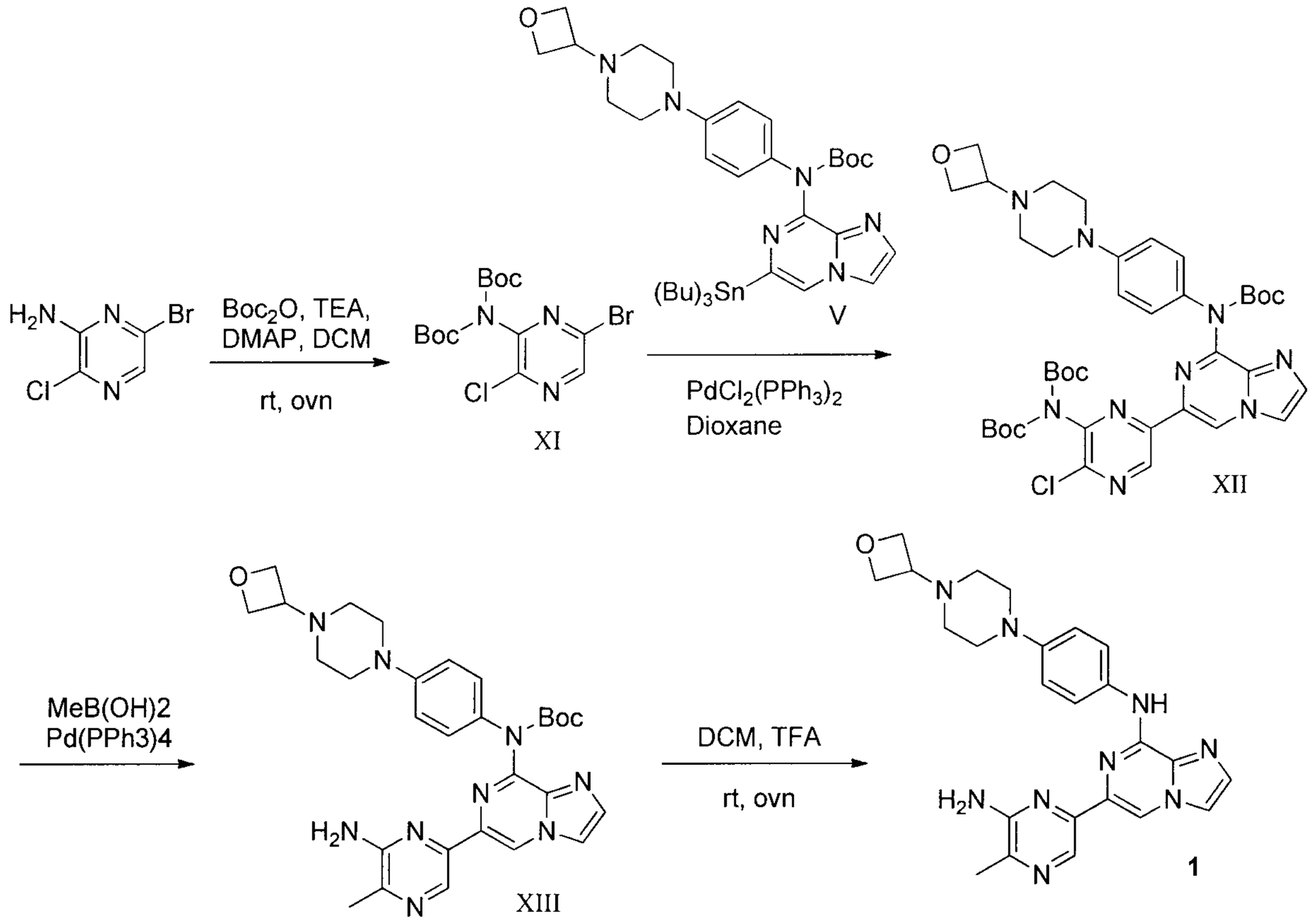
filter cake dried to a constant weight under vacuum to provide 6,8-dibromo-5-methylimidazo[1,2-*a*]pyrazine VIII: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.90 (s, 1H), 7.72 (s, 1H), 2.74 (s, 3H).

6-Bromo-5-methyl-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine IX: The compound IX was prepared from 6,8-dibromo-5-methylimidazo[1,2-*a*]pyrazine VIII using the method as described for preparing 6-bromo-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine III in Intermediate Example 1.01.

tert-Butyl (6-bromo-5-methylimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate X: The compound X was prepared from 6-bromo-5-methyl-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine IX using the method as described for preparing tert-butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate IV in Intermediate Example 1.01. This compound is used in Example 4.

Synthesis of Examples 1-7

Example 1. Preparation of 6-(6-amino-5-methylpyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazn-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (1)



2-Bis(tert-butoxycarbonyl)amino-6-bromo-3-chloropyrazine XI: 6-Bromo-3-chloropyrazin-2-amine (2000 mg, 9.59 mmol) was dissolved in DCM (48 ml) followed by triethylamine (3.99 ml, 28.78 mmol), di-tert-butyl dicarbonate (4188.12 mg, 19.19 mmol), and N,N-dimethylpyridin-4-amine (87.91 mg, 0.72 mmol). The reaction was allowed to stir at room temperature for overnight. The crude material was washed with water, dried, filtered and concentrated. The crude material was dissolved in minimal DCM and loaded onto a 25 g prepacked silica loader and eluted off a 40 g column using 0-30% MeOH/DCM. The title compound XI was isolated and identified by LCMS and NMR. The product was a mix of mono and bis boc-protected material, mainly bis boc-protected as seen by NMR.

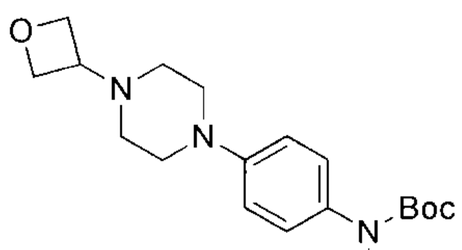
tert-Butyl tert-butoxycarbonyl(6-(8-((tert-butoxycarbonyl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)amino)imidazo[1,2-a]pyrazin-6-yl)-3-chloropyrazin-2-yl)carbamate XII: tert-Butyl 4-(4-(Oxetan-3-yl)piperazin-1-yl)phenyl(6-(tributylstannyl)imidazo[1,2-a]pyrazin-8-yl)carbamate V (1000 mg, 1.4 mmol), 2-Bis(tert-butoxycarbonyl)amino-6-bromo-3-chloropyrazine XI (552 mg, 1.35 mmol), and $PdCl_2(PPh_3)_2$ (142.77 mg, 0.20 mmol), in 1,4-Dioxane (11.27 ml) was irridated in the microwave for 20 min at 140 °C. The reaction was absorbed onto celite and eluted off a 40 g Gold Isco column using 0-10-100% (30% MeOH/DCM) over 20 column volumes. Fractions 34-39 were collected and concentrated. According to NMR, the title compound XII was identified and isolated.

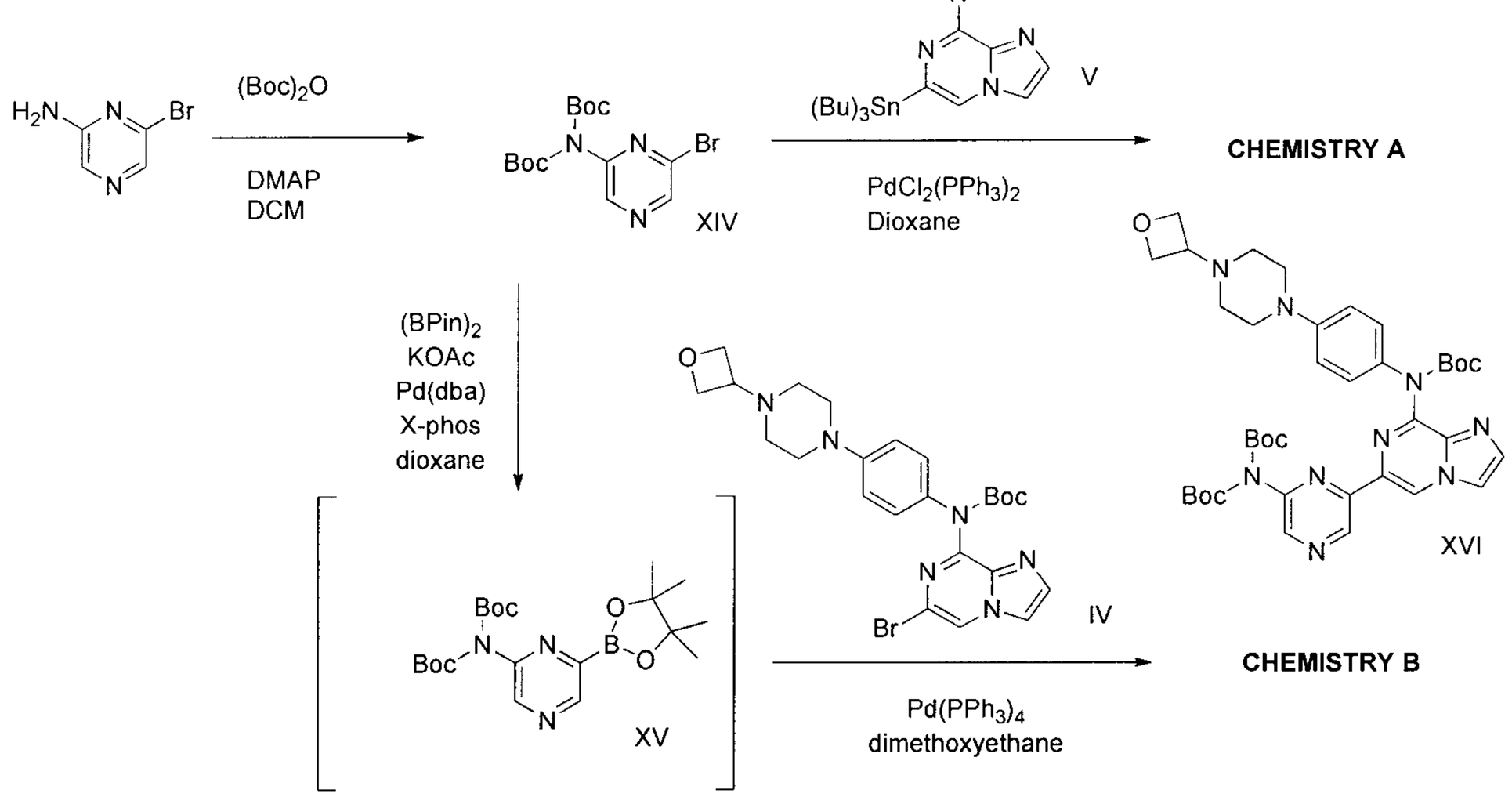
tert-Butyl (6-(6-amino-5-methylpyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate XIII: In a microwave vial, tert-butyl tert-butoxycarbonyl(6-(8-((tert-butoxycarbonyl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)amino)imidazo[1,2-a]pyrazin-6-yl)-3-chloropyrazin-2-yl)carbamate XII (300 mg, 0.44 mmol), methylboronic acid (794.39 mg, 13.27 mmol), tetrakis(triphenylphosphine)palladium (51.12 mg, 0.04 mmol), and 2M Na_2CO_3 (0.44 ml) were combined in DME (1.77 ml) and irridated in the microwave for 20 min at 150 °C. The reaction was worked up using 25% MeOH/DCM and water. The organic layers were combined, dried, filtered and concentrated. The crude material was loaded onto silica and eluted off a 40 g Gold column using 0-5-15-25-50 % (30%MeOH/DCM) over 45 column volumes. The desired fractions were concentrated and provided tert-butyl (6-(6-amino-5-methylpyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate XIII as the minor product and the desired final compound 1 as an inseparable mixture (208mg total) and were taken in to the TFA reaction.

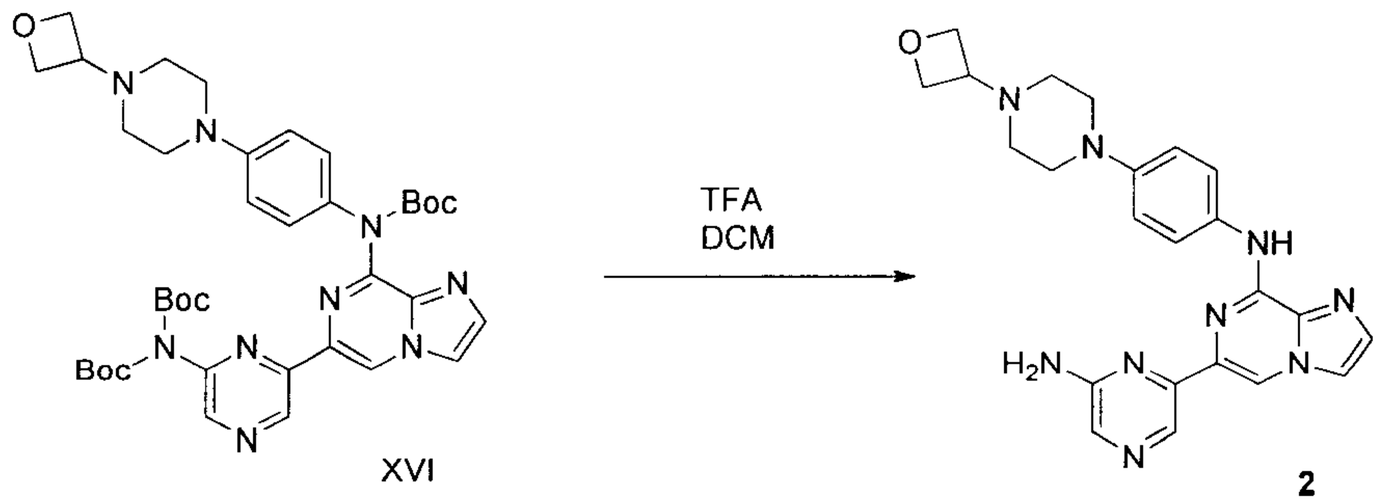
6-(6-Amino-5-methylpyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (1): To a solution of tert-butyl 6-(6-amino-5-methylpyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate XIII (48 mg, 0.09 mmol) and 6-(6-amino-5-methylpyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (1, 160 mg, 0.35 mmol) in DCM (2.5 ml) was added TFA (0.16 ml, 2.15 mmol). Additional TFA (0.48 ml,

6.5 mmol) was added to the reaction mixture to ensure reaction completion. The reaction was cooled to 0 ^{o}C and quenched with sat. $NaHCO_3$, then extracted with DCM (5 ml x 3), and the combined organic layers were washed with water (5 ml x 2), brine (5 ml x 1), dried (Na_2SO_4), and concentrated to give the crude product. The crude material was absorbed onto silica and eluted off a 24 g Gold Isco column using 0-15-25-40-100% (30% MeOH/DCM). The desired fractions were combined and concentrated to provide the desired compound. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$: 458.22. ^{1}H NMR (300 MHz, d_6-DMSO) δ: 9.48 (s, 1H), 8.54 (s, 1H), 8.41 (s, 1H),8.11 (s, 1H), 7.95 (d, 2H), 7.6 (s,1H), 6.98 (d, 2H), 6.2 (s, 2H), 4.58-4.45 (dt, 4H), 3.3 (m, 1H), 3.14 (t, 4H), 2.50-2.4 (dt,4H), 2.33 (s, 1H). Alternatively, compound XII could be taken directly to this step and similarly de-protected to provide the 5-chloropyrazine substituted analog.

Example 2. Preparation of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (2)







2-Bis(tert-butoxycarbonyl)amino-6-bromopyrazine XIV: To a mixture of 6-bromopyrazin-2-amine (5 g, 28.7 mmol) and di-tert-butyl dicarbonate (25.09 g, 114.94 mmol) was added DCM (10 ml) followed by DMAP (0.351 g, 29 mmol). The reaction was heated to 55 °C for 1h, cooled to RT, the reaction was partitioned between water and DCM, purified on silica gel and concentrated to provide 2-bis(tert-butoxycarbonyl)amino-6-bromopyrazine XIV. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$: 374.14. ^{1}H NMR (DMSO) δ: 8.84(d, 2H), 1.39 (s, 18H).

tert-Butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate XVI – CHEMISTRY A route: tert-Butyl 4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl(6-(tributylstannyl)imidazo[1,2-a]pyrazin-8-yl)carbamate V (215 mg, 0.291 mmol), was combined with 2-bis(tert-butoxycarbonyl)amino-6-bromopyrazine XIV (217.58 mg, 0.581 mmol), bis(triphenylphosphine)palladium(II) dichloride(30.61 mg, 0.044 mmol) and 1,4-dioxane (5ml). The reaction mixture was stirred in a microwave reactor at 120 °C for 30 min. The reaction mixture was quenched with saturated KF, extracted with EtOAc, purified on silica gel, eluted with EtOAc. The desired fractions were combined and concentrated to provide 100 mg (46% yield) of tert-butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate XVI. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$: 744.4. ^{1}H NMR (300 MHz d_6-DMSO) δ: 9.37 (s, 1H), 9.18 (s, 1H), 8.77 (s, 1H), 8.33 (d, 1H), 7.87 (d, 1H), 7.28-7.25 (d, 2H), 6.92-6.89 (d, 2H), 4.55-4.41 (m, 4H), 3.4 (m,1H), 3.14-3.11 (m,4H), 2,37-2.34 (m, 4H), 1.37 (s, 18H), 1.3 (s, 9H).

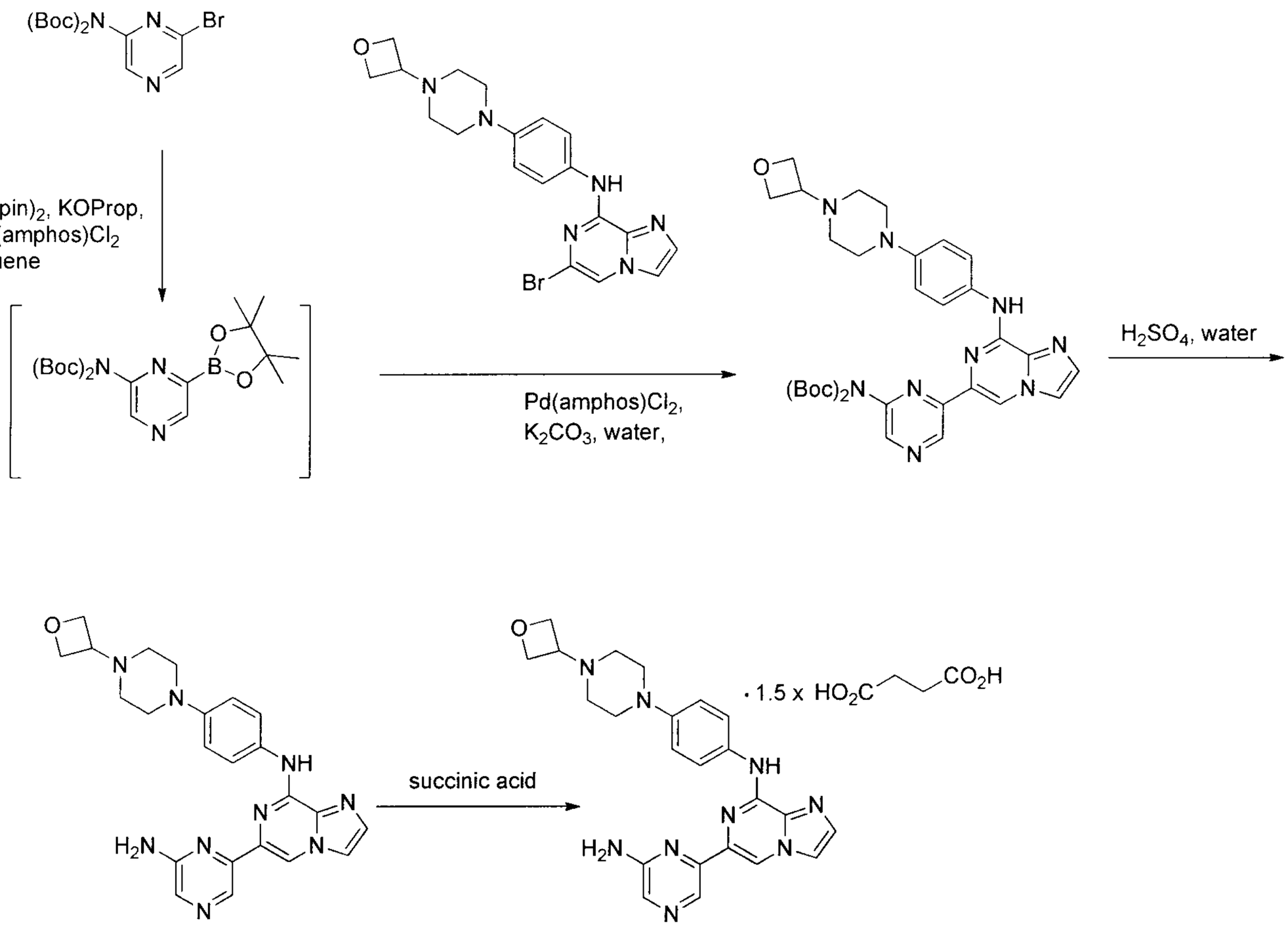
tert-Butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate XVI – CHEMISTRY B route: Step 1: To a dry 250 mL round-bottomed flask was added 2-bis(tert-butoxycarbonyl)amino-6-bromopyrazine XIV (1.0g, 1.0equiv, 2.67mmol), KOAc (790mg, 8.02mmol, 3.0equiv), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (750mg, 2.94mmol, 1.1equiv), Pd(dba) (171mg, 0.187mmol, 0.07equiv) and X-phos (128mg, 0.267mmol, 0.1equiv) followed by 1,4-dioxane (25mL) and the solution was sonicated for 5 min and then purged with N_2 gas for 5 min. The flask with contents was then placed under N_2 atmosphere and heated at 110 °C for 90 min. Once full conversion to the pinacolboronate was achieved by LCMS, the reaction was removed from heat and allowed to cool to RT. Once cool, the reaction contents were filtered through Celite and the filter cake was washed 3 x 20 mL EtOAc. The resultant solution was then concentrated down to a deep red-orange syrup providing N, N-BisBoc 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-amine XV, which was used directly in the next step.

