



(51) International Patent Classification:

C07D 291/04 (2006.01) C07D 295/155 (2006.01)
C07D 215/56 (2006.01)

(21) International Application Number:

PCT/US2017/065448

(22) International Filing Date:

08 December 2017 (08.12.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/432,430 09 December 2016 (09.12.2016) US

(71) Applicants: UNIVERSITY OF IOWA RESEARCH FOUNDATION [US/US]; 112 N Capitol Street, 6 Gilmore Hall, Iowa City, Iowa 52242 (US). REGENTS OF THE UNIVERSITY OF MINNESOTA [US/US]; 600 McNamara Alumni Center, 200 Oak Street SE, Minneapolis, Minnesota 55455 (US).

(72) Inventors; and

(71) Applicants: KERNS, Robert J. [US/US]; 1312 Phoenix Drive, Iowa City, Iowa 52246 (US). TOWLE, Tyrell [US/US]; 9006 East 52nd Avenue, Denver, Colorado 80238 (US). HIASA, Hiroshi [JP/US]; 111 Marquette Avenue, Apartment 2105, Minneapolis, Minnesota 55401 (US).

(74) Agent: PERDOK, Monique M. et al.; P.O. Box 2938, Minneapolis, Minnesota 55402 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))

(54) Title: QUINOLONE-BASED COMPOUNDS WITH ANTICANCER ACTIVITY

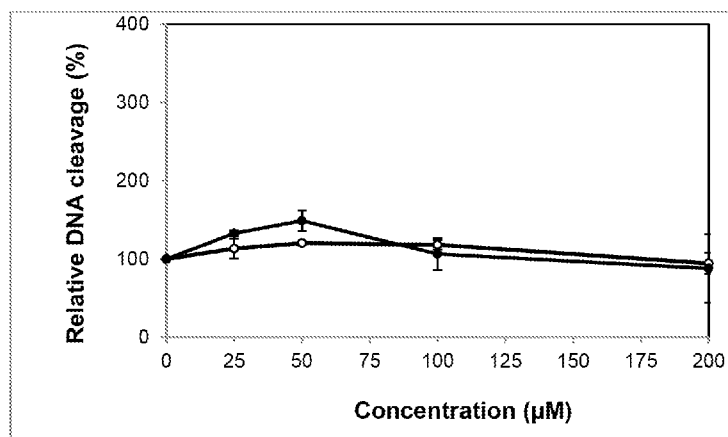


FIG. 1

(57) Abstract: Embodiments are directed to compounds of the formulae (I), (Ia), (Ib), (II), (IIa) (III), (IV), (V), and (VI); methods for treating cancer with one or more compounds of the formulae (I), (Ia), (Ib), (II), (IIa); (III), (IV), (V), and (VI); and methods for inhibiting a human topoisomerase with one or more compounds of the formulae (I), (Ia), (Ib), (II), (IIa); (III), (IV), (V), and (VI).

QUINOLONE-BASED COMPOUNDS WITH ANTICANCER ACTIVITY

5

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit from U.S. Provisional Appl. Ser. No. 62/432,430, filed December 9, 2016, the entirety of which is incorporated by reference as if fully set forth herein.

10

STATEMENT OF GOVERNMENT SUPPORT

[0002] This invention was made with government support under grants R01 AI087671 and TR000114 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

15 **[0003]** Topoisomerases are proven therapeutic targets of anticancer drugs. A number of topoisomerase inhibitors have been developed but clinically successful topoisomerase inhibitors, such as etoposide, doxorubicin, and irinotecan, target a covalent topoisomerase-DNA catalytic intermediate and generate DNA breaks. This unique mechanism of cell killing, which is often referred as to "topoisomerase poisoning," is also the
20 cause of therapy-related acute myeloid leukemia that develops after treatment with topoisomerase II inhibitors. Thus, there is an unmet need to explore new small molecules that inhibit topoisomerases through different mechanisms to develop novel anticancer agents with better safety profiles.

BRIEF DESCRIPTION OF THE FIGURES

25 **[0004]** The drawings illustrate generally, by way of example, but not by way of limitation, various embodiments discussed herein.

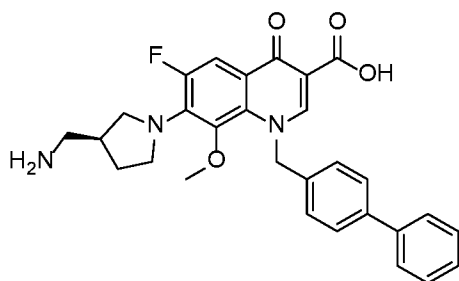
[0005] FIG. 1 is a plot of the relative DNA cleavage (%) as a function of the concentration of the compounds "217" and "227."

[0006] FIG. 2 is a plot of average tumor weight after a 3-week treatment with the
30 compounds "217" and "227."

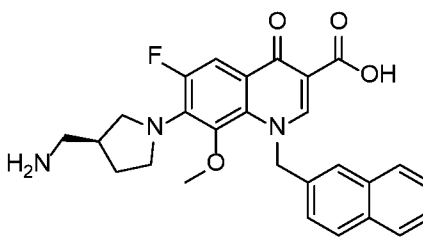
DESCRIPTION

[0007] While the disclosed subject matter will be described in conjunction with the enumerated claims, it will be understood that the exemplified subject matter is not intended to limit the claims to the disclosed subject matter.

35 **[0008]** The inventors recently discovered that two fluoroquinolones, UITT-III-217 (217) and UITT-III-227 (227):



UITT-III-217



UITT-III-227

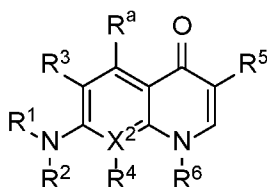
can inhibit human topoisomerase II without generating DNA double-strand breaks. Unexpectedly, these, and other compounds described herein, are active against human topoisomerase I and can be more active against human topoisomerase I than human topoisomerase II. The compounds of the various embodiments described herein are therefore new chemical entities that act through a mechanism different from topoisomerase poisons. This novel mechanism suggests that structural requirements of fluoroquinolones are not essential for the anticancer activity of the compounds of the various embodiments described herein, and allows the utilization of larger variations in the chemical structures of the compounds, to design further analogs.

[0009] Based on the abilities of compounds such as 217 and 227 to intercalate into DNA, and the lack of structural similarities between topoisomerase I and topoisomerase II, it is likely that the compounds of the various embodiments described herein intercalate into DNA, or otherwise bind DNA by some other mechanism (e.g., a combination of intercalation and minor groove binding), and inhibit the catalytic activities of topoisomerase I and topoisomerase II. For example, the National Cancer Institute's (NCI) 60 Developmental Therapeutics Program (DTP) Human Tumor Cell Line Screen demonstrated significant growth inhibition for 217 and 227 (the mean GI₅₀ value of 217 and 227 to be 1.9 μ M and 3.1 μ M, respectively) against the 60 cancer cell lines used in the screen, with the strongest growth inhibition seen in leukemia and colon cancer panels. An *in vivo* toxicity study showed that the intraperitoneal administration of 217 and 227 at up to 30 mg/kg for 3 weeks was well-tolerated and did not have any significant effect on animal weight gain. A proof of concept *in vivo* efficacy study showed that 217 inhibited the proliferation of colon cancer *in vivo* as well as fluorouracil (5-FU), a standard of care treatment for colon cancer. Compound 227 exhibited activity but was not as effective as 217 in this xenograft model. These results suggest that 217 and 227, and other compounds of the various embodiments described herein, might serve as lead compounds for the successful development of novel anticancer agents against colon cancer and potentially other cancers.

[0010] Because the compounds of the various embodiments described herein do not generate DNA double-strand breaks that lead to the development of therapy-related acute myeloid leukemia, the compounds will have a better safety profile. Furthermore, because their mechanisms are different from currently-available topoisomerase-targeting anticancer drugs, the

compounds of the various embodiments described herein may be effective against etoposide- and other drug-resistant cancers.

[0011] Various embodiments are directed to a compound of the formula (I):



(I)

or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

R^a is halo, nitro, cyano, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heteroaryl, or $NR^{a'}R^{a''}$, wherein $R^{a'}$ and $R^{a''}$ are each, independently, H or optionally substituted alkyl;

R^1 and R^2 are each independently H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or R^1 and R^2 , together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl group;

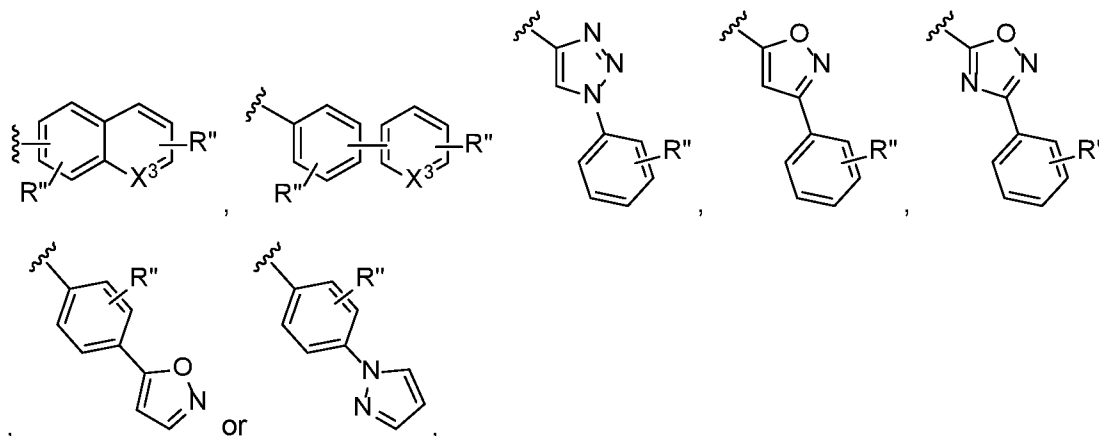
R^3 is H or halo;

R^4 is H, halo, optionally substituted alkyl or optionally substituted alkoxy, but R^4 is absent if X^2 is N;

X^2 is N or C;

R^5 is H, OH, optionally substituted alkoxy, $-C(O)R^{5'}$ (wherein $R^{5'}$ is H, OH, optionally substituted alkyl, optionally substituted aryl, optionally substituted alkoxy or $-N(R^{5''})_2$, wherein each $R^{5''}$ is, independently, H, OH, optionally substituted alkoxy, optionally substituted alkyl or optionally substituted arylalkyl) or $-N(R^{5''})_2$; and

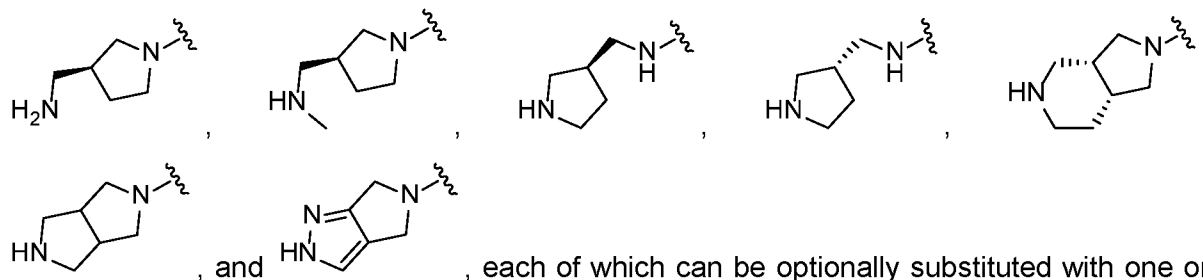
R^6 is the group $-L-R^{6'}$, wherein L is a linker group and $R^{6'}$ is a group having sufficient "steric bulk" such that the compound of the formula (I) is (a) not a topoisomerase II poison, (b) inhibits topoisomerase I and topoisomerase II and/or (c) inhibits topoisomerase I to a greater extent than topoisomerase II. The group R^6 has all the features (a)-(c). X^2 can be C and R^4 is therefore present. $R^{6'}$ can be a group comprising at least two aryl groups (including fused groups), an aryl group and a heterocyclyl group (including fused groups) or two heterocyclyl groups (including fused groups), each of which can be optionally substituted with one or more substituents described herein. Non-limiting examples of aryl and heterocyclyl groups, including fused groups, are provided herein. They include, for example, biphenyl groups, naphthyl groups, and quinolinyl groups, each of which can be optionally substituted with one or more substituents described herein. Other suitable R^6 groups include the groups:



wherein each R'' is, independently H or halo and X³ is N or CH.

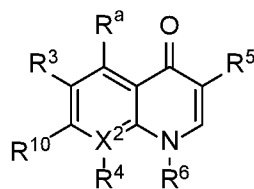
[0012] Non-limiting examples of suitable divalent linkers, -L-, include acyl groups (e.g., -C(O)-); hydrocarbylene groups, such as (C₁-C₂₂)hydrocarbylene groups; hydrocarbyleneacyl groups, such as (C₂-C₂₂)hydrocarbyleneacyl groups; and the like. Examples of (C₁-C₂₂)hydrocarbylene groups include divalent aryl, alkyl, and cycloalkyl groups, each of which can be optionally substituted with one or more substituents described herein.

[0013] Examples of groups that can be formed by R¹ and R² include the groups:



each of which can be optionally substituted with one or more substituents described herein.

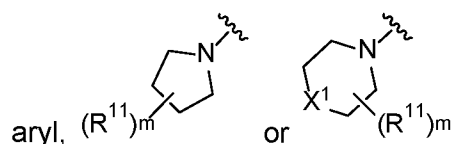
[0014] Various other embodiments are directed to a compound of the formula (Ia):



(Ia)

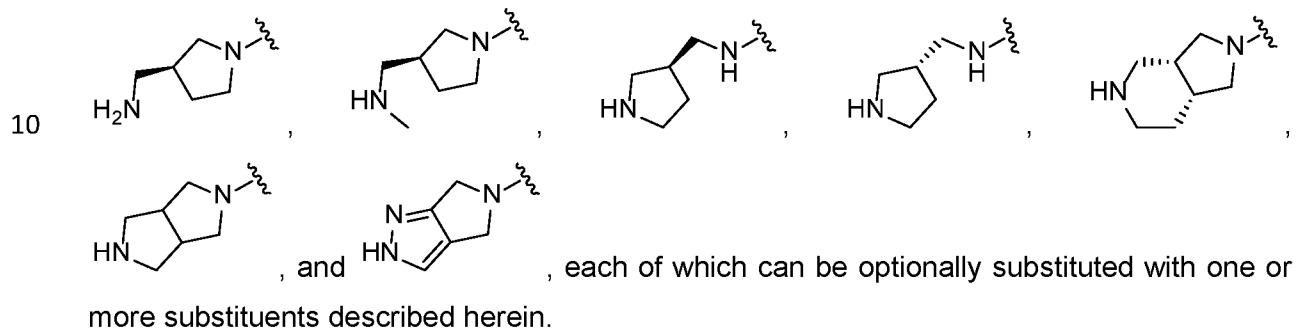
or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

X², R^a, R³, R⁴, R⁵, and R⁶ are as defined for compounds of the formula (I); and R¹⁰ is

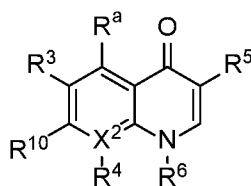


wherein each R^{11} is H, $-N(R^{5''})_2$ (wherein $R^{5''}$ is defined herein), $C(O)N(R)_2$ (wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl), optionally substituted alkyl or two adjacent R^{11} groups, together with the atoms to which they are attached form an optionally substituted cycloalkyl group or an optionally substituted heterocyclyl group; m is an integer from 1 to 3; and X^1 is O or NR^{12} , wherein R^{12} is H or optionally substituted alkyl or R^{12} and an adjacent R^{11} group, together with the atoms to which they are attached, form an optionally substituted heterocyclyl group. X^2 can be C and R^4 is therefore present.

[0015] Examples of R^{10} groups include the groups:



[0016] Various other embodiments are directed to a compound of the formula (Ib):



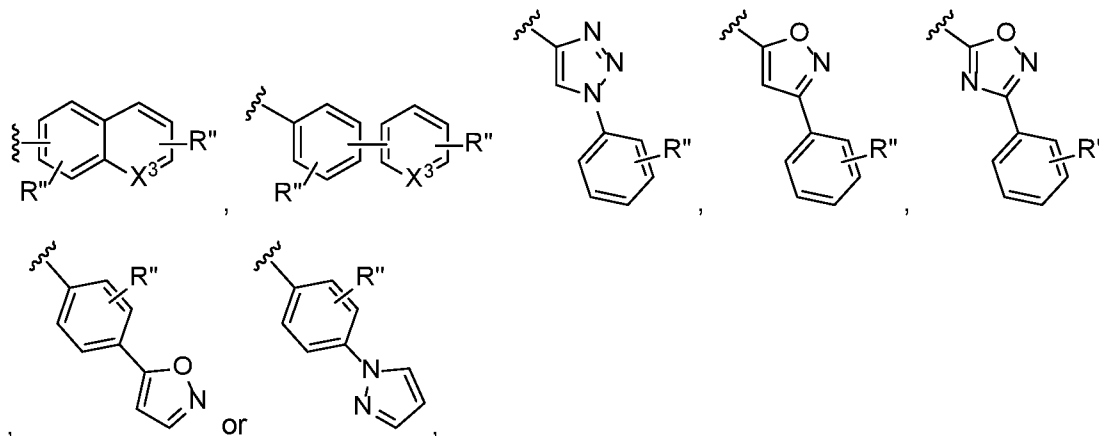
(Ib)

or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

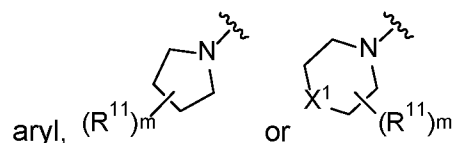
R^a is optionally substituted alkyl or NH_2 ;

X^2 , R^3 , R^4 , and R^5 are as defined for compounds of the formula (I) and (Ia);

20 R^6 is $-(CH_2)_n-R^{6''}$ or $-C(O)R^{6''}$ wherein n is an integer from 1 to 3 (e.g., 1) and $R^{6''}$ is an aryl or heteroaryl group. Examples of aryl and heteroaryl groups represented by $R^{6''}$ include:

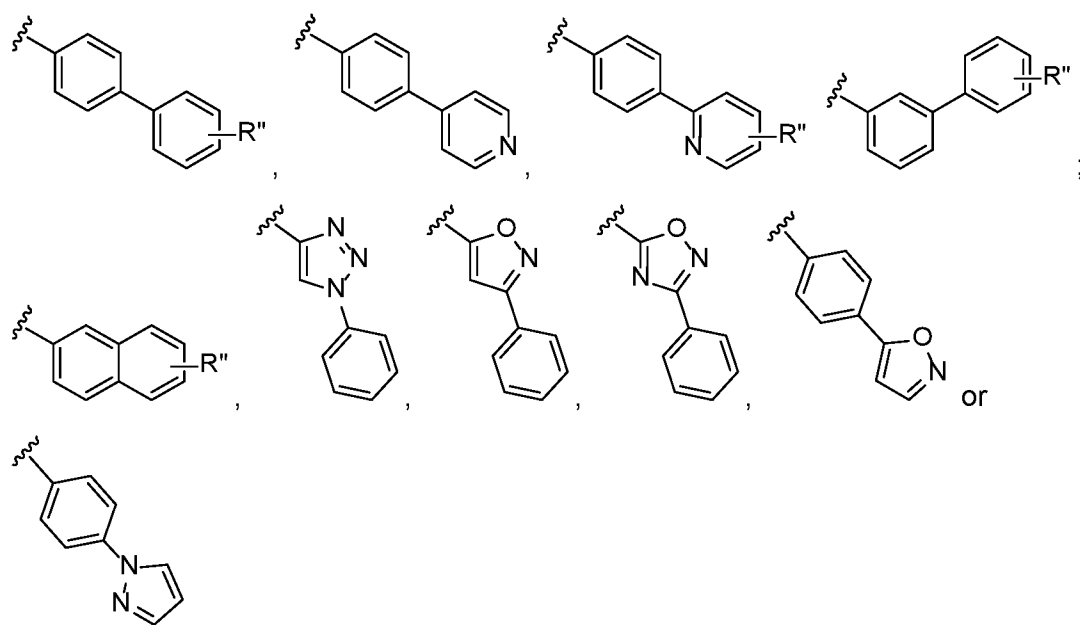


wherein each R¹¹ is, independently H or halo and X³ is N or CH; and
R¹⁰ is



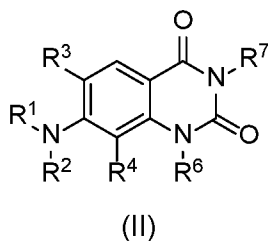
wherein each R¹¹ is H, C(O)N(R)₂ (wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl), optionally substituted alkyl or two adjacent R¹¹ groups, together with the atoms to which they are attached form an optionally substituted cycloalkyl group or an optionally substituted heterocyclyl group; m is an integer from 1 to 3; and X¹ is O or NR¹², wherein R¹² is H or optionally substituted alkyl or R¹² and an adjacent R¹¹ group, together with the atoms to which they are attached, form an optionally substituted heterocyclyl group. X² can be C and R⁴ is therefore present.

[0017] R^{6''} can be:



Compounds where R^{6''} comprises a heteroatom (e.g., N and O) have been found to be more water soluble than their all-carbon counterparts, to the point that compounds where R^{6''} comprises a heteroatom can be dosed at 30 mg/kg or more.

[0018] Various other embodiments are directed to a compound of the formula (II):



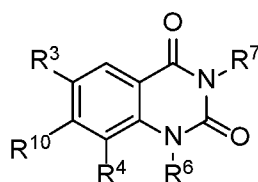
or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

R^1 - R^4 and R^6 are as defined for compounds of the formula (I) and (Ib); and

R^7 is H, OH, optionally substituted alkoxy, optionally substituted alkyl or NR^8R^9 , wherein R^8

5 and R^9 are each independently H, optionally substituted alkyl, optionally substituted aryl or optionally substituted arylalkyl.

[0019] Various other embodiments are directed to a compound of the formula (IIa):



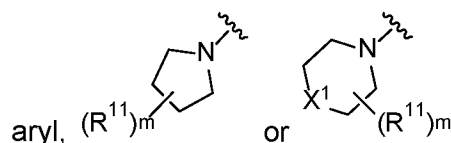
(IIa)

10 or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

R^3 , R^4 , and R^6 are as defined for compounds of the formula (I), (Ia), and (Ib);

R^7 is H, optionally substituted alkyl or NR^8R^9 , wherein R^8 and R^9 are each independently H, optionally substituted alkyl, optionally substituted aryl or optionally substituted arylalkyl; and

15 R^{10} is

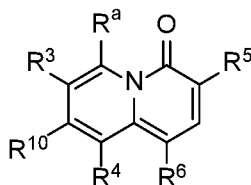


wherein each R^{11} is H, $C(O)N(R)_2$ (wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl), optionally substituted alkyl or two adjacent R^{11} groups, together with the atoms to which they are attached form an optionally substituted cycloalkyl group or an optionally substituted heterocyclyl group; m is an integer from 1 to 3; and X^1 is O or NR^{12} , wherein R^{12} is H or optionally substituted alkyl or R^{12} and an adjacent R^{11} group, together with the atoms to which they are attached, form an optionally substituted heterocyclyl group.

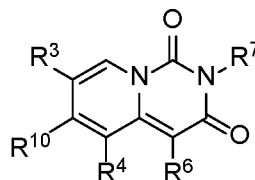
20 attached form an optionally substituted cycloalkyl group or an optionally substituted heterocyclyl group; m is an integer from 1 to 3; and X^1 is O or NR^{12} , wherein R^{12} is H or optionally substituted alkyl or R^{12} and an adjacent R^{11} group, together with the atoms to which they are attached, form an optionally substituted heterocyclyl group.

[0020] Various other embodiments are directed to a compound of the formula (III)

25 and (IV):



(III)



(IV)

wherein the groups R^a , R^3 - R^7 , and R^{10} are as defined for the compounds of the formulae (I), (Ia), (Ib), (II), and (IIa).

[0021] In the compounds of the formulae (I), (Ia), (Ib), (II), (IIa), (III) or (IV) R^3 can be halo (e.g., fluoro). R^3 can also be H.

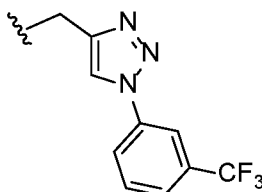
[0022] In the compounds of the formulae (I), (Ia), (Ib), (II), (IIa), (III) or (IV), R^4 can be alkoxy (e.g., methoxy). R^4 can also be H.

5 **[0023]** In the compounds of the formulae (I), (Ia), (Ib) or (III), R^5 can be $-C(O)R^{5'}$. $R^{5'}$ can be OH or optionally substituted alkoxy.

[0024] In the compounds of the formulae (I), (Ia), (II), (IIa), (III) or (IV), R^6 can be optionally substituted arylalkyl. In some embodiments, however, R^6 is not a benzyl group. But R^6 can be a biphenyl or a naphthyl group.

10 **[0025]** In the compounds of the formulae (II) and (IIa), R^7 can be NR^8R^9 . R^8 can be H. And R^8 and R^9 can be H.

[0026] In the compounds of the formula (I), when R^6 is:



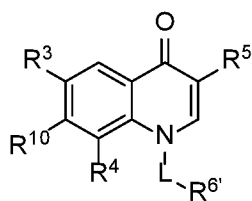
15 R^1 and R^2 , together with the nitrogen atom to which they are attached, form an optionally substituted pyrrolidinyl group.

[0027] In the compounds of the formulae (Ia), (Ib), (IIa), (III) or (IV), R^{11} can be optionally substituted alkyl. R^{11} can be alkyl substituted with $NR^{13}R^{14}$, wherein R^{13} and R^{14} are each independently H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl group. R^{13} can be H. R^{13} and R^{14} can be H.

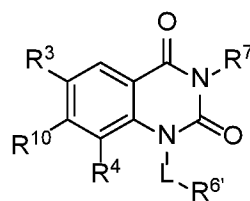
25 **[0028]** In the compounds of the formulae (Ia), (Ib), (IIa), (III) or (IV), R^{11} can be alkyl substituted with OR^{13} , wherein R^{13} is H, optionally substituted alkyl, optionally substituted aryl or optionally substituted arylalkyl.

[0029] In the compounds of the formulae (Ia), (Ib), (IIa), (III) or (IV), R^{11} can be $C(O)N(R)_2$, wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl. At least one R in the $C(O)N(R)_2$ group can be H. The $C(O)N(R)_2$ group can be a $C(O)NH_2$ group.

30 **[0030]** Compounds of the formulae (I), (Ia), (Ib), (II), (IIa), (III) or (IV) include compounds of the formulae (V) and (VI):

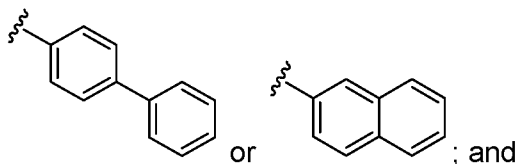


(V)

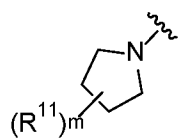


(VI)

wherein R^3 , R^4 , and R^7 are as defined for compounds of the formula (I); L is $-(CH_2)_n$, wherein n is an integer from 1 to 3 (e.g., 1); $R^{6'}$ is:

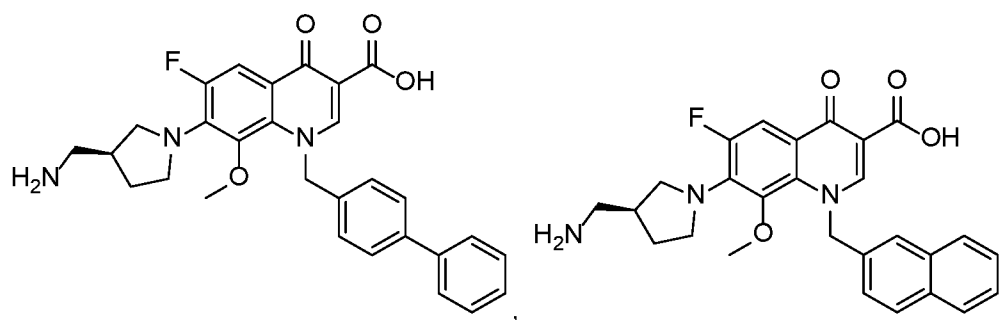


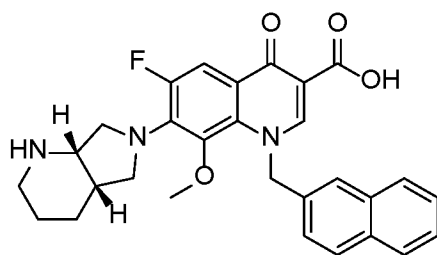
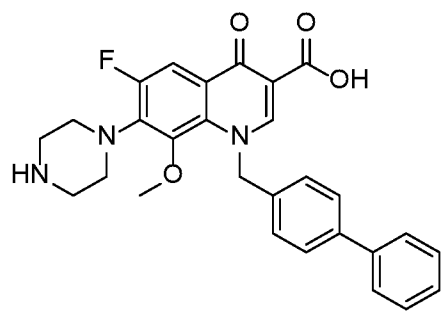
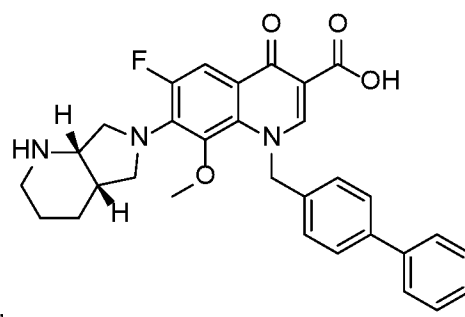
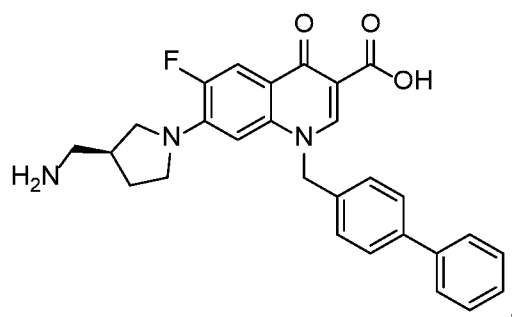
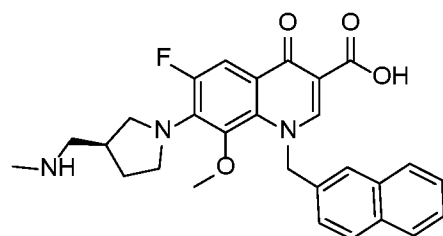
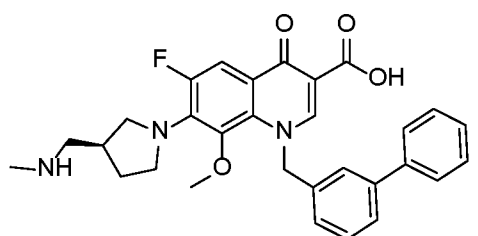
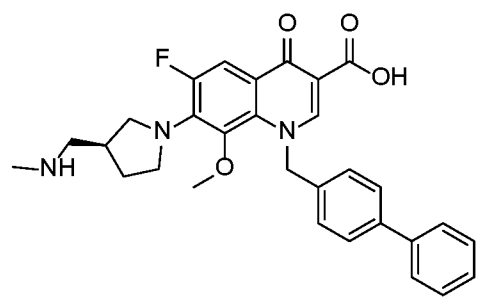
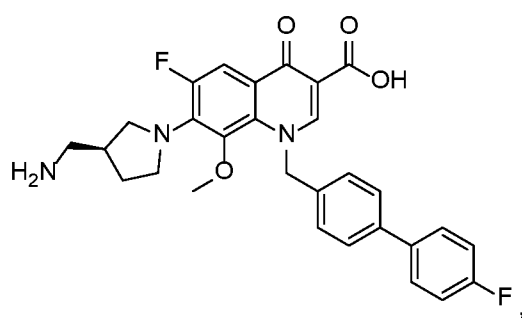
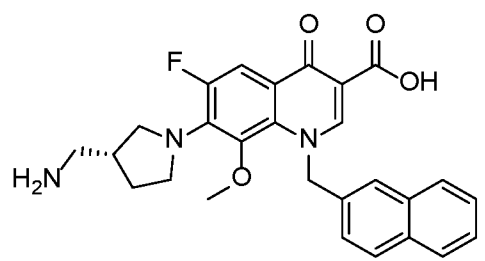
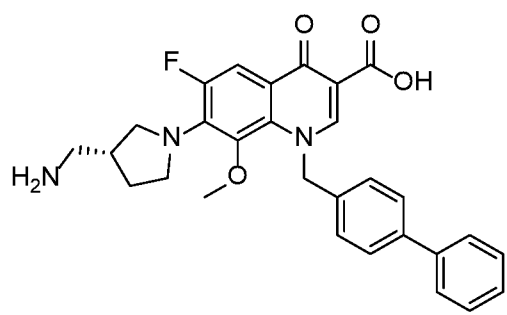
R^{10} is:



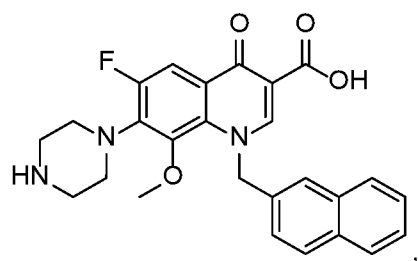
wherein R^{11} is $C(O)N(R)_2$ (wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl), alkyl substituted with -OR or alkyl substituted with $-N(R)_2$. In the compound of the formula (V), R^5 can be $-C(O)OH$. In the compound of the formula (VI), R^7 can be $-NH_2$. In the compounds of the formula (V) or (VI), R^3 can be halo (e.g., fluoro). In the compounds of the formula (V) or (VI), R^4 can optionally substituted alkoxy (e.g., methoxy). In the compounds of the formula (V) or (VI), R^{11} can be alkyl substituted with $-N(R)_2$. R^{11} can be alkyl substituted with $-NRH$ (e.g., R^{11} is $-CH_2NHCH_3$). In the compounds of the formula (V) or (VI), R^{11} can be alkyl substituted with -OR. R^{11} can be alkyl substituted with $-OH$ (e.g., R^{11} is $-CH_2OH$). R^{11} can be $-C(O)N(R)_2$. R^{11} can be $-C(O)NH_2$.

