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(54) Title: HSP-90 BINDING COMPOUNDS, COMPOSITIONS THEREOF, AND THEIR USE IN THE TREATMENT AND PREVENTION OF FUNGAL INFECTIONS

(57) Abstract: The invention relates to therapeutic compounds that bind to HSP90. The compounds disclosed herein bind HSP90 and alter the chaperoning capability of HSP90 proteins. The invention also relates to pharmaceutical compositions comprising these compounds, and methods of treating or preventing fungal infections.



HSP-90 BINDING COMPOUNDS, COMPOSITIONS THEREOF, AND THEIR USE IN THE TREATMENT AND PREVENTION OF FUNGAL INFECTIONS

Background of the Invention

The heat shock protein 90 family, including HSP90 alpha, HSP90 beta, HSP90 N, GRP94 and TRAP-1 (herein generically referred to as HSP90), are essential molecular chaperones that participate in folding of newly synthesized proteins and stabilization and refolding of stress-denatured client proteins. A large number of HSP90 client proteins have been identified many of which are involved in cellular signaling. Consequently, inhibition of HSP90 is widely regarded as a promising therapeutic approach for the treatment of diseases and conditions characterized by inappropriate cellular signaling and stress responses including cancer, neurodegeneration, inflammation and autoimmune disease. Additionally, the use of HSP90 inhibitors in the inhibition of fungal and parasitic infections is expected to be a useful approach to treating pathogenic fungal and parasitic infections.

HSP90 Structure, Sub-cellular Localization and Function

HSP90 and analogues are relatively large proteins that have characteristic Bergerat ATP binding folds and belong to the GHKL protein superfamily of ATPases and protein kinases (Dutta, R. and Inouye, M., *Trends Biochem Sci.*, 2000, 25(1): 24-8). Crystallography studies revealed a pocket in the N-terminal domain with sequence homology to type II topoisomerases and MutL mismatch repair proteins which co-crystallized with ATP/ADP and established that the N-terminal region is a binding site for adenine nucleotides (Prodromou, C. et al., *Cell*, 1997, 90(1): 65-75). Additionally, HSP90 has a middle segment that participates in client protein binding and a c-terminal domain that is responsible for dimerization and binding of some natural products including novobiocin (Pearl, L. H. and Prodromou, C., *Annu Rev Biochem*, 2006, 75: 271-94).

HSP90 is one of the most abundant cellular proteins comprising 1-2% of total cellular protein (Iwasaki, M. et al., *Biochim Biophys Acta*, 1989, 992(1): 1-8). HSP90 alpha and HSP90 beta are dimeric cytosolic proteins whereas GRP94 and TRAP-1 reside in the endoplasmic reticulum and mitochondria respectively. HSP90 binds to a series of co-chaperones in an ATP dependent manner, thereby modulating the structure of client proteins.

ATP binding regulates the conformation of HSP90 modulating interactions with client proteins (Richter, K., et al., *J Biol Chem*, 2008, 283(26): 17757-65).

HSP90 exerts its cellular function through selectively chaperoning, or promoting conformational changes and domain rearrangements in a wide range of client proteins including nuclear hormone receptors (Pratt, W. B. and Toft, D. O., *Exp Biol Med (Maywood)*, 2003, 228(2): 111-33) and protein kinases (Pearl, L. H., *Curr. Opin. Genet. Dev.*, 2005, 15(1): 55-61). Pharmacological inhibition of HSP90 results in induction of a heat shock response as well as destabilization of HSP90 client proteins. In contexts where pathology is driven by proteins that are HSP90 clients it is expected that HSP90 inhibition will result in destabilization of key proteins leading to therapeutic benefit. It is also expected that induction of a heat shock response, including enhanced synthesis of heat shock protein 70 (HSP70) (Lu, A. et al., *J. Neurochem.*, 2002, 81(2): 355-64), following inhibition of HSP90, may protect normal cells from inappropriate toxicity.

Various natural product small molecules have been identified which bind to the N-terminal ATP binding site of HSP90, including geldanamycin (Stebbins, C. E. et al., *Cell*, 1997, 89(2): 239-50 and Whitesell, L. et al., *Proc. Natl. Acad. Sci. U S A*, 1994, 91(18): 8324-8) and related benzoquinone ansamycins.

Anti-Fungal Applications of HSP90 Inhibitors

Diverse fungal species express HSP90 (Finkelstein DB, 1983 *J Biol Chem*. 258(3):1908-13, Swoboda RK et al 1995 *Infect Immun*. 63(11):4506-14). Preclinical data demonstrate that inhibition of fungal HSP90 may be therapeutically useful for the treatment of fungal infections. HSP90 inhibition has been shown to block emergence of drug resistance in fungal cultures (Cowen LE et al. 2005 *Science* 309:2185-2189). Anasamycin-based HSP90 inhibitors have been shown to synergize with fluconazole and caspofungin in vitro. However these compounds were toxic to fungal infected mice (Cowen LE et al. *Proc Natl Acad Sci U S A*. 2009;106(8):2818-23).

Summary of the Invention

The present inventors teach a novel class of HSP90 inhibitors that demonstrate anti-fungal activity as single agents and in combination with standard anti-fungal agents such as

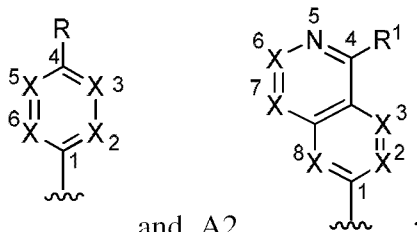
fluconazole and caspofungin. Compounds of the present invention demonstrate good pharmaceutical properties, are orally available, and are well tolerated in mice and rats. These HSP90 inhibitors demonstrate improved synergy with known anti-fungal treatments. These HSP90 inhibitors demonstrate surprising oral bioavailability compared to known HSP90 inhibitors. Unlike other known HSP90 inhibitors, compounds of the present invention are surprisingly well tolerated in multiple species. Thus, the compounds of the instant invention are useful in the treatment of fungal infections.

In certain embodiments, the invention relates to compounds having a structure of Formula 1, or a pharmaceutically acceptable salt thereof



Formula 1

wherein;



A is selected from A1 and A2 ;

each X is independently selected from CR² and N, preferably selected such that no more than two occurrences, and more preferably no more than one occurrence, of X are N;

R is selected from -CN and C(O)NH₂;

R¹ is NH₂;

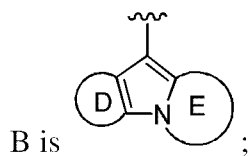
each R² is independently selected from hydrogen halogen, -NO₂, -CN, alkyl, alkenyl, alkynyl, -OR³, -NR⁴R⁵, -S(O)_mR³, -C(O)R³, -C(O)OR³, -C(O)NR⁴R⁵, -S(O)₂NR⁴R⁵, aryl, heteroaryl, carbocyclyl, and heterocyclyl;;

each R³, R⁴, and R⁵ is independently selected from hydrogen, -alkyl-R⁶, carbocyclyl, heterocyclyl, heteroaryl, and aryl; or

R⁴ and R⁵ together are alkylene, thereby forming a ring;

R^6 is selected from hydrogen, hydroxy, alkoxy, $-NHC(O)alkyl$, $-NHSO_2alkyl$, amino, and heterocyclyl;

m is an integer from 0 to 2;



5 D is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl; and

E is selected from carbocyclyl and heterocyclyl.

In certain embodiments, the invention relates to pharmaceutical compositions comprising a compound of Formula 1 and a pharmaceutically acceptable carrier or diluent.

10 In certain embodiments, the invention relates to methods for the treatment of a disease or condition selected from fungal infection comprising administering a compound of Formula 1.

Brief Description of Figures

Figure 1 is a graph showing HSP90 inhibitors block growth of *Candida albicans* and synergize with Fluconazole and Caspofungin

15 Figure 2 is a graph showing HSP90 inhibitors are fungocidal alone and in combination with Fluconazole and Caspofungin.

Figure 3 is a graph showing plasma levels of compound 34 in mice dosed with 100 mg/kg compound 34 formulated in cremophor ELP by oral route.

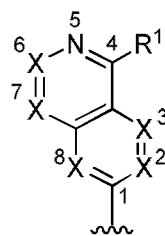
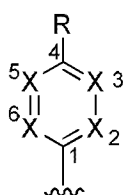
Detailed Description of the Invention

20 In certain embodiments, the invention relates to compounds having a structure of Formula 1, or a pharmaceutically acceptable salt thereof



Formula 1

wherein



A is selected from A1 and A2 (wherein 1-6 and 1-8, respectively refer to positions on the ring);

each X is independently selected from CR^2 and N;

R is selected from $-\text{CN}$ and $-\text{C}(\text{O})\text{NH}_2$;

5 R^1 is NH_2 ;

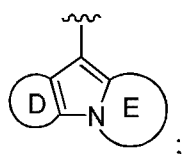
each R^2 is independently selected from hydrogen, halogen, $-\text{NO}_2$, $-\text{CN}$, alkyl, alkenyl, alkynyl, $-\text{OR}^3$, $-\text{NR}^4\text{R}^5$, $-\text{S}(\text{O})_m\text{R}^3$, $-\text{C}(\text{O})\text{R}^3$, $-\text{C}(\text{O})\text{OR}^3$, $-\text{C}(\text{O})\text{NR}^4\text{R}^5$, $-\text{S}(\text{O})_2\text{NR}^4\text{R}^5$, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

10 each R^3 , R^4 , and R^5 is independently selected from hydrogen, $-\text{alkyl-R}^6$, carbocyclyl, heterocyclyl, aryl and heteroaryl; or

R^4 and R^5 together are alkylene, thereby forming a ring;

R^6 is selected from hydrogen, hydroxy, alkoxy, $-\text{NHC}(\text{O})\text{alkyl}$, $-\text{NHSO}_2\text{alkyl}$, amino, and heterocyclyl;

m is an integer from 0 to 2;



15 B is ;

D is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl; and

E is selected from carbocyclyl and heterocyclyl.

In certain embodiments, A is A1, wherein each occurrence of X is independently CR^2 .

20 In certain alternative embodiments, A is A1, wherein one or two occurrences of X are N.

In certain preferred embodiments, wherein A is A1 and X^3 (*i.e.*, X at the 3-position of A1) is CR^2 , R^2 is other than hydrogen.

In certain preferred embodiments, X^3 is CR^2 wherein R^2 is $-NR^4R^5$, R^4 is hydrogen and R^5 is carbocyclyl or heterocyclyl.

5 In certain preferred embodiments, X^3 is CR^2 wherein R^2 is $-NR^4R^5$, R^4 is hydrogen and R^5 is heterocyclyl.

In certain preferred embodiments, X^3 is CR^2 wherein R^2 is $-NR^4R^5$, R^4 is hydrogen and R^5 is carbocyclyl- R^7 wherein

10 R^7 is selected from $-OR^{14}$, $-NR^{12}R^{13}$, $-C(O)NR^{12}R^{13}$, $-SO_2NR^{12}R^{13}$, $-NR^{14}C(O)R^{15}$, $-NR^{14}S(O)_2R^{15}$, $-NR^{14}C(O)NR^{12}R^{13}$, $-OC(O)NR^{12}R^{13}$, $NR^{14}C(O)OR^{15}$, $-C(O)OR^{15}$, $-OC(O)R^{15}$ or heterocyclyl;

each R^{12} and R^{13} is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, aryl and heteroaryl; or

R^{12} and R^{13} together form a substituted or unsubstituted heterocyclyl ring system; and

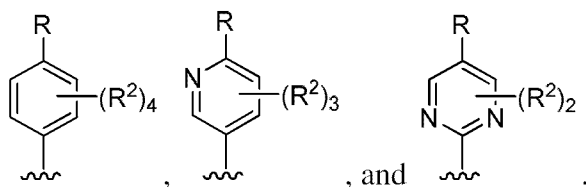
15 R^{14} and R^{15} are selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, aryl and heteroaryl.

In preferred embodiments, the carbocyclyl group of carbocyclyl- R^7 is a trans 1-4 disubstituted 6-membered ring.

20 In certain embodiments as described above, the carbocyclyl group of carbocyclyl- R^7 is a six-membered ring. In certain such embodiments, R^7 is preferably located at the 4-position of the carbocyclyl ring relative to the point of attachment to A.

In certain embodiments as described above where X^3 is CR^2 , wherein R^2 is $-NR^4R^5$, R^4 is hydrogen and R^5 is carbocyclyl- R^7 , other occurrences of R^2 in Formula 1 are independently selected from hydrogen or halogen.

25 In certain embodiments as described above where X^3 is CR^2 , wherein R^2 is $-NR^4R^5$, R^4 is hydrogen and R^5 is heterocyclyl, other occurrences of R^2 in Formula 1 are independently selected from hydrogen or halogen. In certain embodiments, A is selected from

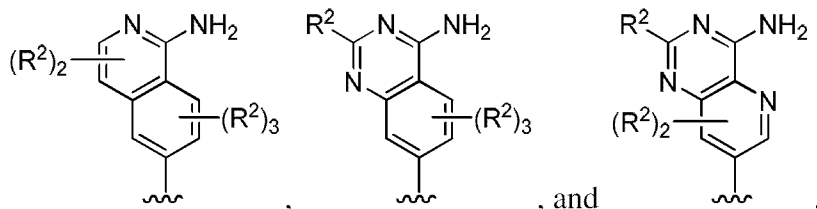


In certain embodiments, A is A2, wherein each occurrence of X is independently CR².

In certain embodiments, A is A2, wherein one or two occurrences of X are N.

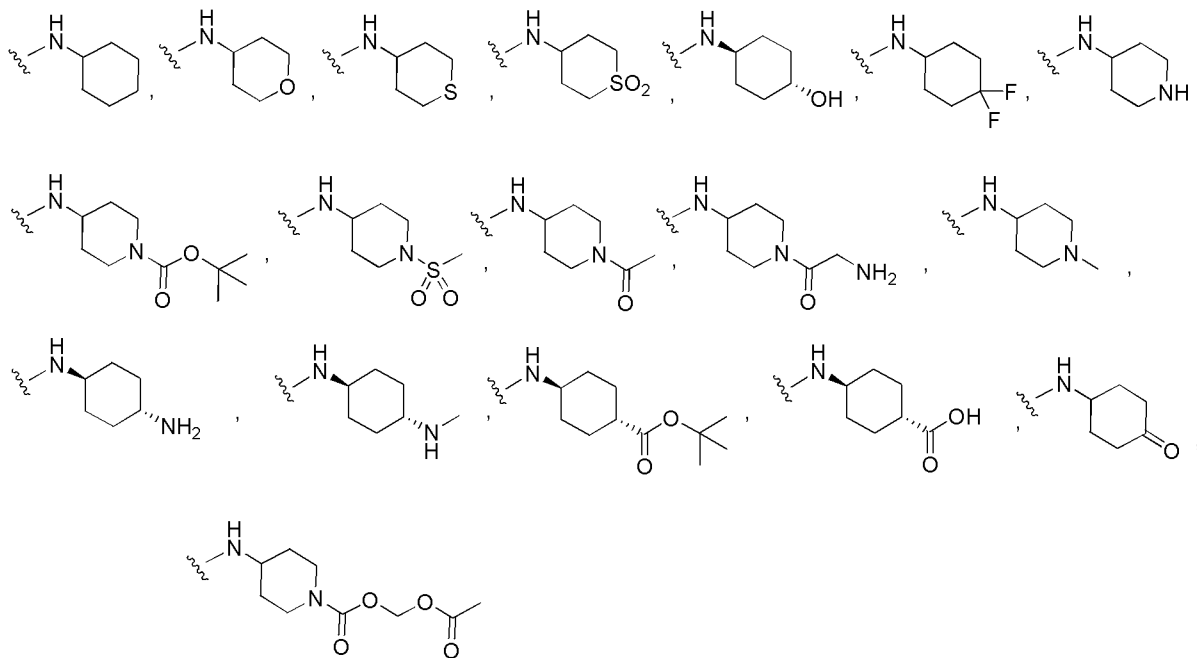
In certain preferred embodiments, the R² attached to X⁶, X⁷, or X⁸, preferably the R² attached to X⁸ of A2 is other than hydrogen.

5 In certain embodiments A is selected from

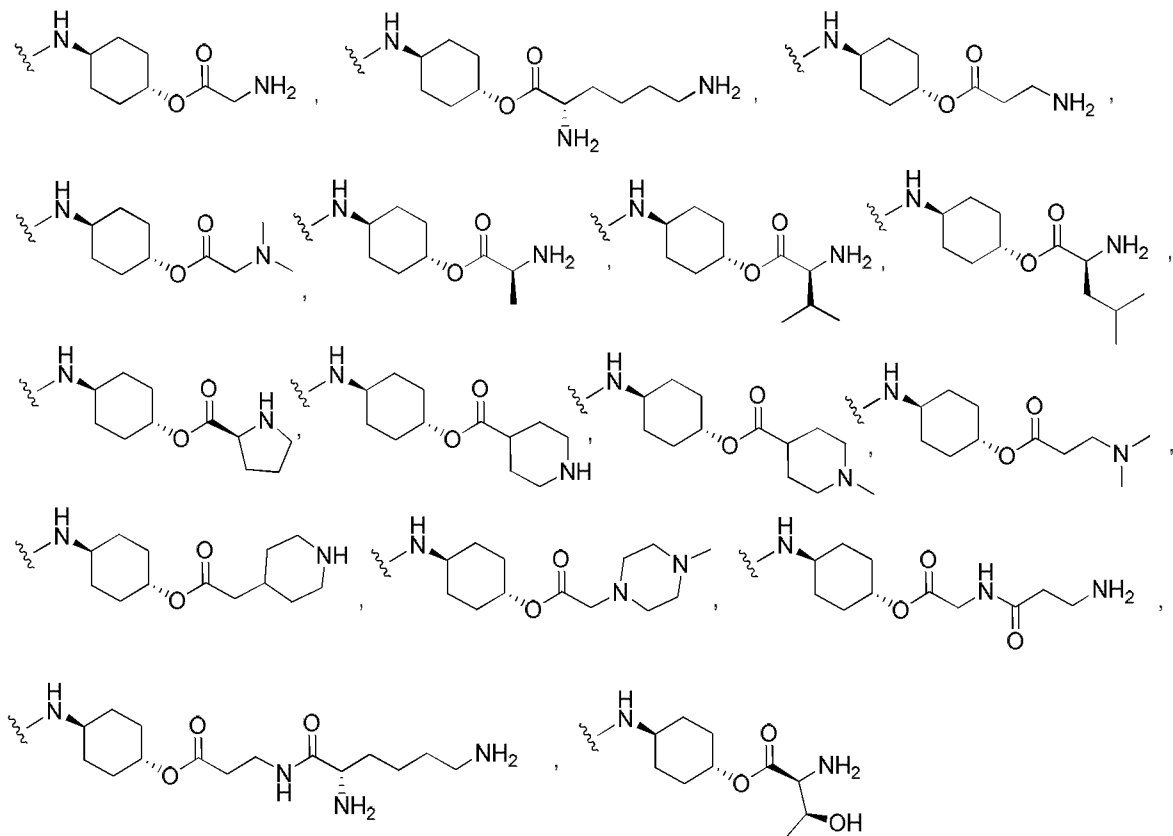


In certain embodiments, R² is selected from hydrogen, halogen, -CN, alkyl, -OR³, -NR⁴R⁵, -S(O)_mR³, and -C(O)NR⁴R⁵. In certain such embodiments, R² is selected from hydrogen and NR⁴R⁵.

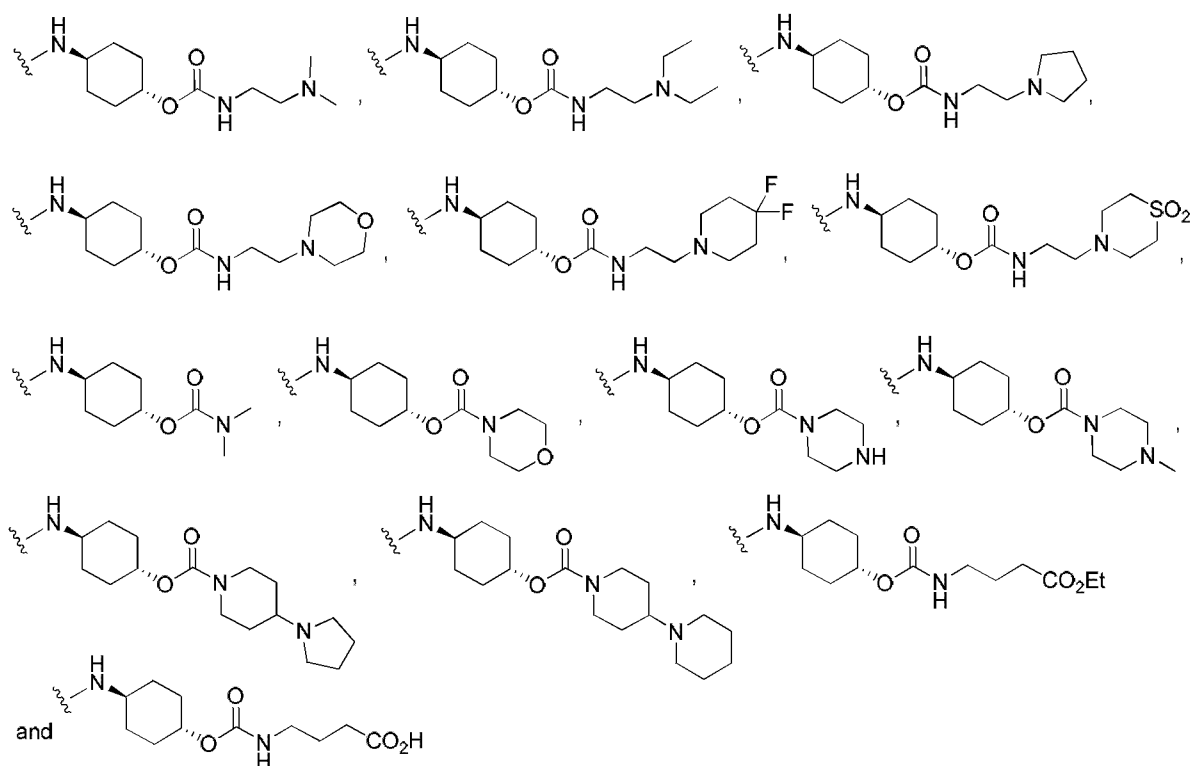
10 In certain embodiments wherein A is A1 and X³ is CR², R² is selected from



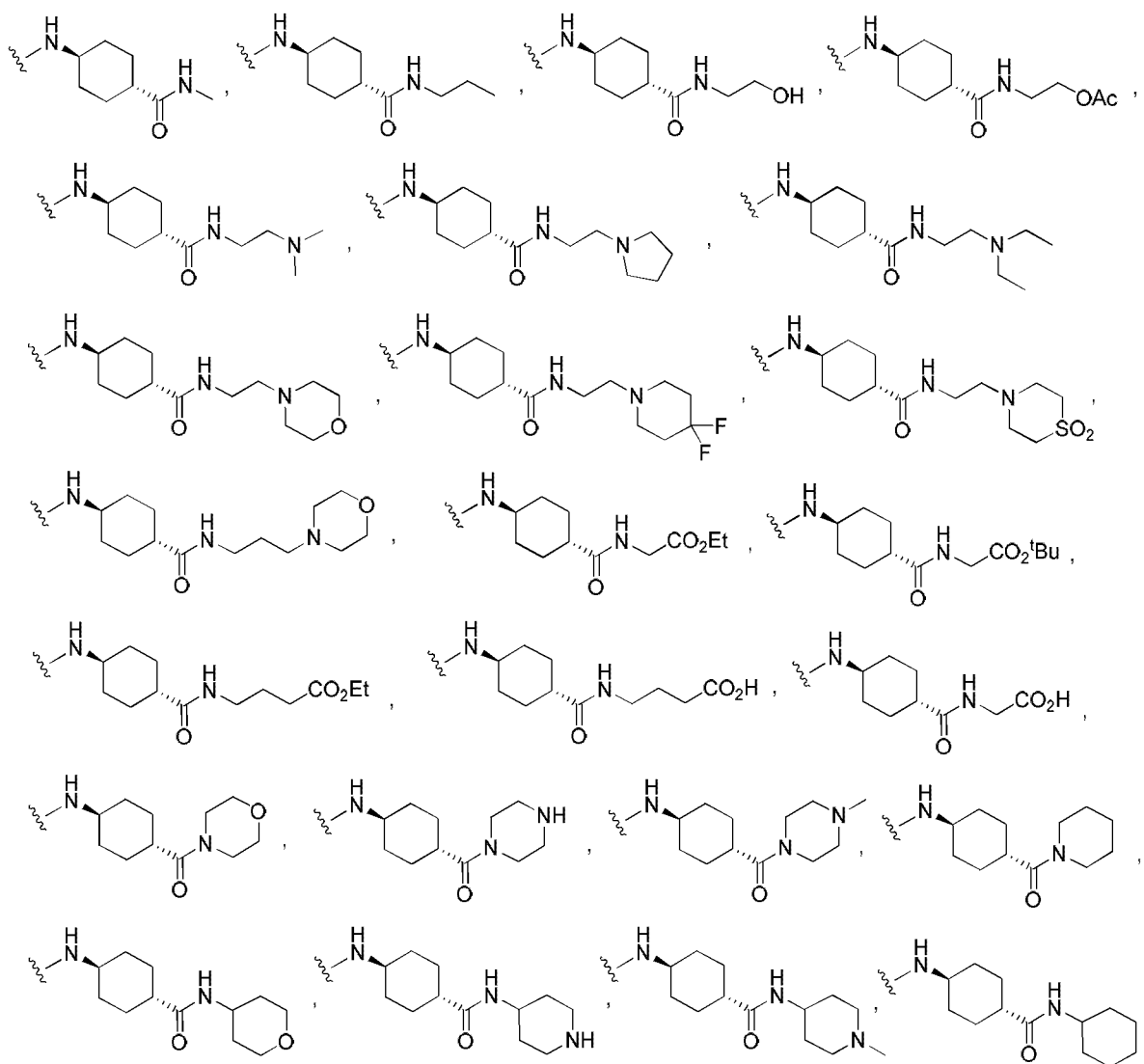
In certain embodiments wherein A is A1 and X³ is CR², R² is selected from



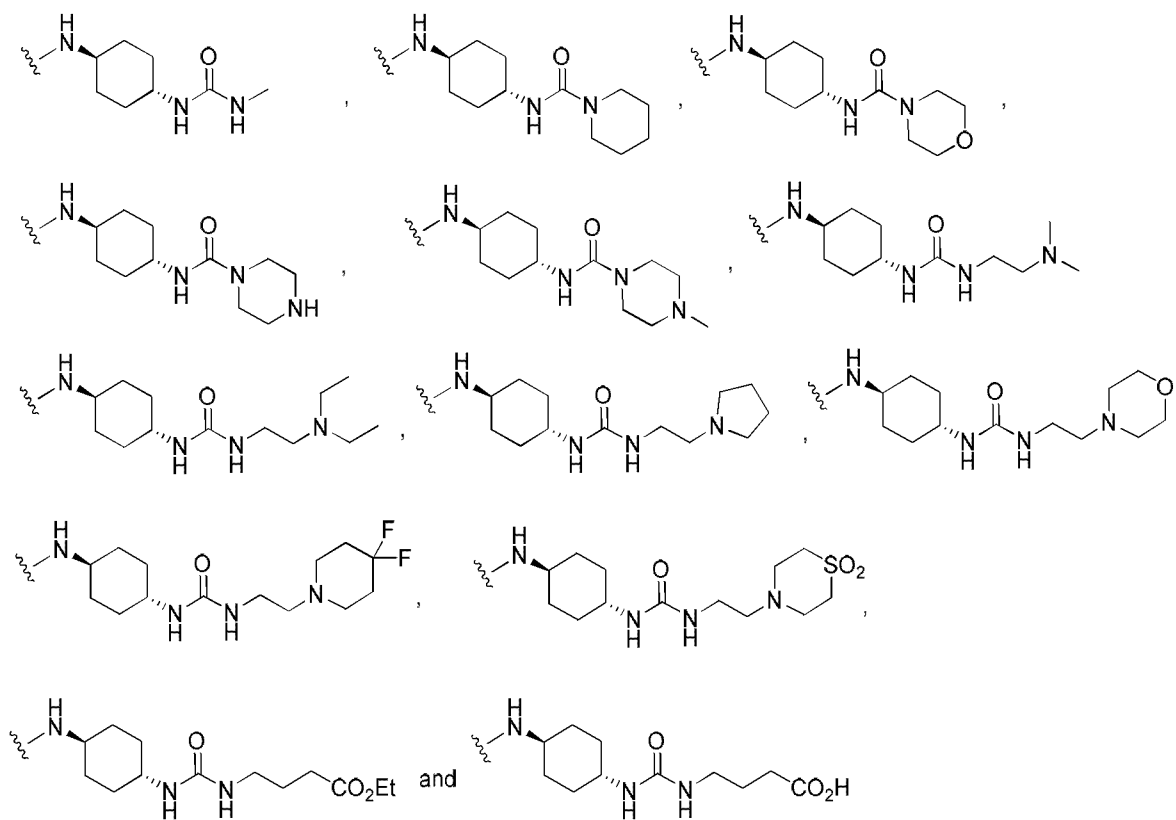
In certain embodiments wherein A is A1 and X³ is CR², R² is selected from



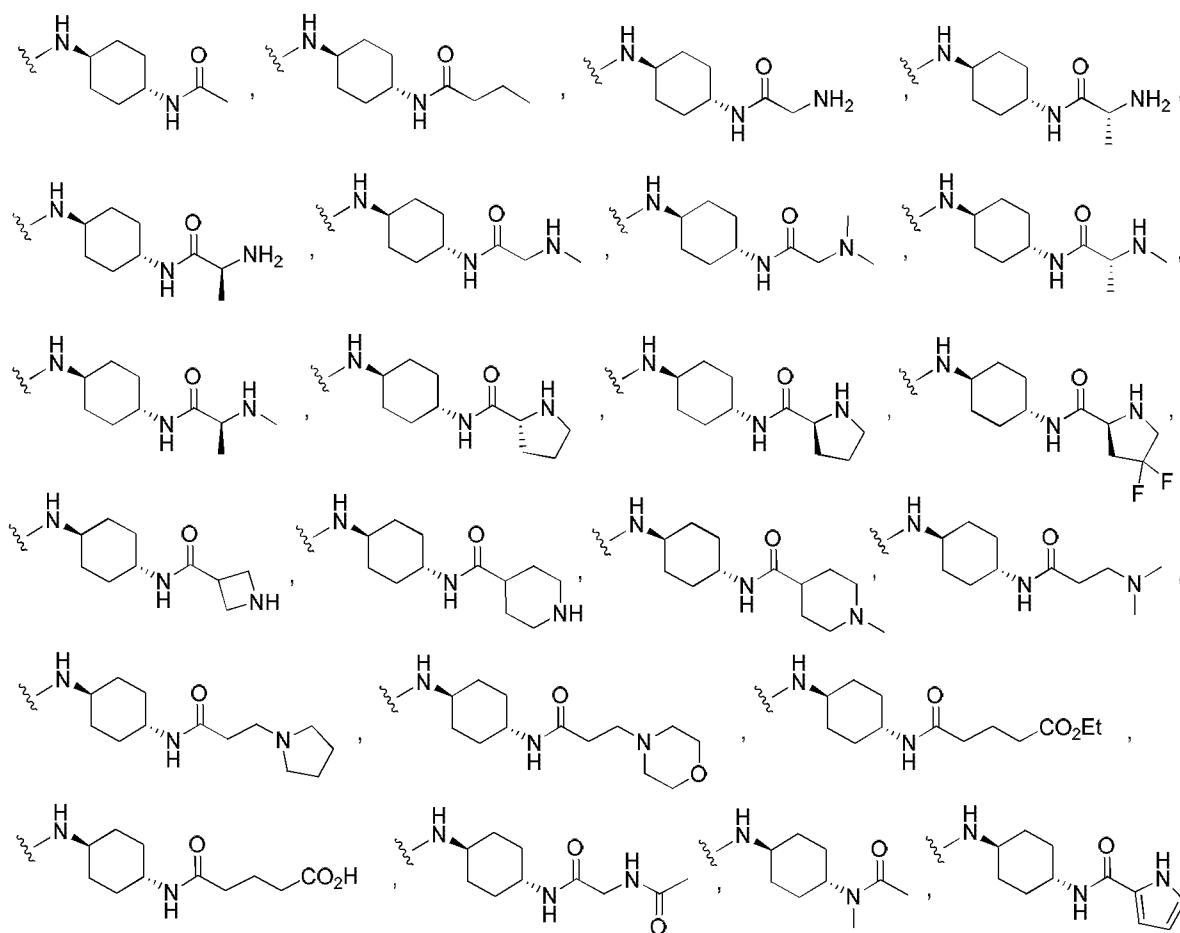
In certain embodiments wherein A is A1 and X³ is CR², R² is selected from



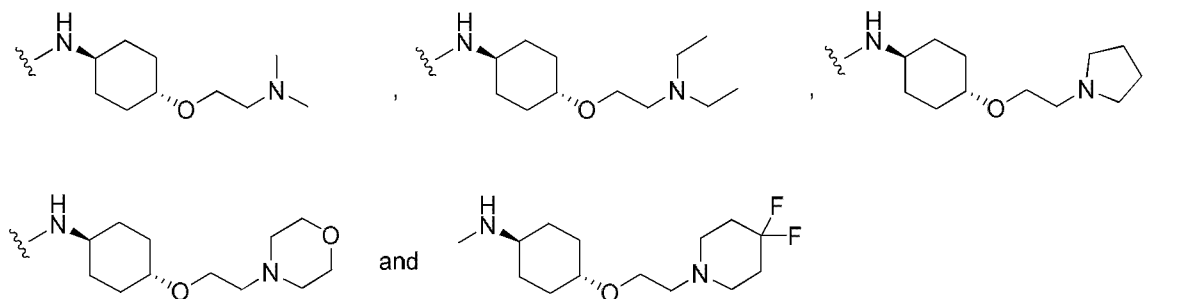
In certain embodiments wherein A is A1 and X^3 is CR^2 , R^2 is selected from



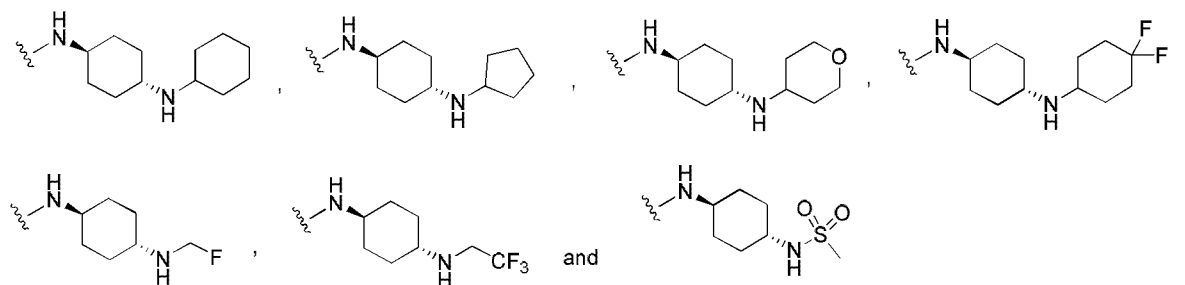
In certain embodiments wherein A is A1 and X³ is CR², R² is selected from



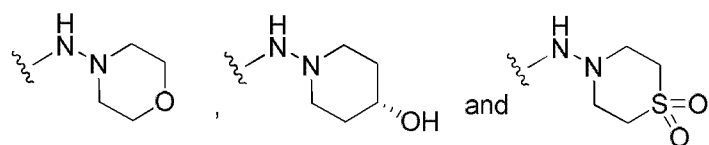
In certain embodiments wherein A is A1 and X^3 is CR^2 , R^2 is selected from



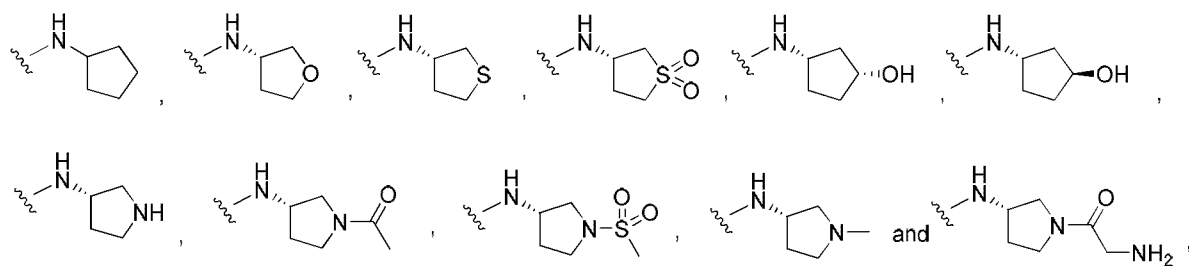
5 In certain embodiments wherein A is A1 and X^3 is CR^2 , R^2 is selected from



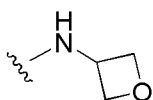
In certain embodiments wherein A is A1 and X^3 is CR^2 , R^2 is selected from



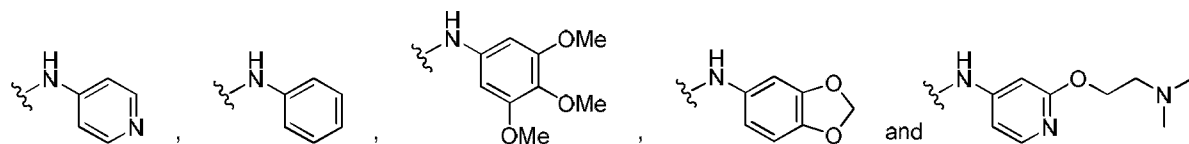
In certain embodiments wherein A is A1 and X^3 is CR^2 , R^2 is selected from



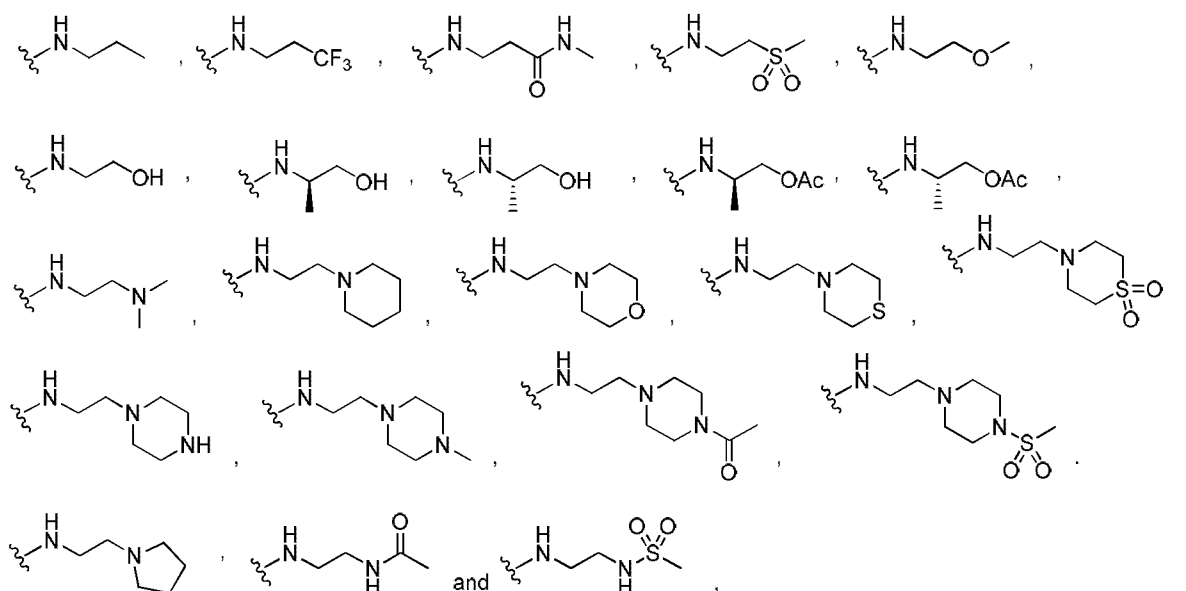
In certain embodiments wherein A is A1 and X³ is CR², R² is selected from



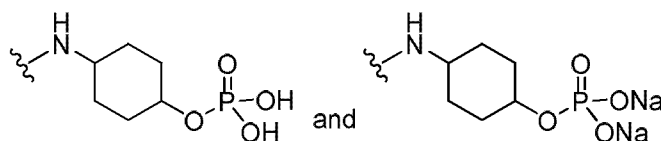
In certain embodiments wherein A is A1 and X^3 is CR^2 , R^2 is selected from



In certain embodiments wherein A is A1 and X^3 is CR^2 , R^2 is selected from



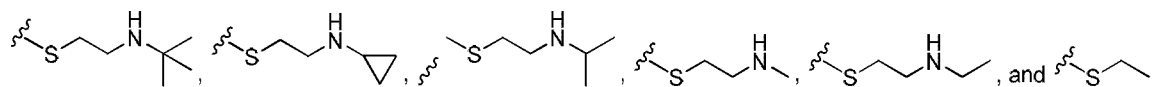
In certain embodiments wherein A is A1 and X^3 is CR^2 , R^2 is selected from



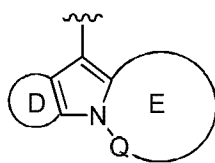
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In certain embodiments, when A is A2 at least one occurrence of R^2 , preferably when X^6 , X^7 , or X^8 is CR^2 more preferably when X^8 is CR^2 , is selected from alkyl, halogen, $-\text{OR}^3$, and $-\text{S}(\text{O})_m\text{R}^3$. In certain such embodiments, R^2 is alkyl, preferably methyl, ethyl, propyl, isopropyl, butyl, or isobutyl. In certain alternative such embodiments, at least one occurrence of R^2 is halogen, preferably Br or F. In certain alternative such embodiments, at least one occurrence of R^2 are $-\text{OR}^3$. In certain such embodiments, R^2 is selected from $-\text{O}(\text{CH}_2)_2\text{OCH}_3$, $-\text{O}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$, $-\text{O}(\text{CH}_2)_2\text{OH}$, and OEt. In certain alternative such embodiments, at least one occurrence of R^2 is $-\text{S}(\text{O})_m\text{R}^3$. In certain such embodiments, R^2 is selected from

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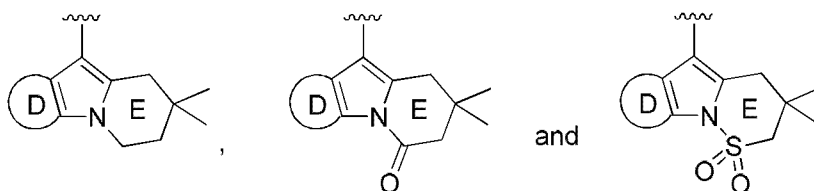
In certain embodiments, B is



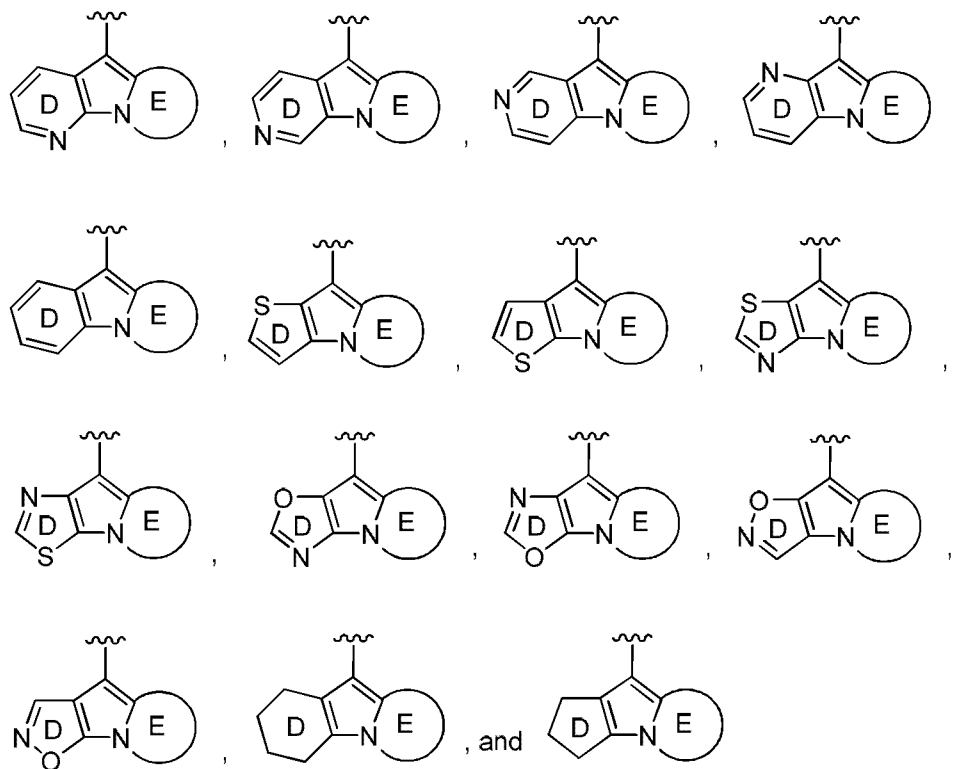
wherein Q is selected from -C(O)-, and -S(O)_n-; and n is an integer from 1 to 2.

In certain embodiments D is aryl or heteroaryl, preferably phenyl, pyridyl, thienyl, thiazolyl, oxazole, or isoxazole. In certain other embodiments, D is carbocyclyl, preferably
 5 cyclopentyl or cyclohexyl.

In certain embodiments, B is selected from



In certain embodiments, B is selected from



In certain embodiments, B is selected such that the D ring is one of the D rings specified in the previous paragraph and the E ring is one of the E rings specified in the paragraph prior to that.

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

Another aspect of the present invention provides a method of treating a proliferative disorder or a disease state, the method comprising administering to a subject in need thereof an amount of a compound or pharmaceutical composition as described above sufficient to treat the proliferative disorder or disease state.

Another aspect of the present invention provides a method of modulating HSP function, the method comprising contacting a cell with a compound of the present invention in an amount sufficient to modulate the binding of a HSP client protein to HSP, thereby modulating the HSP function.

Another aspect of the present invention provides a method of modulating HSP function, the method comprising contacting a cell with a compound of the present invention in an amount sufficient to modulate HSP90 function affecting protein folding, stability and aggregation.

In certain embodiments, the invention relates to methods for the treatment of a disease or condition selected from the treatment of fungal infections. Examples of pathogenic fungal infections that may be treated with compounds of the instant invention include species of: *Candida*, *Aspergillus*, *Cryptococcus*, *Trichophyton*, *Microsporum*, *Epidermophyton*, and *Malassezia*.

Infections which may be treated with compounds of the instant invention include: *Candida albicans*, *Aspergillus fumigatus*, *Aspergillus terreus*, *Trichophyton rubrum* and *Cryptococcus neoformans*.

Compounds of the instant invention may be used to treat fungal infections anywhere in the body including vaginal, dermal, nail, meningial, as well as systemic infections.

Compounds of the instant invention may be used for the treatment of fungal infections either alone or in combination with other agents used in the treatment or prophylaxis of fungal infections. For example, Table 1 summarizes therapeutic agents used in the treatment of fungal infections and is provided to be illustrative of potential combination therapies.

Table 1

Fluconazole	Caspofungin	Isavuconazole
Pramiconazole	Amphotericin	Nystatin
Anidulafungin	Voriconazole	Posaconazole
Itraconazole	Ravuconazole	Anti-fungal antibodies
Nikkomycin Z	Albaconazole	Vaccines

i) Administration

Compounds prepared as described herein can be administered in various forms, depending on the disorder to be treated and the age, condition, and body weight of the patient, as is well known in the art. For example, where the compounds are to be administered orally, they may be formulated as tablets, capsules, granules, powders, or syrups; or for parenteral administration, they may be formulated as injections (intravenous, intramuscular, or subcutaneous), drop infusion preparations, or suppositories. For application by the ophthalmic mucous membrane route, they may be formulated as eye drops or eye ointments. These formulations can be prepared by conventional means, and if desired, the active ingredient may be mixed with any conventional additive or excipient, such as a binder, a disintegrating agent, a lubricant, a corrigent, a solubilizing agent, a suspension aid, an emulsifying agent, a coating agent, a cyclodextrin, and/or a buffer. Although the dosage will vary depending on the symptoms, age and body weight of the patient, the nature and severity of the disorder to be treated or prevented, the route of administration and the form of the drug, in general, a daily dosage of from 0.01 to 2000 mg of the compound is recommended for an adult human patient, and this may be administered in a single dose or in divided doses. The amount of active ingredient which can be combined with a carrier material to produce a

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

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

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

The phrase “pharmaceutically acceptable carrier” as used herein means a pharmaceutically acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically acceptable carriers include: (1) sugars, such as lactose, glucose, and sucrose; (2) starches, such as corn starch, potato starch, and substituted or unsubstituted β -cyclodextrin; (3) cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose, and cellulose acetate; (4) powdered tragacanth; (5) malt; (6) gelatin; (7) talc; (8) excipients, such as cocoa butter and suppository waxes; (9) oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil, and soybean oil; (10) glycols, such as propylene glycol; (11) polyols, such as glycerin, sorbitol, mannitol, and polyethylene glycol; (12) esters, such as ethyl oleate and ethyl laurate; (13) agar; (14) buffering agents, such as magnesium hydroxide and aluminum hydroxide; (15) alginic acid; (16) pyrogen-free water; (17) isotonic saline; (18) Ringer’s

solution; (19) ethyl alcohol; (20) phosphate buffer solutions; and (21) other non-toxic compatible substances employed in pharmaceutical formulations. In certain embodiments, pharmaceutical compositions of the present invention are non-pyrogenic, i.e., do not induce significant temperature elevations when administered to a patient.

5 The term “pharmaceutically acceptable salt” refers to the relatively non-toxic, inorganic and organic acid addition salts of the compound(s). These salts can be prepared *in situ* during the final isolation and purification of the compound(s), or by separately reacting a purified compound(s) in its free base form with a suitable organic or inorganic acid, and isolating the salt thus formed. Representative salts include the hydrobromide, hydrochloride, 10 sulfate, bisulfate, phosphate, nitrate, acetate, valerate, oleate, palmitate, stearate, laurate, benzoate, lactate, phosphate, tosylate, citrate, maleate, fumarate, succinate, tartrate, naphthylate, mesylate, glucoheptonate, lactobionate, laurylsulphonate salts, and amino acid salts, and the like. (See, for example, Berge et al. (1977) “Pharmaceutical Salts”, *J. Pharm. Sci.* 66: 1-19.)

15 In other cases, the compounds useful in the methods of the present invention may contain one or more acidic functional groups and, thus, are capable of forming pharmaceutically acceptable salts with pharmaceutically acceptable bases. The term “pharmaceutically acceptable salts” in these instances refers to the relatively non-toxic inorganic and organic base addition salts of a compound(s). These salts can likewise be 20 prepared *in situ* during the final isolation and purification of the compound(s), or by separately reacting the purified compound(s) in its free acid form with a suitable base, such as the hydroxide, carbonate, or bicarbonate of a pharmaceutically acceptable metal cation, with ammonia, or with a pharmaceutically acceptable organic primary, secondary, or tertiary amine. Representative alkali or alkaline earth salts include the lithium, sodium, potassium, 25 calcium, magnesium, and aluminum salts, and the like. Representative organic amines useful for the formation of base addition salts include ethylamine, diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine, and the like (see, for example, Berge et al., *supra*).

Wetting agents, emulsifiers, and lubricants, such as sodium lauryl sulfate and magnesium stearate, as well as coloring agents, release agents, coating agents, sweetening,

flavoring, and perfuming agents, preservatives and antioxidants can also be present in the compositions.

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

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

In solid dosage forms for oral administration (capsules, tablets, pills, dragees, powders, granules, and the like), the active ingredient is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: (1) fillers or extenders, such as starches, cyclodextrins, lactose, sucrose, glucose, mannitol, and/or silicic acid; (2) binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose, and/or acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as, for example, acetyl alcohol and glycerol monostearate; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and (10) coloring agents. In the case of capsules, tablets, and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a

similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols, and the like.

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

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

25 Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups, and elixirs. In addition to the active ingredient, the liquid dosage forms may contain inert diluents commonly used in the art, such as, for example, water or other solvents, solubilizing agents, and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut,

corn, germ, olive, castor, and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols, and fatty acid esters of sorbitan, and mixtures thereof.

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

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

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

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

20 Dosage forms for the topical or transdermal administration of a compound(s) include powders, sprays, ointments, pastes, creams, lotions, gels, solutions, patches, and inhalants. The active component may be mixed under sterile conditions with a pharmaceutically acceptable carrier, and with any preservatives, buffers, or propellants which may be required or beneficial.

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

Powders and sprays can contain, in addition to a compound(s), excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates, and polyamide powder, or

mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane.