Step 2: The freshly formed N, N-BisBoc 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-amine XV (2.67 mmol based on 100% conversion, 2.0 equiv based on

bromide) was dissolved in 20 Ml of 1,2-dimethoxyethane and to that solution was added tert-butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate IV (707mg, 1.34mmol, 1.0equiv), Na_2CO_3 (283mg, 2.67mmol, 2.0equiv), $Pd(PPh_3)_4$ (155mg, 0.134mmol, 0.1equiv) and water (10mL) and the solution was degassed for 5 min using N_2 gas. The reaction was then placed under N_2 atmosphere and heated at 110 °C for 90 min. LCMS showed complete consumption of the bromide starting material and the reaction was removed from heat and allowed to cool to RT. The reaction was diluted with 100 mL water and 100 mL 20% MeOH/DCM and the organic layer was recovered, extracted 1 x sat. $NaHCO_3$, 1 x sat brine and then dried over Na_2SO_4. The solution was then filtered and concentrated down to an orange-red solid. The sample was then slurried in warm MeOH, sonicated then filtered, washing 2 x 20 mL with cold MeOH and then the cream-colored solid was dried on hi-vacuum overnight to yield 905 mg of tert-butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate XVI.

6-(6-Aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (2): To a solution of tert-butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate XVI (200 mg, 0.269 mmol) in DCM (2 ml) was added TFA (0.5 ml, 6.578 mmol). The reaction was stirred at rt for 16h, saturated sodium bicarbonate was added, extracted with EtOAC and purified on silica gel, eluted with 5%MeOH / EtOAc, 20%MeOH / EtOAc. The desired fractions were combined and concentrated to provide the title compound 2. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$: 444.2. ^{1}H NMR (300 MHz d_6-DMSO) δ: 9.5 (s,1H), 8.588 (s, 1H), 8.47 (s, 1H), 8.12 (d, 1H), 7.95-7.92 (d, 2H), 7.88 (s, 1H), 7.62 (s, 1H), 6.99-6.96 (d, 2H), 6.46 (s, 2H), 4.57-4.53 (m, 2H), 4.48-4.44 (m, 2H), 3.43 (m, 1H), 3.15-3.12 (m, 4H), 2.41-2.38 (m, 4H).

Example 2 - Alternate Synthesis



Di-*tert*-butyl {6-[8-({4-[4-(oxetan-3-yl)piperazin-1-yl]phenyl}amino)imidazo[1,2-*a*]pyrazin-6-yl]pyrazin-2-yl}imidodicarbonate:

To a 720 L reactor, was added di-*tert*-butyl (6-bromopyrazin-2-yl)imidodicarbonate (18.5 kg, 1.41 equiv, 49 mol), bis(pinacolato)diboron (13.8 kg, 1.56 equiv, 54 mol), potassium propionate (11.9 kg, 3.02 equiv, 106 mol), and bis(di-*tert*-butyl(4-dimethylaminophenyl) phosphine)dichloropalladium (1.07 kg, 0.0043 equiv, 1.5 mol), followed by degassed toluene (173 L). The mixture was degassed then heated at 65 °C until the reaction was deemed complete (0% tert-butyl 2-((6-bromopyrazin-2-yl)(tert-butoxycarbonyl)amino)-2-oxoacetate) by UPLC. Upon completion, the reaction was cooled to 23 °C. Once cooled, 6-bromo-*N*-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2- *a*]pyrazin-8-amine (15.0 kg, 1.00 equiv, 35 mol) was added and the mixture was degassed. A degassed aqueous potassium carbonate solution prepared using water (54 L) and potassium carbonate (20.6 g, 4.26 equiv, 149 mol) was then added to the reaction mixture and the reactor contents was degassed. The reactor contents was

heated at 65 °C until reaction was deemed complete (1% 6-bromo-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine) by UPLC. Upon completion, the reaction was cooled to 24 °C.

The cooled mixture was concentrated and then diluted with dichloromethane (300 L), transferred to a 1900 L reactor and rinsed forward with dichloromethane (57 L). *N*-acetyl-L-cysteine (3.8 kg) was charged and the mixture was agitated for 15 h. Water (135 L) was then added and the mixture was filtered and rinsed forward with dichloromethane (68 L). The organic layer was recovered and washed with a brine solution prepared using water (68 L) and sodium chloride (7.5 kg).

The resultant organic layer was polish filtered then concentrated and *tert*-butyl methyl ether (89.9 kg) was slowly charged keeping the temperature at 31 °C. The contents was cooled to 0 °C and aged, then filtered, rinsed with *tert*-butyl methyl ether (32.7 kg) and dried at 40 °C to give di-*tert*-butyl {6-[8-({4-[4-(oxetan-3-yl)piperazin-1-yl]phenyl}amino)imidazo[1,2-*a*]pyrazin-6-yl]pyrazin-2-yl}imidodicarbonate.

LCMS-ESI$^+$ (*m/z*): $[M+H]^+$: 644.3. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.43 (s, 1H), 8.58 (s, 1H), 8.53 (s, 1H), 8.02 (s, 1H), 7.84 (m, 2H), 7.63 (d, 1H), 7.61 (d, 1H), 7.04 (m, 2H), 4.71 (m,4H), 3.59 (m,1H), 3.27 (m, 4H), 2.55 (m, 4H), 1.46 (s, 18H).

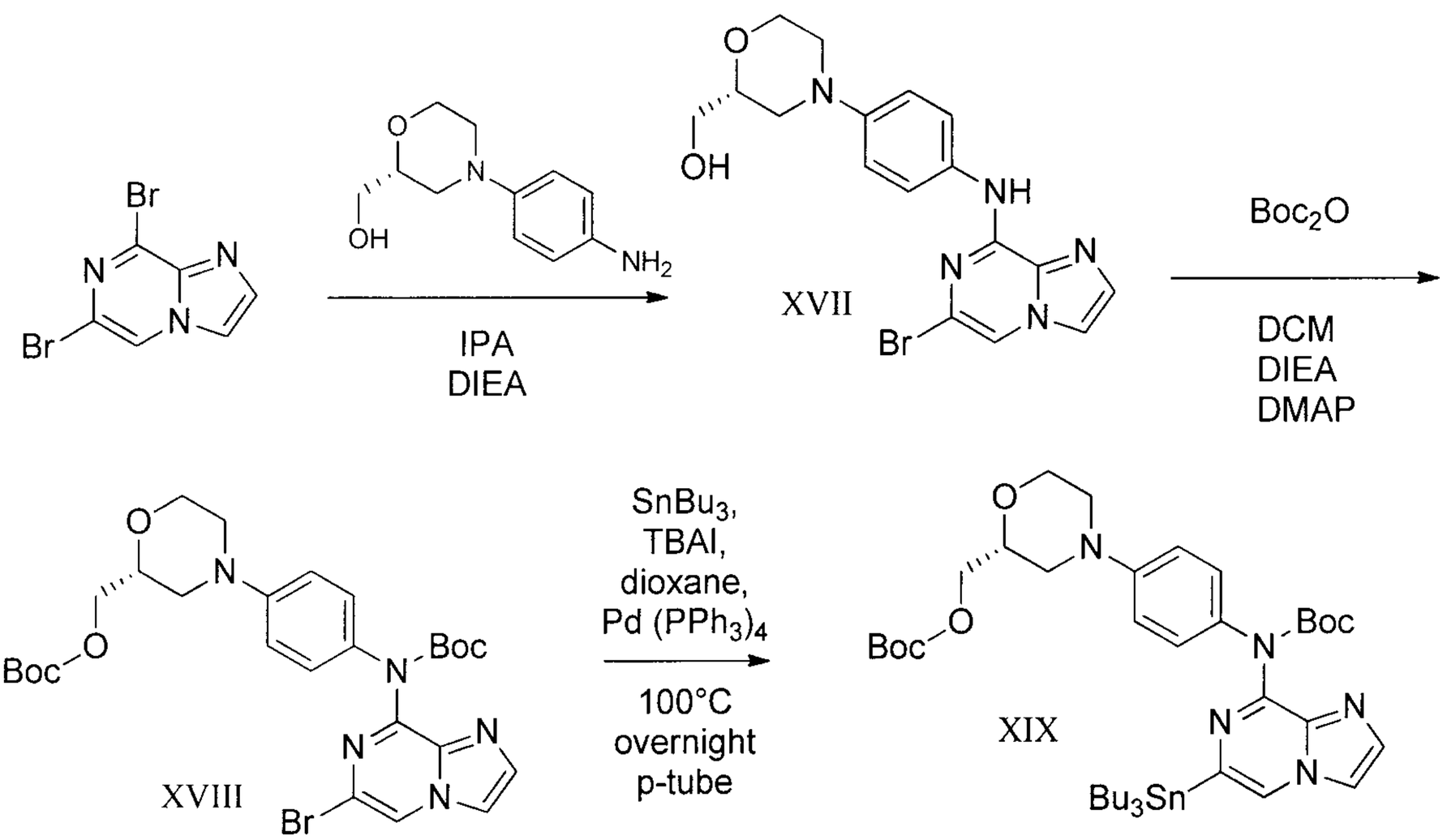
6-(6-Aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine succinate (Example 2):

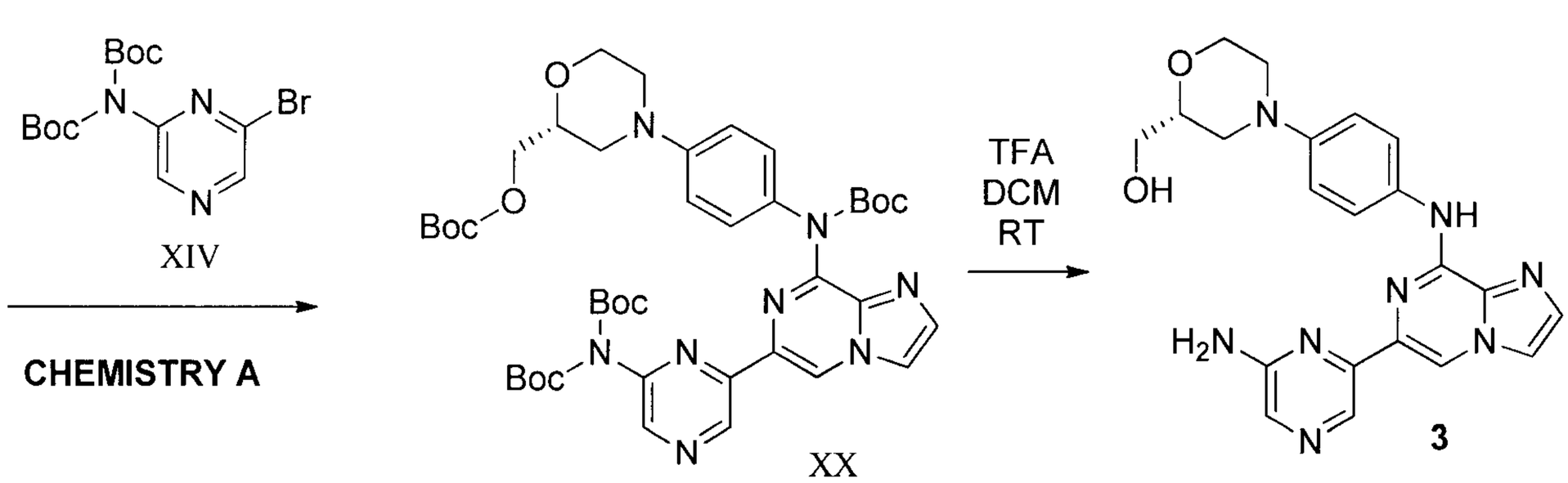
To a slurry of di-tert-butyl {6-[8-({4-[4-(oxetan-3-yl)piperazin-1-yl]phenyl}amino)imidazo[1,2-a]pyrazin-6-yl]pyrazin-2-yl}imidodicarbonate (225 g, 0.35 mol, 1 mol eq.) in water (12 parts) was added a solution of sulfuric acid (3.1 parts, 6.99 mol, 20 mol eq.) in water (5 parts). The reaction was heated to ca. 40 °C and stirred at this temperature for ca. 4 h at which point the reaction is deemed complete. The reaction mixture was cooled to ca. 22 °C, acetone (3 parts) was charged and a solution of sodium carbonate (4.1 parts, 8.75 mol, 25.0 mol eq.) in water (15 parts) was added. The resulting slurry was filtered and the wet cake was washed with water in portions (4 x 1 parts), then with *tert*-butyl methyl ether (4 parts). The wet cake (Example 2 free base) was dried at ca. 60 °C. To the slurry of dry Example 2 free base in 2-propanol (2.3 parts) was added a

solution of succinic acid (Based on the isolated Example 2 free base: 0.43 parts, 1.6 mol eq.) in 2-propanol (15 parts). The resulting slurry was heated to ca. 40 °C and stirred at this temperature for ca. 2 h and then cooled to ca. 22 °C, followed by a stir period of ca. 16 h. The slurry was filtered at ca. 22 °C and the wet cake was washed with 2-propanol (5 parts) and dried at ca. 60 °C to afford the product.

LCMS-ESI$^+$ (*m/z*): $[M+H]^+$: 620.65. ^{1}H NMR (400 MHz d_6-DMSO) δ: 12.2 (broad s,1.5H), 9.58 (s, 1H), 8.63 (s, 1H), 8.50 (s, 1H), 8.15 (s, 1H), 7.95 (d, 2H), 7.90 (s, 1H), 7.64 (s, 1H), 7.00 (d, 2H), 6.50 (s, 2H), 4.52 (dd, 4H), 3.45 (m, 1H), 3.19 (m, 4H), 2.40 (m, 10H).

Example 3. Preparation of (R)-(4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)morpholin-2-yl)methanol (3)





(R)-(4-(4-((6-Bromoimidazo[1,2-a]pyrazin-8-yl)amino)phenyl)morpholin-2-yl)methanol XVII: In a 250 mL round bottom flask equipped with a condenser was placed 6,8-dibromoimidazo[1,2-a]pyrazine (2000 mg, 7.22 mmol) and added 30 mL isopropanol followed by N,N-diisopropylethylamine (2.52 ml, 14.44 mmol) and (R)-(4-(4-aminophenyl)morpholin-2-yl)methanol (1504.12 mg, 7.22 mmol). The reaction was heated to reflux (oil bath 95 °C) overnight. The reaction was cooled and precipitates were collected

by filtration and washed with isopropanol followed by hexanes to give the desired compound XVII.

(R)-tert-Butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(2-(((tert-butoxycarbonyl)oxy)methyl)morpholino)phenyl)carbamate XVIII: In a 250 mL round bottom flask was placed (R)-(4-(4-((6-bromoimidazo[1,2-a]pyrazin-8-yl)amino)phenyl)morpholin-2-yl)methanol XVII (2.80g, 6.9mmol) and added DCM followed by triethylamine (2.9mL, 2.1g, 20.8mmol), DMAP (63g, 0.52mmol) and di-tert-butyl dicarbonate (3.8g, 17.3mmol). The reaction was stirred overnight then diluted with DCM and water, separated, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by chromatograaphy: ISCO 40 g silica with 25 g silica loader, eluting with 0-100% EtOAc/hexanes to give compound XVIII.

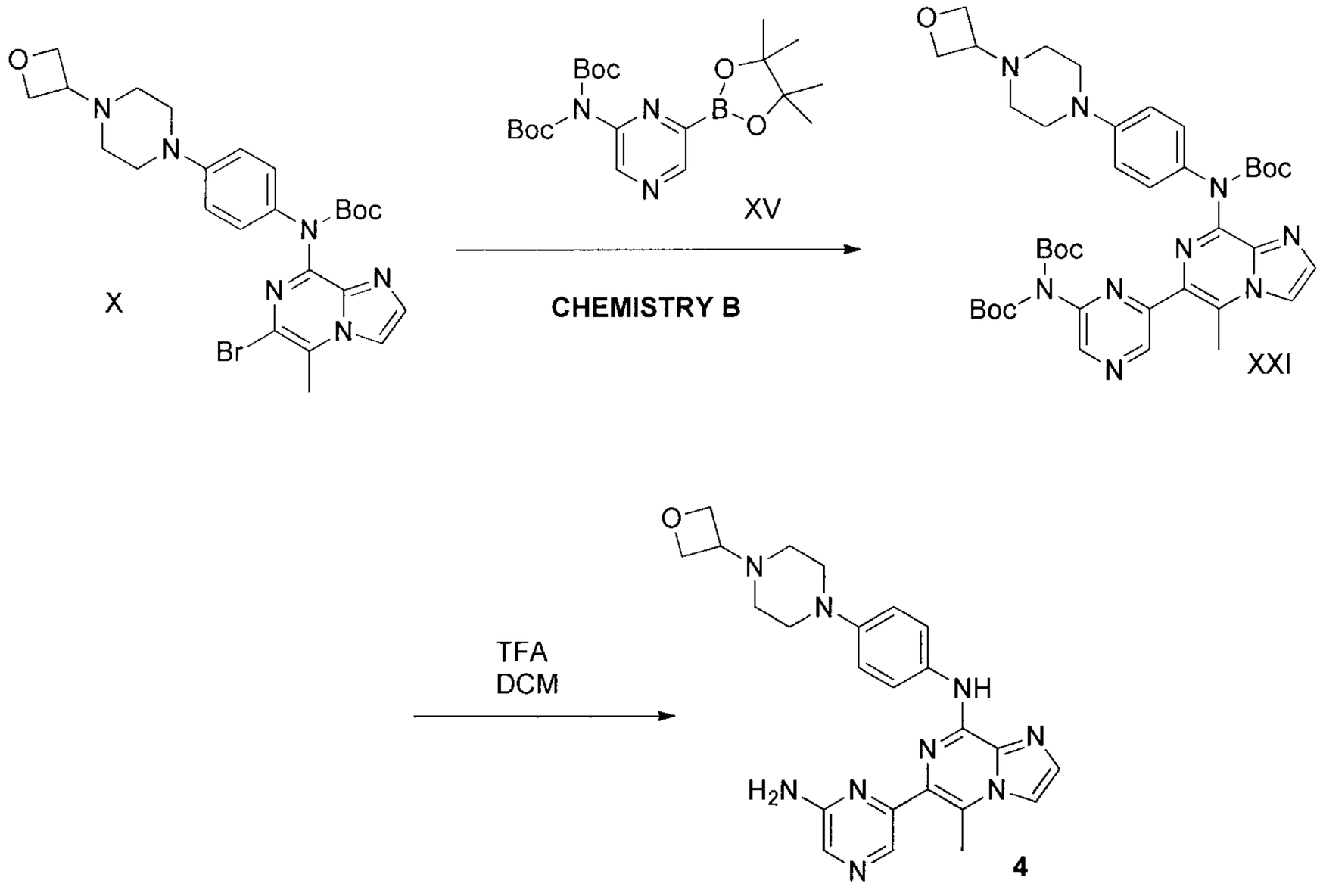
(R)-tert-Butyl (4-(2-(((tert-butoxycarbonyl)oxy)methyl)morpholino)phenyl)(6-(tributylstannyl)imidazo[1,2-a]pyrazin-8-yl)carbamate XIX: (R)-tert-Butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(2-(((tert-butoxycarbonyl)oxy)methyl)morpholino)phenyl)carbamate XVIII was reacted according to the analogous method of Example Intermediate 1.01 to provide (R)-tert-butyl (4-(2-(((tert-butoxycarbonyl)oxy)methyl)morpholino)phenyl)(6-(tributylstannyl)imidazo[1,2-a]pyrazin-8-yl)carbamate XIX.

