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CA 2629136 C 2016/03/08

(11)(21) 2 629 136

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(86) Date de dépôt PCT/PCT Filing Date: 2006/11/08
(87) Date publication PCT/PCT Publication Date: 2007/05/18
(45) Date de délivrance/Issue Date: 2016/03/08
(85) Entrée phase nationale/National Entry: 2008/05/08
(86) N° demande PCT/PCT Application No.: US 2006/043859
(87) N° publication PCT/PCT Publication No.: 2007/056593
(30) Priorité/Priority: 2005/11/08 (US60/734,655)

(51) Cl.Int./Int.Cl. *C07K 5/06* (2006.01), *A61K 31/4985* (2006.01), *A61P 11/00* (2006.01)

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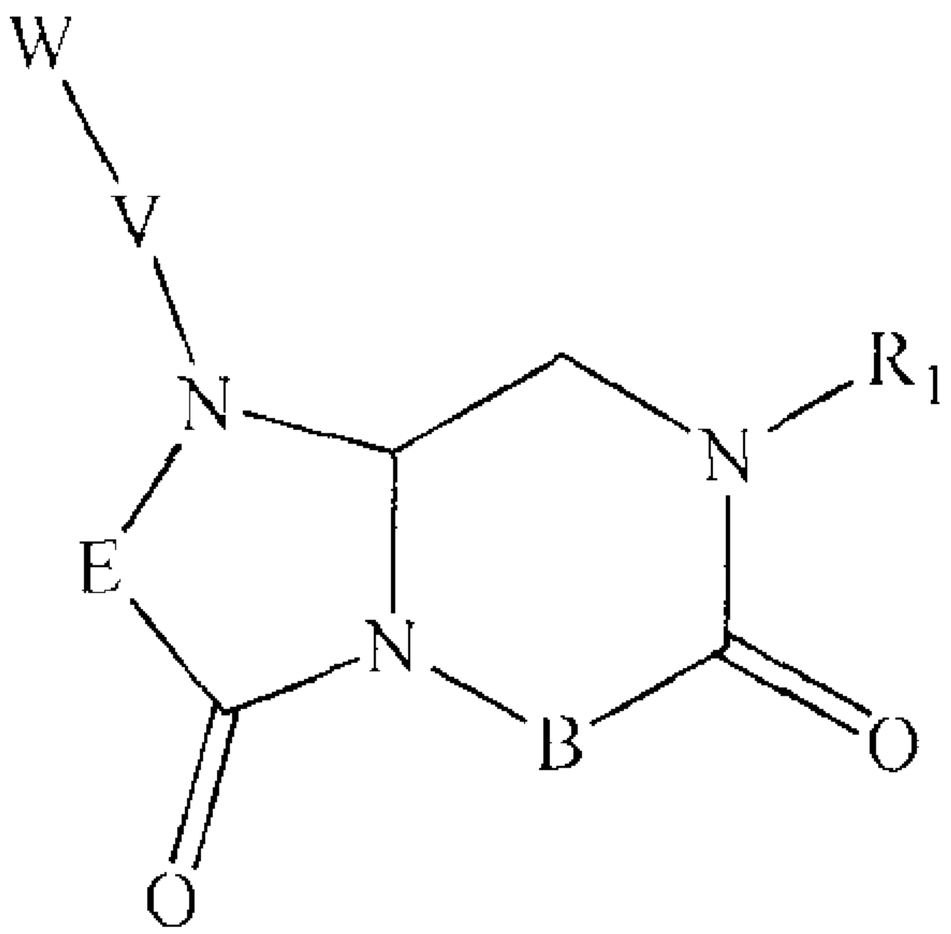
(54) Titre : MIMETIQUES A HELICE-αET PROCEDE RELATIF AU TRAITEMENT DE CELLULES SOUCHES CANCEREUSES

(54) Title: α-HELIX MIMETICS AND METHOD RELATING TO THE TREATMENT OF CANCER STEM CELLS



(VI)

(57) Abrégé/Abstract:
The invention provides alpha -mimetic structure of formula (I) wherein A is -(C=O)-CHR_3-, or -(C=O), B is N-R_3- or -CHR_6-, D is -(C=O)-(CHR_7)- or - (C=O) E is -(ZR_8)- or (C=O), G is -(XR_9)n-, -(CHR_{10})-(NR_6)-, -(C=O)-(XR_{12})-, -(C=N-W-R_1)-, -(C=O)-, X-(C=O)-R_{13}, X-(C=O)-$NR_{13}R_{14}$, X-(SO_2)-R_{13}, or X-(C=O)-OR_{13}, W is -Y(C=O)-, -(C=O)NH-, -(SO_2)-, -CHR_{14}, (C=O)-(NR_{15})-, substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole, or nothing, Y is oxygen or sulfur, X and Z is independently nitrogen or CH, n=0 or 1; and R_1 R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, and R_{15} are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers, salts, and prodrugs thereof, provided that where B is CHR_6 and W is -Y(C=O)-, -(C=O)NH-, -(SO_2), -CHR_{14}, or (C=O)-(NR_{15})-, G cannot be CHR_9, NR_9, (C=O)-CHR_{12}, (C=O)-NR_{12}, or no atom at all. Additionally, the invention provides methods wherein α-mimetic compounds are used to treat cancer stem cells .

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 May 2007 (18.05.2007)

PCT

(10) International Publication Number
WO 2007/056593 A3

(51) International Patent Classification:
C07K 5/06 (2006.01) *A61P 11/00* (2006.01)
A61K 31/4985 (2006.01)

(21) International Application Number:
PCT/US2006/043859

(22) International Filing Date:
8 November 2006 (08.11.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/734,655 8 November 2005 (08.11.2005) US

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

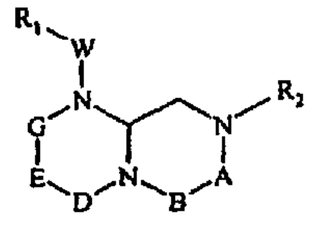
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
12 July 2007

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: α-HELIX MIMETICS AND METHOD RELATING TO THE TREATMENT OF CANCER STEM CELLS



(I)

(57) Abstract: The invention provides alpha -mimetic structure of formula (I) wherein A is -(C=O)-CHR_3-, or -(C=O), B is N-R_3- or -CHR_6-, D is -(C=O)-(CHR_7)- or - (C=O) E is -(ZR_8)- or (C=O), G is -(XR_9)n-, -(CHR_{10})-(NR_6)-, -(C=O)-(XR_{12})-, -(C=N-W-R_1)-, -(C=O)-, X-(C=O)-R_{13}, X-(C=O)-$NR_{13}R_{14}$, X-(SO_2)-R_{13}, or X-(C=O)-OR_{13}, W is -Y(C=O)-, -(C=O)NH-, -(SO_2)-, -CHR_{14}, (C=O)-(NR_{15})-, substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole, or nothing, Y is oxygen or sulfur, X and Z is independently nitrogen or CH, n=0 or 1; and R_1 R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, and R_{15} are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers, salts, and prodrugs thereof, provided that where B is CHR_6 and W is -Y(C=O)-, -(C=O)NH-, -(SO_2), -CHR_{14}, or (C=O)-(NR_{15})-, G cannot be CHR_9, NR_9, (C=O)-CHR_{12}, (C=O)-NR_{12}, or no atom at all. Additionally, the invention provides methods wherein α-mimetic compounds are used to treat cancer stem cells .

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α-HELIX MIMETICS AND METHOD RELATING TO THE TREATMENT OF CANCER STEM CELLS

TECHNICAL FIELD

The present invention relates generally to α-helix mimetic structures and to a chemical library relating thereto. The invention specifically relates to applications in the treatment of cancer and particularly cancer stem cells and pharmaceutical compositions comprising the α-helix mimetics.

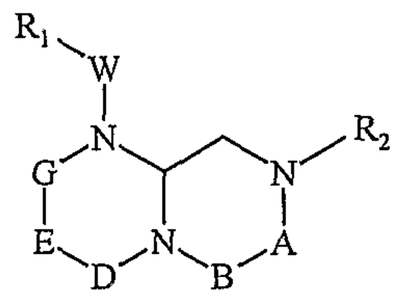
BACKGROUND OF THE INVENTION

Despite the clonal origin of many cancers, most primary tumors display a notable degree of cellular heterogeneity. Although modern chemotherapies kill a majority of the cells in a tumor, evidence clearly indicates that cancer stems cells often remain. The cancer stem cell hypothesis posits that a very rare population of cells within tumors are the only tumor cells with the capacity for limitless self-renewal. This concept has important therapeutic implications, and may explain why it is possible to treat many cancers until the tumor can no longer be detected and yet the cancer returns. There is a need in the art for compositions and methods that will inhibit, reduce, and/or eliminate cancer stem cells from a patient.

The present invention also fulfills these needs, and provides further related advantages by providing conformationally constrained compounds which mimic the secondary structure of α-helix regions of biologically active peptides and proteins and particularly selectively disrupt the β-catenin/CBP interaction.

SUMMARY OF THE INVENTION

Provided is a compound having the following general formula (I):



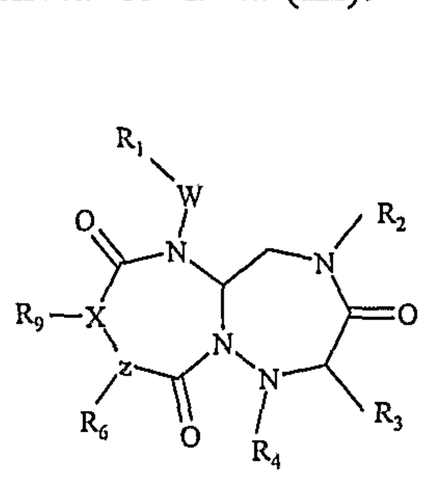
(I)

wherein A is –(C=O)-CHR_3-, or –(C=O), B is N-R_5- or -CHR_6-, D is –(C=O)–(CHR_7)- or –(C=O)-, E is –(ZR_8)- or (C=O), G is –$(XR_9)_n$-, -(CHR_{10})-(NR_6)-,-(C=O)-(XR_{12})-, -(C=N-W-R_1)-, -(C=O)-, X-(C=O)-R_{13}, X-(C=O)-$NR_{13}R_{14}$, X-(SO_2)-R_{13}, or X-(C=O)-OR_{13}, W is –Y(C=O)-, -(C=O)NH-, -(SO_2)-, -CHR_{14}, (C=O)-(NR_{15})-, substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole, or nothing, Y is oxygen or sulfur, X and Z is independently nitrogen or CH, n=0 or 1; and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, and R_{15} are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers, salts, and prodrugs thereof, provided that where B is CHR_6 and W is –Y(C=O)-, -(C=O)NH-, -(SO_2)-, -CHR_{14}, or (C=O)-(NR_{15})-, G cannot be CHR_9, NR_9, (C=O)-CHR_{12}, (C=O)-NR_{12}, or no atom at all.

Also provided is a compound, salts, and prodrugs thereof of formula (I), wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, are R_{15} are independently selected from the group consisting of aminoC_{2-5}alkyl, guanidinoC_{2-5}alkyl, C_{1-4}alkylguanidinoC_{2-5}alkyl, diC_{1-4}alkylguanidino-C_{2-5}alkyl, amidinoC_{2-5}alkyl, C_{1-4}alkylamidinoC_{2-5}alkyl, diC_{1-4}alkylamidinoC_{2-5}alkyl, C_{1-3}alkoxy, phenyl, substituted phenyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), benzyl, substituted benzyl (where the substituents on the benzyl are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), naphthyl, substituted naphthyl (where the substituents are independently selected from one or more of amino, amidino, guanidino,

hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), bis-phenyl methyl, substituted bis-phenyl methyl (where the subsitituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridyl, subsitituted pyridyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridylC_{1-4}alkyl, substituted pyridylC_{1}-$_{4}$alkyl (where the pyridine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyrimidylC_{1-4}alkyl, substituted pyrimidylC_{1-4}alkyl (where the pyrimidine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy or nitro, carboxy, cyano, sulfuryl or hydroxyl), triazin-2-yl-C_{1-4}alkyl, substituted triazin-2-yl-C_{1-4}alkyl (where the triazine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), imidazoC_{1-4}alkyl, substituted imidazol C_{1-4}alkyl (where the imidazole substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, hydroxyl, or methyl), imidazolinylC_{1-4}alkyl, N-amidinopiperazinyl-N-C_{0-4}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, C_{1-5}dialkylaminoC_{2-5}alkyl, N-amidinopiperidinylC_{1-4}alkyl and 4-aminocyclohexylC_{0-2}alkyl.

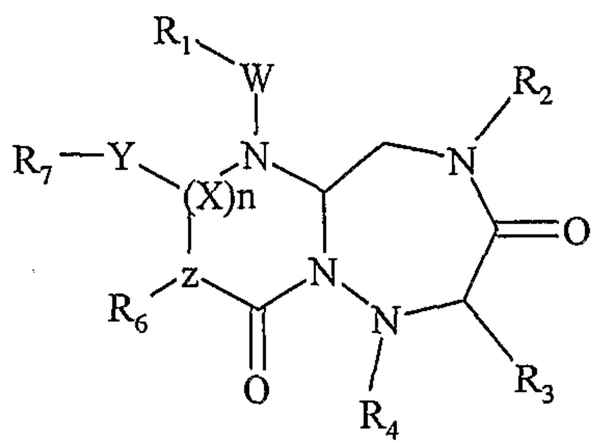
Further provided is the compound, salts, and prodrugs thereof of compound (I) wherein A is –(CHR3)-(C=O)-, B is –(NR4)-, D is (C=O)-, E is –(ZR6)-, G is –(C=O)-(XR9)-, and the compound has the following general formula (III):



(III)

wherein R_1, R_2, R_4, R_6, R_9, W and X are as defined in claim 1, Z is nitrogen or CH (when Z is CH, the X is nitrogen).

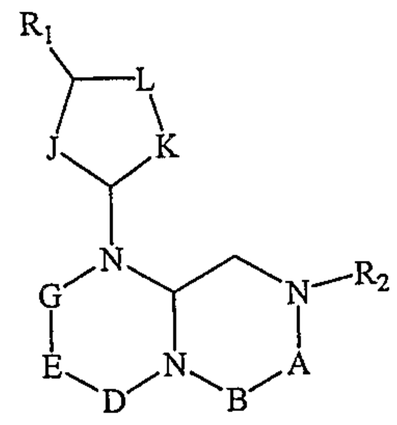
Also provided is a compound, salts, and prodrugs thereof of formula (I) wherein A is –O-CHR_3-, B is –NR_4-, D is –(C=O)-, E is –(ZR_6)-, Gi is $(XR_7)_n$-, the α-helix mimetic compounds of this invention have the following formula (IV):



(IV)

wherein R_1, R_2, R_4, R_6, R_7, R_8 W, X and n are as defined above, Y is –C=O, -(C=O)-O-, -(C=O)-NR_8, -SO_2-, or nothing, and Z is nitrogen or CH (when Z is nitrogen, then n is zero, and when Z is CH, then X is nitrogen and n is not zero). In a preferred embodiment, R_1, R_2, R_6, R_7, and R_8 represent the remainder of the compound, and R_4 is selected from an amino acid side chain moiety. In this case, R_6 or R_7 may be selected from an amino acid side chain moiety when Z and X are CH, respectively.

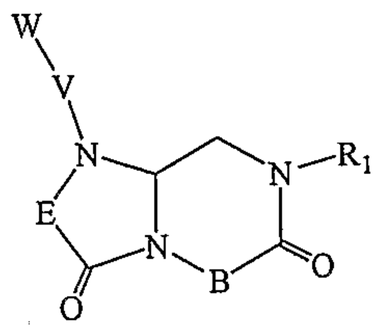
Further provided is a compound, salts, and prodrugs thereof of formula (I) wherein A is –(C=O), B is –(CHR_6)-, D is –(C=O)-, E is –(ZR_8)-, and G is -(NH)- or -(CH_2)-, and W is a substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole, the α-helix mimetic compounds of this invention have the following formula (V):



(V)

wherein K is nitrogen, oxygen, or sulfur, L is nitrogen, oxygen, -(CH)-, or -(CH_2)-, J is nitrogen, oxygen, or sulfur, Z is nitrogen or CH, and R_1, R_2, R_6, R_8, and R_{13} are selected from an amino acid side chain moiety.

Also provided is a compound having the general formula (VI):



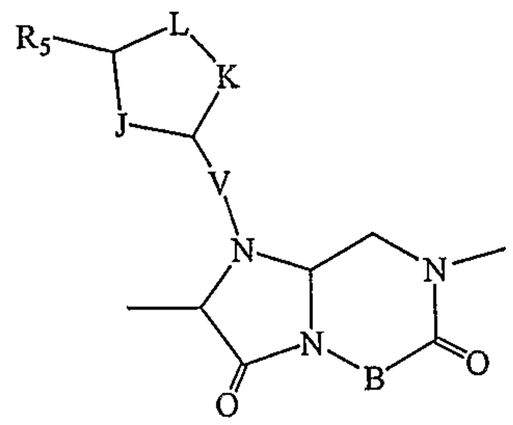
(VI)

wherein B is -(CHR_2)-, -(NR_2)-,, E is -(CHR_3)-, V is -(XR_4)- or nothing, W is -(C=O)-(XR_5R_6), -(SO_2)-, substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole, X is indepentently nitrogen, oxygen, or CH, and R_1, R_2, R_3, R_4, R_5 and R_6 are selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and solid support, and stereoisomers, salts, and prodrugs thereof.

Further provided is a compound, salts, and prodrugs thereof of formula (I), wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, are R_{15} are independently selected from the group consisting of aminoC_{2-5}alkyl, guanidinoC_{2-5}alkyl, C_{1-4}alkylguanidinoC_{2-5}alkyl, diC_{1-4}alkylguanidino-C_{2-5}alkyl, amidinoC_{2-5}alkyl, C_{1-4}alkylamidinoC_{2-5}alkyl, diC_{1-4}alkylamidinoC_{2-5}alkyl, C_{1-3}alkoxy, phenyl, substituted phenyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro,

carboxy, cyano, sulfuryl or hydroxyl), benzyl, substituted benzyl (where the substituents on the benzyl are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), naphthyl, substituted naphthyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), bis-phenyl methyl, substituted bis-phenyl methyl (where the subsitituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridyl, subsitituted pyridyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridylC_{1-4}alkyl, substituted pyridylC_{1-4}alkyl (where the pyridine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyrimidylC_{1-4}alkyl, substituted pyrimidylC_{1-4}alkyl (where the pyrimidine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy or nitro, carboxy, cyano, sulfuryl or hydroxyl), triazin-2-yl-C_{1-4}alkyl, substituted triazin-2-yl-C_{1-4}alkyl (where the triazine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), imidazoC_{1-4}alkyl, substituted imidazol C_{1-4}alkyl (where the imidazole substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, hydroxyl, or methyl), imidazolinylC_{1-4}alkyl, N-amidinopiperazinyl-N-C_{0-4}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, C_{1-5}dialkylaminoC_{2-5}alkyl, N-amidinopiperidinylC_{1-4}alkyl and 4-aminocyclohexylC_{0-2}alkyl. Further provided is a compound, salts, and prodrugs thereof wherein B is -(CH)-(CH_3), E is -(CH)-(CH_3), V is -(XR_4)- or nothing, and W is substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5

dihydroimidazole, and X is independently introgen or CH, the compounds have the following general formula (VII):

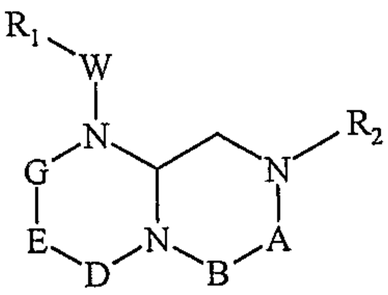


(VII)

wherein K is nitrogen, oxygen, or sulfur, L is nitrogen, oxygen, -(CH)-, or -(CH_2)-, J is nitrogen, oxygen, or sulfur, and R_5 is independently selected from the group consisting of aminoC_{2-5}alkyl, guanidinoC_{2-5}alkyl, C_{1-4}alkylguanidinoC_{2-5}alkyl, diC_{1-4}alkylguanidino-C_{2-5}alkyl, amidinoC_{2-5}alkyl, C_{1-4}alkylamidinoC_{2-5}alkyl, diC_{1-4}alkylamidinoC_{2-5}alkyl, C_{1-3}alkoxy, Phenyl, substituted phenyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), benzyl, substituted benzyl (where the substituents on the benzyl are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), naphthyl, substituted naphthyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), bis-phenyl methyl, substituted bis-phenyl methyl (where the subsitituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridyl, subsitituted pyridyl, (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridylC_{1-4}alkyl, substituted pyridylC_{1}-$_4$alkyl (where the pyridine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyrimidylC_{1-4}alkyl,

substituted pyrimidylC_{1-4}alkyl (where the pyrimidine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy or nitro, carboxy, cyano, sulfuryl or hydroxyl), triazin-2-yl-C_{1-4}alkyl, substituted triazin-2-yl-C_{1-4}alkyl (where the triazine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), imidazoC_{1-4}alkyl, substituted imidazol C_{1-4}alkyl (where the imidazole substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, hydroxyl, or methyl), imidazolinylC_{1-4}alkyl, N-amidinopiperazinyl-N-C_{0-4}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, C_{1-5}dialkylaminoC_{2-5}alkyl, N-amidinopiperidinylC_{1-4}alkyl and 4-aminocyclohexylC_{0-2}alkyl..

Provided is a pharmaceutical composition comprising a compound of the following general formula (I):



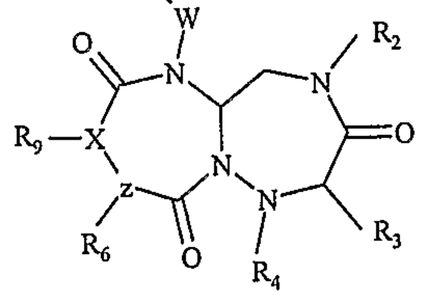
(I)

wherein A is –(C=O)-CHR_3-, or –(C=O), B is N-R_5- or -CHR_6-, D is –(C=O)–(CHR_7)- or –(C=O)-, E is –(ZR_8)- or (C=O), G is –(XR_9)$_n$-, -(CHR_{10})-(NR_6)-,-(C=O)-(XR_{12})-, -(or nothing)-, -(C=O)-, X-(C=O)-R_{13}, X-(C=O)-$NR_{13}R_{14}$, X-(SO_2)-R_{13}, or X-(C=O)-OR_{13}, W is –Y(C=O)-, -(C=O)NH-, -(SO_2)-, -CHR_{14}, (C=O)-(NR_{15})-, substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole, or nothing, Y is oxygen or sulfur, X and Z is independently nitrogen or CH, n=0 or 1; and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, and R_{15} are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers, salts, and prodrugs thereof, and a pharmaceutically acceptable carrier.

Also provided is a pharmaceutical composition comprising the compound of formula (I), wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, are R_{15} are independently

selected from the group consisting of aminoC_{2-5}alkyl, guanidinoC_{2-5}alkyl, C_{1-4}alkylguanidinoC_{2-5}alkyl, diC_{1-4}alkylguanidino-C_{2-5}alkyl, amidinoC_{2-5}alkyl, C_{1-4}alkylamidinoC_{2-5}alkyl, diC_{1-4}alkylamidinoC_{2-5}alkyl, C_{1-3}alkoxy, phenyl, substituted phenyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), benzyl, substituted benzyl (where the substituents on the benzyl are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), naphthyl, substituted naphthyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), bis-phenyl methyl, substituted bis-phenyl methyl (where the subsitituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridyl, substituted pyridyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridylC_{1-4}alkyl, substituted pyridylC_{1}-$_{4}$alkyl (where the pyridine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyrimidylC_{1-4}alkyl, substituted pyrimidylC_{1-4}alkyl (where the pyrimidine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy or nitro, carboxy, cyano, sulfuryl or hydroxyl), triazin-2-yl-C_{1-4}alkyl, substituted triazin-2-yl-C_{1-4}alkyl (where the triazine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), imidazoC_{1-4}alkyl, substituted imidazol C_{1-4}alkyl (where the imidazole substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, hydroxyl, or methyl), imidazolinylC_{1-4}alkyl, N-amidinopiperazinyl-N-C_{0-4}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, C_{1-5}dialkylaminoC_{2-5}alkyl,

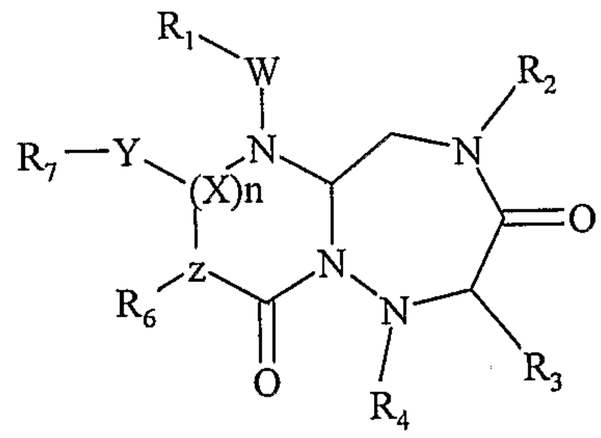
N-amidinopiperidinylC_{1-4}alkyl and 4-aminocyclohexylC_{0-2}alkyl. Further provided is a pharmaceutical composition of formula (I) wherein A is –(CHR_3)-(C=O)-, B is –(NR_4)-, D is (C=O)-, E is –(ZR_6)-, G is –(C=O)-(XR_9)-, and the compound has the following general formula (III):



(III)

wherein Z is nitrogen or CH (when Z is CH, the X is nitrogen).

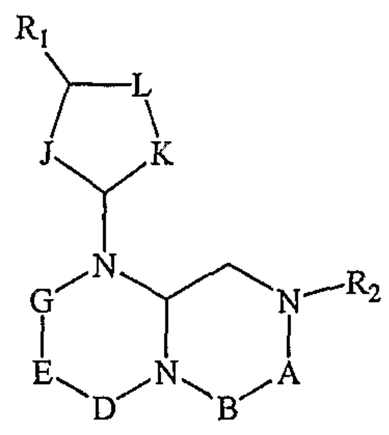
Also provided is a pharmaceutical composition of formula (I) wherein A is –O-CHR_3-, B is –NR_4-, D is –(C=O)-, E is –(ZR_6)-, Gi is $(XR_7)_n$-, the α-helix mimetic compounds have the following formula (IV):



(IV)

wherein R_1, R_2, R_4, R_6, R_7, R_8 W, X and n are as defined above, Y is –C=O, -(C=O)-O-, -(C=O)-NR_8, -SO_2-, or nothing, and Z is nitrogen or CH (when Z is nitrogen, then n is zero, and when Z is CH, then X is nitrogen and n is not zero). In a preferred embodiment, R_1, R_2, R_6, R_7, and R_8 represent the remainder of the compound, and R_4 is selected from an amino acid side chain moiety. In this case, R_6 or R_7 may be selected from an amino acid side chain moiety when Z and X are CH, respectively. Also provided is a pharmaceutical composition wherein A is –(C=O), B is –(CHR_6)-, D is –(C=O)-, E is –(ZR_8)-, and G is -(NH)- or -(CH_2)-, and W is a substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or

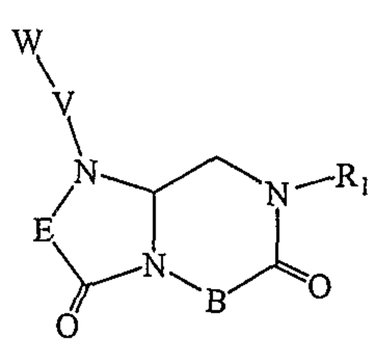
unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole, the α-helix mimetic compounds of this invention have the following formula (V):



(V)

wherein K is nitrogen, oxygen, or sulfur, L is nitrogen, oxygen, - (CH)-, or -(CH_2)-, J is nitrogen, oxygen, or sulfur, Z is nitrogen or CH, and R_1, R_2, R_6, R_8, and R_{13} are selected from an amino acid side chain moiety.

Further provided is a pharmaceutical composition comprising a compound having the general formula (VI):

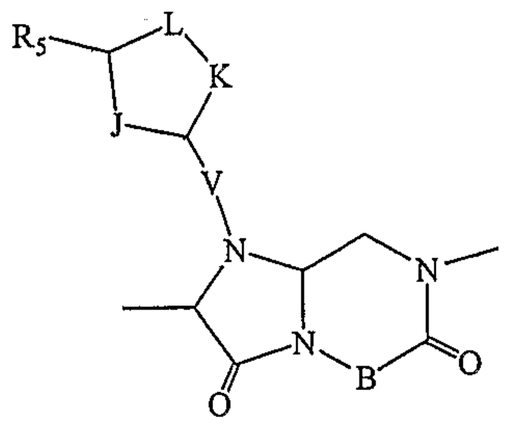


(VI)

wherein B is -(CHR_2)-, -(NR_2)-,, E is -(CHR_3)-, V is -(XR_4)- or nothing, W is -(C=O)-(XR_5R_6), -(SO_2)-, substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole, X is indepentently nitrogen, oxygen, or CH, and R_1, R_2, R_3, R_4, R_5 and R_6 are selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and solid support, and stereoisomers, salts and prodrugs thereof. In this pharmaceutical composition, wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, are R_{15} are independently selected from the group consisting of aminoC_{2-5}alkyl, guanidinoC_{2-5}alkyl, C_{1-4}alkylguanidinoC_{2-5}alkyl, diC_{1-4}alkylguanidino-C_{2-5}alkyl, amidinoC_{2-5}alkyl, C_{1-4}alkylamidinoC_{2-5}alkyl, diC_{1-4}alkylamidinoC_{2-5}alkyl, C_{1-3}alkoxy, phenyl, substituted phenyl

(where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), benzyl, substituted benzyl (where the substituents on the benzyl are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), naphthyl, substituted naphthyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), bis-phenyl methyl, substituted bis-phenyl methyl (where the subsitituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridyl, substituted pyridyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridylC_{1-4}alkyl, substituted pyridylC_{1}-$_{4}$alkyl (where the pyridine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyrimidylC_{1-4}alkyl, substituted pyrimidylC_{1-4}alkyl (where the pyrimidine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy or nitro, carboxy, cyano, sulfuryl or hydroxyl), triazin-2-yl-C_{1-4}alkyl, substituted triazin-2-yl-C_{1-4}alkyl (where the triazine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), imidazoC_{1-4}alkyl, substituted imidazol C_{1-4}alkyl (where the imidazole substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, hydroxyl, or methyl), imidazolinylC_{1-4}alkyl, N-amidinopiperazinyl-N-C_{0-4}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, C_{1-5}dialkylaminoC_{2-5}alkyl, N-amidinopiperidinylC_{1-4}alkyl and 4-aminocyclohexylC_{0-2}alkyl. In certain embodiments, wherein B is -(CH)-(CH_3), E is -(CH)-(CH_3), V is -(XR_4)- or nothing, and W is substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted

thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole, and X is independently introgen or CH, the compounds have the following general formula (VII):



(VII)

wherein K is nitrogen, oxygen, or sulfur, L is nitrogen, oxygen, -(CH)-, or -(CH_2)-, J is nitrogen, oxygen, or sulfur, and R_5 is independently selected from the group consisting of aminoC_{2-5}alkyl, guanidinoC_{2-5}alkyl, C_{1-4}alkylguanidinoC_{2-5}alkyl, diC_{1-4}alkylguanidino-C_{2-5}alkyl, amidinoC_{2-5}alkyl, C_{1-4}alkylamidinoC_{2-5}alkyl, diC_{1-4}alkylamidinoC_{2-5}alkyl, C_{1-3}alkoxy, Phenyl, substituted phenyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), benzyl, substituted benzyl (where the substituents on the benzyl are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), naphthyl, substituted naphthyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), bis-phenyl methyl, substituted bis-phenyl methyl (where the subsitituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridyl, subsitituted pyridyl, (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridylC_{1-4}alkyl, substituted pyridylC_{1-4}alkyl (where the pyridine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl,

C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyrimidylC_{1-4}alkyl, substituted pyrimidylC_{1-4}alkyl (where the pyrimidine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy or nitro, carboxy, cyano, sulfuryl or hydroxyl), triazin-2-yl-C_{1-4}alkyl, substituted triazin-2-yl-C_{1-4}alkyl (where the triazine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), imidazoC_{1-4}alkyl, substituted imidazol C_{1-4}alkyl (where the imidazole substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, hydroxyl, or methyl), imidazolinylC_{1-4}alkyl, N-amidinopiperazinyl-N-C_{0-4}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, C_{1-5}dialkylaminoC_{2-5}alkyl, N-amidinopiperidinylC_{1-4}alkyl and 4-aminocyclohexylC_{0-2}alkyl..

Provided is a compound selected from the group consisting of Compounds 1–2217, and pharmaceutical compositiona comprising at least one compound of Compounds 1-2217. The pharmaceutical composition may comprise an effective amount of the compound and a pharmaceutically acceptable carrier.

Compounds of the invention may be used in the preparation of a medicament for eradicating pathologic stem cells in cancer therapy. The stem cells are leukaemic stem cells, the stem cells may be derived from solid tumors, and the solid tumor may be derived from breast, brain, lung, colon, liver, and intestine.

Therapeutically effective amount of the compounds are provided, wherein the amount is sufficient to cause cell death or inhibit proliferation and cause differentiation of stem cells in solid tumors or leukemias. The compound according to the invention may be used in the preparation of a medicament for achieving the differentiation of pathologic stem cells by causing a switch from CBP/catenin to p300/catenin transcription in cancer therapy. The catenin may be β-catenin or γ/p120-catenin.

The compounds of the invention may inhibit CBP/catenin signaling in cancer stem cells, such as by inhibiting CBP/catenin signaling in cancer stem cells thereby inducing differentiation of cancer stem cells and making them more susceptible to apoptosis induced by at least one specific pathway inhibitor. The specific pathway may be selected from the group consisting of EGFR pathway; Herceptin, Abl or Kit tyrosine kinase pathway (Imantinib).

Also provided are compounds of the invention delivered to the subject orally, transdermally, intravenously, topically, by inhalation or rectally; delivery may be by sustained release. The pharmaceutical composition may be administered by a method selected from the group consisting of capsules, tablets, powders, granules, syrups, injectable fluids, creams, ointments, hydrophilic ointments, inhalable fluids, and suppositories.

Further provided are methods of treating a cancerous condition by administering at least one compound or pharmaceutical composition of the invention, wherein the cancerous condition is at least one selected from the group consisting of acute lymphocytic leukemia, acute nonlymphocytic leukemia, cancer of the adrenal cortex, bladder cancer, brain cancer, breast cancer, cervix cancer, chronic lymphocytic leukemia, chronic myelocytic leukemia, colorectal cancer, cutaneous T-cell lymphoma, endometrial cancer, esophageal cancer, Ewing's sarcoma, gallbladder cancer, hairy cell leukemia, head and neck cancer, Hodgkin's lymphoma, Kaposi's sarcoma, kidney cancer, liver cancer, lung cancer (small and/or non-small cell), malignant peritoneal effusion, malignant pleural effusion, melanoma, mesothelioma, multiple myeloma, neuroblastoma, non-Hodgkin's lymphoma, osteosarcoma, ovary cancer, ovary (germ cell) cancer, pancreatic cancer, penis cancer, prostate cancer, retinoblastoma, skin cancer, soft-tissue sarcoma, squamous cell carcinomas, stomach cancer, testicular cancer, thyroid cancer, trophoblastic neoplasms, cancer of the uterus, vaginal cancer, cancer of the vulva, and Wilm's tumor.

Further provided is a method for eliminating teratoma-forming stem cells prior to transplant into a mammalian subject, comprising incubating a stem cell culture with at least one compound of the invention, wherein the compound inhibits CBP-β-catenin interaction and thereby causes stem cell differentiation.

Also provided is a pharmaceutical composition used in the preparation of a medicament for eradicating pathologic stem cells in cancer therapy.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A-Z shows the chemical structures of compounds 1-200.

Figure 2A-2AD shows the chemical structures of compounds 201-400.

Figure 3A-3AC shows the chemical structures of compounds 401-600.

Figure 4A-4Y shows the chemical structures of compounds 601-800.

Figure 5A-5Y shows the chemical structures of compounds 801-1000.

Figure 6A-6Y shows the chemical structures of compounds 1001-1200.

Figure 7A-7Z shows the chemical structures of compounds 1201-1400.

Figure 8A-8AC shows the chemical structures of compounds 1401-1600.

Figure 9A-9AE shows the chemical structures of compounds 1601-1800.

Figure 10A-10AA shows the chemical structures of compounds 1801-2000.

Figure 11A-11AA shows the chemical structures of compounds 2001-2200.

Figure 12A-12C shows the chemical structures of diasteric and enantiomeric stereo isomers of Compounds 2203-2217.

Figure 13A-C. Figure 13A shows the structure of the compound ASN 06387747. Figure 13B shows the structure of the compound ICG001. Figure 13C shows the structures of ASN 06387747 (green) and ICG001 (red) superimposed. In accordance with an certain embodiments of the present invention, each compound has three pharmacophore rings. Distances measured from the center of each pharmacophore ring may be based on a conformation generated by flexible alignment calculations. As shown in this figure, the distance between F1 and F4 is approximately 9.6 Å, the distance between F1 and F6 is approximately 9.2 Å, and the distance between F4 and F6 is approximately 10.3 Å.

Figure 14A-C shows the levels of cytosolic and nuclear β-catenin as measured by immunoblotting (Figure 14A), and immunofluorescence microscopy (Figure 14B) as compared to drug sensitive counterparts. The increased nuclear β-catenin was blocked using a dominant negative TCF4 construct (Figure 14C).

Figure 15A-E shows that in MES-SA cells, Wnt3a but not Wnt5a increased luciferase activity, which was blocked by cotransfection with a dominant negative TCF4 construct (Figure 15A). Wnt5a conditioned media showed no enhancement of expression of the MDR-1/luciferase reporter construct (Figure 15B). MDR-1 wild-type HCT-116 cells and Hβ18 (KO/*) cells is shown in Figure 15C (MDR-1/luciferase activity) and Figure 15D (RT-PCR). Recruitment of TCF4 and β-catenin to the MDR-1 promoter is shown in Figure 15E.

Figure 16A-E shows the effect of ICG-001 on transcriptional regulation of the MDR-1 gene in MES-SA cells: MDR-1/luciferase activity (16A); MDR-1 protein expression by

immunofluorescence (16B) and immunoblotting (16C); message level by RT-PCR in MES-SA/Dx5 cells (16D) and K562 cells (16E).

Figure 17A-C shows MDR-1 transcriptional regulation in HCT116 cell lines: MDR-1/luciferase expression (17A); effect of ICG-001 (17B); and blocking occupancy of the MDR-1 promoter by CBP (17C).

Figure 18A-E shows the mRNA level of endogenous CBPP coactivator compared to p300 (Fig. 18A); the level of CBP (Fig. 18B); the association of β-catenin with p300 (Fig. 18C); the level of p300 (Fig. 18D); and the effect of p300 siRNA (Fig. 18E).

Figure 19A-F compares MES-SA/Dx5 cells with K562 cells: growth rate (19A, 19B); message levels for survivin and cyclin D1 (19C, 19D); and protein levels for survivin and cyclin D1 (19E, 19F).

Figure 20. RT-PCR shows an increased expression of Oct 4, hTert, Bmi-1 and ABCG-2 in MES-SA/Dx5 and K562 cells. Protein levels for Oct 4 and CD133 were increased in these cell lines.

Figure 21A-D. Figure 21A shows that ICG-001 in combination with the respective chemotherapeutic agent was more effective that the chemotherapeutic agent alone or ICG-001 alone in decreasing cell proliferation/viability. Figure 21B: ICG does not effect CD34+ normal hematopoeitic cells. Figure 21C: ICG-001* aka PRI-004 completely blocks colony formation at 500nM concentration. Figure 21D shows that combination treatment with ICG-001 and imatinib reduced colony forming units more than did either drug treatment alone.

Figure 22A-E. The effect of ICG-001 at different doses, with and without imatinib, is shown in Figure 22A and 22B. Figure 22C and D: RT-PCR analysis for Beta-Catenin, BMI-1, MDR-1, ABCG1, survivin and survivin splice variant delta Ex3in CD34+ cells isolated form bone marrow from an imatinib naïve CML blast crisis patient. Reference is CD34- cells from the same patient. Figure 22D: colony formation assay with CD34+ cells from an imatinib naïve blast crisis CML patient. Figure 22E: hematoxylin and eosin staining for CD34+ blasts treated with 0.5 μM imatinib alone (top) or in combination with ICG-001 5 μM.

Figure 23. Figure 23 shows the sensitivity of IGROV-1 (Fig. 23A), A2780 (Fig. 23B) and CP70 (Fig. 23C) to ICG-001, as tested in repeat experiments with different concentrations.

Figure 24. Figure 24 shows the sensitivity of ovarian cell lines A2780 and CP70 to ICG-001.

Figure 25. Figure 25 shows that increasing concentrations of compounds PRI-001, PRI-002, PRI-003, PRI-004, PRI-005, and PRI-006 were effective, as compared with ICG-001, on SW480 cells.

Figure 26. Figure 26 shows pluc-6270 expression (luciferase) in SW480 cells treated with varying concentrations of ICG-001, PRI-003, and PRI-004.

Figure 27 shows the chemical structures of Compounds 2203-2217.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to conformationally constrained compounds which mimic the secondary structure of α-helix regions of biological peptide and proteins (also referred to herein as "α-helix mimetics" and chemical libraries relating thereto, for the inhibition and/or eradication of cancer cells, particularly cancer cells having significant self-renewal potential, such as cancer stem cells.

Although there have been remarkable advances in the development of molecularly targeted drugs against cancer, for example imantinib (Gleevec) for the treatment of chronic phase CML, these agents in the end often fail. It is clear that new agents are needed to eradicate the cancer stem cells – literally the root of the problem.

Some parallels can be drawn between somatic stem cells and cancer stem cells (Pardal et al. Nat. Rev. Cancer. 3, 895, 2003). Both somatic stem cells and cancer stem cells are endowed with the ability to self renew and to differentiate. However, crucial differences exist. Whereas somatic stem cells differentiate to normal tissues, cancer stem cells differentiate aberrantly (Reya et al, Nature 2001, 414, 105-111). Despite the clonal origin of many cancers, most primary tumors display a notable degree of cellular heterogeneity. Thus, although modern chemotherapies kill a majority of the cells in a tumor, it is believed that the cancer stems cells often remain. ATP-binding cassette (ABC) multidrug resistance (MDR) transporters are believed to play important roles in protecting cancer stem cells from chemotherapy (Dean et al, Nat. Rev. Cancer 5, 275, 2005). The overexpression of P-glycoprotein (Pgp), energy-dependent efflux pumps of a variety of chemotherapeutic agents, resulting in multidrug resistant tumor cells was first demonstrated over two decades ago (Ling V. Cancer Chemother. Pharm. 40, S3-8, 1997; Sharom, F.J. J. Membr. Biol. 160, 161-175, 1997). MDR1 is a "TATA-less" gene, which belongs to a group of proteins whose genes lack a consensus TATA box within the proximal promoter region (Cornwell, M.M. Cell Growth Differ. 1, 607-615, 1990). Cells selected for their resistance to drugs often exhibit constitutive overexpression of *MDR1*. Additionally, efflux of Hoechst 33342 from normal murine hematopoietic cells identifies a "side population" (SP(+)) of negatively staining cells that are enriched for primitive progenitors (Feuring-Buske M., et al., Blood, 15:3882-9, 2001).

Mutations in the gene APC (adenomatous polyposis coli), which is a common early event in the majority of both hereditary and sporadic colorectal cancer, leads to the nuclear accumulation of β-catenin where it forms a complex with members of the T-cell factor (TCF)/lymphoid enhancer factor (LEF-1) family of transcription factors (8). To generate a transcriptionally active complex, β-catenin recruits the transcriptional coactivators Creb-Binding Protein (CBP) or its closely related homolog, p300 (9, 10) as well as other components of the basal transcription machinery. The MDR1 promoter contains several TCF/LEF binding sites between positions -275 and -1813. A link between APC mutations and enhanced MDR-1 expression via TCF/β-catenin driven transcription has been described (Yamada T., et al. Cancer Res. 60, 4761 -4766, 2000).

It is becoming apparent that despite their high degree of homology and similar patterns of expression, CBP and p300 play unique and distinct roles in gene regulation. Data disclosed herein were generated using siRNA, ChIP assay and the chemogenomic tool ICG-001, which selectively disrupts the ß-catenin/CBP interaction but not the corresponding ß-catenin/p300 interaction (Emami et al PNAS, 2004) thereby interfering with a subset of Wnt/ß-catenin regulated gene expression including *survivin* (Ma et al Oncogene 2005). The present disclosure demonstrates that TCF/β-catenin/CBP driven gene expression is essential for MDR-1 transcription. Furthermore, in the broader context, the disclosure shows that a CBP/β-catenin driven transcriptional cassette is critical for the expression of a "cancer stem cell-like" profile.

Embryonic stem cells can proliferate readily, *in vitro* and *in vivo*. *In vivo*, they can form teratocarcinoma-like tumors in adult mice if injected subcutaneously, intramuscularly, or into the testis. Thomson, J.A., et al., Science 282:1145-7:1998; Odorico, J.S., Stem Cells 19:193-204, 2001; Chung, Y., et al., Nature 439:216-9, 2006. Thus, hES cell-based therapy may lead to unwanted tumor formation.

To eliminate contamination of transplant material with residual undifferentiated ES cells, two different approaches have been reported. In one case, ES cell-specific expression in an engineered cell line of a compound that is toxic to undifferentiated ES cells is used and the culture conditions are modified to allow expression. This approach was used to eliminate mouse ES cells from a mixed cell population prior to transplant, Billon, N., et al., J Cell Sci, 115: 3657-65, 2002, and to express a suicide gene in the differentiated stem cells following transplantation, Schuldiner, M., J., Stem Cells 21:257-65, 2003. In another approach, the mixed cell population is treated with the ceramide analogue N-oleoyl serinol (S18) to selectively induce apoptosis of ES cells, Bieberich, E., et al., J Cell Biol. 167:723-34, 2004. In this case, subsequent teratocarcinoma formation following transplantation of mixed populations containing both ES

stem and ES-derived neural stem cells was prevented, Bieberich, E., et al., J Cell Biol 167:723-34, 2004.

The compounds and methods disclosed herein provide another option for eliminating teratoma-forming stem cells prior to transplant. An advantage is that the treatment used a small molecule that has no toxicity in humans at the doses that would be used.

The synthesis and identification of conformationally constrained α-helix mimetics and their application to diseases are discussed in Walensky, L.D. et al *Science* 305, 1466, 2004; and Klein, C. *Br. J. Cancer*. 91, 1415, 2004. This disclosure further demonstrates that in conjunction with other chemotherapeutic agents, targeting cancer stem cells by antagonizing the CBP/β-catenin interaction not only eliminates the cancer stem cells which are resistant to normal chemotherapy, but also has an additive effect on the killing of other cancer cells that are normally sensitive to chemotherapy, by decreasing the transcription of anti-apoptotic genes such as survivin.

As shown in detail in the examples, compounds disclosed herein ICG-001 reduced MDR-1/luciferase activity in a doxorubin-resistant ovarian sarcoma line MES-SA/Dx5 and in the CML derived cell line K562. In these cell lines, there is an increased level of cytosolic and nuclear β-catenin. This activated Wnt/β-catenin pathway leads in twin to activation of the multiding resistance gene (MDR-1) in the cell lines.

By reducing MDR-A/luciferase activity, ICG-001 was a candidate for tsting against patient CML cells. The examples further show that ICG-001 in combination with imatinib reduced total colony forming units in comparison with either drug alone. Morphological examination showed that the treated colonies had an increased state of differentiation.

In addition to being effective against ovarian sarcoma and CML cells, ICG-001 reduced stem cell markers in cells for other ovarian cell lines and melanoma B16 cells. ICG-100 and several other compounds, including PRI-001, PRI-002, PRI-003, PRI-004, PRI-005, and PRI-006 inhibited β-catenin interaction with CBP in SW480 cells, a cell line derived from intestinal carcinoma.

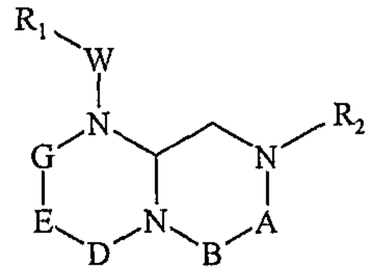
The wide range of cancers amenable to treatment with the compounds disclosed herein is consistent with β-catenin's role in several cancer-related events. These include expression of survivin, expression of MDR-1, and maintenance of a cancer stem cell population.

The compounds and methods herein are therefore suitable for treating cancers including but not limited to acute lymphocytic leukemia, acute nonlymphocytic leukemia, cancer of the adrenal cortex, bladder cancer, brain cancer, breast cancer, cervix cancer, chronic lymphocytic leukemia, chronic myelocytic leukemia, colorectal cancer, cutaneous T-cell lymphoma,

endometrial cancer, esophageal cancer, Ewing's sarcoma, gallbladder cancer, hairy cell leukemia, head and neck cancer, Hodgkin's lymphoma, Kaposi's sarcoma, kidney cancer, liver cancer, lung cancer (small and/or non-small cell), malignant peritoneal effusion, malignant pleural effusion, melanoma, mesothelioma, multiple myeloma, neuroblastoma, non-Hodgkin's lymphoma, osteosarcoma, ovary cancer, ovary (germ cell) cancer, pancreatic cancer, penis cancer, prostate cancer, retinoblastoma, skin cancer, soft-tissue sarcoma, squamous cell carcinomas, stomach cancer, testicular cancer, thyroid cancer, trophoblastic neoplasms, cancer of the uterus, vaginal cancer, cancer of the vulva, and Wilm's tumor.

The α-helix mimetic structures of the present invention are useful as bioactive agents, including (but not limited to) use as diagnostic, prophylactic and/or therapeutic agents. The α-helix mimetic structure libraries of this invention are useful in the identification of such bioactive agents. In the practice of the present invention, the libraries may contain from tens to hundreds to thousands (or greater) of individual α-helix structures (also referred to herein as "members").

In one aspect of the present invention, a α-helix mimetic structure is disclosed having the following formula (I):



(I)

wherein A is –(C=O)-CHR_3-, or –(C=O), B is N-R_5- or -CHR_6-, D is –(C=O)–(CHR_7)- or –(C=O)-, E is –(ZR_8)- or (C=O), G is –$(XR_9)_n$-, -(CHR_{10})-(NR_6)-,-(C=O)-(XR_{12})-, -(C=N-W-R_1)-, -(C=O)-, X-(C=O)-R_{13}, X-(C=O)-$NR_{13}R_{14}$, X-(SO_2)-R_{13}, or X-(C=O)-OR_{13}, W is –Y(C=O)-, -(C=O)NH-, -(SO_2)-, -CHR_{14}, (C=O)-(NR_{15})-, substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole, or nothing, Y is oxygen or sulfur, X and Z is independently nitrogen or CH, n=0 or 1; and R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, and R_{15} are the same or different and independently selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and a solid support, and stereoisomers thereof.

More specifically, R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 R_{10}, R_{11}, R_{12}, R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of aminoC_{2-5}alkyl, guanidineC_{2-5}alkyl,

C_{1-4}alkylguanidinoC_{2-5}alkyl, diC_{1-4}alkylguanidino-C_{2-5}alkyl, amidinoC_{2-5}alkyl, C_{1-4}alkylamidino C_{2-5}alkyl, diC_{1-4}alkylamidinoC_{2-5}alkyl, C_{1-3}alkoxy, phenyl, substituted phenyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), benzyl, substituted benzyl (where the substituents on the benzyl are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), naphthyl, substituted naphthyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), bisphenyl methyl, substituted bis-phenyl methyl (where the subsitituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridyl, substituted pyridyl (where the substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyridylC_{1-4}alkyl, substituted pyridyl$C1-_4$alkyl (where the pyridine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), pyrimidylC_{1-4}alkyl, substituted pyrimidylC_{1-4}alkyl (where the pyrimidine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), triazin-2-yl-C_{1-4}alkyl, substituted triazin-2-yl-C_{1-4}alkyl (where the triazine substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl or hydroxyl), imidazoC_{1-4}alkyl, substituted imidazol C_{1-4}alkyl (where the imidazole substituents are independently selected from one or more of amino, amidino, guanidino, hydrazino, amidrazonyl, C_{1-4}alkylamino, C_{1-4}dialkylamino, halogen, perfluoro C_{1-4}alkyl, C_{1-4}alkyl, C_{1-3}alkoxy, nitro, carboxy, cyano, sulfuryl, hydroxyl or methyl), imidazolinylCalkyl, N-amidinopiperazinyl-N-C_{0-4}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, hydroxyC_{2-5}alkyl, C_{1-5}alkylaminoC_{2-5}alkyl, C_{1-5}dialkylaminoC_{2-5}alkyl, N-amidinopiperidinylC_{1-4}alkyl and 4-aminocyclohexylC_{0-2}alkyl.

In one embodiment, R_1, R_2, R_6 of E, and R_7, R_8 and R_9 of G are the same or different and represent the remainder of the compound, and R_3 or A, R_4 of B or R_5 of D is selected from an amino acid side chain moiety or derivative thereof. As used herein, the term "remainder of the compound" means any moiety, agent, compound, support, molecule, linker, amino acid, peptide or protein covalently attached to the α-helix mimetic structure at R_1, R_2, R_5, R_6, R_7, R_8 and/or R_9 positions. This term also includes amino acid side chain moieties and derivatives thereof.

As used herein, the term "amino acid side chain moiety" represents any amino acid side chain moiety present in naturally occurring proteins including (but not limited to) the naturally occurring amino acid side chain moieties identified in Table 1. Other naturally occurring amino acid side chain moieties of this invention include (but are not limited to) the side chain moieties of 3,5-dibromotyrosine, 3,5-diiodotyrosine, hydroxylysine, γ-carboxyglutamate, phosphotyrosine and phosphoserine. In addition, glycosylated amino acid side chains may also be used in the practice of this invention, including (but not limited to) glycosylated threonine, serine and asparagine.

TABLE 1

Amino Acid Side Chain Moieties

Amino Acid Side Chain Moiety	Amino Acid
-H	Glycine
$-CH_3$	Alanine
$-CH(CH_3)_2$	Valine
$-CH_2CH(CH_3)_2$	Leucine
$-CH(CH_3)CH_2CH_3$	Isoleucine
$-(CH_2)_4NH_3^+$	Lysine
$-(CH_2)_3NHC(NH_2)NH_2^+$	Arginine
	Histidine
$-CH_2COO^-$	Aspartic acid
$-CH_2CH_2COO^-$	Glutamic acid
$-CH_2CONH_2$	Asparagine
$-CH_2CH_2CONH_2$	Glutamine

	Phenylalanine
	Tyrosine
	Tryptophan
$-CH_2SH$	Cysteine
$-CH_2CH_2SCH_3$	Methionine
$-CH_2OH$	Serine
$-CH(OH)CH_3$	Threonine
	Proline
	Hydroxyproline

In addition to naturally occurring amino acid side chain moieties, the amino acid side chain moieties of the present invention also include various derivatives thereof. As used herein, a "derivative" of an amino acid side chain moiety includes modifications and/or variations to naturally occurring amino acid side chain moieties. For example, the amino acid side chain moieties of alanine, valine, leucine, isoleucine and pheylalanine may generally be classified as lower chain alkyl, aryl, or arylalkyl moieties. Derivatives of amino acid side chain moieties include other straight chain or brached, cyclic or noncyclic, substitutes or unsubstituted, saturated or unsaturated lower chain alkyl, aryl or arylalkyl moieties.

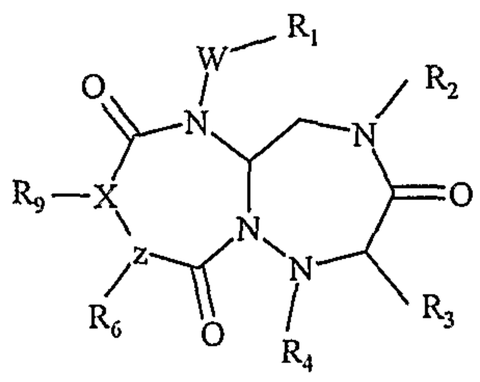
As used herein, "lower chain alkyl moieties" contain from 1-12 carbon atoms, "lower chain aryl moieties" contain from 6-12 carbon atoms and "lower chain aralkyl moieties" contain from 7-12 carbon atoms. Thus, in one embodiment, the amino acid side chain derivative is selected from a C_{1-12} alkyl, a C_{6-12} aryl and a C_{7-12} arylalkyl, and in a more preferred embodiment, from a C_{1-7} alkyl, a C_{6-10} aryl and a C_{7-11} arylalkyl.

Amino side chain derivatives of this invention further include substituted derivatives of lower chain alkyl, aryl, and arylalkyl moieties, wherein the substituents is selected from (but are not limited to) one or more of the following chemical moieties: -OH, -OR, -COOH, -COOR, $-CONH_2$, $-NH_2$, -NHR, -NRR, -SH, -SR, $-SO_2R$, $-SO_2H$, -SOR and halogen (including F, Cl, Br and I), wherein each occurrence of R is independently selected from straight chain or branched, cyclic or noncyclic, substituted or unsubstituted, saturated or unsaturated lower chain alkyl, aryl, and aralkyl moieties. Moreover, cyclic lower chain alkyl, aryl and arylalkyl moieties of this invention include naphthalene, as well as heterocyclic compounds such as thiophene, pyrrole, furan, imidazole, oxazole, thiazole, pyrazole, 3-pyrroline, pyrrolidine, pyridine, pyrimidine, purine, quinoline, isoquinoline and carbazole. Amino acid side chain derivatives further include heteroalkyl derivatives of the alkyl portion of the lower chain alkyl and aralkyl moieties, including (but not limited to) alkyl and aralkyl phosphonates and silanes.

Representative R_1, R_2, R_5, R_6, R_7, R_8 and R_9 moieties specifically include (but are not limited to) –OH, -OR, -COR, -COOR, $-CONH_2$, -CONR, -CONRR, $-NH_2$, -NHR, -NRR, $-SO_2R$ and –COSR, wherein each occurrence of R is as defined above.

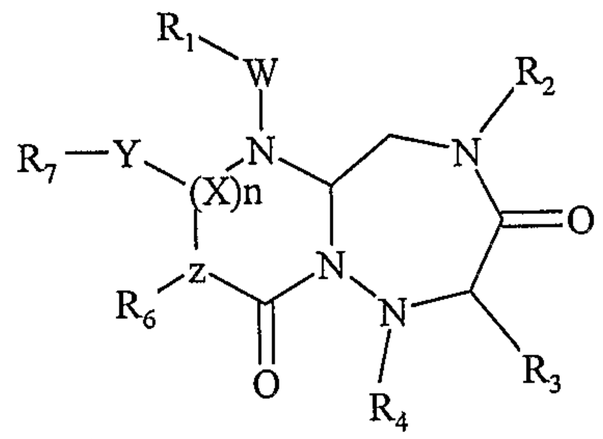
In a further embodiment, and in addition to being an amino acid side chain moiety or derivative thereof (or the remainder of the compound in the case of R_1, R_2, R_5, R_6, R_7, R_8 and R_9), R_1, R_2, R_5, R_6, R_7, R_8 or R_9 may be a linker facilitating the linkage of the compound to another moiety or compound. For example, the compounds of this invention may be linked to one or more known compounds, such as biotin, for use in diagnostic or screening assay. Furthermore, R_1, R_2, R_5, R_6, R_7, R_8 or R_9 may be a linker joining the compound to a solid support (such as a support used in solid phase peptide synthesis) or alternatively, may be the support itself. In this embodiment, linkage to another moiety or compound, or to a solid support, is preferable at the R_1, R_2, R_7 or R_8 position, and more preferably at the R_1 or R_2 position.

In the embodiment wherein A is $-(C=O)-CHR_3-$, B is $-N-R_4$, D is $-(C=O)-$, E is $-(ZR_6)-$, G is $-(C=O)-(XR_9)-$, the α-helix mimetic compounds of this invention have the following general formula (III):



(III)

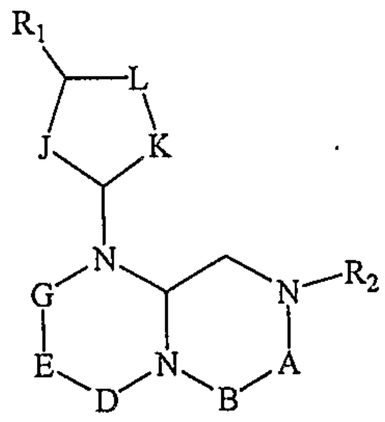
wherein R_1, R_2, R_4, R_6, R_7, R_8, W and X are as defined above, Y is –C=O, -(C=O)-O-, -(C=O)-NR_8, -SO_2-, or nothing, and Z is nitrogen or CH (when Z is CH, then X is nitrogen). In a preferred embodiment, R_1, R_2, R_6, R_7 and R_8 represent the remainder of the compound, and R_4 is selected from an amino acid side chain moiety. In a more specific embodiment wherein A is –O-CHR_3-, B is –NR_4-, D is –(C=O)-, E is –(ZR_6)-, Gi is $(XR_7)_n$-, the α-helix mimetic compounds of this invention have the following formula (IV):



(IV)

wherein R_1, R_2, R_4, R_6, R_7, W, X and n are as defined above, and Z is nitrogen or CH (when Z is nitrogen, then n is zero, and when Z is CH, then X is nitrogen and n is not zero). In a preferred embodiment, R_1, R_2, R_6, and R_7 represent the remainder of the compound, and R_4 is selected from an amino acid side chain moiety. In this case, R_6 or R_7 may be selected from an amino acid side chain moiety when Z and X are CH, respectively.

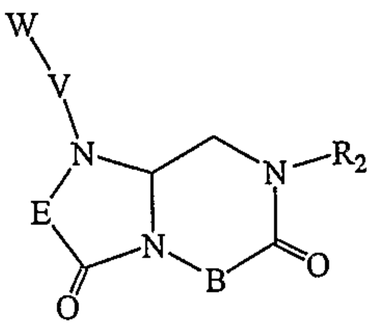
In the embodiment of structure (I) wherein A is –(C=O), B is –(CHR_6)-, D is –(C=O)-, E is –(ZR_8)-, and G is -(NH)- or -(CH_2)-, and W is a substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole, the α-helix mimetic compounds of this invention have the following general formula (V):



(V)

wherein K is nitrogen, oxygen, or sulfur, L is nitrogen, oxygen, -(CH)-, or -(CH_2)-, J is nitrogen, oxygen, or sulfur, Z is nitrogen or CH, and R_1, R_2, R_6, R_8, and R_{13} are selected from an amino acid side chain moiety.

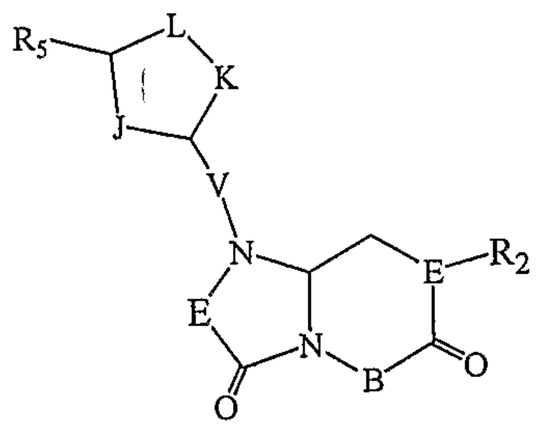
Alternative embodiments of the invention relate to compounds having the general formula (VI):



(VI)

wherein B is -(CHR_3)-, -(NR_3)-,, E is -(CHR_4)-, V is -(XR_5)- or nothing, W is -(C=O)-(XR_6R_7), -(SO_2)-, substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole, X is indepentently nitrogen, oxygen, or CH, and R_1, R_2, R_3, R_4, R_5, R_6, and R_7 are selected from an amino acid side chain moiety or derivative thereof, the remainder of the molecule, a linker and solid support, and stereoisomers thereof.

In the embodiments of formula (VI) wherein V is -(XR_5)- or nothing, and W is substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole, and X is independently introgen or CH, the compounds have the following general formula (VII):



(VII)

wherein K is nitrogen, oxygen, or sulfur, L is nitrogen, oxygen, -(CH)-, or -(CH_2)-, J is nitrogen, oxygen, or sulfur, and R_2 and R_5 are defined as described above.

In preferred embodiments of the invention, R_2 in structures I through VII comprises an aromatic ring substituent such as a phenyl or naphthyl group that is substituted with a basic moiety such a primary or secondary amine. The aromatic ring substituent may also be a

heterocycle, such as a purine or indole. Some embodiments of the invention also provide for aromatic ring substituents that may be substituted with one or two halogen moieties.

A feature of many α-helix mimetic compounds is that they provide a scaffolding that places three hydrophobic functional groups, which may also be referred to as pharmacophore rings, in a specific, spatially-defined orientation referred to as an "optimized chemical space". The optimized chemical space may be triangular, with the centers of three functional groups forming the three points of the triangle. An example of an optimized chemical space is one in which the lengths of the three sides of the triangle are around 9.6 ± 0.5 Angstroms (symbolized hereafter by "Å"), 9.2 ± 0.5 Å, and 10.3± 0.5 Å. Figure 13 depicts two superimposed structures having three such pharmacophore rings forming a triangle in space. A number of different compounds exhibit such an optimized chemical space, and may be considered to be within the scope of the invention.

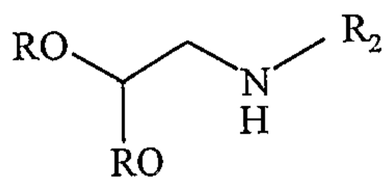
The compounds of general formula (I) of the present invention have one or more asymmetric carbons depending on it's substituents. For example, where the compounds of general formula (I) contains one or more asymmetric carbons, two kinds of optical isomers exist when the number of asymmetric carbon is 1, and when the number of asymmetric carbon is 2, four kinds of optical isomers and two kinds of diastereomers exist. Pure stereoisomers including opticalisomers and diastereoisomers, any mixture, racemates and the like of stereoisomers all fall within the scope of the present invention. Mixtures such as racemates may sometimes be preferred from viewpoint of easiness for manufacture.

When the compounds of general formula (I) of the present invention contains a basic functional group such as amino group, or when the compounds of general formula (I) of the present invention contains an aromatic ring which itself has properties of base (e.g., pyridine ring), the compound can be converted into a pharmaceutically acceptable salt (e.g., salt with inorganic acids such as hydrochloric acid and sulfuric acid, or salts with organic acids such as acetic acid and citric acid) by a known means. When the compounds of general formula (I) of the present invention contains an acidic functional group such as carboxyl group or phenolic hydroxyl group, the compound can be converted into pharmaceutically acceptable salt (e.g., inorganic salts with sodium, ammonia and the like, or organic salts with triethylamine and the like) by a known means. When the compounds of general formula (I) of the present invention contains a prodrugable functional group such as phenolic hydroxyl group, the compound can be converted into prodrug (e.g., acetylate or phosphonate) by a known means. Any pharmaceutically acceptable salt and prodrug all fall within the scope of the present invention.

The various compounds disclosed by the present invention can be purified by known methods such as recrystallization, and variety of chromatography techniques (column chromatography, flash column chromatography, thin layer chromatography, high performance liquid chromatography).

The α-helix mimetic structures of the present invention may be prepared by utilizing appropriate starting component molecules (hereinafter referred to as "component pieces"). Briefly, in the synthesis of α-helix mimetic structures having formula (II), first and second component pieces are coupled to form a combined first-second intermediate, if necessary, third and/or fourth component pieces are coupled to form a combined third-fourth intermediate (or, if commercially available, a single third intermediate may be used), the combined first-second intermediate and third-fourth intermediate (or third intermediate) are then coupled to provide a first-second-third-fourth intermediate (or first-second-third intermediate) which is cyclized to yield the α-helix mimetic structures of this invention. Alternatively, the α-helix mimetic structures of formula (II) may be prepared by sequential coupling of the individual component pieces either stepwise in solution or by solid phase synthesis as commonly practiced in solid phase peptide synthesis.

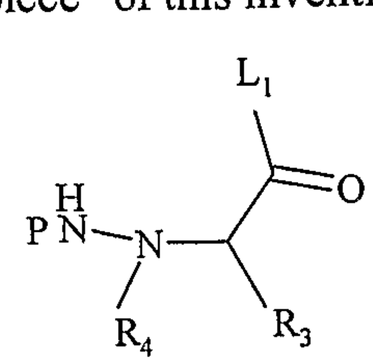
Within the context of the present invention, a "first component piece" has the following formula S1



(S1)

Wherein R_2 as defined above, and R is a protective group suitable for use in peptide synthesis. Suitable R groups include alkyl groups and, in a preferred embodiment, R is a methyl group. Such first component pieces may be readily synthesized by reductive amination or substitution reaction by displacement of H_2N-R_2 from $CH(OR)_2$-CHO or $CH(OR)_2$-CH_2-Hal (wherein Hal means a halogen atom).

A "second component piece" of this invention has the following formula S2:



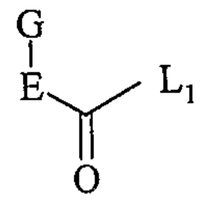
(S2)

Where L_1 is carboxyl-activation group such as halogen atom, R_3, R_4 is as defined above, and P is an amino protective group suitable for use in peptide synthesis. Preferred protective groups include t-butyl dimethylsilyl (TBDMS), t-Butyloxycarbonyl (BOC), Methylosycarbonyl (MOC),

9H-Fluorenylmethyloxycarbonyl (FMOC), and allyloxycarbonyl (Alloc). When L is –C(O)NHR, -NHR may be an carboxyl protective group. N-Protected amino acids are commercially available. For example, FMOC amino acids are available for a variety of sources. The conversion of these compounds to the second component pieces of this invention may be readily achieved by activation of the carboxylic acid group of the N-proctected amino acid. Suitable activated carboxylic acid groups include acid halides where X is a halide such as chloride or bromide, acid anhydrides where X is an acyl group such as acetyl, reactive esters such as an N-hydroxysuccinimide esters and pentafluorophenyl esters, and other activated intermediates such as the active intermediate formed in a coupling reaction using a carbodiimide such as dicyclohexylcarbodiimide (DCC).

In the case of the azido derivative of an amino acid serving as the second component piece, such compounds may be prepared from the corresponding amino acid by the reaction disclosed by Zaloom et al. (*J. Org. Chem.* 46:5173-76, 1981).

A "third component piece" of this invention has the following formula S3:

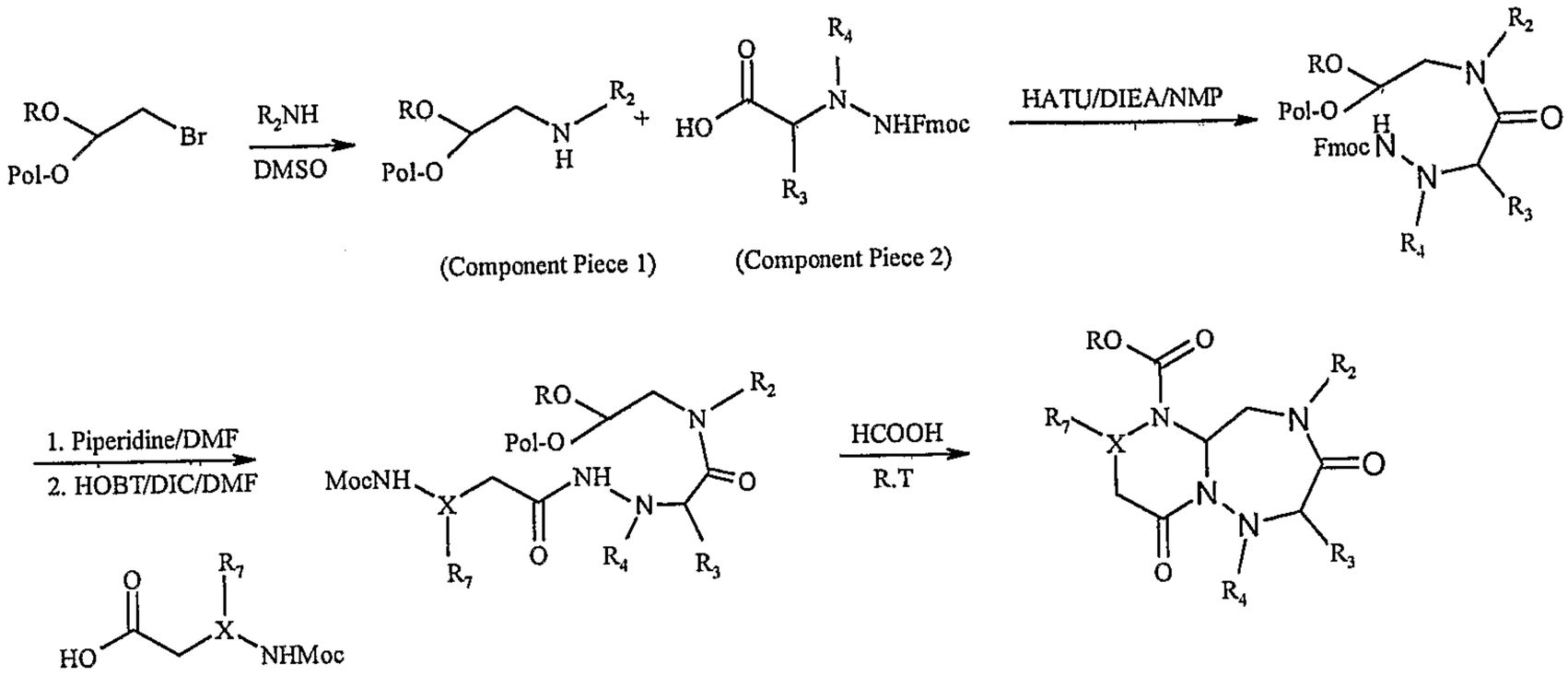


(S3)

where G, E, and L_1 are as defined above. Suitable third component pieces are commercially available from a variety of sources or can be prepared by known methods in organic chemistry.

More specifically, the α-helix mimetic structures of this invention of formula (II) are synthesized by reacting a first component piece with a second component piece to yield a combined first-second intermediate, followed by either reacting the combined first-second intermediate with third component pieces sequentially to provide a combined first-second-third-fourth intermediate, and the cyclizing this intermediate to yield the α-helix mimetic structure.

The general synthesis of an α-helix having structure I' may be carried out by the following technique. A first component piece 1 is coupled with a second component piece 2 by using coupling reagent such as phosgene to yield, after N-deprotection, a combined first-second intermediate 1-2 as illustrated below:



wherein R_1, R_2, R_4, R_7.Fmoc, Moc and X are as defined above, and Pol represents a polymeric support.

The synthesis of representative component pieces of this invention are described in the Examples.

The α-helix mimetic structures of formula (III) and (IV) may be made by techniques analogous to the modular component synthesis disclosed above, but with appropriate modifications to the component pieces.

As mentioned above, the reverse-turn mimetics of USP 6,013,458 to Kahn, et al. are useful as bioactive agents, such as diagnostic, prophylactic, and therapeutic agents. The opiate receptor binding activity of representative reverse-turn mimetics is presented in Example 9 of said USP 6,013,458, wherein the reverse-turn mimetics of this invention were found to effectively inhibit the binding of a radiolabeled enkephalin derivative to the δ and μ opiate receptors, of which data demonstrates the utility of these reverse-turn mimetics as receptor agonists and as potential analgesic agents.

The α-helix mimetic structures of the present invention will be useful as bioactive agents, such as diagnostic, prophylactic, and therapeutic agents.

Therefore, since the compounds according to the present invention are of α-helix mimetic structures, it may be useful for modulating a cell signaling transcription factor related peptides in a warm-blooded animal, comprising administering to the animal an effective amount of the compound of formula (I). Besides being useful for human treatment, the compounds of

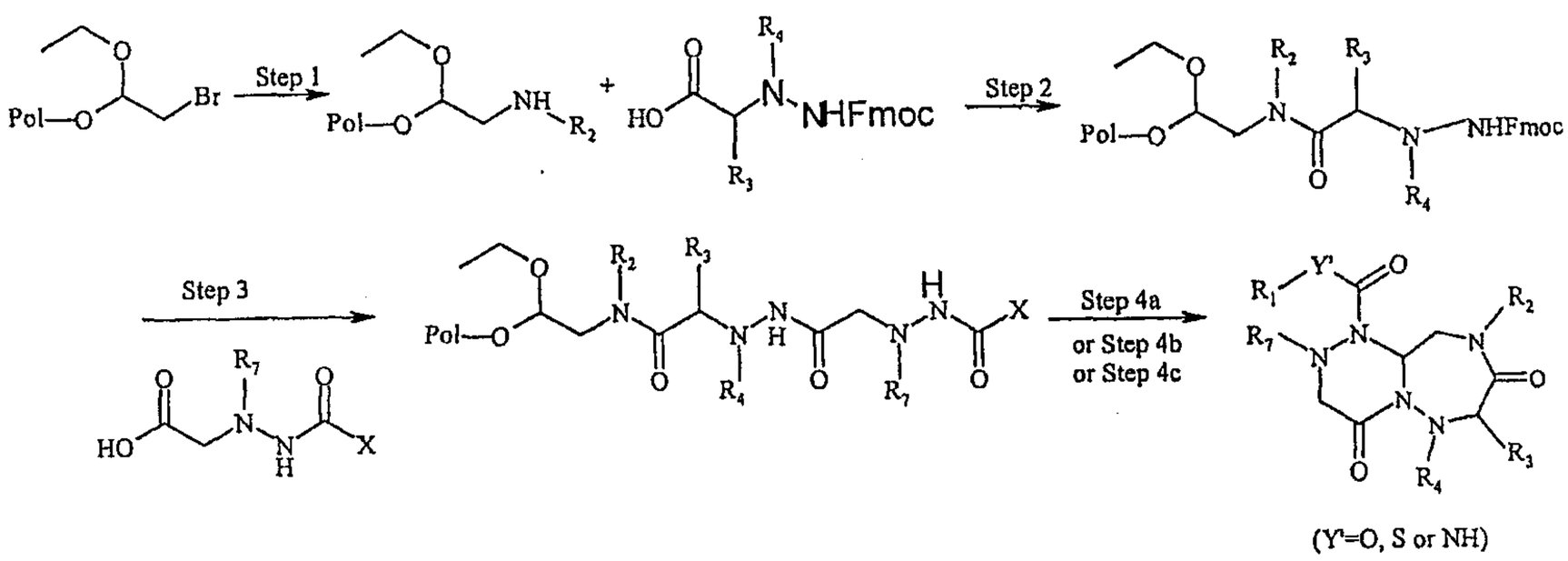
the present invention are also useful for veterinary treatment of mammals, including companion animals and farm animals, such as, but not limited to dogs, cats, horses, cows, sheep, and pigs.

Further, the α-helix mimetic structures of the present invention may also be effective for inhibiting transcription factor/coactivator and transcription factor corepressor interactions.

In another aspect of this invention, libraries containing α-helix mimetic structures of the present invention are disclosed. Once assembled, the libraries of the present invention may be screened to identify individual members having bioactivity. Such screening of the libraries for bioactive members may involve, for example, evaluating the binding activity of the members of the library or evaluating the effect the library members have on a functional assay. Screening is normally accomplished by contacting the library members (or a subset of library members) with a target of interest, such as, for example, an antibody, enzyme, receptor or cell line. Library members, which are capable of interacting with the target of interest, are referred to herein as "bioactive library members" or "bioactive mimetics". For example, a bioactive mimetic may be a library member which is capable of binding to an antibody or receptor, which is capable of inhibiting an enzyme, or which is capable of eliciting or antagonizing a functional response associated, for example, with a cell line. In other words, the screening of the libraries of the present invention determines which library members are capable of interacting with one or more biological targets of interest. Furthermore, when interaction does occur, the bioactive mimetic (or mimetics) may then be identified from the library members. The identification of a single (or limited number) of bioactive mimetic(s) from the library yields α-helix mimetic structures which are themselves biologically active, and thus useful as diagnostic, prophylactic or therapeutic agents, and may further be used to significantly advance identification of lead compounds in these fields.

In another aspect of this invention, methods for constructing the libraries are disclosed. Traditional combinatorial chemistry techniques (see, e.g., Gallop et al., *J. Med. Chem.* 37:1233-1251, 1994) permit a vast number of compounds to be rapidly prepared by the sequential combination of reagents to a basic molecular scaffold. Combinatorial techniques have been used to construct peptide libraries derived from the naturally occurring amino acids. For example, by taking 20 mixtures of 20 suitably protected and different amino acids and coupling each with one of the 20 amino acids, a library of 400 (i.e., 20^2) dipeptides is created. Repeating the procedure seven times results in the preparation of a peptide library comprised of about 26 billion (i.e., 20^8) octapeptides.

Specifically, synthesis of the peptide mimetics of the library of the present invention may be accomplished using known peptide synthesis techniques, for example, the General Scheme of [4,4,0] α-helix Mimetic Library as follows:



Synthesis of the peptide mimetics of the libraries of the present invention was accomplished using a FlexChem™ Reactor Block which has 96 well plates by known techniques. In the above scheme 'Pol' represents a bromoacetal resin (Advanced ChemTech) and detailed procedure is illustrated below.

Step 1

A bromoacetal resin (37mg, 0.98 mmol/g) and a solution of R_2-amine in DMSO (1.4mL) were placed in a Robbins block (FlexChem) having 96 well plates. The reaction mixture was shaken at 60°C using a rotating oven [Robbins Scientific] for 12 hours. The resin was washed with DMF, MeOH, and then DCM

Step 2

A solution of available Fmoc hydrazine Amino Acids (4 equiv.), PyBop (4 equiv.), HOAt (4 equiv.), and DIEA (12 equiv.) in DMF was added to the resin. After the reaction mixture was shaken for 12 hours at room temperature, the resin was washed with DMF, MeOH, and then DCM.

Step 3

To the resin swollen by DMF before reaction was added 25% piperidine in DMF and the reaction mixture was shaken for 30 min at room temperature. This deprotection step was

repeated again and the resin was washed with DMF, Methanol, and then DCM. A solution of hydrazine acid (4 equiv.), HOBt (4 equiv.), and DIC (4 equiv.) in DMF was added to the resin and the reaction mixture was shaken for 12 hours at room temperature. The resin was washed with DMF, MeOH, and then DCM.

Step 4a (Where hydrazine acid is MOC carbamate)

The resin obtained in Step 3 was treated with formic acid (1.2 mL each well) for 18 hours at room temperature. After the resin was removed by filtration, the filtrate was condensed under a reduced pressure using SpeedVac™ [SAVANT] to give the product as oil. The product was diluted with 50% water/acetonitrile and then lyophilized after freezing.

Step 4b (Where Fmoc hydrazine acid is used to make Urea through isocynate)

To the resin swollen by DMF before reaction was added 25% piperidine in DMF and the reaction mixture was shaken for 30 min at room temperature. This deprotection step was repeated again and the resin was washed with DMF, Methanol, then DCM. To the resin swollen by DCM before reaction was added isocynate (5 equiv.) in DCM. After the reaction mixture was shaken for 12 hours at room temperature the resin was washed with DMF, MeOH, then DCM. The resin was treated with formic acid (1.2 mL each well) for 18 hours at room temperature. After the resin was removed by filtration, the filtrate was condensed under a reduced pressure using SpeedVac [SAVANT] to give the product as oil. The product was diluted with 50% water/acetonitrile and then lyophilized after freezing.

Step 4c (Where Fmoc-hydrazine acid is used to make Urea through active carbamate)

To the resin swollen by DMF before reaction was added 25% piperidine in DMF and the reaction mixture was shaken for 30 min at room temperature. This deprotection step was repeated again and the resin was washed with DMF, MeOH, and then DCM. To the resin swollen by DCM before reaction was added p-nitrophenyl chloroformate (5 equiv.) and diisopropyl ethylamine (5 equiv.) in DCM. After the reaction mixture was shaken for 12 hours at room temperature, the resin was washed with DMF, MeOH, and then DCM. To the resin was added primary amines in DCM for 12 hours at room temperature and the resin was washed with DMF, MeOH, and then DCM. After reaction the resin was treated with formic acid (1.2 mL each well) for 18 hours at room temperature. After the resin was removed by filtration, the filtrate was condensed under a reduced pressure using SpeedVac [SAVANT] to give the product as oil. The product was diluted with 50% water/acetonitrile and then lyophilized after freezing.

To generate these block libraries the key intermediate hydrazine acids were synthesized according to the procedure illustrated in the examples.

Administration and Dosage

The inventive compounds may be administered by any means known to one of ordinary skill in the art. For example, the inventive compounds may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally, or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intraperitoneal, intrathecal, intraventricular, intrasternal, intracranial, and intraosseous injection and infusion techniques. The exact administration protocol will vary depending upon various factors including the age, body weight, general health, gender and diet of the patient; the determination of specific administration procedures would be routine to an one of ordinary skill in the art.

The inventive compounds may be administered by a single dose, multiple discrete doses or continuous infusion. Pump means, particularly subcutaneous pump means, are useful for continuous infusion.

Dose levels on the order of about 0.001 mg/kg/d to about 100 mg/kg/d of an inventive compound are useful for the inventive methods. In one embodiment, the dose level is about 0.1 mg/kg/d to about 100 mg/kg/d. In another embodiment, the dose level is about 1 mg/kg/d to about 10 mg/kg/d. The specific dose level for any particular patient will vary depending upon various factors, including the activity and the possible toxicity of the specific compound employed; the age, body weight, general health, sex and diet of the patient; the time of administration; the rate of excretion; the drug combination; the severity of the disease; and the form of administration. Typically, in vitro dosage-effect results provide useful guidance on the proper doses for patient administration. Studies in animal models are also helpful. The considerations for determining the proper dose levels are well known in the art and within the skills of an ordinary physician.

Any known administration regimen for regulating the timing and sequence of drug delivery may be used and repeated as necessary to effect treatment in the inventive methods. The regimen may include pretreatment and/or co-administration with additional therapeutic agent(s).

The inventive compounds can be administered alone or in combination with one or more additional therapeutic agent(s) for simultaneous, separate, or sequential use. Examples of an additional therapeutic agent include, without limitation, compounds of this invention; steroids

(e.g., hydrocortisones such as methylprednisolone); anti-inflammatory or anti-immune drug, such as methotrexate, azathioprine, cyclophosphamide or cyclosporin A; interferon-β; antibodies, such as anti-CD4 antibodies; chemotherapeutic agents; immunotherapeutic compositions; electromagnetic radiosensitizers; and morphine. The inventive compounds may be co-administered with one or more additional therapeutic agent(s) either (i) together in a single formulation, or (ii) separately in individual formulations designed for optimal release rates of their respective active agent.

The pharmaceutical composition may comprise at least one compound disclosed herein, in combination with at least one cancer chemotherapeutic wherein said cancer chemotherapeutic works by a mechanism other than blocking CPB/catenin interaction. The cancer therapeutic can be selected from the group consisting of, but not limited to, cis-platinum, retinoic acid, histone deacetylase (HDAC) inhibitors such as Vorinostat (SAHA), and imatinib.

The pharmaceutical composition may comprise at least one pathway-specific inhibitor such as Her1/Her2 inhibitors; Notch inhibitors; Hedgehog inhibitors; EGF inhibitors; and PI3K pathway inhibitors. The Notch inhibitor can be a gamma secretase inhibitor, the Hedgehog inhibitor can be cyclopamine, the EGF inhibitor can be Iressa, and the PI3K pathway inhibitor can be rapamycin.

Pharmaceutical Compositions

This invention further provides a pharmaceutical composition comprising: (i) an effective amount of a compound of formula I, II or III; and (ii) a pharmaceutically acceptable carrier.

The inventive pharmaceutical composition may comprise one or more additional pharmaceutically acceptable ingredient(s), including without limitation one or more wetting agent(s), buffering agent(s), suspending agent(s), lubricating agent(s), emulsifier(s), disintegrant(s), absorbent(s), preservative(s), surfactant(s), colorant(s), flavorant(s), sweetener(s) and additional therapeutic agent(s).

The inventive pharmaceutical composition may be formulated into solid or liquid form for the following: (1) oral administration as, for example, a drench (aqueous or non-aqueous solution or suspension), tablet (for example, targeted for buccal, sublingual or systemic absorption), bolus, powder, granule, paste for application to the tongue, hard gelatin capsule, soft gelatin capsule, mouth spray, emulsion and microemulsion; (2) parenteral administration by, for example, subcutaneous, intramuscular, intravenous or epidural injection as, for example, a

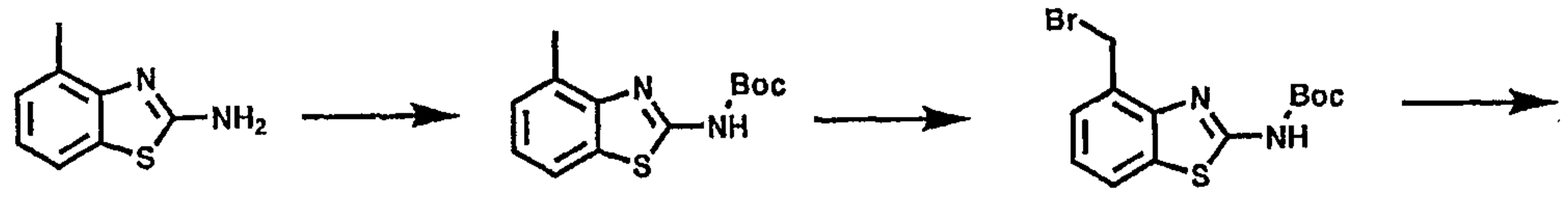
sterile solution, suspension or sustained-release formulation; (3) topical application as, for example, a cream, ointment, or controlled-release patch or spray applied to the skin; (4) intravaginal or intrarectal administration as, for example, a pessary, cream or foam; (5) sublingual administration; (6) ocular administration; (7) transdermal administration; or (8) nasal administration.

It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application.

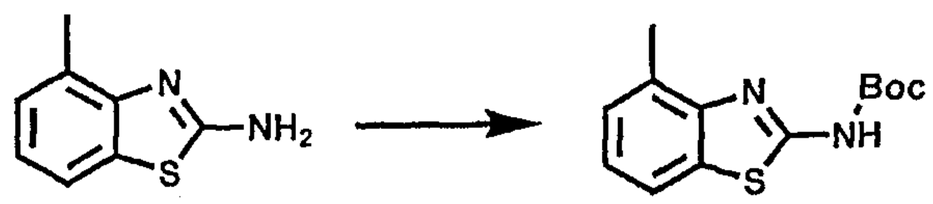
EXAMPLE 1

INTERMEDIATE SYNTHESIS

Synthesis of 2-Boc-amino-benzothiazoleyl-4-methylamine

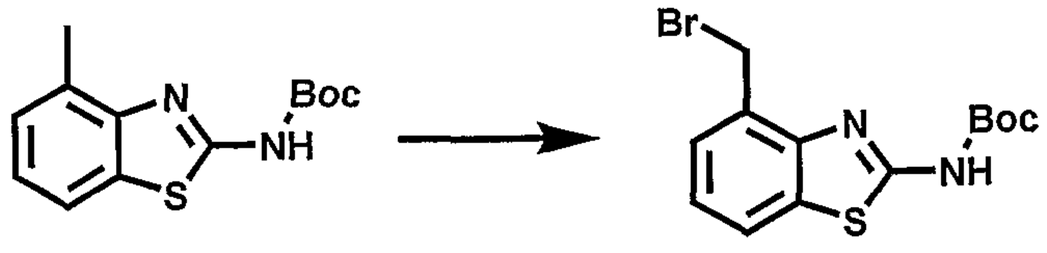


Step-1 (2-Boc-amino-4-methyl benzothiazole)



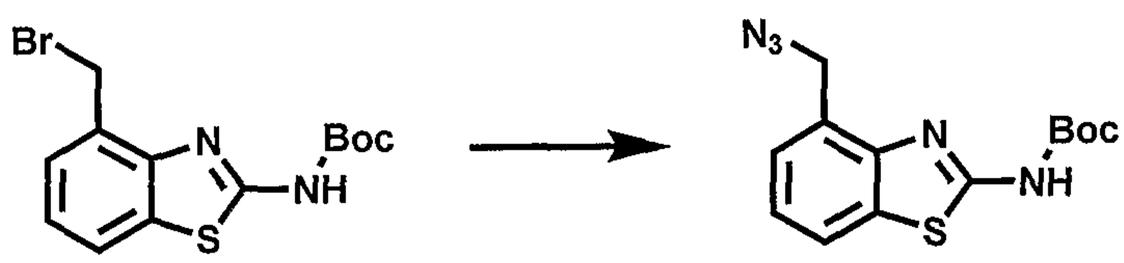
A solution of 2-Amino-4-methyl benzothiazole (25.0 g, 152 mmol) in 456 mL of dry THF was treated with Et_3N (42 mL, 300 mmol), $(Boc)_2O$ (40.0 g, 183 mmol) and DMAP (3.7 g, 30 mmol) at 20 °C and stirred at 30 °C for 12 h. The resulting solution was concentrated *in vacuo*, diluted with EtOAc (200 mL) and filtered through a glass filter (Celite™) washing with EtOAc (200 mL). The filtrate was washed with $NaHCO_3$ (saturated aqueous solution, 100 mL) and NaCl (saturated aqueous solution, 100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a silica gel plug (flash column chromathography) eluting with toluene:Et_2O=15:1 to 8:1 to afford 2-Boc-amino-4-methyl benzothiazole as a colorless oil (41.4 g, quant.) R_f=0.48 (toluene:Et_2O=10:1); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.75 (1H, br s), 7.61 (1H, d, J = 7.8 Hz), 7.19 (3H, m), 2.64 (3H, s), 1.47 (9H, s).

Step-2 (2-Boc-amino-4-bromomethyl benzothiazole)



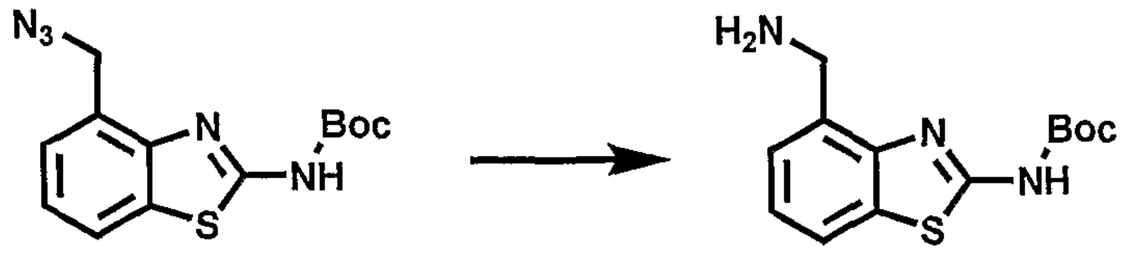
A solution of 2-Boc-amino-4-methyl benzothiazole (152 mmol) in 456 mL of dry CCl4 was treated with NBS (27.1 g, 152 mmol) and AIBN (3.2 g, 20 mmol) at 20 °C and stirred at 80 °C for 3.5 h. The mixture was retreated with NBS (7.2 g, 41 mmol) and AIBN (0.84 g, 5.1 mmol) at 20 °C and stirred at 80 °C for 11 hr. The resulting mixture was cooled to 20 °C and filtered through a glass filter (Celite) washing with Et_2O (200 mL). The filtrate was concentrated *in vacuo*. The residue was filtered through a silica gel column (flash column chromathography) eluting with toluene:Et_2O=20:1 to 10:1 to afford 2-BocNH-4-bromomethyl benzothiazole (46.7 g, 136 mmol, 90%) as a yellowish oil. R_f=0.51 (toluene:Et_2O=15:1); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.27 (1H, br s), 7.72 (1H, d, J = 8.2 Hz), 7.43 (1H, d, J = 7.2 Hz), 7.24 (1H, dd, J = 8.2, 7.2 Hz), 4.91 (2H, s), 1.56 (9H, s).

Step-3 (2-Boc-amino-4-azidemethyl benzothiazole)



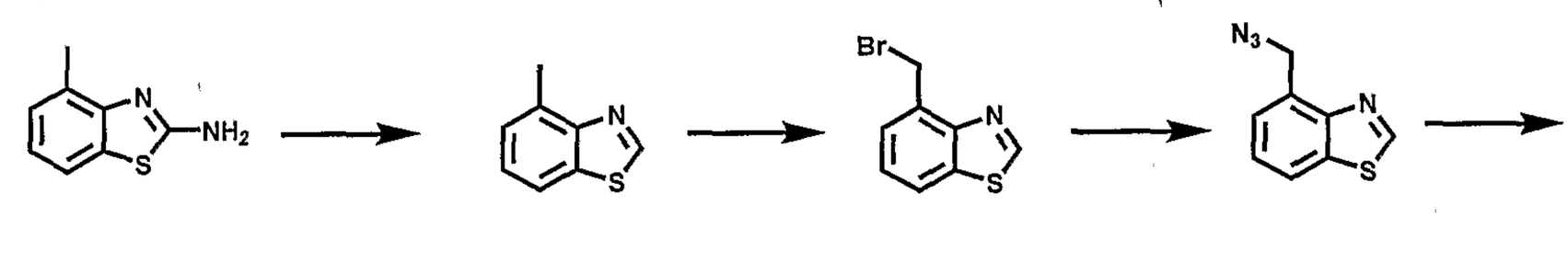
A solution of 2-Boc-amino-4-bromomethyl benzothiazole (46.7 g, 136 mmol) in 205 mL of dry DMF was treated with NaN_3 (8.80 g, 136 mmol) at 15 °C and stirred at 20 °C for 45 min. The resulting mixture was diluted with Et_2O (400 mL), quenched by addition of NaCl (1 g in 150 mL of H_2O) at 0 °C. The solution was extracted with Et_2O (100 mL). The organic phase was washed with NaCl (2 g in 100 mL of H_2O) twice, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was filtered through a silica gel plug (flash column chromathography) eluting with toluene:Et_2O=100:0 to 10:1 to afford 2-Boc-amino-4-azidemethyl benzothiazole (33.2 g, 109 mmol, 80%) as a colorless oil. R_f=0.48 (toluene:Et_2O=10:1); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.75 (1H, d, J = 8.2 Hz), 7.37 (1H, d, J = 7.2 Hz), 7.27 (1H, m), 4.74 (2H, s), 1.52 (9H, s); ^{13}C NMR (99.5MHz, $CDCl_3$) δ 159.8, 151.9, 147.6, 132.5, 127.6, 125.8, 123.5, 121.3, 83.4, 51.4, 28.1.

Step-4 (2-Boc-amino-benzothiazoleyl-4-methylamine)

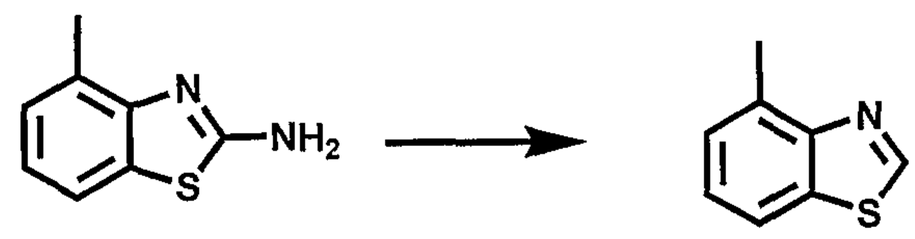


A solution of 2-Boc-amino-4-azidemethyl benzothiazole (11.6 g, 38.0 mmol) in 183 mL of MeOH was treated with $Pd(OH)_2$ (20% on carbon, 2.9 g), placed under an atmosphere of hydrogen and stirred at 20 °C for 1.5 hr. The resulting mixture was filtered through Celite washing with MeOH:NH_4OH (100:3, 100 mL) and concentrated *in vacuo*. The obtained yellowish solid was triturated with toluene (35 mL) and filtered to afford 2-Boc-amino-benzothiazoleyl-4-methylamine (6.90 g, 24.7 mmol, 65%) as a colorless powder. R_f= 0.32 ($CHCl_3$:MeOH:NH_4OH=100:25:1); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.67 (1H, d, J = 7.7 Hz), 7.25-7.15 (2H, m), 4.85 (2H, br s), 1.58 (9H, s); ^{13}C NMR (99.5MHz, $CDCl_3$) δ 160.0, 152.8, 148.0, 134.5, 132.7, 124.4, 123.1, 120.0, 82.4, 44.3, 28.3; LC/MS [ESI+] (m/z) 280.2 $(M+1)^+$.

Synthesis of Benzothiazoleyl-4-methylamine

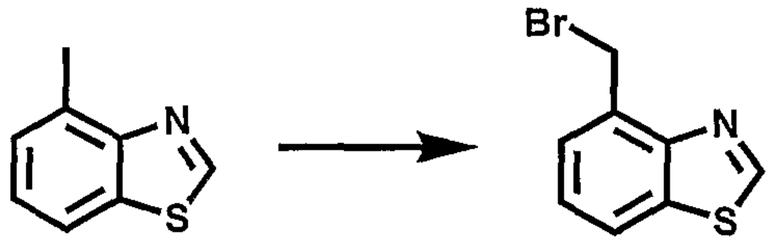


Step-1 (4-Methyl benzothiazole)



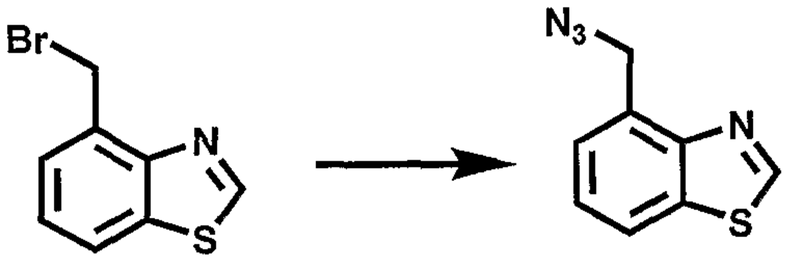
A solution of 2-amino-4-methylbenzothiazolee (24.5 g, 149 mmol) in 745 mL of 1,4-dioxane was treated with isoamylnitrile (40.0 mL, 300 mmol) at 20 °C and stirred at 70 °C for 0.5 hr. After the nitrogen evolution had subsided, the mixture was stirred at the same temperature for 1.5 h and concentrated *in vacuo*. The residue was submitted to silica gel column chromathography with hexane:Et_2O = 3:1 to 2:1 as eluate to afford 4-methyl benzothiazole as a yellowish oil. (16.0 g, 107 mmol, 72%) R_f=0.45 (toluene:Et_2O=10:1); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.98 (1H, s), 7.79 (1H, d, J = 6.8 Hz), 7.33 (2H, m), 2.80 (3H, s).

Step-2 (4-Bromomethyl benzothiazole)



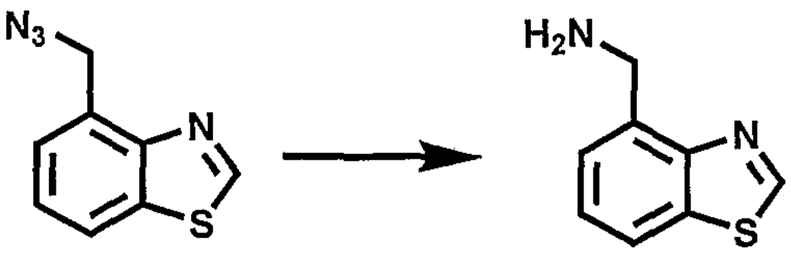
A solution of 4-Methyl benzothiazole (16.0 g, 107 mmol) in 535 mL of CCl_4 was treated with NBS (19.0 g, 107 mmol) and AIBN (2.28 g, 13.9 mmol) at 20 °C and stirred at 70 °C for 2.5 h. The resulting mixture was filtered through Celite washing with Et_2O (150 mL) and concentrated *in vacuo*. The residue was submitted to a silica gel column chromatography with toluene:Et_2O = 50:3 to 50:5 as eluate to afford 4-bromomethyl benzothiazole as a yellowish solid. (20.4 g, 89.9 mmol, 84%) R_f=0.61 (toluene-Et_2O 10:1); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.07 (1H, s), 7.90 (1H, d, J = 7.5 Hz), 7.55 (1H, d, J = 7.5 Hz), 7.41 (1H, t, J = 7.5 Hz), 5.08 (2H, s); ^{13}C NMR (99.5MHz, $CDCl_3$) δ 154.1, 151.4, 134.3, 132.6, 127.0, 125.6, 122.3, 29.5.

Step-3 (4-Azidemethyl benzothiazole)



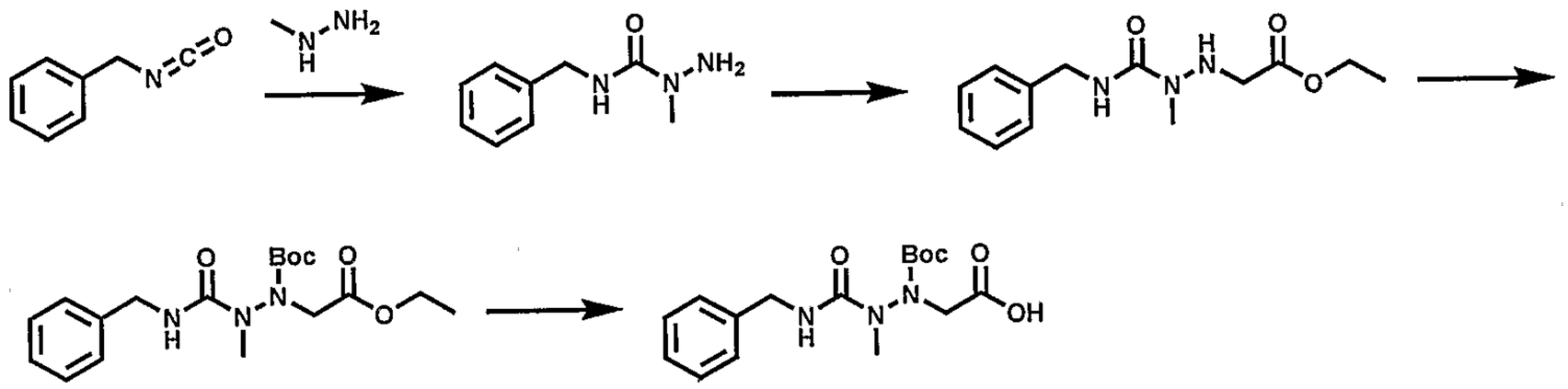
A solution of 4-Bromomethyl benzothiazole (20.4 g, 89.9 mmol) in 272 mL of dry DMF was treated with NaN_3 (7.00 g, 108 mmol) at 20 °C and stirred at the same temperature for 5 min. The resulting mixture was quenched by addition of NaCl (5 g in 150 mL of H_2O) at 0 °C, diluted with Et_2O (200 mL) and extracted with Et_2O (200 mL x 6). The organic phase was washed with NaCl (2 g in 100 mL of H_2O) twice and brine (100 mL). The resulting solution was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was submitted to silica gel column chromathography with toluene:Et_2O = 50:3 to 50:5 as eluate to afford 4-azidemethyl benzothiazole as a colorless oil (15.5 g, 81.5 mmol, 91%). R_f=0.48 (toluene:Et_2O=10:1); ^{1}H NMR (400MHz, $CDCl_3$) δ 9.03 (1H, s), 7.95 (1H, d, J = 7.7 Hz), 7.49 (2H, m), 5.01 (2H, s); ^{13}C NMR (99.5MHz, $CDCl_3$) δ 154.2, 151.7, 134.3, 130.6, 126.0, 125.7, 122.1, 51.6.

Step-4 (Benzothiazole-4-methylamine)

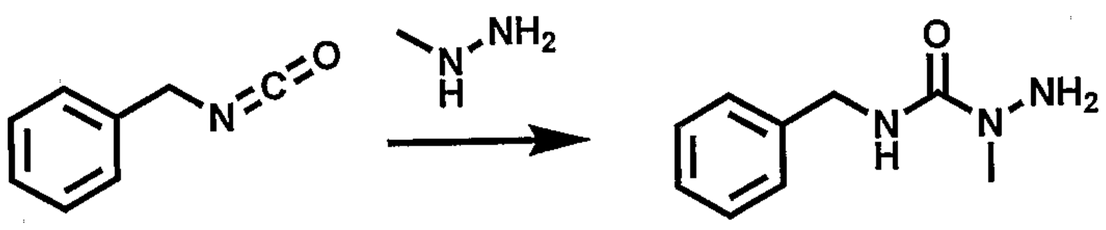


To a solution of 4-Azidemethyl benzothiazole (15.4 g, 81.0 mmol) in 243 mL of MeOH was added $Pd(OH)_2$ (20% on carbon, 3.1 g) and then hydrogenolysis at 20 °C. After 1.5 hr, additional $Pd(OH)_2$ (20% on carbon, 0.87 g) was added and then hydrogenolysis. After further 1.5hr, additional $Pd(OH)_2$ (20% on carbon, 1.27 g) was added and then hydrogenolysis for 1 hr. The resulting mixture was replaced with N_2 and then filtered through Celite washing with MeOH:NH_4OH (25:1, 260 mL) and concentrated *in vacuo*. The residue was submitted to silica gel column chromathography eluting with $CHCl_3$:MeOH:NH_4OH (100:0:0 to 20:5:1) followed by trituration with toluene to afford 4-aminomethyl benzothiazole as a white solid (10.5 g, 63.9 mmol, 79%). R_f=0.49 ($CHCl_3$:MeOH:NH_4OH=100:25:1); ^{1}H NMR (400MHz, CD_3OD) δ 9.23 (1H, s), 7.97 (1H, d, J = 7.7 Hz), 7.46 (2H, m), 4.30 (2H, s); ^{13}C NMR (99.5MHz, CD_3OD) δ 184.2, 180.1, 165.3, 163.5, 154.9, 154.1, 150.1, 72.0; LC/MS [ESI+] (m/z) 165.4 $(M+1)^+$.

Synthesis of 4-Benzyl-3-Boc-2-methylsemicarbazidylacetatic acid

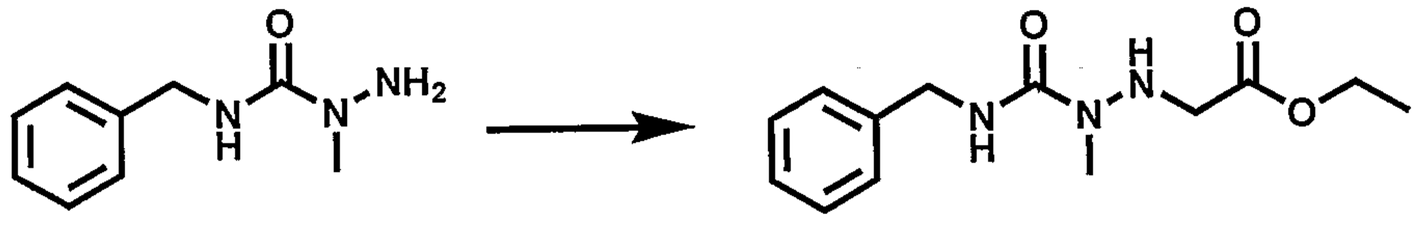


Step-1 (4-Benzyl-2-methylsemicarbazide)



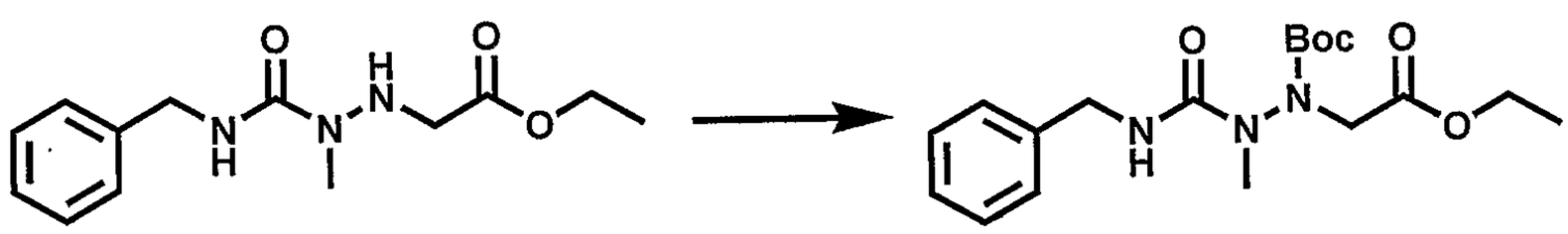
A solution of Benzyl isocyanate (1.85 mL, 15.0 mmol) in 7.5 mL of $CHCl_3$ was treated with methyl hydrazine (795 μL, 15.0 mmol) at 0 °C and stirred at the same temperature for 2 h. The resulting mixture was dissolved in 1N HCl (200 mL) and the solution was washed with $CHCl_3$ (50 mL x 3). The aqueous phase was adjusted to pH 12 with 2 M NaOHaq and then extracted with $CHCl_3$ (100 mL x 3). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was recrystalized from hexane-$CHCl_3$ to afford (1.7 g, 9.5 mmol, 63%) as a colorless crystal. R_f=0.44 ($CHCl_3$:MeOH=9:1); ^{1}H NMR (400MHz, DMSO-d6) δ 7.28-7.19 (5H, m), 4.47 (2H, s), 4.20 (2H, d, J = 6.3 Hz), 2.96 (3H, s); ^{13}C NMR (99.5MHz, DMSO-d6) δ 159.3, 141.1, 128.1, 127.1, 126.5, 43.1, 37.8; LC/MS [ESI+] (m/z) 180.3 $(M+1)^+$.

Step-2 (Ethyl 4-benzyl-2-methylsemicarbazidylacetate)



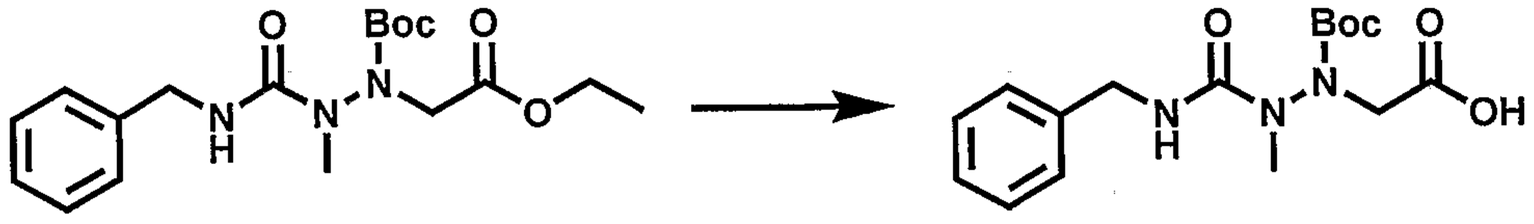
To the solution of 4-Benzyl-2-methylsemicarbazide (5.24 g, 29.2 mmol) in Toluene (58 mL) were added DIPEA (7.63 mL, 43.8 mmol) and Ethyl bromoacetate (4.86 mL, 43.8 mmol) and then stirred at 85δ for 24 hr. The reaction mixture was allowed to cool to room temperature followed by dilution with EtOAc (100 mL). The mixture was washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The crude was submitted to silica gel (250 g) column chromatography with Hex:EtOAc=1:1 to 1:9 as elute to afford a pale yellow oil (5.75 g, 21.7 mmol, 74%). *Rf* = 0.36 (Hex:EtOAc=1:3); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.34-7.21 (5H, m), 6.88 (1H, br s), 4.40 (2H, d, *J* = 5.8 Hz), 4.18 (2H, q, *J* = 7.2 Hz), 3.69 (1H, br t, *J* = 4.8 Hz), 3.58 (2H, d, *J* = 4.8 Hz), 3.08 (3H, s), 1.26 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (99.5MHz, $CDCl_3$) δ 170.8, 159.3, 139.9, 128.6, 127.6, 127.1, 61.4, 50.1, 44.4, 33.1, 14.2; LC/MS [ESI+] (m/z) 266.3 $(M+1)^+$.

Step-3 (Ethyl 4-benzyl-3-Boc-2-methylsemicarbazidylacetate)



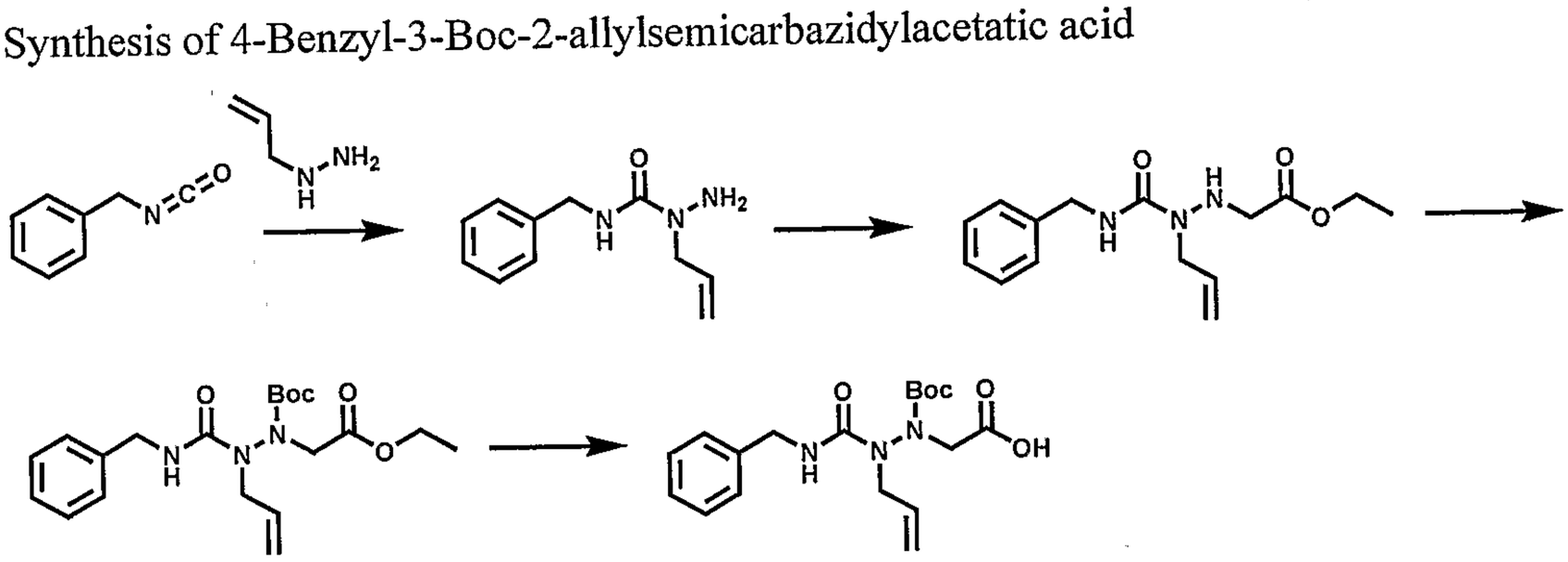
To the solution of Ethyl 4-benzyl-2-methylsemicarbazidylacetate (5.70 g, 21.5 mmol) in CH_2Cl_2 (43 mL) were added DIPEA (7.5 mL, 43 mmol), DMAP (1.1 g, 8.6 mmol) and $(Boc)_2O$ (9.4 g, 43 mmol) and then stirred for 1 hr at room temperature. The reaction miture was concentrated and then submitted to SiO_2 (250 g) column chromatography with Hex:EtOAc = 7:1 to 1:2 as eluate to afford product (2.58 g, 7.06 mmol, 33%) as a pale yellow oil, and starting material (2.80 g, 10.6 mmol, 49%) was recovered. *Rf* = 0.76 (Hex:EtOAc =1:3); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.54 (1H, br s), 7.33-7.20 (5H, m), 4.59-4.46 (2H, m), 4.27-4.19 (4H, m), 3.72 (1H, br d, *J* = 17 Hz), 3.03 (3H, br s), 1.39 (9H, s), 1.26 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (99.5MHz, $CDCl_3$) δ 170.7, 158.3, 139.8, 128.3, 127.6, 126.9, 82.7, 62.0, 51.6, 44.3, 34.4, 28.0, 14.1; LC/MS [ESI+] (m/z) 366.3 $(M+1)^+$.

Step-4 (4-Benzyl-3-Boc-2-methylsemicarbazidylacetatic acid)

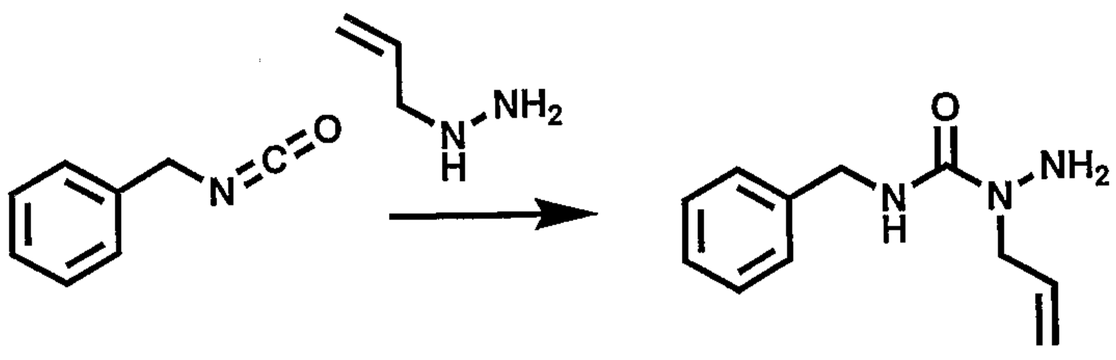


To the solution of Ethyl 4-benzyl-3-Boc-2-methylsemicarbazidylacetate (2.30 g, 6.29 mmol) in THF/MeOH/H_2O (2/3/1, 24mL) was added LiOH H_2O (528 mg, 12.6 mmol) at 0δ. After stirred for 1hr at room temperature, the reaction mixture was diluted with EtOAc (40 mL) at 0δ. The mixture was acidified with 1N HCl and then extracted with EtOAc. The combined extracts were washed with H_2O (30 mL) and brine (30 mL), dried over Na_2SO_4, added Et_3N (2mL), filtered and concentrated. The crude was submitted to SiO_2 column chromatography with $CHCl_3$:MeOH = 100:0 to 85:15 as eluante to afford a pale yellow sticky oil 4-Benzyl-3-Boc-2-methylsemicarbazidylacetatic acidδEt_3N salt (1.99 g, 4.56 mmol, 72%); ^1H NMR (400MHz, $CDCl_3$) δ 8.45 (1H, br s), 7.32-7.18 (5H, m), 4.58-4.22 (3H, m), 3.71-3.57 (1H, m), 3.08 and 3.01 (3H, br s), 2.82 (2.4H, q, J = 7.3 Hz, Et_3N), 1.40 (9H, br s), 1.08 (3.6H, t, J = 7.3 Hz, Et_3N); ^{13}C NMR (99.5MHz, $CDCl_3$) δ 174.2, 159.2, 154.1, 140.1, 128.2, 127.4, 12.7, 81.8, 52.2, 45.1 (Et_3N), 44.1, 34.5, 28.1, 8.3 (Et_3N); LC/MS [ESI+] (m/z) 338.3 $(M+1)^+$.

Synthesis of 4-Benzyl-3-Boc-2-allylsemicarbazidylacetatic acid



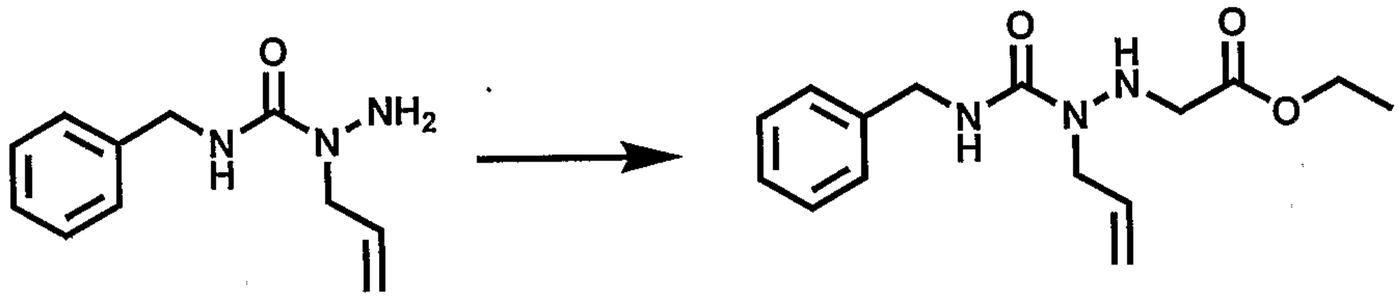
Step-1 (4-Benzyl-2-allylsemicarbazide)



To the solution of Allyl hydrazine (1.55 mL, 15.0 mmol) in 7.5 mL of $CHCl_3$ was added benzyl isocyanate (1.85 mL, 15.0 mmol) slowly at 0 °C and stirred at the same temperature for 2 h. The resulting mixture was dissolved in 1N HCl (200 mL) and the solution was washed with $CHCl_3$

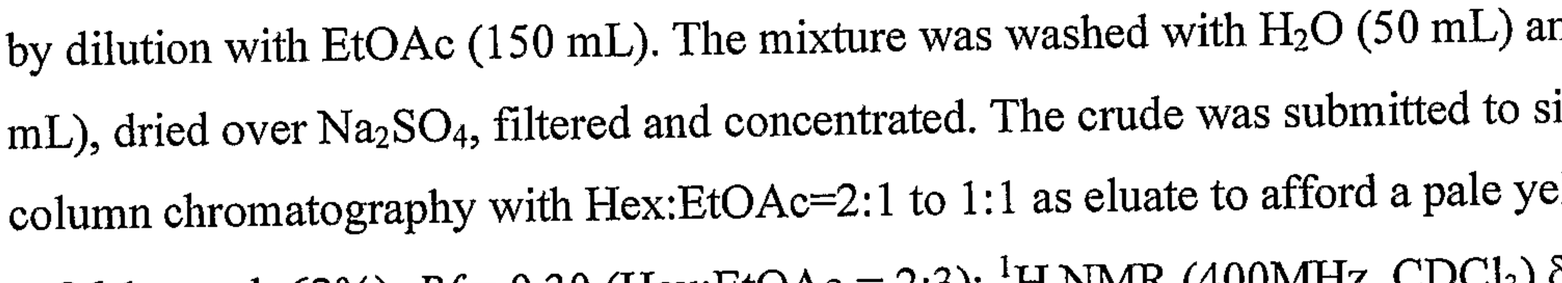
(50 mL x 3). The aqueous phase was adjusted to pH 12 with 2 M NaOH aq and then extracted with $CHCl_3$ (100 mL x 3). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was recrystalized from hexane-$CHCl_3$ to afford a colorless crystal (2.20 g, 10.7 mmol, 70%). R_f=0.50 ($CHCl_3$:MeOH = 9:1); ^{1}H NMR (400MHz, $CDCl_3$) δ7.34-7.23 (5H, m), 6.77 (1H, br s), 5.77 (1H, ddt, J = 16.9, 10.1, 6.3 Hz), 5.28 (1H, d, J = 10.1 Hz), 5.22 (1H, dd, J = 16.9, 1.5 Hz), 4.42 (2H, d, J = 6.3 Hz), 4.14 (2H, d, J = 6.3 Hz), 3.47 (2H, s); ^{13}C NMR (99.5MHz, $CDCl_3$) δ159.0, 139.9, 132.7, 128.6, 127.6, 127.2, 119.2, 52.8, 44.3; LC/MS [ESI+] (m/z) 206.3 $(M+1)^+$.

Step-2 (Ethyl 4-benzyl-2-allylsemicarbazidylacetate)



To the solution of 4-Benzyl-2-allylsemicarbazide (8.60 g, 41.9 mmol) in toluene (50 mL) were added DIPEA (14.6 mL, 83.8 mmol) and Ethyl bromoacetate (8.1 mL, 73 mmol) and then stirred at 95δ for 39 hr. The reaction mixture was allowed to cool to room temperature followed by dilution with EtOAc (150 mL). The mixture was washed with H_2O (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated. The crude was submitted to silica gel (250 g) column chromatography with Hex:EtOAc=2:1 to 1:1 as eluate to afford a pale yellow oil (7.60 g, 26.1 mmol, 62%). *Rf* = 0.30 (Hex:EtOAc = 2:3); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.32-7.23 (5H, m), 7.02 (1H, br,s), 5.78 (1H, ddt, J = 17.4, 10.1, 6.3 Hz), 5.25 (2H, m), 4.42 (2H, d, J = 5.8 Hz), 4.16 (3H, q and br m, J = 7.2 Hz), 3.98 (1H, t, J = 4.8 Hz), 3.55 (2H, d, J = 4.8 Hz), 1.25 (3H, t, J = 7.2 Hz); ^{13}C NMR (99.5MHz, $CDCl_3$) δ 170.5, 158.9, 139.8, 132.5, 128.5, 127.6, 127.1, 119.2, 61.3, 50.0, 46.7, 44.3, 14.1; LC/MS [ESI+] (m/z) 292.3 $(M+1)^+$.

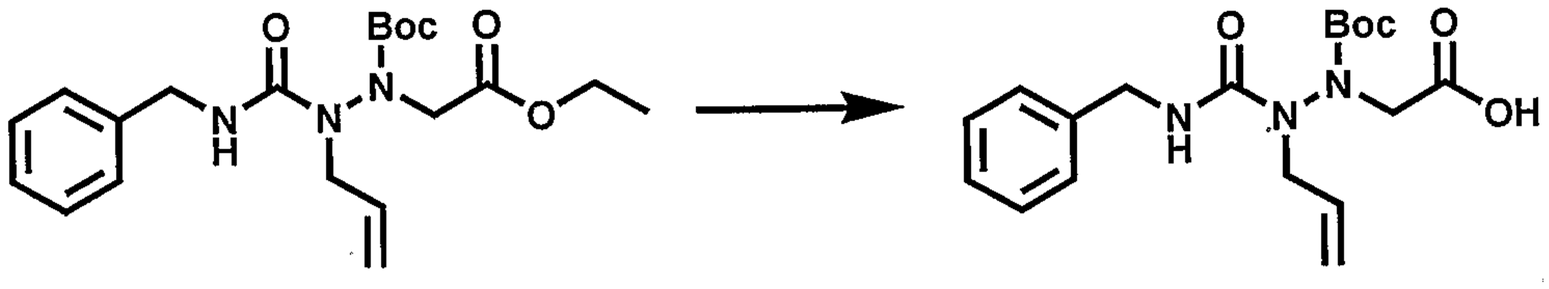
Step-3 (Ethyl 4-benzyl-3-Boc-2-allylsemicarbazidylacetate)



To the solution of Ethyl 4-benzyl-2-allylsemicarbazidylacetate (7.10 g, 24.4 mmol) in CH_2Cl_2 (50 mL) were added DIPEA (8.5 mL, 49 mmol), DMAP (1.19 g, 9.76 mmol) and $(Boc)_2O$ (10.6 g, 48.8 mmol). After the mixture was stirred for 3.5 hr at room temperature, additional DIPEA

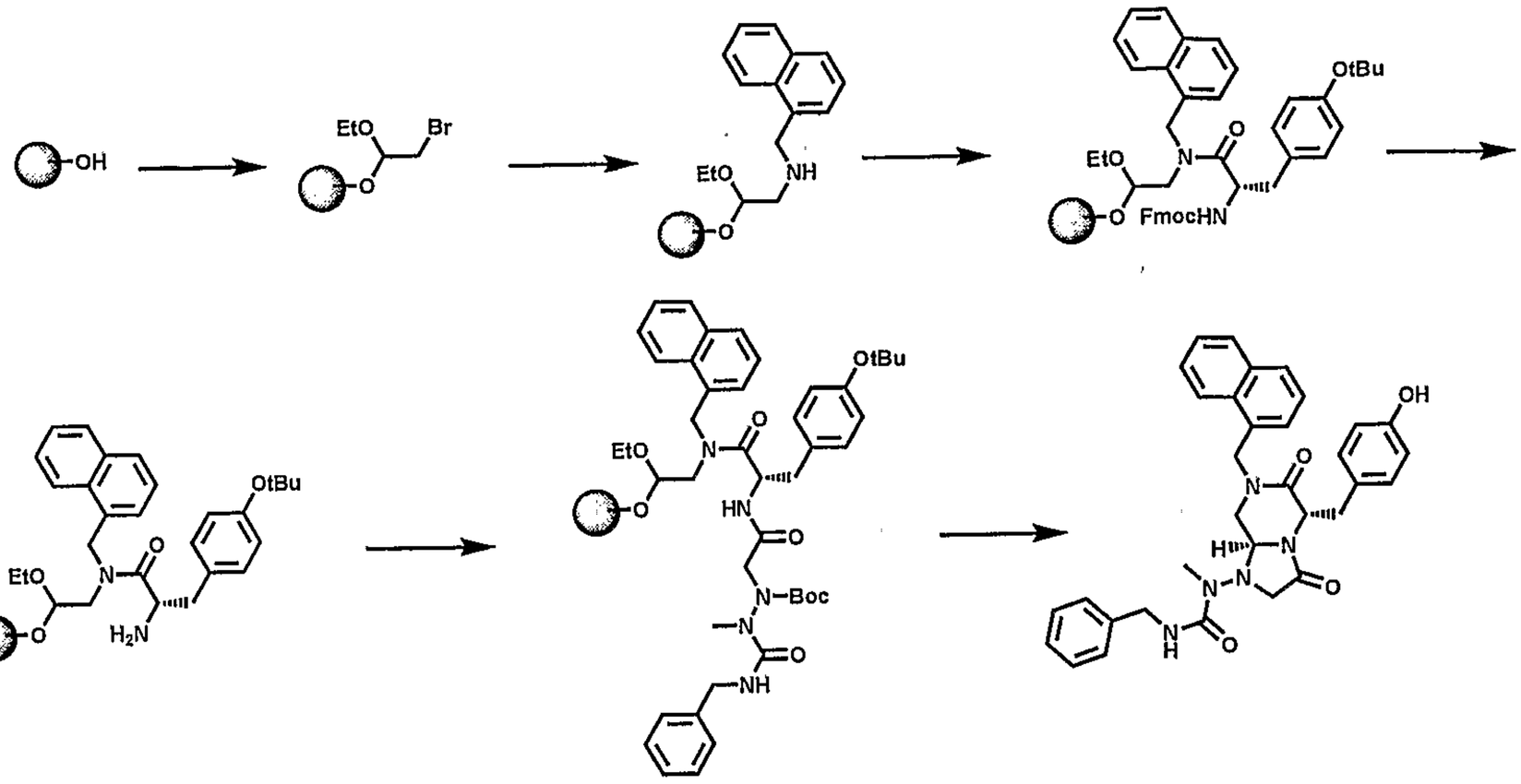
(2.12 mL, 12.2 mmol) and $(Boc)_2O$ (2.66 g, 12.2 mmol) were added. After the reaction mixture was stirred for additional 6 hr, the mixture was diluted with CH_2Cl_2 (100 mL) and then sat.$NaHCO_3$ (50 mL) was added at 0δ. The separated aqueous phase was extracted with CH_2Cl_2 (100 mL x 2). The combined organic phases were washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The crude was submitted to SiO_2 (300 g) column chromatography with Hex:EtOAc = 7:1 to 1:1 as eluate to afford product as a pale yellow oil (6.61 g, 16.9 mmol, 69%). *Rf* = 0.57 (Hex:EtOAc = 1:1); ^{1}H NMR (400MHz, $CDCl_3$) δ 7.77 (1H, br s), 7.34-7.21 (5H, br m), 5.88 (1H, br m), 5.20 (2H, br m), 4.62-4.46 (3H, m), 4.37-4.13 (3H, m), 3.92-3.65 (2H, m), 1.48 and 1.38 (9H, s), 1.26 (3H, t, *J* = 7.2 Hz); ^{13}C NMR (99.5MHz, $CDCl_3$) δ 170.8, 157.8, 154.1, 139.8, 128.4, 127.6, 127.0, 119.6, 82.7, 62.0, 51.2, 44.3, 30.9, 28.0, 14.1; LC/MS [ESI+] (m/z) 392.4 $(M+1)^+$.

Step-4 (4-Benzyl-3-Boc-2-allylsemicarbazidylacetatic acid)

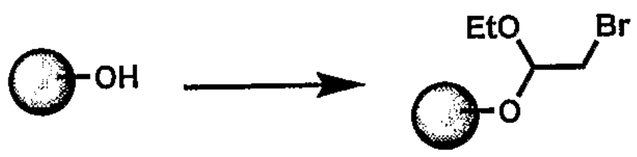


To the solution of Ethyl 4-benzyl-3-Boc-2-allylsemicarbazidylacetate (3.20 g, 8.17 mmol) in THF/MeOH/H_2O (2/3/1, 25 mL) was added LiOH H_2O (685 mg, 16.3 mmol) at 0δ. After stirred for 40 min at room temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL) at 0δ. The mixture was acidified with 1N HCl and then extracted with CH_2Cl_2. The combined extraction were washed with H_2O (30 mL) and Brine (30mL), dried over Na_2SO_4, added Et_3N (3 mL), filtered and concentrated. The crude was submitted to SiO_2 column chromatography with $CHCl_3$:MeOH = 100:0 to 85:15 as eluate to afford orange sticky oil 4-Benzyl-3-Boc-2-allylsemicarbazidylacetatic acidδEt_3N salt (3.66 g, 7.87 mmol, 96%); ^{1}H NMR (400MHz, $CDCl_3$, rotamer) δ 9.44 and 9.34 (1H, br s), 7.35-7.18 (5H, m), 5.91 (1H, m), 5.17 (2H, m), 4.58 and 4.87 (2H, dd, *J* = 15.5, 6.3 and 14.5, 5.8 Hz), 4.39-4.23 (2H, m), 3.89 and 3.80 (1H, dd, *J* = 14.0, 8.2 and 14.5, 8.2 Hz), 3.58 and 3.52 (1H, d, *J* = 17.4 and 16.9 Hz), 2.81 (5H, q, *J* = 7.2 Hz, Et_3N), 1.44 and 1.42 (9H, s), 1.11 (7.5H, t, *J* = 7.2 Hz, Et_3N); ^{13}C NMR (99.5MHz, $CDCl_3$) δ 158.9, 154.3, 153.6, 140.6, 134.2, 128.1, 127.4, 126.5, 118.8, 81.1, 55.6, 51.4, 44.9 (Et_3N), 44.2, 28.2, 8.3 (Et_3N); LC/MS [ESI+] (m/z) 364.3 $(M+1)^+$.

Synthesis of Compound No.61

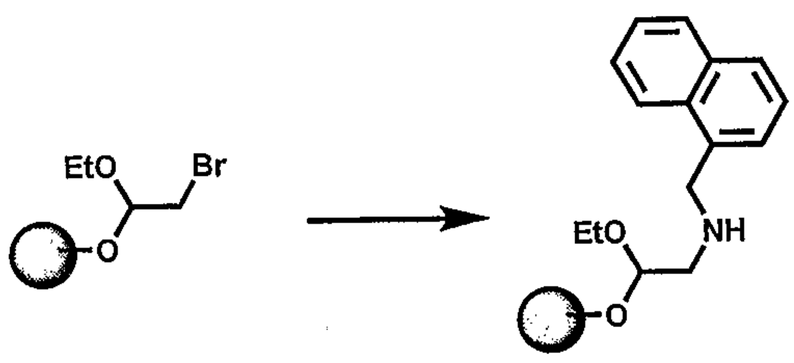


Step-1



The hydroxy-functionalized resin (5.0 g, 0.68 mmol/g, Novabiochem) was placed in 200 mL round-bottom flask. To the mixture of the resin and PPTS (1.7 g, 6.8 mmol) in 1,2-dichloromethane (51 mL) was added bromoacetaldehyde diethylacetal (4.2 mL, 27 mmol) at room temperature. After being stirred under reflux for 4.0 hr, the mixture was filtered and the resin was washed with DMF 50 mL x 3, DMSO 50 mL x 3, 1,4-dioxane 50 mL x 3, CH_2Cl_2 50 mL x 3, MeOH 50 mL x 3, Et_2O 50 mL x 3. The resin was dried under reduced pressure for over night to afford the desired bromoacetal resin (5.5 g).

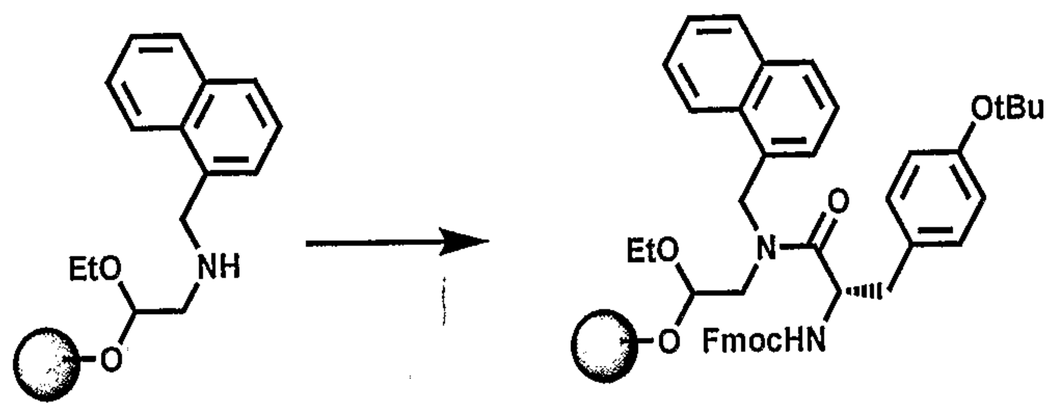
Step-2



Bromoacetal resin (1.0 g, 0.9 mmol/g) was placed in 30 mL round-bottom flask. The resin was swollen with DMF (9.0 mL x 5 min x 1) and then treated with 1.0 M solution of 1-naphtylmethylamine (1.4 g, 9.0 mmol) in DMSO (9.0 mL) at 70 °C. After being stirred for 12 hr, the resin was filtered and rinsed with DMSO (9.0 mL x 5 min x 3). The resin was washed with

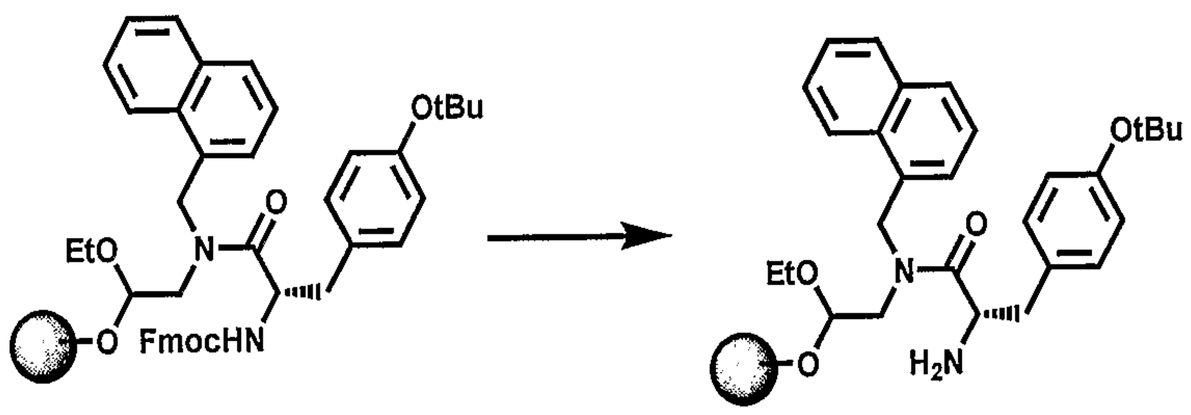
DMF (5.0 mL x 5 min x 3) and CH_2Cl_2 (5.0 mL x 5 min x 3). The resin was dried under reduced pressure to afford desired resin (1.18g).

Step-3



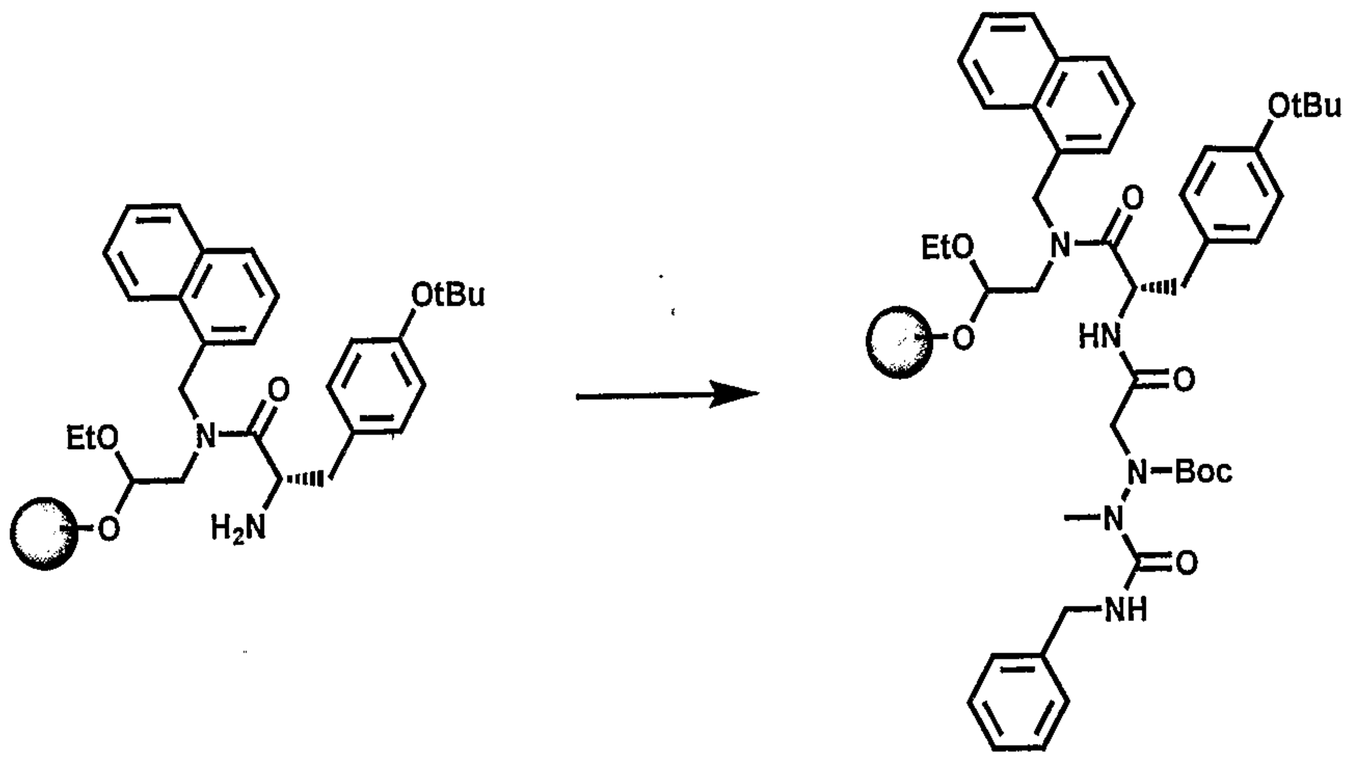
Naphthylmethylamino resin (1.18 g, 0.84 mmol/g) was placed in 20 mL plastic disposable syringe. The resin was swollen with DMF (9.0 mL x 5 min x 1) and then DMF (9.0 mL), Fmoc-Tyr(*t*-Bu)-OH (620 mg, 1.35 mmol), DIPEA (470 μL, 2.70 mmol) and HATU (513 mg, 1.35 mmol) were added at room temperature. After being shaken for 12 hr, in case of Kaiser test was positive, the same procedure was repeated. The mixture was filtered and the resin was washed with DMF (10.0 mL x 5 min x 3) and CH_2Cl_2 (10.0 mL x 5 min x 3). The resin was dried under reduced pressure to afford desired resin (1.50 g).

Step-4



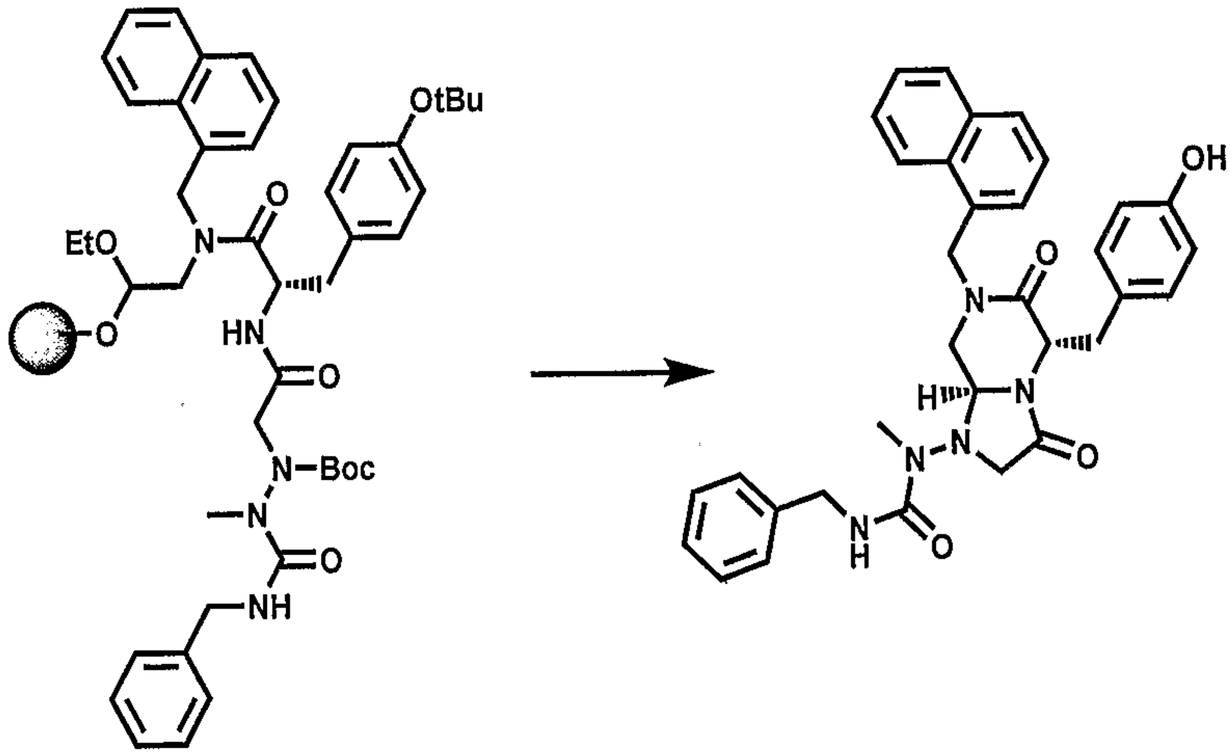
The 1-Naphthylmethylamino-Fmoc-Tyr(*t*Bu) resin (1.50 g, 0.61 mmol/g) was placed in 20 mL plastic disposable syringe. The resin was swollen in DMF (10.0 mL) and DMF was sucked out. The resin was treated with 20 v/v% piperidine/DMF (10.0 mL) at room temperature. After being shaken for 1.0 hr, the mixture was filtered and the resin was washed with DMF (10 mL x 5 min x 3) and CH_2Cl_2 (10 mL x 5 min x 3). The resin was dried under reduced pressure to afford desired resin (1.48 g).

Step-5



The Amino resin (300 mg, 0.71 mmol/g) was placed in 20 mL plastic disposable syringe. The resin was swollen in DMF (3.0 mL) and DMF was sucked out. To the resin was added 0.3 M stocked CH_2Cl_2 soltuion of 4-Benzyl-3-Boc-2-methylsemicarbazidylacetatic acid (2.5 mL, 0.75 mmol), DIPEA (260 μL, 1.49 mmol) and HATU (284 mg, 0.75 mmol) at room temperature. After being shaken for 12 hr, the mixture was filtered and the resin was washed with DMF (5.0 mL x 5 min x 3) and CH_2Cl_2 (5.0 mL x 5 min x 3). The resin was dried under reduced pressure to afford desired resin.

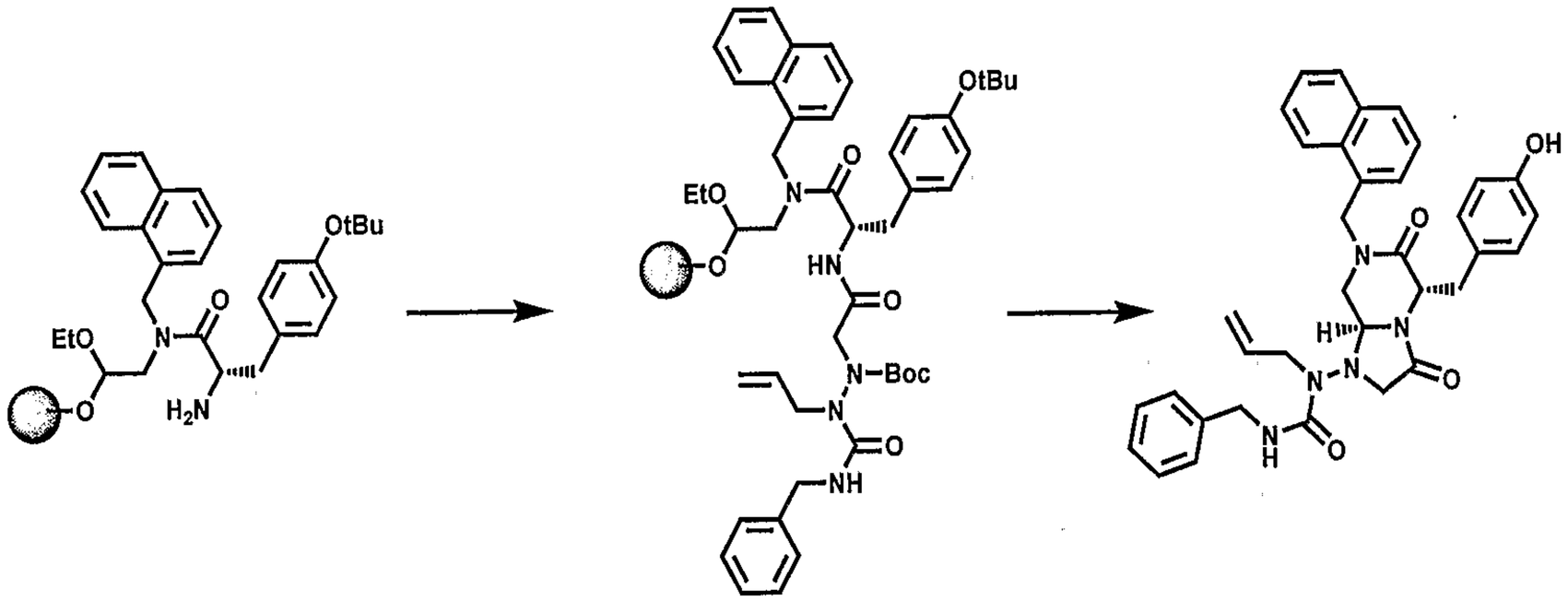
Step-6



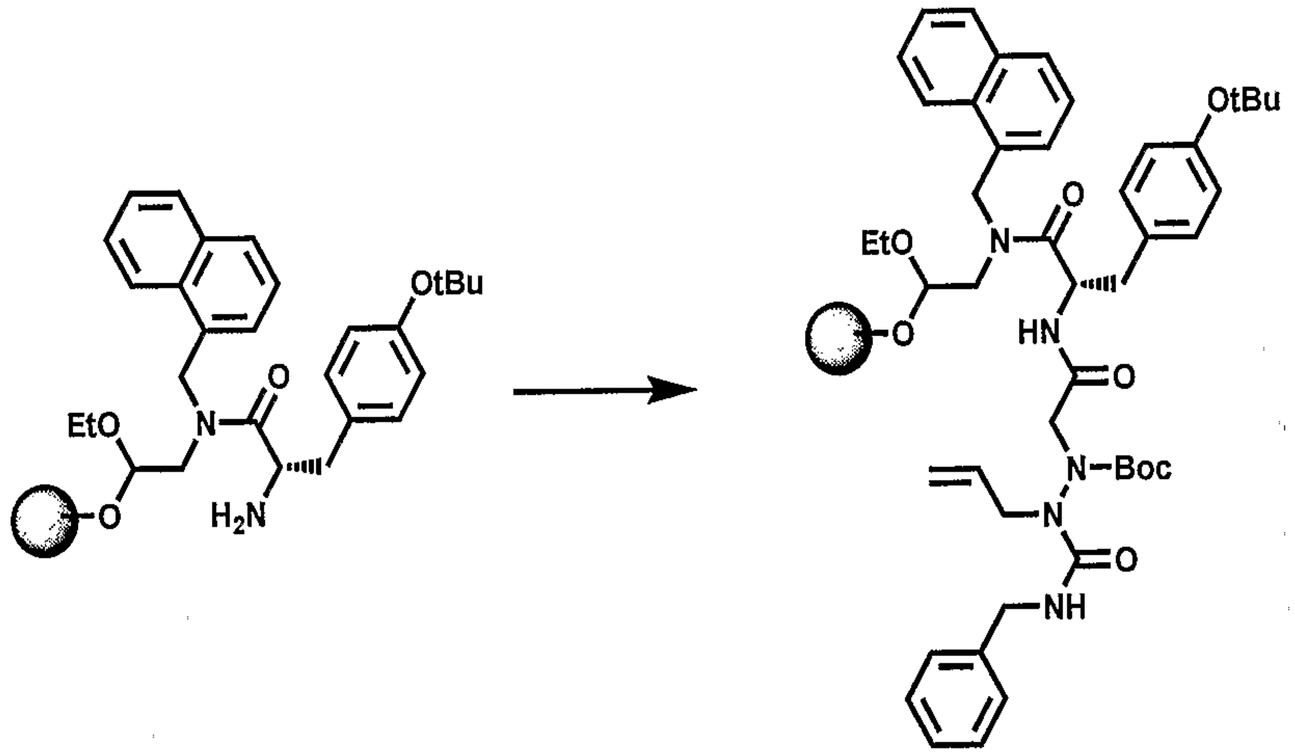
The resin (115 mg, 0.58 mmol/g) was placed in 5.0 mL plastic disposable syringe. After addition of 99% HCO_2H (1.0 mL), the mixture was shaken for 12 hr at room temperature, the solution was collected by filteration. The resin was washed with 99% HCO_2H (1.5 mL x 5 min x 2). The combined HCO_2H solutions were concentrated and then submitted to silica gel column chromatography to afford Compound No.61 (7.1 mg, 19% from bromoacetal resin). *Rf* = 0.63 ($CHCl_3$:MeOH = 9:1); ^{1}H NMR (400MHz, $CDCl_3$) δ 8.06 (1H, d, *J* = 8.2 Hz), 7.89 (1H, m),

7.84 (1H, d, J = 8.2 Hz), 7.56 (2H, m), 7.38 (1H, dd, J = 8.2, 7.2 Hz), 7.20 (3H, m), 7.12 (1H, d, J = 6.8 Hz), 7.05 (2H, dd, J = 7.7, 2.9 Hz), 7.02 (2H, d, J = 8.2 Hz), 6.88 (0.5H, br s), 6.71 (2H, d, J = 8.2 Hz), 6.05 (1H, t, J = 5.8 Hz), 5.06 (2H, ABq, J = 14.5 Hz), 4.80 (1H, dd, J = 5.8, 2.5 Hz), 4.23 (2H, ABX, J = 14.5, 5.8 Hz), 3.67-3.44 (4H, m), 3.21 (1H, dd, J = 14.0, 5.8 Hz), 3.12 (1H, dd, J = 11.0, 3.9 Hz), 2.86 (1H. dd. J = 11.0, 9.1 Hz), 2.59 (3H, s); LC/MS [ESI+] (m/z) 564.4 $(M+1)^+$.

Synthesis of Compound No.71

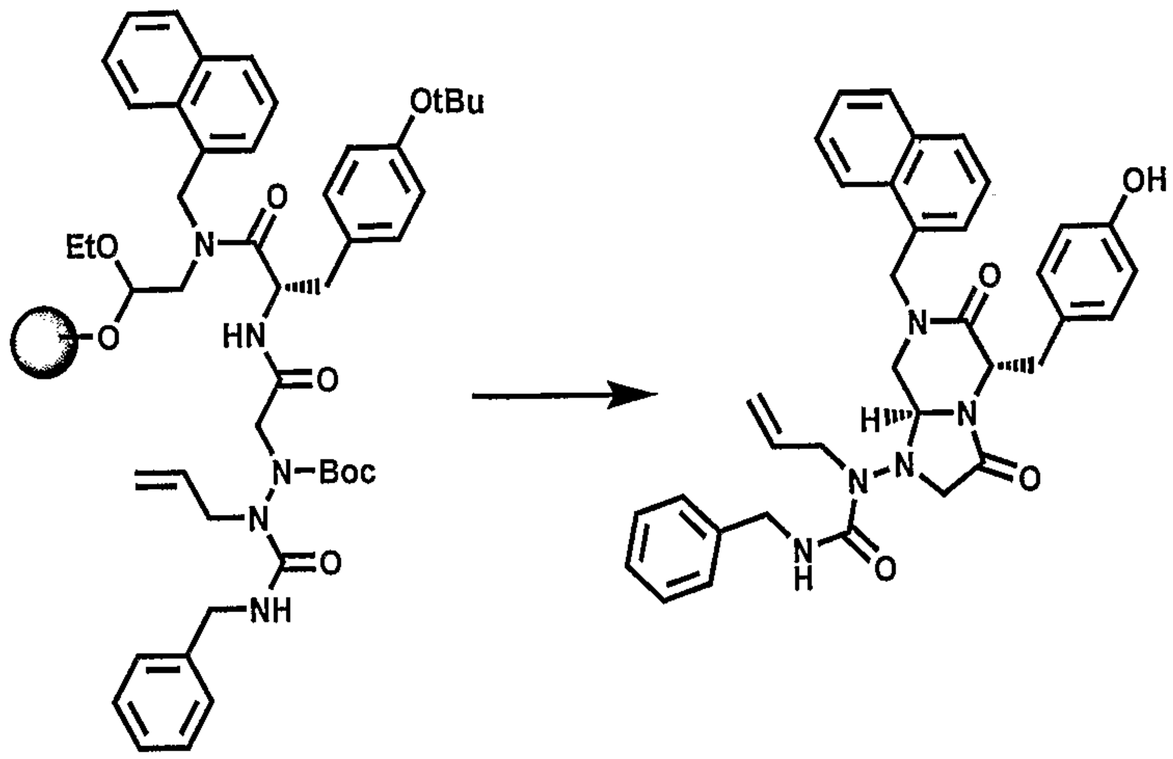


Step-1



The Amino resin (100 mg, 0.71 mmol/g) was placed in 5 mL plastic disposable syringe. The resin was swollen in DMF (1.0 mL) and DMF was sucked out. To the resin was added 0.3 M stocked CH_2Cl_2 soltuion of 4-Benzyl-3-Boc-2-allylsemicarbazidylacetatic acid (830 μL, 0.25 mmol), DIPEA (87 μL, 0.50 mmol) and HATU (95 mg, 0.25 mmol) at room temperature. After being shaken for 12 hr, the mixture was filtered and the resin was washed with DMF (1.0 mL x 5 min x 3) and CH_2Cl_2 (1.0 mL x 5 min x 3). The resin was dried under reduced pressure to afford desired resin.

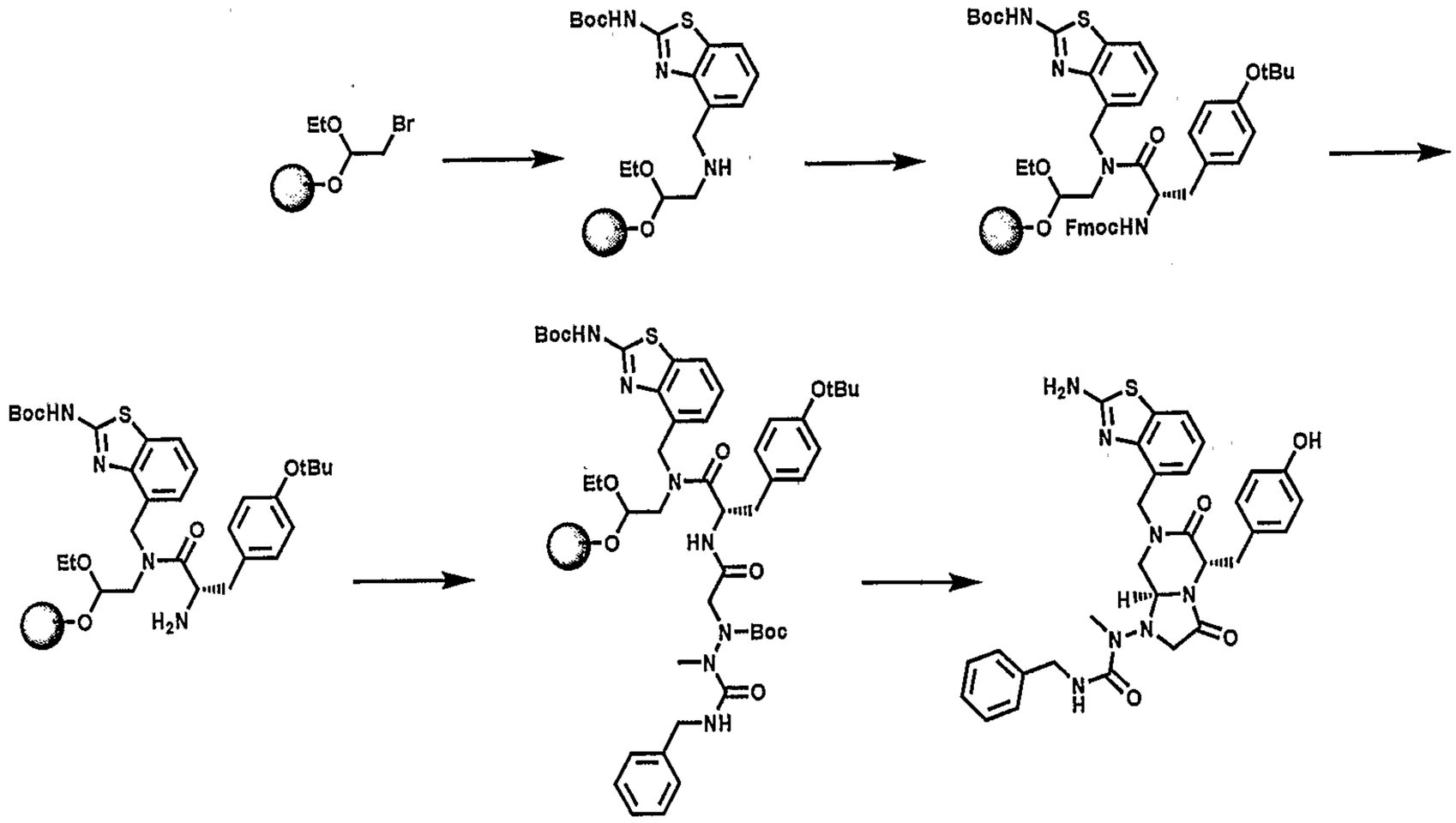
Step-2



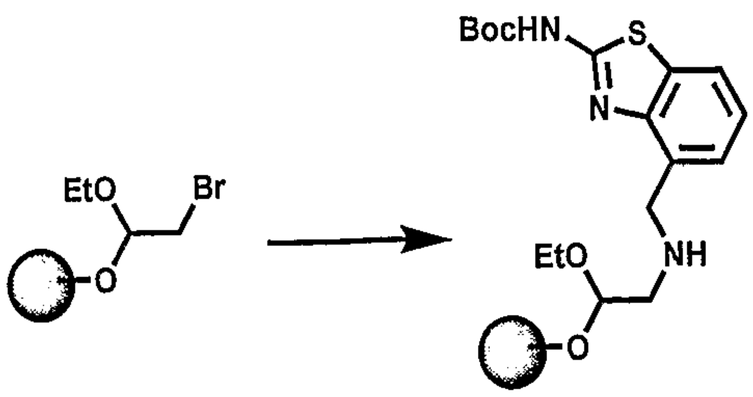
The resin (100 mg, 0.57 mmol/g) was placed in 5.0 mL plastic disposable syringe. After addition of 99% HCO_2H (1.0 mL), the mixture was shaken for 12 hr at room temperature, the solution was collected by filteration. The resin was washed with 99% HCO_2H (1.5 mL x 5 min x 2). The combined HCO_2H solutions were concentrated and then submitted to silica gel column chromatography to afford Compound No.71 (11 mg, 26% from bromoacetal resin). *Rf* = 0.63 ($CHCl_3$:MeOH = 9:1).

Similar synthesis was carried out to obtain the compounds as shown as Compounds 1-1200 in Figures 1-6.

Synthesis of Compound No.1273

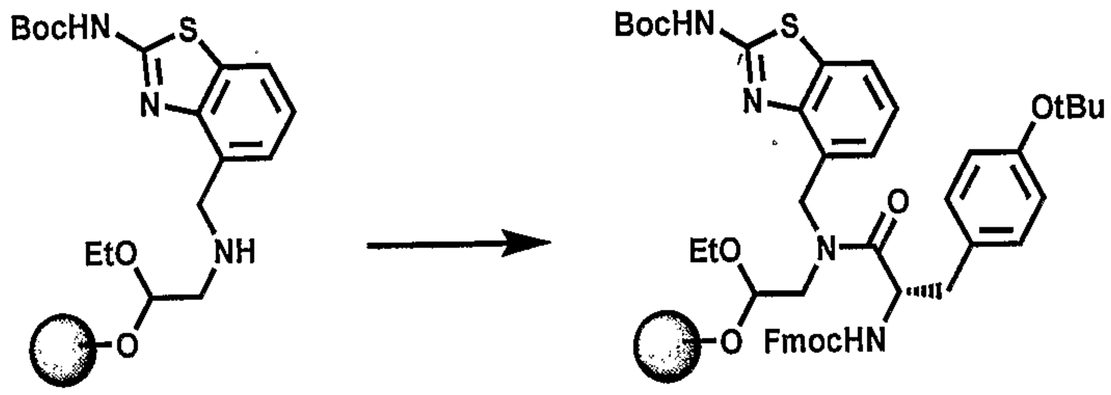


Step-1



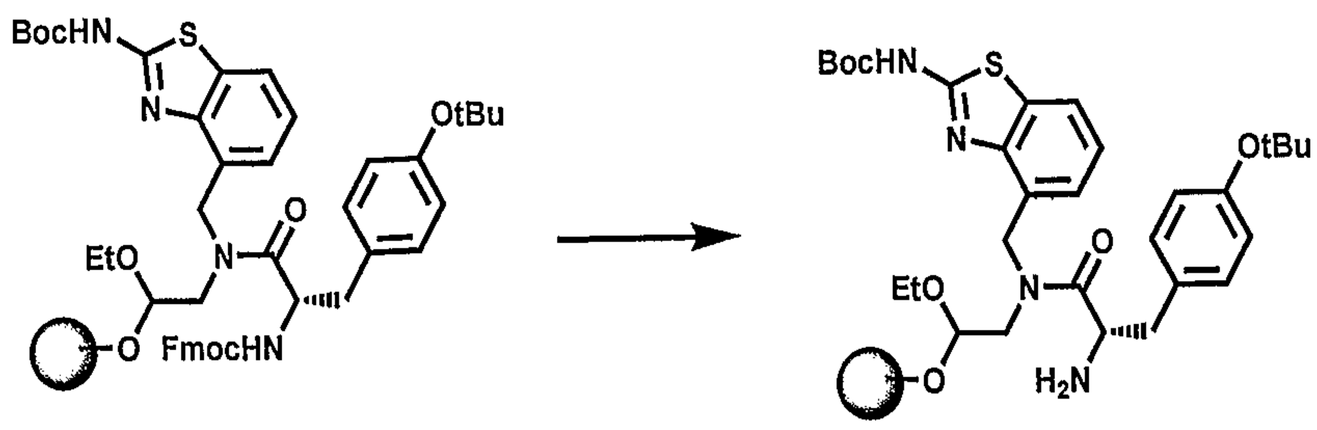
Bromoacetal resin (1.0 g, 0.9 mmol/g) was placed in 30 mL round-bottom flask. The resin was swollen with DMF (9.0 mL x 5 min x 1) and then treated with 1.0 M suspension of 2-tert-Butoxycarbonylaminobenzothiazole-4-methylamine (2.5 g, 9.0 mmol) in DMSO (9.0 mL) at 70 °C. After being stirred for 12 hr, the resin was filtered and rinsed with DMSO (9.0 mL x 5 min x 3). The resin was washed with DMF (5.0 mL x 5 min x 3) and CH_2Cl_2 (5.0 mL x 5 min x 3). The resin was dried under reduced pressure to afford desired resin (1.16 g).

Step-2



2-tert-Butoxycarbonylaminoebenzothiazole-4-methylamino resin (1.16 g, 0.76 mmol/g) was placed in 20 mL plastic disposable syringe. The resin was swollen with DMF (9.0 mL x 5 min x 1) and then DMF (9.0 mL), Fmoc-Tyr(*t*-Bu)-OH (620 mg, 1.35 mmol), DIPEA (470 μL, 2.70 mmol) and HATU (513 mg, 1.35 mmol) were added at room temperature. After being shaken for 12 hr, in case of Kaiser test was positive, the same procedure was repeated. The mixture was filtered and the resin was washed with DMF (10.0 mL x 5 min x 3) and CH_2Cl_2 (10.0 mL x 5 min x 3). The resin was dried under reduced pressure to afford desired resin (1.76 g).

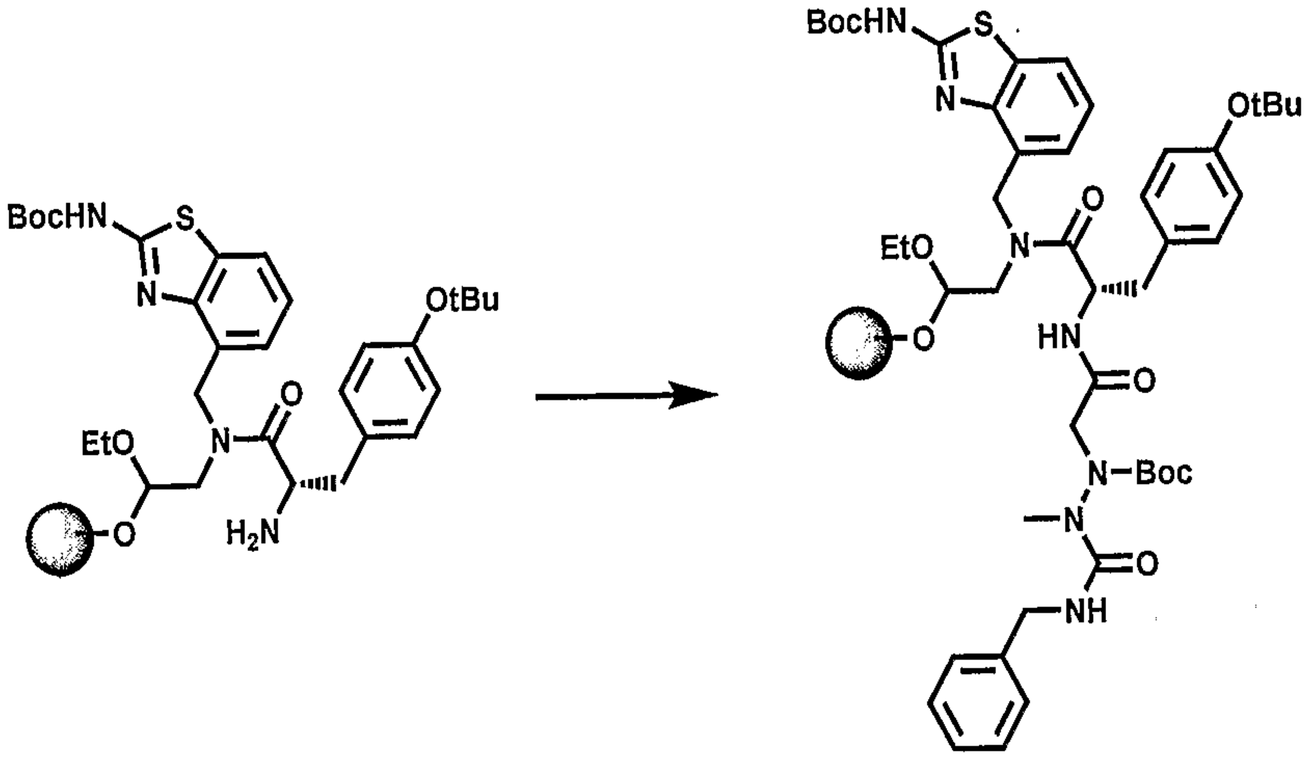
Step-3



The 2-tert-Butoxycarbonylbenzothiazole-4-methylamino-Fmoc-Tyr(*t*Bu) resin (1.76 g, 0.57 mmol/g) was placed in 20 mL plastic disposable syringe. The resin was swollen in DMF (10.0

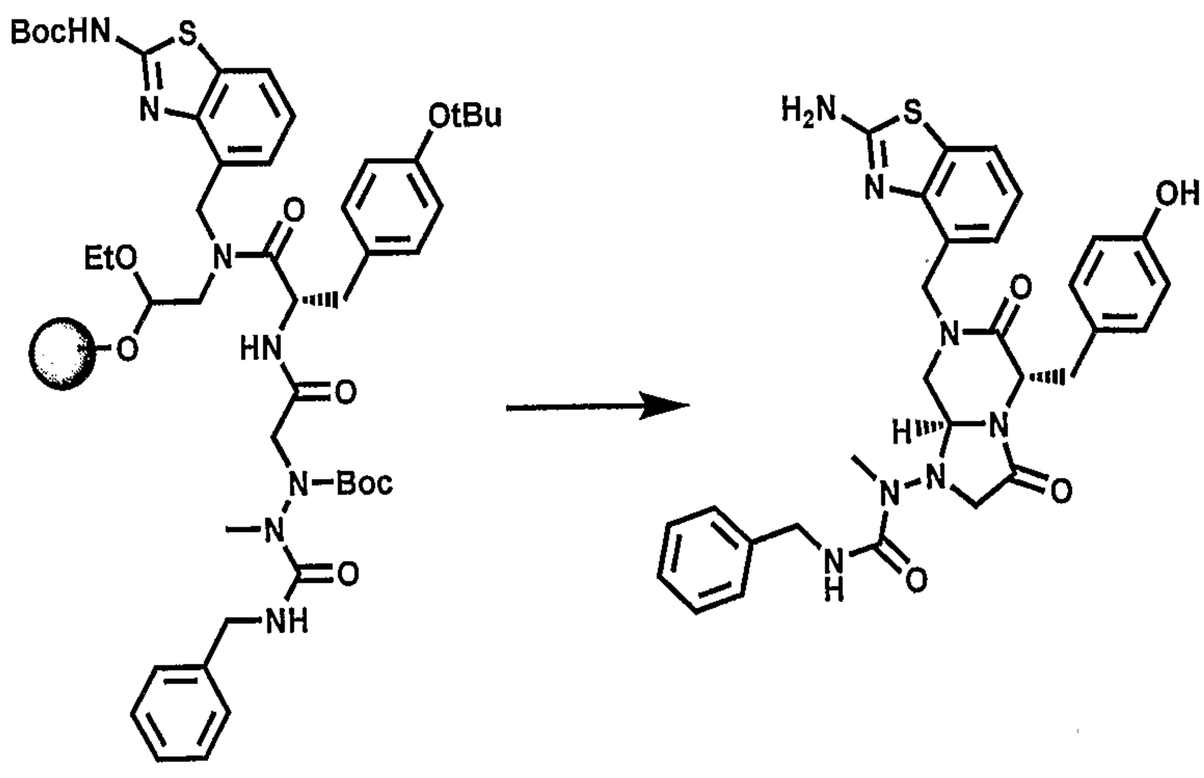
mL) and DMF was sucked out. The resin was treated with 20 v/v% piperidine/DMF (10.0 mL) at room temperature. After being shaken for 1.0 hr, the mixture was filtered and the resin was washed with DMF (10 mL x 5 min x 3) and CH_2Cl_2 (10 mL x 5 min x 3). The resin was dried under reduced pressure to afford desired resin (1.42 g).

Step-4



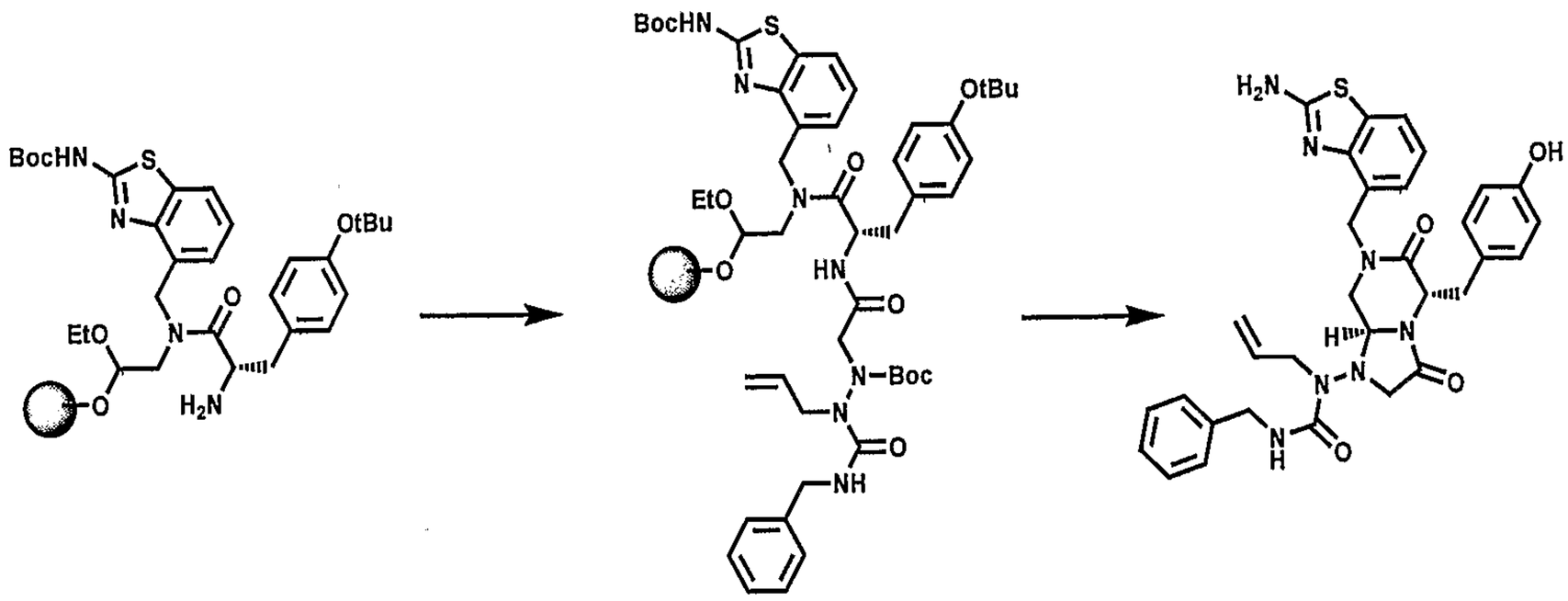
The Amino resin (350 mg, 0.65 mmol/g) was placed in 20 mL plastic disposable syringe. The resin was swollen in DMF (3.0 mL) and DMF was sucked out. To the resin was added 0.3 M stocked CH_2Cl_2 soltuion of 4-Benzyl-3-Boc-2-methylsemicarbazidylacetatic acid (2.7 mL, 0.80 mmol), DIPEA (277 μL, 1.59 mmol) and HATU (302 mg, 0.80 mmol) at room temperature. After being shaken for 12 hr, the mixture was filtered and the resin was washed with DMF (5.0 mL x 5 min x 3) and CH_2Cl_2 (5.0 mL x 5 min x 3). The resin was dried under reduced pressure to afford desired resin.

Step-5

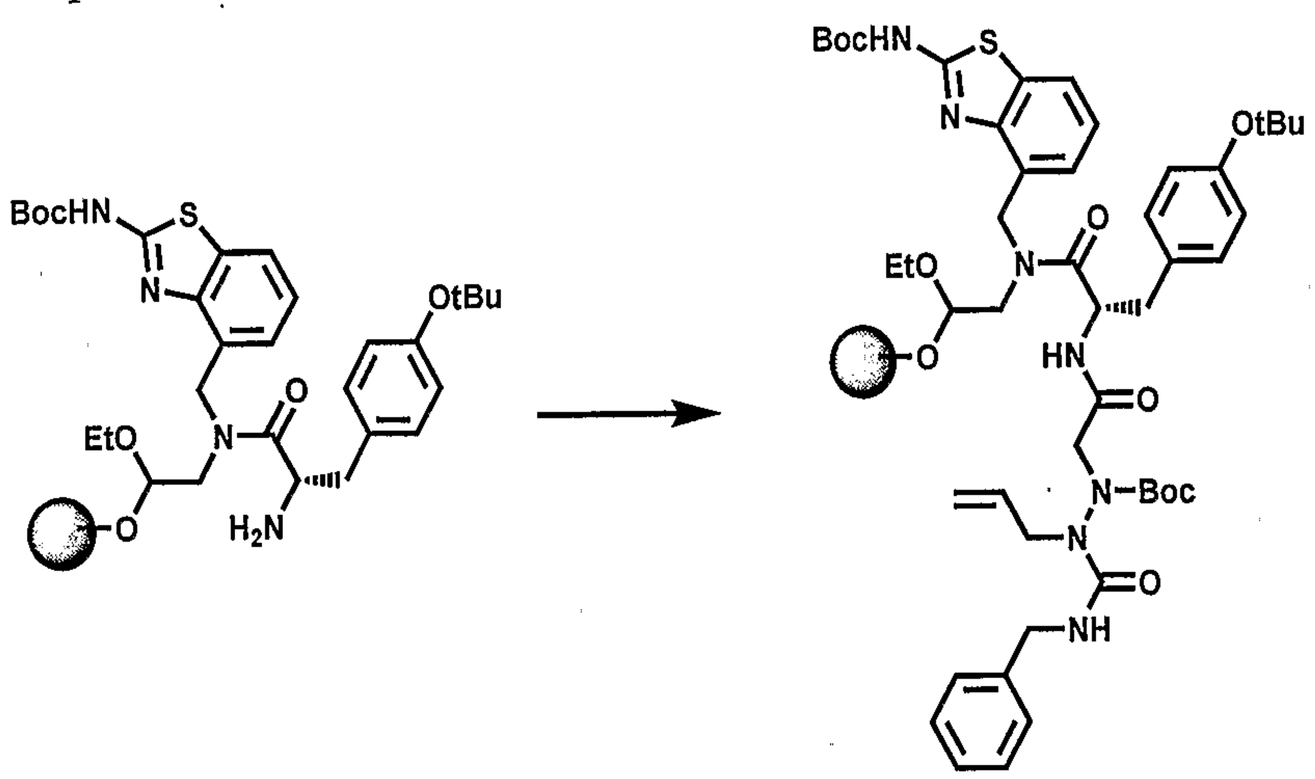


The resin (350 mg, 0.54 mmol/g) was placed in 20 mL plastic disposable syringe. After addition of 99% HCO_2H (4.0 mL), the mixture was shaken for 12 hr at room temperature, the solution was collected by filteration. The resin was washed with 99% HCO_2H (4.0 mL x 5 min x 2). The combined HCO_2H solutions were concentrated and then submitted to silica gel column chromatography to afford Compound No.1273 (9.1 mg, 6.8% from bromoacetal resin). *Rf* = 0.47 ($CHCl_3$:MeOH = 9:1).

Synthesis of Compound No.1285

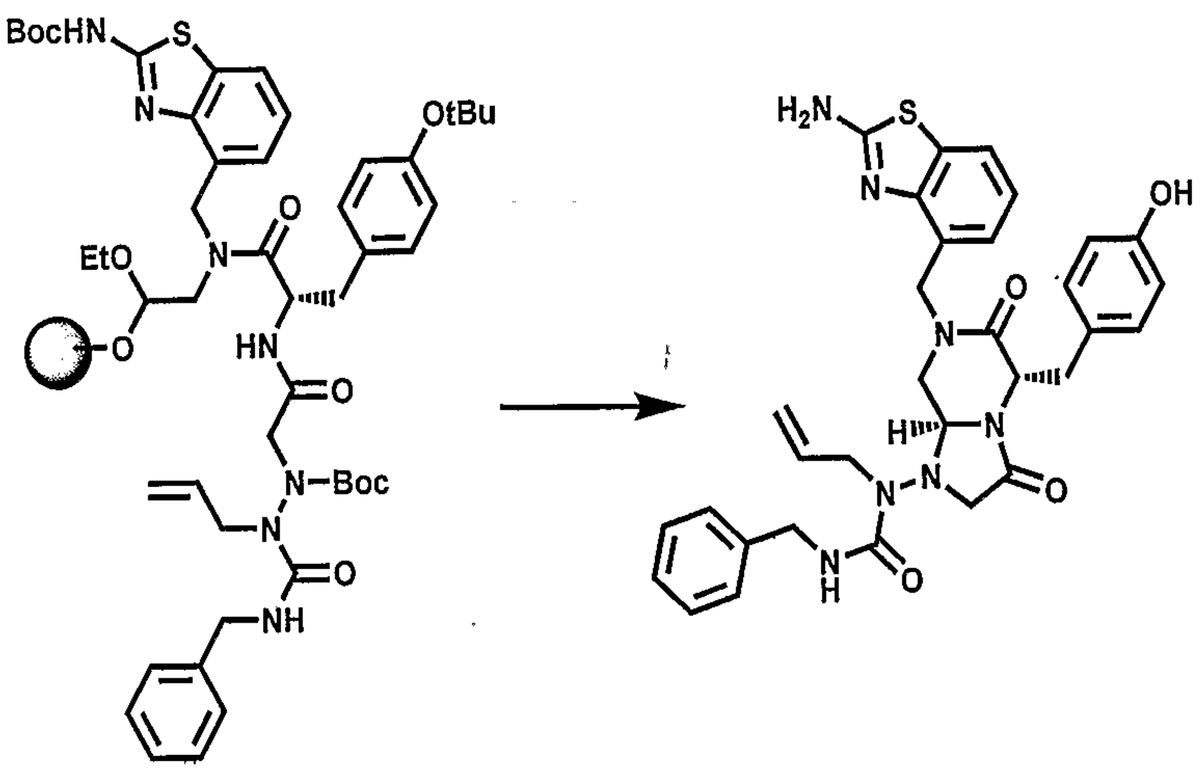


Step-1



The Amino resin (350 mg, 0.65 mmol/g) was placed in 20 mL plastic disposable syringe. The resin was swollen in DMF (3.0 mL) and DMF was sucked out. To the resin was added 0.3 M stocked CH_2Cl_2 soltuion of 4-Benzyl-3-Boc-2-allylsemicarbazidylacetatic acid (2.7 mL, 0.80 mmol), DIPEA (277 μL, 1.59 mmol) and HATU (302 mg, 0.80 mmol) at room temperature. After being shaken for 12 hr, the mixture was filtered and the resin was washed with DMF (5.0 mL x 5 min x 3) and CH_2Cl_2 (5.0 mL x 5 min x 3). The resin was dried under reduced pressure to afford desired resin.

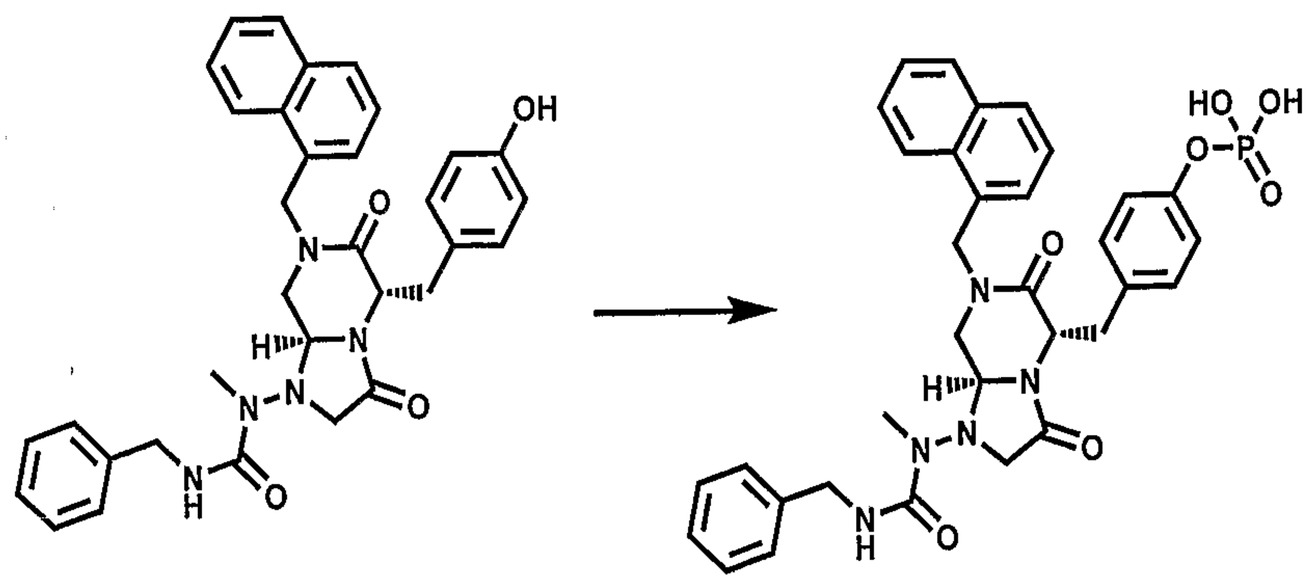
Step-2



The resin (350 mg, 0.53 mmol/g) was placed in 20 mL plastic disposable syringe. After addition of 99% HCO_2H (4.0 mL), the mixture was shaken for 12 hr at room temperature, the solution was collected by filteration. The resin was washed with 99% HCO_2H (4.0 mL x 5 min x 2). The combined HCO_2H solutions were concentrated and then submitted to silica gel column chromatography to afford Compound No. 1285 (18 mg, 13% from bromoacetal resin). *Rf* = 0.52 ($CHCl_3$:MeOH = 9:1).

Similar synthesis was carried out to obtain Compounds 1201-2200 as shown in Figures 7-11.

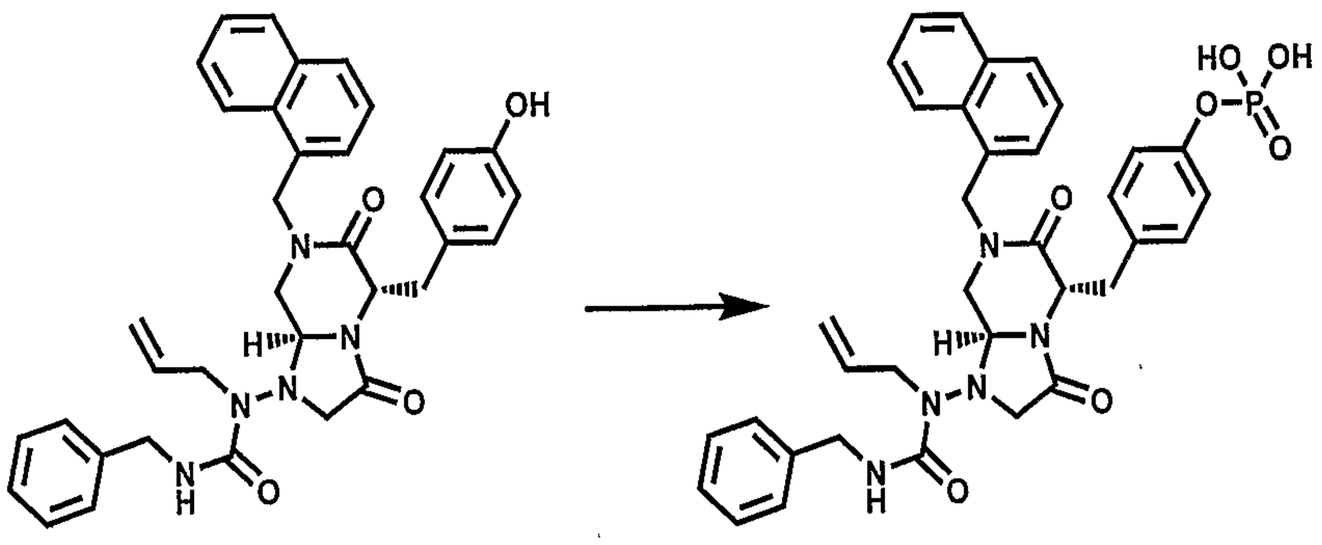
Synthesis of Compound No. 2201



To the cooled (0δ) solution of Compound No. 61 (18 mg, 0.032 mmol) in THF (500 δL) were added Et_3N (13.4 μL, 0.096 mmol) and $POCl_3$ (14.9 μL, 0.160 mmol) and then the mixture was stirred till SM was disappeared on TLC (4 hr). The mixture was diluted with H_2O (1mL) and then $NaHCO_3$ was added at 0δ to pH 8. After stirred overnight, the mixture was acidified to pH 3 with 1N HCl followed by extraction with $CHCl_3$ (5 mL x 3). The combined extracts were dried over Na_2SO_4, filtered and concentrated to afford pale yellow powder Compound No. 2201 (17.1 mg, 83%). TLC: *Rf* = 0.45δSilica gel F254,

$CHCl_3$:MeOH:EtOH:H_2O:AcOH:nBuOH=100:40:10:10:8:5δ; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.98 (1H, d, *J* = 7.7 Hz), 7.83 (1H, m), 7.77 (1H, d, *J* = 8.2 Hz), 7.51 (2H, m), 7.35 (1H, t, *J* = 7.3 Hz), 7.24-6.93 (10H, m), 6.07 (1H, br s), 5.86 (3H, br s), 5.34 (1H, br d, *J* = 15.0 Hz), 4.76 (2H, m), 4.11 (2H, br ABX, *J* = 15.5, 5.3 Hz), 3.62 (2H, m), 3.47 and 3.31 (2H, br ABq, *J* = 15.0 Hz), 3.22 (2H, br m), 3.02 (1H, br m), 2.77 (1H, br t, *J* = 10.6 Hz), 2.56 (3H, s); ^{31}P NMR (160.26MHz, $CDCl_3$) δ -3.57.

Synthesis of Compound No. 2202



To the cooled (0δ) solution of Compound No. 71 (21 mg, 0.036 mmol) in THF (1.0 mL) were added Et_3N (14.9 μL, 0.107 mmol) and $POCl_3$ (16.6 μL, 0.178 mmol) and then the mixture was stirred till SM was disappeared on TLC (4 hr). The mixture was diluted with H_2O (1mL) and then $NaHCO_3$ was added at 0δ to pH 8. After stirred overnight, the mixture was acidified to pH 3 with 1N HCl followed by extraction with $CHCl_3$ (5 mL x 3). The combined extracts were dried over Na_2SO_4, filtered and concentrated to afford pale yellow powder Compound No. 2202 (21.0 mg, 88%). TLC: *Rf* = 0.53δSilica gel F254, $CHCl_3$:MeOH:EtOH:H_2O:AcOH:nBuOH=100:40:10:10:8:5δ.

Similar synthesis was carried out to obtain Compounds 2203-2217 as shown in Figure 27. Diastereomeric and Enantiomeric stereo isomers of Compounds 2203-2217 were obtained and are shown Figure 12.

Table 2 below shows the molecular weight (M.W.) and mass for compounds 1-2217.

TABLE 2

Compound No.	M.W.	Mass
1	533	534
2	551	552
3	563	564
4	602	603
5	457	458
6	561	562
7	579	580
8	591	592
9	630	631
10	485	486
11	559	560
12	577	578
13	589	590
14	628	629
15	483	484
16	557	558
17	575	576
18	587	588
19	626	627
20	481	482
21	561	562
22	579	580
23	591	592
24	630	631
25	485	486
26	558	559
27	576	577
28	588	589
29	627	628
30	482	483
31	547	548
32	565	566
33	577	578
34	616	617
35	471	472
36	575	576
37	593	594
38	605	606
39	644	645
40	499	500
41	573	574
42	591	592
43	603	604
44	642	643
45	497	498
46	571	572
47	589	590
48	601	602
49	640	641
50	495	496
51	575	576
52	593	594
53	605	606
54	644	645
55	499	500
56	572	573
57	590	591
58	602	603
59	641	642
60	496	497
61	563	564
62	581	582
63	593	594
64	632	633
65	487	488
66	591	592
67	609	610
68	621	622
69	660	661
70	515	516
71	589	590
72	607	608
73	619	620
74	658	659
75	513	514
76	587	588
77	605	606
78	617	618
79	656	657
80	511	512
81	591	592
82	609	610
83	621	622
84	660	661
85	515	516
86	588	589
87	606	607
88	618	619
89	657	658
90	512	513
91	563	564
92	581	582
93	609	610
94	648	649
95	503	504
96	607	608
97	625	626
98	637	638
99	676	677
100	531	532
101	605	606
102	623	624
103	635	636
104	674	675
105	529	530
106	603	604
107	621	622
108	633	634
109	672	673
110	527	528
111	607	608
112	625	626
113	637	638
114	676	677
115	531	532
116	604	605
117	622	623
118	634	635
119	673	674
120	528	529

Compound No.	M.W.	Mass
121	562	563
122	580	581
123	592	593
124	631	632
125	486	487
126	590	591
127	608	609
128	620	621
129	659	660
130	514	515
131	588	589
132	606	607
133	618	619
134	657	658
135	512	513
136	586	587
137	604	605
138	616	617
139	655	656
140	510	511
141	590	591
142	608	609
143	620	621
144	659	660
145	514	515
146	587	588
147	605	606
148	617	618
149	656	657
150	511	512
151	590	591
152	608	609
153	620	621
154	659	660
155	514	515
156	618	619
157	636	637
158	648	649
159	687	688
160	542	543

Compound No.	M.W.	Mass
161	616	617
162	634	635
163	646	647
164	685	686
165	540	541
166	614	615
167	632	633
168	644	645
169	683	684
170	538	539
171	618	619
172	636	637
173	648	649
174	687	688
175	542	543
176	615	616
177	633	634
178	645	646
179	684	685
180	539	540
181	666	667
182	684	685
183	696	697
184	735	736
185	590	591
186	694	695
187	712	713
188	724	725
189	763	764
190	618	619
191	692	693
192	710	711
193	722	723
194	761	762
195	616	617
196	690	691
197	708	709
198	720	721
199	759	760
200	614	615

Compound No.	M.W.	Mass
201	694	695
202	712	713
203	724	725
204	763	764
205	618	619
206	691	692
207	709	710
208	721	722
209	760	761
210	615	616
211	696	697
212	714	715
213	726	727
214	765	766
215	620	621
216	724	725
217	742	743
218	754	755
219	793	794
220	648	649
221	722	723
222	740	741
223	752	753
224	791	792
225	646	647
226	720	721
227	738	739
228	750	751
229	789	790
230	644	645
231	724	725
232	742	743
233	754	755
234	793	794
235	648	649
236	721	722
237	739	740
238	751	752
239	790	791
240	645	646

Compound No.	M.W.	Mass
241	590	591
242	608	609
243	620	621
244	659	660
245	514	515
246	618	619
247	636	637
248	648	649
249	687	688
250	542	543
251	616	617
252	634	635
253	646	647
254	685	686
255	540	541
256	614	615
257	632	633
258	644	645
259	683	684
260	538	539
261	618	619
262	636	637
263	648	649
264	687	688
265	542	543
266	615	616
267	633	634
268	645	646
269	684	685
270	539	540
271	592	593
272	610	611
273	622	623
274	661	662
275	516	517
276	620	621
277	638	639
278	650	651
279	689	690
280	544	545

Compound No.	M.W.	Mass
281	618	619
282	636	637
283	648	649
284	687	688
285	542	543
286	616	617
287	634	635
288	646	647
289	685	686
290	540	541
291	620	621
292	638	639
293	650	651
294	689	690
295	544	545
296	617	618
297	635	636
298	647	648
299	686	687
300	541	542
301	577	578
302	595	596
303	607	608
304	646	647
305	501	502
306	605	606
307	623	624
308	635	636
309	674	675
310	529	530
311	603	604
312	621	622
313	633	634
314	672	673
315	527	528
316	601	602
317	619	620
318	631	632
319	670	671
320	525	526

Compound No.	M.W.	Mass
321	605	606
322	623	624
323	635	636
324	674	675
325	529	530
326	602	603
327	620	621
328	632	633
329	671	672
330	526	527
331	635	636
332	653	654
333	665	666
334	704	705
335	559	560
336	663	664
337	681	682
338	693	694
339	732	733
340	587	588
341	661	662
342	679	680
343	691	692
344	730	731
345	585	586
346	659	660
347	677	678
348	689	690
349	728	729
350	583	584
351	663	664
352	681	682
353	693	694
354	732	733
355	587	588
356	660	661
357	678	679
358	690	691
359	729	730
360	584	585

Compound No.	M.W.	Mass
361	716	717
362	734	735
363	746	747
364	785	786
365	640	641
366	744	745
367	762	763
368	774	775
369	813	814
370	668	669
371	742	743
372	760	761
373	772	773
374	811	812
375	666	667
376	740	741
377	758	759
378	770	771
379	809	810
380	664	665
381	744	745
382	762	763
383	774	775
384	813	814
385	668	669
386	741	742
387	759	760
388	771	772
389	810	811
390	665	666
391	565	566
392	583	584
393	595	596
394	634	635
395	489	490
396	593	594
397	611	612
398	623	624
399	662	663
400	517	518

Compound No.	M.W.	Mass		Compound No.	M.W.	Mass
401	591	592		441	606	607
402	609	610		442	624	625
403	621	622		443	636	637
404	660	661		444	675	676
405	515	516		445	530	531
406	589	590		446	603	604
407	607	608		447	621	622
408	619	620		448	633	634
409	658	659		449	672	673
410	513	514		450	527	528
411	593	594		451	634	635
412	611	612		452	652	653
413	623	624		453	664	665
414	662	663		454	703	704
415	517	518		455	558	559
416	590	591		456	662	663
417	608	609		457	680	681
418	620	621		458	692	693
419	659	660		459	731	732
420	514	515		460	586	587
421	578	579		461	660	661
422	596	597		462	678	679
423	608	609		463	690	691
424	647	648		464	729	730
425	502	503		465	584	585
426	606	607		466	658	659
427	624	625		467	676	677
428	636	637		468	688	689
429	675	676		469	727	728
430	530	531		470	582	583
431	604	605		471	662	663
432	622	623		472	680	681
433	634	635		473	692	693
434	673	674		474	731	732
435	528	529		475	586	587
436	602	603		476	659	660
437	620	621		477	677	678
438	632	633		478	689	690
439	671	672		479	728	729
440	526	527		480	583	584

Compound No.	M.W.	Mass	Compound No.	M.W.	Mass	Compound No.	M.W.	Mass
481	677	678	521	633	634	561	668	669
482	695	696	522	651	652	562	686	687
483	707	708	523	663	664	563	698	699
484	746	747	524	702	703	564	737	738
485	601	602	525	557	558	565	592	593
486	705	706	526	631	632	566	665	666
487	723	724	527	649	650	567	683	684
488	735	736	528	661	662	568	695	696
489	774	775	529	700	701	569	734	735
490	629	630	530	555	556	570	589	590
491	703	704	531	635	636	571	587	588
492	721	722	532	653	654	572	605	606
493	733	734	533	665	666	573	617	618
494	772	773	534	704	705	574	656	657
495	627	628	535	559	560	575	511	512
496	701	702	536	632	633	576	615	616
497	719	720	537	650	651	577	633	634
498	731	732	538	662	663	578	645	646
499	770	771	539	701	702	579	684	685
500	625	626	540	556	557	580	539	540
501	705	706	541	640	641	581	613	614
502	723	724	542	658	659	582	631	632
503	735	736	543	670	671	583	643	644
504	774	775	544	709	710	584	682	683
505	629	630	545	564	565	585	537	538
506	702	703	546	668	669	591	615	616
507	720	721	547	686	687	592	633	634
508	732	733	548	698	699	593	645	646
509	771	772	549	737	738	594	684	685
510	626	627	550	592	593	595	539	540
511	607	608	551	666	667	586	611	612
512	625	626	552	684	685	587	629	630
513	637	638	553	696	697	588	641	642
514	676	677	554	735	736	589	680	681
515	531	532	555	590	591	590	535	536
516	635	636	556	664	665	596	612	613
517	653	654	557	682	683	597	630	631
518	665	666	558	694	695	598	642	643
519	704	705	559	733	734	599	681	682
520	559	560	560	588	589	600	536	537

Compound No.	M.W.	Mass
601	551	552
602	579	580
603	577	578
604	565	566
605	593	594
606	591	592
607	581	582
608	609	610
609	607	608
610	497	498
611	525	526
612	523	524
613	511	512
614	539	540
615	537	538
616	527	528
617	555	556
618	553	554
619	513	514
620	541	542
621	539	540
622	527	528
623	555	556
624	553	554
625	543	544
626	571	572
627	569	570
628	483	484
629	511	512
630	509	510
631	497	498
632	525	526
633	523	524
634	513	514
635	541	542
636	539	540
637	518	519
638	546	547
639	544	545
640	532	533

Compound No.	M.W.	Mass
641	560	561
642	558	559
643	548	549
644	576	577
645	574	575
646	553	554
647	581	582
648	579	580
649	567	568
650	595	596
651	593	594
652	583	584
653	611	612
654	609	610
655	553	554
656	581	582
657	579	580
658	567	568
659	595	596
660	593	594
661	583	584
662	611	612
663	609	610
664	563	564
665	591	592
666	589	590
667	577	578
668	605	606
669	603	604
670	593	594
671	621	622
672	619	620
673	545	546
674	573	574
675	571	572
676	559	560
677	587	588
678	585	586
679	575	576
680	603	604

Compound No.	M.W.	Mass
681	601	602
682	518	519
683	546	547
684	544	545
685	532	533
686	560	561
687	558	559
688	548	549
689	576	577
690	574	575
691	497	498
692	525	526
693	523	524
694	511	512
695	539	540
696	537	538
697	527	528
698	555	556
699	553	554
700	497	498
701	525	526
702	523	524
703	511	512
704	539	540
705	537	538
706	527	528
707	555	556
708	553	554
709	497	498
710	525	526
711	523	524
712	511	512
713	539	540
714	537	538
715	527	528
716	555	556
717	553	554
718	541	542
719	569	570
720	567	568

Compound No.	M.W.	Mass
721	555	556
722	583	584
723	581	582
724	571	572
725	599	600
726	597	598
727	554	555
728	582	583
729	580	581
730	568	569
731	596	597
732	594	595
733	584	585
734	612	613
735	610	611
736	554	555
737	582	583
738	580	581
739	568	569
740	596	597
741	594	595
742	584	585
743	612	613
744	610	611
745	554	555
746	582	583
747	580	581
748	568	569
749	596	597
750	594	595
751	584	585
752	612	613
753	610	611
754	561	562
755	589	590
756	587	588
757	575	576
758	603	604
759	601	602
760	591	592

Compound No.	M.W.	Mass
761	619	620
762	617	618
763	562	563
764	590	591
765	588	589
766	576	577
767	604	605
768	602	603
769	592	593
770	620	621
771	618	619
772	568	569
773	596	597
774	594	595
775	582	583
776	610	611
777	608	609
778	598	599
779	626	627
780	624	625
781	603	604
782	631	632
783	629	630
784	617	618
785	645	646
791	555	556
792	553	554
793	541	542
794	569	570
795	567	568
786	643	644
787	633	634
788	661	662
789	659	660
790	527	528
796	557	558
797	585	586
798	583	584
799	544	545
800	572	573

Compound No.	M.W.	Mass
801	570	571
802	558	559
803	586	587
804	584	585
805	574	575
806	602	603
807	600	601
808	526	527
809	554	555
810	552	553
811	540	541
812	568	569
813	566	567
814	556	557
815	584	585
816	582	583
817	526	527
818	554	555
819	552	553
820	540	541
821	568	569
822	566	567
823	556	557
824	584	585
825	582	583
826	519	520
827	547	548
828	545	546
829	533	534
830	561	562
831	559	560
832	549	550
833	577	578
834	575	576
835	534	535
836	562	563
837	560	561
838	548	549
839	576	577
840	574	575

Compound No.	M.W.	Mass
841	564	565
842	592	593
843	590	591
844	569	570
845	597	598
846	595	596
847	583	584
848	611	612
849	609	610
850	599	600
851	627	628
852	625	626
853	603	604
854	631	632
855	629	630
856	617	618
857	645	646
858	643	644
859	633	634
860	661	662
861	659	660
862	534	535
863	562	563
864	560	561
865	548	549
866	576	577
867	574	575
868	564	565
869	592	593
870	590	591
871	534	535
872	562	563
873	560	561
874	548	549
875	576	577
876	574	575
877	564	565
878	592	593
879	590	591
880	484	485

Compound No.	M.W.	Mass
881	512	513
882	510	511
883	498	499
884	526	527
885	524	525
886	514	515
887	542	543
888	540	541
889	484	485
890	512	513
891	510	511
892	498	499
893	526	527
894	524	525
895	514	515
896	542	543
897	540	541
898	534	535
899	562	563
900	560	561
901	548	549
902	576	577
903	574	575
904	564	565
905	592	593
906	590	591
907	534	535
908	562	563
909	560	561
910	548	549
911	576	577
912	574	575
913	564	565
914	592	593
915	590	591
916	519	520
917	547	548
918	545	546
919	533	534
920	561	562

Compound No.	M.W.	Mass
921	559	560
922	549	550
923	577	578
924	575	576
925	519	520
926	547	548
927	545	546
928	533	534
929	561	562
930	559	560
931	549	550
932	577	578
933	575	576
934	537	538
935	565	566
936	563	564
937	551	552
938	579	580
939	577	578
940	567	568
941	595	596
942	593	594
943	573	574
944	601	602
945	599	600
946	587	588
947	615	616
948	613	614
949	603	604
950	631	632
951	629	630
952	501	502
953	529	530
954	527	528
955	515	516
956	543	544
957	541	542
958	531	532
959	559	560
960	557	558

Compound No.	M.W.	Mass
961	501	502
962	529	530
963	527	528
964	515	516
965	543	544
966	541	542
967	531	532
968	559	560
969	557	558
970	501	502
971	529	530
972	527	528
973	515	516
974	543	544
975	541	542
976	531	532
977	559	560
978	557	558
979	552	553
980	580	581
981	578	579
982	566	567
983	594	595
984	592	593
985	582	583
986	610	611
987	608	609
988	566	567
989	594	595
990	592	593
991	580	581
992	608	609
993	606	607
994	596	597
995	624	625
996	622	623
997	523	524
998	551	552
999	549	550
1000	537	538

Compound No.	M.W.	Mass
1001	565	566
1002	563	564
1003	553	554
1004	581	582
1005	579	580
1006	537	538
1007	565	566
1008	563	564
1009	551	552
1010	579	580
1011	577	578
1012	567	568
1013	595	596
1014	593	594
1015	523	524
1016	551	552
1017	549	550
1018	537	538
1019	565	566
1020	563	564
1021	553	554
1022	581	582
1023	579	580
1024	537	538
1025	565	566
1026	563	564
1027	551	552
1028	579	580
1029	577	578
1030	567	568
1031	595	596
1032	593	594
1033	561	562
1034	589	590
1035	587	588
1036	575	576
1037	603	604
1038	601	602
1039	591	592
1040	619	620

Compound No.	M.W.	Mass
1041	617	618
1042	523	524
1043	551	552
1044	549	550
1045	537	538
1046	565	566
1047	563	564
1048	553	554
1049	581	582
1050	579	580
1051	537	538
1052	565	566
1053	563	564
1054	551	552
1055	579	580
1056	577	578
1057	567	568
1058	595	596
1059	593	594
1060	671	672
1061	699	700
1062	697	698
1063	685	686
1064	713	714
1065	711	712
1066	701	702
1067	729	730
1068	727	728
1069	561	562
1070	589	590
1071	587	588
1072	575	576
1073	603	604
1074	601	602
1075	591	592
1076	619	620
1077	617	618
1078	561	562
1079	589	590
1080	587	588

Compound No.	M.W.	Mass
1081	575	576
1082	603	604
1083	601	602
1084	591	592
1085	619	620
1086	617	618
1087	524	525
1088	552	553
1089	550	551
1090	538	539
1091	566	567
1092	564	565
1093	554	555
1094	582	583
1095	580	581
1096	538	539
1097	566	567
1098	564	565
1099	552	553
1100	580	581
1101	578	579
1102	568	569
1103	596	597
1104	594	595
1105	538	539
1106	566	567
1107	564	565
1108	552	553
1109	580	581
1110	578	579
1111	568	569
1112	596	597
1113	594	595
1114	540	541
1115	568	569
1116	566	567
1117	554	555
1118	582	583
1119	580	581
1120	570	571
1121	598	599
1122	596	597
1123	523	524
1124	551	552
1125	549	550
1126	537	538
1127	565	566
1128	563	564
1129	553	554
1130	581	582
1131	579	580
1132	539	540
1133	567	568
1134	565	566
1135	553	554
1136	581	582
1137	579	580
1138	569	570
1139	597	598
1140	595	596
1141	539	540
1142	567	568
1143	565	566
1144	553	554
1145	581	582
1146	579	580
1147	569	570
1148	597	598
1149	595	596
1150	540	541
1151	568	569
1152	566	567
1153	554	555
1154	582	583
1155	580	581
1156	570	571
1157	598	599
1158	596	597
1159	524	525
1160	552	553
1161	550	551
1162	538	539
1163	566	567
1164	564	565
1165	554	555
1166	582	583
1167	580	581
1168	540	541
1169	568	569
1170	566	567
1171	554	555
1172	582	583
1173	580	581
1174	570	571
1175	598	599
1176	596	597
1177	554	555
1178	582	583
1179	580	581
1180	568	569
1181	596	597
1182	594	595
1183	584	585
1184	612	613
1185	610	611
1186	583	584
1187	611	612
1188	609	610
1189	597	598
1190	625	626
1191	623	624
1192	613	614
1193	641	642
1194	639	640
1195	558	559
1196	586	587
1197	584	585
1198	572	573
1199	600	601
1200	598	599

Compound No.	M.W.	Mass
1201	555	556
1202	573	574
1203	585	586
1204	624	625
1205	479	480
1206	521	522
1207	583	584
1208	601	602
1209	613	614
1210	652	653
1211	507	508
1212	549	550
1213	581	582
1214	599	600
1215	611	612
1216	650	651
1217	505	506
1218	547	548
1219	579	580
1220	597	598
1221	609	610
1222	648	649
1223	503	504
1224	545	546
1225	583	584
1226	601	602
1227	613	614
1228	652	653
1229	507	508
1230	549	550
1231	580	581
1232	598	599
1233	610	611
1234	649	650
1235	504	505
1236	546	547
1237	569	570
1238	587	588
1239	599	600
1240	638	639

Compound No.	M.W.	Mass
1241	493	494
1242	535	536
1243	597	598
1244	615	616
1245	627	628
1246	666	667
1247	521	522
1248	563	564
1249	595	596
1250	613	614
1251	625	626
1252	664	665
1253	519	520
1254	561	562
1255	593	594
1256	611	612
1257	623	624
1258	662	663
1259	517	518
1260	559	560
1261	597	598
1262	615	616
1263	627	628
1264	666	667
1265	521	522
1266	563	564
1267	594	595
1268	612	613
1269	624	625
1270	663	664
1271	518	519
1272	560	561
1273	585	586
1274	603	604
1275	615	616
1276	654	655
1277	509	510
1278	551	552
1279	613	614
1280	631	632

Compound No.	M.W.	Mass
1281	643	644
1282	682	683
1283	537	538
1284	579	580
1285	611	612
1286	629	630
1287	641	642
1288	680	681
1289	535	536
1290	577	578
1291	609	610
1292	627	628
1293	639	640
1294	678	679
1295	533	534
1296	575	576
1297	613	614
1298	631	632
1299	643	644
1300	682	683
1301	537	538
1302	579	580
1303	610	611
1304	628	629
1305	640	641
1306	679	680
1307	534	535
1308	576	577
1309	601	602
1310	619	620
1311	631	632
1312	670	671
1313	525	526
1314	567	568
1315	629	630
1316	647	648
1317	659	660
1318	698	699
1319	553	554
1320	595	596

Compound No.	M.W.	Mass
1321	627	628
1322	645	646
1323	657	658
1324	696	697
1325	551	552
1326	593	594
1327	625	626
1328	643	644
1329	655	656
1330	694	695
1331	549	550
1332	591	592
1333	629	630
1334	647	648
1335	659	660
1336	698	699
1337	553	554
1338	595	596
1339	626	627
1340	644	645
1341	656	657
1342	695	696
1343	550	551
1344	592	593
1345	584	585
1346	602	603
1347	614	615
1348	653	654
1349	508	509
1350	550	551
1351	612	613
1352	630	631
1353	642	643
1354	681	682
1355	536	537
1356	578	579
1357	610	611
1358	628	629
1359	640	641
1360	679	680

Compound No.	M.W.	Mass
1361	534	535
1362	576	577
1363	608	609
1364	626	627
1365	638	639
1366	677	678
1367	532	533
1368	574	575
1369	612	613
1370	630	631
1371	642	643
1372	681	682
1373	536	537
1374	578	579
1375	609	610
1376	627	628
1377	639	640
1378	678	679
1379	533	534
1380	575	576
1381	612	613
1382	630	631
1383	642	643
1384	681	682
1385	536	537
1386	578	579
1387	640	641
1388	658	659
1389	670	671
1390	709	710
1391	564	565
1392	606	607
1393	638	639
1394	656	657
1395	668	669
1396	707	708
1397	562	563
1398	604	605
1399	636	637
1400	654	655

Compound No.	M.W.	Mass
1401	666	667
1402	705	706
1403	560	561
1404	602	603
1405	640	641
1406	658	659
1407	670	671
1408	709	710
1409	564	565
1410	606	607
1411	637	638
1412	655	656
1413	667	668
1414	706	707
1415	561	562
1416	603	604
1417	688	689
1418	706	707
1419	718	719
1420	757	758
1421	612	613
1422	654	655
1423	716	717
1424	734	735
1425	746	747
1426	785	786
1427	640	641
1428	682	683
1429	714	715
1430	732	733
1431	744	745
1432	783	784
1433	638	639
1434	680	681
1435	712	713
1436	730	731
1437	742	743
1438	781	782
1439	636	637
1440	678	679

Compound No.	M.W.	Mass
1441	716	717
1442	734	735
1443	746	747
1444	785	786
1445	640	641
1446	682	683
1447	713	714
1448	731	732
1449	743	744
1450	782	783
1451	637	638
1452	679	680
1453	718	719
1454	736	737
1455	748	749
1456	787	788
1457	642	643
1458	684	685
1459	746	747
1460	764	765
1461	776	777
1462	815	816
1463	670	671
1464	712	713
1465	744	745
1466	762	763
1467	774	775
1468	813	814
1469	668	669
1470	710	711
1471	742	743
1472	760	761
1473	772	773
1474	811	812
1475	666	667
1476	708	709
1477	746	747
1478	764	765
1479	776	777
1480	815	816

Compound No.	M.W.	Mass
1481	670	671
1482	712	713
1483	743	744
1484	761	762
1485	773	774
1486	812	813
1487	667	668
1488	709	710
1489	612	613
1490	630	631
1491	642	643
1492	681	682
1493	536	537
1494	578	579
1495	640	641
1496	658	659
1497	670	671
1498	709	710
1499	564	565
1500	606	607
1501	638	639
1502	656	657
1503	668	669
1504	707	708
1505	562	563
1506	604	605
1507	636	637
1508	654	655
1509	666	667
1510	705	706
1511	560	561
1512	602	603
1513	640	641
1514	658	659
1515	670	671
1516	709	710
1517	564	565
1518	606	607
1519	637	638
1520	655	656

Compound No.	M.W.	Mass
1521	667	668
1522	706	707
1523	561	562
1524	603	604
1525	614	615
1526	632	633
1527	644	645
1528	683	684
1529	538	539
1530	580	581
1531	642	643
1532	660	661
1533	672	673
1534	711	712
1535	566	567
1536	608	609
1537	640	641
1538	658	659
1539	670	671
1540	709	710
1541	564	565
1542	606	607
1543	638	639
1544	656	657
1545	668	669
1546	707	708
1547	562	563
1548	604	605
1549	642	643
1550	660	661
1551	672	673
1552	711	712
1553	566	567
1554	608	609
1555	639	640
1556	657	658
1557	669	670
1558	708	709
1559	563	564
1560	605	606

Compound No.	M.W.	Mass
1561	599	600
1562	617	618
1563	629	630
1564	668	669
1565	523	524
1566	565	566
1567	627	628
1568	645	646
1569	657	658
1570	696	697
1571	551	552
1572	593	594
1573	625	626
1574	643	644
1575	655	656
1576	694	695
1577	549	550
1578	591	592
1579	623	624
1580	641	642
1581	653	654
1582	692	693
1583	547	548
1584	589	590
1585	627	628
1586	645	646
1587	657	658
1588	696	697
1589	551	552
1590	593	594
1591	624	625
1592	642	643
1593	654	655
1594	693	694
1595	548	549
1596	590	591
1597	657	658
1598	675	676
1599	687	688
1600	726	727

Compound No.	M.W.	Mass	Compound No.	M.W.	Mass
1601	581	582	1641	796	797
1602	623	624	1642	835	836
1603	685	686	1643	690	691
1604	703	704	1644	732	733
1605	715	716	1645	764	765
1606	754	755	1646	782	783
1607	609	610	1647	794	795
1608	651	652	1648	833	834
1609	683	684	1649	688	689
1610	701	702	1650	730	731
1611	713	714	1651	762	763
1612	752	753	1652	780	781
1613	607	608	1653	792	793
1614	649	650	1654	831	832
1615	681	682	1655	686	687
1616	699	700	1656	728	729
1617	711	712	1657	766	767
1618	750	751	1658	784	785
1619	605	606	1659	796	797
1620	647	648	1660	835	836
1621	685	686	1661	690	691
1622	703	704	1662	732	733
1623	715	716	1663	763	764
1624	754	755	1664	781	782
1625	609	610	1665	793	794
1626	651	652	1666	832	833
1627	682	683	1667	687	688
1628	700	701	1668	729	730
1629	712	713	1669	587	588
1630	751	752	1670	605	606
1631	606	607	1671	617	618
1632	648	649	1672	656	657
1633	738	739	1673	511	512
1634	756	757	1674	553	554
1635	768	769	1675	615	616
1636	807	808	1676	633	634
1637	662	663	1677	645	646
1638	704	705	1678	684	685
1639	766	767	1679	539	540
1640	784	785	1680	581	582

Compound No.	M.W.	Mass
1681	613	614
1682	631	632
1683	643	644
1684	682	683
1685	537	538
1686	579	580
1687	611	612
1688	629	630
1689	641	642
1690	680	681
1691	535	536
1692	577	578
1693	615	616
1694	633	634
1695	645	646
1696	684	685
1697	539	540
1698	581	582
1699	612	613
1700	630	631
1701	642	643
1702	681	682
1703	536	537
1704	578	579
1705	600	601
1706	618	619
1707	630	631
1708	669	670
1709	524	525
1710	566	567
1711	628	629
1712	646	647
1713	658	659
1714	697	698
1715	552	553
1716	594	595
1717	626	627
1718	644	645
1719	656	657
1720	695	696

Compound No.	M.W.	Mass
1721	550	551
1722	592	593
1723	624	625
1724	642	643
1725	654	655
1726	693	694
1727	548	549
1728	590	591
1729	628	629
1730	646	647
1731	658	659
1732	697	698
1733	552	553
1734	594	595
1735	625	626
1736	643	644
1737	655	656
1738	694	695
1739	549	550
1740	591	592
1741	656	657
1742	674	675
1743	686	687
1744	725	726
1745	580	581
1746	622	623
1747	684	685
1748	702	703
1749	714	715
1750	753	754
1751	608	609
1752	650	651
1753	682	683
1754	700	701
1755	712	713
1756	751	752
1757	606	607
1758	648	649
1759	680	681
1760	698	699

Compound No.	M.W.	Mass
1761	710	711
1762	749	750
1763	604	605
1764	646	647
1765	684	685
1766	702	703
1767	714	715
1768	753	754
1769	608	609
1770	650	651
1771	681	682
1772	699	700
1773	711	712
1774	750	751
1775	605	606
1776	647	648
1777	699	700
1778	717	718
1779	729	730
1780	768	769
1781	623	624
1782	665	666
1783	727	728
1784	745	746
1785	757	758
1786	796	797
1787	651	652
1788	693	694
1789	725	726
1790	743	744
1791	755	756
1792	794	795
1793	649	650
1794	691	692
1795	723	724
1796	741	742
1797	753	754
1798	792	793
1799	647	648
1800	689	690

Compound No.	M.W.	Mass
1801	727	728
1802	745	746
1803	757	758
1804	796	797
1805	651	652
1806	693	694
1807	724	725
1808	742	743
1809	754	755
1810	793	794
1811	648	649
1812	690	691
1813	629	630
1814	647	648
1815	659	660
1816	698	699
1817	553	554
1818	595	596
1819	657	658
1820	675	676
1821	687	688
1822	726	727
1823	581	582
1824	623	624
1825	655	656
1826	673	674
1827	685	686
1828	724	725
1829	579	580
1830	621	622
1831	653	654
1832	671	672
1833	683	684
1834	722	723
1835	577	578
1836	619	620
1837	657	658
1838	675	676
1839	687	688
1840	726	727

Compound No.	M.W.	Mass
1841	581	582
1842	623	624
1843	654	655
1844	672	673
1845	684	685
1846	723	724
1847	578	579
1848	620	621
1849	662	663
1850	680	681
1851	692	693
1852	731	732
1853	586	587
1854	628	629
1855	690	691
1856	708	709
1857	720	721
1858	759	760
1859	614	615
1860	656	657
1861	688	689
1862	706	707
1863	718	719
1864	757	758
1865	612	613
1866	654	655
1867	686	687
1868	704	705
1869	716	717
1870	755	756
1871	610	611
1872	652	653
1873	690	691
1874	708	709
1875	720	721
1876	759	760
1877	614	615
1878	656	657
1879	687	688
1880	705	706

Compound No.	M.W.	Mass
1881	717	718
1882	756	757
1883	611	612
1884	653	654
1885	609	610
1886	627	628
1887	639	640
1888	678	679
1889	533	534
1890	575	576
1891	637	638
1892	655	656
1893	667	668
1894	706	707
1895	561	562
1896	603	604
1897	635	636
1898	653	654
1899	665	666
1900	704	705
1901	559	560
1902	601	602
1903	633	634
1904	651	652
1905	663	664
1906	702	703
1907	557	558
1908	599	600
1909	637	638
1910	655	656
1911	667	668
1912	706	707
1913	561	562
1914	603	604
1915	634	635
1916	652	653
1917	664	665
1918	703	704
1919	558	559
1920	600	601

Compound No.	M.W.	Mass
1921	609	610
1922	627	628
1923	639	640
1924	678	679
1925	533	534
1926	575	576
1927	637	638
1928	655	656
1929	667	668
1930	706	707
1931	561	562
1932	603	604
1933	635	636
1934	653	654
1935	665	666
1936	704	705
1937	559	560
1938	601	602
1939	633	634
1940	651	652
1941	663	664
1942	702	703
1943	557	558
1944	599	600
1945	637	638
1946	655	656
1947	667	668
1948	706	707
1949	561	562
1950	603	604
1951	634	635
1952	652	653
1953	664	665
1954	703	704
1955	558	559
1956	600	601
1957	626	627
1958	644	645
1959	656	657
1960	695	696

Compound No.	M.W.	Mass
1961	550	551
1962	592	593
1963	654	655
1964	672	673
1965	684	685
1966	723	724
1967	578	579
1968	620	621
1969	652	653
1970	670	671
1971	682	683
1972	721	722
1973	576	577
1974	618	619
1975	650	651
1976	668	669
1977	680	681
1978	719	720
1979	574	575
1980	616	617
1981	654	655
1982	672	673
1983	684	685
1984	723	724
1985	578	579
1986	620	621
1987	651	652
1988	669	670
1989	681	682
1990	720	721
1991	575	576
1992	617	618
1993	626	627
1994	644	645
1995	656	657
1996	695	696
1997	550	551
1998	592	593
1999	654	655
2000	672	673

Compound No.	M.W.	Mass
2001	684	685
2002	723	724
2003	578	579
2004	620	621
2005	652	653
2006	670	671
2007	682	683
2008	721	722
2009	576	577
2010	618	619
2011	650	651
2012	668	669
2013	680	681
2014	719	720
2015	574	575
2016	616	617
2017	654	655
2018	672	673
2019	684	685
2020	723	724
2021	578	579
2022	620	621
2023	651	652
2024	669	670
2025	681	682
2026	720	721
2027	575	576
2028	617	618
2029	586	587
2030	604	605
2031	616	617
2032	655	656
2033	510	511
2034	552	553
2035	614	615
2036	632	633
2037	644	645
2038	683	684
2039	538	539
2040	580	581

Compound No.	M.W.	Mass
2041	612	613
2042	630	631
2043	642	643
2044	681	682
2045	536	537
2046	578	579
2047	610	611
2048	628	629
2049	640	641
2050	679	680
2051	534	535
2052	576	577
2053	614	615
2054	632	633
2055	644	645
2056	683	684
2057	538	539
2058	580	581
2059	611	612
2060	629	630
2061	641	642
2062	680	681
2063	535	536
2064	577	578
2065	640	641
2066	658	659
2067	670	671
2068	709	710
2069	564	565
2070	606	607
2071	668	669
2072	686	687
2073	698	699
2074	737	738
2075	592	593
2076	634	635
2077	666	667
2078	684	685
2079	696	697
2080	735	736

Compound No.	M.W.	Mass
2081	590	591
2082	632	633
2083	664	665
2084	682	683
2085	694	695
2086	733	734
2087	588	589
2088	630	631
2089	668	669
2090	686	687
2091	698	699
2092	737	738
2093	592	593
2094	634	635
2095	665	666
2096	683	684
2097	695	696
2098	734	735
2099	589	590
2100	631	632
2101	637	638
2102	655	656
2103	667	668
2104	706	707
2105	561	562
2106	603	604
2107	665	666
2108	683	684
2109	695	696
2110	734	735
2111	589	590
2112	631	632
2113	663	664
2114	681	682
2115	693	694
2116	732	733
2117	587	588
2118	629	630
2119	661	662
2120	679	680

Compound No.	M.W.	Mass
2121	691	692
2122	730	731
2123	585	586
2124	627	628
2125	665	666
2126	683	684
2127	695	696
2128	734	735
2129	589	590
2130	631	632
2131	662	663
2132	680	681
2133	692	693
2134	731	732
2135	586	587
2136	628	629
2137	659	660
2138	677	678
2139	689	690
2140	728	729
2141	583	584
2142	625	626
2143	687	688
2144	705	706
2145	717	718
2146	756	757
2147	611	612
2148	653	654
2149	685	686
2150	703	704
2151	715	716
2152	754	755
2153	609	610
2154	651	652
2155	683	684
2156	701	702
2157	713	714
2158	752	753
2159	607	608
2160	649	650

Compound No.	M.W.	Mass
2161	687	688
2162	705	706
2163	717	718
2164	756	757
2165	611	612
2166	653	654
2167	684	685
2168	702	703
2169	714	715
2170	753	754
2171	608	609
2172	650	651
2173	559	560
2174	577	578
2175	589	590
2176	628	629
2177	483	484
2178	525	526
2179	587	588
2180	605	606
2181	617	618
2182	656	657
2183	511	512
2184	553	554
2185	585	586
2186	603	604
2187	615	616
2188	654	655
2189	509	510
2190	551	552
2191	583	584
2192	601	602
2193	613	614
2194	652	653
2195	507	508
2196	549	550
2197	587	588
2198	605	606
2199	617	618
2200	656	657

Compound No.	M.W.	Mass
2203	661	662
2204	673	674
2205	671	672
2206	669	670
2207	687	688
2208	683	684
2209	695	696
2210	693	592
2211	691	692
2212	709	710
2213	559	560
2214	701	702
2215	713	714
2216	711	712
2217	709	710

EXAMPLE 3

EFFECT OF ICG-001 AND IMATINIB ON CANCER CELL LINES

The human ovarian sarcoma cells MES-SA and the corresponding doxorubicin-resistant line MES-SA/Dx5 (Hua J et al Gynecologic Oncol. 2005) and the CML derived cell line K562 and the corresponding imatinib mesylate resistant K562 cells (Dai Y et al JBC 279, 34227, 2004) were used for this example. Both resistant (R) cell lines showed dramatically increased levels of both cytosolic and nuclear β-catenin as judged by both immunoblotting (Fig. 14A) and immunofluoresence microscopy (Fig. 14B) compared to their drug sensitive (S) counterparts. The increased nuclear β-catenin was reflected in dramatically increased TCF/β-catenin transcriptional activity as judged by the TOPFLASH reporter, which could be completely blocked using a dominant negative TCF4 construct (Fig. 14C).

To confirm that activation of the Wnt/β-catenin pathway was critical for the activation of *MDR-1* expression in MES-SA cells, the following set of experiments were performed. MES-SA cells were transfected with either the TOPFLASH or FOPFLASH reporters and treated with media alone, or with added Wnt3a or Wnt5a. Addition of "canonical" Wnt3a but not "non-canonical" Wnt5a increased luciferase activity ~ 4 fold and the increased activation was completely blocked by cotransfection of a dnTCF4 construct (Fig. 15A). Similarly, an ~ 2 fold increase in *MDR-1*/lucifearse activity was observed upon treatment with Wnt3a. This activation was also completely inhibited by cotransfection of the dnTCF4 construct. Wnt5a conditioned media showed no enhancement of expression of the *MDR-1*/luciferase reporter construct (Fig. 15B).

To further confirm the importance of the role of nuclear β-catenin in driving *MDR-1* expression, isogenic HCT-116 cell lines were utilized (Waldmann 2002). Wild-type HCT-116 cells demonstrated the highest *MDR-1* expression as judged by both *MDR*-1/luciferase activity and real time RT-PCR (Fig. 15C, D). Hβ18(ko/*) cells, in which the wild type allele of β-catenin is deleted but the oncogenic allele is maintained, and have somewhat lower levels of nuclear β-catenin, showed slightly reduced *MDR-1*/luciferase activity and a reduction in *MDR-1* message (Fig. 15C, D). Hβ92 (wt/ko) cells, in which the wild type allele is retained and the oncogenic allele is deleted, showed even more dramatic reduction of *MDR-1*/luciferase activity and message (Fig. 15C, D).

TCF/β-catenin recruitment at the *MDR-1* promoter in MES-SA and MES-SA/Dx5 cells was investigated. In the MES-SA/Dx5 cells, in which *MDR-1* is actively transcribed as judged

by the level of acetylated Histone H3 at the promoter, and expressed, there was obvious recruitment of both TCF4 and β-catenin to the promoter, which was absent in the parental MES-SA cell line (Fig. 15E).

To investigate differential coactivator usage for the transcriptional regulation of the *MDR-1* gene in MES-SA cells, the chemogenomic tool ICG-001 was used (Emami et al. 2004). ICG-001 reduced *MDR-1*/luciferase activity in MES-SA/Dx5 cells with an IC_{50} ~ 16uM (Fig. 16A). The level of MDR-1 protein expression in the MES-SA/Dx5 cells was also significantly reduced by ICG-001 as judged by immunofluoresence (Fig. 16B) and immunoblotting (Fig. 16C) in a dose dependent manner. This effect was reflected at the message level as judged by real time RT-PCR in both MES-SA/Dx5 cells (Fig. 16D) and the imatinib mesylate resistant K562 cells (Fig. 16E).

MDR-1 transcriptional regulation in the isogenic HCT116 cell lines was also investigated. In all of the isogenic HCT116 cell lines, cotransfection of point mutant constitutively translocating β-catenin and CBP increased *MDR-1*/luciferase expression (Fig. 17A), whereas transfection of point mutant β-catenin alone only increased luciferase activity compared to non-transfected control in the Hβ92(wt/ko) cells (Fig. 17A), which have severely limiting amounts of nuclear β-catenin. Transfection of p300 decreased *MDR-1*/luciferase activity below control levels in all 3 cell lines (Fig. 17A). ICG-001 dose dependency decreased *MDR-1*/luciferase activity in the HCT-116 wild type and Hβ18(ko/*) cell lines, whereas essentially no further reduction below basal levels was observed in the Hβ92(wt/ko) cells (Fig. 17B), consistent with a lack of β-catenin/CBP driven transcription in these cells (MA.H. et al., Differential Roles for the Coactivators CBP and p300 on TCV/β-Catenin-Mediated Survivin Gene Expression, *Oncogene* 24:3619-3631, 2005).

ChIP assay in the MES-SA/Dx5 cells demonstrated that in untreated cells, there was significant occupancy of the *MDR-1* promoter by CBP, which was blocked in a dose dependent fashion by ICG-001(Fig. 17C). On the contrary, in the absence of ICG-001, there was minimal occupancy of the *MDR-1* promoter by p300, however occupancy increased with 25uM ICG-001 treatment (Fig. 17C). Similar ICG-001 induced p300 recruitment at the *survivin* promoter has been previously observed, which was associated with recruitment of proteins associated with transcriptional repression (i.e., HDAC6 and PML) (H Ma et al. Oncogene 2005). A proposed non-binding mechanism is repressive transcriptional apparatus recruitment to the *MDR-1* promoter by p300.

The mRNA level of endogenous CBP coactivator was also significantly increased in the MES-SA/Dx5 cells compared to the MES-SA cells, whereas p300 levels message remained essentially equal (Fig. 18A). Immunofluoresence also demonstrated a substantial increase in

CBP (Fig. 18B) as did immunoblotting in the MES-SA/Dx5 compared to the MES-SA parental line; although p300 protein levels remained essentially equal (Fig. 18C).

Coimmunoprecipitation of CBP or p300 showed a strong association of β-catenin with CBP in the MES-SA/Dx5 cells that was not present in the MES-SA cells while virtually no association of β-catenin with p300 could be detected in either cell line (Fig. 18D). Finally, coactivator specific siRNA was utilized (H Ma Oncogene 2005) to knockdown either CBP or p300 in the MES-SA/Dx5 cells. *MDR-1* message was specifically decreased by treatment with siRNA to CBP compared to the siRNA control treated cells, whereas p300 siRNA increased *MDR-1* message levels compared to control (Fig. 18E). In culture, the MES-SA/Dx5 and K562 imatinib resistant cells grew at a somewhat faster rate than the corresponding sensitive cell lines (Fig. 19A, B). Consistent with previous data (Emami et al PNAS 2004, H. Ma et al Oncogene 2005, and J Teo et al 2005), enhanced β-catenin/CBP driven transcription was reflected at both the message (Fig. 19C, D) and protein levels (Fig. 19E, F) for both survivin and cyclin D1, in both resistant cell lines compared to their sensitive counterparts.

To further investigate the "cancer stem cell" nature of these resistant cell lines, the expression of a number of markers associated with stem cell pluripotency and survival was evaluated. Real time RT-PCR demonstrated an increased expression of *Oct4, hTert, Bmi-1* and *ABCG-2* in the MES-SA/DX5 and imatinib resistant K562 cells compared to their sensitive counterparts (Fig. 20A). Protein levels for both Oct4 and the stem cell surface marker CD133 were also increased in both resistant cell lines (Fig. 20B).

Although modern chemotherapies kill a majority of the cells in a tumor, it is believed that the resistant "cancer stems cells" are significantly associated with disease relapse. MDR transporters are believed to play important roles in protecting cancer stem cells from chemotherapy (Dean et al, Nat. Rev. Cancer 5, 275, 2005). To further study this phenomenon, a series of experiments was performed. Drug resistant MES-SA/Dx5 and K562 imatinib resistant cells were treated with Doxorubicin +/- ICG-001 or Imatinib mesylate +/- 001. As can be seen in Figure 21A, ICG-001 in combination with the respective chemotherapeutic agent was significantly more effective than the chemotherapeutic agent alone or ICG-001 alone in decreasing cell proliferation/viability. The addition of ICG-001 to MES-SA/Dx5 cells treated with either 1mg/ml or 5 mg/ml of Doxorubicin increased caspase3/7 activation significantly.

EXAMPLE 4

EFFECT OF ICG-001 ON CHRONIC MYELOCYTIC LEUKEMIA (CML)

Despite the significant clinical success achieved in CML patients with imatinib to date, in advanced phase disease, the responses are often short-lived and patients invariably undergo disease progression (Melo J Hematology, 2003). This is the result of the emergence of leukemic drug resistant clones associated with increased nuclear β-catenin levels, a hallmark of increased TCF/β-catenin transcription (Weissman NEJM 2003). The efficacy of ICG-001 either alone or in combination with imatnib mesylate was investigated in both normal CD34+ blast cells (mostly early stem/progenitors) and from bone barrow of CML patients at various stages of progression. CD34+ CML blasts showed significantly higher expression of *β-catenin, ABCB1, htert, survivin/variant ΔEx3* and *BMI-1* relative to CD34- cells, indicating constitutive activation of Wnt/catenin signaling and confirming the increased "stem/progenitor-like" features of this CD34+ CML blast cell population (Fig. 21C) (Jamieson et al., 2004).

Combination ICG-001 and imatinib treatment resulted in the most significant reduction in total colony forming units (CFU) as compared to the control of either drug treatment alone in all samples (Fig. 21D). Moreover, the morphological features of the colonies after drug treatment are also altered; the colonies became small and dispersed, and the dispersed colony phenotypes were more profound in the combination treatments, indicating that the treated colonies have an increased state of differentiation. In sharp contrast, the control colonies were large and compact. The H&E staining displayed reduced nuclear/cytoplasmic ratio in the treated cells (Fig. 21E). Importantly, treatment of normal CD34+ cells with ICG-001 had minimal effects on total cellularity, CFU-Es and BFU-Es. ICG-001 did not affect colony formation of normal CD34+ hematopoietic cells.

In summary, whereas imatinib itself had limited effect, imatinib plus IGC-001 had a significant additive effect. ICG-001 up to 20μM did not have significant adverse effects on normal CD34+ cells and induced differentiation but not capase activation in K562 cells.

EXAMPLE 5

THE EFFECT OF ICG-001 AND OF CISPLATIN ON CULTURED OVARIAN CARCINOMA AND MELANOMA CELLS EXPRESSING THE STEM CELL MARKERS CD133 OR PROMININ-1, RESPECTIVELY

This example describes measurements of the sensitivity of ovarian carcinoma cells and to ICG-001.

Colony inhibition assays were performed, in which plated cells from A2780, CP70, IGROV-1 and B16 cells were exposed to doses of ICG-001 within the range of 0.625 to 10 μM. An exemplary experiment is illustrated in Table 3.

Table 3

Colony numbers formed by plated cells from the cisplatin-sensitive A2780 exposed in vitro to ICG-001.

CONCENTRATION OF ICG-001 (μM)	COLONIES (n=4) M +/- SD	P-VALUE≤ *
Control	160 +/- 21.5	-
0.625	74 +/- 4.7	0.003
1.25	28 +/- 13.2	0.004
2.5	0.25 +/- 0.5	0.001
5	0	0.000
* 10	0	0.000

Statistical difference, according to t-test, when compared to control.

As shown Table 3, there were statistically significant differences between the control group (medium containing DMSO) and all the experimental groups (medium containing ICG-001 dissolved in DMSO) even at an ICG-001 concentration of 0.625 μM.

Table 4 presents data on the plating efficiencies of cultured cells from A2780, CP70, IGROV-1 and B16 in control wells as well as in wells exposed to ICG-001. The data indicate that the plating efficiency of the various cell lines was high, varying between 21 and 83%, which is commensurate with the fact that most of the plated cells expressed the CD133 marker of CSC.

Table 4

Average plating efficiency of 80 cells/well of the ovarian carcinoma lines and the mouse melanoma line treated with ICG-001.

CONCENTRATION OF ICG-001 (μM)	A2780 %	CP70 %	IGROV-1 %	IGROV-1/CP %	B16 %
Control	83	23	36	54	21
0.625	25	35	31	59	24
1.25	35	35	24	25	18
2.5	6	13	8	13	3
5	0	1	1	6	0
10	0	0	0	0	0

The cells were tested at range of concentrations of ICG-001 between 0.625 and 10 μM and at cisplatin concentrations between 1.25 to 20 μM. All three ovarian cancer lines tested (A2780, CP70 and IGROV-1) were more sensitive to ICG-001 than to cisplatin. For the cisplatin-resistant line CP70, >90% inhibition was achieved at 5 μM of ICG-001, as compared to 20 μM of cisplatin (Figure 23C). The cisplatin-sensitive lines, IGROV-1 and A2780, had similar sensitivity to ICG-001 as to cisplatin (Figure 23A and B). Figure 24 shows experiments in which the sensitivity of ovarian carcinoma lines to ICG-001 and cisplatin were compared.

The cells were tested at range of concentrations of ICG-001 between 0.625 and 10 μM and at cisplatin concentrations between 1.25 to 20 μM. All three ovarian cancer lines tested (A2780, CP70 and IGROV-1) were more sensitive to IC G-001 than to cisplatin. For the cisplatin-resistant line CP70,>90% inhibition was achieved at 5 μM of ICG-001.

EXAMPLE 6

INHIBITION OF CBP-β-CATENIN INTERACTION IN SW480 CELLS

The effect of several compounds on CBP-β-catenin binding was tested using the TOPFlash reporter system in SW480 cells.

As shown in Figure 25, increasing concentrations of compounds PRI-001, PRI-002, PRI-003, PRI-004, PRI-005 and PRI-006 were effective, as compared with ICG-001. Figure 26 shows pluc-6270 expression (luciferase) in SW480 cells treated with varying concentrations of ICG-001, PRI-003, and PRI-004.

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __3___

NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

JUMBO APPLICATIONS / PATENTS

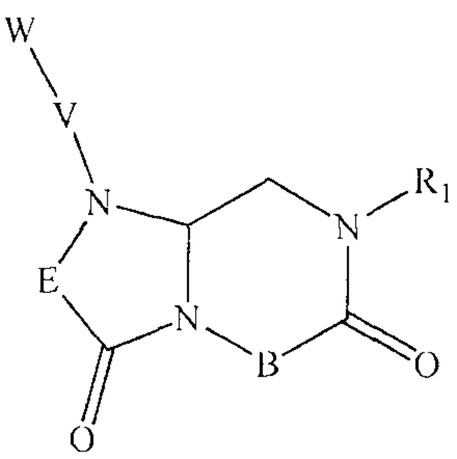
THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

THIS IS VOLUME __1___ OF __3___

NOTE: For additional volumes please contact the Canadian Patent Office.

CLAIMS:

1. A compound having formula (VI):



(VI)

or a pharmaceutically acceptable salt thereof, wherein

B is $-(CHR_2)-$,

E is $-(CHR_3)-$,

V is $-(XR_4)-$,

W is $-(C=O)-(XR_5R_6)$, substituted or unsubstituted oxadiazole, substituted or unsubstituted triazole, substituted or unsubstituted thiadiazole, substituted or unsubstituted 4,5 dihydrooxazole, substituted or unsubstituted 4,5 dihydrothiazole, substituted or unsubstituted 4,5 dihydroimidazole,

X is independently nitrogen, or CH,

R_1 is naphthylmethyl optionally substituted with alkyl; benzyl optionally substituted with one or more substituents selected from halogen, alkoxy, alkyl, dialkylamino, amino, and heterocyclic alkyl; or heterocyclic alkyl optionally substituted with one or more substituents selected from oxo, halogen, alkyl, alkynyl, dialkylamino, 2-methylformyl benzyl and amino;

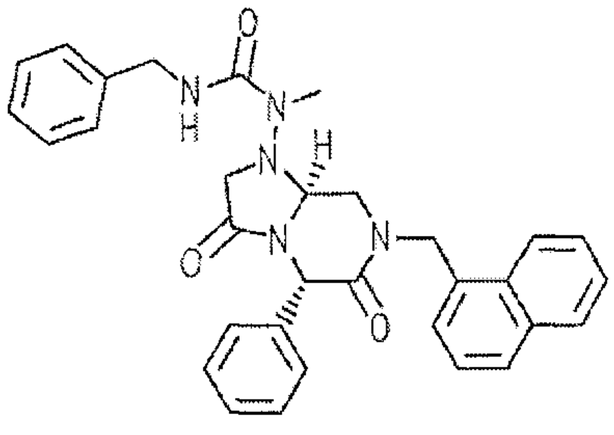
R_2 is phenyl; benzyl optionally substituted with one or more substituents selected from hydroxy, -NHCHO,

nitro, -NHC(O)-aryl, -NHC(O)O-benzyl; $-OC(O)N(alkyl)_2$, $-OCH_2COOCH_3$, $-OC(O)(CH_2)_2N(alkyl)_2$, $-OC(O)(CH_2)_2OH$, $-NHSO_2CH_3$, triazolyl and phosphate; or heterocyclic alkyl optionally substituted with one or more substituents selected from alkyl, oxo, halogen and hydroxy;

R_3 is hydrogen or alkyl;

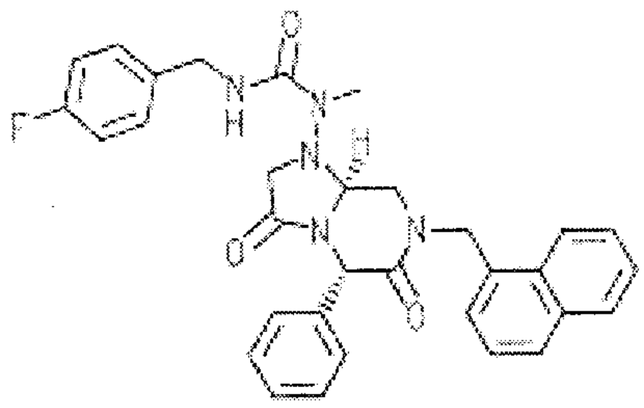
R_4 is saturated alkyl optionally substituted with –CN, or unsaturated alkyl; and
R_5 and R_6 are each independently hydrogen, alkyl or benzyl optionally substituted with one or more substituents selected from halogen and alkoxy.

2. compound of claim 1, which is:



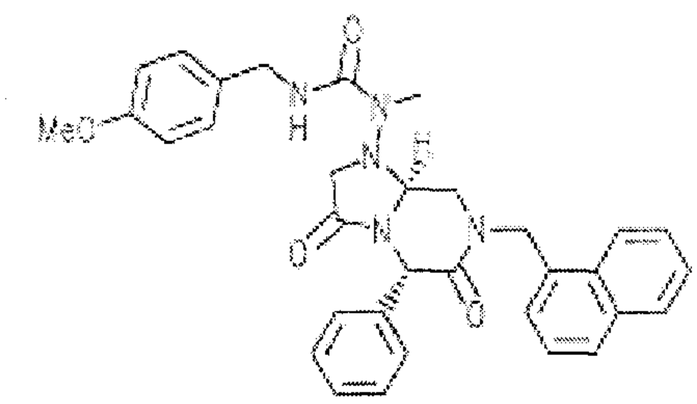
or a pharmaceutically acceptable salt thereof.

3. The compound of claim 1, which is:



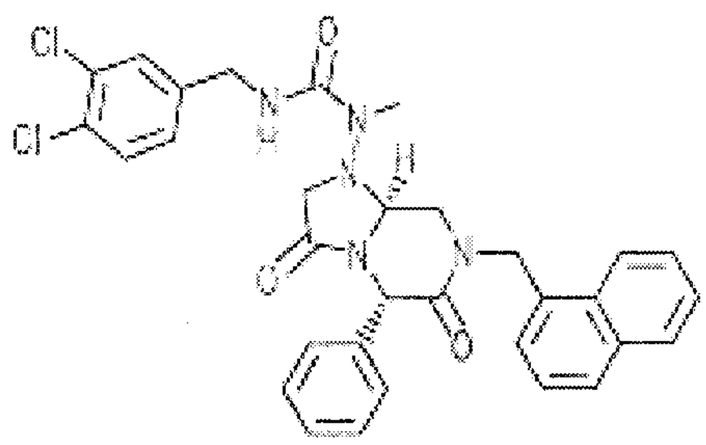
or a pharmaceutically acceptable salt thereof.

4. The compound of claim 1, which is:



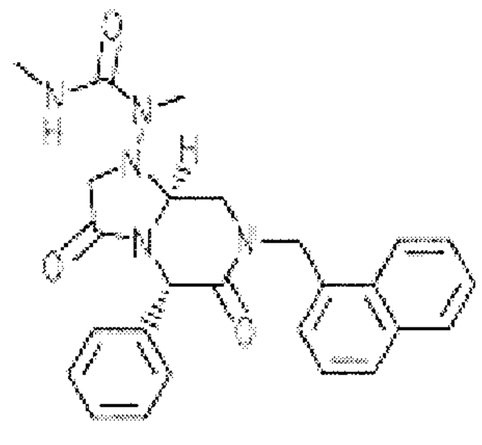
or a pharmaceutically acceptable salt thereof.

5. The compound of claim 1, which is:



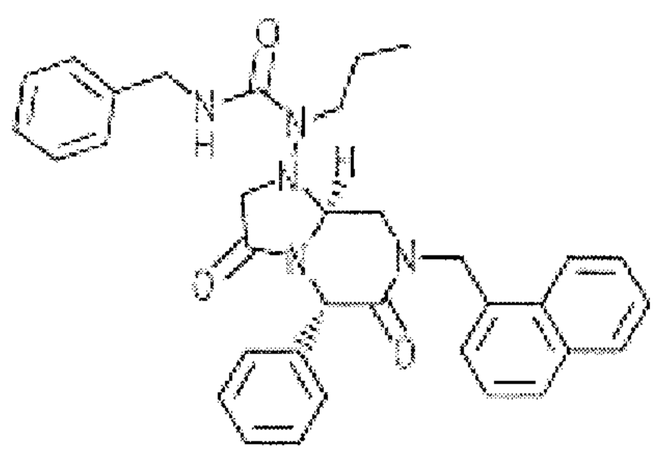
or a pharmaceutically acceptable salt thereof.

6. The compound of claim 1, which is:



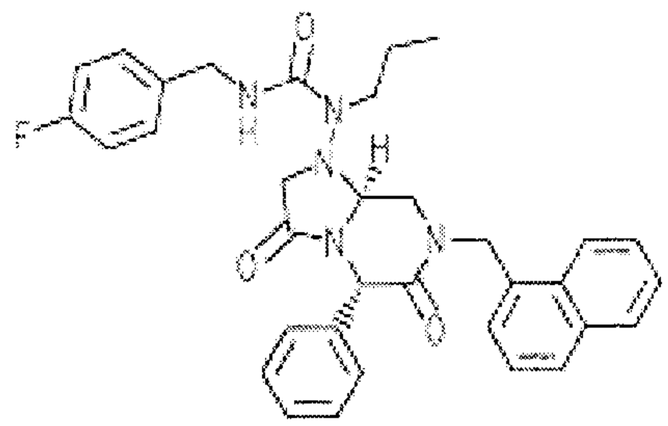
or a pharmaceutically acceptable salt thereof.

7. The compound of claim 1, which is:



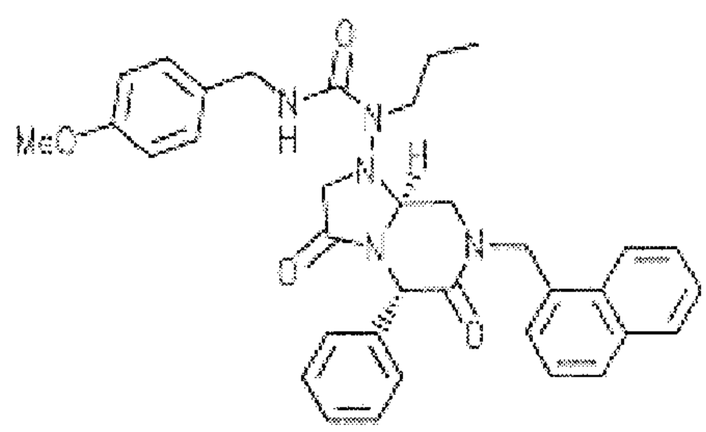
or a pharmaceutically acceptable salt thereof.

8. The compound of claim 1, which is:



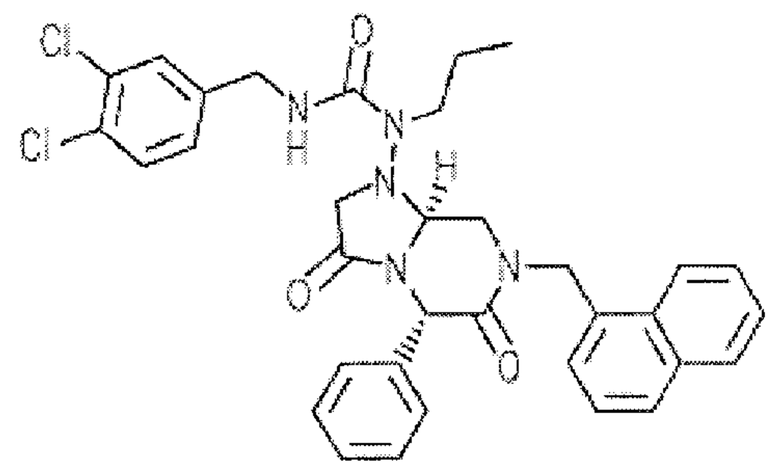
or a pharmaceutically acceptable salt thereof.

9. The compound of claim 1, which is:



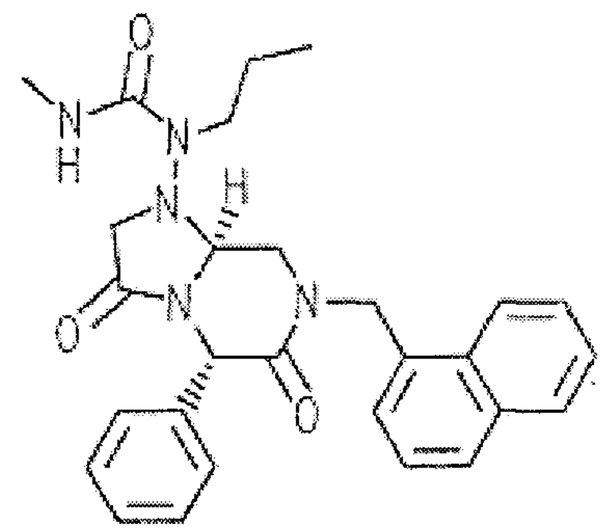
or a pharmaceutically acceptable salt thereof.

10. The compound of claim 1, which is:



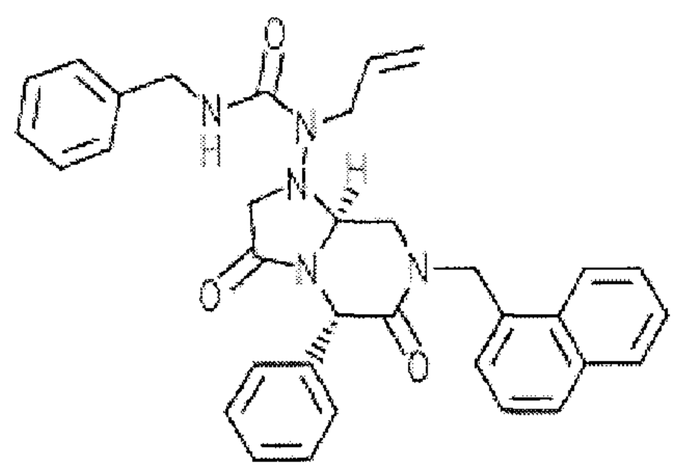
or a pharmaceutically acceptable salt thereof.

11. The compound of claim 1, which is:



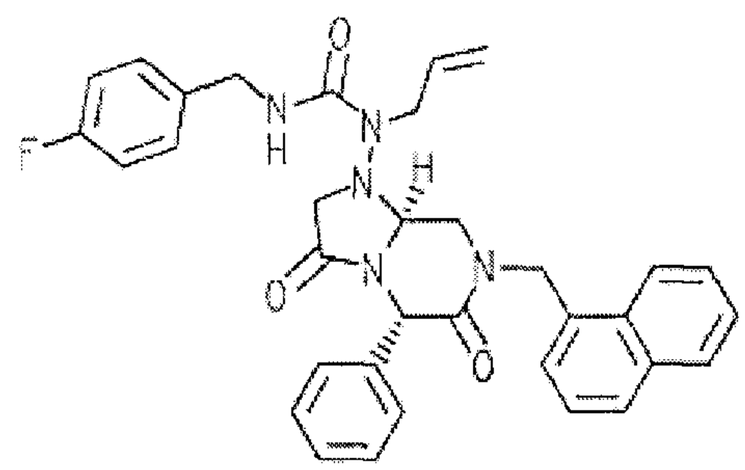
or a pharmaceutically acceptable salt thereof.

12. The compound of claim 1, which is:



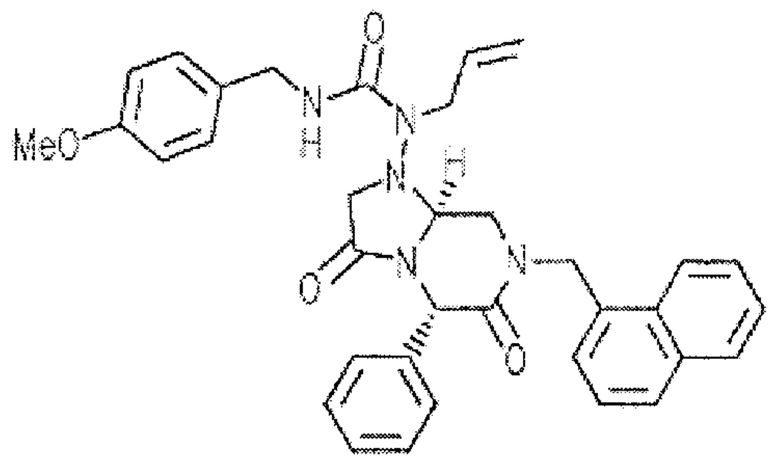
or a pharmaceutically acceptable salt thereof.

13. The compound of claim 1, which is:



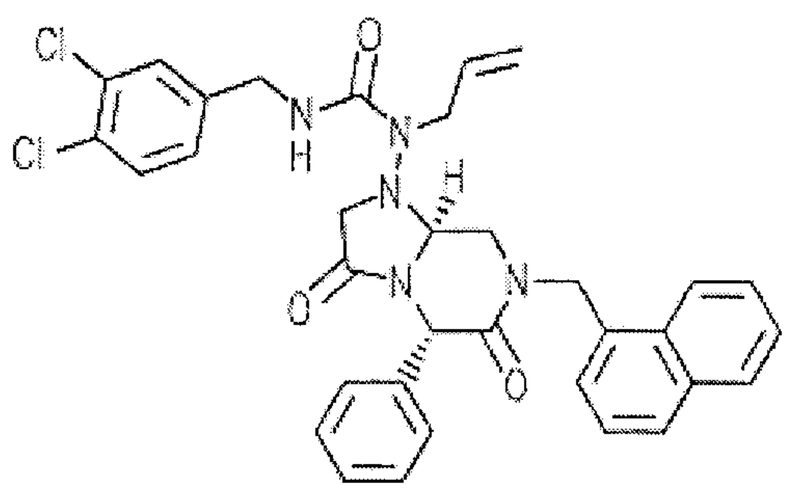
or a pharmaceutically acceptable salt thereof.

14. The compound of claim 1, which is:



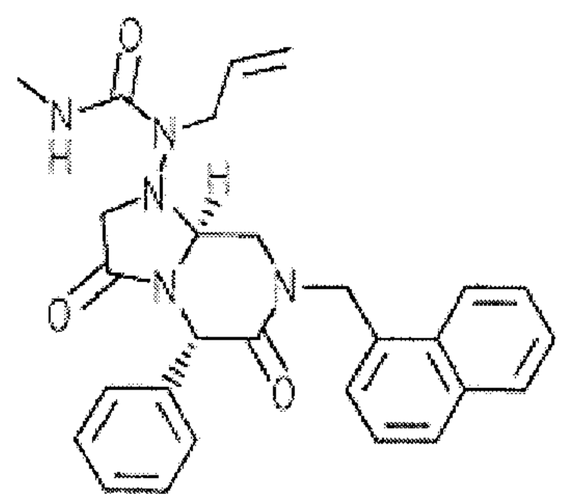
or a pharmaceutically acceptable salt thereof.

15. The compound of claim 1, which is:



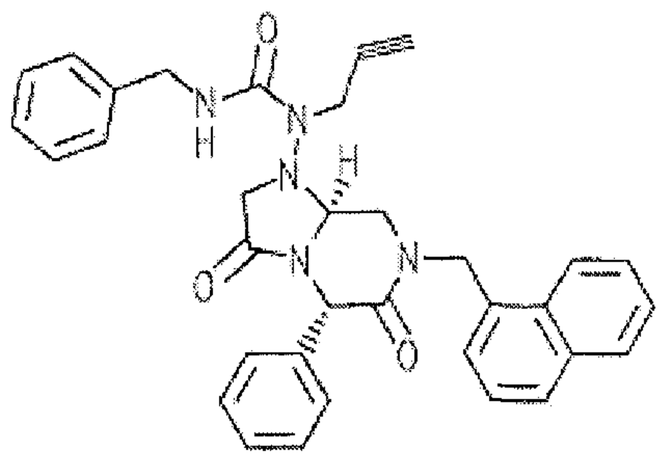
or a pharmaceutically acceptable salt thereof.

16. The compound of claim 1, which is:



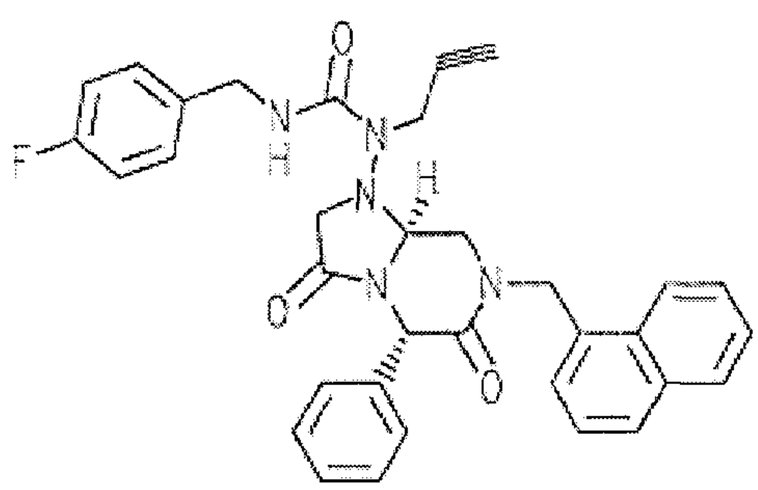
or a pharmaceutically acceptable salt thereof.

17. The compound of claim 1, which is:



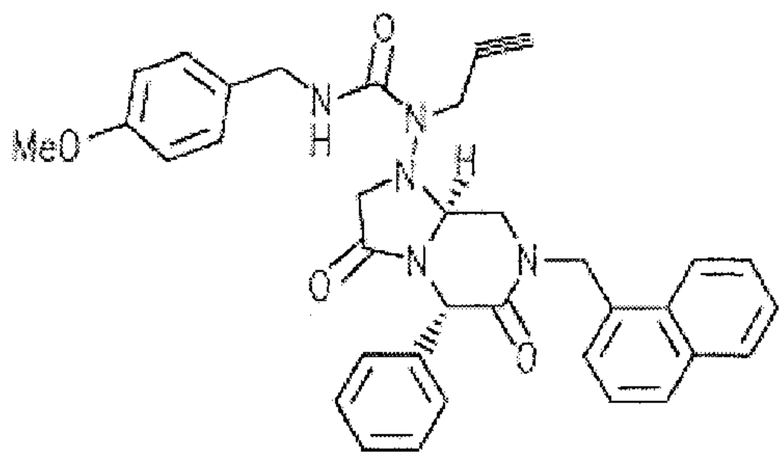
or a pharmaceutically acceptable salt thereof.

18. The compound of claim 1, which is:



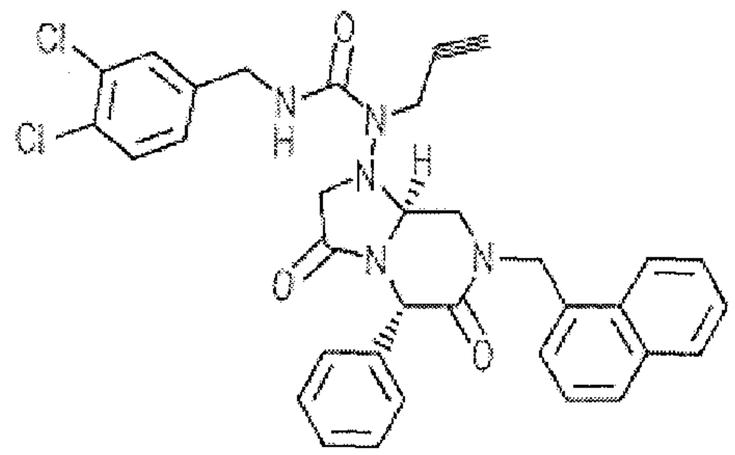
or a pharmaceutically acceptable salt thereof.

19. The compound of claim 1, which is:



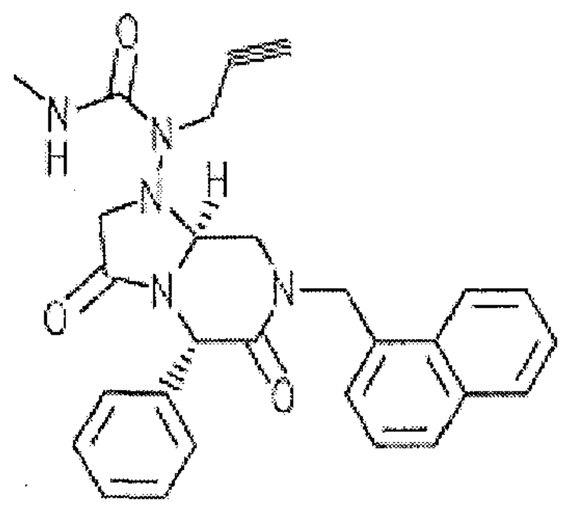
or a pharmaceutically acceptable salt thereof.

20. The compound of claim 1, which is:



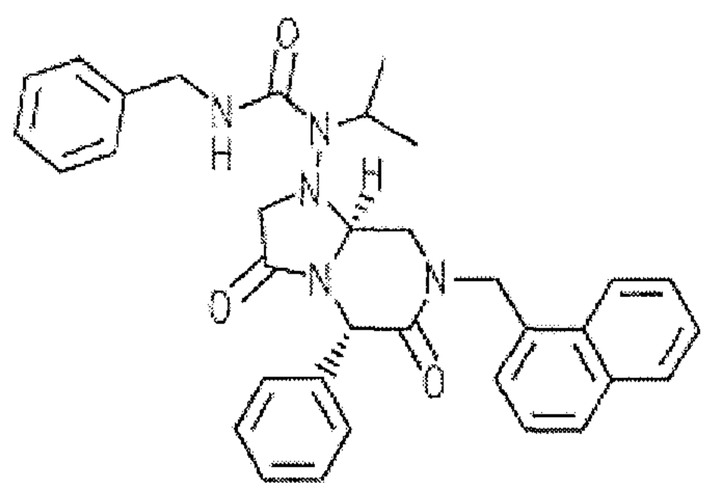
or a pharmaceutically acceptable salt thereof.

21. The compound of claim 1, which is:



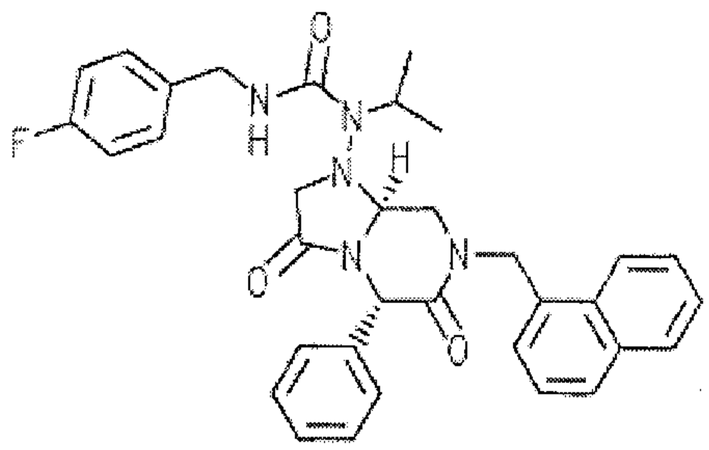
or a pharmaceutically acceptable salt thereof.

22. The compound of claim 1, which is:



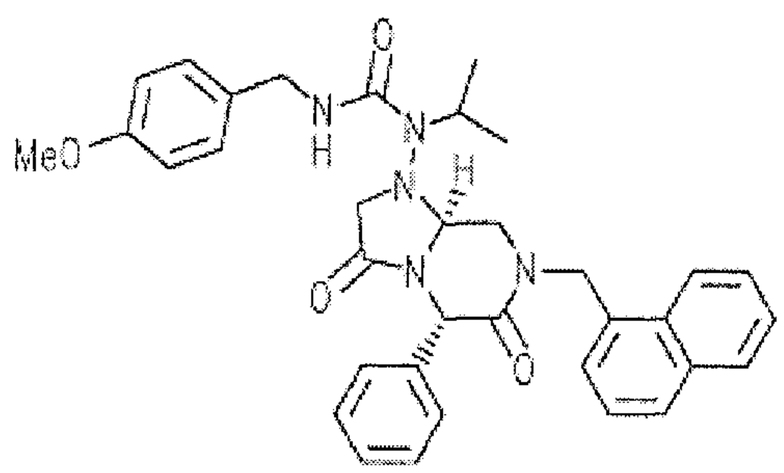
or a pharmaceutically acceptable salt thereof.

23. The compound of claim 1, which is:



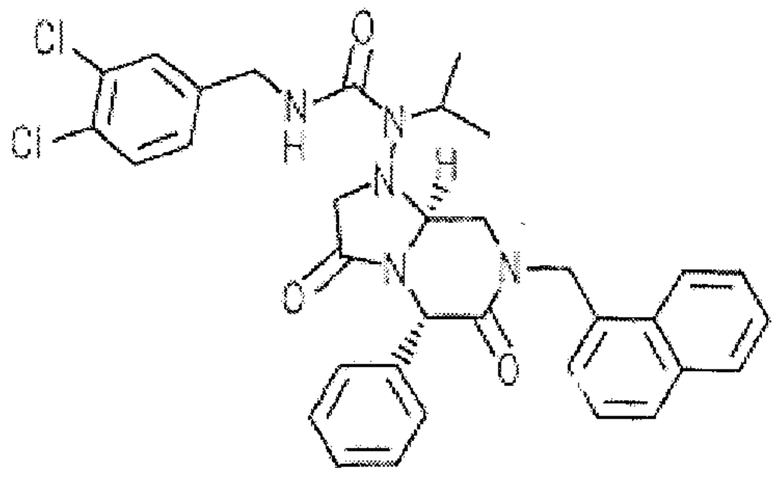
or a pharmaceutically acceptable salt thereof.

24. The compound of claim 1, which is:



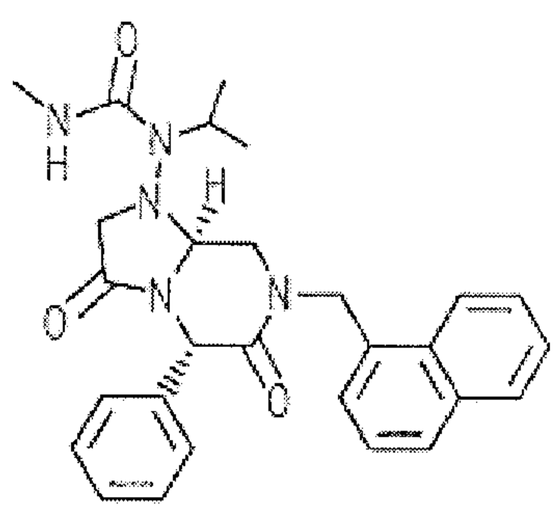
or a pharmaceutically acceptable salt thereof.

25. The compound of claim 1, which is:



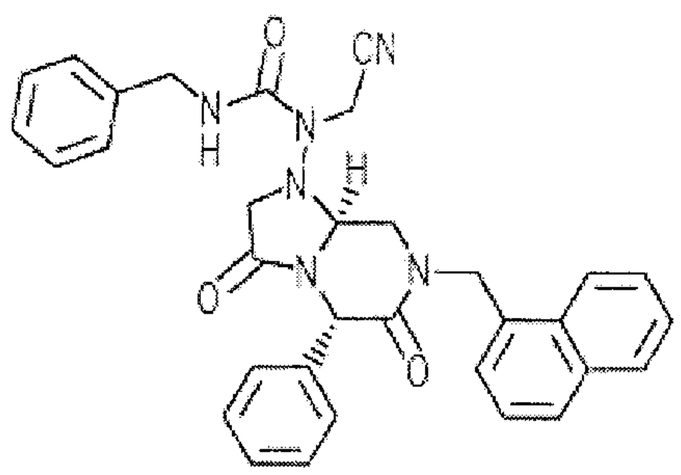
or a pharmaceutically acceptable salt thereof.

26. The compound of claim 1, which is:



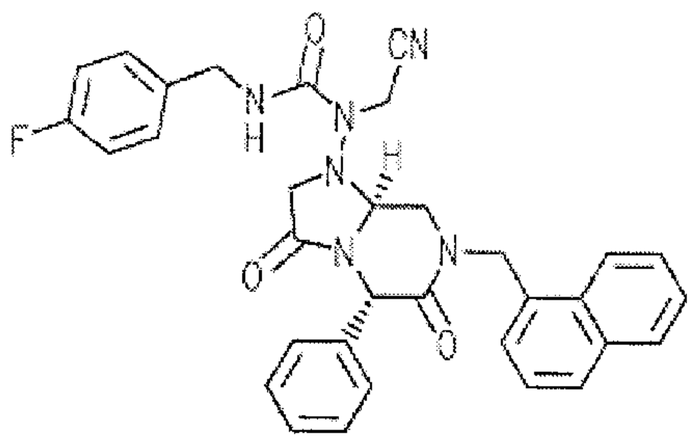
or a pharmaceutically acceptable salt thereof.

27. The compound of claim 1, which is:



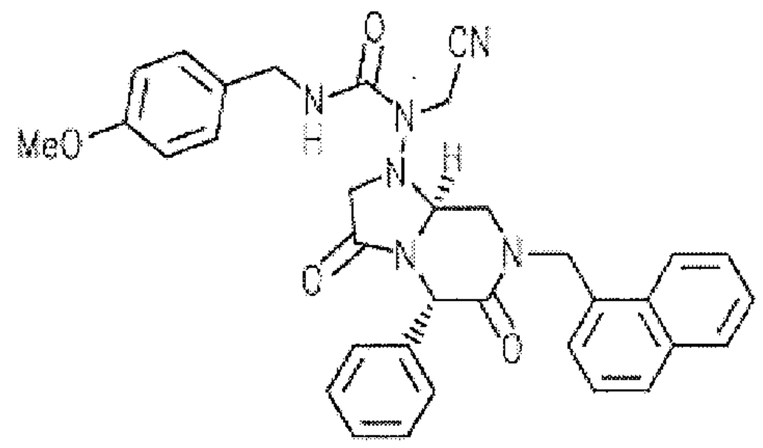
or a pharmaceutically acceptable salt thereof.

28. The compound of claim 1, which is:



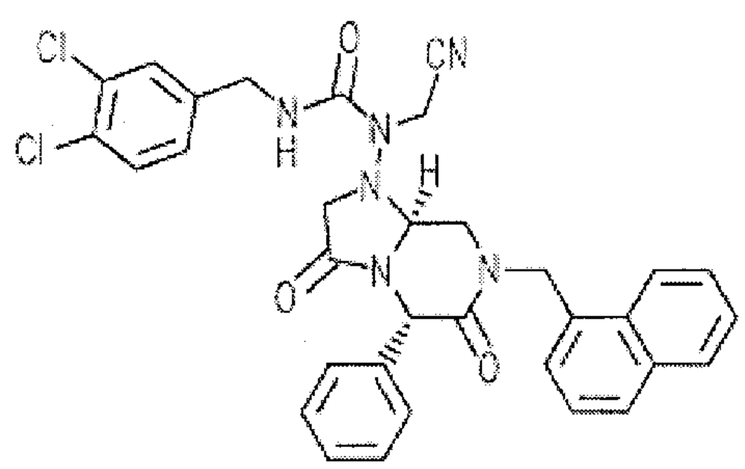
or a pharmaceutically acceptable salt thereof.

29. The compound of claim 1, which is:



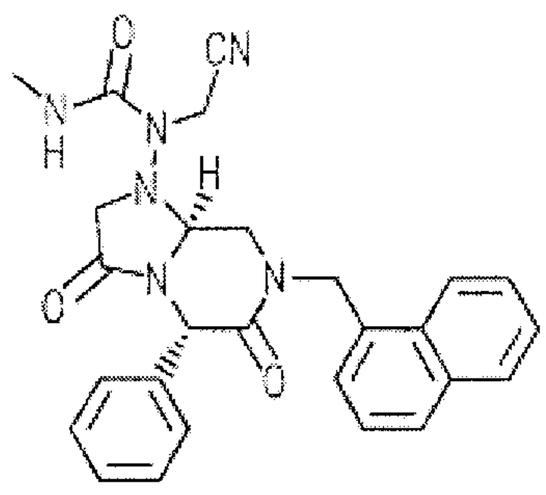
or a pharmaceutically acceptable salt thereof.

30. The compound of claim 1, which is:



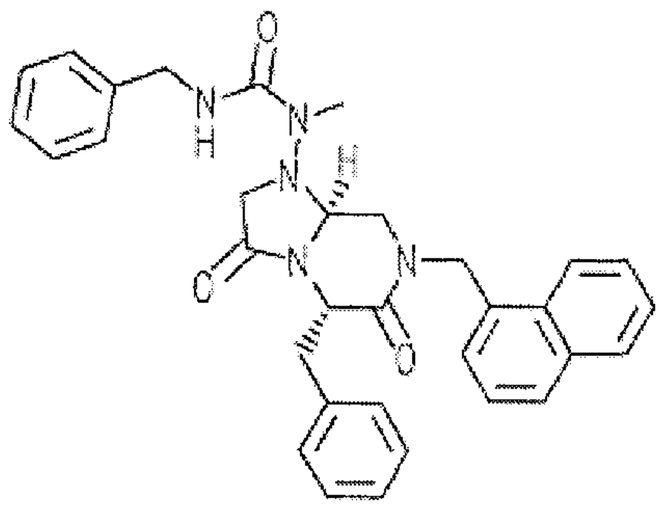
or a pharmaceutically acceptable salt thereof.

31. The compound of claim 1, which is:



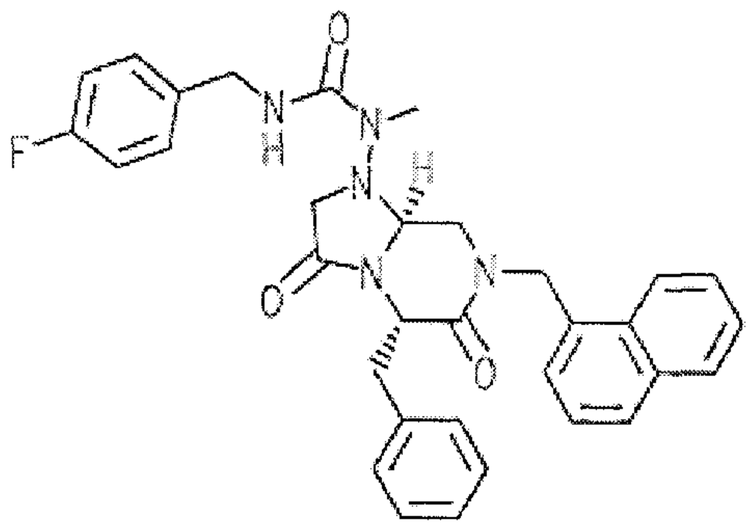
or a pharmaceutically acceptable salt thereof.

32. The compound of claim 1, which is:



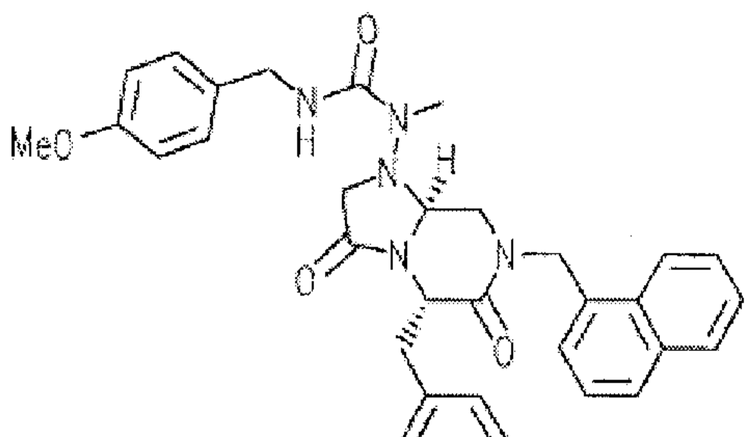
or a pharmaceutically acceptable salt thereof.

33. The compound of claim 1, which is:



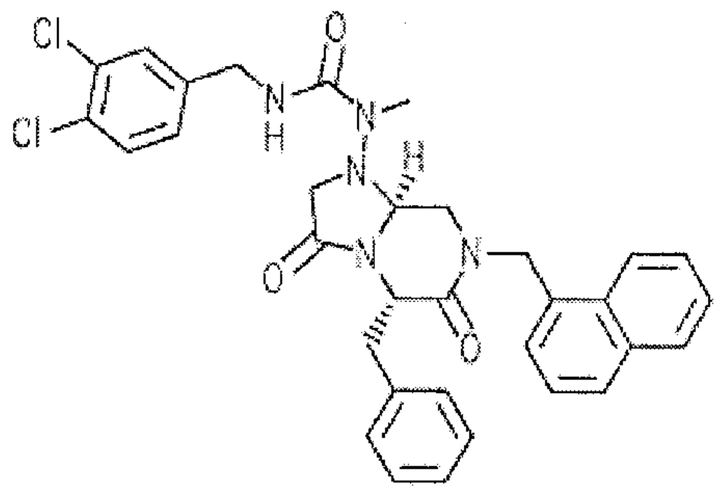
or a pharmaceutically acceptable salt thereof.

34. The compound of claim 1, which is:



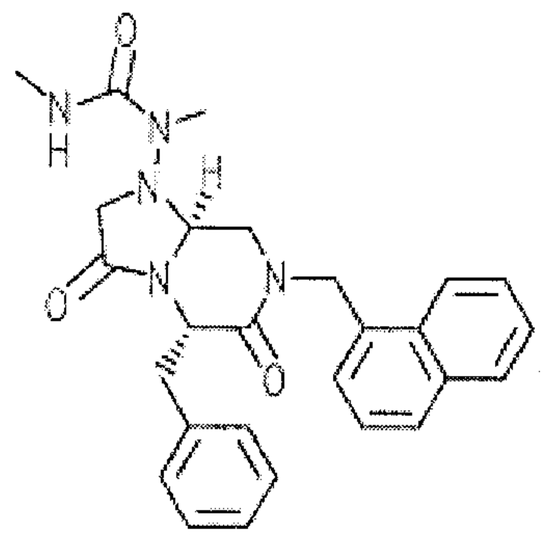
or a pharmaceutically acceptable salt thereof.

35. The compound of claim 1, which is:



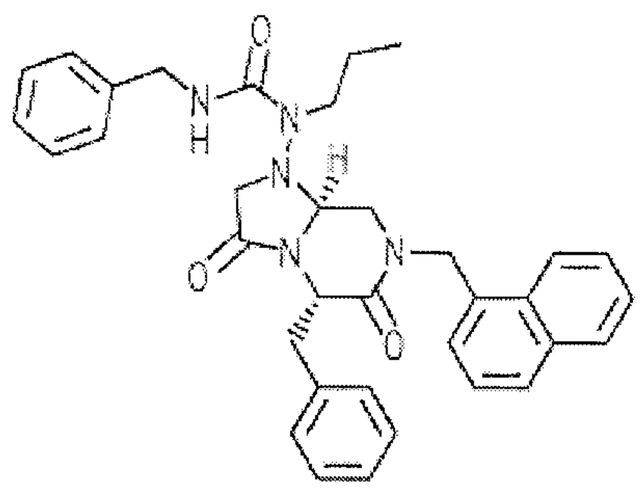
or a pharmaceutically acceptable salt thereof.

36. The compound of claim 1, which is:



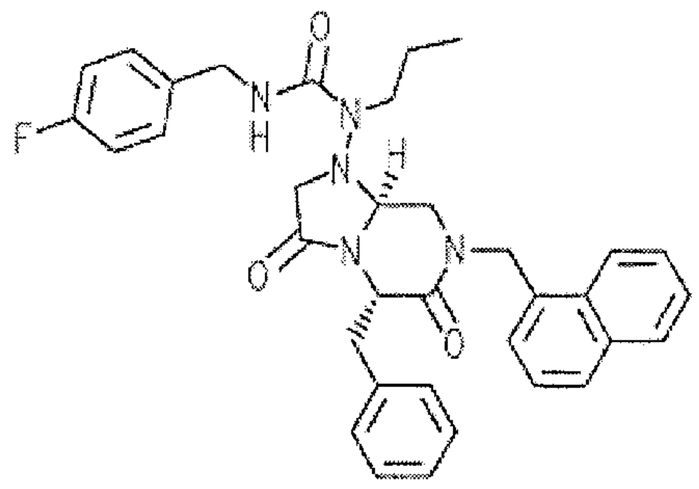
or a pharmaceutically acceptable salt thereof.

37. The compound of claim 1, which is:



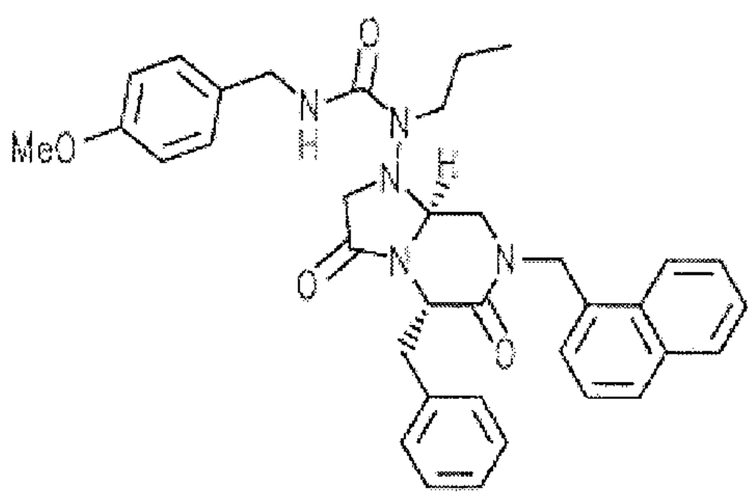
or a pharmaceutically acceptable salt thereof.

38. The compound of claim 1, which is:



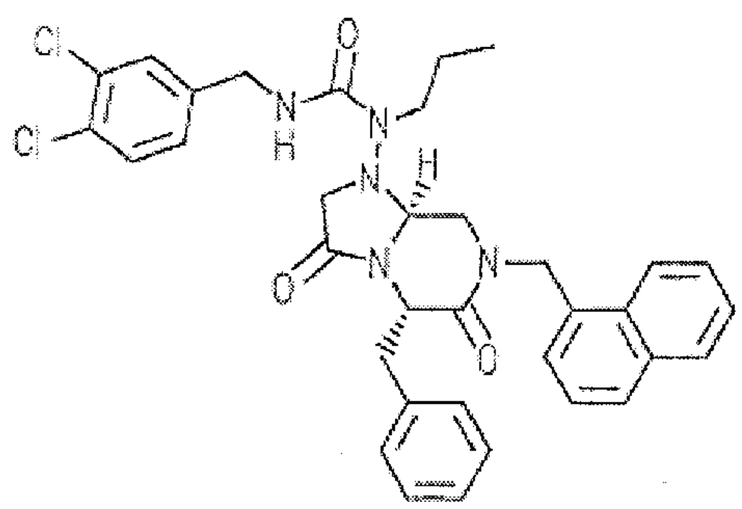
or a pharmaceutically acceptable salt thereof.

39. The compound of claim 1, which is:



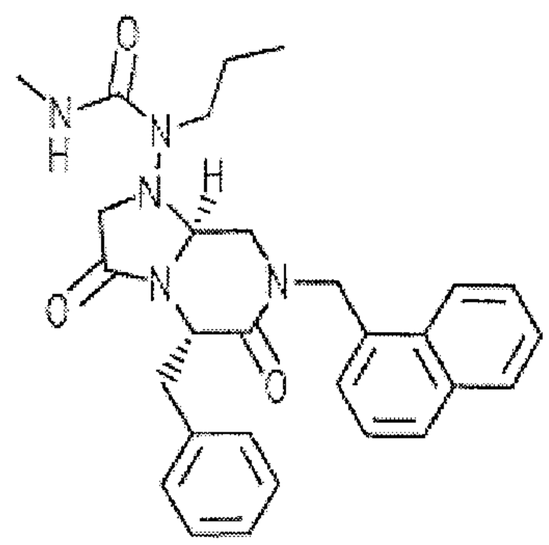
or a pharmaceutically acceptable salt thereof.

40. The compound of claim 1, which is:



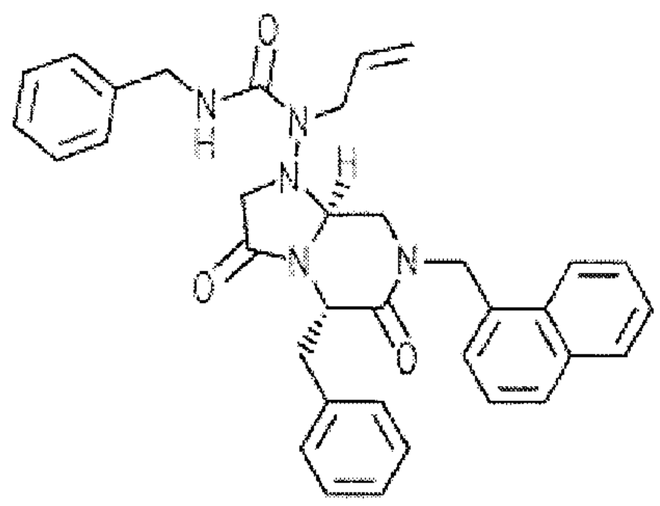
or a pharmaceutically acceptable salt thereof.

41. The compound of claim 1, which is:



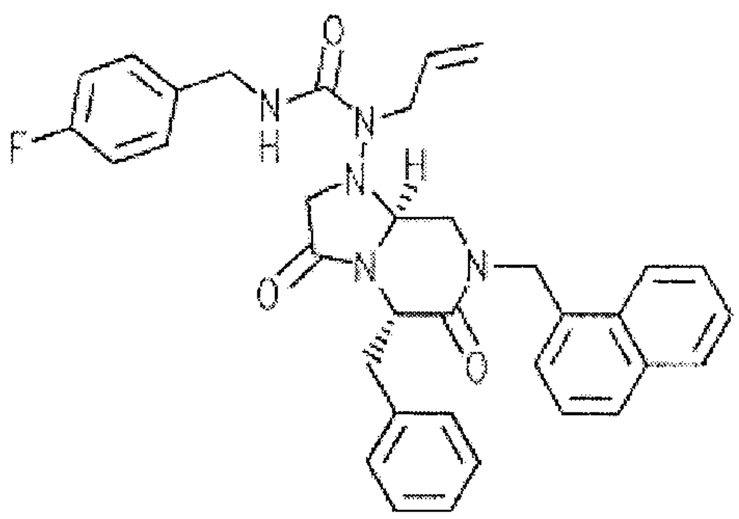
or a pharmaceutically acceptable salt thereof.

42. The compound of claim 1, which is:



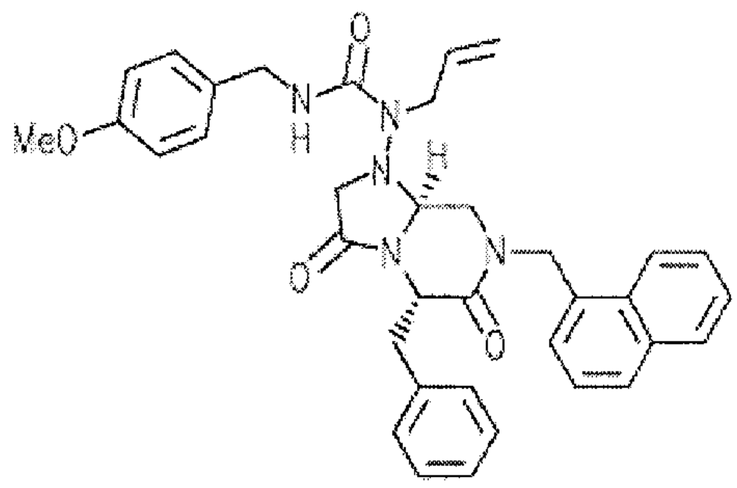
or a pharmaceutically acceptable salt thereof.

43. The compound of claim 1, which is:



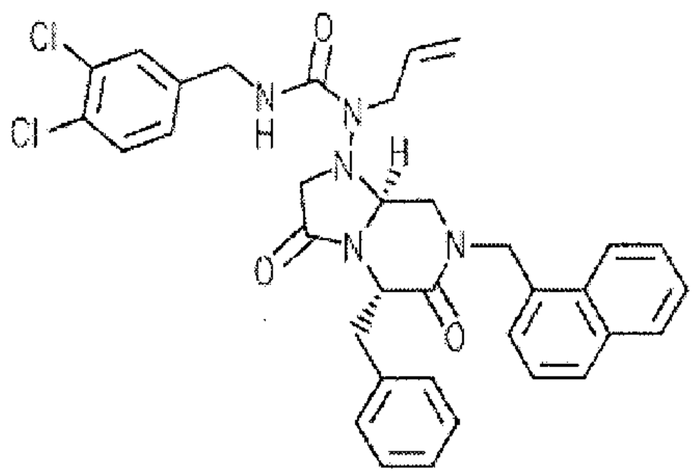
or a pharmaceutically acceptable salt thereof.

44. The compound of claim 1, which is:



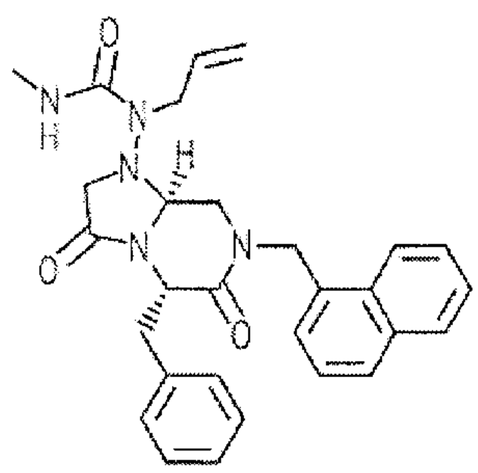
or a pharmaceutically acceptable salt thereof.

45. The compound of claim 1, which is:



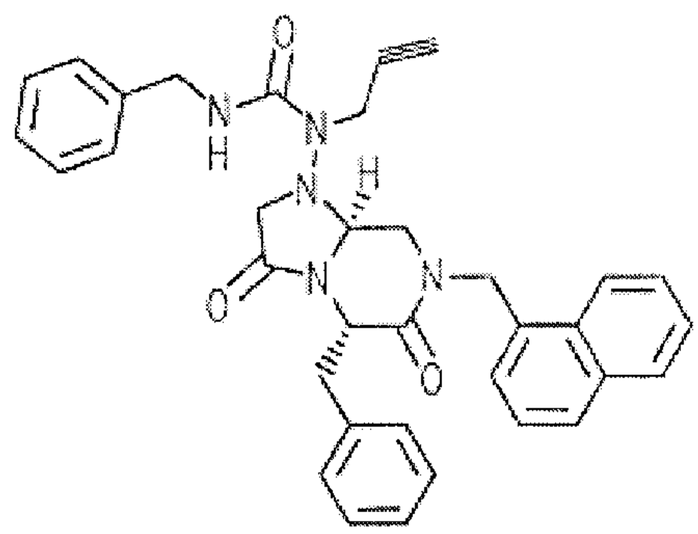
or a pharmaceutically acceptable salt thereof.

46. The compound of claim 1, which is:



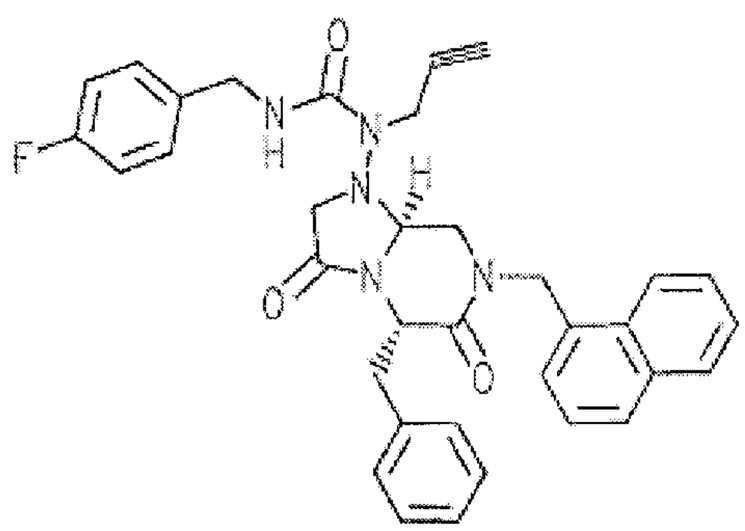
or a pharmaceutically acceptable salt thereof.

47. The compound of claim 1, which is:



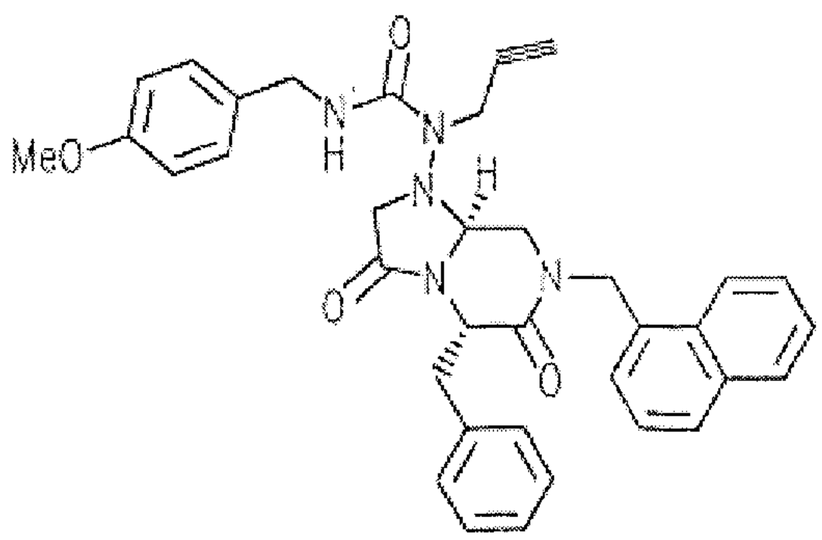
or a pharmaceutically acceptable salt thereof.

48. The compound of claim 1, which is:



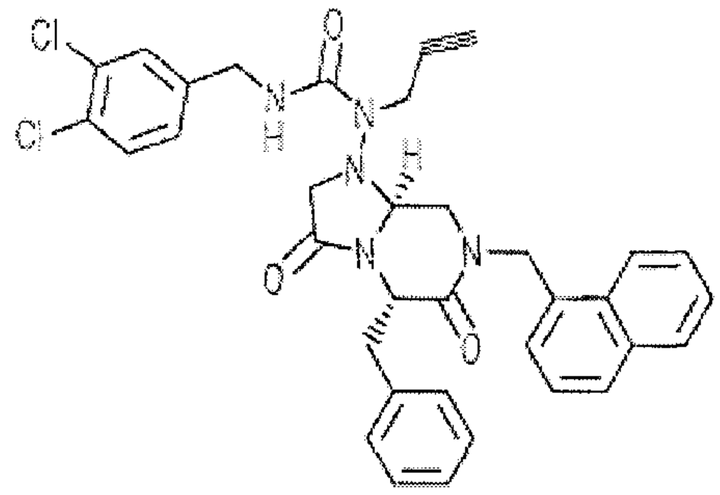
or a pharmaceutically acceptable salt thereof.

49. The compound of claim 1, which is:



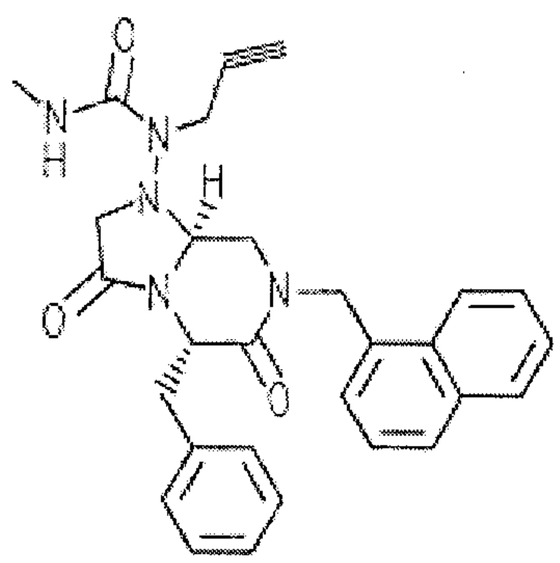
or a pharmaceutically acceptable salt thereof.

50. The compound of claim 1, which is:



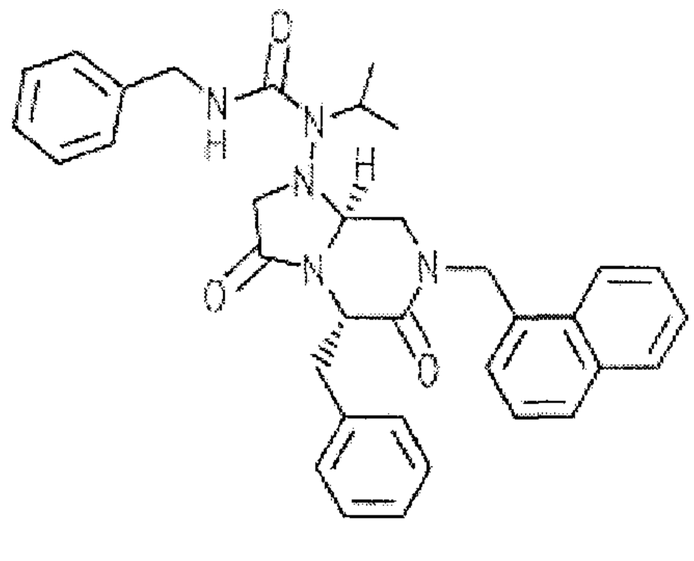
or a pharmaceutically acceptable salt thereof.

51. The compound of claim 1, which is:



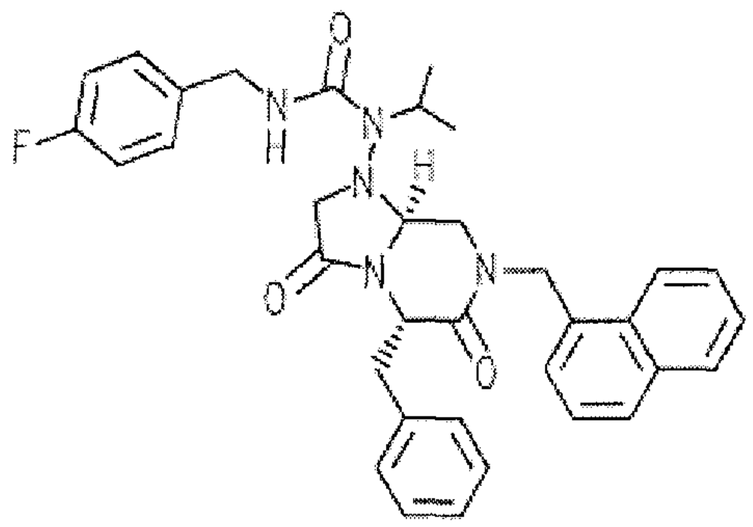
or a pharmaceutically acceptable salt thereof.

52. compound of claim 1, which is:



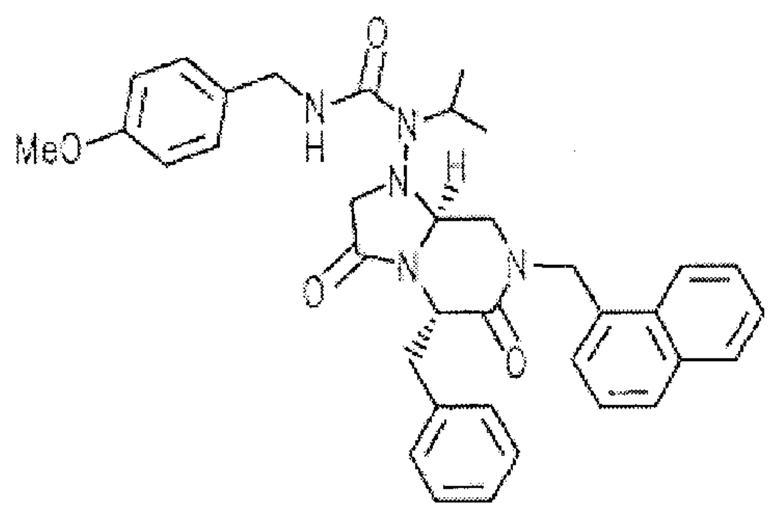
or a pharmaceutically acceptable salt thereof.