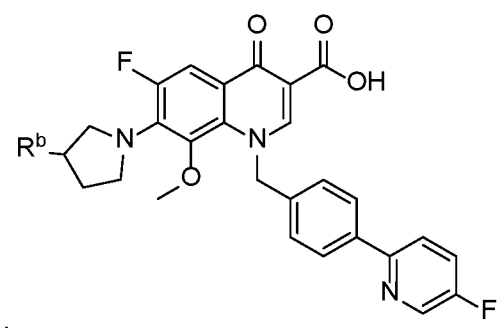
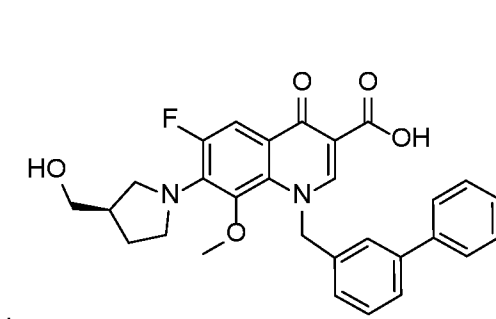
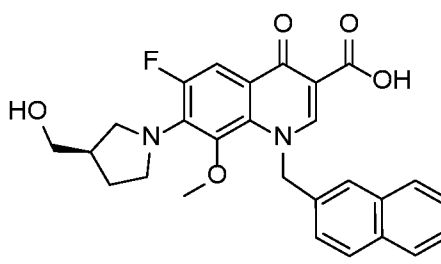
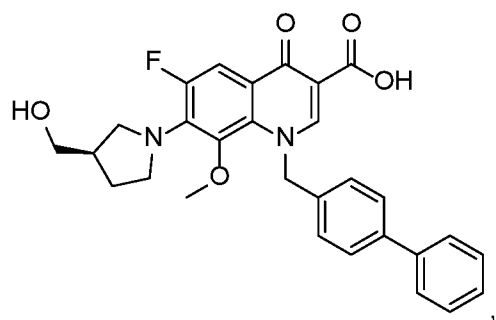
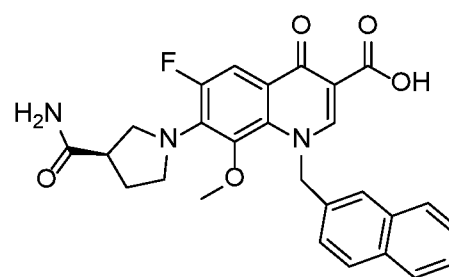
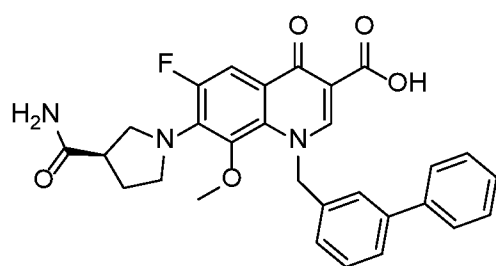
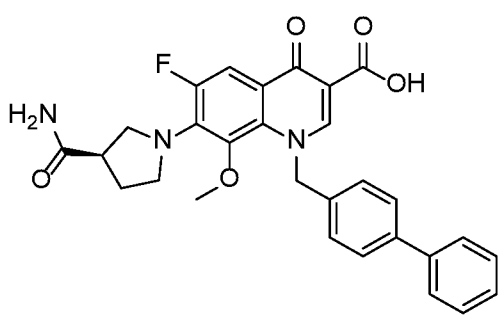
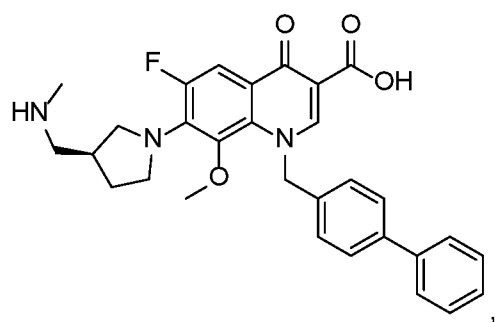
[0031] Representative compounds of the formulae (I), (Ia), (Ib), (II), (IIa), (V) or (VI) include compounds of the formulae:



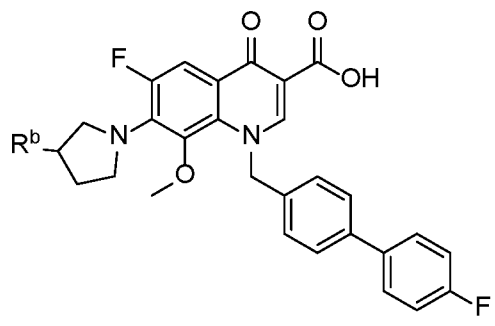
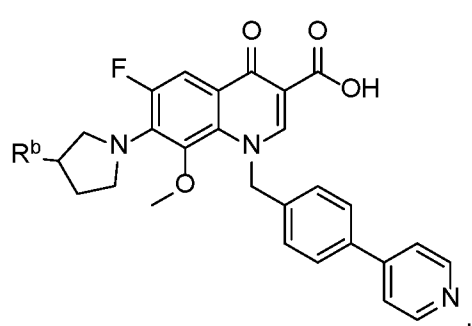


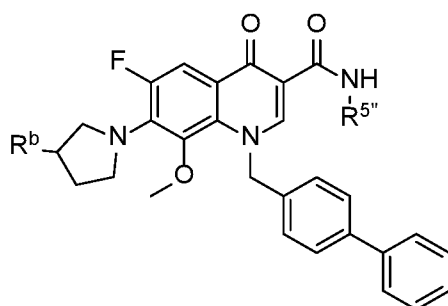
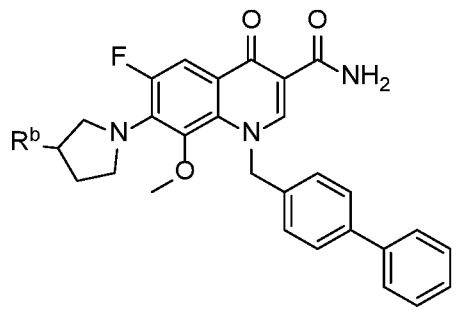
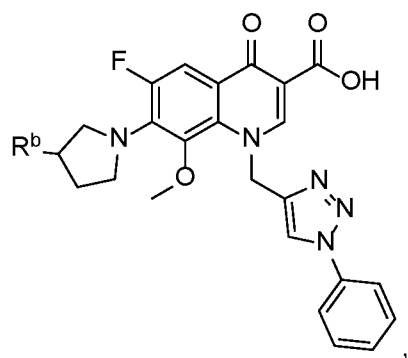
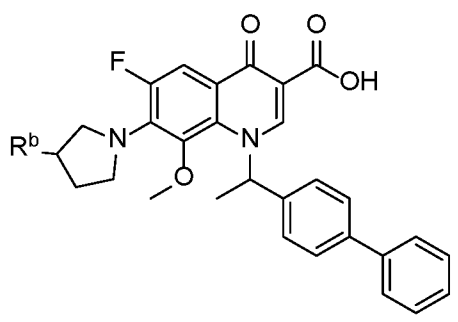
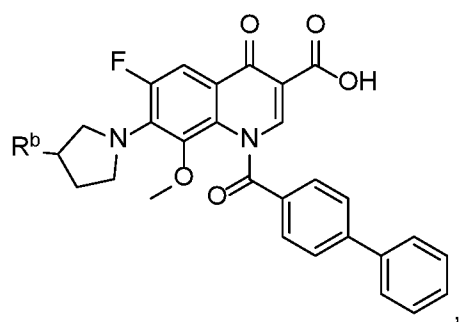
5



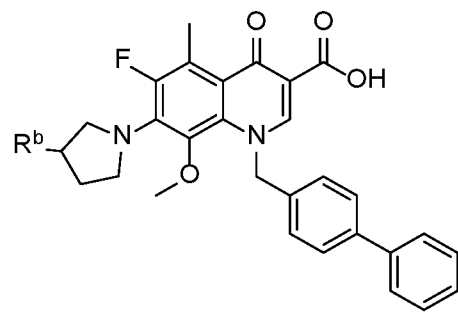
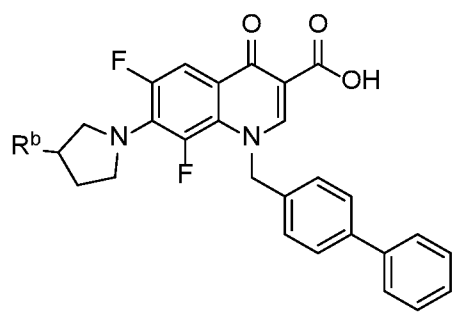
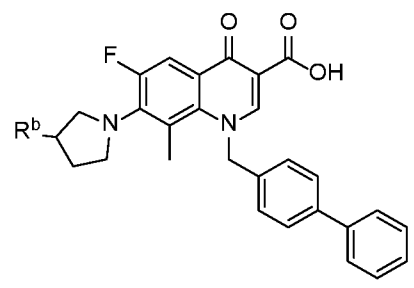
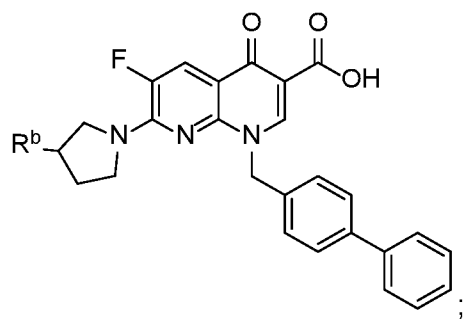


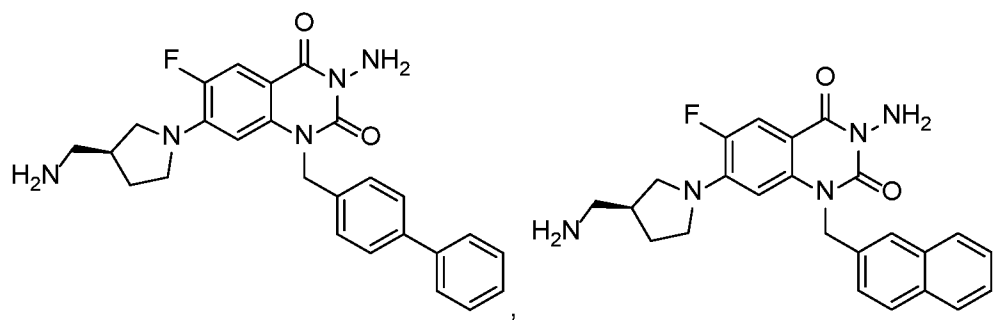
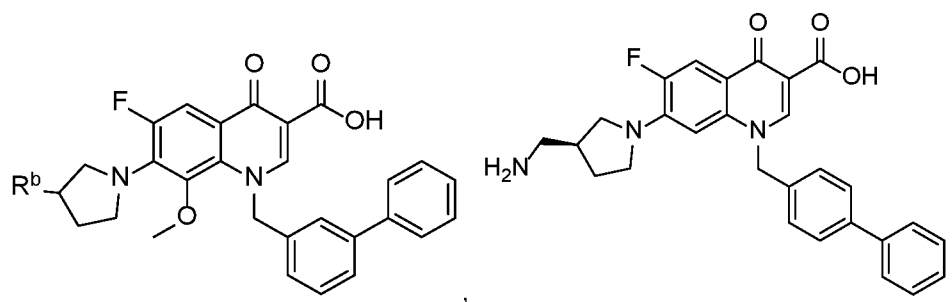
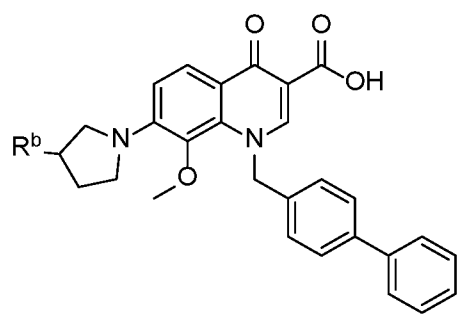
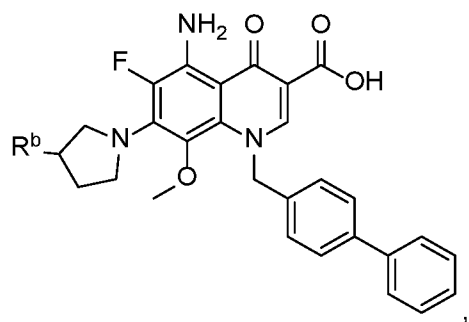
5 (wherein R^b is -CH₂NHCH₃, -CH₂OH or C(O)NH₂),

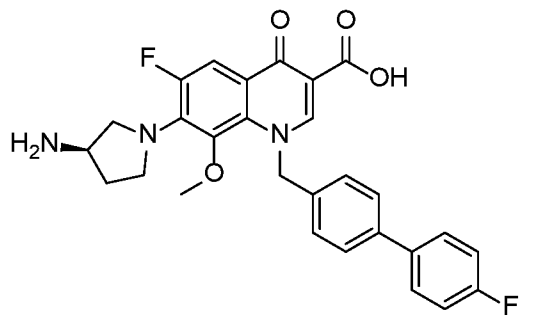
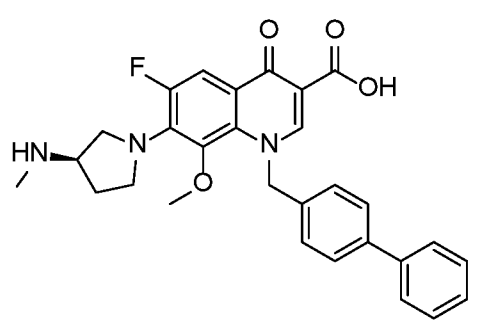
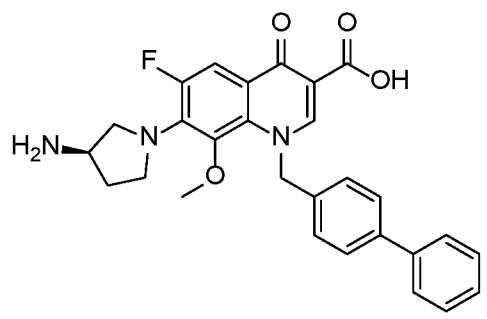
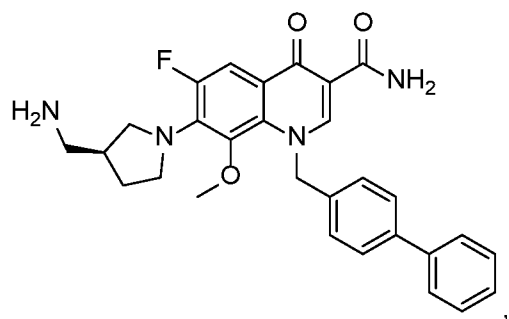
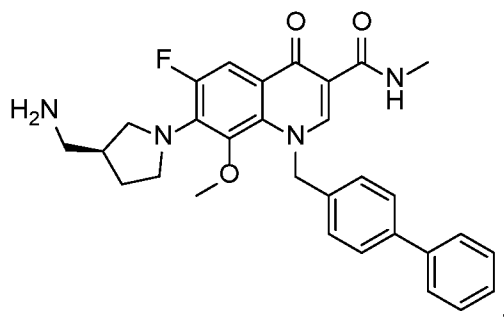
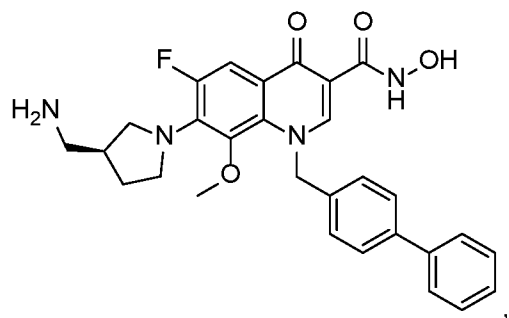
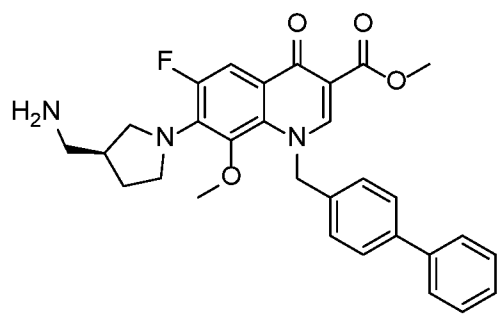
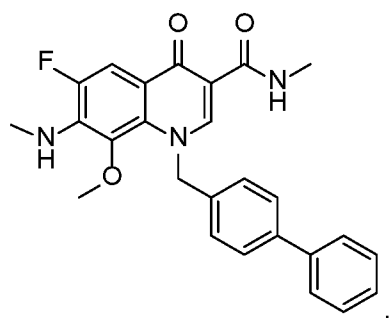
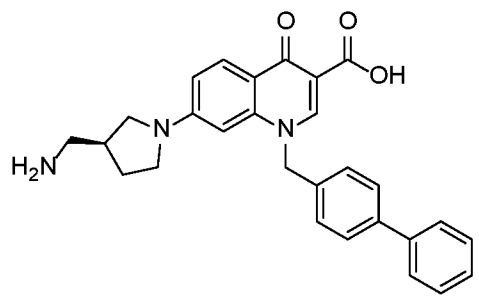
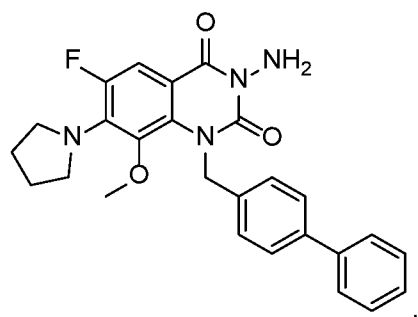


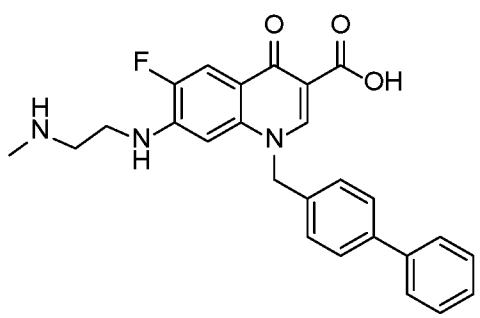
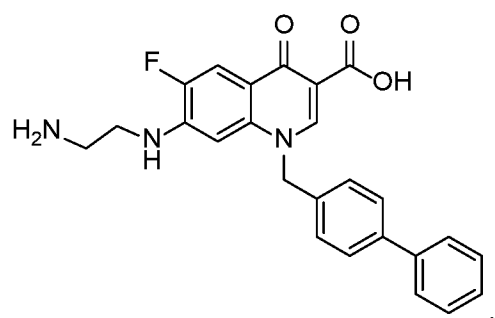
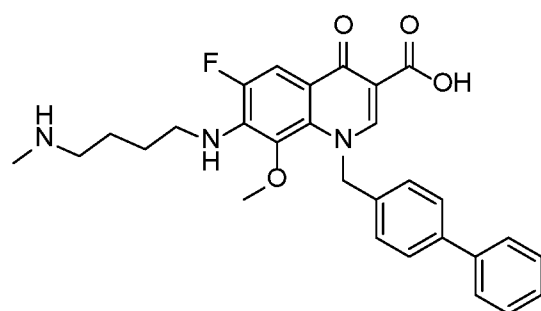
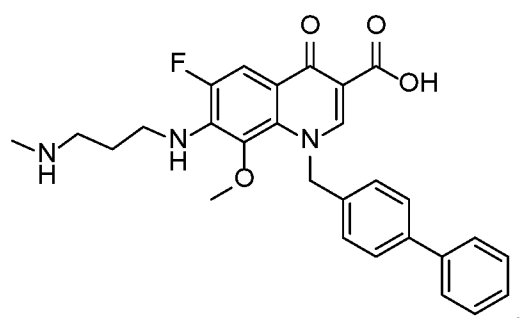
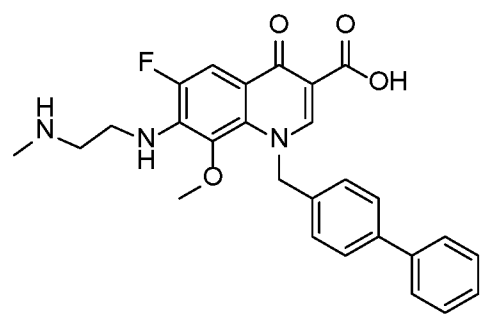
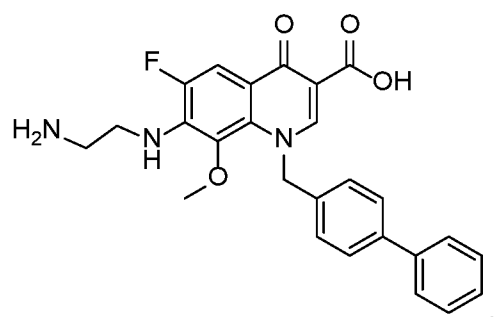


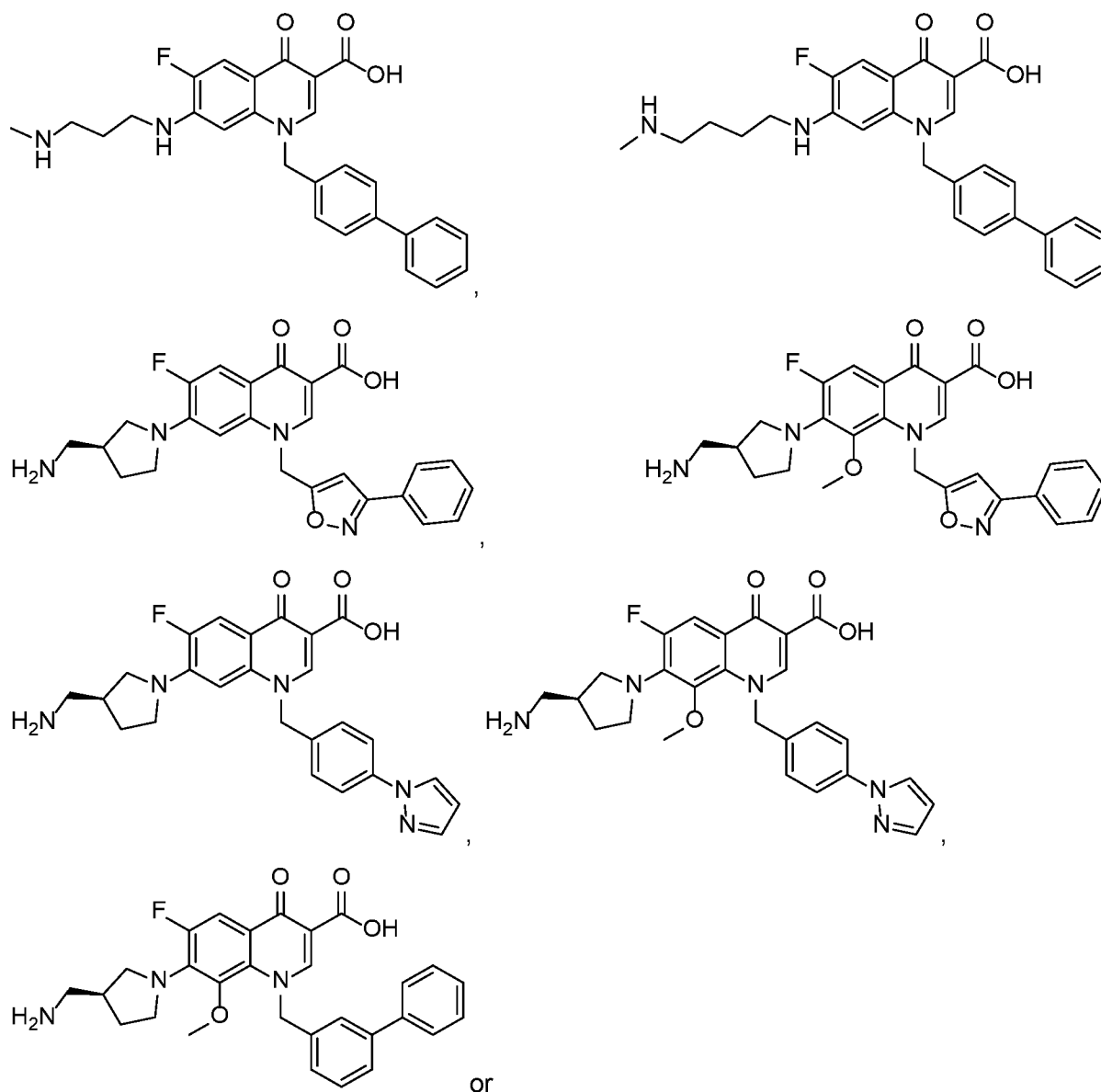
(wherein $R^{5''}$ is defined herein);











- 5 pharmaceutically acceptable salts (e.g., the hydrochloride salts, where a primary or secondary amine group is protonated), polymorphs, prodrugs, solvates or clathrates thereof.

[0032] Those of ordinary skill in the art will recognize that compounds described herein can contain chiral centers. All diastereomers of the compounds described herein are contemplated herein, as well as racemates.

- 10 **[0033]** Various embodiments also contemplate pharmaceutical compositions comprising one or more compounds described herein and one or more pharmaceutically acceptable carriers, diluents, excipients or combinations thereof. A “pharmaceutical composition” refers to a chemical or biological composition suitable for administration to a subject (e.g., mammal). Such compositions may be specifically formulated for administration
- 15 via one or more of a number of routes, including but not limited to buccal, cutaneous, epicutaneous, epidural, infusion, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal,

intravenous, oral, parenteral, pulmonary, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal. In addition, administration can be by means of capsule, drops, foams, gel, gum, injection, liquid, patch, pill, porous pouch, powder, tablet, or other suitable means of administration.

5 **[0034]** A “pharmaceutical excipient” or a “pharmaceutically acceptable excipient” comprises a carrier, sometimes a liquid, in which an active therapeutic agent is formulated. The excipient generally does not provide any pharmacological activity to the formulation, though it may provide chemical and/or biological stability, and release characteristics. Examples of suitable formulations can be found, for example, in Remington, The Science
10 And Practice of Pharmacy, 20th Edition, (Gennaro, A. R., Chief Editor), Philadelphia College of Pharmacy and Science, 2000, which is incorporated by reference in its entirety.

[0035] As used herein “pharmaceutically acceptable carrier” or “excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents that are physiologically compatible. In one embodiment, the
15 carrier is suitable for parenteral administration. Alternatively, the carrier can be suitable for intravenous, intraperitoneal, intramuscular, sublingual, or oral administration. Pharmaceutically acceptable carriers include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. The use of such media and agents for pharmaceutically active substances is well
20 known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the pharmaceutical compositions of the invention is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0036] Pharmaceutical compositions may be sterile and stable under the conditions
25 of manufacture and storage. The composition can be formulated as a solution, microemulsion, liposome, or other ordered structure suitable to high drug concentration. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (e.g., glycerol, propylene glycol, and liquid polyethylene glycol), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as
30 lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

[0037] In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the
35 composition an agent which delays absorption, for example, monostearate salts and gelatin. Moreover, the compounds described herein can be formulated in a time release formulation, for example in a composition that includes a slow release polymer. The active compounds

can be prepared with carriers that will protect the compound against rapid release, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers may be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, polylactic acid and polylactic, 5 polyglycolic copolymers (PLG). Many methods for the preparation of such formulations are known to those skilled in the art.

[0038] Oral forms of administration are also contemplated herein. The pharmaceutical compositions may be orally administered as a capsule (hard or soft), tablet (film coated, enteric coated or uncoated), powder or granules (coated or uncoated) or liquid 10 (solution or suspension). The formulations may be conveniently prepared by any of the methods well-known in the art. The pharmaceutical compositions may include one or more suitable production aids or excipients including fillers, binders, disintegrants, lubricants, diluents, flow agents, buffering agents, moistening agents, preservatives, colorants, sweeteners, flavors, and pharmaceutically compatible carriers.

[0039] For each of the recited embodiments, the compounds can be administered by a variety of dosage forms as known in the art. Any biologically-acceptable dosage form known to persons of ordinary skill in the art, and combinations thereof, are contemplated. Examples of such dosage forms include, without limitation, chewable tablets, quick dissolve tablets, effervescent tablets, reconstitutable powders, elixirs, liquids, solutions, suspensions, 20 emulsions, tablets, multi-layer tablets, bi-layer tablets, capsules, soft gelatin capsules, hard gelatin capsules, caplets, lozenges, chewable lozenges, beads, powders, gum, granules, particles, microparticles, dispersible granules, cachets, douches, suppositories, creams, topicals, inhalants, aerosol inhalants, patches, particle inhalants, implants, depot implants, ingestibles, injectables (including subcutaneous, intramuscular, intravenous, and 25 intradermal), infusions, and combinations thereof.