(R)-tert-Butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(2-(((tert-butoxycarbonyl)oxy)methyl)morpholino)phenyl)carbamate XX: (R)-tert-Butyl (4-(2-(((tert-butoxycarbonyl)oxy)methyl)morpholino)phenyl)(6-(tributylstannyl)imidazo[1,2-a]pyrazin-8-yl)carbamate XIX was reacted with 2-Bis(tert-butoxycarbonyl)amino-6-bromopyrazine XIV according to the analogous method of CHEMISTRY A as described in Example 2 to provide the desired compound (R)-tert-butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(2-(((tert-butoxycarbonyl)oxy)methyl)morpholino)phenyl)carbamate XX.

(R)-(4-(4-((6-(6-Amino-5-methylpyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)morpholin-2-yl)methanol (3): (R)-tert-butyl (6-(6-(bis(tert-

butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(2-(((tert-butoxycarbonyl)oxy)methyl)morpholino)phenyl)carbamate XX (460 mg, 0.56 mmol) in DCM was added to a round bottom flask, and TFA (1.29 ml, 16.85 mmol) was added. The reaction was partially complete after stirring ~5 hours. Added an additional 10 eq TFA and stirred overnight, then concentrated under reduced pressure. 10% MeOH/DCM (~100mL) and sat.aq. sodium bicarbonate were added and stirred 15 min, separated, extracted with ~100mL 10%MeOH/DCM. The organic layers were combined, washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure and dried under vacuum. The resulting solid was triturated with DCM, collected solids via filtration and dried under vacuum to give compound 3. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$: 419.2. ^{1}H NMR (300 MHz d_6-DMSO) δ: 9.57 (s, 1H), 8.59 (s, 1H), 8.47 (s, 1H), 8.13 (d, *J* = 1.2 Hz, 1H), 8.06 – 7.90 (m, 2H), 7.87 (s, 1H), 7.62 (d, *J* = 1.1 Hz, 1H), 7.05 – 6.93 (m, 2H), 6.49 (s, 2H), 4.78 (t, *J* = 5.8 Hz, 1H), 3.98 – 3.87 (m, 1H), 3.71 – 3.36 (m, 7H), 2.63 (td, *J* = 11.7, 3.4 Hz, 1H), 2.37 (dd, *J* = 12.1, 10.5 Hz, 1H). The corresponding (S) isomer, or racemic mixture of compounds is prepared similarly, using (S)-(4-(4-aminophenyl)morpholin-2-yl)methanol or a racemic mixture of (4-(4-aminophenyl)morpholin-2-yl)methanol, respectively, in the first step.

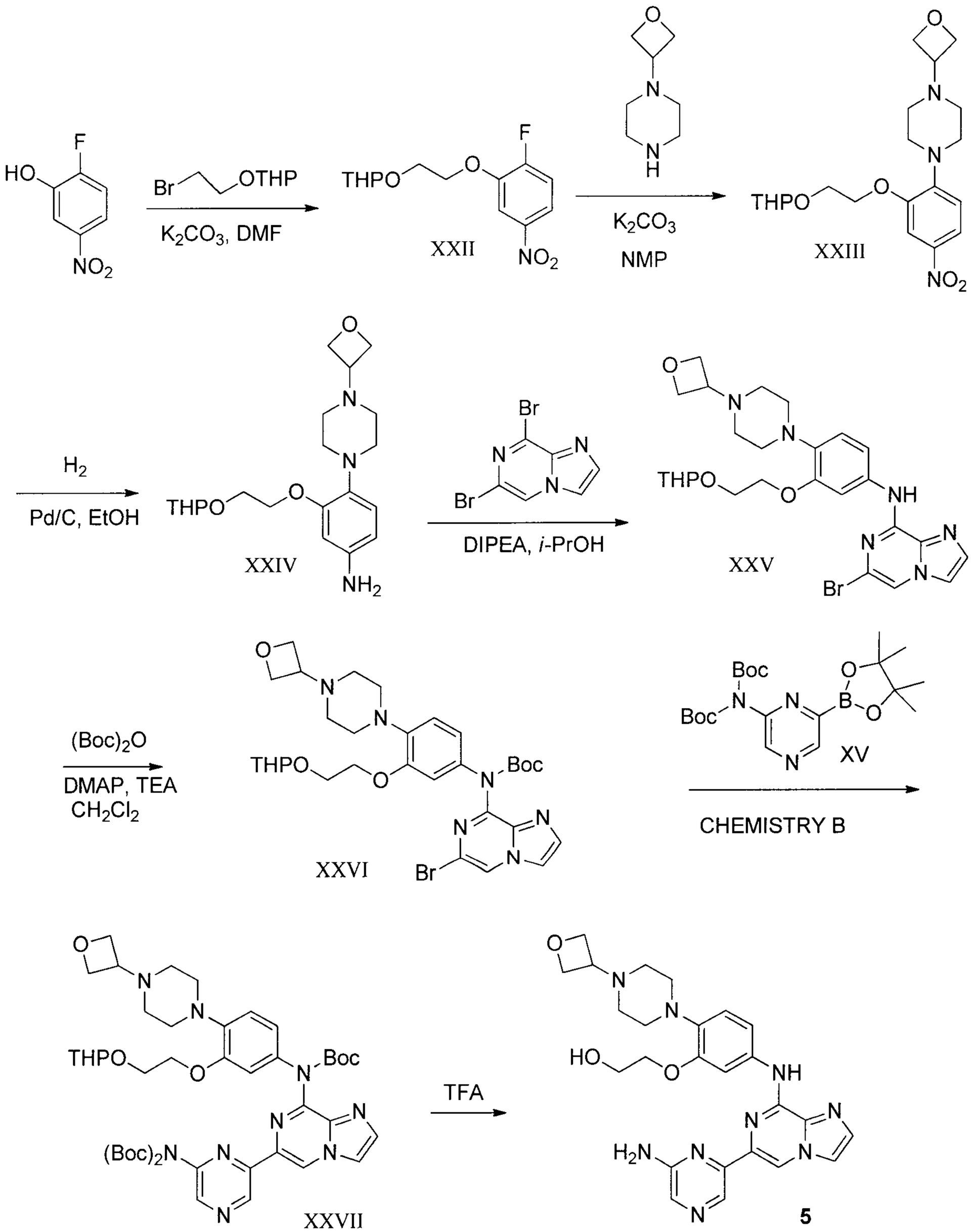
Example 4. Preparation of 6-(6-aminopyrazin-2-yl)-5-methyl-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (4)



tert-Butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)-5-methylimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate XXI: tert-Butyl (6-bromo-5-methylimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate X was reacted with XV according to the methods of CHEMISTRY B as described in Example 2 to provide the desired compound XXI.

6-(6-aminopyrazin-2-yl)-5-methyl-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (4): The compound tert-butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)-5-methylimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)carbamate XXI was de-protected by the analogous method described in Example 2 to provide the desired compound 4. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$: 458.32. ^{1}H NMR (300 MHz, d_6-DMSO) δ: 9.28 (s, 1H), 8.28 (s, 1H), 8.04 (s, 1H), 7.89 (d, 2H), 7.83 (s, 1H), 7.7 (s,1H), 6.91 (d, 2H), 6.46 (s, 2H), 4.6-4.4 (dt, 4H), 3.43 (m, 1H), 3.1 (t, 4H), 2.49 (s,3H), 2.4 (t,4H).

Example 5. Preparation of 2-(5-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol (5)



2-(2-(2-Fluoro-5-nitrophenoxy)ethoxy)tetrahydro-2H-pyran XXII: A mixture of 2-fluoro-5-nitrophenol (4 g, 25 mmol), 2-(2-bromoethoxy)tetrahydro-2H-pyran (4.4 mL, 28 mmol) and potassium carbonate (4.2 g 30 mmol) in DMF (50 mL) was stirred at 50 °C for 16h. The reaction was cooled to room temperature, diluted with EtOAc and H_2O. The aqueous layer was separated and extracted with EtOAc. The combined organic extracts were washed with H_2O (5x's to remove DMF) and brine and dried over sodium sulfate. The resulting residue was purified by column chromatography ISCO Rf (40 g column) eluting with a gradient of 100% hexanes – 1:1 hexanes:EtOAc to provide 2-(2-(2-fluoro-5-nitrophenoxy)ethoxy)tetrahydro-2H-pyran XXII.

1-(4-Nitro-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)-4-(oxetan-3-yl)piperazine XXIII: A mixture of 2-(2-(2-fluoro-5-nitrophenoxy)ethoxy)tetrahydro-2H-pyran XXII (1550 mg, 5.43 mmol), 1-(oxetan-3-yl)piperazine (772 mg, 5.43 mmol) and potassium carbonate (1126.41 mg, 8.15 mmol) in NMP (6 mL) was stirred at 100 °C for 8h. The aqueous layer was separated and extracted with EtOAc. The combined organic extracts were washed with H_2O (5 x to remove NMP) and brine and dried over sodium sulfate. The resulting residue was purified by column chromatography ISCO Rf (24 g column) eluting with a gradient of 100% DCM – 60:35:5 DCM:Et_2O:MeOH to provide 1-(4-nitro-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)-4-(oxetan-3-yl)piperazine XXIII.

4-(4-(Oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)aniline XXIV: To a suspension of 1-(4-nitro-2-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)-4-(oxetan-3-yl)piperazine XXIII (2100 mg, 5.1 mmol) in ethanol (50 mL) was added 10% Pd/C (50% wet, 390 mg dry weight) in a 500-mL Parr hydrogenation bottle. The bottle was evacuated, charged with hydrogen gas to a pressure of 50 psi and shaken at rt for 2 h on a Parr hydrogenation apparatus. The reaction mixture was filtered, and washed with ethanol. The filtrate was concentrated *in vacuo* to give 4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)aniline XXIV.

6-Bromo-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2yl)oxy)ethoxy)phenyl)imidazo[1,2-a]pyrazin-8-amine XXV: To a solution of 4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)aniline XXIV

(619 mg, 2.17 mmol) and 6,8-dibromoimidazo[1,2-a]pyrazine (601 mg, 2.2 mmol) in IPA (15 mL) was added N,N-Diisopropylethylamine (0.95 ml, 5.43 mmol). The mixture was stirred at 110 °C for 16 h. After this time, DCM (10 mL) and sat aqueous $NaHCO_3$ (15 mL) were added. The aqueous layer was separated and extracted with DCM (2 × 10 mL). The combined organic extracts were washed with brine (10 mL) and dried over sodium sulfate. The resulting residue was purified by column chromatography ISCO Rf (24 g column) eluting with a gradient of 100% DCM – 60:35:5 DCM:Et_2O:MeOH to provide 6-bromo-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)imidazo[1,2-a]pyrazin-8-amine XXV.

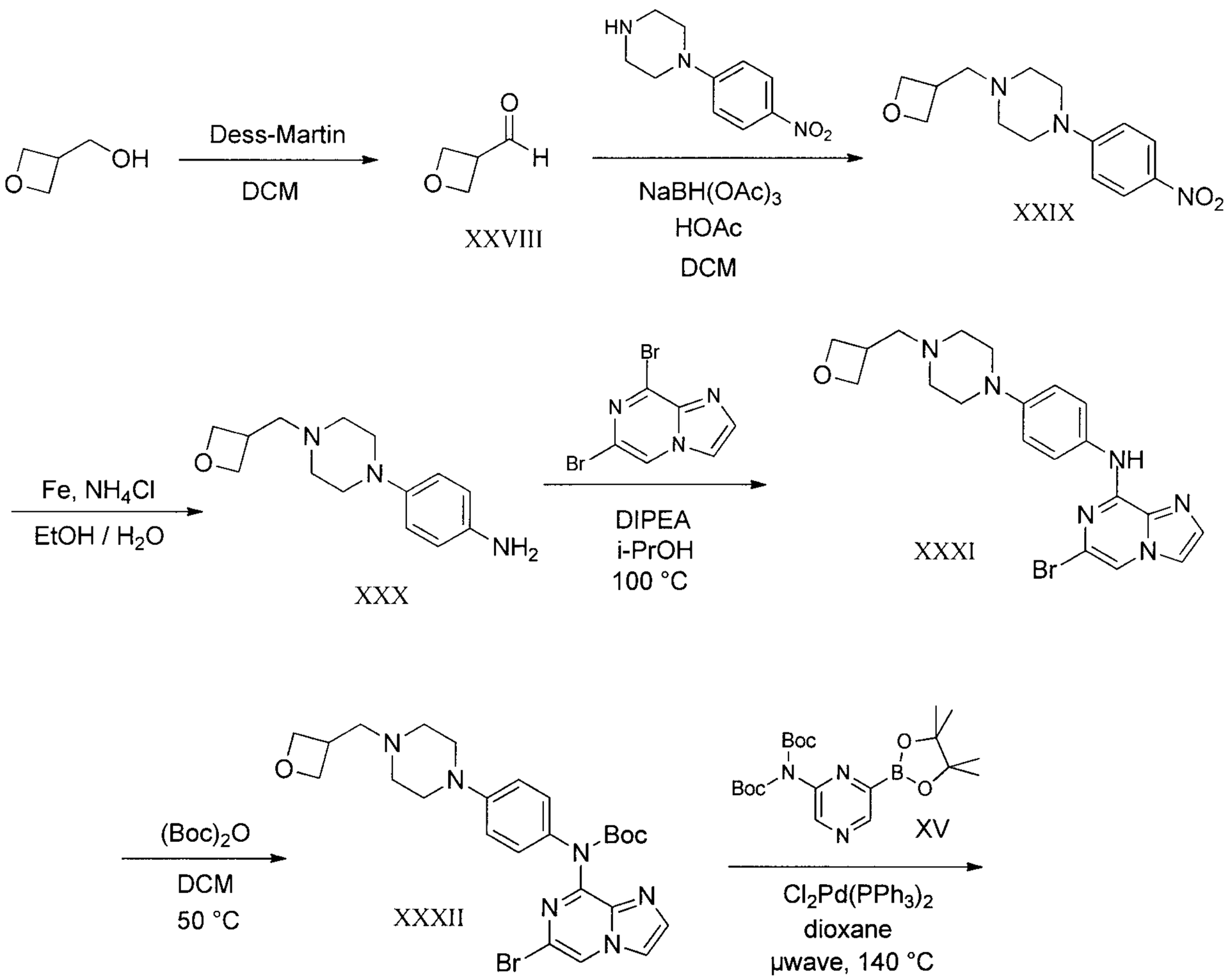
tert-Butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)carbamate XXVI: 6-Bromo-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)imidazo[1,2-a]pyrazin-8-amine XXV (1.2 g, 2.4 mmol) was reacted according to the analogous method described in Intermediate Example 1.01 (conversion of III to IV) to provide tert-butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)carbamate XXVI.

tert-butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)carbamate XXVII: tert-Butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)carbamate XXVI was reacted with XV according to the methods of CHEMISTRY B as described in Example 2 to provide the desired compound tert-butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)carbamate XXVII.

2-(5-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol (5): The compound tert-butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)carbamate XXVII (313 mg, 0.35 mmol) was de-protected by the analogous method described in Example 2 to provide 2-(5-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-

yl)piperazin-1-yl)phenoxy)ethanol (5). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$: 504.3. ^{1}H NMR (300 MHz, d_6-DMSO) δ: 9.52 (s, 1H), 8.61 (s, 1H), 8.51 (s, 1H), 8.14 (d, *J* = 1.1 Hz, 1H), 7.89 (s, 1H), 7.81 (d, *J* = 2.3 Hz, 1H), 7.74 – 7.60 (m, 2H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.47 (s, 2H), 5.74 (s, 1H), 4.86 – 4.76 (m, 1H), 4.50 (dt, *J* = 25.6, 6.3 Hz, 4H), 4.04 (t, *J* = 5.1 Hz, 2H), 3.73 (q, *J* = 5.1 Hz, 2H), 3.51 – 3.42 (m, 1H), 3.02 (s, 4H), 2.40 (s, 4H).

Example 6. Preparation of 2-((4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)piperazin-1-yl)methyl)propane-1,3-diol (6)



Oxetane-3-carbaldehyde XXVIII: To a round-bottomed flask equipped with a stirring bar, oxetan-3-ylmethanol (2.00 g, 22.7 mmol) was dissolved in DCM (50 mL) and Dess-Martin periodinane (10.67 g, 28.38 mmol) was added in one portion. The reaction

mixture was stirred at RT overnight. The solids were filtered through celite, and washed with DCM (3 mL x 5). The filtrate was removed and concentrated *in vacuo* and the resulting crude oxetane-3-carbaldehyde XXVIII was used in the next step directly.

1-(4-Nitrophenyl)-4-(oxetan-3-ylmethyl)piperazine XXIX: To a round-bottomed falsk equipped with a stirring bar, oxetane-3-carbaldehyde XXVIII (0.977 g, 11.35 mmol), 1-(4-nitrophenyl)piperazine (1.18 g, 5.68 mmol) in DCM (100 mL), and HOAc (1.70 g, 28.38 mmol) in DCM (2 mL) were added. After 5 minutes, $NaBH(OAc)_3$ (24.06 g, 113.05 mmol) was added. The resulting mixture was stirred at room temperature for 2 h. Most volatiles were removed *in vacuo*. DCM (200 mL) was added, followed by saturated $NaHCO_3$ aquous solution (20 mL), and the resulting mixture was stirred for 20 minutes. The organic phase was separated and washed with saturated $NaHCO_3$ aqueous solution (20 mL x 3), brine (20 mL x 1), dried over Na_2SO_4, filtered and solvents were removed *in vacuo*. The residue was passed through a silica gel column (MeOH: DCM = 0: 100 to 5: 95 to 25: 75) to provide the desired compound XXIX.

4-(4-(Oxetan-3-ylmethyl)piperazin-1-yl)aniline XXX: To a round-bottomed flask equipped with a stirring bar, were added 1-(4-nitrophenyl)-4-(oxetan-3-ylmethyl)piperazine XXIX (3.20 g, 11.54 mmol), ethanol (60 mL) and water (60 mL). Following the addition of iron (4.51 g, 80.77 mmol) and ammonium chloride (4.32 g, 80.77 mmol), the reaction mixture was heated at 80 ^oC for 1 h, then filtered through Celite and washed with DCM (5 mL x 5). The resulting filtrate was extracted with DCM (20 mL x 3). The combined organic extracts were washed with water (20 mL x 2), brine (20 mL x 1), dried over Na_2SO_4, and concentrated *in vacuo*. The desired 4-(4-(oxetan-3-ylmethyl)piperazin-1-yl)aniline XXX was obtained.

6-Bromo-N-(4-(4-(oxetan-3-ylmethyl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine XXXI: To a seal tube equipped with a stirring bar, 4-(4-(oxetan-3-ylmethyl)piperazin-1-yl)aniline XXX (1.19 g, 4.81 mmol), 6,8-dibromoimidazo[1,2-a]pyrazine (1.33 g, 4.81 mmol), isopropanol (24.1 mL), and diisopropylethylamine (1.37 g, 10.58 mmol) were added, and the reaction mixture was heated at 100 °C overnight. Most solvents were removed *in vacuo* and DCM (200 mL) was added to the mixture. The solution

was washed with H_2O (20 mL x 2), brine (20 mL x 1), dried over Na_2SO_4, filtered and solvents were removed *in vacuo*. The resulting residue was passed through a silica gel column (MeOH: DCM = 5: 95) and light red solids were obtained as the desired compound XXXI.