53. The compound of claim 1, which is:



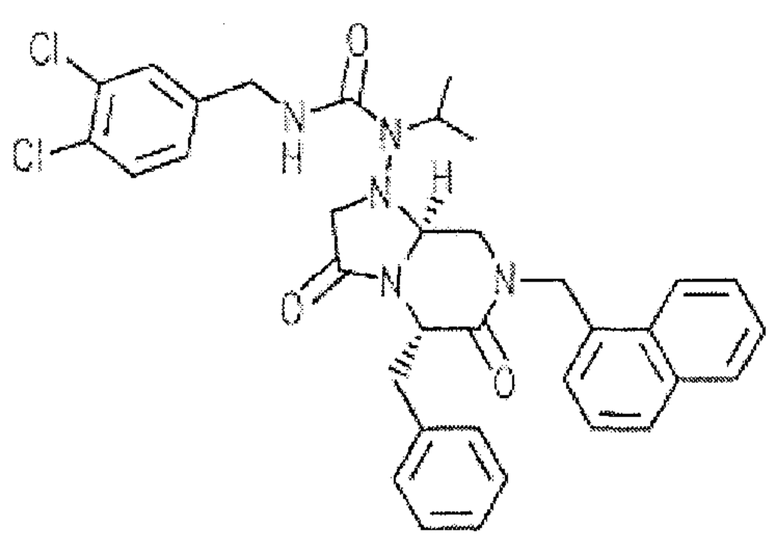
or a pharmaceutically acceptable salt thereof.

54. The compound of claim 1, which is:



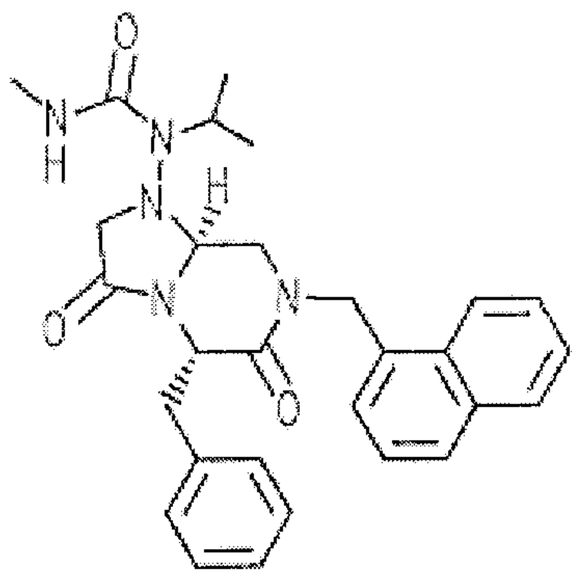
or a pharmaceutically acceptable salt thereof.

55. The compound of claim 1, which is:



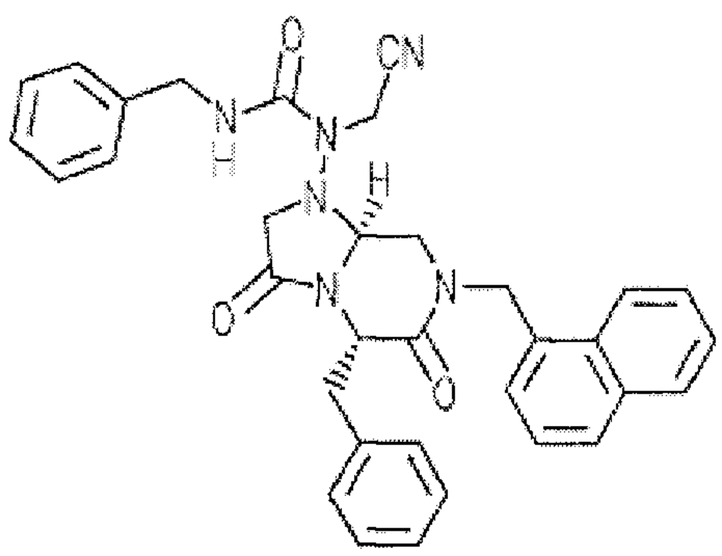
or a pharmaceutically acceptable salt thereof.

56. The compound of claim 1, which is:



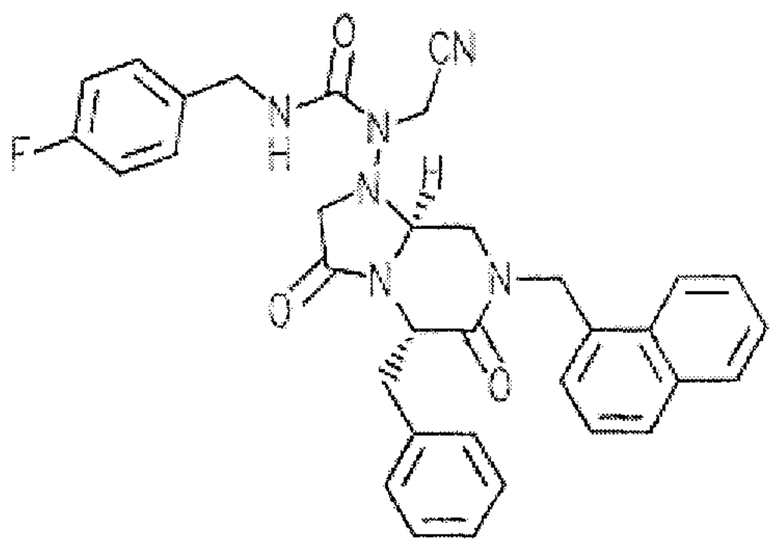
or a pharmaceutically acceptable salt thereof.

57. The compound of claim 1, which is:



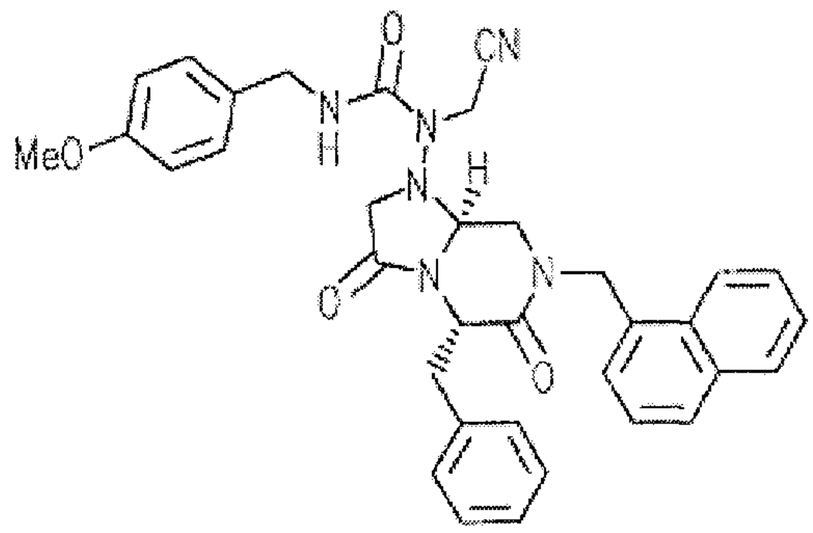
or a pharmaceutically acceptable salt thereof.

58. The compound of claim 1, which is:



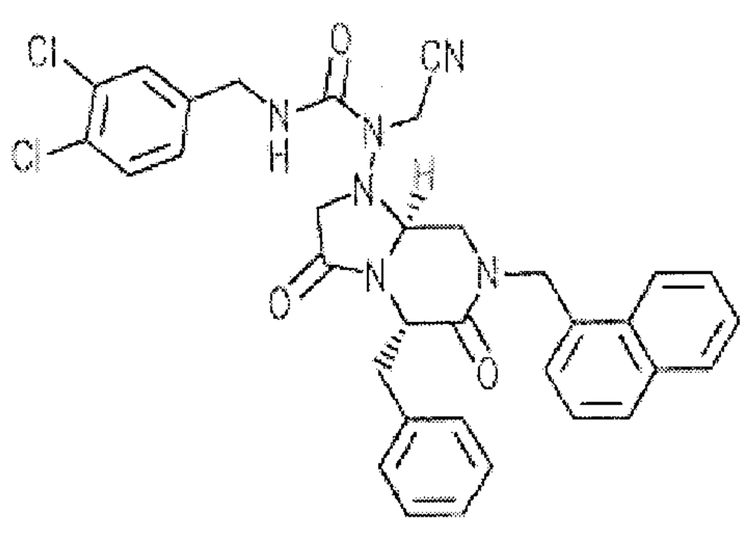
or a pharmaceutically acceptable salt thereof.

59. The compound of claim 1, which is:



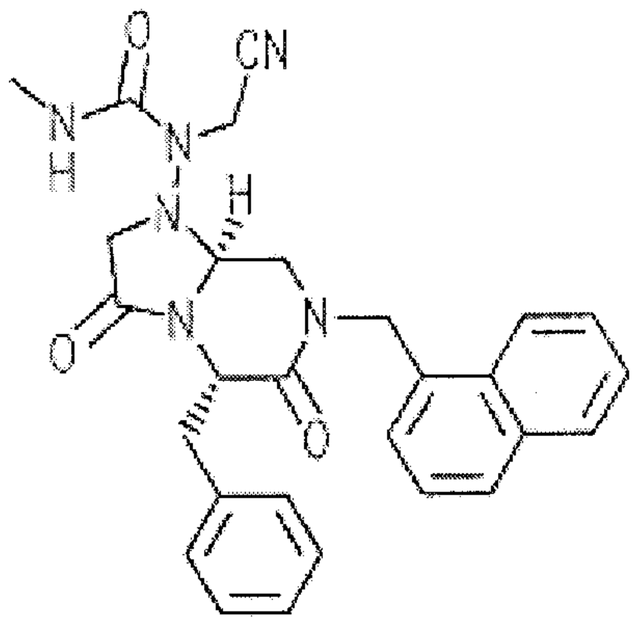
or a pharmaceutically acceptable salt thereof.

60. The compound of claim 1, which is:



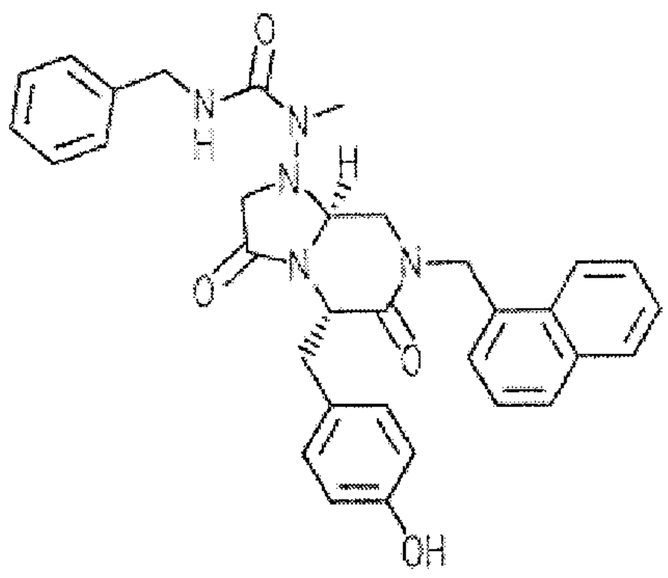
or a pharmaceutically acceptable salt thereof.

61. The compound of claim 1, which is:



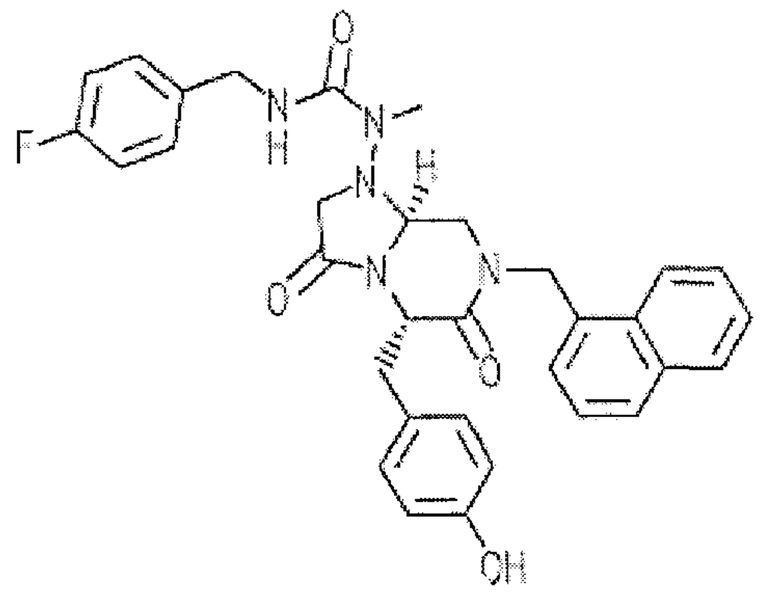
or a pharmaceutically acceptable salt thereof.

62. The compound of claim 1, which is:



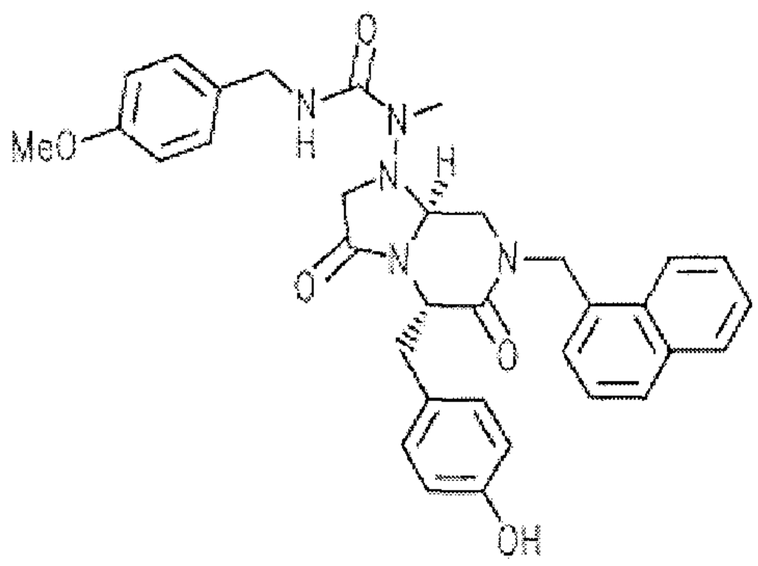
or a pharmaceutically acceptable salt thereof.

63. The compound of claim 1, which is:



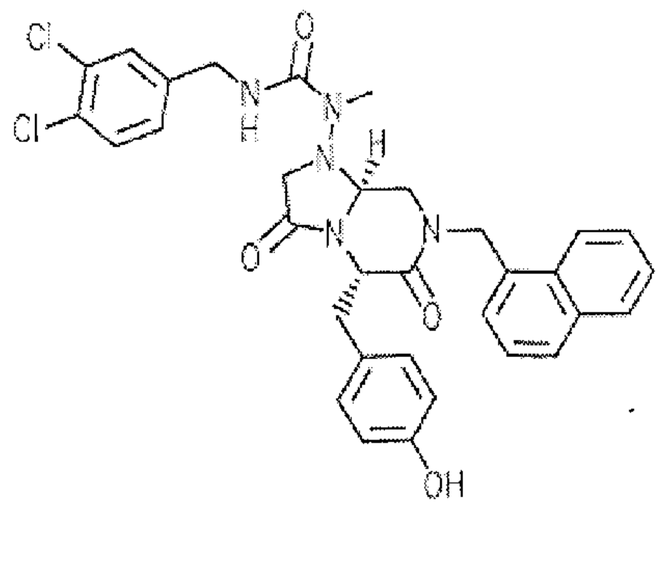
or a pharmaceutically acceptable salt thereof.

64. The compound of claim 1, which is:



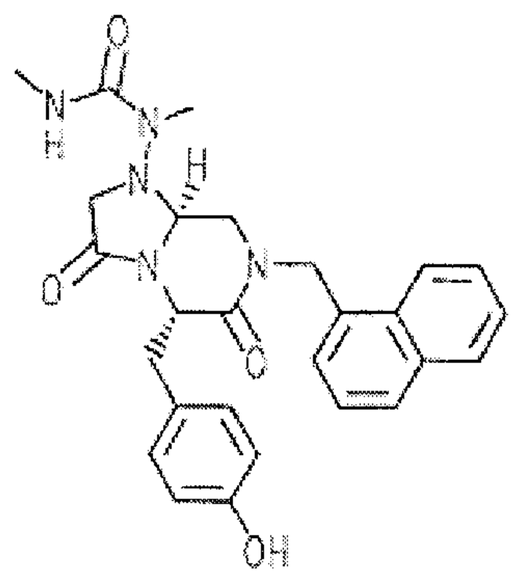
or a pharmaceutically acceptable salt thereof.

65. The compound of claim 1, which is:



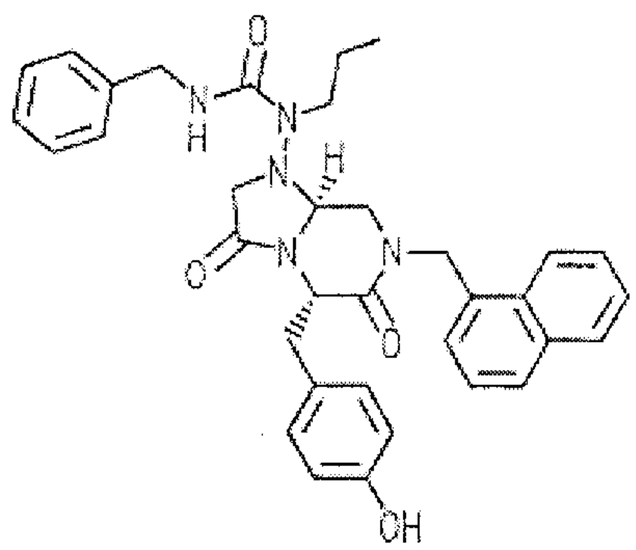
or a pharmaceutically acceptable salt thereof.

66. The compound of claim 1, which is:



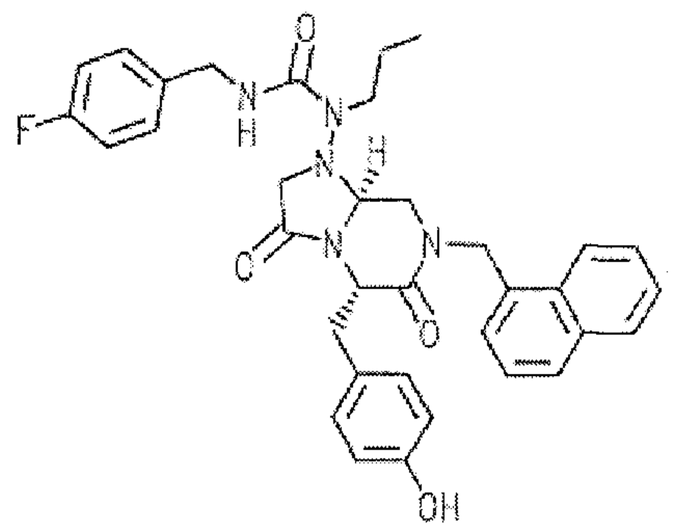
or a pharmaceutically acceptable salt thereof.

67. The compound of claim 1, which is:



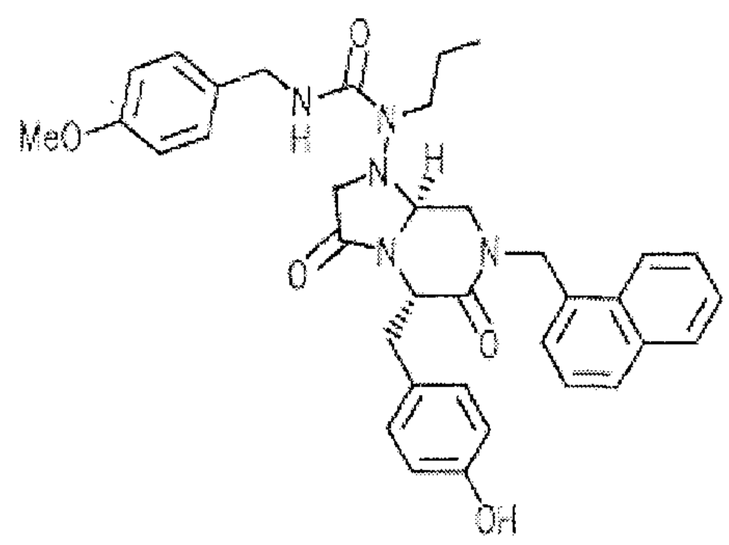
or a pharmaceutically acceptable salt thereof.

68. The compound of claim 1, which is:



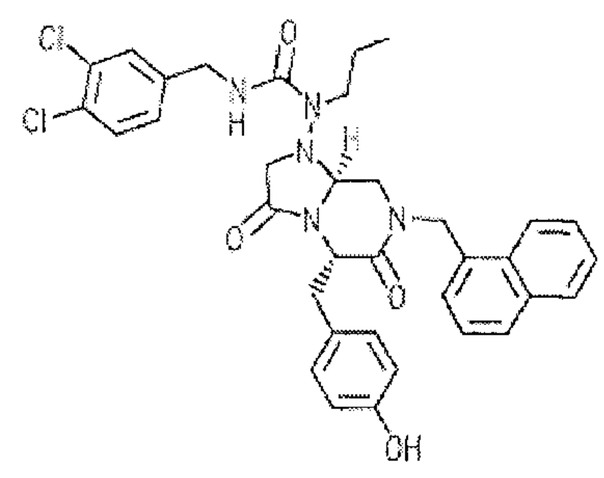
or a pharmaceutically acceptable salt thereof.

69. The compound of claim 1, which is:



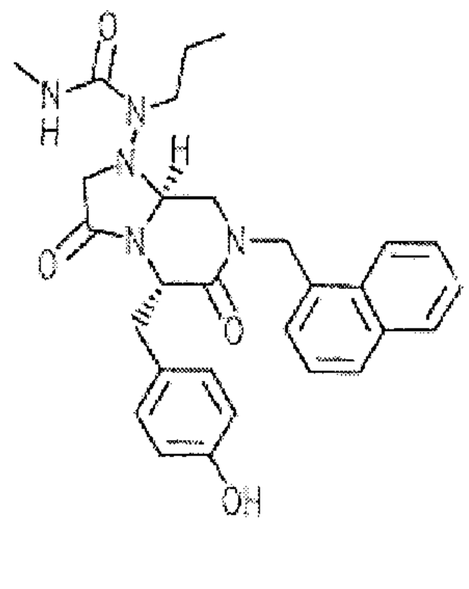
or a pharmaceutically acceptable salt thereof.

70. The compound of claim 1, which is:



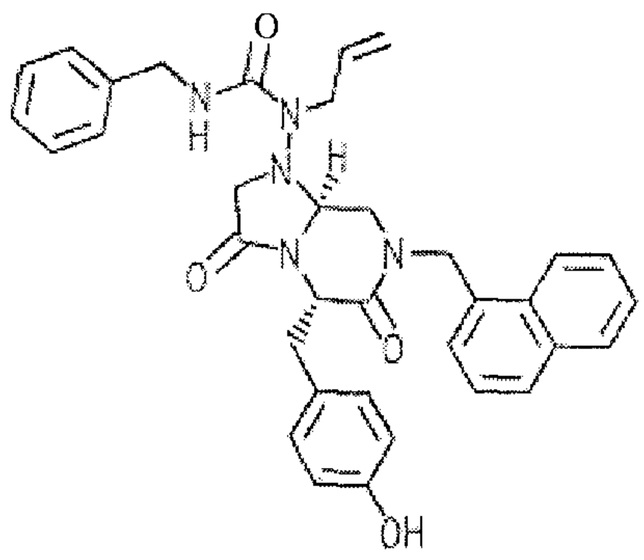
or a pharmaceutically acceptable salt thereof.

71. The compound of claim 1, which is:



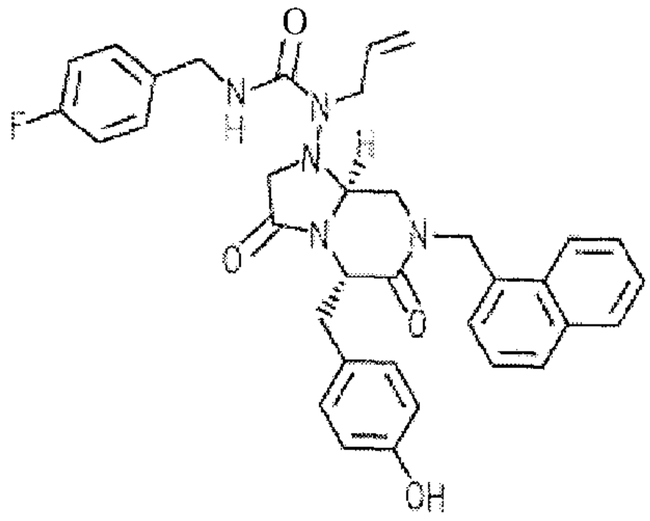
or a pharmaceutically acceptable salt thereof.

72. The compound of claim 1, which is:



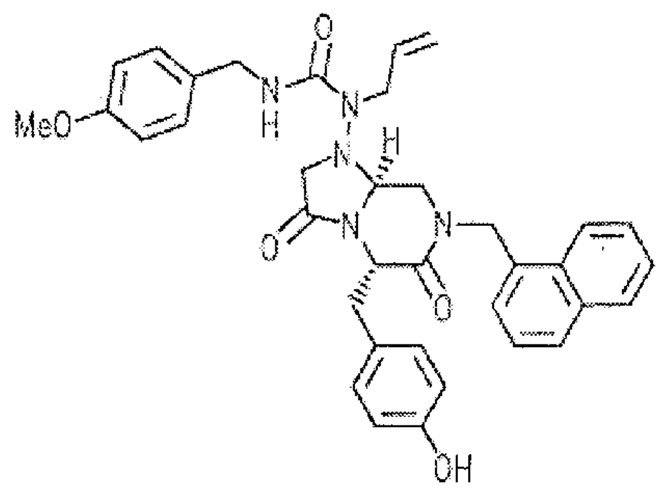
or a pharmaceutically acceptable salt thereof.

73. The compound of claim 1, which is:



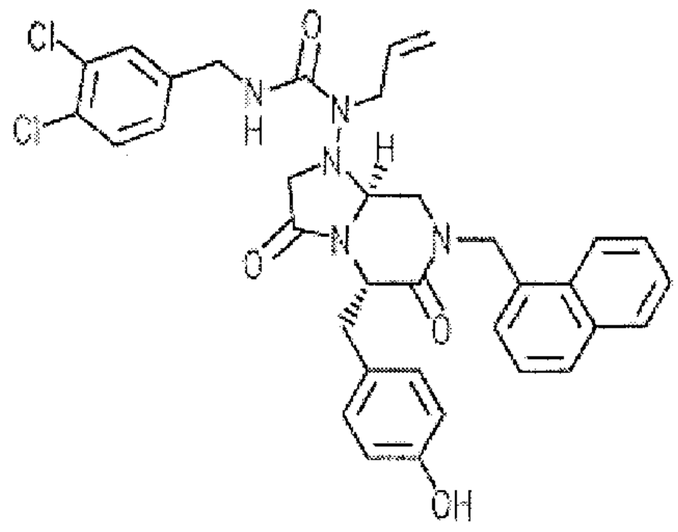
or a pharmaceutically acceptable salt thereof.

74. The compound of claim 1, which is:



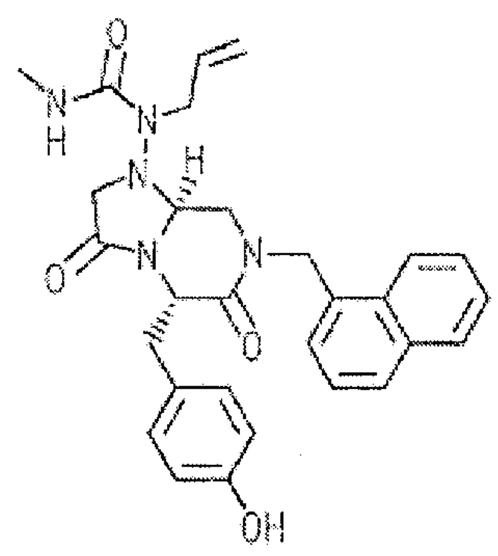
or a pharmaceutically acceptable salt thereof.

75. The compound of claim 1, which is:



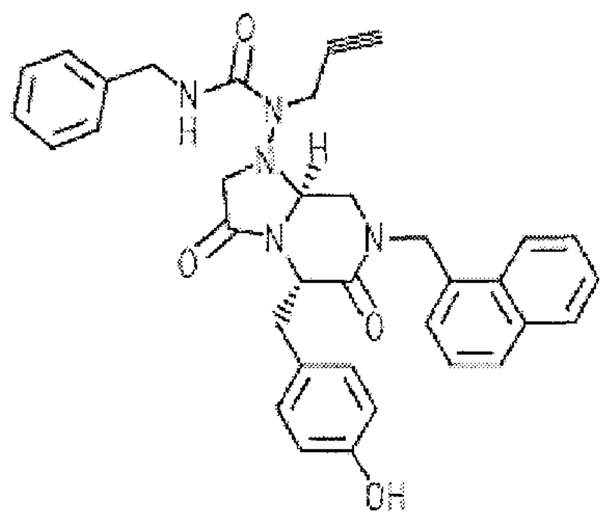
or a pharmaceutically acceptable salt thereof.

76. The compound of claim 1, which is:



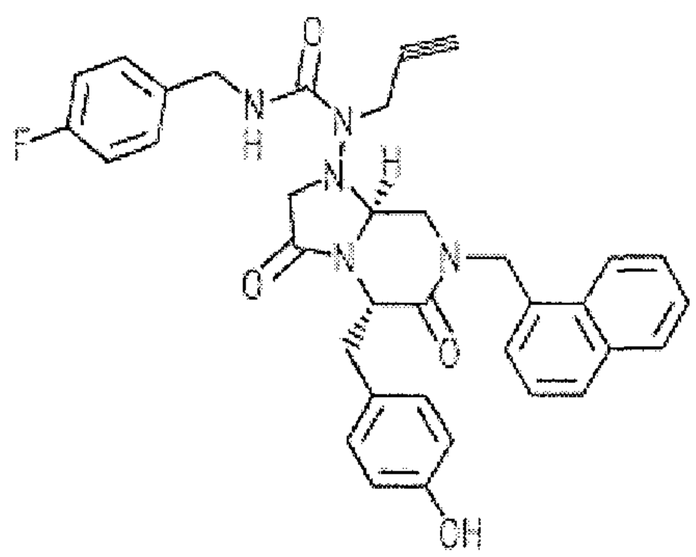
or a pharmaceutically acceptable salt thereof.

77. The compound of claim 1, which is:



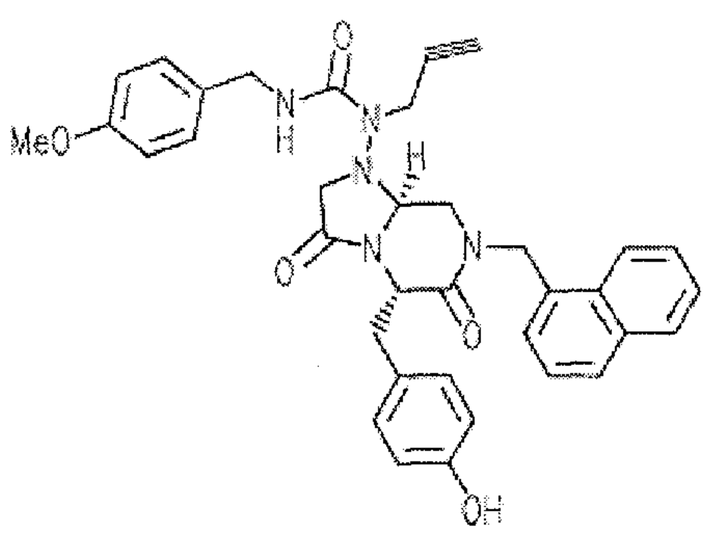
or a pharmaceutically acceptable salt thereof.

78. The compound of claim 1, which is:



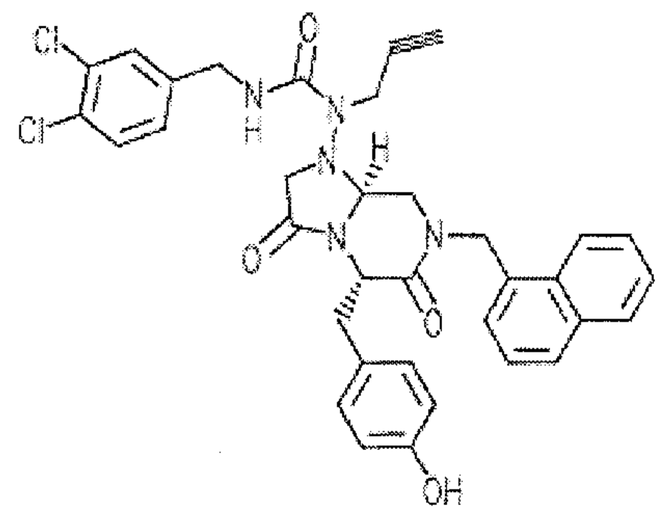
or a pharmaceutically acceptable salt thereof.

79. The compound of claim 1, which is:



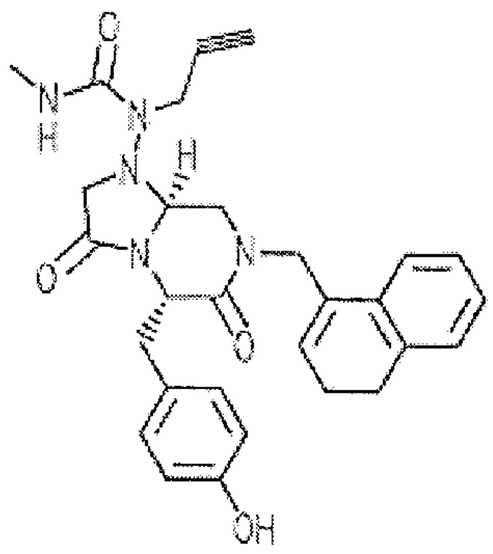
or a pharmaceutically acceptable salt thereof.

80. The compound of claim 1, which is:



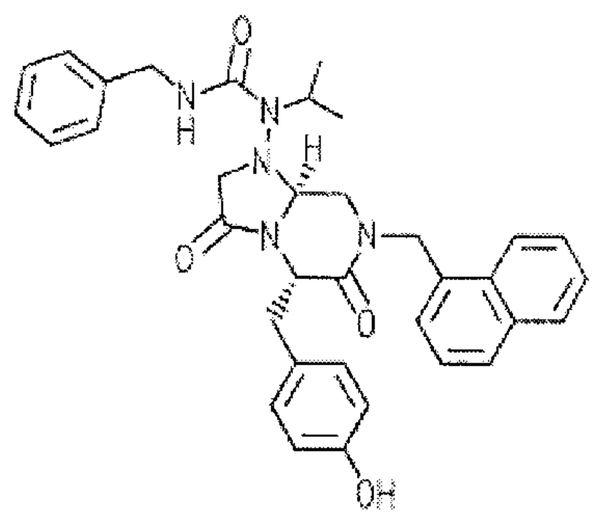
or a pharmaceutically acceptable salt thereof.

81. The compound of claim 1, which is:



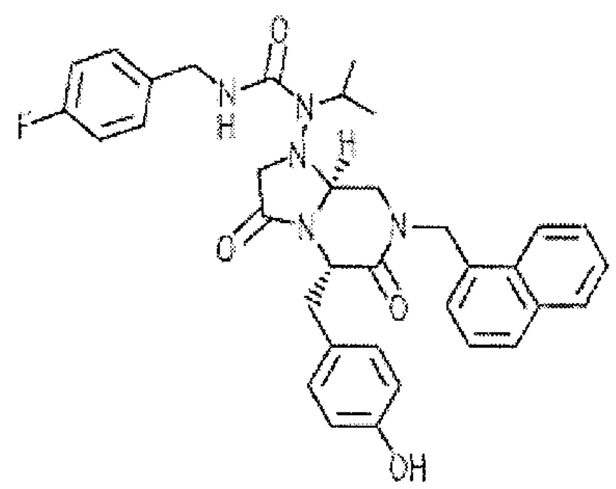
or a pharmaceutically acceptable salt thereof.

82. The compound of claim 1, which is:



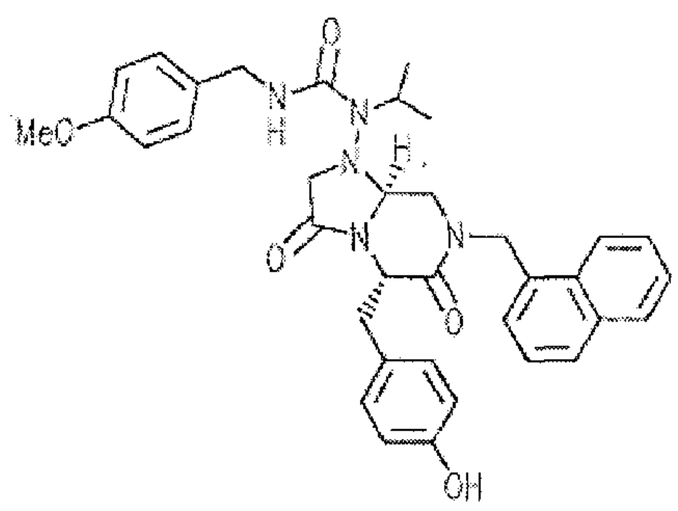
or a pharmaceutically acceptable salt thereof.

83. The compound of claim 1, which is:



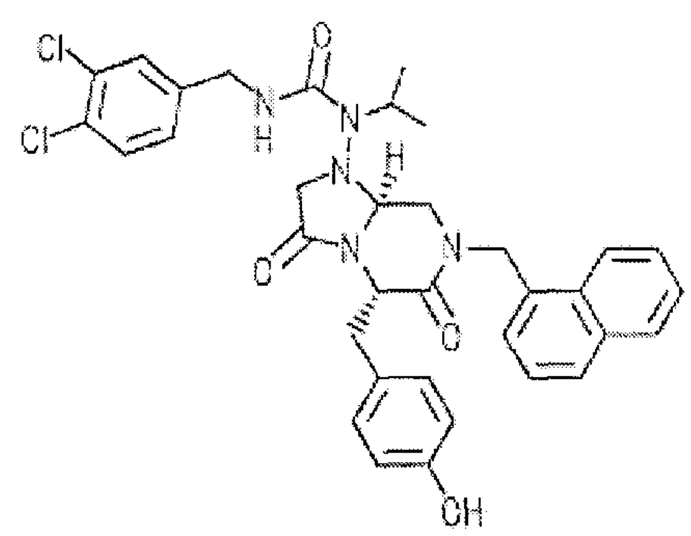
or a pharmaceutically acceptable salt thereof.

84. The compound of claim 1, which is:



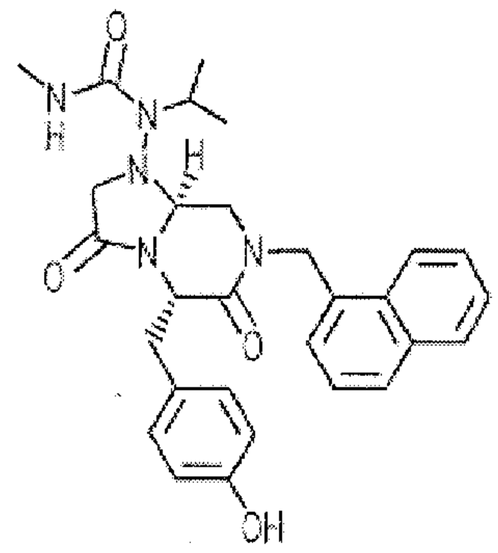
or a pharmaceutically acceptable salt thereof.

85. The compound of claim 1, which is:



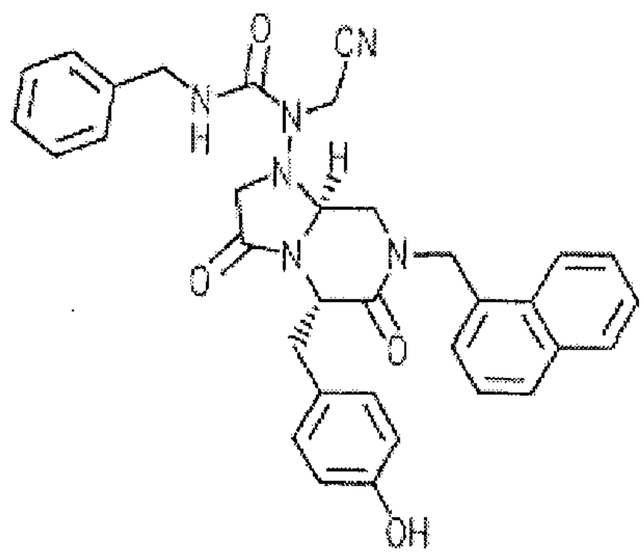
or a pharmaceutically acceptable salt thereof.

86. The compound of claim 1, which is:



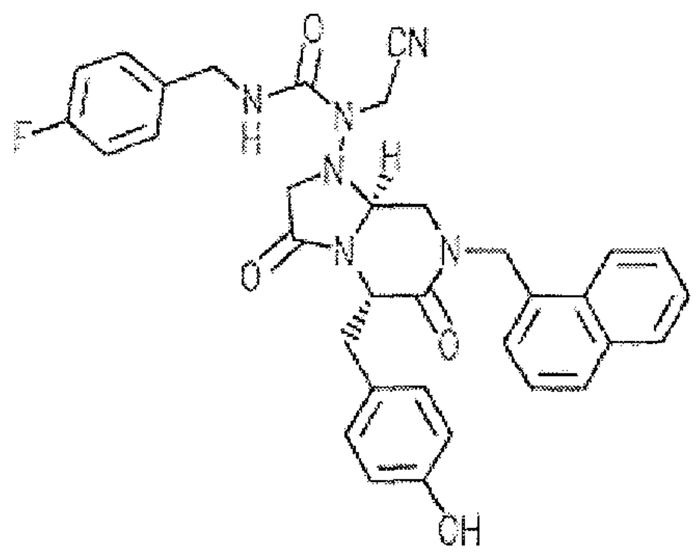
or a pharmaceutically acceptable salt thereof.

87. The compound of claim 1, which is:



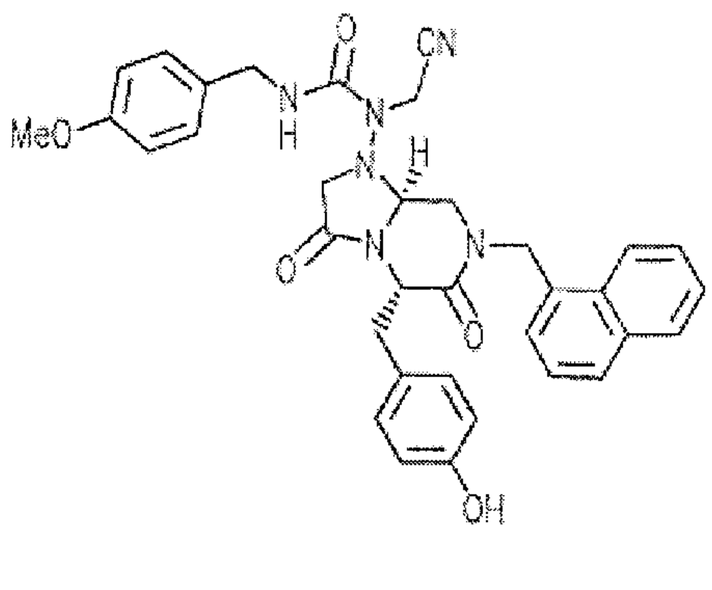
or a pharmaceutically acceptable salt thereof.

88. The compound of claim 1, which is:



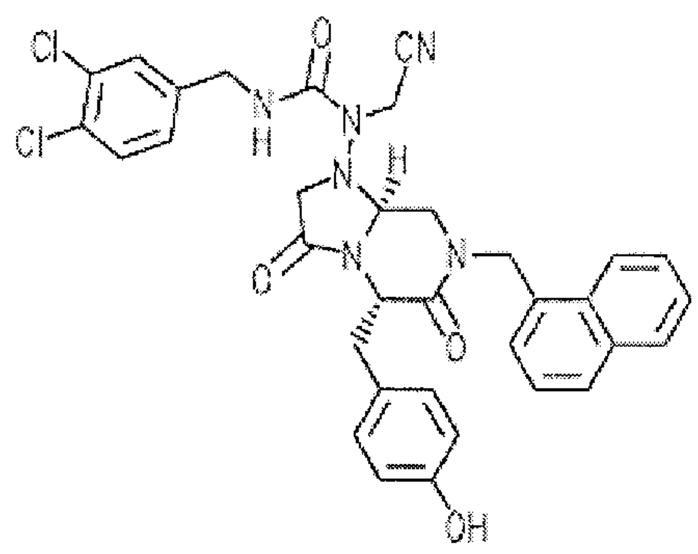
or a pharmaceutically acceptable salt thereof.

89. The compound of claim 1, which is:



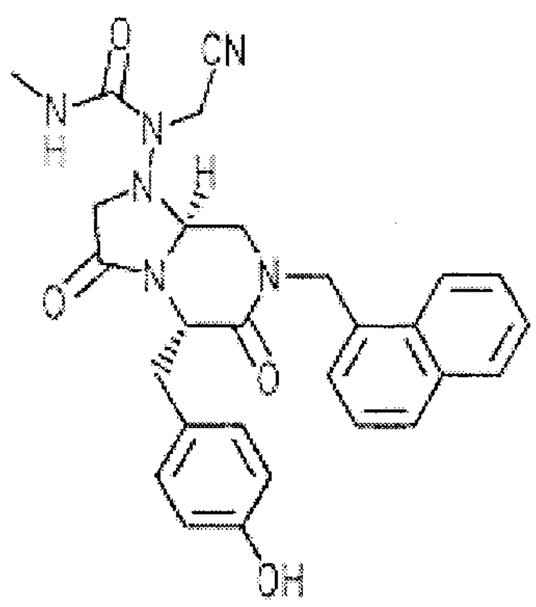
or a pharmaceutically acceptable salt thereof.

90. The compound of claim 1, which is:



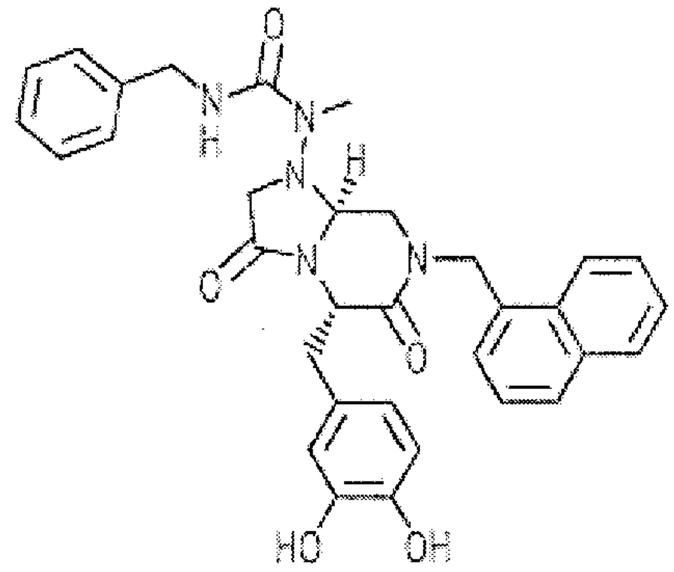
or a pharmaceutically acceptable salt thereof.

91. The compound of claim 1, which is:



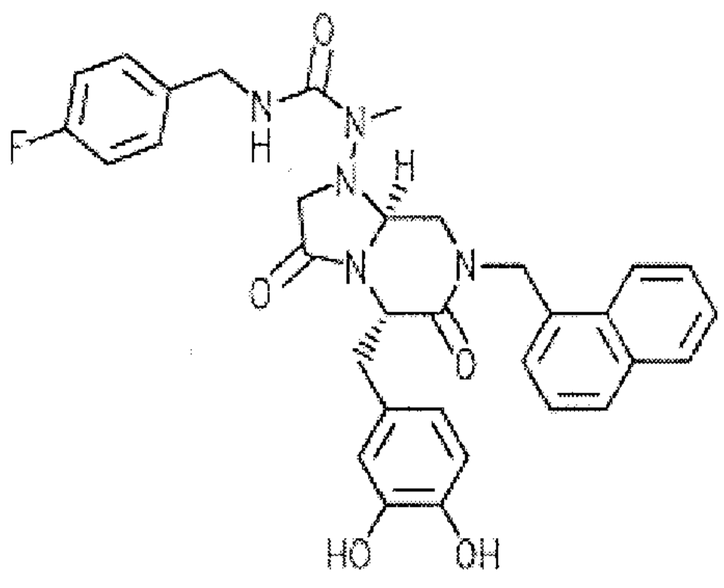
or a pharmaceutically acceptable salt thereof.

92. The compound of claim 1, which is:



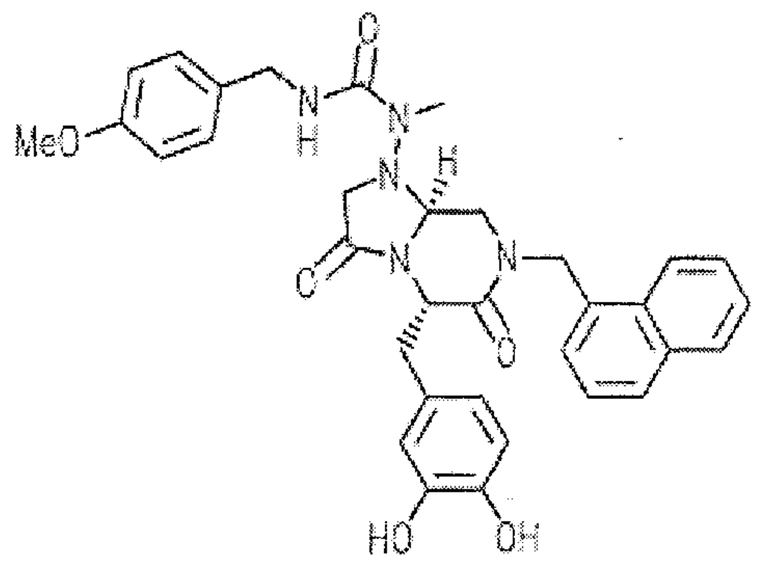
or a pharmaceutically acceptable salt thereof.

93. The compound of claim 1, which is:



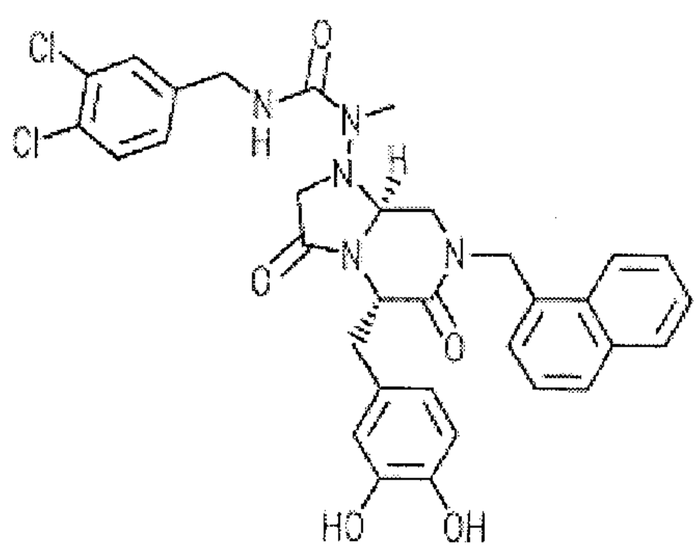
or a pharmaceutically acceptable salt thereof.

94. The compound of claim 1, which is:



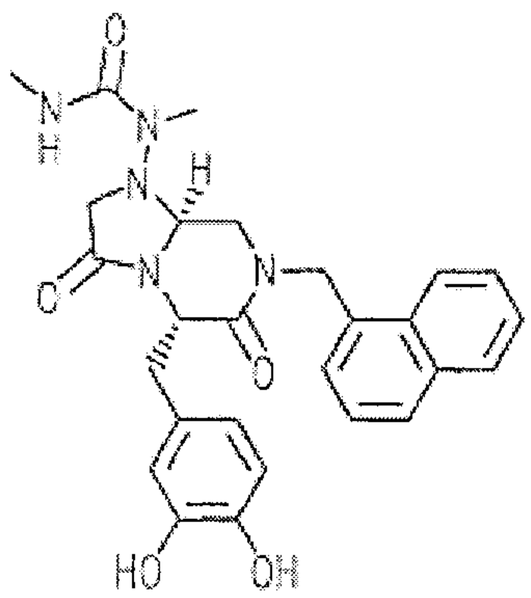
or a pharmaceutically acceptable salt thereof.

95. The compound of claim 1, which is:



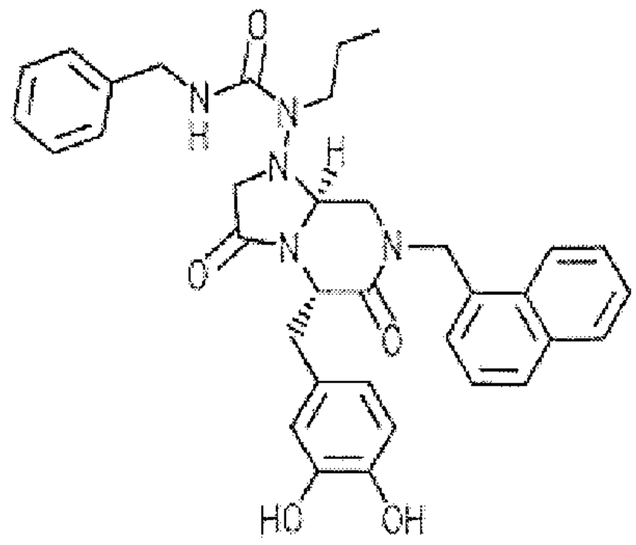
or a pharmaceutically acceptable salt thereof.

96. The compound of claim 1, which is:



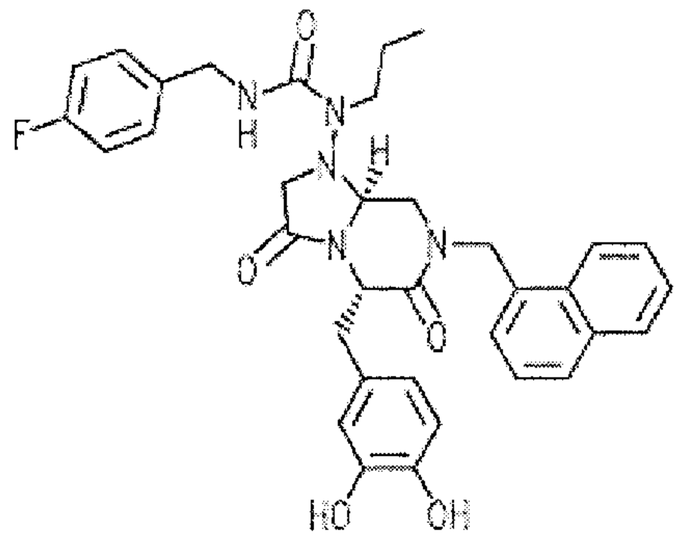
or a pharmaceutically acceptable salt thereof.

97. The compound of claim 1, which is:



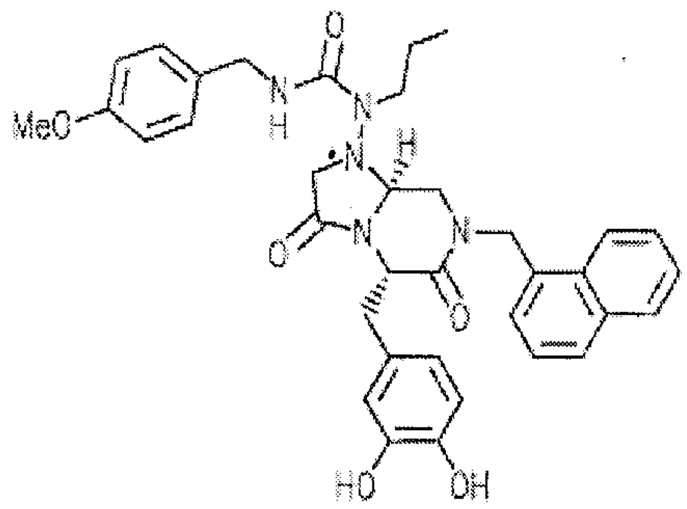
or a pharmaceutically acceptable salt thereof.

98. The compound of claim 1, which is:



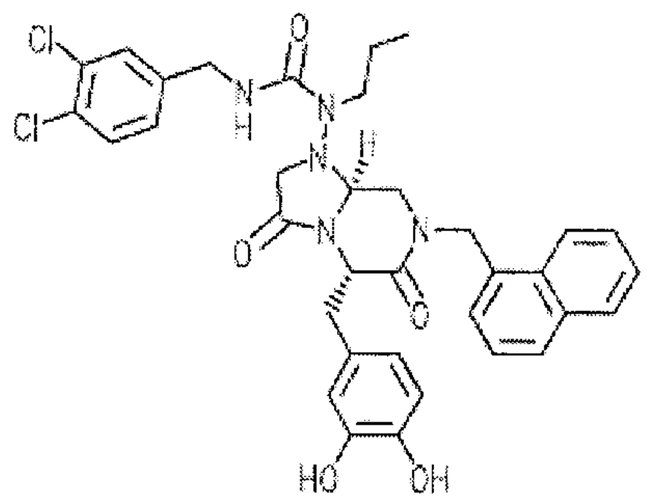
or a pharmaceutically acceptable salt thereof.

99. The compound of claim 1, which is:



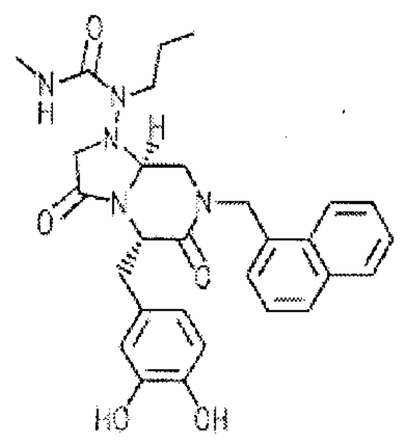
or a pharmaceutically acceptable salt thereof.

100. The compound of claim 1, which is:



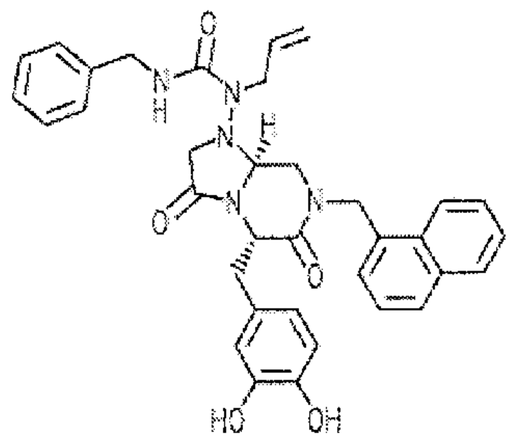
or a pharmaceutically acceptable salt thereof.

101. The compound of claim 1, which is:



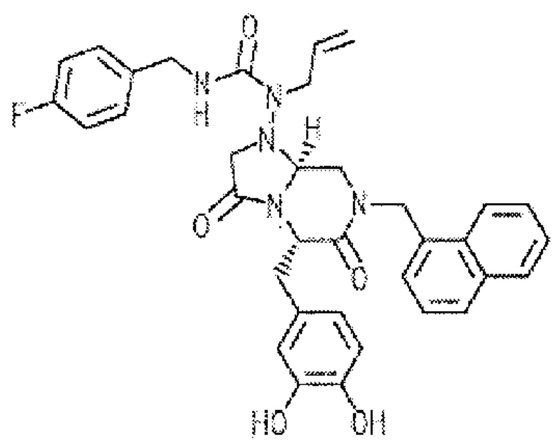
or a pharmaceutically acceptable salt thereof.

102. compound of claim 1, which is:



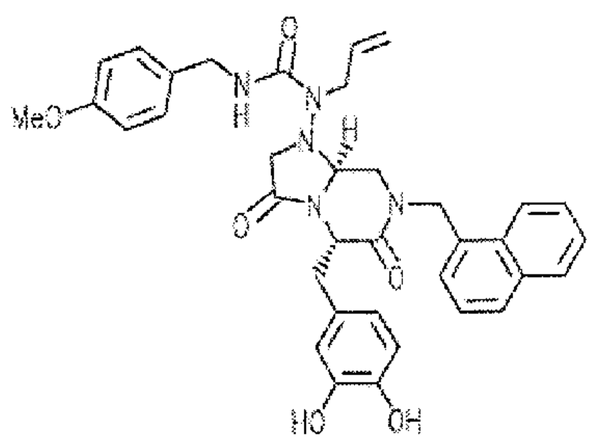
or a pharmaceutically acceptable salt thereof.

103. The compound of claim 1, which is:



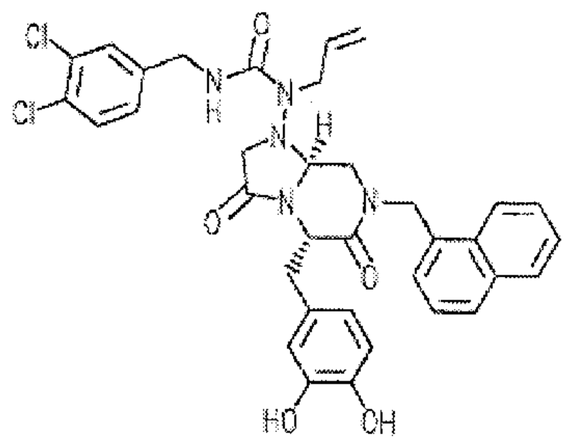
or a pharmaceutically acceptable salt thereof.

104. The compound of claim 1, which is:



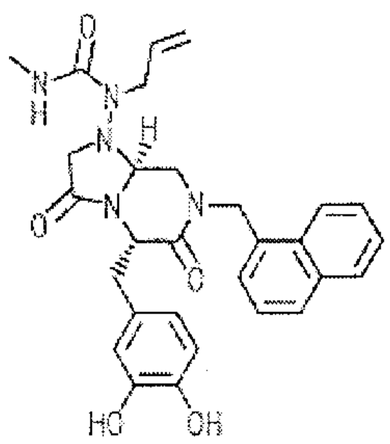
or a pharmaceutically acceptable salt thereof.

105. The compound of claim 1, which is:



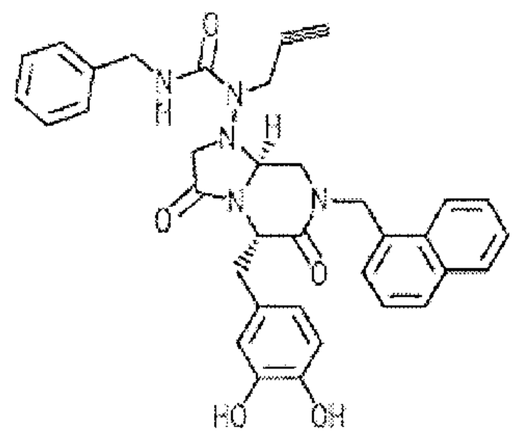
or a pharmaceutically acceptable salt thereof.

106. The compound of claim 1, which is:



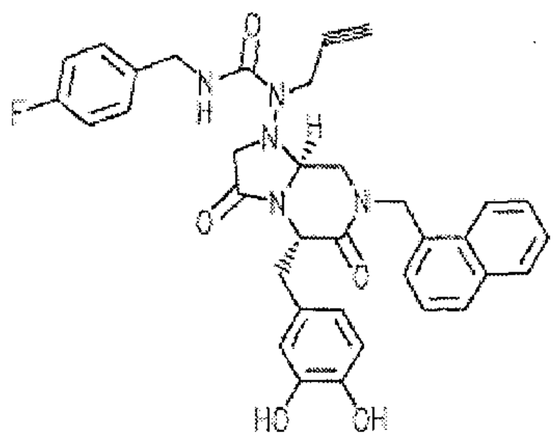
or a pharmaceutically acceptable salt thereof.

107. The compound of claim 1, which is:



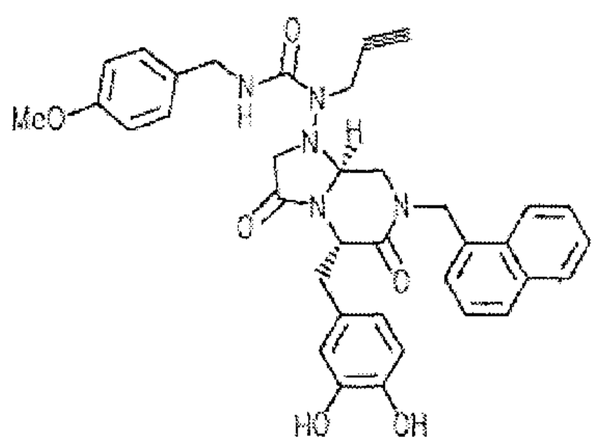
or a pharmaceutically acceptable salt thereof.

108. The compound of claim 1, which is:



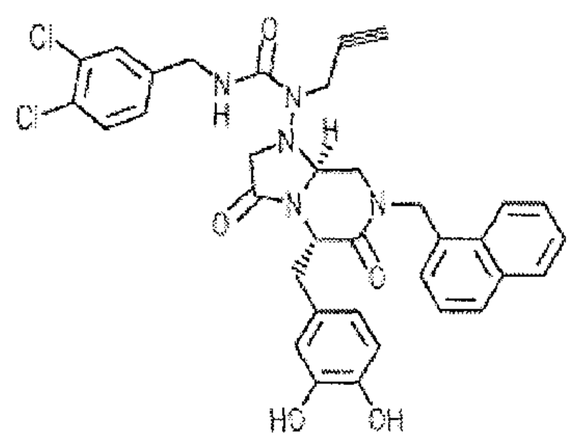
or a pharmaceutically acceptable salt thereof.

109. The compound of claim 1, which is:



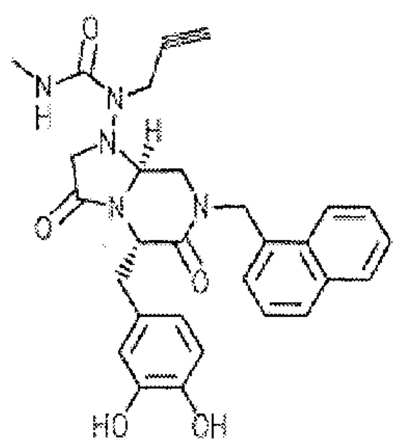
or a pharmaceutically acceptable salt thereof.

110. The compound of claim 1, which is:



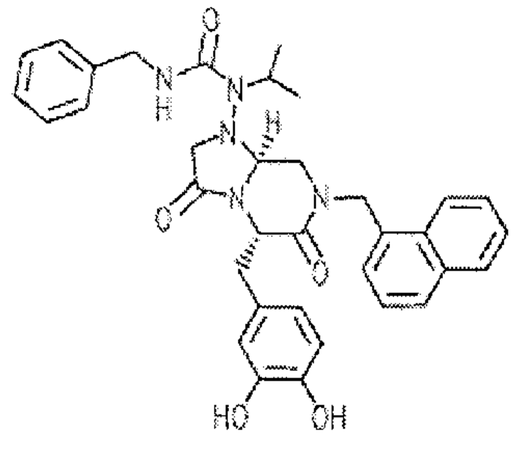
or a pharmaceutically acceptable salt thereof.

111. The compound of claim 1, which is:



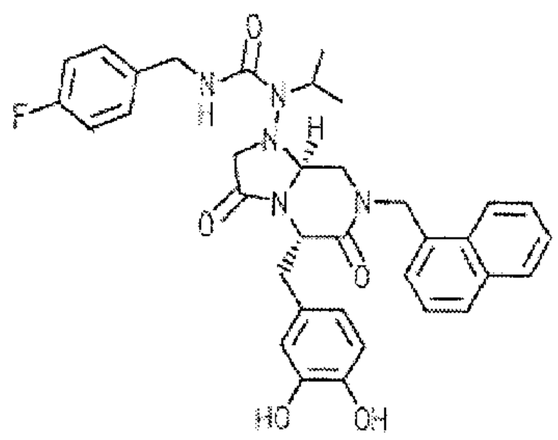
or a pharmaceutically acceptable salt thereof.

112. The compound of claim 1, which is:



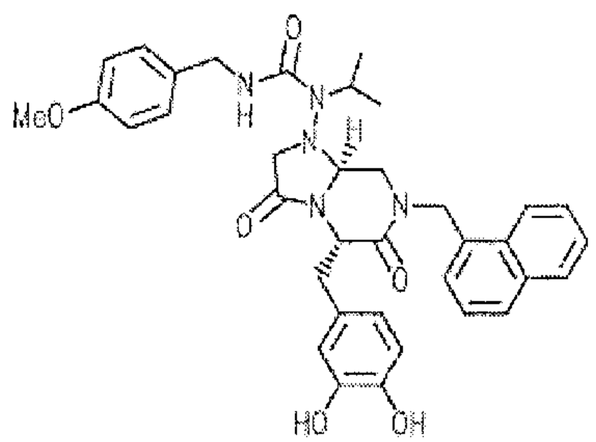
or a pharmaceutically acceptable salt thereof.

113. The compound of claim 1, which is:



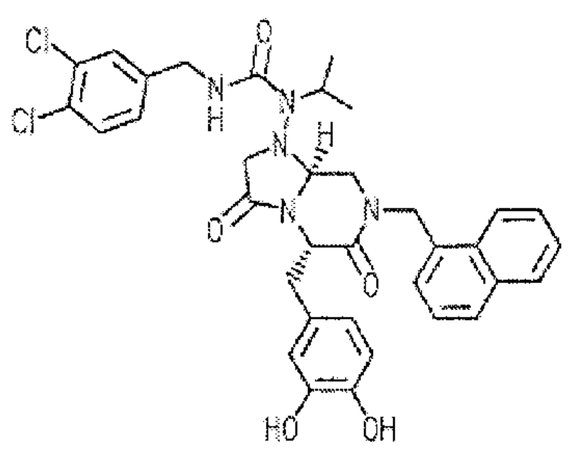
or a pharmaceutically acceptable salt thereof.

114. The compound of claim 1, which is:



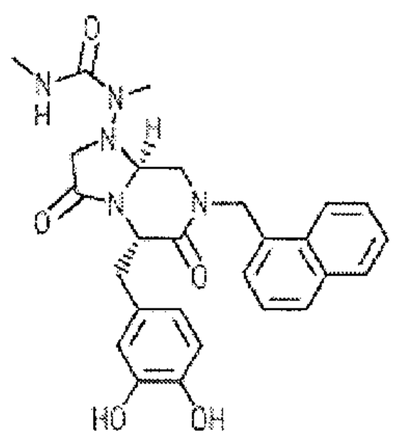
or a pharmaceutically acceptable salt thereof.

115. The compound of claim 1, which is:



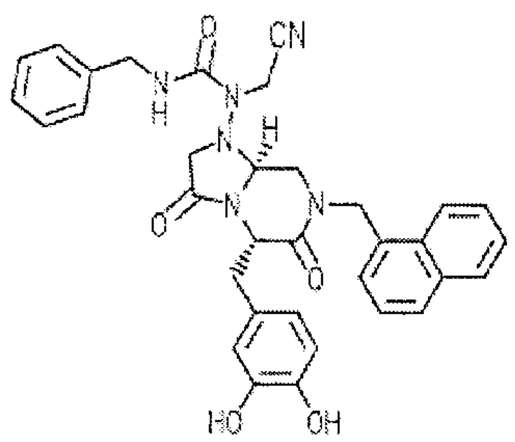
or a pharmaceutically acceptable salt thereof.

116. The compound of claim 1, which is:



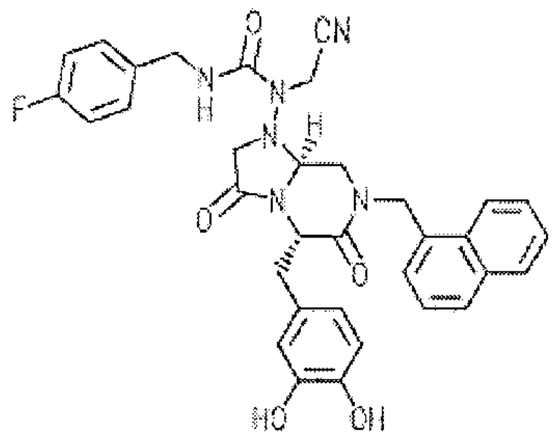
or a pharmaceutically acceptable salt thereof.

117. The compound of claim 1, which is:



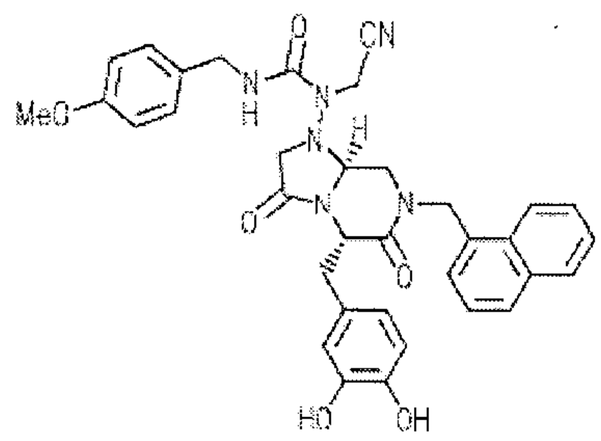
or a pharmaceutically acceptable salt thereof.

118. The compound of claim 1, which is:



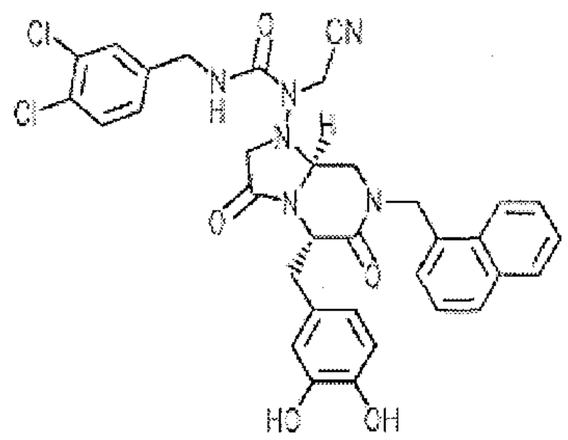
or a pharmaceutically acceptable salt thereof.

119. The compound of claim 1, which is:



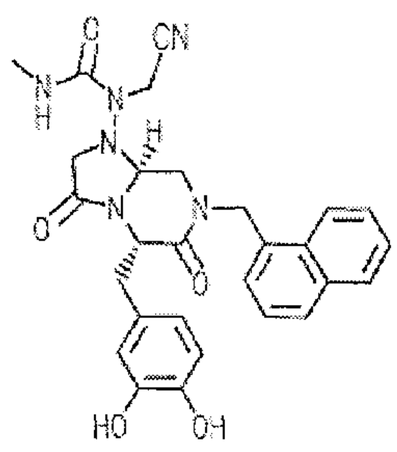
or a pharmaceutically acceptable salt thereof.

120. The compound of claim 1, which is:



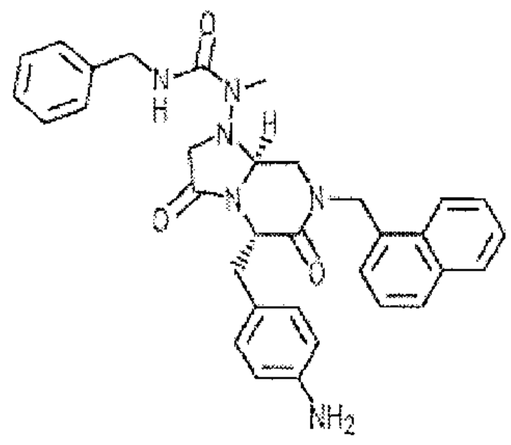
or a pharmaceutically acceptable salt thereof.

121. The compound of claim 1, which is:



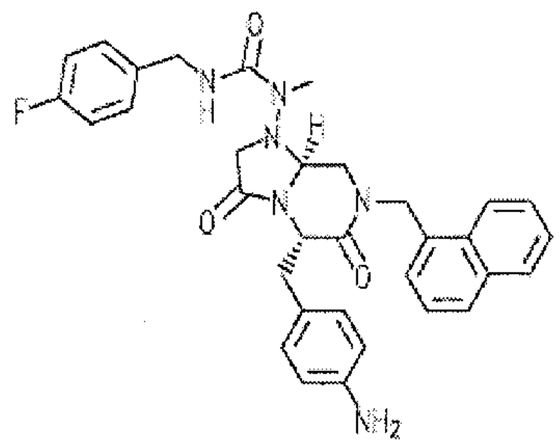
or a pharmaceutically acceptable salt thereof.

122. The compound of claim 1, which is:



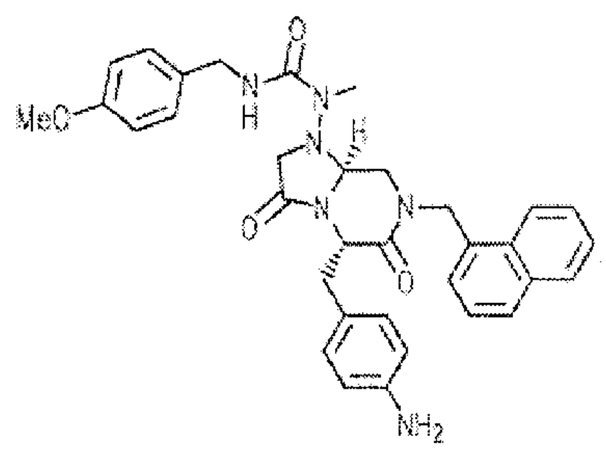
or a pharmaceutically acceptable salt thereof.

123. The compound of claim 1, which is:



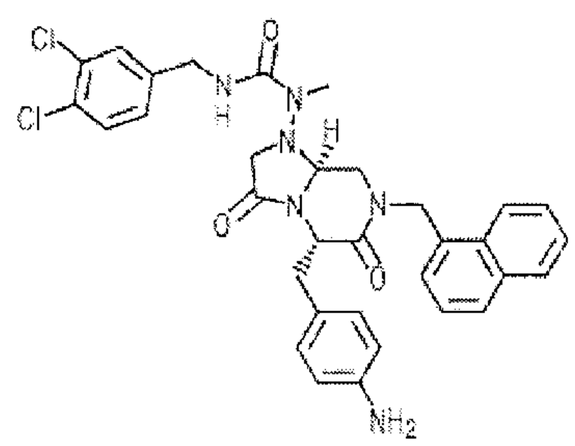
or a pharmaceutically acceptable salt thereof.

124. The compound of claim 1, which is:



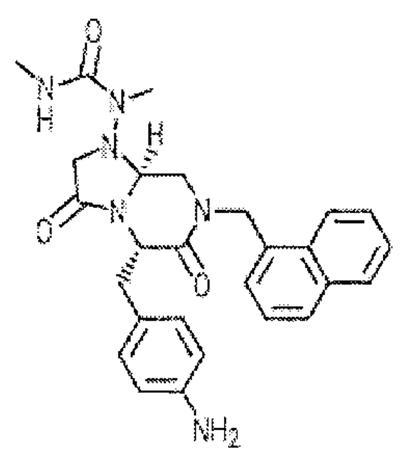
or a pharmaceutically acceptable salt thereof.

125. The compound of claim 1, which is:



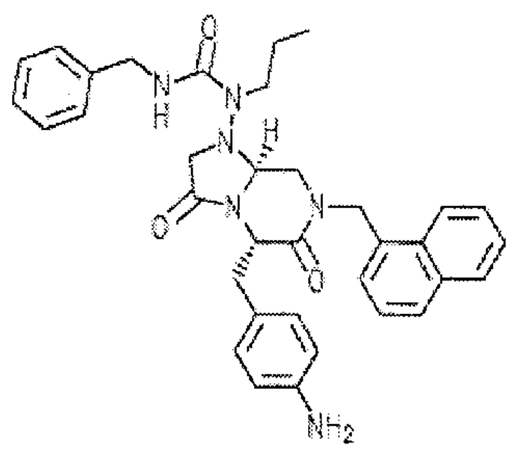
or a pharmaceutically acceptable salt thereof.

126. The compound of claim 1, which is:



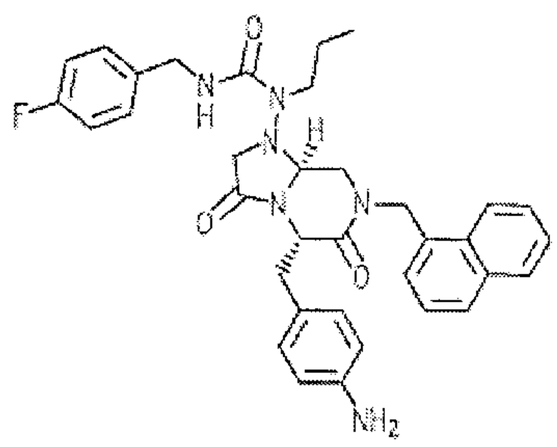
or a pharmaceutically acceptable salt thereof.

127. The compound of claim 1, which is:



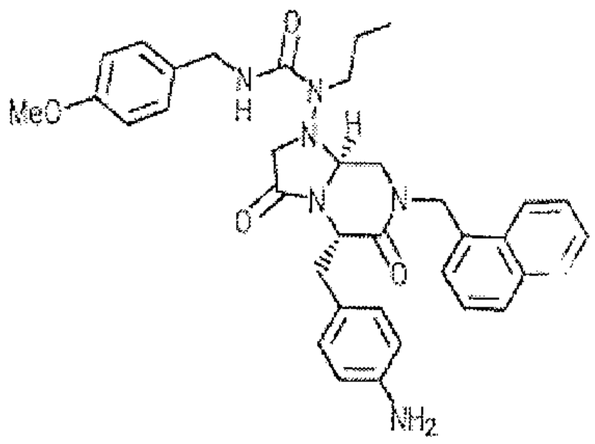
or a pharmaceutically acceptable salt thereof.

128. The compound of claim 1, which is:



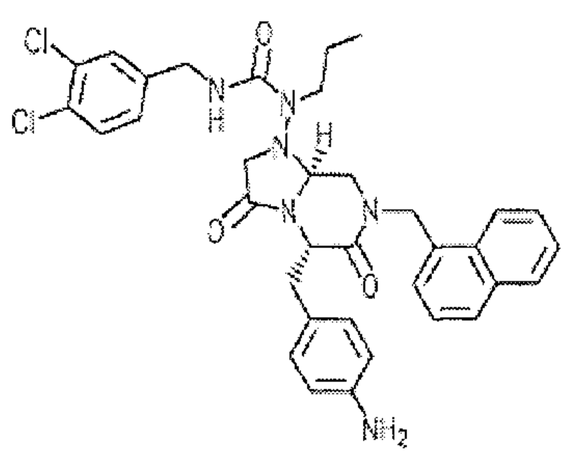
or a pharmaceutically acceptable salt thereof.

129. The compound of claim 1, which is:



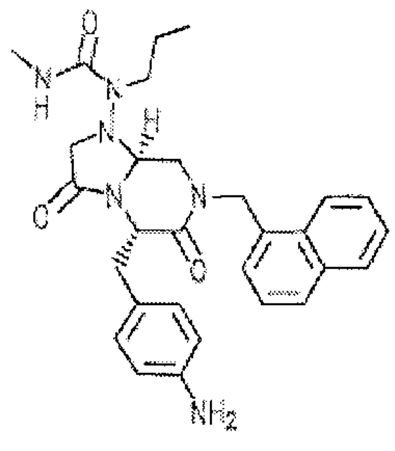
or a pharmaceutically acceptable salt thereof.

130. The compound of claim 1, which is:



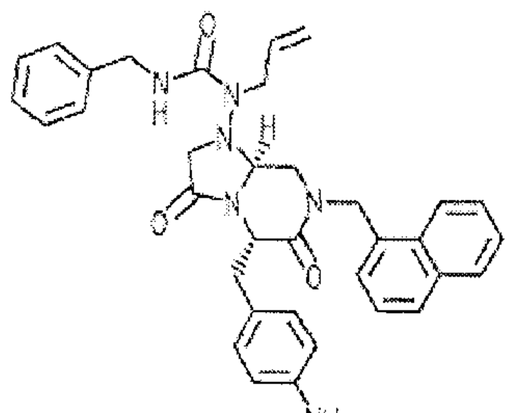
or a pharmaceutically acceptable salt thereof.

131. The compound of claim 1, which is:



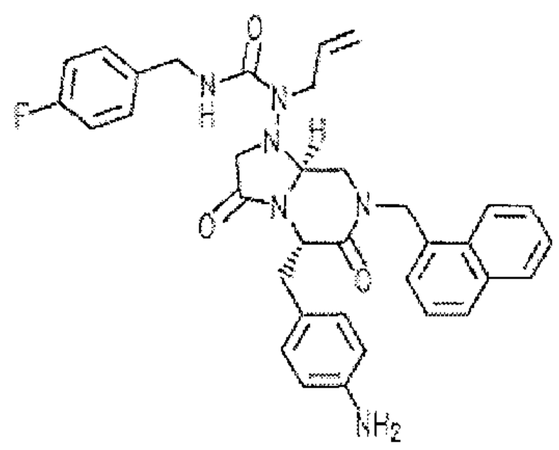
or a pharmaceutically acceptable salt thereof.

132. The compound of claim 1, which is:



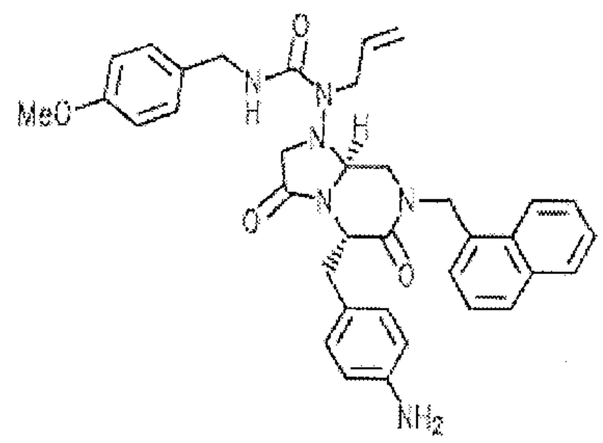
or a pharmaceutically acceptable salt thereof.

133. The compound of claim 1, which is:



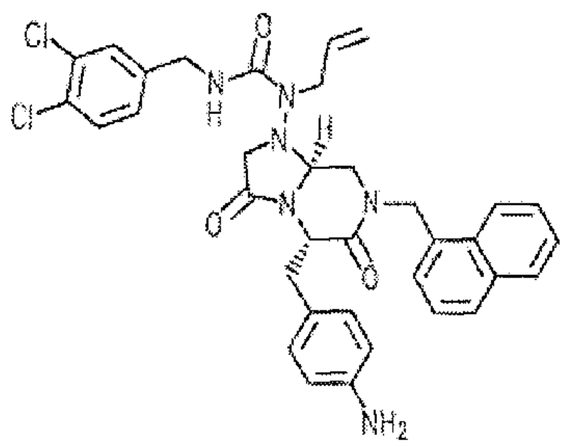
or a pharmaceutically acceptable salt thereof.

134. The compound of claim 1, which is:



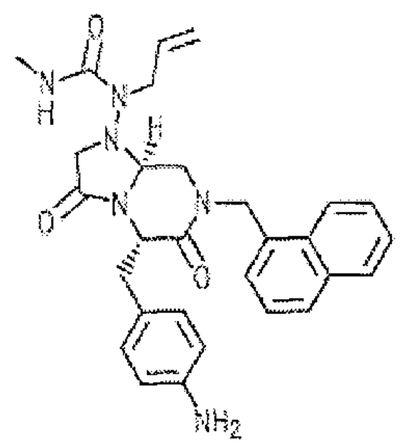
or a pharmaceutically acceptable salt thereof.

135. The compound of claim 1, which is:



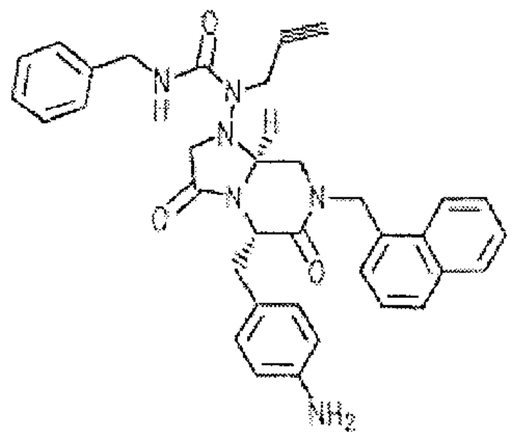
or a pharmaceutically acceptable salt thereof.

136. The compound of claim 1, which is:



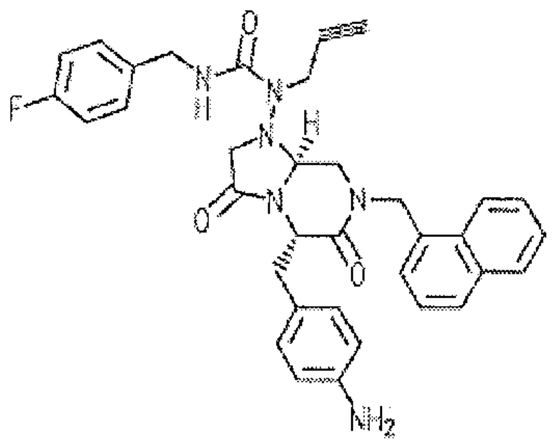
or a pharmaceutically acceptable salt thereof.

137. The compound of claim 1, which is:



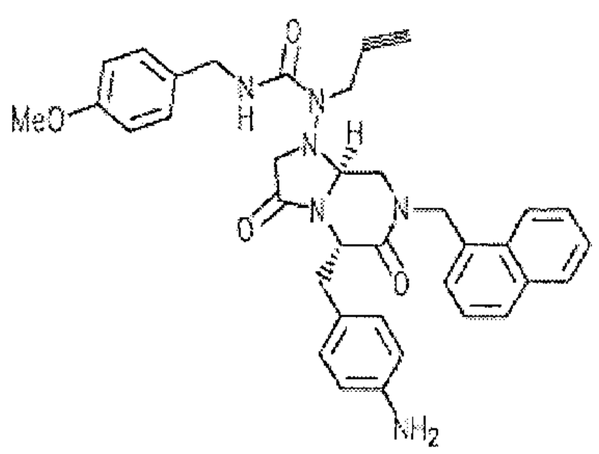
or a pharmaceutically acceptable salt thereof.

138. The compound of claim 1, which is:



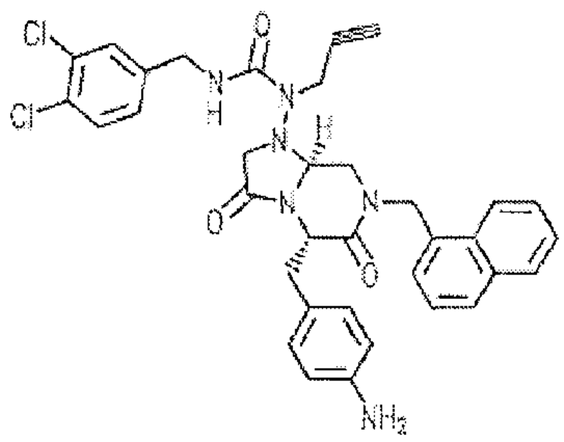
or a pharmaceutically acceptable salt thereof.

139. The compound of claim 1, which is:



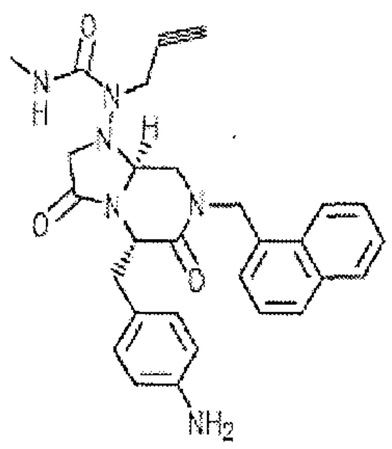
or a pharmaceutically acceptable salt thereof.

140. The compound of claim 1, which is:



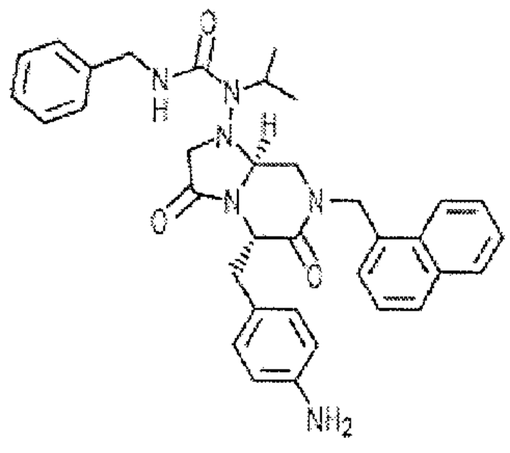
or a pharmaceutically acceptable salt thereof.

141. The compound of claim 1, which is:



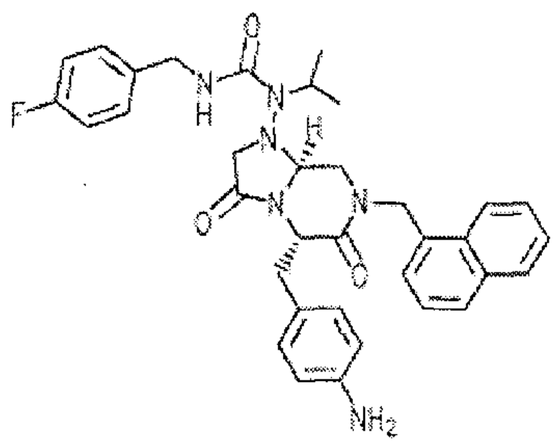
or a pharmaceutically acceptable salt thereof.

142. The compound of claim 1, which is:



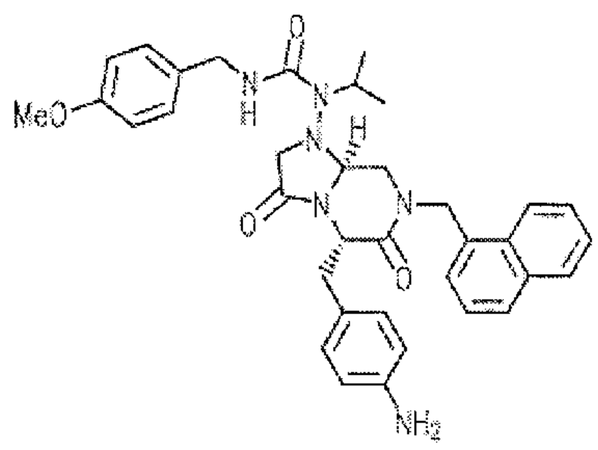
or a pharmaceutically acceptable salt thereof.

143. The compound of claim 1, which is:



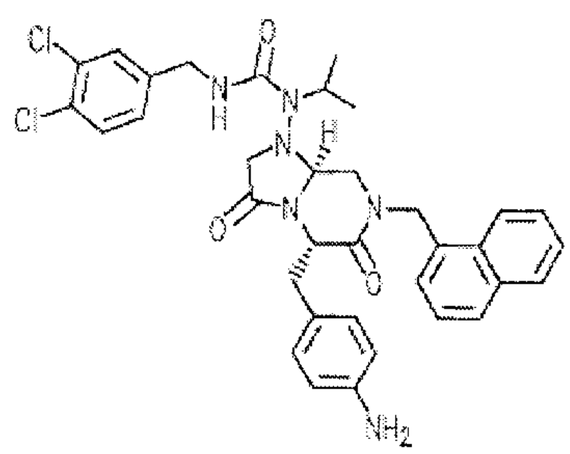
or a pharmaceutically acceptable salt thereof.

144. The compound of claim 1, which is:



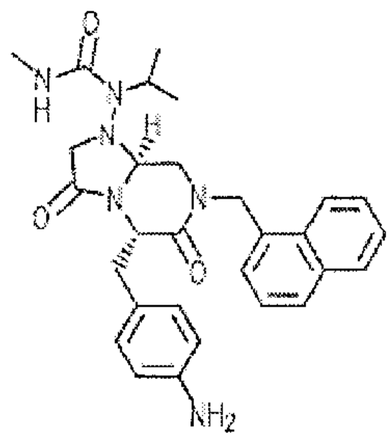
or a pharmaceutically acceptable salt thereof.

145. The compound of claim 1, which is:



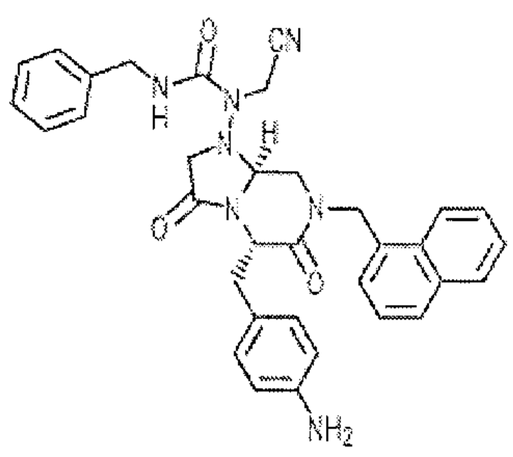
or a pharmaceutically acceptable salt thereof.

146. The compound of claim 1, which is:



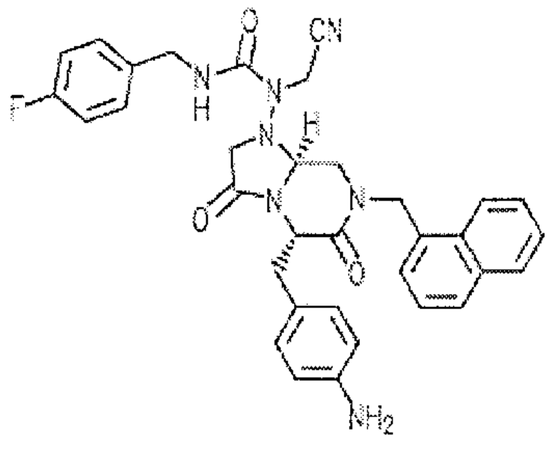
or a pharmaceutically acceptable salt thereof.

147. The compound of claim 1, which is:



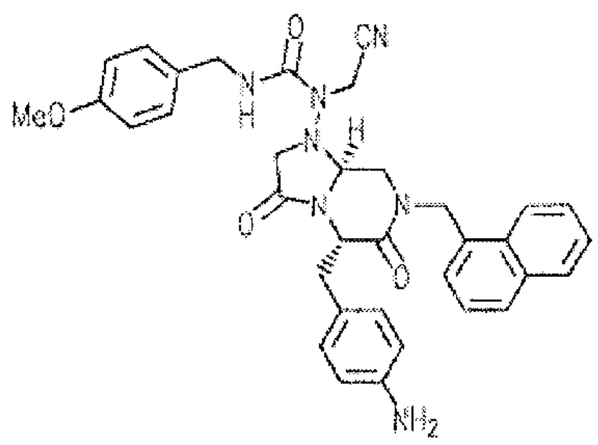
or a pharmaceutically acceptable salt thereof.

148. The compound of claim 1, which is:



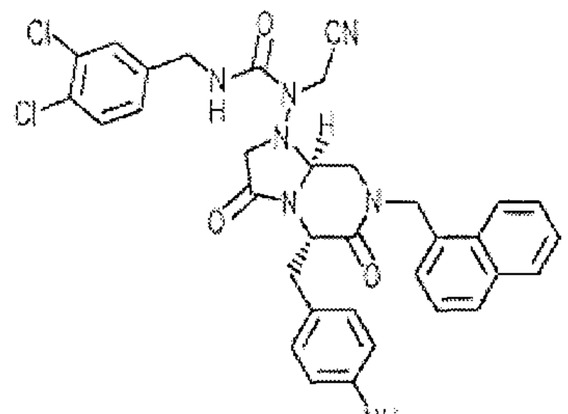
or a pharmaceutically acceptable salt thereof.

149. The compound of claim 1, which is:



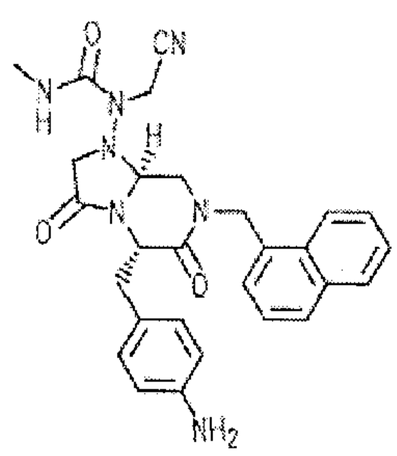
or a pharmaceutically acceptable salt thereof.

150. The compound of claim 1, which is:



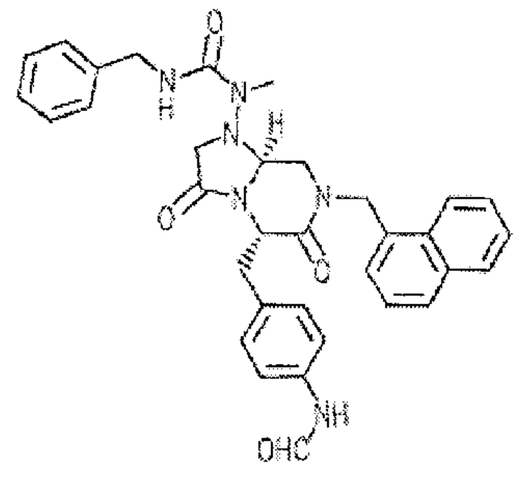
or a pharmaceutically acceptable salt thereof.

151. The compound of claim 1, which is:



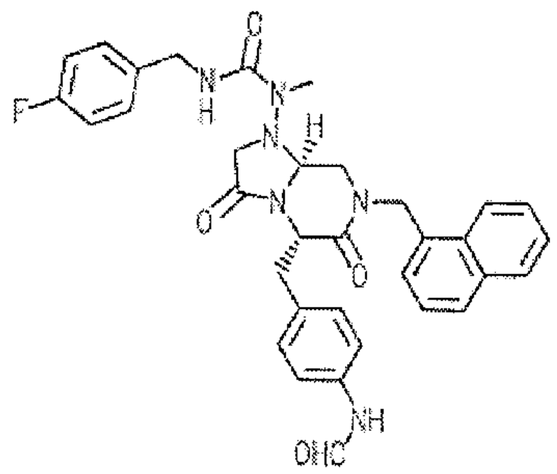
or a pharmaceutically acceptable salt thereof.

152. compound of claim 1, which is:



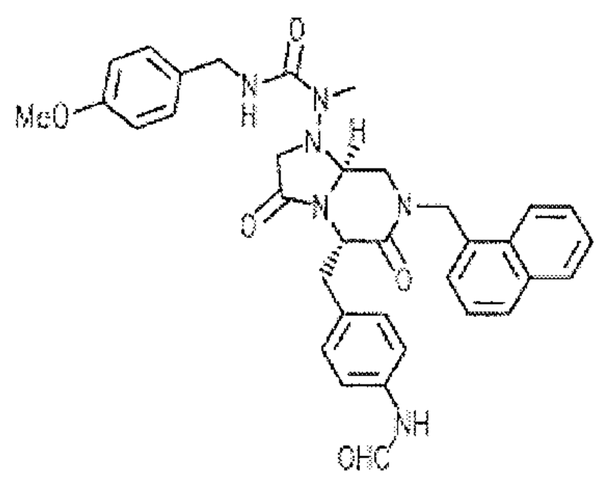
or a pharmaceutically acceptable salt thereof.

153. The compound of claim 1, which is:



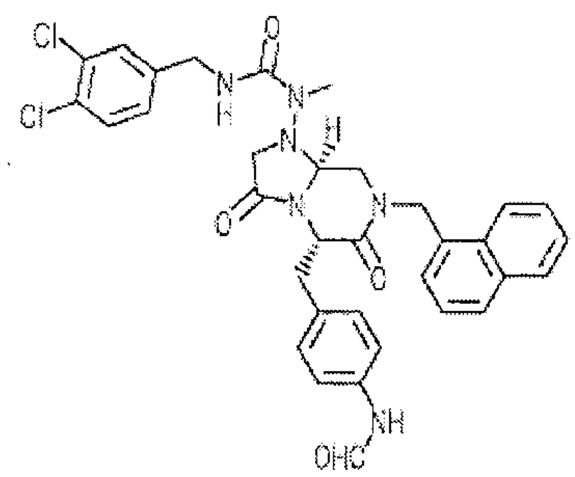
or a pharmaceutically acceptable salt thereof.

154. The compound of claim 1, which is:



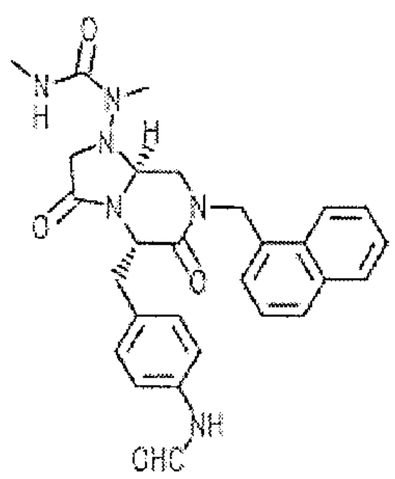
or a pharmaceutically acceptable salt thereof.

155. The compound of claim 1, which is:



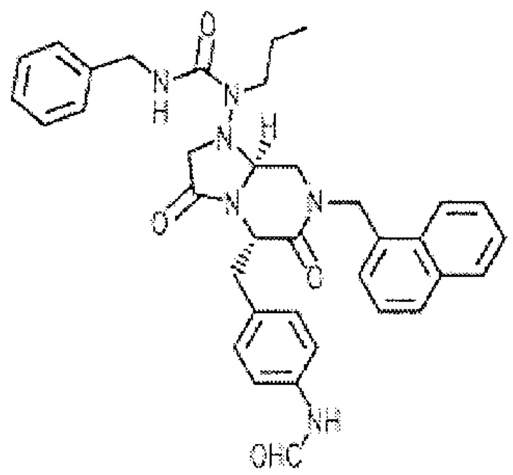
or a pharmaceutically acceptable salt thereof.

156. The compound of claim 1, which is:



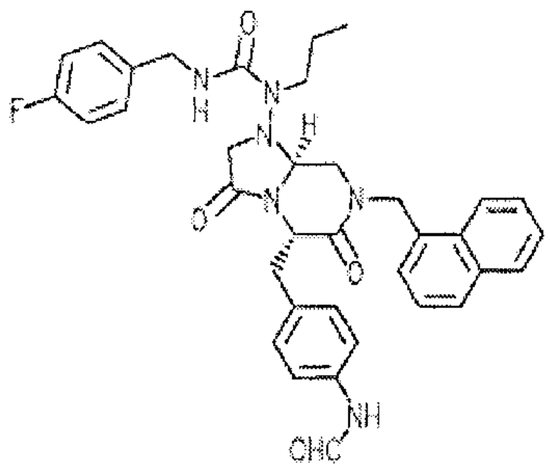
or a pharmaceutically acceptable salt thereof.

157. The compound of claim 1, which is:



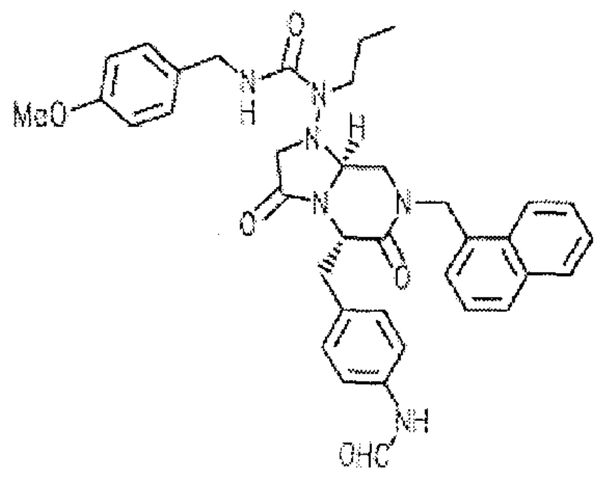
or a pharmaceutically acceptable salt thereof.

158. The compound of claim 1, which is:



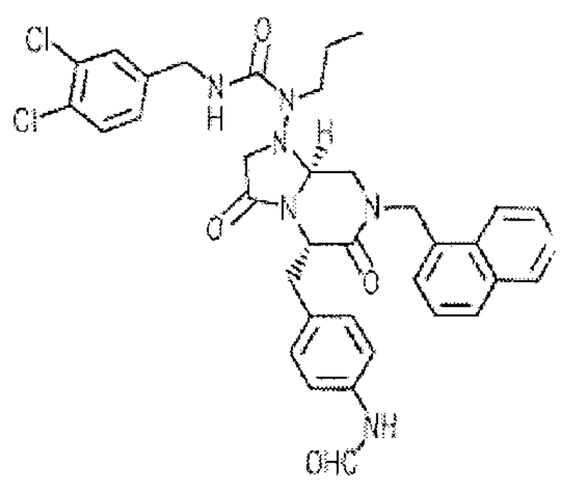
or a pharmaceutically acceptable salt thereof.

159. The compound of claim 1, which is:



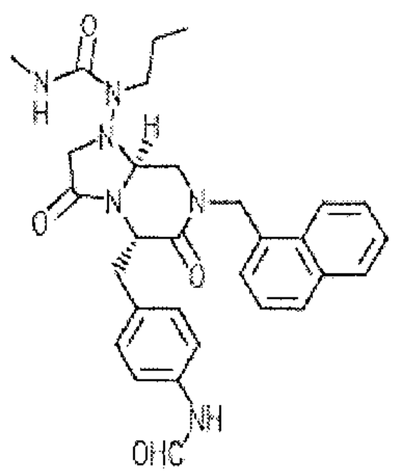
or a pharmaceutically acceptable salt thereof.

160. The compound of claim 1, which is:



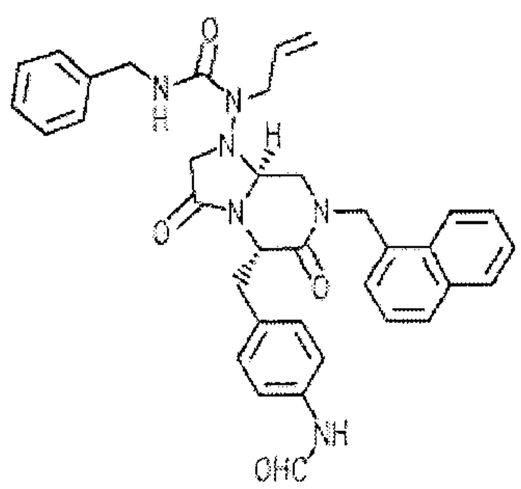
or a pharmaceutically acceptable salt thereof.

161. The compound of claim 1, which is:



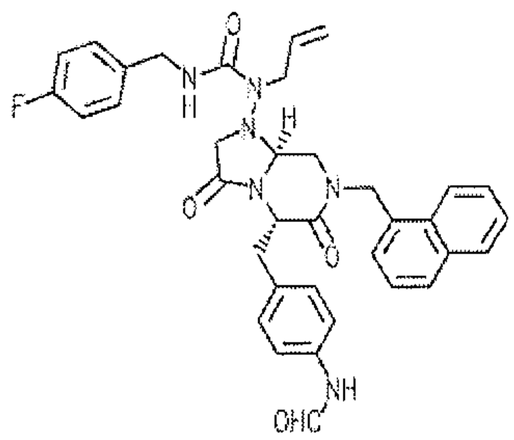
or a pharmaceutically acceptable salt thereof.

162. The compound of claim 1, which is:



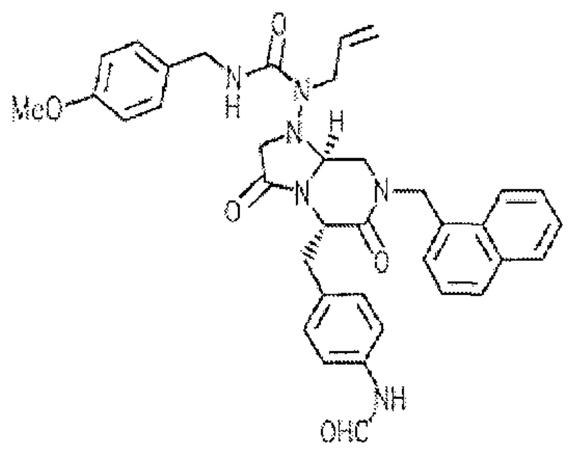
or a pharmaceutically acceptable salt thereof.

163. The compound of claim 1, which is:



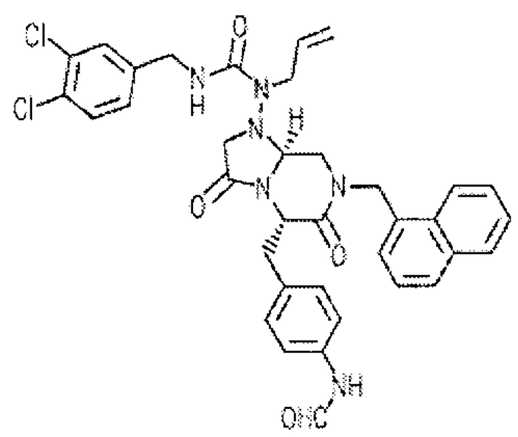
or a pharmaceutically acceptable salt thereof.

164. The compound of claim 1, which is:



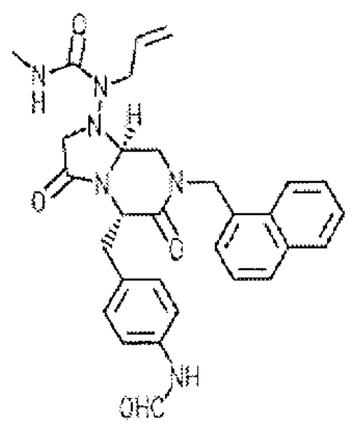
or a pharmaceutically acceptable salt thereof.

165. The compound of claim 1, which is:



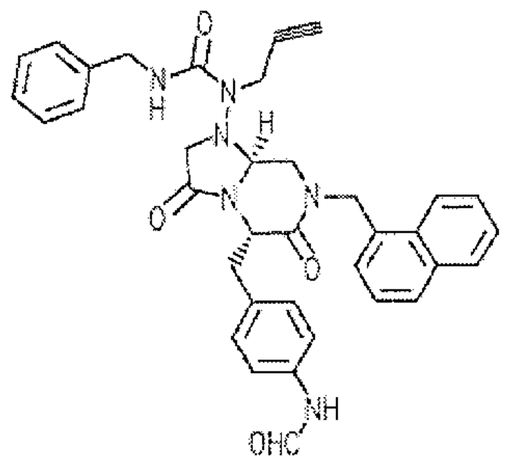
or a pharmaceutically acceptable salt thereof.

166. The compound of claim 1, which is:



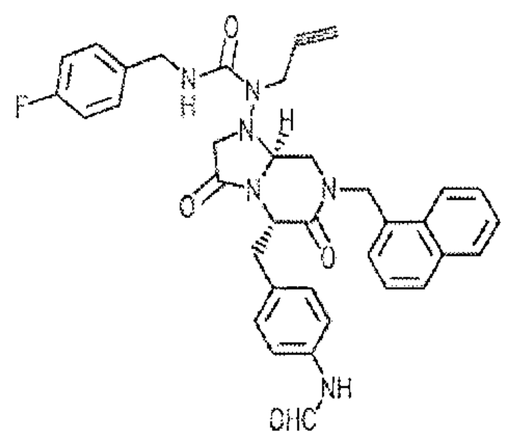
or a pharmaceutically acceptable salt thereof.

167. The compound of claim 1, which is:



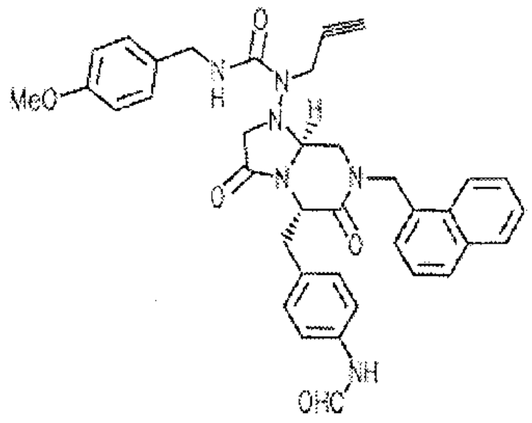
or a pharmaceutically acceptable salt thereof.

168. The compound of claim 1, which is:



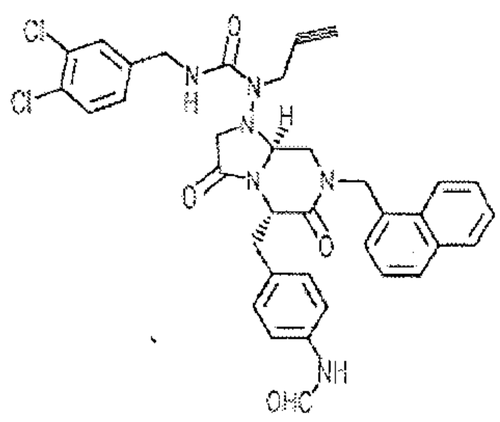
or a pharmaceutically acceptable salt thereof.

169. The compound of claim 1, which is:



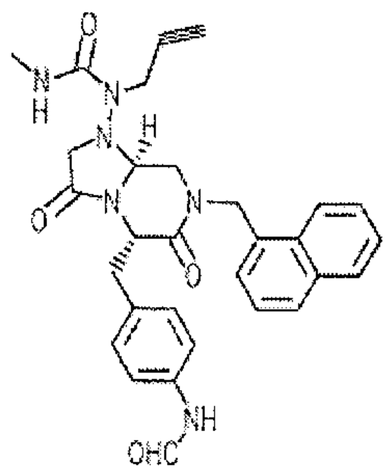
or a pharmaceutically acceptable salt thereof.

170. The compound of claim 1, which is:



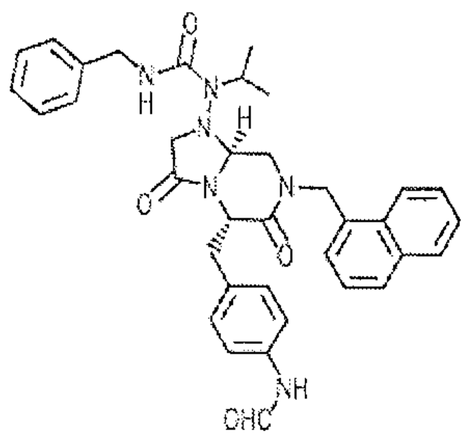
or a pharmaceutically acceptable salt thereof.

171. The compound of claim 1, which is:



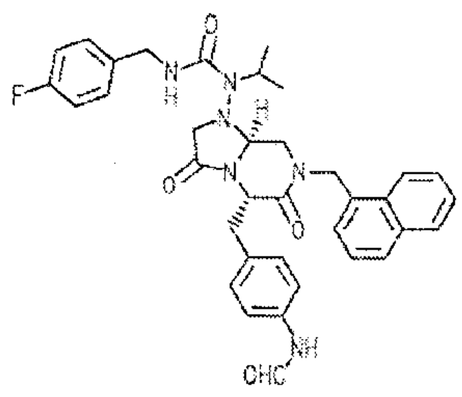
or a pharmaceutically acceptable salt thereof.

172. The compound of claim 1, which is:



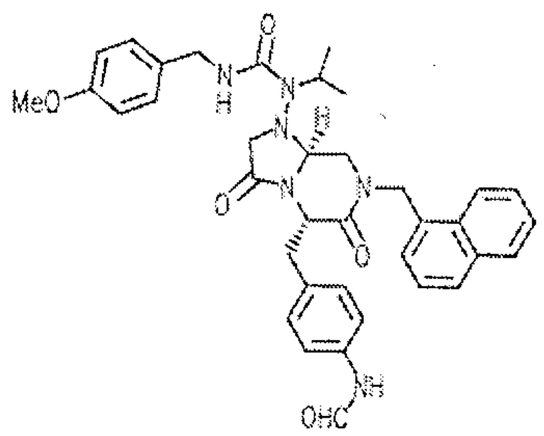
or a pharmaceutically acceptable salt thereof.

173. The compound of claim 1, which is:



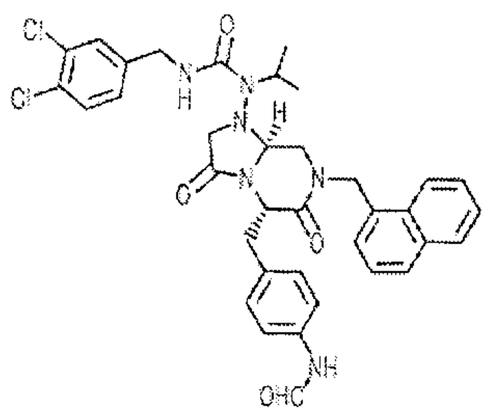
or a pharmaceutically acceptable salt thereof.

174. The compound of claim 1, which is:



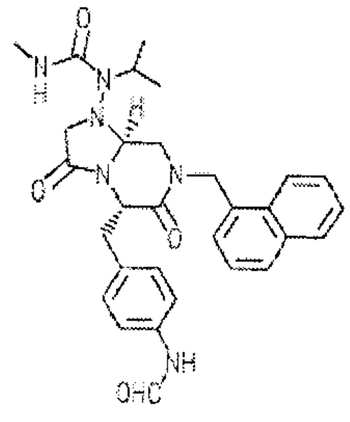
or a pharmaceutically acceptable salt thereof.

175. The compound of claim 1, which is:



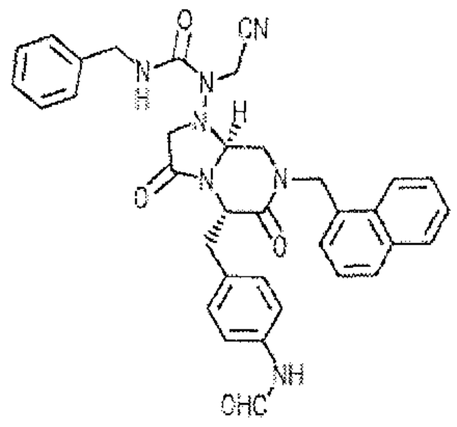
or a pharmaceutically acceptable salt thereof.

176. The compound of claim 1, which is:



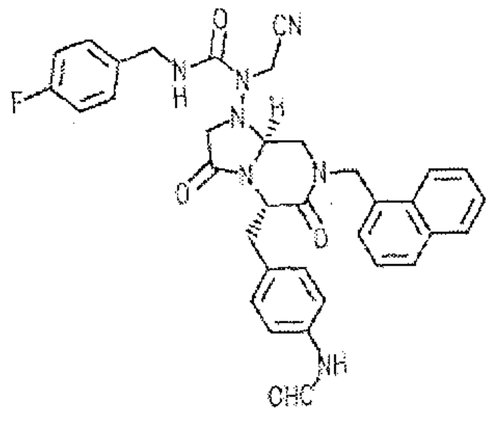
or a pharmaceutically acceptable salt thereof.

177. The compound of claim 1, which is:



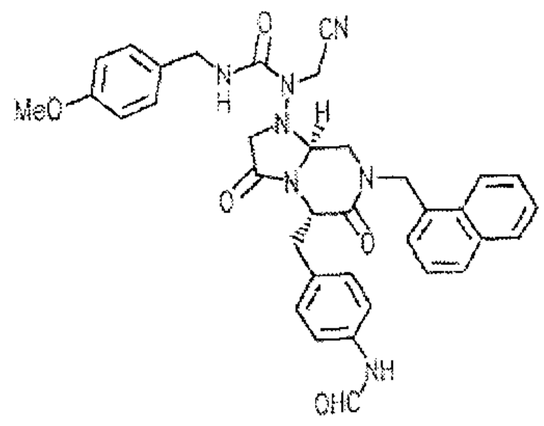
or a pharmaceutically acceptable salt thereof.

178. The compound of claim 1, which is:



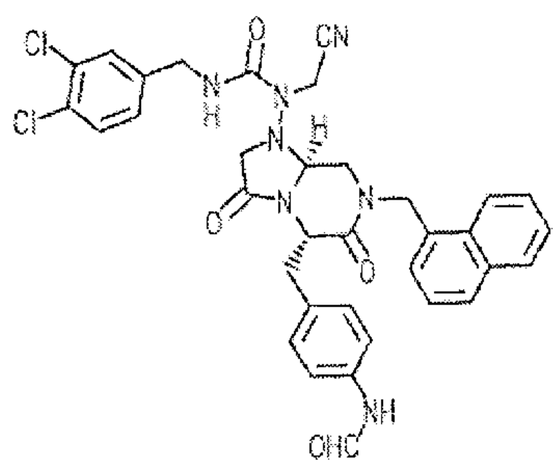
or a pharmaceutically acceptable salt thereof.

179. The compound of claim 1, which is:



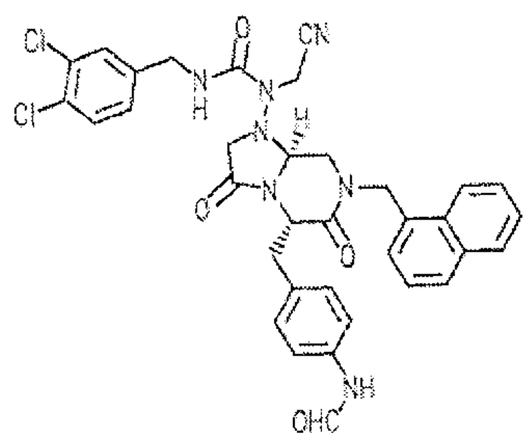
or a pharmaceutically acceptable salt thereof.

180. The compound of claim 1, which is:



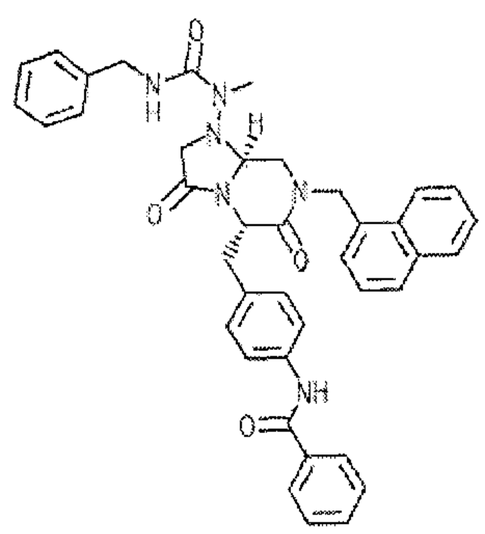
or a pharmaceutically acceptable salt thereof.

181. The compound of claim 1, which is:



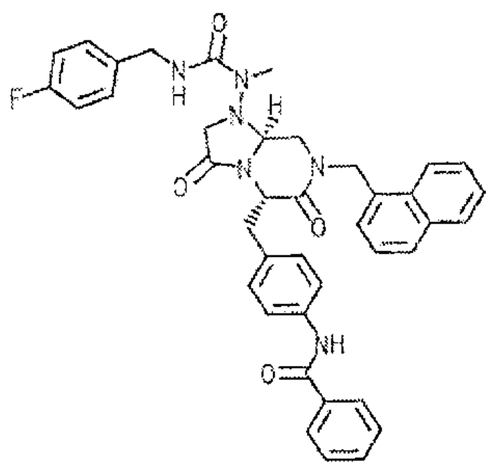
or a pharmaceutically acceptable salt thereof.

182. The compound of claim 1, which is:



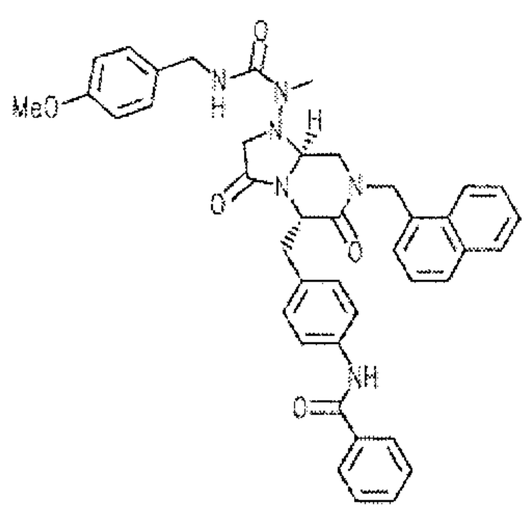
or a pharmaceutically acceptable salt thereof.

183. The compound of claim 1, which is:



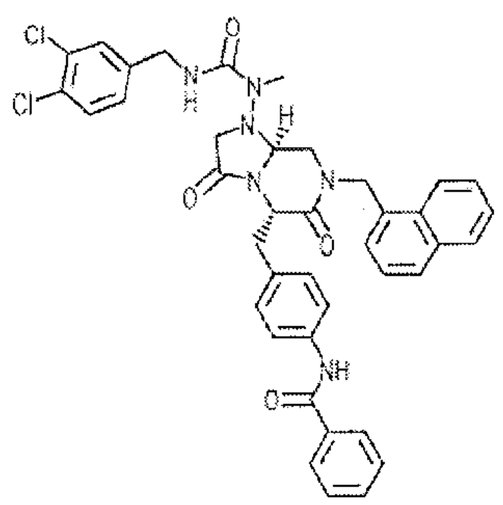
or a pharmaceutically acceptable salt thereof.

184. The compound of claim 1, which is:



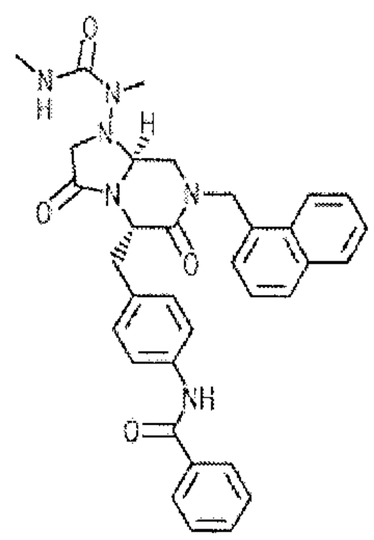
or a pharmaceutically acceptable salt thereof.

185. The compound of claim 1, which is:



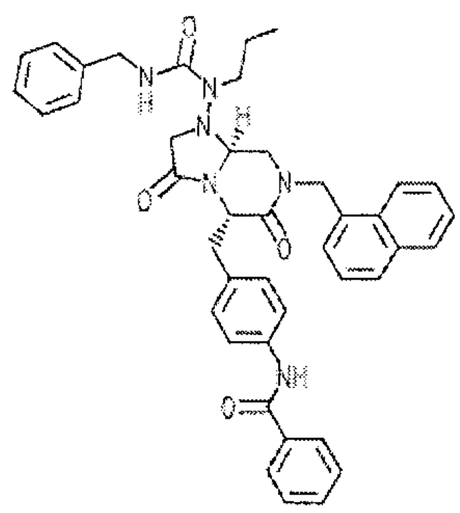
or a pharmaceutically acceptable salt thereof.

186. The compound of claim 1, which is:



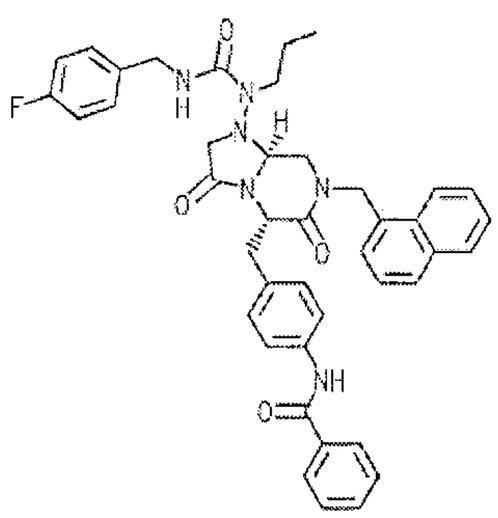
or a pharmaceutically acceptable salt thereof.

187. The compound of claim 1, which is:



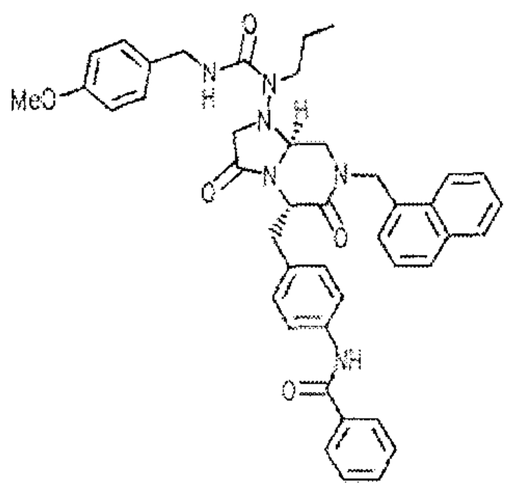
or a pharmaceutically acceptable salt thereof.

188. The compound of claim 1, which is:



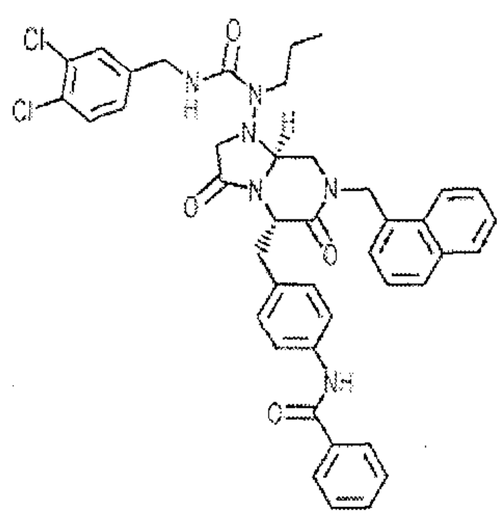
or a pharmaceutically acceptable salt thereof.

189. The compound of claim 1, which is:



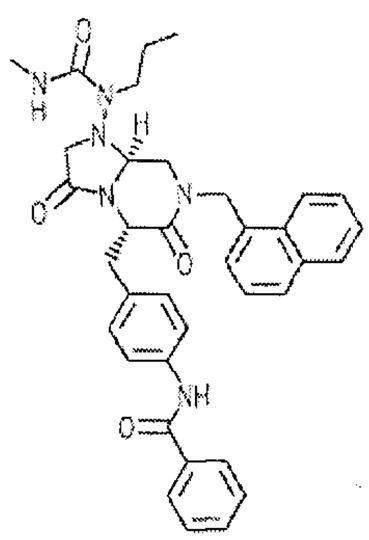
or a pharmaceutically acceptable salt thereof.

190. The compound of claim 1, which is:



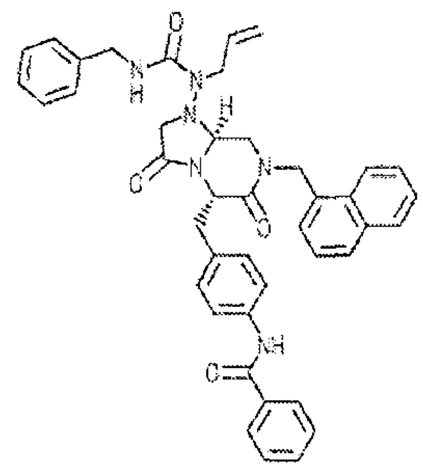
or a pharmaceutically acceptable salt thereof.

191. The compound of claim 1, which is:



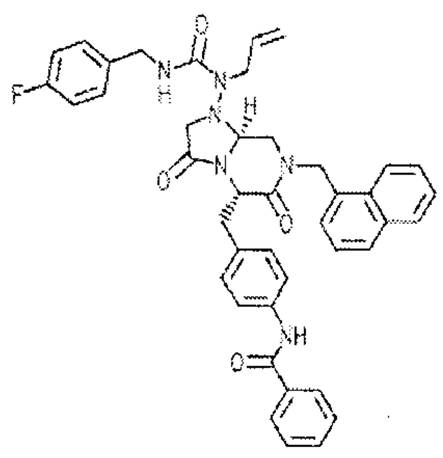
or a pharmaceutically acceptable salt thereof.

192. The compound of claim 1, which is:



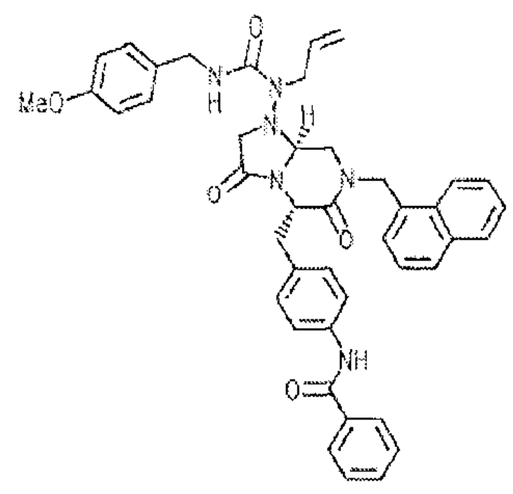
or a pharmaceutically acceptable salt thereof.

193. The compound of claim 1, which is:



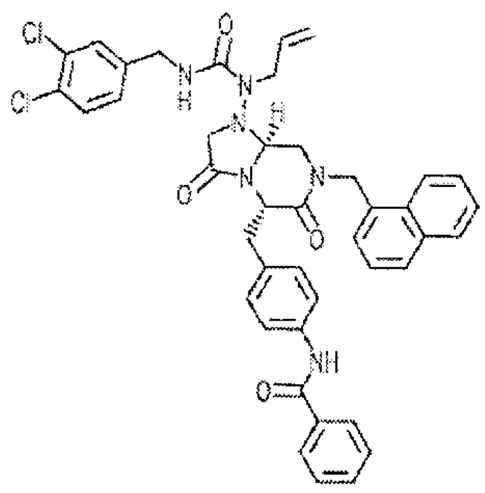
or a pharmaceutically acceptable salt thereof.

194. The compound of claim 1, which is:



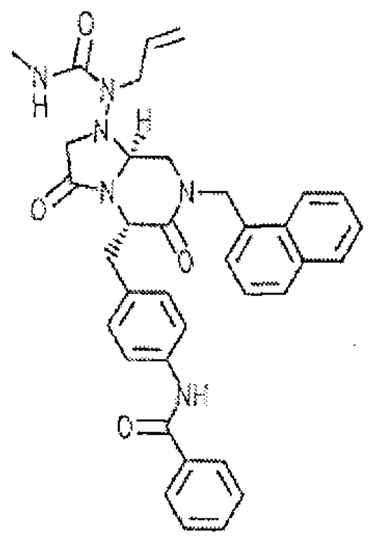
or a pharmaceutically acceptable salt thereof.

195. The compound of claim 1, which is:



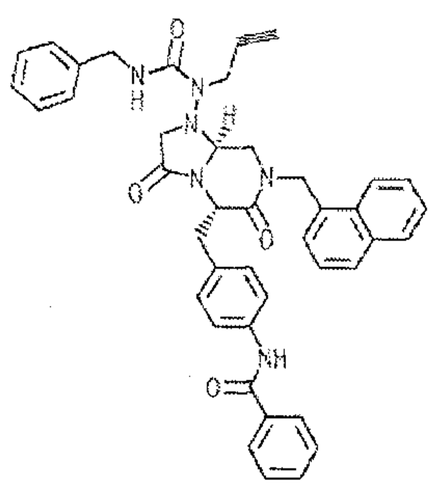
or a pharmaceutically acceptable salt thereof.

196. The compound of claim 1, which is:



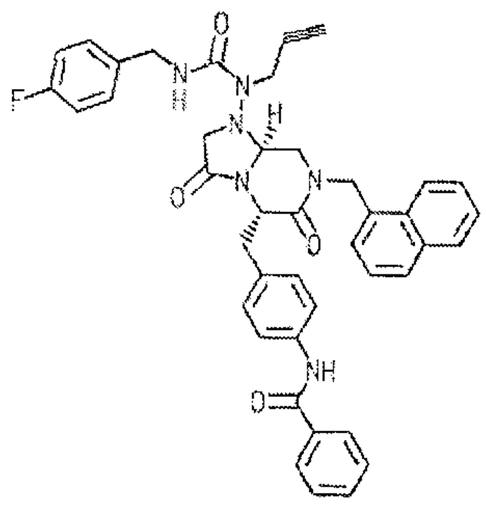
or a pharmaceutically acceptable salt thereof.

197. The compound of claim 1, which is:



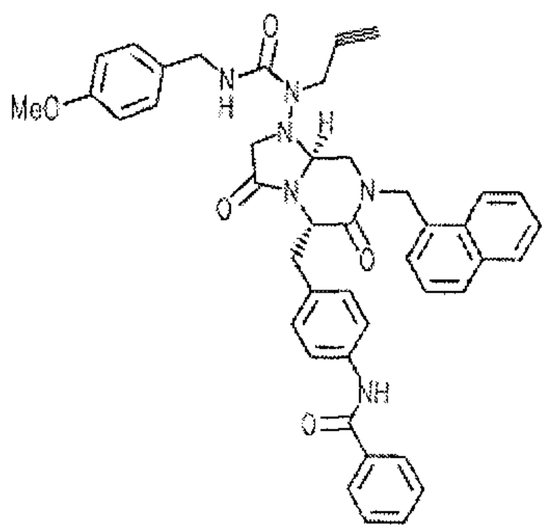
or a pharmaceutically acceptable salt thereof.

198. The compound of claim 1, which is:



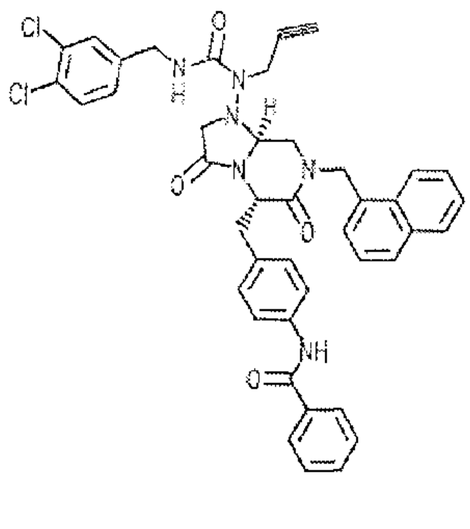
or a pharmaceutically acceptable salt thereof.

199. The compound of claim 1, which is:



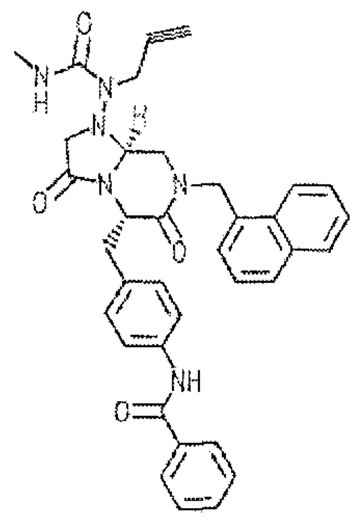
or a pharmaceutically acceptable salt thereof.

200. The compound of claim 1, which is:



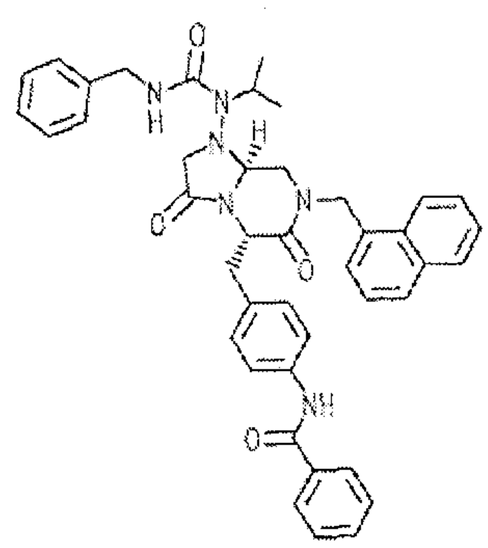
or a pharmaceutically acceptable salt thereof.

201. The compound of claim 1, which is:



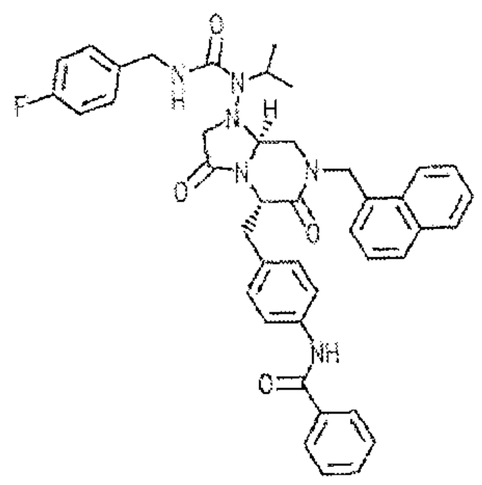
or a pharmaceutically acceptable salt thereof.

202. The compound of claim 1, which is:



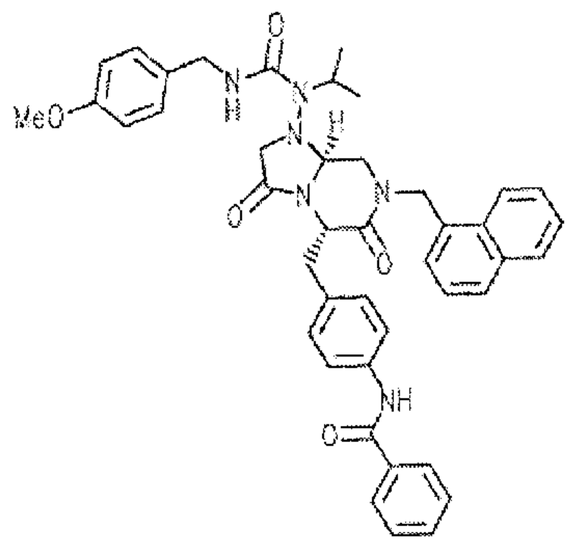
or a pharmaceutically acceptable salt thereof.

203. The compound of claim 1, which is:



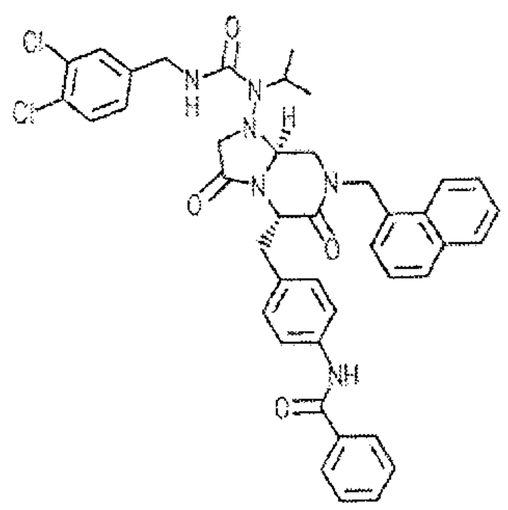
or a pharmaceutically acceptable salt thereof.

204. The compound of claim 1, which is:



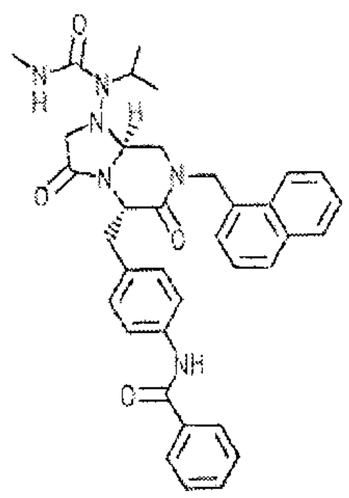
or a pharmaceutically acceptable salt thereof.

205. The compound of claim 1, which is:



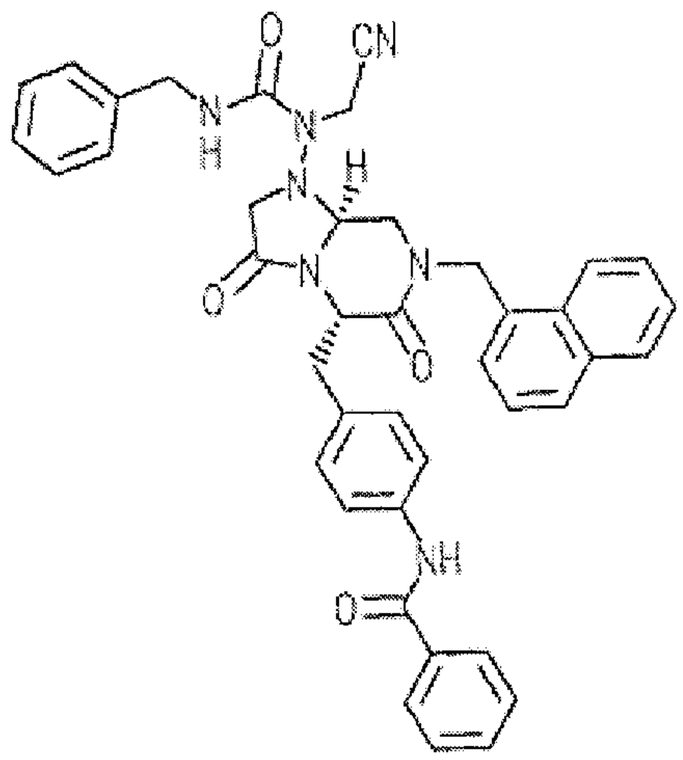
or a pharmaceutically acceptable salt thereof.

206. The compound of claim 1, which is:



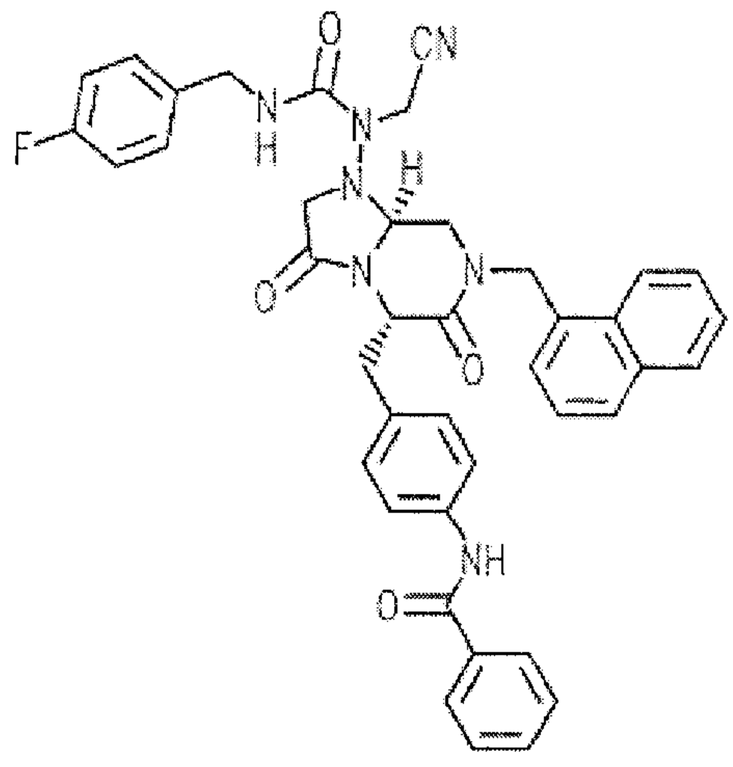
or a pharmaceutically acceptable salt thereof.

207. The compound of claim 1, which is:



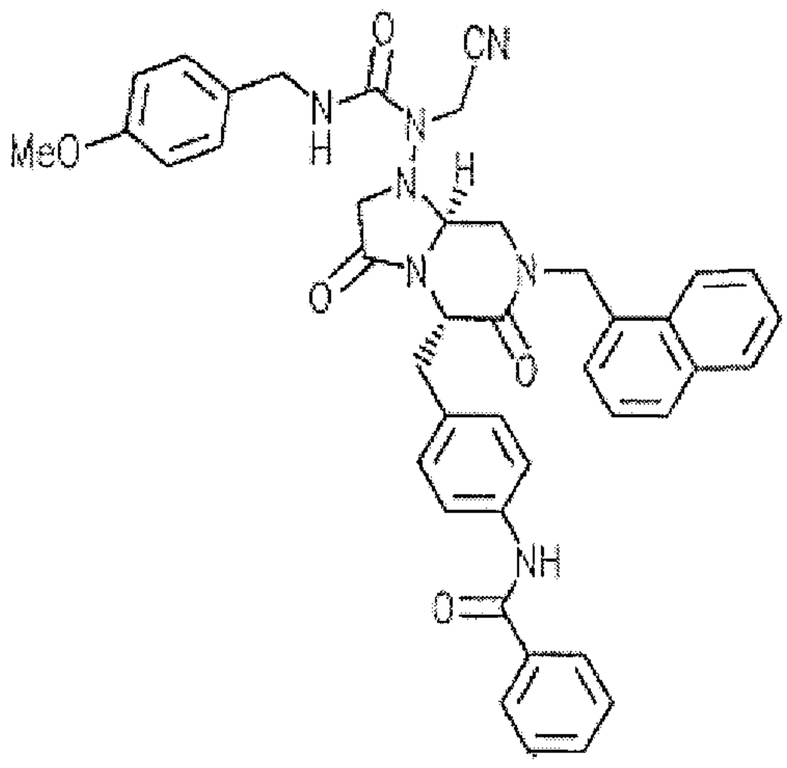
or a pharmaceutically acceptable salt thereof.

208. The compound of claim 1, which is:



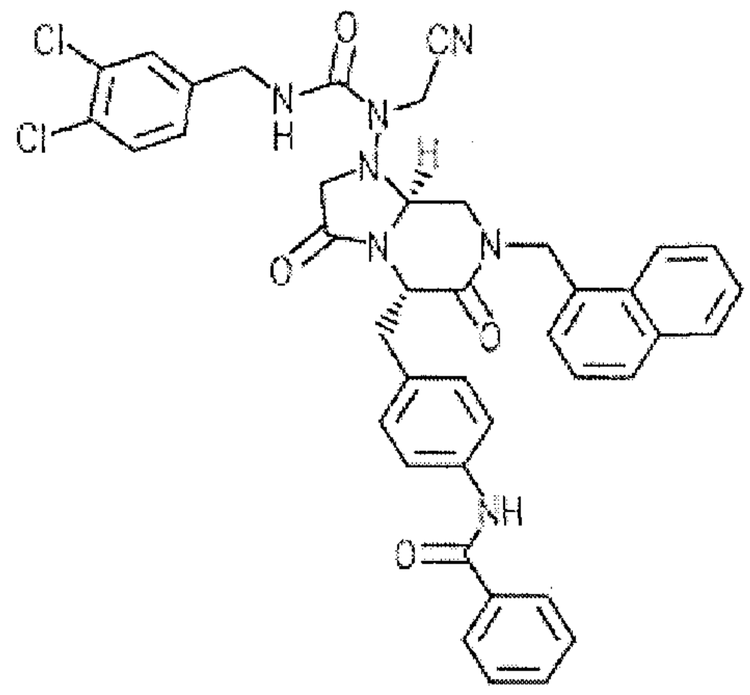
or a pharmaceutically acceptable salt thereof.

209. The compound of claim 1, which is:



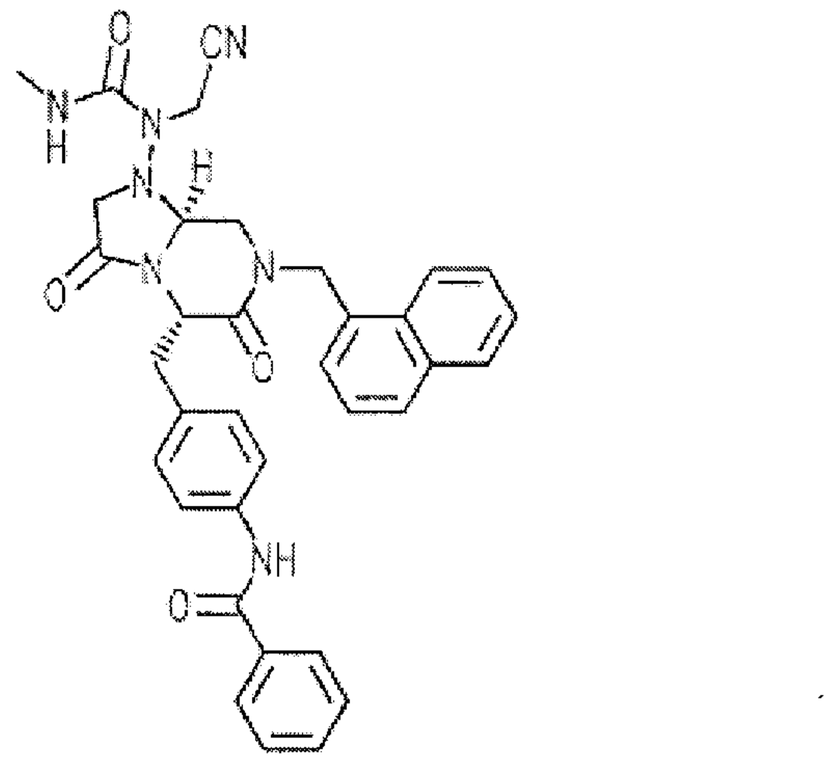
or a pharmaceutically acceptable salt thereof.

210. The compound of claim 1, which is:



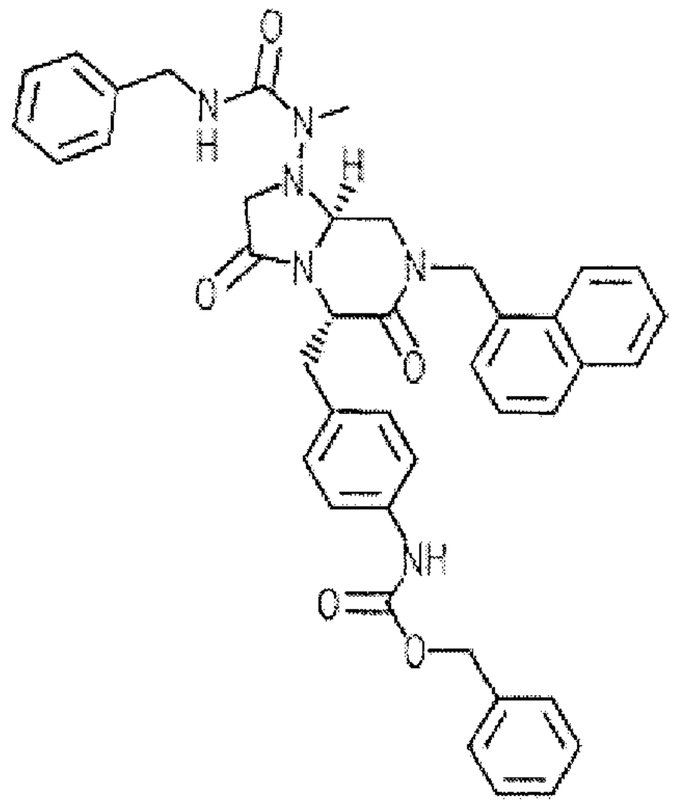
or a pharmaceutically acceptable salt thereof.

211. The compound of claim 1, which is:



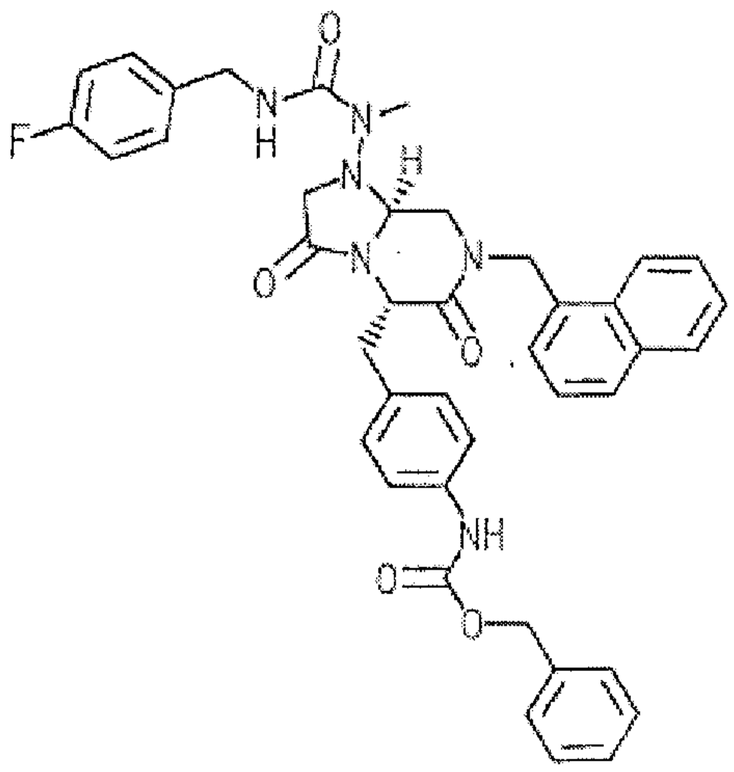
or a pharmaceutically acceptable salt thereof.

212. The compound of claim 1, which is:



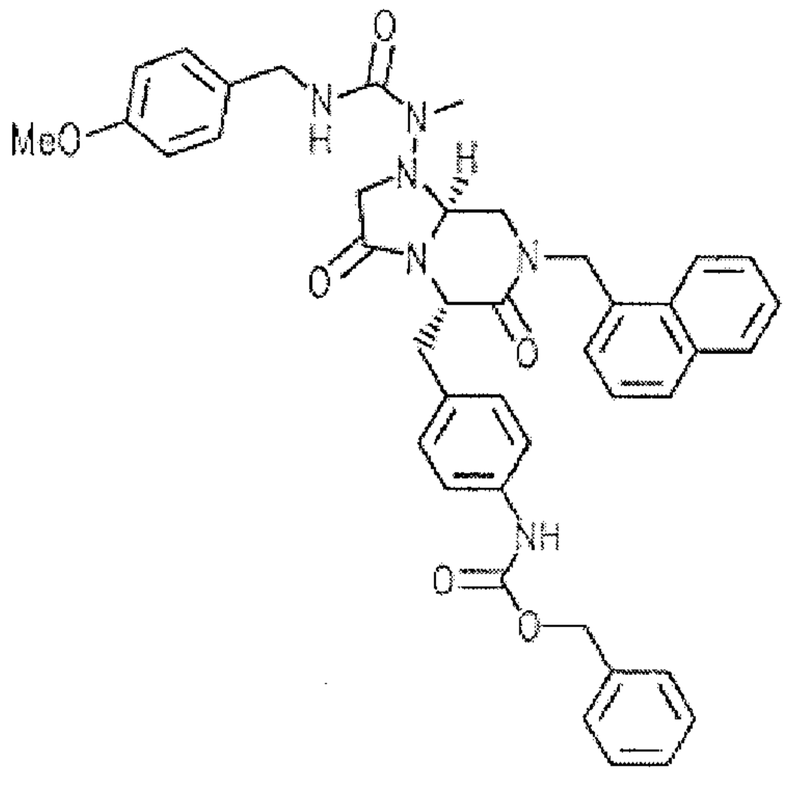
or a pharmaceutically acceptable salt thereof.

213. The compound of claim 1, which is:



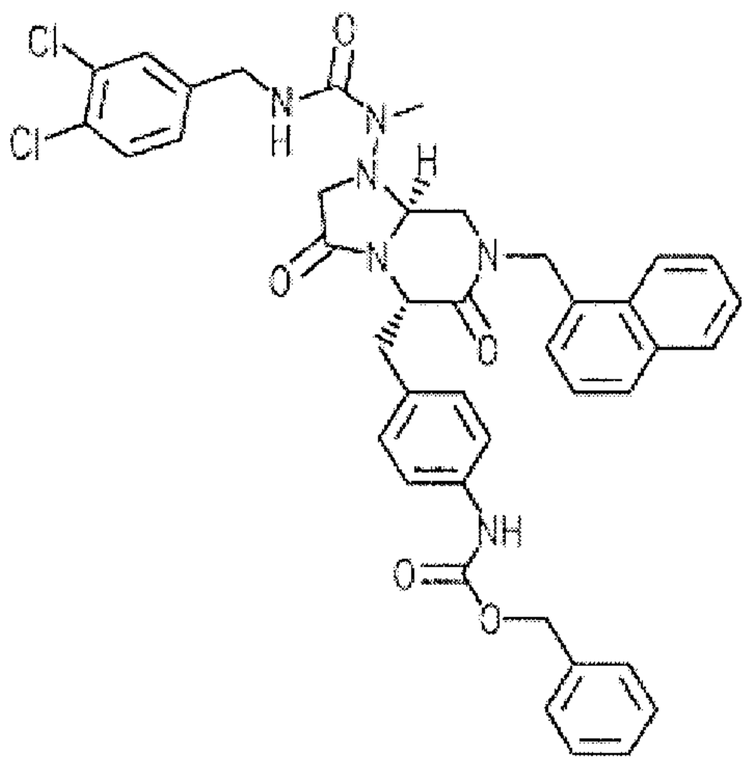
or a pharmaceutically acceptable salt thereof.

214. The compound of claim 1, which is:



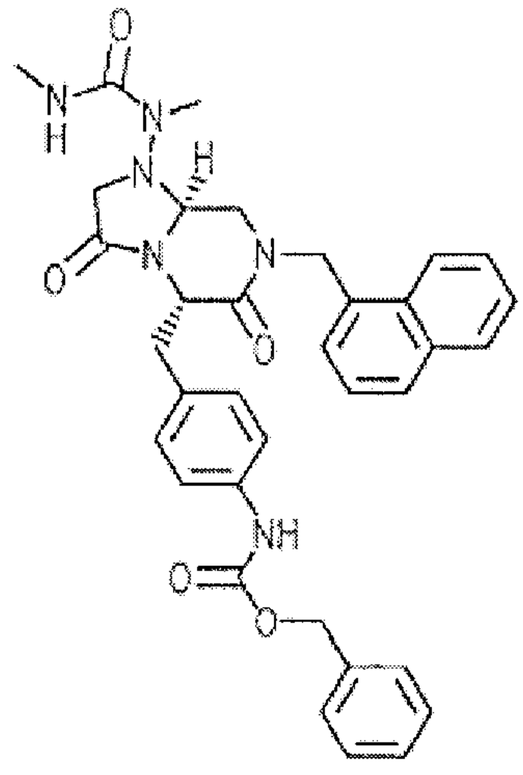
or a pharmaceutically acceptable salt thereof.

215. The compound of claim 1, which is:



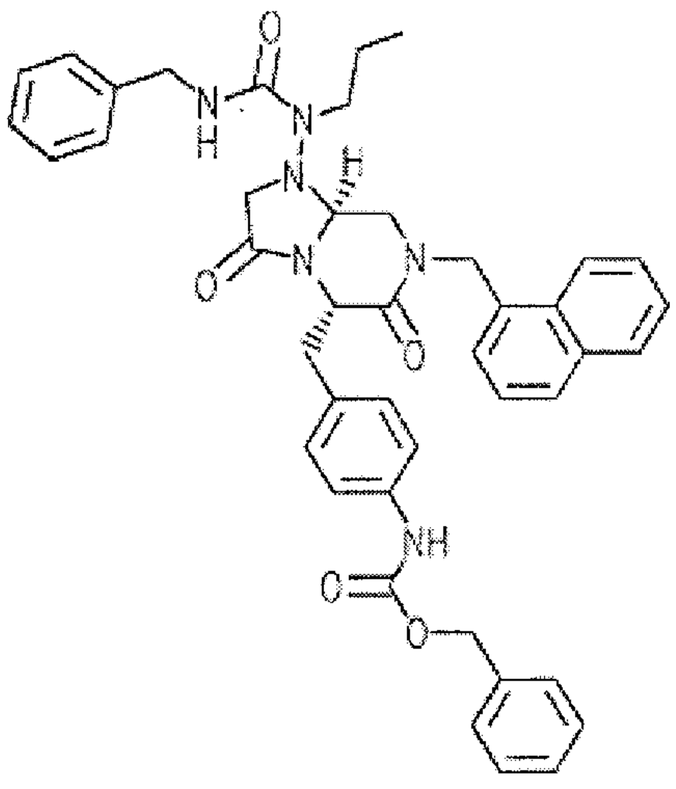
or a pharmaceutically acceptable salt thereof.

216. The compound of claim 1, which is:



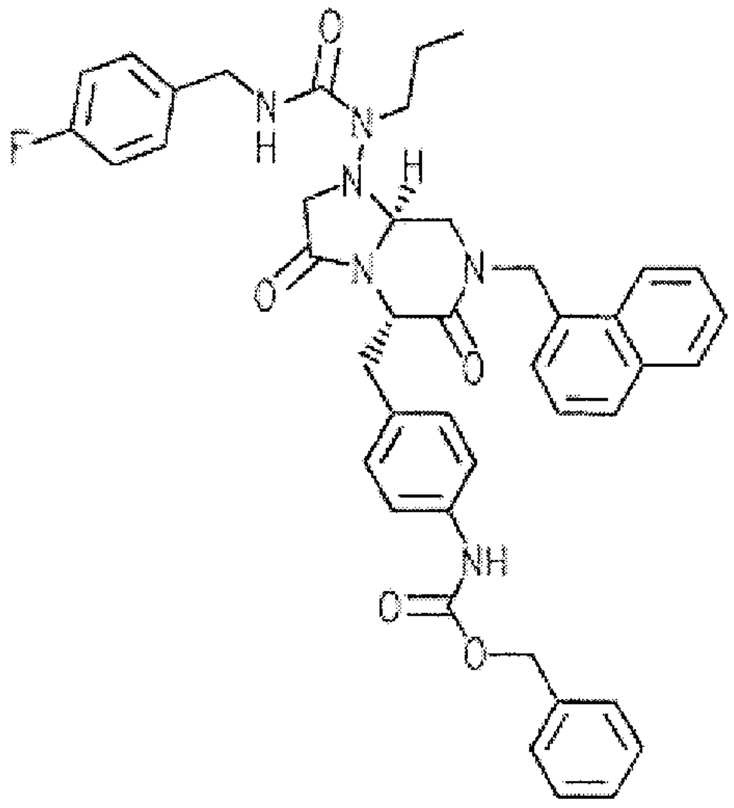
or a pharmaceutically acceptable salt thereof.

217. The compound of claim 1, which is:



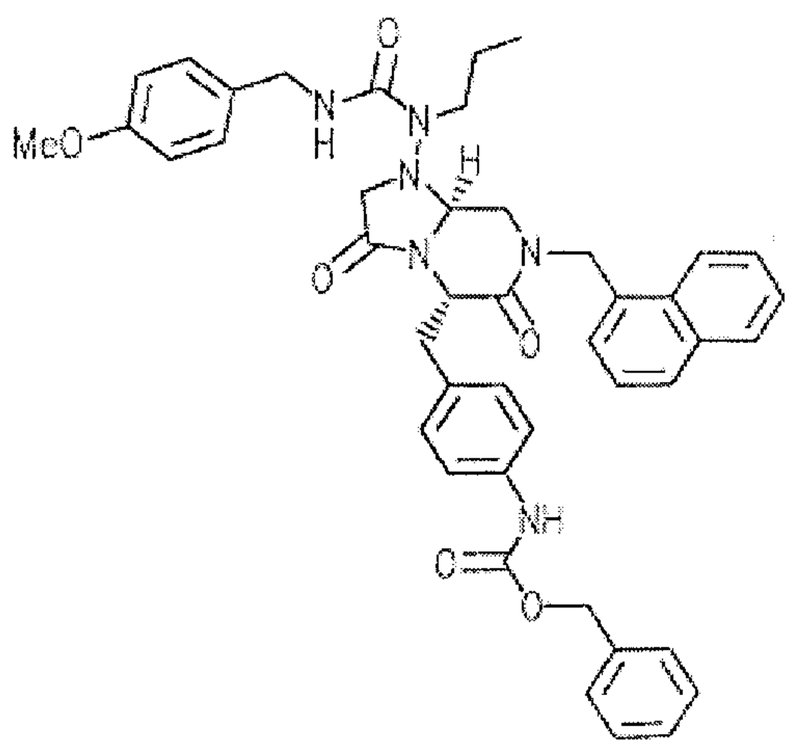
or a pharmaceutically acceptable salt thereof.

218. The compound of claim 1, which is:



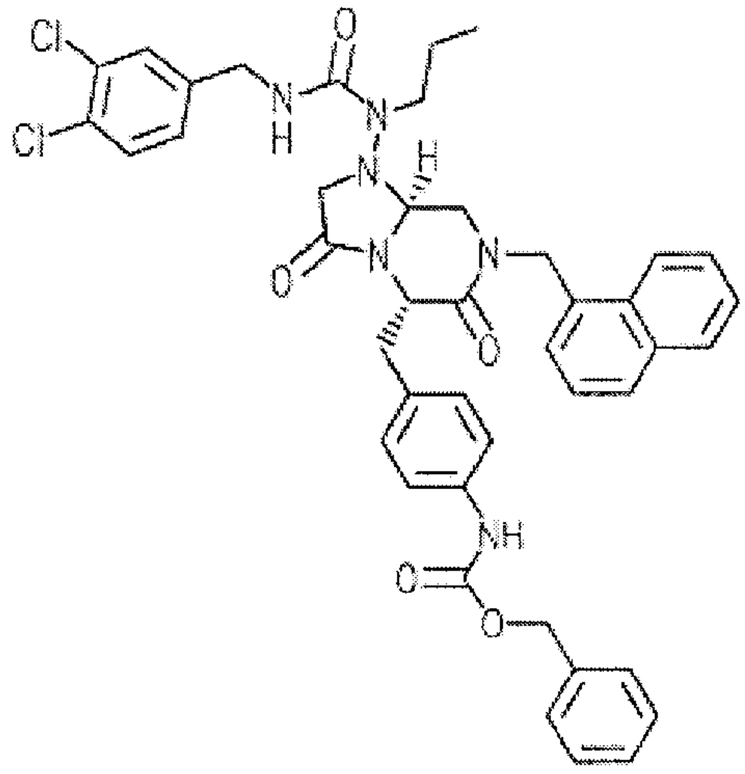
or a pharmaceutically acceptable salt thereof.

219. The compound of claim 1, which is:



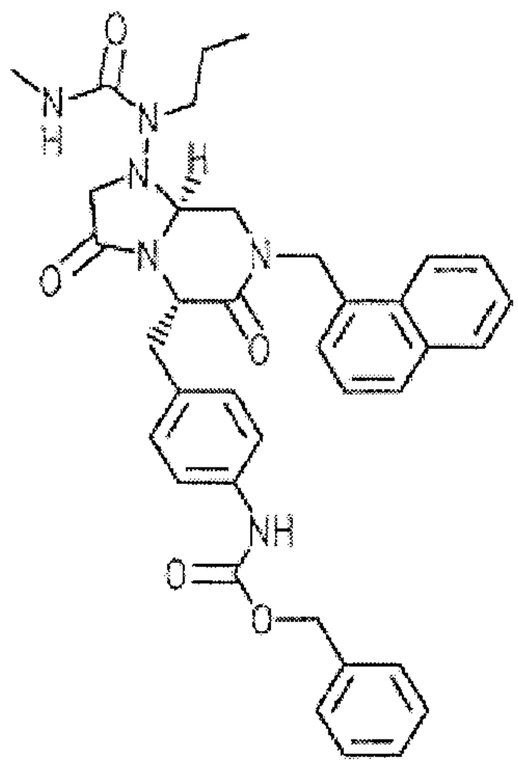
or a pharmaceutically acceptable salt thereof.

220. The compound of claim 1, which is:



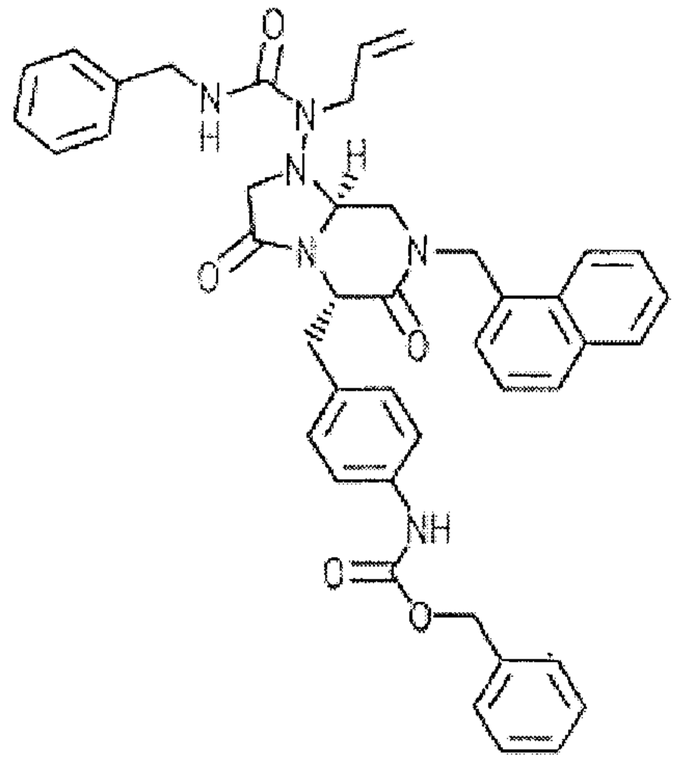
or a pharmaceutically acceptable salt thereof.

221. The compound of claim 1, which is:



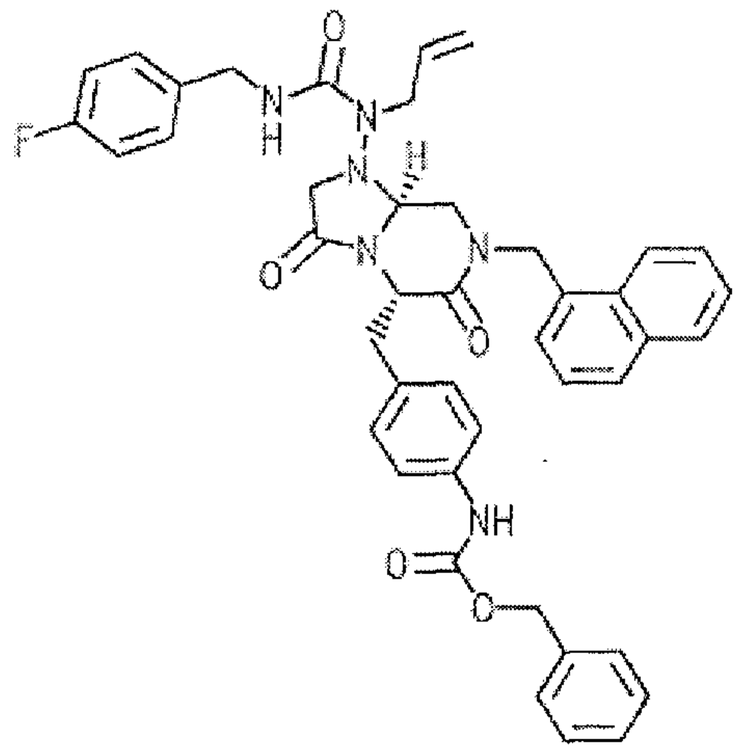
or a pharmaceutically acceptable salt thereof.

222. The compound of claim 1, which is:



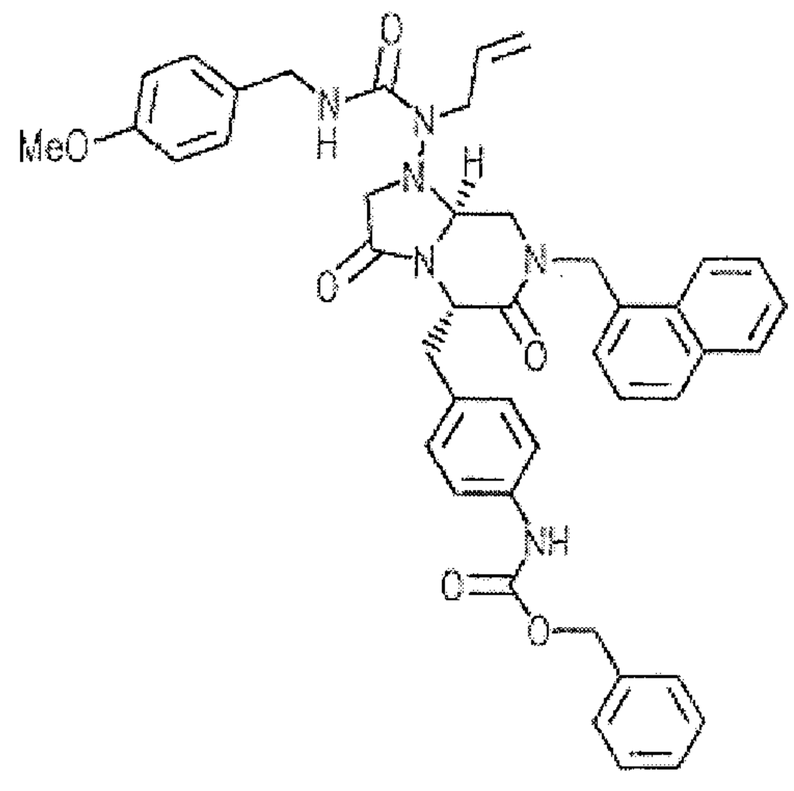
or a pharmaceutically acceptable salt thereof.

223. The compound of claim 1, which is:



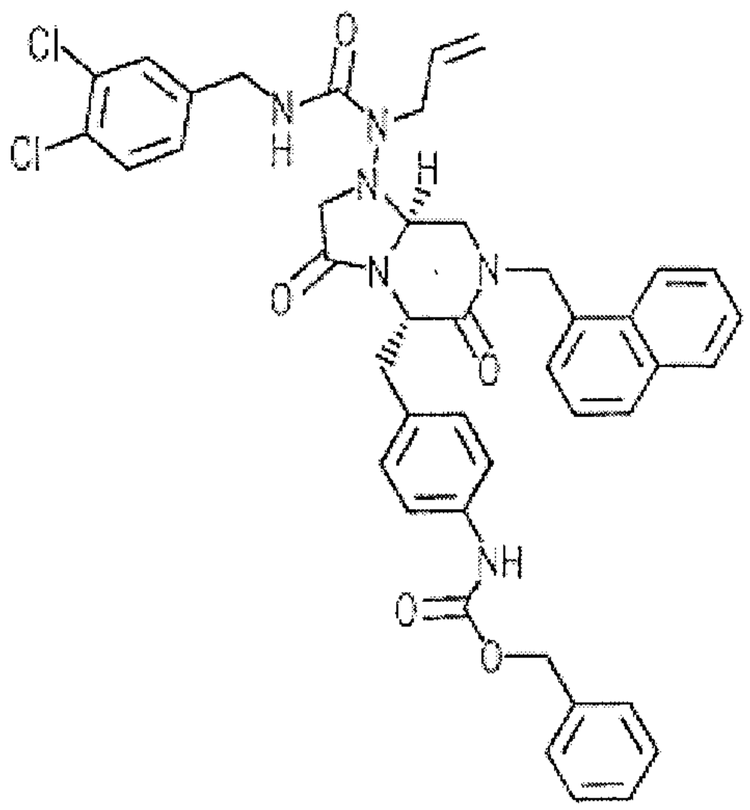
or a pharmaceutically acceptable salt thereof.

224. The compound of claim 1, which is:



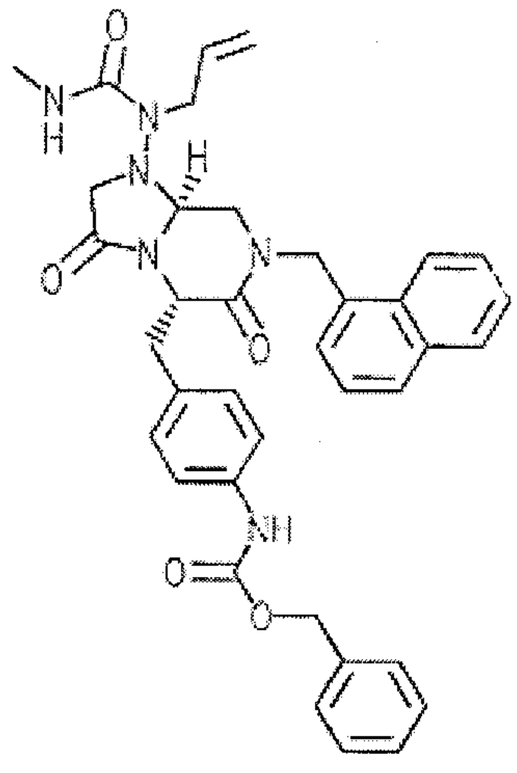
or a pharmaceutically acceptable salt thereof.

225. The compound of claim 1, which is:



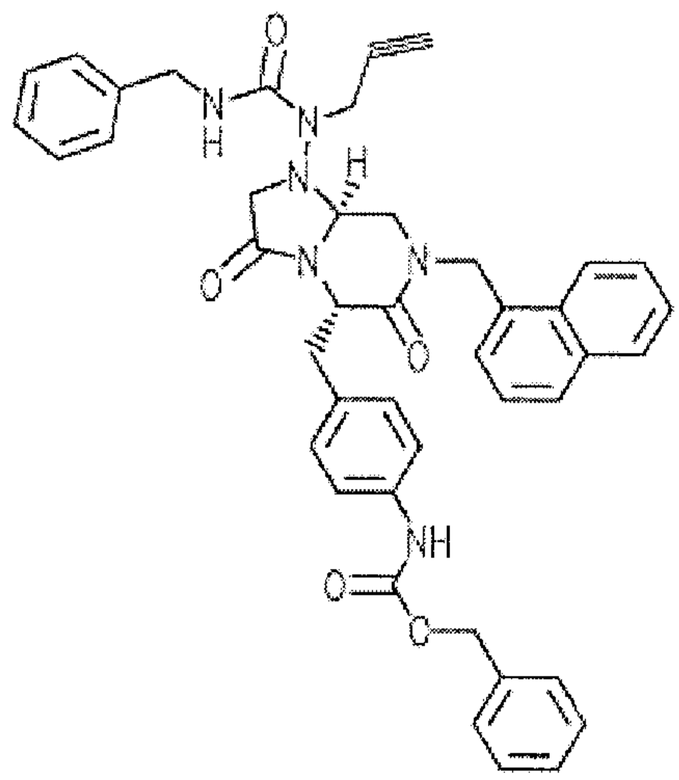
or a pharmaceutically acceptable salt thereof.

226. The compound of claim 1, which is:



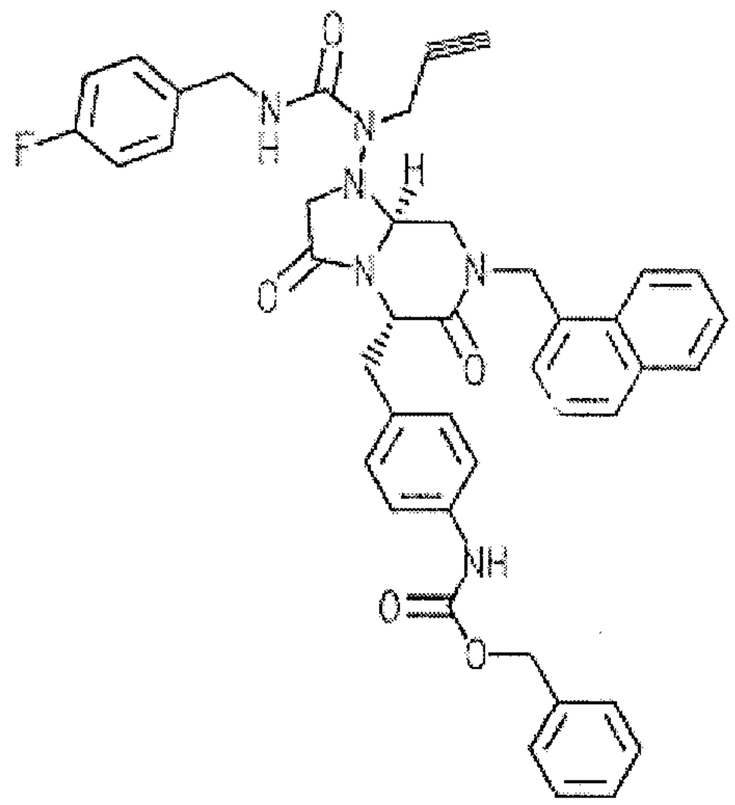
or a pharmaceutically acceptable salt thereof.

227. The compound of claim 1, which is:



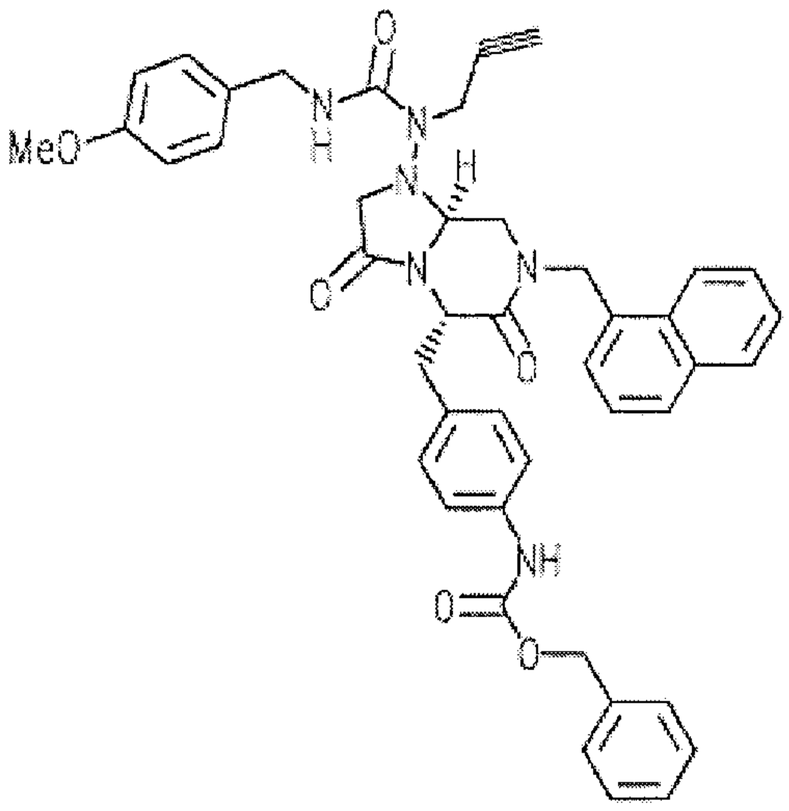
or a pharmaceutically acceptable salt thereof.

228. The compound of claim 1, which is:



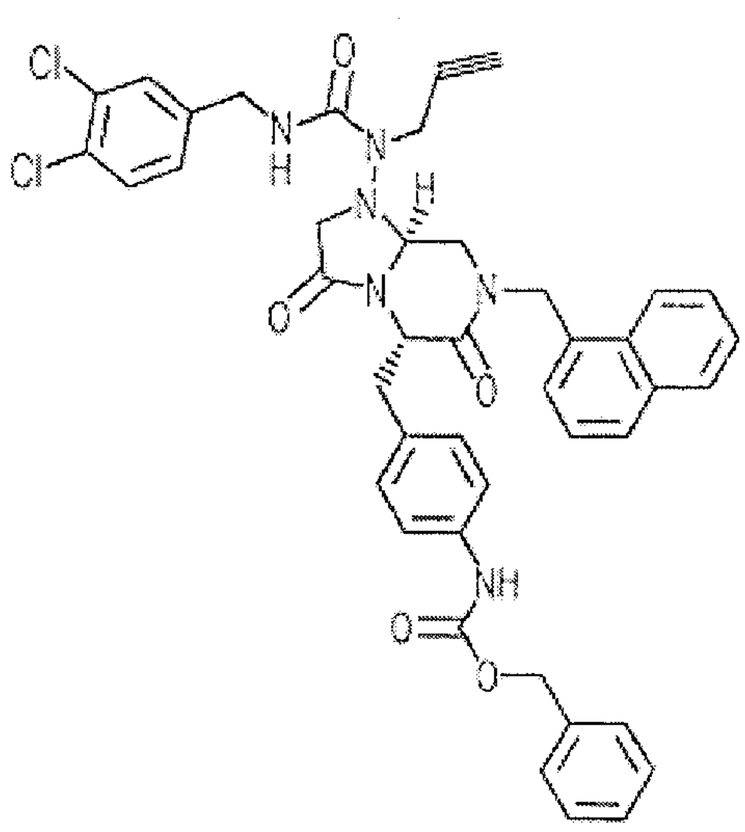
or a pharmaceutically acceptable salt thereof.

229. The compound of claim 1, which is:



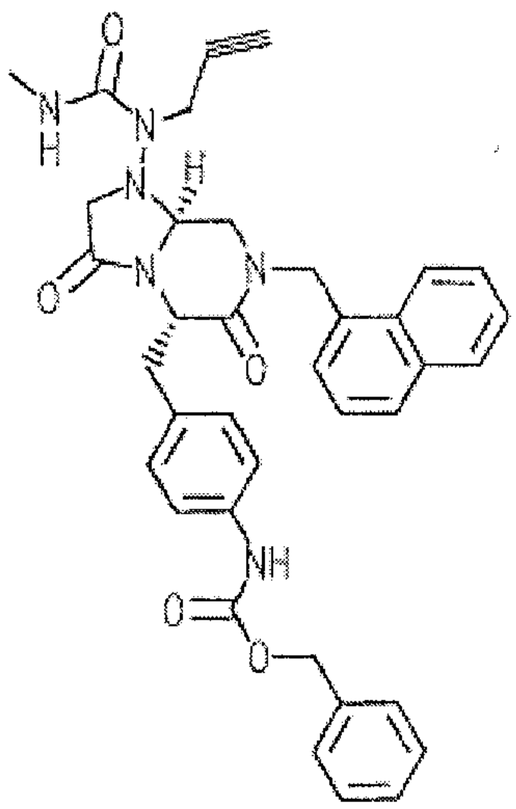
or a pharmaceutically acceptable salt thereof.

230. The compound of claim 1, which is:



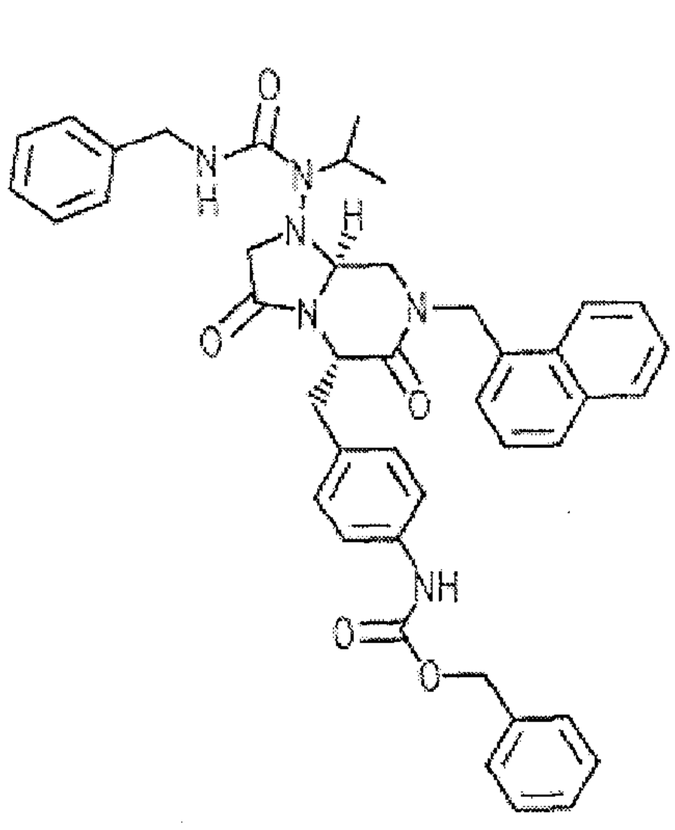
or a pharmaceutically acceptable salt thereof.

231. The compound of claim 1, which is:



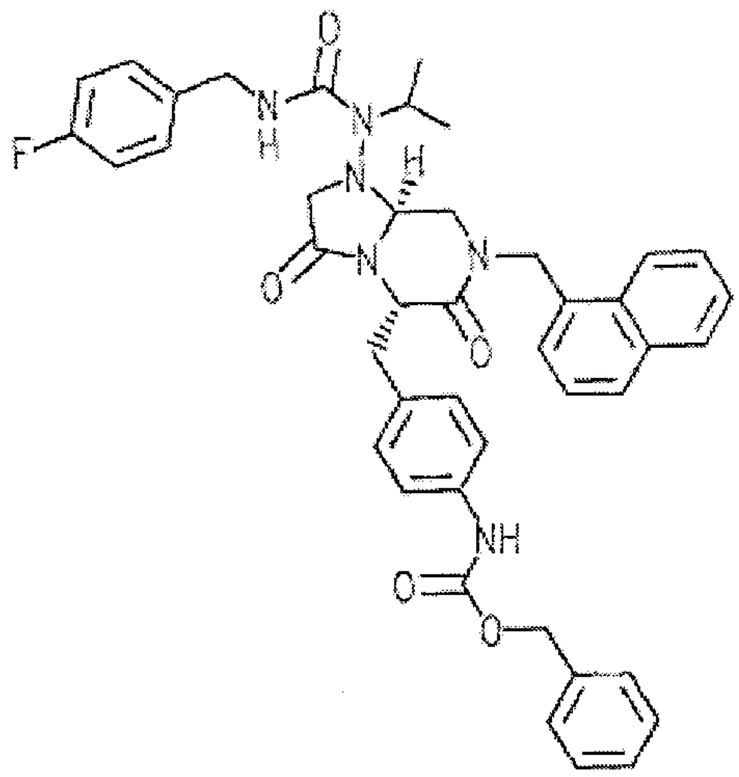
or a pharmaceutically acceptable salt thereof.

232. The compound of claim 1, which is:



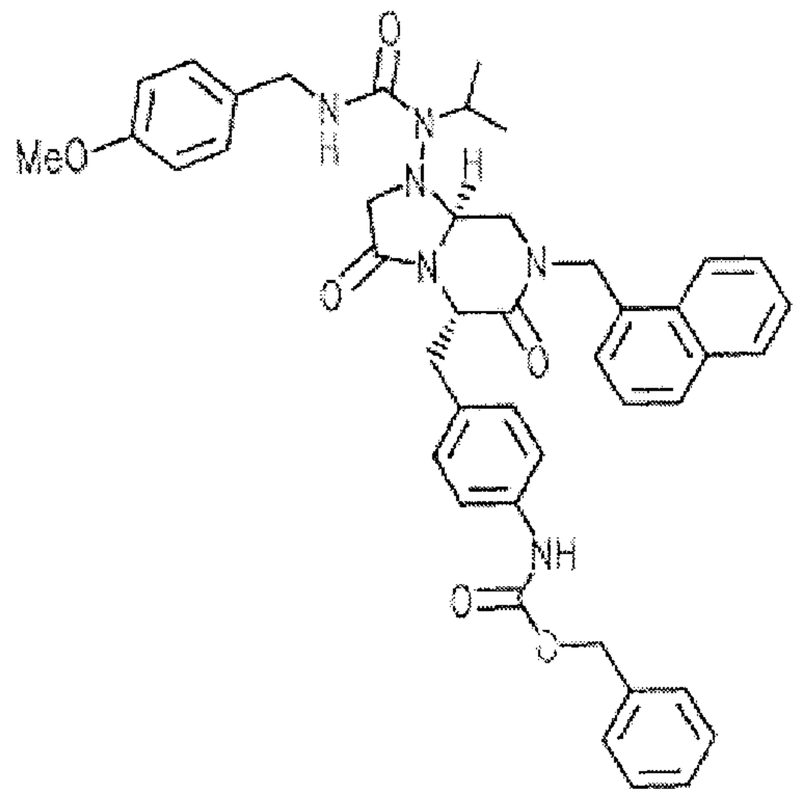
or a pharmaceutically acceptable salt thereof.

233. The compound of claim 1, which is:



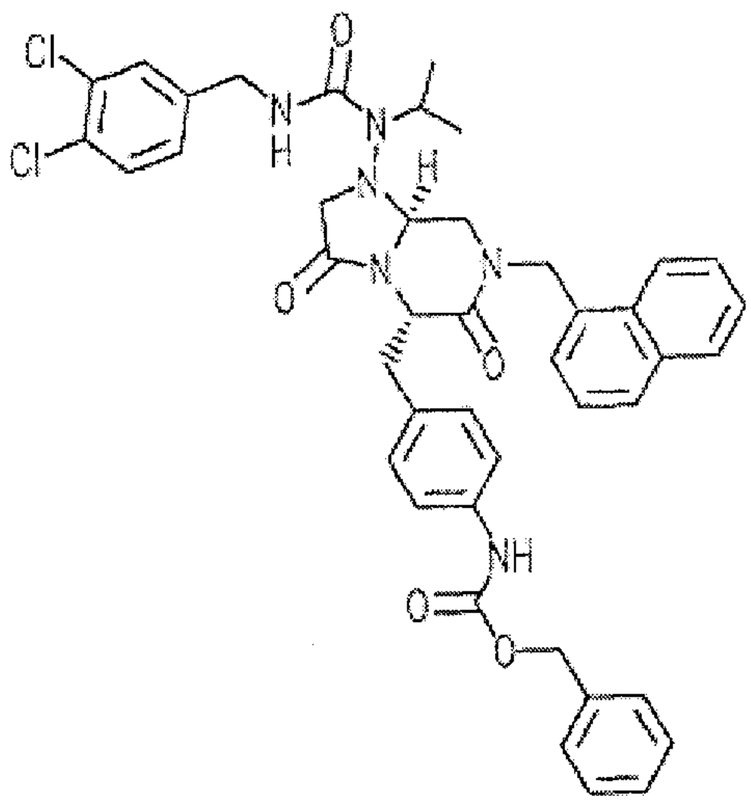
or a pharmaceutically acceptable salt thereof.

234. The compound of claim 1, which is:



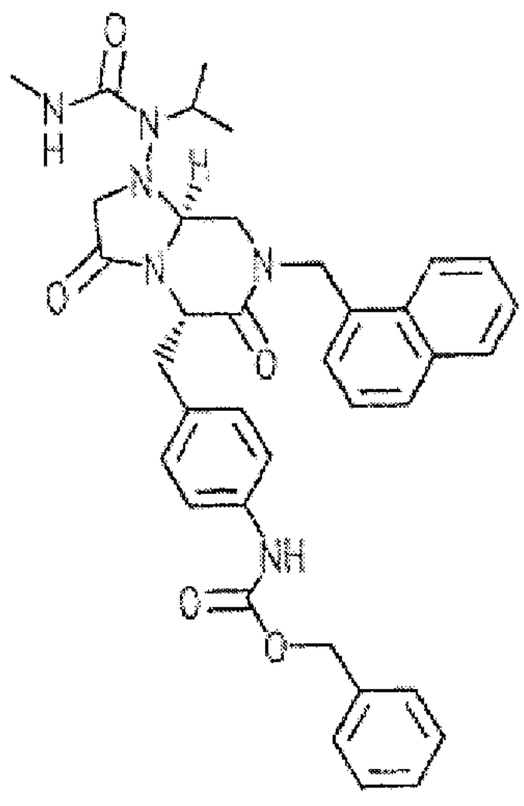
or a pharmaceutically acceptable salt thereof.

235. The compound of claim 1, which is:



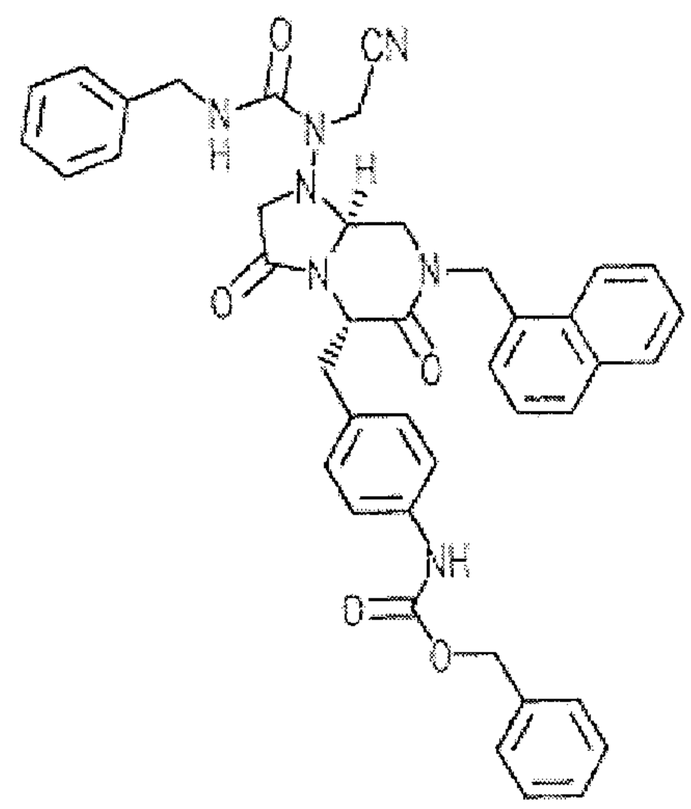
or a pharmaceutically acceptable salt thereof.

236. The compound of claim 1, which is:



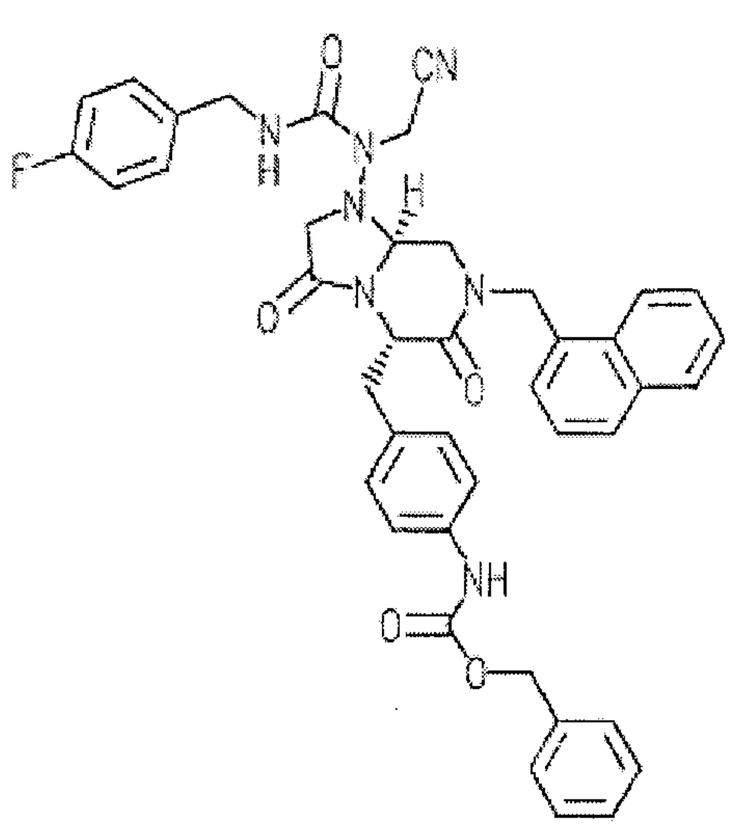
or a pharmaceutically acceptable salt thereof.

237. The compound of claim 1, which is:



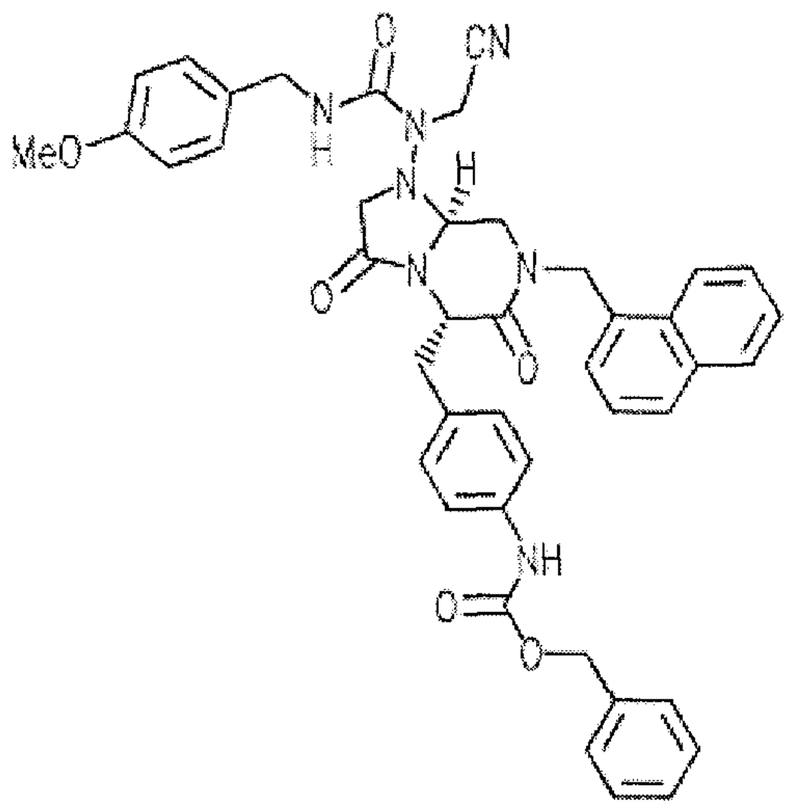
or a pharmaceutically acceptable salt thereof.

238. The compound of claim 1, which is:



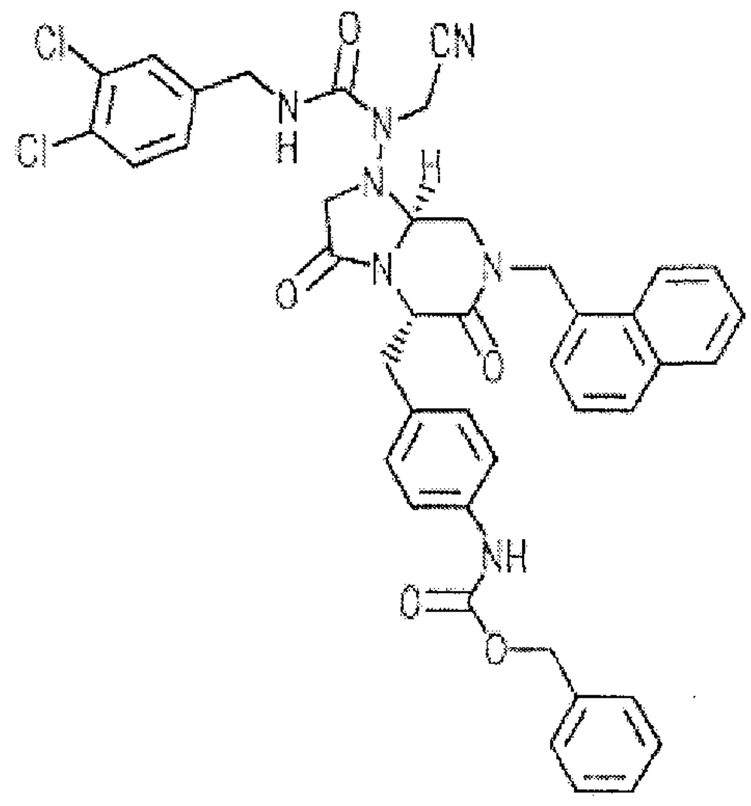
or a pharmaceutically acceptable salt thereof.

239. The compound of claim 1, which is:



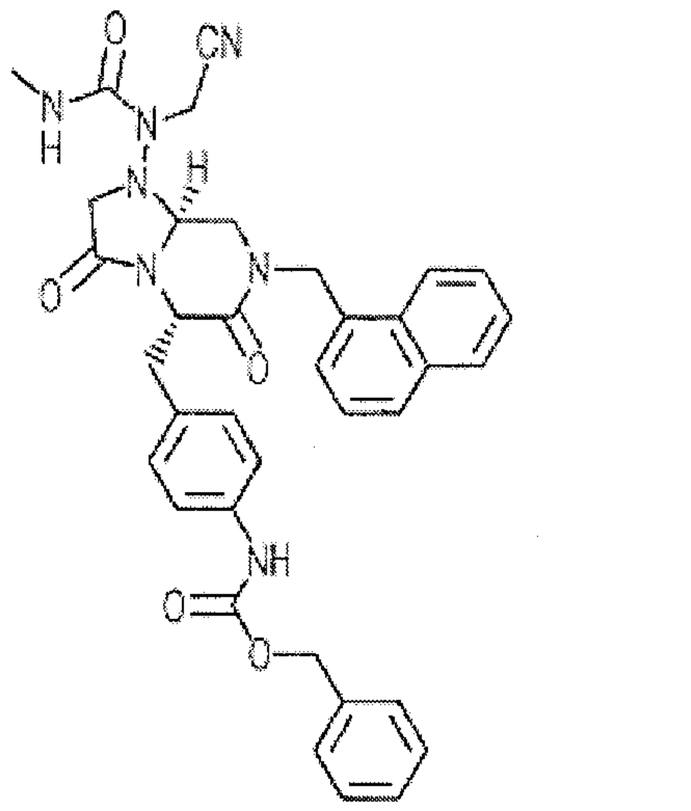
or a pharmaceutically acceptable salt thereof.

240. The compound of claim 1, which is:



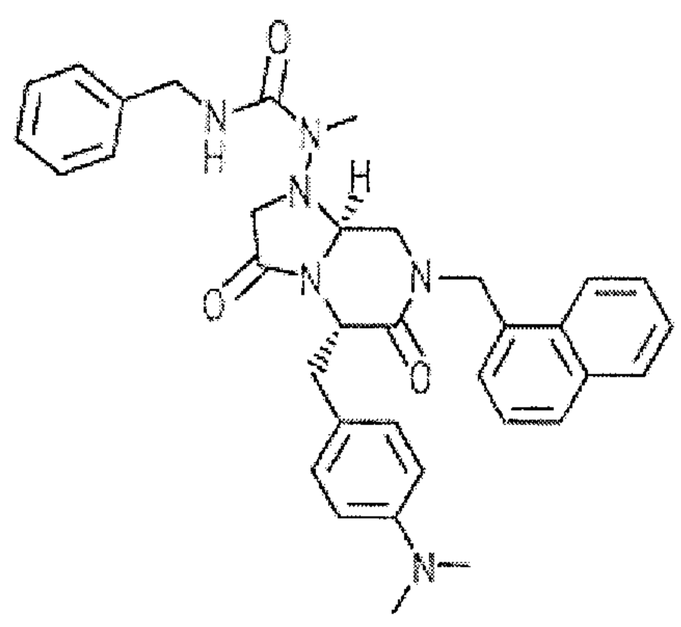
or a pharmaceutically acceptable salt thereof.

241. The compound of claim 1, which is:



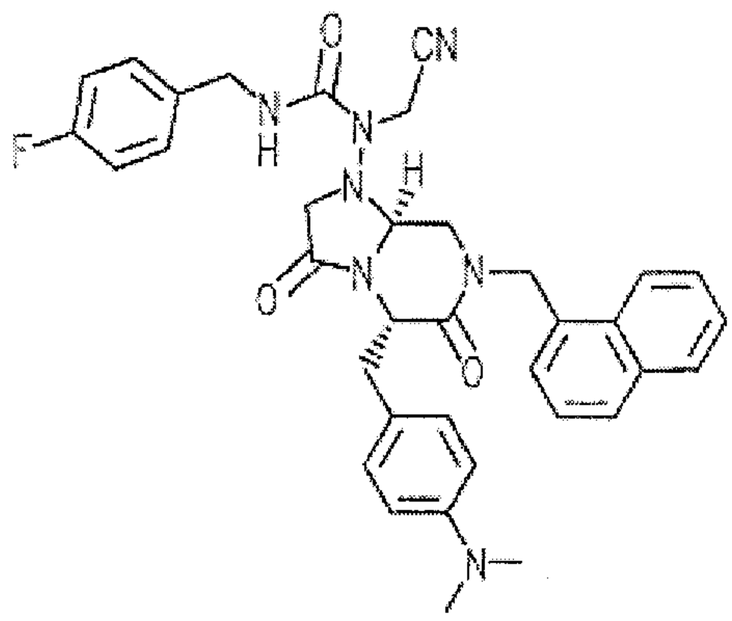
or a pharmaceutically acceptable salt thereof.

242. The compound of claim 1, which is:



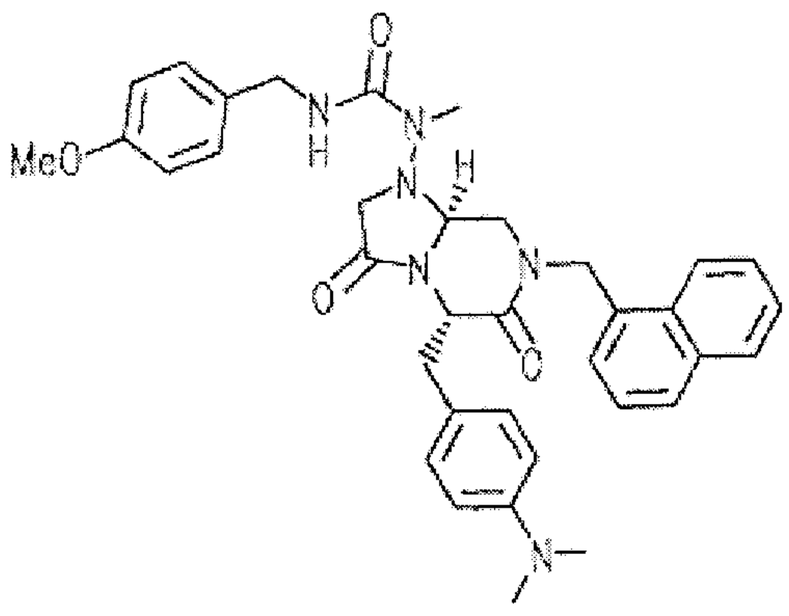
or a pharmaceutically acceptable salt thereof.

243. The compound of claim 1, which is:



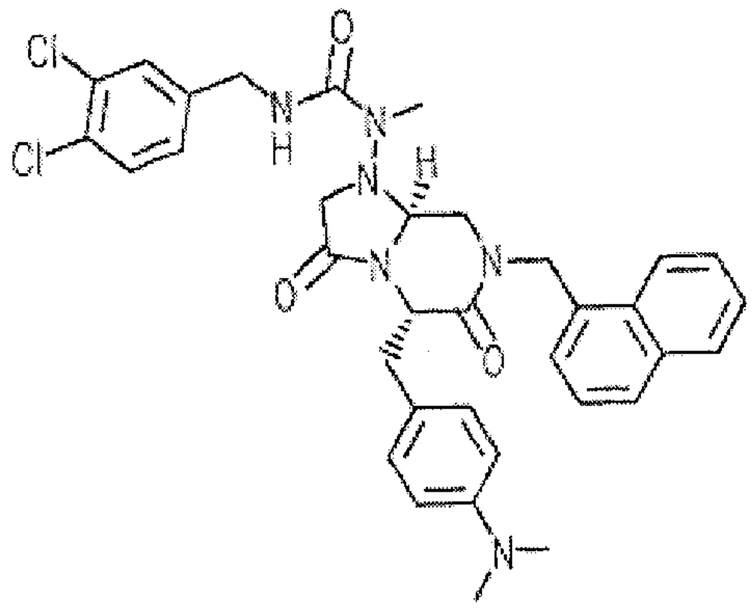
or a pharmaceutically acceptable salt thereof.

244. The compound of claim 1, which is:



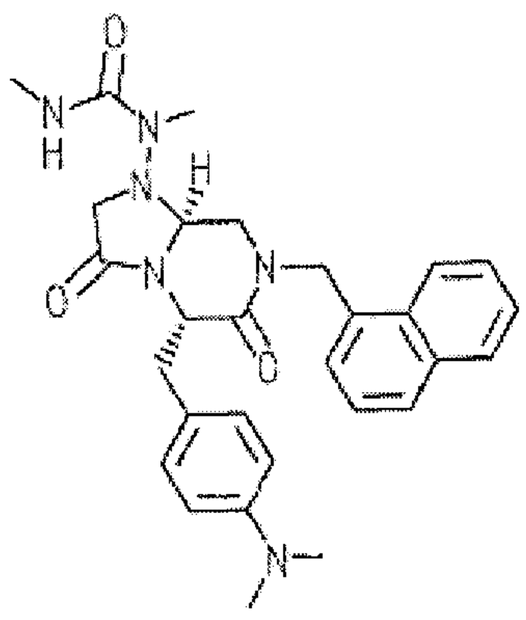
or a pharmaceutically acceptable salt thereof.

245. The compound of claim 1, which is:



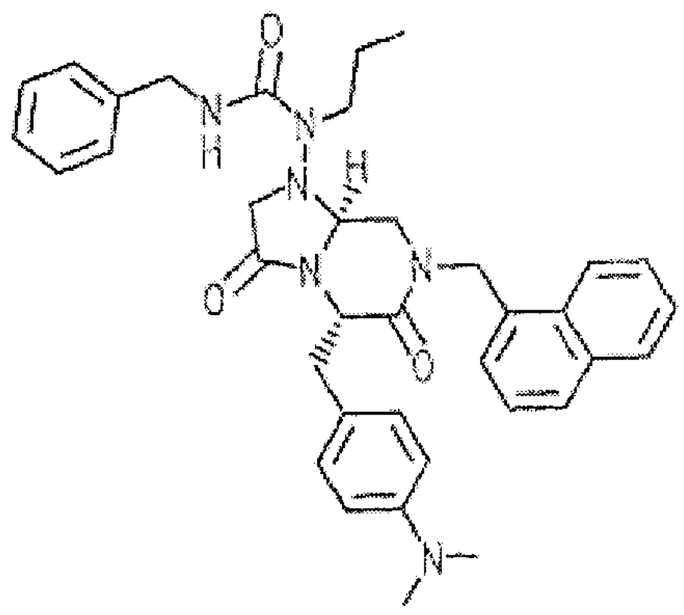
or a pharmaceutically acceptable salt thereof.

246. The compound of claim 1, which is:



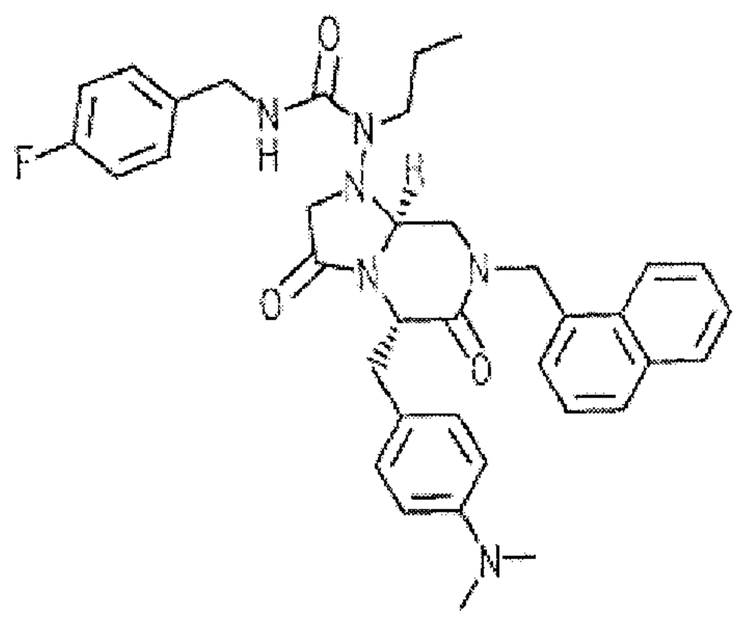
or a pharmaceutically acceptable salt thereof.

247. The compound of claim 1, which is:



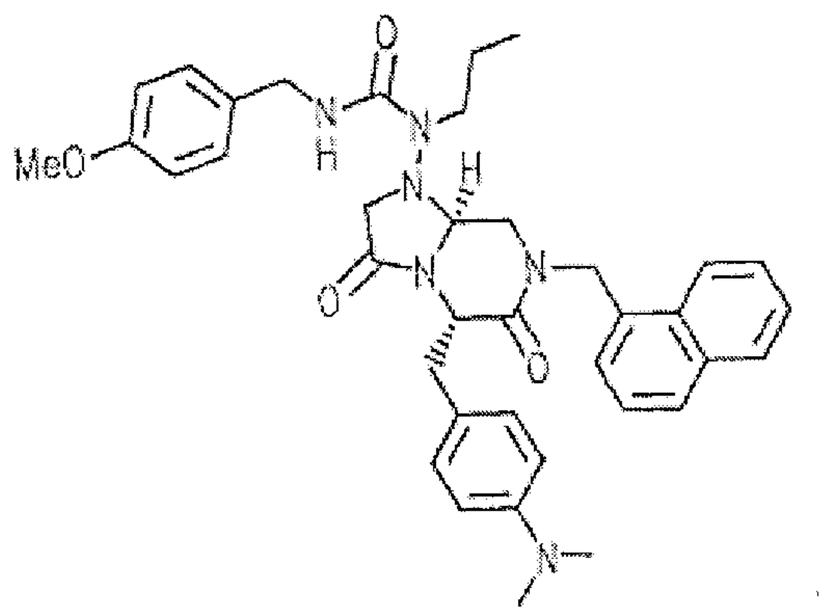
or a pharmaceutically acceptable salt thereof.

248. The compound of claim 1, which is:



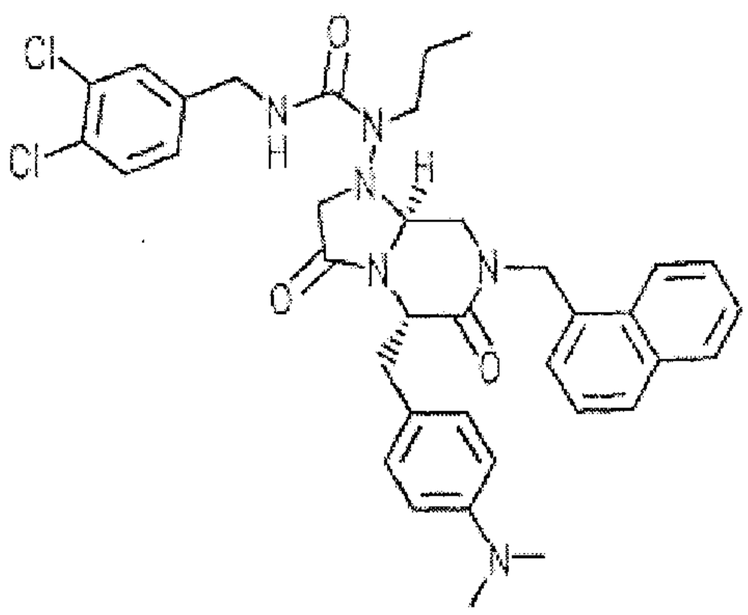
or a pharmaceutically acceptable salt thereof.

249. The compound of claim 1, which is:



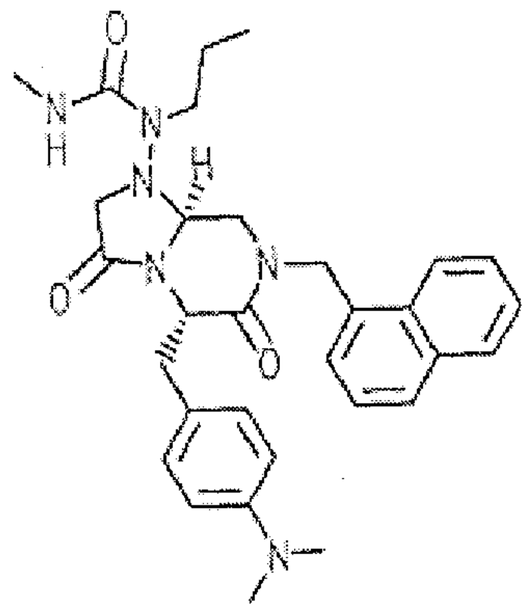
or a pharmaceutically acceptable salt thereof.

250. The compound of claim 1, which is:



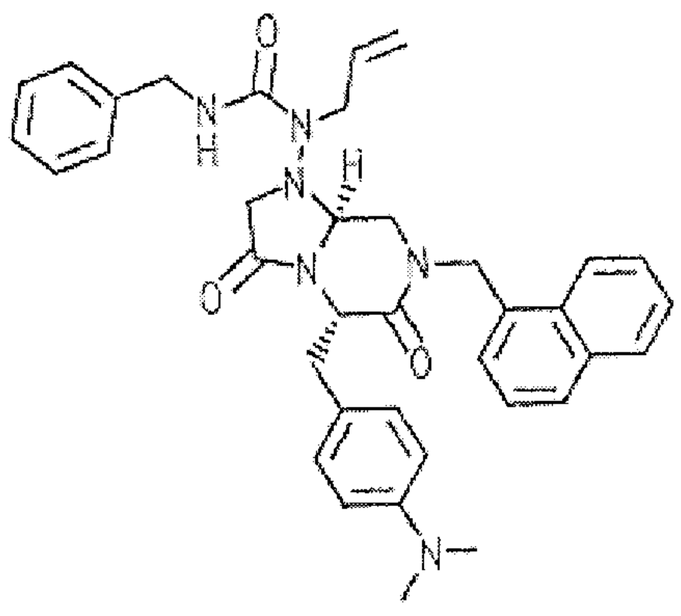
or a pharmaceutically acceptable salt thereof.

251. The compound of claim 1, which is:



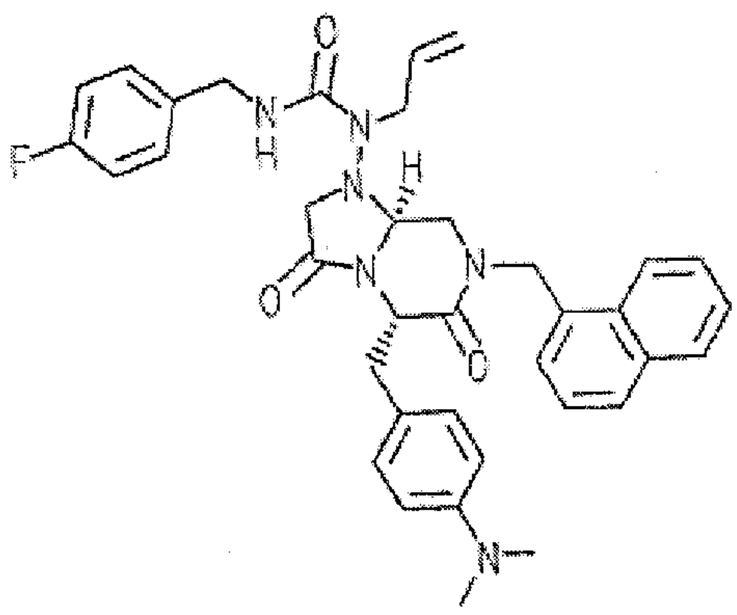
or a pharmaceutically acceptable salt thereof.

252. The compound of claim 1, which is:



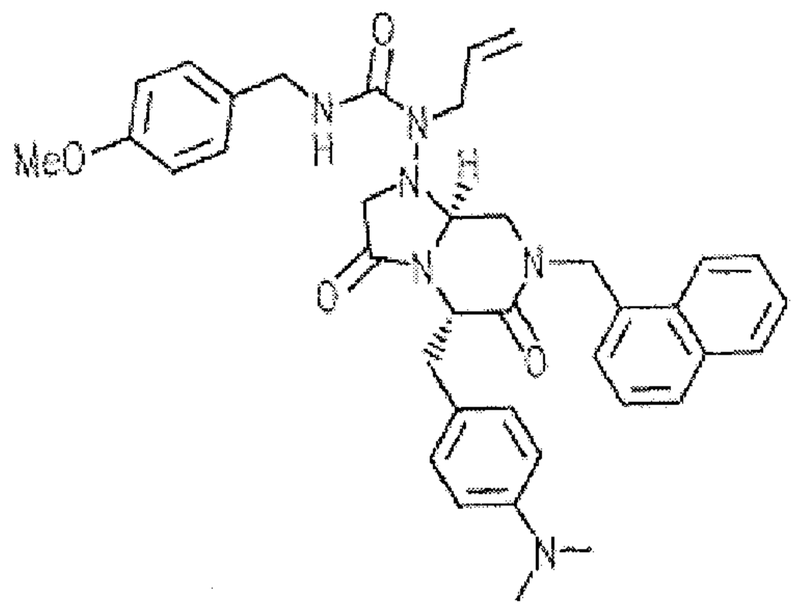
or a pharmaceutically acceptable salt thereof.

253. The compound of claim 1, which is:



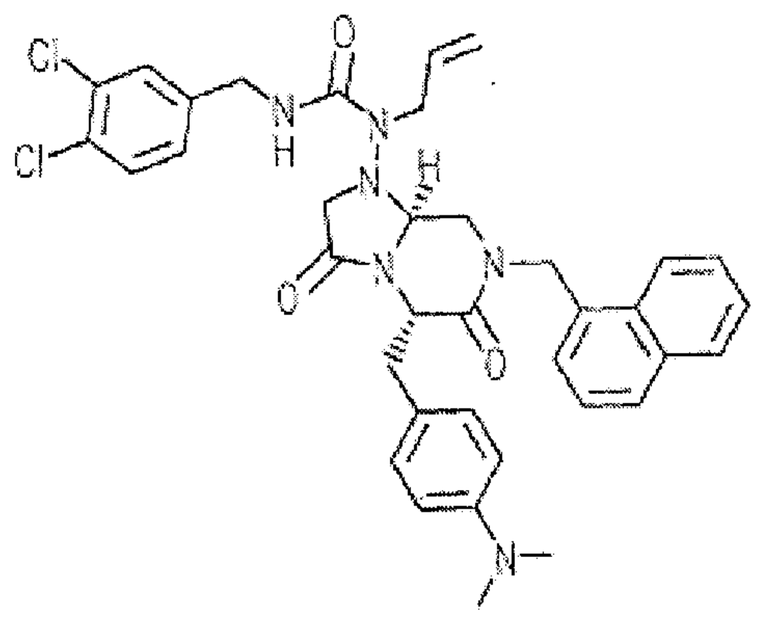
or a pharmaceutically acceptable salt thereof.

254. The compound of claim 1, which is:



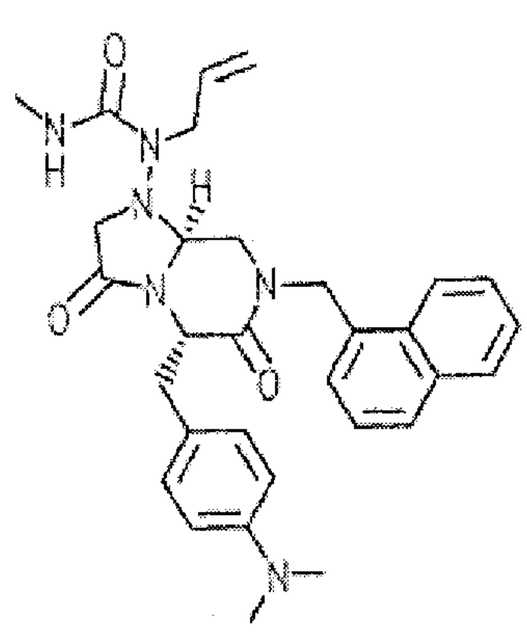
or a pharmaceutically acceptable salt thereof.

255. The compound of claim 1, which is:



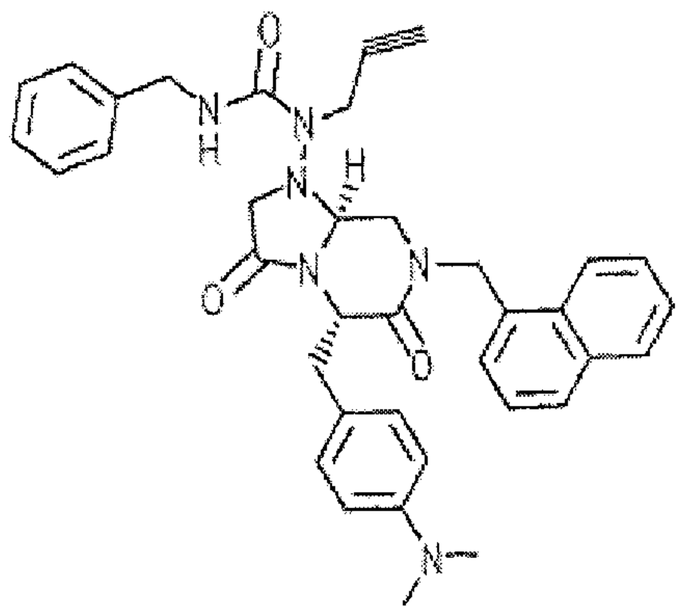
or a pharmaceutically acceptable salt thereof.

256. The compound of claim 1, which is:



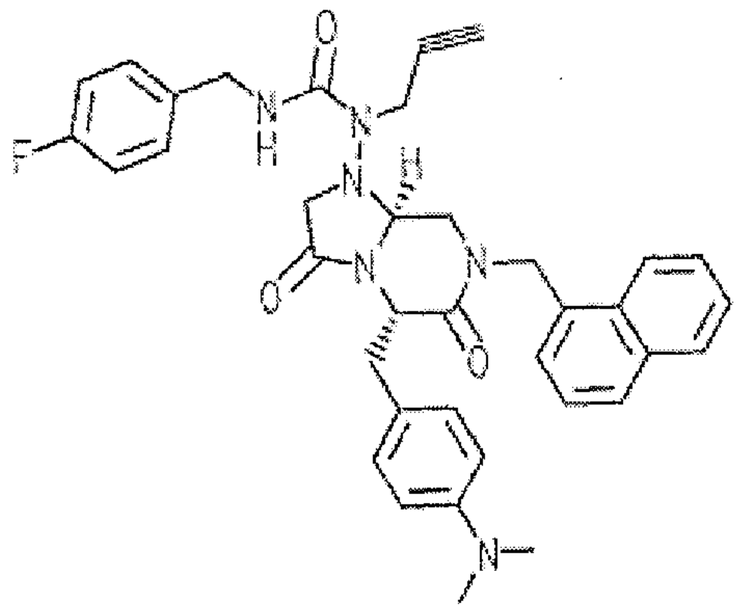
or a pharmaceutically acceptable salt thereof.

257. The compound of claim 1, which is:



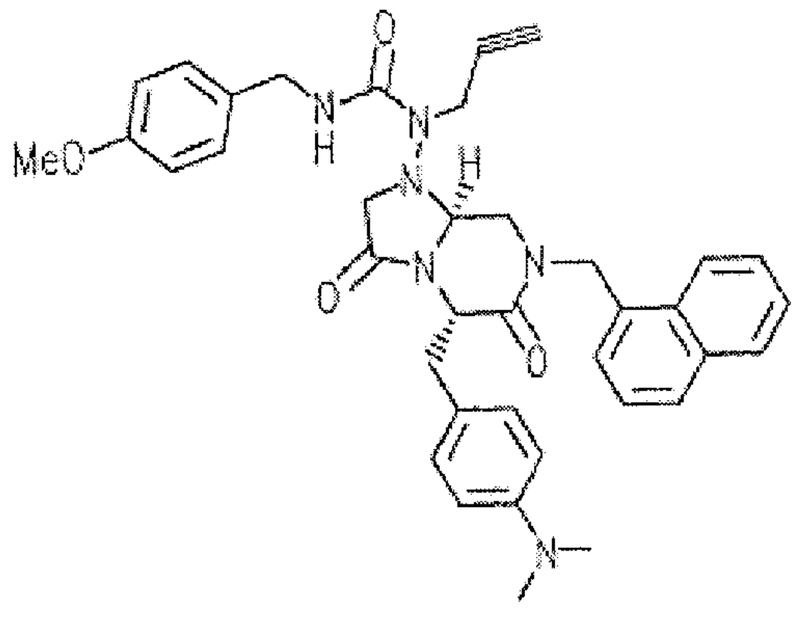
or a pharmaceutically acceptable salt thereof.

258. The compound of claim 1, which is:



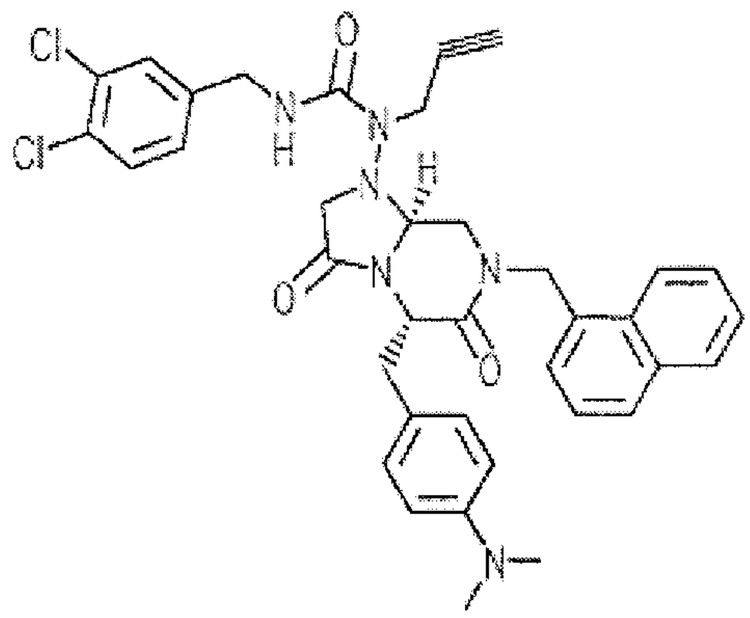
or a pharmaceutically acceptable salt thereof.

259. The compound of claim 1, which is:



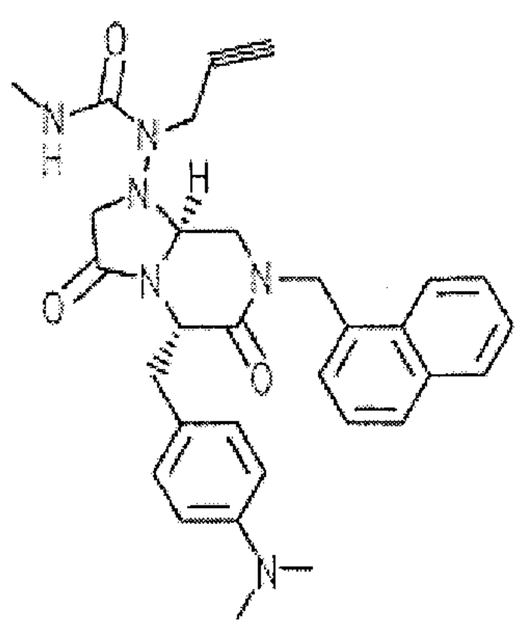
or a pharmaceutically acceptable salt thereof.

260. The compound of claim 1, which is:



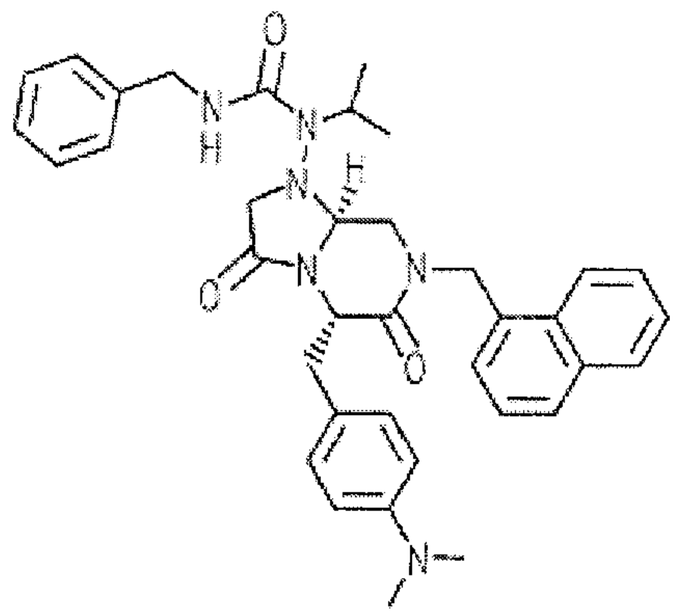
or a pharmaceutically acceptable salt thereof.

261. The compound of claim 1, which is:



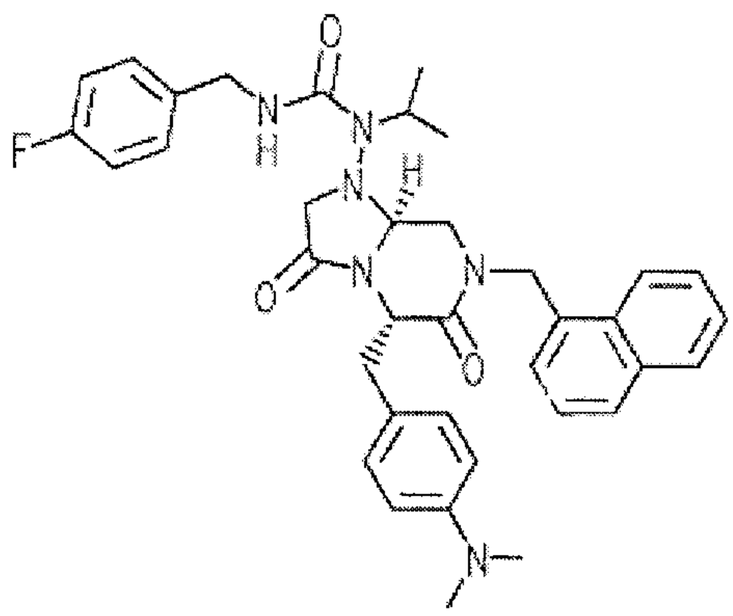
or a pharmaceutically acceptable salt thereof.

262. The compound of claim 1, which is:



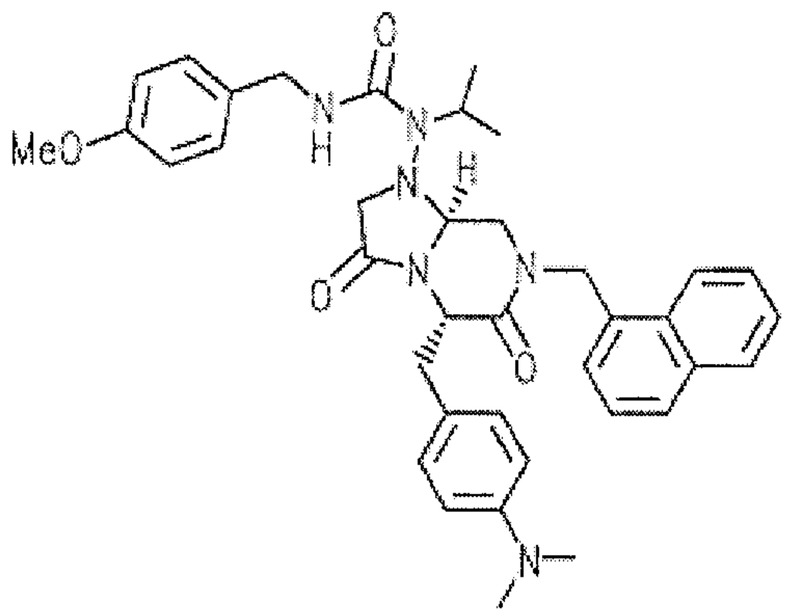
or a pharmaceutically acceptable salt thereof.

263. The compound of claim 1, which is:



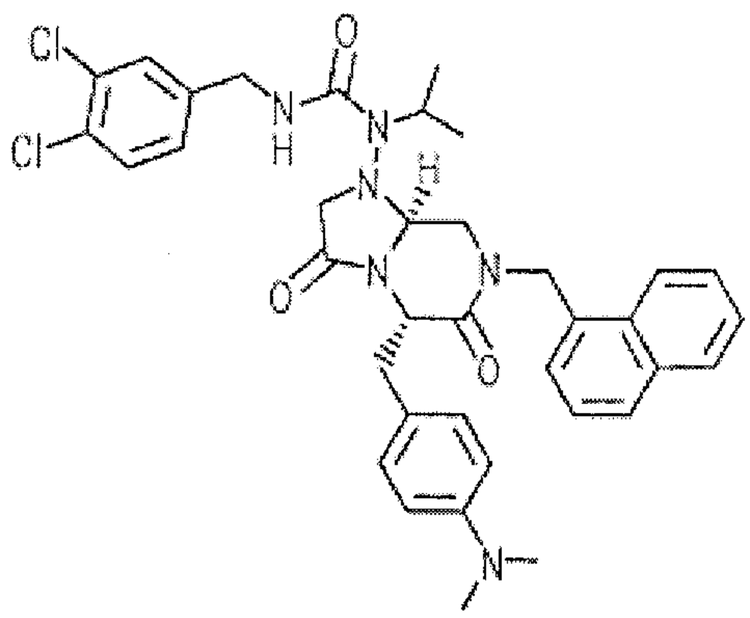
or a pharmaceutically acceptable salt thereof.

264. The compound of claim 1, which is:



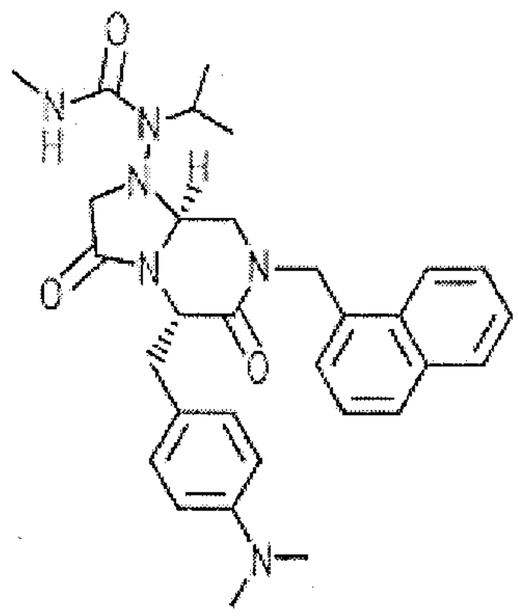
or a pharmaceutically acceptable salt thereof.

265. The compound of claim 1, which is:



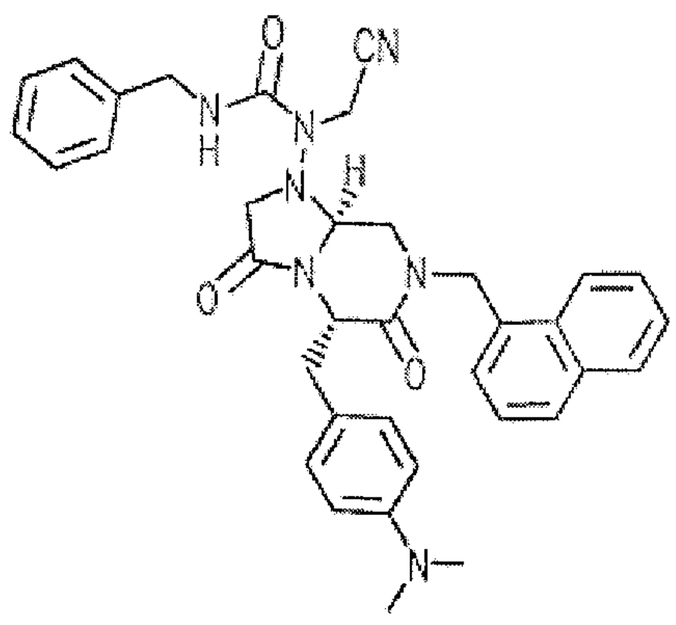
or a pharmaceutically acceptable salt thereof.

266. The compound of claim 1, which is:



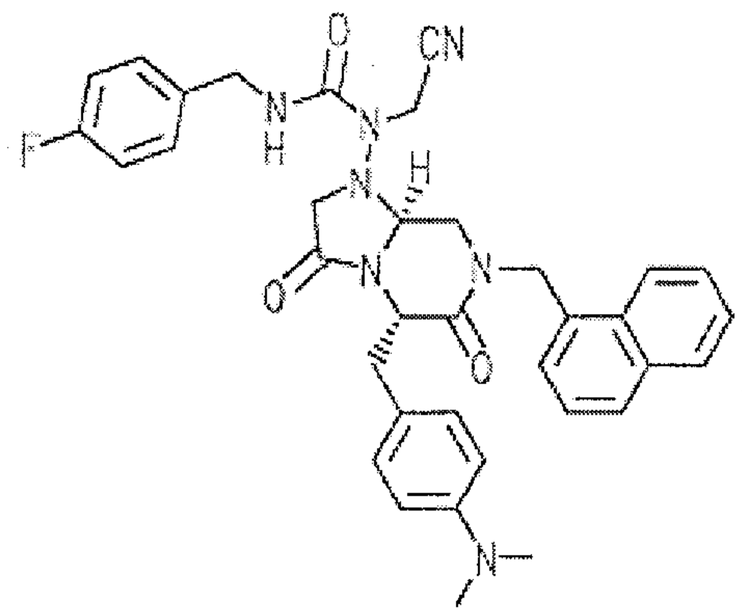
or a pharmaceutically acceptable salt thereof.

267. The compound of claim 1, which is:



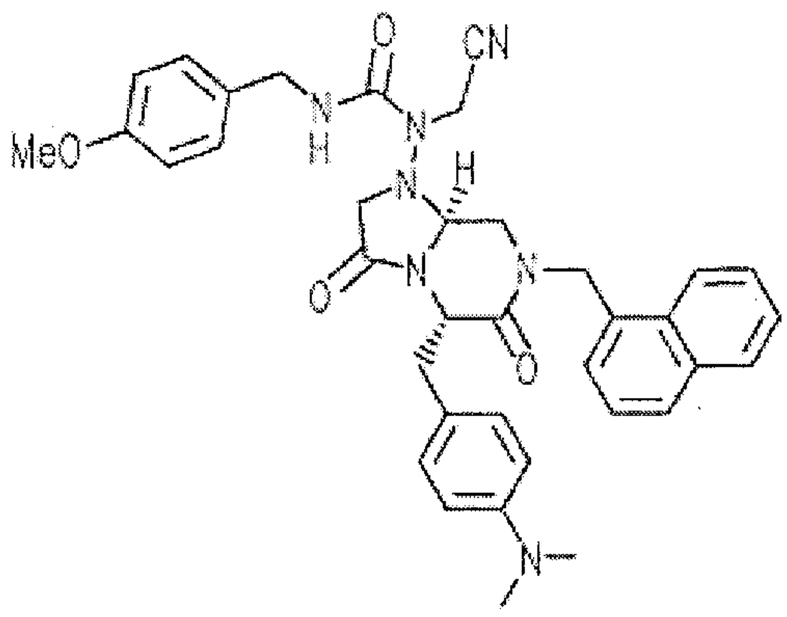
or a pharmaceutically acceptable salt thereof.

268. The compound of claim 1, which is:



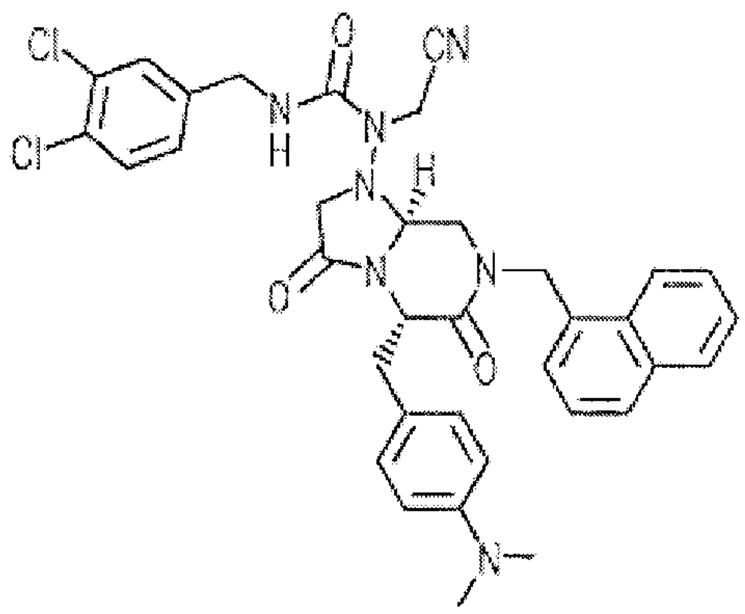
or a pharmaceutically acceptable salt thereof.

269. The compound of claim 1, which is:



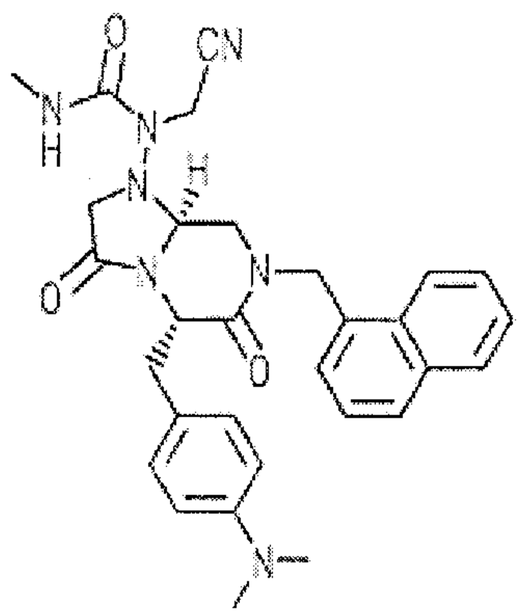
or a pharmaceutically acceptable salt thereof.

270. The compound of claim 1, which is:



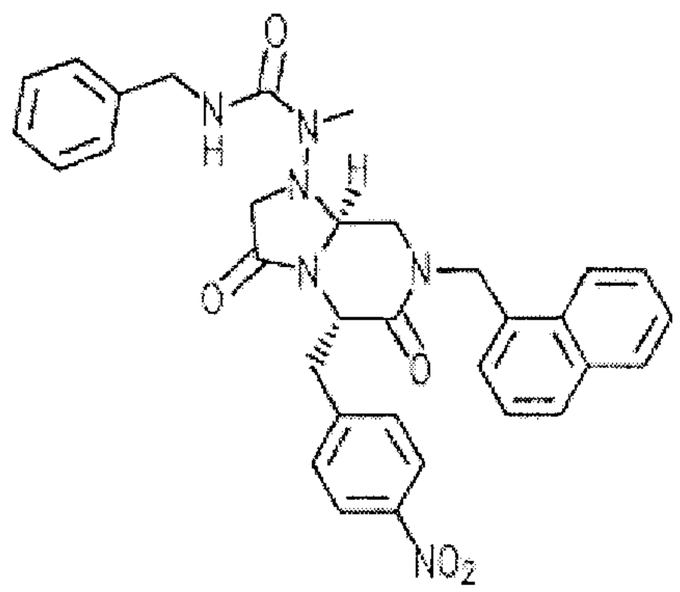
or a pharmaceutically acceptable salt thereof.

271. The compound of claim 1, which is:



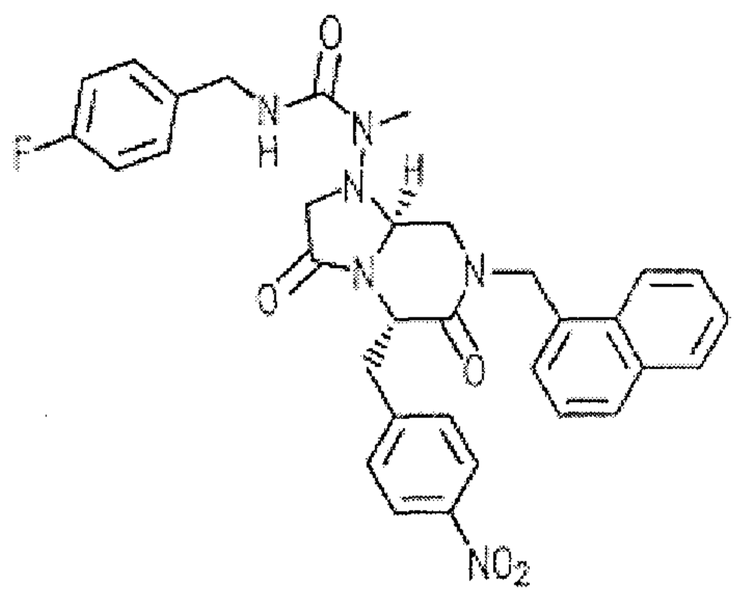
or a pharmaceutically acceptable salt thereof.

272. The compound of claim 1, which is:



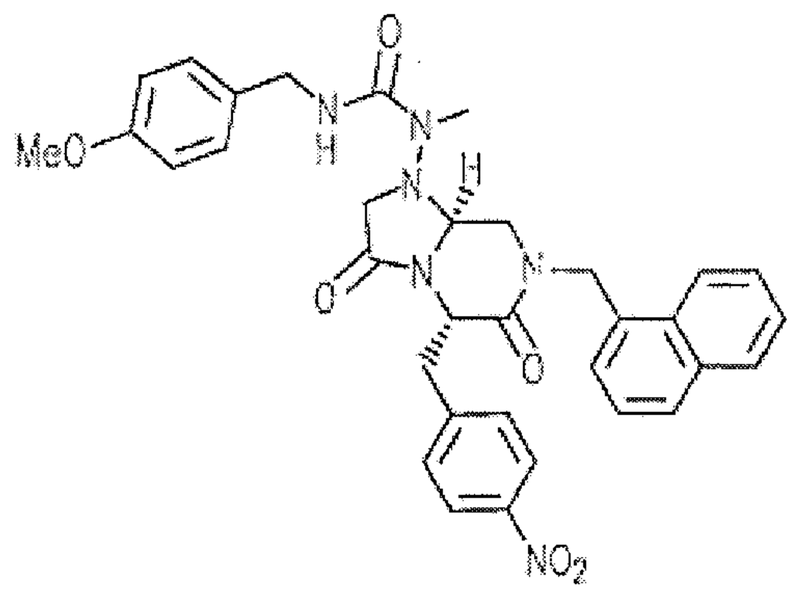
or a pharmaceutically acceptable salt thereof.

273. The compound of claim 1, which is:



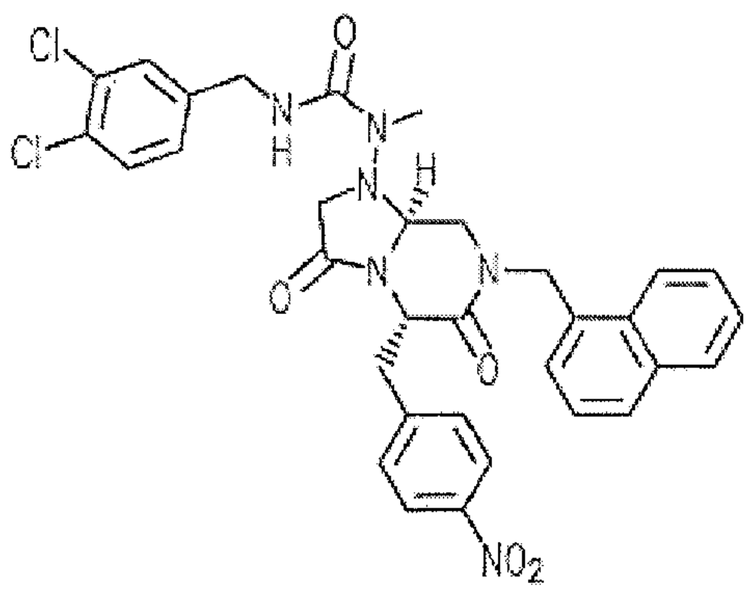
or a pharmaceutically acceptable salt thereof.

274. The compound of claim 1, which is:



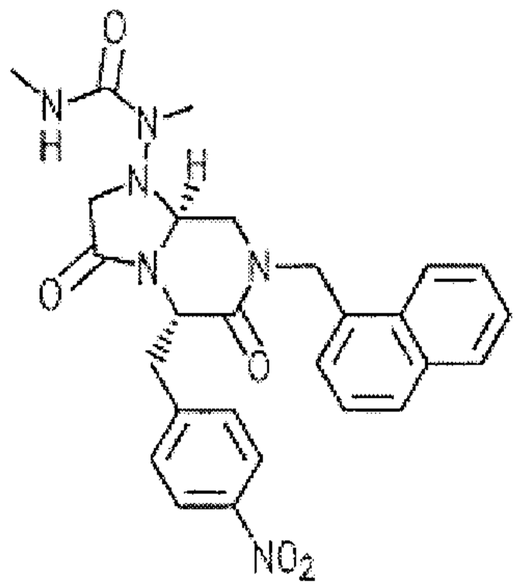
or a pharmaceutically acceptable salt thereof.

275. The compound of claim 1, which is:



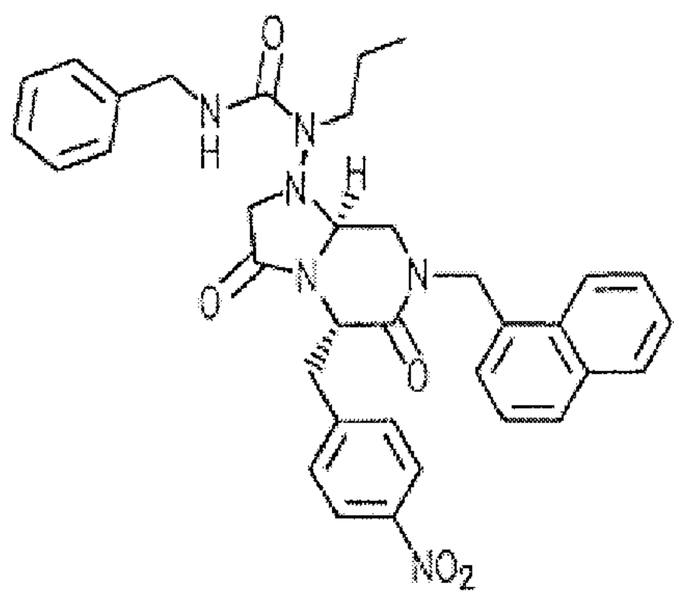
or a pharmaceutically acceptable salt thereof.

276. The compound of claim 1, which is:



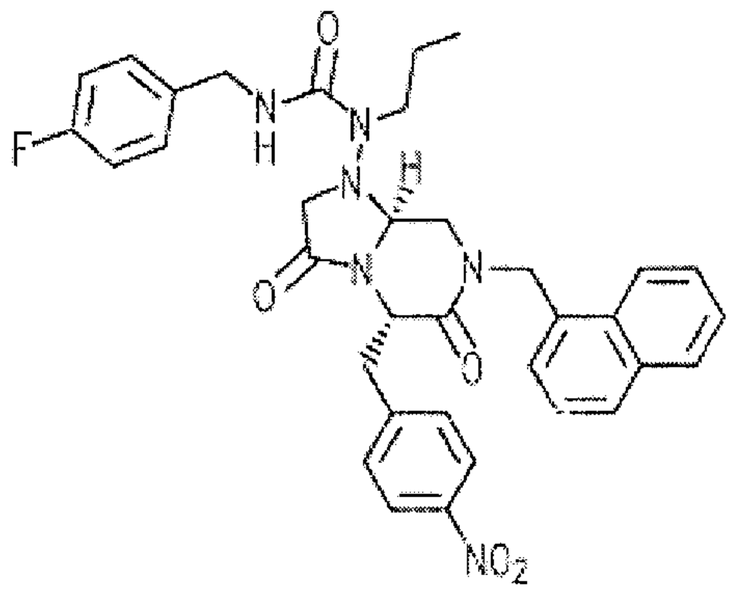
or a pharmaceutically acceptable salt thereof.

277. The compound of claim 1, which is:



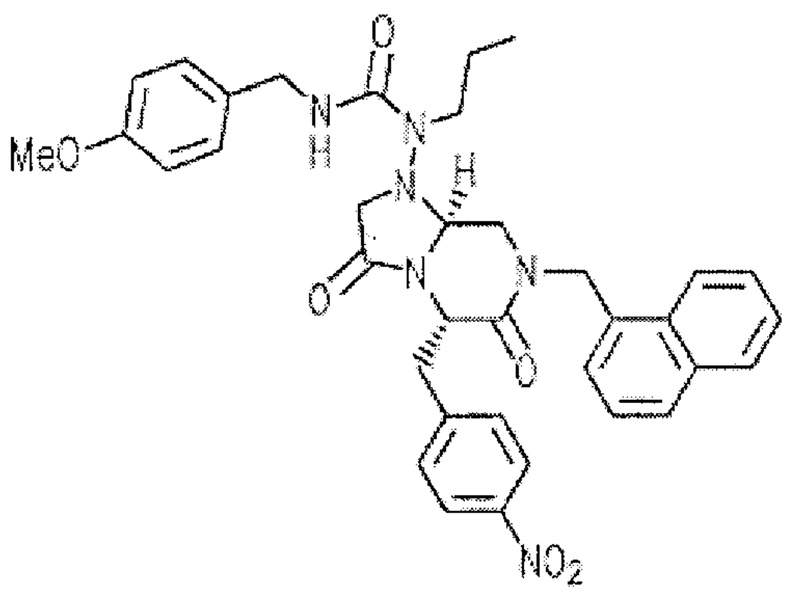
or a pharmaceutically acceptable salt thereof.

278. The compound of claim 1, which is:



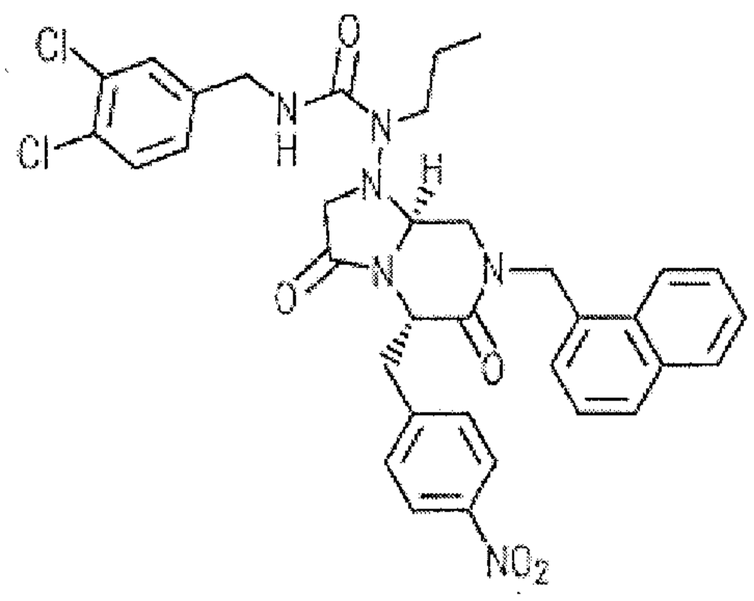
or a pharmaceutically acceptable salt thereof.

279. The compound of claim 1, which is:



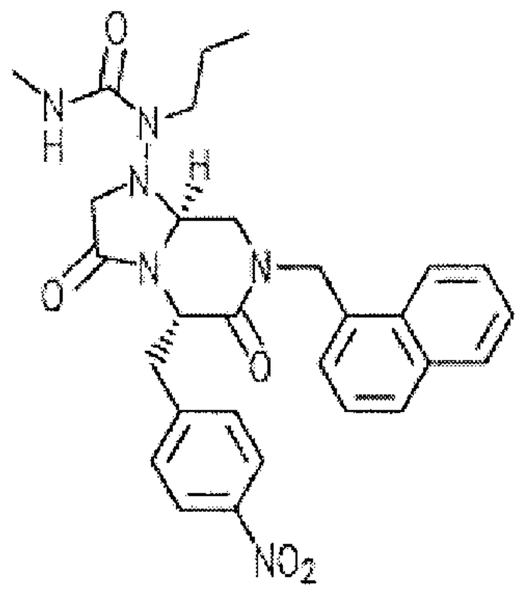
or a pharmaceutically acceptable salt thereof.

280. The compound of claim 1, which is:



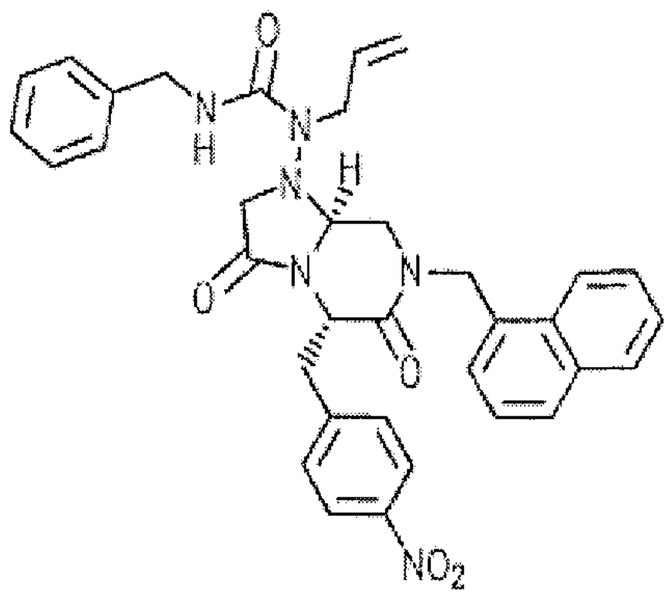
or a pharmaceutically acceptable salt thereof.

281. The compound of claim 1, which is:



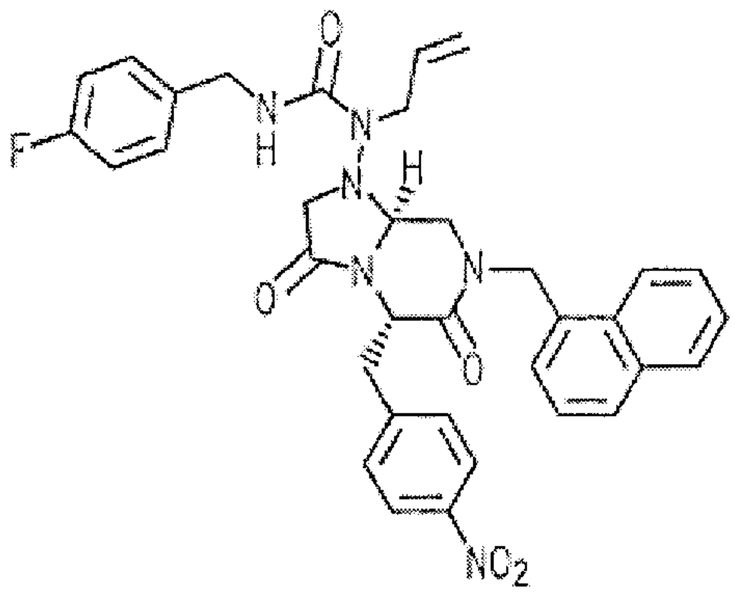
or a pharmaceutically acceptable salt thereof.

282. The compound of claim 1, which is:



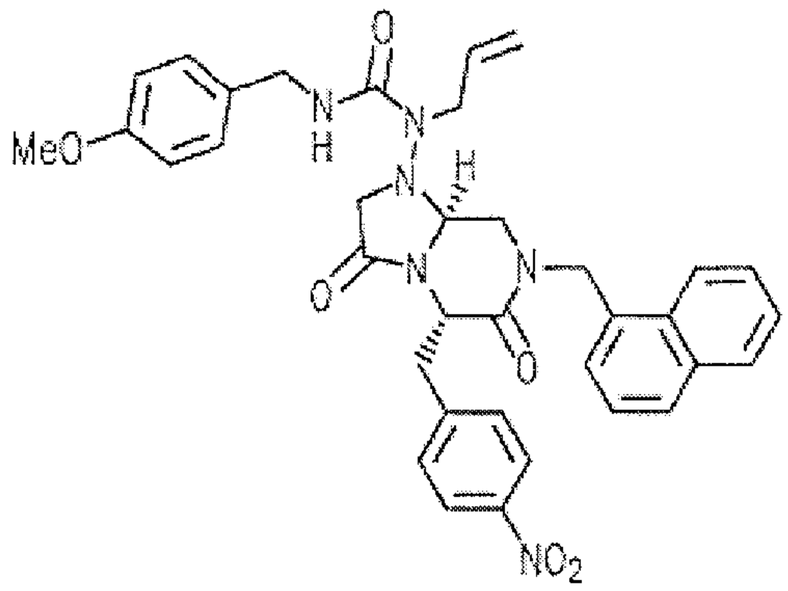
or a pharmaceutically acceptable salt thereof.

283. The compound of claim 1, which is:



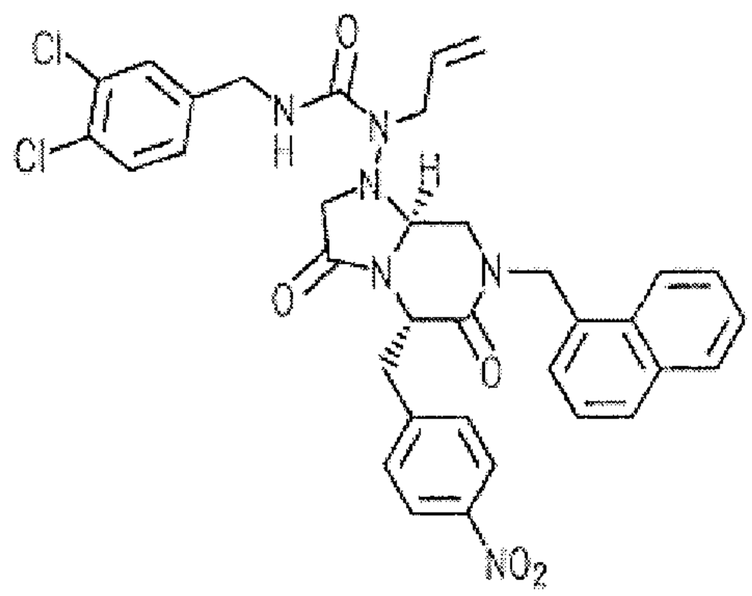
or a pharmaceutically acceptable salt thereof.

284. The compound of claim 1, which is:



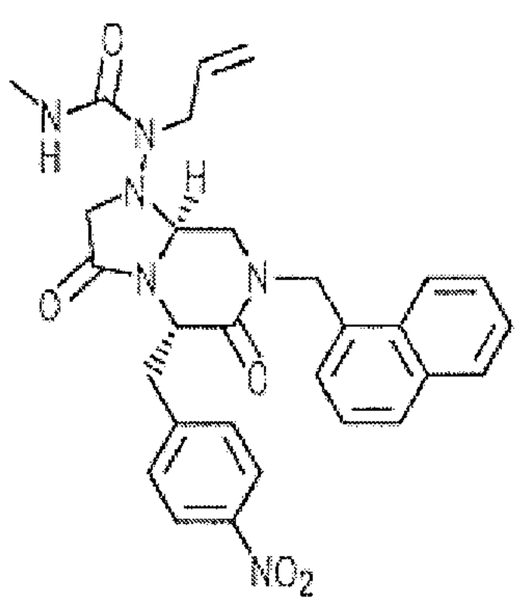
or a pharmaceutically acceptable salt thereof.

285. The compound of claim 1, which is:



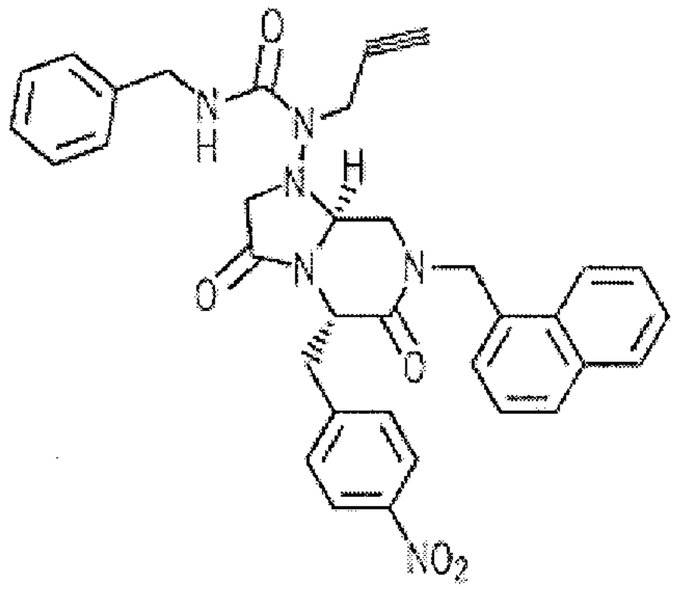
or a pharmaceutically acceptable salt thereof.

286. The compound of claim 1, which is:



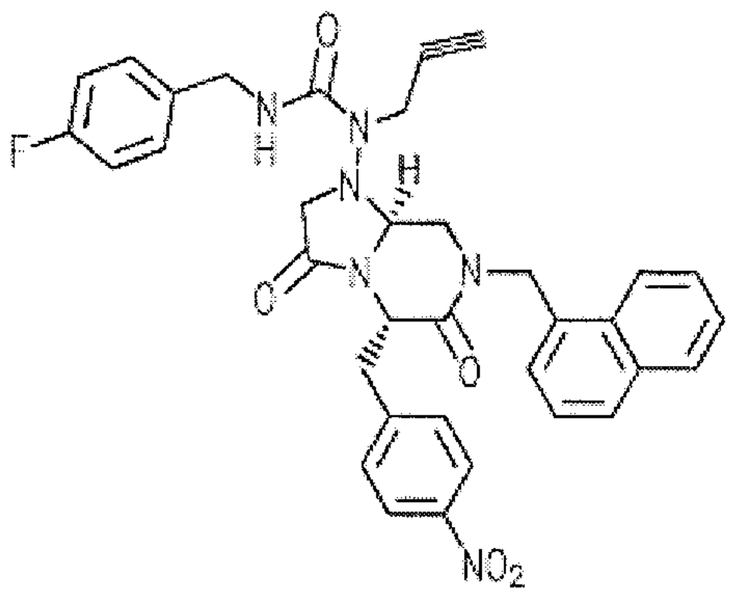
or a pharmaceutically acceptable salt thereof.

287. The compound of claim 1, which is:



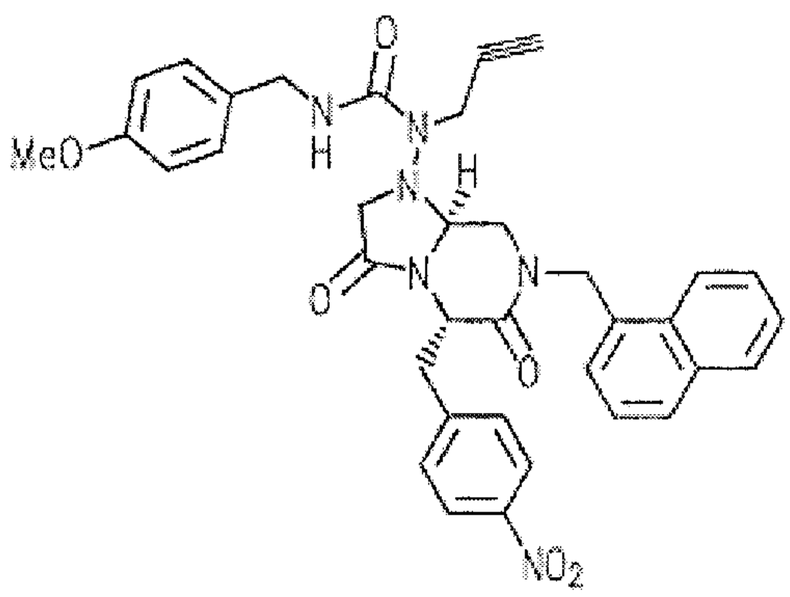
or a pharmaceutically acceptable salt thereof.

288. The compound of claim 1, which is:



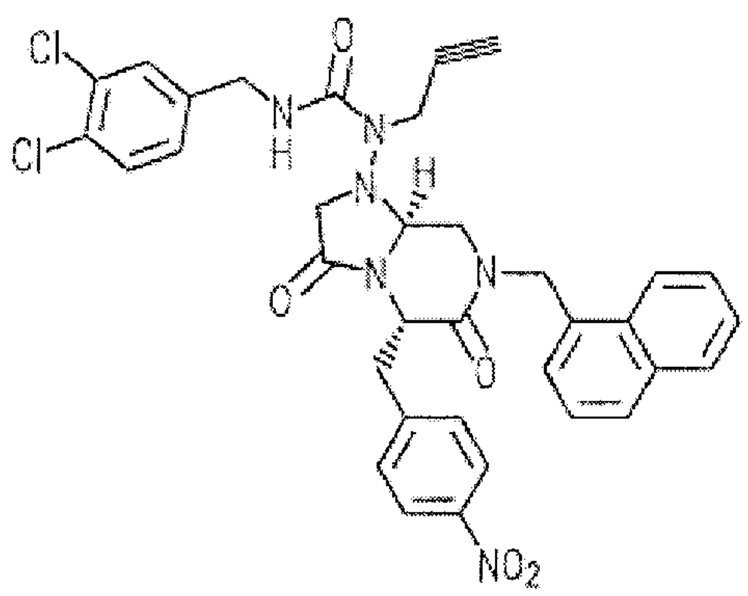
or a pharmaceutically acceptable salt thereof.

289. The compound of claim 1, which is:



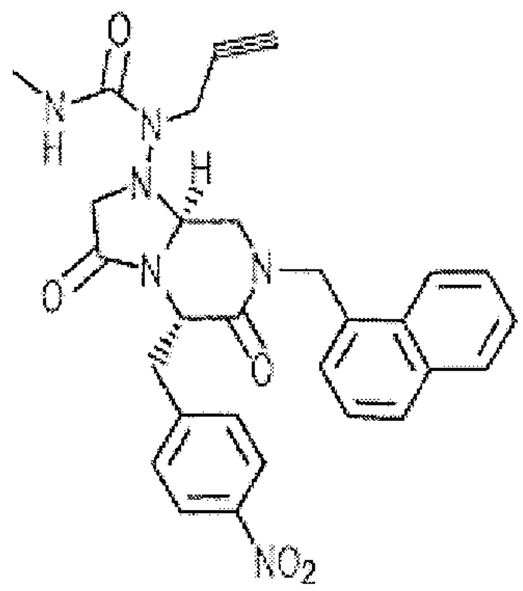
or a pharmaceutically acceptable salt thereof.

290. The compound of claim 1, which is:



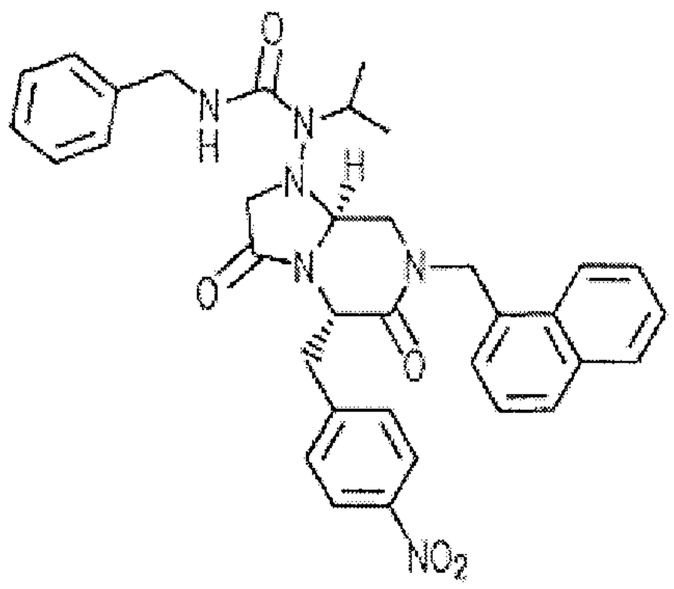
or a pharmaceutically acceptable salt thereof.

291. The compound of claim 1, which is:



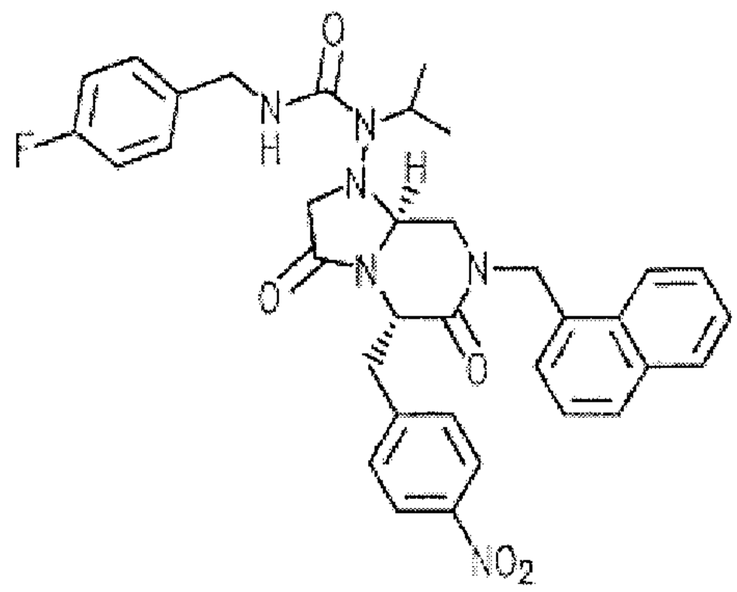
or a pharmaceutically acceptable salt thereof.

292. The compound of claim 1, which is:



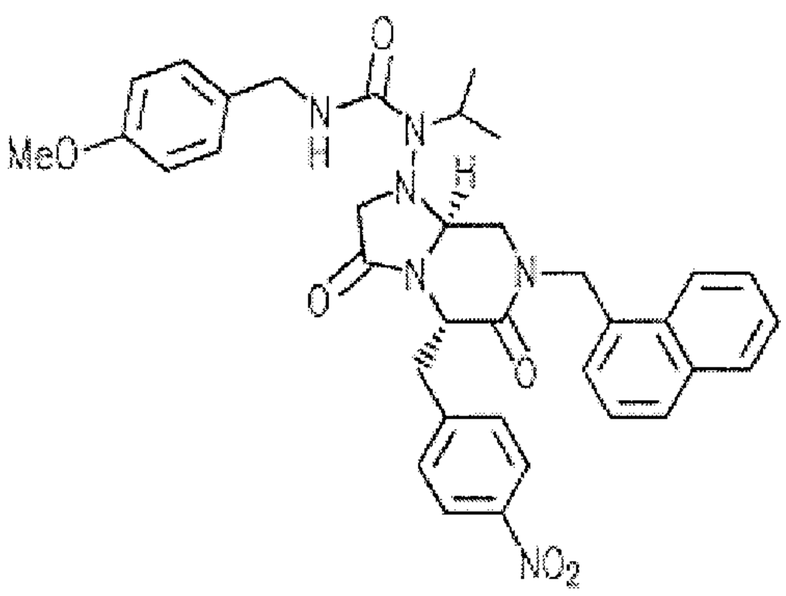
or a pharmaceutically acceptable salt thereof.

293. The compound of claim 1, which is:



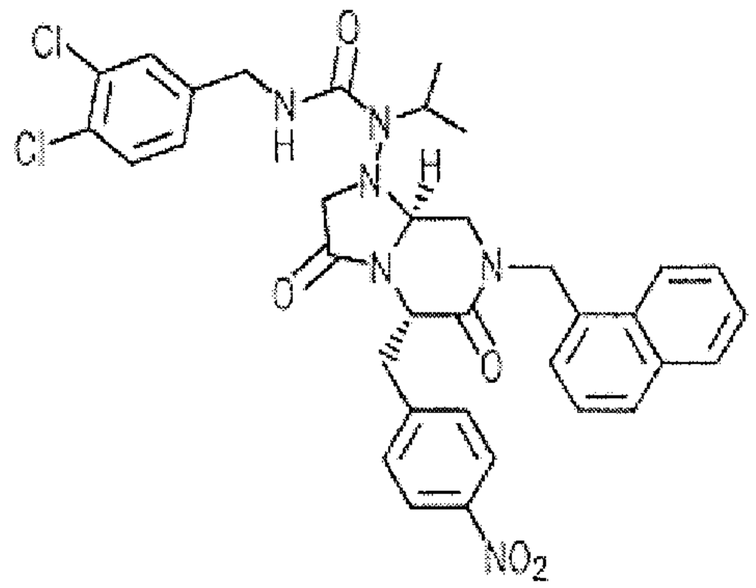
or a pharmaceutically acceptable salt thereof.

294. The compound of claim 1, which is:



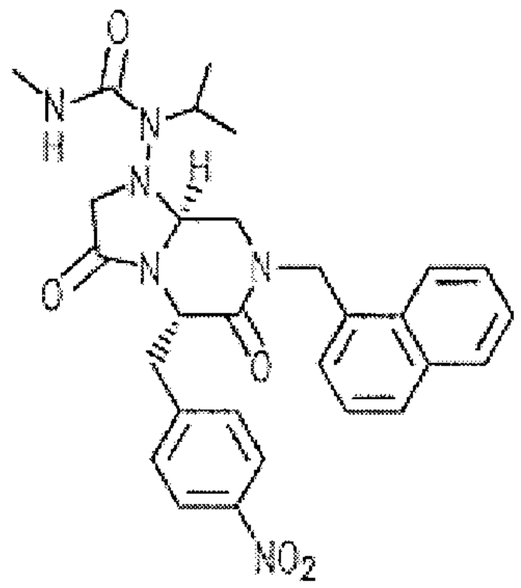
or a pharmaceutically acceptable salt thereof.

295. The compound of claim 1, which is:



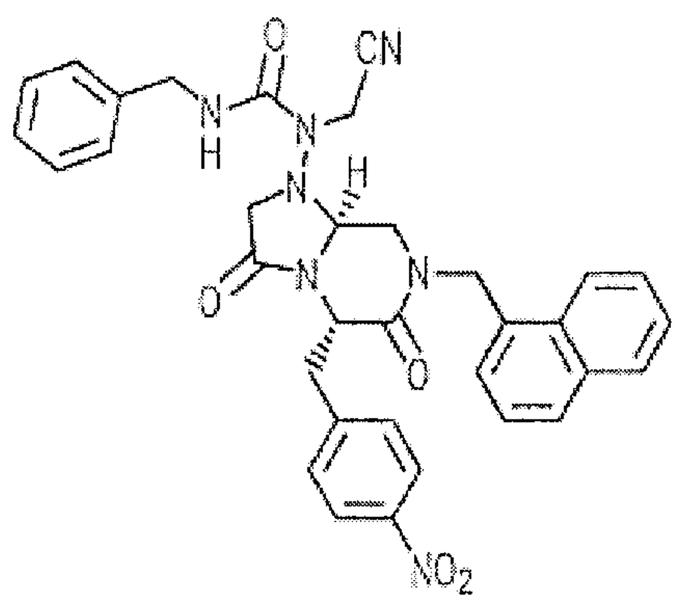
or a pharmaceutically acceptable salt thereof.

296. The compound of claim 1, which is:



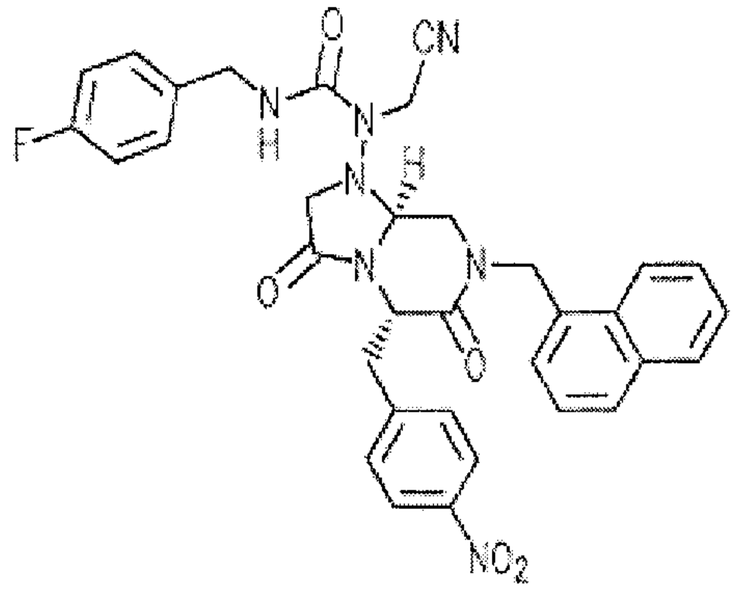
or a pharmaceutically acceptable salt thereof.

297. The compound of claim 1, which is:



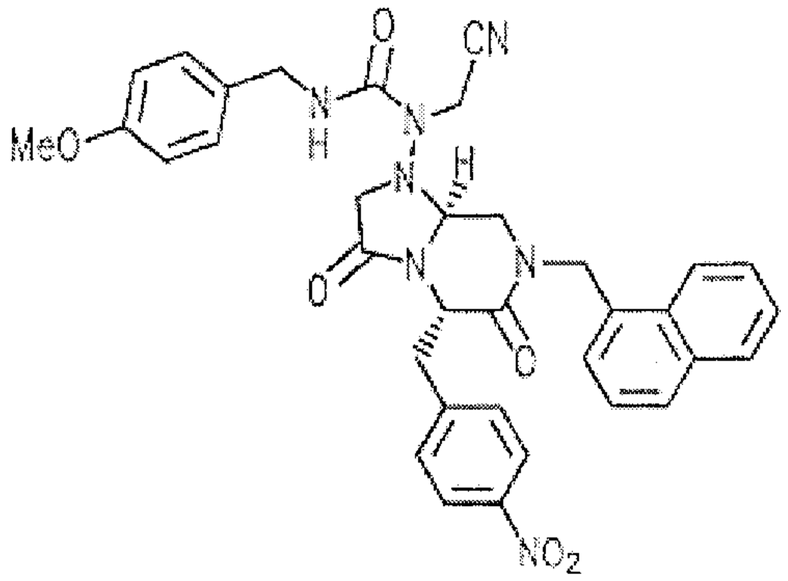
or a pharmaceutically acceptable salt thereof.

298. The compound of claim 1, which is:



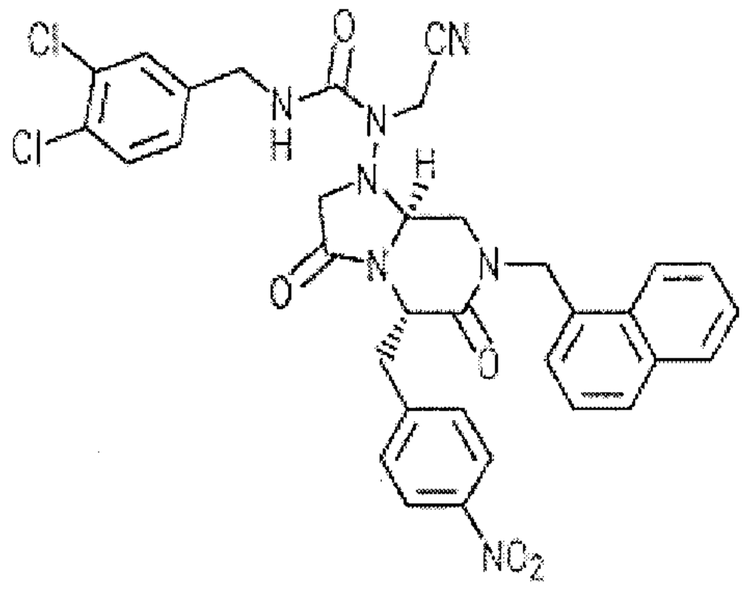
or a pharmaceutically acceptable salt thereof.

299. The compound of claim 1, which is:



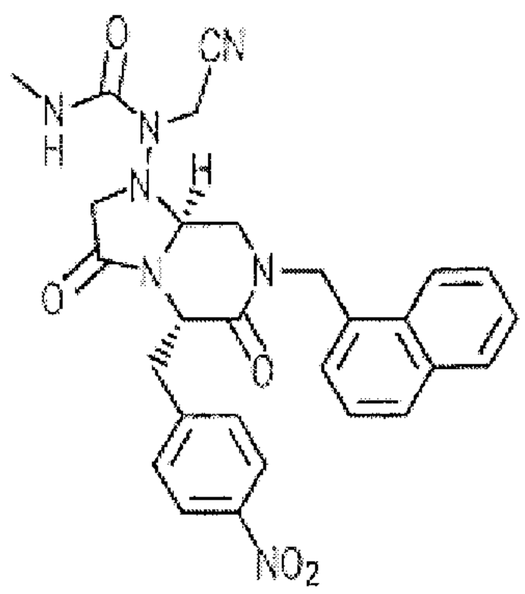
or a pharmaceutically acceptable salt thereof.

300. The compound of claim 1, which is:



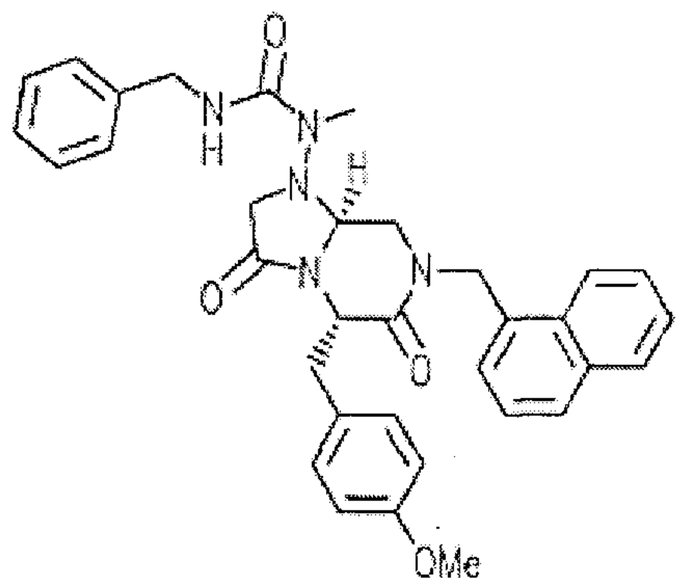
or a pharmaceutically acceptable salt thereof.

301. The compound of claim 1, which is:



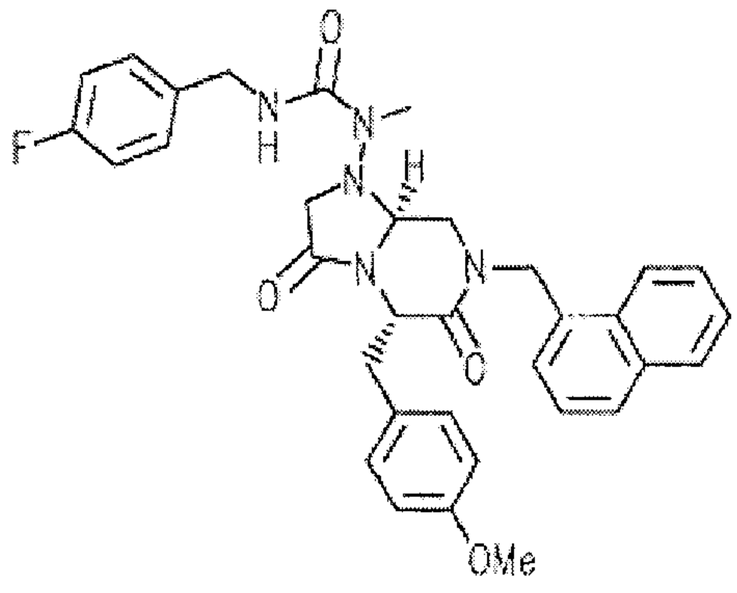
or a pharmaceutically acceptable salt thereof.

302. The compound of claim 1, which is:



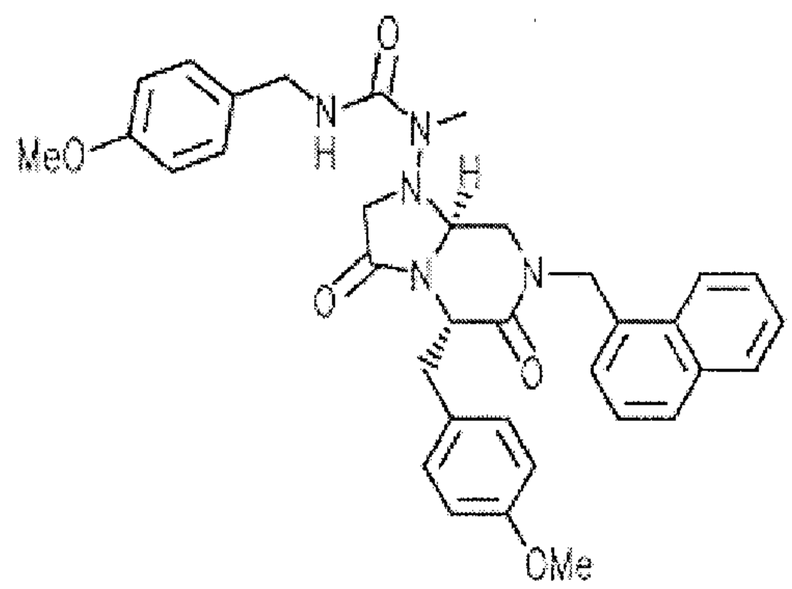
or a pharmaceutically acceptable salt thereof.

303. The compound of claim 1, which is:



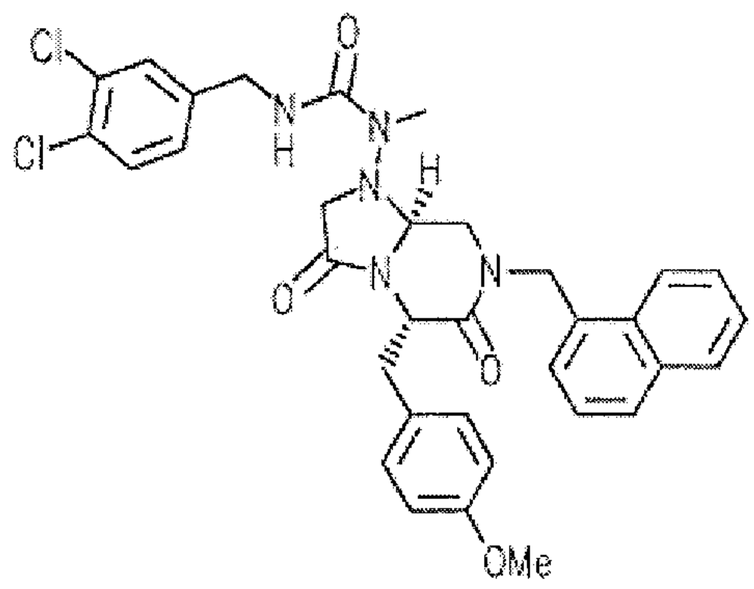
or a pharmaceutically acceptable salt thereof.

304. The compound of claim 1, which is:



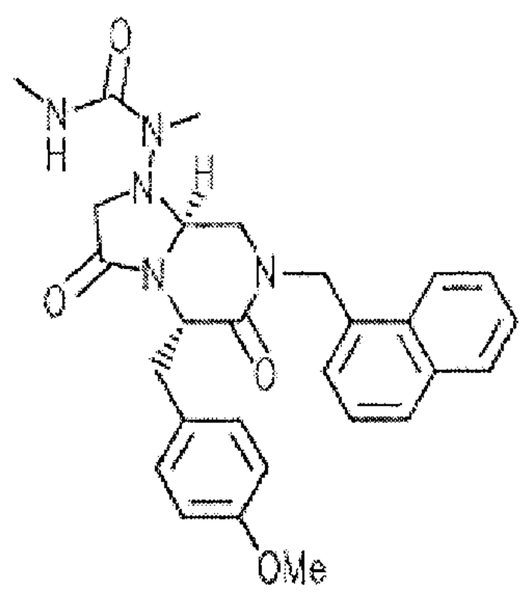
or a pharmaceutically acceptable salt thereof.

305. The compound of claim 1, which is:



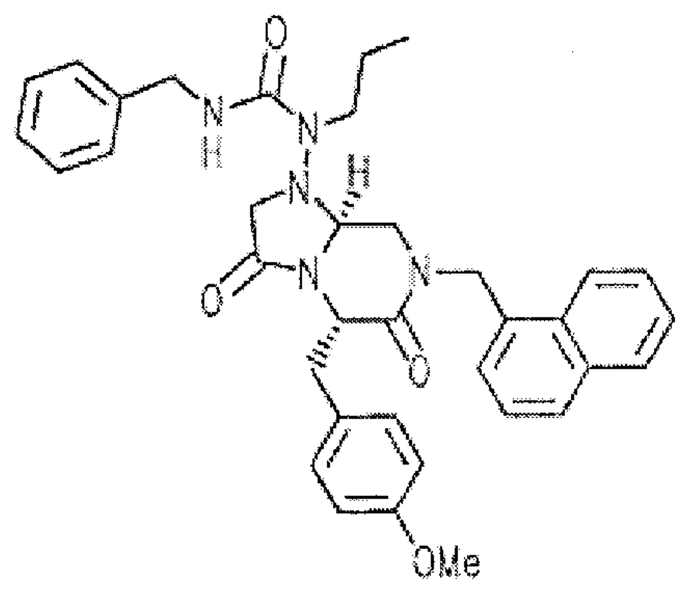
or a pharmaceutically acceptable salt thereof.

306. The compound of claim 1, which is:



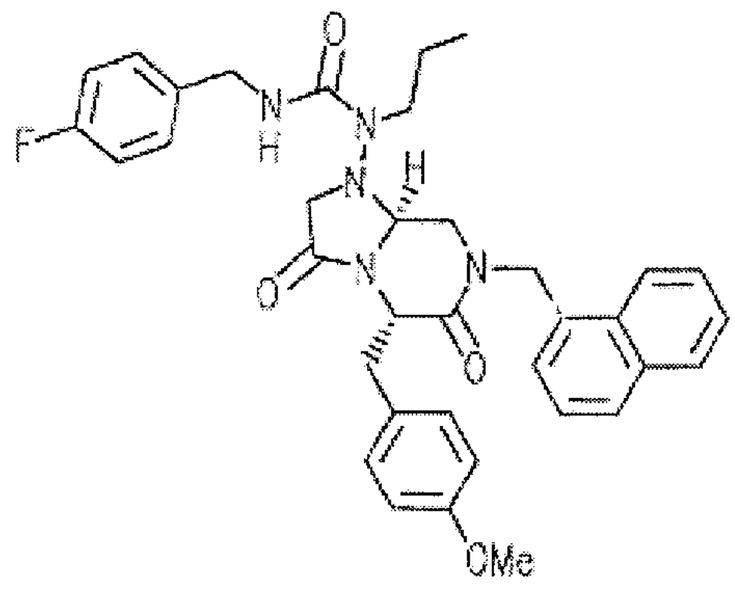
or a pharmaceutically acceptable salt thereof.

307. The compound of claim 1, which is:



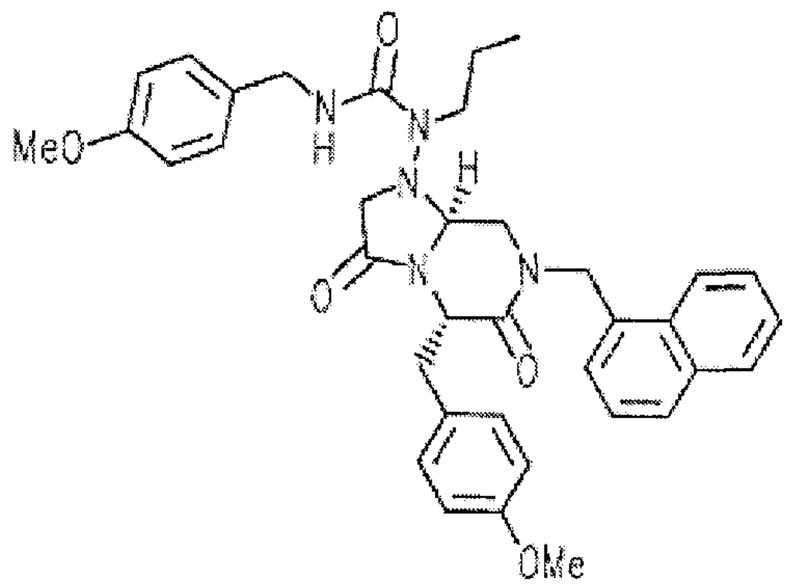
or a pharmaceutically acceptable salt thereof.

308. The compound of claim 1, which is:



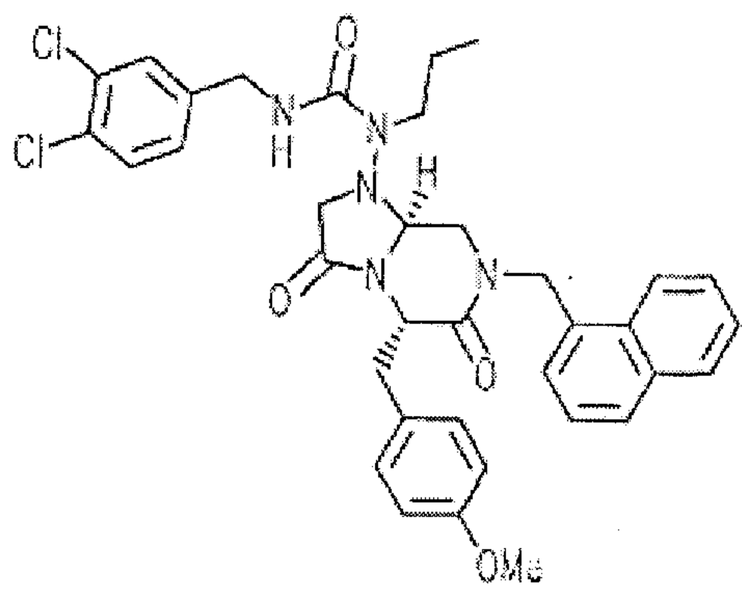
or a pharmaceutically acceptable salt thereof.

309. The compound of claim 1, which is:



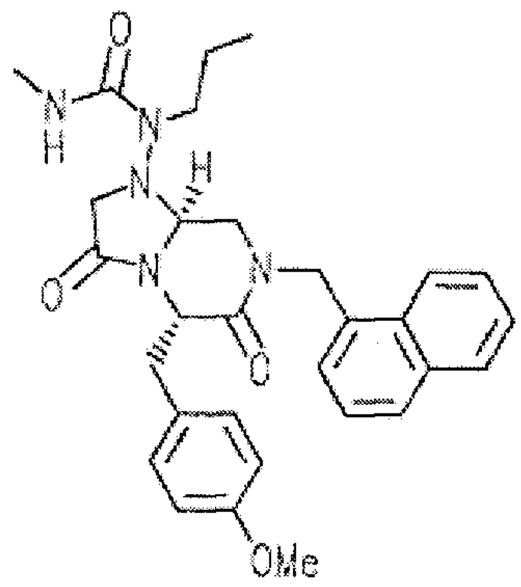
or a pharmaceutically acceptable salt thereof.

