

DOSAGE FORMS OF AN ESTROGEN RECEPTOR ANTAGONIST RELATED APPLICATIONS

[0001] This application claims priority to and benefit of U.S. Application No. 63/431,515, filed December 9, 2022, the entire contents of which are hereby incorporated by reference.

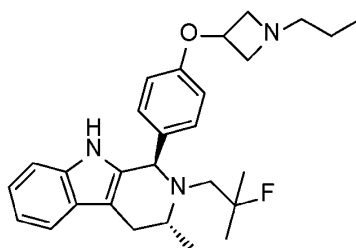
BACKGROUND

[0002] The estrogen receptor (ER) plays an important roles in various cancers, including breast cancers. A variety of treatments have been developed to target the estrogen receptor and/or its activities.

SUMMARY

[0003] There remains a need for anti-estrogen agents that can completely inhibit estrogen receptors, including those coded for by both wild-type and mutant versions (e.g., those containing activating mutations) of the gene encoding Estrogen Receptor-alpha (ER α), Estrogen Receptor 1 (ESR1). Selective estrogen receptor modulators (SERMs) or degraders (SERDs) are a particularly useful or promising tools for such therapy. Recently, classes of estrogen receptor antagonists, termed Complete Estrogen Receptor Antagonists (CERANs) have emerged as promising therapies for completely inhibiting the estrogen receptor. The only approved CERAN for treating estrogen receptor mediated diseases to date is fulvestrant. Fulvestrant, however, is administered parenterally, which is invasive and inconvenient. Thus, there is a need for CERANs that can be administered orally.

[0004] The compound (1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole ("Compound 1"):

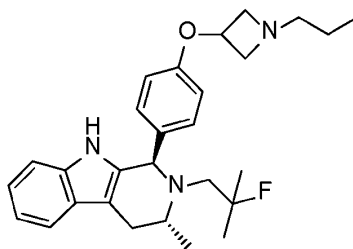


Compound 1

[0005] is a complete estrogen receptor antagonist published in PCT Publication No. WO 2017/059139 (the entire contents of which are hereby incorporated by reference), designated as

Compound B. The present application provides unit dosage forms and uses thereof that are suitable for oral administration of Compound 1.

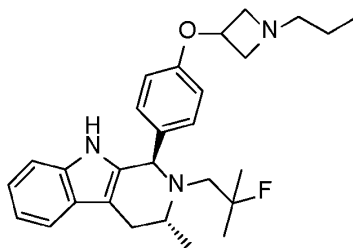
[0006] In some embodiments, the present disclosure provides a unit dosage form comprising Compound 1:



Compound 1

or a pharmaceutically acceptable salt thereof; a first diluent; a second diluent; and a disintegrant.

[0007] In some embodiments, the present disclosure provides a unit dosage form comprising granules, wherein the granules comprise Compound 1:



Compound 1

or a pharmaceutically acceptable salt thereof; a first diluent; a second diluent; and a disintegrant.

[0008] In some embodiments, the present disclosure provides a method of treating an estrogen-receptor mediated disease, disorder, or condition, comprising administering to a subject in need thereof, the unit dosage form as described herein.

BRIEF DESCRIPTION OF THE DRAWING

[0009] FIG. 1 is a plot illustrating dissolution of tablets of Formulation 1 after being subjected to certain conditions for an indicated period of time.

[0010] FIG. 2A is a plot illustrating dissolution of tablets of Formulation 2 after being subjected to certain conditions after 1 month.

[0011] FIG. 2B is a plot illustrating dissolution of tablets of Formulation 2 after being subjected to certain conditions after 3 months.

DETAILED DESCRIPTION OF CERTAIN EMBODIMENTS

[0012] The present disclosure provides unit dosage forms comprising Compound 1, or a pharmaceutically acceptable salt thereof, and particular pharmaceutically acceptable excipients that are suitable for oral administration. The present disclosure encompasses, among other things, an insight that formulation of Compound 1 into a unit dosage form suitable for oral delivery presents particular challenges due, at least in part, to slow dissolution rates, and sticking and caking of Compound 1 onto a roller compactor during manufacturing. Without being bound by theory, it is understood that Compound 1, when in the form of a free base, has a low glass transition temperature (of about 70 to about 72 °C), and undergoes physical changes when exposed to temperatures above its glass transition temperature. It was discovered by Applicant that this glass transition temperature is lowered when exposed to particular pharmaceutically acceptable excipients commonly used in formulation development, causing Compound 1 to become rubbery and unworkable. The present disclosure reports the discovery of this problem with Compound 1, and provides certain solutions to this problem.

Definitions

[0013] *About or approximately:* As used herein, the term "approximately" or "about," as applied to one or more values of interest, refers to a value that is similar to a stated reference value. In general, those skilled in the art, familiar within the context, will appreciate the relevant degree of variance encompassed by "about" or "approximately" in that context. For example, in some embodiments, the term "approximately" or "about" may encompass a range of values that are within (i.e., $\pm$) 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less of the referred value.

[0014] *Administering:* As used herein, the term "administering" or "administration" typically refers to the administration of a composition to a subject to achieve delivery of an agent that is, or is included in, a composition to a target site or a site to be treated. Those of ordinary skill in the art will be aware of a variety of routes that may, in appropriate circumstances, be utilized for administration to a subject, for example a human. For example, in some embodiments,

administration may be ocular, oral, parenteral, topical, *etc.* In some particular embodiments, administration may be bronchial (*e.g.*, by bronchial instillation), buccal, dermal (which may be or comprise, for example, one or more of topical to the dermis, intradermal, interdermal, transdermal, *etc.*), enteral, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intravenous, intraventricular, within a specific organ (*e.g.*, intrahepatic), mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (*e.g.*, by intratracheal instillation), vaginal, vitreal, *etc.* In some embodiments, administration may be parenteral. In some embodiments, administration may be oral. In some particular embodiments, administration may be intravenous. In some particular embodiments, administration may be subcutaneous. In some embodiments, administration may involve only a single dose. In some embodiments, administration may involve application of a fixed number of doses. In some embodiments, administration may involve dosing that is intermittent (*e.g.*, a plurality of doses separated in time) and/or periodic (*e.g.*, individual doses separated by a common period of time) dosing. In some embodiments, administration may involve continuous dosing (*e.g.*, perfusion) for at least a selected period of time. In some embodiments, administration may comprise a prime-and-boost protocol. A prime-and-boost protocol can include administration of a first dose of a pharmaceutical composition (*e.g.*, an immunogenic composition, *e.g.*, a vaccine) followed by, after an interval of time, administration of a second or subsequent dose of a pharmaceutical composition (*e.g.*, an immunogenic composition, *e.g.*, a vaccine). In the case of an immunogenic composition, a prime-and-boost protocol can result in an increased immune response in a patient.

[0015] Antagonist: As will be understood by those skilled in the art, the term “antagonist” generally refers to an agent whose presence or level correlates with decreased level or activity of a target, as compared with that observed absent the agent (or with the agent at a different level). In some embodiments, an antagonist is one whose presence or level correlates with a target level or activity that is comparable to or less than a particular reference level or activity (*e.g.*, that observed under appropriate reference conditions, such as presence of a known antagonist, *e.g.*, a positive control). In some embodiments, an antagonist may be a direct antagonist in that it exerts its influence directly on (*e.g.*, interacts directly with) the target; in some embodiments, an antagonist may be an indirect antagonist in that it exerts its influence indirectly (*e.g.*, by acting on, such as interacting with, a regulator of the target, or with some other component or entity).

[0016] *Biological sample:* As used herein, the term “biological sample” typically refers to a sample obtained or derived from a biological source (e.g., a tissue or organism or cell culture) of interest, as described herein. In some embodiments, a source of interest comprises an organism, such as an animal or human. In some embodiments, a biological sample is or comprises biological tissue or fluid. In some embodiments, a biological sample may be or comprise bone marrow; blood; blood cells; ascites; tissue or fine needle biopsy samples; cell-containing body fluids; free floating nucleic acids; sputum; saliva; urine; cerebrospinal fluid; peritoneal fluid; pleural fluid; feces; lymph; gynecological fluids; skin swabs; vaginal swabs; oral swabs; nasal swabs; washings or lavages such as a ductal lavages or bronchoalveolar lavages; aspirates; scrapings; bone marrow specimens; tissue biopsy specimens; surgical specimens; feces, other body fluids, secretions, and/or excretions; and/or cells therefrom, etc. In some embodiments, a biological sample is or comprises cells obtained from an individual. In some embodiments, obtained cells are or include cells from an individual from whom the sample is obtained. In some embodiments, a sample is a “primary sample” obtained directly from a source of interest by any appropriate means. For example, in some embodiments, a primary biological sample is obtained by methods selected from the group consisting of biopsy (e.g., fine needle aspiration or tissue biopsy), surgery, collection of body fluid (e.g., blood, lymph, feces etc.), etc. In some embodiments, as will be clear from context, the term “sample” refers to a preparation that is obtained by processing (e.g., by removing one or more components of and/or by adding one or more agents to) a primary sample. For example, filtering using a semi-permeable membrane. Such a “processed sample” may comprise, for example, nucleic acids or proteins extracted from a sample or obtained by subjecting a primary sample to techniques such as amplification or reverse transcription of mRNA, isolation and/or purification of certain components, etc.

[0017] *Carrier:* As used herein, the term “carrier” refers to a diluent, adjuvant, excipient, or vehicle with which a composition is administered. In some exemplary embodiments, carriers can include sterile liquids, such as, for example, water and oils, including oils of petroleum, animal, vegetable or synthetic origin, such as, for example, peanut oil, soybean oil, mineral oil, sesame oil and the like. In some embodiments, carriers are or include one or more solid components.

[0018] *Combination therapy:* As used herein, the term “combination therapy” refers to those situations in which a subject is simultaneously exposed to two or more therapeutic regimens (e.g., two or more therapeutic agents or modality(ies)). In some embodiments, the two or more regimens

may be administered simultaneously; in some embodiments, such regimens may be administered sequentially (e.g., all “doses” of a first regimen are administered prior to administration of any doses of a second regimen); in some embodiments, such agents are administered in overlapping dosing regimens. In some embodiments, “administration” of combination therapy may involve administration of one or more agent(s) or modality(ies) to a subject receiving the other agent(s) or modality(ies) in the combination. For clarity, combination therapy does not require that individual agents be administered together in a single composition (or even necessarily at the same time), although in some embodiments, two or more agents, or active moieties thereof, may be administered together in a combination composition, or even in a combination compound (e.g., as part of a single chemical complex or covalent entity).

[0019] *Comparable:* As used herein, the term “comparable” refers to two or more agents, entities, situations, sets of conditions, etc., that may not be identical to one another but that are sufficiently similar to permit comparison therebetween so that one skilled in the art will appreciate that conclusions may reasonably be drawn based on differences or similarities observed. In some embodiments, comparable sets of conditions, circumstances, individuals, or populations are characterized by a plurality of substantially identical features and one or a small number of varied features. Those of ordinary skill in the art will understand, in context, what degree of identity is required in any given circumstance for two or more such agents, entities, situations, sets of conditions, etc. to be considered comparable. For example, those of ordinary skill in the art will appreciate that sets of circumstances, individuals, or populations are comparable to one another when characterized by a sufficient number and type of substantially identical features to warrant a reasonable conclusion that differences in results obtained or phenomena observed under or with different sets of circumstances, individuals, or populations are caused by or indicative of the variation in those features that are varied.

[0020] *Composition:* Those skilled in the art will appreciate that the term “composition” may be used to refer to a discrete physical entity that comprises one or more specified components. In general, unless otherwise specified, a composition may be of any form – e.g., gas, gel, liquid, solid, etc.

[0021] *Dosage form or unit dosage form:* Those skilled in the art will appreciate that the term “dosage form” may be used to refer to a physically discrete unit of an active agent (e.g., a therapeutic or diagnostic agent) for administration to a subject. Typically, each such unit contains

a predetermined quantity of active agent. In some embodiments, such quantity is a unit dosage amount (or a whole fraction thereof) appropriate for administration in accordance with a dosing regimen that has been determined to correlate with a desired or beneficial outcome when administered to a relevant population (i.e., with a therapeutic dosing regimen).

[0022] *Dosing regimen or therapeutic regimen:* Those skilled in the art will appreciate that the terms “dosing regimen” and “therapeutic regimen” may be used to refer to a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In some embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which is separated in time from other doses. In some embodiments, individual doses are separated from one another by a time period of the same length; in some embodiments, a dosing regimen comprises a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first dose amount. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount same as the first dose amount. In some embodiments, a dosing regimen is correlated with a desired or beneficial outcome when administered across a relevant population (i.e., is a therapeutic dosing regimen).