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

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

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

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

Examples of suitable aqueous and nonaqueous carriers which may be employed in the pharmaceutical compositions of the invention include water, ethanol, polyols (such as
30 glycerol, propylene glycol, polyethylene glycol, and the like), and suitable mixtures thereof,

vegetable oils, such as olive oil, and injectable organic esters, such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials, such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

5 These compositions may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include tonicity-adjusting agents, such as sugars, sodium chloride, and the like into the compositions.

10 In addition, prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

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

 Injectable depot forms can be made by forming microencapsulated matrices of compound(s) in biodegradable polymers such as polylactide-polyglycolide. Depending on the ratio of drug to polymer, and the nature of the particular polymer employed, the rate of
20 drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissue.

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

 The phrases "parenteral administration" and "administered parenterally" as used herein means modes of administration other than enteral and topical administration, usually
30 by injection, and includes, without limitation, intravenous, intramuscular, intraarterial,

intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection, and infusion.

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

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

15 Regardless of the route of administration selected, the compound(s), which may be used in a suitable hydrated form, and/or the pharmaceutical compositions of the present invention, are formulated into pharmaceutically acceptable dosage forms by conventional methods known to those of skill in the art.

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

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

30

Definitions

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

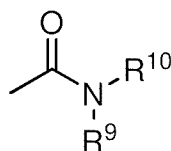
The term “alkyl” refers to substituted or unsubstituted saturated hydrocarbon groups, including straight-chain alkyl and branched-chain alkyl groups, including haloalkyl groups such as trifluoromethyl and 2,2,2-trifluoroethyl, etc. Representative alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, (cyclohexyl)methyl, cyclopropylmethyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. The terms “alkenyl” and “alkynyl” refer to substituted or unsubstituted unsaturated aliphatic groups analogous in length and possible substitution to the alkyls described above, but that contain at least one double or triple bond respectively. Representative alkenyl groups include vinyl, propen-2-yl, crotyl, isopenten-2-yl, 1,3-butadien-2-yl, 2,4-pentadienyl, and 1,4-pentadien-3-yl.

Representative alkynyl groups include ethynyl, 1- and 3-propynyl, and 3-butylnyl. In certain preferred embodiments, alkyl substituents are lower alkyl groups, e.g., having from 1 to 6 carbon atoms. Similarly, alkenyl and alkynyl preferably refer to lower alkenyl and alkynyl groups, e.g., having from 2 to 6 carbon atoms. As used herein, “alkylene” refers to an alkyl group with two open valencies (rather than a single valency), such as $-(CH_2)_{1-10}-$ and substituted variants thereof.

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

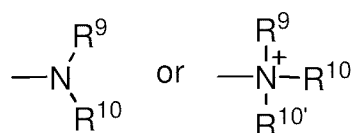
The term “alkoxyalkyl” refers to an alkyl group substituted with an alkoxy group, thereby forming an ether.

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



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

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



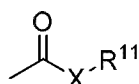
wherein R^9 , R^{10} and $\text{R}^{10'}$ each independently represent a hydrogen, an alkyl, an alkenyl, $-(\text{CH}_2)_m\text{—R}^8$, or R^9 and R^{10} taken together with the N atom to which they are attached complete a heterocycle having from 4 to 8 atoms in the ring structure; R^8 represents an aryl, a cycloalkyl, a cycloalkenyl, a heterocyclyl or a polycyclyl; and m is zero or an integer from 1 to 8. In preferred embodiments, only one of R^9 or R^{10} can be a carbonyl, e.g., R^9 , R^{10} , and the nitrogen together do not form an imide. In even more preferred embodiments, R^9 and R^{10} (and optionally $\text{R}^{10'}$) each independently represent a hydrogen, an alkyl, an alkenyl, or $-(\text{CH}_2)_m\text{—R}^8$. In certain embodiments, the amino group is basic, meaning the protonated form has a $\text{pK}_a \geq 7.00$.

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

The term “aryl” as used herein includes 5-, 6-, and 7-membered substituted or unsubstituted single-ring aromatic groups in which each atom of the ring is carbon. The term “aryl” also includes polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is aromatic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Aryl groups include benzene, naphthalene, phenanthrene, phenol, aniline, anthracene, and phenanthrene.

The terms “carbocycle” and “carbocyclyl”, as used herein, refer to a non-aromatic substituted or unsubstituted ring in which each atom of the ring is carbon. The terms “carbocycle” and “carbocyclyl” also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is carbocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryls, and/or heterocyclyls. Representative carbocyclic groups include cyclopentyl, cyclohexyl, 1-cyclohexenyl, and 3-cyclohexen-1-yl, cycloheptyl.

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



wherein X is a bond or represents an oxygen or a sulfur, and R^{11} represents a hydrogen, an alkyl, an alkenyl, $-(\text{CH}_2)_m\text{-R}^8$ or a pharmaceutically acceptable salt. Where X is an oxygen and R^{11} is not hydrogen, the formula represents an “ester”. Where X is an oxygen, and R^{11} is a hydrogen, the formula represents a “carboxylic acid”.

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

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

The terms “heterocyclyl” or “heterocyclic group” refer to substituted or unsubstituted non-aromatic 3- to 10-membered ring structures, more preferably 3- to 7-membered rings,

whose ring structures include one to four heteroatoms. The term terms “heterocyclyl” or “heterocyclic group” also include polycyclic ring systems having two or more cyclic rings in which two or more carbons are common to two adjoining rings wherein at least one of the rings is heterocyclic, e.g., the other cyclic rings can be cycloalkyls, cycloalkenyls, cycloalkynyls, aryls, heteroaryl, and/or heterocyclyls. Heterocyclyl groups include, for example, tetrahydrofuran, piperidine, piperazine, pyrrolidine, morpholine, lactones, and lactams.

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

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

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

untreated control population, and/or delaying the onset of symptoms of the infection in a treated population versus an untreated control population. Prevention of pain includes, for example, reducing the magnitude of, or alternatively delaying, pain sensations experienced by subjects in a treated population versus an untreated control population.

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

 The term “substituted” refers to moieties having substituents replacing a hydrogen on one or more carbons of the backbone. It will be understood that “substitution” or “substituted with” includes the implicit proviso that such substitution is in accordance with permitted valence of the substituted atom and the substituent, and that the substitution results
15 in a stable compound, e.g., which does not spontaneously undergo transformation such as by rearrangement, cyclization, elimination, etc. As used herein, the term “substituted” is contemplated to include all permissible substituents of organic compounds. In a broad aspect, the permissible substituents include acyclic and cyclic, branched and unbranched, carbocyclic and heterocyclic, aromatic and non-aromatic substituents of organic compounds.
20 The permissible substituents can be one or more and the same or different for appropriate organic compounds. For purposes of this invention, the heteroatoms such as nitrogen may have hydrogen substituents and/or any permissible substituents of organic compounds described herein which satisfy the valences of the heteroatoms. Substituents can include, for example, a halogen, a hydroxyl, a carbonyl (such as a carboxyl, an alkoxycarbonyl, a formyl, or an acyl), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an alkoxy, a
25 phosphoryl, a phosphate, a phosphonate, a phosphinate, an amino, an amido, an amidine, an imine, a cyano, a nitro, an azido, a sulfhydryl, an alkylthio, a sulfate, a sulfonate, a sulfamoyl, a sulfonamido, a sulfonyl, a heterocyclyl, an aralkyl, or an aromatic or heteroaromatic moiety. It will be understood by those skilled in the art that the moieties substituted on the
30 hydrocarbon chain can themselves be substituted, if appropriate.

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

As used herein, the term “well tolerated” refers to a substance, such as a
5 pharmaceutical compound or composition, that is not poisonous or harmful to humans or other higher life forms when used in a therapeutically effective dose.

As used herein, the term “orally bioavailable” refers to a substance, such as a pharmaceutical compound or composition, that can be taken orally for therapeutic efficacy.

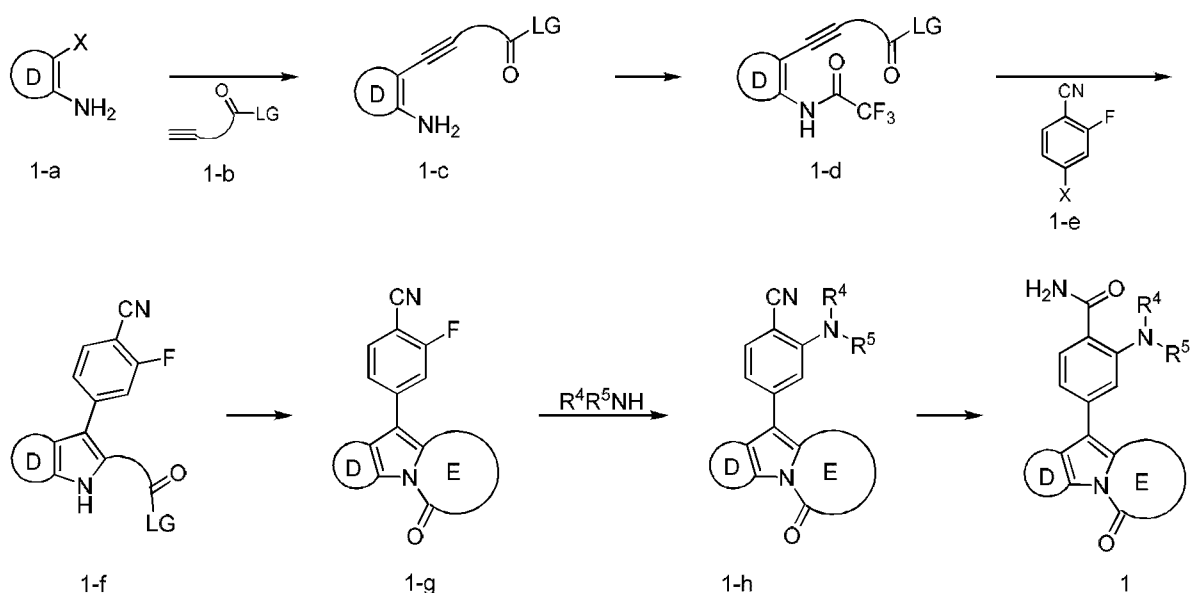
Compounds of the invention also include all isotopes of atoms present in the
10 intermediates and/or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include deuterium and tritium.

Examples

Schemes 1, 2, 3, 4, 5 and 6 illustrate general synthetic procedures for the preparation
15 of compounds of formula 1.

Method A

Sonogashira coupling reaction of intermediate 1-a with terminal alkyne 1-b affords intermediate 1-c which is then converted to the corresponding trifluoroacetamide intermediate 1-d. Intermediate 1-f may be prepared by reacting o-alkynyltrifluoroacetanilide
20 intermediate 1-d with aryl halide 1-e in the presence of a ligand, a catalyst and a base. Treatment of intermediate 1-f with an appropriate base provides intermediate 1-g. Cyclized intermediate 1-g can also be obtained from intermediate 1-d in a one step-method under suitable conditions. Treatment of intermediate 1-g with an amine of formula R^4R^5NH provides intermediate 1-h. Nitrile hydrolysis of intermediate 1-h provides compounds of
25 formula 1.



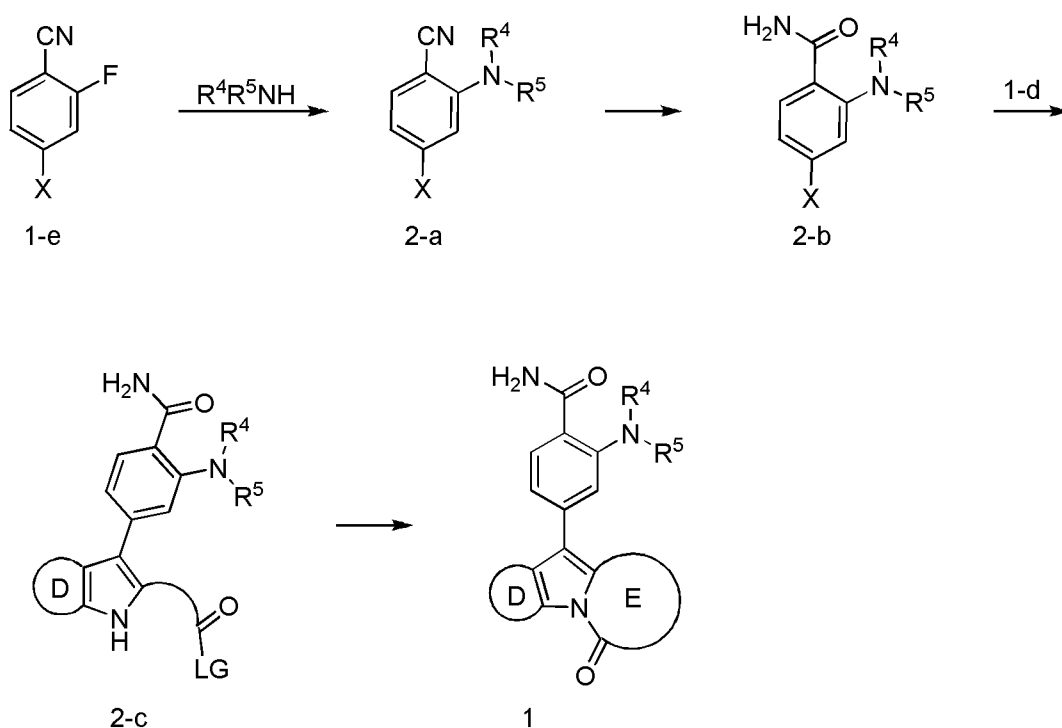
Scheme 1

Method B

Treatment of commercially available aryl halide 1-e with an amine of formula R⁴R⁵NH provides nitrile intermediate 2-a which is then converted to the corresponding amide intermediate 2-b. Intermediates 2-c may be prepared by reacting o-alkynyltrifluoroacetanilide intermediates 1-d with aryl halide 2-b in the presence of a ligand, a catalyst and a base.

Treatment of intermediate 2-c with an appropriated base provides compounds of formula 1.

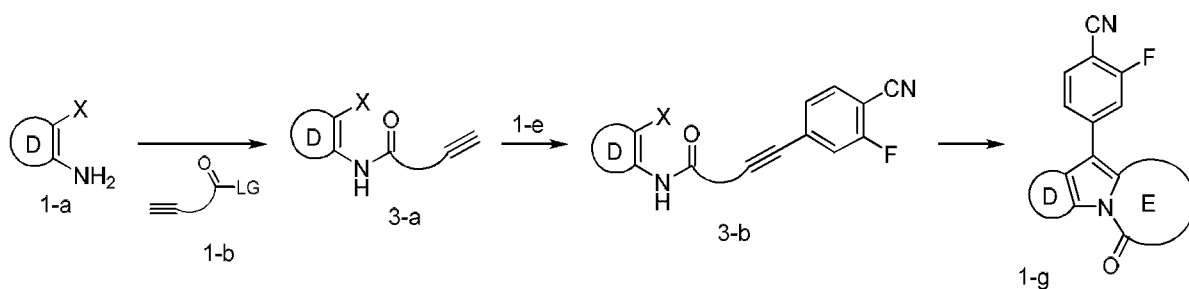
Compounds of formula 1 may also be obtained from intermediates 2-b and 1-d in a one step-method under appropriated conditions.



Scheme 2

Method C

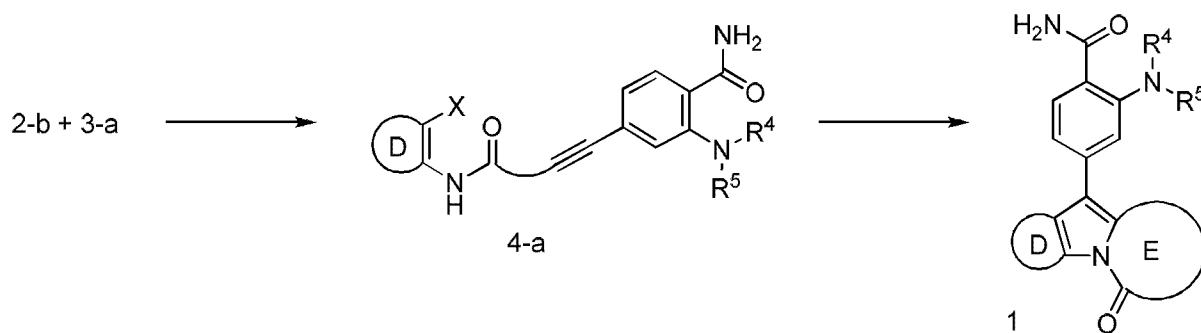
Treatment of intermediate 1-a, preferentially a chlorine derivative, with intermediate 1-b afford intermediate 3-a. Sonogashira coupling reaction of aryl halide 1-e with terminal alkyne intermediate 3-a provides intermediate 3-b. Treatment of intermediate 3-b with an appropriate base, ligand and catalyst provides polycyclic intermediate 1-g.



Scheme 3

Method D

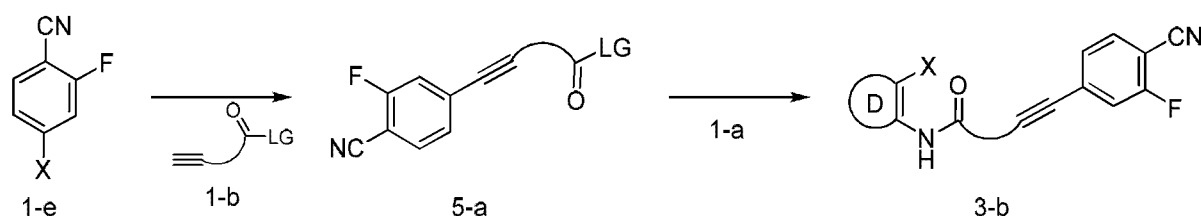
Sonogashira coupling reaction of aryl halide 2-b with terminal alkyne intermediate 3-a provides intermediate 4-a. Treatment of intermediate 4-a with an appropriate base, ligand and catalyst provides a compound of formula 1.



Scheme 4

Method E

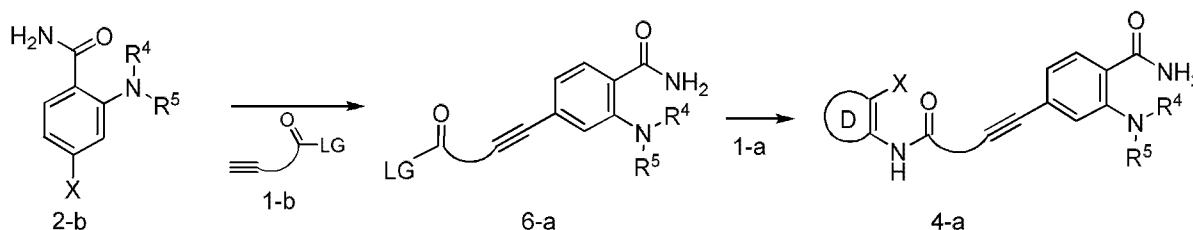
Sonogashira coupling reaction of aryl halide 1-e with an alkyne intermediate 1-b provides intermediate 5-a. Treatment of intermediate 1-a with intermediate 5-a affords intermediate 3-b.



Scheme 5

Method F

Sonogashira coupling reaction of aryl halide 2-b with an alkyne intermediate 1-b provides intermediate 6-a. Treatment of intermediate 1-a with intermediate 6-a affords intermediate 4-a.

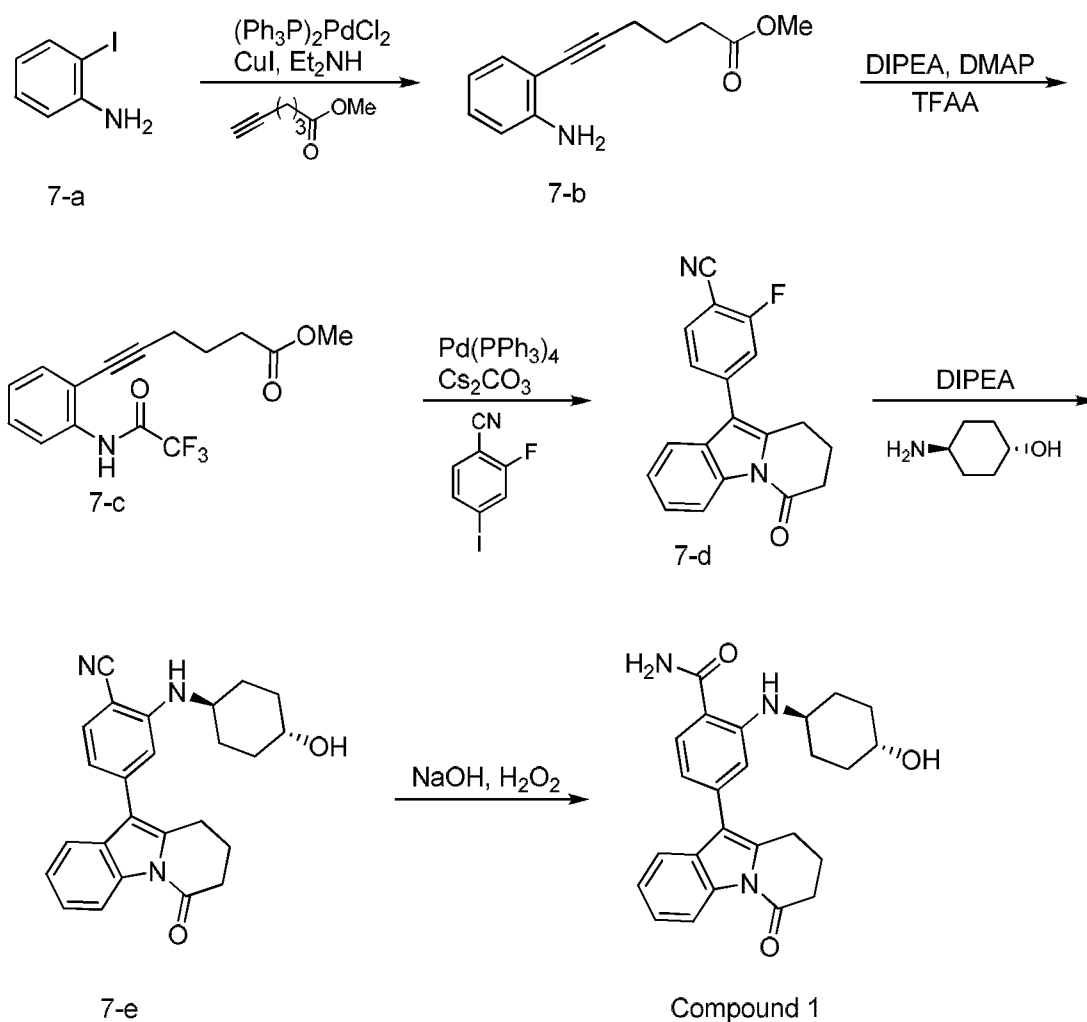


Scheme 6

SYNTHETIC METHODS

Preparation of representative examples:

Synthesis of Compound 1



Scheme 7

Step 1: 7-b

To a solution of 2-iodoaniline 7-a (5.0 g, 22.83 mmol) in DMF cooled to 0 °C were sequentially added diethylamine (5 mL, 22.83 mmol), copper(I) iodide (870 mg, 4.57 mmol) and dichlorobis(triphenylphosphine) palladium (II) (1.60 g, 2.28 mmol). After complete dissolution of copper(I) iodide, methyl hex-5-ynoate (3.17 g, 25.1 mmol) was added

dropwise at 0 °C and the reaction was then stirred at room temperature for 1 hour. Water and ethyl acetate were added; the organic layer was separated, washed with 10% citric acid, saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 7-b as colorless oil.

5 MS (m/z) M+H= 218.1

Step 2: 7-c

To a solution of intermediate 7-b (4.8 g, 22.09 mmol) in DCM cooled to 0 °C was sequentially added DIPEA (15.48 mL, 88.00 mmol), DMAP (135 mg, 1.10 mmol) and
10 TFAA (6.87 mL, 48.60 mmol) and the reaction was then stirred at room temperature for 18 hours. Water and ethylacetate were added; the organic layer was separated, washed with 10% citric acid, saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 7-c as colorless oil. MS (m/z) M+H= 314.3

15 Step 3: 7-d

To a solution of intermediate 7-c (1.0 g, 3.19 mmol) in acetonitrile was added 2-fluoro-4-iodobenzonitrile (1.18 g, 4.79 mmol), Cs₂CO₃ (1.56 g, 4.79 mmol) and Pd(PPh₃)₄ (184 mg, 0.16 mmol) and the reaction was stirred at 100 °C for 18 hours and then cooled to room temperature. Water and ethyl acetate were added; the organic layer was separated,
20 washed with 10% citric acid, saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 7-d as a beige solid. MS (m/z) M+H= 305.9

Step 4: 7-e

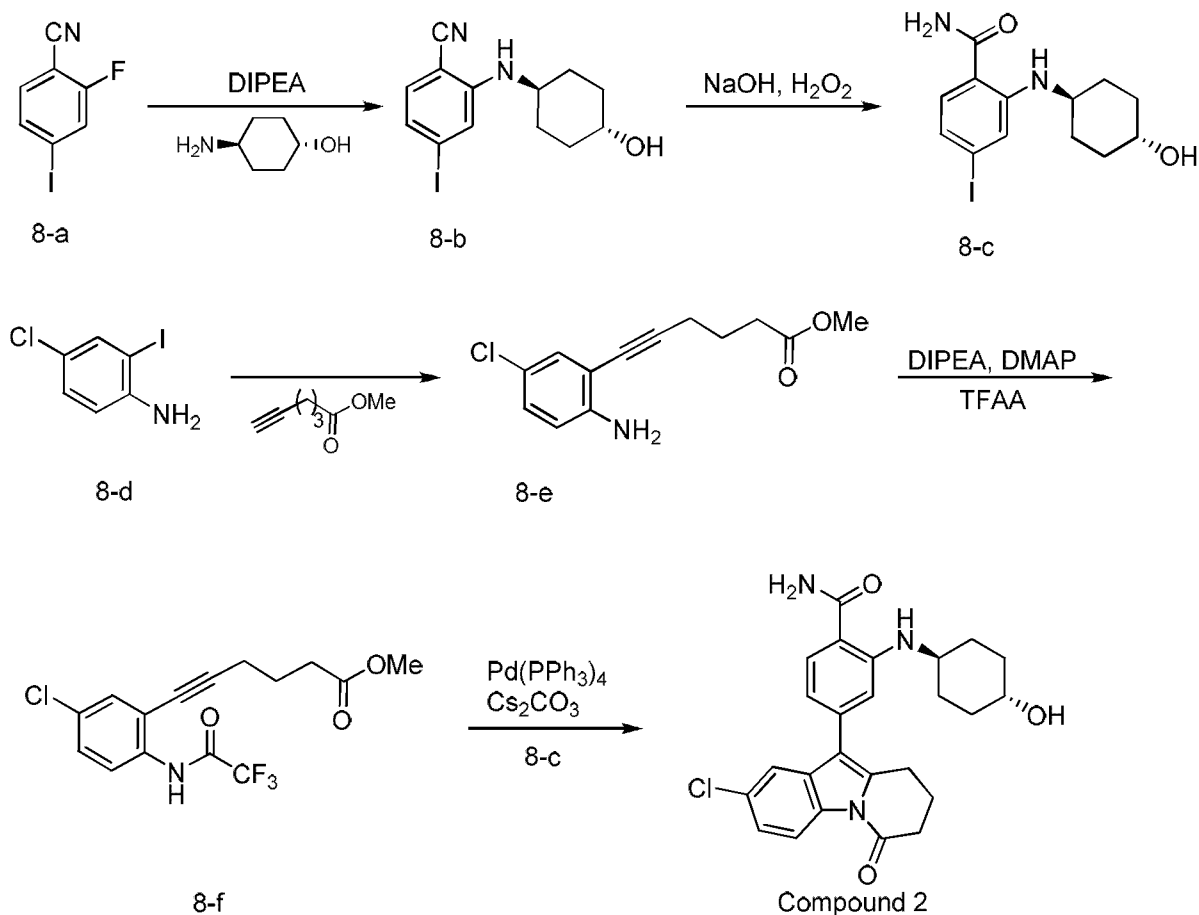
25 To a suspension of intermediate 7-d (440 mg, 1.44 mmol) in DMSO were sequentially added DIPEA (1.26 mL, 7.23 mmol) and trans-4-aminocyclohexanol (666 mg, 5.78 mmol) and the mixture was then heated at 100 °C for 18 hours and then cooled to room temperature. Water and ethyl acetate were added, the organic layer was separated, washed

with saturated NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 7-e as a beige solid. MS (m/z) M+H= 400.6

5 **Step 5: Compound 1**

To a solution of intermediate 7-e (50 mg, 0.12 mmol) in 1,4-dioxane was sequentially added NaOH 1N (38 μL , 0.038 mmol) and 30% aqueous hydrogen peroxide (0.40 mL, 3.92 mmol) and the reaction was stirred at room temperature for 15 hours. Water and ethyl acetate were added; the organic layer was separated, washed with saturated ammonium chloride,
10 10% aqueous $\text{Na}_2\text{S}_2\text{O}_3$ and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 1 as a white solid. MS (m/z) M+H= 418.3

Synthesis of compound 2



Scheme 8

5 Step 1: 8-b

A solution of intermediate 2-fluoro-4-iodobenzonitrile 8-a (2.50 g, 10.12 mmol), trans-4-aminocyclohexanol (3.50 g, 30.40 mmol) and DIPEA (7.07 mL, 40.50 mmol) in DMSO was heated at 150 °C for 2 hours and then cooled to room temperature. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 8-b as a white solid. MS (m/z) M+H= 343.1

10

Step 2: 8-c

To a solution of intermediate 8-b (750 mg, 2.19 mmol) in DMSO/EtOH (4:1, 10 mL) was sequentially added NaOH 1N (3.0 mL, 3.0 mmol) and 30% aqueous hydrogen peroxide (2.0 mL, 19.58 mmol) and the reaction was stirred at room temperature for 4 hours. Saturated aqueous ammonium chloride and ethyl acetate were added, the organic layer was separated, the aqueous phase was extracted with ethyl acetate, the combined organic extracts were washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo to provide intermediate 8-c as beige solid. MS (m/z) $\text{M}+\text{H}= 361.1$

Step 3: 8-e

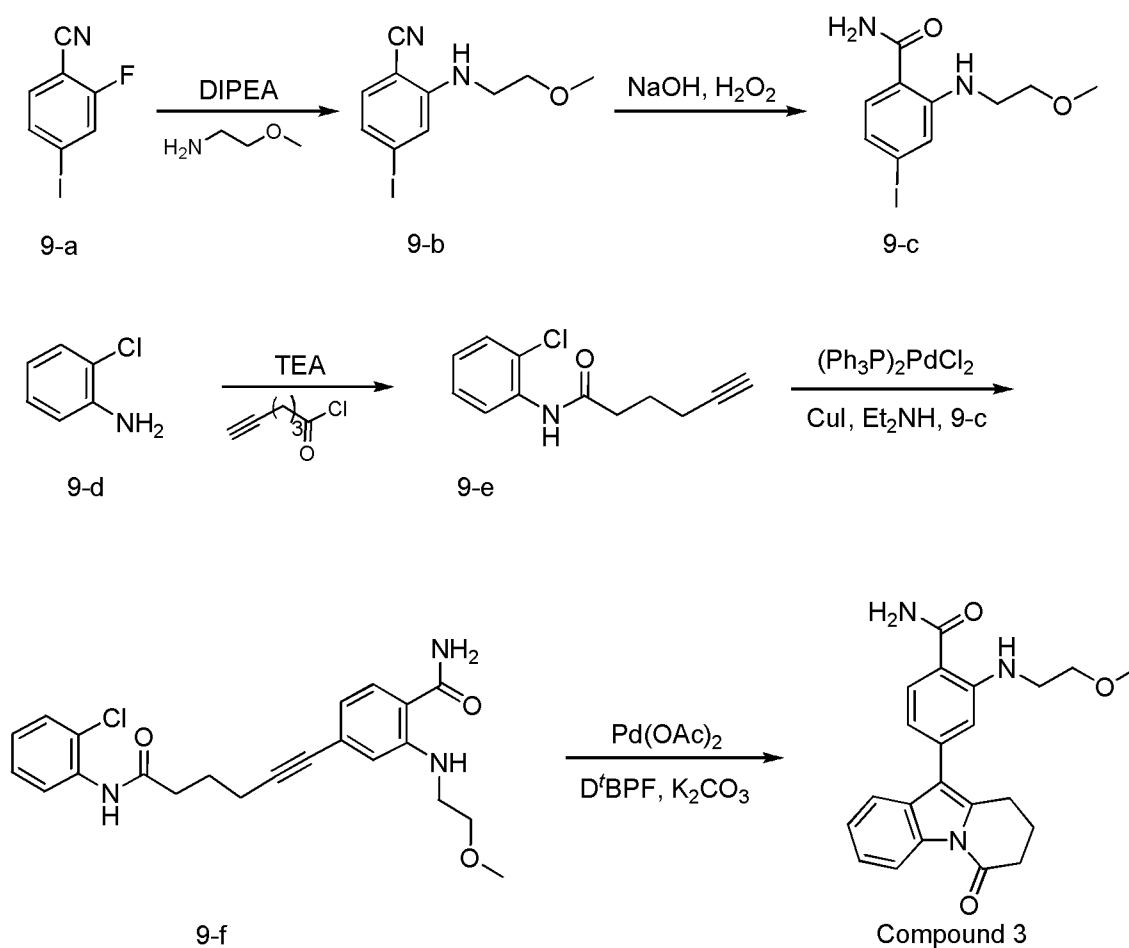
To a solution of 4-chloro-2-iodoaniline 8-d (2.0 g, 7.89 mmol) in DMF cooled to 0 °C was sequentially added diethylamine (5 mL, 22.83 mmol), copper (I) iodide (301 mg, 1.57 mmol) and dichlorobis(triphenylphosphine) palladium (II) (554 mg, 0.78 mmol). After complete dissolution of copper (I) iodide, methyl hex-5-ynoate (1.09 g, 8.68 mmol) was added dropwise at 0 °C and the reaction was then stirred at room temperature overnight. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 8-e as a beige solid. MS (m/z) $\text{M}+\text{H}= 252.2$

Step 4: 8-f

To a solution of intermediate 8-e (1.78 g, 7.07 mmol) in DCM cooled to 0 °C were sequentially added DIPEA (4.94 mL, 28.3 mmol), DMAP (43 mg, 0.35 mmol) and TFAA (2.19 mL, 15.56 mmol) and the reaction was then stirred at room temperature for 18 hours. Water and ethyl acetate were added; the organic layer was separated, washed with 10% citric acid, saturated NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo to provide intermediate 8-f as yellow oil. MS (m/z) $\text{M}+\text{H}= 349.0$

Step 5: Compound 2

To a solution of intermediate 8-c (544 mg, 1.51 mmol) in acetonitrile was added intermediate 8-f (350 mg, 1.0 mmol), Cs₂CO₃ (492 mg, 1.51 mmol) and Pd(PPh₃)₄ (23 mg, 0.02 mmol) and the reaction was stirred at 110 °C overnight and then cooled to room temperature. Water and ethyl acetate were added; the organic layer was separated, washed with 10% citric acid, saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 2 as a beige solid. MS (m/z) M+H= 452.4

Synthesis of compound 3**Scheme 9**

Step 1: 9-b

A solution of intermediate 9-a (1.0 g, 4.05 mmol), 2-methoxyethanamine (912 mg, 12.15 mmol) and DIPEA (2.83 mL, 16.19 mmol) in DMSO was heated at 150 °C for 2 hours and then cooled to room temperature. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 9-b as a white solid.

Step 2: 9-c

To a solution of intermediate 9-b (1.10 g, 3.64 mmol) in DMSO (8.0 mL) and MeOH (8.0 mL) was sequentially added NaOH 1N (3.0 mL, 3.0 mmol) and 30% aqueous hydrogen peroxide (2.0 mL, 19.58 mmol) and the reaction was stirred at room temperature for 4 hours. Saturated aqueous ammonium chloride and ethyl acetate were added, the organic layer was separated, the aqueous phase was extracted with ethyl acetate, the combined organic extracts were washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo to provide intermediate 9-c as a white solid. MS (m/z) $\text{M}+\text{H}= 321.5$

Step 3: 9-e

To a solution of hex-5-ynoic acid (1.0 g, 8.92 mmol) in THF was added DMF (119 uL) and oxalyl chloride (820 uL, 9.36 mmol) and the mixture was stirred for 1 hour at room temperature. 2-chloroaniline 9-d (1.13 g, 8.92 mmol) and TEA (1.30 mL, 9.36 mmol) were added; the reaction was stirred at reflux for 2 hours and then cooled to room temperature. Saturated aqueous ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 9-e as a white solid. MS (m/z) $\text{M}+\text{H}= 222.2$

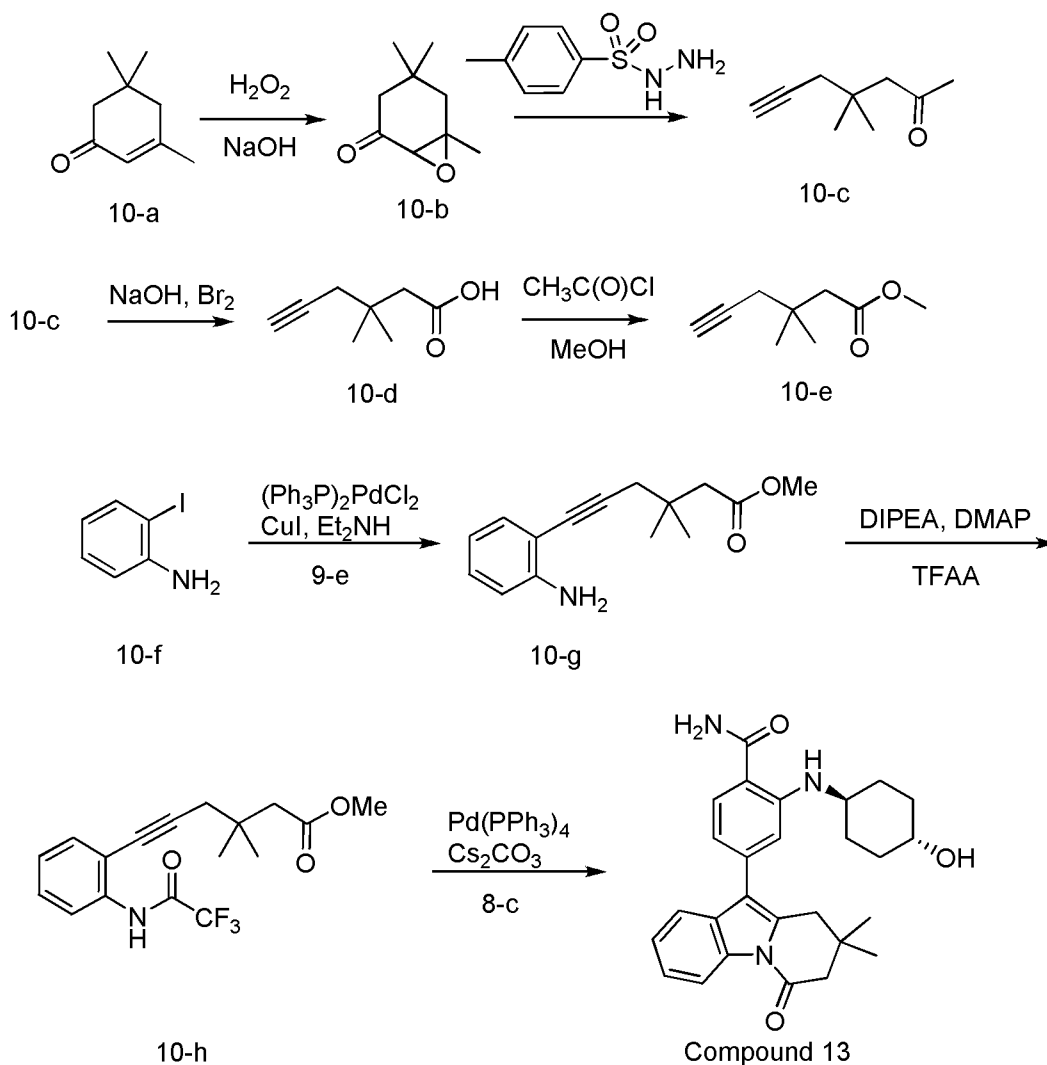
Step 4: 9-f

A mixture of dichlorobis(triphenylphosphine) palladium (II) (21 mg, 0.03 mmol), copper(I) iodide (11 mg, 0.06 mmol), intermediate 9-c (500 mg, 1.56 mmol) and intermediate 9-e (330 mg, 1.48 mmol) in TEA (4.96 mL) was heated at 50 °C for 1 hour. Saturated aqueous ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 9-f as a white solid. MS (m/z) M+H= 414.5

Step 5: Compound 3

A mixture of intermediate 9-f (100 mg, 0.24 mmol), palladium (II) acetate (5.59 mg, 0.02 mmol), bis(di-tert-butylphosphino)ferrocene (23.9 mg, 0.05 mmol), and K₂CO₃ (86 mg, 0.62 mmol) in NMP was heated at 130 °C overnight and then cooled to room temperature. Saturated aqueous ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 3 as a beige solid. MS (m/z) M+H= 378.4

Synthesis of compound 13



Scheme 10

Step 1: 10-b

- 5 To a solution of 3,5,5-trimethylcyclohex-2-en-1-one, 10-a (25.0 mL, 181 mmol), in MeOH cooled to 15 °C were sequentially added hydrogen peroxide (11.5 mL, 181 mmol) and 5N NaOH (4 mL, 20.0 mmol) and the reaction was then stirred at 15 °C for 20 minutes and then at room temperature for 3 hours. Water and ether were added, the organic layer was separated, the aqueous phase was extracted twice with diethyl ether, the combined organic
- 10 extracts were washed with water, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo to provide intermediate 10-b as colorless oil.

Step 2: 10-c

To a solution of intermediate 10-b (3.0 g, 19.45 mmol) in EtOH was added 4-methylbenzenesulfonohydrazide (3.62 g, 19.45 mmol) and the reaction was then stirred at room temperature for 20 minutes and 55 °C for 2 hours. Water and CH₂Cl₂ were added; the organic layer was separated, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 10-c as colorless oil.

Step 3: 10-d

To a solution of 3N NaOH (53.3 mL, 160 mmol) in 1,4-dioxane:water (200 mL) cooled to -5 °C was added bromine (2.09 mL, 40.6 mmol). The solution was stirred at -5 °C for 5 minutes and then diluted with 1,4-dioxane (40 mL). The resulting hypobromite solution was then slowly added to a solution of intermediate 10-c (1.70 g, 12.30 mmol) in 1,4-dioxane:water 3:1 (200 mL) and the reaction was then stirred at 0 °C for 2 hours. Sodium thiosulfate (3 g) was added and the mixture was stirred for 15 minutes at room temperature. Concentrated HCl and CH₂Cl₂ were added, the organic layer was separated, the aqueous phase was extracted with CH₂Cl₂, the combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 10-d as yellow oil.

Step 4: 10-e

To a solution of intermediate 10-d (600 mg, 4.28 mmol) in MeOH was added acetyl chloride (304 uL, 4.28 mmol) and the reaction was then stirred at 40 °C for 2 hours. Water and CH₂Cl₂ were added, the organic layer was separated, the aqueous phase was extracted with CH₂Cl₂, and the combined organic layer was separated, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 10-e as yellow oil.

Step 5: 10-g

To a solution of 2-iodoaniline, 10-f (383 mg, 1.75 mmol), in DMF cooled to 0 °C were sequentially added diethylamine (10 mL, 96.2 mmol), copper(I) iodide (13.3 mg, 0.07 mmol) and dichlorobis(triphenylphosphine) palladium (II) (24.5 mg, 0.03 mmol). After complete dissolution of copper(I) iodide, methyl 3,3-dimethylhex-5-ynoate (270 mg, 1.75 mmol) was added dropwise at 0 °C and the reaction was then stirred at room temperature overnight. Water and ethyl acetate were added; the organic layer was separated, washed with 10% citric acid, saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 10-g as a yellow oil. MS (m/z) M+H= 246.1

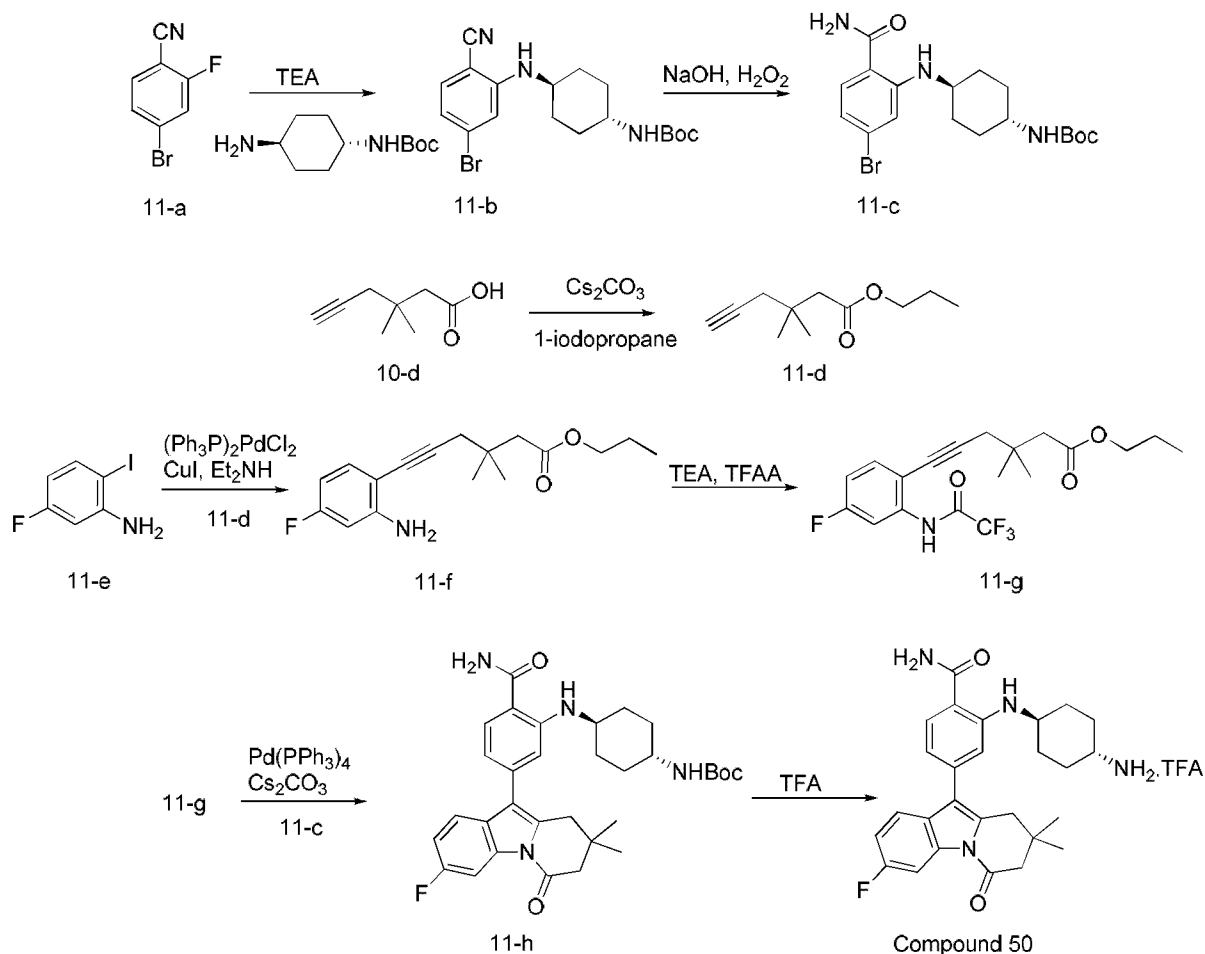
Step 6: 10-h

To a solution of intermediate 10-g (110 mg, 0.44 mmol) in CH₂Cl₂ cooled to 0°C were sequentially added DIPEA (313 uL, 1.79 mmol), DMAP (2.7 mg, 0.02 mmol) and TFAA (139 uL, 0.98 mmol) and the reaction was then stirred at room temperature for 18 hours. Water and ethyl acetate were added; the organic layer was separated, washed with 10% citric acid, saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 10-h as yellow oil. MS (m/z) M+H= 342.3

Step 7: Compound 13

To a solution of intermediate 10-h (154 mg, 0.45 mmol) in acetonitrile were added intermediate 8-c (162 mg, 0.45 mmol), Cs₂CO₃ (220 mg, 0.67 mmol) and Pd(PPh₃)₄ (26 mg, 0.02 mmol) and the reaction was stirred at 100 °C overnight and then cooled to room temperature. Water and ethyl acetate were added; the organic layer was separated, washed with 10% citric acid, saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 13 as a yellow solid. MS (m/z) M+H= 446.4

Synthesis of compound 50



Scheme 11

5 **Step 1: 11-b**

A solution of 4-bromo-2-fluorobenzonitrile 11-a (2.91 g, 14.56 mmol), tert-butyl 4-aminocyclohexylcarbamate (3.12 g, 14.56 mmol) and TEA (6.13 mL, 43.70 mmol) in DMSO was heated at 130°C for 5 hours and then cooled to room temperature. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Diethyl ether was added to the residue and intermediate 11-b was collected by filtration as a white solid.

Step 2: 11-c

To a solution of intermediate 11-b (4.30 g, 10.91 mmol) in DMSO (15.0 mL) and MeOH (15 mL) were sequentially added 1N NaOH (10.91 mL) and 30% aqueous hydrogen peroxide (1.67 mL, 16.36 mmol) and the reaction was stirred at room temperature for 1 hour. Saturated aqueous ammonium chloride and ethyl acetate were added, the organic layer was separated, the aqueous phase was extracted with ethyl acetate, the combined organic extracts were washed with brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 11-c as a white solid. MS (m/z) M+H= 413.9

Step 3: 11-d

To a solution of intermediate 10-d (15.2 g, 108.0 mmol) in DMF cooled to 0°C were sequentially added cesium carbonate (42.4 g, 130.0 mmol) and 1-iodopropane (31.70 mL, 325.0 mmol) and the reaction was then stirred at room temperature overnight. Water and DCM were added, the organic layer was separated, the aqueous phase was extracted with DCM, the combined organic extracts were dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 11-d as yellowish oil.