310. The compound of claim 1, which is:



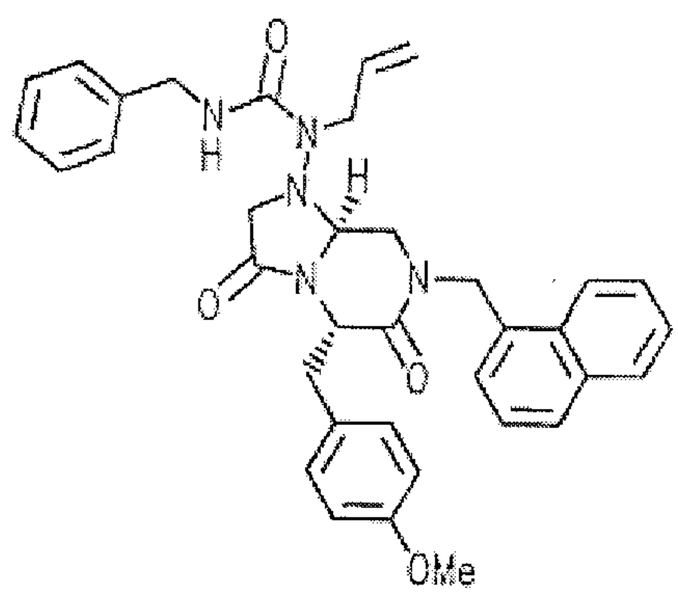
or a pharmaceutically acceptable salt thereof.

311. The compound of claim 1, which is:



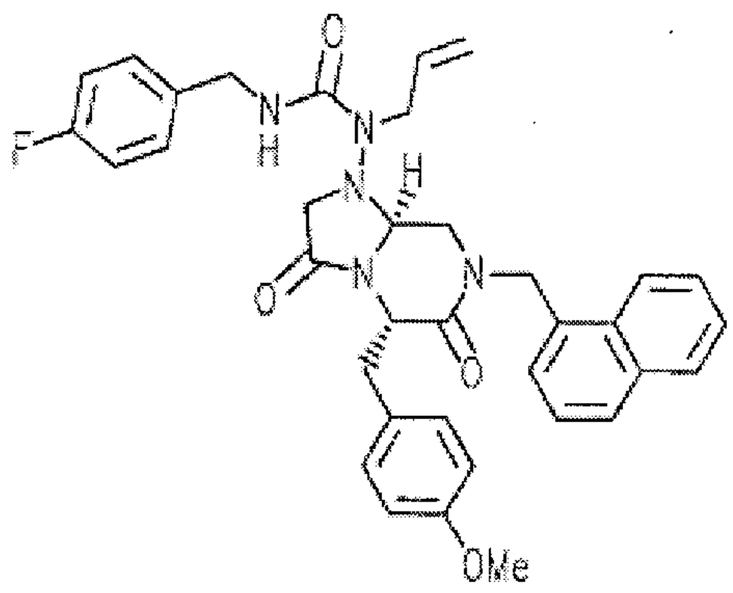
or a pharmaceutically acceptable salt thereof.

312. The compound of claim 1, which is:



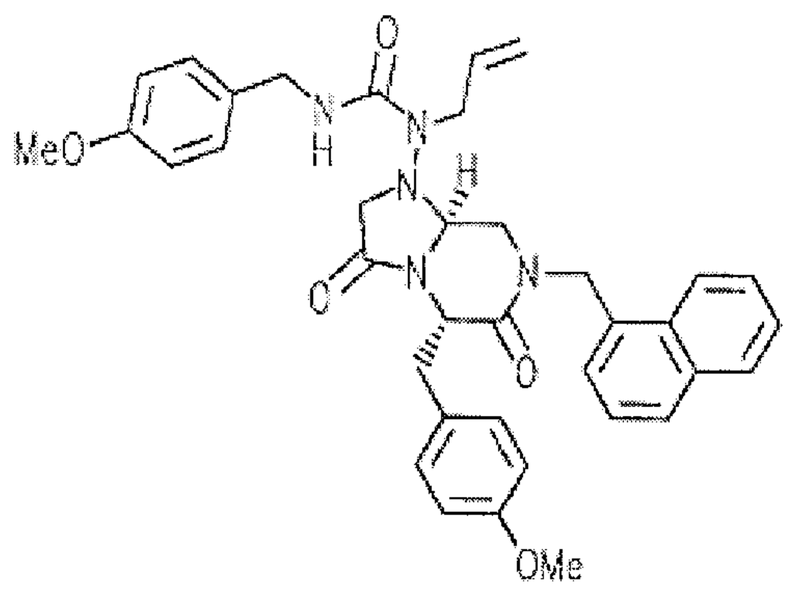
or a pharmaceutically acceptable salt thereof.

313. The compound of claim 1, which is:



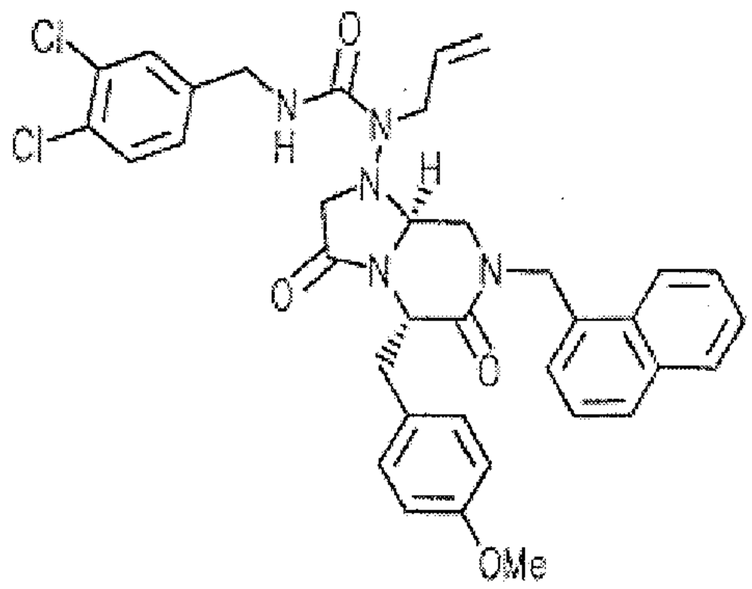
or a pharmaceutically acceptable salt thereof.

314. The compound of claim 1, which is:



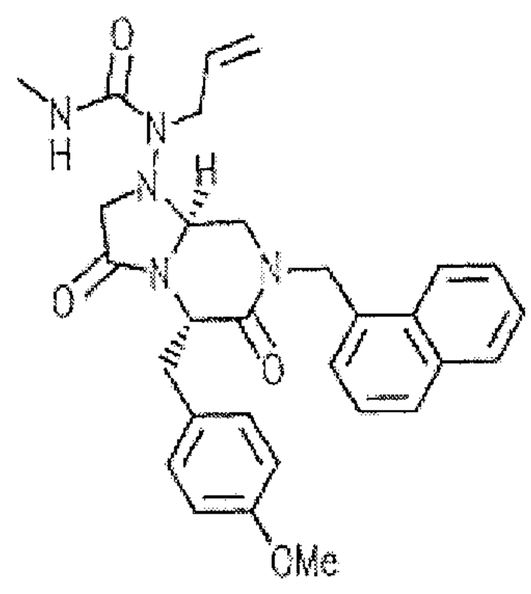
or a pharmaceutically acceptable salt thereof.

315. The compound of claim 1, which is:



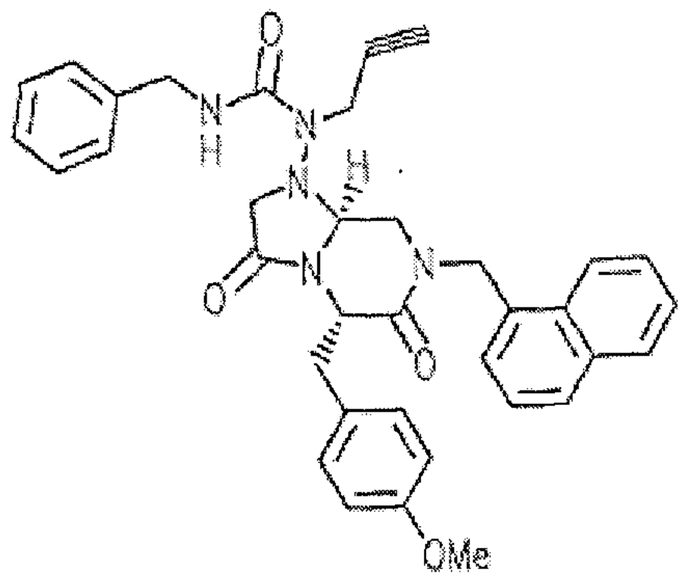
or a pharmaceutically acceptable salt thereof.

316. The compound of claim 1, which is:



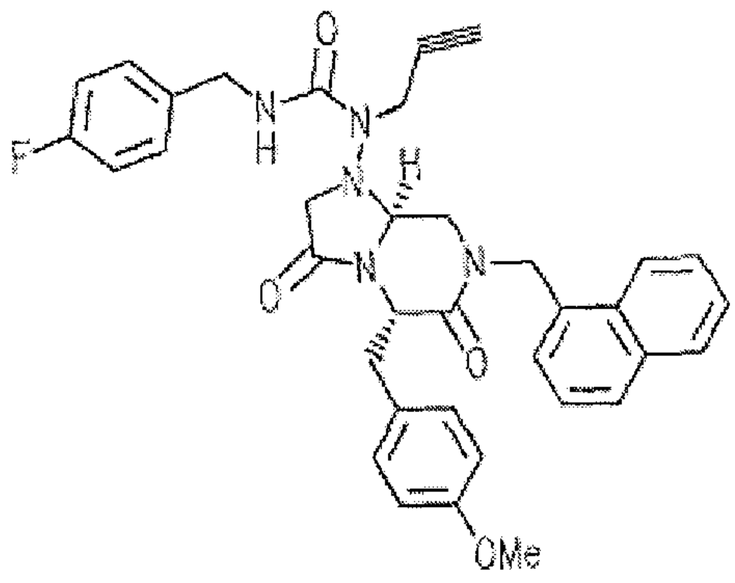
or a pharmaceutically acceptable salt thereof.

317. The compound of claim 1, which is:



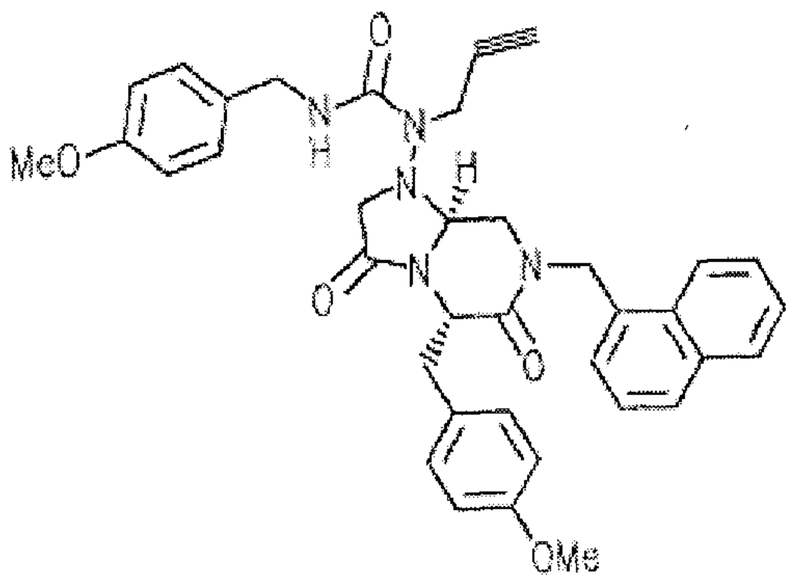
or a pharmaceutically acceptable salt thereof.

318. The compound of claim 1, which is:



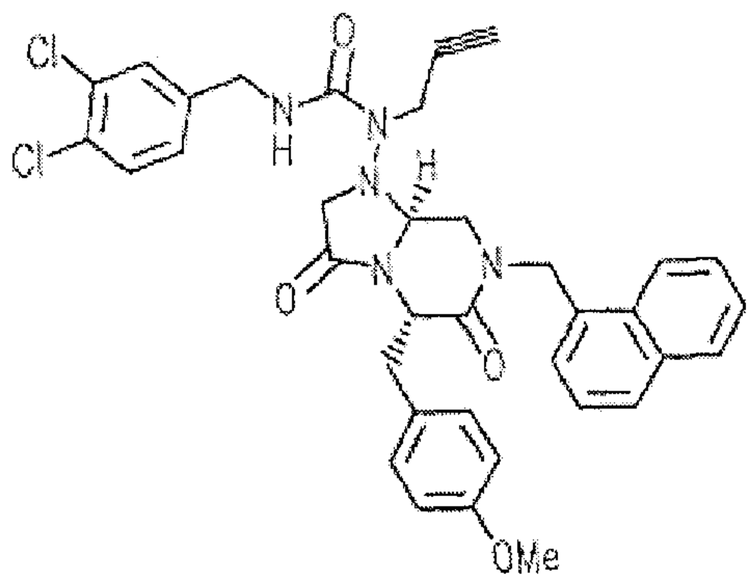
or a pharmaceutically acceptable salt thereof.

319. The compound of claim 1, which is:



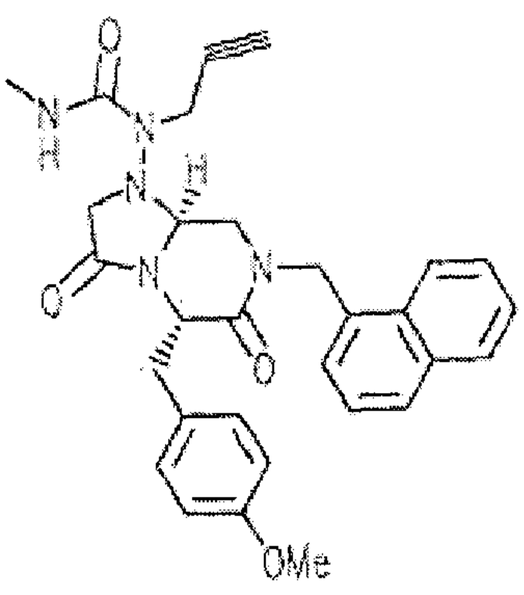
or a pharmaceutically acceptable salt thereof.

320. The compound of claim 1, which is:



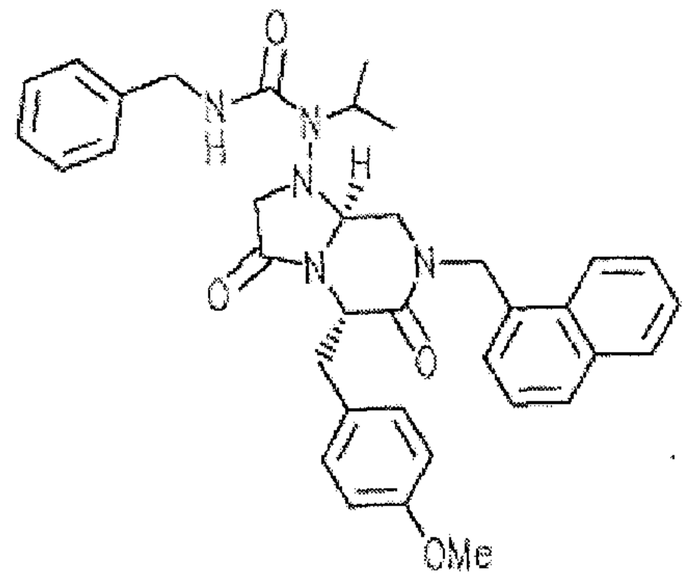
or a pharmaceutically acceptable salt thereof.

321. The compound of claim 1, which is:



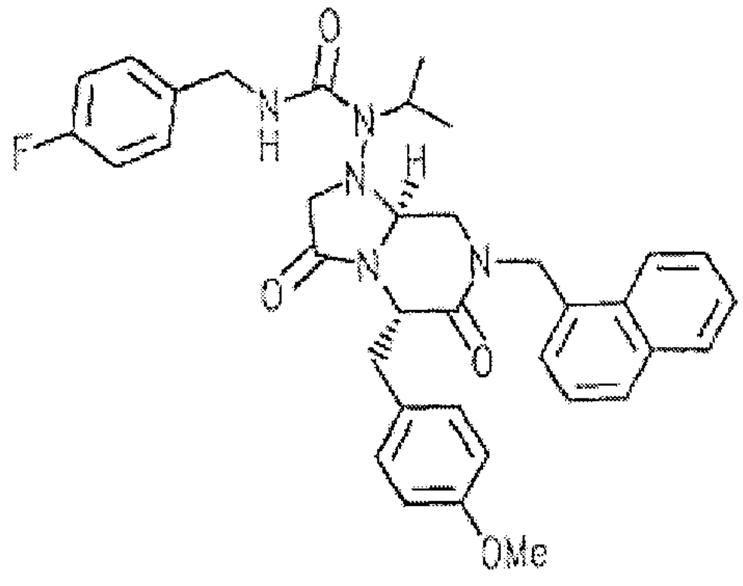
or a pharmaceutically acceptable salt thereof.

322. The compound of claim 1, which is:



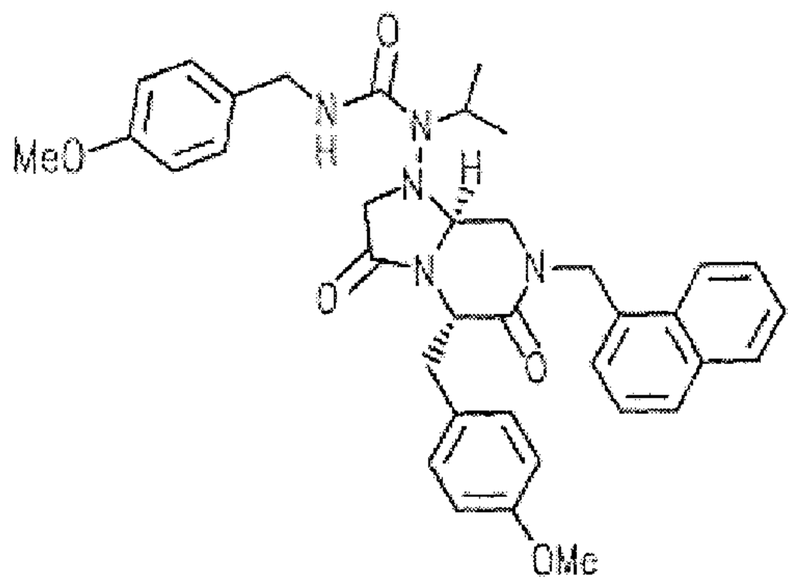
or a pharmaceutically acceptable salt thereof.

323. The compound of claim 1, which is:



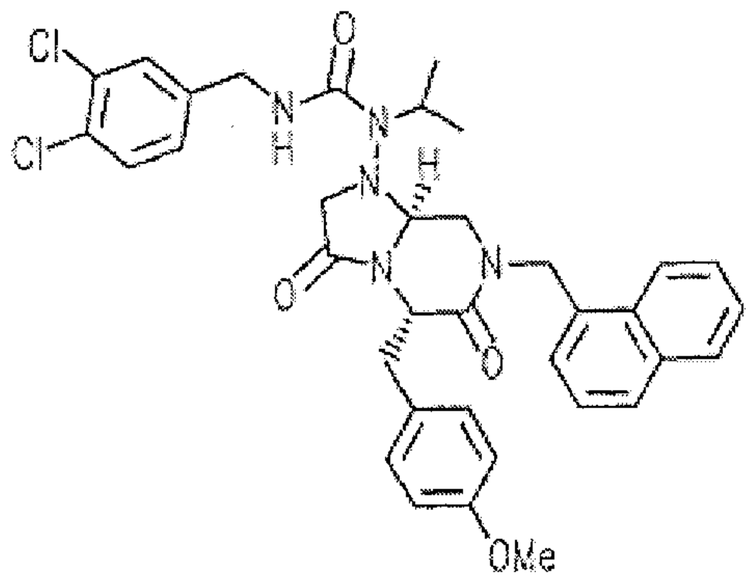
or a pharmaceutically acceptable salt thereof.

324. The compound of claim 1, which is:



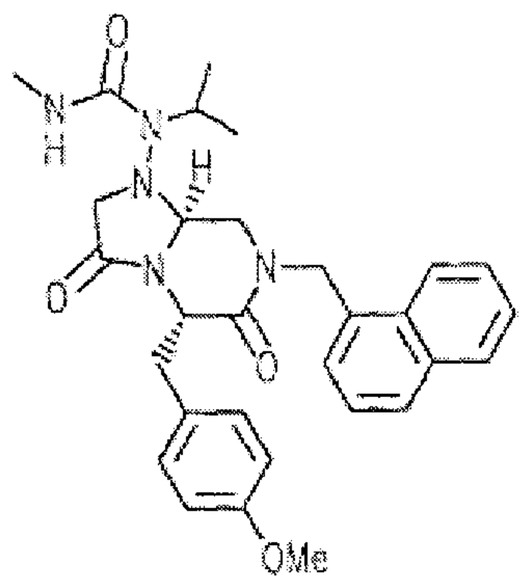
or a pharmaceutically acceptable salt thereof.

325. The compound of claim 1, which is:



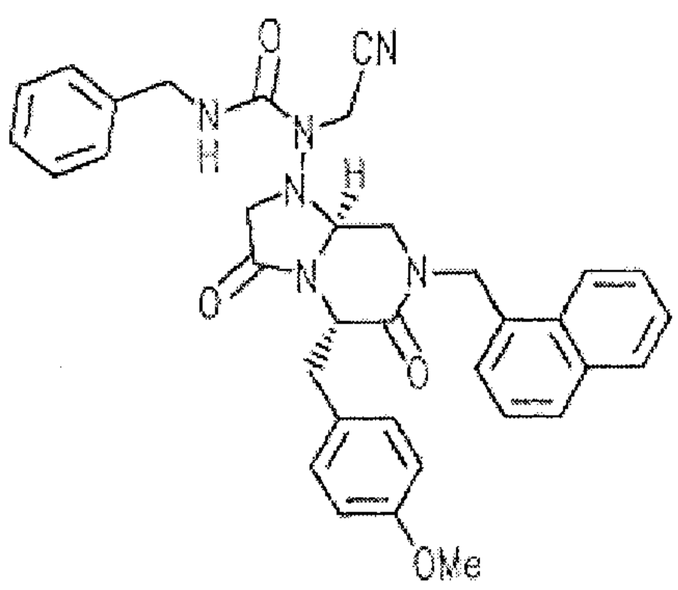
or a pharmaceutically acceptable salt thereof.

326. The compound of claim 1, which is:



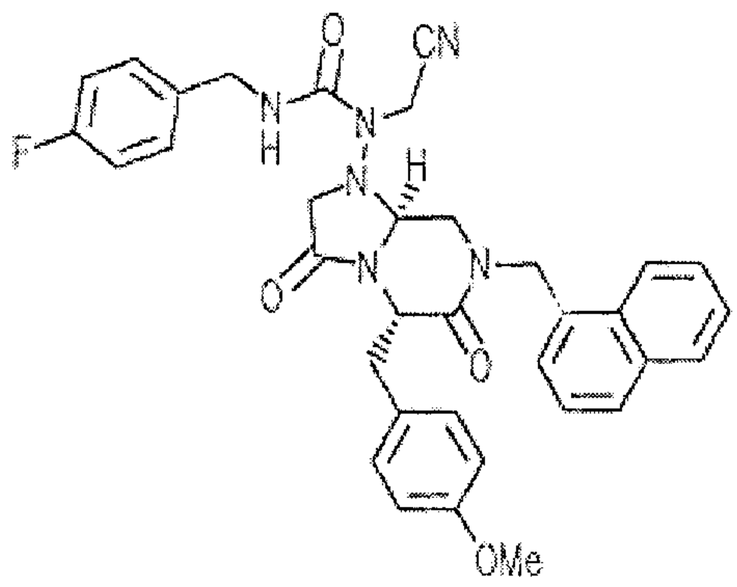
or a pharmaceutically acceptable salt thereof.

327. The compound of claim 1, which is:



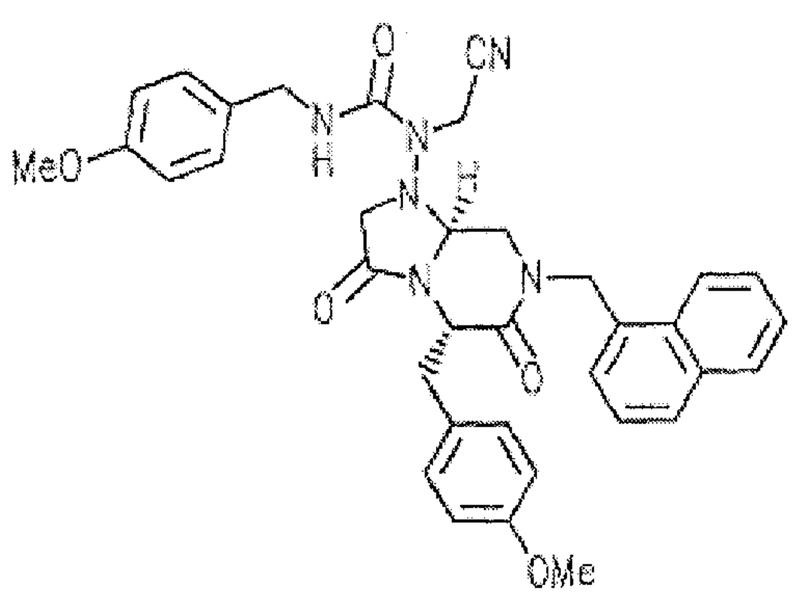
or a pharmaceutically acceptable salt thereof.

328. The compound of claim 1, which is:



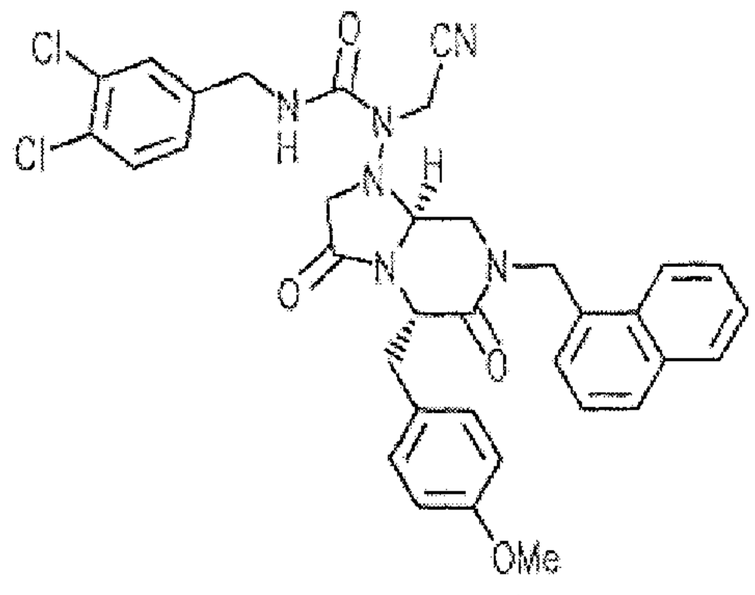
or a pharmaceutically acceptable salt thereof.

329. The compound of claim 1, which is:



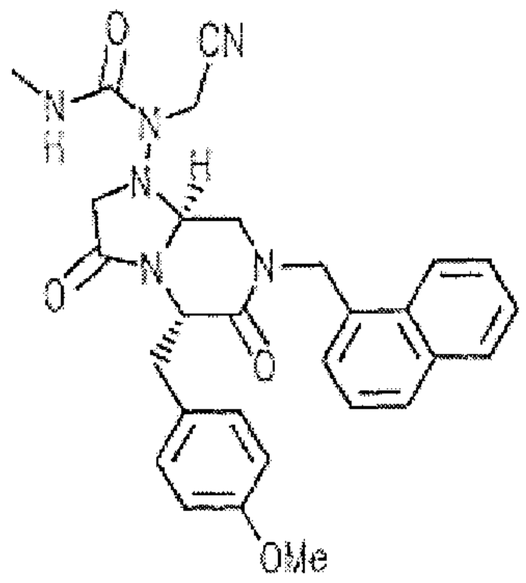
or a pharmaceutically acceptable salt thereof.

330. The compound of claim 1, which is:



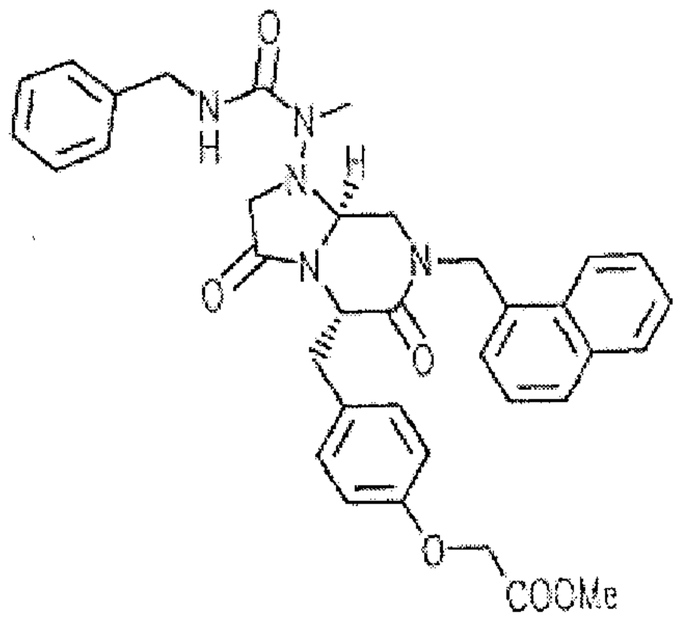
or a pharmaceutically acceptable salt thereof.

331. The compound of claim 1, which is:



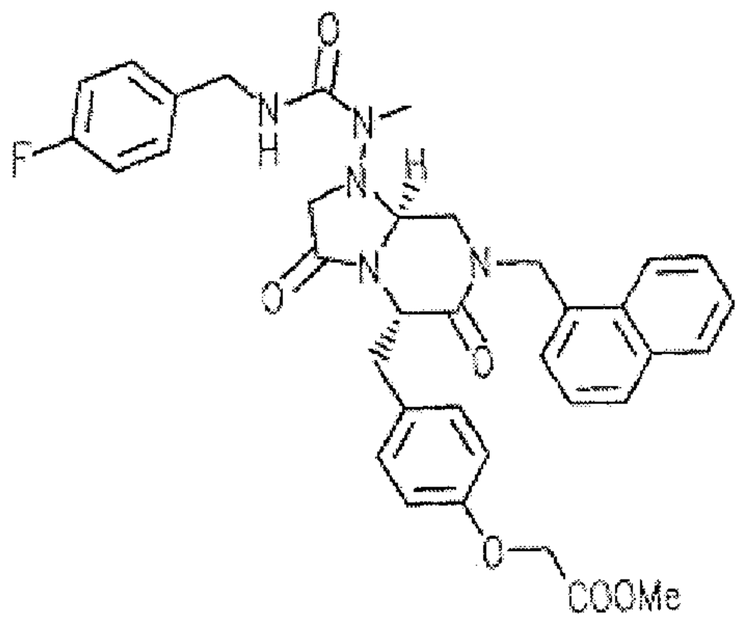
or a pharmaceutically acceptable salt thereof.

332. The compound of claim 1, which is:



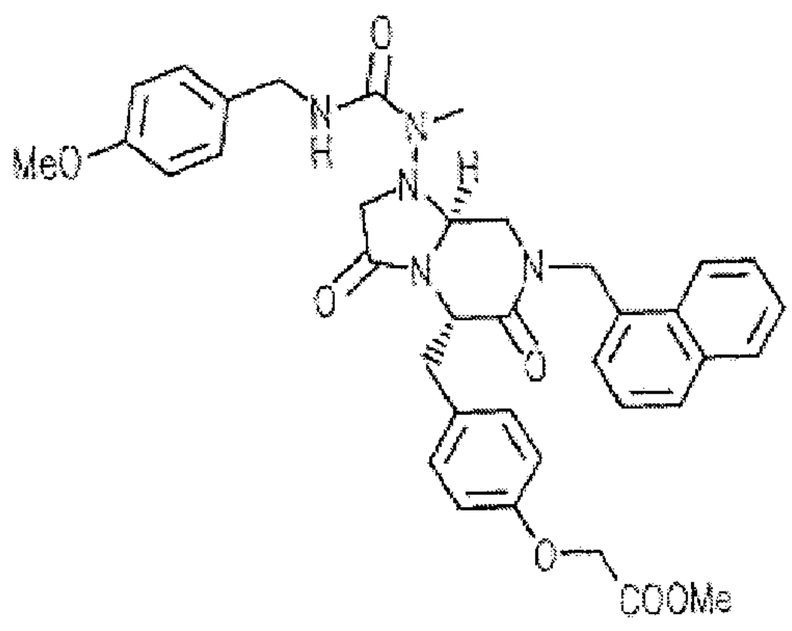
or a pharmaceutically acceptable salt thereof.

333. The compound of claim 1, which is:



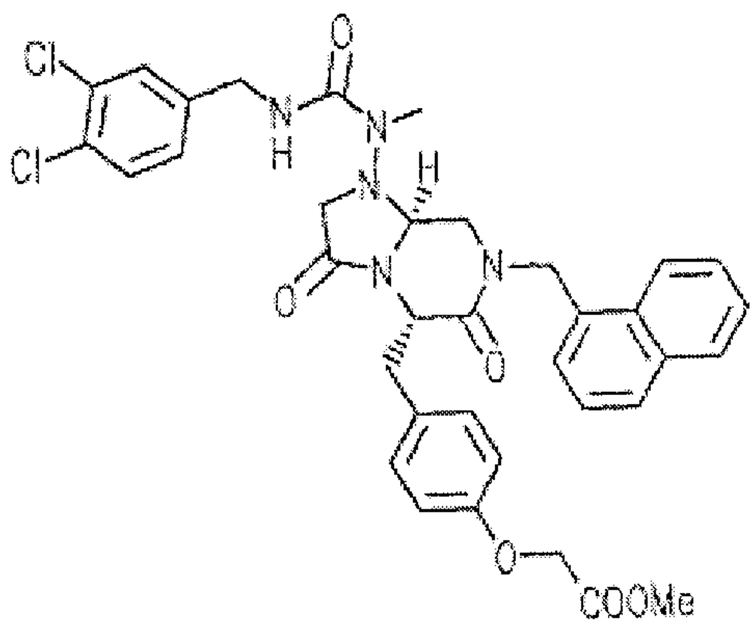
or a pharmaceutically acceptable salt thereof.

334. The compound of claim 1, which is:



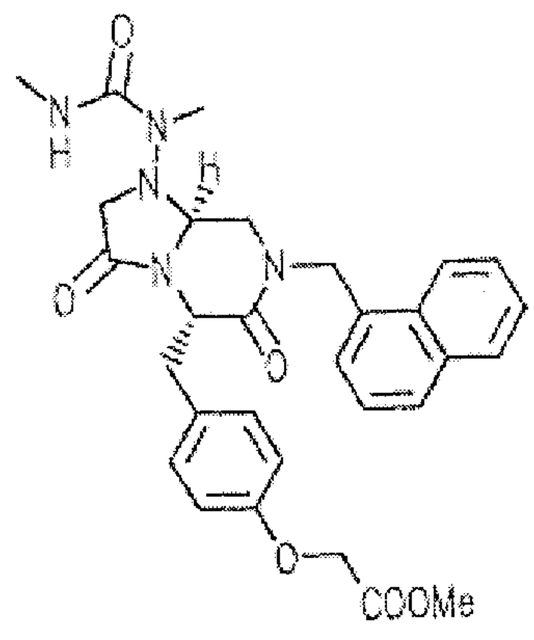
or a pharmaceutically acceptable salt thereof.

335. The compound of claim 1, which is:



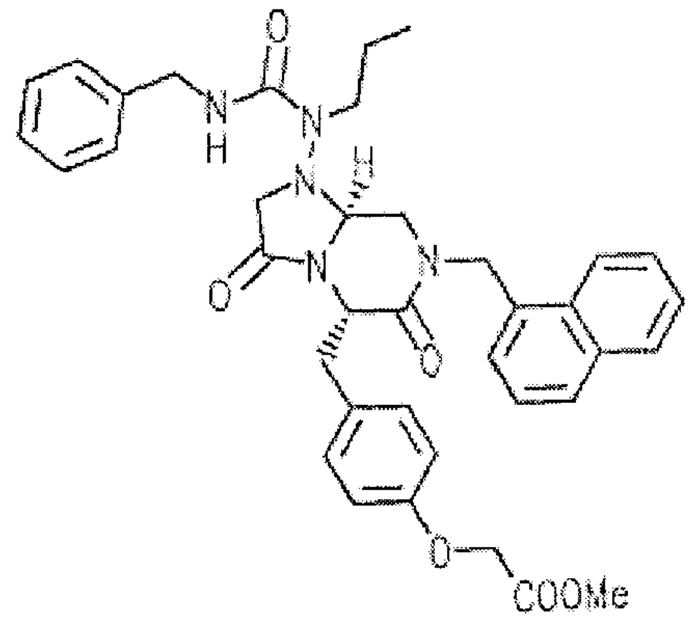
or a pharmaceutically acceptable salt thereof.

336. The compound of claim 1, which is:



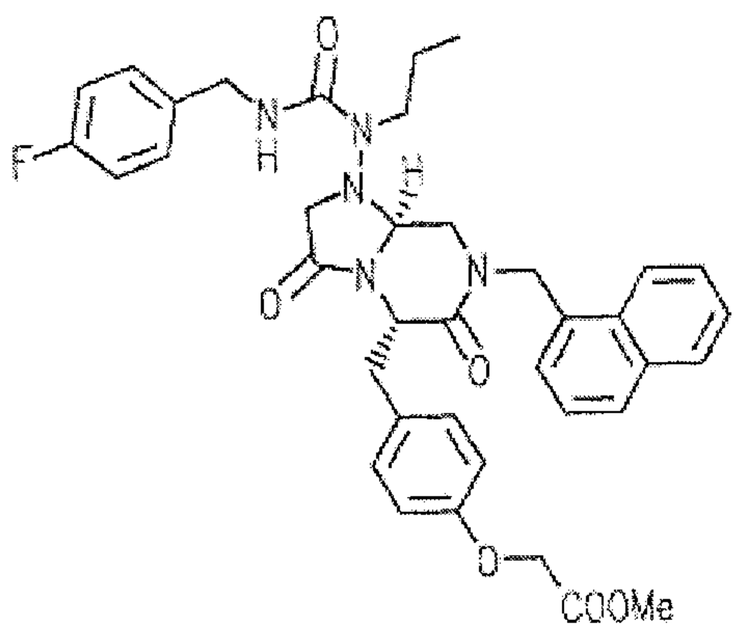
or a pharmaceutically acceptable salt thereof.

337. The compound of claim 1, which is:



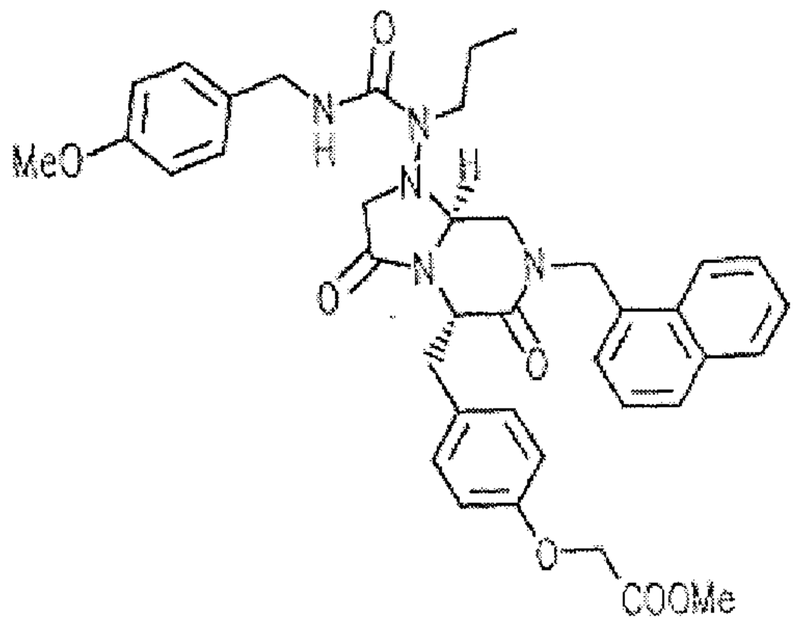
or a pharmaceutically acceptable salt thereof.

338. The compound of claim 1, which is:



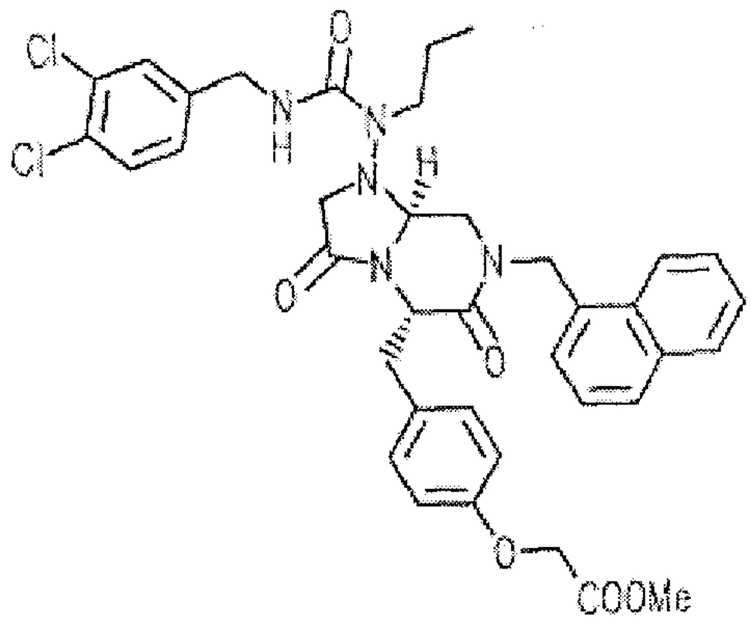
or a pharmaceutically acceptable salt thereof.

339. The compound of claim 1, which is:



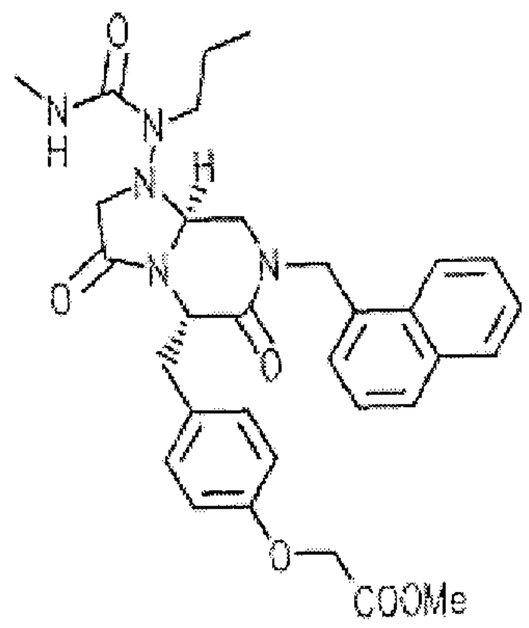
or a pharmaceutically acceptable salt thereof.

340. The compound of claim 1, which is:



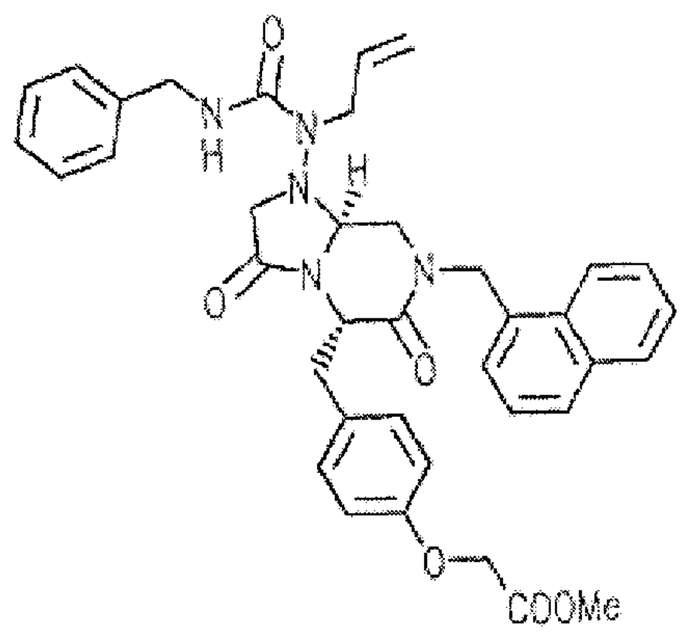
or a pharmaceutically acceptable salt thereof.

341. The compound of claim 1, which is:



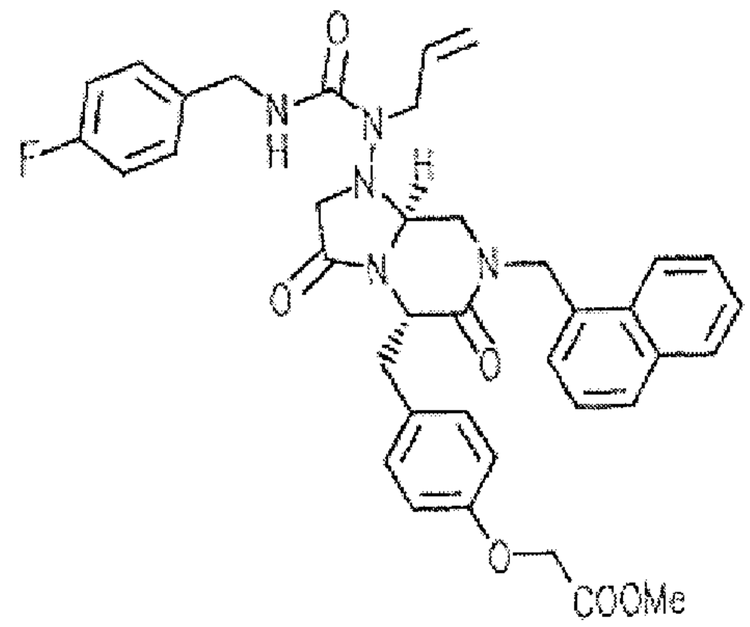
or a pharmaceutically acceptable salt thereof.

342. The compound of claim 1, which is:



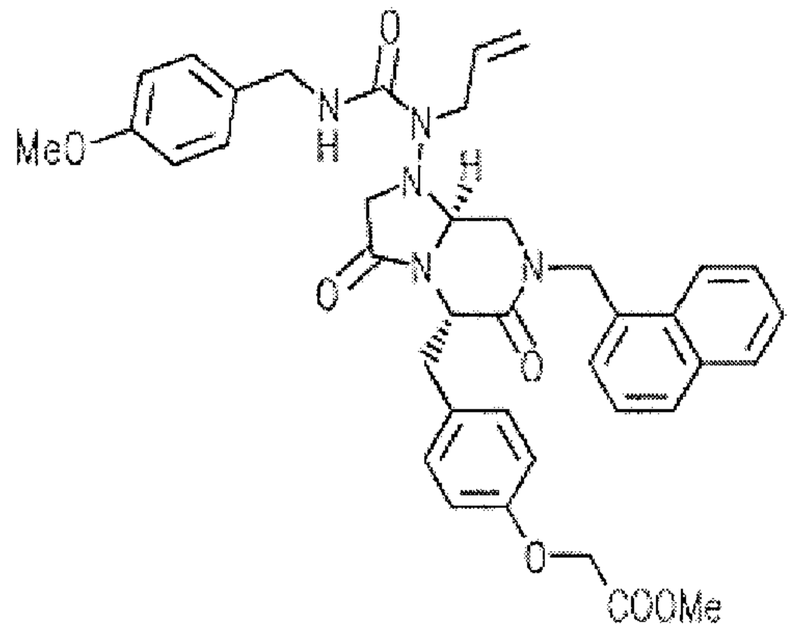
or a pharmaceutically acceptable salt thereof.

343. The compound of claim 1, which is:



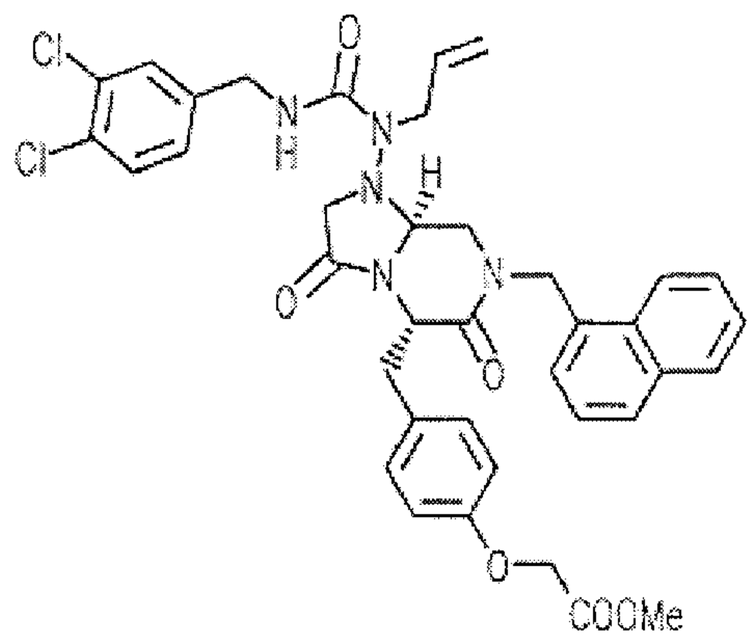
or a pharmaceutically acceptable salt thereof.

344. The compound of claim 1, which is:



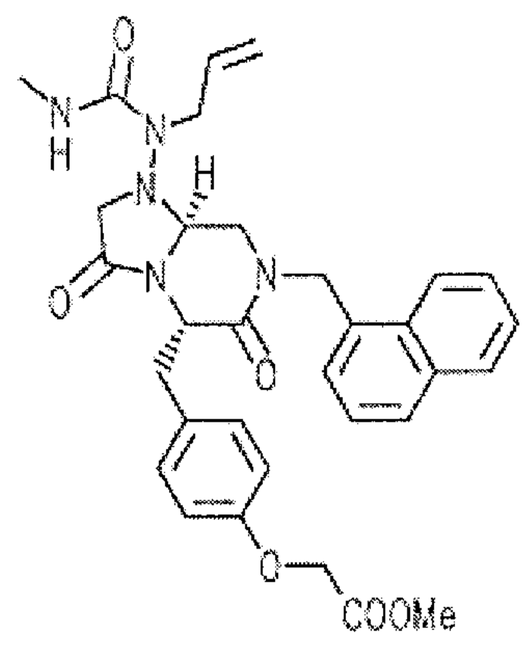
or a pharmaceutically acceptable salt thereof.

345. The compound of claim 1, which is:



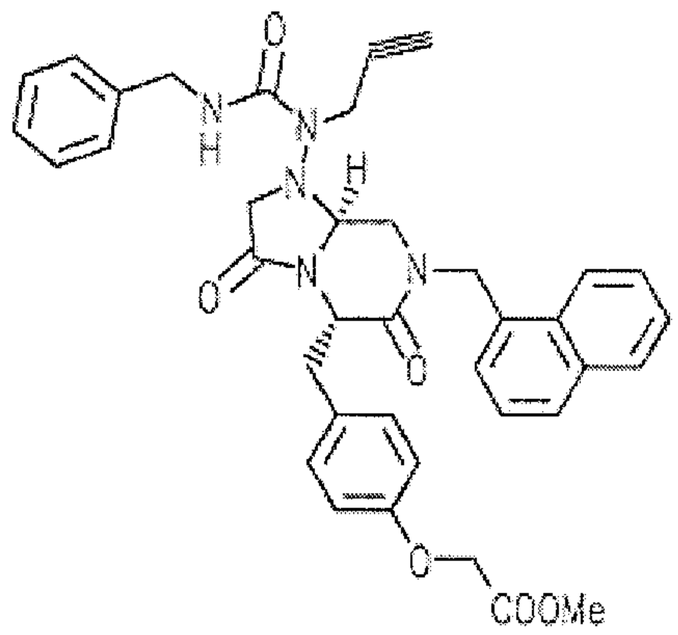
or a pharmaceutically acceptable salt thereof.

346. The compound of claim 1, which is:



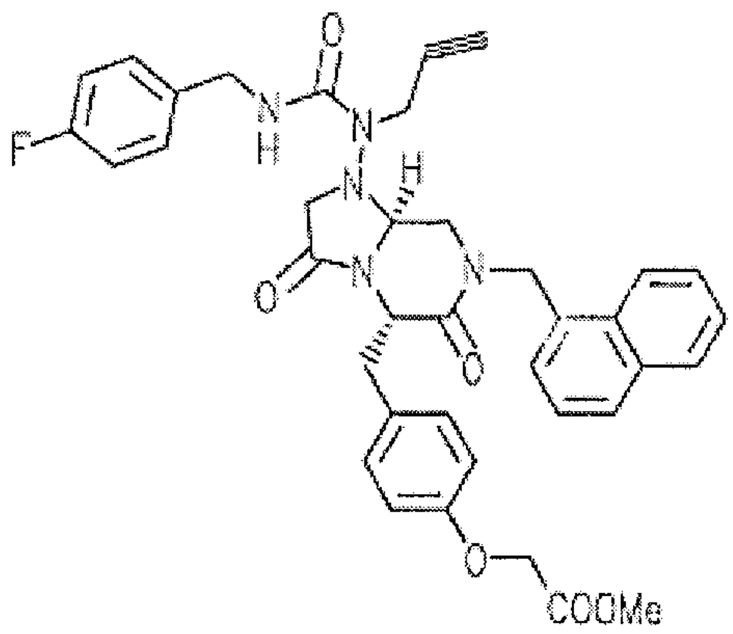
or a pharmaceutically acceptable salt thereof.

347. The compound of claim 1, which is:



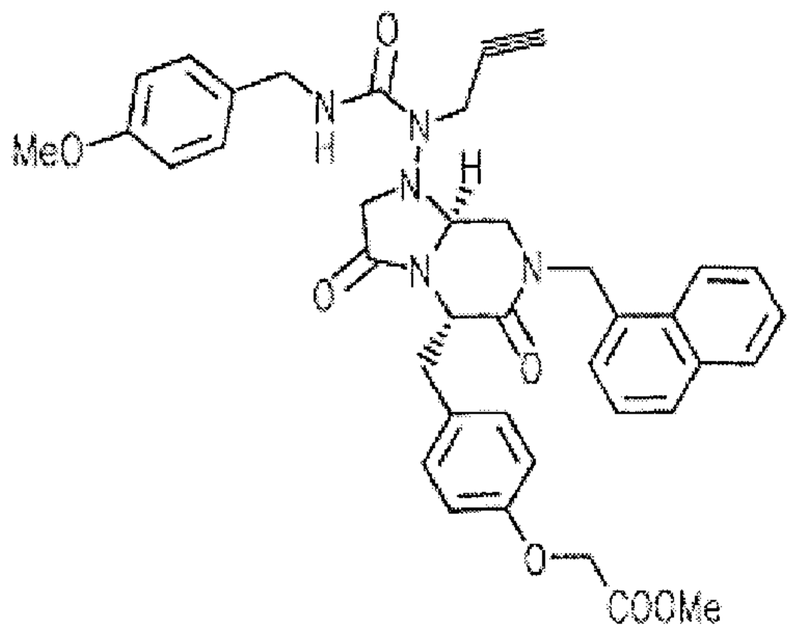
or a pharmaceutically acceptable salt thereof.

348. The compound of claim 1, which is:



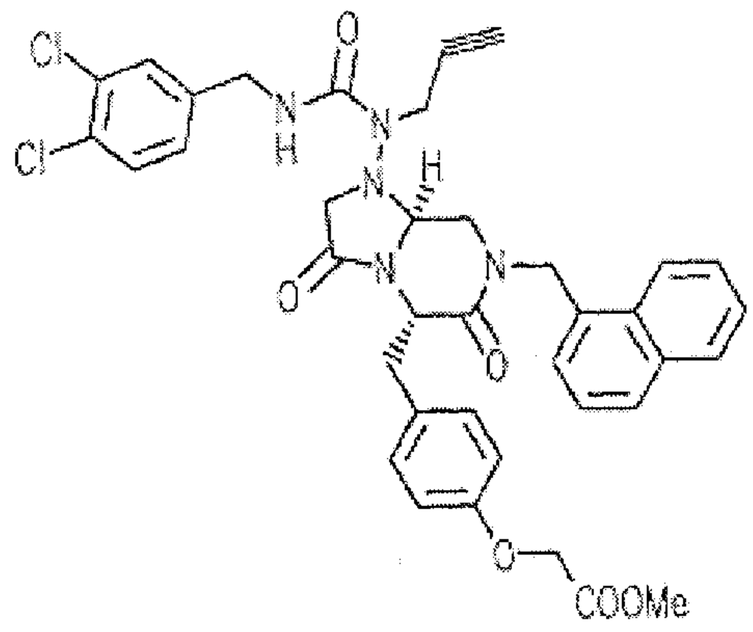
or a pharmaceutically acceptable salt thereof.

349. The compound of claim 1, which is:



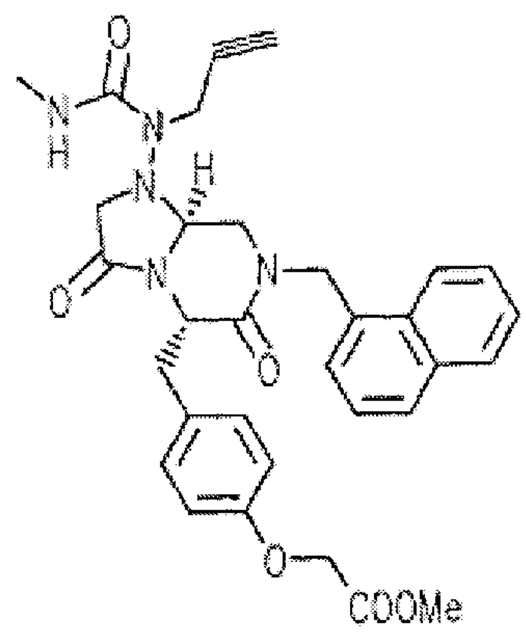
or a pharmaceutically acceptable salt thereof.

350. The compound of claim 1, which is:



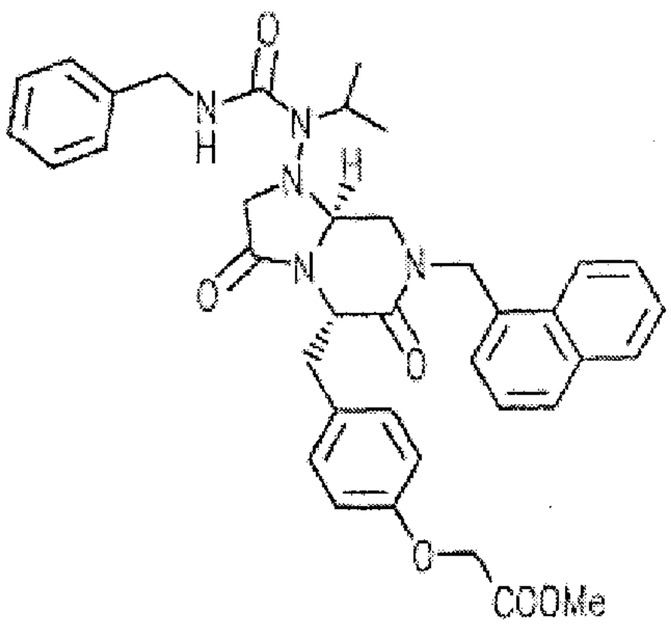
or a pharmaceutically acceptable salt thereof.

351. The compound of claim 1, which is:



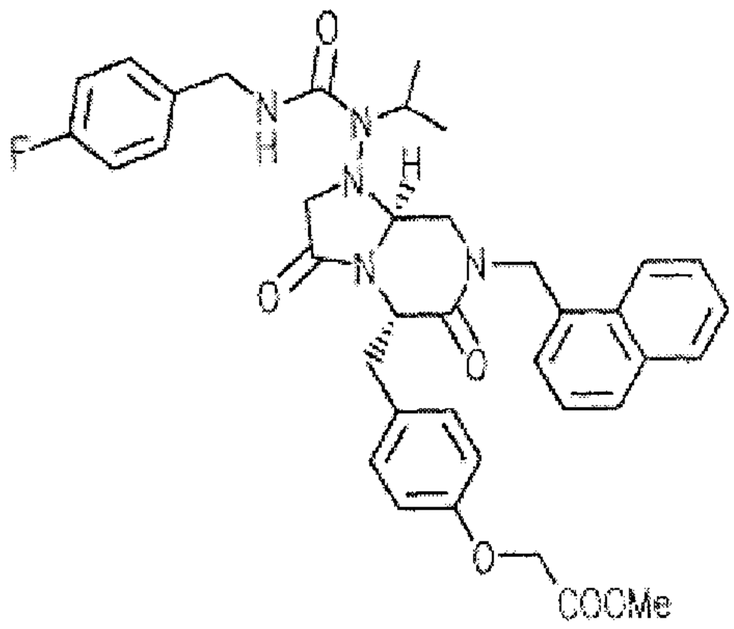
or a pharmaceutically acceptable salt thereof.

352. The compound of claim 1, which is:



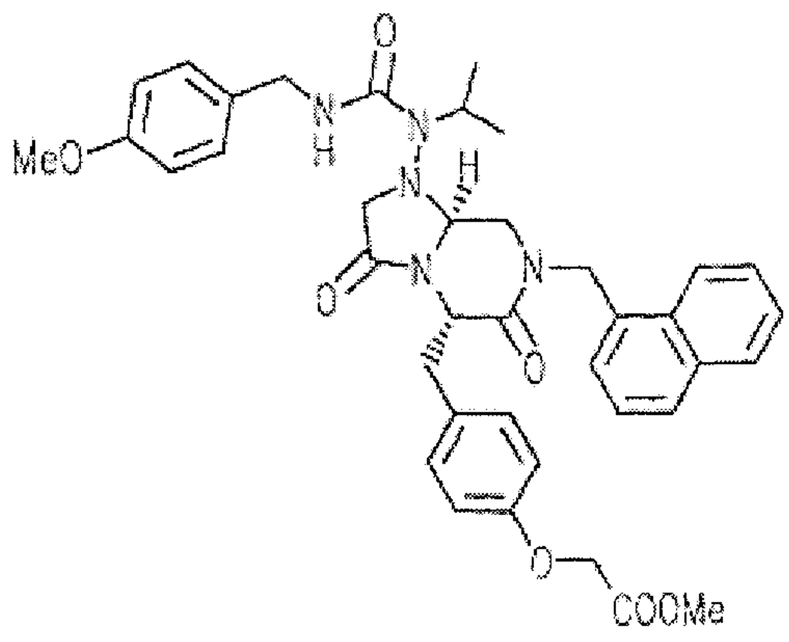
or a pharmaceutically acceptable salt thereof.

353. The compound of claim 1, which is:



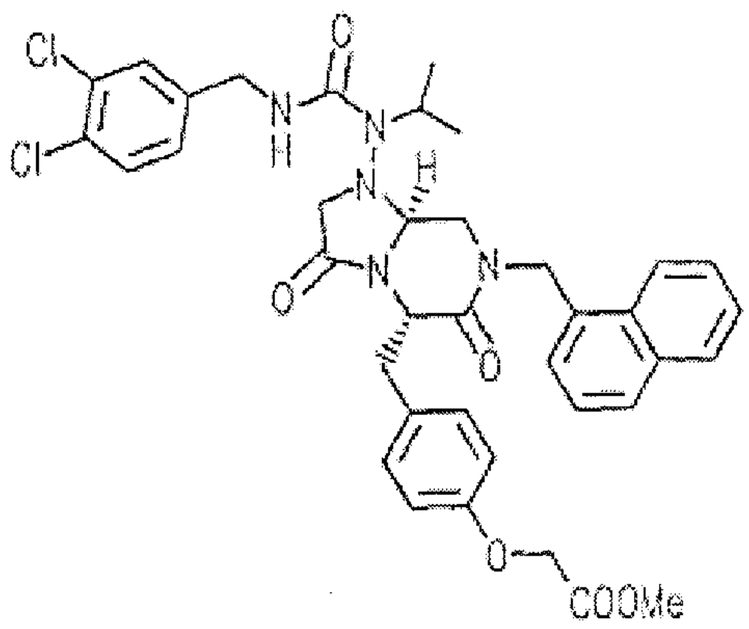
or a pharmaceutically acceptable salt thereof.

354. The compound of claim 1, which is:



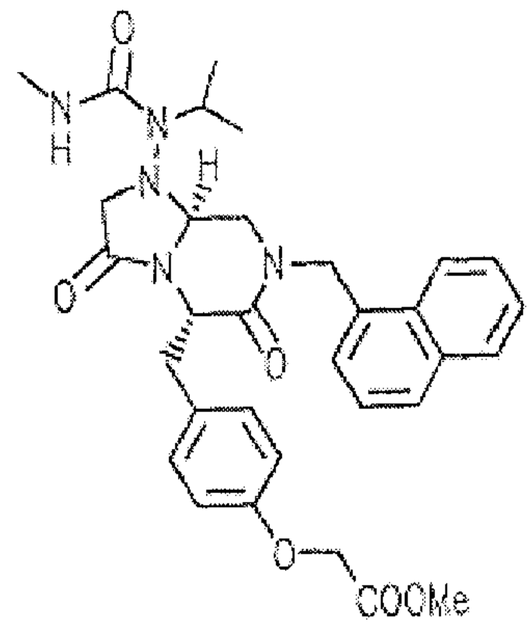
or a pharmaceutically acceptable salt thereof.

355. The compound of claim 1, which is:



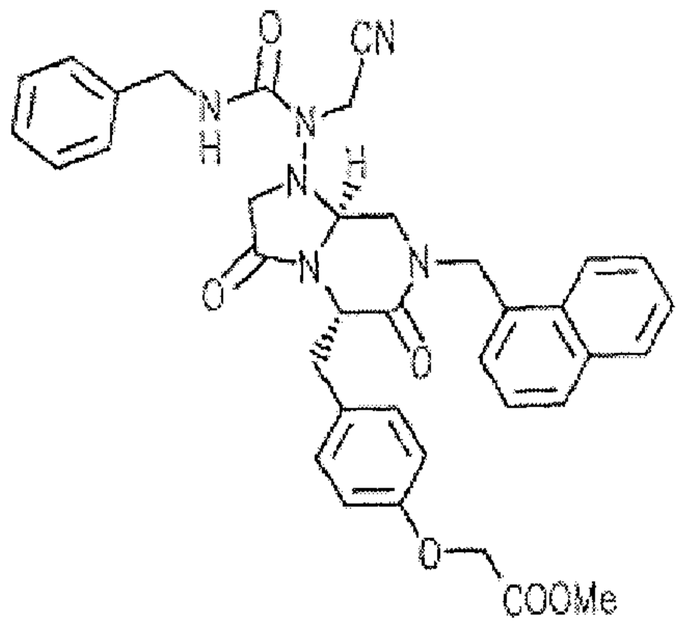
or a pharmaceutically acceptable salt thereof.

356. The compound of claim 1, which is:



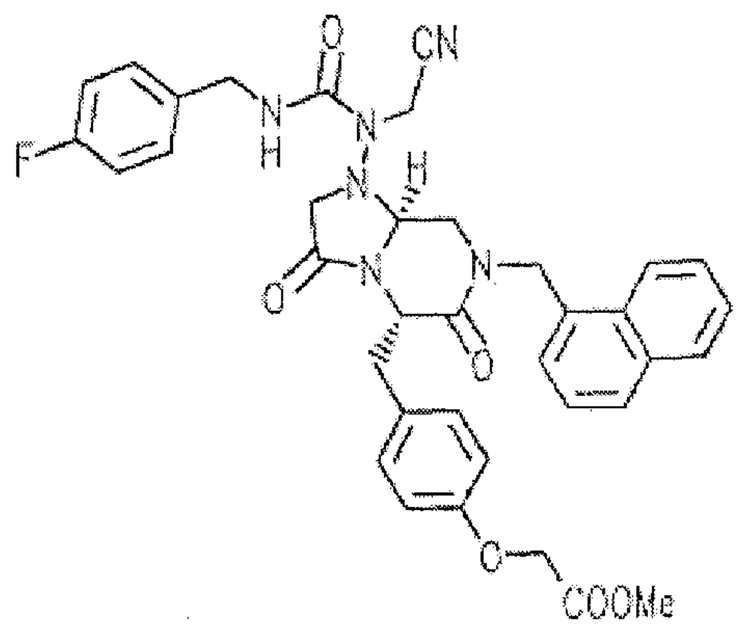
or a pharmaceutically acceptable salt thereof.

357. The compound of claim 1, which is:



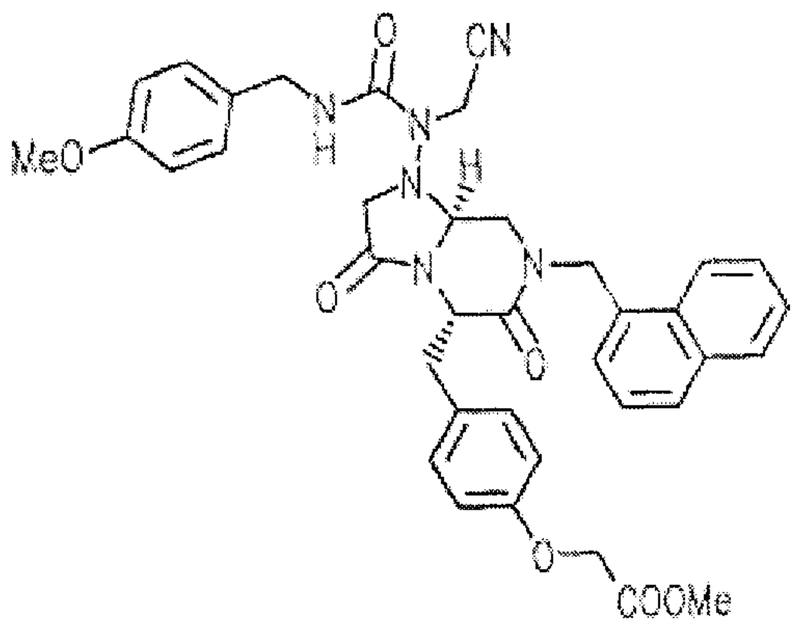
or a pharmaceutically acceptable salt thereof.

358. The compound of claim 1, which is:



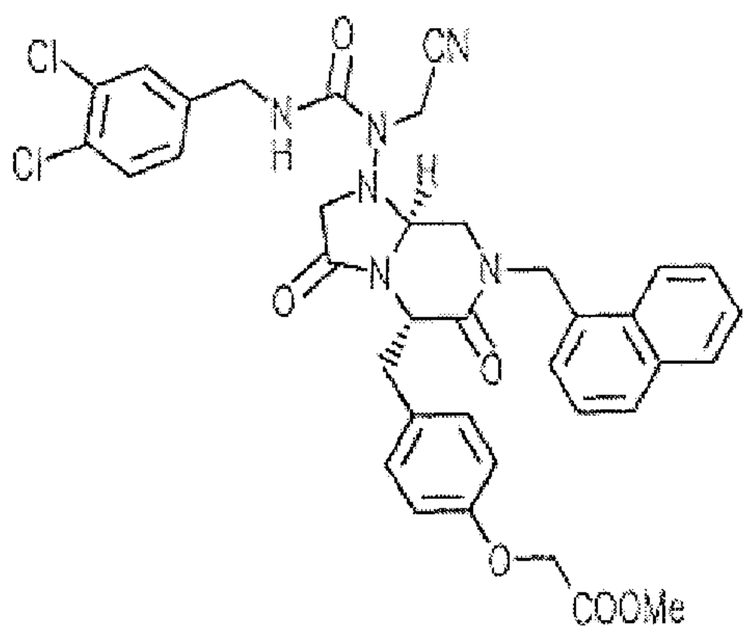
or a pharmaceutically acceptable salt thereof.

359. The compound of claim 1, which is:



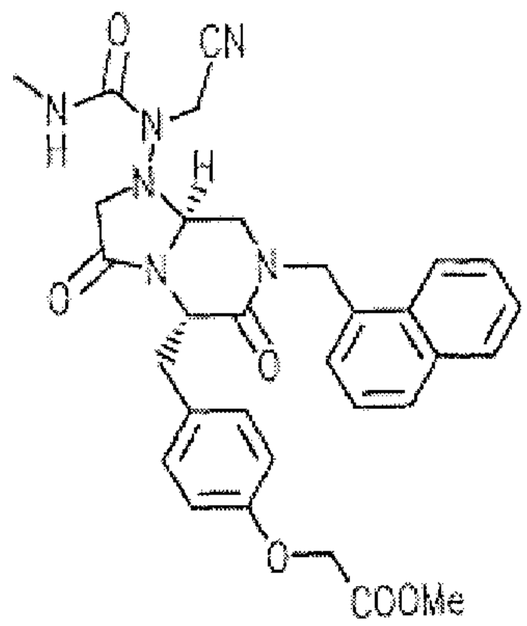
or a pharmaceutically acceptable salt thereof.

360. The compound of claim 1, which is:



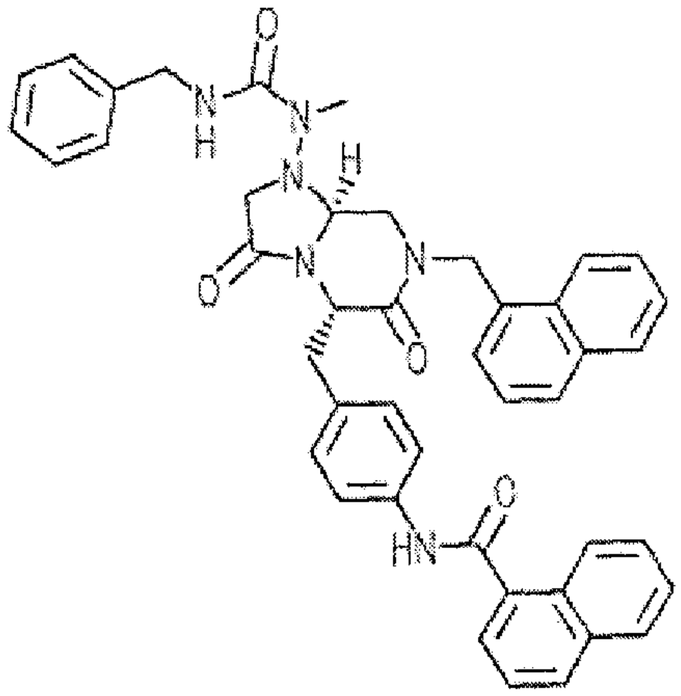
or a pharmaceutically acceptable salt thereof.

361. The compound of claim 1, which is:



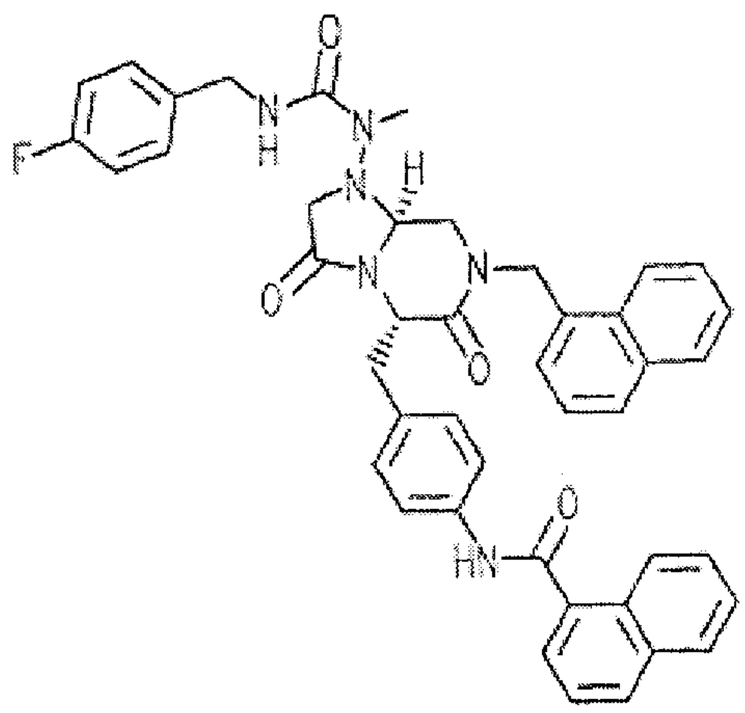
or a pharmaceutically acceptable salt thereof.

362. The compound of claim 1, which is:



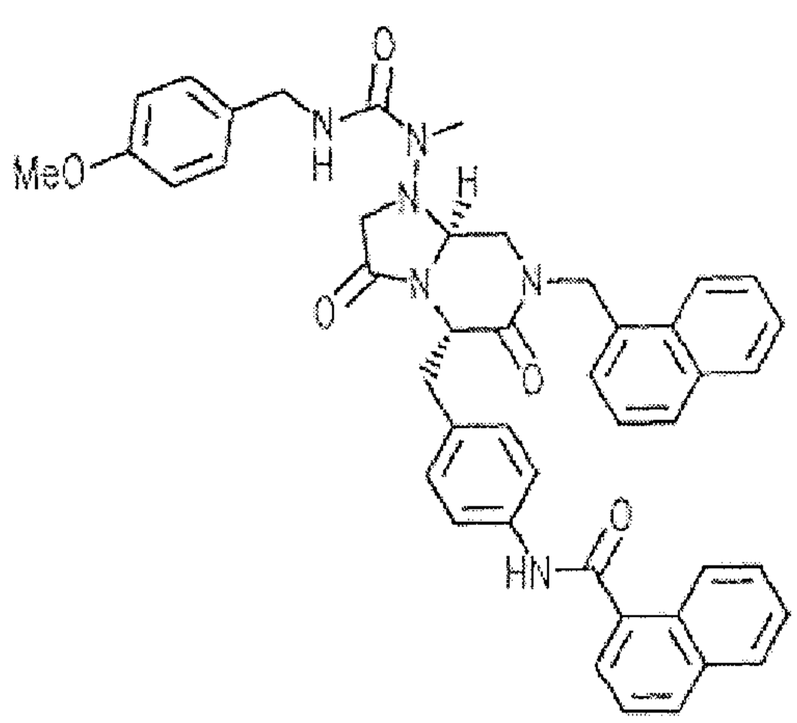
or a pharmaceutically acceptable salt thereof.

363. The compound of claim 1, which is:



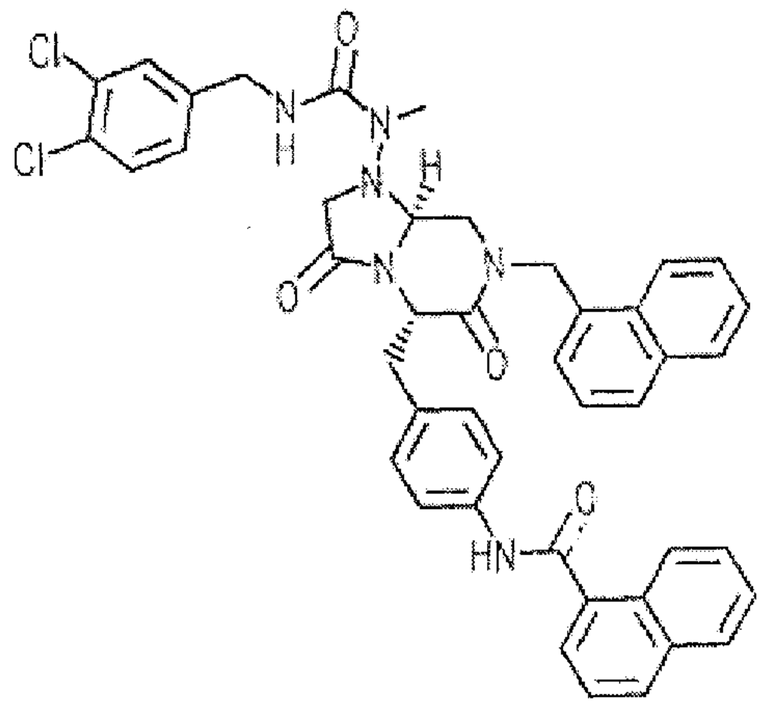
or a pharmaceutically acceptable salt thereof.

364. The compound of claim 1, which is:



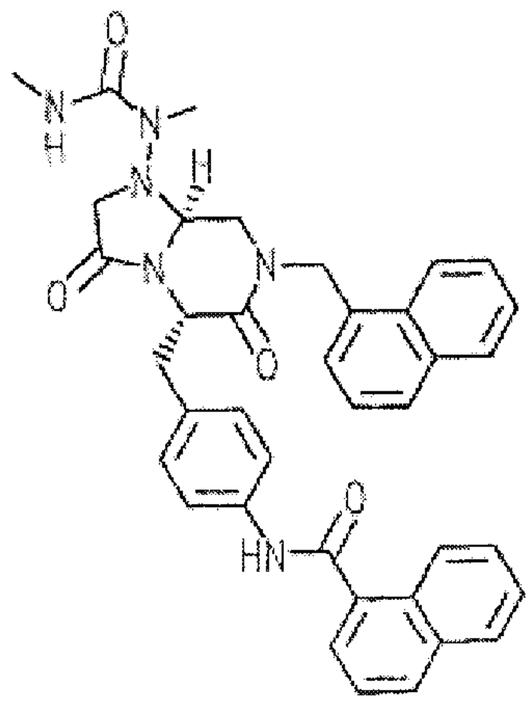
or a pharmaceutically acceptable salt thereof.

365. The compound of claim 1, which is:



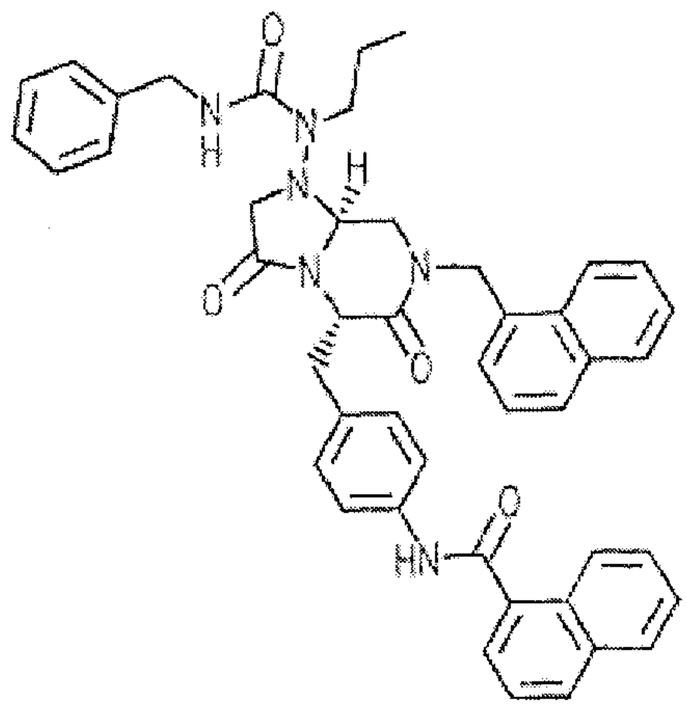
or a pharmaceutically acceptable salt thereof.

366. The compound of claim 1, which is:



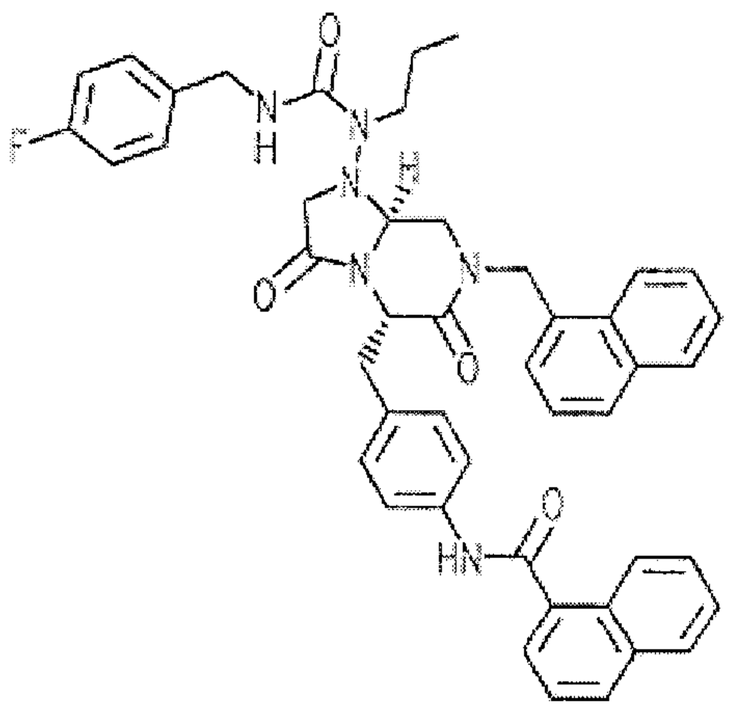
or a pharmaceutically acceptable salt thereof.

367. The compound of claim 1, which is:



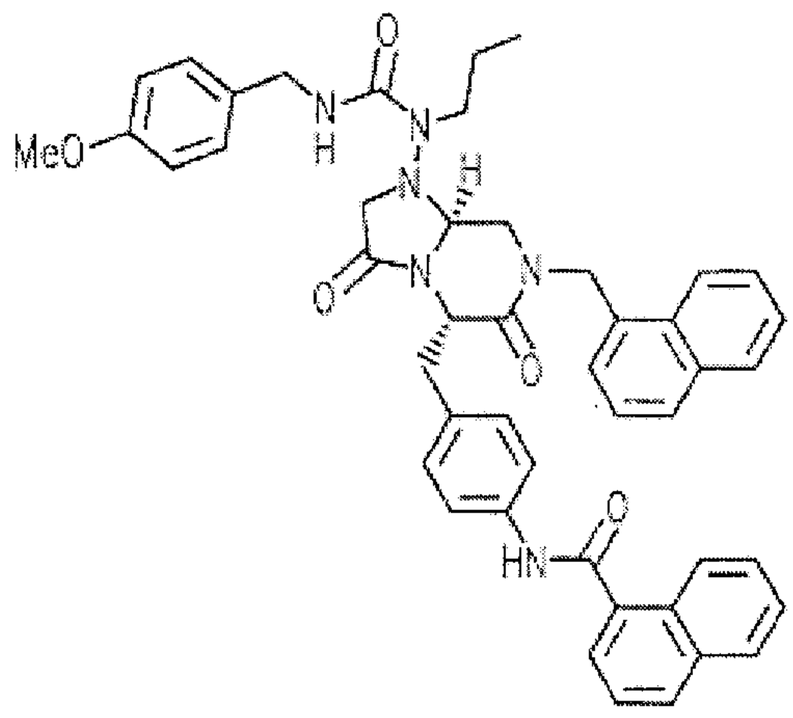
or a pharmaceutically acceptable salt thereof.

368. The compound of claim 1, which is:



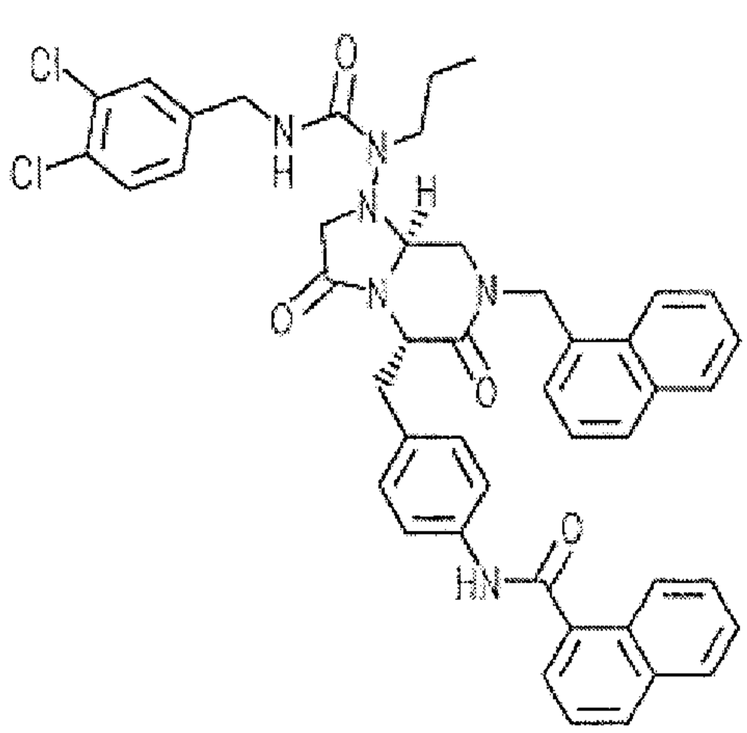
or a pharmaceutically acceptable salt thereof.

369. The compound of claim 1, which is:



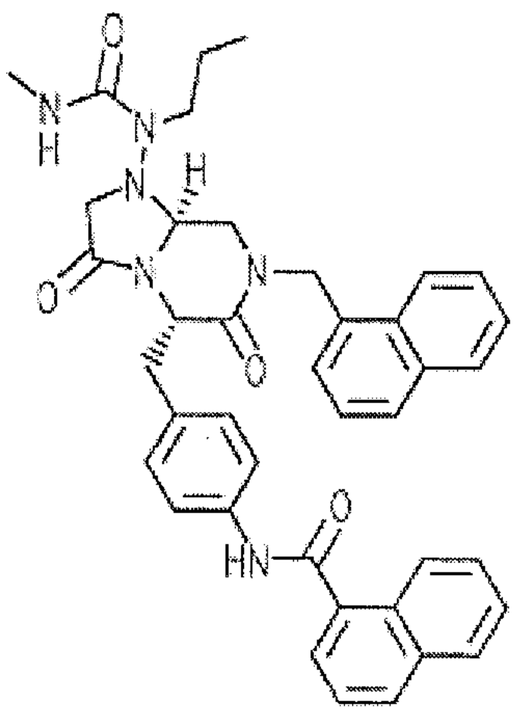
or a pharmaceutically acceptable salt thereof.

370. The compound of claim 1, which is:



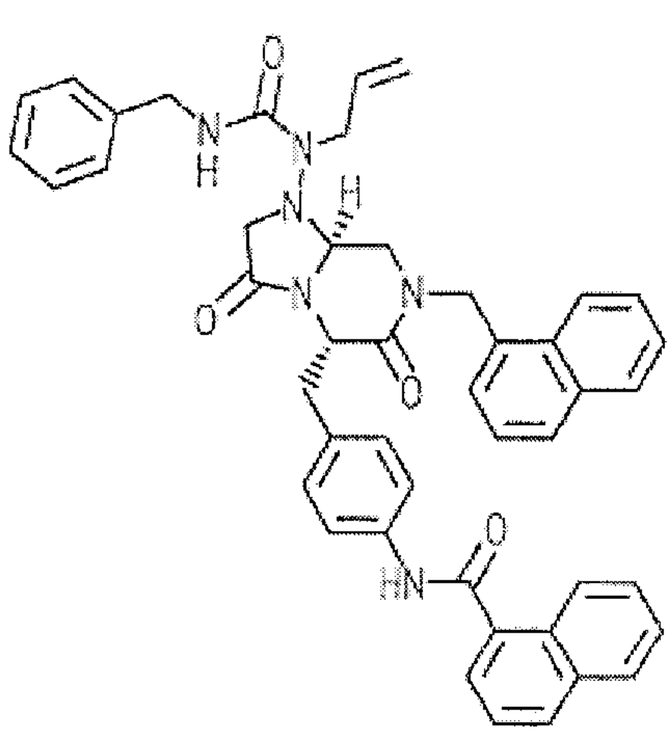
or a pharmaceutically acceptable salt thereof.

371. The compound of claim 1, which is:



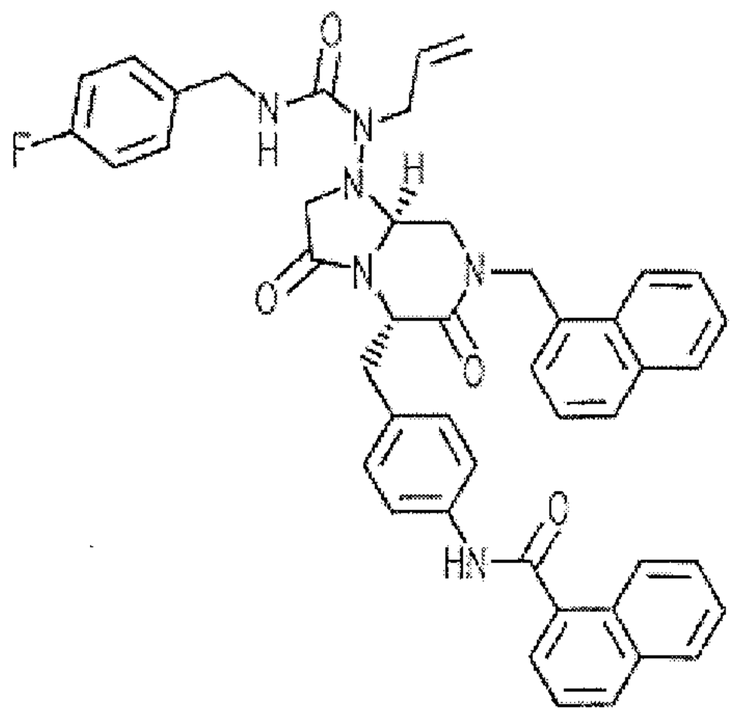
or a pharmaceutically acceptable salt thereof.

372. The compound of claim 1, which is:



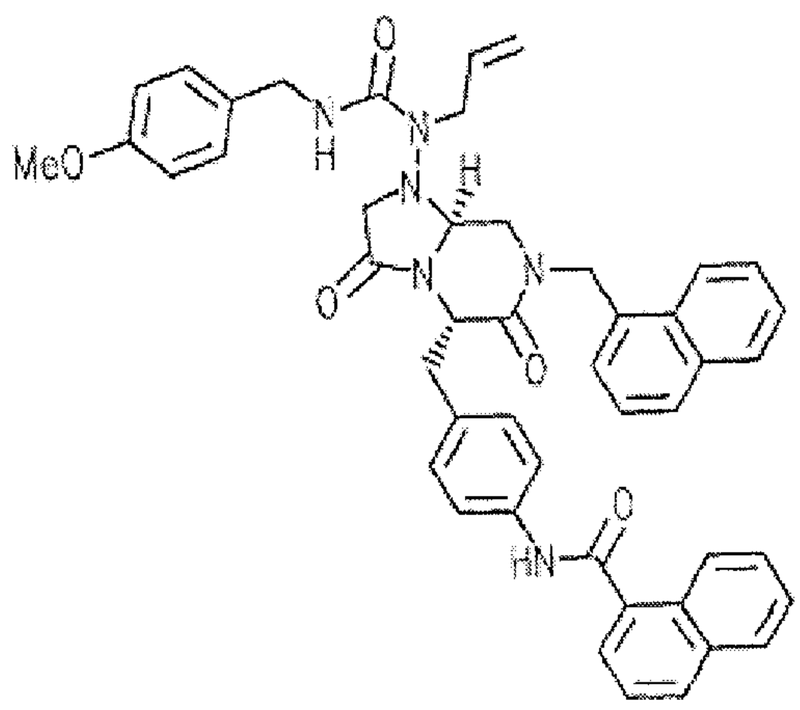
or a pharmaceutically acceptable salt thereof.

373. The compound of claim 1, which is:



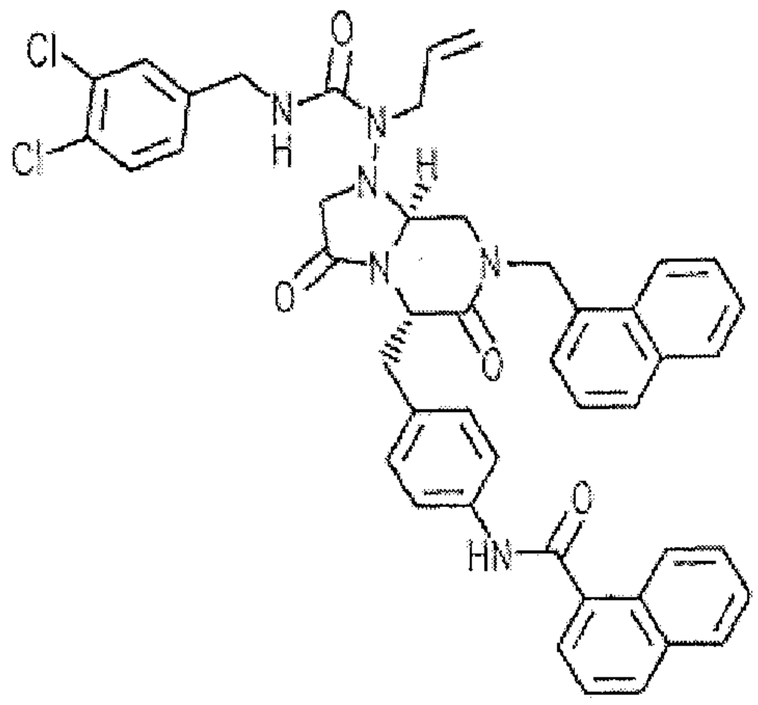
or a pharmaceutically acceptable salt thereof.

374. The compound of claim 1, which is:



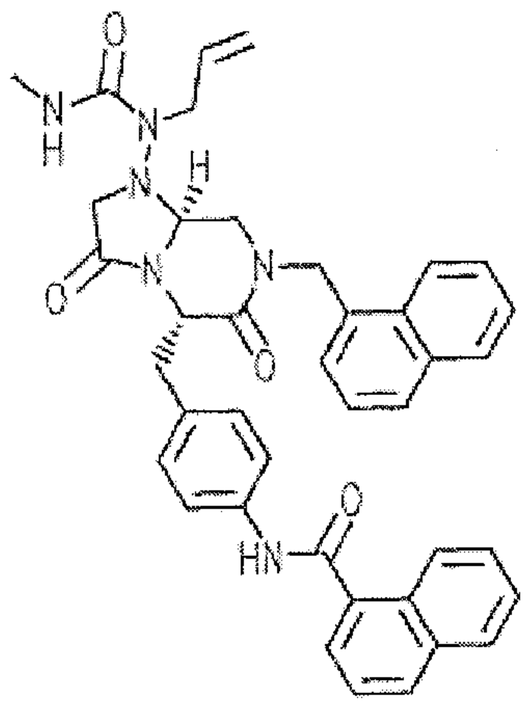
or a pharmaceutically acceptable salt thereof.

375. The compound of claim 1, which is:



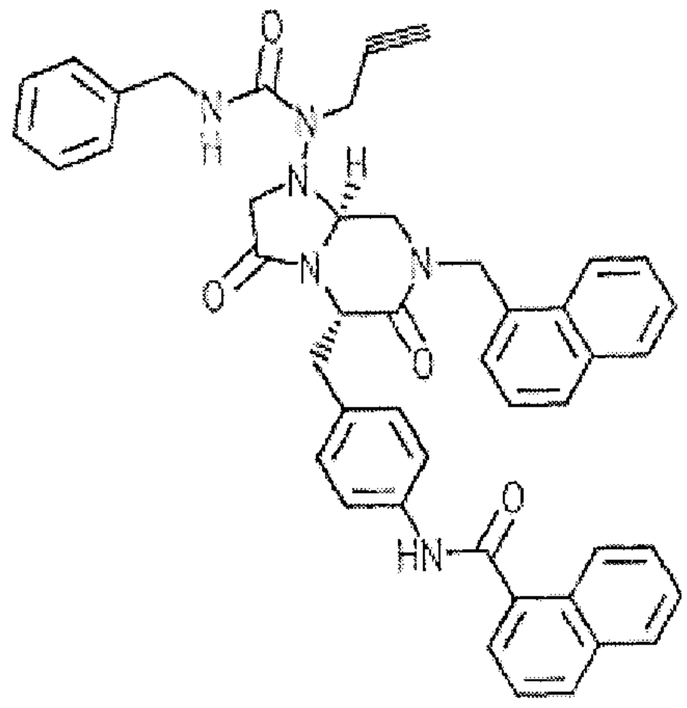
or a pharmaceutically acceptable salt thereof.

376. The compound of claim 1, which is:



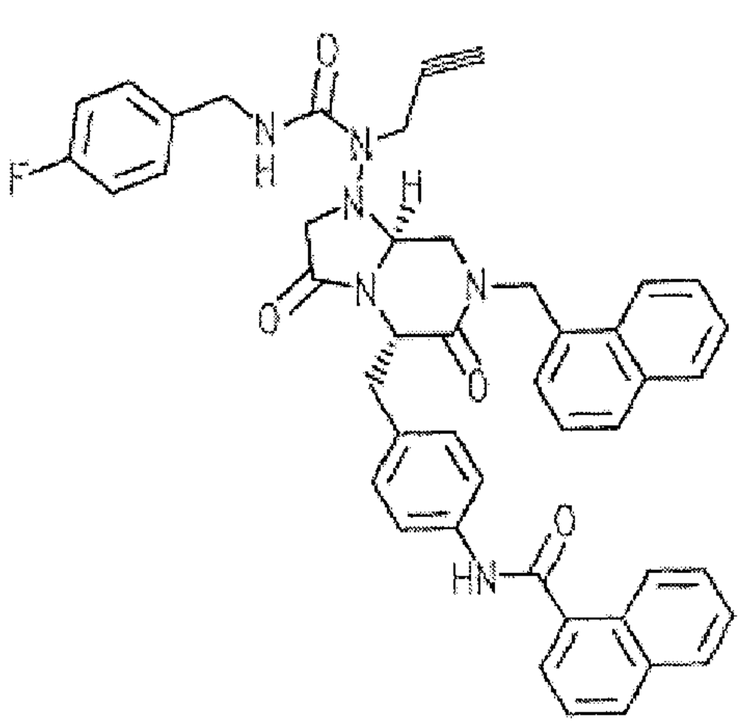
or a pharmaceutically acceptable salt thereof.

377. The compound of claim 1, which is:



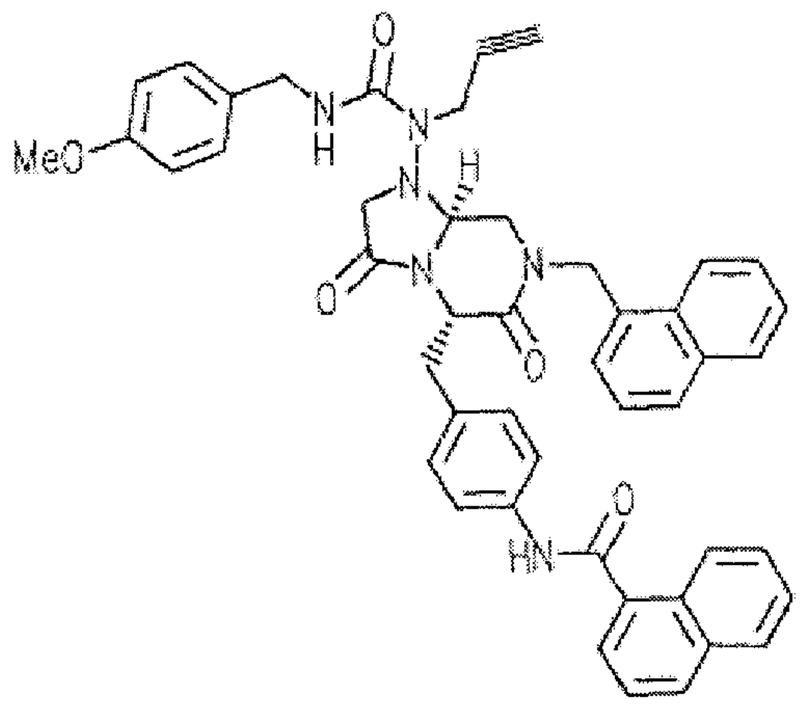
or a pharmaceutically acceptable salt thereof.

378. The compound of claim 1, which is:



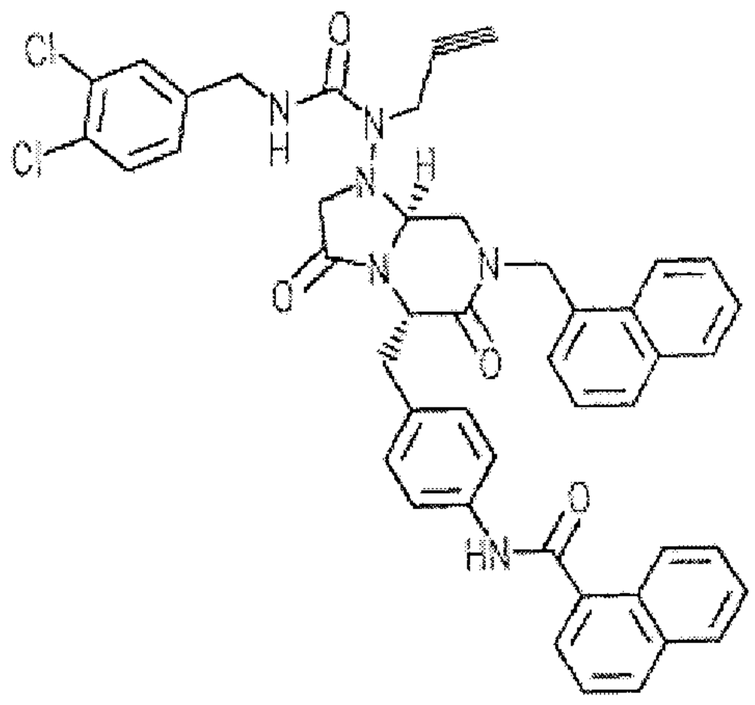
or a pharmaceutically acceptable salt thereof.

379. The compound of claim 1, which is:



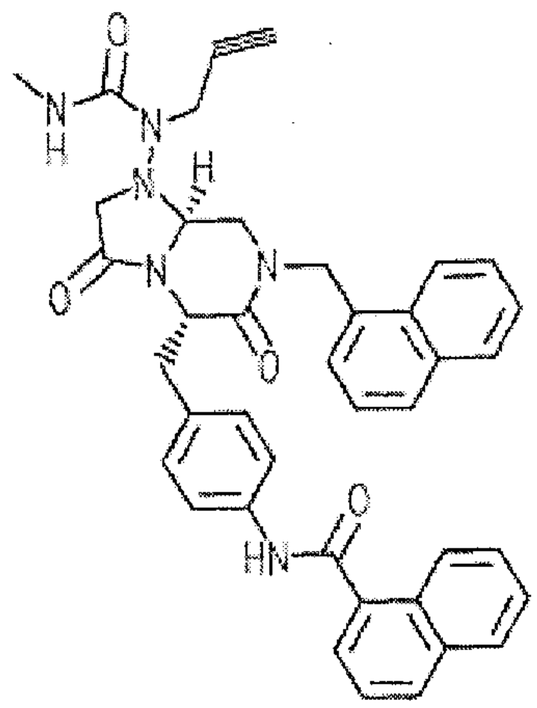
or a pharmaceutically acceptable salt thereof.

380. The compound of claim 1, which is:



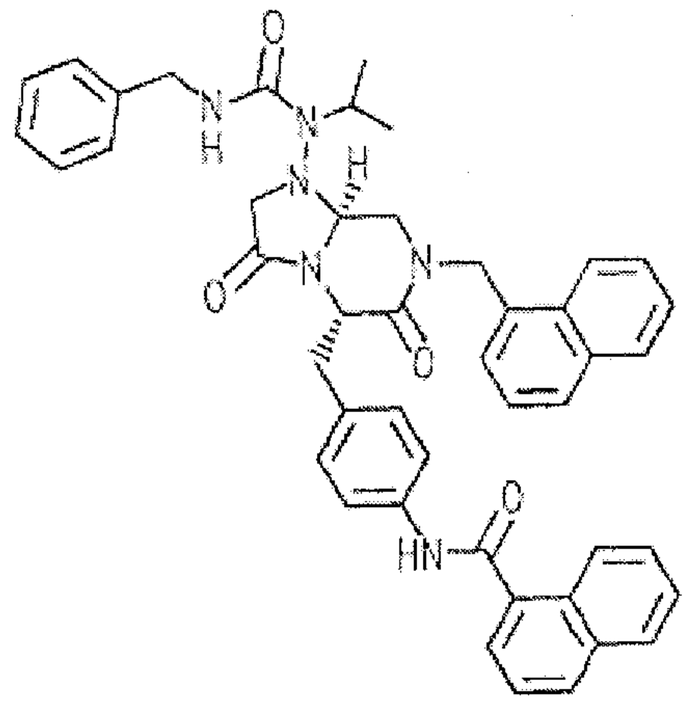
or a pharmaceutically acceptable salt thereof.

381. The compound of claim 1, which is:



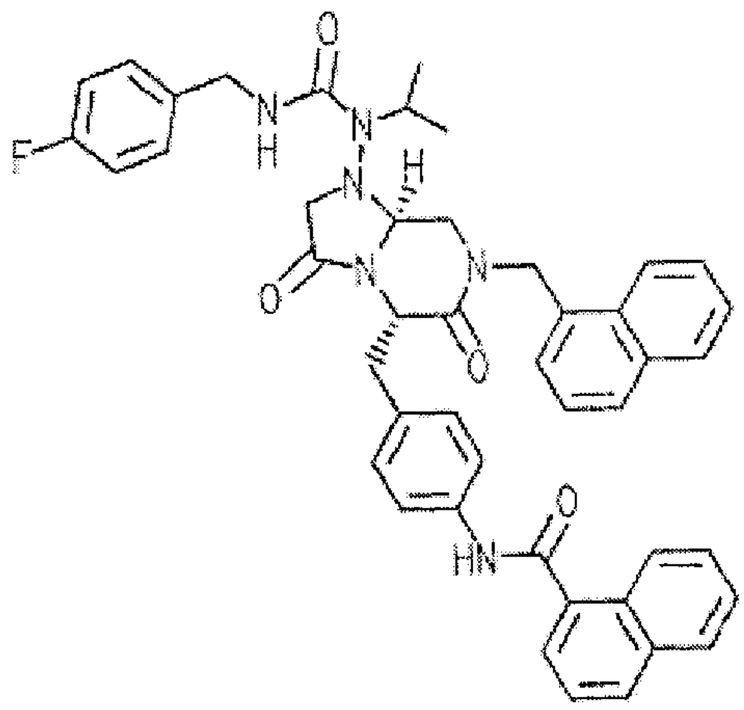
or a pharmaceutically acceptable salt thereof.

382. The compound of claim 1, which is:



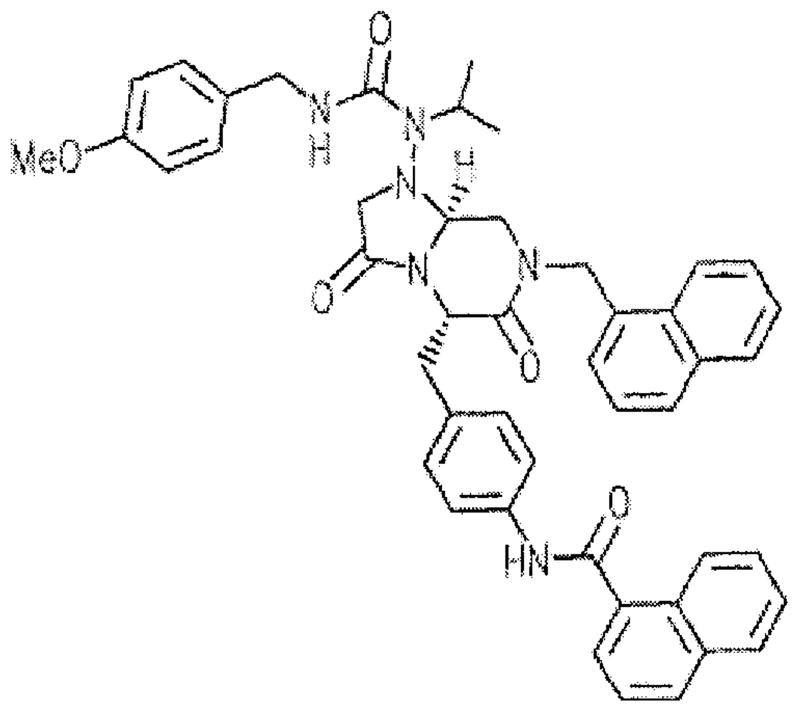
or a pharmaceutically acceptable salt thereof.

383. The compound of claim 1, which is:



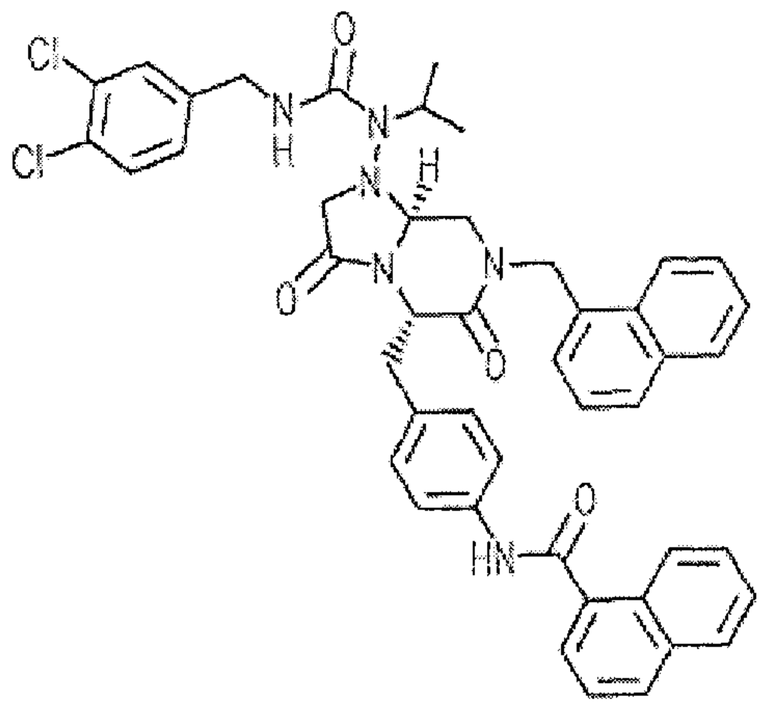
or a pharmaceutically acceptable salt thereof.

384. The compound of claim 1, which is:



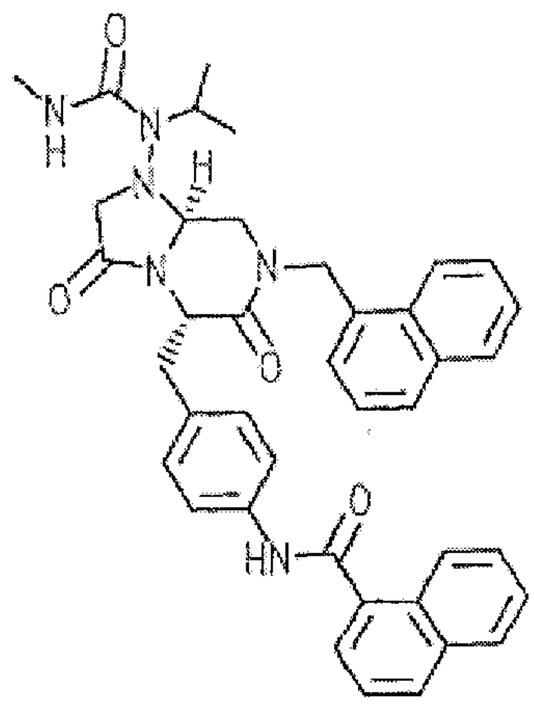
or a pharmaceutically acceptable salt thereof.

385. The compound of claim 1, which is:



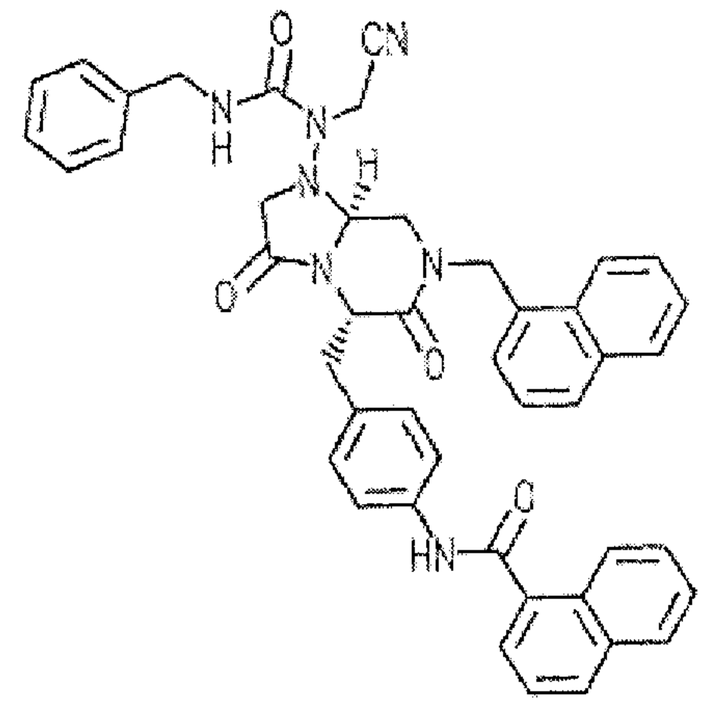
or a pharmaceutically acceptable salt thereof.

386. The compound of claim 1, which is:



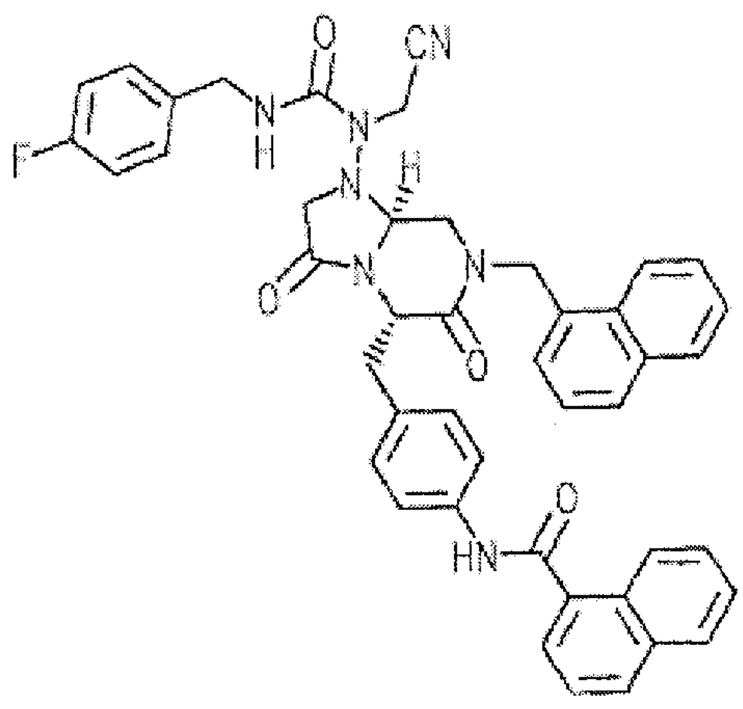
or a pharmaceutically acceptable salt thereof.

387. The compound of claim 1, which is:



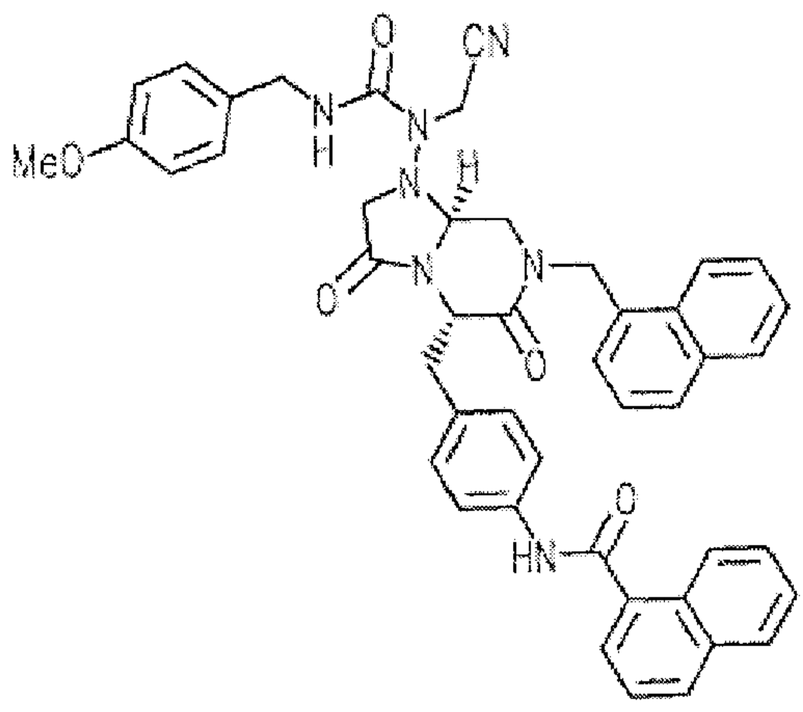
or a pharmaceutically acceptable salt thereof.

388. The compound of claim 1, which is:



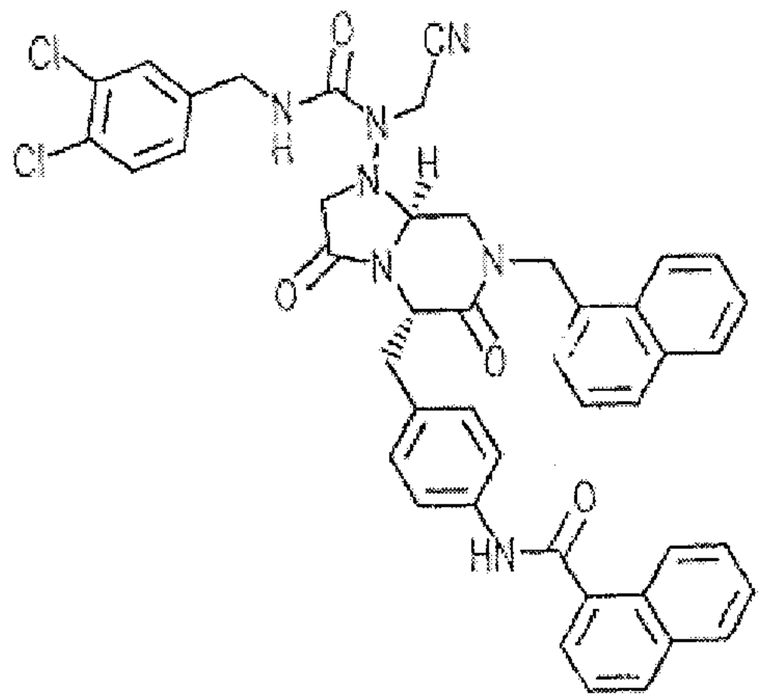
or a pharmaceutically acceptable salt thereof.

389. The compound of claim 1, which is:



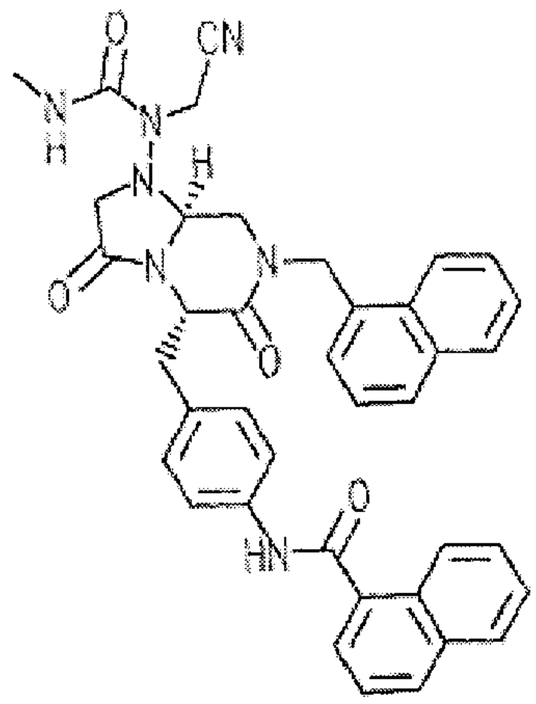
or a pharmaceutically acceptable salt thereof.

390. The compound of claim 1, which is:



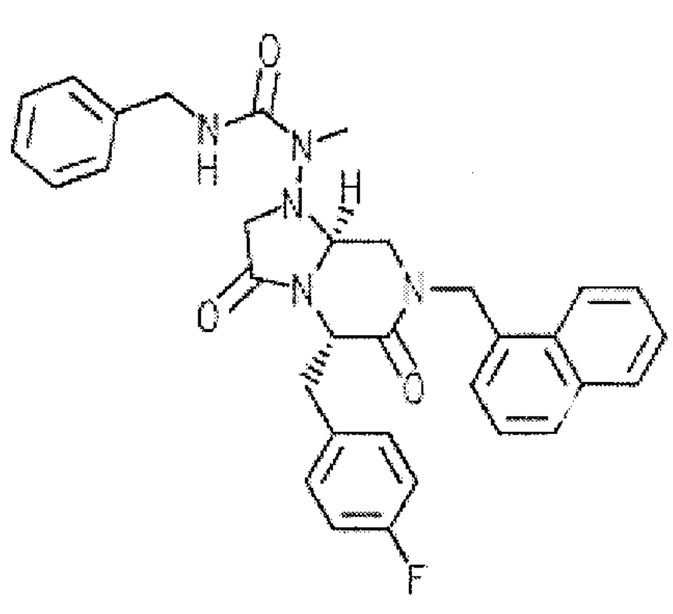
or a pharmaceutically acceptable salt thereof.

391. The compound of claim 1, which is:



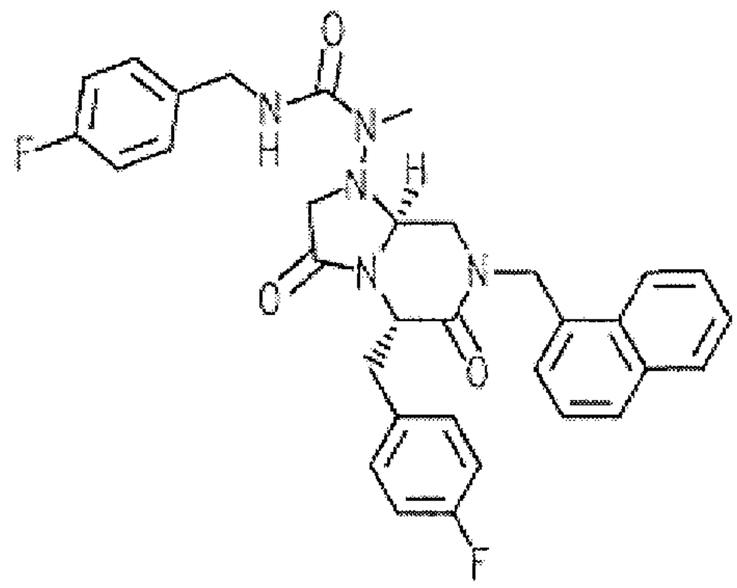
or a pharmaceutically acceptable salt thereof.

392. The compound of claim 1, which is:



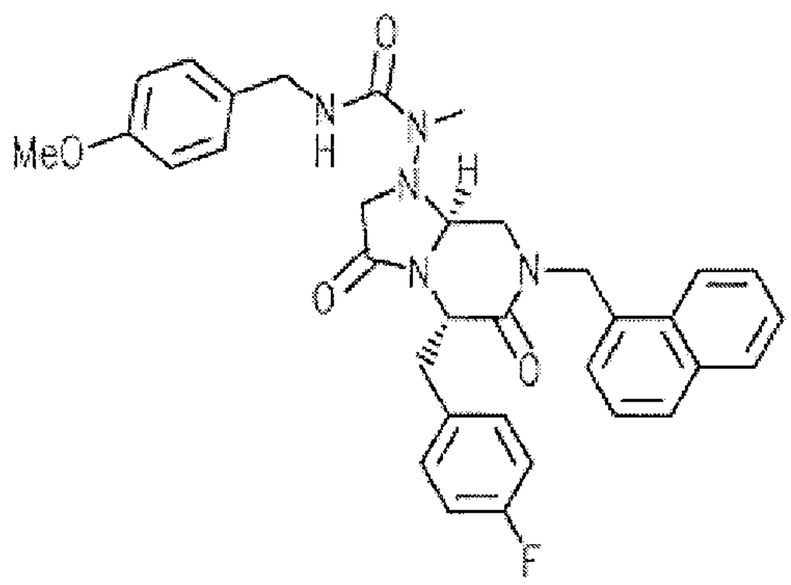
or a pharmaceutically acceptable salt thereof.

393. The compound of claim 1, which is:



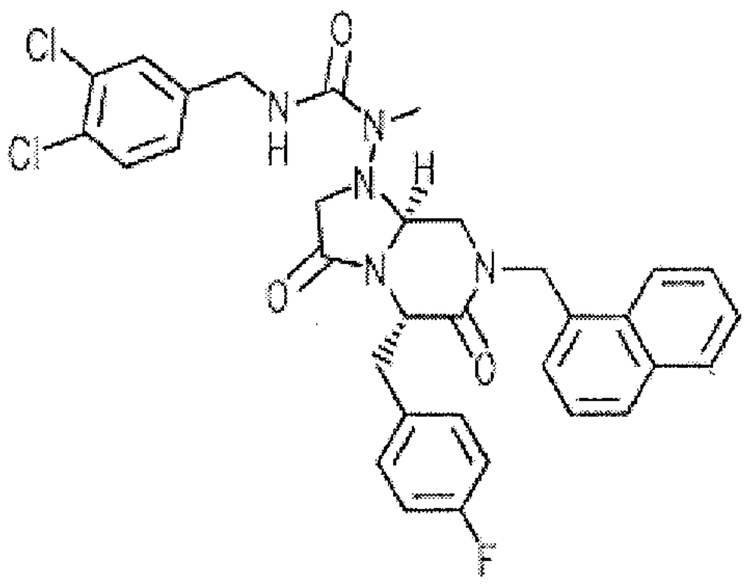
or a pharmaceutically acceptable salt thereof.

394. The compound of claim 1, which is:



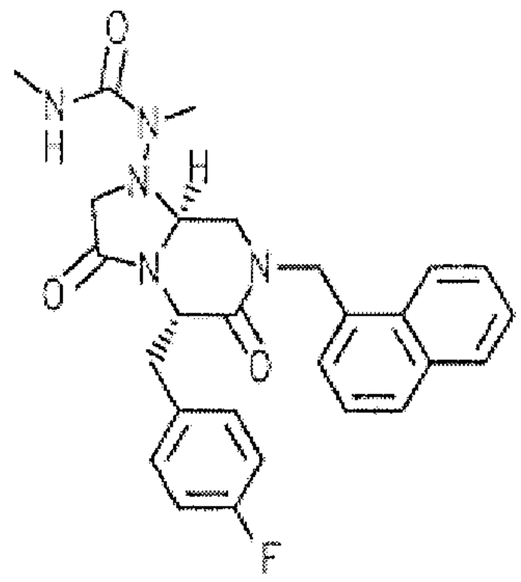
or a pharmaceutically acceptable salt thereof.

395. The compound of claim 1, which is:



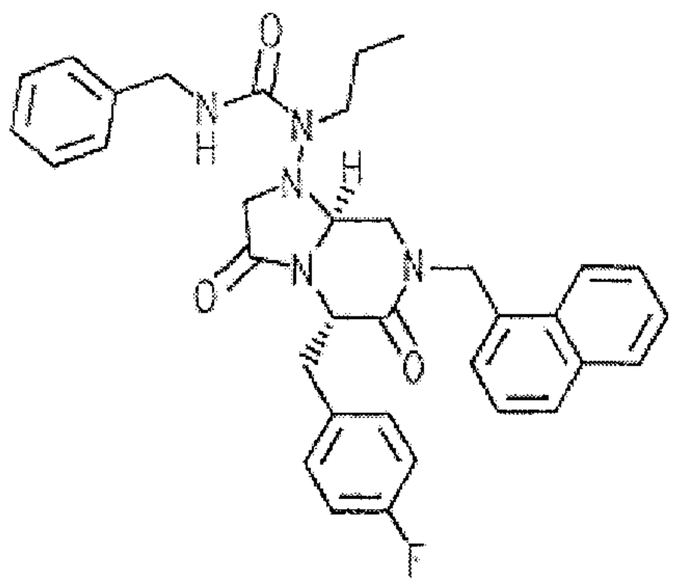
or a pharmaceutically acceptable salt thereof.

396. The compound of claim 1, which is:



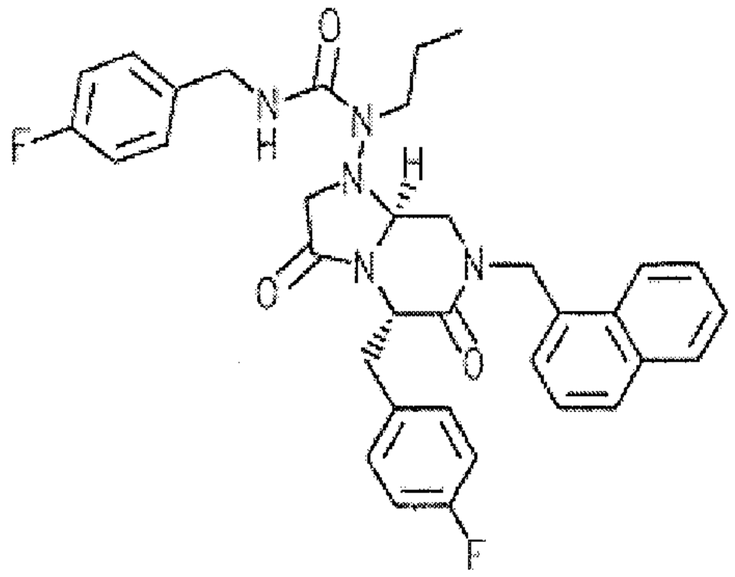
or a pharmaceutically acceptable salt thereof.

397. The compound of claim 1, which is:



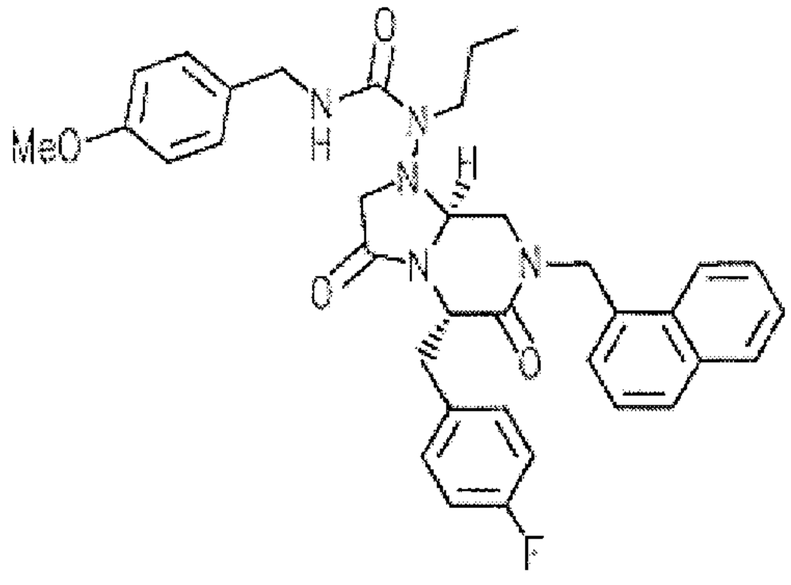
or a pharmaceutically acceptable salt thereof.

398. The compound of claim 1, which is:



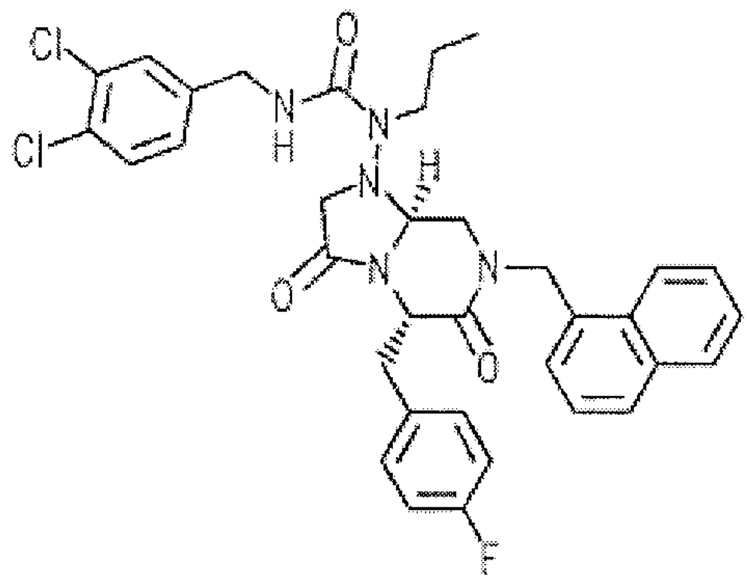
or a pharmaceutically acceptable salt thereof.

399. The compound of claim 1, which is:



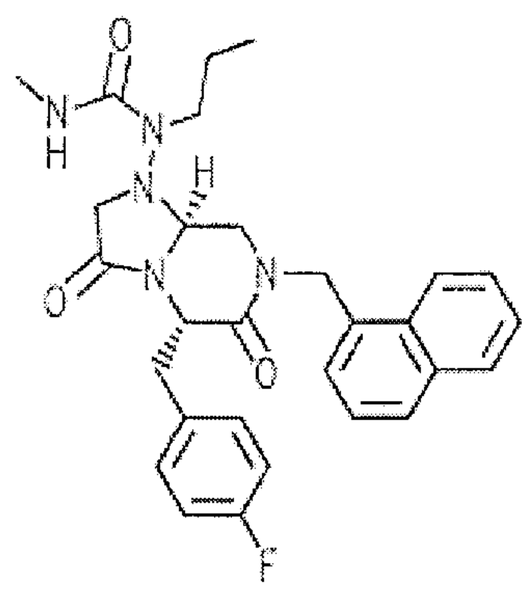
or a pharmaceutically acceptable salt thereof.

400. The compound of claim 1, which is:



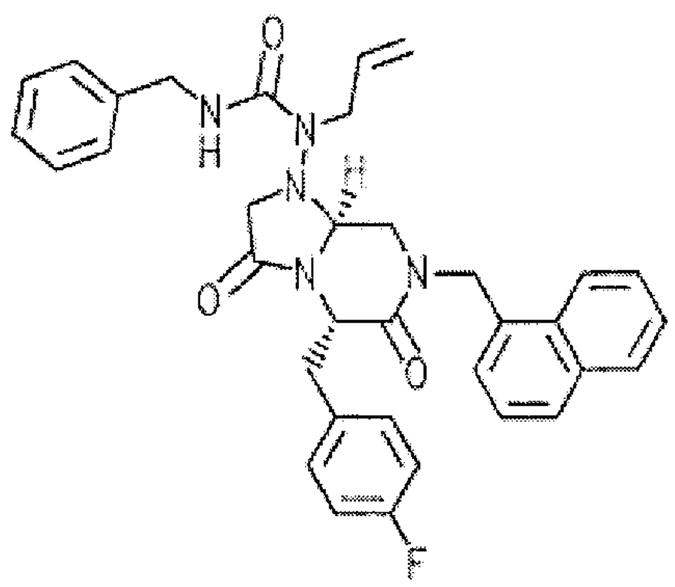
or a pharmaceutically acceptable salt thereof.

401. The compound of claim 1, which is:



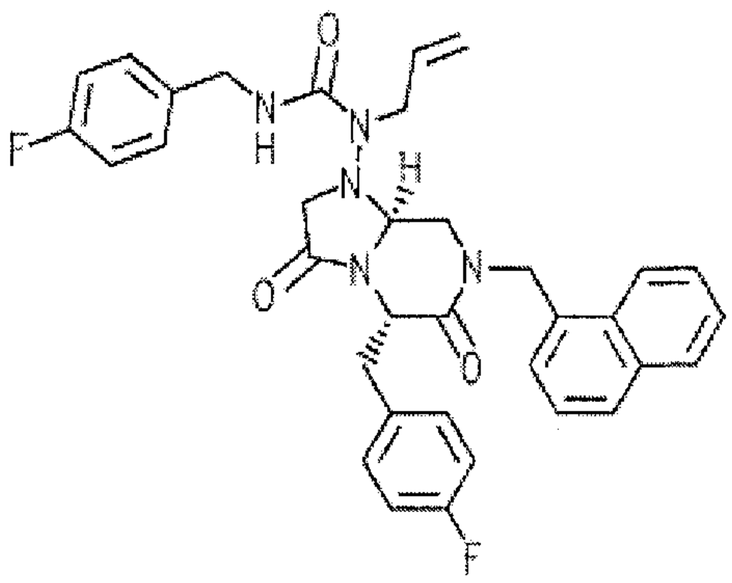
or a pharmaceutically acceptable salt thereof.

402. The compound of claim 1, which is:



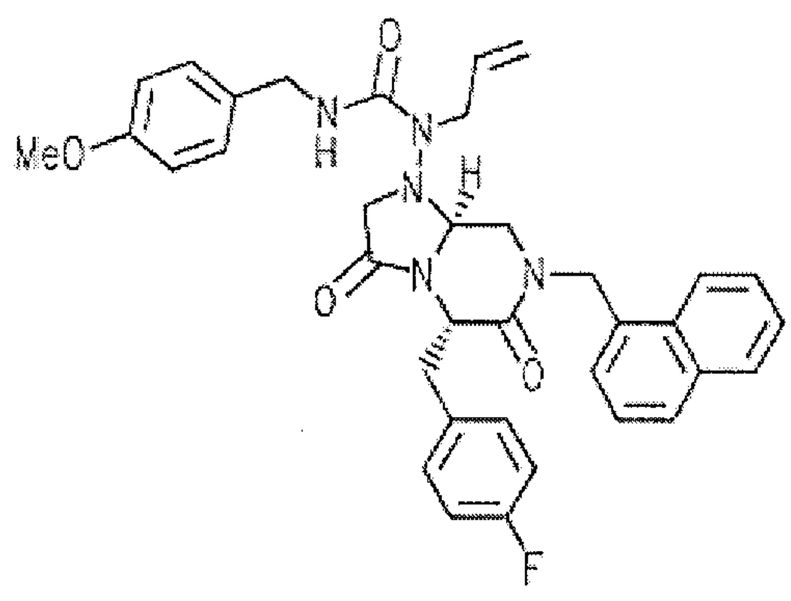
or a pharmaceutically acceptable salt thereof.

403. The compound of claim 1, which is:



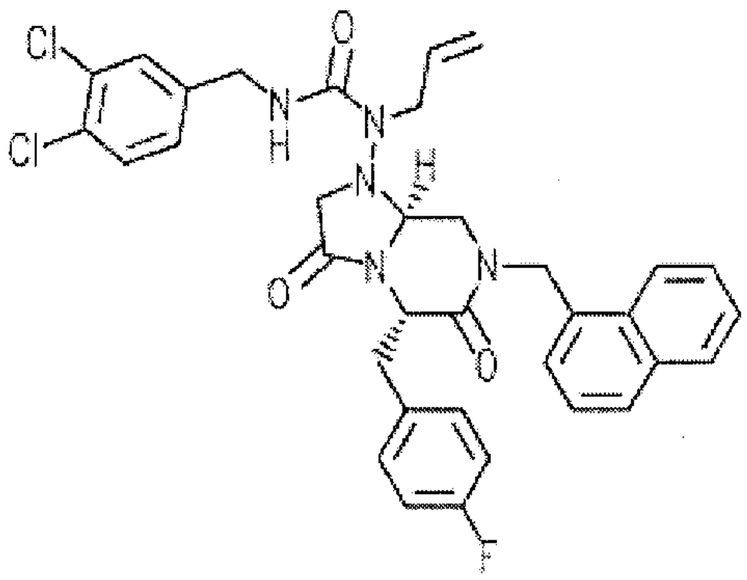
or a pharmaceutically acceptable salt thereof.

404. The compound of claim 1, which is:



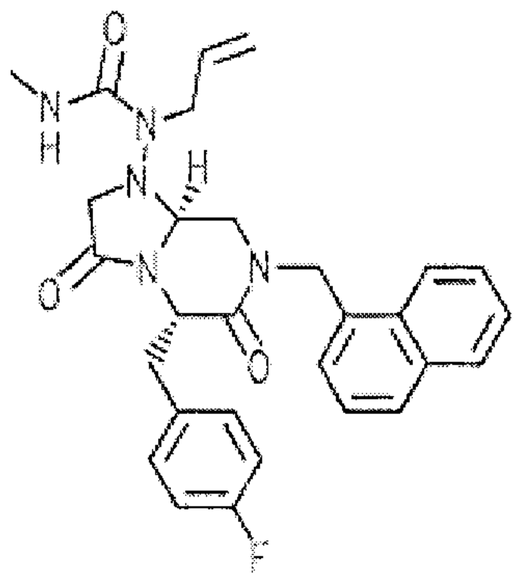
or a pharmaceutically acceptable salt thereof.

405. The compound of claim 1, which is:



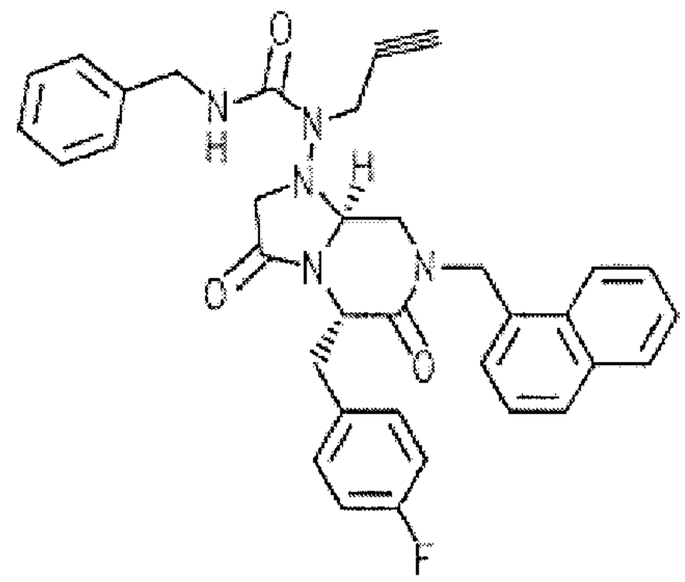
or a pharmaceutically acceptable salt thereof.

406. The compound of claim 1, which is:



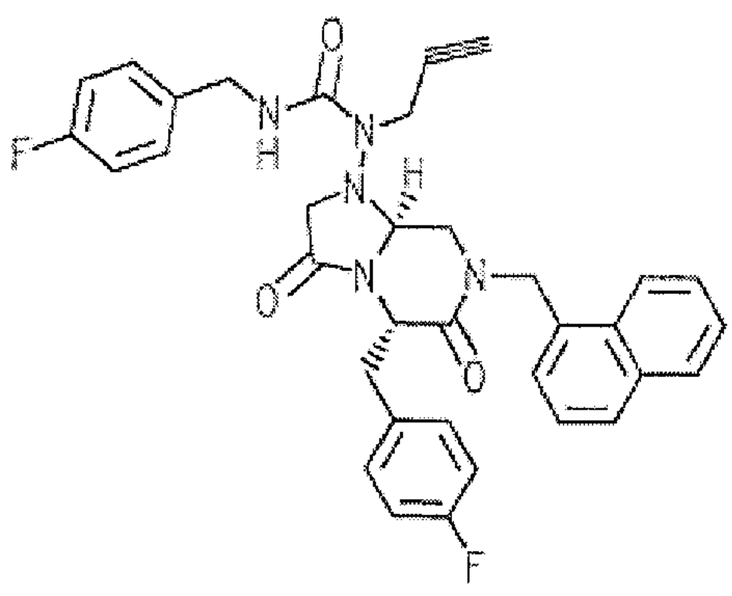
or a pharmaceutically acceptable salt thereof.

407. The compound of claim 1, which is:



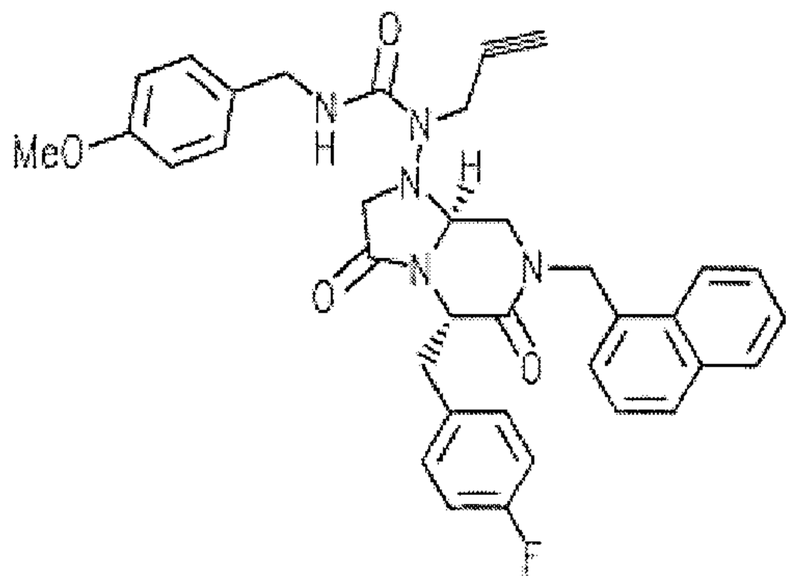
or a pharmaceutically acceptable salt thereof.

408. The compound of claim 1, which is:



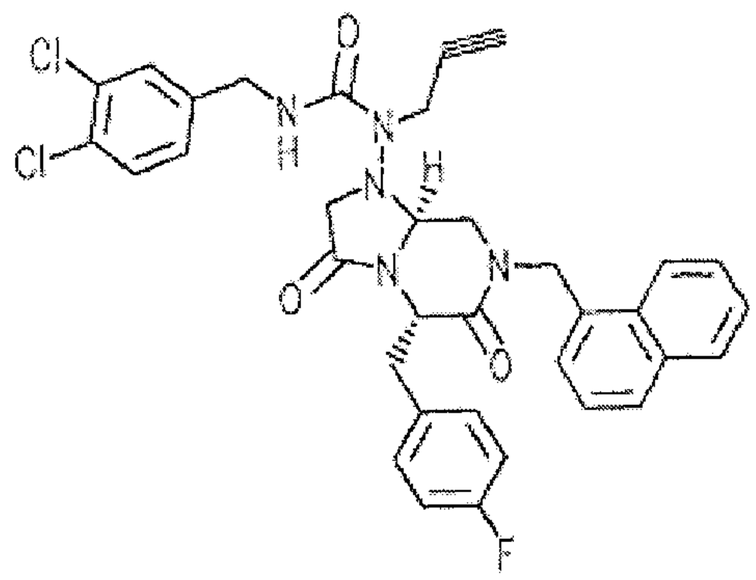
or a pharmaceutically acceptable salt thereof.

409. The compound of claim 1, which is:



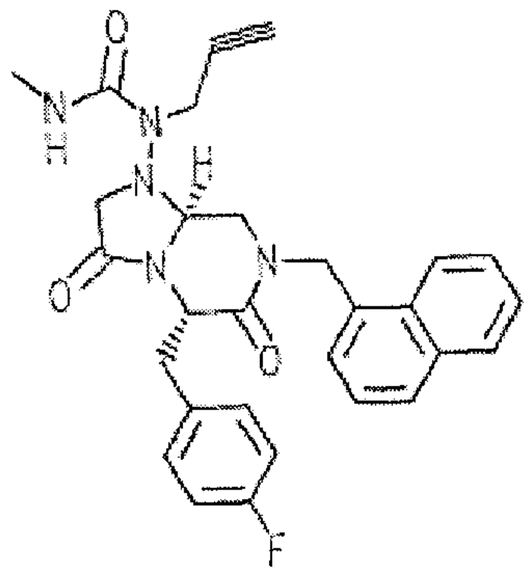
or a pharmaceutically acceptable salt thereof.

410. The compound of claim 1, which is:



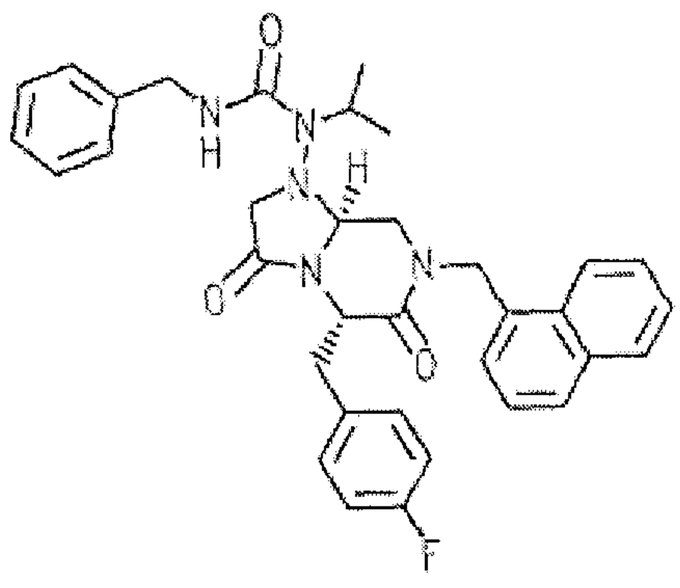
or a pharmaceutically acceptable salt thereof.

411. The compound of claim 1, which is:



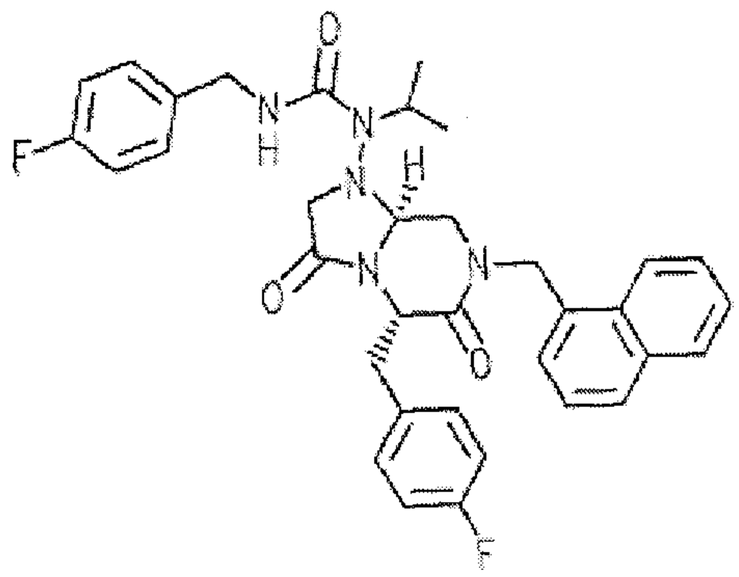
or a pharmaceutically acceptable salt thereof.

412. The compound of claim 1, which is:



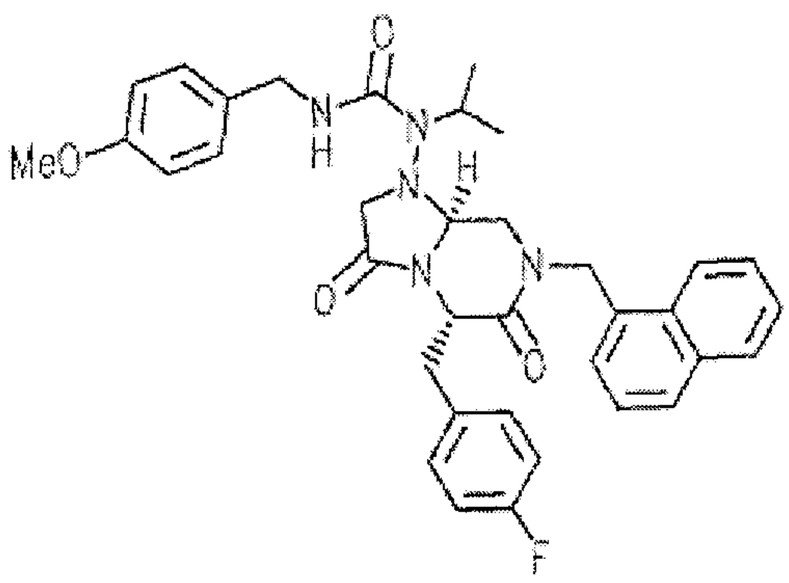
or a pharmaceutically acceptable salt thereof.

413. The compound of claim 1, which is:



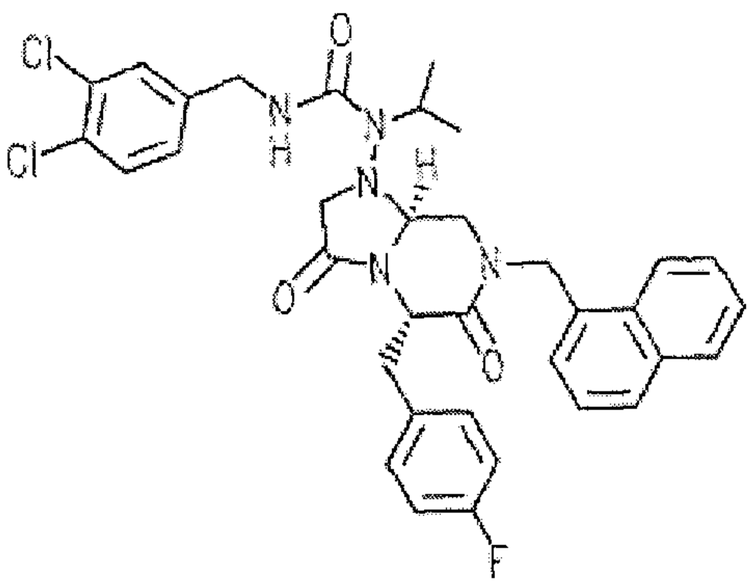
or a pharmaceutically acceptable salt thereof.

414. The compound of claim 1, which is:



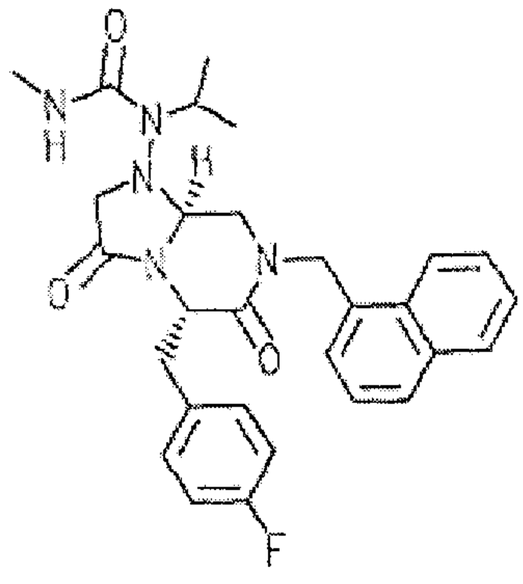
or a pharmaceutically acceptable salt thereof.

415. The compound of claim 1, which is:



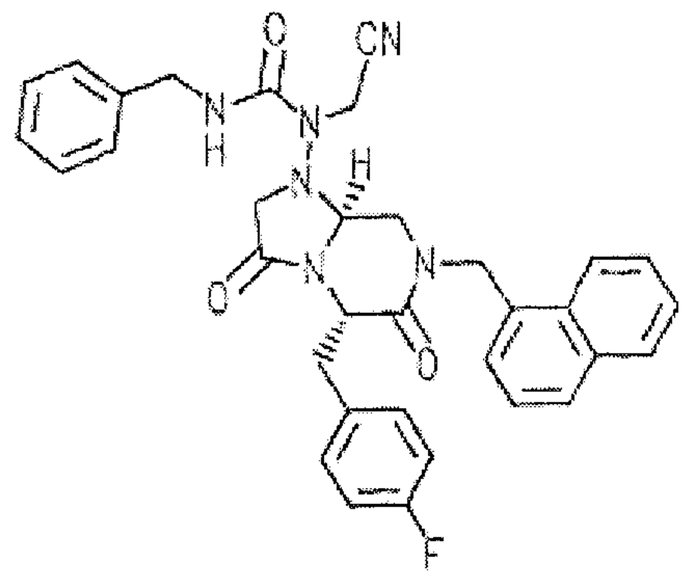
or a pharmaceutically acceptable salt thereof.

416. The compound of claim 1, which is:



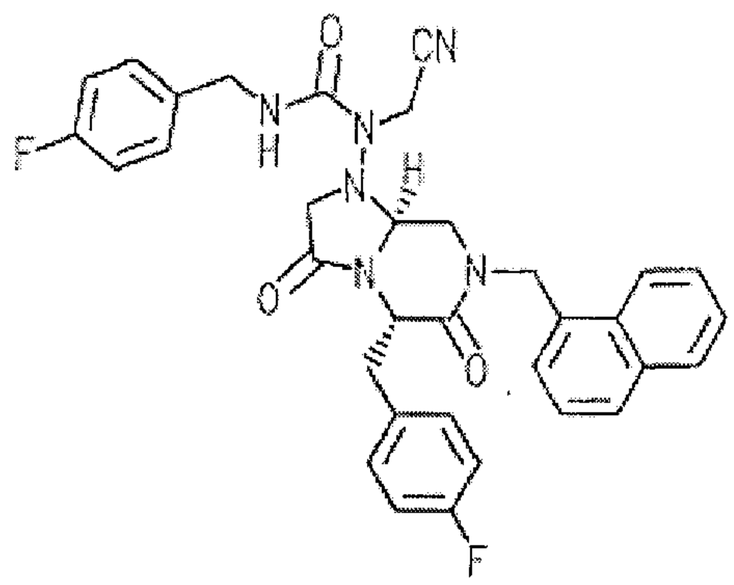
or a pharmaceutically acceptable salt thereof.

417. The compound of claim 1, which is:



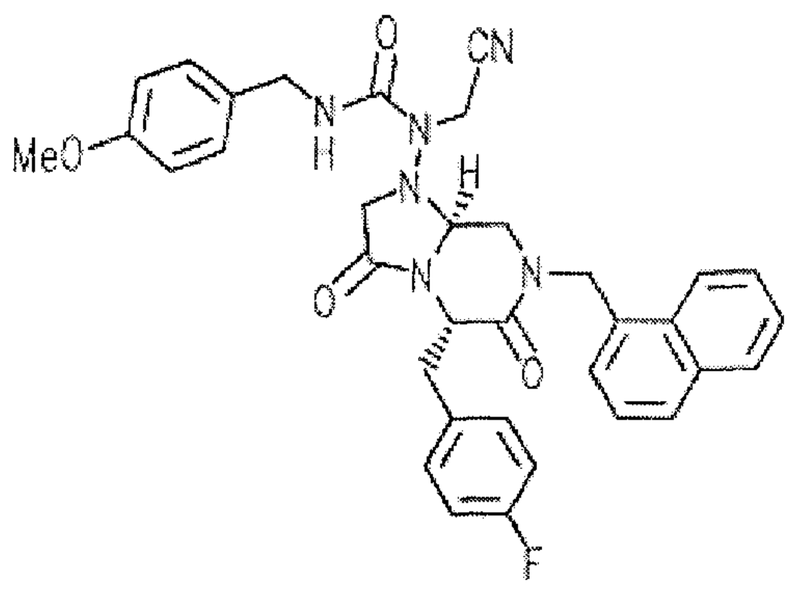
or a pharmaceutically acceptable salt thereof.

418. The compound of claim 1, which is:



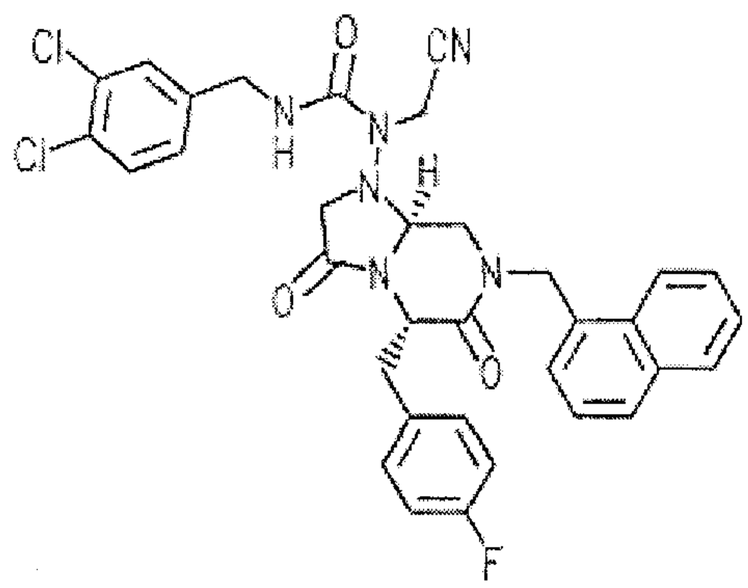
or a pharmaceutically acceptable salt thereof.

419. The compound of claim 1, which is:



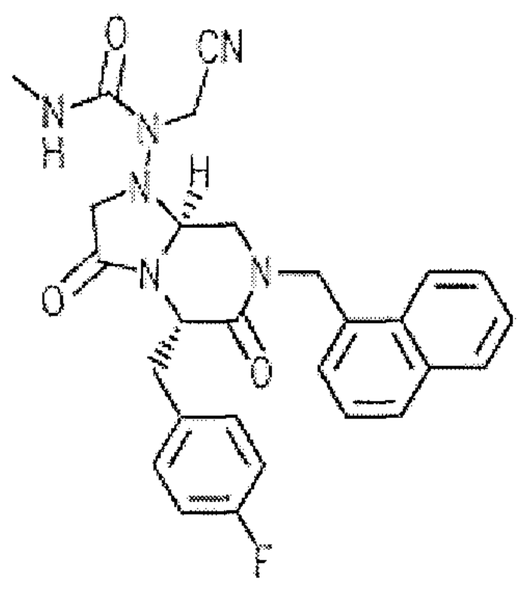
or a pharmaceutically acceptable salt thereof.

420. The compound of claim 1, which is:



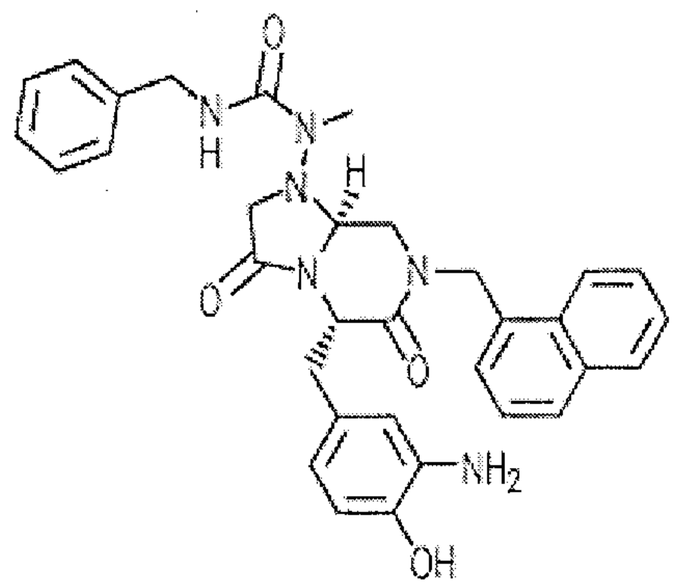
or a pharmaceutically acceptable salt thereof.

421. The compound of claim 1, which is:



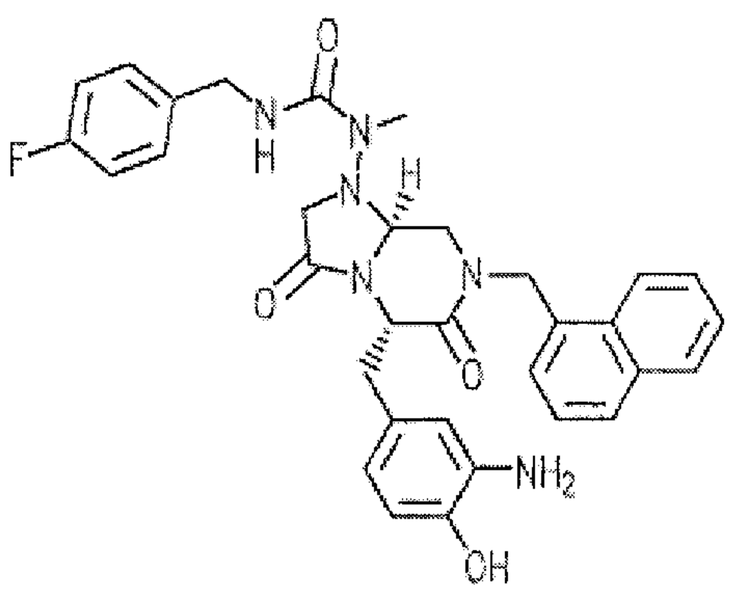
or a pharmaceutically acceptable salt thereof.

422. The compound of claim 1, which is:



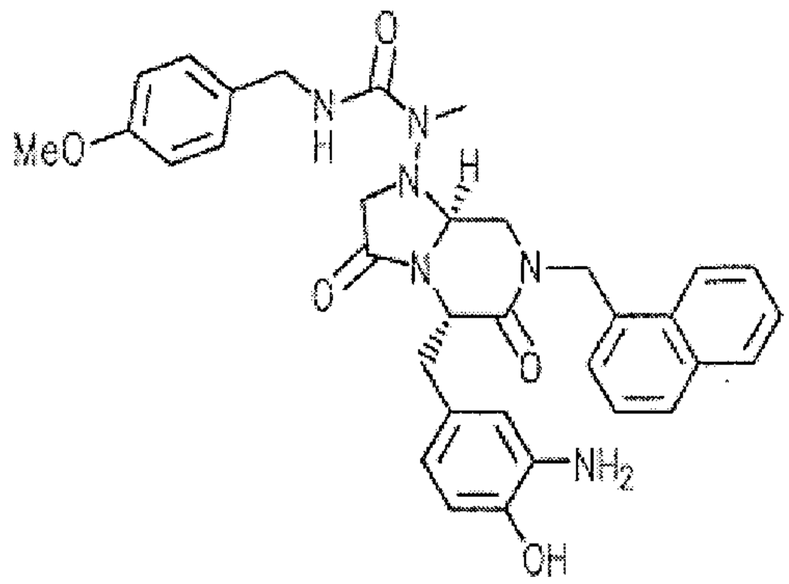
or a pharmaceutically acceptable salt thereof.

423. The compound of claim 1, which is:



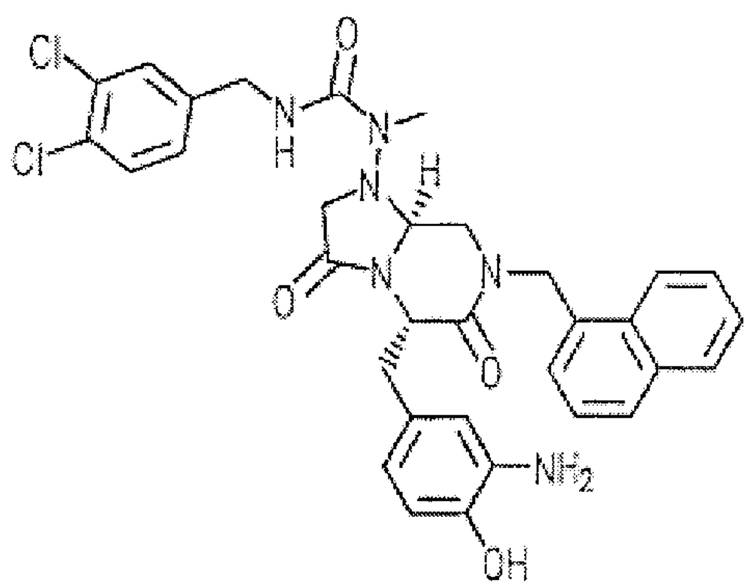
or a pharmaceutically acceptable salt thereof.

424. The compound of claim 1, which is:



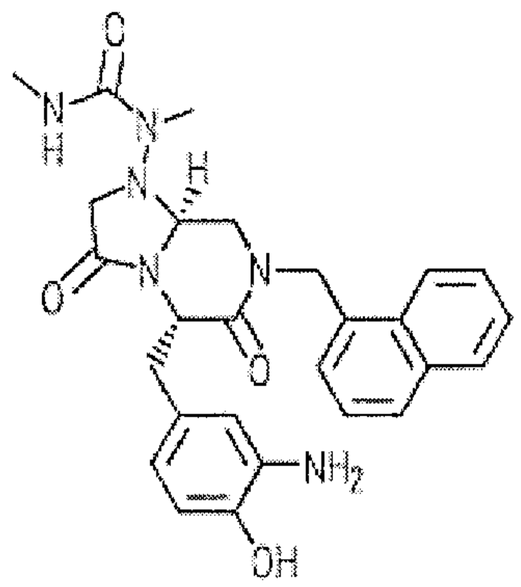
or a pharmaceutically acceptable salt thereof.

425. The compound of claim 1, which is:



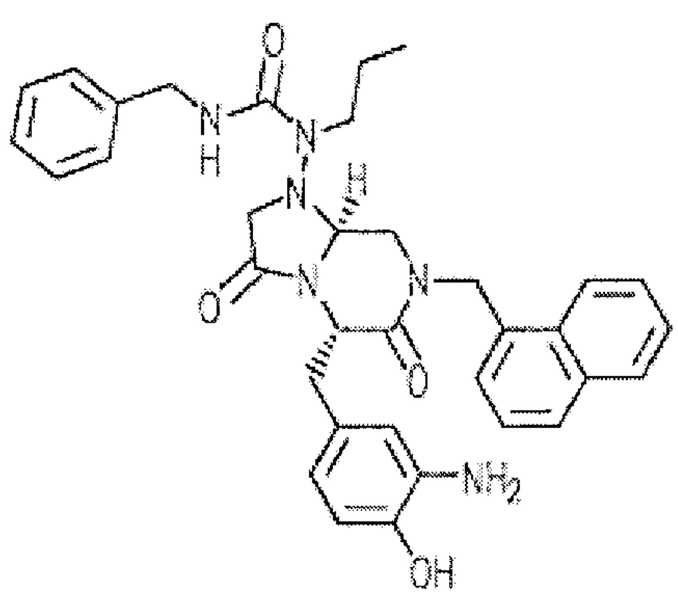
or a pharmaceutically acceptable salt thereof.

426. The compound of claim 1, which is:



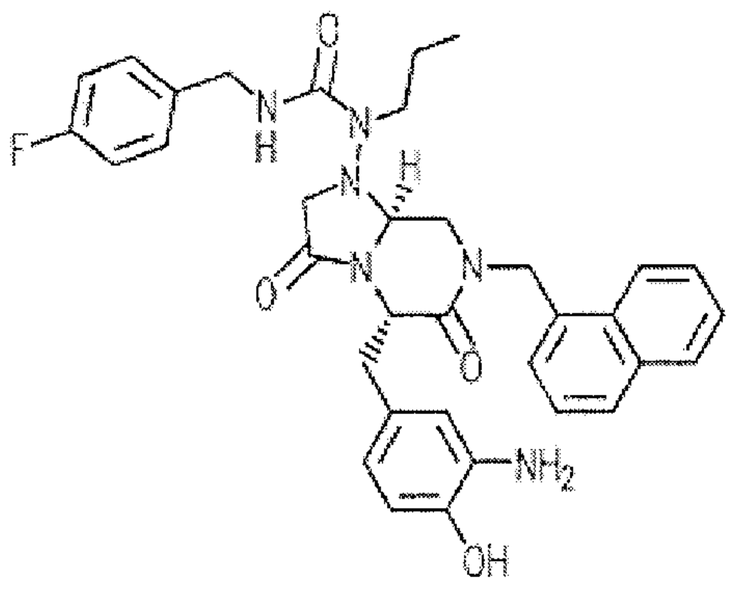
or a pharmaceutically acceptable salt thereof.

427. The compound of claim 1, which is:



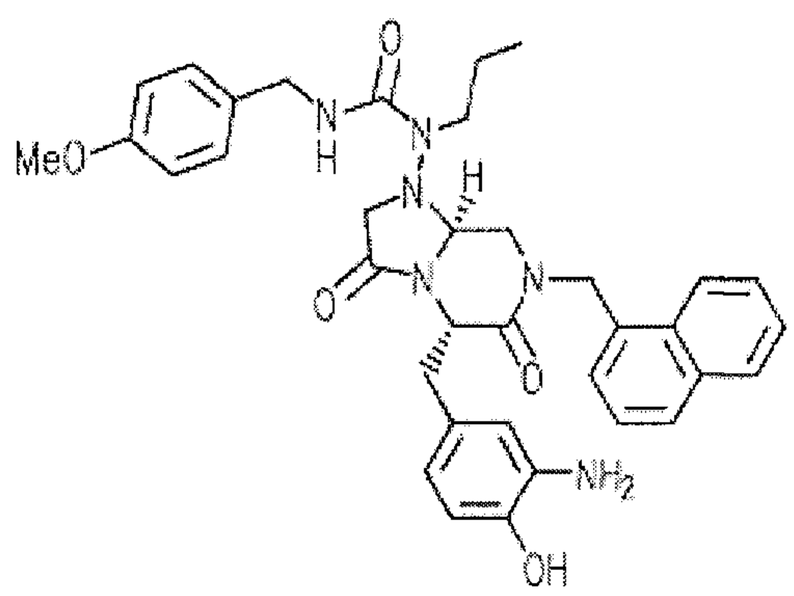
or a pharmaceutically acceptable salt thereof.

428. The compound of claim 1, which is:



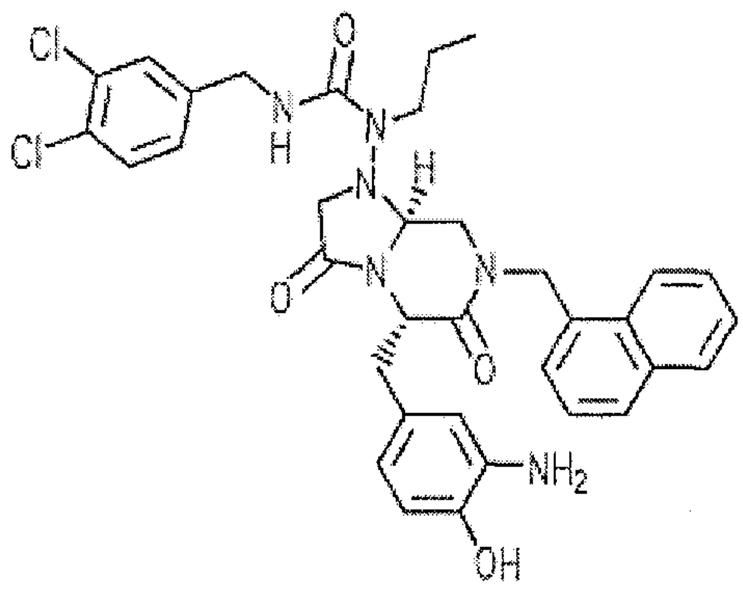
or a pharmaceutically acceptable salt thereof.

429. The compound of claim 1, which is:



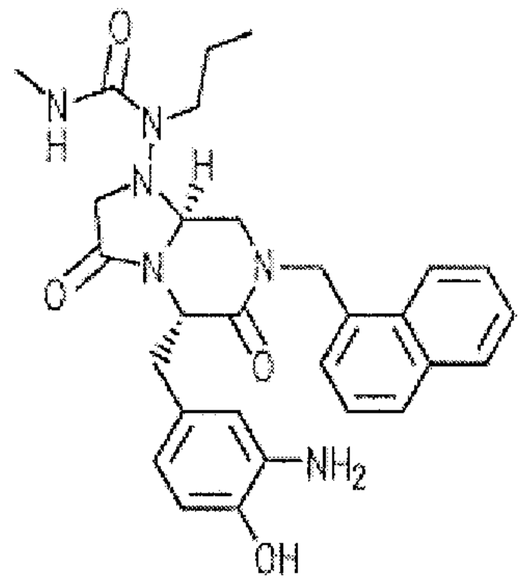
or a pharmaceutically acceptable salt thereof.

430. The compound of claim 1, which is:



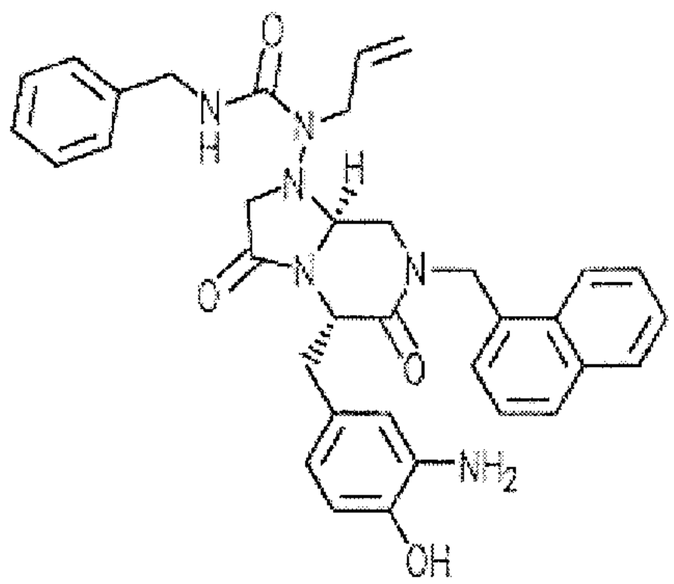
or a pharmaceutically acceptable salt thereof.

431. The compound of claim 1, which is:



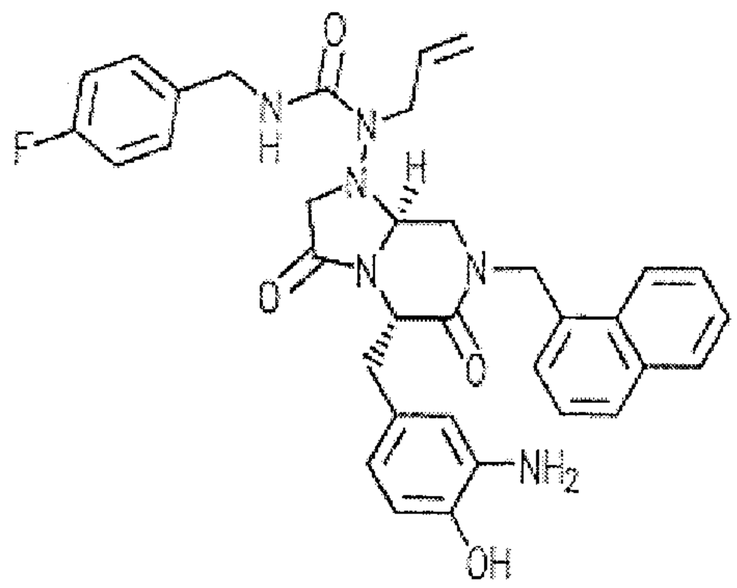
or a pharmaceutically acceptable salt thereof.

432. The compound of claim 1, which is:



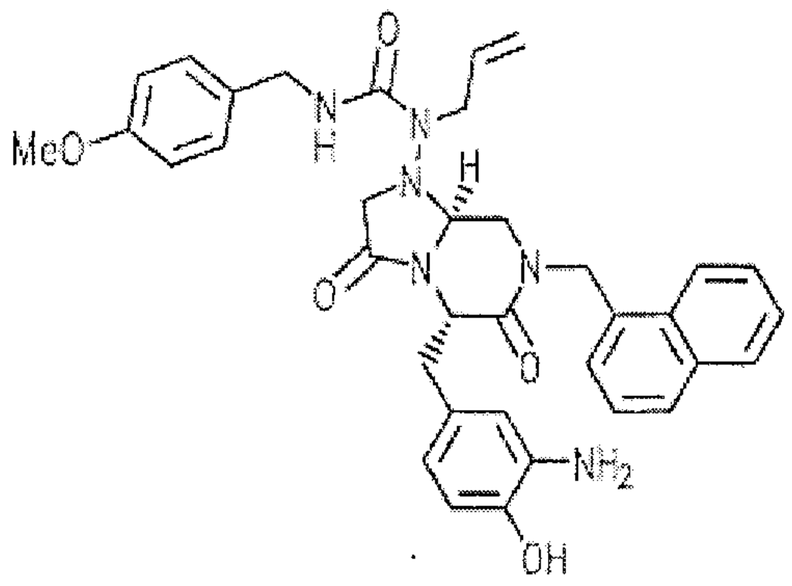
or a pharmaceutically acceptable salt thereof.

433. The compound of claim 1, which is:



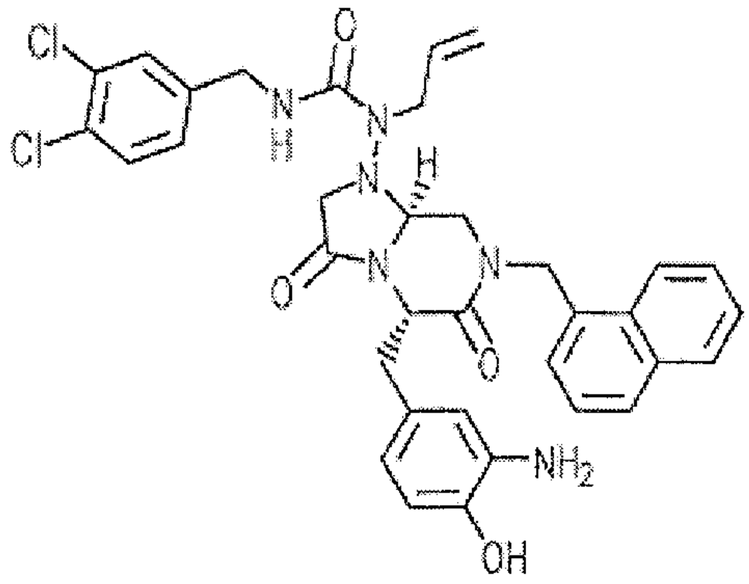
or a pharmaceutically acceptable salt thereof.

434. The compound of claim 1, which is:



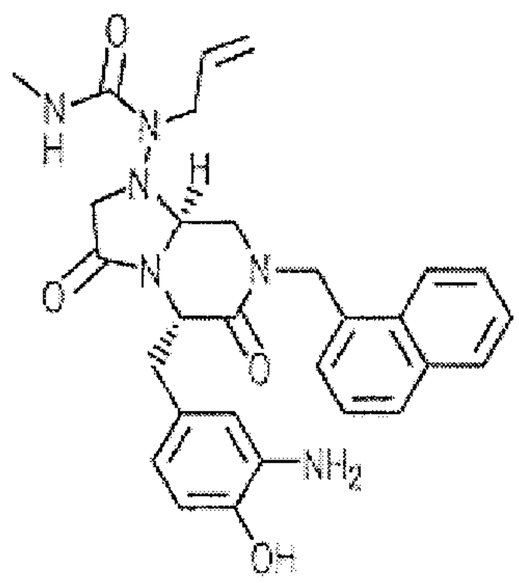
or a pharmaceutically acceptable salt thereof.

435. The compound of claim 1, which is:



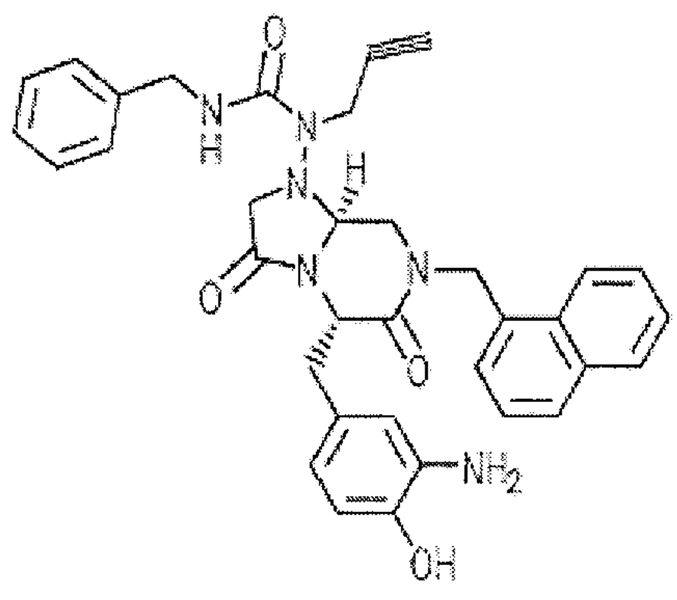
or a pharmaceutically acceptable salt thereof.

436. The compound of claim 1, which is:



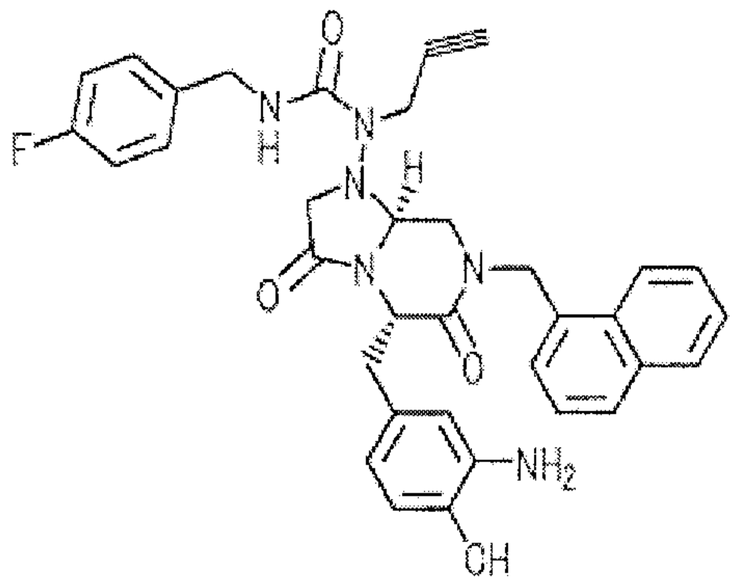
or a pharmaceutically acceptable salt thereof.

437. The compound of claim 1, which is:



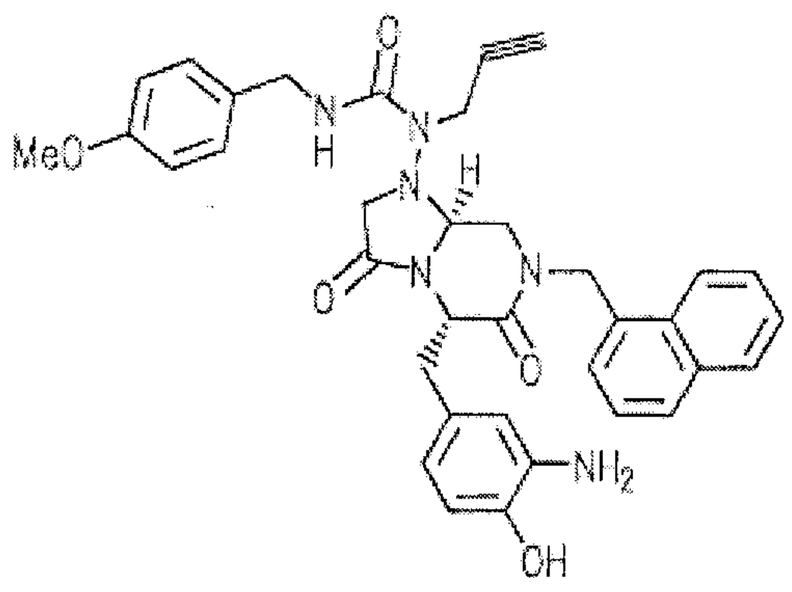
or a pharmaceutically acceptable salt thereof.

438. The compound of claim 1, which is:



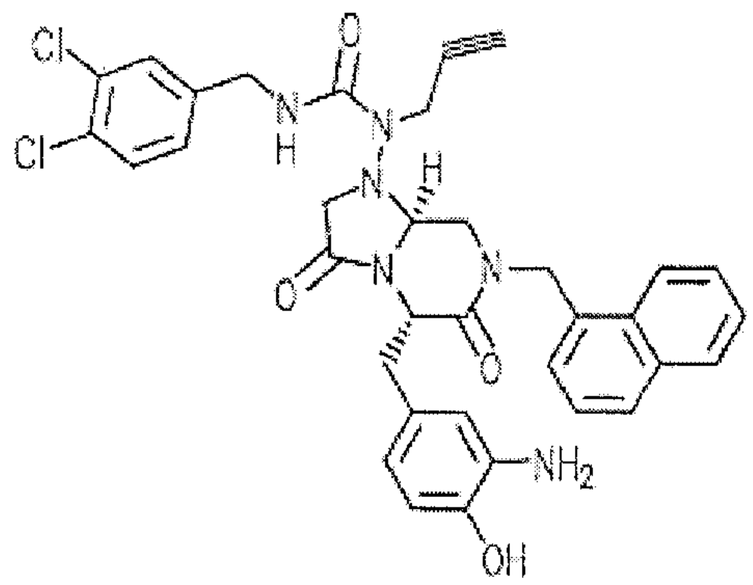
or a pharmaceutically acceptable salt thereof.

439. The compound of claim 1, which is:



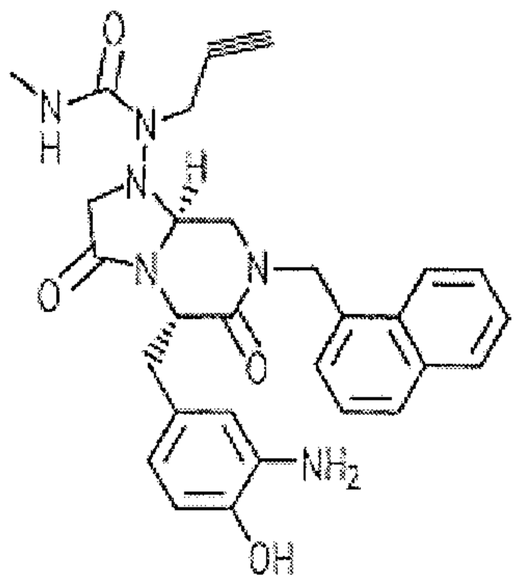
or a pharmaceutically acceptable salt thereof.

440. The compound of claim 1, which is:



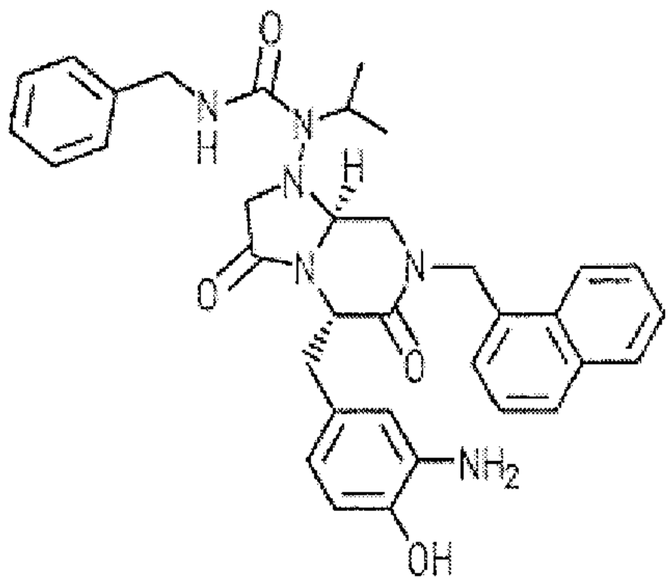
or a pharmaceutically acceptable salt thereof.

441. The compound of claim 1, which is:



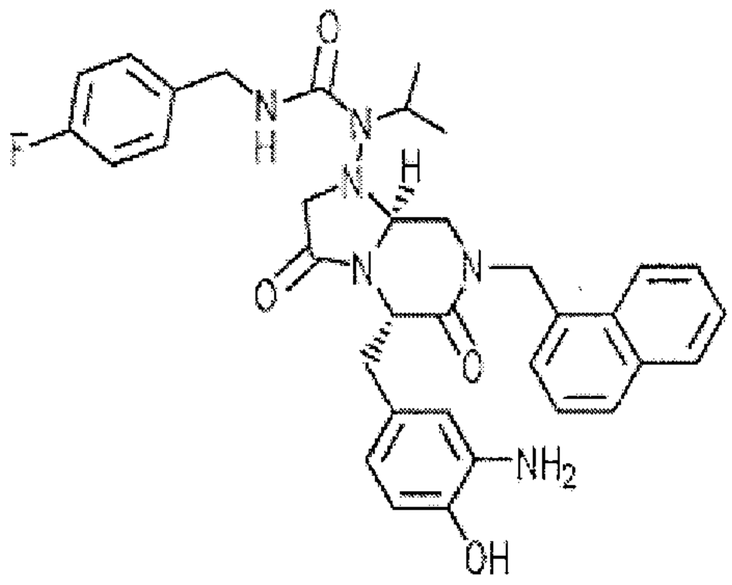
or a pharmaceutically acceptable salt thereof.

442. The compound of claim 1, which is:



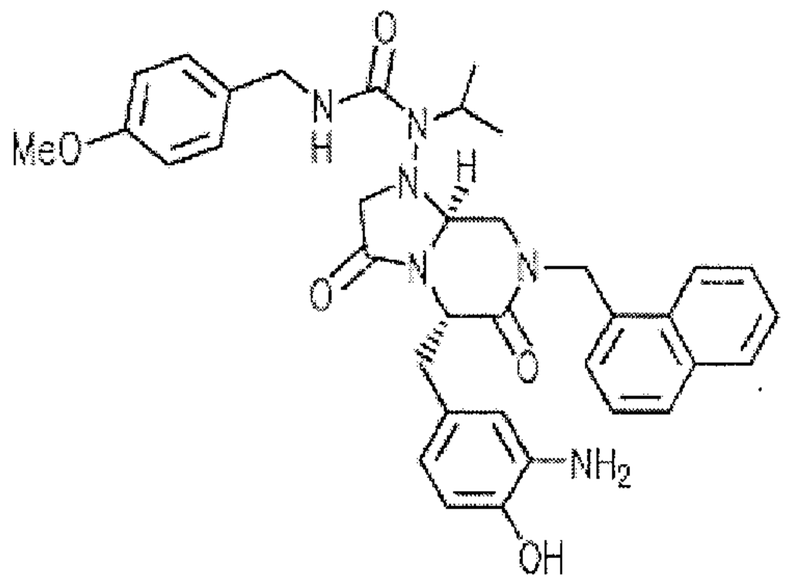
or a pharmaceutically acceptable salt thereof.

443. The compound of claim 1, which is:



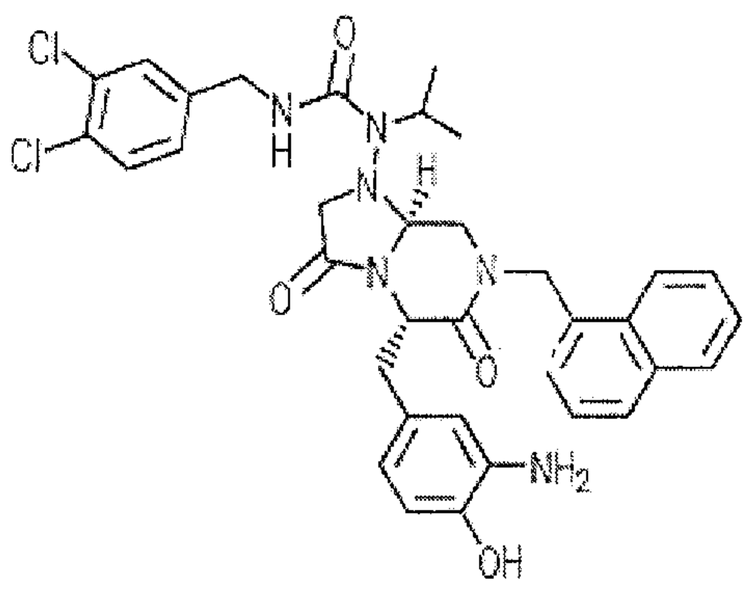
or a pharmaceutically acceptable salt thereof.

444. The compound of claim 1, which is:



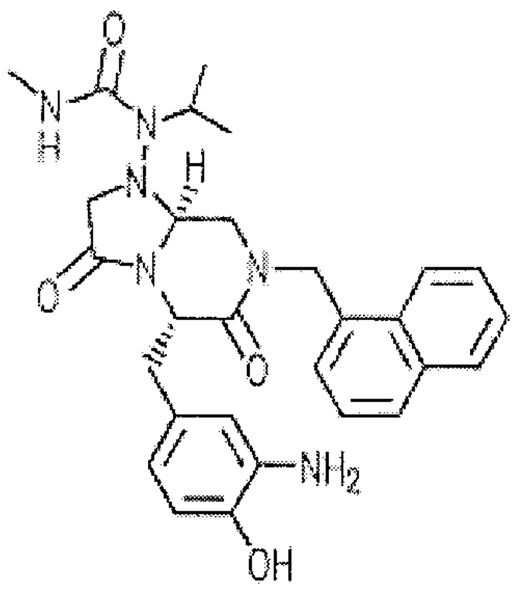
or a pharmaceutically acceptable salt thereof.

445. The compound of claim 1, which is:



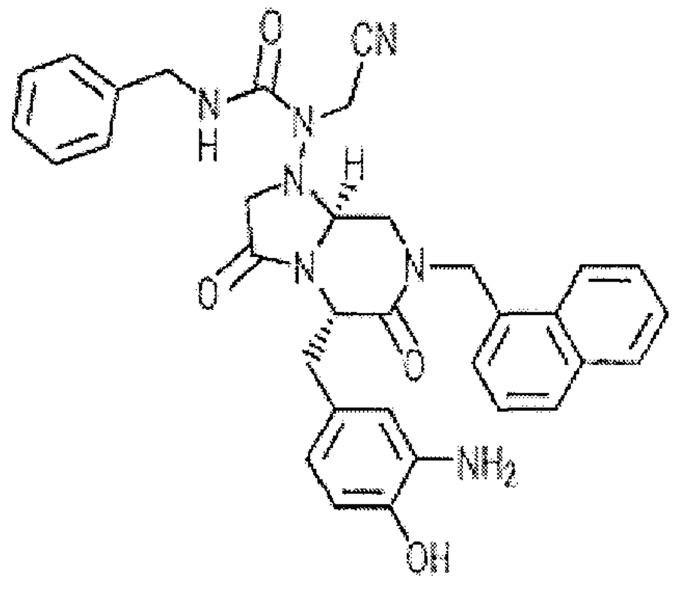
or a pharmaceutically acceptable salt thereof.

446. The compound of claim 1, which is:



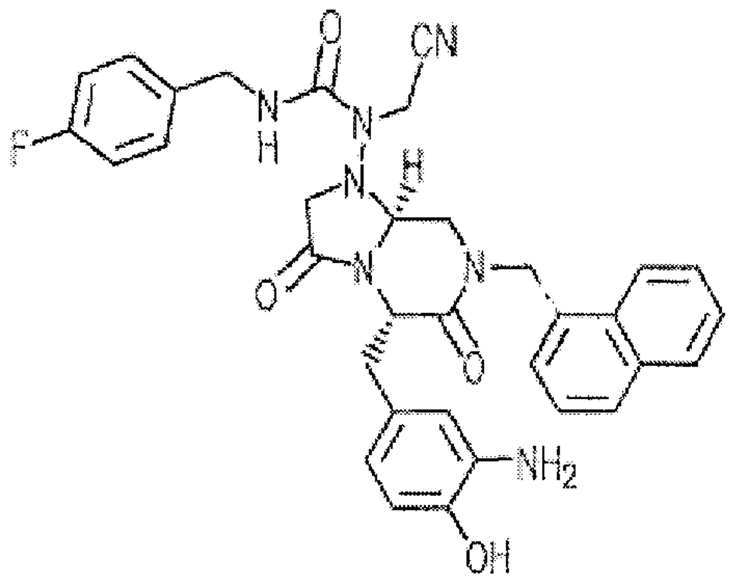
or a pharmaceutically acceptable salt thereof.

447. The compound of claim 1, which is:



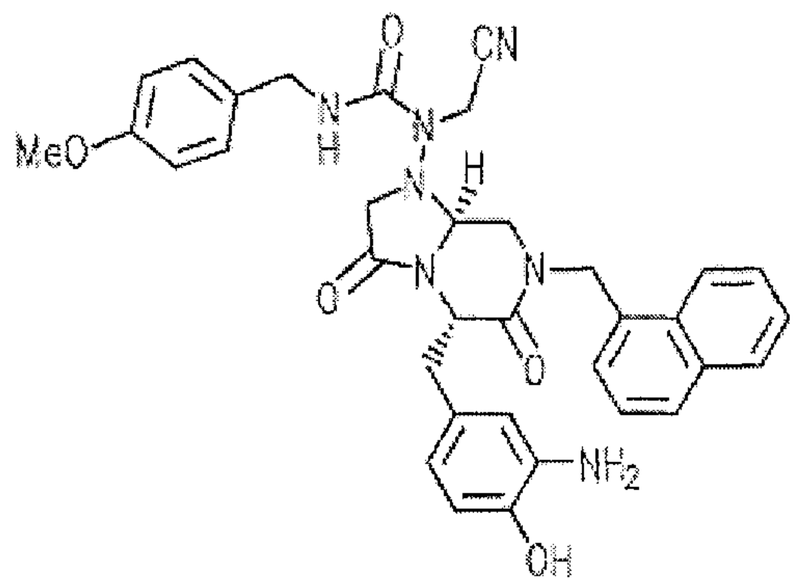
or a pharmaceutically acceptable salt thereof.

448. The compound of claim 1, which is:



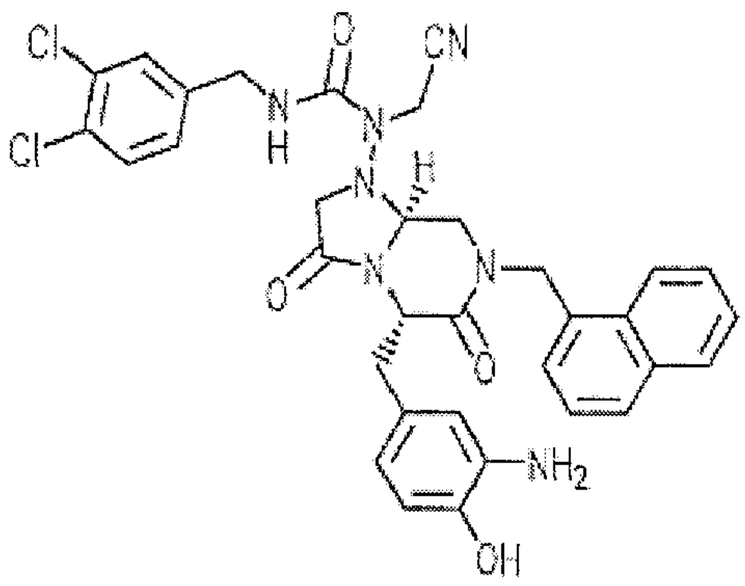
or a pharmaceutically acceptable salt thereof.

449. The compound of claim 1, which is:



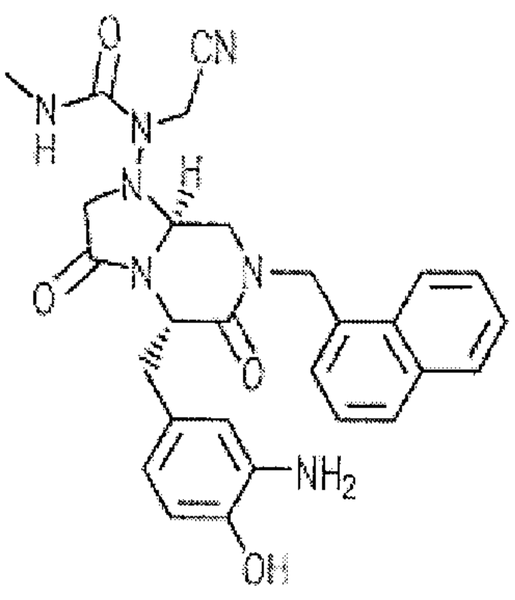
or a pharmaceutically acceptable salt thereof.

450. The compound of claim 1, which is:



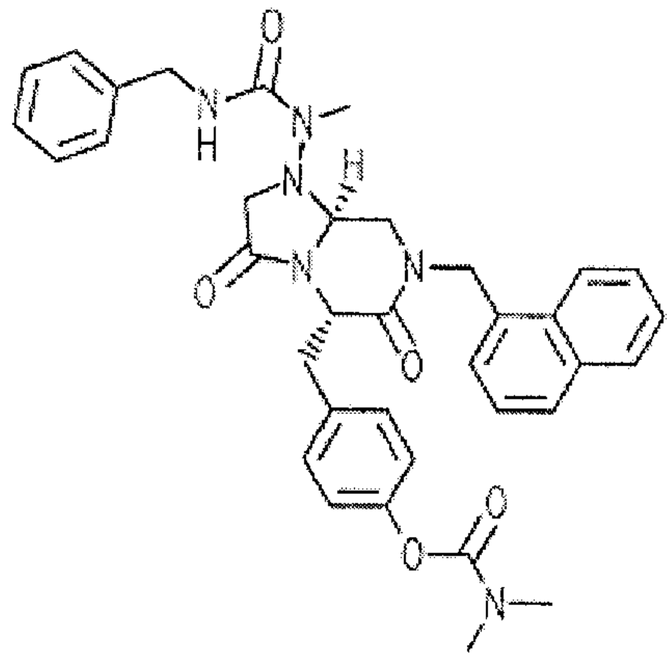
or a pharmaceutically acceptable salt thereof.

451. The compound of claim 1, which is:



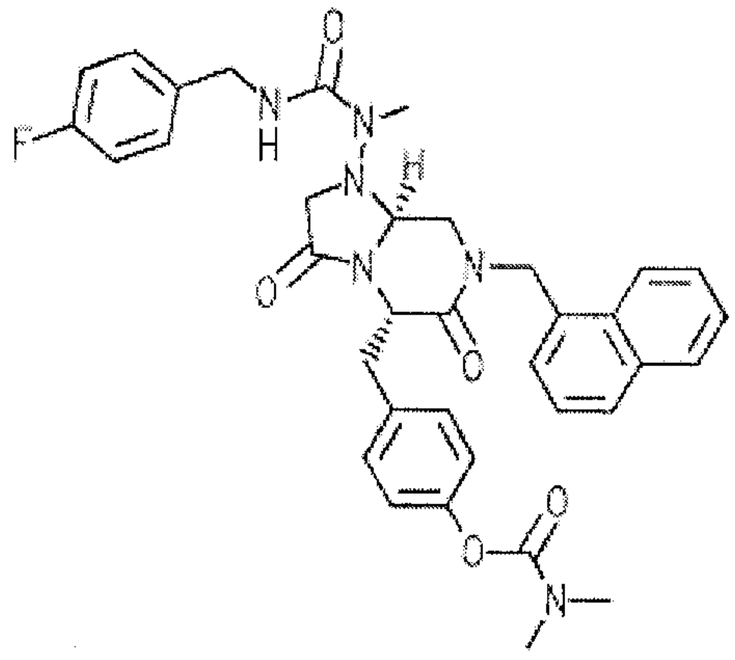
or a pharmaceutically acceptable salt thereof.

452. The compound of claim 1, which is:



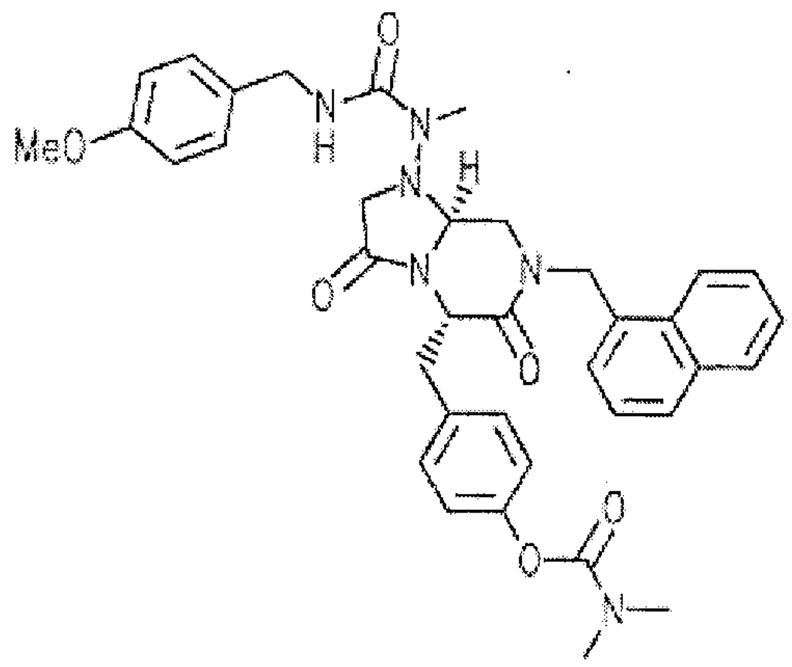
or a pharmaceutically acceptable salt thereof.

453. The compound of claim 1, which is:



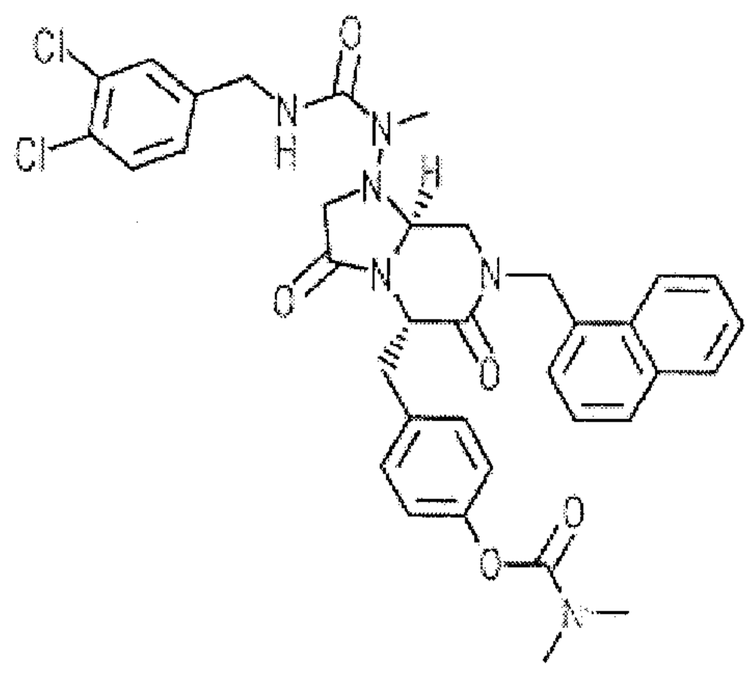
or a pharmaceutically acceptable salt thereof.

454. The compound of claim 1, which is:



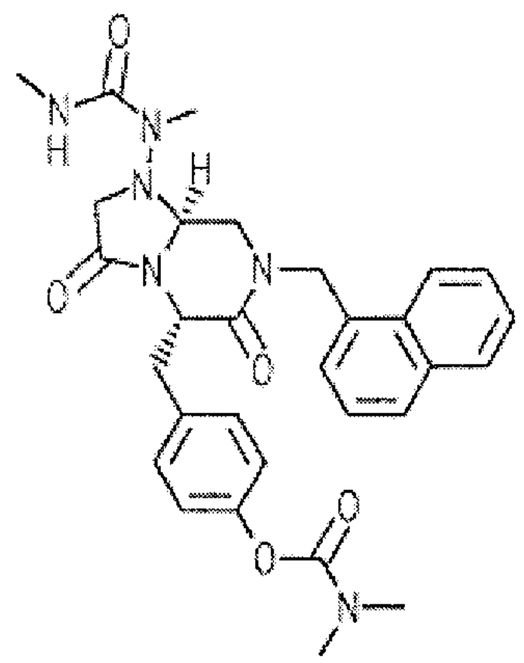
or a pharmaceutically acceptable salt thereof.

455. The compound of claim 1, which is:



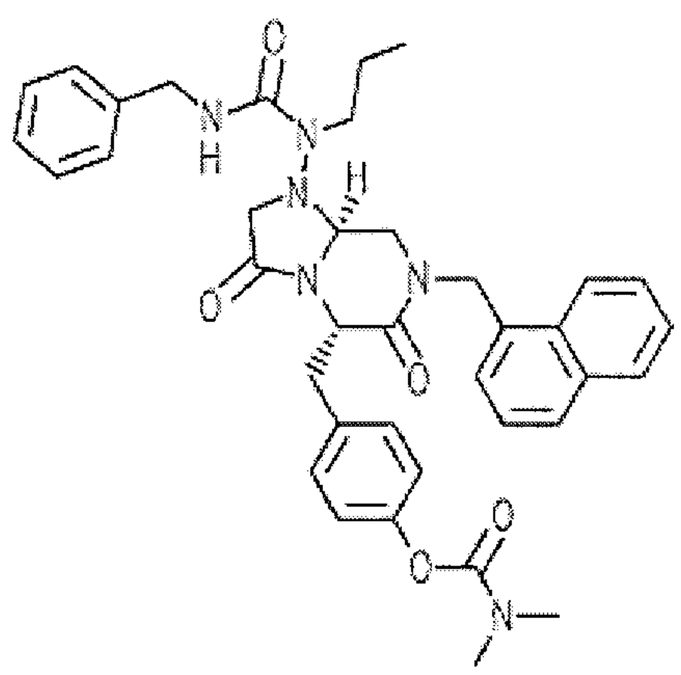
or a pharmaceutically acceptable salt thereof.

456. The compound of claim 1, which is:



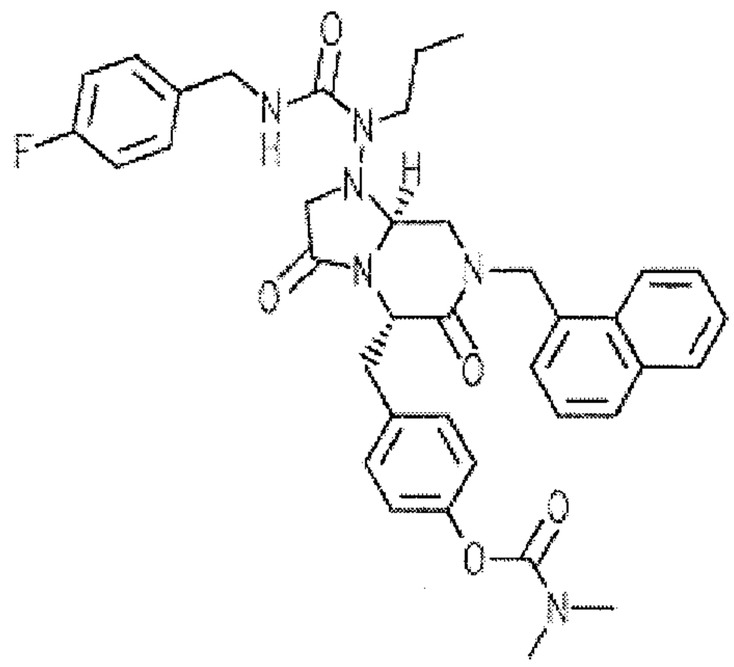
or a pharmaceutically acceptable salt thereof.

457. The compound of claim 1, which is:



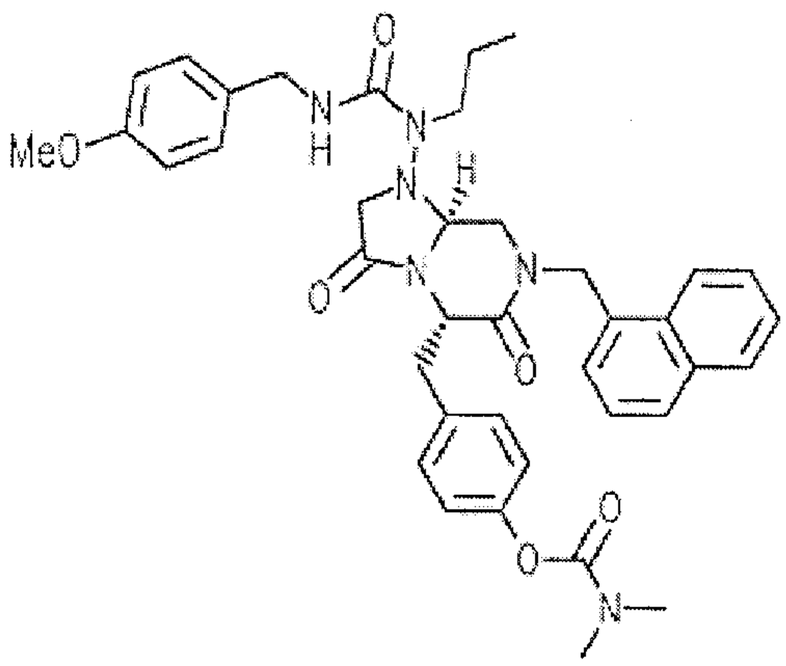
or a pharmaceutically acceptable salt thereof.

458. The compound of claim 1, which is:



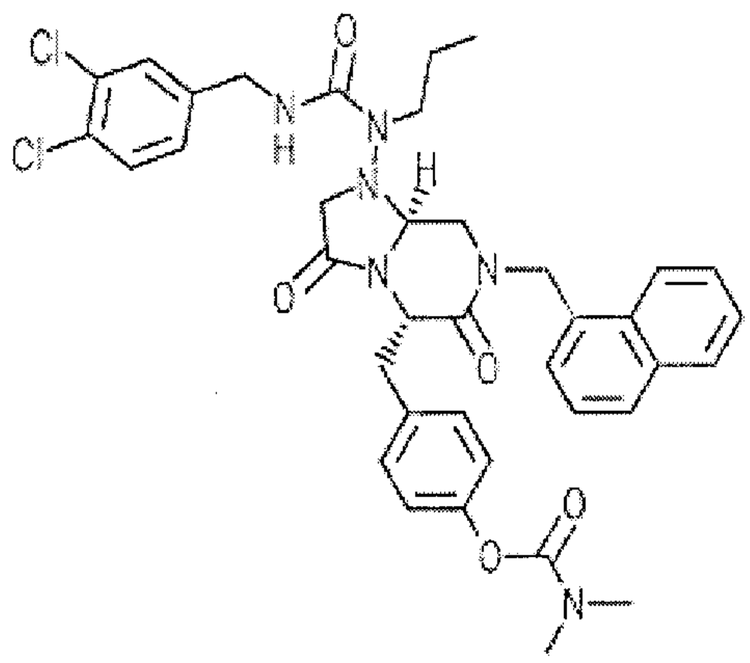
or a pharmaceutically acceptable salt thereof.

459. The compound of claim 1, which is:



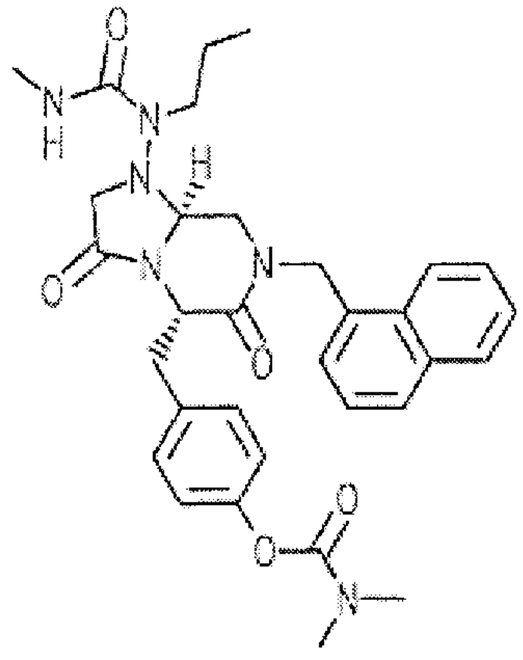
or a pharmaceutically acceptable salt thereof.

460. The compound of claim 1, which is:



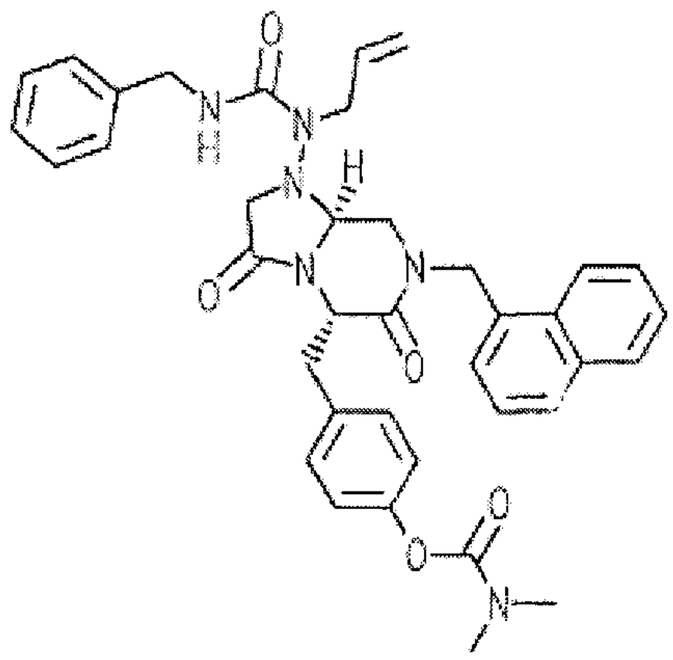
or a pharmaceutically acceptable salt thereof.

461. The compound of claim 1, which is:



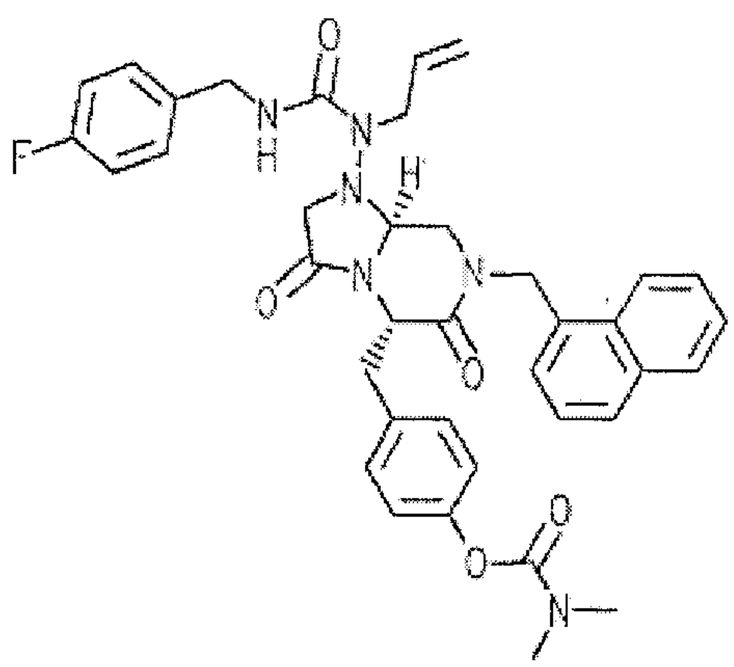
or a pharmaceutically acceptable salt thereof.

462. The compound of claim 1, which is:



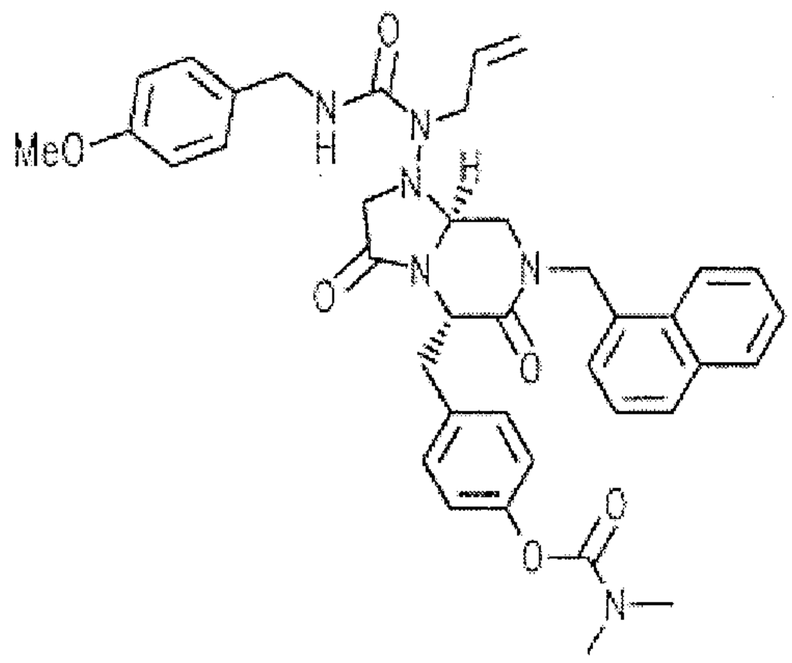
or a pharmaceutically acceptable salt thereof.

463. The compound of claim 1, which is:



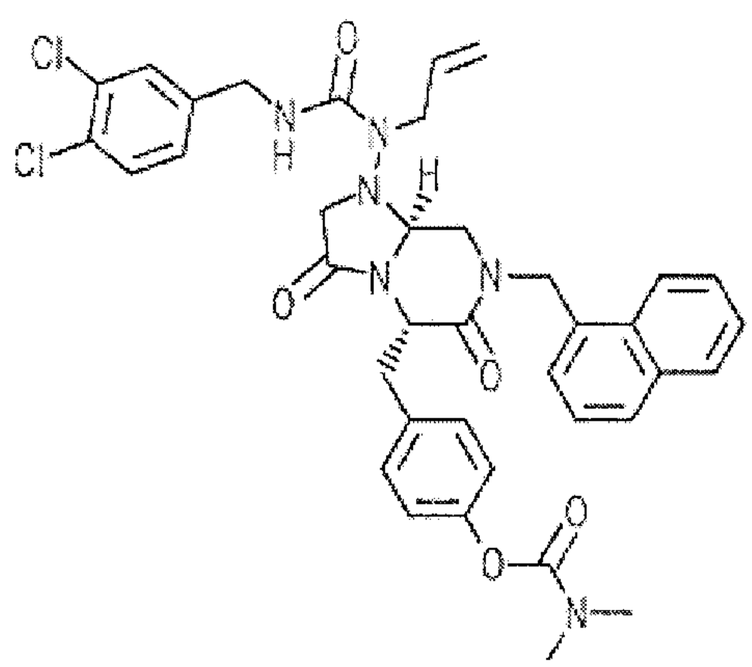
or a pharmaceutically acceptable salt thereof.

464. The compound of claim 1, which is:



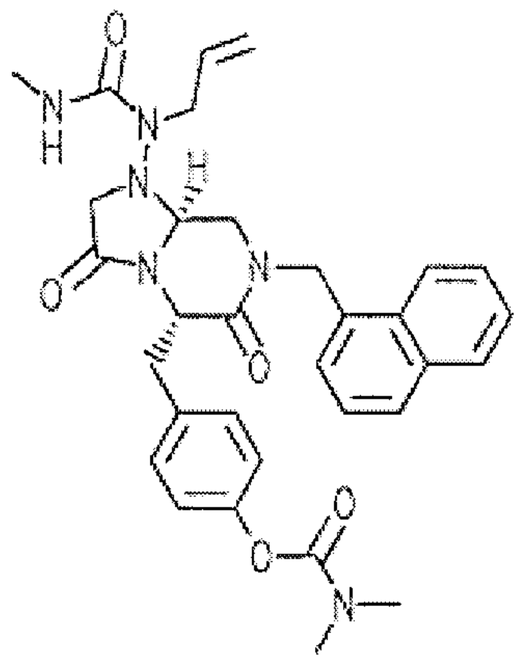
or a pharmaceutically acceptable salt thereof.

465. The compound of claim 1, which is:



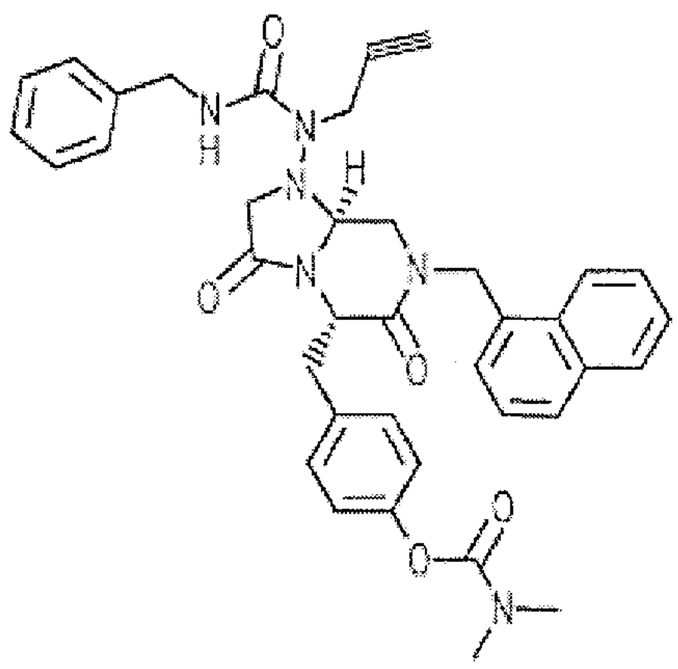
or a pharmaceutically acceptable salt thereof.

466. The compound of claim 1, which is:



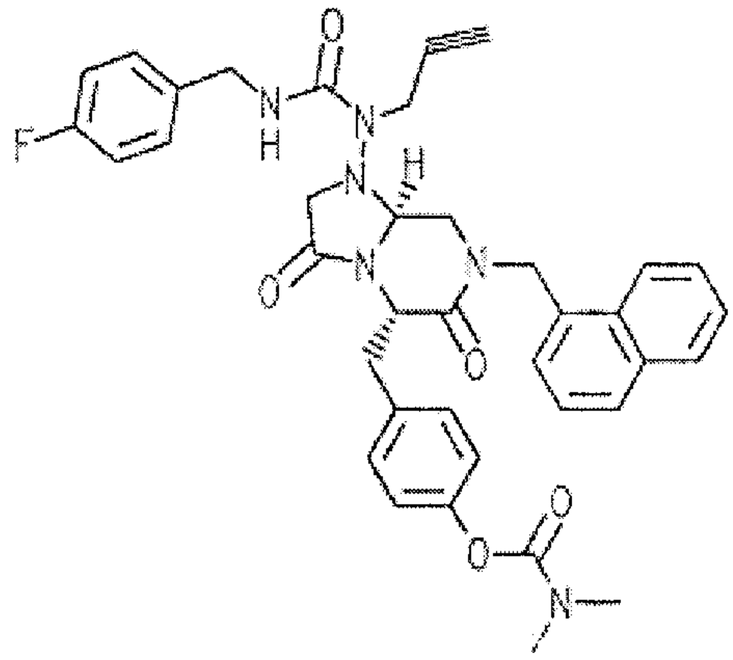
or a pharmaceutically acceptable salt thereof.

467. The compound of claim 1, which is:



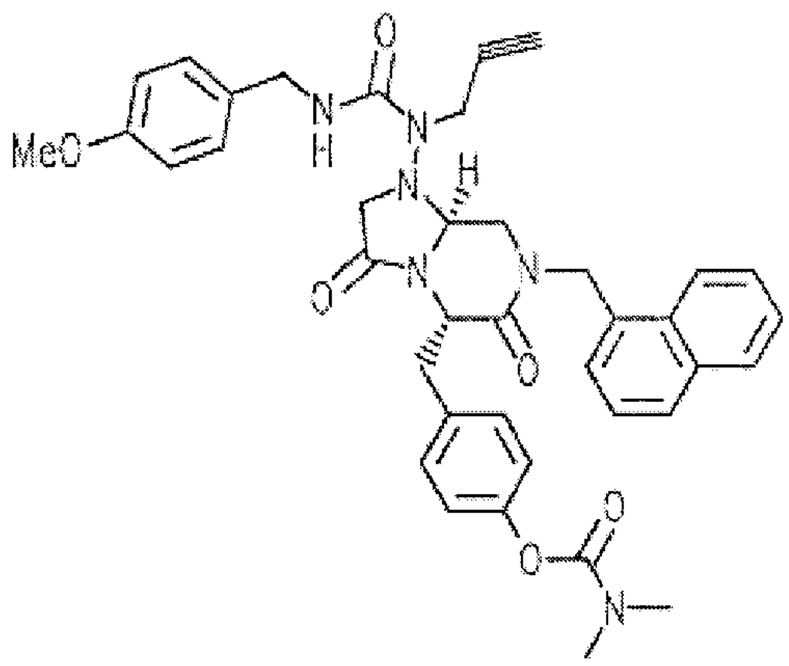
or a pharmaceutically acceptable salt thereof.

468. The compound of claim 1, which is:



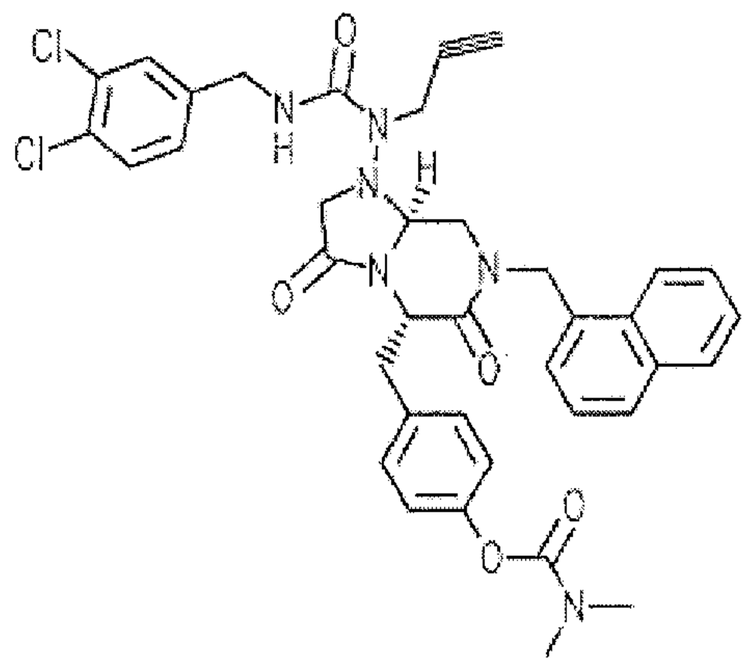
or a pharmaceutically acceptable salt thereof.

469. The compound of claim 1, which is:



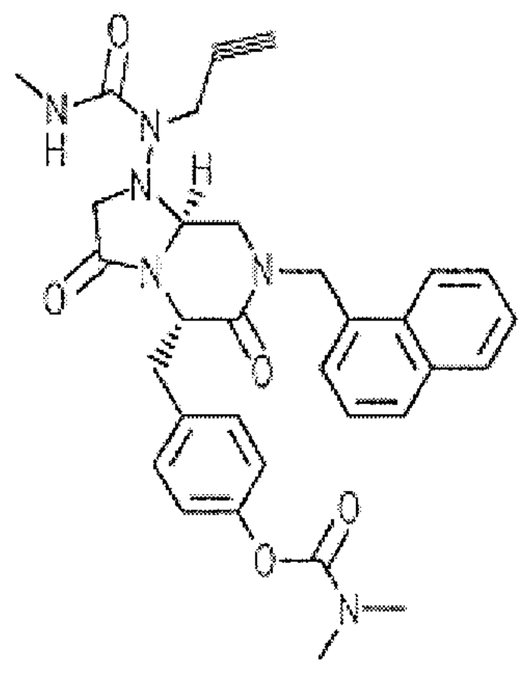
or a pharmaceutically acceptable salt thereof.

470. The compound of claim 1, which is:



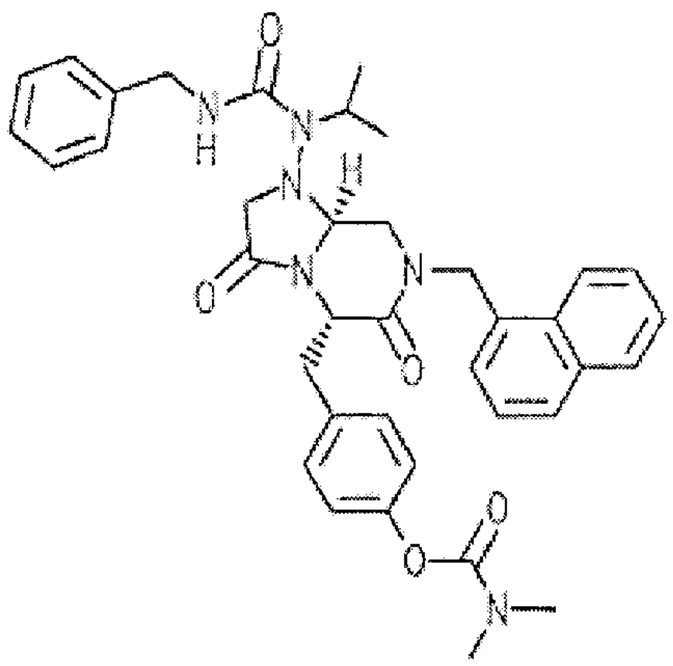
or a pharmaceutically acceptable salt thereof.

471. The compound of claim 1, which is:



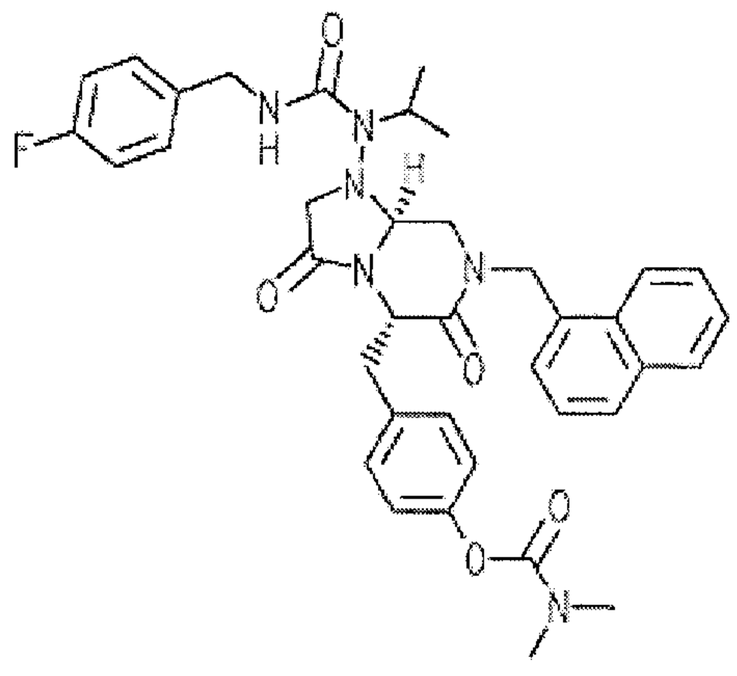
or a pharmaceutically acceptable salt thereof.

472. The compound of claim 1, which is:



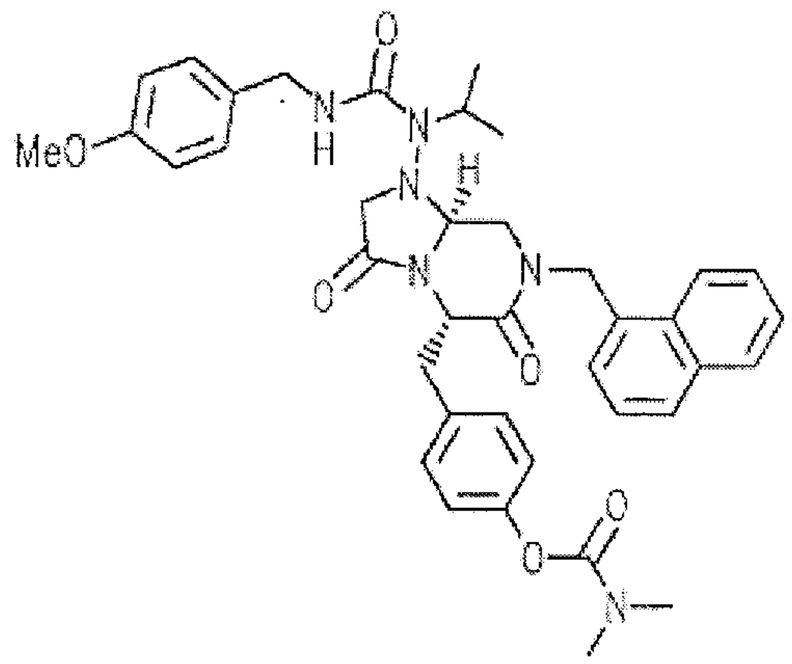
or a pharmaceutically acceptable salt thereof.

473. The compound of claim 1, which is:



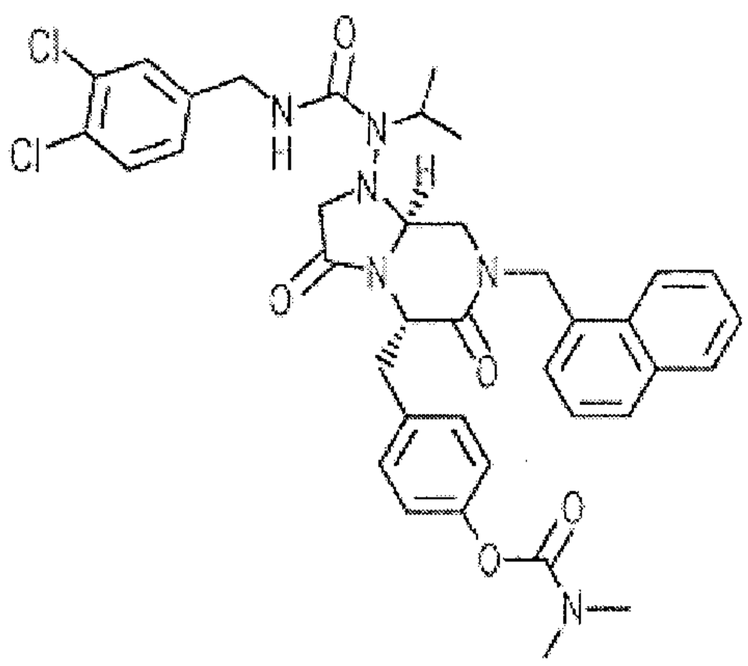
or a pharmaceutically acceptable salt thereof.

474. The compound of claim 1, which is:



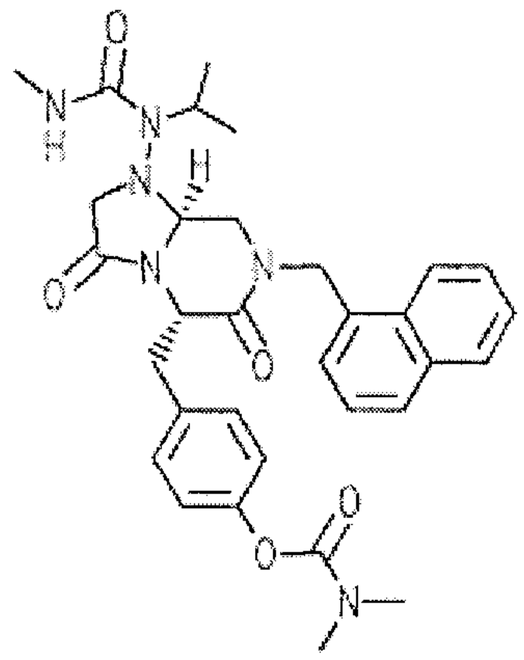
or a pharmaceutically acceptable salt thereof.

475. The compound of claim 1, which is:



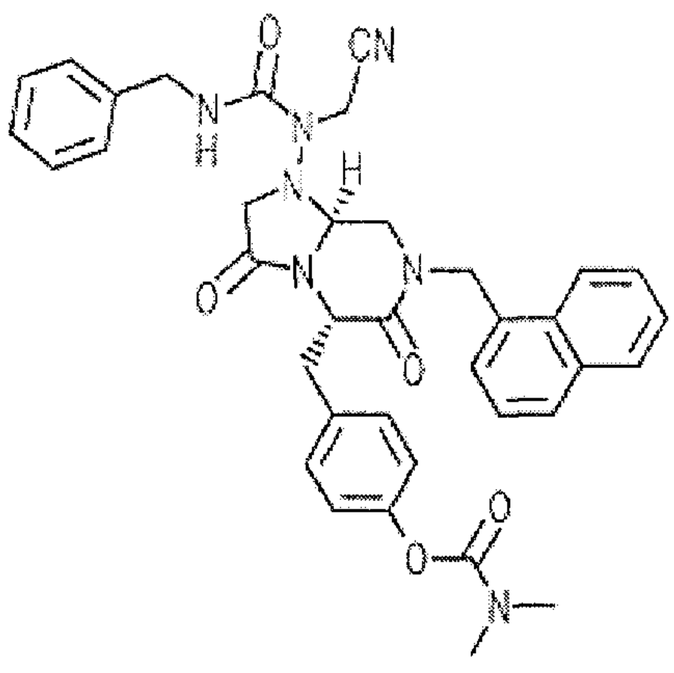
or a pharmaceutically acceptable salt thereof.

476. The compound of claim 1, which is:



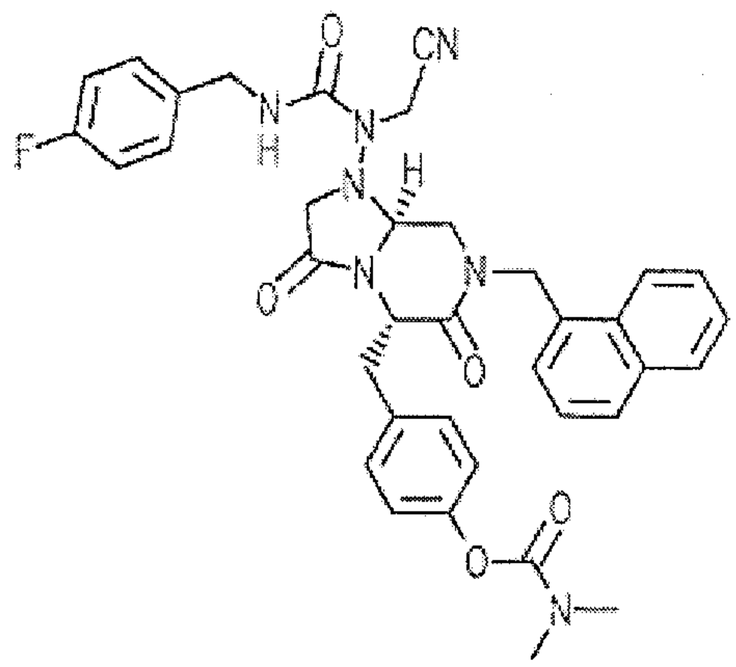
or a pharmaceutically acceptable salt thereof.

477. The compound of claim 1, which is:



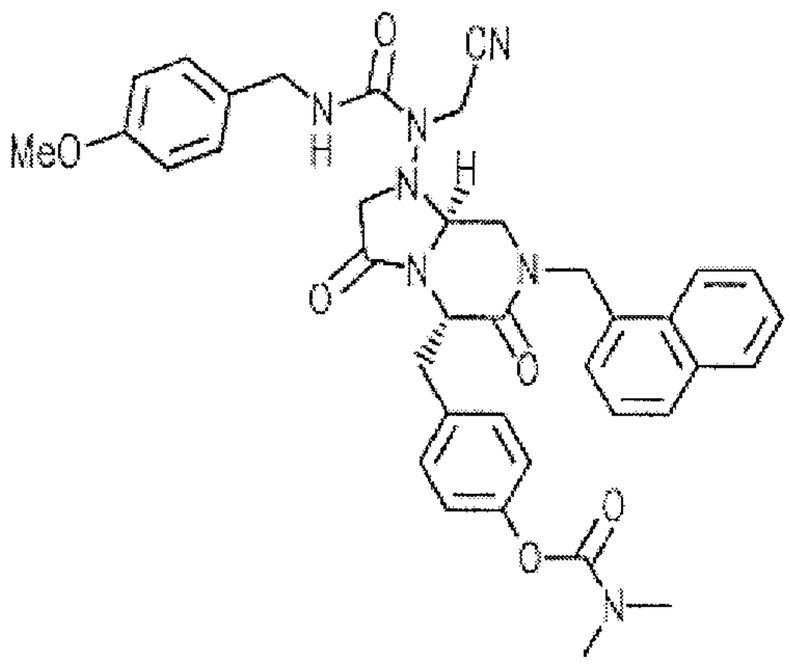
or a pharmaceutically acceptable salt thereof.

478. The compound of claim 1, which is:



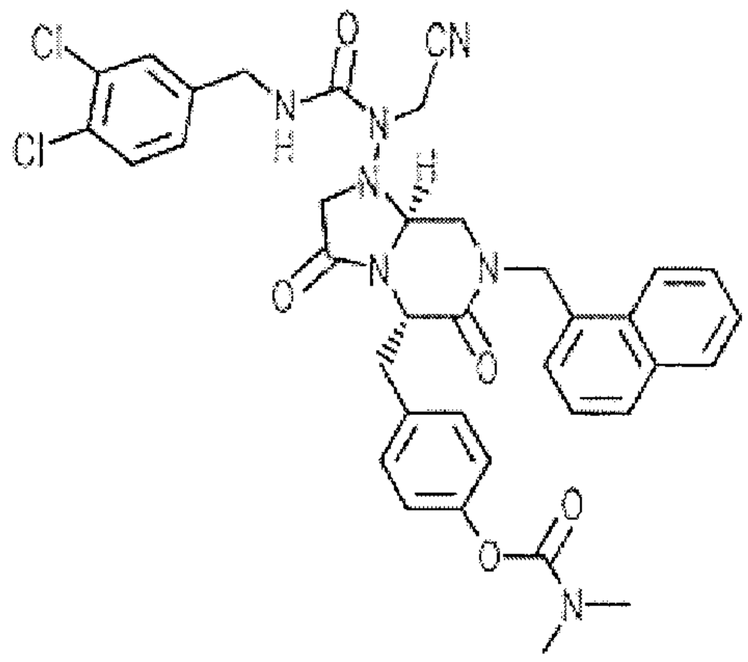
or a pharmaceutically acceptable salt thereof.

479. The compound of claim 1, which is:



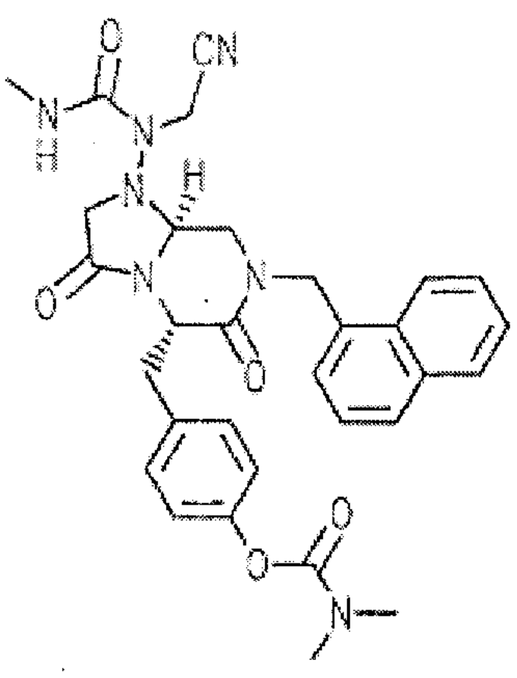
or a pharmaceutically acceptable salt thereof.

480. The compound of claim 1, which is:



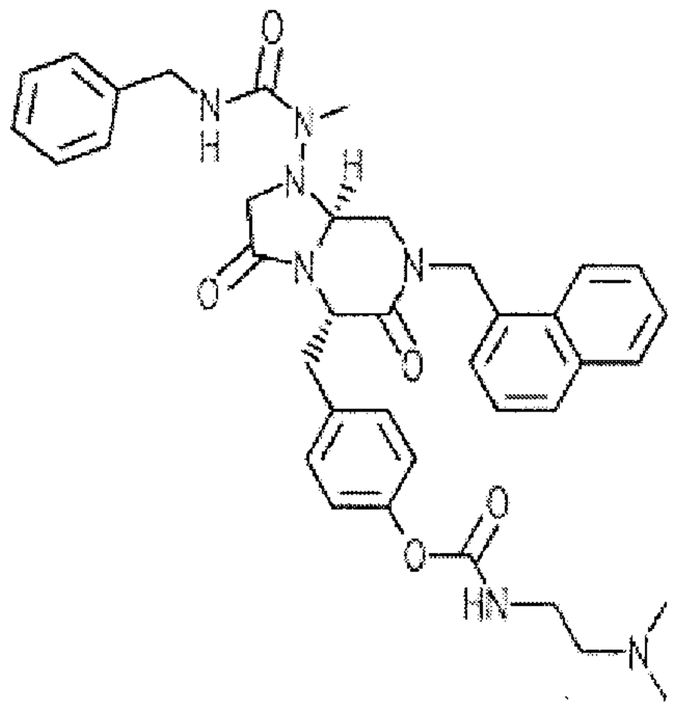
or a pharmaceutically acceptable salt thereof.

481. The compound of claim 1, which is:



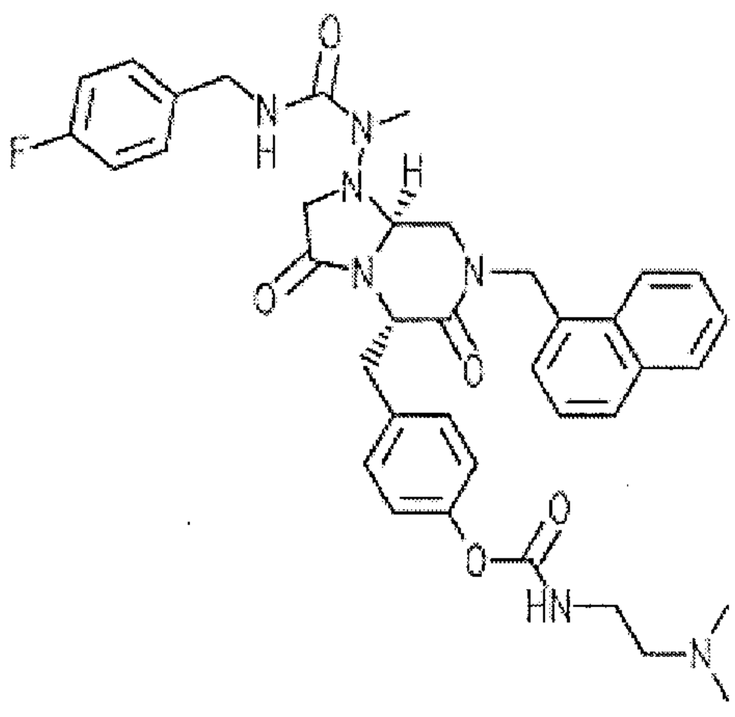
or a pharmaceutically acceptable salt thereof.

482. The compound of claim 1, which is:



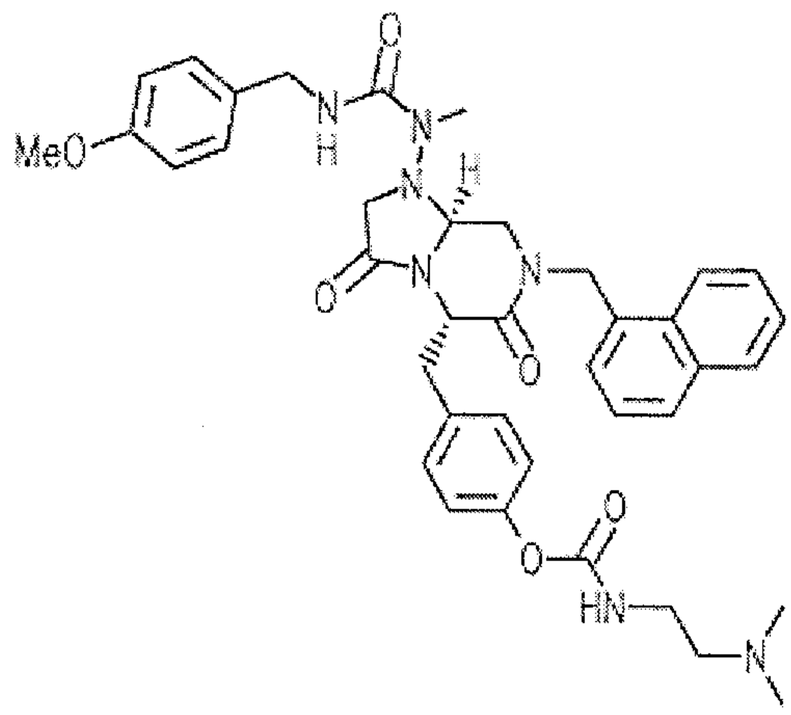
or a pharmaceutically acceptable salt thereof.

483. The compound of claim 1, which is:



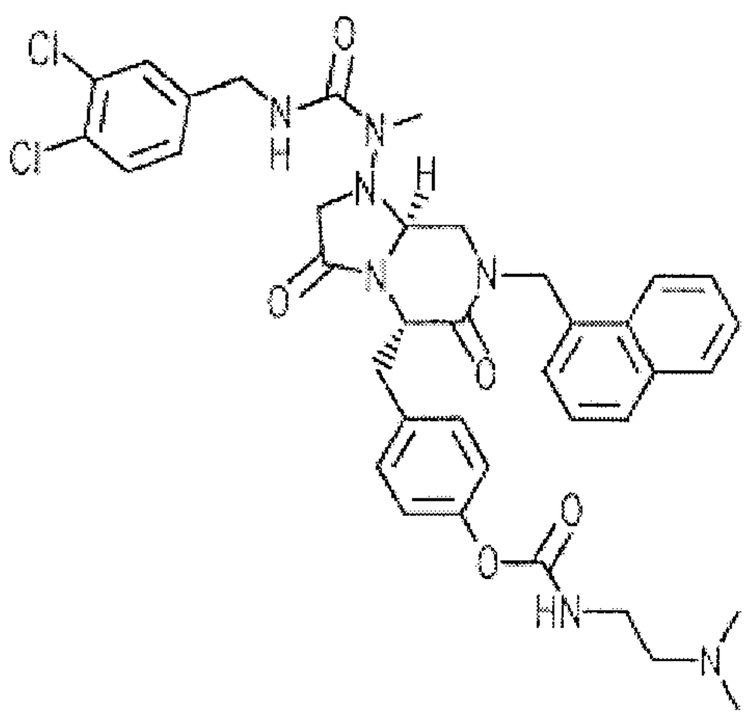
or a pharmaceutically acceptable salt thereof.

484. The compound of claim 1, which is:



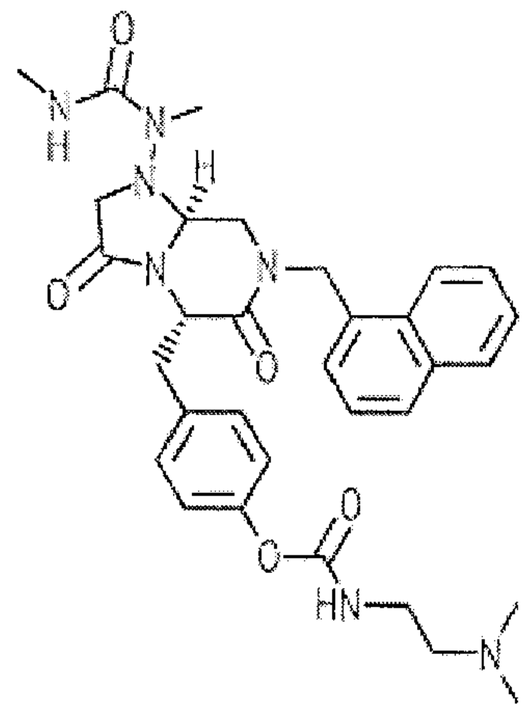
or a pharmaceutically acceptable salt thereof.

485. The compound of claim 1, which is:



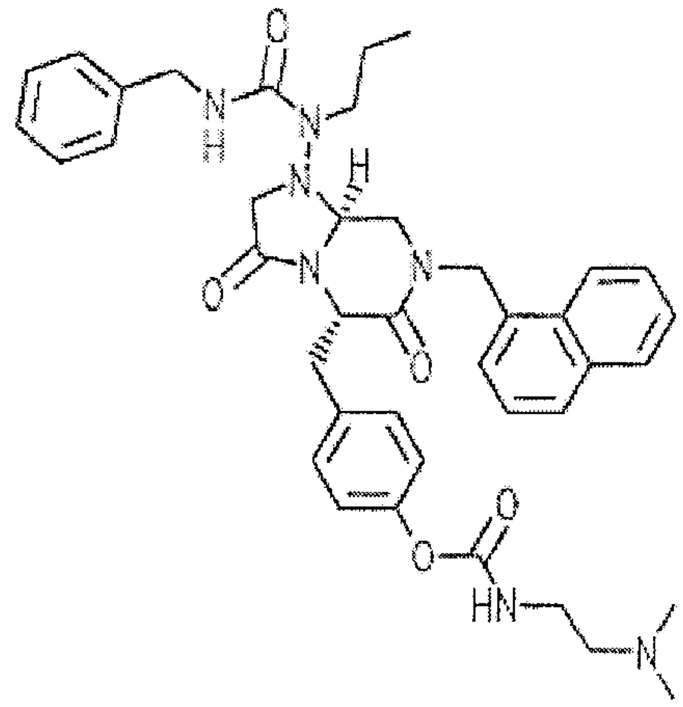
or a pharmaceutically acceptable salt thereof.

486. The compound of claim 1, which is:



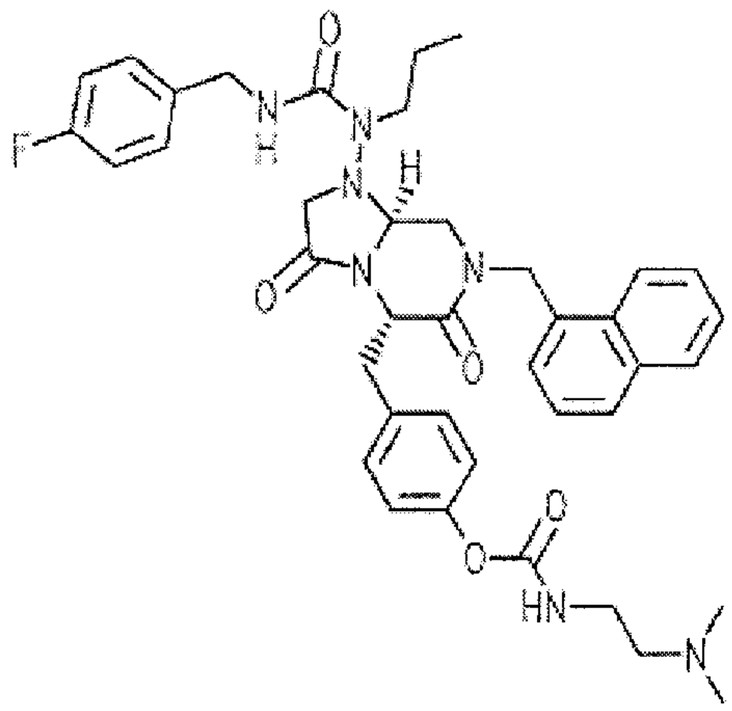
or a pharmaceutically acceptable salt thereof.

487. The compound of claim 1, which is:



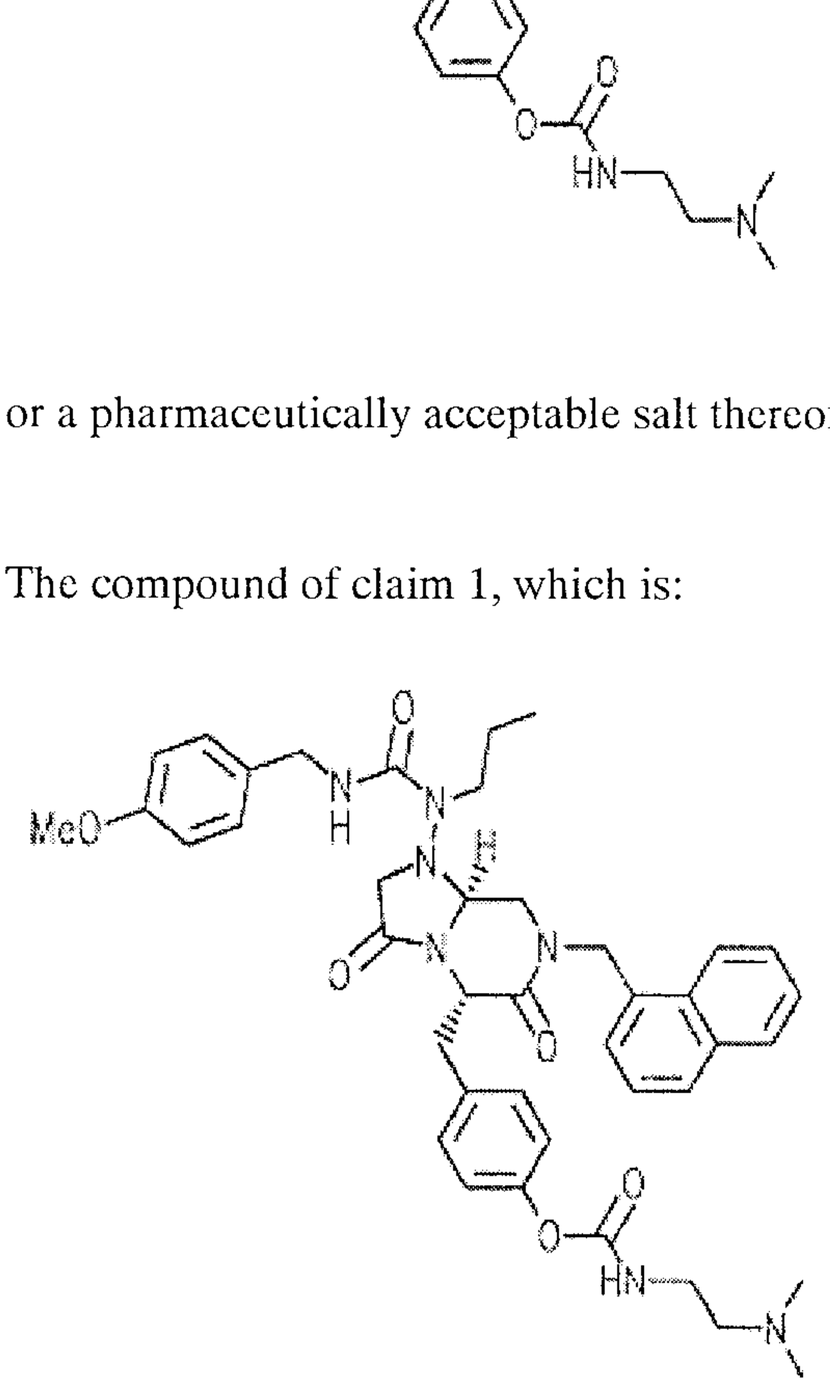
or a pharmaceutically acceptable salt thereof.

488. The compound of claim 1, which is:



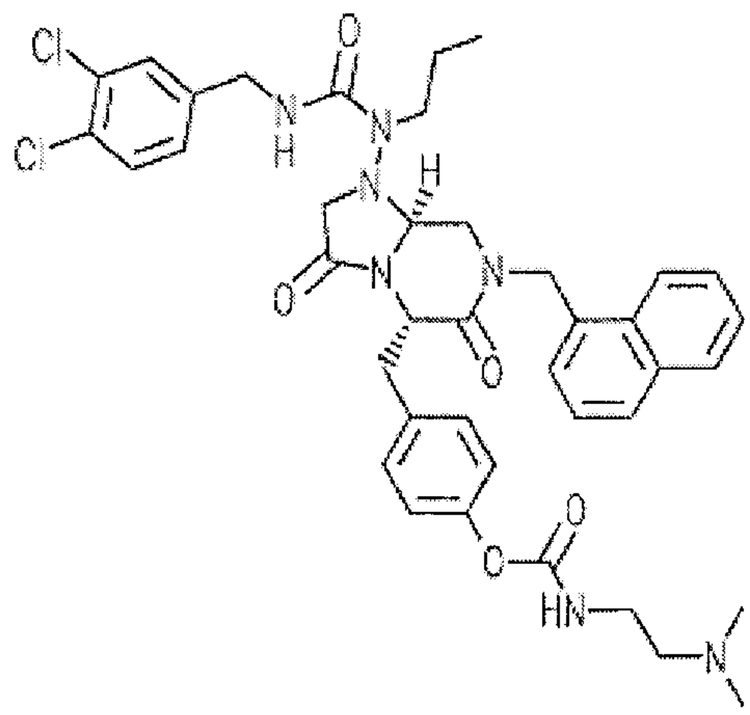
or a pharmaceutically acceptable salt thereof.

489. The compound of claim 1, which is:



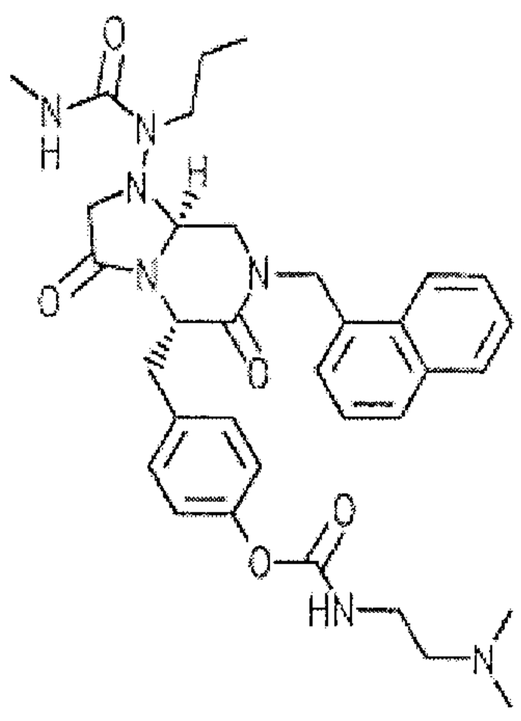
or a pharmaceutically acceptable salt thereof.

490. The compound of claim 1, which is:



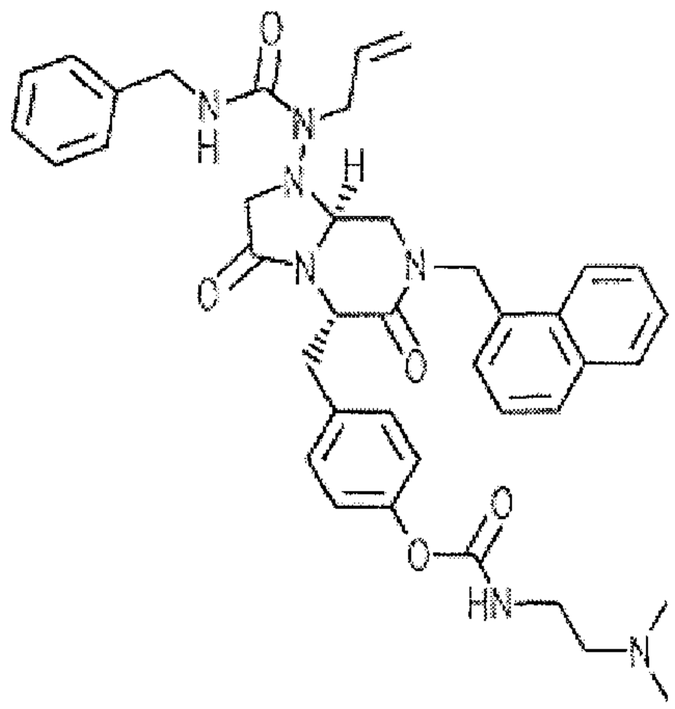
or a pharmaceutically acceptable salt thereof.

491. The compound of claim 1, which is:



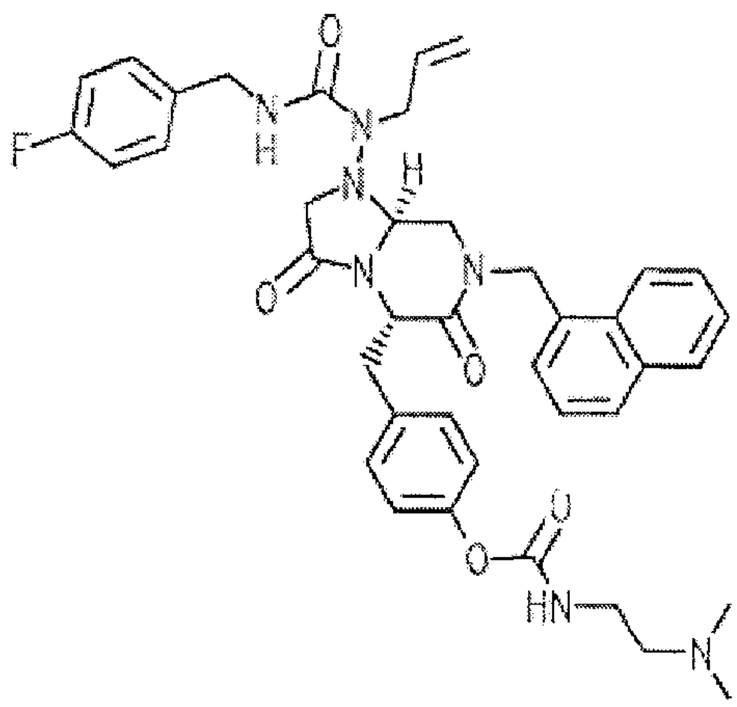
or a pharmaceutically acceptable salt thereof.

492. The compound of claim 1, which is:



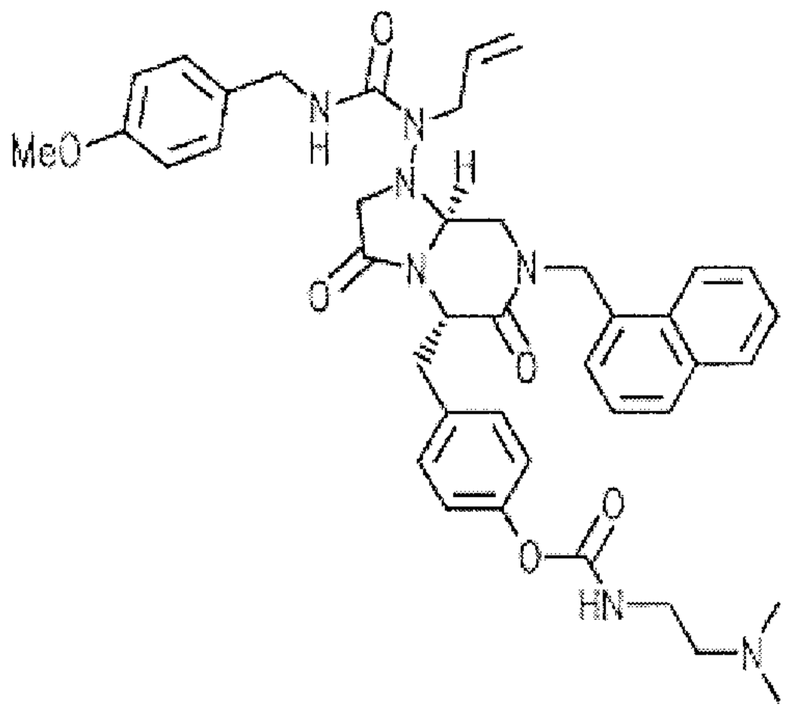
or a pharmaceutically acceptable salt thereof.

493. The compound of claim 1, which is:



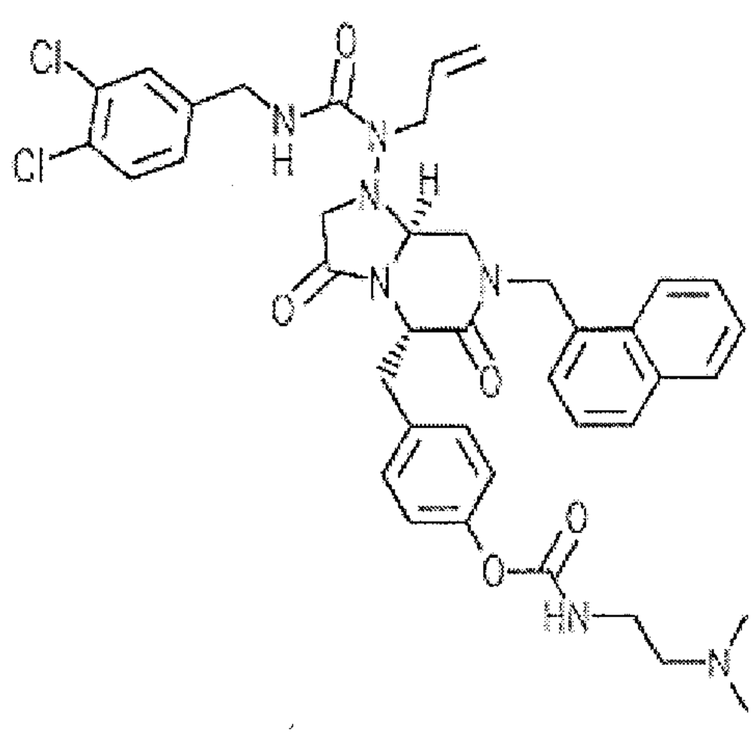
or a pharmaceutically acceptable salt thereof.

494. The compound of claim 1, which is:



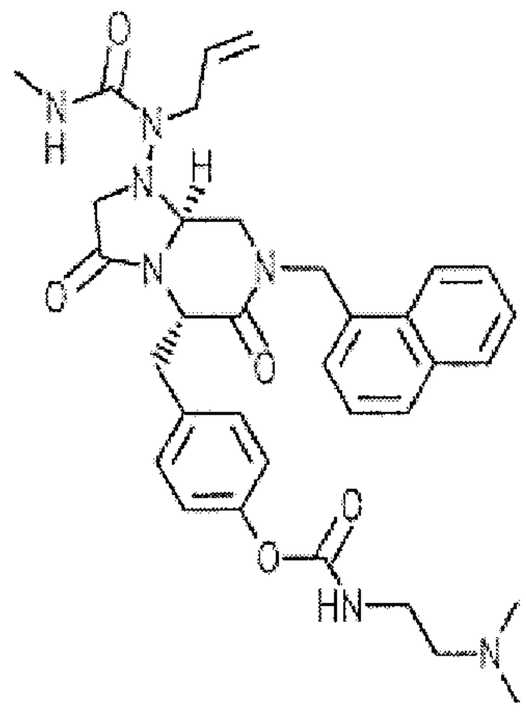
or a pharmaceutically acceptable salt thereof.

495. The compound of claim 1, which is:



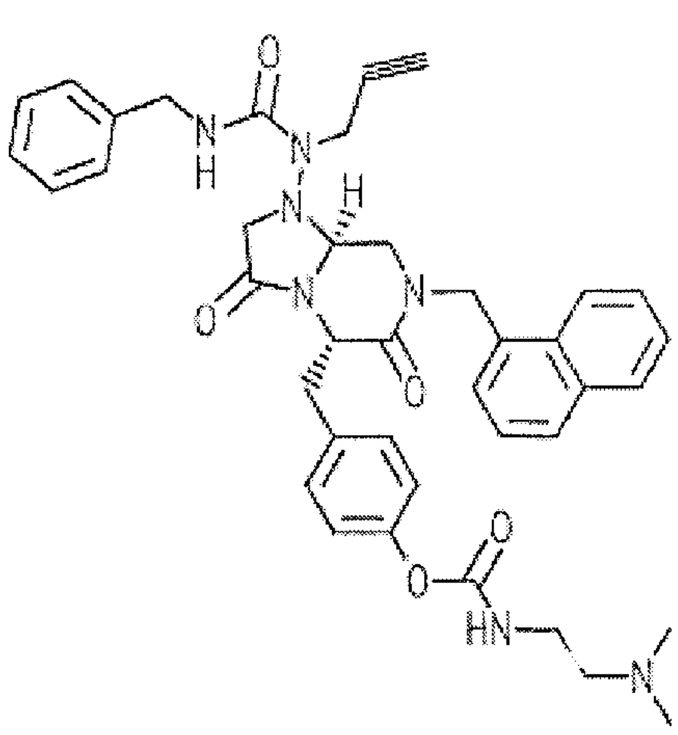
or a pharmaceutically acceptable salt thereof.

496. The compound of claim 1, which is:



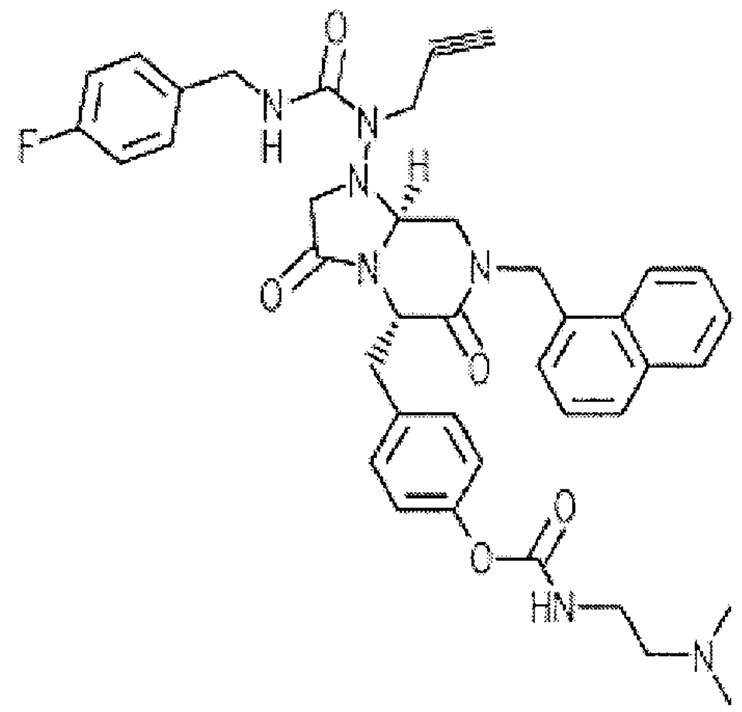
or a pharmaceutically acceptable salt thereof.

497. The compound of claim 1, which is:



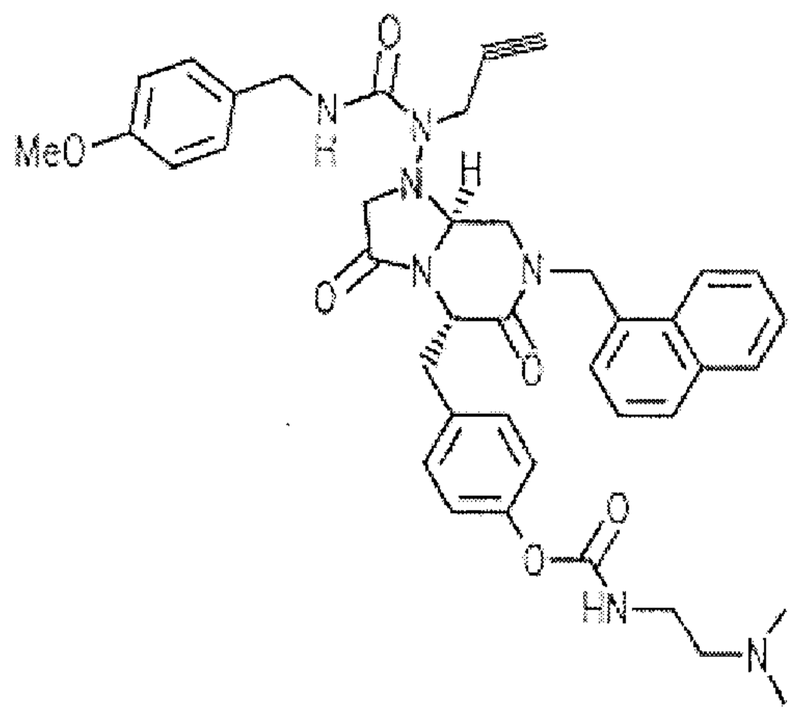
or a pharmaceutically acceptable salt thereof.

498. The compound of claim 1, which is:



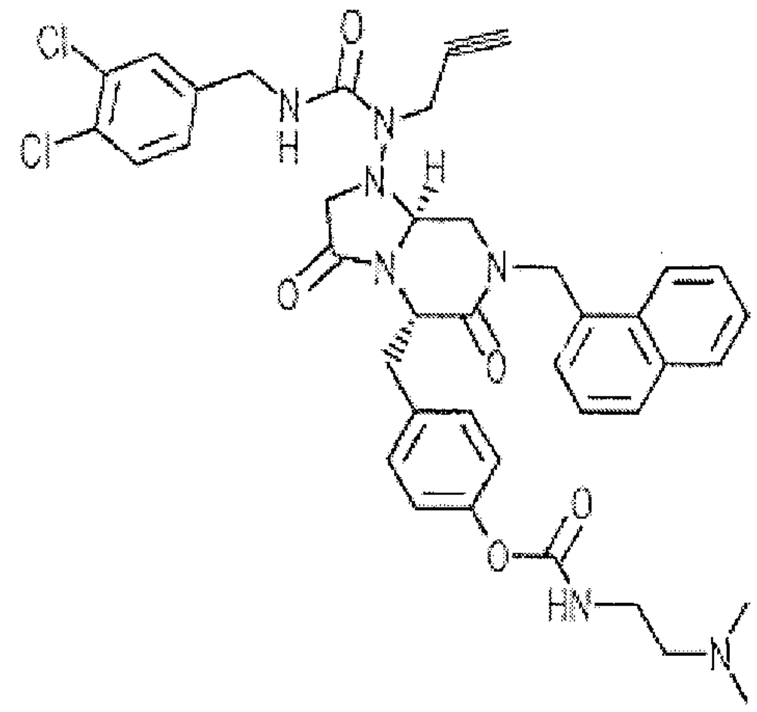
or a pharmaceutically acceptable salt thereof.

499. The compound of claim 1, which is:



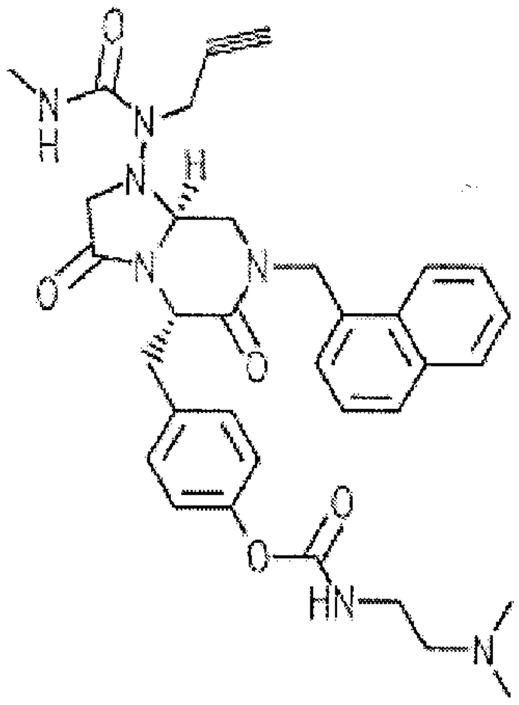
or a pharmaceutically acceptable salt thereof.

500. The compound of claim 1, which is:



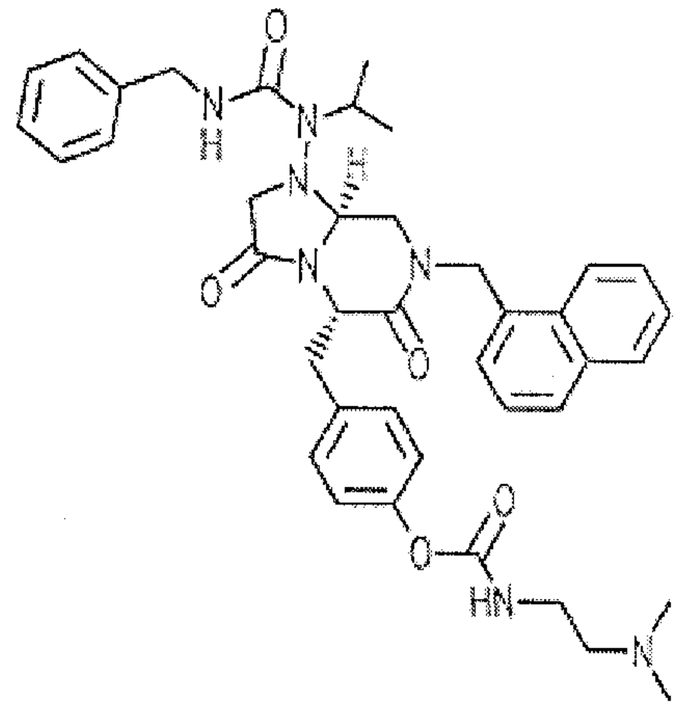
or a pharmaceutically acceptable salt thereof.

501. The compound of claim 1, which is:



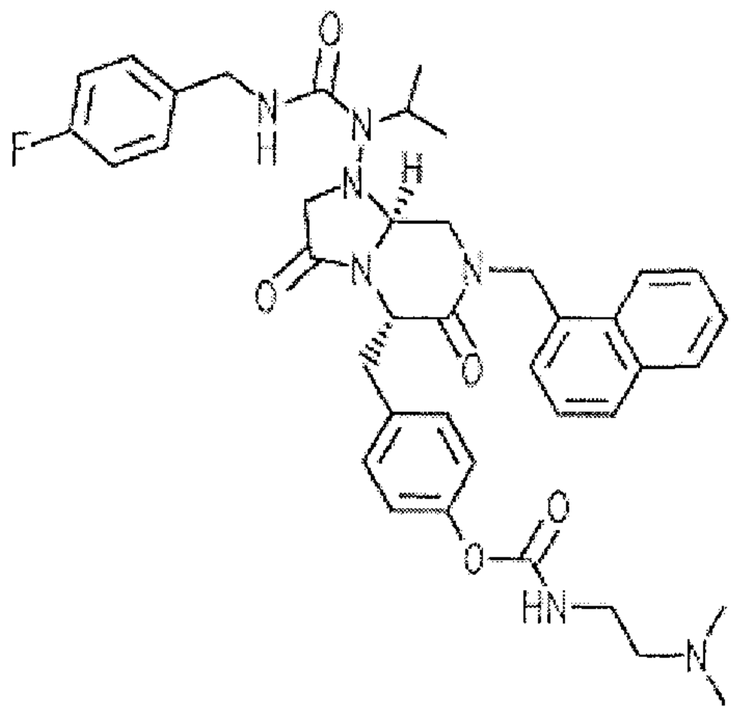
or a pharmaceutically acceptable salt thereof.

502. The compound of claim 1, which is:



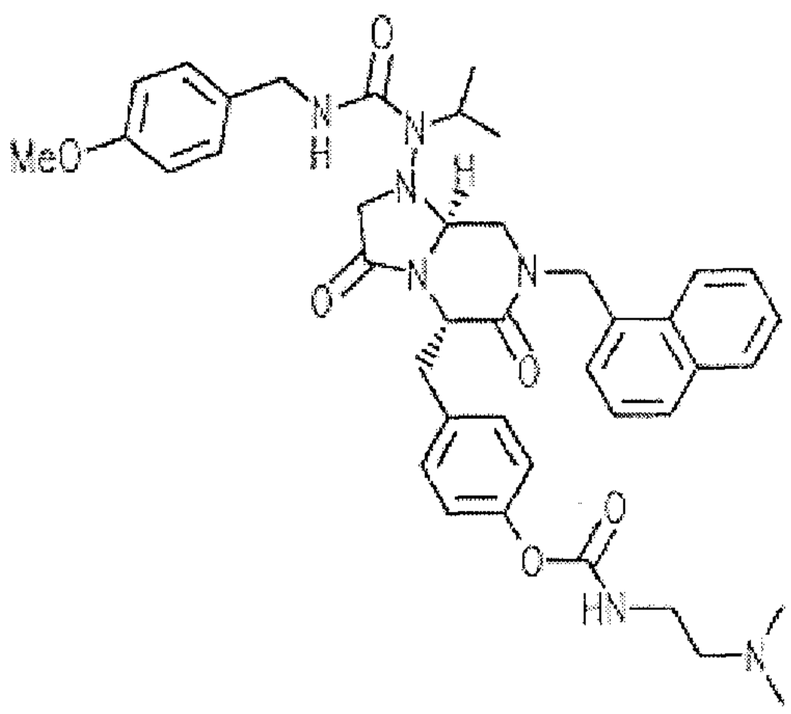
or a pharmaceutically acceptable salt thereof.

503. The compound of claim 1, which is:



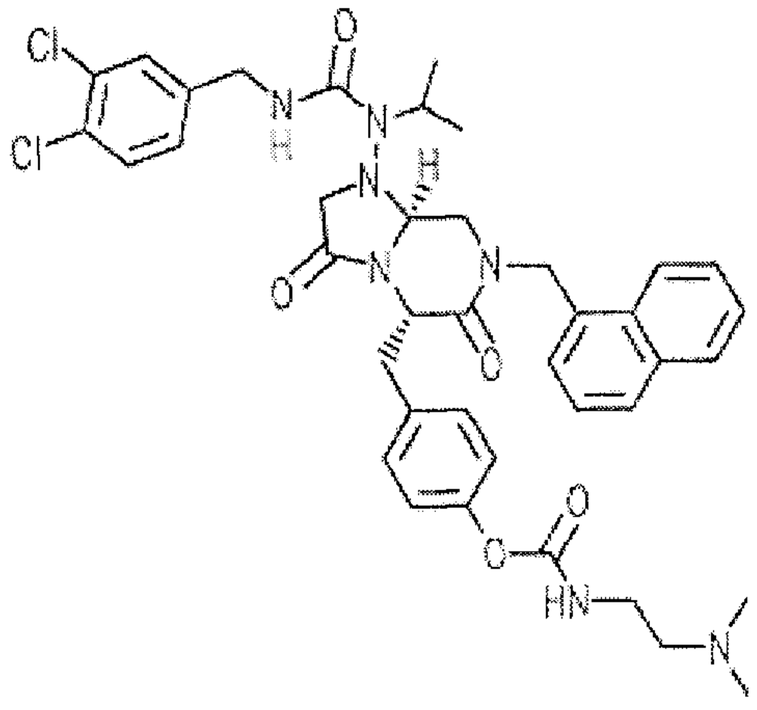
or a pharmaceutically acceptable salt thereof.

504. The compound of claim 1, which is:



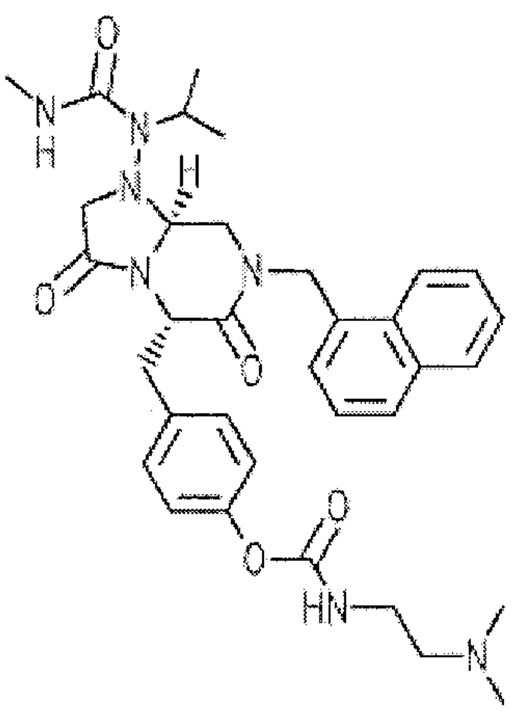
or a pharmaceutically acceptable salt thereof.

505. The compound of claim 1, which is:



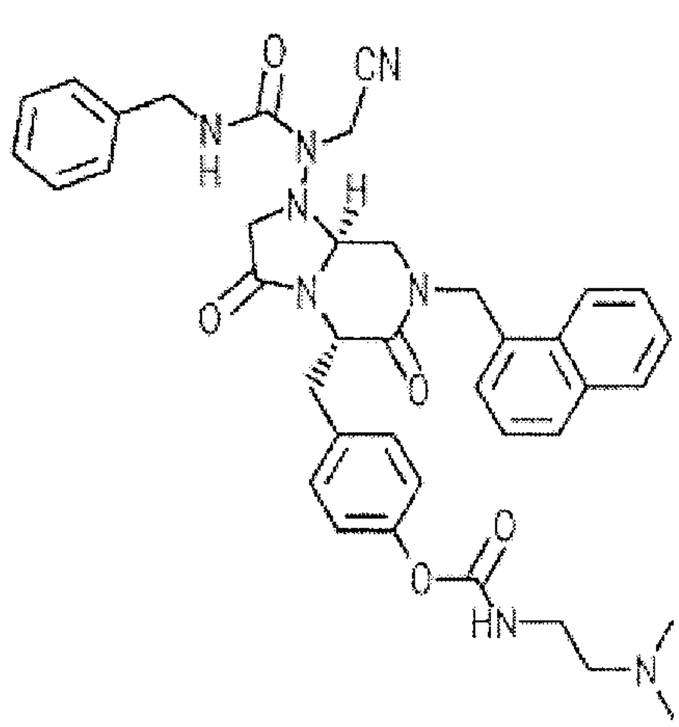
or a pharmaceutically acceptable salt thereof.

506. The compound of claim 1, which is:



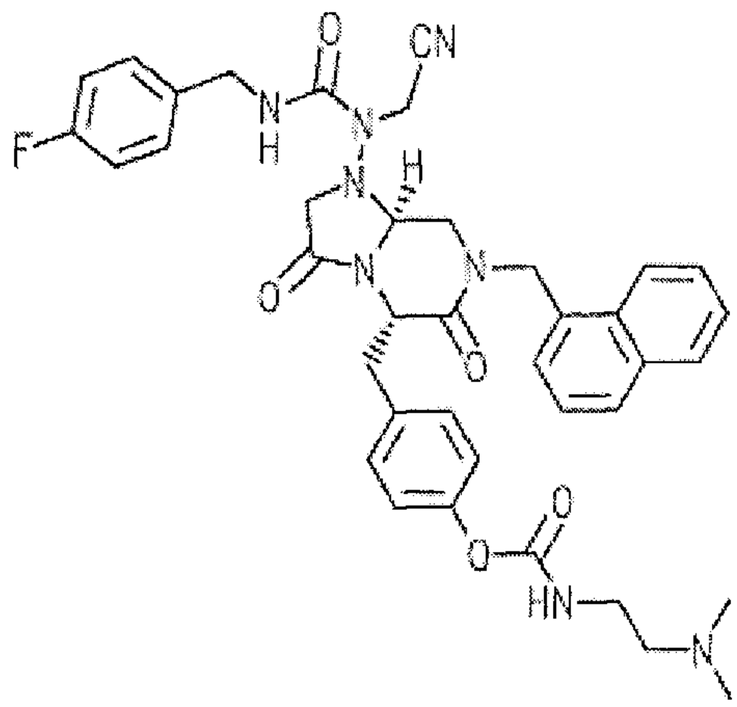
or a pharmaceutically acceptable salt thereof.

507. The compound of claim 1, which is:



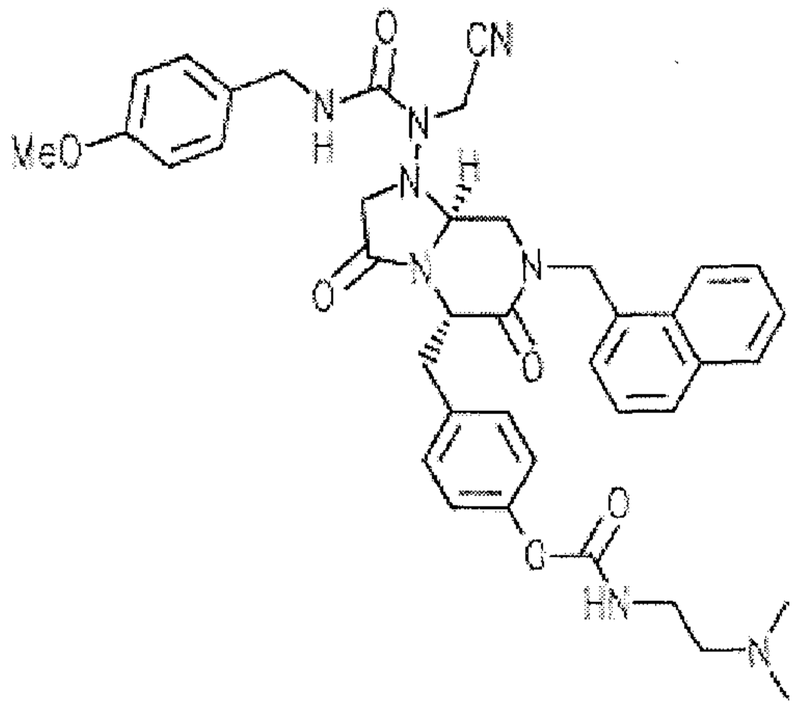
or a pharmaceutically acceptable salt thereof.

508. The compound of claim 1, which is:



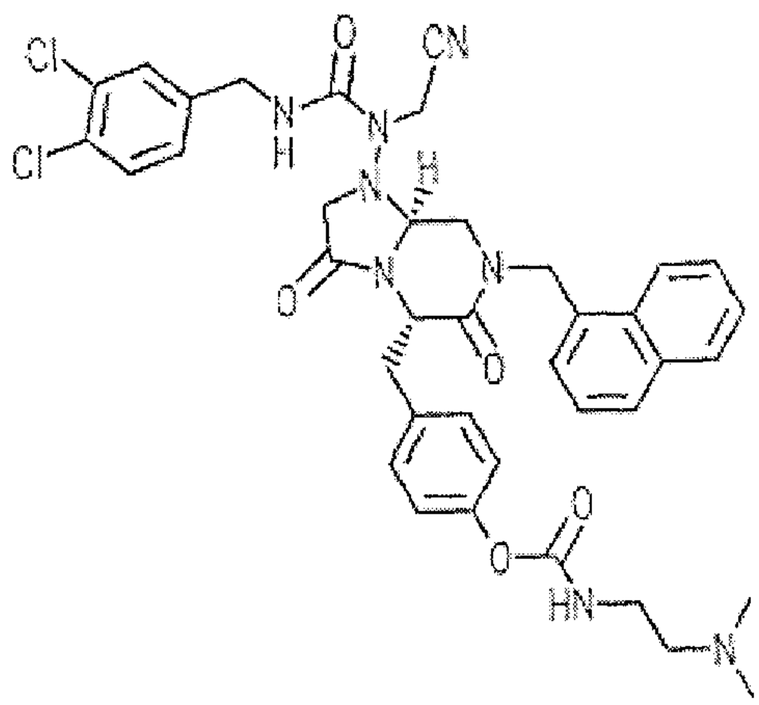
or a pharmaceutically acceptable salt thereof.

509. The compound of claim 1, which is:



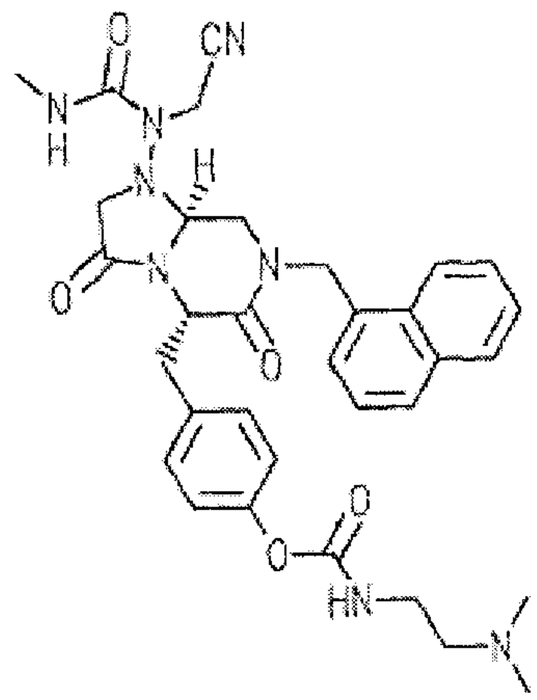
or a pharmaceutically acceptable salt thereof.

510. The compound of claim 1, which is:



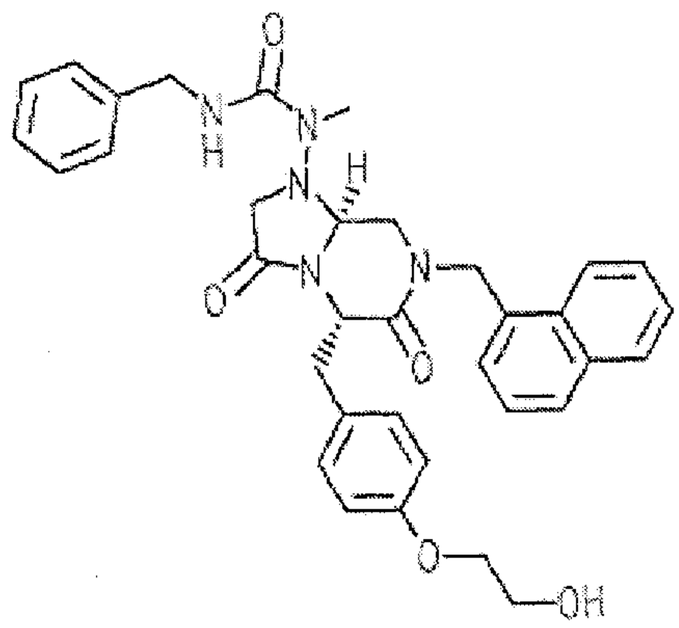
or a pharmaceutically acceptable salt thereof.

511. The compound of claim 1, which is:



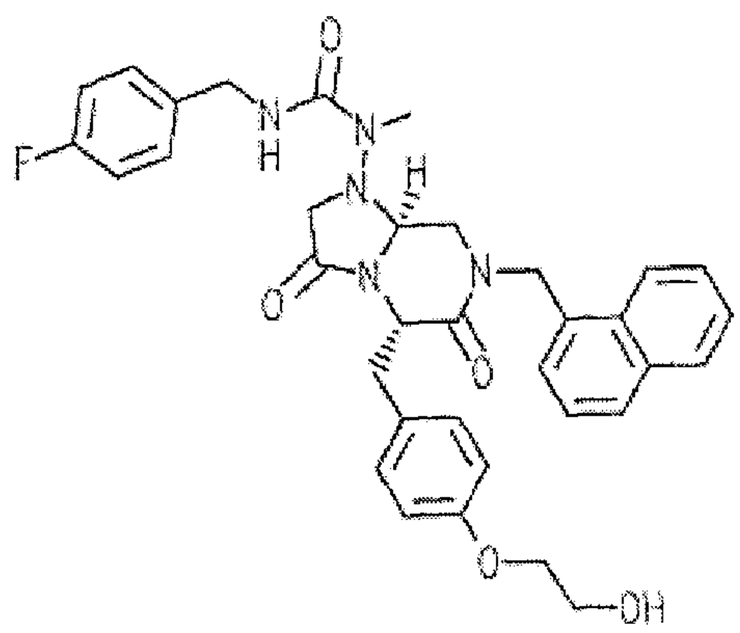
or a pharmaceutically acceptable salt thereof.

512. The compound of claim 1, which is:



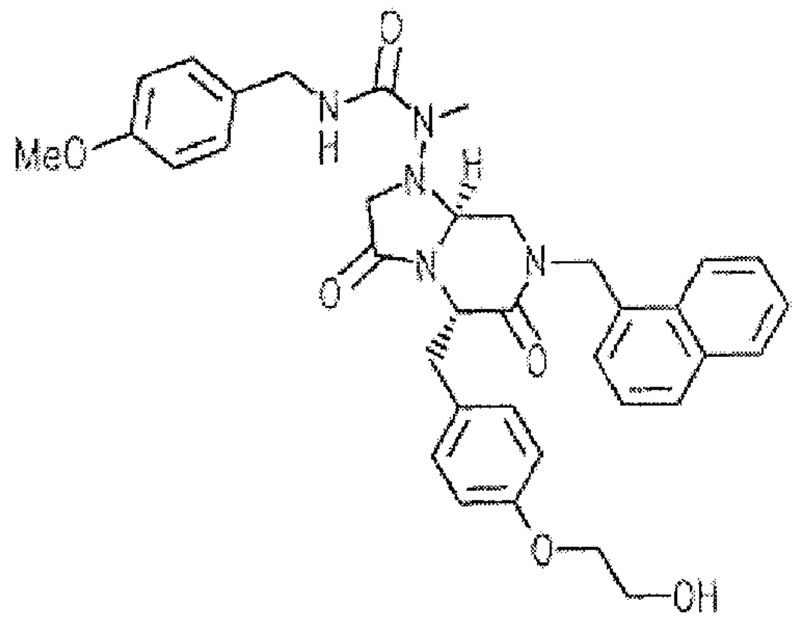
or a pharmaceutically acceptable salt thereof.

513. The compound of claim 1, which is:



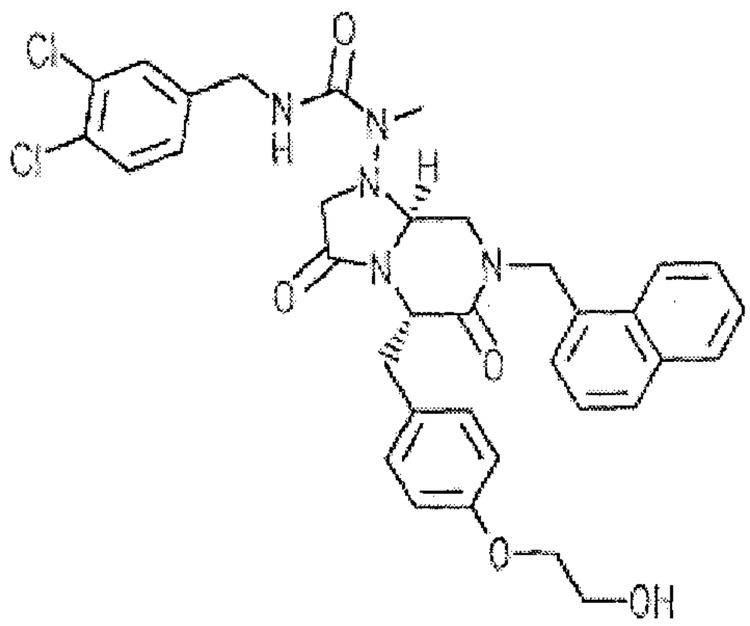
or a pharmaceutically acceptable salt thereof.