[0040] Other compounds which can be included by admixture are, for example, medically inert ingredients (e.g., solid and liquid diluent), such as lactose, dextrosesaccharose, cellulose, starch or calcium phosphate for tablets or capsules, olive oil or ethyl oleate for soft capsules and water or vegetable oil for suspensions or emulsions; 30 lubricating agents such as silica, talc, stearic acid, magnesium or calcium stearate and/or polyethylene glycols; gelling agents such as colloidal clays; thickening agents such as gum tragacanth or sodium alginate, binding agents such as starches, arabic gums, gelatin, methylcellulose, carboxymethylcellulose or polyvinylpyrrolidone; disintegrating agents such as starch, alginic acid, alginates or sodium starch glycolate; effervescing mixtures; dyestuff; 35 sweeteners; wetting agents such as lecithin, polysorbates or laurylsulphates; and other therapeutically acceptable accessory ingredients, such as humectants, preservatives, buffers and antioxidants, which are known additives for such formulations.

[0041] Liquid dispersions for oral administration can be syrups, emulsions, solutions, or suspensions. The syrups can contain as a carrier, for example, saccharose or saccharose with glycerol and/or mannitol and/or sorbitol. The suspensions and the emulsions can contain a carrier, for example a natural gum, agar, sodium alginate, pectin, methylcellulose, 5 carboxymethylcellulose, or polyvinyl alcohol.

[0042] The amount of active compound in a therapeutic composition according to various embodiments described herein may vary according to factors such as the disease state, age, gender, weight, patient history, risk factors, predisposition to disease, administration route, pre-existing treatment regime (e.g., possible interactions with other 10 medications), and weight of the individual. Dosage regimens may be adjusted to provide the optimum therapeutic response. For example, a single bolus may be administered, several divided doses may be administered over time, or the dose may be proportionally reduced or increased as indicated by the exigencies of therapeutic situation.

[0043] "Dosage unit form," as used herein, refers to physically discrete units suited 15 as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, 20 and the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals. In therapeutic use for treatment of conditions in mammals (e.g., humans) for which the compounds described herein or an appropriate pharmaceutical composition thereof are effective, the compounds may be administered in an effective amount. The suitable dosages may be a composition, a pharmaceutical 25 composition or any other compositions described herein.

[0044] For each of the recited embodiments, the dosage is typically administered once, twice, or thrice a day, although more frequent dosing intervals are possible. The dosage may be administered every day, every 2 days, every 3 days, every 4 days, every 5 30 days, every 6 days, and/or every 7 days (once a week). In one embodiment, the dosage may be administered daily for up to and including 30 days, preferably between 7-10 days. In another embodiment, the dosage may be administered twice a day for 10 days. If the patient requires treatment for a chronic disease or condition, the dosage may be administered for as long as signs and/or symptoms persist. The patient may require "maintenance treatment" where the patient is receiving dosages every day for months, years, or the remainder of their 35 lives. In addition, the composition of this invention may be to effect prophylaxis of recurring symptoms. For example, the dosage may be administered once or twice a day to prevent the onset of symptoms in patients at risk, especially for asymptomatic patients.

[0045] The compositions described herein may be administered in any of the following routes: buccal, epicutaneous, epidural, infusion, inhalation, intraarterial, intracardial, intracerebroventricular, intradermal, intramuscular, intranasal, intraocular, intraperitoneal, intraspinal, intrathecal, intravenous, oral, parenteral, pulmonary, rectally via an enema or suppository, subcutaneous, subdermal, sublingual, transdermal, and transmucosal. The preferred routes of administration are buccal and oral. The administration can be local, where the composition is administered directly, close to, in the locality, near, at, about, or in the vicinity of, the site(s) of disease, e.g., inflammation, or systemic, wherein the composition is given to the patient and passes through the body widely, thereby reaching the site(s) of disease. Local administration can be administration to the cell, tissue, organ, and/or organ system, which encompasses and/or is affected by the disease, and/or where the disease signs and/or symptoms are active or are likely to occur. Administration can be topical with a local effect, composition is applied directly where its action is desired. Administration can be enteral wherein the desired effect is systemic (non-local), composition is given via the digestive tract. Administration can be parenteral, where the desired effect is systemic, composition is given by other routes than the digestive tract.

[0046] Various embodiments contemplate compositions comprising a therapeutically effective amount of one or more compounds of the various embodiments described herein. In some embodiments, the compositions are useful in a method for treating cancer, the method comprising administering a therapeutically effective amount of one or more compounds to a patient in need thereof. Various embodiments are directed to compounds of the various embodiments described herein for use as a medicament for treating a patient in need of relief from cancer.

[0047] The term "therapeutically effective amount" as used herein, refers to that amount of one or more compounds of the various embodiments described herein that elicits a biological or medicinal response in a tissue system, animal or human, that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated. In some embodiments, the therapeutically effective amount is that which may treat or alleviate the disease or symptoms of the disease at a reasonable benefit/risk ratio applicable to any medical treatment. However, it is to be understood that the total daily usage of the compounds and compositions described herein may be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically-effective dose level for any particular patient will depend upon a variety of factors, including the condition being treated and the severity of the condition; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, gender and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific

compound employed; the duration of the treatment; drugs used in combination or coincidentally with the specific compound employed; and like factors well known to the researcher, veterinarian, medical doctor or other clinician. It is also appreciated that the therapeutically effective amount can be selected with reference to any toxicity, or other undesirable side effect, that might occur during administration of one or more of the compounds described herein.

[0048] In some embodiments, the compounds of the various embodiments described herein have a half maximal inhibitory concentration (IC_{50}) for human topoisomerase I, using relaxation assays, of from about 100 nM to about 200 μ M (e.g., about 900 nM to about 50 μ M, about 1 μ M to about 100 μ M, about 10 μ M to about 100 μ M, about 20 μ M to about 100 μ M, about 20 μ M to about 50 μ M, about 20 μ M to about 30 μ M or about 10 μ M to about 90 μ M).

[0049] In some embodiments, the compounds of the various embodiments described herein have an IC_{50} for human topoisomerase II, using decatenation assays, of from about 200 nM to about 400 μ M (e.g., about 50 μ M to about 250 μ M, about 50 μ M to about 180 μ M, about 100 μ M to about 300 μ M, about 100 μ M to about 200 μ M, about 100 μ M to about 150 μ M, about 110 μ M to about 180 μ M or about 120 μ M to about 180 μ M).

[0050] In some embodiments, the IC_{50} for human topoisomerase I is about four times lower than the IC_{50} for human topoisomerase II. In other embodiments, the IC_{50} for human topoisomerase I is at least about two (e.g., about two to about 10,000) times lower than the IC_{50} for human topoisomerase II (e.g., the IC_{50} for human topoisomerase II is about two to about 10,000 times greater than the IC_{50} for human topoisomerase I).

[0051] Values expressed in a range format should be interpreted in a flexible manner to include not only the numerical values explicitly recited as the limits of the range, but also to include all the individual numerical values or sub-ranges encompassed within that range as if each numerical value and sub-range were explicitly recited. For example, a range of "about 0.1% to about 5%" or "about 0.1% to 5%" should be interpreted to include not just about 0.1% to about 5%, but also the individual values (e.g., 1%, 2%, 3%, and 4%) and the sub-ranges (e.g., 0.1% to 0.5%, 1.1% to 2.2%, 3.3% to 4.4%) within the indicated range. The statement "about X to Y" has the same meaning as "about X to about Y," unless indicated otherwise. Likewise, the statement "about X, Y, or about Z" has the same meaning as "about X, about Y, or about Z," unless indicated otherwise.

[0052] In this document, the terms "a," "an," or "the" are used to include one or more than one unless the context clearly dictates otherwise. The term "or" is used to refer to a nonexclusive "or" unless otherwise indicated. In addition, it is to be understood that the phraseology or terminology employed herein, and not otherwise defined, is for the purpose of description only and not of limitation. Any use of section headings is intended to aid

reading of the document and is not to be interpreted as limiting. Further, information that is relevant to a section heading may occur within or outside of that particular section. Furthermore, all publications, patents, and patent documents referred to in this document are incorporated by reference herein in their entirety, as though individually incorporated by reference. In the event of inconsistent usages between this document and those documents so incorporated by reference, the usage in the incorporated reference should be considered supplementary to that of this document; for irreconcilable inconsistencies, the usage in this document controls.

[0053] In the methods described herein, the steps can be carried out in any order without departing from the principles of the invention, except when a temporal or operational sequence is explicitly recited. Furthermore, specified steps can be carried out concurrently unless explicit claim language recites that they be carried out separately. For example, a claimed step of doing X and a claimed step of doing Y can be conducted simultaneously within a single operation, and the resulting process will fall within the literal scope of the claimed process.

[0054] The term “about” as used herein can allow for a degree of variability in a value or range, for example, within 10%, within 5%, or within 1% of a stated value or of a stated limit of a range.

[0055] The term “substantially” as used herein refers to a majority of, or mostly, as in at least about 50%, 60%, 70%, 80%, 90%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, 99.99%, or at least about 99.999% or more.

[0056] The term “substituted” or “substituent” as used herein refers to a group that can be or is substituted onto a molecule or onto another group. Examples of substituents include, but are not limited to, a halogen (e.g., F, Cl, Br, and I), OR, OC(O)N(R)₂, CN, NO, NO₂, ONO₂, azido, CF₃, OCF₃, R, O (oxo), S (thiono), C(O), S(O), methylenedioxy, ethylenedioxy, N(R)₂, SR, SOR, SO₂R, SO₂N(R)₂, SO₃R, -(CH₂)₀₋₂P(O)(OR)₂, C(O)R, C(O)C(O)R, C(O)CH₂C(O)R, C(S)R, C(O)OR, OC(O)R, C(O)N(R)₂, OC(O)N(R)₂, C(S)N(R)₂, (CH₂)₀₋₂N(R)C(O)R, (CH₂)₀₋₂N(R)C(O)OR, (CH₂)₀₋₂N(R)N(R)₂, N(R)N(R)C(O)R, N(R)N(R)C(O)OR, N(R)N(R)CON(R)₂, N(R)SO₂R, N(R)SO₂N(R)₂, N(R)C(O)OR, N(R)C(O)R, N(R)C(S)R, N(R)C(O)N(R)₂, N(R)C(S)N(R)₂, N(COR)COR, N(OR)R, C(=NH)N(R)₂, C(O)N(OR)R, or C(=NOR)R wherein each R can be, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl, wherein any alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl or two R groups bonded to a nitrogen atom or to adjacent nitrogen atoms can together with the nitrogen atom or atoms form a heterocyclyl, which can be mono- or independently multi-substituted.

[0057] The term “alkyl” as used herein refers to substituted or unsubstituted straight chain and branched alkyl groups and cycloalkyl groups having from 1 to 40 carbon atoms

(C₁-C₄₀), 1 to about 20 carbon atoms (C₁-C₂₀), 1 to 12 carbons (C₁-C₁₂), 1 to 8 carbon atoms (C₁-C₈), or, in some embodiments, from 1 to 6 carbon atoms (C₁-C₆). Examples of straight chain alkyl groups include those with from 1 to 8 carbon atoms such as methyl, ethyl, n-propyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, and n-octyl groups. Examples of branched alkyl groups include, but are not limited to, isopropyl, iso-butyl, sec-butyl, t-butyl, neopentyl, isopentyl, and 2,2-dimethylpropyl groups. As used herein, the term "alkyl" encompasses n-alkyl, isoalkyl, and anteisoalkyl groups as well as other branched chain forms of alkyl. Representative substituted alkyl groups can be substituted one or more times with any of the groups listed herein, for example, amino, hydroxy, cyano, carboxy, nitro, thio, alkoxy, and halogen groups.

[0058] The term "cycloalkyl" as used herein refers to substituted or unsubstituted cyclic alkyl groups such as, but not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl groups. In some embodiments, the cycloalkyl group can have 3 to about 8-12 ring members, whereas in other embodiments the number of ring carbon atoms range from 3 to 4, 5, 6, or 7. In some embodiments, cycloalkyl groups can have 3 to 6 carbon atoms (C₃-C₆). Cycloalkyl groups further include polycyclic cycloalkyl groups such as, but not limited to, norbornyl, adamantyl, bornyl, camphenyl, isocamphenyl, and carenyl groups, and fused rings such as, but not limited to, decalinyl, and the like.

[0059] The term "cycloalkylalkyl" as used herein refers to substituted or unsubstituted alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group as defined herein is replaced with a bond to a cycloalkyl group as defined herein. Representative cycloalkylalkyl groups include, but are not limited to, cyclopentylalkyl.

[0060] The term "alkylcycloalkyl" as used herein refers to substituted or unsubstituted cycloalkyl groups as defined herein in which a hydrogen of a cycloalkyl group as defined herein is replaced with a bond to an alkyl group as defined herein. Representative alkylcycloalkyl groups include, but are not limited to, alkylcyclopropyl.

[0061] The term "acyl" as used herein refers to a group containing a carbonyl moiety wherein the group is bonded via the carbonyl carbon atom. The carbonyl carbon atom is also bonded to another carbon atom, which can be part of a substituted or unsubstituted alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclalkyl, heteroaryl, heteroarylalkyl group or the like. In the special case wherein the carbonyl carbon atom is bonded to a hydrogen, the group is a "formyl" group, an acyl group as the term is defined herein. An acyl group can include 0 to about 12-40, 6-10, 1-5 or 2-5 additional carbon atoms bonded to the carbonyl group. An acryloyl group is an example of an acyl group. An acyl group can also include heteroatoms within the meaning here. A nicotinoyl group (pyridyl-3-carbonyl) is an example of an acyl group within the meaning herein. Other examples include acetyl, benzoyl, phenylacetyl, pyridylacetyl, cinnamoyl, and acryloyl groups and the like.

When the group containing the carbon atom that is bonded to the carbonyl carbon atom contains a halogen, the group is termed a "haloacyl" group. An example is a trifluoroacetyl group.

[0062] The term "heterocyclylcarbonyl" is an example of an acyl group that is bonded to a substituted or unsubstituted heterocyclyl group, as the term "heterocyclyl" is defined herein. An example of a heterocyclylcarbonyl group is a prolyl group, wherein the prolyl group can be a D- or an L-prolyl group.

[0063] The term "aryl" as used herein refers to substituted or unsubstituted cyclic aromatic hydrocarbons that do not contain heteroatoms in the ring. Thus aryl groups include, but are not limited to, phenyl, azulenyl, heptalenyl, biphenyl, indacenyl, fluorenyl, phenanthrenyl, triphenylenyl, pyrenyl, naphthacenyl, chrysenyl, biphenylenyl, anthracenyl, and naphthyl groups. In some embodiments, aryl groups contain about 6 to about 14 carbons (C_6 - C_{14}) or from 6 to 10 carbon atoms (C_6 - C_{10}) in the ring portions of the groups. Aryl groups can be unsubstituted or substituted, as defined herein. Representative substituted aryl groups can be mono-substituted or substituted more than once, such as, but not limited to, 2-, 3-, 4-, 5-, or 6-substituted phenyl or 2-8 substituted naphthyl groups, which can be substituted with carbon or non-carbon groups such as those listed herein.

[0064] The term "aralkyl" and "arylalkyl" as used herein refers to alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined herein. Representative aralkyl groups include benzyl and phenylethyl groups and fused (cycloalkylaryl)alkyl groups such as 4-ethyl-indanyl. Aralkenyl groups are alkenyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to an aryl group as defined herein.

[0065] The term "heterocyclyl" as used herein refers to substituted or unsubstituted aromatic and non-aromatic ring compounds containing 3 or more ring members, of which, one or more (e.g., 1, 2 or 3) is a heteroatom such as, but not limited to, N, O, and S. Thus, a heterocyclyl can be a cycloheteroalkyl, or a heteroaryl, or if polycyclic, any combination thereof. In some embodiments, heterocyclyl groups include 3 to about 20 ring members, whereas other such groups have 3 to about 15 ring members. In some embodiments, heterocyclyl groups include heterocyclyl groups that include 3 to 8 carbon atoms (C_3 - C_8), 3 to 6 carbon atoms (C_3 - C_6), 3 to 5 carbon atoms (C_3 - C_5) or 6 to 8 carbon atoms (C_6 - C_8). A heterocyclyl group designated as a C_2 -heterocyclyl can be a 5-ring with two carbon atoms and three heteroatoms, a 6-ring with two carbon atoms and four heteroatoms and so forth. Likewise a C_4 -heterocyclyl can be a 5-ring with one heteroatom, a 6-ring with two heteroatoms, and so forth. The number of carbon atoms plus the number of heteroatoms equals the total number of ring atoms. A heterocyclyl ring can also include one or more double bonds. A heteroaryl ring is an embodiment of a heterocyclyl group. The phrase

“heterocyclyl group” includes fused ring species including those that include fused aromatic and non-aromatic groups. Representative heterocyclyl groups include, but are not limited to pyrrolidinyl, azetidiny, piperidiny, piperaziny, morpholinyl, chromanyl, indolinonyl, isoindolinonyl, furanyl, pyrrolidinyl, pyridinyl, pyrazinyl, pyrimidinyl, triazinyl, thiophenyl, tetrahydrofuranyl, pyrrolyl, oxazolyl, oxadiazolyl, imidazolyl, triazyolyl, tetrazolyl, benzoxazolinyl, benzthiazolinyl, and benzimidazolinyl groups.

[0066] The term “heterocyclylalkyl” as used herein refers to alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group as defined herein is replaced with a bond to a heterocyclyl group as defined herein. Representative heterocyclylalkyl groups include, but are not limited to, furan-2-yl methyl, furan-3-yl methyl, pyridine-3-yl methyl, tetrahydrofuran-2-yl methyl, and indol-2-yl propyl.

[0067] The term “heterocyclylalkoxy” as used herein refers to alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group as defined herein is replaced with a bond to a heterocyclyl group as defined herein and the alkyl group is attached to an oxygen. Representative heterocyclylalkoxy groups include, but are not limited to, -O-(CH₂)_qheterocyclyl, wherein q is an integer from 1 to 5. In some embodiments, heterocyclylalkoxy groups include -O-(CH₂)_qmorpholinyl such as -O-CH₂CH₂-morpholine.

[0068] The term “heteroarylalkyl” as used herein refers to alkyl groups as defined herein in which a hydrogen or carbon bond of an alkyl group is replaced with a bond to a heteroaryl group as defined herein.

[0069] The term “alkoxy” as used herein refers to an oxygen atom connected to an alkyl group, including a cycloalkyl group, as are defined herein. Examples of linear alkoxy groups include but are not limited to methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, and the like. Examples of branched alkoxy include but are not limited to isopropoxy, sec-butoxy, tert-butoxy, isopentyloxy, isohexyloxy, and the like. Examples of cyclic alkoxy include but are not limited to cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, and the like. An alkoxy group can include one to about 12-20 or about 12-40 carbon atoms bonded to the oxygen atom, and can further include double or triple bonds, and can also include heteroatoms. For example, an allyloxy group is an alkoxy group within the meaning herein. A methoxyethoxy group is also an alkoxy group within the meaning herein, as is a methylenedioxy group in a context where two adjacent atoms of a structure are substituted therewith.

[0070] The term “amine” as used herein refers to primary, secondary, and tertiary amines having, e.g., the formula N(group)₃ wherein each group can independently be H or non-H, such as alkyl, aryl, and the like. Amines include but are not limited to R-NH₂, for example, alkylamines, arylamines, alkylarylamines; R₂NH wherein each R is independently selected, such as dialkylamines, diarylamines, aralkylamines, heterocyclylamines and the

like; and R_3N wherein each R is independently selected, such as trialkylamines, dialkylarylamines, alkyl diarylamines, triarylamines, and the like. The term "amine" also includes ammonium ions as used herein.

[0071] The term "amino group" as used herein refers to a substituent of the form -
5 NH_2 , -NHR, -NR₂, -NR₃⁺, wherein each R is independently selected, and protonated forms of each, except for -NR₃⁺, which cannot be protonated. Accordingly, any compound substituted with an amino group can be viewed as an amine. An "amino group" within the meaning herein can be a primary, secondary, tertiary, or quaternary amino group. An "alkylamino" group includes a monoalkylamino, dialkylamino, and trialkylamino group.

10 **[0072]** The terms "halo," "halogen," or "halide" group, as used herein, by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom.

[0073] The term "haloalkyl" group, as used herein, includes mono-halo alkyl groups, poly-halo alkyl groups wherein all halo atoms can be the same or different, and per-halo
15 alkyl groups, wherein all hydrogen atoms are replaced by halogen atoms, such as fluoro. Examples of haloalkyl include trifluoromethyl, 1,1-dichloroethyl, 1,2-dichloroethyl, 1,3-dibromo-3,3-difluoropropyl, -CF(CH₃)₂ and the like.

[0074] As used herein, the term "salts" and "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by
20 making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic groups such as amines; and alkali or organic salts of acidic groups such as carboxylic acids. Pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For
25 example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, and nitric; and the salts prepared from organic acids such as acetic, trifluoroacetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic,
30 methanesulfonic, ethane disulfonic, oxalic, and isethionic acids, and the like.

[0075] Pharmaceutically acceptable salts can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. In some instances, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an
35 organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in

Remington's Pharmaceutical Sciences, 17th ed., Mack Publishing Company, Easton, Pa., 1985, the disclosure of which is hereby incorporated by reference.

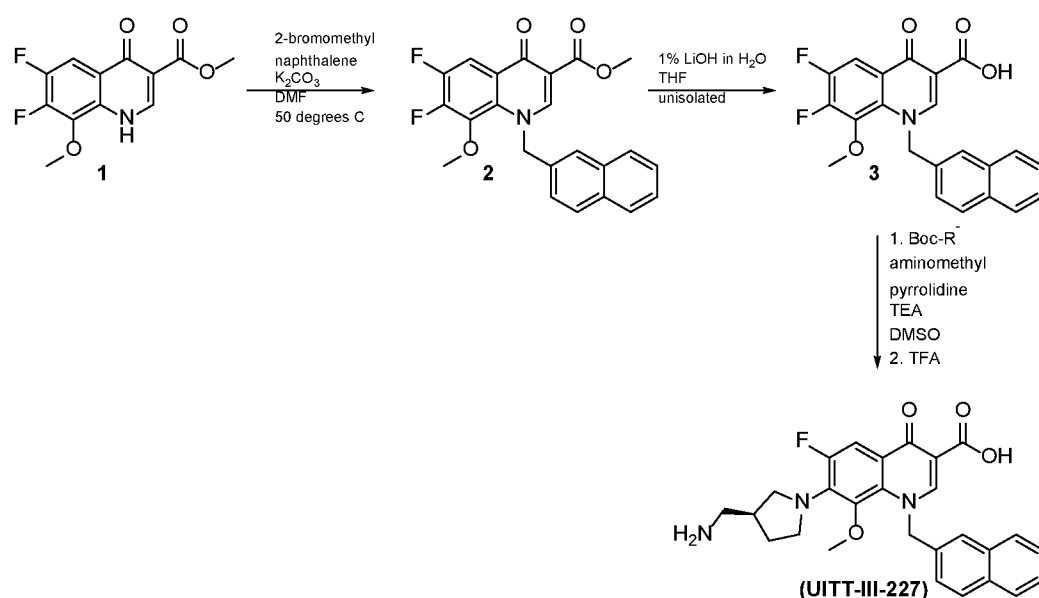
[0076] The term "solvate" means a compound, or a salt thereof, that further includes a stoichiometric or non-stoichiometric amount of solvent bound by non-covalent intermolecular forces. Where the solvent is water, the solvate is a hydrate.

[0077] The term "prodrug" means a derivative of a compound that can hydrolyze, oxidize, or otherwise react under biological conditions (in vitro or in vivo) to provide an active compound, particularly a compound of the invention. Examples of prodrugs include, but are not limited to, derivatives and metabolites of a compound of the invention that include biohydrolyzable moieties such as biohydrolyzable amides, biohydrolyzable esters, biohydrolyzable carbamates, biohydrolyzable carbonates, biohydrolyzable ureides, and biohydrolyzable phosphate analogues. Specific prodrugs of compounds with carboxyl functional groups are the lower alkyl esters of the carboxylic acid. The carboxylate esters are conveniently formed by esterifying any of the carboxylic acid moieties present on the molecule. Prodrugs can typically be prepared using well-known methods, such as those described by Burger's Medicinal Chemistry and Drug Discovery 6th ed. (Donald J. Abraham ed., 2001, Wiley) and Design and Application of Prodrugs (H. Bundgaard ed., 1985, Harwood Academic Publishers GmbH).

Examples

[0078] The following examples which are offered by way of illustration and do not limit the scope of the claims presented herein.

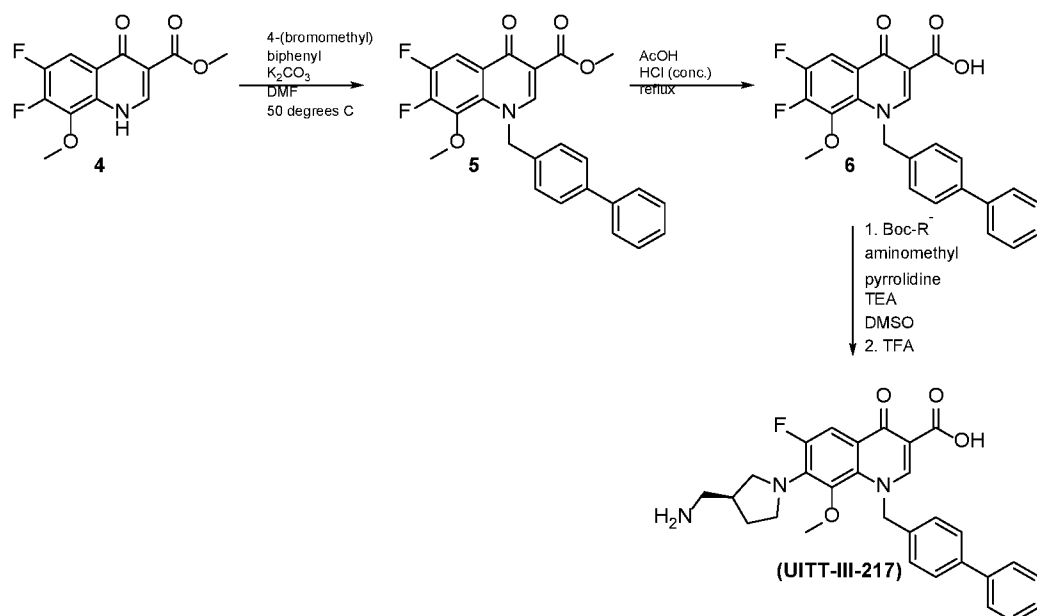
Example 1: Preparation of (S)-7-(3-(aminomethyl)pyrrolidin-1-yl)-6-fluoro-8-methoxy-1-(naphthalen-2-ylmethyl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (UITT-III-227)



[0079] Compound **2** (56.6 mg, 0.138 mmol) was dissolved in 2:1 THF:1 % LiOH in

H₂O and stirred at room temperature for 1 hour. The THF was removed by rotary evaporation and the aqueous layer was acidified to pH 1 with 4.0 N HCl. The aqueous layer was then extracted four times with 10 mL dichloromethane (DCM) and the combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated by rotary evaporation. The residue was then dissolved in 1.5 mL anhydrous dimethylsulfoxide (DMSO) and heated to 50°C with stirring. Boc-(R)-aminomethylpyrrolidine (61.6 mg, 0.308 mmol) and TEA (100 µL, 0.717 mmol) were added and the reaction stirred for 24 hours. Trifluoroacetic acid (TFA; 3 mL) was added and the reaction was allowed to cool to room temperature and stir overnight. The solution was then diluted with water and the product 4 was purified by preparatory HPLC. 89 % yield over 3 steps. ¹H NMR (300 MHz, dDMSO) δ = 15.24 (bs, 1H), 9.13 (s, 1H), 7.96 (bs, 3H), 7.86 (m, 3H), 7.69 (m, 2H), 7.47 (m, 2H), 7.31 (d, J = 9.0 Hz, 1H), 6.04 (m, 2H), 3.48 (m, 3H), 3.39 (s, 3H), 3.35 (m, 1H), 2.91 (m, 2H), 2.43 (m, 1H), 2.04 (m, 1H), 1.65 (m, 1H). ¹⁹F NMR (282 MHz, dDMSO) δ = -120.60 (d, J = 14.4 Hz, 1F). LRMS (ESI) calculated for (M+H⁺) 476.20, found 476.33. Retention time (analytical HPLC) = 17.85 min.

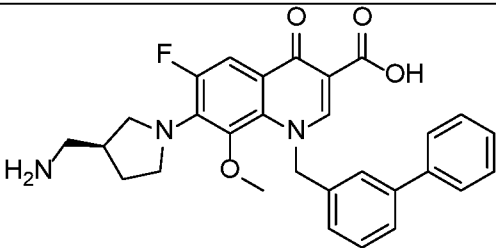
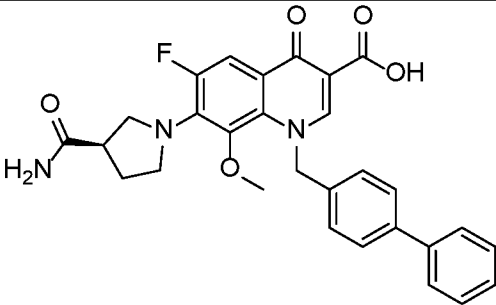
Example 2: Preparation of (S)-1-([1,1'-biphenyl]-4-ylmethyl)-7-(3-(aminomethyl)pyrrolidin-1-yl)-6-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (UITT-III-217)

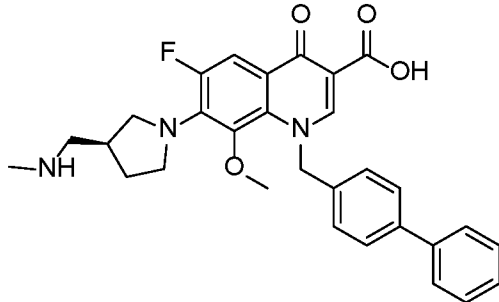
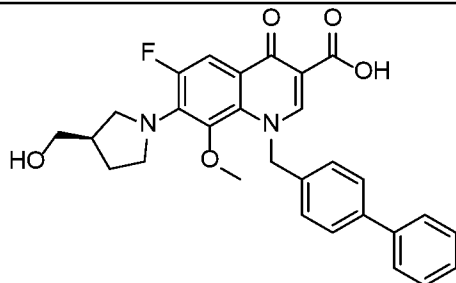


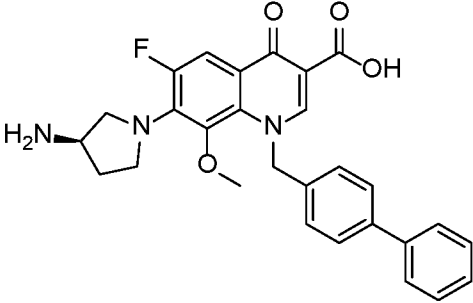
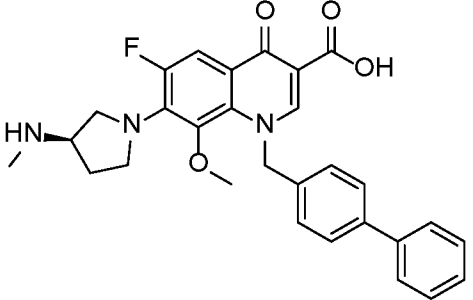
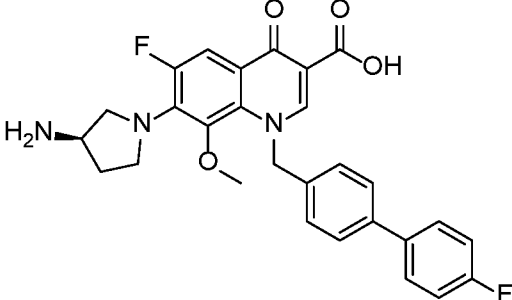
[0080] UITT-III-219 (19f) (56.6 mg, 0.138 mmol) was dissolved in 2:1 THF:1 % LiOH in H₂O and stirred at room temperature for 1 h. The THF was removed by rotary evaporation and the aqueous layer was acidified to pH 1 with 4.0 N HCl. The aqueous layer was then extracted four times with 10 mL DCM and the combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated by rotary evaporation. The residue was then dissolved in 1.5 mL anhydrous DMSO and heated to 50 °C with stirring. Boc-(R)-aminomethylpyrrolidine (61.6 mg, 0.308 mmol) and TEA (100 µL, 0.717 mmol) were added

and the reaction stirred for 24 h. TFA (3 mL) was added and the reaction was allowed to cool to room temperature and stir overnight. The solution was then diluted with water and the product purified by preparatory HPLC. 89 % yield over 3 steps. ^1H NMR (300 MHz, dDMSO) δ = 15.24 (bs, 1H), 9.13 (s, 1H), 7.96 (bs, 3H), 7.86 (m, 3H), 7.69 (m, 2H), 7.47 (m, 2H), 7.31 (d, J = 9.0 Hz, 1H), 6.04 (m, 2H), 3.48 (m, 3H), 3.39 (s, 3H), 3.35 (m, 1H), 2.91 (m, 2H), 2.43 (m, 1H), 2.04 (m, 1H), 1.65 (m, 1H). ^{19}F NMR (282 MHz, dDMSO) δ = -120.60 (d, J = 14.4 Hz, 1F). LRMS (ESI) calculated for $(\text{M}+\text{H}^+)$ 476.20, found 476.33. Retention time (analytical HPLC) = 17.85 min.