[0023] *Excipient:* As used herein, the term “excipient” refers to a non-therapeutic agent that may be included in a pharmaceutical composition, for example, to provide or contribute to a desired consistency or stabilizing effect. Suitable pharmaceutical excipients include, for example, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like.

[0024] *Modulator:* The term “modulator,” as used herein, refers to a compound (e.g., a small molecule) that can alter the activity of another molecule (e.g., a protein). For example, in some embodiments, a modulator can cause an increase or decrease in the magnitude of a certain activity of a type of molecule as compared to the magnitude of the activity in the absence of the modulator. For example, a modulator can be an agonist or an antagonist of a particular target, as those terms

are defined herein. For example, in some embodiments, a modulator is an agonist. In some embodiments, a modulator is an antagonist.

[0025] *Oral:* The phrases “oral administration” and “administered orally” as used herein have their art-understood meaning referring to administration by mouth of a compound or composition.

[0026] *Parenteral:* The phrases “parenteral administration” and “administered parenterally” as used herein have their art-understood meaning referring to modes of administration other than enteral and topical administration, usually by injection, and include, without limitation, intravenous, intramuscular, intra-arterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal, and intrasternal injection and infusion.

[0027] *Patient* or *subject:* As used herein, the term “patient” or “subject” refers to any organism to which a provided composition is or may be administered, e.g., for experimental, diagnostic, prophylactic, cosmetic, and/or therapeutic purposes. Typical patients or subjects include animals (e.g., mammals such as mice, rats, rabbits, non-human primates, and/or humans). In some embodiments, a patient is a human. In some embodiments, a patient or a subject is suffering from or susceptible to one or more disorders or conditions. In some embodiments, a patient or subject displays one or more symptoms of a disorder or condition. In some embodiments, a patient or subject has been diagnosed with one or more disorders or conditions. In some embodiments, a patient or a subject is receiving or has received certain therapy to diagnose and/or to treat a disease, disorder, or condition.

[0028] *Pharmaceutical composition:* As used herein, the term “pharmaceutical composition” refers to an active agent, formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, the active agent is present in unit dose amount appropriate for administration in a therapeutic or dosing regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments, pharmaceutical compositions may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release

formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

[0029] *Pharmaceutically acceptable:* As used herein, the phrase “pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

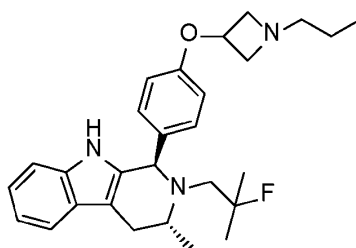
[0030] *Pharmaceutically acceptable salt:* The term “pharmaceutically acceptable salt”, as used herein, refers to salts of such compounds that are appropriate for use in pharmaceutical contexts, i.e., salts which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like, and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well known in the art. For example, S. M. Berge, et al. describes pharmaceutically acceptable salts in detail in *J. Pharmaceutical Sciences*, 66: 1-19 (1977).

[0031] *Prevent* or *prevention:* As used herein, the terms “prevent” or “prevention”, when used in connection with the occurrence of a disease, disorder, and/or condition, refer to reducing the risk of developing the disease, disorder and/or condition and/or to delaying onset of one or more characteristics or symptoms of the disease, disorder or condition. Prevention may be considered complete when onset of a disease, disorder or condition has been delayed for a predefined period of time.

[0032] *Treat:* As used herein, the terms “treat,” “treatment,” or “treating” refer to any method used to partially or completely alleviate, ameliorate, relieve, inhibit, prevent, delay onset of, reduce severity of, and/or reduce incidence of one or more symptoms or features of a disease, disorder, and/or condition. Treatment may be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition. In some embodiments, treatment may be administered to a subject who exhibits only early signs of the disease, disorder, and/or condition, for example, for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition.

Compound 1

[0033] Compound 1, otherwise known as (1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (“Compound 1”):



Compound 1

[0034] is a complete estrogen receptor antagonist, published in PCT Publication No. WO 2017/059139 (the entirety of which is incorporated herein by reference), designated as Compound B. Exemplary methods for using Compound 1 are described in PCT Publication Nos. WO 2021/007146 and WO 2021/178846, the entirety of each of which are incorporated herein by reference. A synthesis of Compound 1 is described in detail in Example 10 of WO 2017/059139.

Unit Dosage Forms of Compound 1

[0035] In some embodiments, the present disclosure provides a unit dosage form comprising Compound 1. The present disclosure encompasses, among other thing, the surprising discovery that particular excipients, when used to prepare a unit dosage form comprising Compound 1, provide particular desirable properties and avoid problems associated with other formulations and excipients.

[0036] When attempting to develop formulations of Compound 1, it was discovered that Compound 1, being amorphous, had low bulk and tap densities, and poor flow properties. Moreover, it was discovered that Compound 1 has a low glass transition temperature, and undergoes physical changes when exposed to temperatures greater than about 70 °C. Without being bound by theory, it is understood that, when exposed to particular excipients, the glass transition temperature of Compound 1 lowers, which causes Compound 1 to become rubbery and difficult to process and incorporate into pharmaceutical formulations suitable for oral delivery.

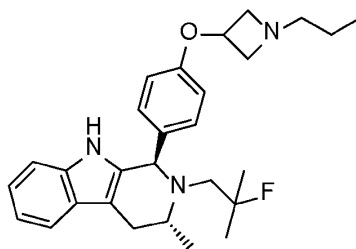
[0037] The present disclosure provides certain solutions to problems associated with developing a unit dosage form suitable for oral delivery that comprises Compound 1, or a pharmaceutically acceptable salt thereof. In some embodiments, a unit dosage form comprising Compound 1, or a pharmaceutically acceptable salt thereof, is prepared by a direct compression method. In some embodiments, a unit dosage form comprises granules comprising Compound 1, or a pharmaceutically acceptable salt thereof, and is prepared by roller compaction.

[0038] Further, during development of unit dosage forms described herein, it was discovered that certain unit dosage forms prepared by a granulation/roller compaction method exhibited slow dissolution after storage, in particular when stored at elevated temperatures and humidity. These properties are demonstrated, for example, in Example 2, herein.

[0039] The present disclosure provides unit dosage forms that, among other things, solve problems associated with preparing formulations of Compound 1, and in some embodiments avoid the need for use of a roller compactor and granulation process, and further, surprisingly exhibit improved stability relative to other formulations of Compound 1. For example, Applicant discovered that reducing a weight percent of Compound 1 in a unit dosage form, as well as increasing an amount of a first diluent, e.g., a water soluble diluent, while reducing an amount of a less water soluble second diluent provided a unit dosage form that exhibited acceptable properties and avoided the problems associated with earlier formulations.

Dry Powder Blend Formulations

[0040] In some embodiments, the present disclosure provides a unit dosage form comprising Compound 1:



Compound 1

or a pharmaceutically acceptable salt thereof; a first diluent; a second diluent; and a disintegrant.

[0041] In some embodiments, a unit dosage form comprises about 10% to about 20% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base.

As used herein, and unless otherwise specified, a weight of Compound 1, when incorporated into a unit dosage form described herein, is calculated according to its free base weight, regardless of whether Compound 1 is incorporated into a unit dosage form as a free base or as a salt form. It is understood that a molecular weight of Compound 1 as a free base will be less than a salt of Compound 1. A person of skill in the art will readily understand how to determine an amount of Compound 1 in a unit dosage form described herein by using a free base weight of Compound 1, regardless of the form Compound 1 is used.

[0042] Moreover, reference to a weight percentage of a unit dosage form described herein does not include the weight of any coating. That is, a weight percentage described herein refers to a combination of active ingredient (e.g., Compound 1), and pharmaceutically acceptable excipients, with the exception of any coating.

[0043] In some embodiments, a unit dosage form comprises about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, or about 20% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base. In some embodiments, a unit dosage form comprises about 10% to about 15% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base. In some embodiments, a unit dosage form comprises about 10% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base. In some embodiments, a unit dosage form comprises about 11% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base. In some embodiments, a unit dosage form comprises about 12% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base. In some embodiments, a unit dosage form comprises about 13% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base. In some embodiments, a unit dosage form comprises about 14% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base. In some embodiments, a unit dosage form comprises about 15% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base.

[0044] In some embodiments, a unit dosage form comprises about 10 mg to about 120 mg of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base. In some embodiments, a unit dosage form comprises about 20 mg to about 90 mg of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base. In some embodiments, a unit

dosage form comprises about 20 mg to about 60 mg of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base. In some embodiments, a unit dosage form comprises about 10 mg, about 15mg, about 20 mg, about 25 mg, 30 mg, about 35 mg, about 40 mg, about 45 mg, about 50 mg, about 55 mg, about 60 mg, about 65 mg, about 70 mg, about 75 mg, about 80 mg, about 85 mg, about 90 mg, about 95 mg, about 100 mg, about 105 mg, about 110 mg, about 115 mg, or about 120 mg of Compound, or a pharmaceutically acceptable salt thereof, calculated as a free base.

[0045] In some embodiments, Compound 1 is a free base form of Compound 1.

[0046] In some embodiments, a unit dosage form comprises about 10% to about 80% by weight of a first diluent. In some embodiment, a unit dosage form comprises about 20% to about 70% by weight of a first diluent. In some embodiment, a unit dosage form comprises about 30% to about 70% by weight of a first diluent. In some embodiment, a unit dosage form comprises about 40% to about 70% by weight of a first diluent. In some embodiment, a unit dosage form comprises about 50% to about 65% by weight of a first diluent. In some embodiment, a unit dosage form comprises about 55% to about 65% by weight of a first diluent. In some embodiments a unit dosage form comprises about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, or about 80% by weight a first diluent. In some embodiments, a unit dosage form comprises about 50% by weight of a first diluent. In some embodiments, a unit dosage form comprises about 55% by weight of a first diluent. In some embodiments, a unit dosage form comprises about 60% by weight of a first diluent. In some embodiments, a unit dosage form comprises about 65% by weight of a first diluent.

[0047] In some embodiments, a first diluent is selected from lactose monohydrate, microcrystalline cellulose, mannitol, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch. In some embodiments, a first diluent is selected from lactose monohydrate, mannitol, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch. In some embodiments, a first diluent is selected from lactose monohydrate and calcium phosphate. In some embodiments, a first diluent is lactose monohydrate. In some embodiments, a first diluent is microcrystalline cellulose. In some embodiments, a first diluent is mannitol. In some embodiments, a first diluent is calcium phosphate (e.g., calcium phosphate (dibasic)). In some

embodiments, a first diluent is lactose anhydrate. In some embodiments, a first diluent is calcium silicate. In some embodiments, a first diluent is pregelatinized starch.

[0048] In some embodiments, a unit dosage form comprises about 40% to about 70% by weight of lactose monohydrate. In some embodiment, a unit dosage form comprises about 50% to about 65% by weight of lactose monohydrate. In some embodiments, a unit dosage form comprises about 60% by weight of lactose monohydrate. In some embodiment, a unit dosage form comprises about 55% to about 65% by weight of lactose monohydrate. In some embodiments, a unit dosage form comprises about 40% to about 70% by weight of calcium phosphate. In some embodiment, a unit dosage form comprises about 50% to about 65% by weight of calcium phosphate. In some embodiment, a unit dosage form comprises about 55% to about 65% by weight of calcium phosphate. In some embodiments, a unit dosage form comprises about 60% by weight of calcium phosphate.

[0049] In some embodiments, a unit dosage form comprises about 10% to about 20% by weight of a second diluent. In some embodiments, a unit dosage form comprises about 15% to about 20% by weight of a second diluent. In some embodiments, a unit dosage form comprises about 15%, about 16%, about 17%, about 18%, about 19%, or about 20% by weight of a second diluent. In some embodiments, a unit dosage form comprises about 18% to about 20% by weight of a second diluent. In some embodiments, a unit dosage form comprises about 18.0%, about 18.5%, about 19.0%, about 19.5%, or about 20.0% by weight of a second diluent.

[0050] In some embodiments, a second diluent is selected from the group consisting of microcrystalline cellulose, lactose monohydrate, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch. In some embodiments, a second diluent is selected from the group consisting of microcrystalline cellulose, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch. In some embodiments, a second diluent is microcrystalline cellulose. In some embodiments, a second diluent is a microcrystalline cellulose having an average particle size that is about 180 μm . In some embodiments, a second diluent is lactose monohydrate. In some embodiments, a second diluent is calcium phosphate. In some embodiments, a second diluent is lactose anhydrate. In some embodiments, a second diluent is calcium silicate. In some embodiments, a second diluent is pregelatinized starch.