514. The compound of claim 1, which is:



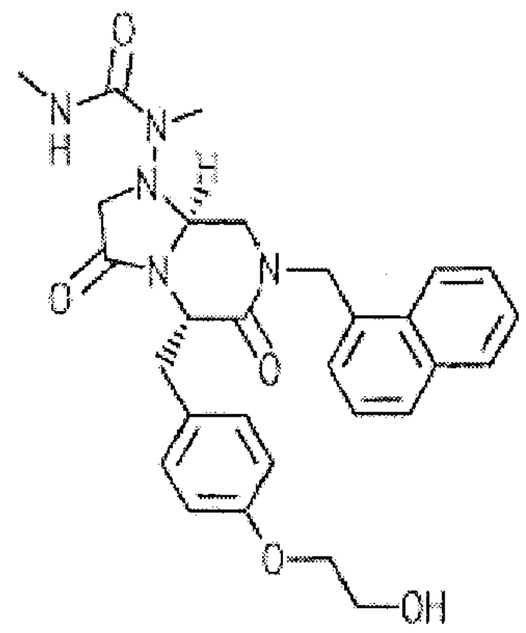
or a pharmaceutically acceptable salt thereof.

515. The compound of claim 1, which is:



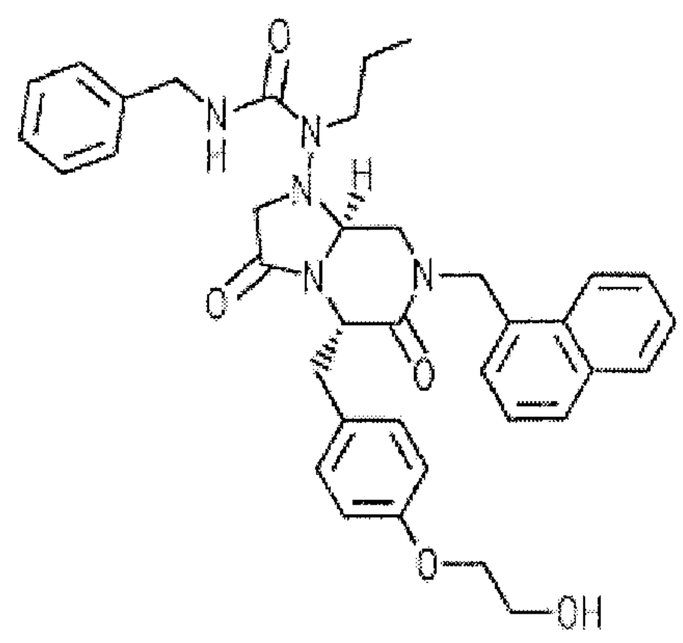
or a pharmaceutically acceptable salt thereof.

516. The compound of claim 1, which is:



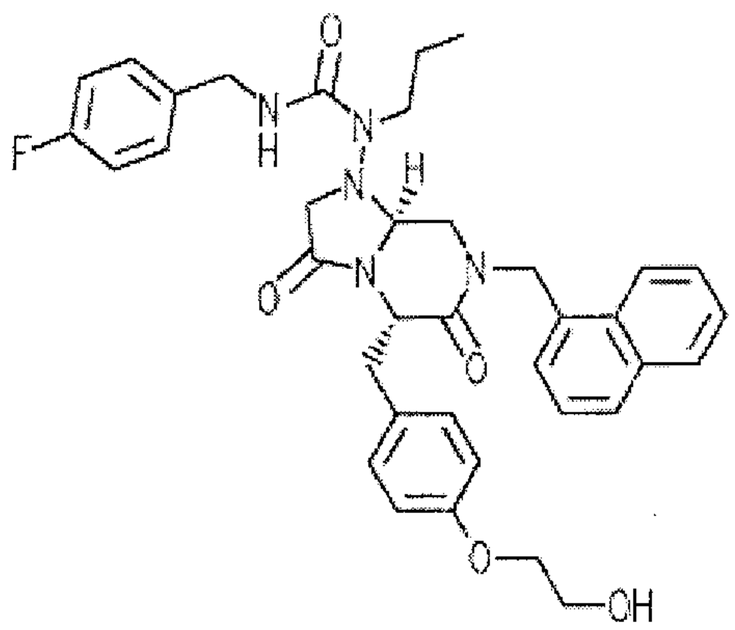
or a pharmaceutically acceptable salt thereof.

517. The compound of claim 1, which is:



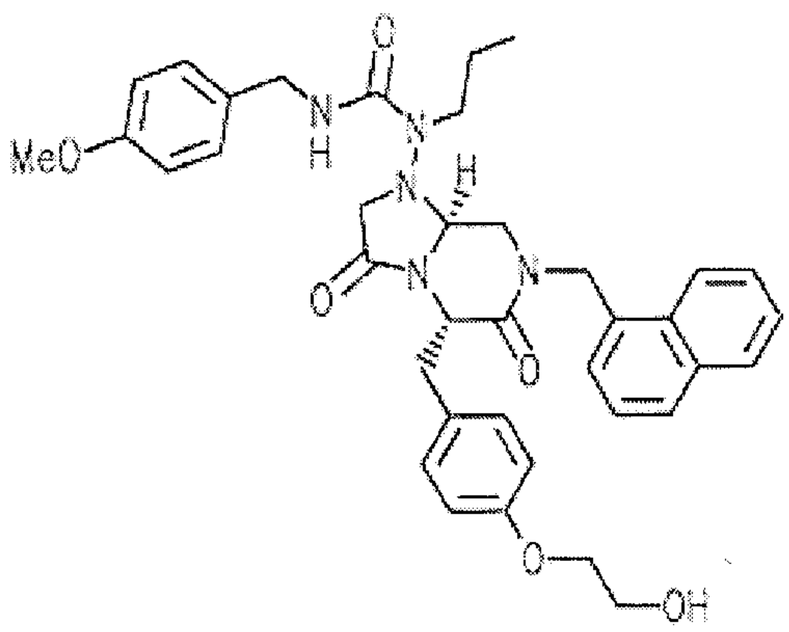
or a pharmaceutically acceptable salt thereof.

518. The compound of claim 1, which is:



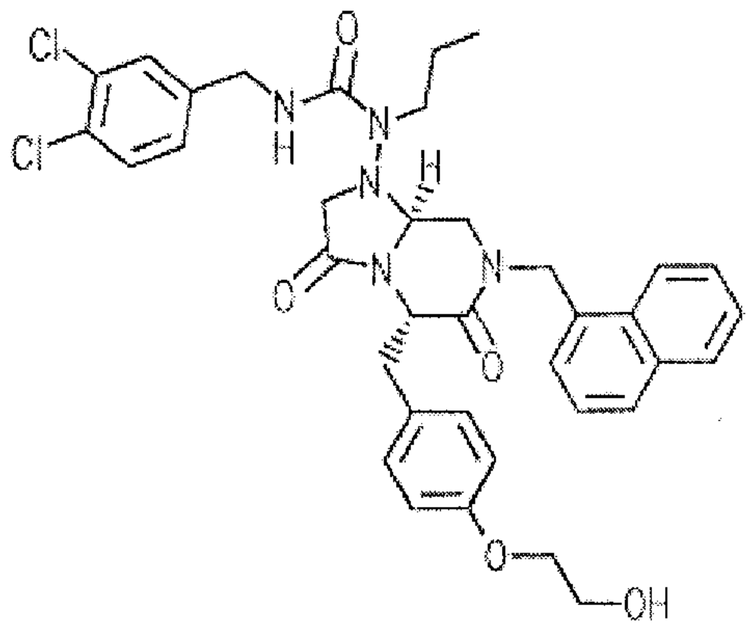
or a pharmaceutically acceptable salt thereof.

519. The compound of claim 1, which is:



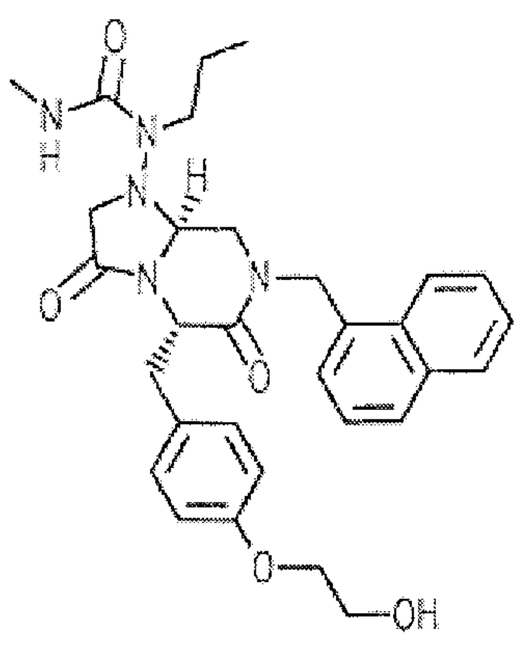
or a pharmaceutically acceptable salt thereof.

520. The compound of claim 1, which is:



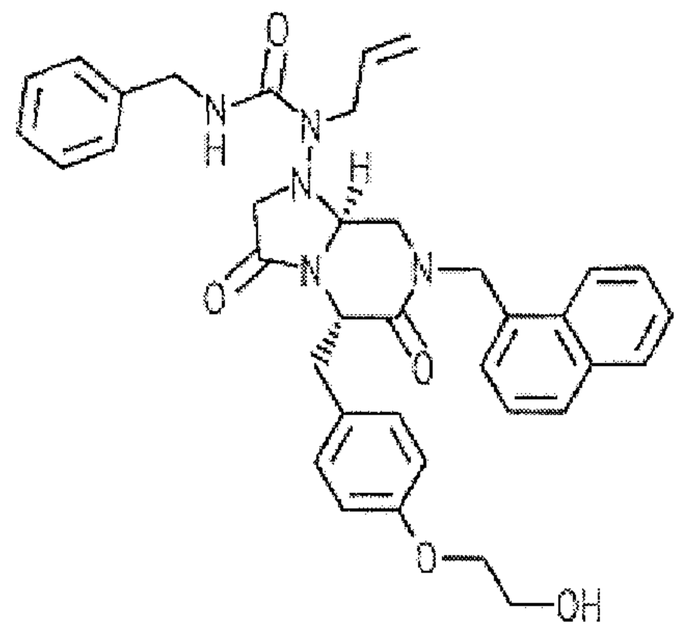
or a pharmaceutically acceptable salt thereof.

521. The compound of claim 1, which is:



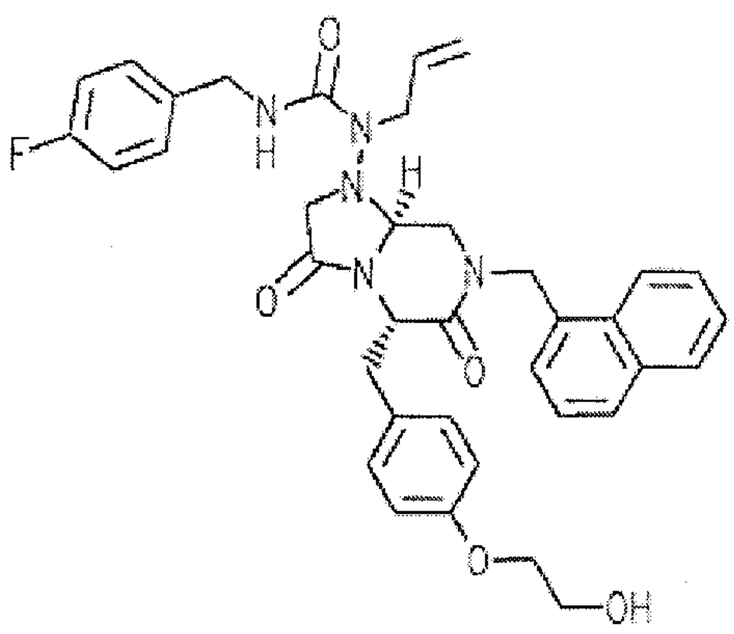
or a pharmaceutically acceptable salt thereof.

522. The compound of claim 1, which is:



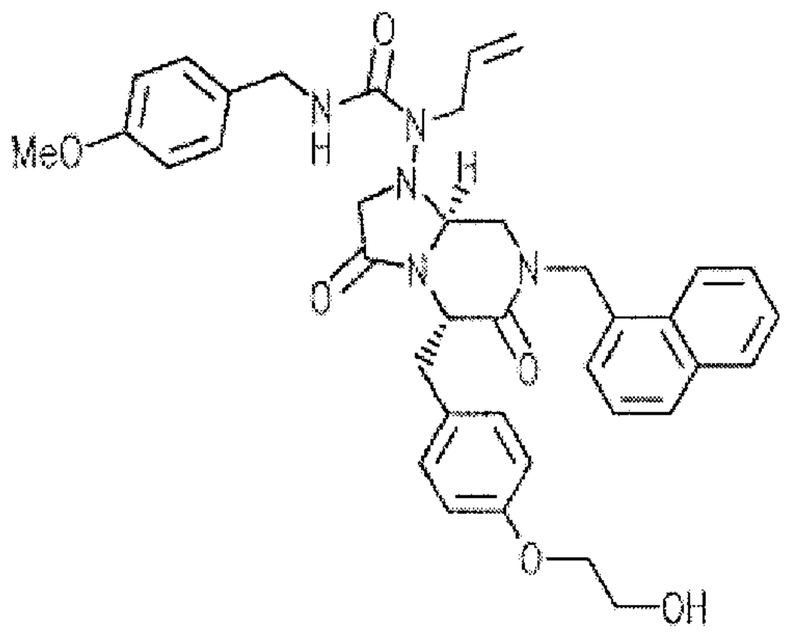
or a pharmaceutically acceptable salt thereof.

523. The compound of claim 1, which is:



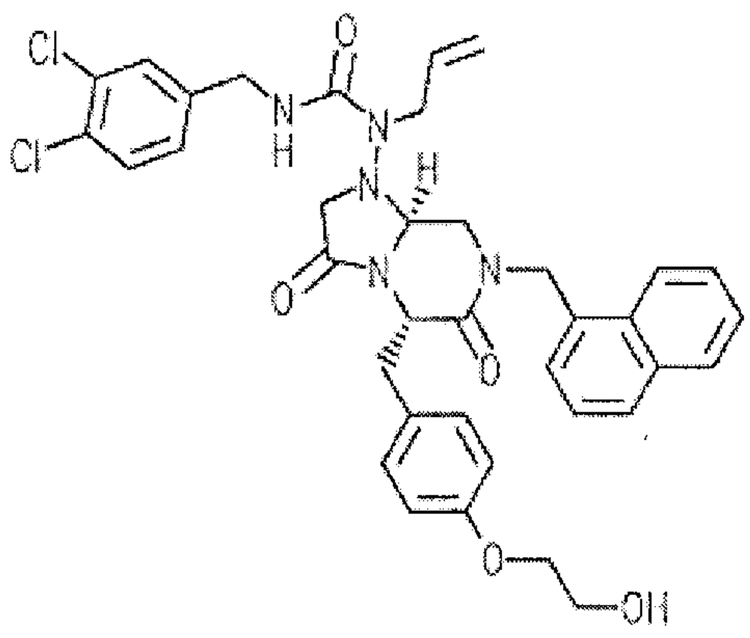
or a pharmaceutically acceptable salt thereof.

524. The compound of claim 1, which is:



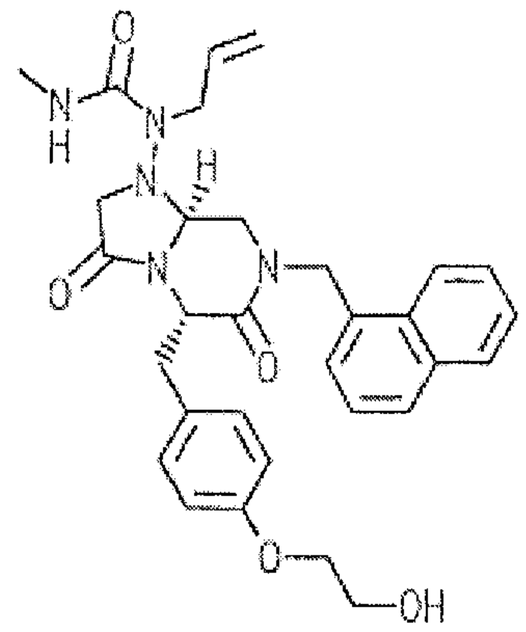
or a pharmaceutically acceptable salt thereof.

525. The compound of claim 1, which is:



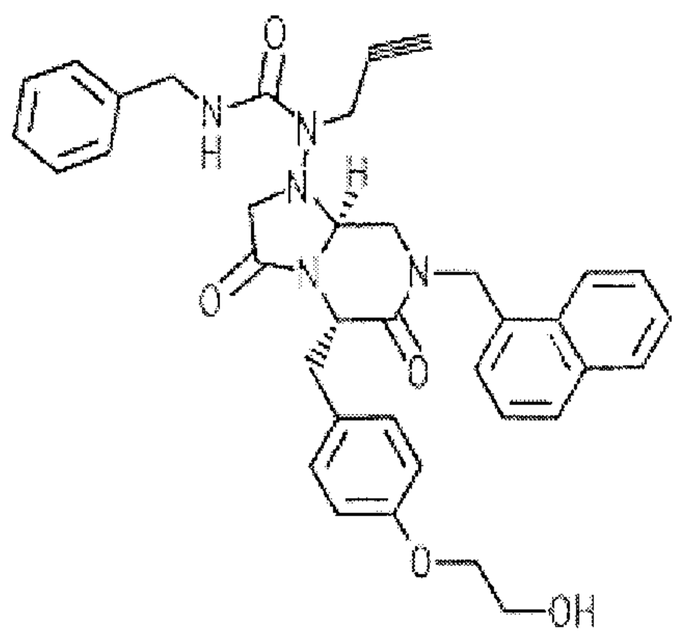
or a pharmaceutically acceptable salt thereof.

526. The compound of claim 1, which is:



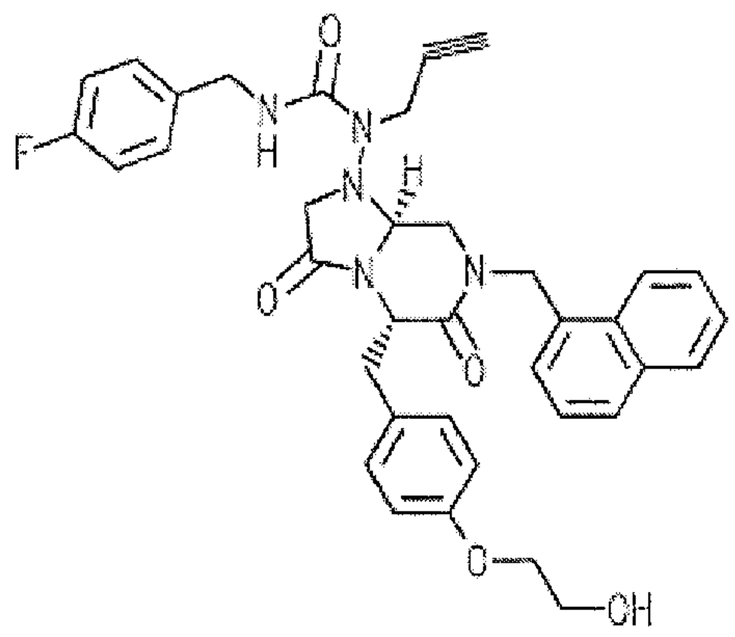
or a pharmaceutically acceptable salt thereof.

527. The compound of claim 1, which is:



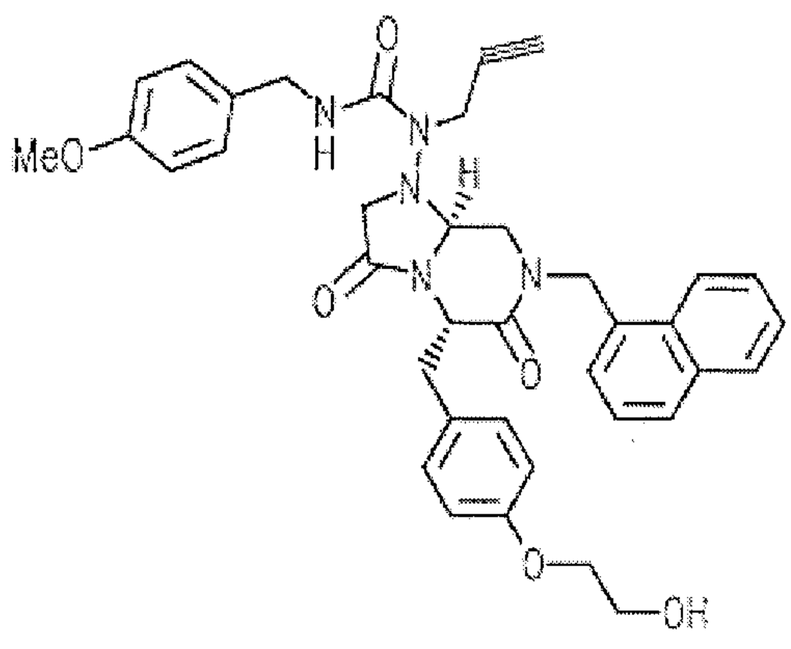
or a pharmaceutically acceptable salt thereof.

528. The compound of claim 1, which is:



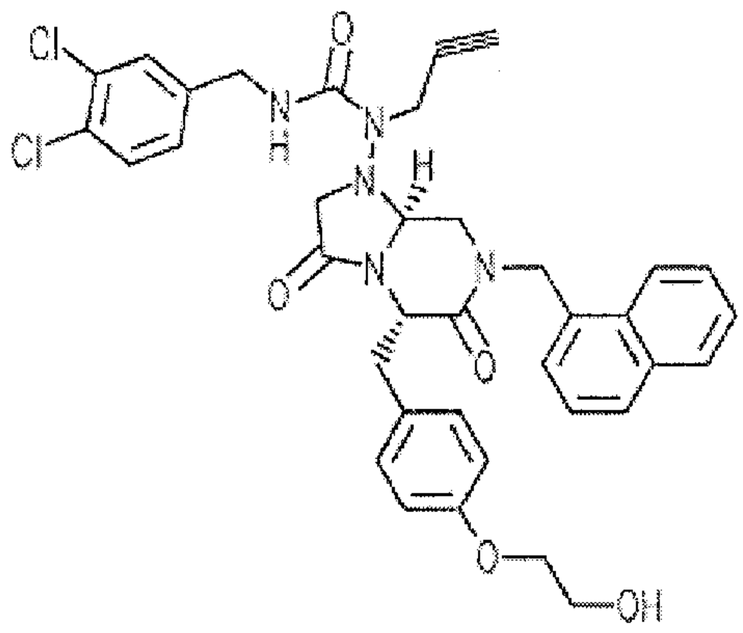
or a pharmaceutically acceptable salt thereof.

529. The compound of claim 1, which is:



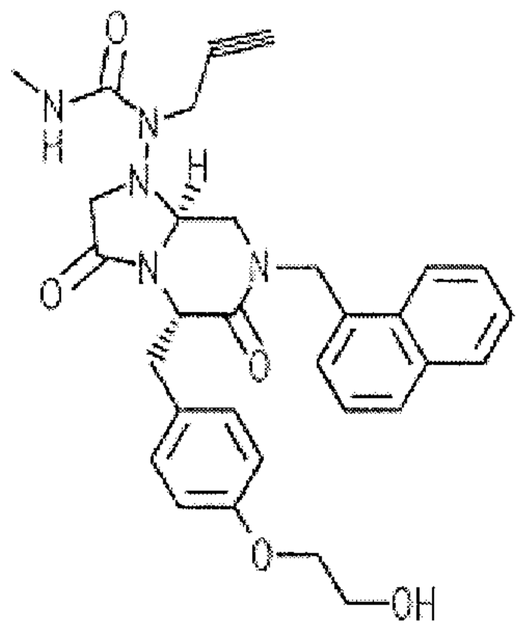
or a pharmaceutically acceptable salt thereof.

530. The compound of claim 1, which is:



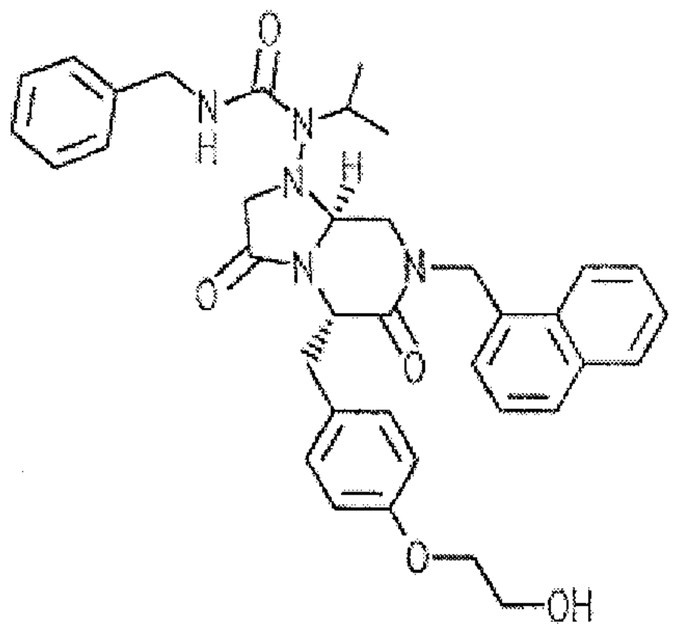
or a pharmaceutically acceptable salt thereof.

531. The compound of claim 1, which is:



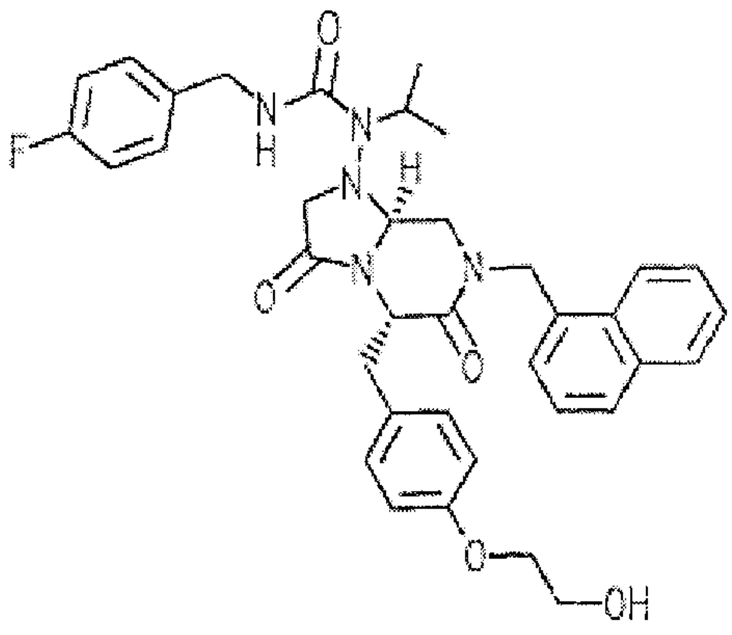
or a pharmaceutically acceptable salt thereof.

532. The compound of claim 1, which is:



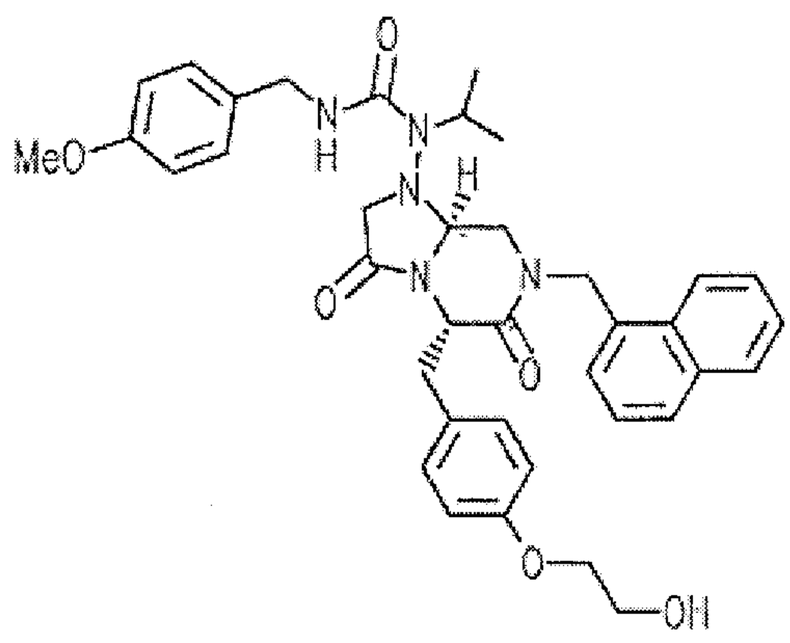
or a pharmaceutically acceptable salt thereof.

533. The compound of claim 1, which is:



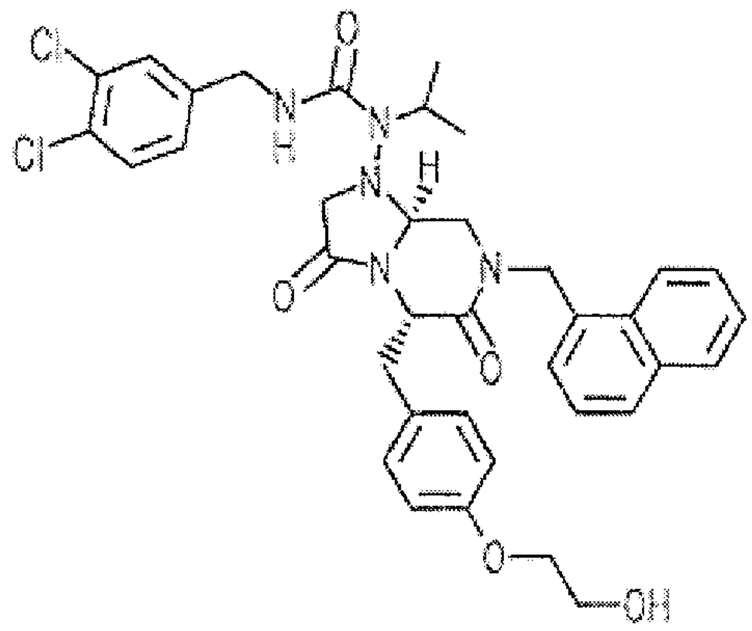
or a pharmaceutically acceptable salt thereof.

534. The compound of claim 1, which is:



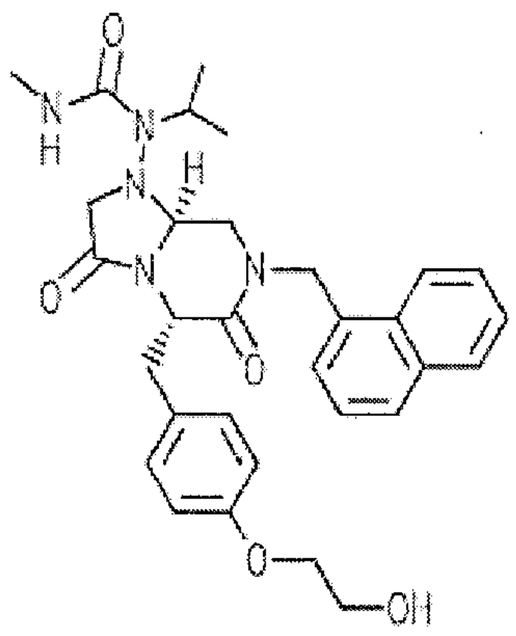
or a pharmaceutically acceptable salt thereof.

535. The compound of claim 1, which is:



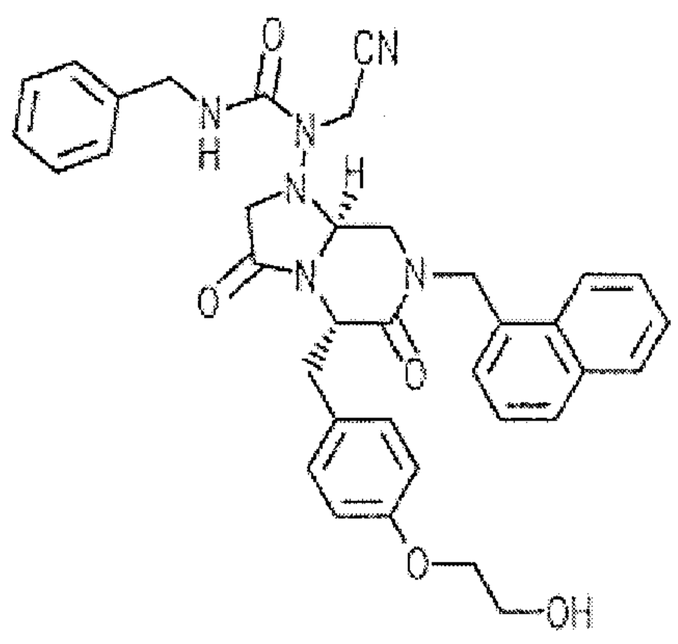
or a pharmaceutically acceptable salt thereof.

536. The compound of claim 1, which is:



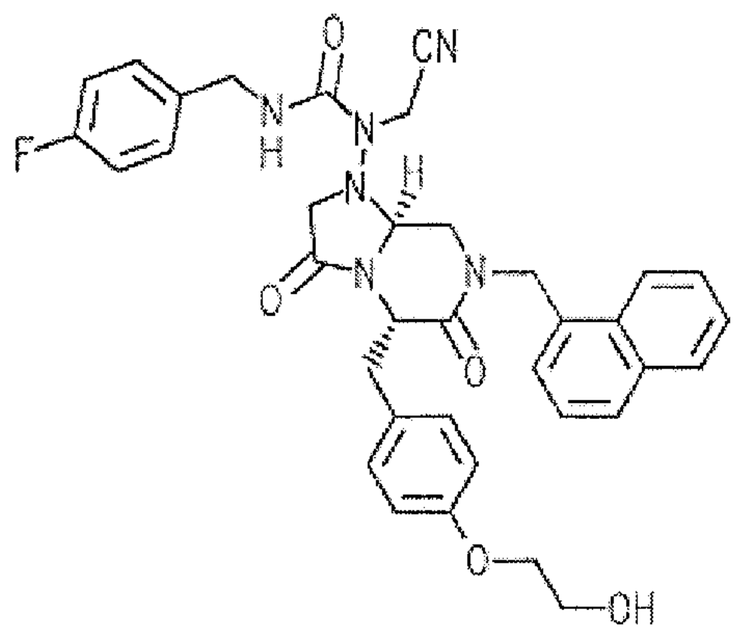
or a pharmaceutically acceptable salt thereof.

537. The compound of claim 1, which is:



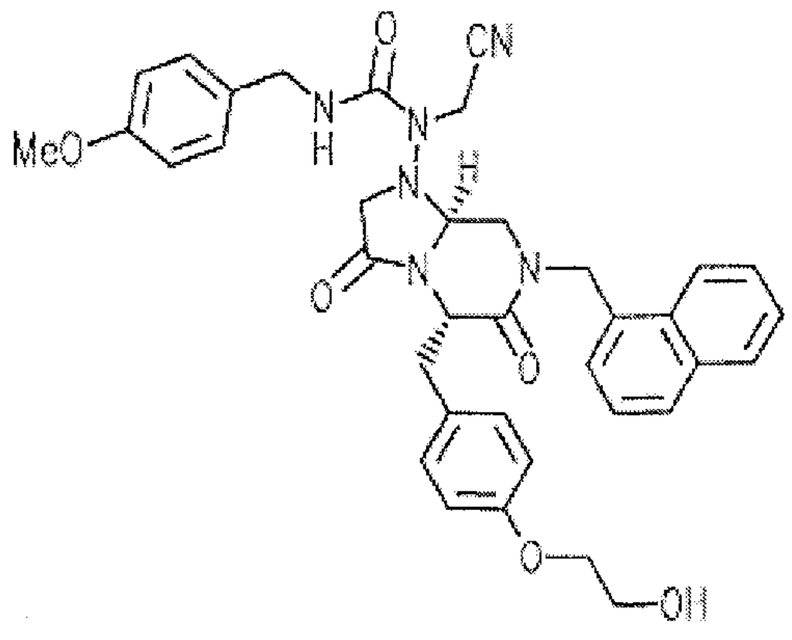
or a pharmaceutically acceptable salt thereof.

538. The compound of claim 1, which is:



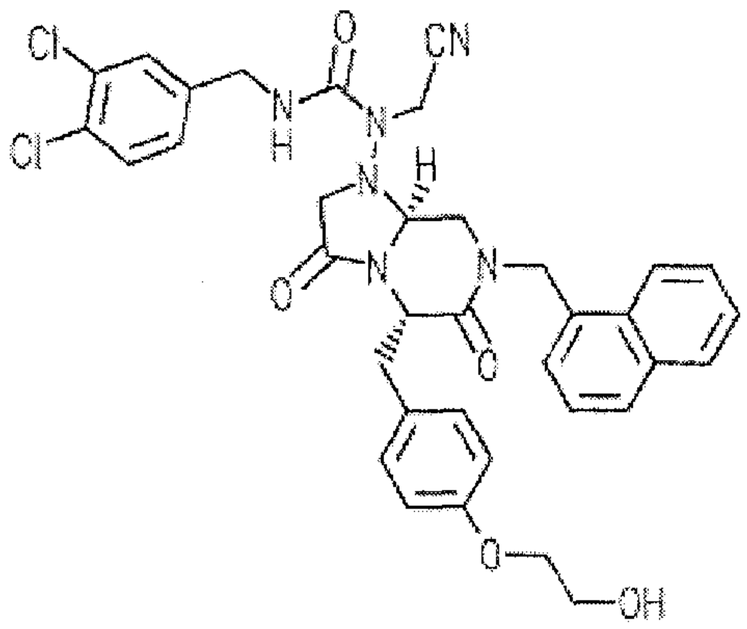
or a pharmaceutically acceptable salt thereof.

539. The compound of claim 1, which is:



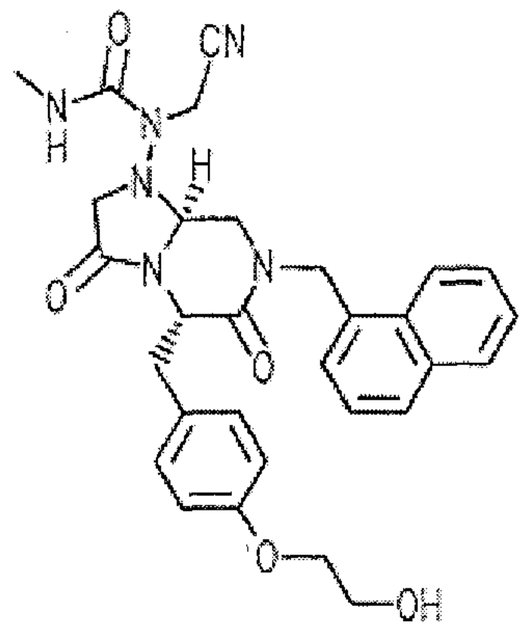
or a pharmaceutically acceptable salt thereof.

540. The compound of claim 1, which is:



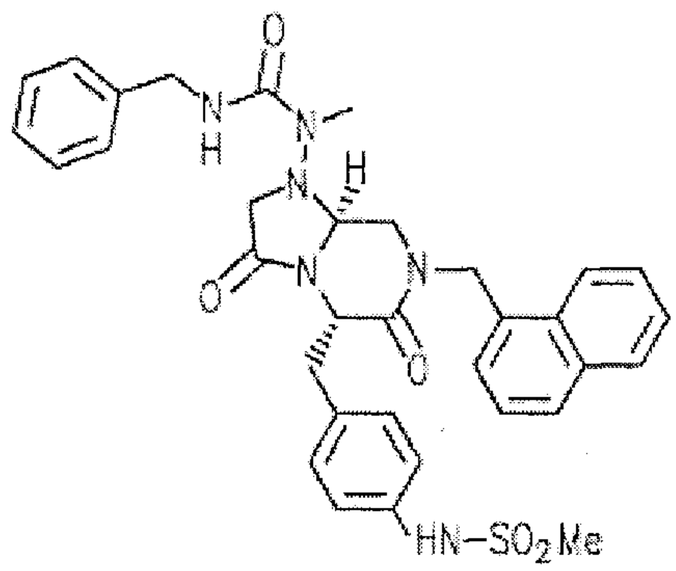
or a pharmaceutically acceptable salt thereof.

541. The compound of claim 1, which is:



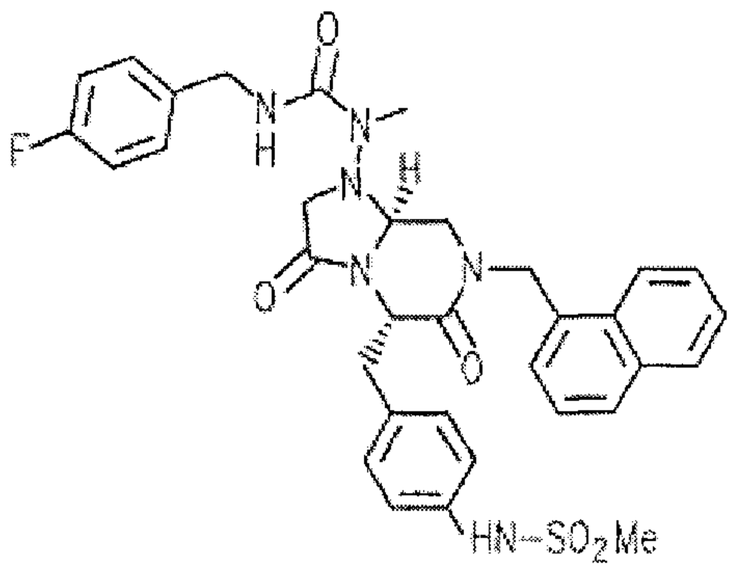
or a pharmaceutically acceptable salt thereof.

542. The compound of claim 1, which is:



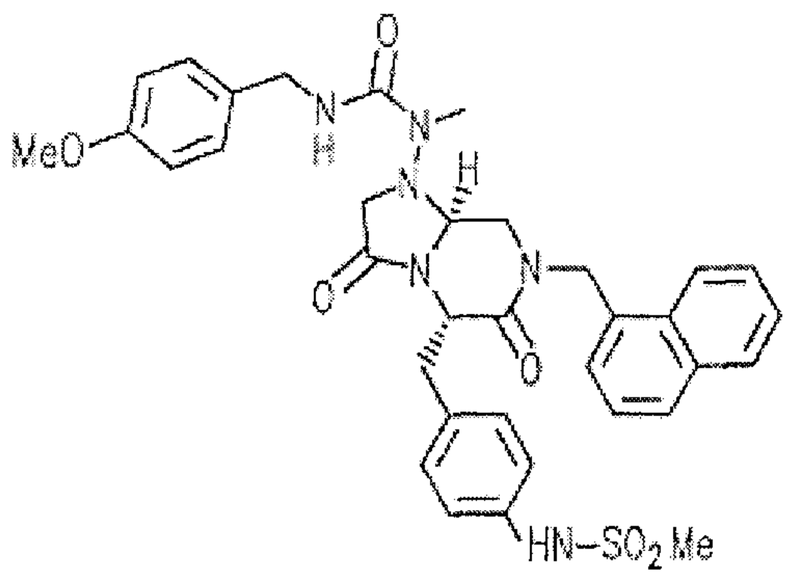
or a pharmaceutically acceptable salt thereof.

543. The compound of claim 1, which is:



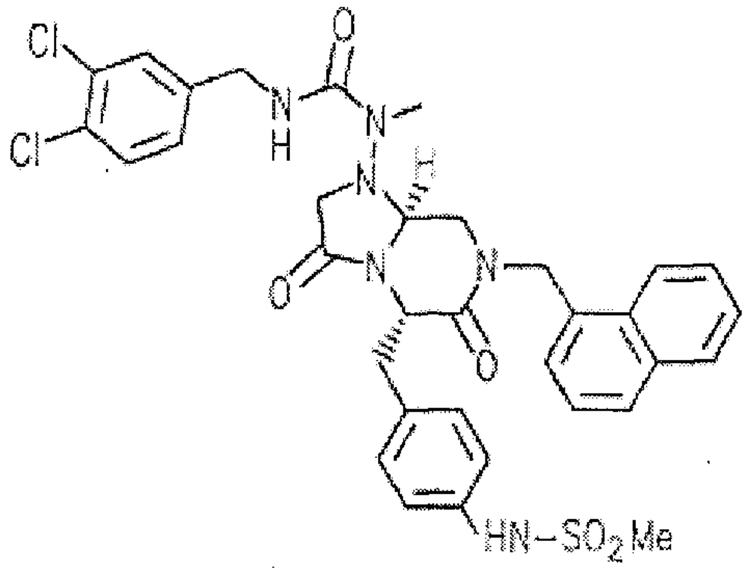
or a pharmaceutically acceptable salt thereof.

544. The compound of claim 1, which is:



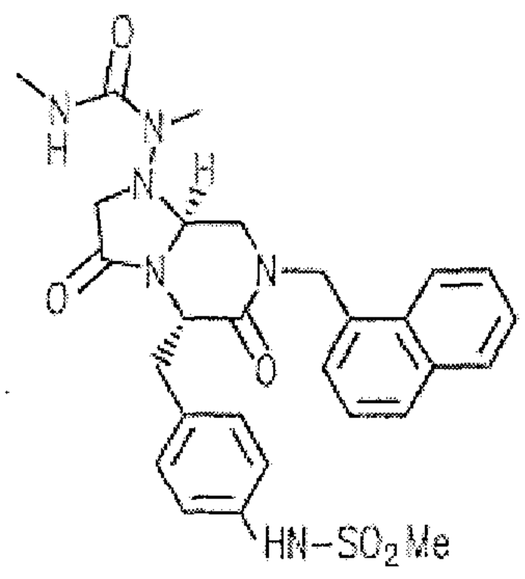
or a pharmaceutically acceptable salt thereof.

545. The compound of claim 1, which is:



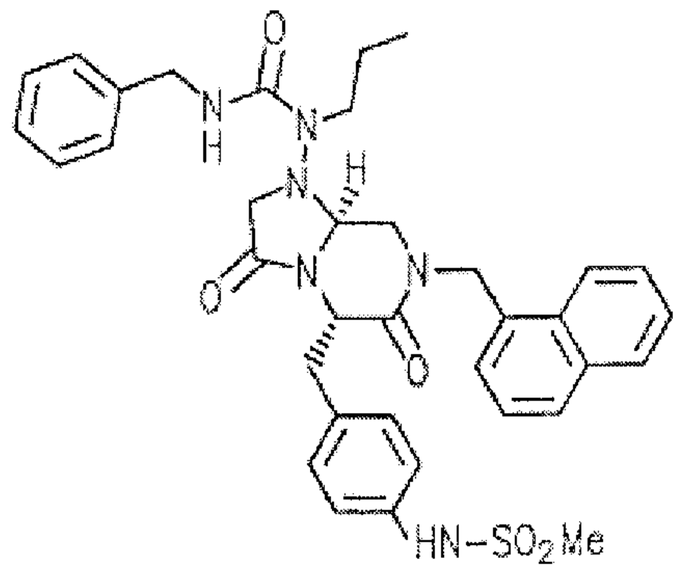
or a pharmaceutically acceptable salt thereof.

546. The compound of claim 1, which is:



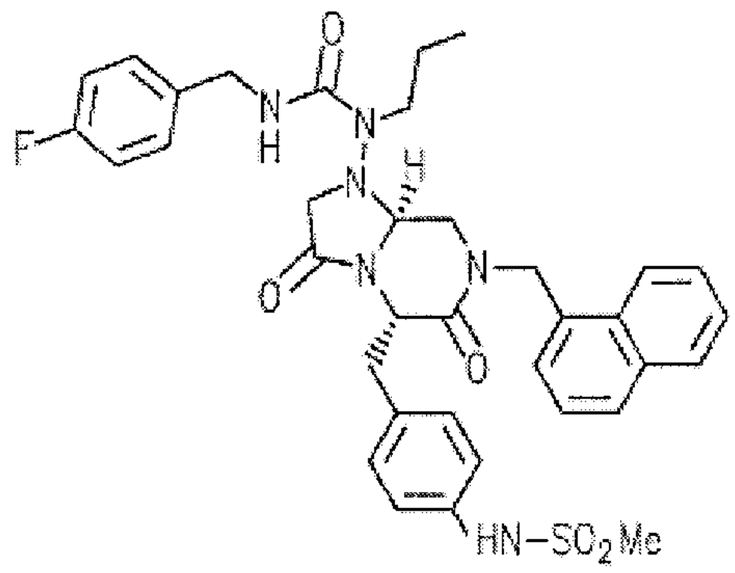
or a pharmaceutically acceptable salt thereof.

547. The compound of claim 1, which is:



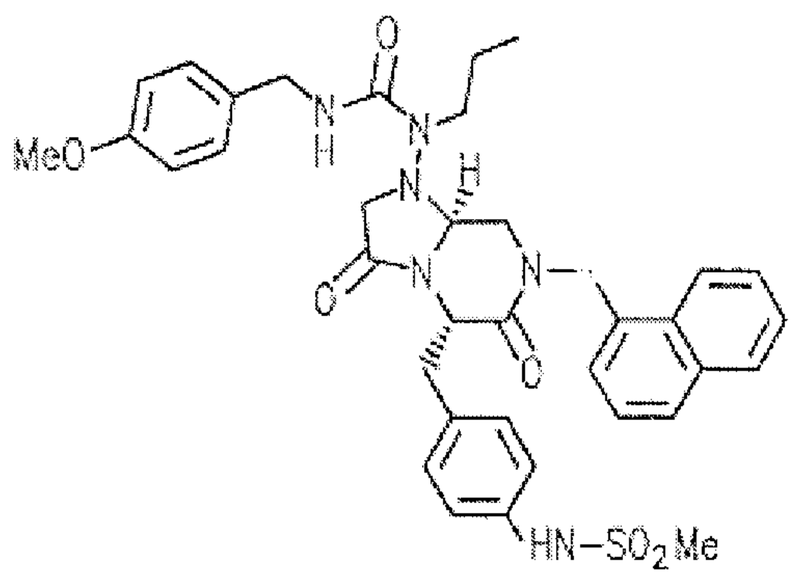
or a pharmaceutically acceptable salt thereof.

548. The compound of claim 1, which is:



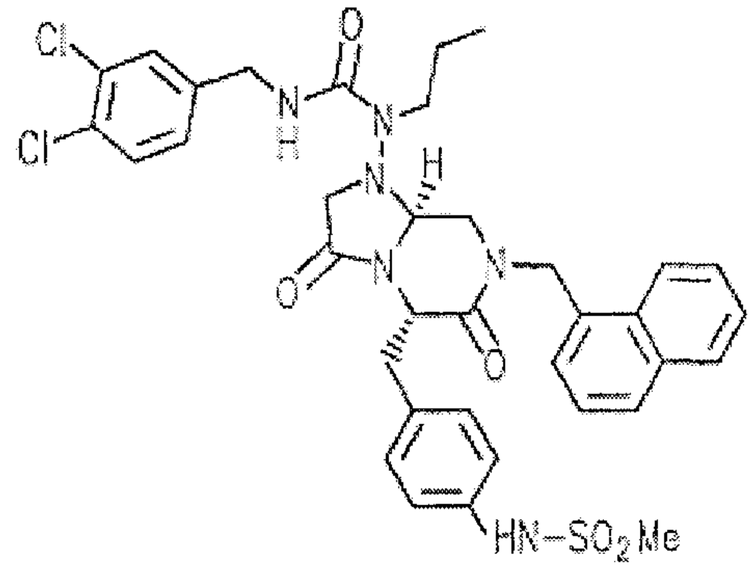
or a pharmaceutically acceptable salt thereof.

549. The compound of claim 1, which is:



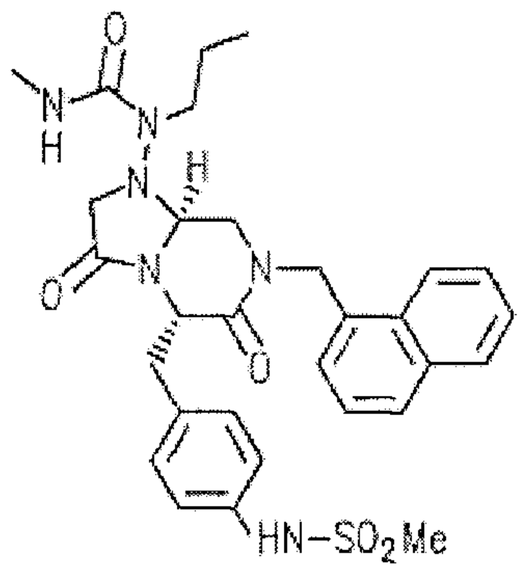
or a pharmaceutically acceptable salt thereof.

550. The compound of claim 1, which is:



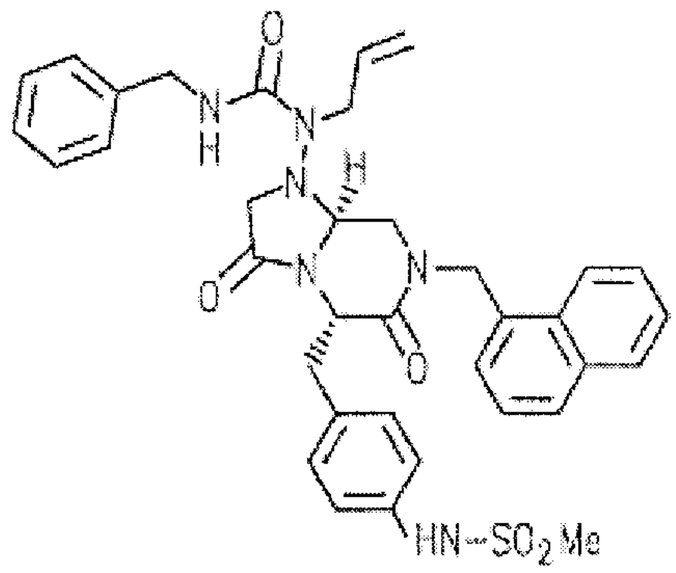
or a pharmaceutically acceptable salt thereof.

551. The compound of claim 1, which is:



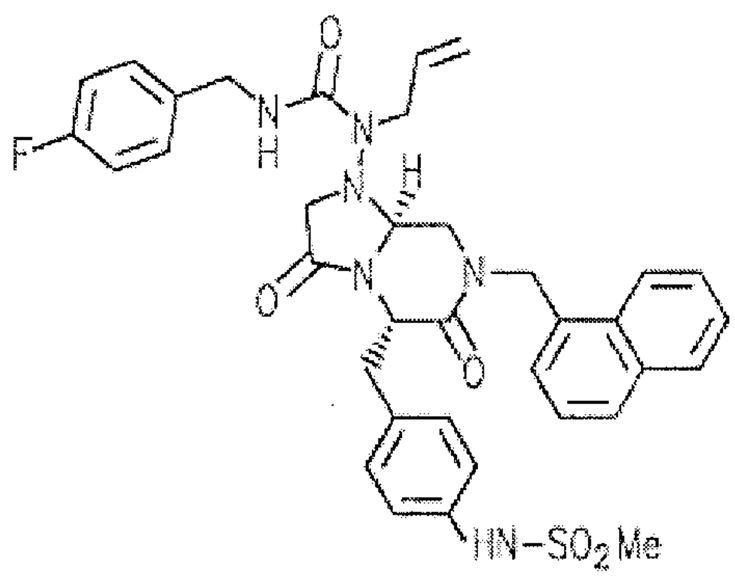
or a pharmaceutically acceptable salt thereof.

552. The compound of claim 1, which is:



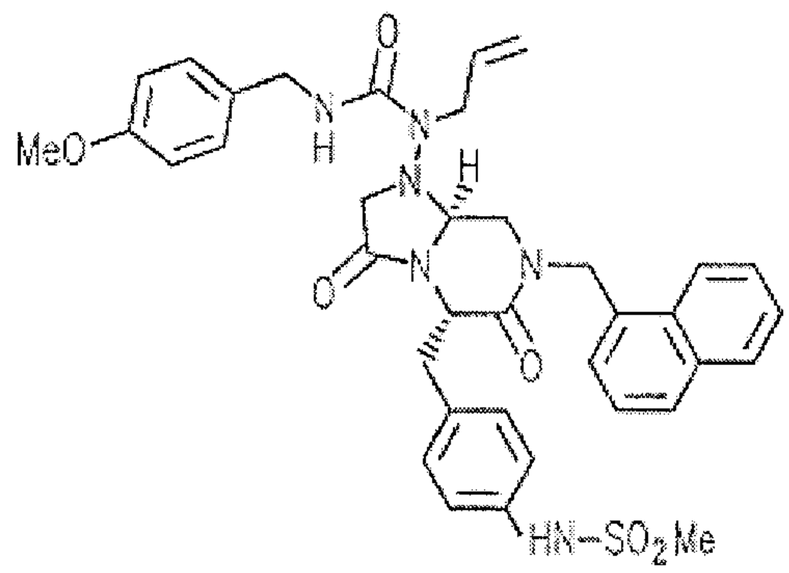
or a pharmaceutically acceptable salt thereof.

553. The compound of claim 1, which is:



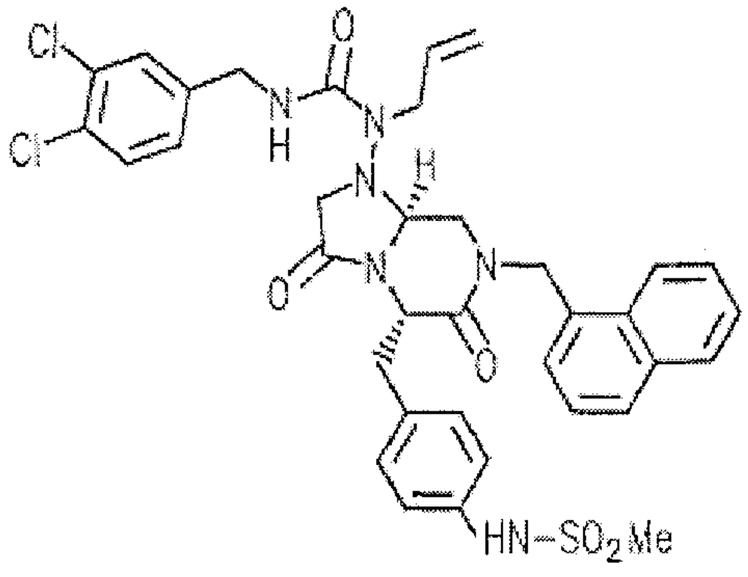
or a pharmaceutically acceptable salt thereof.

554. The compound of claim 1, which is:



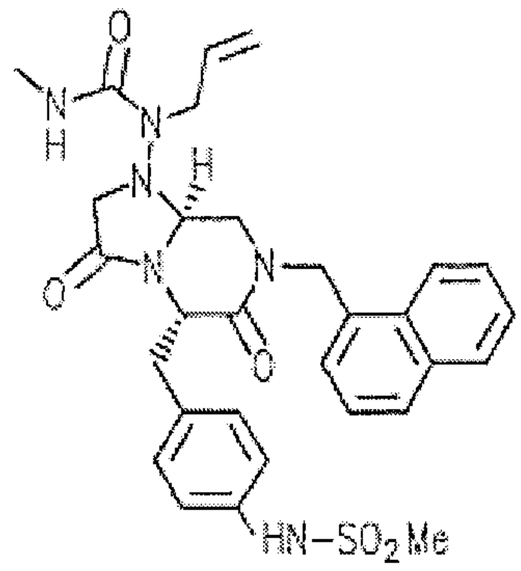
or a pharmaceutically acceptable salt thereof.

555. The compound of claim 1, which is:



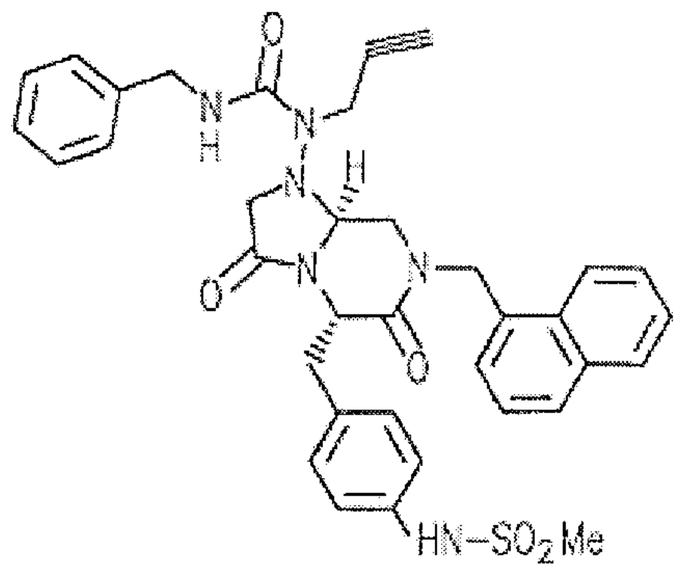
or a pharmaceutically acceptable salt thereof.

556. The compound of claim 1, which is:



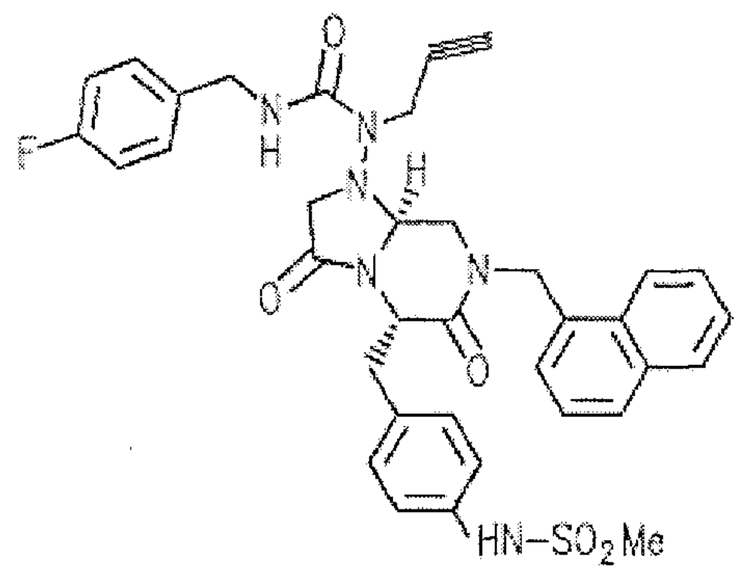
or a pharmaceutically acceptable salt thereof.

557. The compound of claim 1, which is:



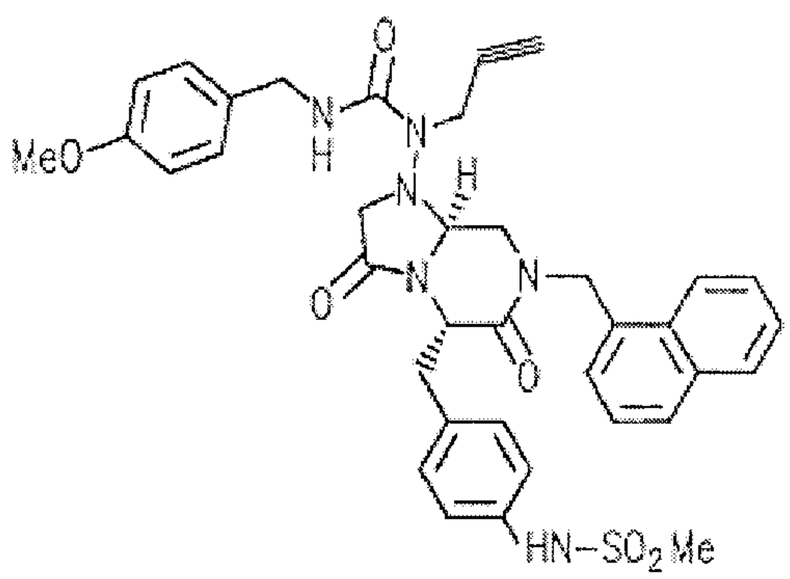
or a pharmaceutically acceptable salt thereof.

558. The compound of claim 1, which is:



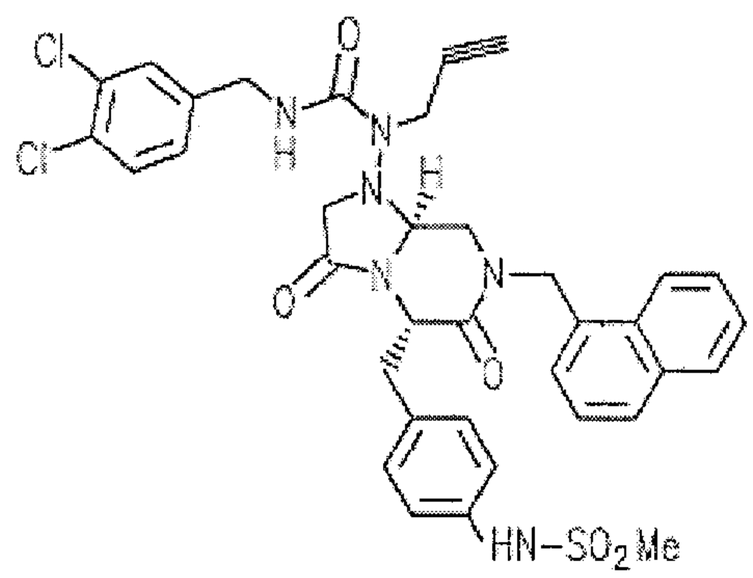
or a pharmaceutically acceptable salt thereof.

559. The compound of claim 1, which is:



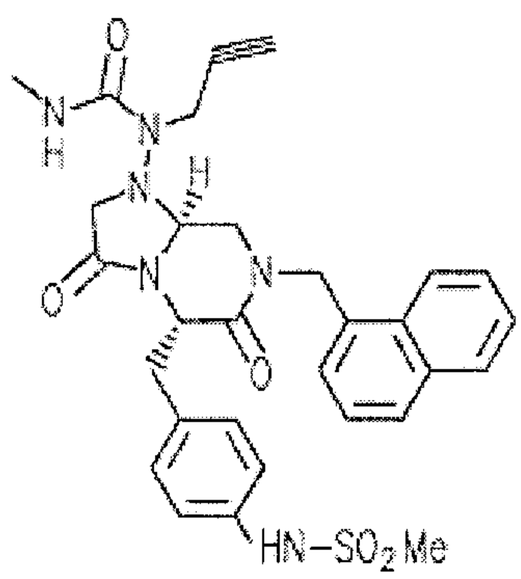
or a pharmaceutically acceptable salt thereof.

560. The compound of claim 1, which is:



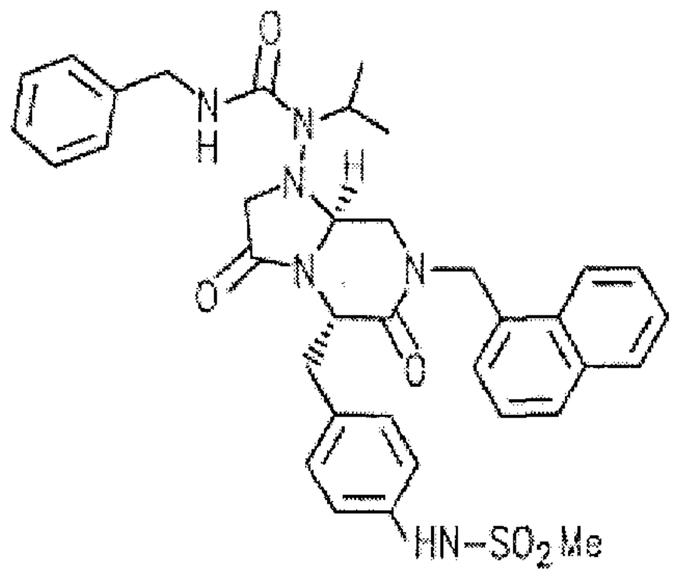
or a pharmaceutically acceptable salt thereof.

561. The compound of claim 1, which is:



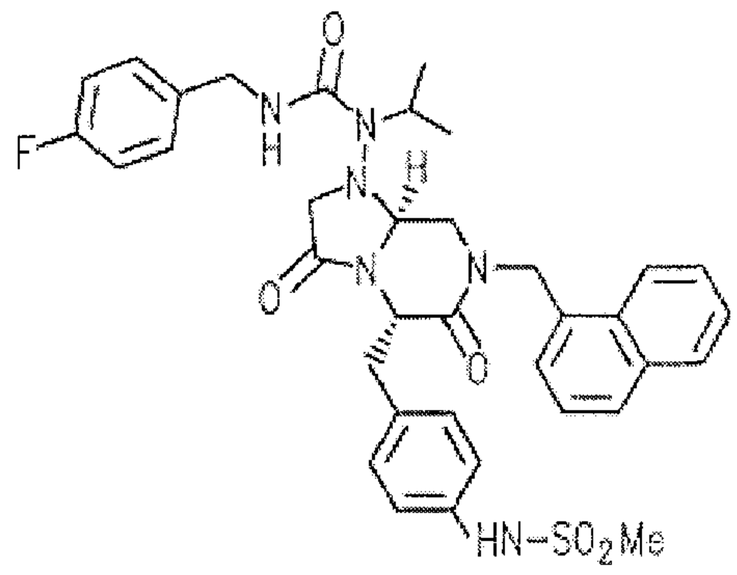
or a pharmaceutically acceptable salt thereof.

562. The compound of claim 1, which is:



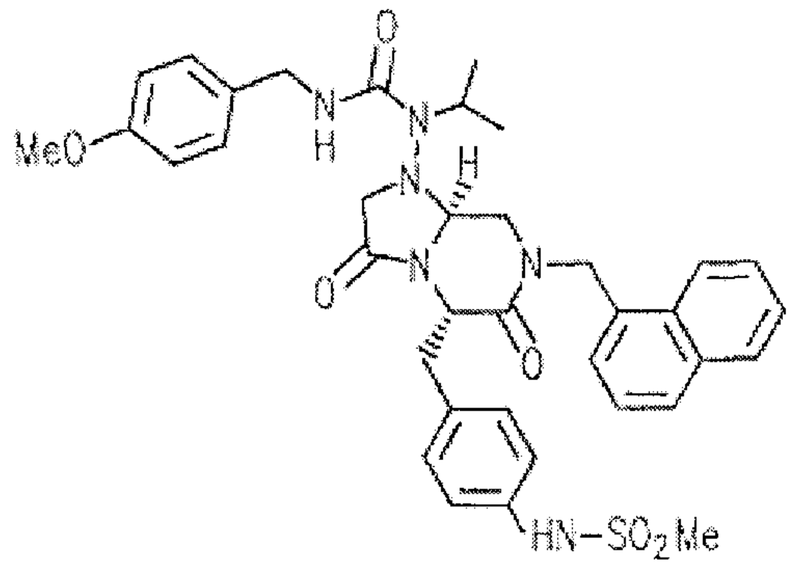
or a pharmaceutically acceptable salt thereof.

563. The compound of claim 1, which is:



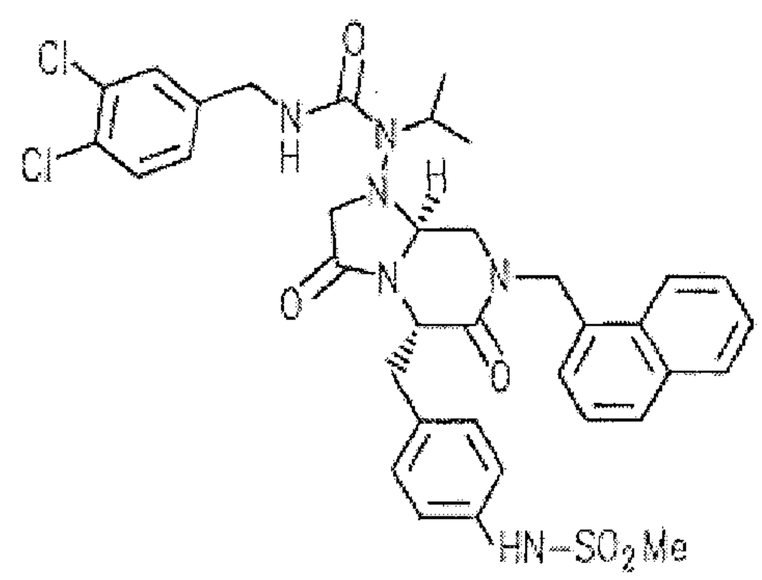
or a pharmaceutically acceptable salt thereof.

564. The compound of claim 1, which is:



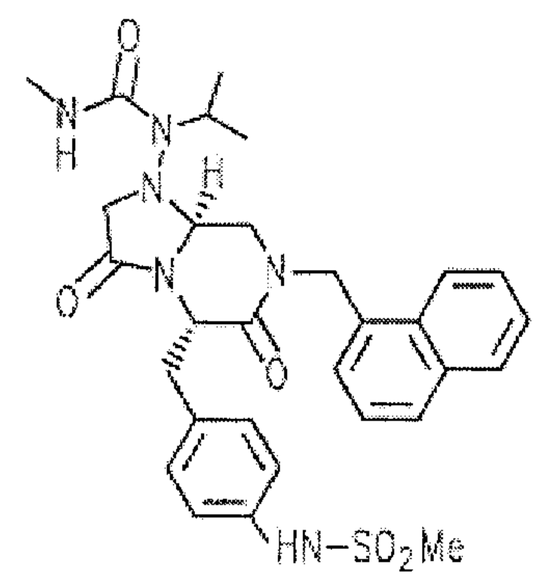
or a pharmaceutically acceptable salt thereof.

565. The compound of claim 1, which is:



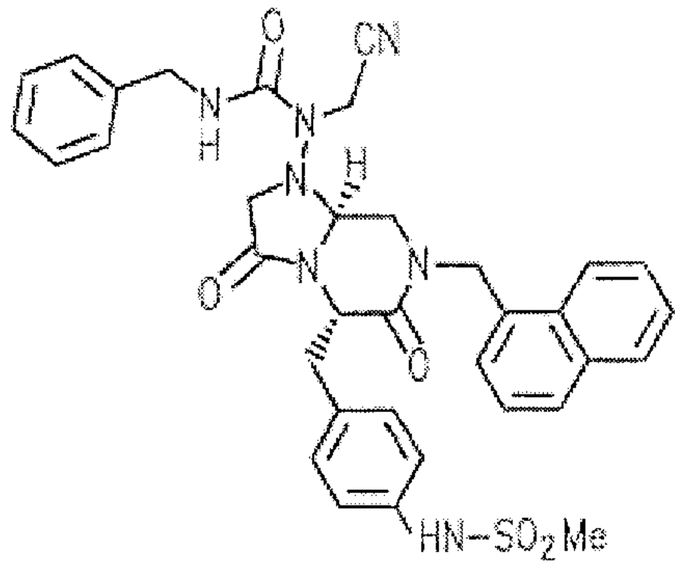
or a pharmaceutically acceptable salt thereof.

566. The compound of claim 1, which is:



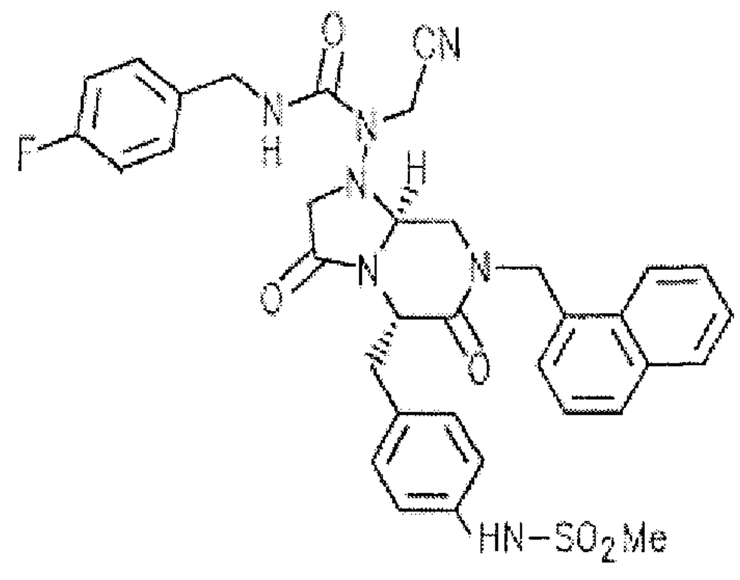
or a pharmaceutically acceptable salt thereof.

567. The compound of claim 1, which is:



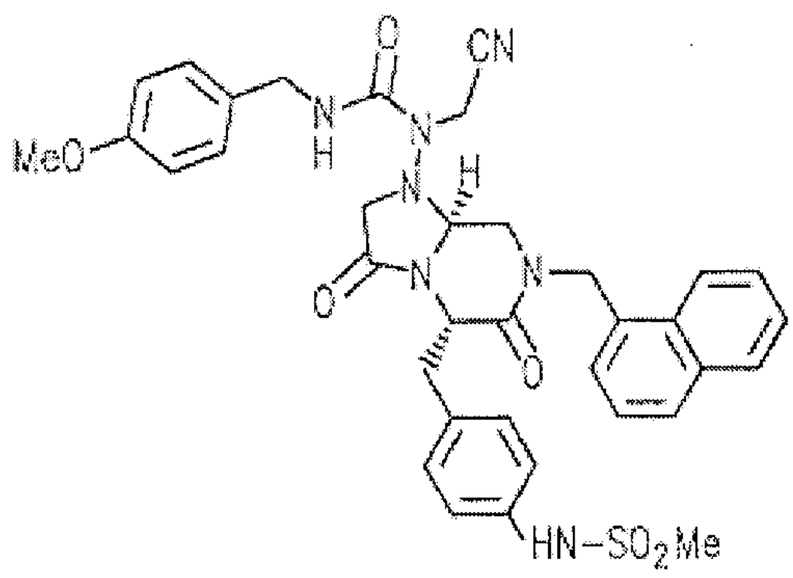
or a pharmaceutically acceptable salt thereof.

568. The compound of claim 1, which is:



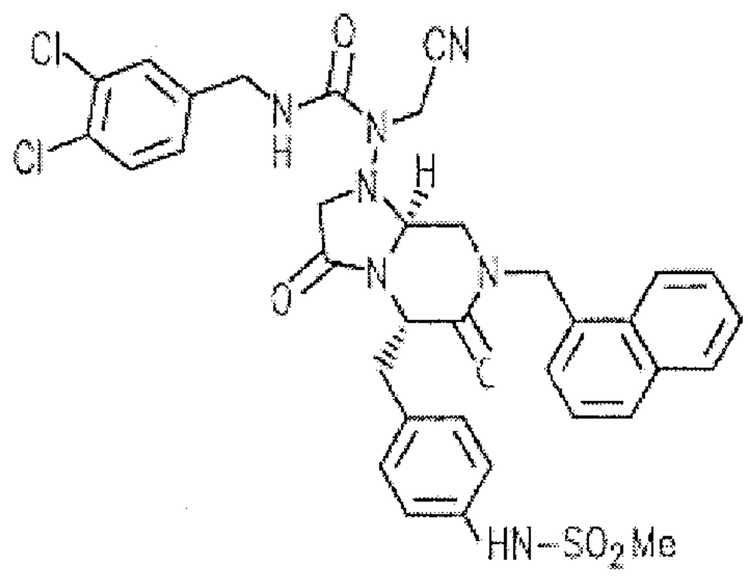
or a pharmaceutically acceptable salt thereof.

569. The compound of claim 1, which is:



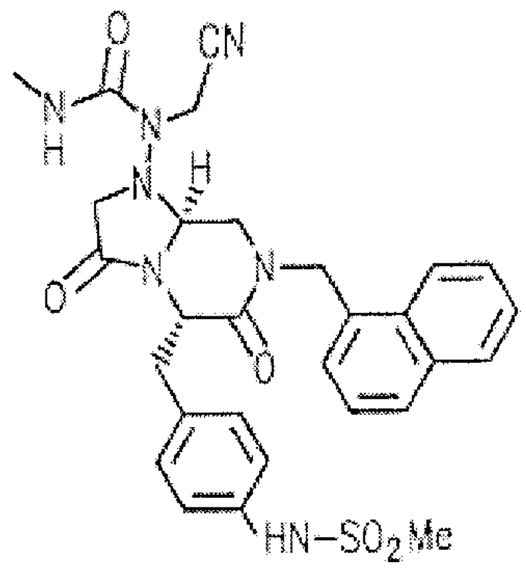
or a pharmaceutically acceptable salt thereof.

570. The compound of claim 1, which is:



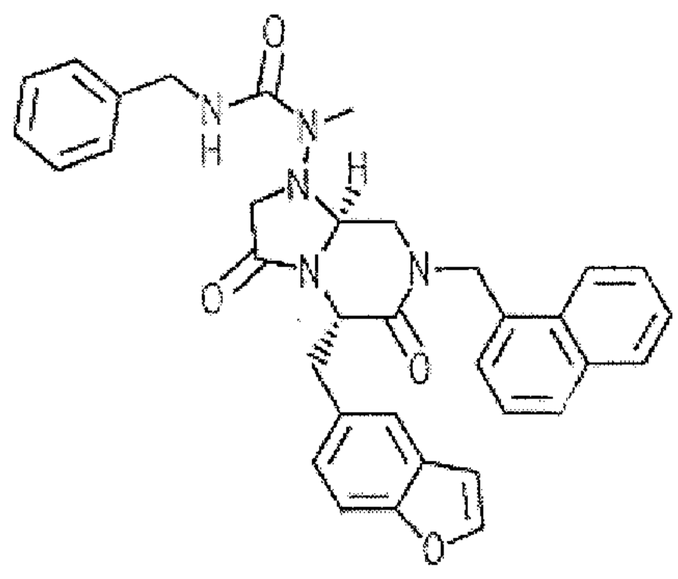
or a pharmaceutically acceptable salt thereof.

571. The compound of claim 1, which is:



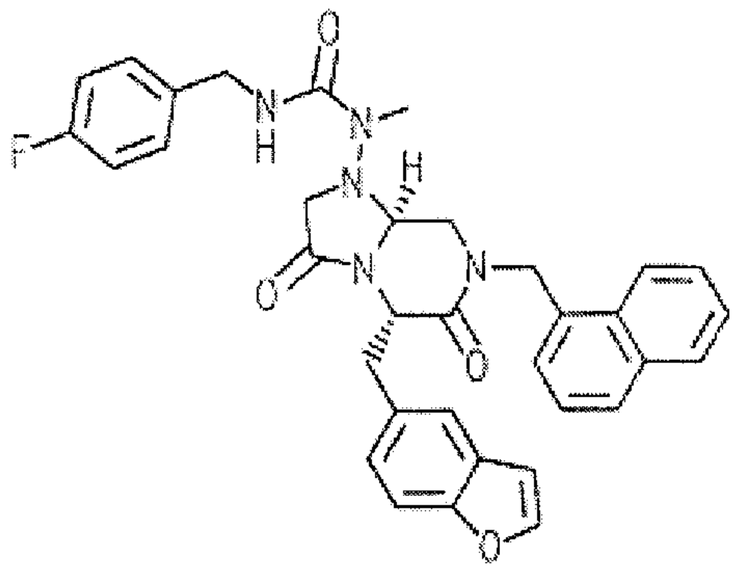
or a pharmaceutically acceptable salt thereof.

572. The compound of claim 1, which is:



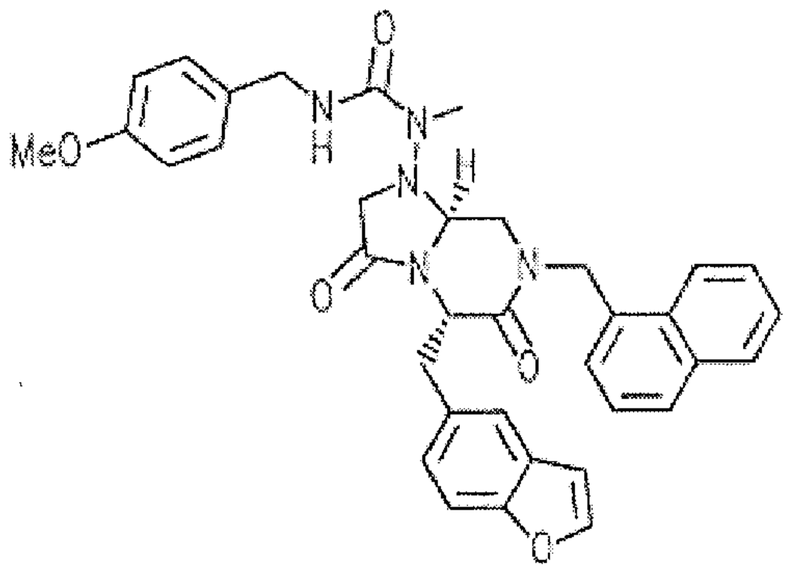
or a pharmaceutically acceptable salt thereof.

573. The compound of claim 1, which is:



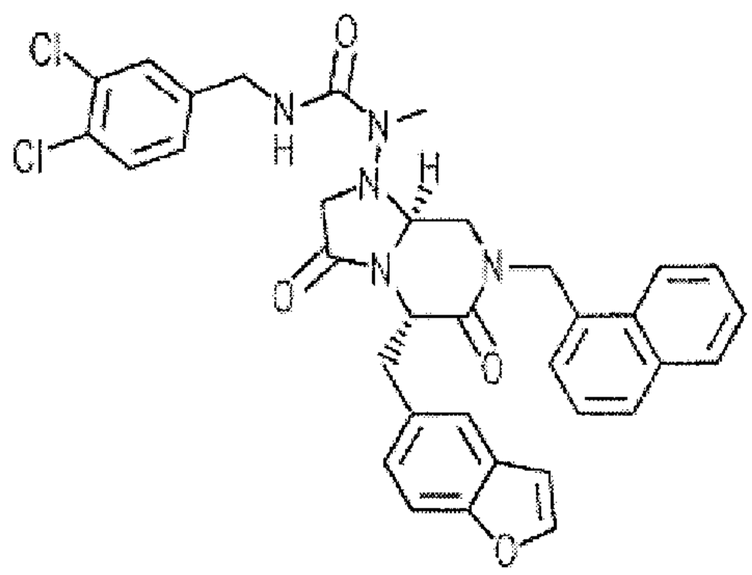
or a pharmaceutically acceptable salt thereof.

574. The compound of claim 1, which is:



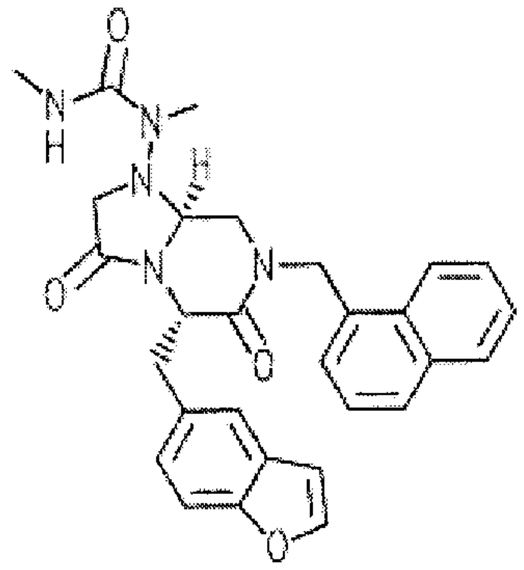
or a pharmaceutically acceptable salt thereof.

575. The compound of claim 1, which is:



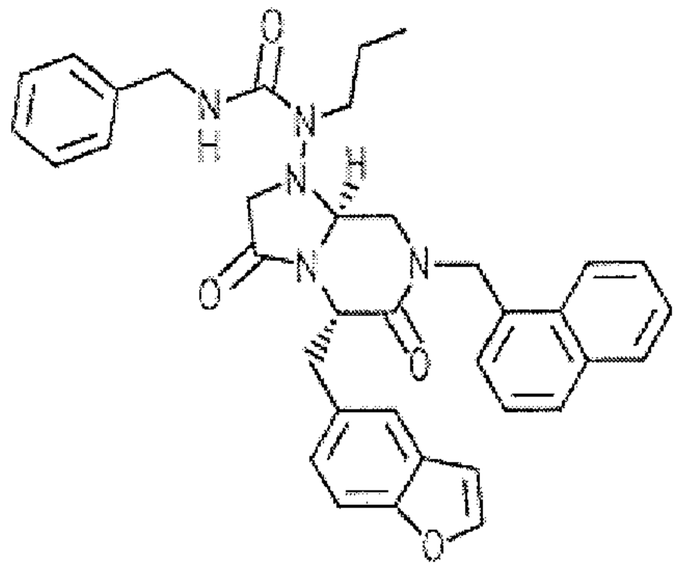
or a pharmaceutically acceptable salt thereof.

576. The compound of claim 1, which is:



or a pharmaceutically acceptable salt thereof.

577. The compound of claim 1, which is:



or a pharmaceutically acceptable salt thereof.

DEMANDES OU BREVETS VOLUMINEUX

LA PRÉSENTE PARTIE DE CETTE DEMANDE OU CE BREVETS COMPREND PLUS D'UN TOME.

CECI EST LE TOME __1___ DE __3___

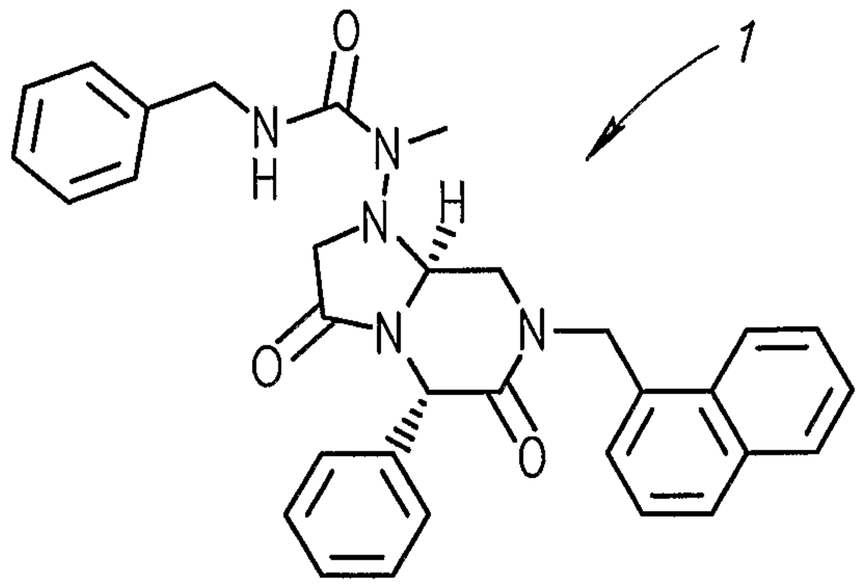
NOTE: Pour les tomes additionels, veillez contacter le Bureau Canadien des Brevets.

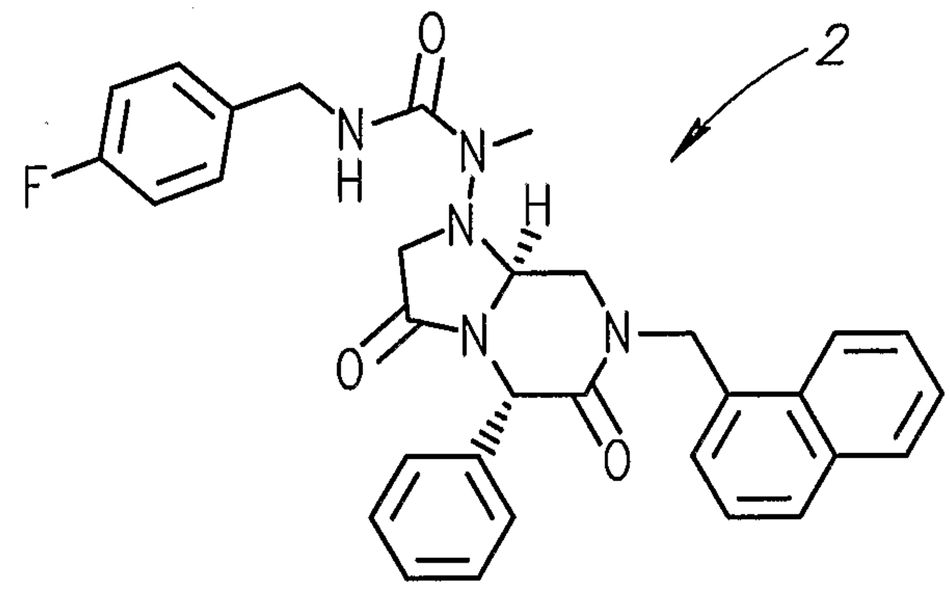
JUMBO APPLICATIONS / PATENTS

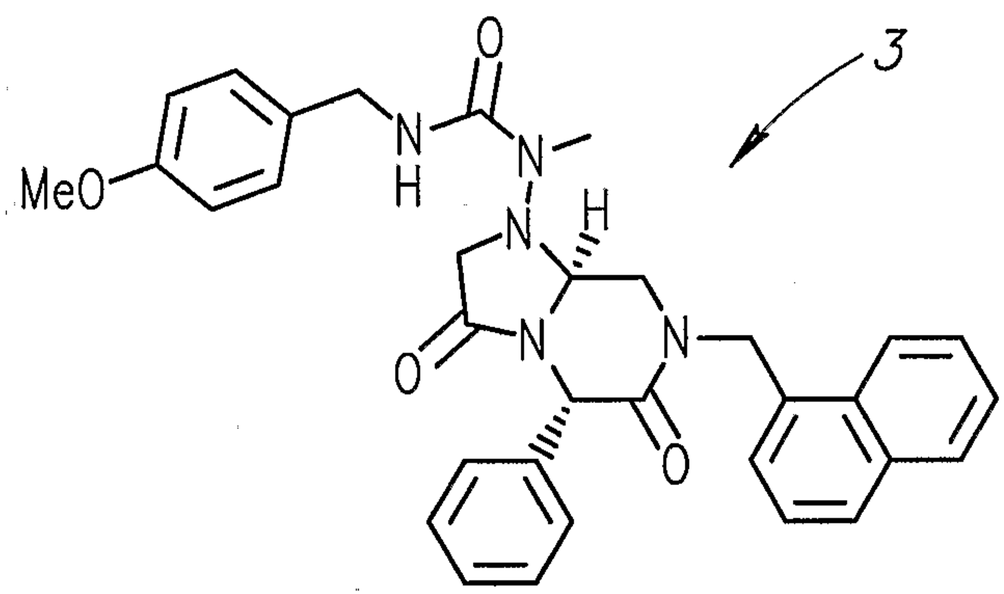
THIS SECTION OF THE APPLICATION / PATENT CONTAINS MORE THAN ONE VOLUME.

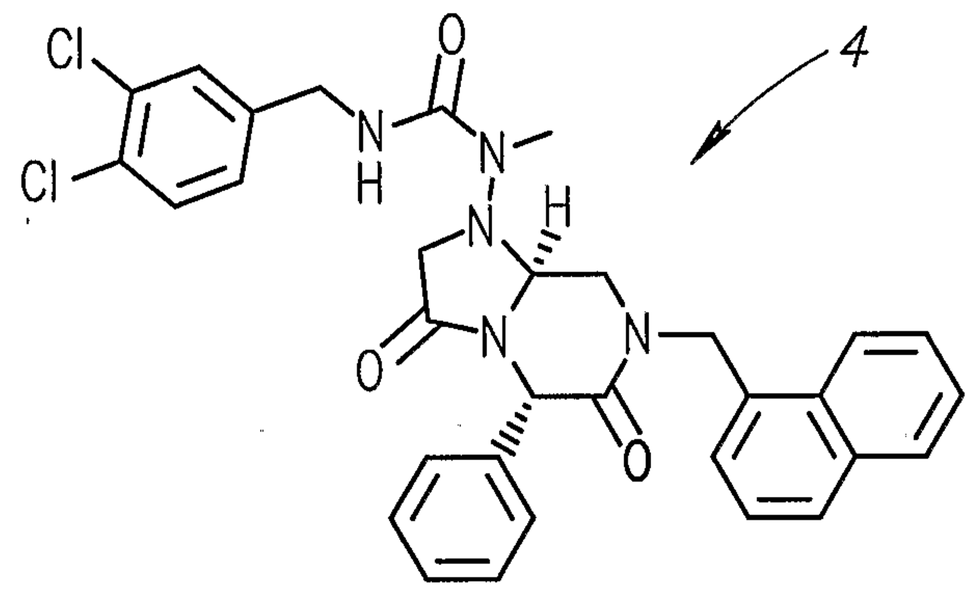
THIS IS VOLUME __1___ OF __3___

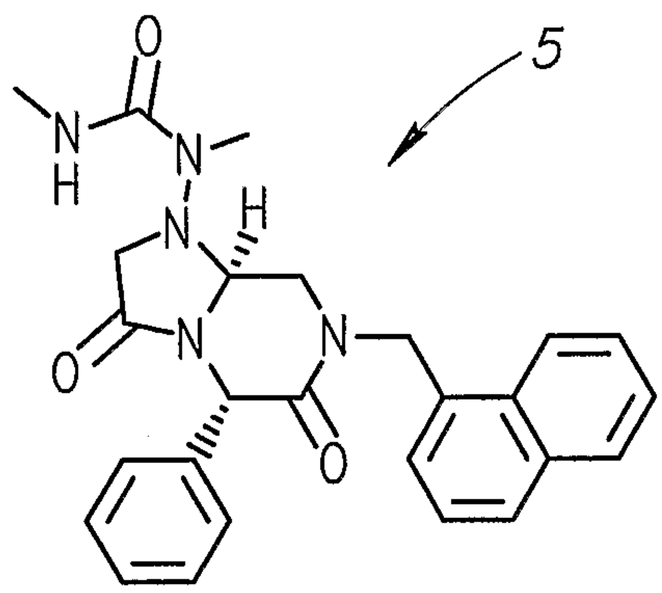
NOTE: For additional volumes please contact the Canadian Patent Office.

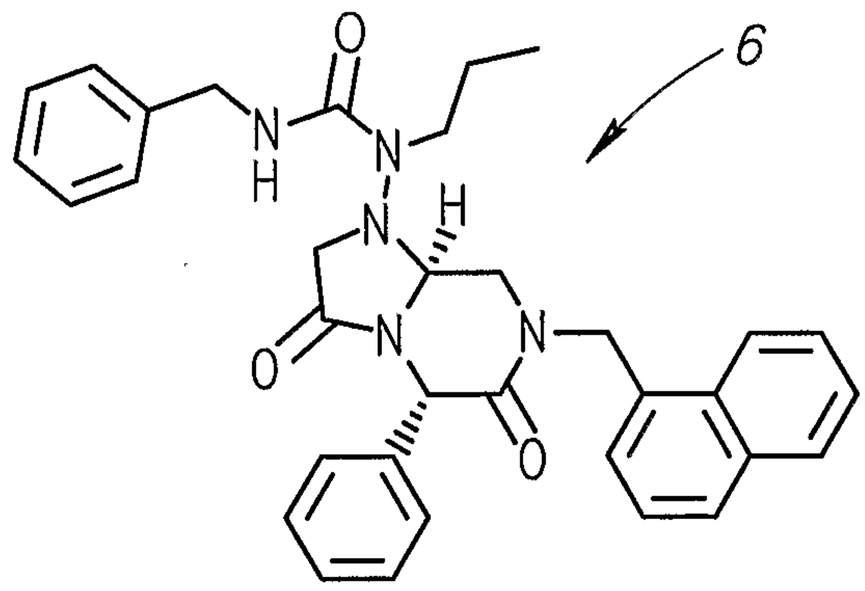


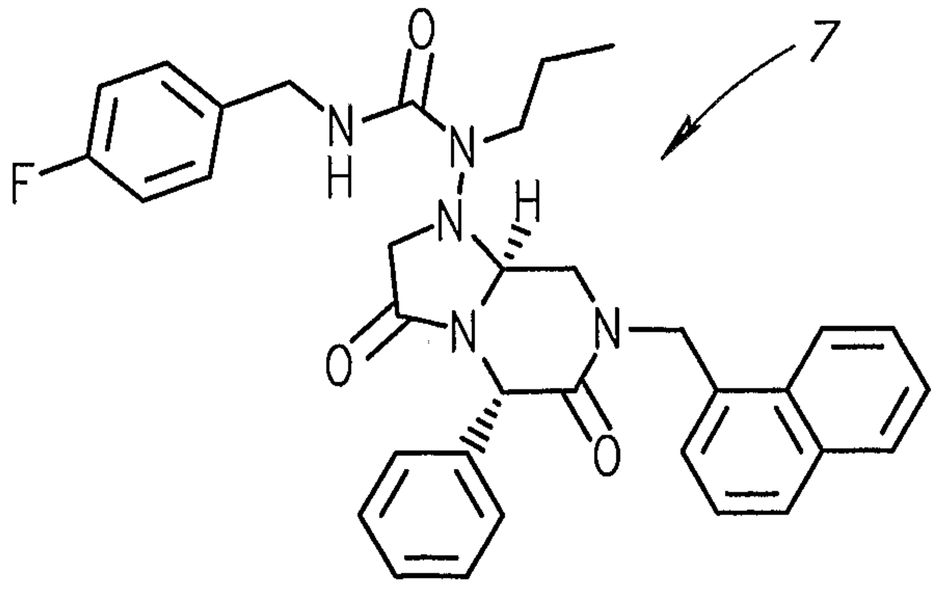












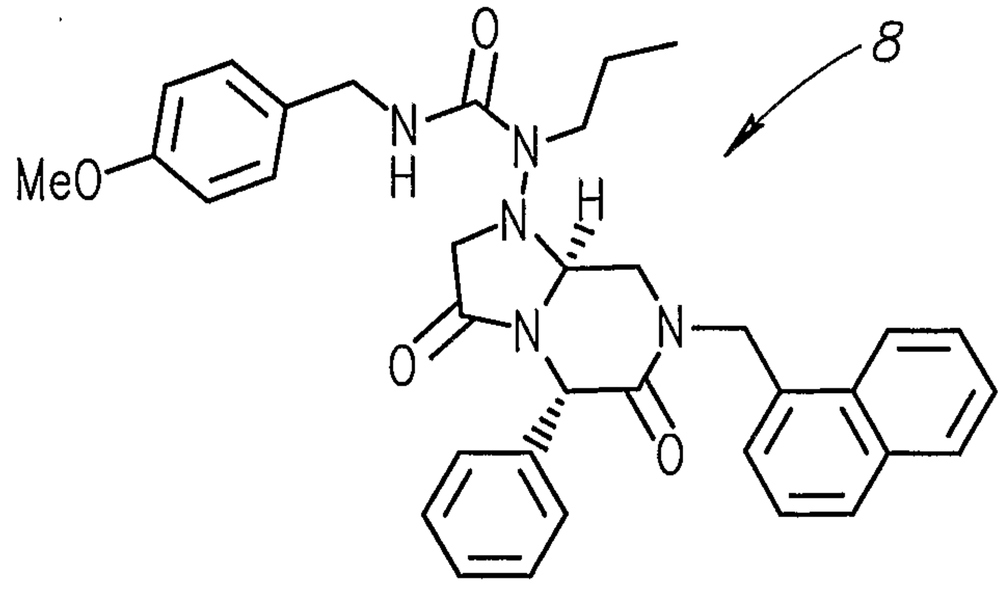
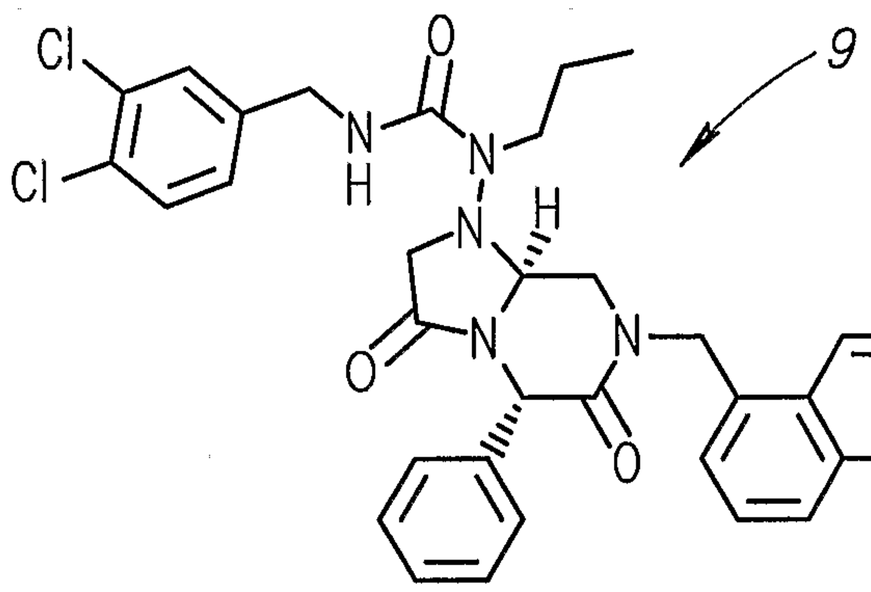
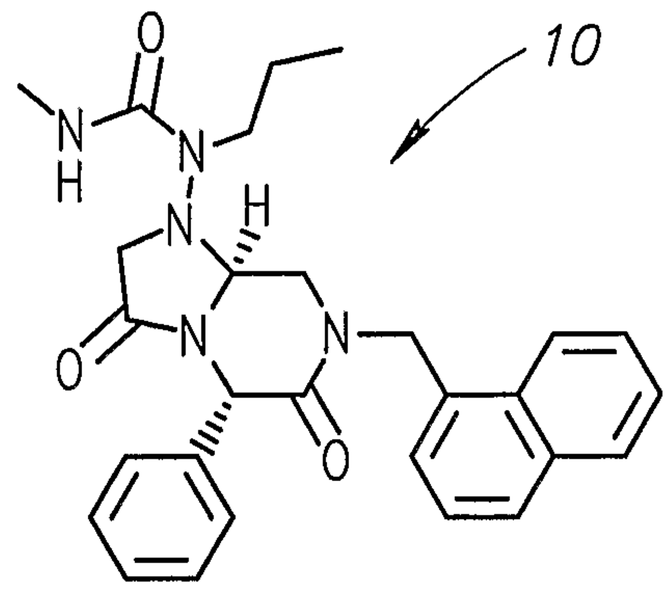
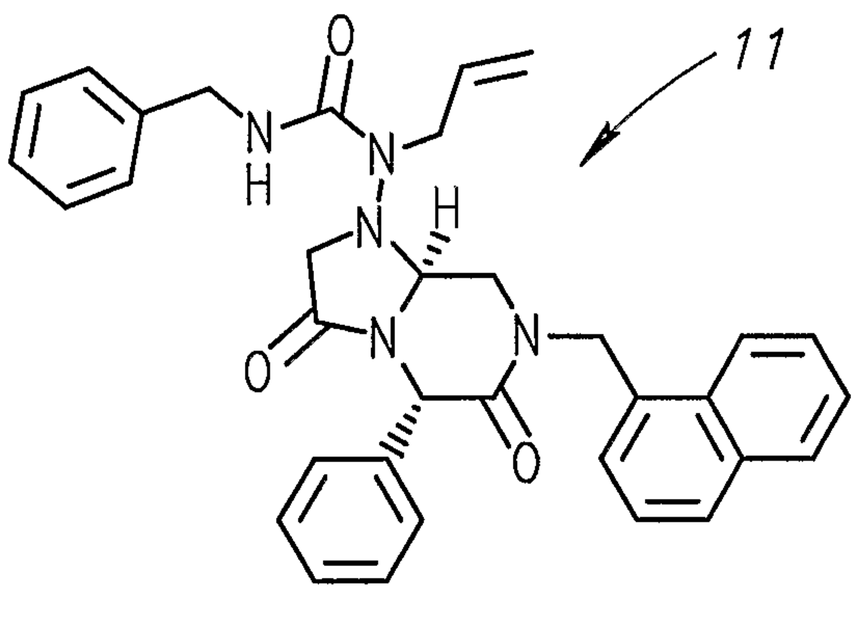
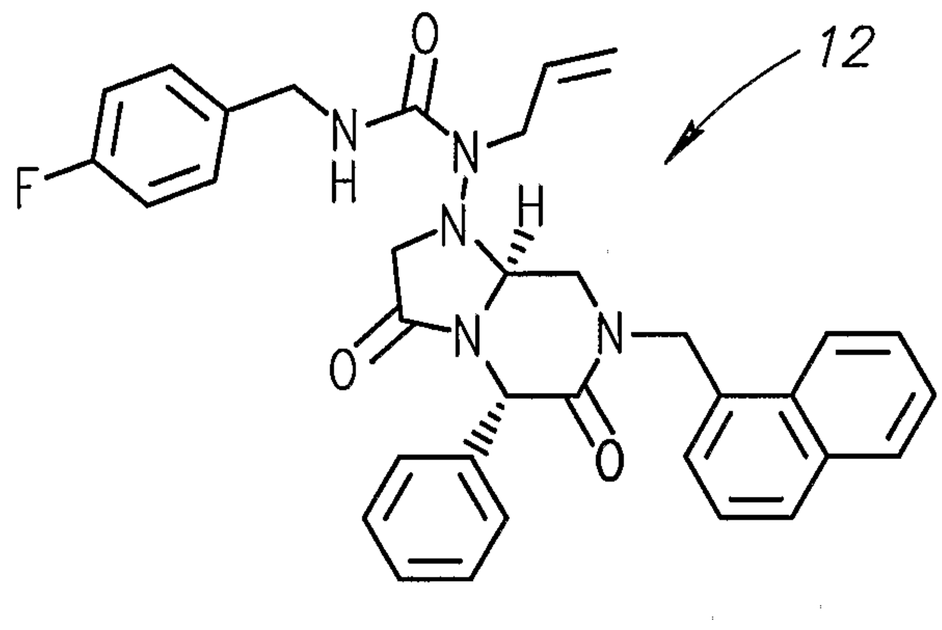


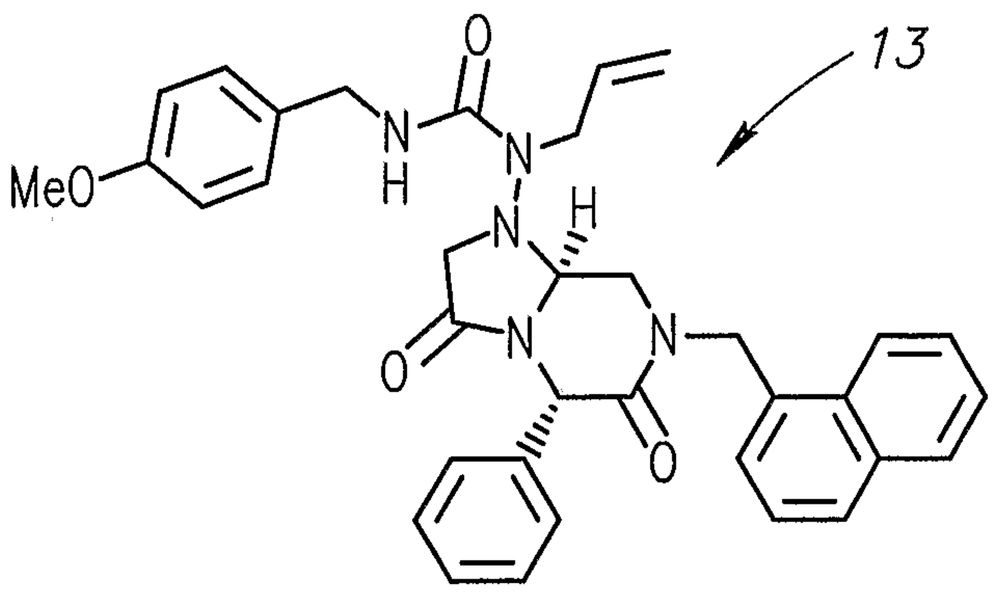
FIG.1A

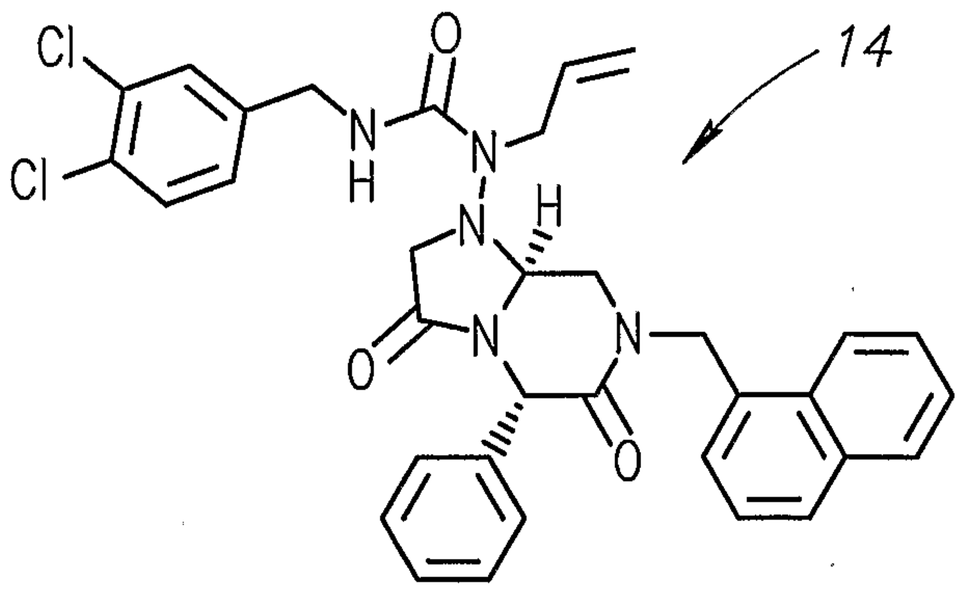


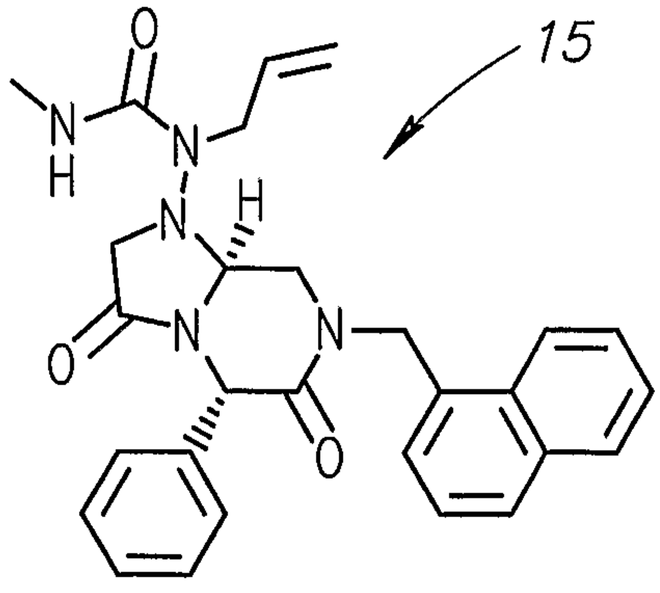












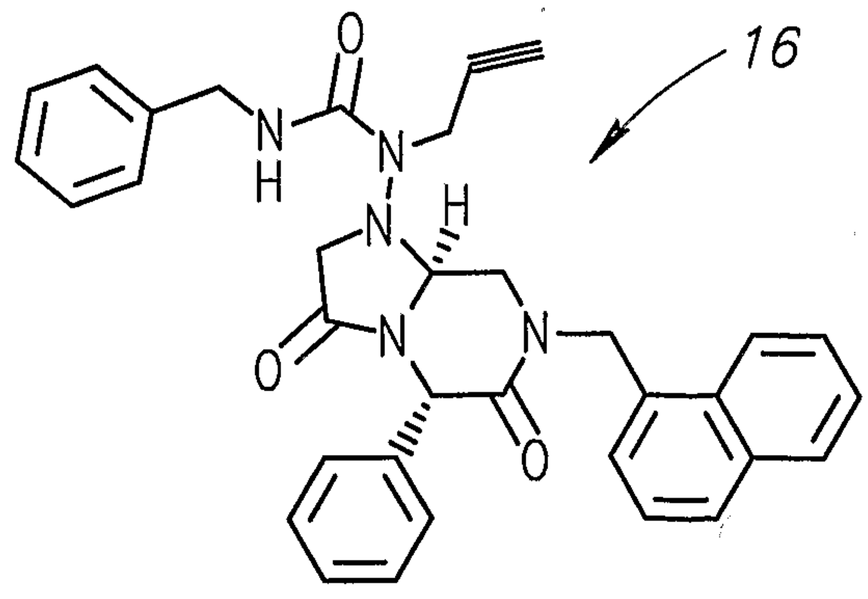
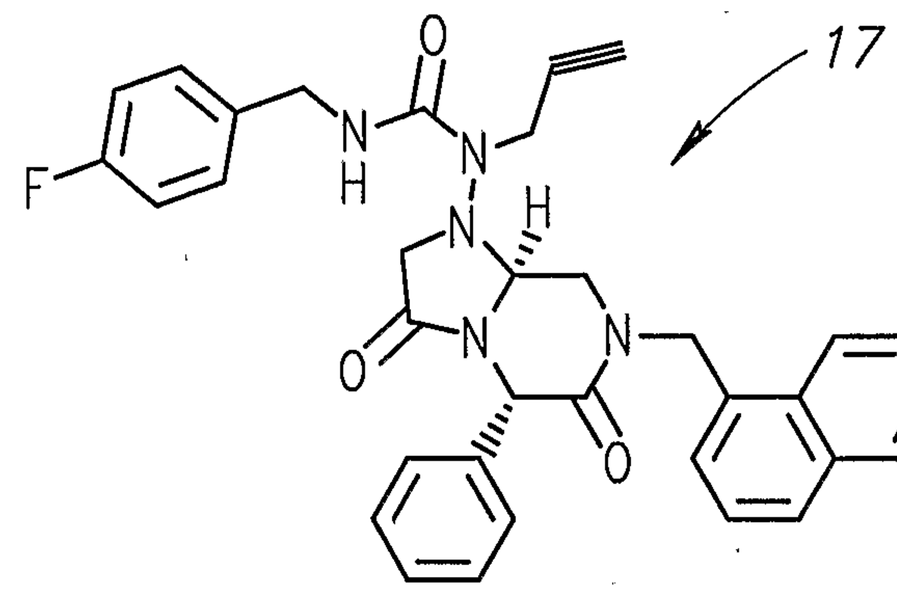
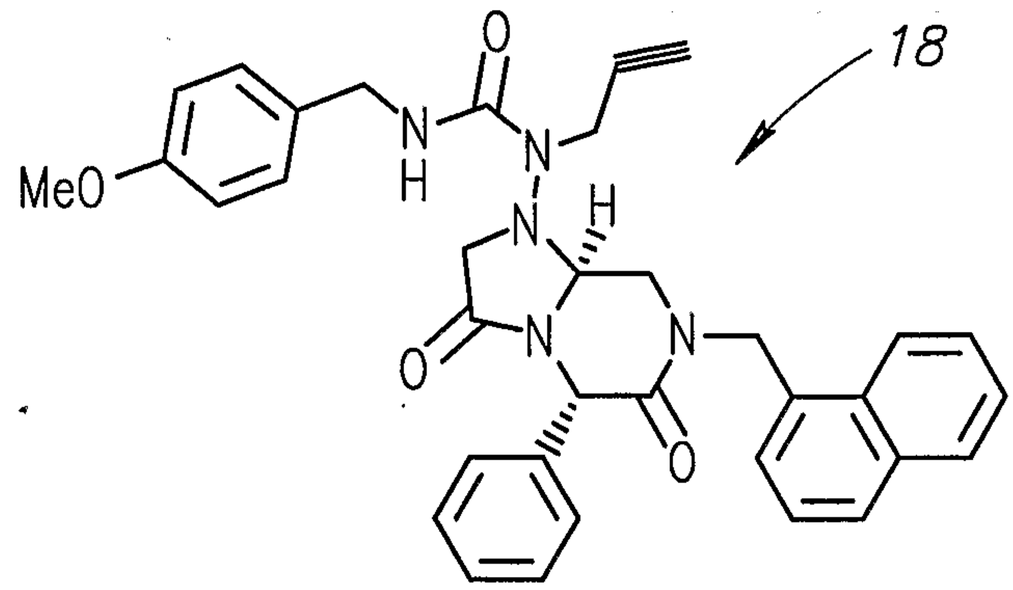
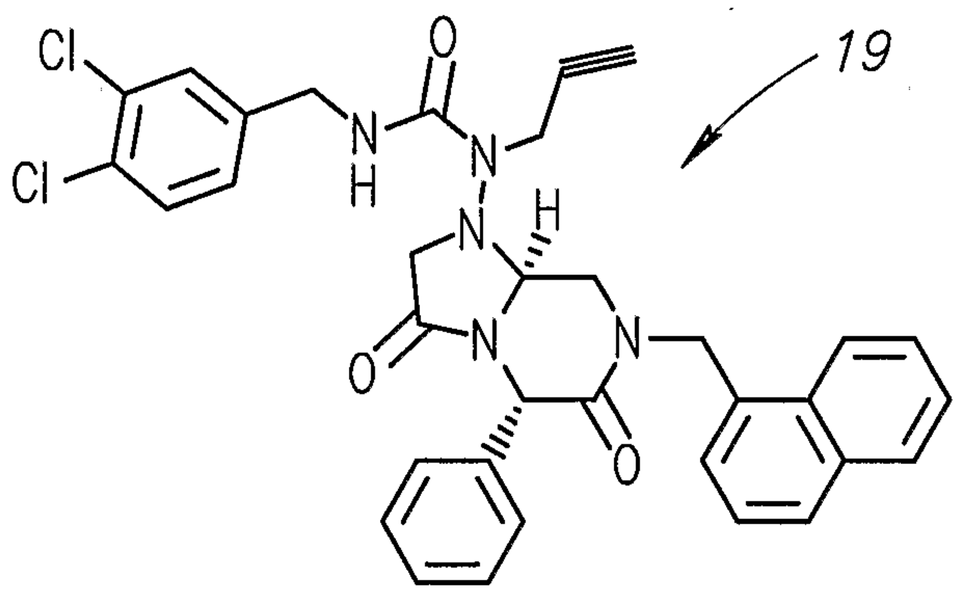
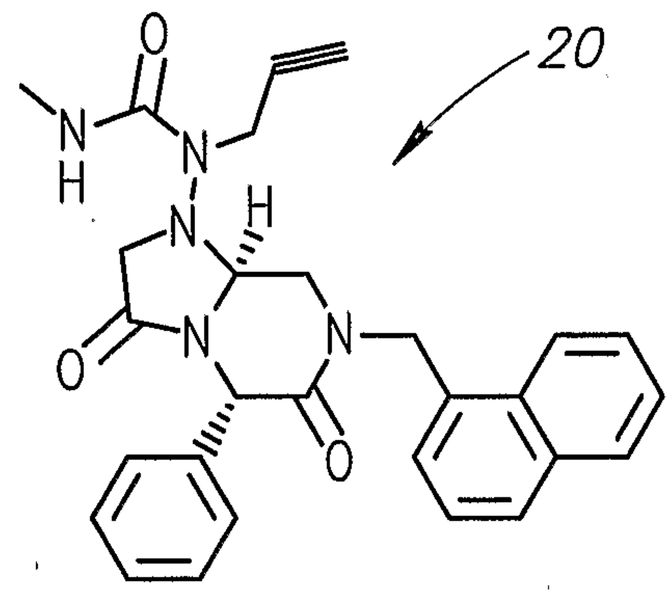


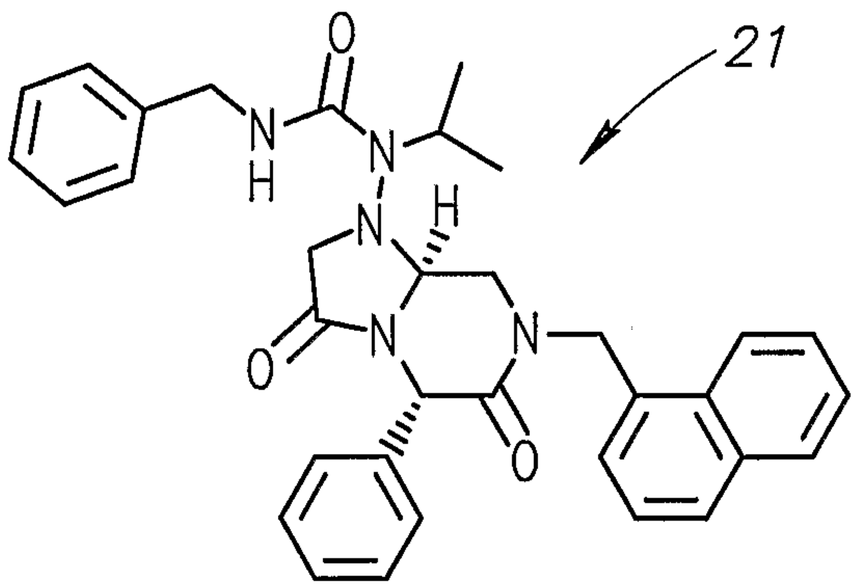
FIG.1B

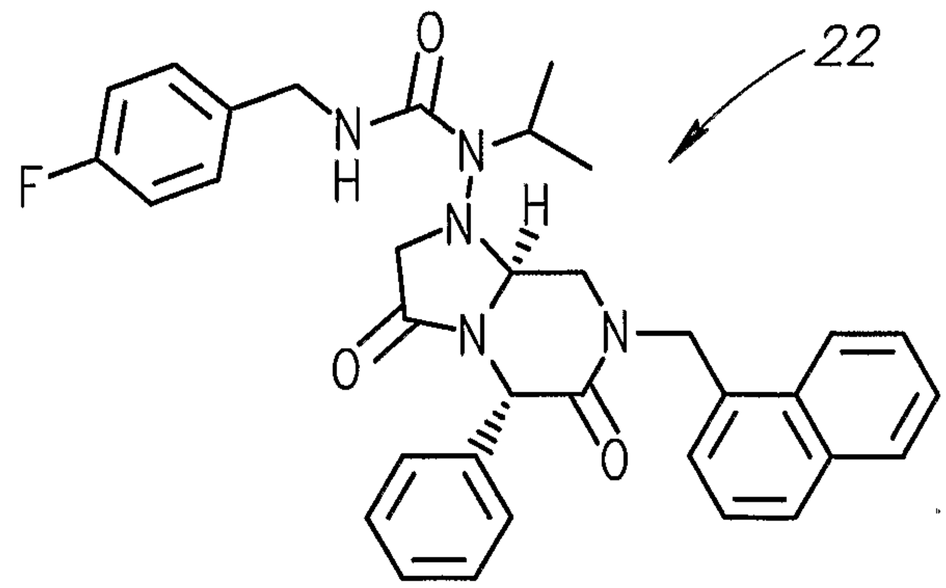


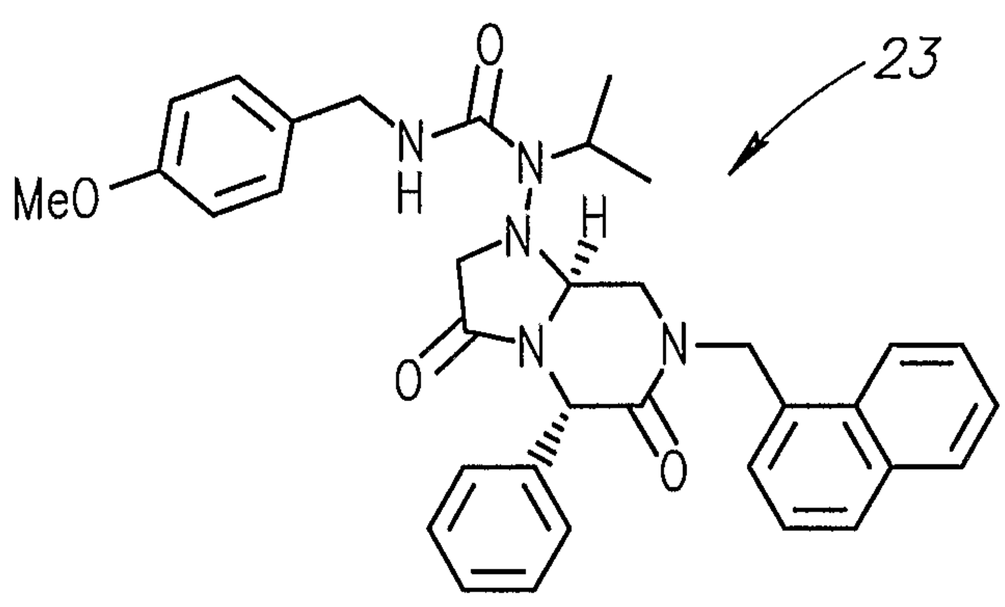












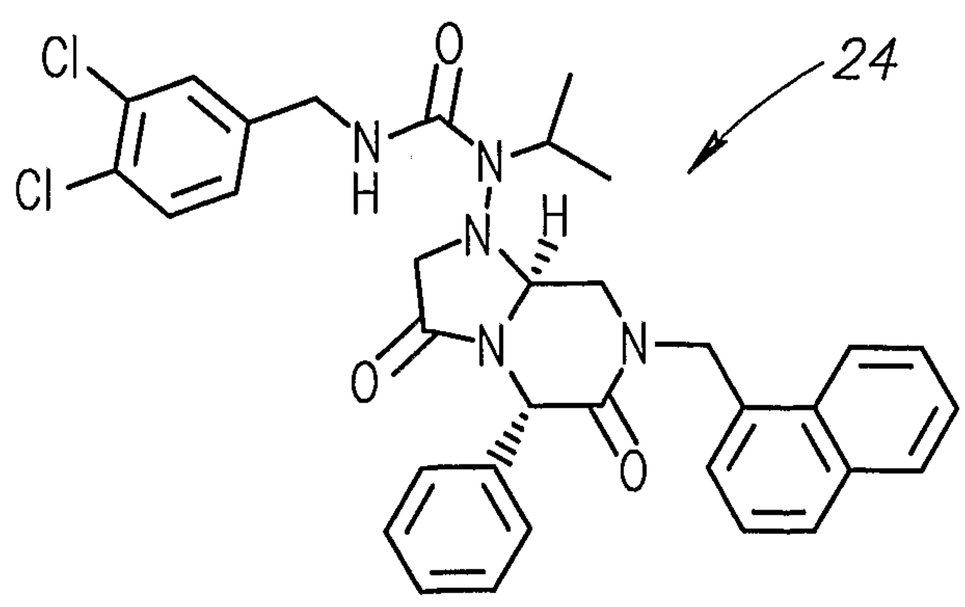
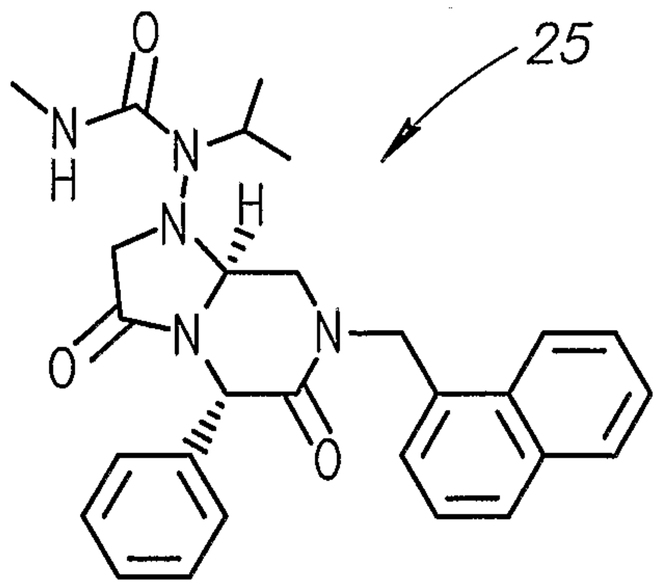
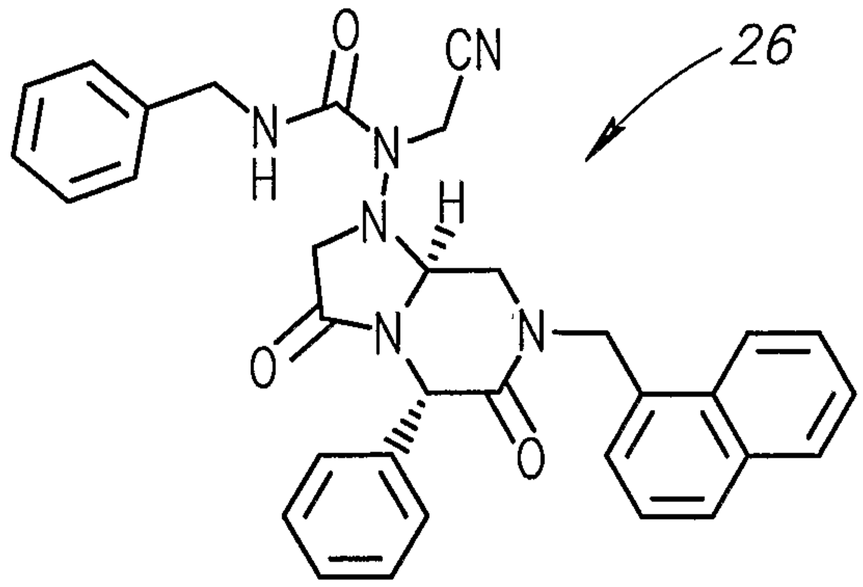
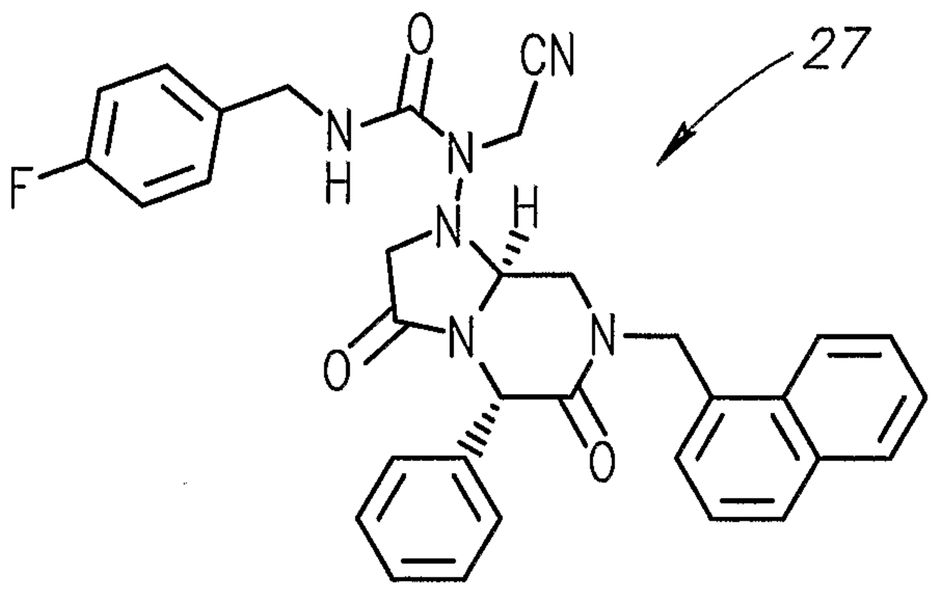
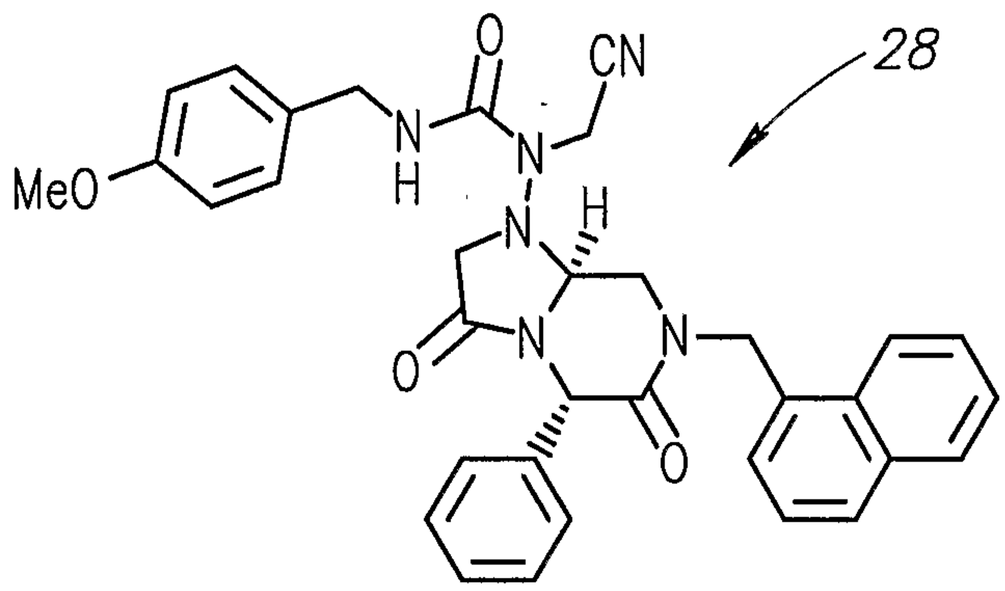


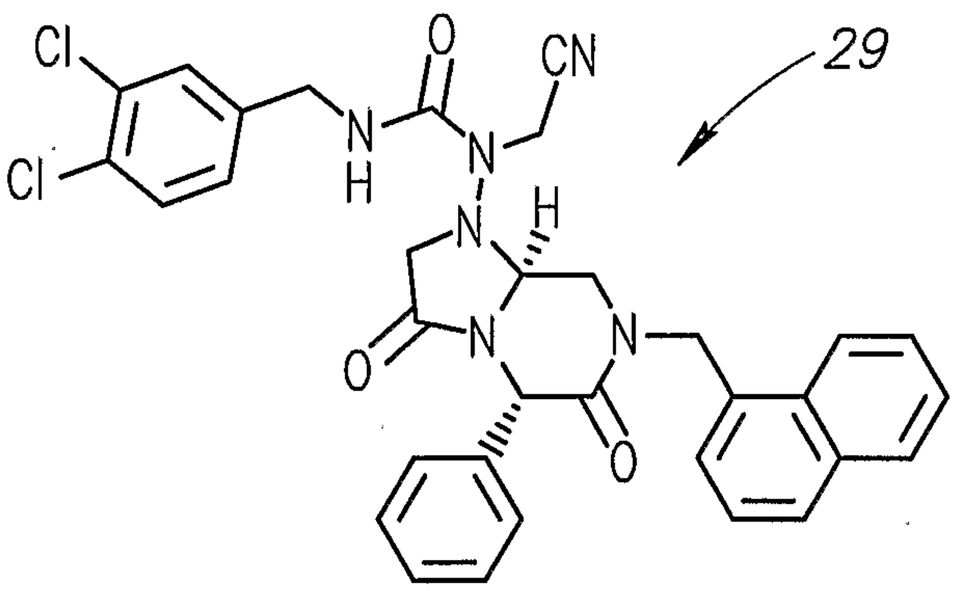
FIG.1C

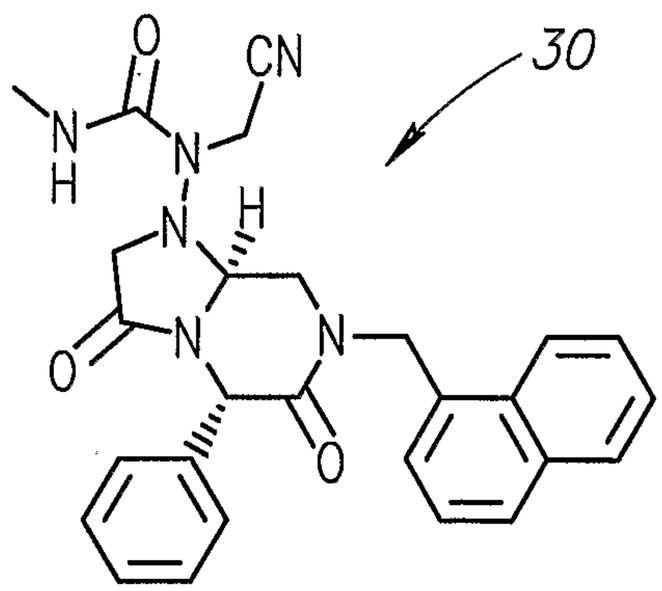


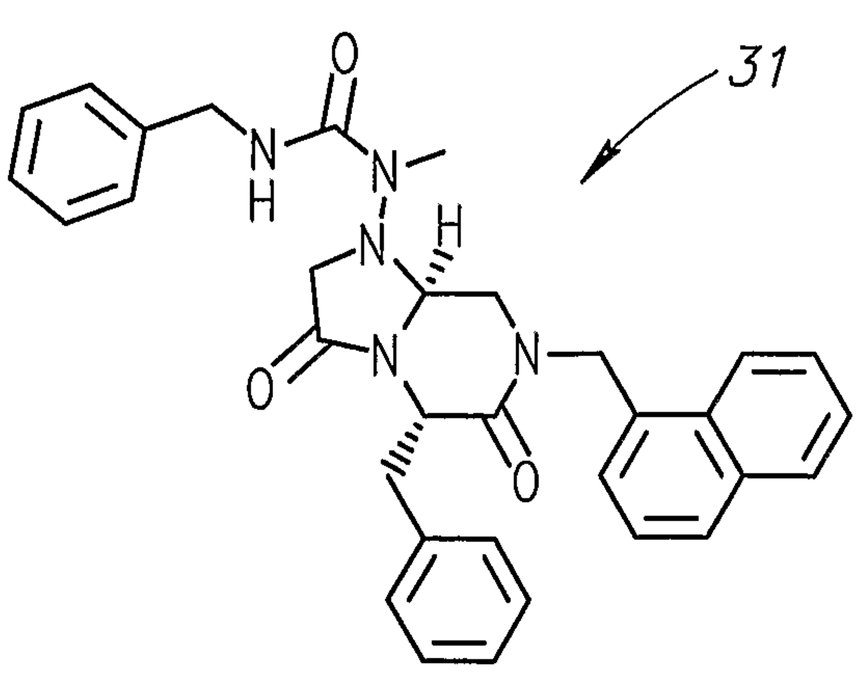












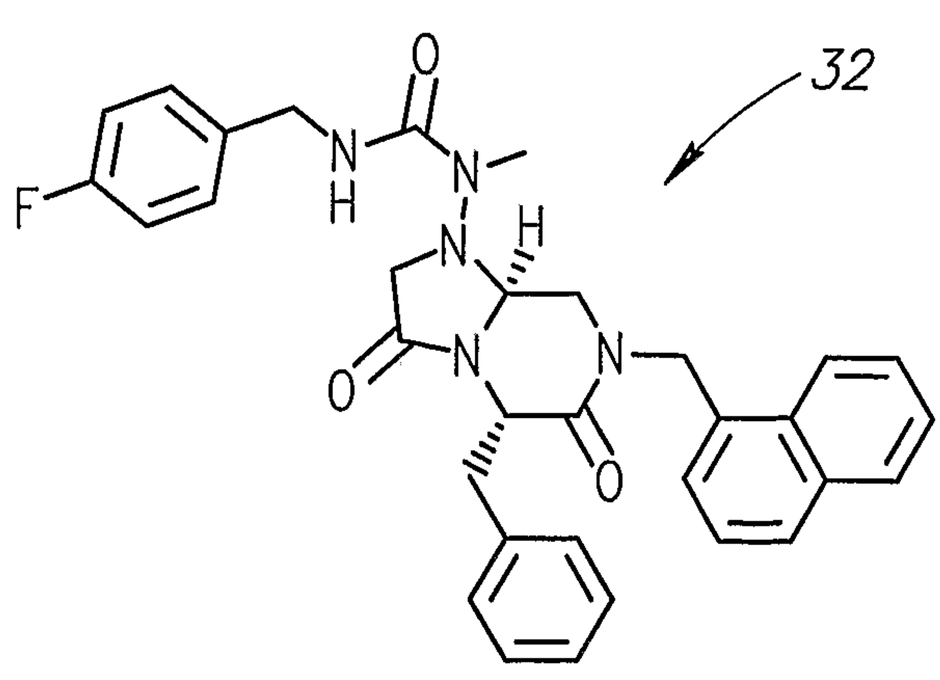
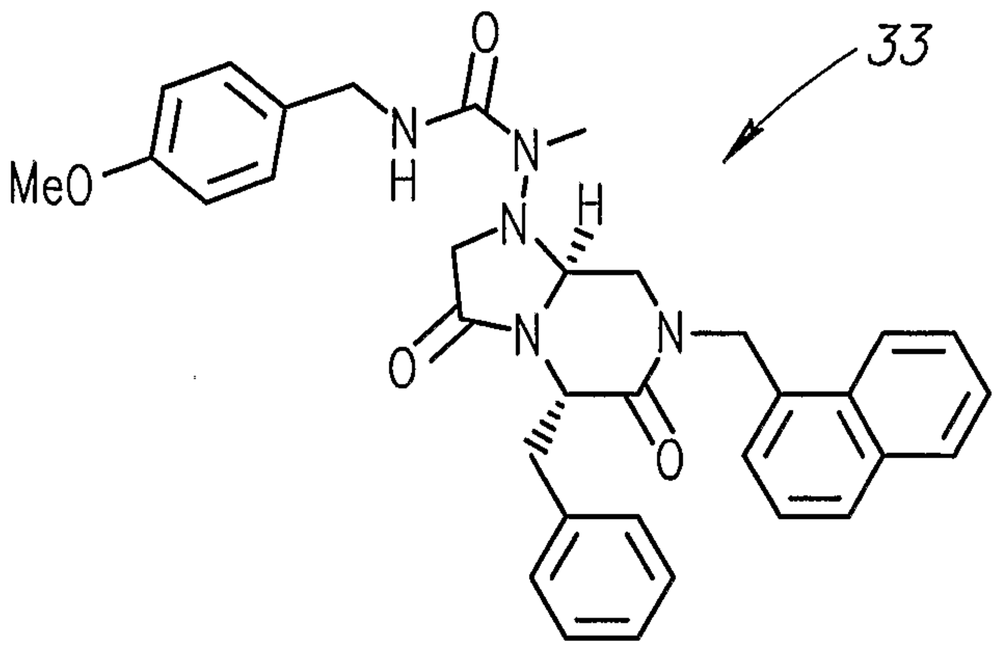
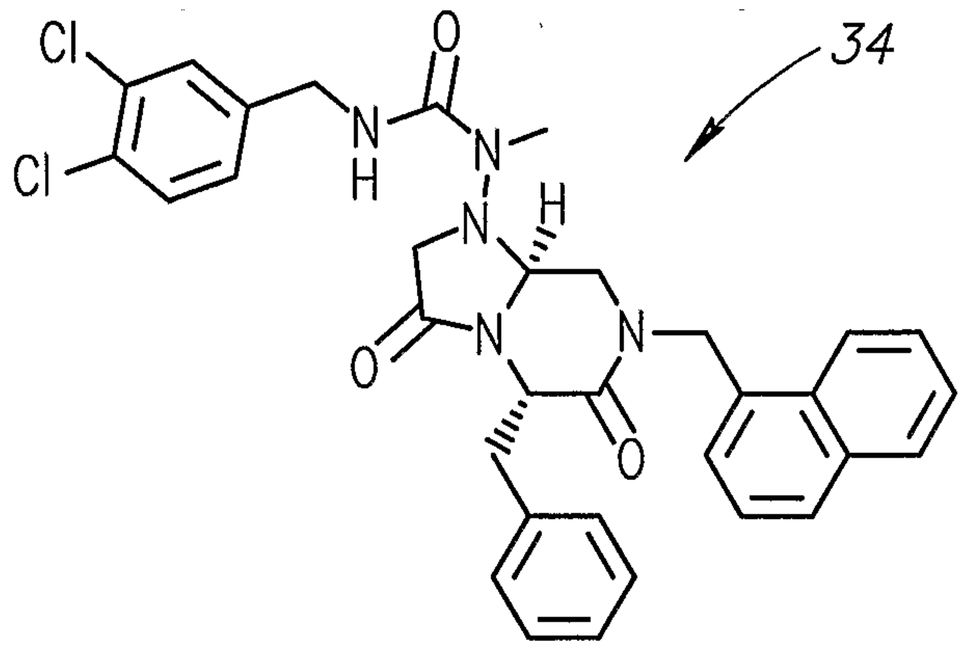
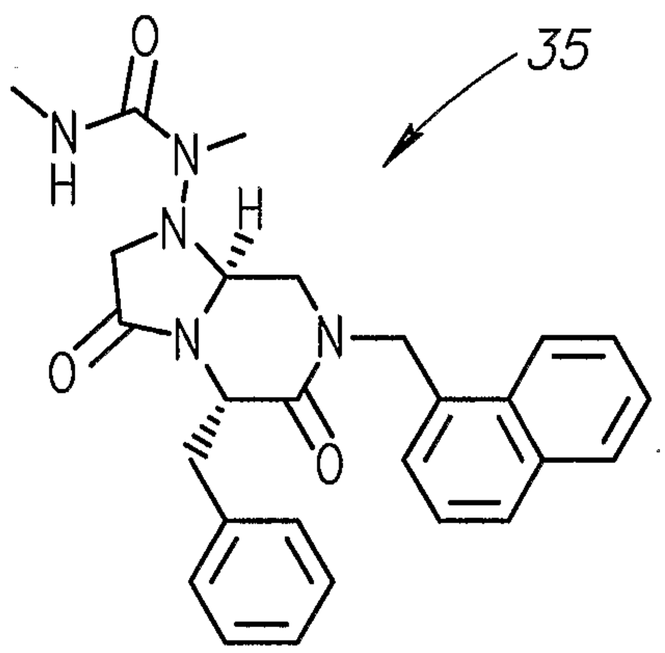
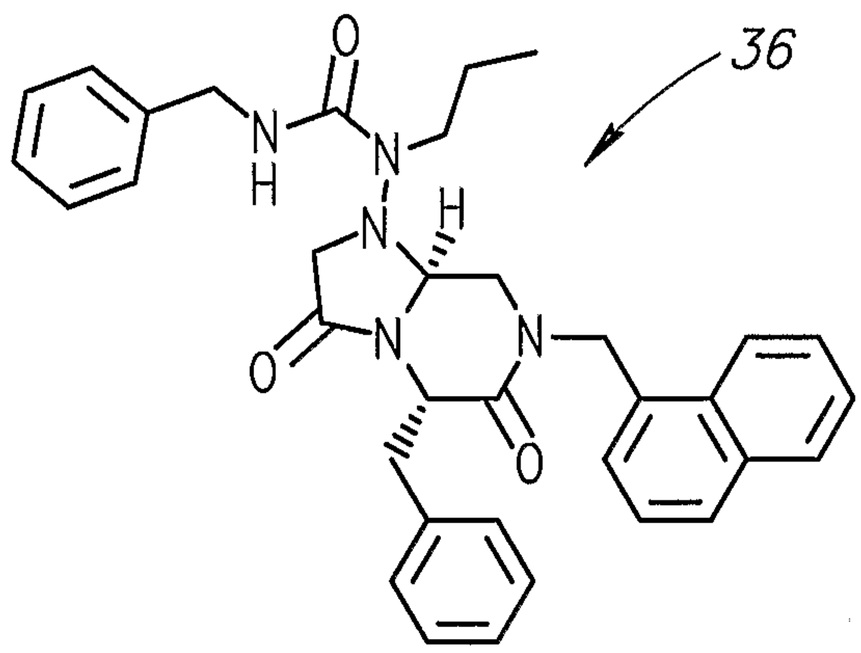


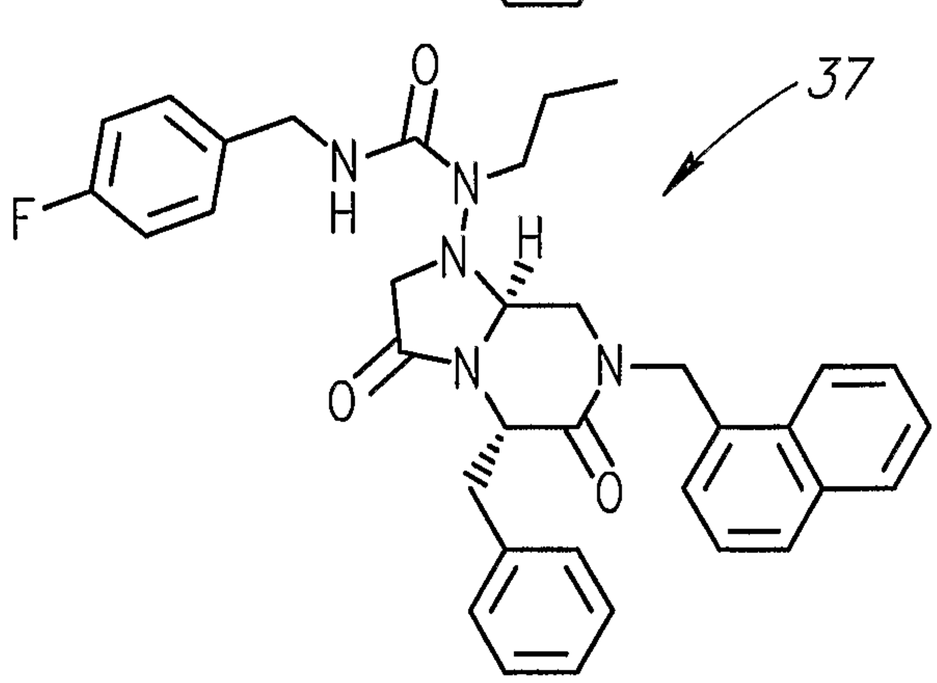
FIG.1D

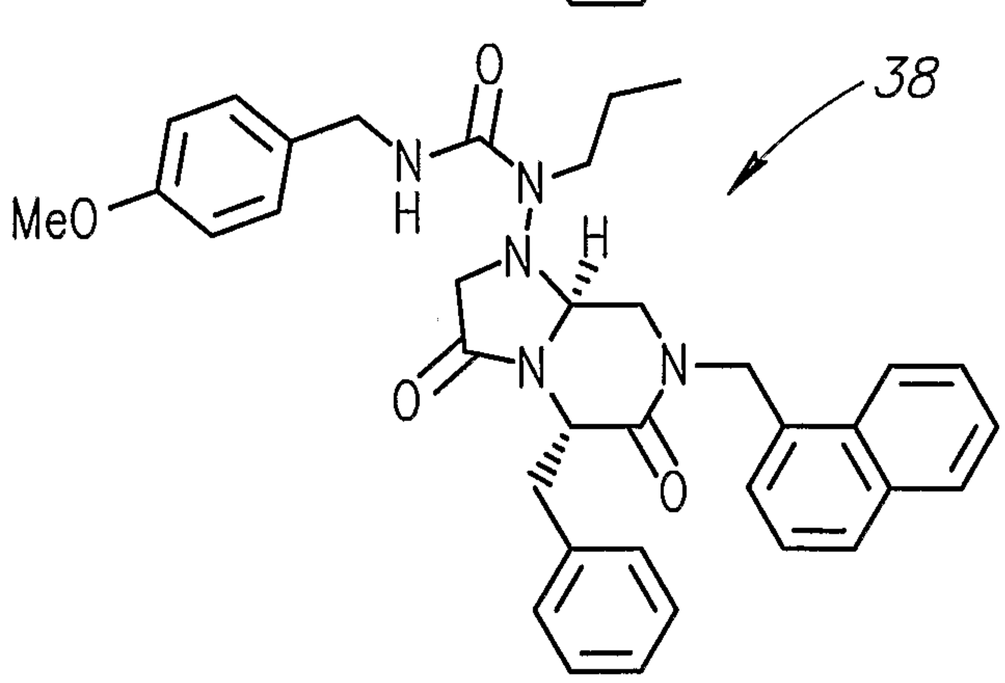


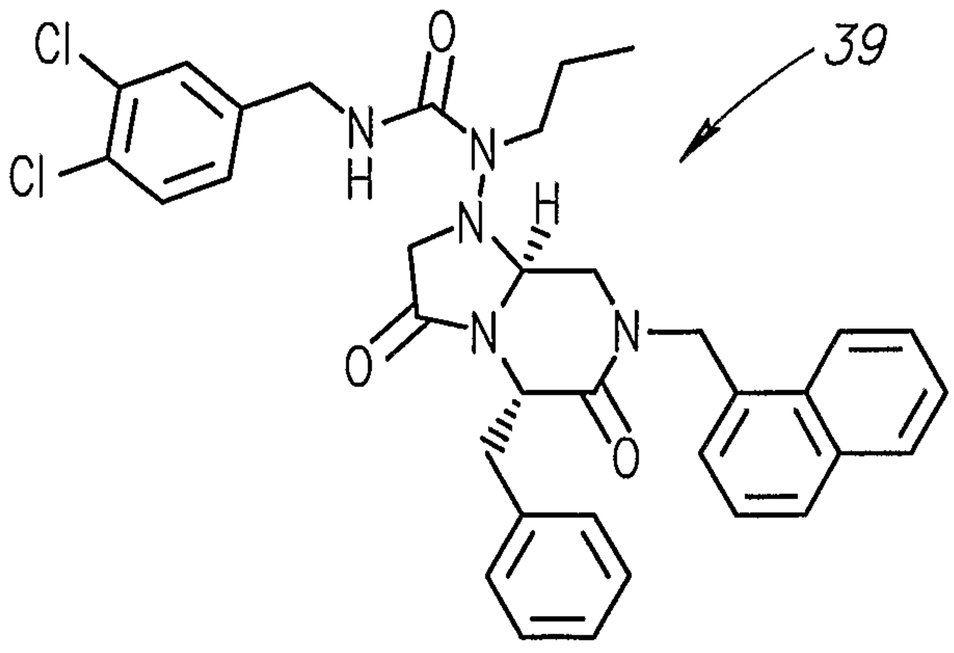












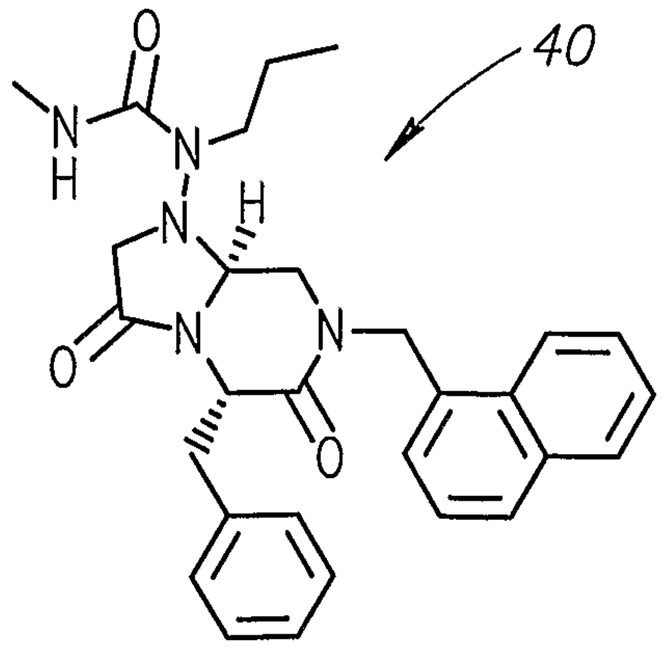
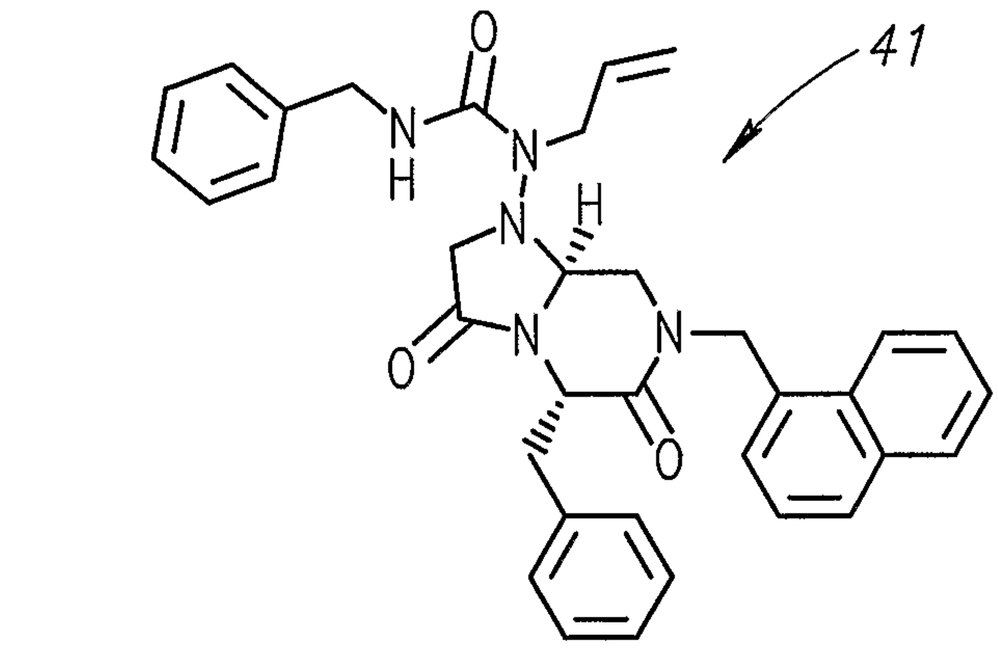
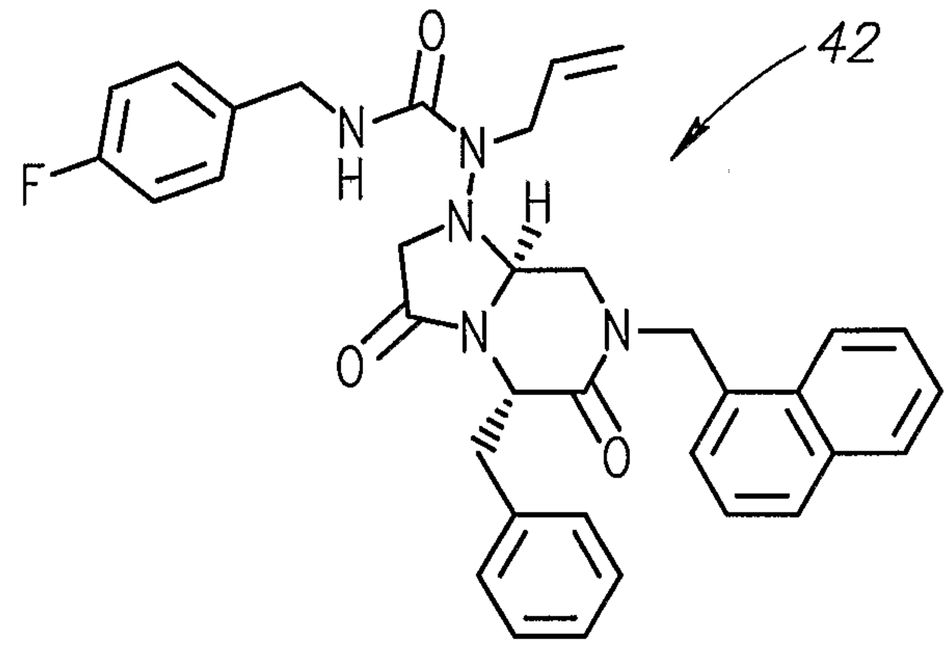
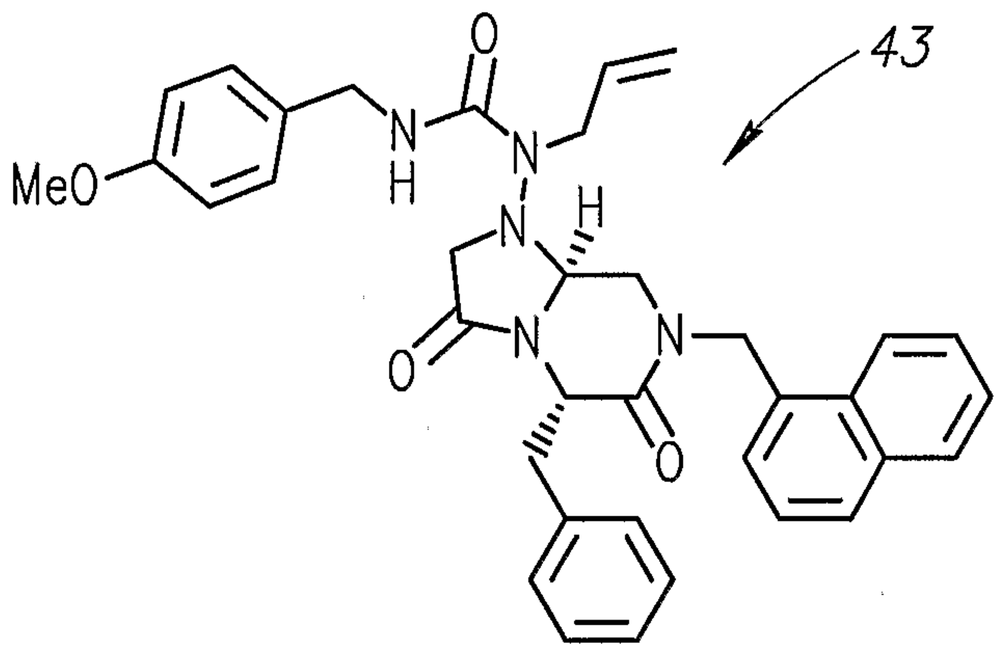
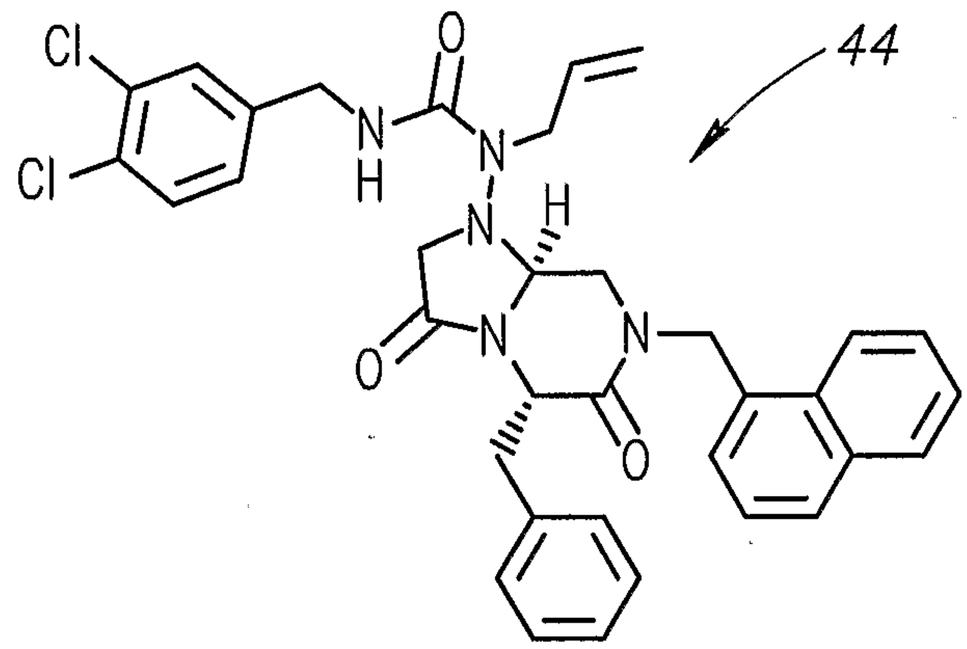


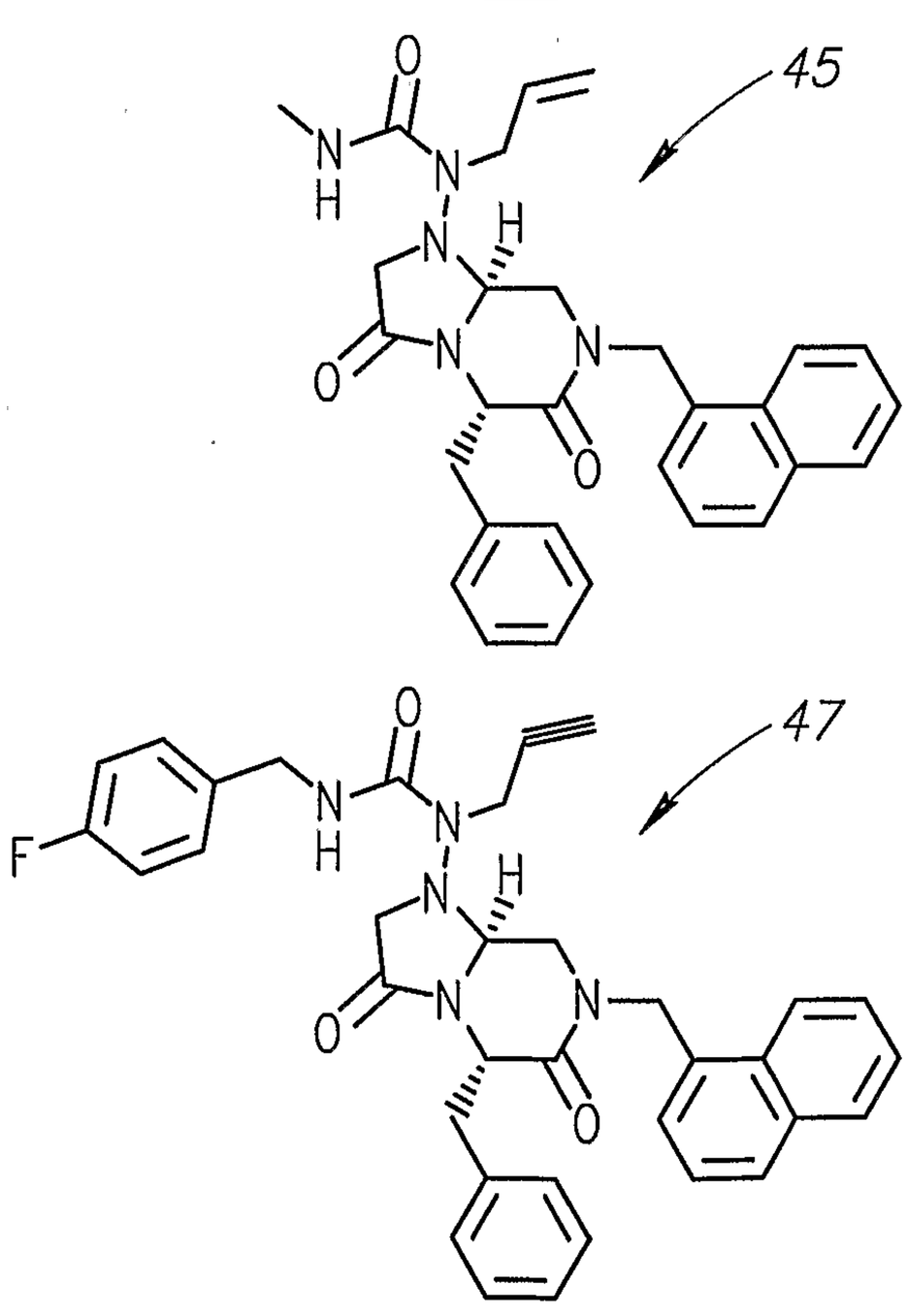
FIG.1E











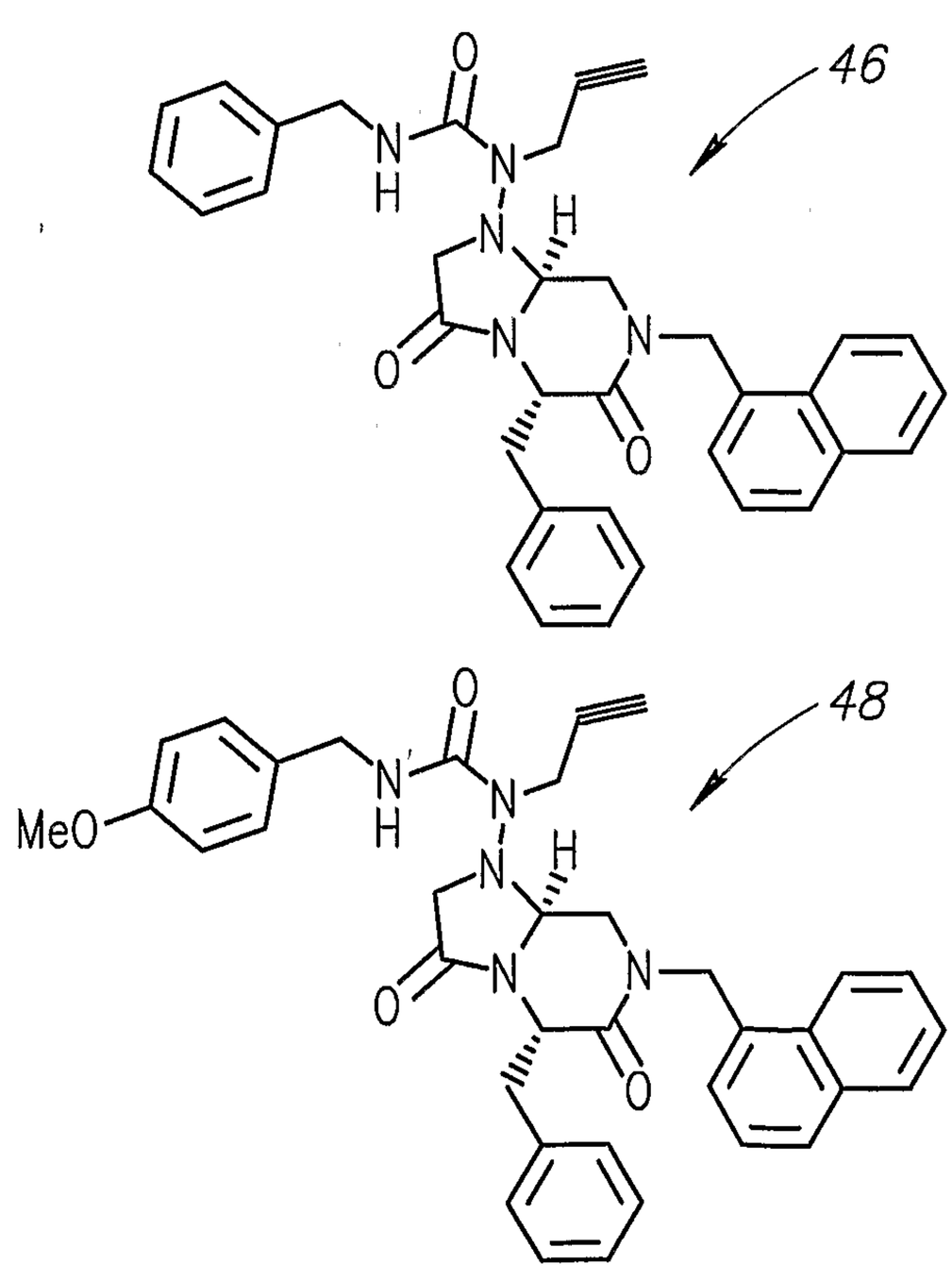
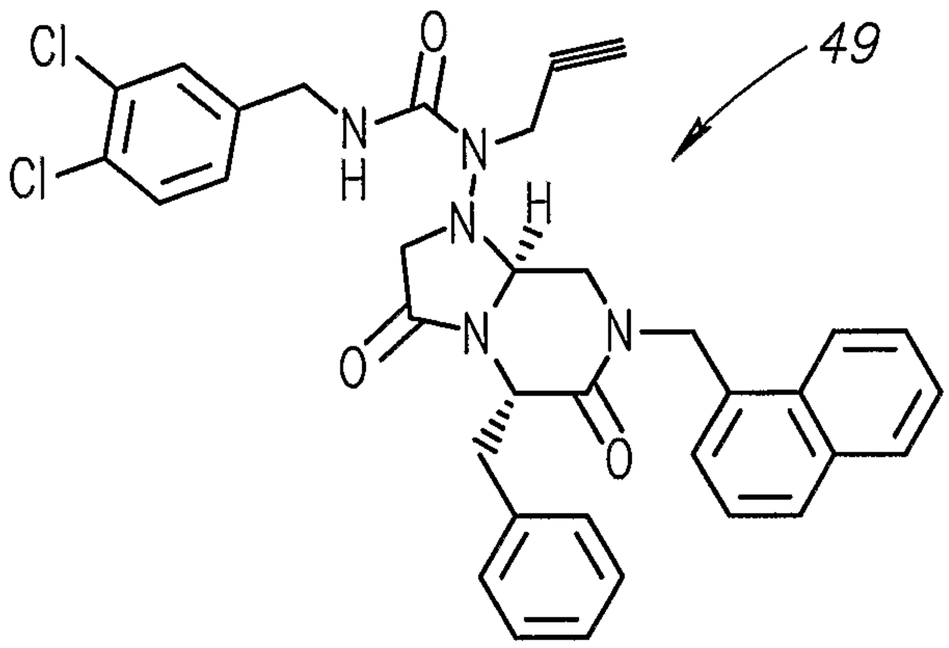
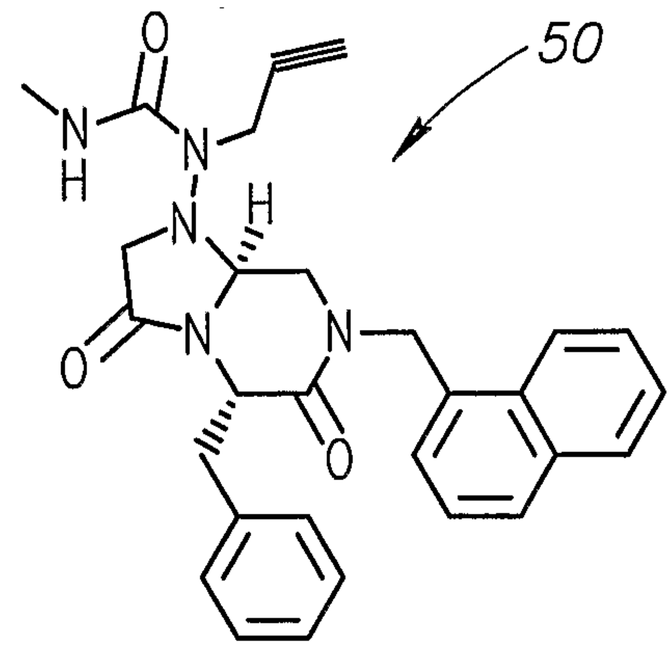
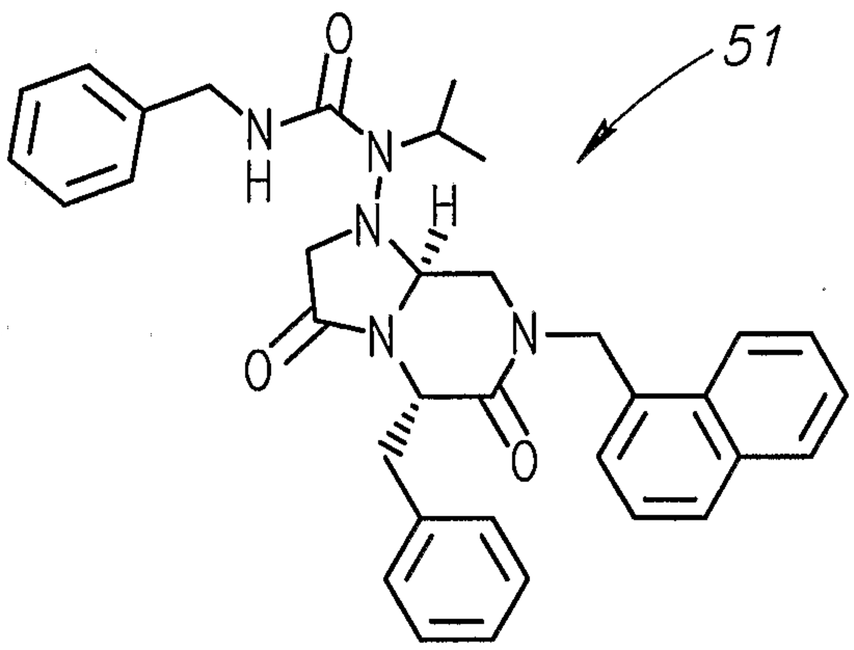
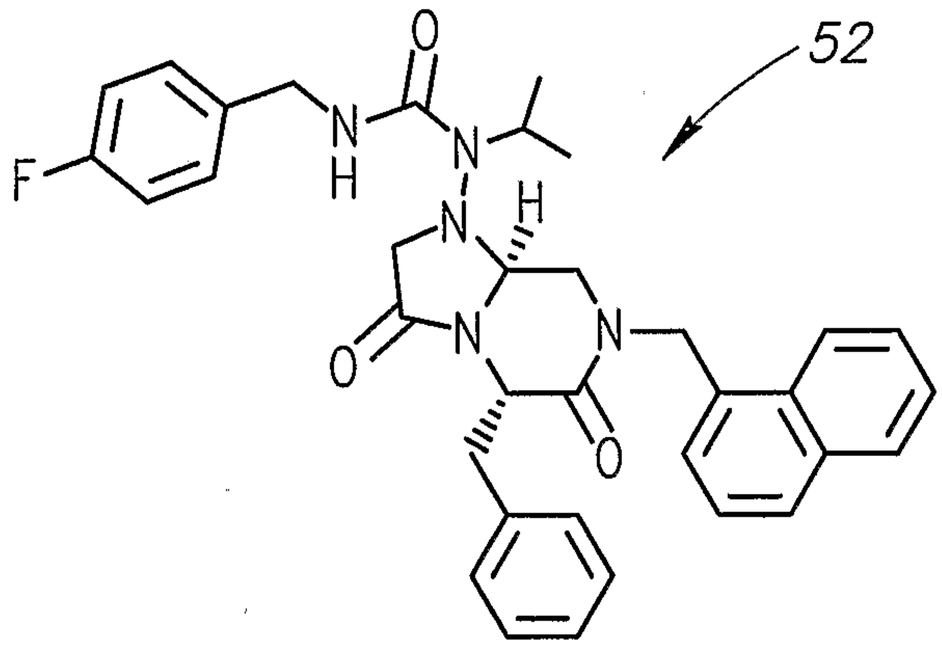


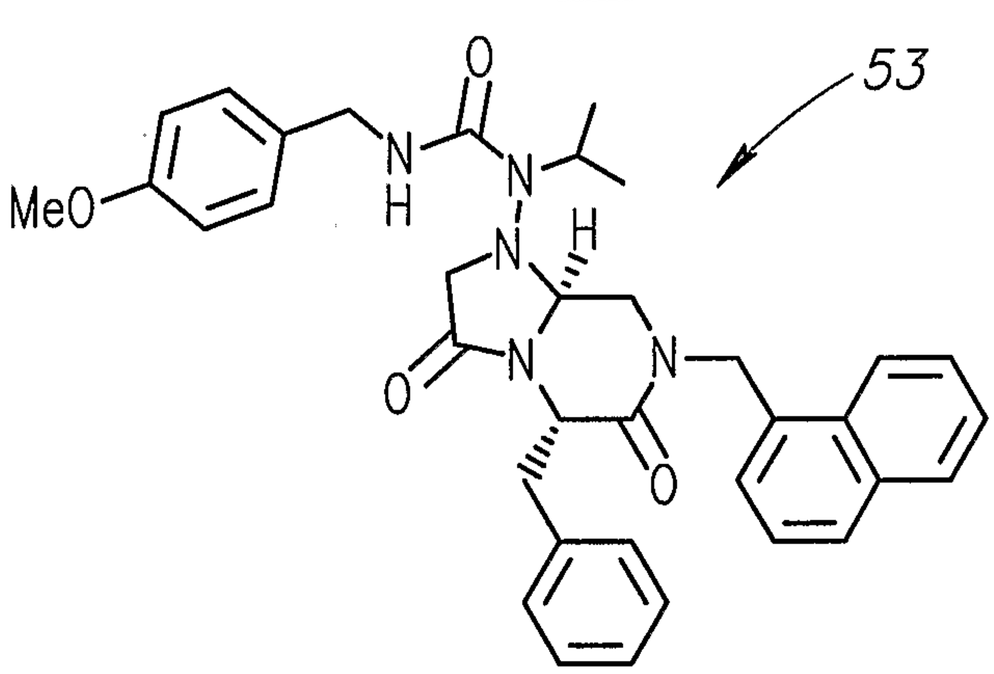
FIG.1F

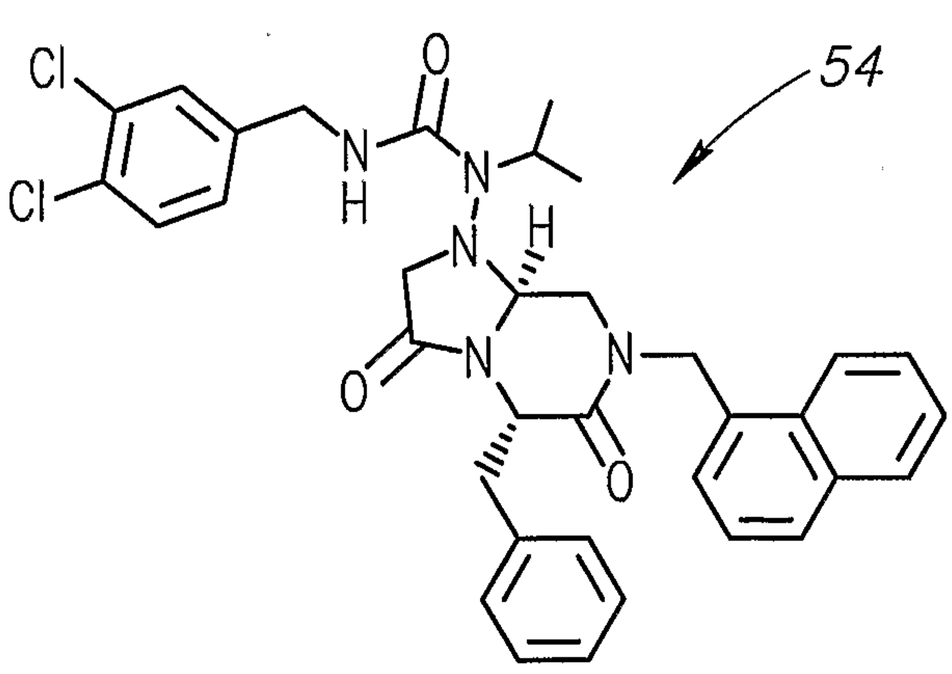


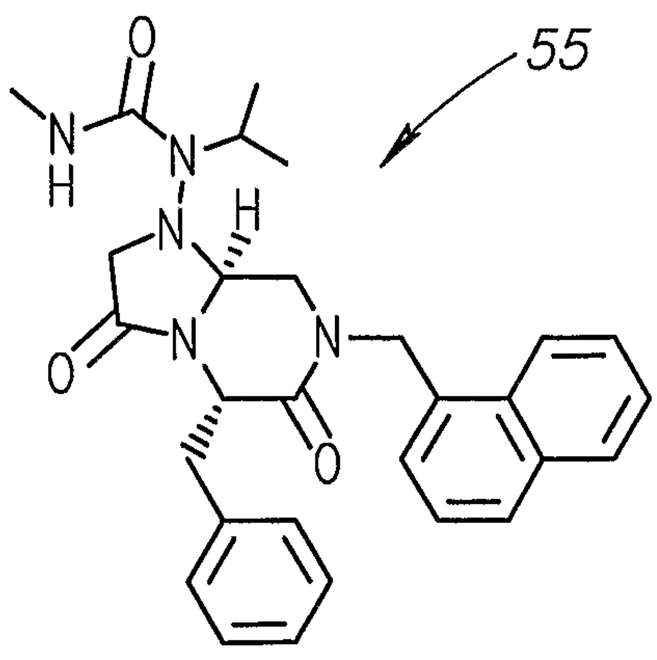












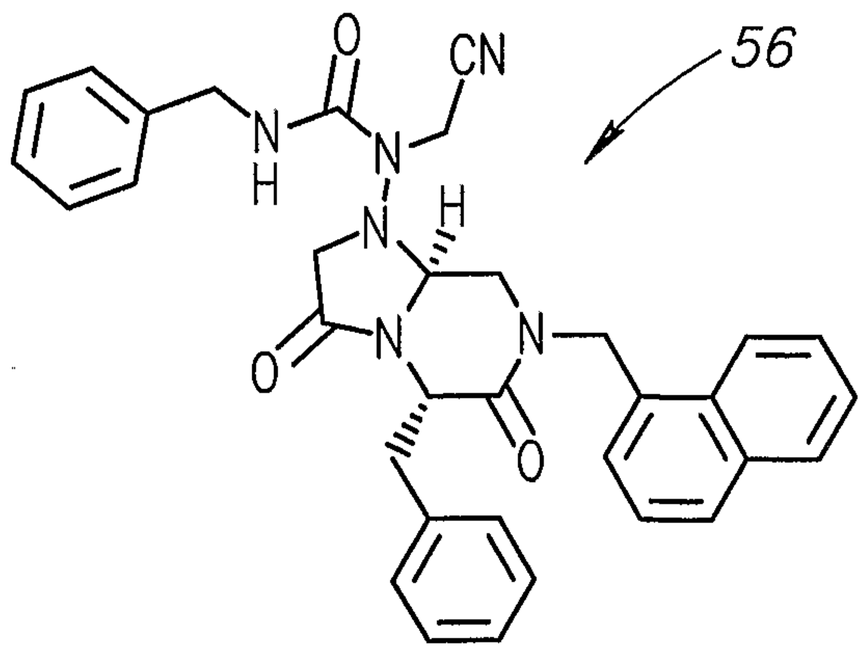
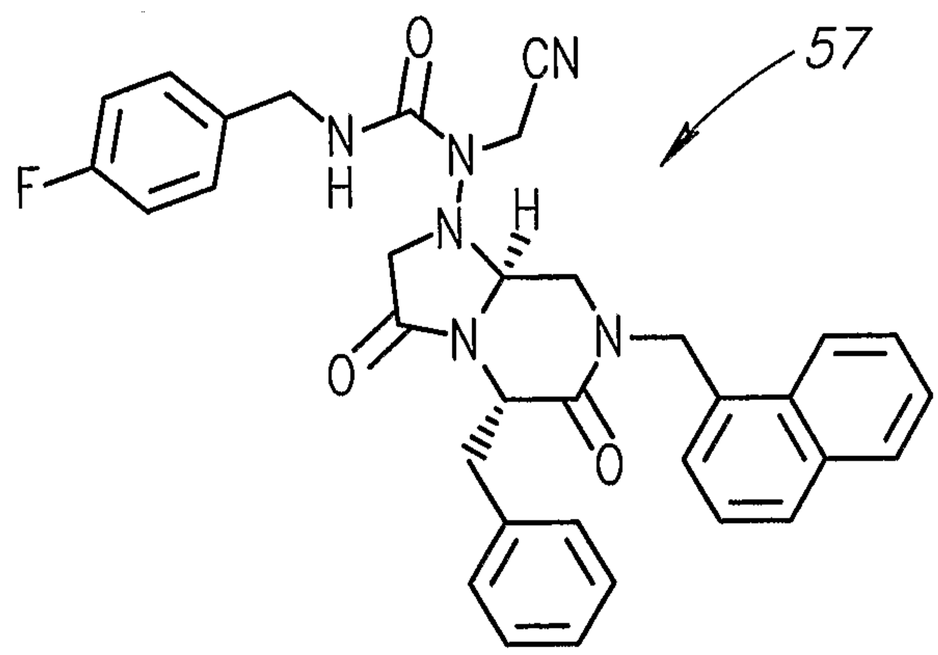
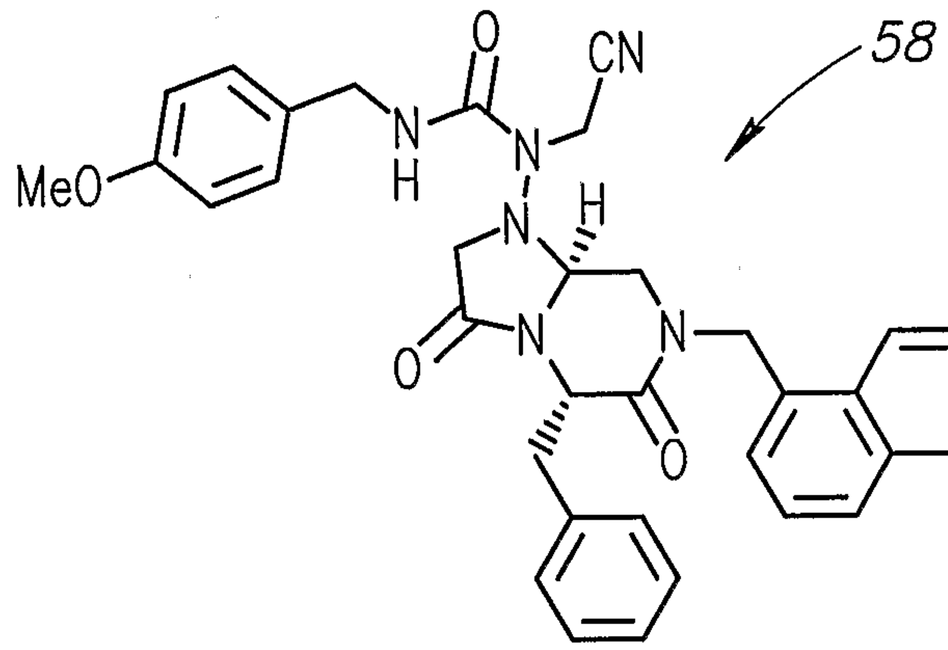
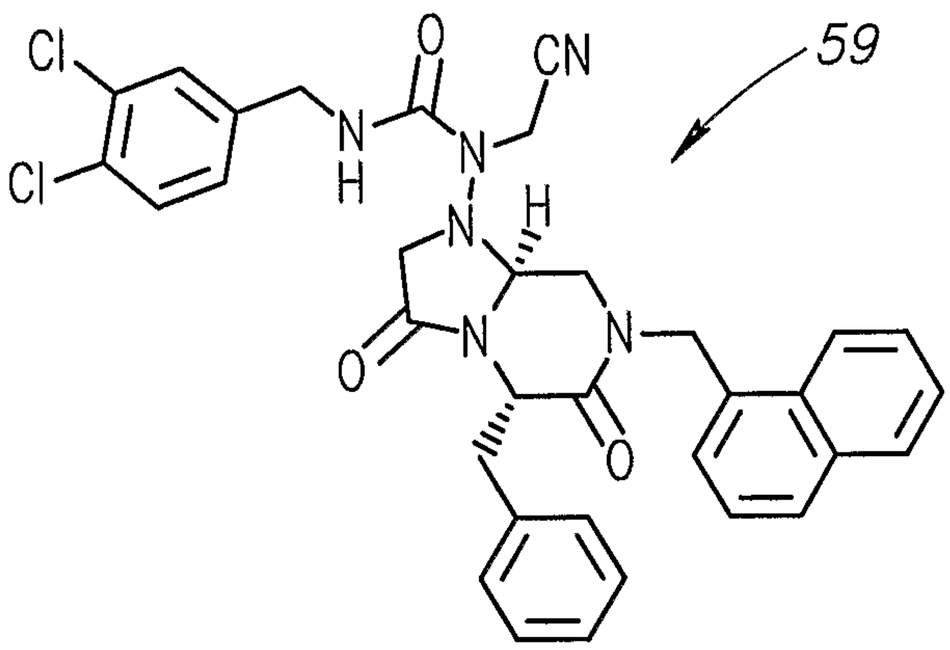
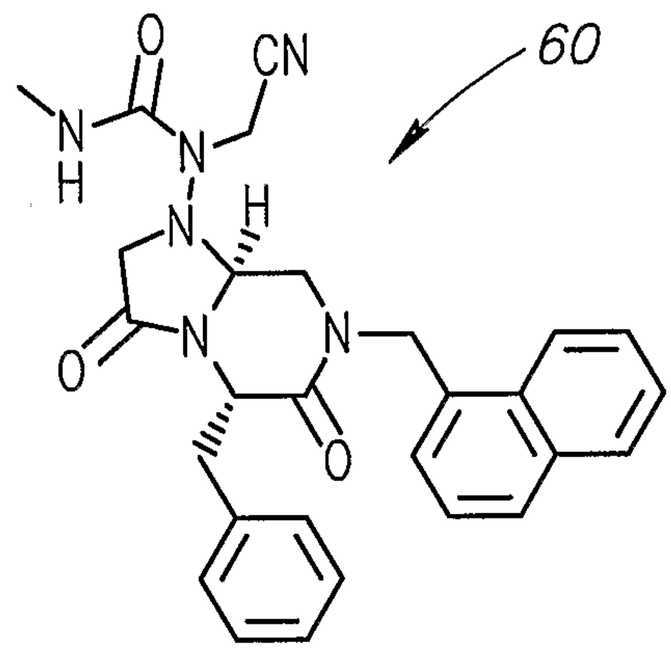


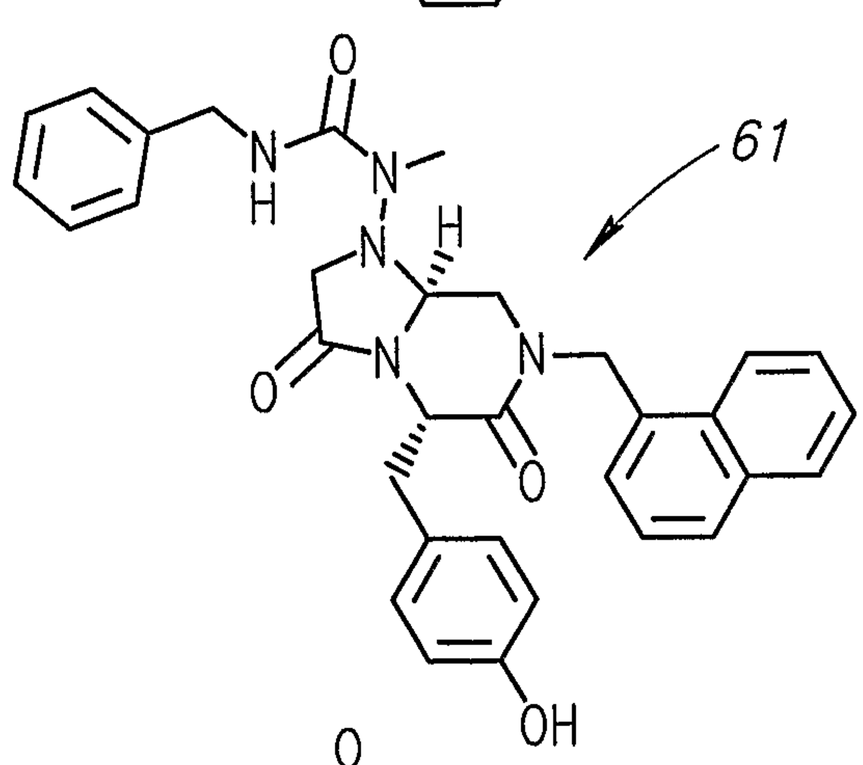
FIG.1G

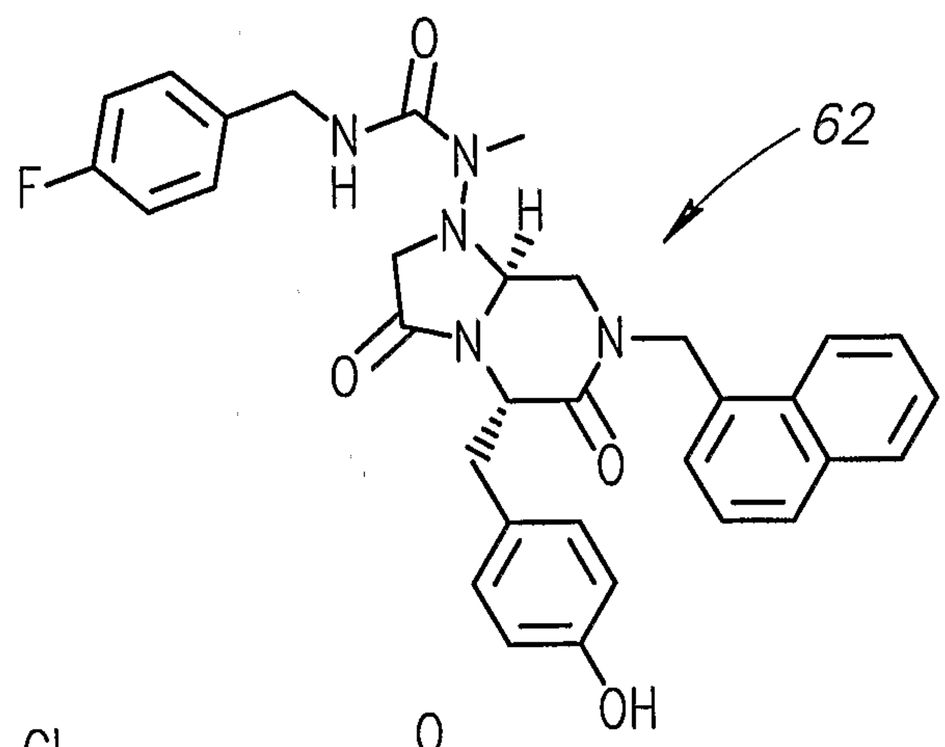


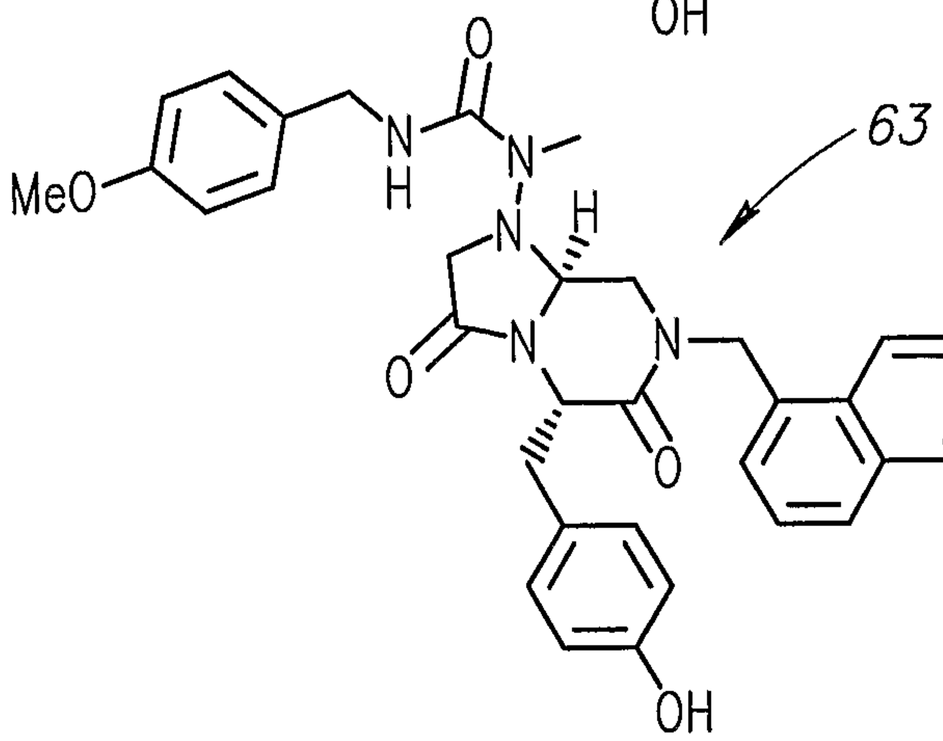












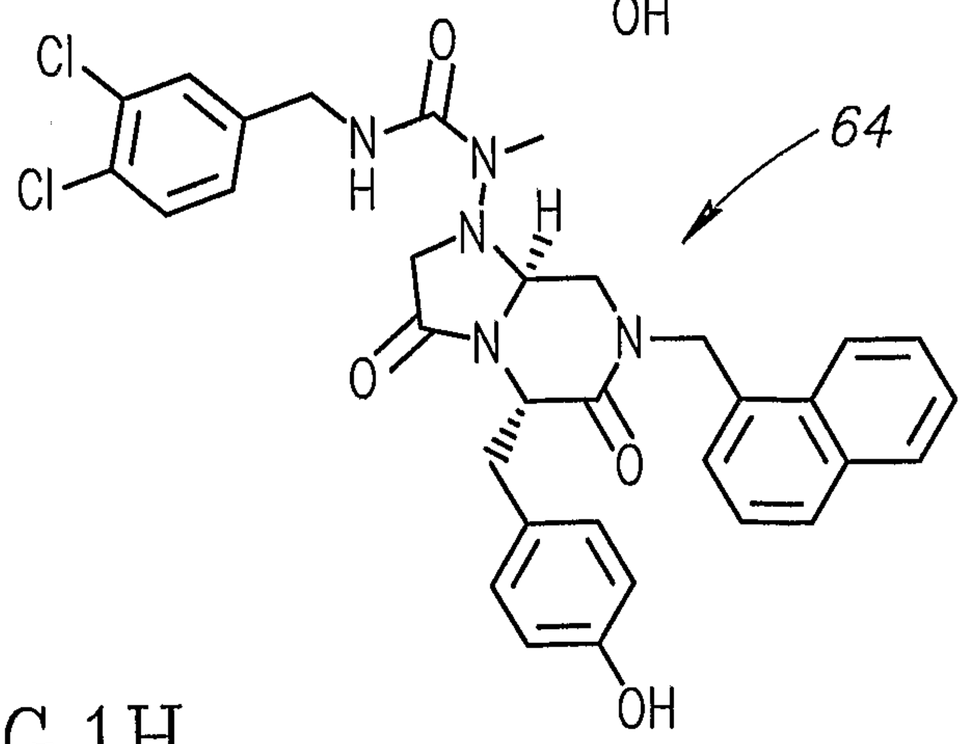
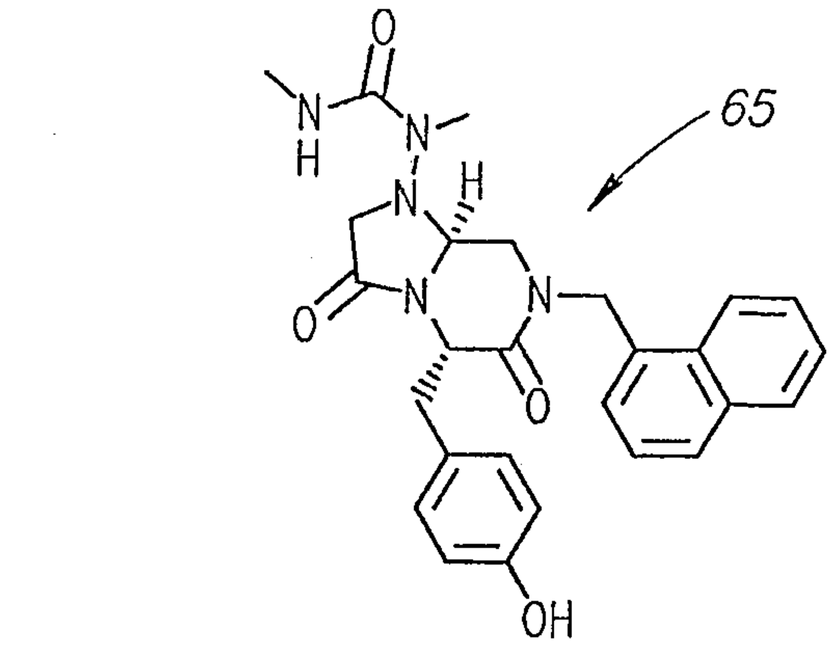
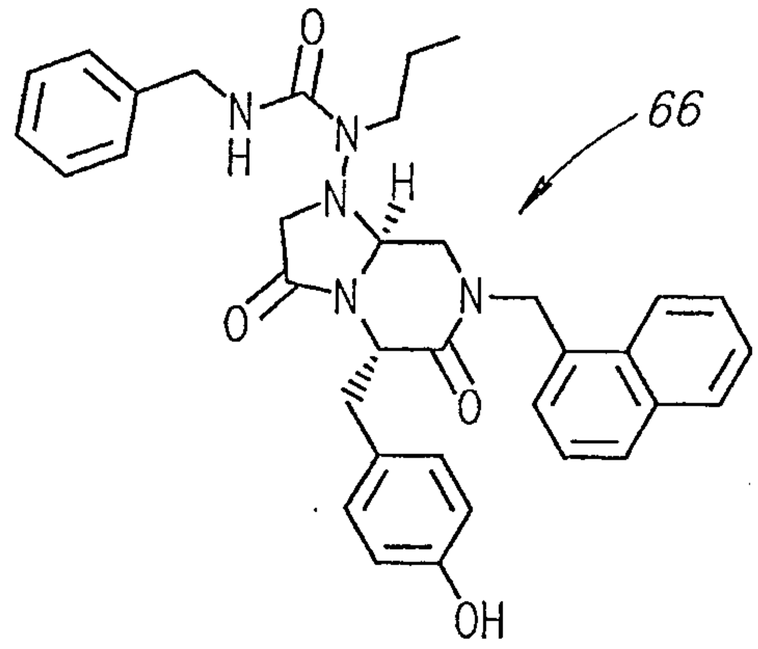
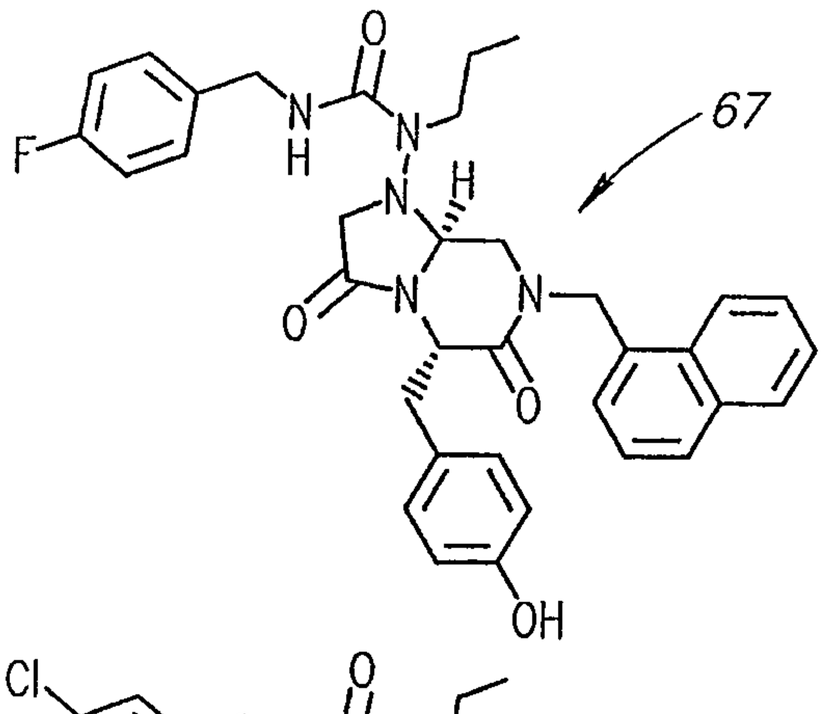
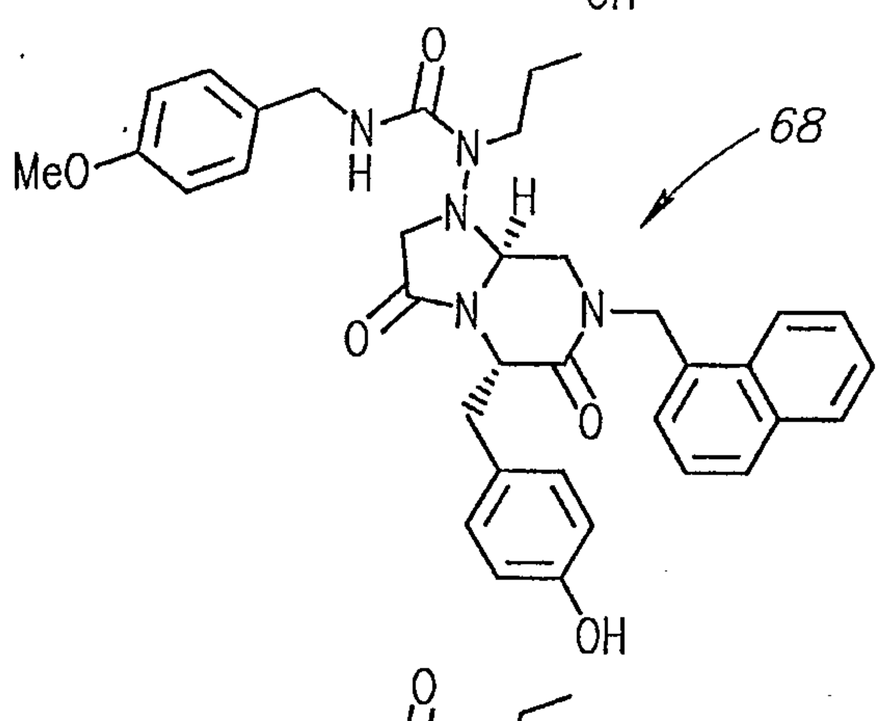


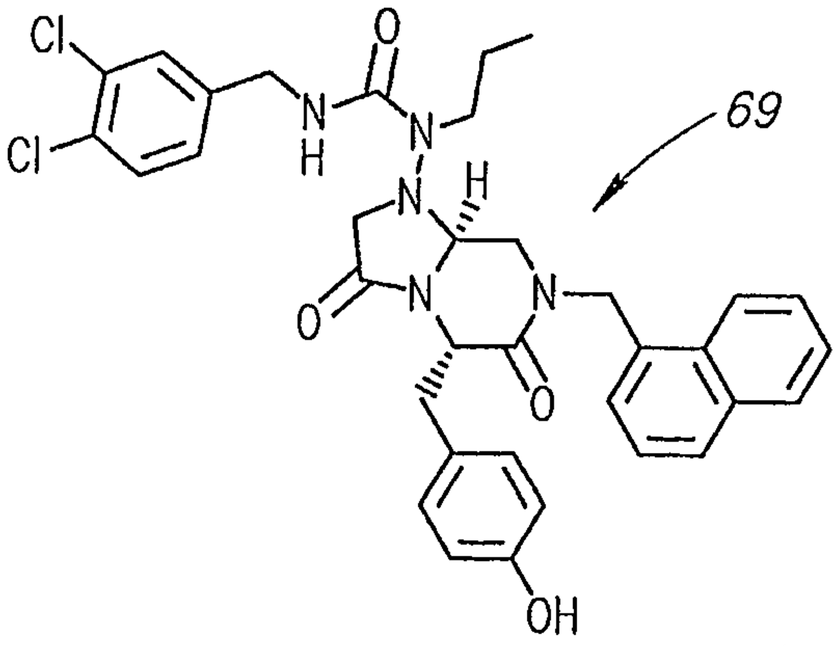
FIG.1H

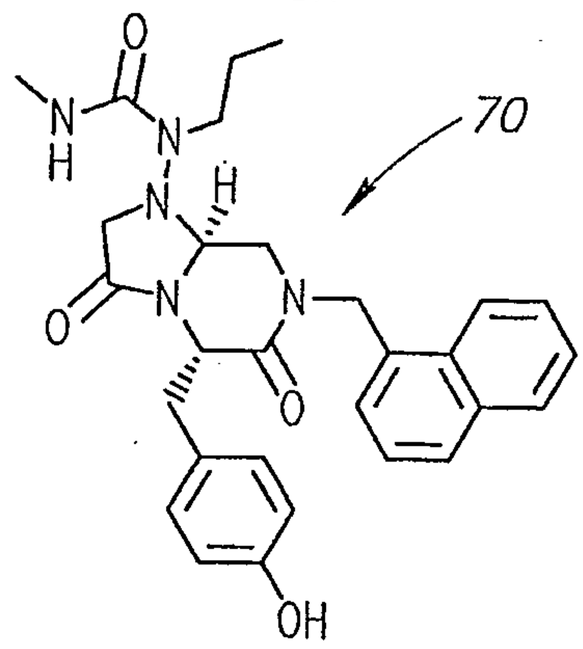


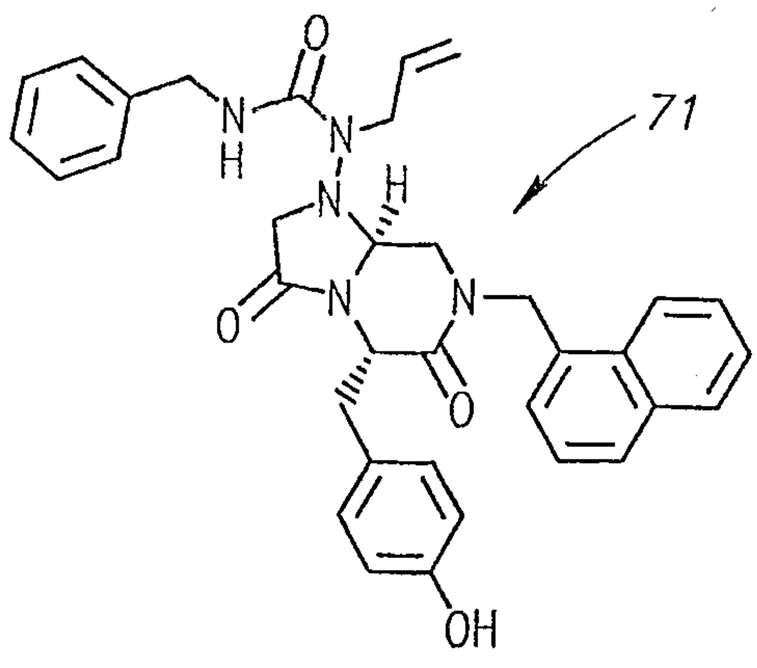












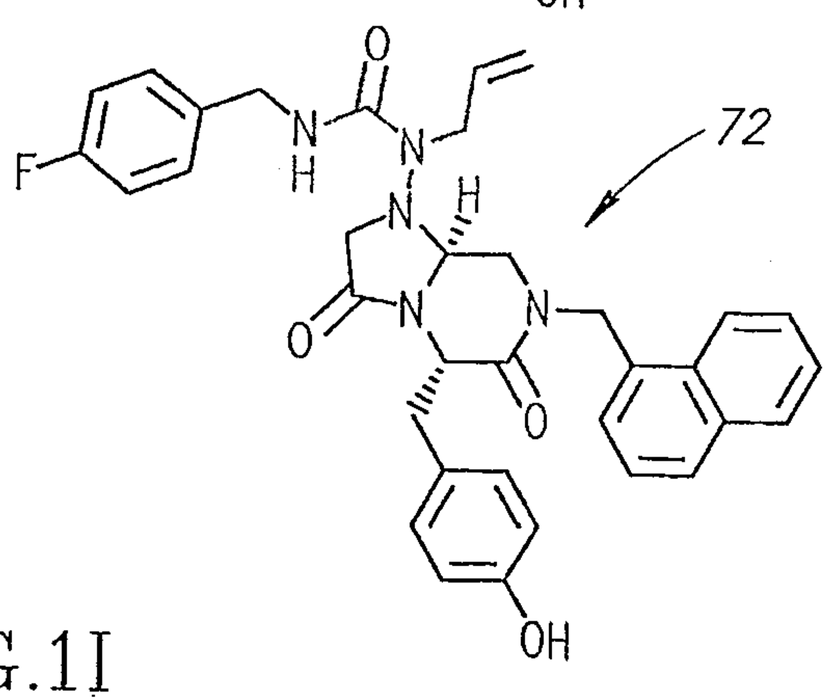
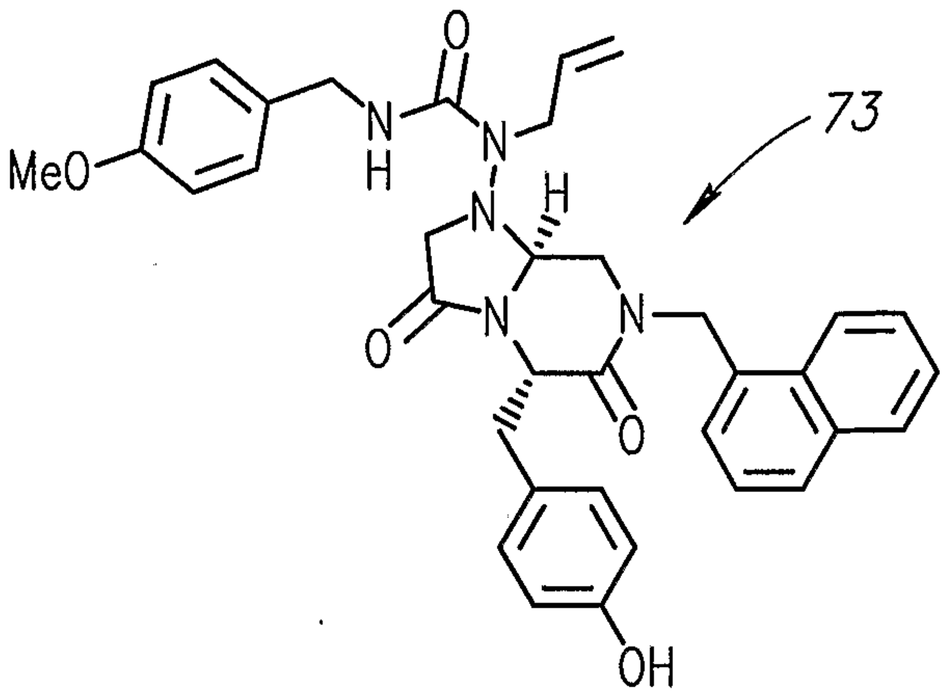


FIG.1I



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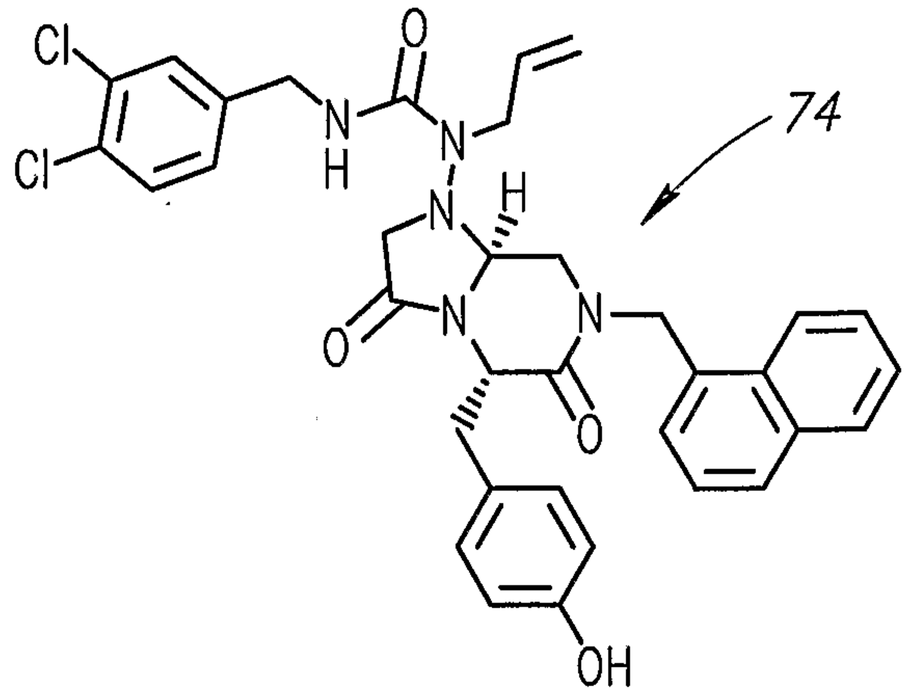

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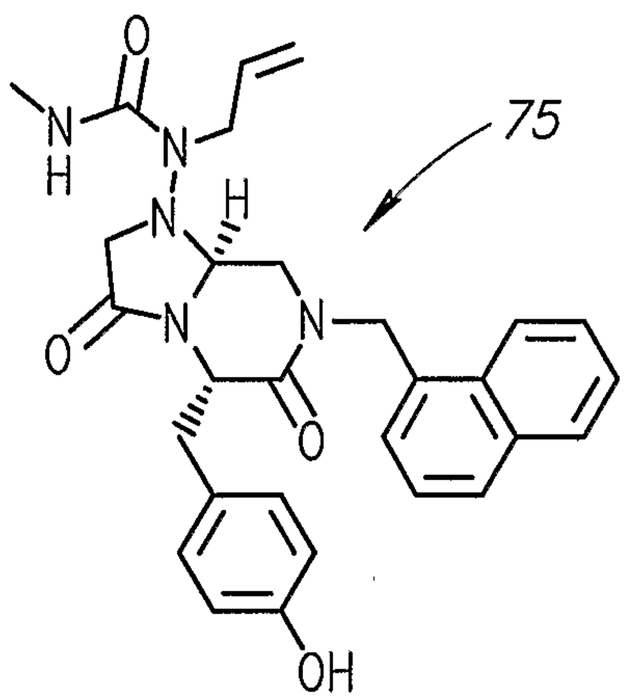

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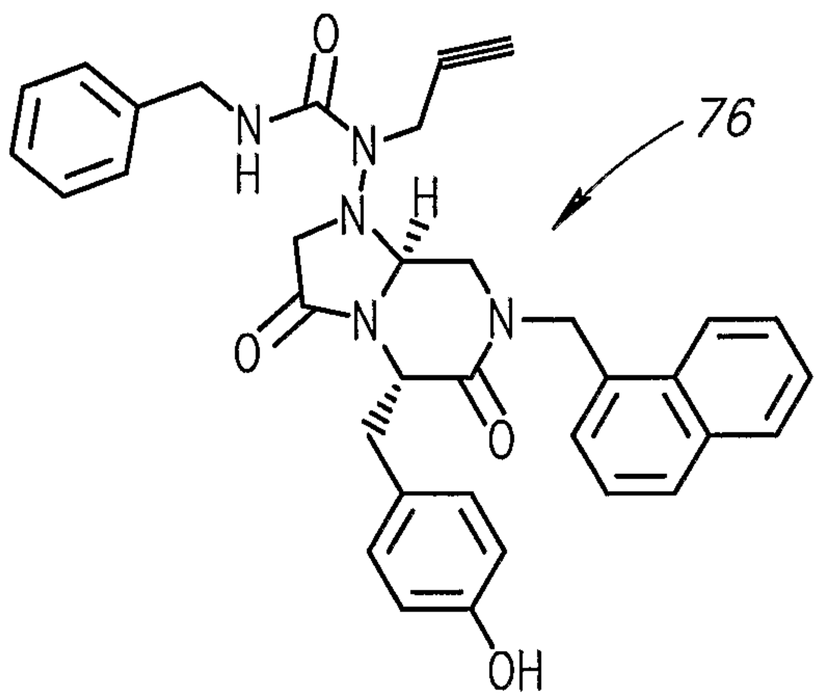

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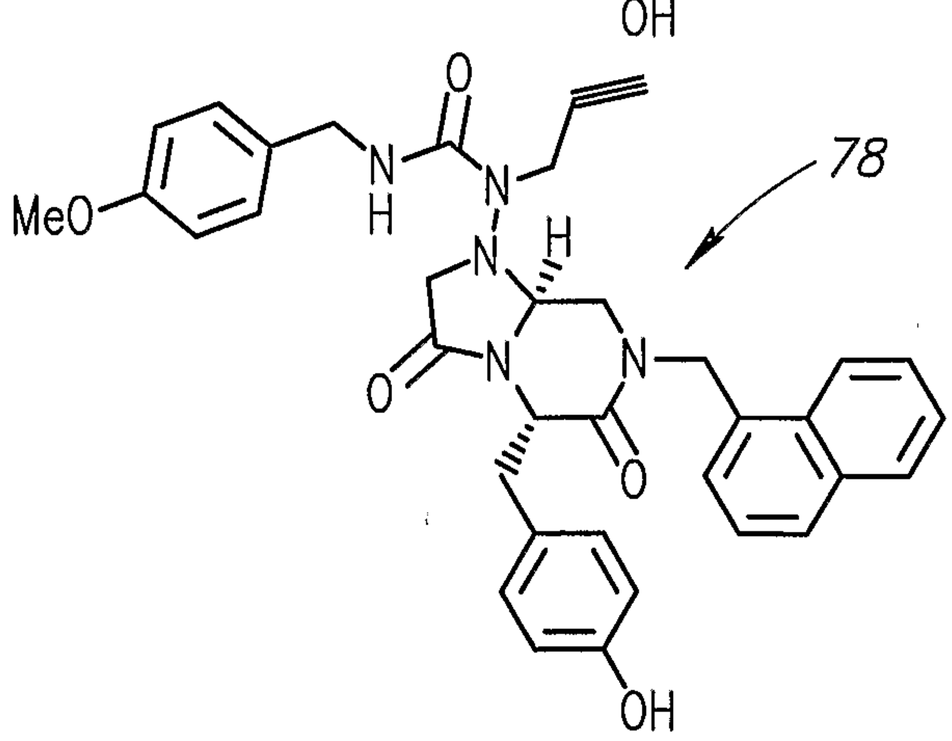

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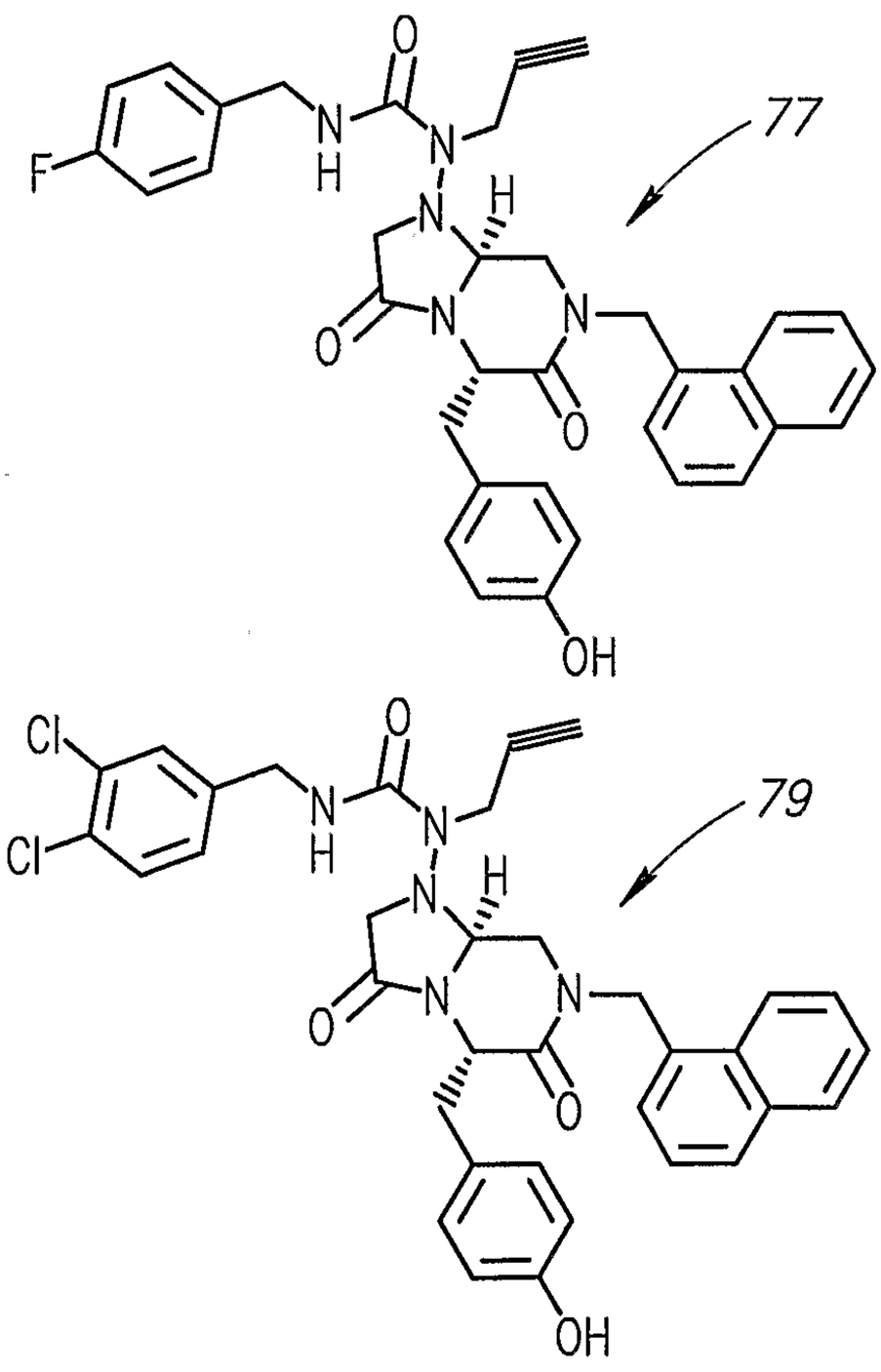

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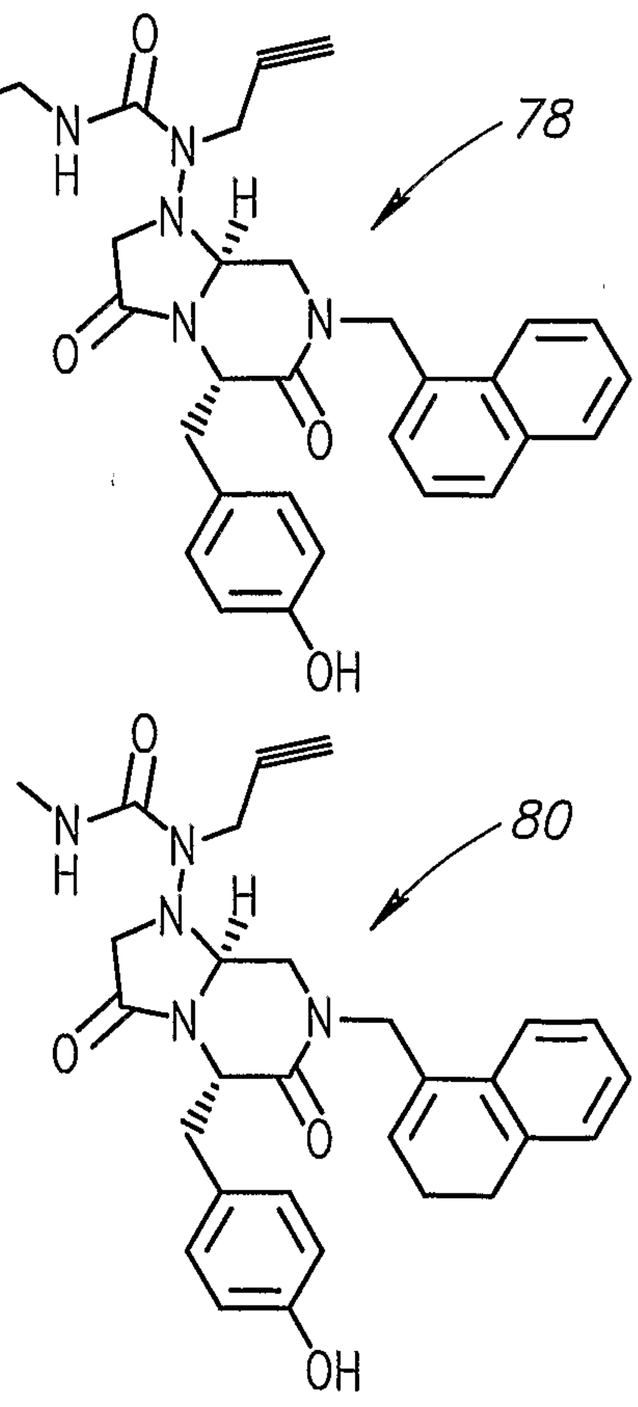

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FIG.1J

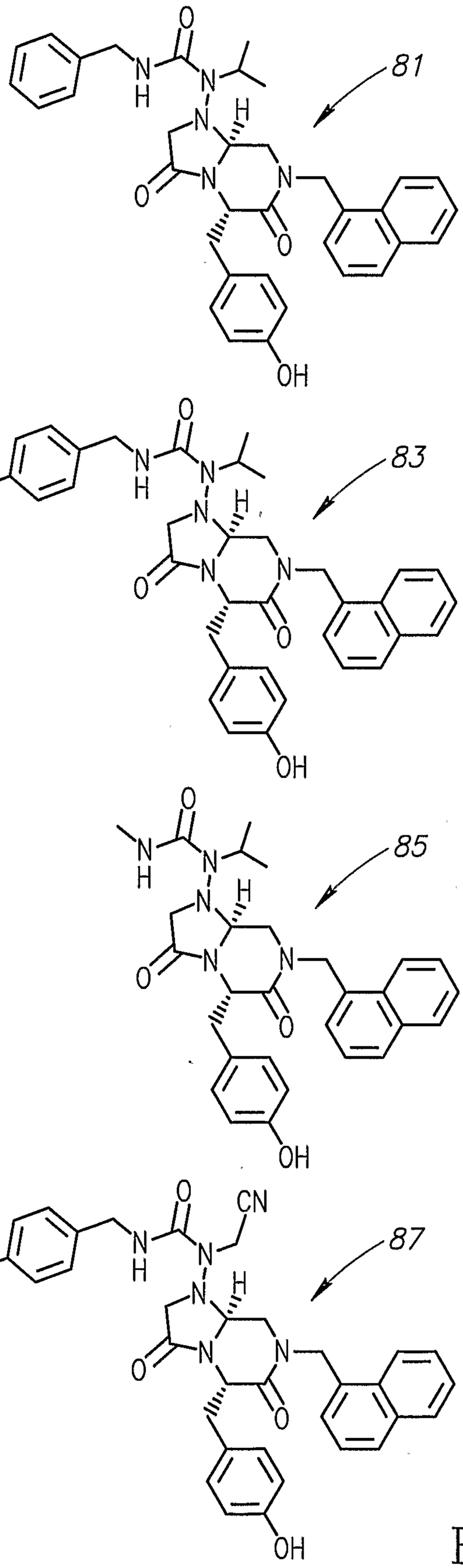
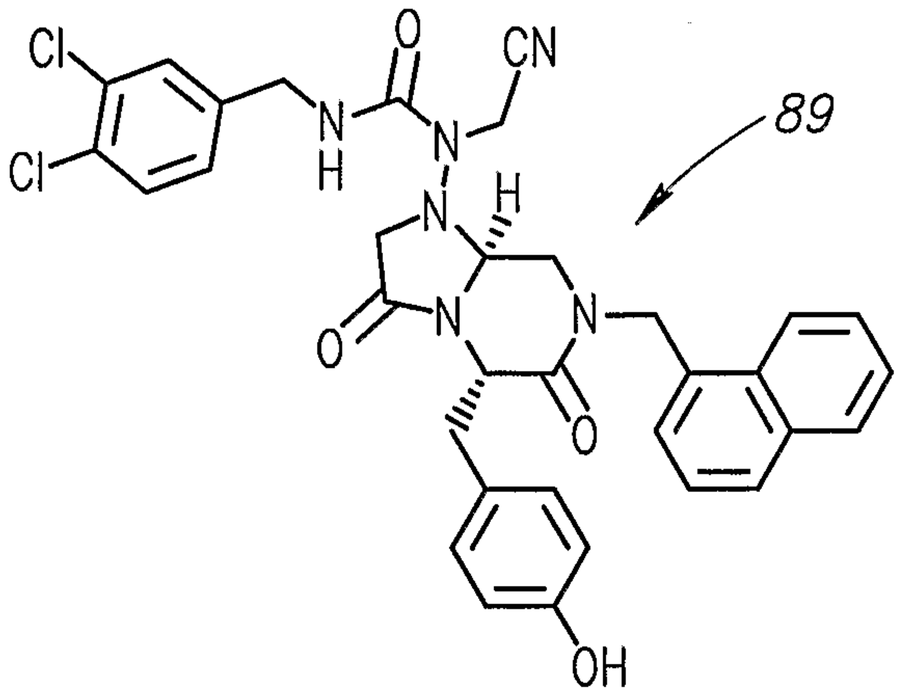
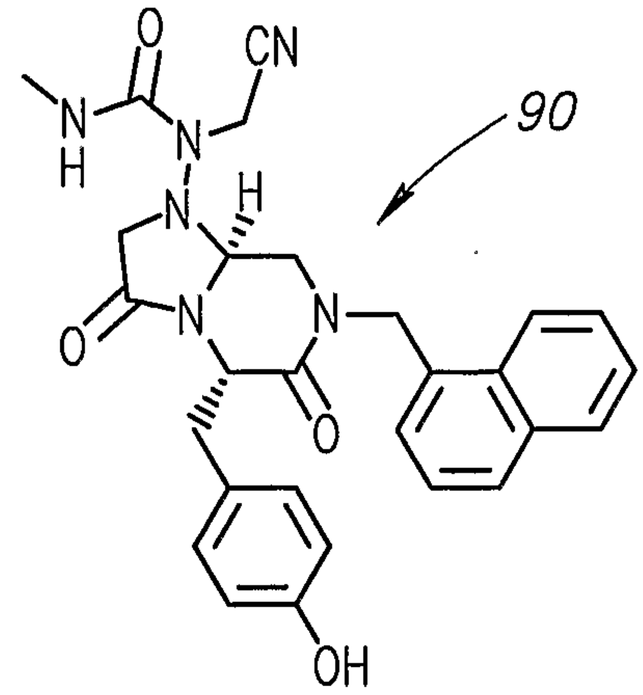
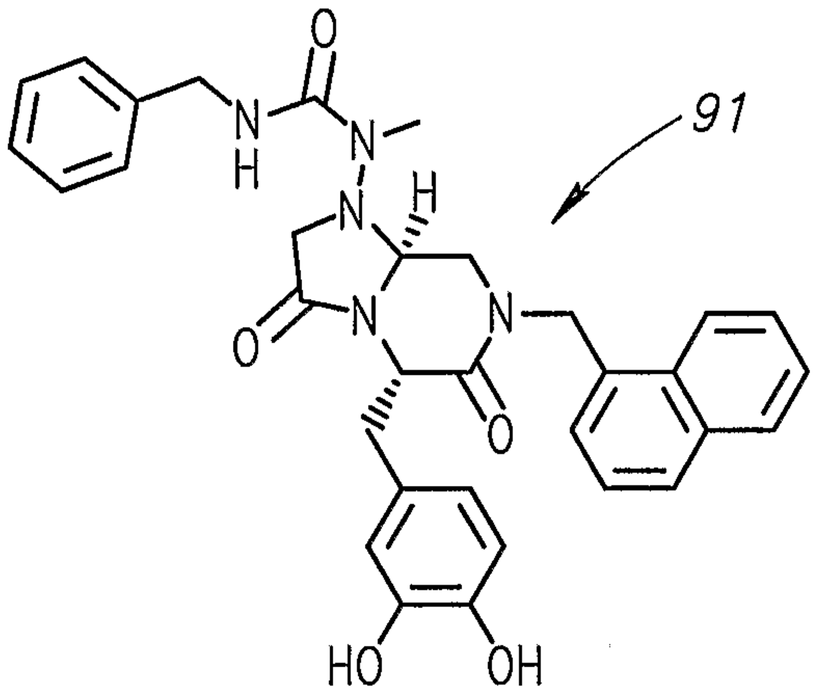
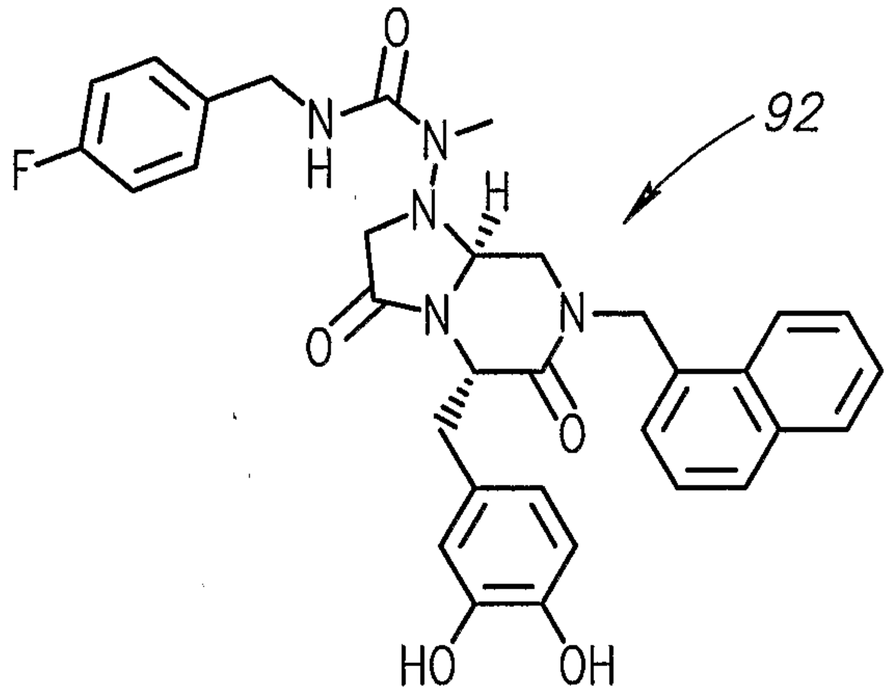


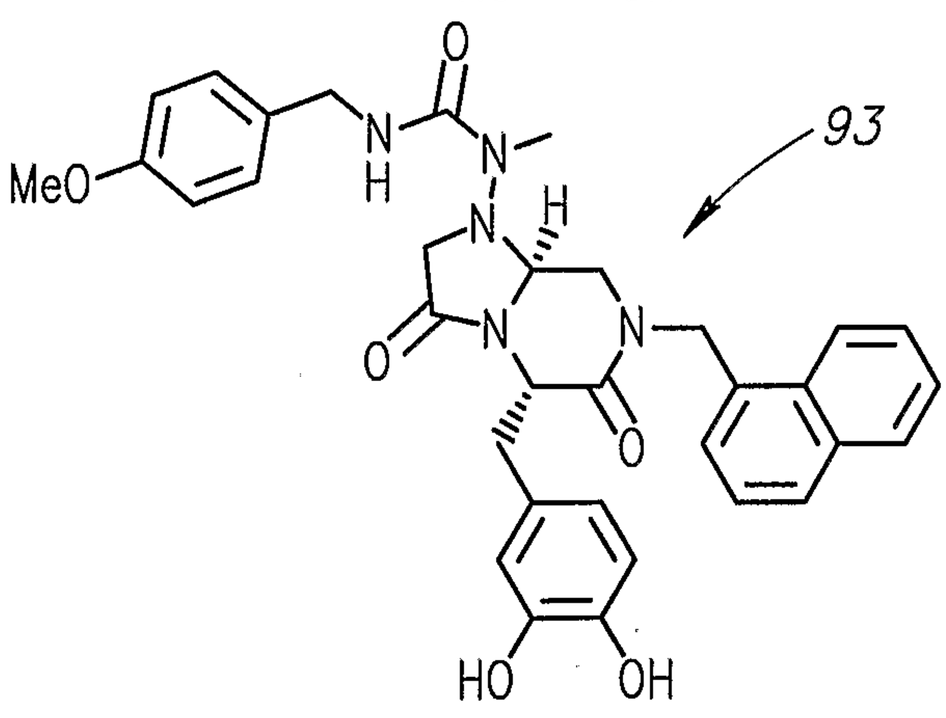
FIG.1K

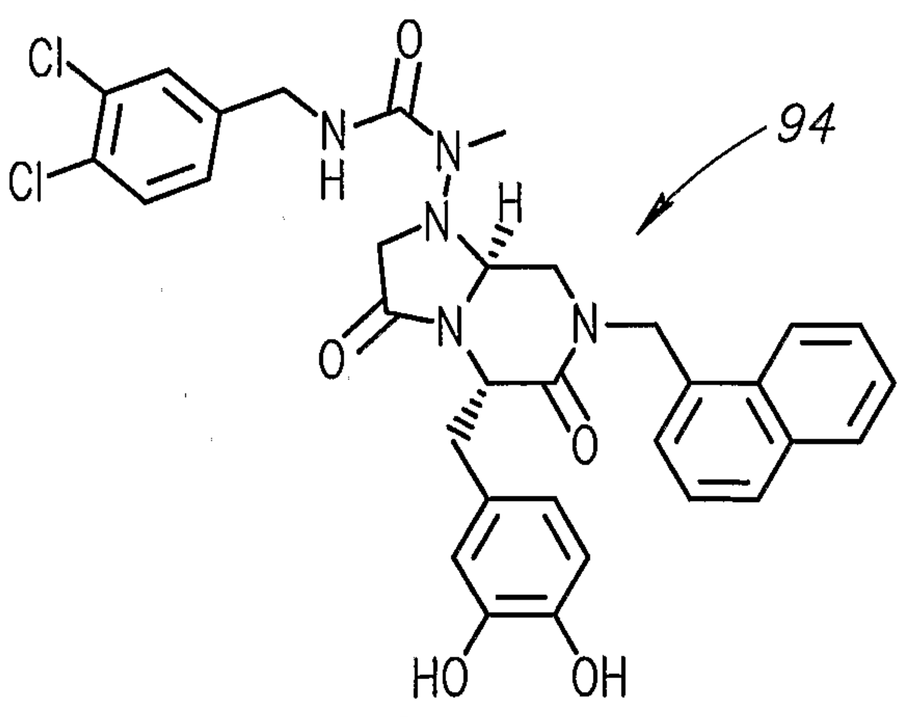


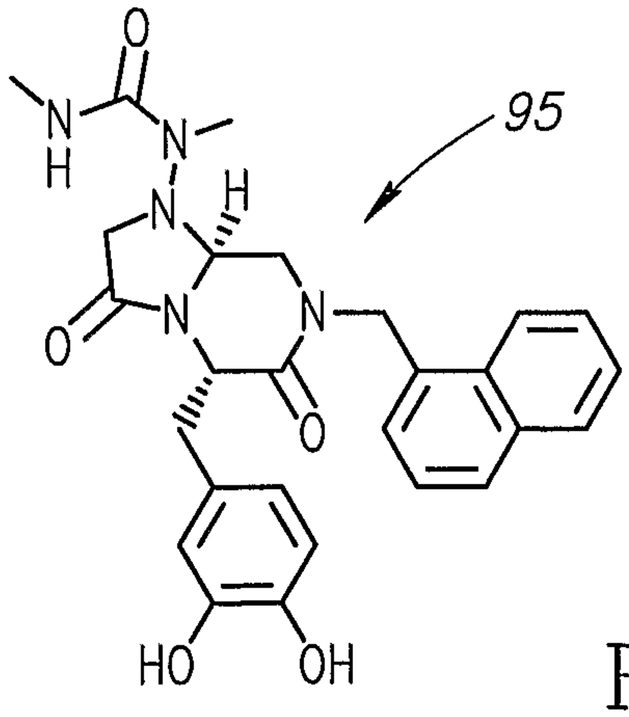












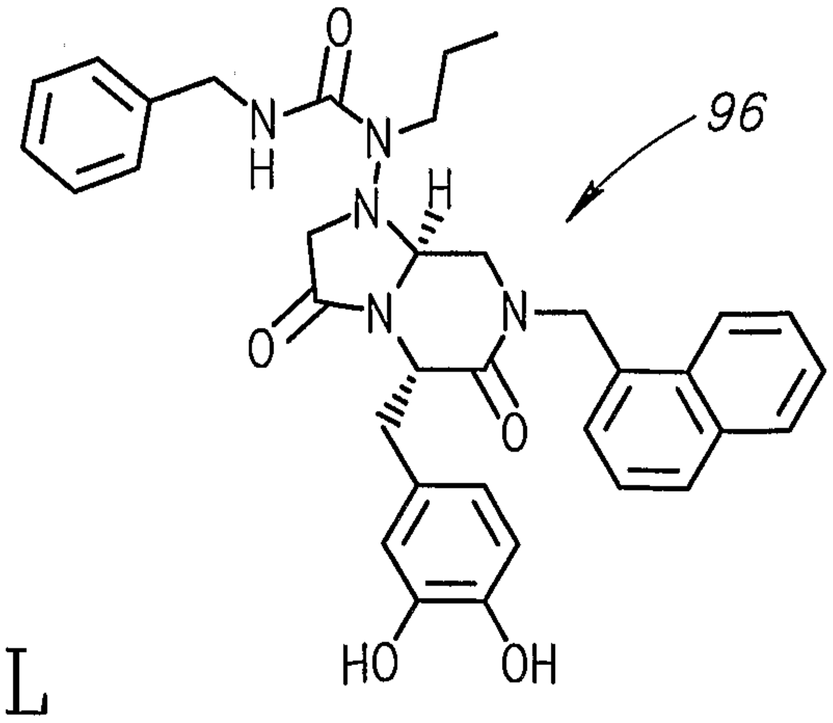
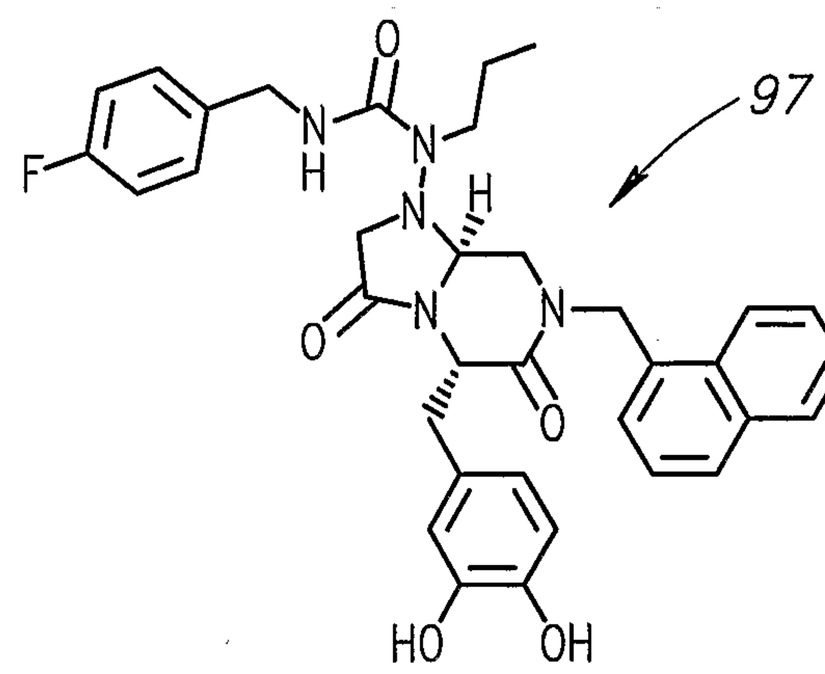


FIG.1L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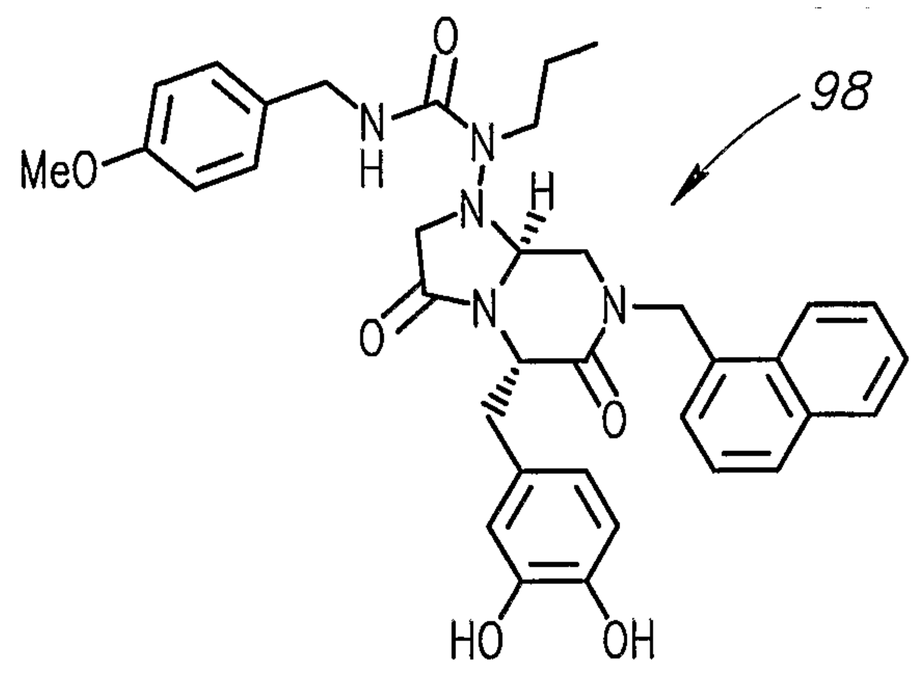
98
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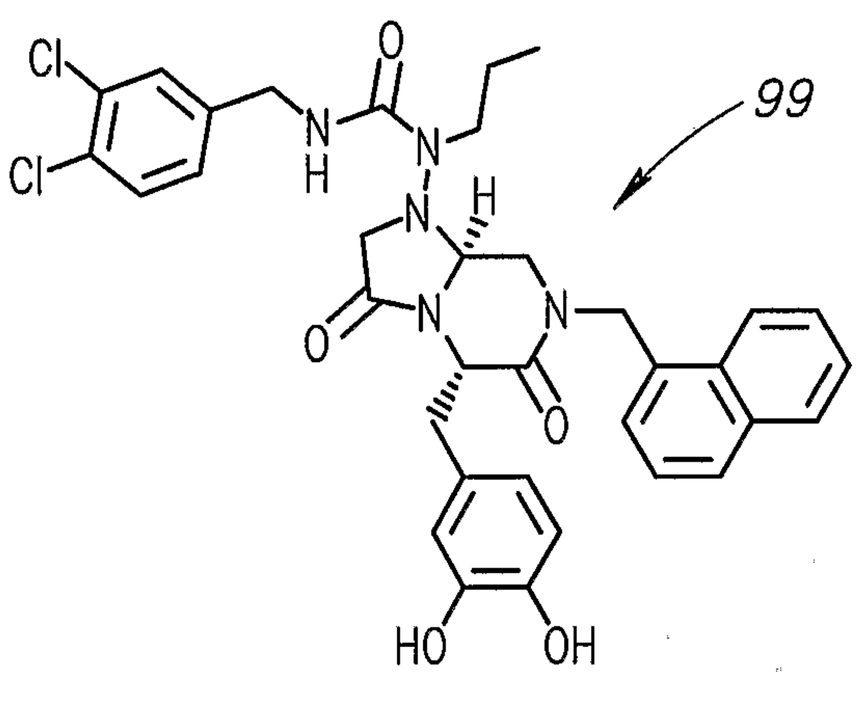
O
N
H
HO
OH


99
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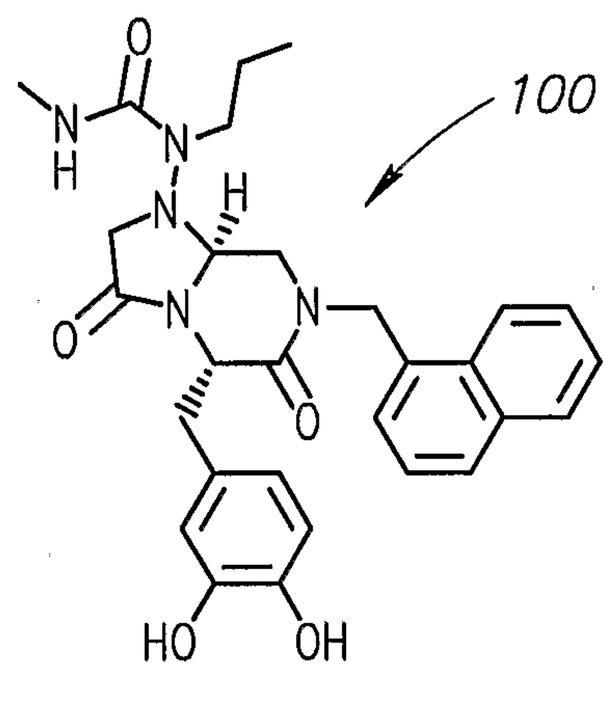
Cl
O
N
H
HO
OH


100
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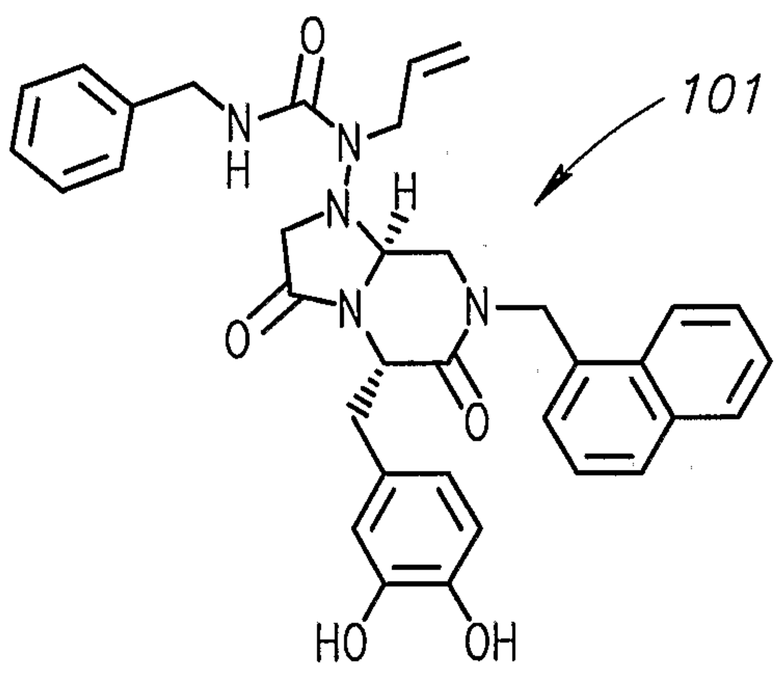
N
H
HO
OH


101
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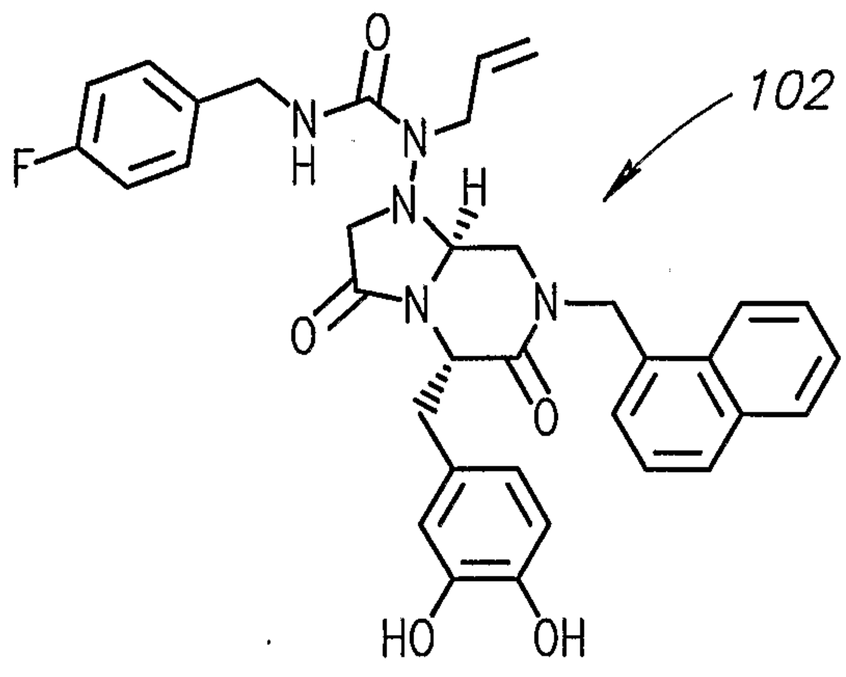
N
H
HO
OH


102
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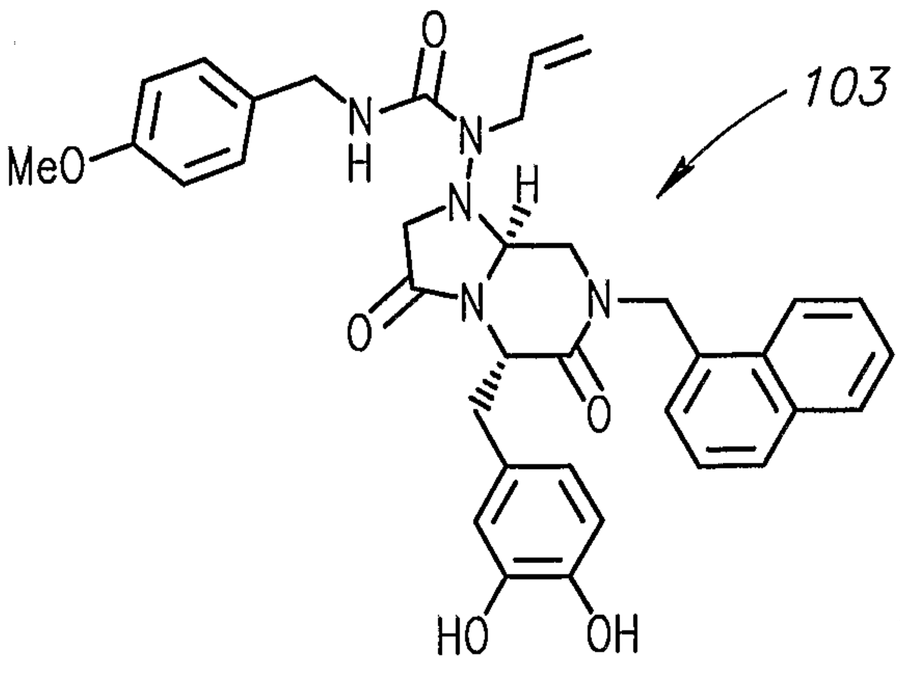
N
H
HO
OH


103
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N
H
HO
OH

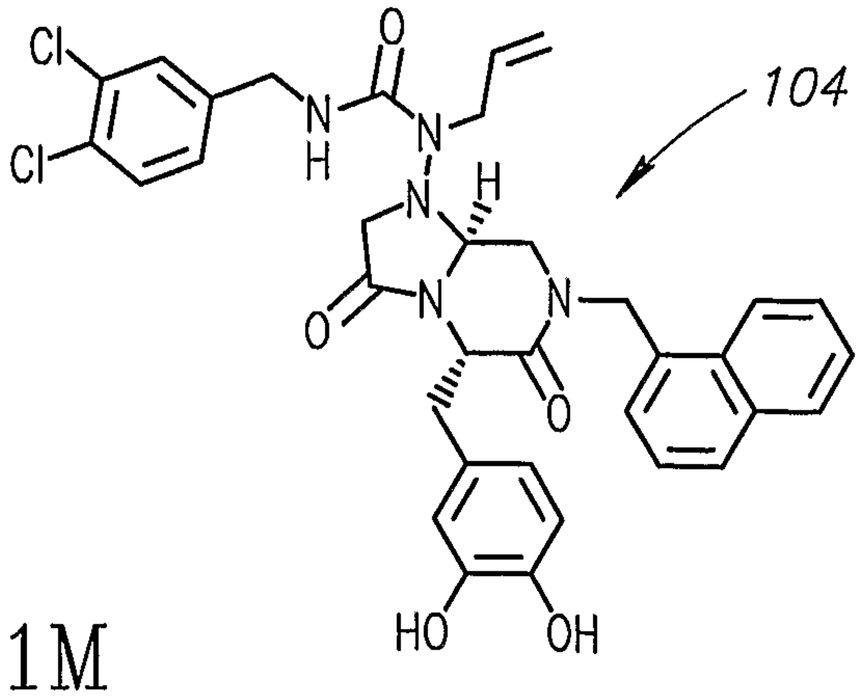
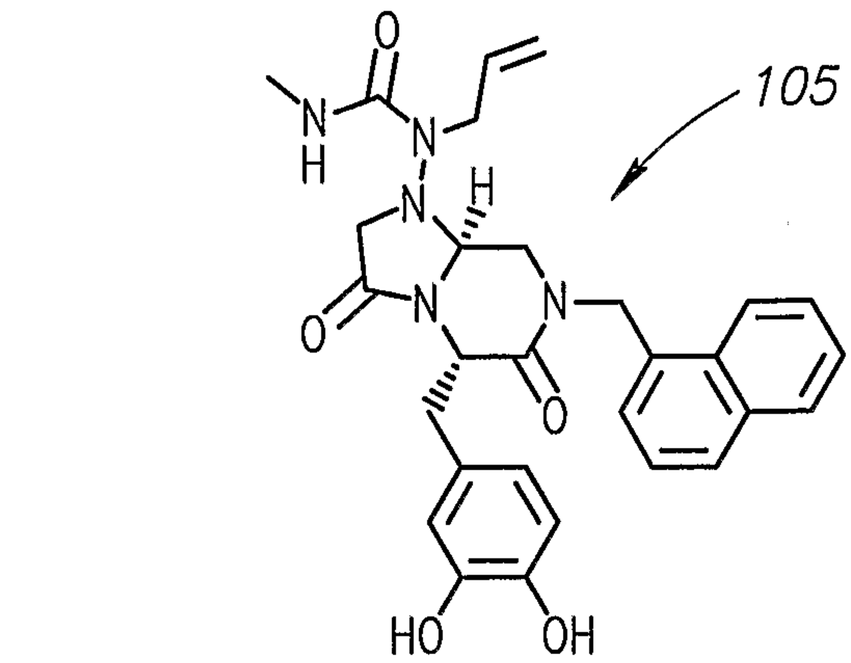
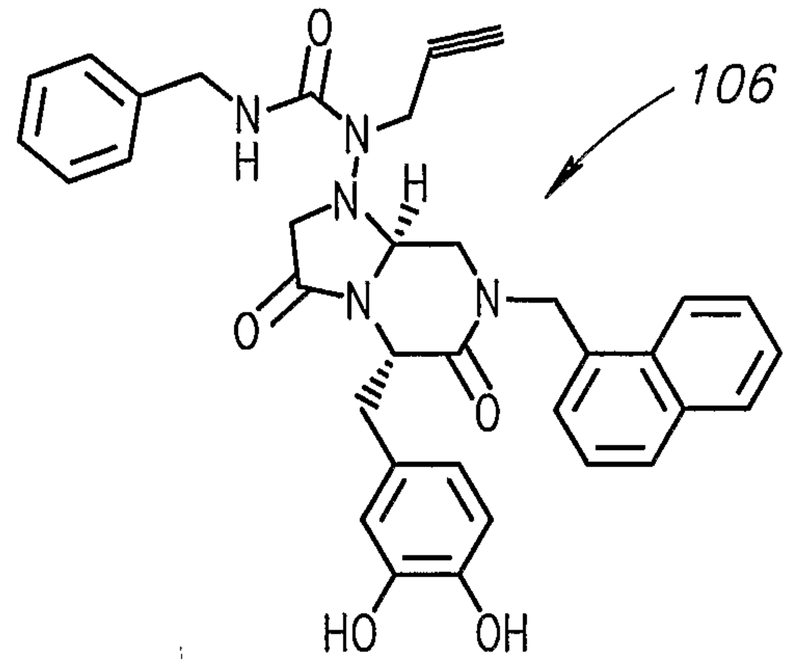
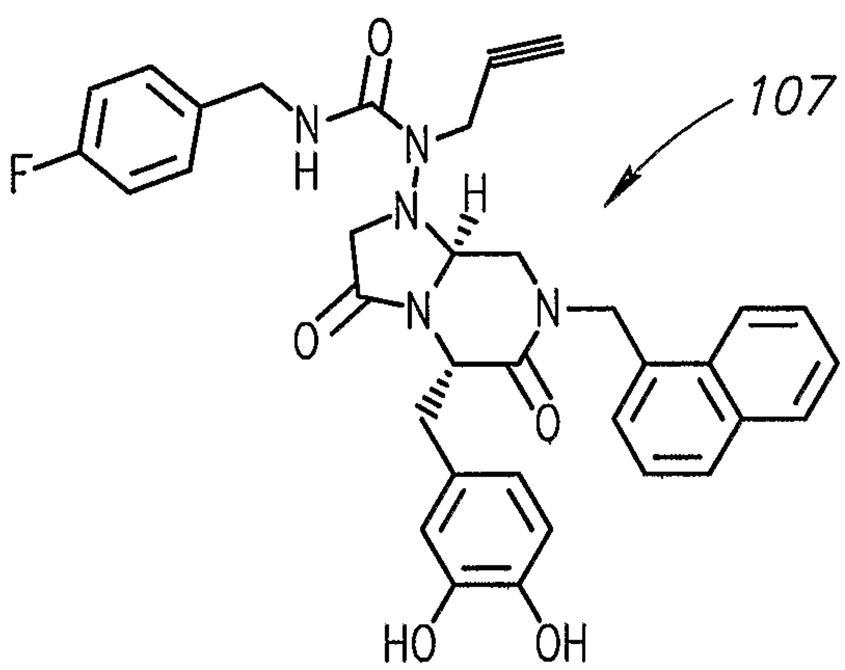
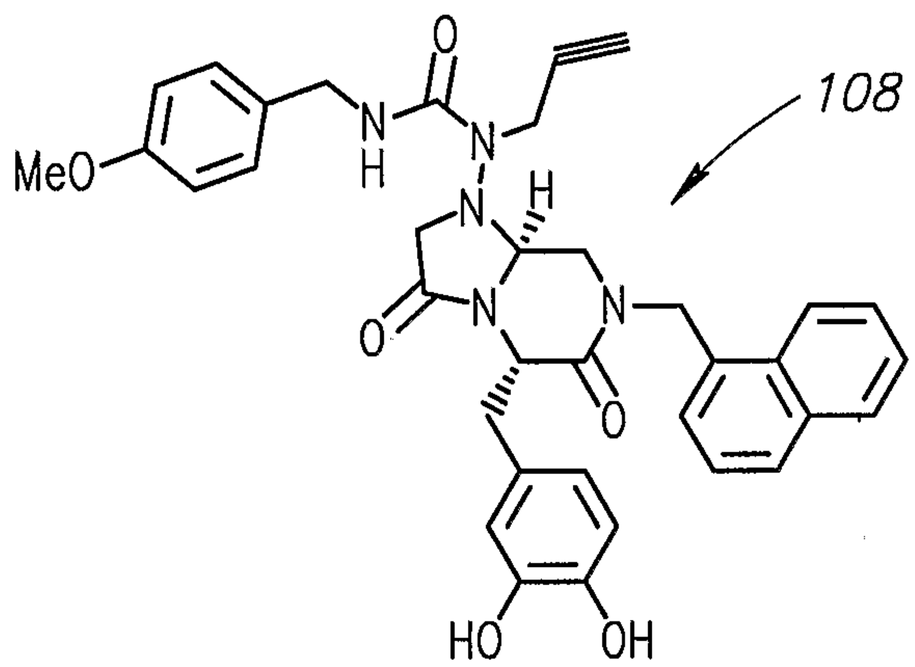

104
Cl
Cl
O
N
H
HO
OH

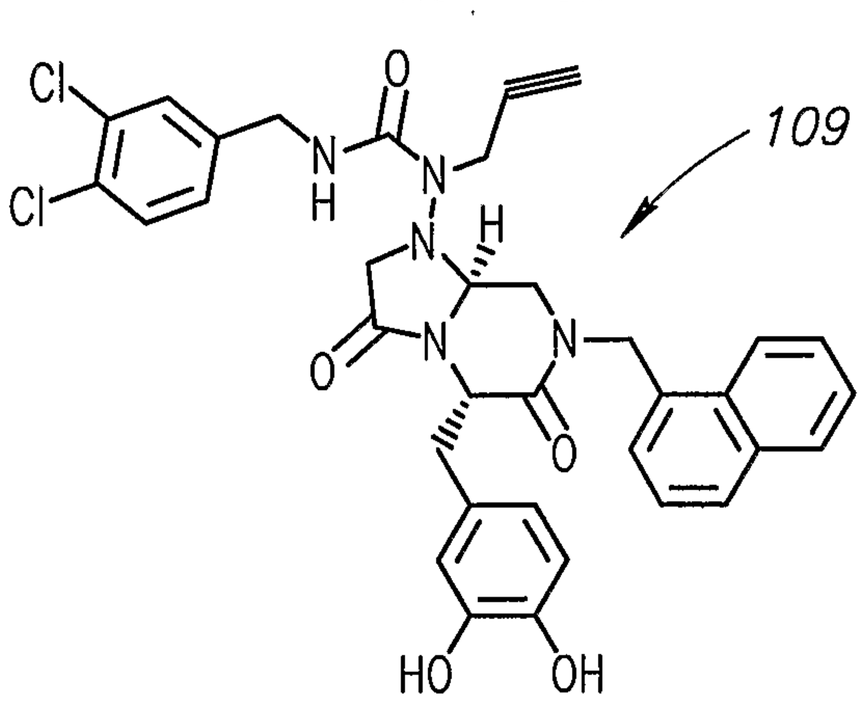
FIG.1M

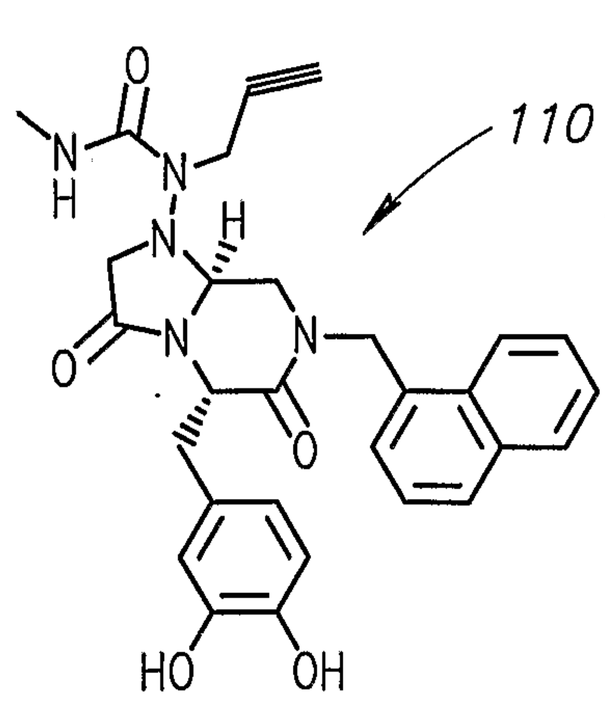


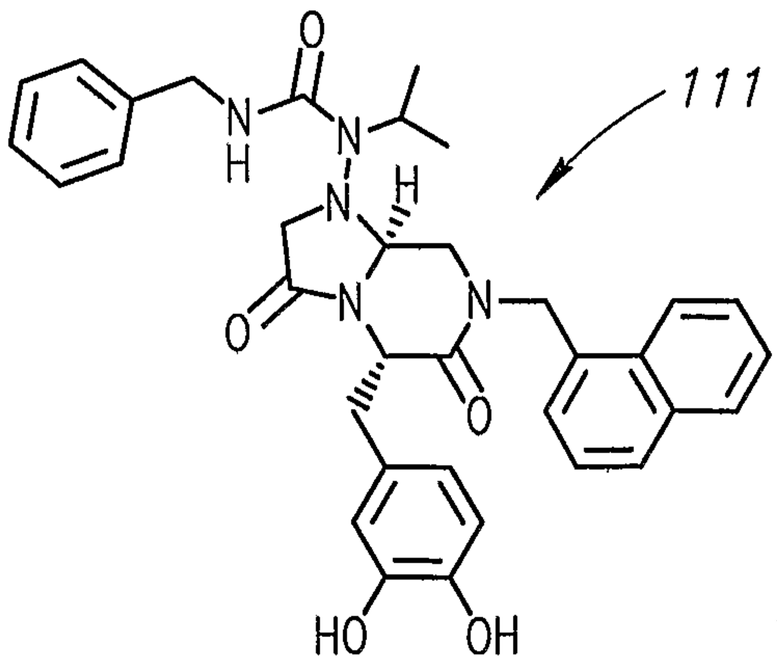












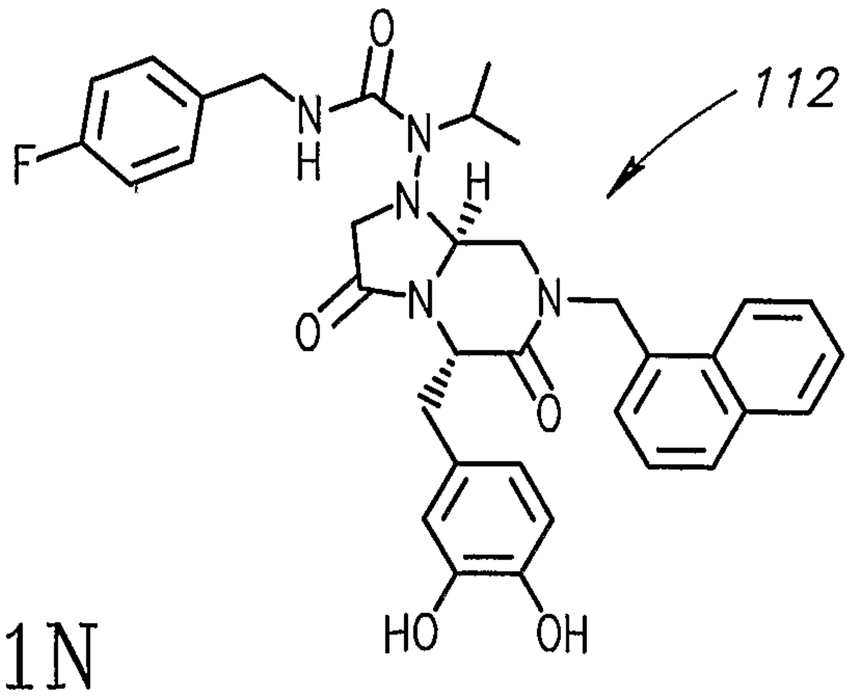
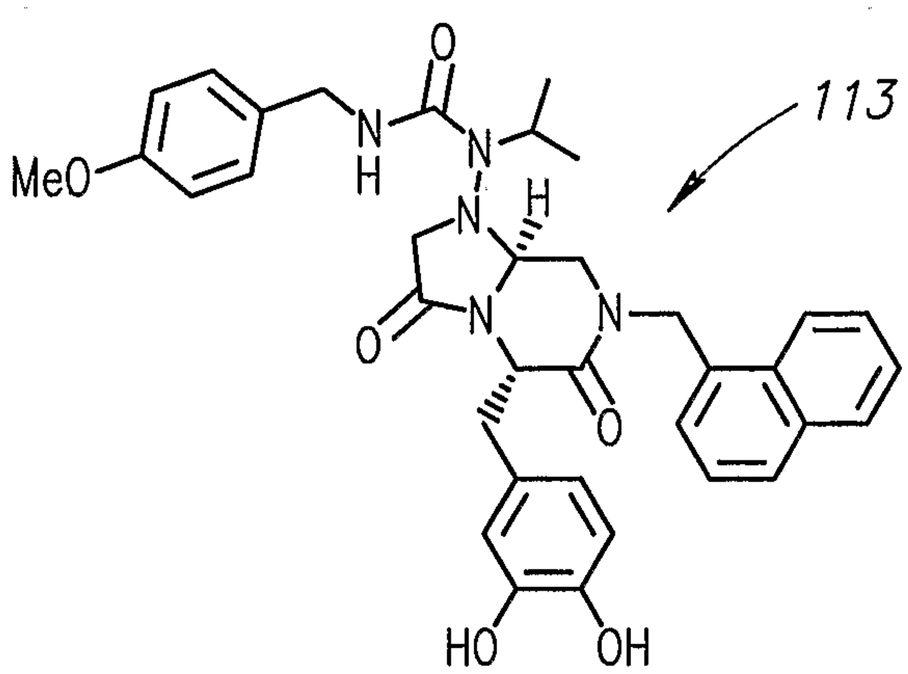
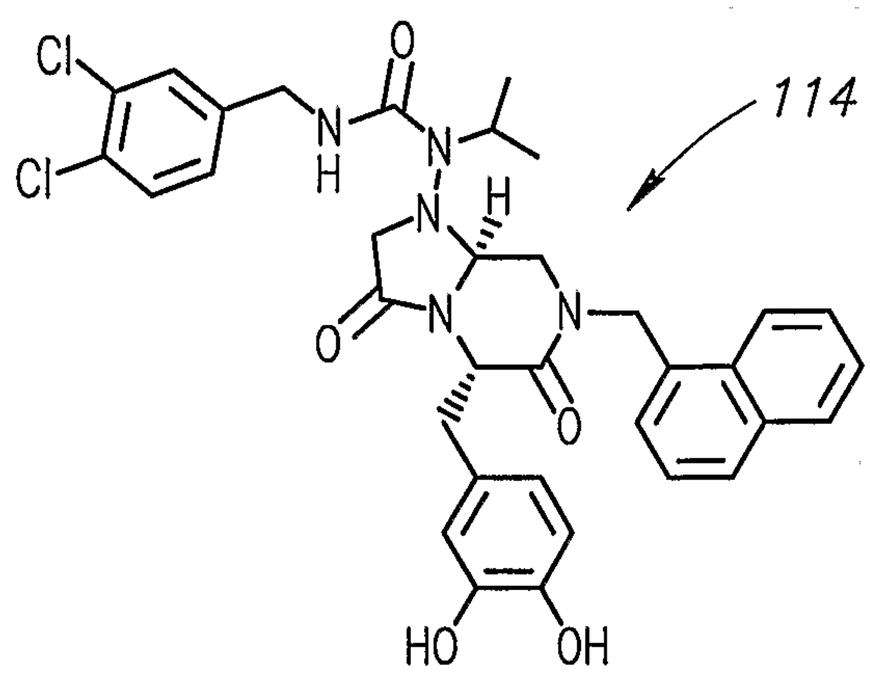
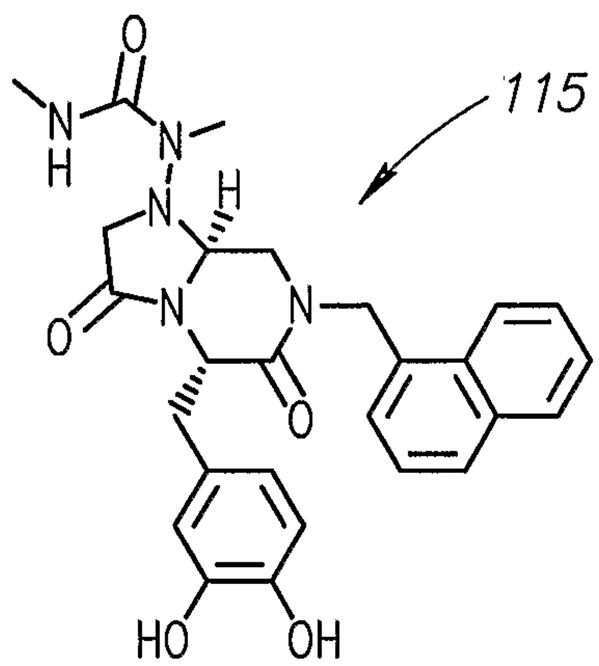
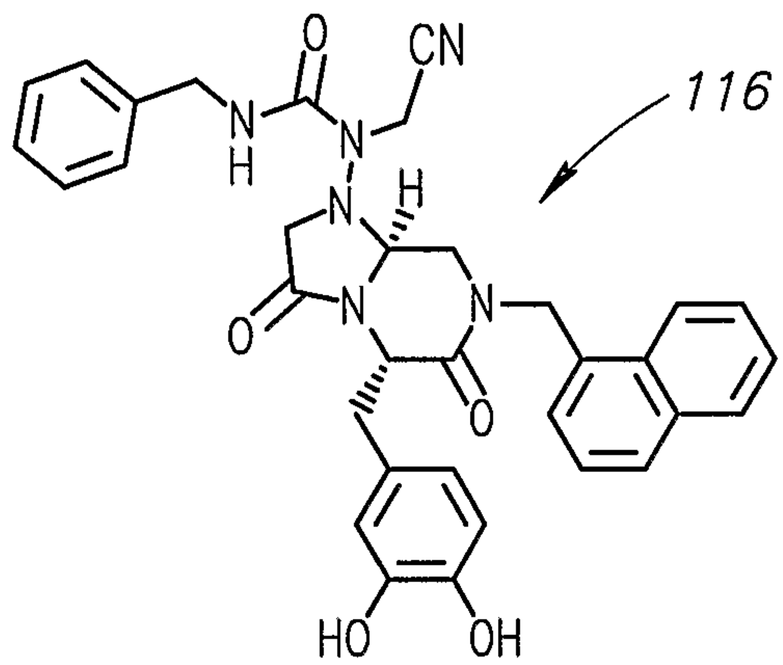


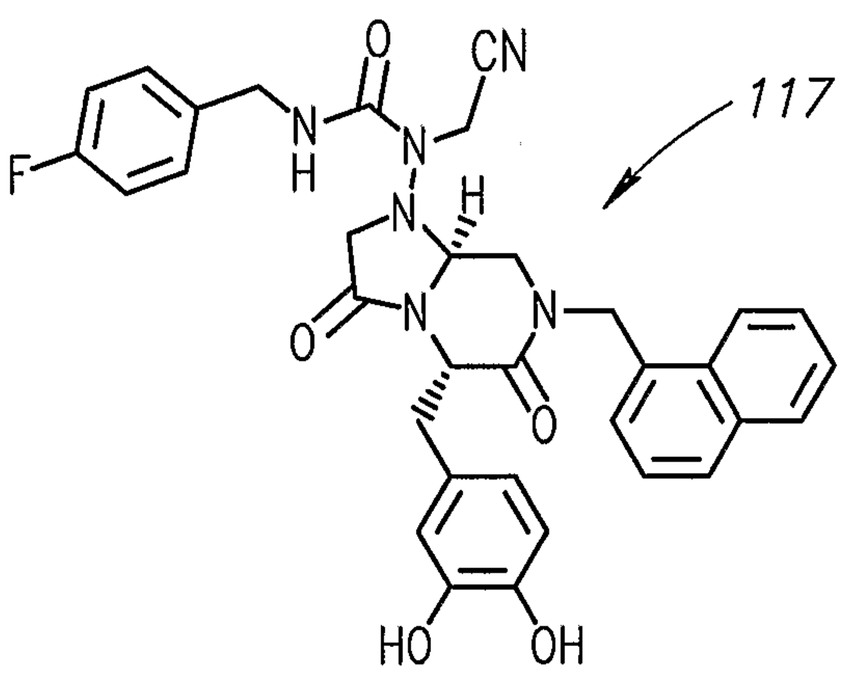
FIG.1N


MeO
O
N
H
N
N
H
O
N
N
O
O
HO
OH
113


Cl
Cl
O
N
H
N
N
H
O
N
N
O
O
HO
OH
114


N
H
O
N
N
H
O
N
N
O
O
HO
OH
115


CN
O
N
H
N
N
H
O
N
N
O
O
HO
OH
116


F
CN
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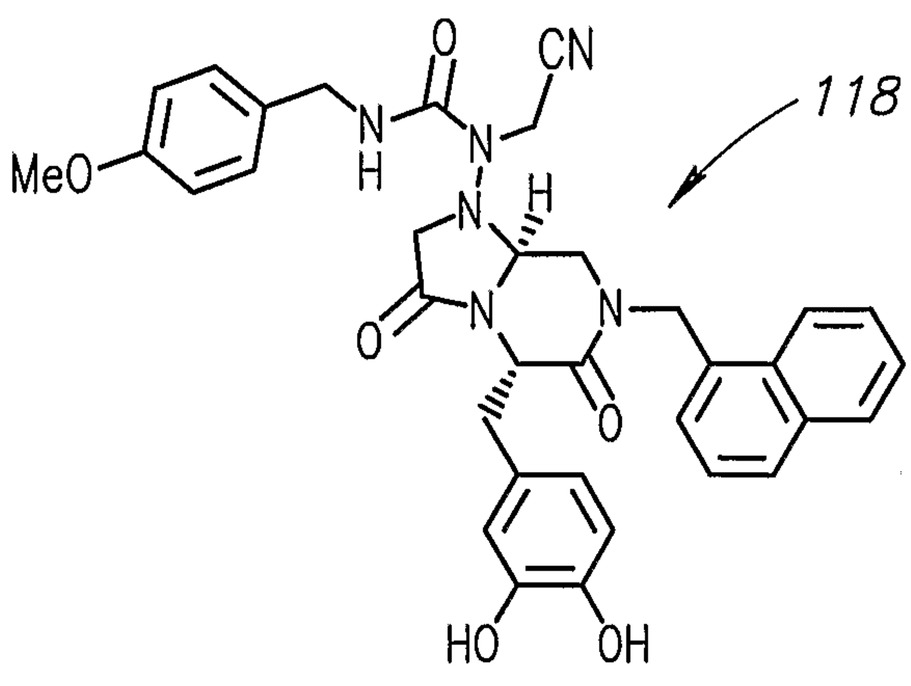
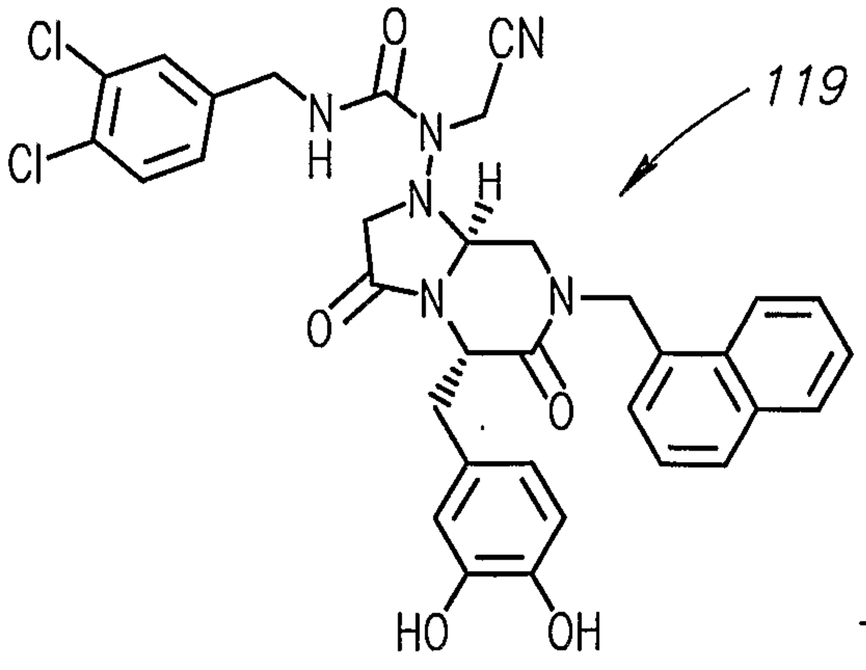
N
H
N
N
H
O
N
N
O
O
HO
OH
117


MeO
CN
O
N
H
N
N
H
O
N
N
O
O
HO
OH
118


Cl
Cl
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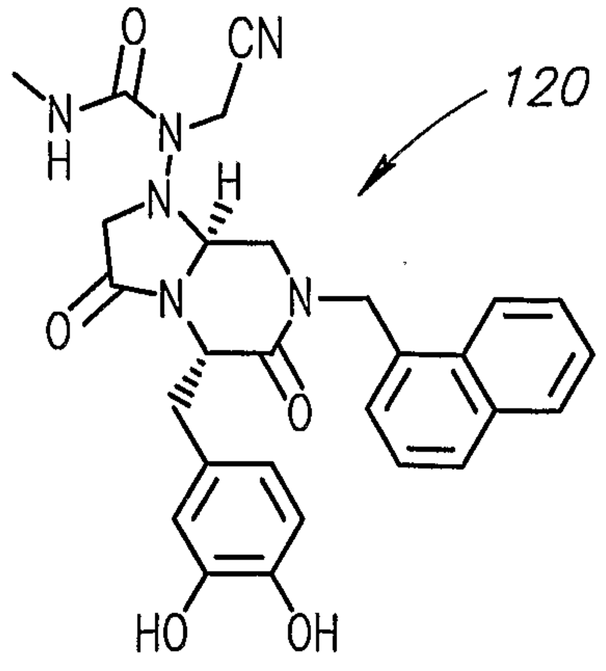
N
H
N
N
H
O
N
N
O
O
HO
OH
119


CN
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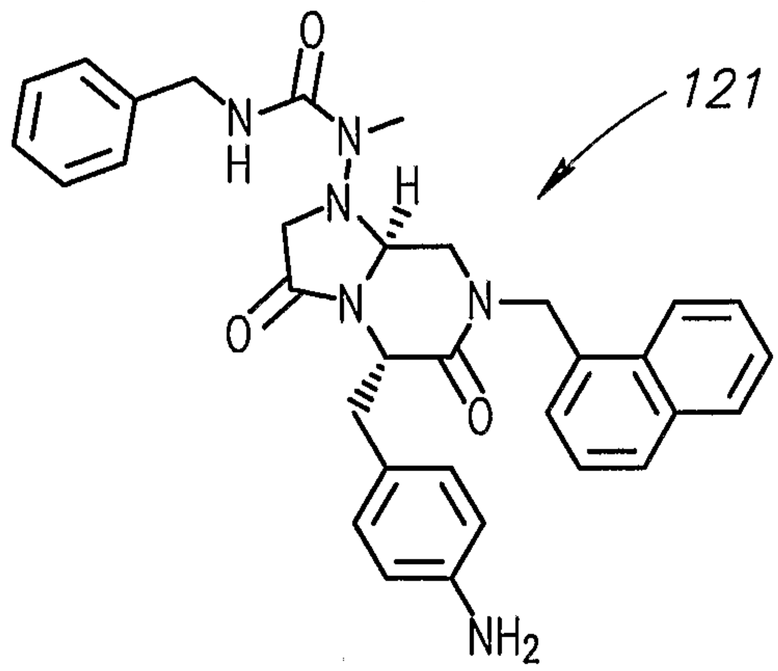
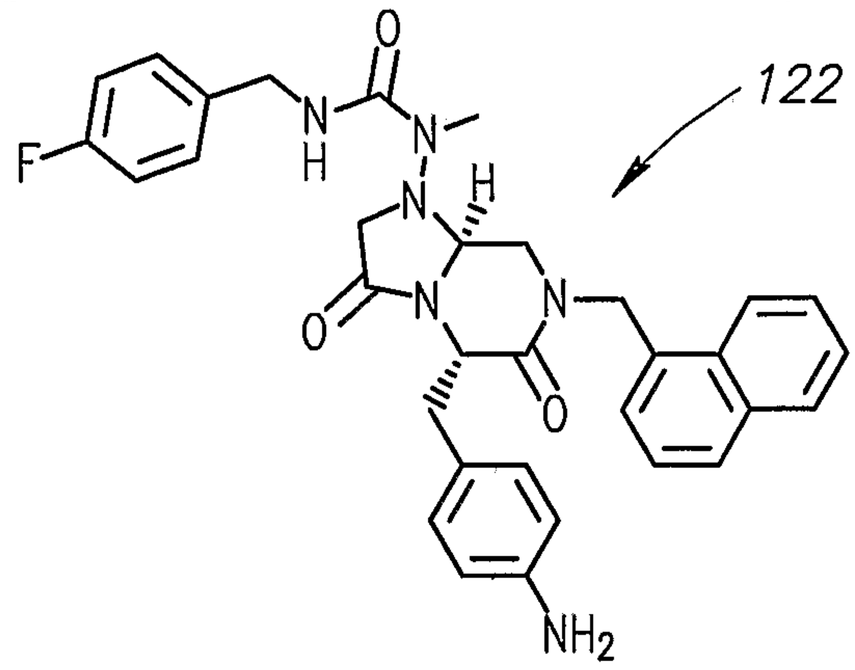
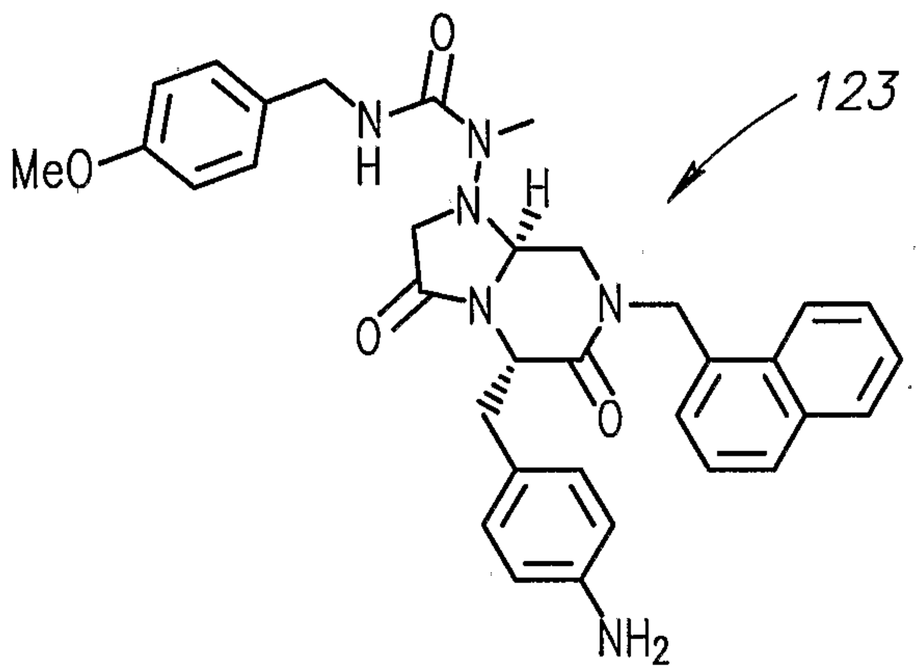
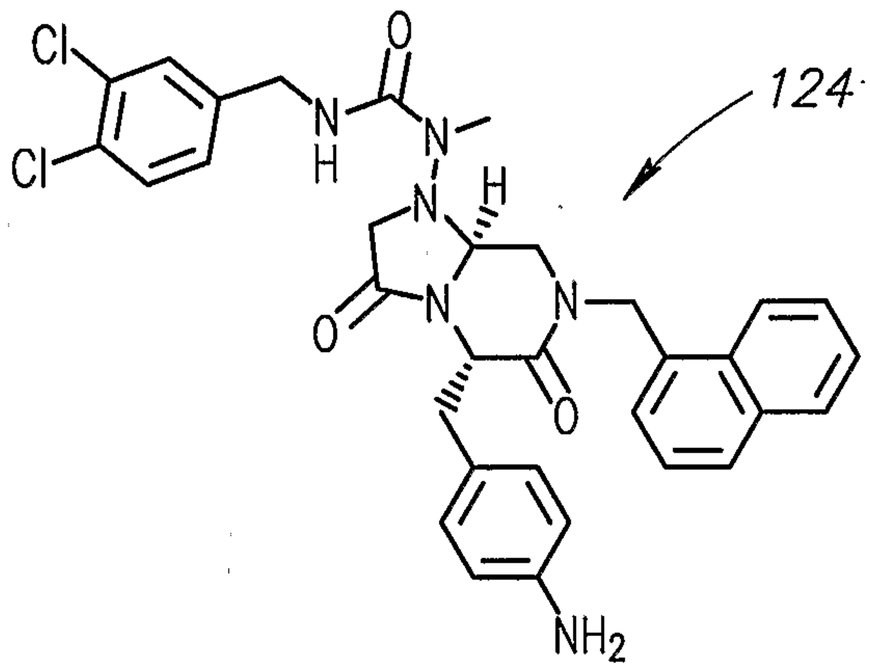
N
H
N
N
H
O
N
N
O
O
HO
OH
120

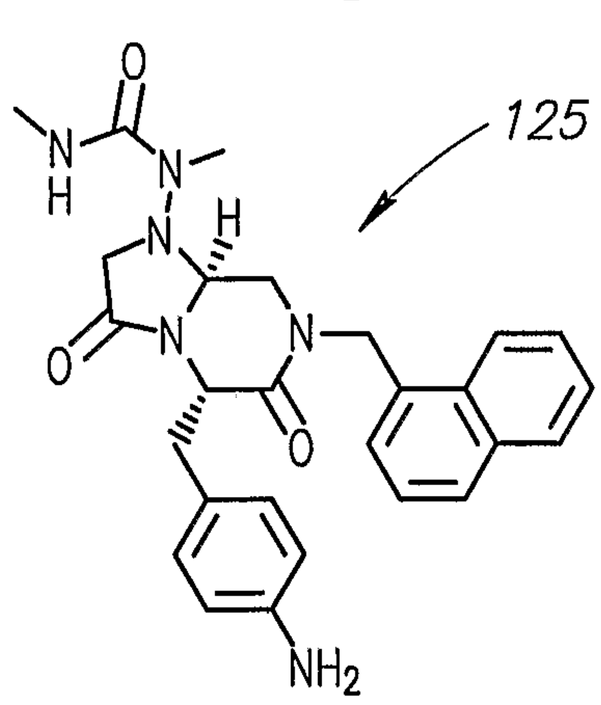
FIG.10











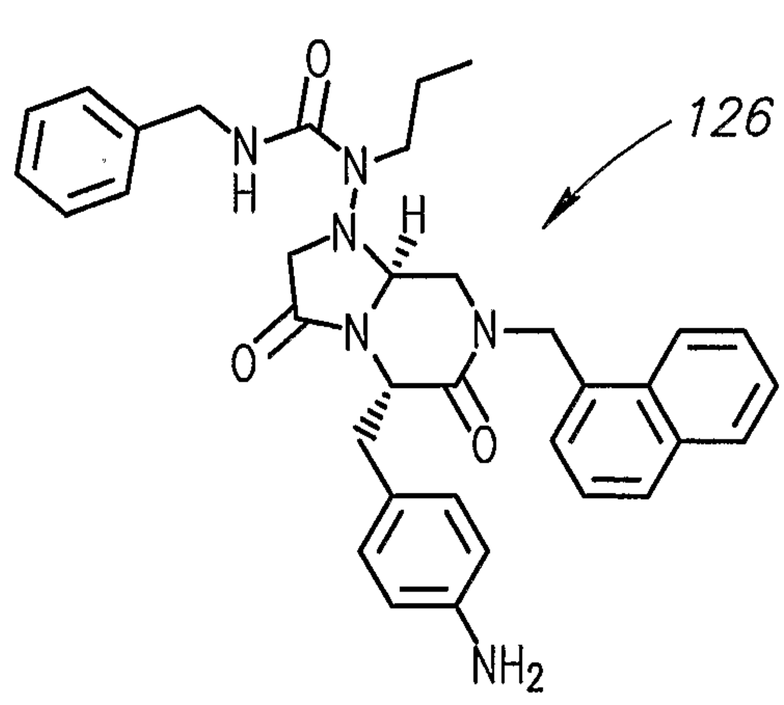
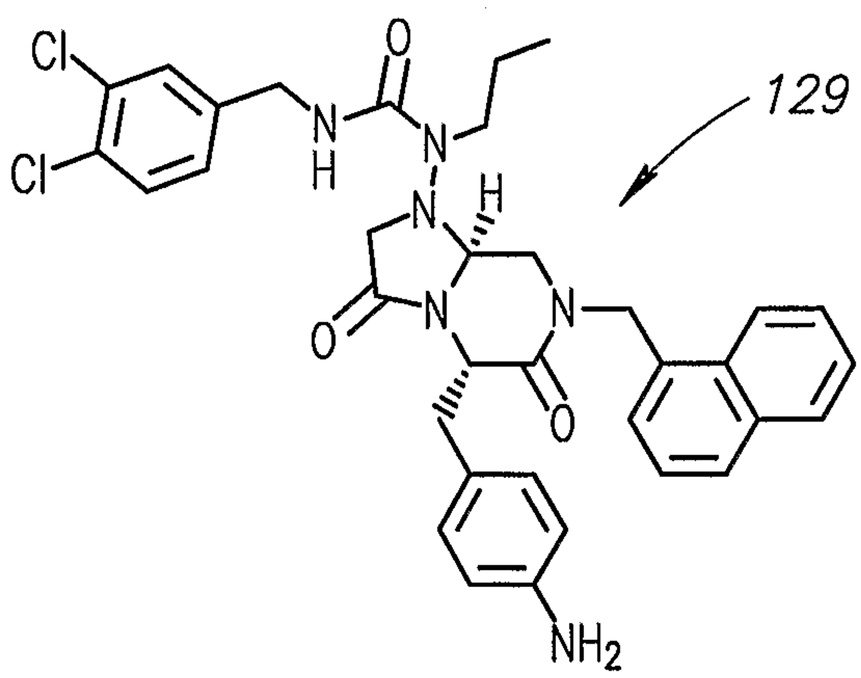
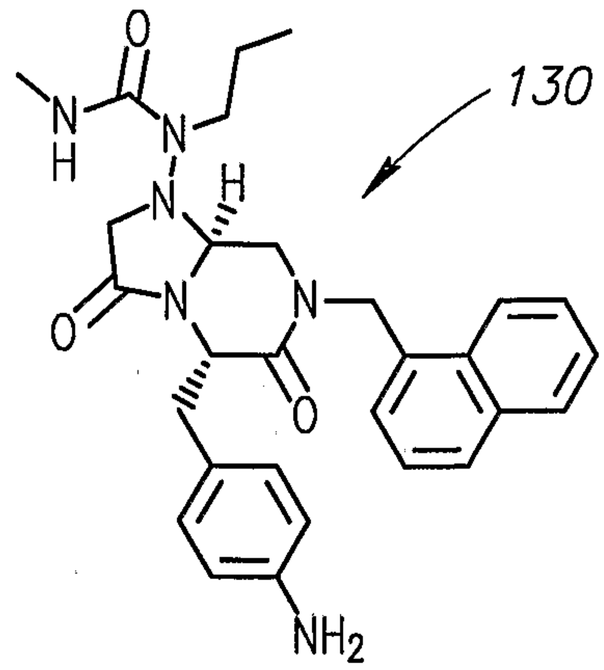


FIG.1P


129
Cl
Cl
O
N
H
N
N
H
O
N
N
O
NH2


130
O
N
H
N
N
H
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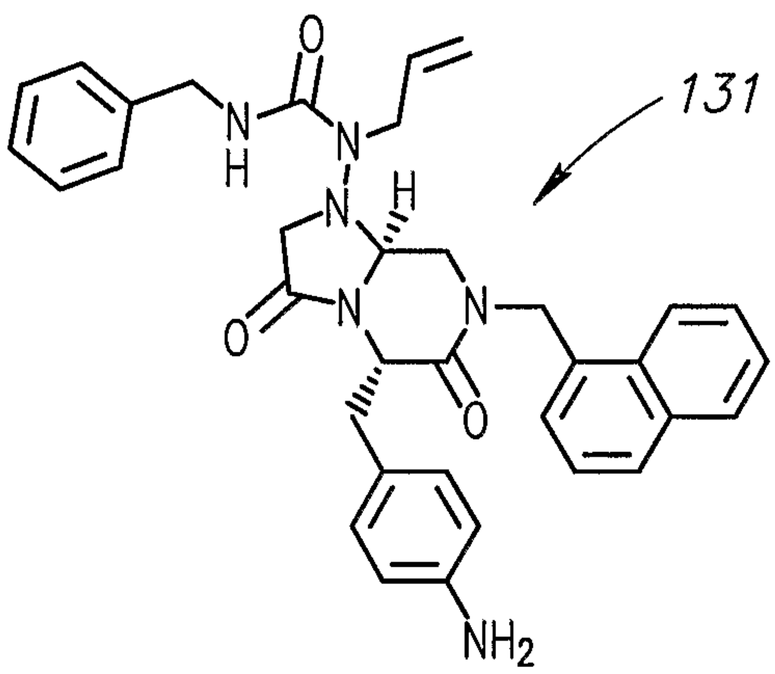
N
N
O
NH2


131
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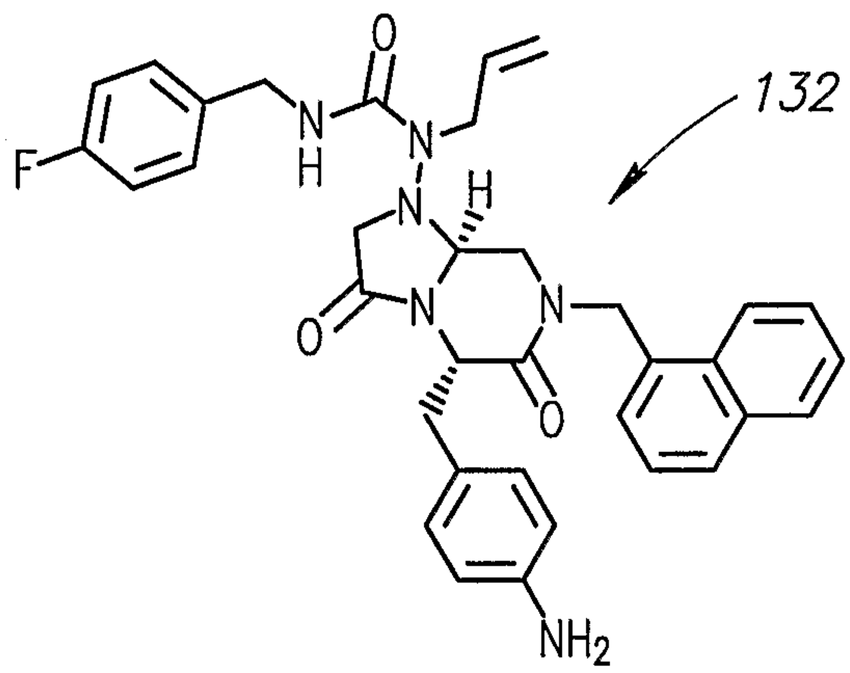
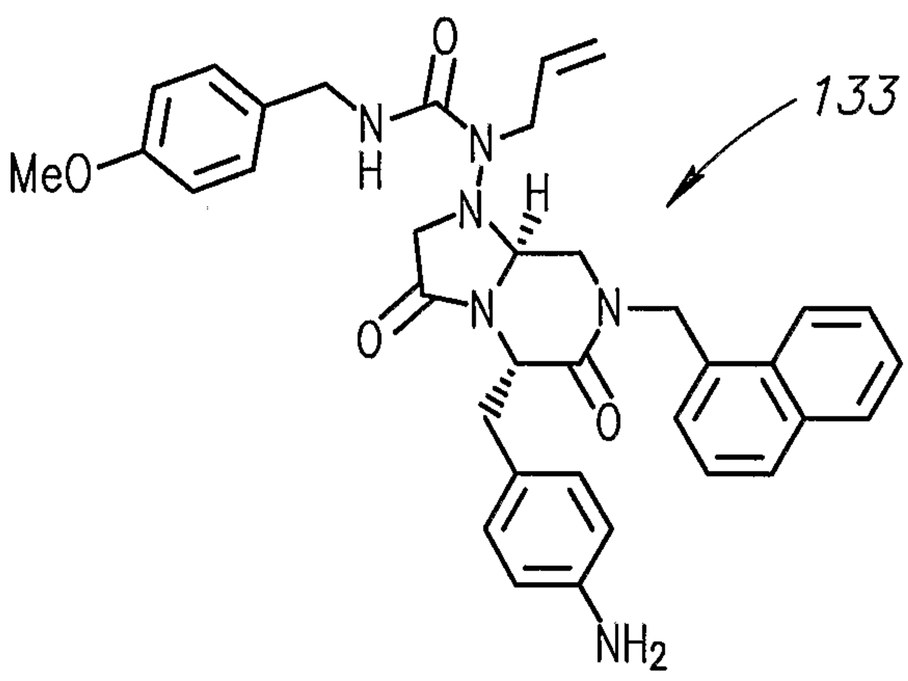
N
N
H
O
N
N
O
NH2