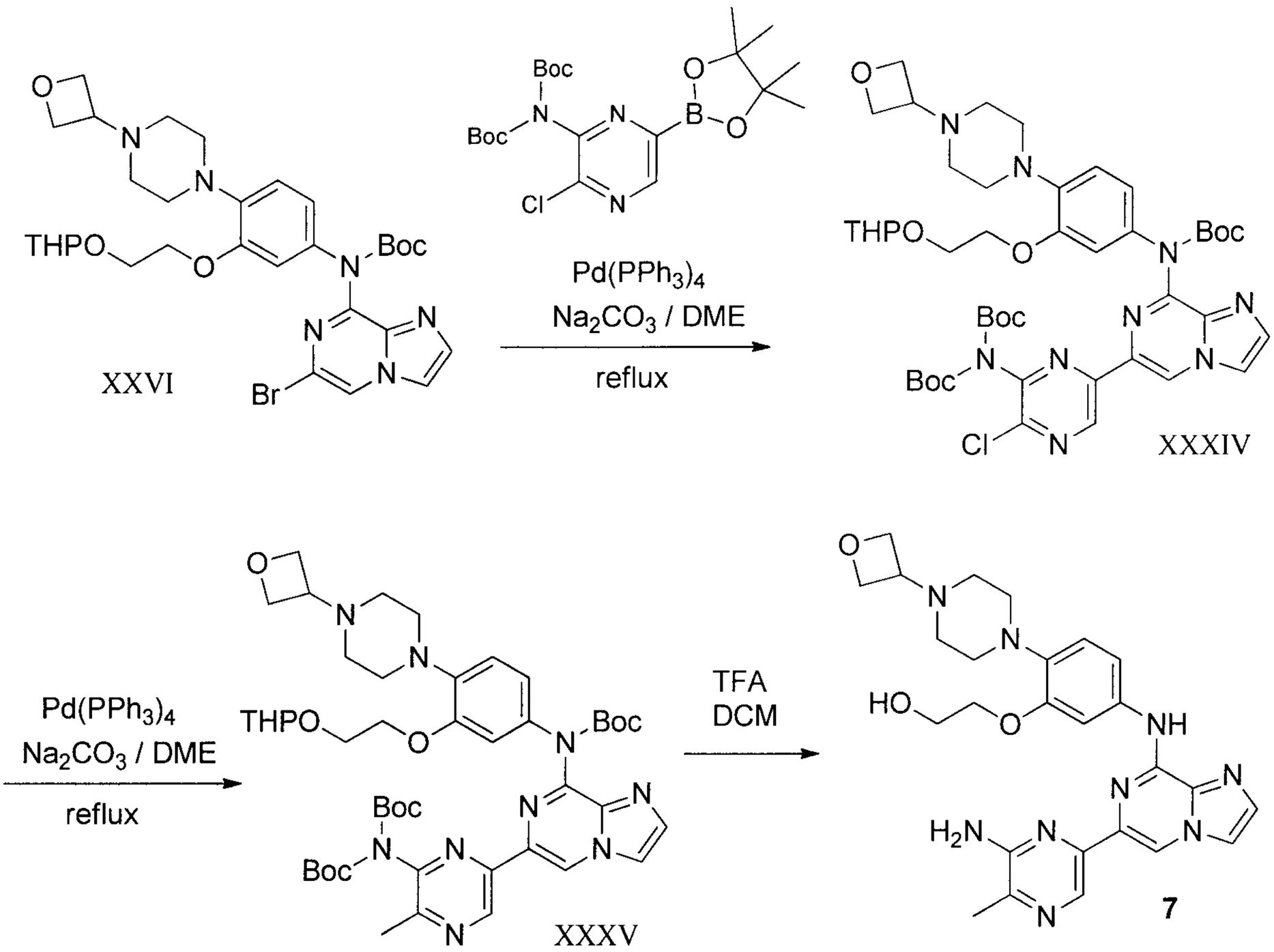
tert-Butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(1-(oxetan-3-ylmethyl)piperidin-4-yl)phenyl)carbamate XXXII: To a round-bottomed flask equipped with a stirring bar, were added 6-bromo-N-(4-(4-(oxetan-3-ylmethyl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine XXXI (560 mg, 1.27 mmol), DCM (11 mL), di-tert-butyl dicarbonate (414.4 mg, 1.90 mmol), and triethylamine (640.5 mg, 6.33 mmol). The reaction mixture was heated at 50 °C overnight. DCM (200 mL) was added, and the resulting solution was washed with water (20 mL x 2), brine (20 mL x 1), dried over Na_2SO_4, filtered and solvents were removed *in vacuo*. Column chromatography gave the desired compound XXXII.

tert-Butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-ylmethyl)piperazin-1-yl)phenyl)carbamate XXXIII: To a round-bottomed flask equipped with a stirring bar, tert-butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-ylmethyl)piperazin-1-yl)phenyl)carbamate XXXII (150 mg, 0.276 mmol), N, N-BisBoc 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazin-2-amine XV (255.8 mg, 0.607 mmol) in DME (2.3 mL), $Pd(PPh_3)_4$ (16.0 mg, 0.14 mmol), Na_2CO_3 aqueous solution (1.0 N, 0.91 mL, 0.91 mmol), and DME (2 mL) were added. The mixture was heated at 75 °C for 2 , then DCM (200 mL) was added and the resulting mixture was washed with water (30 mL x 3), brine (30 mL x 1), dried over $MgSO_4$, filtered, and solvents were removed *in vacuo*. Purification by silica gel column (MeOH: DCM = 5: 95) gave the desired compound XXXIII.

2-((4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)piperazin-1-yl)methyl)propane-1,3-diol (6): To a solution of tert-butyl (6-(6-(bis(tert-butoxycarbonyl)amino)pyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-ylmethyl)piperazin-1-yl)phenyl)carbamate XXXIII (250 mg, 0.33 mmol) in DCM (30 mL) was added TFA (940.3 mg, 8.25 mmol). The resulting mixture was stirred at room temperature for overnight. More TFA (752.2 mg, 6.60 mmol) was added and stirred at room

temperature overnight. Most solvents were removed *in vacuo*, DCM (200 mL) and saturated $NaHCO_3$ aqueous solution (30 mL) were added and the resulting mixture was stirred for 30 minutes. The organic phase was separated, washed with saturated $NaHCO_3$ aqueous solution (20 mL x 4), brine (20 mL x 1). The aqueous phase was extracted with DCM (30 mL x 2). The combined organic phases were washed with brine (20 mL x 1), dried over Na_2SO_4, filtered, and solvents were removed *in vacuo*. The crude material was purified on ISCO column, MeOH: DCM = 0:100 to 5:95 to 7.5: 92.5 to 25: 75 to elute the desired compounds. Two compounds were obtained, the first is the oxetane compound; and the other the desired compound. LCMS-ESI$^+$ (*m/z*): $[M+H]^+$: 476. ^{1}H NMR (300 MHz, d_6-DMSO) δ: 9.51 (s, 1 H), 8.60 (s, 1 H), 8.49 (s, 1 H), 8.14 (d, J = 1.5 Hz, 1 H), 7.95 (d, J = 9 Hz, 2 H), 7.90 (s, 1 H), 7.64 (s, 1 H), 6.99 (d, J = 9 Hz, 2 H), 6.48 (s, 2 H), 4.51 (broad S, 2 H), 3.43 (d, J = 6 Hz, 4 H), 3.12 (broad m, 4 H), 2.54 (broad m, 4 H), 2.34 (d, J = 7.2 Hz, 2 H), 1.83 (m, 1 H).

Example 7. Preparation of 2-(5-((6-(6-amino-5-methylpyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol (7)



tert-butyl tert-butoxycarbonyl(6-(8-((tert-butoxycarbonyl)(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)amino)imidazo[1,2-a]pyrazin-6-yl)-3-chloropyrazin-2-yl)carbamate XXXIV: A flask equipped with a reflux condenser was charged with tert-butyl (6-bromoimidazo[1,2-a]pyrazin-8-yl)(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)carbamate XXVI (prepared as described in Example 5) (352 mg, 0.52 mmol), 2-(bis-boc-amino)-3-chloro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyrazine (prepared by analogous method as used in Example 2 for the preparation of compound XV) (500 mg, 1.1 mmol), $Pd(PPh_3)_4$ (30 mg, 0.03 mmol) in sodium carbonate (1.6 mL, 1M in H_2O) and DME (4.8 mL). The mixture was heated to reflux for 1 h. The reaction was cooled to room temperature, diluted with DCM and H_2O. The aqueous layer was separated and extracted with DCM. The combined organic extracts

were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography ISCO Rf (4 g column) eluting with a gradient of 100% DCM – 100% 60/35/5 DCM/Et_2O/MeOH, appropriate fractions were combined and concentrated to provide the desired compound tert-butyl tert-butoxycarbonyl(6-(8-((tert-butoxycarbonyl)(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)amino)imidazo[1,2-a]pyrazin-6-yl)-3-chloropyrazin-2-yl)carbamate XXXIV.

tert-butyl tert-butoxycarbonyl(6-(8-((tert-butoxycarbonyl)(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)amino)imidazo[1,2-a]pyrazin-6-yl)-3-methylpyrazin-2-yl)carbamate XXXV: A microwave vial was charged with tert-butyl tert-butoxycarbonyl(6-(8-((tert-butoxycarbonyl)(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)amino)imidazo[1,2-a]pyrazin-6-yl)-3-chloropyrazin-2-yl)carbamate XXXIV (258 mg, 0.28 mmol), methylboronic acid (503 mg, 8.4 mmol), $Pd(PPh_3)_4$ (32 mg, 0.03 mmol) in sodium carbonate (0.8 mL, 1M in H_2O) and DME (2.5 mL). The mixture was heated at 150 °C for 20 min. The reaction was cooled to room temperature, diluted with DCM and H_2O. The aqueous layer was separated and extracted with DCM. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography ISCO Rf (4 g column) eluting with a gradient of 100% DCM – 100% 75/18/7 DCM/Et_2O/MeOH to provide the desired compound tert-butyl tert-butoxycarbonyl(6-(8-((tert-butoxycarbonyl)(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)amino)imidazo[1,2-a]pyrazin-6-yl)-3-methylpyrazin-2-yl)carbamate XXXV.

2-(5-((6-(6-Amino-5-methylpyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol (7): To a solution of tert-butyl tert-butoxycarbonyl(6-(8-((tert-butoxycarbonyl)(4-(4-(oxetan-3-yl)piperazin-1-yl)-3-(2-((tetrahydro-2H-pyran-2-yl)oxy)ethoxy)phenyl)amino)imidazo[1,2-a]pyrazin-6-yl)-3-methylpyrazin-2-yl)carbamate XXXV (165 mg, 0.18 mmol) in DCM (2.2 mL) was added TFA (1.1 mL, 0.11 mmol). The mixture was stirred at rt for 16 h. The reaction was diluted

with 9:1 DCM:MeOH and H_2O. The aqueous layer was separated and extracted with 9:1 DCM:MeOH. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography eluting with a gradient of 100% 75/18/7 DCM/Et_2O/MeOH - 100% 70/20/10 DCM/Et_2O/MeOH to provide the desired comopund 2-(5-((6-(6-amino-5-methylpyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol (7, 56 mg, 59%). LCMS-ESI$^+$ (*m/z*): $[M+H]^+$: 518.2. ^{1}H NMR (300 MHz, d_6-DMSO) δ: 9.49 (s, 1H), 8.56 (s, 1H), 8.44 (s, 1H), 8.13 (d, J = 1.1 Hz, 1H), 7.85 – 7.66 (m, 2H), 7.62 (d, J = 1.1 Hz, 1H), 6.90 (d, J = 8.6 Hz, 1H), 6.25 (s, 2H), 4.87 – 4.77 (m, 1H), 4.50 (dt, J = 25.2, 6.3 Hz, 4H), 4.04 (t, J = 5.1 Hz, 2H), 3.74 (q, J = 5.2 Hz, 2H), 3.51 – 3.39 (m, 1H), 3.10 - 2.95 (m, 4H), 2.45 - 2.35 (m, 4H), 2.34 (s, 3H). Alternatively, compound XXXIV could be taken directly to this step and similarly de-protected to provide the 5-chloropyrazine substituted analog.

Monomesylate and Succinate Forms

X-ray powder diffraction (XRPD) analysis of the monomesylate (MSA) and succinate forms of the compound of Example 2 herein were conducted on a diffractometer (PANanalytical XPERT-PRO, PANalytical B.V., Almelo, Netherlands) using copper radiation (Cu Kα, λ = 1.5418 Å). Samples were prepared for analysis by depositing the powdered sample in the center of an aluminum holder equipped with a zero background plate. The generator was operated at a voltage of 45 kV and amperage of 40 mA. Slits used were Soller 0.02 rad., antiscatter 1.0°, and divergence. The sample rotation speed was 2 sec. Scans were performed from 2 to 40° 2-theta. Data analysis was performed by X'Pert Highscore version 2.2c (PANalytical B.V., Almelo, Netherlands) and X'Pert data viewer version 1.2d (PANalytical B.V., Almelo, Netherlands). The XRPD patterns for Mono MSA Forms I & II were obtained using the instrument setting as follows: 45 KV, 40 mA, Cu Kα, λ = 1.5418 Å, scan range 2. - 40°, step size 0.0167°, counting time: 15.875 s. The XRPD patterns for Succinate Forms I & II were obtained using the instrument setting as follows: 45 KV, 40 mA, Cu Kα, λ = 1.5418 Å, scan range 2. - 40°, step size 0.0084°, counting time: 95.250 s.

^{1}H NMR spectra of the monomesylate (MSA) and succinate forms of the compound of Example 2 were collected on a Varian 400-MR 400MHz instrument with 7620AS sample changer. The default proton parameters are as follows: spectral width: 14 to -2 ppm (6397.4 Hz); relaxation delay: 1 sec; acquisition time: 2.5559 sec; number of scans or repetitions: 8; temperature: 25 C. Samples were prepared in dimethyl sulfoxide-d6, unless otherwise stated. Off-line analysis was carried out using MNova software.

Example 8 - 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine monomesylate Form I

Methanesulfonic acid (MSA) salt Form I was prepared by dissolving 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine (Example 2) in 11 volumes of acetone/H_2O (36:64 vol. %) with 1 molar equivalent of methane sulfonic acid (MSA) at room temperature. The solution was then charged with 19 volumes of acetone over 1 hour and the reactor contents were stirred at room temperature overnight.

XRPD analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine monomesylate Form I was conducted as described above and provided the diffraction pattern seen in Figure 1, with the peaks in the table below.

No.	Pos. [°2Th.]	Rel. Int. [%]
1	19.6606	100
2	17.2746	93.07
3	17.8971	69.96
4	21.6306	65.74
5	25.7805	59.16
6	18.7593	51.5
7	13.7252	48.77
8	15.7206	41.91
9	24.7364	38.09
10	18.4345	36.84

In one embodiment 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine monomesylate Form I may be characterized by XRPD peaks 19.7 (19.6606), 17.3 (17.2746), 17.9 (17.8971), 21.6 (21.6306), and 25.8 (25.7805). In a further embodiment 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine monomesylate Form I may be characterized by XRPD peaks 19.7 (19.6606), 17.3 (17.2746), 17.9 (17.8971), and 21.6 (21.6306). In another embodiment 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine monomesylate Form I may be characterized by XRPD peaks 6.0, 6.2, 8.6, and 9.6.

NMR Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form I, conducted as described above, provided the NMR spectrum seen in Figure 2.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.57 (s, 1H), 9.60 (s, 1H), 8.62 (s, 1H), 8.47 (s, 1H), 8.17 (d, J = 1.2 Hz, 1H), 8.03 – 7.96 (m, 2H), 7.90 (s, 1H), 7.69 (d, J = 1.2 Hz, 1H), 7.09 (d, J = 9.0 Hz, 2H), 4.78 (p, J = 8.0 Hz, 4H), 4.49 (m, 1H), 4.00 – 2.8 (m, 10H), 2.32 (s, 3H).

Differential scanning calorimetry (DSC): DSC was performed for each of the examples indicated herein using a TA Instruments Q2000 DSC instrument. The sample was placed into an aluminum DSC pan, and the weight accurately recorded. The pan was covered with a lid, and then either crimped or hermetically sealed. The same cell was heated under a nitrogen purge at a rate of 10 °C/min, up to a final temperature of 300 °C. Indium was used as the calibration standard.

A DSC analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form I, conducted as described above, is seen in Figure 3.

Thermogravimetric analysis (TGA): TGA was performed for each of the examples indicated herein using a TA Instruments Q5000 TGA instrument. Each sample was placed in an aluminum sample pan and inserted into the TG furnace. The furnace was heated under

nitrogen at a rate of 10 °C/min, up to a final temperature of 300 °C. The TGA furnace was calibrated using the magnetic Curie point method.

A TGA analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form I, conducted as described above, is seen in Figure 4.

Example 9 - 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine monomesylate Form II

6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form II was prepared by drying 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form I (Example 8) in a vacuum oven at ~40 °C with a N_2 purge.

XRPD analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine monomesylate Form II was conducted as described above and provided the diffraction pattern seen in Figure 3, with the peaks in the table below.

No.	Pos. [°2Th.]	Rel. Int. [%]
1	17.2698	100
2	25.1384	67.84
3	20.4423	63.66
4	19.5732	62.11
5	18.5264	50.36
6	17.7884	50.07
7	21.6273	45.52
8	15.2397	44
9	6.855	35.01
10	13.65	26

In one embodiment 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine monomesylate Form II may be characterized by XRPD peaks 17.3 (17.2698), 25.1 (25.1384), 20.4 (20.4423), 19.6 (19.5732), and 18.5 (18.5264). In an additional embodiment 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine monomesylate Form II may be

characterized by XRPD peaks 17.3 (17.2698), 25.1 (25.1384), 20.4 (20.4423), and 19.6 (19.5732). In another embodiment 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine monomesylate Form II may be characterized by XRPD peaks 6.1, 6.9, 11.0, and 13.6.

NMR Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form II, conducted as described above, provided the NMR spectrum seen in Figure 6.

^{1}H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 8.63 (s, 1H), 8.47 (s, 1H), 8.19 (d, J = 1.2 Hz, 1H), 8.02 – 7.95 (m, 2H), 7.91 (s, 1H), 7.72 (d, J = 1.2 Hz, 1H), 7.13 – 7.06 (m, 2H), 4.85 – 4.72 (m, 4H), 4.53 – 4.45 (m, 1H), 4.30 – 2.75 (m, 10H), 2.34 (s, 3H).

A DSC analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form II, conducted as described above, is seen in Figure 7.

A TGA analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form II, conducted as described above, is seen in Figure 8.

Example 10 - 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine succinate Form I

6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form I was prepared by first dissolving 1.6 mol. eq. of succinic acid in THF, and then charging the acidic solution to 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine. The material was then stirred at room temperature with a magnetic stir bar overnight.

XRPD analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine succinate Form I was conducted as described above and provided the diffraction pattern seen in Figure 9, with the peaks in the table below.

No.	Pos. [°2Th.]	Rel. Int. [%]
1	16.5	100
2	24.5	38.64
3	17.7	9.27
4	28.4	8.68
5	21.8	7.57
6	8.0	6.53
7	23.1	4.59
8	12.1	4.38
9	8.3	3.78
10	27.1	3.65

In one embodiment 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form I may be characterized by XRPD peaks 16.5, 24.5, 17.7, 28.4, and 21.8. In another embodiment 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form I may be characterized by XRPD peaks 16.5, 24.5, 8.0 and 8.3.

NMR Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form I, conducted as described above, provided the NMR spectrum seen in Figure 6.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.12 (s, 2H), 9.48 (s, 1H), 8.59 (s, 1H), 8.48 (s, 1H), 8.12 (d, J = 1.1 Hz, 1H), 7.97 – 7.86 (m, 3H), 7.62 (d, J = 1.1 Hz, 1H), 7.01 – 6.94 (m, 2H), 6.45 (s, 2H), 4.55 (t, J = 6.5 Hz, 2H), 4.46 (t, J = 6.1 Hz, 2H), 3.49 – 3.38 (m, 1H), 3.13 (t, J = 4.9 Hz, 4H), 2.40 (s, 10H).

A DSC analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form I, conducted as described above, is seen in Figure 11.

A TGA analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form I, conducted as described above, is seen in Figure 12.

The process for preparing 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine succinate Form I was also repeated using IPA, Acetone, and 2-MeTHF as solvents.

Example 11 - 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine succinate Form II

6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine free base was charged with 10.0 parts 2-propanol, followed by rapid agitation, to form a slurry. A separate solution of succinic acid (0.43 parts, 1.6 mol eq.) in 2-propanol (15 parts) was prepared at ambient temperature and was added to the slurry. The resulting slurry was then agitated at ambient temperature for about 1 day. Another solution of succinic acid (0.09 parts, 0.3 mol eq.) in 2-propanol (3 parts) was added to the slurry and the resulting slurry was agitated at ambient temperature for about two days. An additional solution of succinic acid (0.27 parts, 1.0 mol eq.) in 2-propanol (8 parts) was prepared at ambient temperature and added to the slurry and the resulting slurry was agitated for about 2 days. Then the content temperature was adjusted to 40°C and the slurry was agitated for about two hours. The content was then returned to ambient temperature and agitated for about 16 hours. The resulting slurry was then filtered, rinsed with 2-propanol (7.0 parts), and dried at 60°C.

XRPD analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine succinate Form II was conducted as described above and provided the diffraction pattern seen in Figure 13, with the peaks in the table below.

No.	Pos. [°2Th.]	Rel. Int. [%]
1	24.9821	100
2	16.3186	38.39
3	21.952	18.44
4	7.8958	17.62
5	7.5828	6.9
6	28.5998	6.52
7	11.3329	5.73
8	30.8568	5.48
9	28.0273	5.21
10	21.5026	4.73

In one embodiment 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form II may be characterized by XRPD peaks 25.0 (24.9821), 16.3 (16.3186), 22.0 (21.952), 7.9 (7.8958), and 7.6 (7.5828). In a further embodiment 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form II may be characterized by XRPD peaks 25.0 (24.9821), 16.3 (16.3186), 7.9 (7.8958), and 7.6 (7.5828).