Step 4: 11-f

To a solution of 5-fluoro-2-iodoaniline 11-e (4.29 g, 18.11 mmol) in DMF, cooled to 0°C, were sequentially added diethylamine (2.50 mL, 24.0 mmol), copper (I) iodide (125 mg, 0.65 mmol) and dichlorobis(triphenylphosphine) palladium (II) (231 mg, 0.32 mmol). After complete dissolution of copper(I)iodide, propyl 3,3-dimethylhex-5-ynoate (3.0 g, 16.46 mmol) was added dropwise at 0°C and the reaction was then stirred at room temperature for 3 hours. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 11-f as a yellow oil. MS (m/z) M+H=292.2

Step 5: 11-g

To a solution of intermediate 11-f (4.80 g, 16.47 mmol) in DCM cooled to 0°C were sequentially added TEA (4.59 mL, 32.9 mmol) and TFAA (3.49 mL, 24.71 mmol) and the reaction was then stirred at room temperature for 1 hour. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 11-g as yellow oil. MS (m/z) M+H=388.3

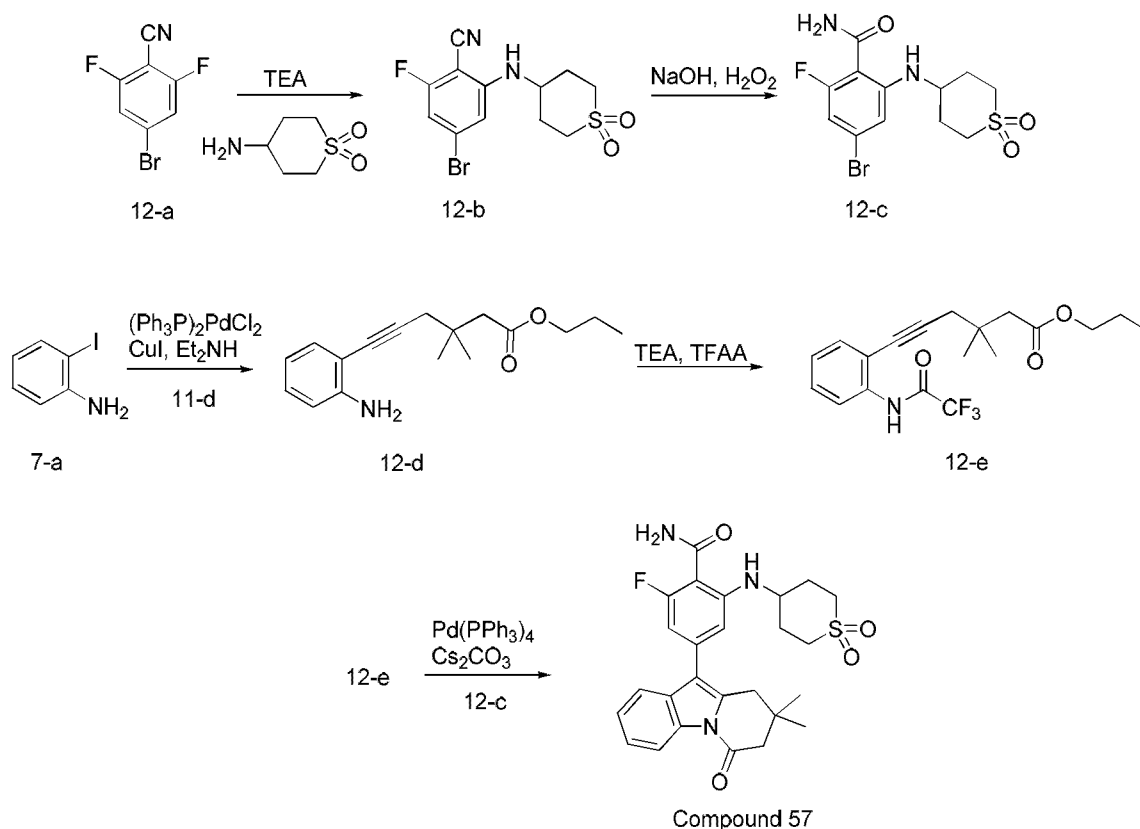
Step 6: 11-h

To a solution of intermediate 11-g (458 mg, 1.18 mmol) in acetonitrile were added intermediate 11-c (443 mg, 1.07 mmol), Cs₂CO₃ (700 mg, 2.14 mmol) and Pd(PPh₃)₄ (37 mg, 0.03 mmol) and the reaction was stirred at 120°C overnight and then cooled to room temperature. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 11-h as a yellow solid. MS (m/z) M+H= 563.4

Step 7: Compound 50

To a solution of intermediate 11-h (600 mg, 1.06 mmol) in DCM (1 mL) cooled to 0°C was added 2,2,2-trifluoroacetic acid (1 mL) and the reaction was then stirred at room temperature for 1 hour. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide compound 50·TFA as an off-white solid. MS (m/z) M+H= 463.4

Synthesis of compound 57



Scheme 12

5 **Step 1: 12-b**

A solution of 4-bromo-2,6-difluorobenzonitrile 12-a (587 mg, 2.69 mmol), 4-aminotetrahydro-2H-thiopyran-1,1-dioxide (500 mg, 2.69 mmol) and TEA (831 uL, 5.92 mmol) in DMSO was stirred at room temperature overnight. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with

10 saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo to provide intermediate 12-b as a white solid.

Step 2: 12-c

To a solution of intermediate 12-b (950 mg, 2.74 mmol) in DMSO (15.0 mL) and MeOH (15 mL) were sequentially added NaOH 1N (2.74 mL) and 30% aqueous hydrogen

15

peroxide (419 μ L, 4.10 mmol) and the reaction was stirred at room temperature for 1 hour. Saturated aqueous ammonium chloride and ethyl acetate were added, the organic layer was separated, the aqueous phase was extracted with ethyl acetate, the combined organic extracts were washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo to provide intermediate 12-c as a white solid.

Step 3: 12-d

To a solution of 2-iodoaniline 7-a (14.54 g, 66.4 mmol) in DMF cooled to 0°C were sequentially added diethylamine (12.61 mL, 121.0 mmol), copper(I) iodide (460 mg, 2.41 mmol) and dichlorobis(triphenylphosphine) palladium (II) (847 mg, 1.20 mmol). After complete dissolution of copper(I)iodide, propyl 3,3-dimethylhex-5-ynoate (11.0 g, 60.4 mmol) was added dropwise at 0°C and the reaction was then stirred at room temperature overnight. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 12-d as a yellow oil. MS (m/z) $\text{M}+\text{H}=274.2$

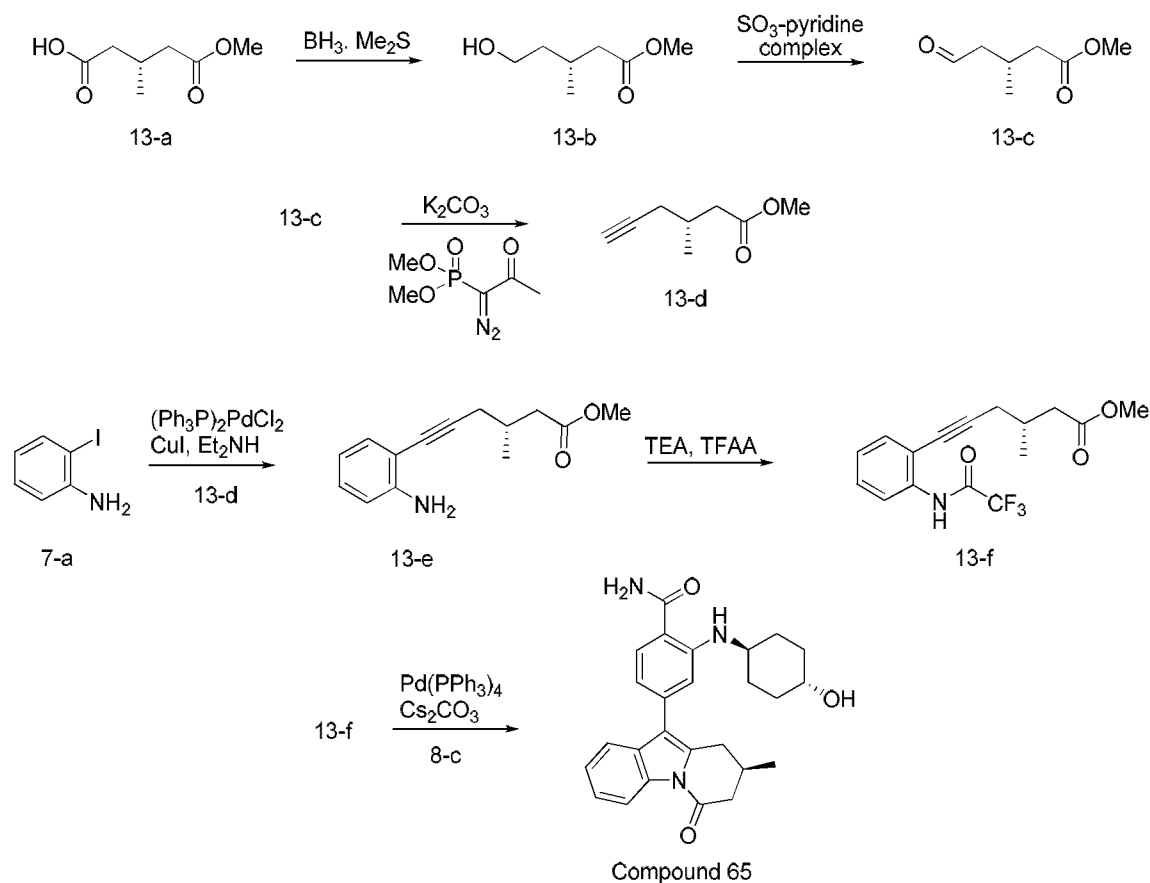
Step 4: 12-e

To a solution of intermediate 12-d (7.10 g, 26.0 mmol) in DCM cooled to 0°C were sequentially added DIPEA (18.14 mL, 104.0 mmol) and TFAA (8.07 mL, 51.1 mmol) and the reaction was then stirred at room temperature for 4 hours. Water and ethylacetate were added; the organic layer was separated, washed with 10% citric acid, saturated aqueous NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 12-e as colorless oil. MS (m/z) $\text{M}+\text{H}=370.5$

Step 5: Compound 57

To a solution of intermediate 12-e (223 mg, 0.60 mmol) in acetonitrile were added intermediate 12-c (200 mg, 0.54 mmol), Cs₂CO₃ (357 mg, 1.09 mmol) and Pd(PPh₃)₄ (19 mg, 0.01 mmol) and the reaction was stirred at 110°C overnight and then cooled to room temperature. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 57 as a yellow solid. MS (m/z) M+H= 498.4

Synthesis of compound 65



Scheme 13

Step 1: 13-b

To a solution of (R)-5-methoxy-3-methyl-5-oxopentanoic acid (1.0 g, 6.24 mmol) in THF, cooled to -15°C, was added a 1N THF solution of borane-methyl sulfide complex (624 uL, 6.24 mmol) and the reaction was stirred at room temperature overnight. Water and ethyl acetate were added; the organic layer was separated, washed with 10% citric acid, saturated aqueous NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 13-b as colorless oil.

Step 2: 13-c

To a solution of intermediate 13-b (900 mg, 6.16 mmol) in DCM cooled to 0°C were sequentially added DMSO (1.96 mL, 27.7 mmol), DIPEA (4.29 mL, 24.63 mmol) and pyridine-SO₃ complex (2.94 g, 18.47 mmol) in DMSO (2 mL) and the reaction was stirred at 0°C for 2 hours. Diethyl ether and saturated aqueous ammonium chloride were added; the organic layer was separated, washed with 1N HCl, saturated aqueous NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 13-c as colorless oil.

Step 3: 13-d

To a solution of intermediate 13-c (880 mg, 6.10 mmol) in MeOH cooled to 0°C were sequentially added dimethyl 1-diazo-2-oxopropylphosphonate (2.34 g, 12.21 mmol) and K₂CO₃ (2.10 g, 15.26 mmol) and the reaction was stirred at room temperature overnight. Ether and saturated aqueous ammonium chloride were added; the organic layer was separated, washed with saturated aqueous NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 13-d as colorless oil.

Step 4: 13-e

To a solution of 2-iodoaniline 7-a (1.07 g, 4.89 mmol) in DMF cooled to 0°C were sequentially added diethylamine (561 uL, 5.38 mmol), copper(I) iodide (37 mg, 0.19 mmol)

and intermediate 13-d (720 mg, 5.14 mmol). After complete dissolution of Copper (I) iodide, dichlorobis(triphenylphosphine) palladium (II) (69 mg, 0.09 mmol) was added and the reaction was then stirred at room temperature for 2 days. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and
5 brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 13-e as a yellow oil. MS (m/z) $\text{M}+\text{H}=232.1$

Step 5: 13-f

To a solution of intermediate 13-e (600 mg, 2.59 mmol) in DCM cooled to 0°C were
10 sequentially added TEA (723 μL , 5.19 mmol) and TFAA (550 μL , 3.89 mmol) and the reaction was then stirred at room temperature for 1 hour. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo to provide intermediate 13-f as yellow oil.

Step 6: Compound 65

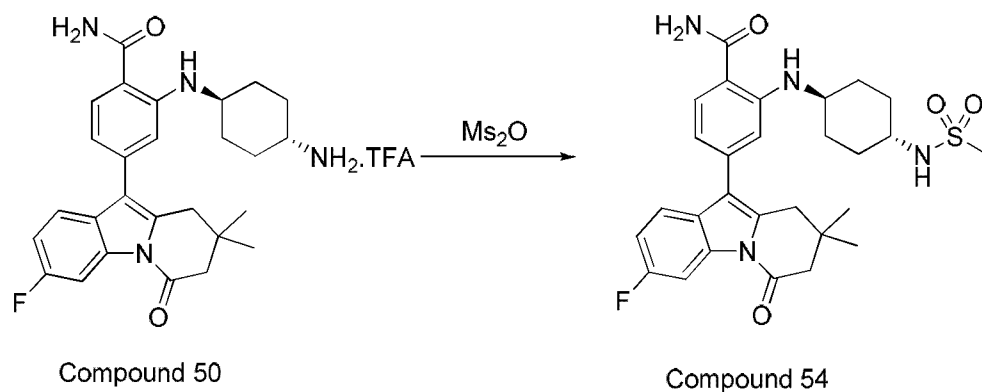
To a solution of intermediate 13-f (274 mg, 0.83 mmol) in acetonitrile were added intermediate 8-c (250 mg, 0.79 mmol), Cs_2CO_3 (520 mg, 1.59 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (28 mg, 0.02 mmol) and the reaction was stirred at 120°C overnight and then cooled to room
20 temperature. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 65 as a yellow solid. MS (m/z) $\text{M}+\text{H}=432.4$

Synthesis of compound 67

Step 1: 14-a

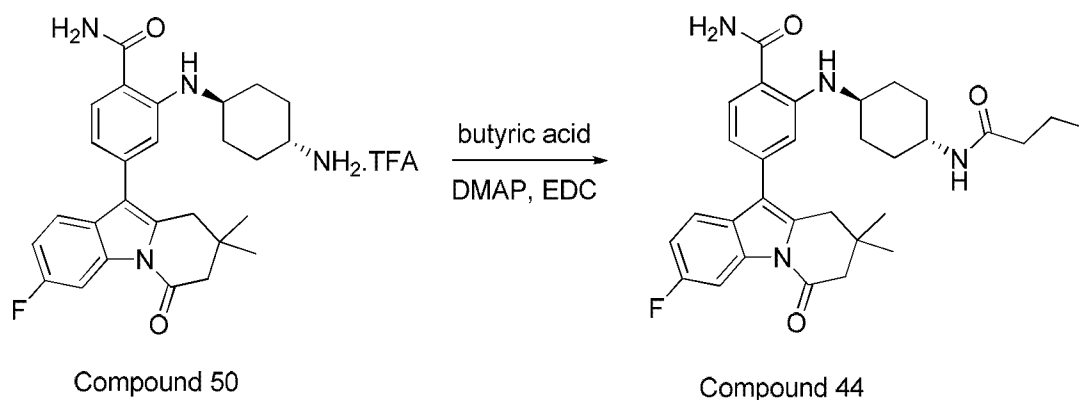
Step 2: Compound 67

- 54 -

Synthesis of compound 54**Scheme 15**

To a solution of compound 50·TFA (100 mg, 0.17 mmol) in DCM were sequentially added TEA (100 μL , 0.72 mmol) and methanesulfonic anhydride (33 mg) and the reaction was stirred for 2 hours. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with saturated NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Diethyl ether was added to the residue and compound 54 was isolated by filtration. MS (m/z) $\text{M}+\text{H}^+= 541.4$

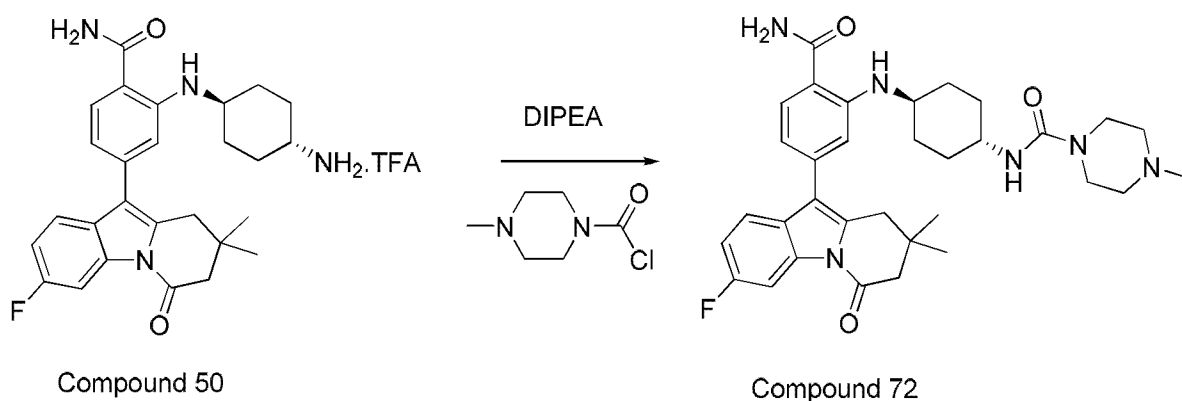
Synthesis of compound 44



Scheme 16

To a solution of compound 50·TFA (200 mg, 0.34 mmol) in DCM were sequentially
5 added butyric acid (61 mg, 0.69 mmol), DMAP (4 mg) and EDC (133 mg, 0.69 mmol) and
the reaction was then stirred at room temperature overnight. Saturated aqueous ammonium
chloride and ethyl acetate were added; the organic layer was separated, washed with
saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in
vacuo. Purification by silica gel chromatography provided compound 44 as a white solid. MS
10 (m/z) M+H= 533.4

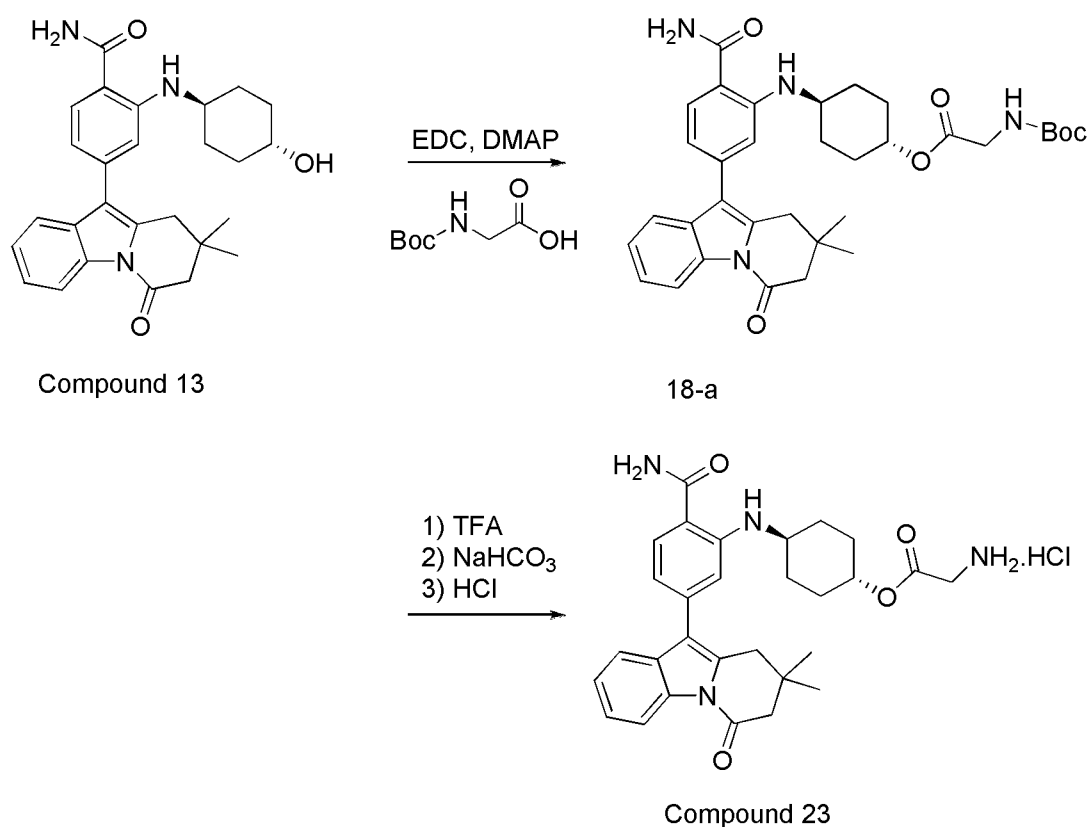
Synthesis of compound 72



Scheme 17

To a solution of compound 50-TFA (100 mg, 0.17 mmol) in DCM were sequentially added 4-methylpiperazine-1-carbonyl chloride (69 mg, 0.35 mmol) and DIPEA (121 μ L, 0.69 mmol) and the reaction was then stirred at room temperature overnight. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with saturated NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. The residue was dissolved in 1N HCl, ethyl acetate was added, the aqueous layer was separated and the PH was adjusted to 10 with aqueous NaHCO_3 . Compound 72 was collected by filtration as a white solid. MS (m/z) M+H= 589.5

Synthesis of compound 23



Scheme 18

Step 1: 18-a

To a solution of Boc-Gly-OH (1.99 g, 11.38 mmol) in DCM cooled to 0°C were sequentially added EDC (2.34 g, 12.25 mmol), DMAP (53 mg, 0.43 mmol) and compound 13 (3.9 g, 8.75 mmol) and the reaction was then stirred overnight at room temperature. Water and ethyl acetate were added; the organic layer was separated, washed with 10% citric acid, saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 18-a as an off white solid.

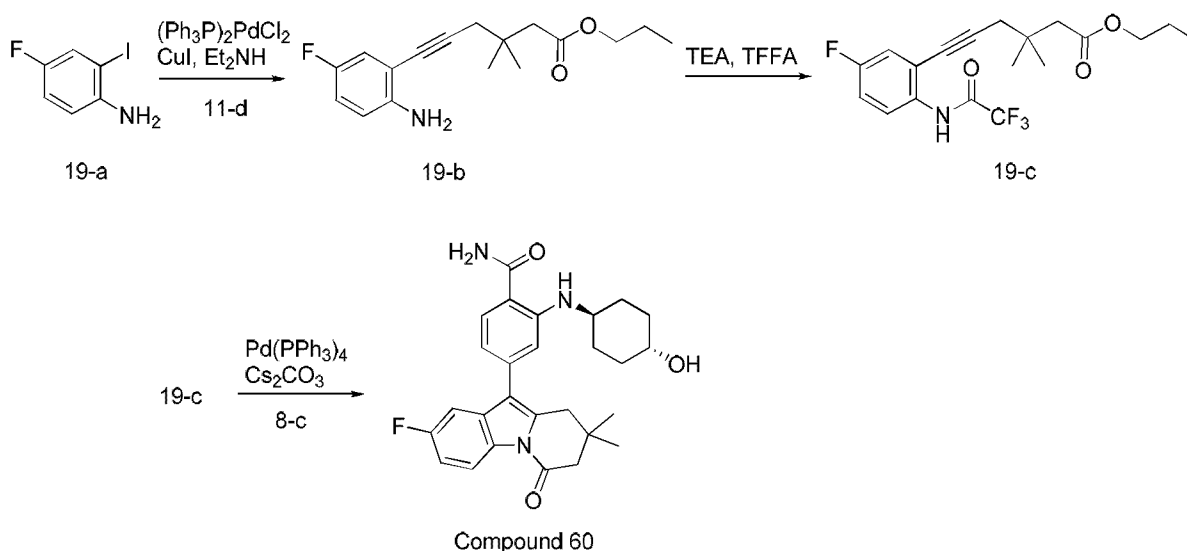
Step 2: Compound 23

To a solution of intermediate 18-a (2.0 g, 3.32 mmol) in DCM (7.70 mL) was added 2,2,2-trifluoroacetic acid (7.70 mL) and the reaction was then stirred at room temperature for 1 hour. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide compound 23·TFA as a white solid. MS (m/z) M+H= 503.5

A suspension of compound 23·TFA (2.05 g, 3.32 mmol) in ethyl acetate was washed twice with saturated aqueous NaHCO₃ and brine. The organic layer was separated, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide compound 23 as a white solid. MS (m/z) M+H= 503.5

To a solution of compound 23 (1.67g, 3.32 mmol) in 1,4-dioxane was added 4N HCl in 1,4-dioxane (2.49 mL, 9.97 mmol) and the solution was stirred for 10 minutes at room temperature. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide compound 23·HCl as a white solid. MS (m/z) M+H= 503.5

Synthesis of compound 60



Scheme 19

Step 1: 19-b

To a solution of 4-fluoro-2-iodoaniline 19-a (1.50 g, 6.33 mmol) in DMF cooled to 0°C were sequentially added diethylamine (2.5 mL, 6.33 mmol), copper(I) iodide (241 mg, 1.26 mmol) and dichlorobis(triphenylphosphine) palladium (II) (444 mg, 0.63 mmol). After complete dissolution of copper(I)iodide, propyl 3,3-dimethylhex-5-ynoate (1.26 g, 6.96 mmol) was added dropwise at 0°C and the reaction was then stirred at room temperature overnight. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 19-b as a yellow oil. MS (m/z) M+H=292.4

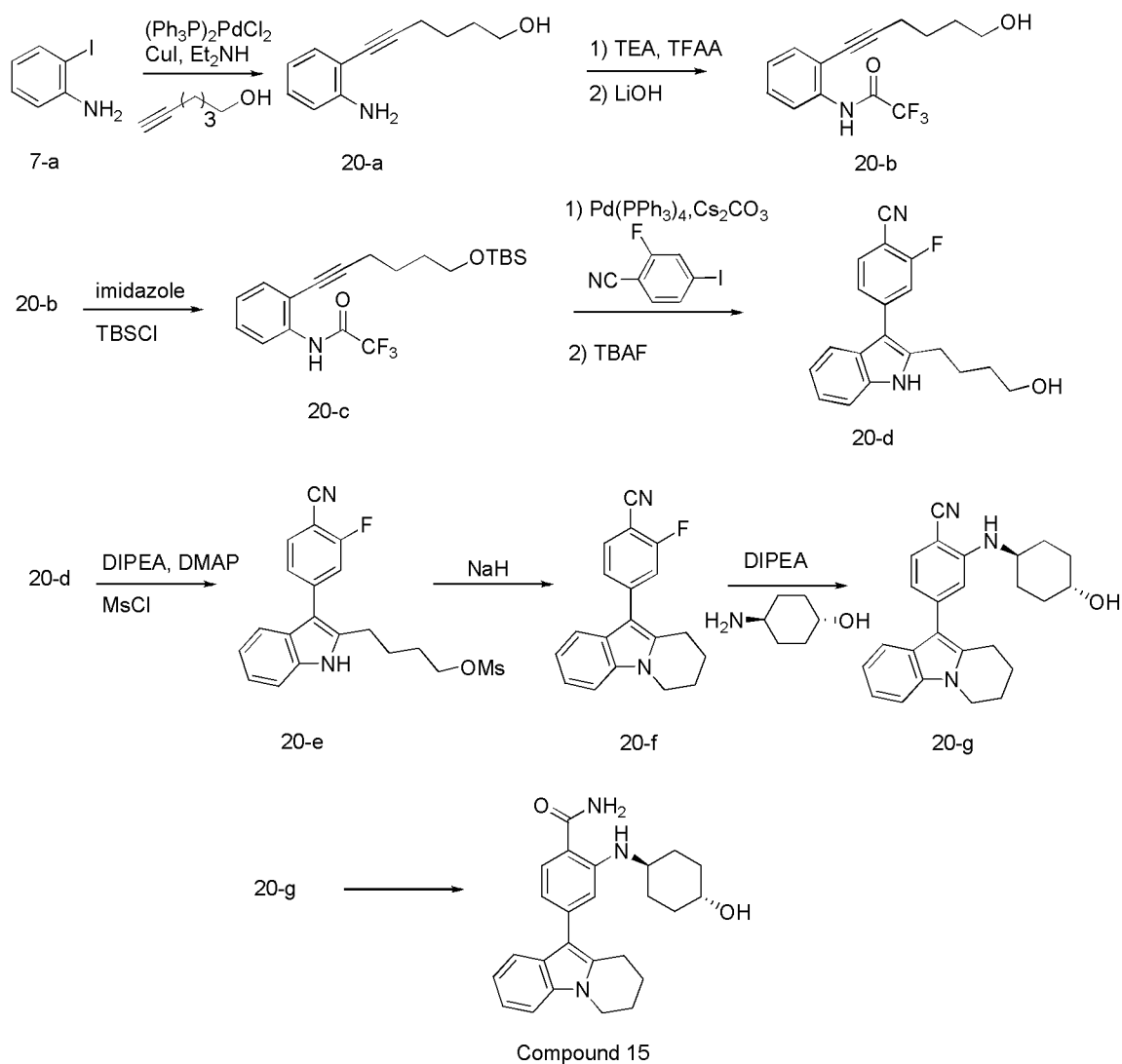
Step 2: 19-c

To a solution of intermediate 19-b (1.84 g, 6.33 mmol) in DCM cooled to 0°C were sequentially added DIPEA (4.42 mL, 25.3 mmol), DMAP (39 mg, 0.31 mmol) and TFAA (1.96 mL, 13.92 mmol) and the reaction was then stirred at room temperature for 1 hour. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 19-c as a yellow oil.

Step 3: Compound 60

To a solution of intermediate 19-c (2.0 g, 5.16 mmol) in acetonitrile were added intermediate 8-c (1.54 g, 4.92 mmol), Cs₂CO₃ (2.40 g, 7.38 mmol) and Pd(PPh₃)₄ (170 mg, 0.15 mmol) and the reaction was stirred at 120°C overnight and then cooled to room temperature. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 60 as a white solid. MS (m/z) M+H=464.4

Synthesis of Compound 15



Scheme 20

Step 1: 20-a

5 To a solution of 2-iodoaniline 7-a (5.0 g, 22.83 mmol) in DMF cooled to 0°C were sequentially added diethylamine (1.0 mL, 35.7 mmol), copper(I) iodide (870 mg, 4.57 mmol) and dichlorobis(triphenylphosphine) palladium (II) (1.60 g, 2.28 mmol). After complete

10 dissolution of copper(I)iodide, 5-hexyne-1-ol (2.80 mL, 25.1 mmol) was added dropwise at 0°C and the reaction was then stirred at room temperature for 1 hour. Water and ethyl acetate were added; the organic layer was separated, washed with 10% aqueous citric acid, saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo.

Purification by silica gel chromatography provided intermediate 20-a as a white solid. MS (m/z) M+H=190.1

Step 2: 20-b

5 To a solution of intermediate 20-a (3.60 g, 19.0 mmol) in DCM cooled to 0°C were sequentially added DIPEA (13.29 mL, 76.0 mmol), DMAP (116 mg, 0.95 mmol) and TFAA (5.91 mL, 41.8 mmol) and the reaction was then stirred at room temperature overnight. Water and ethyl acetate were added; the organic layer was separated, washed with 10% citric acid, saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in
10 vacuo. The residue was dissolved in MeOH (20.0 mL), the solution was cooled to 0°C, 1N LiOH in MeOH (0.5 mL) was added and the reaction was then stirred at room temperature for 4 hours. Water and ethyl acetate were added; the organic layer was separated, washed with 10% aqueous citric acid, saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide intermediate 20-b as a yellow oil. MS (m/z)
15 M+H=286.6

Step 3: 20-c

To a solution of intermediate 20-b (3.63 g, 12.73 mmol) in DCM cooled to 0°C were sequentially added imidazole (1.04 g, 15.27 mmol) and *tert*-butylchlorodimethylsilane (2.11
20 g, 14.0 mmol) and the reaction was then stirred at room temperature overnight. Water and ethyl acetate were added; the organic layer was separated, washed with 10% citric acid, saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 20-c as a yellow oil.

25 Step 4: 20-d

To a solution of intermediate 20-c (2.50 g, 6.26 mmol) in acetonitrile were added intermediate 4-bromo-2-fluorobenzonitrile (1.87 g, 9.39 mmol), Cs₂CO₃ (3.06 g, 9.39 mmol) and Pd(PPh₃)₄ (362 mg, 0.31 mmol) and the reaction was stirred at 100°C overnight and then

cooled to room temperature. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. The residue was dissolved in THF (20.0 mL), the solution was cooled to 0°C , 1N tetrabutylammonium fluoride in THF (20 mL, 20 mmol) was added and the reaction was then stirred at room temperature for 1 hour. Water and ethyl acetate were added; the organic layer was separated, washed with 10% aqueous citric acid, saturated NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 20-d as a white solid.

Step 5: 20-e

To a solution of intermediate 20-d (1.0 g, 3.24 mmol) in DCM cooled to 0°C were sequentially added DIPEA (1.69 mL, 9.73 mmol), DMAP (20 mg, 0.16 mmol) and methanesulfonyl chloride (278 μL , 3.57 mmol) and the reaction was then stirred at room temperature overnight. Water and ethyl acetate were added; the organic layer was separated, washed with 10% citric acid, saturated NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 20-e as a white solid.

Step 6: 20-f

To a solution of intermediate 20-e (200 mg, 0.51 mmol) in DMF cooled to 0°C was added sodium hydride (20.70 mg, 0.51 mmol) and the reaction was then stirred at room temperature for 1 hour. Water was added and after stirring for 30 minutes intermediate 20-f was collected by filtration as a tan solid.

Step 7: 20-g

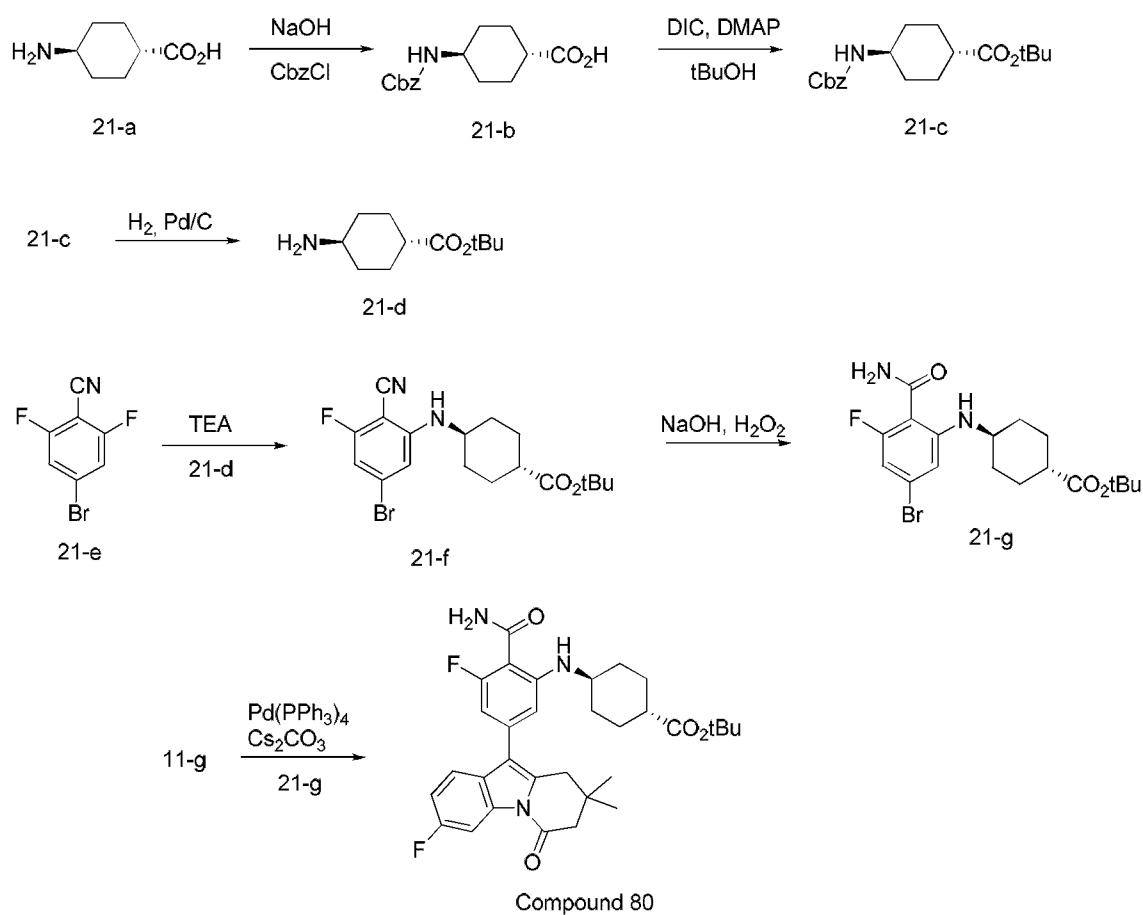
To a solution of intermediate 20-f (127 mg, 0.43 mmol) in DMSO were sequentially added DIPEA (382 μL , 2.18 mmol) and trans-4-aminocyclohexanol (202 mg, 1.75 mmol)

and the mixture was then heated at 100°C for 18 hours and then cooled to room temperature. Water and ethyl acetate were added, the organic layer was separated, washed with saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 20-g as a white solid. MS (m/z) M+H=386.5

Step 8: Compound 15

To a solution of intermediate 20-g (40 mg, 0.10 mmol) in DMSO were sequentially added K₂CO₃ (28.7 mg, 0.20 mmol) and 30% aqueous hydrogen peroxide (0.40 mL, 3.92 mmol) and the reaction was stirred at room temperature for 1 hour. Water and ethyl acetate were added; the organic layer was separated, washed with saturated ammonium chloride, 10% aqueous Na₂S₂O₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 15 as a beige solid. MS (m/z) M+H= 404.4

Synthesis of compound 80



Scheme 21

Step 1: 21-b

5 To a solution of (1r,4r)-4-aminocyclohexanecarboxylic acid (2.0 g, 13.97 mmol) in 2N NaOH (14 mL) was added dropwise benzyl chloroformate (2.12 mL, 14.88 mmol) and the reaction was then stirred at room temperature for 1.5 hours. The mixture was acidified to PH=3 with 1N HCl and then diluted with water. Intermediate 21-b was collected by filtration as a white solid.

10

Step 2: 21-c

To a solution of intermediate 21-b (2.0 g, 7.21 mmol) in DMF were sequentially added tBuOH (2.76 mL, 28.8 mmol), DMAP (352 mg, 2.88 mmol) and 1,3-diisopropylcarbodiimide (2.48 mL, 15.87 mmol) and the reaction was stirred at room

temperature for 4 days. Water and ethyl acetate were added; the organic layer was separated, washed with 10% citric acid, saturated NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 21-c as a white solid.

5

Step 3: 21-d

To a solution of intermediate 21-c (1.2 g, 3.60 mmol) in MeOH and stirred under N_2 was added 10% Pd/C (38 mg). The reaction mixture was purged with H_2 and stirred for 2 hours. The reaction was then filtered through celite and the filtrate was concentrated in vacuo to provide intermediate 21-d as a white solid. MS (m/z) $\text{M}+\text{H}= 200.0$

10

Step 4: 21-f

To a suspension of intermediate 21-d (357 mg, 1.79 mmol) and 4-bromo-2,6-difluorobenzonitrile (391 mg, 1.79 mmol) in DMSO was added TEA (553 μL , 3.94 mmol) and the reaction was then stirred at room temperature for 2 days. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 21-f as a white solid.

15

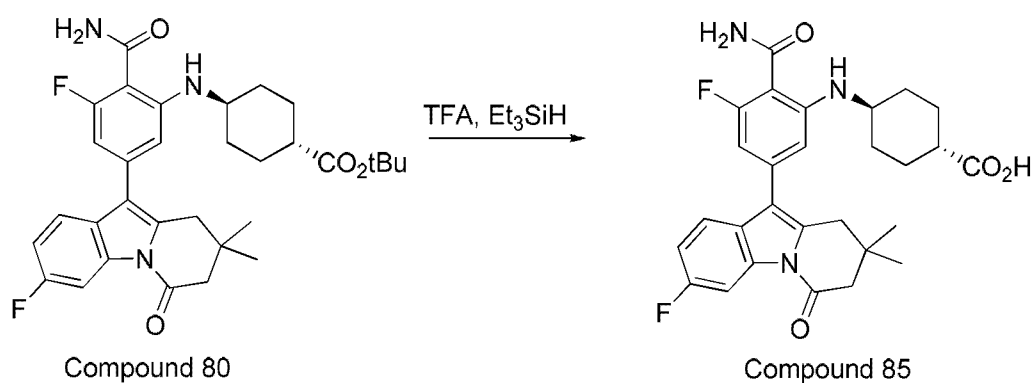
Step 5: 21-g

To a solution of intermediate 21-f (700 mg, 1.76 mmol) in DMSO (7 mL) and MeOH (7 mL) were sequentially added NaOH 1N (1.76 mL, 1.76 mmol) and 30% aqueous hydrogen peroxide (270 μL , 2.64 mmol) and the reaction was stirred at room temperature for 1 hour. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 21-g as a white solid. MS (m/z) $\text{M}+\text{H}= 416.8$

25

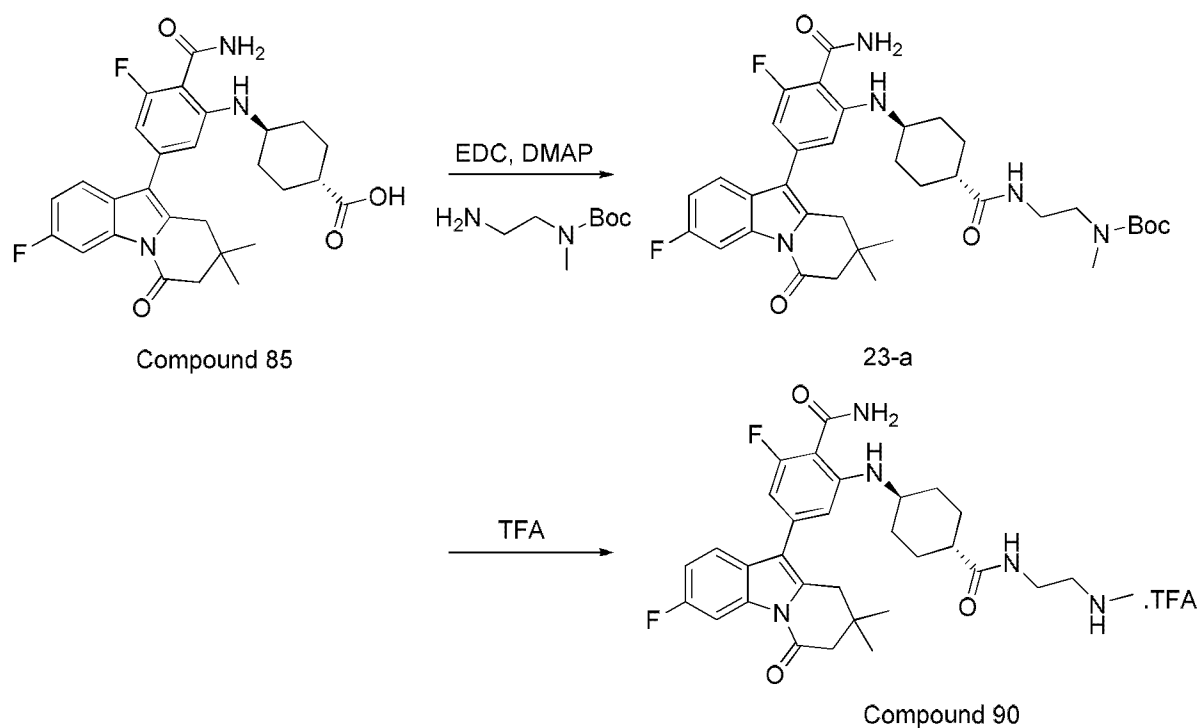
Step 6: Compound 80

To a solution of intermediate 11-g (585 mg, 1.51 mmol) in acetonitrile were added intermediate 21-g (570 mg, 1.37 mmol), Cs₂CO₃ (894 mg, 2.75 mmol) and Pd (PPh₃)₄ (48 mg, 0.04 mmol) and the reaction was stirred at 120°C overnight and then cooled to room temperature. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 80 as a yellow solid. MS (m/z) M+H= 566.4

Synthesis of compound 85**Scheme 22**

To a solution of Compound 80 (23 mg, 0.04 mmol) in DCM (1 mL) was added 2,2,2-trifluoroacetic acid (1 mL) and the reaction was then stirred at room temperature for 1 hour. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide compound 85 as a white solid. MS (m/z) M+H= 510.3

Synthesis of compound 90



Scheme 23

5 **Step 1: 23-a**

To a solution of Compound 85 (80 mg, 0.16 mmol) in DCM cooled to 0°C were sequentially added EDC (45 mg, 0.23 mmol), DMAP (1.9 mg, 0.01 mmol) and tert-butyl-2-aminoethyl(methyl)carbamate (55 mg, 0.31 mmol) and the reaction was then stirred overnight at room temperature. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 23-a as a white solid.

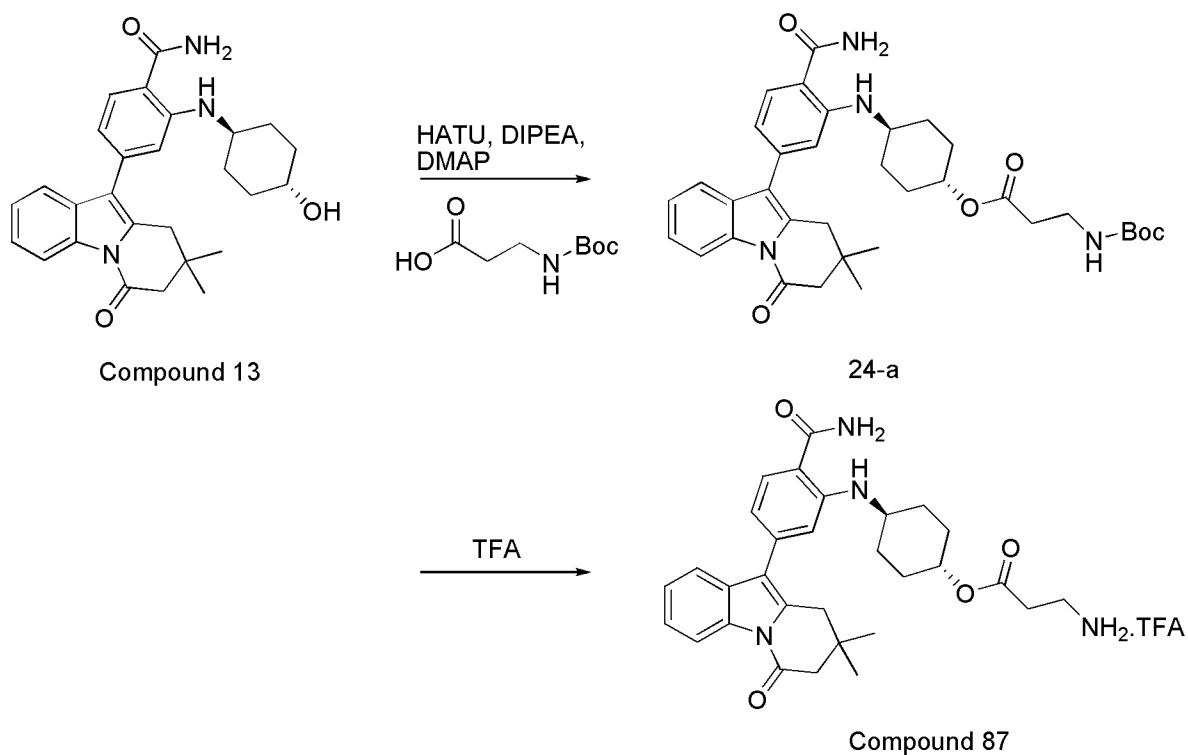
Step 2: Compound 90

15 To a solution of intermediate 23-a (60 mg, 0.09 mmol) in DCM (1 mL) was added 2,2,2-trifluoroacetic acid (1 mL) and the reaction was then stirred at room temperature for 1

hour. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide compound 90·TFA as a white solid. MS (m/z) M+H= 566.4

Synthesis of compound 87

5



Scheme 24

10

Step 1: 24-a

To a solution of Boc-β-Ala-OH (93 mg, 0.49 mmol) in DMF cooled to 0°C were sequentially added HATU (188 mg, 0.49 mmol), DIPEA (314 uL, 1.79 mmol), DMAP (catalytic) and compound 13 (200 mg, 0.44 mmol) and the reaction was then stirred for 4 hours at room temperature. Water and ethyl acetate were added; the organic layer was separated, washed with saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered

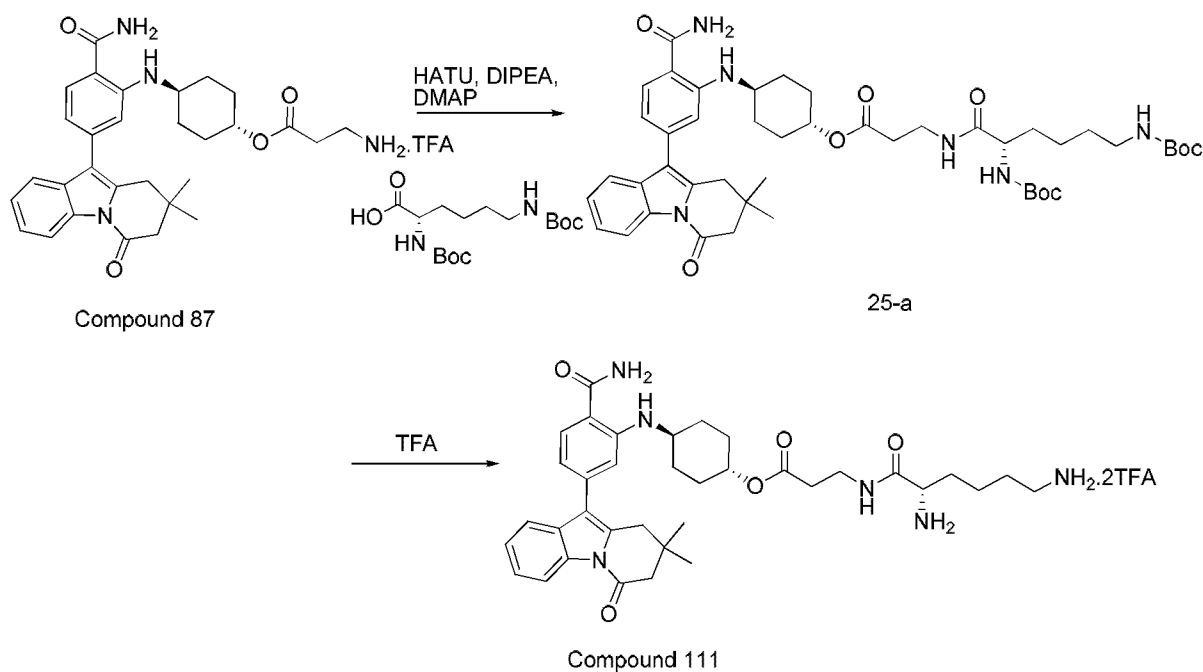
15

and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 24-a as an off white solid.

Step 2: Compound 87

To a solution of intermediate 24-a (200 mg, 0.32 mmol) in DCM (2 mL) was added 2,2,2-trifluoroacetic acid (2 mL) and the reaction was then stirred at room temperature for 1 hour. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide compound 87·TFA as a white solid. MS (m/z) M+H= 517.5

Synthesis of compound 111



Scheme 25

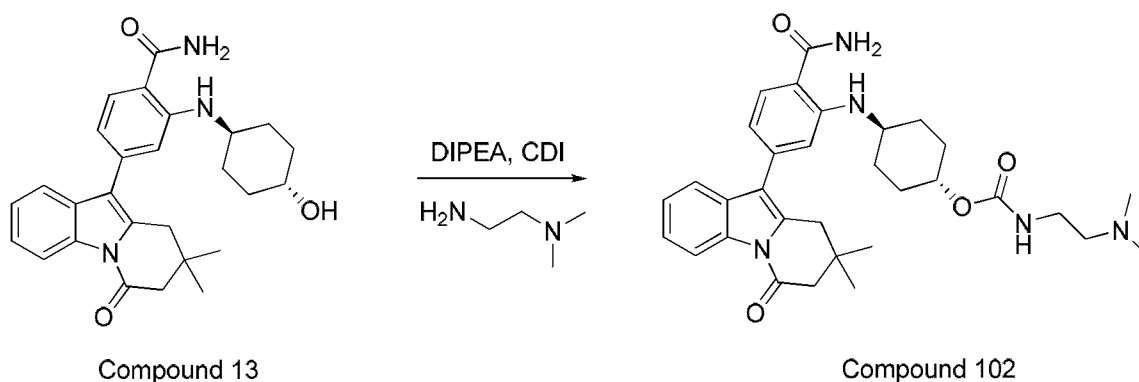
Step 1: 25-a

To a solution of Boc-Lys(Boc)-OH (327 mg, 0.94 mmol) in DMF cooled to 0°C were sequentially added HOBt (19.2 mg, 0.12 mmol), HBTU (310 mg, 0.82 mmol) and DIPEA (220 μ L, 1.25 mmol). After stirring for 10 minutes, compound 87-TFA (325 mg, 0.63 mmol) was added and the reaction was then stirred overnight at room temperature. Water and ethyl acetate were added; the organic layer was separated, washed with saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 25-a as an off white solid.