132
F
O
N
H
N
N
H
O
N
N
O
NH2


133
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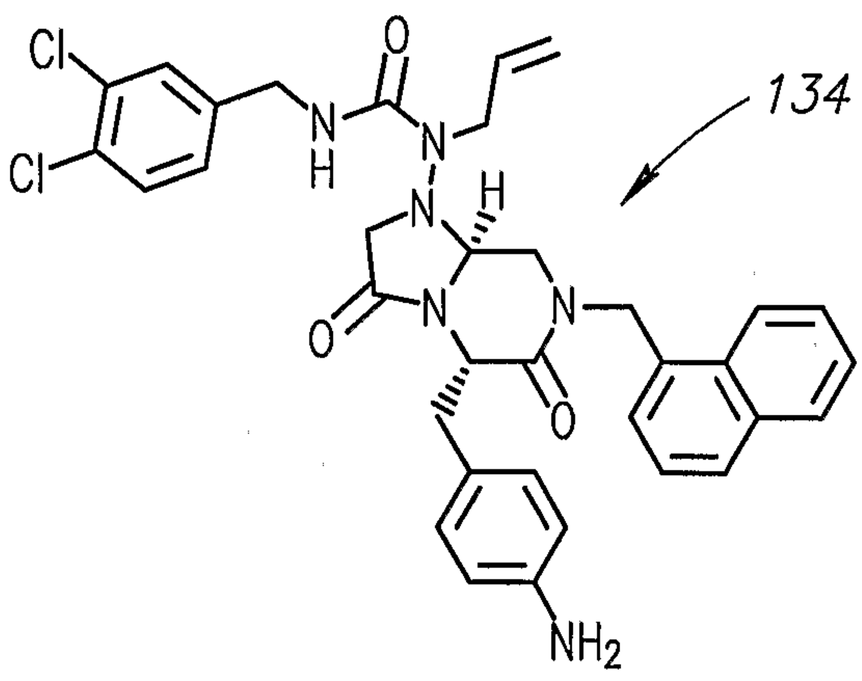
N
N
H
O
N
N
O
NH2


134
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Cl
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N
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N
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H
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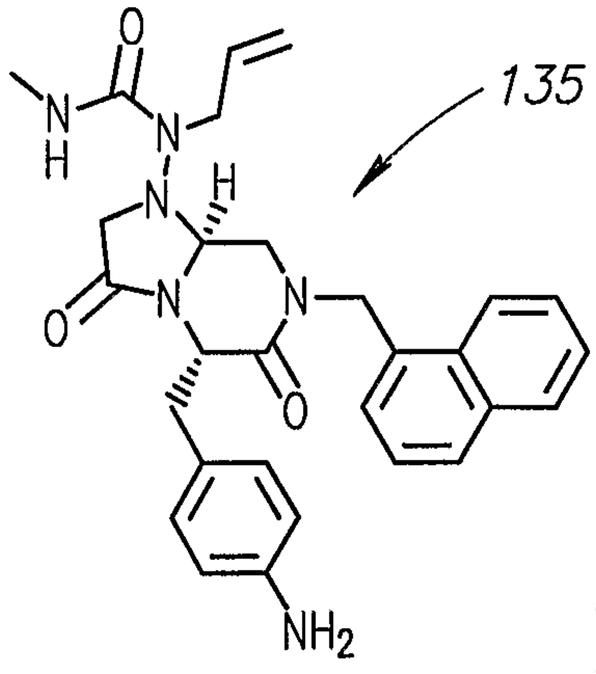
N
N
O
NH2


135
O
N
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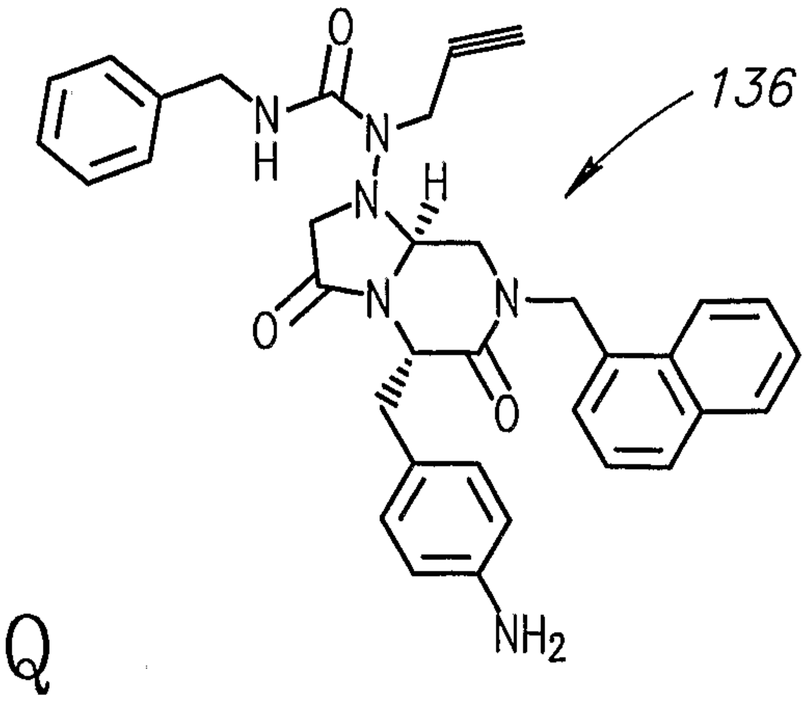
N
H
O
N
N
O
NH2


136
O
N
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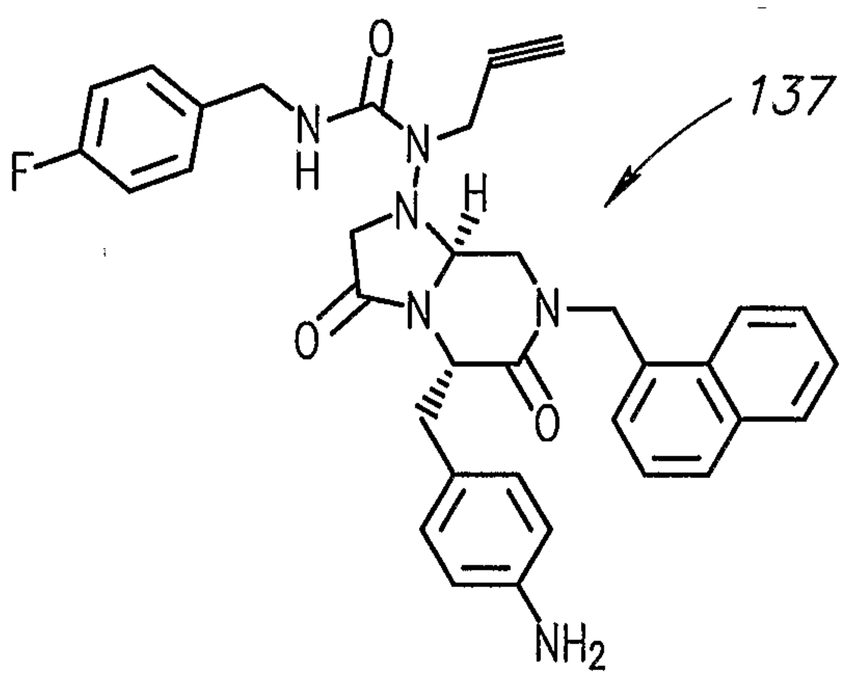
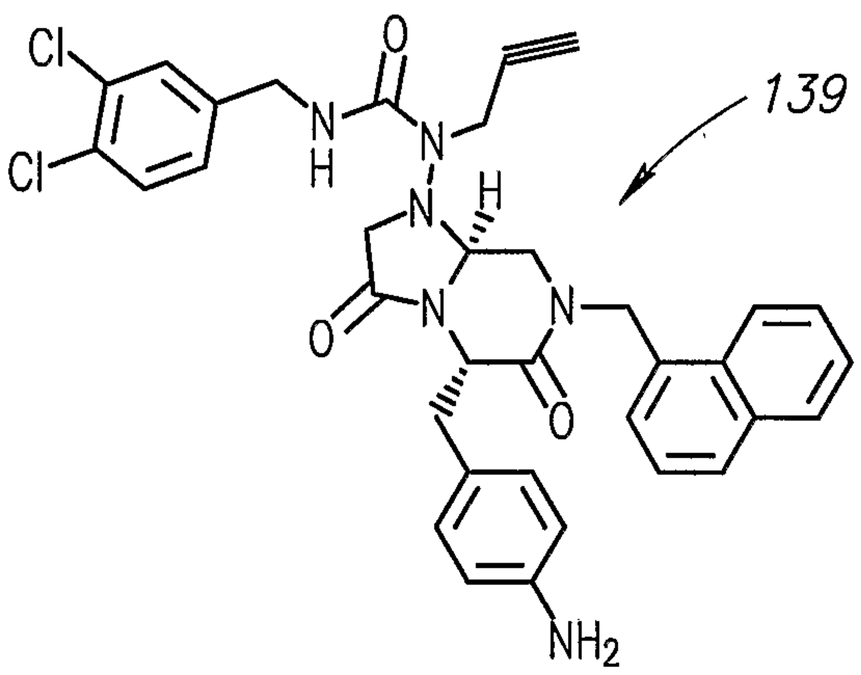
N
N
H
O
N
N
O
NH2

FIG.1Q





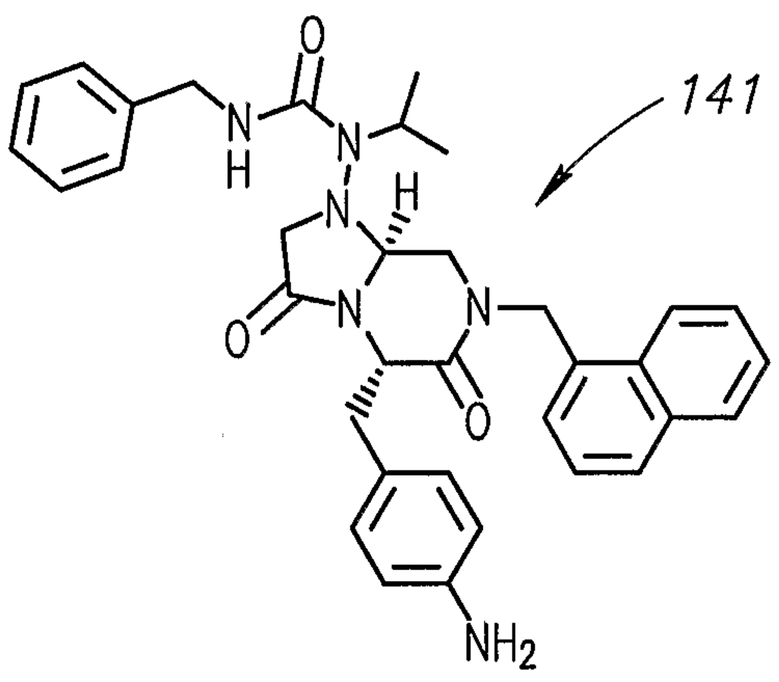


FIG.1R

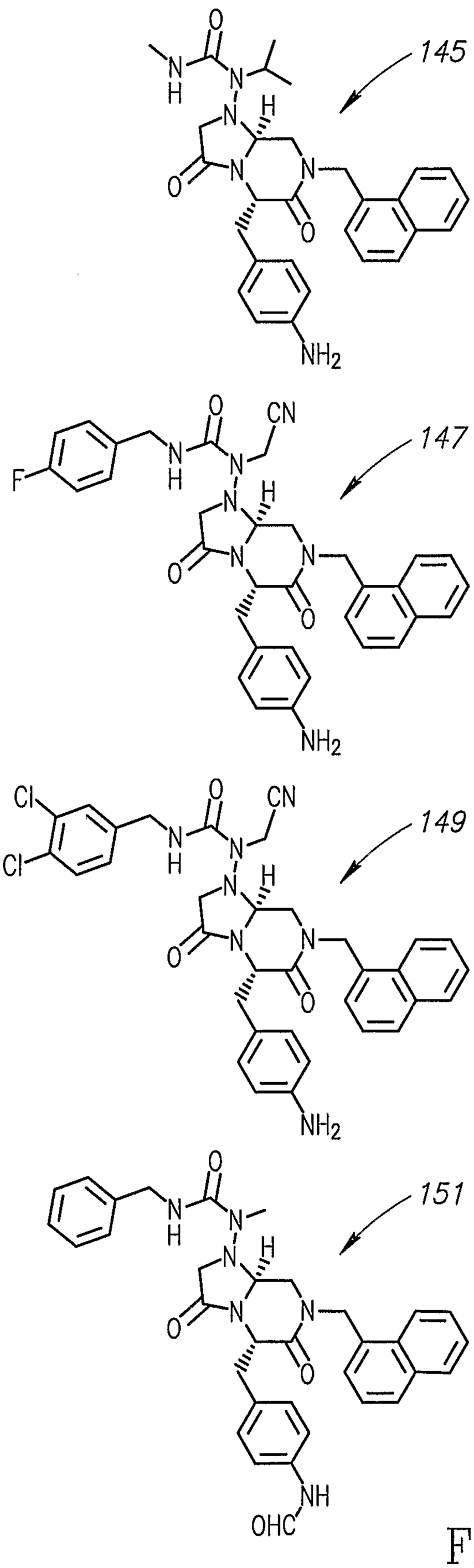


FIG.1S

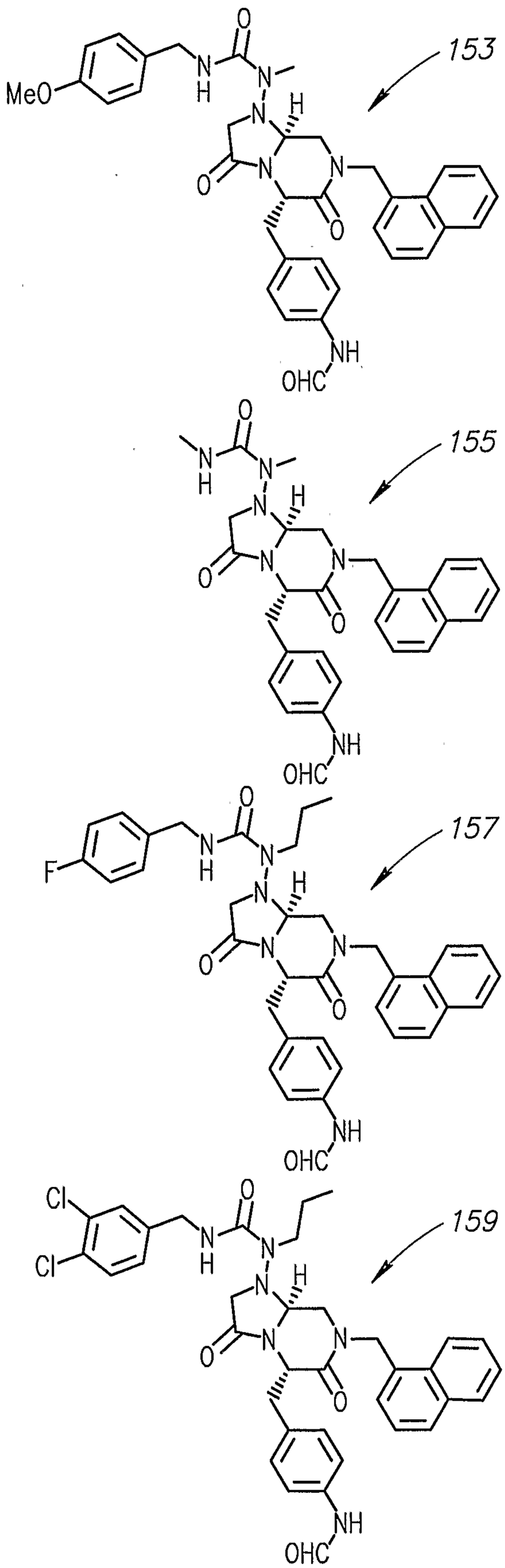


FIG.1T

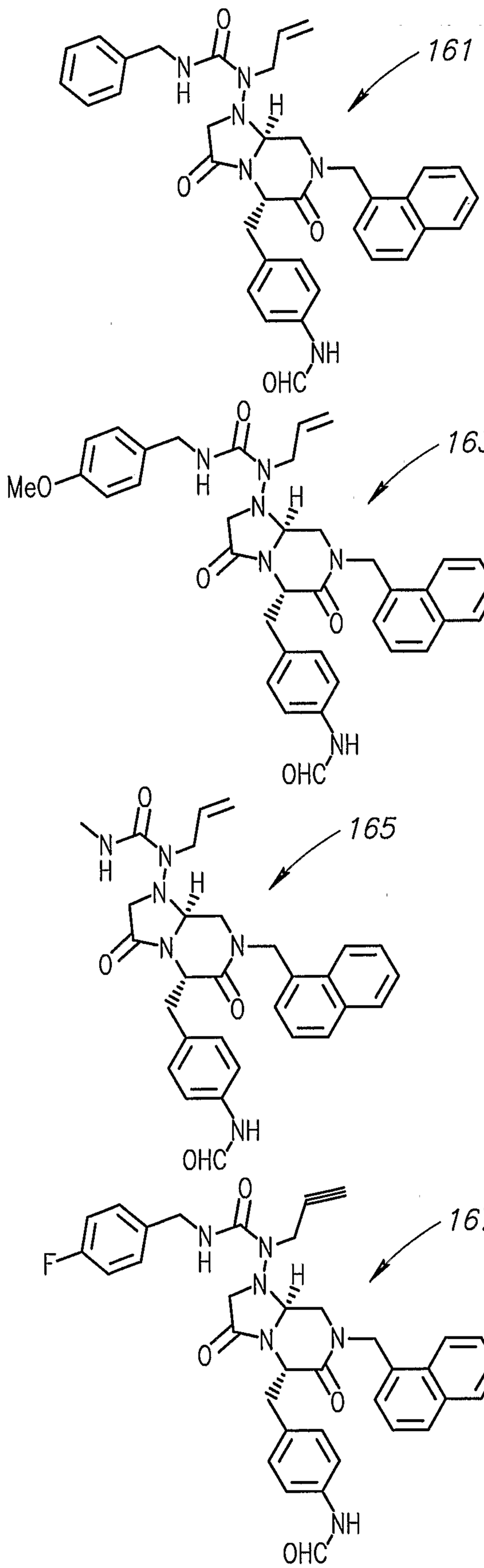


FIG.1U

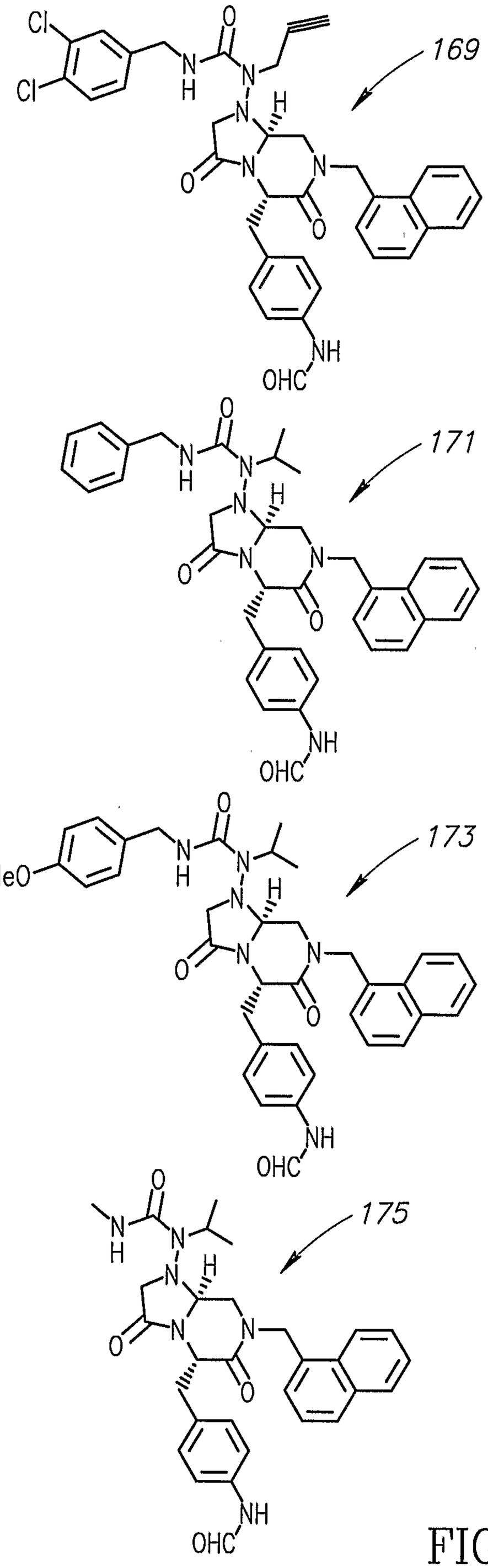
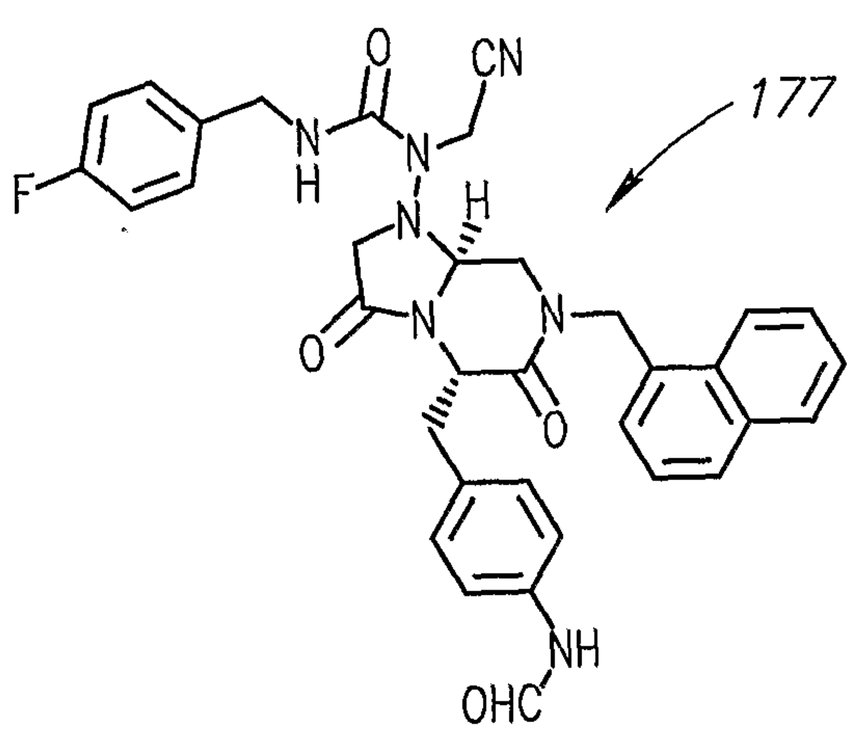


FIG.1V


177
F
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CN
N
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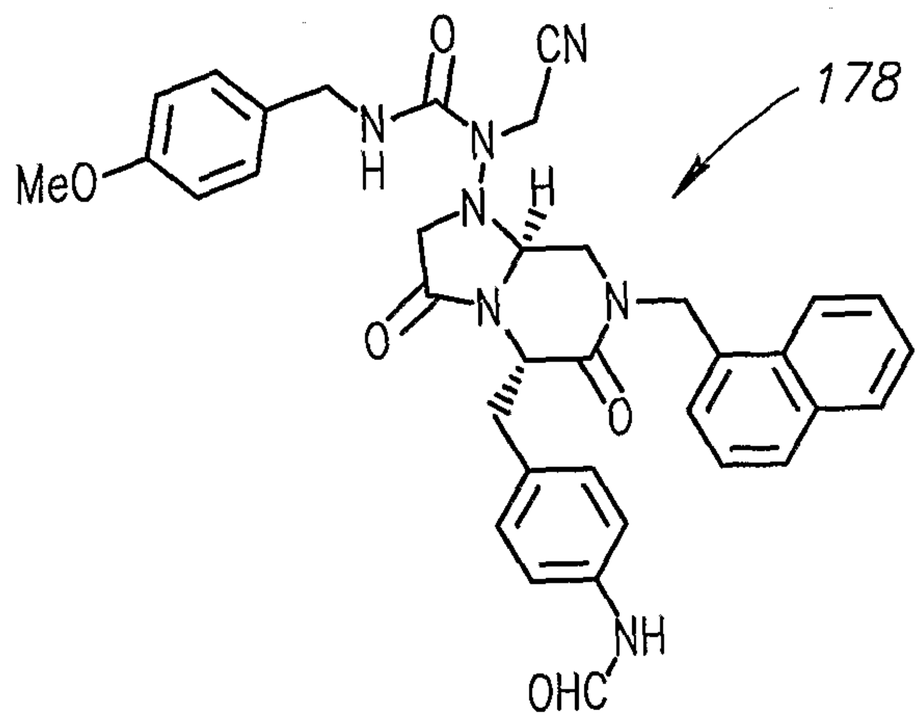
N
O
N
N
O
O
NH
OHC


178
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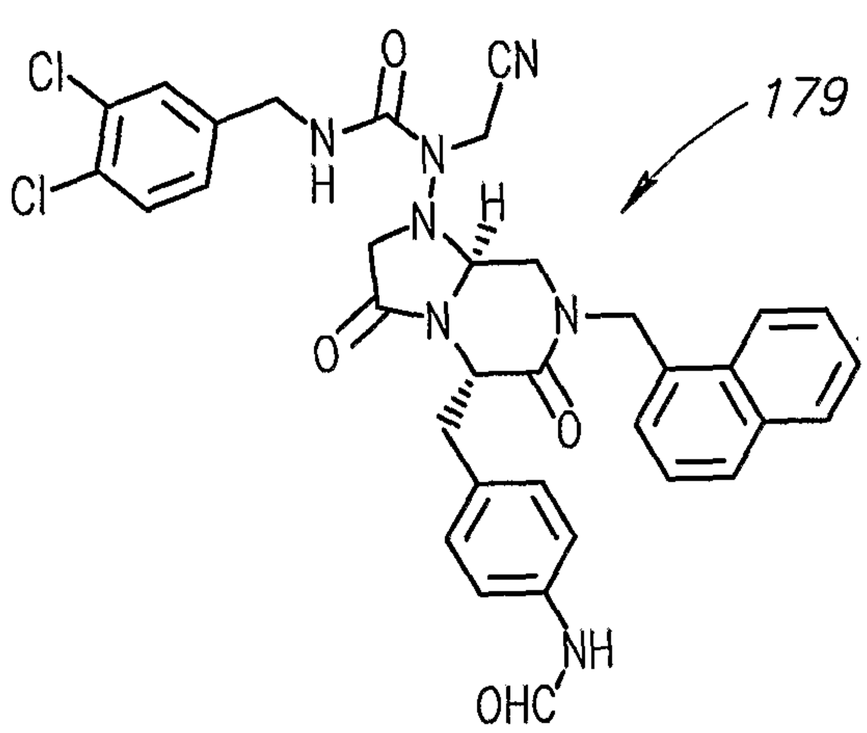
O
O
NH
OHC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Cl
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CN
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O
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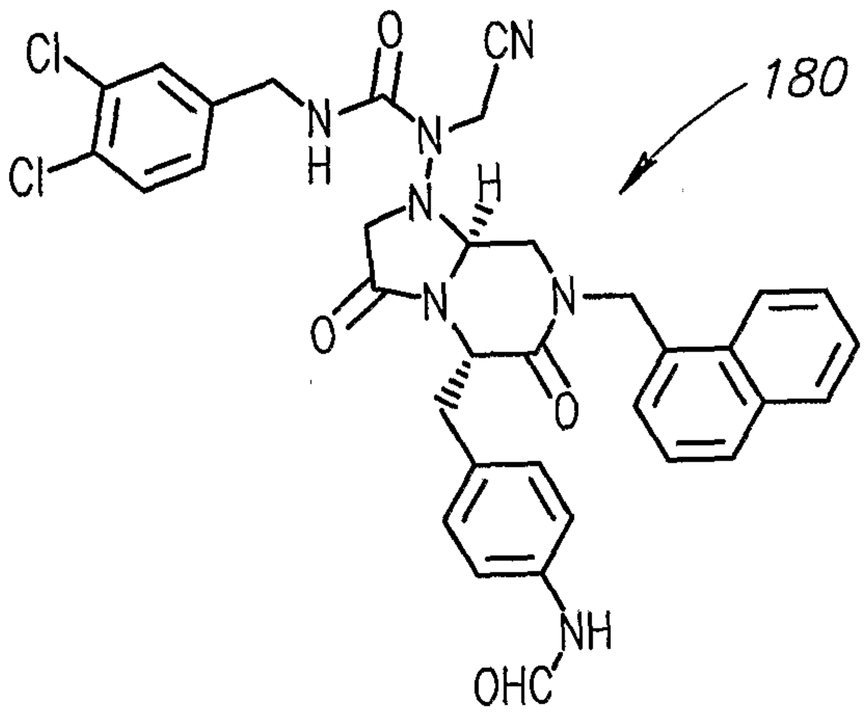
NH
OHC


180
Cl
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N
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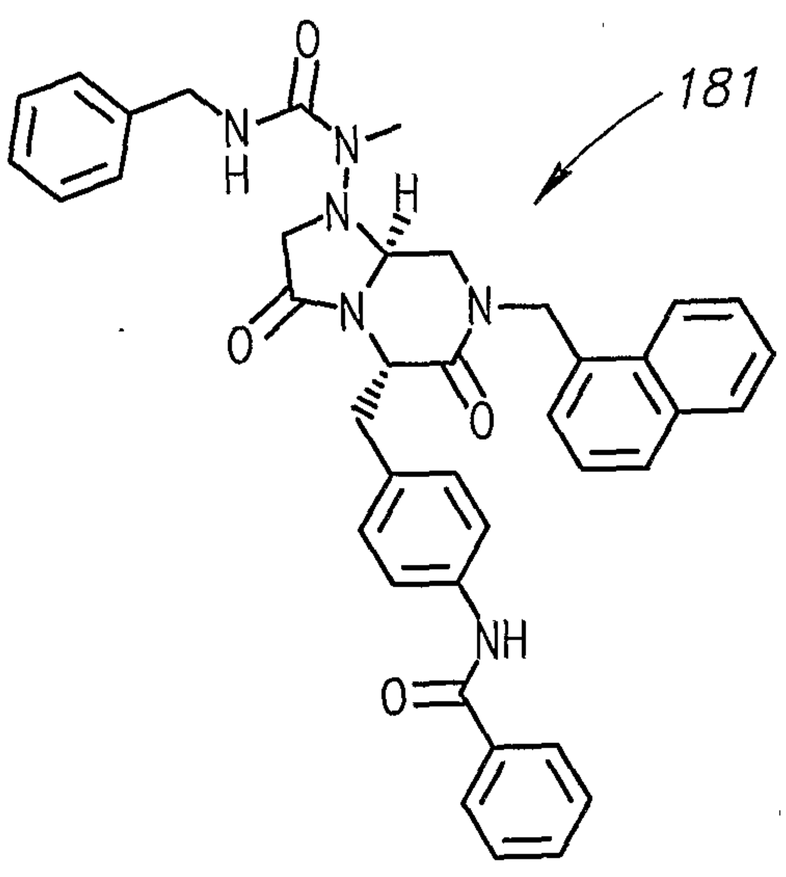
O
O
NH
OHC


181
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N
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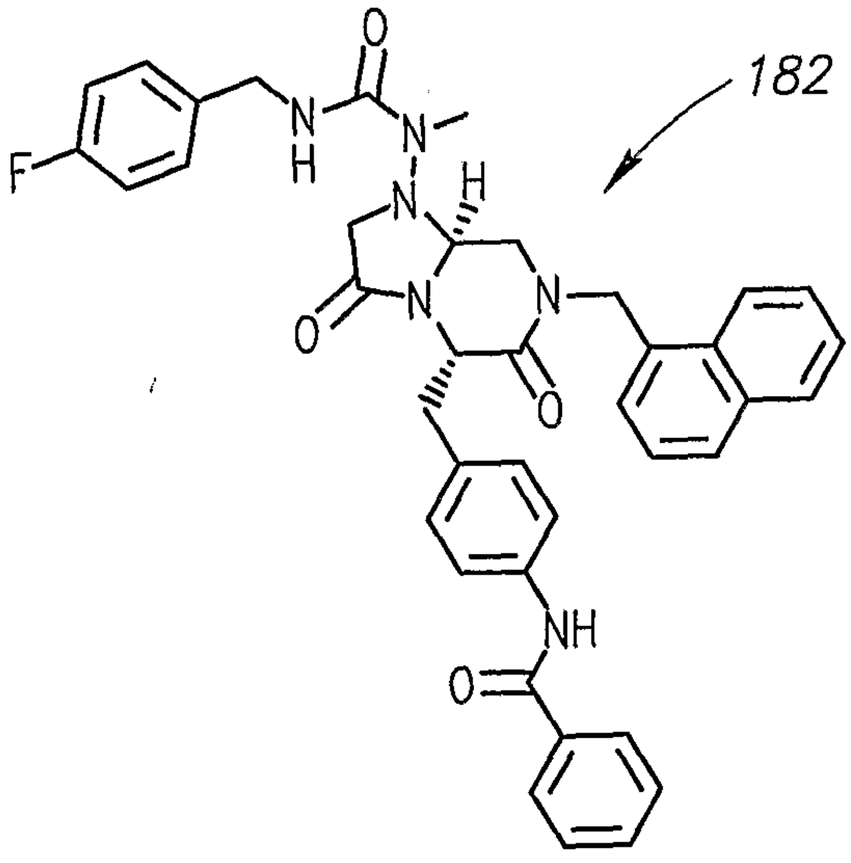
O
O
NH
O


182
F
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H
N
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N
O
N
N
O
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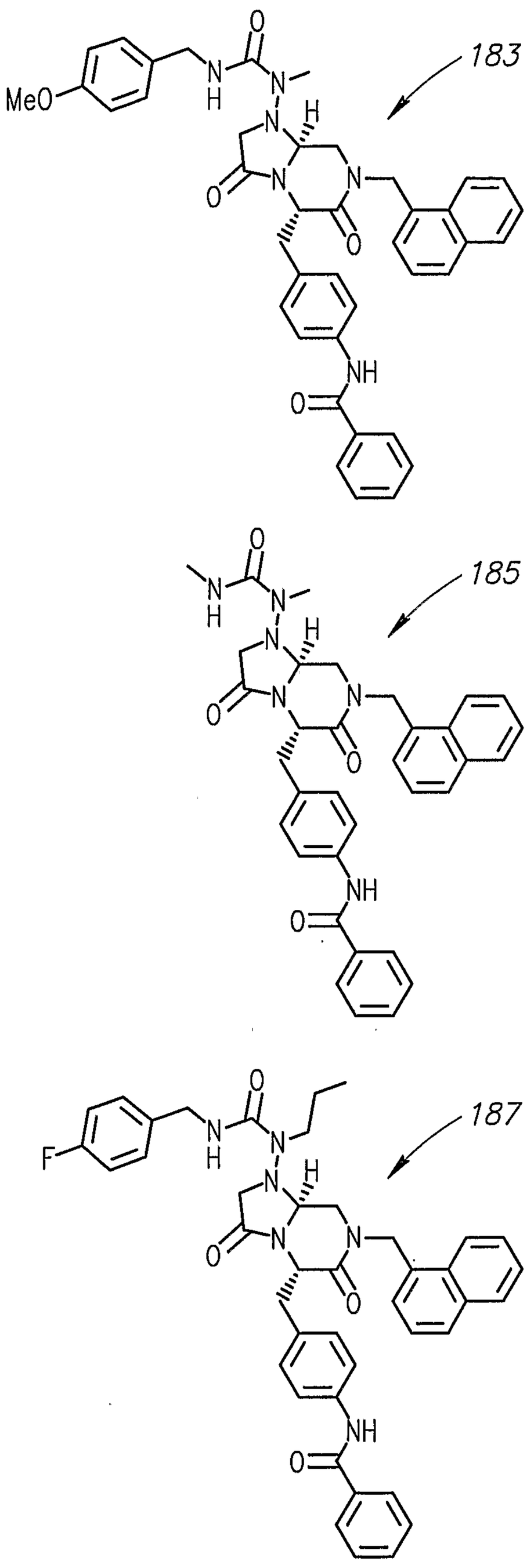
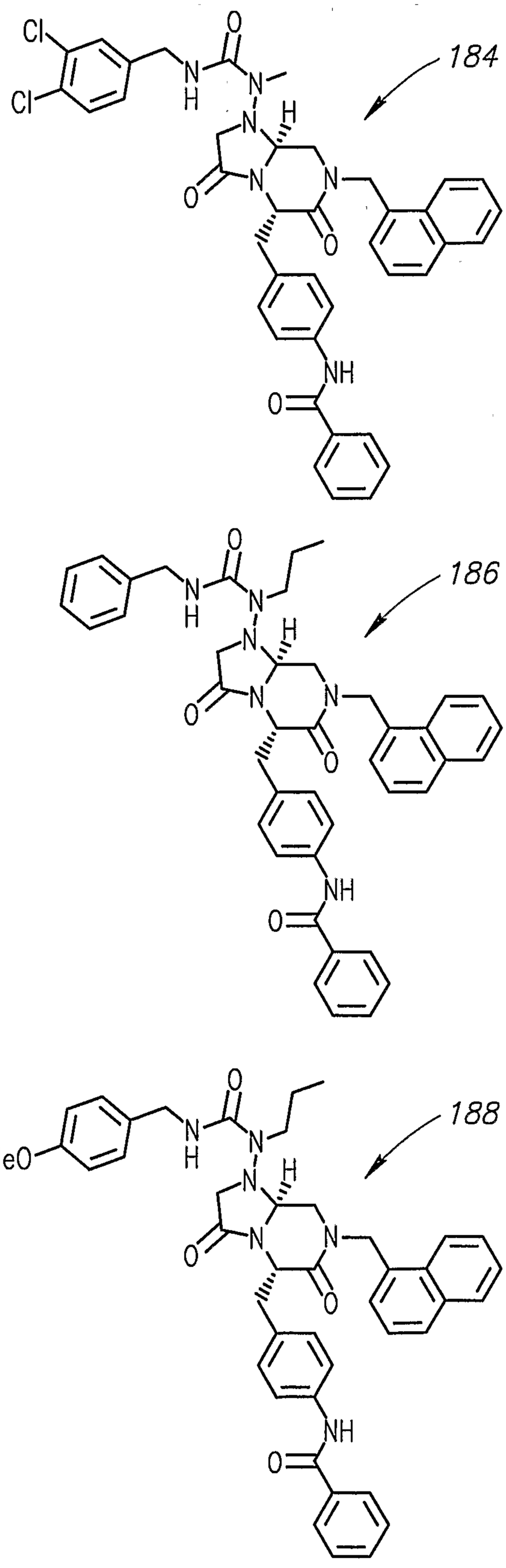
NH
O

FIG.1W


183
MeO
N
H
O
N
H
N
N
O
O
NH
O


184
Cl
Cl
N
H
O
N
H
N
N
O
O
NH
O

185
N
H
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N
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N
N
O
O
NH
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186
N
H
O
N
H
N
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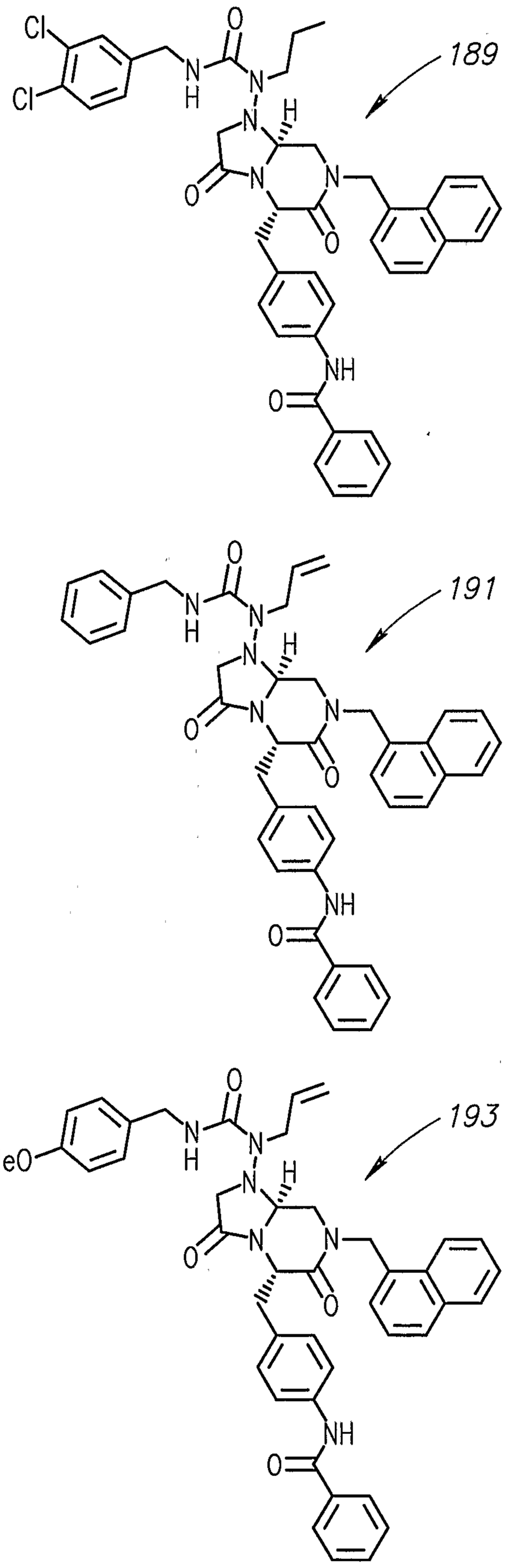
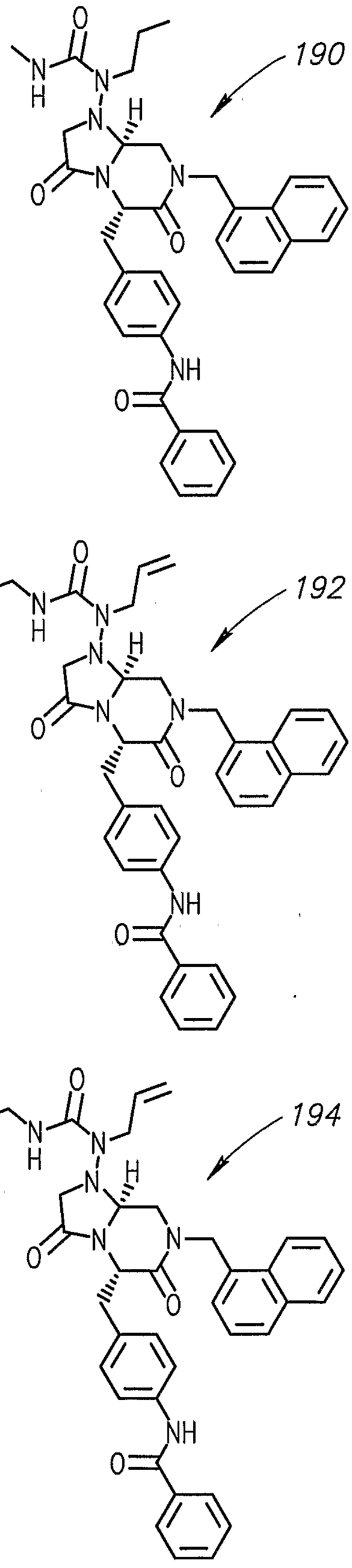
NH
O

187
F
N
H
O
N
H
N
N
O
O
NH
O

188
MeO
N
H
O
N
H
N
N
O
O
NH
O

FIG.1X





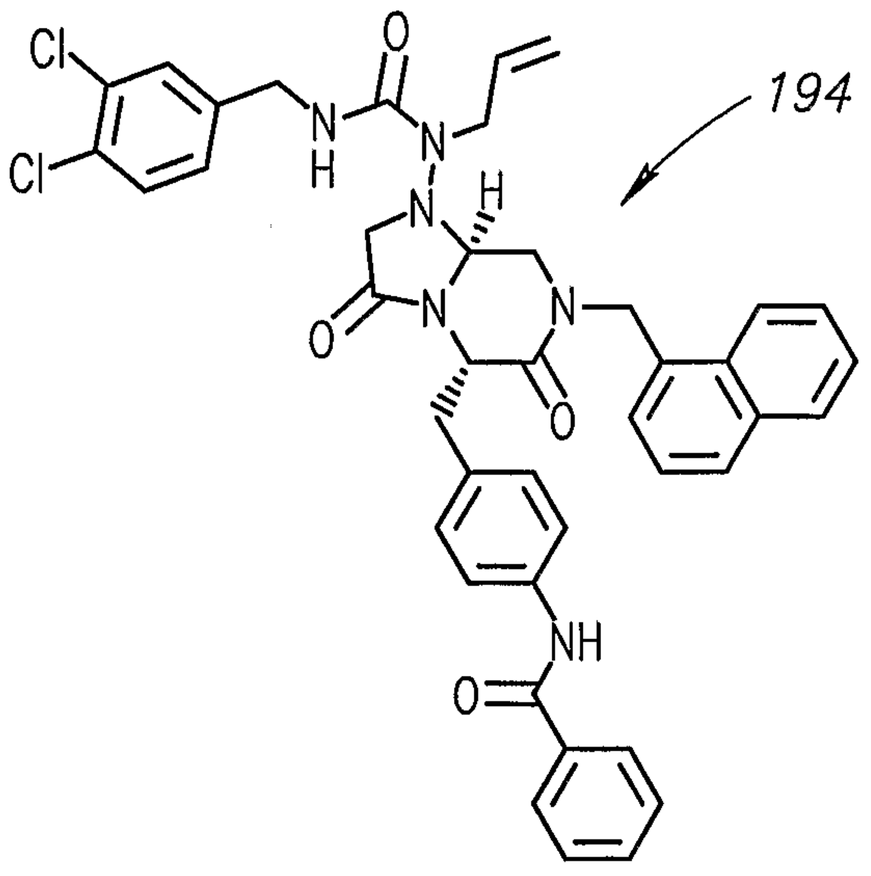
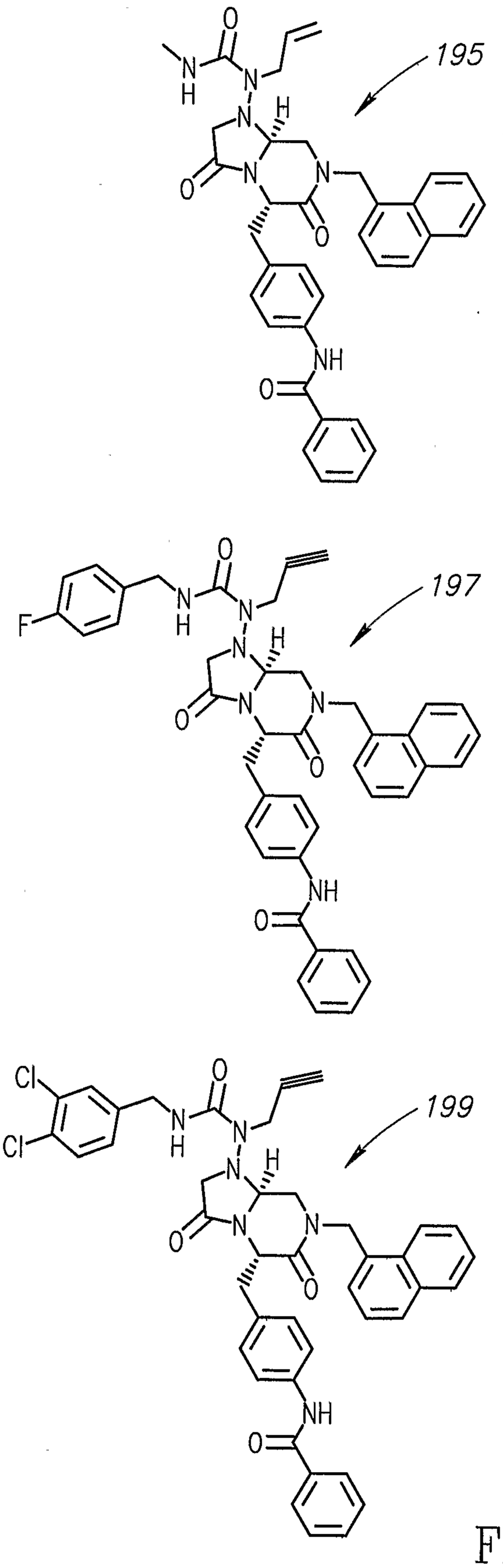


FIG.1Y



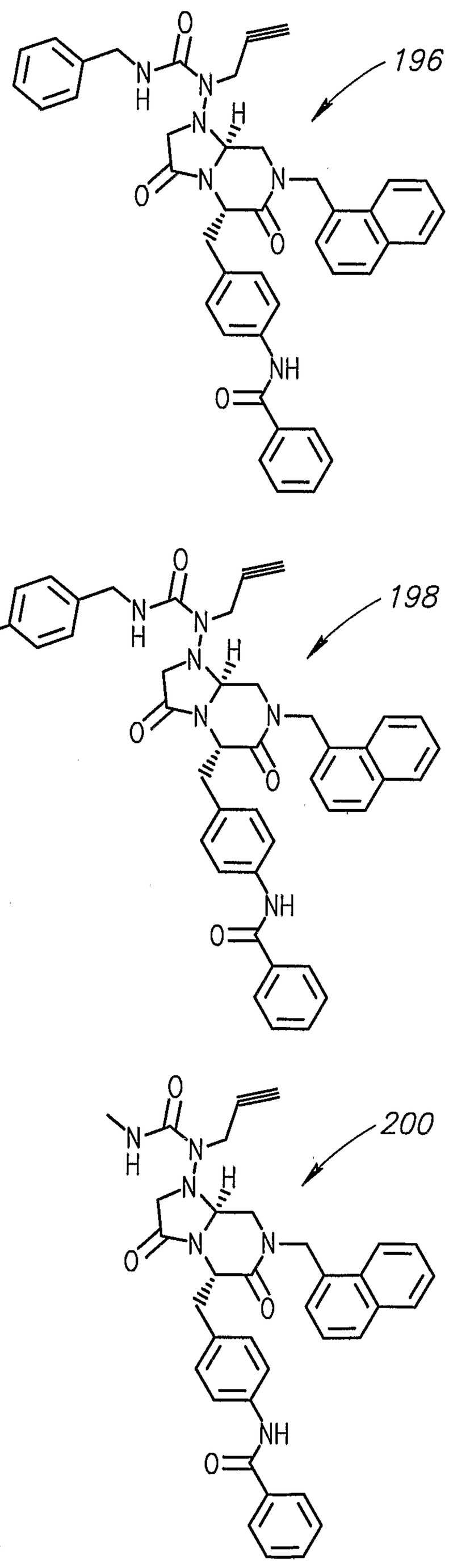
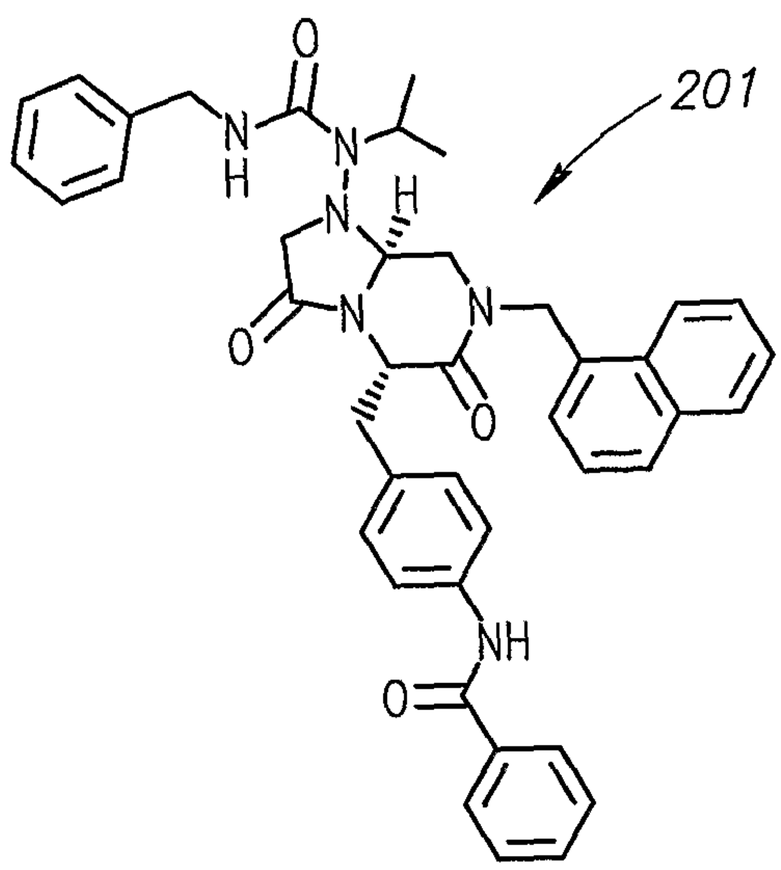
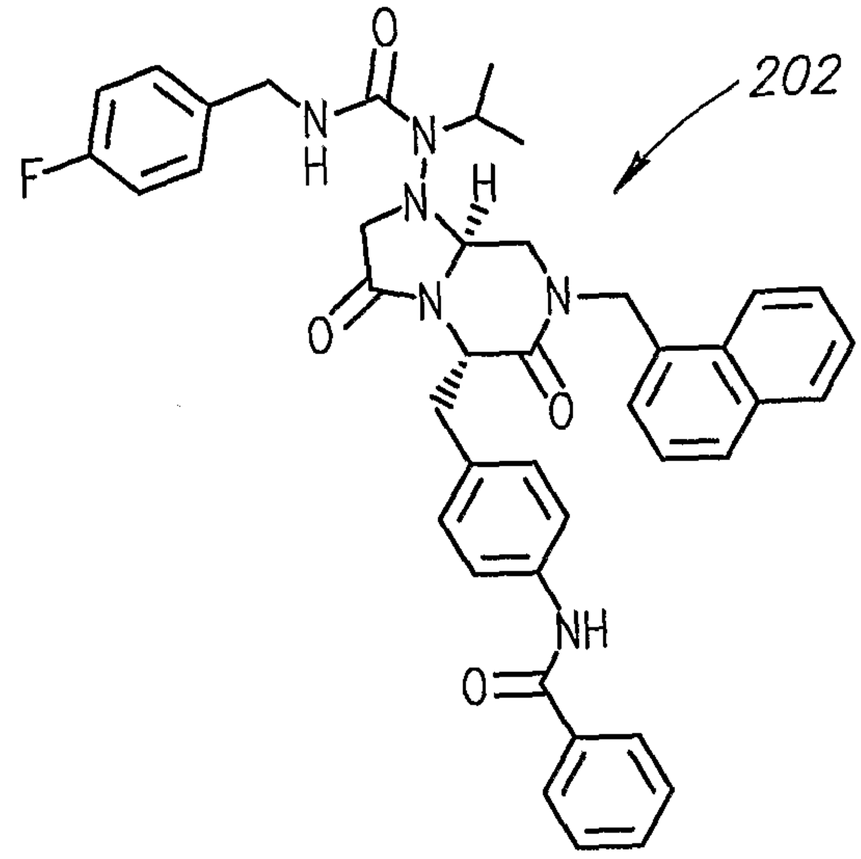
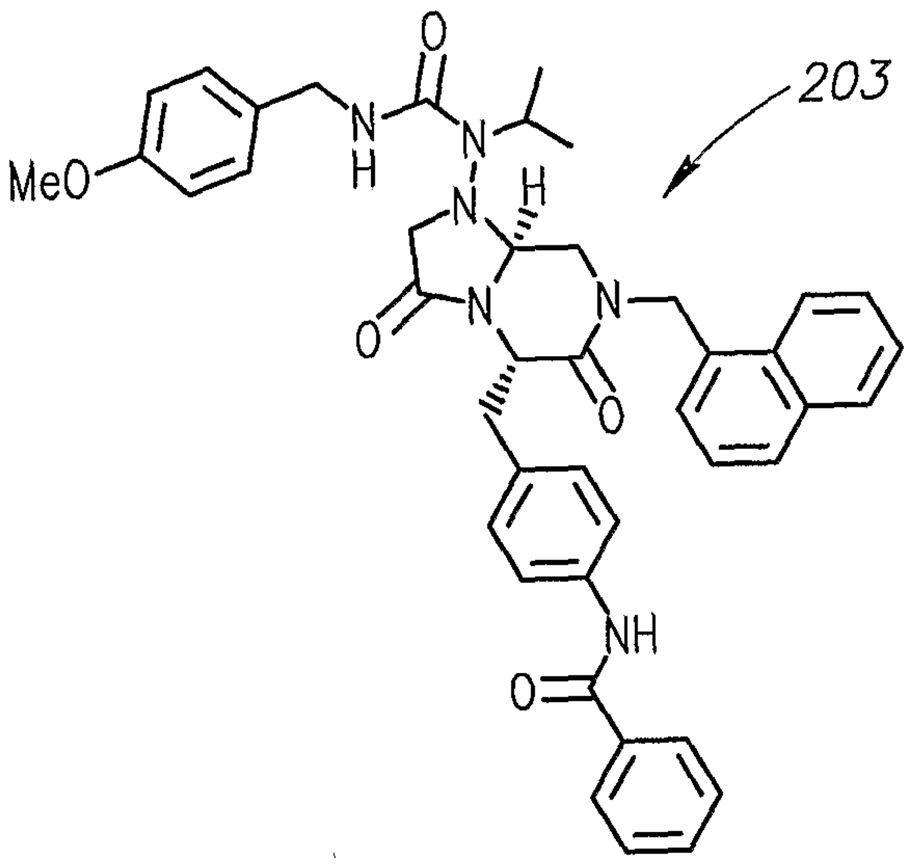
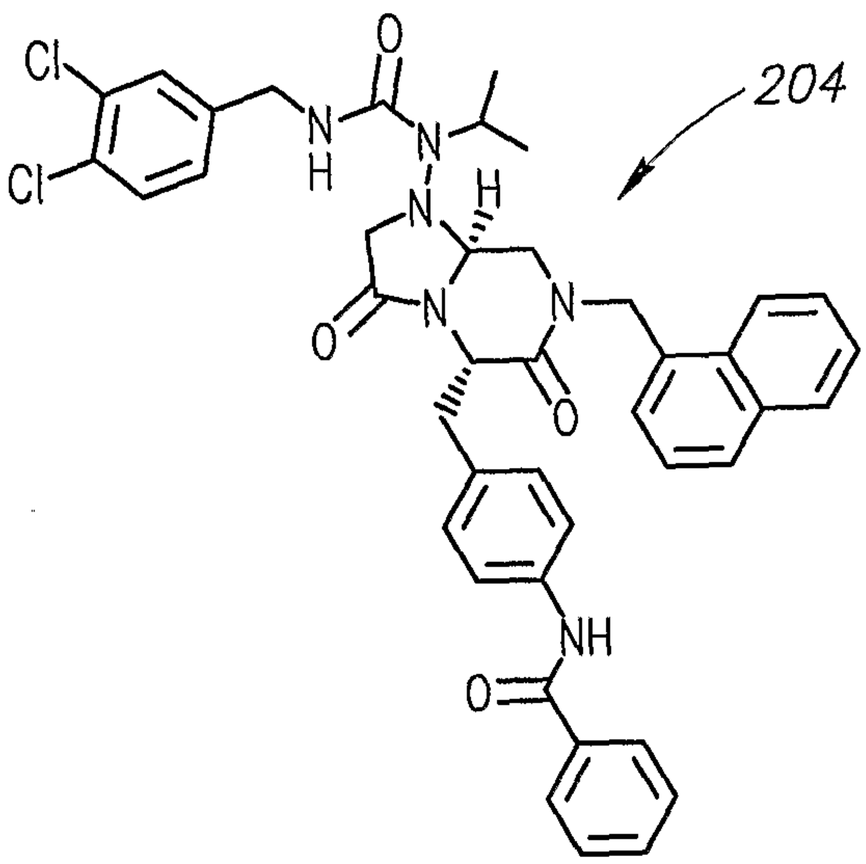


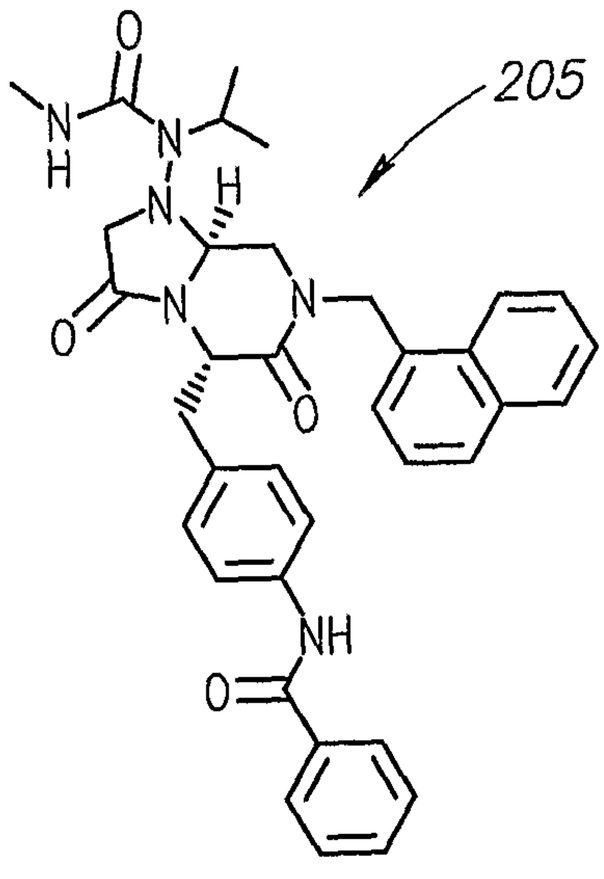
FIG.1Z











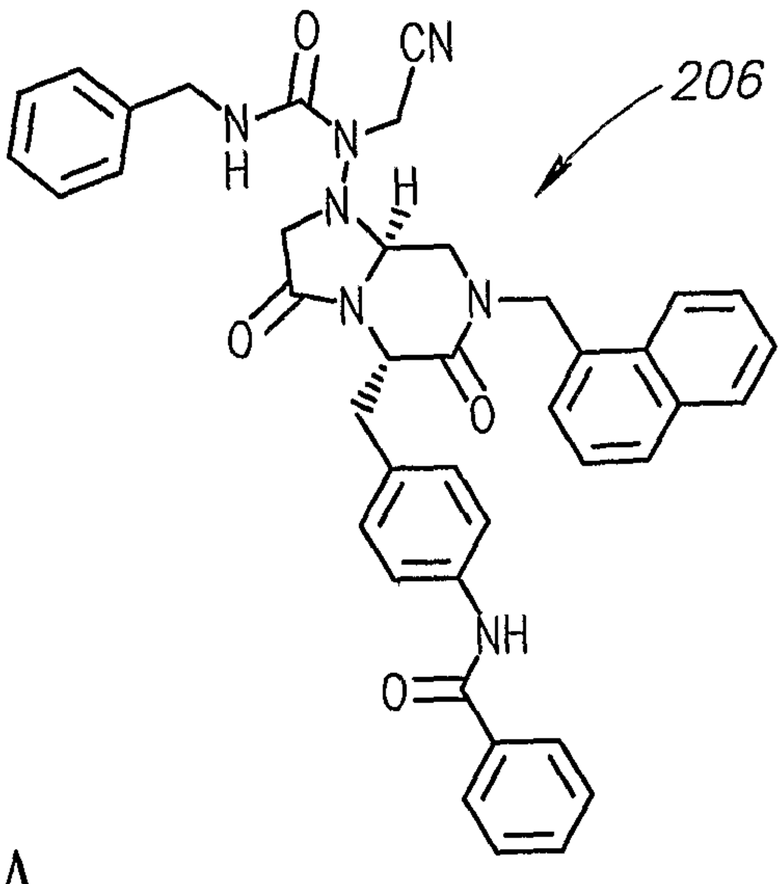


FIG.2A

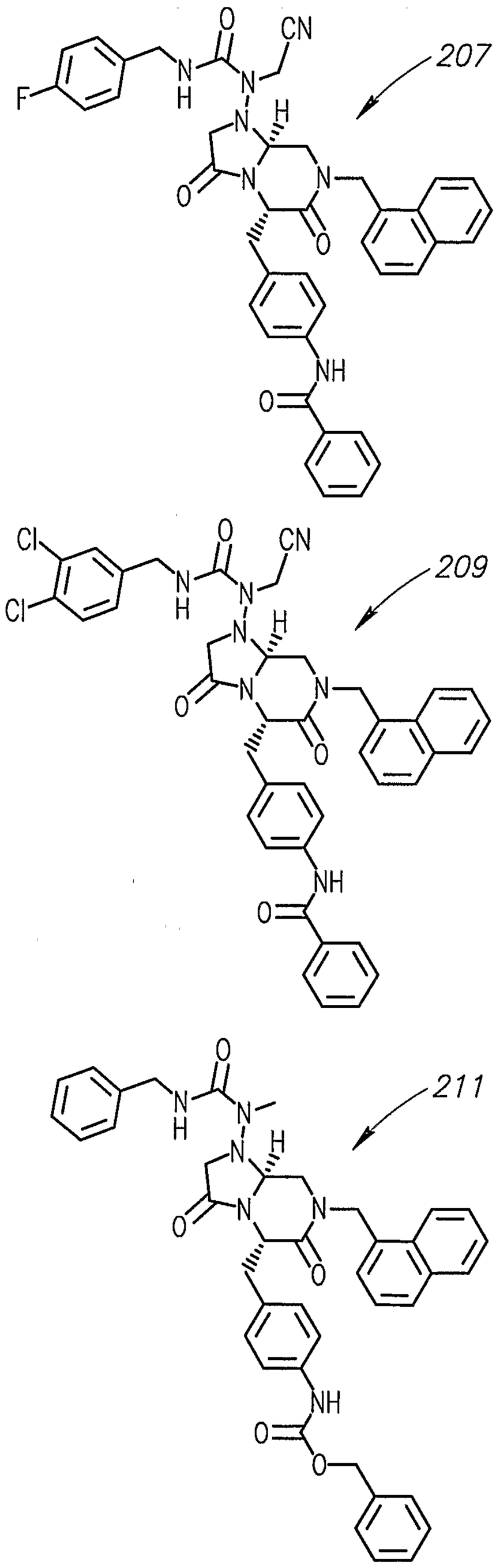


FIG.2B

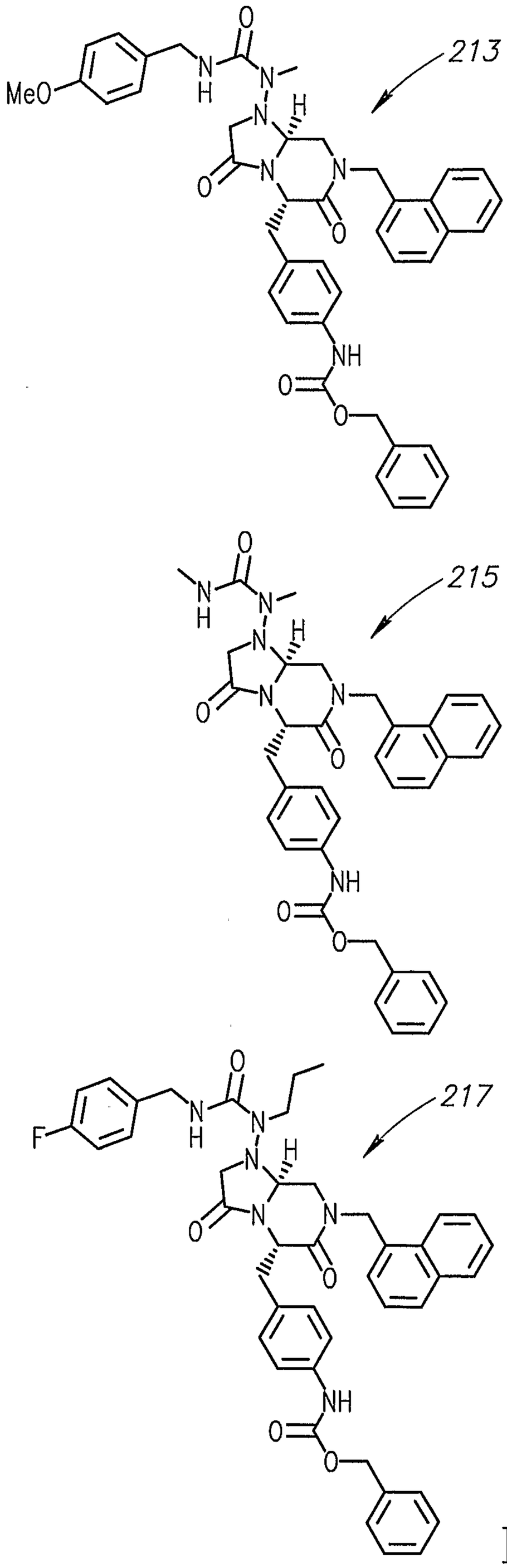
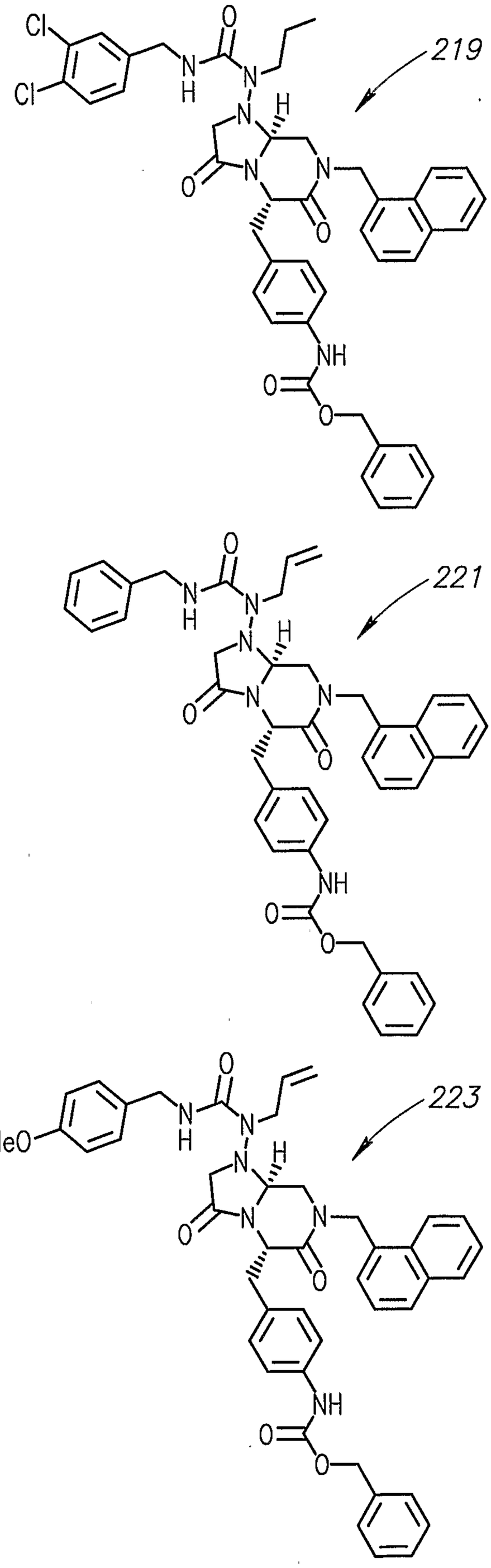
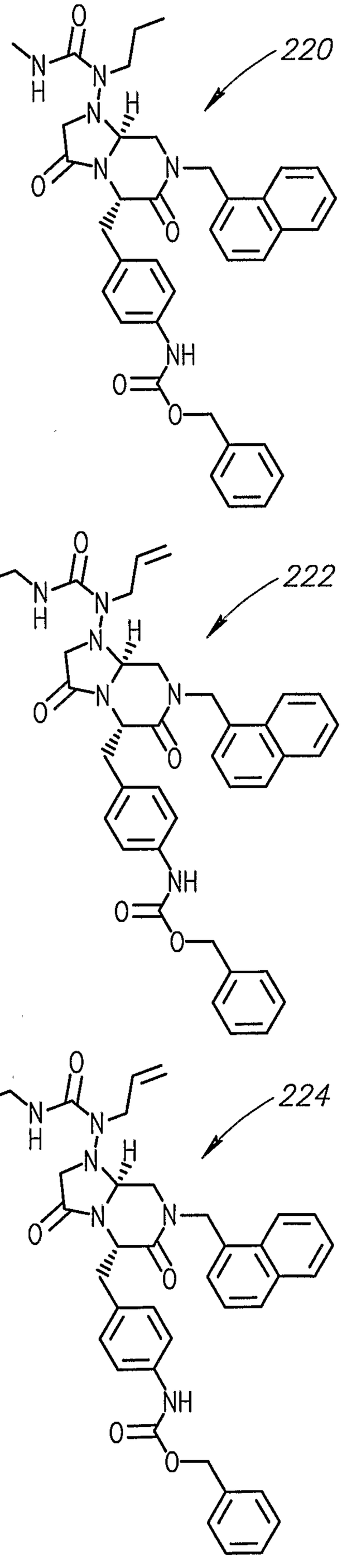


FIG.2C





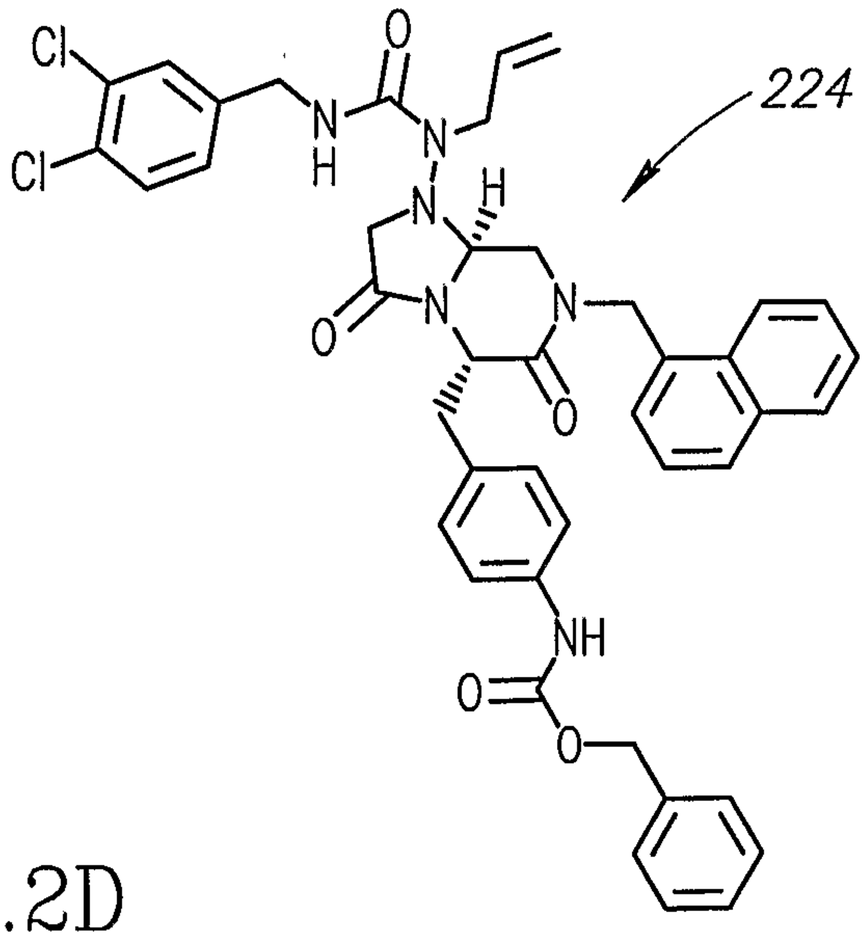
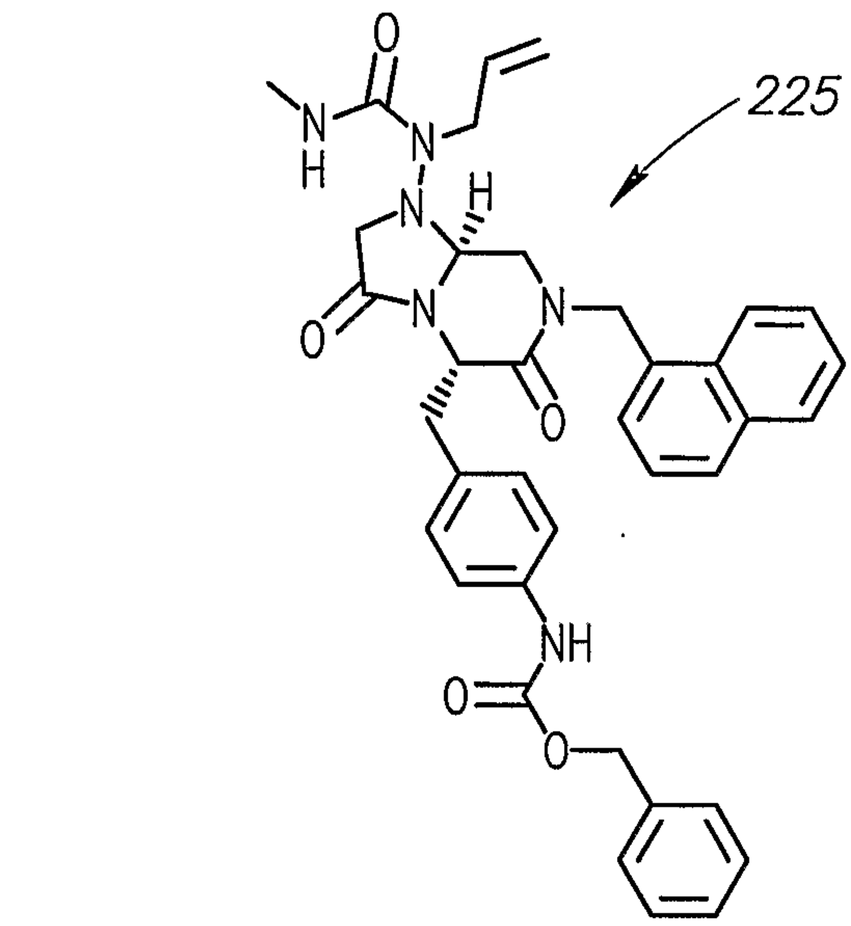
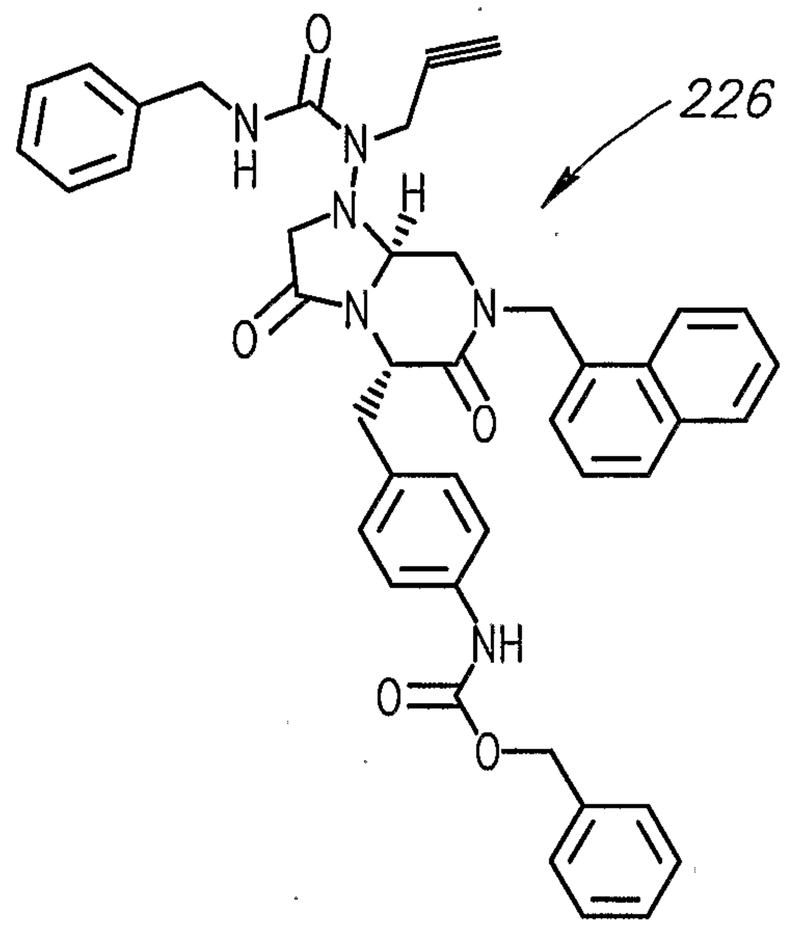
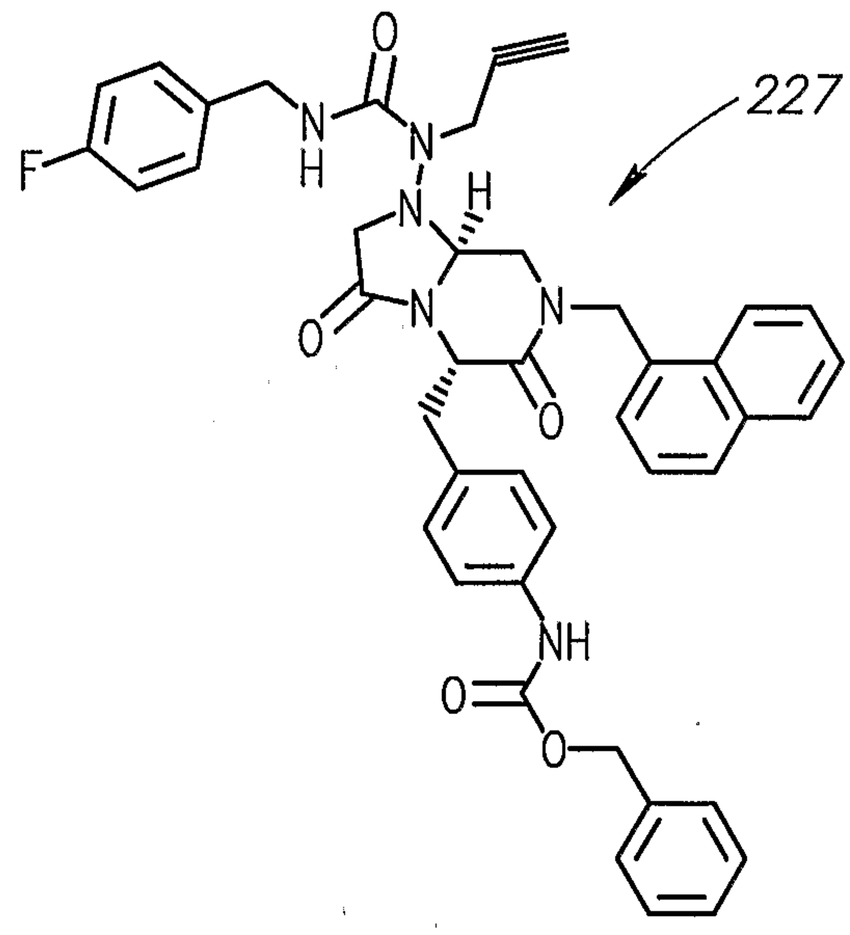
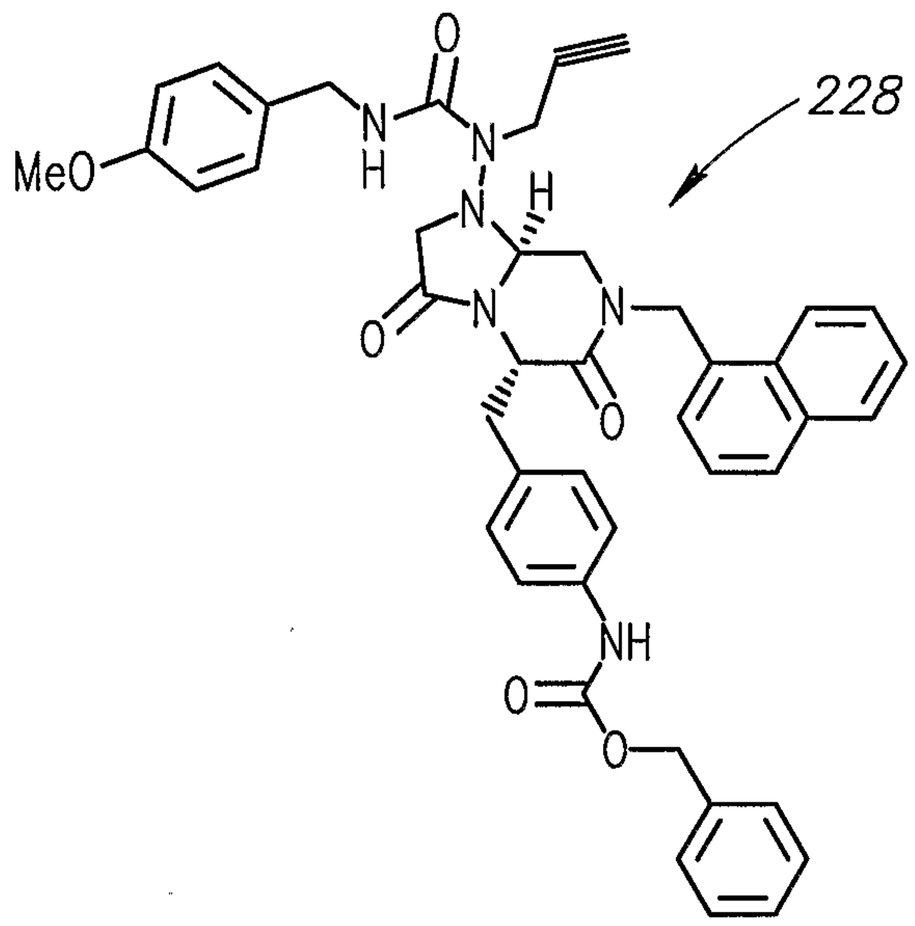


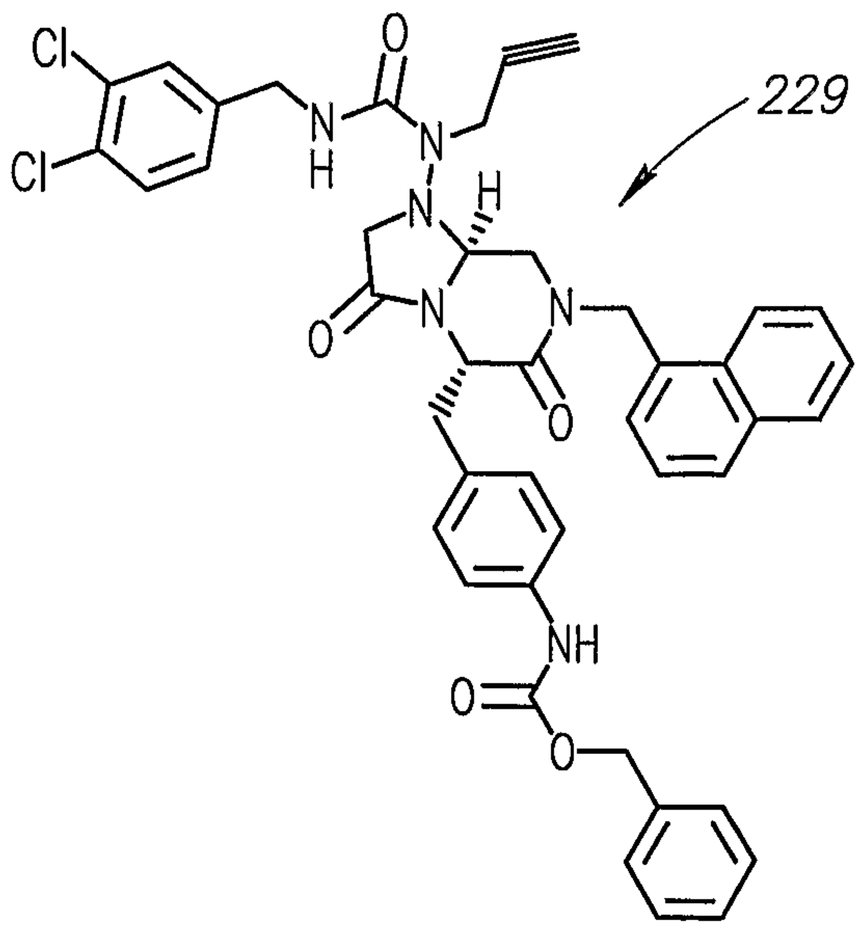
FIG.2D











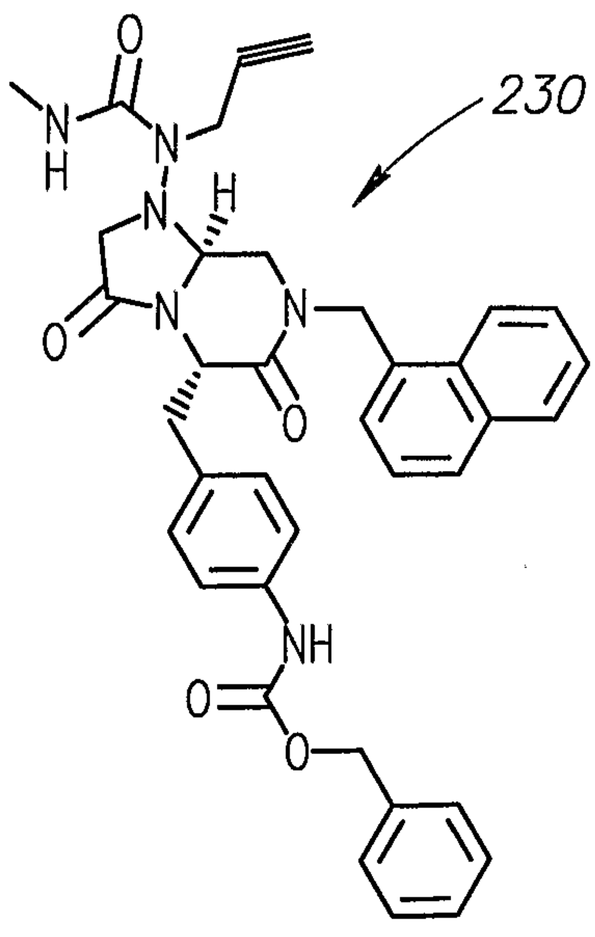
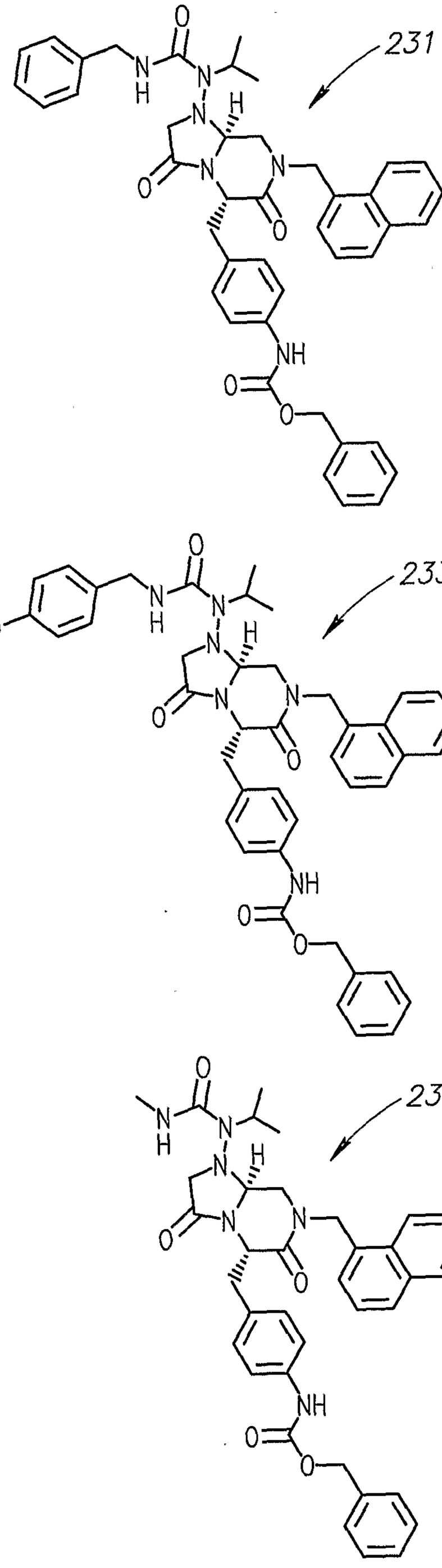


FIG.2E



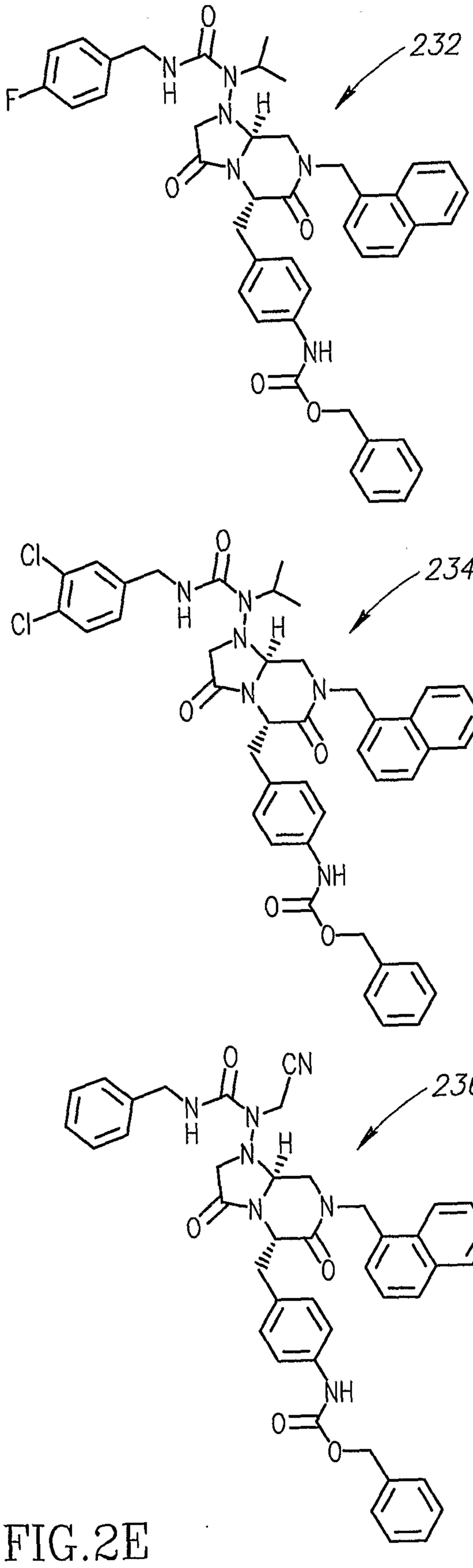


FIG.2E

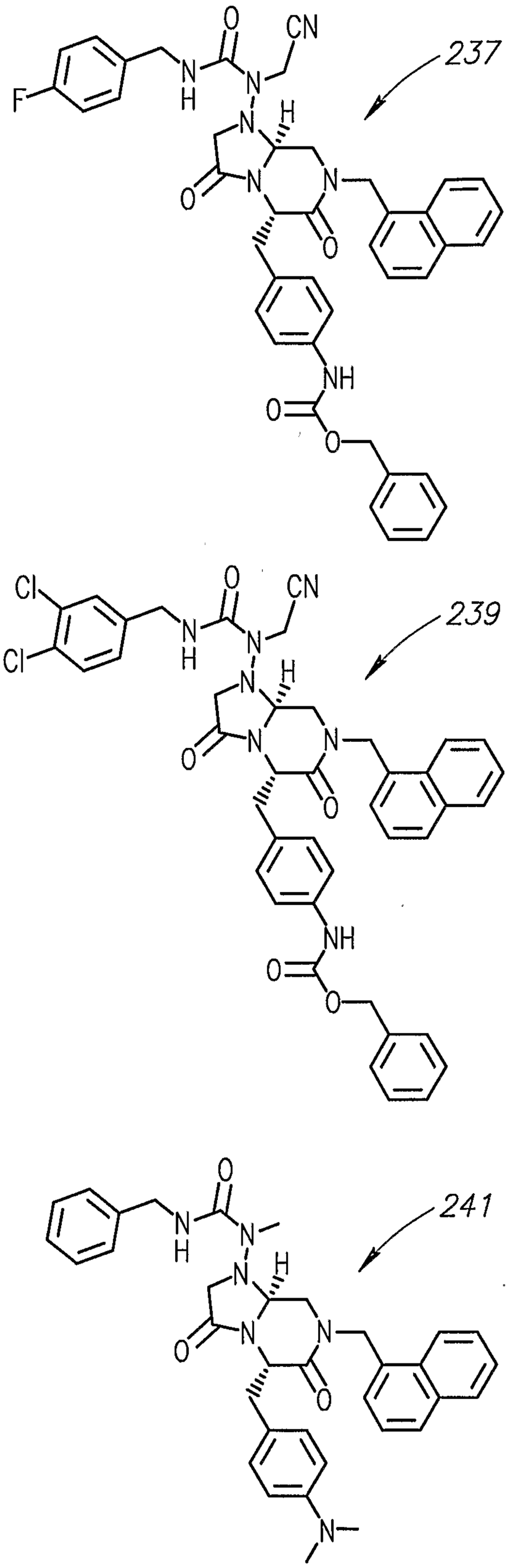


FIG.2G

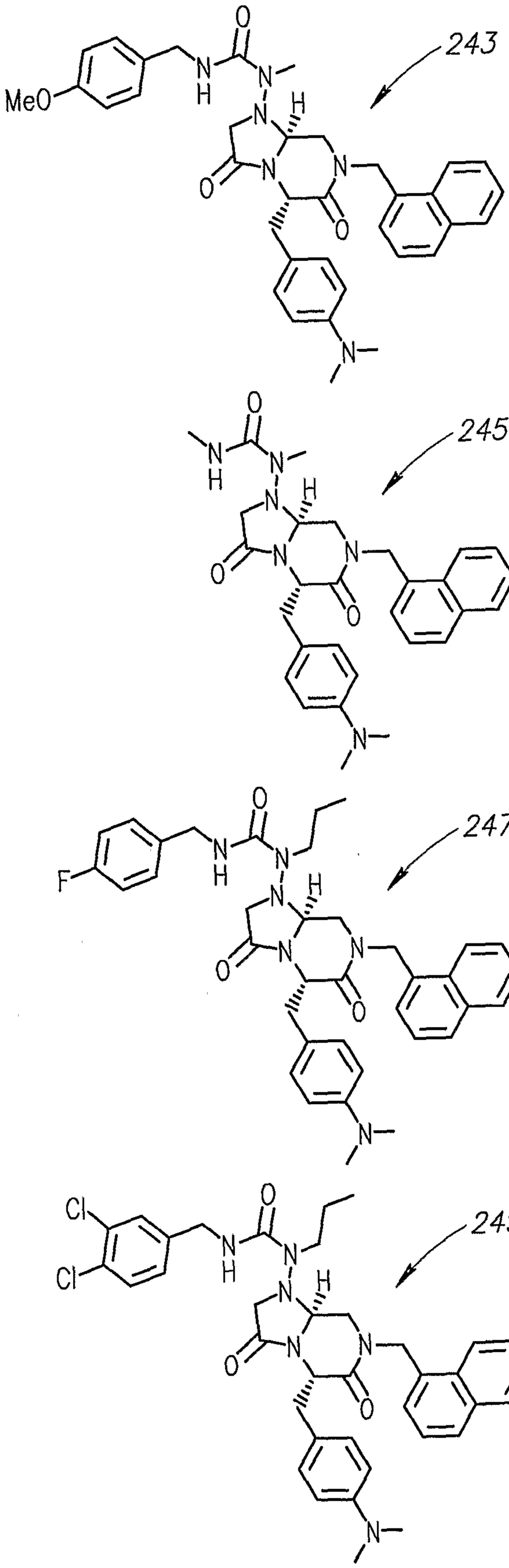


FIG.2H

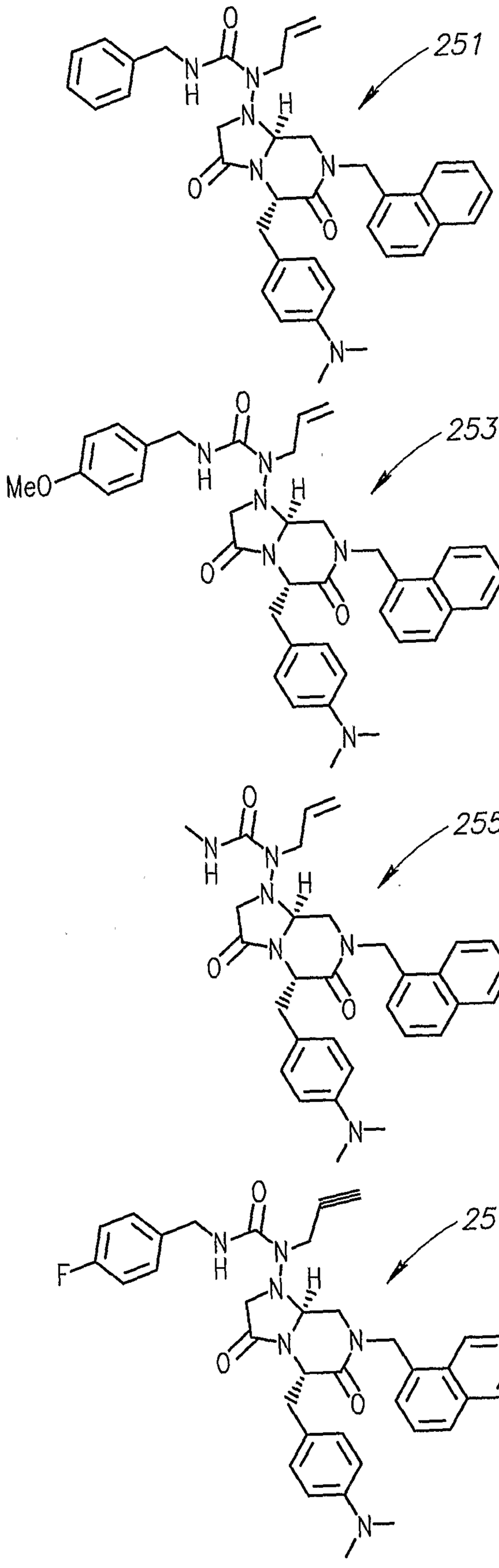
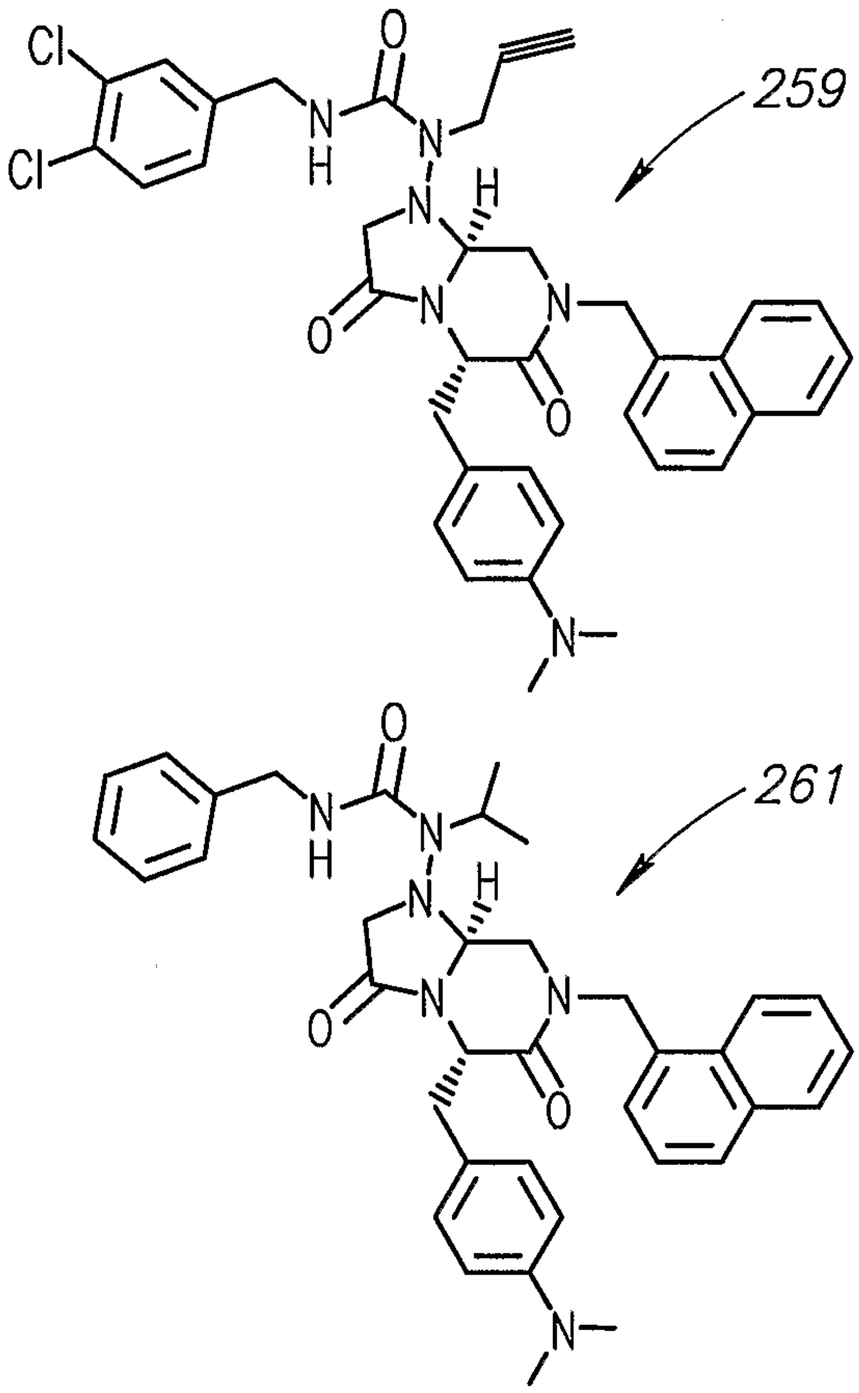
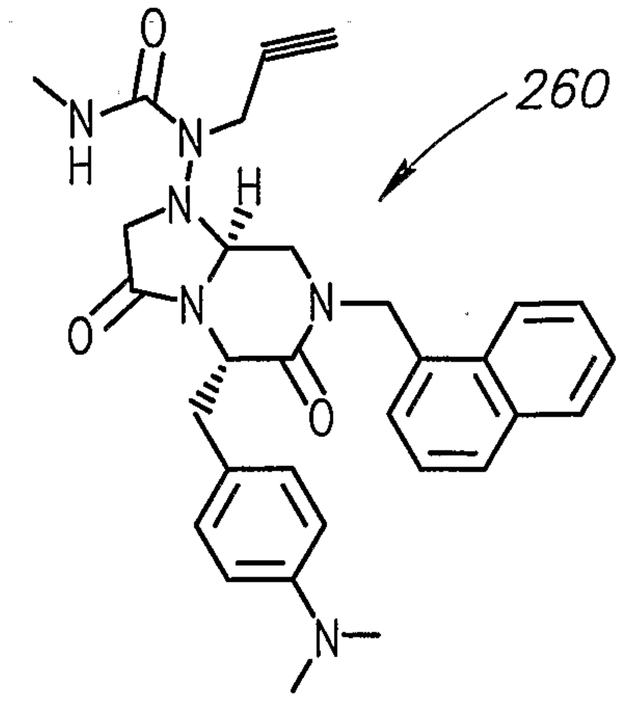
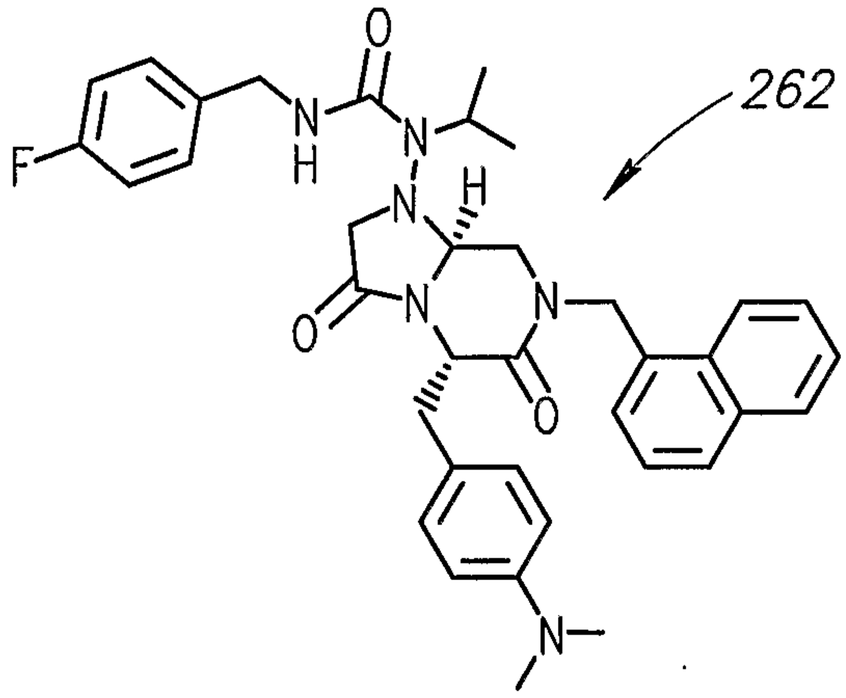
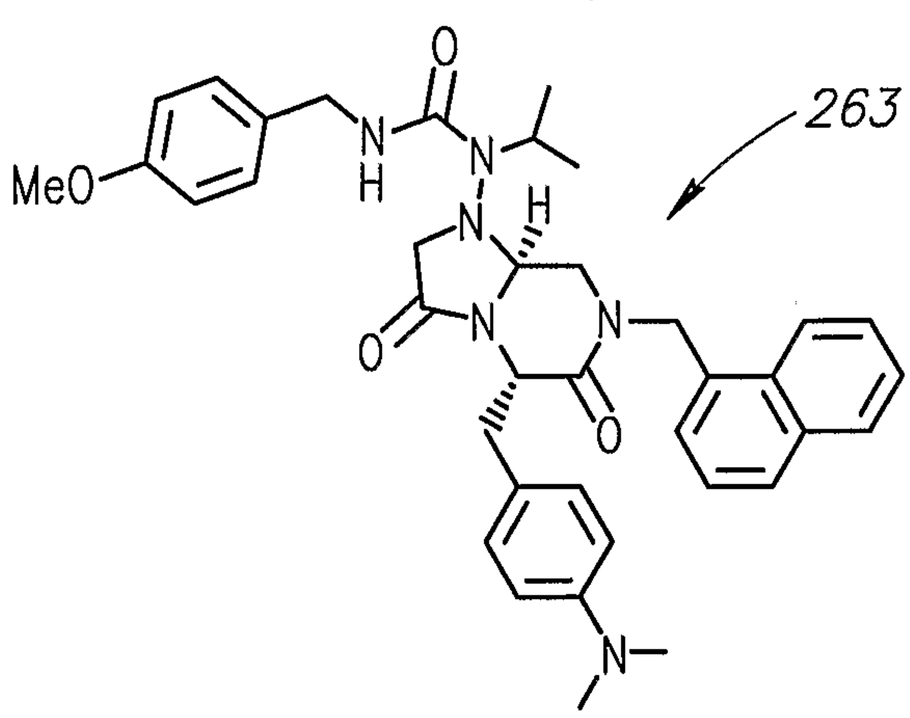


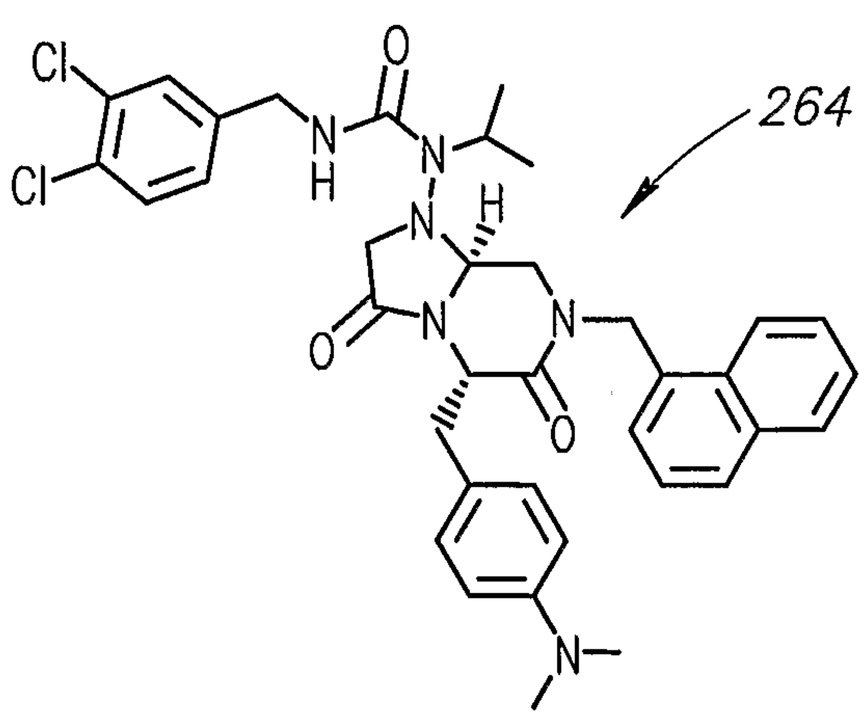
FIG.2I

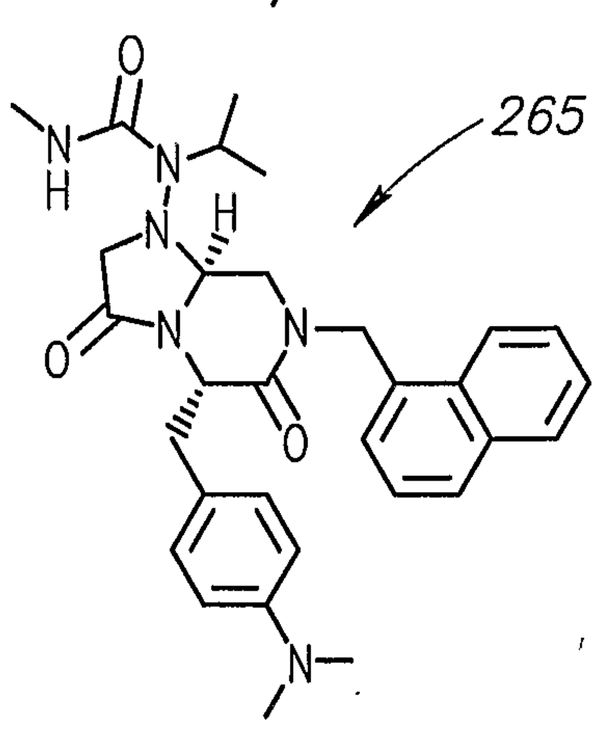












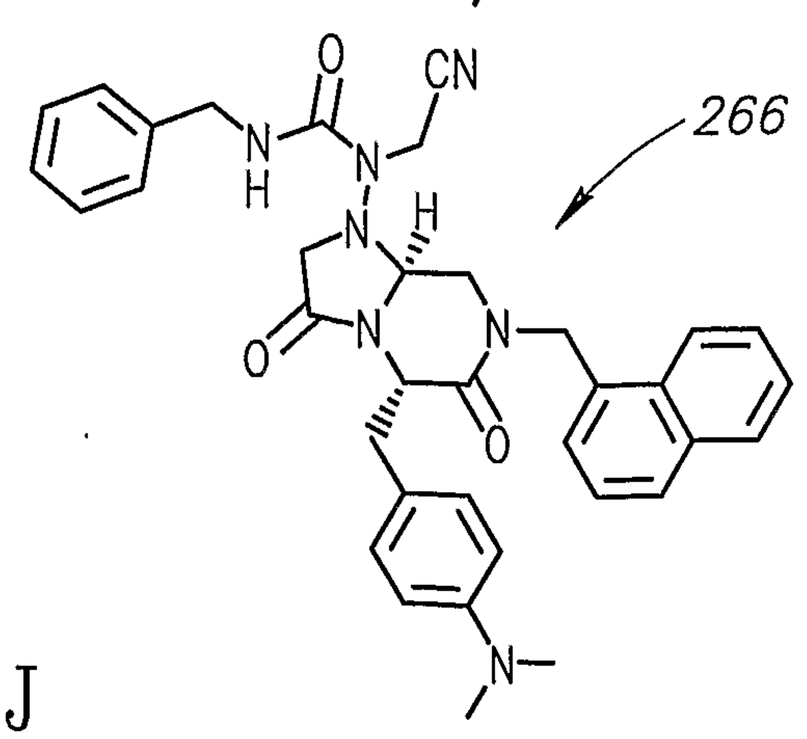


FIG.2J

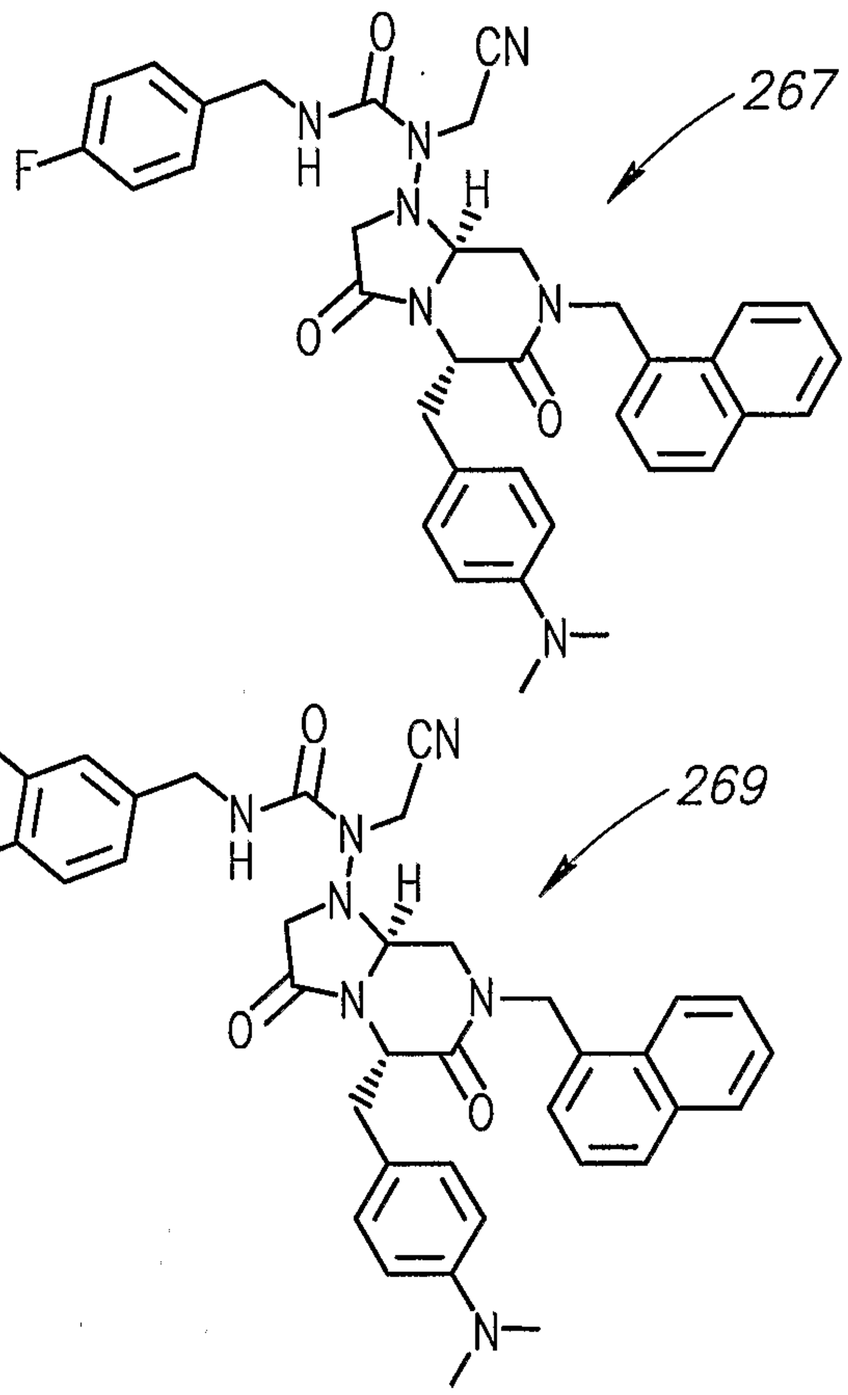
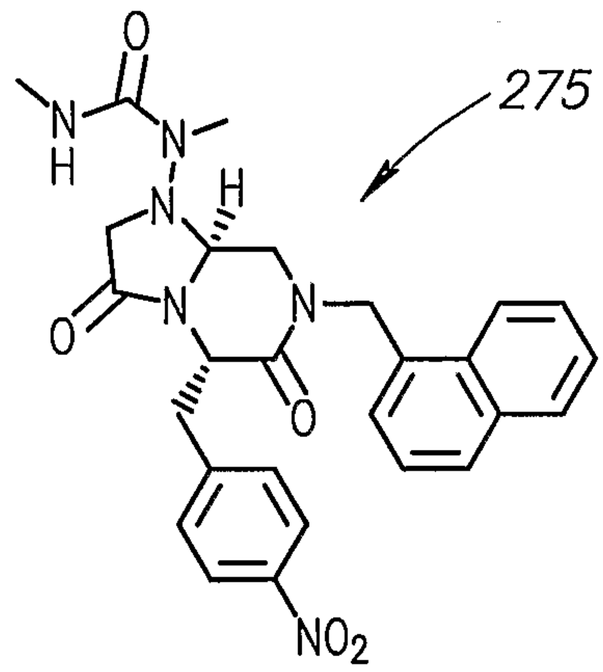
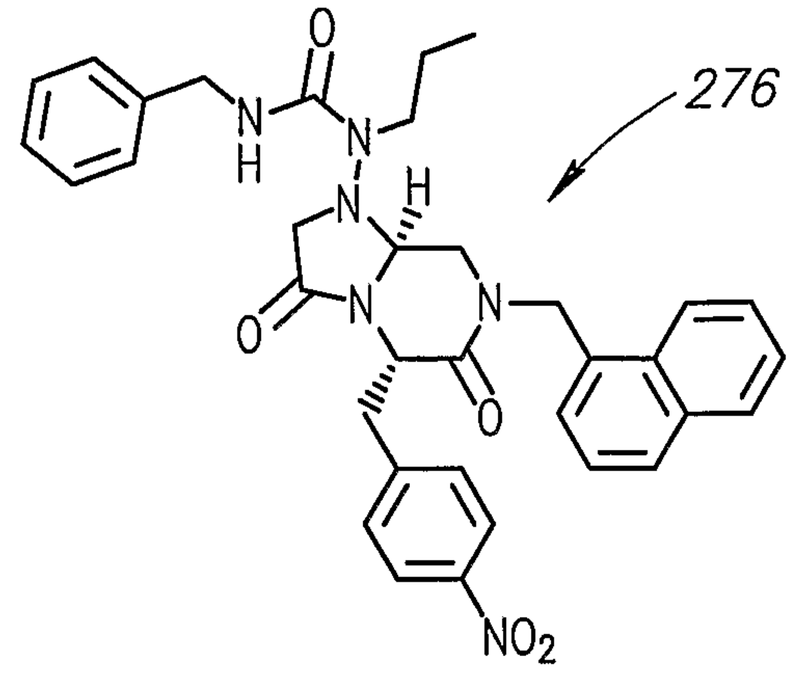
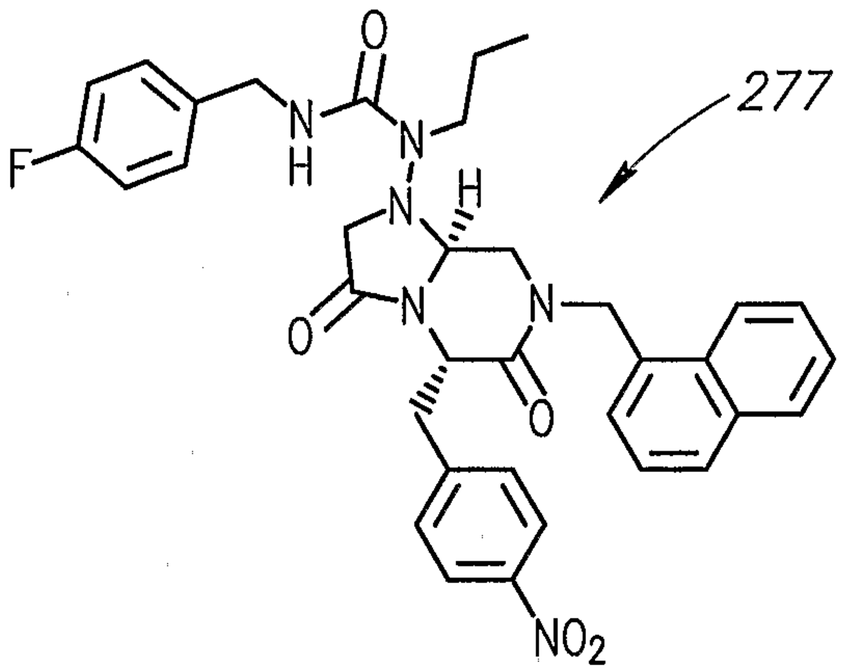
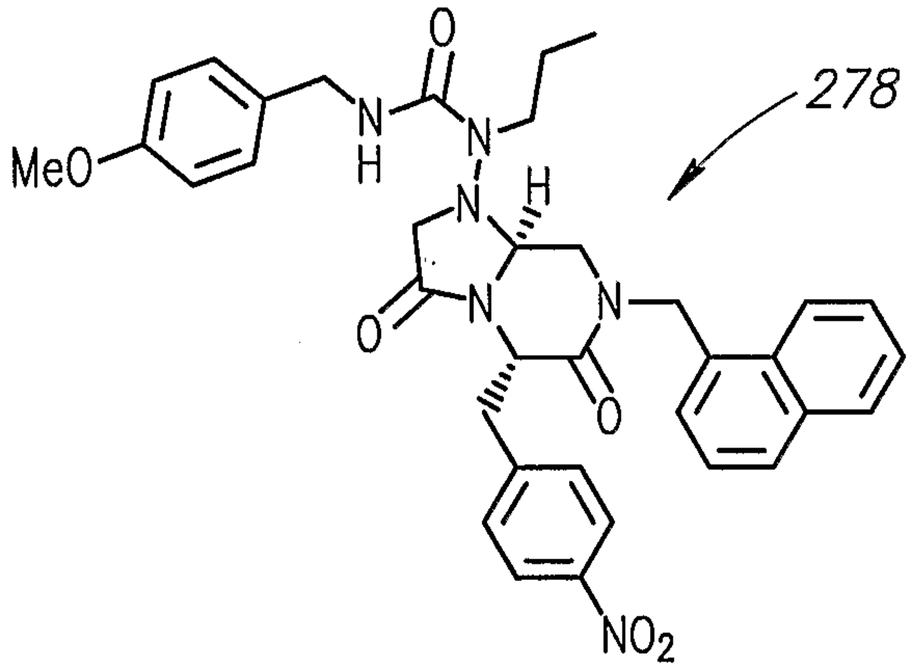


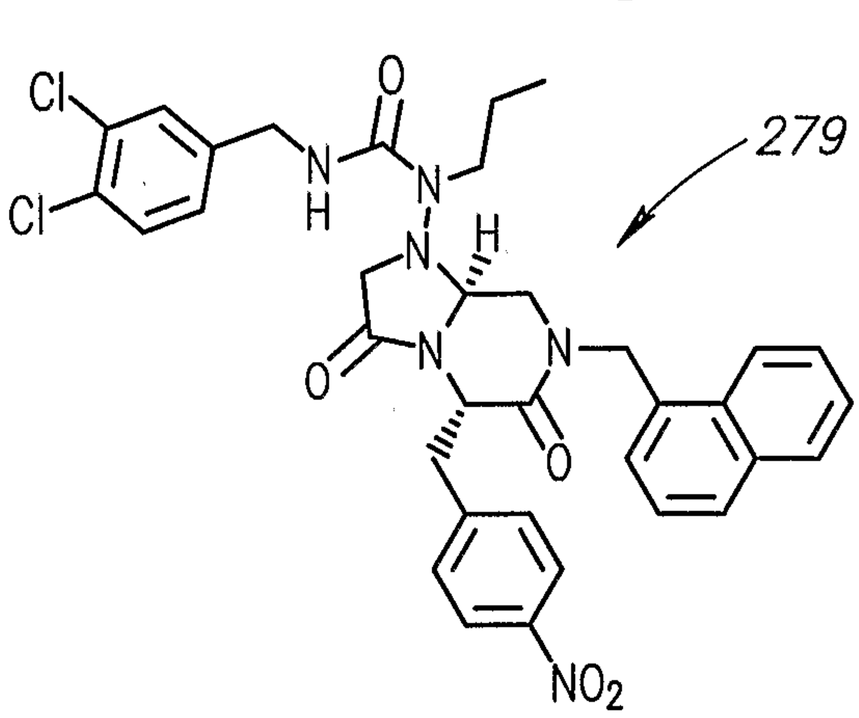
FIG.2K

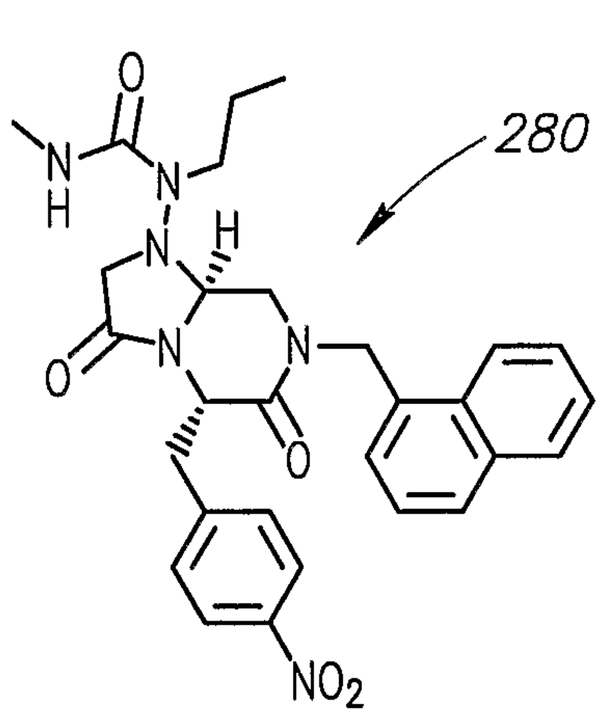


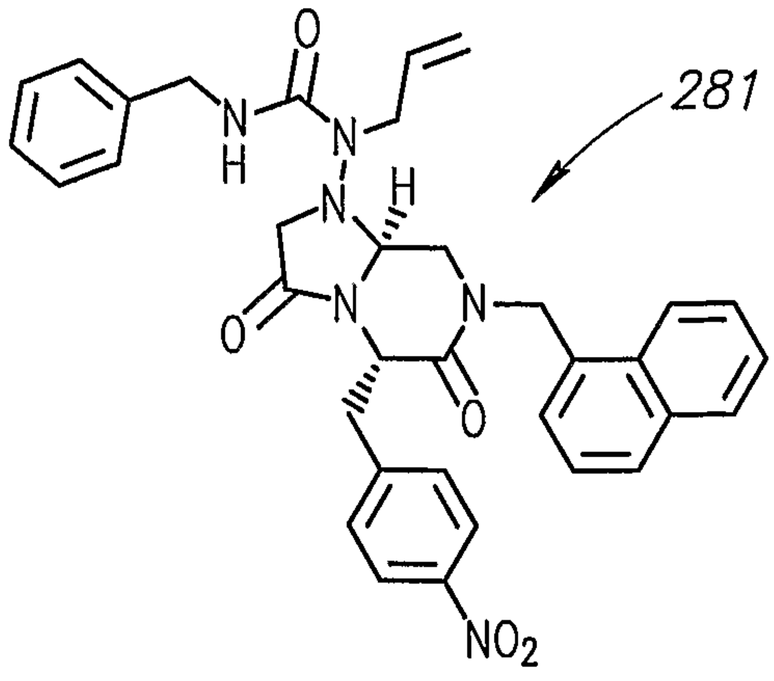












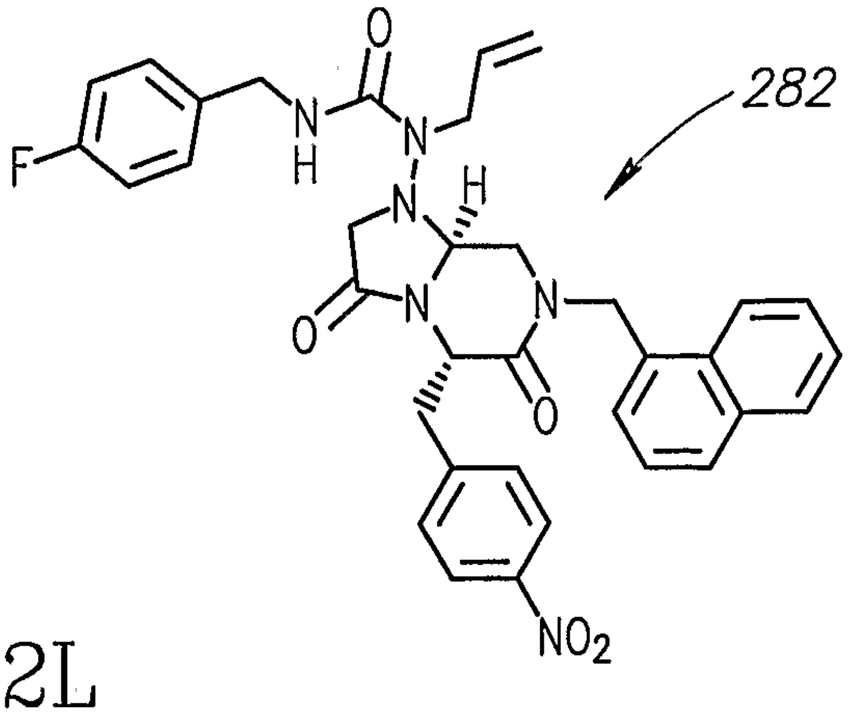
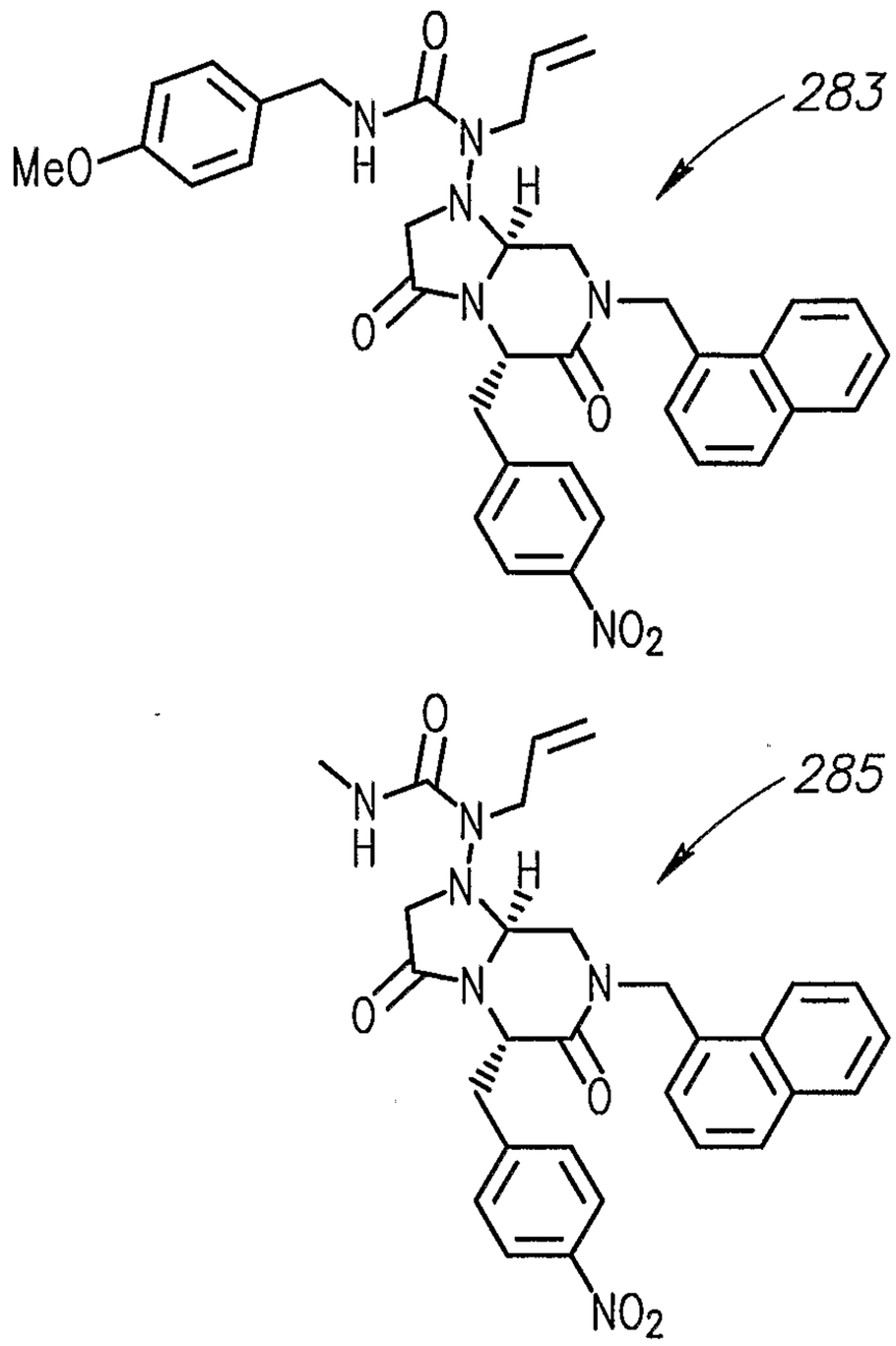


FIG.2L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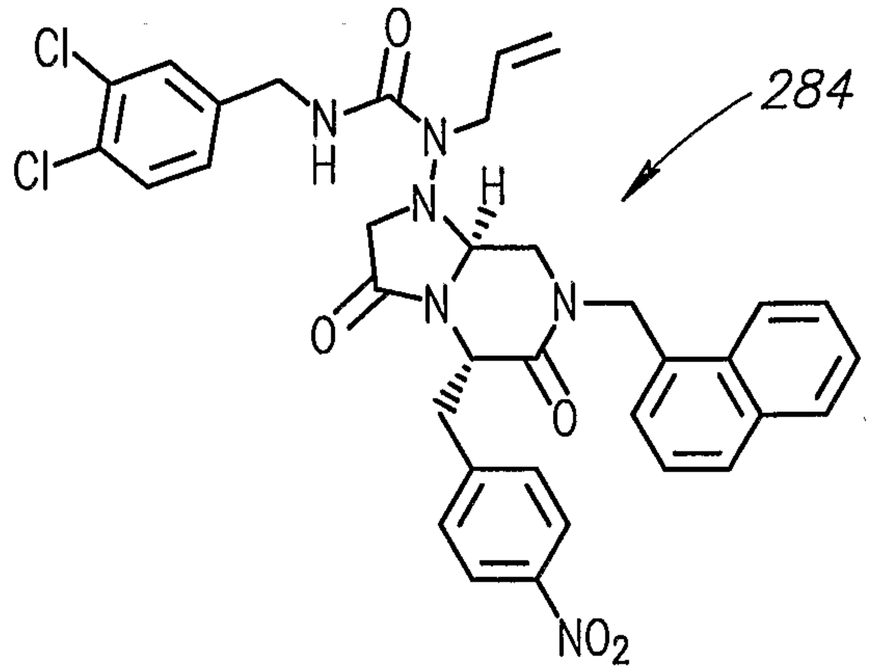
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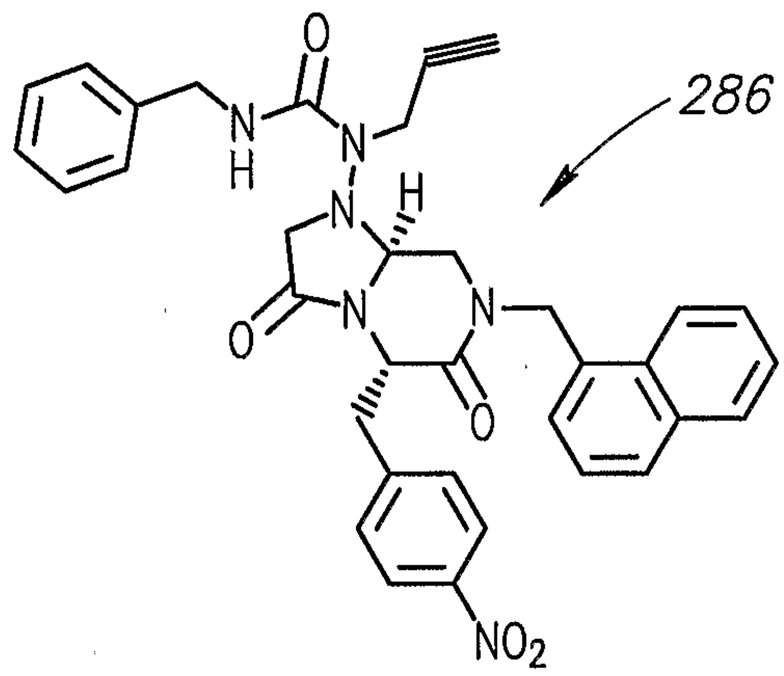
NO2

285
NO2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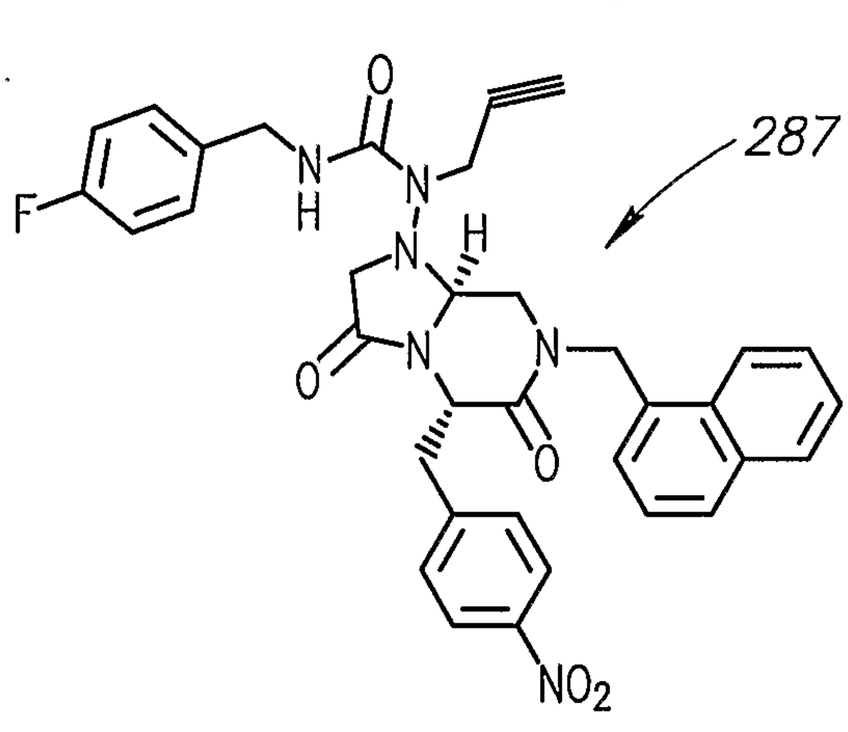
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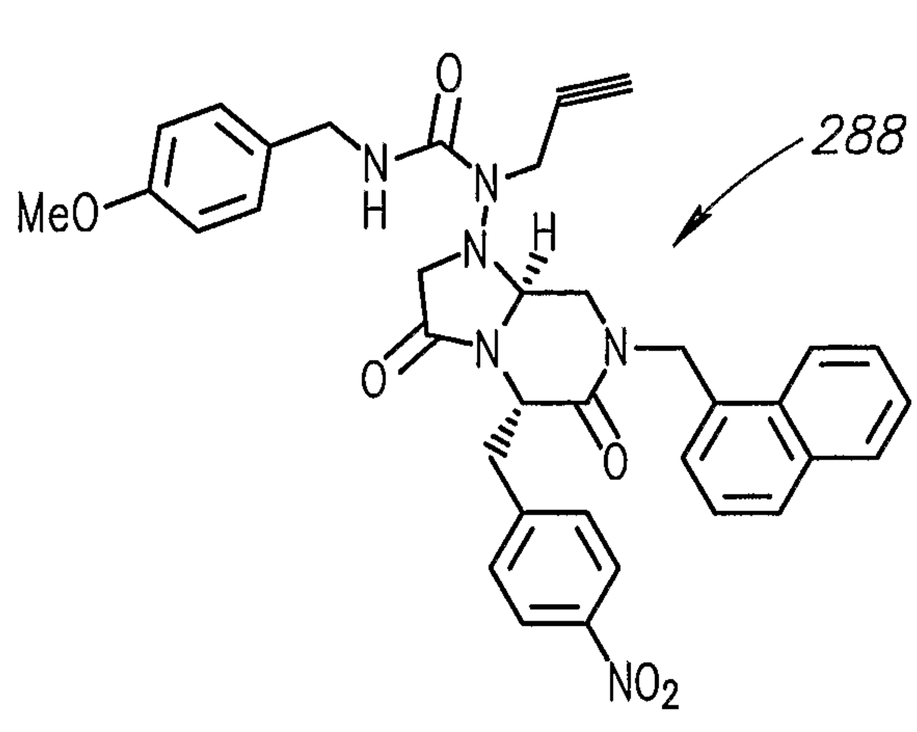
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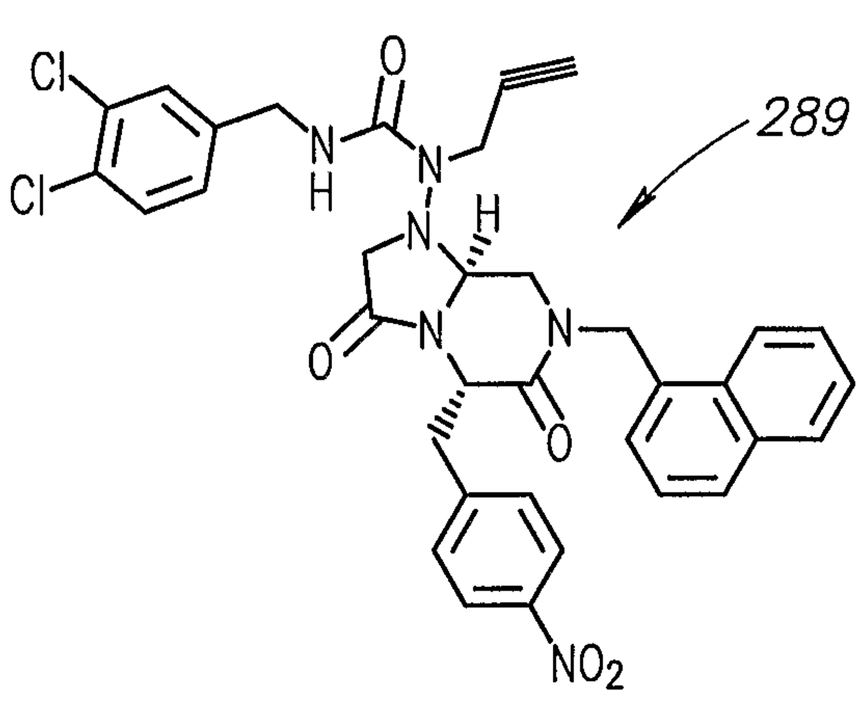
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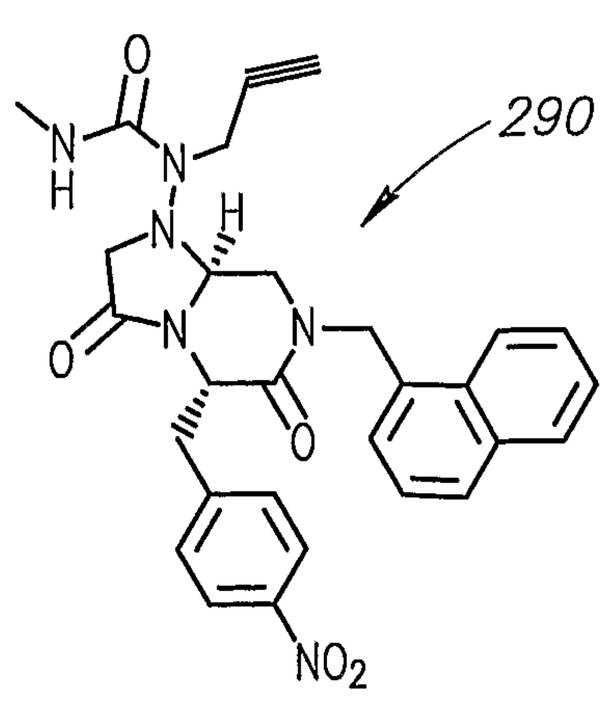
Cl
NO2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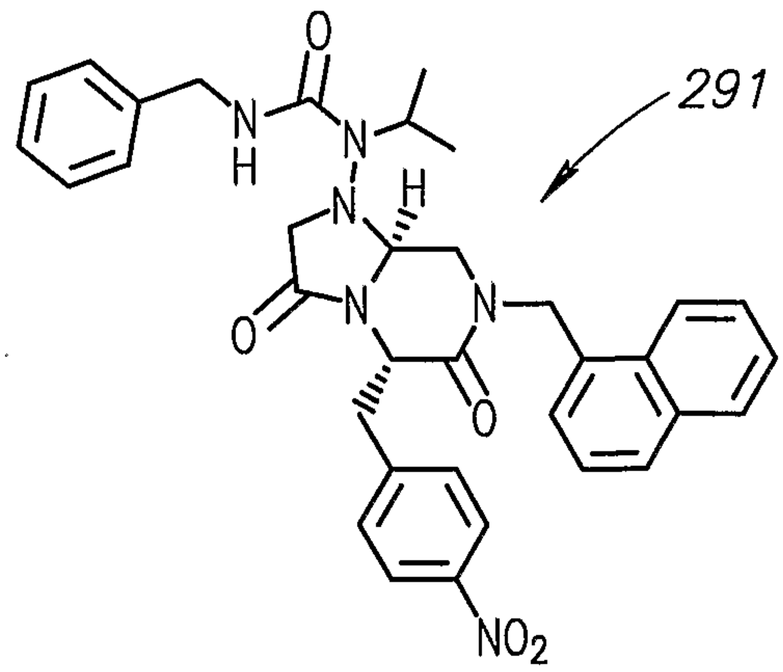
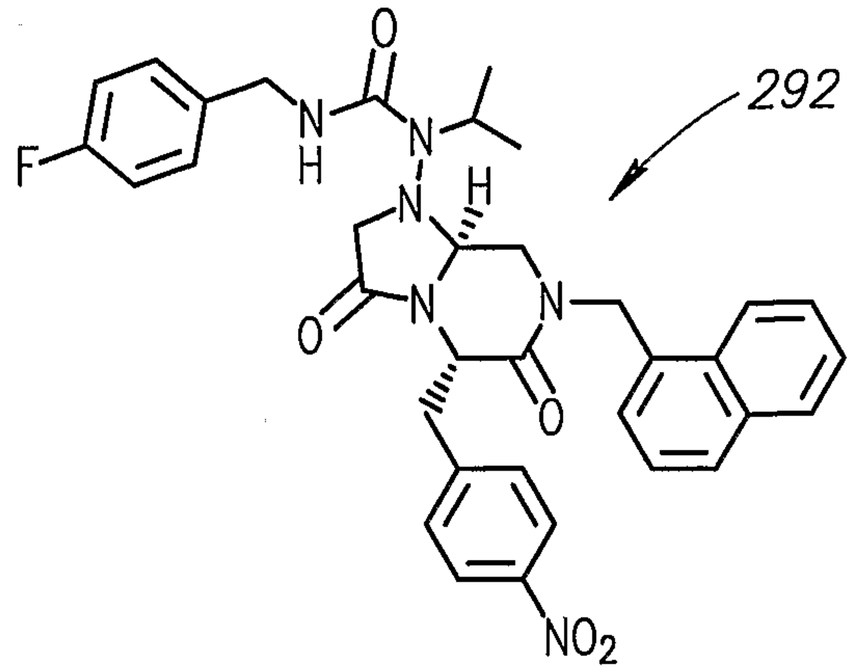
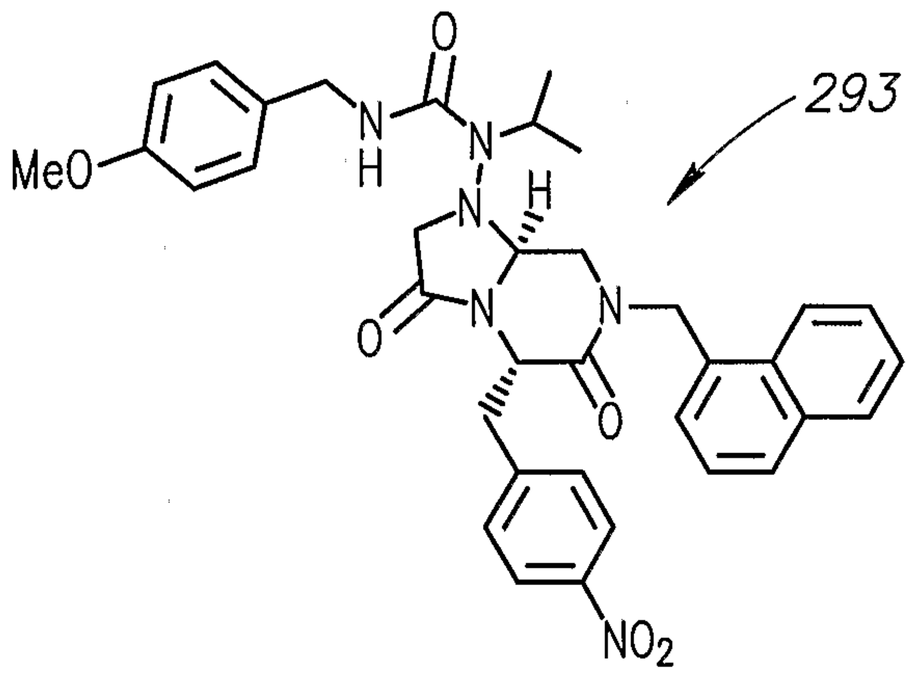
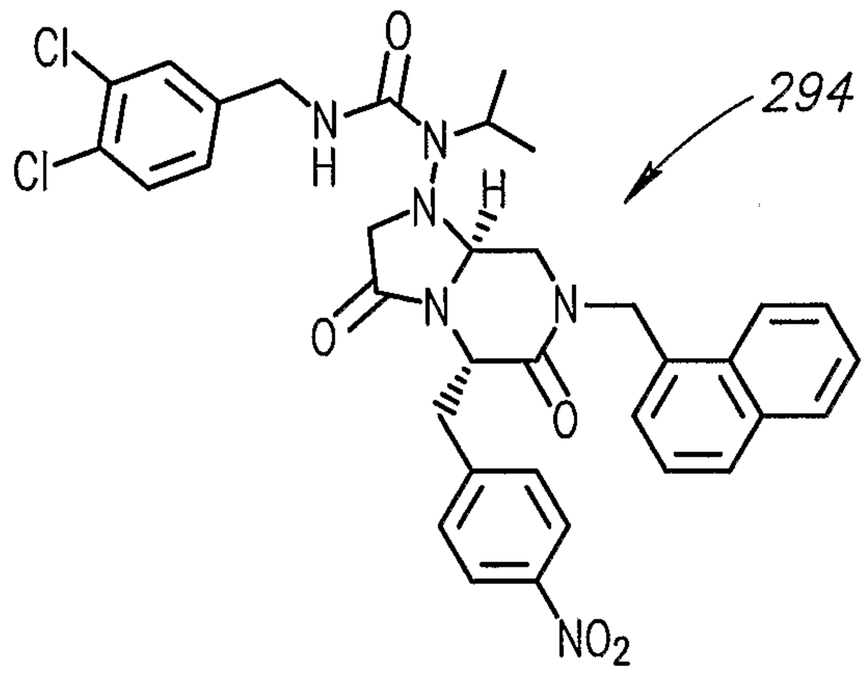
NO2

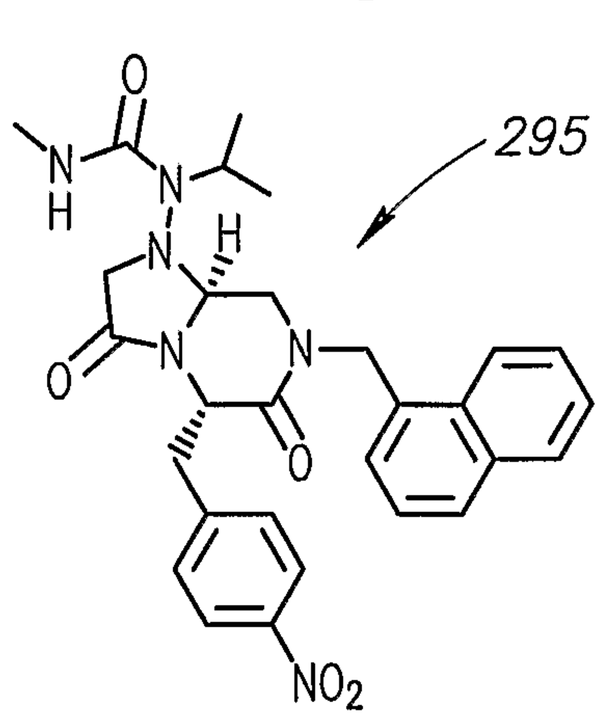
FIG.2M











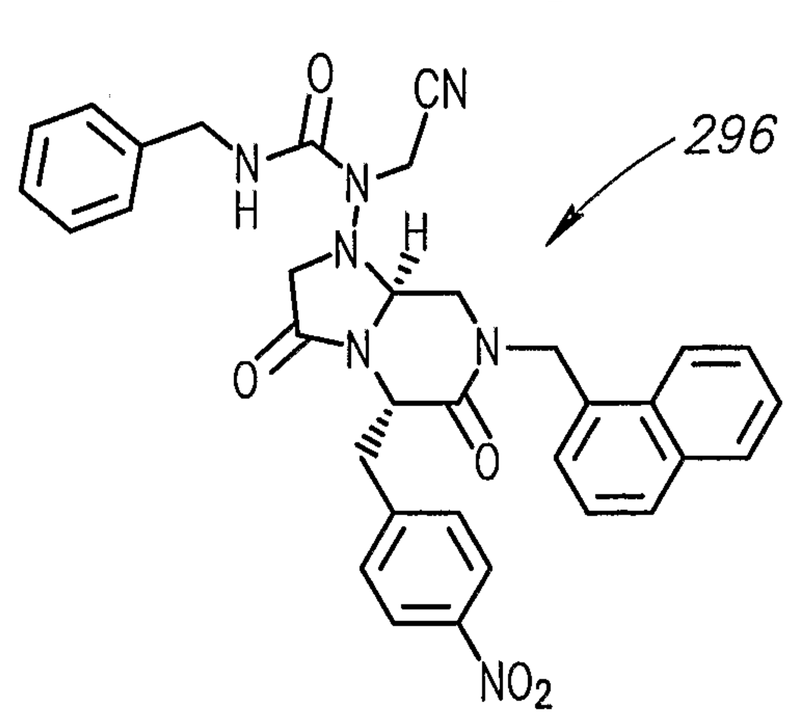
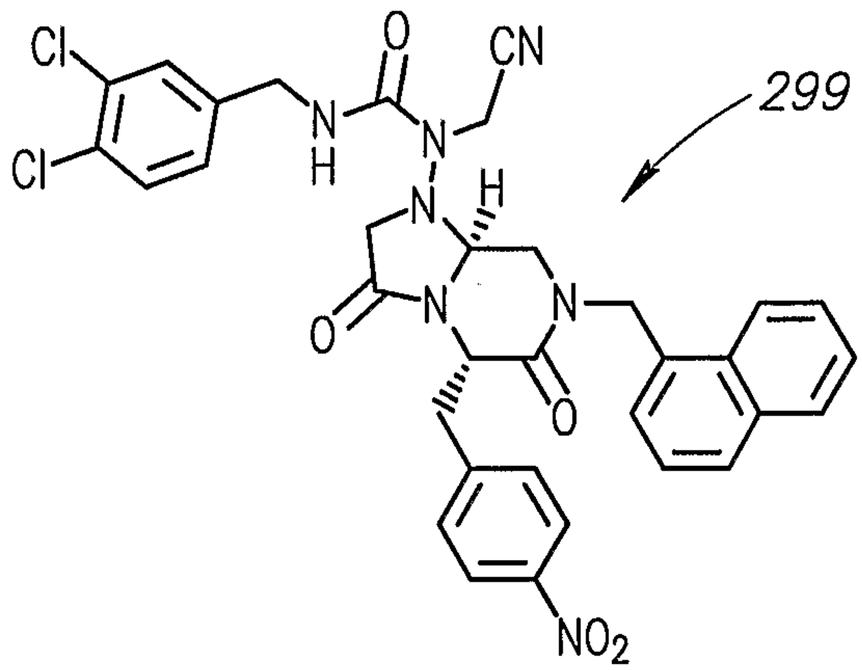
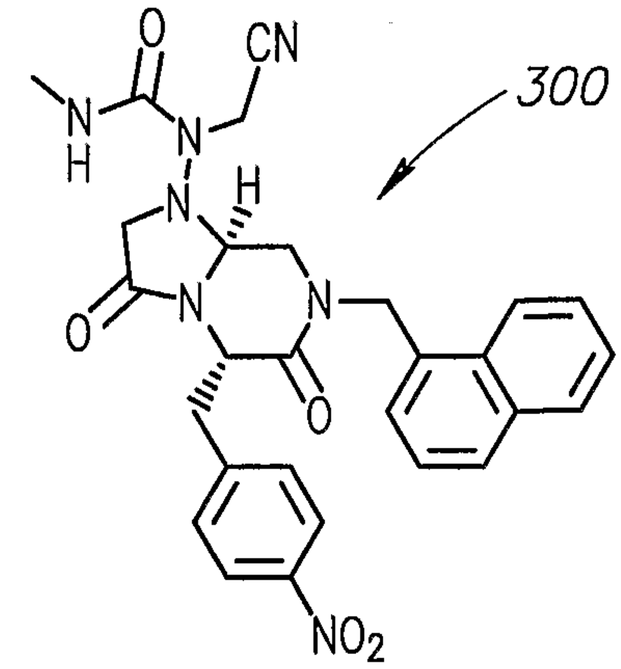
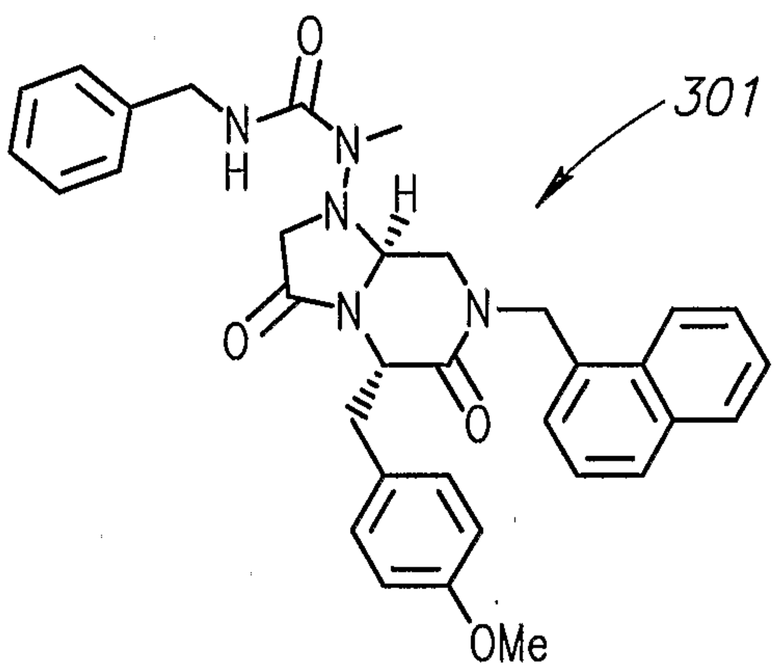
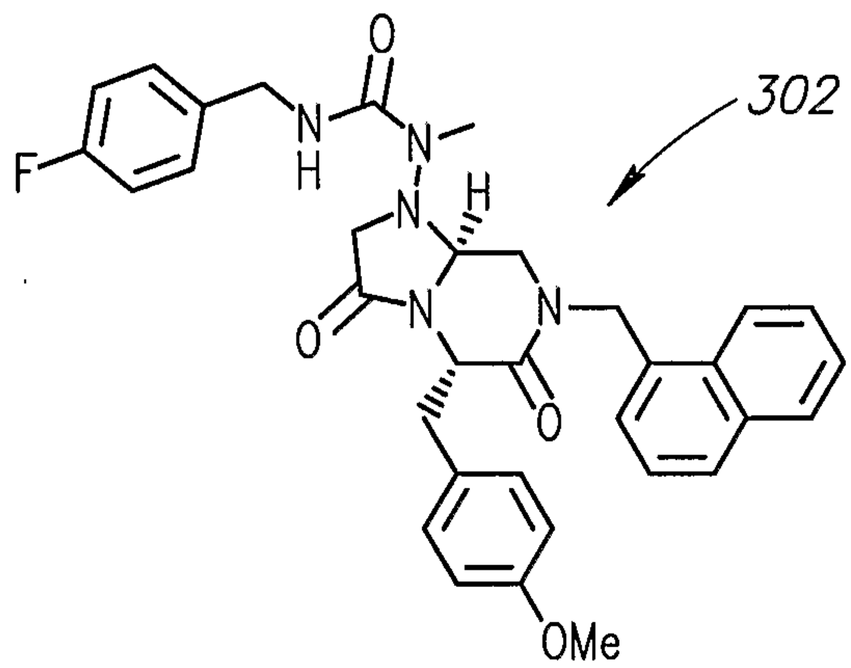


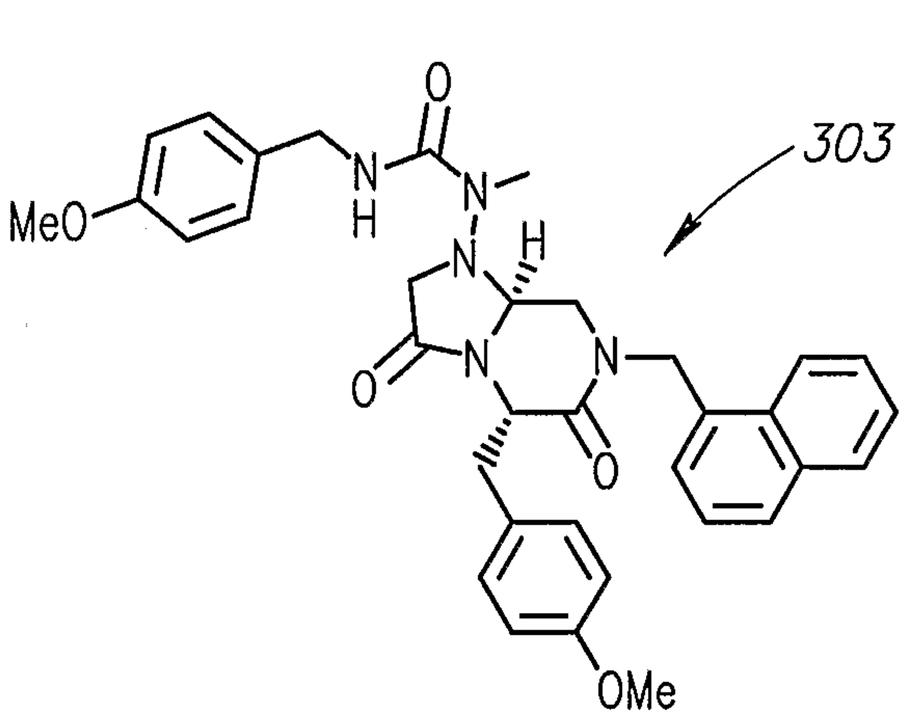
FIG.2N











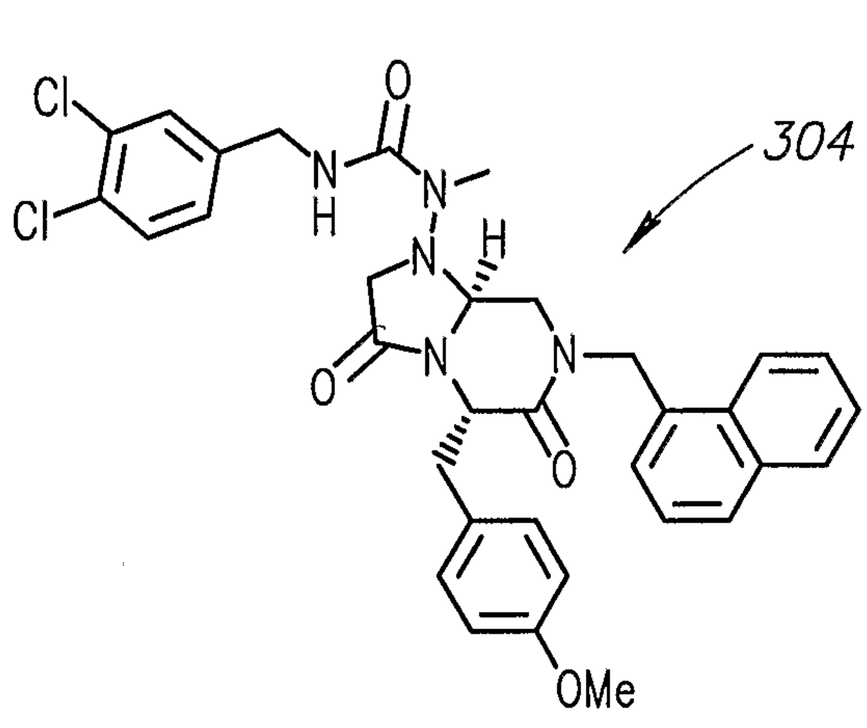
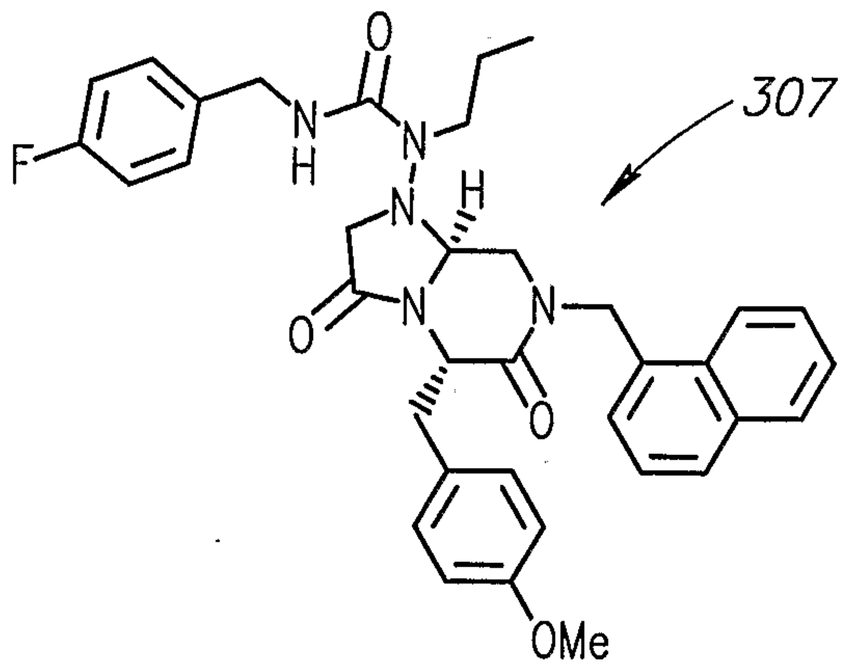


FIG.20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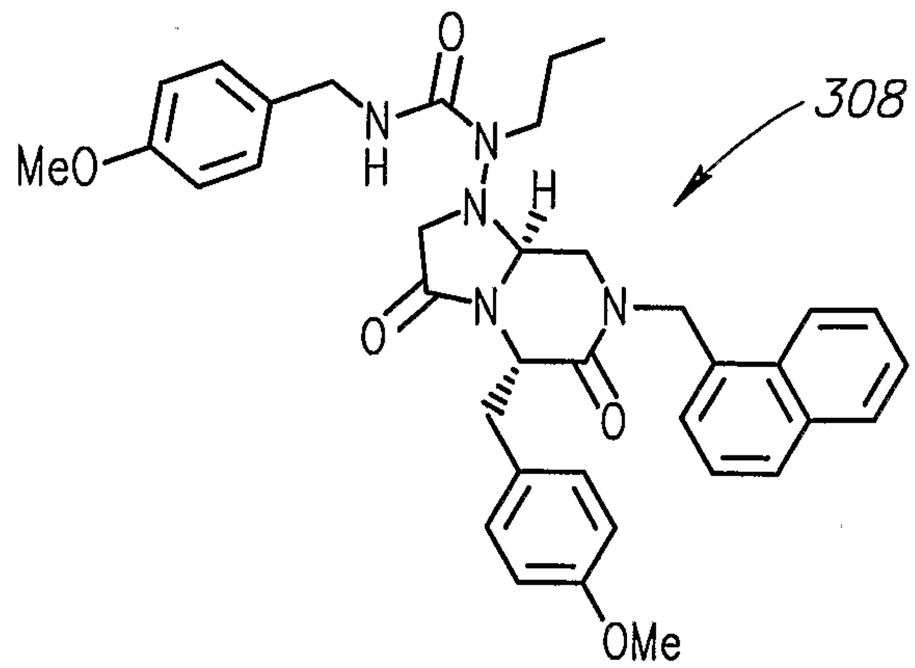
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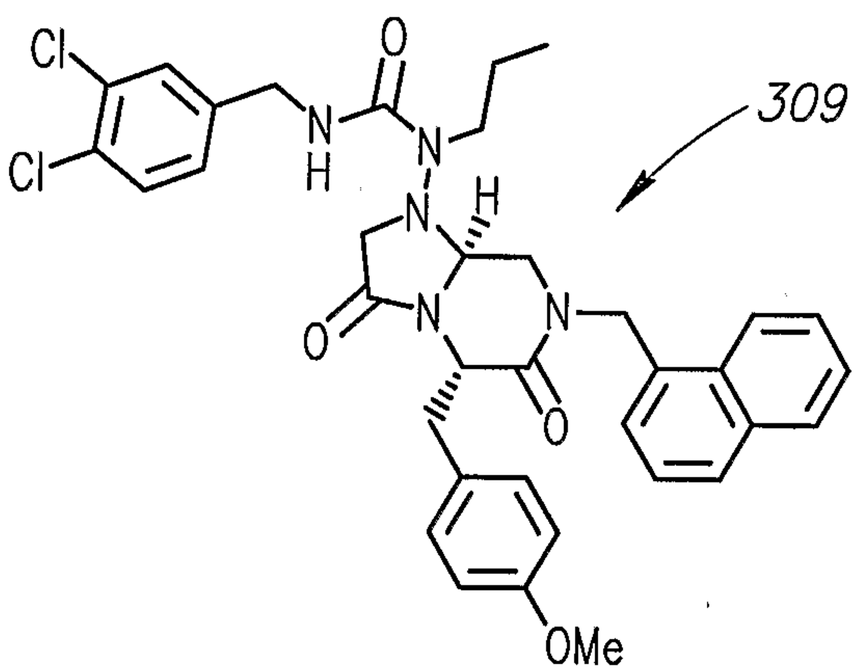
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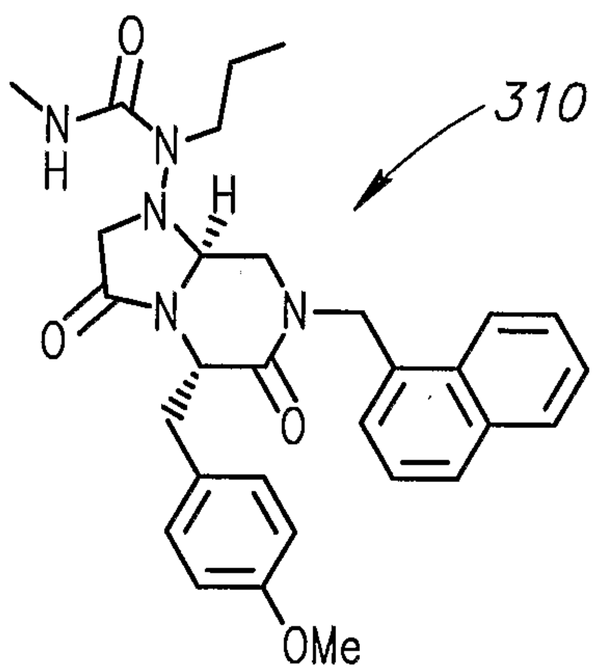
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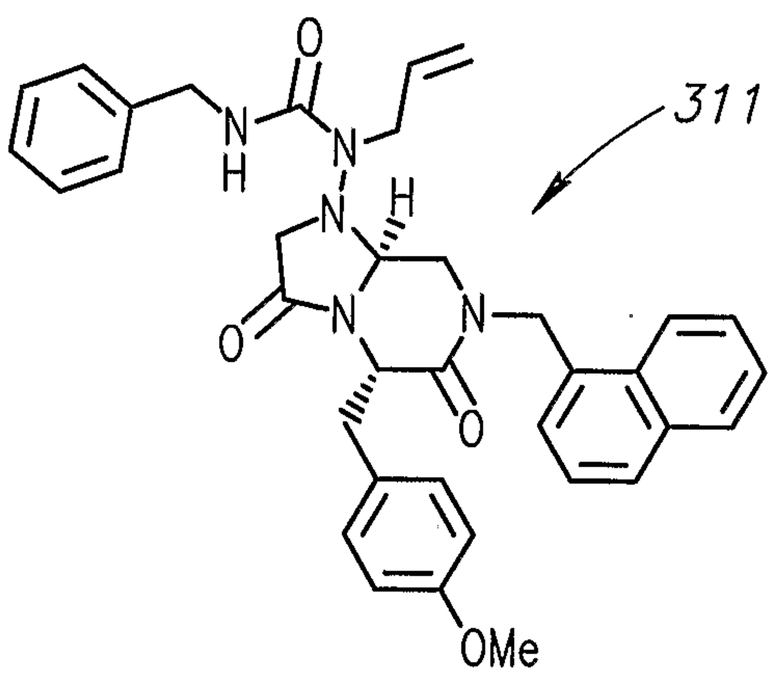
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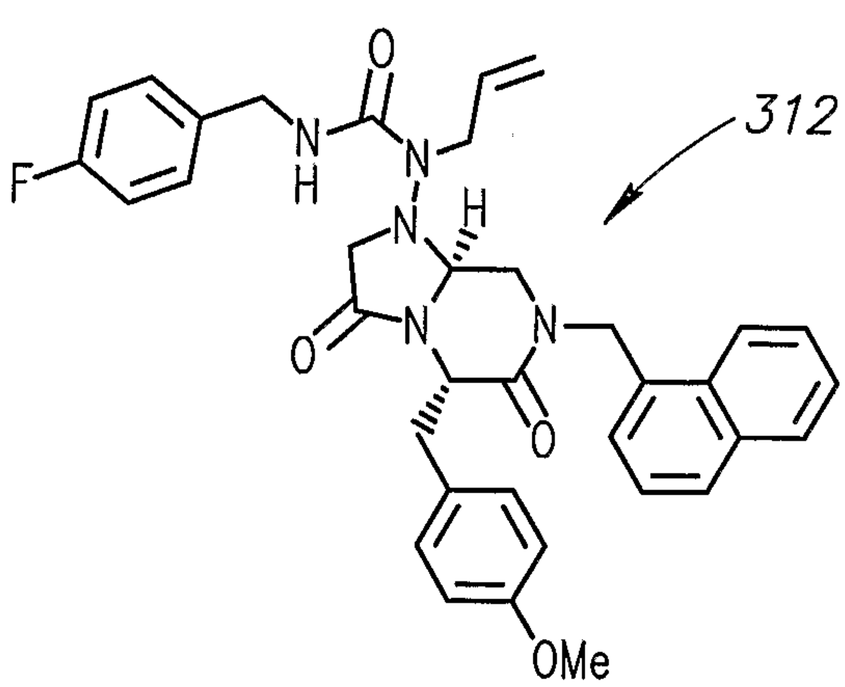
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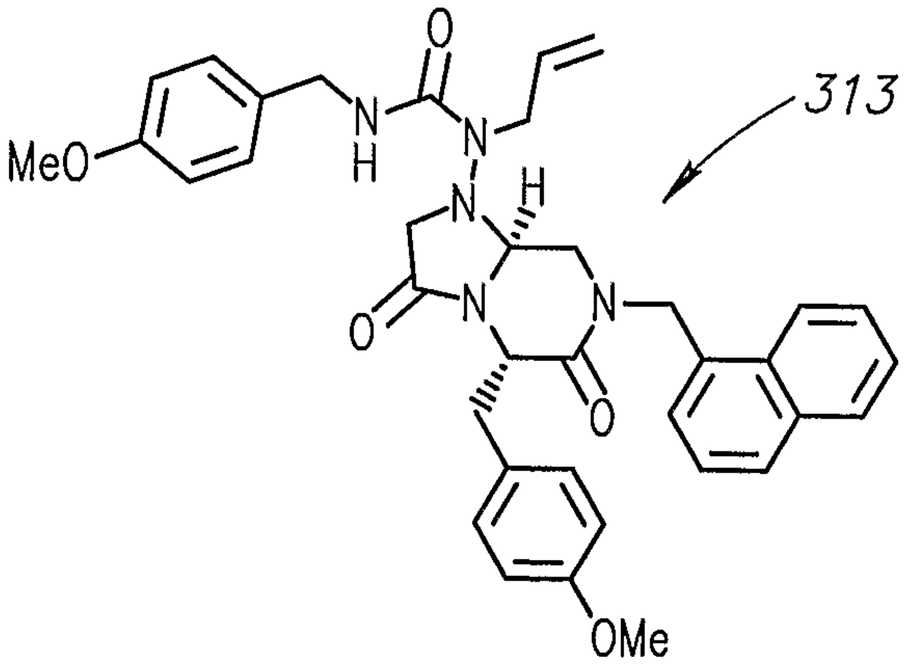
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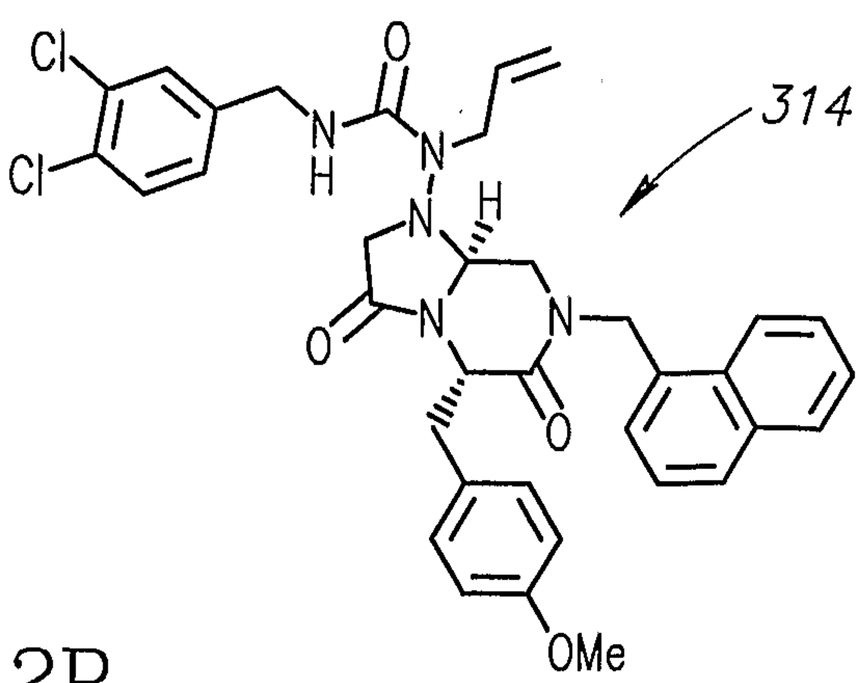
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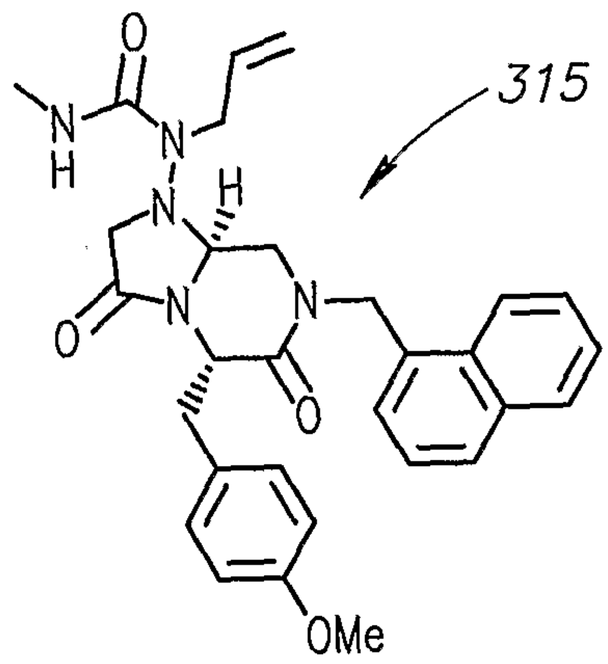
FIG.2P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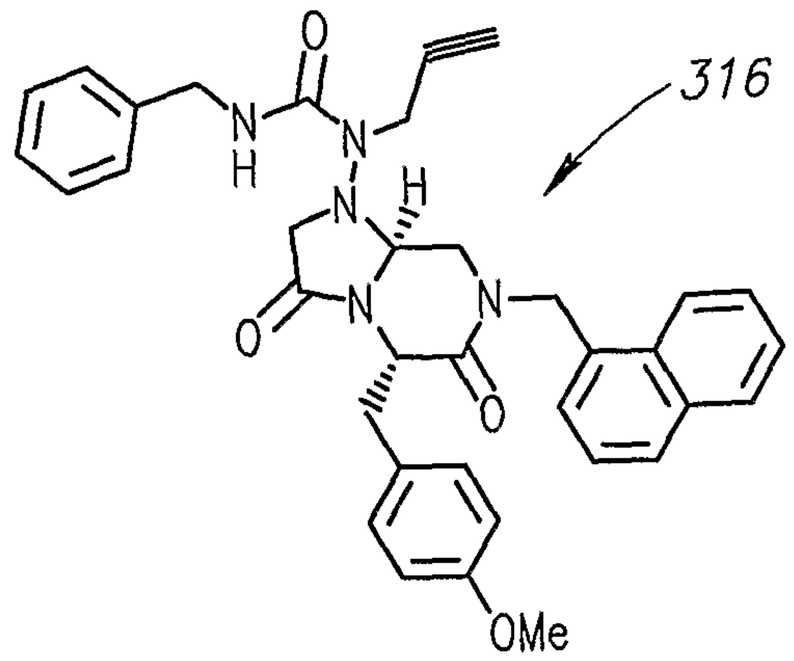
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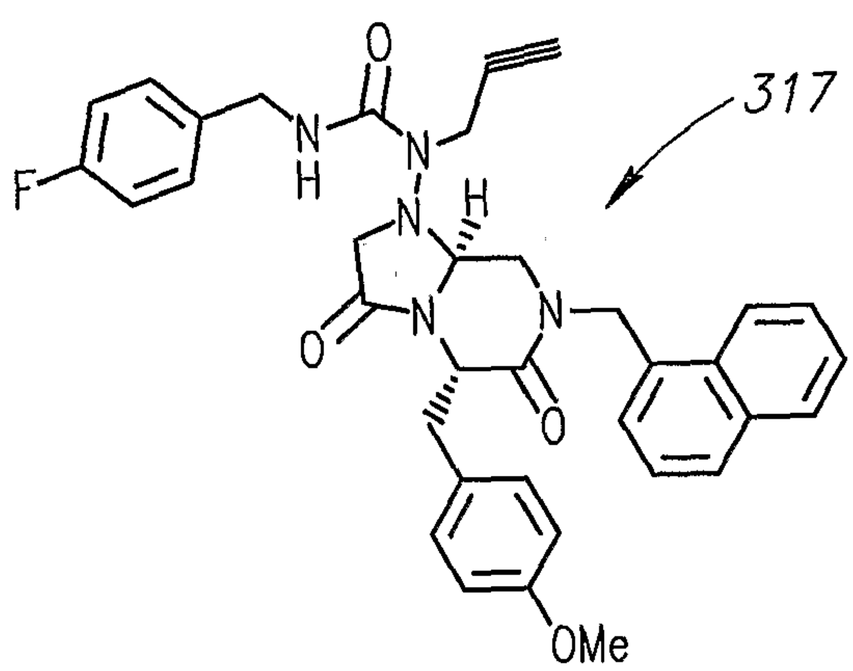
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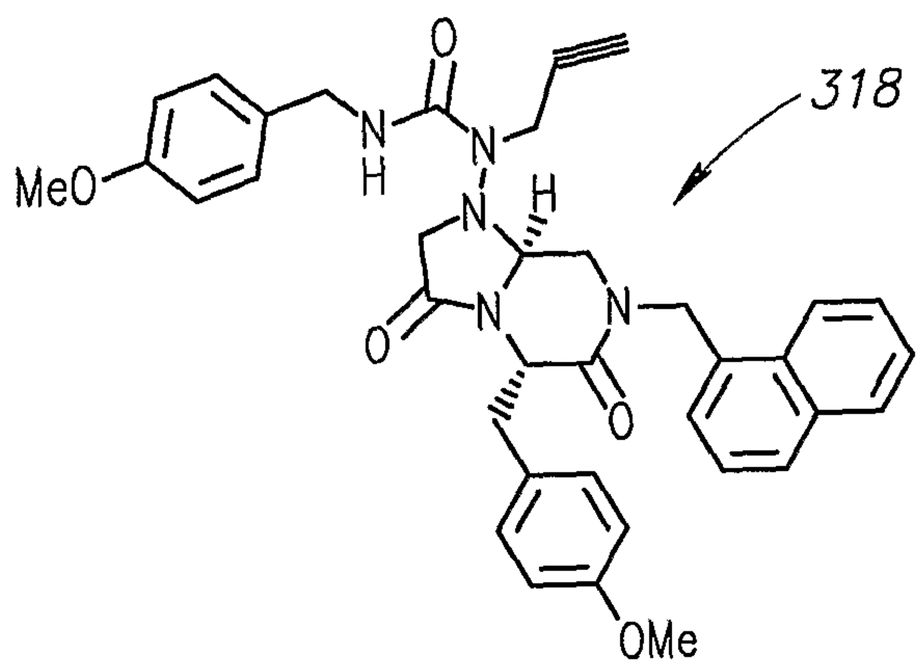
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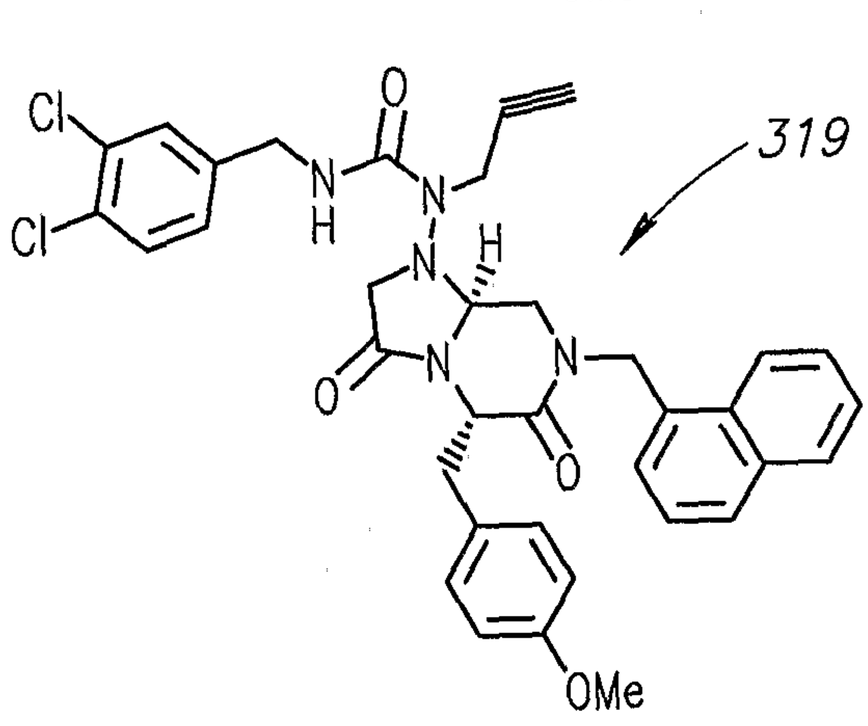
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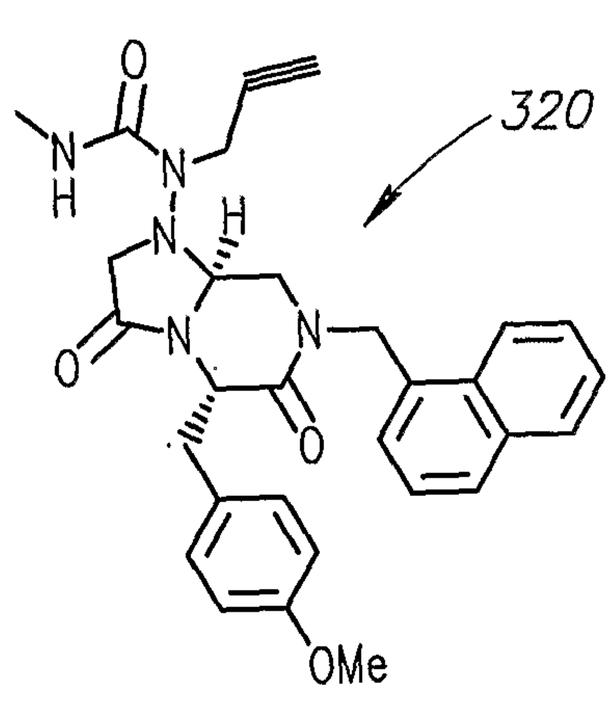
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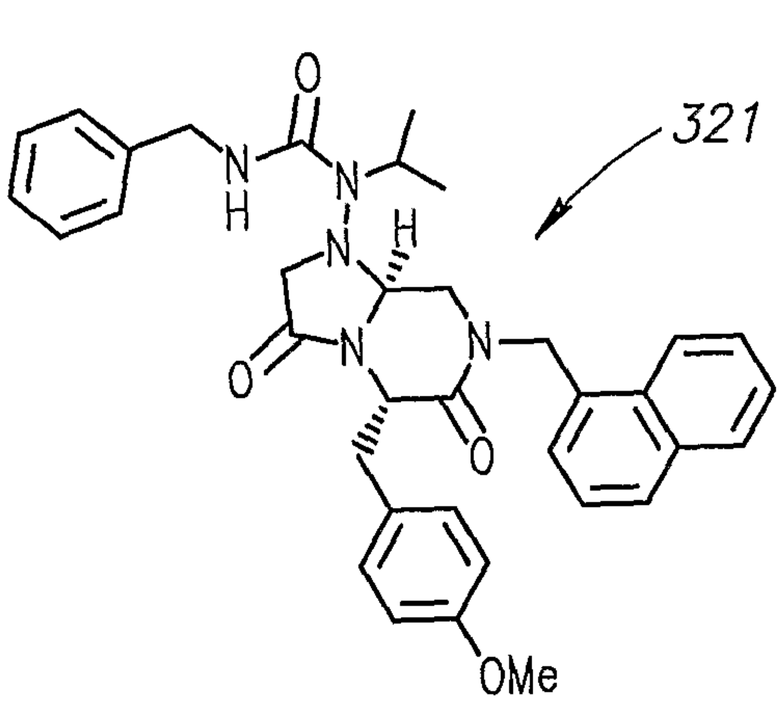
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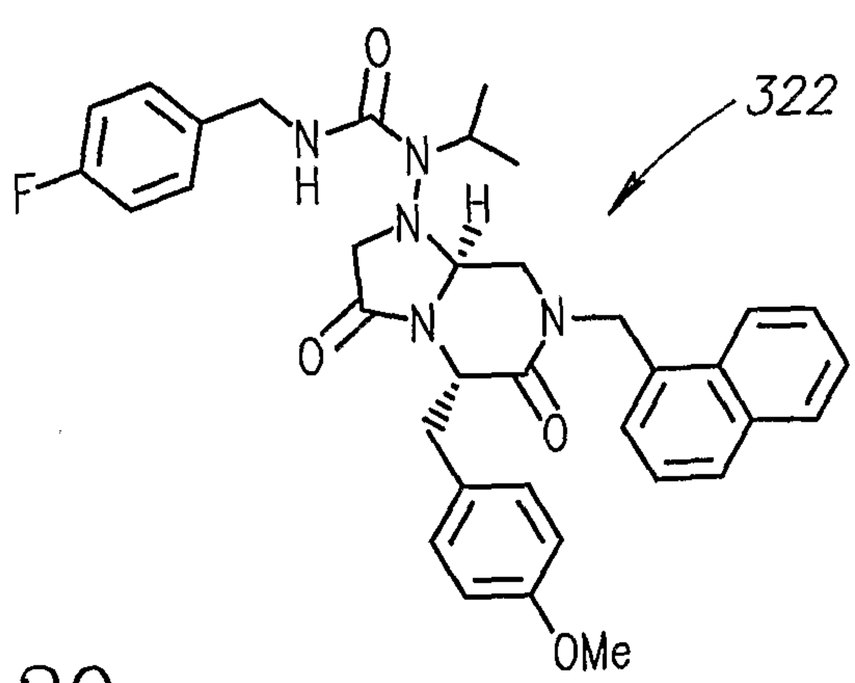
322
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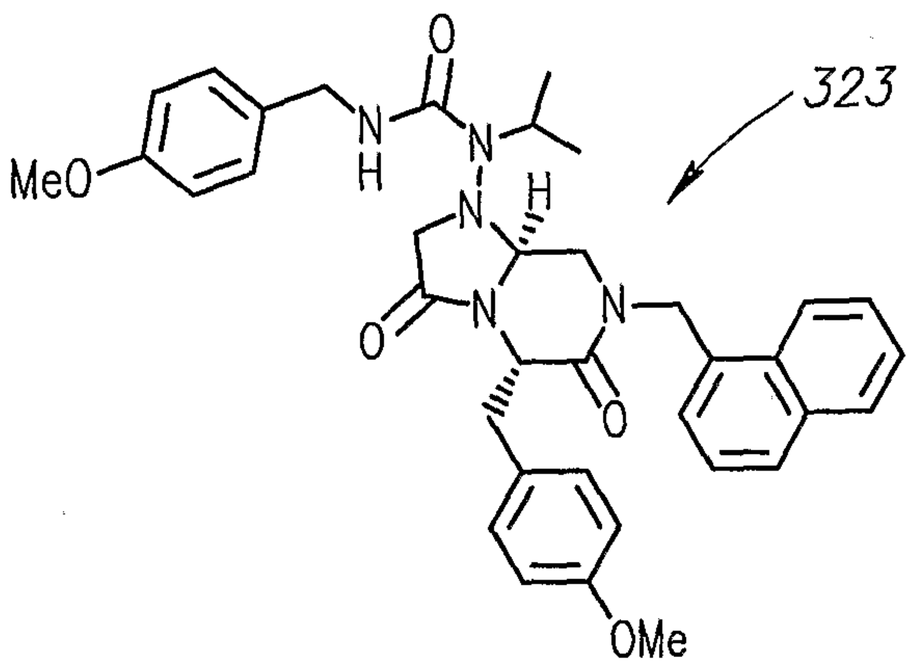
FIG.2Q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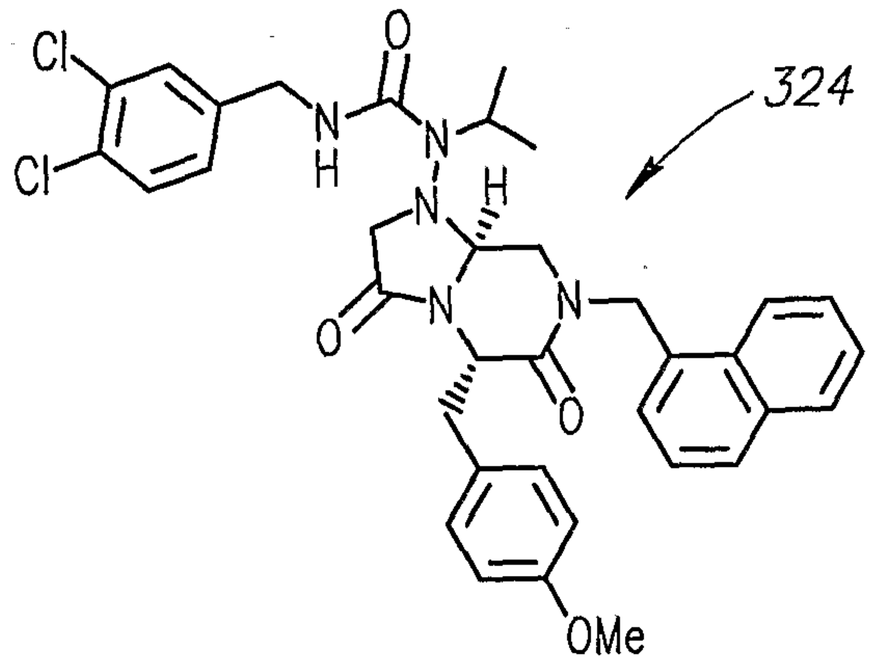
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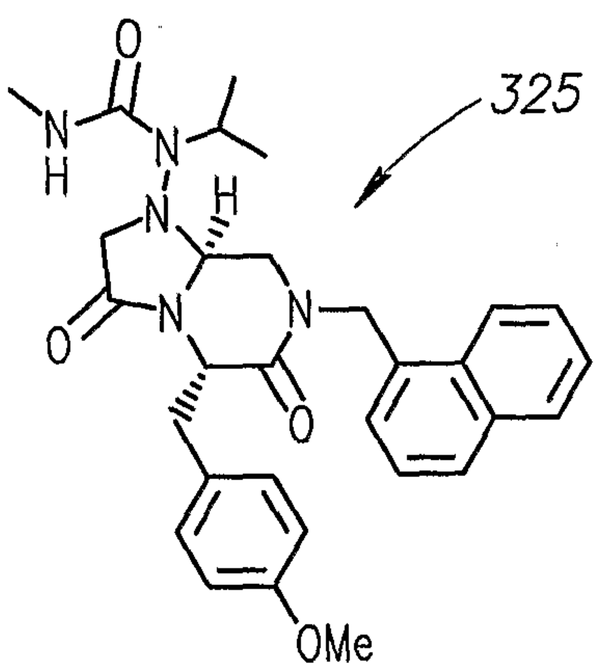
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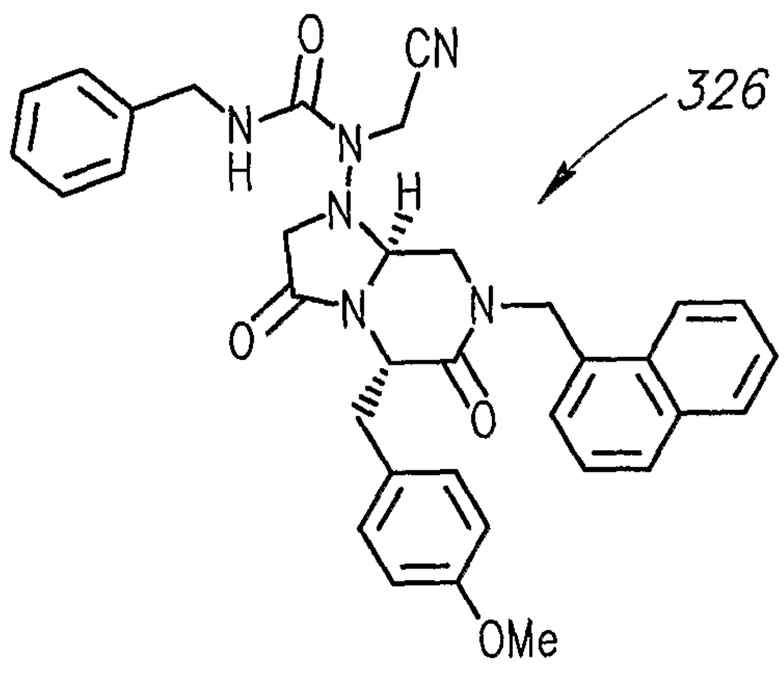
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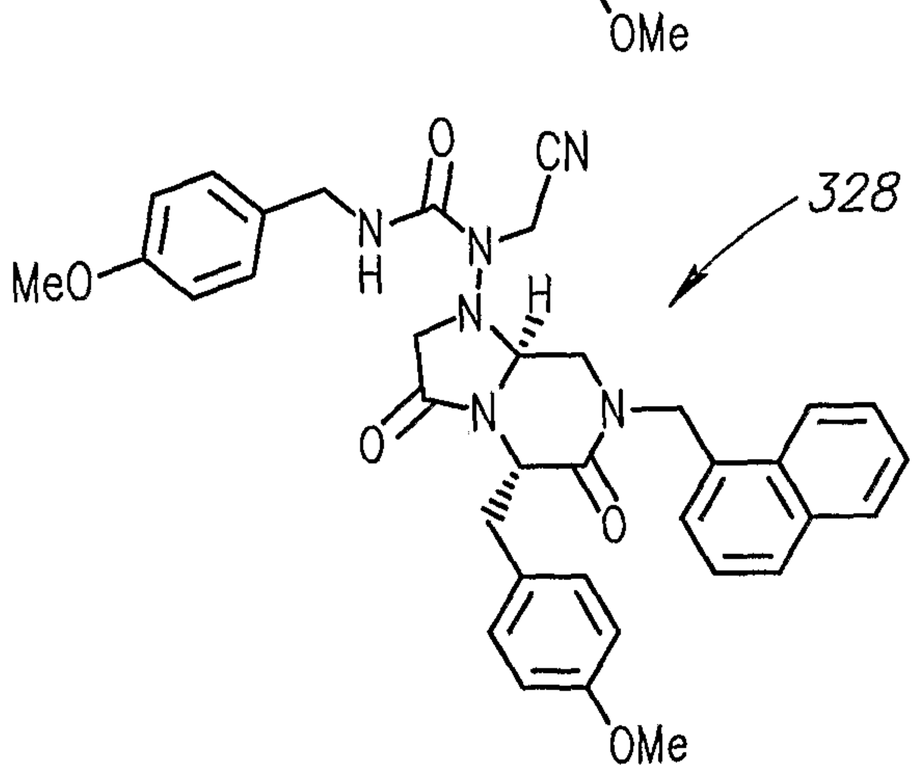
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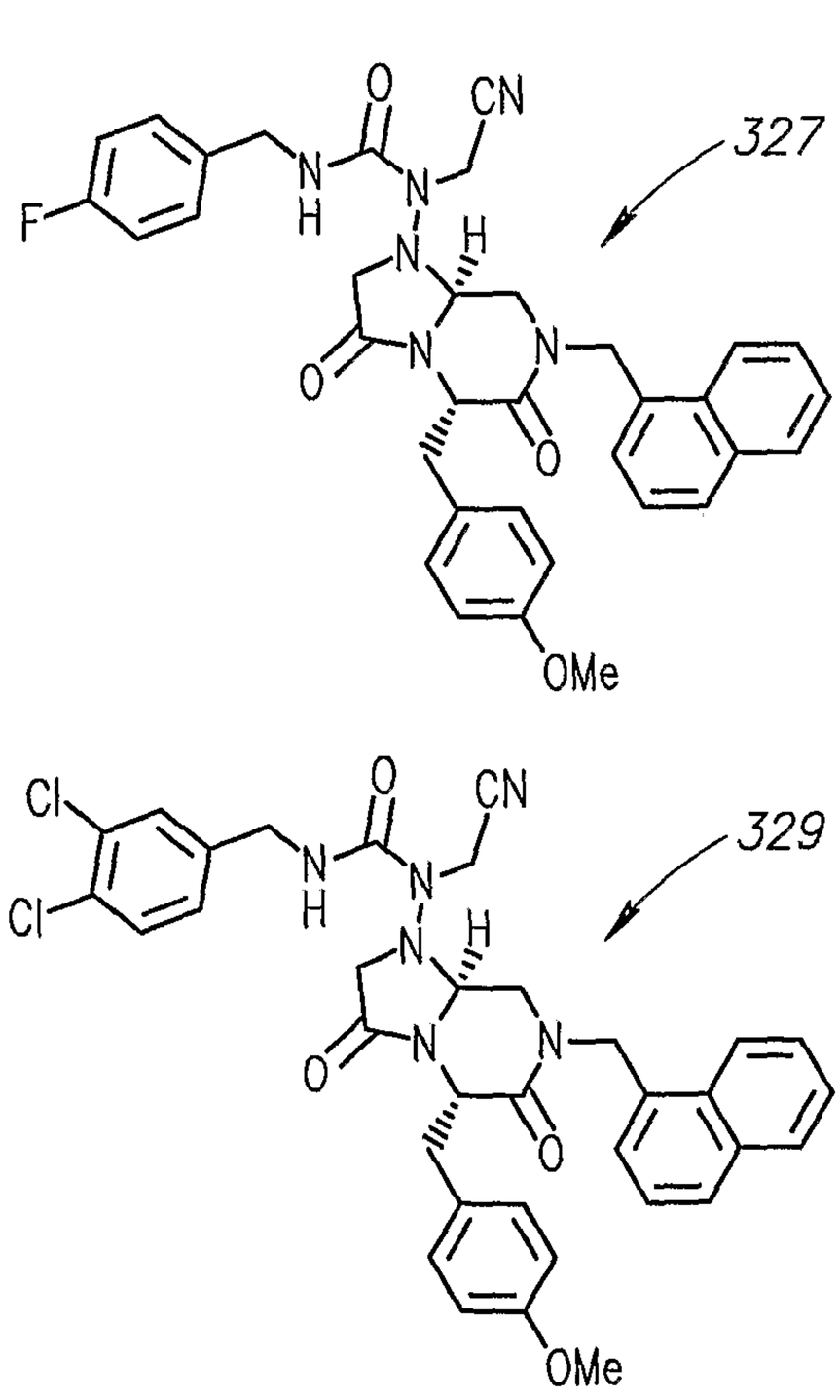
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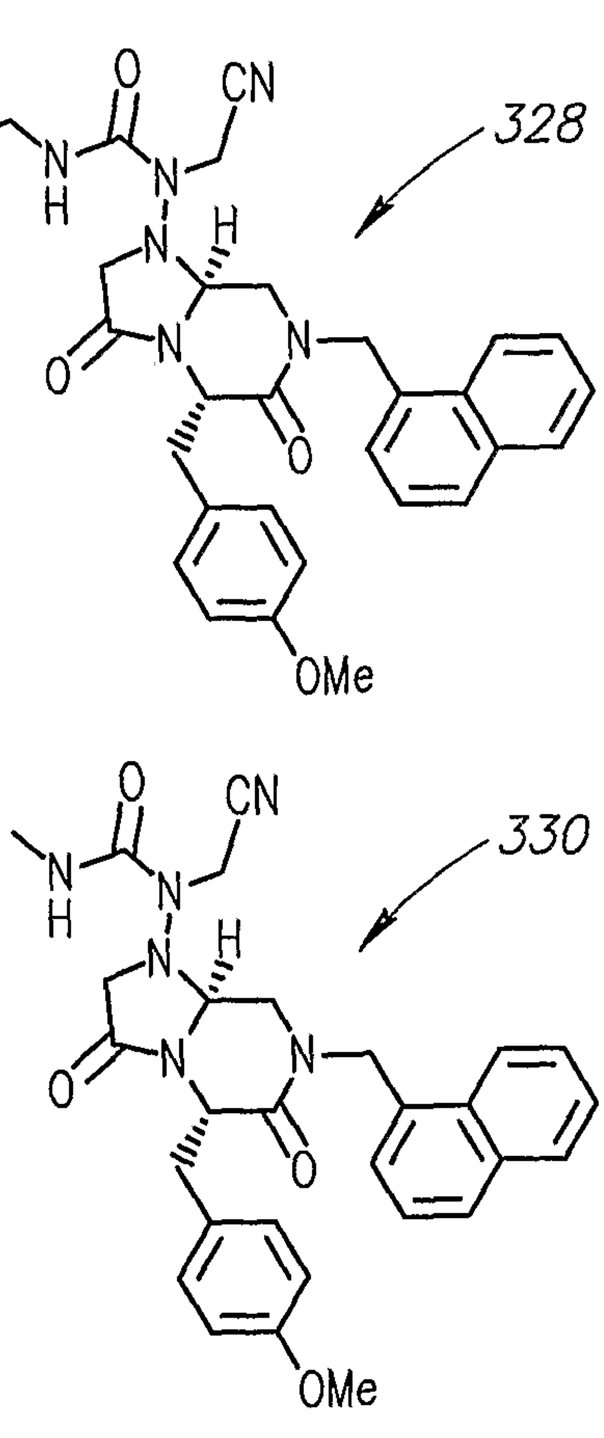
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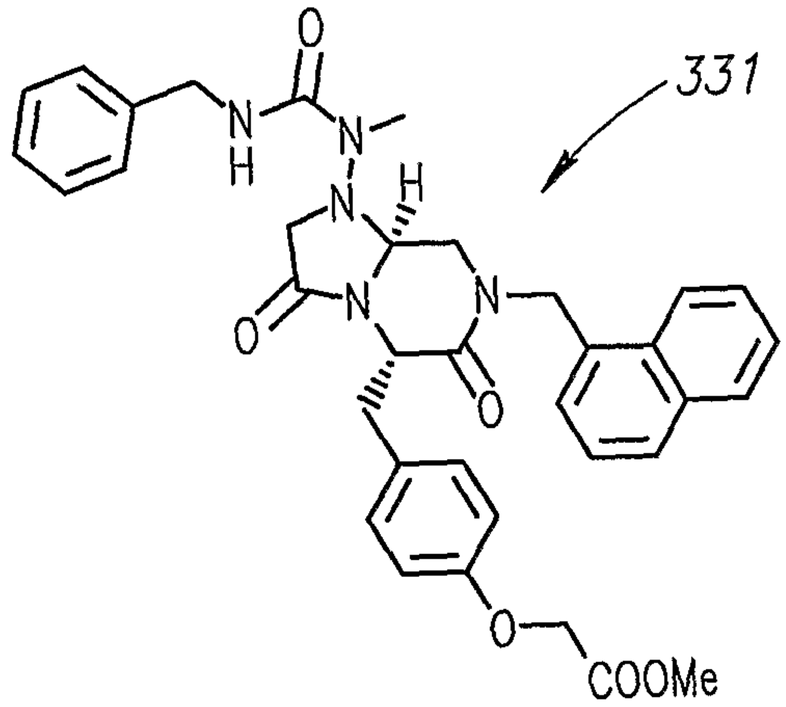
FIG.2R

331



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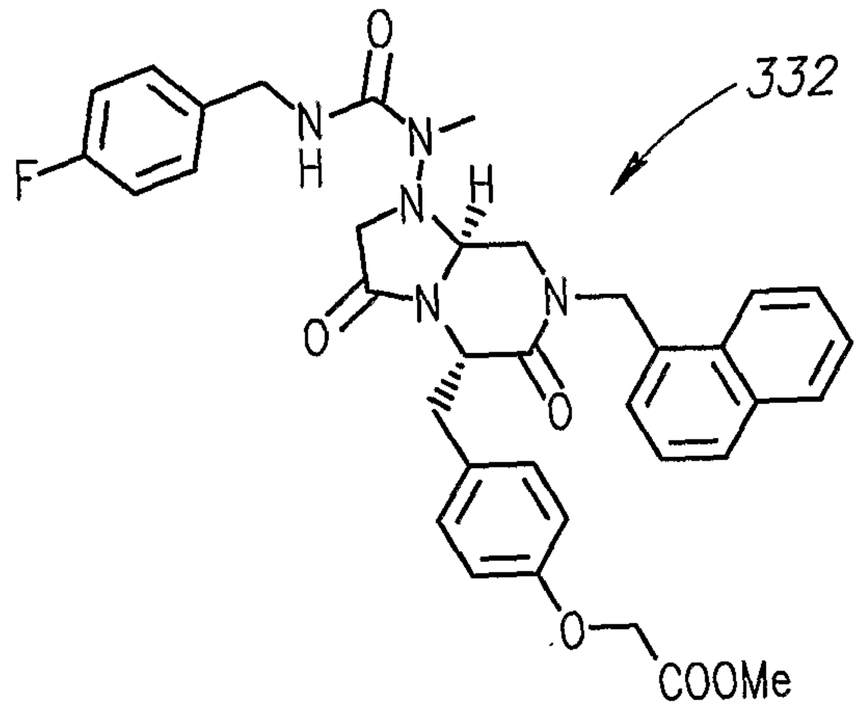

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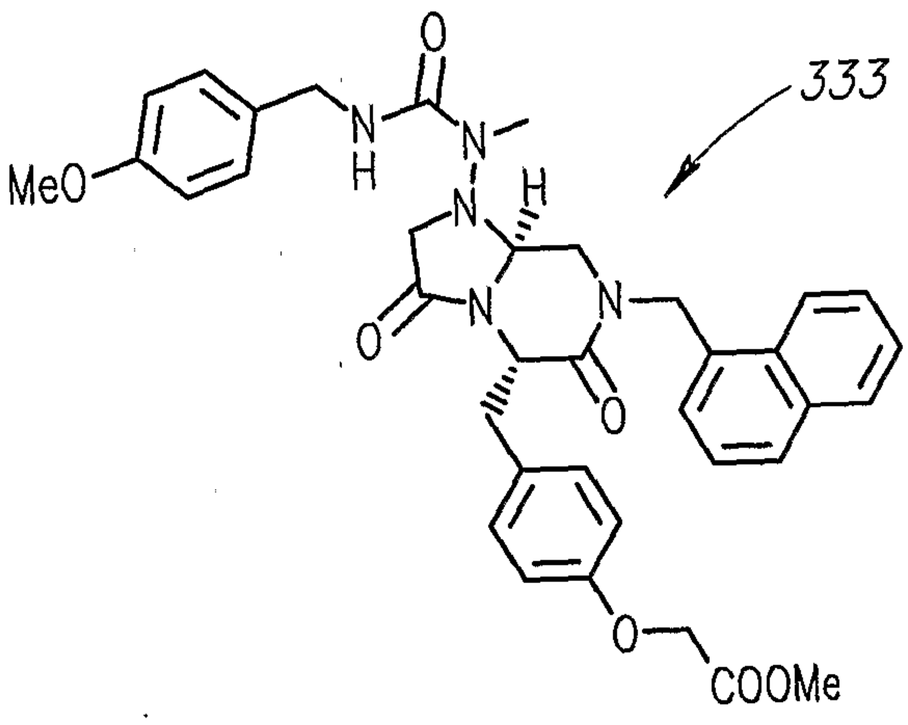

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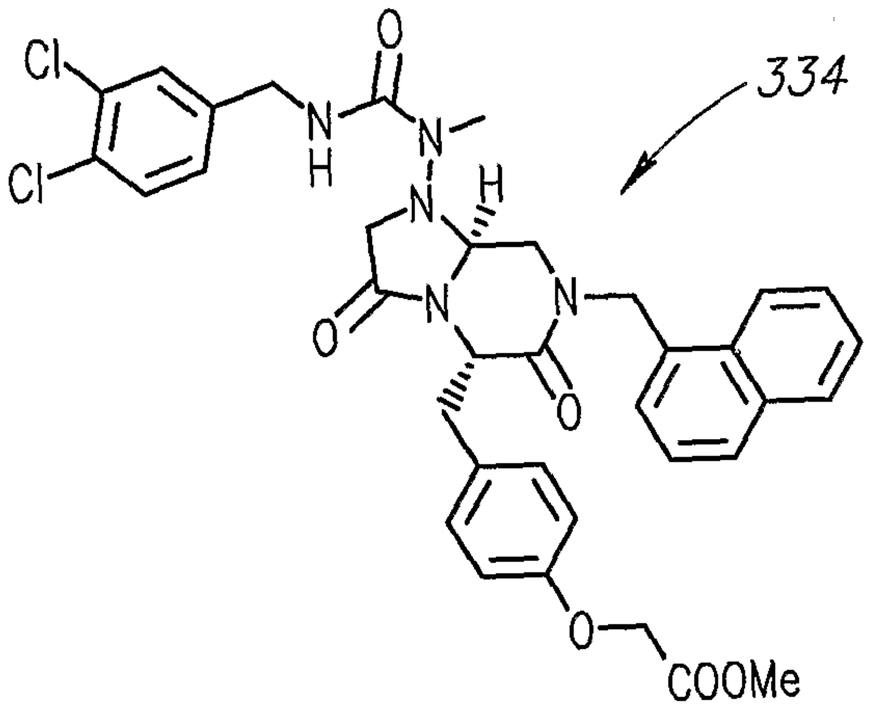

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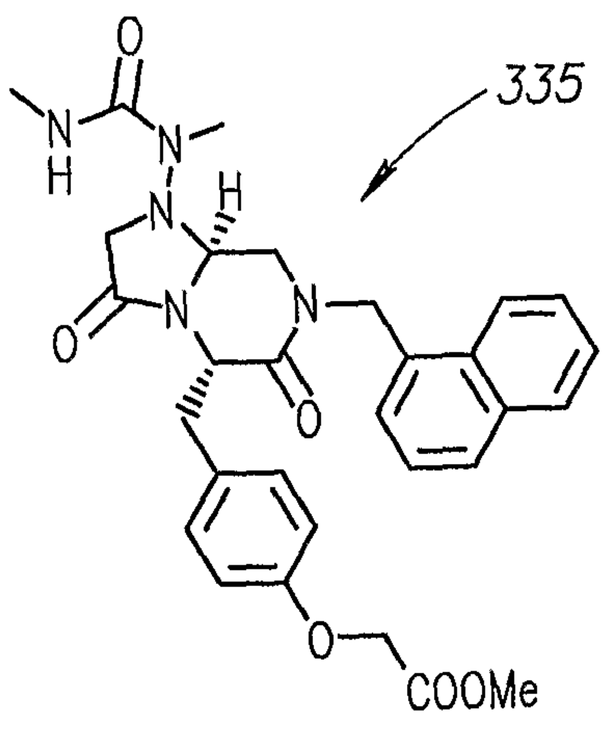

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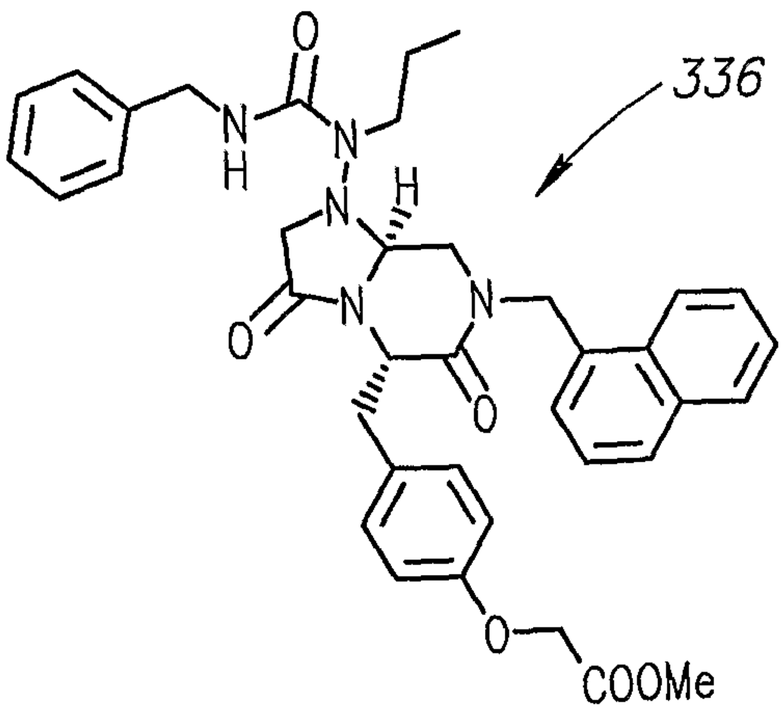
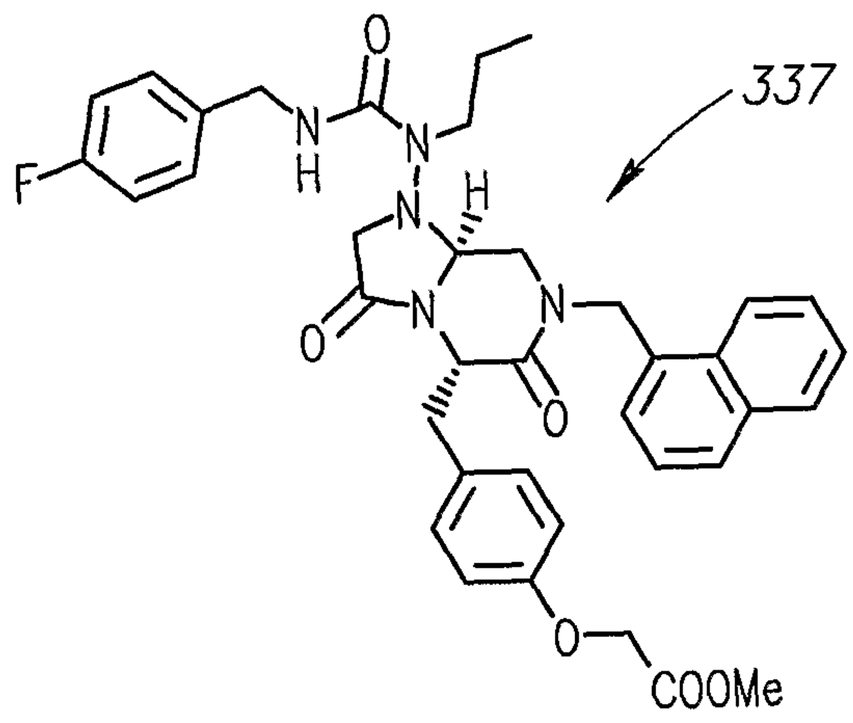


FIG.2S

337



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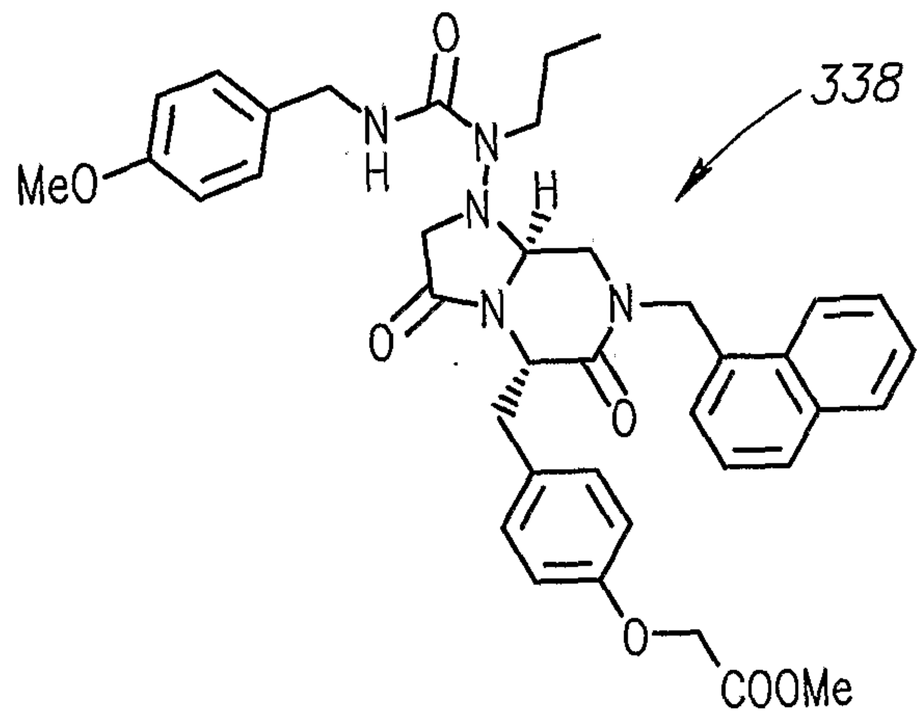

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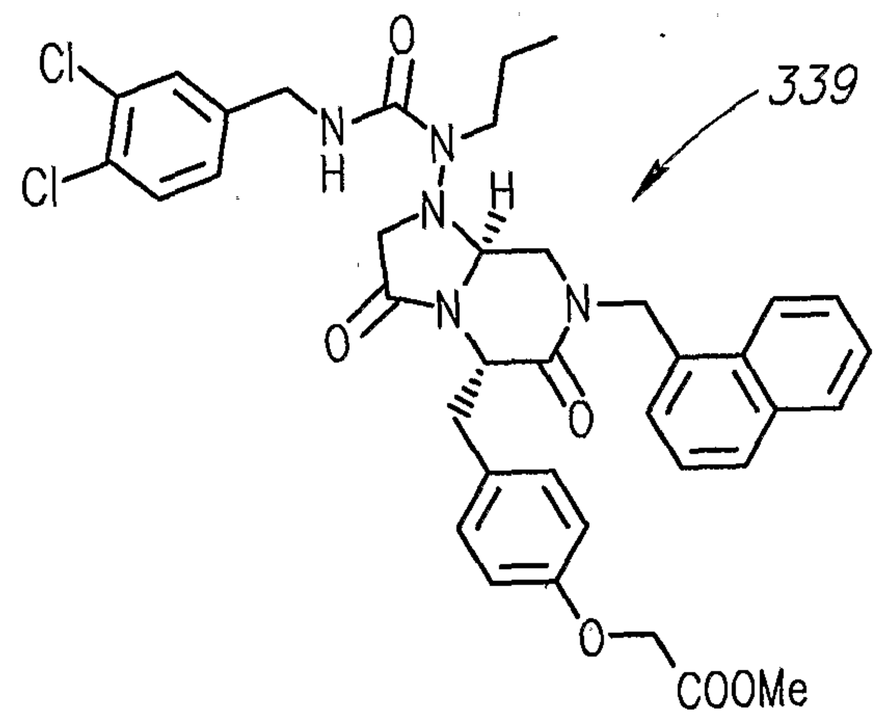

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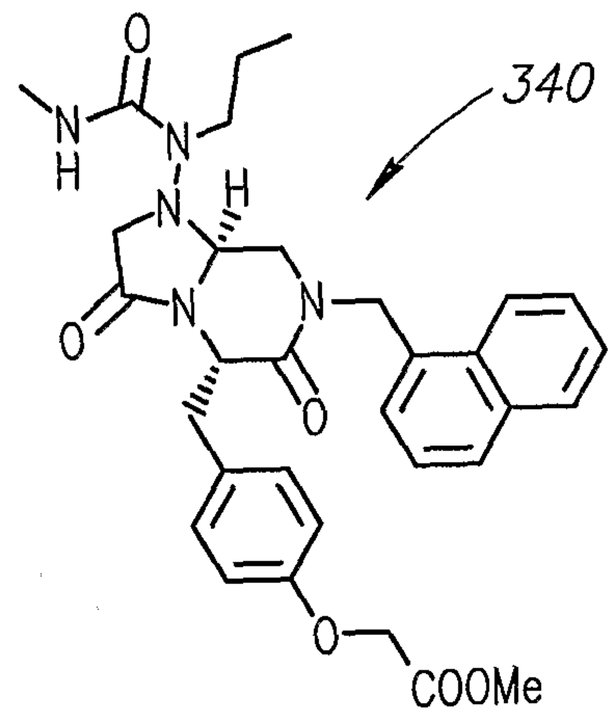

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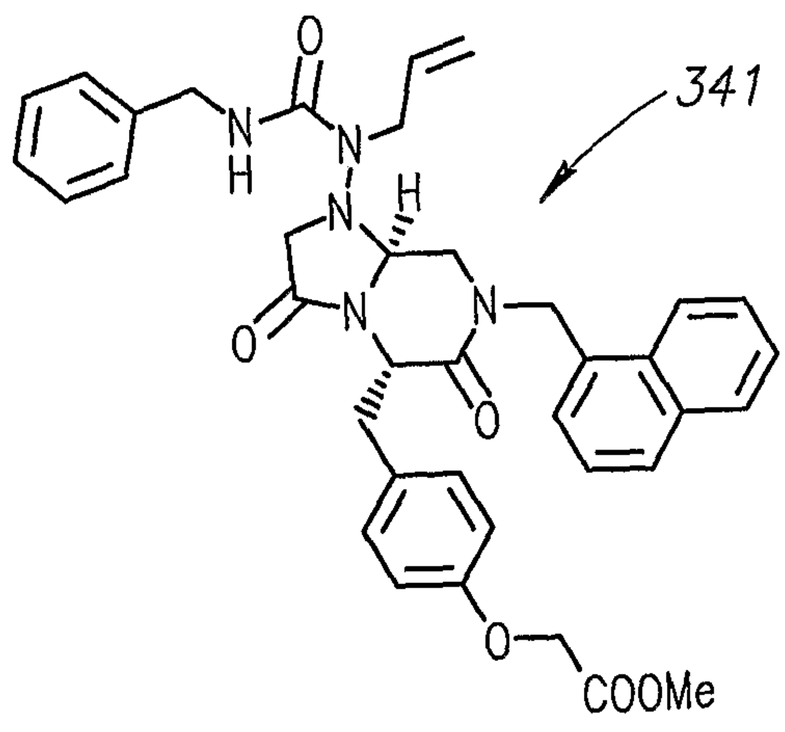

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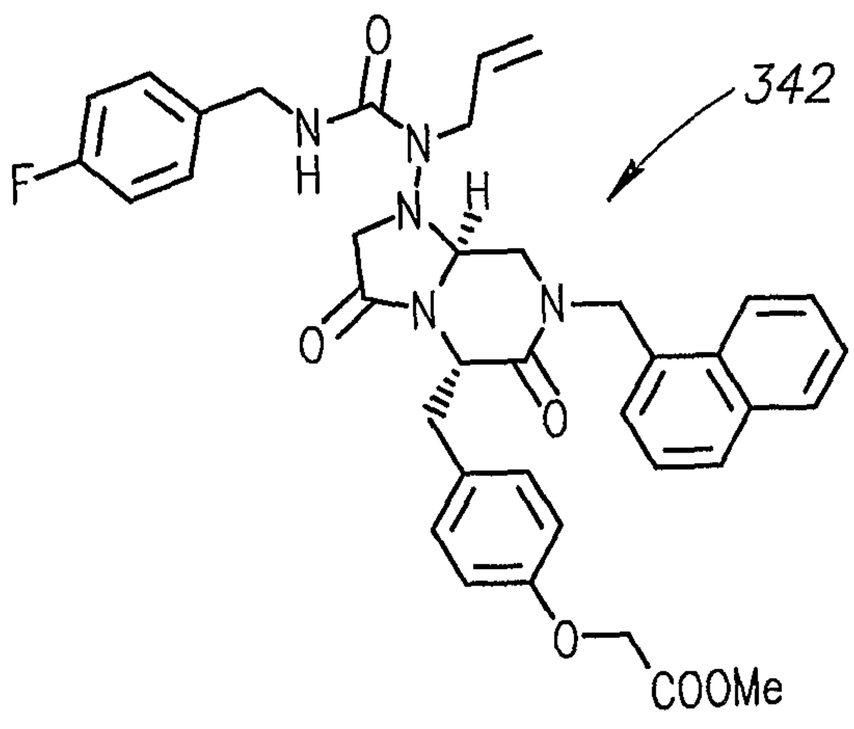
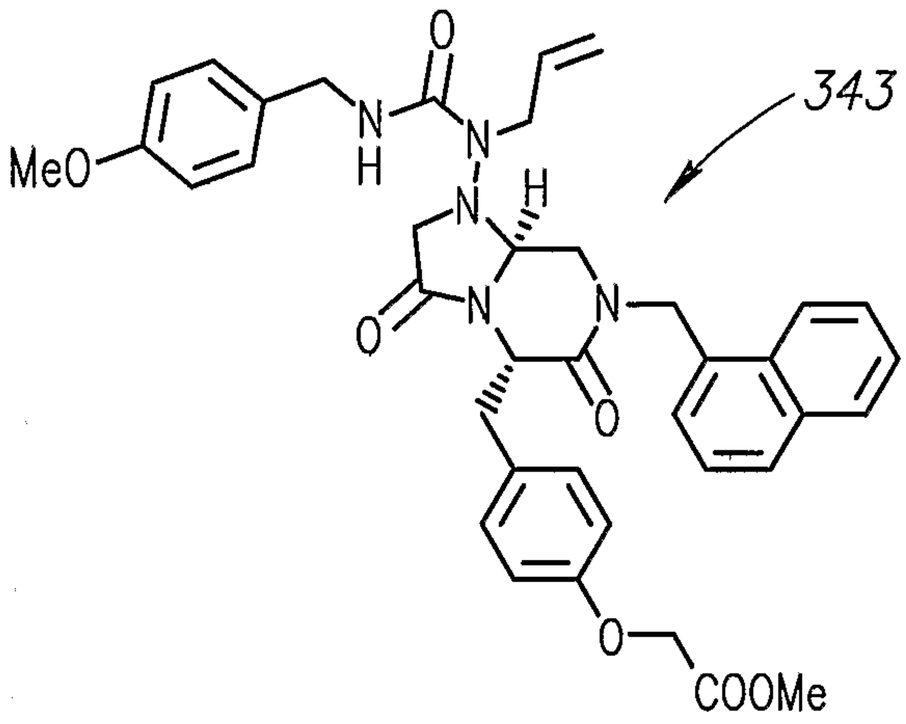


FIG.2T



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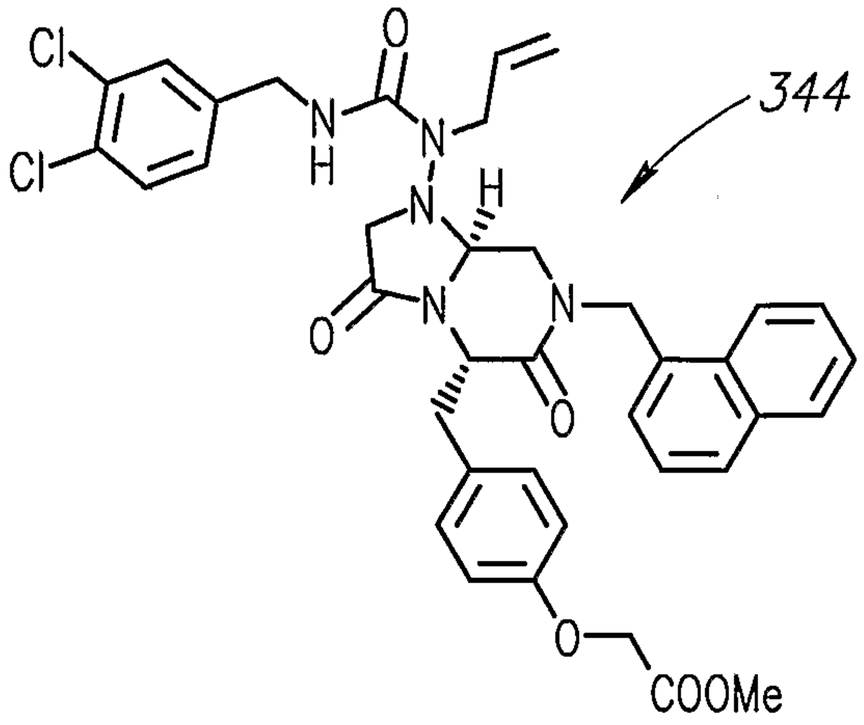
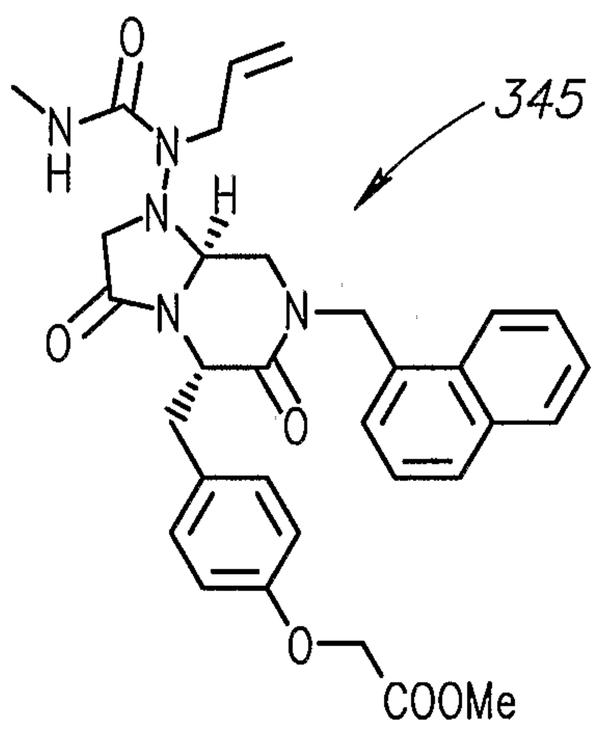


344



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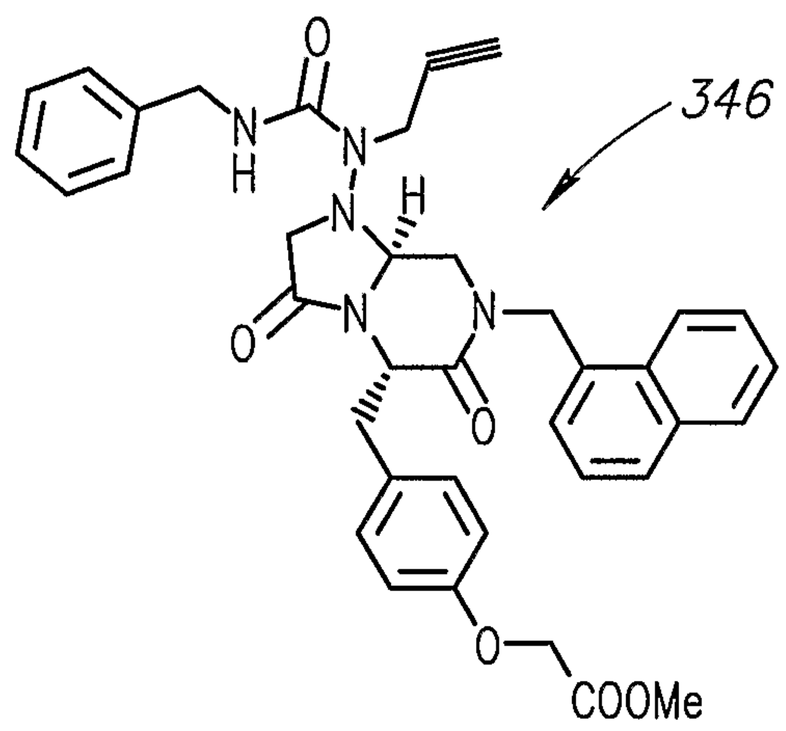
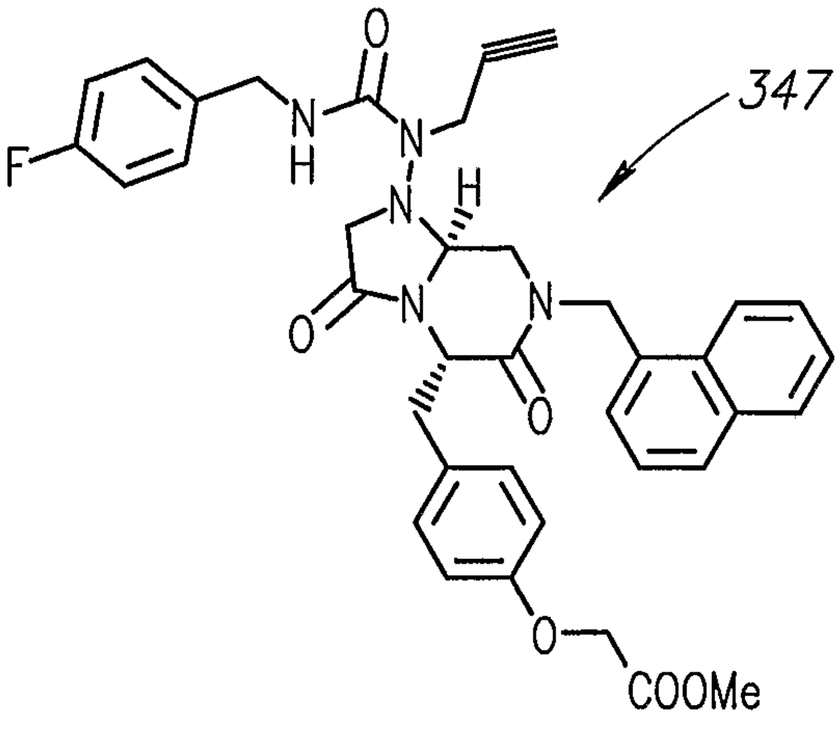
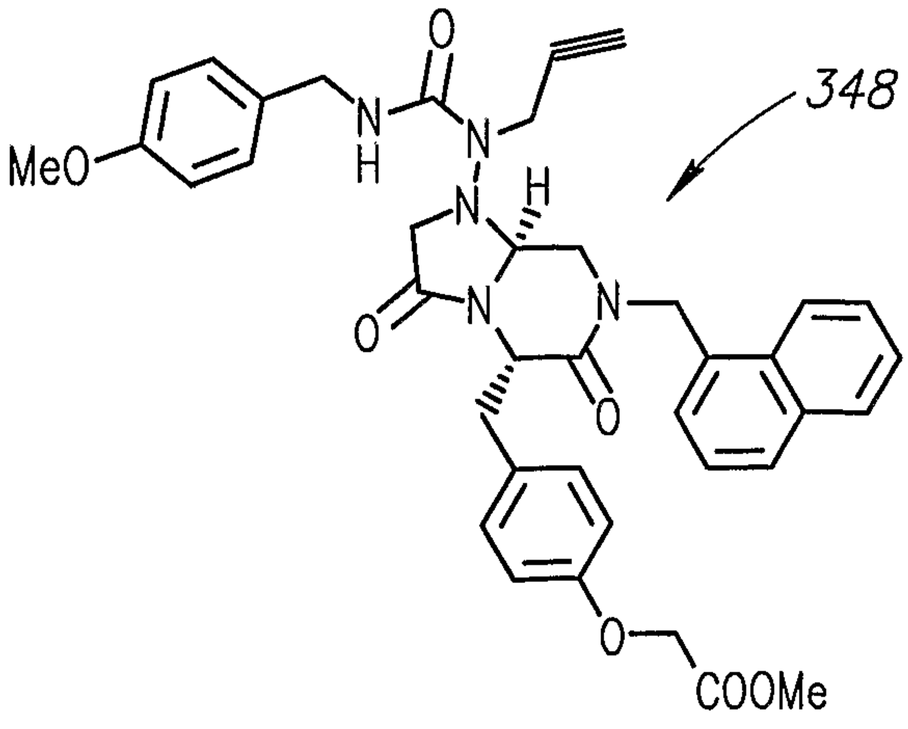


346

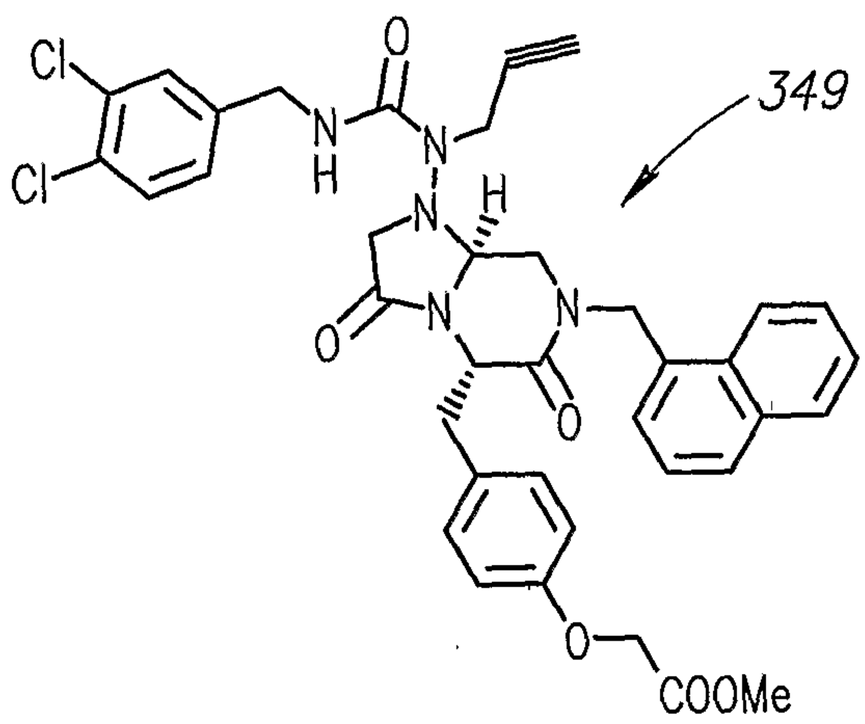


347



348

FIG.2U



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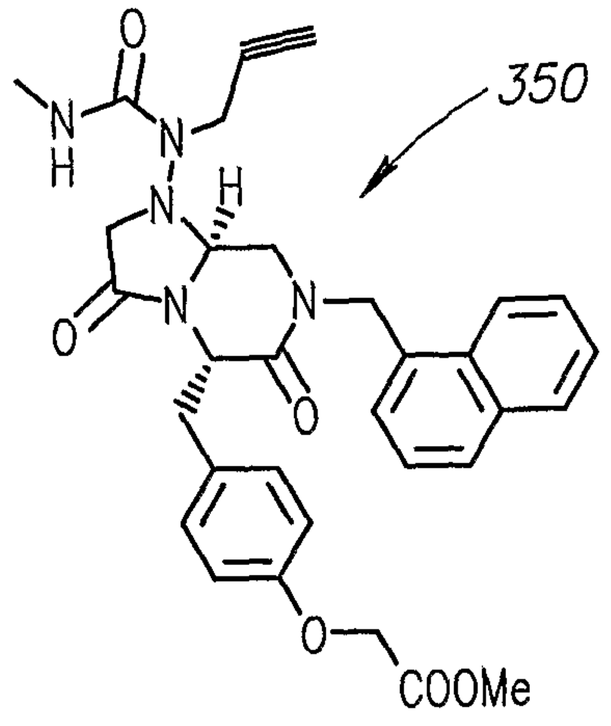

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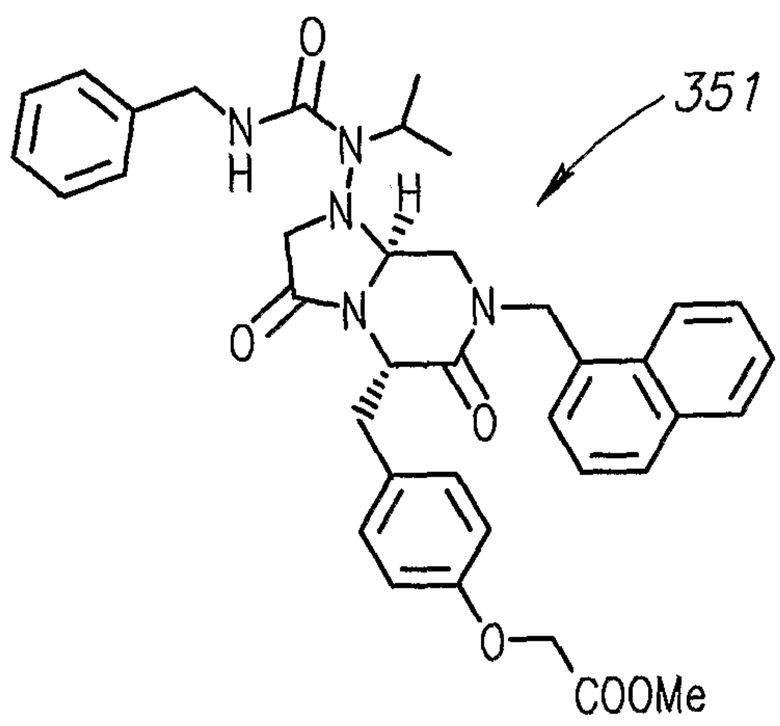

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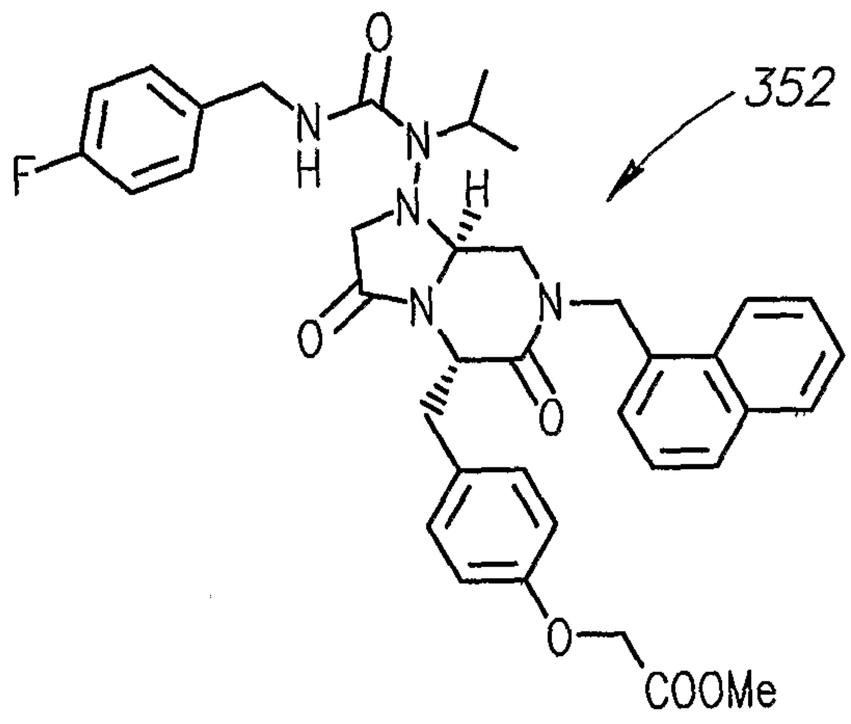

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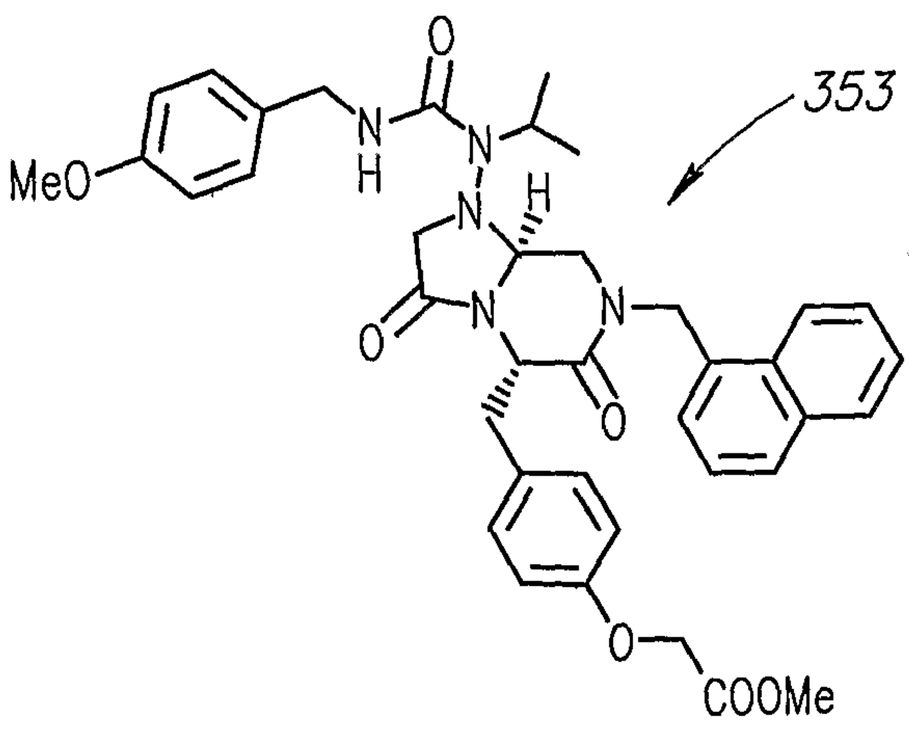

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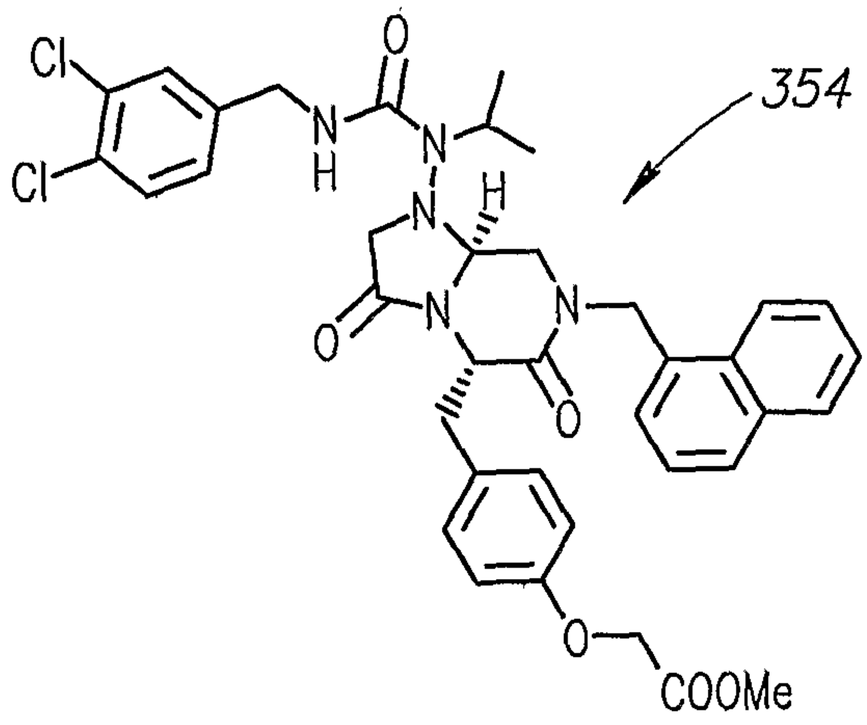
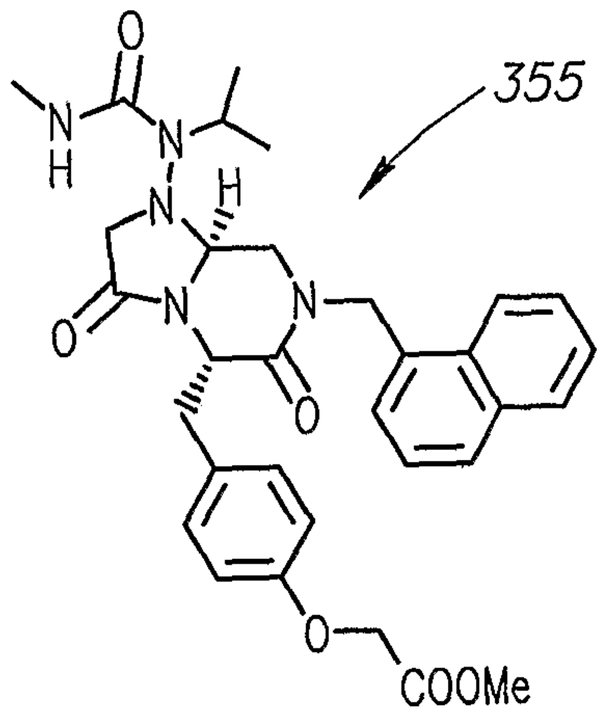


354

FIG.2V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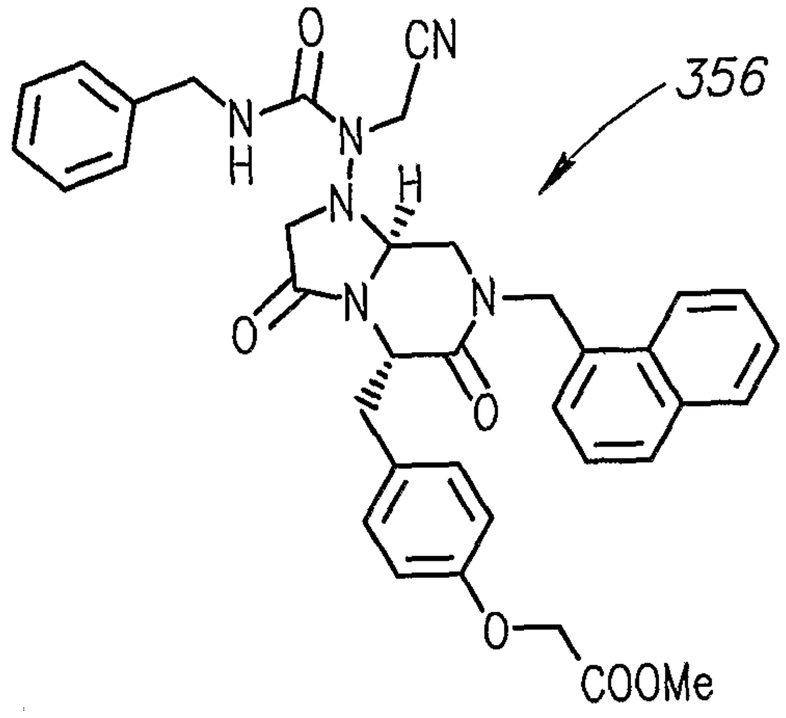
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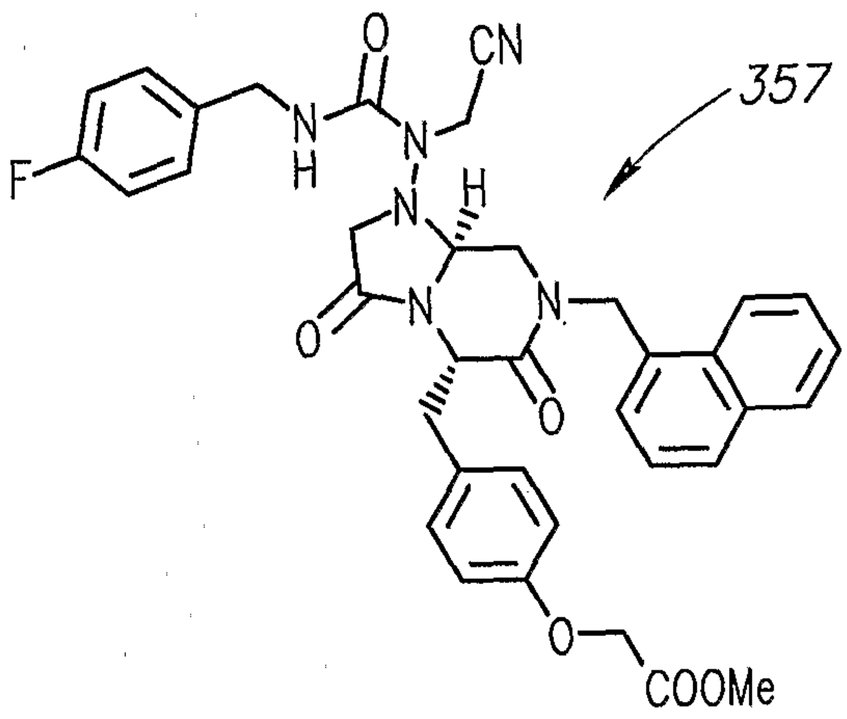
COOMe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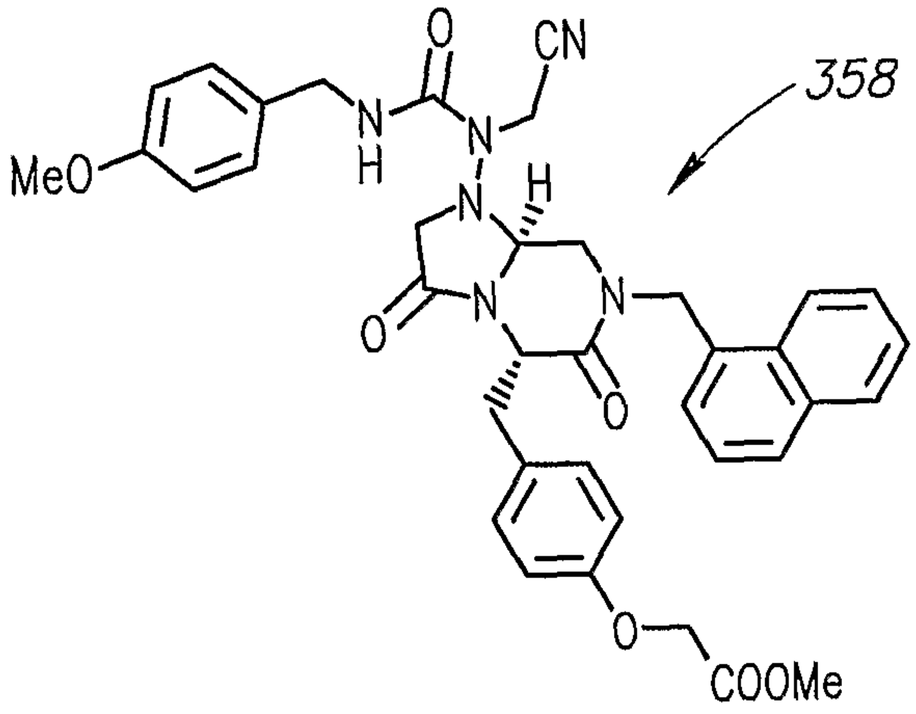
358
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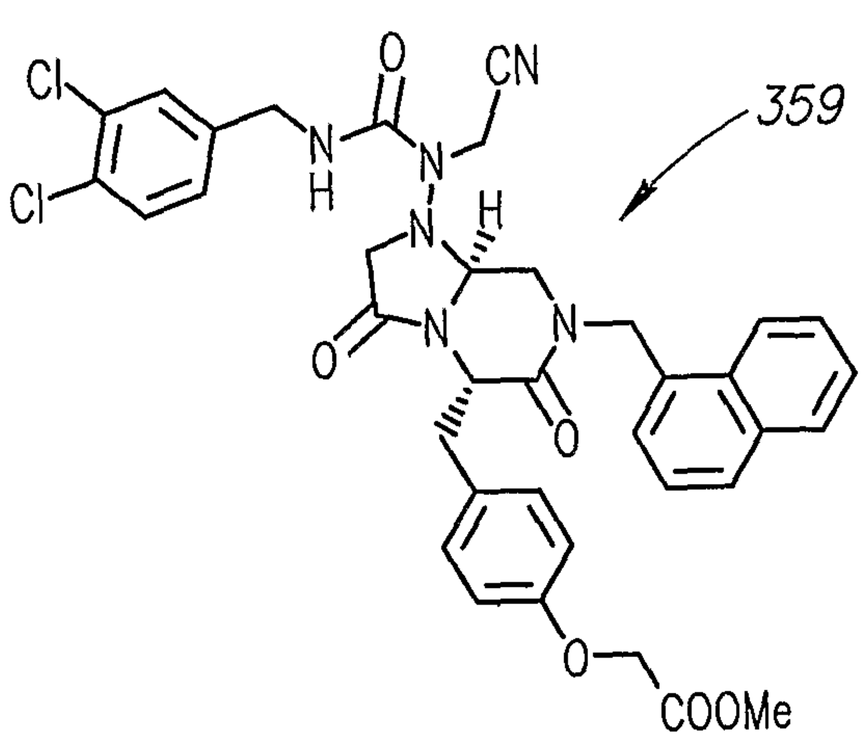
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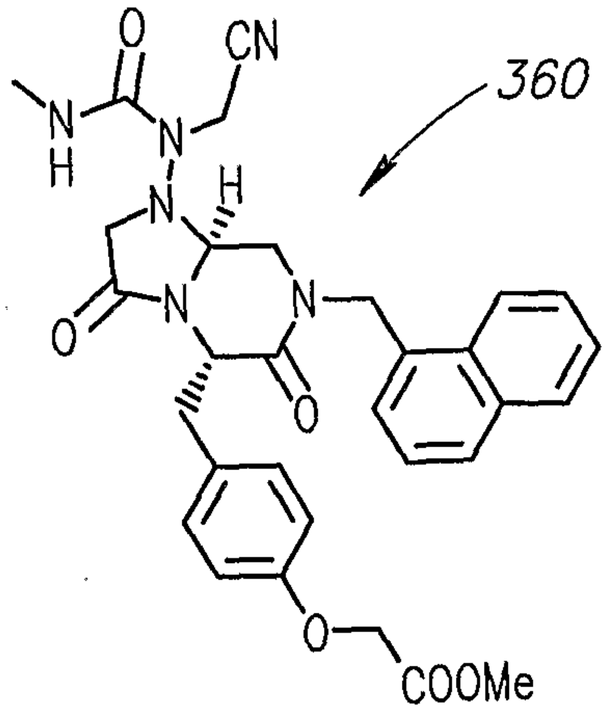
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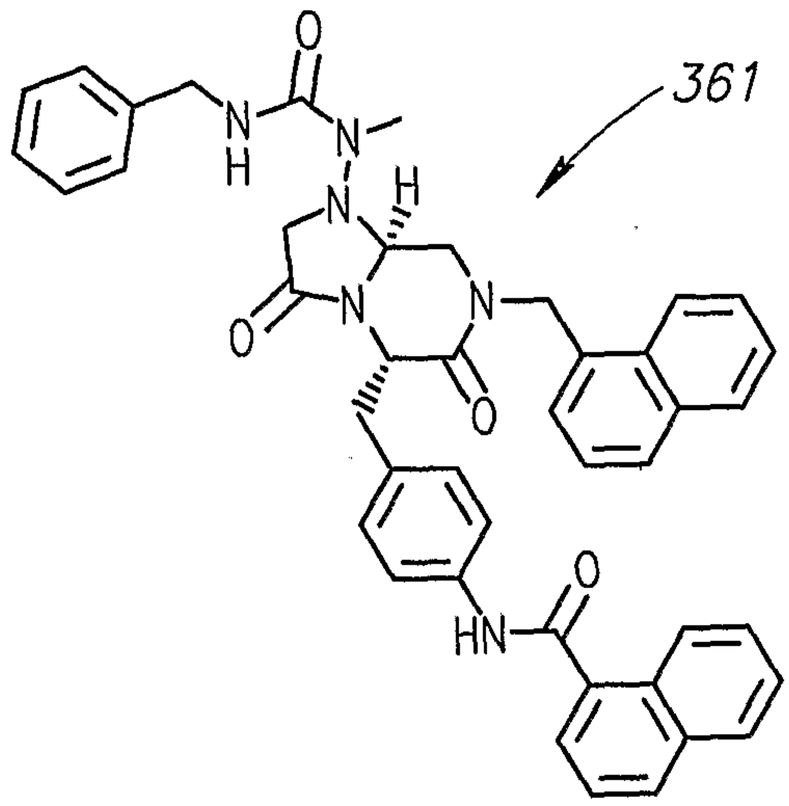
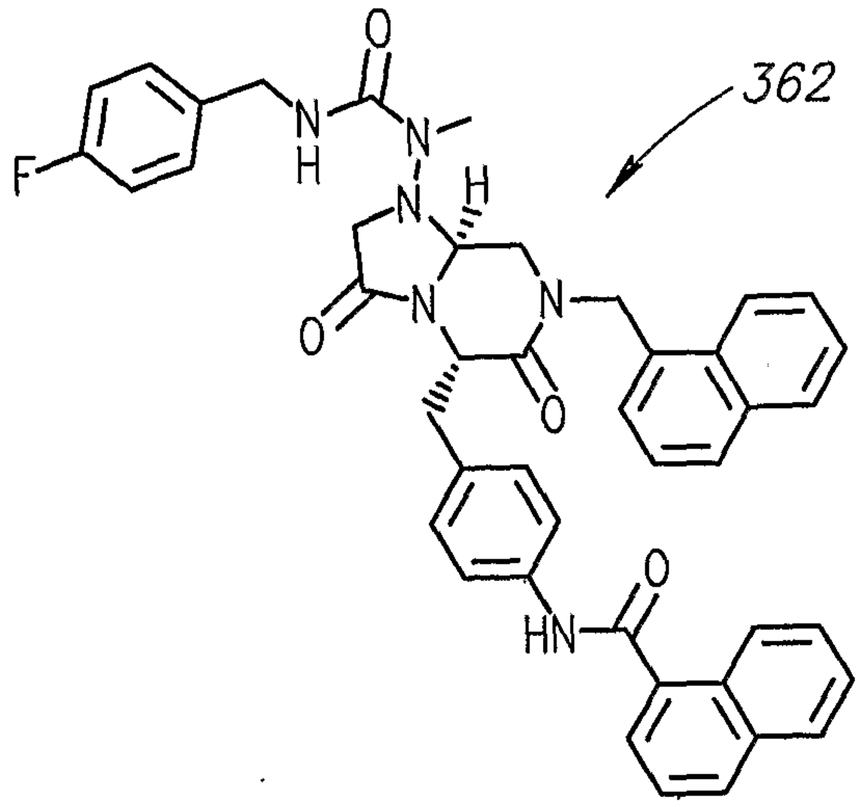
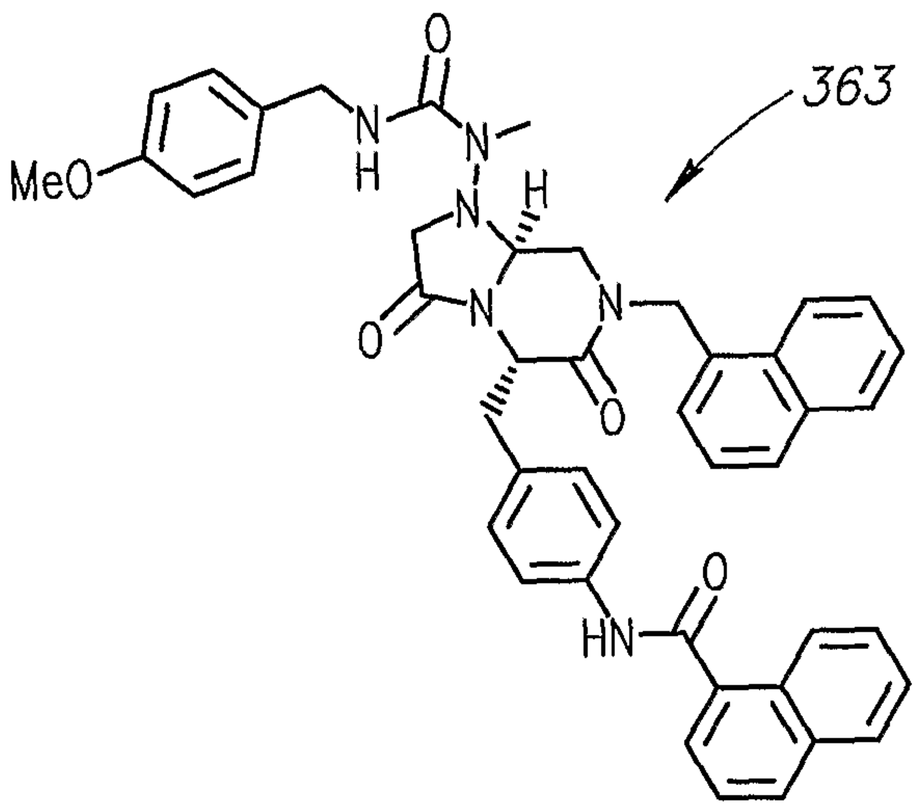
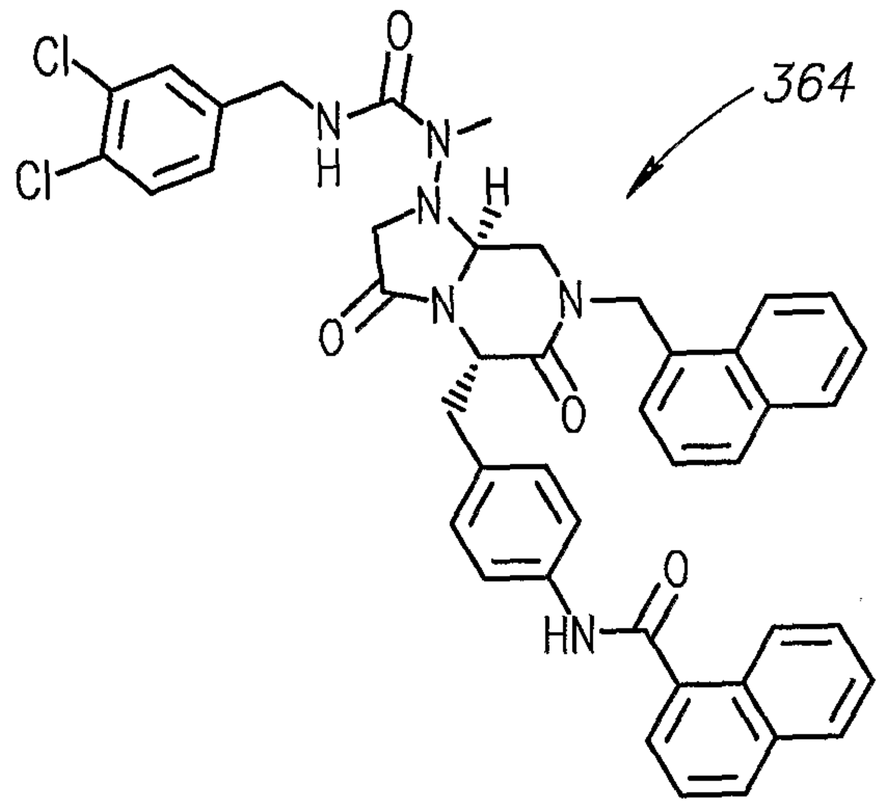
COOMe

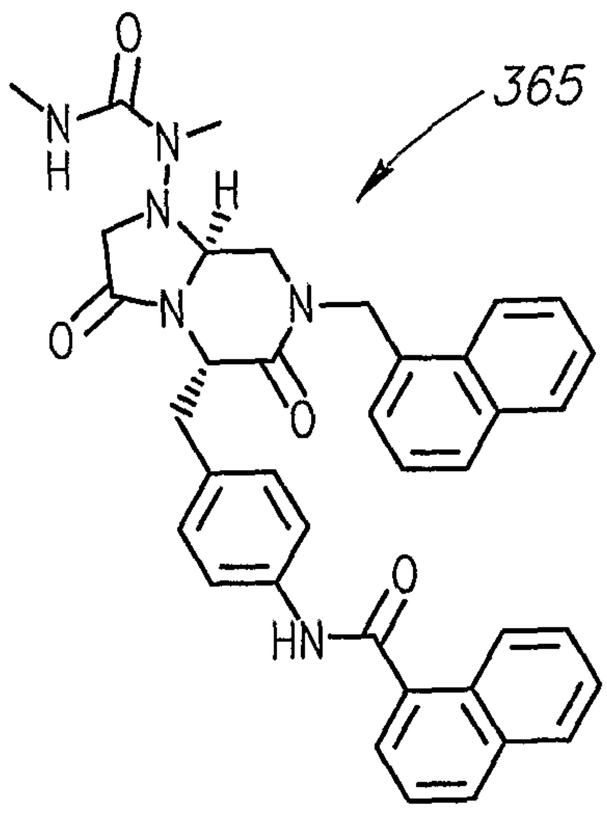
FIG.2W











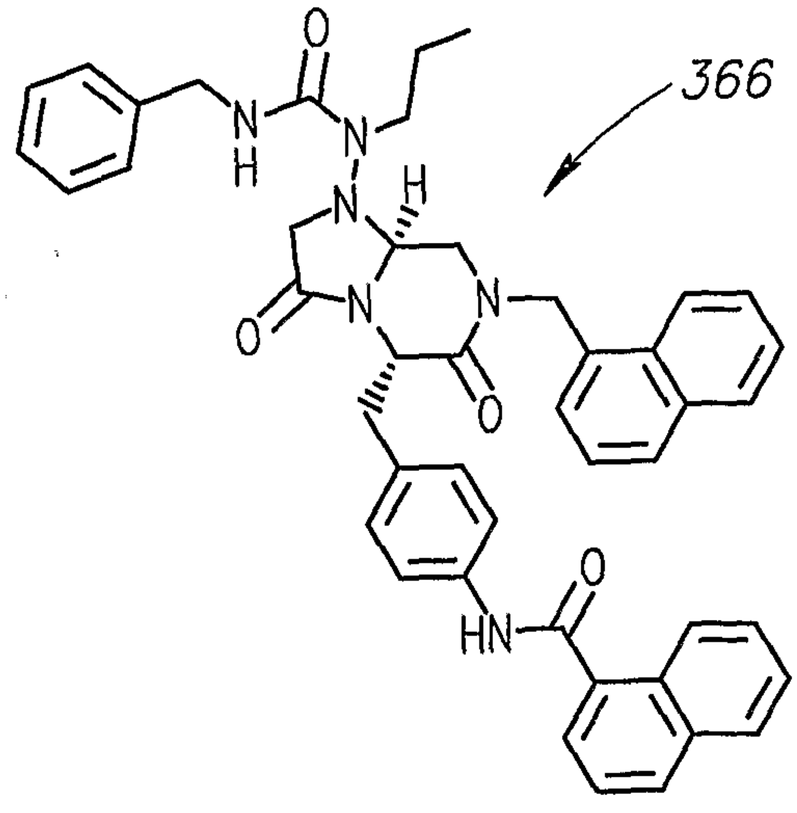
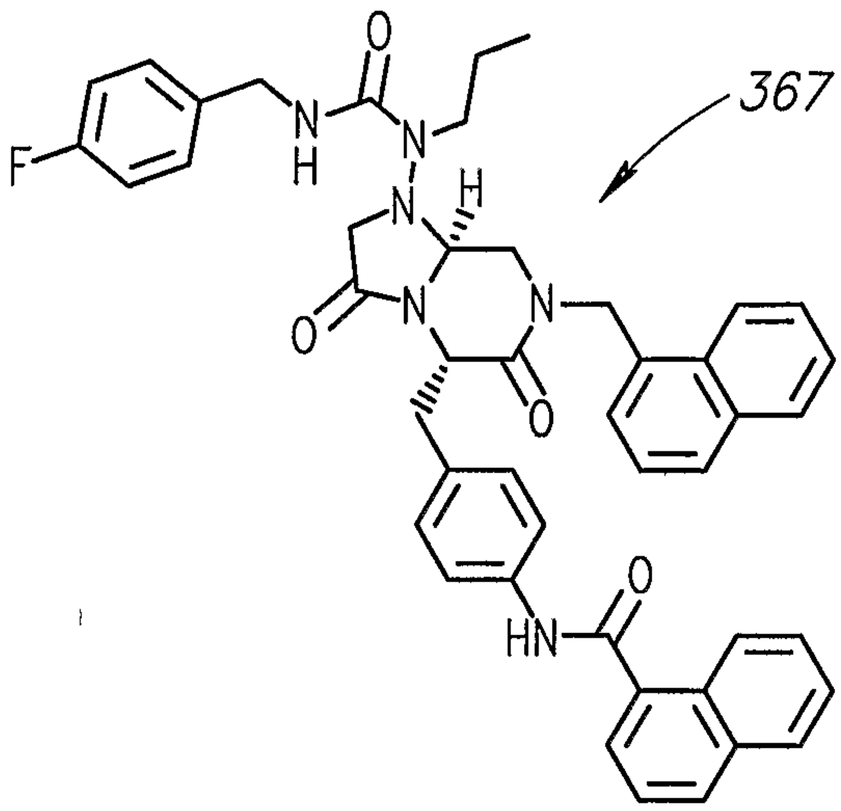


FIG.2X



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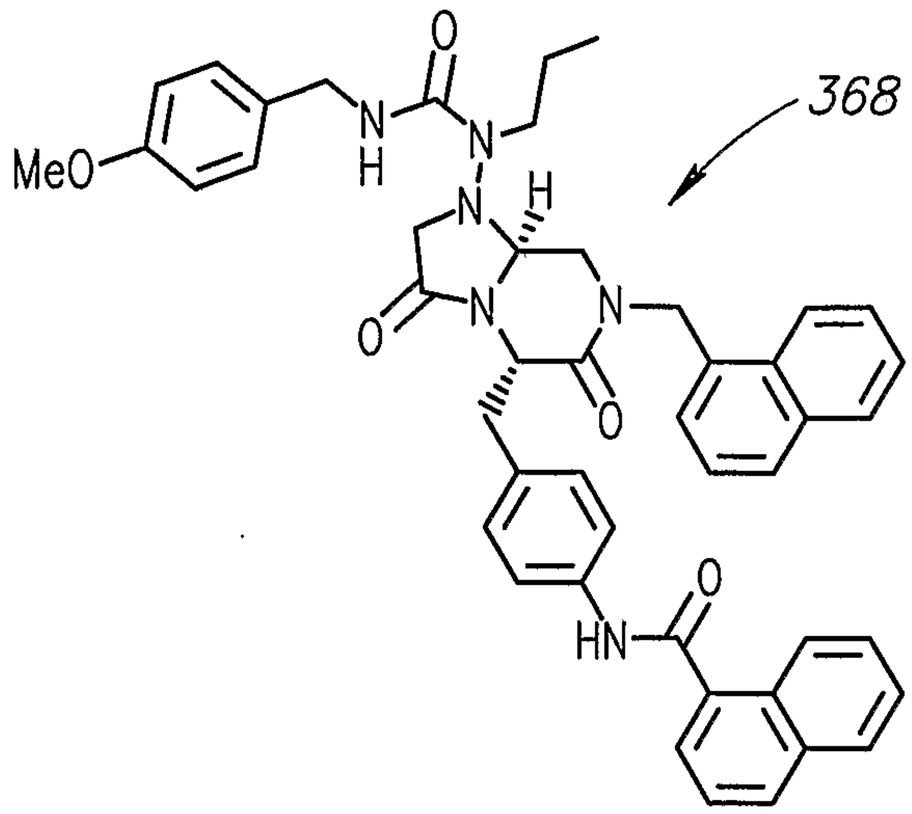

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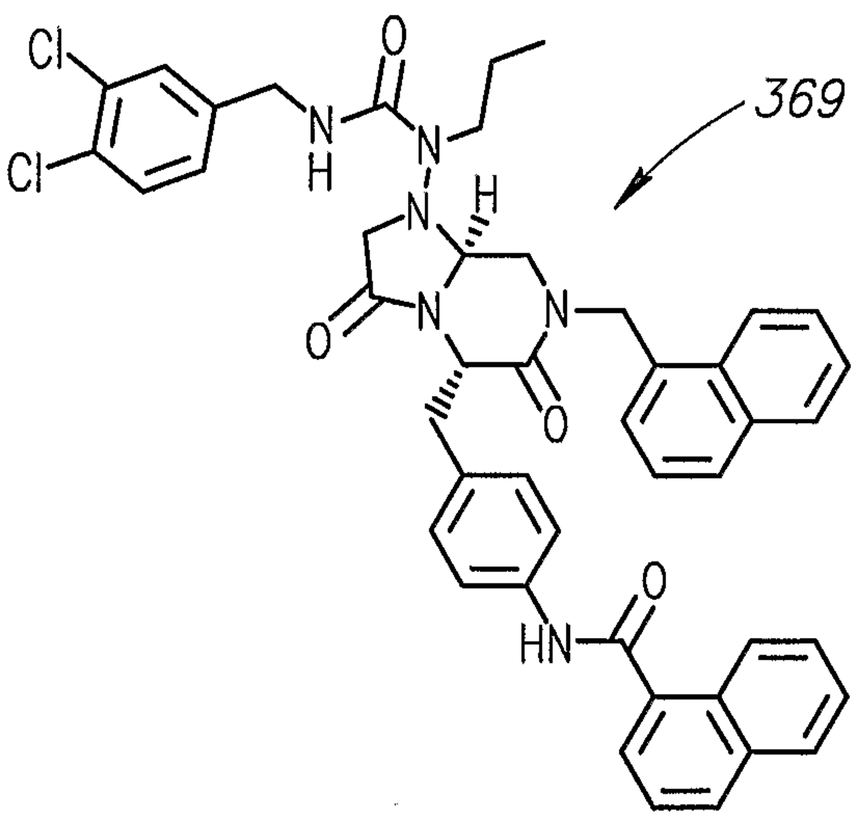

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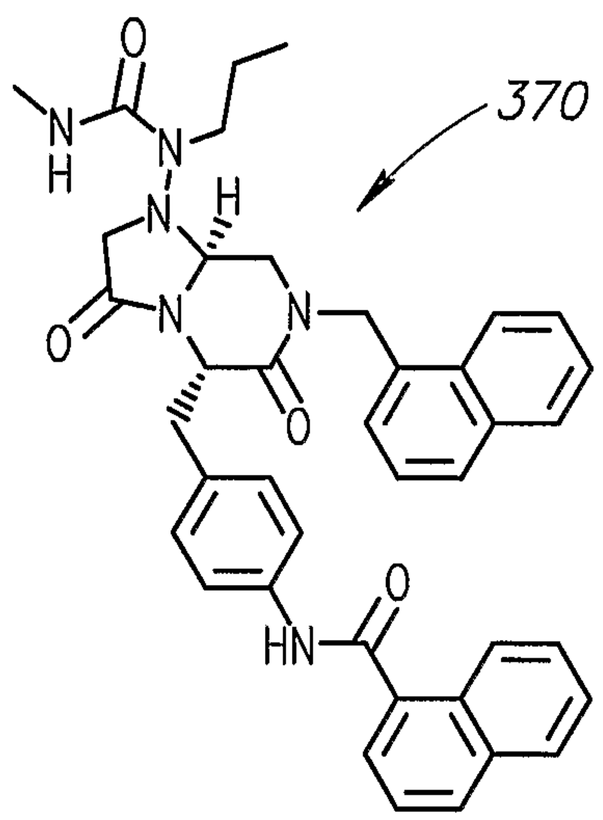

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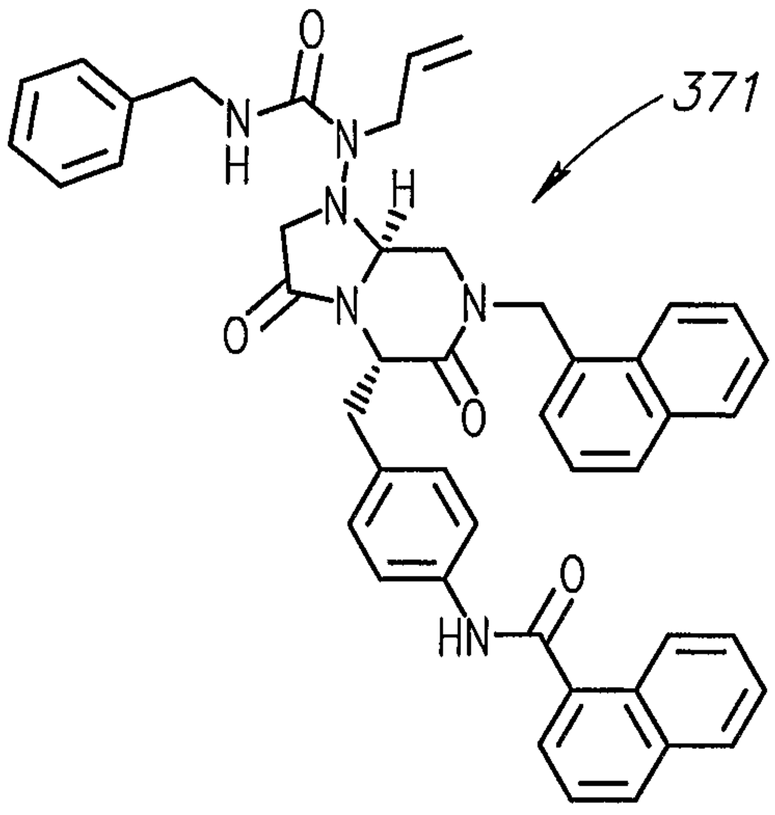

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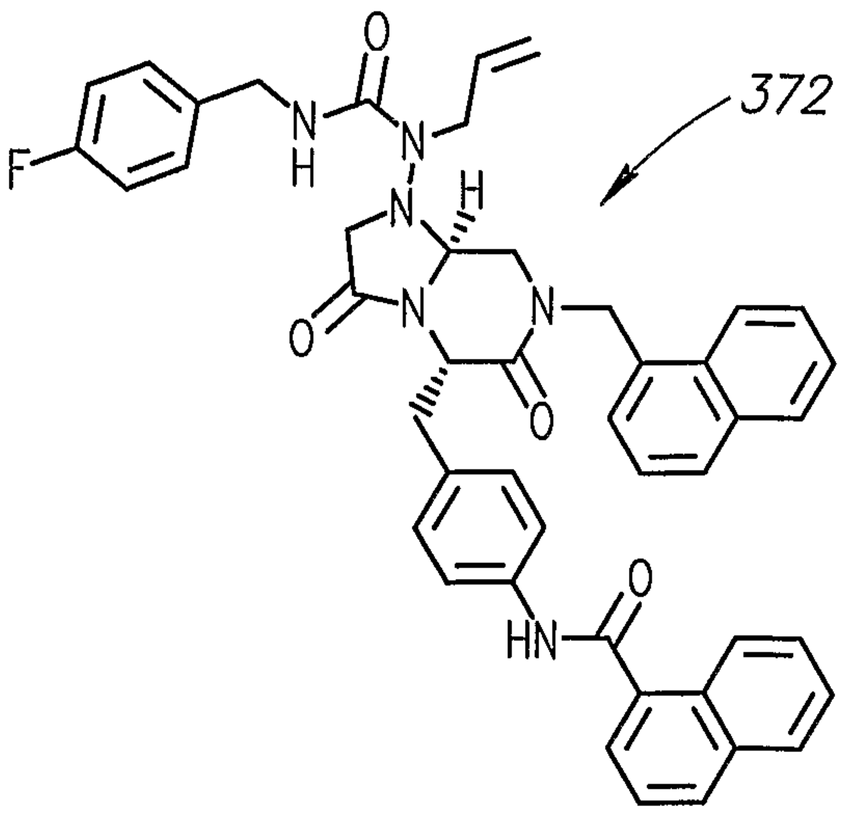
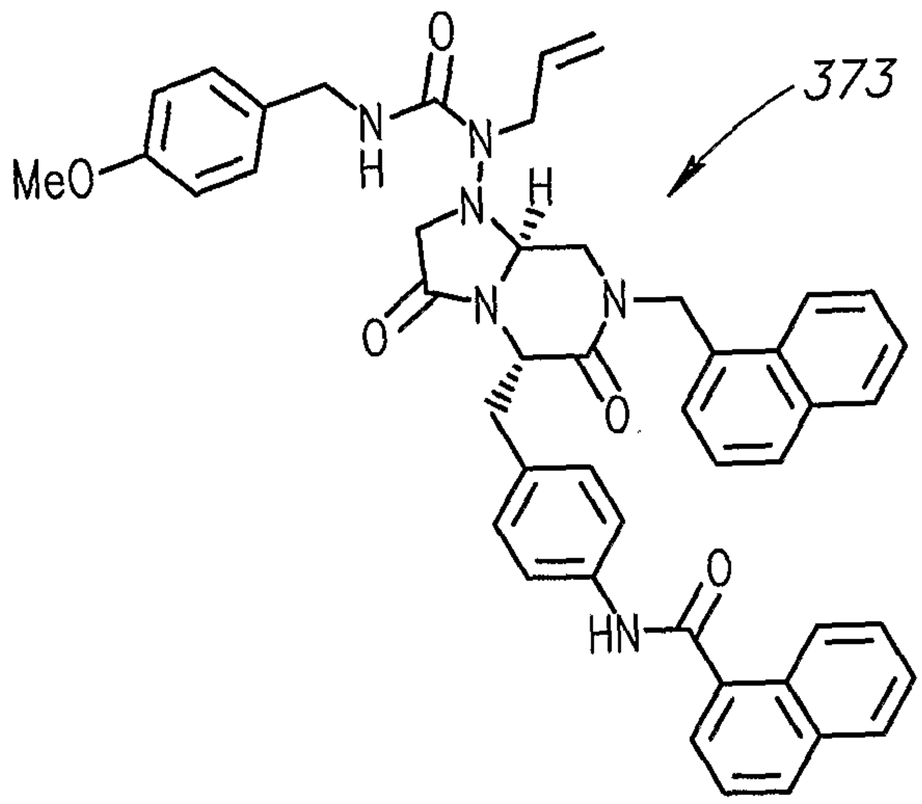


372

FIG.2Y

373



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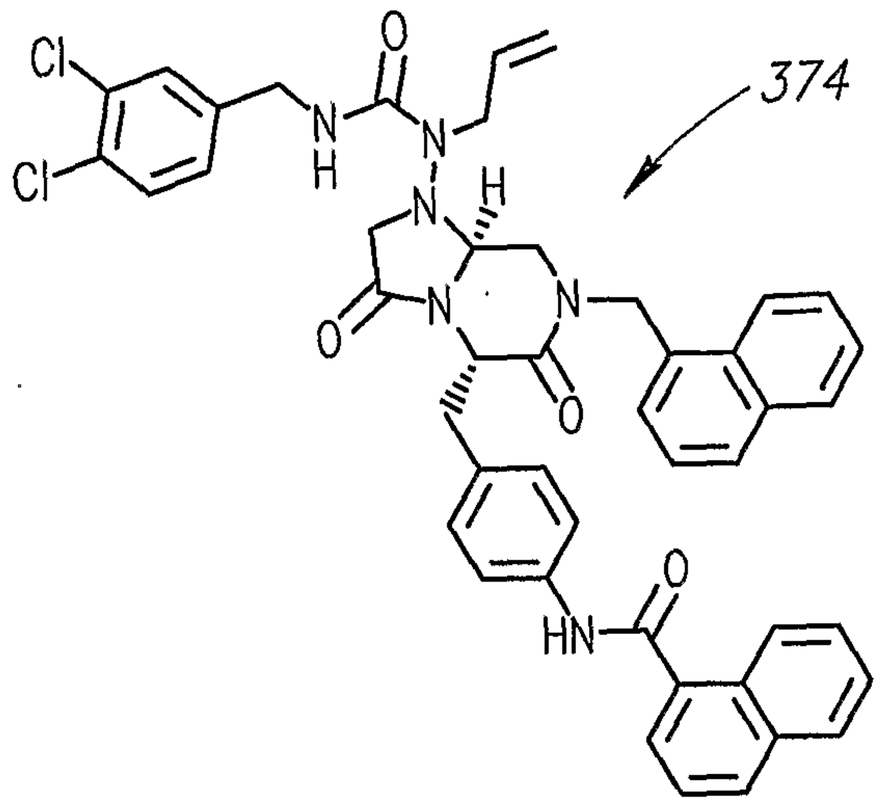

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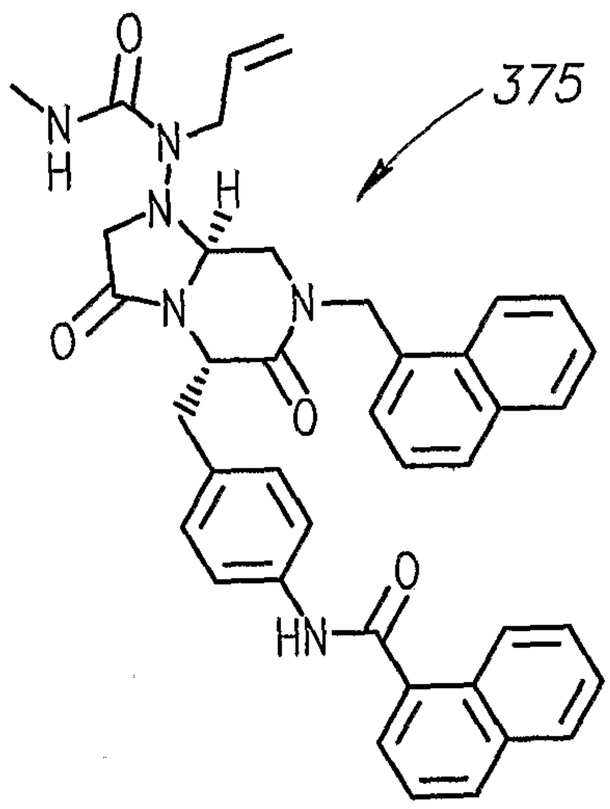

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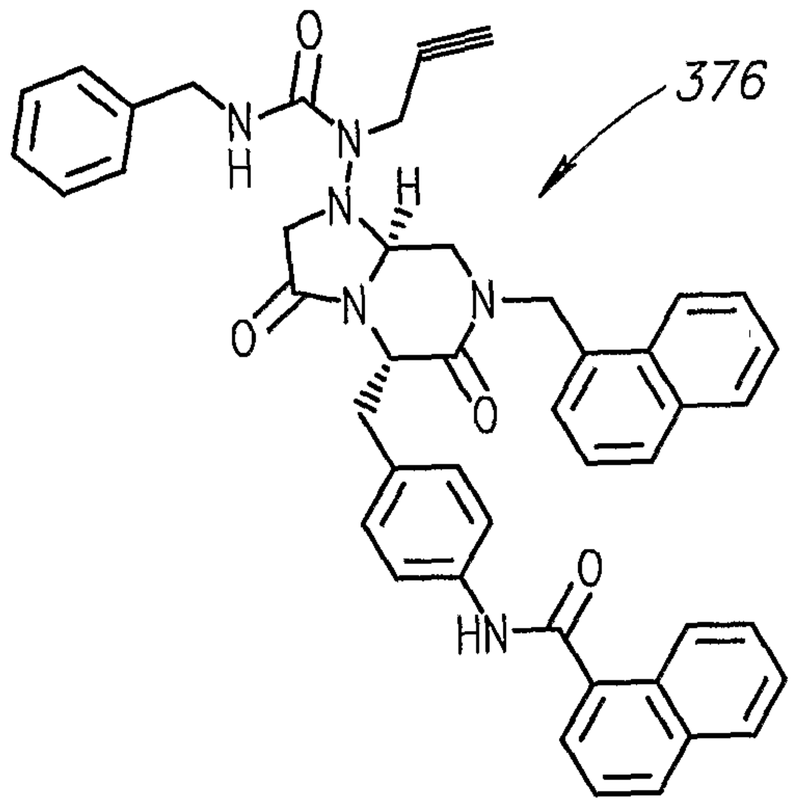

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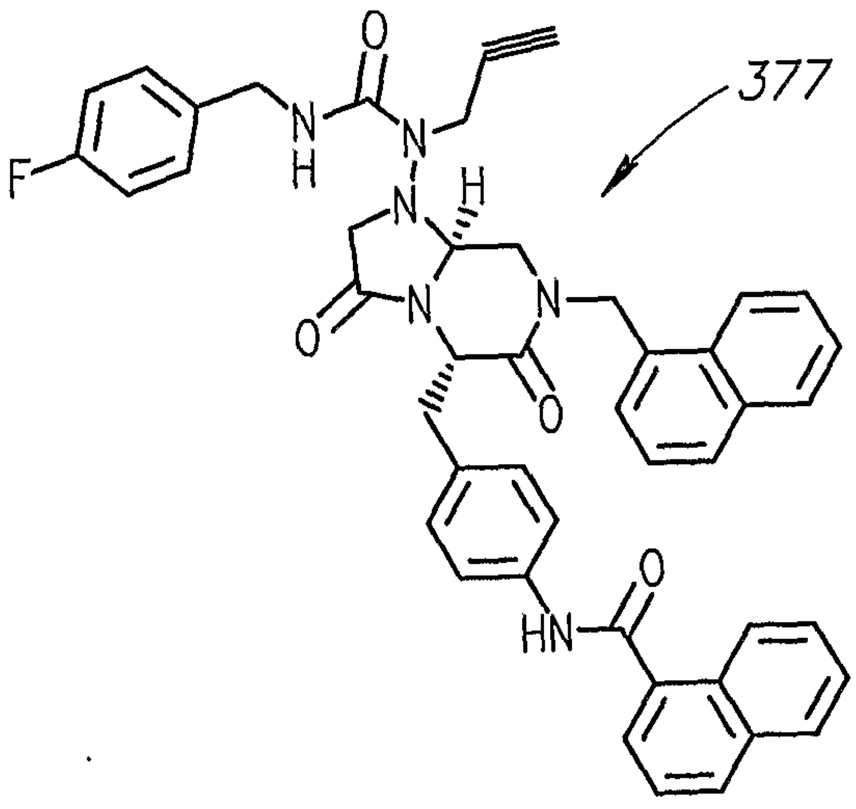

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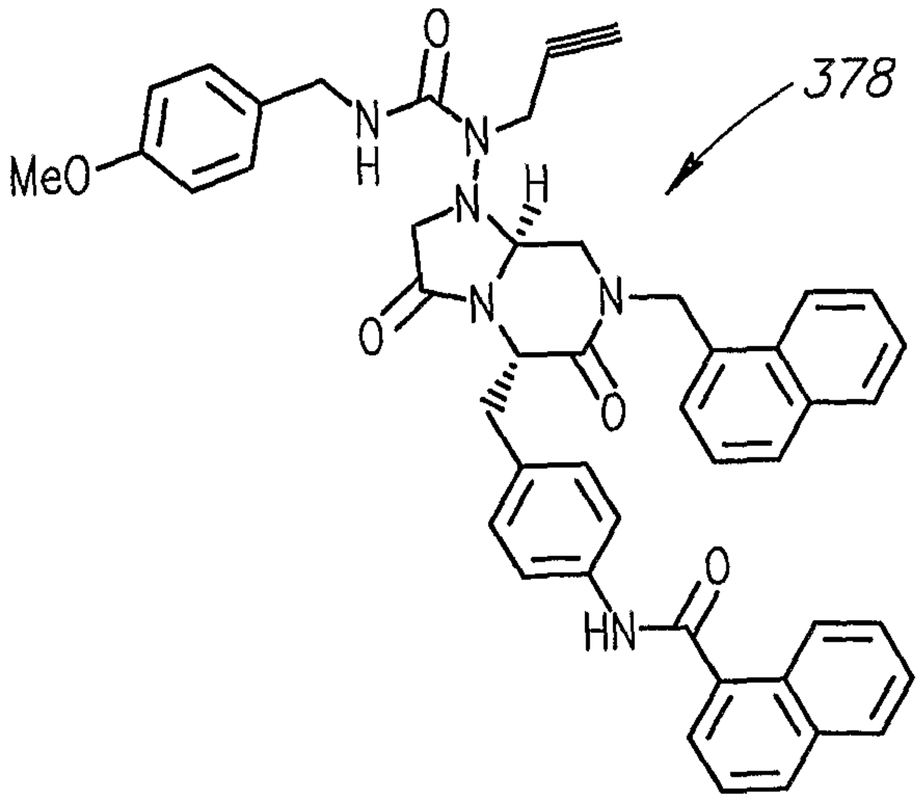
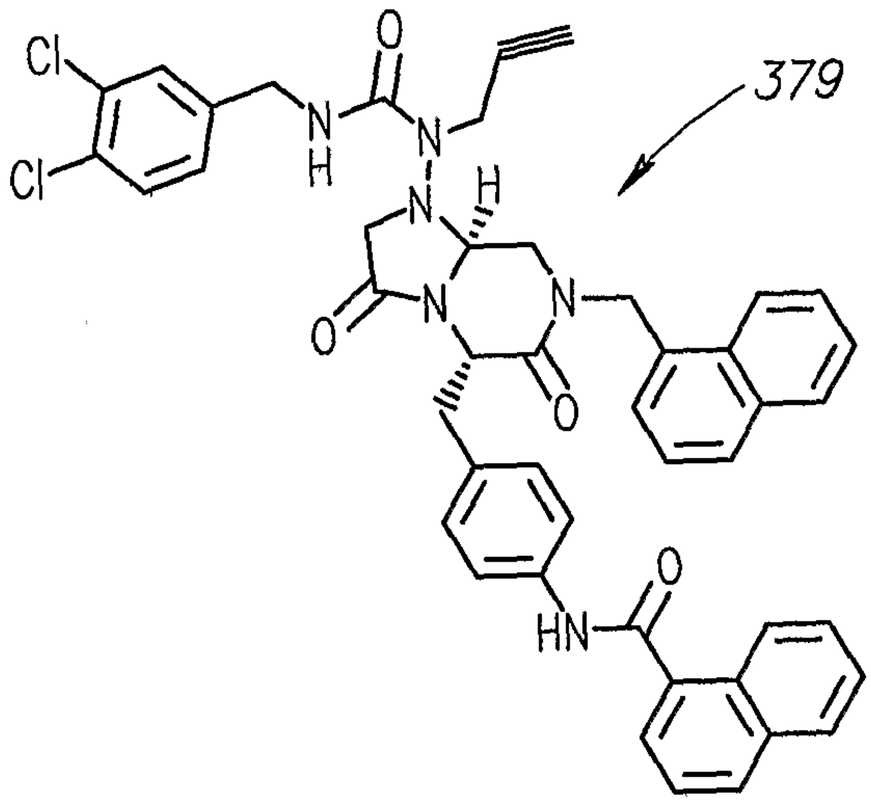


FIG.2Z

379



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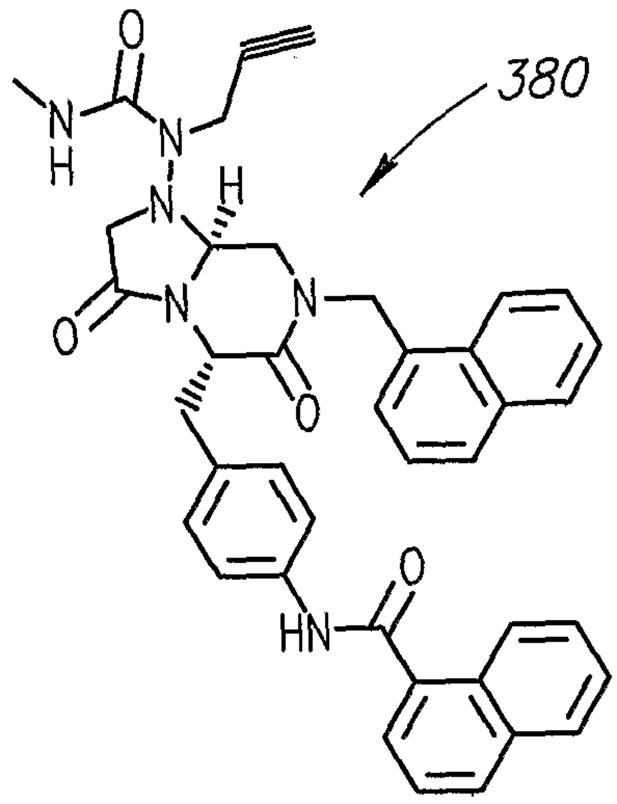

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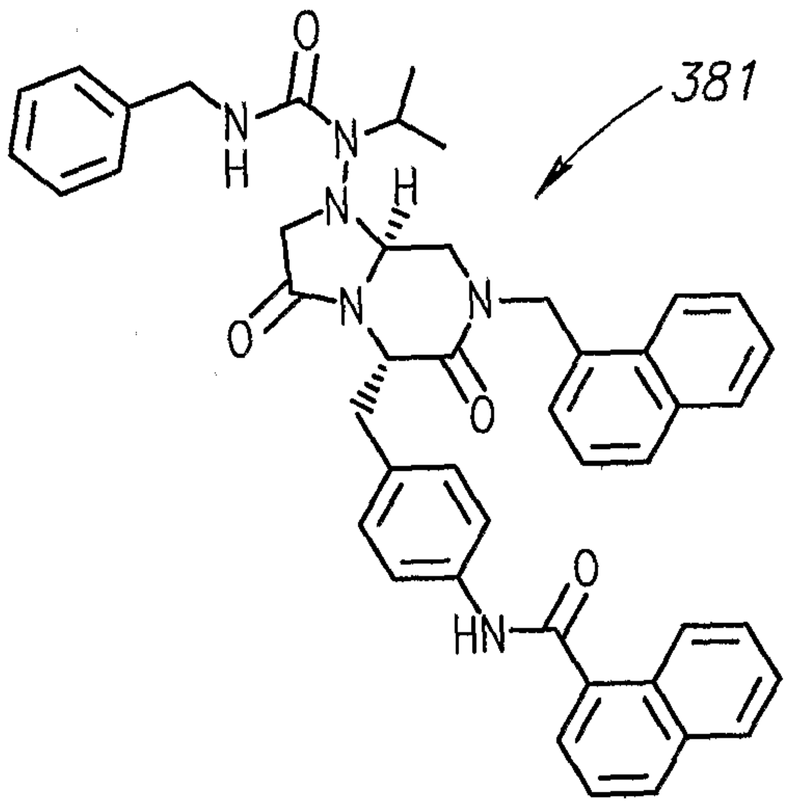