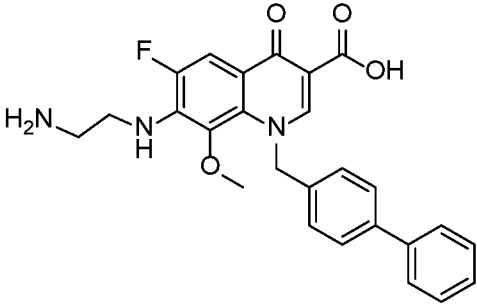
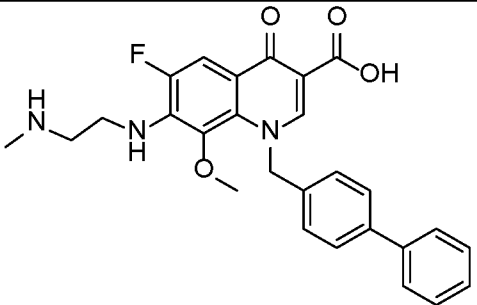
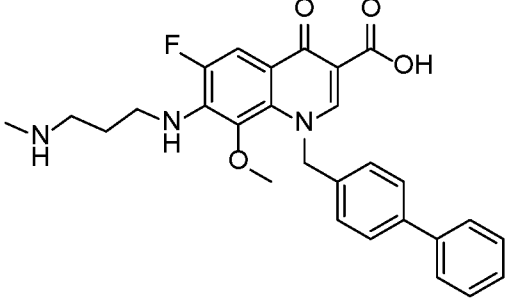
[0081] Compounds that can be synthesized by the methods described in Examples 1 and 2 include:

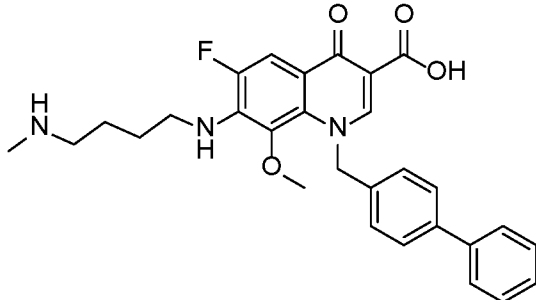
Compound ID	Structure	Characterization
UIJD-II-175		^1H NMR (400 MHz, DMSO) δ 9.10 (s, 1H), 7.69 (d, J = 13.9 Hz, 1H), 7.56 (dd, J = 11.5, 4.3 Hz, 4H), 7.45 (t, J = 7.6 Hz, 2H), 7.36 (t, J = 7.5 Hz, 2H), 7.04 (d, J = 7.7 Hz, 1H), 5.94 (dd, J = 29.7, 15.2 Hz, 2H), 5.21 – 5.06 (m, 3H), 4.73 (dd, J = 12.4, 5.7 Hz, 2H), 3.54 – 3.46 (m, 1H), 3.44 (s, 3H), 2.80 – 2.69 (m, 2H), 1.60 (dd, J = 12.1, 8.0 Hz, 1H). ^{19}F NMR (300 MHz, CDCl_3) δ -121.36 (d, J = 13.9 Hz). ESI calculated $(\text{M}+\text{H})^+$ 502.21, found $\text{M}+\text{H}$ =502.21. Retention time (analytical HPLC) 25.5min.
UIJD-II-115		^1H NMR (400 MHz, DMSO) δ 9.16 – 8.98 (m, 1H), 7.69 (d, J = 13.9 Hz, 1H), 7.61 – 7.57 (m, 3H), 7.47 (s, 1H), 7.42 (t, J = 7.5 Hz, 2H), 7.33 (t, J = 7.2 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 5.92 (dd, J = 30.0, 15.4 Hz, 2H), 3.69 – 3.61 (m, 1H), 3.51 (d, J = 8.2 Hz, 1H), 3.43 (d, J = 12.1 Hz, 3H), 3.11 – 3.02 (m, 1H), 2.98 – 2.89 (m, 1H), 2.10 – 1.95 (m, 1H), 1.17 (t, J = 7.1 Hz,

		2H). ^{19}F NMR (300 MHz, DMSO) δ -73.49 (d, J = 19.6 Hz), -120.57 (s). ESI calculated $M+H^+$=516.19, found 516.2. RT=19.7min
UIJD-II-086		^1H NMR (400 MHz, DMSO) δ 15.17 (s, 1H), 9.10 (s, 1H), 8.79 (s, 2H), 7.71 (d, J = 13.9 Hz, 1H), 7.60 (d, J = 8.2 Hz, 4H), 7.42 (t, J = 7.7 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.24 (d, J = 8.2 Hz, 2H), 5.93 (dd, J = 31.4, 15.3 Hz, 2H), 3.60 (t, J = 7.6 Hz, 1H), 3.52 (d, J = 8.0 Hz, 1H), 3.47 (s, 3H), 3.39 (d, J = 7.2 Hz, 3H), 2.99 (d, J = 6.4 Hz, 2H), 2.54 (t, J = 4.8 Hz, 3H), 2.14 – 2.02 (m, 1H), 1.71 (dd, J = 12.1, 8.0 Hz, 1H). ^{19}F NMR (282 MHz, DMSO) δ -120.45 (d, J = 13.3 Hz). ESI calculated $(M+H)^+$ 516.22, found 515.2298. Retention time (analytical HPLC)=23.9 min
UIJD-II-116		^1H NMR (400 MHz, DMSO) δ 9.10 (s, 1H), 7.70 (d, J = 14.0 Hz, 1H), 7.63 – 7.57 (m, 4H), 7.44 (dd, J = 10.3, 4.8 Hz, 2H), 7.38 – 7.32 (m, 1H), 7.25 (d, J = 8.3 Hz, 2H), 5.94 (dd, J = 30.9, 15.2 Hz, 2H), 3.52 (ddd, J = 11.6, 9.5, 4.2 Hz, 3H), 3.46 (s, 3H), 3.45 – 3.32 (m, 3H), 2.33 (dt, J = 14.5, 7.2 Hz, 1H), 1.96 (dt, J = 11.3, 5.8 Hz, 1H), 1.64 (dq, J = 12.2, 7.8 Hz, 1H). ^{19}F NMR (400 MHz, DMSO) δ -120.50 (s). ESI calculated $(M+H)^+$ 503.19, found 503.2. Retention time (analytical HPLC) = 21.7min

UIJD-II-226		¹ H NMR (400 MHz, MeOD) δ 8.97 (s, 1H), 7.77 (d, <i>J</i> = 13.6 Hz, 1H), 7.54 (d, <i>J</i> = 7.2 Hz, 4H), 7.38 (t, <i>J</i> = 7.3 Hz, 2H), 7.31 (dd, <i>J</i> = 13.6, 6.6 Hz, 1H), 7.24 (s, 2H), 5.89 (s, 2H), 4.09 – 3.81 (m, 2H), 3.74 (s, 2H), 3.56 (d, <i>J</i> = 9.3 Hz, 3H), 3.51 (dd, <i>J</i> = 12.6, 6.0 Hz, 1H), 2.41 (s, 1H), 2.10 (s, 1H). ¹⁹ F NMR (300 MHz, DMSO) δ -120.22 (d, <i>J</i> = 12.7 Hz). Retention time (analytical HPLC): 19.82 min. ESI calculated (M+H) ⁺ 488.19, found M+H=488.2.
UIJD-II-228		¹ H NMR (400 MHz, MeOD) δ 8.93 (s, 1H), 7.69 (d, <i>J</i> = 13.5 Hz, 1H), 7.53 (d, <i>J</i> = 7.9 Hz, 4H), 7.38 (t, <i>J</i> = 7.3 Hz, 2H), 7.28 (dd, <i>J</i> = 19.6, 12.4 Hz, 3H), 5.88 (s, 2H), 3.86 (d, <i>J</i> = 26.0 Hz, 2H), 3.73 (s, 3H), 3.55 (s, 3H), 2.75 (s, 3H), 2.44 (s, 1H), 2.16 (s, 1H). ¹⁹ F NMR (300 MHz, DMSO) δ -121.37 (d, <i>J</i> = 13.4 Hz). Retention time (analytical HPLC): 20.668. ESI calculated (M+H) ⁺ 502.21, found 502.2.
UIJD-II-244		¹ H NMR (400 MHz, MeOD) δ 8.99 (s, 1H), 7.82 (d, <i>J</i> = 13.7 Hz, 1H), 7.56 (dd, <i>J</i> = 14.5, 8.8 Hz, 4H), 7.23 (d, <i>J</i> = 7.8 Hz, 2H), 7.13 (t, <i>J</i> = 8.7 Hz, 2H), 5.90 (s, 2H), 3.96 (d, <i>J</i> = 0.4 Hz, 1H), 3.86 (dd, <i>J</i> = 10.7, 5.6 Hz, 1H), 3.77 – 3.70 (m, 2H), 3.58 (s, 3H), 3.56 – 3.46 (m, 1H), 2.41 (dd, <i>J</i> = 13.1, 6.4 Hz, 1H), 2.07 (dd, <i>J</i> = 12.6, 5.9 Hz, 1H). ¹⁹ F NMR (300 MHz,

		MeOD) δ -117.37 -- 117.58 (m), -121.26 (d, J = 14.3 Hz). Retention time (analytical HPLC): 20.678. ESI calculated (M+H) ⁺ 506.18, found 506.2.
--	--	--

UIJD-II-264		¹ H NMR (400 MHz, DMSO) δ 15.23 (s, 1H), 9.06 (s, 1H), 8.24 (s, 3H), 7.77 (d, J = 12.9 Hz, 1H), 7.59 (d, J = 8.2 Hz, 4H), 7.37 (dt, J = 35.8, 7.3 Hz, 3H), 7.18 (d, J = 8.2 Hz, 2H), 6.41 (t, J = 5.3 Hz, 1H), 5.93 (s, 2H), 3.71 (s, 3H), 3.65 (d, J = 5.9 Hz, 2H), 2.95 (d, J = 5.8 Hz, 2H). ¹⁹ F NMR (300 MHz, DMSO) δ -126.65 (d, J = 12.9 Hz). Retention time (analytical HPLC) 18.77 min. ESI calculated (M+H) ⁺ : 462.18, found 462.18.
UIJD-II-276B		¹ H NMR (400 MHz, DMSO) δ 9.08 (s, 1H), 8.85 (s, 2H), 7.79 (d, J = 12.9 Hz, 1H), 7.59 (d, J = 8.1 Hz, 4H), 7.42 (t, J = 7.6 Hz, 2H), 7.34 (d, J = 7.4 Hz, 1H), 7.16 (d, J = 8.3 Hz, 2H), 6.40 (d, J = 5.4 Hz, 1H), 5.93 (s, 2H), 3.71 (s, 3H), 3.65 (d, J = 5.4 Hz, 2H), 3.05 – 2.97 (m, 2H), 2.47 (d, J = 5.4 Hz, 3H). ¹⁹ F NMR (300 MHz, DMSO) δ -126.55 (d, J = 19.6 Hz). Retention time (analytical HPLC) 19.739min. ESI calculated (M+H) ⁺ : 476.19, found 476.19.
UIJD-II-275B		¹ H NMR (400 MHz, DMSO) δ 9.04 (s, 1H), 8.72 (s, 2H), 7.77 (d, J = 13.1 Hz, 1H), 7.59 (d, J = 8.2 Hz, 4H), 7.42 (t, J = 7.6 Hz, 2H), 7.33 (t, J = 7.3 Hz, 1H), 7.16 (d, J = 8.2 Hz, 2H), 6.46 (s, 1H), 5.93 (s, 2H), 3.68 (s, 3H), 3.42 (d, J = 2.1 Hz, 2H), 2.86 – 2.76 (m, 2H), 2.45 (t, J = 5.4 Hz, 3H), 1.83 – 1.75 (m, 2H). ¹⁹ F NMR (282 MHz, CDCl ₃) δ -127.30 --

		127.74 (m). Retention time (analytical HPLC) 20.23min. ESI calculated (M+H) ⁺ : 490.21, found 490.21.
UIJD-II-285B		¹ H NMR (400 MHz, DMSO) δ 9.05 (s, 1H), 8.82 (s, 2H), 7.75 (d, <i>J</i> = 13.0 Hz, 1H), 7.63 – 7.55 (m, 4H), 7.42 (dd, <i>J</i> = 10.4, 4.8 Hz, 2H), 7.33 (ddd, <i>J</i> = 7.3, 6.0, 1.0 Hz, 1H), 7.14 (d, <i>J</i> = 8.3 Hz, 2H), 6.40 (s, 1H), 5.92 (s, 2H), 3.66 (s, 3H), 3.33 (t, <i>J</i> = 5.5 Hz, 2H), 2.76 – 2.64 (m, 2H), 2.36 (t, <i>J</i> = 5.4 Hz, 3H), 1.53 (dt, <i>J</i> = 15.2, 7.6 Hz, 2H), 1.45 – 1.33 (m, 2H). ¹⁹ F NMR (282 MHz, CDCl ₃) δ -127.58 – -127.83 (m). Retention time (analytical HPLC) 20.819. ESI calculated (M+H) ⁺ : 504.22, found 504.22.

Example 3

[0082] Fluoroquinolones are selective inhibitors of bacterial type II topoisomerases (DNA gyrase and topoisomerase IV) although a few of them have shown to inhibit human and other eukaryotic type II topoisomerases (topoisomerase II). Fluoroquinolones poisons type II topoisomerases and generate double strand breaks. No activity of fluoroquinolones against either type IA (topoisomerase III and bacterial topoisomerase I) or type IB (eukaryotic topoisomerase I) has been reported. As shown in Table 1, UITT-III-217 (217) and UITT-III-227 (227), exhibit higher activities against human topoisomerase II than bacterial type II topoisomerases.

Table 1. 217 and 227 are effective against human topoisomerases

Compound	DNA gyrase	Topo I (h/c)	Topo II
217	137.0 ± 10.1	26.0 ± 0.5/32.2 ± 0.01	127.6 ± 4.7
227	>200	43.7 ± 0.6/66.6 ± 0.4	164.6 ± 20.2

The IC₅₀ values (the 50% inhibitory concentration, μM) of 217 and 227 against *E. coli* DNA gyrase, human/calf topoisomerase I, and human topoisomerase II were determined in the supercoiling, relaxation, and decatenation assays, respectively.

[0083] Further studies revealed that these fluoroquinolones are more active against human topoisomerase I, a type IB topoisomerase (IC₅₀ values of 217 and 227 in the relaxation assay are 26.5 μM and 43.1 μM, respectively), than human topoisomerase II (IC₅₀ values for 217 and 227 in the decatenation assay are 127.6 μM and 164.6 μM, respectively).

Note that topoisomerase-targeting anticancer drugs achieve potent cell-based killing with modest (low to mid micromolar) inhibitory effects on the catalytic activity of topoisomerases in biochemical assays. For instance, the IC₅₀ value for the clinically-used etoposide is approximately 160 μM in the decatenation assay. These fluoroquinolones also inhibited bacterial topoisomerase I, a type IA topoisomerase, better than type II topoisomerases.

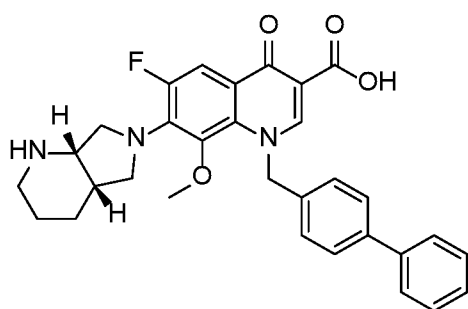
[0084] Several fluoroquinolone analogs of 217 and 227 described herein were synthesized by introducing a series of changes at the C-7 and C-8 positions, and determined that among these initial analogs, 217 and 227 exhibit the strongest inhibitory effects on both topoisomerases—even though the other compounds described herein show inhibitory effects on both topoisomerases. See Table 2.

Table 2. Activities of initial analogs of 217 and 227

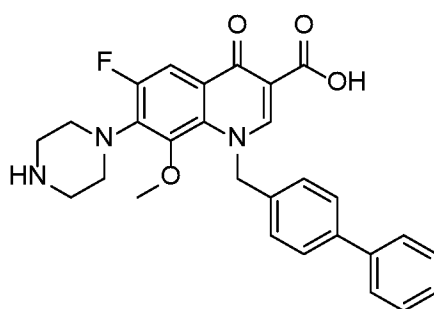
Compound	Topo I	Topo II
217	26.0 ± 0.5	127.6 ± 4.7
205	44.4 ± 0.8	196.1 ± 22.4
207	54.2 ± 3.2	237.6 ± 15.2
215a	25.9 ± 5.4	87.7 ± 7.0
227	43.7 ± 0.6	164.6 ± 20.2
213	127.9 ± 0.8	345.8 ± 34.9
215	132.2 ± 3.5	318.4 ± 21.1
213a	59.0 ± 2.9	67.9 ± 3.3

*The IC₅₀ values (μM) against human topoisomerase I and human topoisomerase II were determined in the relaxation and decatenation assays, respectively.

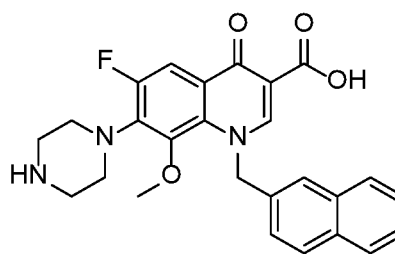
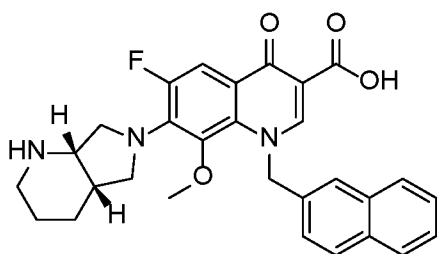
wherein compounds 205, 207, 213, 213a, 215, and 215a have the following structures:



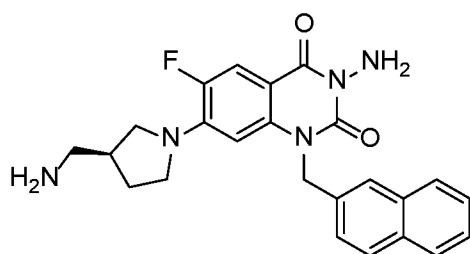
UITT-III-205 (205)



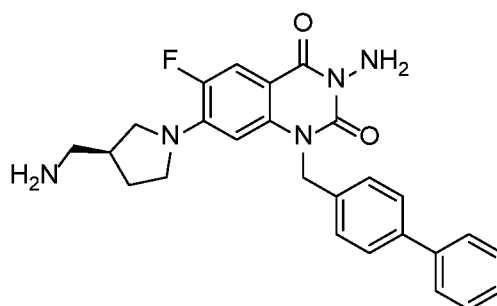
UITT-III-207 (207)



UITT-III-213 (213)



UITT-III-215 (215)

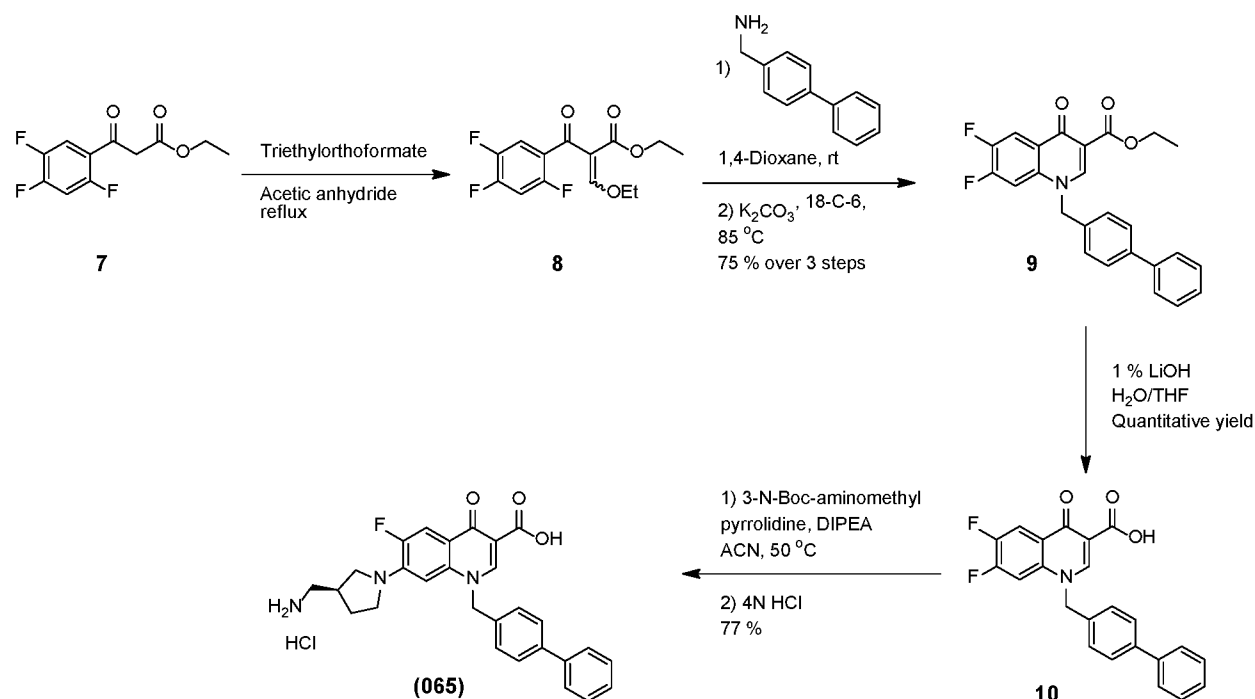


UITT-III-213a (213a)

UITT-III-215a (215a)

[0085] Topoisomerase poisoning results in the accumulation of covalent topoisomerase-DNA complexes, which can be detected as the generation of nicked and/or linear DNA in DNA cleavage assays. Poisoning of human topoisomerase II generate double-strand breaks that lead to the development of therapy-related acute myeloid leukemia. DNA cleavage assays for human topoisomerase II with 217 and 227 did not detect any significant increase (two-fold or less) in the amounts of linear DNA (FIG. 1). Similarly, 217 and 227 did not poison mammalian topoisomerase I. Thus, 217 and 227 inhibit activity of, but do not poison either topoisomerase I or topoisomerase II.

[0086] In FIG. 1, the amounts of the full-length linear DNA were determined in the absence (100% cleavage) and the presence of various concentrations of either 217 (○) or 227 (●) in the DNA cleavage assay using two preparations of human topoisomerase II. A control topoisomerase II poison (5 or 10 μ M etoposide) produced 400%-800% of linear DNA under the same condition.

Example 4: alternative synthetic route to 217 and analogs.

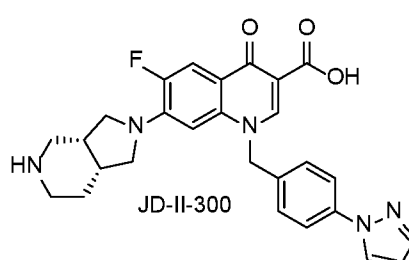
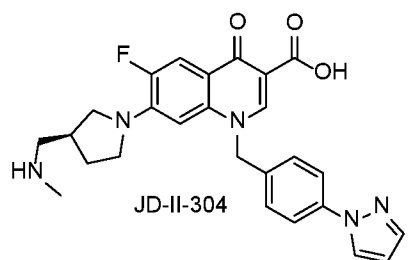
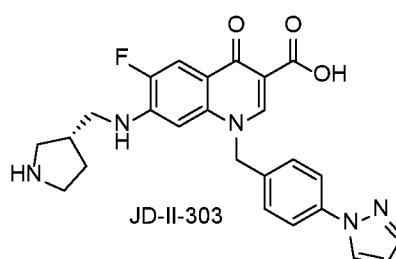
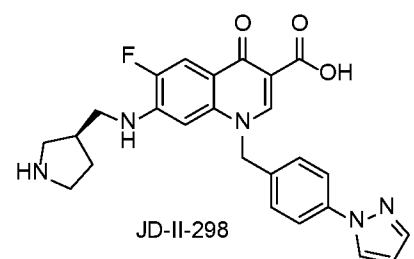
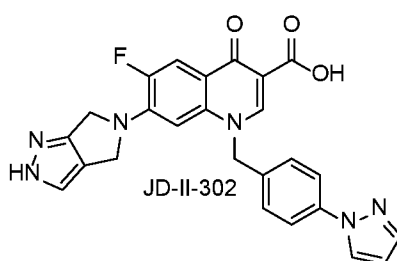
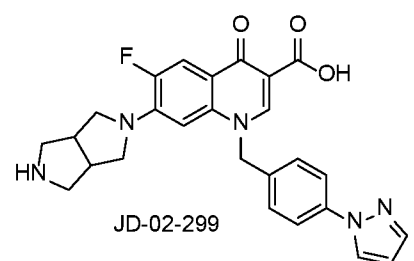
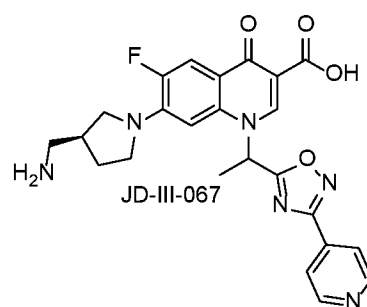
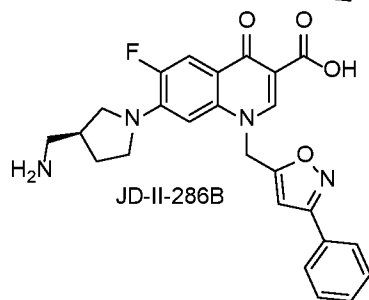
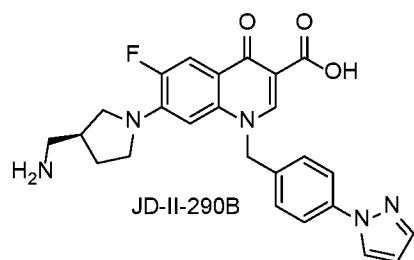
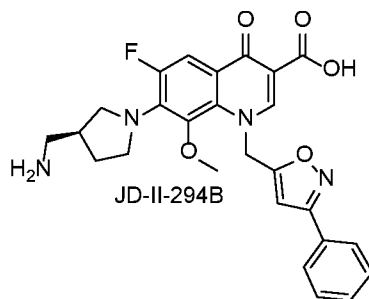
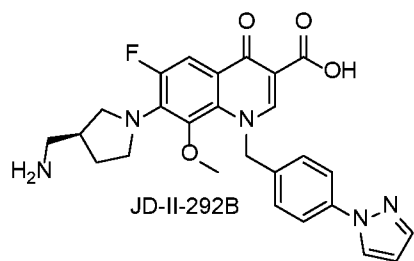
[0087] Commercially available ethyl 3-oxo-3-(2,4,5-trifluorophenyl)propanoate (**7**) (5.0 g, 20.31 mmol) was refluxed in triethylorthoformate (5.0 mL, 30.465 mmol) and acetic anhydride (5.8 mL, 60.93 mmol) for 4 h to yield enol ether **8**. After the reaction was complete, the mixture was concentrated *in vacuo* and then dissolved in 1,4-dioxane (170 mL). 4-Phenylbenzylamine (3.5 g, 19.285 mmol) was added and the reaction stirred at room temperature for 6 h. K_2CO_3 (4.2 g, 30.465 mmol) and 18-crown-6 (1.0 g, 4.062 mmol) was added and the reaction was heated to 85 °C and stirred for an additional 2 h. The reaction mixture was then concentrated *in vacuo* and the resultant precipitate was washed with water and then purified by flash chromatography using a gradient starting with 1 % MeOH in DCM and ending with 7 % MeOH in DCM to give pure compound CK-III-195 (**9**). Yield = 6.4 g, 75 % over 3 steps.

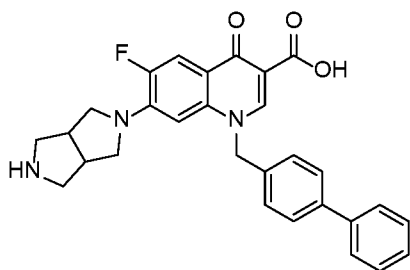
[0088] CK-III-195 (**9**) (6.4 g, 15.259 mmol) was dissolved in 250 mL of 1:1 THF: 1 % aqueous LiOH and stirred at room temperature for 24 h. The reaction was diluted with water and acidified to pH 1 with HCl. The aqueous layer was extracted three times with 300 mL DCM. The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered and concentrated *in vacuo* to give pure CK-III-197 (**10**) in quantitative yield.

[0089] CK-III-197 (**10**) (1.5 g, 3.833 mmol) was dissolved in 40 mL ACN to which was added Boc-(*R*)-aminomethylpyrrolidine (921.1 mg, 4.600 mmol) and DIPEA (1 mL, 5.750 mmol). The reaction was set to stir at 70 °C for 4 h. 25 mL 4N HCl was then added and the reaction was stirred for additional 12 h. The resultant precipitate was filtered and washed with ACN to give pure CK-II-065 (**065**). Yield 1.5 g, 77 %. 1H NMR (300 MHz,

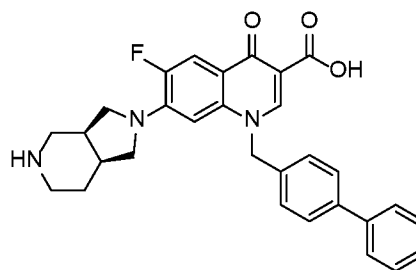
DMSO) δ 15.61 (s, 1H, exchangeable), 9.19 (s, 1H), 8.16 (bs, 2H), 7.80 (d, J = 14.3 Hz, 1H), 7.66 (dd, J = 12.5, 7.9 Hz, 4H), 7.42 (m, 5H), 6.67 (d, J = 7.5 Hz, 1H), 5.83 (s, 2H), 3.68 (m, 1H), 3.48 (m, 3H), 2.90 (m, 2H), 2.55 (m, 1H), 2.11 (m, 1H), 1.79 (m, 1H). ^{19}F NMR (282 MHz, DMSO) δ -126.75 (s, 1F). HRMS (ESI) calculated for (M+H⁺) 472.2031, found 472.2026. Retention time (analytical HPLC) = 19.01 min.