[0051] In some embodiments, a unit dosage form comprises about 15% to about 20% by weight of microcrystalline cellulose. In some embodiments, a unit dosage form comprises about

15% by weight of microcrystalline cellulose. In some embodiments, a unit dosage form comprises about 16% by weight of microcrystalline cellulose. In some embodiments, a unit dosage form comprises about 17% by weight of microcrystalline cellulose. In some embodiments, a unit dosage form comprises about 18% by weight of microcrystalline cellulose. In some embodiments, a unit dosage form comprises about 18.5% by weight of microcrystalline cellulose. In some embodiments, a unit dosage form comprises about 19% by weight of microcrystalline cellulose. In some embodiments, a unit dosage form comprises about 19.5% by weight of microcrystalline cellulose. In some embodiments, a unit dosage form comprises about 20% by weight of microcrystalline cellulose.

[0052] In some embodiments, a weight ratio of a first diluent to a second diluent in a unit dosage form is from about 3:1 to about 4:1. In some embodiments, a weight ratio of a first diluent to a second diluent is about 3:1, about 3.1:1, about 3.15:1, about 3.2:1, about 3.25:1, about 3.3:1, about 3.35:1, about 3.4:1, about 3.45:1, about 3.5:1, about 3.55:1, about 3.6:1, about 3.65:1, about 3.7:1, about 3.75:1, about 3.8:1, about 3.85:1, about 3.9:1, 3.95:1, or about 4:1.

[0053] In some embodiments, a first diluent and a second diluent are different.

[0054] In some embodiments, a unit dosage form comprises about 5% to about 10% by weight of a disintegrant. In some embodiments, a unit dosage form comprises about 5%, about 6%, about 7%, about 8%, about 9%, or about 10% by weight of a disintegrant. In some embodiments, a unit dosage form comprises about 5% of a disintegrant. In some embodiments, a unit dosage form comprises about 6% of a disintegrant. In some embodiments, a unit dosage form comprises about 7% of a disintegrant. In some embodiments, a unit dosage form comprises about 8% of a disintegrant. In some embodiments, a unit dosage form comprises about 9% of a disintegrant. In some embodiments, a unit dosage form comprises about 10% of a disintegrant.

[0055] In some embodiments, a disintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate, crospovidone, and hydroxypropyl cellulose. In some embodiments, a disintegrant is croscarmellose sodium. In some embodiments, a disintegrant is sodium starch glycolate. In some embodiments, a unit dosage form comprise about 5% to about 10% by weight of croscarmellose sodium. In some embodiments, a unit dosage form comprises about 5% to about 10% by weight of sodium starch glycolate.

[0056] In some embodiments, a unit dosage form comprises about 10% to about 15% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base;

about 10% to about 80% by weight of a first diluent; about 10% to about 20% by weight a second diluent; and about 5% to about 10% by weight of a disintegrant. In some embodiments, a unit dosage form comprises about 10% to about 15% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base; about 40% to about 70% by weight of a first diluent; about 10% to about 20% by weight of a second diluent; and about 5% to about 10% by weight of a disintegrant.

[0057] In some embodiments, a unit dosage form comprises about 10% to about 15% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base; about 10% to about 80% by weight of lactose monohydrate; about 10% to about 20% by weight of microcrystalline cellulose; and about 5% to about 10% by weight of croscarmellose sodium. In some embodiments, a unit dosage form comprises about 10% to about 15% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base; about 40% to about 70% by weight of lactose monohydrate; about 10% to about 20% by weight of microcrystalline cellulose; and about 5% to about 10% by weight of croscarmellose sodium.

[0058] In some embodiments, a unit dosage form comprises about 12% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base; about 60% by weight of a first diluent; about 19% by weight of a second diluent; and about 8% by weight of a disintegrant.

[0059] In some embodiments, a unit dosage form comprises about 12% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base; about 60% by weight of lactose monohydrate; about 19% by weight of microcrystalline cellulose; and about 8% by weight of croscarmellose sodium.

[0060] In some embodiments, a unit dosage form further comprises a lubricant. In some embodiments, a unit dosage form comprises about 0.1% to about 1.5% by weight of a lubricant. In some embodiments, a unit dosage form comprises about 0.5% to about 1.5% by weight of a lubricant. In some embodiments, a unit dosage form comprises about 0.5%, about 1.0% or about 1.5% by weight of a lubricant.

[0061] In some embodiments, a lubricant is selected from the group consisting of magnesium stearate and sodium stearyl fumarate. In some embodiments, a lubricant is magnesium stearate. In some embodiments, a unit dosage form comprises about 0.1% to about 1.5% by weight of a lubricant. In some embodiments, a unit dosage form comprises about 0.5% to about 1.5% by

weight of a lubricant. In some embodiments, a unit dosage form comprises about 0.5%, about 1.0%, or about 1.5% by weight of a lubricant. In some embodiments, a unit dosage form comprises about 0.5% to about 1.5% by weight of magnesium stearate. In some embodiments, a unit dosage form comprises about 0.5%, about 1.0%, or about 1.5% by weight of magnesium stearate.

[0062] In some embodiments, a unit dosage form comprises about 0.1 to about 1% by weight of a glidant. In some embodiments, a glidant is silicon dioxide. In some embodiments, a glidant is colloidal silicon dioxide.

[0063] In some embodiments, a unit dosage form comprises about 12% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base; about 60% by weight of lactose monohydrate; about 19% by weight of microcrystalline cellulose; about 8% by weight of croscarmellose sodium; about 0.5% by weight of silicon dioxide; and about 1% by weight of magnesium stearate.

[0064] In some embodiments, a unit dosage form is in the form of a tablet. In some embodiments, a unit dosage form is a dry powder blend. In some embodiments, a unit dosage form is prepared by a direct compression process. In some embodiments, a unit dosage form is a tablet prepared by direct compression of a dry powder blend. In some embodiments, a unit dosage form described herein does not comprise granules. In some embodiments, a unit dosage form is a tablet comprising a film coating.

[0065] The presently claimed unit dosage forms exhibit improved stability and solubility relative to alternative formulations. For example, in some embodiments, a unit dosage form described herein is characterized in that it is about 80% or more dissolved in about 30 minutes or less (e.g., about 30 minutes, about 25 minutes, about 20 minutes, about 15 minutes, about 10 minutes, about 5 minutes) using conditions known to those of skill in the art for assessing dissolution. For example, in some embodiments, conditions suitable for assessing dissolution include: using USP Apparatus 2 (paddles) at 75 RPM in 900mL of 50mM Citrate buffer, pH 3.5 with 0.1% Sodium Lauryl Sulfate maintained at 37 ± 0.5 °C; or using USP Apparatus 1 (baskets) at 50 RPM in 500mL of 0.01N HCl maintained at 37 ± 0.5 °C.

Granule Formulations

[0066] In some embodiments, a unit dosage form described herein comprises granules, wherein the granules comprise Compound 1, or a pharmaceutically acceptable salt thereof; a first

diluent; a second diluents; and a disintegrant. In some embodiments, a unit dosage form comprises granules and one or more extra-granular excipients.

[0067] In some embodiments, a granule comprises Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 15% to about 20% of the total weight of the unit dosage form, calculated as a free base of Compound 1. As used herein, reference to a weight percentage refers to a weight percentage of that particular component relative to the entire weight of the unit dosage form (e.g., the combination of the intra-granular and extra-granular components), and not only the granule itself.

[0068] In some embodiments, a granule comprises Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 15%, about 16%, about 17%, about 18%, about 19%, or about 20% of the total weight of the unit dosage form, calculated as a free base Compound 1. In some embodiments, a granule comprises Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 15% of the total weight of the unit dosage form, calculated as a free base Compound 1. In some embodiments, a granule comprises Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 16% of the total weight of the unit dosage form, calculated as a free base Compound 1. In some embodiments, a granule comprises Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 17% of the total weight of the unit dosage form, calculated as a free base Compound 1. In some embodiments, a granule comprises Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 18% of the total weight of the unit dosage form, calculated as a free base Compound 1. In some embodiments, a granule comprises Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 19% of the total weight of the unit dosage form, calculated as a free base Compound 1. In some embodiments, a granule comprises Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 20% of the total weight of the unit dosage form, calculated as a free base Compound 1.

[0069] In some embodiments, a granule comprises a first diluent in an amount that is about 5% to about 20% of the total weight of the unit dosage form. In some embodiments, a granule comprises a first diluent in an amount that is about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 11%, about 12%, about 13%, about 14%, about 15%, about 16%, about 17%, about 18%, about 19%, or about 20% of the total weight of the unit dosage form.

[0070] In some embodiments, a first diluent is selected from lactose monohydrate, microcrystalline cellulose, mannitol, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch. In some embodiments, a first diluent is selected from lactose monohydrate and calcium phosphate. In some embodiments, a first diluent is lactose monohydrate. In some embodiments, a first diluent is microcrystalline cellulose. In some embodiments, a first diluent is mannitol. In some embodiments, a first diluent is calcium phosphate (e.g., calcium phosphate (dibasic)). In some embodiments, a first diluent is lactose anhydrate. In some embodiments, a first diluent is calcium silicate. In some embodiments, a first diluent is pregelatinized starch.

[0071] In some embodiments, a granule comprises a second diluent in an amount that is about 50% to about 70% of the total weight of the unit dosage form. In some embodiments, a granule comprises about a second diluent in an amount that is about 50% to about 60% of the total weight of the unit dosage form. In some embodiments, a granule comprises a second diluent in an amount that is about 50%, about 50.5%, about 51%, about 51.5%, about 52%, about 52.5%, about 53%, about 53.5%, about 54%, about 54.5%, about 55%, about 55.5%, about 56%, about 56.5%, about 57%, about 57.5%, about 58%, about 58.5%, about 59%, about 59.5%, or about 60% of the total weight of the unit dosage form.

[0072] In some embodiments, a second diluent is selected from the group consisting of microcrystalline cellulose, lactose monohydrate, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch. In some embodiments, a second diluent is selected from the group consisting of microcrystalline cellulose, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch. In some embodiments, a second diluent is microcrystalline cellulose. In some embodiments, a second diluent is lactose monohydrate. In some embodiments, a second diluent is calcium phosphate. In some embodiments, a second diluent is lactose anhydrate. In some embodiments, a second diluent is calcium silicate. In some embodiments, a second diluent is pregelatinized starch.

[0073] In some embodiments, a granule comprises a disintegrant in an amount that is about 1% to about 5% of the total weight of the unit dosage form. In some embodiments, a granule comprises a disintegrant in an amount that is about 1% of the total weight of the unit dosage form. In some embodiments, a granule comprises a disintegrant in an amount that is about 2% of the total weight of the unit dosage form. In some embodiments, a granule comprises a disintegrant in an amount that is about 3% of the total weight of the unit dosage form. In some embodiments, a

granule comprises a disintegrant in an amount that is about 4% of the total weight of the unit dosage form. In some embodiments, a granule comprises a disintegrant in an amount that is about 5% of the total weight of the unit dosage form.

[0074] In some embodiments, a disintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate, crospovidone, and hydroxypropyl cellulose. . In some embodiments, a disintegrant is sodium starch glycolate. In some embodiments, a disintegrant is croscarmellose sodium.

[0075] In some embodiments, a unit dosage form described herein comprises granules, wherein the granules comprise Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 15% to about 20% of the total weight of the unit dosage form; a first diluent in an amount that is about 5% to about 20% of the total weight of the unit dosage form; a second diluent in an amount that is about 50% to about 70% of the total weight of the unit dosage form; and a disintegrant in an amount that is about 1% to about 5% of the total weight of the unit dosage form.

[0076] In some embodiments, a granule further comprises a lubricant. In some embodiments, a lubricant is magnesium stearate or sodium stearyl fumarate. In some embodiments, a lubricant is magnesium stearate. In some embodiments, a granule comprises a lubricant in an amount that is about 0.1% to about 3% of the total weight of the unit dosage form.

[0077] In some embodiments, a granule further comprises a glidant. In some embodiments, a granule comprises a glidant in an amount that is about 1% to about 5% of the total weight of the unit dosage form. In some embodiments, a glidant is silicon dioxide. In some embodiments, a glidant is colloidal silicon dioxide.

[0078] In some embodiments, a unit dosage form comprises one or more extra-granular excipients. In some embodiments, one or more extra-granular excipients are selected from the group consisting of: lactose monohydrate, microcrystalline cellulose, mannitol, calcium phosphate, lactose anhydrate, calcium silicate, pregelatinized starch, magnesium stearate, sodium stearyl fumarate, sodium starch glycolate, croscarmellose sodium, sodium chloride, and potassium chloride.