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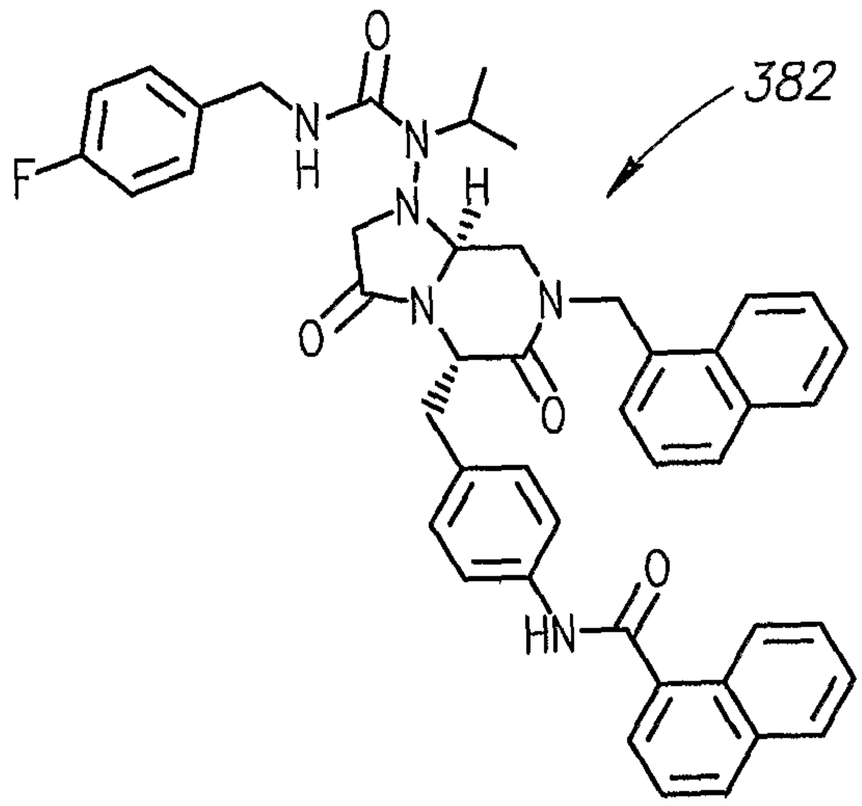

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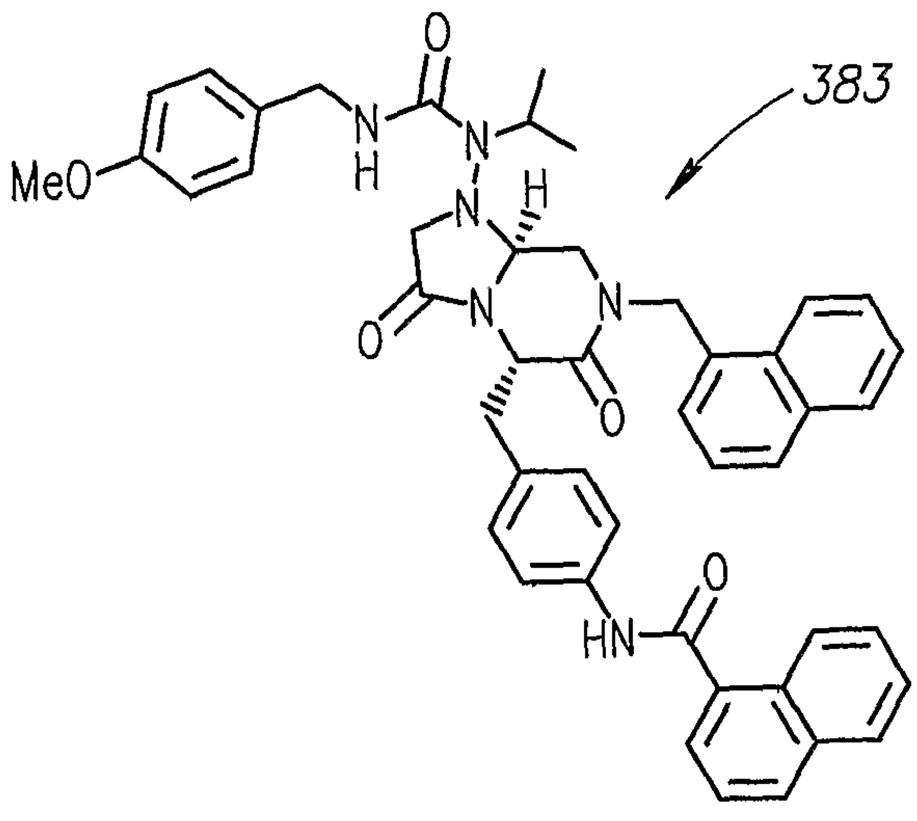

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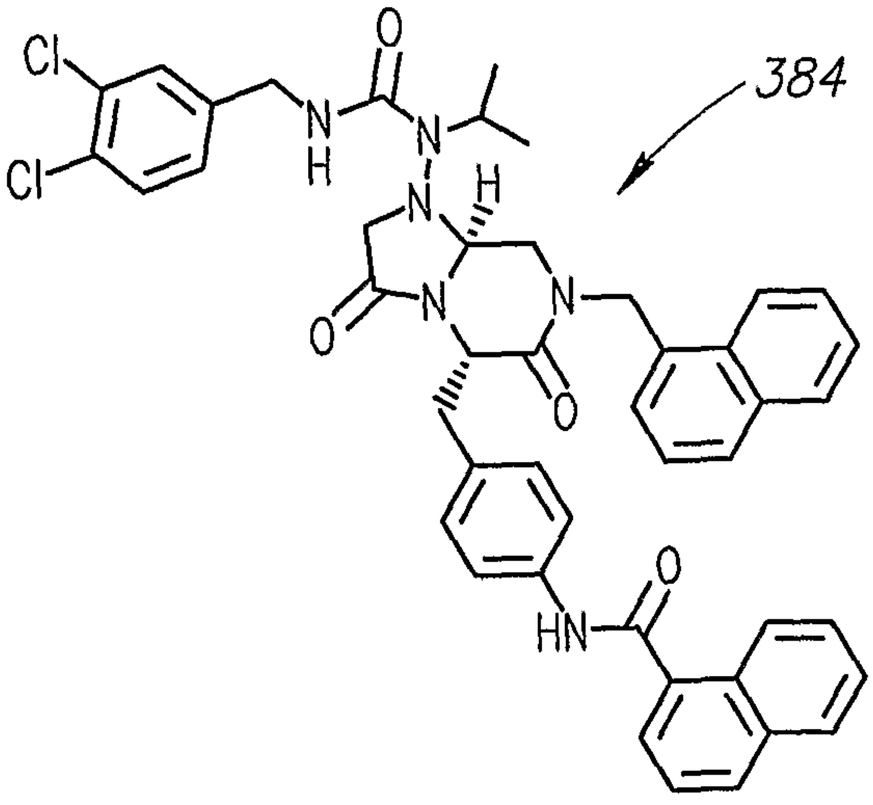
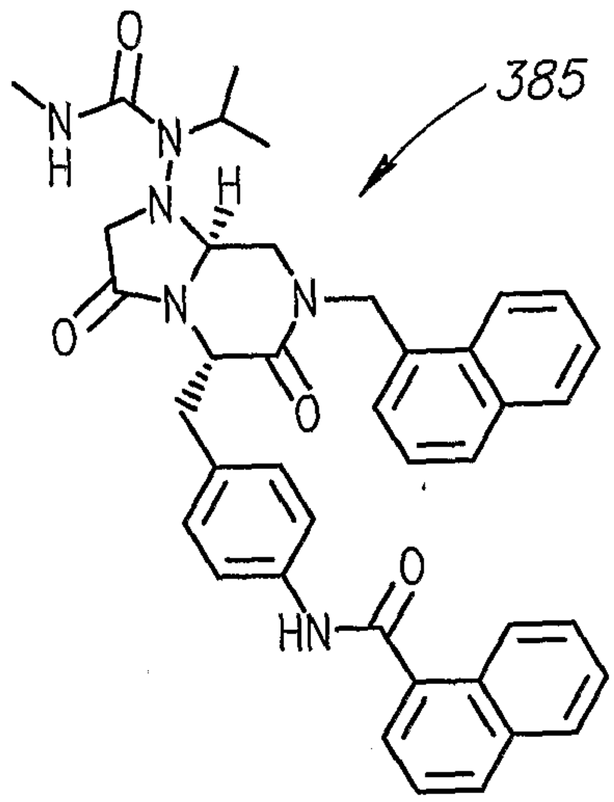
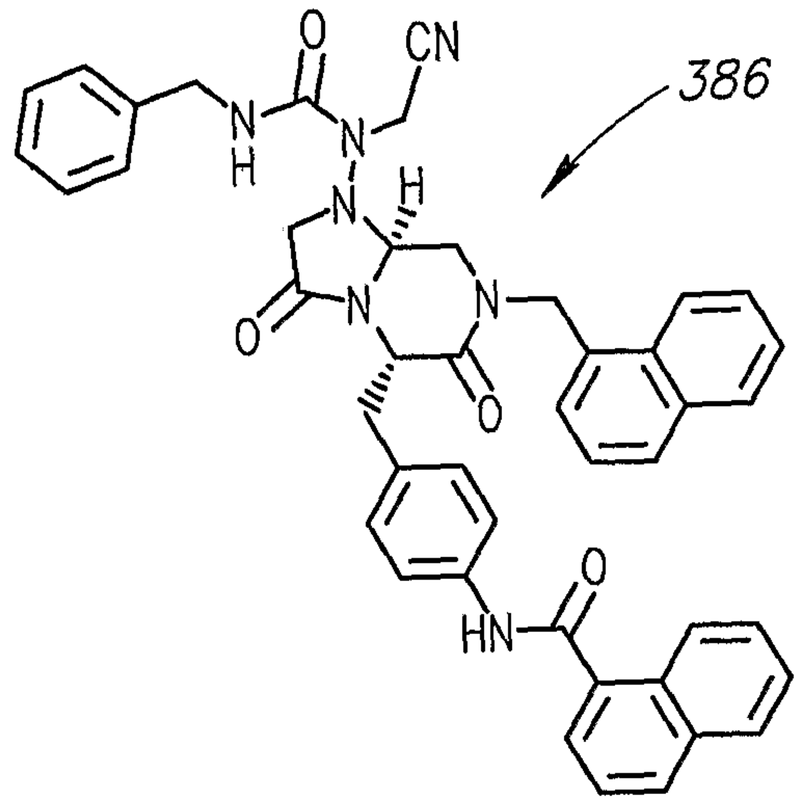
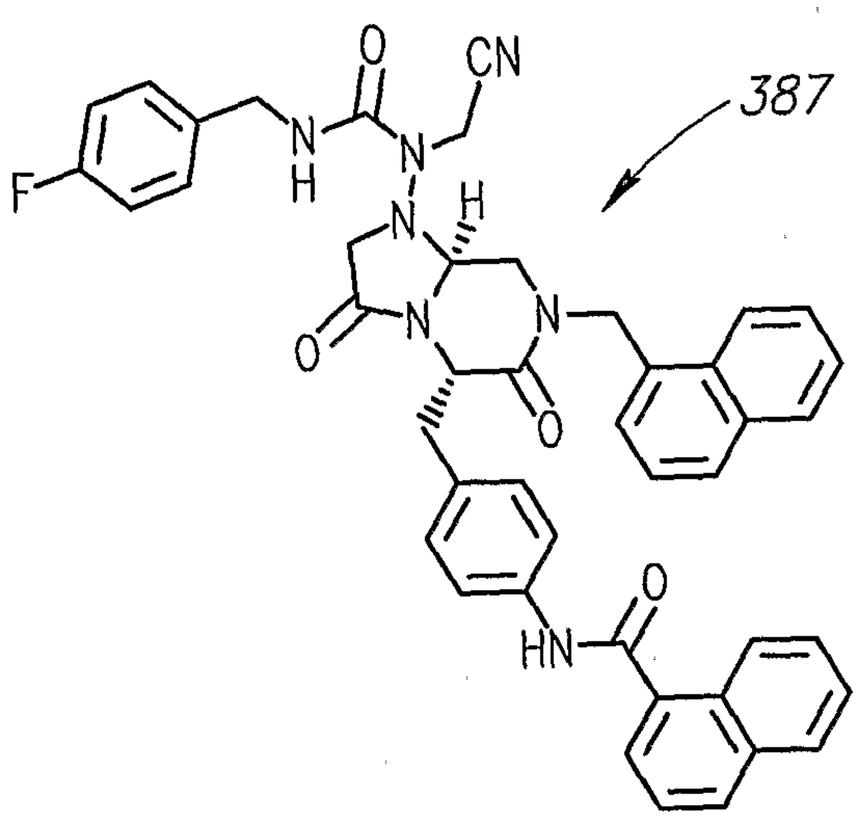
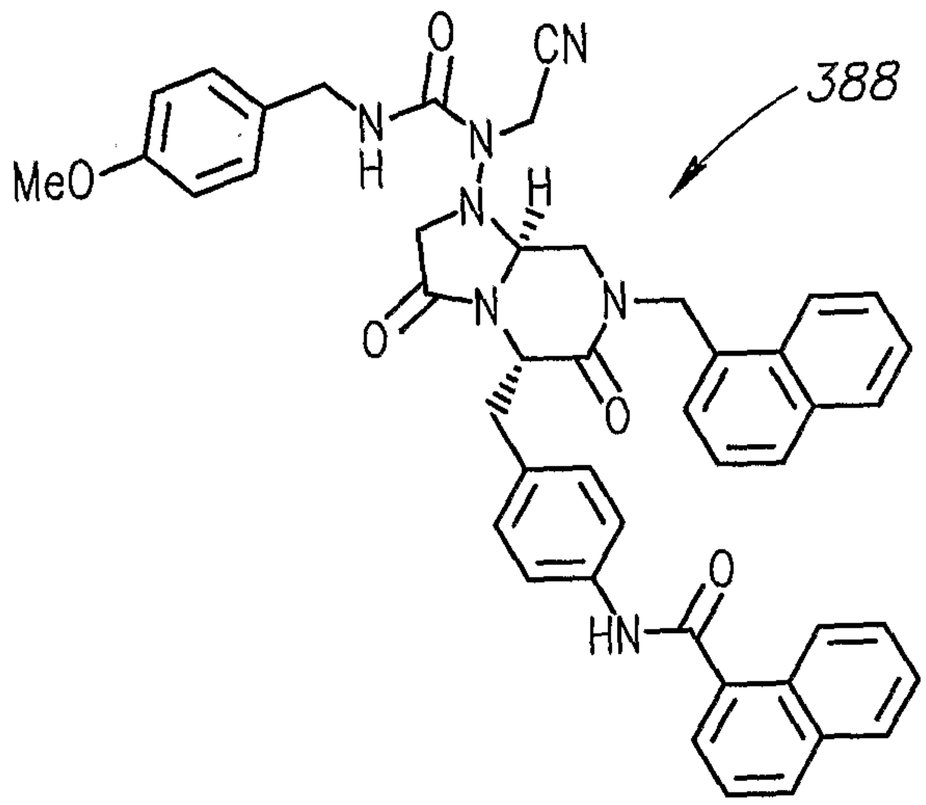


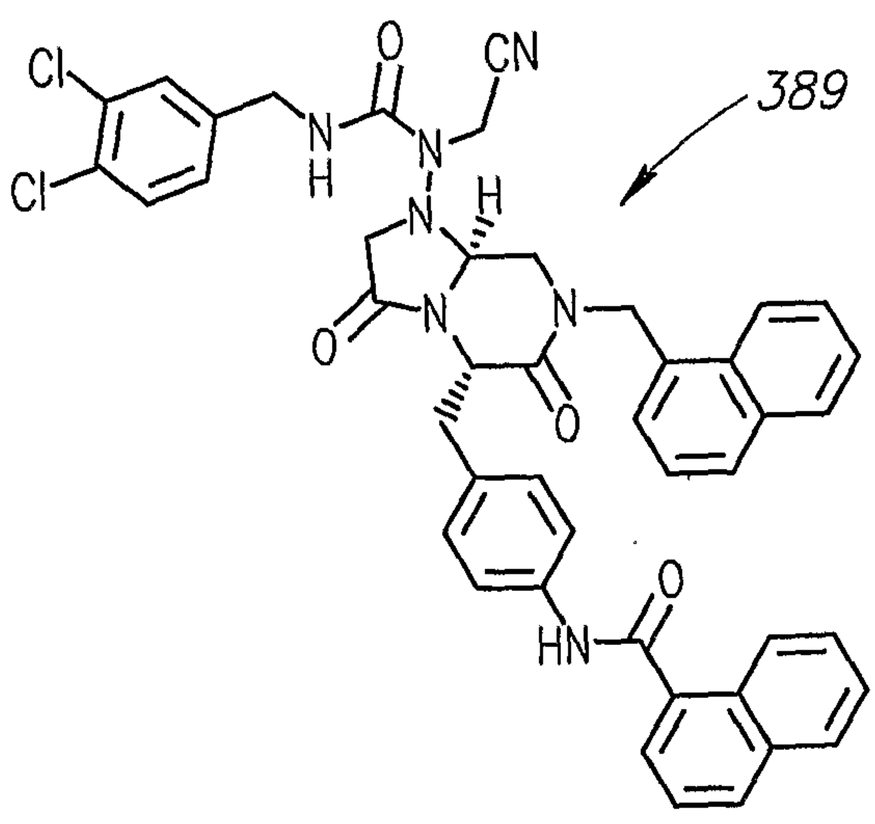
FIG.2AA











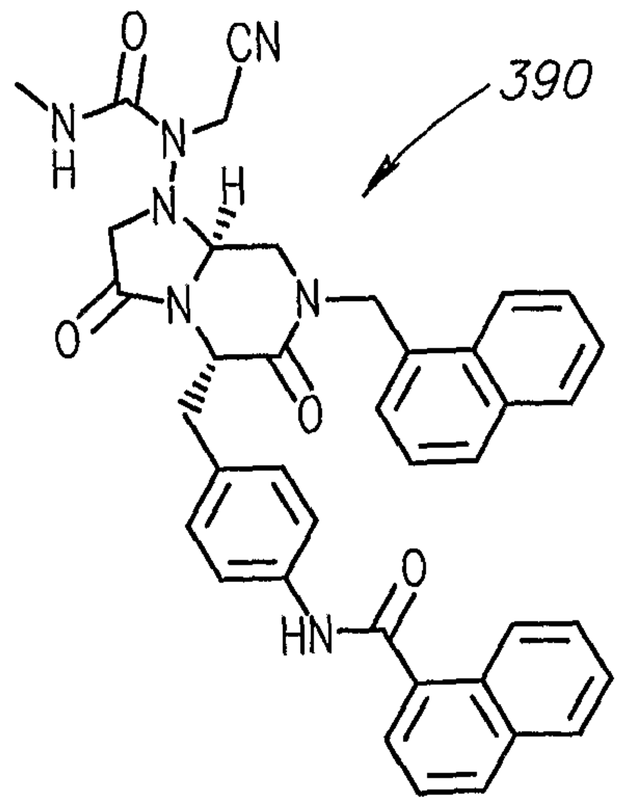
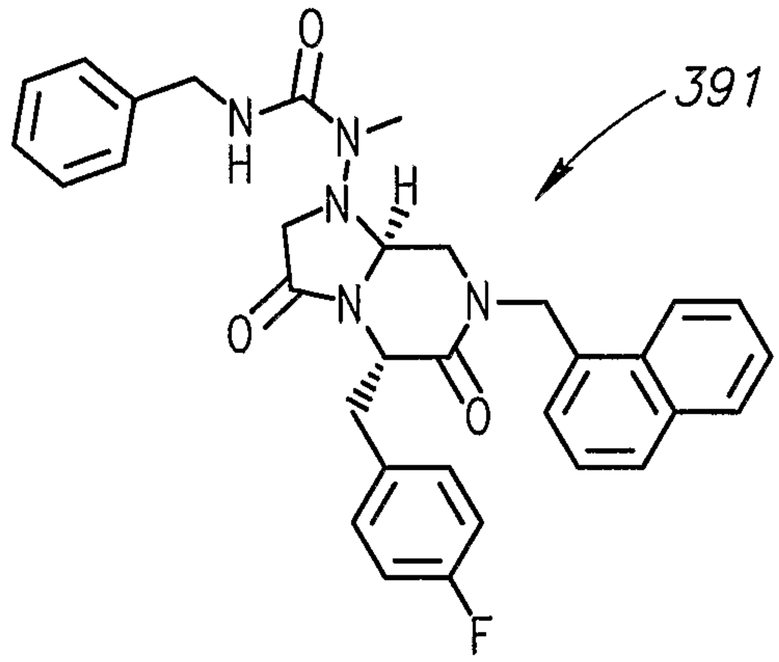
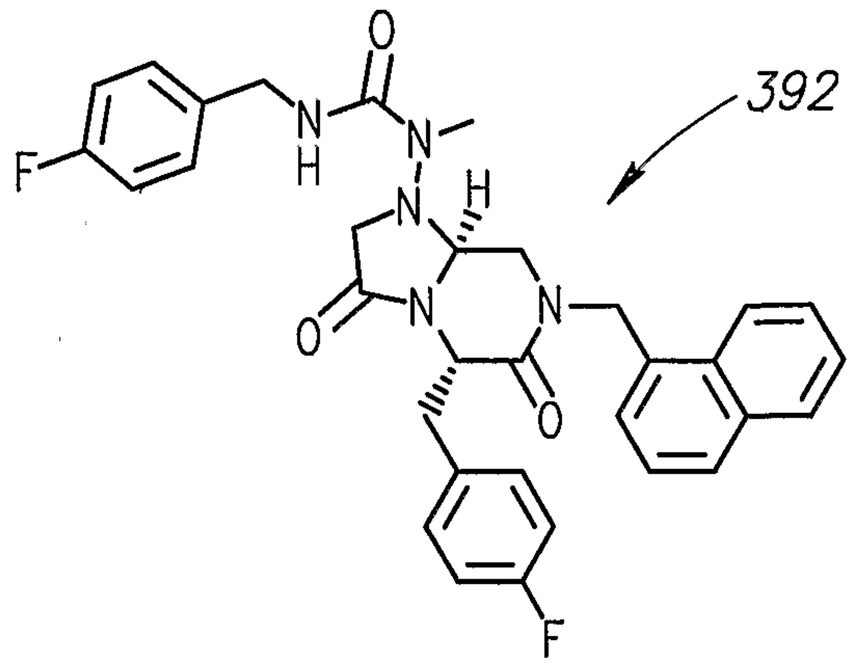
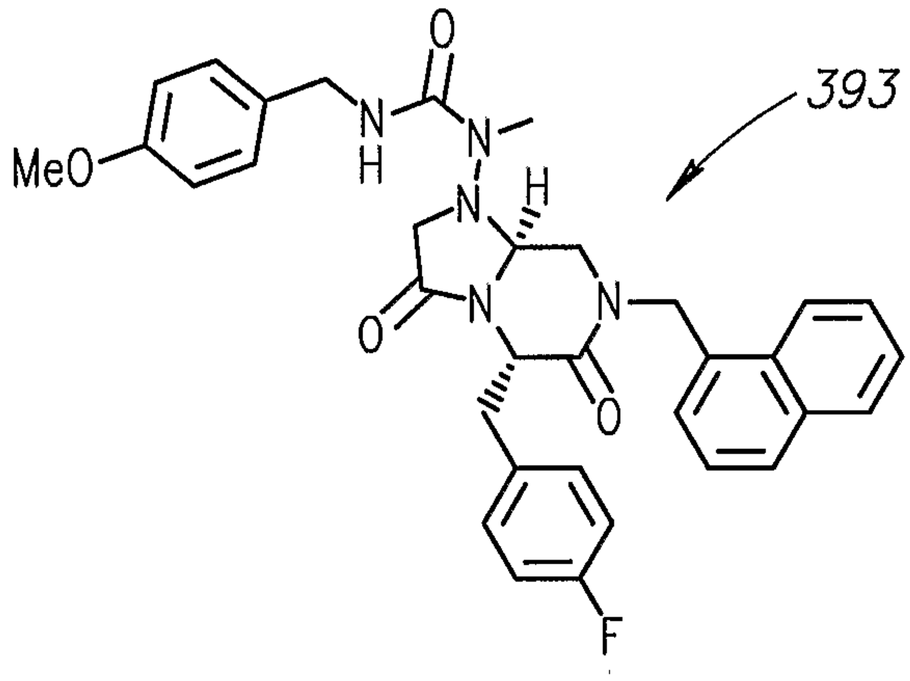
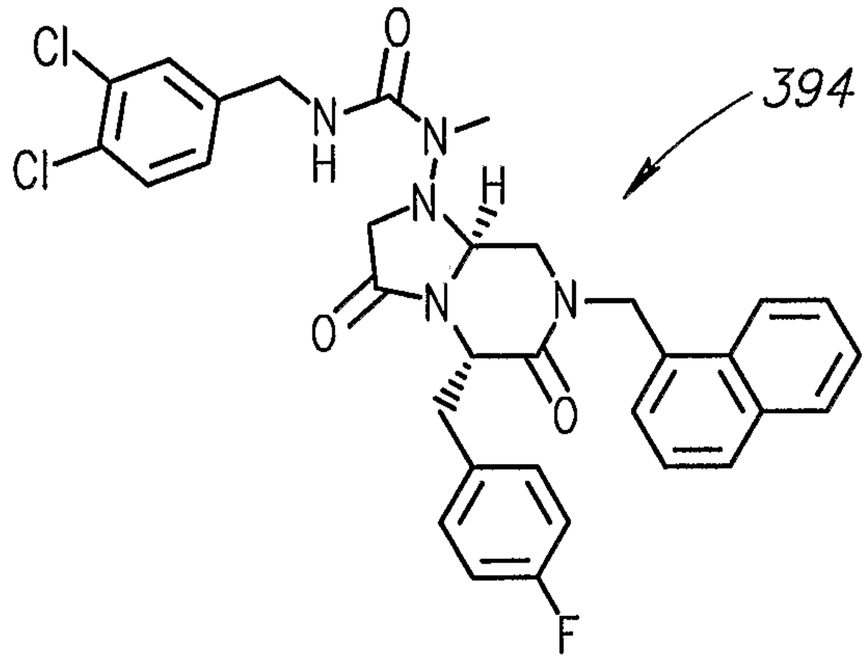


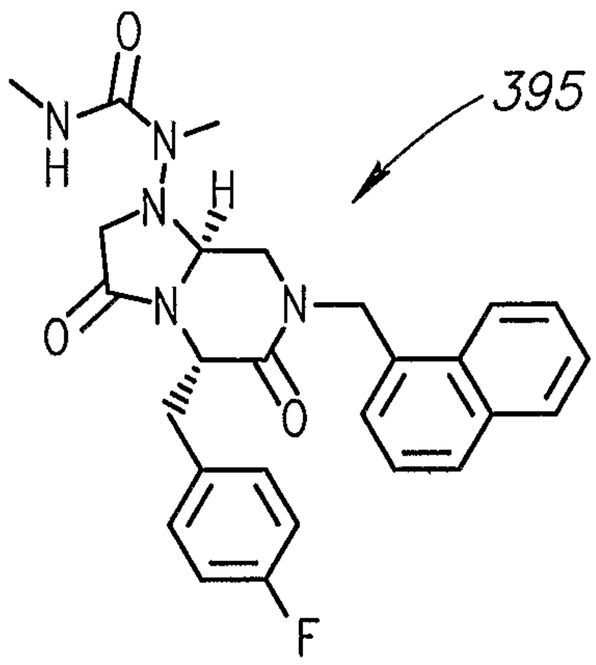
FIG.2AB











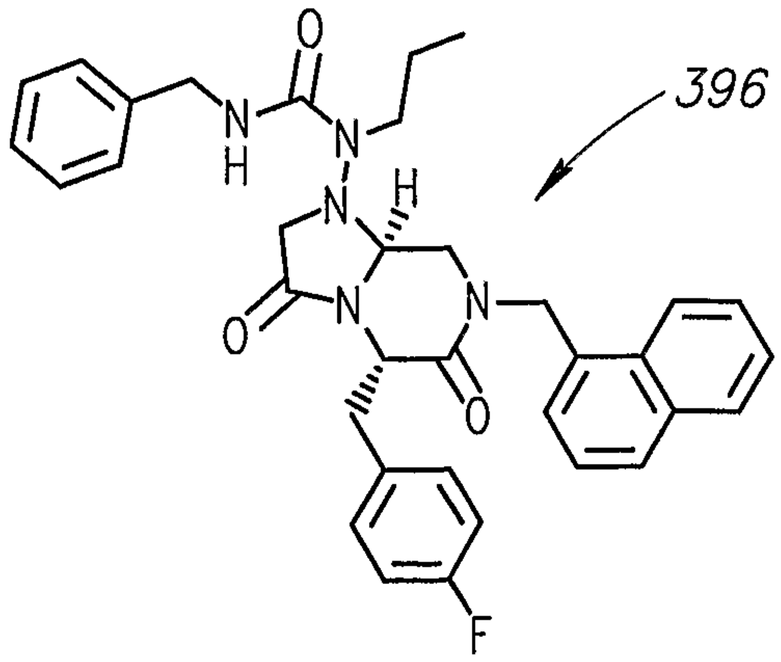
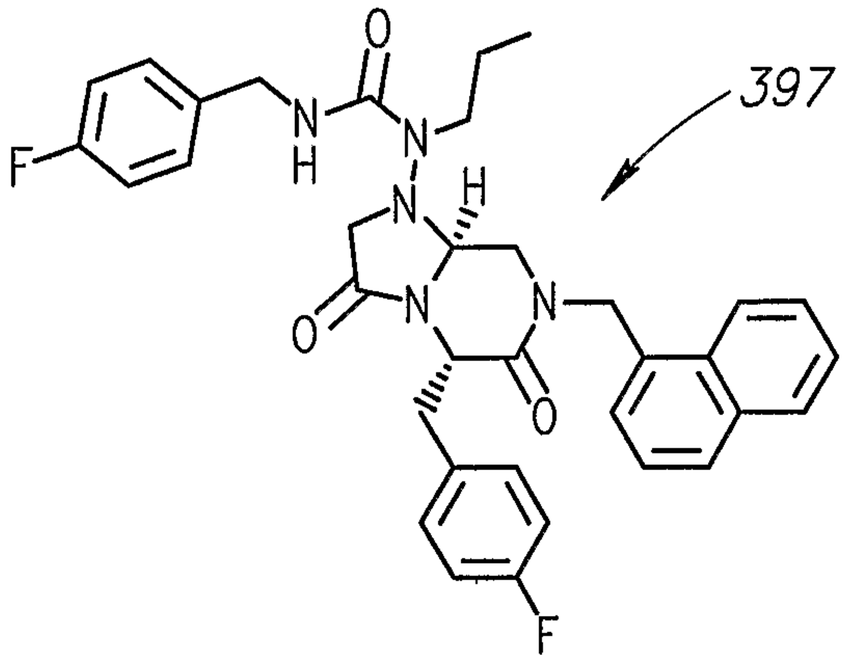
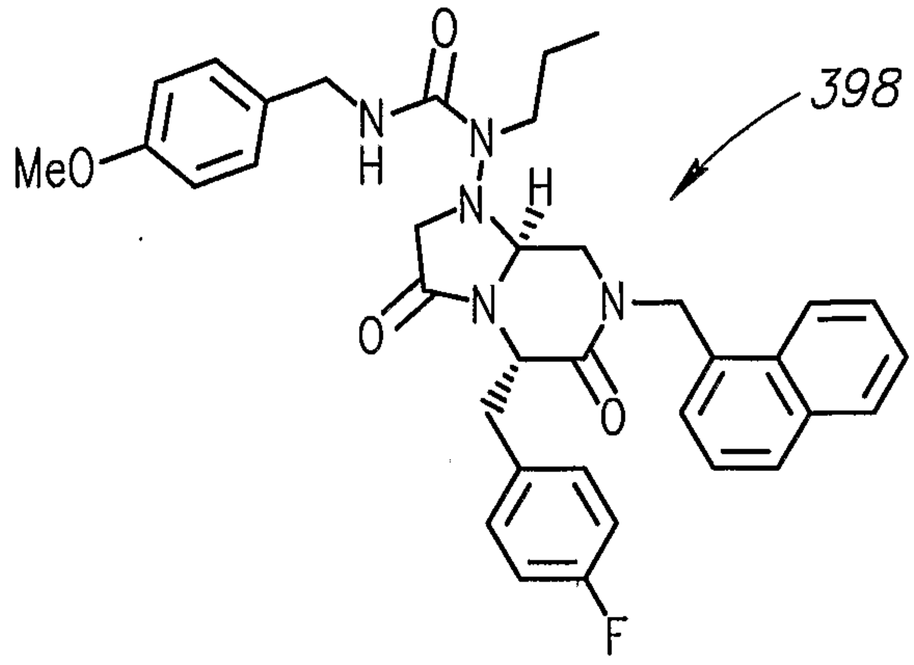
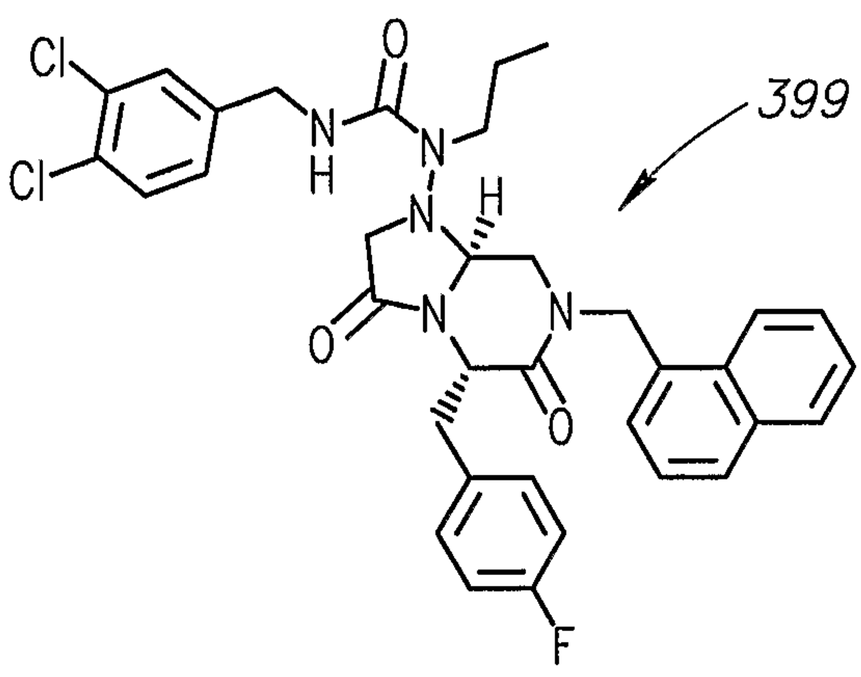


FIG.2AC







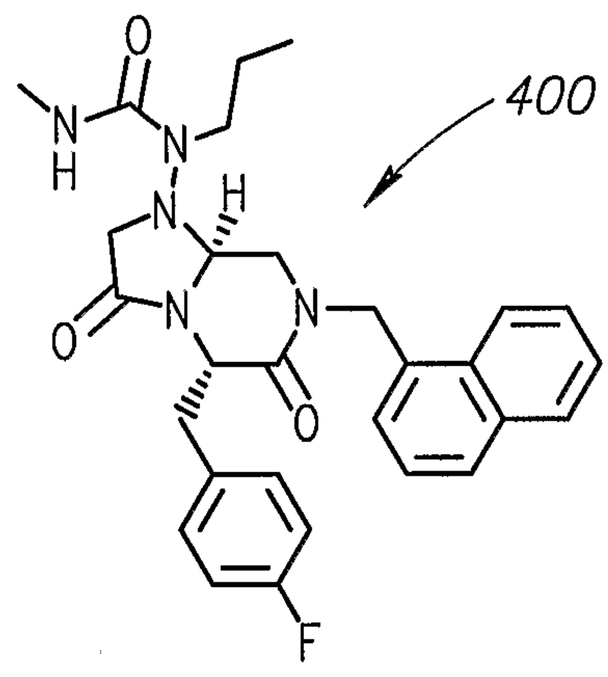
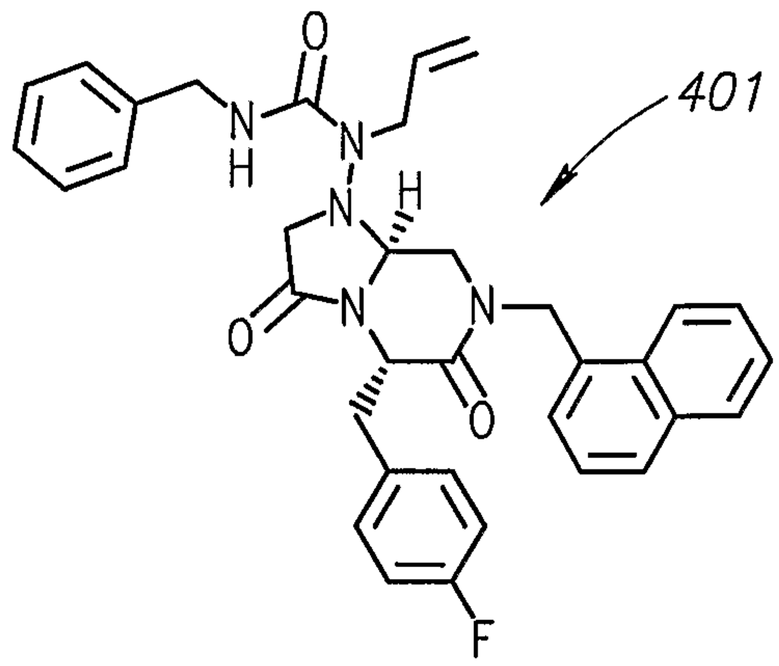
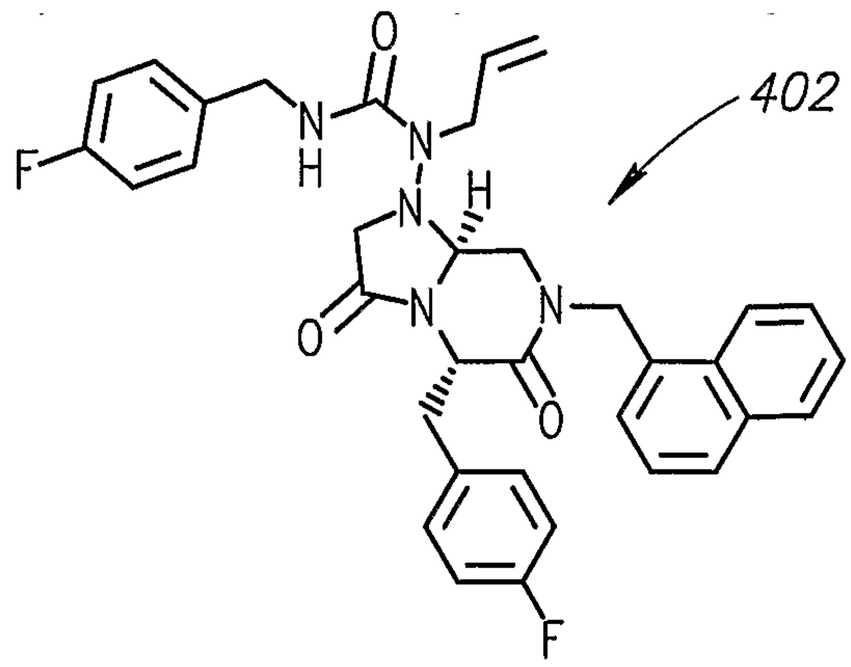
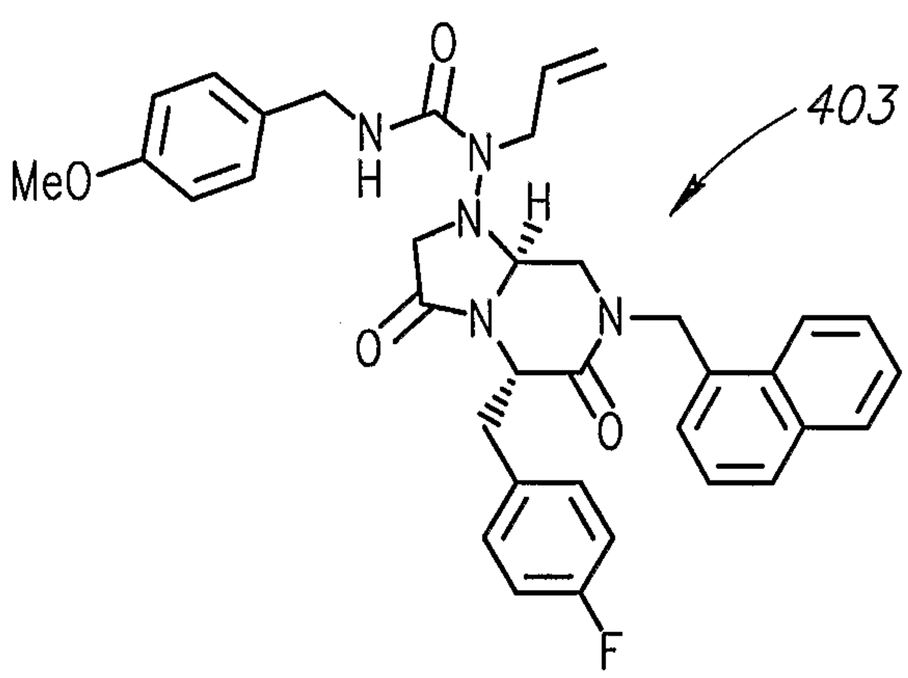
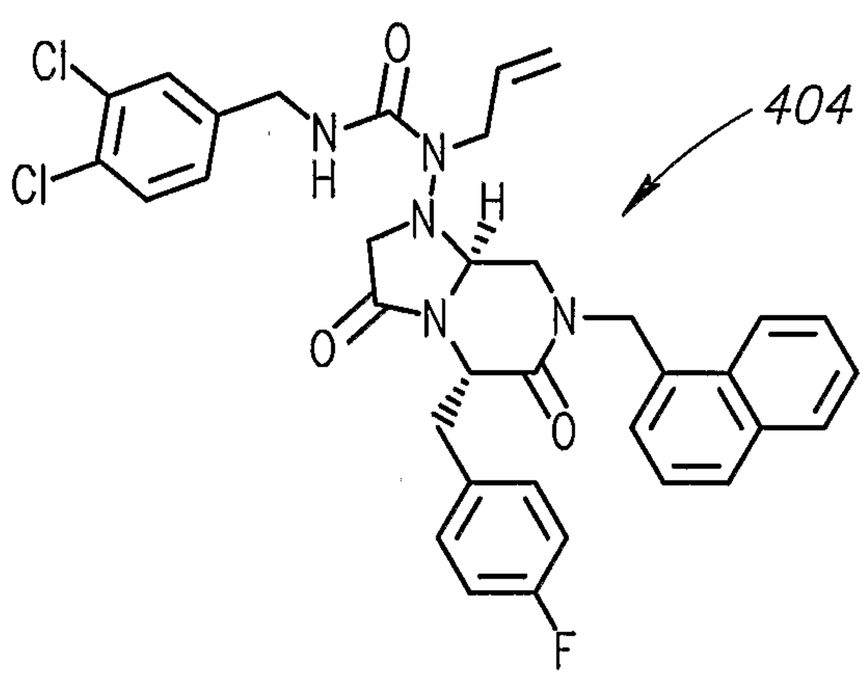


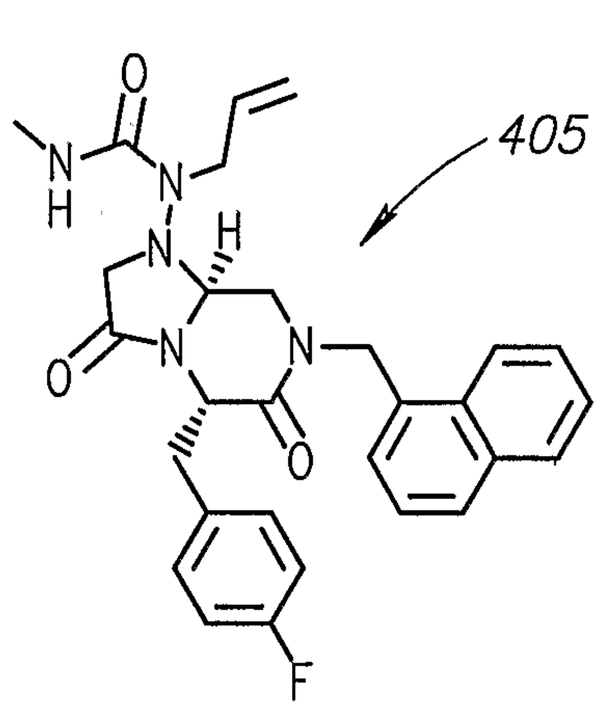
FIG.2AD











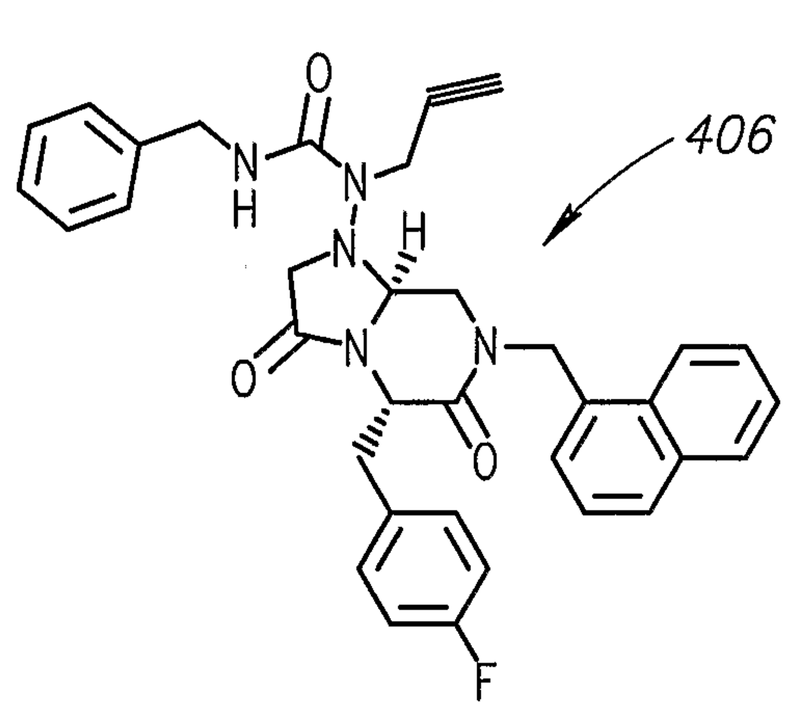
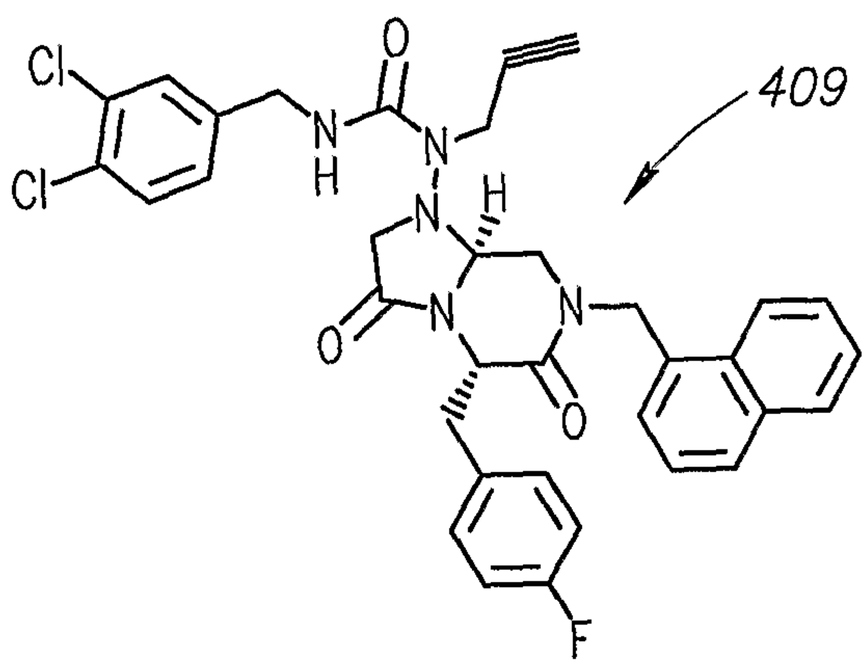
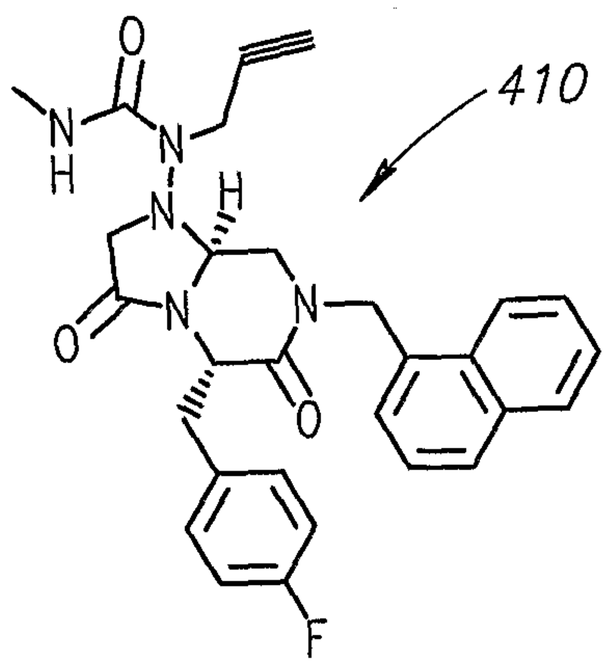
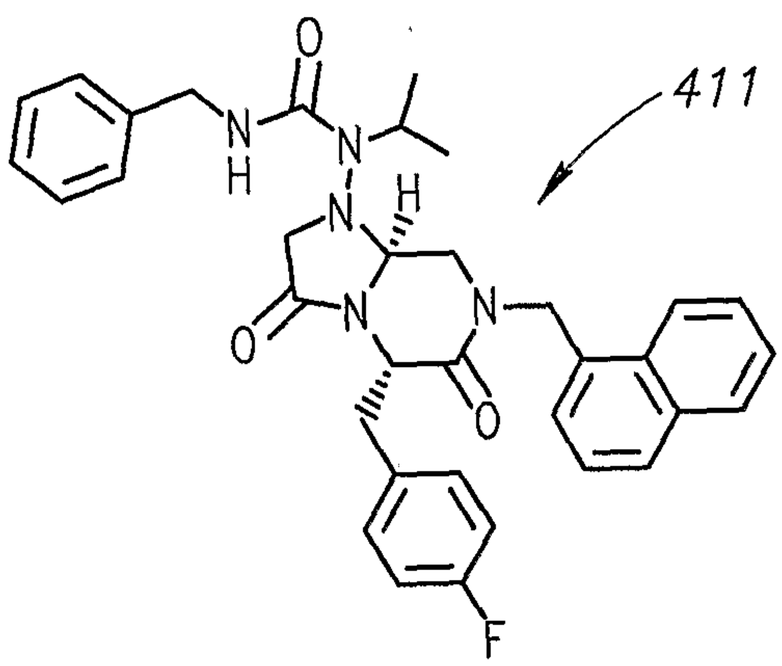
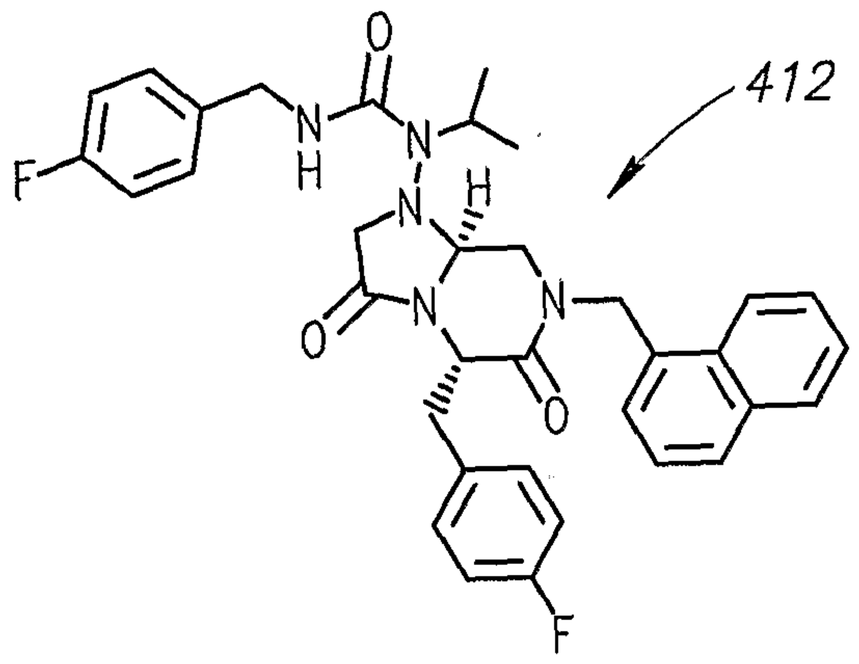


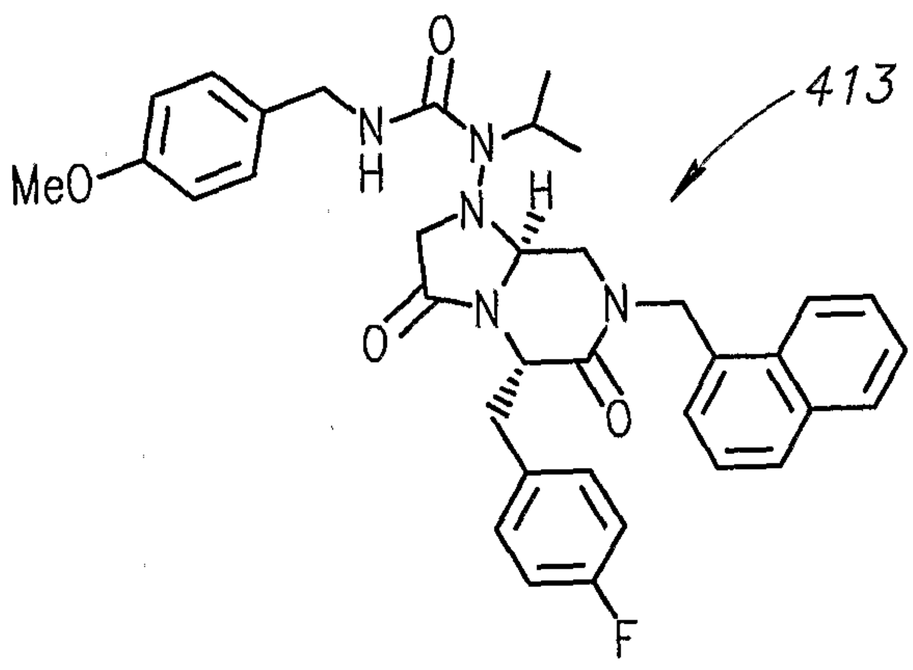
FIG.3A

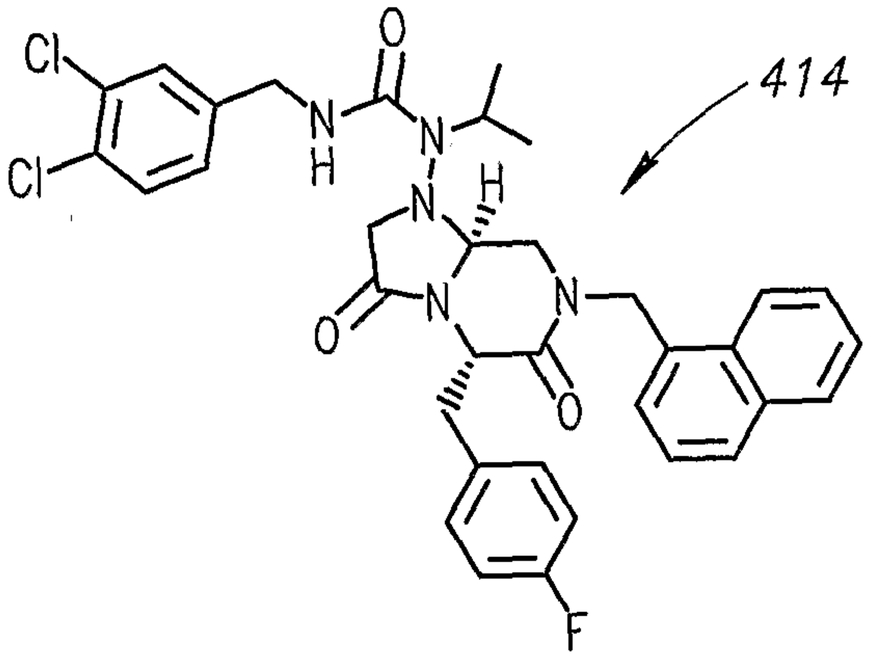


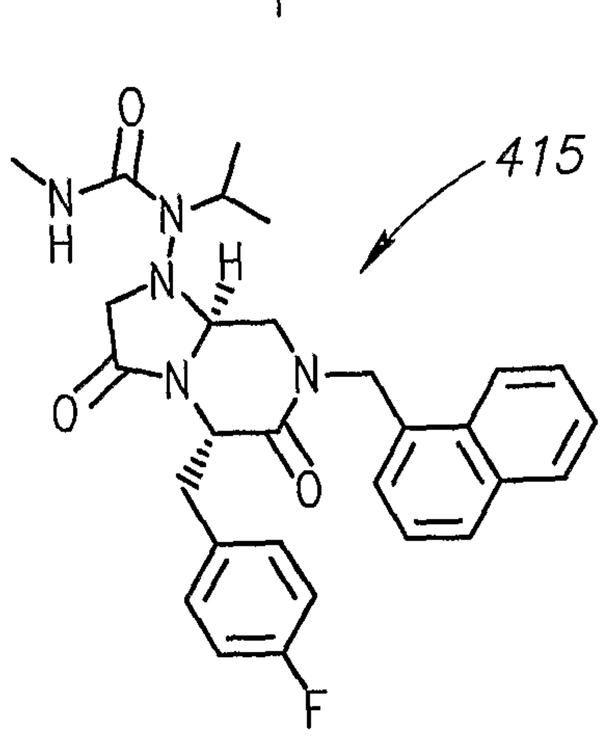












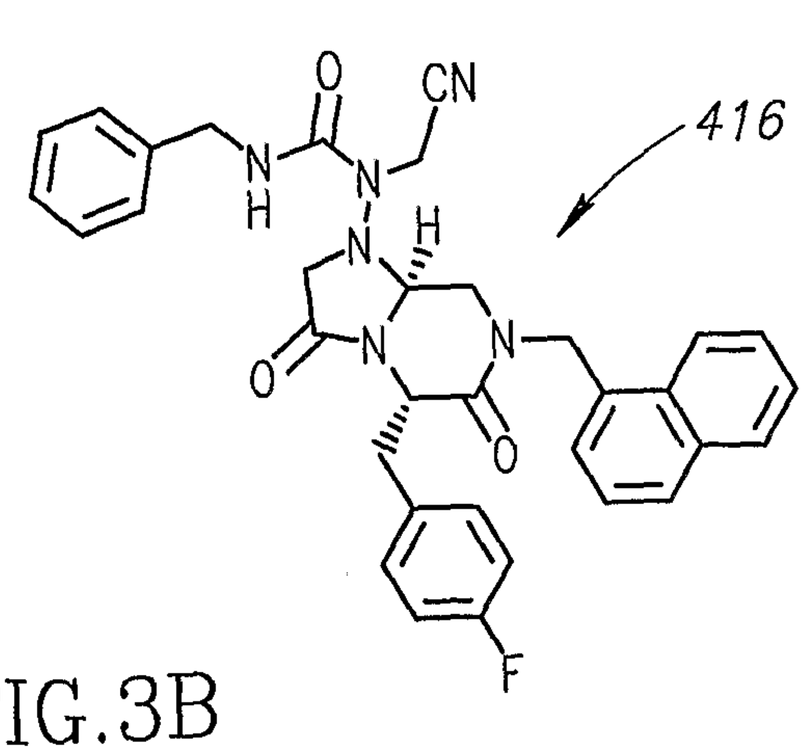
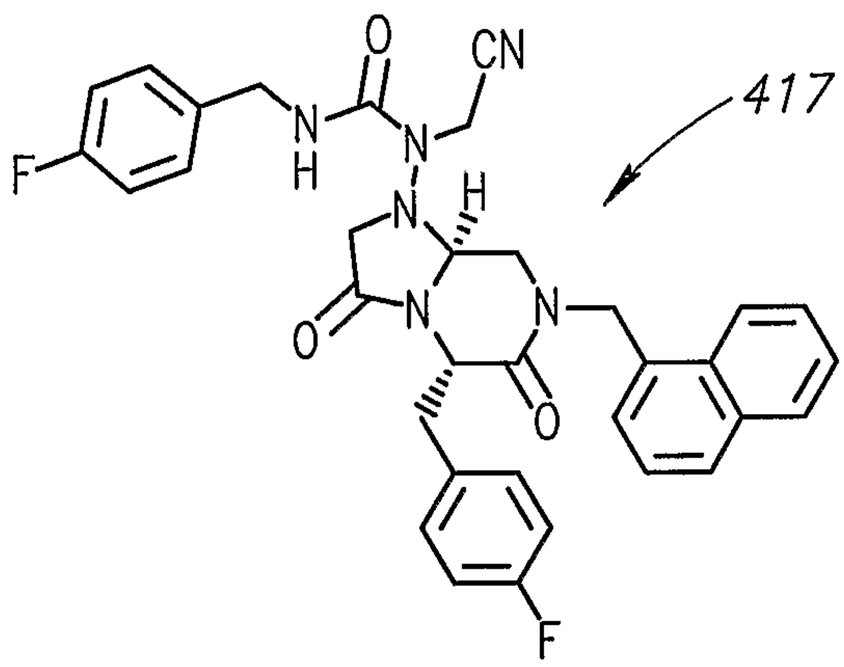
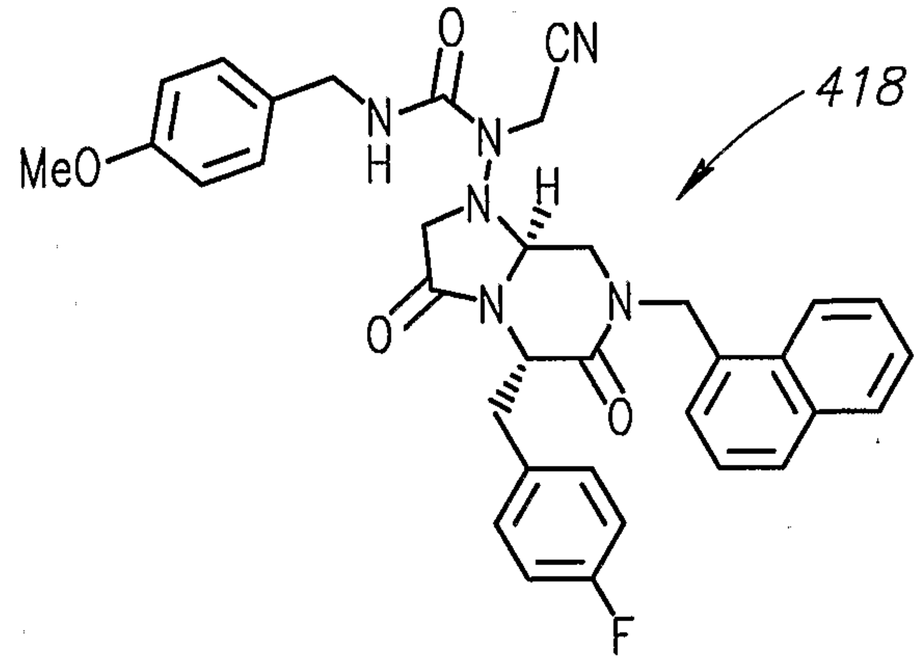
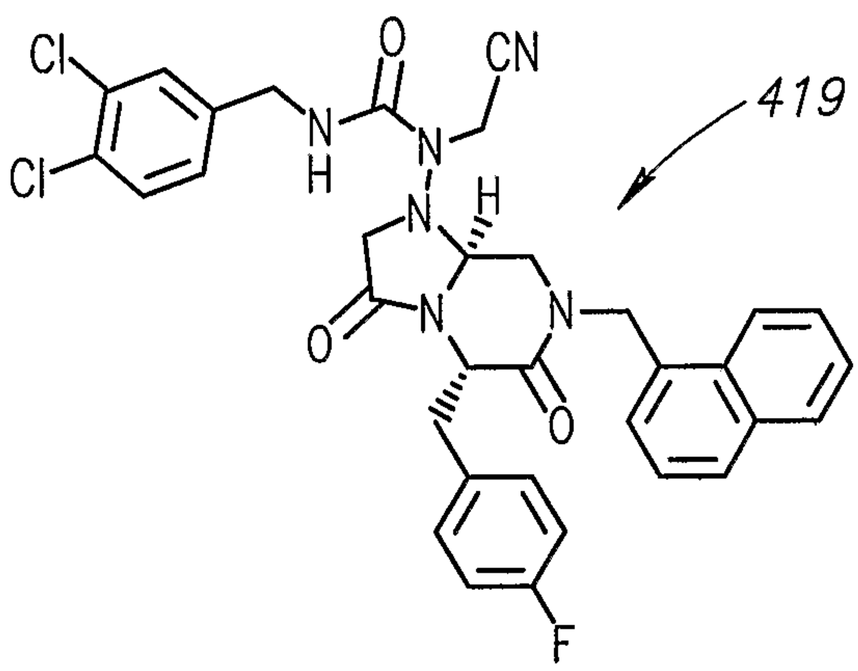
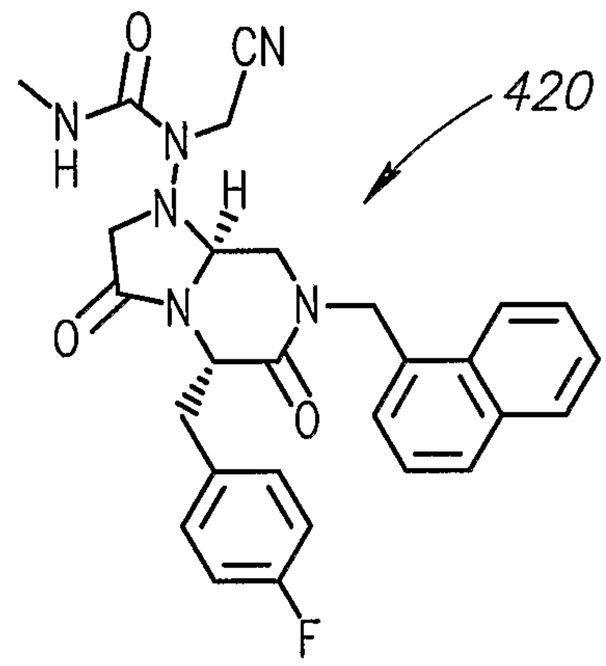


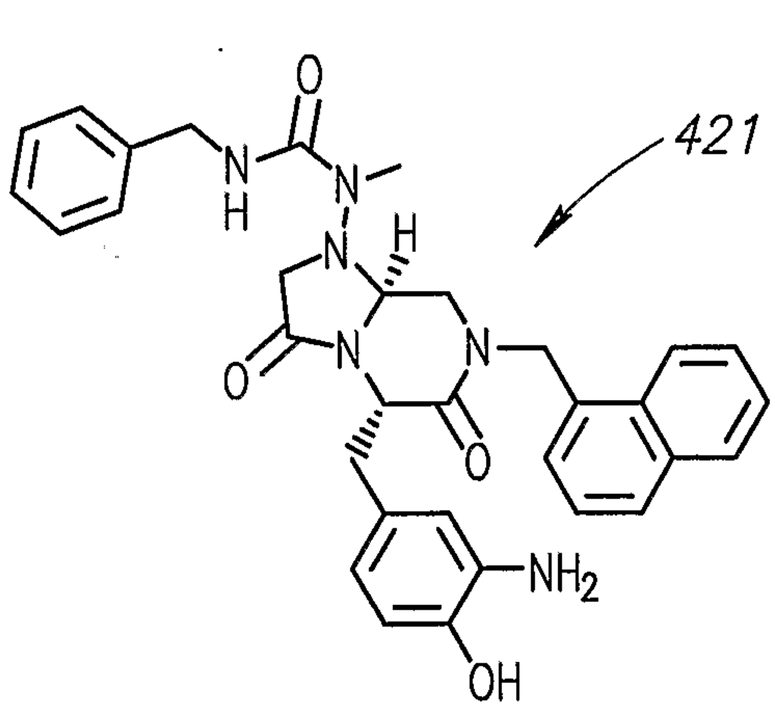
FIG.3B











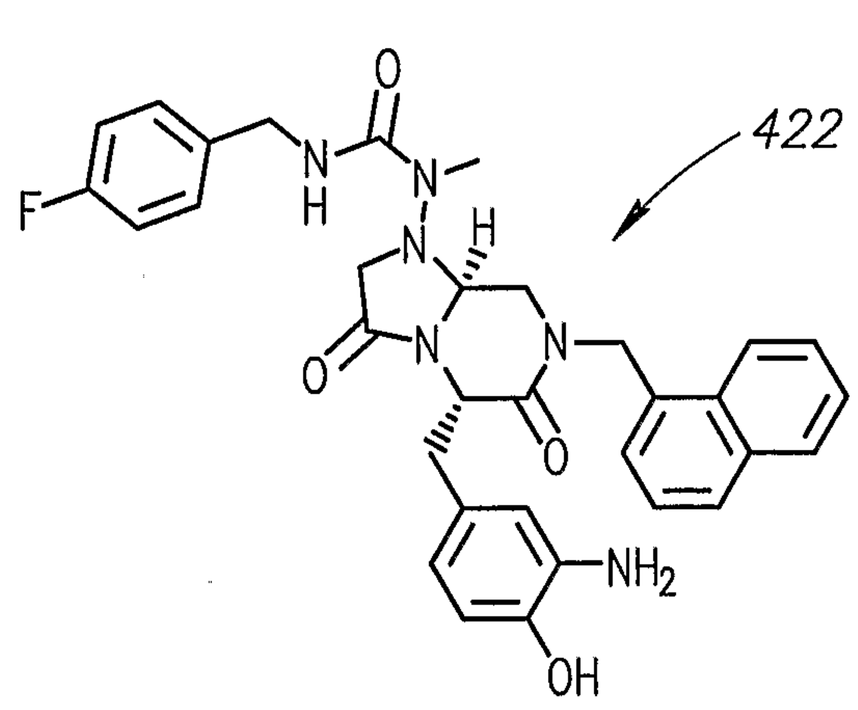
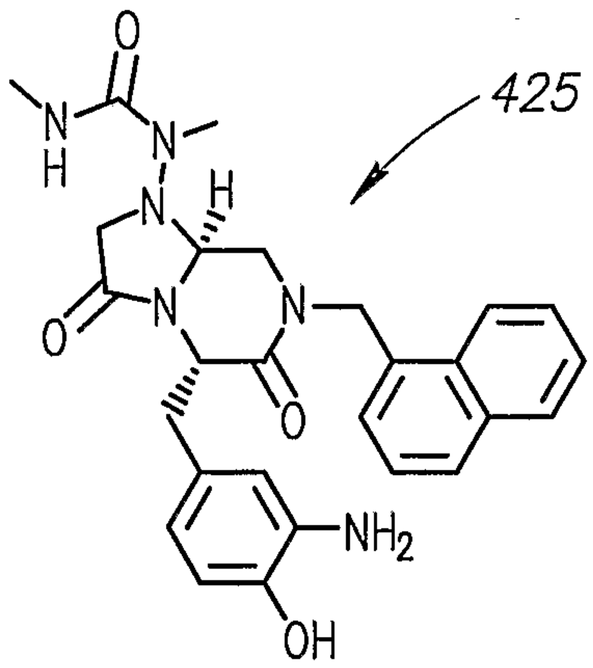


FIG.3C


425
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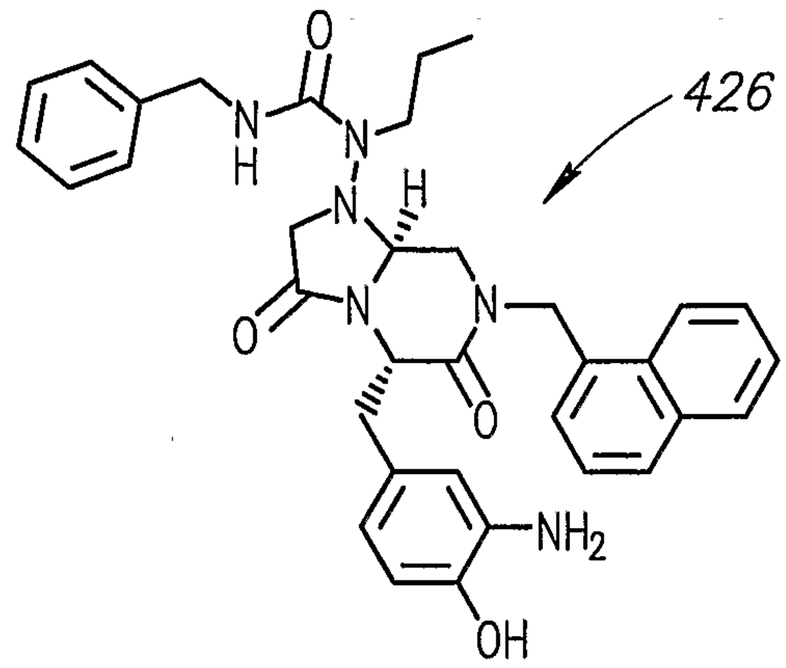
N
H
N
N
H
O
N
N
O
NH2
OH


426
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O
N
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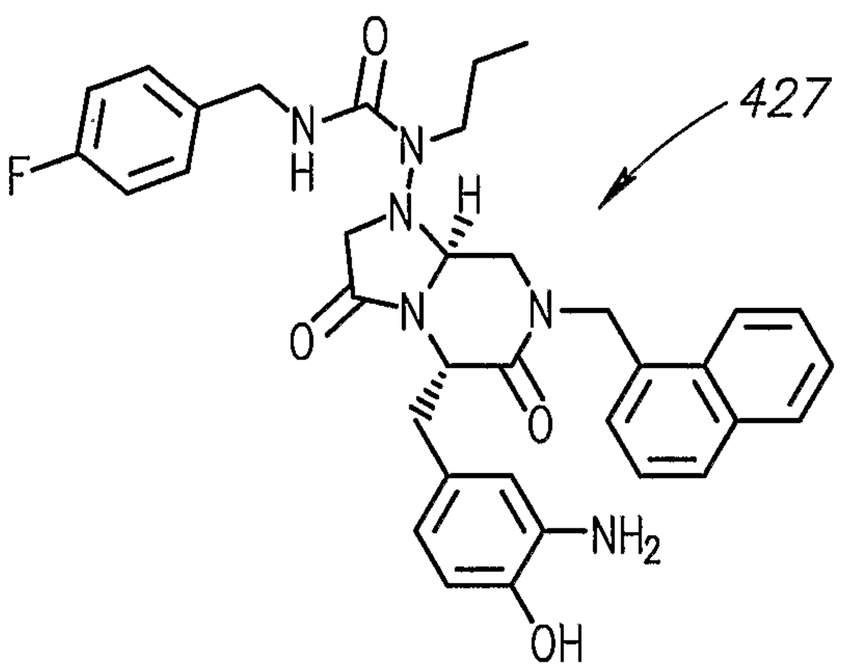
O
NH2
OH


427
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O
NH2
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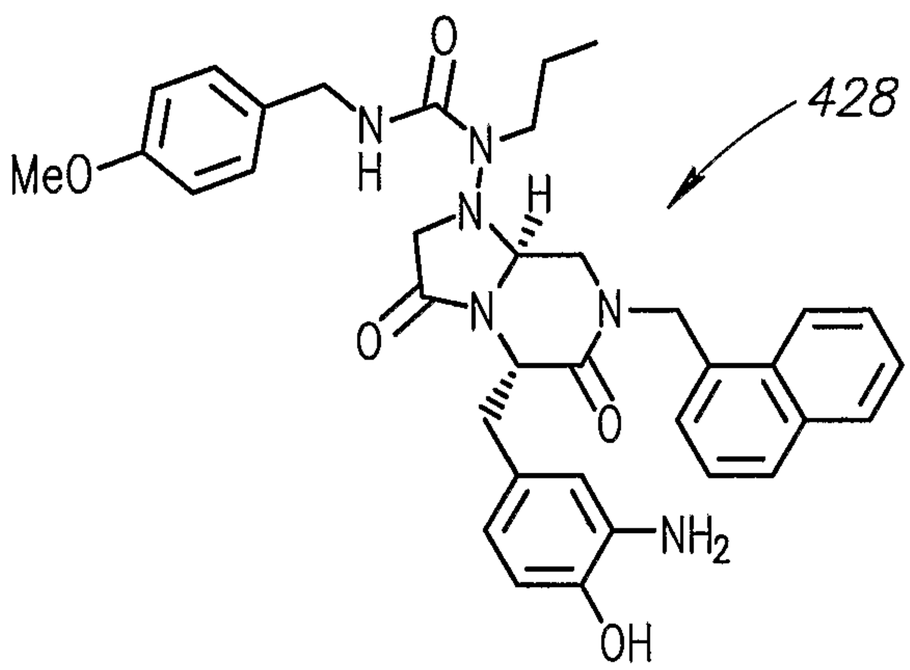
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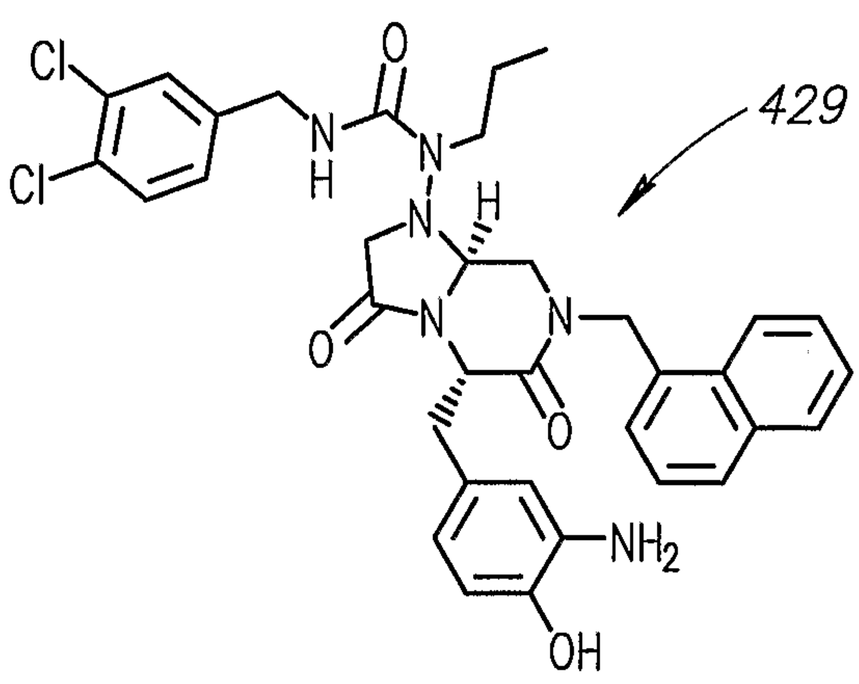
N
O
NH2
OH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N
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N
H
O
N
N
O
NH2
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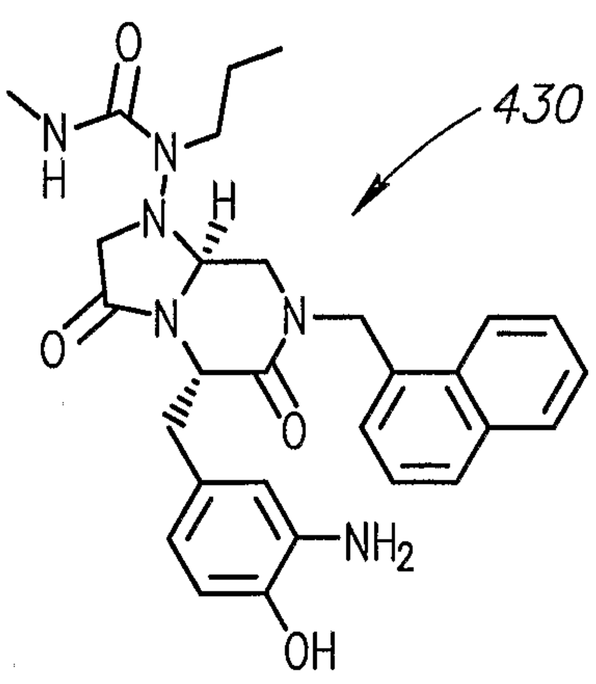
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NH2
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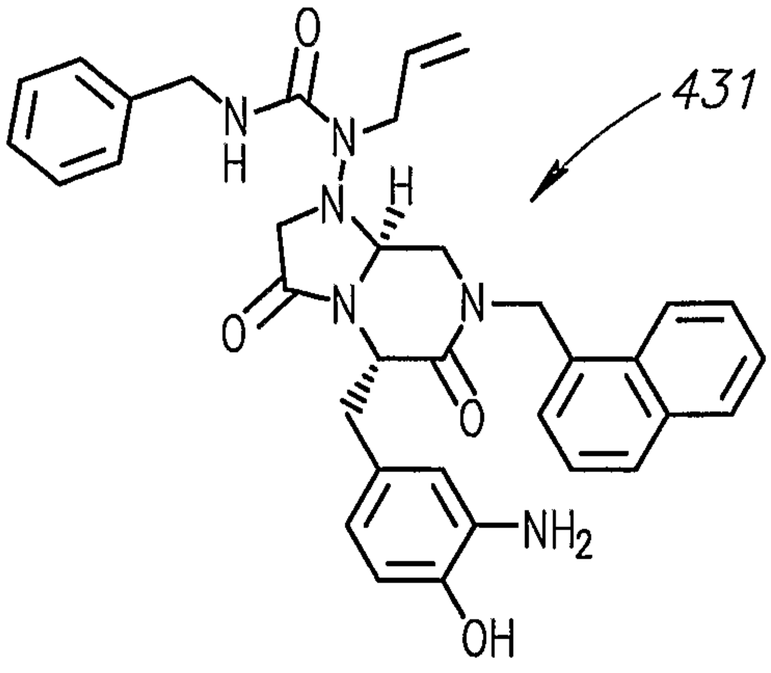
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O
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NH2
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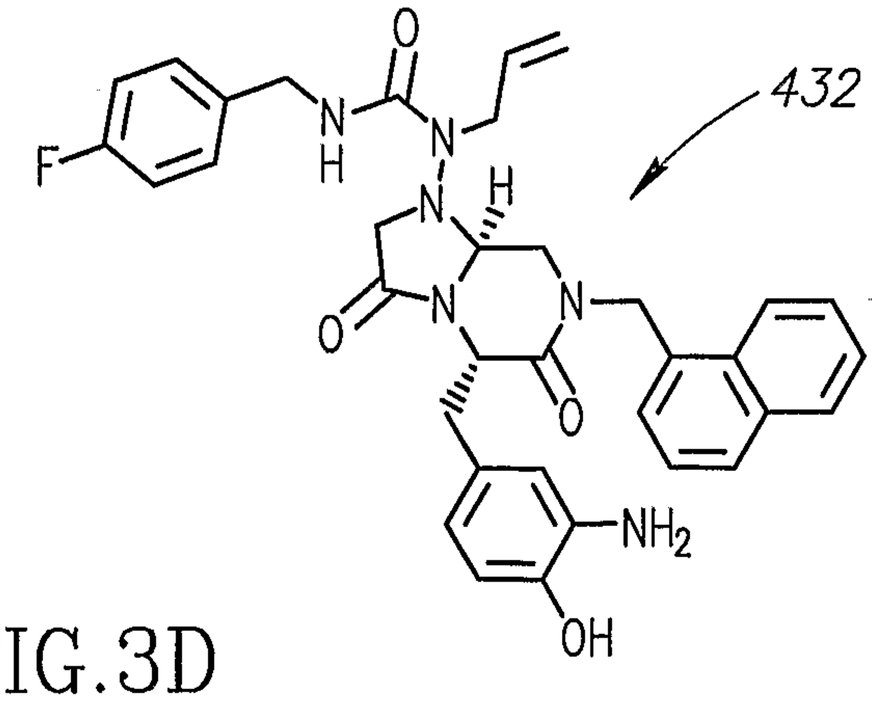
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H
O
N
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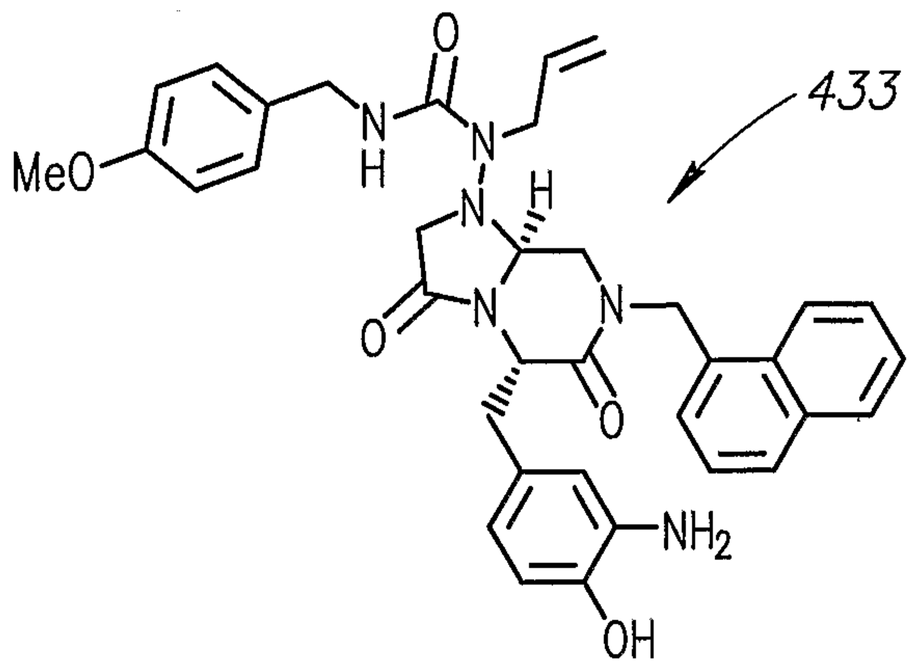
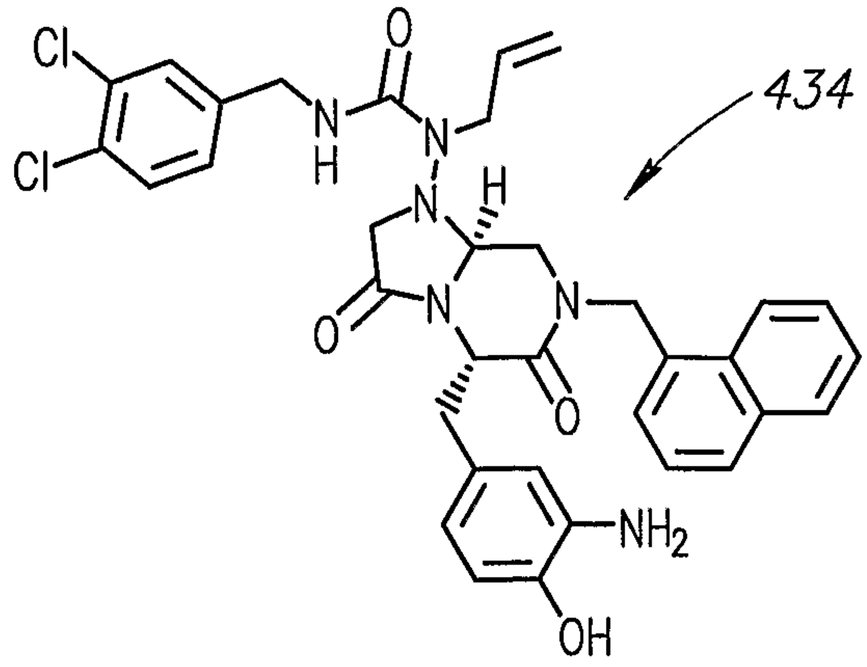
O
NH2
OH

FIG.3D


433
MeO
NH2
OH


434
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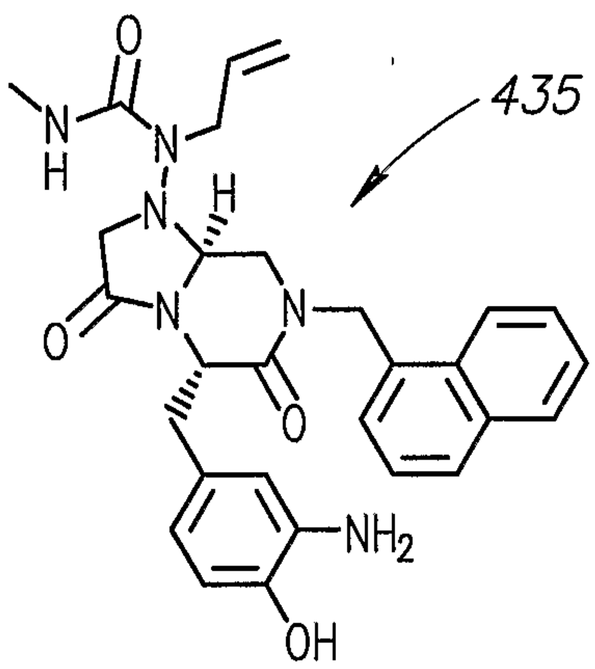
Cl
NH2
OH


435
NH2
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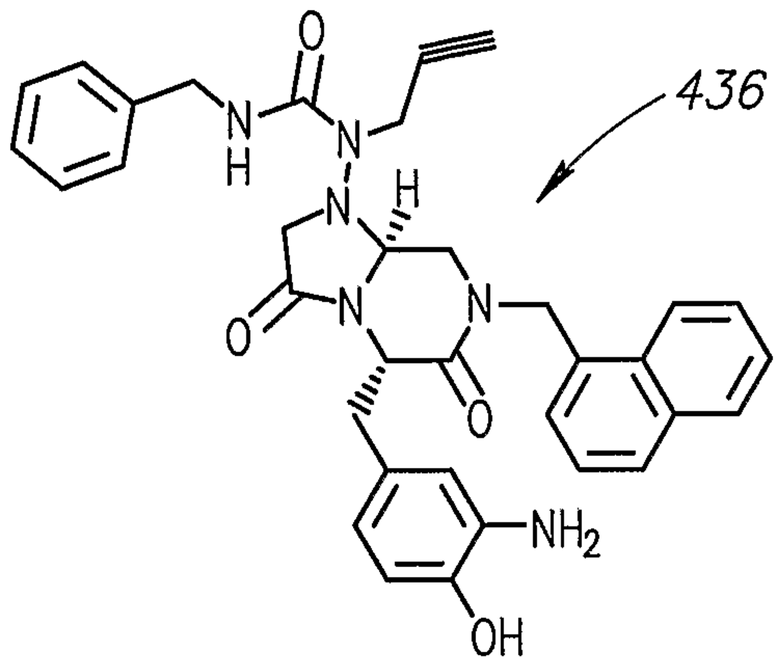
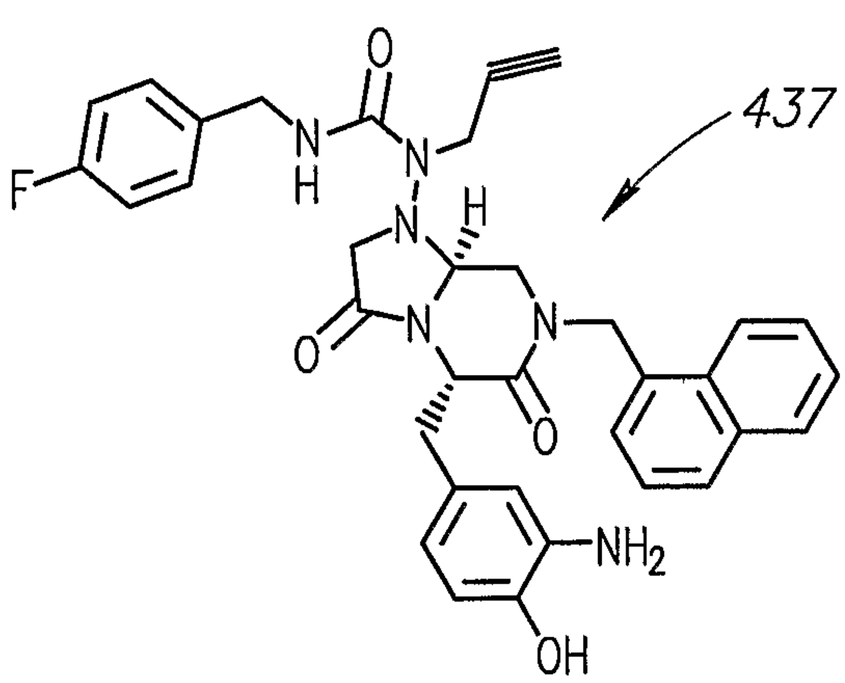
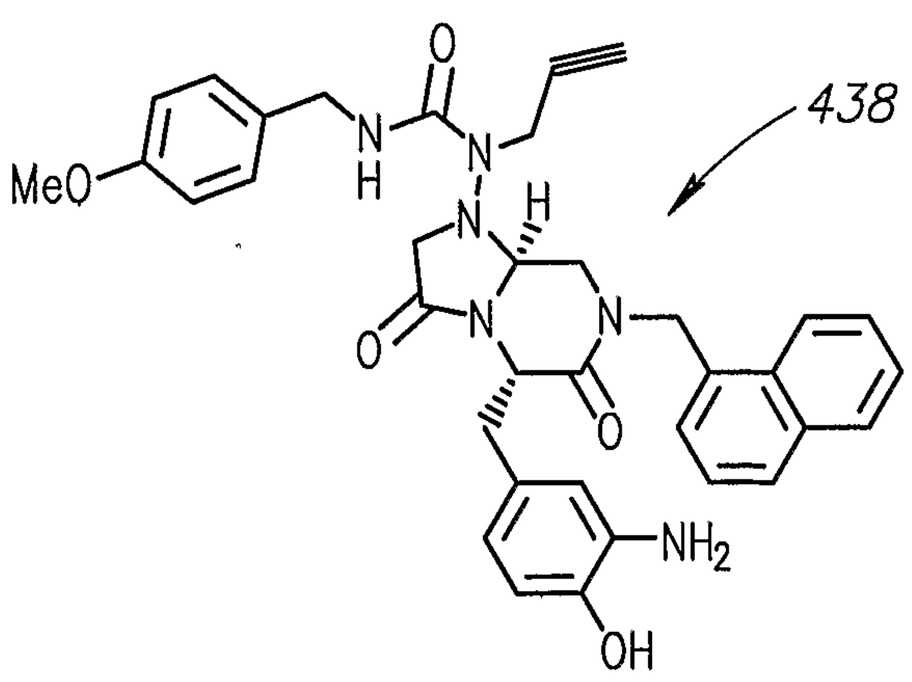
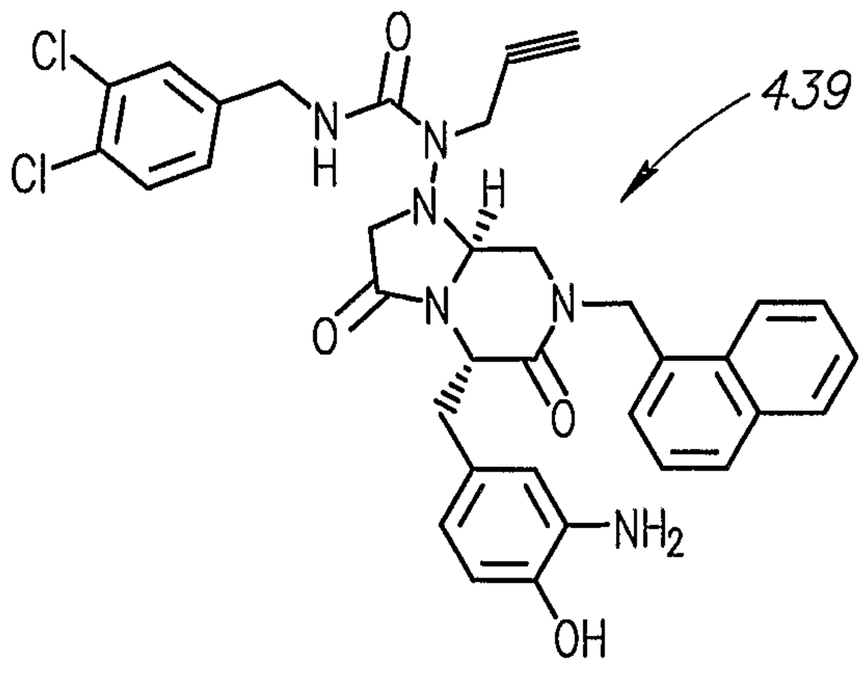

436
NH2
OH


437
F
NH2
OH


438
MeO
NH2
OH


439
Cl
Cl
NH2
OH

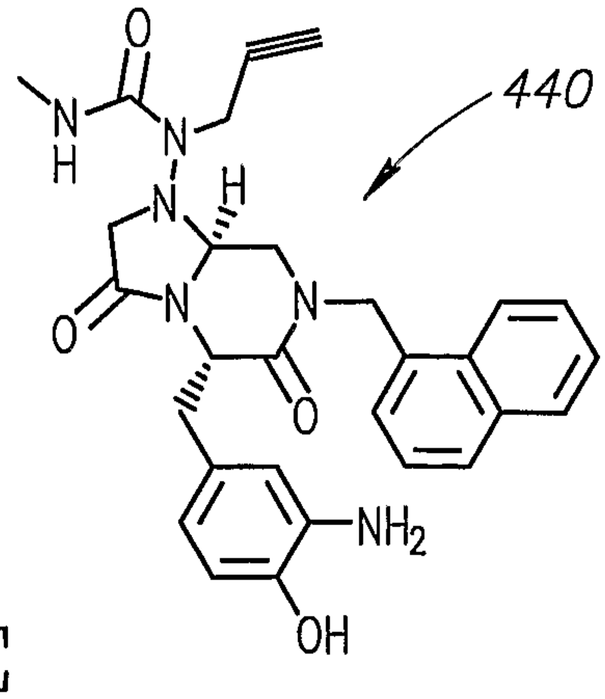
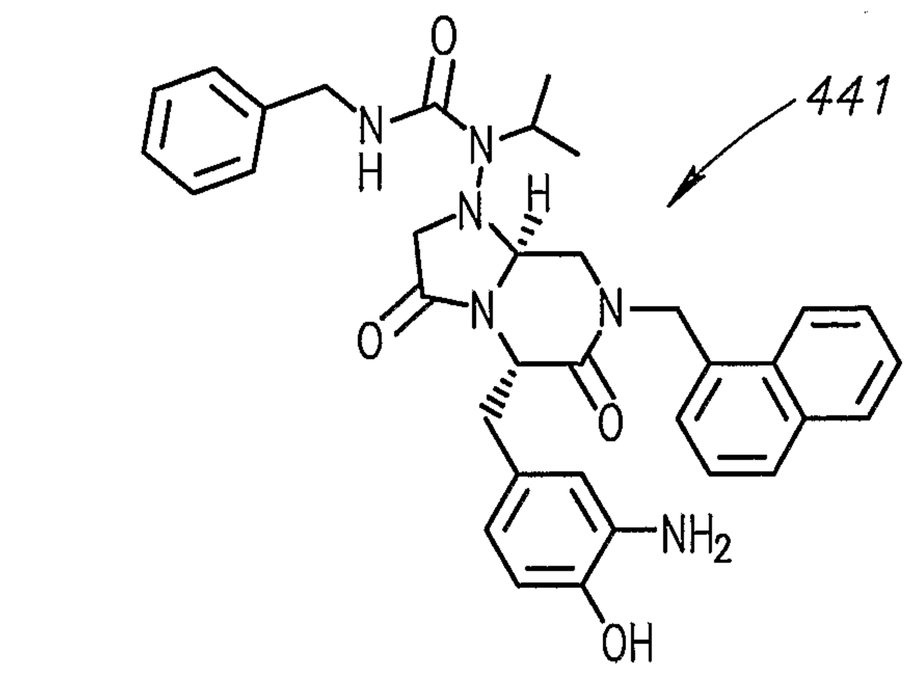
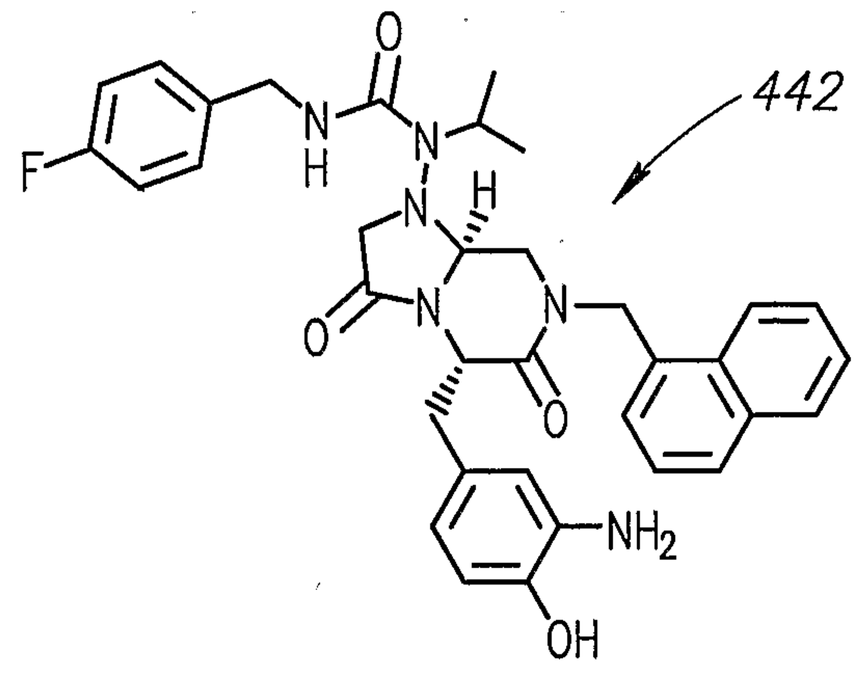
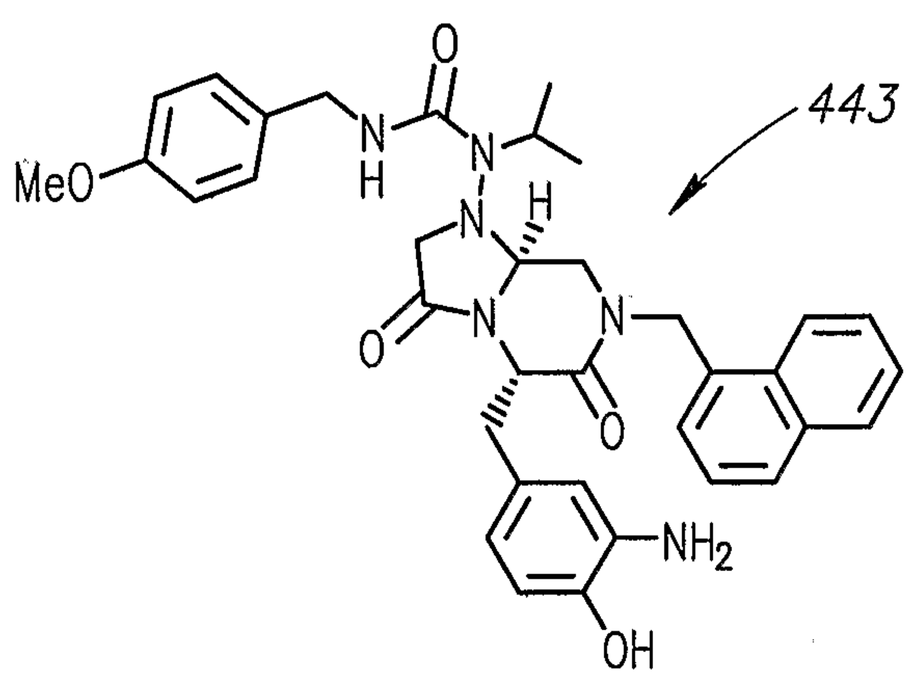
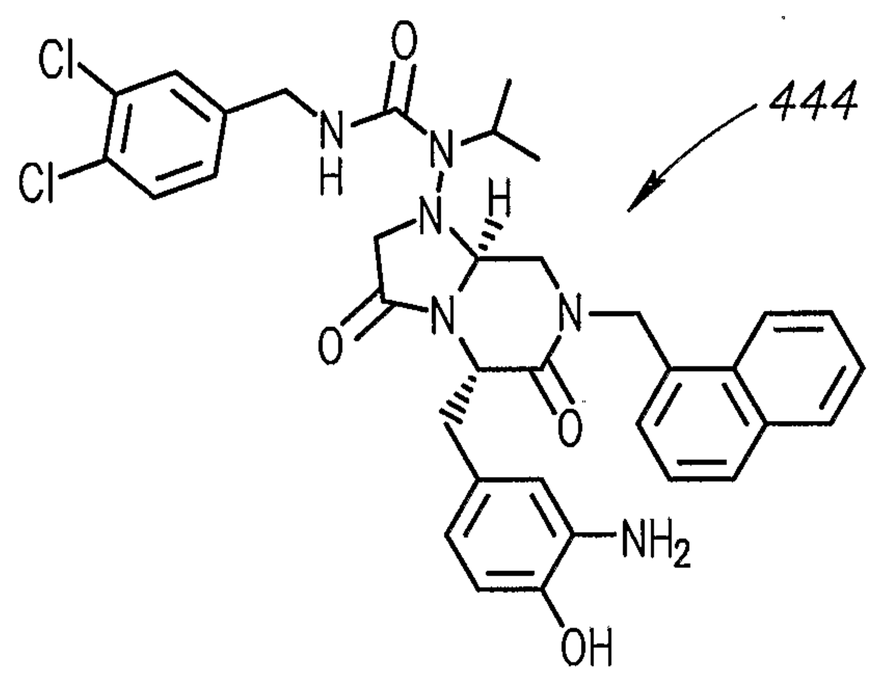

440
NH2
OH

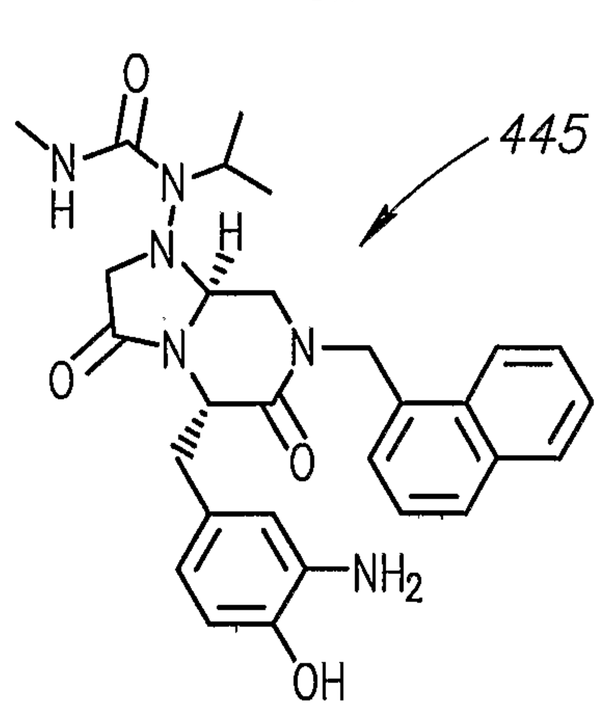
FIG.3E











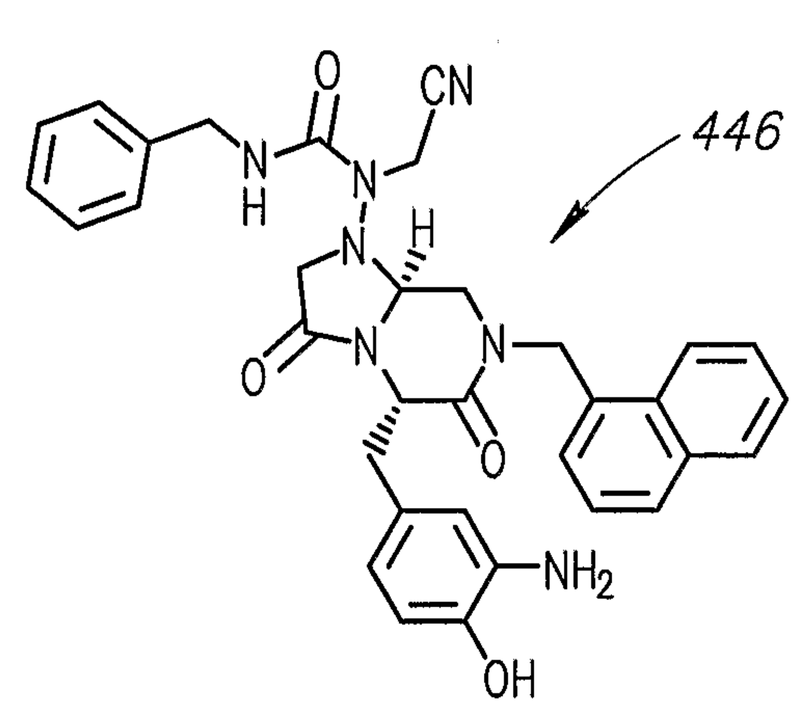
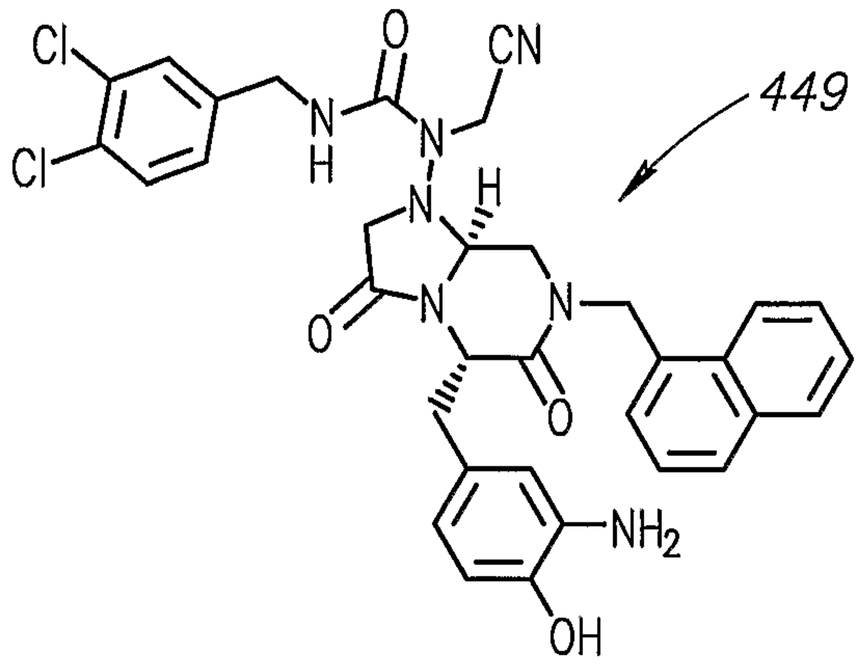
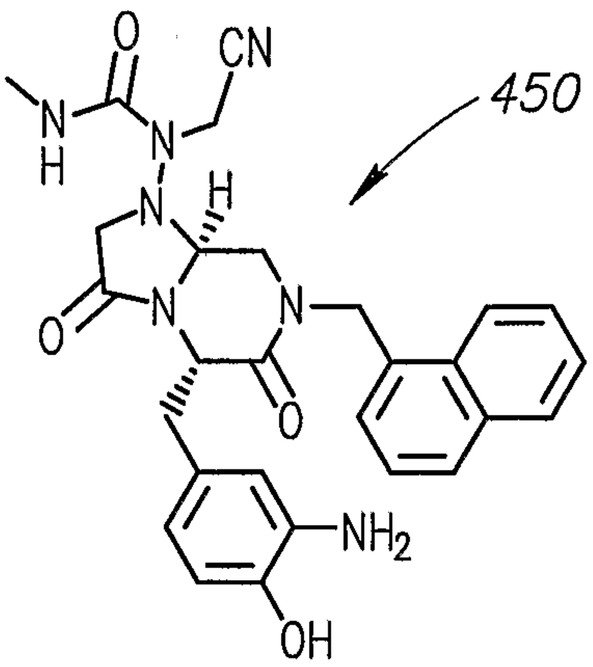
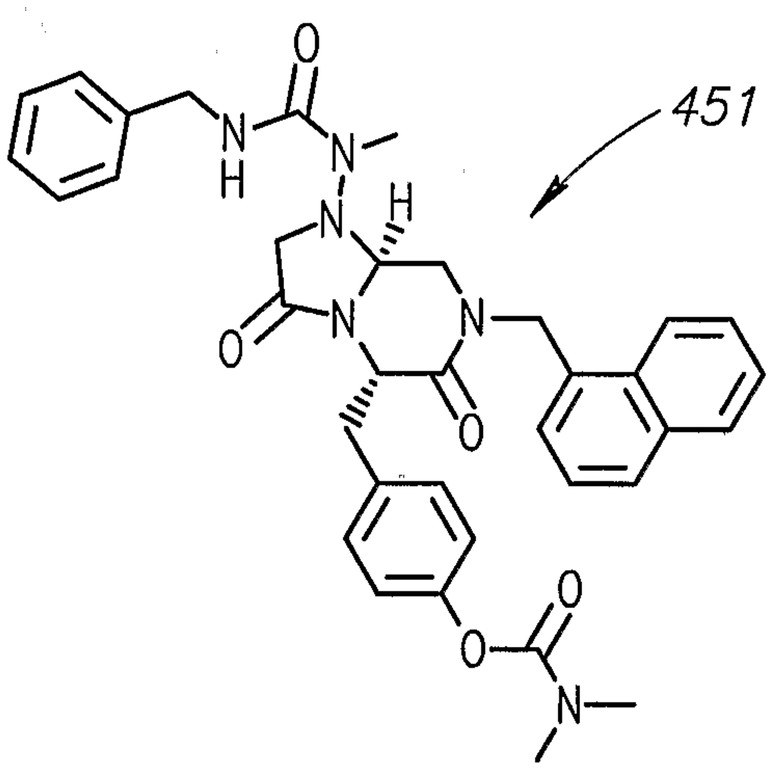
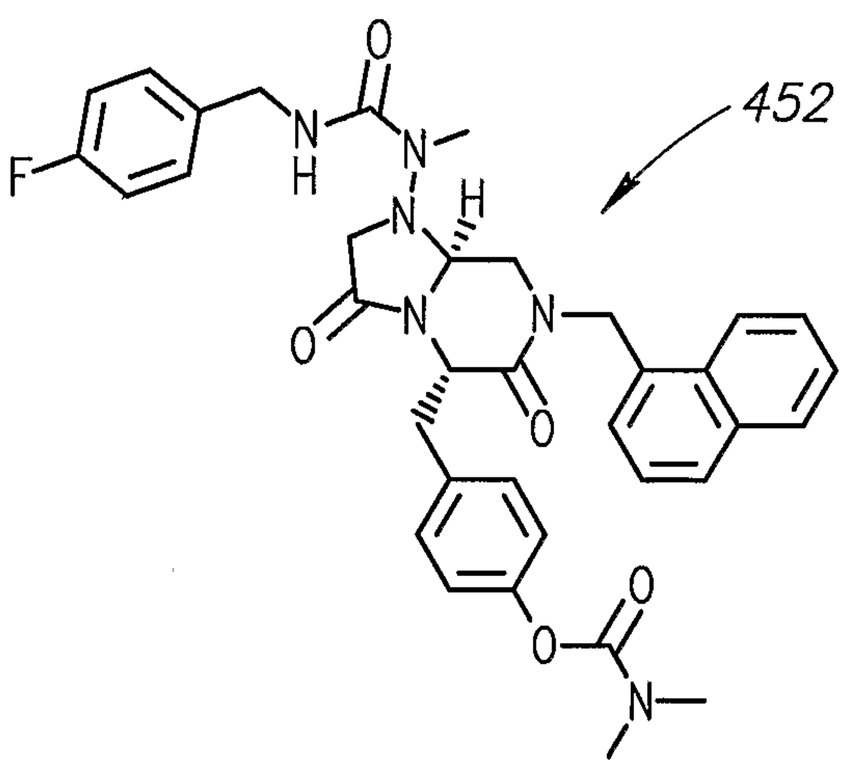


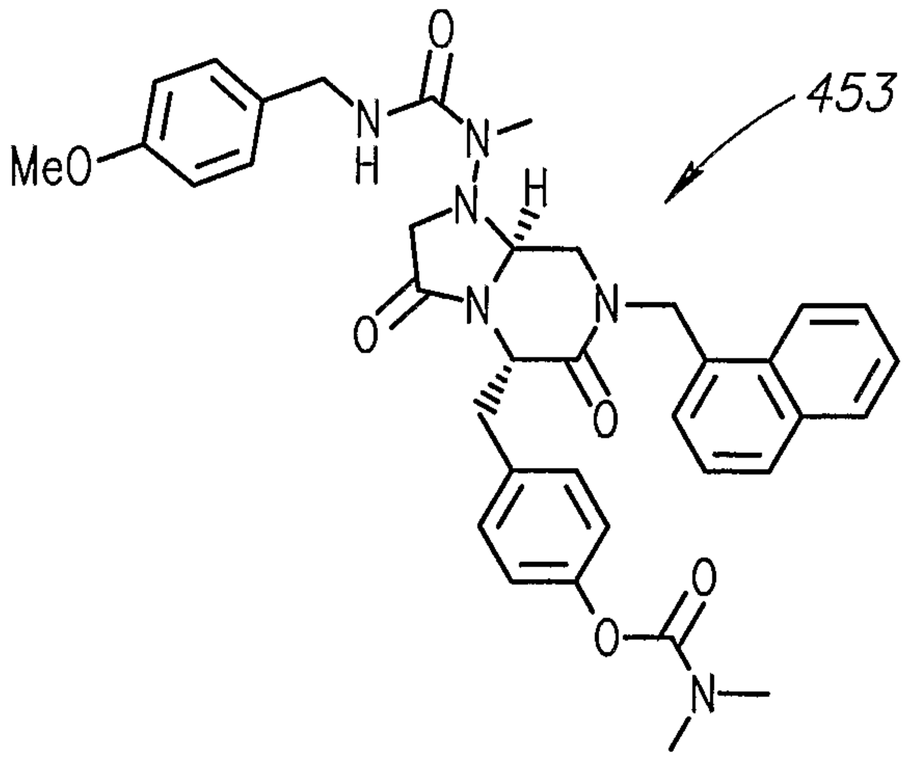
FIG.3F











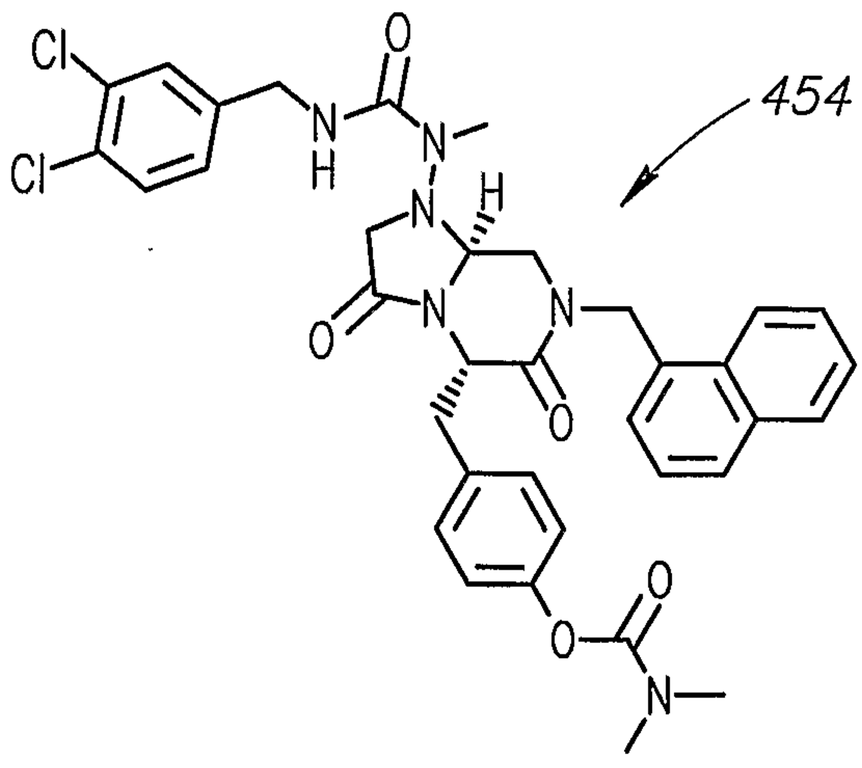
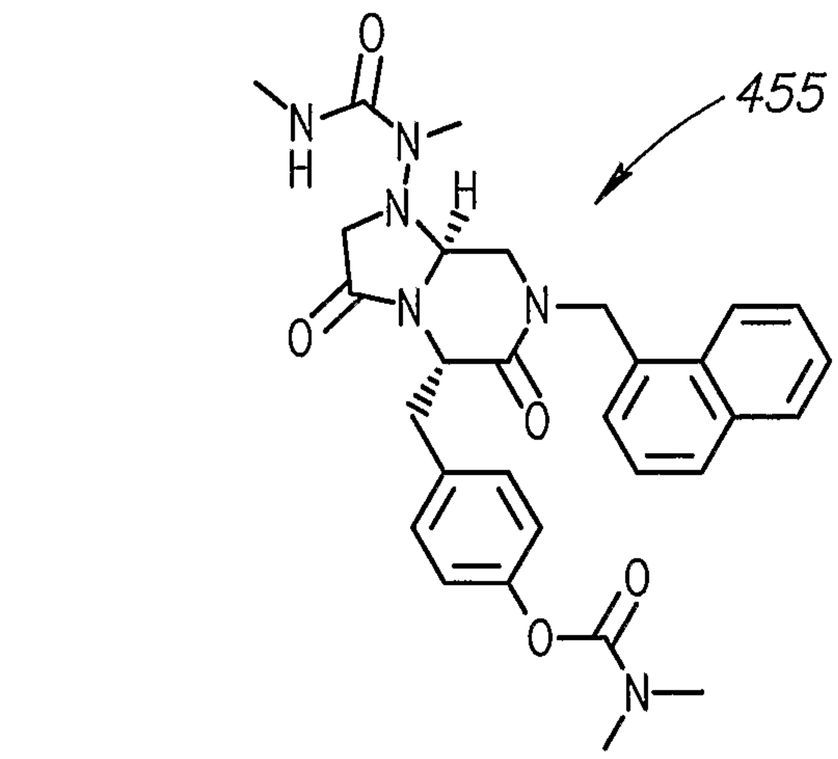
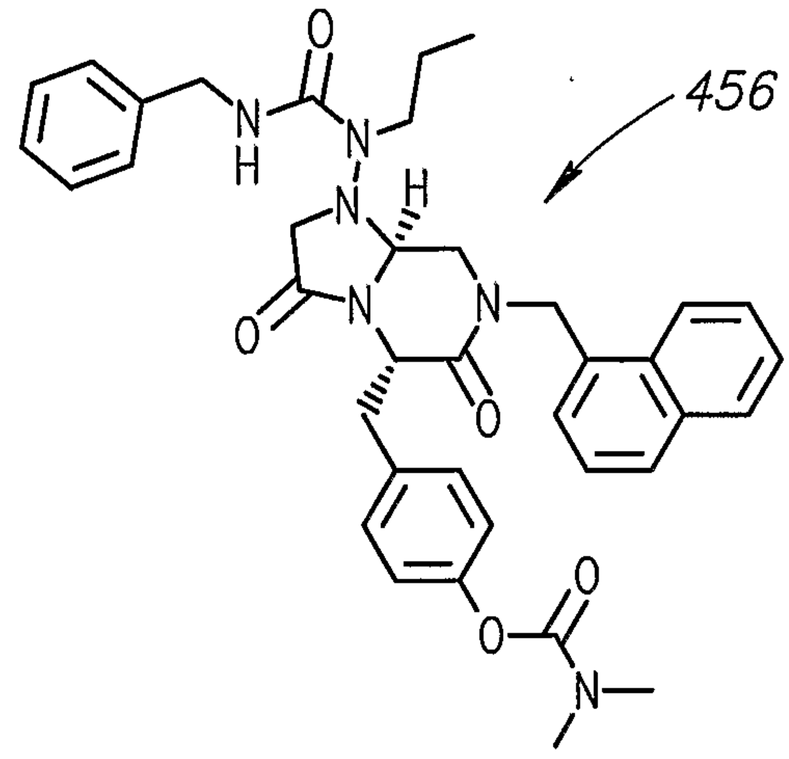
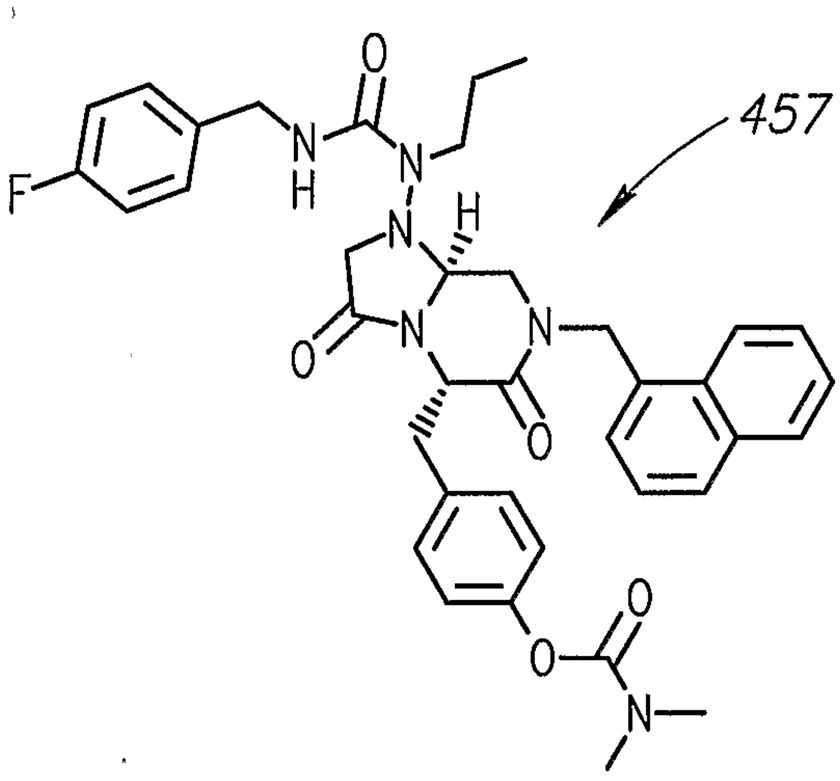
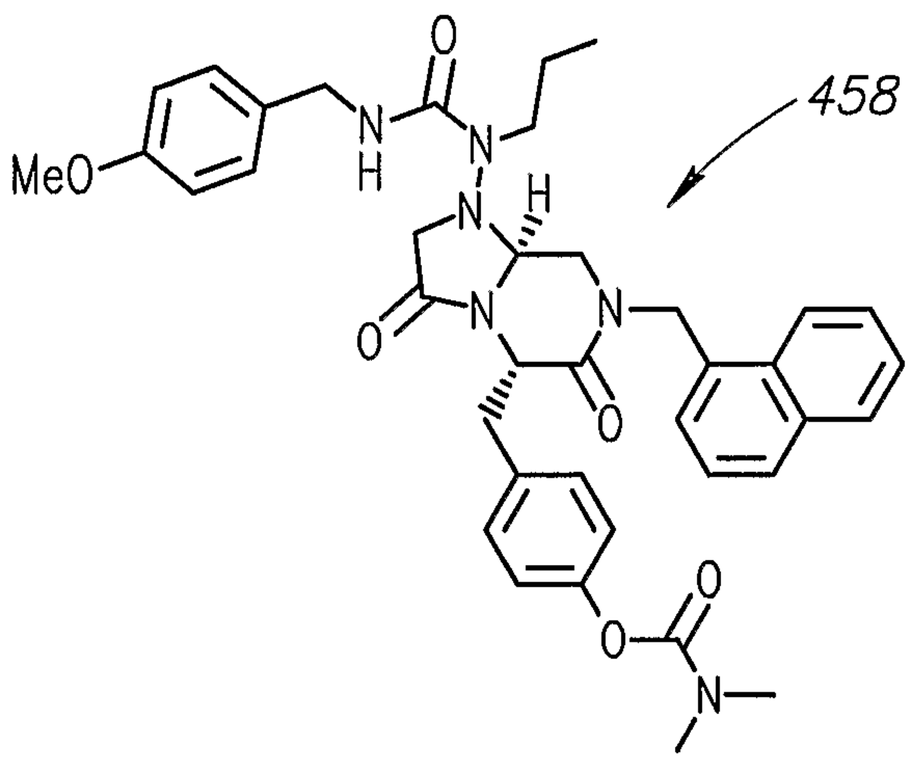


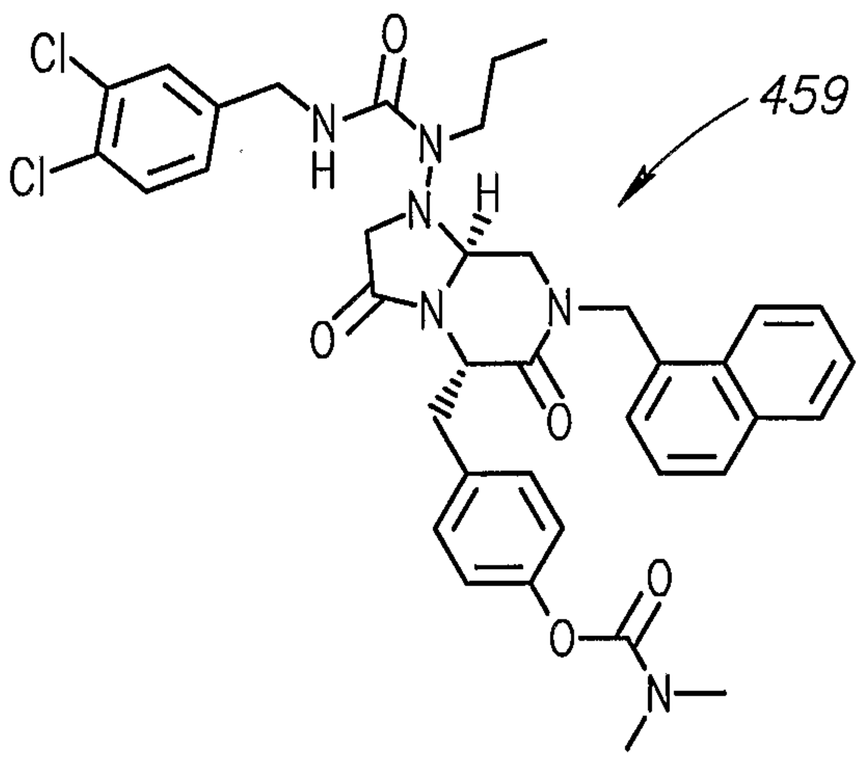
FIG.3G











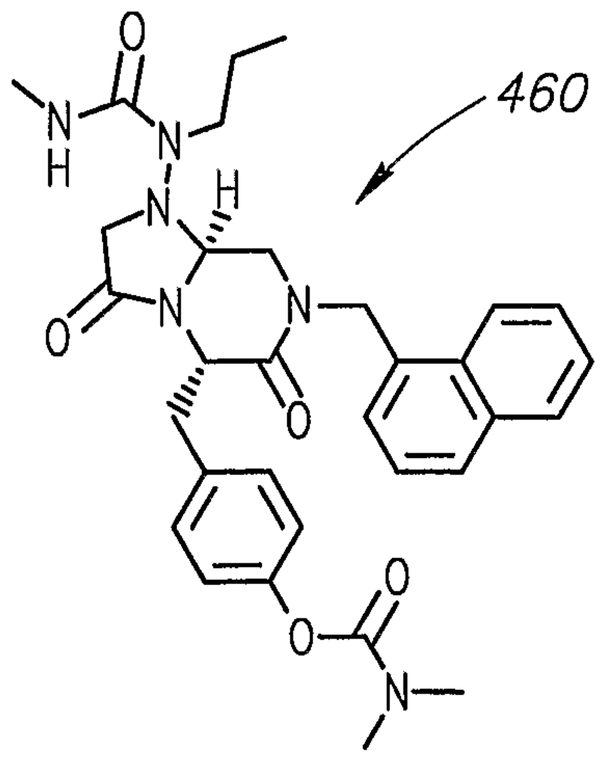
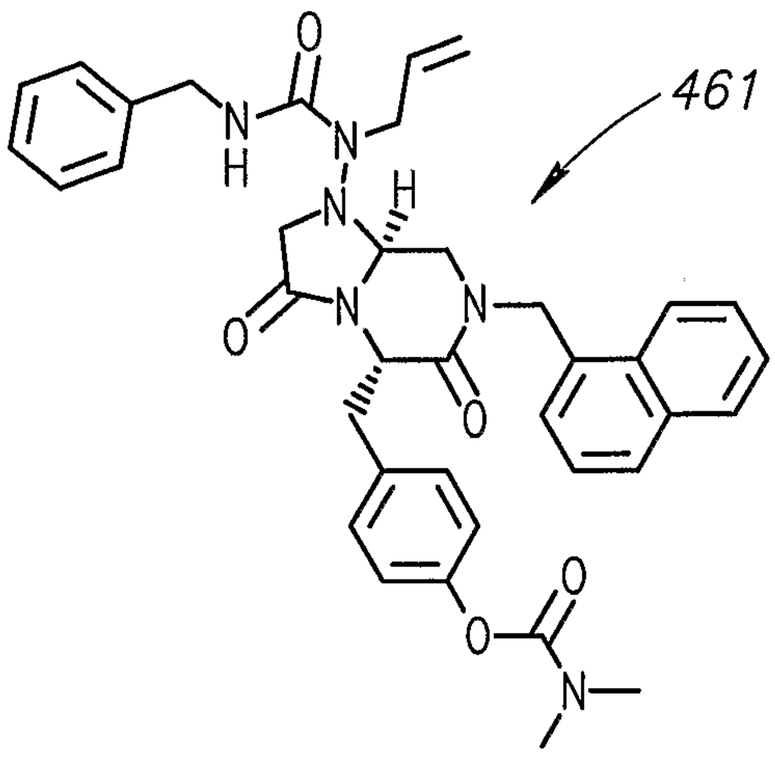
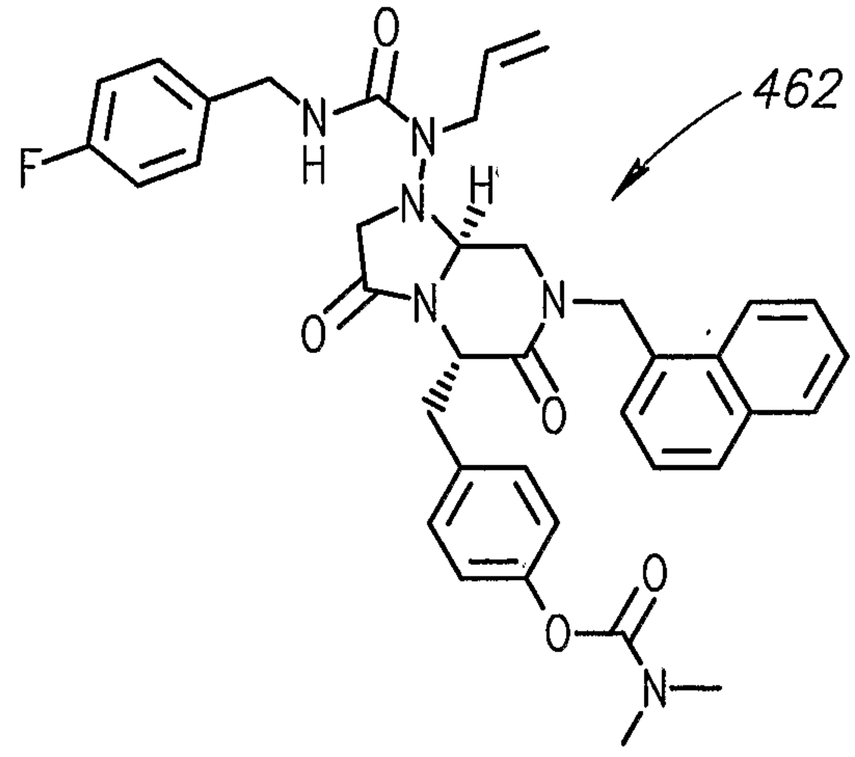
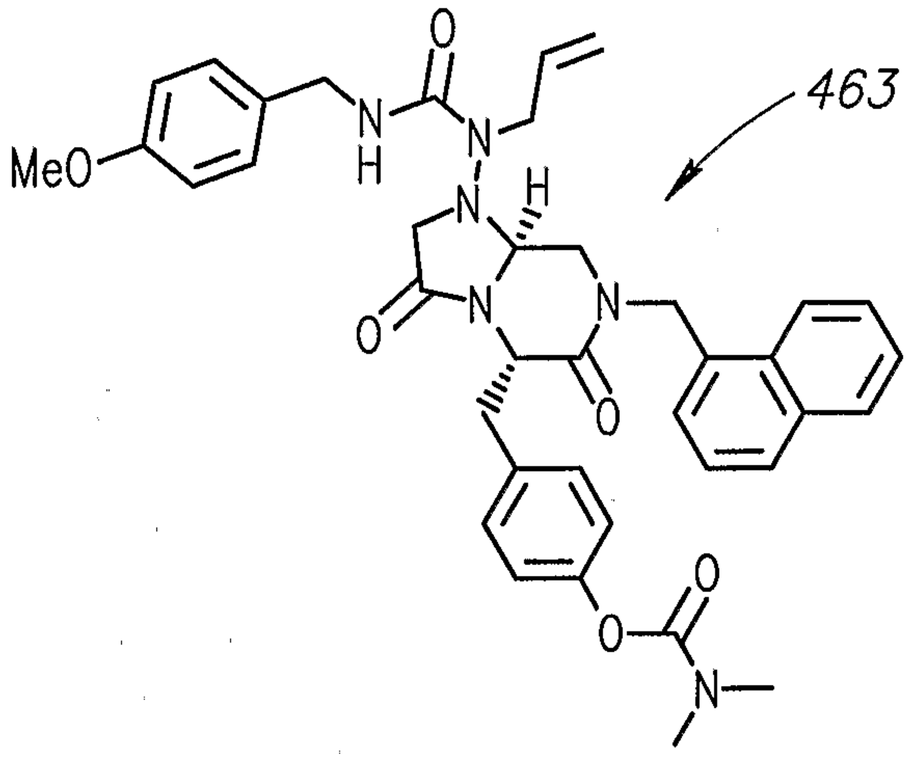
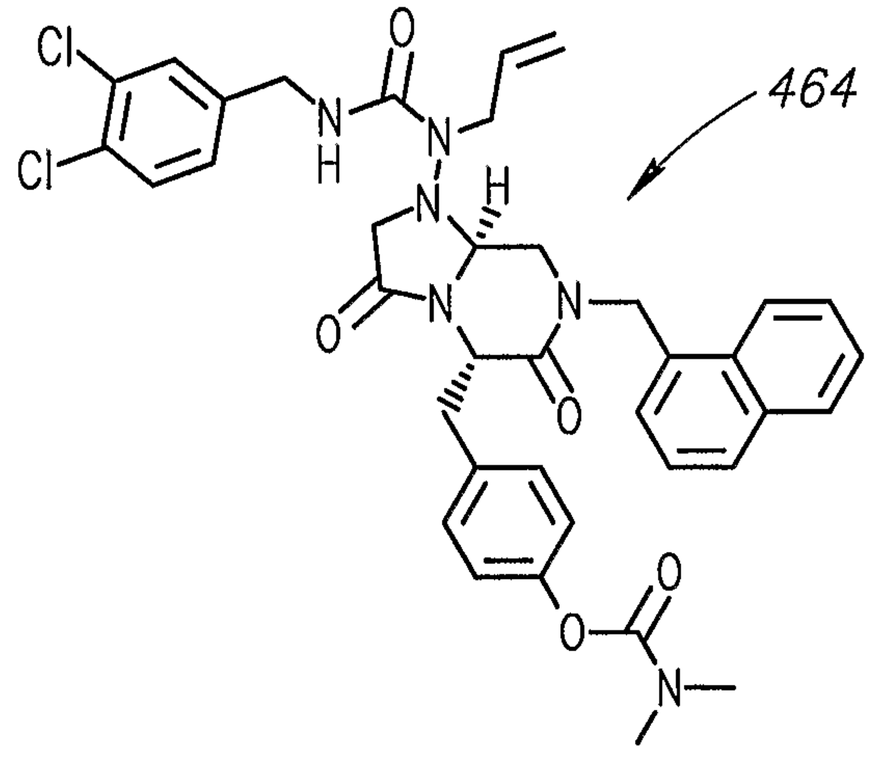


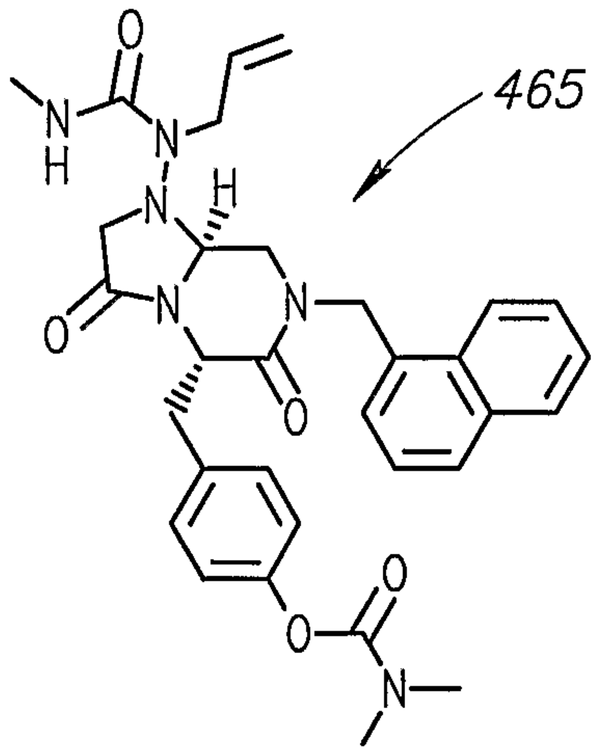
FIG.3H











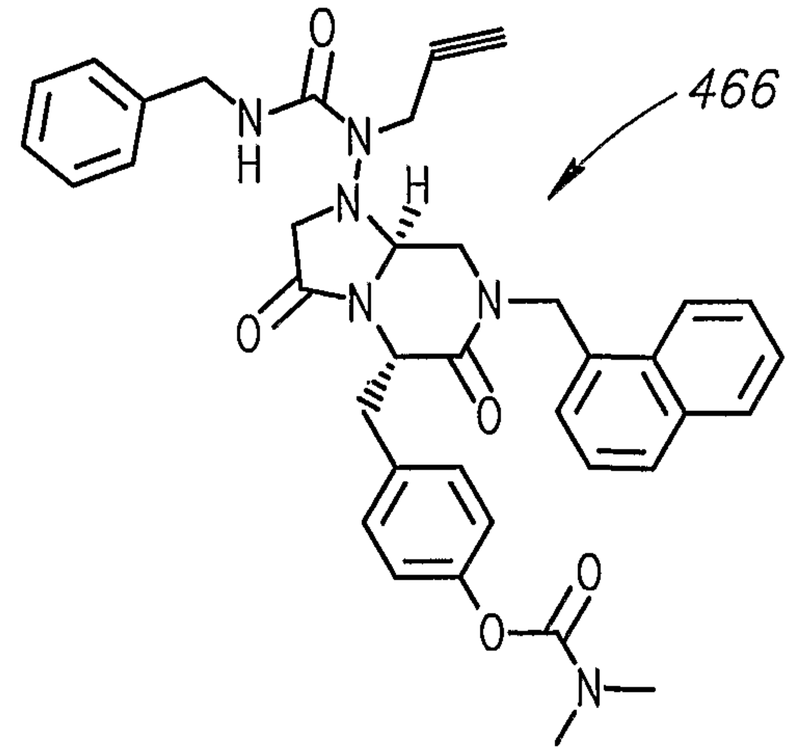
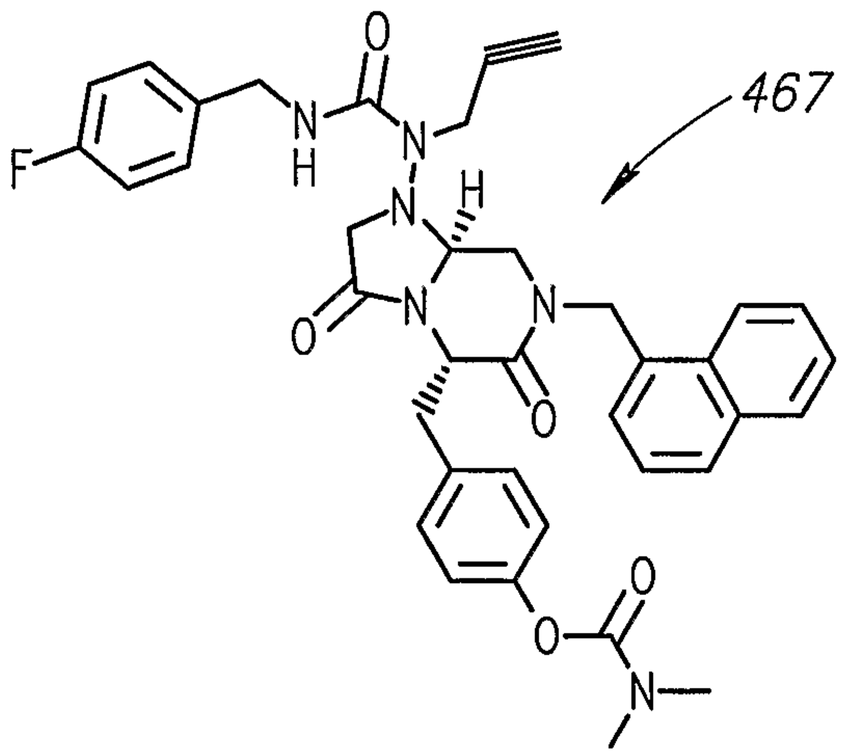
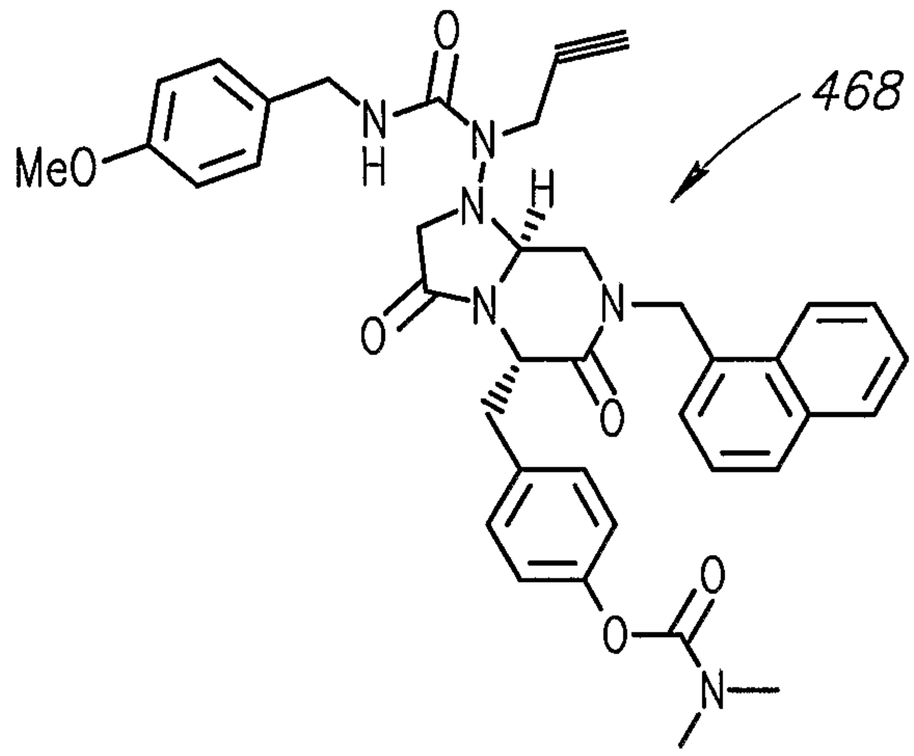
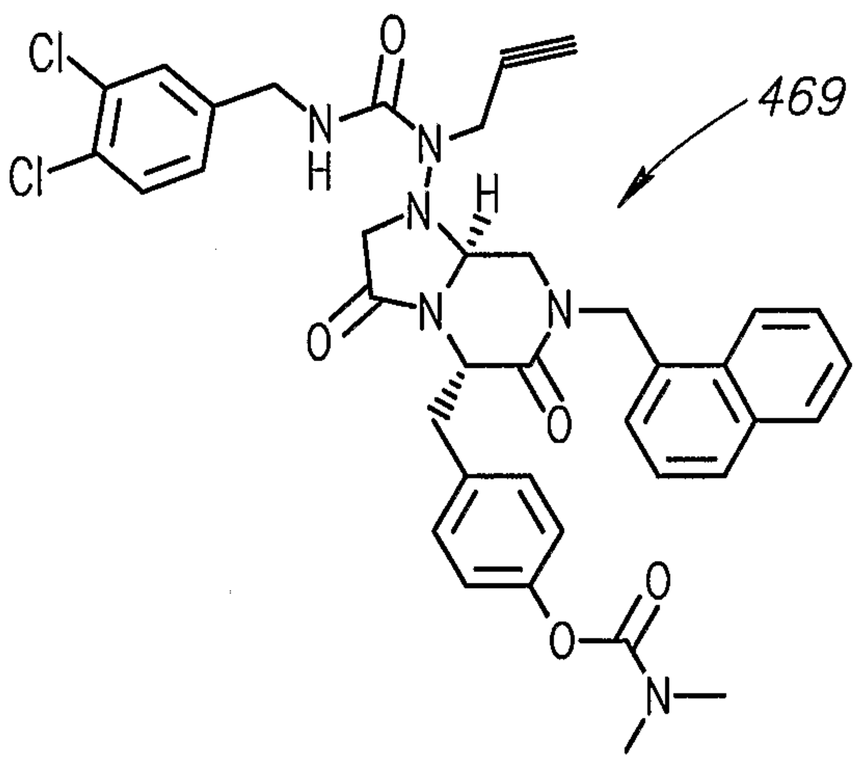
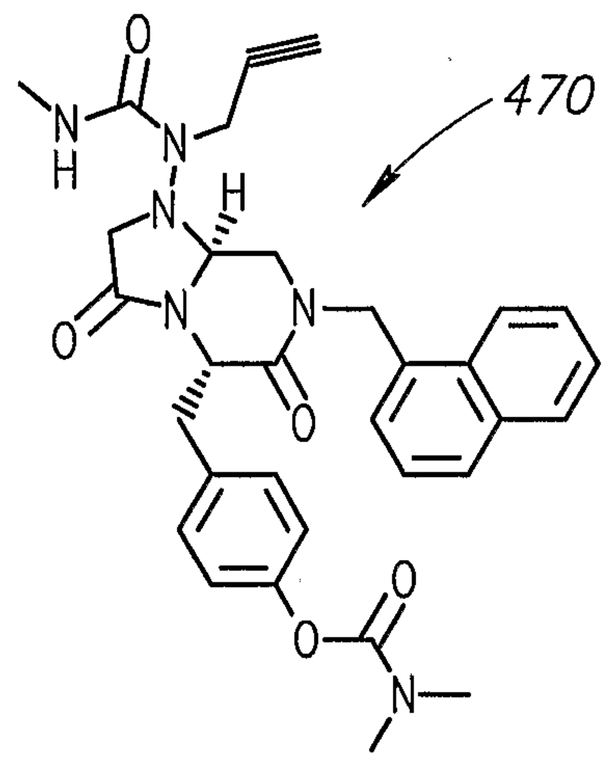


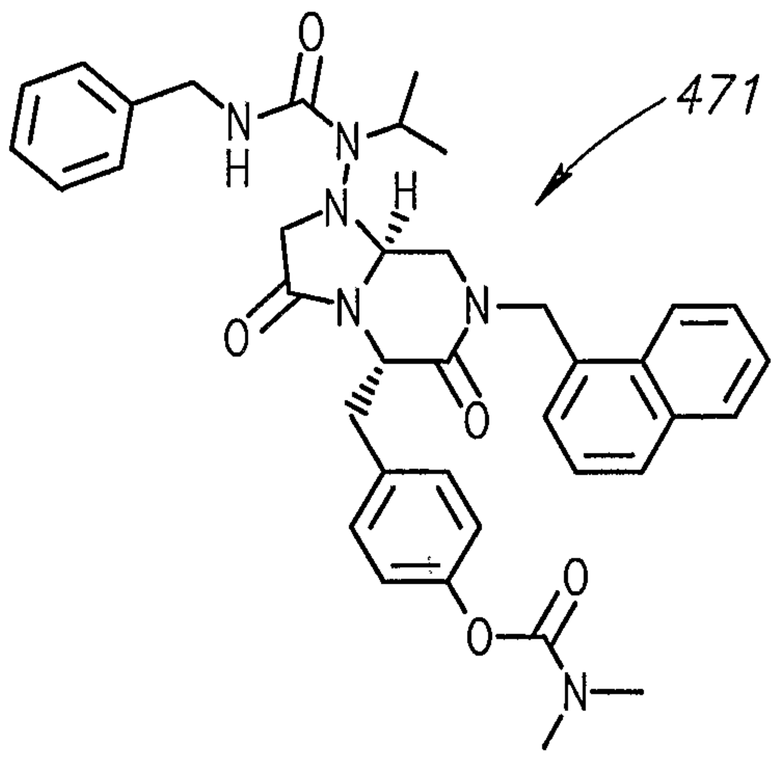
FIG.3I











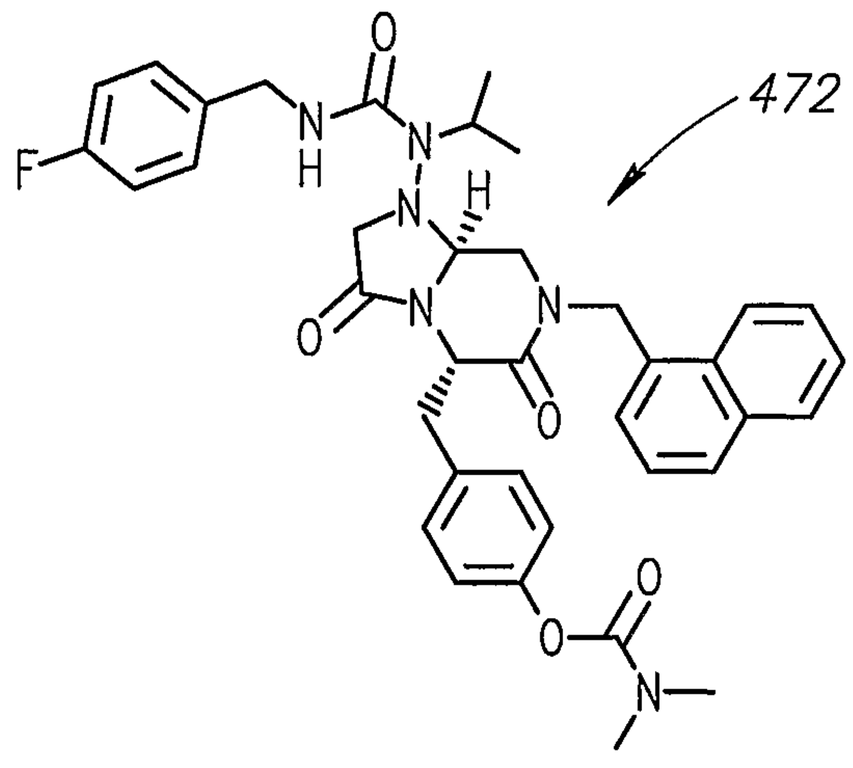
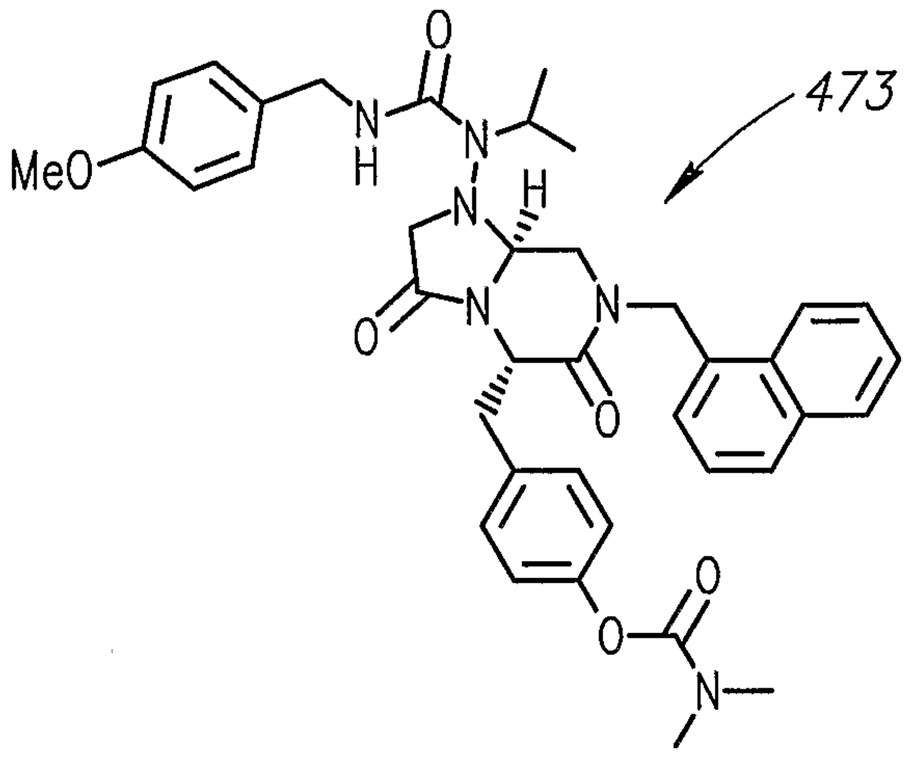
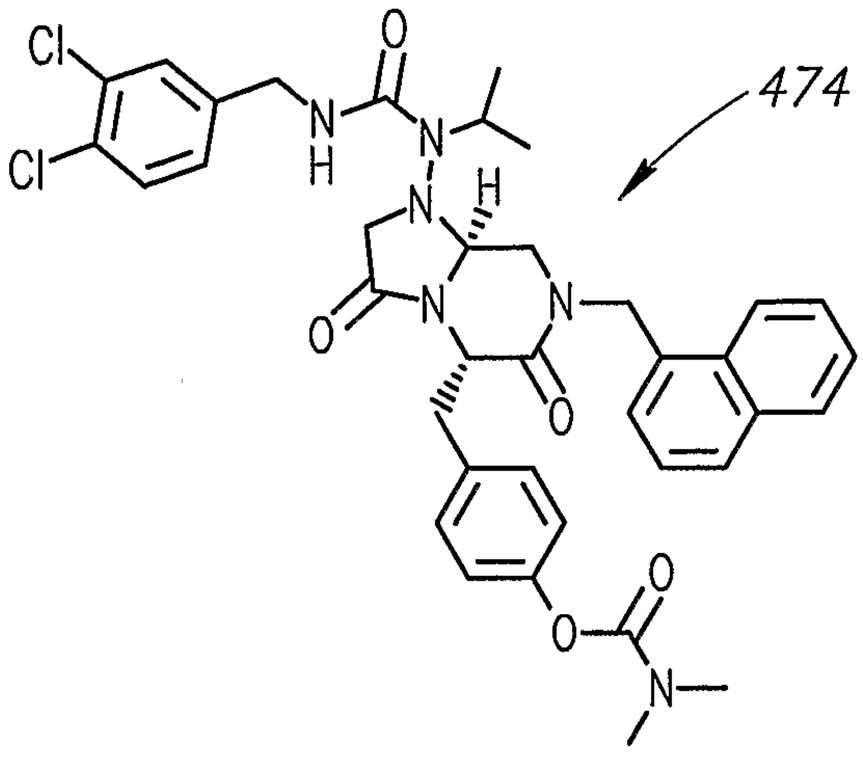
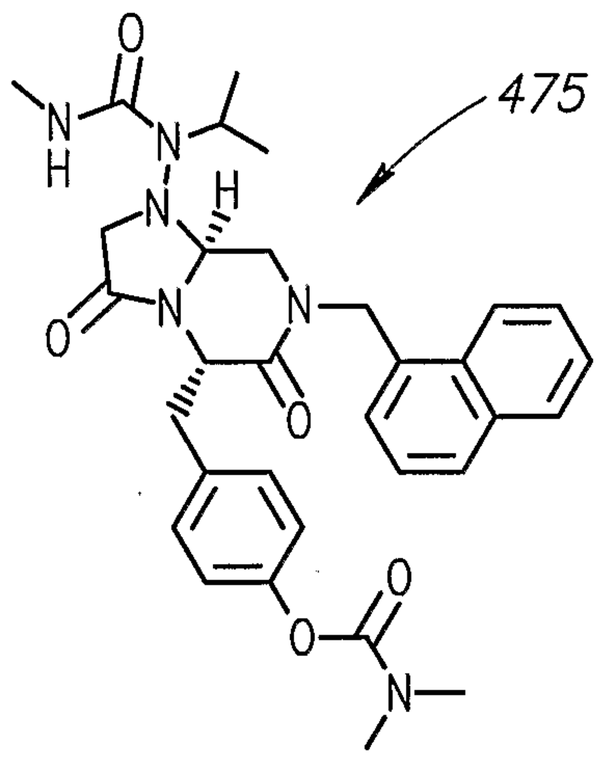
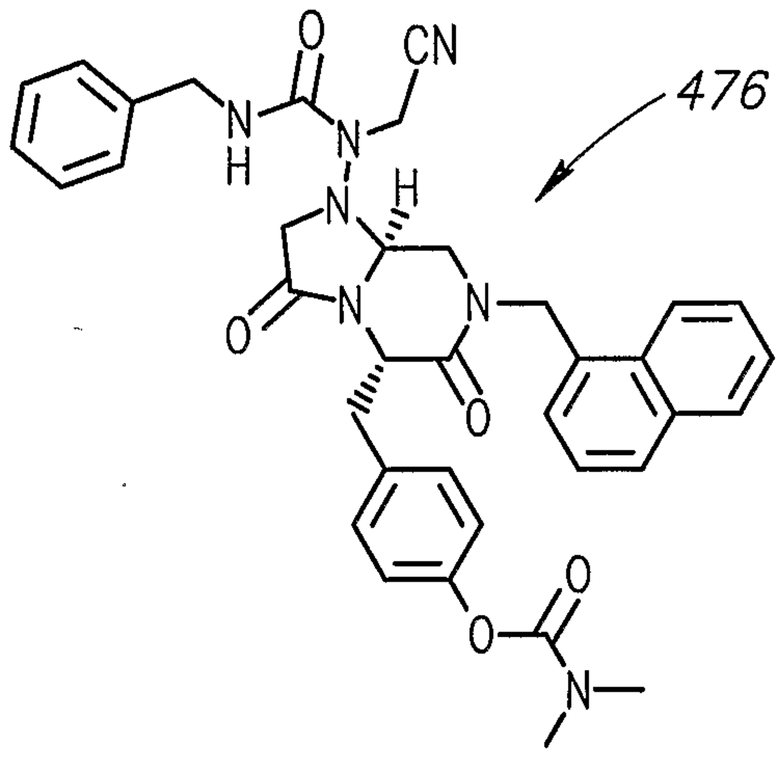


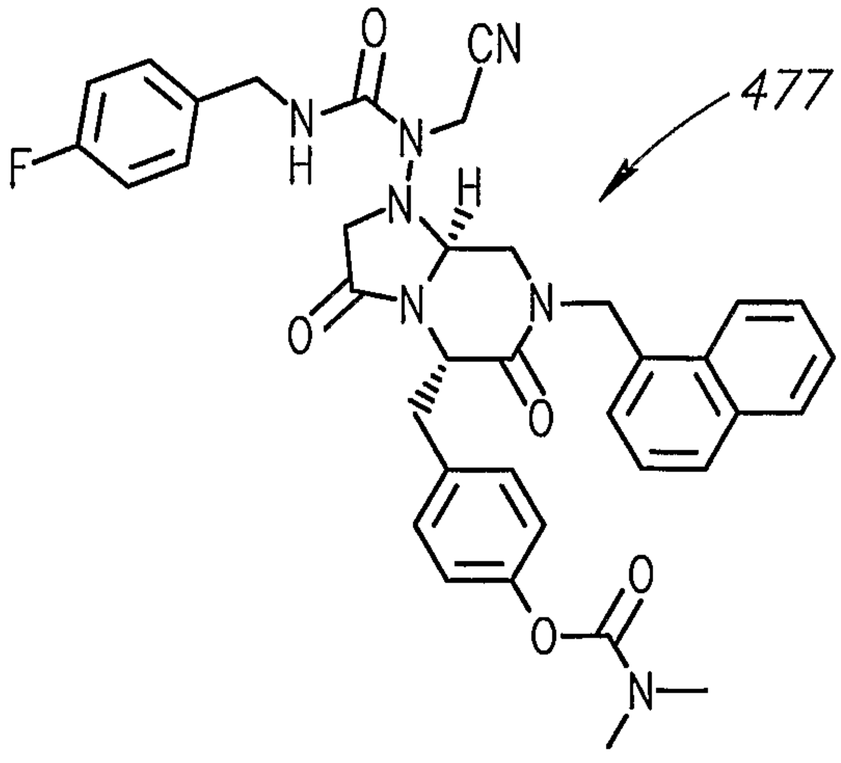
FIG.3J











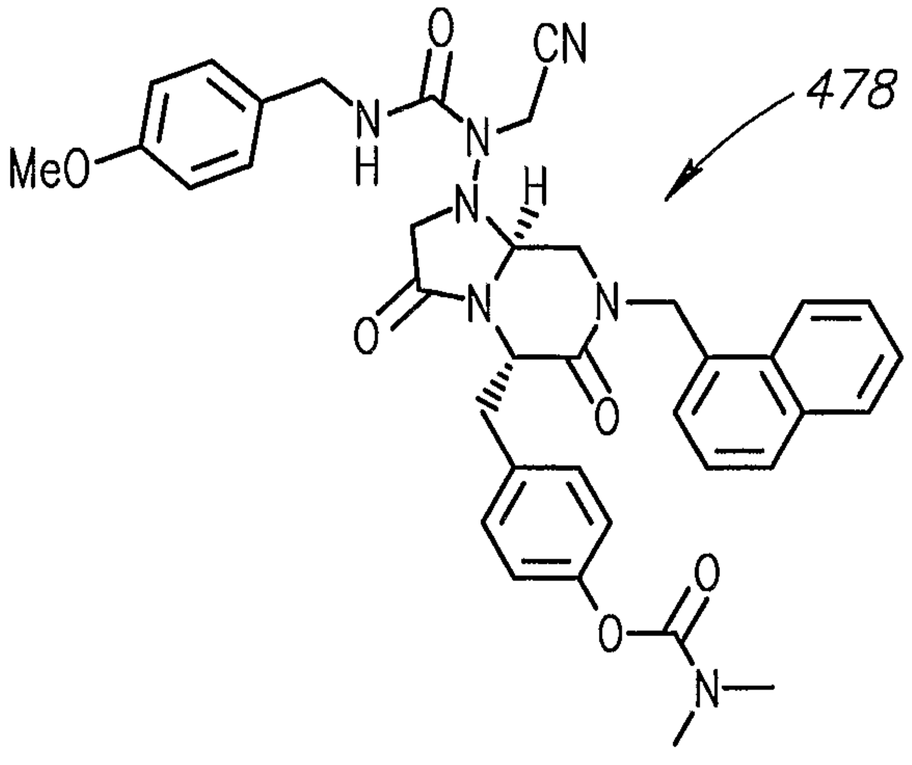
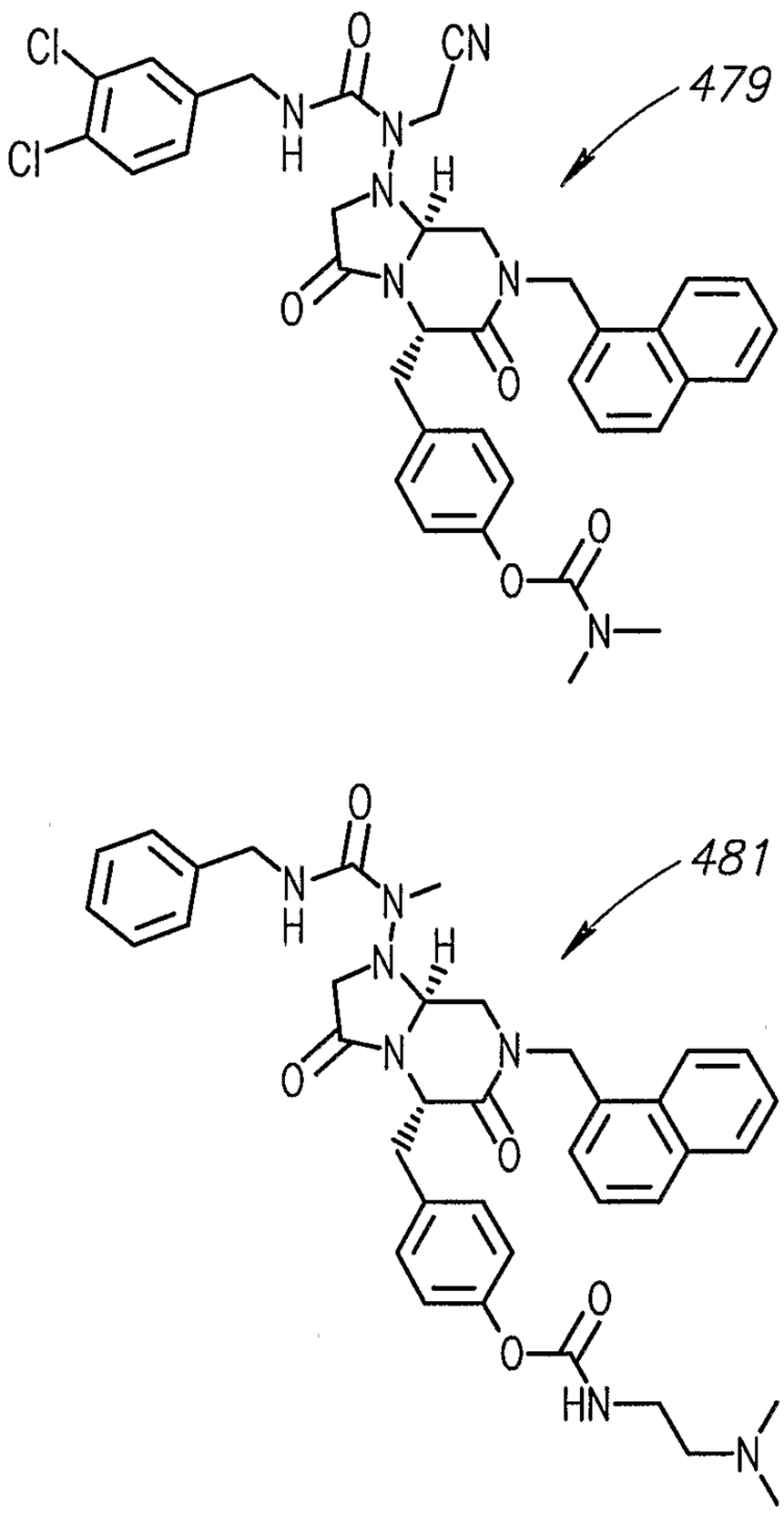
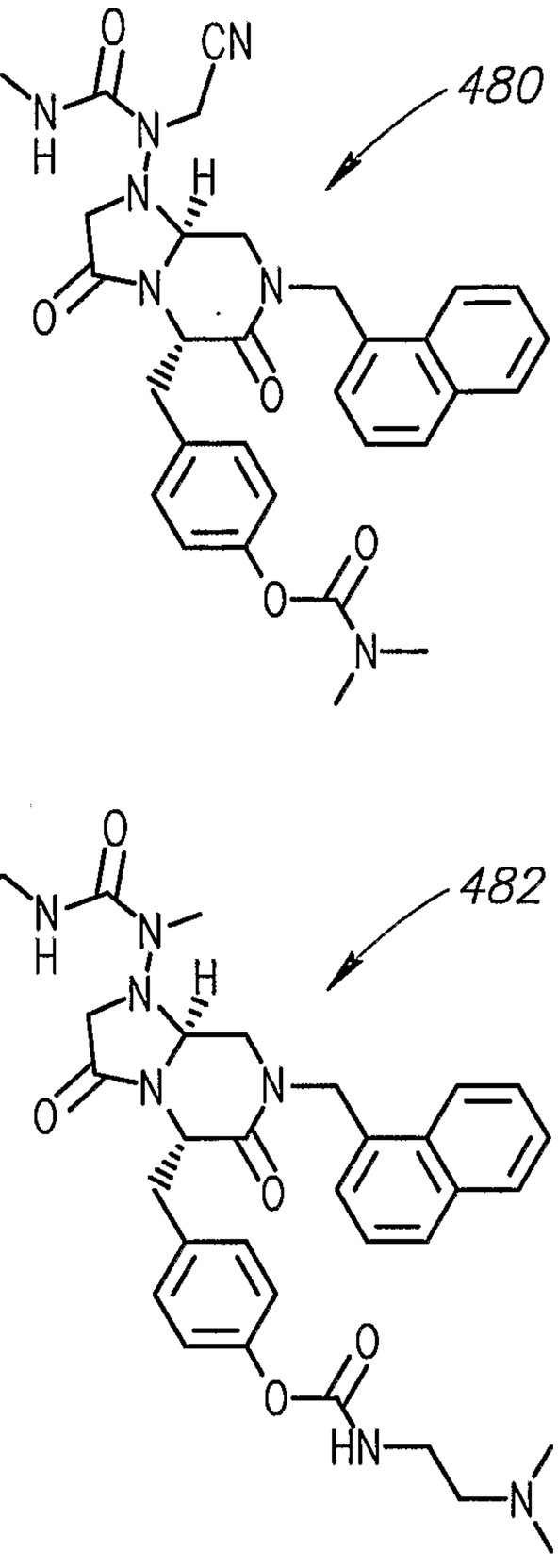
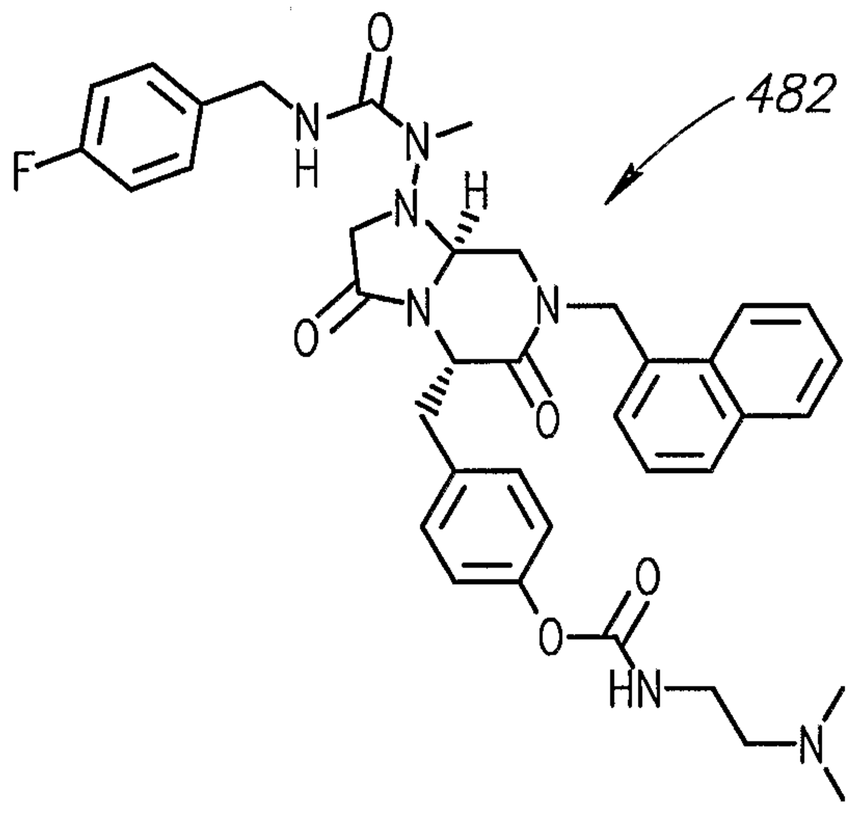
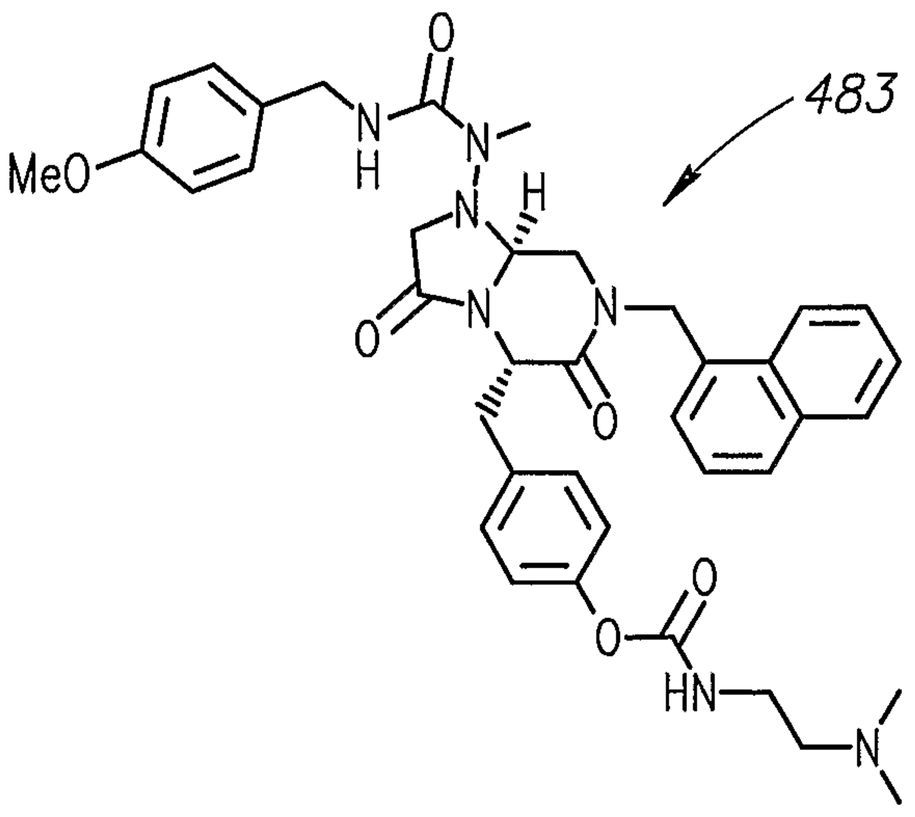


FIG.3K









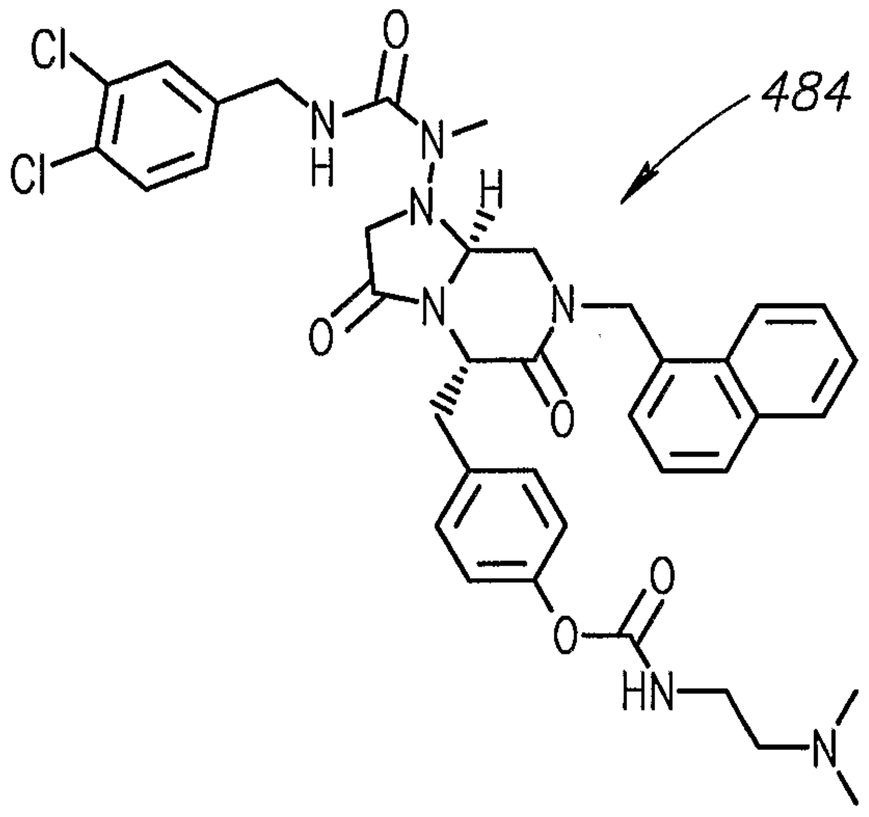
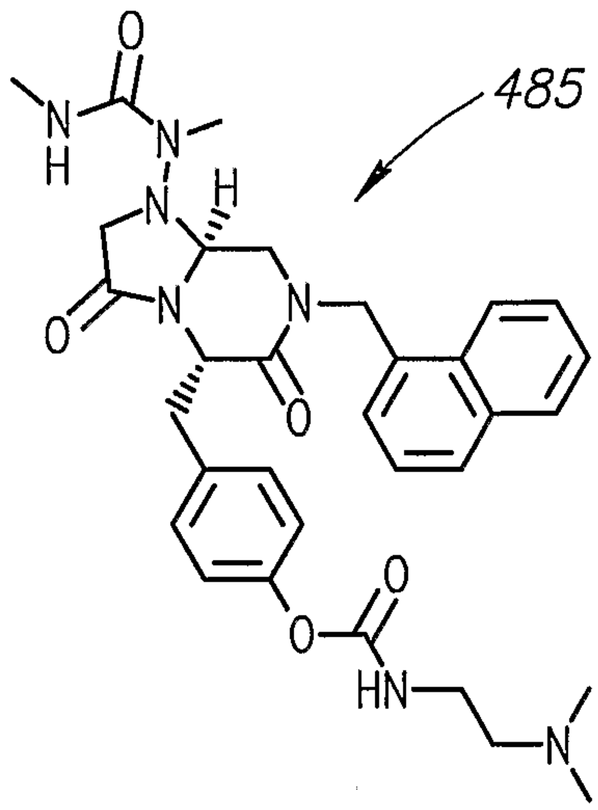
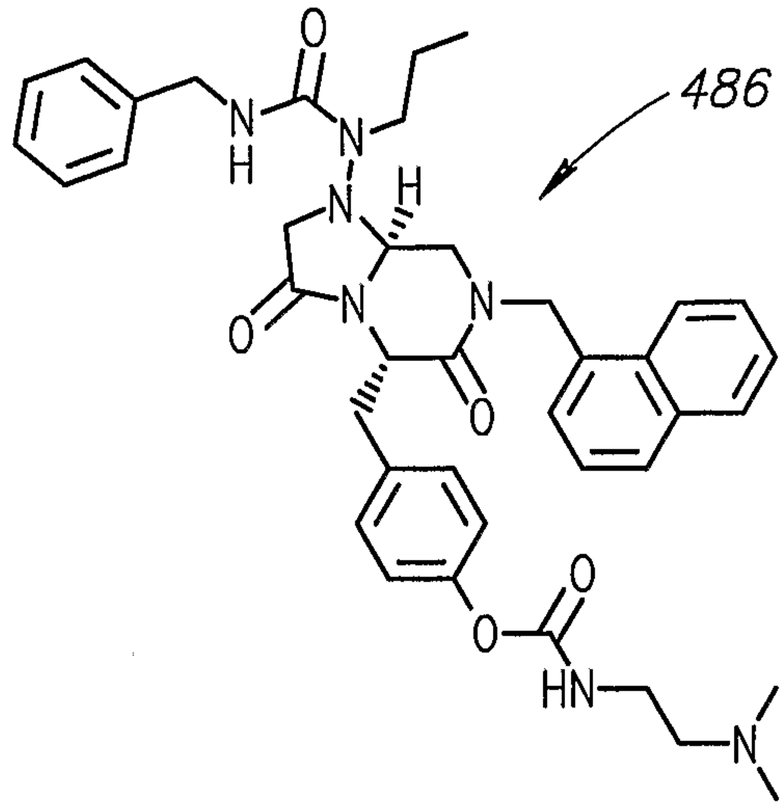
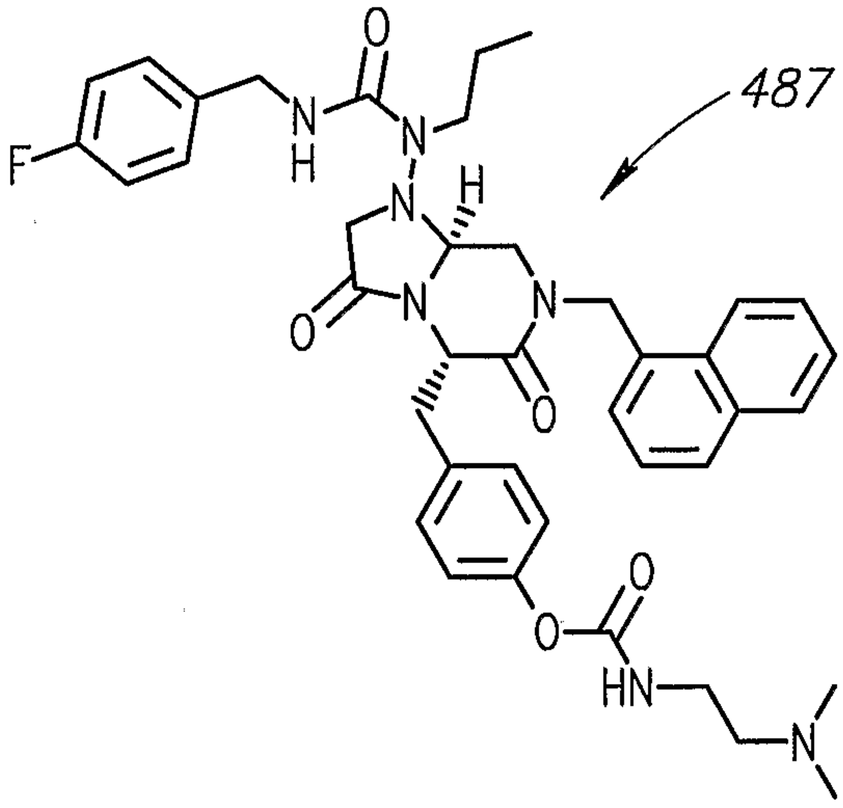
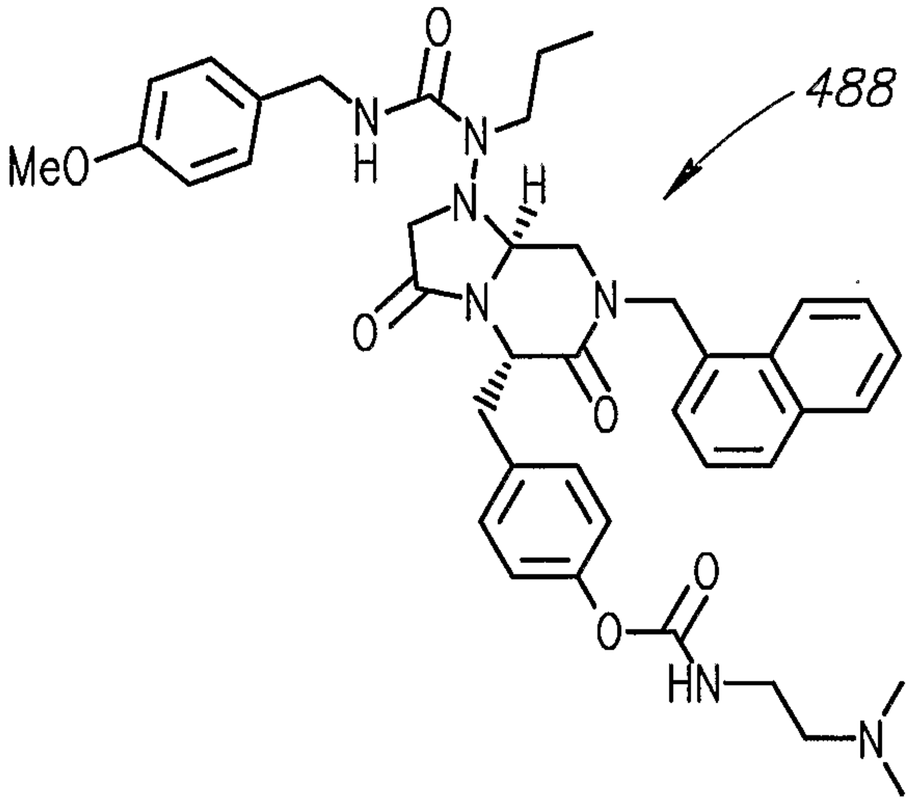


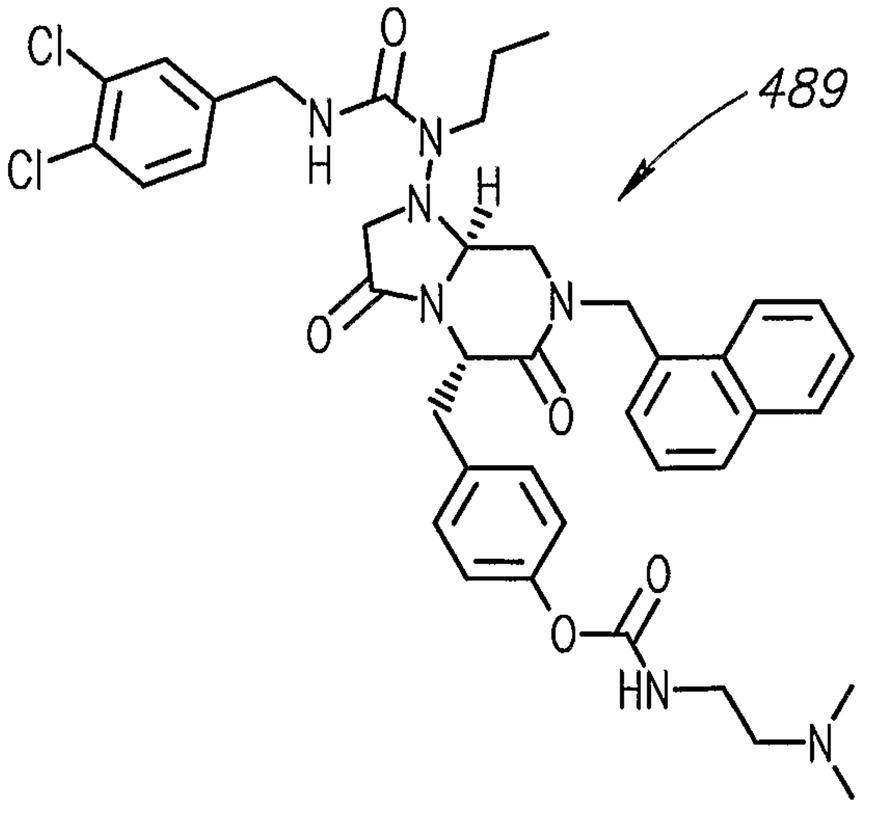
FIG.3L











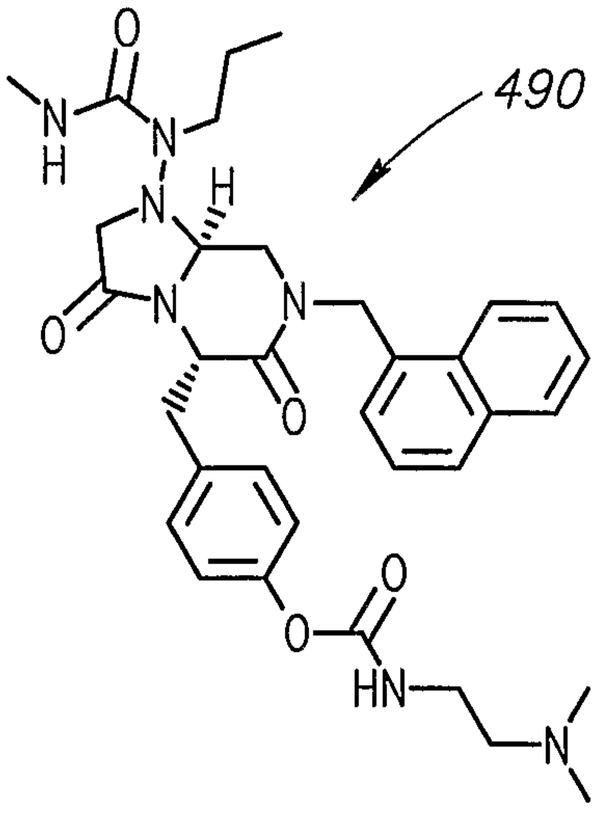
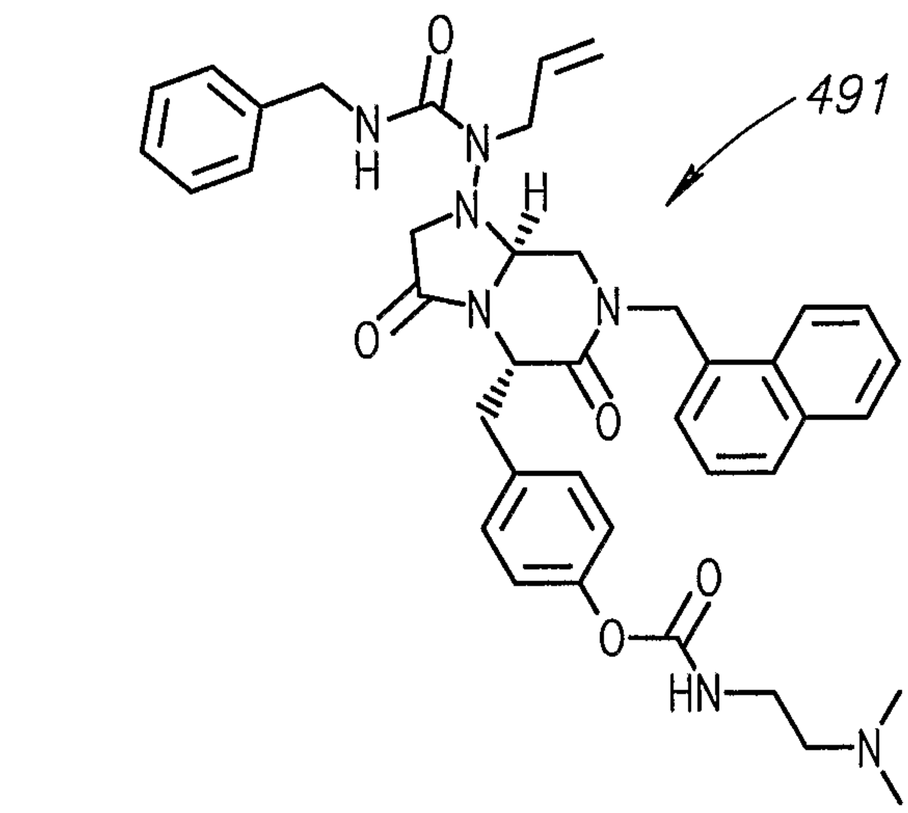
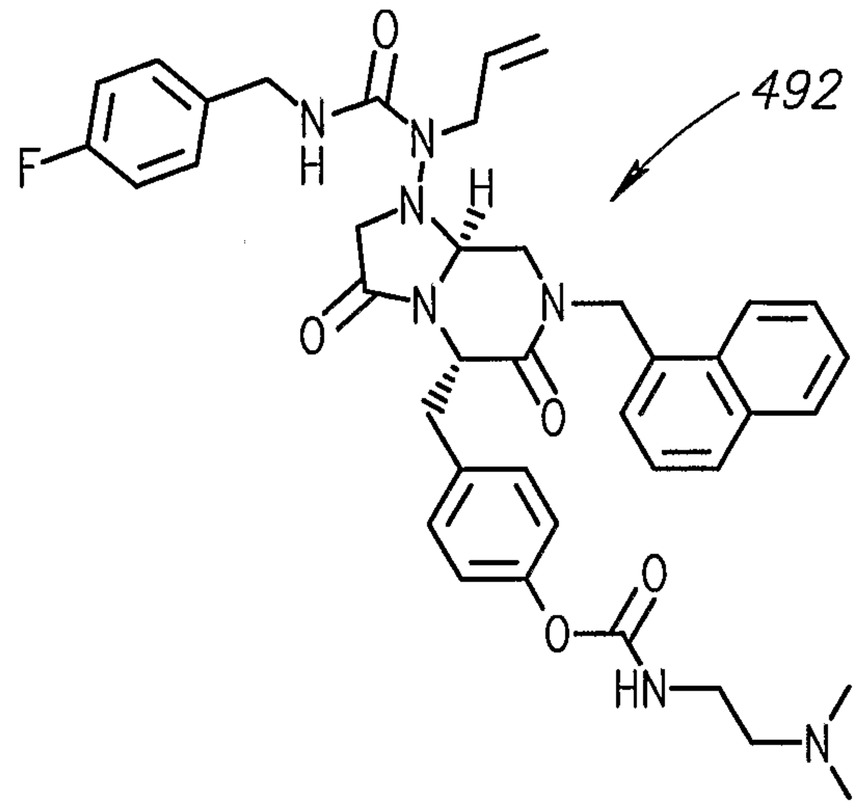
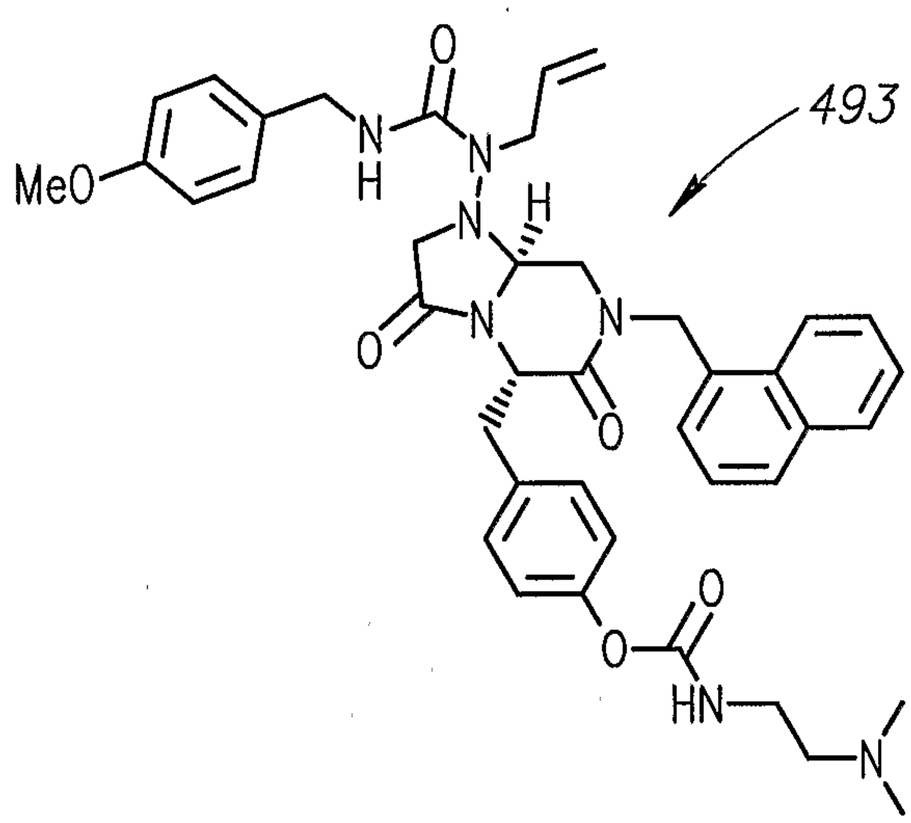
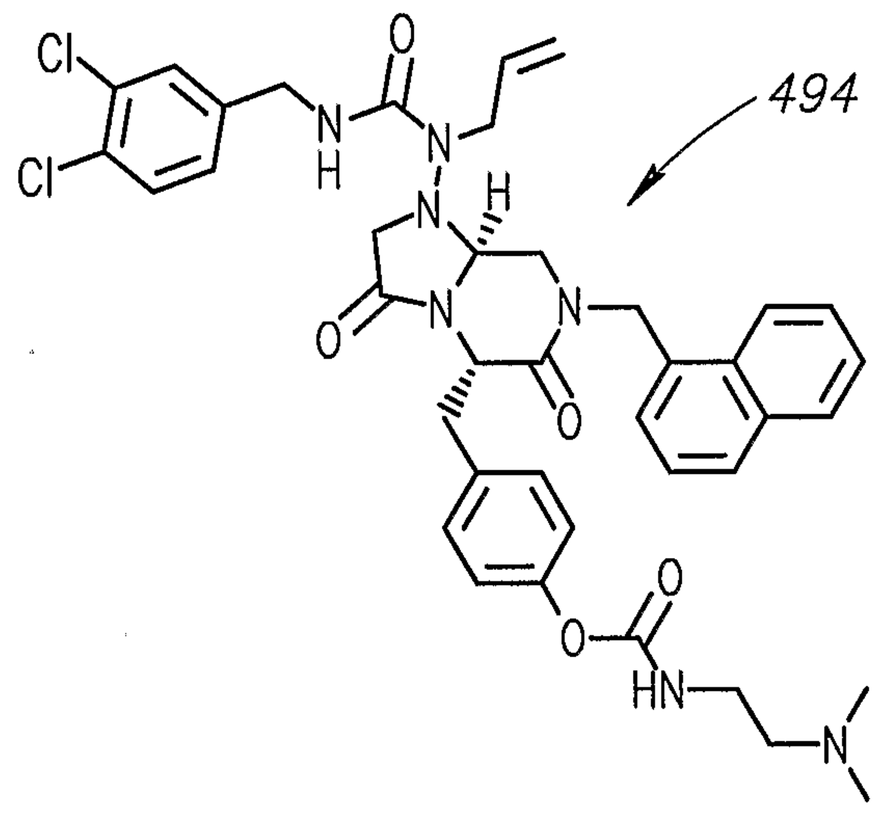


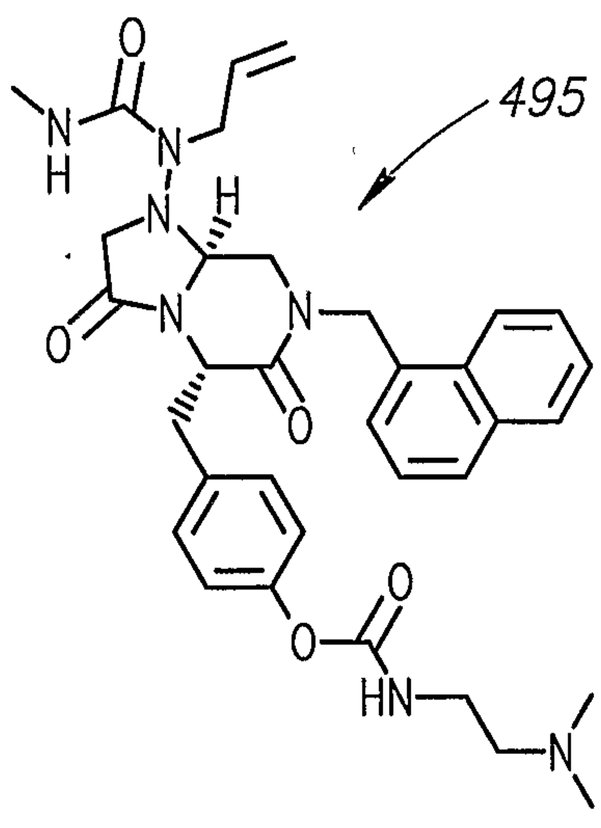
FIG.3M











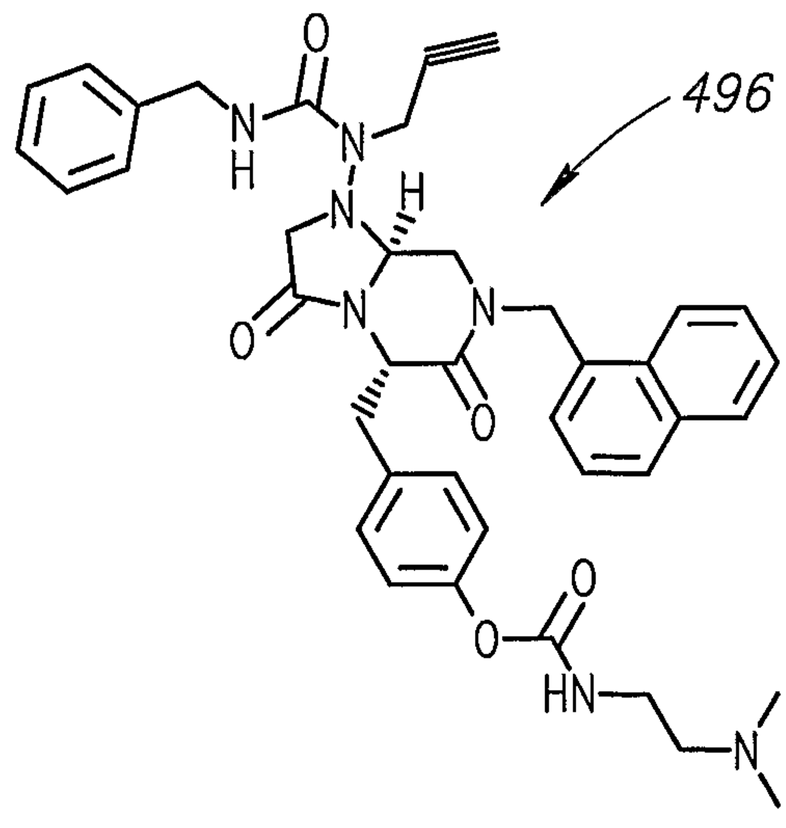
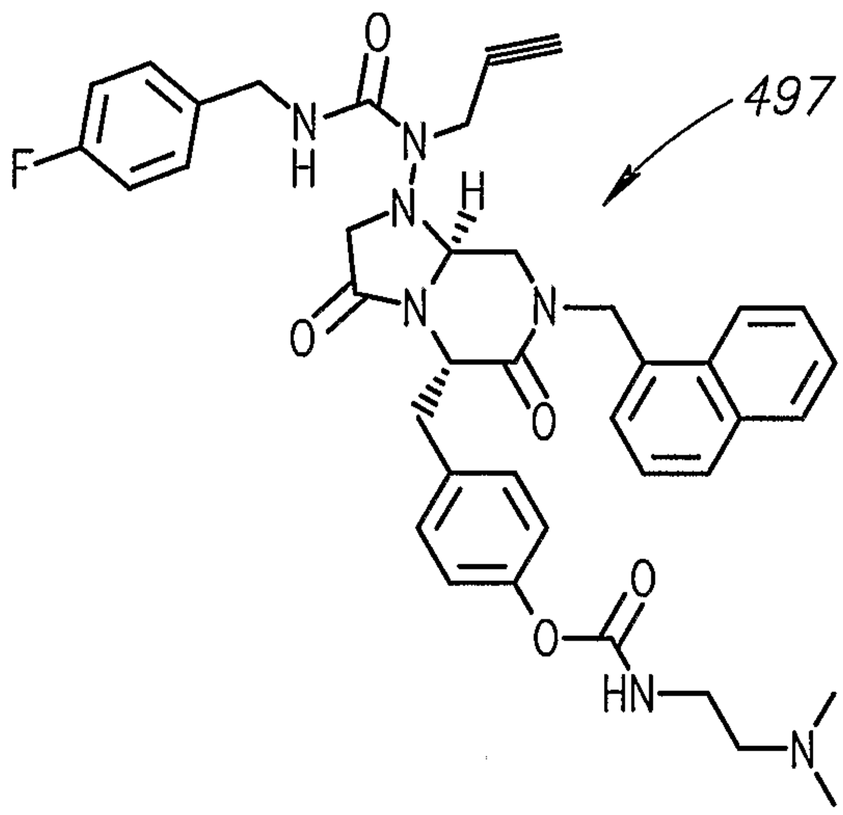
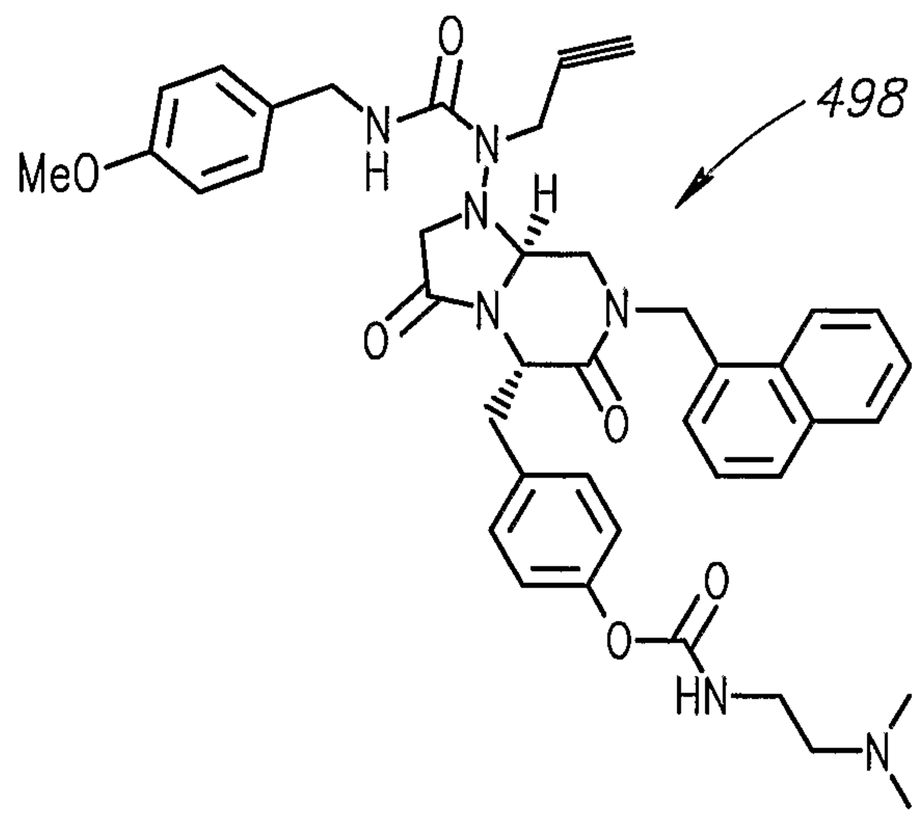
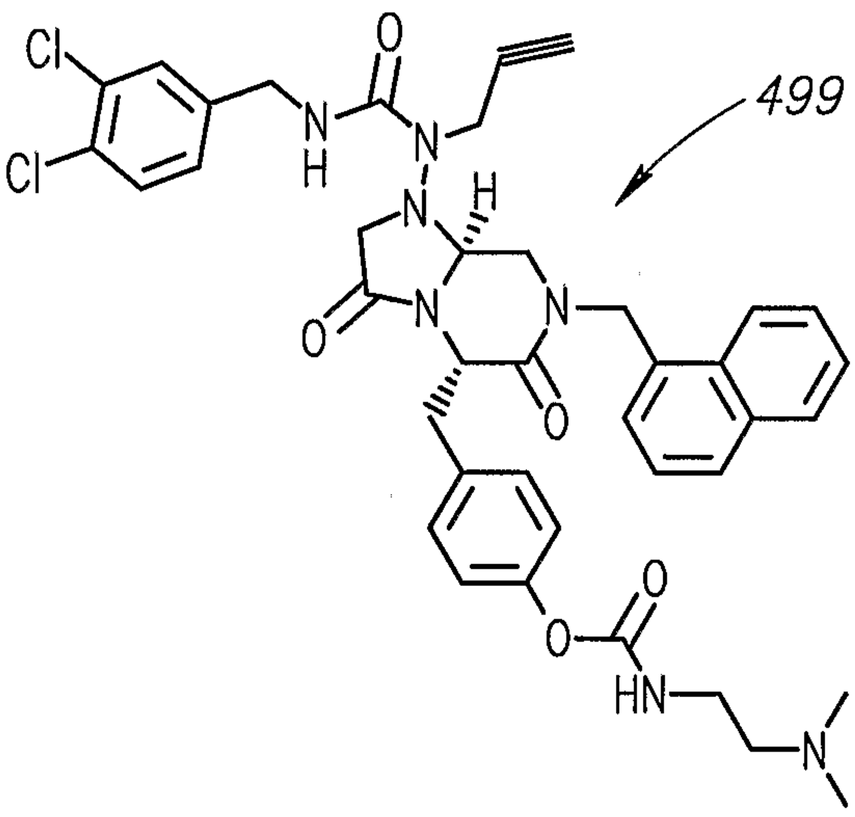
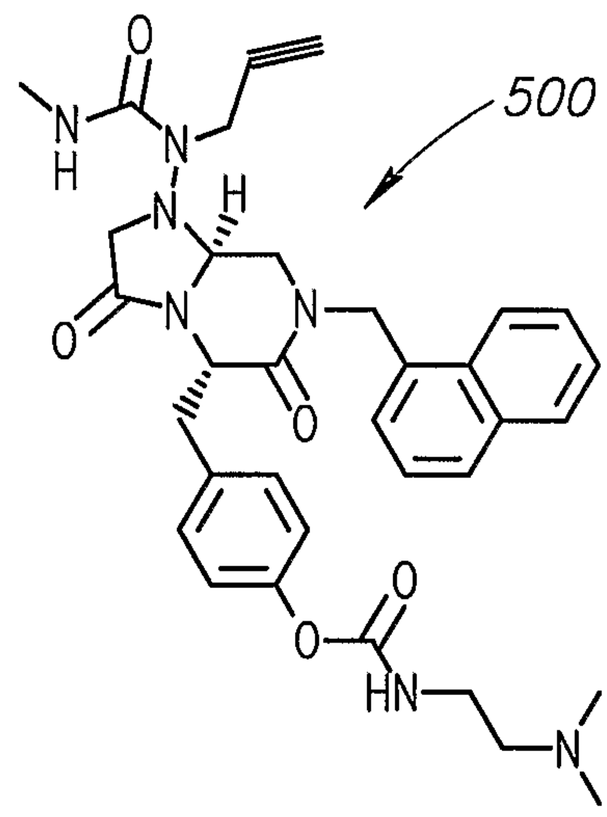


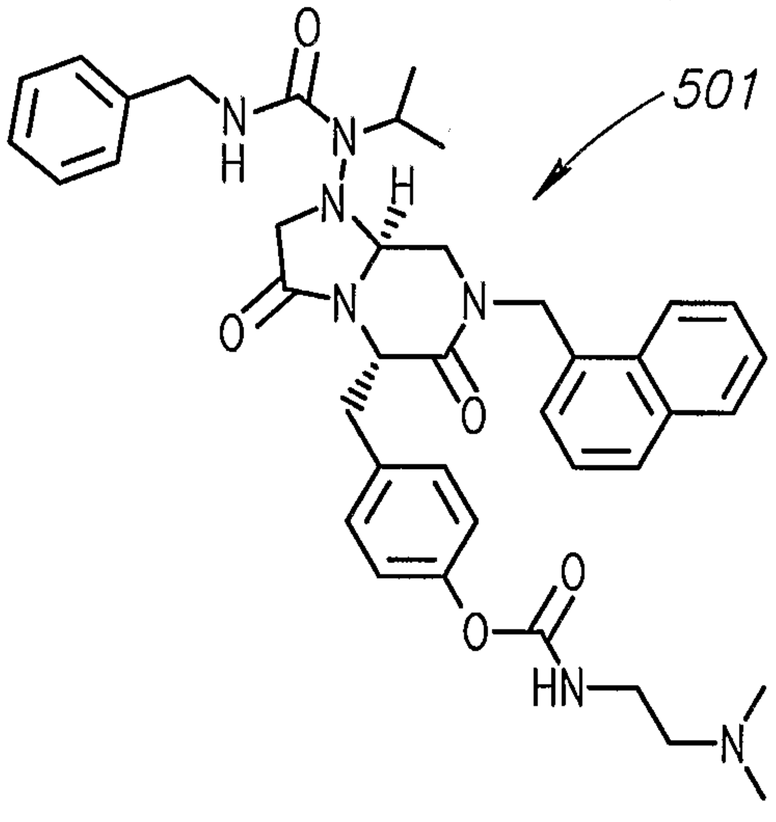
FIG.3N











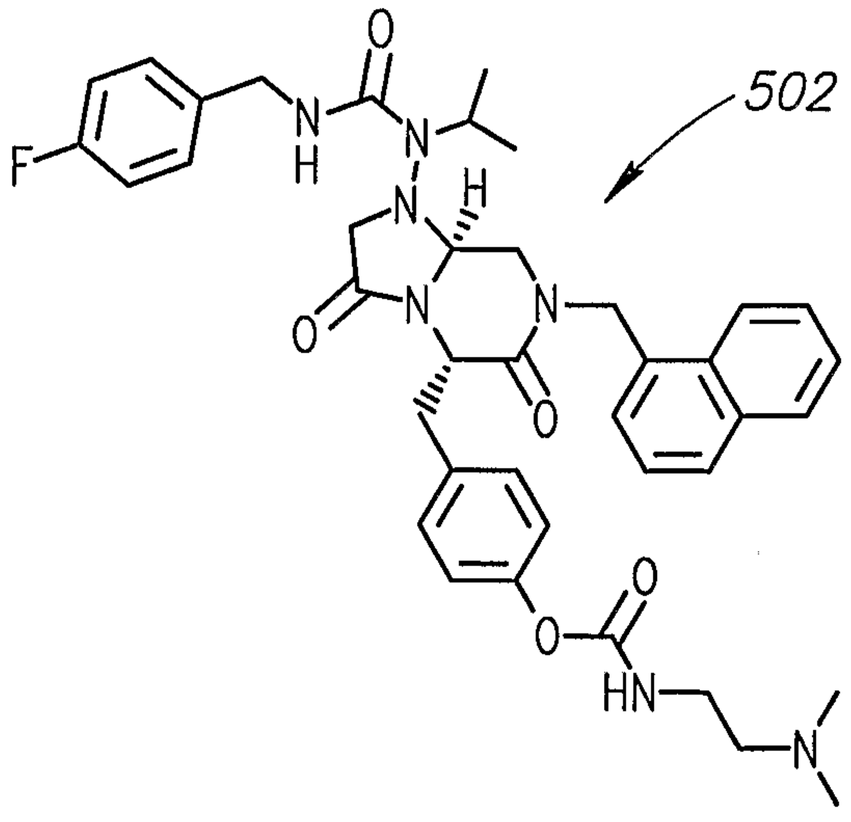
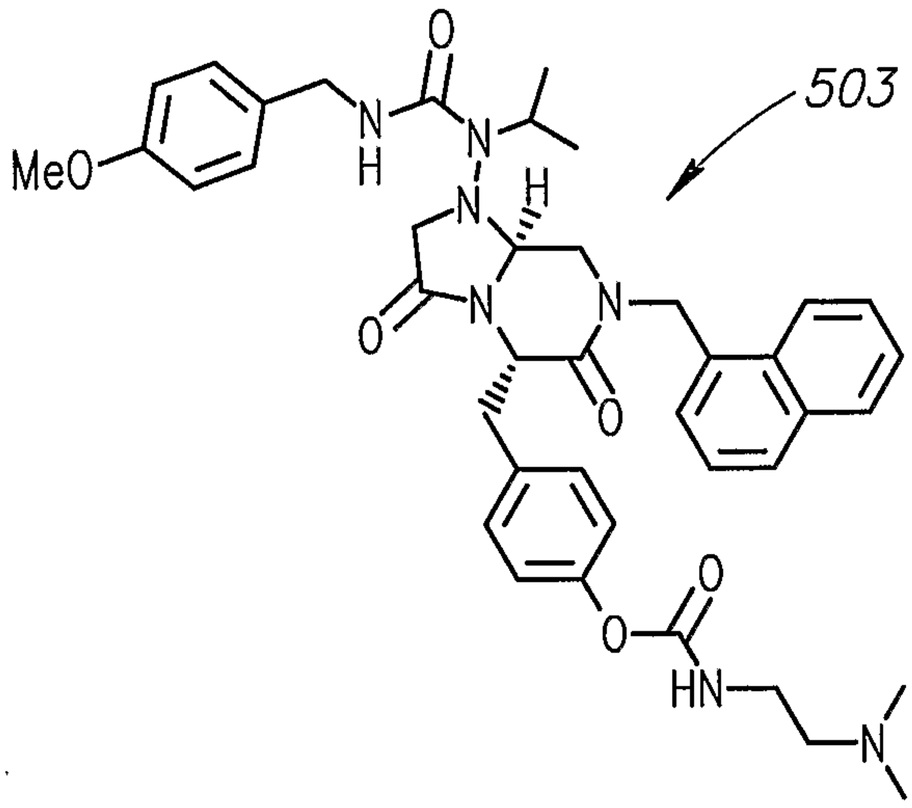


FIG.30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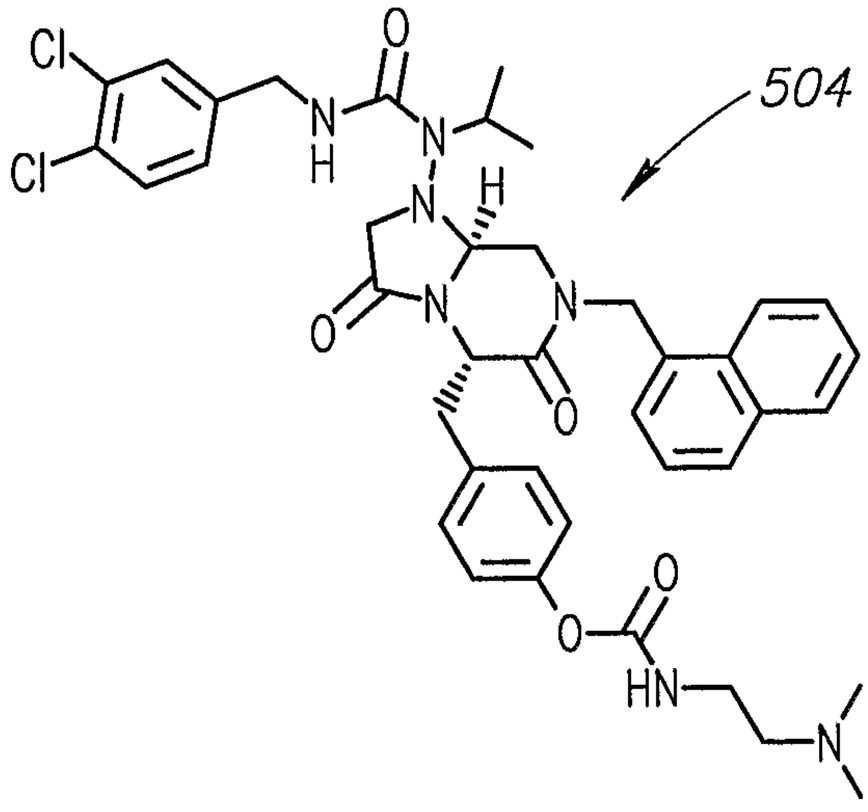
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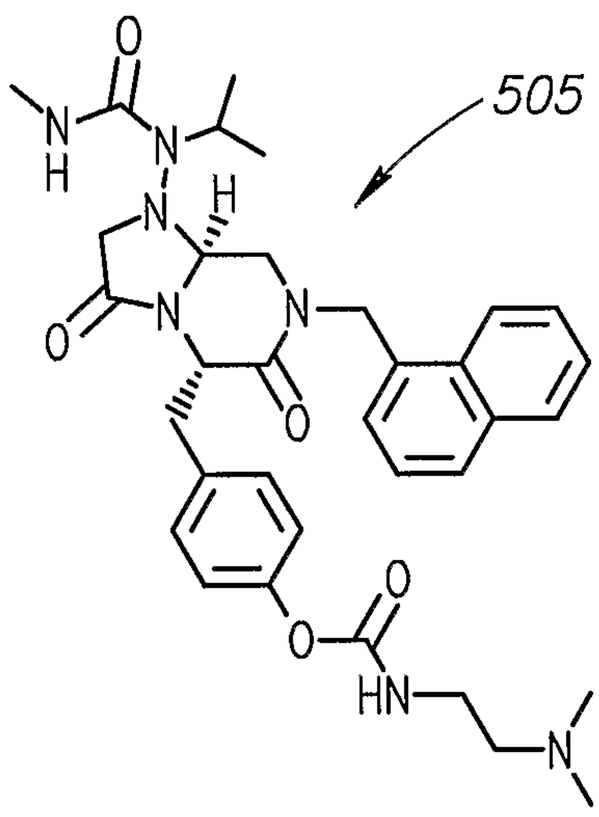
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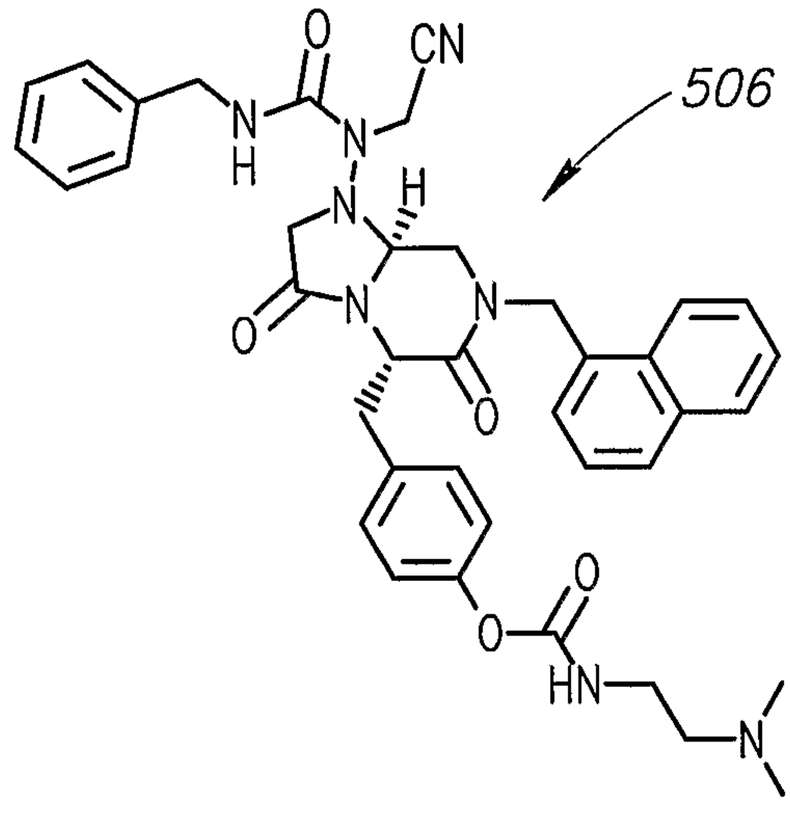
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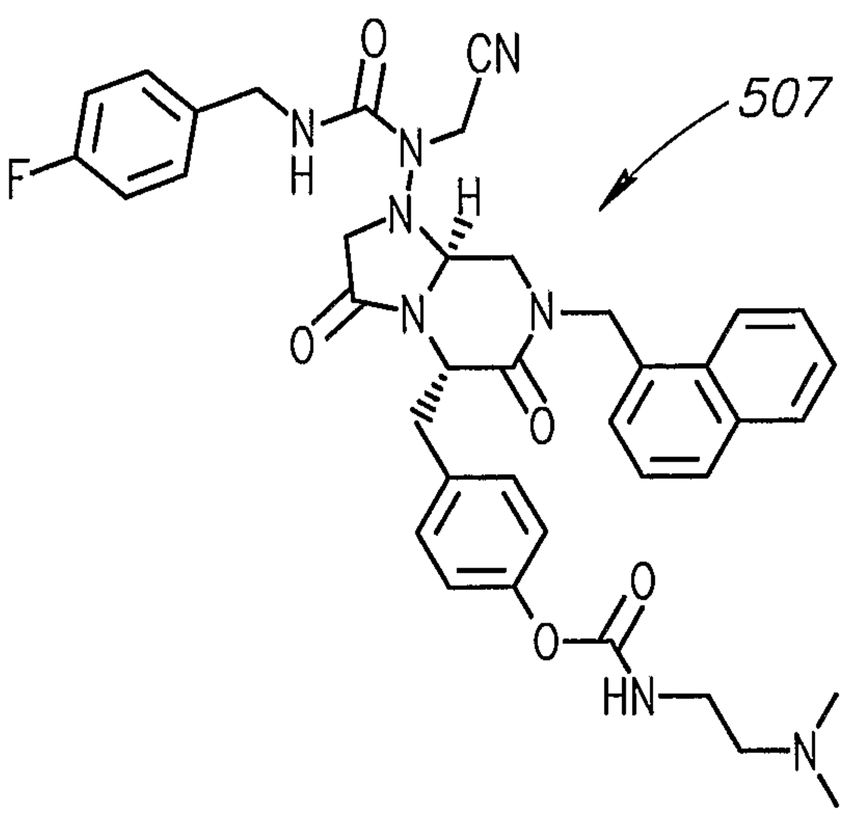
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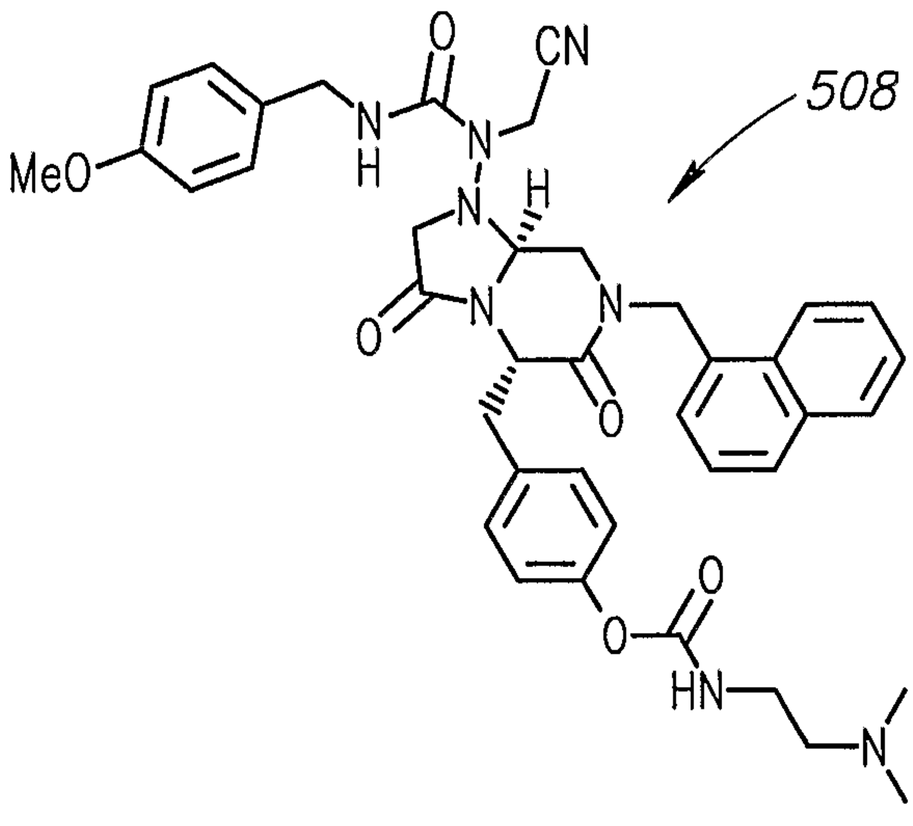
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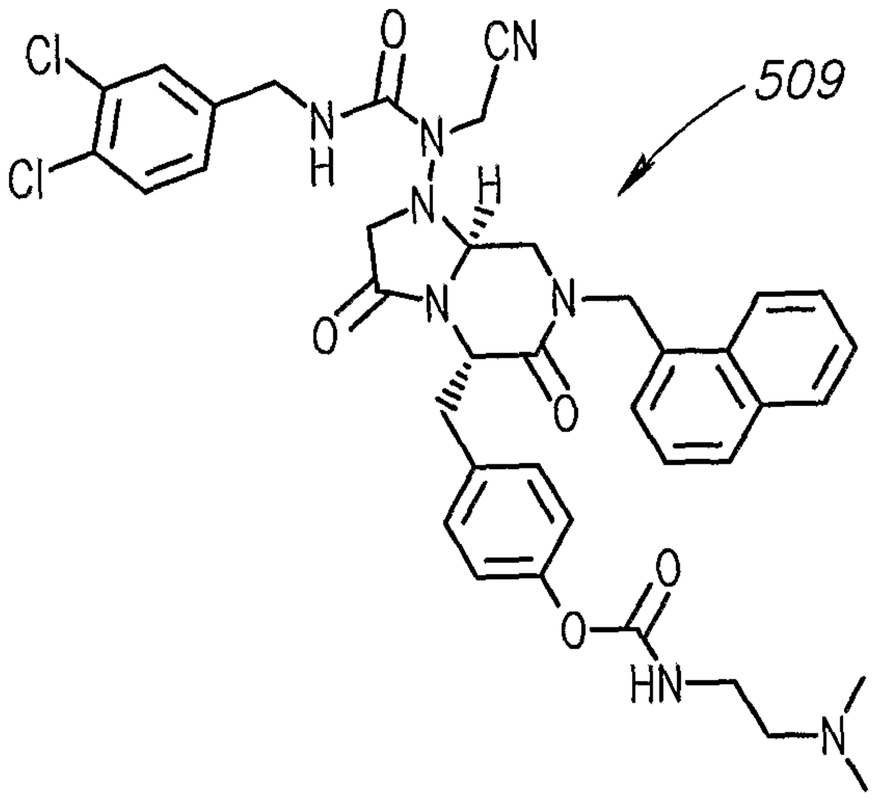
FIG.3P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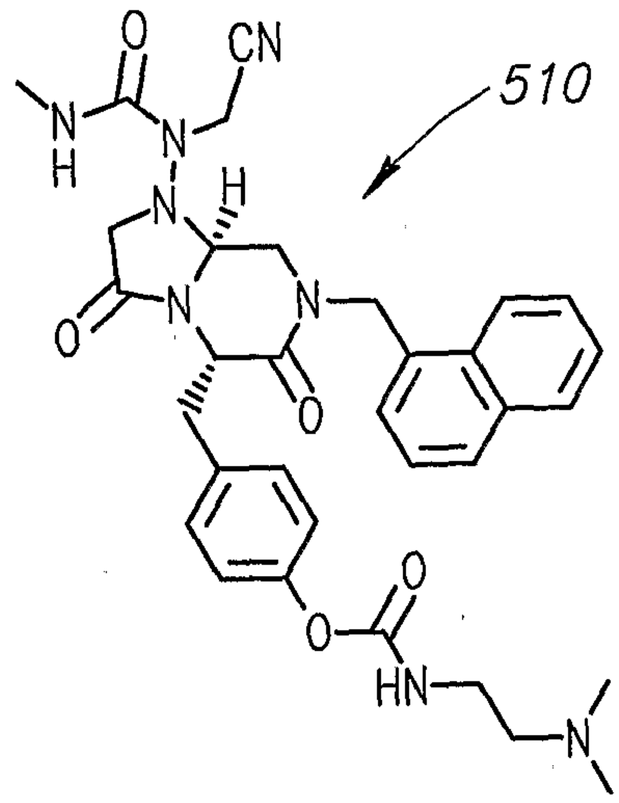
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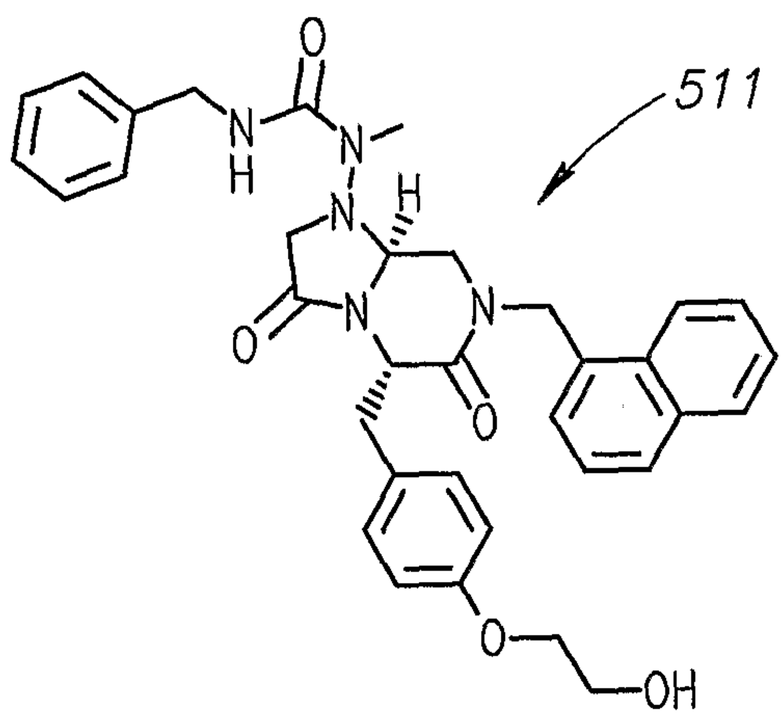
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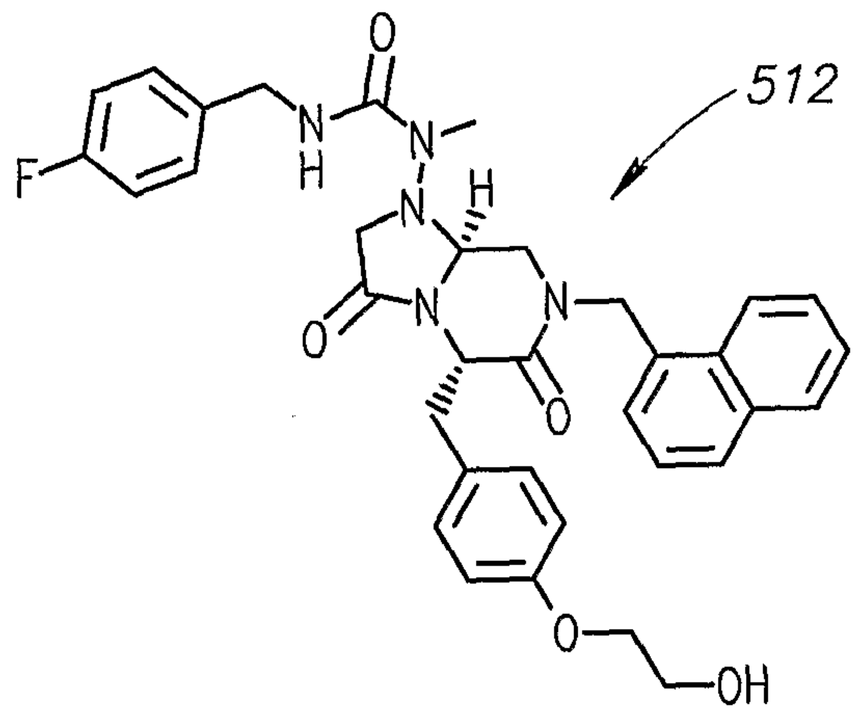
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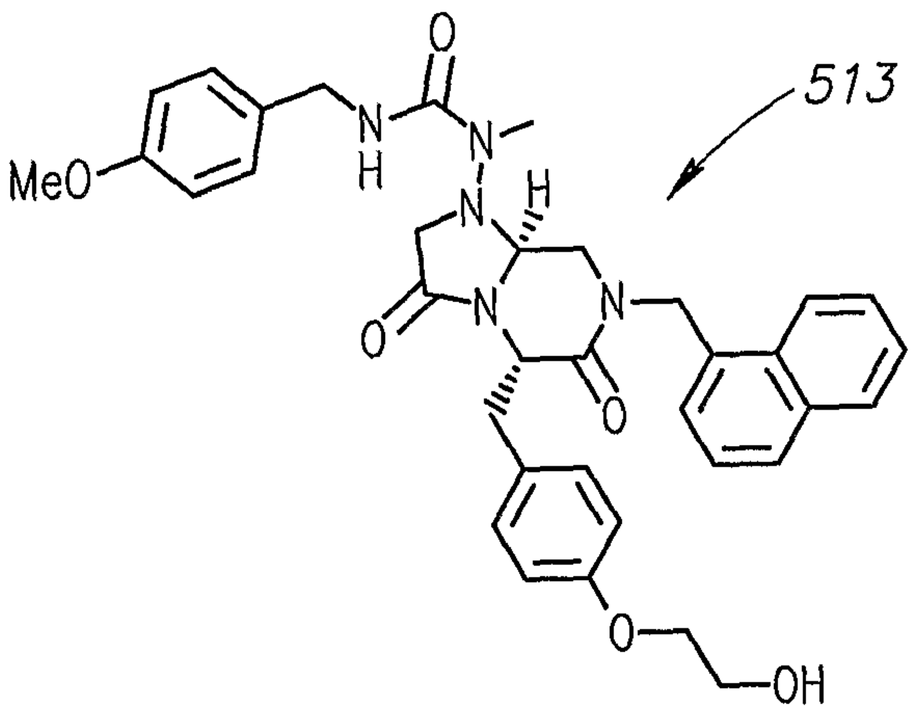
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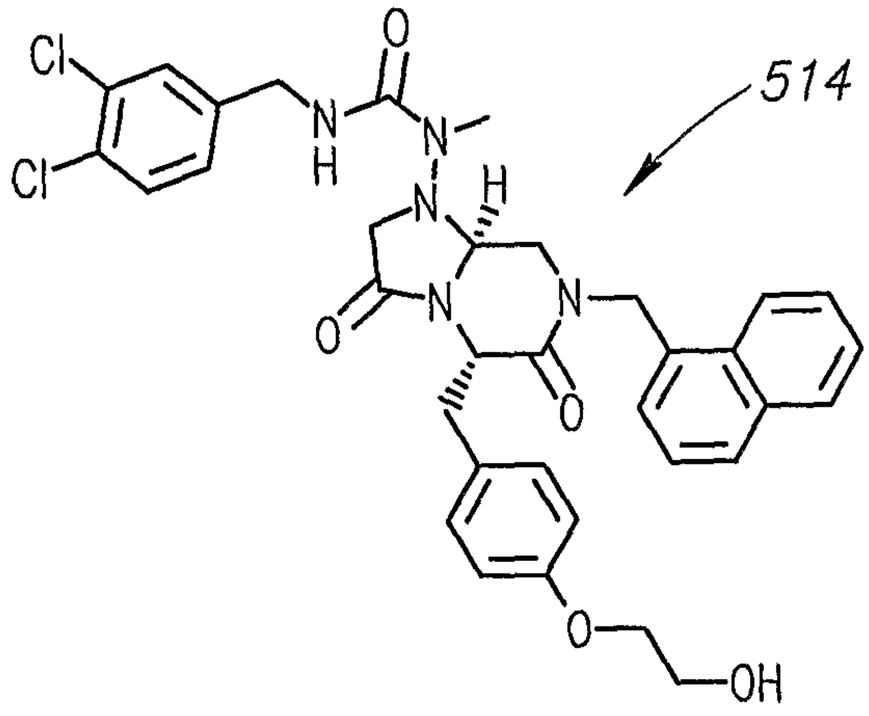
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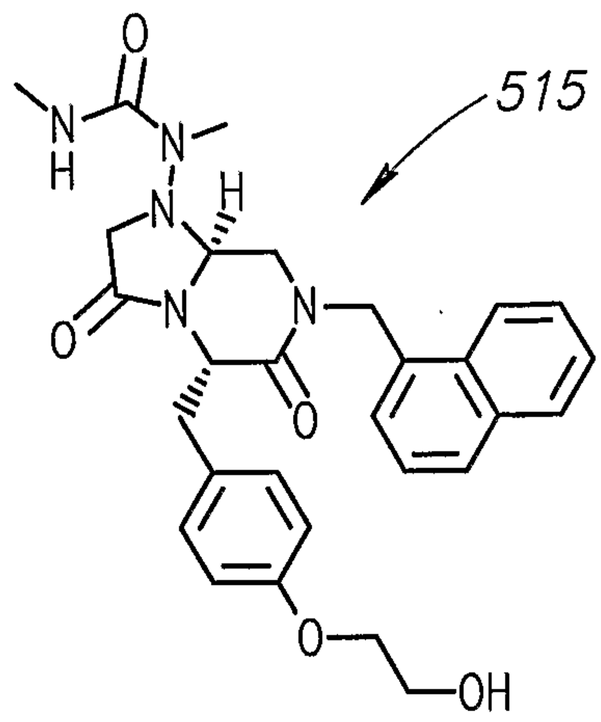
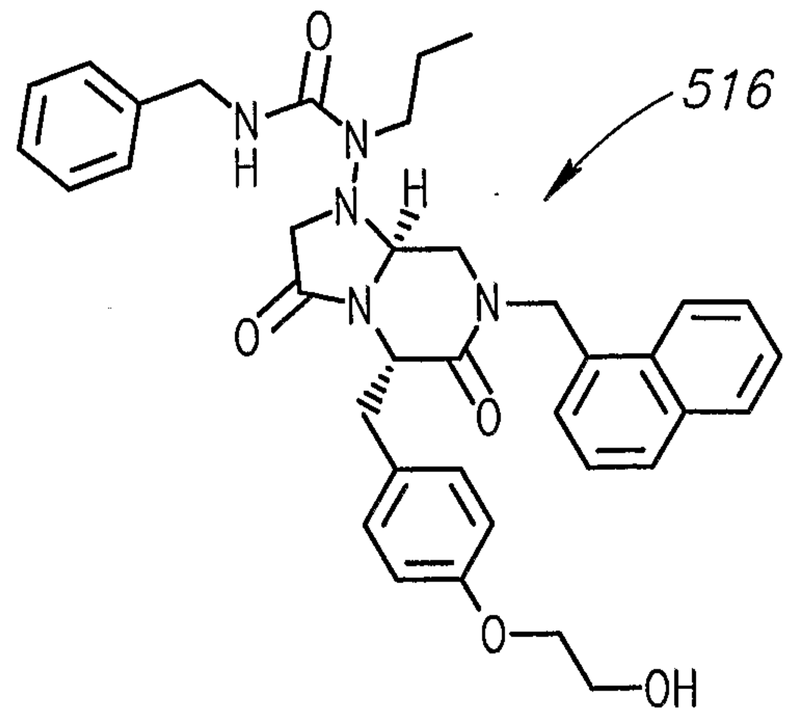
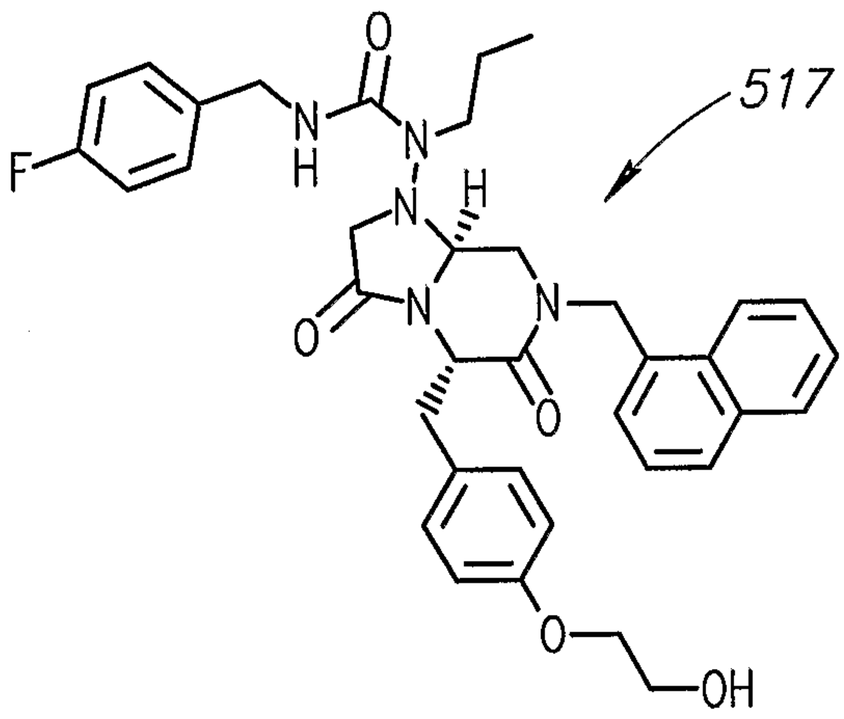
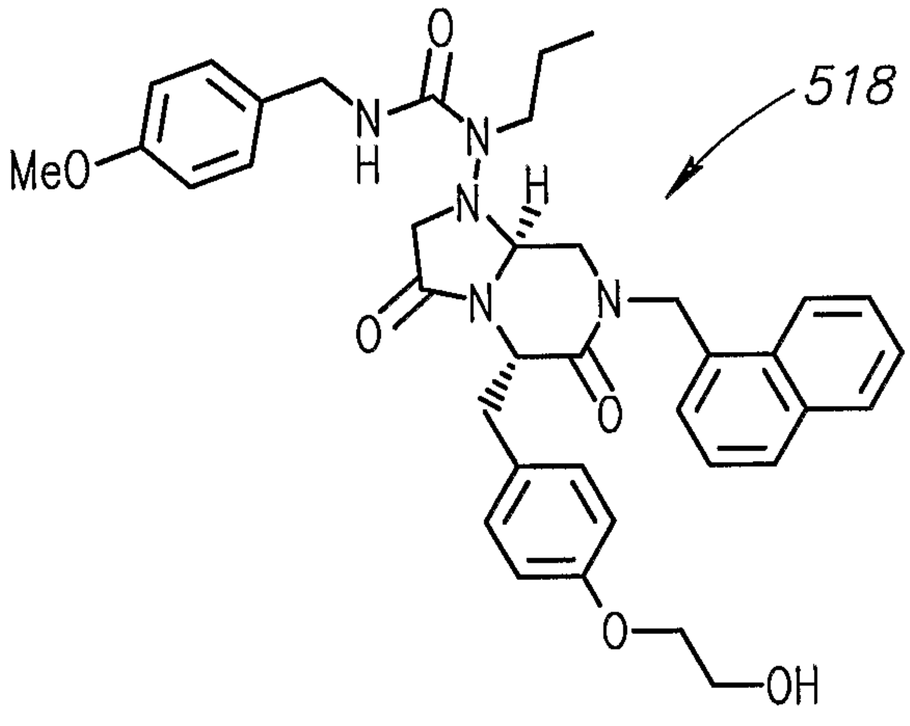
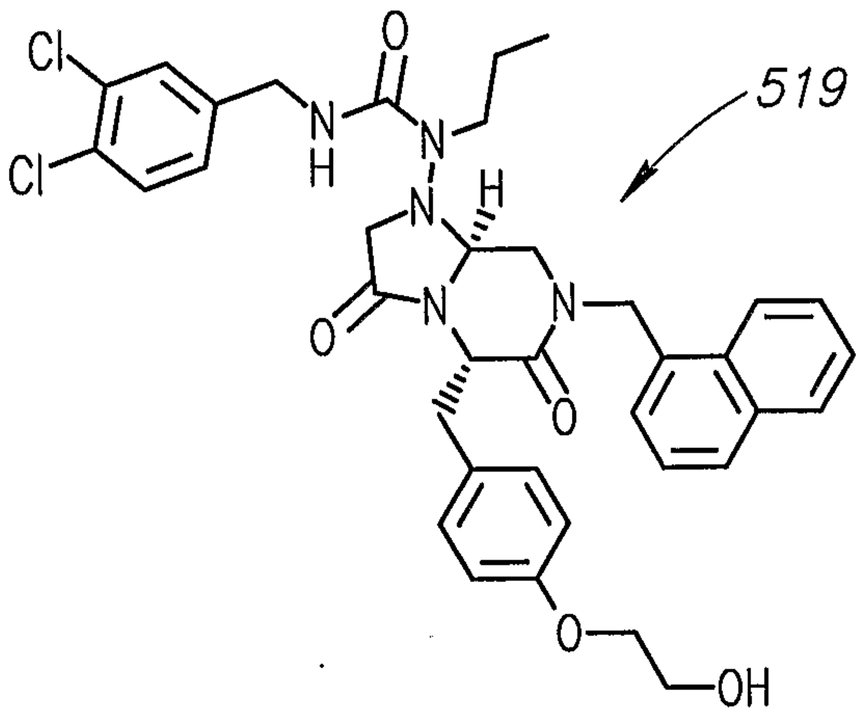
FIG.3Q











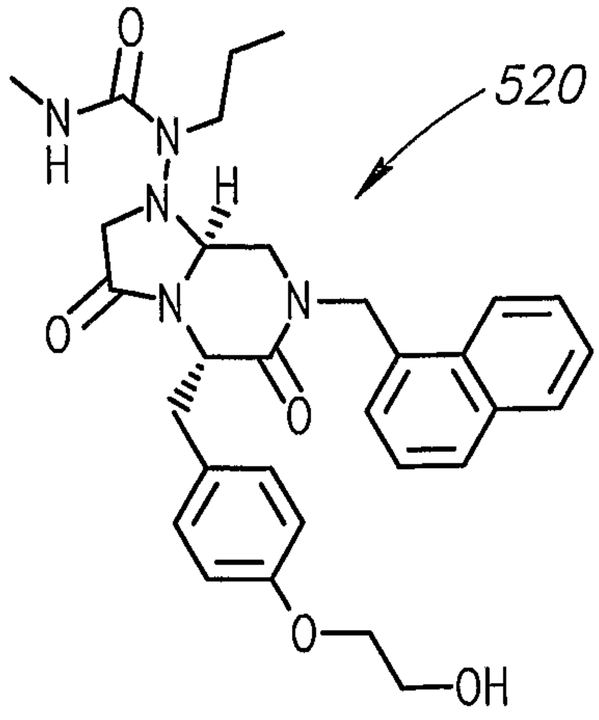
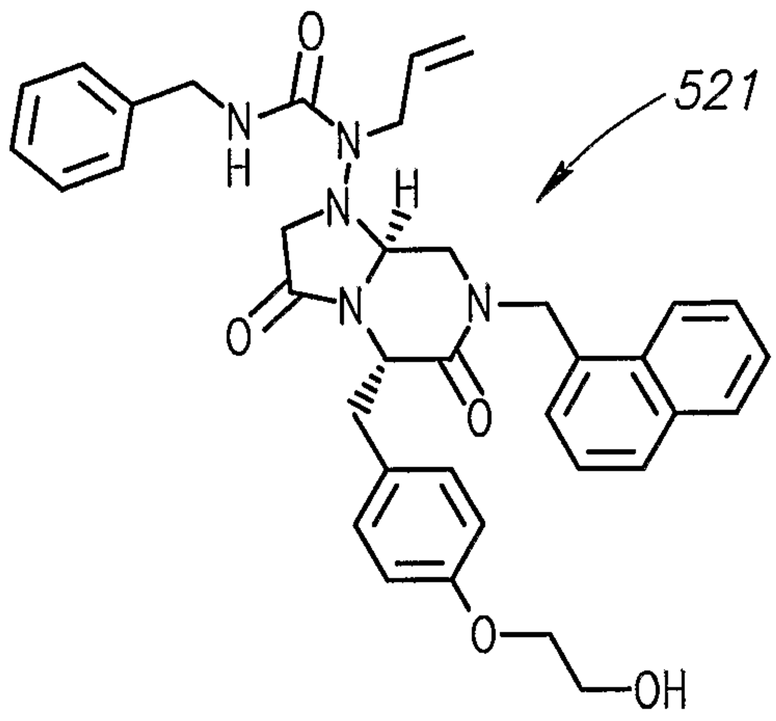
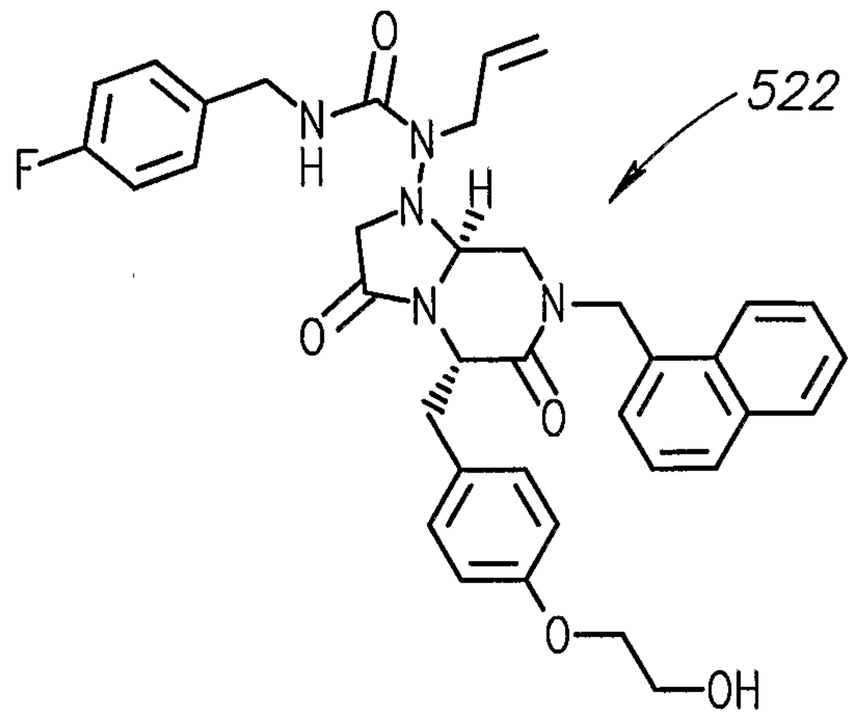
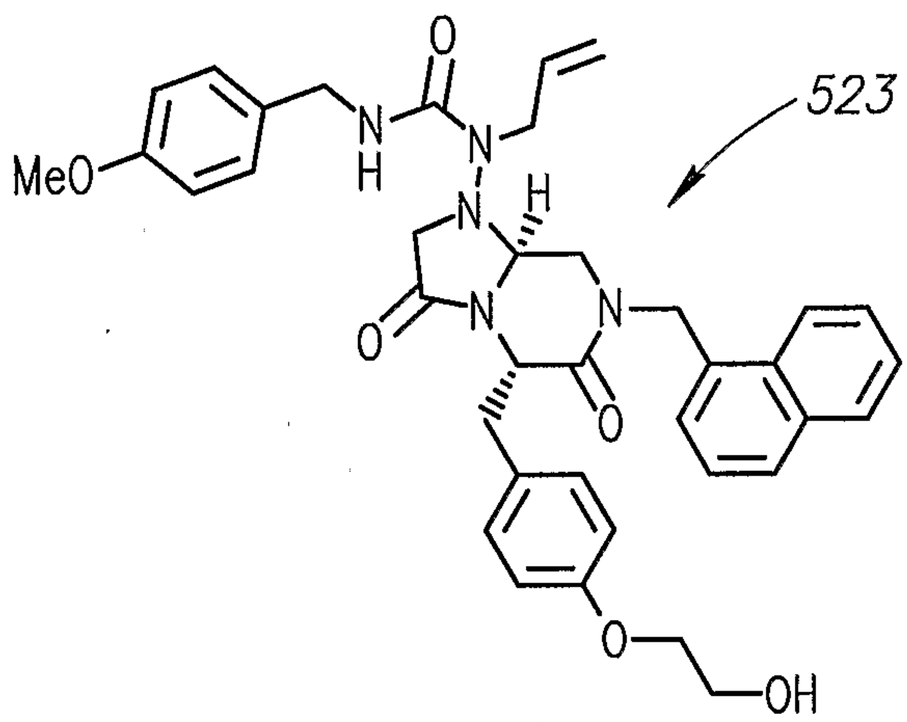
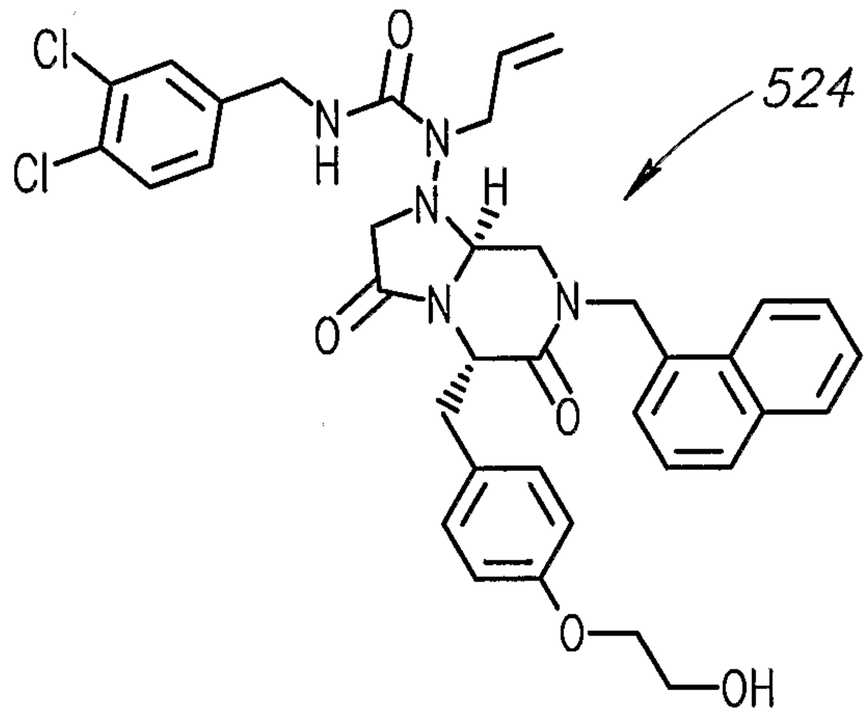


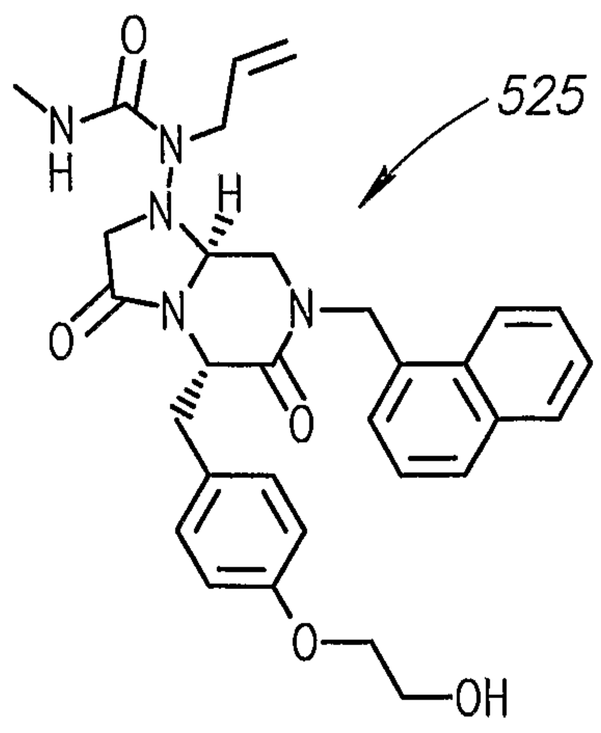
FIG.3R











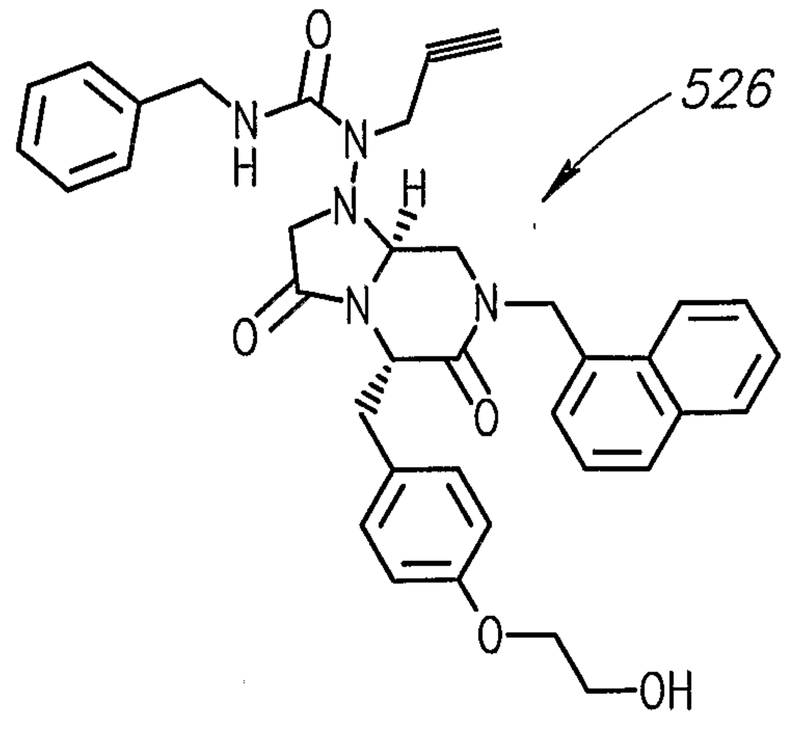
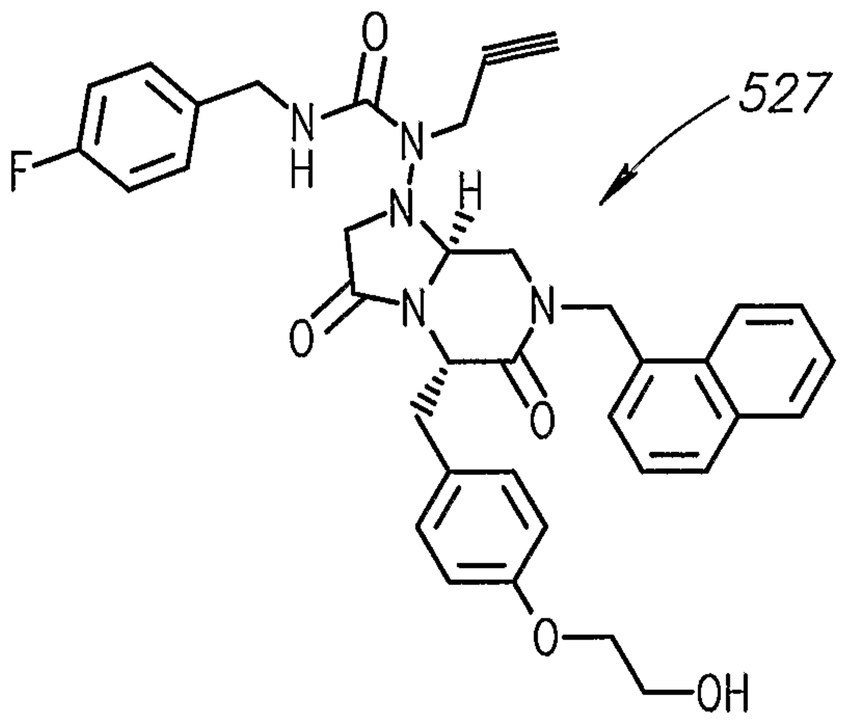
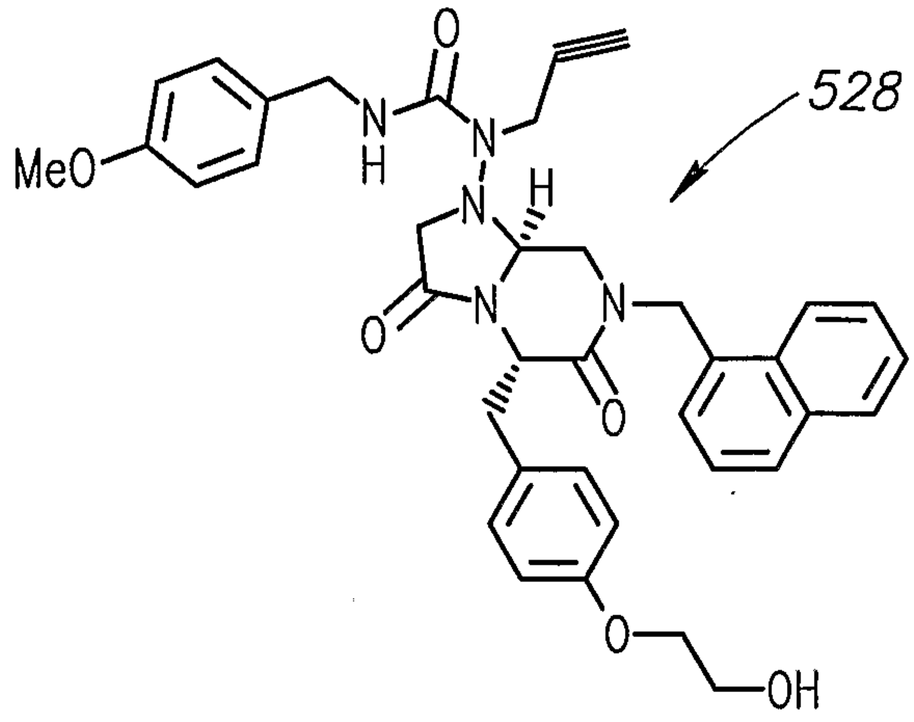
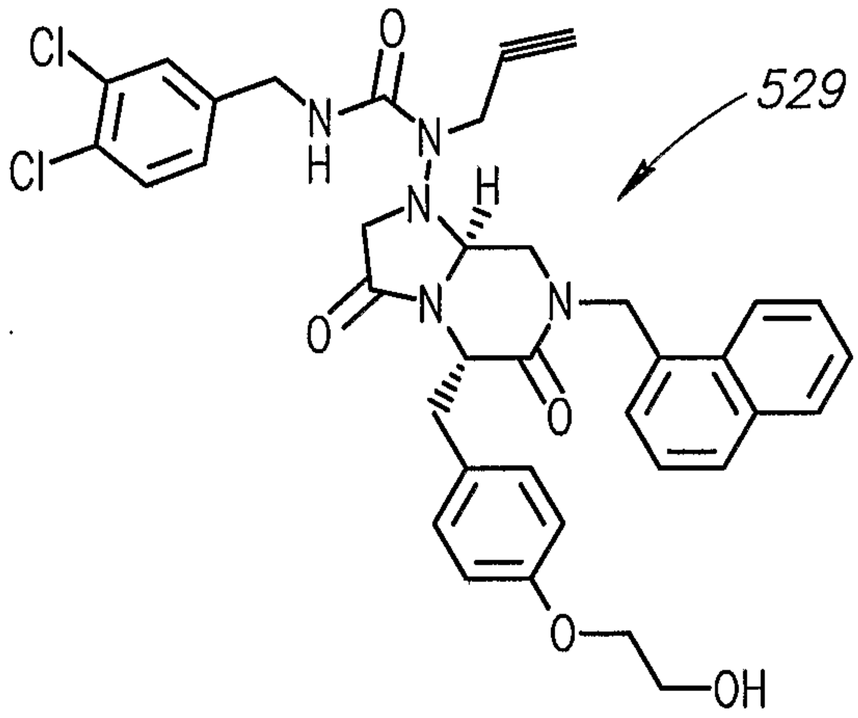
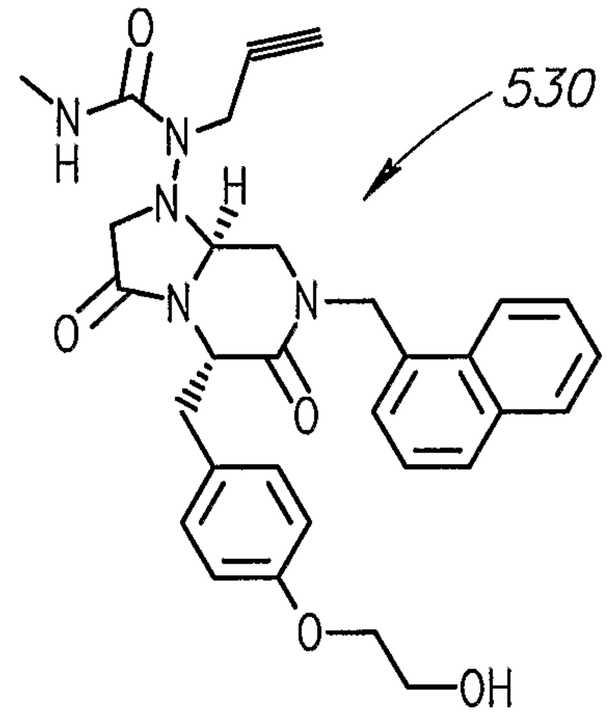


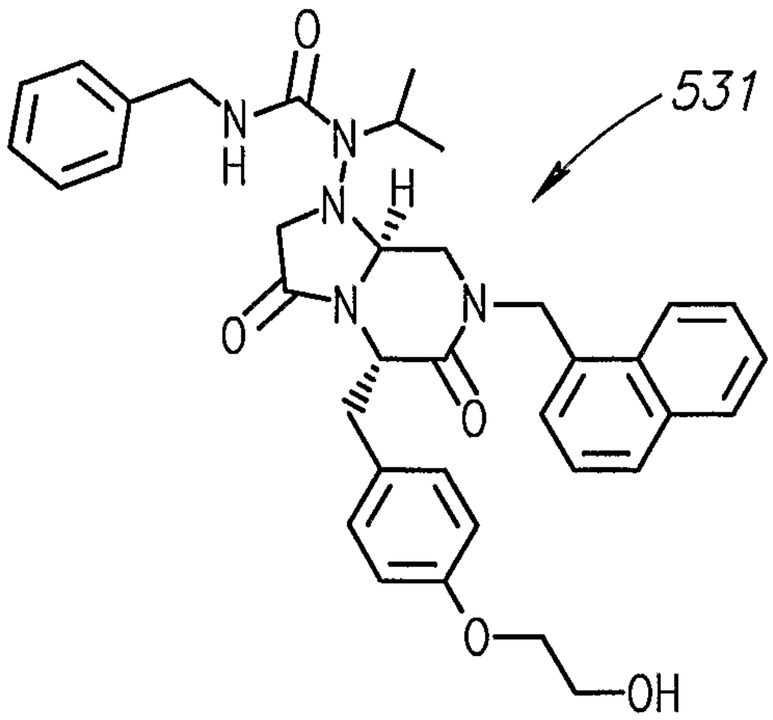
FIG.3S











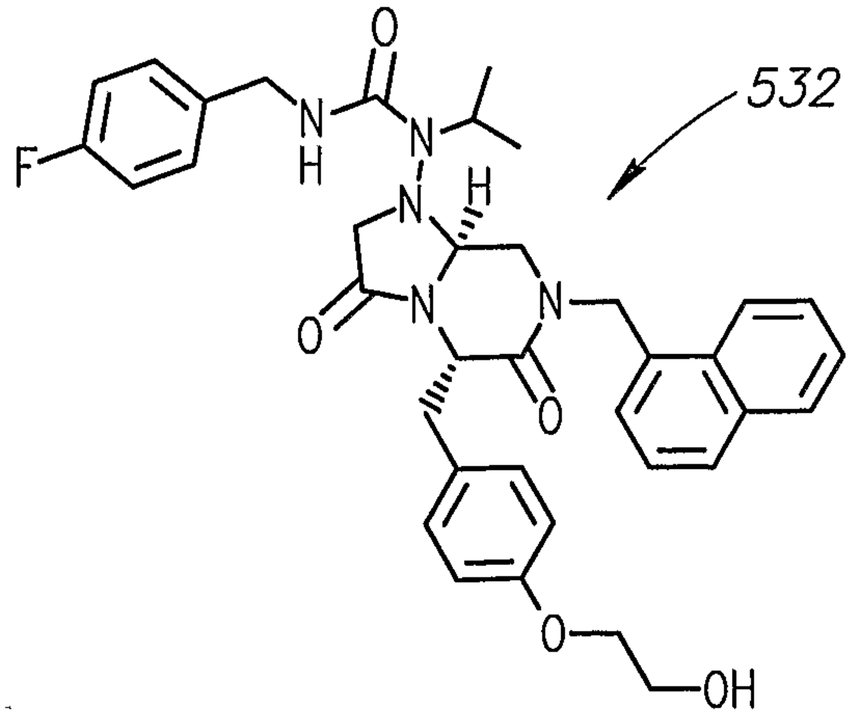
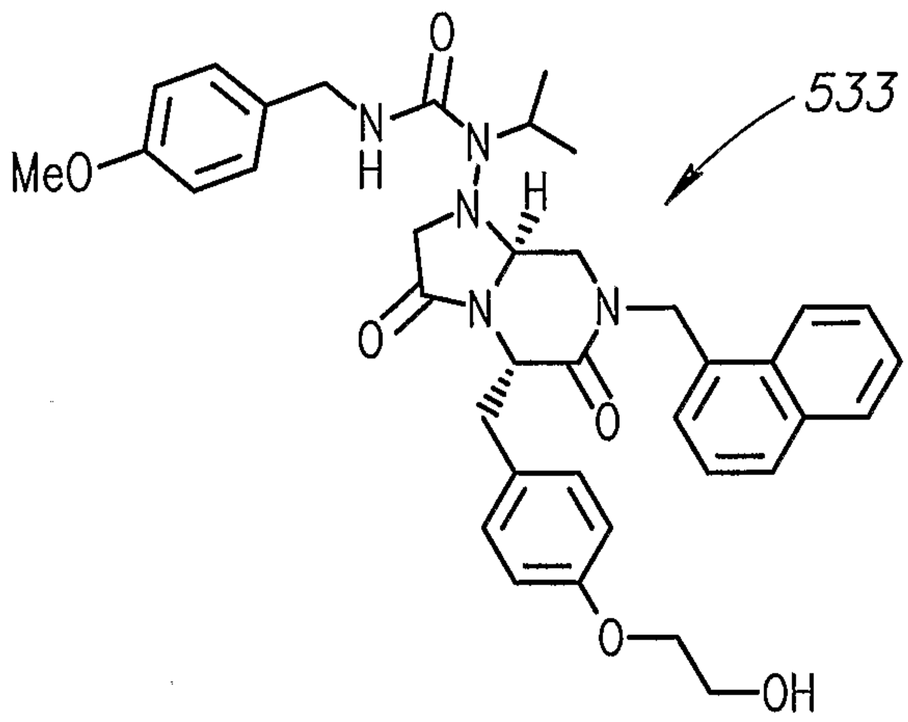


FIG.3T



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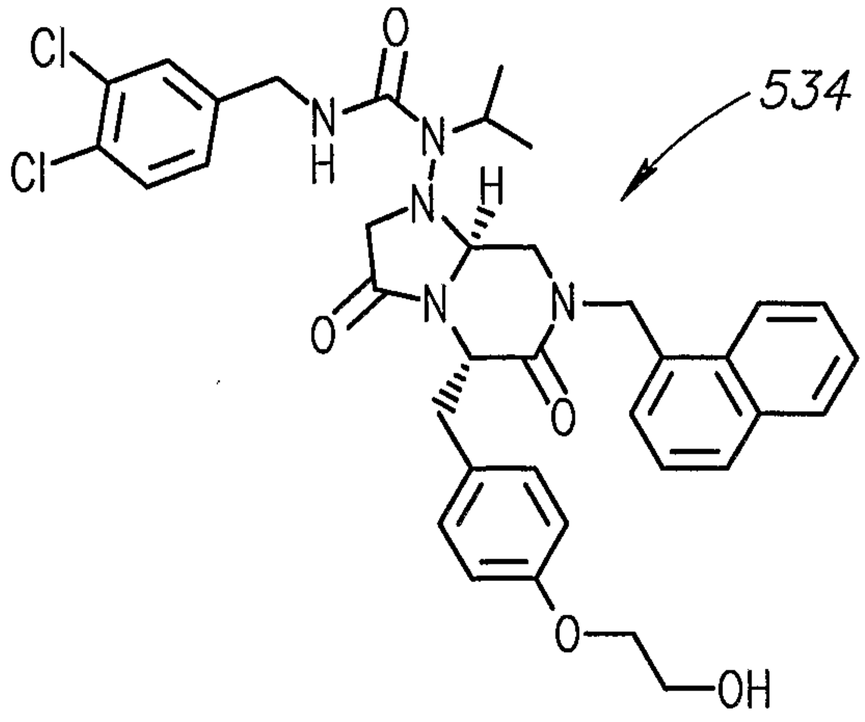

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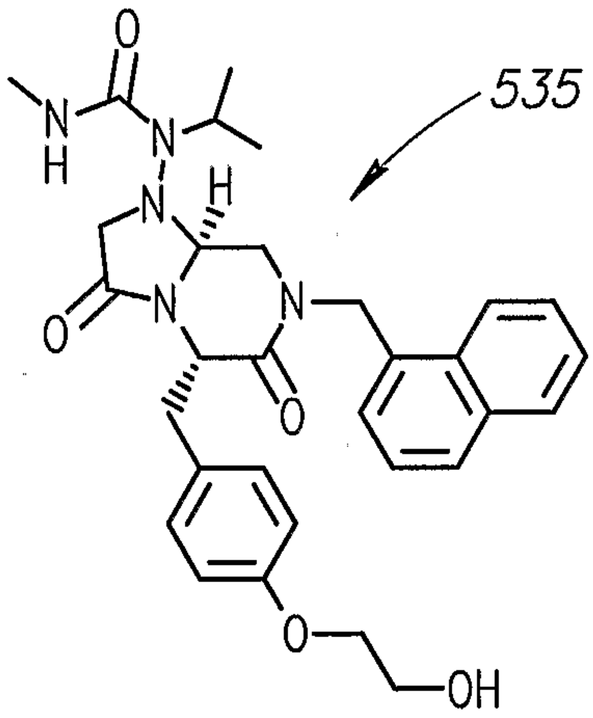

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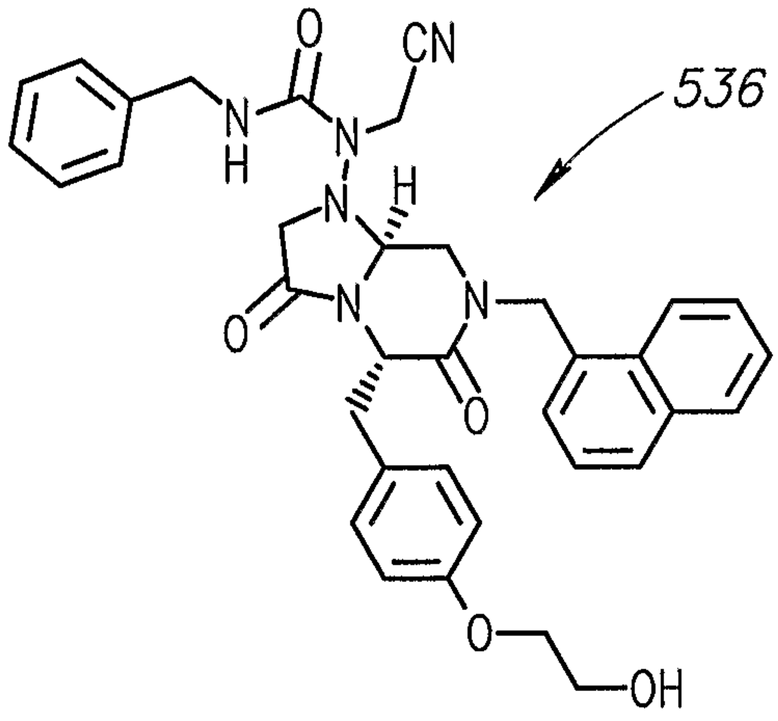

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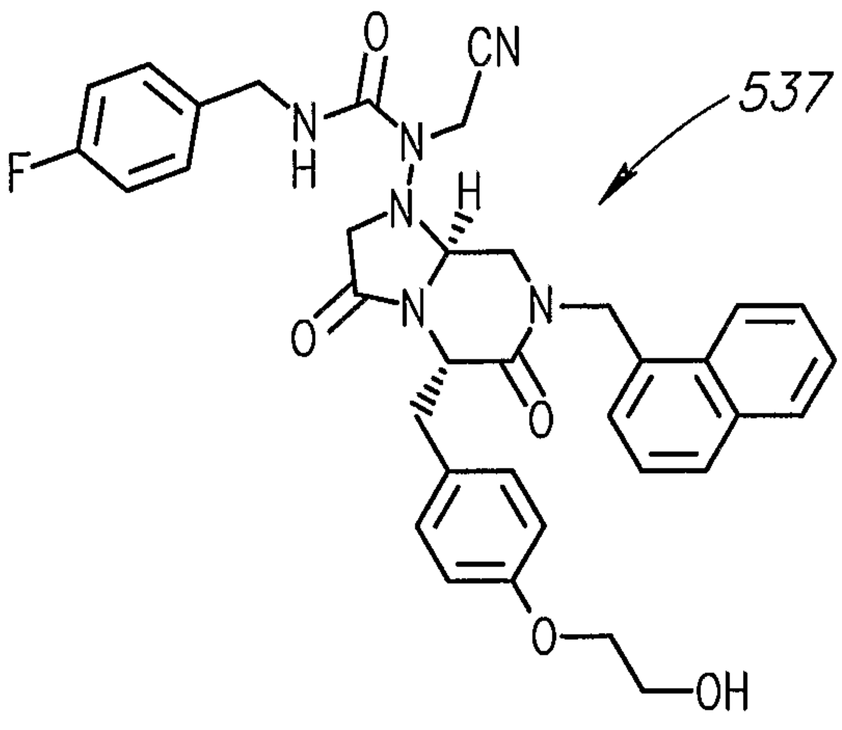

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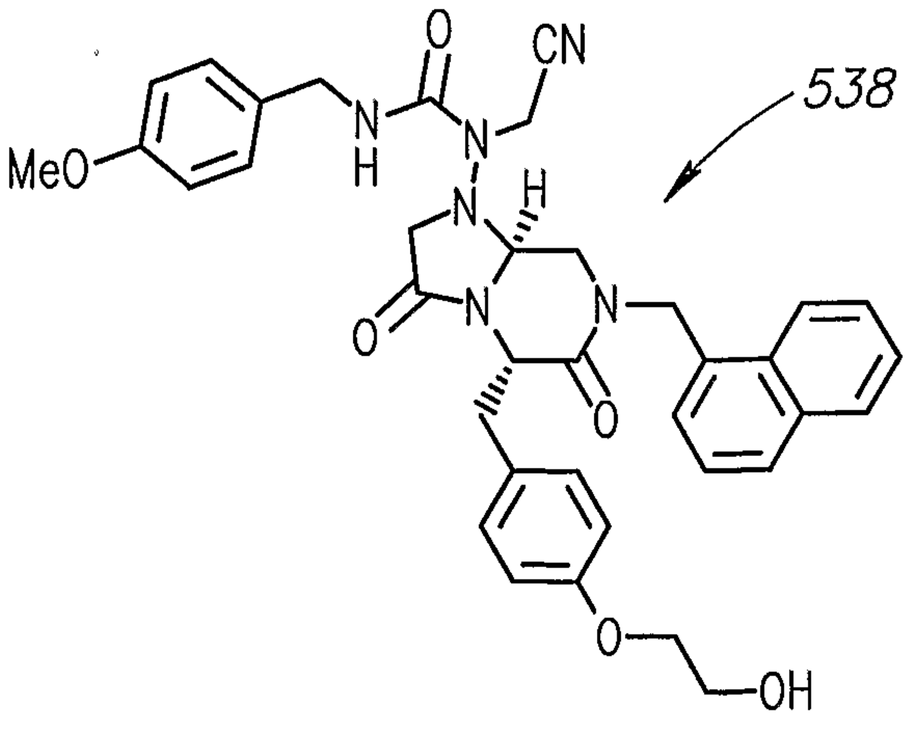
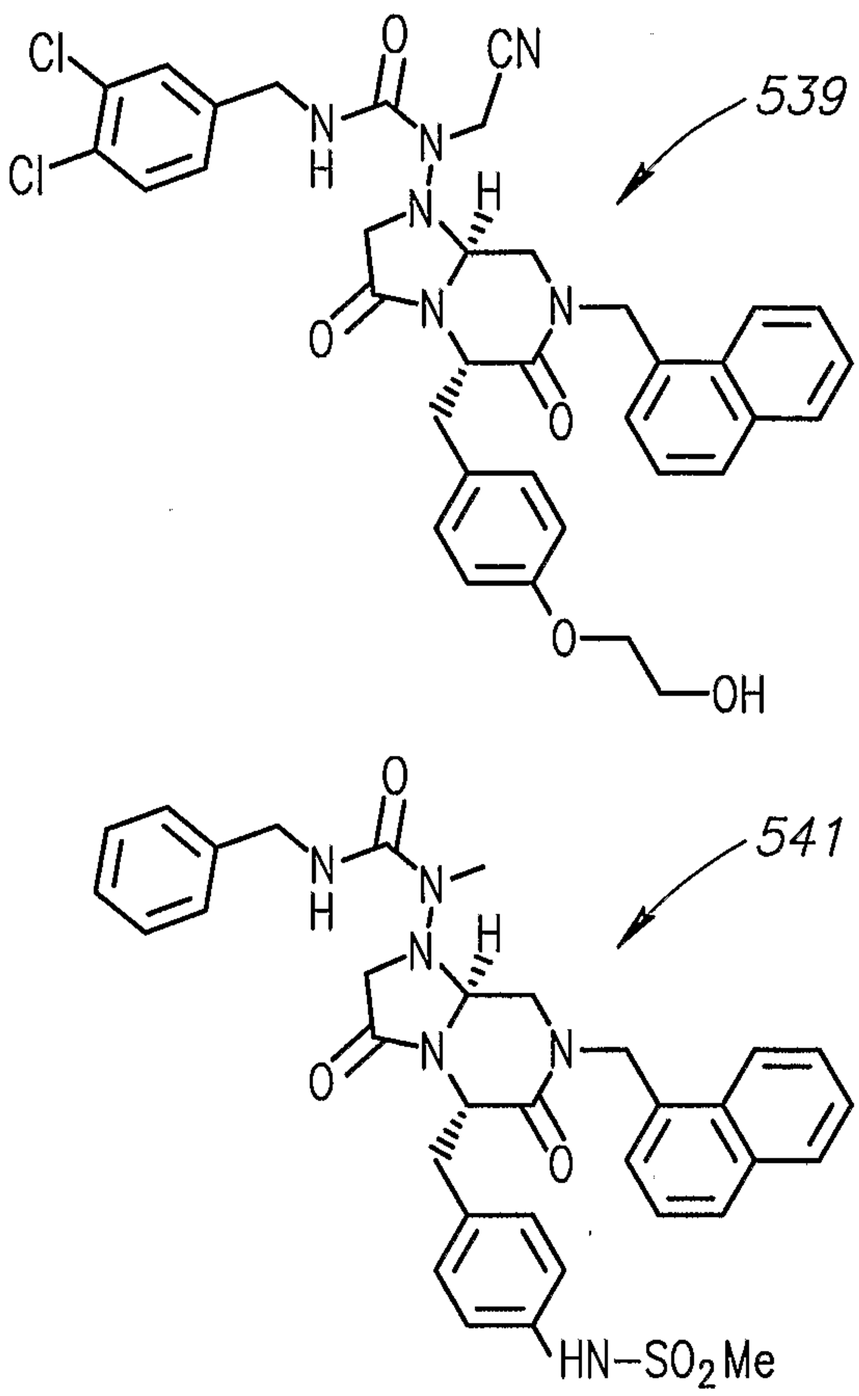


538

FIG.3U


539
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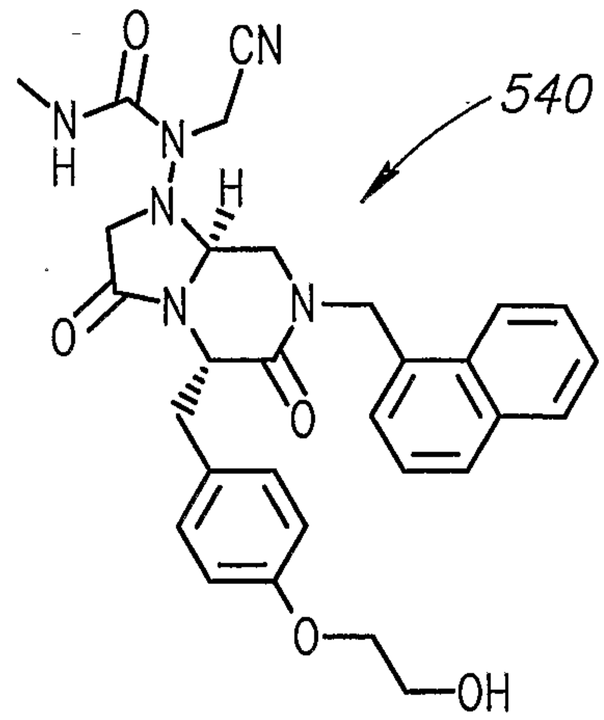
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541
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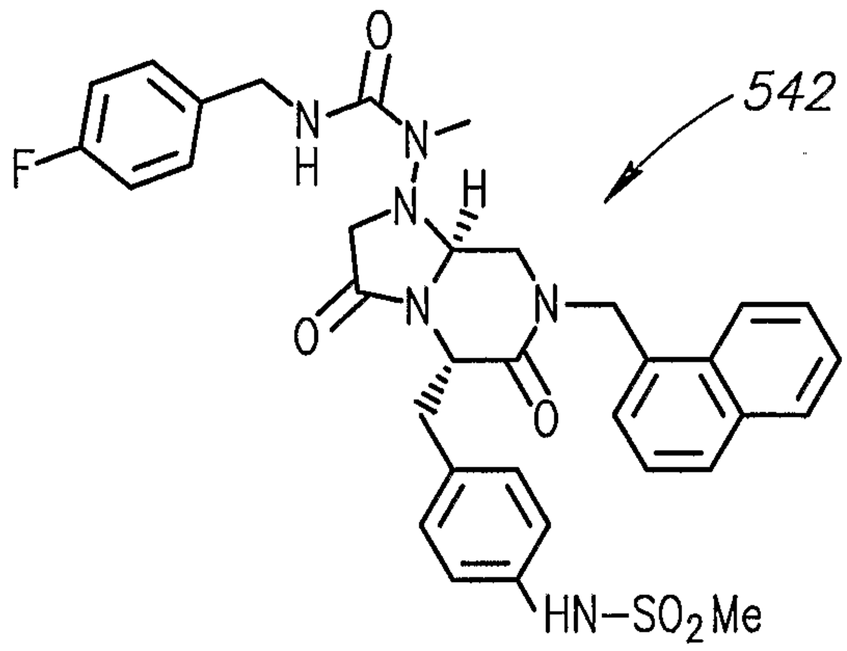
542
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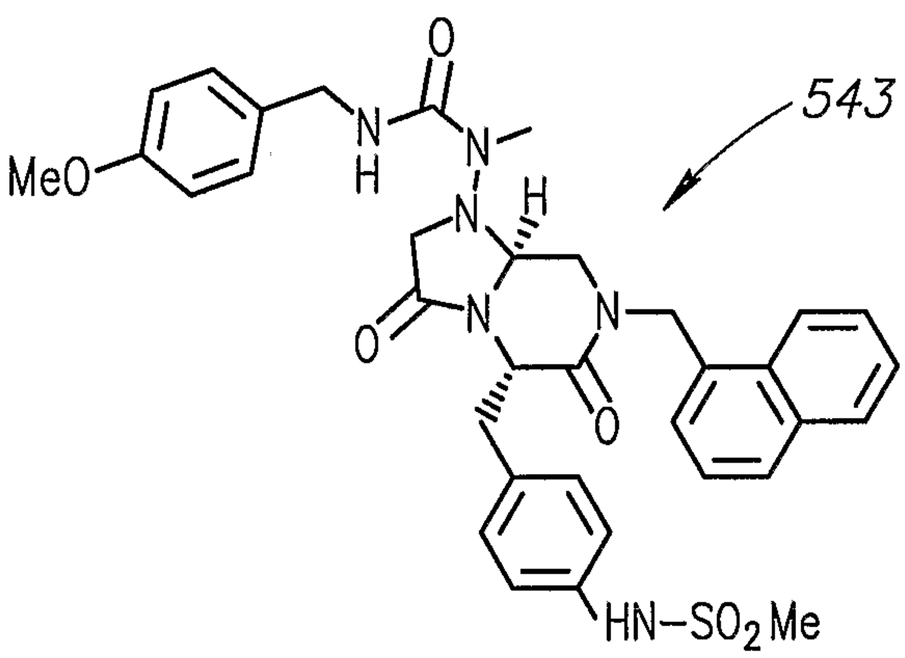
HN–SO2Me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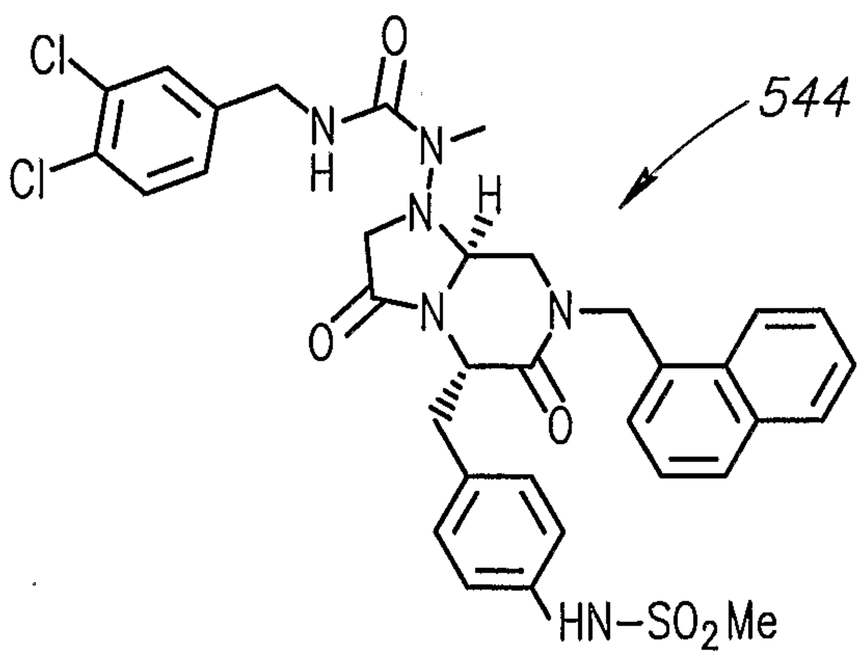
HN–SO2Me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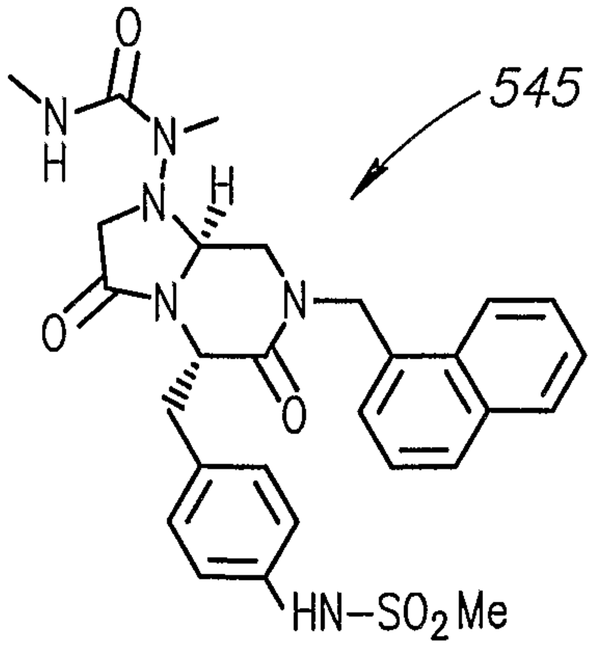
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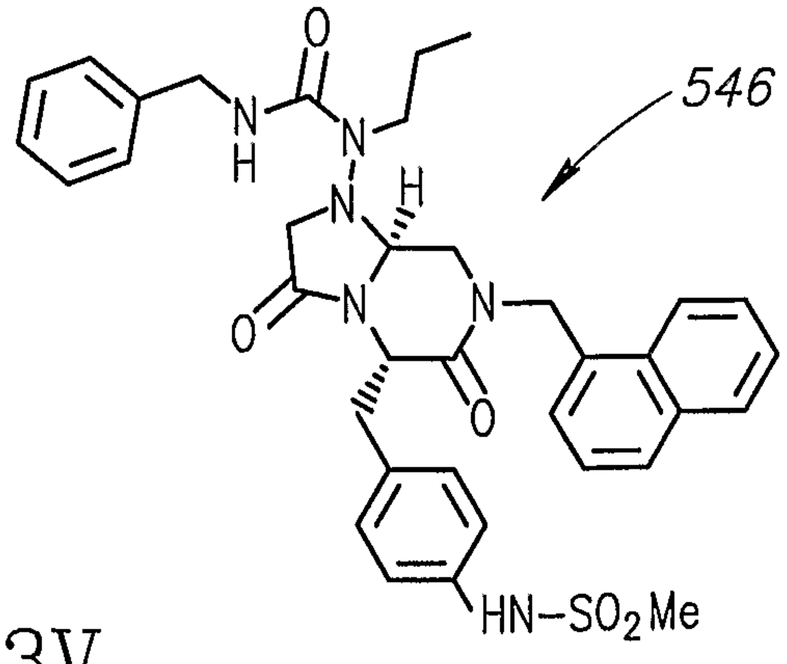
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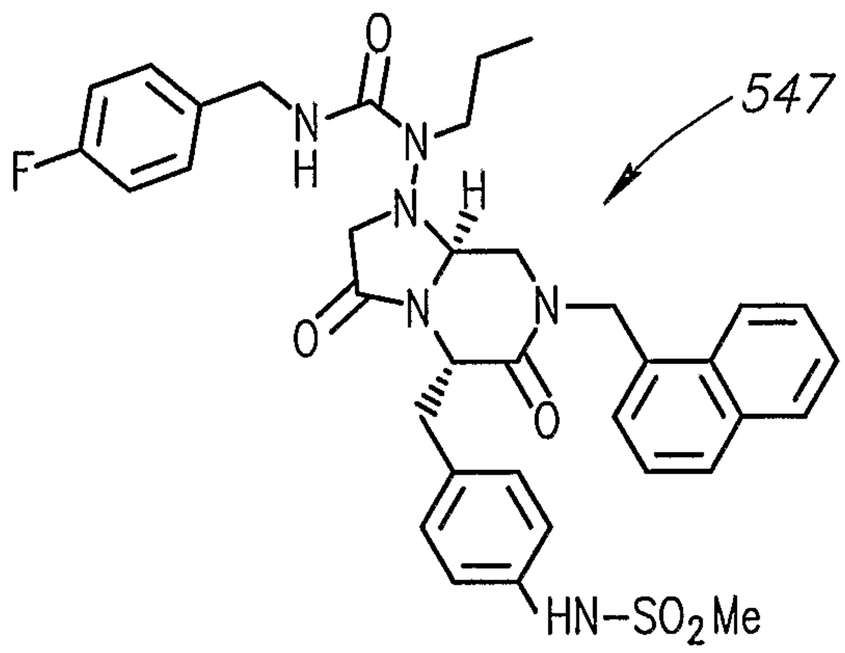
HN–SO2Me

FIG.3V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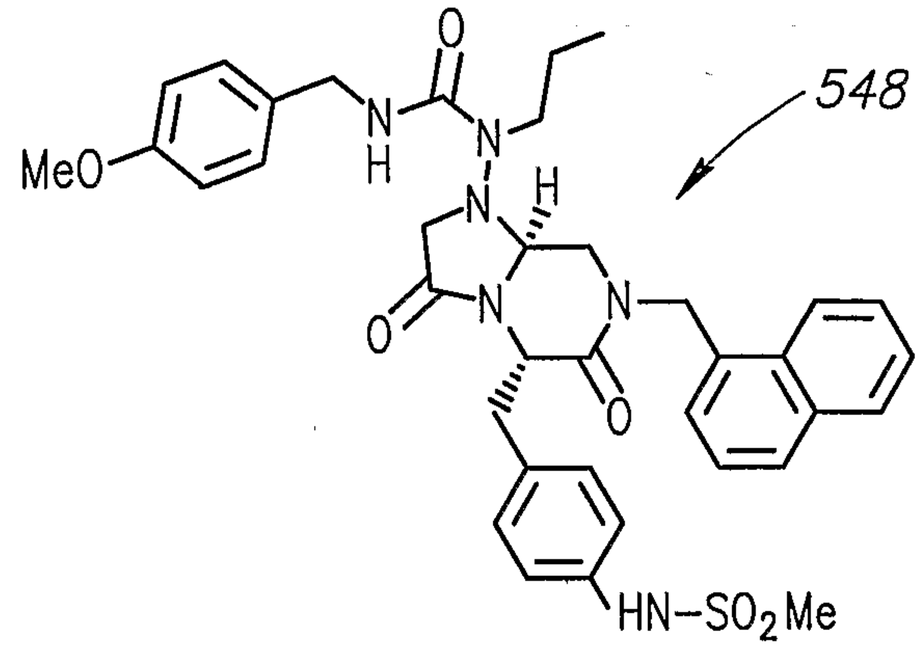
HN–SO2Me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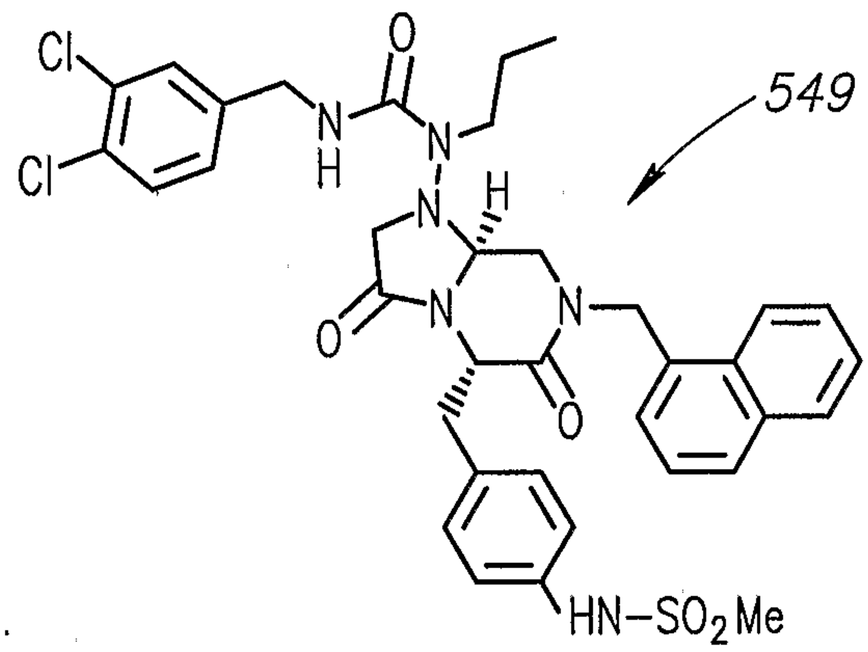
HN–SO2Me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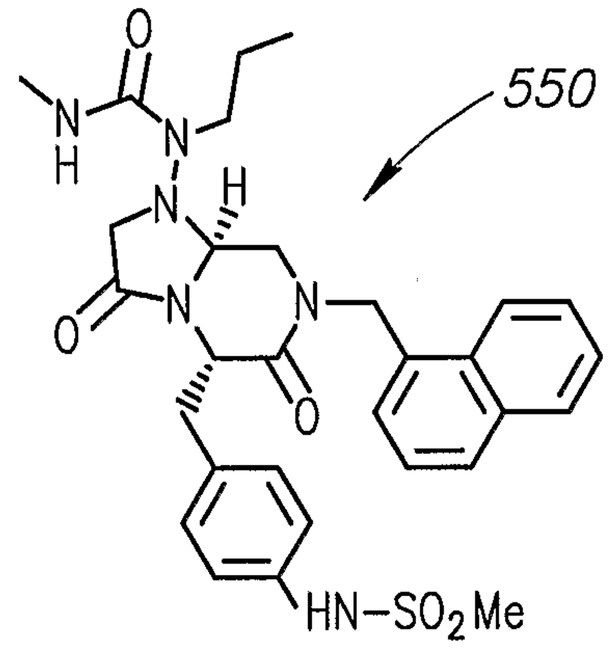
HN–SO2Me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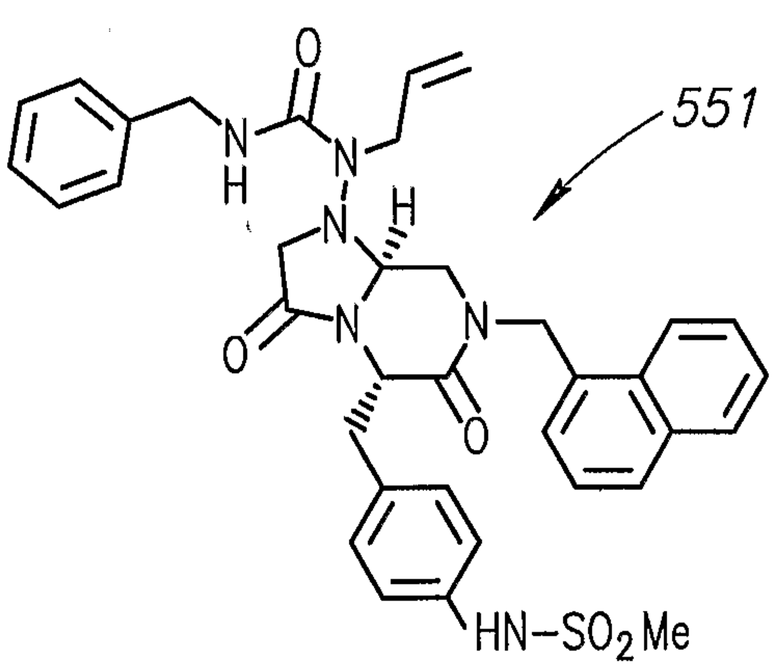
HN–SO2Me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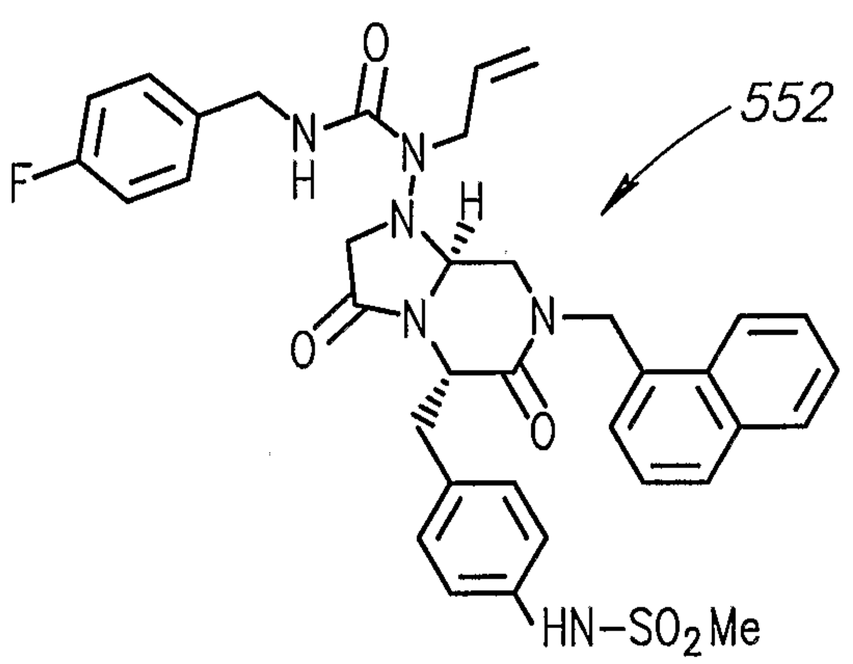
HN–SO2Me


552
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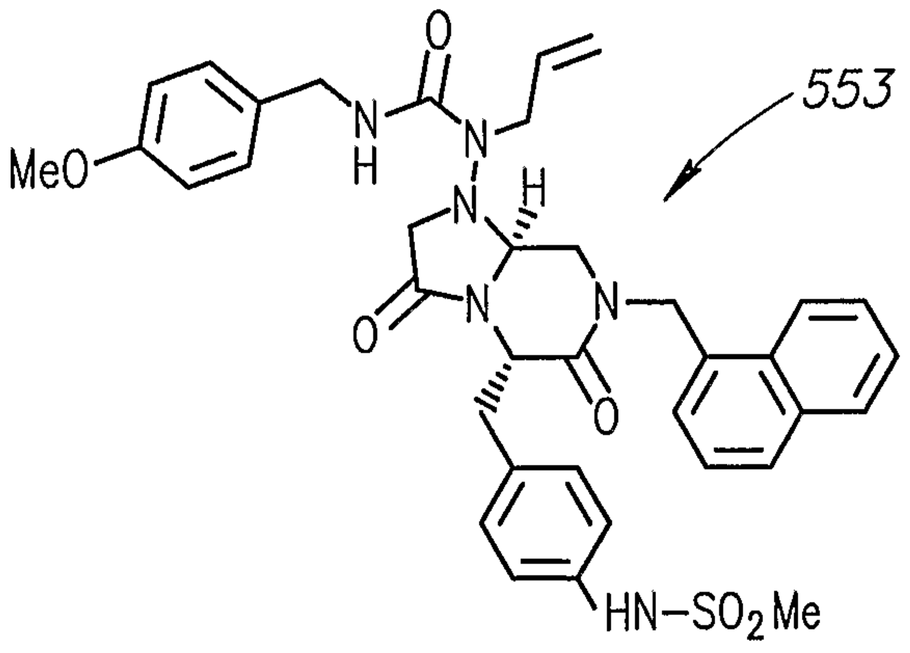
HN–SO2Me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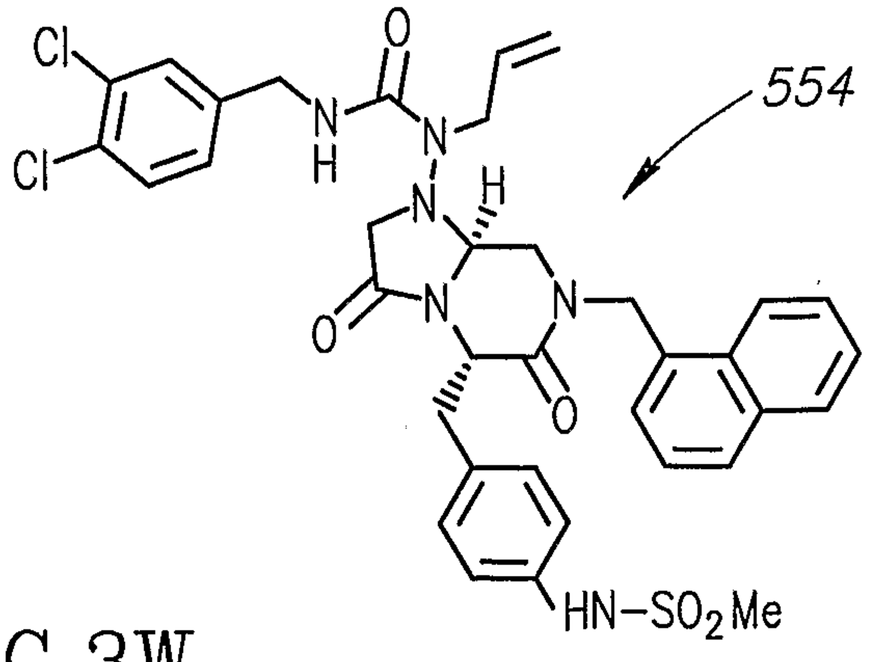
HN–SO2Me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N
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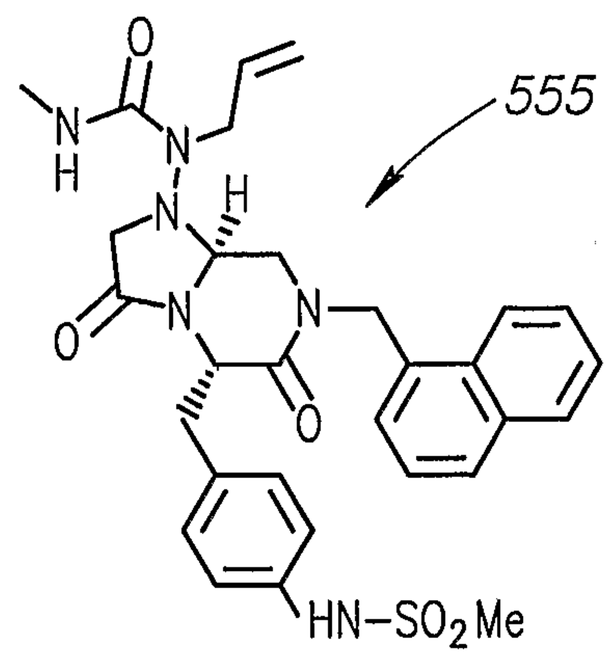
O
O
HN–SO2Me