[0090] Many other compounds can be accessed with this method, including the following compounds:

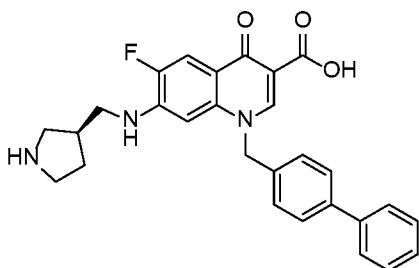




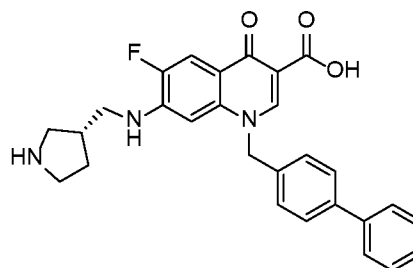
UICK-IV-089



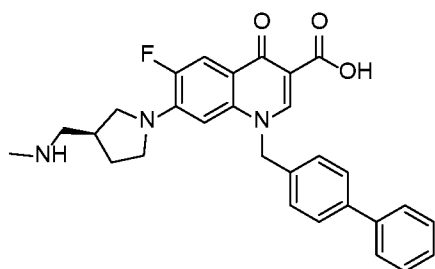
UICK-IV-091



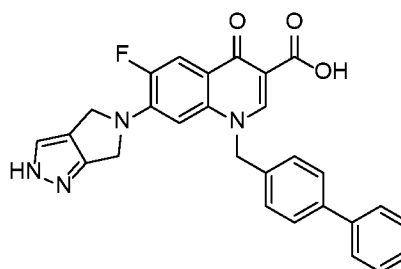
UICK-IV-093



UICK-IV-095

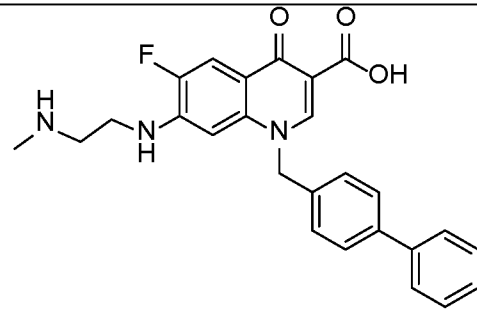
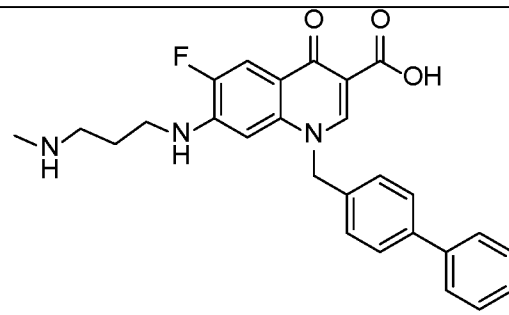
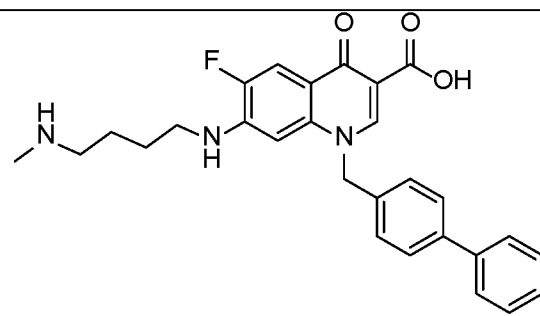


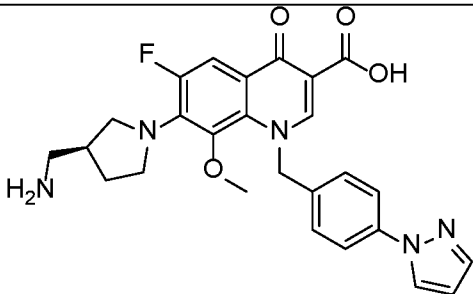
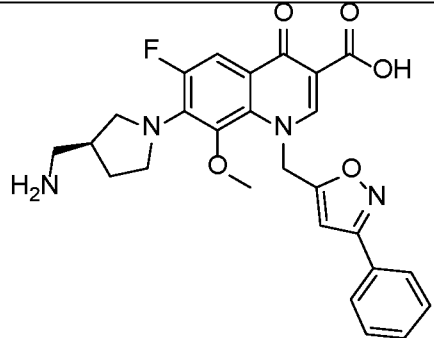
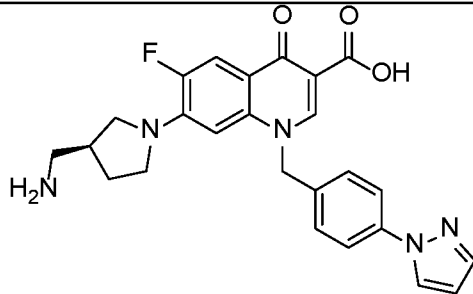
UICK-IV-097

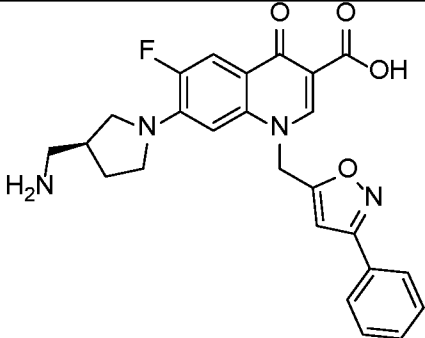


UICK-IV-103

Compound ID	Structure	Characterization
UIJD-II-281B		¹ H NMR (400 MHz, DMSO) δ 9.17 (s, 1H), 7.83 (d, <i>J</i> = 11.7 Hz, 1H), 7.68 – 7.60 (m, 4H), 7.44 (t, <i>J</i> = 8.4 Hz, 4H), 7.35 (dd, <i>J</i> = 8.3, 6.4 Hz, 1H), 6.89 (d, <i>J</i> = 7.2 Hz, 1H), 5.89 (s, 2H), 3.50 (q, <i>J</i> = 5.9 Hz, 2H), 3.05 (s, 2H). ¹⁹ F NMR (282 MHz, CDCl ₃) δ -131.78 – -132.05 (m). Retention time (analytical HPLC) 18.007. ESI calculated (M+H) ⁺ : 432.16, found 432.17.

Compound ID	Structure	Characterization
UIJD-II-282B		^1H NMR (400 MHz, DMSO) δ 15.61 (s, 1H), 9.16 (s, 1H), 8.87 (s, 2H), 7.83 (d, J = 11.7 Hz, 1H), 7.69 – 7.60 (m, 4H), 7.43 (dd, J = 8.0, 6.9 Hz, 4H), 7.34 (t, J = 7.3 Hz, 1H), 7.09 (d, J = 2.1 Hz, 1H), 6.91 (d, J = 7.2 Hz, 1H), 5.93 (s, 2H), 3.56 (dd, J = 11.6, 5.8 Hz, 2H), 2.96 (s, 2H), 2.47 (s, 3H). ^{19}F NMR (282 MHz, CDCl_3) δ -131.68 – -131.96 (m). Retention time (analytical HPLC) 18.748min. ESI calculated $(\text{M}+\text{H})^+$ 446.18, found 446.19.
UIJD-II-269B		^1H NMR (400 MHz, DMSO) δ 9.13 (s, 1H), 7.80 (d, J = 11.8 Hz, 1H), 7.69 – 7.61 (m, 4H), 7.47 – 7.40 (m, 4H), 7.34 (t, J = 7.3 Hz, 1H), 6.80 (d, J = 7.2 Hz, 1H), 5.87 (s, 2H), 3.30 (dd, J = 12.3, 6.2 Hz, 2H), 2.90 – 2.81 (m, 2H), 2.43 (t, J = 5.2 Hz, 3H), 1.80 (dd, J = 13.6, 7.0 Hz, 2H). ^{19}F NMR (282 MHz, CDCl_3) δ -132.24 – -132.45 (m). Retention time (analytical HPLC) 19.16 min. ESI calculated $(\text{M}+\text{H})^+$ 460.20, found 460.20.
UIJD-II-271B		^1H NMR (400 MHz, DMSO) δ 9.15 (s, 1H), 7.79 (d, J = 11.9 Hz, 1H), 7.70 (d, J = 8.3 Hz, 2H), 7.67 – 7.62 (m, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.36 (dd, J = 9.6, 5.1 Hz, 3H), 6.65 (d, J = 7.2 Hz, 1H), 5.85 (s, 2H), 3.16 (dd, J = 12.6, 6.5 Hz, 2H), 2.61 (q, J = 12.7 Hz, 2H), 2.32 (t, J = 5.3 Hz, 3H), 1.55 – 1.46 (m, 2H), 1.34 – 1.25 (m, 2H). ^{19}F NMR (282 MHz, CDCl_3) δ -132.46 – -

Compound ID	Structure	Characterization
		132.79 (m). Retention time (analytical HPLC) 19.5 min. ESI calculated (M+H) ⁺ 474.21, found 474.21.
UIJD-II-292B		¹ H NMR (400 MHz, DMSO) δ 9.10 (s, 1H), 8.42 (d, <i>J</i> = 2.5 Hz, 1H), 7.75 (d, <i>J</i> = 8.6 Hz, 2H), 7.28 (d, <i>J</i> = 8.4 Hz, 3H), 6.50 (s, 2H), 5.93 – 5.84 (m, 2H), 3.62 – 3.54 (m, 3H), 3.46 (s, 3H), 3.36 (m, 2H), 2.94 – 2.86 (m, 1H), 2.07 (m, 1H), 1.74 – 1.63 (m, 1H). ¹⁹ F NMR (282 MHz, CDCl ₃) δ -120.41 – -120.57 (m). ESI calculated (M+H) ⁺ 492.2, found 492.2. Retention time (analytical HPLC) 16.9 min.
UIJD-II-294B		¹ H NMR (400 MHz, DMSO) δ 9.07 (s, 1H), 7.81 (dd, <i>J</i> = 6.6, 2.9 Hz, 2H), 7.74 (d, <i>J</i> = 13.8 Hz, 1H), 7.49 – 7.42 (m, 3H), 7.01 (s, 1H), 6.13 – 6.00 (m, 2H), 3.63 – 3.44 (m, 5H), 3.41 (s, 3H), 2.96 – 2.83 (m, 2H), 2.07 (dd, <i>J</i> = 11.6, 5.3 Hz, 1H), 1.75 – 1.62 (m, 1H). ¹⁹ F NMR (282 MHz, DMSO) δ -120.43 – -120.63 (m). ESI calculated (M+H) ⁺ 493.18, found 493.19. Retention time (analytical HPLC) 18.2 min.
UIJD-II-290B		¹ H NMR (400 MHz, DMSO) δ 9.16 (s, 1H), 8.47 (d, <i>J</i> = 2.5 Hz, 1H), 7.81 (m, 3H), 7.72 (d, <i>J</i> = 1.6 Hz, 1H), 7.48 (d, <i>J</i> = 8.6 Hz, 2H), 6.63 (d, <i>J</i> = 7.5 Hz, 1H), 6.54 – 6.49 (m, 1H), 5.80 (s, 2H), 3.70 – 3.63 (m, 2H), 3.46 – 3.36 (m, 3H), 2.92 – 2.85 (m, 2H), 2.11 (dd, <i>J</i> = 11.6, 5.3 Hz, 1H), 1.80 – 1.72 (m, 1H). ¹⁹ F NMR

Compound ID	Structure	Characterization
		(282 MHz, DMSO) δ -126.68 – -127.19 (m). ESI calculated (M+H) ⁺ 462.19, found 462.19. Retention time (analytical HPLC) 15.7 min.
UIJD-II-286B		¹ H NMR (400 MHz, DMSO) δ 9.12 (s, 1H), 7.88 – 7.79 (m, 3H), 7.52 – 7.43 (m, 3H), 7.21 (s, 1H), 6.71 (d, <i>J</i> = 7.3 Hz, 1H), 6.07 (s, 2H), 3.75 (t, <i>J</i> = 7.2 Hz, 1H), 3.60 (s, 1H), 3.52 (dd, <i>J</i> = 16.8, 8.1 Hz, 1H), 2.95 – 2.85 (m, 2H), 2.61 – 2.52 (m, 1H), 2.14 (dd, <i>J</i> = 11.5, 5.1 Hz, 1H), 1.78 (dd, <i>J</i> = 12.4, 8.1 Hz, 1H). ¹⁹ F NMR (282 MHz, CDCl ₃) δ -126.57 – -126.85 (m). ESI calculated (M+H) ⁺ 463.17, found 463.17. Retention time (analytical HPLC) 17.36.

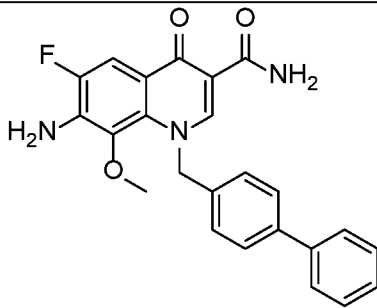
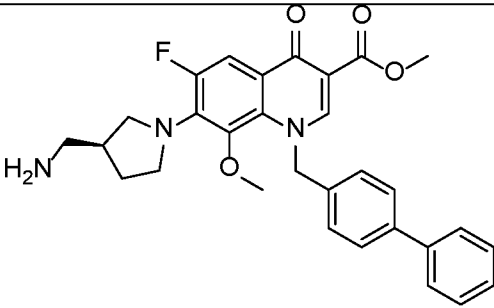
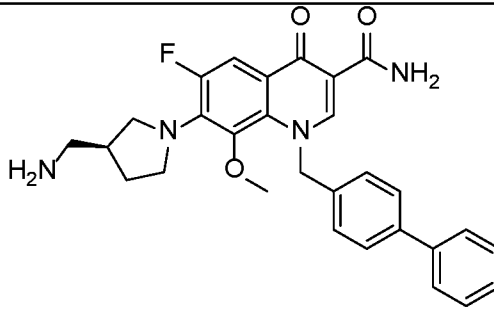
[0091] UICK-IV-093. ¹H NMR (300 MHz, DMSO) δ 9.15 (s, 1H), 9.03 (bs, 1H, exchangeable), 7.82 (d, *J* = 11.9 Hz, 1H), 7.67 (m, 4H), 7.42 (m, 5H), 7.22 (bs, 1H, exchangeable), 6.81 (d, *J* = 7.1 Hz, 1H), 5.88 (s, 2H), 3.29 (m, 2H), 3.16 (m, 2H), 2.92 (m, 2H), 2.36 (m, 1H), 1.87 (m, 1H), 1.57 (m, 1H). ¹⁹F NMR (282 MHz, DMSO) δ -132.24 (s, 1F). HRMS (ESI) calculated for (M+H)⁺ 472.2031, found 472.1980. Retention time (analytical HPLC) = 19.08 min.

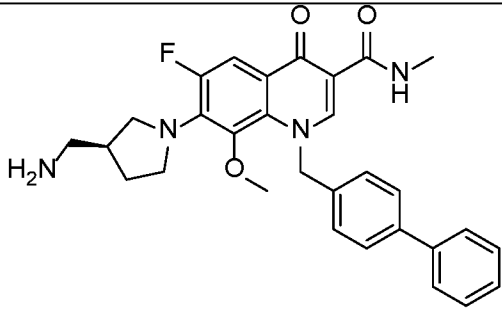
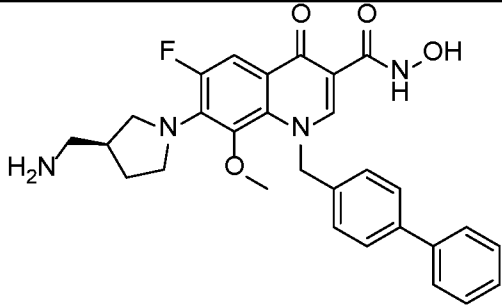
[0092] UICK-IV-095. ¹H NMR (300 MHz, DMSO) δ 9.15 (s, 1H), 8.97 (bs, 1H, exchangeable), 7.82 (d, *J* = 11.9 Hz, 1H), 7.67 (m, 4H), 7.39 (m, 5H), 7.21 (bs, 1H, exchangeable), 6.81 (d, *J* = 7.2 Hz, 1H), 5.88 (s, 2H), 3.28 (m, 2H), 3.17 (m, 2H), 2.92 (m, 2H), 2.34 (m, 1H), 1.85 (m, 1H), 1.57 (m, 1H). ¹⁹F NMR (282 MHz, DMSO) -132.26 (s, 1F). HRMS (ESI) calculated for (M+H)⁺ 472.2031, found 472.2005. Retention time (analytical HPLC) = 19.10 min

Example 5

[0093] The compounds listed in the table below were synthesized using methods that are effectively modified versions of the methods described in Examples 1, 2, and 4.

Compound	Structure	Characterization
----------	-----------	------------------

ID		
UIJD-II-215B		¹ H NMR (300 MHz, Acetone) δ 9.78 (d, <i>J</i> = 4.9 Hz, 1H), 8.82 (s, 1H), 7.70 (d, <i>J</i> = 13.4 Hz, 1H), 7.62 – 7.57 (m, 4H), 7.43 (t, <i>J</i> = 7.4 Hz, 2H), 7.33 (t, <i>J</i> = 7.3 Hz, 1H), 7.14 (d, <i>J</i> = 8.2 Hz, 2H), 5.85 (s, 2H), 3.64 (s, 3H), 3.44 (s, 1H), 2.97 (t, <i>J</i> = 4.4 Hz, 3H), 2.85 (d, <i>J</i> = 4.8 Hz, 3H). ¹⁹ F NMR (300 MHz, DMSO) δ -129.73 – -130.14 (m). Retention time (analytic HPLC): 21.8 min. ESI calculated (M+Na) ⁺ 468.18, found (M+Na) ⁺ 468.16
UIJD-II-237 UIJD-II-224		¹ H NMR (400 MHz, MeOD) δ 8.96 (s, 1H), 7.77 (d, <i>J</i> = 14.1 Hz, 1H), 7.60 – 7.52 (m, 4H), 7.44 – 7.36 (m, 2H), 7.34 – 7.27 (m, 1H), 7.23 (d, <i>J</i> = 8.3 Hz, 2H), 5.87 (dd, <i>J</i> = 63.8, 15.4 Hz, 2H), 3.92 (s, 3H), 3.71 – 3.63 (m, 2H), 3.53 (ddd, <i>J</i> = 7.3, 6.6, 3.6 Hz, 1H), 3.50 (s, 3H), 3.46 (ddd, <i>J</i> = 10.5, 5.9, 1.8 Hz, 1H), 3.07 (d, <i>J</i> = 7.2 Hz, 2H), 2.55 (dt, <i>J</i> = 11.0, 5.5 Hz, 1H), 2.25 – 2.16 (m, 1H), 1.74 (dq, <i>J</i> = 16.6, 8.2 Hz, 1H). ¹⁹ F NMR (300 MHz, CDCl ₃) δ -121.79 – -122.05 (m). Retention time (analytical HPLC) 19.7. ESI calculated (M+H) ⁺ : 516.22, found 516.2.
UIJD-II-251		¹ H NMR (300 MHz, CDCl ₃) δ 8.90 (s, 1H), 7.68 (d, <i>J</i> = 14.0 Hz, 1H), 7.59 (t, <i>J</i> = 10.0 Hz, 4H), 7.47 – 7.29 (m, 3H), 7.23 (d, <i>J</i> = 8.1 Hz, 2H), 5.86 (q, <i>J</i> = 15.3 Hz, 2H), 4.51 (s, 1H), 3.57 (dd, <i>J</i> = 13.4, 5.7 Hz, 2H), 3.47 (s, 3H), 3.37 (dd, <i>J</i> = 15.2, 9.0 Hz, 2H), 2.90 (s, 2H), 2.09 (dd, <i>J</i> = 10.6, 4.3 Hz, 1H), 1.75 – 1.66 (m,

		^1H). ^{19}F NMR (300 MHz, DMSO) δ -122.44 (d, J = 13.6 Hz). Retention time (analytical HPLC) 17.438min. ESI calculated (M+H)⁺: 501.22, found 501.23.
UIJD-II-242		^1H NMR (400 MHz, MeOD) δ 8.94 (s, 1H), 7.76 (d, J = 14.1 Hz, 1H), 7.57 – 7.49 (m, 4H), 7.41 – 7.35 (m, 2H), 7.32 – 7.27 (m, 1H), 7.22 (d, J = 8.3 Hz, 2H), 5.87 (dd, J = 67.3, 15.5 Hz, 2H), 3.69 (ddd, J = 9.4, 8.0, 4.0 Hz, 2H), 3.55 – 3.50 (m, 1H), 3.48 (d, J = 8.0 Hz, 3H), 3.46 – 3.40 (m, 1H), 3.10 – 3.04 (m, 2H), 2.98 (s, 3H), 2.57 (dt, J = 14.5, 7.3 Hz, 1H), 2.21 (dt, J = 10.7, 6.7 Hz, 1H), 1.75 (dq, J = 12.2, 8.3 Hz, 1H). ^{19}F NMR (282 MHz, MeOD) δ -122.16 (d, J = 14.7 Hz). Retention time (analytical HPLC): 18.45. ESI calculate (M+H)⁺ 515.24, found 515.2.
UIJD-II-246		^1H NMR (300 MHz, DMSO) δ 11.66 (s, 1H), 8.90 (s, 1H), 7.68 (d, J = 14.1 Hz, 1H), 7.61 (d, J = 8.3 Hz, 4H), 7.43 (t, J = 7.5 Hz, 2H), 7.35 (d, J = 7.3 Hz, 1H), 7.22 (d, J = 8.2 Hz, 2H), 5.89 (q, J = 15.6 Hz, 2H), 3.62 – 3.53 (m, 3H), 3.48 (s, 3H), 3.43 – 3.31 (m, 2H), 2.98 – 2.84 (m, 2H), 2.08 (dd, J = 7.8, 4.7 Hz, 1H), 1.76 – 1.67 (m, 1H). ^{19}F NMR (300 MHz, DMSO) δ -121.96 – -122.25 (m). Retention time (analytical HPLC): 21.8 min. ESI calculated (M+H)⁺ 517.22, found 517.22.

Example 6

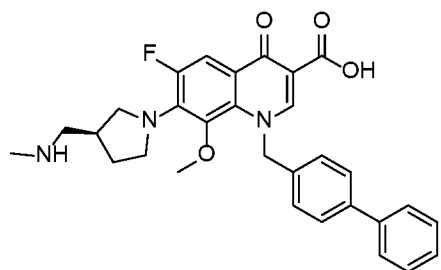
[0094] Both 217 and 227 were submitted to the NCI for the 60 DTP Human Tumor Cell Line Screen. The single dose (10 μ M) screening showed significant growth inhibition for 217 and 227 (mean growth of 40.3% and 44.1%, respectively), and the further evaluation of their activities has determined the mean GI₅₀ value of 217 and 227 to be 1.9 μ M and 3.1 μ M, respectively, against the 60 cancer cell lines used in the screen. Comparison (NCI's COMPARE program) of GI₅₀ and LD₅₀ values has demonstrated that both 217 and 227 are significantly more effective than etoposide against the majority of the 60 cancer cell lines tested. Although these compounds were active against all 60 cancer cell lines, the strongest growth inhibition was seen in leukemia and colon cancer panels.

Example 7

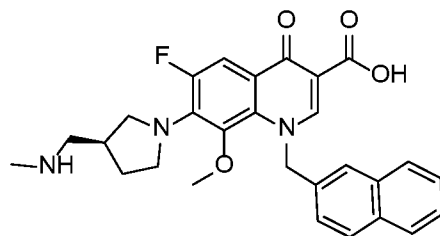
[0095] *In vivo* toxicity studies were performed to establish the maximum tolerated dose of 217 and 227 in mice. The daily intraperitoneal administration of 217 and 227 at up to 30 mg/kg for 3 weeks was well-tolerated and did not have any significant effect on animal weight gain. Higher doses could not be used due to the limited aqueous solubility of 217 and 227. A proof of concept efficacy study was also conducted in mice with 217 and 227. Based on the *in vitro* susceptibility to 217 and 227, and the availability of the established xenograft models, a colon cancer (HT-29) xenograft model was used. 217 inhibited the proliferation of colon cancer *in vivo* as well as 5-FU (FIG. 2). 227 exhibited activity but was not as effective as 217 in this xenograft model. These results suggested that at least 217 might serve as a lead compound for the successful development of novel anticancer agents against colon cancer. The maximum doses used in the efficacy studies were limited by the compounds' solubility, not their toxicity, suggesting that modifying the 217 or 227 formulations and/or developing analogs with improved aqueous solubility could lead to fluoroquinolones with even better anticancer activity while retaining an improved safety profile.

Example 8

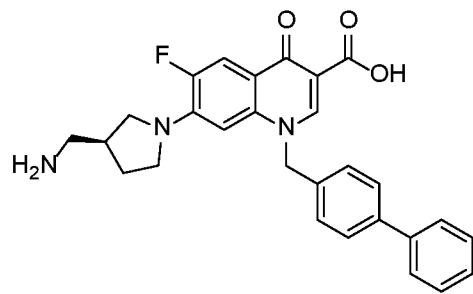
[0096] An MTT assay was performed with 277 and with the following compounds:



(086),



(126), and

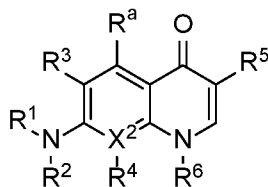


(065)

- 5 against colon (HT-29) and leukemia (K-562) cell lines to determine their *in vitro* anti-proliferative activities. The anti-proliferative activity of 086, 126, and 227 was similar to that of 217, whereas the anti-proliferative activity of 065 was higher, roughly 2-5 fold higher than that of 217.

[0097] The following Embodiments are encompassed by the instant disclosure:

- 10 **[0098]** Embodiment 1 relates to a compound of the formula (I):



(I)

15 or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

R^a is halo, nitro, cyano, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heteroaryl, or $NR^{a'}R^{a''}$, wherein $R^{a'}$ and $R^{a''}$ are each, independently, H or optionally substituted alkyl;

20 R^1 and R^2 are each independently H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or R^1 and R^2 , together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl group;

R^3 is H or halo;

R^4 is H, halo, optionally substituted alkyl or optionally substituted alkoxy, but R^4 is absent if X^2 is N;

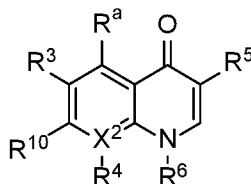
X^2 is N or C;

R^5 is H, OH, optionally substituted alkoxy, $-C(O)R^{5'}$ (wherein $R^{5'}$ is H, OH, optionally substituted alkyl, optionally substituted aryl, optionally substituted alkoxy or

$-N(R^{5''})_2$, wherein each $R^{5''}$ is, independently, H, OH, optionally substituted alkoxy, optionally substituted alkyl or optionally substituted arylalkyl) or $-N(R^{5''})_2$; and

R^6 is the group $-L-R^{6'}$, wherein L is a linker group and $R^{6'}$ is a group having sufficient "steric bulk" such that the compound of the formula (I) is (a) not a topoisomerase II poison, (b) inhibits topoisomerase I and topoisomerase II and/or (c) inhibits topoisomerase I to a greater extent than topoisomerase II.

[0099] Embodiment 2 relates to the compound of Embodiment 1, wherein the compound of the formula (I) is a compound of the formula (Ia):

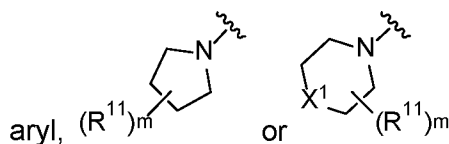


(Ia)

or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

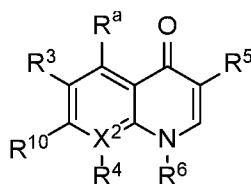
X^2 , R^a , R^3 , R^4 , R^5 , and R^6 are as defined for compounds of the formula (I); and

R^{10} is



wherein each R^{11} is H, $-N(R^{5''})_2$, $C(O)N(R)_2$ (wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl), optionally substituted alkyl or two adjacent R^{11} groups, together with the atoms to which they are attached form an optionally substituted cycloalkyl group or an optionally substituted heterocyclyl group; m is an integer from 1 to 3; and X^1 is O or NR^{12} , wherein R^{12} is H or optionally substituted alkyl or R^{12} and an adjacent R^{11} group, together with the atoms to which they are attached, form an optionally substituted heterocyclyl group.

[00100] Embodiment 3 relates to the compound of Embodiment 1, wherein the compound of the formula (I) is a compound of the formula (Ib):



(Ib)

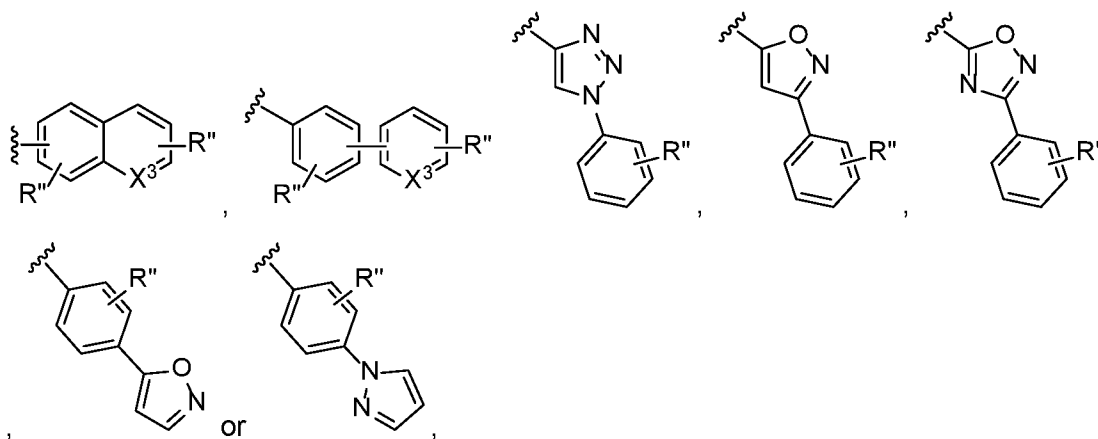
or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

R^a is optionally substituted alkyl or NH_2 ;

X^2 , R^3 , R^4 , and R^5 are as defined for compounds of the formula (I);

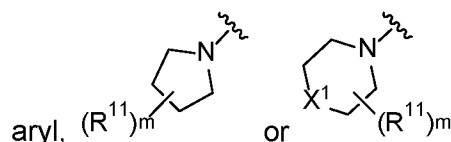
R^6 is $-(CH_2)_n-R^{6''}$ or $-C(O)R^{6''}$ wherein n is an integer from 1 to 3 (e.g., 1) and $R^{6''}$ is an aryl or heteroaryl group.