[0079] In some embodiments a unit dosage form comprises granules, wherein the granules comprise: Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 15% to about 20% of the total weight of the unit dosage form, calculated as a free base; a first

diluent that is about 5% to about 20% of the total weight of the unit dosage form; a second diluent that is about 50% to about 70% of the total weight of the unit dosage form; and a disintegrant that is about 1% to about 5% of the total weight of the unit dosage form.

[0080] In some embodiments, a unit dosage form comprises granules, wherein the granules comprise: Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 15% to about 20% of the total weight of the unit dosage form, calculated as a free base; lactose monohydrate in an amount that is about 5% to about 20% of the total weight of the unit dosage form; microcrystalline cellulose that is about 50% to about 70% of the total weight of the unit dosage form; and sodium starch glycolate that is about 1% to about 5% of the total weight of the unit dosage form.

[0081] In some embodiments, a unit dosage form comprises granules, wherein the granules comprise: Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 18% of the total weight of the unit dosage form, calculated as a free base; lactose monohydrate in an amount that is about 10% of the total weight of the unit dosage form; microcrystalline cellulose that is about 56.5% of the total weight of the unit dosage form; and sodium starch glycolate that is about 3% of the total weight of the unit dosage form.

[0082] In some embodiments, a unit dosage form comprises granules and one or more extra-granular excipients, wherein the granules comprise: Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 18% of the total weight of the unit dosage form, calculated as a free base; lactose monohydrate in an amount that is about 10% of the total weight of the unit dosage form; microcrystalline cellulose that is about 56.5% of the total weight of the unit dosage form; sodium starch glycolate that is about 3% of the total weight of the unit dosage form; and the one or more extra-granular excipients are selected from microcrystalline cellulose, sodium starch glycolate, magnesium stearate, and combinations thereof.

[0083] In some embodiments, a unit dosage form further comprises a coating.

[0084] In some embodiments, a unit dosage form is in the form of a tablet. In some embodiments, the tablet is prepared by roller compaction.

Uses

[0085] Unit dosage forms described herein are generally useful for the inhibition of the estrogen receptor (ER) and mutants thereof. In some embodiments, the present disclosure

encompasses the insight that unit dosage forms described herein are useful for treatment of an estrogen receptor (ER)-associated disorder (e.g., an ER-associated cancer, such as breast cancer, including metastatic brain cancer), detection of the same, and/or characterization of certain tumors.

[0086] For example, in some embodiments, the present disclosure provides certain methods of treatment in a subject having an ER-associated disease, disorder, or condition. In some embodiments, an ER-associated disease, disorder or condition is a cancer. In some embodiments, an ER-associated disease, disorder or condition is selected from breast cancer, bone cancer, lung cancer, colorectal cancer, endometrial cancer, prostate cancer, ovarian cancer, vaginal cancer, endometriosis, and uterine cancer. In some embodiments, an ER-associated disease, disorder, or condition is breast cancer.

[0087] In some embodiments, a subject has been determined or is suspected of having a cancer that has metastasized (e.g., to the brain, bones, lungs, liver, or the central nervous system). In some embodiments, a subject has been determined or is suspected of having brain metastases. In some embodiments, the subject has developed brain metastases related to an ER-associated cancer, e.g., breast cancer, or a mutation to the estrogen receptor.

[0088] In some embodiments, a provided method comprises administering a unit dosage form described herein to a subject previously treated with another ER inhibitor. In some such embodiments, a provided method comprises administering a unit dosage form described herein to a subject previously treated with a Selective Estrogen Receptor Modulator (SERM), including, for example, tamoxifen, endoxifene, raloxifene, toremifene, lasofoxifene, and ospemifene.

[0089] In some embodiments, a provided method comprises administering a unit dosage form described herein to a subject suffering from an ER-associated disorder (e.g., breast cancer) that is unresponsive to therapy with a SERM, including, for example, tamoxifen, endoxifene, raloxifene, toremifene, lasofoxifene, and ospemifene.

[0090] In some embodiments, a subject has relapsed during or following therapy with a SERM, including, for example, tamoxifen, endoxifene, raloxifene, toremifene, lasofoxifene, and ospemifene.

[0091] In some embodiments, a provided method comprises administering a unit dosage form described herein to a subject with estrogen receptor positive (ER+) and human epidermal growth factor receptor negative (HER-) disease. In some embodiments, a provided method comprises

administering a unit dosage form described herein to a subject with estrogen receptor positive (ER+) and human epidermal growth factor receptor positive (HER+) disease.

[0092] In some embodiments, a unit dosage form described herein is administered to the subject such that the subject is administered Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is from about 15 mg to about 360 mg, calculated as a free base. In some embodiments, Compound 1 is administered to the subject in an amount that is from about 30 mg to about 360 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is from about 30 mg to about 300 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is from about 60 mg to about 120 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is from about 15 mg to about 100 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is about 120 mg, about 150 mg, about 210 mg, or about 300 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is about 20 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is about 30 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is about 60 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is about 90 mg. In some embodiments, Compound 1 is administered to the subject in an amount that is about 120 mg.

[0093] In some embodiments, a unit dosage form described herein is administered such that Compound 1, or a pharmaceutically acceptable salt thereof, is administered to the subject in an amount that is about 15 mg to about 360 mg per day (QD), calculated as a free base. In some embodiments, Compound 1 is administered to the subject in an amount that is about 20 mg to about 360 mg per day (QD). In some embodiments, Compound 1 is administered to the subject in an amount that is about 30 mg to about 300 mg per day (QD). In some embodiments, Compound 1 is administered to the subject in an amount that is about 60 mg to about 120 mg per day (QD). In some embodiments, Compound 1 is administered to the subject in an amount that is from about 15 mg to about 100 mg QD. In some embodiments, Compound 1 is administered to the subject in an amount that is about 15 mg, about 20 mg, about 30 mg, about 40 mg, about 50 mg, about 60 mg, about 70 mg, about 80 mg, about 90 mg, or about 100 mg QD. In some embodiments,

Compound 1 is administered to the subject in an amount that is about 120 mg, about 150 mg, about 210 mg, or about 300 mg QD. In some embodiments, Compound 1 is administered to the subject in an amount that is about 30 mg QD. In some embodiments, Compound 1 is administered to the subject in an amount that is about 60 mg QD. In some embodiments, Compound 1 is administered to the subject in an amount that is about 90 mg QD. In some embodiments, Compound 1 is administered to the subject in an amount that is about 120 mg QD.

Combination Therapy

[0094] In some embodiments, a unit dosage form described herein is administered to a subject suffering from a disease, disorder, or condition described herein, in combination with a secondary anti-cancer agent. In some embodiments, a secondary anti-cancer agent is a CDK 4/6 inhibitor, a PI3KCA inhibitor, or an mTOR inhibitor.

[0095] In some embodiments, a secondary anti-cancer agent is a CDK4/6 inhibitor (i.e., an agent that inhibits one or both of CDK4 and CDK6). In some embodiments, a secondary anti-cancer agent is a CDK4/6 inhibitor selected from palbociclib, ribociclib, abemaciclib, lerociclib, trilaciclib, and SHR6390. In some embodiments, a CDK4/6 inhibitor is palbociclib. In some embodiments, a CDK4/6 inhibitor is ribociclib. In some embodiments, a CDK4/6 inhibitor is abemaciclib. In some embodiments, a CDK4/6 inhibitor is lerociclib. In some embodiments, a CDK4/6 inhibitor is trilaciclib. In some embodiments, a CDK 4/6 inhibitor is SHR6390.

[0096] In some embodiments, a secondary anti-cancer agent is a PIK3CA inhibitor. In some embodiments, a PIK3CA inhibitor is selected from alpelisib, taselisib, and LY3023414. In some embodiments, a PIK3CA inhibitor is alpelisib. In some embodiments, a PIK3CA inhibitor is taselisib. In some embodiments, a PIK3CA inhibitor is LY3023414.

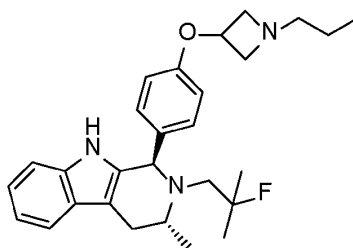
[0097] In some embodiments, a secondary anti-cancer agent is an mTOR inhibitor. In some embodiments, an mTOR inhibitor is selected from sirolimus, temsirolimus, everolimus, and LY3023414. In some embodiments, an mTOR inhibitor is sirolimus. In some embodiments, an mTOR inhibitor is temsirolimus. In some embodiments, an mTOR inhibitor is everolimus. In some embodiments, an mTOR inhibitor is LY3023414.

[0098] In some embodiments, a secondary anti-cancer agent is a HER2 inhibitor. In some embodiments, a HER2 inhibitor is selected from tucatinib, pertuzumab, lapatinib, trastuzumab, ado-trastuzumab emtansine, trastuzumab deruxtecan, and neratinib.

[0099] It is understood that combination therapy comprising a complete estrogen receptor antagonist and an anti-cancer agent described herein can comprise administration of the agents simultaneously or separately. For example, in some embodiments, a complete estrogen receptor antagonist and an anti-cancer agent are administered simultaneously. In some embodiments, an anti-cancer agent is administered prior to administration of a complete estrogen receptor antagonist. In some embodiments, an anti-cancer agent is administered after administration of a complete estrogen receptor antagonist.

Exemplary Embodiments

1. A unit dosage form comprising Compound 1:



Compound 1

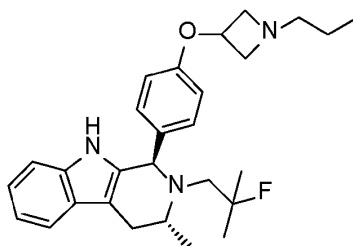
- or a pharmaceutically acceptable salt thereof;
a first diluent;
a second diluent; and
a disintegrant.
2. The unit dosage form of Embodiment 1, wherein the unit dosage form comprises about 10% to about 20% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base.
 3. The unit dosage form of Embodiments 1 or 2, wherein the unit dosage form comprises about 10% to about 15% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base.

4. The unit dosage form of any one of Embodiments 1-3, wherein the unit dosage form comprises about 10% to about 80% by weight of the first diluent.
5. The unit dosage form of any one of Embodiments 1-4, wherein the unit dosage form comprises about 10% to about 20% by weight of the second diluent.
6. The unit dosage form any one of Embodiments 1-5, wherein a weight ratio of the first diluent to the second diluent is from about 3:1 to about 4:1.
7. The unit dosage form of any one of Embodiments 1-6, wherein the first diluent and the second diluent are different.
8. The unit dosage form of any one of Embodiments 1-7, wherein the unit dosage form comprises about 5 to about 10% by weight of the disintegrant.
9. The unit dosage form of any one of Embodiments 1-8, wherein the first diluent is selected from the group consisting of lactose monohydrate, microcrystalline cellulose, mannitol, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch.
10. The unit dosage form of any one of Embodiments 1-9, wherein the first diluent is selected from the group consisting of lactose monohydrate and mannitol.
11. The unit dosage form of any one of Embodiments 1-10, wherein the first diluent is lactose monohydrate.
12. The unit dosage form of any one of Embodiments 1-11, wherein the second diluent is selected from the group consisting of microcrystalline cellulose, lactose monohydrate, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch.
13. The unit dosage form of any one of Embodiments 1-12, wherein the second diluent is microcrystalline cellulose.

14. The unit dosage form of any one of Embodiments 1-13, wherein the disintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate, crospovidone, and hydroxypropyl cellulose.
15. The unit dosage form of any one of Embodiments 1-14, wherein the disintegrant is croscarmellose sodium.
16. The unit dosage form of any one of Embodiments 1-15, wherein the unit dosage form comprises:
- about 12% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base;
 - about 60% by weight of the first diluent;
 - about 19% by weight of the second diluent; and
 - about 8% by weight of the disintegrant.
17. The unit dosage form of any one of Embodiments 1-16, further comprising a lubricant.
18. The unit dosage form of Embodiment 17, wherein the unit dosage form comprises about 0.1 to about 1.5% by weight of the lubricant.
19. The unit dosage form of Embodiments 17 or 18, wherein the lubricant is magnesium stearate.
20. The unit dosage form of any one of Embodiments 1-19, wherein the unit dosage form comprises about 20 mg to about 120 mg of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base.
21. The unit dosage form of any one of Embodiments 1-20, wherein the unit dosage form is in the form of a tablet.

22. The unit dosage form of any one of Embodiments 1-21, characterized in that the unit dosage form, when stored at 40 °C/75% RH for 1 month or more, exhibits greater than 80% dissolution in about 30 minutes or less using suitable dissolution conditions.