Step 2: Compound 111

To a solution of intermediate 25-a (516 mg, 0.61 mmol) in DCM (2 mL) was added 2,2,2-trifluoroacetic acid (2 mL) and the reaction was then stirred at room temperature for 1 hour. Volatiles were removed under reduced pressure and the residue was triturated with diethyl ether to provide compound 111-TFA as a white solid. MS (m/z) M+H= 645.5

Synthesis of compound 102



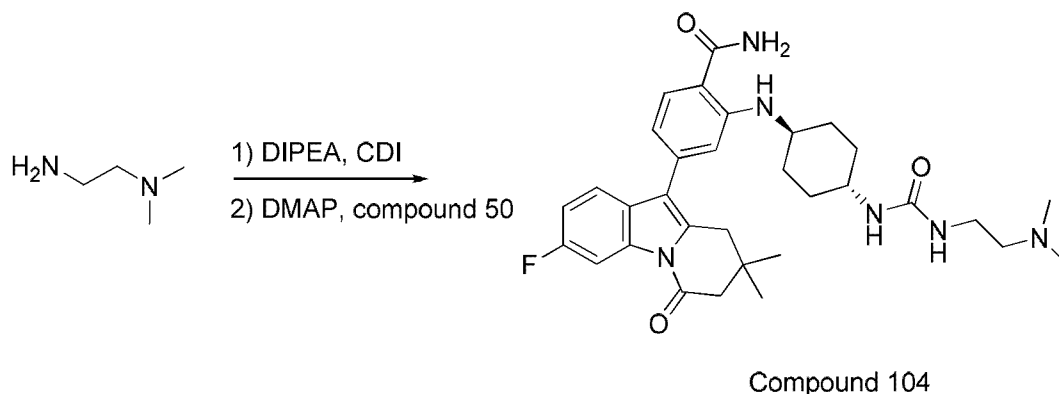
Scheme 26

To a solution of compound 13 (4.0 g, 8.98 mmol) in THF were sequentially added DIPEA (4.70 mL, 26.9 mmol) and 1,1'-carbonyldiimidazole (2.91 g, 17.96 mmol) and the reaction was stirred at 55°C for 3 hours. N,N-dimethylethylenediamine (4.90 mL, 44.9 mmol) was then added, the reaction was stirred at 55°C for 4 hours and at room temperature

overnight. Water and ethyl acetate were added; the organic layer was separated, washed with saturated NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Methanol was added to the residue and compound 102 was isolated by filtration as a white solid. MS (m/z) $\text{M}+\text{H}= 560.4$

5 To a solution of compound 102 (3.27 g, 5.86 mmol) in CH_2Cl_2 cooled to 0°C was added 1N HCl in diethyl ether (15 mL) and the mixture was stirred for 5 minutes. Volatiles were removed in vacuo, diethyl ether was added to the residue and compound 102-HCl was collected by filtration as a white solid. MS (m/z) $\text{M}+\text{H}= 560.4$

10 **Synthesis of compound 104**

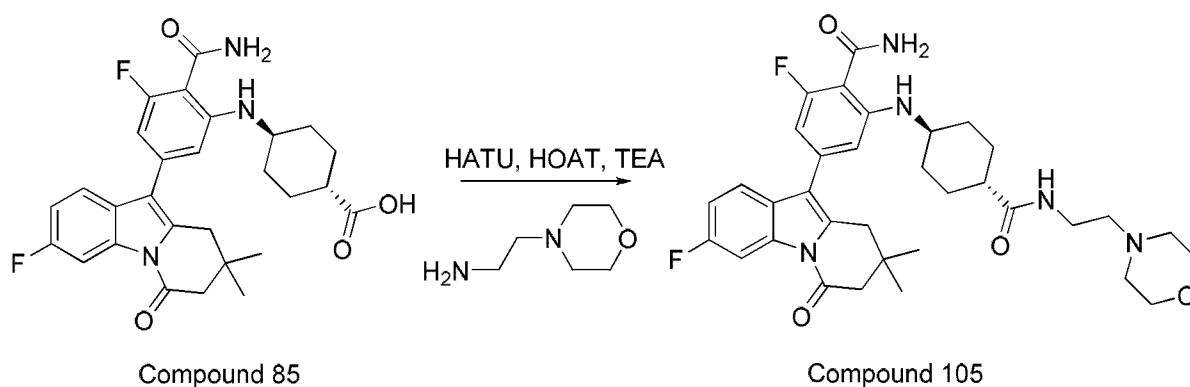


Scheme 27

15 To a solution of N,N-dimethylethylenediamine (22 mg, 0.25 mmol) in THF cooled to 0°C were sequentially added 1,1'-carbonyldiimidazole (3 mg, 0.22 mmol) and DIPEA (9 μL , 0.52 mmol), the reaction was then stirred for 1 hour at 0°C and at room temperature overnight. Compound 50 (100 mg, 0.17 mmol) and DMAP (cat) were then added and the reaction was heated at reflux overnight and then cooled to room temperature. Saturated
20 aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with saturated NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered and

concentrated in vacuo. Purification by silica gel chromatography provided compound 104 as an off-white solid. MS (m/z) M+H=577.5

5 **Synthesis of compound 105**



Scheme 28

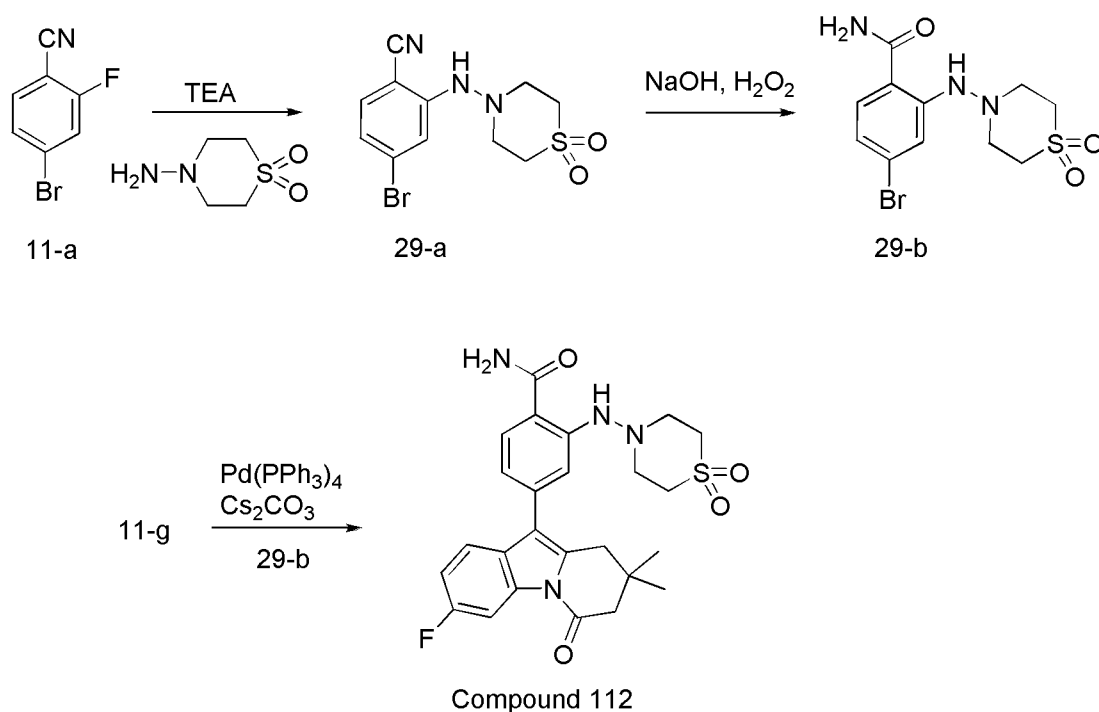
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To a solution of compound 85 (415 mg, 0.81 mmol) in DMF were sequentially added HATU (310 mg, 0.81 mmol), and 2-morpholinoethanamine (212 mg, 1.62 mmol), HOAT (136 μ L, 0.81 mmol) and TEA (454 μ L, 3.26 mmol) and the reaction was then stirred at room for 30 minutes. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with saturated NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo to provide compound 105 as a white solid. MS (m/z) M+H=622.4

15

20

To a solution of compound 105 (503 mg, 0.80 mmol) in CH₂Cl₂ cooled to 0°C was added 1N HCl in diethyl ether (5 mL) and the mixture was stirred for 5 minutes. Volatiles were removed in vacuo, diethyl ether was added to the residue and compound 105·HCl was collected by filtration as a white solid. MS (m/z) M+H= 622.4

Synthesis of compound 112**Scheme 29****Step 1: 29-a**

To a solution of intermediate 11-a (1.65 g, 6.66 mmol) in DMSO were sequentially added TEA (2.80 mL, 19.97 mmol) and 4-aminothiomorpholine 1,1-dioxide (1.0 g, 6.66 mmol) and the mixture was then heated at 130°C for 7 days and then cooled to room temperature. Saturated aqueous ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 29-a as a beige solid.

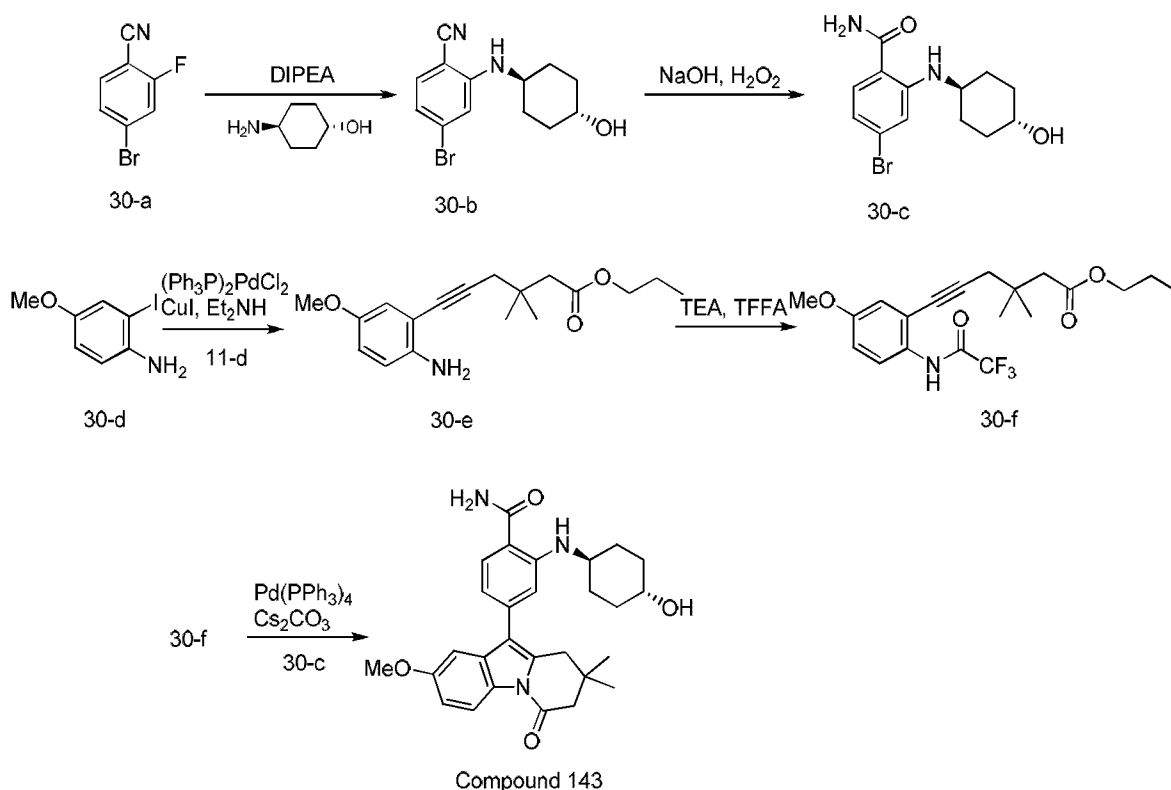
Step 2: 29-b

To a solution of intermediate 29-a (1.10 g, 2.92 mmol) in DMSO (15.0 mL) and MeOH (15 mL) were sequentially added NaOH 1N (2.92 mL, 2.92 mmol) and 30% aqueous hydrogen peroxide (447 μ L, 4.37 mmol) and the reaction was stirred at room temperature for 1 hour. Saturated aqueous ammonium chloride and ethyl acetate were added, the organic
5 layer was separated, the aqueous phase was extracted with ethyl acetate, the combined organic extracts were washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo to provide intermediate 29-b as a white solid. MS (m/z) $\text{M}+\text{H}= 321.5$

Step 3: Compound 112

To a solution of intermediate 11-g (196 mg, 0.51 mmol) in acetonitrile were added intermediate 29-b (200 mg, 0.51 mmol), Cs_2CO_3 (330 mg, 1.0 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (29 mg, 0.02 mmol) and the reaction was stirred at 120°C overnight and then cooled to room temperature. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO_4 , filtered
15 and concentrated in vacuo. Purification by silica gel chromatography provided compound 112 as an off-white solid. MS (m/z) $\text{M}+\text{H}= 499.4$

Synthesis of compound 143



Scheme 30

5 Step 1: 30-b

A solution of intermediate 4-bromo-2-fluorobenzonitrile 30-a (25.0 g, 125.0 mmol), trans-4-aminocyclohexanol (14.4 g, 125.0 mmol) and TEA (52.3 mL, 375.0 mmol) in DMSO was heated at 150 °C overnight and then cooled to room temperature. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Diethyl ether and hexane were added to the residue and intermediate 30-b was collected by filtration as an off-white solid.

15 Step 2: 30-c

To a solution of intermediate 30-b (31.4 g, 106.0 mmol) in DMSO/MeOH (1:1, 304 mL) was sequentially added NaOH 1N (106.0 mL, 106.0 mmol) and 30% aqueous hydrogen

peroxide (16.30 mL, 160.0 mmol) and the reaction was stirred at room temperature for 1 hour. Saturated aqueous ammonium chloride and ethyl acetate were added, the organic layer was separated, washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo to provide intermediate 30-c an off-white solid.

5 **Step 3: 30-e**

To a solution of 2-iodo-4-methoxyaniline 30-d (1.00 g, 4.02 mmol) in DMF cooled to 0°C were sequentially added diethylamine (419 μL , 4.02 mmol), copper(I) iodide (143 mg, 0.80 mmol) and dichlorobis(triphenylphosphine) palladium (II) (282 mg, 0.40 mmol). After complete dissolution of copper(I)iodide, propyl 3,3-dimethylhex-5-ynoate 11-d (805 mg, 4.42 mmol) was added dropwise at 0°C and the reaction was then stirred at room temperature overnight. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 30-e as a beige oil. MS (m/z) $\text{M}+\text{H}=304.4$

15 **Step 4: 30-f**

To a solution of intermediate 30-e (1.21 g, 4.0 mmol) in DCM cooled to 0°C were sequentially added DIPEA (2.80 mL, 16.06 mmol), DMAP (25 mg, 0.20 mmol) and TFAA (1.24 mL, 8.83 mmol) and the reaction was then stirred at room temperature for 4 hours. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride, saturated aqueous NaHCO_3 and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 30-f as a beige solid.

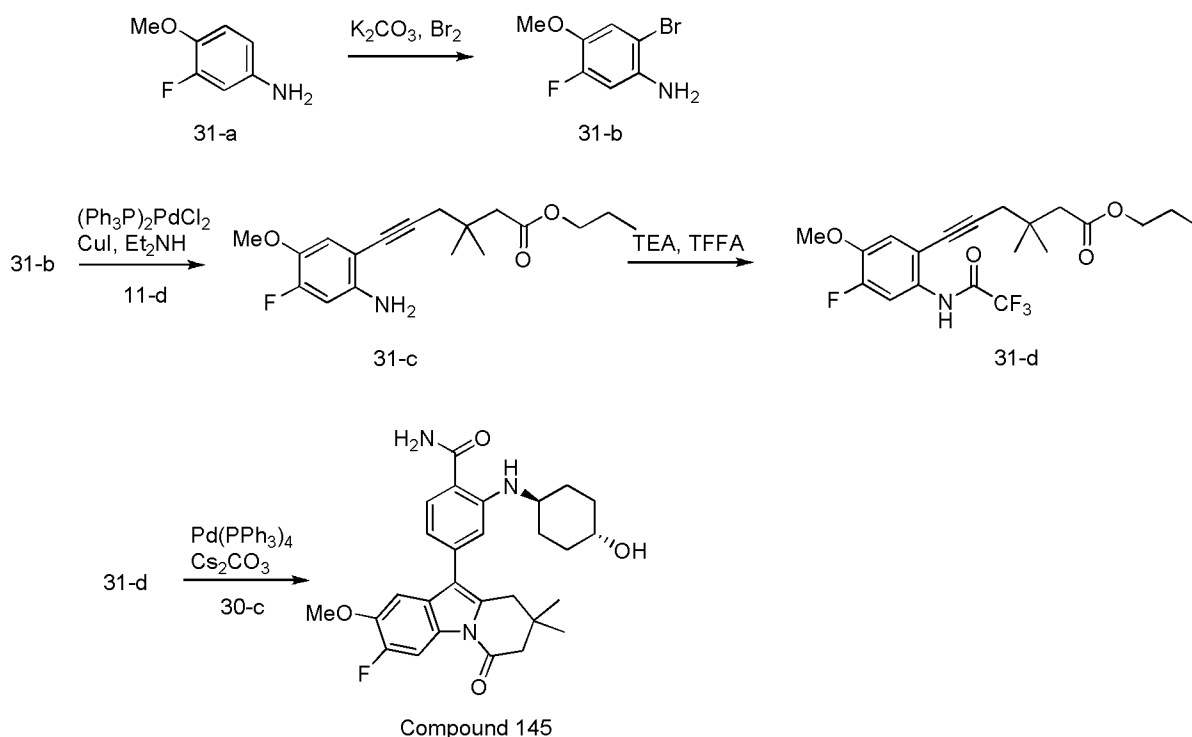
Step 5: Compound 143

25 To a solution of intermediate 30-f (1.10 g, 2.75 mmol) in acetonitrile were added intermediate 30-c (821 mg, 2.62 mmol), Cs_2CO_3 (1.28 g, 3.93 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (91 mg, 0.08 mmol) and the reaction was stirred at 120°C overnight and then cooled to room temperature. Water and ethylacetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride, dried over anhydrous MgSO_4 , filtered and

concentrated in vacuo. Purification by silica gel chromatography provided compound 143 as a white solid. MS (m/z) M+H=476.5

Synthesis of compound 145

5



Scheme 31

Step 1: 31-b

10 A solution of bromine (1.82 mL, 35.4 mmol) in DCM was added dropwise to a suspension of 3-fluoro-4-methoxyaniline (5.0 g, 35.4 mmol) and potassium carbonate (5.14 g, 37.2 mmol) in DCM at -15°C and the reaction was then stirred at -15°C for 30 minutes. Water was added, the organic layer was separated, the aqueous phase was extracted with DCM, the combined organic extracts were washed with brine, dried over anhydrous MgSO₄,
 15 filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 31-b as an orange solid. MS (m/z) M+H=221.7

Step 2: 31-c

To a solution of intermediate 31-b (4.0 g, 18.18 mmol) in DMF cooled to 0°C were sequentially added TEA (36.4 mL), copper(I) iodide (143 mg, 0.80 mmol) and dichlorobis(triphenylphosphine) palladium (II) (282 mg, 0.40 mmol). After complete dissolution of copper(I)iodide, propyl 3,3-dimethylhex-5-ynoate 11-d (3.64 g, 20.0 mmol) was added dropwise at 0°C and the reaction was then stirred at room temperature overnight. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 31-c as a yellow oil. MS (m/z) M+H=322.3

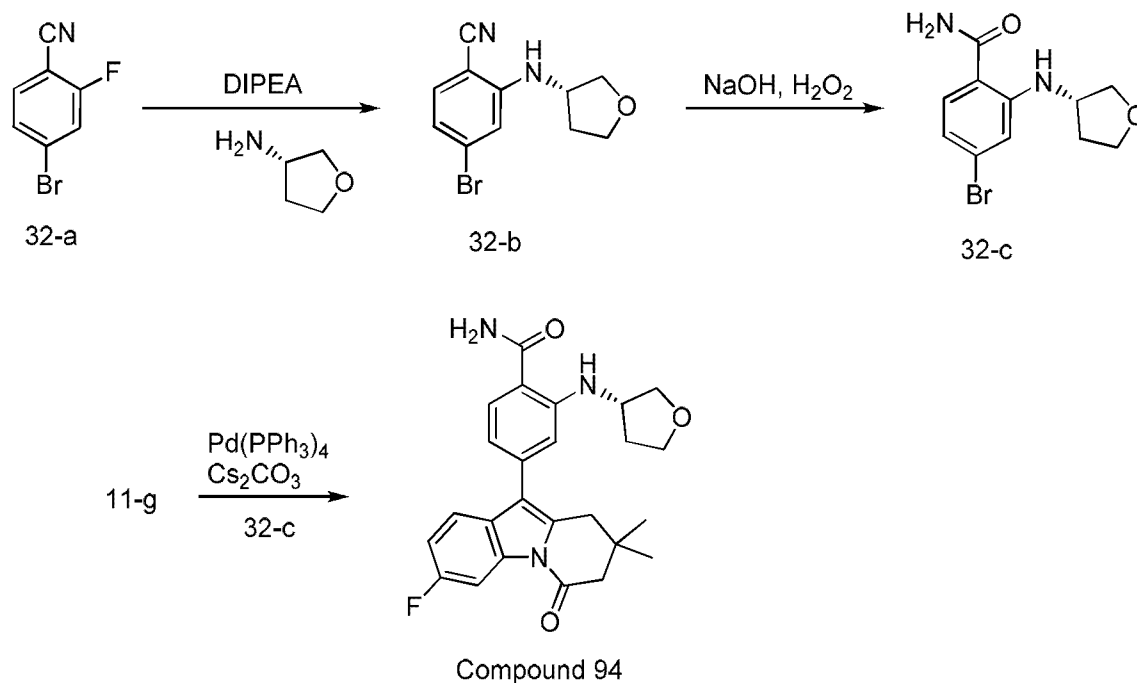
Step 3: 31-d

To a solution of intermediate 31-c (2.60 g, 8.09 mmol) in DCM cooled to 0°C were sequentially added DIPEA (5.65 mL, 32.4 mmol) , DMAP (49 mg, 0.40 mmol) and TFAA (2.51 mL, 17.80 mmol) and the reaction was then stirred at room temperature for 2 hours. Water and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride, saturated aqueous NaHCO₃ and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 31-d as a yellow oil.

Step 5: Compound 143

To a solution of intermediate 31-d (1.00 g, 2.39 mmol) in acetonitrile were added intermediate 30-c (715 mg, 2.28 mmol), Cs₂CO₃ (1.11 g, 3.42 mmol) and Pd(PPh₃)₄ (79 mg, 0.07 mmol) and the reaction was stirred at 120°C overnight and then cooled to room temperature. Water and ethylacetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 145 as a white solid. MS (m/z) M+H=494.4

Synthesis of compound 94



Scheme 32

Step 1: 32-b

A solution of intermediate 4-bromo-2-fluorobenzonitrile 30-a (4.89 g, 24.46 mmol), (s)-3-aminotetrahydrofuran tosylate (6.0 g, 24.46 mmol) and DIPEA (17.09 mL, 98.0 mmol) in DMSO was heated at 100 °C overnight and then cooled to room temperature. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO₄, filtered and concentrated in vacuo. Purification by silica gel chromatography provided intermediate 32-b as an off-white solid.

Step 2: 32-c

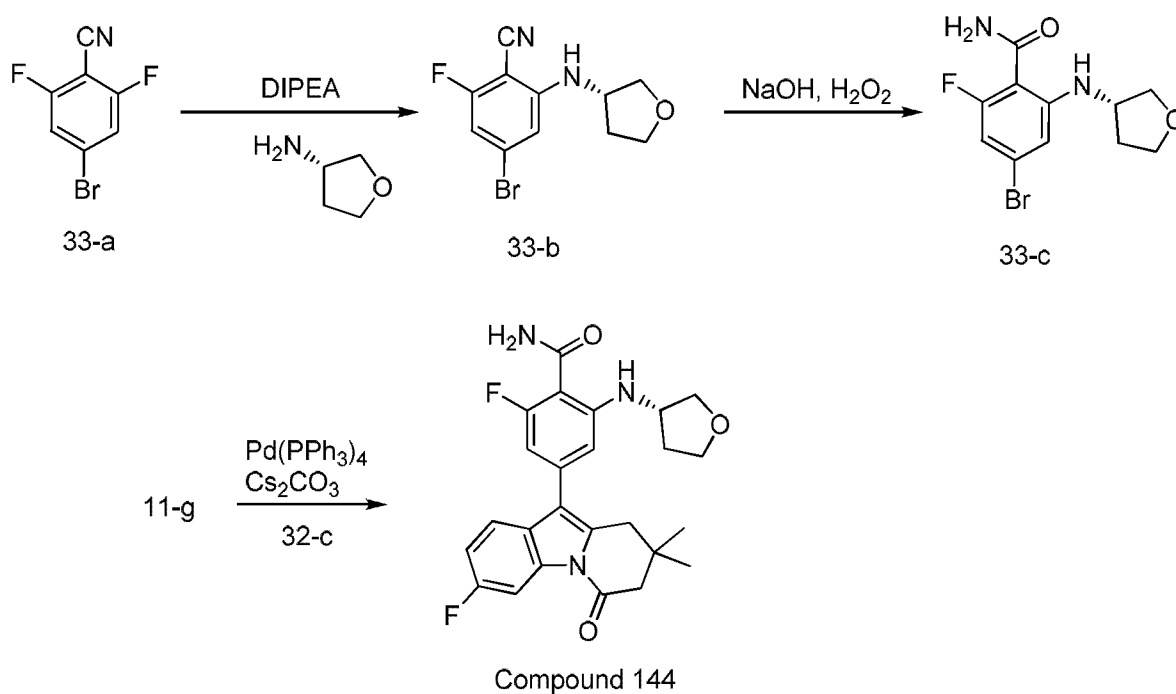
To a solution of intermediate 32-b (4.70 g, 17.59 mmol) in DMSO/MeOH (1:1, 352 mL) was sequentially added NaOH 1N (17.59 mL, 17.59 mmol) and 30% aqueous hydrogen peroxide (1.70 mL, 26.4 mmol) and the reaction was stirred at room temperature for 1 hour. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was

separated, washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo to provide intermediate 32-c as an off-white solid.

Step 3: Compound 94

5 To a solution of intermediate 11-g (3.0 g, 7.74 mmol) in acetonitrile were added intermediate 32-c (2.10 mg, 7.38 mmol), Cs_2CO_3 (4.81 g, 14.75 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (25 mg, 0.22 mmol) and the reaction was stirred at 120°C overnight and then cooled to room temperature. Water and ethylacetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 94 as a
10 pale yellow solid. MS (m/z) $\text{M}+\text{H}=436.8$

Synthesis of compound 144



Scheme 33

Step 1: 33-b

A solution of intermediate 4-bromo-2,6-difluorobenzonitrile 33-a (5.04 g, 23.14 mmol), (s)-3-aminotetrahydrofuran tosylate (6.0 g, 23.14 mmol) and DIPEA (12.12 mL, 69.4 mmol) in DMSO was stirred at room temperature for 2 days. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride and brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Hexane was added and intermediate 33-b was collected by filtration as pale yellow solid.

Step 2: 33-c

To a solution of intermediate 33-b (1.20 g, 4.21 mmol) in DMSO/MeOH (1:1, 84.2 mL) was sequentially added NaOH 1N (4.21 mL, 4.21 mmol) and 30% aqueous hydrogen peroxide (645 μL , 6.31 mmol) and the reaction was stirred at room temperature for 1 hour. Saturated aqueous ammonium chloride and ethyl acetate were added; the organic layer was separated, washed with brine, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Hexane was added and intermediate 33-b was collected by filtration as an off-white solid.

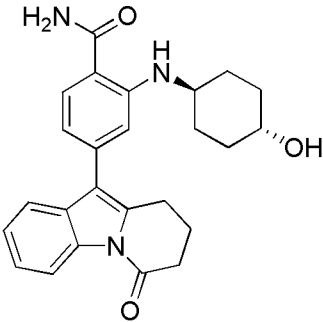
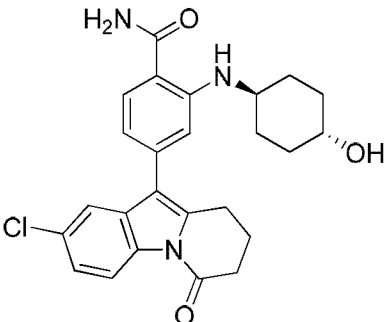
Step 3: Compound 144

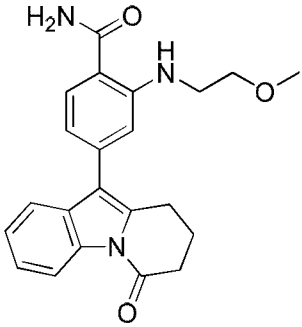
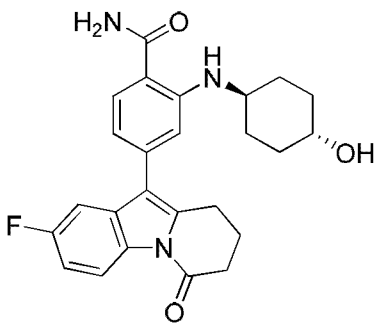
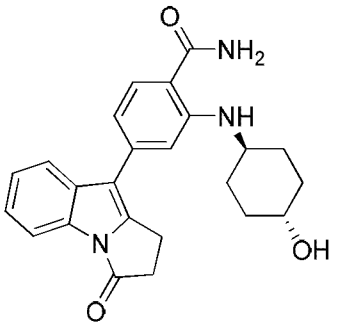
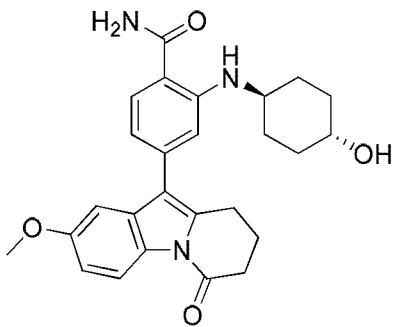
To a solution of intermediate 11-g (671 mg, 1.73 mmol) in acetonitrile were added intermediate 33-c (500 mg, 1.64 mmol), Cs_2CO_3 (1.0 g, 3.30 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (57 mg, 0.049 mmol) and the reaction was stirred at 120°C overnight and then cooled to room temperature. Water and ethylacetate were added; the organic layer was separated, washed with saturated aqueous ammonium chloride, dried over anhydrous MgSO_4 , filtered and concentrated in vacuo. Purification by silica gel chromatography provided compound 144 as an off-white solid. MS (m/z) $\text{M}+\text{H}=454.2$

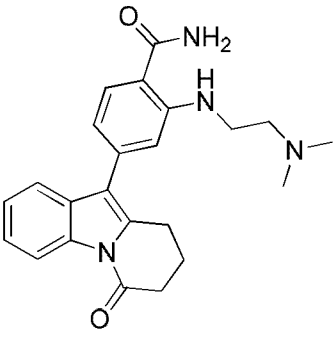
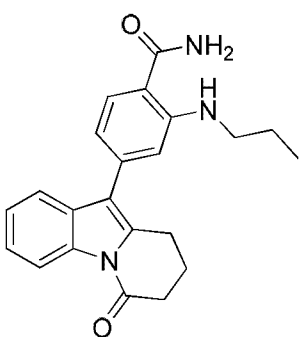
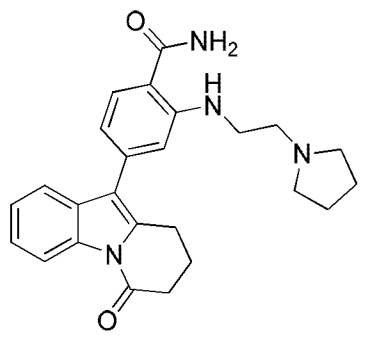
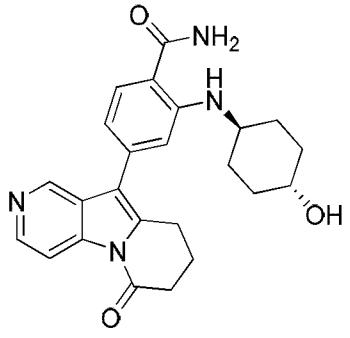
Representative compounds of the instant inventions are listed below:

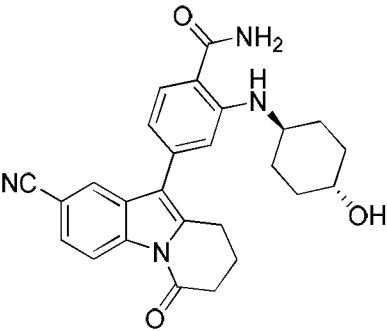
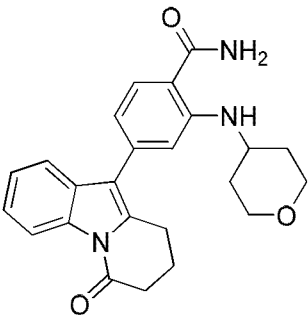
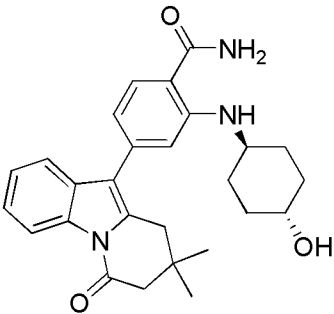
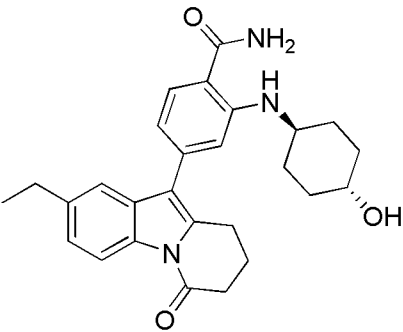
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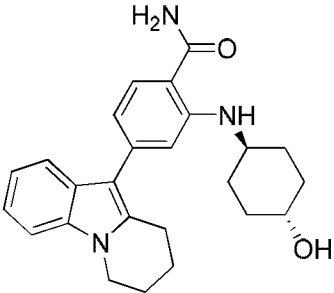
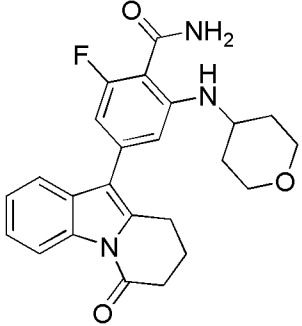
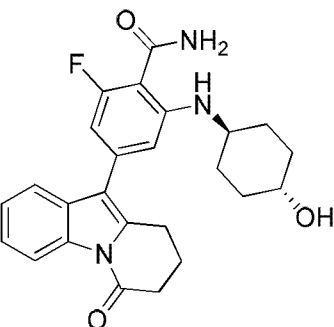
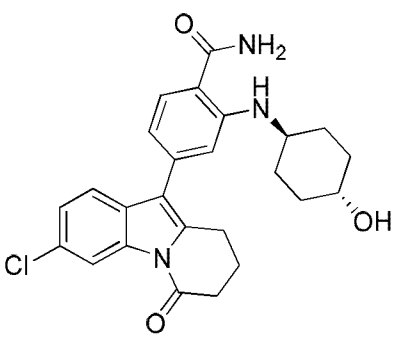
TABLE 2

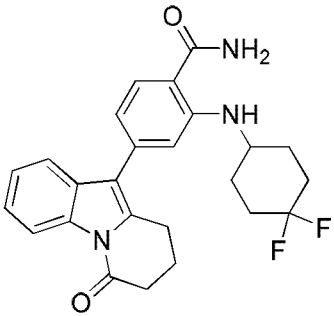
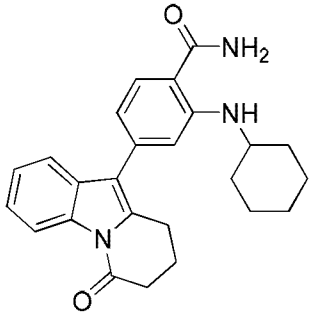
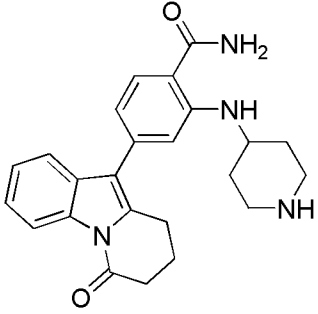
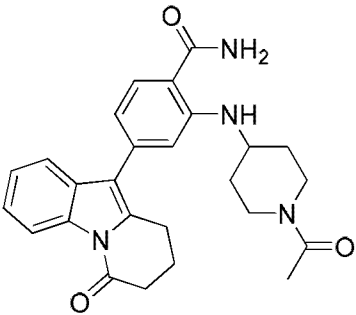
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2		$[M+H]^+ = 452.4$

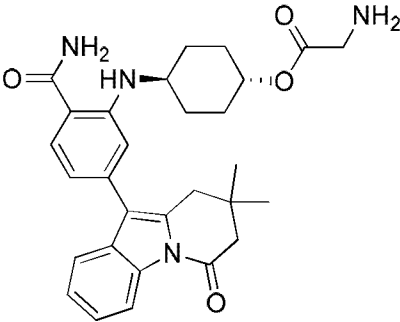
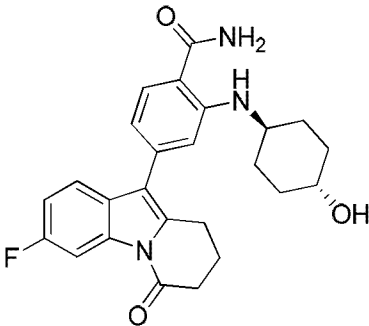
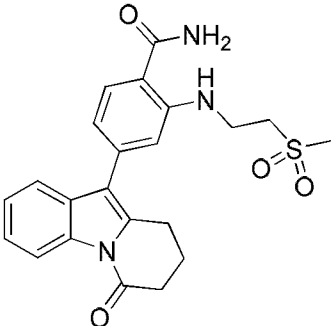
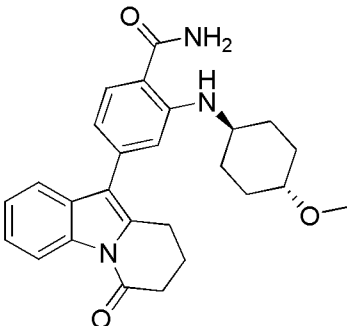
COMPOUND	STRUCTURE	MS (m/z)
3		$[M+H]^+ = 378.5$
4		$[M+H]^+ = 436.3$
5		$[M+H]^+ = 404.4$
6		$[M+H]^+ = 448.4$

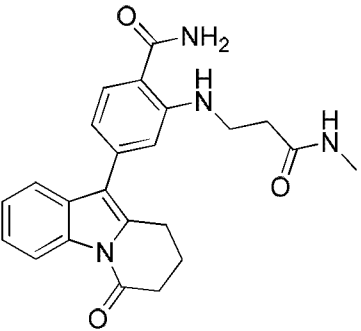
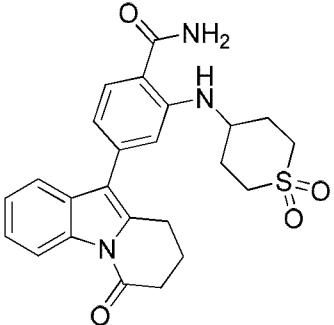
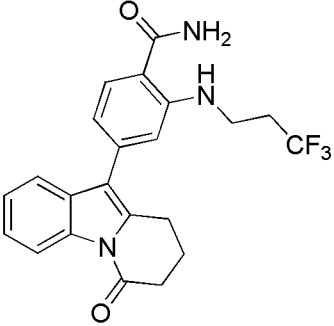
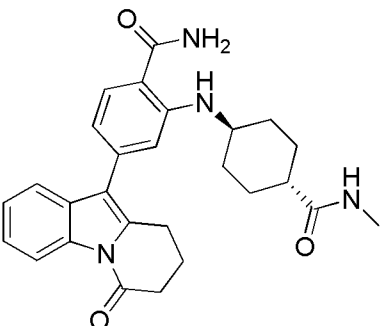
COMPOUND	STRUCTURE	MS (m/z)
7		$[M+H]^+=391.5$
8		$[M+H]^+=362.4$
9		$[M+H]^+=417.4$
10		$[M+H]^+=419.4$

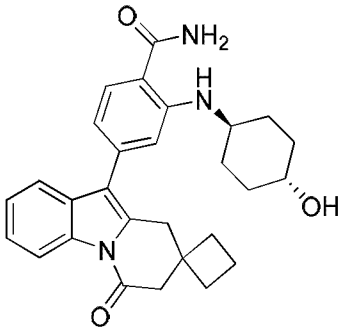
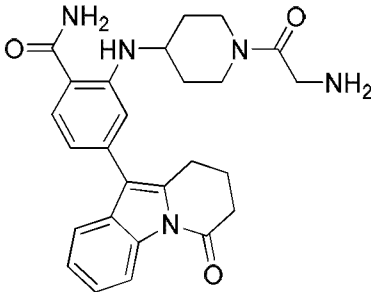
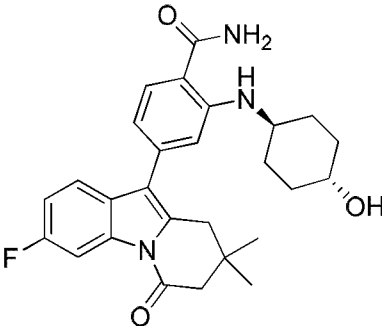
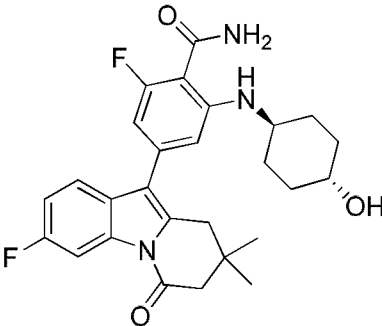
COMPOUND	STRUCTURE	MS (m/z)
11		$[M+H]^+=443.4$
12		$[M+H]^+=404.5$
13		$[M+H]^+=446.4$
14		$[M+H]^+=446.5$

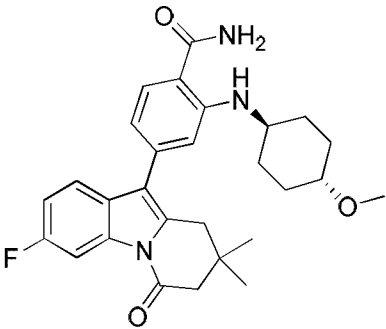
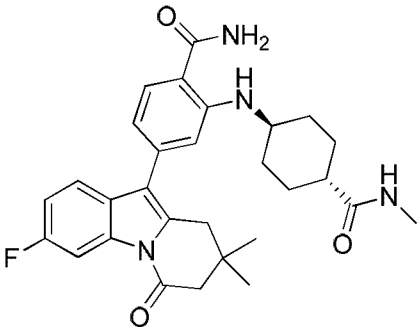
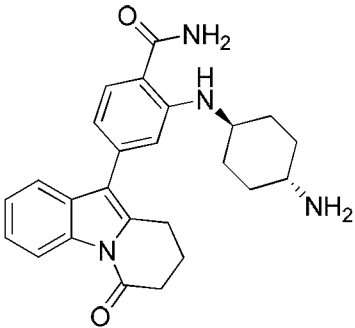
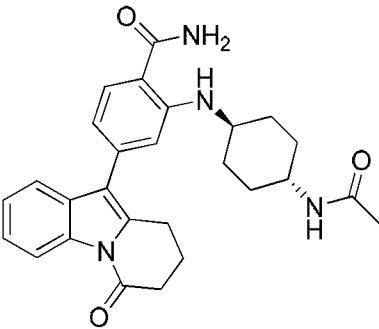
COMPOUND	STRUCTURE	MS (m/z)
15		$[M+H]^+ = 404.4$
16		$[M+H]^+ = 422.6$
17		$[M+H]^+ = 436.5$
18		$[M+H]^+ = 452.5$

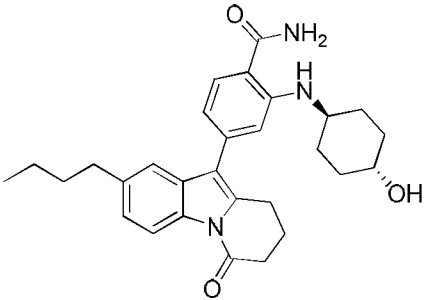
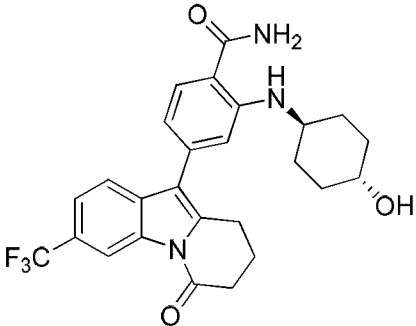
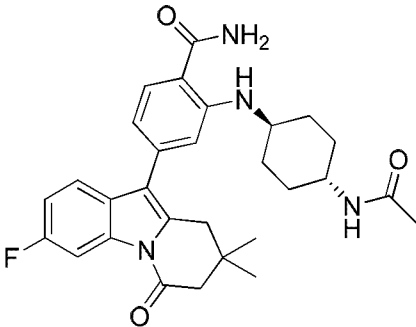
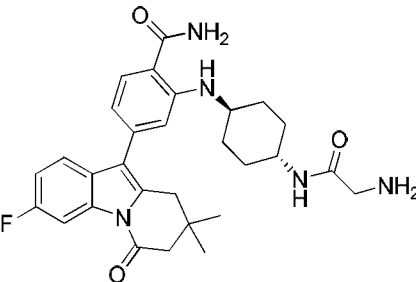
COMPOUND	STRUCTURE	MS (m/z)
19		$[M+H]^+ = 438.4$
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21		$[M+H]^+ = 403.4$
22		$[M+H]^+ = 445.4$

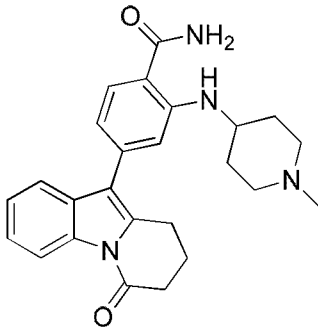
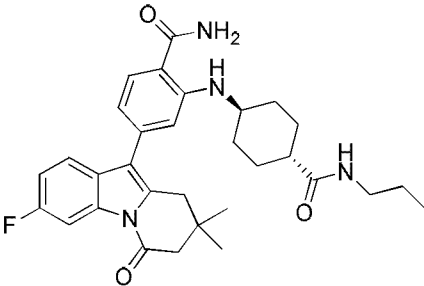
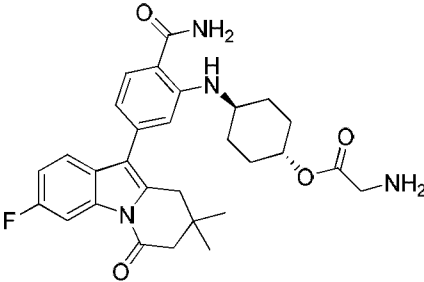
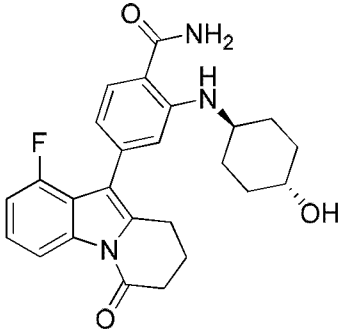
COMPOUND	STRUCTURE	MS (m/z)
23		$[M+H]^+=503.5$
24		$[M+H]^+=436.4$
25		$[M+H]^+=426.3$
26		$[M+H]^+=432.3$

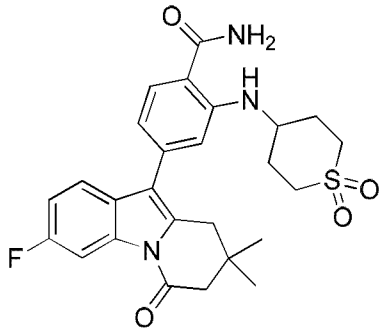
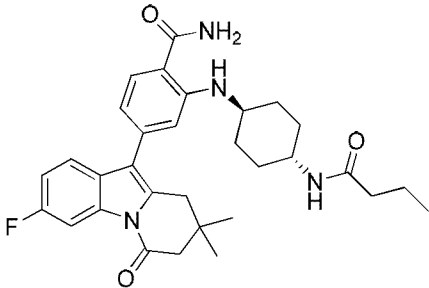
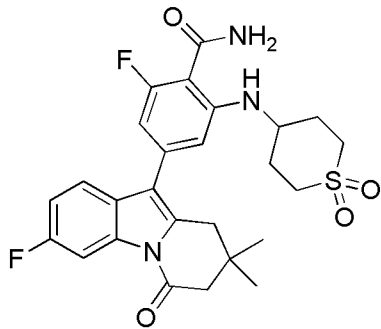
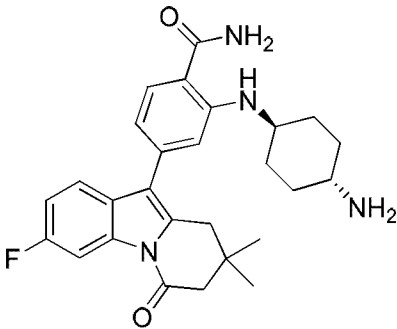
COMPOUND	STRUCTURE	MS (m/z)
27		$[M+H]^+ = 405.4$
28		$[M+H]^+ = 452.3$
29		$[M+H]^+ = 416.7$
30		$[M+H]^+ = 459.3$

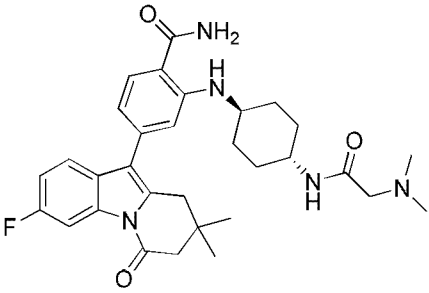
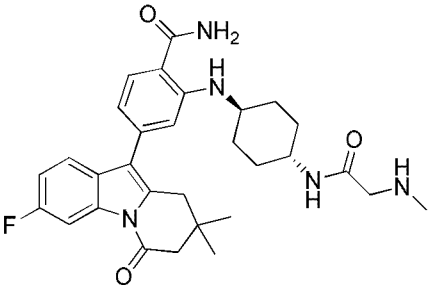
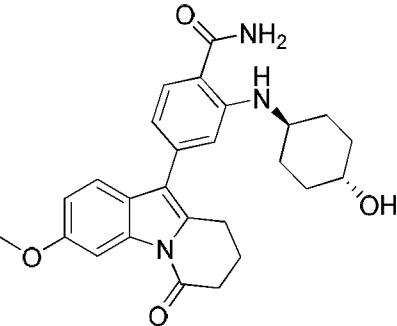
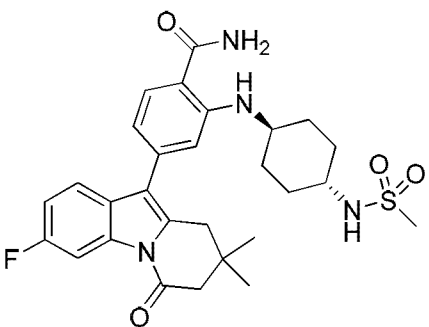
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32		$[M+H]^+ = 460.4$
33		$[M+H]^+ = 464.4$
34		$[M+H]^+ = 482.4$

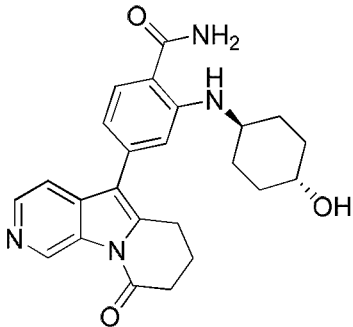
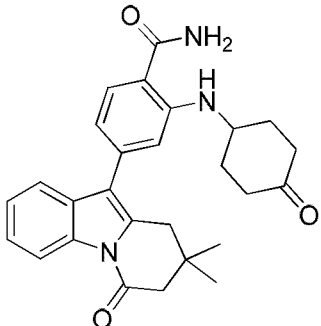
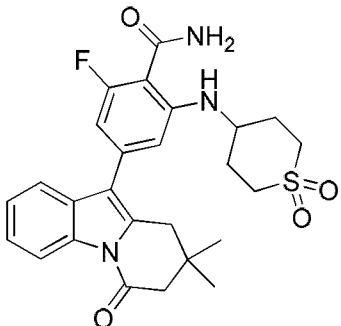
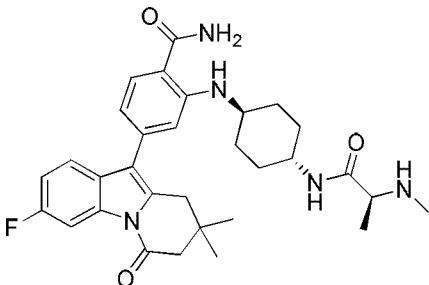
COMPOUND	STRUCTURE	MS (m/z)
35		$[M+H]^+=478.4$
36		$[M+H]^+=505.3$
37		$[M+H]^+=417.4$
38		$[M+H]^+=459.4$