NMR Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form II, conducted as described above, provided the NMR spectrum seen in Figure 14.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.13 (s, 2H), 9.48 (s, 1H), 8.58 (s, 1H), 8.47z (s, 1H), 8.12 (d, J = 1.1 Hz, 1H), 7.97 – 7.86 (m, 3H), 7.62 (d, J = 1.1 Hz, 1H), 7.02 – 6.94 (m, 2H), 6.45 (s, 2H), 4.55 (t, J = 6.5 Hz, 2H), 4.46 (t, J = 6.0 Hz, 2H), 3.44 (p, J = 6.3 Hz, 1H), 3.17 – 3.10 (m, 4H), 2.40 (s, 10H), 1.02 (d, J = 6.1 Hz, 2H).

A DSC analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form II, conducted as described above, is seen in Figure 15.

A TGA analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form II, conducted as described above, is seen in Figure 16.

Biological Examples

Example 12: High Throughput Syk Biochemical Assay

Syk activity was measured using KinEASE (Cisbio), a time-resolved fluorescence resonance energy transfer (TR-FRET) immunoassay. In this assay, Syk-catalyzes the phosporylation of a XL665-labeled peptide substrate. Europium conjugated phospho-tyrosine specific antibody binds the resulting phosphorylated peptide. Formation of phosphorylated peptide is quantified by TR-FRET with Europium as the donor and XL665 the acceptor in a 2-step endpoint assay. In brief, test compounds serially diluted in DMSO were delivered into Corning white, low volume, non-binding 384 well plates using the Echo 550 acoustic liquid dispenser (Labcyte®). Syk enzyme and substrates were dispensed into assay plates using a Multi-Flo (Bio-Tek Instruments). The standard 5 µL reaction mixture contained 20 µM ATP, 1 µM biotinylated peptide, 0.015 nM of Syk in reaction buffer (50 mM Hepes, pH 7.0, 0.02% NaN_3, 0.1% BSA, 0.1 mM Orthovanadate, 5 mM $MgCl_2$, 1mM DTT, 0.025% NP-40). After 30 minutes of incubation at room temperature, 5 µL of Stop and Detect Solution (1:200 Europium Cryptate labeled anti-phosphorylated peptide antibody solution and 125 nM strepavidin-XL665 Tracer in a 50mM Hepes pH 7.0 detection buffer containing sufficient EDTA) was added. The plate was then further incubated for 120 minutes at room temperature and read using an Envision 2103 Multilabeled reader (PerkinElmer) with excitation/emission/FRET emission at 340nm/615nm/665nm, respectively. Fluorescence intensities at 615nm and 665nm emission wavelengths were expressed as a ratio (665nm/615nm). Percent inhibition was calculated as follows:

$$\% \text{ Inhibition} = 100 \times (\text{Ratio}_{\text{Sample}} - \text{Ratio}_{\text{0\% Inhibition}})/(\text{Ratio}_{\text{100\% Inhibition}} - \text{Ratio}_{\text{0\% Inhibition}})$$

where 0.1% DMSO (0% inhibition) was the negative control and 1 µM K252a (100% inhibition) was used as the positive control. Activity of the compounds of Examples 1-7 are provided in the following table, demonstrating the compounds are Syk inhibitors with IC_{50} below 50 nM.

Example No.: Compound Name	Syk IC_{50} (nM)
Ex.-1: 6-(6-amino-5-methylpyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	6.2
Ex.-2: 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	13.5
Ex.-3: (R)-(4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)morpholin-2-yl)methanol	13.3
Ex.-4: 6-(6-aminopyrazin-2-yl)-5-methyl-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	44
Ex.-5: 2-(5-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol	12.2
Ex.-6: 2-((4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)piperazin-1-yl)methyl)propane-1,3-diol	14.5
Ex.-7: 2-(5-((6-(6-amino-5-methylpyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol	8.7

Example 13: 384-well HTBS Whole Blood CD63 Basophil Assay

Syk activity was assessed in relation to reduced activation of basophils as measured by the expression of CD63 in a human whole blood basophil cellular assay (25% blood). Basophil activation was measured in human whole blood using the Flow CAST kit (Buhlmann Laboratories AG, Baselstrasse, Switzerland) following the protocol provided by the manufacturer with minor modifications. Fresh human whole blood in heparin was collected and delivered same day (AllCells, Emeryville, CA). Whole blood samples were incubated with either DMSO (1% final) or serial diluted compounds in DMSO for 60 minutes at 37 °C. Basophils were activated using the anti-FceRI mAb and stained with anti-CD63-FITC and anti-CCR3-PE for 20 minutes at 37 °C (per well: 50 µL of whole blood was mixed with 113 µL of stimulation buffer, 8.5 µL anti-FceRI mAb, 8.5 µL Ab stain CCR3-PE/CD63-FITC). Cells were centrifuged at 1000 x g for 18 minutes and 150 µL/well of supernatant removed. Red blood cells were lysed and cells fixed by 2 rounds of cell lysing: resuspending cell pellets with 150 µL/well 1X lysis buffer, incubating at room temperature for 10 minutes, and collecting cell pellets by centrifuging for 1200 rpms for 5 minutes. Cells were washed with 150 µL/well wash buffer twice, and resuspended in a final volume of 75 µL/well of wash buffer for either immediate flow cytometery analysis or

overnight incubation at 4 °C followed by flow cytometry analysis. Degranulation (basophil activation) was detected by CD63 surface expression on CCR3 positive cells. The percent CD63 positive cells within the gated basophil population were determined and normalized to the DMSO (negative control) and control compound (positive control). Activity of the compounds of Examples 1-7 are provided in the following table, demonstrating the compounds are effective in reducing the activation of basophils, with EC_{50} below 200 nM.

Example No.: Compound Name	**CD63 EC_{50} (nM)**
Ex.-1: 6-(6-amino-5-methylpyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	51
Ex.-2: 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	80
Ex.-3: (R)-(4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)morpholin-2-yl)methanol	63
Ex.-4: 6-(6-aminopyrazin-2-yl)-5-methyl-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	157
Ex.-5: 2-(5-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol	120
Ex.-6: 2-((4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)piperazin-1-yl)methyl)propane-1,3-diol	128
Ex.-7: 2-(5-((6-(6-amino-5-methylpyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol	167

Example 14: Kinetic Solubility

The kinetic solubility of compounds in phosphate buffer at pH 7.4 was assessed. The compounds to be tested were dissolved in dimethylsulfoxide at a 10 mM concentration. Stock samples were diluted, 3 μ l with 297 μ l of the phosphate buffer at pH 7.4 (DulBecco's phosphate buffered saline (Sigma-Aldrich D8662), overall molarity is 0.149M and pH 7.43). The samples were then incubated for 24 hours at 37 °C with shaking, the centrifuged and an aliquot taken and tested relative to a known standard concentration of 0.1 mM. The kinetic solubility of the compounds of Examples 1-7 are provided in the following table, demonstrating the compounds have kinetic solubility at pH 7.4 of greater than 90 μM.

Example No.: Compound Name	Solubility pH 7.4 (μM)
Ex.-1: 6-(6-amino-5-methylpyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	95
Ex.-2: 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	95
Ex.-3: (R)-(4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)morpholin-2-yl)methanol	91
Ex.-4: 6-(6-aminopyrazin-2-yl)-5-methyl-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	100
Ex.-5: 2-(5-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol	97
Ex.-6: 2-((4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)piperazin-1-yl)methyl)propane-1,3-diol	99

Example 15: Human Hepatocyte Stability Assay

The human hematocyte stability of the compounds as predicted hepatocyte clearance in L/hr/kg was assessed. Compounds to be tested were diluted to 200 μM (4 μl of 10 mM DMSO stock into 196 μl ACN:H_2O (50:50). Propranolol was used as a positive control, and buffer only without hepatocytes as 0% control. These were further diluted 4 μl with 891 μl KHB buffer (InVitroGRO catalog number Z99074) to provide 2X dosing solution. To each well of 24 well plate, 250 μl of the 2X dosing solution was added to each well with 250 μl of hepatocytes cells (1 x 10^6 viable cells/ml per well) or KHB for control samples to achieve a final compound concentration of 1 μM during incubation. The final solvent concentration was 0.01% DMSO and 0.25% ACN. The culture plate was placed on a rocker and incubated at 37 °C, 5% CO_2. Samples were collected at time 0, 1, 3, and 6 hours. The loss of parent compound was determined using LC-MS methods against a standard curve. Activity of the compounds of Examples 1-7 are provided in the following table, showing hepatocyte clearance of about 0.12 L/hr/kg or less.

Example No.: Compound Name	Hheps CL (L/hr/kg)
Ex.-1: 6-(6-amino-5-methylpyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	0.12
Ex.-2: 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	0.055

Ex.-3: (R)-(4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)morpholin-2-yl)methanol	0.09
Ex.-4: 6-(6-aminopyrazin-2-yl)-5-methyl-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	0.08
Ex.-5: 2-(5-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol	0.07
Ex.-6: 2-((4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)piperazin-1-yl)methyl)propane-1,3-diol	0.08
Ex.-7: 2-(5-((6-(6-amino-5-methylpyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol	0.05

Example 16: Comparison to known Syk inhibitors

The assays of Examples 8-11 were used to compare the compounds as described herein with compounds known in the art. The data comparing the compounds of Examples 1-7 to previously described compounds is provided in the following table. From these results, it is clear that compounds as described herein are desirable as Syk inhibitors, with improved Syk and CD63 activity relative to the known compounds, improved kinetic solubility (at least about 9-fold more soluble) and hepatocyte clearance (at least about 2-fold less clearance). As such, the combination of improved Syk and CD63 inhibitory activity with improved kinetic solubility and clearance provides compounds that may therefore be effective at treating diseases responsive to Syk inhibition with improved pharmacokinetic properties.

Compound Name	**Syk IC_{50} (nM)**	**CD63 IC_{50} (nM)**	**Solubility pH 7.4 (µM)**	**Hheps CL (units)**
Ex.-1: 6-(6-amino-5-methylpyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	6.2	51	95	0.12
Ex.-2: 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	13.5	80	95	0.055
Ex.-3: (R)-(4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)morpholin-2-	13.3	63	91	0.09

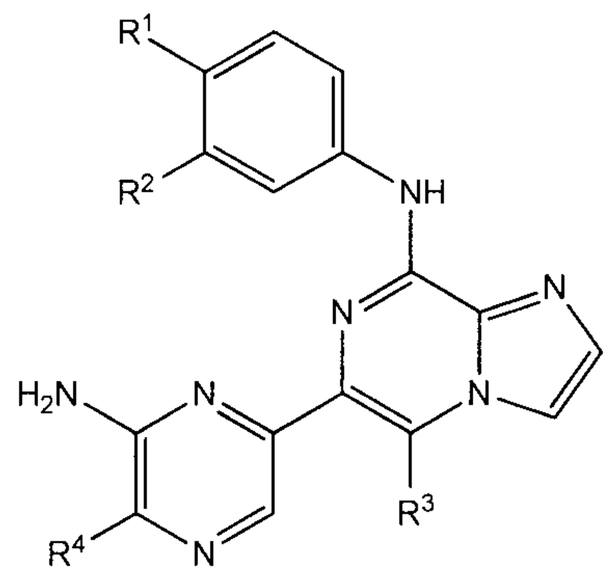
yl)methanol				
Ex.-4: 6-(6-aminopyrazin-2-yl)-5-methyl-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine	44	157	100	0.08
Ex.-5: 2-(5-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol	12.2	120	97	0.07
Ex.-6: 2-((4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)piperazin-1-yl)methyl)propane-1,3-diol	14.5	128	99	0.08
Ex.-7: 2-(5-((6-(6-amino-5-methylpyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol	8.7	167	nd	0.05
Known compounds:				
6-(5-aminopyridin-3-yl)-N-(4-morpholinophenyl)imidazo[1,2-a]pyrazin-8-amine	31	101	5	0.68
6-(3-aminophenyl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazin-8-amine	188	809	3	0.24
6-(5-amino-6-methylpyridin-3-yl)-N-(4-morpholinophenyl)imidazo[1,2-a]pyrazin-8-amine	16	250	5	0.80
6-(6-aminopyridin-3-yl)-N-(3,4-dimethoxyphenyl)imidazo[1,2-a]pyrazin-8-amine	53	734	10	0.90

Throughout this specification, various patents, patent applications and other types of publications (e.g., journal articles) are referenced. The disclosure of all patents, patent applications, and publications cited herein are hereby incorporated by reference in their entirety for all purposes.

CLAIMS

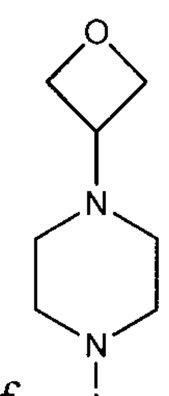
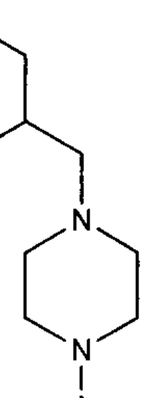
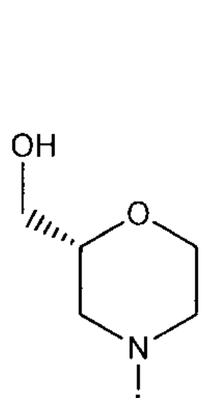
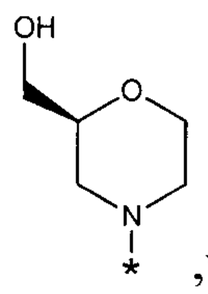
What is claimed:

1. A compound having the structure of Formula I:



Formula I

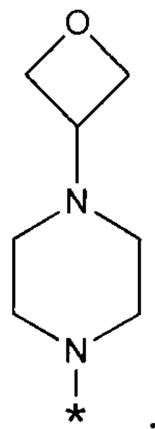
or a pharmaceutically acceptable salt or co-crystal thereof, or a pharmaceutically acceptable ester, stereoisomer, mixture of stereoisomers or tautomer thereof, wherein:

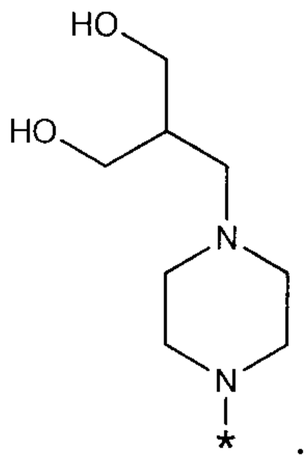
R^1 is selected from the group consisting of , , , and ,wherein * indicates the carbon atom of the indicated phenyl ring of Formula I to which R^1 is attached;

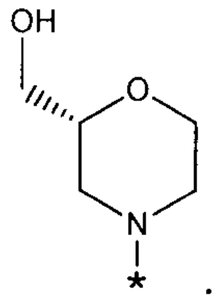
R^2 is H or 2-hydroxyethoxyl;

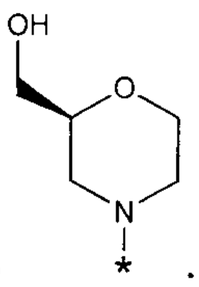
R^3 is H or methyl; and

R^4 is H or methyl.

2. A compound according to Claim 1, or a pharmaceutically acceptable salt or co-crystal thereof, wherein R^1 is .

3. A compound according to Claim 1, or a pharmaceutically acceptable salt or co-crystal thereof, wherein R^1 is .

4. A compound according to Claim 1, or a pharmaceutically acceptable salt or co-crystal thereof, wherein R^1 is .

5. A compound according to Claim 1, or a pharmaceutically acceptable salt or co-crystalthereof, wherein R^I is .

6. A compound according to Claim 1, 2, 3, 4, or 5, or a pharmaceutically acceptable salt or co-crystal thereof, wherein R^2 is H or 2-hydroxyethoxyl.

7. A compound according to Claim 1, 2, 3, 4, or 5, or a pharmaceutically acceptable salt orco-crystal thereof, wherein R^2 is H.

8. A compound according to Claim 1, 2, 3, 4, 5, 6, or 7, or a pharmaceutically acceptable salt or co-crystal thereof, wherein R^3 is methyl.

9. A compound according to Claim 1, 2, 3, 4, 5, 6, or 7, or a pharmaceutically acceptable salt or co-crystal thereof, wherein R^3 is H.

10. A compound according to Claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, or a pharmaceutically acceptable salt or co-crystal thereof, wherein R^4 is methyl.

11. A compound according to Claim 1, 2, 3, 4, 5, 6, 7, 8, or 9, or a pharmaceutically acceptable salt or co-crystal thereof, wherein R^4 is H.

12. A compound according to Claim 1, 2, 3, 4, 5, 6, 7 8, 9, 10, or 11, or a pharmaceutically acceptable salt or co-crystal thereof, wherein R^2 is H and R^4 is H.

13. A compound according to Claim 1, 2, 3, 4, 5, 6, 7 8, 9, 10, or 11, or a pharmaceutically acceptable salt or co-crystal thereof, wherein R^2 is H and R^4 is methyl.

14. The compound according to Claim 1selected from the group consisting of:

2-(5-((6-(6-amino-5-methylpyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol;
6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine;
2-((4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)piperazin-1-yl)methyl)propane-1,3-diol;
2-(5-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)-2-(4-(oxetan-3-yl)piperazin-1-yl)phenoxy)ethanol;
(R)-(4-(4-((6-(6-aminopyrazin-2-yl)imidazo[1,2-a]pyrazin-8-yl)amino)phenyl)morpholin-2-yl)methanol;
6-(6-aminopyrazin-2-yl)-5-methyl-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine; and
6-(6-amino-5-methylpyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine;
or a pharmaceutically acceptable salt or co-crystal thereof.

15. 6-(6-Aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine.

16. 6-(6-Aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine succinate.

17. A pharmaceutical composition comprising a compound of Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14, or a pharmaceutically acceptable salt or co-crystal thereof, and at least one pharmaceutically acceptable vehicle.

18. A pharmaceutical composition comprising 6-(6-Aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine, and at least one pharmaceutically acceptable vehicle.

19. A pharmaceutical composition comprising 6-(6-Aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine succinate, and at least one pharmaceutically acceptable vehicle.

20. Use of a compound of Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14, or a pharmaceutically acceptable salt or co-crystal thereof, for the inhibition of Syk activity.

21. Use of 6-(6-Aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine, or a pharmaceutically acceptable salt or co-crystal thereof, for the inhibition of Syk activity.