23. A unit dosage form comprising granules, wherein the granules comprise Compound 1:



Compound 1

or a pharmaceutically acceptable salt thereof;

a first diluent;

a second diluent; and

a disintegrant.

24. The unit dosage form of Embodiment 23, wherein the granules comprise Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 15% to about 20% of the total weight of the unit dosage form, calculated as a free base of Compound 1.

25. The unit dosage form of Embodiments 23 or 24, wherein the granules comprise the first diluent in an amount that is about 5% to about 20% of the total weight of the unit dosage form.

26. The unit dosage form of any one of Embodiments 23-25, wherein the granules comprise the second diluent in an amount that is about 50% to about 60% of the total weight of the unit dosage form.

27. The unit dosage form of any one of Embodiments 23-26, wherein the granules comprise the disintegrant in an amount that is about 1% to about 5% of the total weight of the unit dosage form.

28. The unit dosage form of any one of Embodiments 23-27, wherein the first diluent is selected from lactose monohydrate, microcrystalline cellulose, mannitol, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch.
29. The unit dosage form of any one of Embodiments 23-28, wherein the second diluent is selected from microcrystalline cellulose, lactose monohydrate, mannitol, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch.
30. The unit dosage form of any one of Embodiments 23-29, wherein the disintegrant selected from the group consisting of is croscarmellose sodium, sodium starch glycolate, crospovidone, and hydroxypropyl cellulose.
31. The unit dosage form of any one of Embodiments 23-30, further comprising one or more extra-granular excipients.
32. The unit dosage form of any one of Embodiments 23-31, wherein the unit dosage form is in the form of a tablet.
33. A method of treating an estrogen-receptor mediated disease, disorder, or condition, comprising administering to a subject in need thereof, the unit dosage form of any one of Embodiments 1-32.
34. The method of Embodiment 33, wherein the estrogen-receptor mediated disease, disorder, or condition is a cancer.
35. The method of Embodiment 34, wherein the cancer is a breast cancer.
36. The method of Embodiment 34, wherein the cancer is a breast cancer that has metastasized to the lungs, liver, bones, or brain.

37. The method of any one of Embodiments 33-36, further comprising administering a secondary anti-cancer agent.
38. The method of Embodiment 37, wherein the secondary anti-cancer agent is a CDK 4/6 inhibitor, a PI3KCA inhibitor, or an mTOR inhibitor.
39. The method of Embodiment 38, wherein the secondary anti-cancer agent is a CDK 4/6 inhibitor.
40. The method of Embodiment 39, wherein the CDK 4/6 inhibitor is selected from the group consisting of palbociclib, ribociclib, abemaciclib, lerociclib, trilaciclib, and SHR6390.
41. The method of Embodiment 38, wherein the secondary anti-cancer agent is a PIK3CA inhibitor.
42. The method of Embodiment 41, wherein the PIK3CA inhibitor is selected from the group consisting of alpelisib, taselisib, and LY3023414.
43. The method of Embodiment 38, wherein the secondary anti-cancer agent is an mTOR inhibitor.
44. The method of Embodiment 44, wherein the mTOR inhibitor is selected from the group consisting of sirolimus, temsirolimus, everolimus, and LY3023414.
45. The method of Embodiment 38, wherein the secondary anti-cancer agent is a HER2 inhibitor.
46. The method of Embodiment 45, wherein the HER2 inhibitor is selected from the group consisting of tucatinib, pertuzumab, lapatinib, trastuzumab, ado-trastuzumab emtansine, trastuzumab deruxtecan, and neratinib.

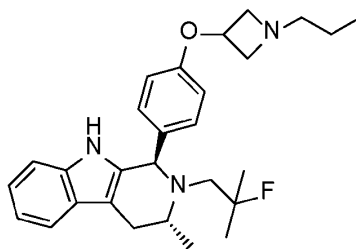
EXAMPLES

[0100] Certain abbreviations are used in this example section, as indicated by the table below:

Abbreviation	Meaning
°C	degrees Celsius
RH	relative humidity
mm	millimeter
nm	nanometer
mL	milliliter
μL	microliter
nL	nanoliter
g	gram
mg	milligram
M	molar
mM	millimolar
N	normal
min	minute
rpm or RPM	revolutions per minute
w/w	by weight
ND	no data
avg	average
RRT	Relative retention time
%RSD	percent relative standard deviation
HDPE	high density polyethylene
ACN	acetonitrile
TFA	trifluoroacetic acid
HPLC	high-pressure liquid chromatography
UV-VIS	Ultraviolet-Visible spectrometry

Example 1 – Development of a Unit Dosage Form of Compound 1

[0101] The present example describes unit dosage forms of (1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole (“Compound 1”):

**Compound 1****Example 1a – Granular Formulations of Compound 1**

[0102] Initial formulations (Formulation 1) were prepared by a granulation process.

Ingredient	Function	%, w/w	mg/Tablet	
			20 mg	60 mg
Tablet Core				
Intra-Granular				
Compound 1	Active Ingredient	18.00	20.00	60.00
Lactose Monohydrate	Diluent	10.00	11.11	33.33
Microcrystalline Cellulose PH 102	Diluent	56.50	62.78	188.34
Sodium Starch Glycolate	Disintegrant	3.00	3.33	9.99
Colloidal Silicon Dioxide	Glidant	3.00	3.33	9.99
Magnesium Stearate (Vegetable Grade-Non Bovine)	Lubricant	1.00	1.11	3.33
Extra-Granular				
Microcrystalline Cellulose PH 102	Diluent	5.00	5.56	16.68
Sodium Starch Glycolate	Disintegrant	3.00	3.33	9.99
Magnesium Stearate Vegetable Grade-Non Bovine	Lubricant	0.50	0.56	1.68
Tablet Core Total		100.00	111.00	333.33

Ingredient	Function	%, w/w	mg/Tablet	
			20 mg	60 mg
Film Coating				
Opadry AMB II White	Coating	5.00 ^a	5.55	16.65
Purified Water ^b	Dispersing Vehicle	n/a	n/a	n/a
Film Coated Tablet Total		n/a	117.00	350.00

a Percent approximate weight gain

b Does not appear in the finished drug product

[0103] Tablets of Formulation 1 were prepared by the following process. Compound 1 and microcrystalline cellulose were blended and screened through a 20 mesh. The screened material was blended with lactose, colloidal silicon dioxide and sodium starch glycolate pre-screened individually through a 20 mesh. The blend was then blended with magnesium stearate pre-screened through a 30 mesh. In-process blend uniformity samples were collected from three (3) pre-determined locations in the Blender. Once the blend uniformity was confirmed, this intra-granular blend was roller compacted to produce ribbons, which were milled through a Comil mill to produce the granules. Extra-granular microcrystalline cellulose and sodium starch glycolate were then screened through a 20 mesh and blended with the intra-granules. The blend was then blended with magnesium stearate pre-screened through a 30 mesh. In-process control blend uniformity samples are collected from three (3) pre-determined locations in the Blender. Once the blend uniformity was confirmed, the blend is compressed into tablets using round tooling for 20 mg strength tablets or oval tooling for 60 mg strength tablets. Tablets were passed through a deduster and a metal checker after compression.

[0104] Tablets are film coated in a Coating Pan with Opadry AMB II White dispersion to a target weight gain of 5% w/w of core tablets

Example 1b – Direct Compression Formulation of Compound 1

[0105] Formulation 2 is prepared by a direct compression process, which is a unit dosage form having the following components:

Ingredient	Function	%, w/w
Tablet Core		
Compound 1	Drug Substance	12.0
Lactose Monohydrate (Fast Flo 316)	Diluent	60.0
Microcrystalline Cellulose (Avicel PH 200)	Diluent	19
Croscarmellose Sodium (Ac-Di-Sol SD-711)	Disintegrant	8.0
Colloidal Silicon Dioxide (Aerosil 200)	Glidant	0.5
Magnesium Stearate (HyQual 2257)	Lubricant	0.5
Tablet Core Total		100
Film Coating		
Opadry AMB II White	Film Coat	5

[0106] Tablets of Formulation 2 were made using a dry blend/direct compression process. A stepwise description of the manufacturing process is provided below.

[0107] Lactose monohydrate, microcrystalline cellulose/colloidal silicon dioxide, croscarmellose sodium and magnesium stearate were screened individually through a suitable mesh (e.g., 30 mesh screen).

[0108] Compound 1 was added to a blender (e.g., tote blender) between approximately equal portions of pre-screened lactose monohydrate and mixed. The Compound 1/lactose monohydrate mixture was then passed through a suitable mill (e.g., Comil mill fitted with a 30 mesh).

[0109] The pre-screened microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium and lactose monohydrate/Compound 1 mixture were transferred into a blender (e.g., tote blender) and mixed. This combined mixture was passed through a suitable mill (e.g., Comil fitted with a 30 mesh).

[0110] The above combined mixture and pre-screened magnesium stearate were transferred into a blender (e.g., tote blender) and mixed. In-process blend uniformity samples were collected from five (5) pre-determined locations in the blender and analyzed. The blend was compressed

into core tablets using oval tooling. Tablets were passed through a deduster and a metal checker after compression.

[0111] Tablets were film coated in a Coating Pan with Opadry AMB II White dispersion to a target weight gain of 5% w/w of core tablets.

Example 2 – Stability and Dissolution Studies of Unit Dosage Forms Comprising Compound 1

[0112] Tablets of Formulation 1 and Formulation 2 were subjected to stability tests and the dissolution properties of tablets were tested after various testing conditions. Tablets were analyzed by methods provided herein.

HPLC Retention Time, Assay, and Organic Impurities

[0113] Tablets were assessed by high-pressure liquid chromatography (HPLC) using an HPLC instrument equipped with a UV-VIS detector under the conditions provided in the table below. Compound 1 elutes at about 23-25 minutes. Impurities $\geq 0.05\%$ are reported.

Parameter	Condition / Set Point		
Column	Waters XSelect CSH C18, 3.5 μm , 4.6 x 150 mm		
Wavelength	225 nm		
Column Oven Temperature	40°C		
Flow Rate	1.0 mL/min		
Injection Volume	10 μL		
Mobile Phase A	10 mM KH_2PO_4 (aq) pH 7.0		
Mobile Phase B	ACN		
Gradient Program	Time (min)	A%	B%
	0.0	50	50
	10.0	35	65
	25.0	35	65
	30.0	20	80
	40.0	20	80
	41.0	50	50
	50.0	50	50
Data Acquisition Time	50 min		
Run Time	50 min		
Diluent	90:10 acetonitrile:water		
Needle Wash	Diluent		

Content Uniformity

[0114] HPLC conditions for assessing content uniformity is provided in the table below. The analysis was performed using an HPLC instrument equipped with a UV-VIS detector. Compound 1 elutes at about 1.7 minutes.

Parameter	Condition / Set Point		
Column	Agilent Poroshell 120 EC-C18, 4.6 x 50 mm, 2.7 µm		
Wavelength	Formulation 1: 225 nm Formulation 2: 280 nm		
Column Oven Temperature	35°C		
Flow Rate	1.0 mL/min		
Injection Volume	5 µL		
Mobile Phase A	0.1% TFA in Water		
Mobile Phase B	0.1% TFA in ACN		
Gradient Program	Time (min)	A%	B%
	0.0	70	30
	2.0	50	50
	2.1	70	30
	6.0	70	30
Data Acquisition Time	6 min		
Run Time	6 min		
Diluent	Formulation 1: 75:25 acetonitrile:water Formulation 2: 70:30 acetonitrile:water		
Needle Wash	90:10 acetonitrile:water		

Dissolution

[0115] The conditions for assessing dissolution of example tablets are provided in the tables below for Formulation 1 and Formulation 2. The analysis of the dissolution study was analyzed the HPLC methods provided below.