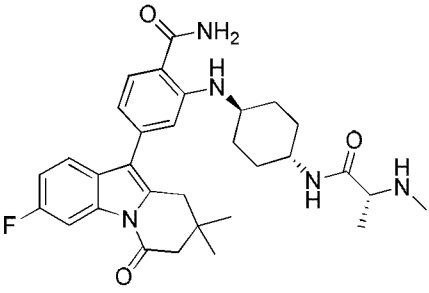
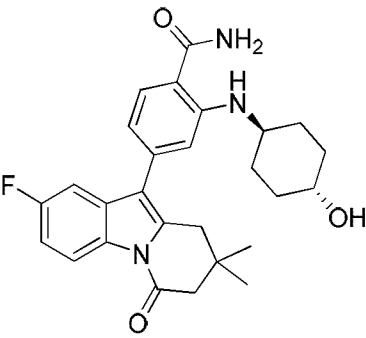
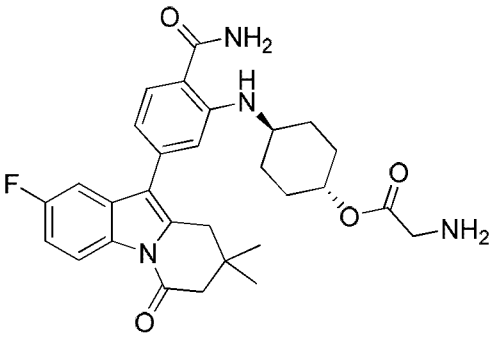
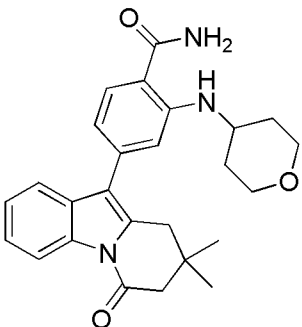
COMPOUND	STRUCTURE	MS (m/z)
39		$[M+H]^+ = 474.4$
40		$[M+H]^+ = 486.3$
41		$[M+H]^+ = 505.3$
42		$[M+H]^+ = 520.6$

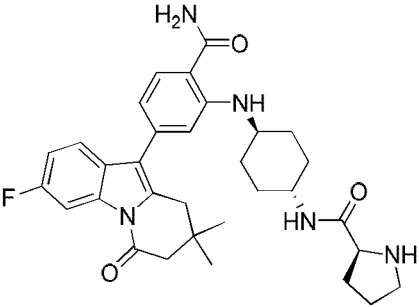
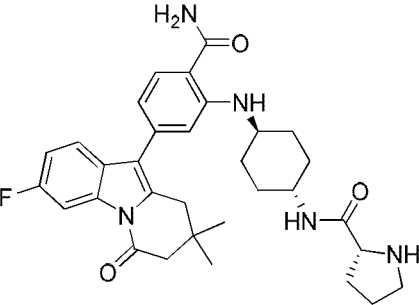
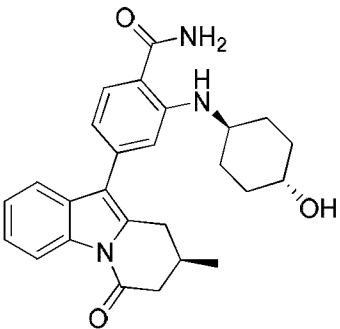
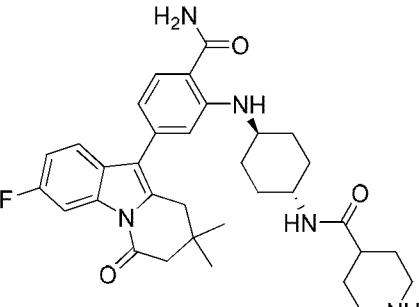
COMPOUND	STRUCTURE	MS (m/z)
43		$[M+H]^+=417.4$
44		$[M+H]^+=533.4$
45		$[M+H]^+=521.5$
46		$[M+H]^+=436.3$

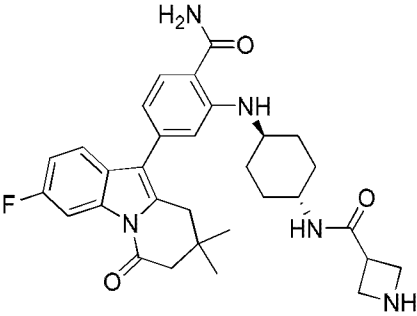
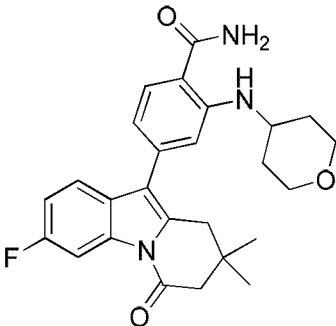
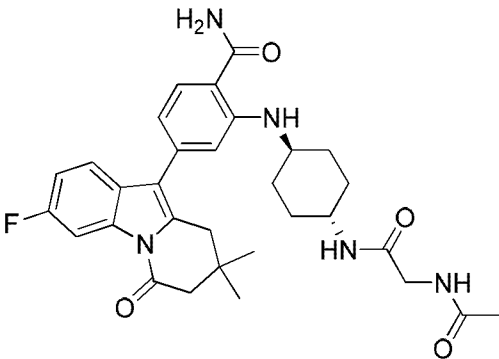
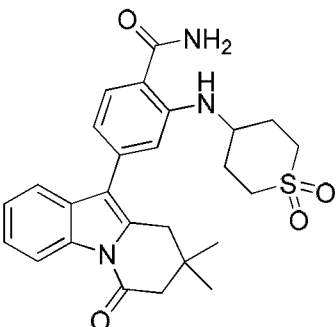
COMPOUND	STRUCTURE	MS (m/z)
47		$[M+H]^+=498.4$
48		$[M+H]^+=533.4$
49		$[M+H]^+=516.3$
50		$[M+H]^+=463.4$

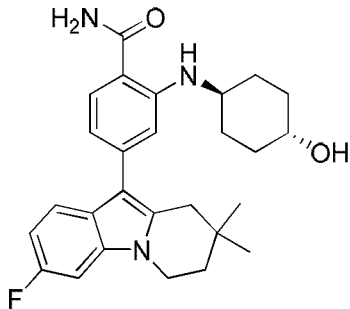
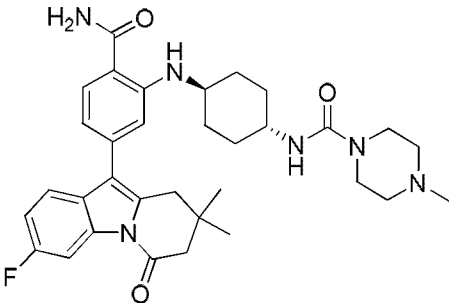
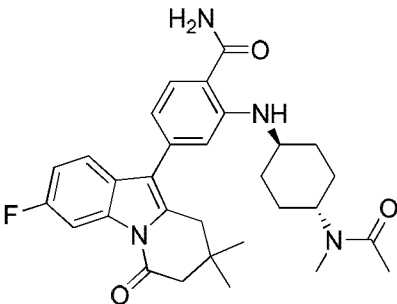
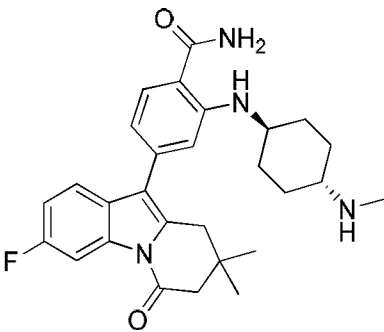
COMPOUND	STRUCTURE	MS (m/z)
51		$[M+H]^+=548.4$
52		$[M+H]^+=534.5$
53		$[M+H]^+=448.3$
54		$[M+H]^+=541.4$

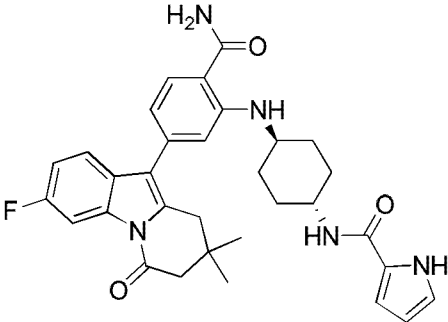
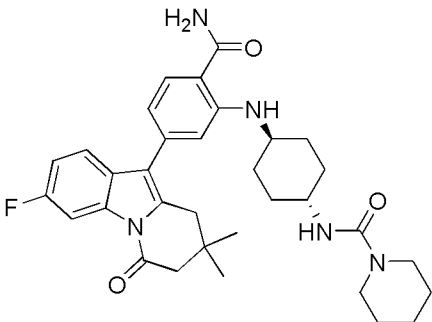
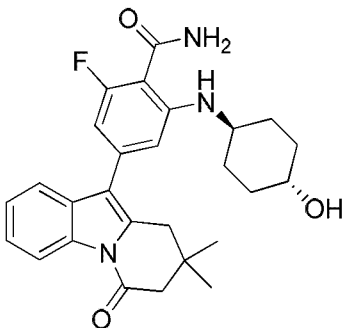
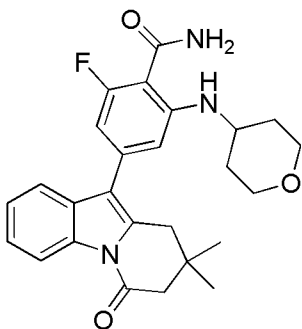
COMPOUND	STRUCTURE	MS (m/z)
55		$[M+H]^+ = 419.3$
56		$[M+H]^+ = 444.9$
57		$[M+H]^+ = 498.4$
58		$[M+H]^+ = 548.4$

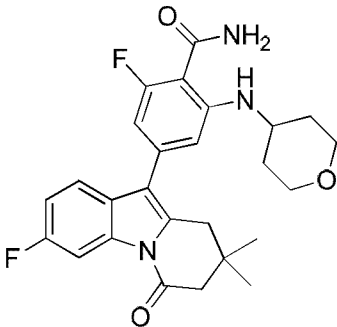
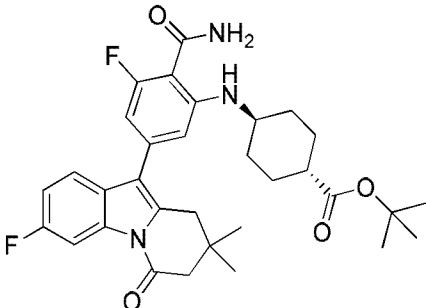
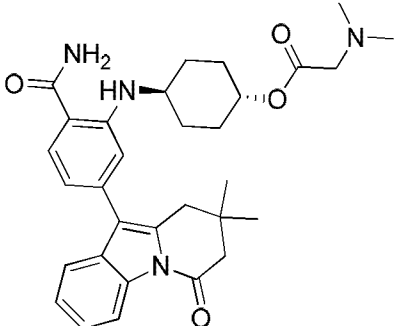
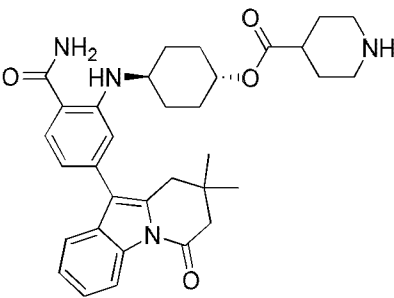
COMPOUND	STRUCTURE	MS (m/z)
59		$[M+H]^+=548.4$
60		$[M+H]^+=464.4$
61		$[M+H]^+=521.5$
62		$[M+H]^+=432.5$

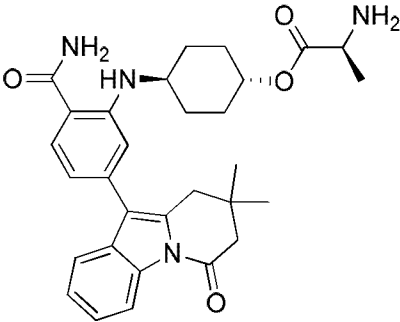
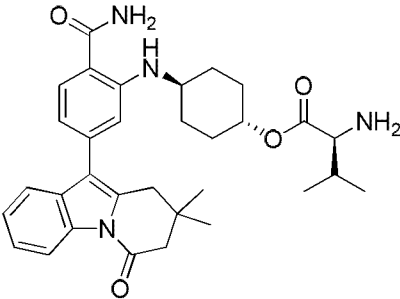
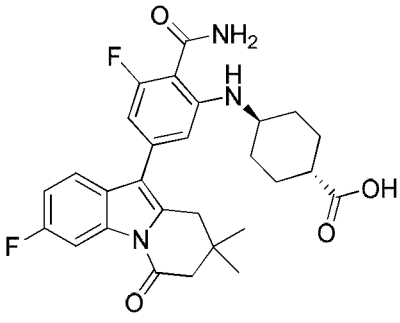
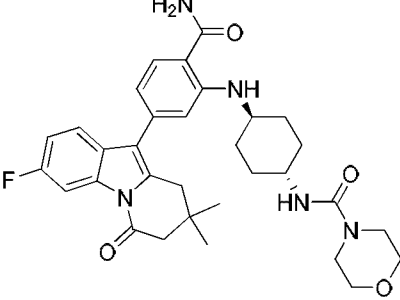
COMPOUND	STRUCTURE	MS (m/z)
63		$[M+H]^+ = 560.4$
64		$[M+H]^+ = 560.4$
65		$[M+H]^+ = 432.4$
66		$[M+H]^+ = 574.4$

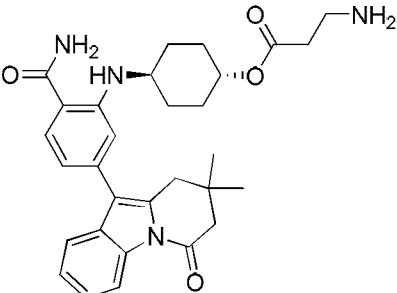
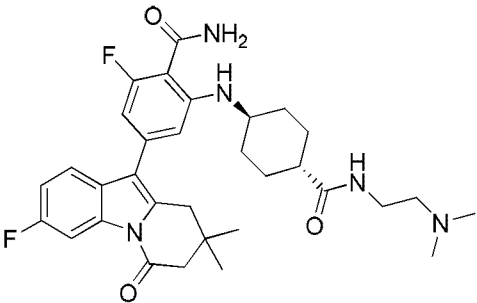
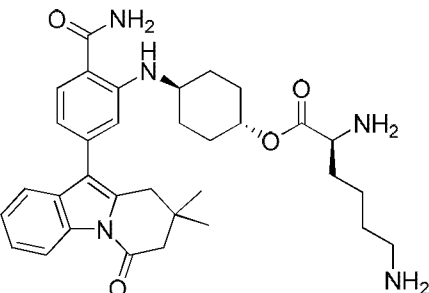
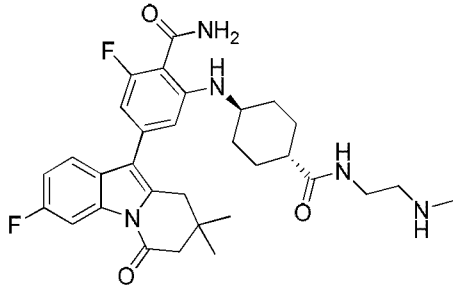
COMPOUND	STRUCTURE	MS (m/z)
67		$[M+H]^+ = 546.4$
68		$[M+H]^+ = 450.6$
69		$[M+H]^+ = 562.3$
70		$[M+H]^+ = 480.3$

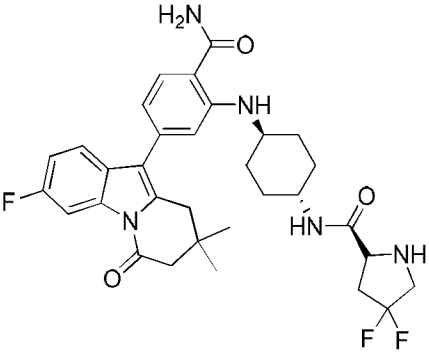
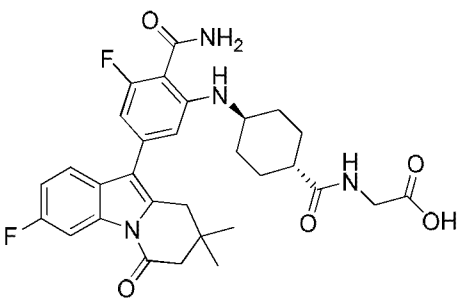
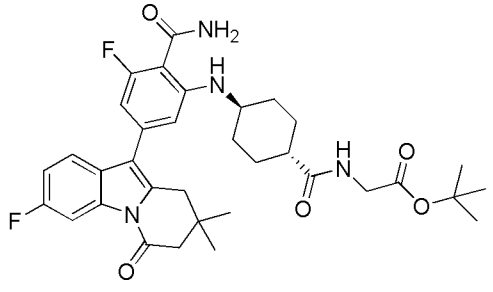
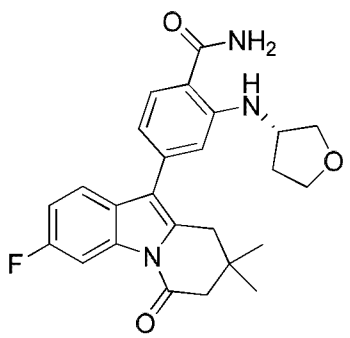
COMPOUND	STRUCTURE	MS (m/z)
71		$[M+H]^+=450.3$
72		$[M+H]^+=589.5$
73		$[M+H]^+=519.4$
74		$[M+H]^+=477.4$

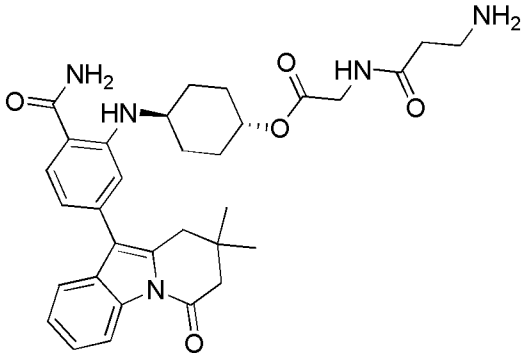
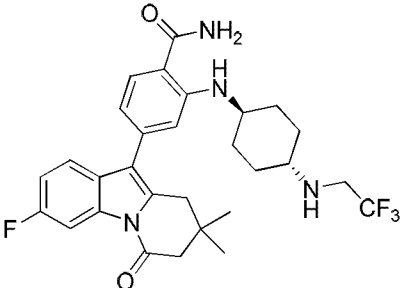
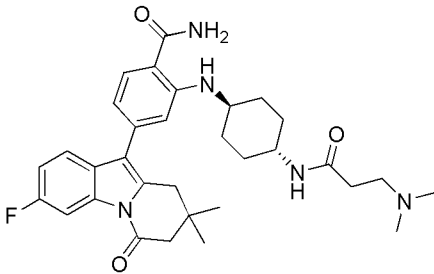
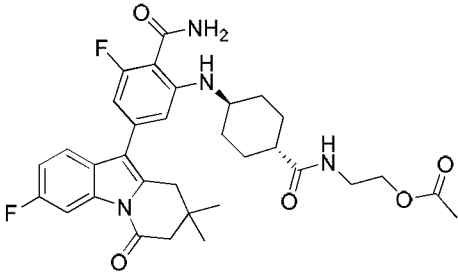
COMPOUND	STRUCTURE	MS (m/z)
75		$[M+H]^+ = 556.4$
76		$[M+H]^+ = 574.4$
77		$[M+H]^+ = 464.4$
78		$[M+H]^+ = 451.0$

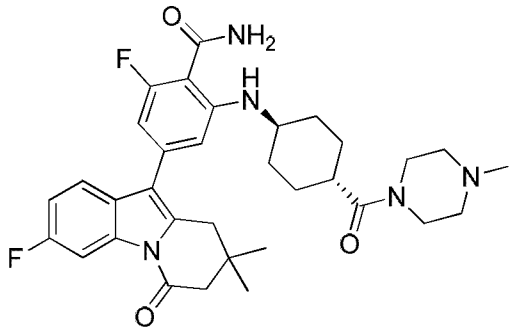
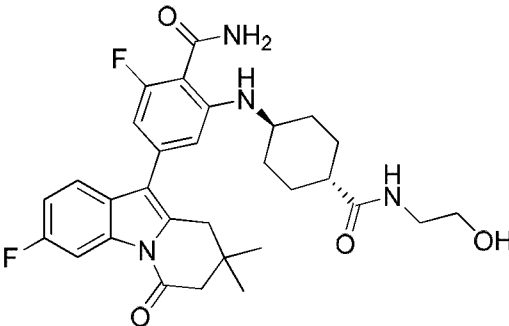
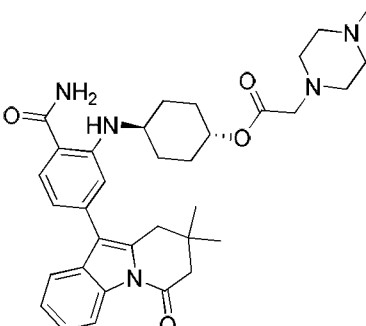
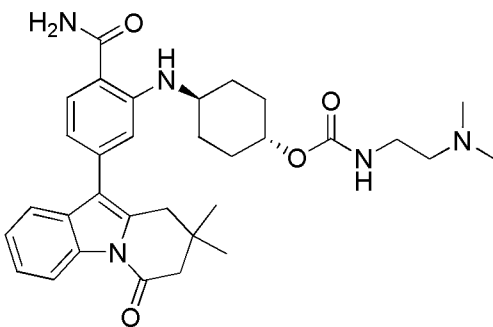
COMPOUND	STRUCTURE	MS (m/z)
79		$[M+H]^+=468.5$
80		$[M+H]^+=566.4$
81		$[M+H]^+=531.4$
82		$[M+H]^+=557.4$

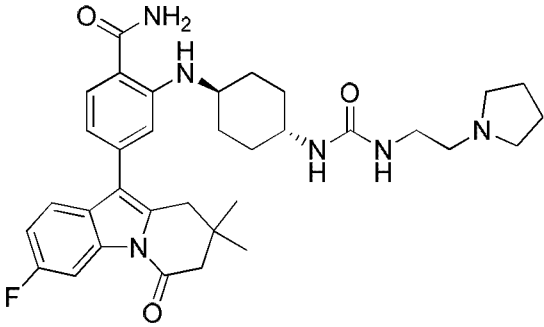
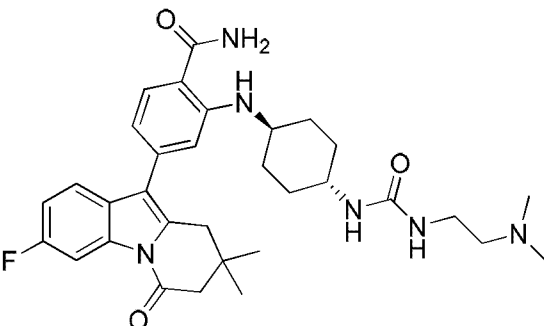
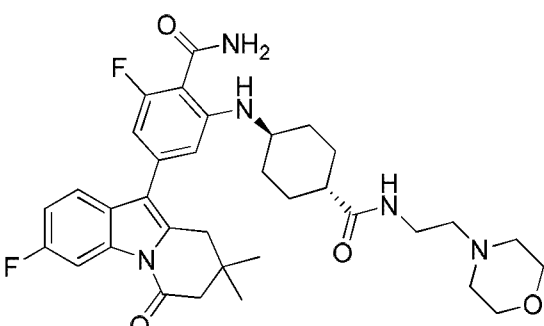
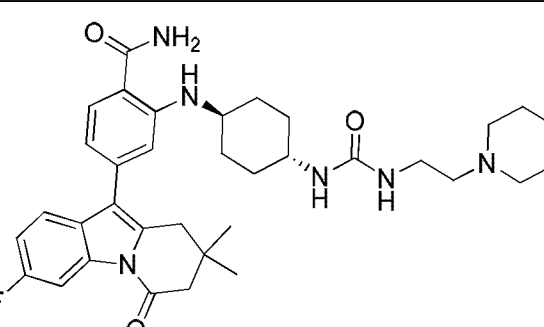
COMPOUND	STRUCTURE	MS (m/z)
83		$[M+H]^+=515.5$
84		$[M+H]^+=545.4$
85		$[M+H]^+=510.3$
86		$[M+H]^+=576.4$

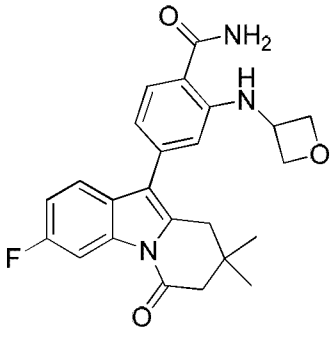
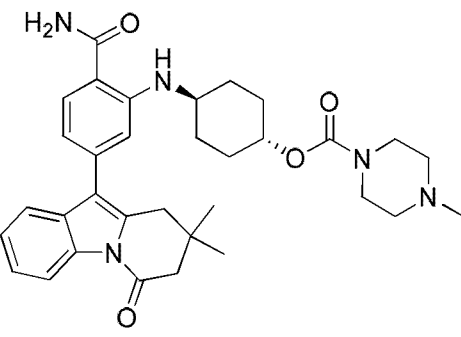
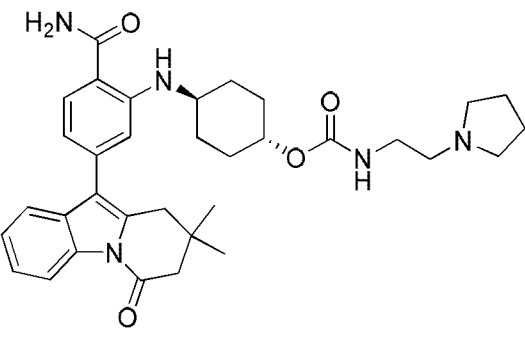
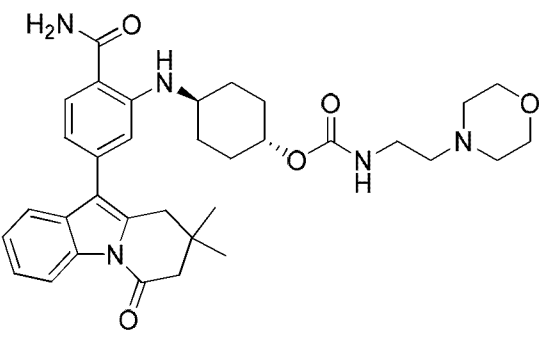
COMPOUND	STRUCTURE	MS (m/z)
87		$[M+H]^+=517.5$
88		$[M+H]^+=580.4$
89		$[M+H]^+=574.4$
90		$[M+H]^+=566.4$

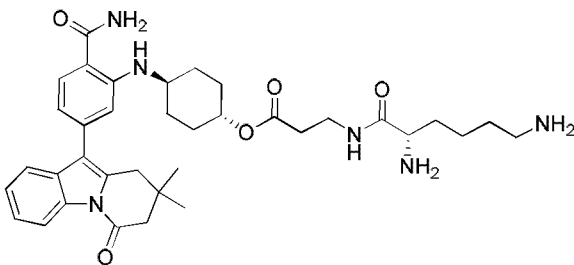
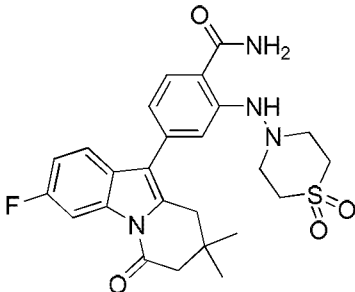
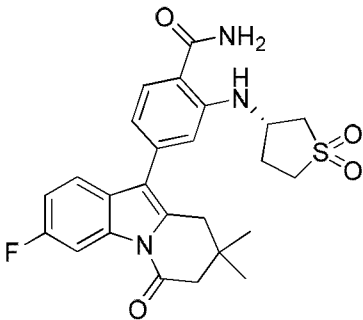
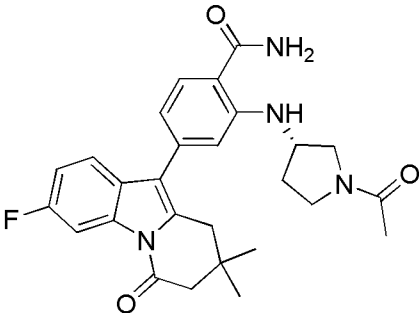
COMPOUND	STRUCTURE	MS (m/z)
91		$[M+H]^+ = 596.4$
92		$[M+H]^+ = 567.3$
93		$[M+H]^+ = 623.4$
94		$[M+H]^+ = 436.7$

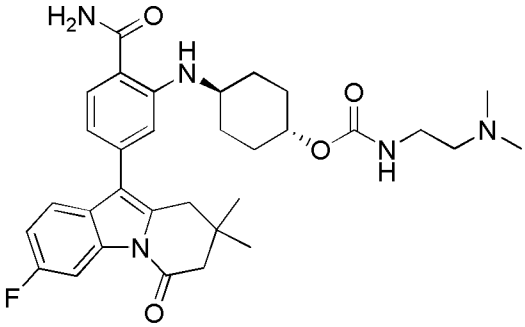
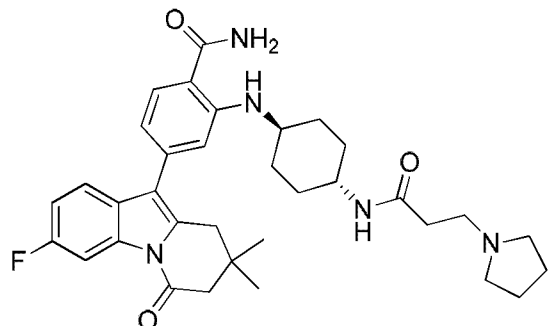
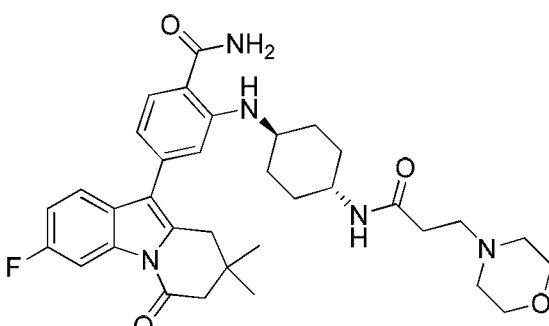
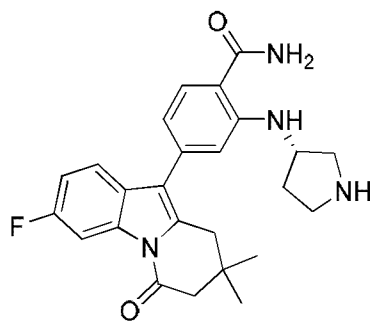
COMPOUND	STRUCTURE	MS (m/z)
95		$[M+H]^+=574.4$
96		$[M+H]^+=545.3$
97		$[M+H]^+=562.4$
98		$[M+H]^+=595.3$

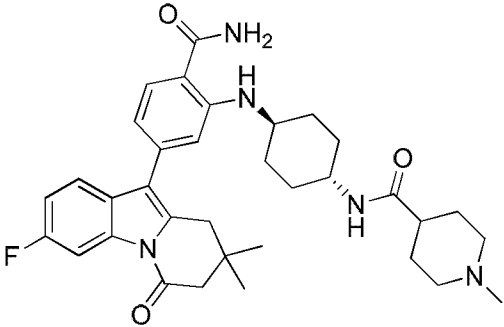
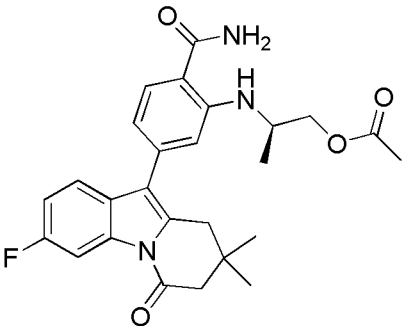
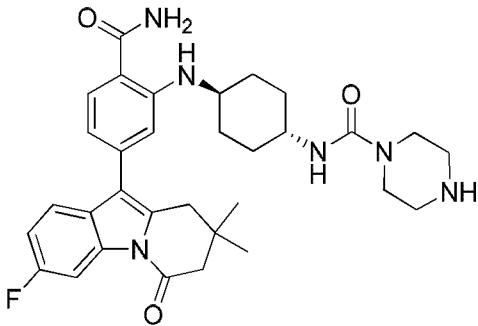
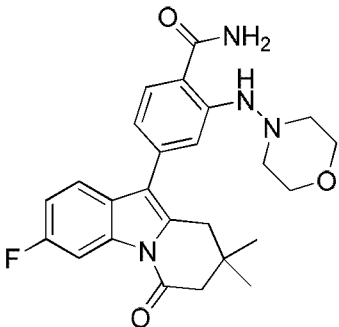
COMPOUND	STRUCTURE	MS (m/z)
99		$[M+H]^+ = 592.3$
100		$[M+H]^+ = 553.4$
101		$[M+H]^+ = 586.4$
102		$[M+H]^+ = 560.4$

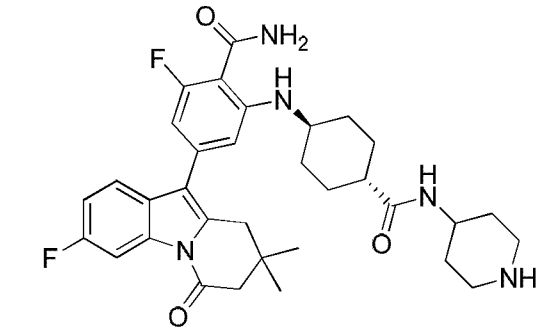
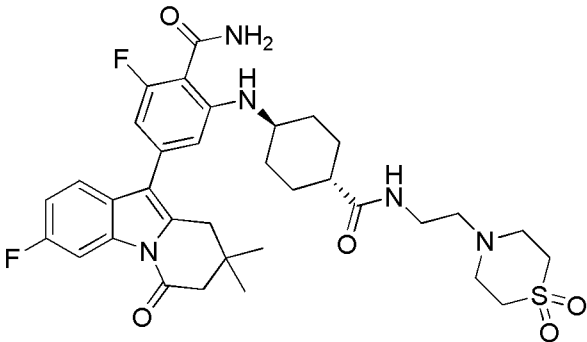
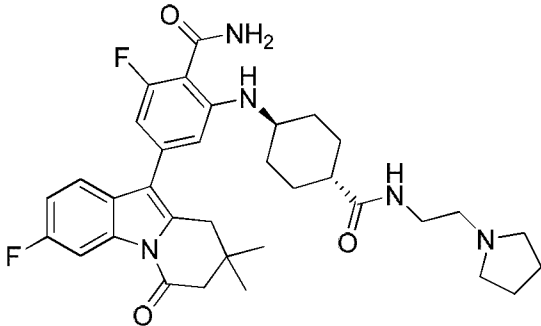
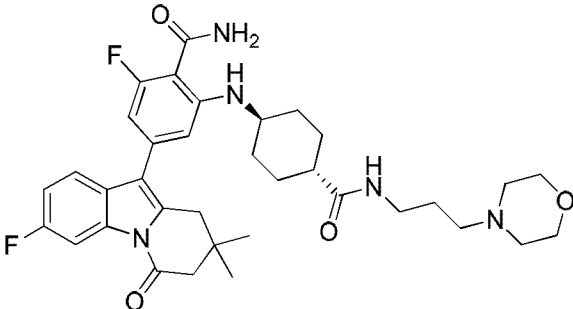
COMPOUND	STRUCTURE	MS (m/z)
103		$[M+H]^+ = 603.4$
104		$[M+H]^+ = 577.5$
105		$[M+H]^+ = 622.4$
106		$[M+H]^+ = 619.4$

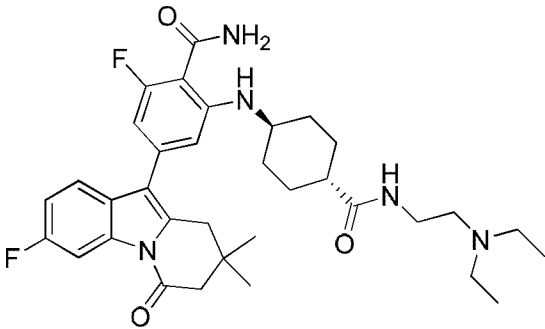
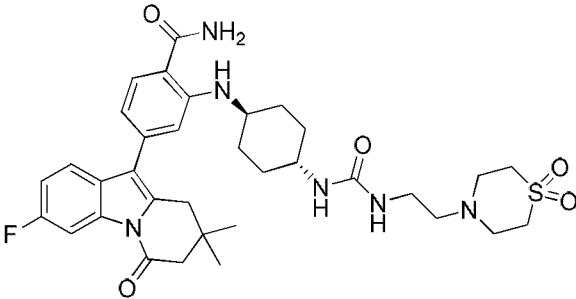
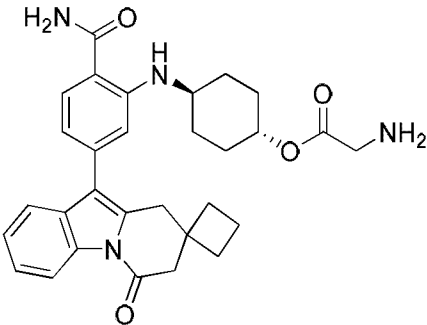
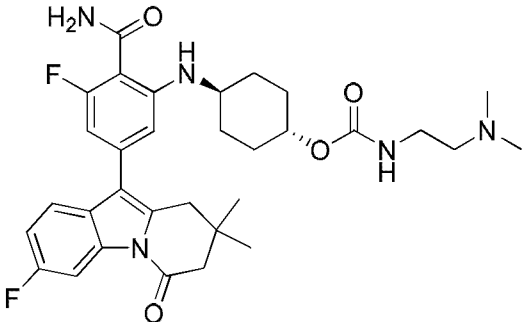
COMPOUND	STRUCTURE	MS (m/z)
107		$[M+H]^+=422.4$
108		$[M+H]^+=572.5$
109		$[M+H]^+=586.5$
110		$[M+H]^+=602.5$

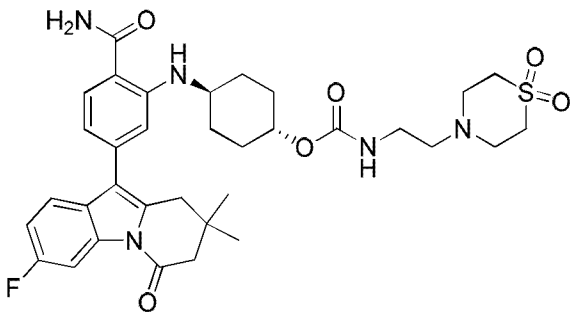
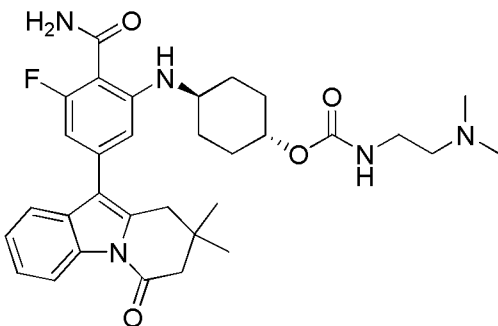
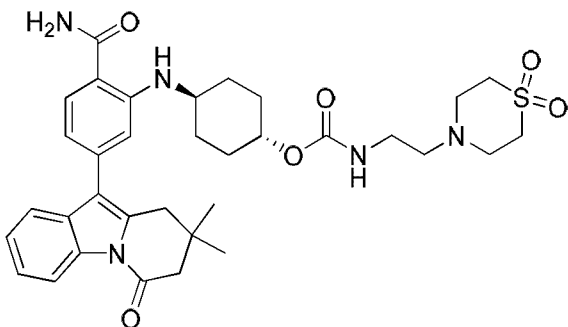
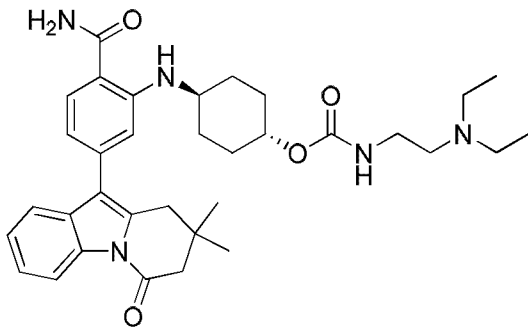
COMPOUND	STRUCTURE	MS (m/z)
111		$[M+H]^+=645.5$
112		$[M+H]^+=499.4$
113		$[M+H]^+=484.5$
114		$[M+H]^+=477.4$

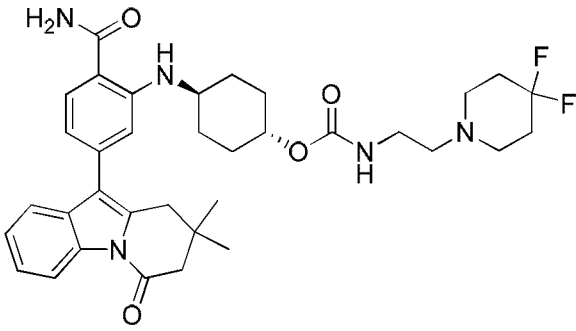
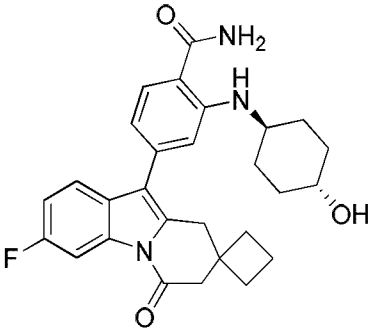
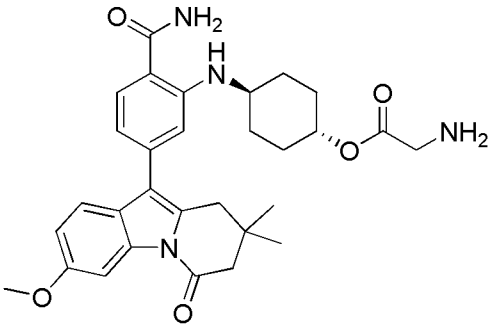
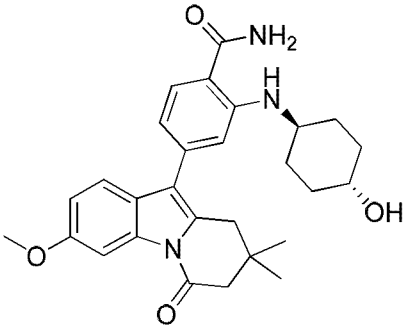
COMPOUND	STRUCTURE	MS (m/z)
115		$[M+H]^+=578.5$
116		$[M+H]^+=588.5$
117		$[M+H]^+=604.5$
118		$[M+H]^+=435.4$

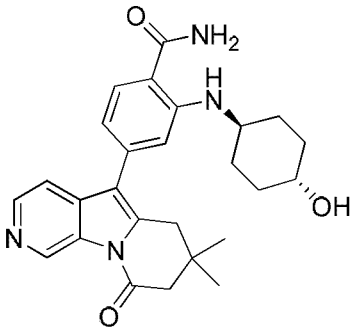
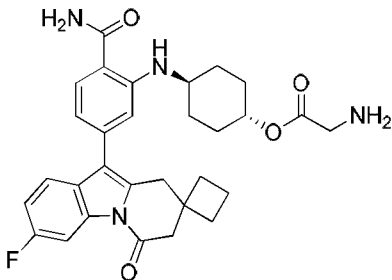
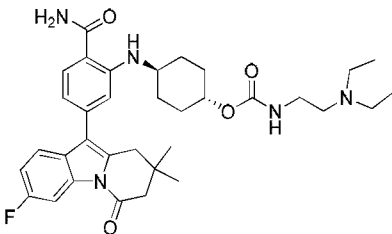
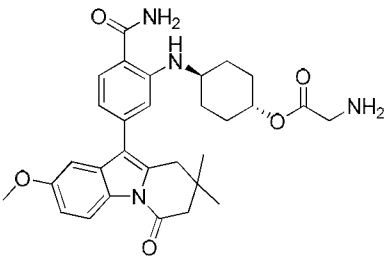
COMPOUND	STRUCTURE	MS (m/z)
119		$[M+H]^+=588.6$
120		$[M+H]^+=466.5$
121		$[M+H]^+=575.4$
122		$[M+H]^+=451.4$

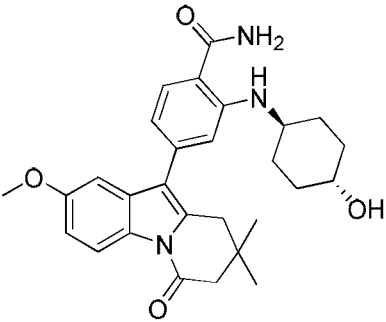
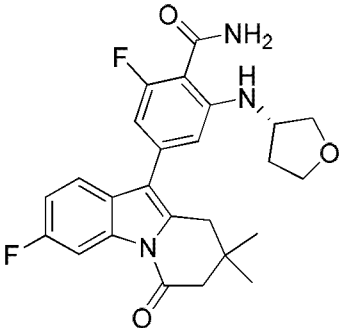
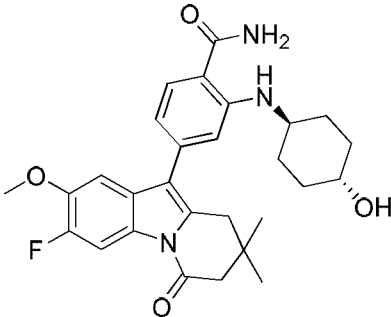
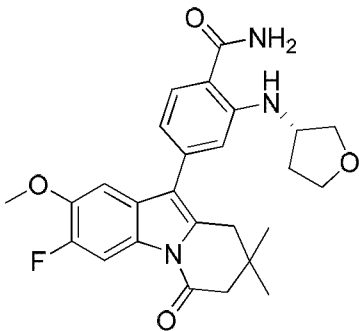
COMPOUND	STRUCTURE	MS (m/z)
123		$[M+H]^+=592.5$
124		$[M+H]^+=670.5$
125		$[M+H]^+=606.5$
126		$[M+H]^+=636.5$

COMPOUND	STRUCTURE	MS (m/z)
127		$[M+H]^+=608.5$
128		$[M+H]^+=667.5$
129		$[M+H]^+=515.7$
130		$[M+H]^+=588.6$

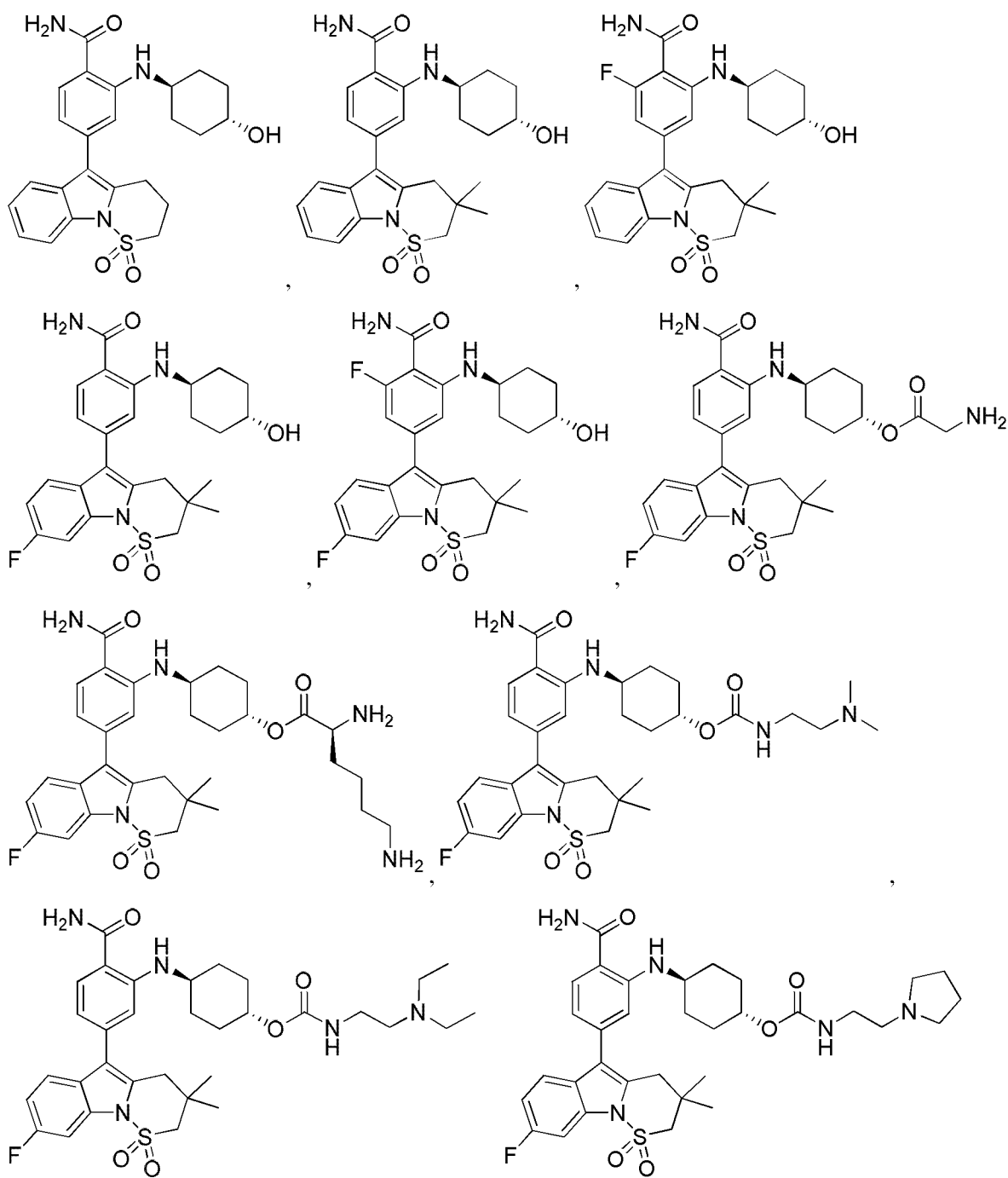
COMPOUND	STRUCTURE	MS (m/z)
131		[M+H] ⁺ =672.4
132		[M+H] ⁺ =578.5
133		[M+H] ⁺ =690.4
134		[M+H] ⁺ =596.4

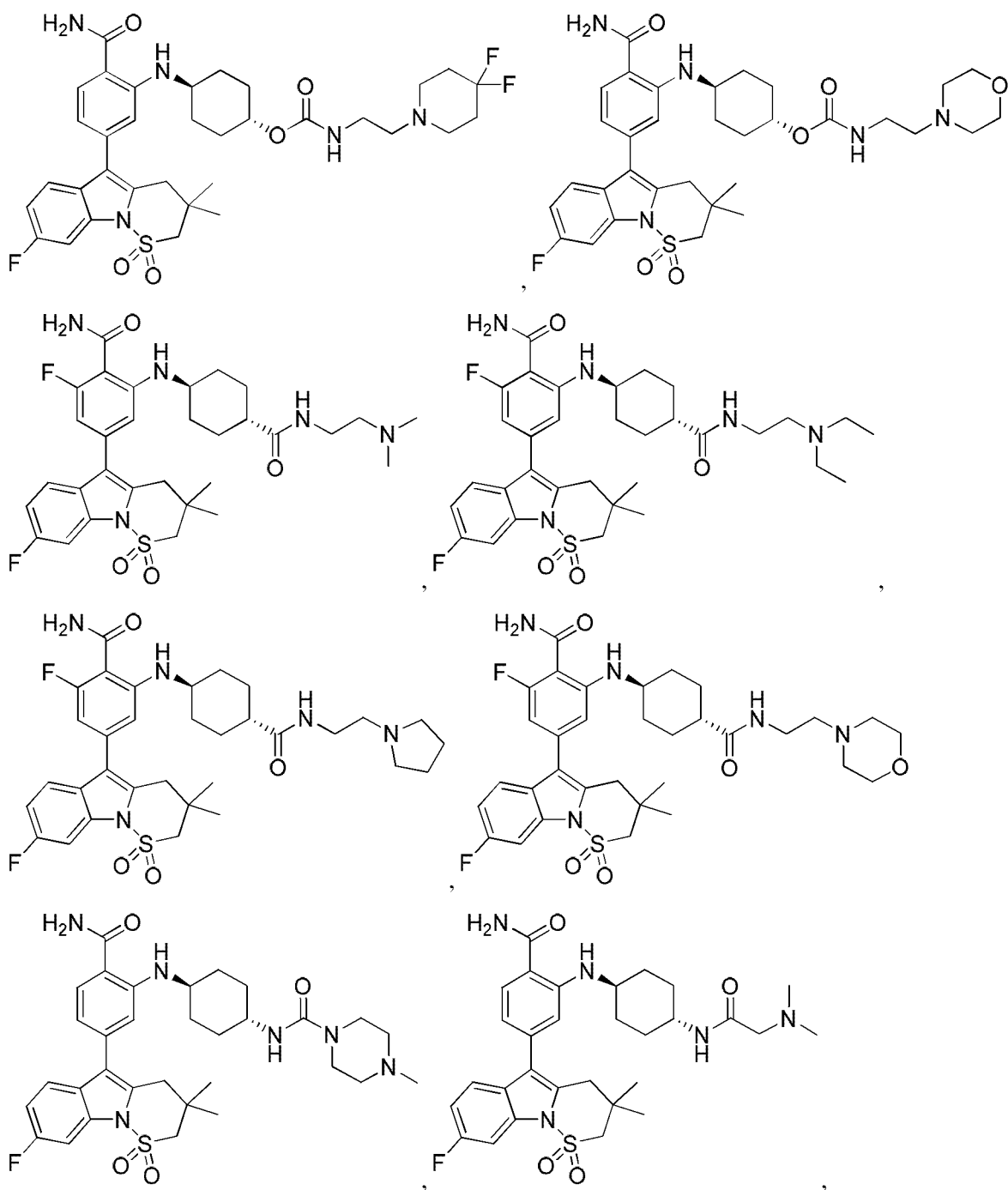
COMPOUND	STRUCTURE	MS (m/z)
135		$[M+H]^+=636.5$
136		$[M+H]^+=476.5$
137		$[M+H]^+=533.5$
138		$[M+H]^+=476.5$