22. Use of 6-(6-Aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine for the inhibition of Syk activity.

FIG. 1

XRPD Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form I

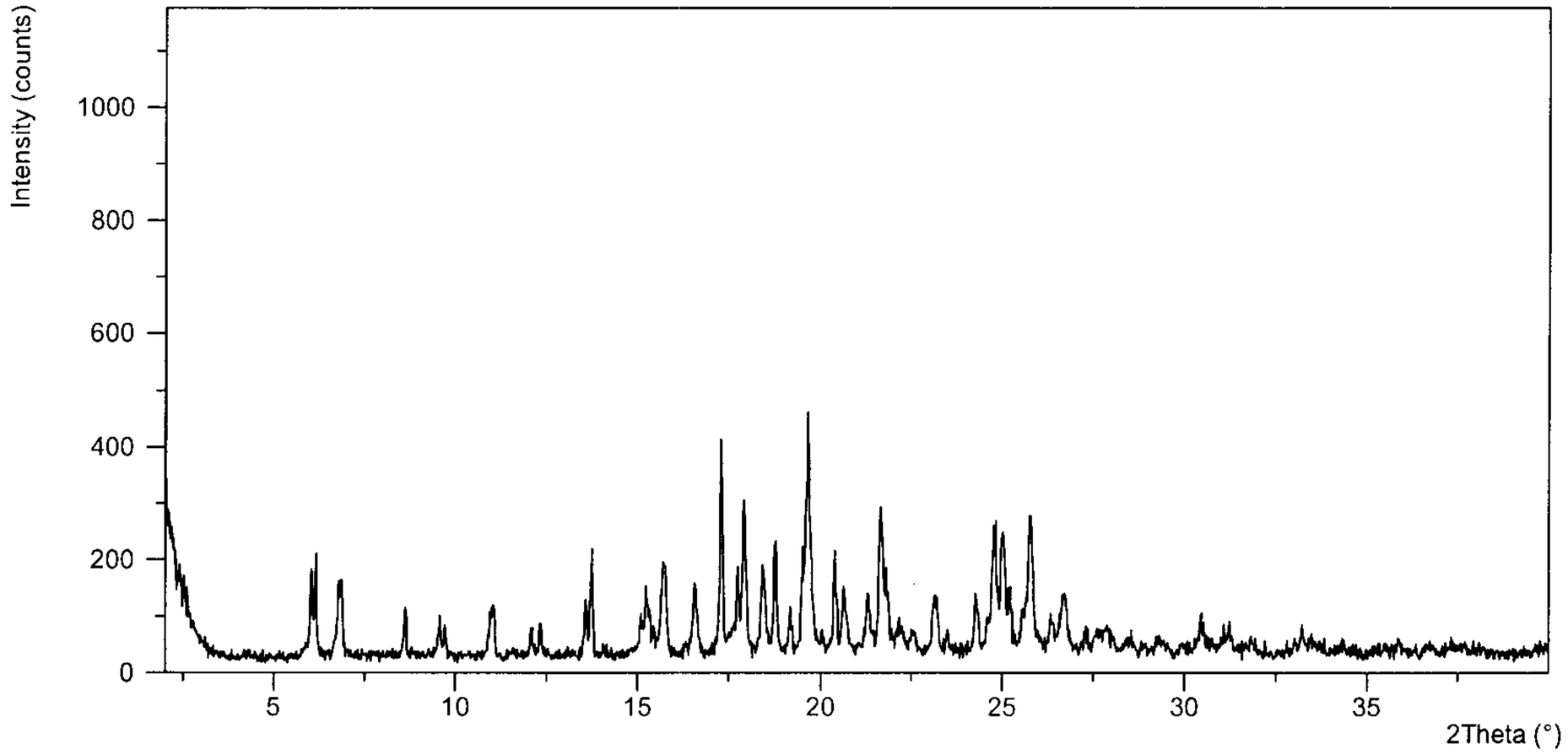


FIG. 2

NMR Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form I

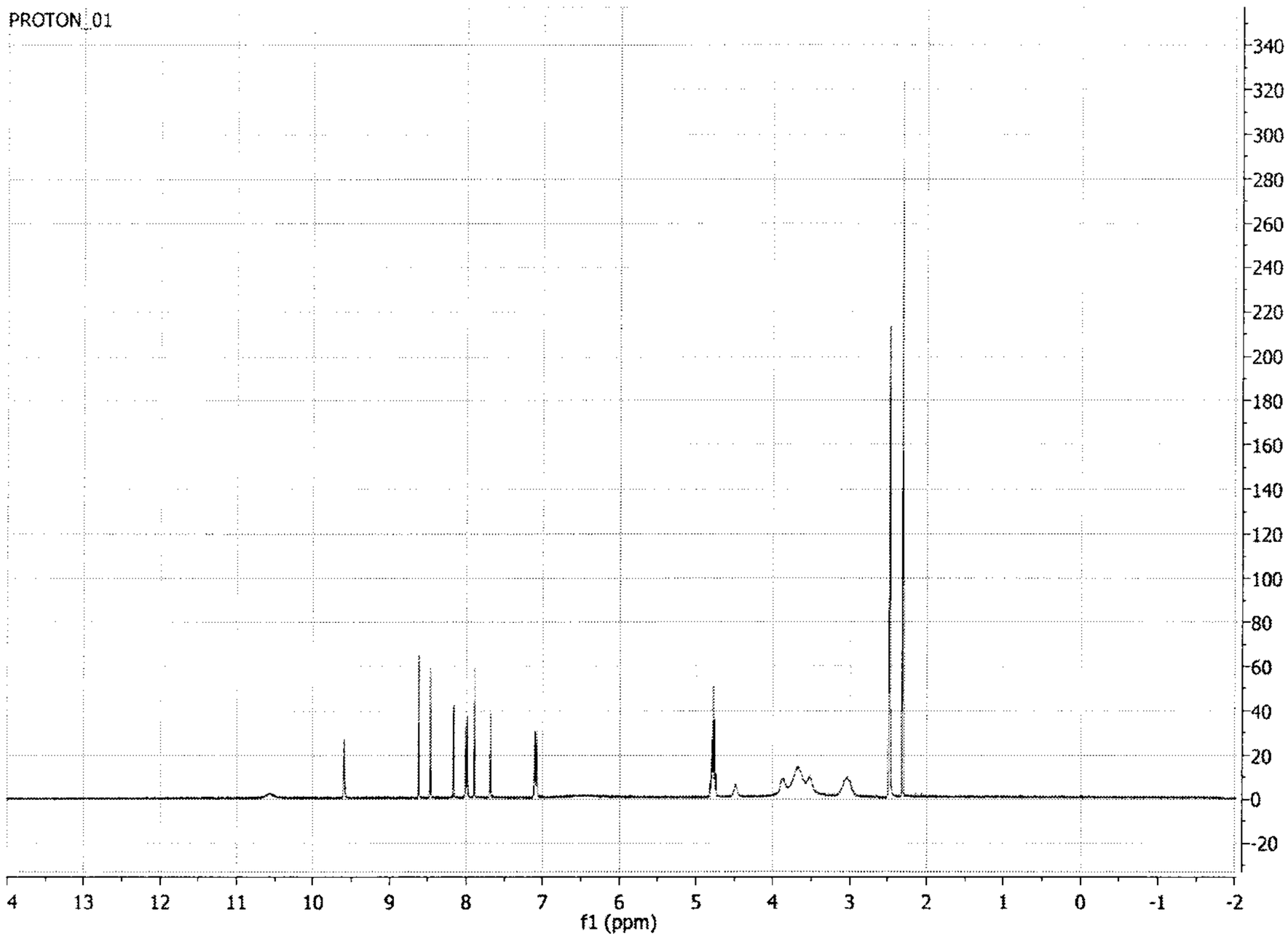


FIG. 3

DSC Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form I

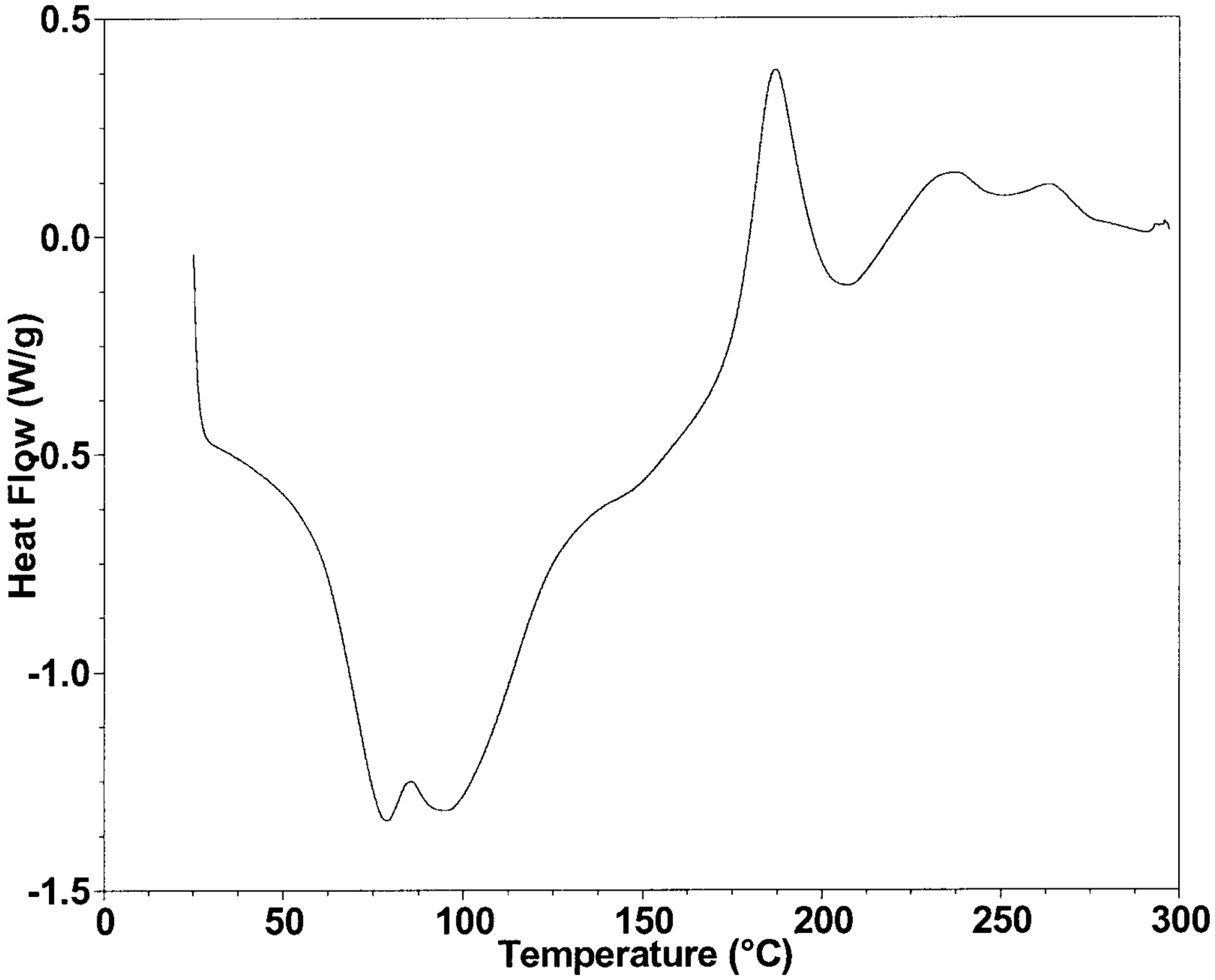


FIG. 4

TGA Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form I

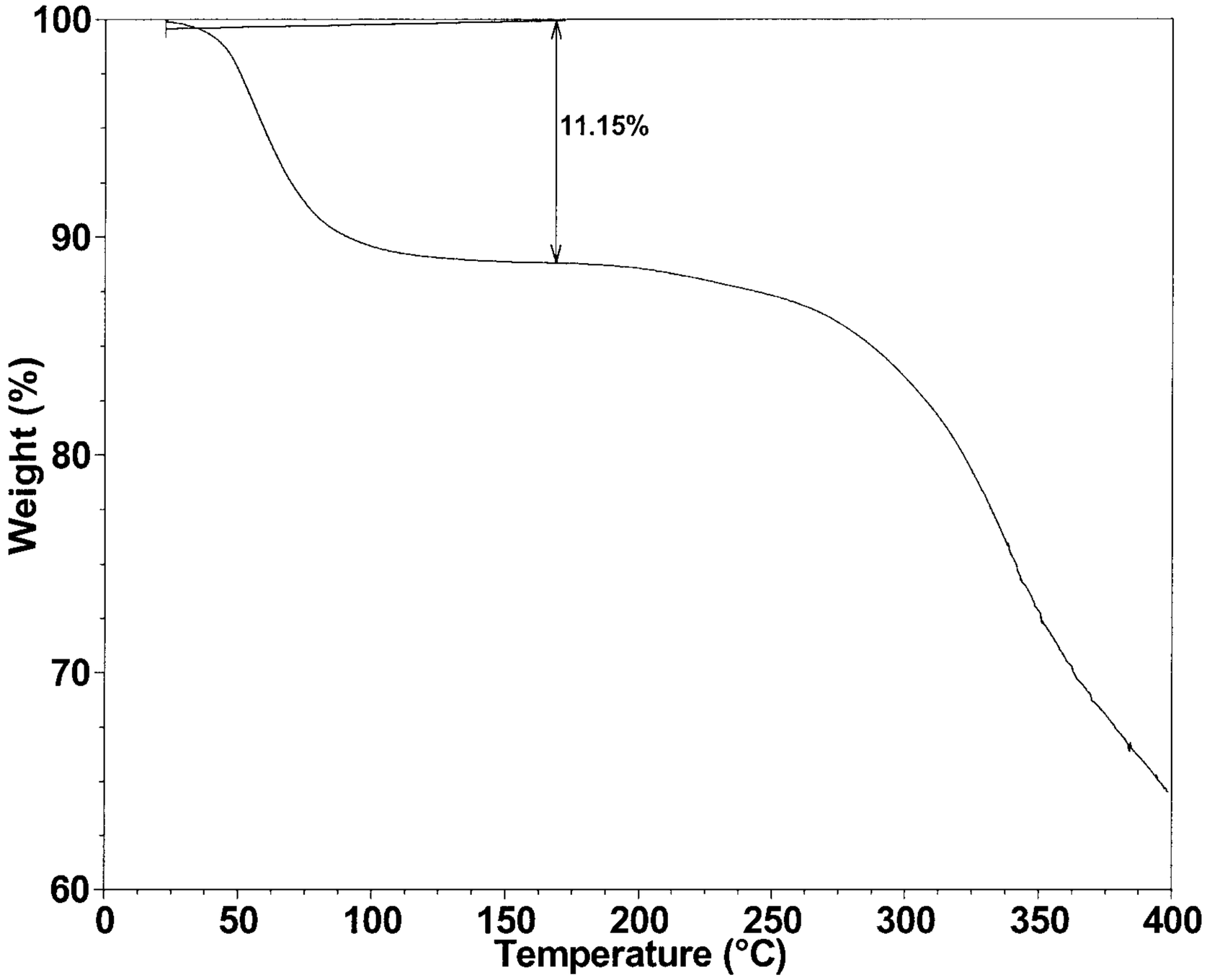


FIG. 5

XRPD Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form II

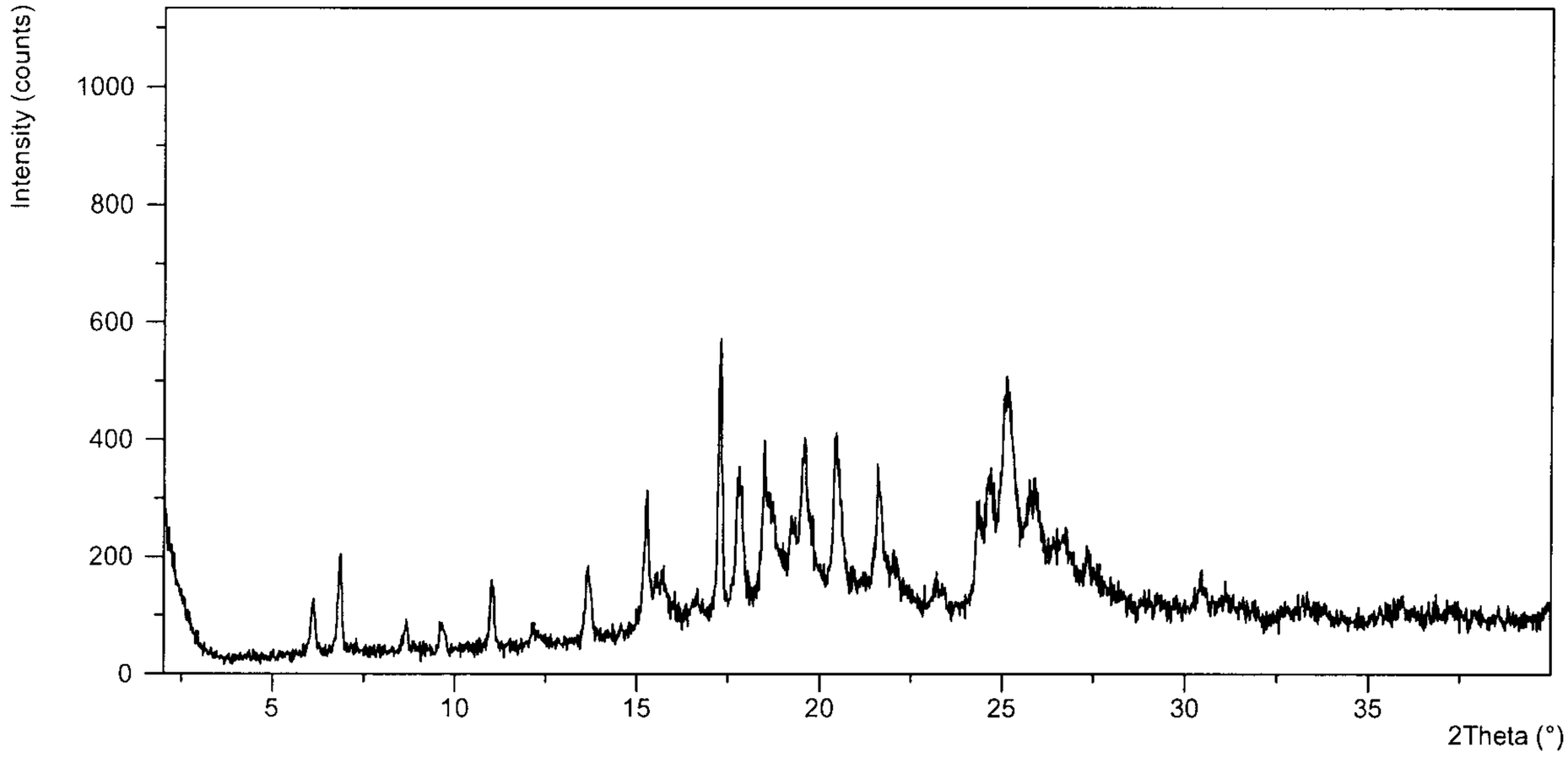


FIG. 6