Formulation 1 Dissolution Parameters

Parameter	Condition / Set Point
Apparatus	USP Rotating Baskets (Apparatus 1)
Temperature	37°C ± 0.5°C
Stirring Speed	50 rpm
Media	0.01N HCl
Media Volume	500 mL
Pull Volume	10 mL

Syringe filter	10 µm PE cannula filter
Media Sampling	5, 10, 15, 20, 30, and 45 min

Formulation 2 Dissolution Parameters

Parameter	Condition / Set Point
Apparatus	USP Rotating Paddle (Apparatus 2)
Temperature	37°C ± 0.5°C
Stirring Speed	75 rpm
Media	50 mM Citrate Buffer pH 3.5 with 0.1% SLS
Media Volume	900 mL
Pull Volume	3 mL
Syringe filter	10 µm PE cannula filter
Media Sampling	5, 10, 15, 20, 30, 45, and 60 min

HPLC Method Parameters for Dissolution

Parameter	Condition / Set Point		
Column	Agilent Poroshell 120 EC-C18, 4.6 x 50 mm, 2.7 µm		
Wavelength	280 nm		
Column Oven Temperature	35°C		
Flow Rate	1.0 mL/min		
Injection Volume	5 µL		
Mobile Phase A	0.1% TFA in Water		
Mobile Phase B	0.1% TFA in ACN		
Gradient Program	Time (min)	A%	B%
	0.0	70	30
	2.0	50	50
	2.1	70	30
	6.0	70	30
Data Acquisition Time	6 min		
Run Time	6 min		
Needle Wash	50:50 acetonitrile:water		

Example 2a – Stability and Dissolution Data Formulation 1

[0116] In the following example, 20 and 60 mg tablets were examined in HDPE bottles with heat-sealed, child-resistant caps containing a 2 g desiccant canister and subjected to the conditions indicated in the tables below

5 °C (20 mg Tablets)						
Attribute		Initial		1 month		
Appearance		White round biconvex tablets		White round biconvex tablets		
Assay		98.7%		98.0%		
Organic Impurities		Individual	RRT	% Area	RRT	% Area
			0.25	0.06%	0.25	0.06%
			0.93	0.12%	0.93	0.12%
			1.28	0.09%	1.28	0.09%
		Total	0.27%		0.27%	
Water Content		3.9%		4.2%		
Dissolution		Time (min)	Avg %	%RSD	Avg %	%RSD
		5	15	38	11	71
		10	68	20	67	27
		15	97	4	97	8
		20	103	2	104	3
		30	104	2	105	3
		45	104	2	106	3

25 °C/60%RH (20 mg Tablets)													
Attribute	Initial		1 month		3 month		6 month		9 month		12 month		
Appearance	White round biconvex tablets		White round biconvex tablets		White round biconvex tablets		White round biconvex tablets		White round biconvex tablets		White round biconvex tablets		
Assay	98.7%		100.8%		96.9%		97.3%		97.1%		94.1%		
	Individual	RRT	% Area	RRT	% Area	RRT	% Area	RRT	% Area	RRT	% Area	RRT	% Area
		0.25	0.06	0.25	0.07	0.25	0.06	0.25	0.07	0.25	0.07	0.25	0.08
				0.34	0.05	0.34	<0.05	0.34	0.06	0.34	0.06	0.34	0.08
										0.93	0.12	0.93	0.12
Organic Impurities	1.28	0.09	1.28	0.09	1.28	0.09	1.28	0.10	1.28	0.10	1.28	0.10	
	Total	0.27%	0.33%		0.27%		0.35%		0.41%		0.38%		
Water Content		3.9%		4.2%		4.2%		3.9%		4.4%		4.5%	
Dissolution	Time (min)	Avg %	%RSD	Avg %	%RSD	Avg %	%RSD	Avg %	%RSD	Avg %	%RSD	Avg %	%RSD
	5	15	38	10	53	10	30	5	15	5	44	5	23
	10	68	20	55	24	52	9	36	19	40	23	33	16
	15	97	4	96	10	91	4	77	14	81	15	68	12
	20	103	2	105	2	100	3	95	6	101	2	92	7
	30	104	2	107	2	102	3	100	3	104	2	100	3
45	104	2	106	2	102	3	101	3	105	3	100	3	

40°C/75%RH (20 mg Tablets)									
Attribute	Initial		1 month		3 month		6 month		
Appearance	White round biconvex tablets		White round biconvex tablets		White round biconvex tablets		White round biconvex tablets		
Assay	98.7%		98.5%		97.1%		96.7%		
Organic Impurities	Individual	RRT	% Area	RRT	% Area	RRT	% Area	RRT	% Area
		0.25	0.06	0.25	0.08	0.25	0.07	0.25	0.10
				0.34	0.05	0.34	0.06	0.34	0.09
				0.35	0.05	0.54	0.09		
	0.93	0.12	0.93	0.12	0.93	0.12	0.93	0.12	
Total	1.28	0.09	1.28	0.10	1.28	0.11	1.28	0.13	
	0.27%		0.35%		0.36%		0.58%		
Water Content	3.9%		4.4%		4.8%		4.9%		
Dissolution	Time (min)	Avg %	%RSD	Avg %	%RSD	Avg %	%RSD	Avg %	%RSD
	5	15	38	5	37	4	42	2	19
	10	68	20	30	23	15	24	9	14
	15	97	4	67	17	35	18	26	15
	20	103	2	93	6	55	14	48	11
	30	104	2	103	2	85	7	82	5
	45	104	2	104	3	100	3	100	2

5°C (60 mg Tablets)							
Attribute		Initial		IM			
Appearance		White oval biconvex tablets		White oval biconvex tablets			
Assay		98.2%		99.1%			
Organic Impurities	Individual	RRT	% Area		RRT	% Area	
		0.25	0.06%		0.25	0.06%	
		0.93	0.12%		0.93	0.12%	
		1.28	0.09%		1.28	0.10%	
	Total	0.27%		0.28%			
Water Content		3.8%		3.7%			
Dissolution	Time (min)	Avg %	%RSD	Avg %	%RSD		
	5	4	45	4	45		
	10	32	18	31	20		
	15	65	13	64	14		
	20	92	6	91	8		
	30	101	2	103	2		
	45	102	2	104	2		

25°C/60%RH (60 mg Tablets)													
Attribute	Initial		1 month		3 month		6 month		9 month		12 month		
Appearance	White oval biconvex tablets		White oval biconvex tablets		White oval biconvex tablets		White oval biconvex tablets		White oval biconvex tablets		White oval biconvex tablets		
Assay	98.2%		99.1%		96.2%		97.4%		96.7%		96.1%		
Organic Impurities	Individual	RRT	% Area	RRT	% Area	RRT	% Area	RRT	% Area	RRT	% Area	RRT	% Area
		0.25	0.06	0.25	0.07	0.25	0.05	0.25	0.07	0.25	0.07	0.25	0.08
	0.93	0.12	0.93	0.13	0.93	0.12	0.93	0.12	0.93	0.12	0.93	0.12	
Total	1.28		1.28		1.28		1.28		1.28		1.28		
	0.27%		0.35%		0.26%		0.34%		0.41%		0.44%		
Water Content	3.8%		4.1%		3.7%		4.1%		4.2%		4.0%		
Dissolution	Time (min)	Avg %	%RSD	Avg %	%RSD	98	2	Avg %	%RSD	Avg %	%RSD	Avg %	%RSD
	5	4	45	3	13	3	42	2	45	3	14	2	35
	10	32	18	23	13	26	31	17	22	19	16	17	16
	15	65	13	56	15	55	22	44	18	45	13	38	13
	20	92	6	83	10	80	14	68	12	67	5	63	10
	30	101	2	101	2	98	2	97	2	98	2	96	4
	45	102	2	103	2	100	2	101	3	103	2	101	1

40°C/75%RH (60 mg Tablets)									
Attribute	Initial		1 month		3 month		6 month		
Appearance	White oval biconvex tablets		White oval biconvex tablets		White oval biconvex tablets		White oval biconvex tablets		
Assay	98.2%		99.2%		96.0%		94.6%		
Organic Impurities	Individual	RRT	% Area	RRT	% Area	RRT	% Area	RRT	% Area
		0.25	0.06	0.25	0.08	0.25	0.07	0.25	0.10
						0.34	0.06	0.34	0.11
						0.42	0.05	0.35	0.06
	0.93	0.12	0.93	0.13	0.54	0.05	0.42	0.05	
0.93					0.12	0.54	0.10		
	1.28	0.09	1.28	0.11	1.28	0.11	1.28	0.12	
	Total	0.27%		0.38%		0.52%		0.66%	
Water Content	3.8%		4.1%		4.2%		4.3%		
Dissolution	Time (min)	Avg %	%RSD	Avg %	%RSD	Avg %	%RSD	Avg %	%RSD
	5	4	45	2	32	3	22	2	32
	10	32	18	15	29	12	12	6	12
	15	65	13	36	13	28	13	16	14
	20	92	6	55	19	44	10	29	12
	30	101	2	91	11	79	8	61	7
	45	102	2	102	2	98	3	97	2

[0117] FIG. 1 is a plot illustrating dissolution of tablets of Formulation 1 after being subjected to certain conditions for an indicated period of time. As can be seen, about 80% of Compound 1 was dissolved after about 45 minutes at conditions provided above, e.g., dissolving using USP Apparatus 1 (baskets) at 50 RPM in 500mL of 0.01N HCl, and maintained at $37 \pm 0.5^\circ \text{C}$.

Example 2b – Stability and Dissolution Data Formulation 2

[0118] In the following example, the tablets were examined in HDPE bottles with heat-sealed, child-resistant cap containing a 2 g desiccant canister and subjected to the conditions indicated in the tables below.

25 °C/60% RH (60 mg Tablet)							
Attribute		Initial		1 month		3 month	
Appearance		white oval biconvex tablets		white oval biconvex tablets		white oval biconvex tablets	
Assay		97.7%		97.8%		97.6%	
Organic Impurities	Individual	RRT	% Area	RRT	% Area	RRT	% Area
		0.23	0.18	0.23	ND	0.23	ND
		0.54	0.05	0.54	0.05	0.54	0.05
		0.93	0.10	0.93	0.10	0.93	0.11
		1.28	0.08	1.28	0.09	1.28	0.09
	Total	0.41%		0.24%		0.25%	
Water Content		3.6%		3.3%		3.4%	
Dissolution	Time (min)	Avg %	%RSD	Avg %	%RSD	Avg %	%RSD
	5	79	3	88	2	83	2
	10	92	2	96	1	91	1
	15	95	1	98	1	94	1
	20	96	1	99	1	95	1
	30	97	1	100	1	96	2
	45	98	1	101	1	96	3
	60	99	1	101	1	97	2

30 °C/65% RH (60 mg Tablet)							
Attribute		Initial		1 month		3 month	
Appearance		white oval biconvex tablets		white oval biconvex tablets		white oval biconvex tablets	
Assay		97.7%		97.4%		99.7%	
Organic Impurities	Individual	RRT	% Area	RRT	% Area	RRT	% Area
		0.23	0.18	0.23	ND	0.23	ND
		0.54	0.05	0.54	0.05	0.49	0.05
						0.54	<0.05
		0.93	0.10	0.93	0.10	0.93	0.11
		1.28	0.08	1.28	0.09	1.28	0.09
	Total	0.41%		0.24%		0.25%	
Water Content		3.6%		3.4%		3.4%	
Dissolution	Time (min)	Avg %	%RSD	Avg %	%RSD	Avg %	%RSD
	5	79	3	78	4	83	3
	10	92	2	93	3	90	4
	15	95	1	96	2	93	3
	20	96	1	98	2	94	2
	30	97	1	99	2	96	2
	45	98	1	99	2	96	1
	60	99	1	100	3	97	2

40 °C/75% RH (60 mg Tablet)							
Attribute		Initial		1 month		3 month	
Appearance		white oval biconvex tablets		white oval biconvex tablets		white oval biconvex tablets	
Assay		97.7%		98.1%		97.7%	
Organic Impurities	Individual	RRT	% Area	RRT	% Area	RRT	% Area
		0.23	0.18	0.23	ND	0.23	ND
		0.54	0.05	0.54	0.05	0.54	0.05
		0.93	0.10	0.93	0.10	0.93	0.11
		1.28	0.08	1.28	0.09	1.28	0.10
	Total	0.41%		0.24%		0.26%	
Water Content		3.6%		3.3%		3.5%	
Dissolution	Time (min)	Avg %	%RSD	Avg %	%RSD	Avg %	%RSD
	5	79	3	80	2	84	2
	10	92	2	93	2	92	3

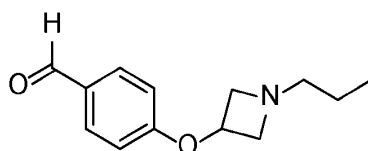
40 °C/75% RH (60 mg Tablet)							
Attribute		Initial		1 month		3 month	
	15	95	1	96	2	95	4
	20	96	1	96	2	96	3
	30	97	1	97	3	97	3
	45	98	1	97	3	97	2
	60	99	1	98	2	98	2

[0119] FIG. 2A is a plot illustrating dissolution of tablets of Formulation 2 after being subjected to certain conditions after 1 month. As can be seen, about 80% or more of Compound 1 was dissolved after about 10 minutes at conditions provided above, e.g., dissolved using USP Apparatus 2 (paddles) at 75 RPM in 900mL of 50mM Citrate buffer, pH 3.5 with 0.1% Sodium Lauryl Sulfate, and maintained at 37 ± 0.5 °C. FIG. 2B is a plot illustrating dissolution of tablets of Formulation 2 after being subjected to certain conditions after 3 months. As can be seen, about 80% or more of Compound 1 was dissolved after about 10 minutes at conditions provided above, e.g., dissolved using USP Apparatus 2 (paddles) at 75 RPM in 900mL of 50mM Citrate buffer, pH 3.5 with 0.1% Sodium Lauryl Sulfate, and maintained at 37 ± 0.5 °C.