[00101] Embodiment 4 relates to the compound of Embodiment 3, wherein $R^{6''}$ is:



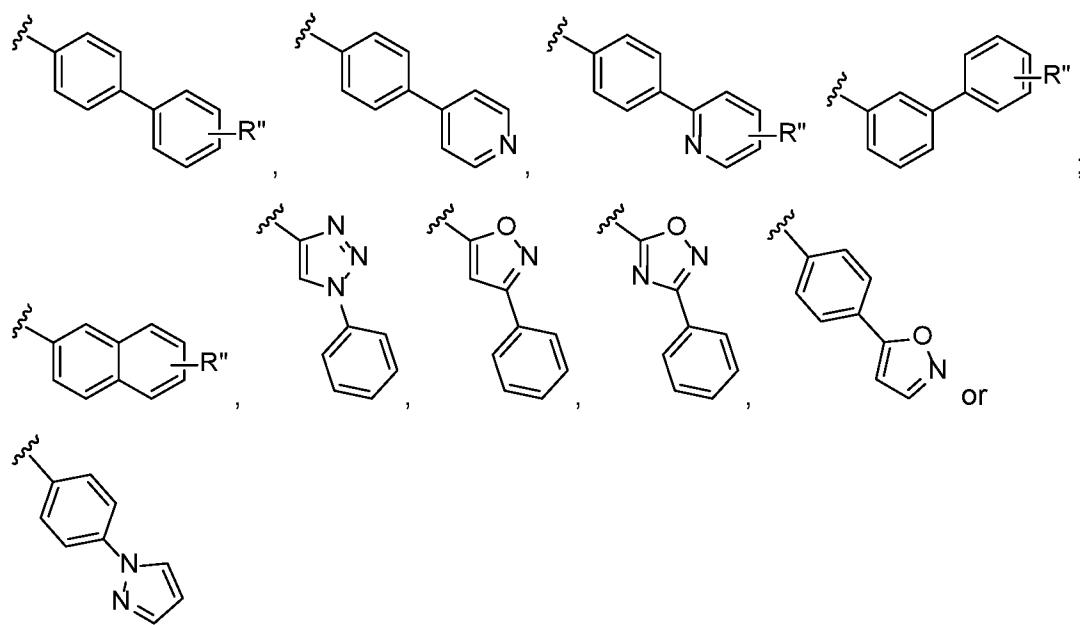
wherein each R'' is, independently H or halo and X^3 is N or CH; and

R^{10} is

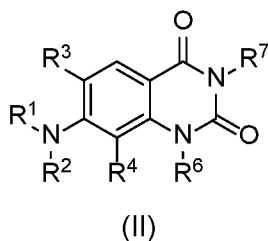


wherein each R^{11} is H, $C(O)N(R)_2$ (wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl), optionally substituted alkyl or two adjacent R^{11} groups, together with the atoms to which they are attached form an optionally substituted cycloalkyl group or an optionally substituted heterocyclyl group; m is an integer from 1 to 3; and X^1 is O or NR^{12} , wherein R^{12} is H or optionally substituted alkyl or R^{12} and an adjacent R^{11} group, together with the atoms to which they are attached, form an optionally substituted heterocyclyl group.

[00102] Embodiment 5 relates to the compound of Embodiment 3, wherein R^{6''} is:



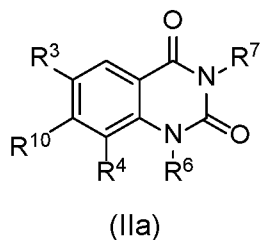
5 [00103] Embodiment 6 relates to a compound of the formula (II):



or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

10 R¹-R⁴ and R⁶ are as defined for compounds of the formula (I); and
 R⁷ is H, OH, optionally substituted alkoxy, optionally substituted alkyl or NR⁸R⁹,
 wherein R⁸ and R⁹ are each independently H, optionally substituted alkyl, optionally substituted aryl or optionally substituted arylalkyl.

15 [00104] Embodiment 7 relates to the compound of Embodiment 6, wherein the compound of the formula (II) is a compound of the formula (IIa):

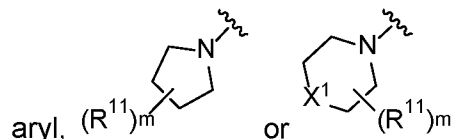


or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

20 R³, R⁴, and R⁶ are as defined for compounds of the formula (I);

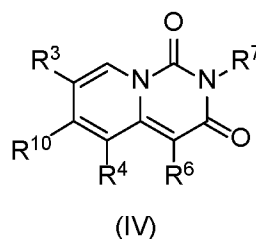
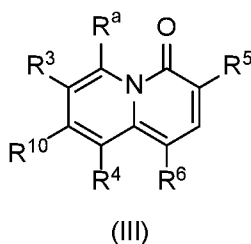
R⁷ is H, optionally substituted alkyl or NR⁸R⁹, wherein R⁸ and R⁹ are each independently H, optionally substituted alkyl, optionally substituted aryl or optionally substituted arylalkyl; and

R^{10} is



wherein each R¹¹ is H, C(O)N(R)₂ (wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl), optionally substituted alkyl or two adjacent R¹¹ groups, together with the atoms to which they are attached form an optionally substituted cycloalkyl group or an optionally substituted heterocyclyl group; m is an integer from 1 to 3; and X¹ is O or NR¹², wherein R¹² is H or optionally substituted alkyl or R¹² and an adjacent R¹¹ group, together with the atoms to which they are attached, form an optionally substituted heterocyclyl group.

[00105] Embodiment 8 relates to a compound of the formula (III) and (IV):



wherein the groups R^a, R³-R⁷, and R¹⁰ are as defined in Embodiments 1-7.

[00106] Embodiment 9 relates to a compound of any one of Embodiments 1-8, wherein R³ is halo.

[00107] Embodiment 10 relates to a compound of any one of Embodiments 1-8, wherein R³ is H.

[00108] Embodiment 11 relates to a compound of any one of Embodiments 1-9, wherein R⁴ is alkoxy.

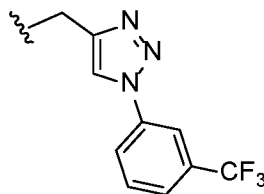
[00109] Embodiment 12 relates to a compound of any one of Embodiments 1-9, wherein R⁴ is H.

[00110] Embodiment 13 relates to a compound of any one of Embodiments 1-12, wherein R^5 is $-C(O)R^5$.

[00111] Embodiment 14 relates to a compound of any one of Embodiments 1-12, wherein R^6 is optionally substituted arylalkyl.

5 [00112] Embodiment 15 relates to a compound of Embodiment 6 or 7, wherein R^7 is NR^8R^9 .

[00113] Embodiment 16 relates to a compound as in any one of Embodiments 1-15, wherein when R^6 is:



10

R^1 and R^2 , together with the nitrogen atom to which they are attached, form an optionally substituted pyrrolidinyl group.

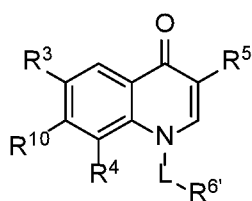
[00114] Embodiment 17 relates to a compound of any one of Embodiments 1-16, wherein R^{11} is optionally substituted alkyl.

[00115] Embodiment 18 relates to a compound of any one of Embodiments 1-16, wherein R^{11} is alkyl substituted with $NR^{13}R^{14}$, wherein R^{13} and R^{14} are each independently H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or R^{13} and R^{14} , together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl group.

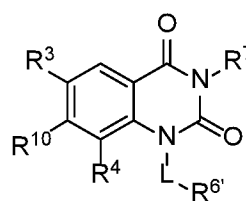
[00116] Embodiment 19 relates to a compound of any one of Embodiments 1-16, wherein R^{11} is alkyl substituted with OR^{13} , wherein R^{13} is H, optionally substituted alkyl, optionally substituted aryl or optionally substituted arylalkyl.

[00117] Embodiment 20 relates to a compound of any one of Embodiments 1-16, wherein R^{11} is $C(O)N(R)_2$, wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl.

[00118] Embodiment 21 relates to a compound of any one of Embodiments 1-20, wherein the compound is a compound of the formula (V) or (VI):

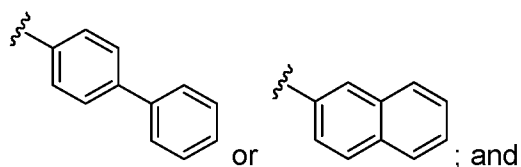


(V)

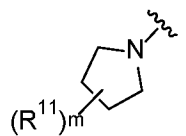


(VI)

wherein R^3 , R^4 , and R^7 are as defined for compounds of the formula (I); L is $-(CH_2)_n-$, wherein n is an integer from 1 to 3 (e.g., 1); $R^{6'}$ is:



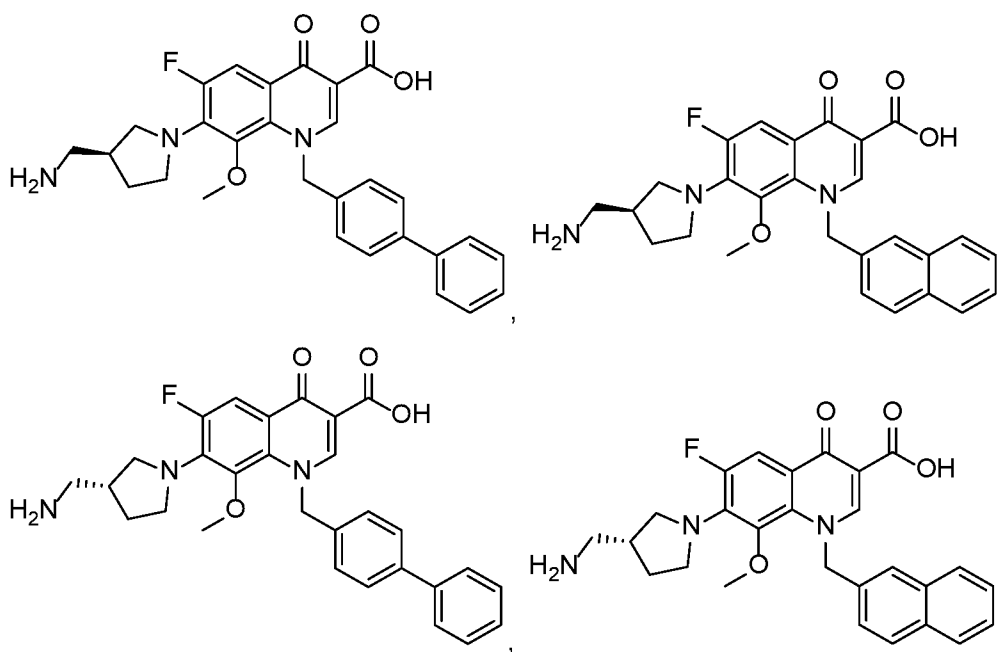
R^{10} is:

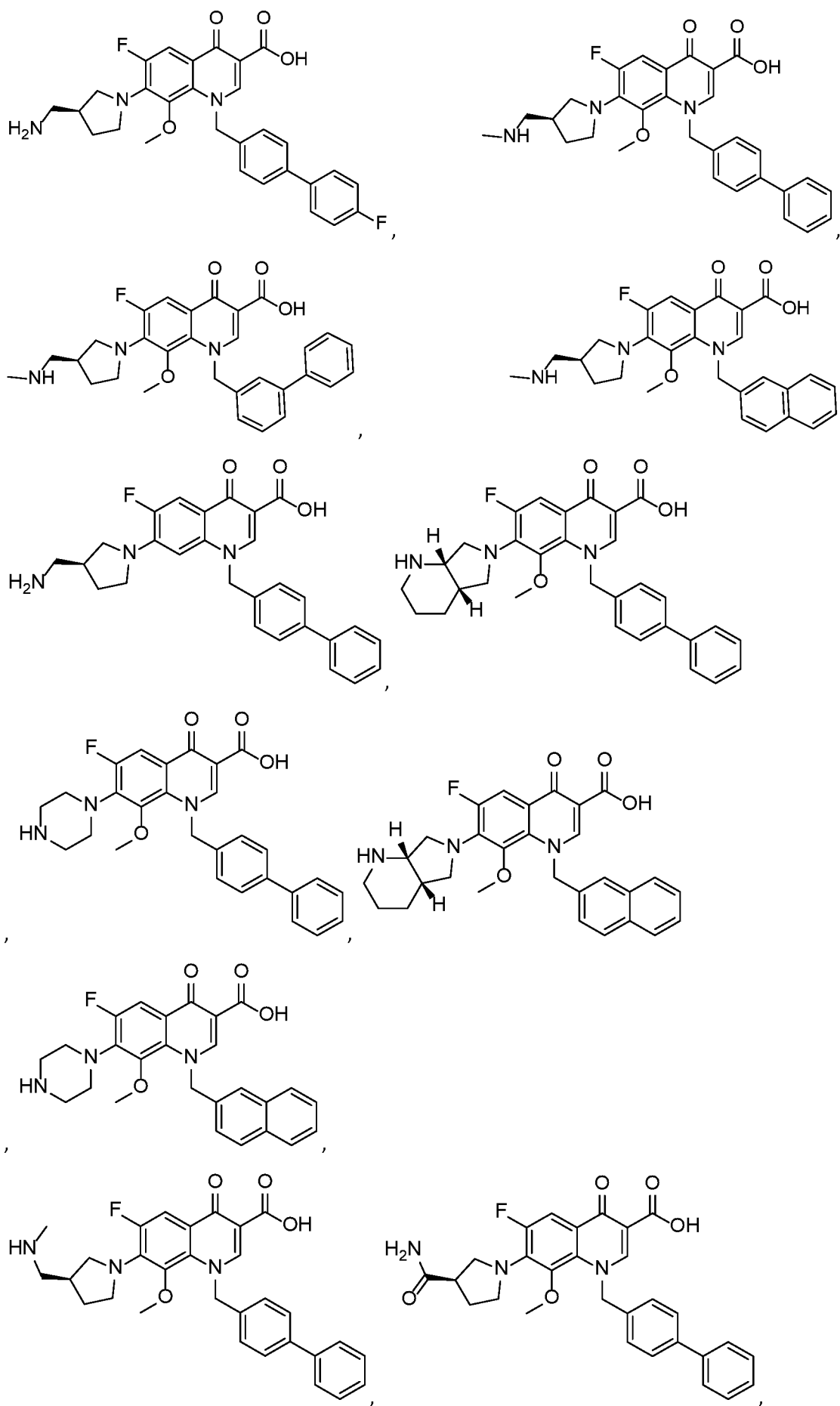


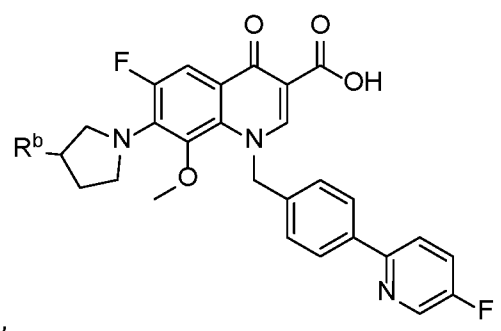
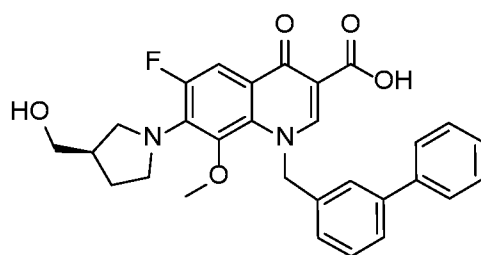
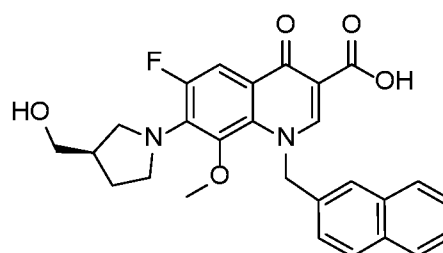
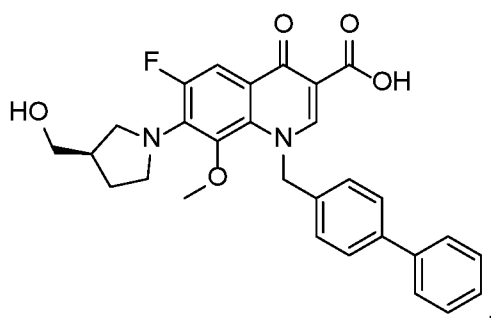
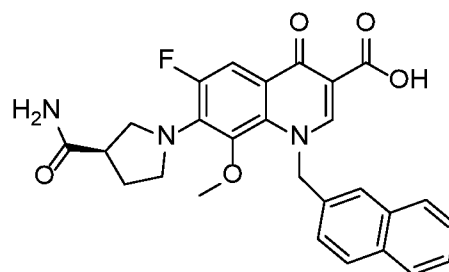
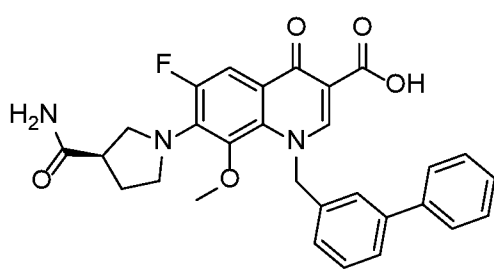
wherein R^{11} is $C(O)N(R)_2$ (wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl), alkyl substituted with -OR or alkyl substituted with $-N(R)_2$.

[00119] Embodiment 22 relates to a compound of any one of Embodiments 1-7,

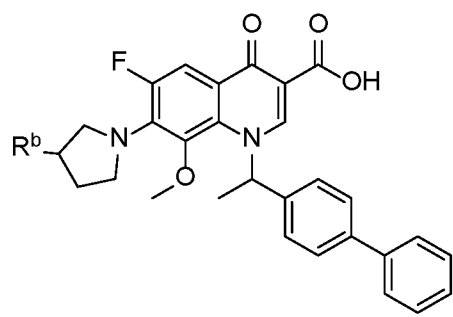
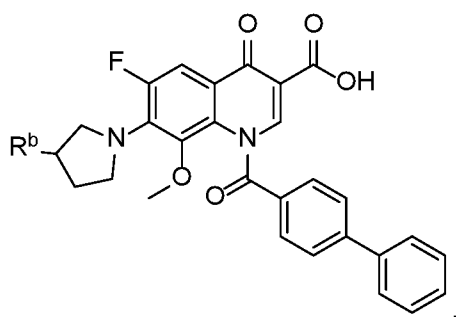
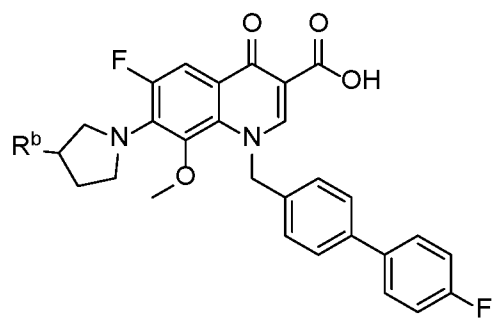
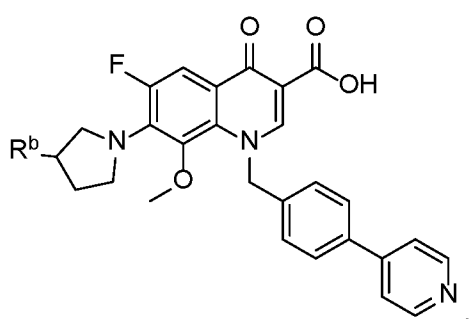
wherein the compound has the formula:

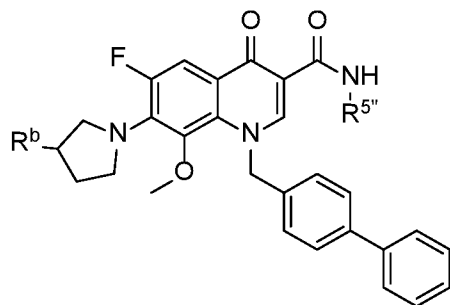
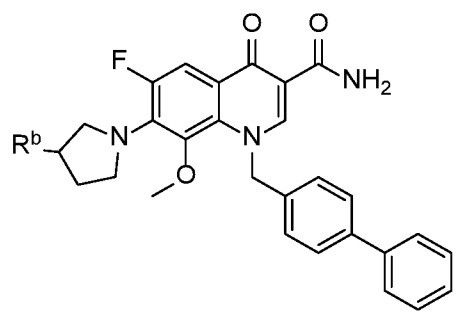
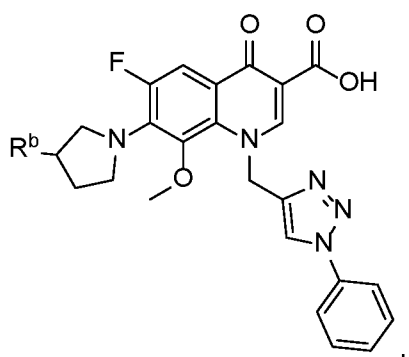




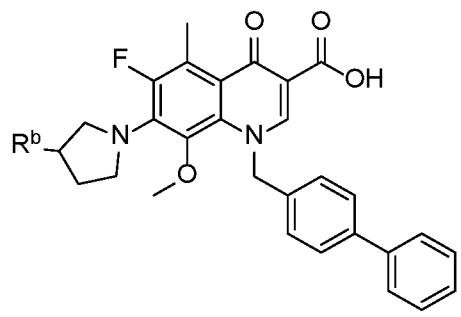
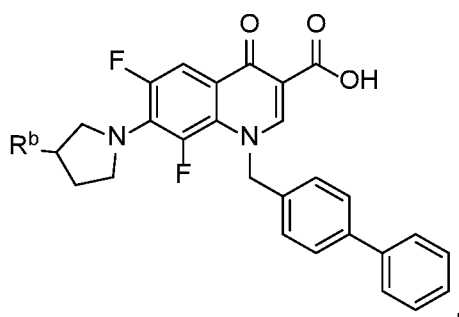
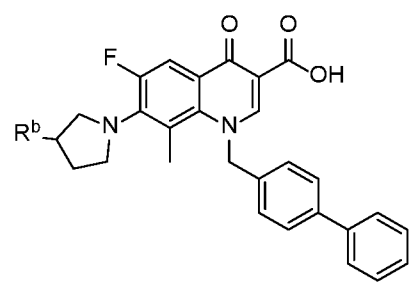
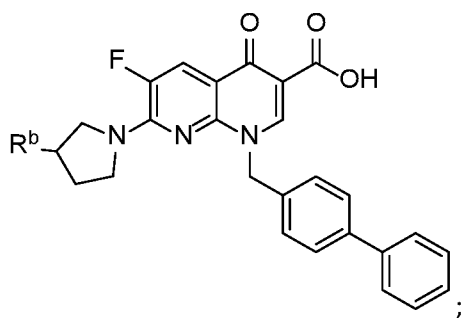


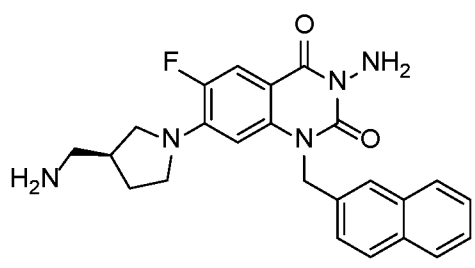
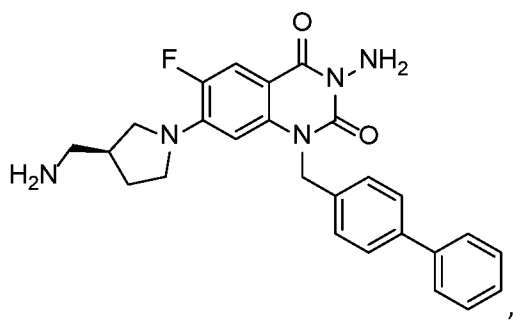
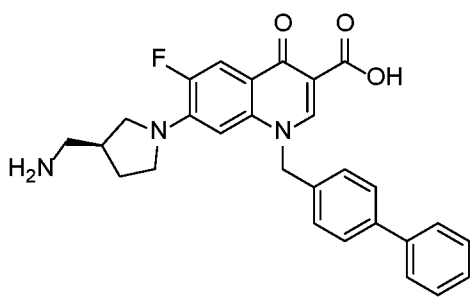
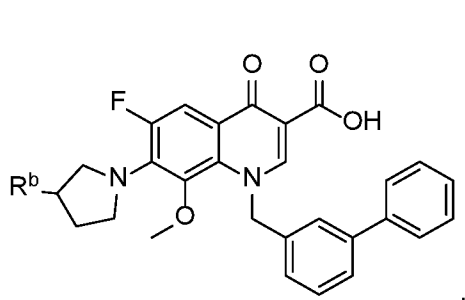
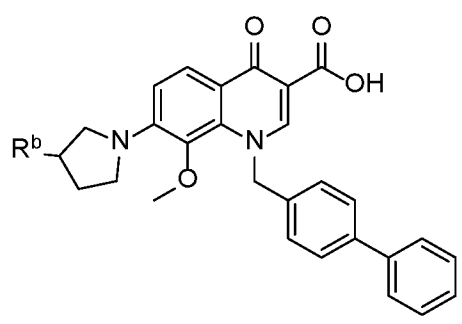
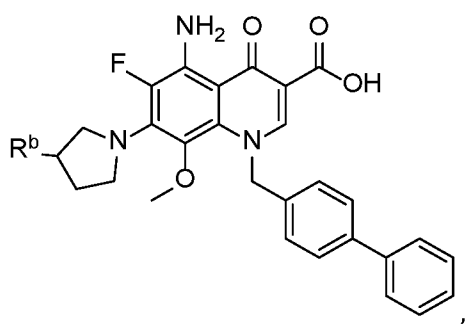
(wherein R^b is -CH₂NHCH₃, -CH₂OH or C(O)NH₂),

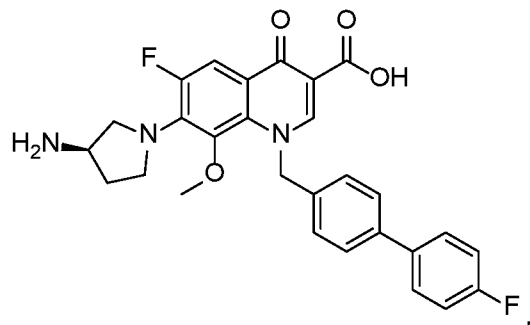
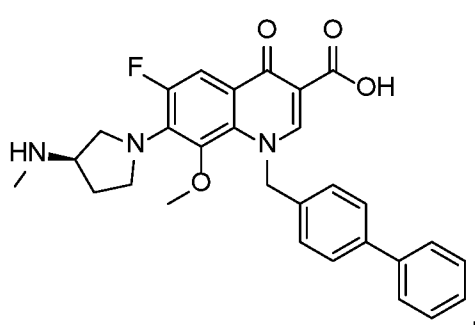
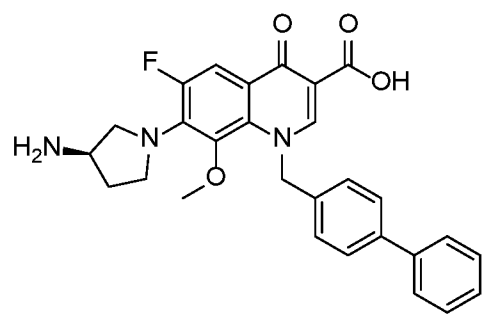
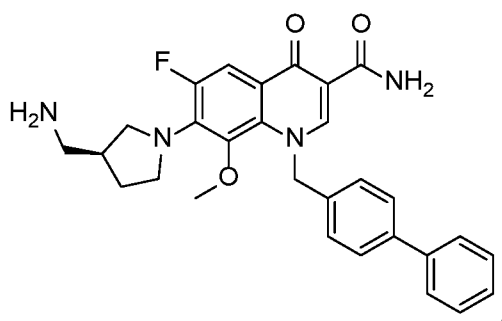
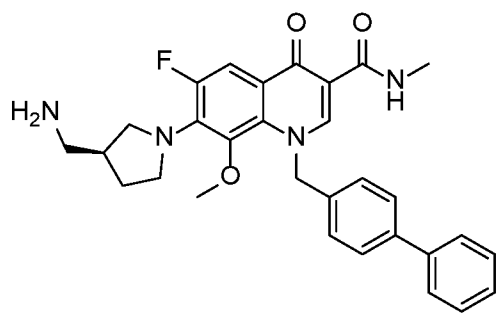
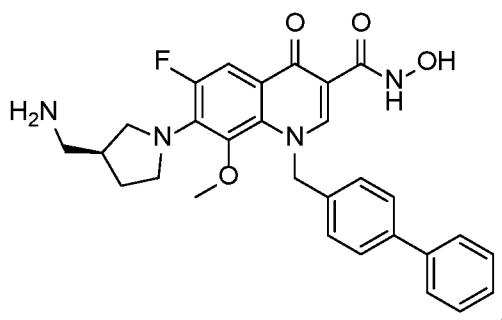
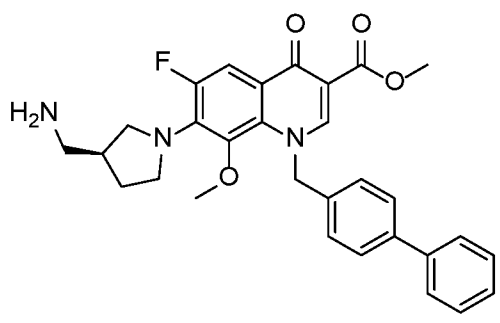
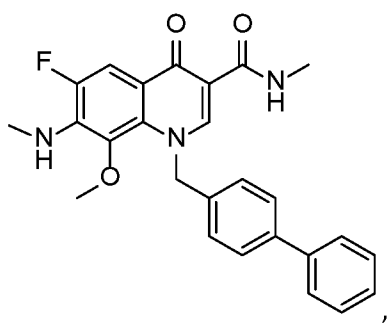
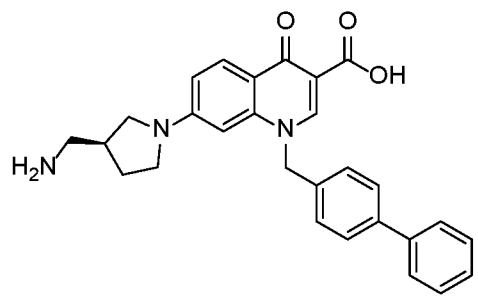
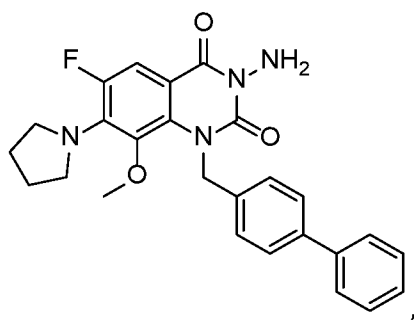


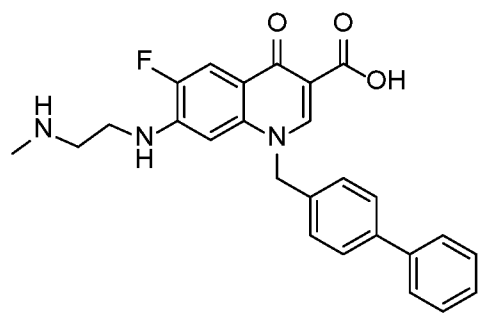
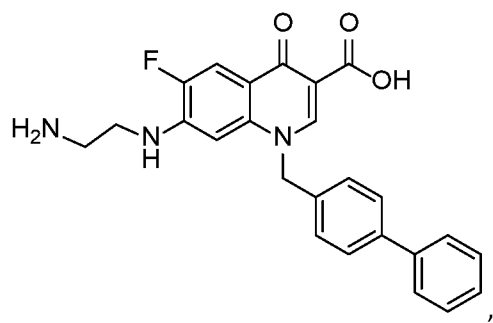
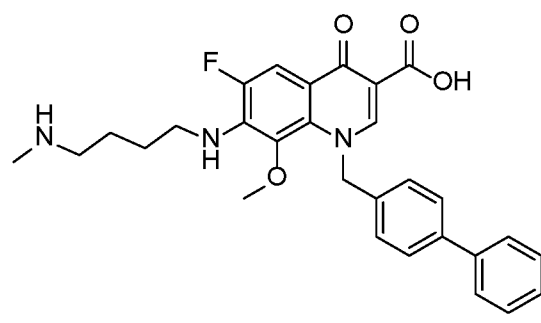
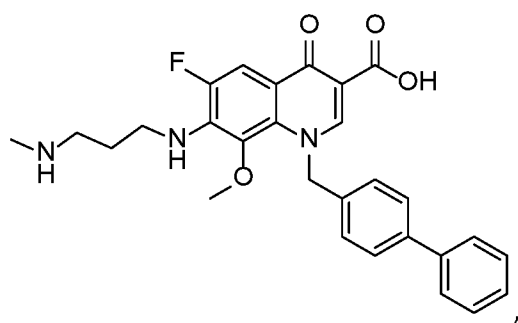
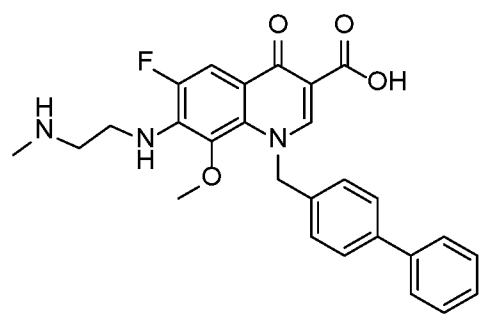
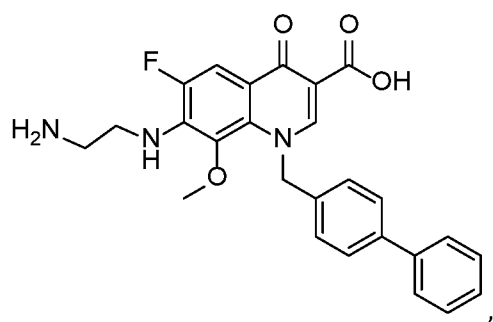