FIG.3W


555
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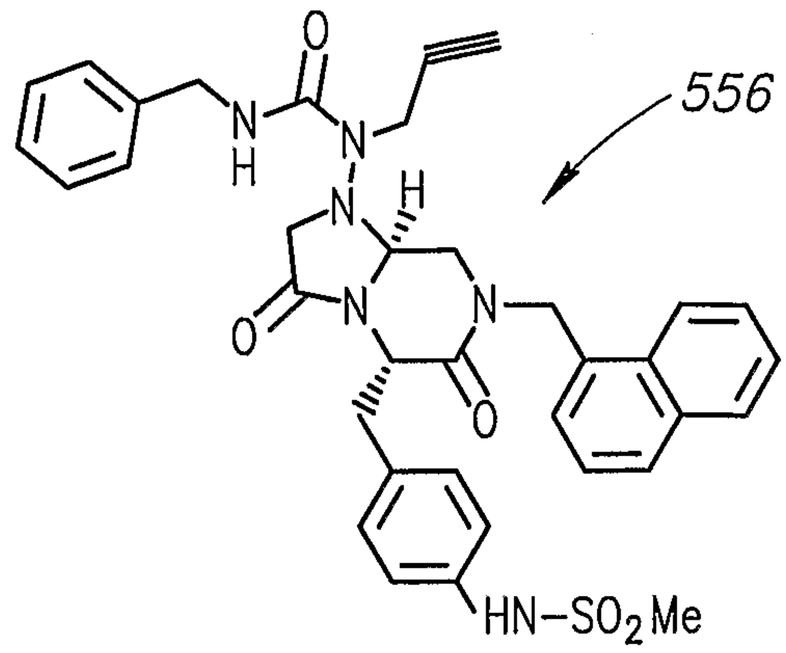
556
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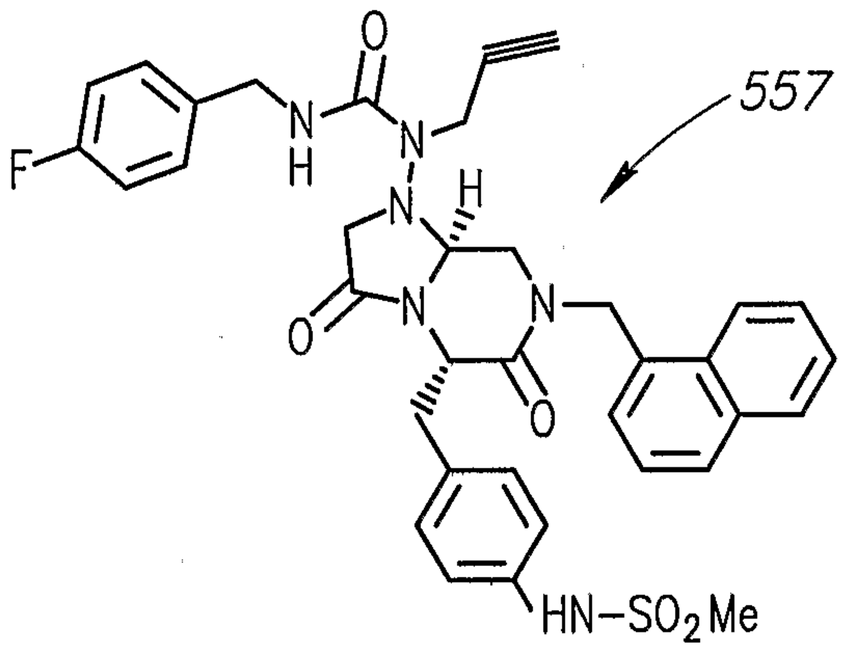
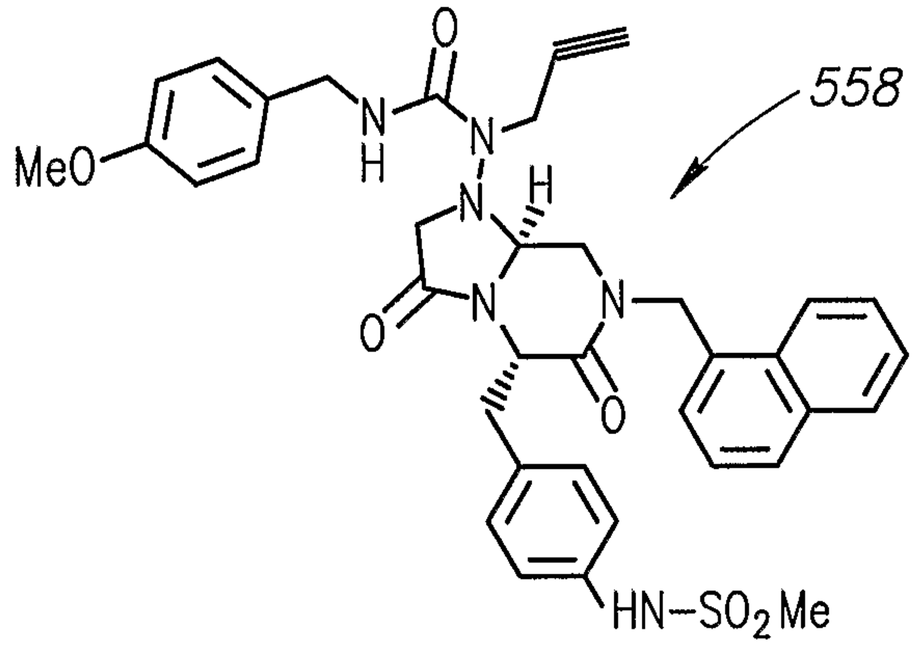
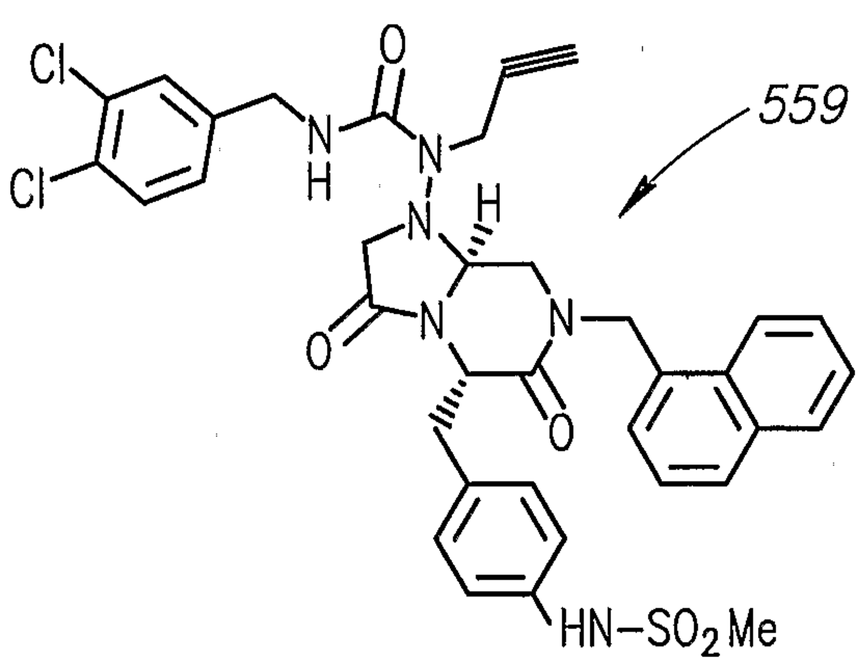
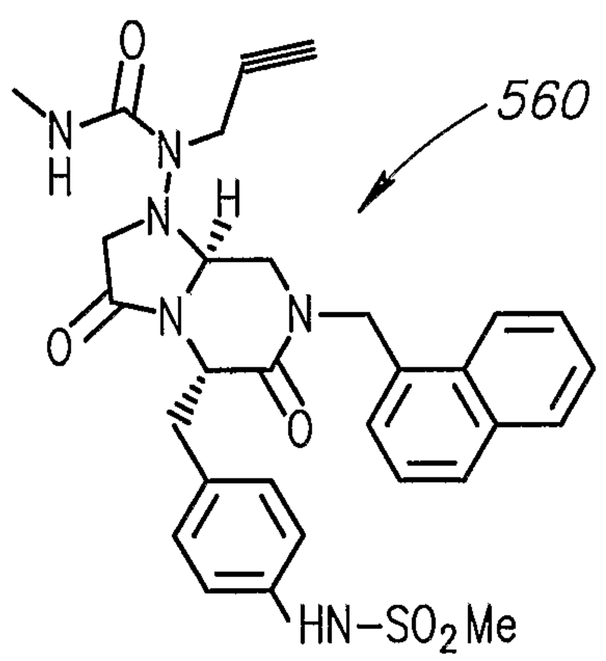

557
F
HN–SO2Me


558
MeO
HN–SO2Me


559
Cl
Cl
HN–SO2Me


560
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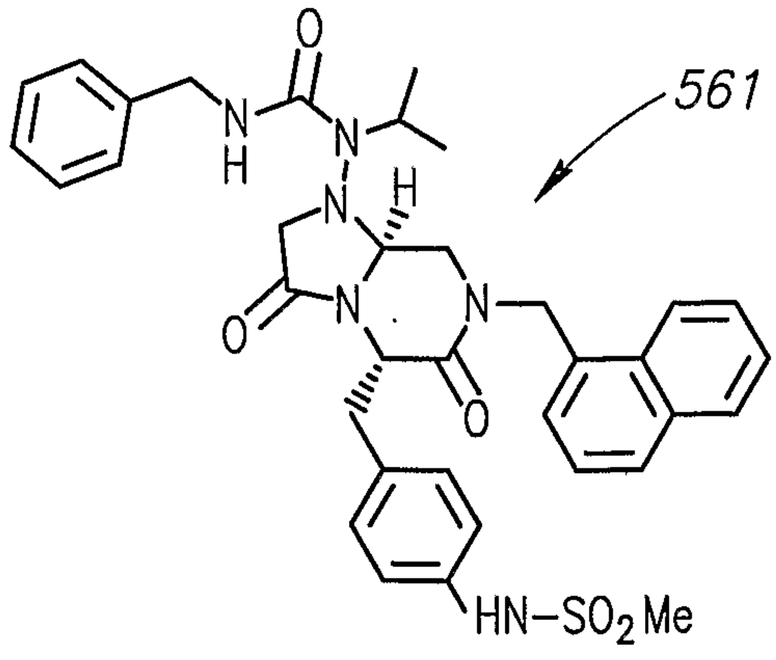
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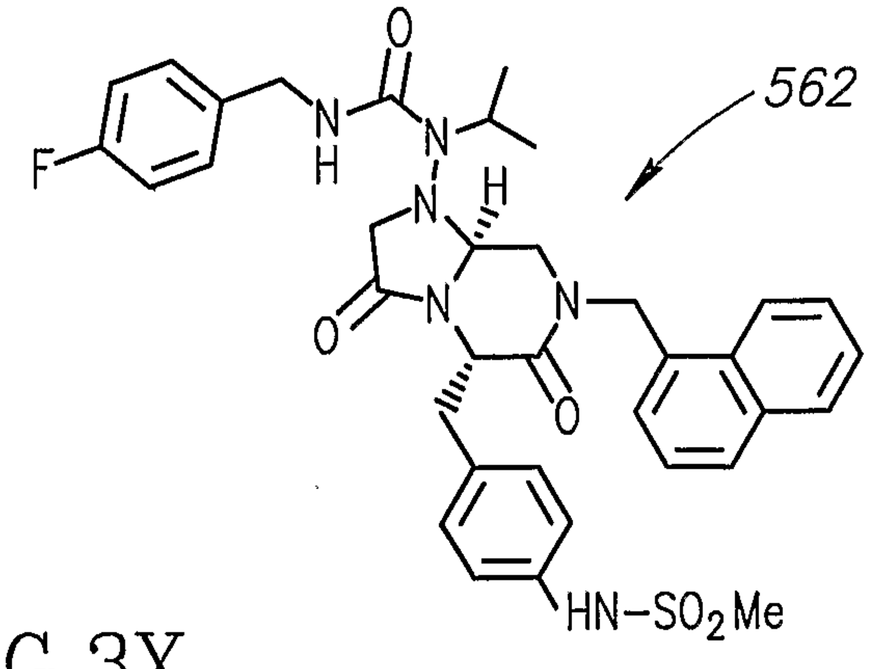
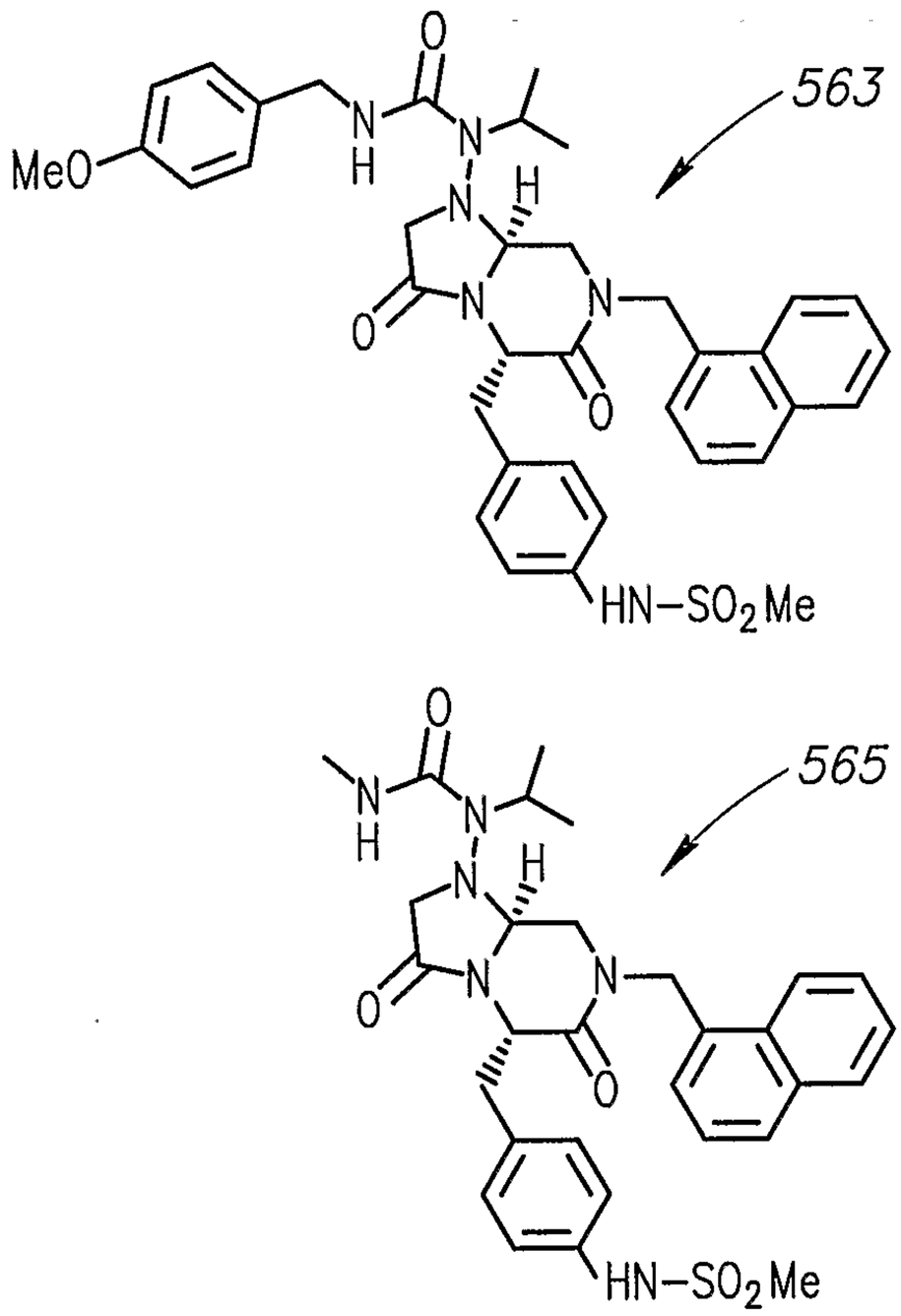
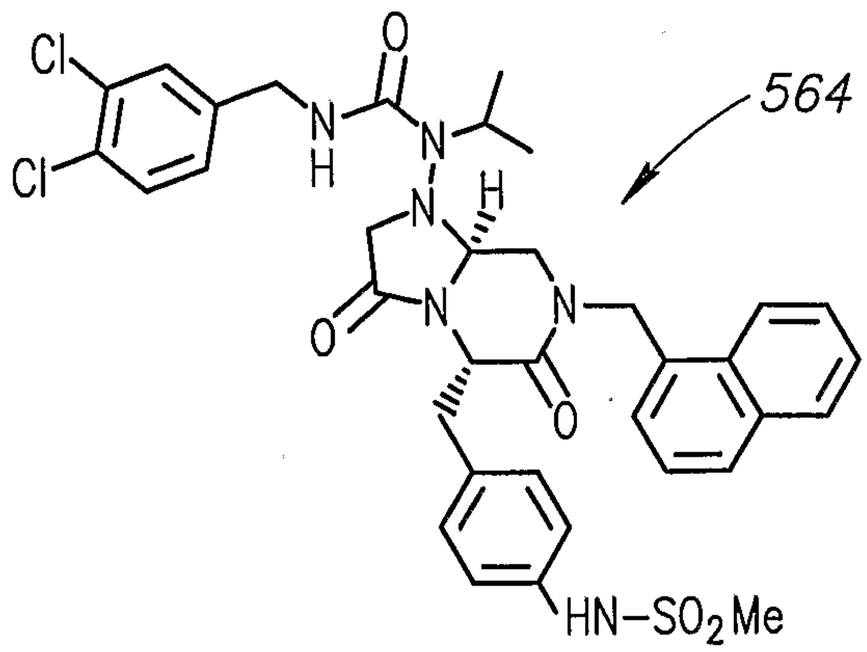

562
F
HN–SO2Me

FIG.3X


MeO
563
HN–SO2Me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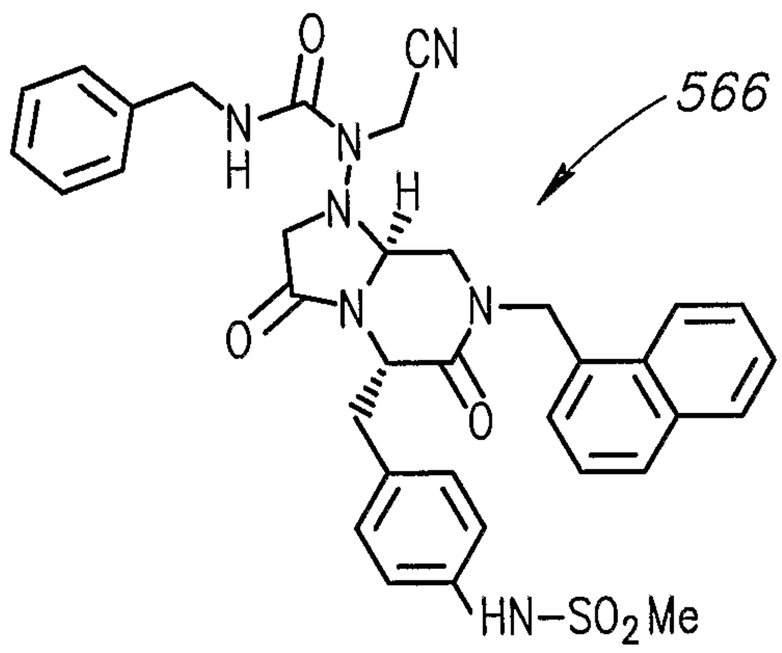
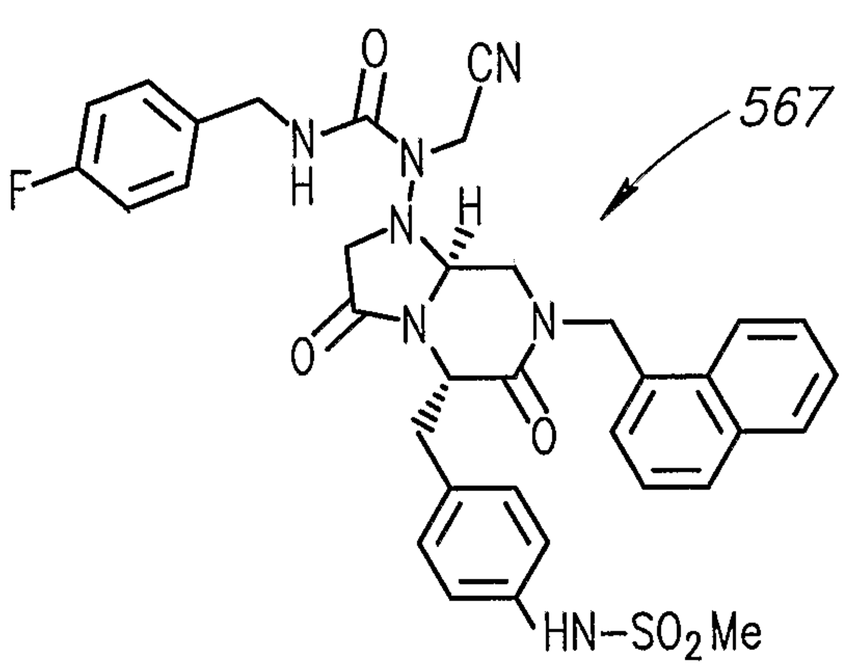
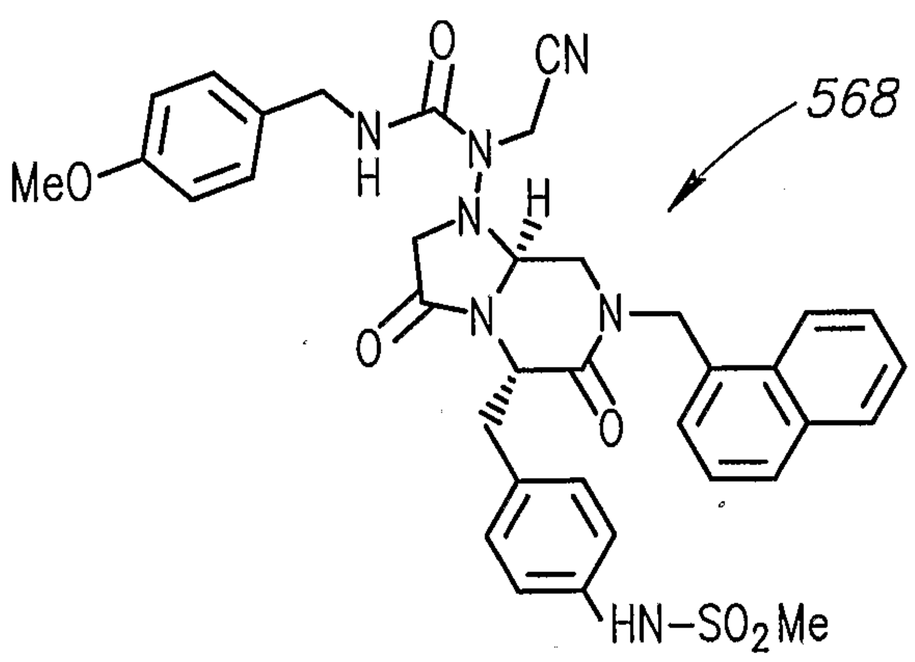
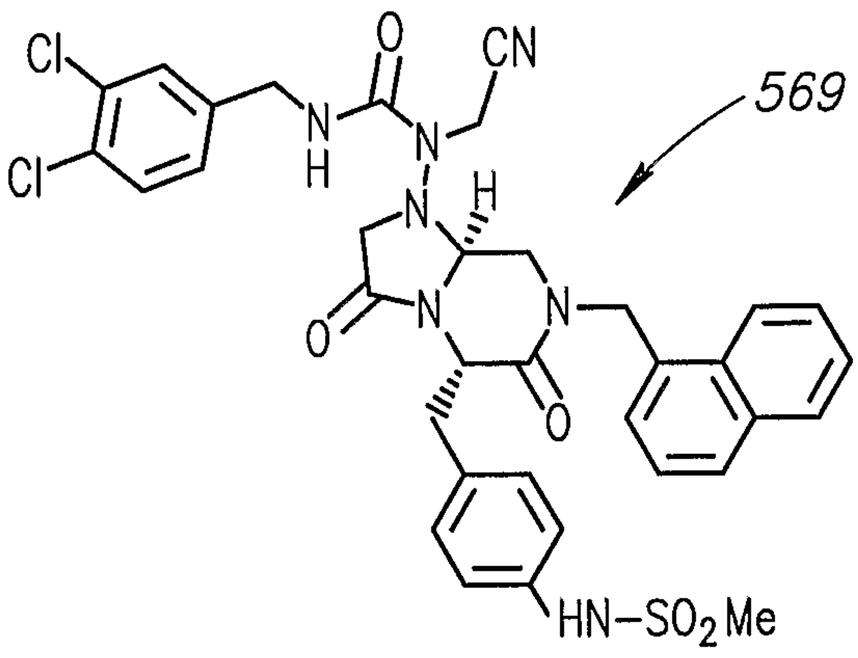
Cl
564
HN–SO2Me

565
HN–SO2Me


CN
566
HN–SO2Me


F
CN
567
HN–SO2Me


MeO
CN
568
HN–SO2Me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Cl
CN
569
HN–SO2Me

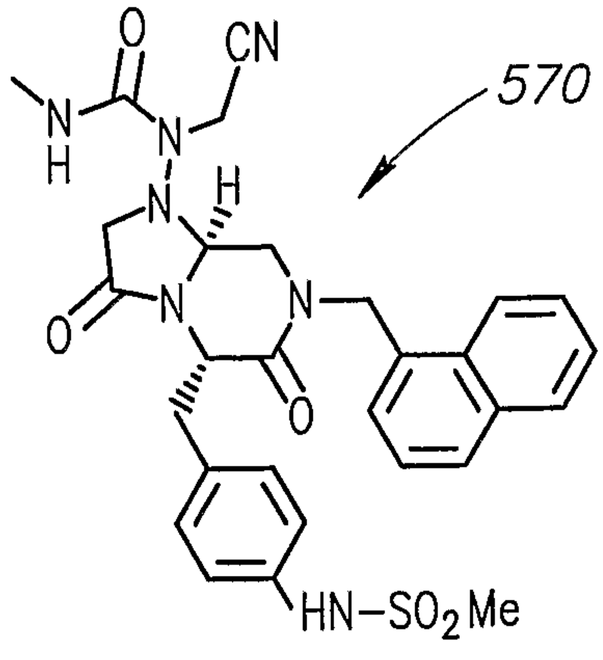
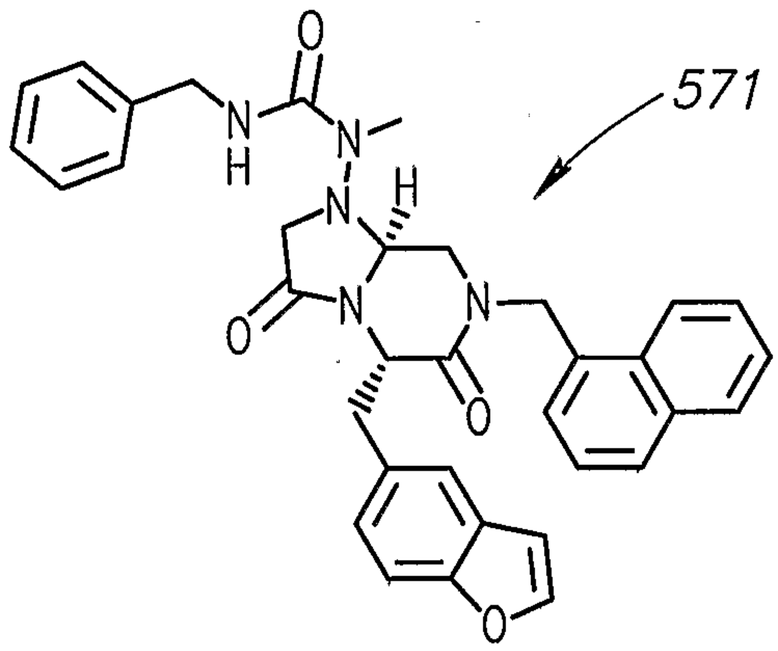
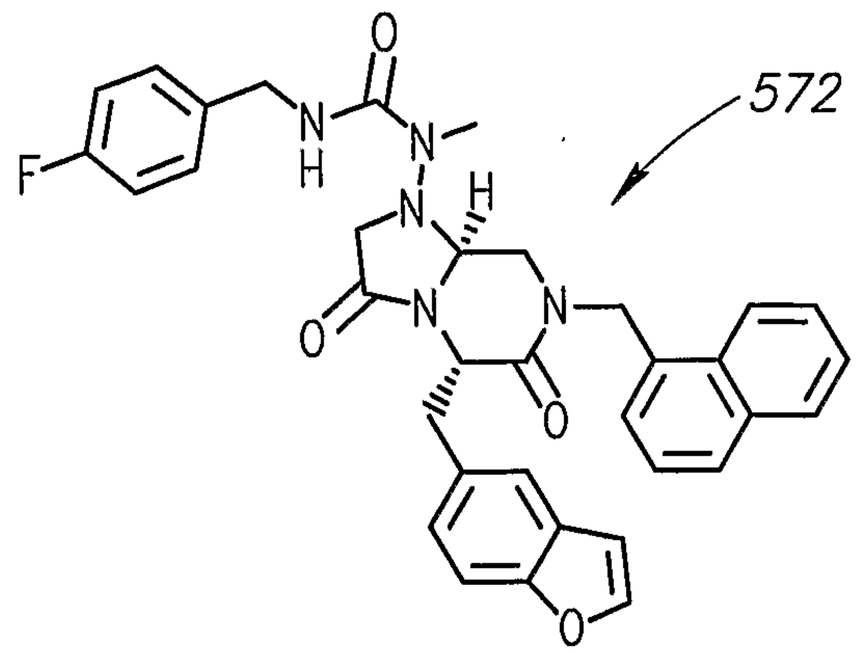
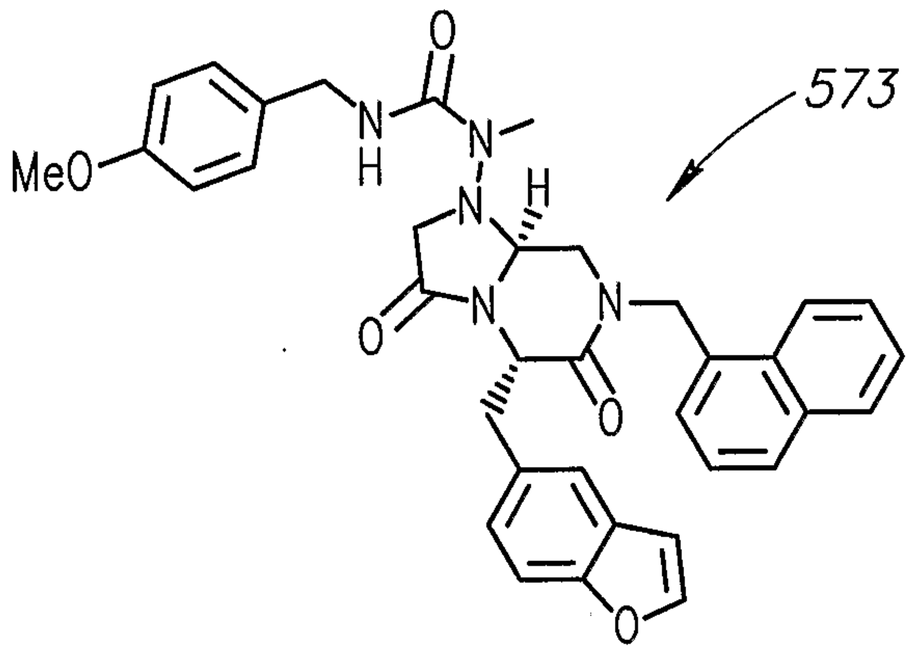
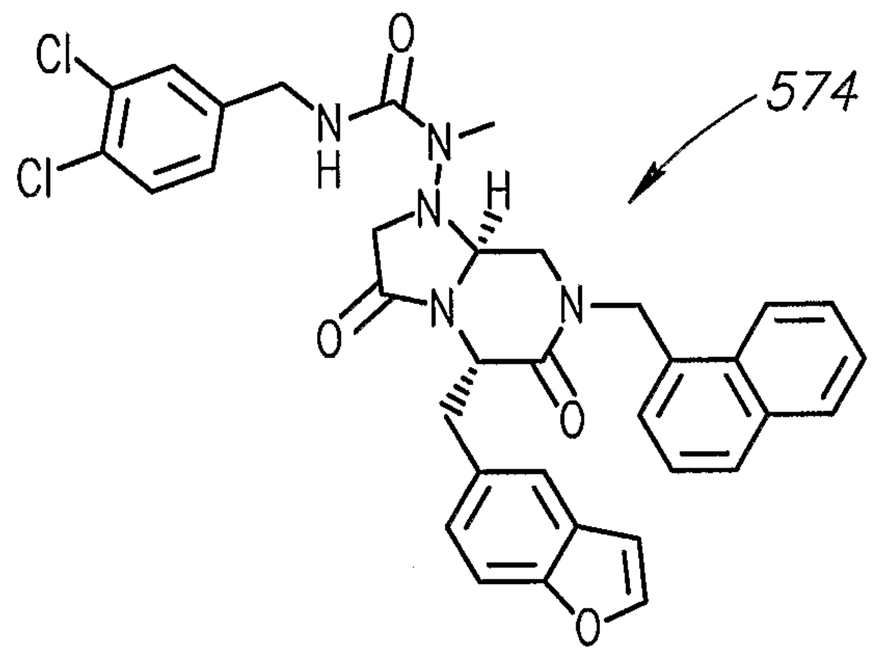

CN
570
HN–SO2Me

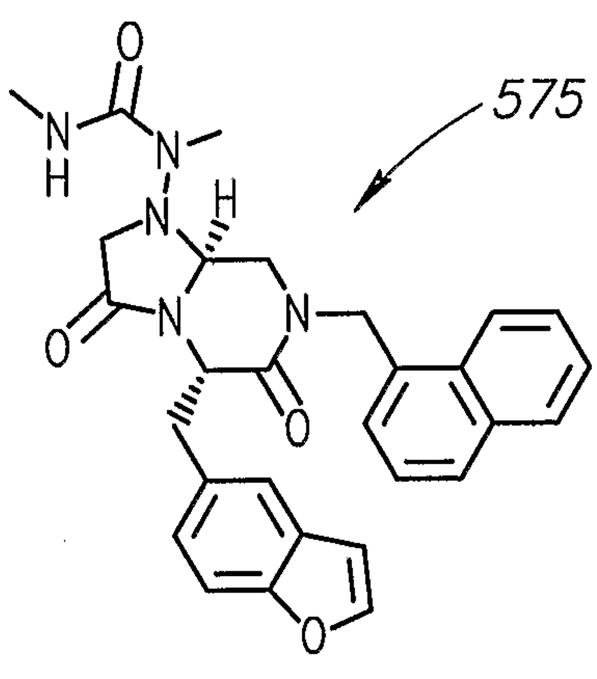
FIG.3Y

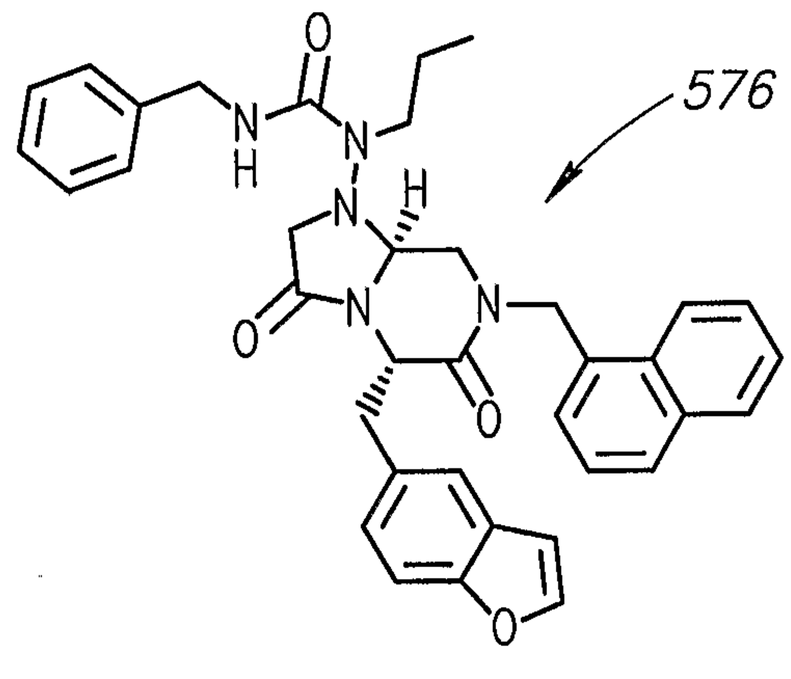


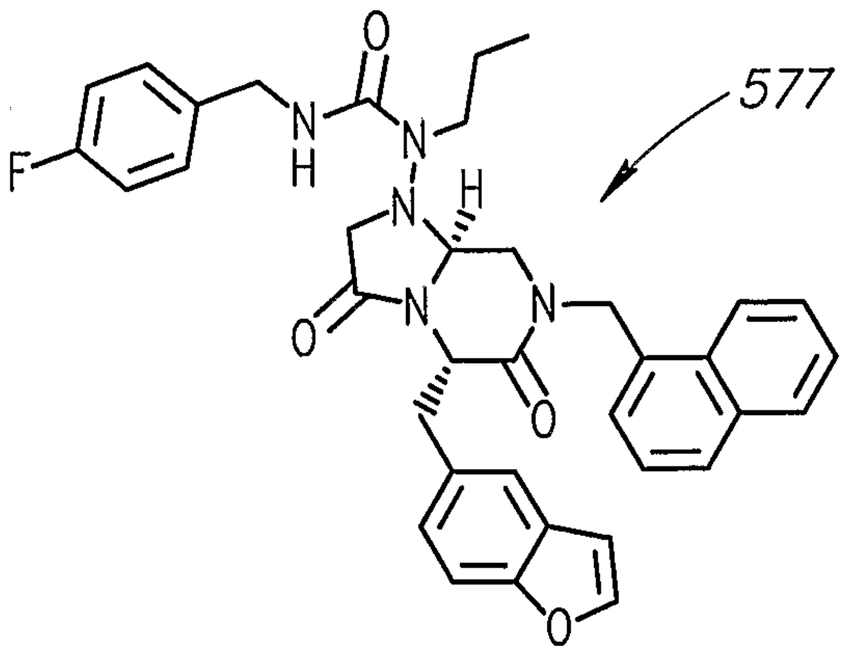












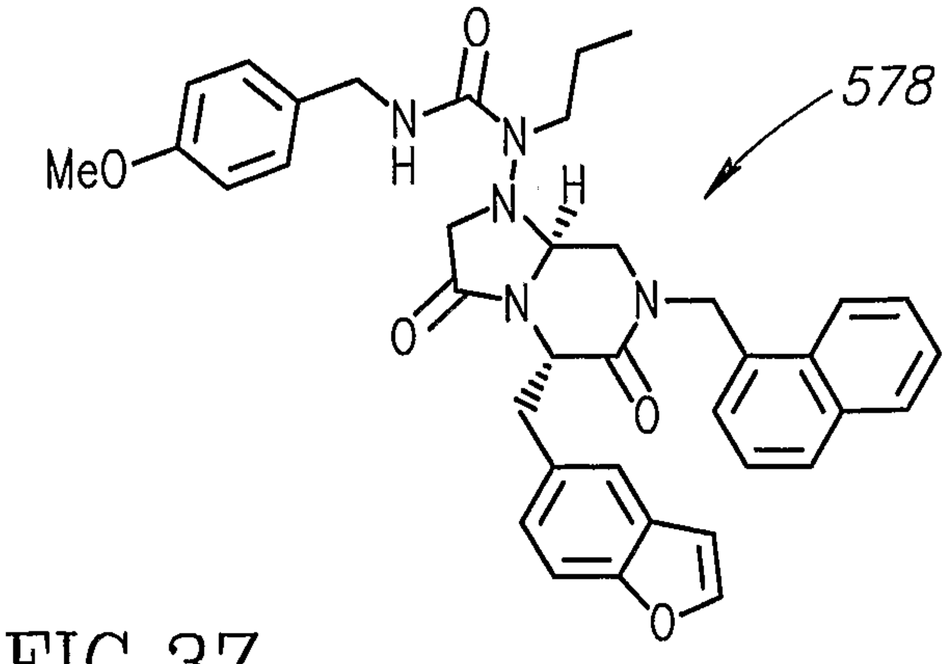
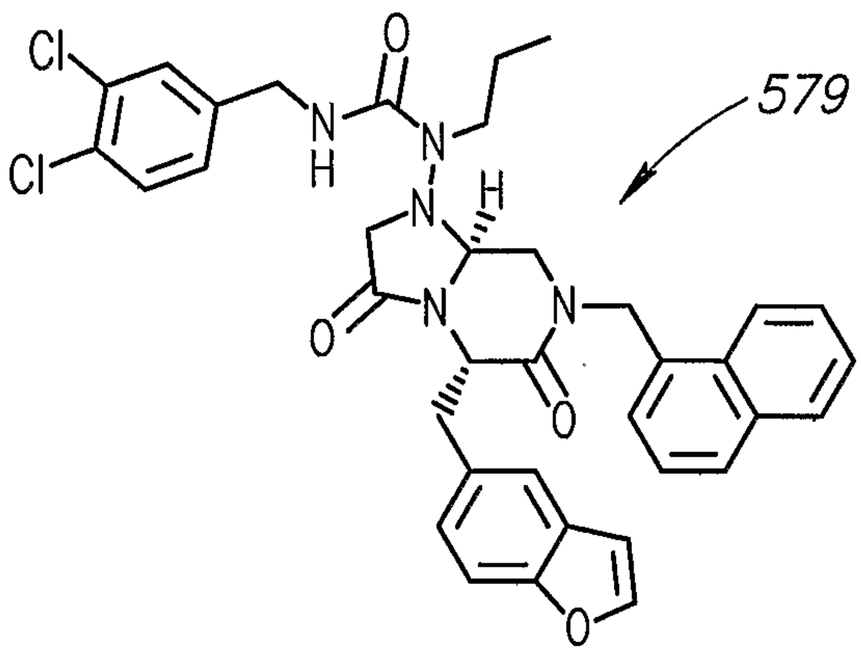
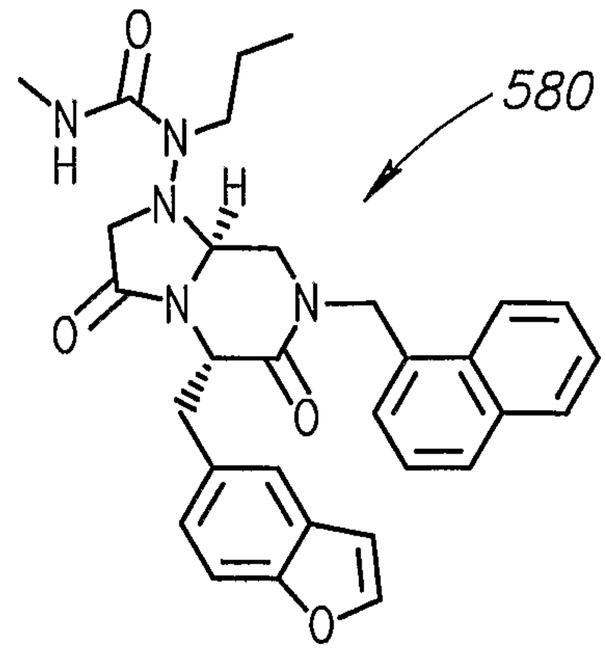
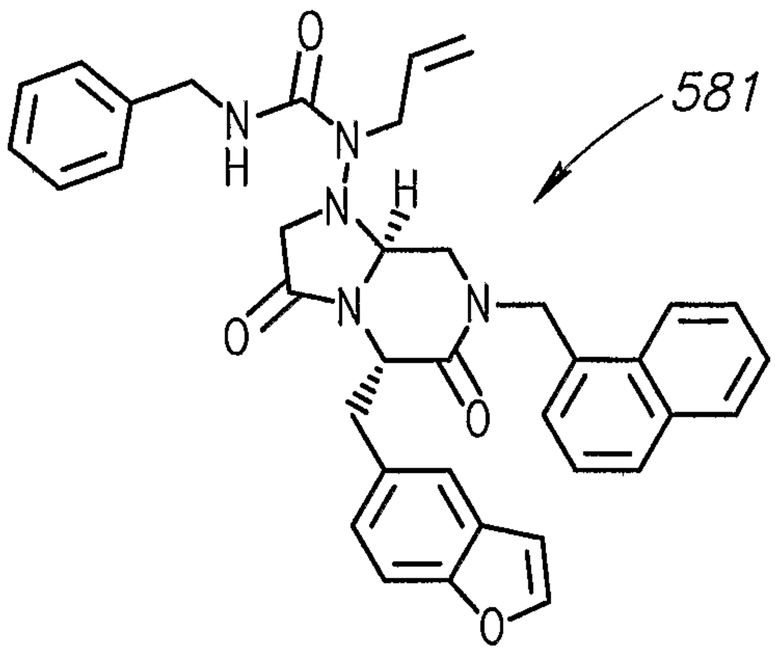
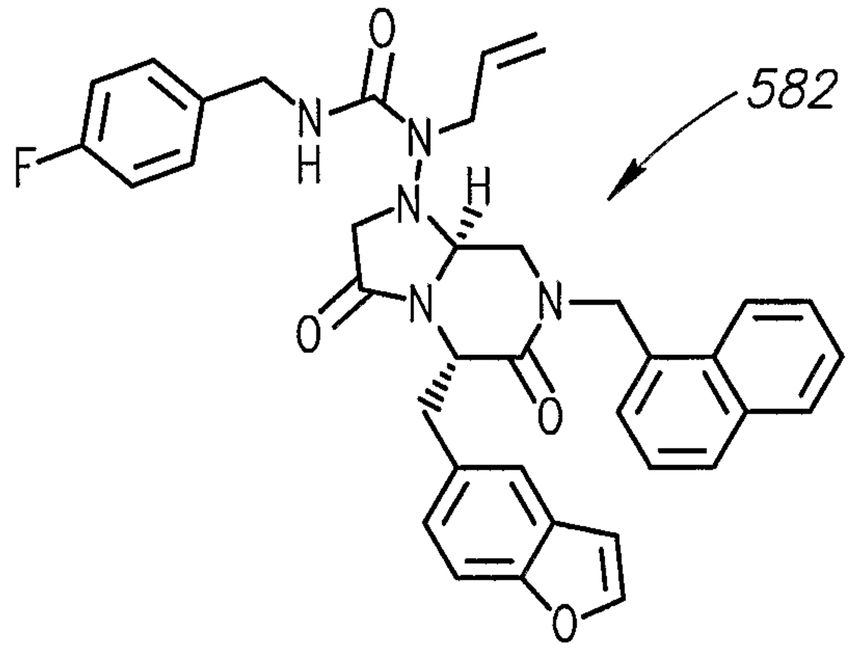


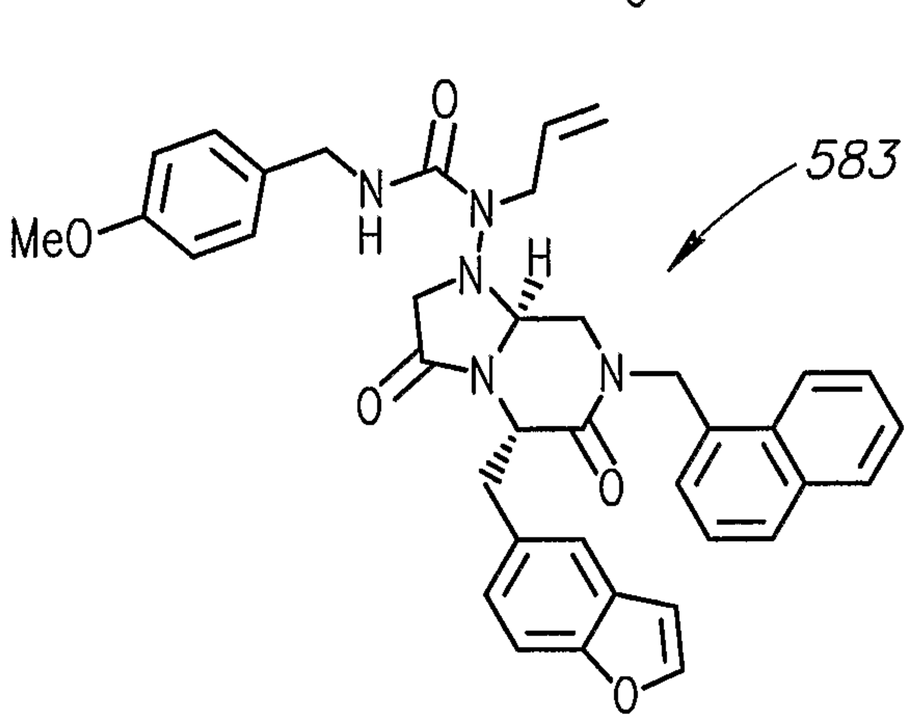
FIG.3Z











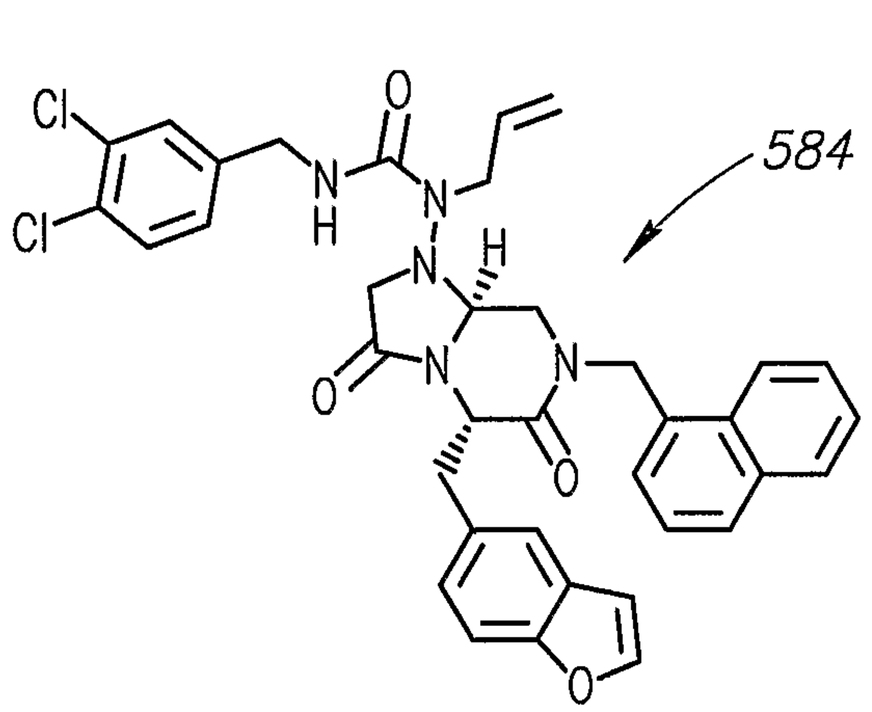
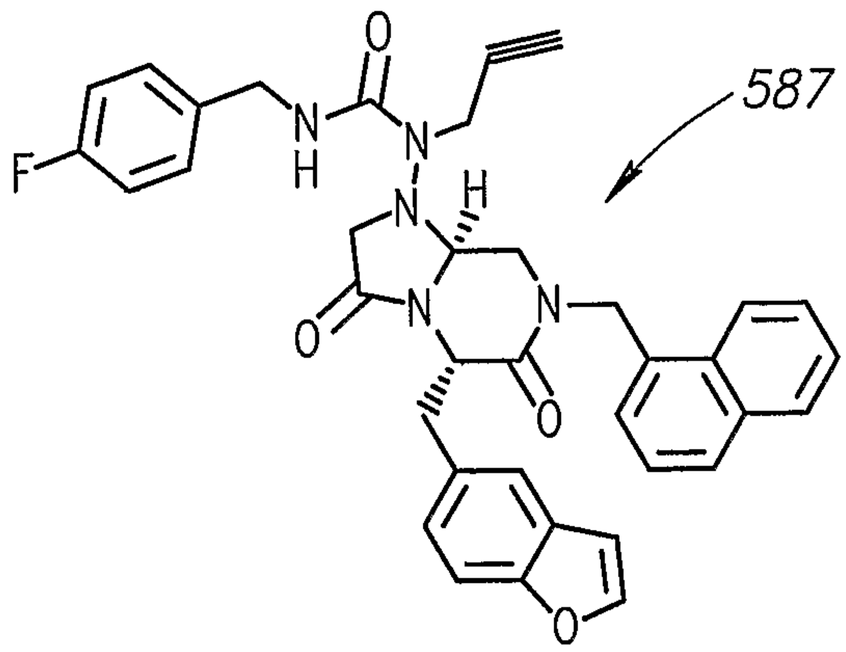
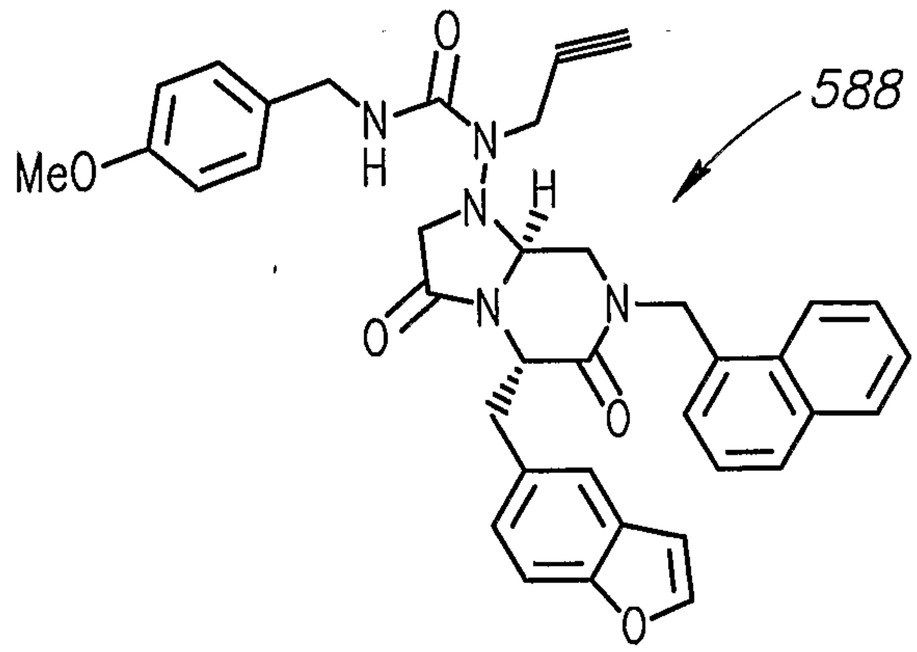
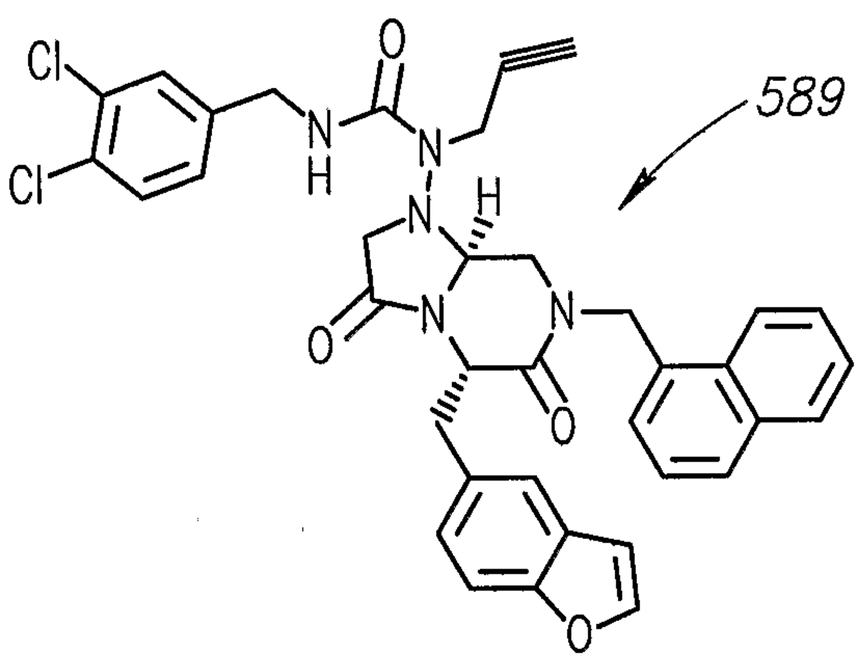
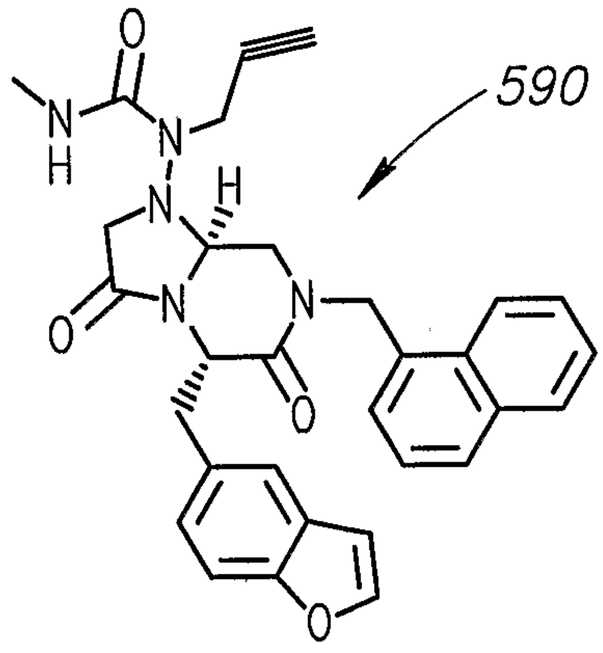


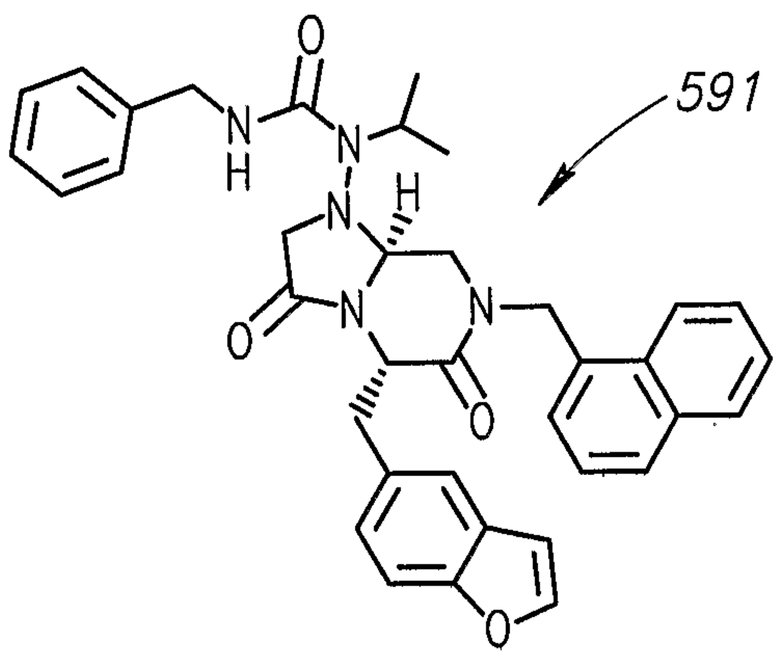
FIG.3AA

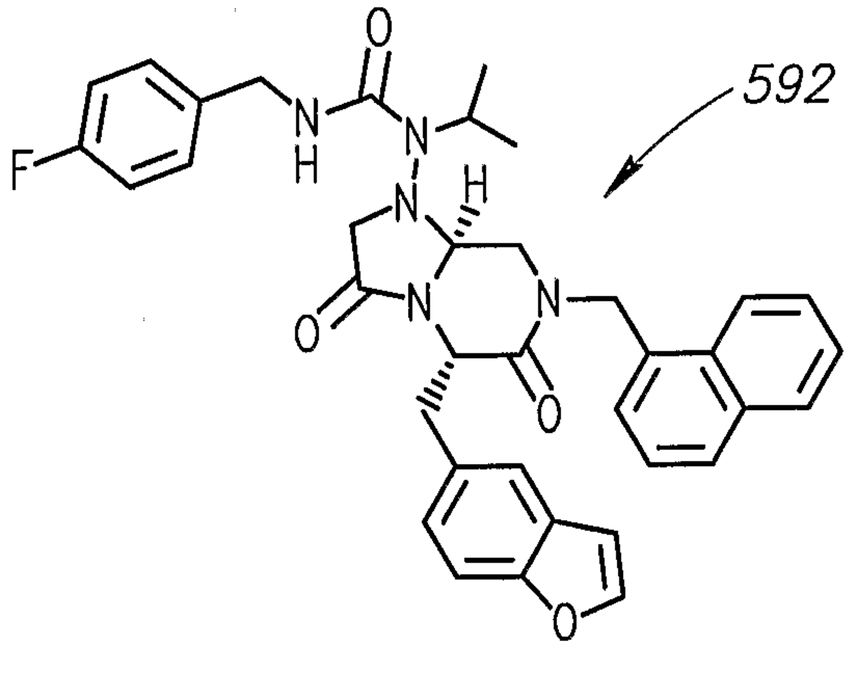


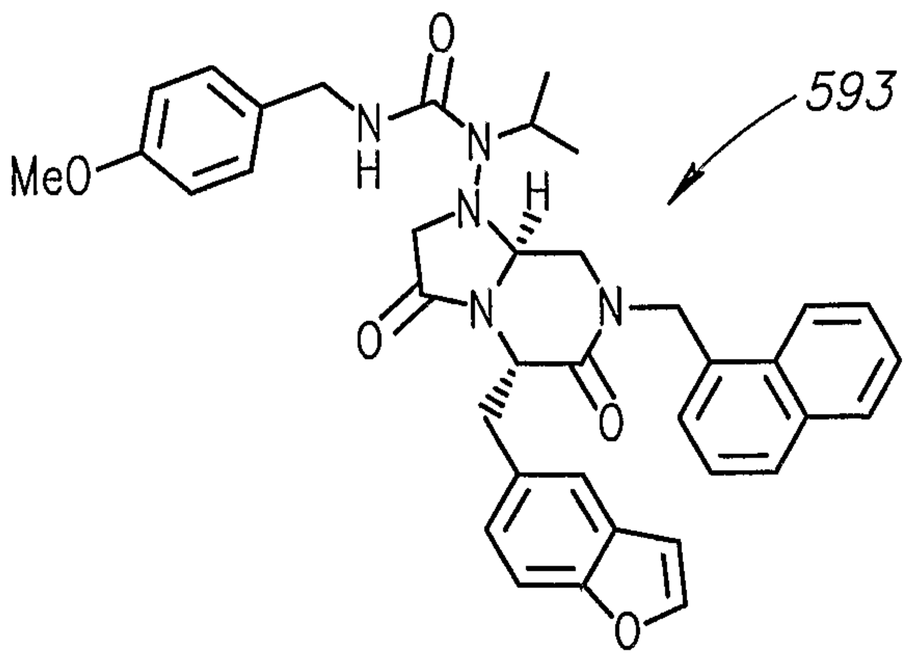












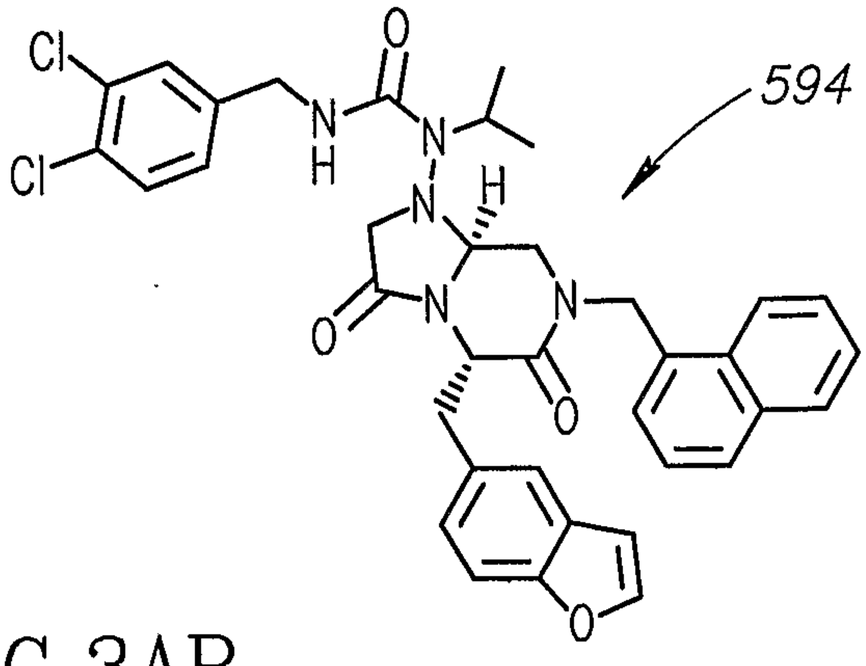
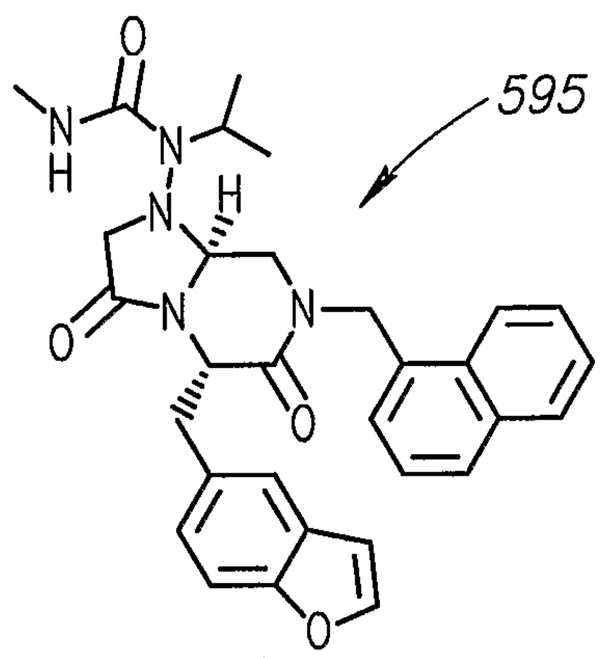
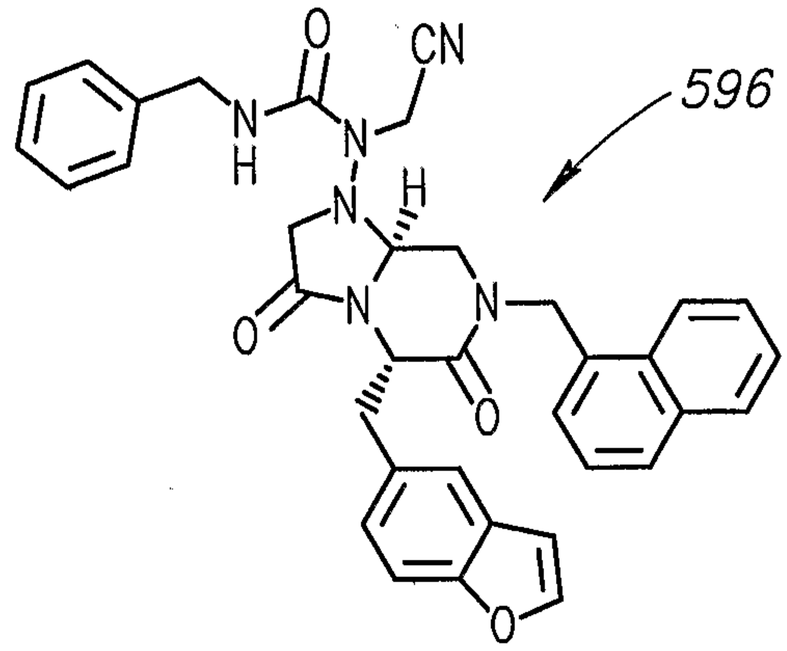
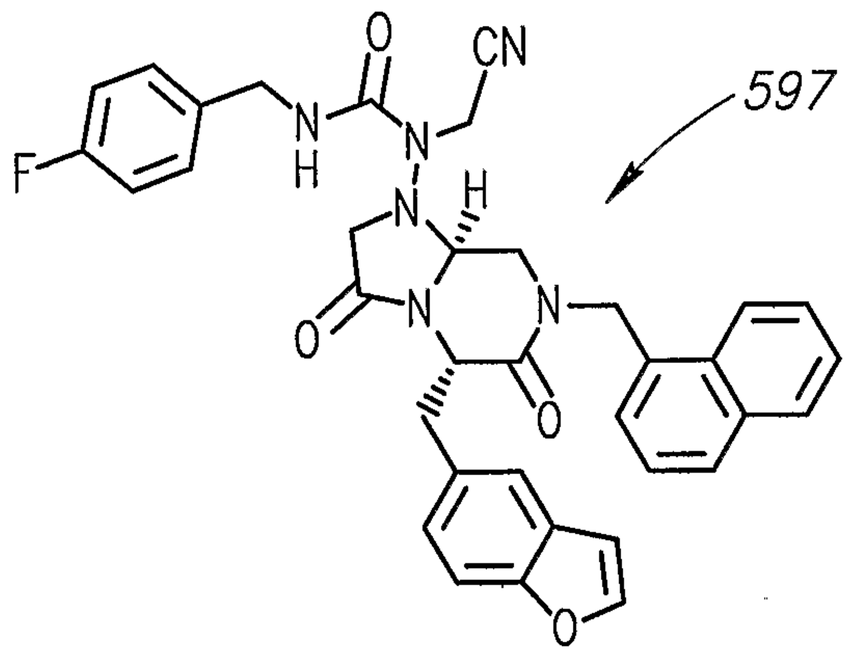
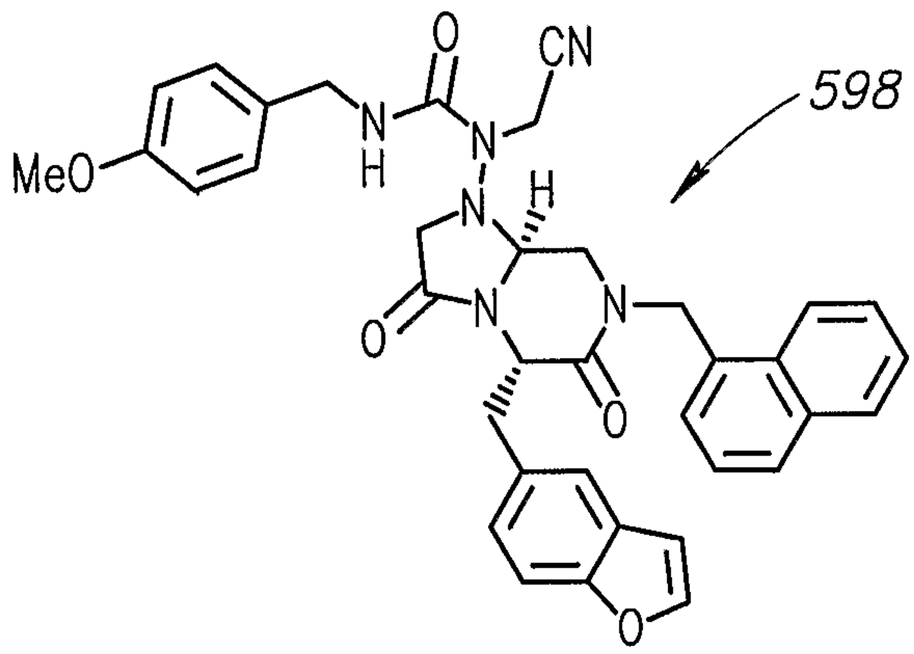


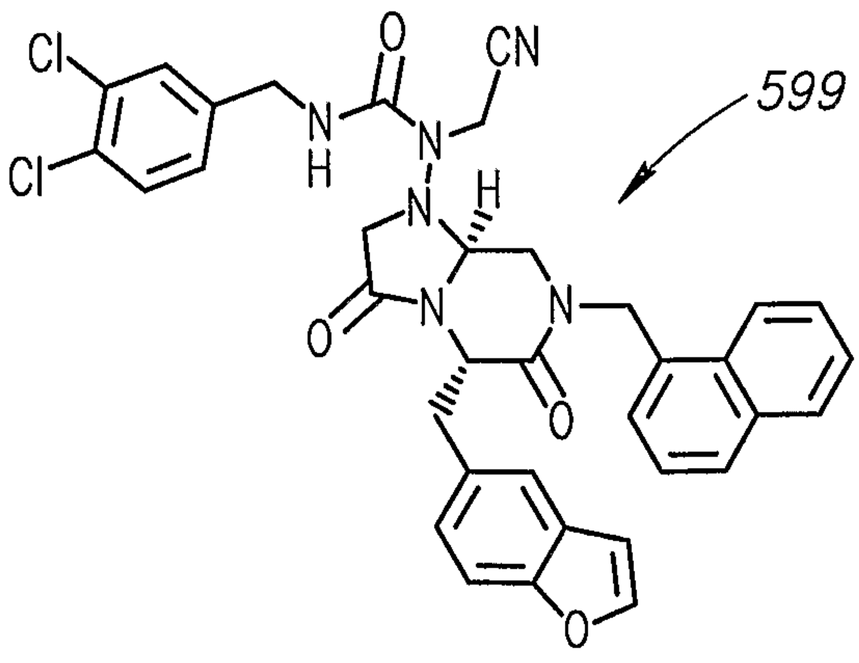
FIG.3AB











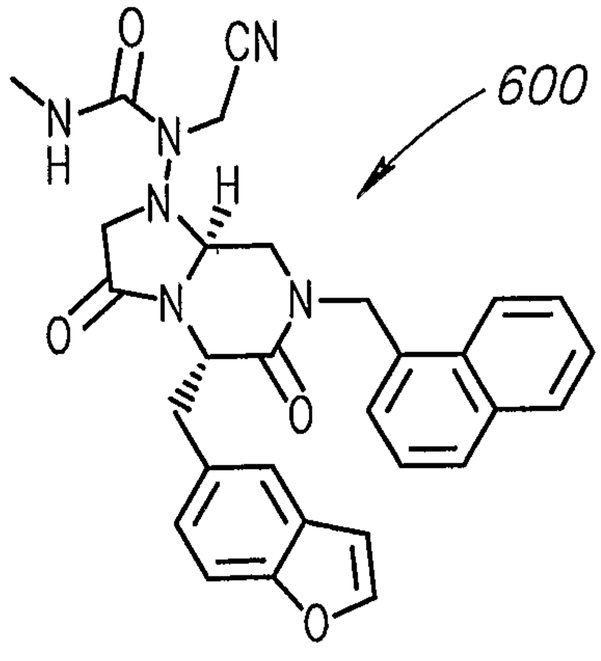
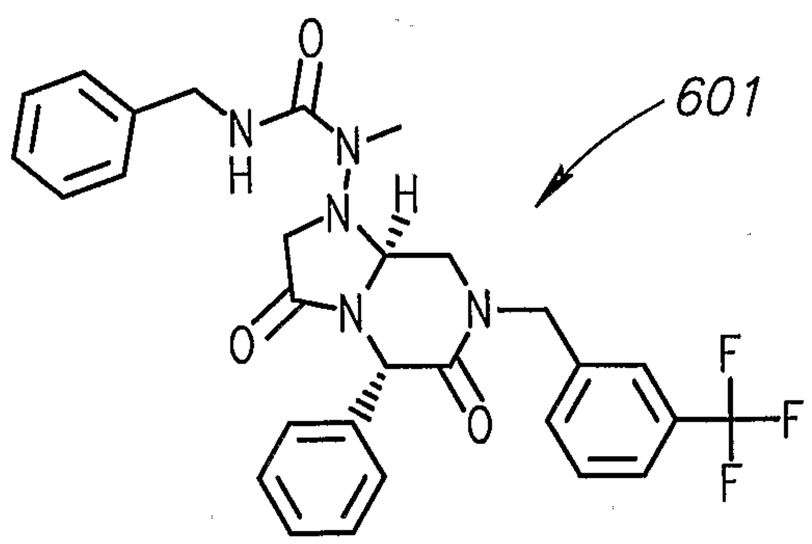
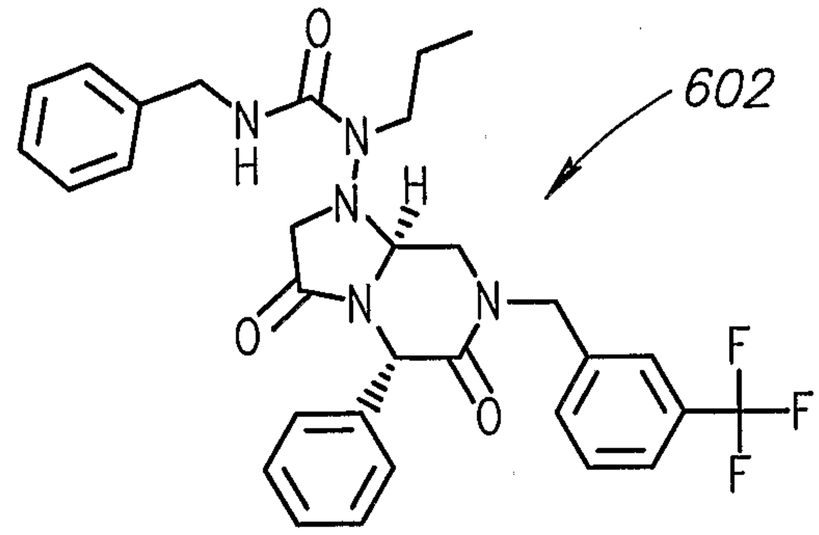
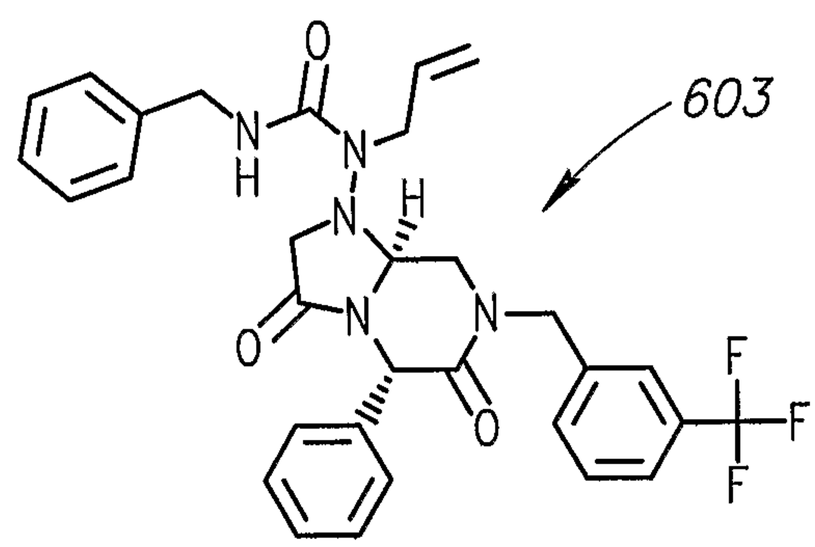
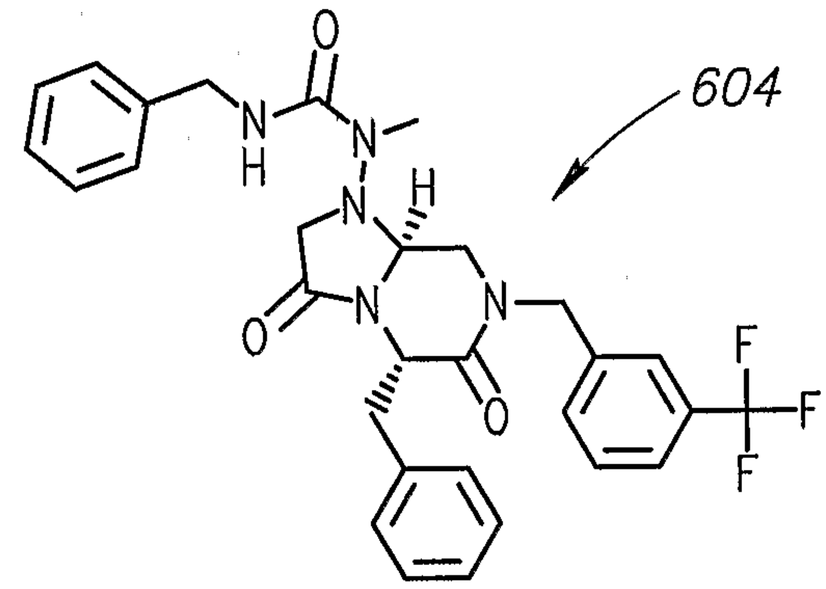


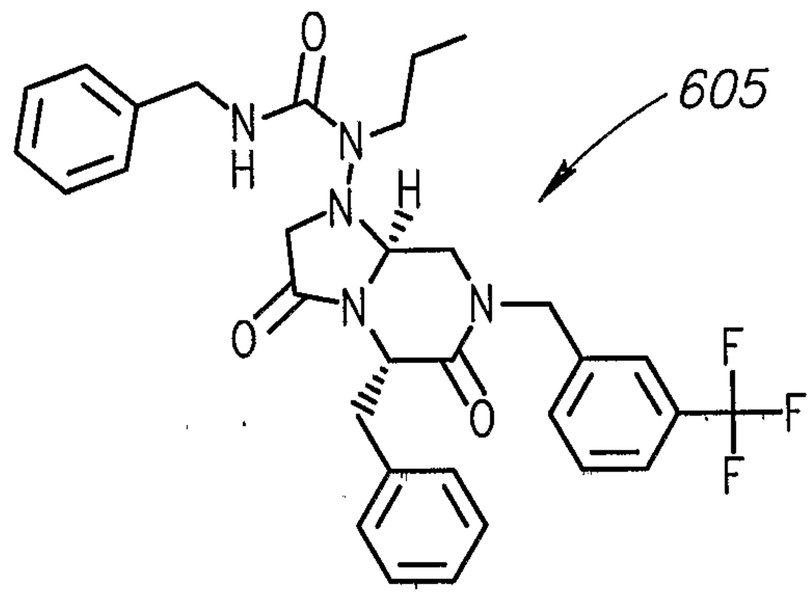
FIG.3AC

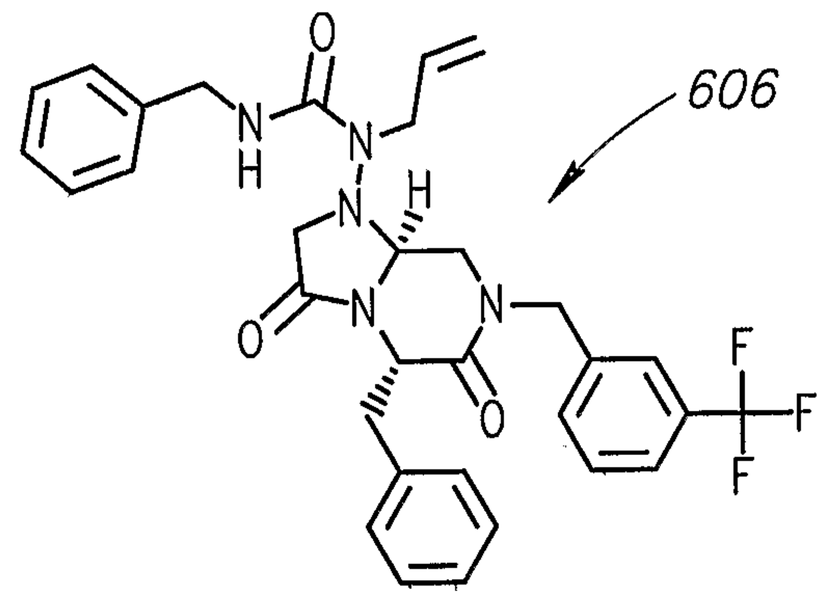


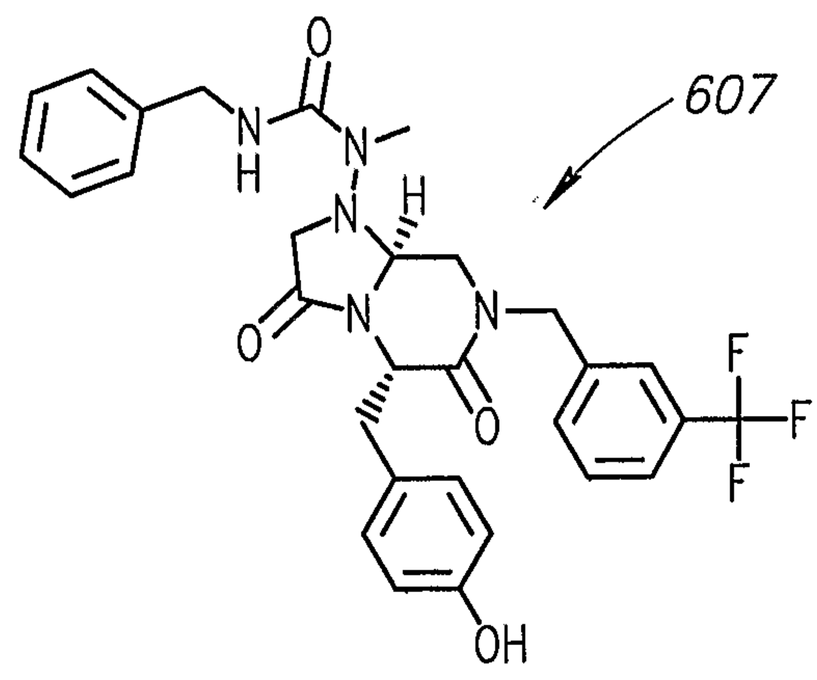












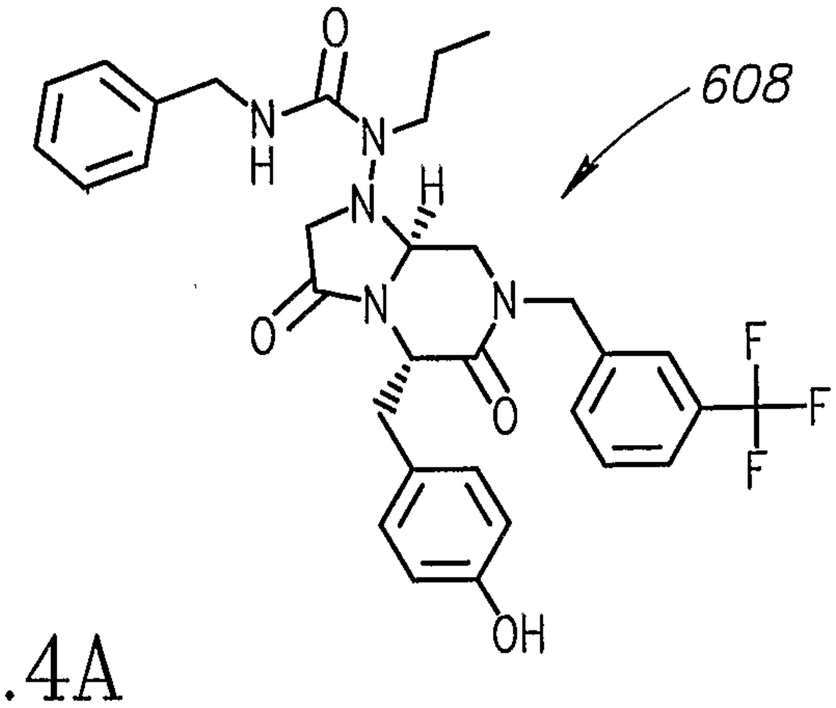
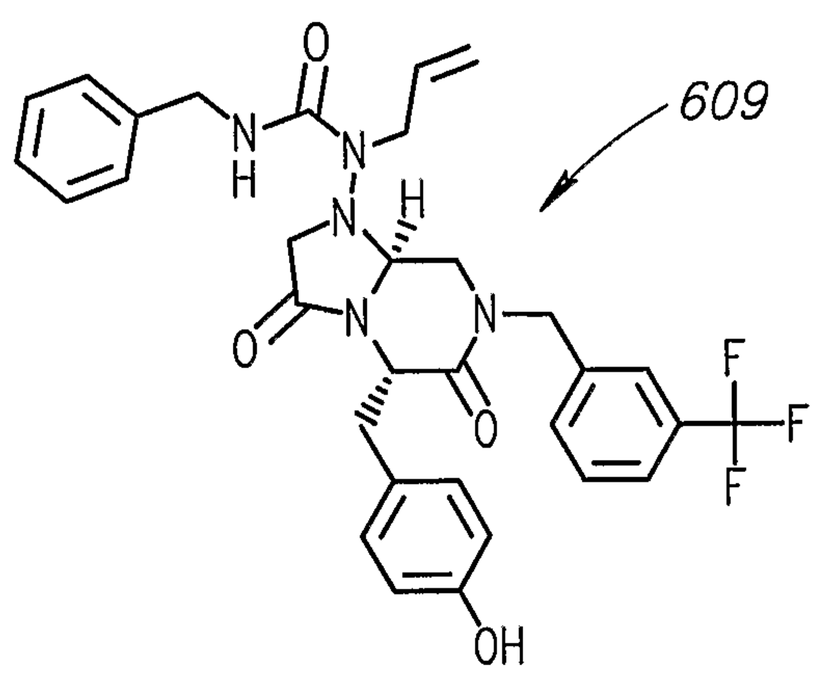
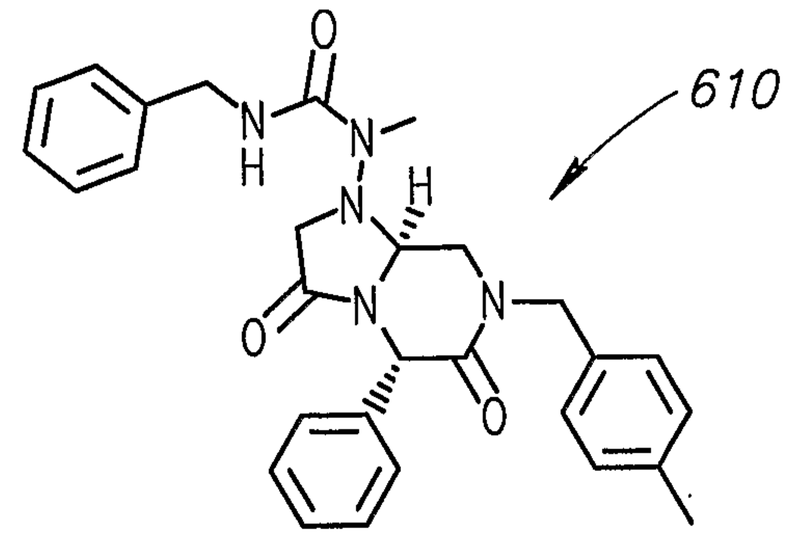
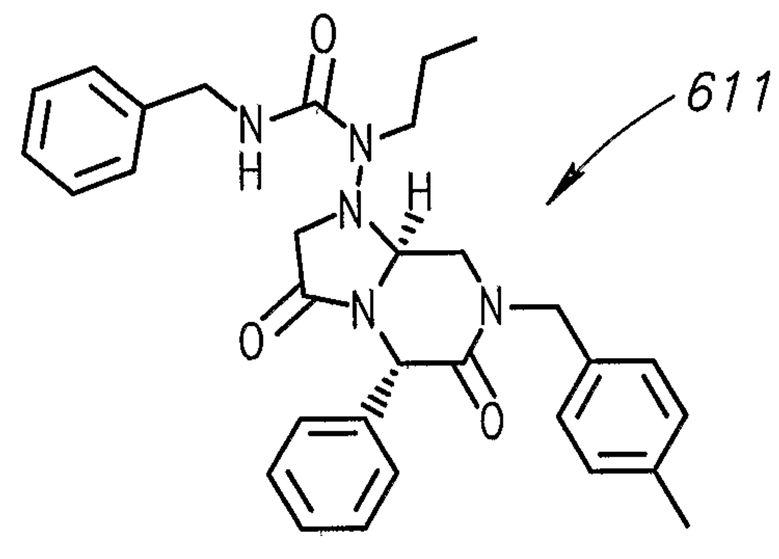
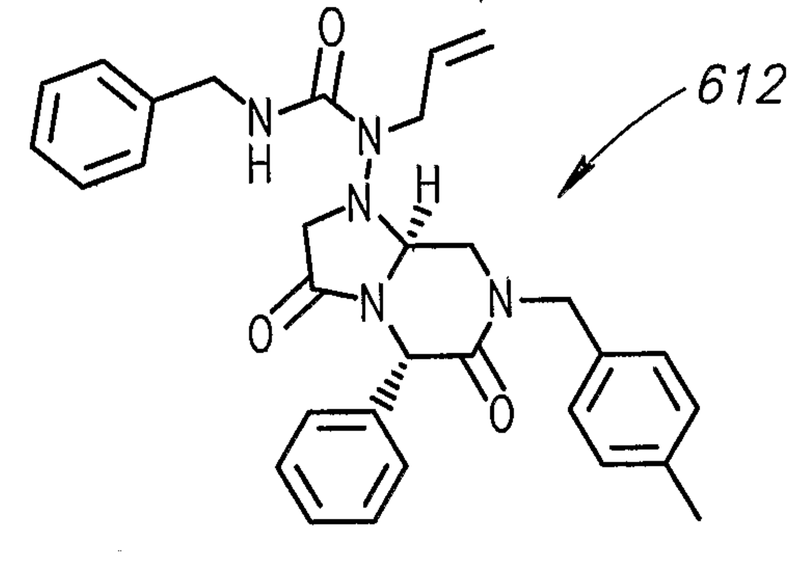


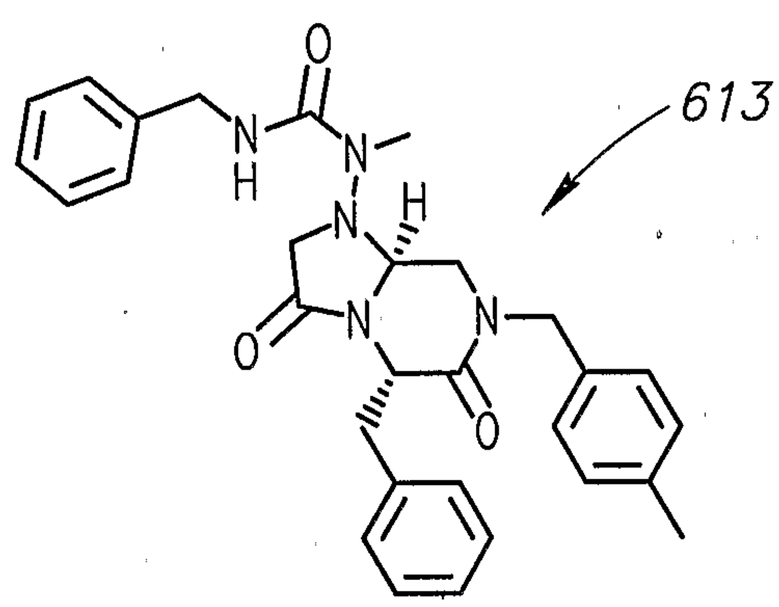
FIG.4A

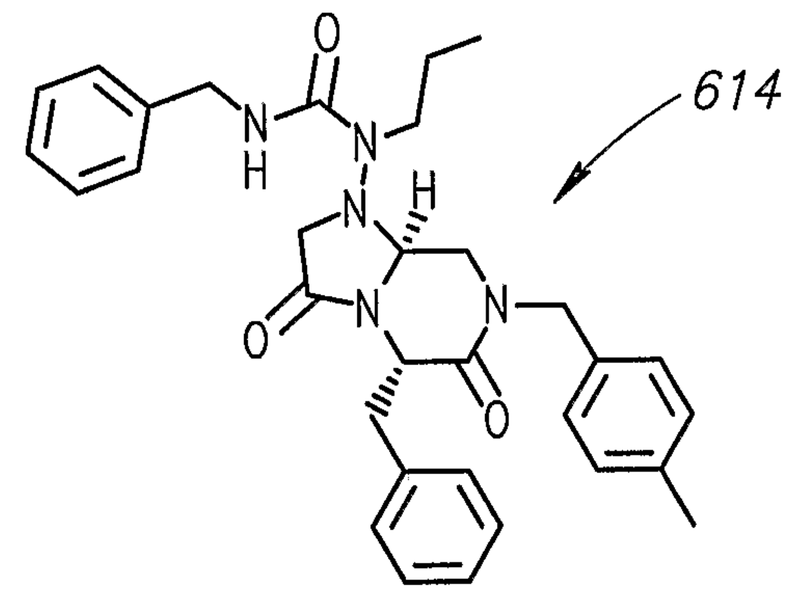


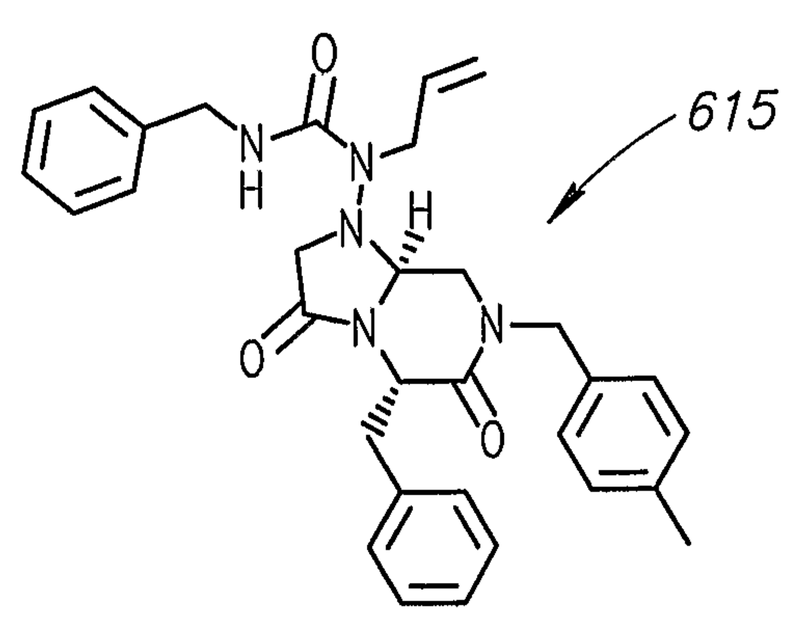












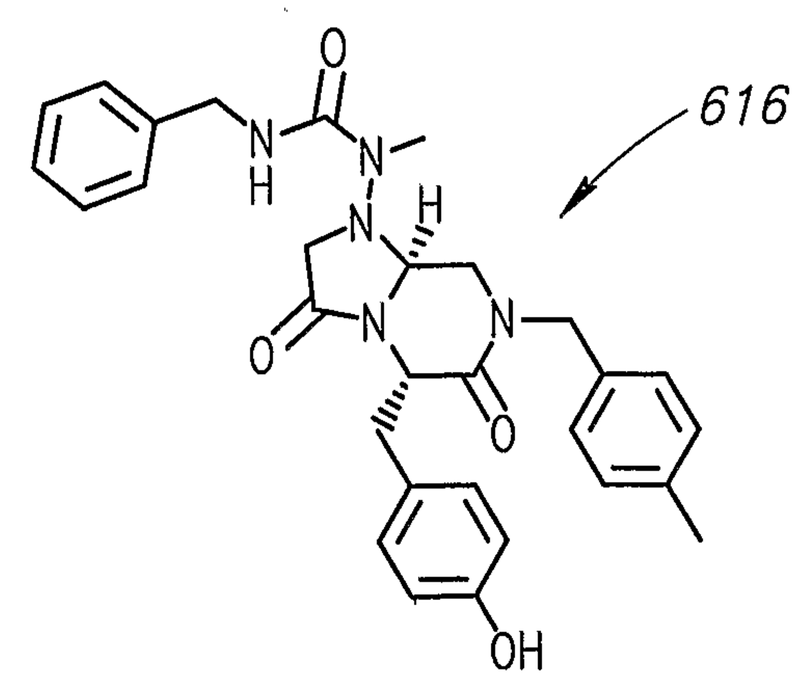
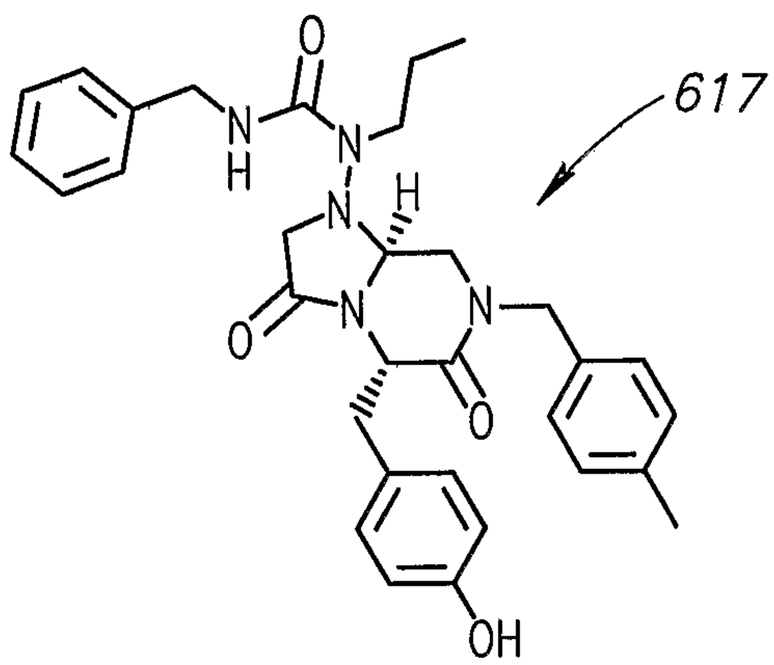
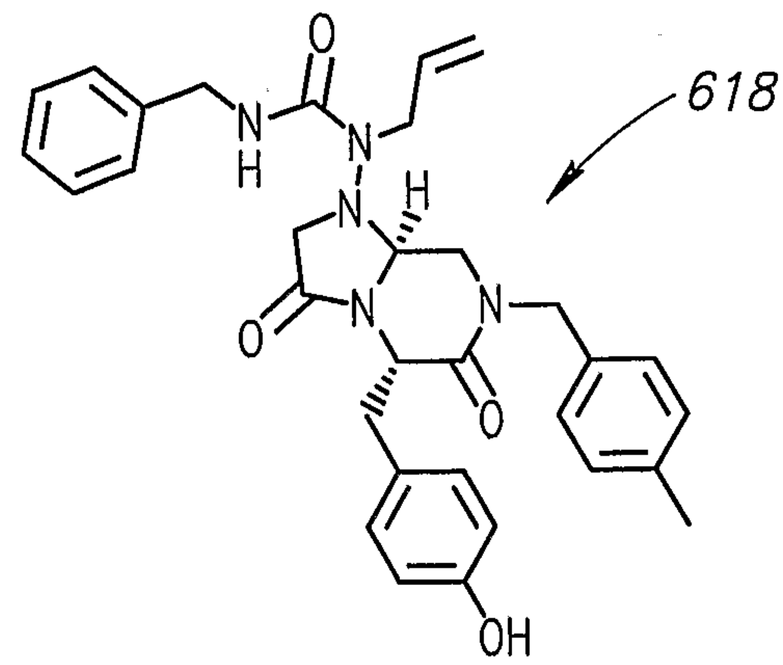
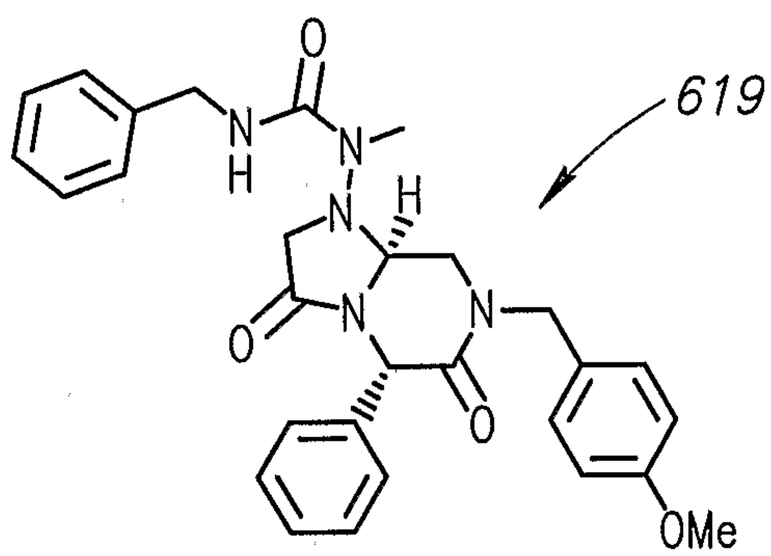
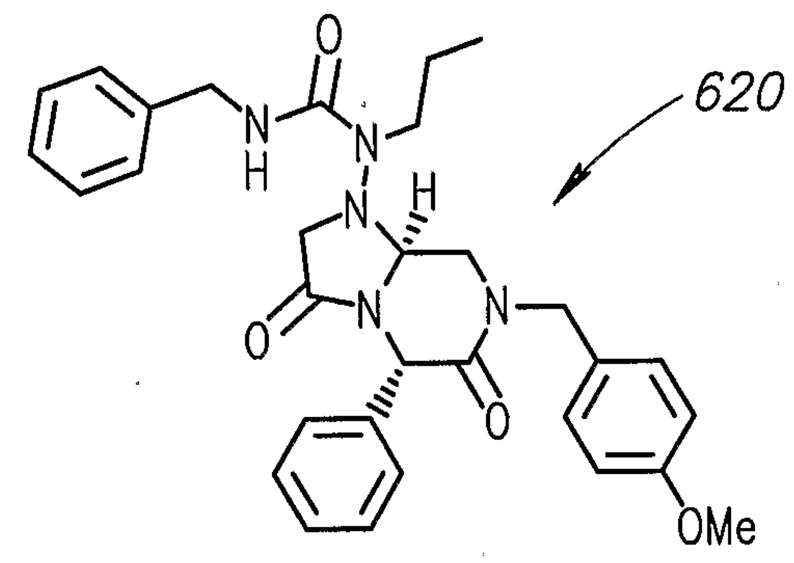


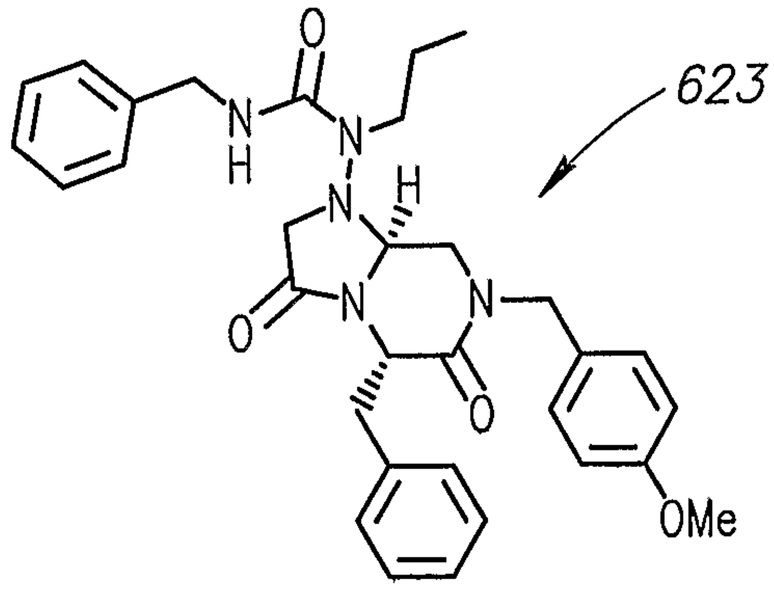
FIG.4B











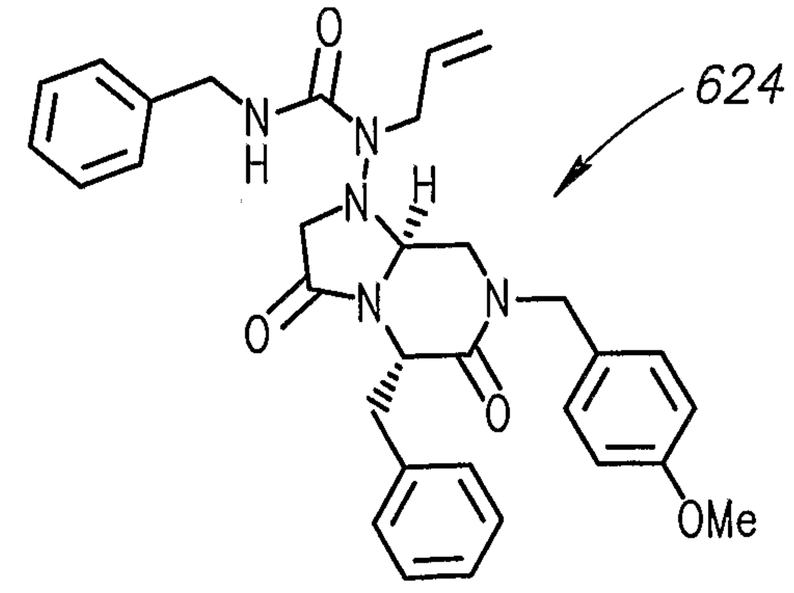


FIG.4C

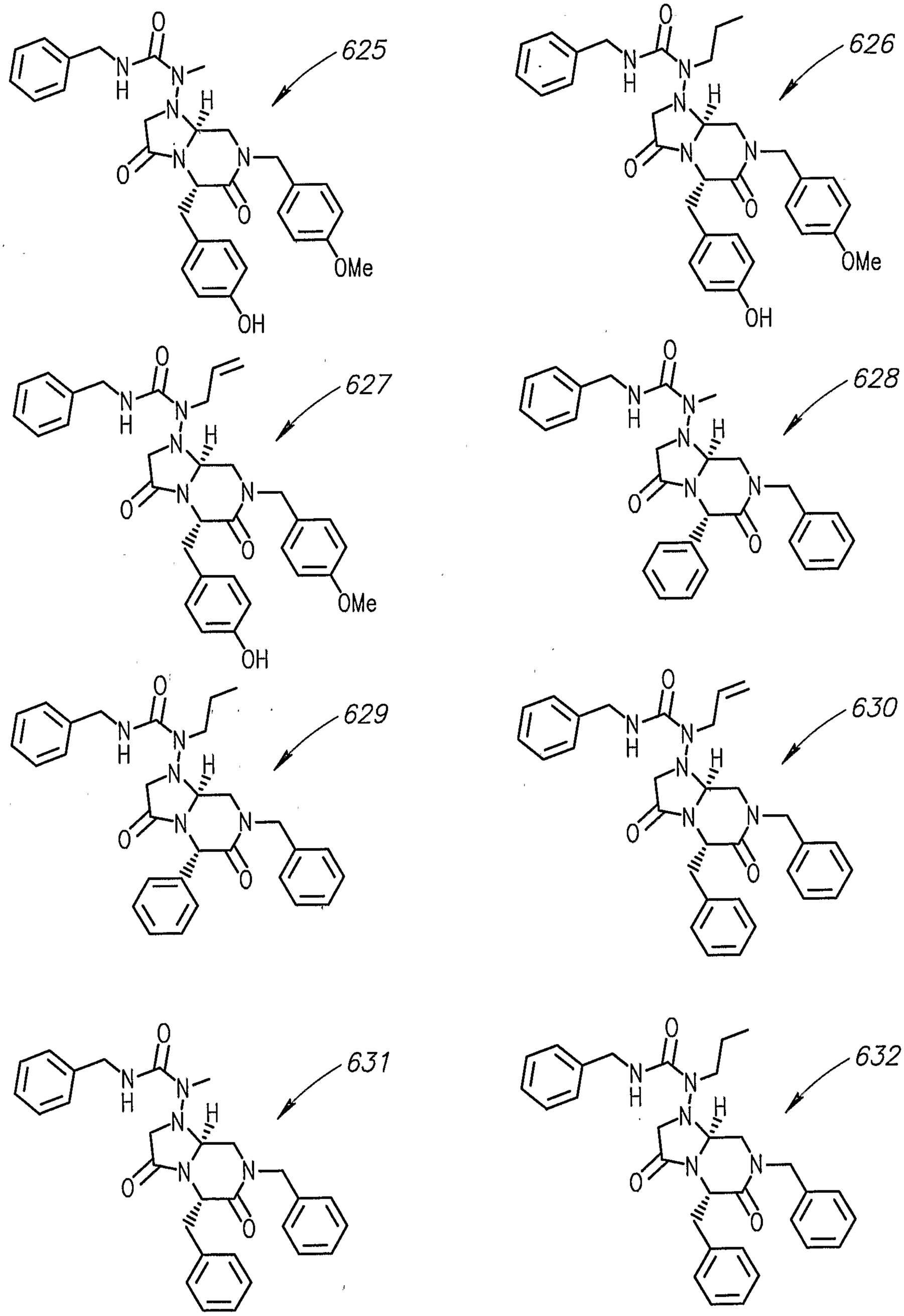
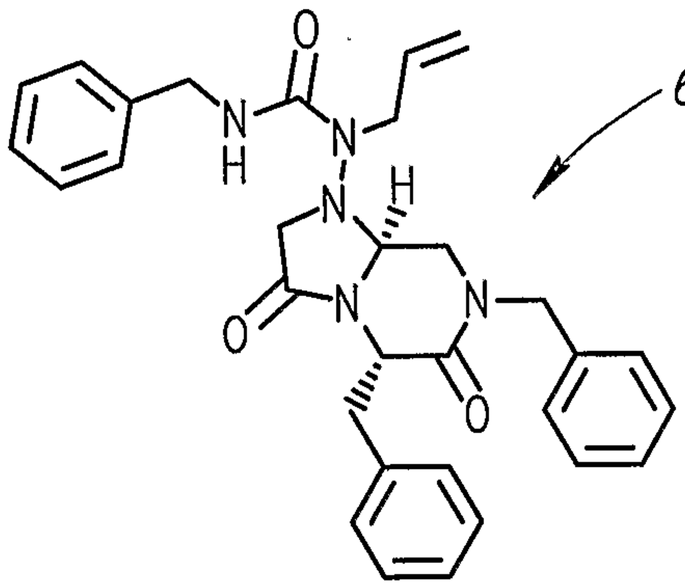
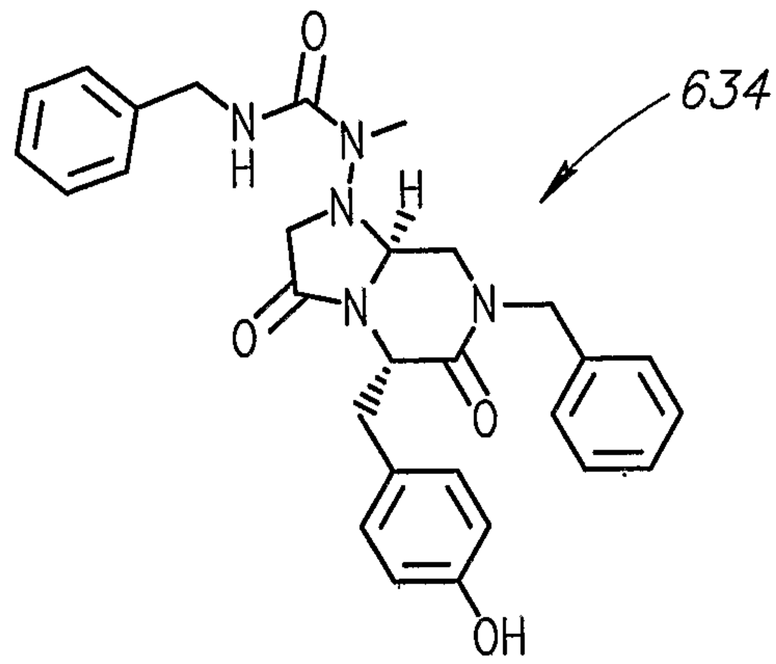
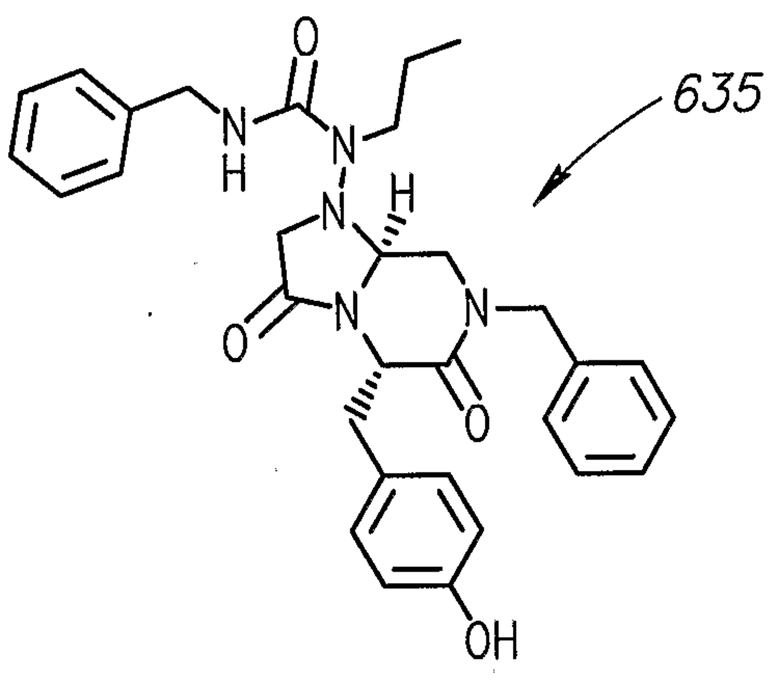
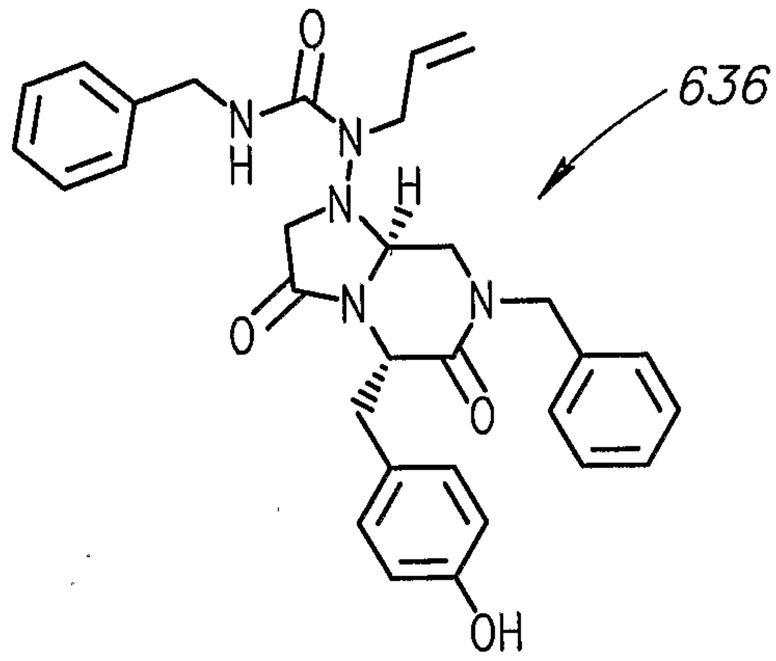


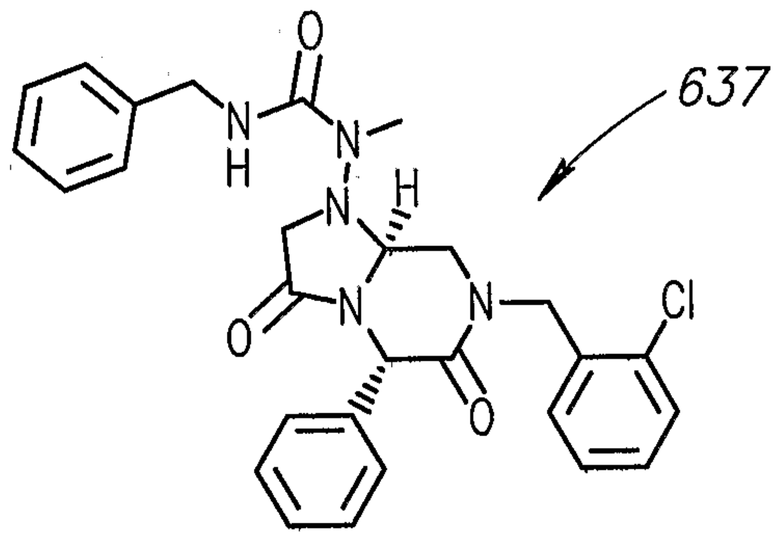
FIG.4D

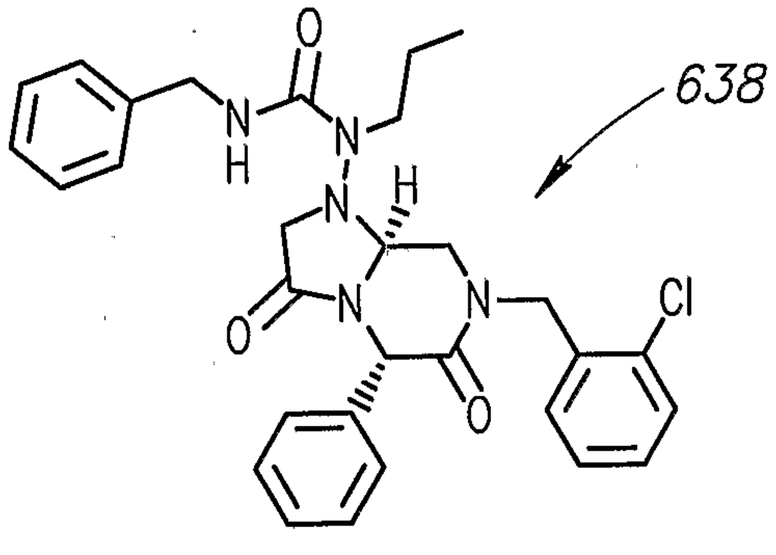


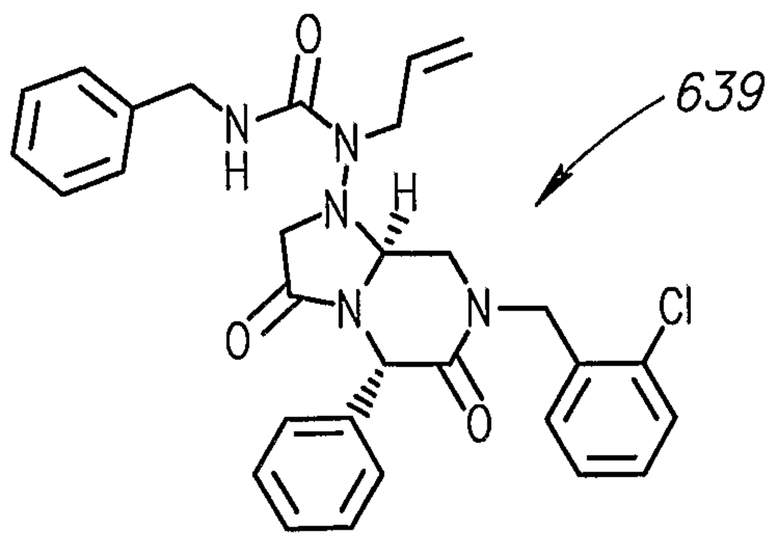












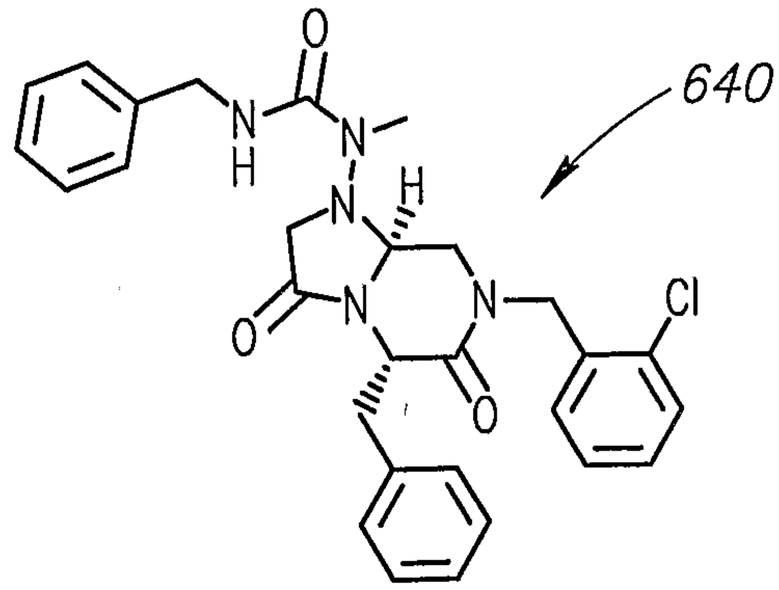
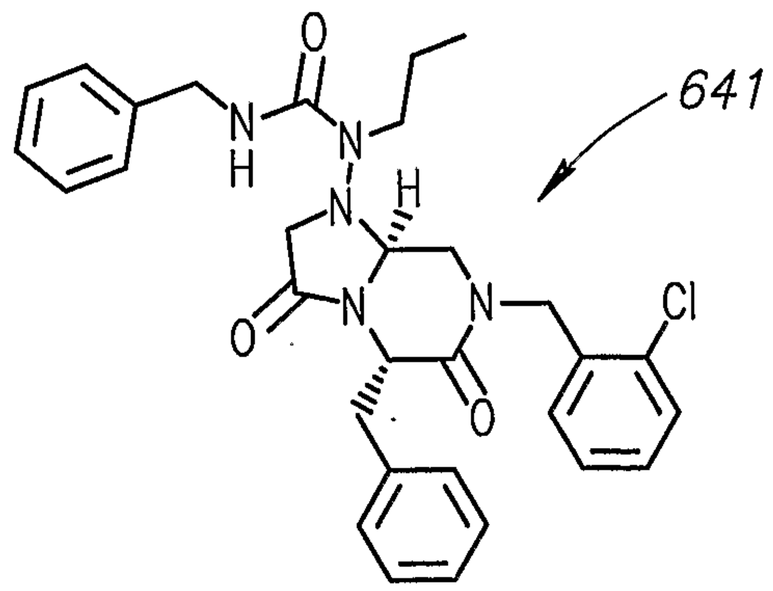
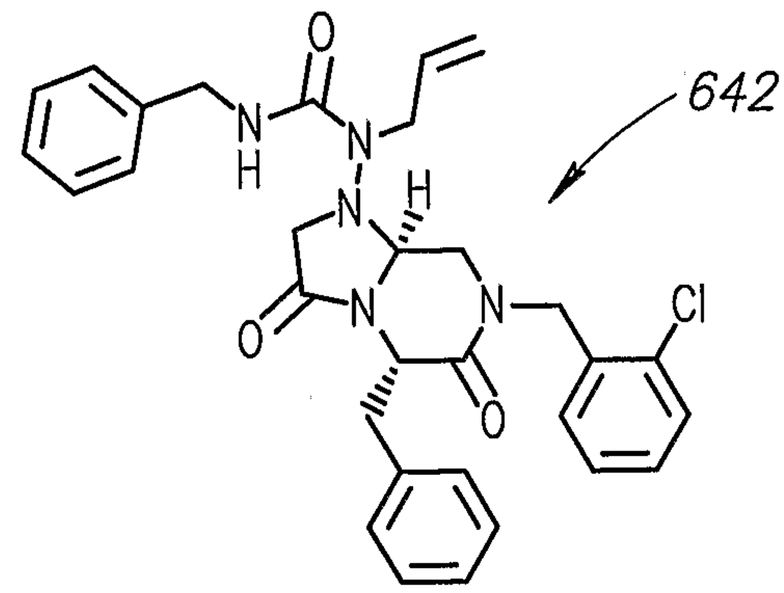
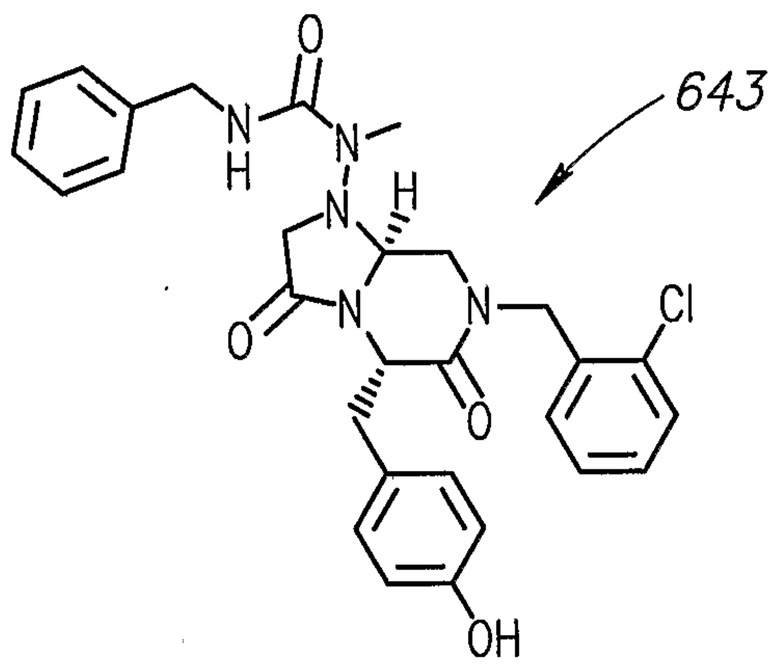
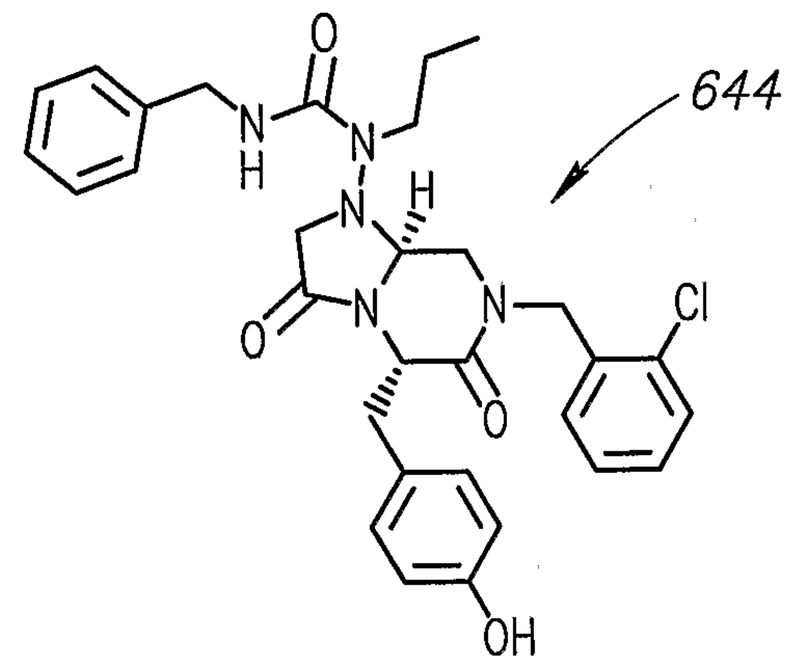


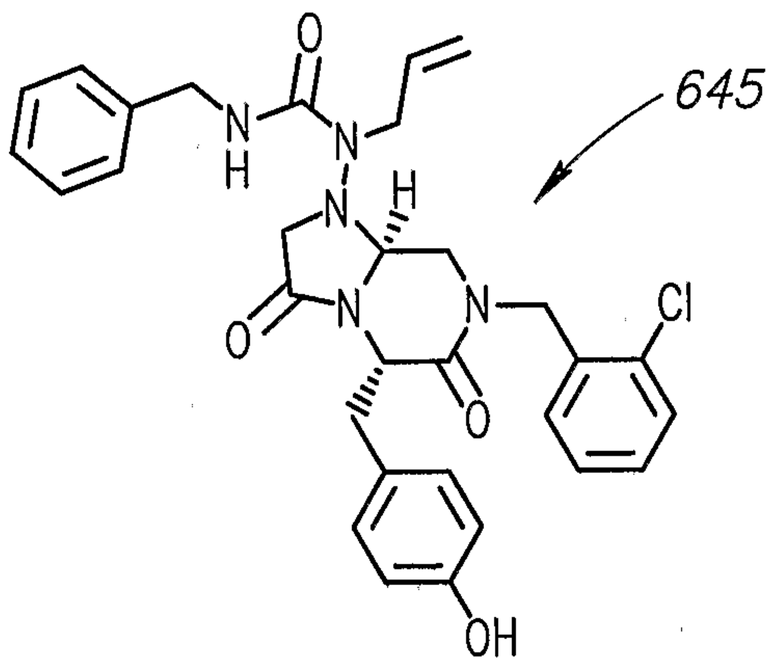
FIG.4E

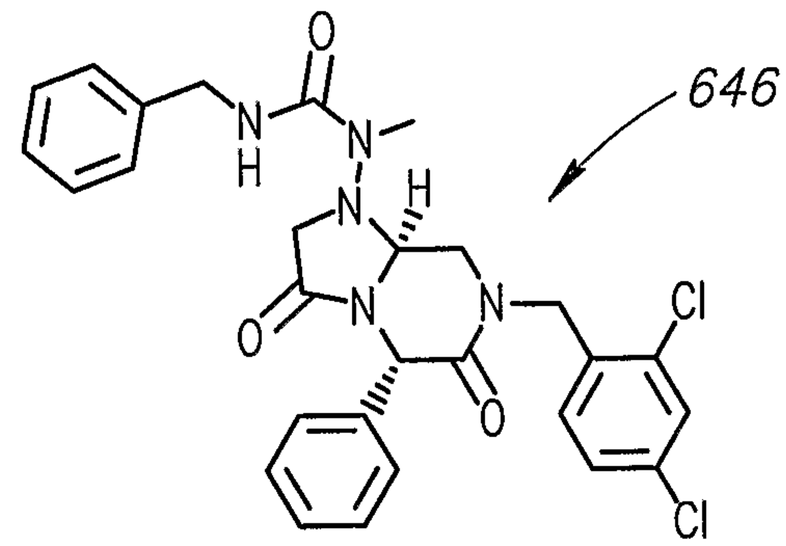


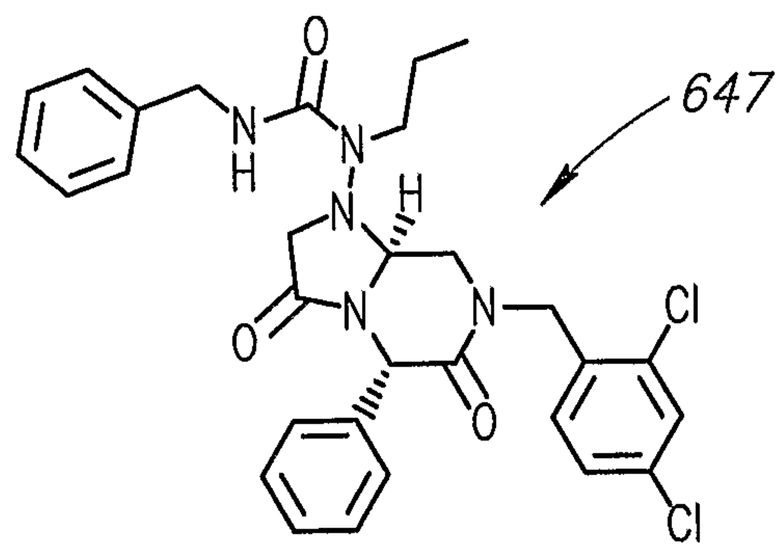












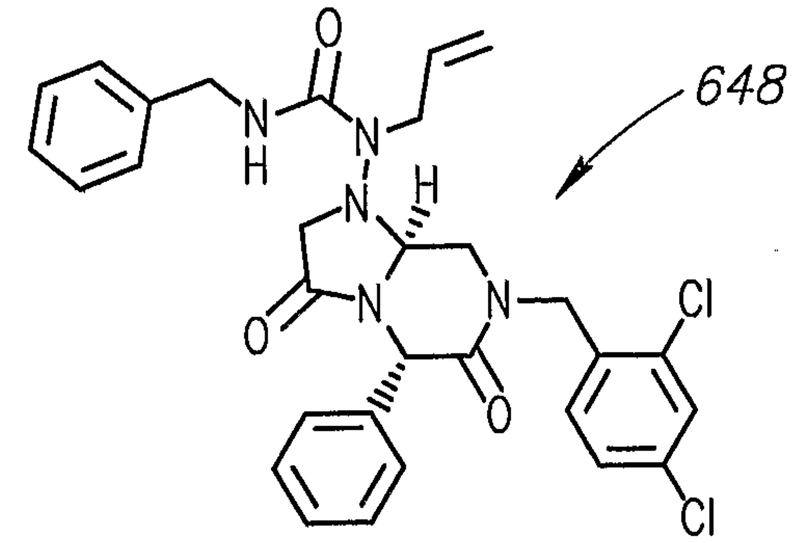
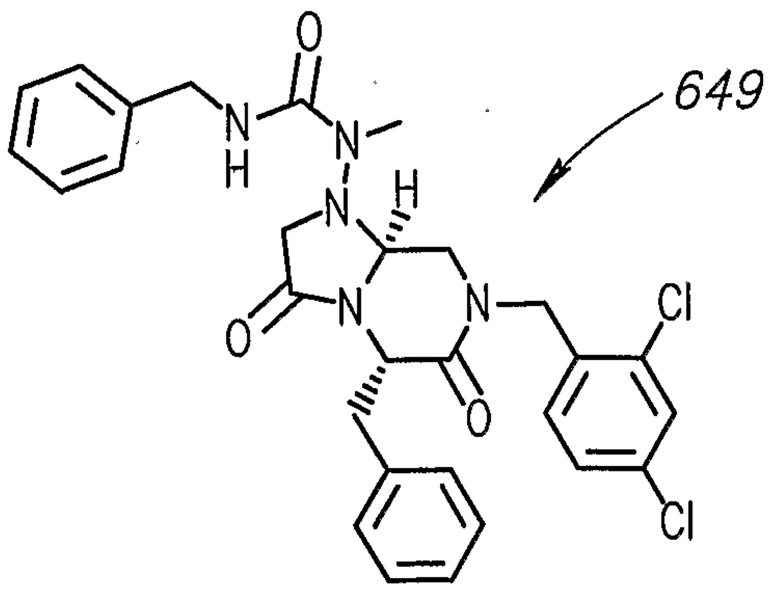


FIG.4F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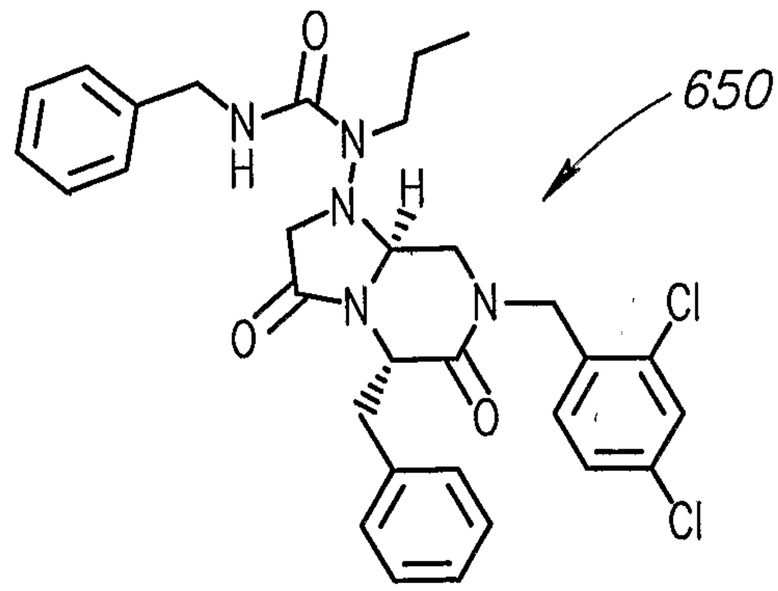
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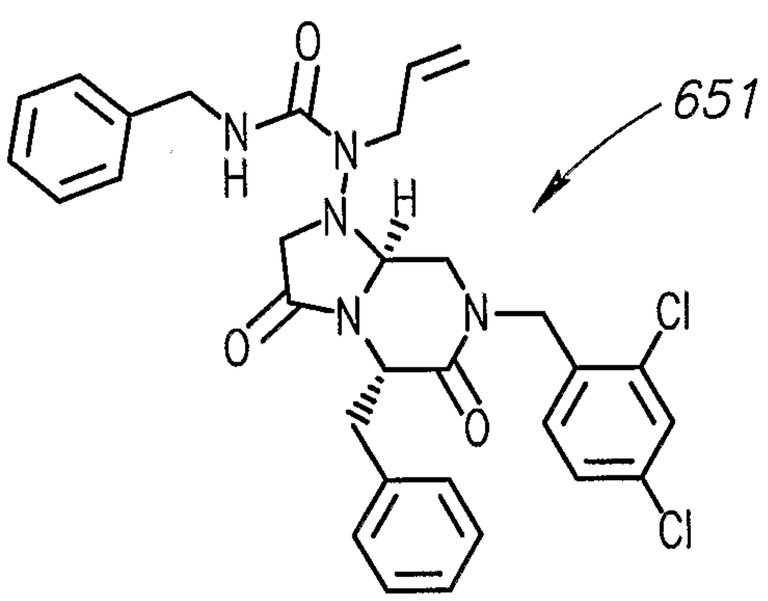
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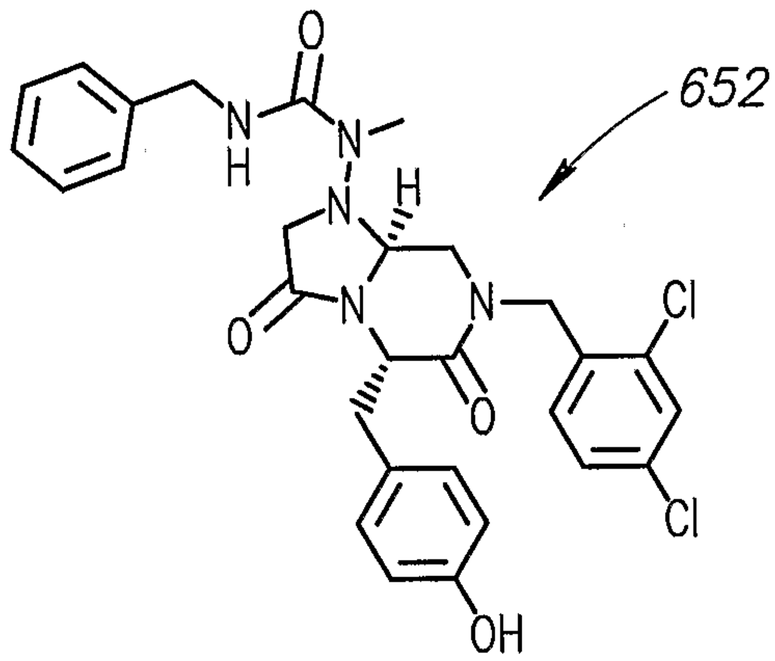
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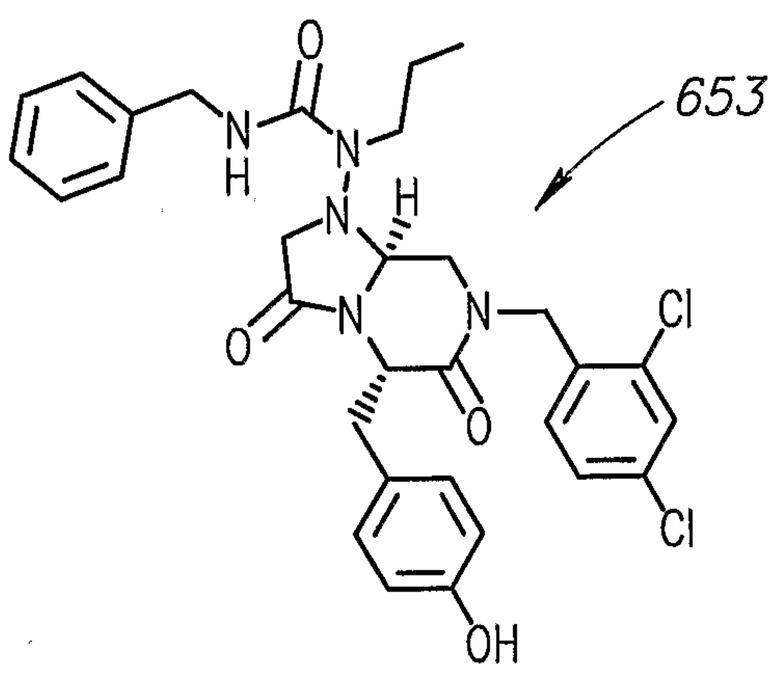
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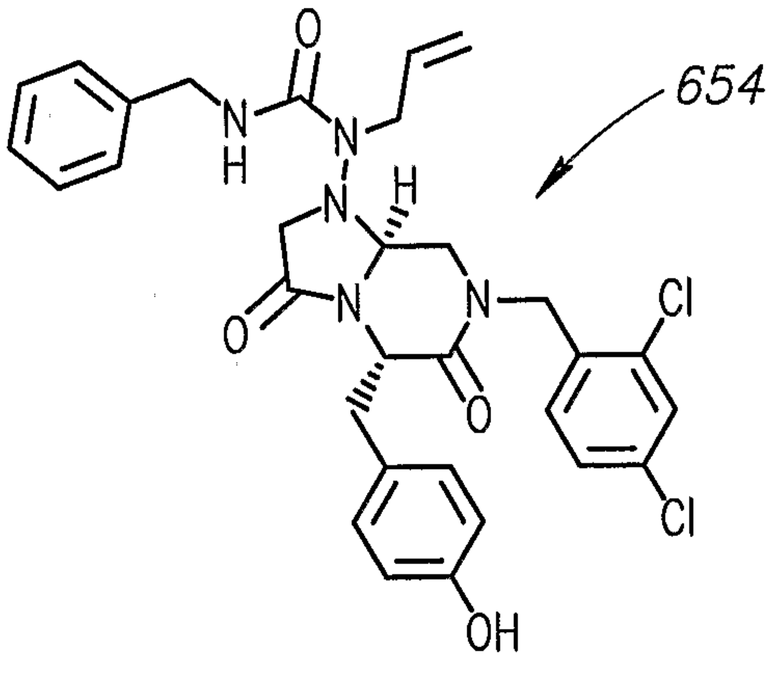
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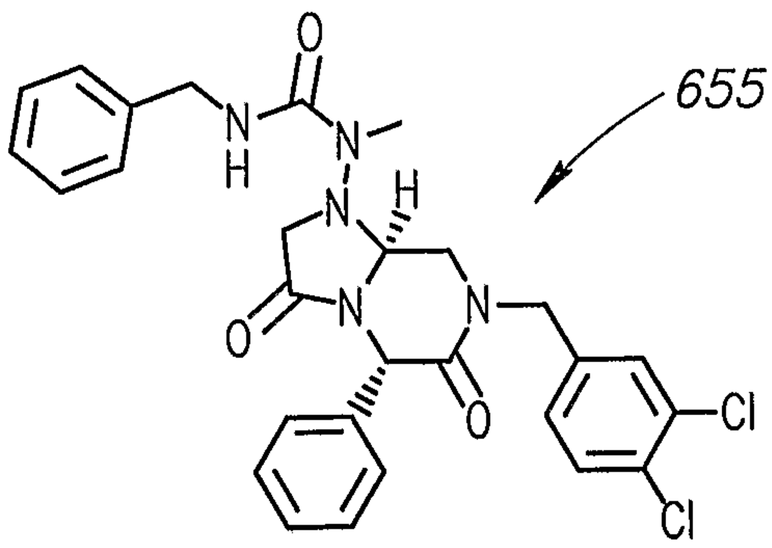
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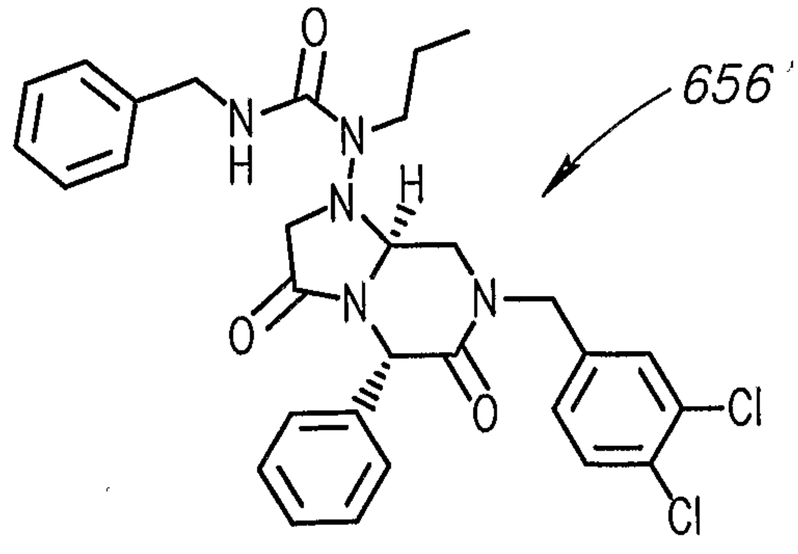
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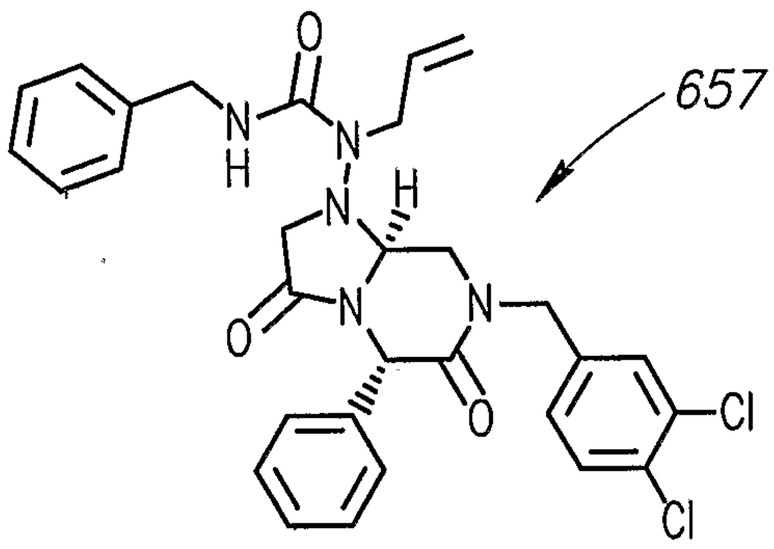
FIG.4G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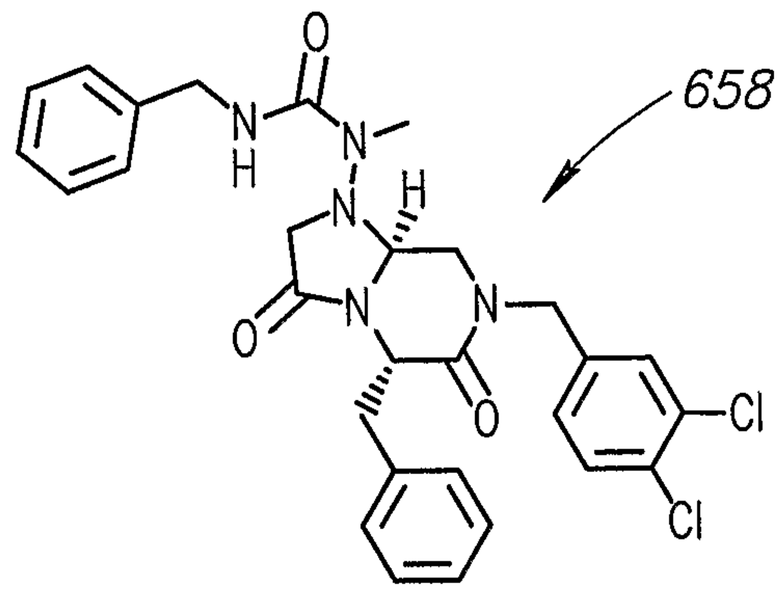
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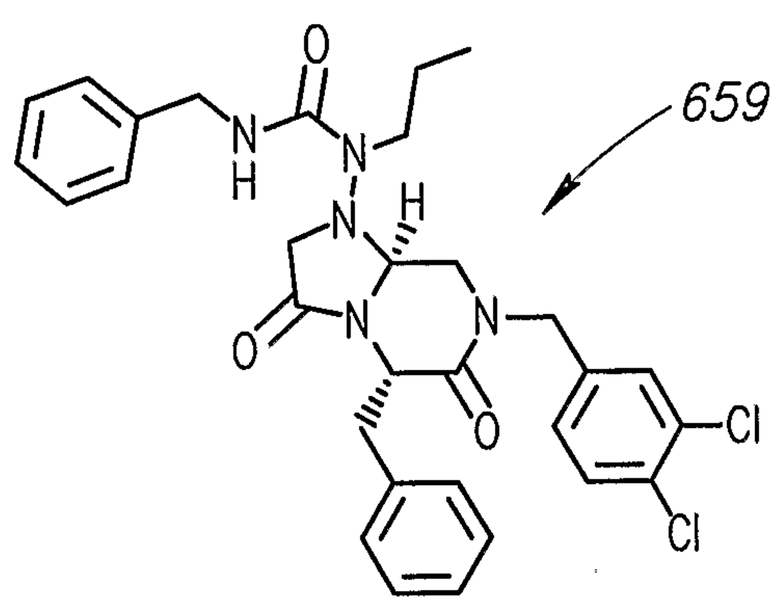
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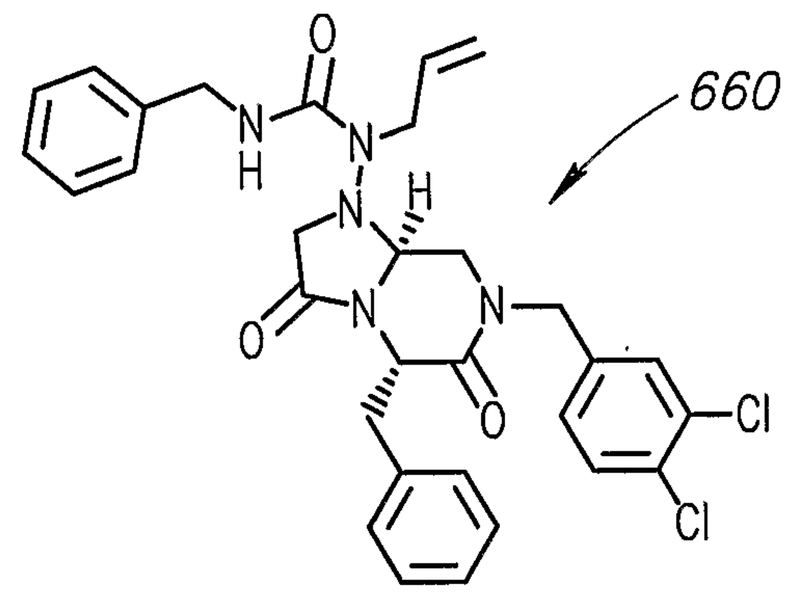
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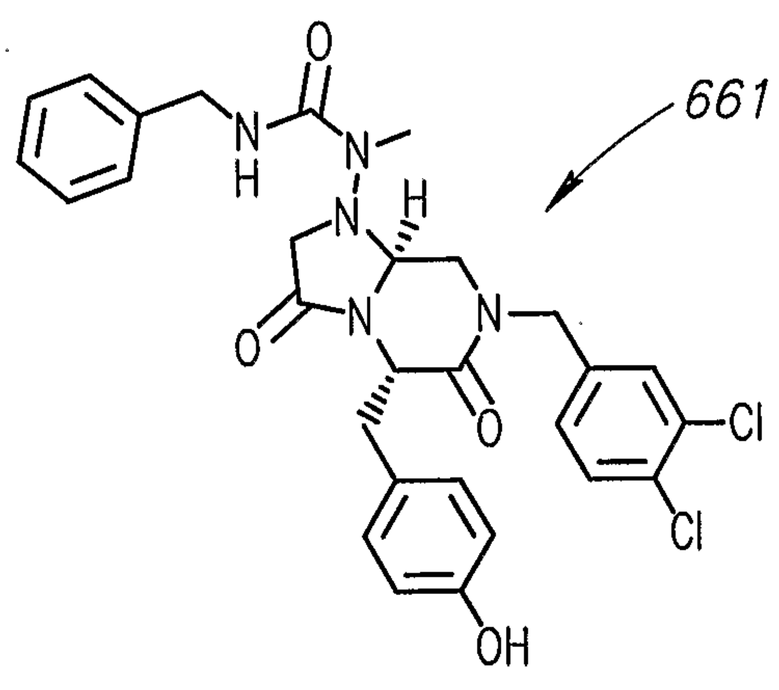
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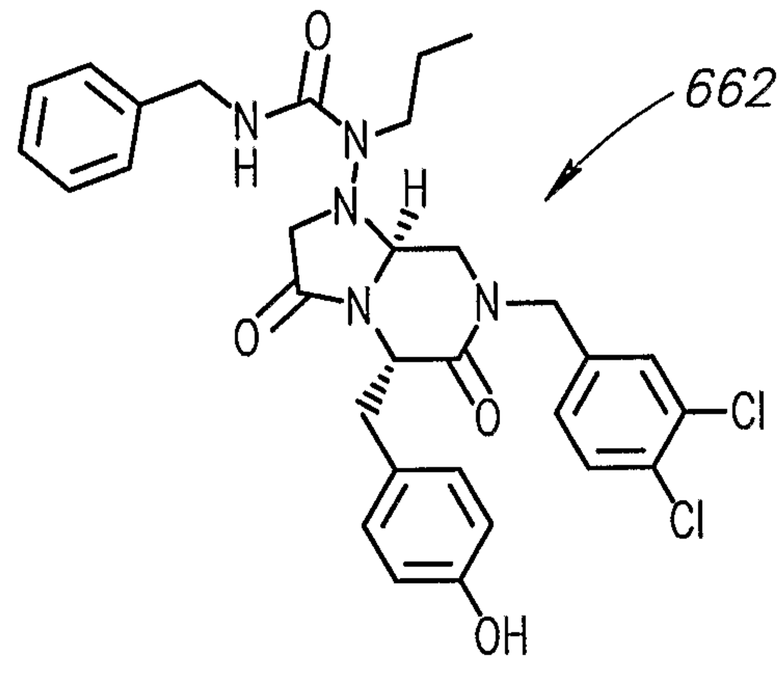
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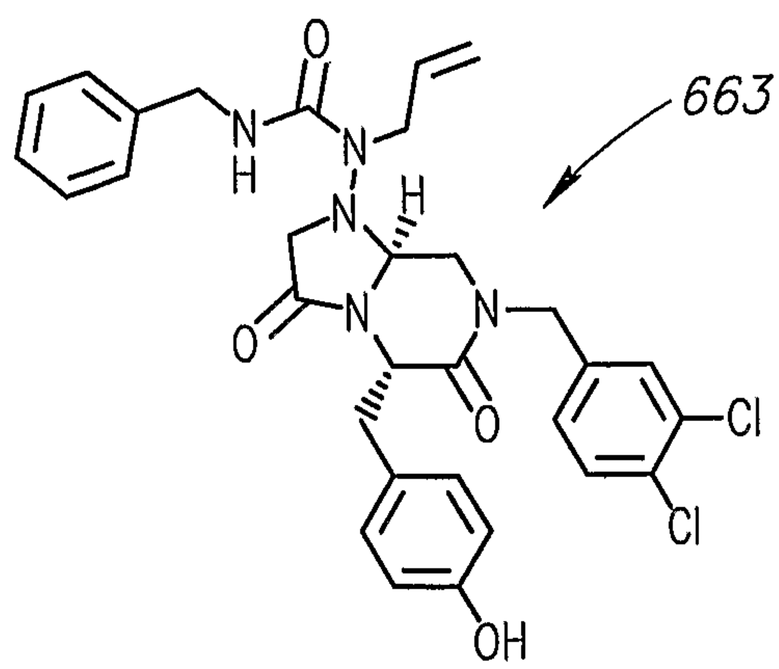
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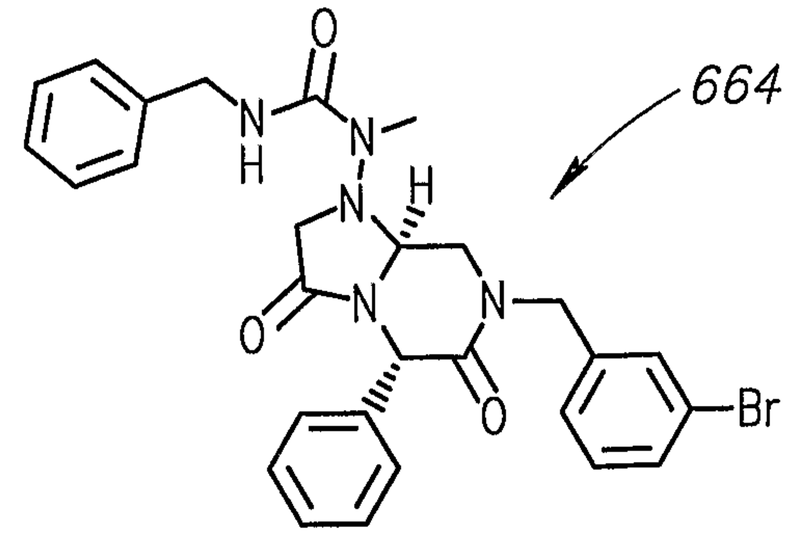
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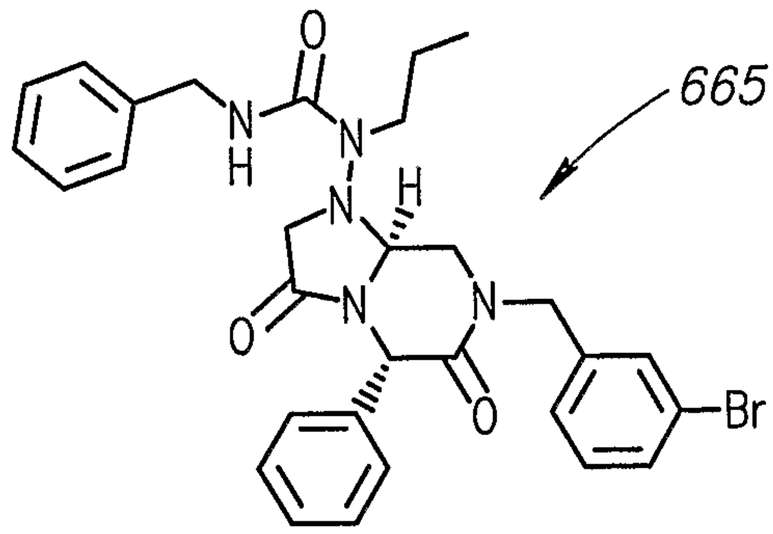
FIG.4H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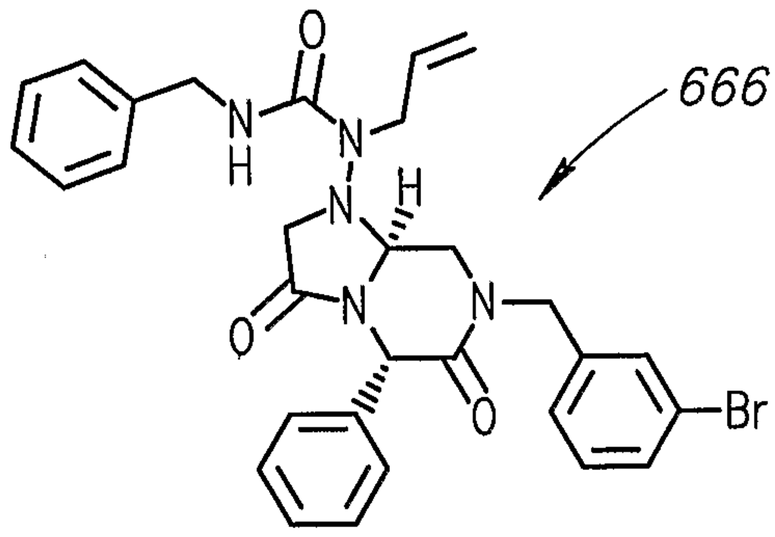
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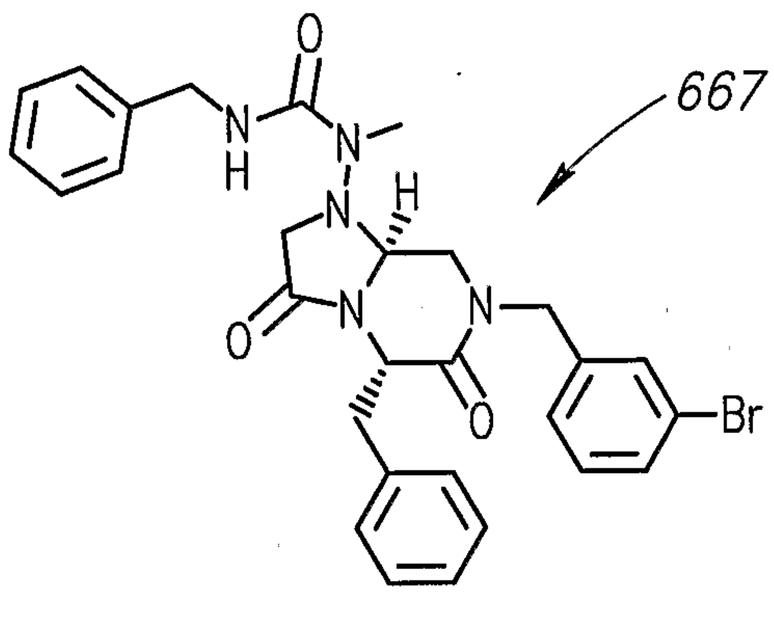
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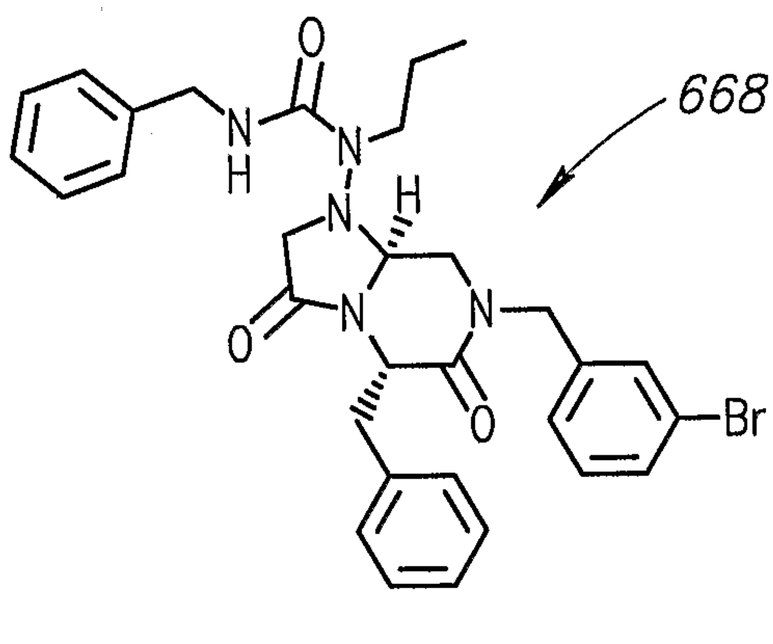
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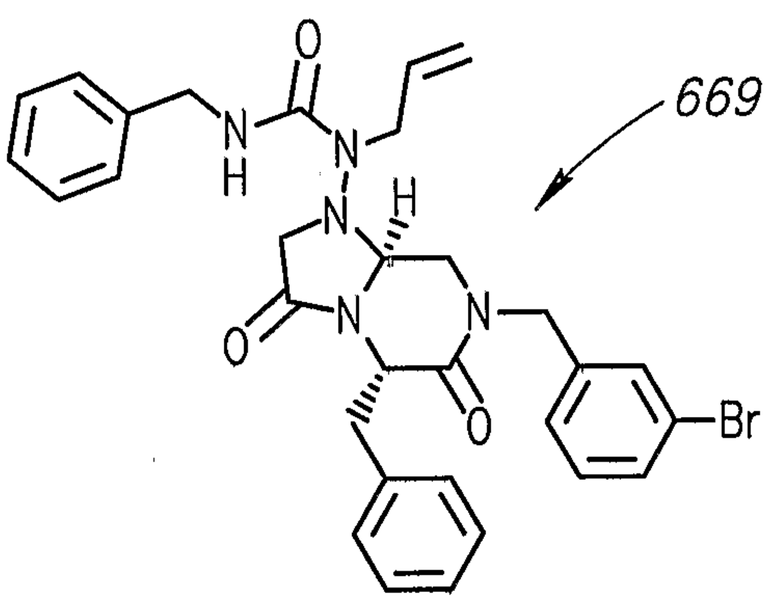
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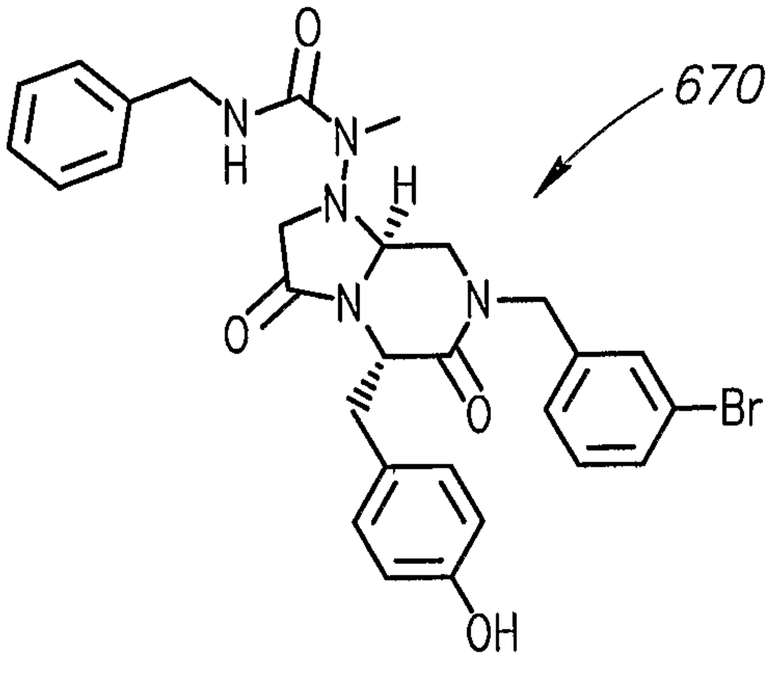
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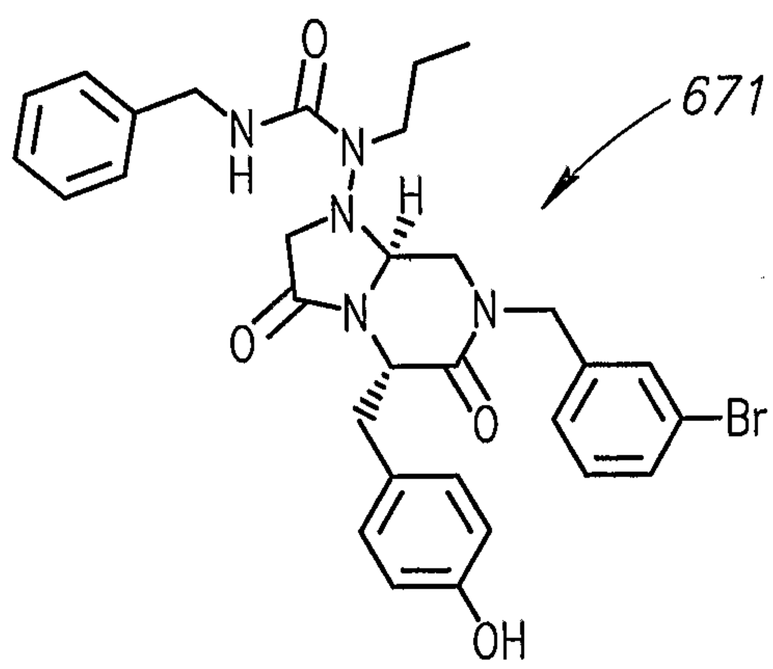
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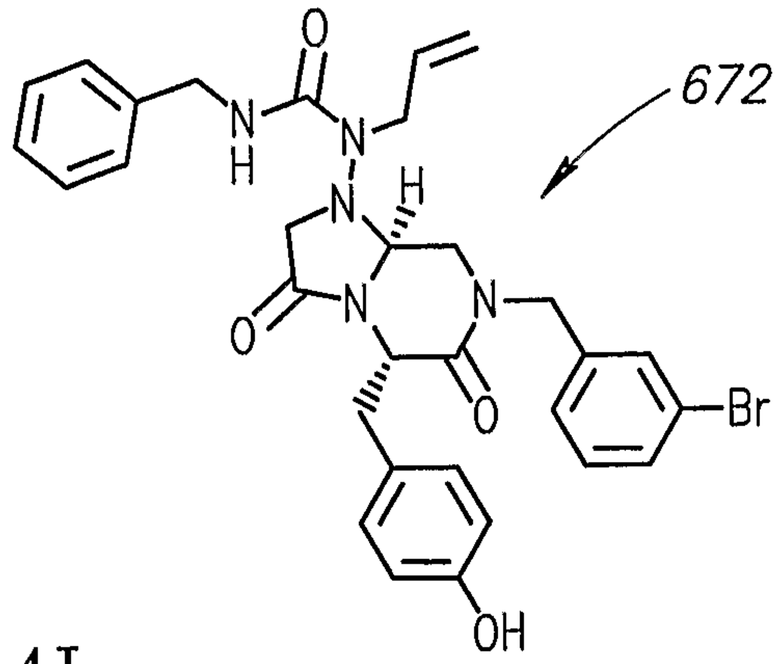
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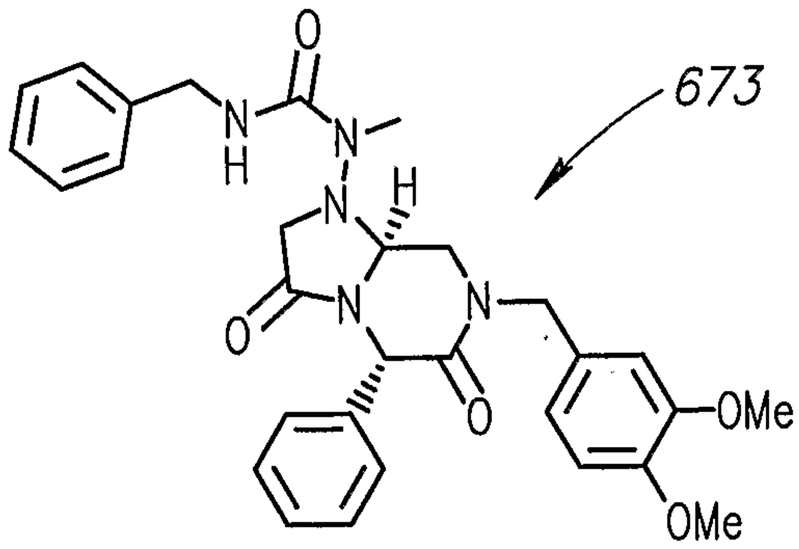
FIG.4I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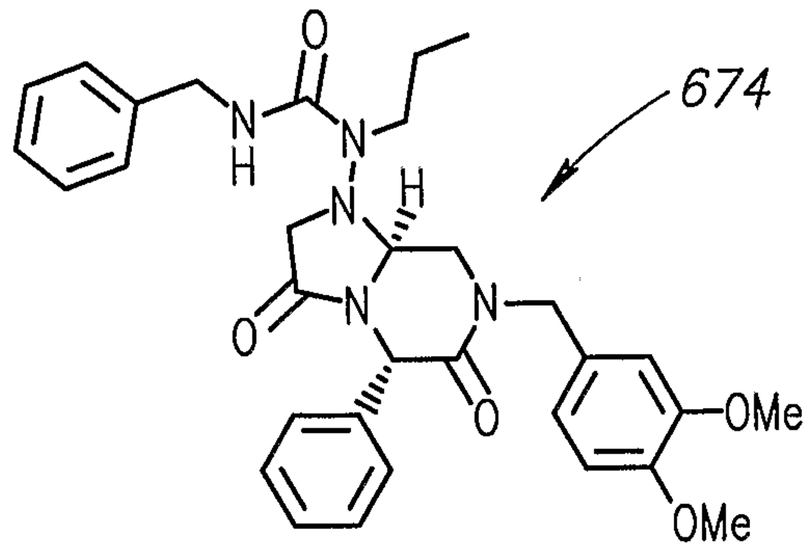
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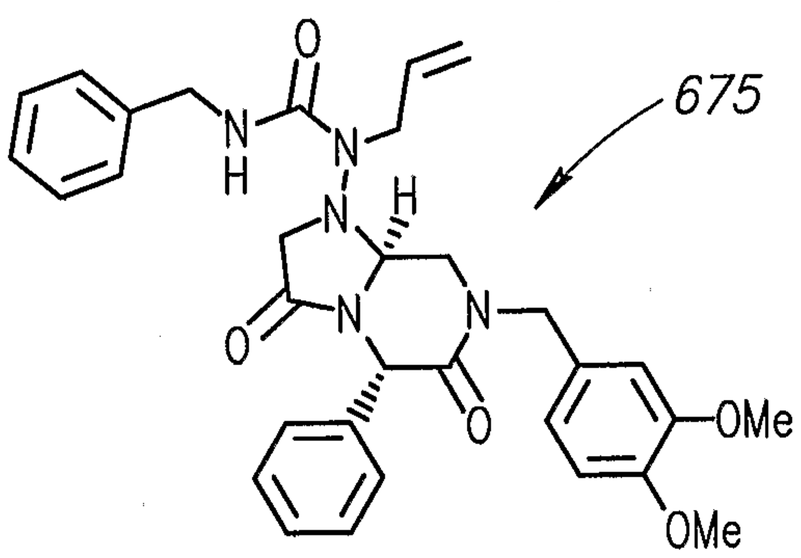
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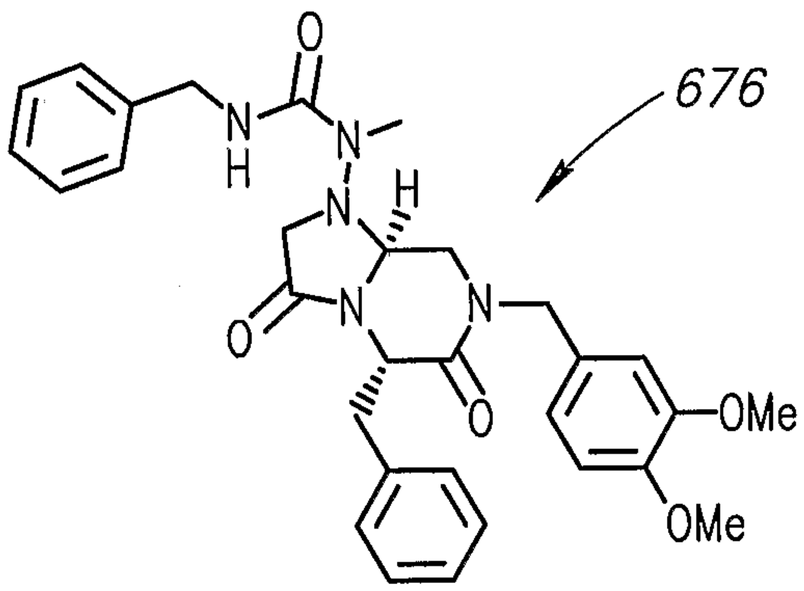
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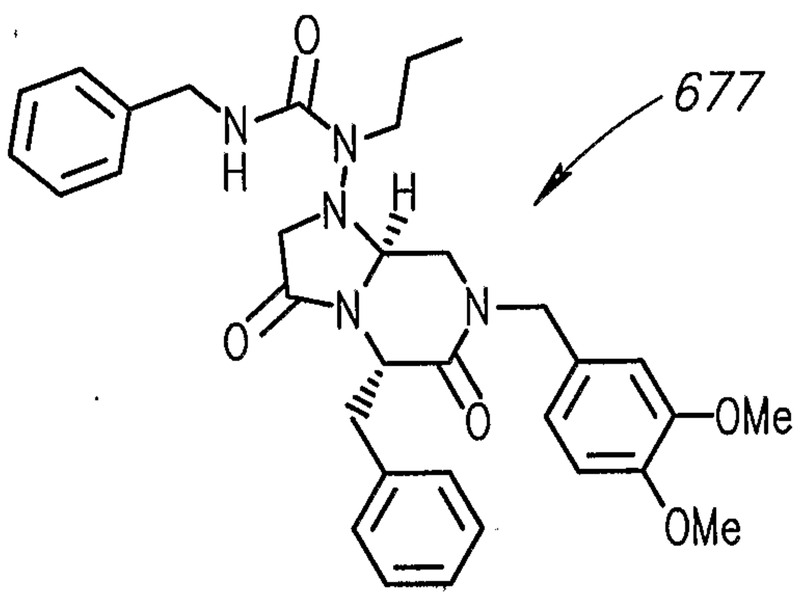
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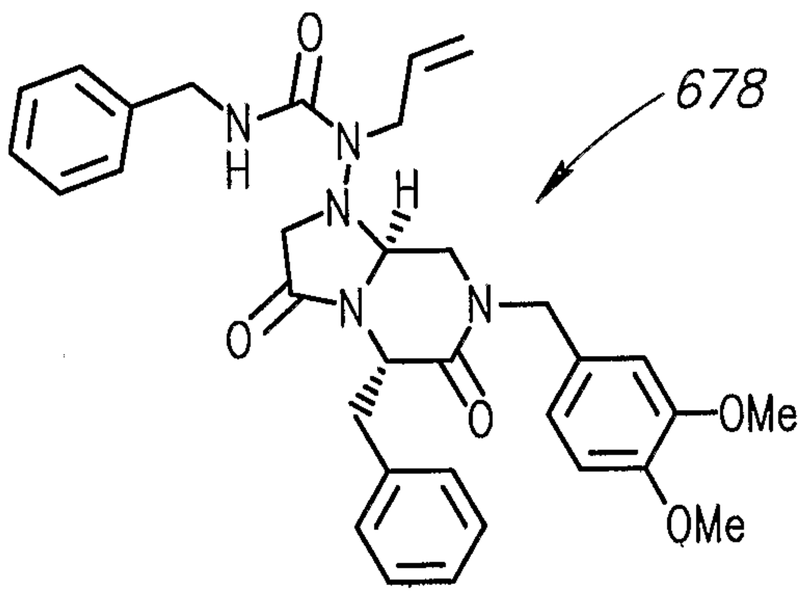
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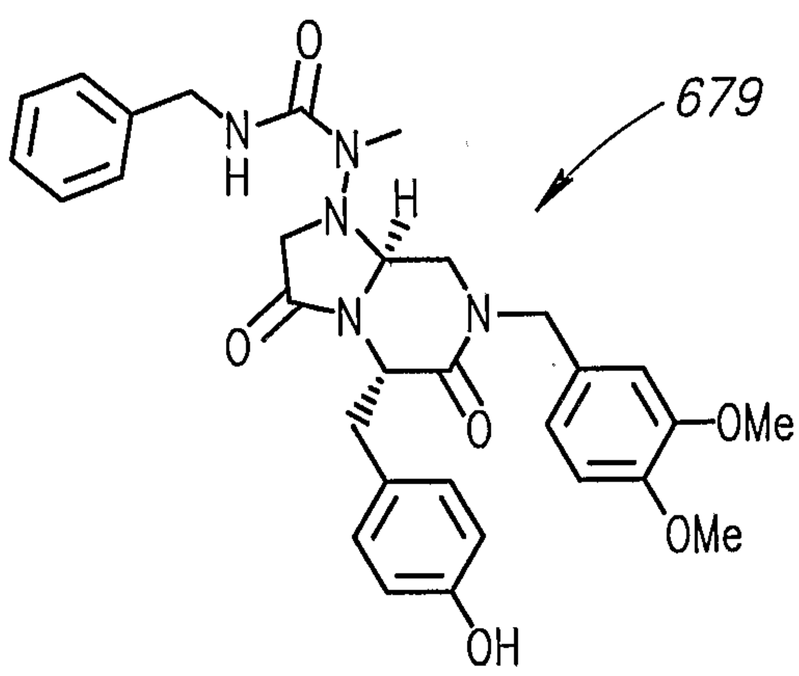
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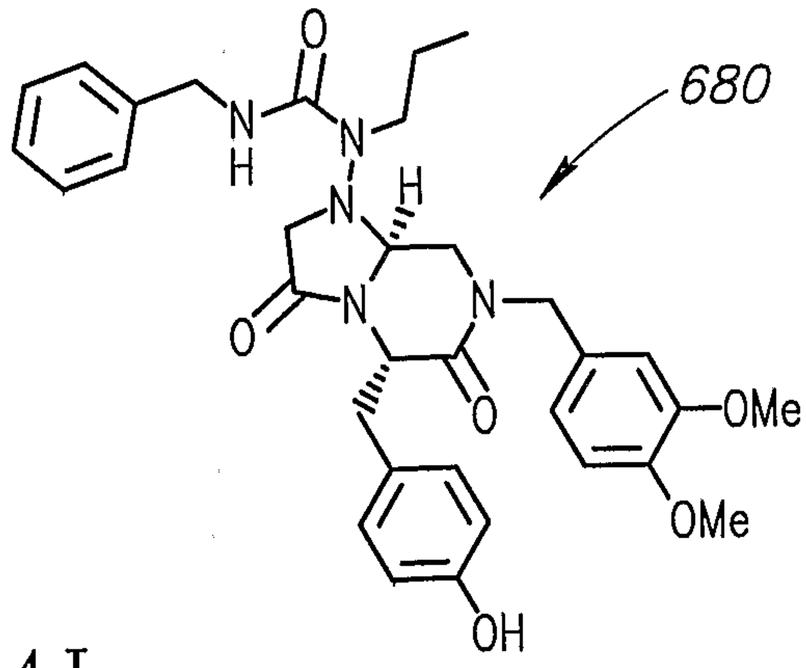
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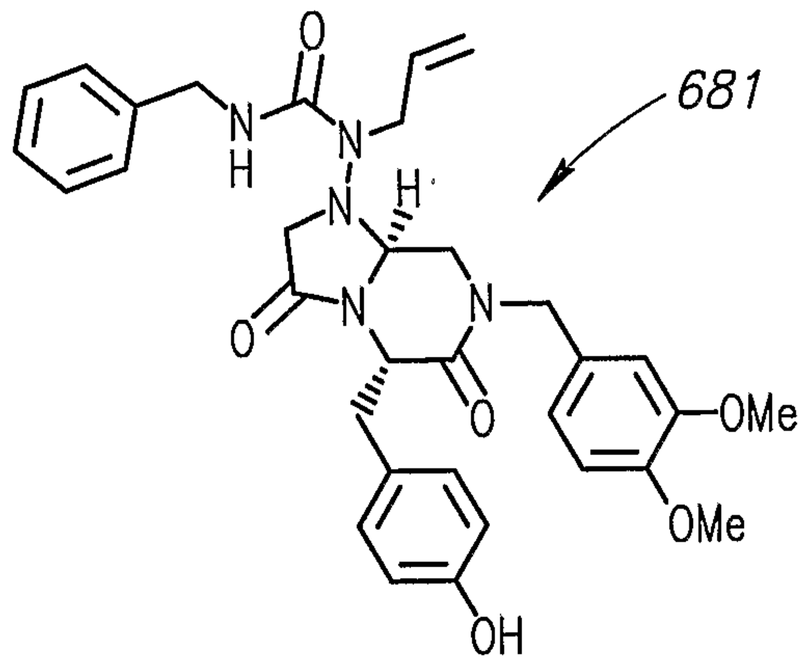
FIG.4J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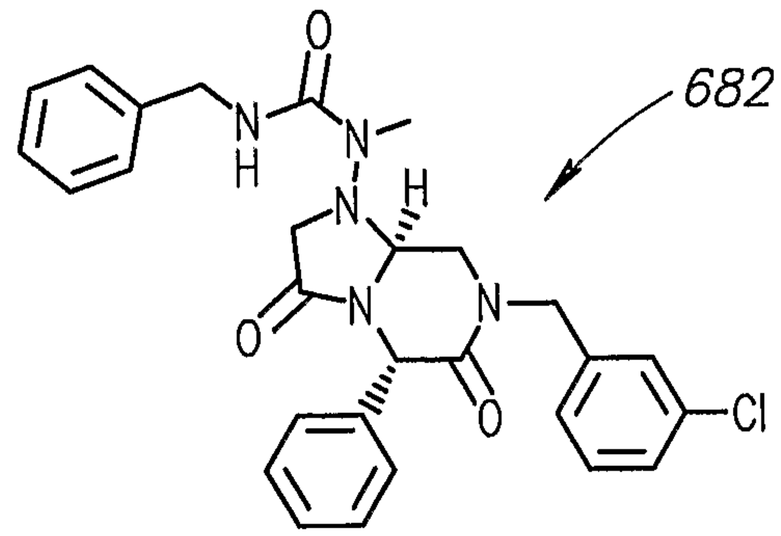
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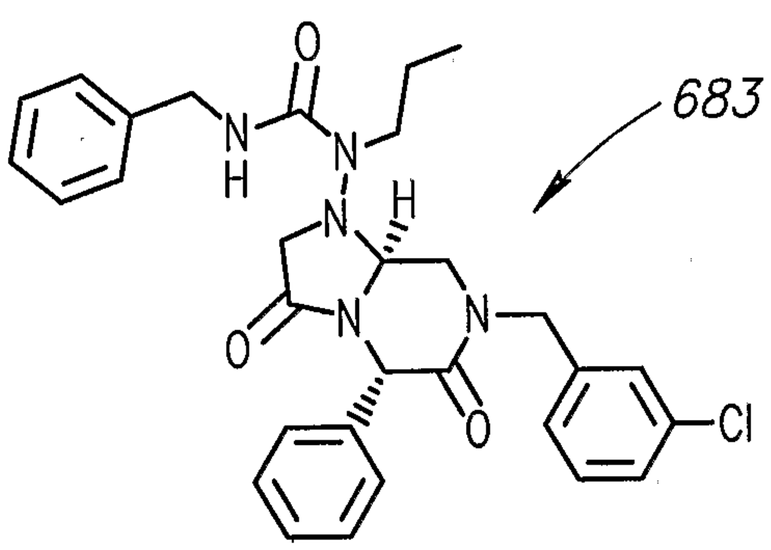
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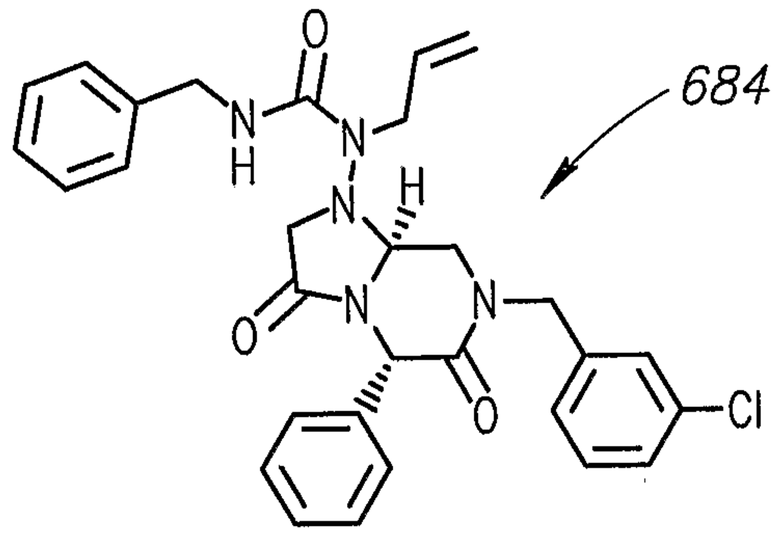
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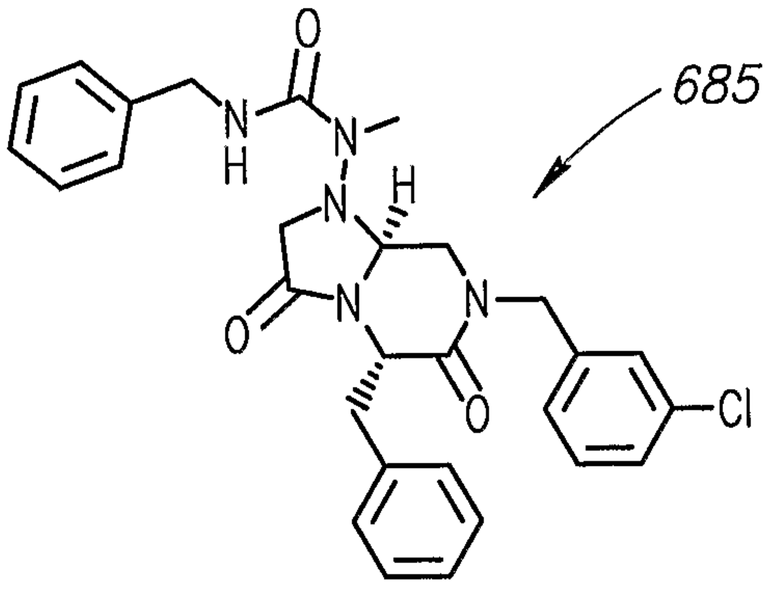
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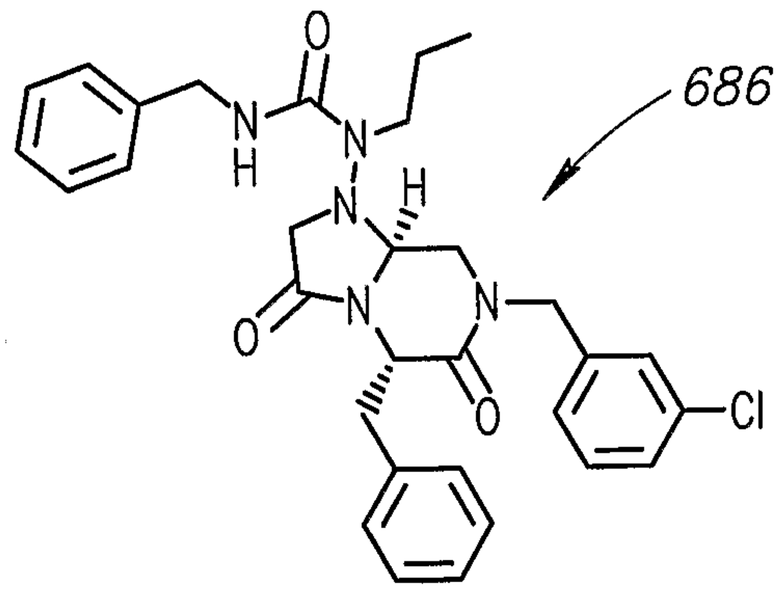
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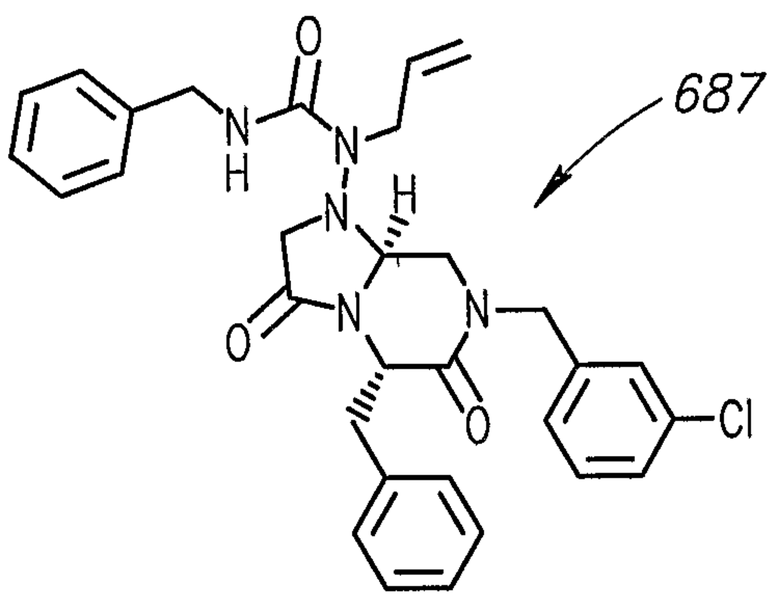
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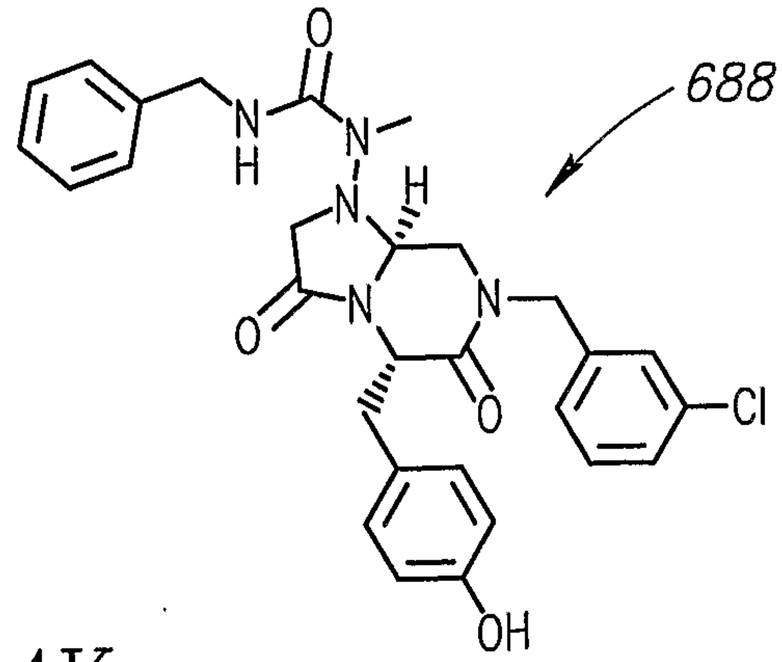
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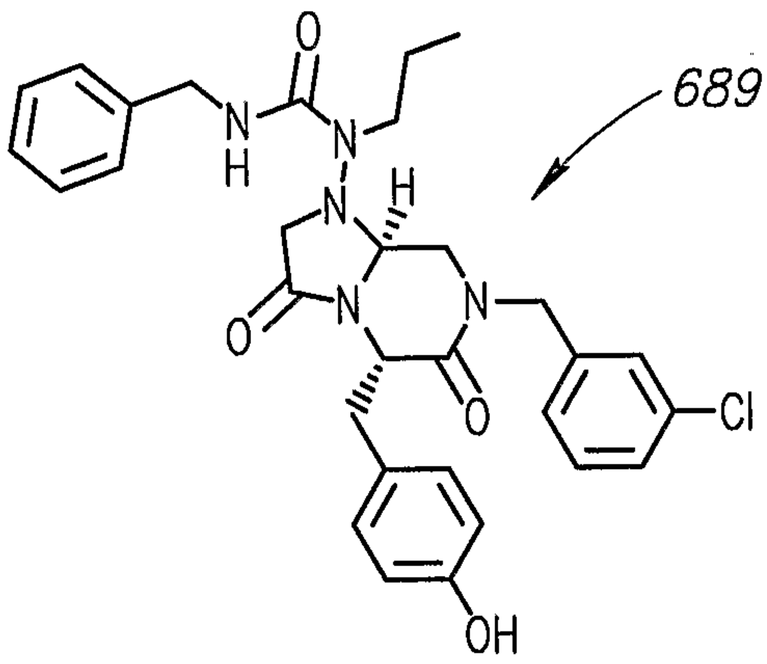
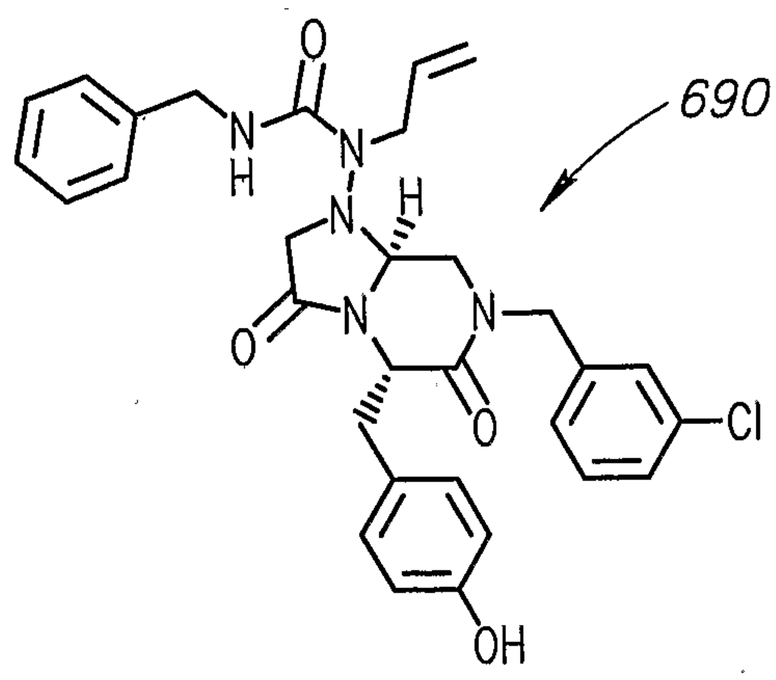
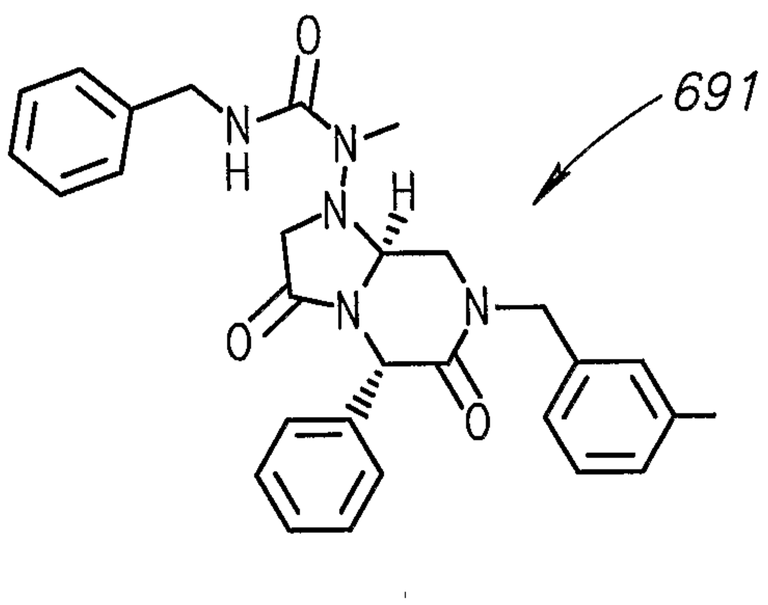
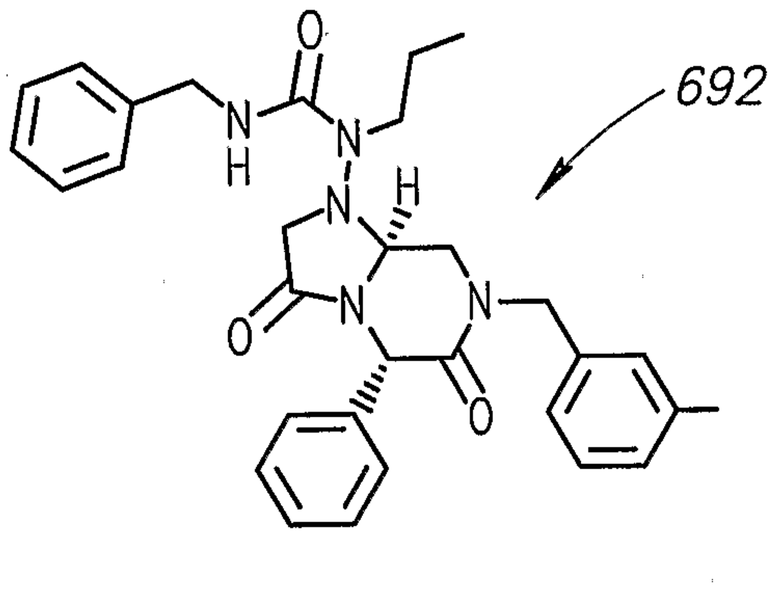
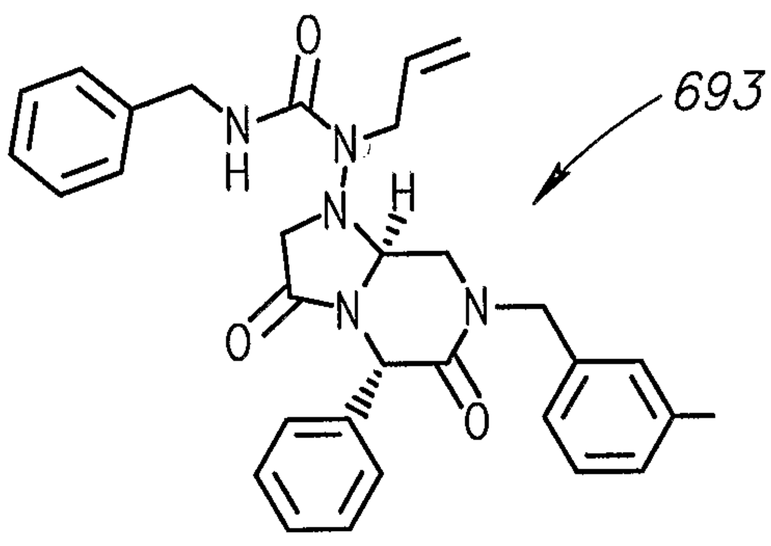
FIG.4K

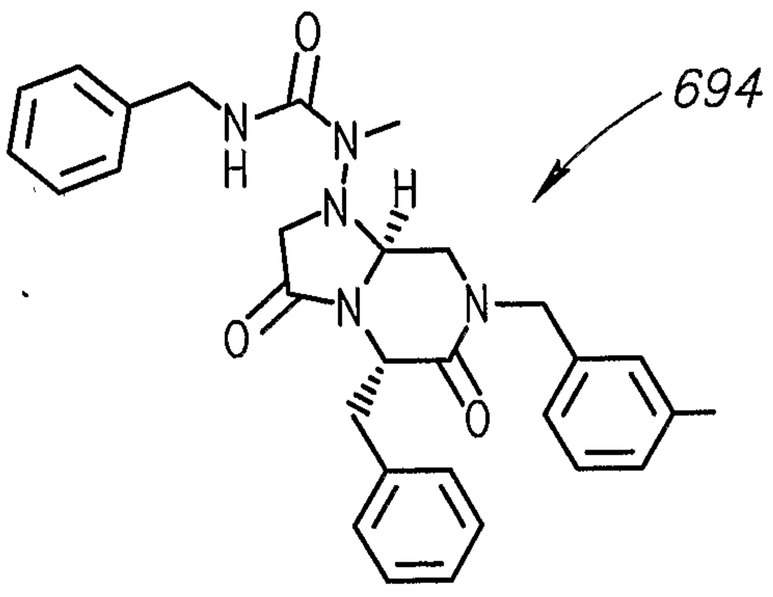


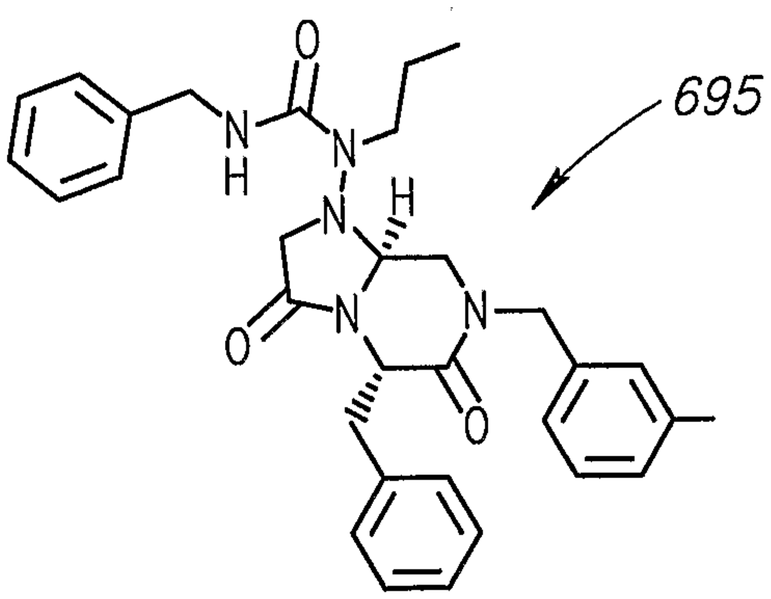












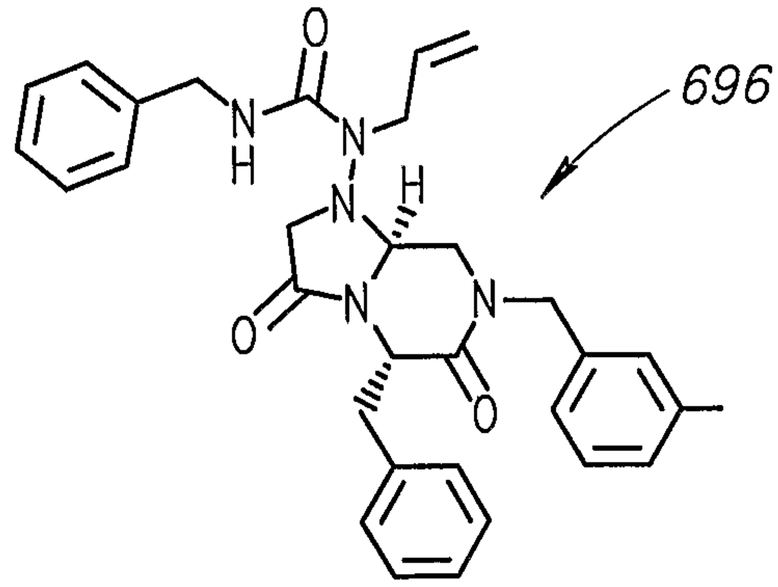
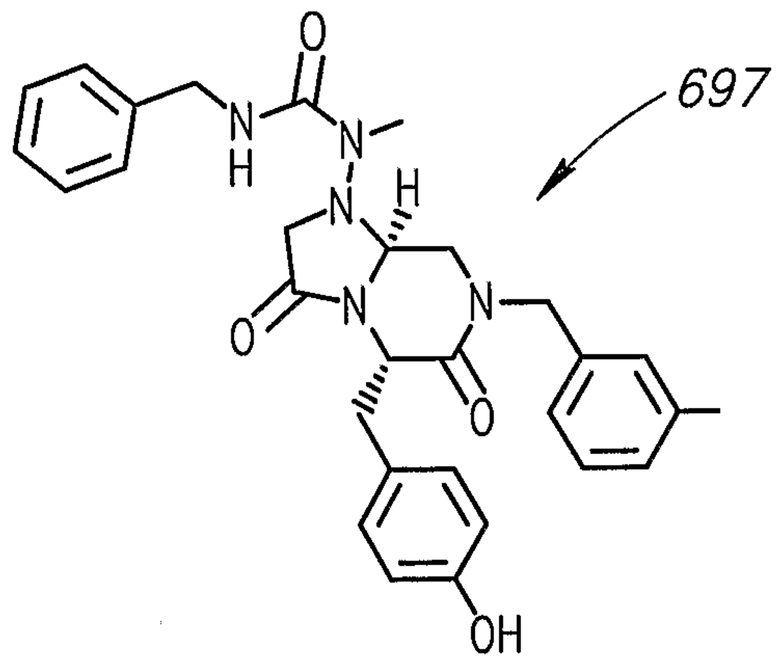
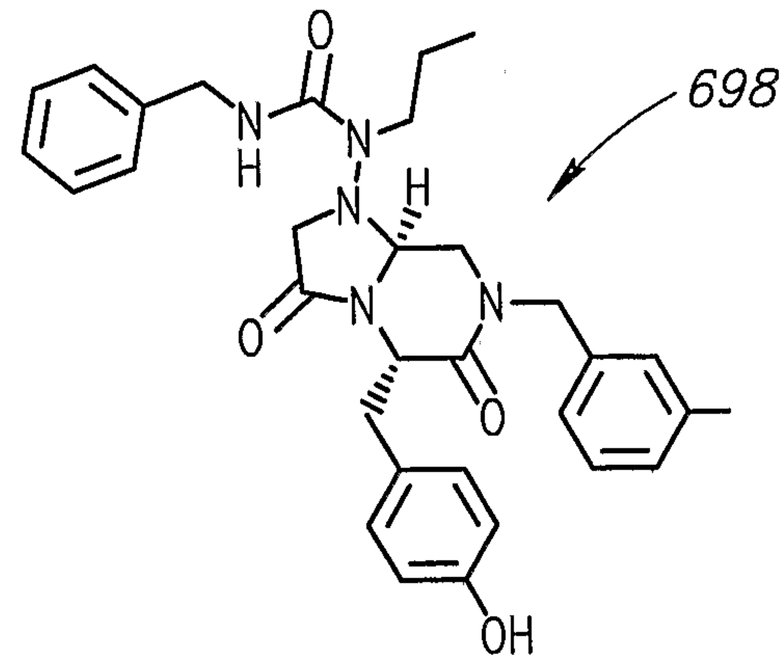
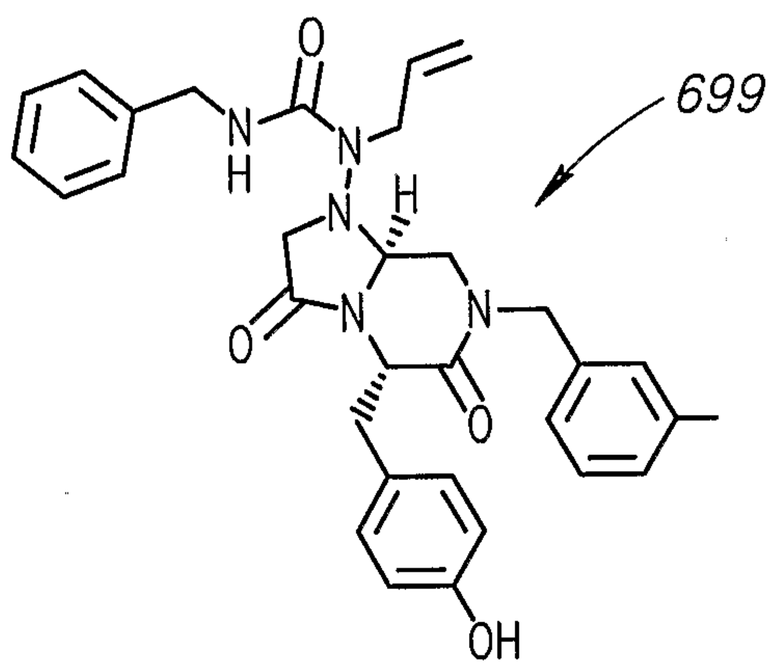
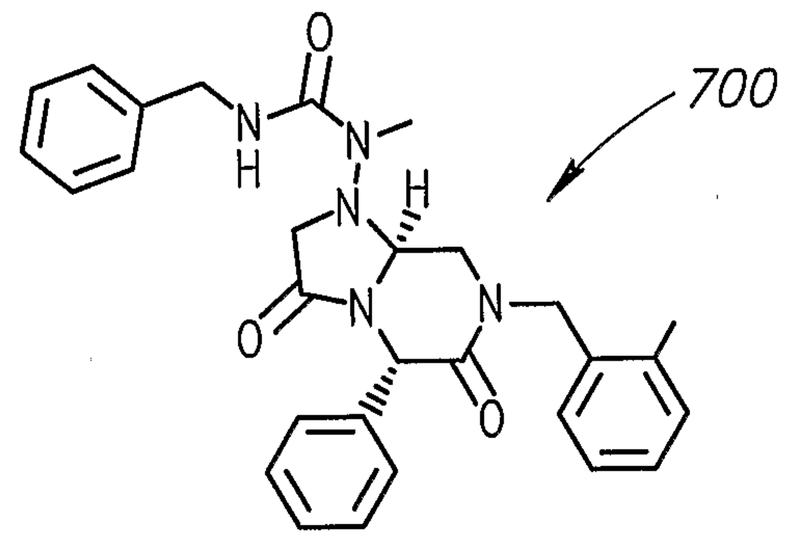


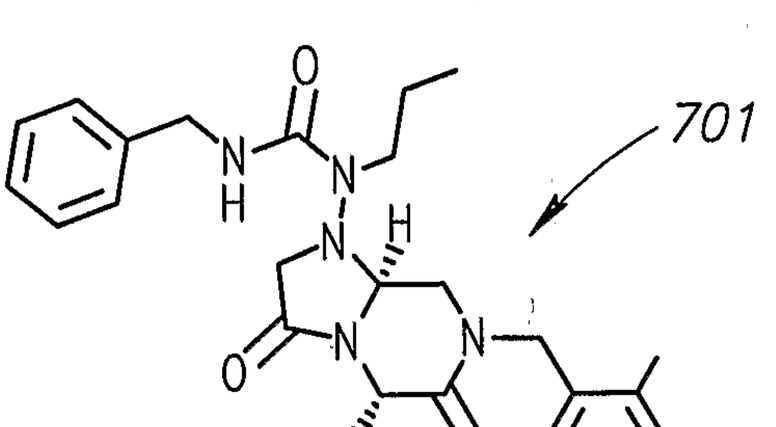
FIG.4L











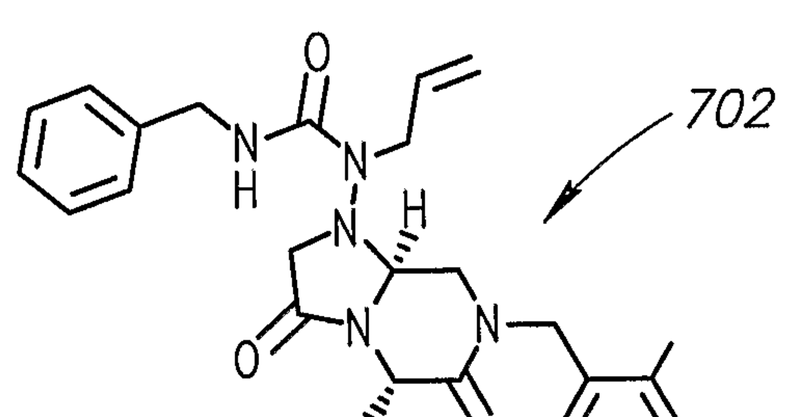
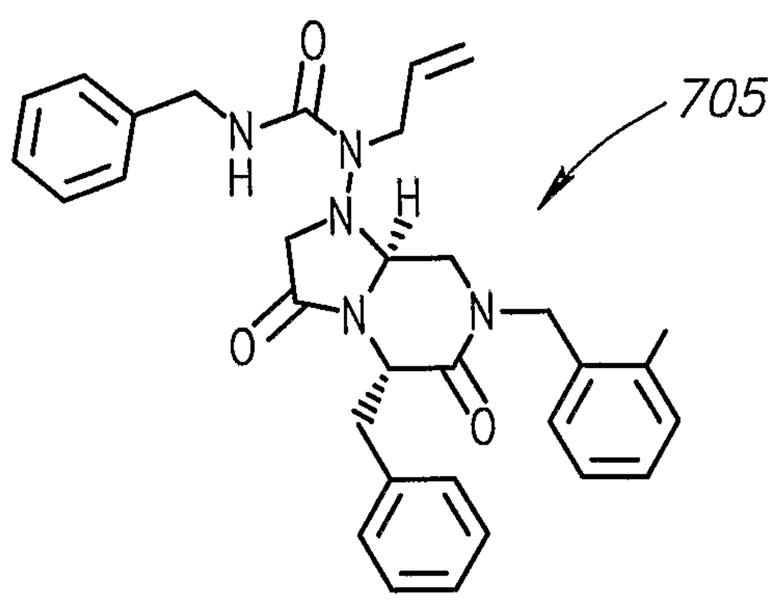
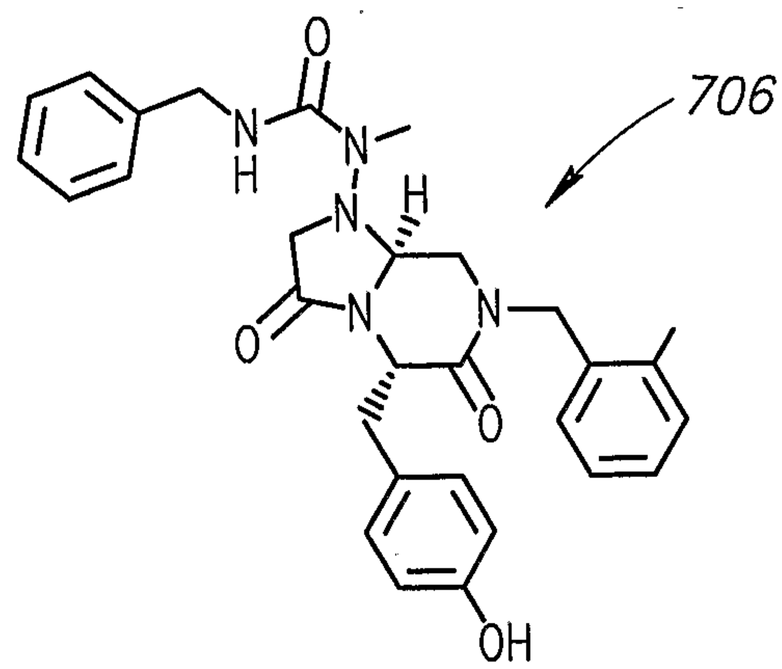
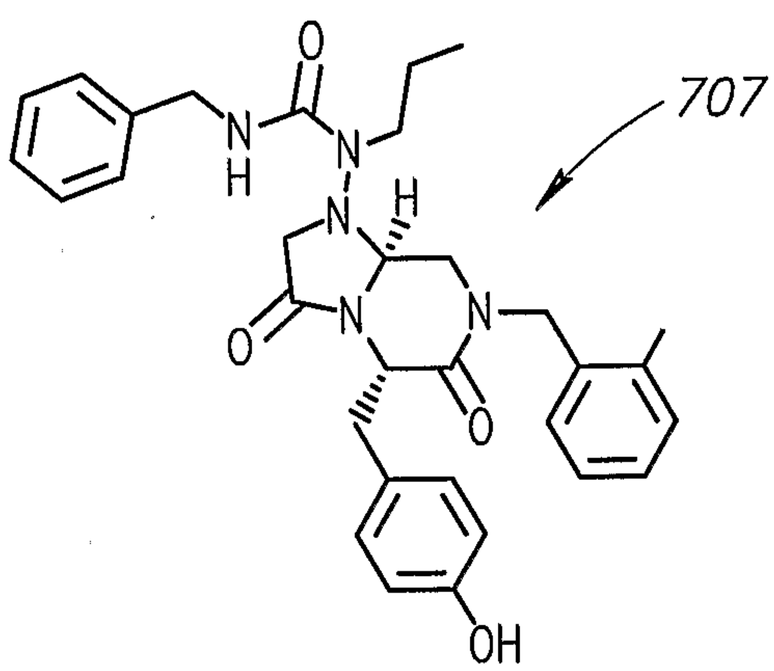
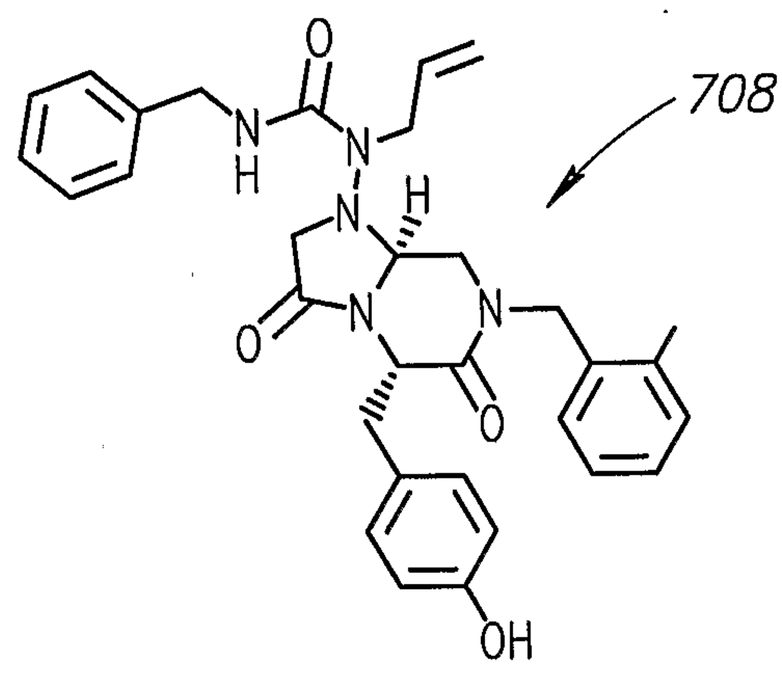


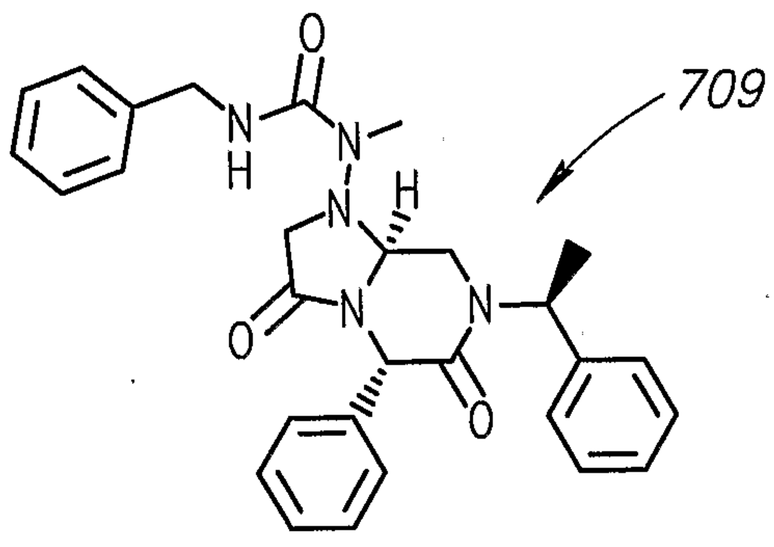
FIG.4M

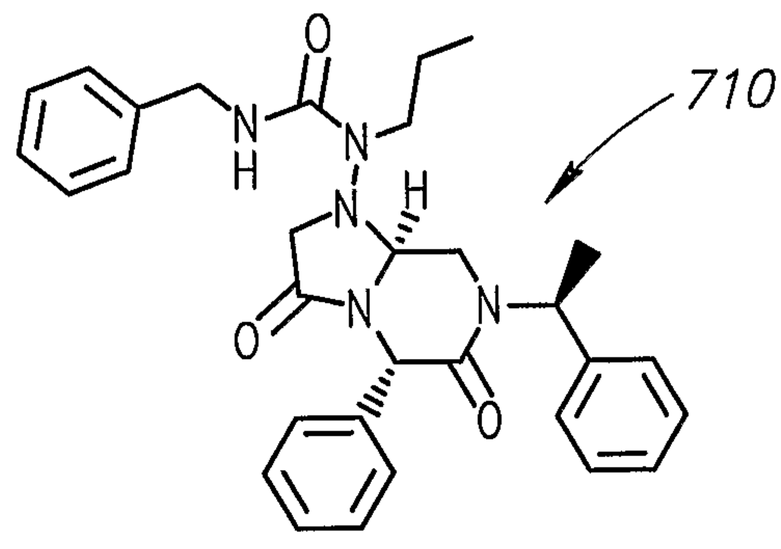


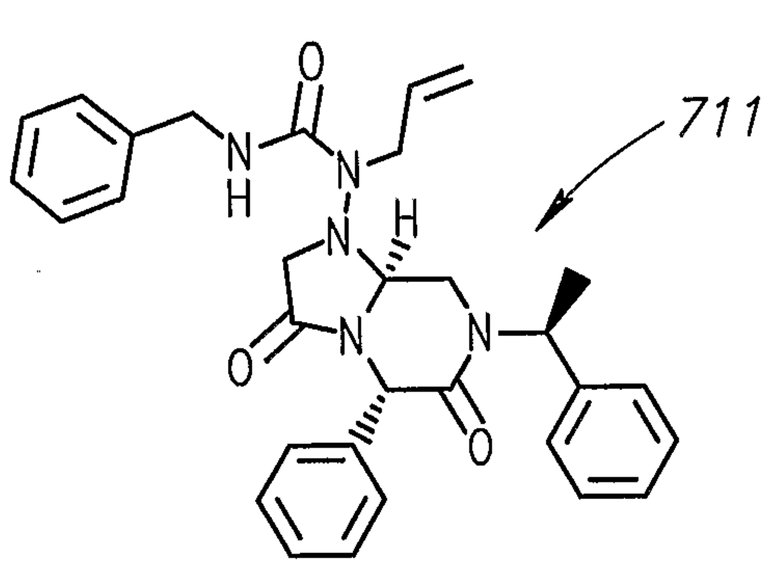












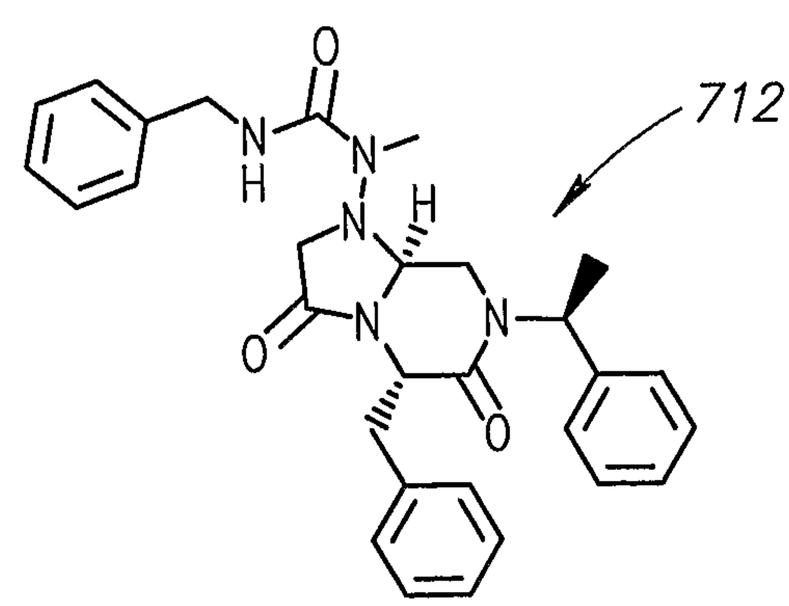
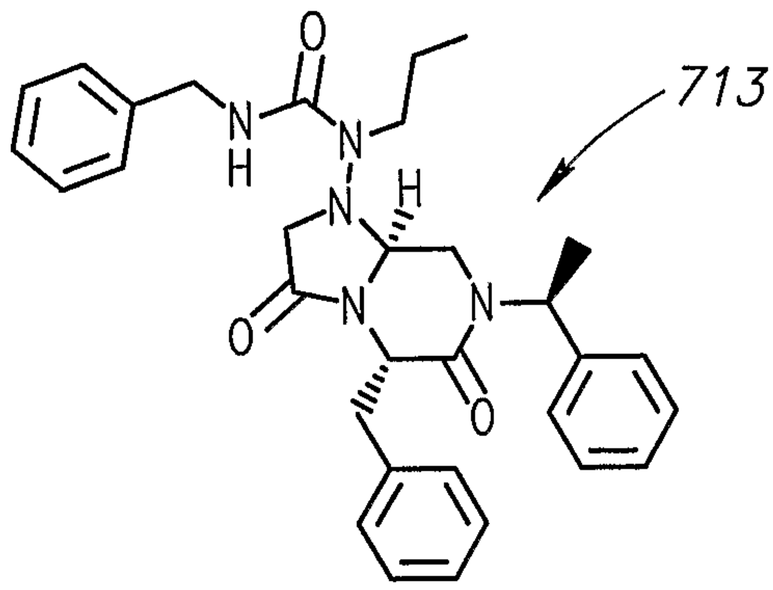
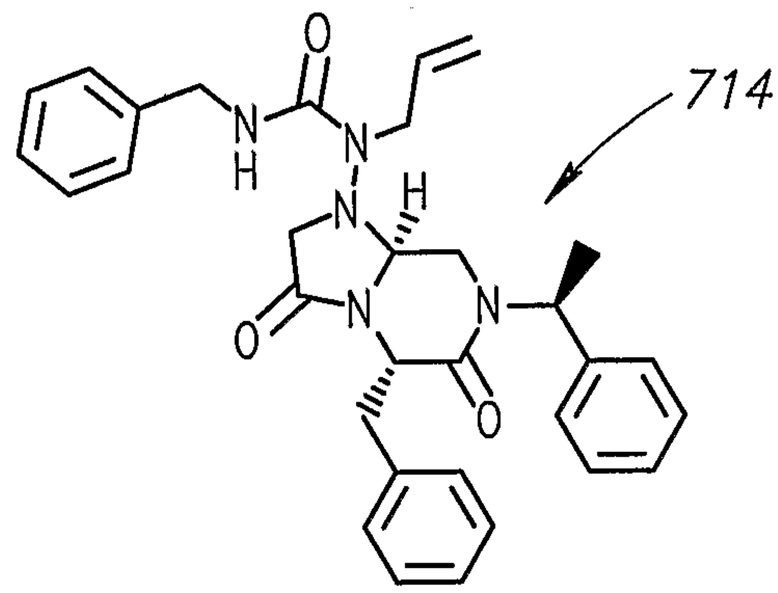
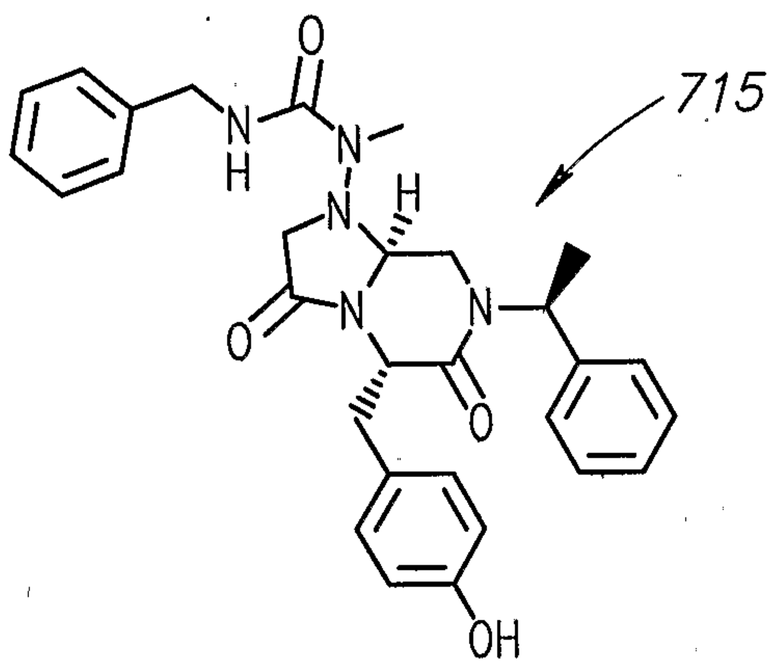
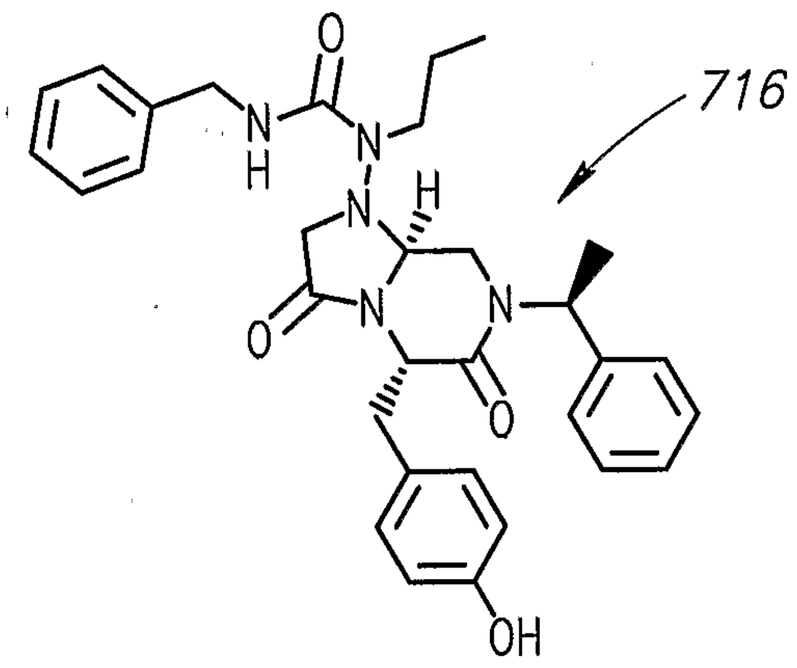


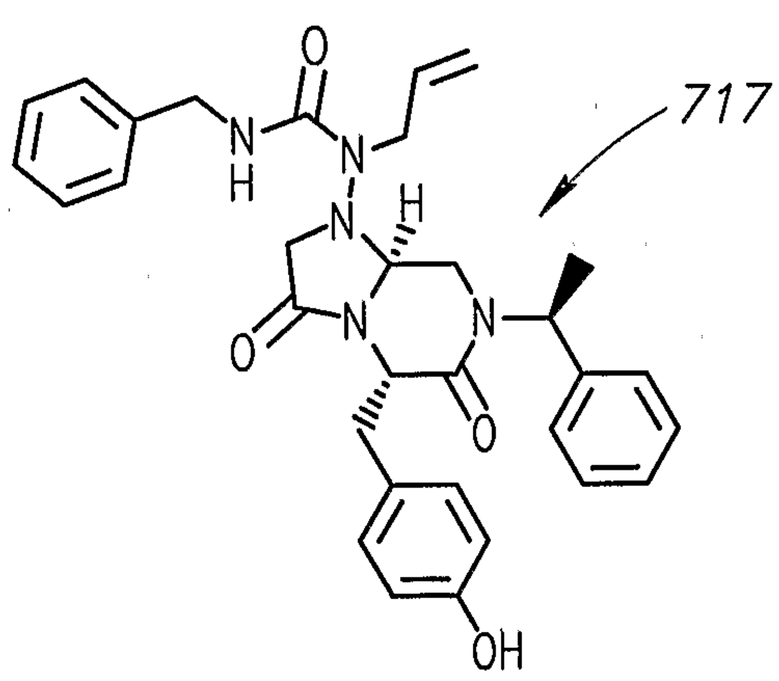
FIG.4N

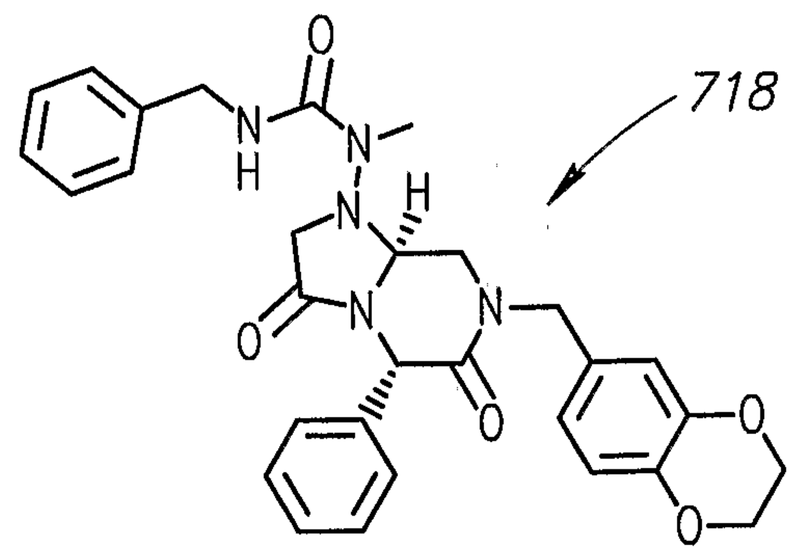


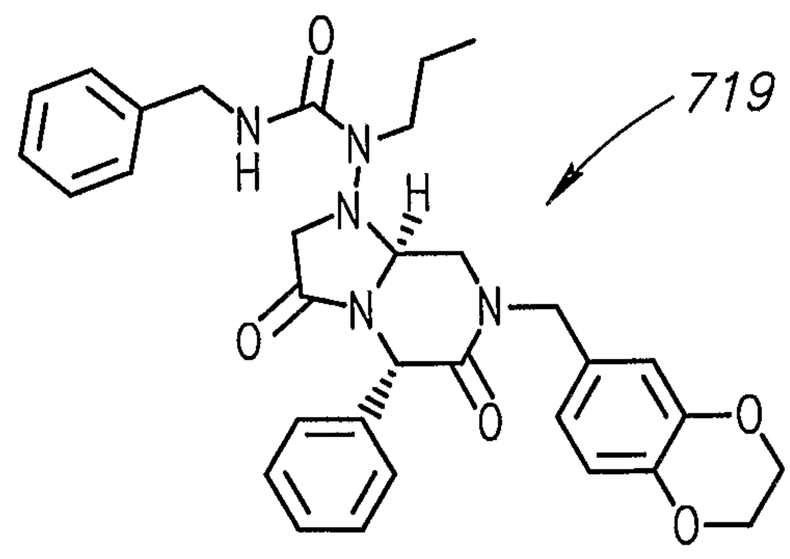












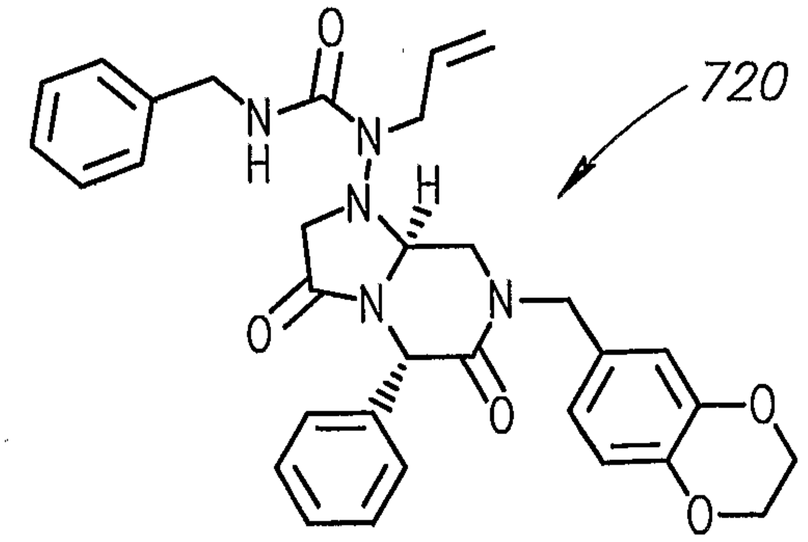
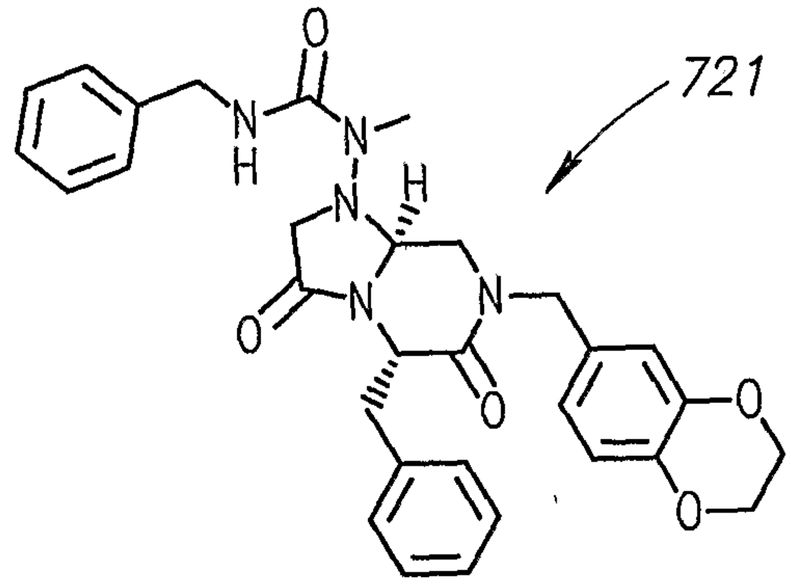
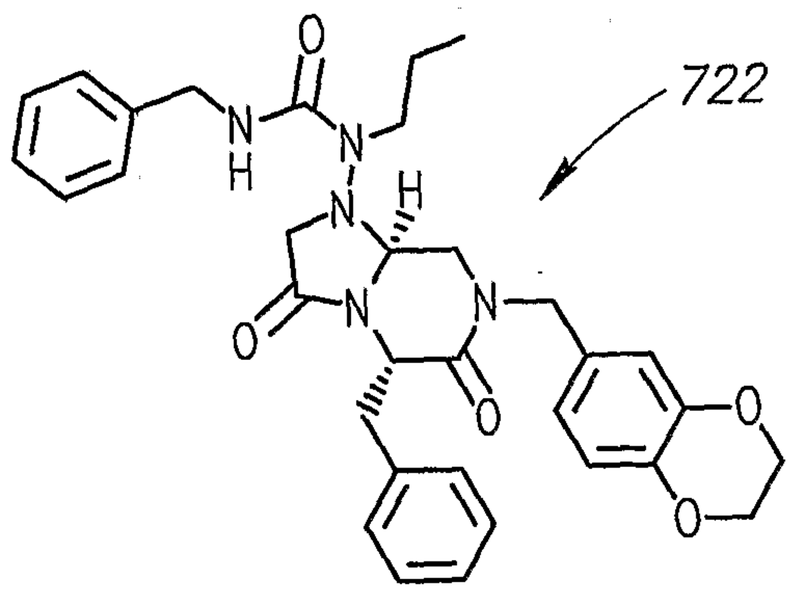
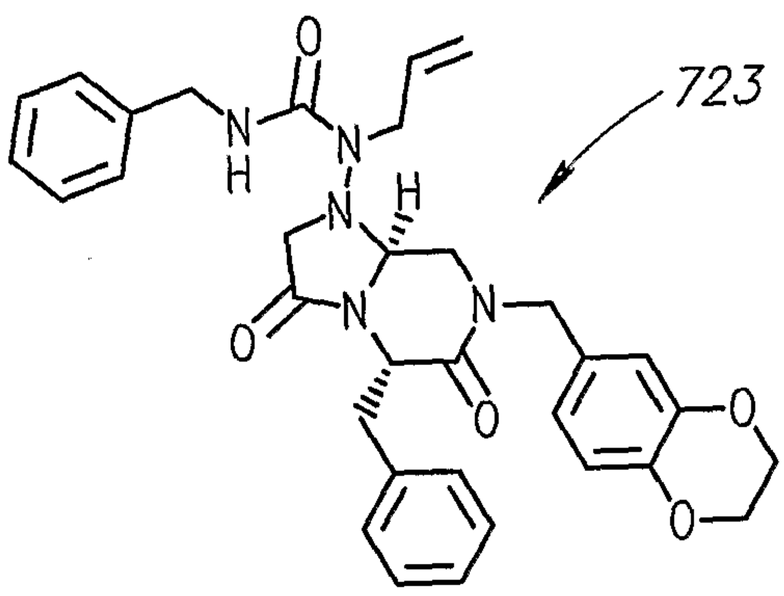
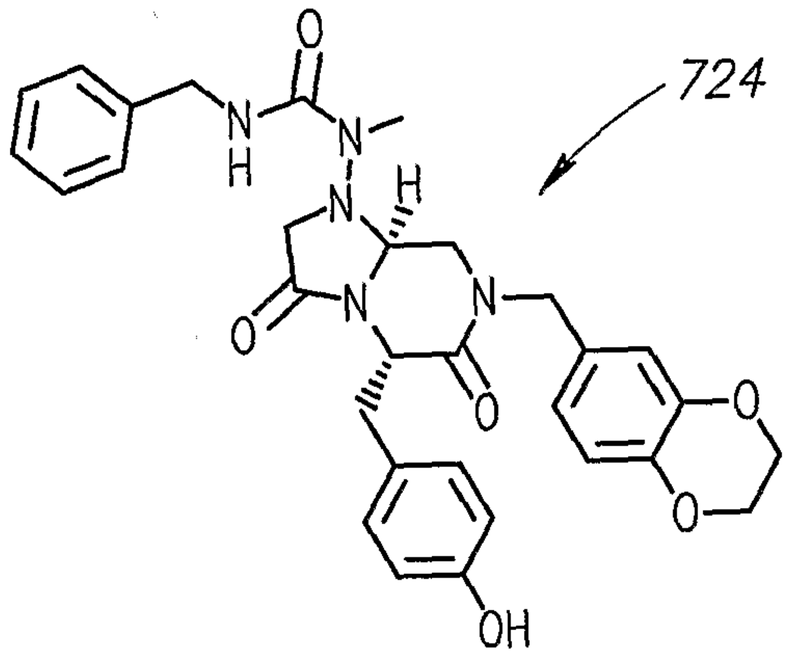


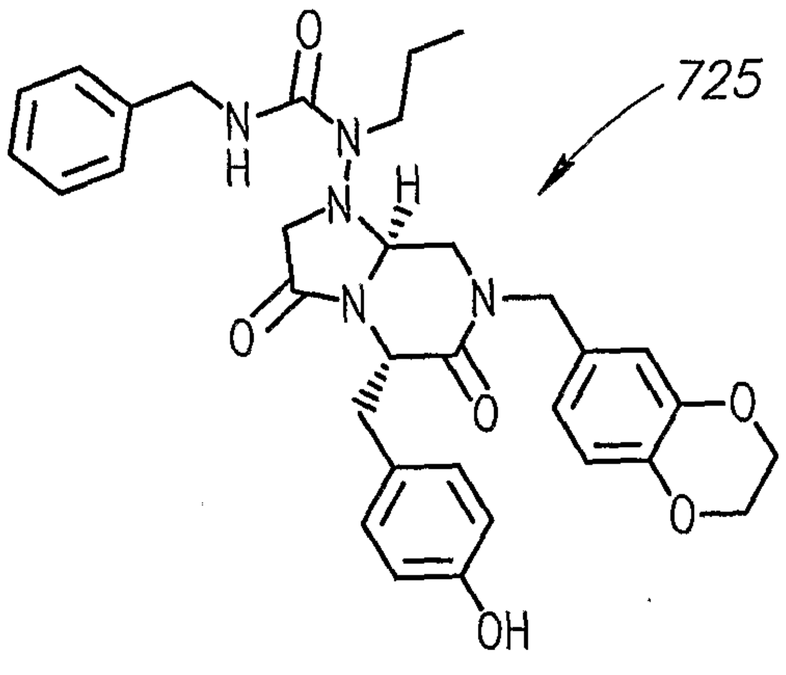
FIG.40

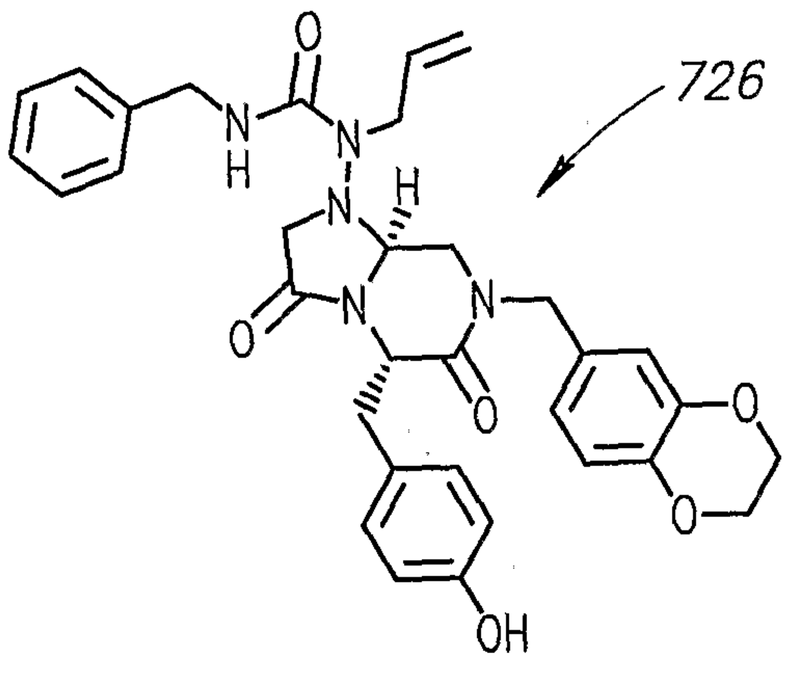


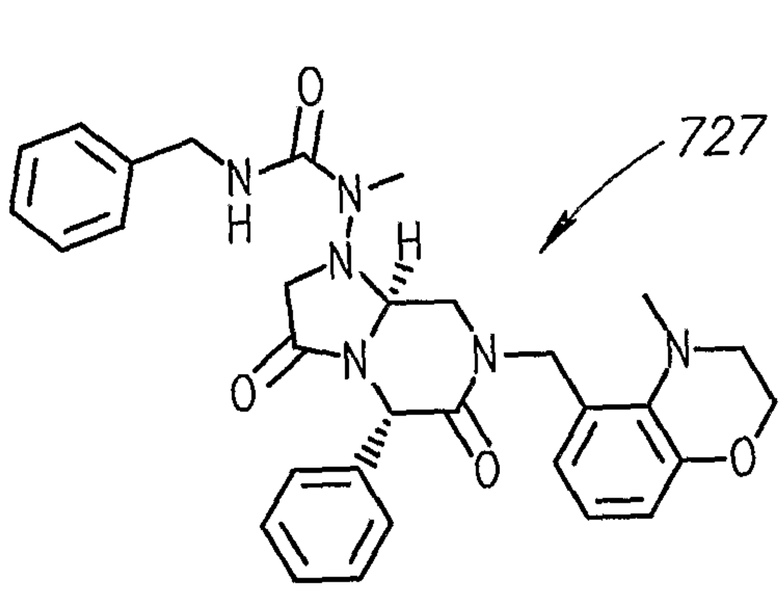












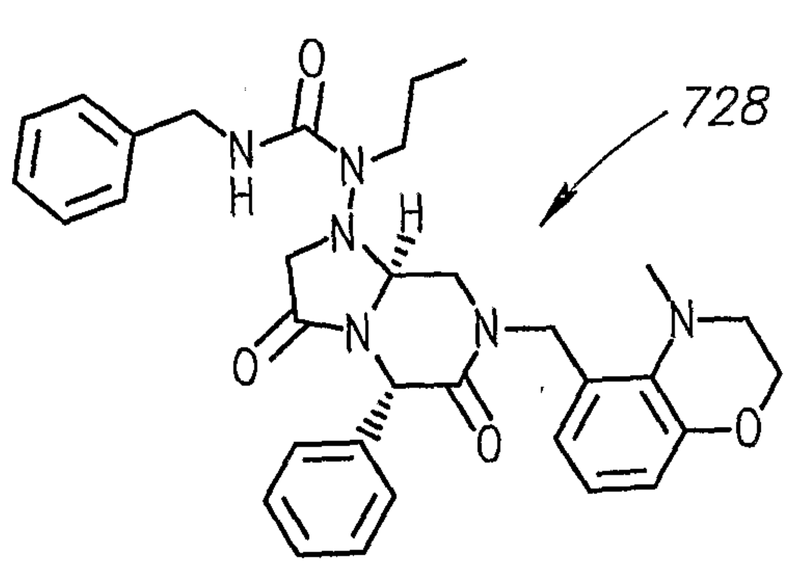
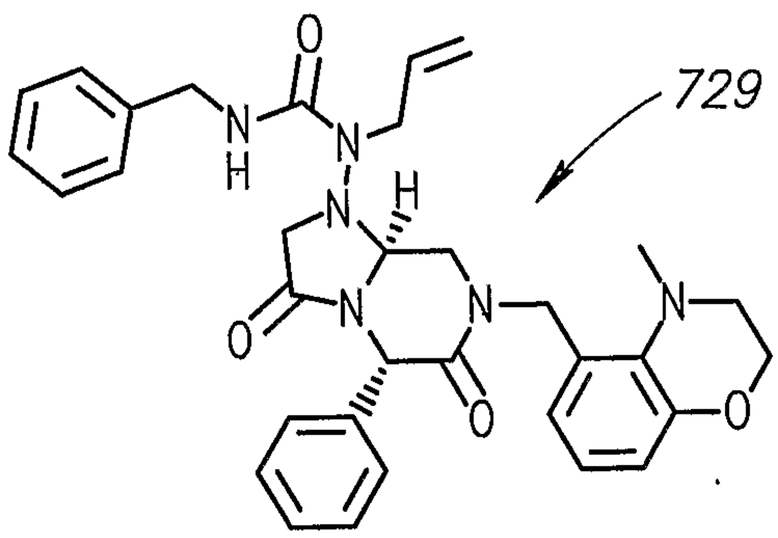
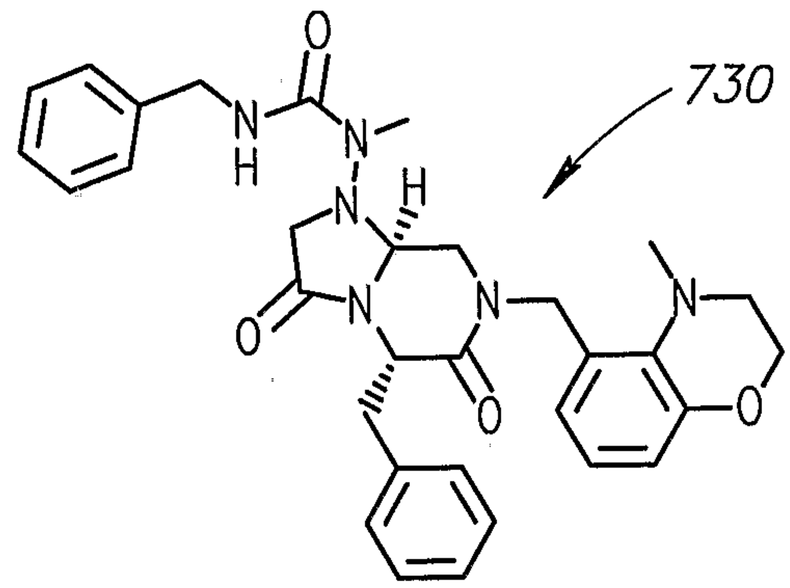
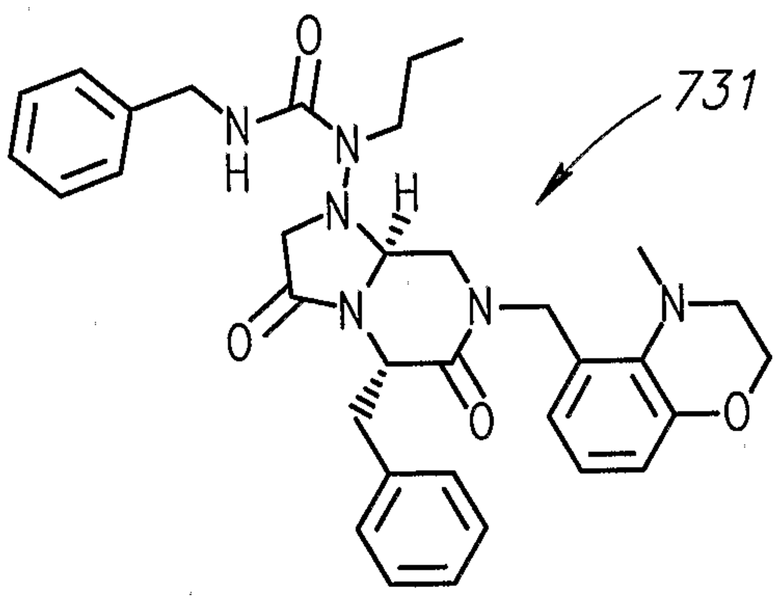
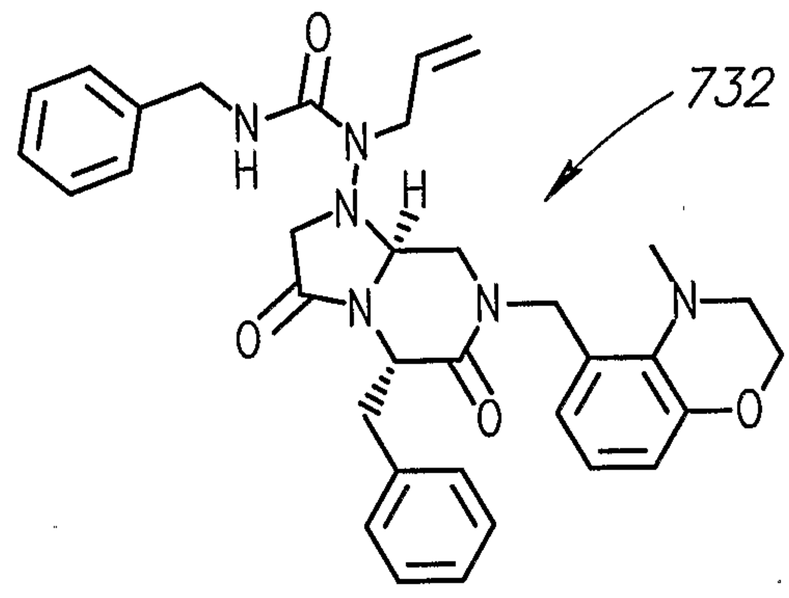


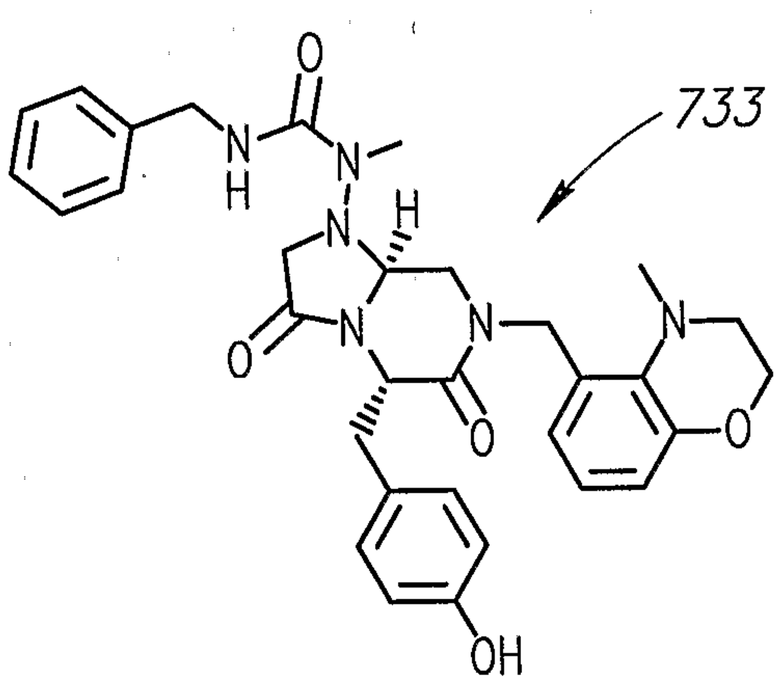
FIG.4P

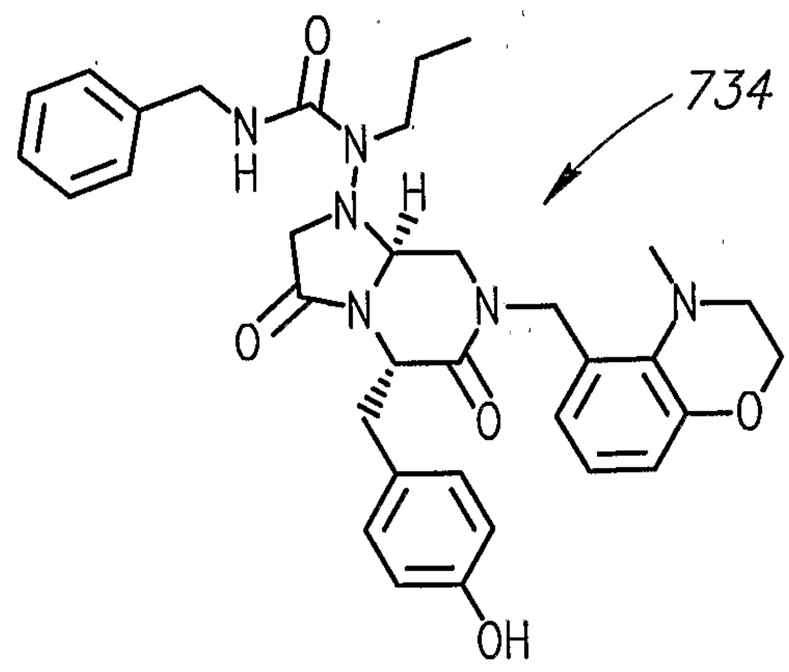


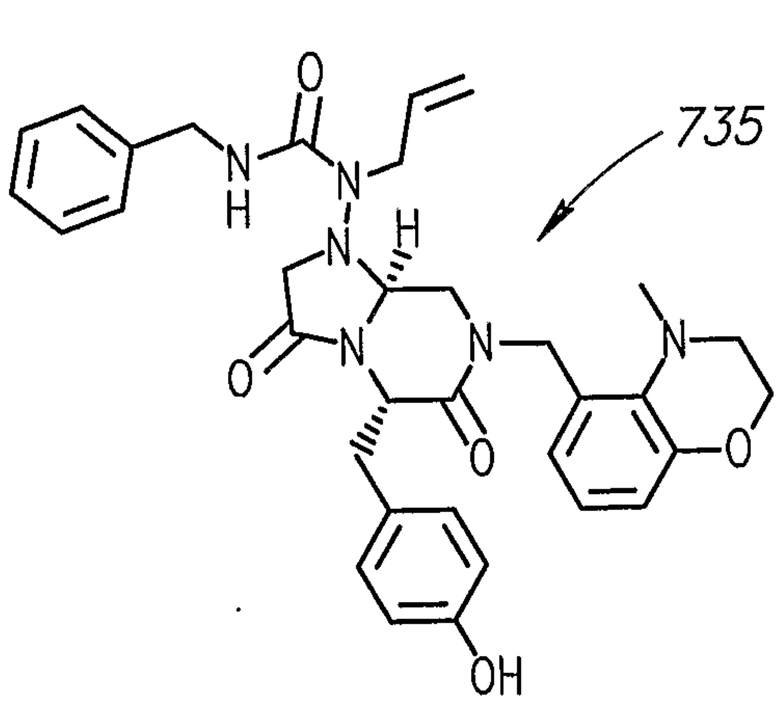












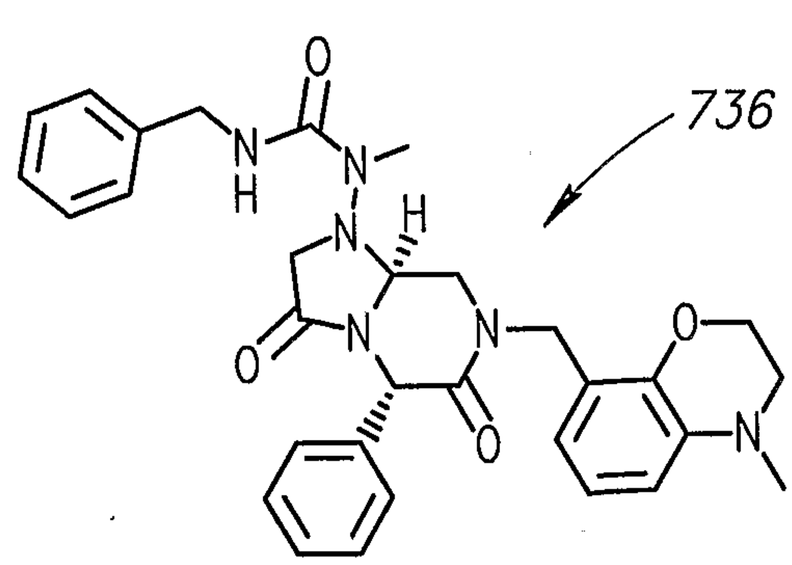
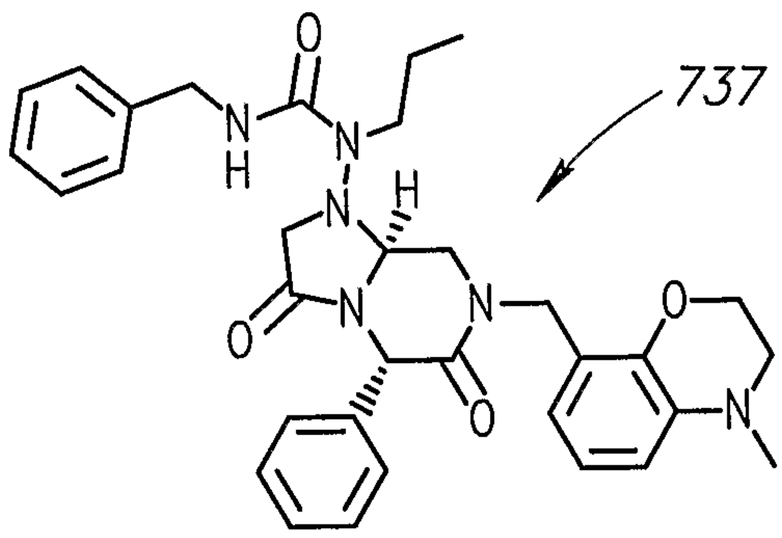
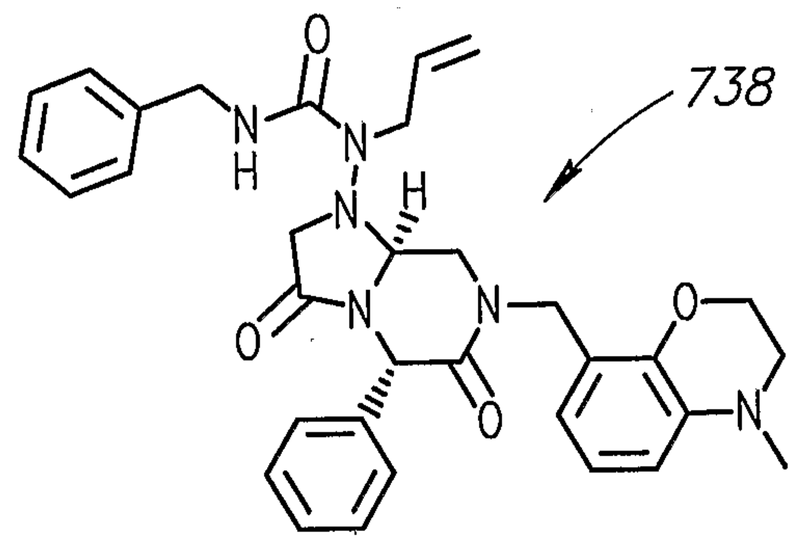
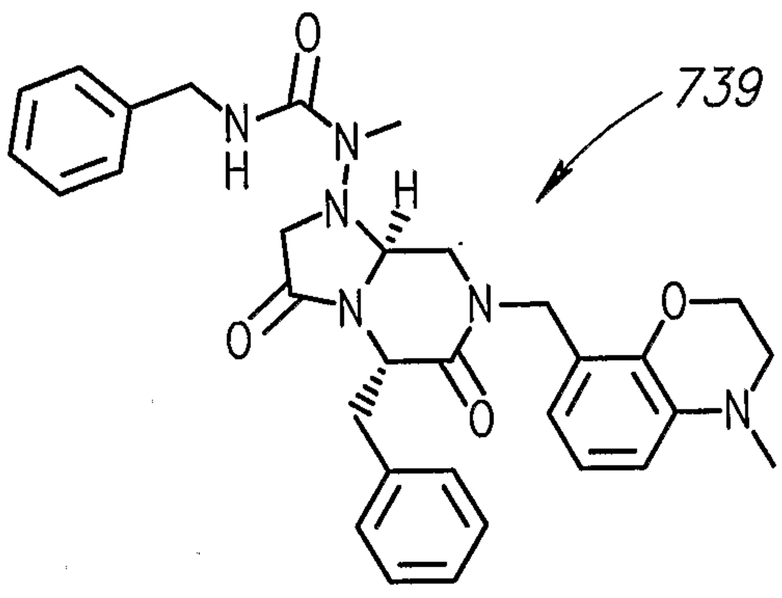
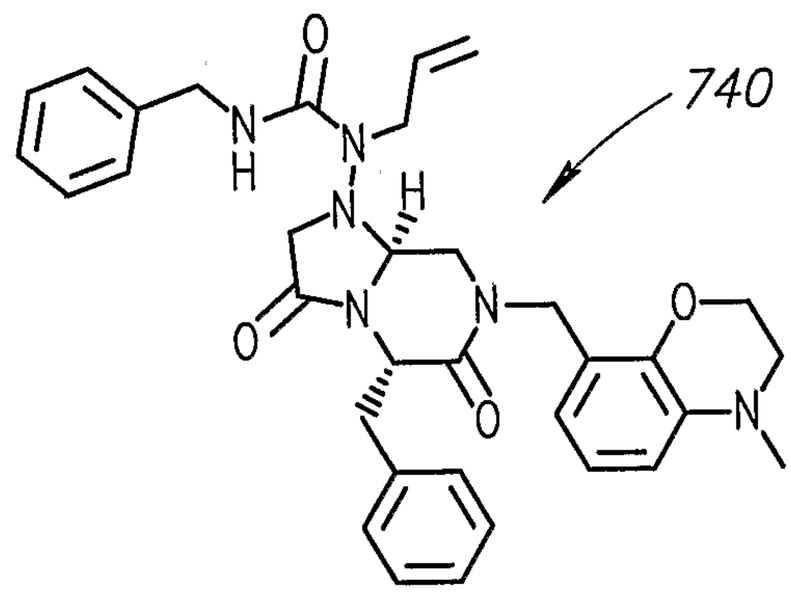


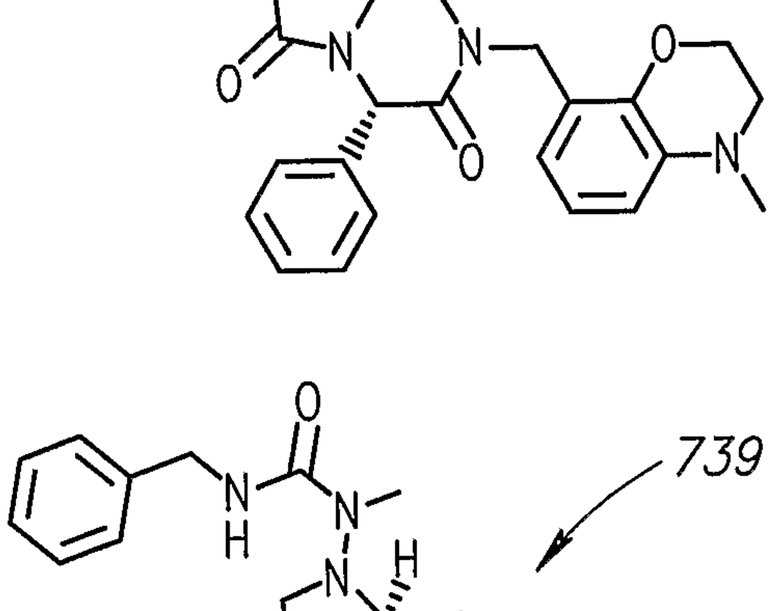
FIG.4Q

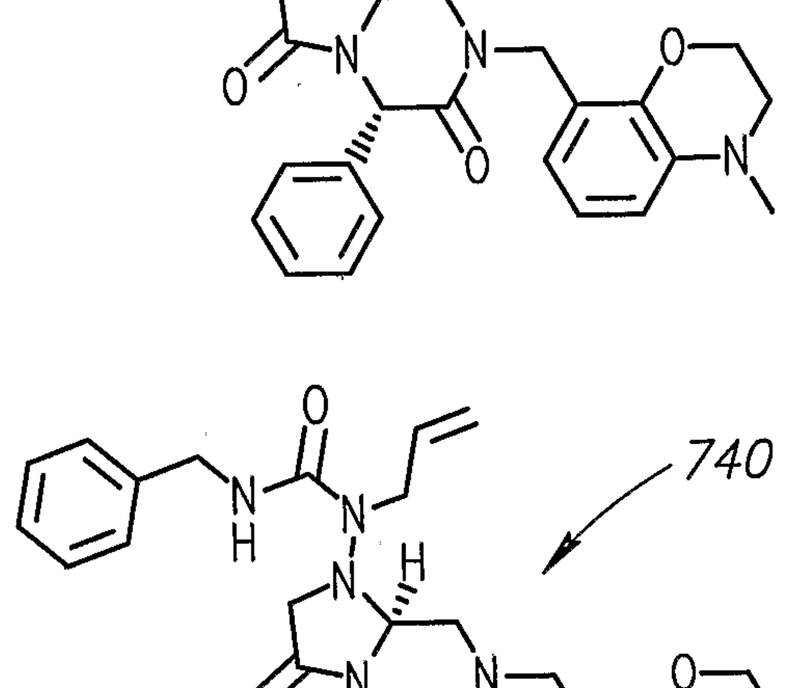


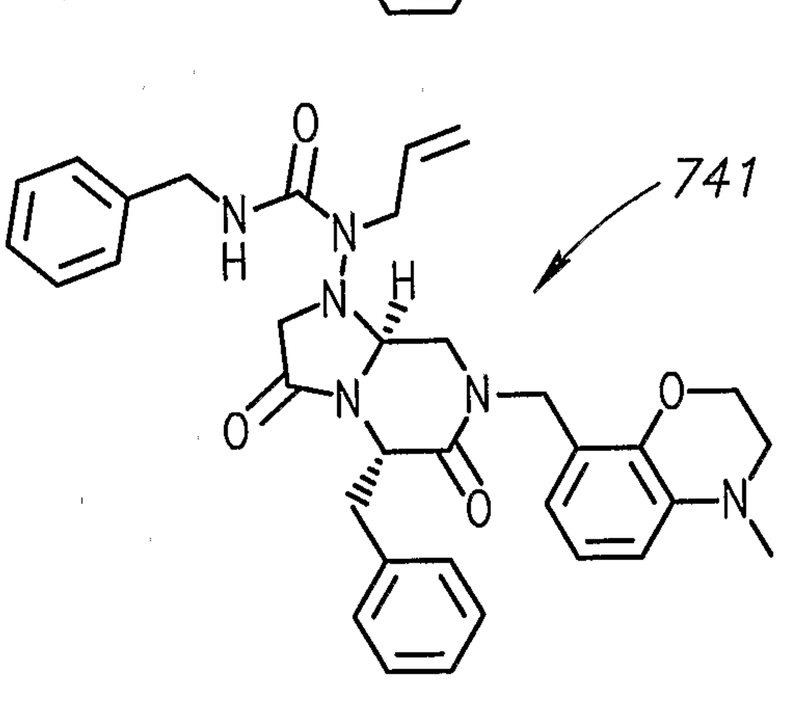












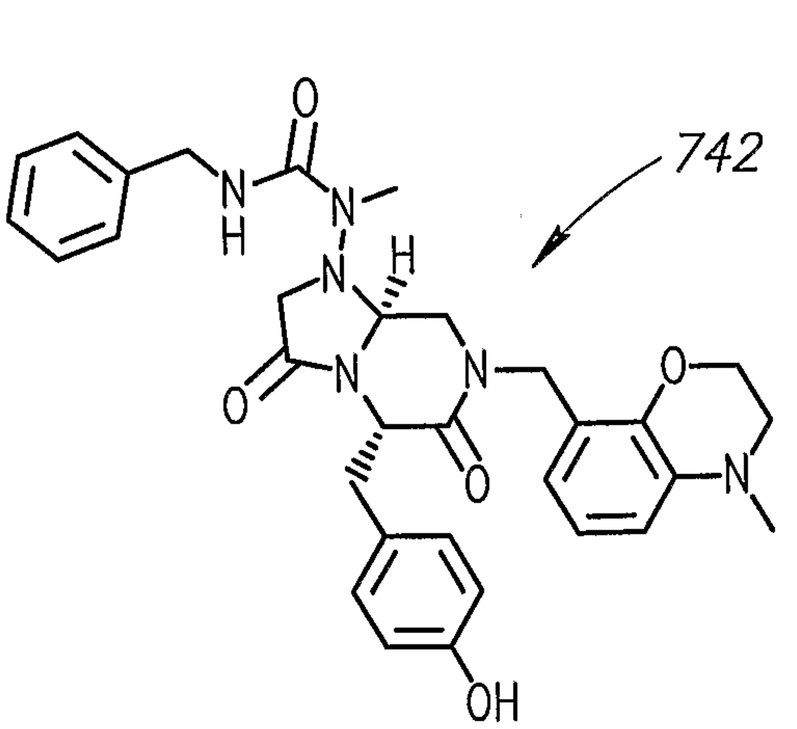
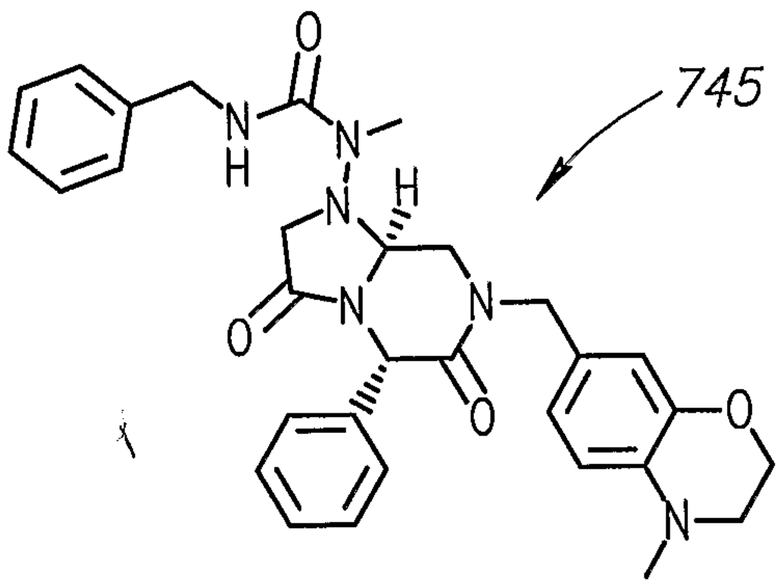
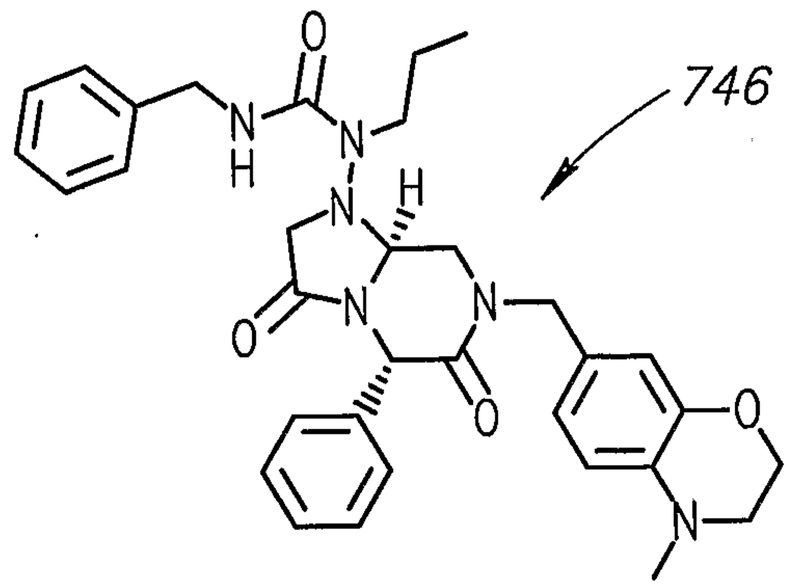
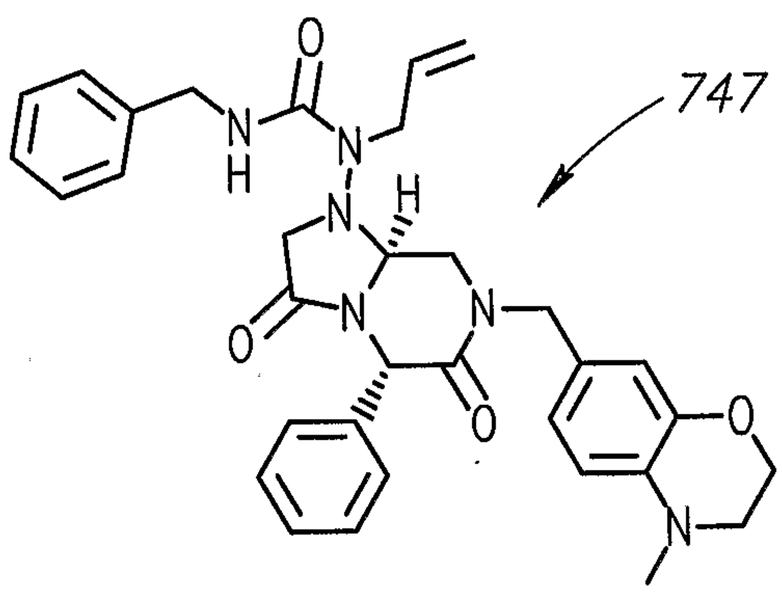


FIG.4R







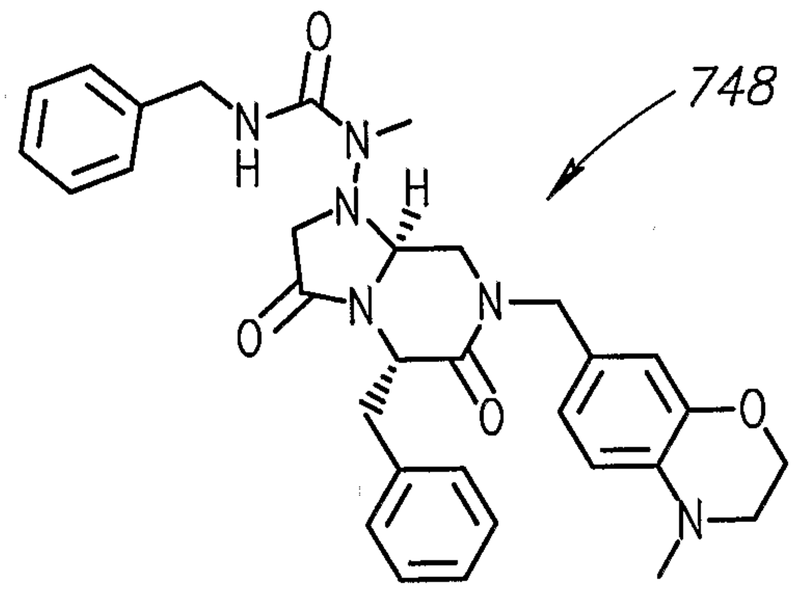
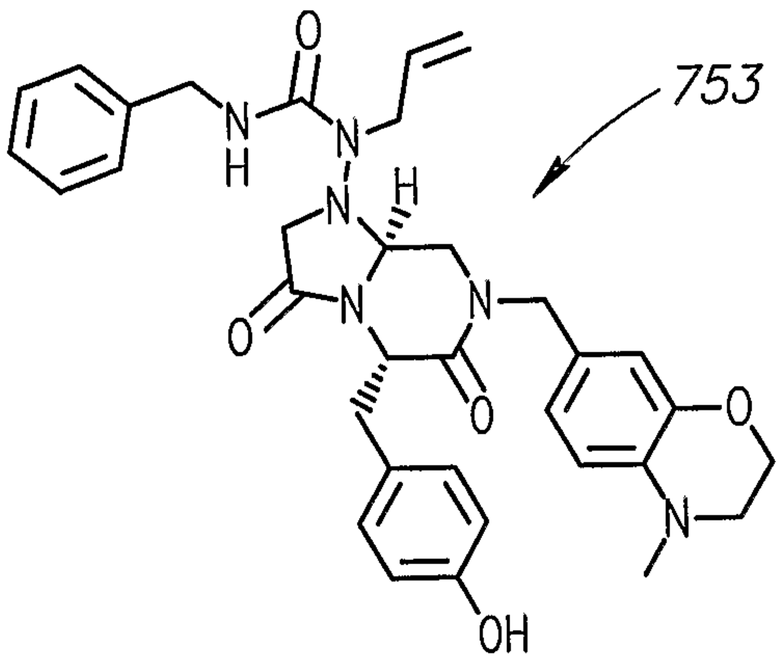


FIG.4S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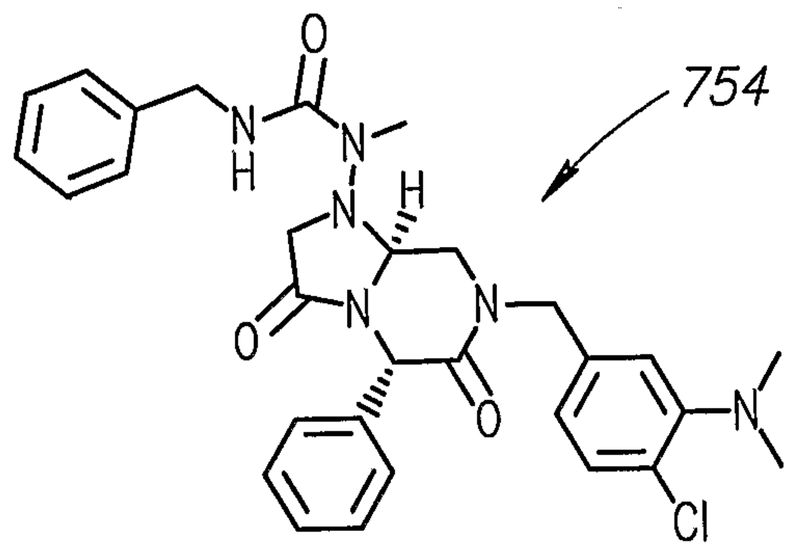
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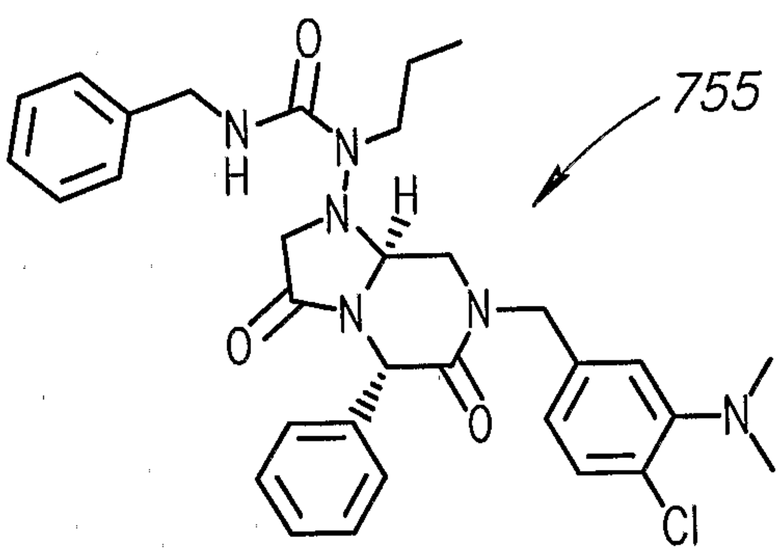
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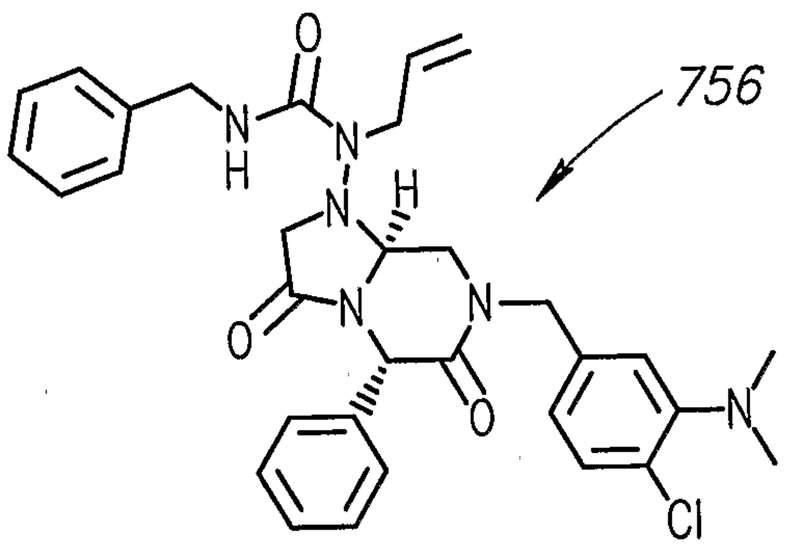
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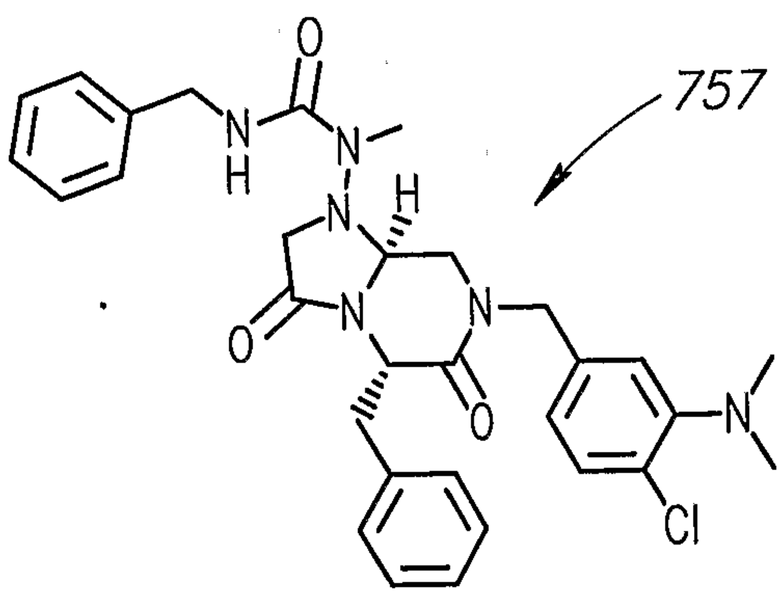
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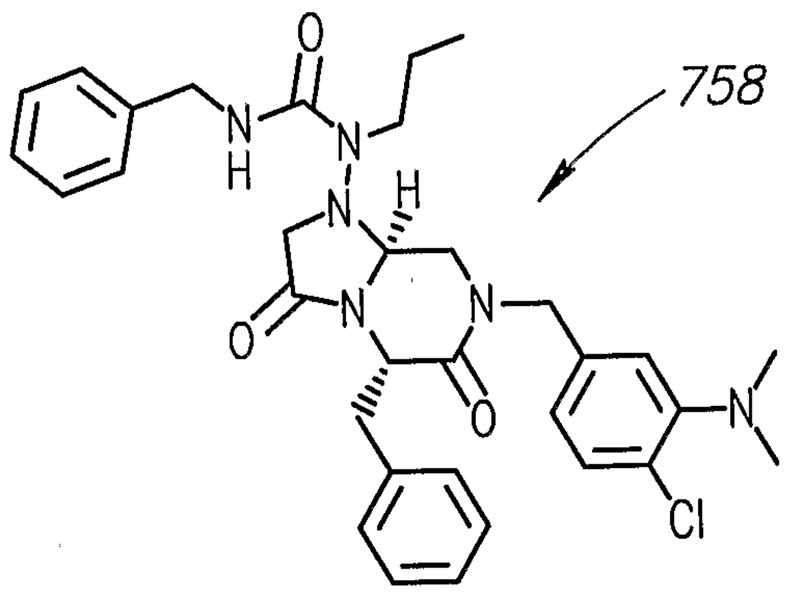
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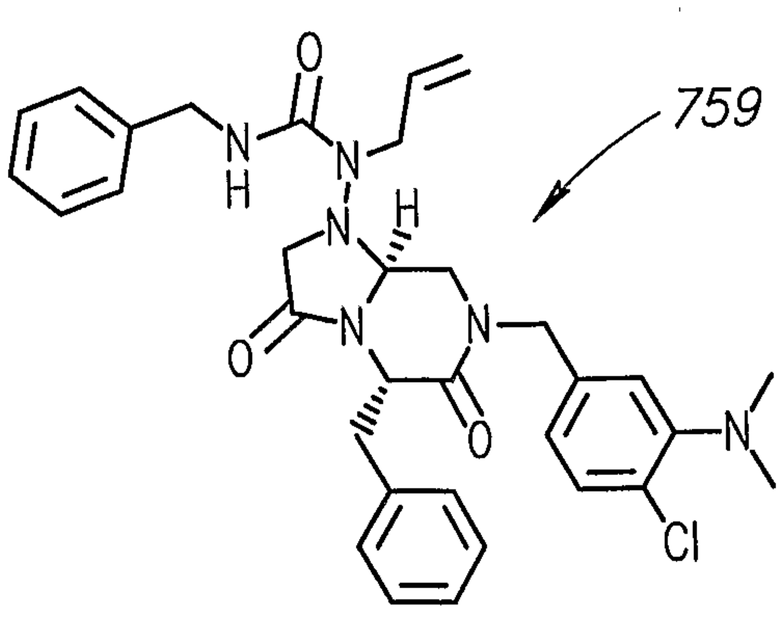
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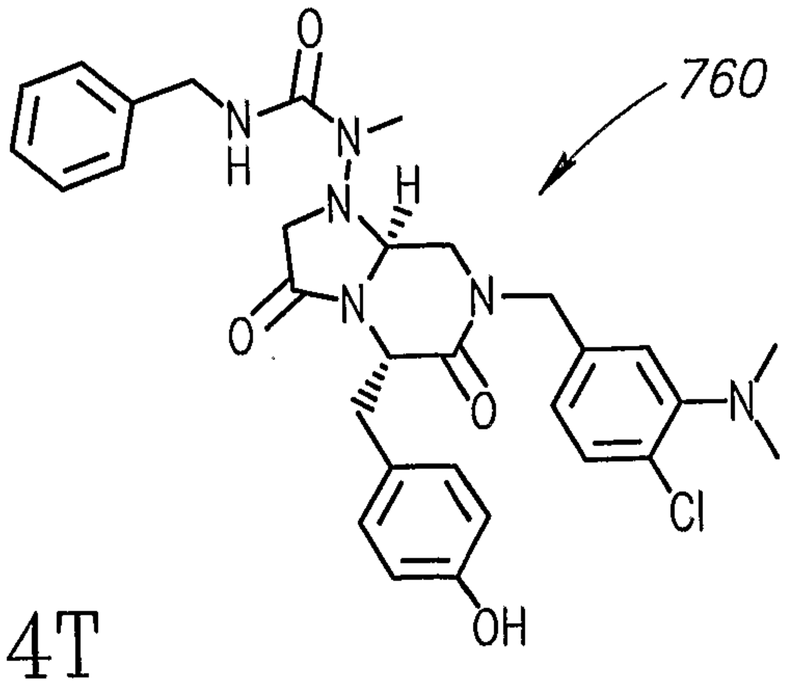
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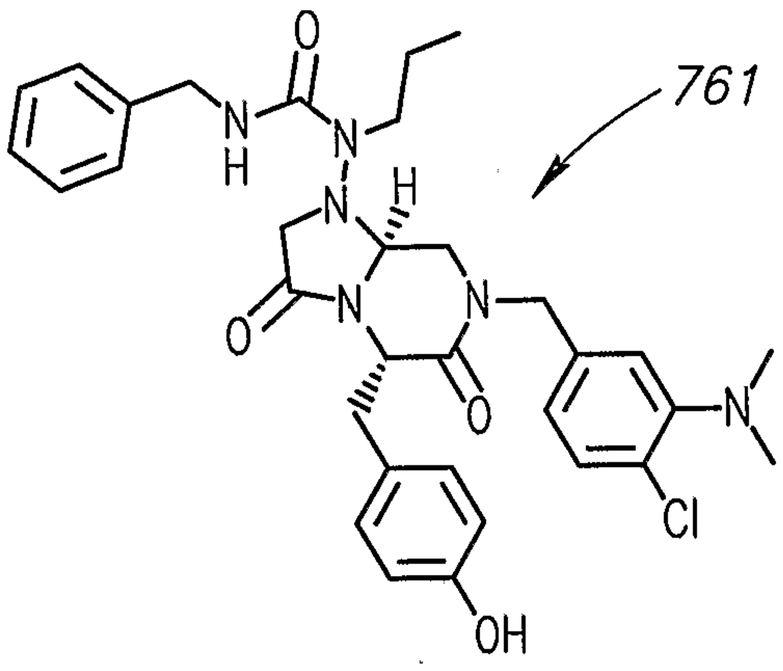
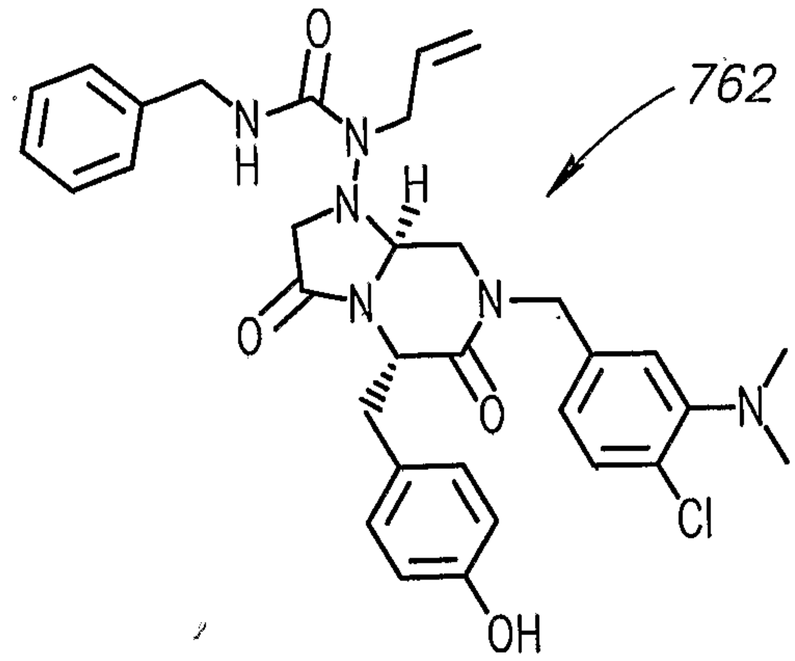
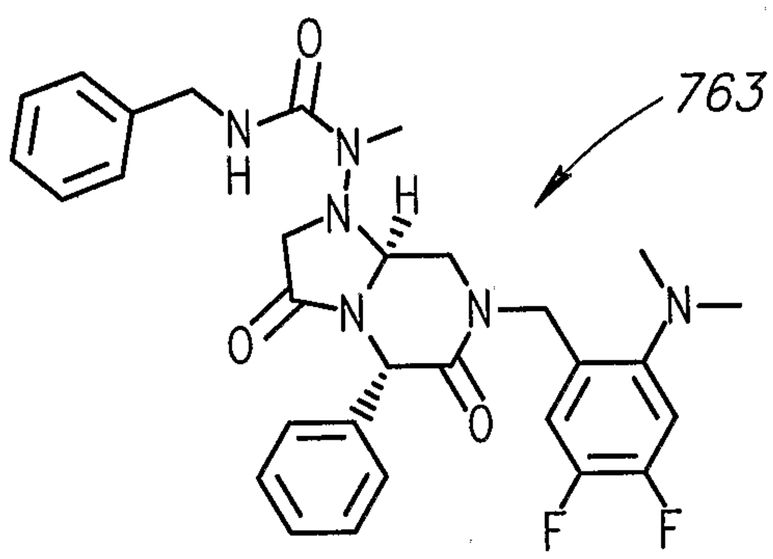
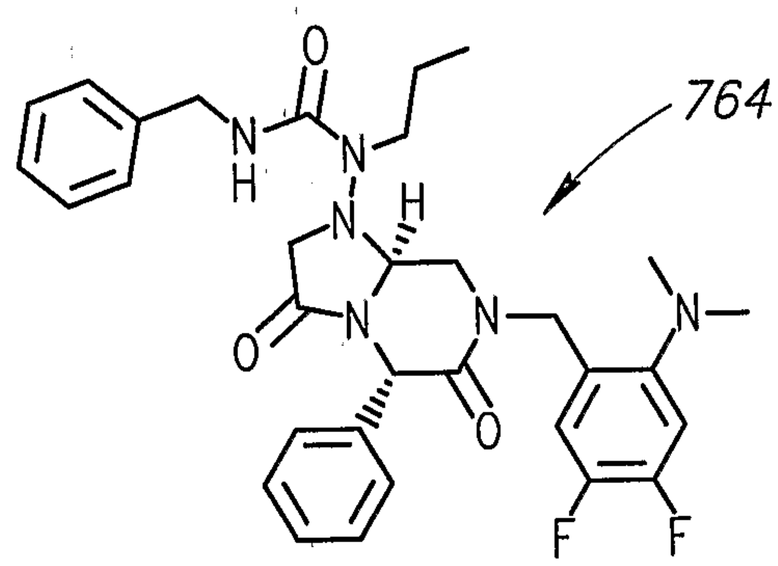
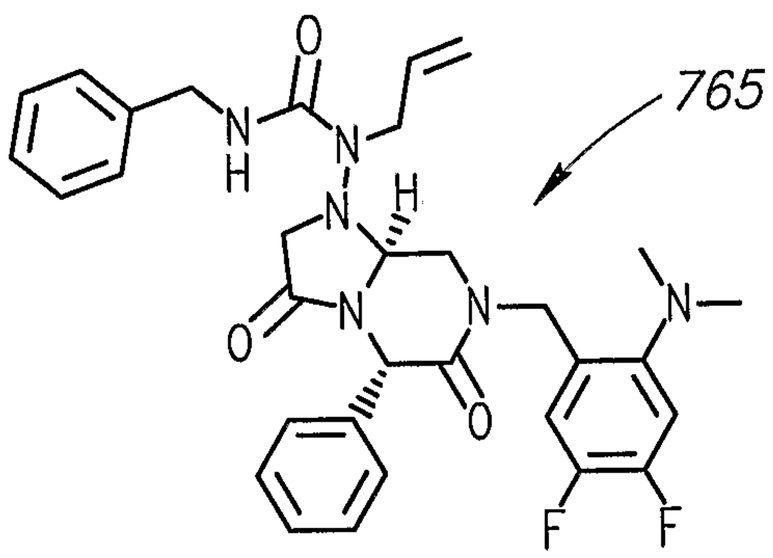
FIG.4T

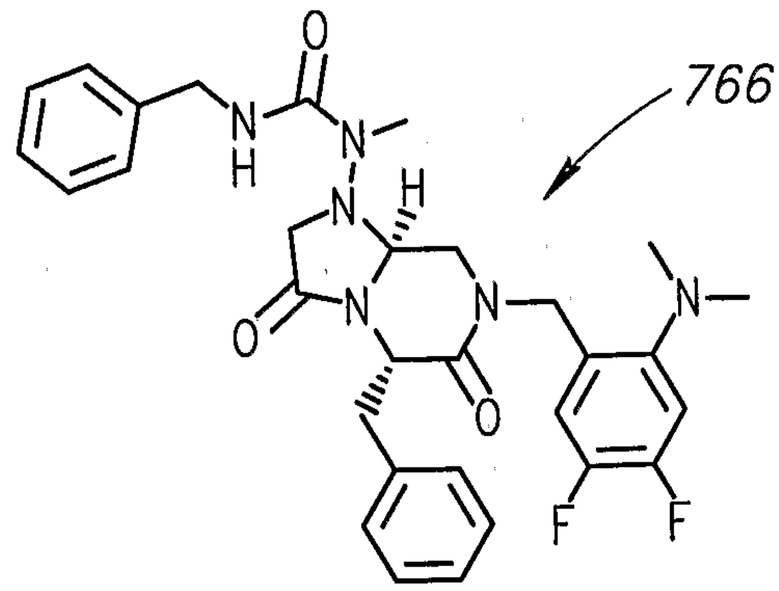


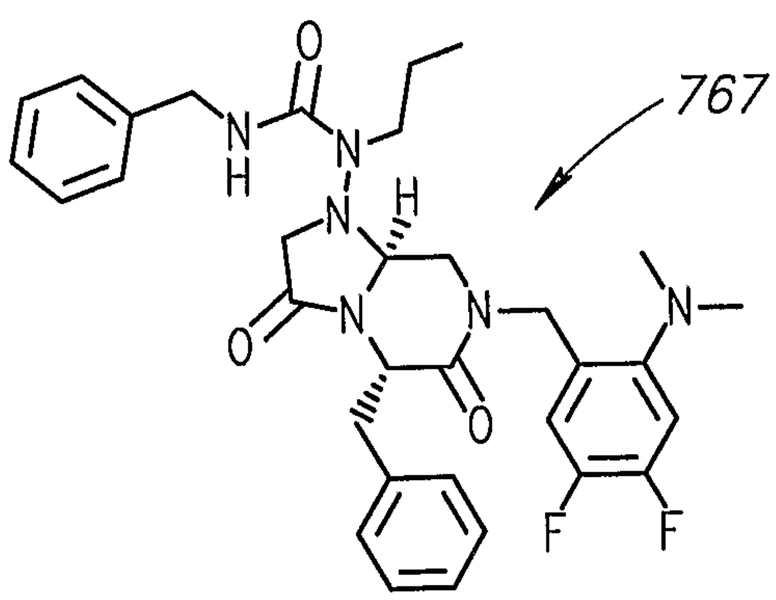












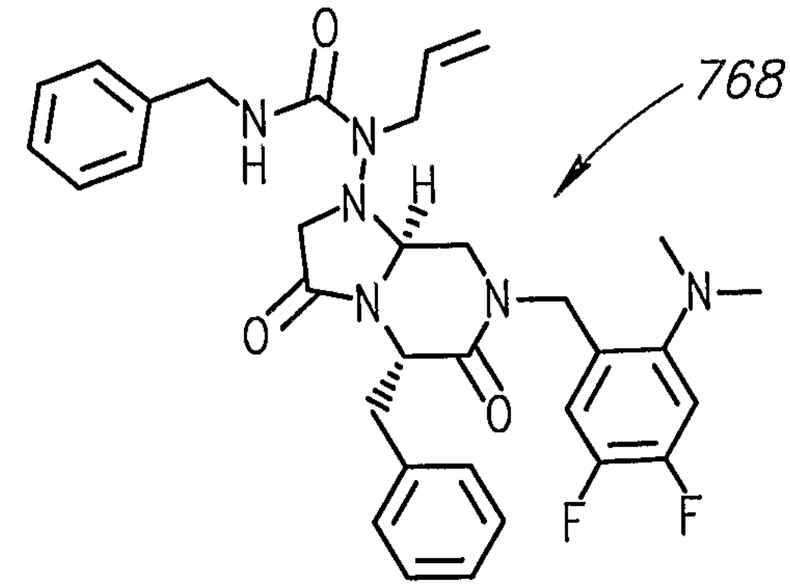
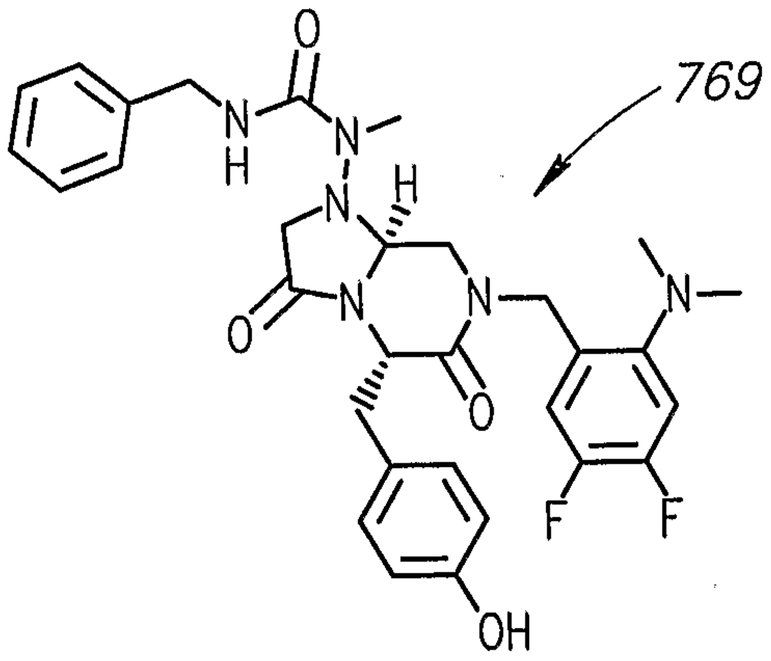
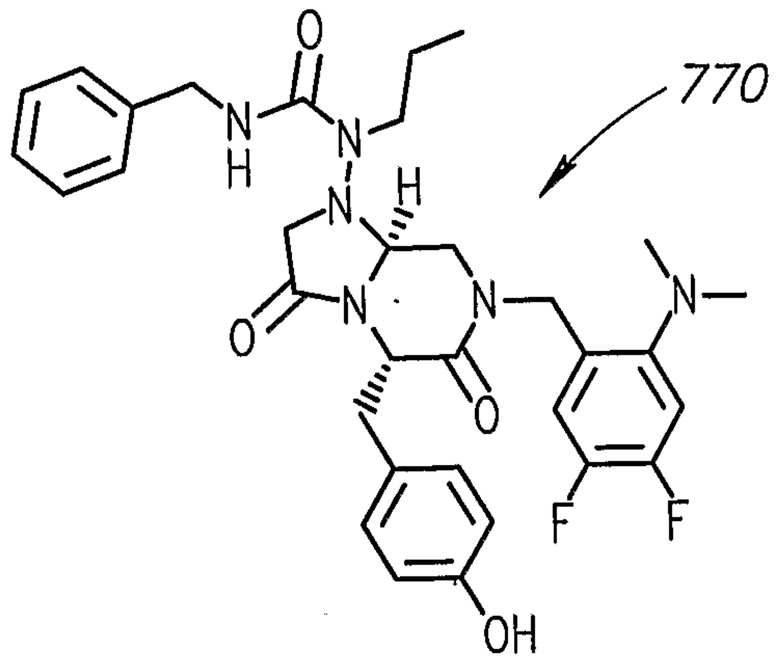
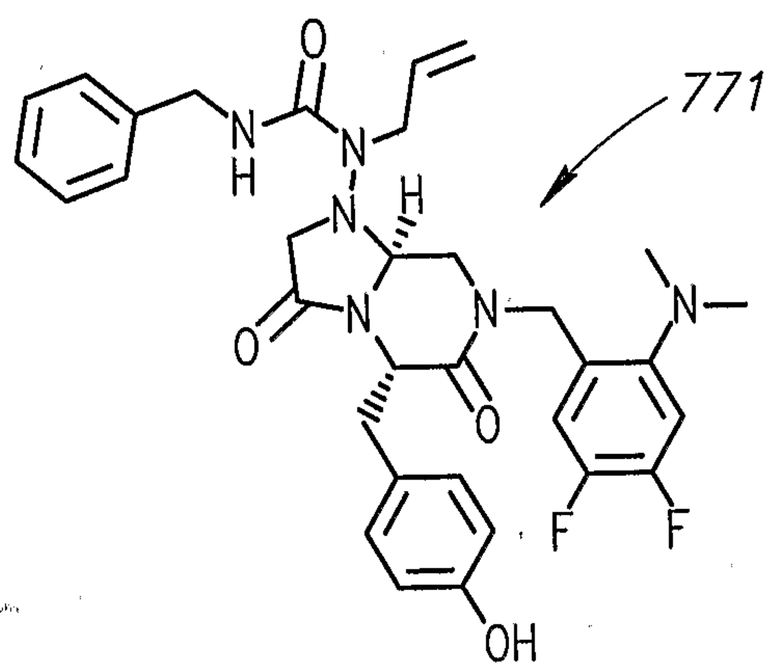
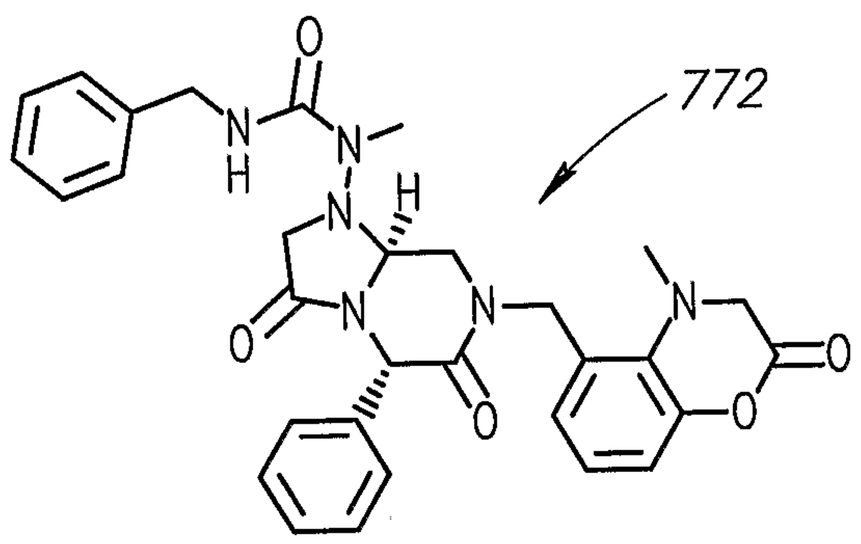