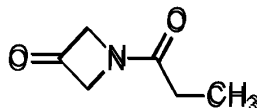
Example 3 – Synthesis of Compound 1

[0120] A complete synthesis of Compound 1 is provided in PCT Pub. No. WO 2017/059139, which is incorporated herein by reference and repeated below.

Preparation of 4-((1-propylazetidin-3-yl)oxy)benzaldehyde:



Step 1: Preparation of 1-propionylazetidin-3-one

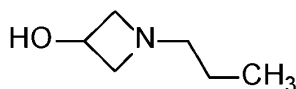


[0121] The compound 3-azetidinone hydrochloride (10.000 g, 93.0 mmol, 1.0 equiv.), anhydrous 1,2-dichloroethane (200 mL) and diisopropylethylamine (38.9 mL, 223 mmol, 2.4 equiv.) were added to a round bottom flask (500 mL) to provide a light yellow suspension. The

suspension was sonicated for 1 h and then cooled to -10 °C (dry-ice/MeOH) for 10 min. Propionyl chloride (9.8 mL, 112 mmol, 1.2 equiv.) was added dropwise to the cooled suspension to provide an orange solution. The reaction was removed from the bath and stirred at room temperature for 16 h. The solvent was removed to provide a semi-solid. The semi-solid was suspended into EA (300 mL) and the suspension was filtered. The solid was rinsed with EA (2 x 100 mL). TLC analysis (10% MeOH/DCM, KMnO₇ stain/Heat) indicated there were three spots: R_f: 0.2, 0.5, 0.7. TLC (50% EA/Hex, KMnO₇ stain/Heat) indicated there were two spots: R_f: 1, 0.3. The filtrate was concentrated, adsorbed onto silica gel (25 g) and chromatographed through silica gel (100 g cartridge) with DCM (5 min) then 0-10 % MeOH over 15 min. The product came off early from the column in DCM and continued to elute from the column with up to 10 % MeOH. TLC in both solvent systems was carried out to determine if any propionyl chloride was present in early fractions. Fractions containing product were pooled and concentrated to afford the title compound as a yellow liquid (11.610 g, 98.2%).

[0122] ¹H NMR (300 MHz, CDCl₃) δ: 4.80 (d, *J* = 5.6 Hz, 4H), 2.29 (q, *J* = 7.5 Hz, 2H), 2.01 (s, 3H), 1.18 (t, *J* = 7.5 Hz, 3H).

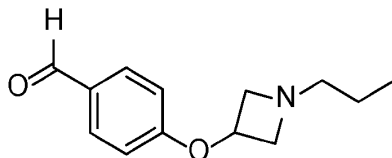
Step 2. Preparation of 1-propylazetidin-3-ol



[0123] Lithium aluminum hydride (10.397 g, 273.9 mmol, 3.0 equiv.) was suspended into THF (200 mL) and cooled in an ice bath. A solution of 1-propionylazetidin-3-one (11.610 g, 91.3 mmol, 1.0 equiv.) in THF (100 mL) was added dropwise to the reaction mixture via a pressure equalizing addition funnel over 30 min. The addition funnel was removed. The flask was then fitted with a condenser and the reaction was heated at reflux in an oil bath at 75 °C for 16 h. The reaction was cooled in an ice bath for 20 min and sodium sulfate decahydrate (Glauber's salt, 25 g) was added in small portions over 20 min. After complete addition, the mixture was stirred at room temperature for 2 h. The mixture was filtered through a bed of Celite® (2 cm) and the solids rinsed with EA (2 x 250 mL). The clear solution was concentrated to a pale yellow liquid (9.580 g, 91.1%). NMR indicated the presence of THF and EA. This material was used without further purification in the preparation of the compounds of the examples below.

[0124] ¹H NMR (300 MHz, CDCl₃) δ: 4.39 (pent, *J* = 6 Hz, 1H), 3.62 – 3.56 (m, 2H), 2.90 – 2.85 (m, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 1.34 (hextet, *J* = 7.2 Hz, 2H), 0.87 (t, *J* = 7.8 Hz, 3H).

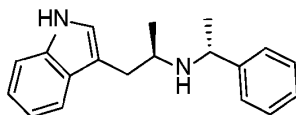
Step 3. Preparation of 4-((1-propylazetidin-3-yl)oxy)benzaldehyde



[0125] 4-Fluorobenzaldehyde (15.00 g, 120.9 mmol, 0.9 equiv.), 1-propylazetidin-3-ol (15.00g, 130.2 mmol, 1.0 equiv.), cesium carbonate (88.40 g, 271.3 mmol, 2.1 equiv.) and *N,N*-dimethylformamide (284 mL) were mixed together with a Teflon™ stir bar in a 500 mL round bottomed flask. The flask was sealed and heated in a heat block at 95 °C for 6 h. The reaction was analyzed by LCMS to indicate the aldehyde was consumed. The suspension was filtered through a sintered glass funnel and the solid was washed with ethyl acetate (100 mL). The filtrate was concentrated to an orange suspension. The suspension was mixed with water (200 mL) and ethyl acetate (200 mL) and the organic layer was washed with water (3 x 200 mL), brine, dried over anhydrous magnesium sulfate, filtered and concentrated to an orange liquid (21.74 g, 76.1 %). The material was used without further purification.

[0126] ¹HNMR (300 MHz, CDCl₃), δ 9.87 (s, 1H), 7.82 (d, *J* = 9.0 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.86 (quintet, *J* = 5.7 Hz, 1H), 3.85 - 3.80 (m, 2H), 3.13 - 3.08 (m, 2H), 2.48 (t, *J* = 7.2 Hz, 2H), 1.46 - 1.34 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H).

Preparation of (*R*)-1-(1*H*-indol-3-yl)-*N*-((*R*)-1-phenylethyl)propan-2-amine:



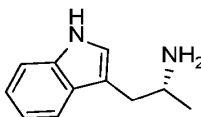
[0127] Indole-3-acetone (25.0 g, 144 mmol, 1.0 equiv.) was added to a solution of (*R*)-(+)-1-phenylethylamine (23.0 mL, 181 mmol, 1.3 equiv.) in dichloromethane (600 mL) under N₂ at 25 °C and the mixture was allowed to stir for 1 hr. The reaction was cooled to 0-5 °C and sodium triacetoxyborohydride (100 g, 472 mmol, 3.3 equiv.) was added over 30 minutes via powder addition funnel to the ice cooled solution. The orange solution was stirred for 1 h at 0 °C and then was allowed to warm to RT. The reaction was stirred at RT for 19 h. At this time, ESI+ indicated that no indole starting material was present. Saturated NaHCO₃ solution (100mL) was added in 5 mL portions over 15 min at 10 °C with vigorous stirring. The solution was stirred for 15 min and sat. Na₂CO₃ solution (200 mL) was added over 15 minutes. Solid K₂CO₃ (9 g) was added in 3 g

portions at which point the aqueous layer was pH 12 and bubbles had stopped forming. The layers were filtered and separated. The red organic layer was washed with sat. aq. NaHCO_3 (2 x 100 mL). The aqueous layers were combined and extracted with DCM (2 x 100 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated to give the crude product (49 g). TLC (90:10 DCM:MeOH) showed four spots (R_f = 0.63, 0.50, 0.16, 0.26), two of which were the separated diastereomeric major products (R_f = 0.16 and 0.26). The crude was adsorbed onto silica gel and purified via flash chromatography (330 g cartridge, 0-100% EA:Hex). Fractions containing the *R,R* diastereomer were pooled and purified a second time with the same flash chromatography conditions to afford 24 g of product (~82% ee). Previous successful separation was achieved by a silica gel:crude ratio of 40:1, so the mixture was divided into 3 portions and separated on 3 x 330 g silica gel cartridges (0-40% EA/Hex for 20 min, isocratic 40% EA/Hex 40 min). All fractions containing the desired product were > 99 % diastereomerically pure. Pure fractions were concentrated and pooled to yield (*R*)-1-(1H-indol-3-yl)-*N*-((*R*)-1-phenylethyl)propan-2-amine as an orange semi-solid (11.91 g, 29.6 %).

[0128] ^1H NMR (CDCl_3 , 300 MHz) *R,R* diastereomer: δ 0.96 (d, J = 6.6 Hz, 3H), 1.30 (d, J = 6.6 Hz, 3H), 2.68 (q, J = 7.2 Hz, 1H), 2.97 (m, 2H) 4.00 (q, J = 6.3 Hz, 1H), 7.43-6.97 (m, 10H), 7.96 (br s, 1H). *R,S* diastereomer: δ 1.11 (d, J = 5.7 Hz, 3H), 1.30 (d, J = 5.4 Hz, 3H) 2.80 (m, 3H), 3.92 (q, J = 6.9 Hz, 1H), 6.93-7.40 (m, 10H), 8.13 (br s, 1H); the aromatic region was difficult to distinguish from the *R,R* diastereomer due to lack of purity.

[0129] LCMS: ES+ $[\text{M}+\text{H}]^+$ 279.0.

Preparation of (2R)-1-(1H-indol-3-yl)propan-2-amine:



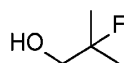
[0130] The compound (*R*)-1-(1H-indol-3-yl)-*N*-((*R*)-1-phenylethyl)propan-2-amine (11.91 g, 42.8 mmol, 1.0 equiv.) was dissolved in methanol (250 mL) and added to a 2 L Parr bottle and the solution was sparged with N_2 for 10 min. 20% $\text{Pd}(\text{OH})_2$ on carbon wet with water (10.71 g, 76.3 mmol, 1.8 equiv.) was added and the bottle was pressurized with 50 psi of hydrogen and shaken in a Parr apparatus for 22 h, LCMS analysis indicated that the reaction was completed. The suspension was filtered through Celite® and concentrated to remove MeOH. The crude was dissolved into DCM and washed with saturated Na_2CO_3 solution (50 mL) and the aqueous layer

was extracted with DCM (2 x 50 mL). The organic layers were combined, dried, and concentrated to yield (2*R*)-1-(1*H*-indol-3-yl)propan-2-amine as a light brown solid that did not require further purification (6.68 g, 89.6 %).

[0131] ^1H NMR (CDCl_3 , 300 MHz) δ 1.17 (d, J = 6.6 Hz, 3H), 2.66 (dd, J = 8.4, 14.7 Hz, 1H), 2.88 (dd, J = 5.4, 14.1 Hz, 1H), 3.27 (sextet, J = 1.5 Hz, 1H), 7.05-7.22 (m, 3H), 7.37 (d, J = 7.5 Hz, 1H), 7.62 (d, J = 8.7 Hz, 1H), 8.00 (br s, 1H).

[0132] LCMS: ES+ $[\text{M}+\text{H}]^+$ 174.9.

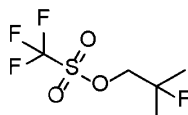
Preparation of 2-fluoro-2-methylpropanol:



[0133] Methyl 2-fluoro-2-methylpropionate (5.01 g, 40.5 mmol, 1.0 equiv.) was added dropwise over 15 min to a stirred suspension of lithium aluminum hydride (2.50 g, 65.9 mmol, 1.6 equiv.) in anhydrous diethyl ether (100 mL) cooled in an ice bath. After 2 hours, 2.0 mL water, 2.0 mL 15% w/v NaOH, and 5.0 mL water were added sequentially dropwise. After 15 min, the white suspension was diluted with DCM, gravity filtered through Celite®, and the solids were washed with DCM. The filtrate was concentrated (200 mbar, 25 °C) to afford 2-fluoro-2-methylpropanol as a colorless oil (2.09 g, 56.1 %).

[0134] ^1H NMR (300 MHz, CDCl_3) δ 1.34 (d, J = 21.3 Hz, 6H), 1.95 (br t, 1H), 3.56 (dd, J = 6.6, 20.7 Hz, 2H).