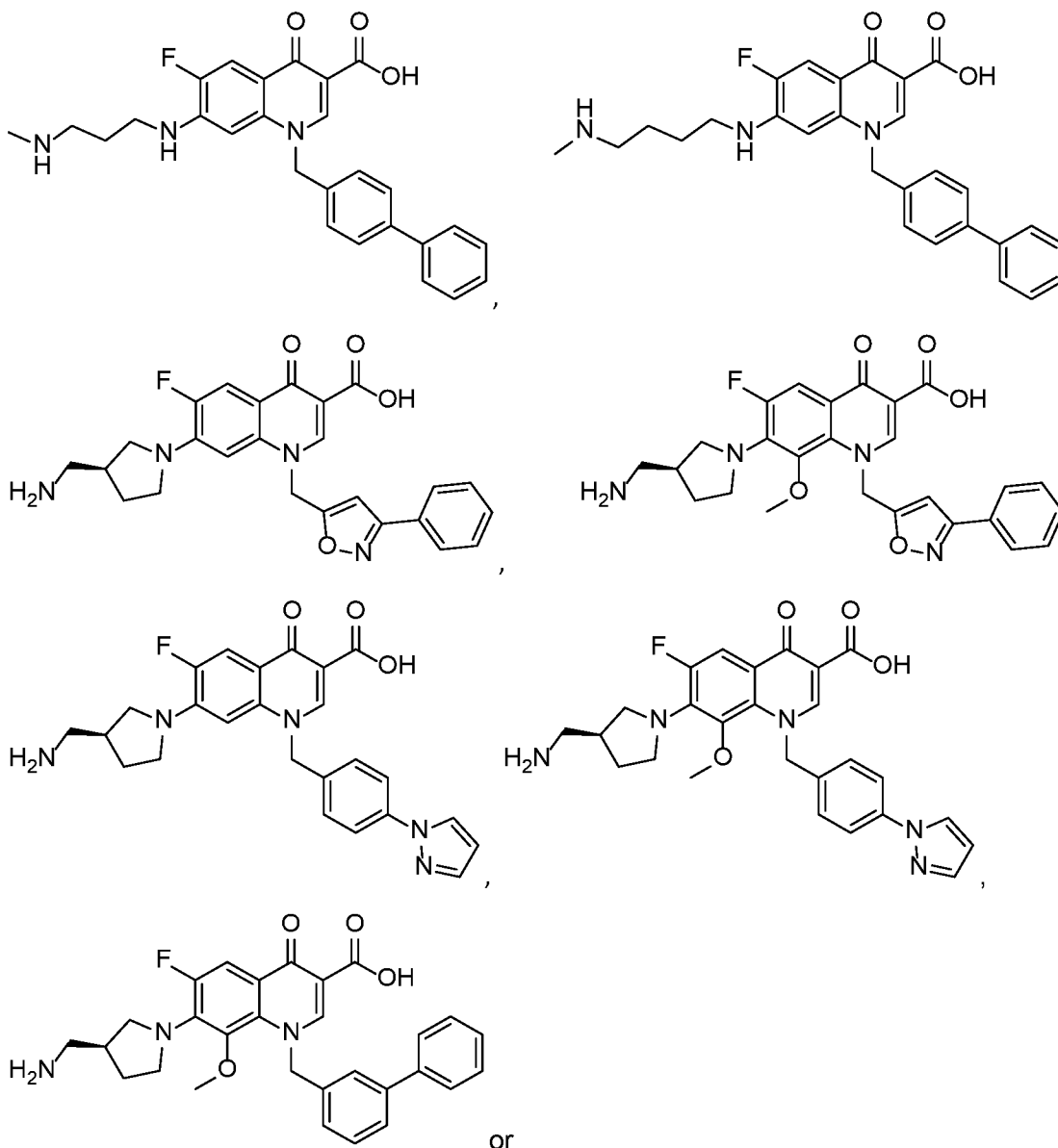
(wherein R^{5''} is defined herein);











5 pharmaceutically acceptable salts, polymorphs, prodrugs, solvates or clathrates thereof.

[00120] Embodiment 23 relates to the compound as in any preceding Embodiment, wherein the IC₅₀ for human topoisomerase II is about four to about 1000 times greater than the IC₅₀ for human topoisomerase I.

10 **[00121]** Embodiment 24 relates to the compound as in any preceding Embodiment, wherein the compound does not substantially increase an amount of nicked and linear DNAs in DNA cleavage assays.

[00122] Embodiment 25 relates to a pharmaceutical composition comprising one or more compounds as in any preceding Embodiment and one or more pharmaceutically acceptable carriers, diluents, excipients or combinations thereof.

15 **[00123]** Embodiment 26 relates to a method for treating cancer comprising administering a therapeutically effective amount of one, or more compounds as in any one of

Embodiments 1-24 or a pharmaceutical composition of Embodiment 25, to a patient in need thereof.

[00124] Embodiment 27 relates to a method of modulating a human topoisomerase, comprising contacting the topoisomerase with an effective amount or concentration of a compound as in any one of Embodiments 1-24.

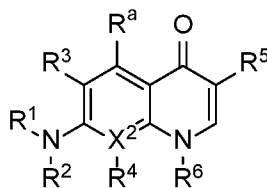
[00125] Embodiment 28 relates to the method of Embodiment 27, wherein the human topoisomerase is human topoisomerase I.

[00126] Embodiment 9 relates to the method of Embodiment 28, wherein the compound has an IC_{50} for human topoisomerase II that is about four to about 1000 times greater than an IC_{50} of the same compound for human topoisomerase I.

CLAIMS

What is claimed is:

1. A compound of the formula (I):



(I)

or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

R^a is halo, nitro, cyano, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted aryl, optionally substituted aryloxy, optionally substituted heteroaryl, or $NR^{a'}R^{a''}$, wherein $R^{a'}$ and $R^{a''}$ are each, independently, H or optionally substituted alkyl;

R^1 and R^2 are each independently H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or R^1 and R^2 , together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl group;

R^3 is H or halo;

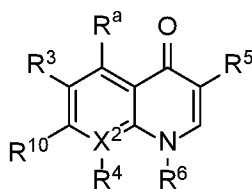
R^4 is H, halo, optionally substituted alkyl or optionally substituted alkoxy, but R^4 is absent if X^2 is N;

X^2 is N or C;

R^5 is H, OH, optionally substituted alkoxy, $-C(O)R^{5'}$ (wherein $R^{5'}$ is H, OH, optionally substituted alkyl, optionally substituted aryl, optionally substituted alkoxy or $-N(R^{5''})_2$, wherein each $R^{5''}$ is, independently, H, OH, optionally substituted alkoxy, optionally substituted alkyl or optionally substituted arylalkyl) or $-N(R^{5''})_2$; and

R^6 is the group $-L-R^{6'}$, wherein L is a linker group and $R^{6'}$ is a group having sufficient "steric bulk" such that the compound of the formula (I) is (a) not a topoisomerase II poison, (b) inhibits topoisomerase I and topoisomerase II and/or (c) inhibits topoisomerase I to a greater extent than topoisomerase II.

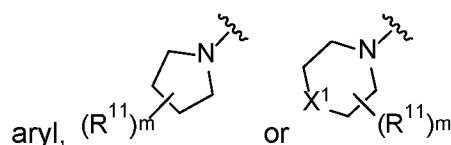
2. The compound of claim 1, wherein the compound of the formula (I) is a compound of the formula (Ia):



(Ia)

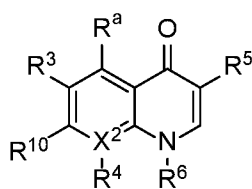
or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

X^2 , R^a , R^3 , R^4 , R^5 , and R^6 are as defined for compounds of the formula (I); and R^{10} is



wherein each R^{11} is H, $-N(R^{5'})_2$, $C(O)N(R)_2$ (wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl), optionally substituted alkyl or two adjacent R^{11} groups, together with the atoms to which they are attached form an optionally substituted cycloalkyl group or an optionally substituted heterocyclyl group; m is an integer from 1 to 3; and X^1 is O or NR^{12} , wherein R^{12} is H or optionally substituted alkyl or R^{12} and an adjacent R^{11} group, together with the atoms to which they are attached, form an optionally substituted heterocyclyl group.

3. The compound of claim 1, wherein the compound of the formula (I) is a compound of the formula (Ib):



(Ib)

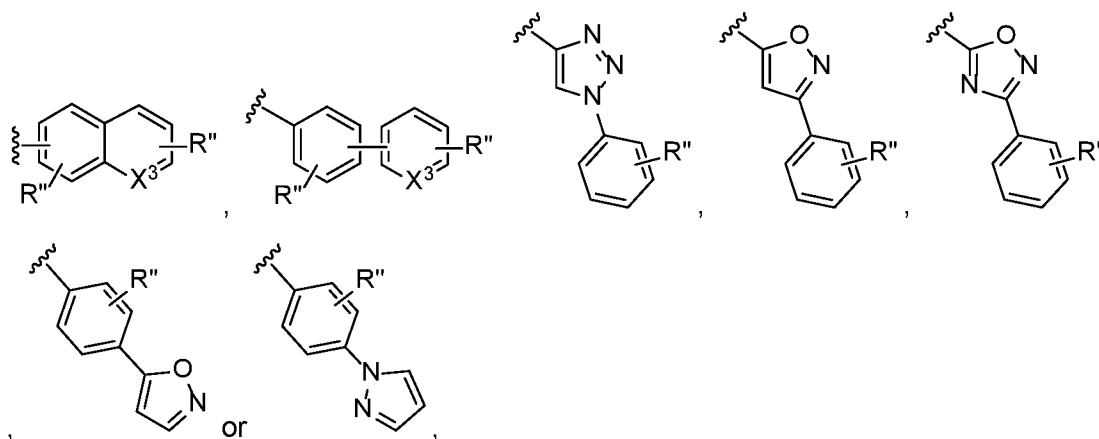
or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

R^a is optionally substituted alkyl or NH_2 ;

X^2 , R^3 , R^4 , and R^5 are as defined for compounds of the formula (I);

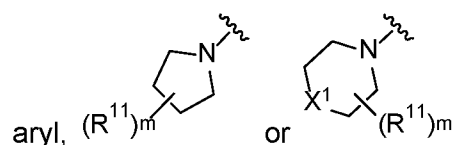
R^6 is $-(CH_2)_n-R^{6''}$ or $-C(O)R^{6''}$ wherein n is an integer from 1 to 3 (e.g., 1) and $R^{6''}$ is an aryl or heteroaryl group.

4. The compound of claim 3, wherein $R^{6''}$ is:



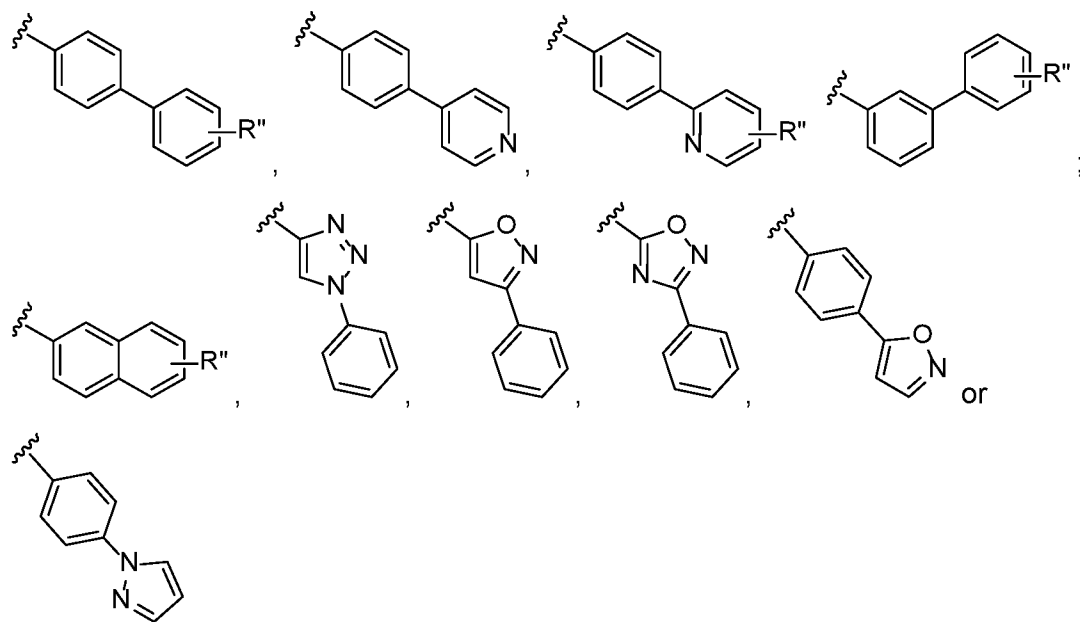
wherein each R'' is, independently H or halo and X^3 is N or CH; and

R^{10} is

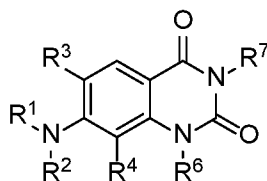


wherein each R^{11} is H, $C(O)N(R)_2$ (wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl), optionally substituted alkyl or two adjacent R^{11} groups, together with the atoms to which they are attached form an optionally substituted cycloalkyl group or an optionally substituted heterocyclyl group; m is an integer from 1 to 3; and X^1 is O or NR^{12} , wherein R^{12} is H or optionally substituted alkyl or R^{12} and an adjacent R^{11} group, together with the atoms to which they are attached, form an optionally substituted heterocyclyl group.

5. The compound of claim 3, wherein $R^{6''}$ is:



6. A compound of the formula (II):



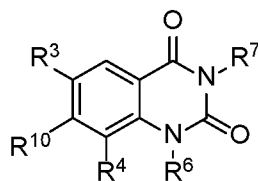
(II)

or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

R¹-R⁴ and R⁶ are as defined for compounds of the formula (I); and

R⁷ is H, OH, optionally substituted alkoxy, optionally substituted alkyl or NR⁸R⁹, wherein R⁸ and R⁹ are each independently H, optionally substituted alkyl, optionally substituted aryl or optionally substituted arylalkyl.

7. The compound of claim 6, wherein the compound of the formula (II) is a compound of the formula (IIa):



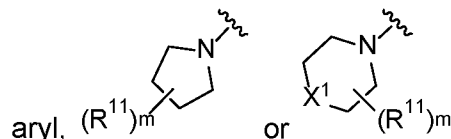
(IIa)

or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein:

R³, R⁴, and R⁶ are as defined for compounds of the formula (I);

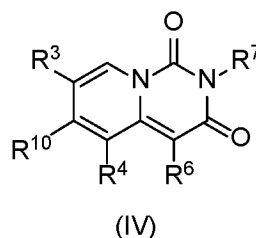
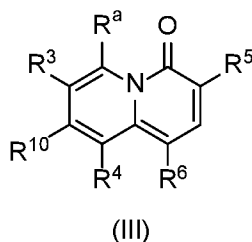
R⁷ is H, optionally substituted alkyl or NR⁸R⁹, wherein R⁸ and R⁹ are each independently H, optionally substituted alkyl, optionally substituted aryl or optionally substituted arylalkyl; and

R^{10} is



wherein each R¹¹ is H, C(O)N(R)₂ (wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl), optionally substituted alkyl or two adjacent R¹¹ groups, together with the atoms to which they are attached form an optionally substituted cycloalkyl group or an optionally substituted heterocyclyl group; m is an integer from 1 to 3; and X¹ is O or NR¹², wherein R¹² is H or optionally substituted alkyl or R¹² and an adjacent R¹¹ group, together with the atoms to which they are attached, form an optionally substituted heterocyclyl group.

8. A compound of the formula (III) and (IV):



wherein the groups R^a, R³-R⁷, and R¹⁰ are as defined in claims 1-7.

9. A compound of claim 1, wherein R³ is halo.

10. A compound of claim 1, wherein R³ is H.

11. A compound of claim 1, wherein R⁴ is alkoxy.

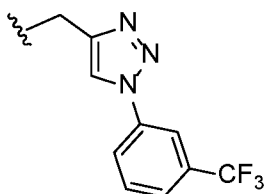
12. A compound of claim 1, wherein R⁴ is H.

13. A compound of claim 1, wherein R⁵ is -C(O)R^{5'}.

14. A compound of claim 1, wherein R⁶ is optionally substituted arylalkyl.

15. A compound of claim 6 or 7, wherein R^7 is NR^8R^9 .

16. A compound of claim 1, wherein when R^6 is:



R¹ and R², together with the nitrogen atom to which they are attached, form an optionally substituted pyrrolidinyl group.

5

17. A compound of claim 1, wherein R¹¹ is optionally substituted alkyl.

10

18. A compound of claim 1, wherein R¹¹ is alkyl substituted with NR¹³R¹⁴, wherein R¹³ and R¹⁴ are each independently H, optionally substituted alkyl, optionally substituted aryl, optionally substituted arylalkyl or R¹³ and R¹⁴, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl group.

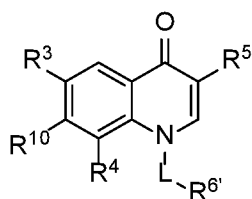
15

19. A compound of claim 1, wherein R¹¹ is alkyl substituted with OR¹³, wherein R¹³ is H, optionally substituted alkyl, optionally substituted aryl or optionally substituted arylalkyl.

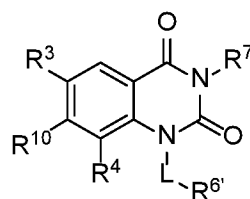
20

20. A compound of claim 1, wherein R¹¹ is C(O)N(R)₂, wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl.

21. A compound of claim 1, wherein the compound is a compound of the formula (V) or (VI):

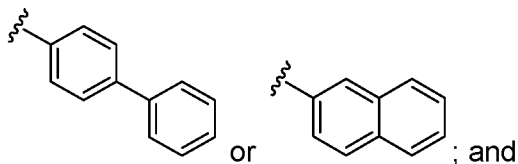


(V)



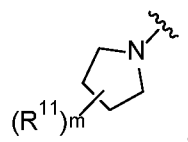
(VI)

wherein R³, R⁴, and R⁷ are as defined for compounds of the formula (I); L is -(CH₂)_n-, wherein n is an integer from 1 to 3 (e.g., 1); R^{6'} is:



25

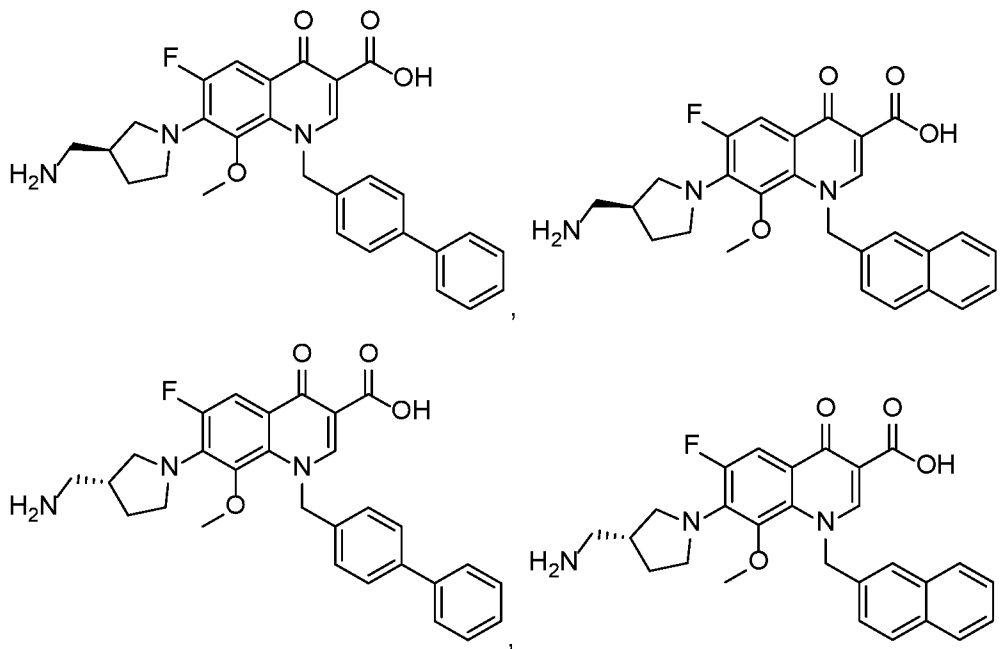
R¹⁰ is:

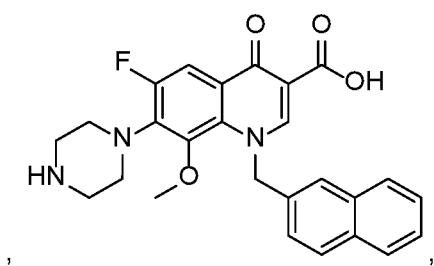
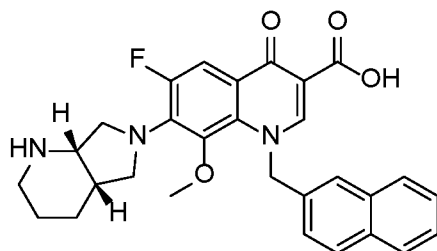
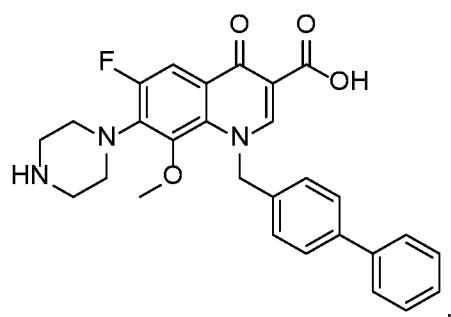
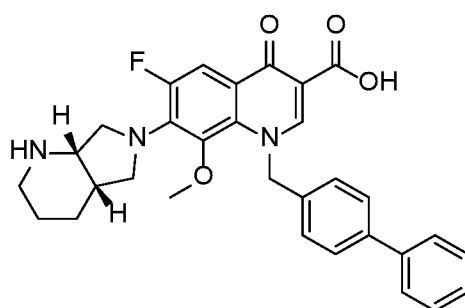
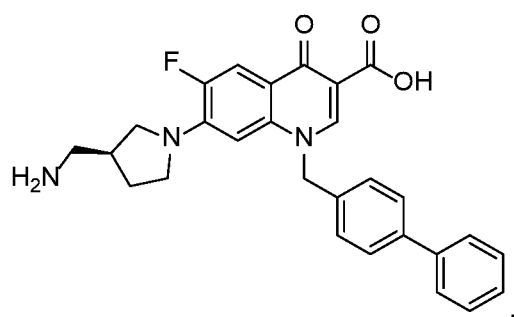
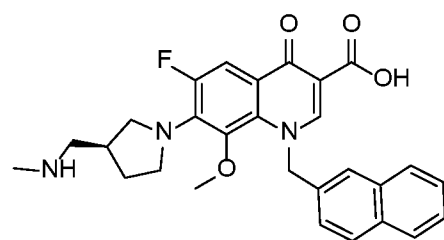
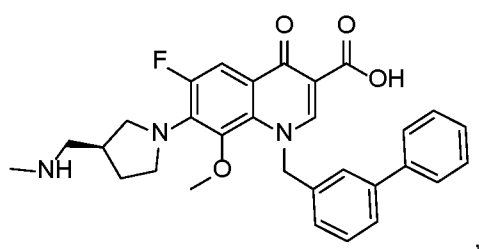
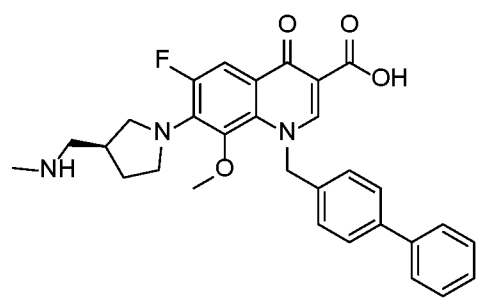
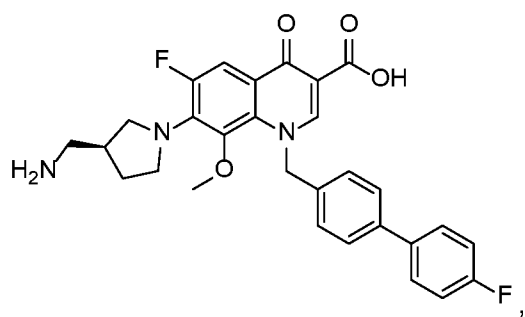


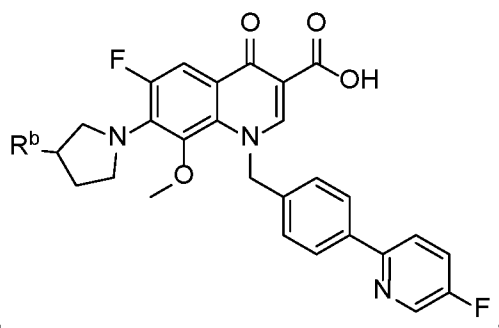
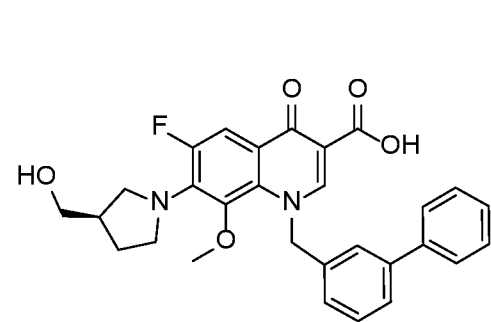
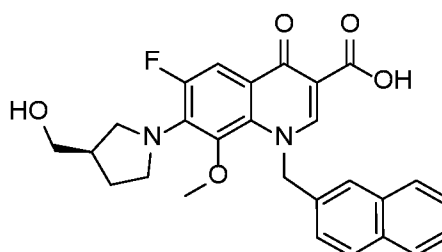
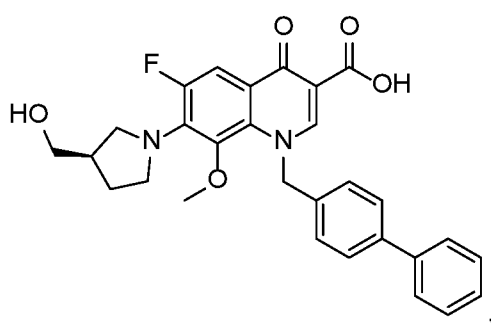
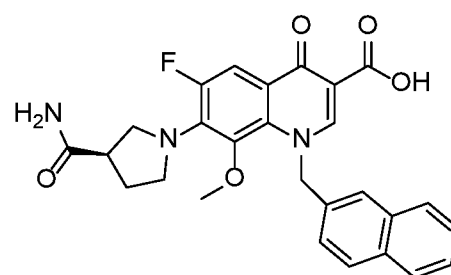
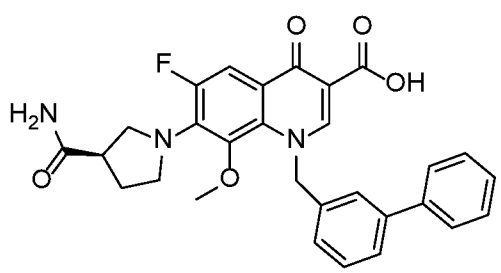
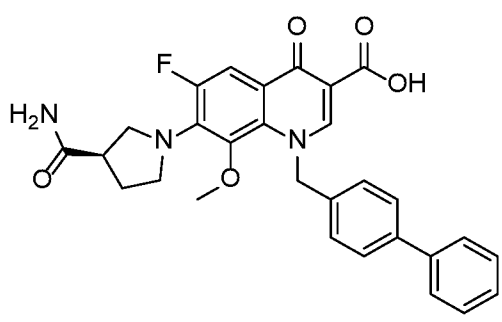
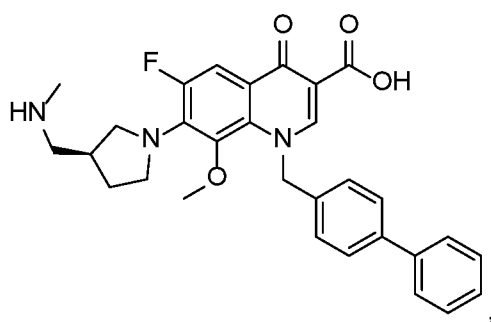
wherein R¹¹ is C(O)N(R)₂ (wherein each R group is, independently, hydrogen, alkyl, acyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heteroaryl, or heteroarylalkyl), alkyl substituted with -OR or alkyl substituted with -N(R)₂.