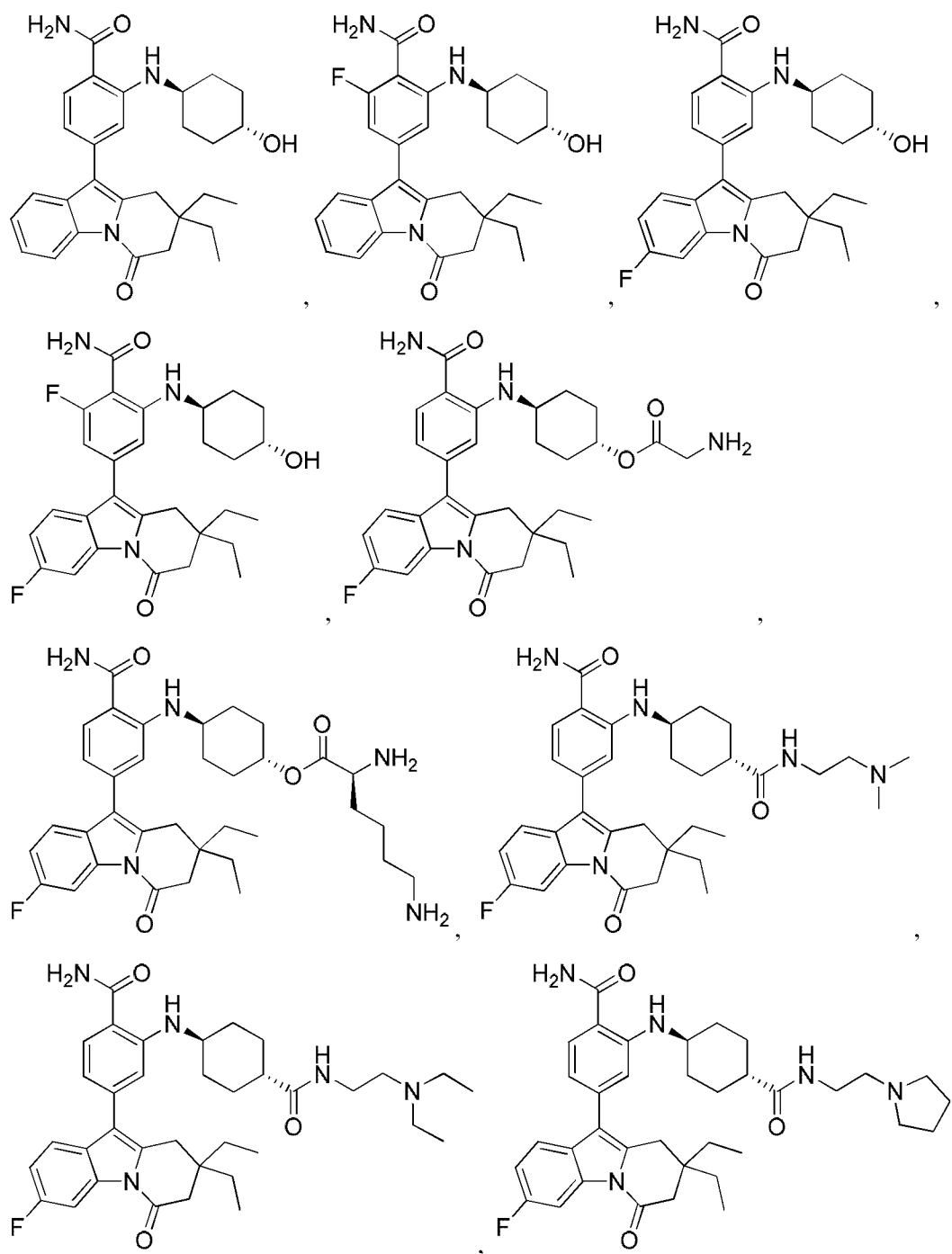
COMPOUND	STRUCTURE	MS (m/z)
139		$[M+H]^+ = 447.4$
140		$[M+H]^+ = 533.6$
141		$[M+H]^+ = 606.6$
142		$[M+H]^+ = 533.5$

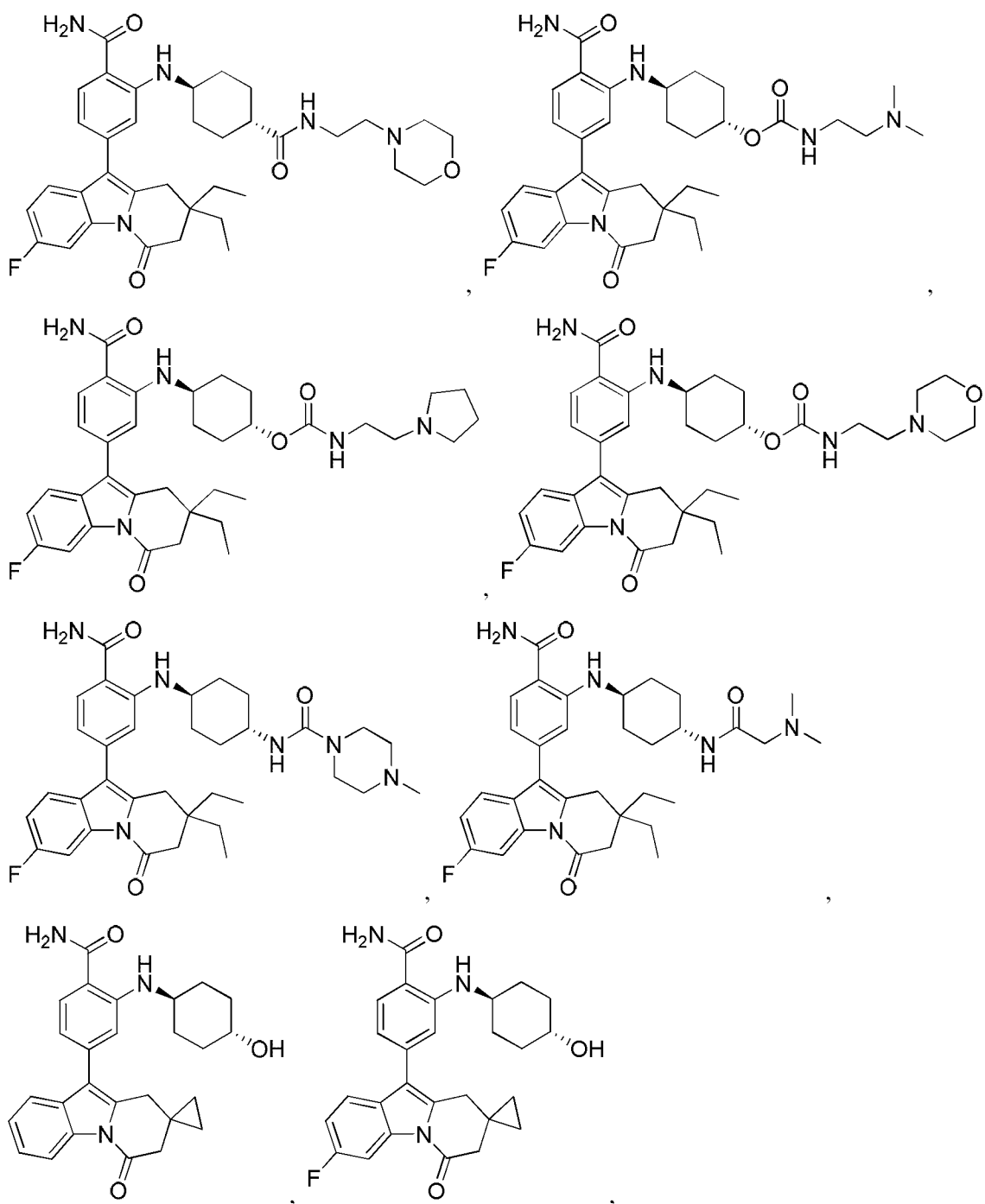
COMPOUND	STRUCTURE	MS (m/z)
143		$[M+H]^+ = 476.5$
144		$[M+H]^+ = 454.2$
145		$[M+H]^+ = 494.4$
146		$[M+H]^+ = 466.5$

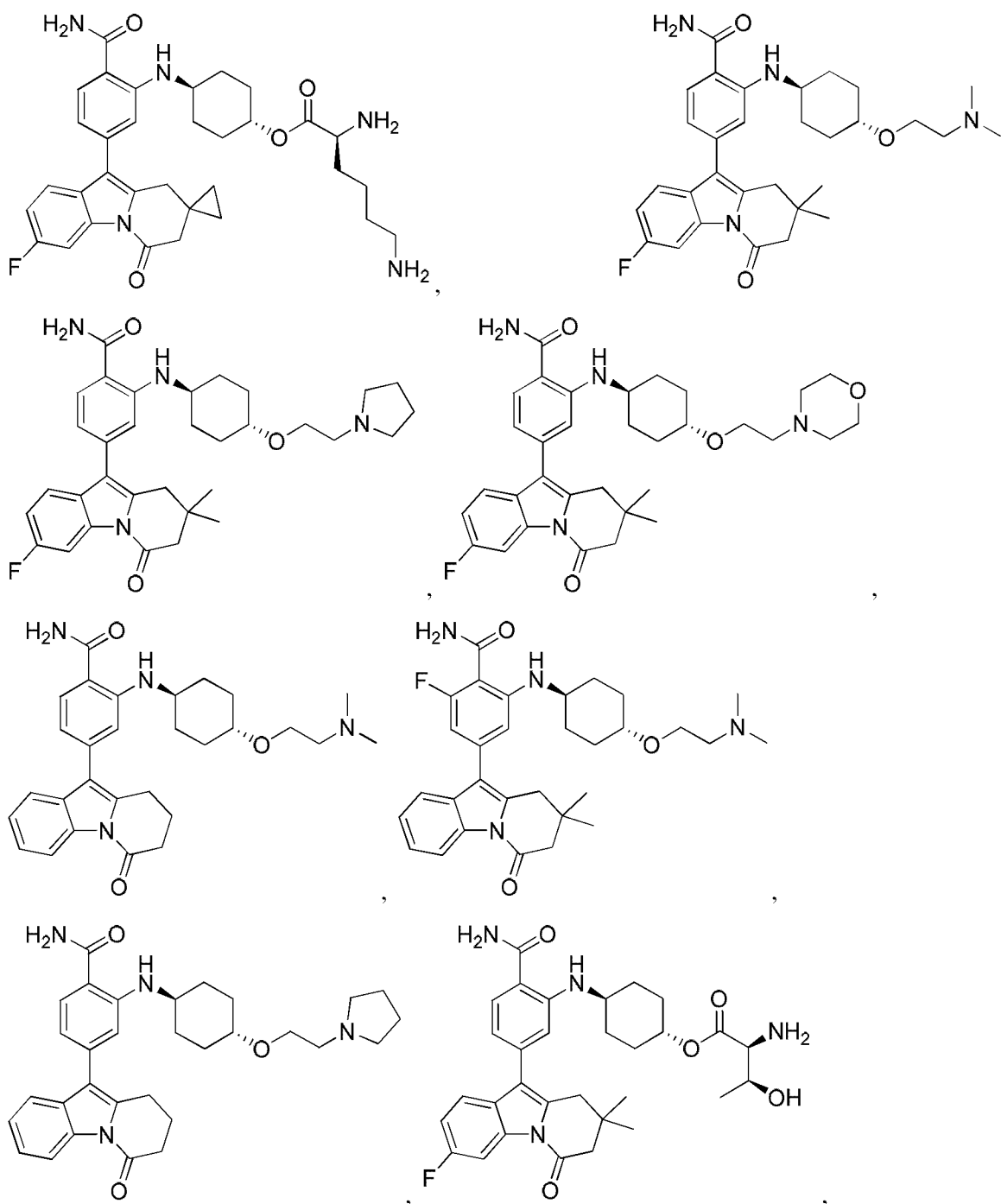
Other compounds of the instant invention include the following:

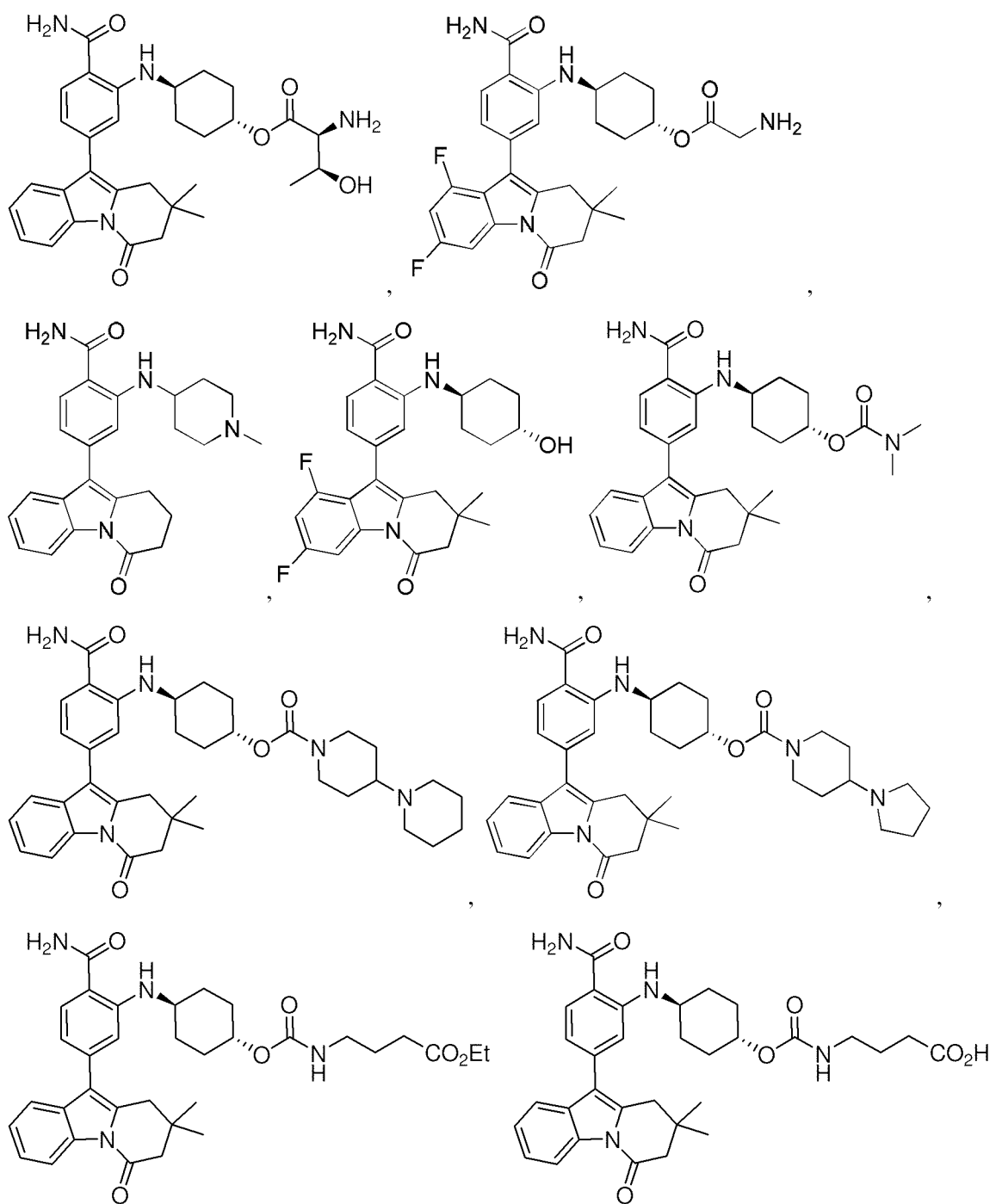


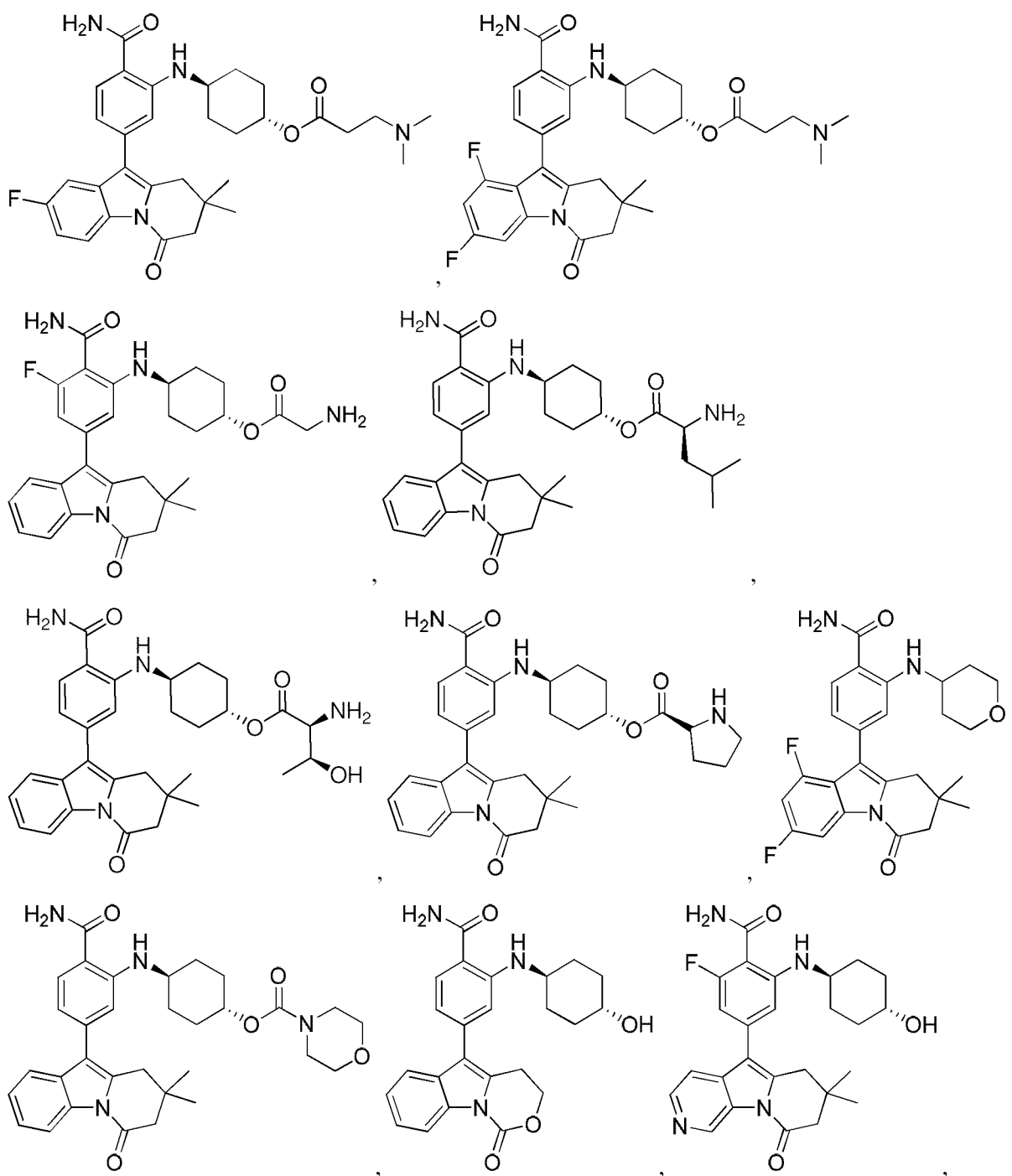


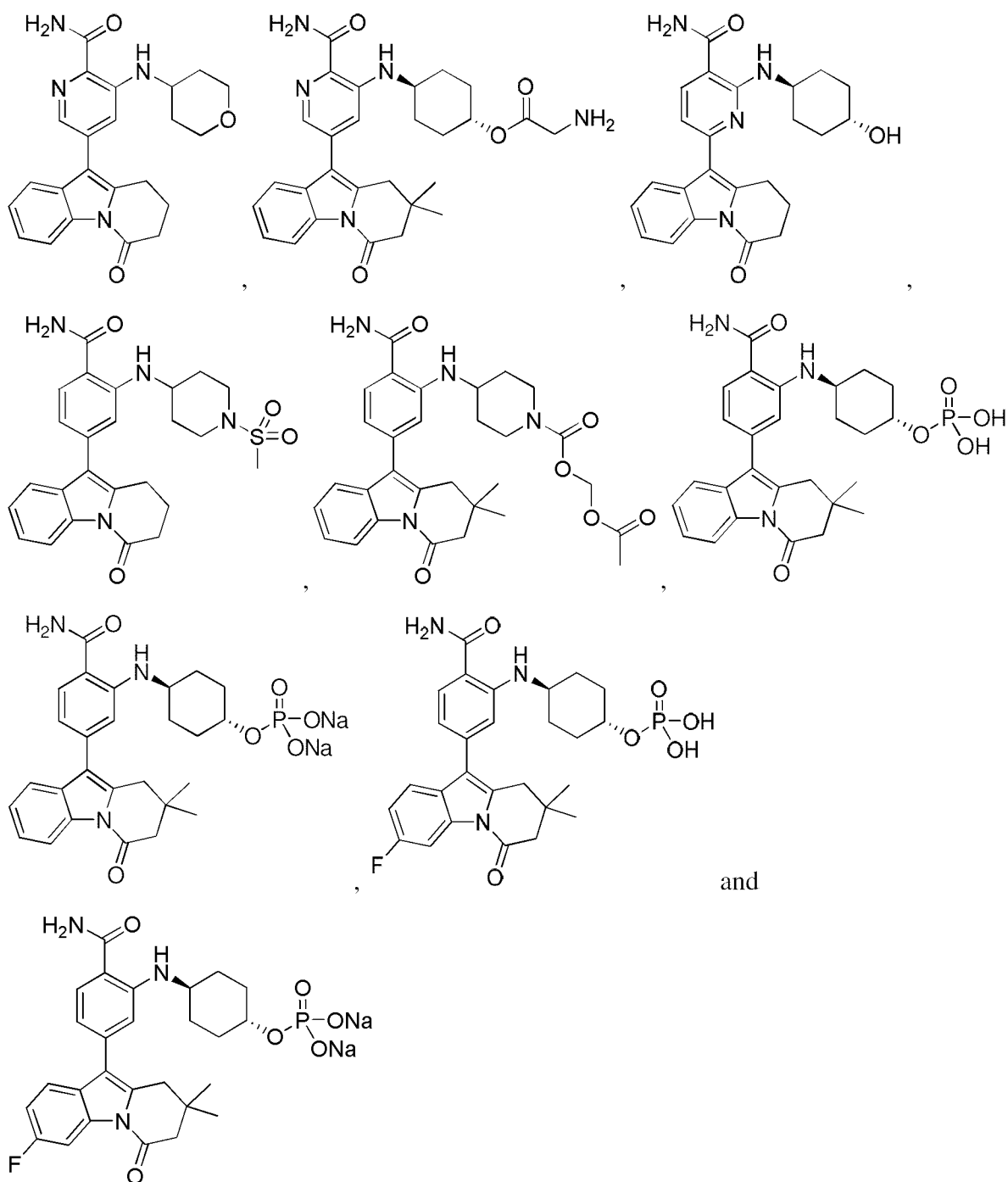












Fluorescence polarization HSP90 binding assay

Fluorescence polarization based HSP90 binding assay was performed using modifications to previously described methods using full length HSP90 and a geldanamycin-FITC probe (see Llauger-Bufi, L. et al., *Bioorg. Med. Chem. Lett.* 13 (2003) 3975-3978).

Briefly, geldanamycin-FITC probe was diluted into HFB buffer [20 mM HEPES (K) pH 7.3, 50 mM KCl, 1 mM DTT, 5 mM MgCl₂, 20 mM Na₂MoO₄, 0.01% NP40, 0.1 mg/mL of Bovine gamma-globuline] to obtain a working concentration of 8 nM. HSP90 protein (Hsp90 Native Protein, Stressgen, SPP-770) was diluted in order to obtain a 4X stock protein solution into HFB buffer. The final amount of protein used in the assay corresponds to the amount of protein necessary to obtain 80% of the maximum FP value in a 2 nM probe saturation experiment. Assay were carried out in duplicates, into not treated black 96-well plate (Corning #3915), in a total volume of 100 µl, for a final concentration of 2 nM of geldanamycin-FITC probe, various concentrations of compound and Hsp-90 protein into HFB buffer. Buffer only (blank) or probe only in buffer (G-factor) were also added to be used as controls for calibration. The plate was left on a shaker at 4 °C for 3 hours and the FP values in mP were recorded using Genios Pro FP reader (TECAN). The measured FP values (mP) were then plotted against compound concentration and EC₅₀, corresponding to the competitor concentrations where 50% of the tracer was displaced, calculated based on a sigomoidal dose-response (variable-slope) curve fit using GraphPad Prism version 4.02 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com.

Several representative compounds of the invention are listed below and their respective magnitude of potency is provided.

IC₅₀ **A**: less than 100 nM; **B** between 100 and 1000 nM; **C** greater than 1000 nM.

Compound	IC ₅₀ FP assay (nM)
1	B
2	-
3	-
4	B
5	-
6	-

7	-
8	-
9	-
10	C
11	-
12	-
13	B
14	-
15	-
16	B
17	B
18	B
19	B
20	-
21	C
22	B
23	A
24	B
25	C
26	B
27	C
28	B
29	C
30	B
31	B

32	B
33	B
34	B
35	B
36	B
37	B
39	C
40	-
41	B
42	A
43	-
44	B
45	A
46	-
47	A
48	B
49	B
50	B
51	A
52	A
53	-
54	B
55	-
56	B
57	A

58	A
59	A
62	B
63	-
64	B
65	B
66	B
67	A
69	-
70	A
71	B
72	A
73	-
74	B
75	B
76	B
77	B
78	B
79	B
80	-
81	B
82	A
83	B
84	B
85	B

86	B
87	A
88	A
89	A
90	A
91	-
92	A
93	B
94	B
95	A
96	-
97	A
98	B
99	A
101	B
102	A
103	A
104	A
105	A
106	B
107	B
108	B
109	A
110	B
111	A

112	A
113	B
114	B
115	A
116	A
117	A
118	B
119	A
120	C
121	A
122	B
123	A
124	A
125	A
126	A
127	A
128	A
129	B
130	A
131	B
132	A
133	B
134	A
135	B
136	B

137	B
138	B
139	C
140	B
141	A
142	B
143	B
144	A
145	B
146	B

Anti-Fungal Activities of HSP90 Inhibitors

Anti-fungal activity was determined in vitro by incubation of *Candida albicans* cultures with serial two fold dilutions of HSP90 inhibitors alone or in combination with serial two fold dilutions of fluconazole or caspofungin. Fungal growth was measured by absorbance at 600 nM (Figure 1).

Fungicidal activity was demonstrated by plating cells from the above liquid cultures on solid media in the absence of HSP90 inhibitor, fluconazole or caspofungin and allowing fungal growth to occur before photography (Figure 2).

Figure 1 shows that HSP90 inhibitors block growth of *Candida albicans* and synergize with Fluconazole and Caspofungin. *Candida albicans* cultures were treated with 2 fold dilutions of compound 34 or compound 117 in combination with 2 fold dilutions of either fluconazole or caspofungin. Cell growth was determined by light absorbance.

Figure 2 shows that HSP90 inhibitors are fungocidal alone and in combination with Fluconazole and Caspofungin. On the left side, *Candida albicans* cultures were treated with 2 fold dilutions of compound 117 or compound 34 in the absence of drug or in the presence

of fixed concentrations of Fluconazole or Caspofungin. Fungal growth was determined by light absorption. On the right, culture aliquots were then plated on solid drug and compound free media and allowed to grow before photography.

Data indicate that Compound 34 and compound 117 blocked fungal growth as single agents (Figure 1). Both compounds were synergistic when applied in combination with either Fluconazole or Caspofungin. Compound 34 was fungocidal as demonstrated by failure of treated cells to grow on compound free media (Figure 2 upper right). The combination of either compound 34 or compound 117 with Fluconazole or Caspofungin was fungocidal (Figure 2 middle and bottom right).

These data show that compounds of the instant invention are fungostatic and fungocidal and that they synergize with anti-fungal drugs to increase their potency.

Pharmacokinetics (PK) of Compound in Plasma

The PK of compounds of formula 1, such as compounds 33, 45 and 102, were determined in the plasma of mice after treating CD-1 mice with compound via IV or oral administration. Compound concentrations were determined using acetonitrile extraction of compound from the appropriate matrix and calculation of drug concentrations using a spiked standard curve from the same matrix (ie. plasma).

Compounds of formula 1 demonstrated good oral absorption (10-50 % F) and exposure in plasma which can exceed the concentration required to have anti-fungal activity. These results indicate that compounds of formula 1 are orally available and can cross the blood brain barrier. Therefore compounds of formula 1 may be useful in the treatment of fungal infections in a variety of compartments.

Figure 3 shows the plasma levels of compound 34 in mice dosed with 100 mg/kg compound 34 formulated in cremophor ELP by the oral route. Data indicate that oral administration to mice can deliver active concentrations of compound to plasma. Following oral dosing exposure of compound 34 was in excess of 2 uM which is above the concentration required to affect fungal growth in vitro for at least 8 hours.

Equivalents

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, numerous equivalents to the compounds and methods of use thereof described herein. Such equivalents are considered to be within the scope of this invention
5 and are covered by the following claims.

All of the above-cited references and publications are hereby incorporated by reference.

We Claim:

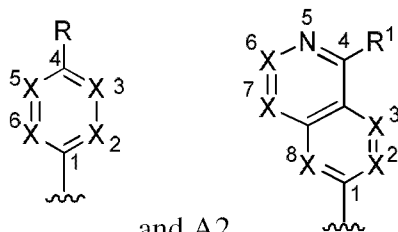
1. A compound having a structure of Formula 1 or a pharmaceutically acceptable salt thereof



5

Formula 1

wherein



A is selected from A1 and A2 (wherein 1-6 and 1-8, respectively refer to positions on the ring);

each X is independently selected from CR² and N;

10 R is selected from -CN and -C(O)NH₂;

R¹ is NH₂;

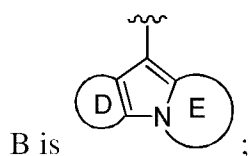
each R² is independently selected from hydrogen, halogen, -NO₂, -CN, alkyl, alkenyl, alkynyl, -OR³, -NR⁴R⁵, -S(O)_mR³, -C(O)R³, -C(O)OR³, -C(O)NR⁴R⁵, -S(O)₂NR⁴R⁵, aryl, heteroaryl, carbocyclyl, and heterocyclyl;

15 each R³, R⁴, and R⁵ is independently selected from hydrogen, -alkyl-R⁶, carbocyclyl, heterocyclyl, heteroaryl, and aryl; or

R⁴ and R⁵ together are alkylene, thereby forming a ring;

R⁶ is selected from hydrogen, hydroxy, alkoxy, -NHC(O)alkyl, -NHSO₂alkyl, amino, and heterocyclyl;

20 m is an integer from 0 to 2;



D is selected from aryl, heteroaryl, carbocyclyl and heterocyclyl; and

E is selected from carbocyclyl and heterocyclyl.

2. A compound of claim 1, wherein A is A1 and each occurrence of X is independently CR².

3. A compound of claim 1, wherein A is A1 and one or two occurrences of X are N.

4. A compound of any of claims 1 to 3, wherein X³ of A1 is CR² and R² is other than hydrogen. compound of claim 4, wherein X³ of A1 is CR², R² is NR⁴R⁵, R⁴ is hydrogen and R⁵ is carbocyclyl-R⁷

R⁷ is selected from -OR¹⁴, -NR¹²R¹³, -C(O)NR¹²R¹³, -SO₂NR¹²R¹³, -NR¹⁴C(O)R¹⁵, -NR¹⁴S(O)₂R¹⁵, -NR¹⁴C(O)NR¹²R¹³, -OC(O)NR¹²R¹³, NR¹⁴C(O)OR¹⁵, -C(O)OR¹⁵, -OC(O)R¹⁵ or heterocyclyl;

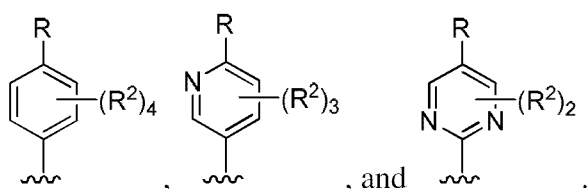
each R¹² and R¹³ is independently selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, aryl and heteroaryl; or

R¹² and R¹³ together form a substituted or unsubstituted heterocyclyl ring system; and

R¹⁴ and R¹⁵ are selected from hydrogen, alkyl, carbocyclyl, heterocyclyl, aryl and heteroaryl.

5. A compound of claim 4, wherein X³ of A1 is CR², R² is NR⁴R⁵, R⁴ is hydrogen and R⁵ is heterocyclyl.

6. A compound of claim 1 or 4, wherein A is selected from

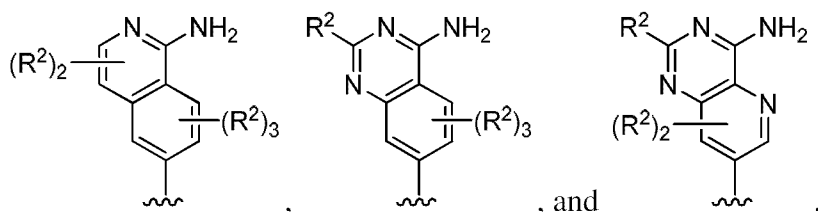


7. A compound of claim 1, wherein A is A2 and each occurrence of X is independently CR².

8. A compound of claim 1, wherein A is A2 and one or two occurrences of X are N.

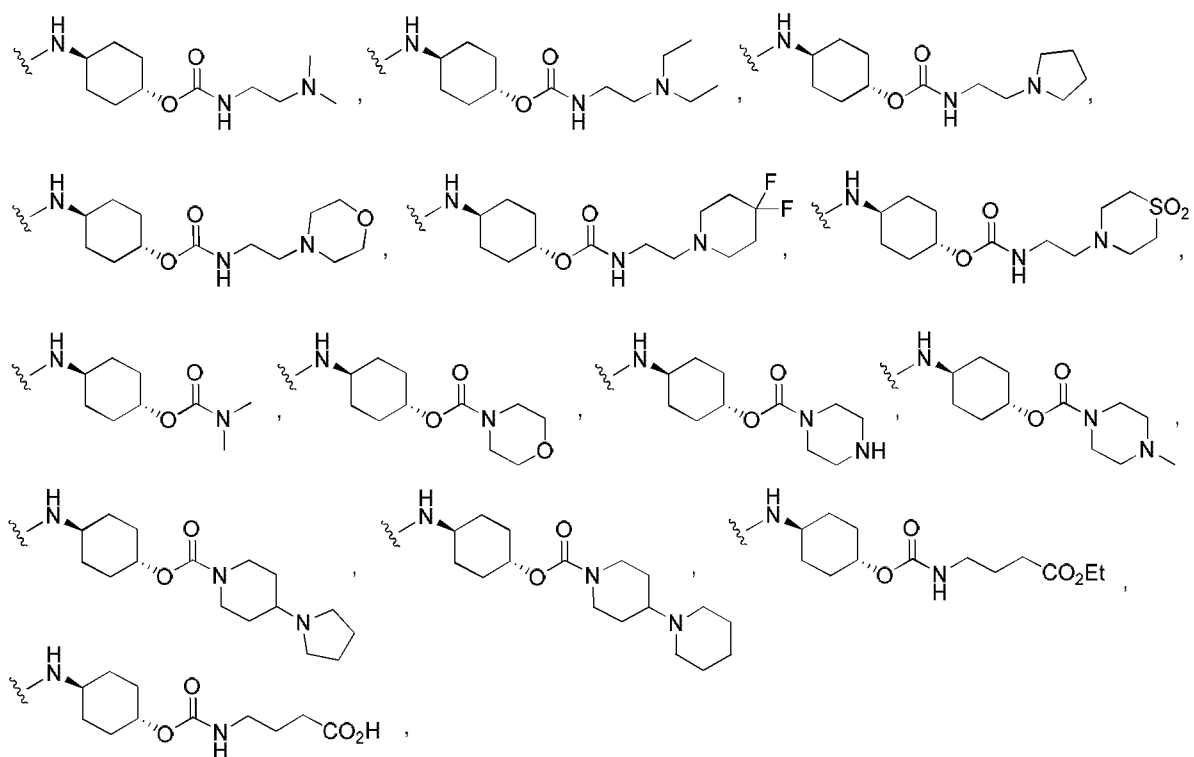
9. A compound of any one of claims 1, 7, or 8, preferably where X⁶, X⁷, or X⁸ is CR², more preferably the R² attached to X⁸ is CR² of A2, is other than hydrogen.

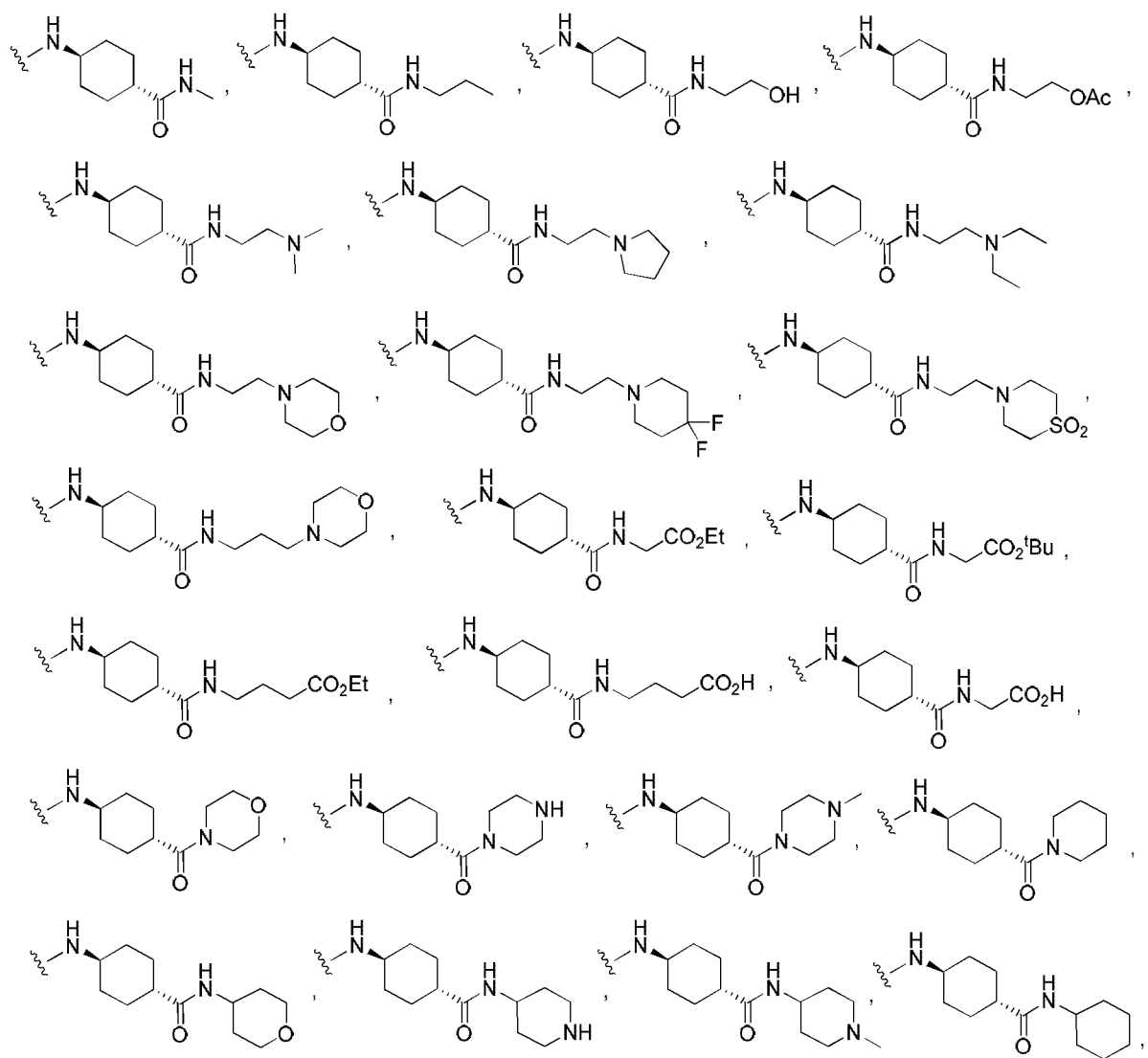
10. A compound of claim 1, wherein A is selected from

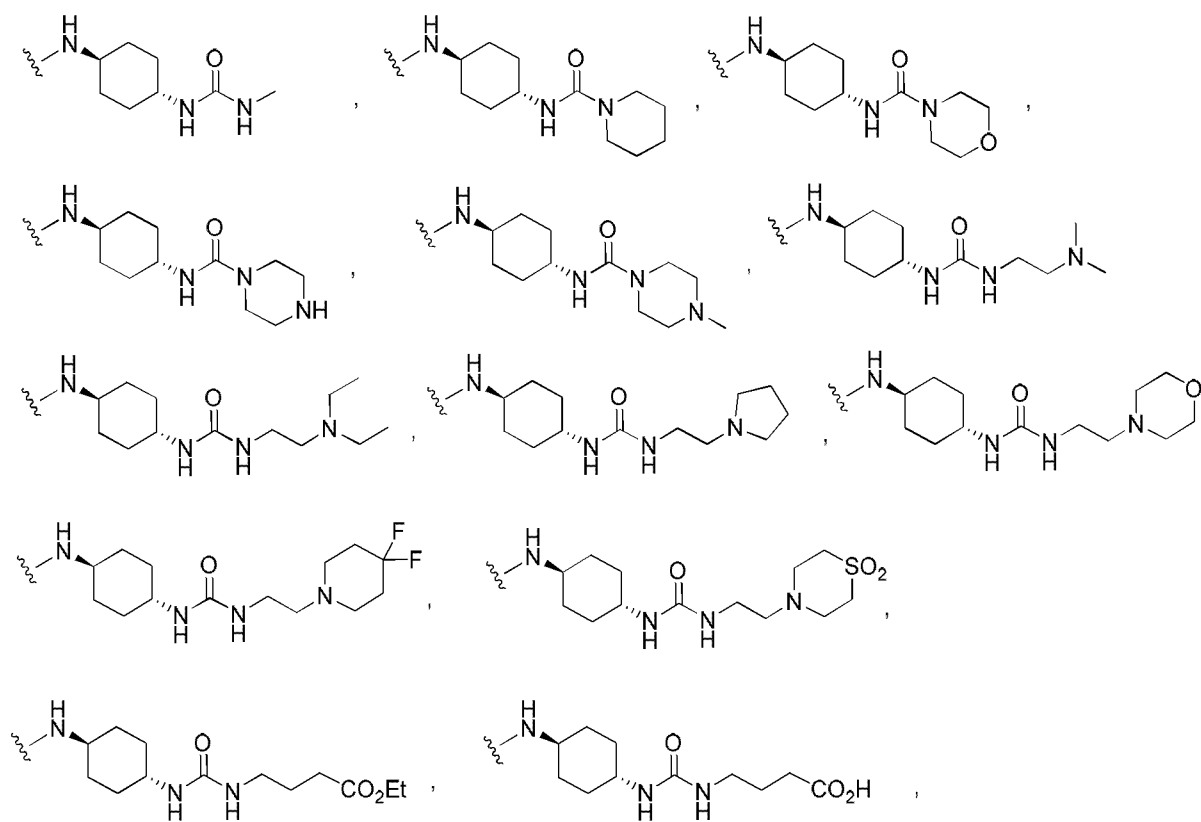


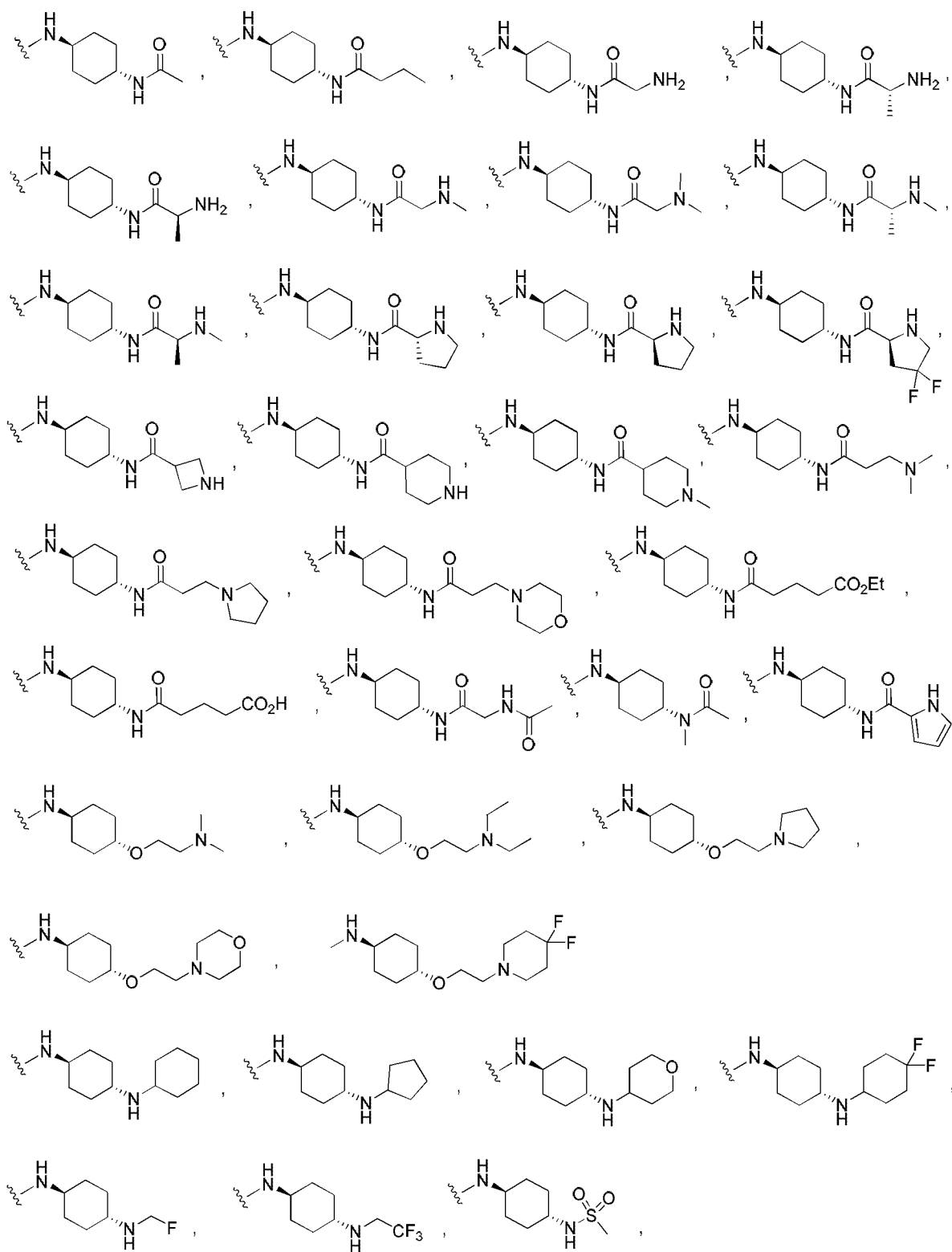
11. A compound of any one of claims 1 to 10, wherein each R² is independently selected from hydrogen, halogen, -CN, alkyl, -OR³, -NR⁴R⁵, -S(O)_mR³, and -C(O)NR⁴R⁵.

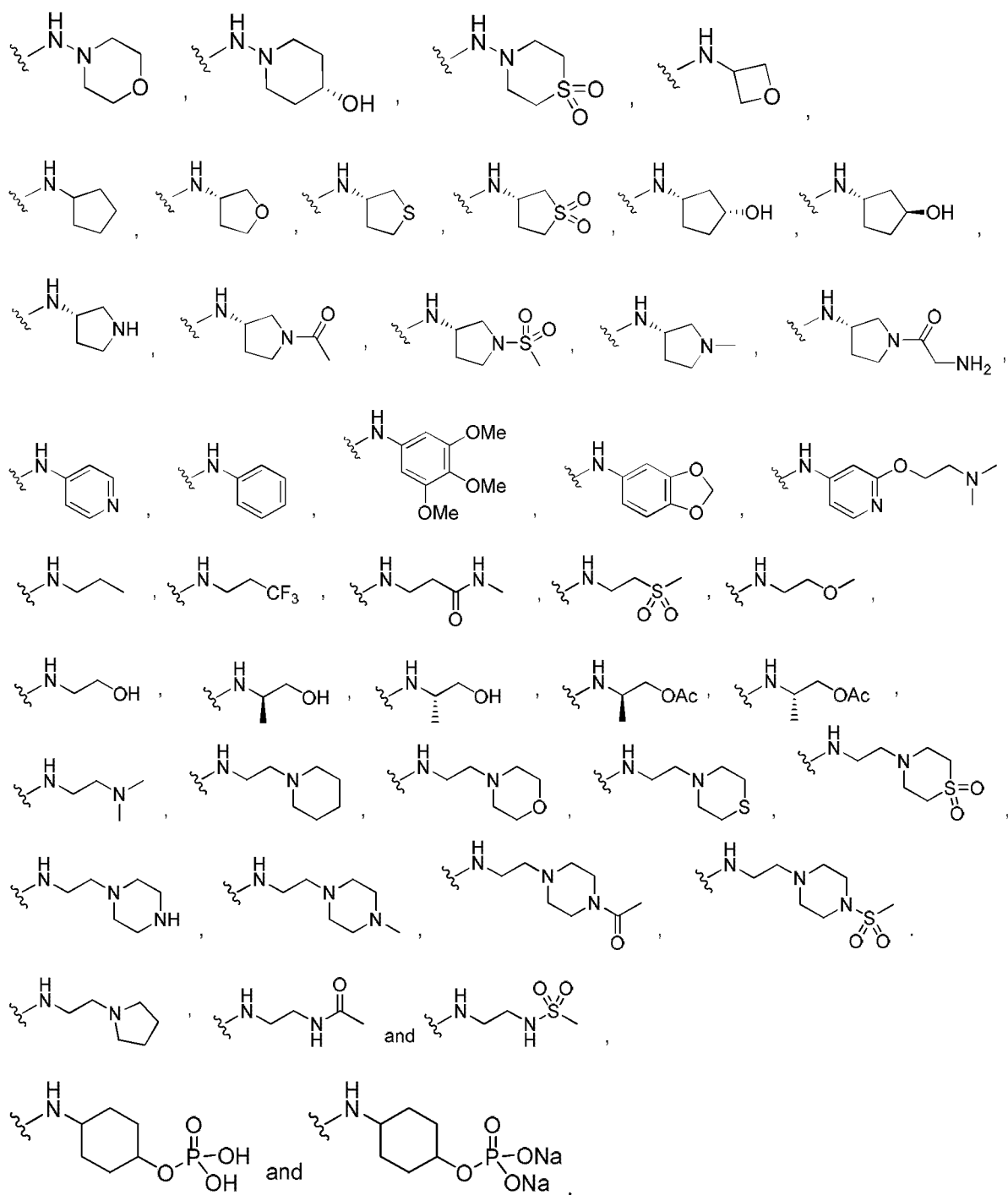
12. A compound of any one of claims 1 to 11, wherein at least one occurrence of R², preferably R² attached to X³ of A1, is selected from











13. A compound of any one of claims 1 to 11, wherein A is A2 and at least one occurrence of R^2 , preferably where X^6 , X^7 , or X^8 is CR^2 is alkyl, preferably methyl, ethyl, propyl, isopropyl, butyl, or isobutyl.

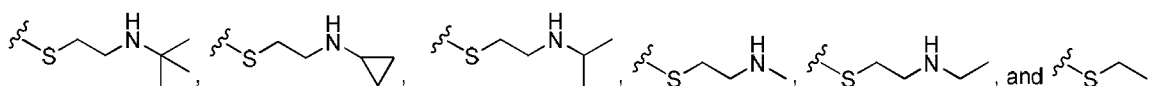
14. A compound of any one of claims 1 to 11, wherein A is A2 and at least one occurrence of R^2 , preferably where X^6 , X^7 , or X^8 is CR^2 is selected from alkyl, halogen, $-OR^3$, and $-S(O)_mR^3$.