NMR Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form II

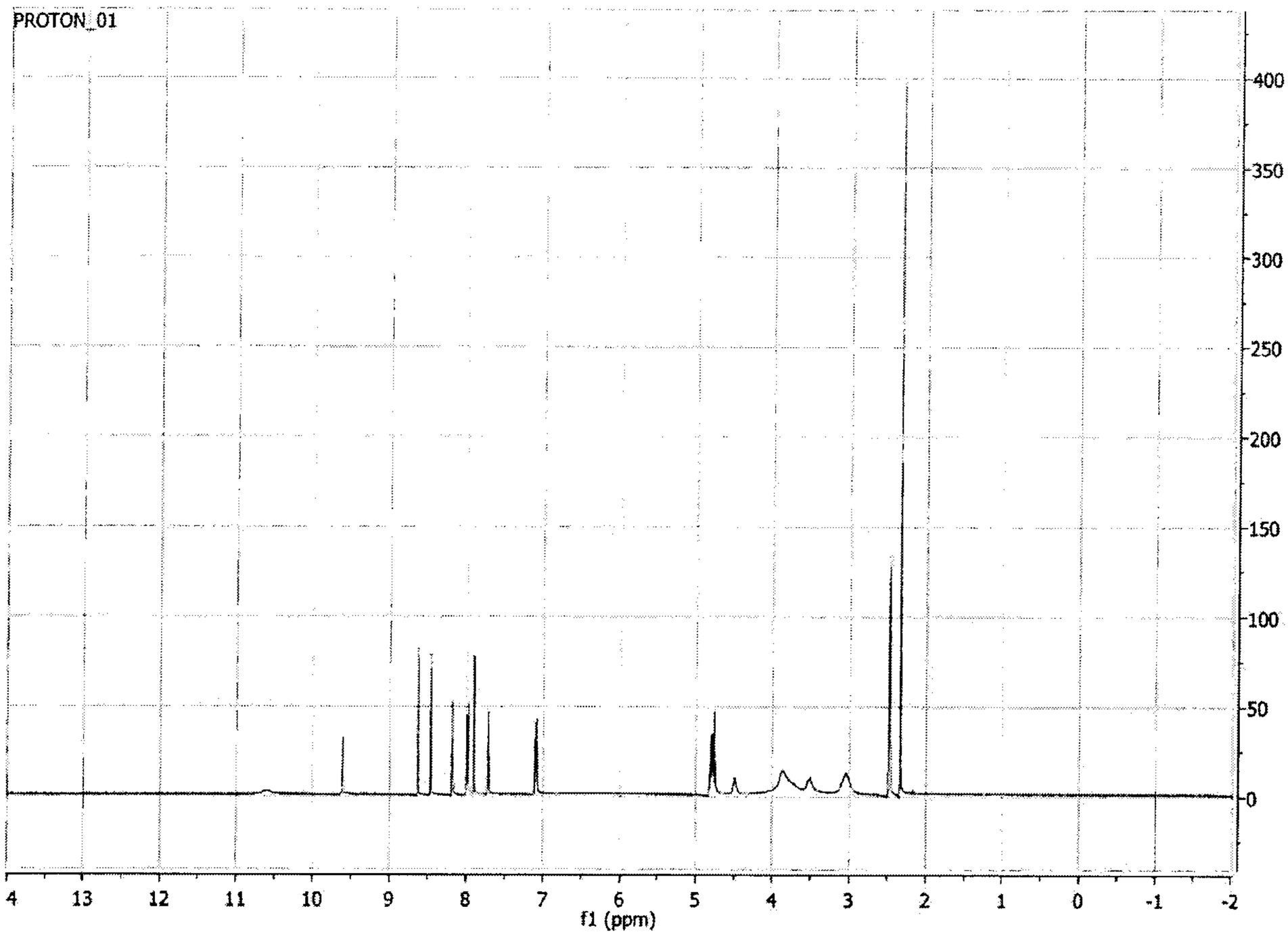


FIG. 7

DSC Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form II

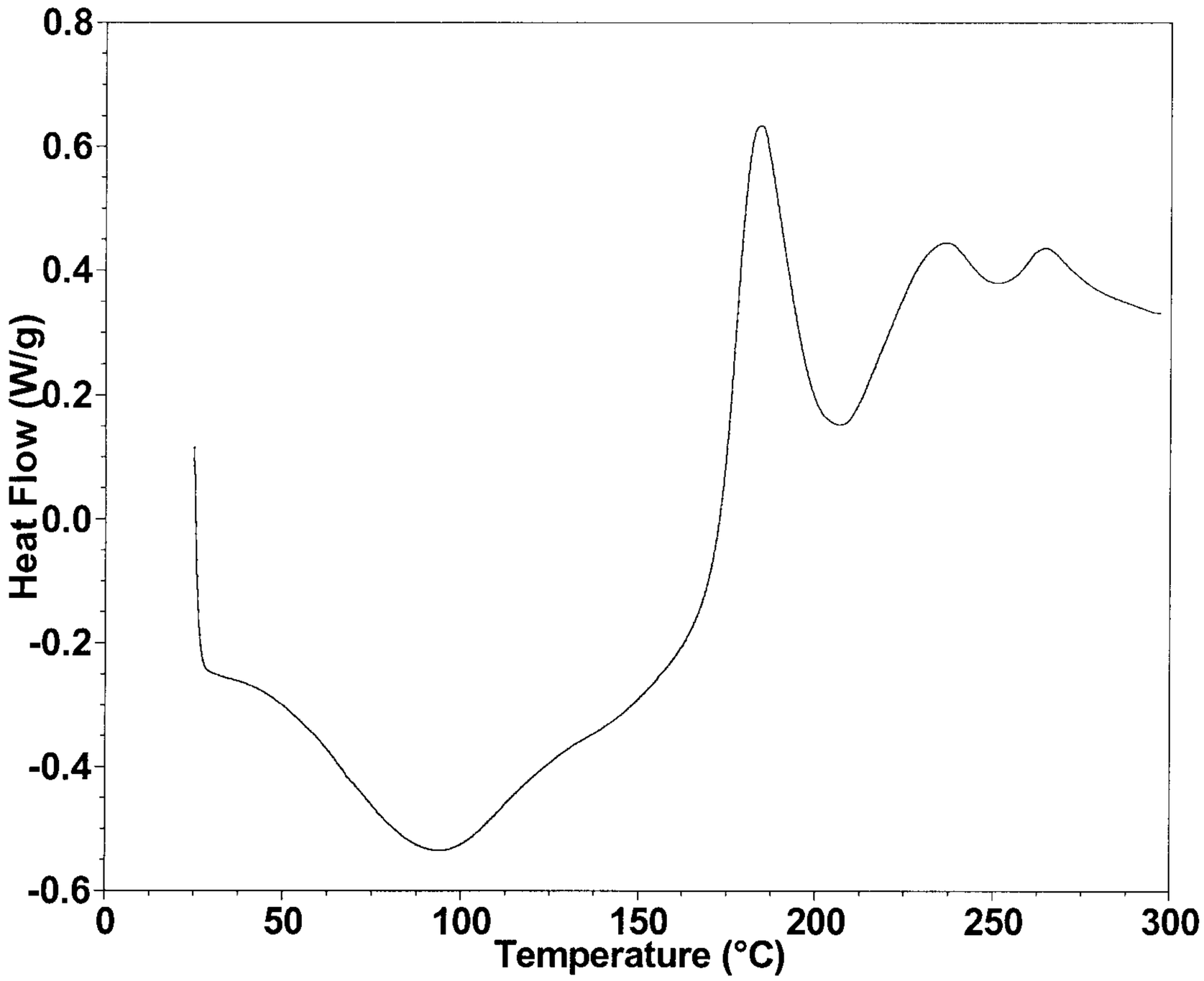


FIG. 8

TGA Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Mono MSA Salt Form II

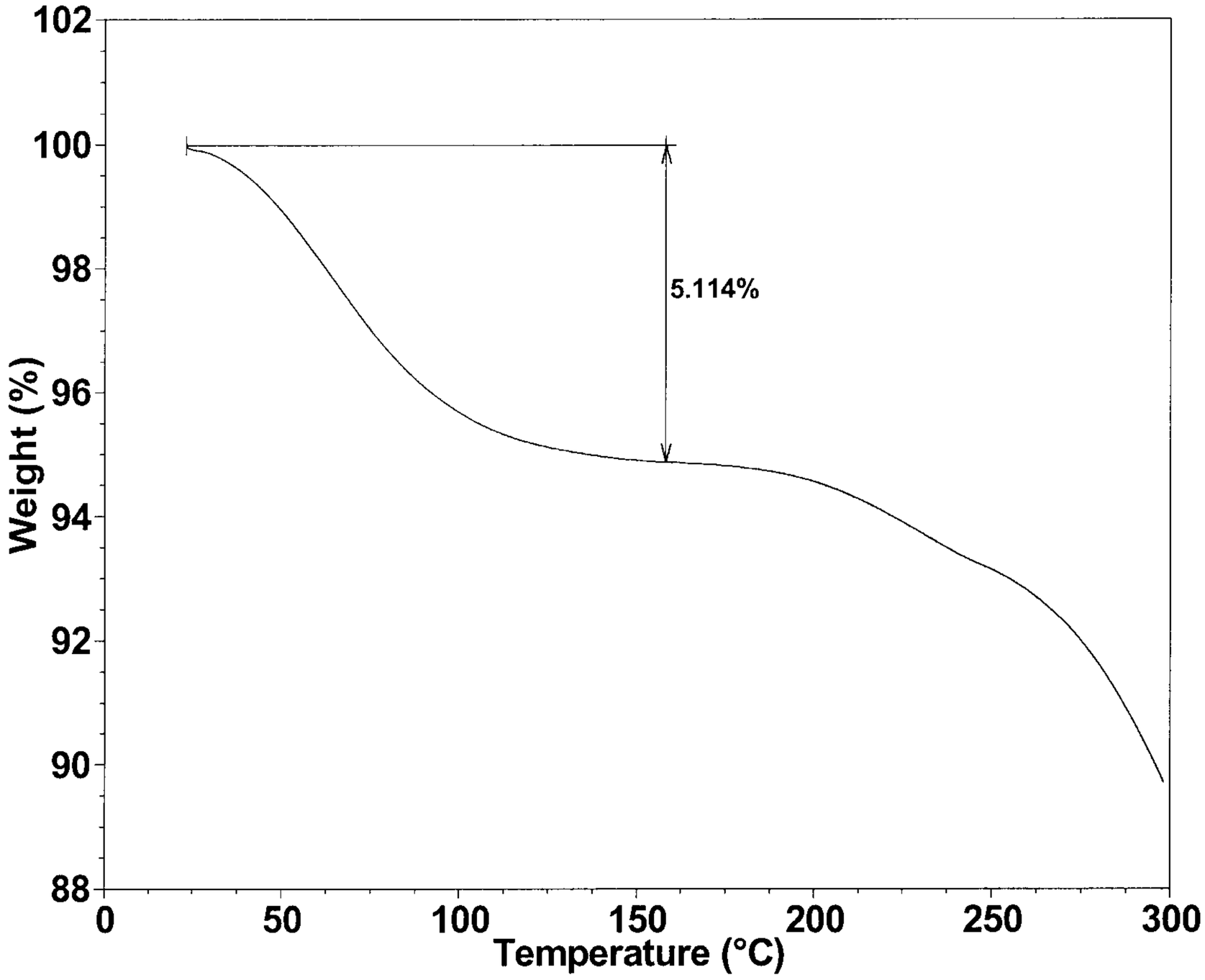


FIG. 9

XRPD Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form I

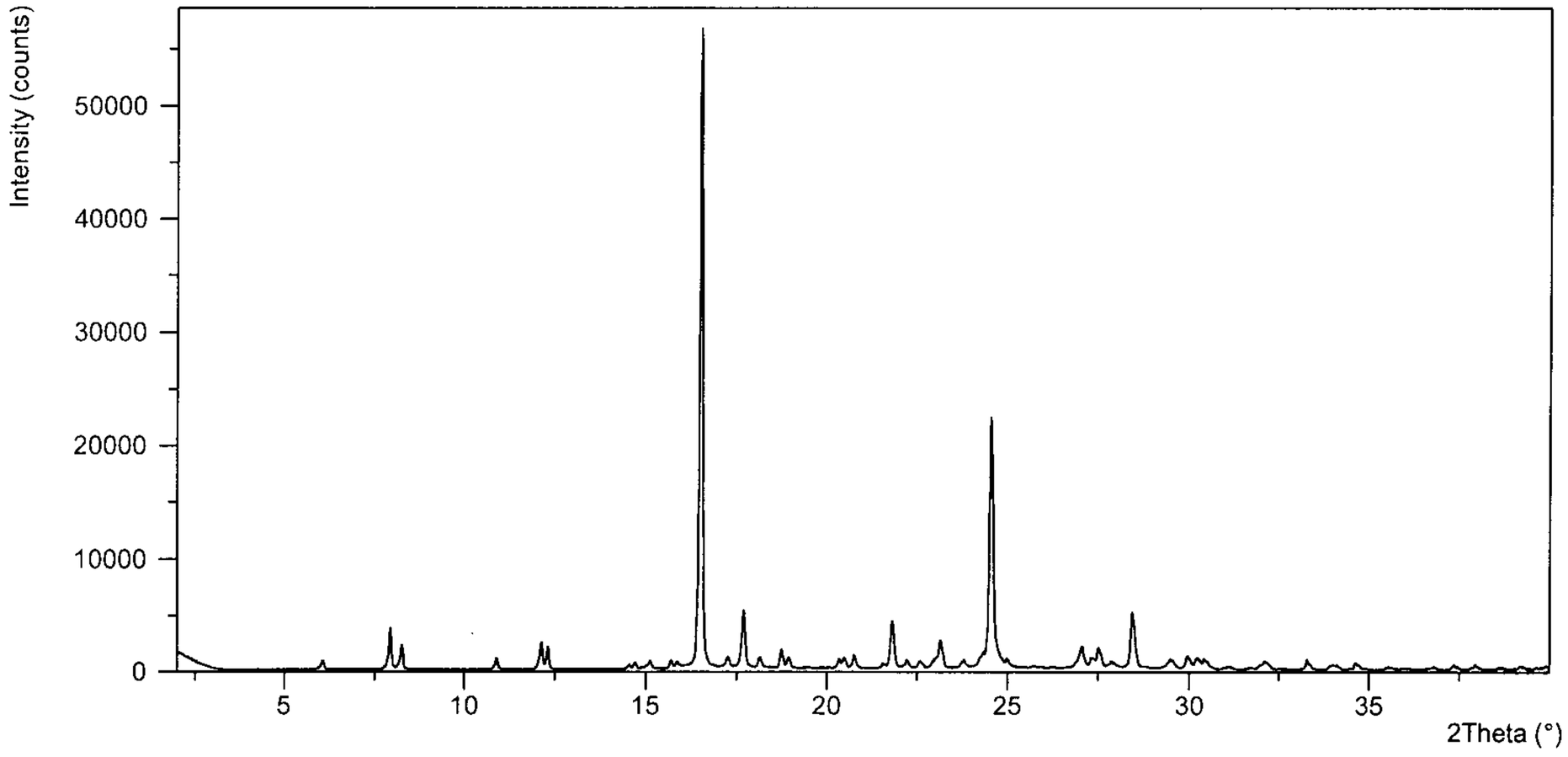


FIG. 10

NMR Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form I

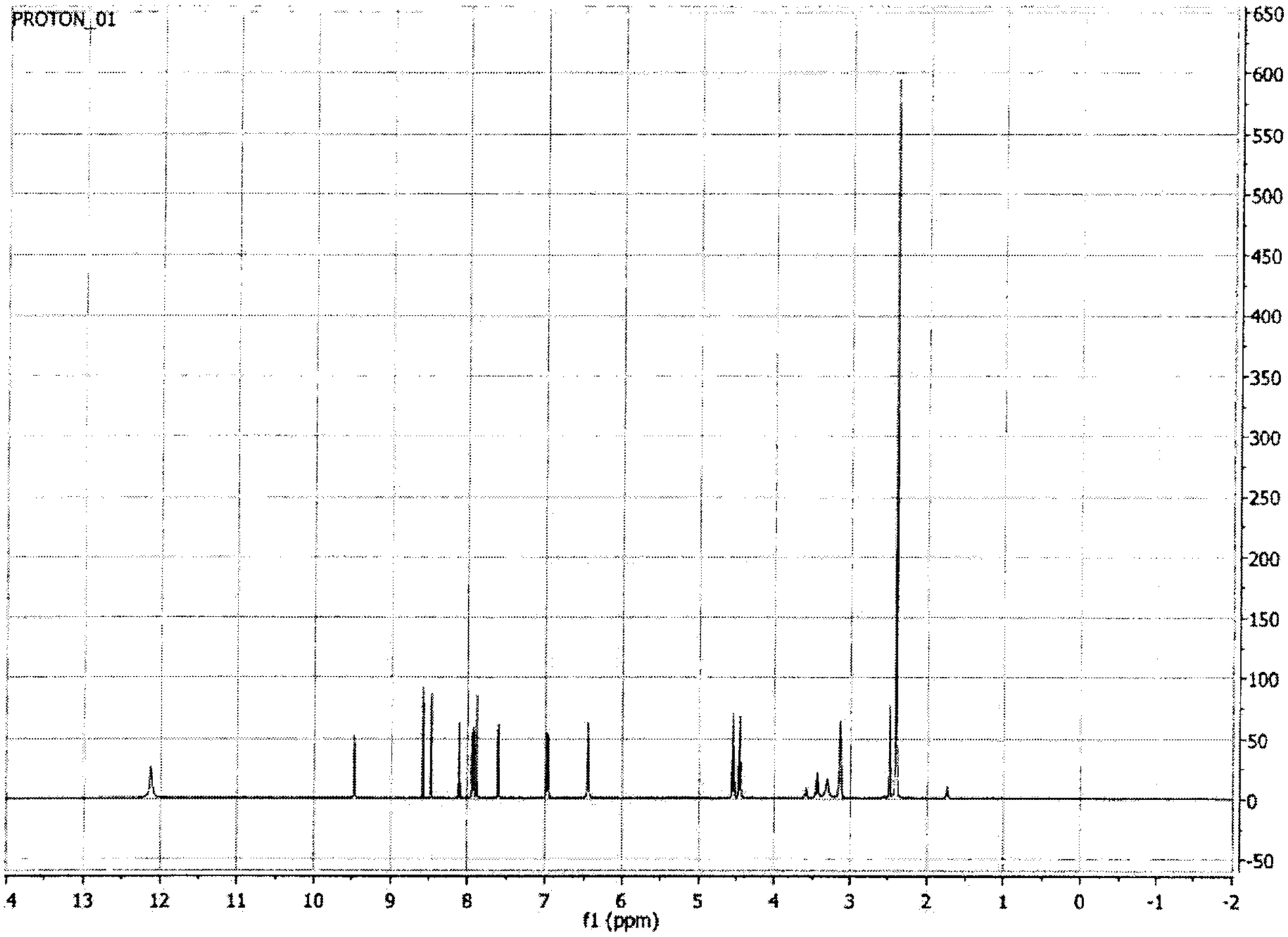


FIG. 11

DSC Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form I

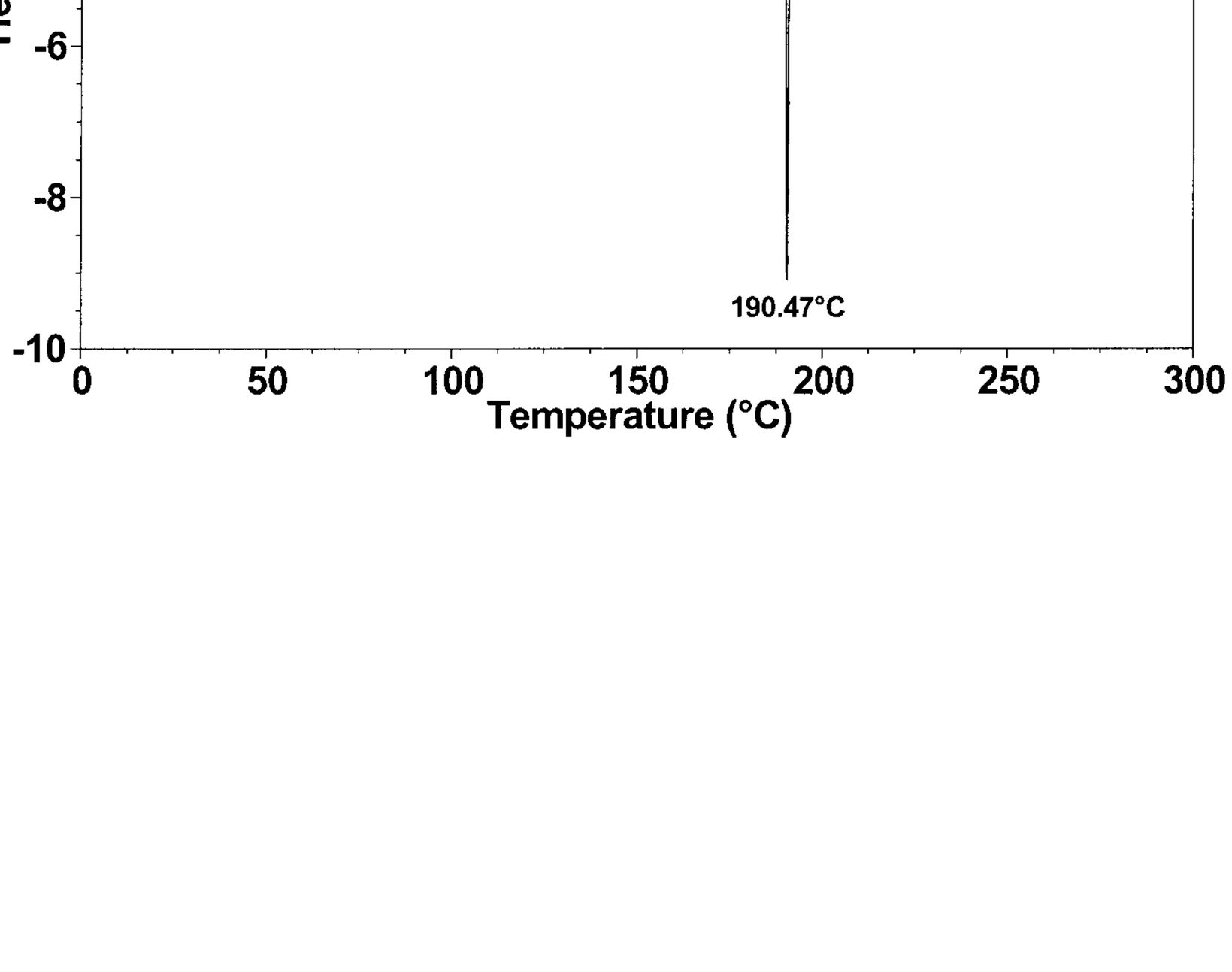