5

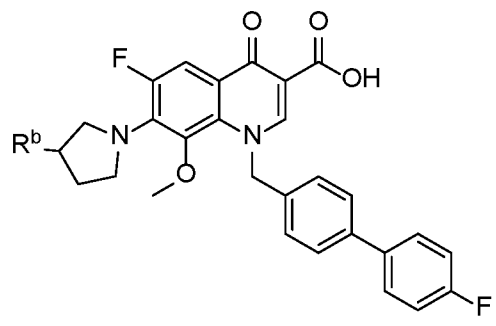
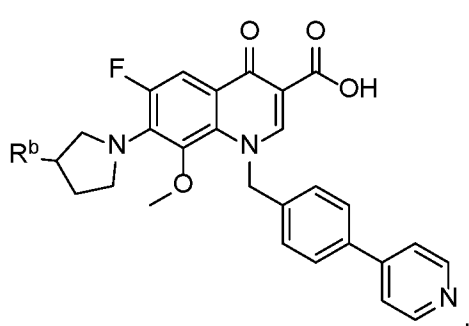
22. A compound of claim 1, wherein the compound has the formula:

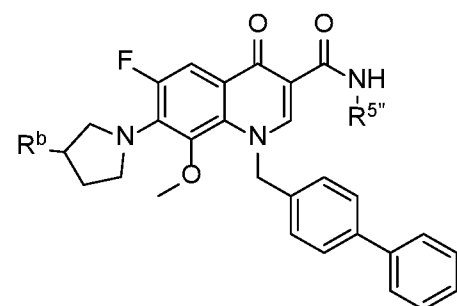
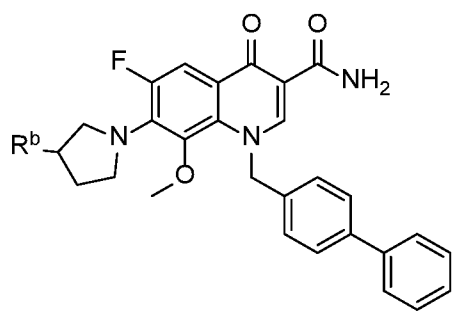
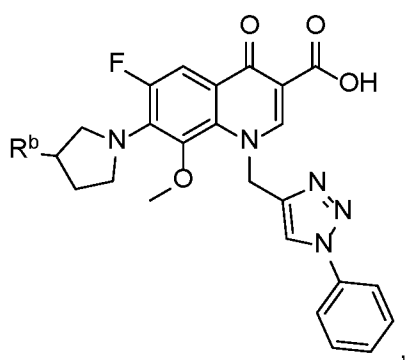
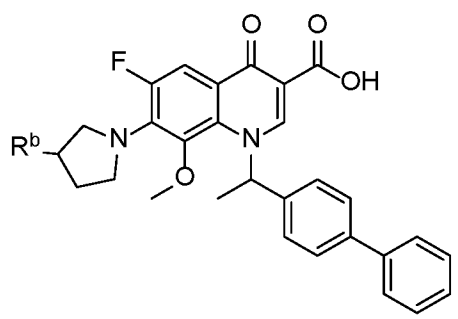
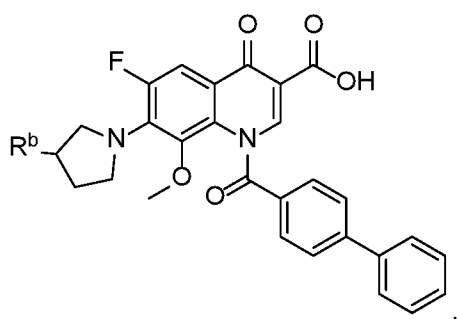




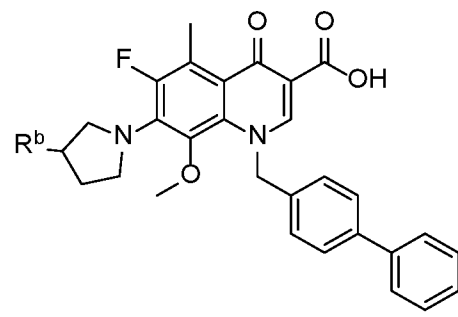
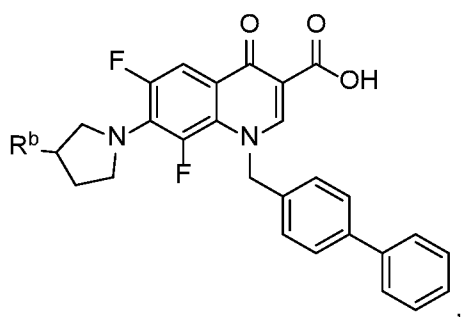
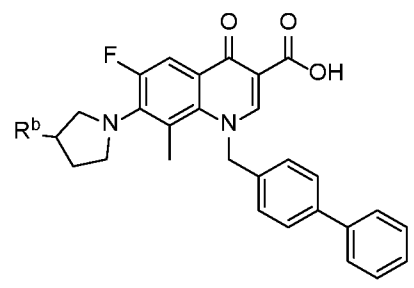
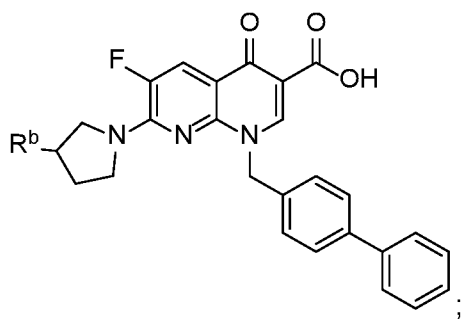


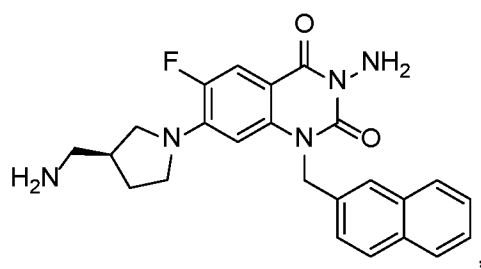
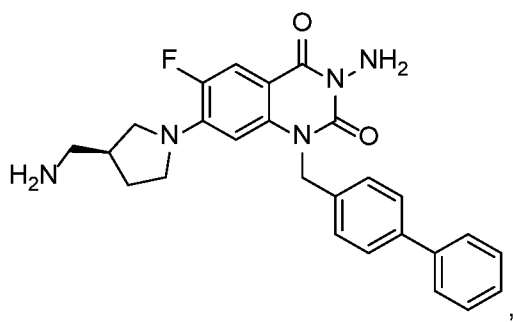
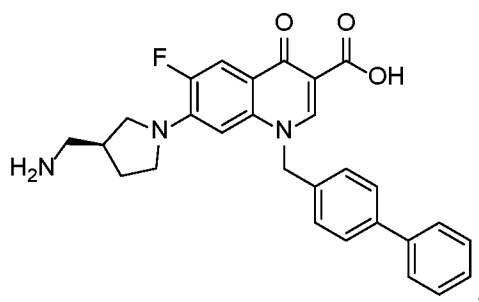
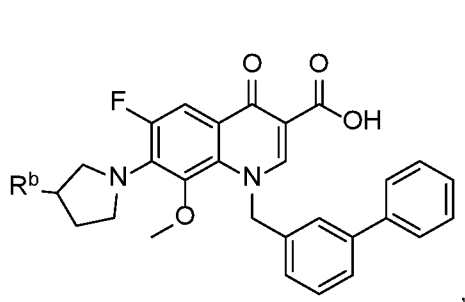
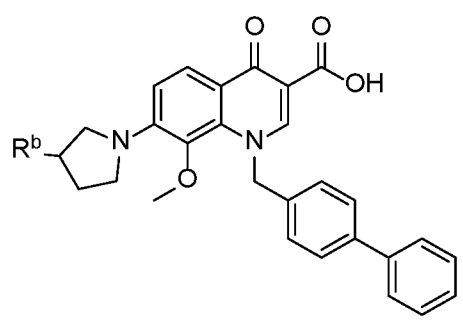
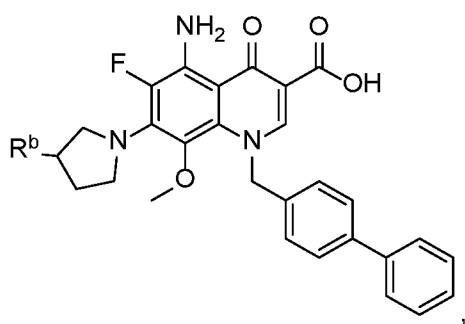
5

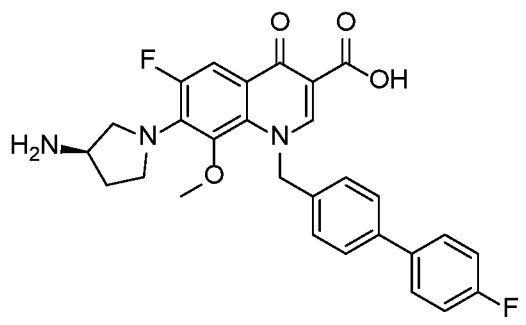
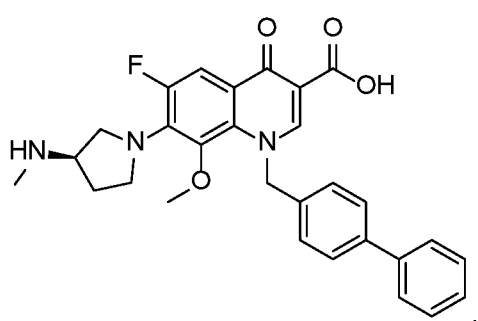
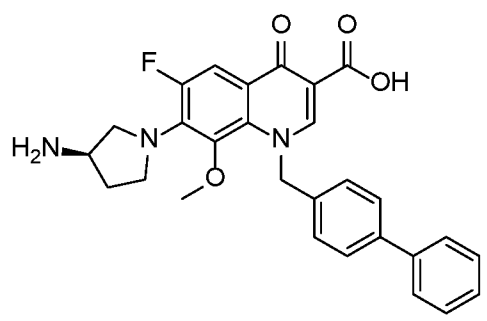
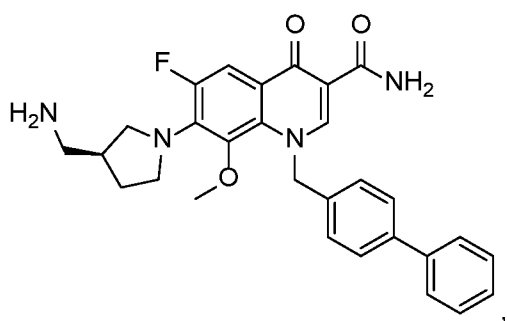
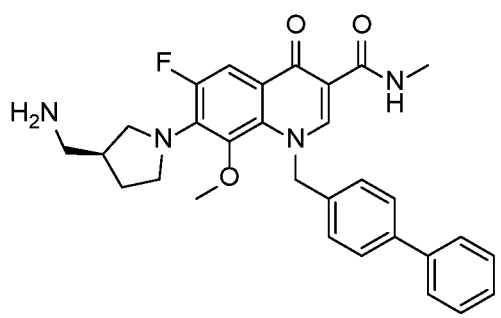
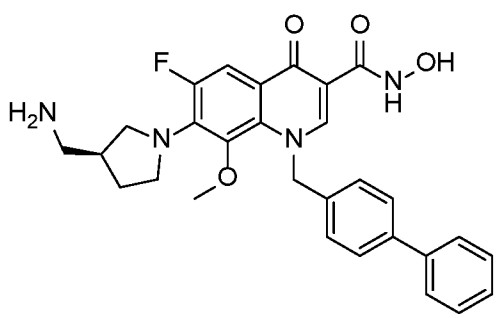
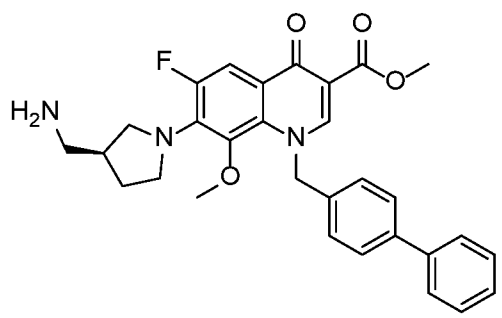
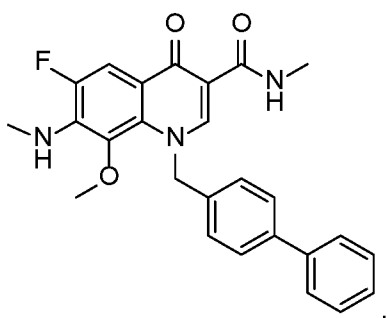
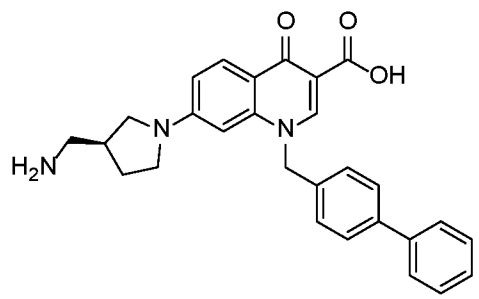
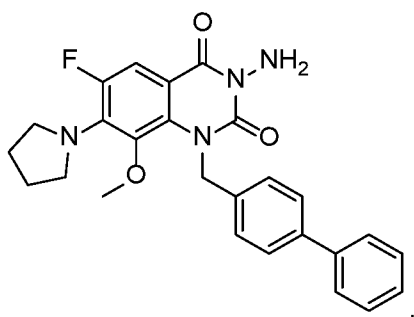
(wherein R^b is -CH₂NHCH₃, -CH₂OH or C(O)NH₂),

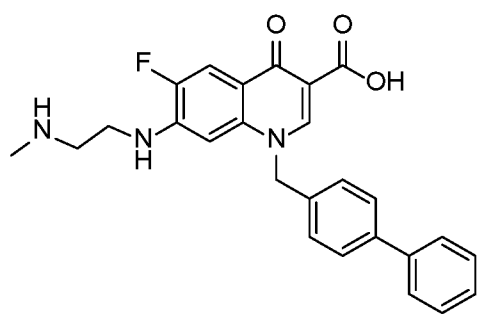
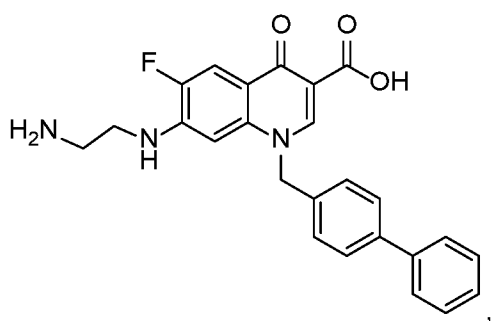
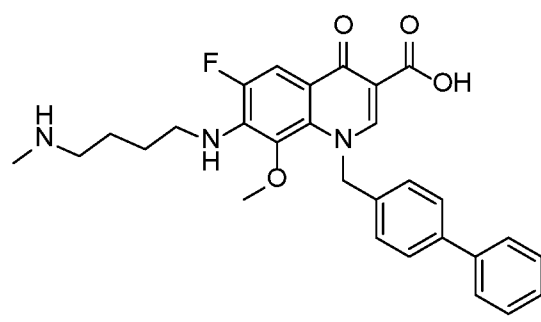
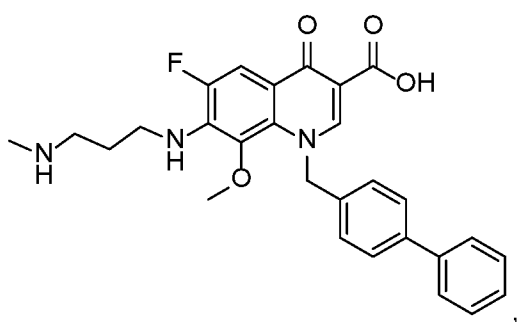
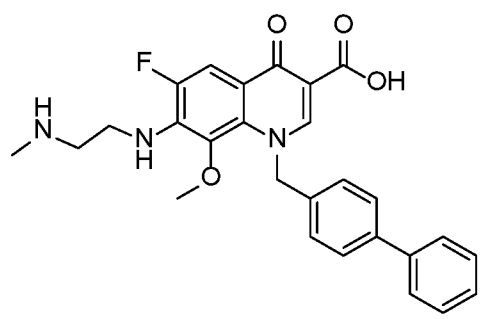
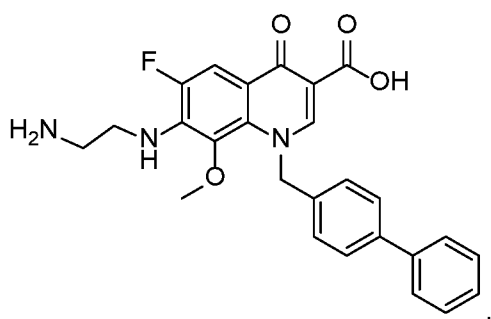


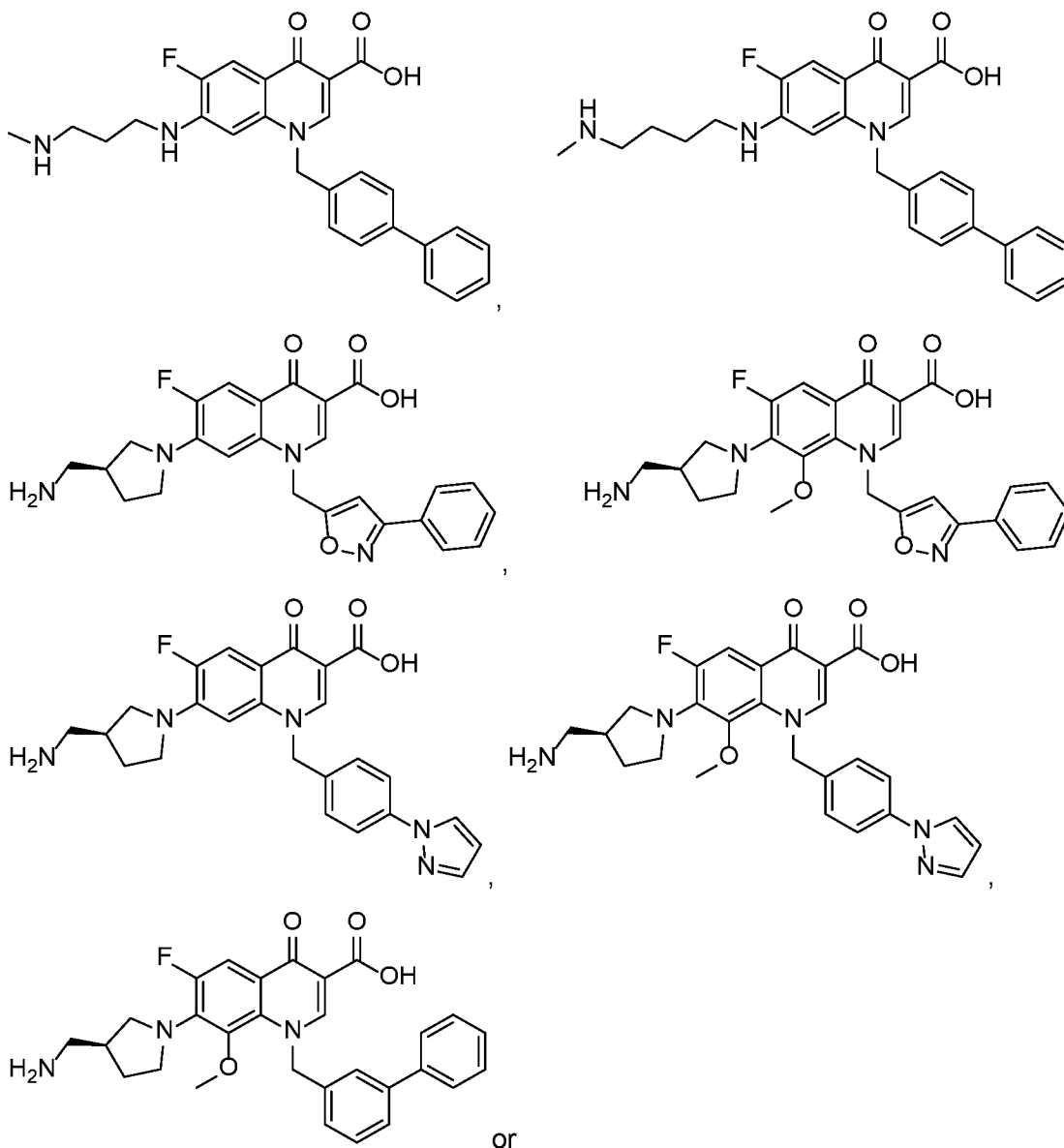
(wherein R^{5''} is defined herein);











5 pharmaceutically acceptable salts, polymorphs, prodrugs, solvates or clathrates thereof.

23. The compound of claim 1, wherein the IC_{50} for human topoisomerase II is about four to about 1000 times greater than the IC_{50} for human topoisomerase I.

10

24. The compound of claim 1, wherein the compound does not substantially increase an amount of nicked and linear DNAs in DNA cleavage assays.

25. A pharmaceutical composition comprising one or more compounds of claim 1 and one or more pharmaceutically acceptable carriers, diluents, excipients or combinations thereof.

15

26. A method for treating cancer comprising administering a therapeutically effective amount of one, or more compounds of claim 1 or a pharmaceutical composition of claim 25, to a patient in need thereof.

5 27. A method of modulating a human topoisomerase, comprising contacting the topoisomerase with an effective amount or concentration of a compound of claim 1.

28. The method of claim 27, wherein the human topoisomerase is human topoisomerase I.

10 29. The method of claim 28, wherein the compound has an IC_{50} for human topoisomerase II that is about four to about 1000 times greater than an IC_{50} of the same compound for human topoisomerase I.

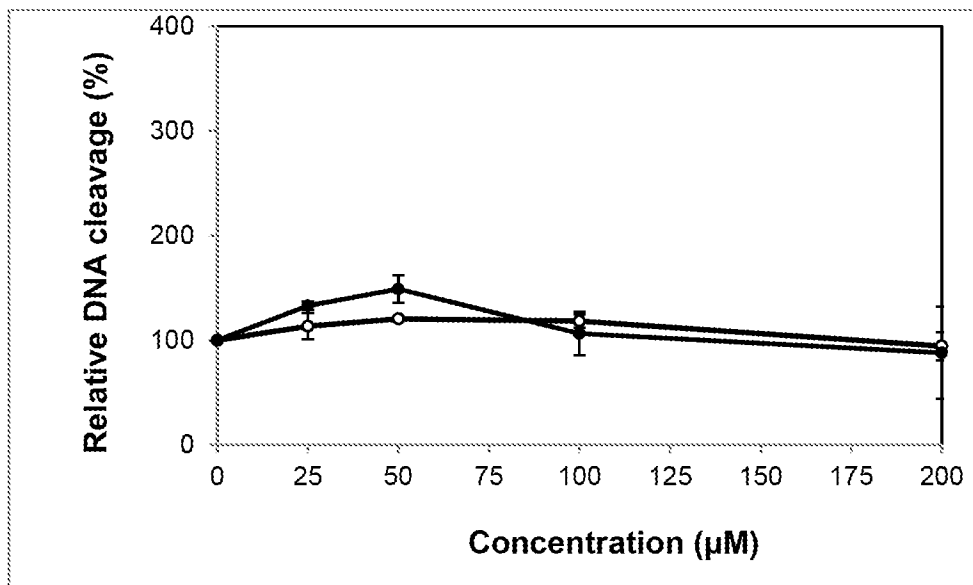


FIG. 1

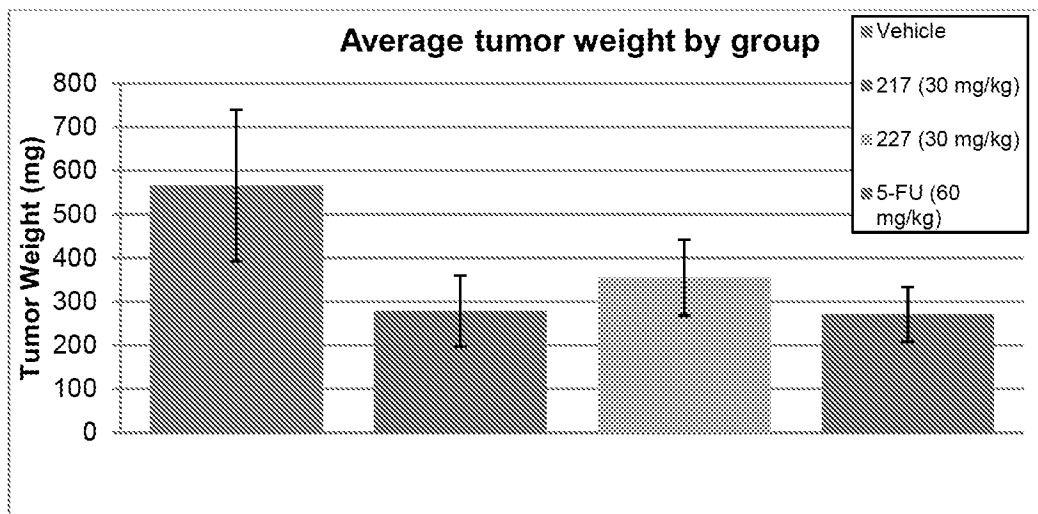


FIG. 2

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/65448

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of 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. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims 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. ☐ Claims 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:

See Supplemental Box

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 claims 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 claims Nos.:
1, 10, 23-29

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

International application No.

PCT/US 17/65448

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 291/04, C07D 215/56, C07D 295/155 (2018.01)
CPC - C07D 401/04, C07D 215/56, C07D 498/06

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)

See Search History Document

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

See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2003/0232818 A1 (Anderson et al.) 18 December 2003 (18.12.2003); p39, p428, p434, para[0004], para[0013], para[0014], para[0016], para[0019], para[0045], para[0310], para[0653]	1, 10, 23-29
Y	Abdel-Aziz et al. 'Novel N-4-piperazinyl-ciprofloxacin-chalcone hybrids: Synthesis, physicochemical properties, anticancer and topoisomerase I and II inhibitory activity', European Journal of Medicinal Chemistry, 12 September 2013 (12.09.2013), Vol.69, pages427-438; Abstract, p427, p428, p433, p434, p436	1, 10, 23-29
A	Kathiravan et al. 'Topoisomerase as target for antibacterial and anticancer drug discovery', Journal of Enzyme Inhibition and Medicinal Chemistry, 01 Mar 2012 (01.03.2012), Vol.28, pages419-435; p422	1
A	Pubmed Compound Summary for 88183736, 'SCHEMBL7672985', U.S. National Library of Medicine, 12 February 2015 (12.02.2015) pages1-11 (https://pubchem.ncbi.nlm.nih.gov/compound/88183736); p4	1, 10, 23-29
A	Pubmed Compound Summary for 28961, 'N-Formylformamide', U.S. National Library of Medicine, 19 July 2005 (19.07.2005) pages1-17 (https://pubchem.ncbi.nlm.nih.gov/compound/28961); p3	1, 10, 23-29
A	Pubmed Compound Summary for 7847, 'ACROLEIN', U.S. National Library of Medicine, 16 September 2004 (16.09.2004) pages1-10 (https://pubchem.ncbi.nlm.nih.gov/compound/7847); p4	1, 10, 23-29
A	Pubmed Compound Summary for 712, 'Formaldehyde', U.S. National Library of Medicine, 16 September 2004 (16.09.2004) pages1-10 (https://pubchem.ncbi.nlm.nih.gov/compound/712); p4	1, 10, 23-29

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"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)

"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

"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

"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

"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

"&" document member of the same patent family

Date of the actual completion of the international search

30 January 2018 (30.01.2018)

Date of mailing of the international search report

16 APR 2018

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, Virginia 22313-1450
Facsimile No. 571-273-8300

Authorized officer:

Lee W. Young

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/65448

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I+: Claims 1-5, 9-14, 16-29 directed to a compound of formula (I) or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, in claim 1. The compound of formula (I) will be searched to the extent that it encompasses the compound having formula (I) or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof: wherein: R_a is halo; R₁ and R₂ are H; R₃ is H; R₄ is absent if X₂ is N; X₂ is N; R₅ is H; R₆ is the group -L-R₆', wherein L is a linker group and R₆' is a group having sufficient "steric bulk" such that the compound of the formula (I) is (a) not a topoisomerase II poison, (b) inhibits topoisomerase I and topoisomerase II and/or (c) inhibits topoisomerase I to a greater extent than topoisomerase II. It is believed that claims 1, 10, 23-29 read on this first named invention, and thus this claim will be searched without fee. Applicant is invited to elect additional compounds of claim 1, wherein each additional compound elected will require one additional invention fee. Applicants must specify the claims that encompass any additionally elected compound. Applicants must further indicate, if applicable, the claims which encompass the first named invention, if different than what was indicated above for this group. Failure to clearly identify how any paid additional invention fees are to be applied to the '+' group(s) will result in only the first claimed invention to be searched. Additionally, an exemplary election wherein different actual variables are selected is suggested. An exemplary election would be the compound of formula (I) or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, wherein: R_a is H; R₁ and R₂, together with the nitrogen atom to which they are attached, form an optionally substituted heterocyclyl group; R₃ is halo; R₄ is optionally substituted alkoxy; X₂ is C; R₅ is -C(O)R₅' (wherein R₅' is H, OH, optionally substituted alkyl, optionally substituted aryl, optionally substituted alkoxy or -N(R₅')₂, wherein each R₅' is, independently, H, OH, optionally substituted alkoxy, optionally substituted alkyl or optionally substituted arylalkyl) or -N(R₅')₂; and R₆ is the group -L-R₆', wherein L is a linker group and R₆' is a group having sufficient "steric bulk" such that the compound of the formula (I) is (a) not a topoisomerase II poison, (b) inhibits topoisomerase I and topoisomerase II and/or (c) inhibits topoisomerase I to a greater extent than topoisomerase II (i.e., claims 1-2, 9, 11, 13-14, 17, 18(in part), 21(in part), 22(in part), and 23-29).

Group II: claims 6-7, and 15 directed to a compound of the formula (II) or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof.

Group III: claim 8 directed to a compound of the formula (III) and (IV).

The group of inventions listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Special Technical Features:

Group I+ includes the technical feature of a unique compound of formula (I) or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof in claim 1 containing the same, which is not required by any other invention of Group I+.

Group II includes the technical feature of a compound of the formula (II) or a pharmaceutically acceptable salt, polymorph, prodrug, solvate or clathrate thereof, not required by Group I+ and III.

Group III includes the technical feature of a compound of the formula (III) and (IV), not required by Group I+ and II.

Common technical features:

The inventions of Group I+ share the technical feature of compound of formula containing the same. These shared technical features, however, do not provide a contribution over the prior art, as being obvious over US 6,136,823 A to Sakae et al. (hereinafter 'Sakae'), in view of the journal article entitled 'Novel N-4-piperazinyl-ciprofloxacin-chalcone hybrids: Synthesis, physicochemical properties, anticancer and topoisomerase I and II inhibitory activity' by Abdel-Aziz et al. (hereinafter 'Abdel-Aziz'). Sakae teaches a compound of the formula (I), wherein R_a is alkyl; R₁ is H, R₂ is alkyl; R₃ is halo; R₄ is H; X₂ is C; R₅ is -C(O)R₅' (wherein R₅' is H); and R₆ is the group -L-R₆', wherein L is a linker group and R₆' is a group having sufficient "steric bulk" (col20, Example 18 "Synthesis of 1-(5-Amino-2,4-difluorophenyl)-6-fluoro-5-methyl-7-methylamino-4-oxo-1,4-dihydroquinoline-3-carboxylic Acid"), but does not teach that the compound of the formula (I) (b) inhibits topoisomerase I and topoisomerase II. However, Abdel-Aziz teaches analogous compounds (p428, "Scheme 1. Compound 3a-j") inhibit topoisomerase I and topoisomerase II (p434, left col 1st para "Most of the tested compounds have shown good topo I and topo II inhibitory activity at 100 mM"). Thus, it would have been obvious to one of ordinary skill in the art to be motivated to formulate the compound by routine experimentation, in order to identify whether the antibacterial activity of the compound disclosed by Sakae occurs by inhibition of topoisomerases, as disclosed by Abdel-Aziz (p427, left col 1st para "topo II represents the cellular target for quinolone antibacterial agents and a wide variety of anticancer drugs that was attributed to the mechanistic similarities and sequence homologies of their target topoisomerase II").

Groups I+ and II share the technical feature of a 2-amino-4-methylaminobenzaldehyde, wherein amino and methylamino can be optionally substituted. However, these shared technical features do not provide a contribution over the prior art, as being anticipated by PubChem CID 88183736 (hereinafter 'CID736'). CID736 discloses 2,4-bis(methylamino)benzaldehyde (p4, "2D Structure").

Groups II and III share the technical feature of N-formylformamide moiety. However, these shared technical features do not provide a contribution over the prior art, as being anticipated by PubChem CID 28961 (hereinafter 'CID961'). CID961 discloses N-formylformamide moiety (p3, "2D Structure").

Groups I+ and III share the technical feature of prop-2-enal moiety. However, these shared technical features do not provide a contribution over the prior art, as being anticipated by PubChem CID 7847 (hereinafter 'CID847'). CID847 discloses prop-2-enal moiety (p4, "2D Structure").

Continues in the next page

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 17/65448

lack of unity continuation

Groups I+, II and III share the technical feature of formaldehyde or ketone moiety. However, these shared technical features do not provide a contribution over the prior art, as being anticipated by PubChem CID 712 (hereinafter CID712). CID712 discloses formaldehyde moiety (p4, "2D Structure").

As said compound and compositions were known in the art at the time of the invention, these cannot be considered special technical features that would otherwise unify the inventions of Groups I+, II and III. The inventions of Group I+, II and III thus lack unity under PCT Rule 13.