15. A compound of any one of claims 1 to 11, wherein A is A2 and at least one occurrence of R^2 , preferably where X^6 , X^7 , or X^8 is CR^2 , is halogen, preferably Br or F.

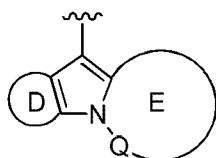
16. A compound of any one of claims 1 to 11, wherein A is A2 and at least one occurrence of R^2 , preferably where X^6 , X^7 , or X^8 is CR^2 is $-OR^3$.

17. A compound of claim 16, wherein $-OR^3$ is selected from $-O(CH_2)_2OCH_3$, $-O(CH_2)_2N(CH_3)_2$, $-O(CH_2)_2OH$, and OEt.

18. A compound of claim 17, wherein $-S(O)_mR^3$ is selected from



19. A compound of any one of claims 1 to 18, wherein B is

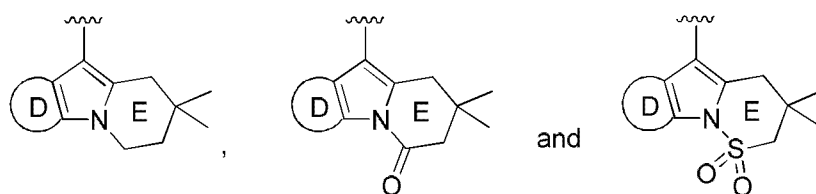


wherein Q is selected from $-C(O)-$, and $-S(O)_n-$; and n is an integer from 1 to 2.

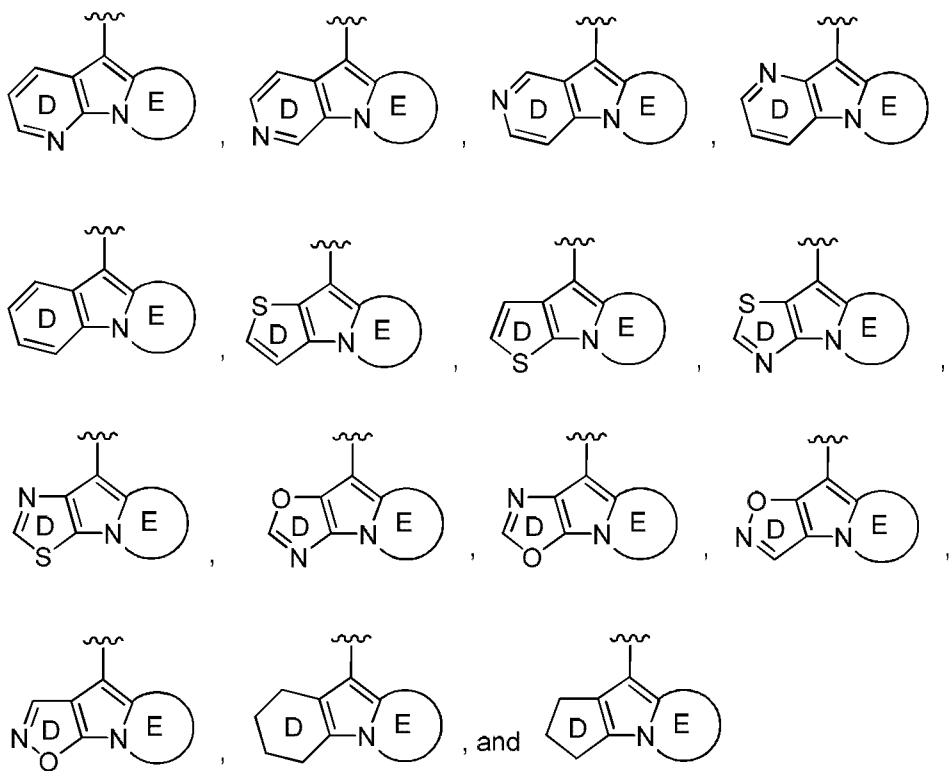
20. A compound of any one of claims 1 to 19, wherein D is aryl or heteroaryl, preferably phenyl, pyridyl, thienyl, thiazolyl, oxazole, or isoxazole.

21. A compound of any one of claims 1 to 20, wherein D is carbocyclyl, preferably cyclopentyl or cyclohexyl.

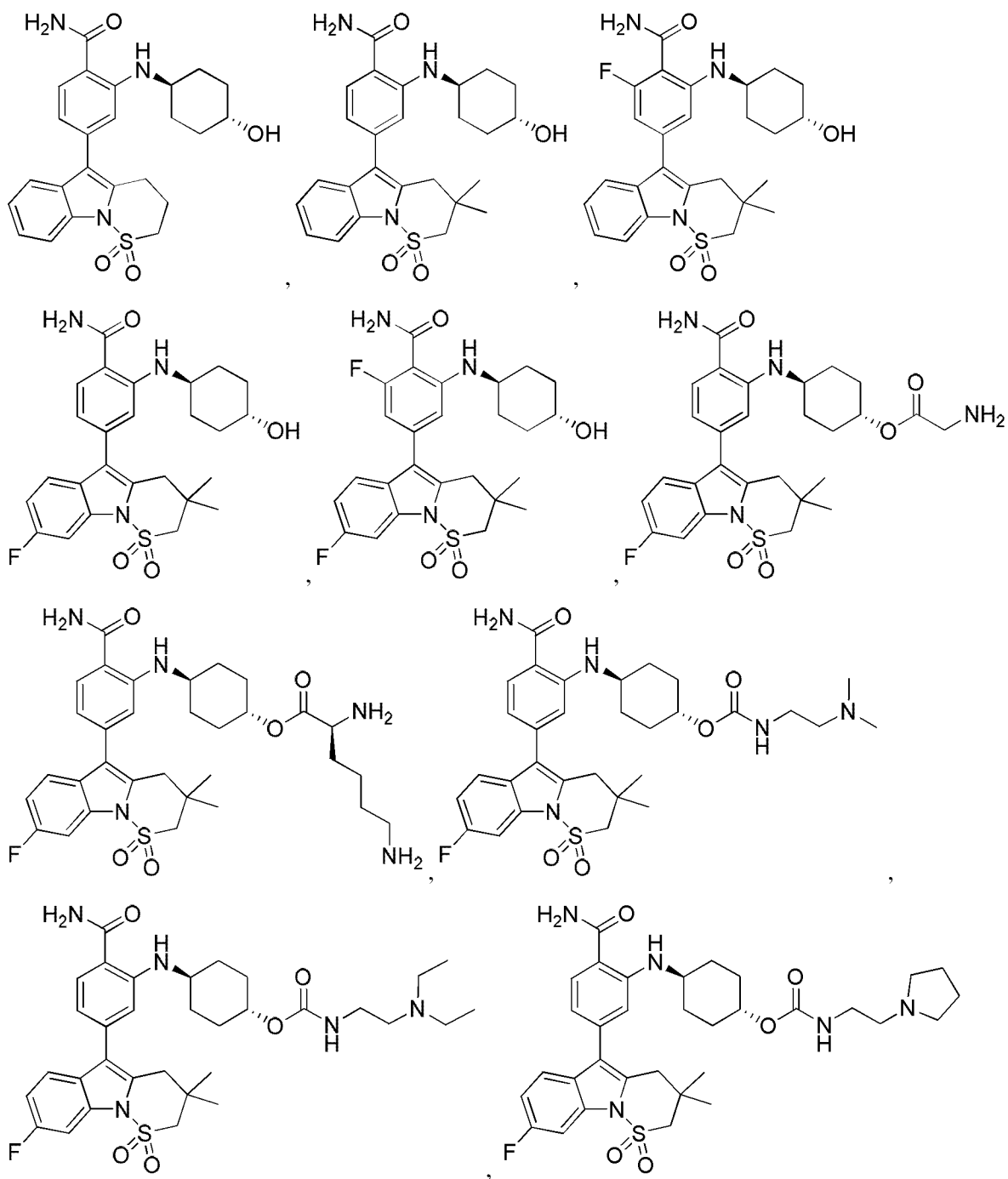
22. A compound of any one of claims 1 to 21, wherein B is selected from

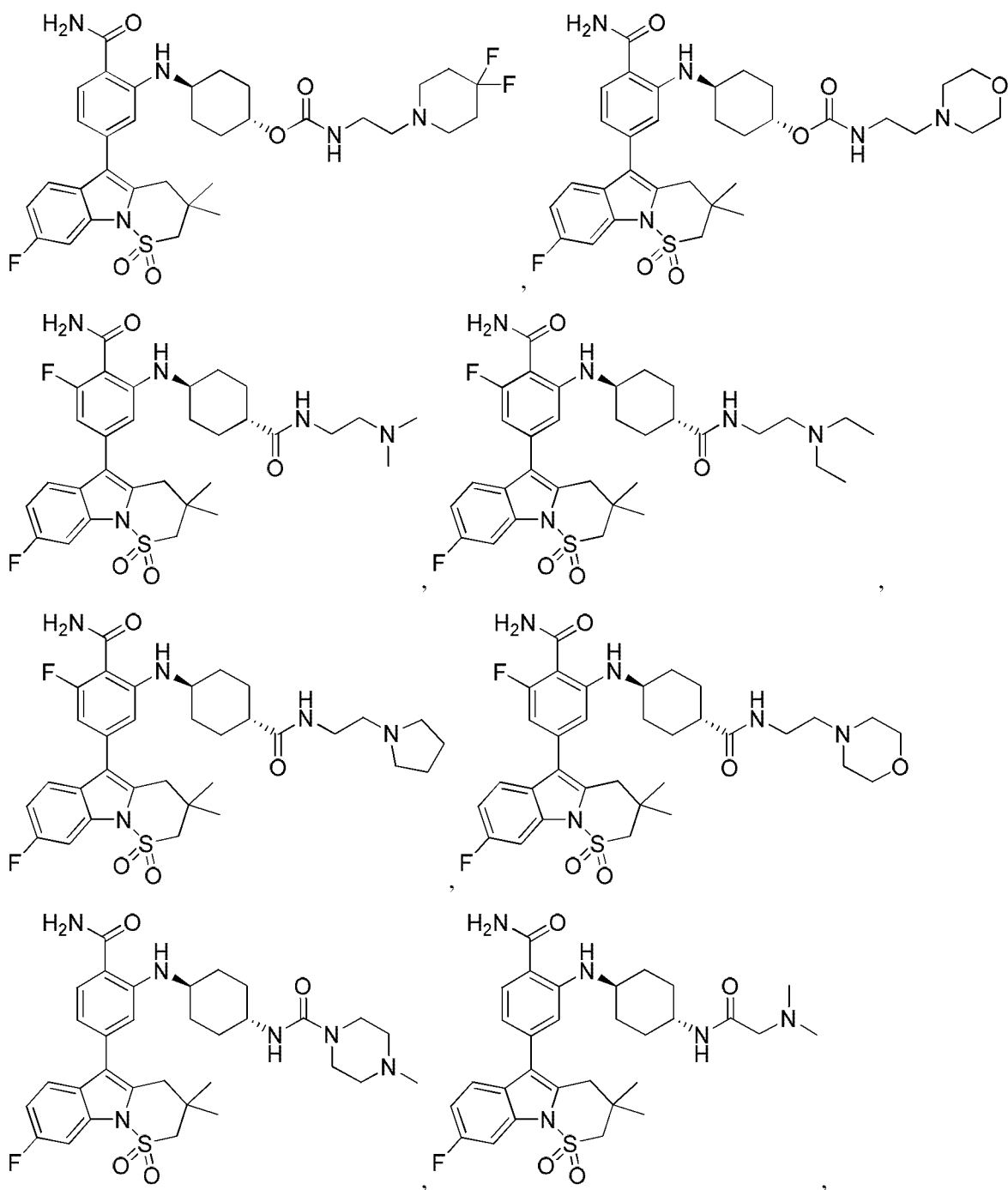


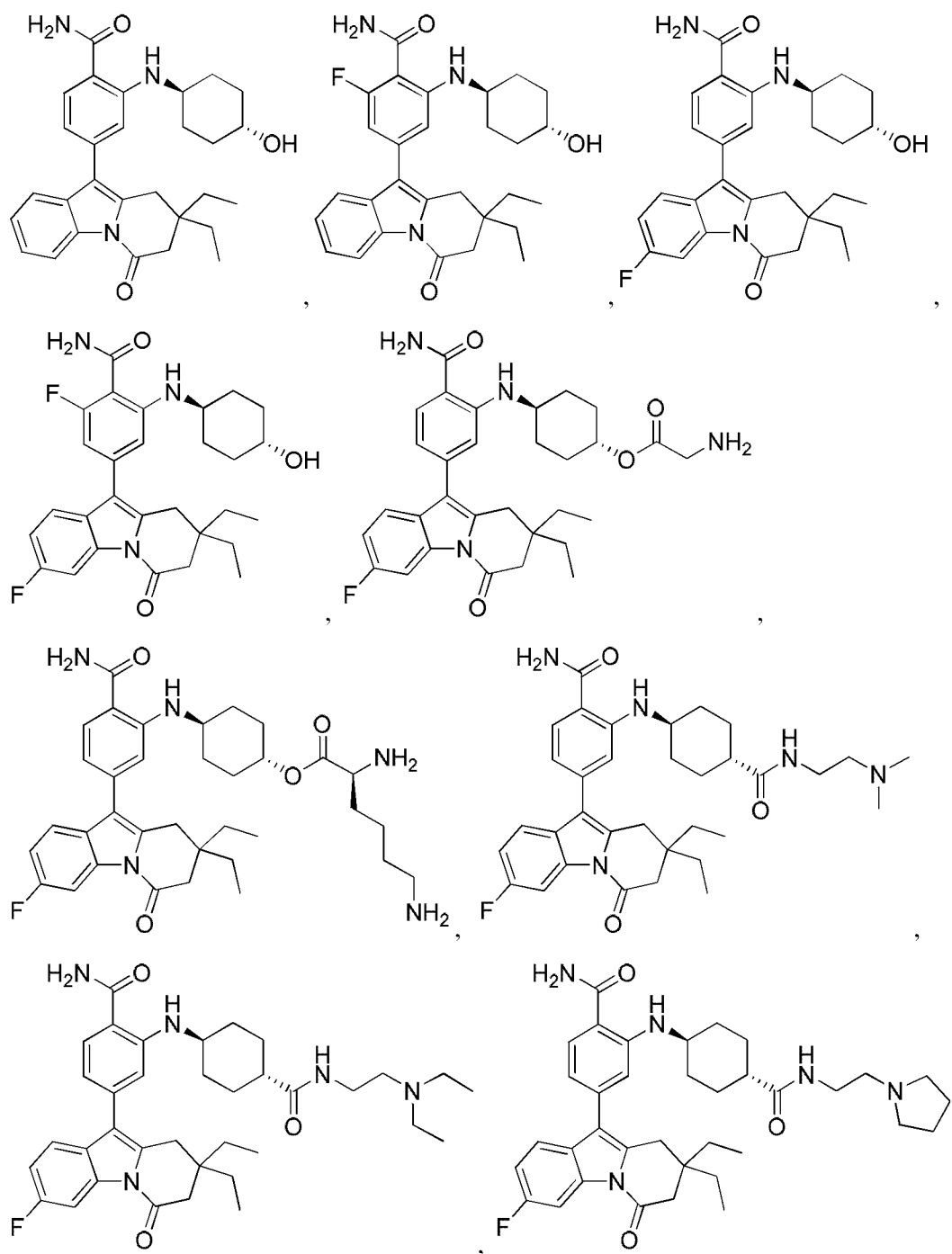
23. A compound of any one of claims 1 to 22, wherein B is selected from

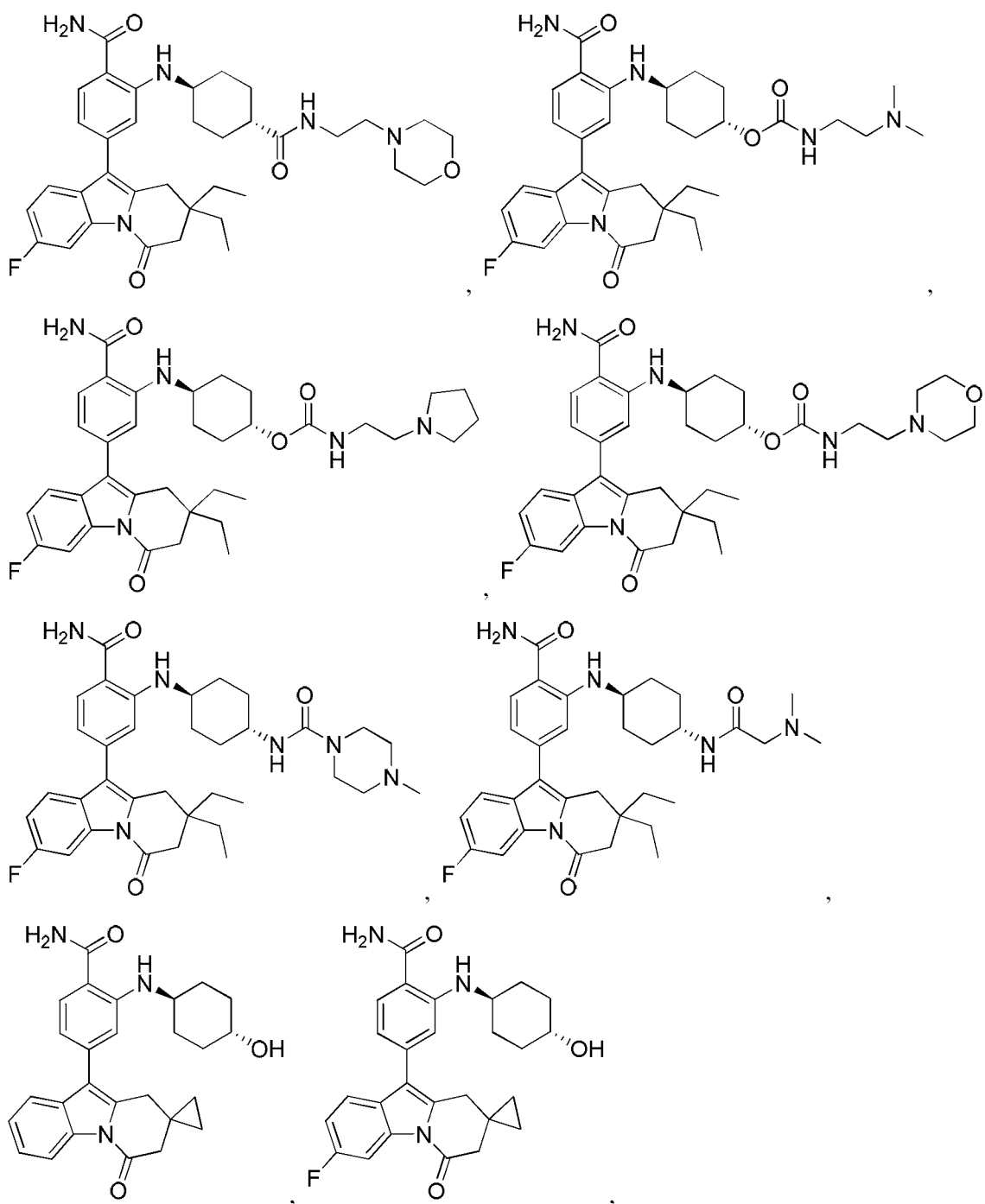


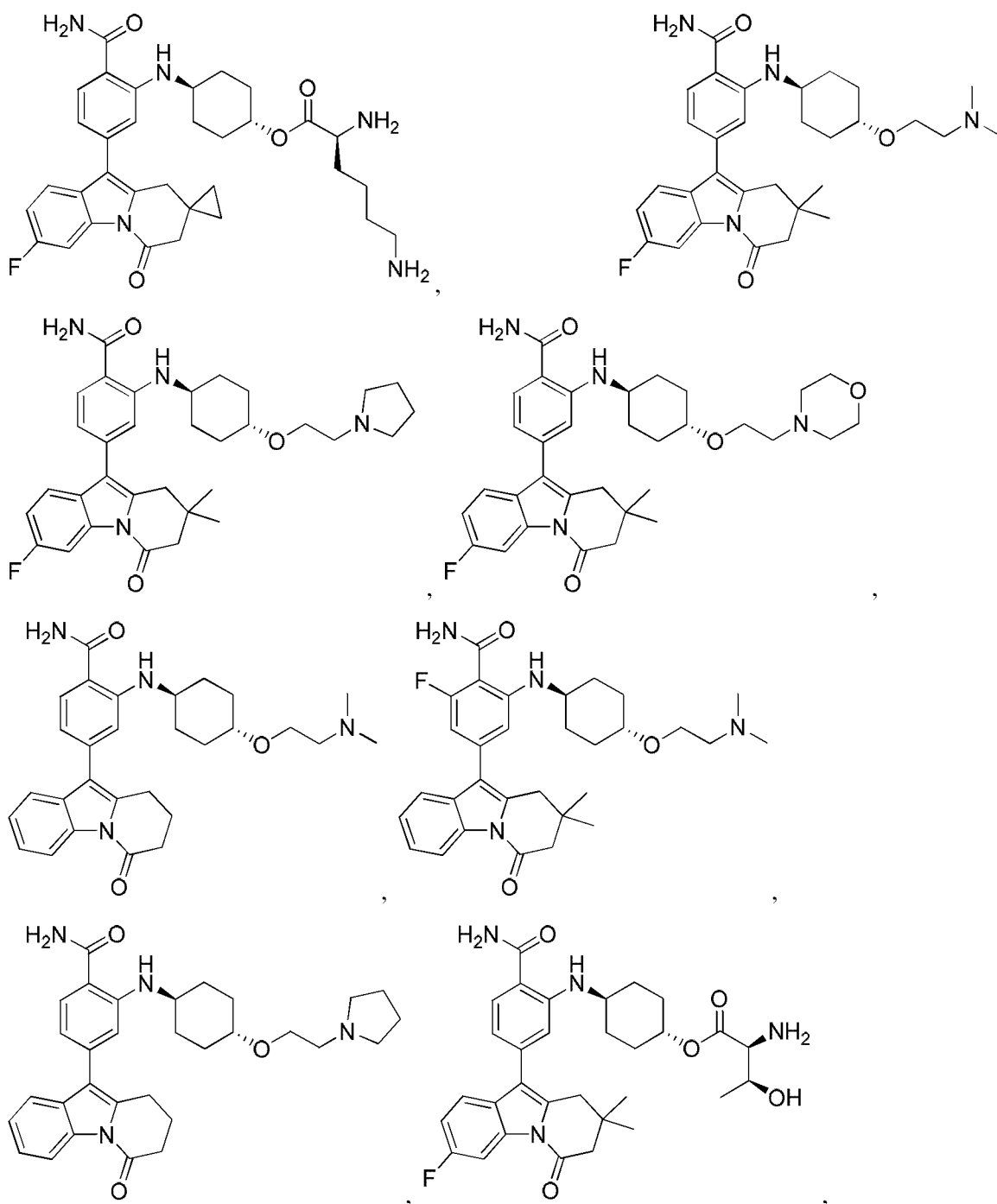
24. A compound of claim 1, wherein a compound of Formula 1 is selected from

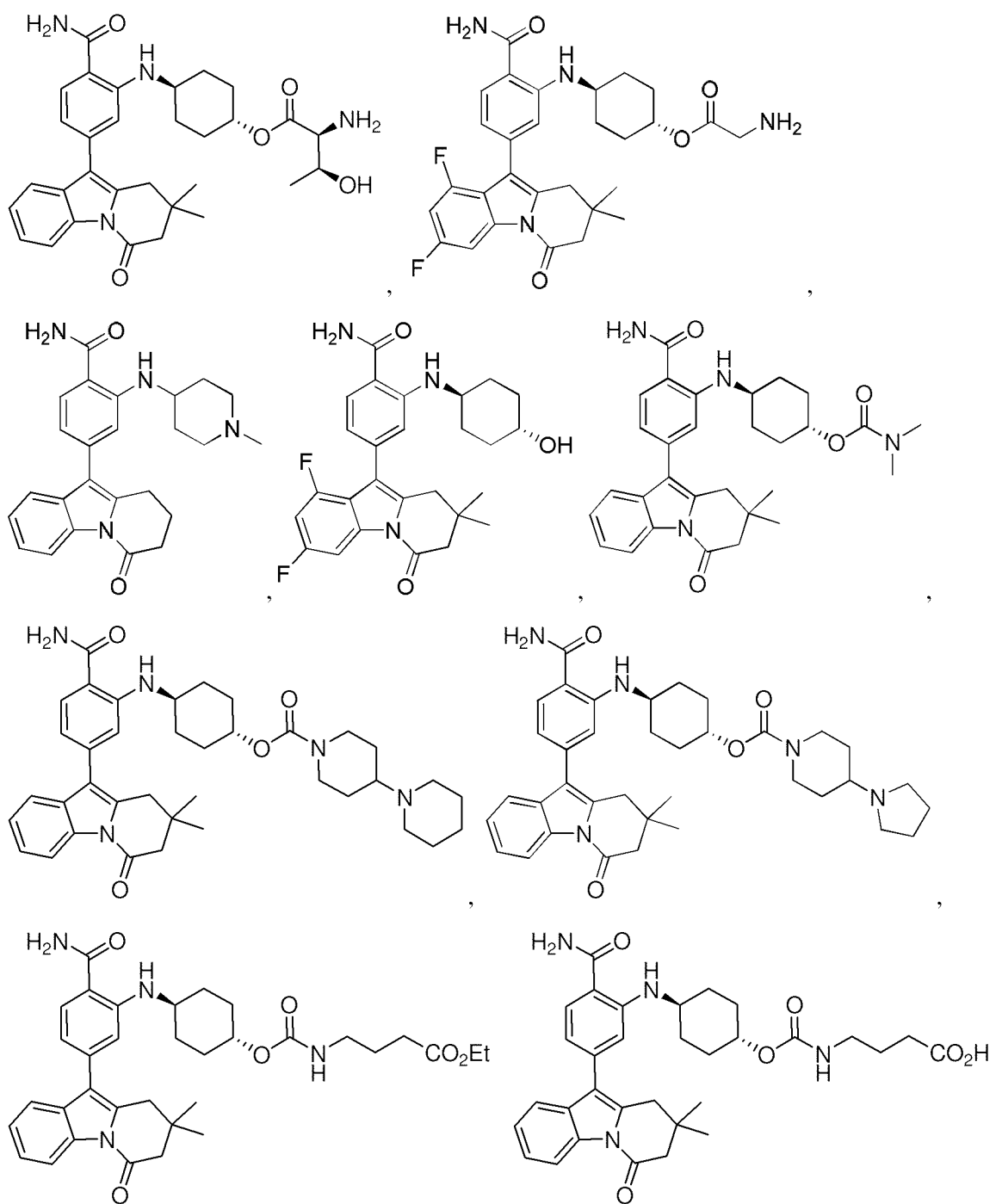


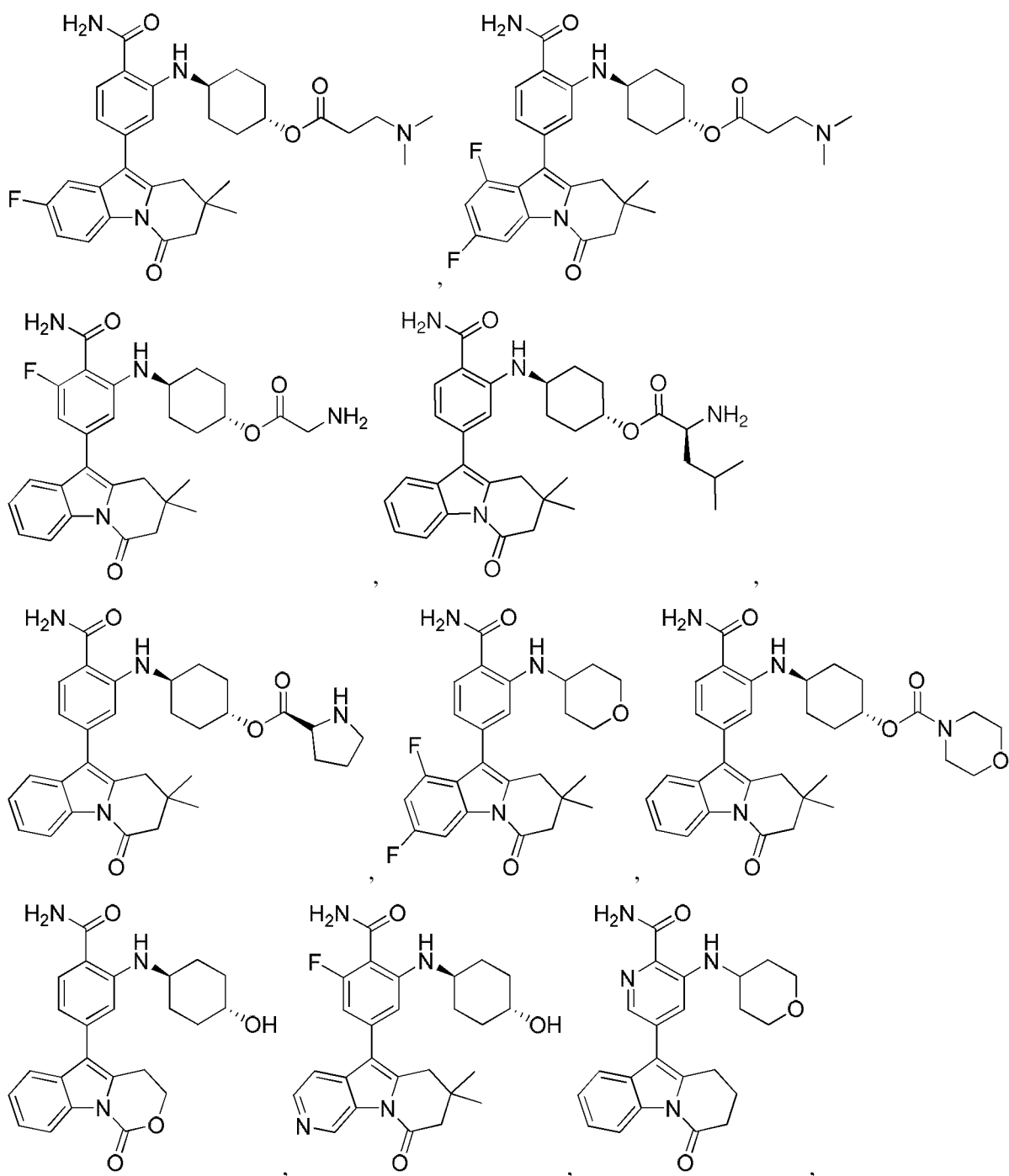


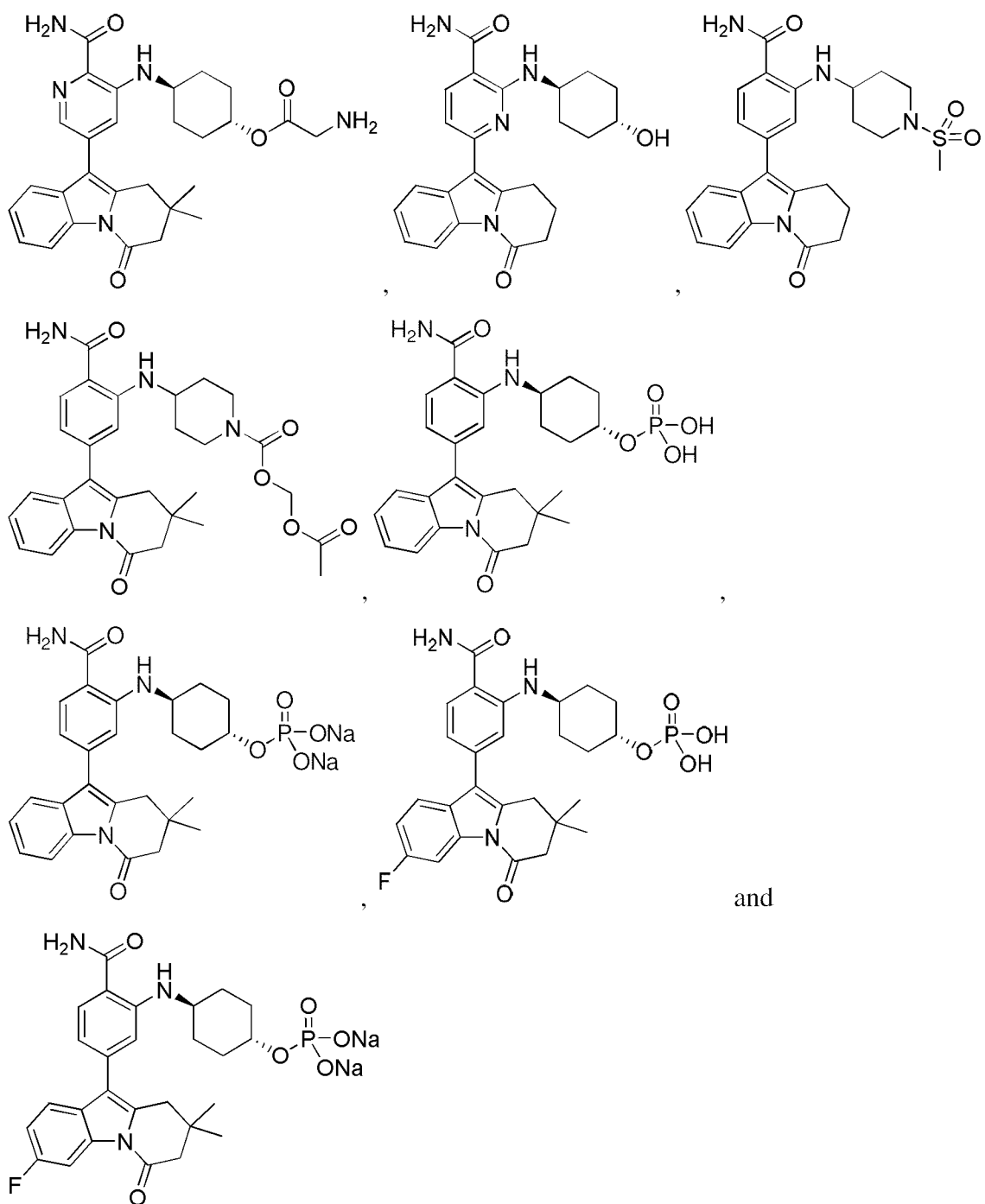




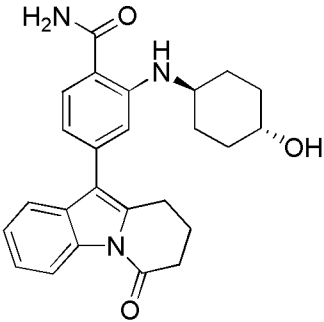
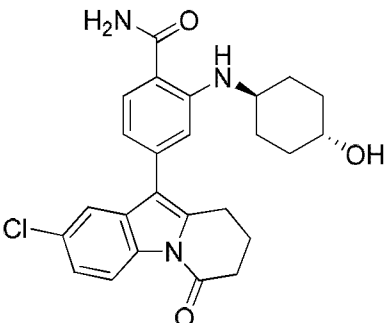
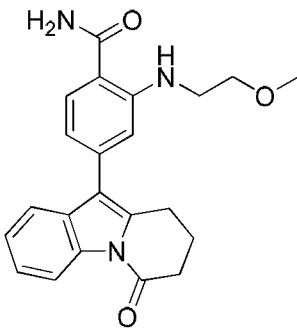


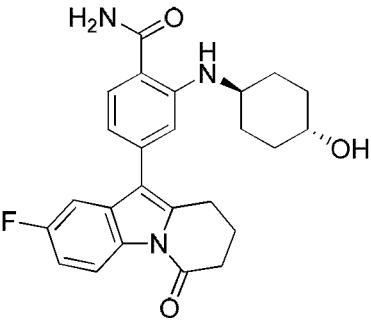
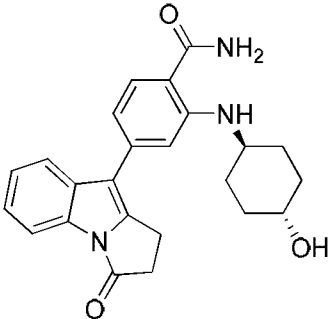
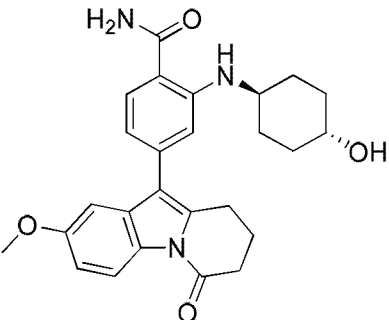
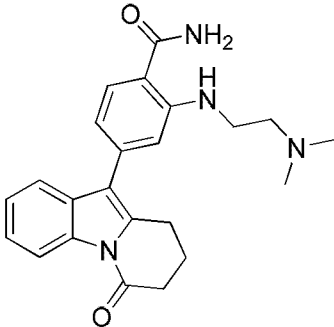




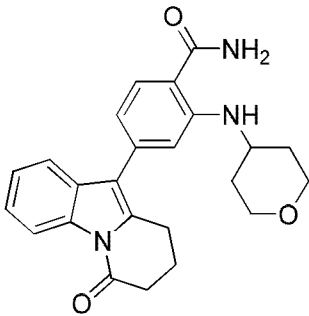
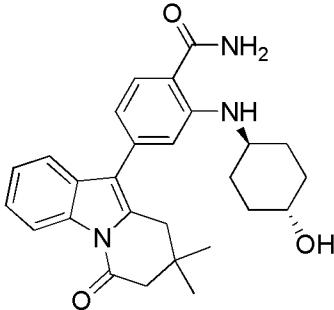
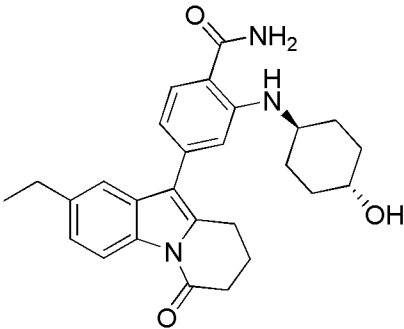
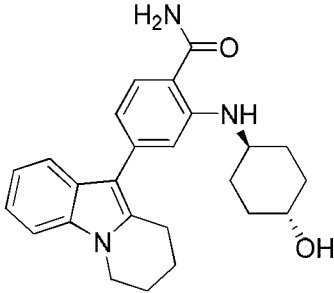


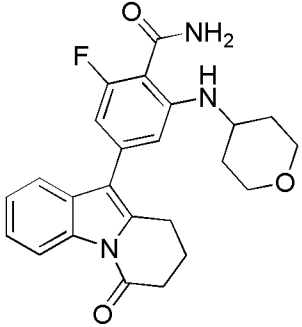
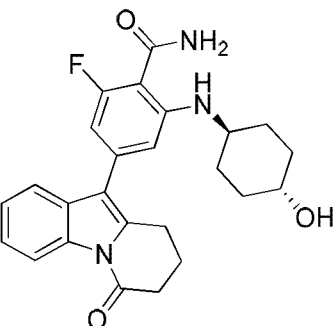
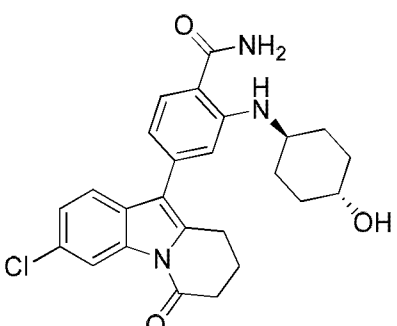
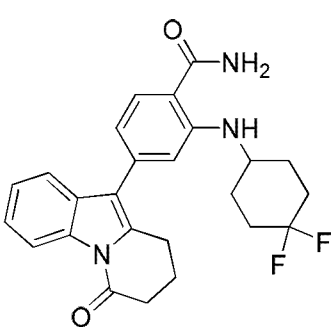
25. A compound of claim 1, wherein a compound of Formula 1 is selected from

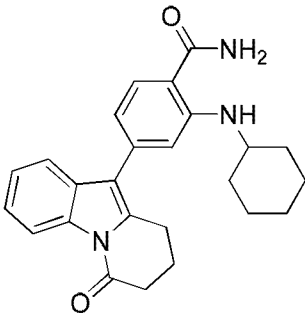
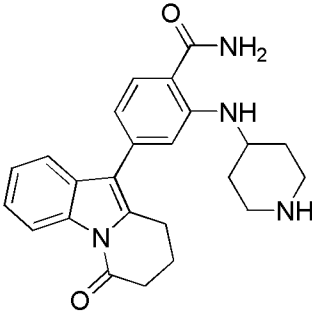
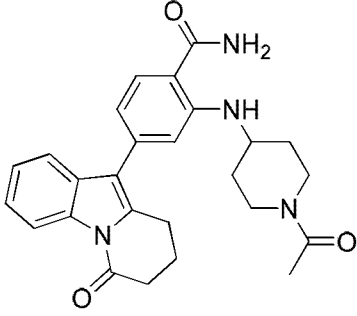
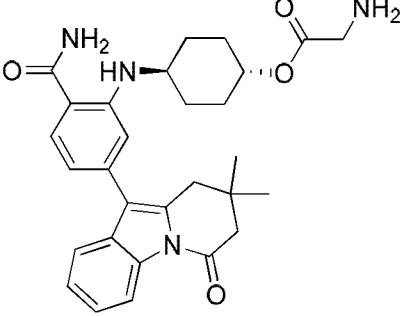
COMPOUND	STRUCTURE
1	
2	
3	

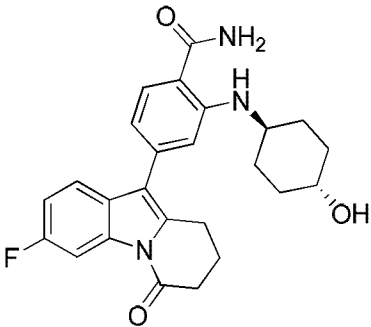
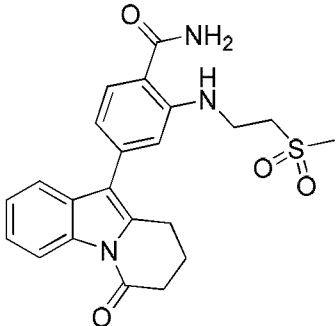
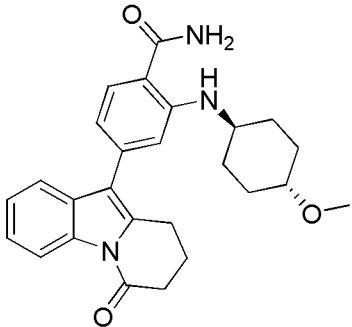
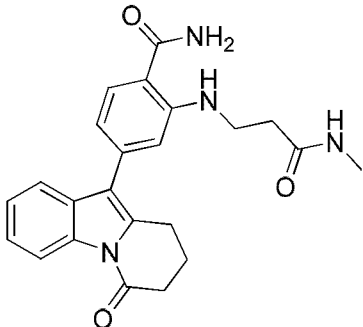
COMPOUND	STRUCTURE
4	
5	
6	
7	

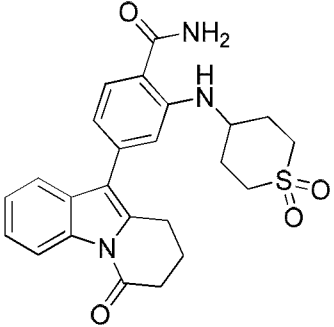
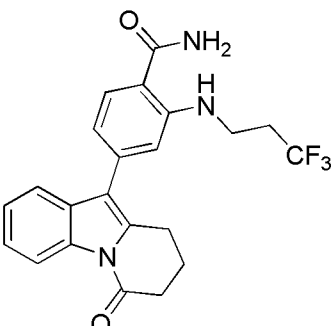
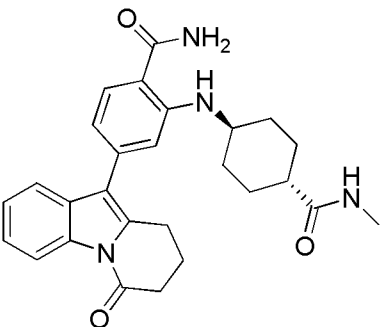
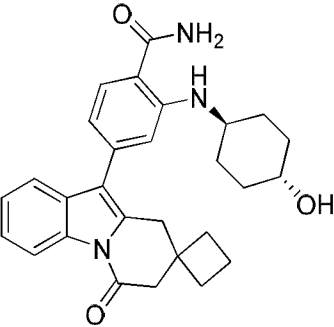
COMPOUND	STRUCTURE
8	 <chem>CCCNc1ccc(cc1C2=CN3CCCCC3C(=O)N2)c4ccccc4C#N</chem>
9	 <chem>C1CCNCC1Nc2ccc(cc2C3=CN4CCCC4C(=O)N3)c5ccccc5C#N</chem>
10	 <chem>C1CCC(CC1)CNC2=CN3CCCCC3C(=O)N2c4ccc(cc4C5=CN6CCCCC6C(=O)N5)c7ccccc7C#N</chem>
11	 <chem>C1CCC(CC1)CNC2=CN3CCCCC3C(=O)N2c4ccc(cc4C5=CN6CCCCC6C(=O)N5)c7ccccc7C#N</chem>

COMPOUND	STRUCTURE
12	
13	
14	
15	

COMPOUND	STRUCTURE
16	
17	
18	
19	

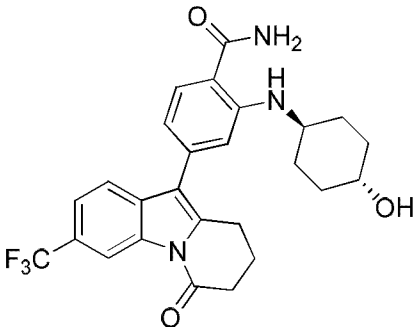
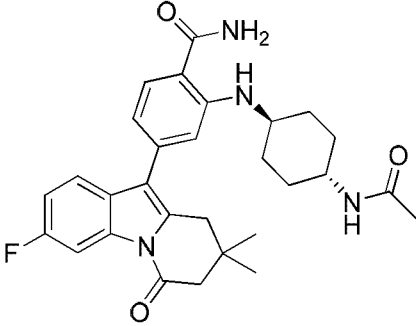
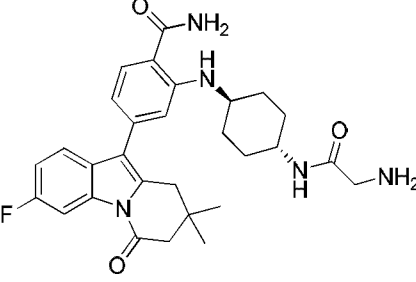
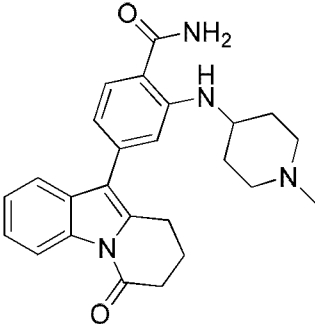
COMPOUND	STRUCTURE
20	
21	
22	
23	

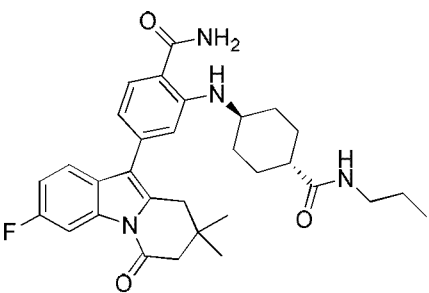
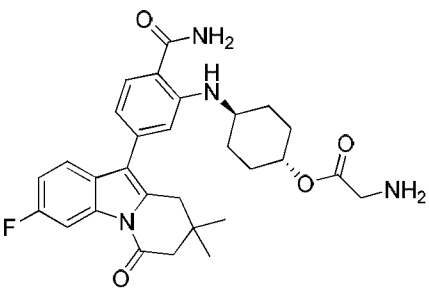
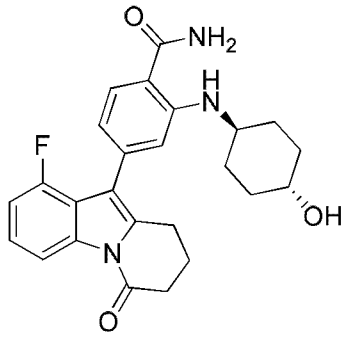
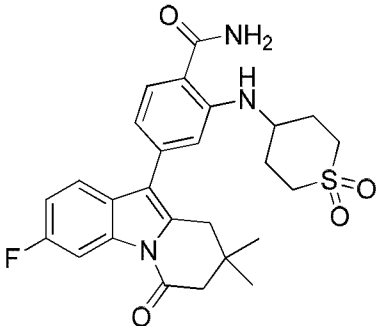
COMPOUND	STRUCTURE
24	
25	
26	
27	

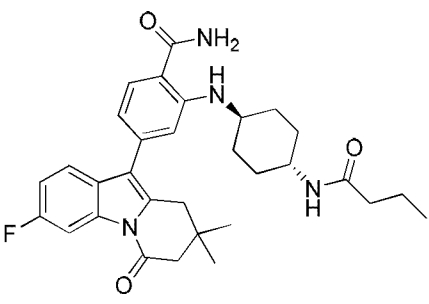
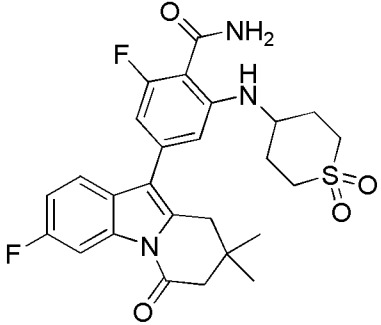
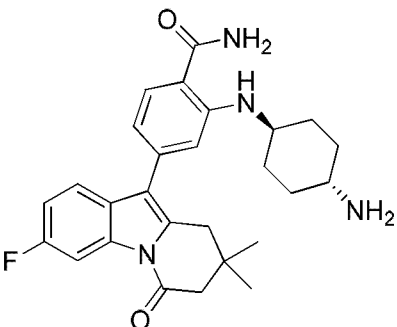
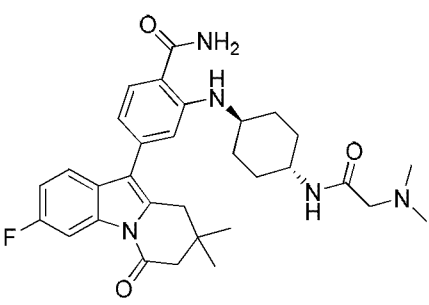
COMPOUND	STRUCTURE
28	
29	
30	
31	

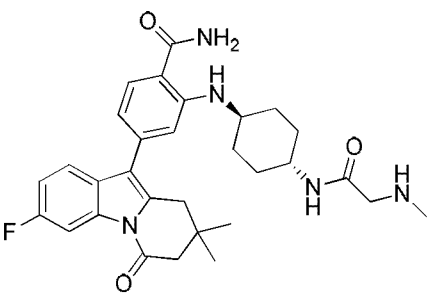
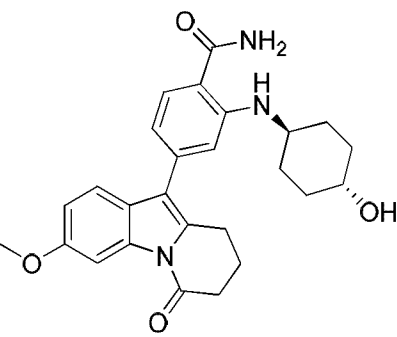
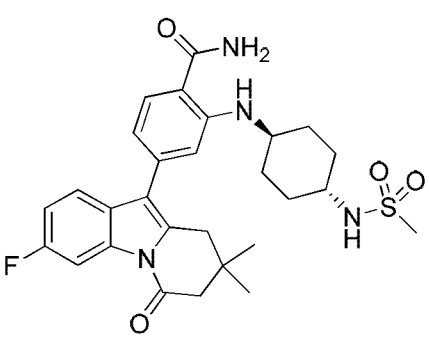
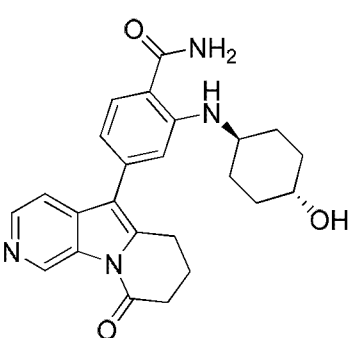
COMPOUND	STRUCTURE
32	Chemical structure of compound 32: A benzamide derivative. The benzamide core is substituted with a piperidine ring at the 2-position and a 2,3-dihydro-1H-indolizin-5(1H)-one system at the 4-position.
33	Chemical structure of compound 33: A benzamide derivative. The benzamide core is substituted with a 4-fluoro-2,3-dihydro-1H-indolizin-5(1H)-one system at the 2-position and a 4-hydroxycyclohexyl group at the 4-position.
34	Chemical structure of compound 34: A benzamide derivative. The benzamide core is substituted with a 4-fluoro-2,3-dihydro-1H-indolizin-5(1H)-one system at the 2-position and a 4-hydroxycyclohexyl group at the 4-position.
35	Chemical structure of compound 35: A benzamide derivative. The benzamide core is substituted with a 4-fluoro-2,3-dihydro-1H-indolizin-5(1H)-one system at the 2-position and a 4-methoxycyclohexyl group at the 4-position.