FIG. 12

TGA Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form I

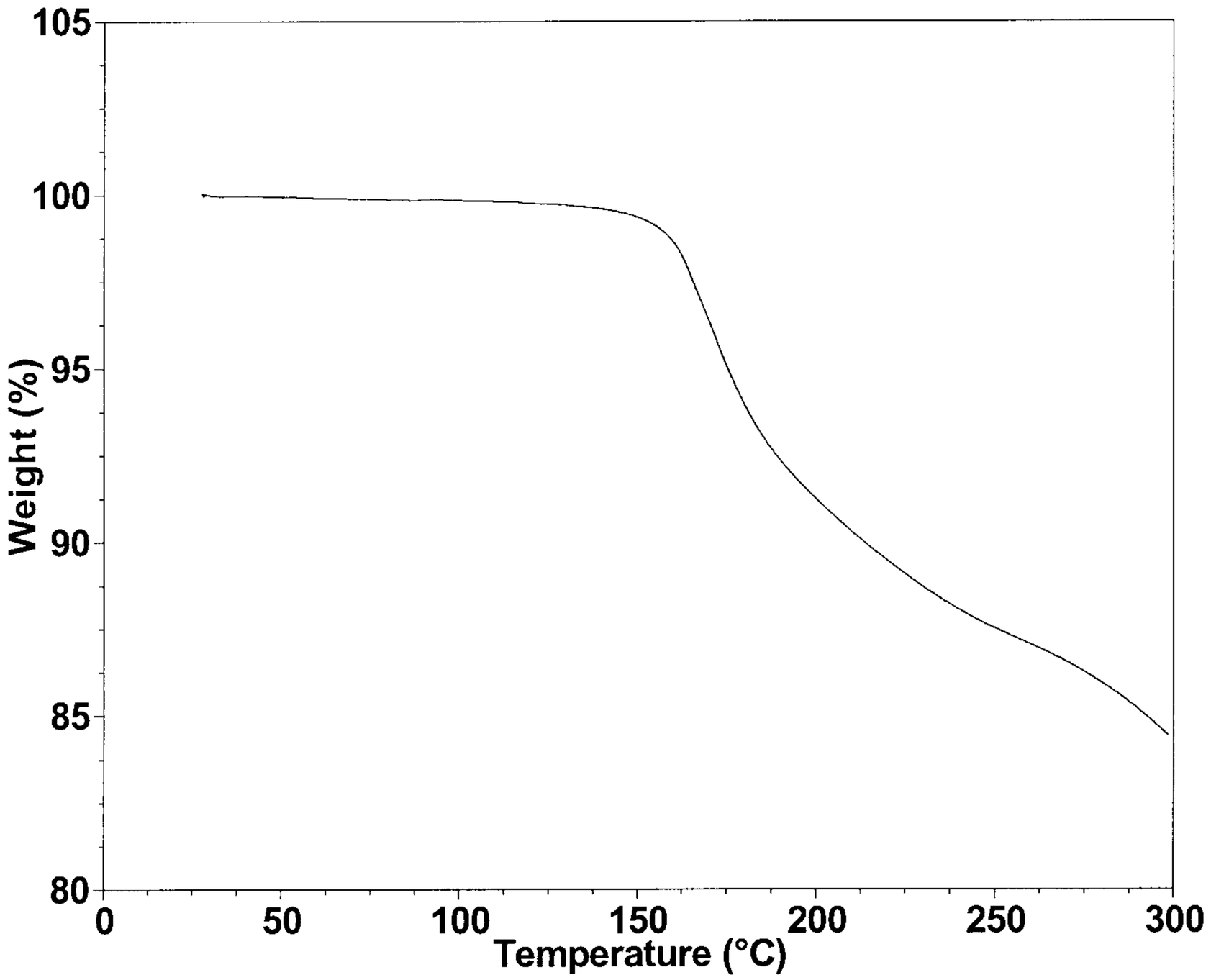


FIG. 13

XRPD Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form II

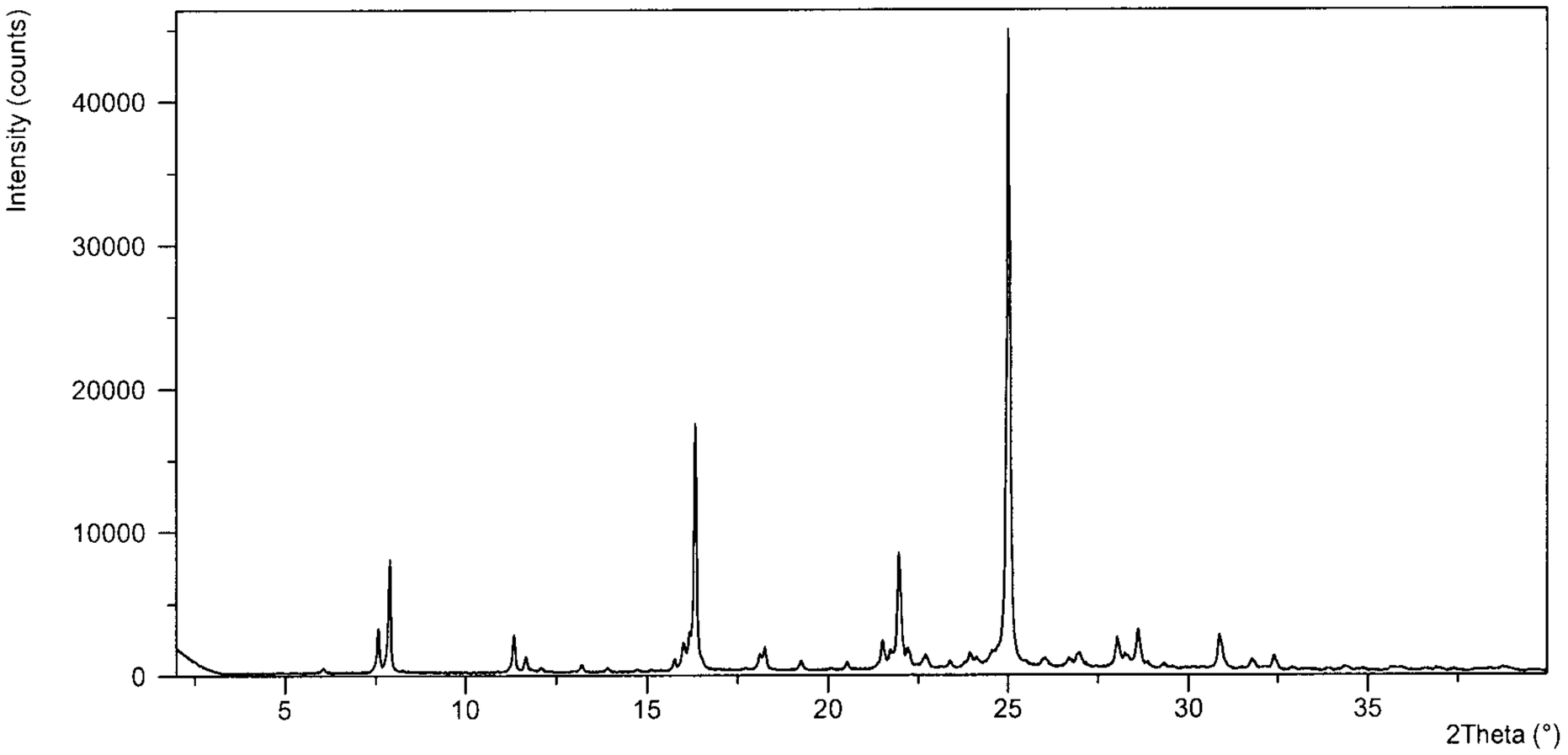


FIG. 14

NMR Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form II

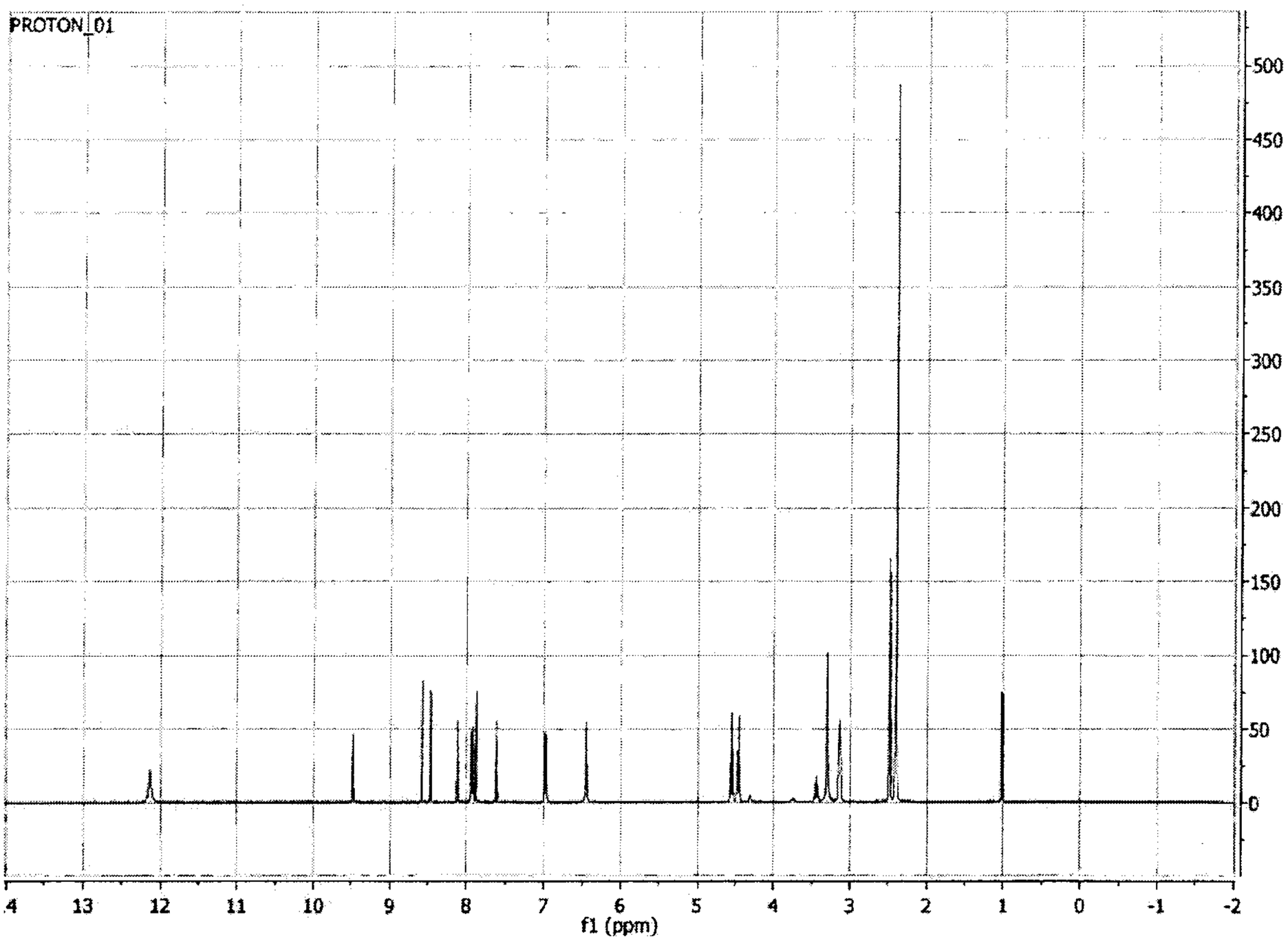


FIG. 15

DSC Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form II

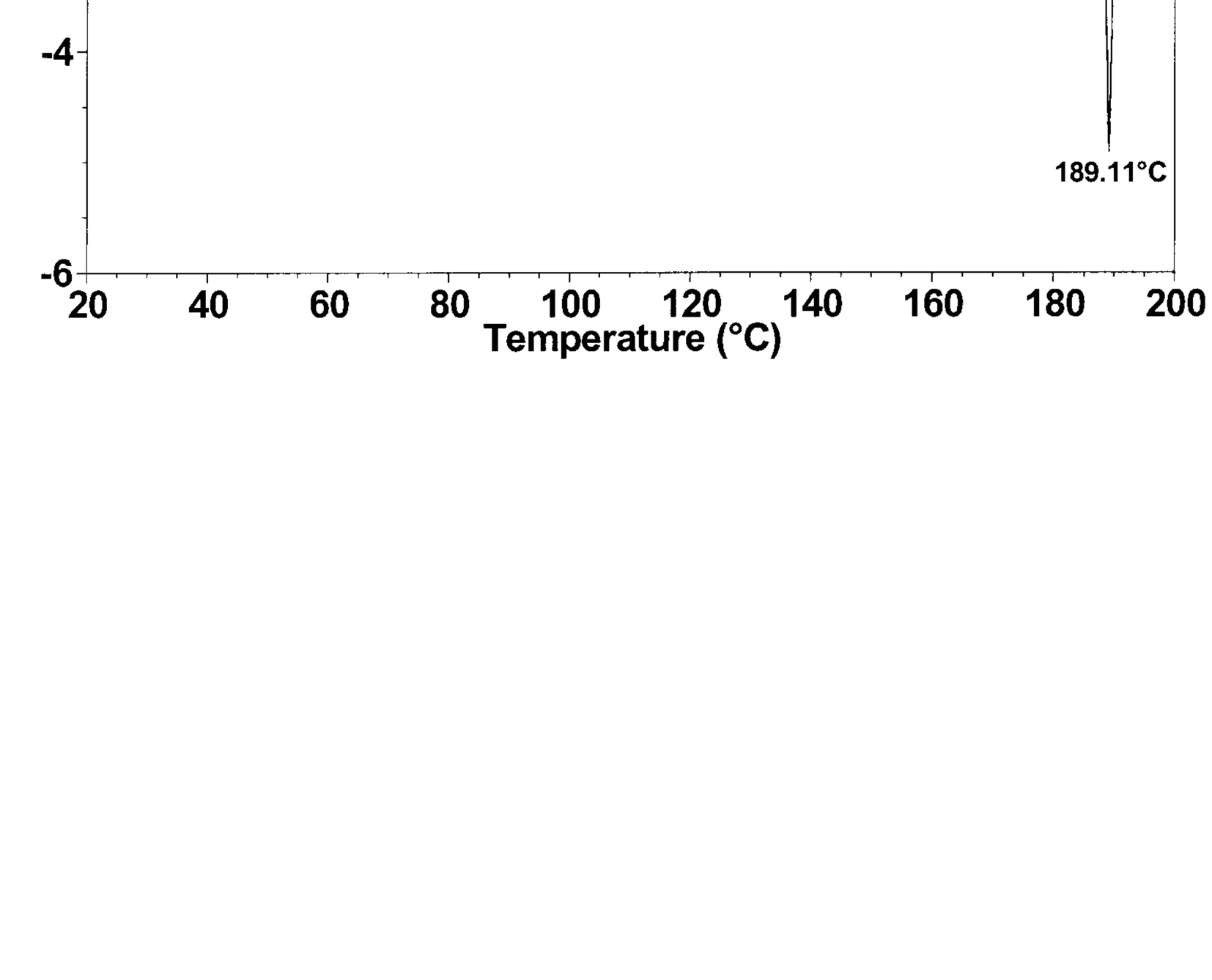
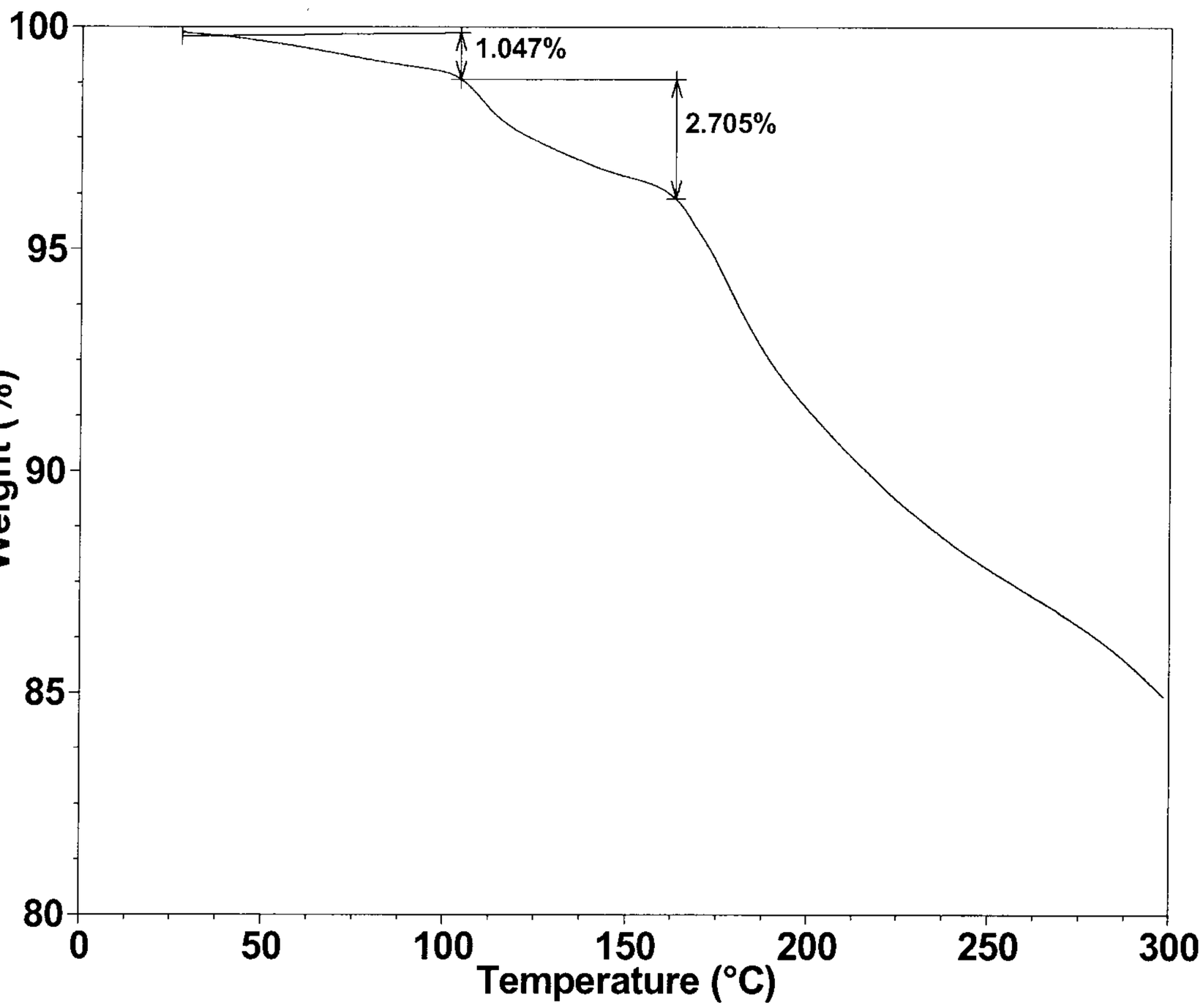
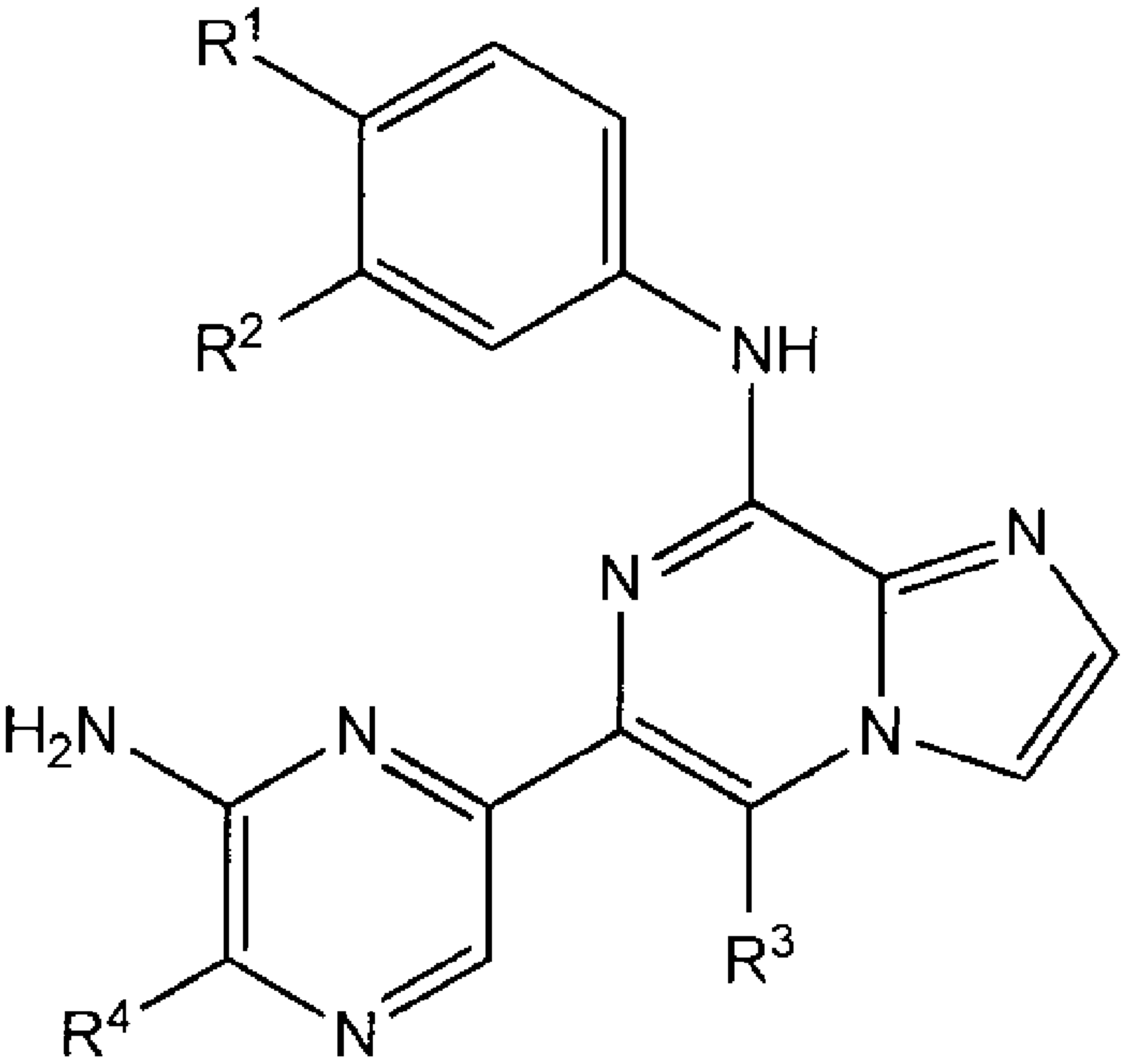


FIG. 16

TGA Analysis of 6-(6-aminopyrazin-2-yl)-N-(4-(4-(oxetan-3-yl)piperazin-1-yl)phenyl)imidazo[1,2-a]pyrazin-8-amine Succinate Form II





Formula I