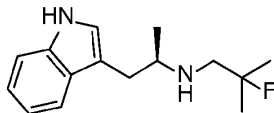
Preparation of 2-fluoro-2-methylpropyl trifluoromethanesulfonate:



[0135] Trifluoromethanesulfonic anhydride (5.0 mL, 29.7 mmol, 1.3 equiv.) was added dropwise to a 0 °C solution of 2-fluoro-2-methylpropanol (2.090 g, 22.7 mmol, 1.0 equiv.) and 2,6-lutidine (3.40 mL, 29.4 mmol, 1.3 equiv.) in DCM (25 mL) over 30 minutes. After 2 hours, the red solution had turned light brown. TLC (20:80 EA:Hex, KMnO_4 stain) indicated that the starting material was not present. The reaction mixture was washed with 1M HCl solution (2 x 20 mL) and sat. NaHCO_3 solution (2 x 20 mL). The aqueous layers were each back extracted with DCM (20 mL). The combined organic layers were dried with Na_2SO_4 , filtered and concentrated under reduced pressure (150 mbar, 25 °C) to afford 2-fluoro-2-methylpropyl trifluoromethanesulfonate as a red oil (4.39 g, 86.3%).

[0136] ^1H NMR (300 MHz, CDCl_3) δ 1.46 (d, J = 20.4 Hz, 6H), 4.41 (d, J = 18.6 Hz, 2H). ^{19}F NMR (282 MHz, CDCl_3) δ -147.1, -74.5.

Preparation of (R)-N-(1-(1H-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine:



[0137] The compound 2-fluoro-2-methylpropyl trifluoromethanesulfonate (9.587 g, 42.8 mmol, 1.1 equiv.) (solution in DCM, 16% DCM by wt%, 11.4384 g) was added to a solution of (2R)-1-(1H-indol-3-yl)propan-2-amine (6.680 g, 38.3 mmol, 1.0 equiv.), anhydrous 1,4-dioxanes (60.000 ml, 701.4 mmol, 18.3 equiv.), and freshly-distilled diisopropylethylamine (8.500 ml, 48.8 mmol, 1.3 equiv.). The dark brown solution was heated at 90 °C for 3 hours. After 3h, LCMS indicated that a small amount of indolamine starting material was still present. TLC (10% MeOH/DCM) indicated triflate (R_f = 0.54) had been used up. NMR of unused triflate SM (286-30) indicated the triflate had not decomposed overnight, so another 0.1 equiv (0.9883 g, 13% DCM wt%, 0.8563 g triflate SM) was added and the reaction was heated for 2 h at 90 °C. LCMS indicated the reaction had completed and TLC (10% MeOH/DCM) showed one spot (R_f = 0.24) (TLC with 50% EA/Hex, 1 streaked spot R_f <= 0.12, another spot at R_f = 0). EtOAc (50 mL) was added and the solution was washed with NaHCO_3 (2 x 50 mL) and the combined aqueous layer was washed with EtOAc (50 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The crude (brown oil, 14.8 g) was purified via flash silica chromatography (240 g cartridge, 0-100% EA/Hex). The desired product eluted as a long tailing peak. Pure fractions were concentrated to yield (R)-N-(1-(1H-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (4.211 g, 17.0 mmol) as a dark yellow oil.

[0138] ^1H NMR (300 MHz, CDCl_3) δ 1.10 (d, J = 6.3 Hz, 3H), 1.34 (dd, J = 3.0, 21.9 Hz, 6H), 2.68-2.95 (m, 4H), 3.02 (sextet, J = 6.6 Hz, 1H), 7.05 (d, J = 2.4 Hz, 1H), 7.26-7.11 (m, 2H), 7.36 (d, J = 6.9 Hz, 1H), 7.62 (d, J = 7.5 Hz, 1H), 8.18 (br s, 1H). ^{19}F NMR (282 MHz, CDCl_3) δ -144.2. m/z: ES+ $[M+H]^+$ 249.0.

Preparation of Compound 1

[0139] 4-((1-propylazetidin-3-yl)oxy)benzaldehyde (0.096 g, 0.4 mmol, 1.3 equiv.) was added to a solution of (R)-N-(1-(1H-indol-3-yl)propan-2-yl)-2-fluoro-2-methylpropan-1-amine (0.070 g, 0.3 mmol, 1.0 equiv.) in anhydrous toluene (1.50 mL) and glacial acetic acid (0.100 mL, 1.7 mmol,

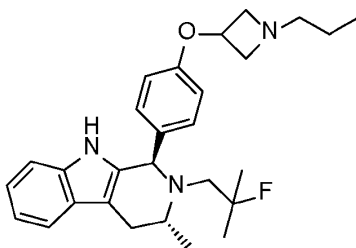
6.2 equiv.). Molecular sieves were added and the solution was stirred under N₂ in the dark at 80 °C for 8 hours. The reaction solution was diluted in DCM, filtered, and washed with saturated Na₂CO₃ solution. The aqueous layer was extracted with DCM and the combined organic layers were dried over Na₂SO₄. The solution was filtered and concentrated. The residue was dissolved into acetonitrile (2 mL) and filtered through a syringe filter before purification via prep LC (40 to 90% ACN:H₂O over 18 min, followed by isocratic 90% ACN for 7 min). Pure fractions were concentrated and dried to afford (1R,3R)-2-(2-fluoro-2-methylpropyl)-3-methyl-1-(4-((1-propylazetidin-3-yl)oxy)phenyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole as a white powder.

[0140] ¹H NMR (300 MHz, CDCl₃) δ 0.90 (t, *J* = 7.5 Hz, 3H), 1.09 (d, *J* = 7.2 Hz, 3H), 1.26-1.50 (m, 8H), 2.45-2.77 (m, 6H), 3.01 (t, *J* = 7.2 Hz, 2H), 3.34 (m, 1H), 3.77 (m, 2H), 4.60 (quin, *J* = 5.7 Hz, 1H), 5.03 (s, 1H), 6.64 (d, *J* = 8.1 Hz, 2H), 7.10-7.21 (m, 5H), 7.54 (d, *J* = 7.5 Hz, 1H), 8.19 (br s, 1H). m/z: ES+ [M+H]⁺ 450.2.

[0141] The embodiments of the disclosure described above are intended to be merely exemplary, numerous variations and modifications will be apparent to those skilled in the art. All such variations and modifications are intended to be within the scope of the present invention as defined in any appended claims.

CLAIMS

1. A unit dosage form comprising Compound 1:



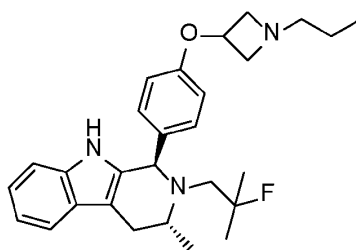
Compound 1

- or a pharmaceutically acceptable salt thereof;
a first diluent;
a second diluent; and
a disintegrant.
2. The unit dosage form of claim 1, wherein the unit dosage form comprises about 10% to about 20% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base.
3. The unit dosage form of claims 1 or 2, wherein the unit dosage form comprises about 10% to about 15% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base.
4. The unit dosage form of any one of claims 1-3, wherein the unit dosage form comprises about 10% to about 80% by weight of the first diluent.
5. The unit dosage form of any one of claims 1-4, wherein the unit dosage form comprises about 10% to about 20% by weight of the second diluent.
6. The unit dosage form any one of claims 1-5, wherein a weight ratio of the first diluent to the second diluent is from about 3:1 to about 4:1.

7. The unit dosage form of any one of claims 1-6, wherein the first diluent and the second diluent are different.
8. The unit dosage form of any one of claims 1-7, wherein the unit dosage form comprises about 5 to about 10% by weight of the disintegrant.
9. The unit dosage form of any one of claims 1-8, wherein the first diluent is selected from the group consisting of lactose monohydrate, microcrystalline cellulose, mannitol, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch.
10. The unit dosage form of any one of claims 1-9, wherein the first diluent is selected from the group consisting of lactose monohydrate and mannitol.
11. The unit dosage form of any one of claims 1-10, wherein the first diluent is lactose monohydrate.
12. The unit dosage form of any one of claims 1-11, wherein the second diluent is selected from the group consisting of microcrystalline cellulose, lactose monohydrate, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch.
13. The unit dosage form of any one of claims 1-12, wherein the second diluent is microcrystalline cellulose.
14. The unit dosage form of any one of claims 1-13, wherein the disintegrant is selected from the group consisting of croscarmellose sodium, sodium starch glycolate, crospovidone, and hydroxypropyl cellulose.
15. The unit dosage form of any one of claims 1-14, wherein the disintegrant is croscarmellose sodium.
16. The unit dosage form of any one of claims 1-15, wherein the unit dosage form comprises:

about 12% by weight of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base;
about 60% by weight of the first diluent;
about 19% by weight of the second diluent; and
about 8% by weight of the disintegrant.

17. The unit dosage form of any one of claims 1-16, further comprising a lubricant.
18. The unit dosage form of claim 17, wherein the unit dosage form comprises about 0.1 to about 1.5% by weight of the lubricant.
19. The unit dosage form of claims 17 or 18, wherein the lubricant is magnesium stearate.
20. The unit dosage form of any one of claims 1-19, wherein the unit dosage form comprises about 10 mg to about 120 mg of Compound 1, or a pharmaceutically acceptable salt thereof, calculated as a free base.
21. The unit dosage form of any one of claims 1-20, wherein the unit dosage form is in the form of a tablet.
22. The unit dosage form of any one of claims 1-21, characterized in that the unit dosage form, when stored at 40 °C/75% RH for 1 month or more, exhibits greater than 80% dissolution in about 30 minutes or less using suitable dissolution conditions.
23. A unit dosage form comprising granules, wherein the granules comprise Compound 1:

**Compound 1**

or a pharmaceutically acceptable salt thereof;

a first diluent;

a second diluent; and

a disintegrant.

24. The unit dosage form of claim 23, wherein the granules comprise Compound 1, or a pharmaceutically acceptable salt thereof, in an amount that is about 15% to about 20% of the total weight of the unit dosage form, calculated as a free base of Compound 1.

25. The unit dosage form of claims 23 or 24, wherein the granules comprise the first diluent in an amount that is about 5% to about 20% of the total weight of the unit dosage form.

26. The unit dosage form of any one of claims 23-25, wherein the granules comprise the second diluent in an amount that is about 50% to about 60% of the total weight of the unit dosage form.

27. The unit dosage form of any one of claims 23-26, wherein the granules comprise the disintegrant in an amount that is about 1% to about 5% of the total weight of the unit dosage form.

28. The unit dosage form of any one of claims 23-27, wherein the first diluent is selected from lactose monohydrate, microcrystalline cellulose, mannitol, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch.

29. The unit dosage form of any one of claims 23-28, wherein the second diluent is selected from microcrystalline cellulose, lactose monohydrate, mannitol, calcium phosphate, lactose anhydrate, calcium silicate, and pregelatinized starch.
30. The unit dosage form of any one of claims 23-29, wherein the disintegrant selected from the group consisting of is croscarmellose sodium, sodium starch glycolate, crospovidone, and hydroxypropyl cellulose.
31. The unit dosage form of any one of claims 23-30, further comprising one or more extra-granular excipients.
32. The unit dosage form of any one of claims 23-31, wherein the unit dosage form is in the form of a tablet.
33. A method of treating an estrogen-receptor mediated disease, disorder, or condition, comprising administering to a subject in need thereof, the unit dosage form of any one of claims 1-32.
34. The method of claim 33, wherein the estrogen-receptor mediated disease, disorder, or condition is a cancer.
35. The method of claim 34, wherein the cancer is a breast cancer.
36. The method of claim 34, wherein the cancer is a breast cancer that has metastasized to the lungs, liver, bones, or brain.
37. The method of any one of claims 33-36, further comprising administering a secondary anti-cancer agent.
38. The method of claim 37, wherein the secondary anti-cancer agent is a CDK 4/6 inhibitor, a PI3KCA inhibitor, or an mTOR inhibitor.

39. The method of claim 38, wherein the secondary anti-cancer agent is a CDK 4/6 inhibitor.
40. The method of claim 39, wherein the CDK 4/6 inhibitor is selected from the group consisting of palbociclib, ribociclib, abemaciclib, lerociclib, trilaciclib, and SHR6390.
41. The method of claim 38, wherein the secondary anti-cancer agent is a PIK3CA inhibitor.
42. The method of claim 41, wherein the PIK3CA inhibitor is selected from the group consisting of alpelisib, taselisib, and LY3023414.
43. The method of claim 38, wherein the secondary anti-cancer agent is an mTOR inhibitor.
44. The method of claim 43, wherein the mTOR inhibitor is selected from the group consisting of sirolimus, temsirolimus, everolimus, and LY3023414.
45. The method of claim 38, wherein the secondary anti-cancer agent is a HER2 inhibitor.
46. The method of claim 45, wherein the HER2 inhibitor is selected from the group consisting of tucatinib, pertuzumab, lapatinib, trastuzumab, ado-trastuzumab emtansine, trastuzumab deruxtecan, and neratinib.