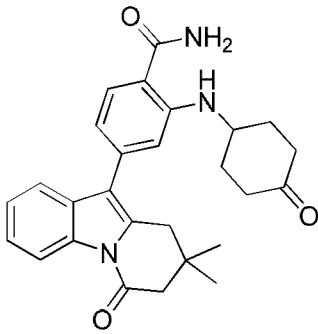
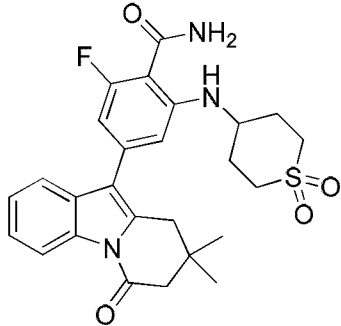
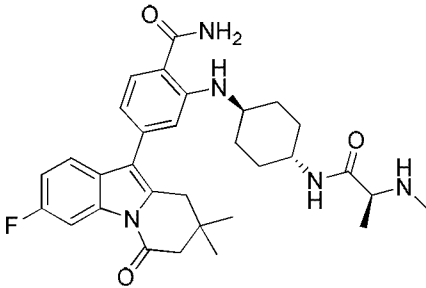
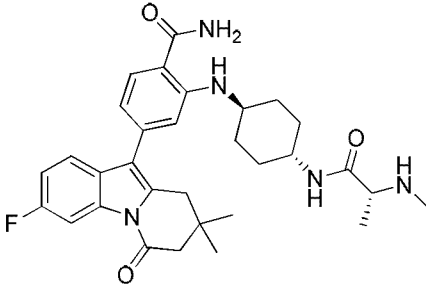
COMPOUND	STRUCTURE
36	 <chem>CC(=O)N[C@H]1CCCC[C@H]1NC(=O)c2ccc(NC(=O)c3ccccc3)cc2C4=Cc5cc(F)ccc5N4C(=O)C6(C)CCCC6=O</chem>
37	 <chem>NC(=O)c1ccc(NC(=O)c2ccccc2)cc1C3=Cc4ccccc4N3C(=O)C5(C)CCCC5=O</chem>
38	 <chem>CC(=O)N[C@H]1CCCC[C@H]1NC(=O)c2ccc(NC(=O)c3ccccc3)cc2C4=Cc5ccccc5N4C(=O)C6(C)CCCC6=O</chem>
39	 <chem>NC(=O)c1ccc(NC(=O)c2ccccc2)cc1C3=Cc4cc(CCCC)ccc4N3C(=O)C5(C)CCCC5=O</chem>

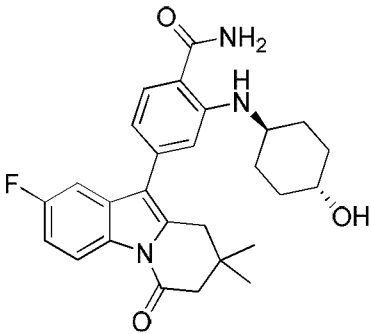
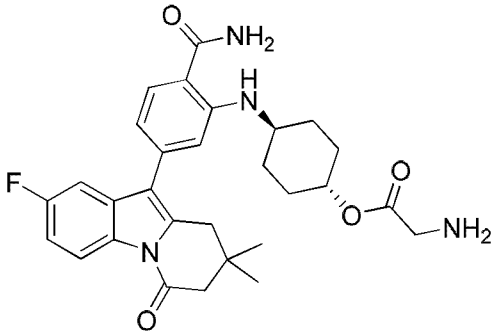
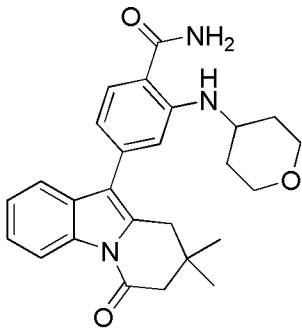
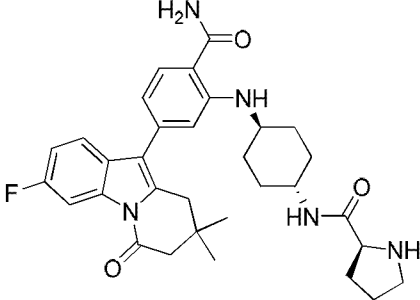
COMPOUND	STRUCTURE
40	
41	
42	
43	

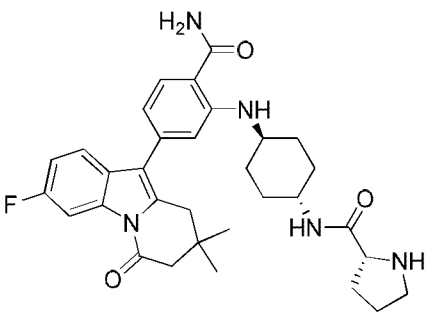
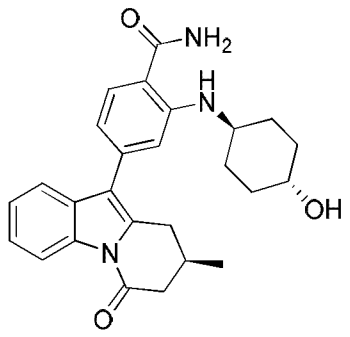
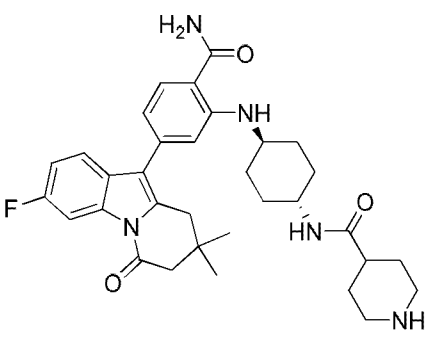
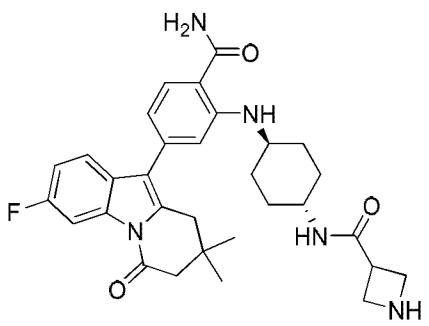
COMPOUND	STRUCTURE
44	
45	
46	
47	

COMPOUND	STRUCTURE
48	
49	
50	
51	

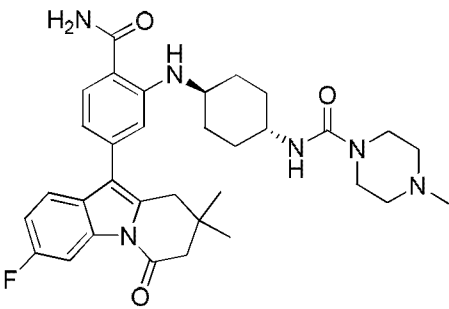
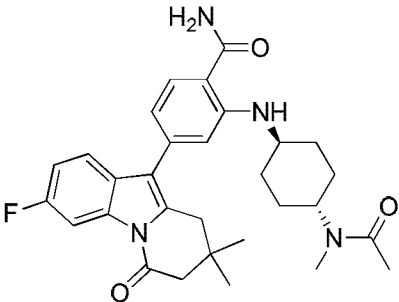
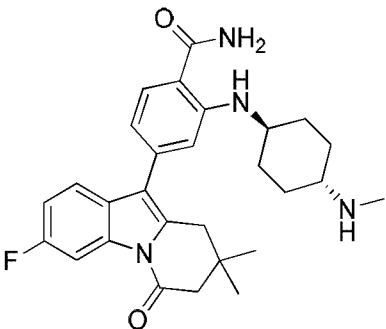
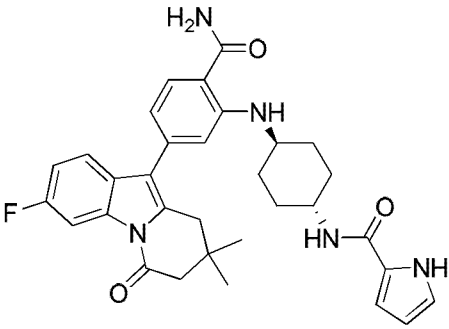
COMPOUND	STRUCTURE
52	
53	
54	
55	

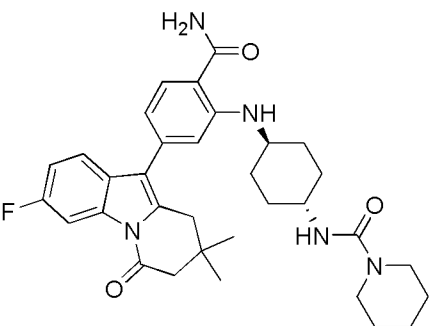
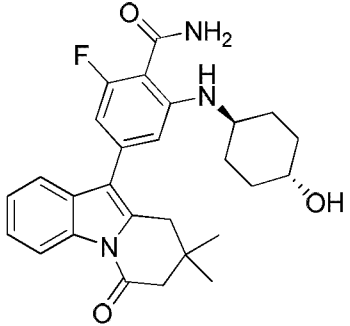
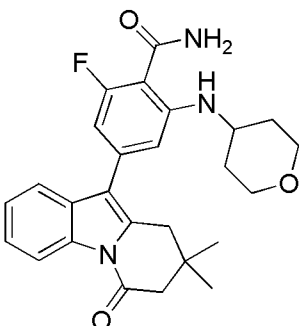
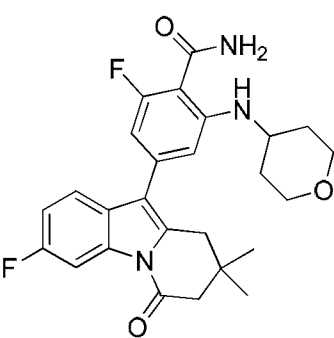
COMPOUND	STRUCTURE
56	
57	
58	
59	

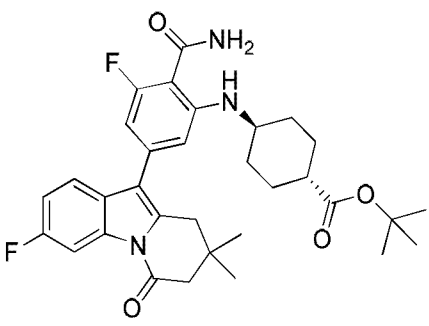
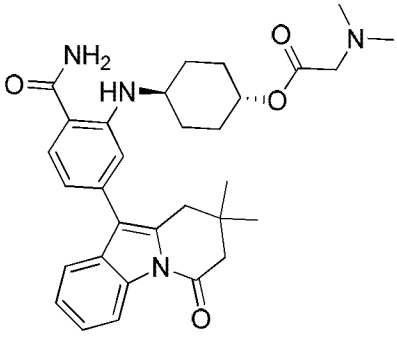
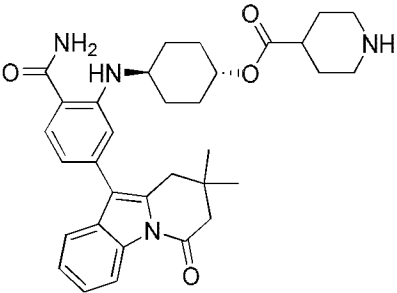
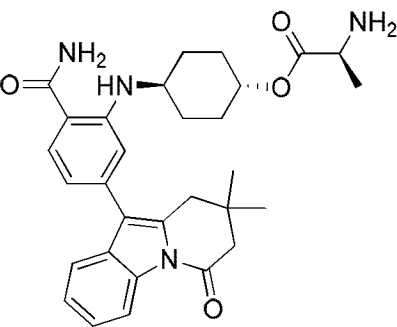
COMPOUND	STRUCTURE
60	
61	
62	
63	

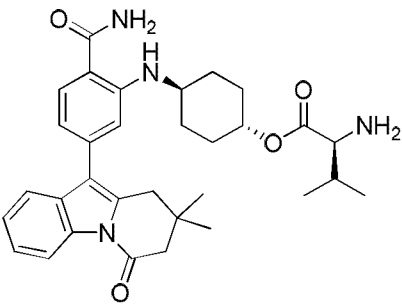
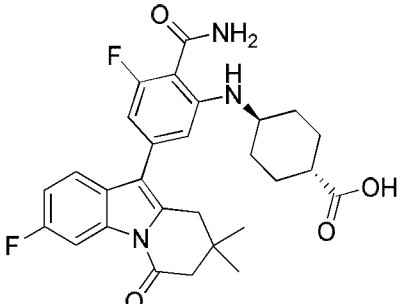
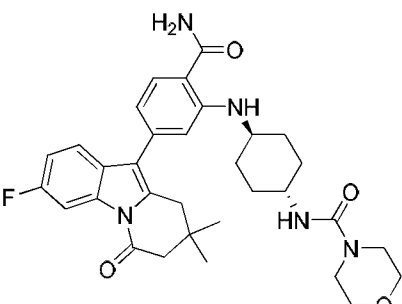
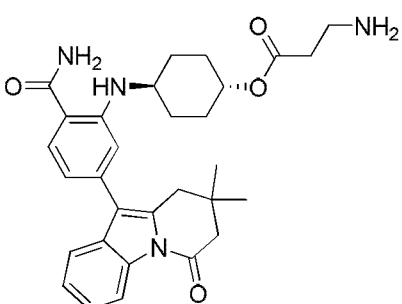
COMPOUND	STRUCTURE
64	
65	
66	
67	

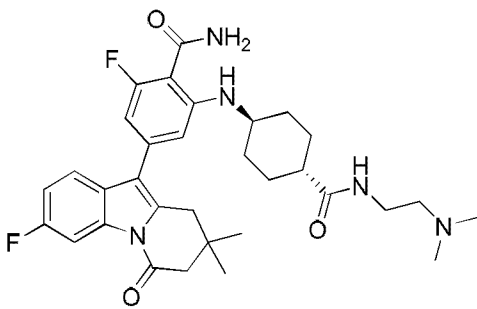
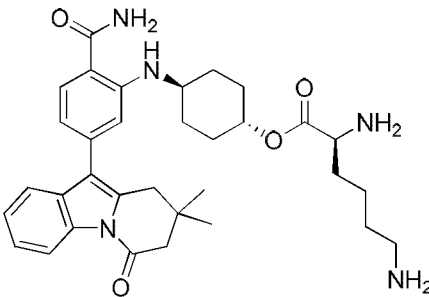
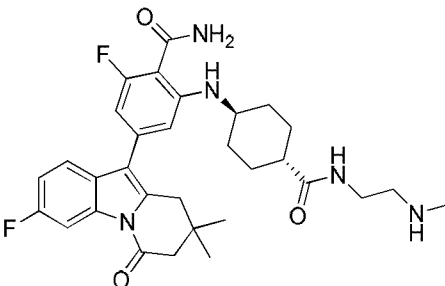
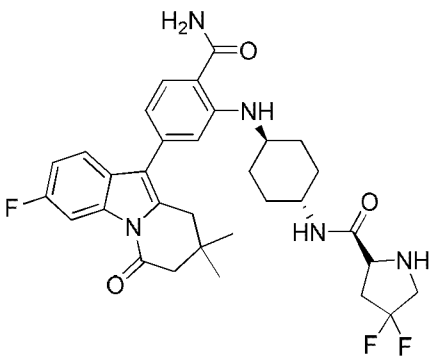
COMPOUND	STRUCTURE
68	 Chemical structure of compound 68: A 4-fluoro-1-(4-((4-aminocarbonylphenyl)amino)-4-oxotetrahydropyran-2-yl)-5,6,7,8-tetrahydro-2H-indolo[1,2-b]pyridine-2-one derivative.
69	 Chemical structure of compound 69: A 4-fluoro-1-(4-((4-aminocarbonylphenyl)amino)-4-oxocyclohexyl)-5,6,7,8-tetrahydro-2H-indolo[1,2-b]pyridine-2-one derivative.
70	 Chemical structure of compound 70: A 4-fluoro-1-(4-((4-aminocarbonylphenyl)amino)-4-oxocyclohexyl)-5,6,7,8-tetrahydro-2H-indolo[1,2-b]pyridine-2-one derivative.
71	 Chemical structure of compound 71: A 4-fluoro-1-(4-((4-aminocarbonylphenyl)amino)-4-oxocyclohexyl)-5,6,7,8-tetrahydro-2H-indolo[1,2-b]pyridine-2-one derivative.

COMPOUND	STRUCTURE
72	
73	
74	
75	

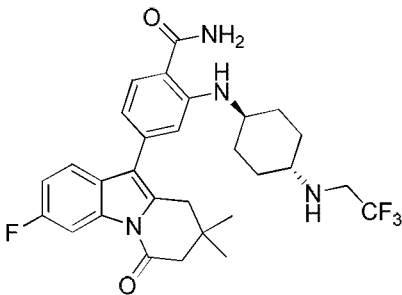
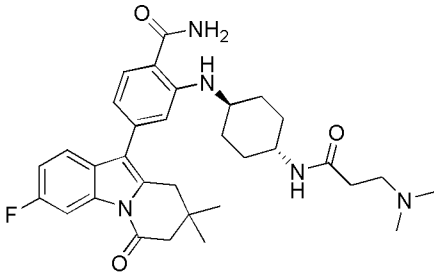
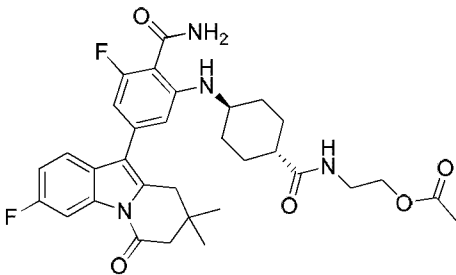
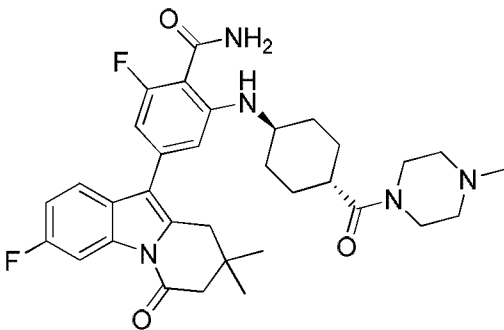
COMPOUND	STRUCTURE
76	
77	
78	
79	

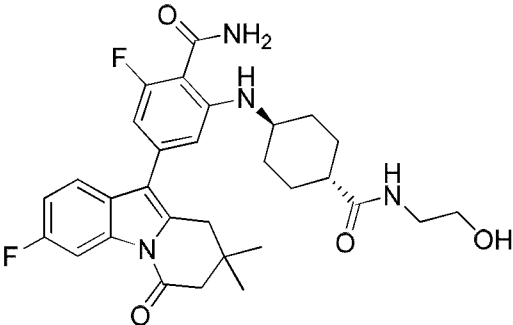
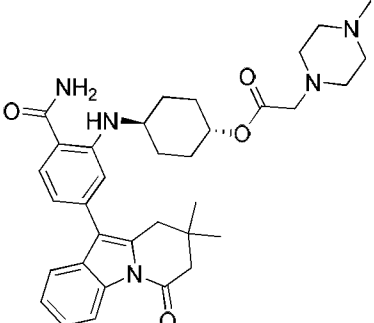
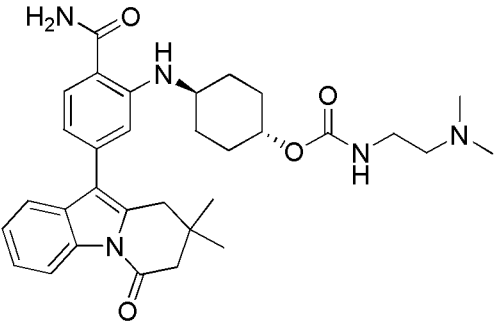
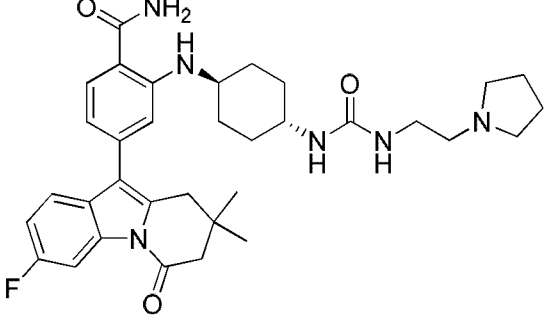
COMPOUND	STRUCTURE
80	
81	
82	
83	

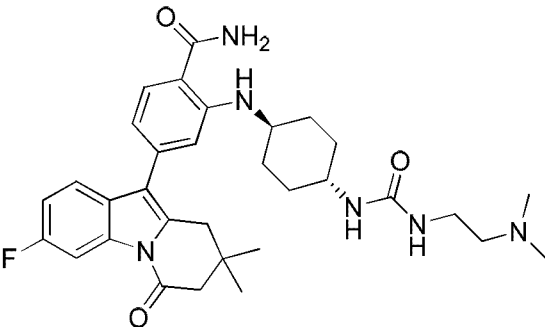
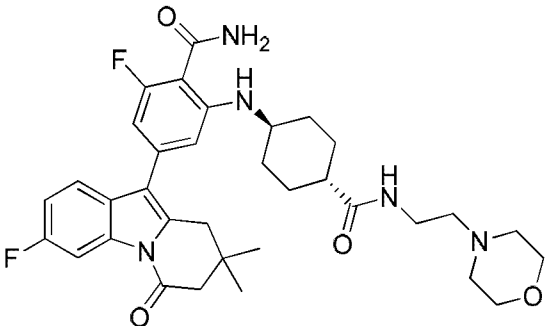
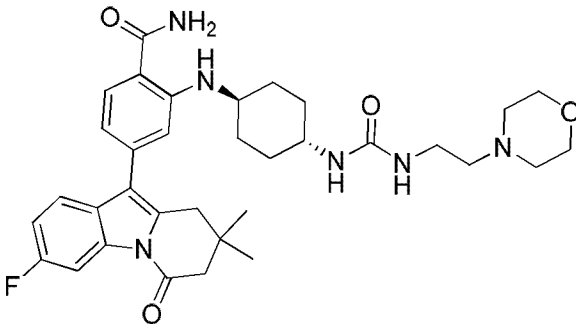
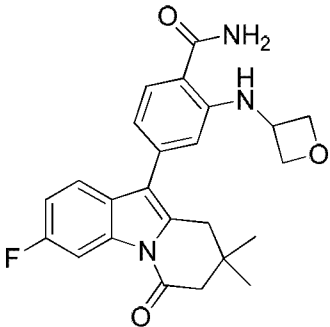
COMPOUND	STRUCTURE
84	
85	
86	
87	

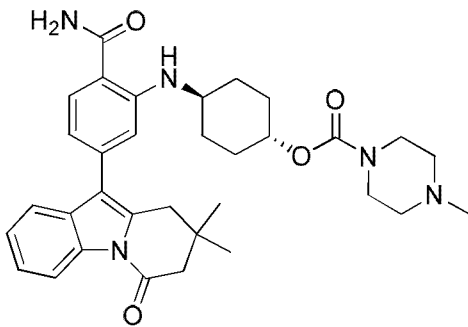
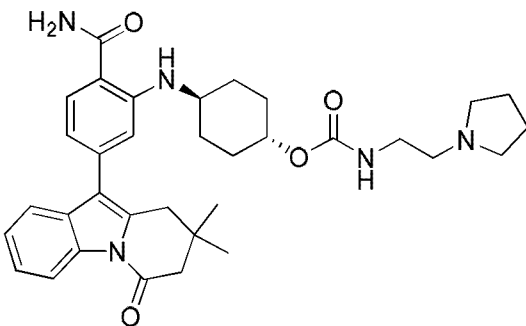
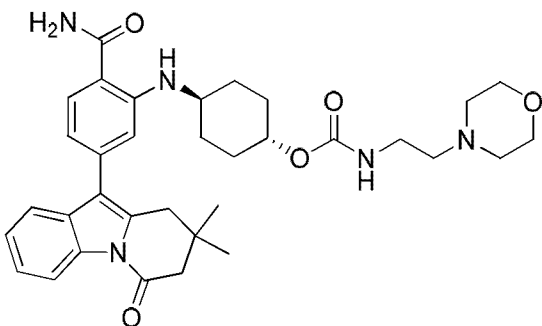
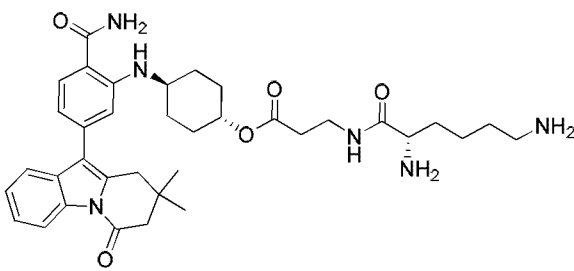
COMPOUND	STRUCTURE
88	
89	
90	
91	

COMPOUND	STRUCTURE
92	
93	
94	
95	

COMPOUND	STRUCTURE
96	
97	
98	
99	

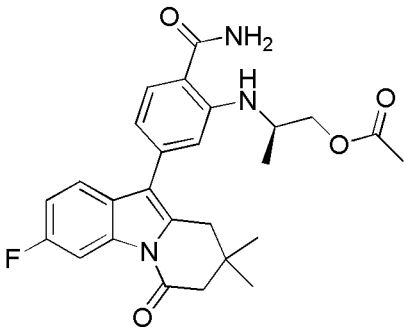
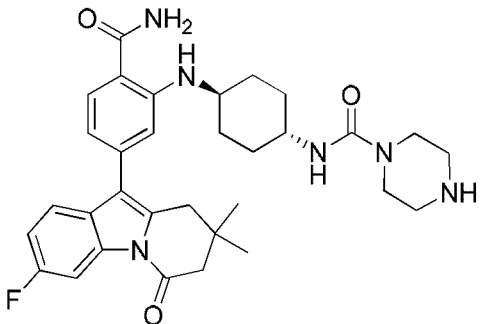
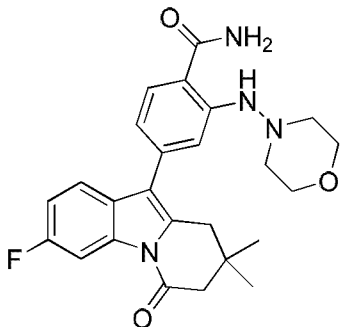
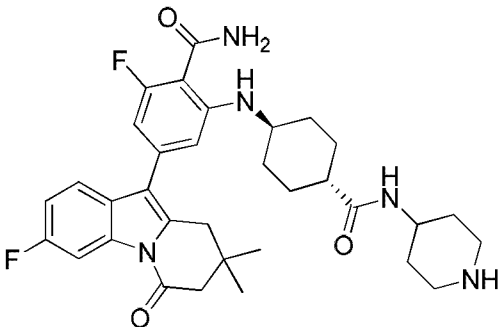
COMPOUND	STRUCTURE
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101	
102	
103	

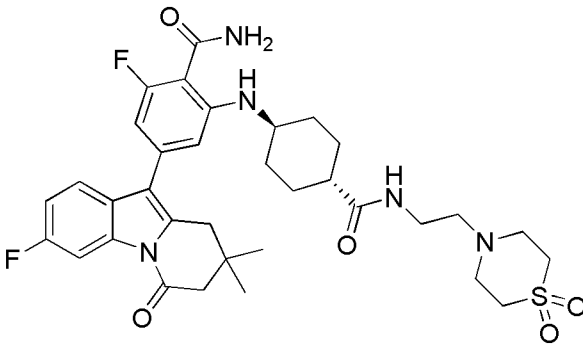
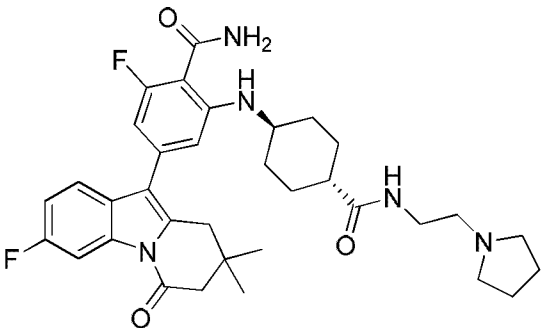
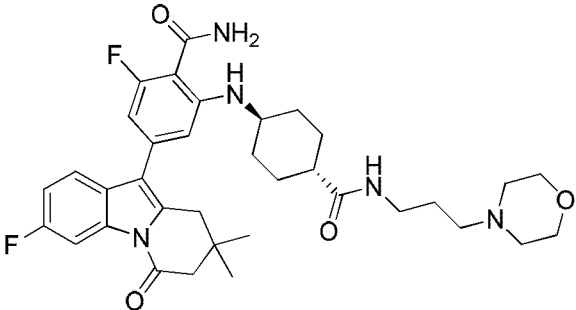
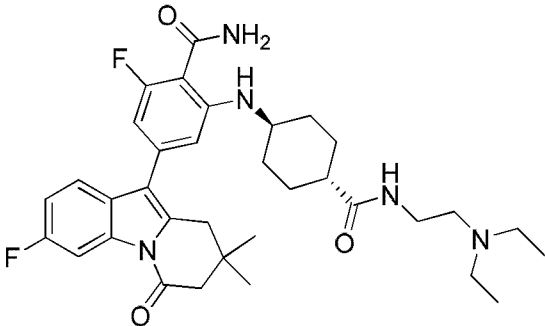
COMPOUND	STRUCTURE
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105	
106	
107	

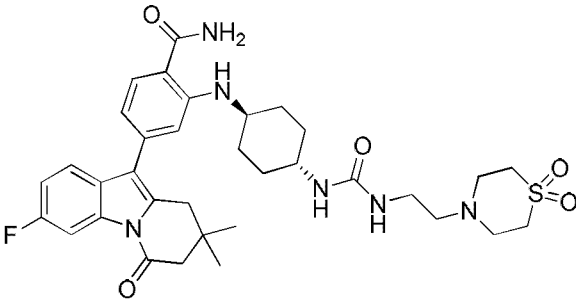
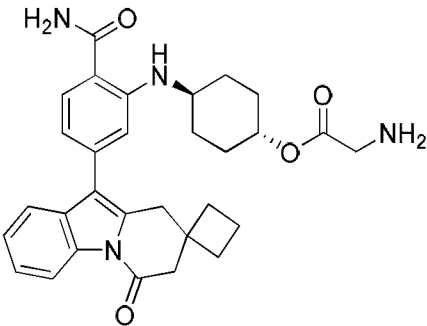
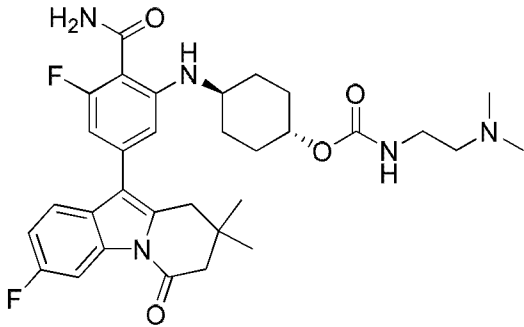
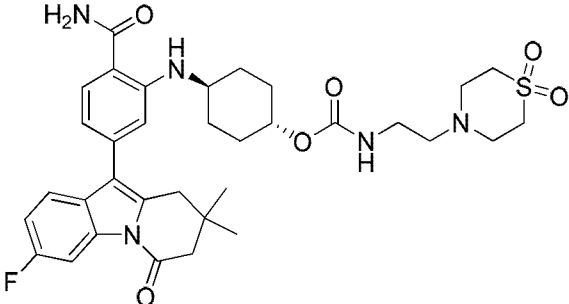
COMPOUND	STRUCTURE
108	
109	
110	
111	

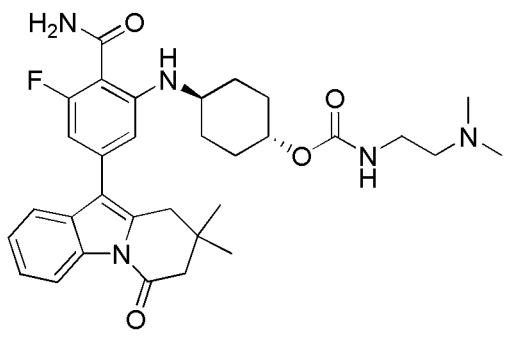
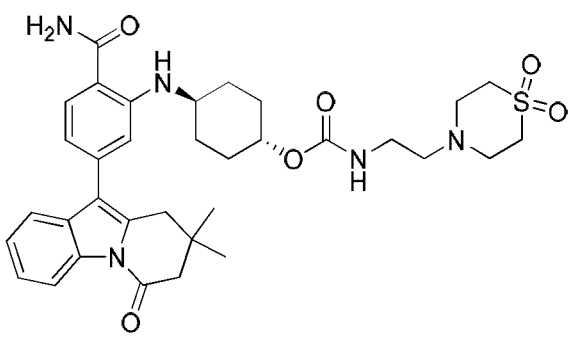
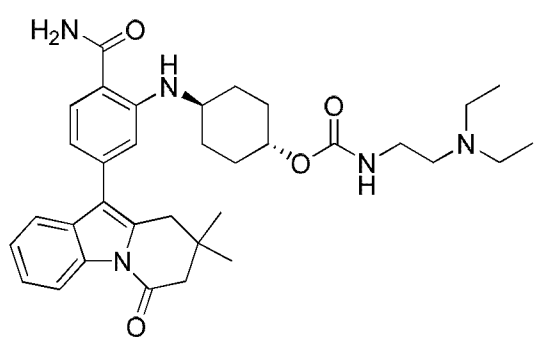
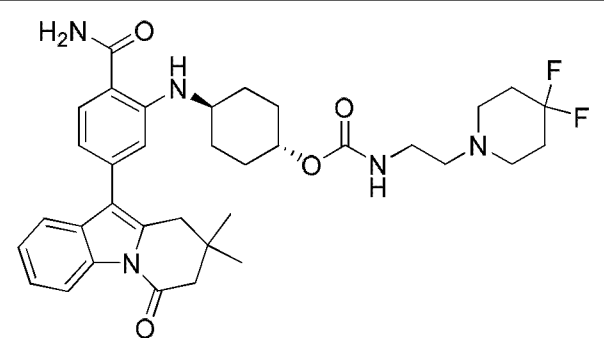
COMPOUND	STRUCTURE
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113	
114	
115	

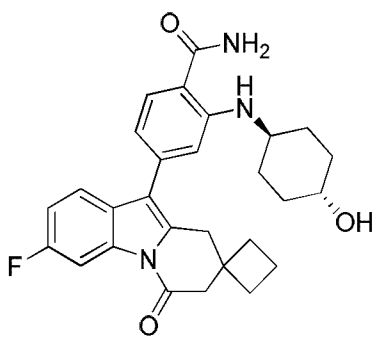
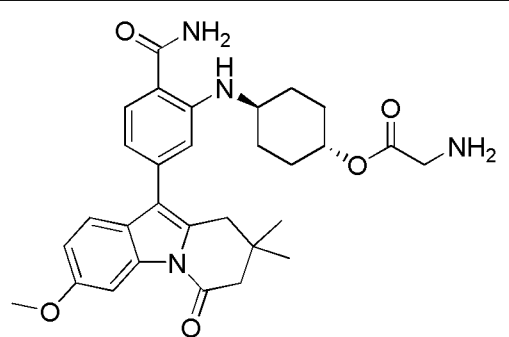
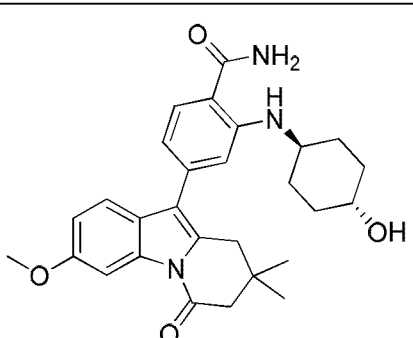
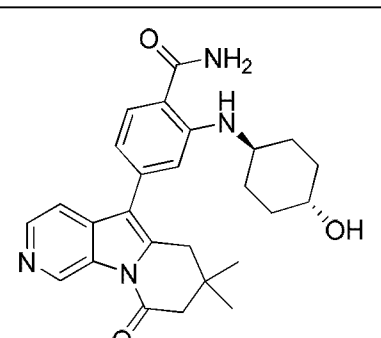
COMPOUND	STRUCTURE
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117	 <chem>NC(=O)c1ccc(NC2CCCCC2NC(=O)CCN3CCOCC3)cc1C4=C(C5=CC=CC=C5F)N6C(=O)CCC(C)(C)C6=O</chem>
118	 <chem>NC(=O)c1ccc(NC2CCCCC2NC(=O)CCN3CCCC3)cc1C4=C(C5=CC=CC=C5F)N6C(=O)CCC(C)(C)C6=O</chem>
119	 <chem>NC(=O)c1ccc(NC2CCCCC2NC(=O)CCN3CCCCC3C)cc1C4=C(C5=CC=CC=C5F)N6C(=O)CCC(C)(C)C6=O</chem>

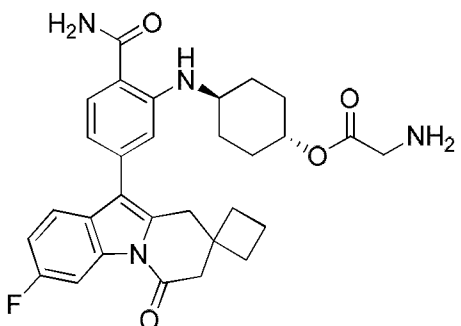
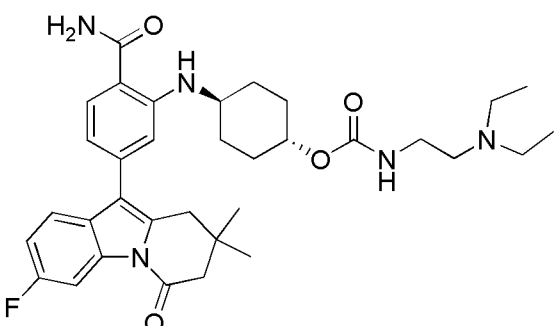
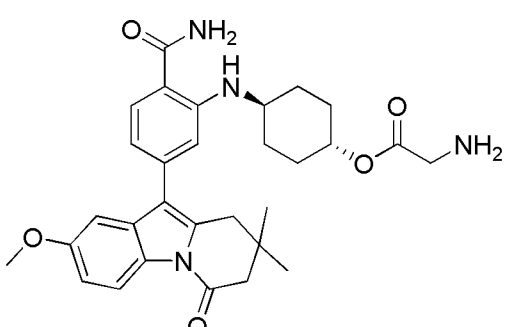
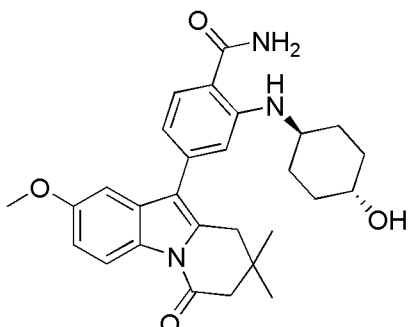
COMPOUND	STRUCTURE
120	
121	
122	
123	

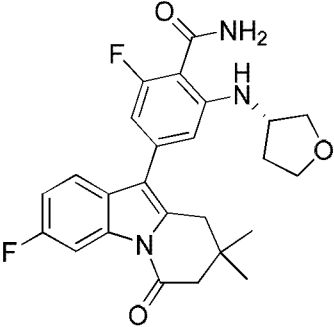
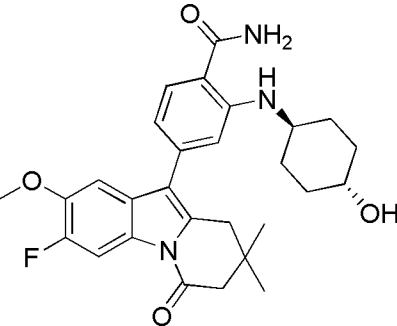
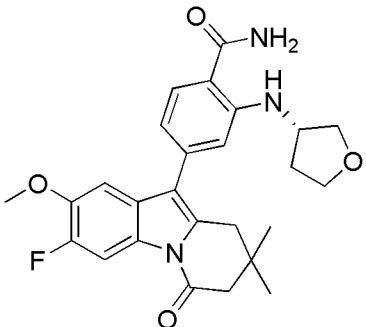
COMPOUND	STRUCTURE
124	
125	
126	
127	

COMPOUND	STRUCTURE
128	
129	
130	
131	

COMPOUND	STRUCTURE
132	
133	
134	
135	

COMPOUND	STRUCTURE
136	
137	
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COMPOUND	STRUCTURE
140	
141	
142	
143	

COMPOUND	STRUCTURE
144	
145	
146	

26. A compound of claim 25, wherein a compound of Formula 1 is selected from compound 33, 34, 45, 102 and 117.

27. A compound of claim 25, wherein a compound of Formula 1 is selected from compound 1, 4, 13, 16, 17, 18, 19, 22, 23, 24, 26, 28, 30, 31, 32, 33, 34, 35, 36, 37, 41, 42, 44, 45, 47, 48, 49, 50, 51, 52, 54, 56, 57, 58, 59, 62, 64, 65, 66, 67, 70, 71, 74, 75, 76, 77, 78, 79, 81, 812, 83, 84, 85, 86, 87, 88, 89, 90, 92, 92, 94, 95, 97, 98, 99, 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 121, 123, 124, 125,

126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 140, 141, 142, 143, 144, 145, and 146.

28. A compound of claim 27, wherein a compound of Formula 1 is selected from compound 23, 42, 45, 47, 51, 52, 57, 58, 59, 67, 70, 82, 87, 88, 89, 90, 92, 95, 97, 99, 102, 103, 104, 105, 109, 11, 112, 115, 116, 117, 119, 121, 123, 124, 125, 126, 127, 128, 130, 132, 134, 141 and 144.

29. A pharmaceutical composition comprising a compound of any one of claims 1 to 28 and a pharmaceutically acceptable carrier or diluent.

30. A pharmaceutical composition comprising a compound of any one of claims 1 to 28 and a second anti-fungal compound.

31. A pharmaceutical composition of claim 30, wherein the second anti-fungal compound is selected from the group consisting of fluconazole, caspofungin, isavuconazole, pramiconazole, amphotericin, nystatin, anidulafungin, voriconazole, posaconazole, itraconazole, ravuconazole, anti-fungal antibodies, nikkomycin Z, albaconazole, and anti-fungal vaccines.

32. A pharmaceutical composition of claim 31, wherein the second anti-fungal compound is selected from the group consisting of fluconazole and caspofungin.

33. A pharmaceutical composition of claim 32, wherein the compound of Formula 1 is selected from compound 34 and 117.

34. A method for treating or preventing fungal infections comprising administering a compound of any one of claims 1 to 28 or a pharmaceutical composition of any one of claims 29 to 33.

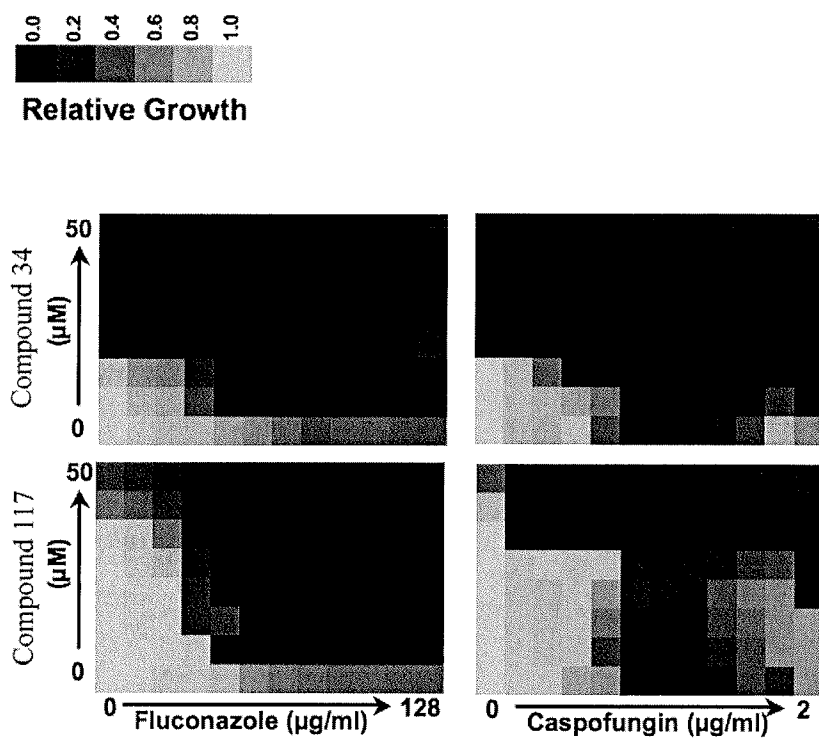
35. Use of a compound of any one of claims 1 to 28 or a pharmaceutical composition of any one of claims 29 to 33 for the preparation of a medicament for treating or preventing fungal infections.

5 36. A compound of any one of claims 1 to 28 or a pharmaceutical composition of any one of claims 29 to 33 for treating or preventing fungal infections.

37. Use of a compound of any one of claims 1 to 28 or a pharmaceutical composition of any one of claims 29 to 33 for the treatment or prevention of fungal infections.

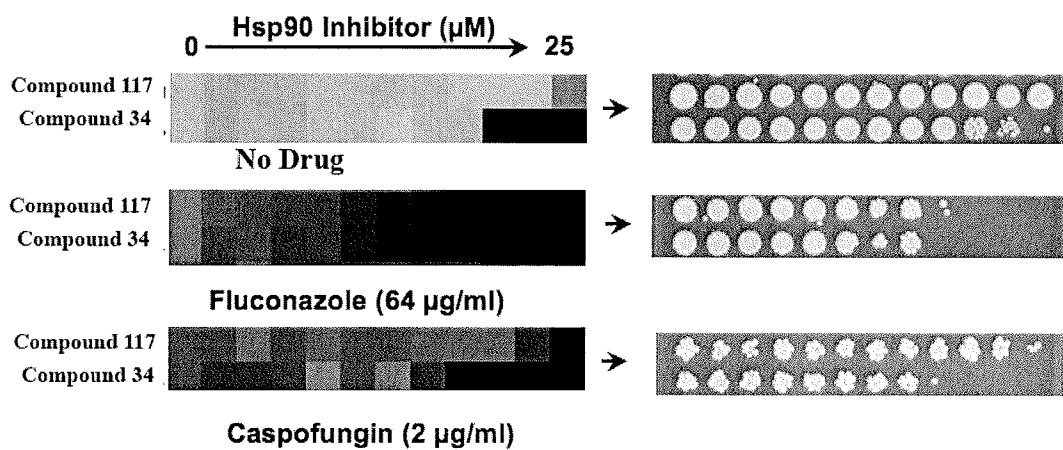
Figure 1.

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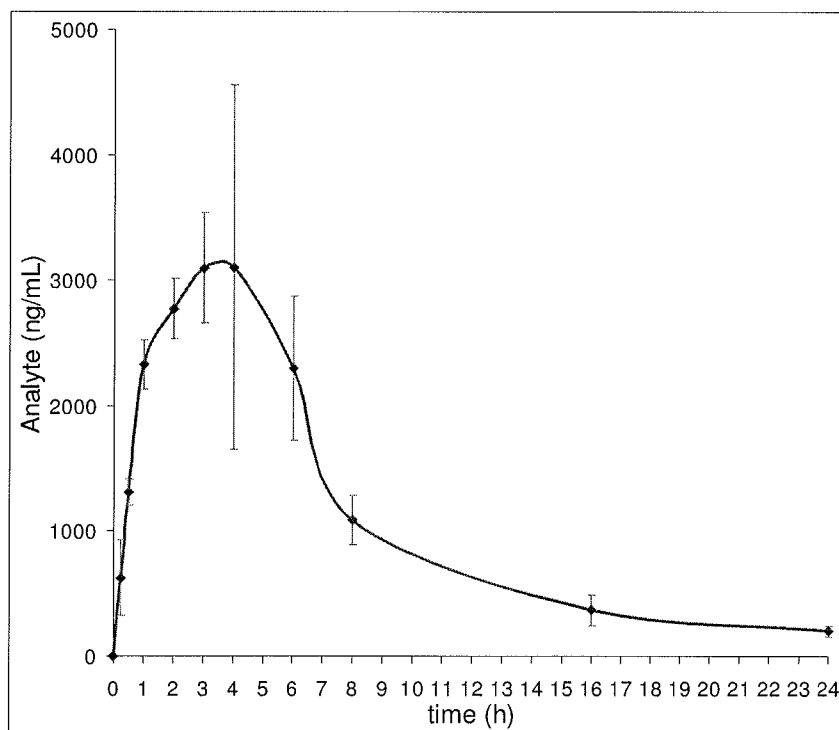
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Figure 2



5

Figure 3



INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA2011/050158

A. CLASSIFICATION OF SUBJECT MATTER

IPC: *C07D 471/04* (2006.01), *A61K 31/395* (2006.01), *A61K 31/437* (2006.01), *A61K 31/542* (2006.01), *A61P 31/10* (2006.01), *C07D 471/14* (2006.01), *C07D 487/04* (2006.01), *C07D 513/04* (2006.01), *C07F 9/6561* (2006.01)
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: *C07D 471/04* (2006.01), *A61K 31/395* (2006.01), *A61K 31/437* (2006.01), *A61K 31/542* (2006.01), *A61P 31/10* (2006.01), *C07D 471/14* (2006.01), *C07D 487/04* (2006.01), *C07D 513/04* (2006.01), *C07F 9/6561* (2006.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database(s) consulted during the international search (name of database(s) and, where practicable, search terms used)
STN, Canadian Patent Database, Scopus, EPOQUE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E,X	WO2011/035417 (BUREAU et al.) 31 March 2011 (31.03.2011) Examples and Claims	1-37
A	WO2004/014917 (BAILLY et al.) 19 February 2004 (19.02.2004) Examples and Claims	1-37
A	WO02/094830 (WANG et al.) 28 November 2002 (28.11.2002) Examples and Claims	1-37
A	Tardy et al.; Topoisomerase I-mediated DNA cleavage as a guide to the development of antitumor agents derived from the marine alkaloid lamellarin D: triester derivatives incorporating amino acid residues; <u>Bioorganic and Medicinal Chemistry</u> (2004), 12, 1697-1712. Compounds 1-42	1-37

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A" document defining the general state of the art which is not considered to be of particular relevance	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E" earlier application or patent but published on or after the international filing date	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&" document member of the same patent family
"O" document referring to an oral disclosure, use, exhibition or other means	
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

8 November 2011 (08.11.2011)

Date of mailing of the international search report

28 December 2011 (28-12-2011)

Name and mailing address of the ISA/CA
Canadian Intellectual Property Office
Place du Portage I, C114 - 1st Floor, Box PCT
50 Victoria Street
Gatineau, Quebec K1A 0C9
Facsimile No.: 001-819-953-2476

Authorized officer

Daniel Black (819) 994-3470

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of the first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons :

1. ☒ Claim Nos. : 34

because they relate to subject matter not required to be searched by this Authority, namely :

Claim 34 is directed to a method for treatment of the human or animal body by surgery or therapy which the International Search Authority is not required to search. However, this Authority has carried out a search based on the alleged effects or purposes/uses of the product defined in claim 34.

2. ☐ Claim Nos. :

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically :

3. ☐ Claim Nos. :

because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows :

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claim Nos. :

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim Nos. :

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CA2011/050158

Patent document Cited in Search report	Publication Date	Patent Family Member(s)	Publication Date
WO2011035417 A1	31-03-2011	WO2011035417 A1	2011-03-31
WO2004014917 A2	19-02-2004	HK1078580 A1 US2006173030 A1 NO20051282 A KR20050053613 A MXPA05001731 A RU2328500 C2 NZ537935 A JP2005536529 A WO2004014917 A2 EP2138496 A1 EP1551844 A2 CN101941977 A CN1688585 A CA2493725 A1 AU2003252997 A1 AT475663T T	2010-10-29 2006-08-03 2005-05-11 2005-06-08 2005-08-16 2005-11-10 2007-02-23 2005-12-02 2004-02-19 2009-12-30 2005-07-13 2011-01-12 2005-10-26 2004-02-19 2004-02-25 2010-08-15
WO02094830 A2	28-11-2002	JP2004534774 A ES2272712T T3 EP1395590 A2 DE60215000T T2 WO02094830 A2 CA2447779 A1 AU2002302248B B2 AT340796T T	2004-11-18 2007-05-01 2004-03-10 2007-08-09 2002-11-28 2002-11-28 2008-03-06 2006-10-15