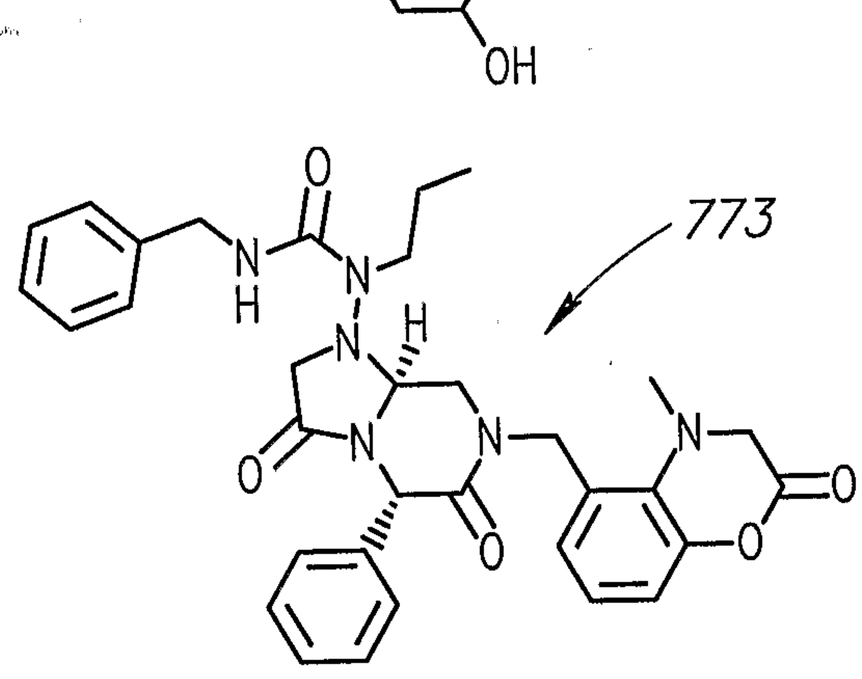
FIG.4U











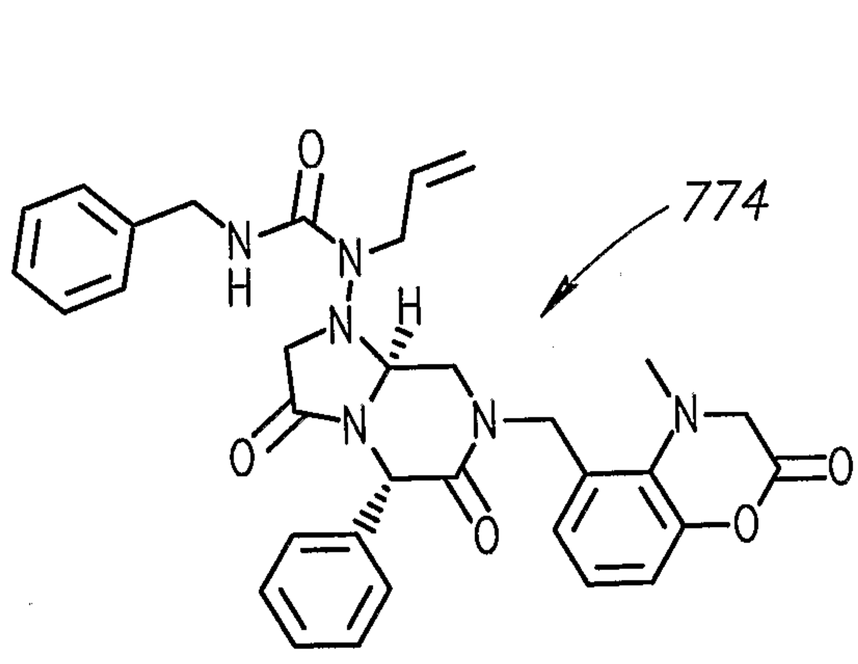
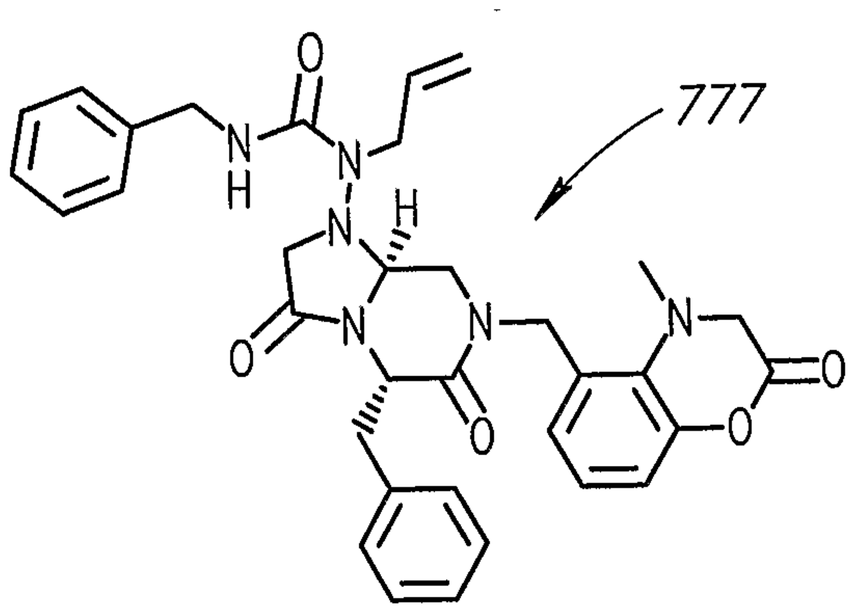
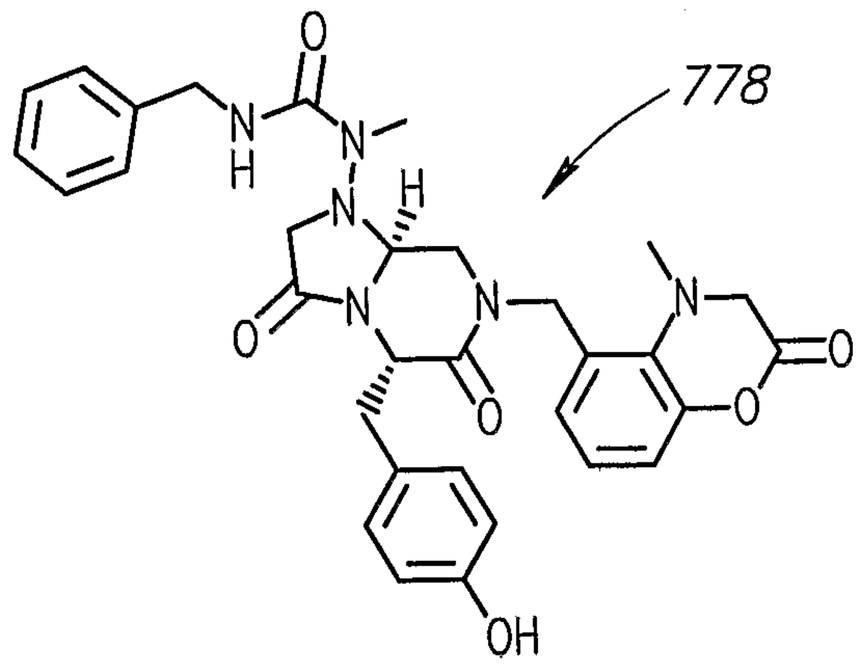
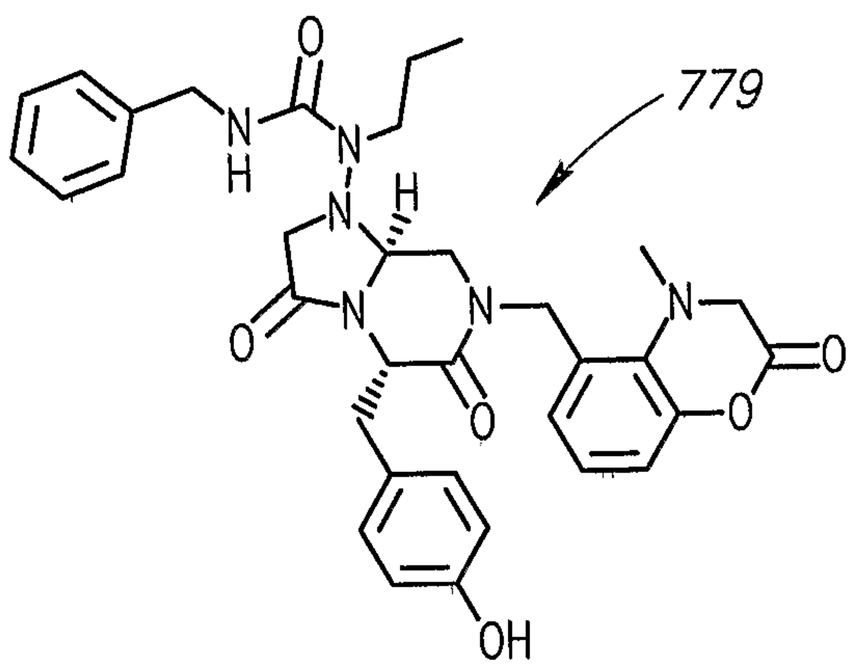
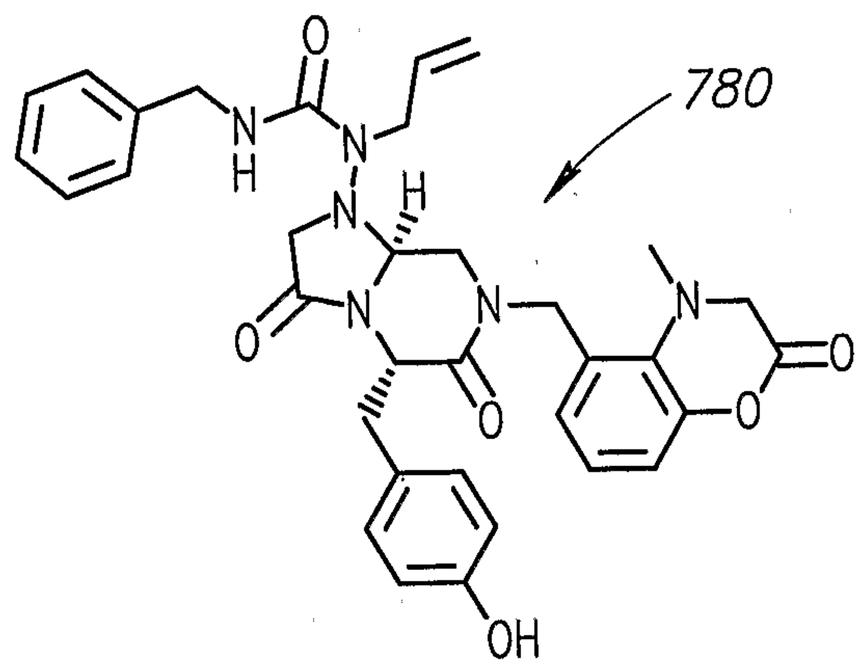


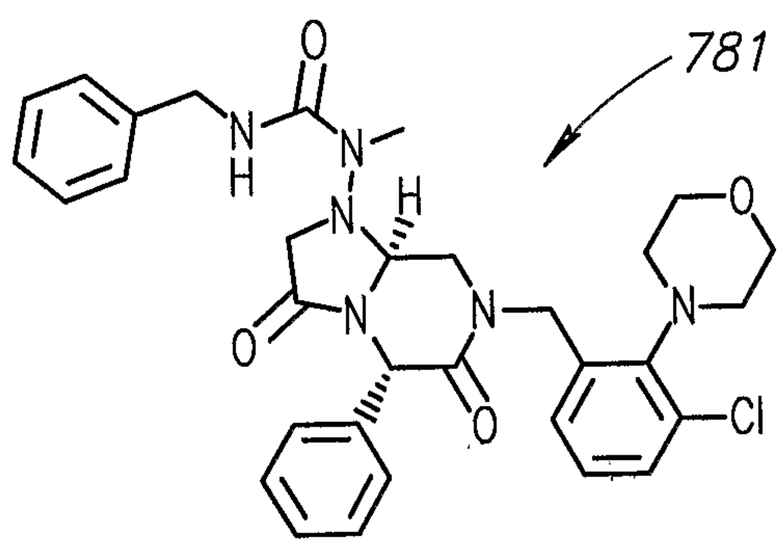
FIG.4V











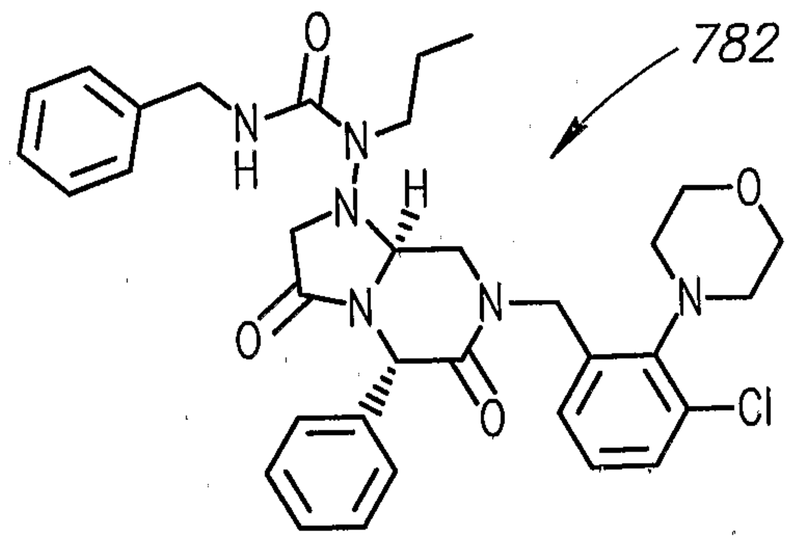
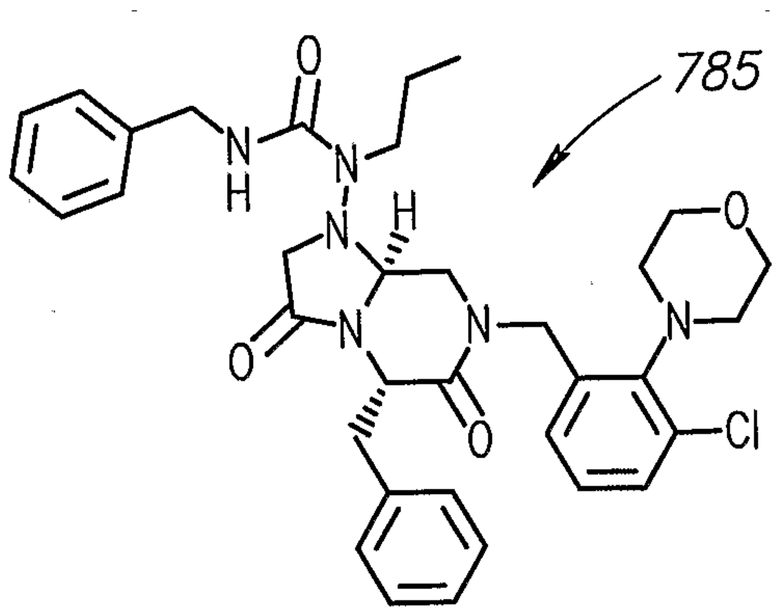
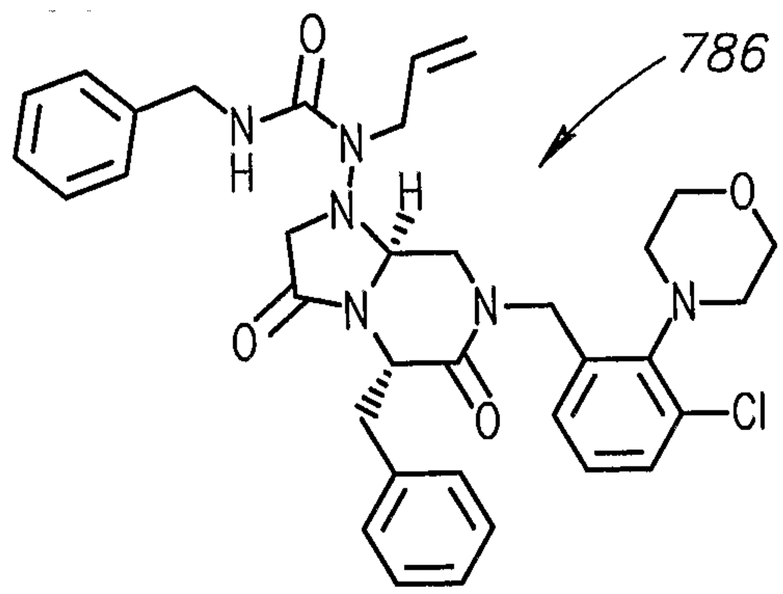
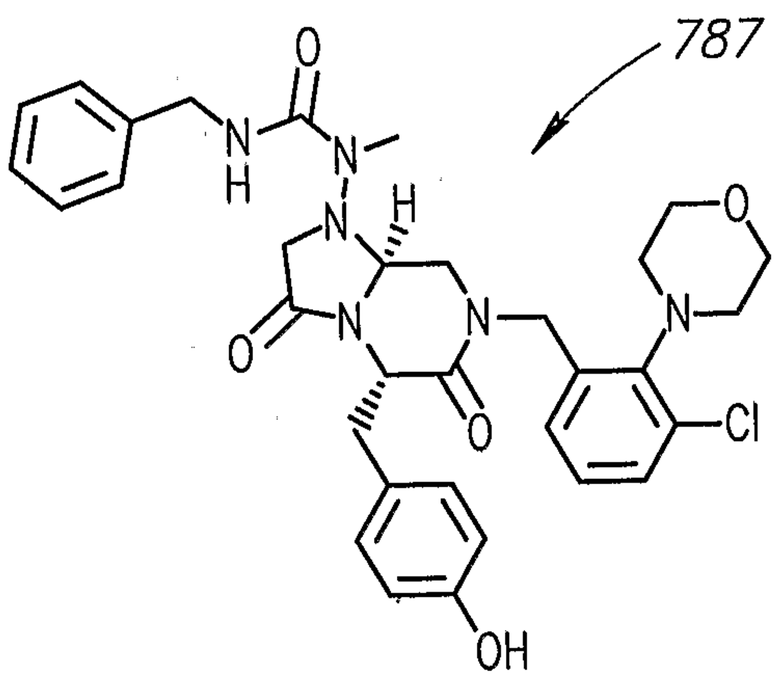
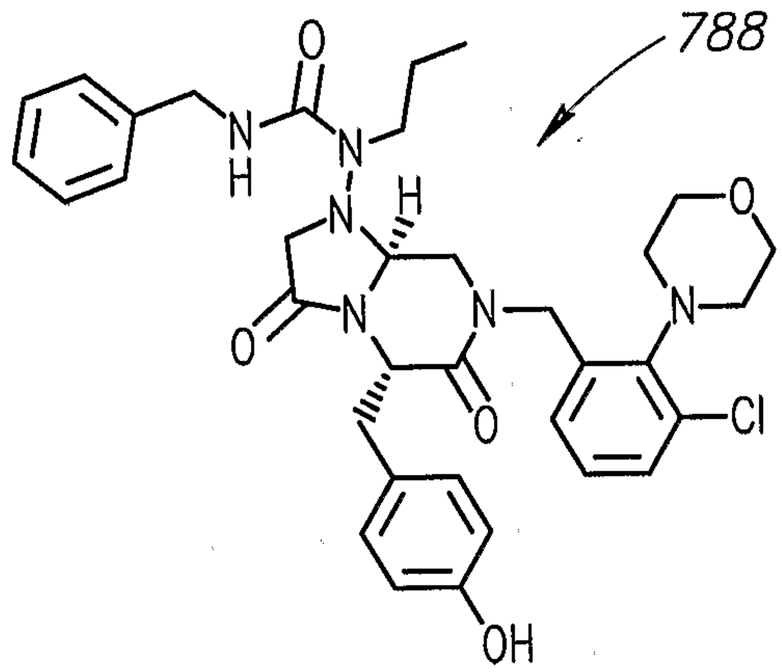


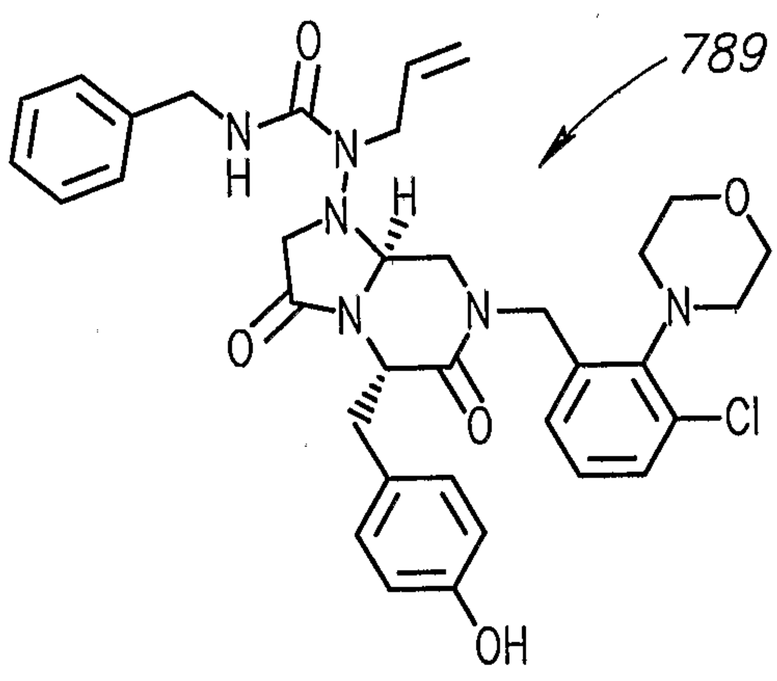
FIG.4W

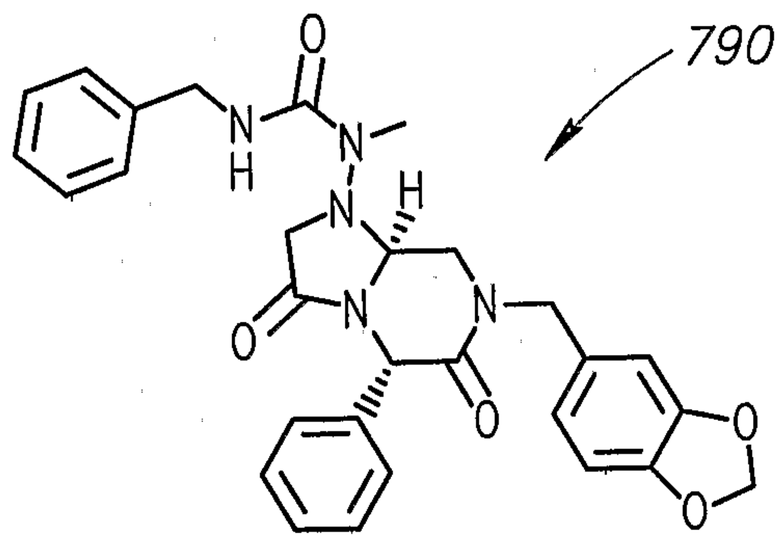


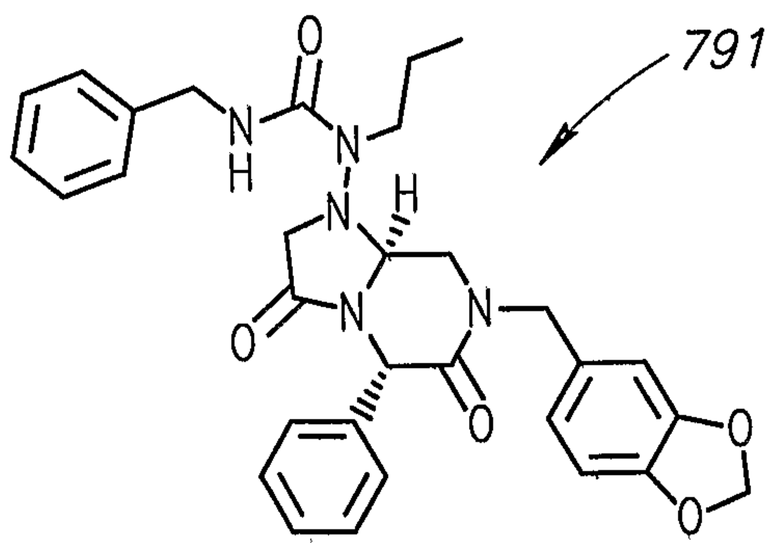












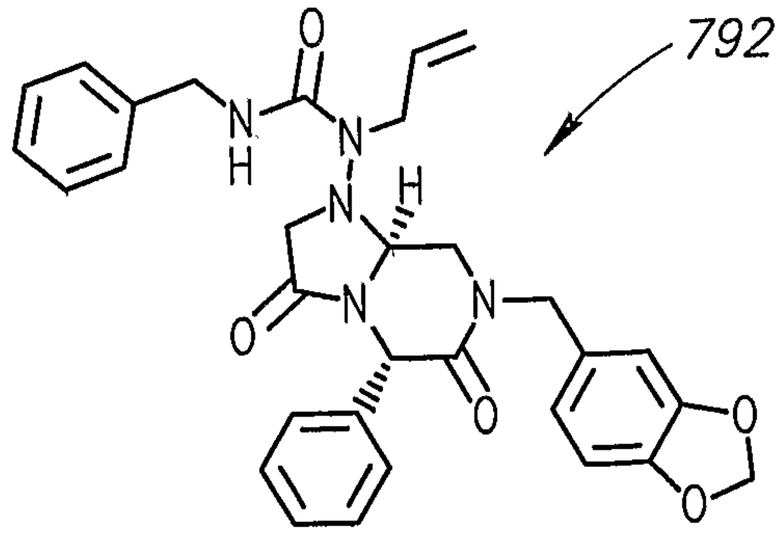
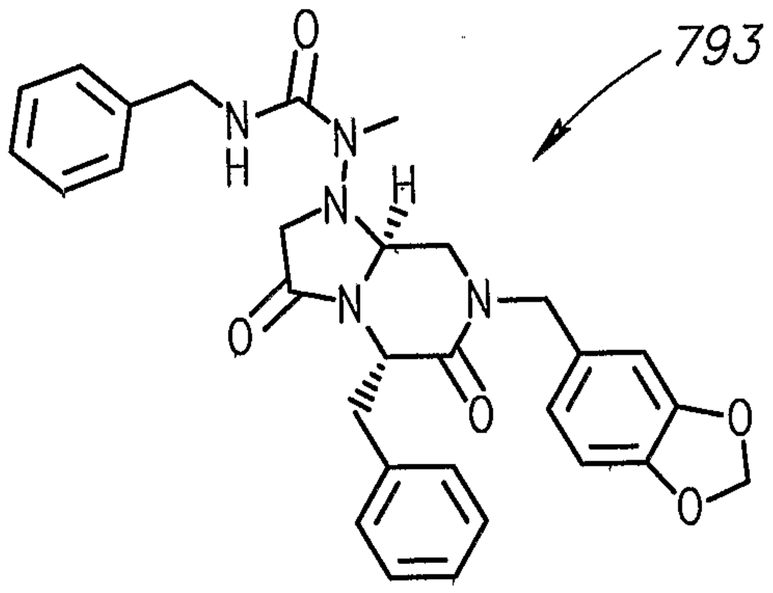
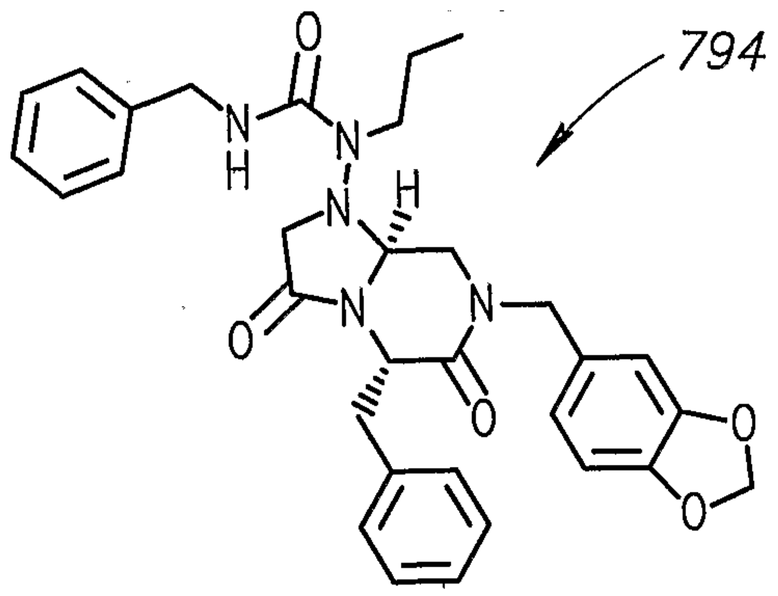
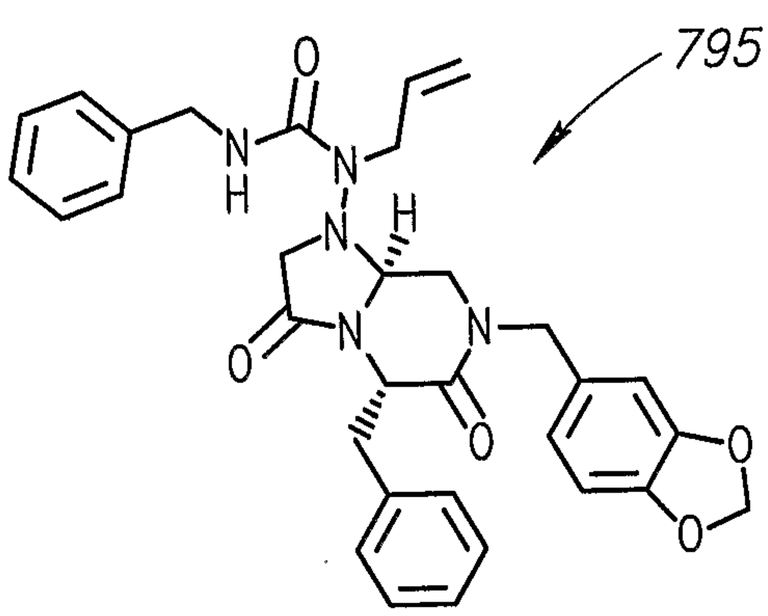
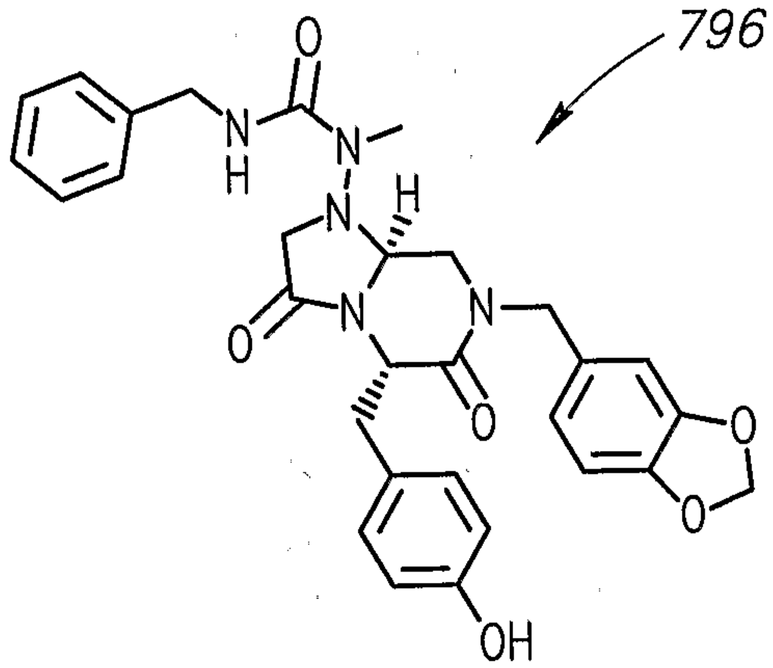


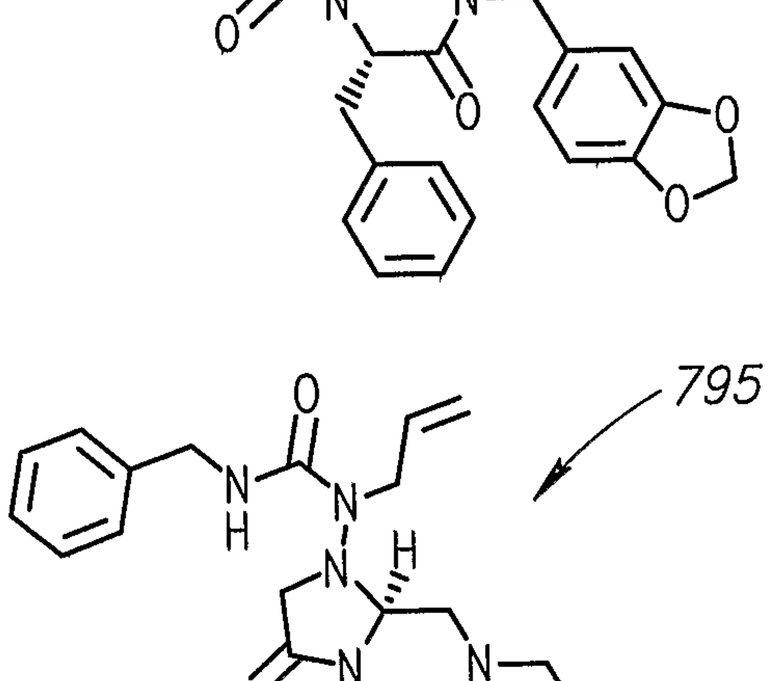
FIG.4X

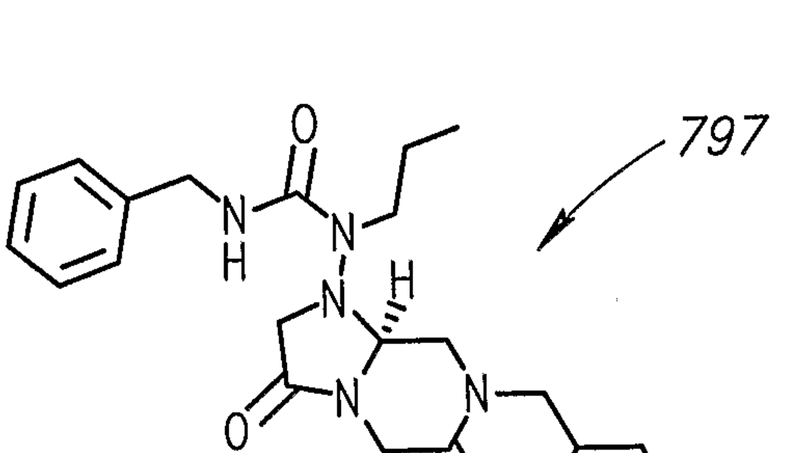












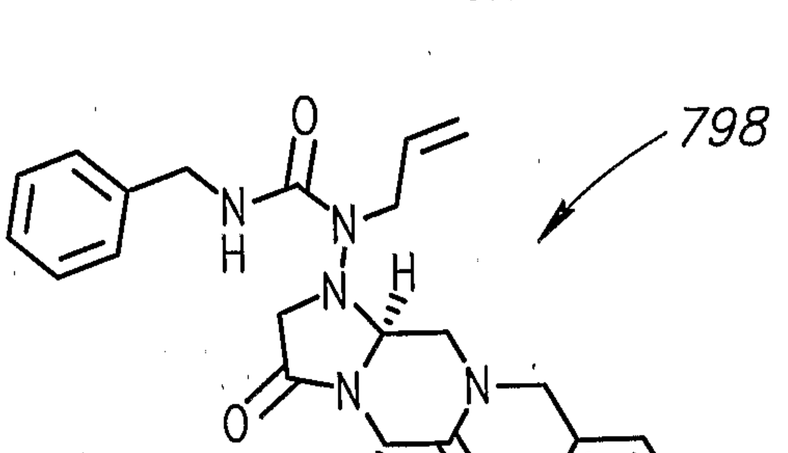
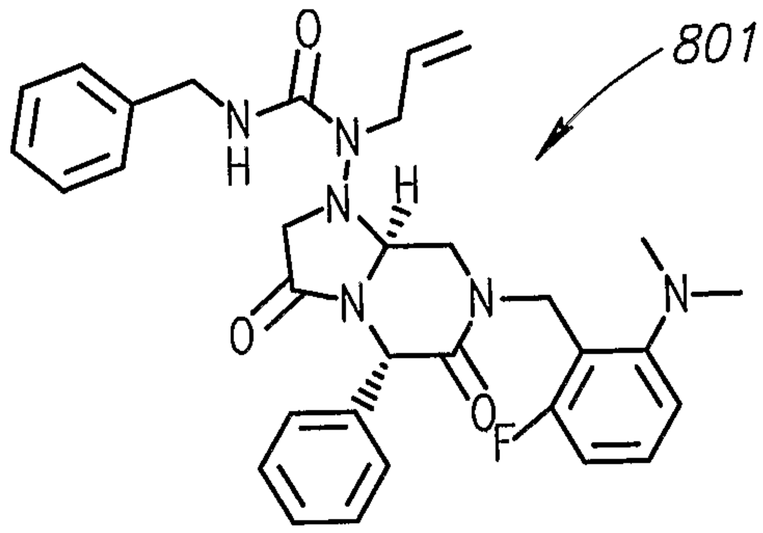
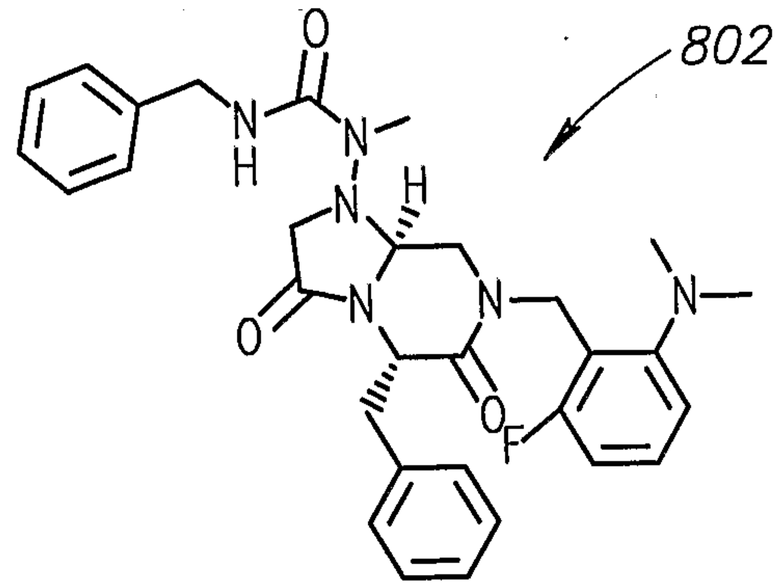
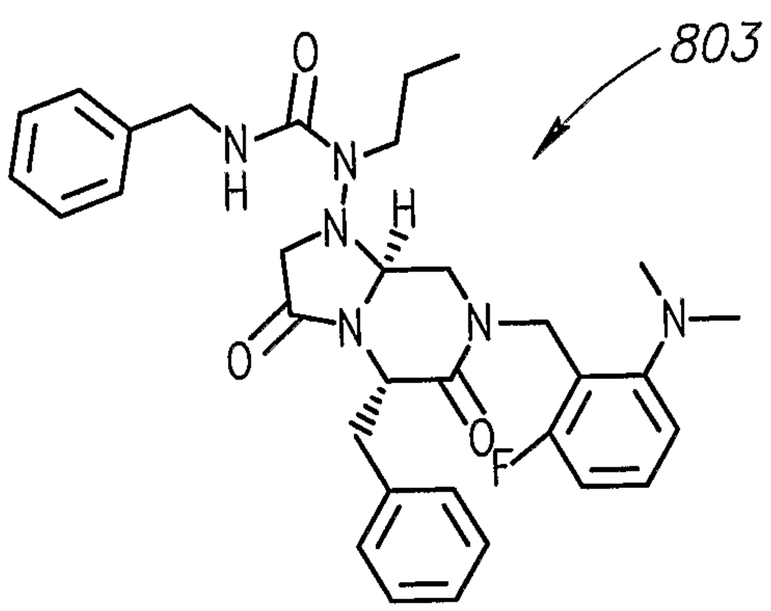
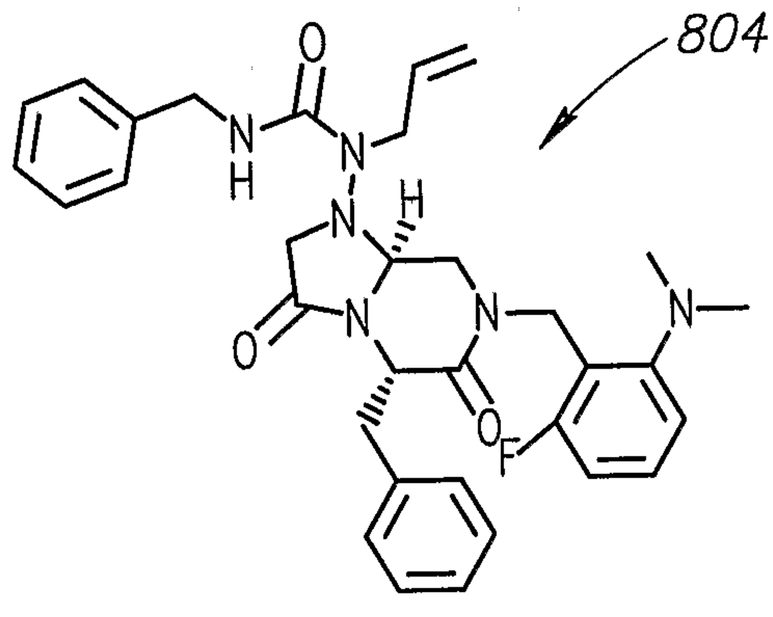


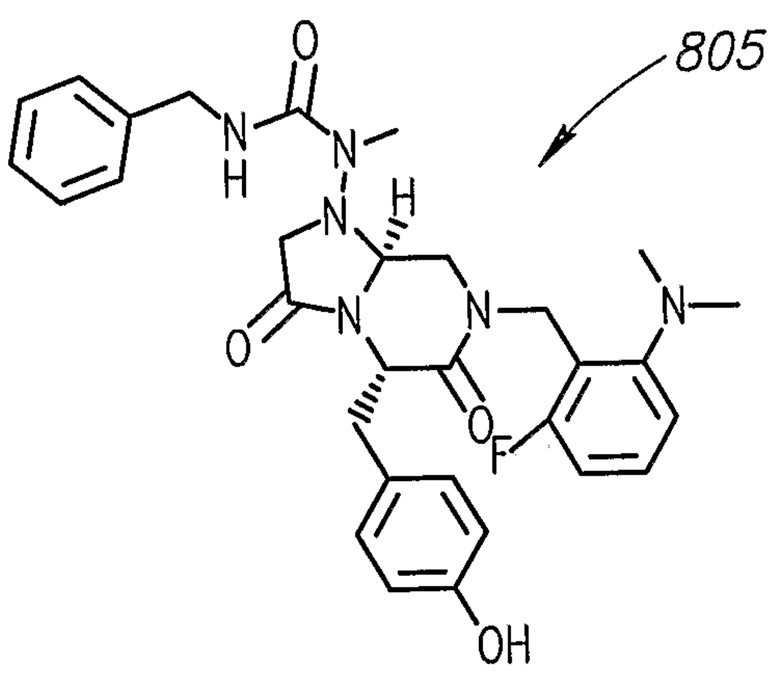
FIG.4Y

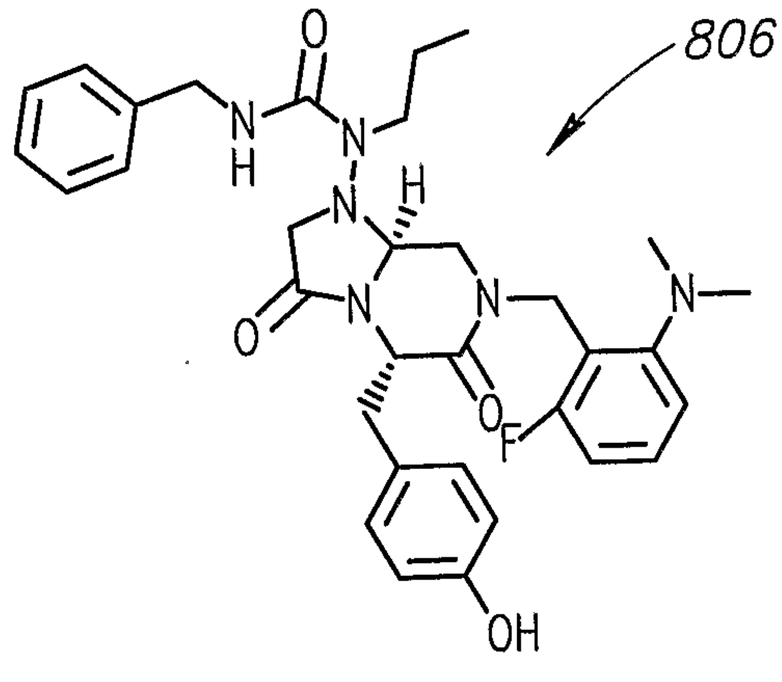


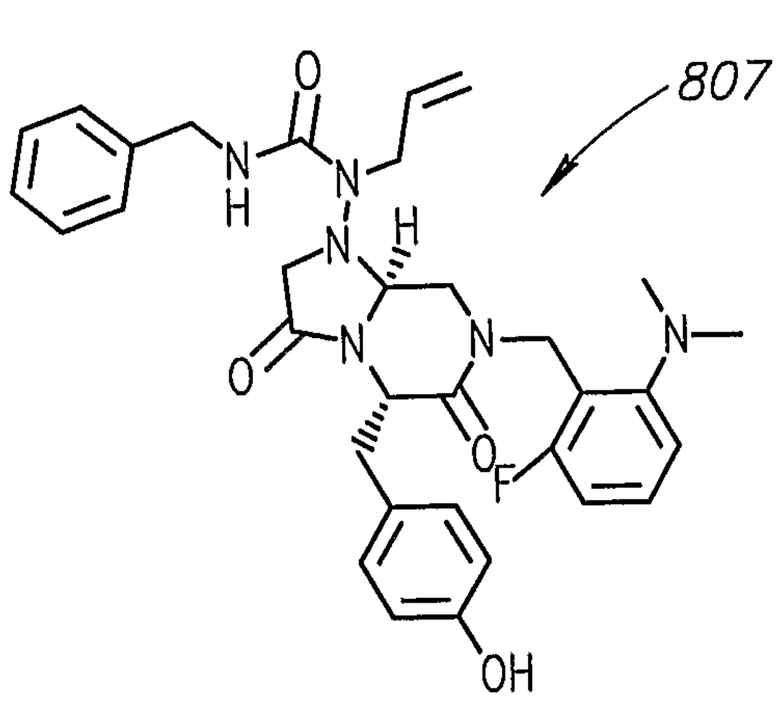












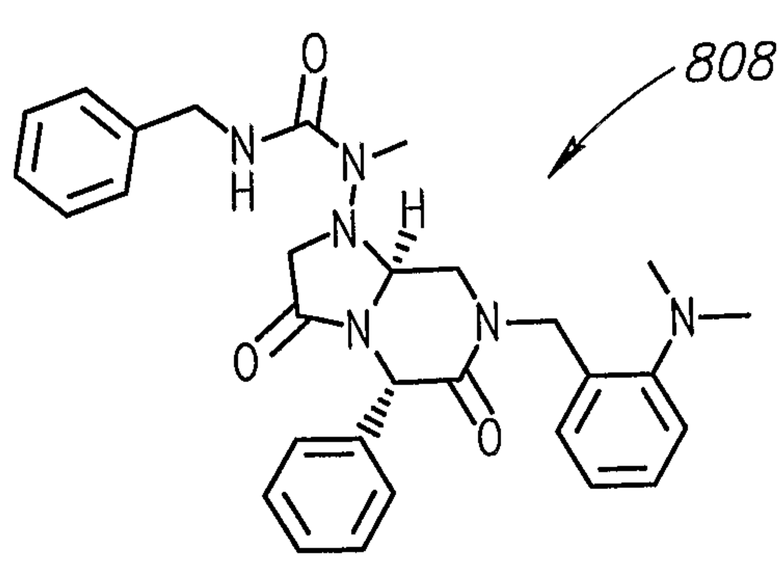
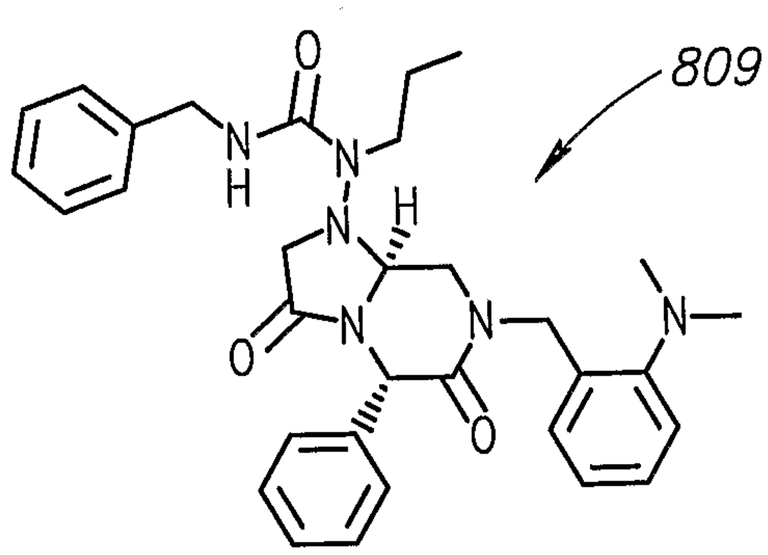
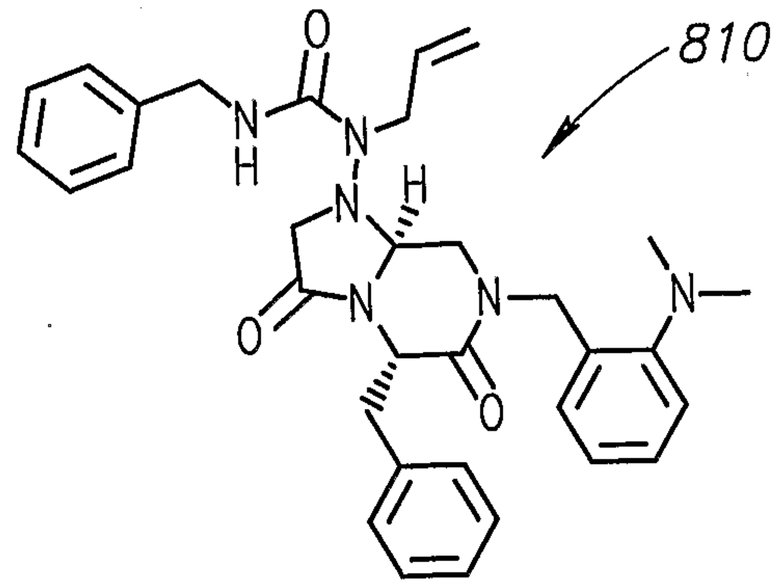
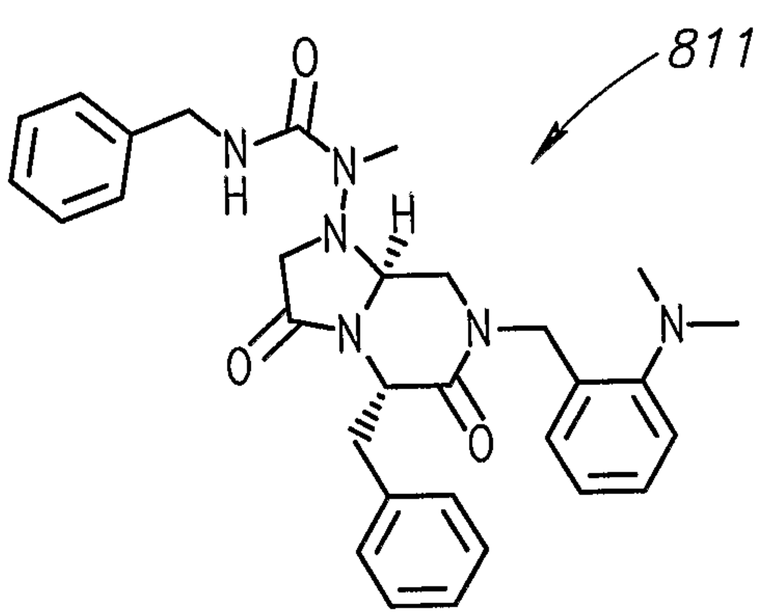
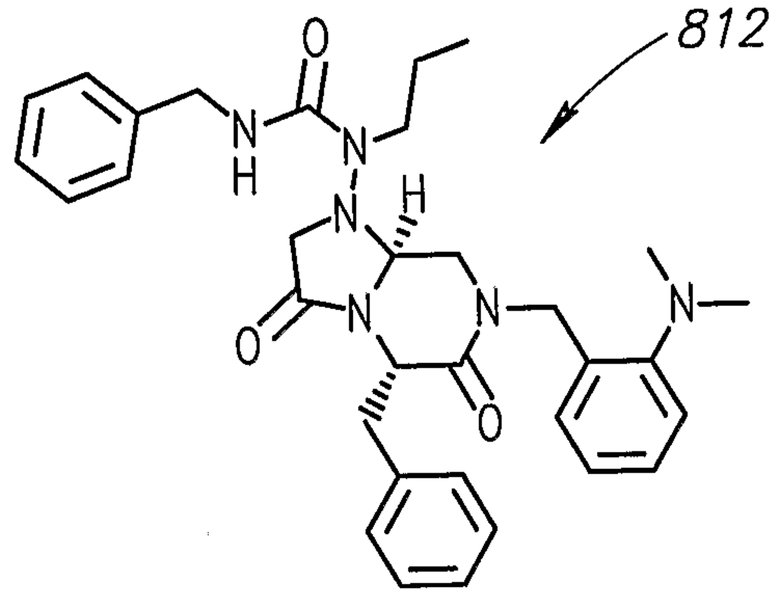


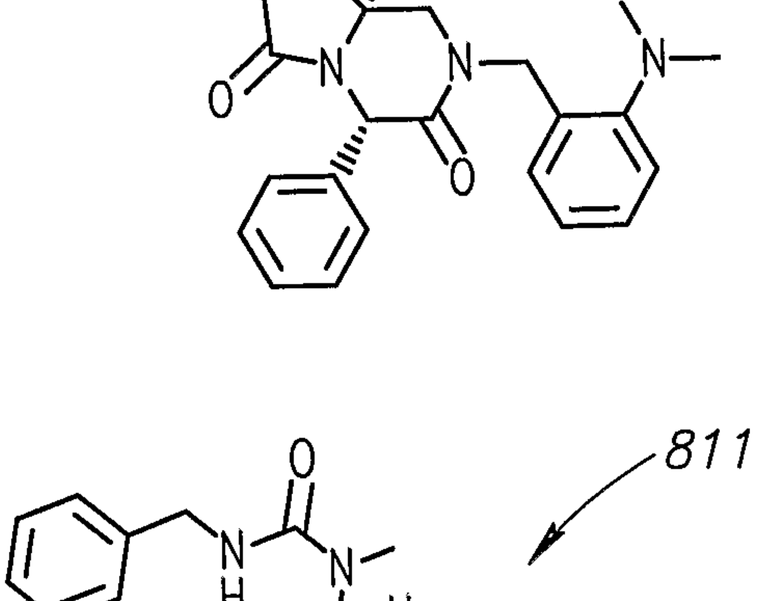
FIG.5A

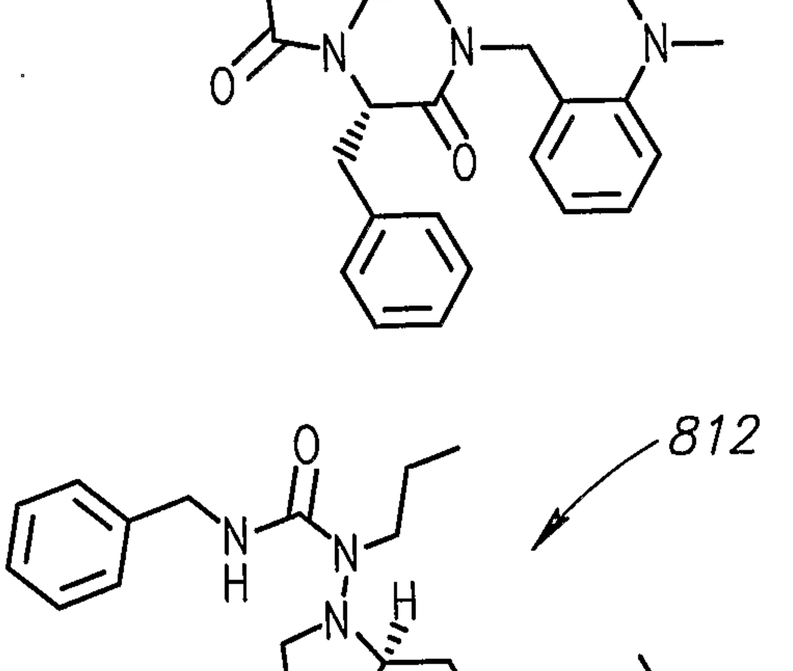


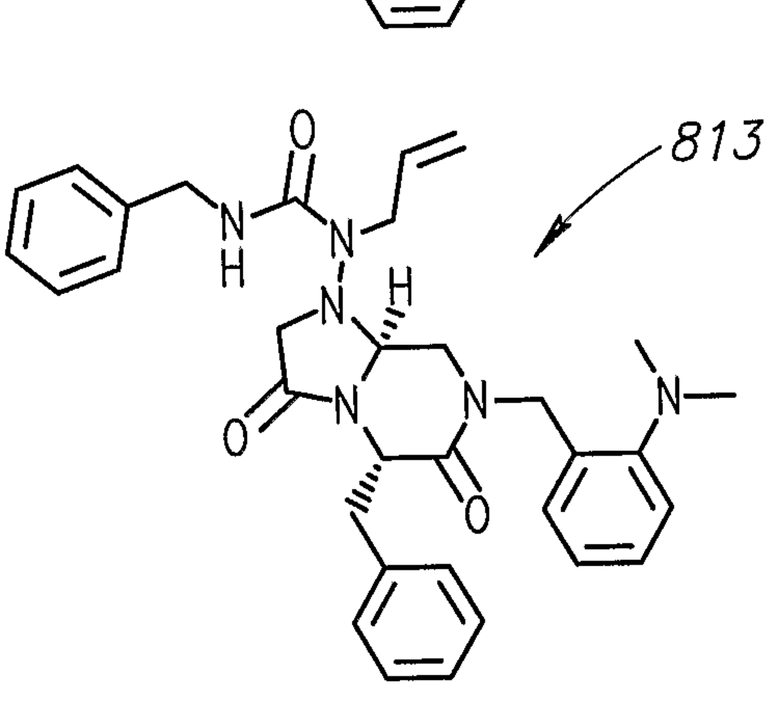












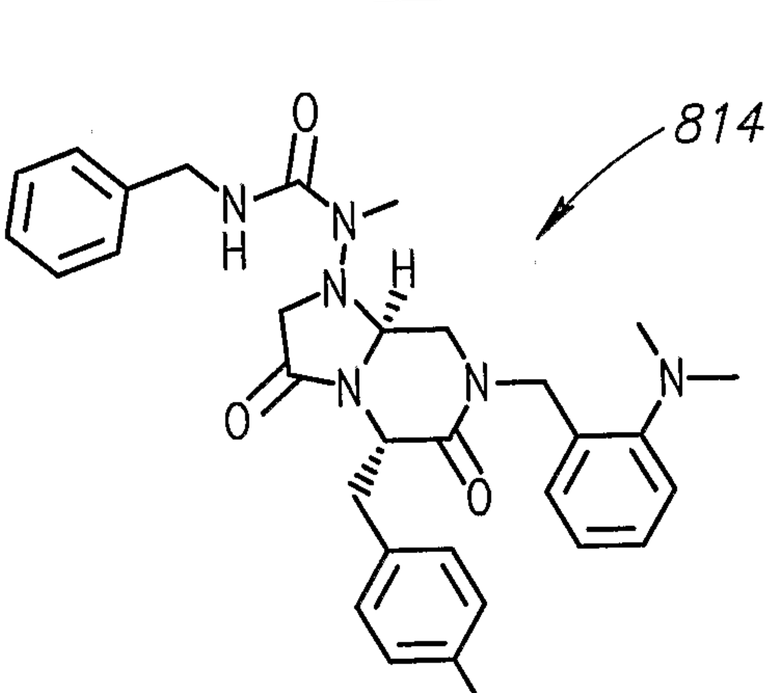
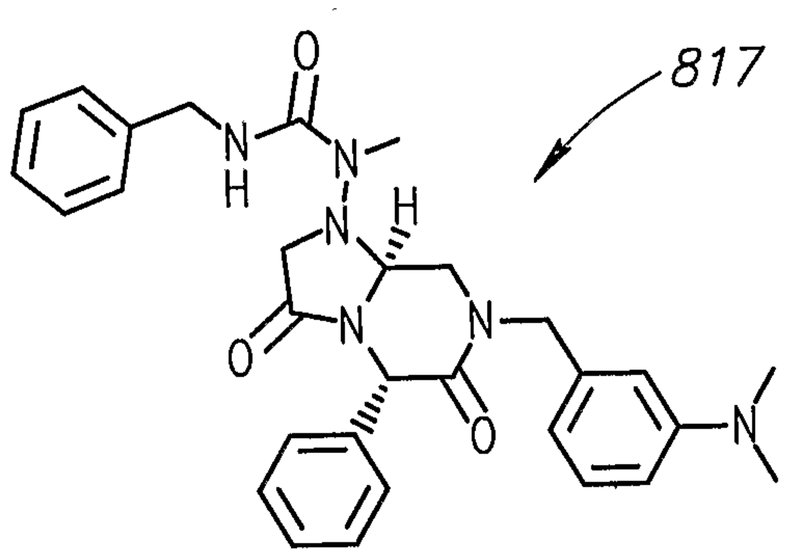
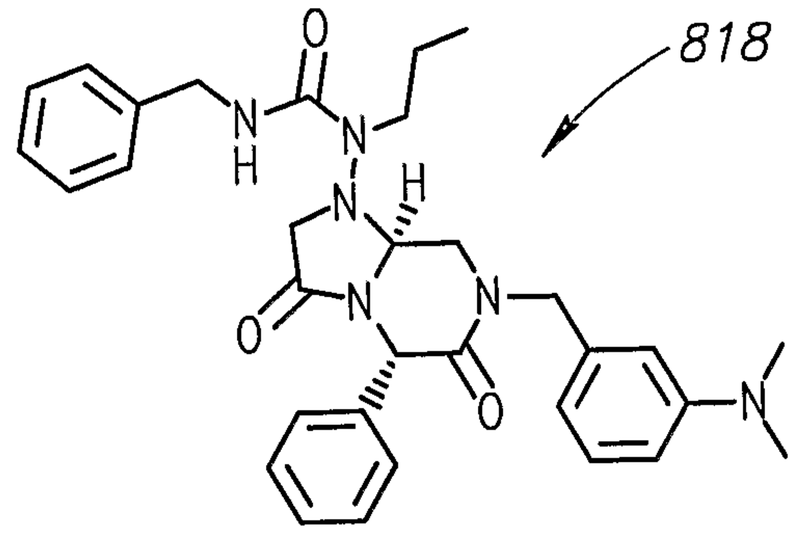
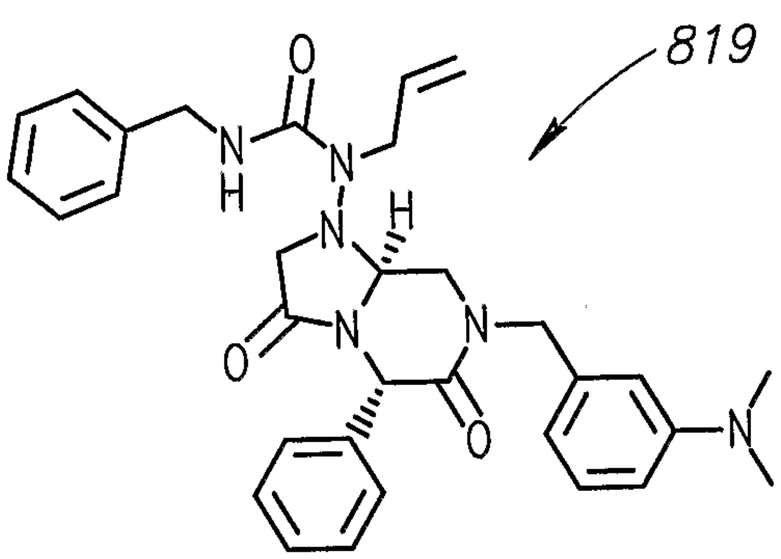
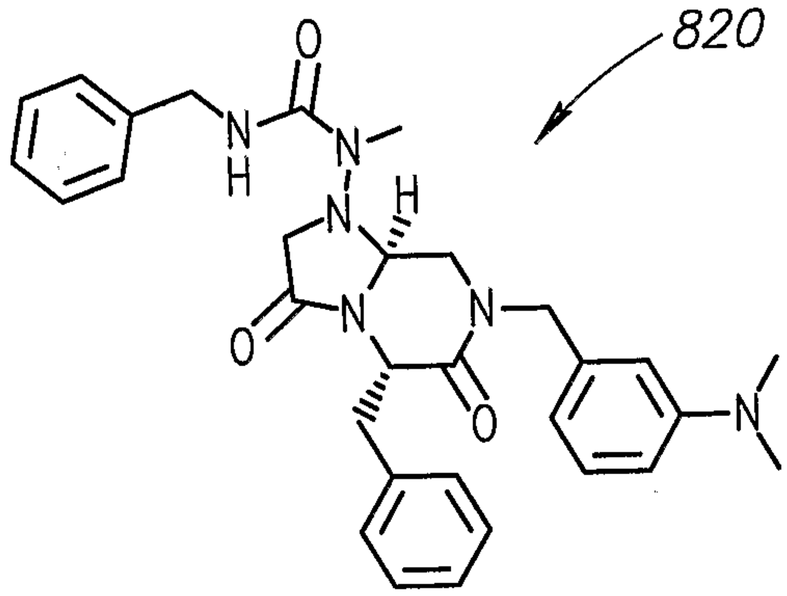


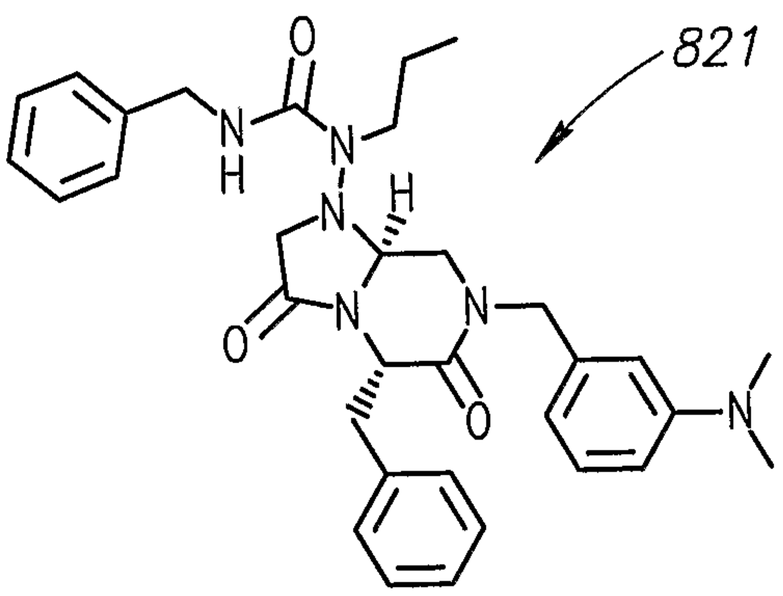
FIG.5B

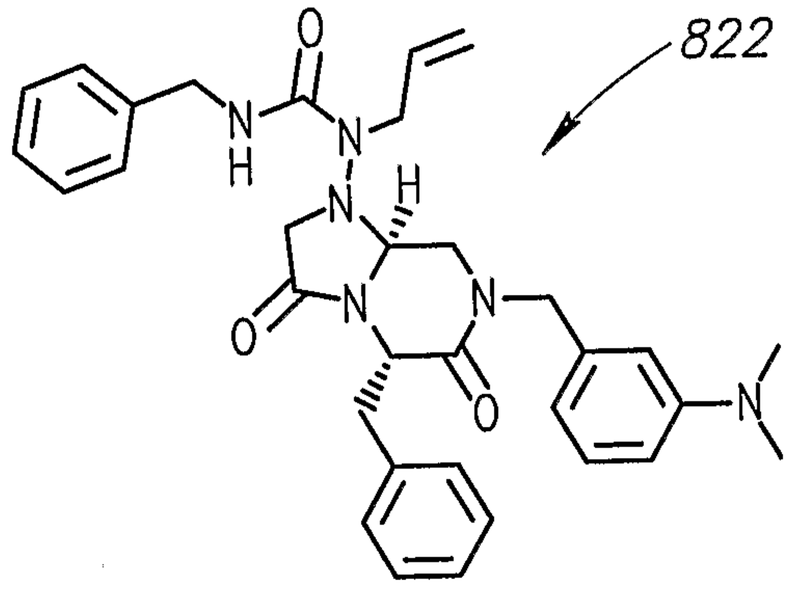


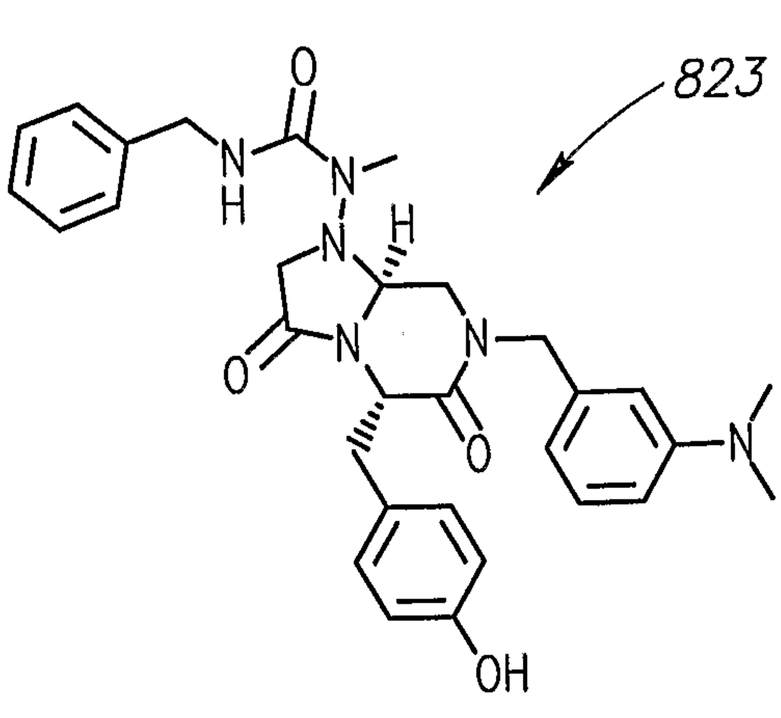












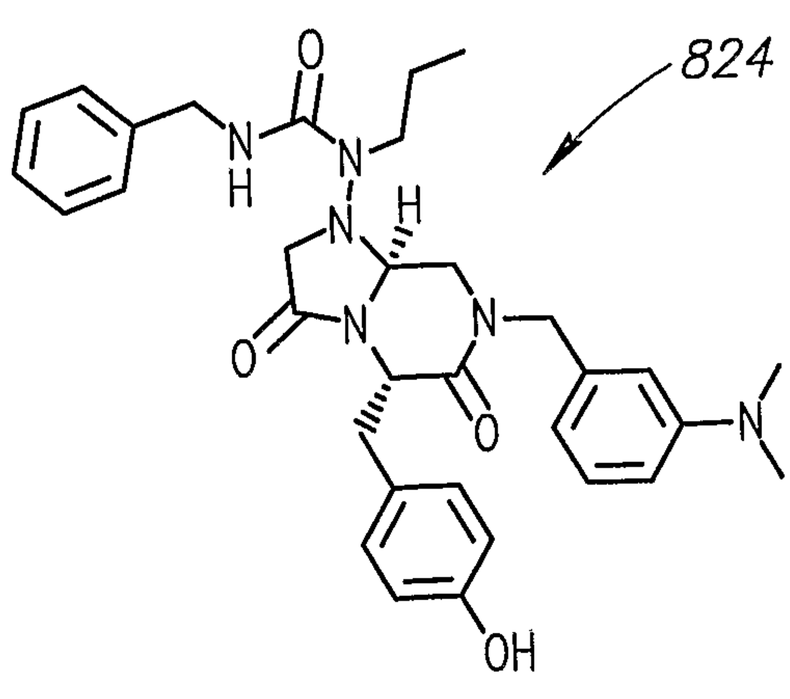
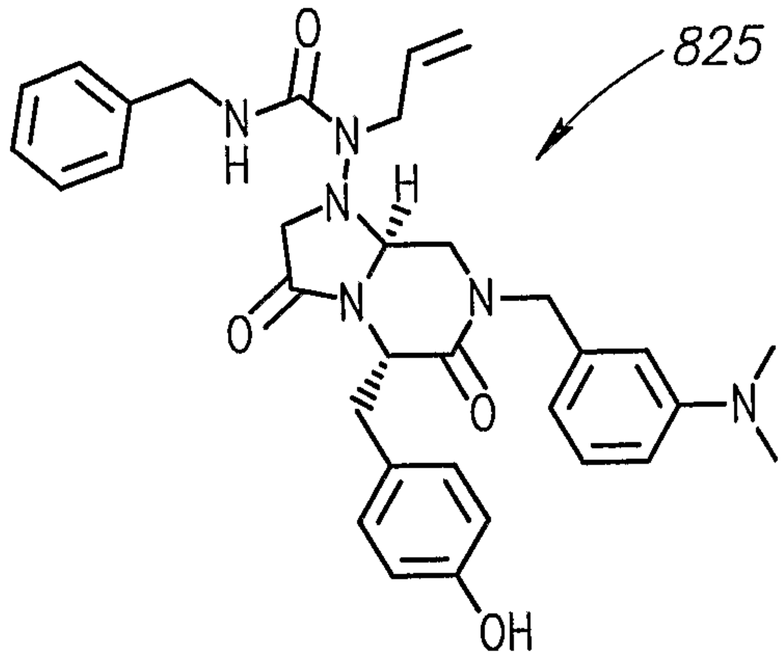


FIG.5C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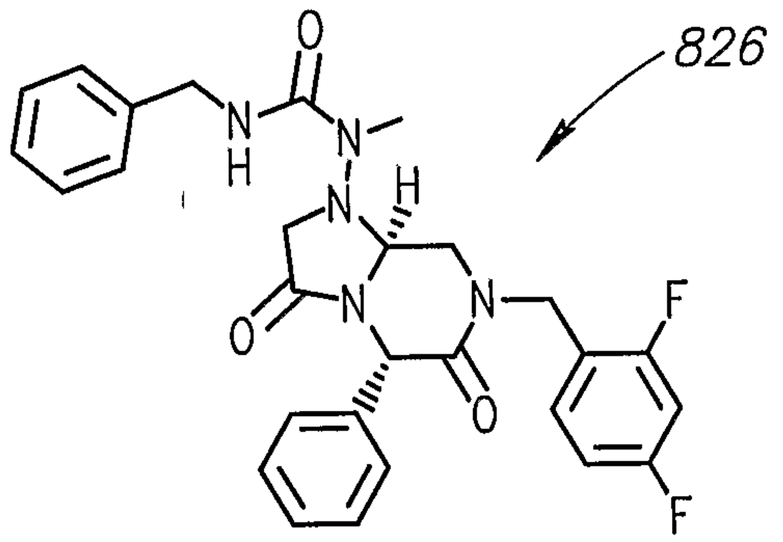
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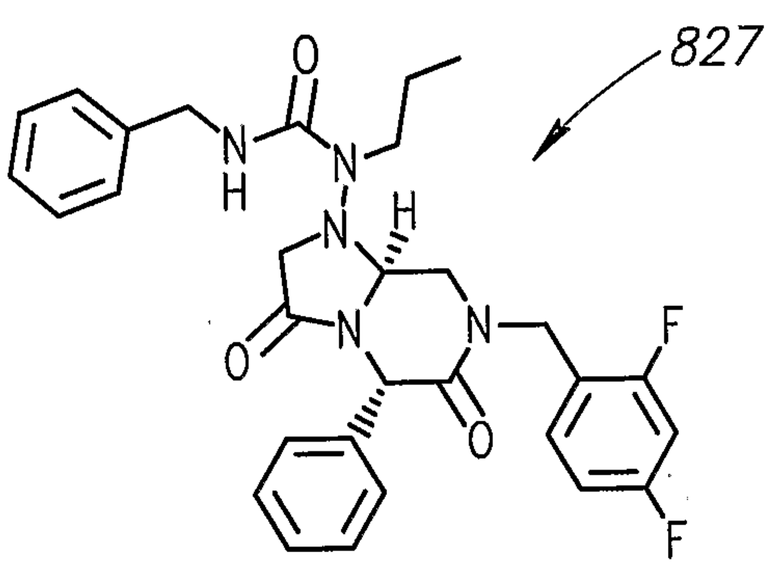
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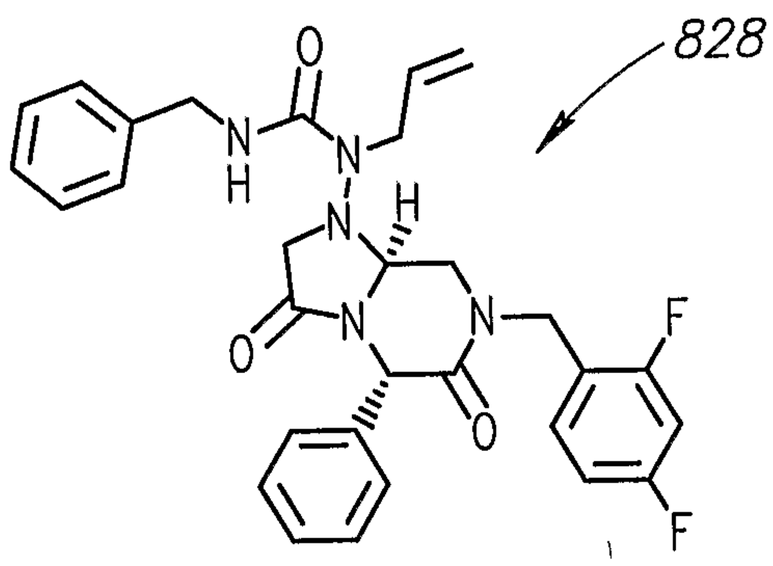
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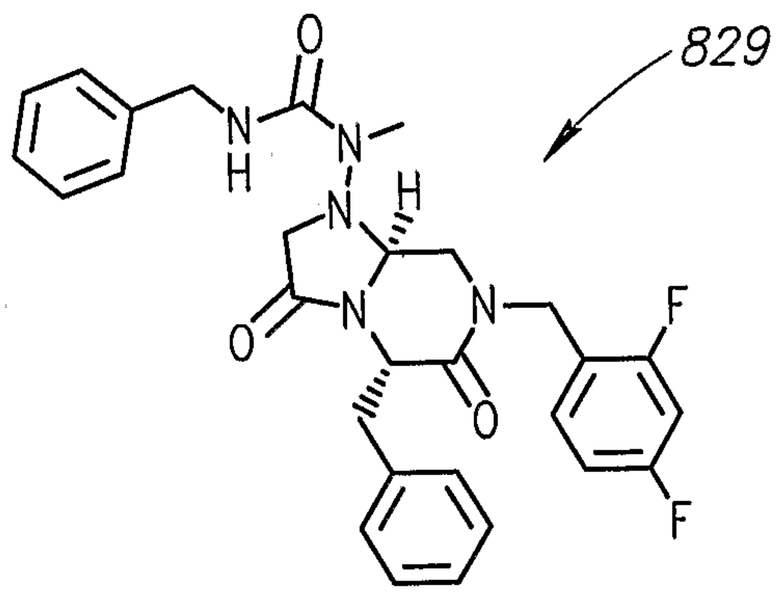
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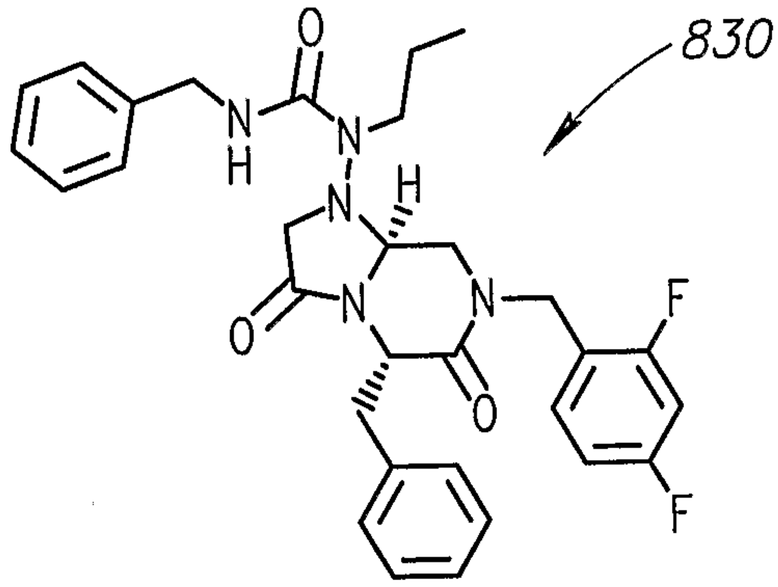
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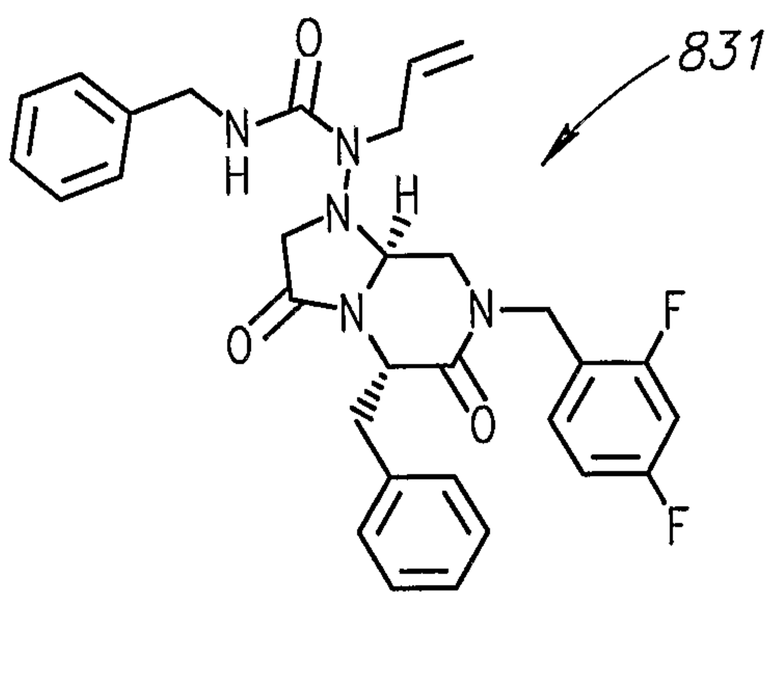
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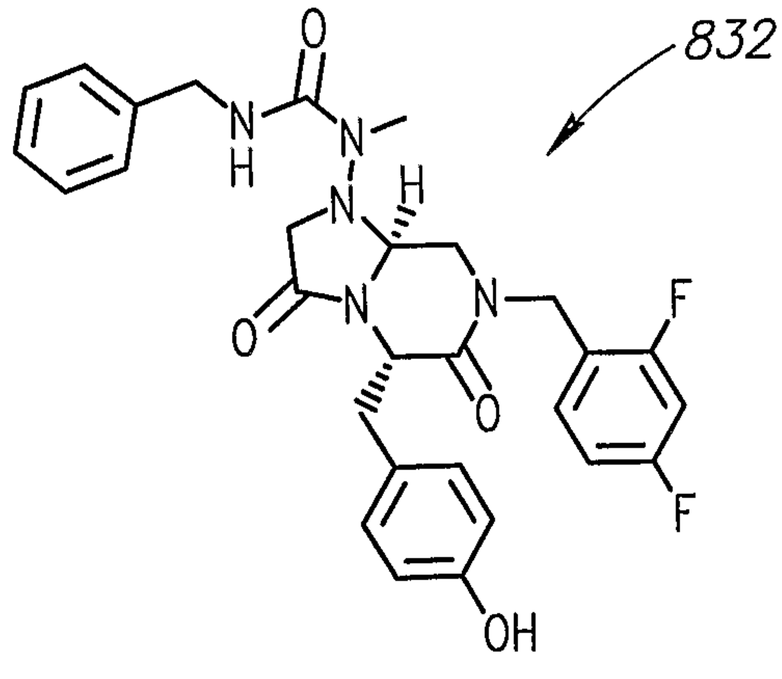
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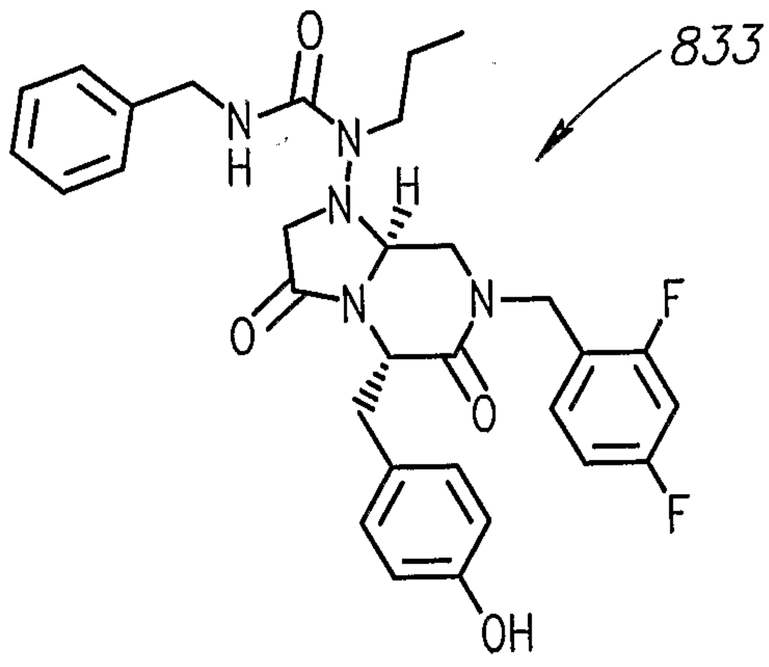
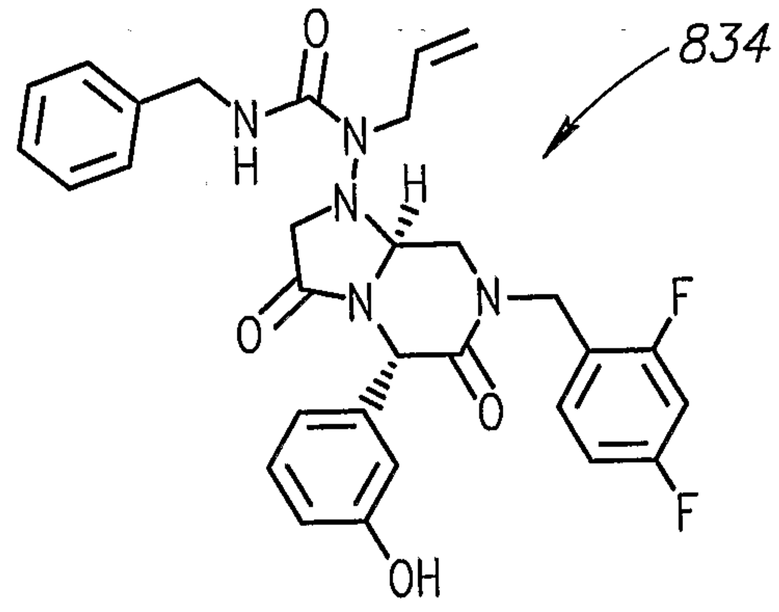
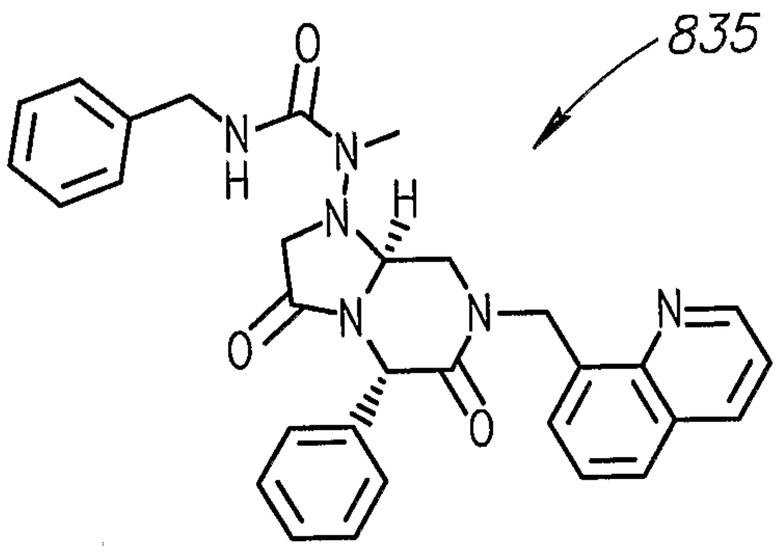
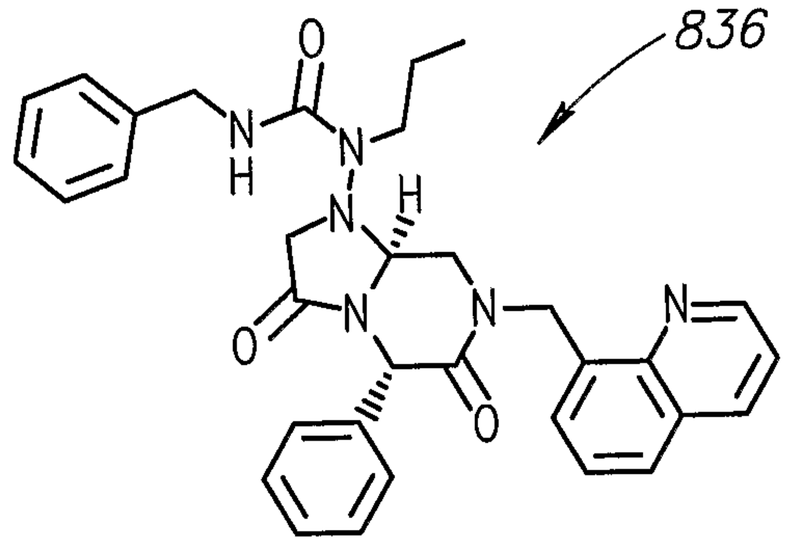
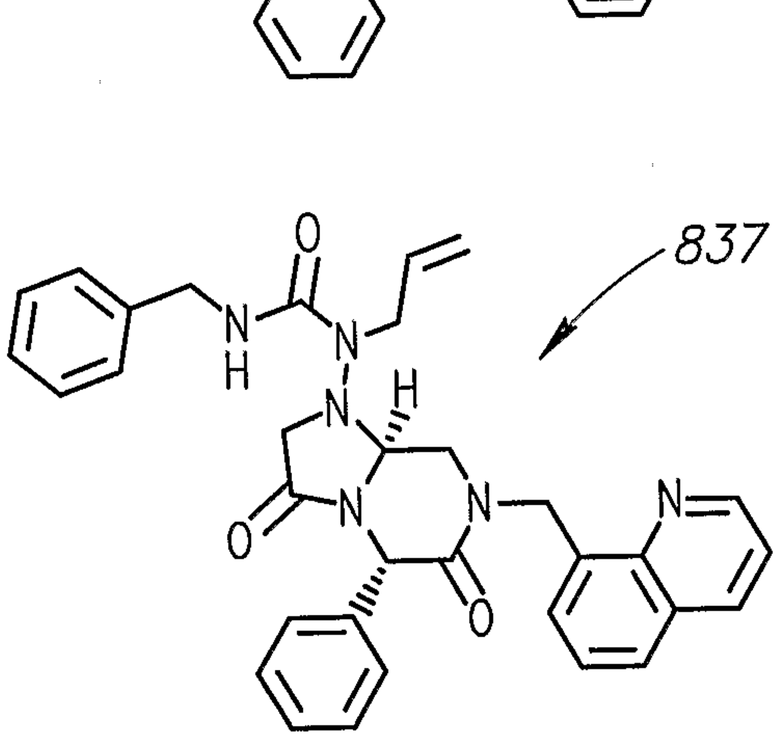
FIG.5D











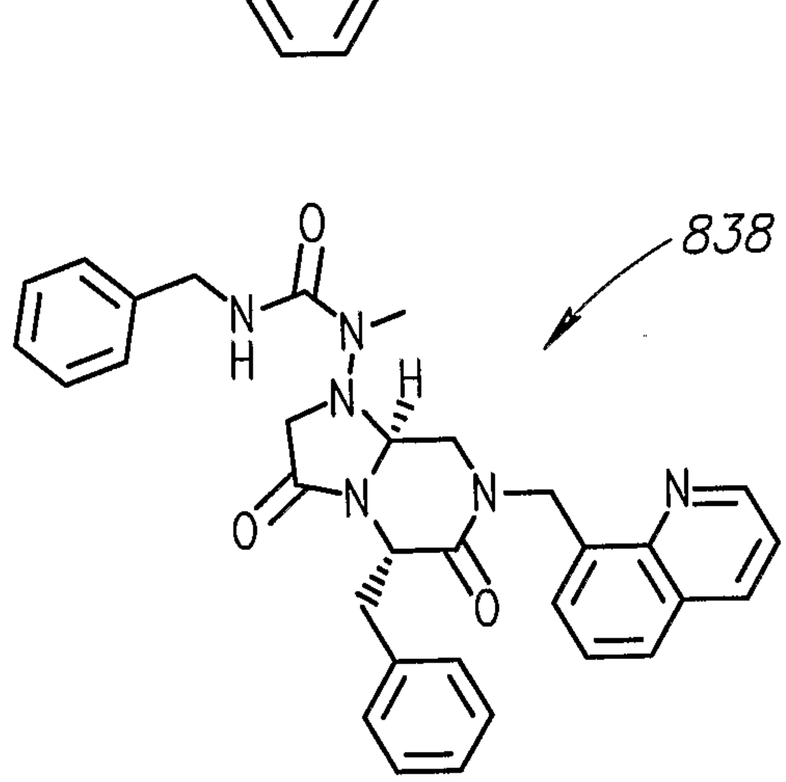
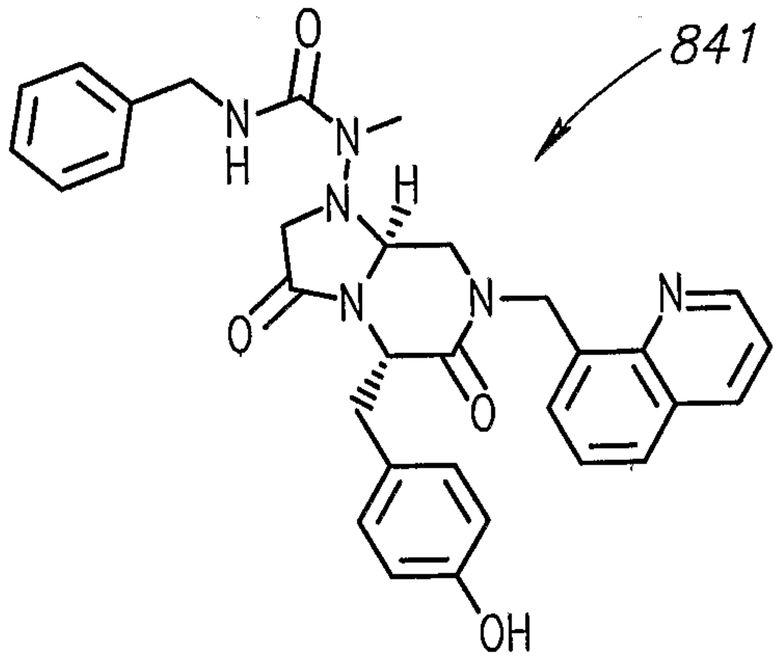
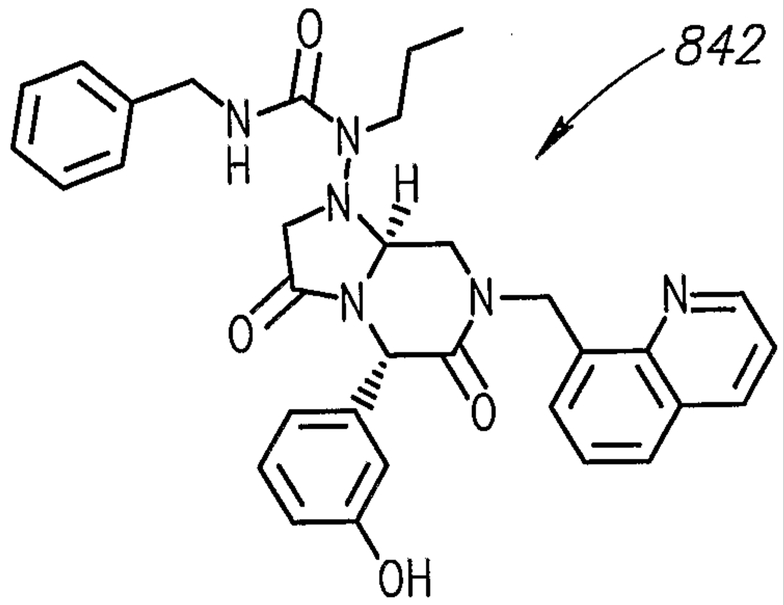
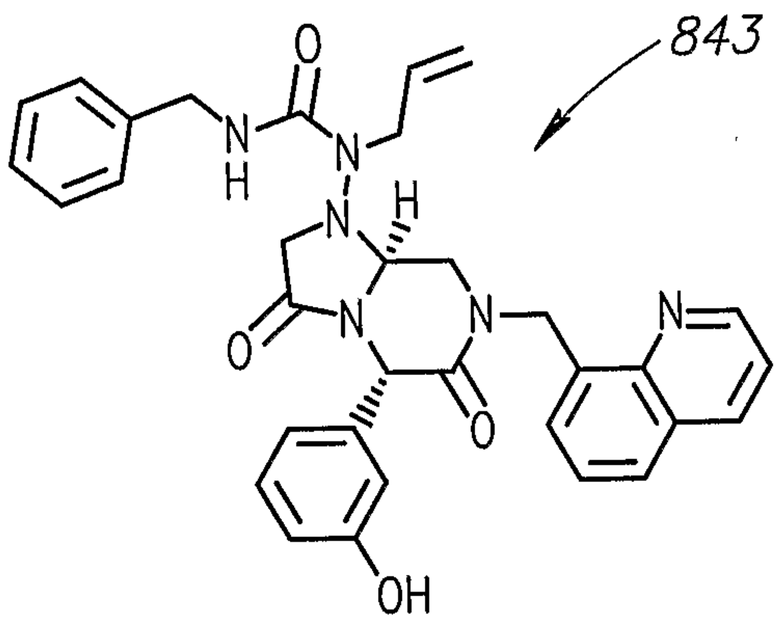
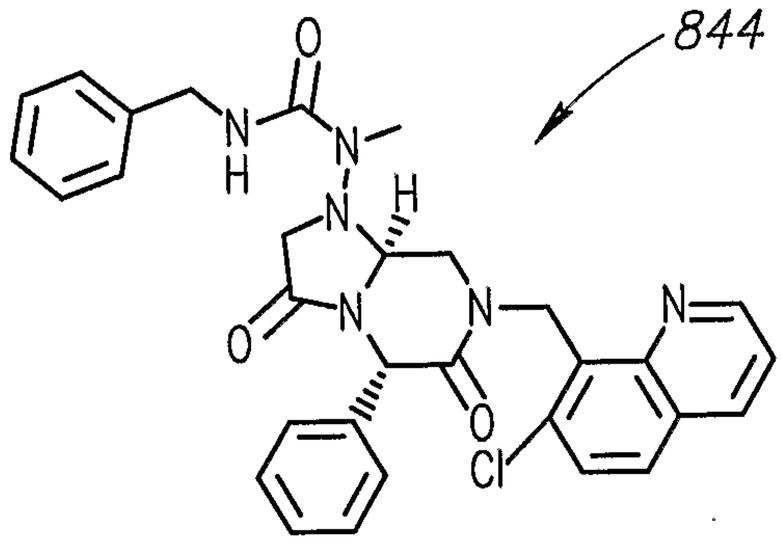


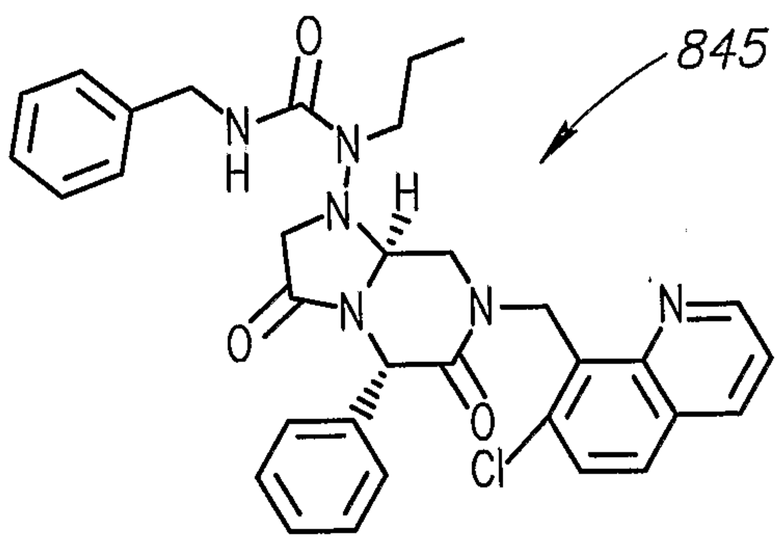
FIG.5E

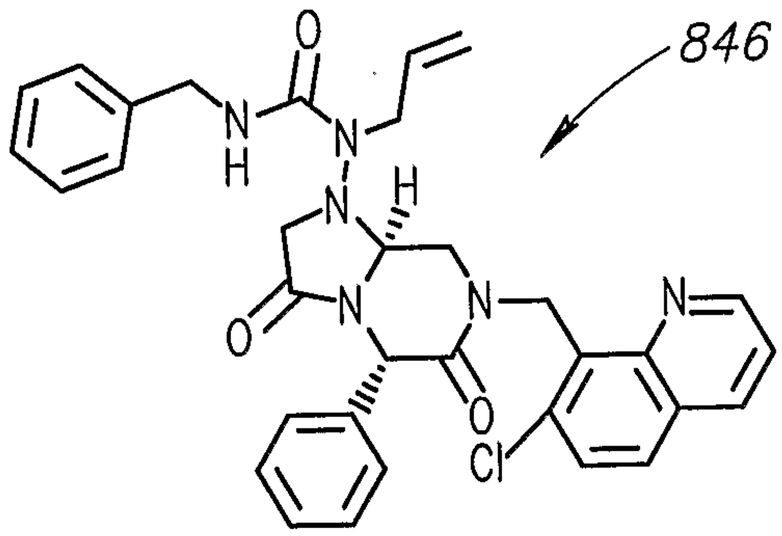


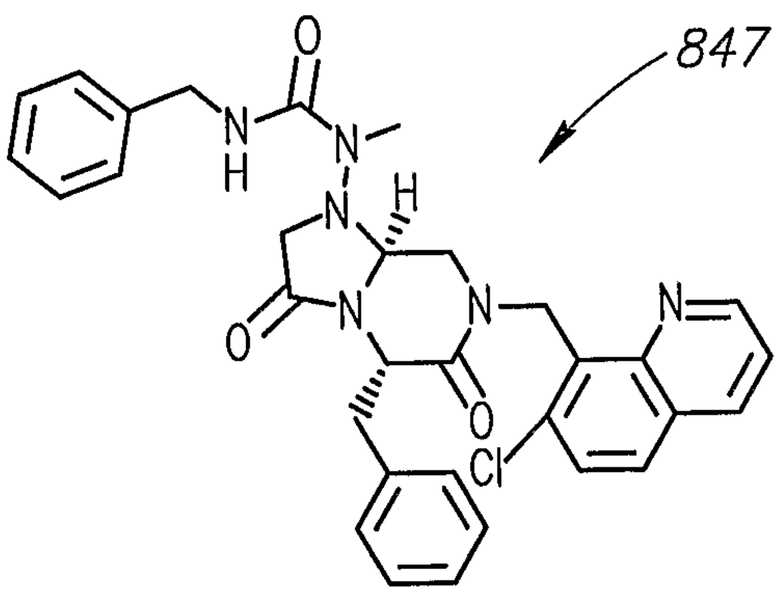












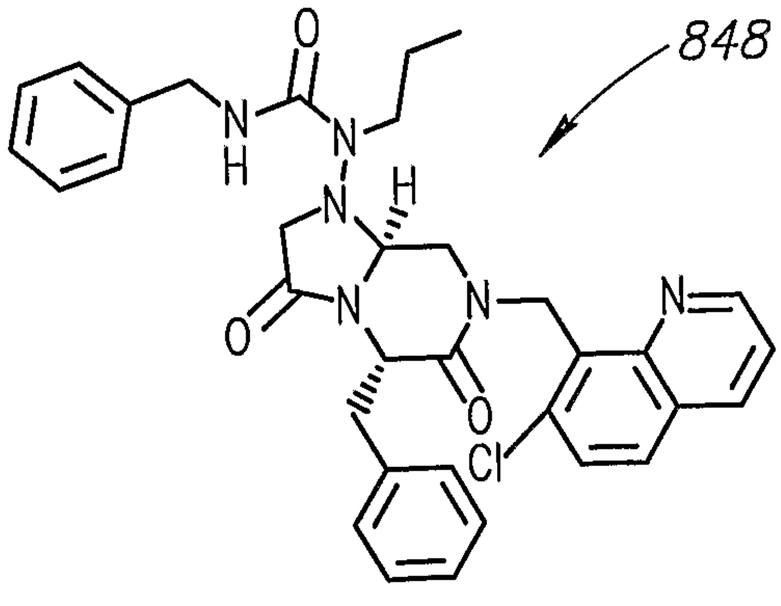
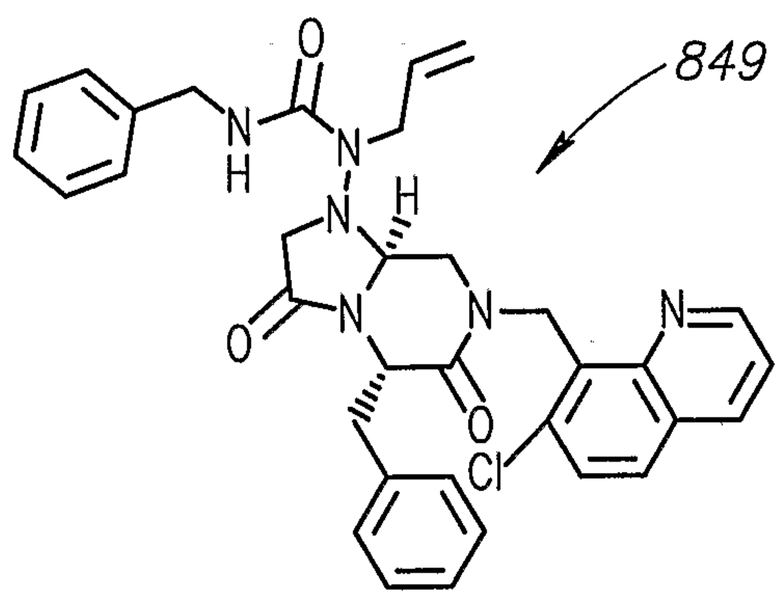
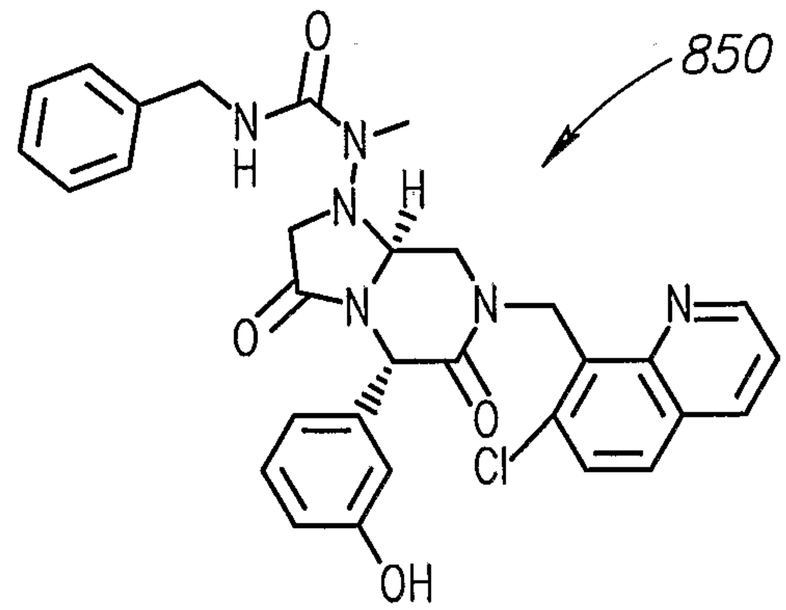
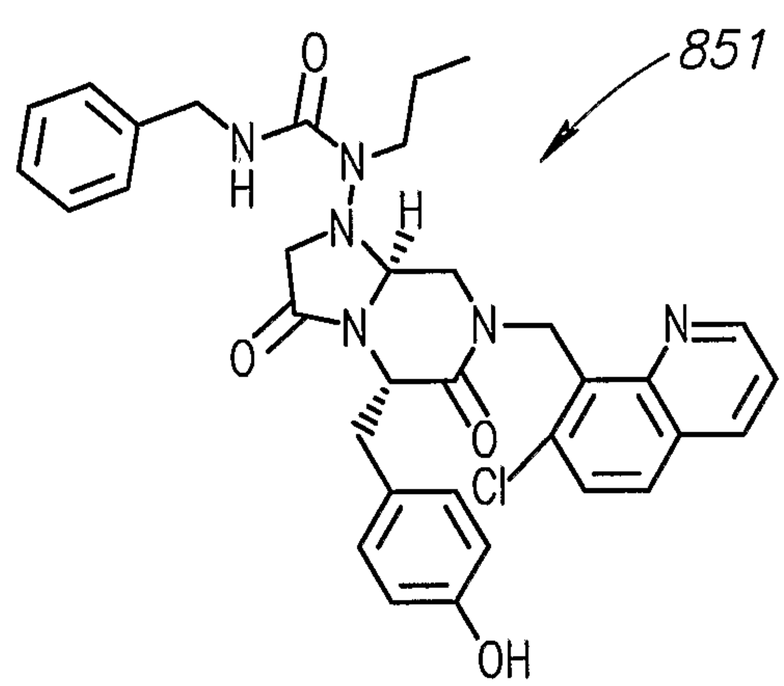
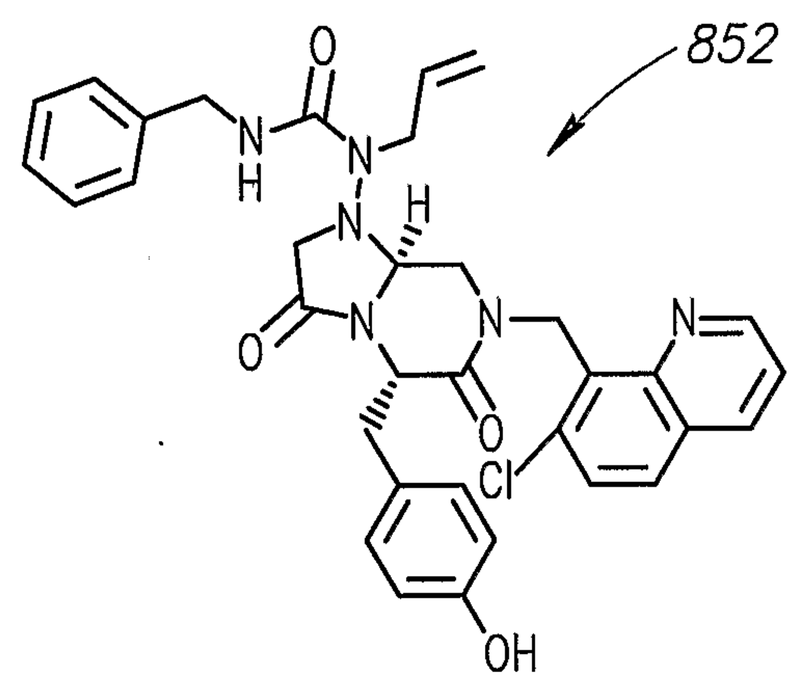


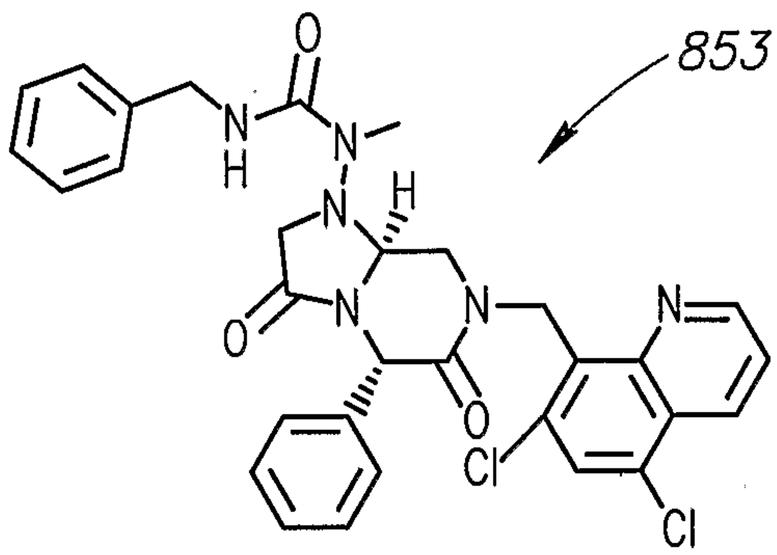
FIG.5F

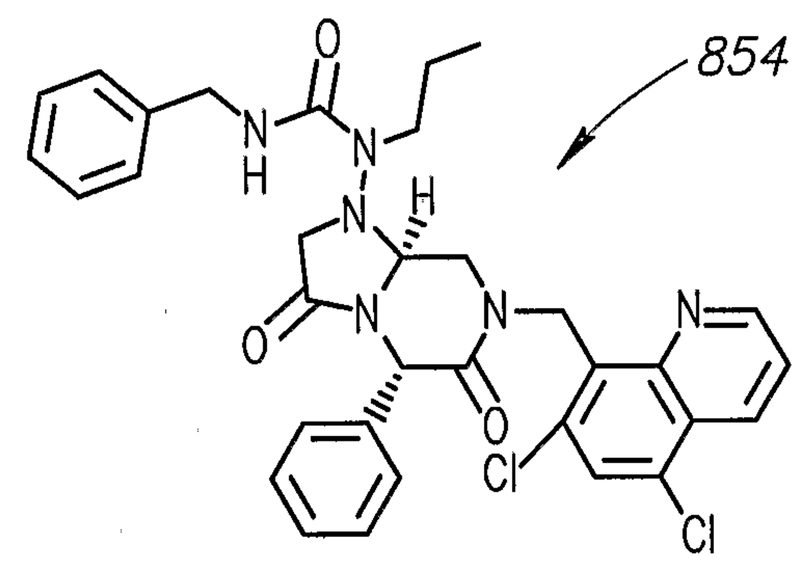


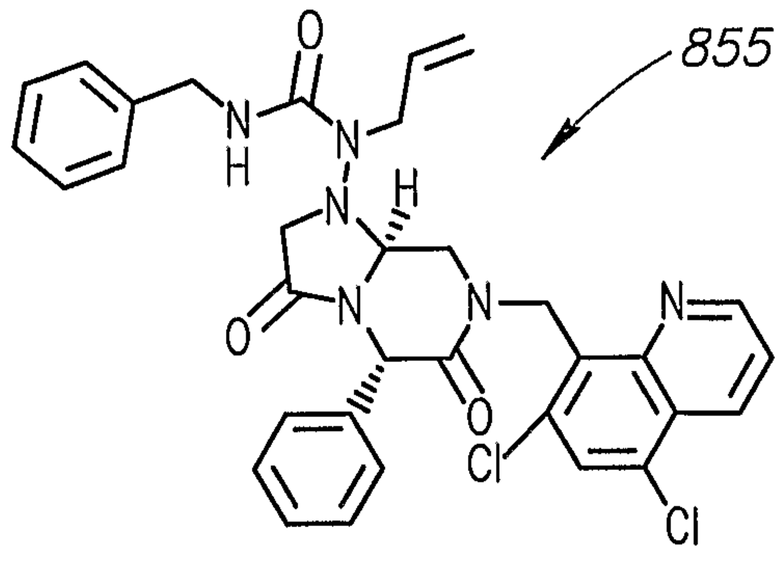












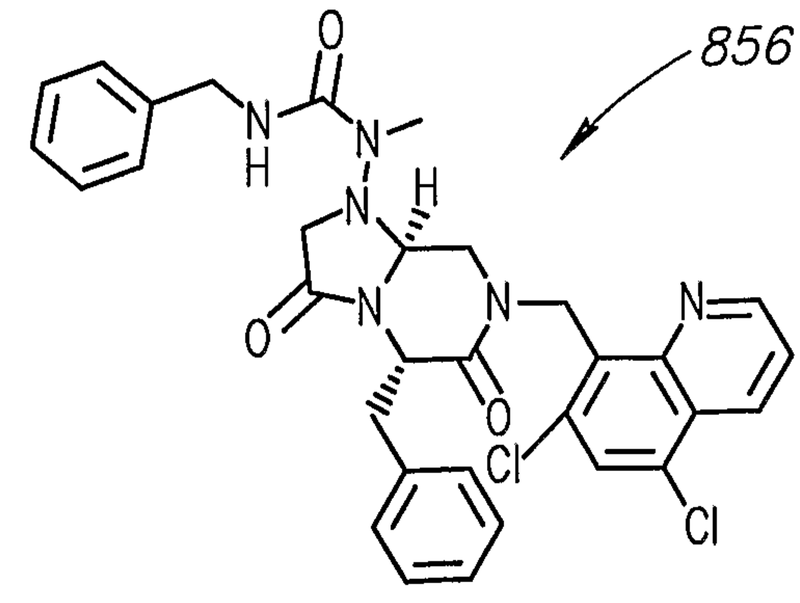
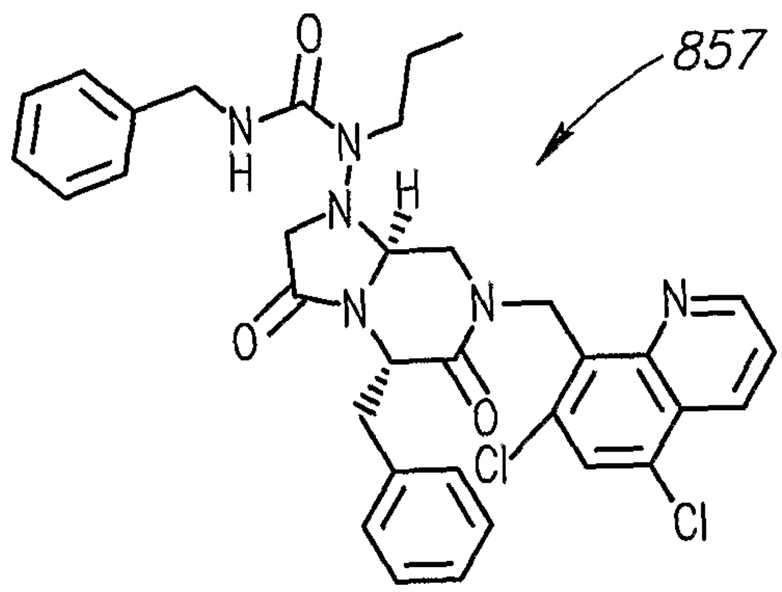
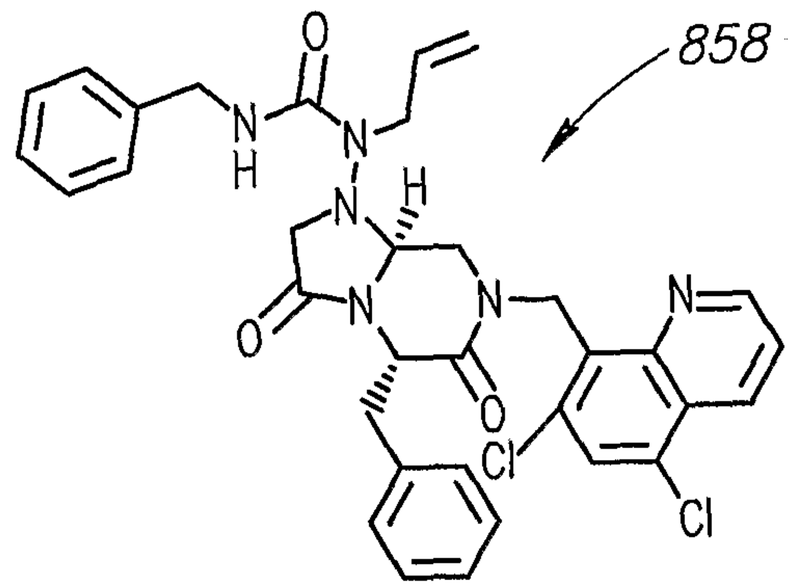
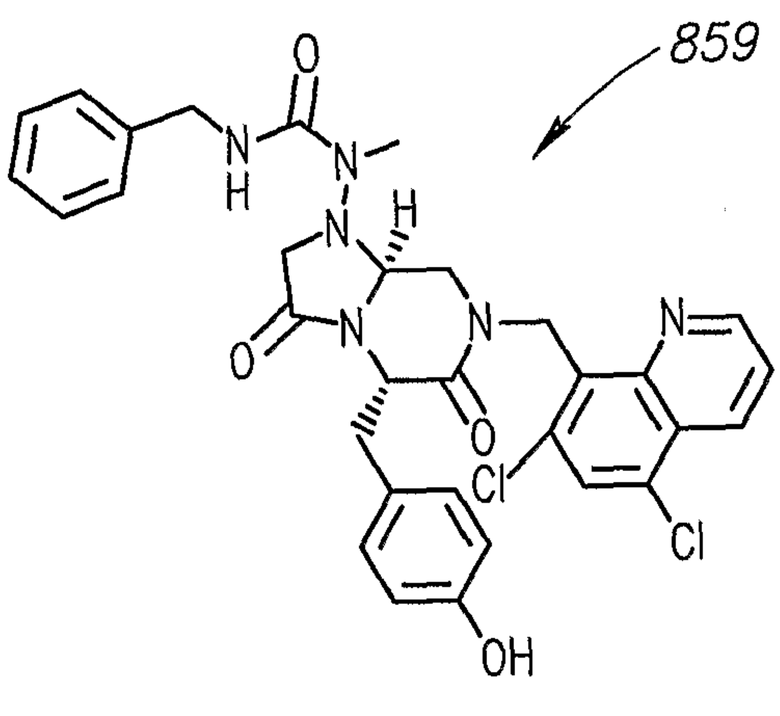
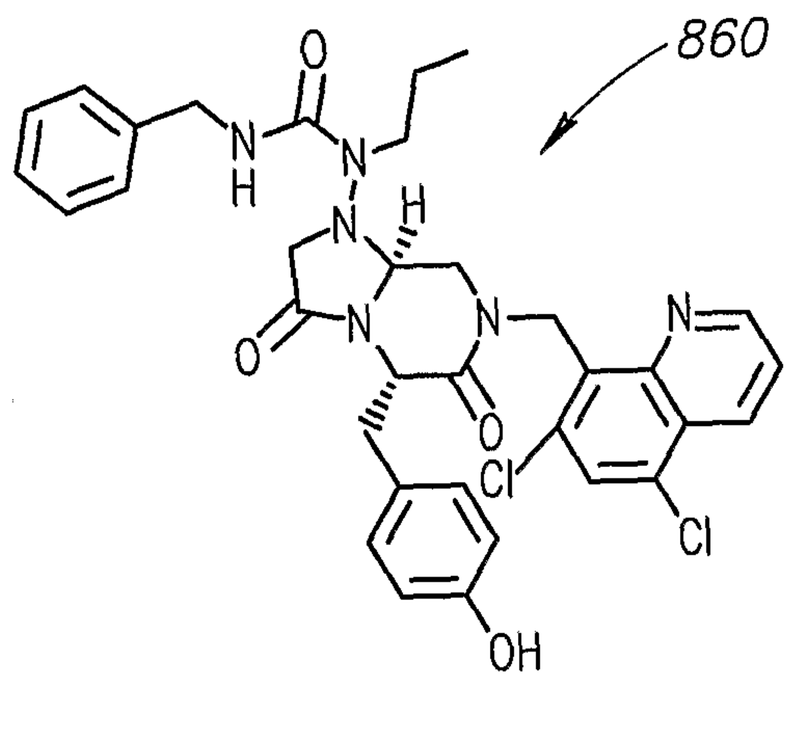


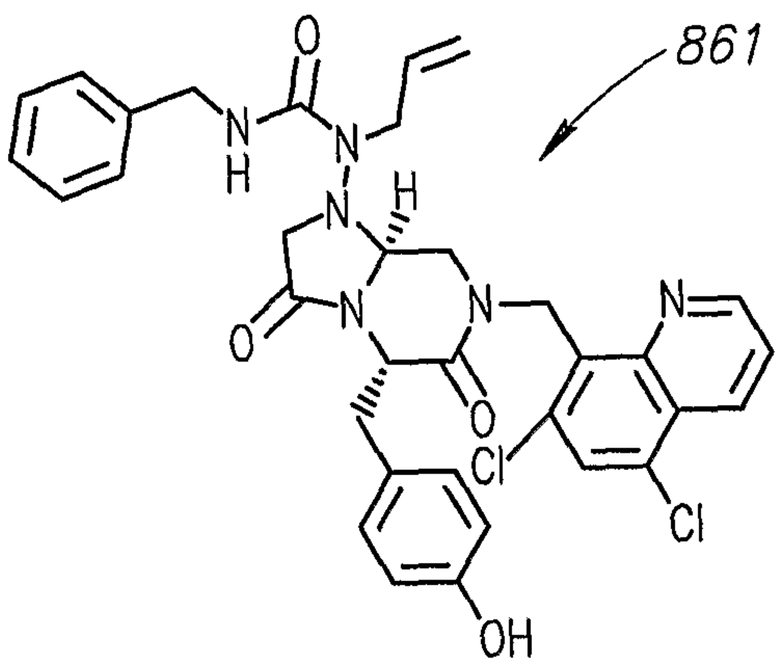
FIG.5G

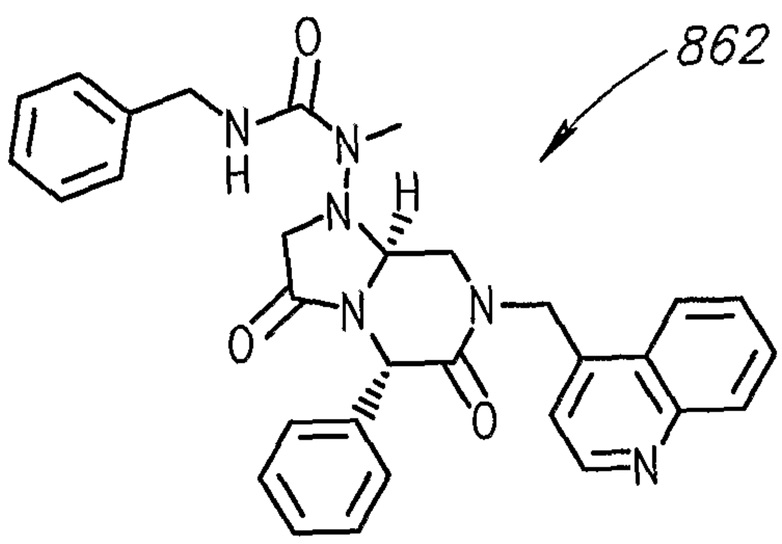


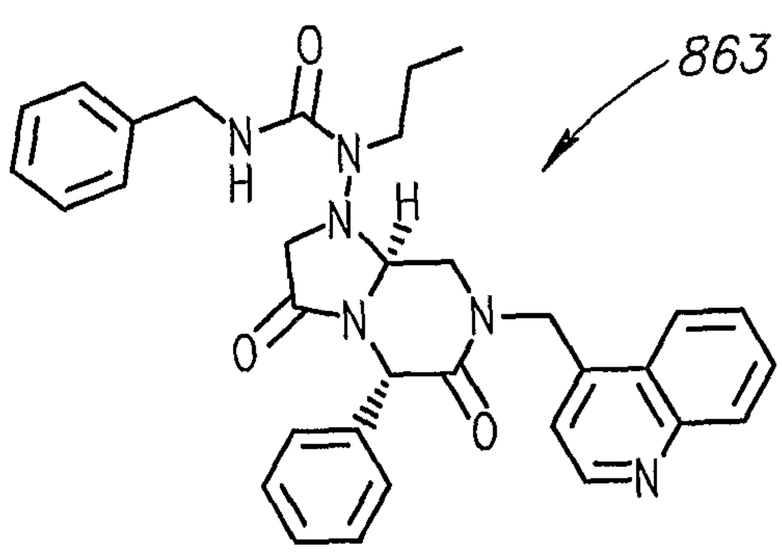












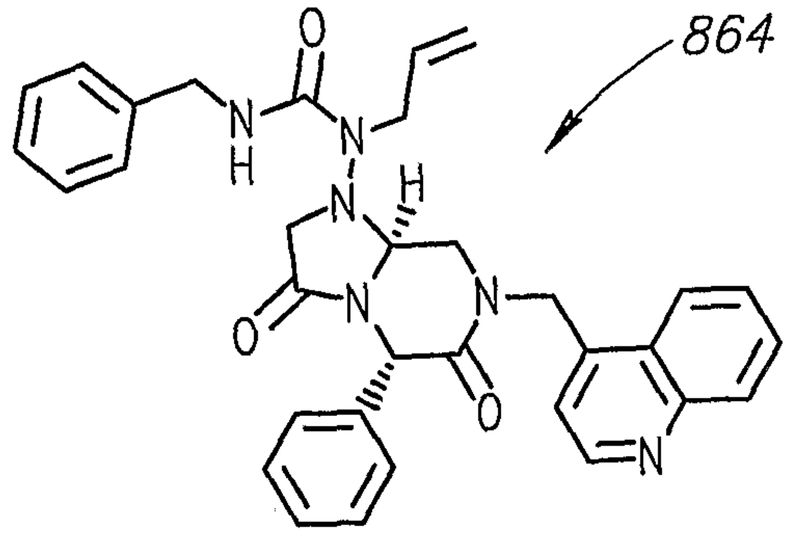
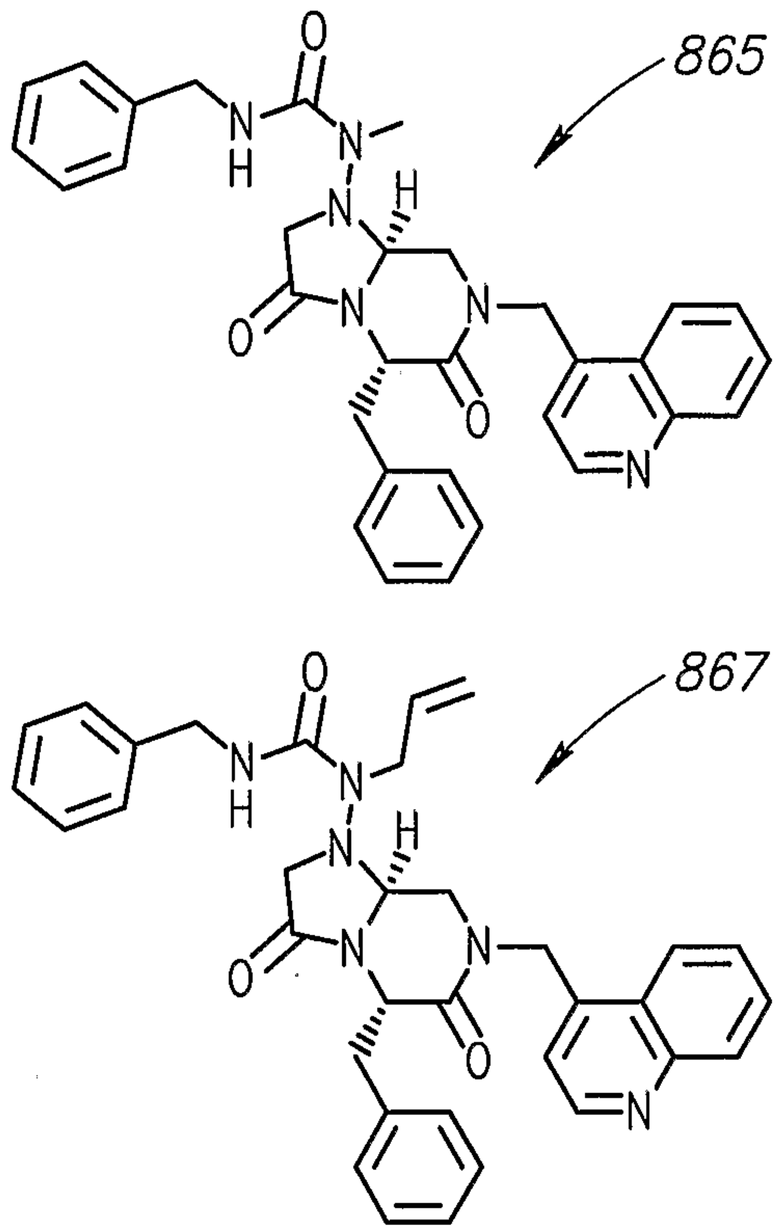
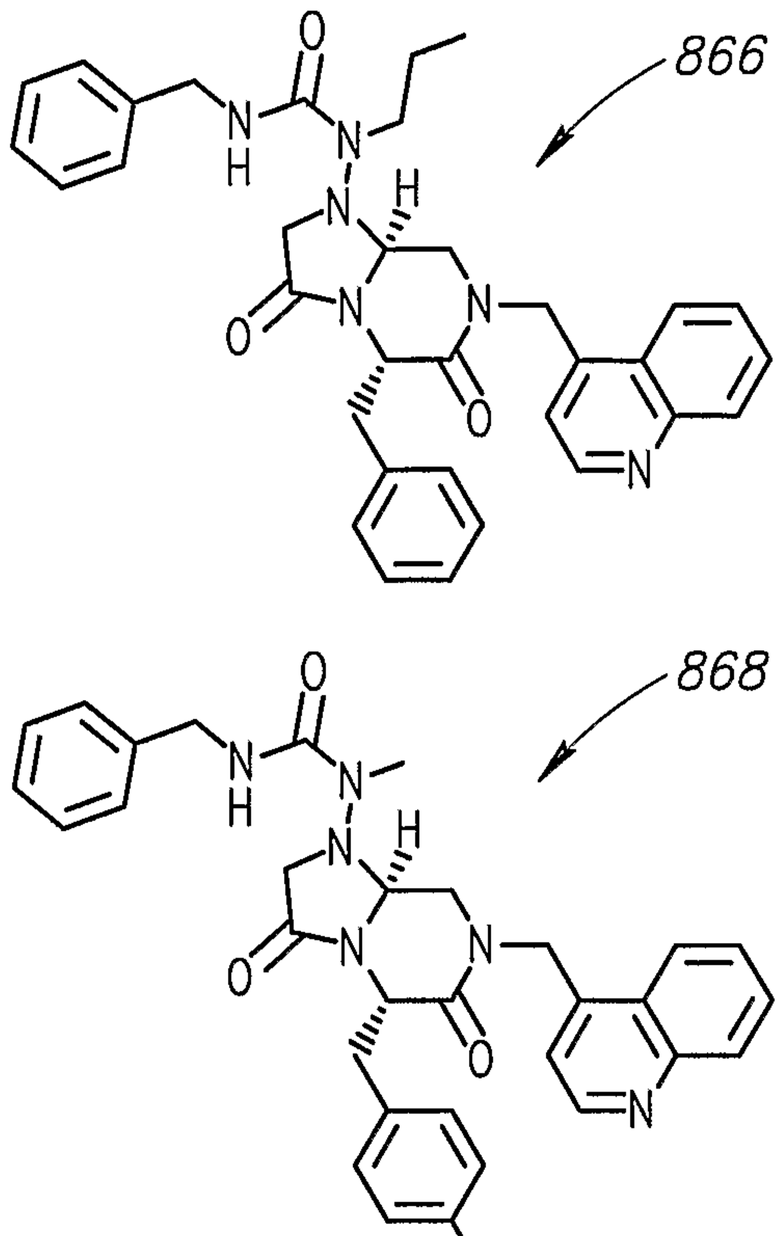
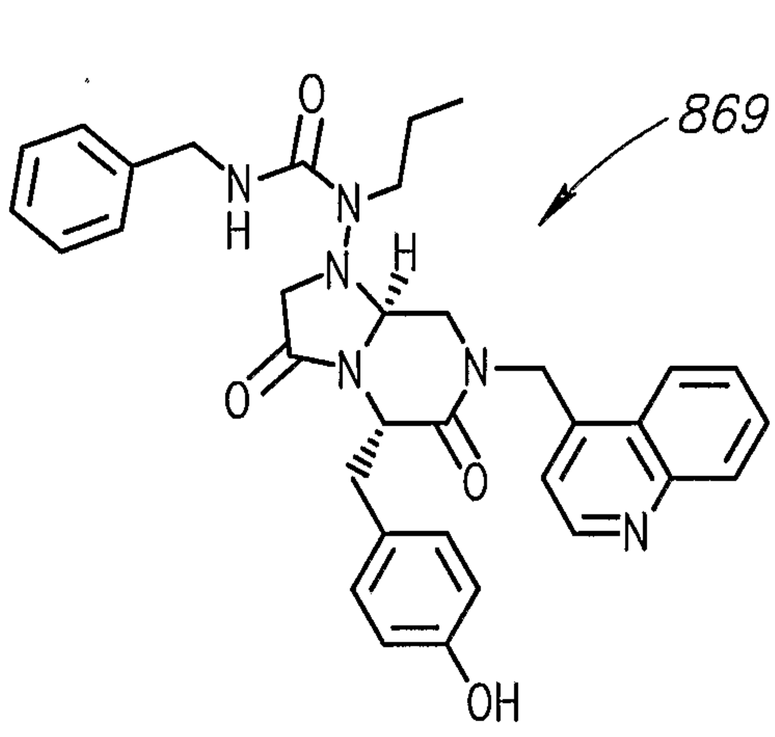


FIG.5H







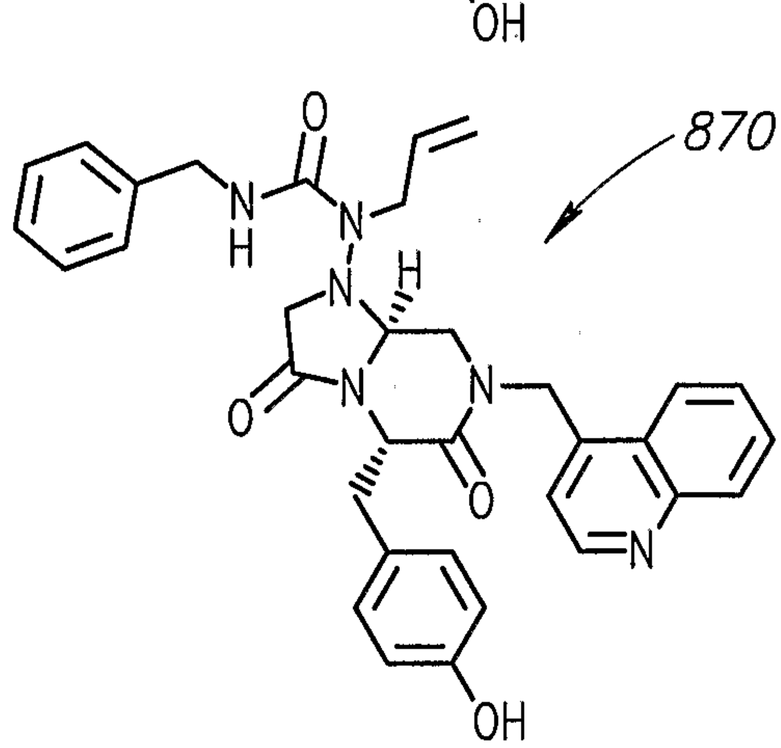


FIG.5I

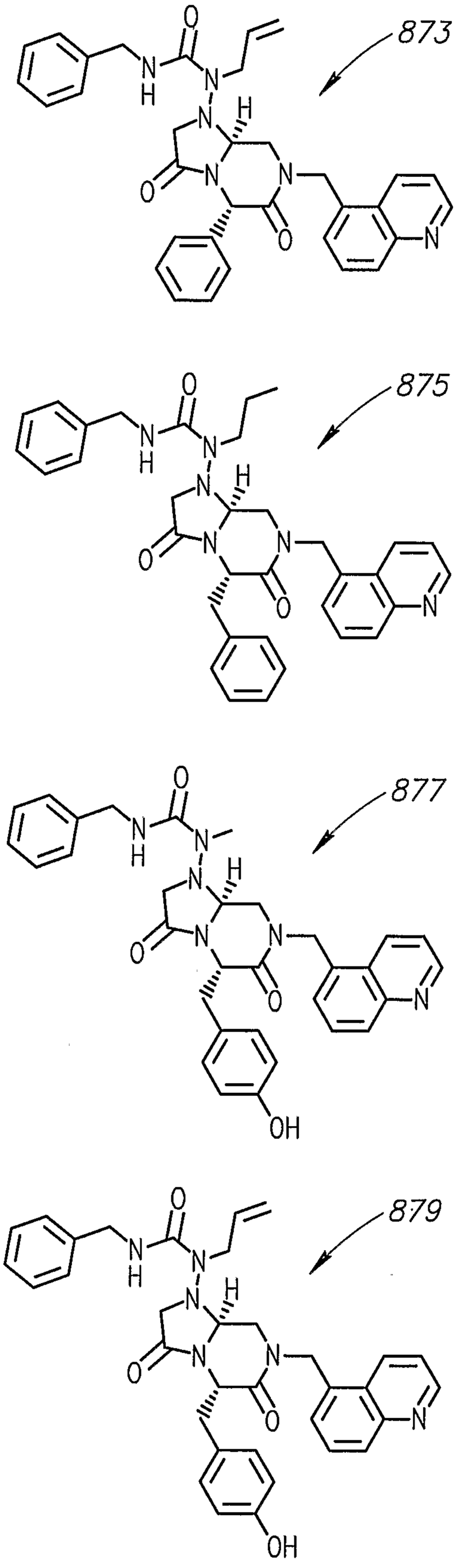


FIG.5J

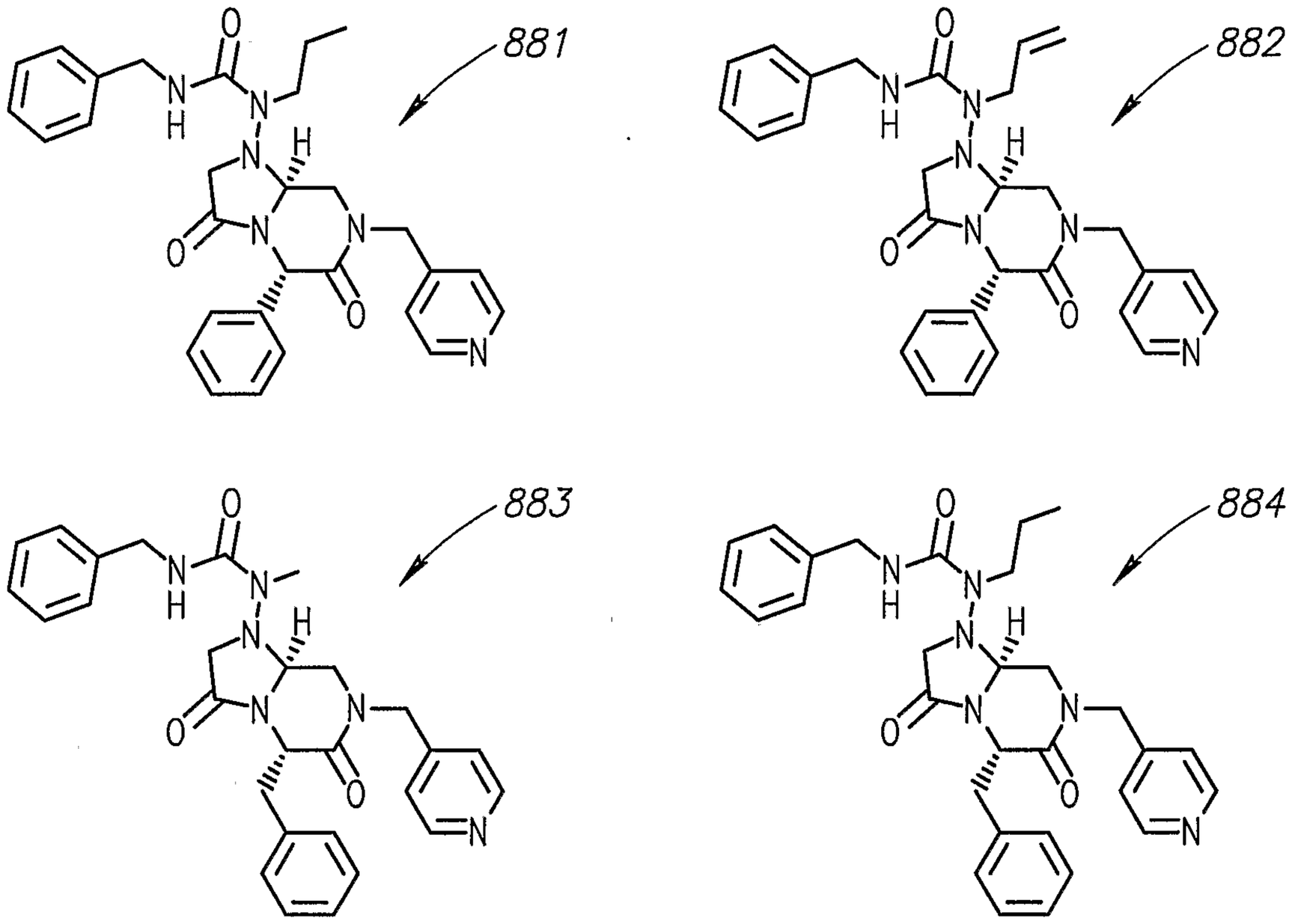


FIG.5K

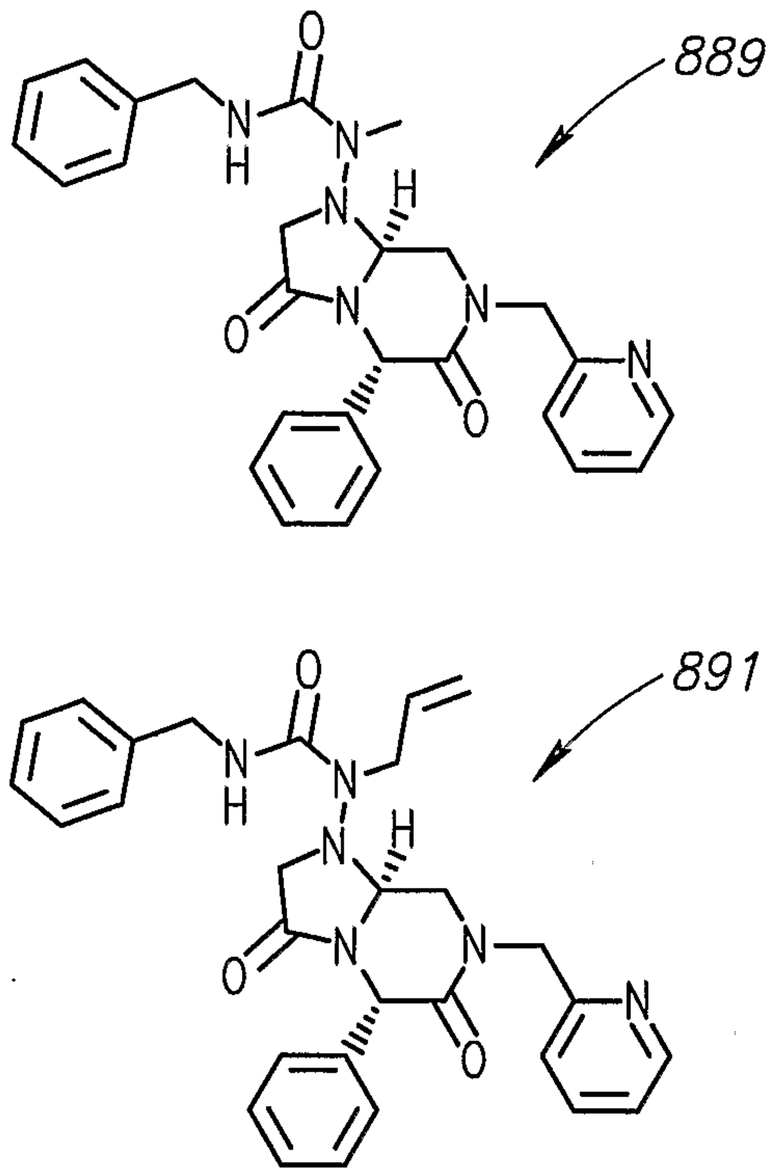
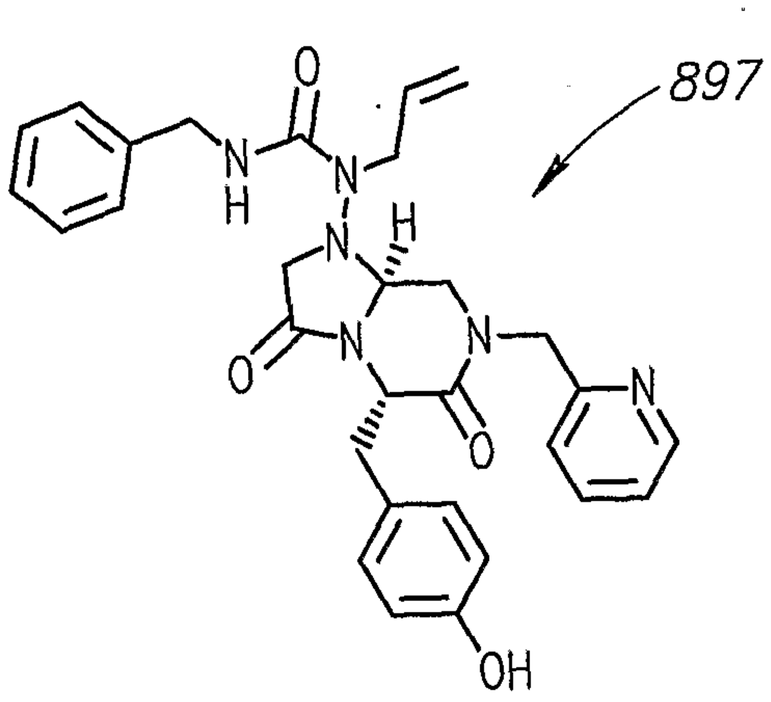


FIG.5L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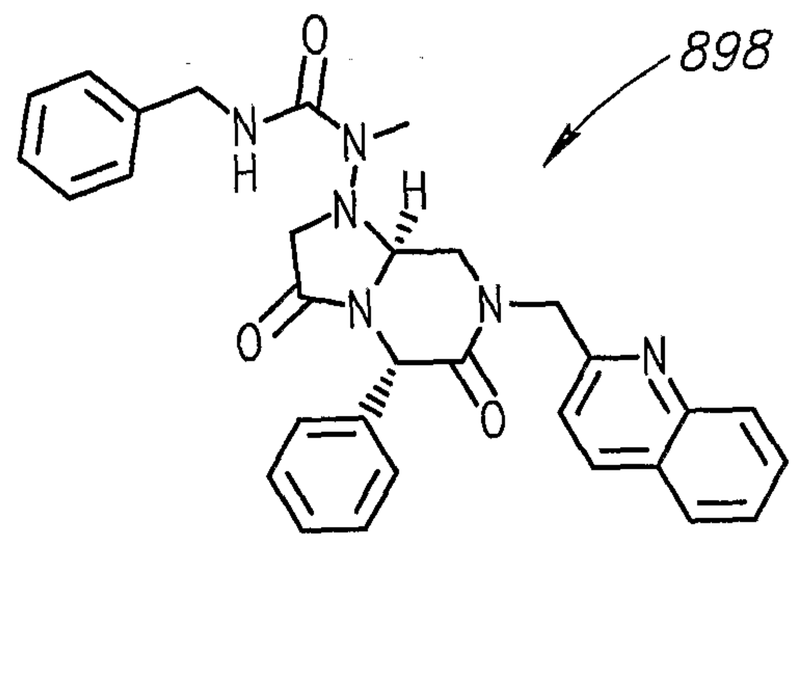
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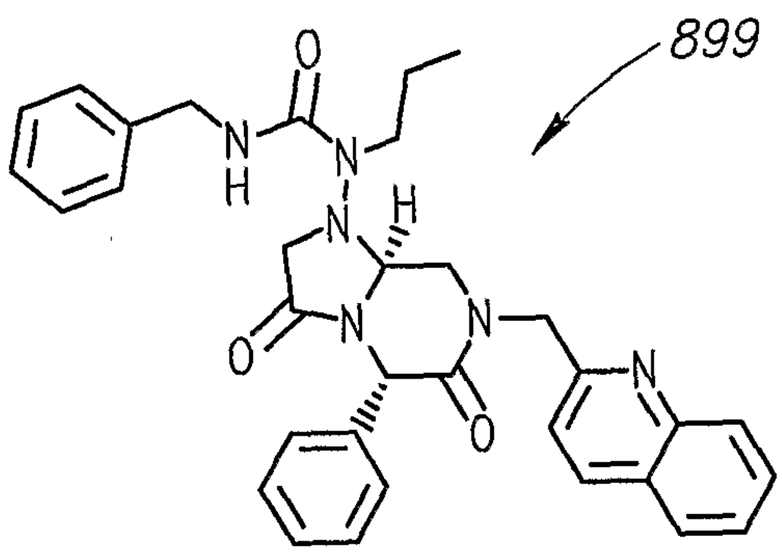
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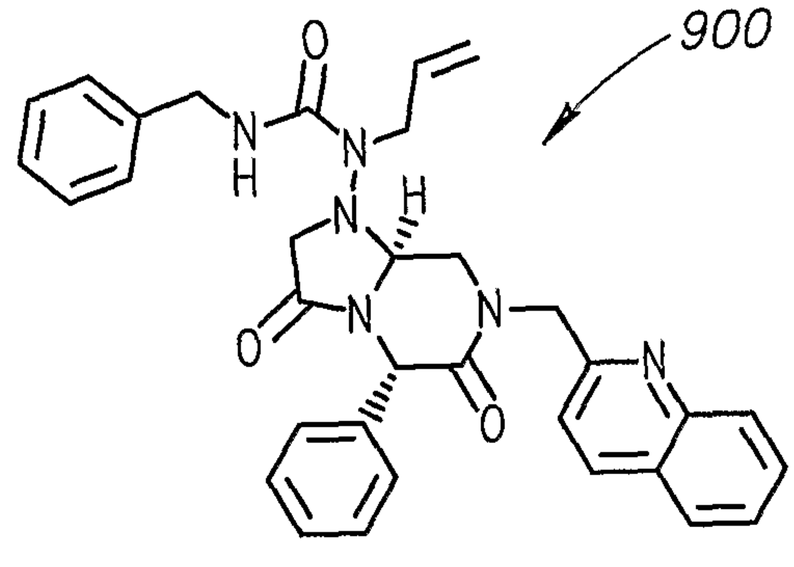
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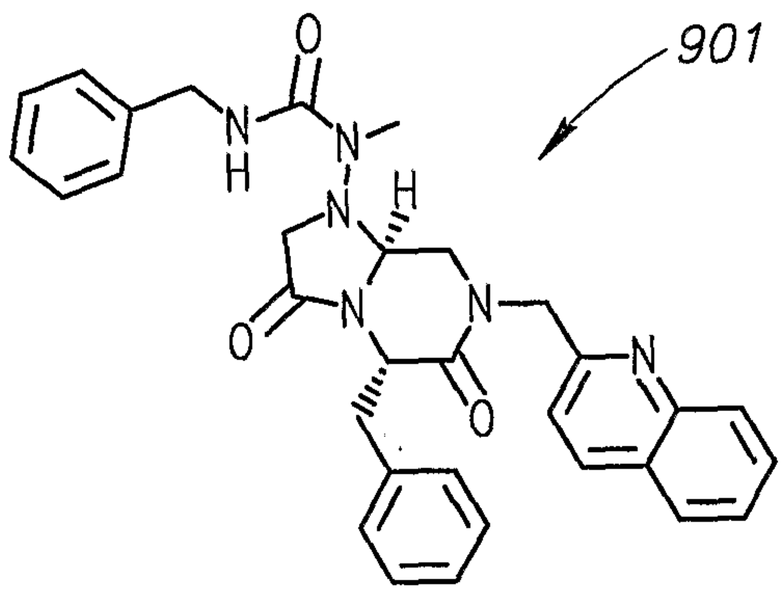
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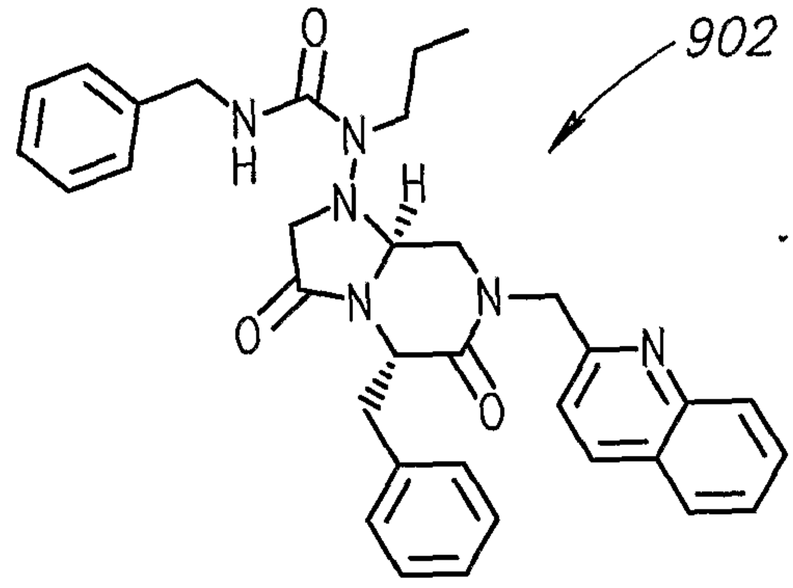
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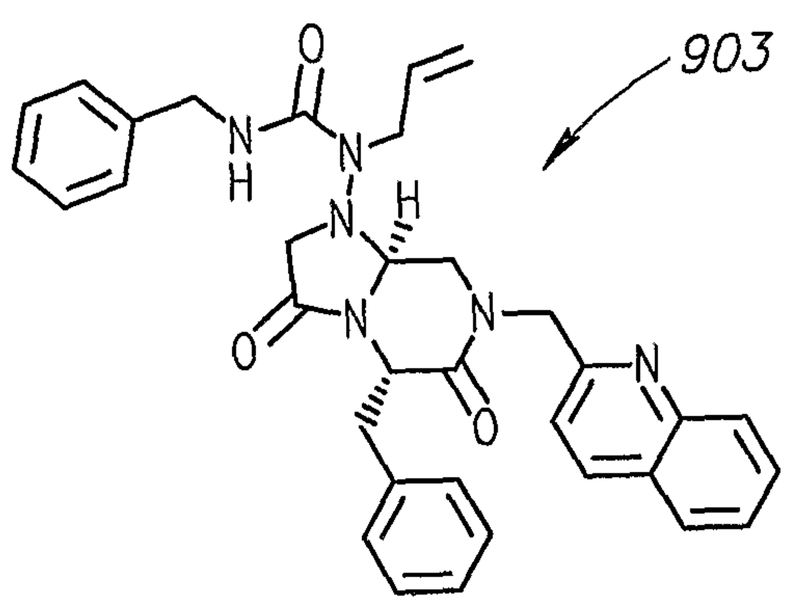
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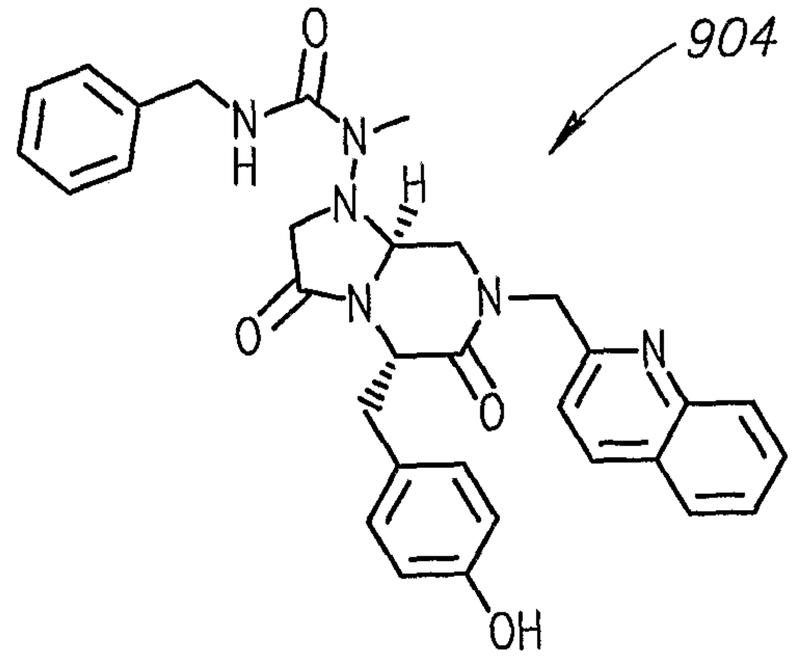
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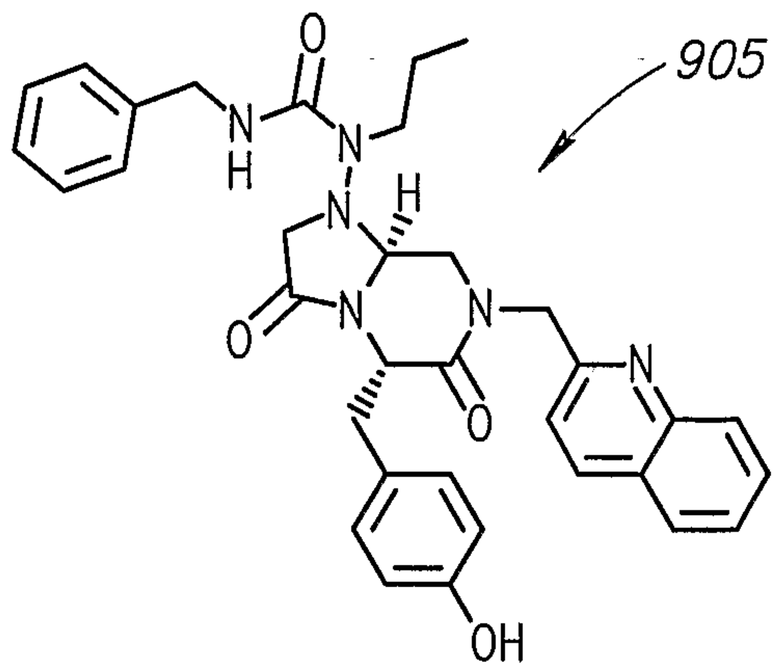
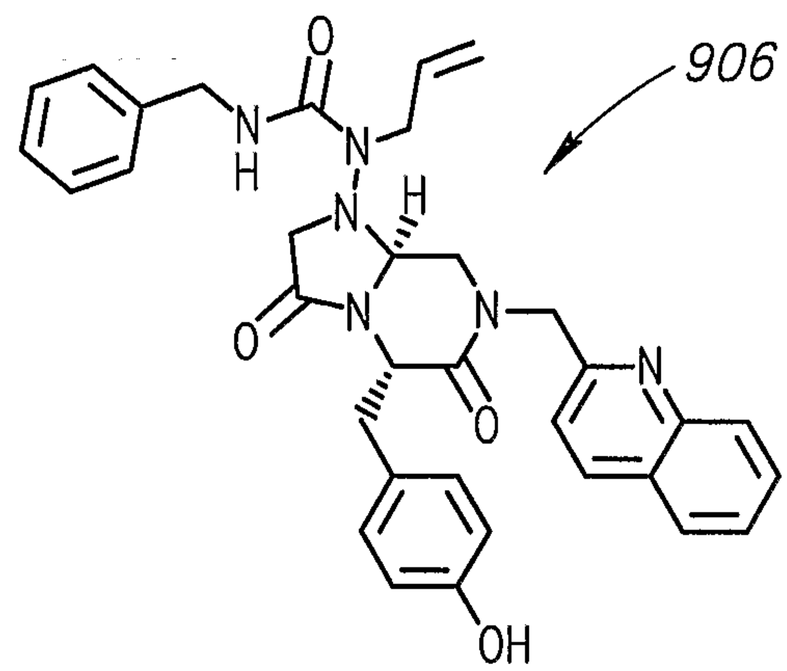
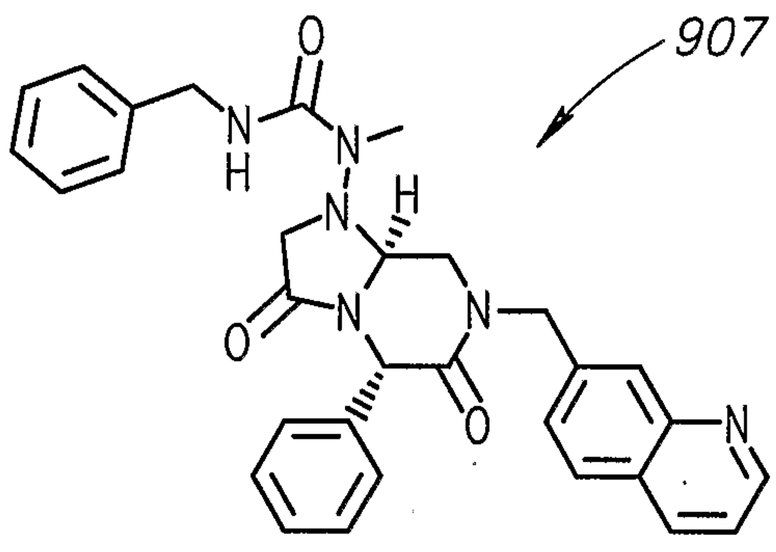
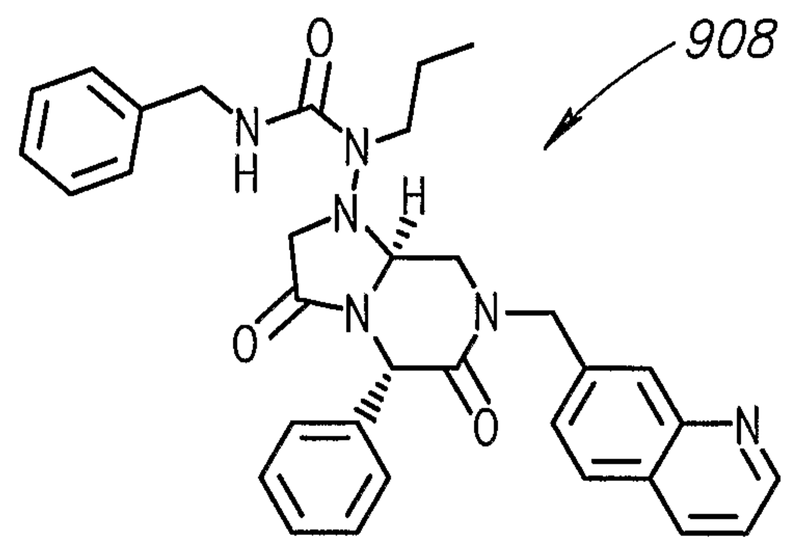
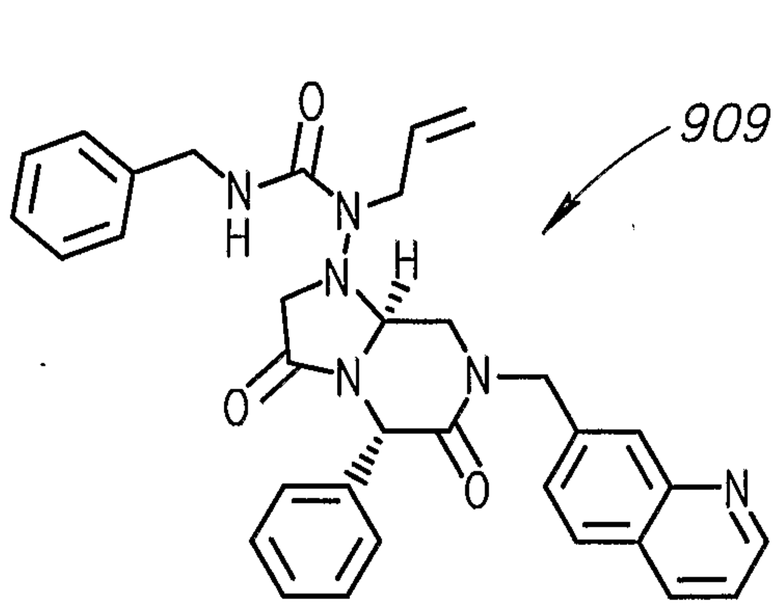
FIG.5M











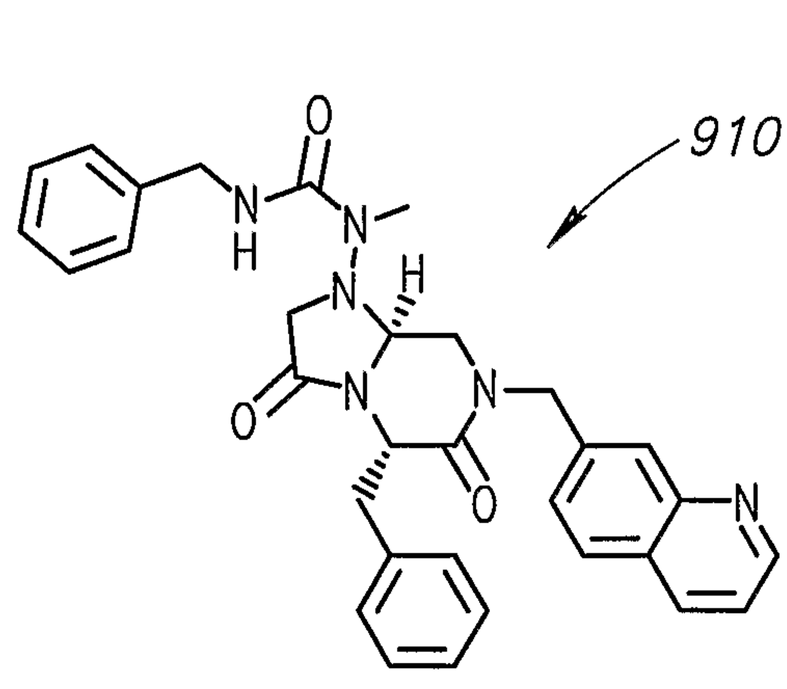
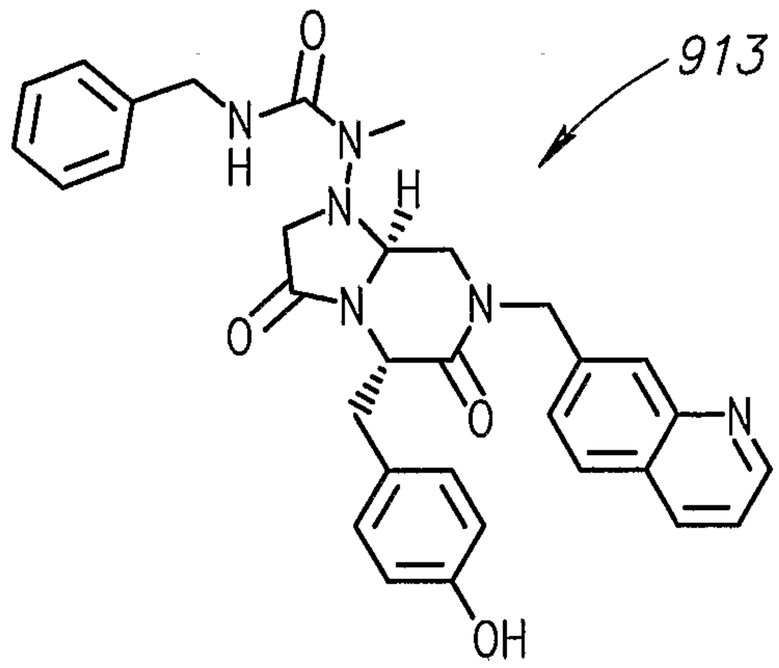
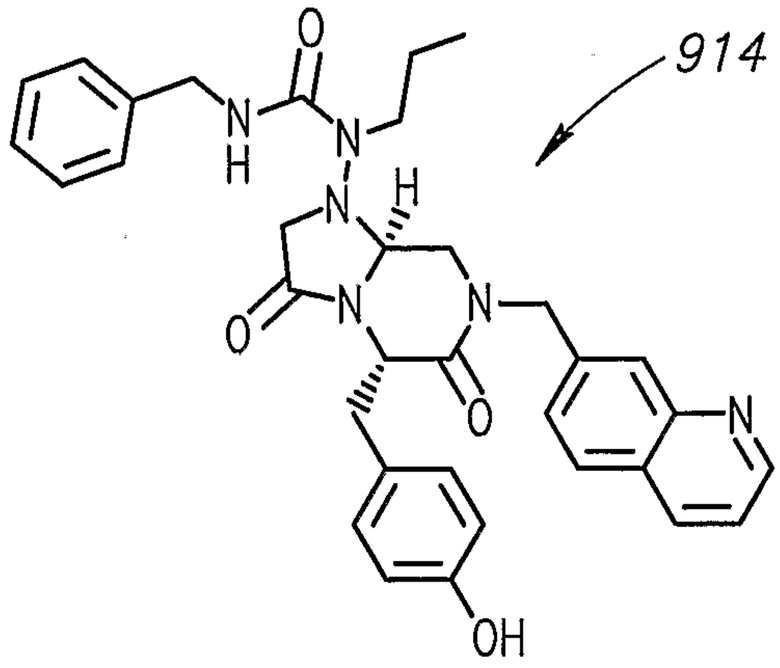
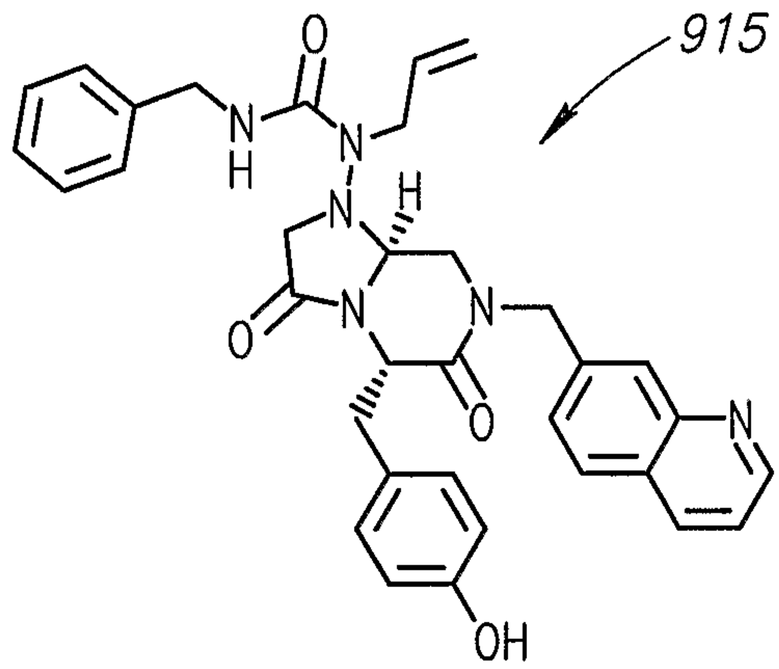
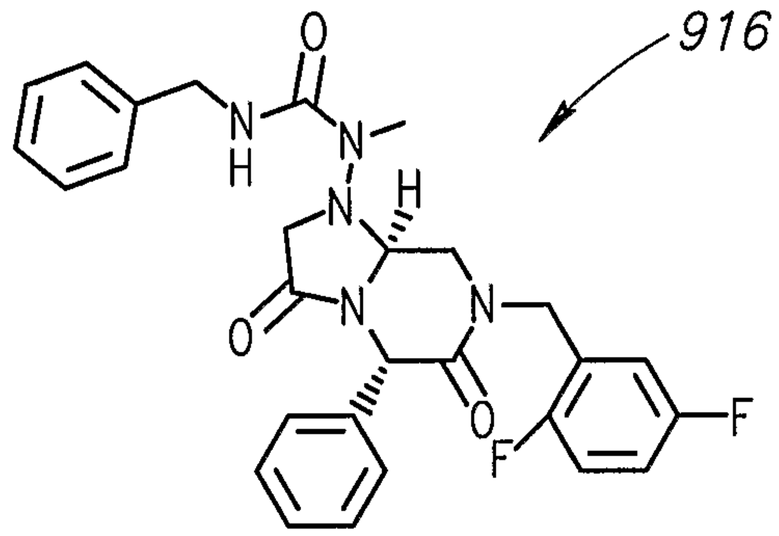


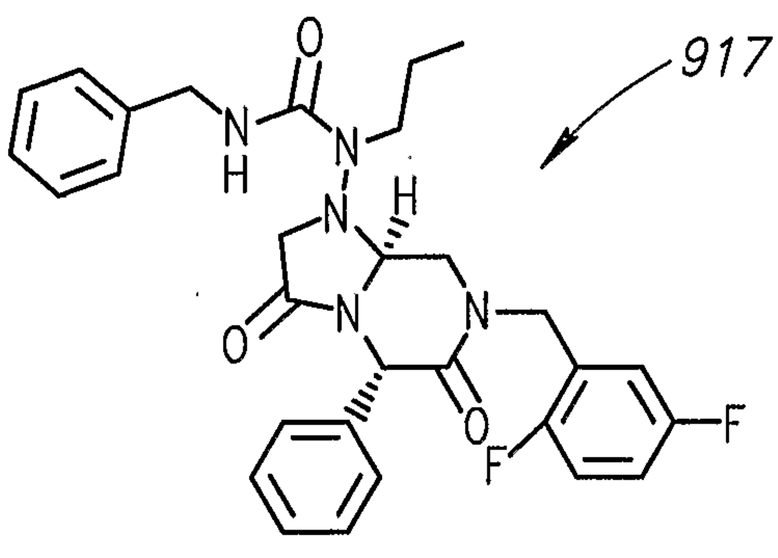
FIG.5N

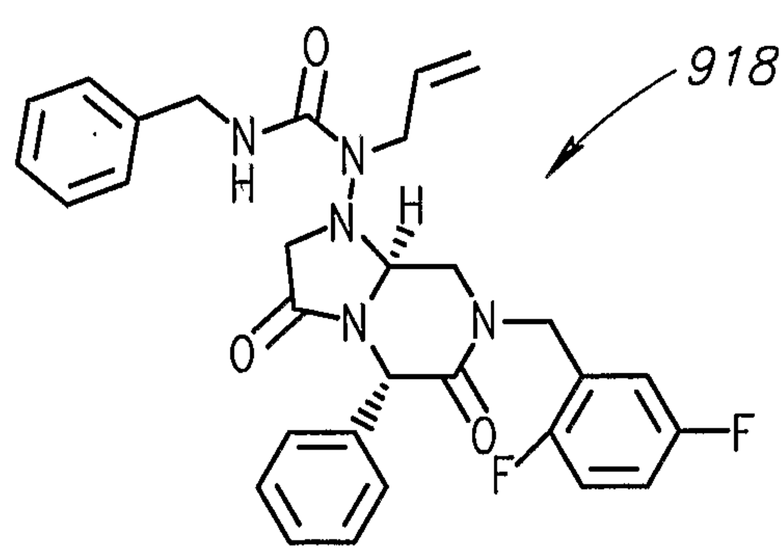


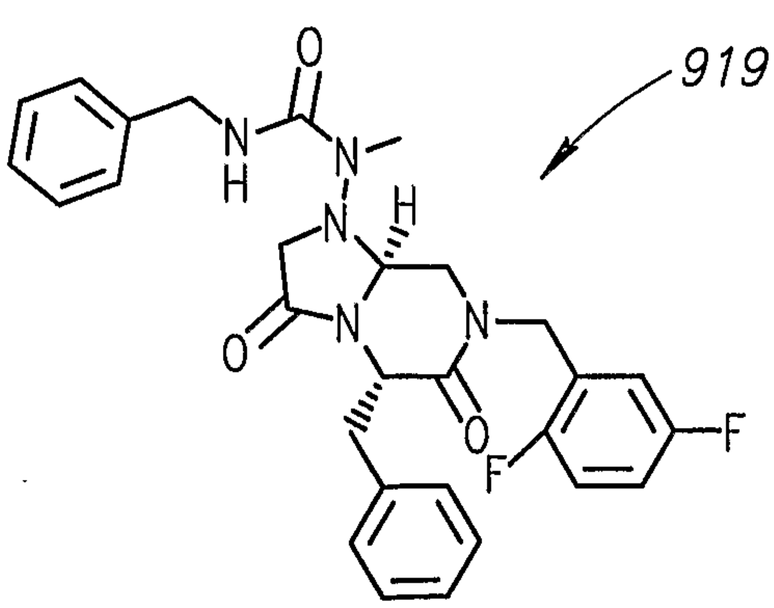












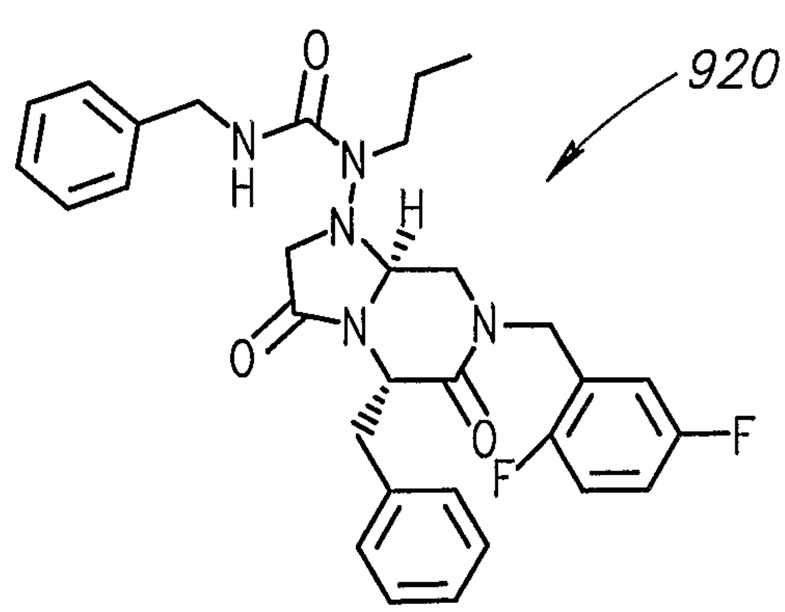
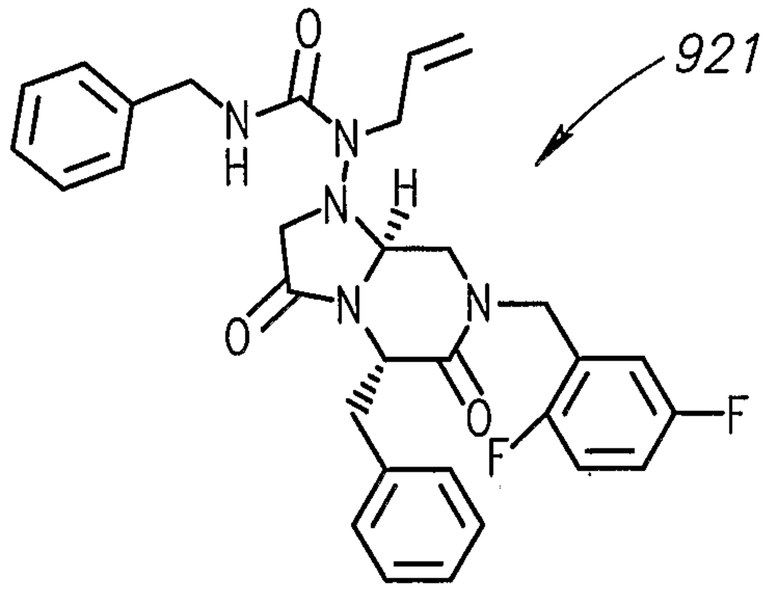
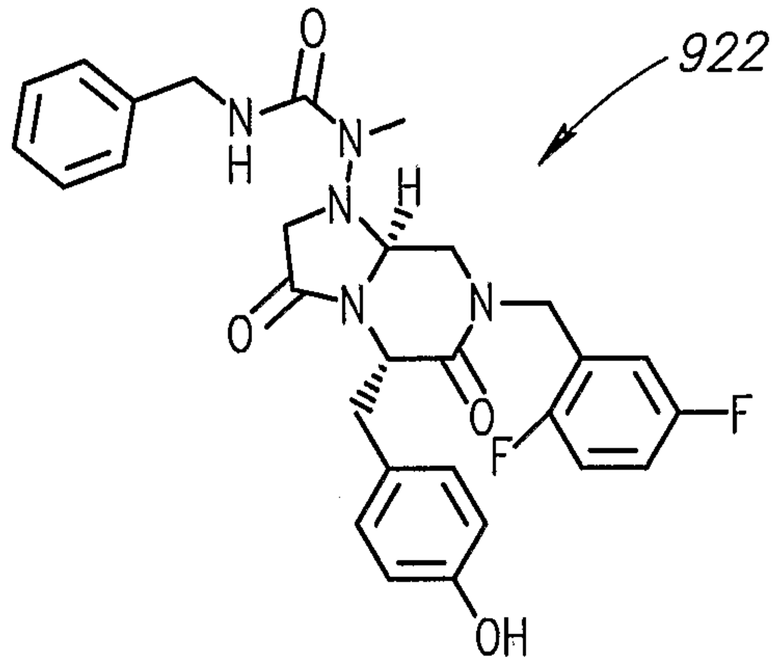
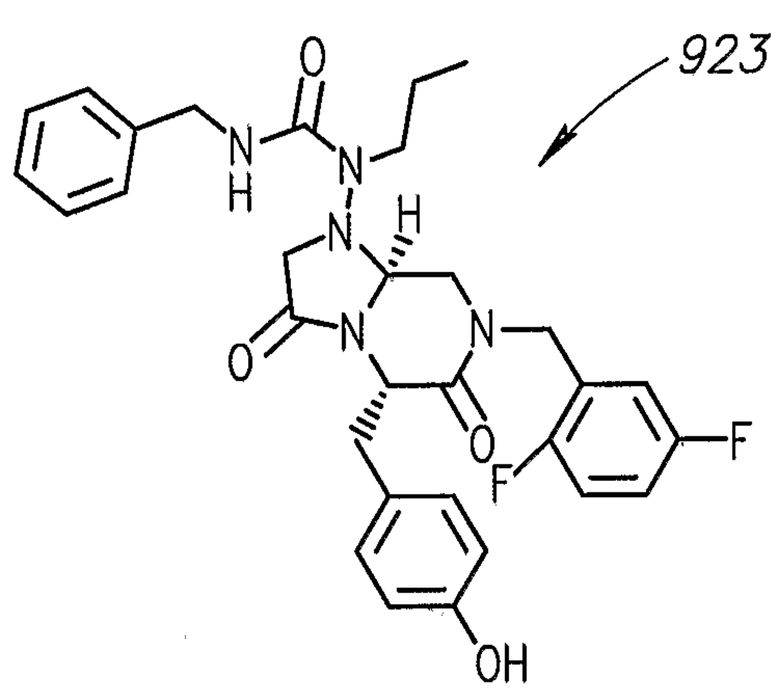
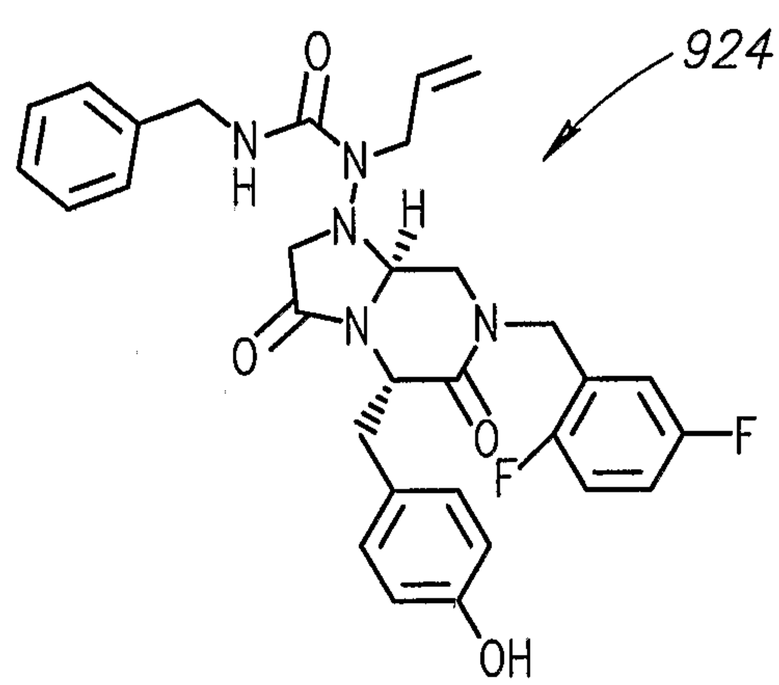


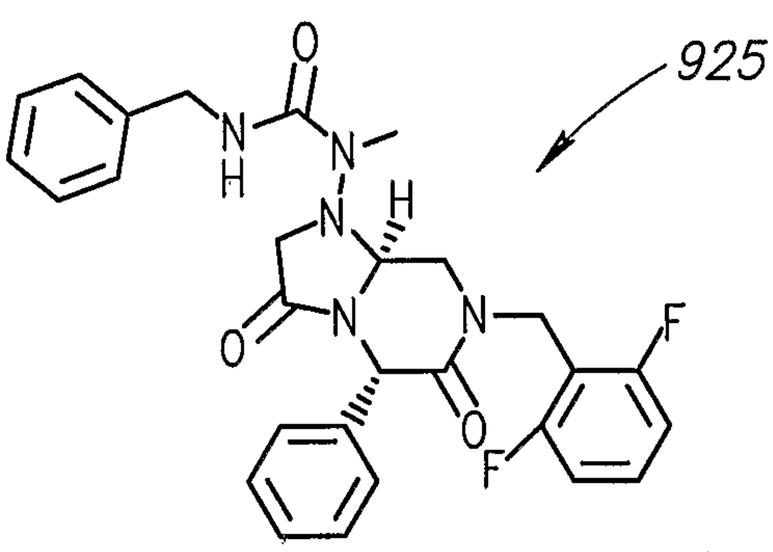
FIG.50

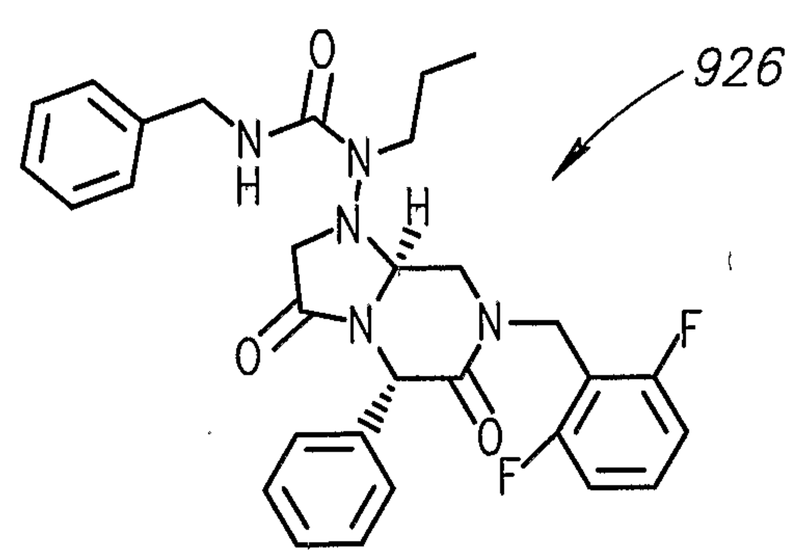


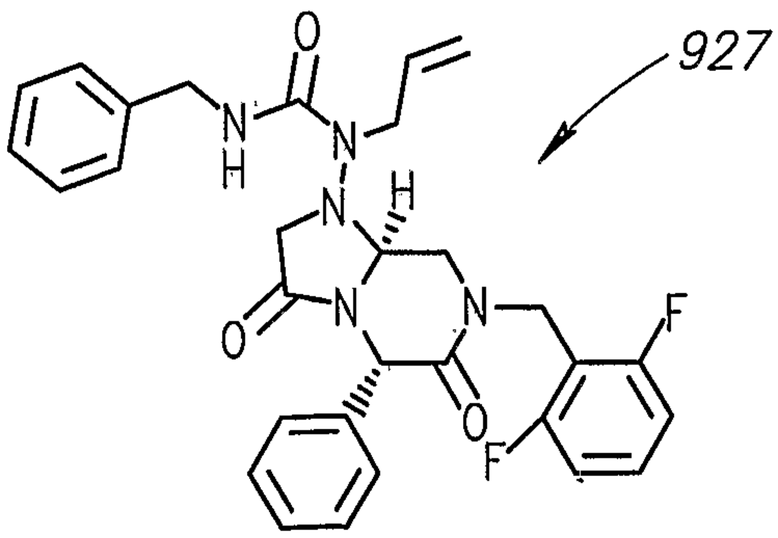












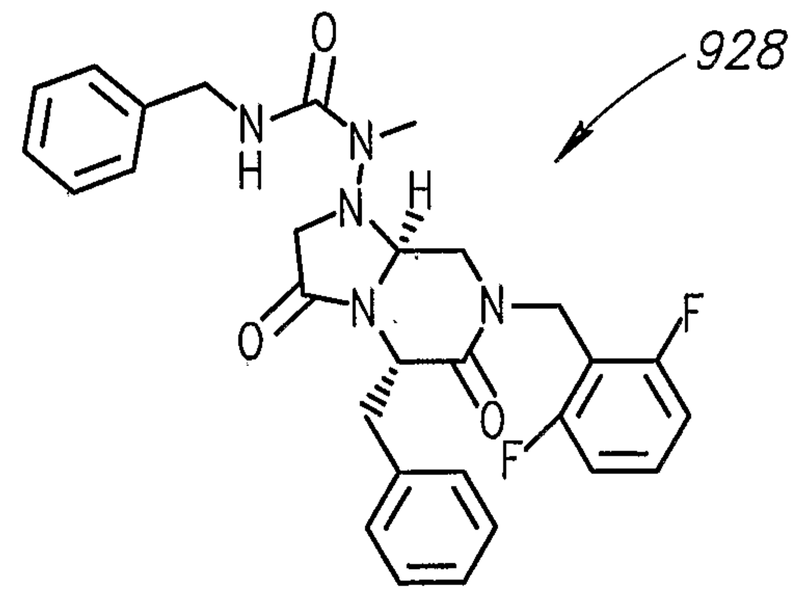
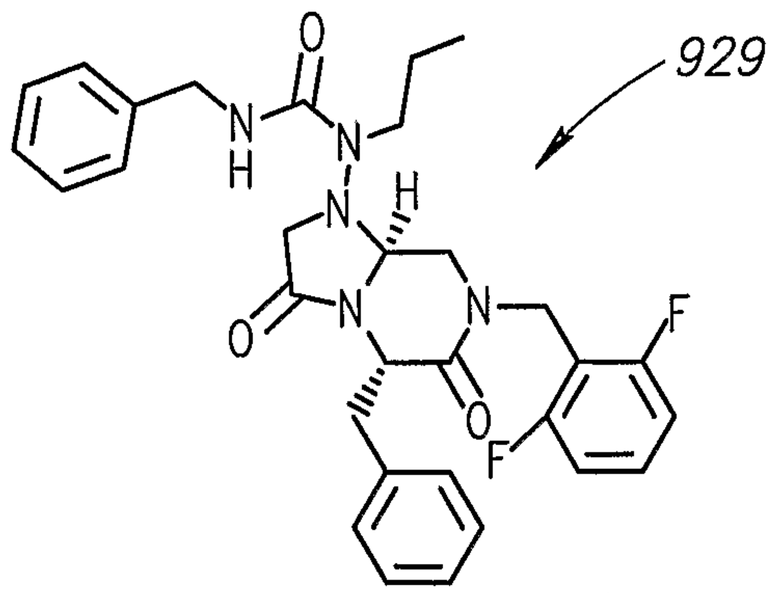
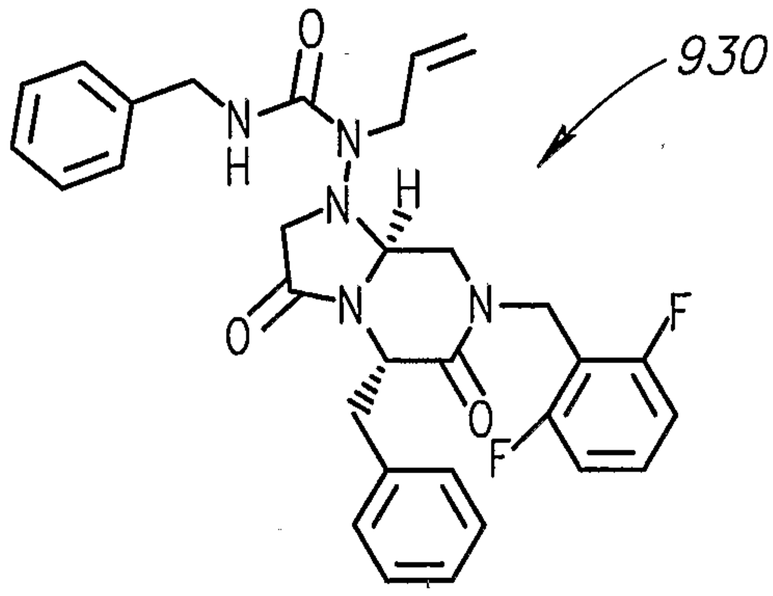
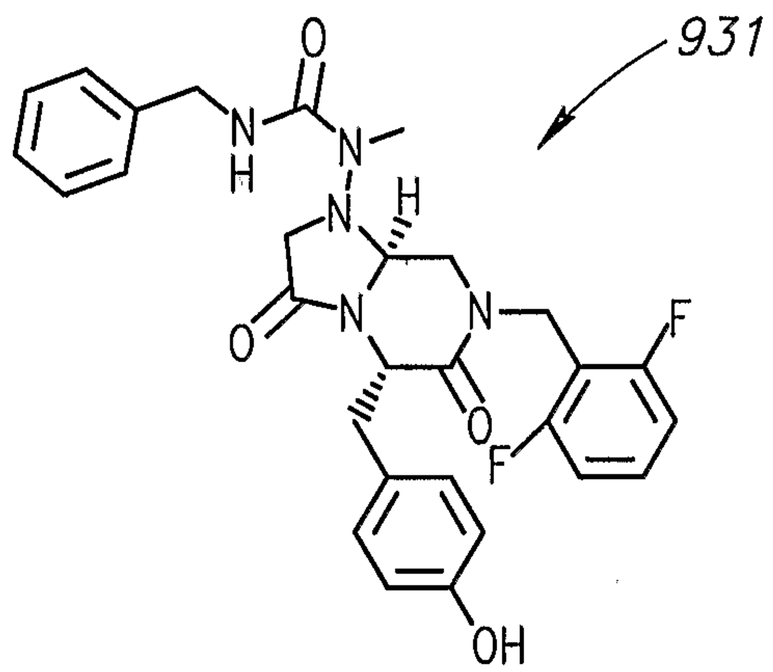
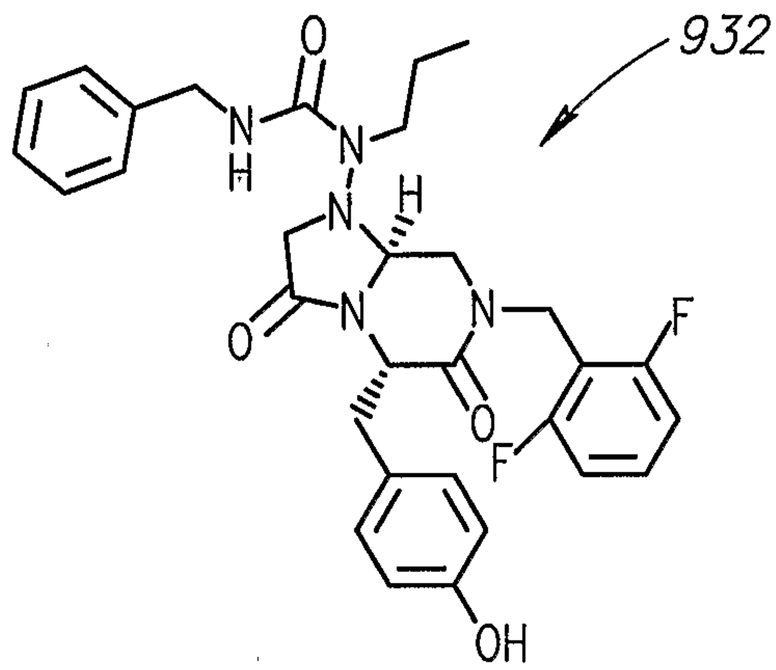


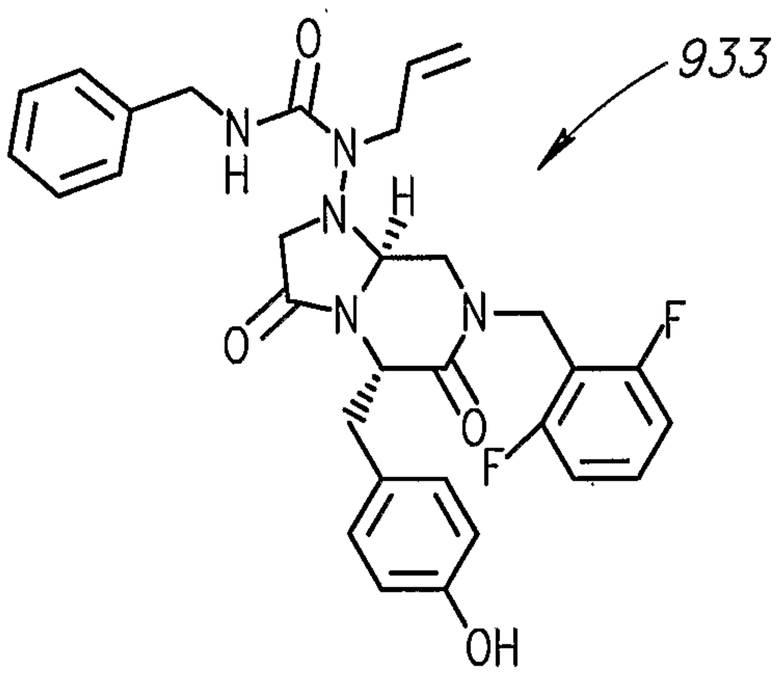
FIG.5P

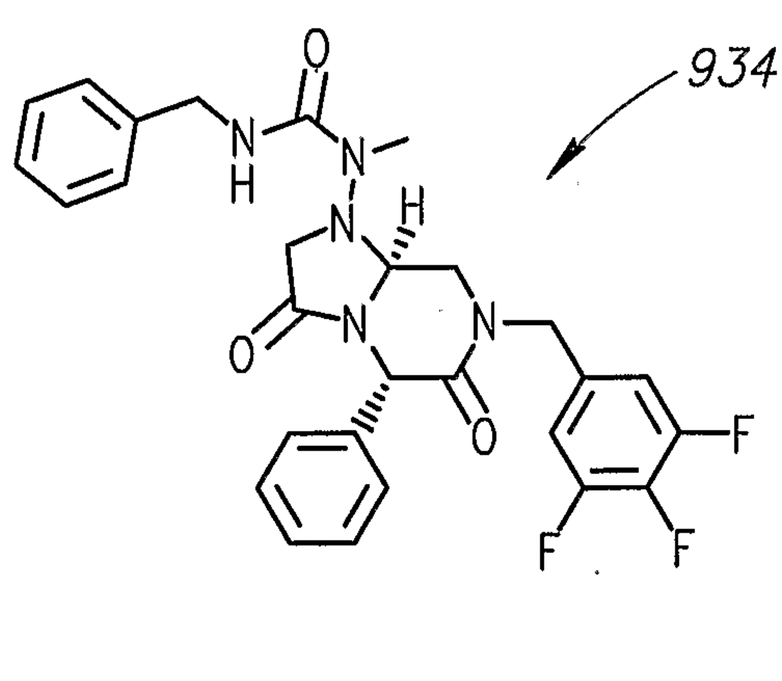


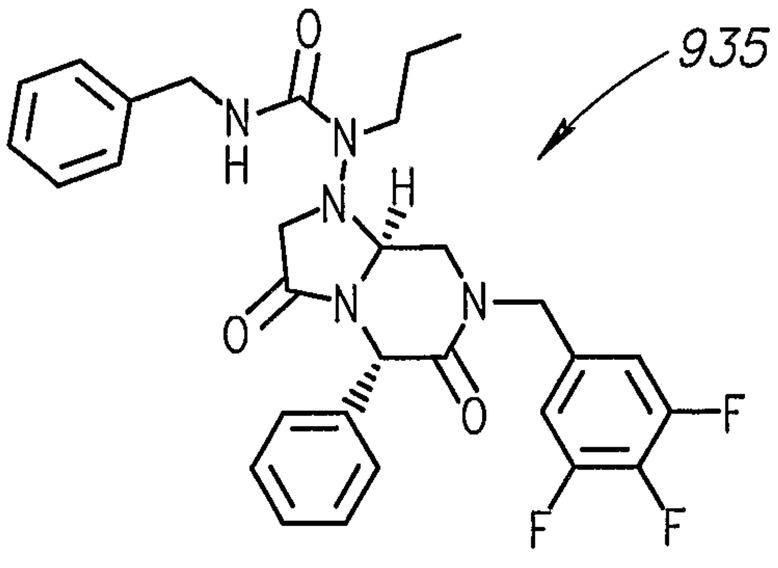












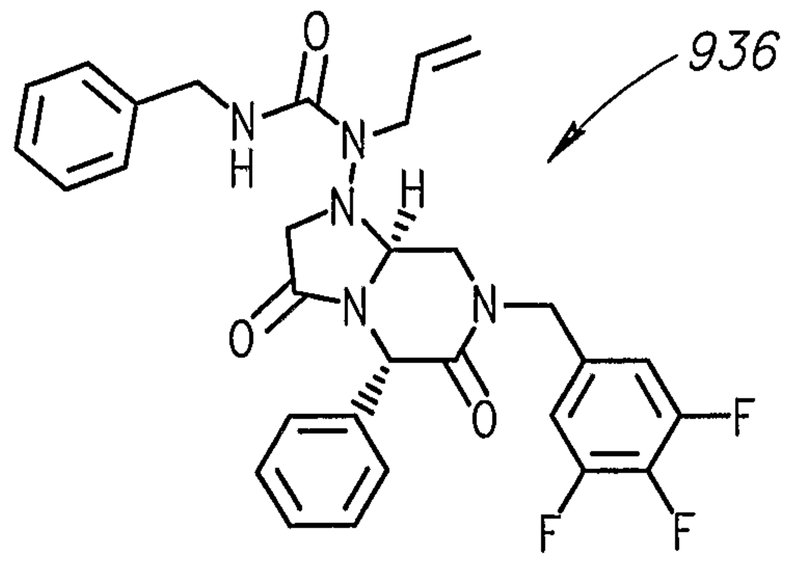
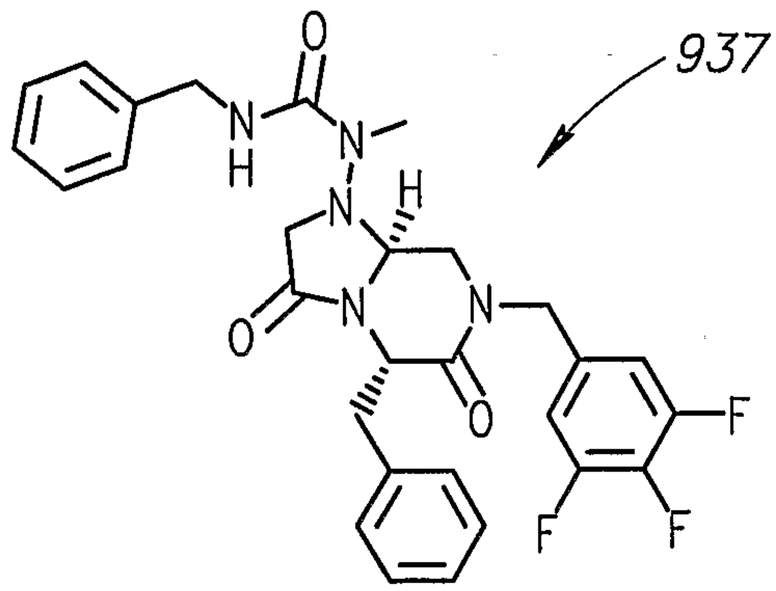
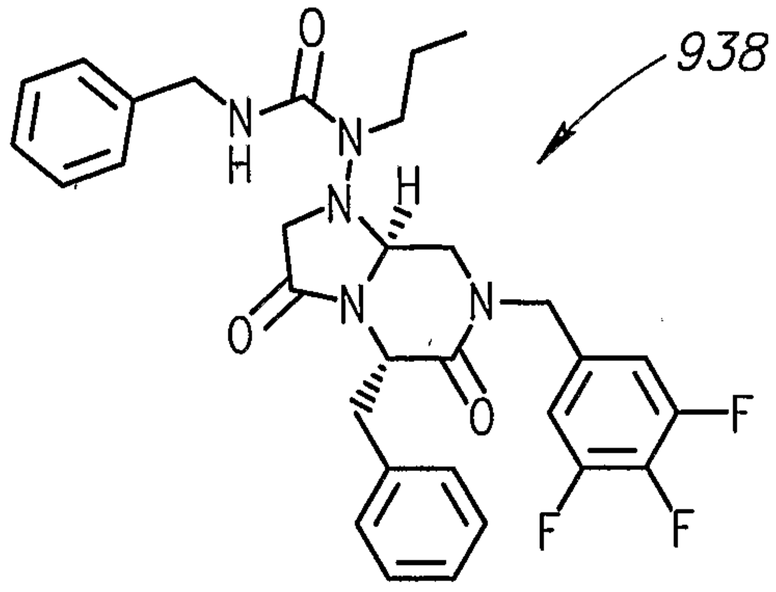
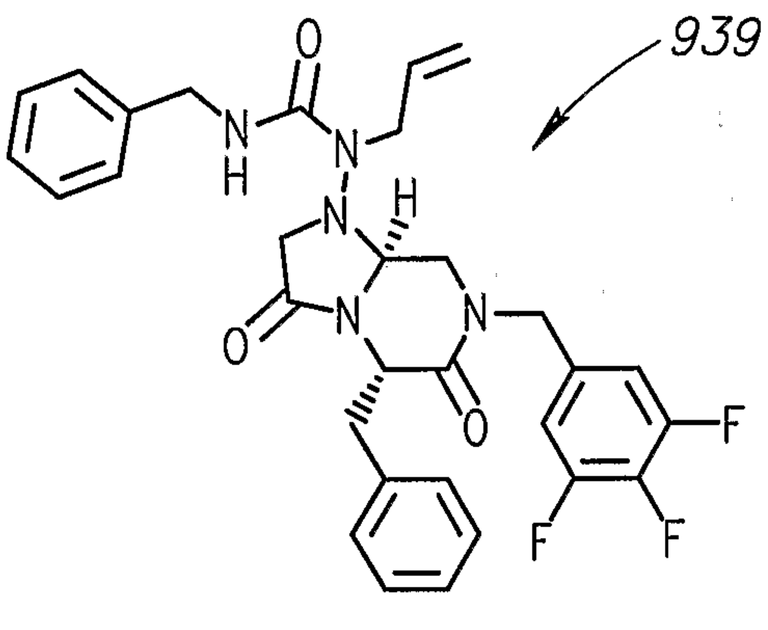
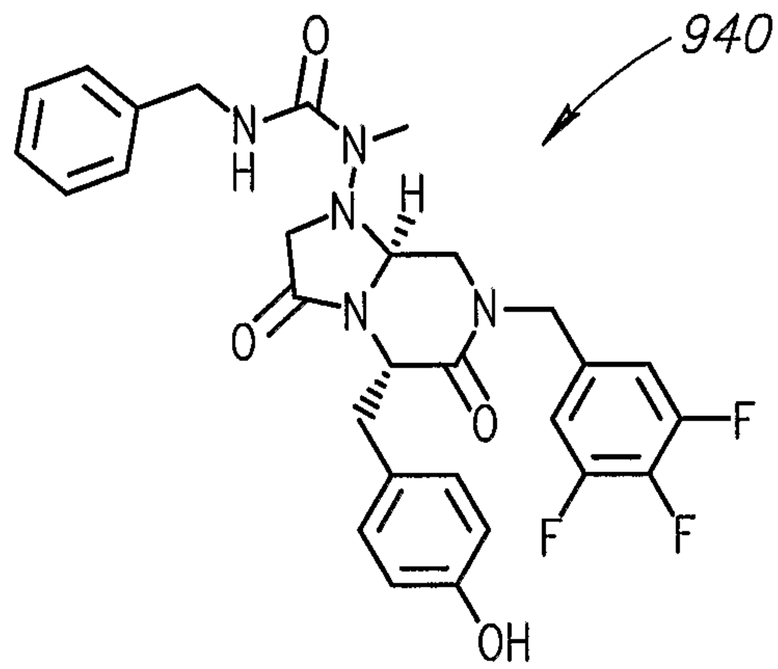


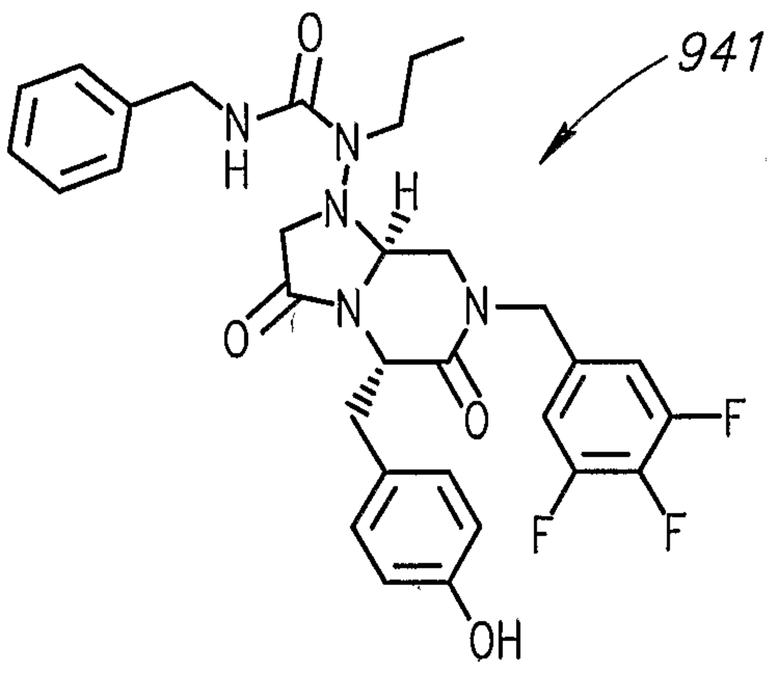
FIG.5Q

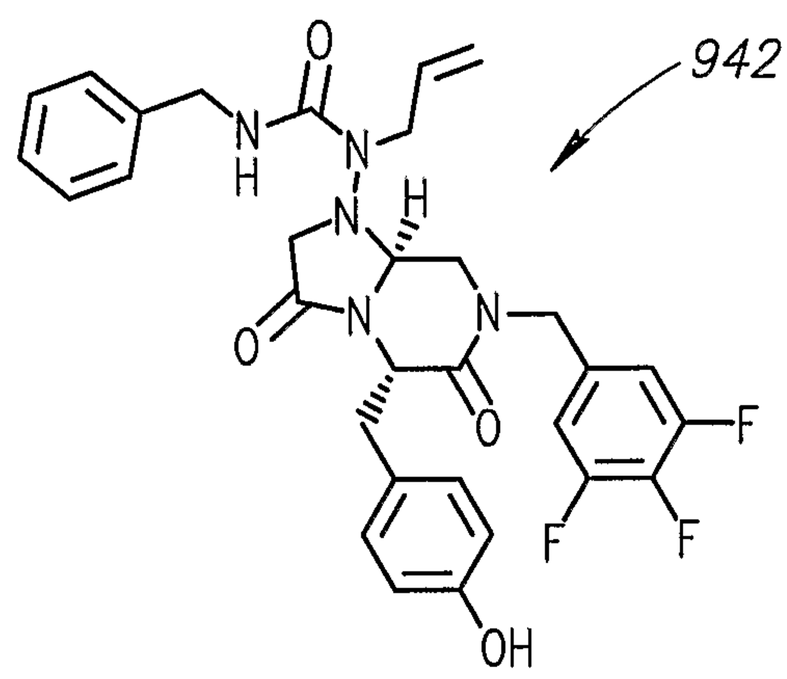


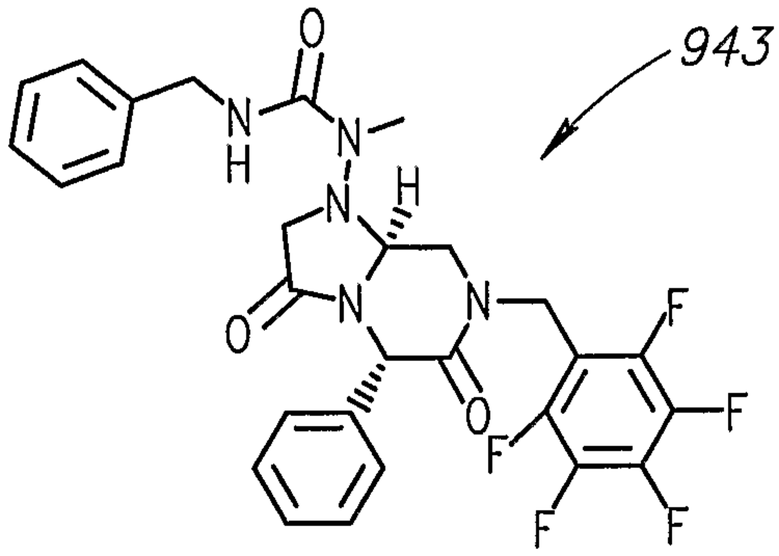












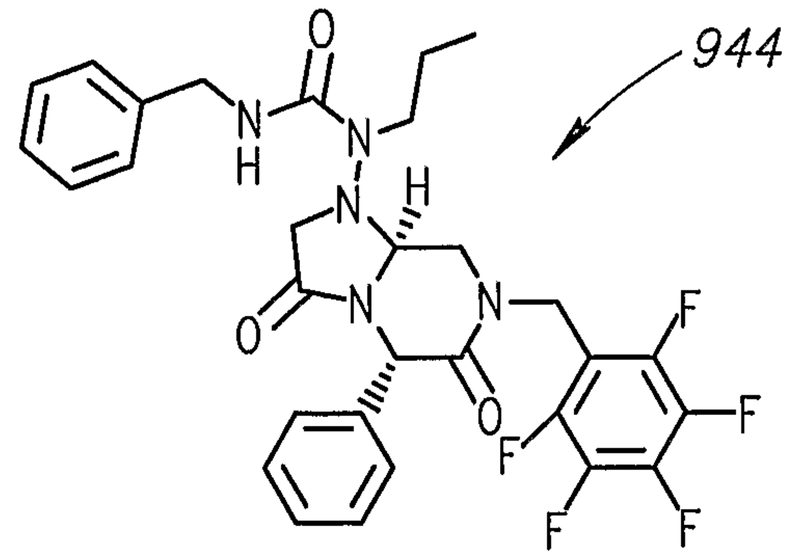
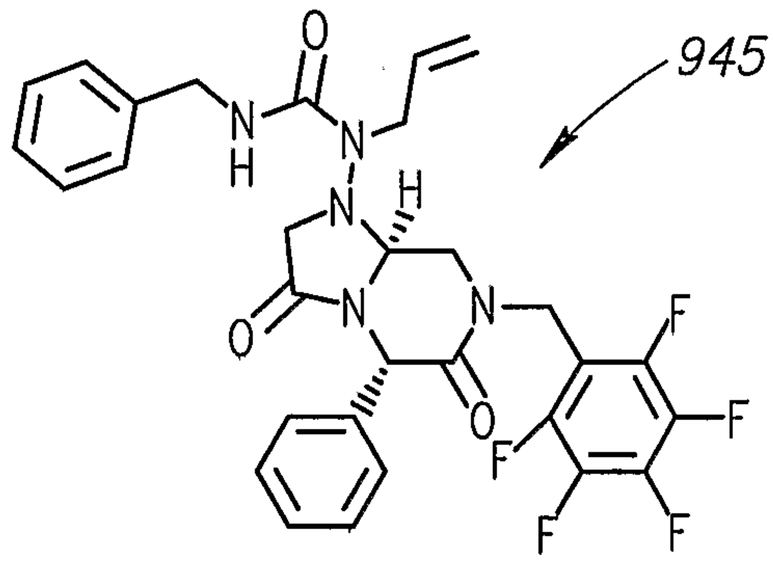
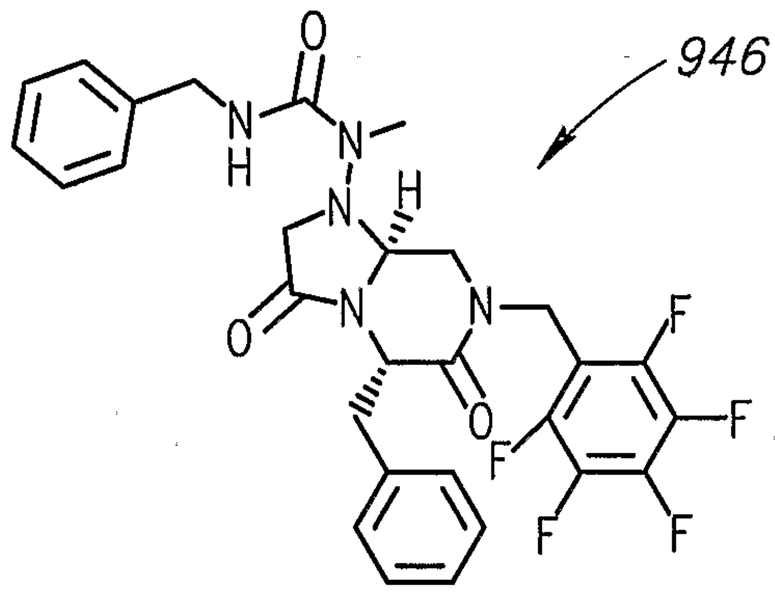
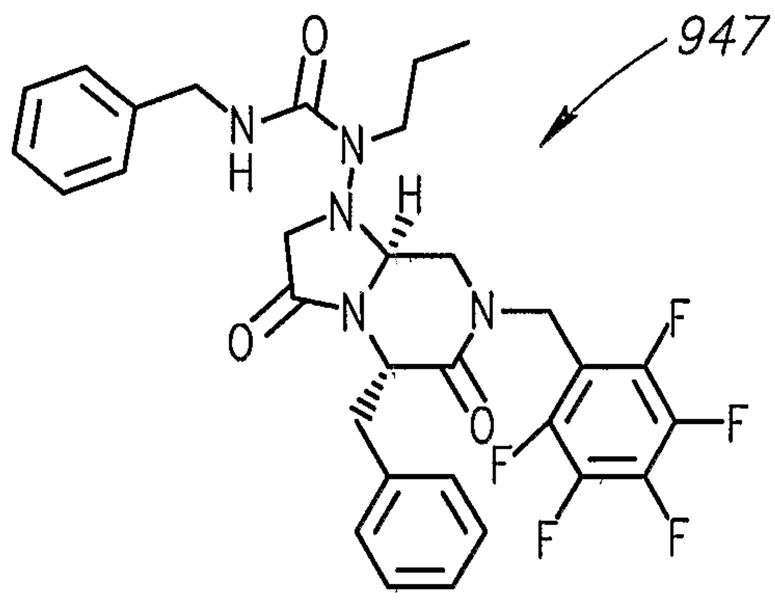
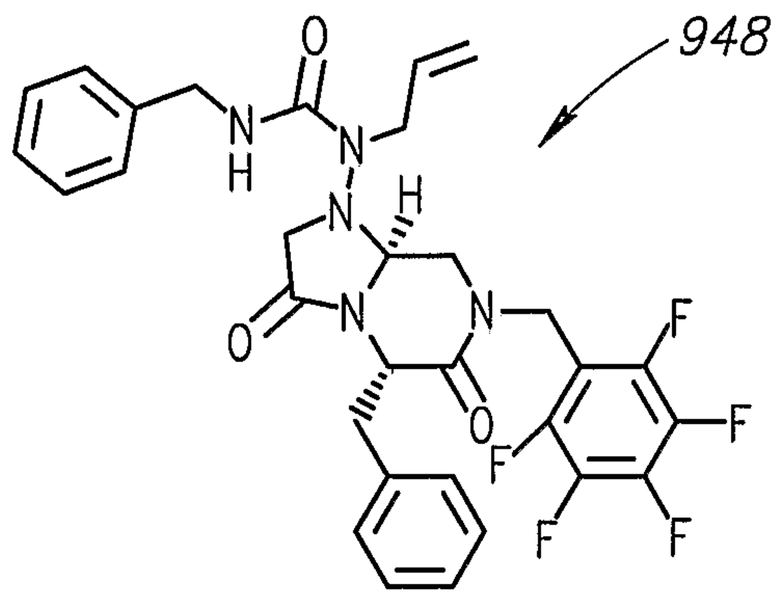


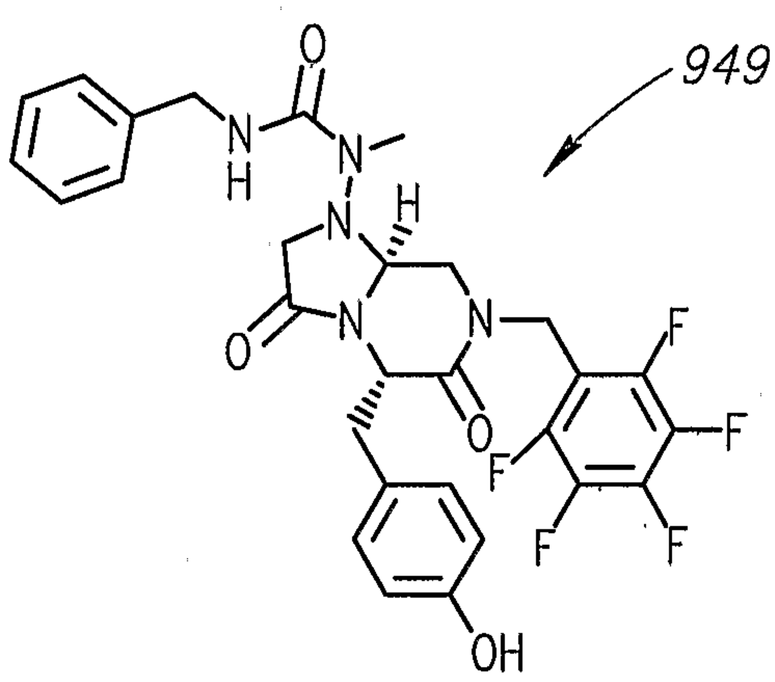
FIG.5R

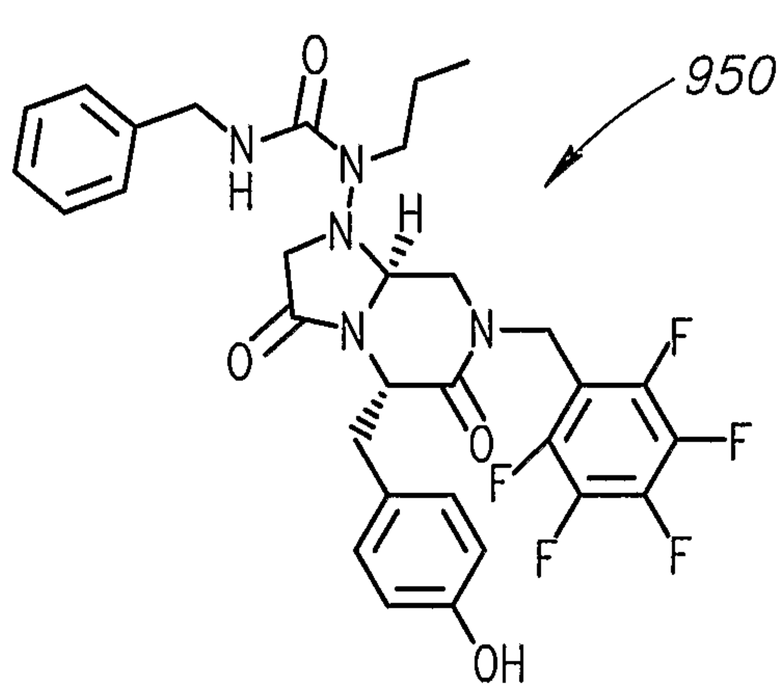


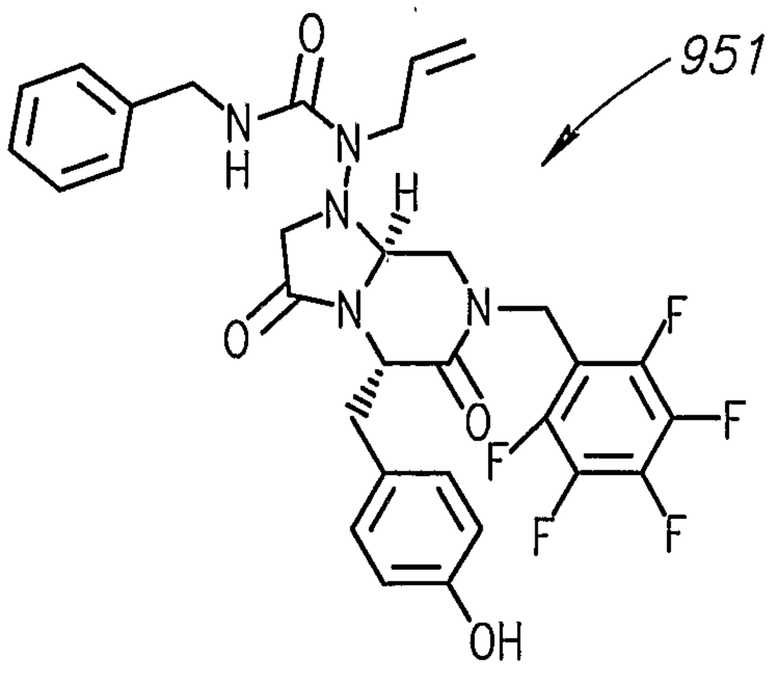












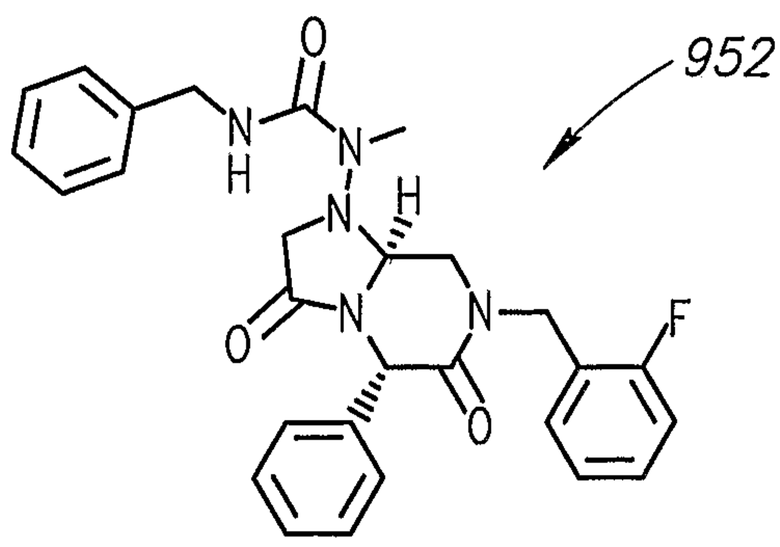
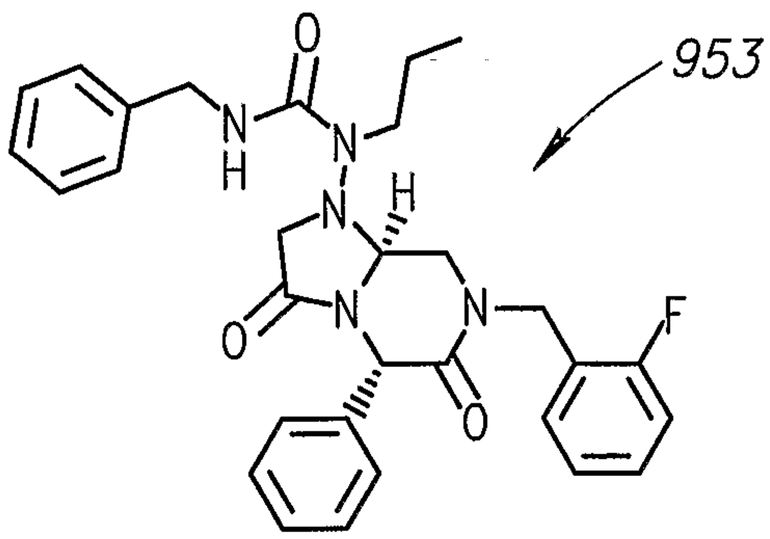
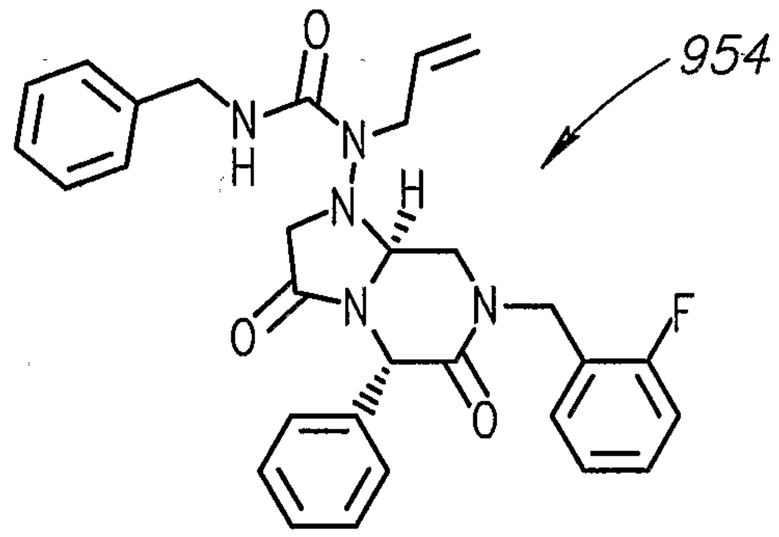
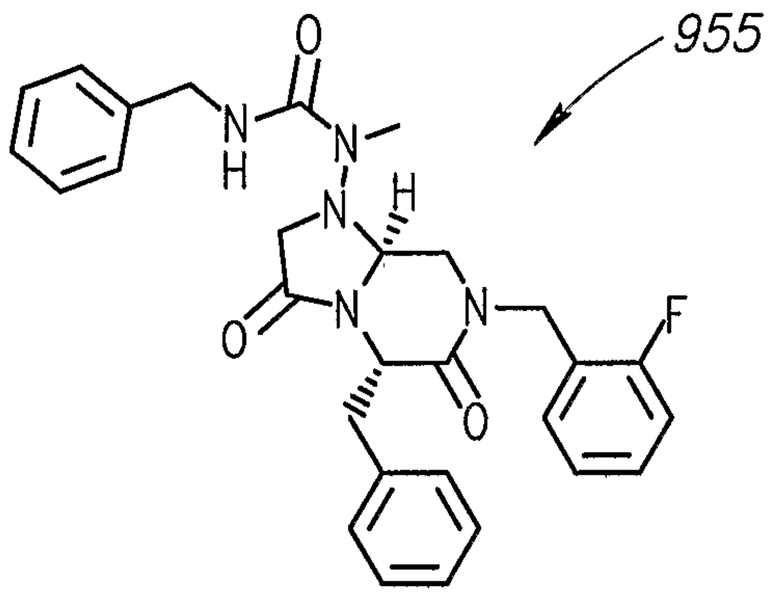
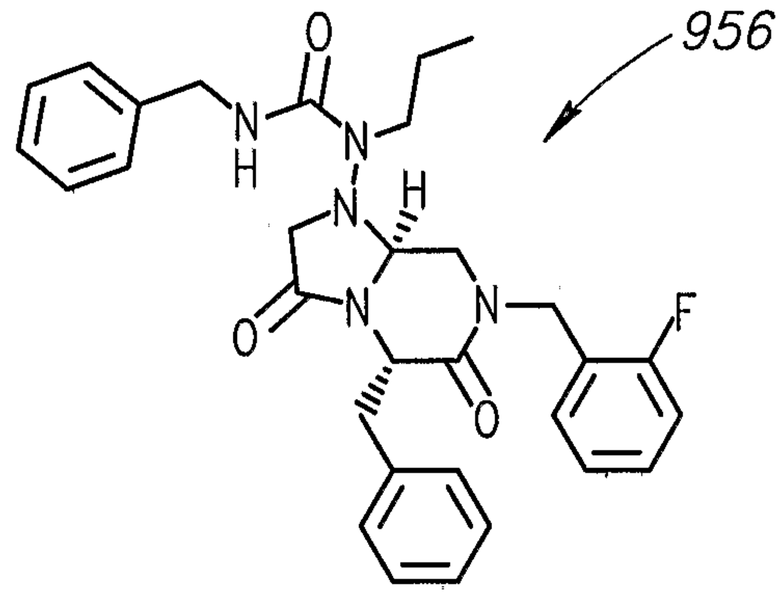


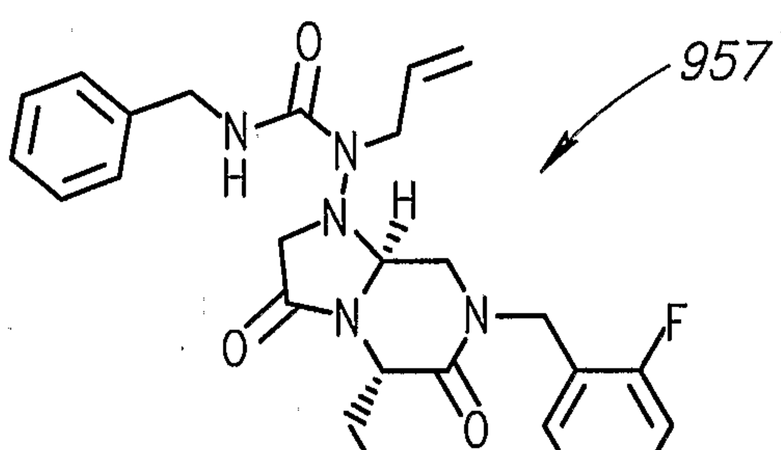
FIG.5S











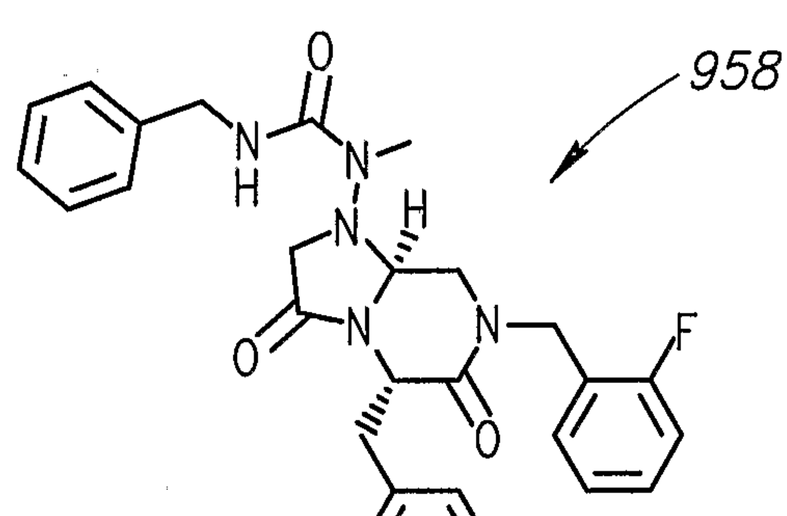
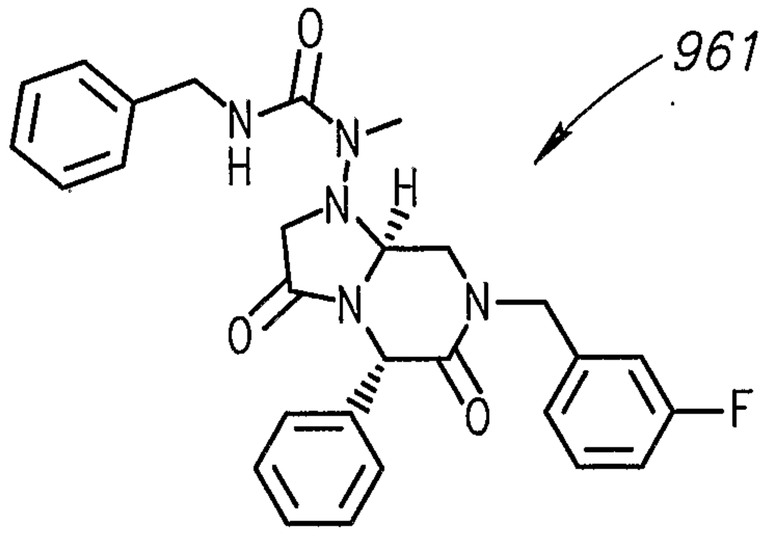


FIG.5T

961



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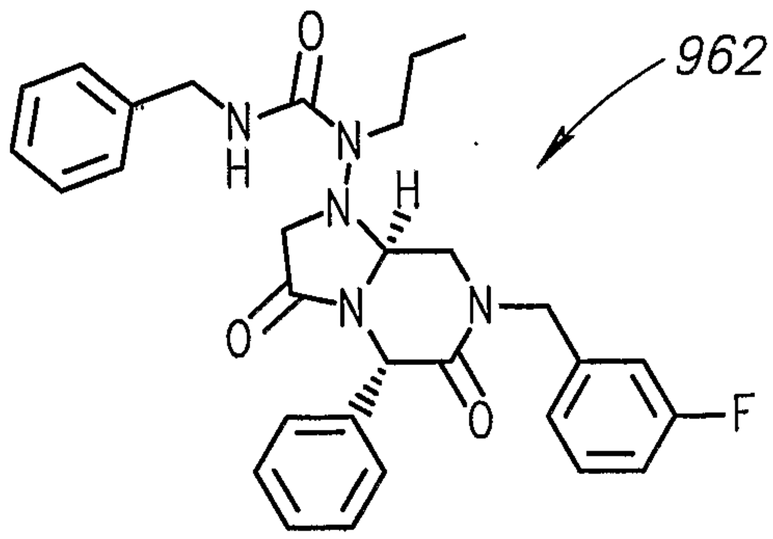

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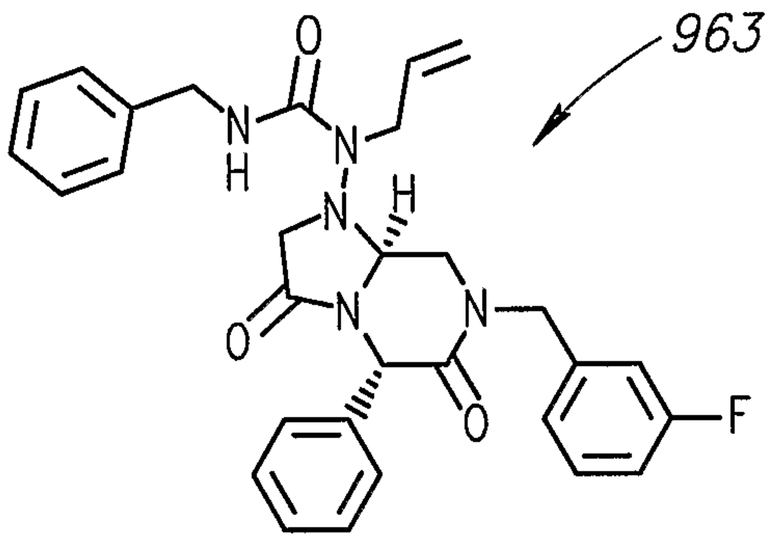

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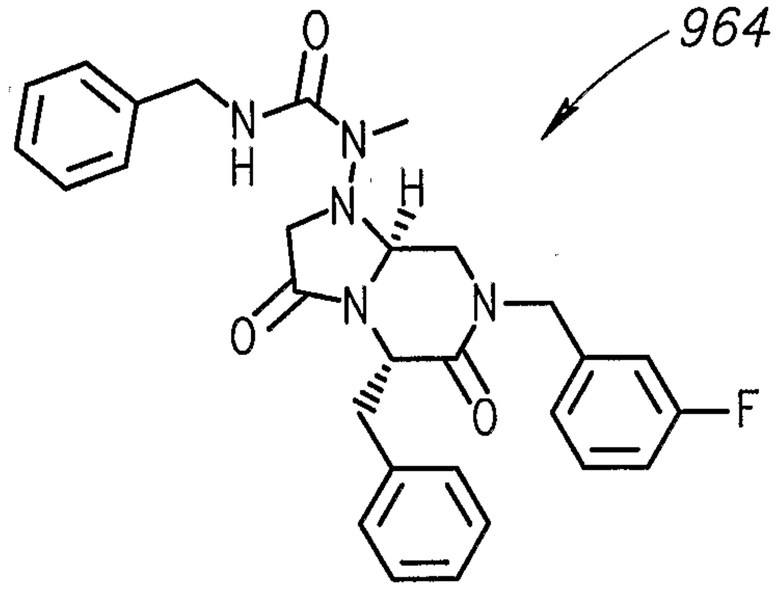

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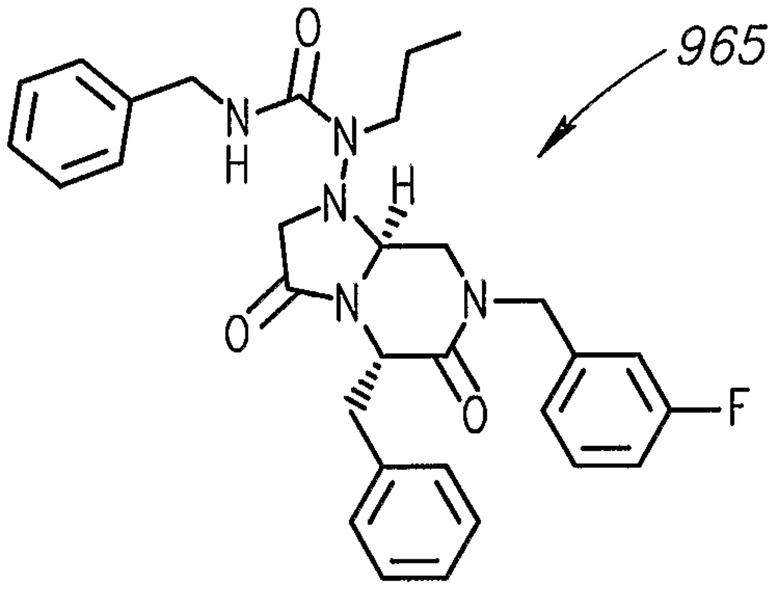

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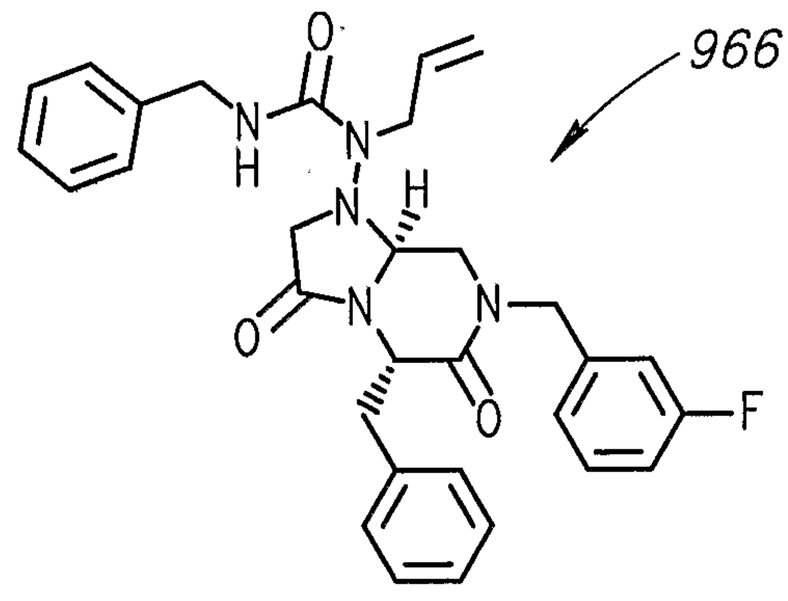

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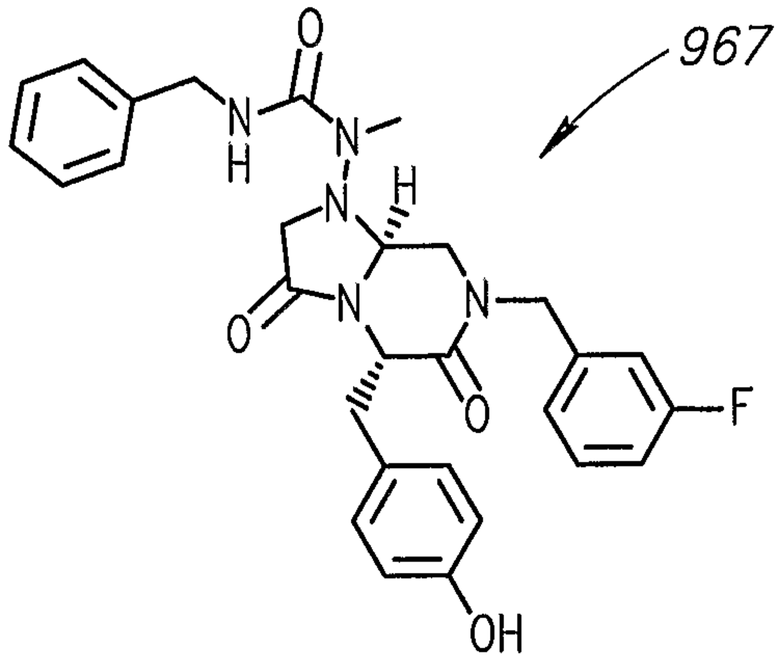

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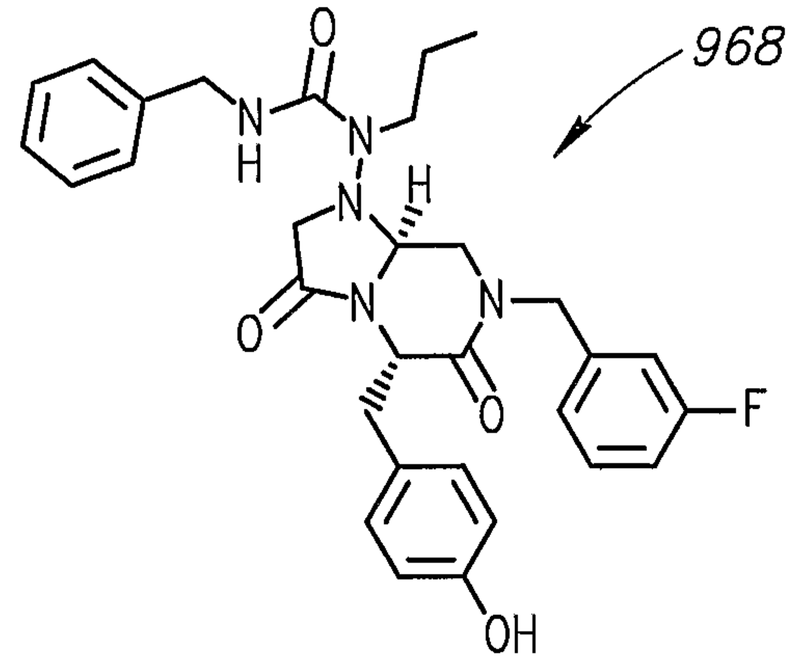
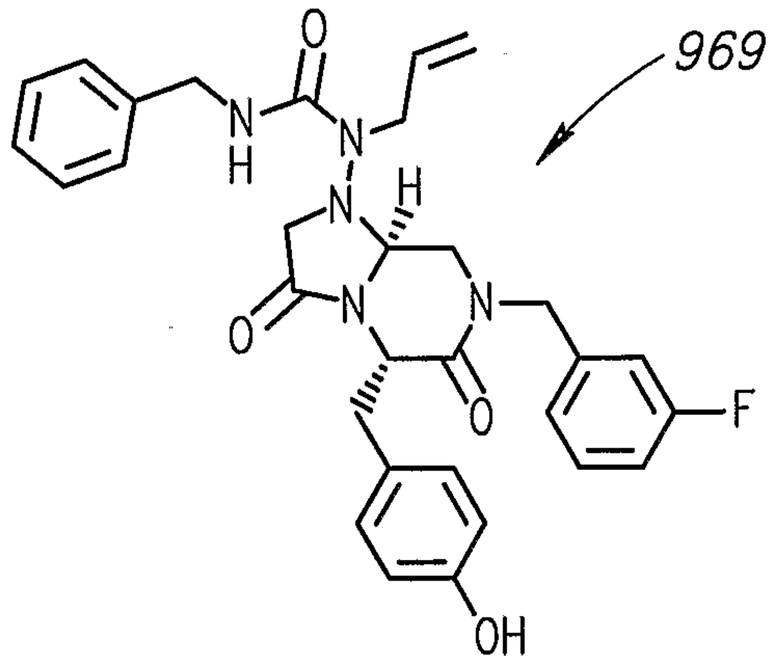


FIG.5U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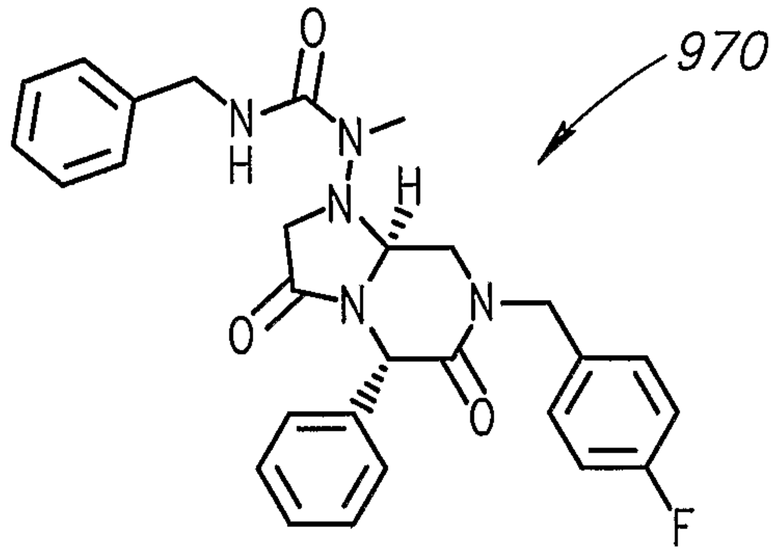
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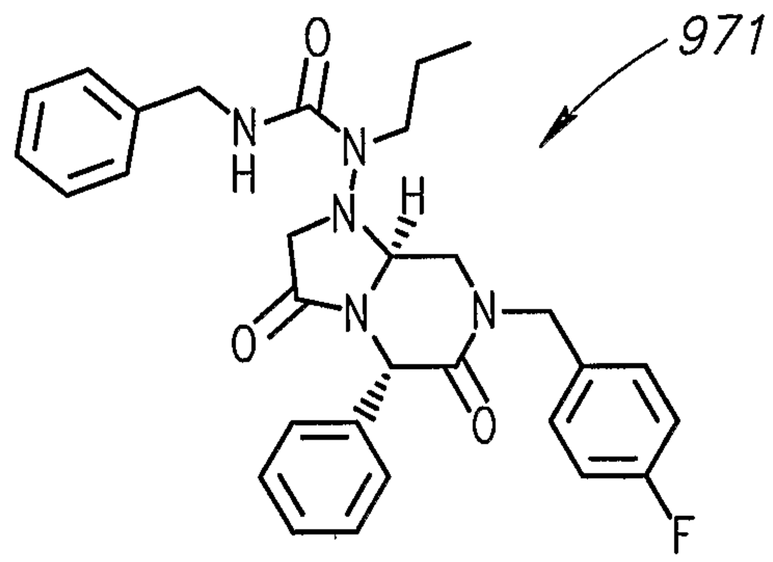
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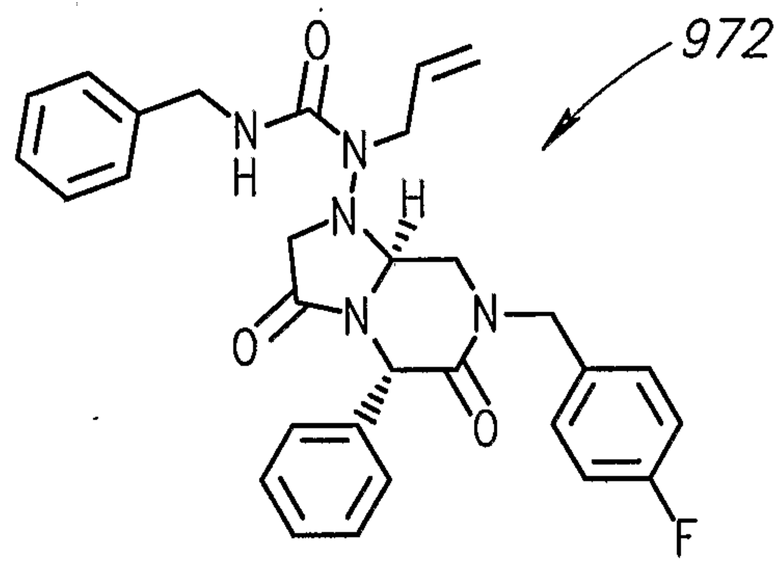
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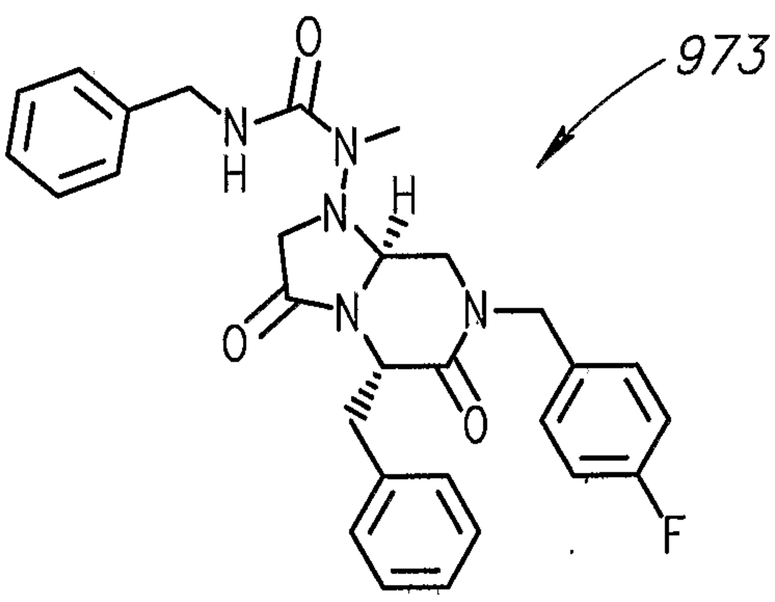
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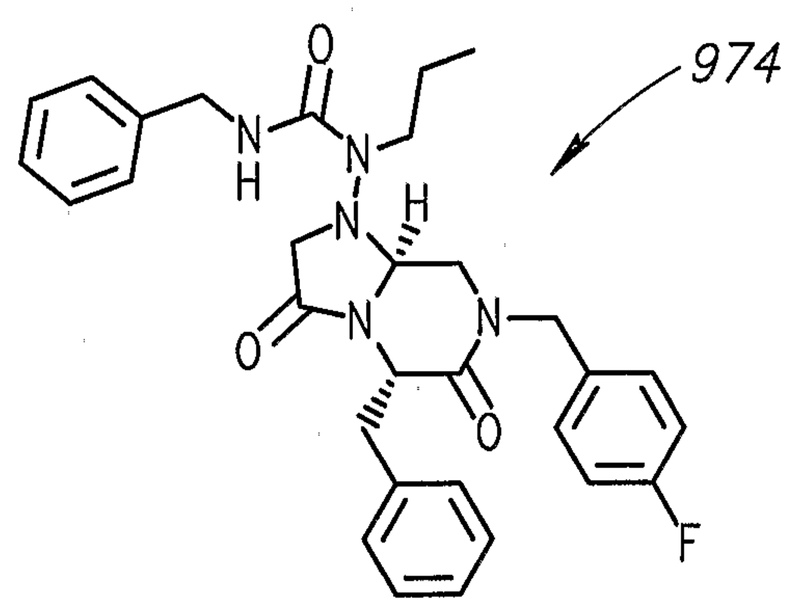
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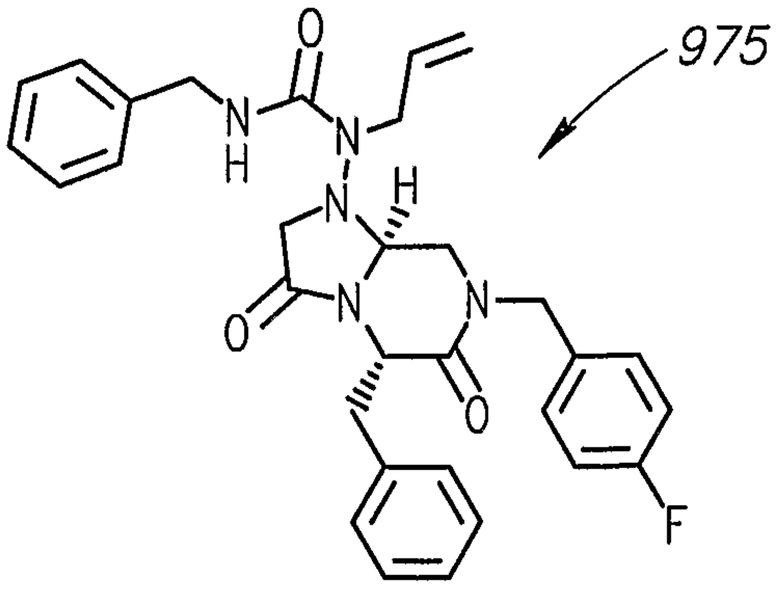
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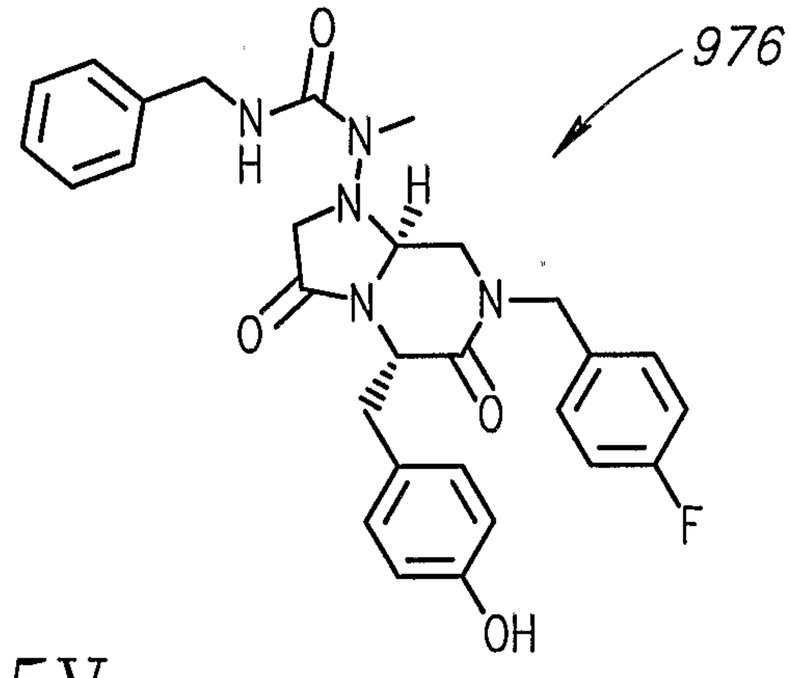
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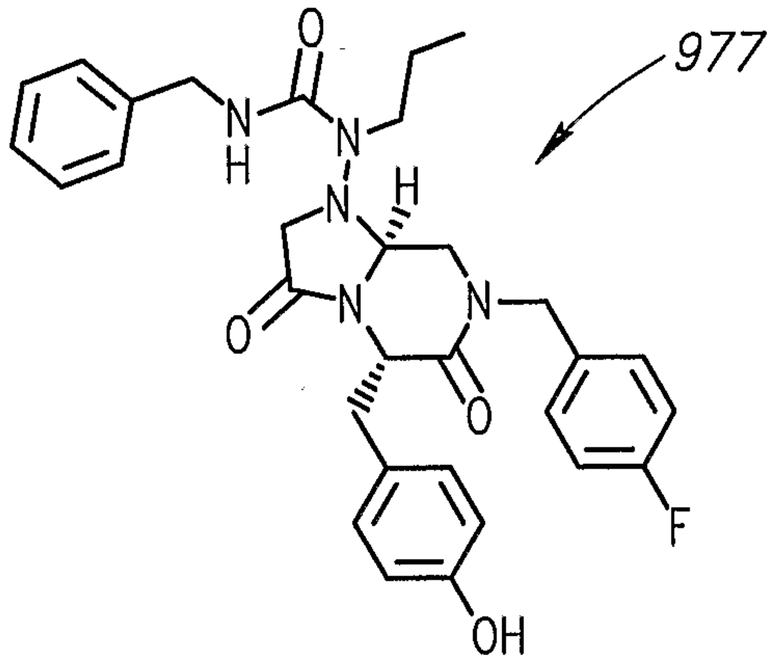
OH

FIG.5V

977



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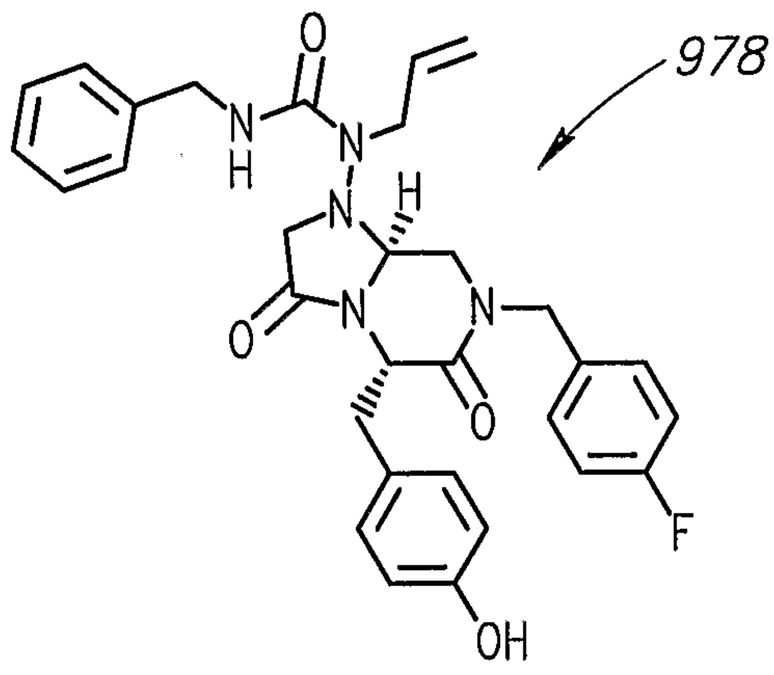

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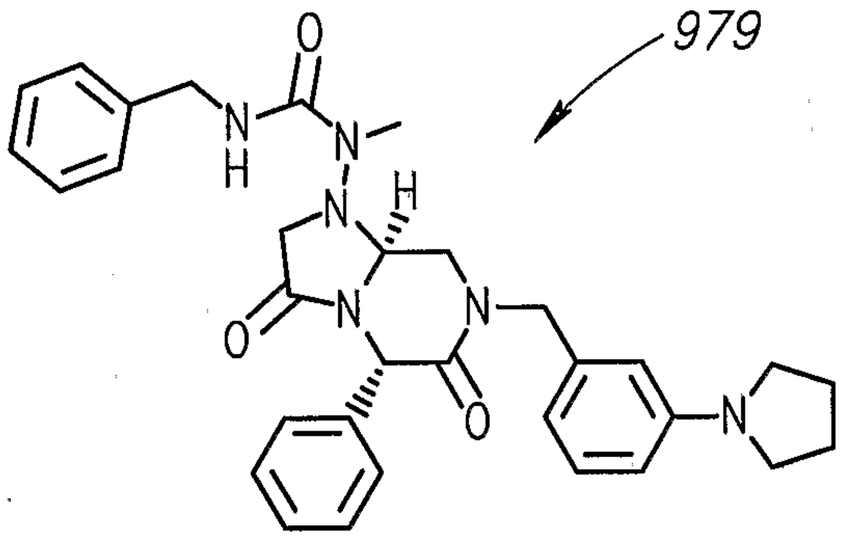

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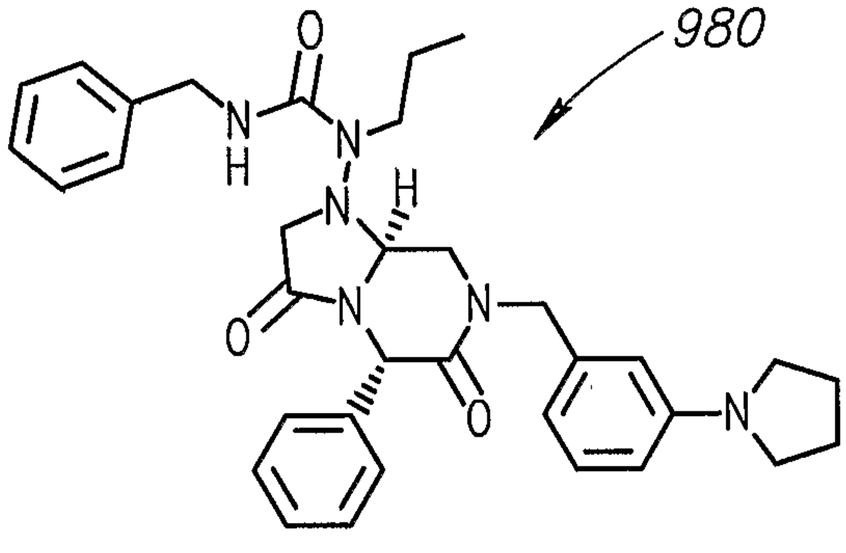

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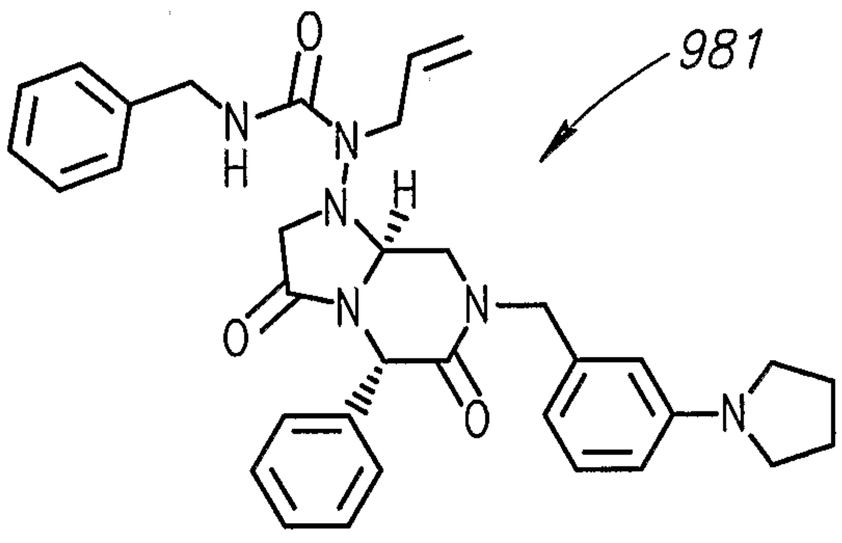

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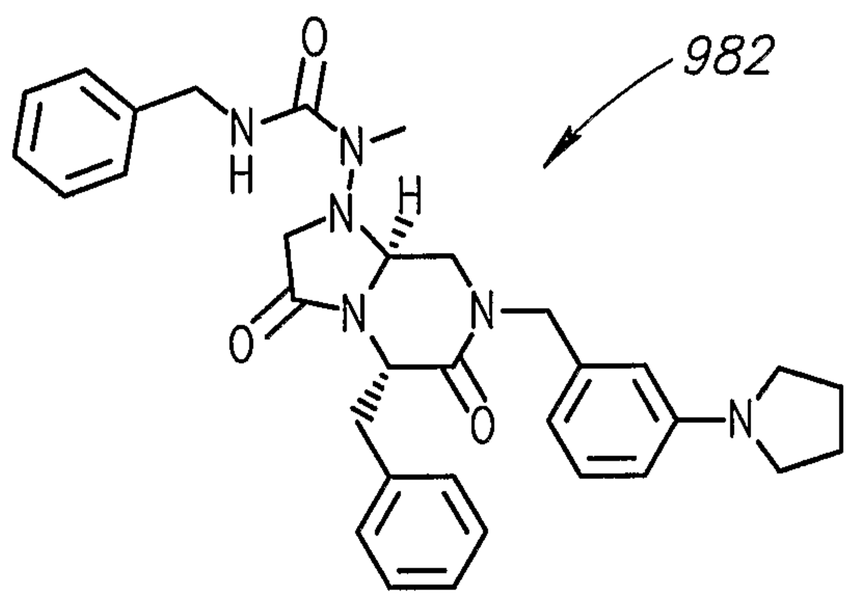


983

984

FIG.5W

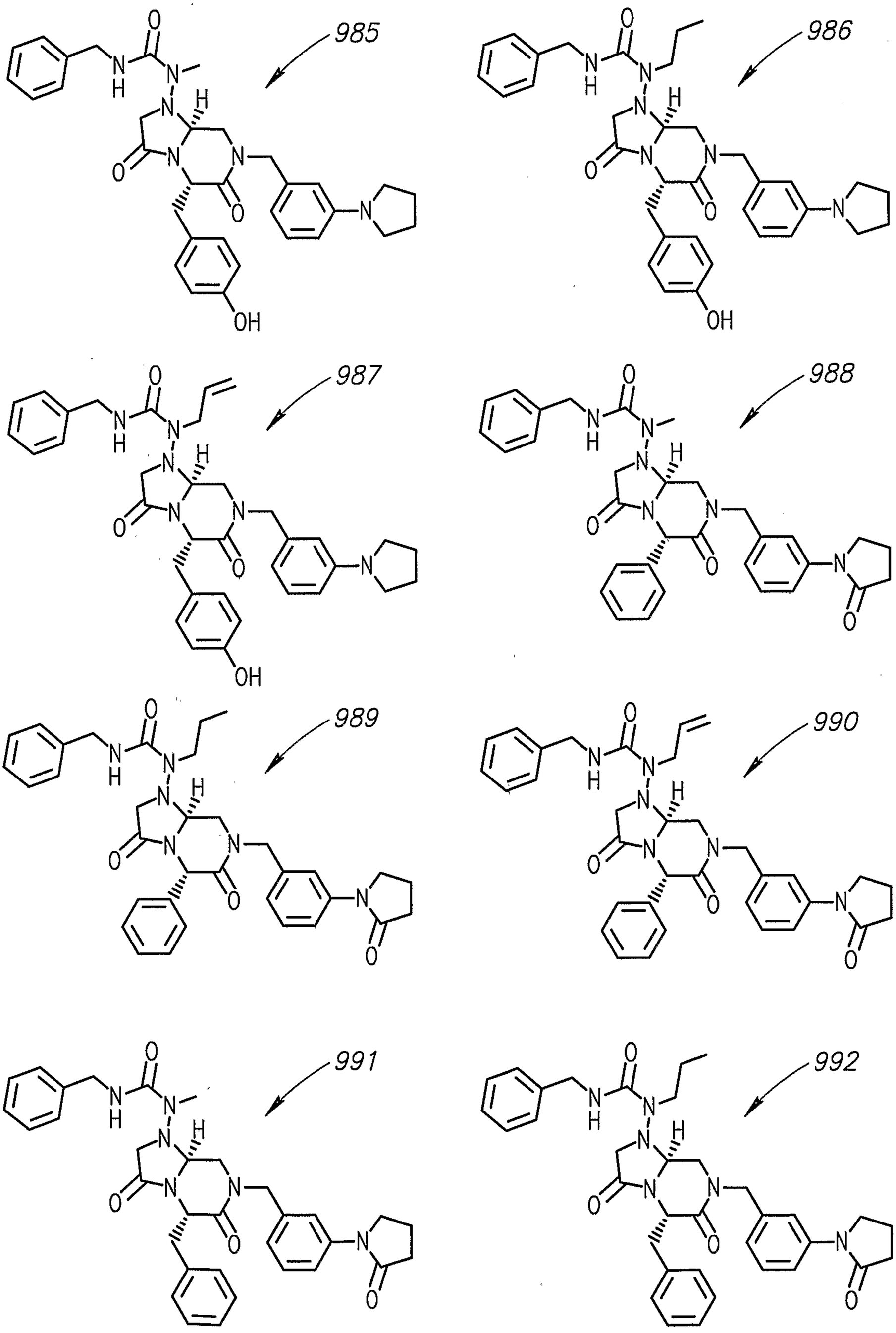
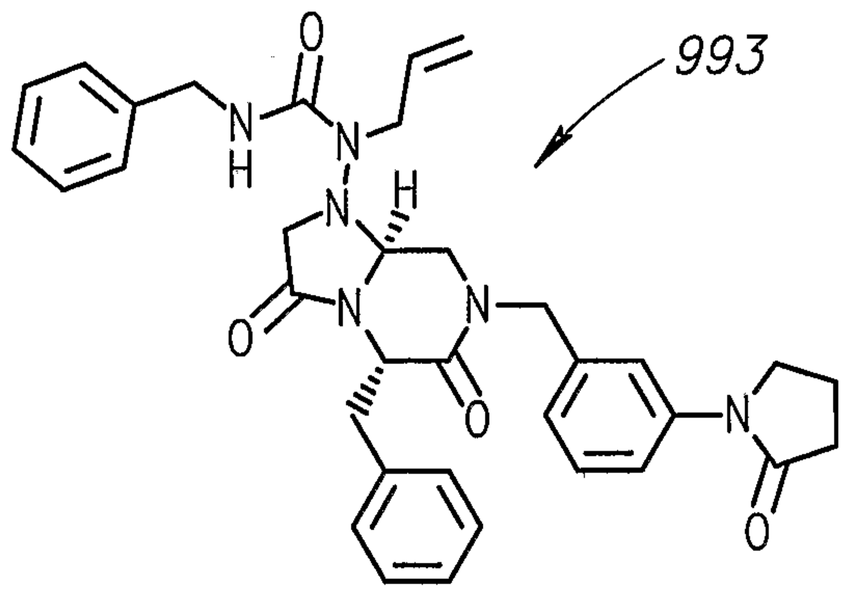
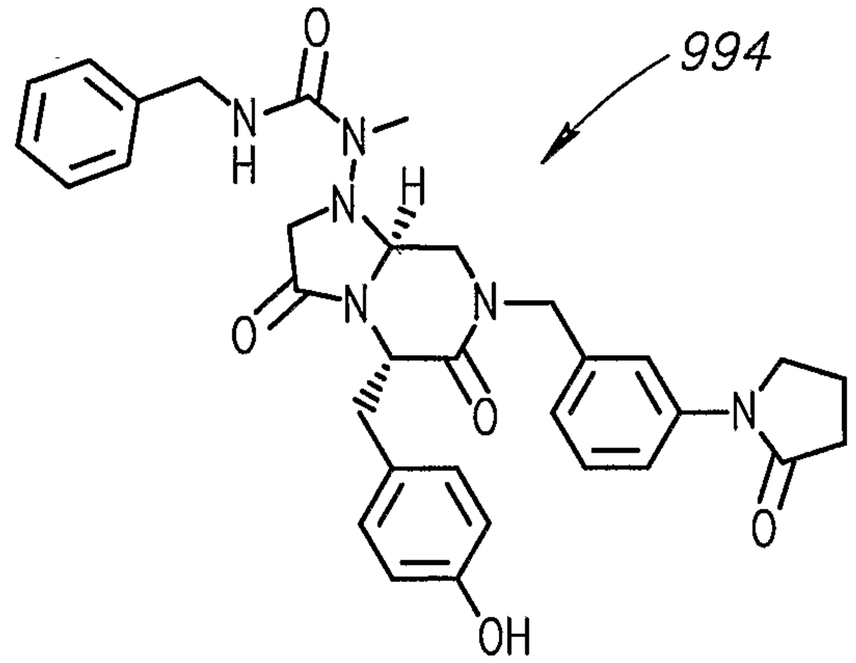
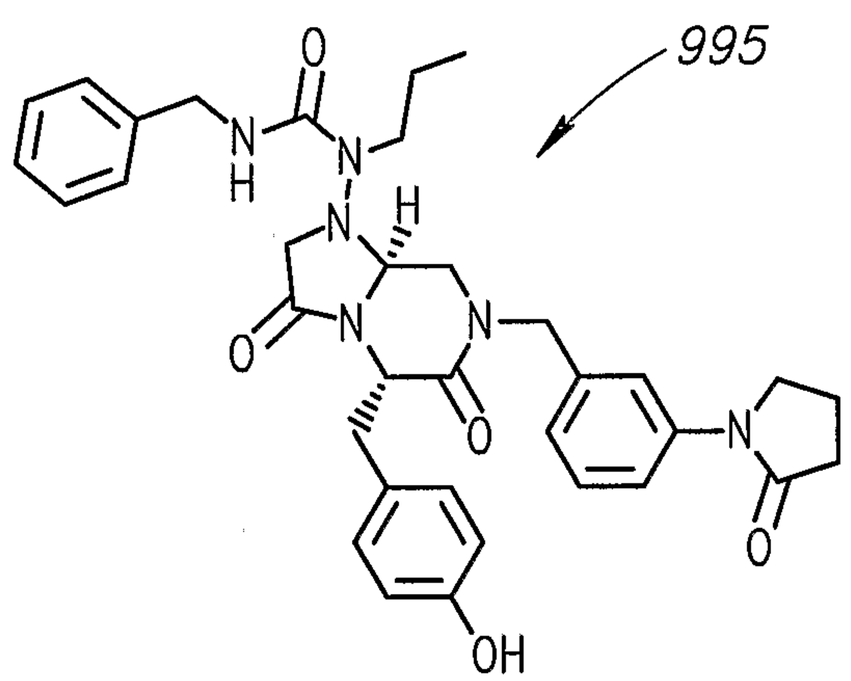
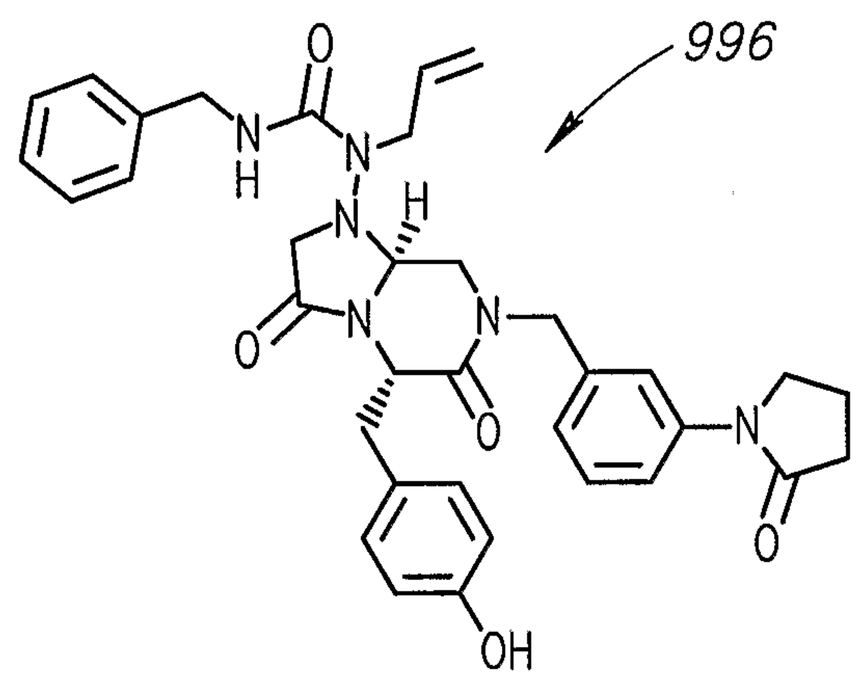


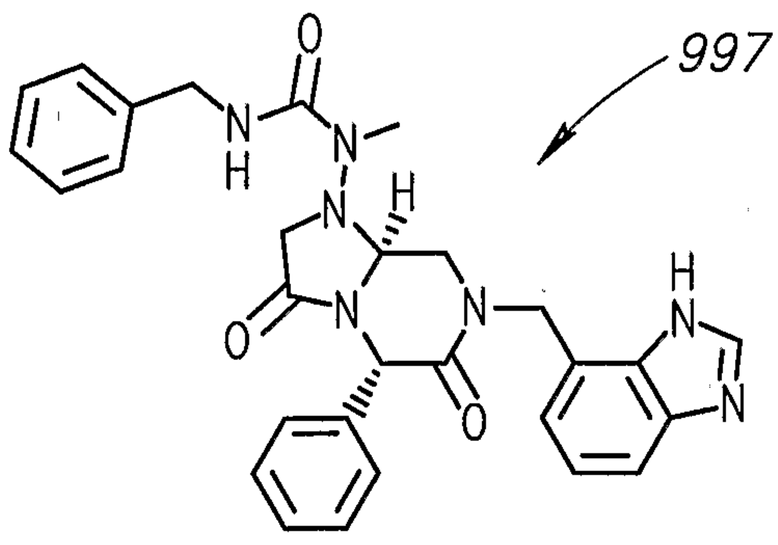
FIG.5X

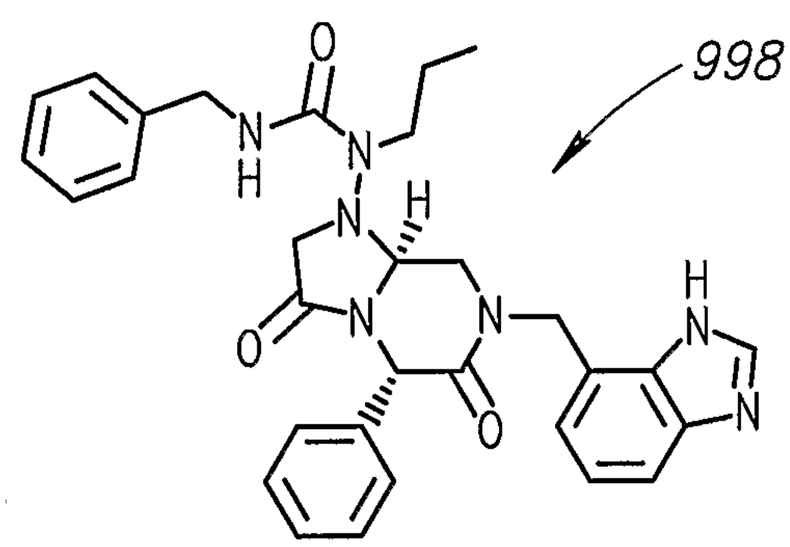


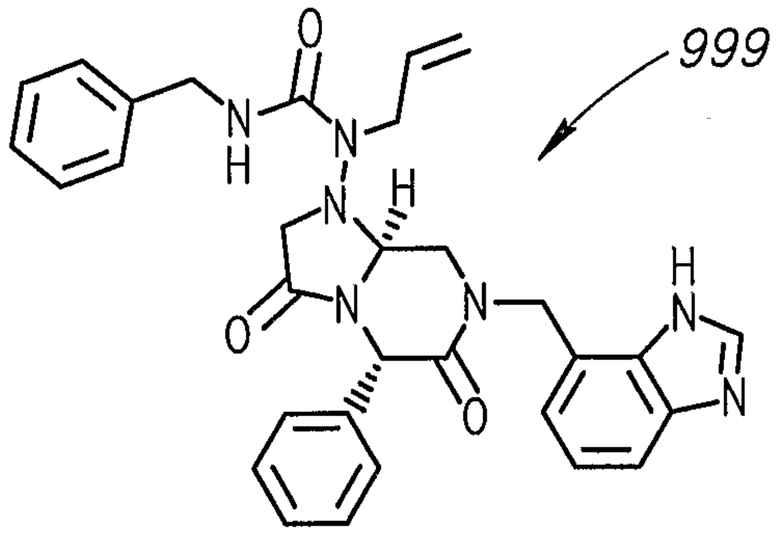












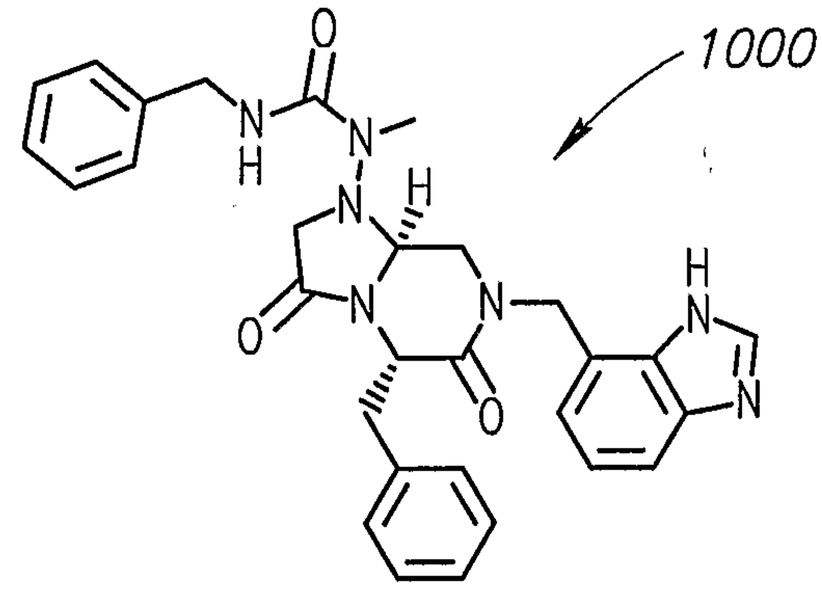
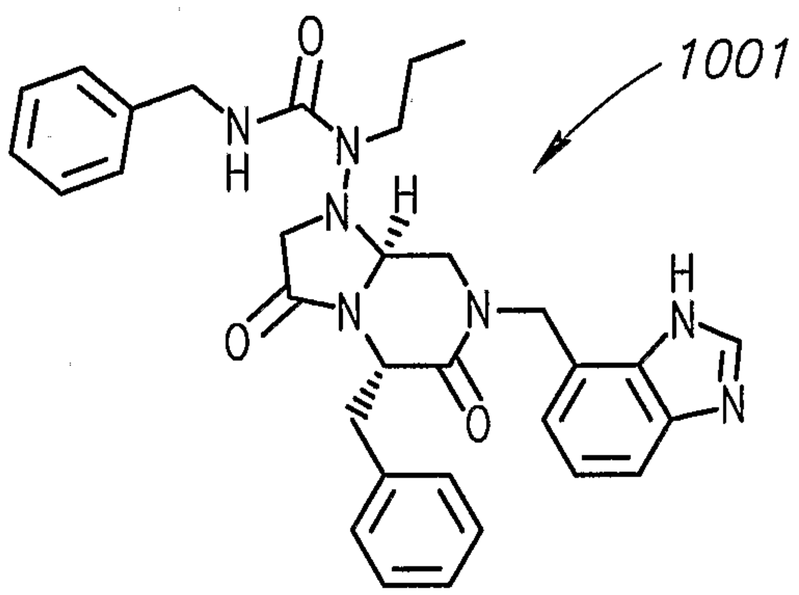
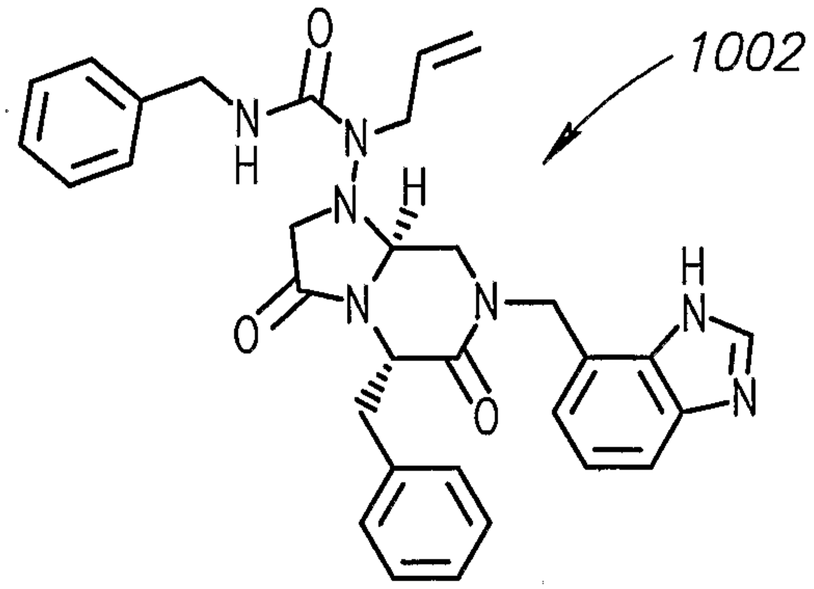
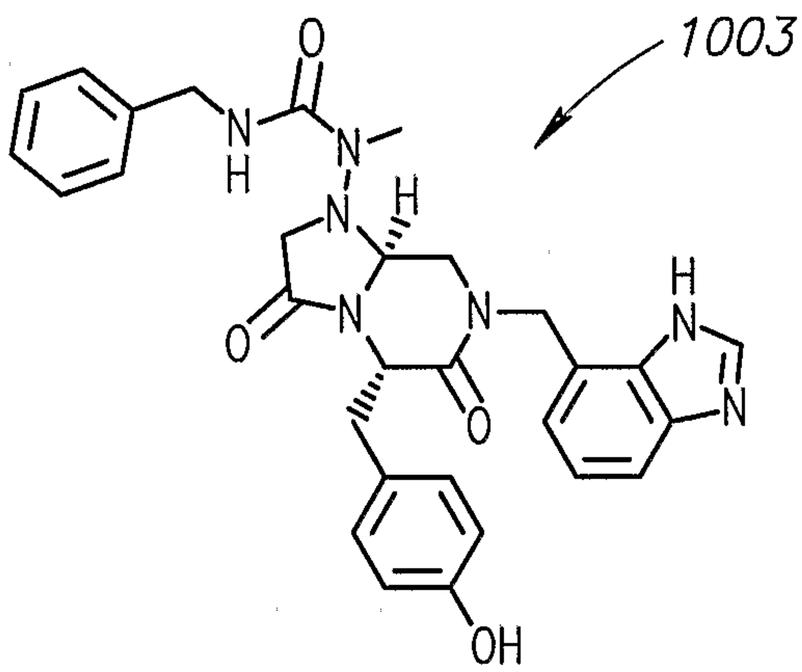
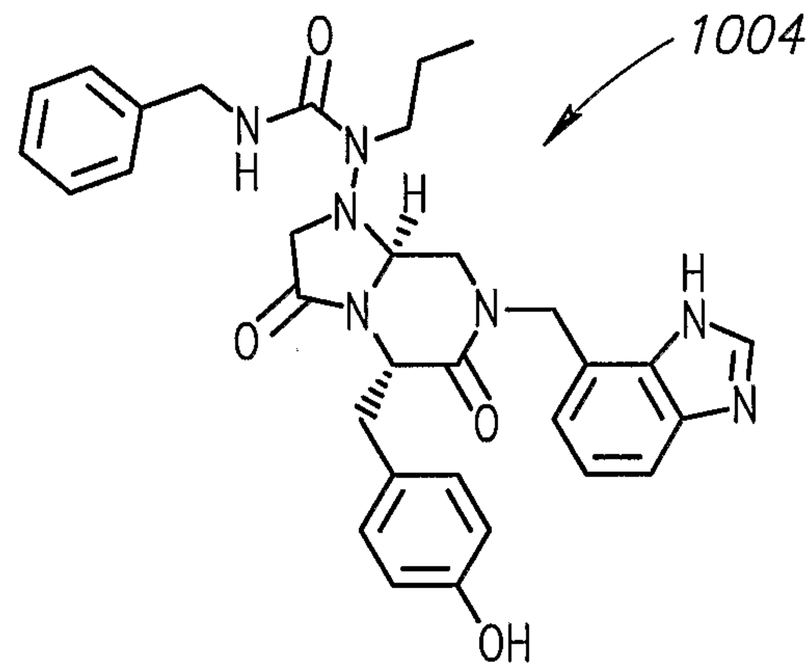


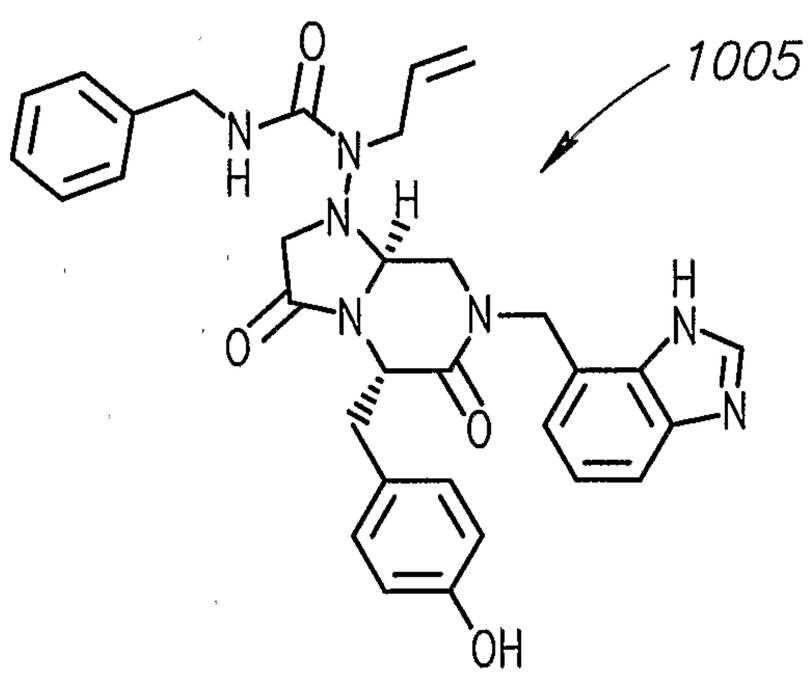
FIG.5Y

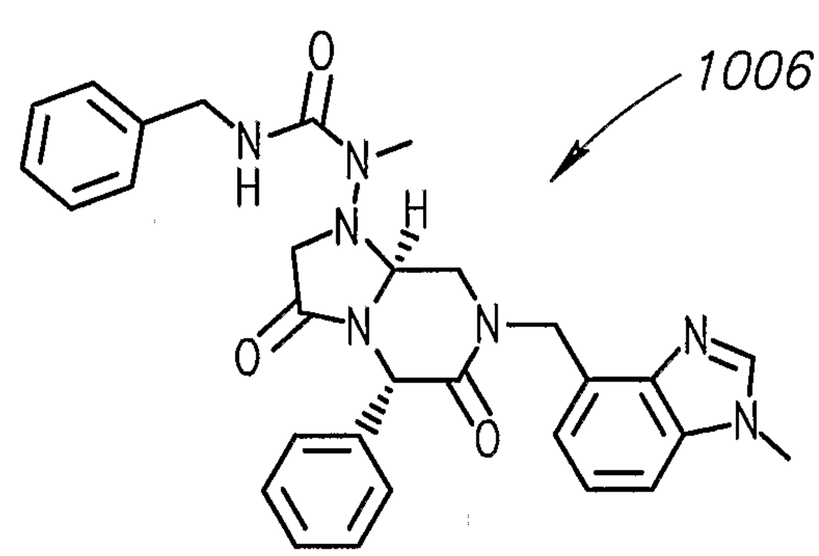


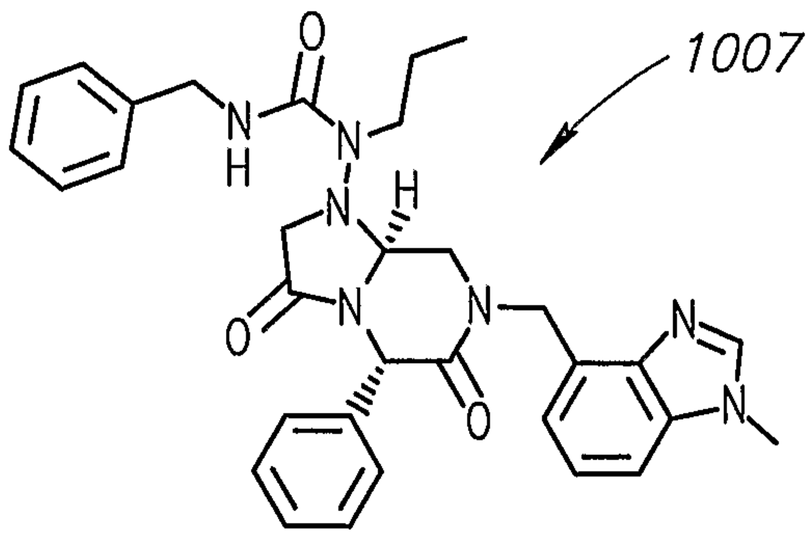












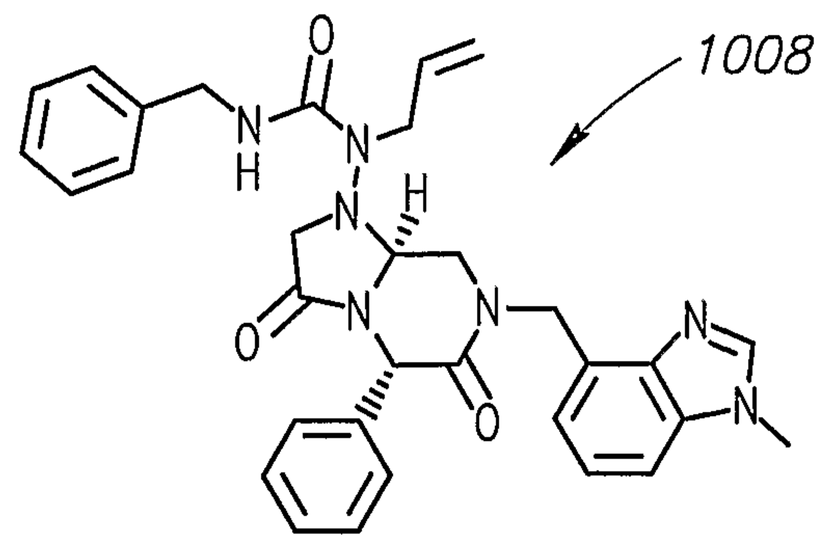
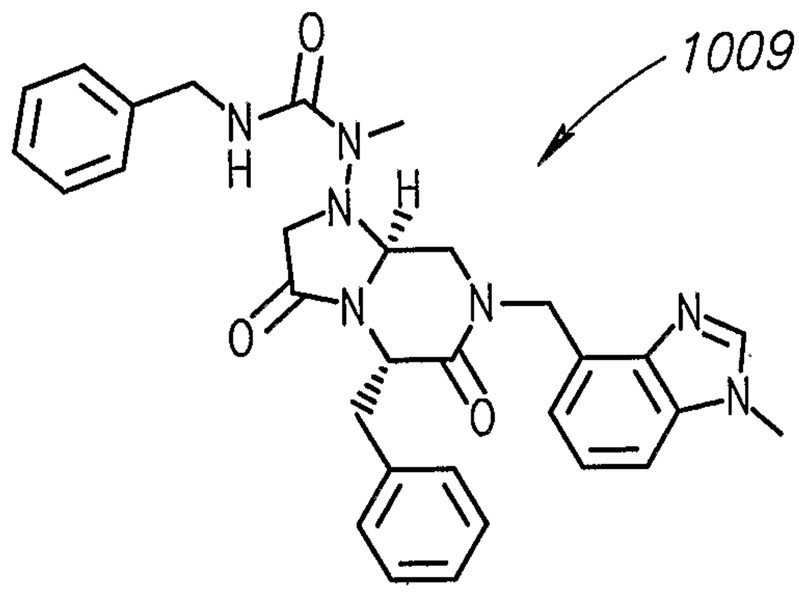
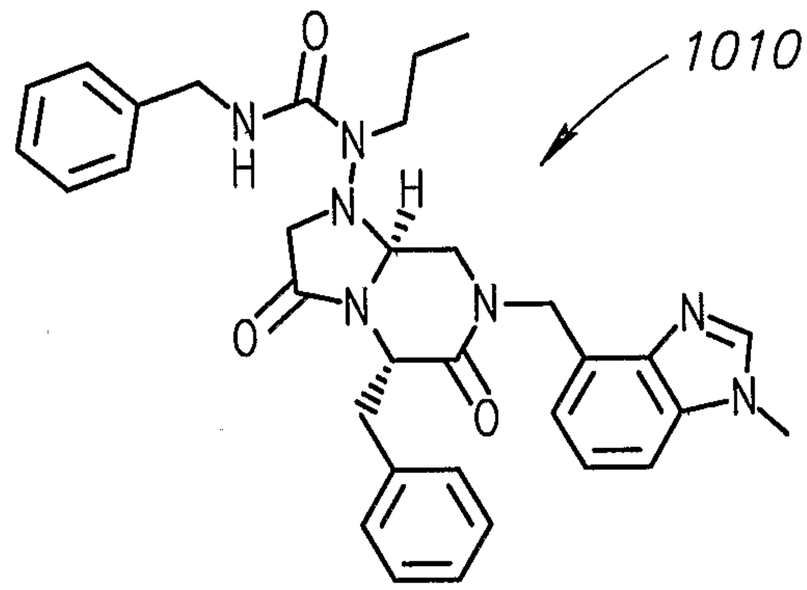
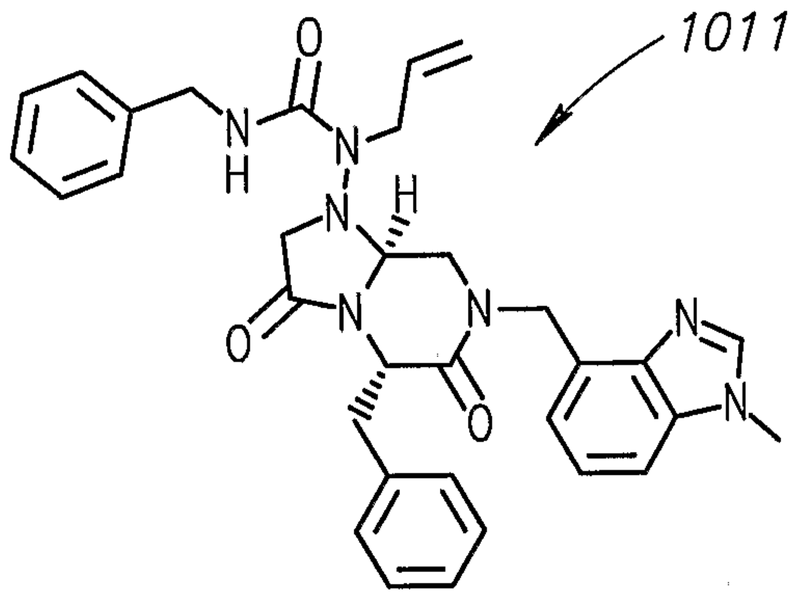
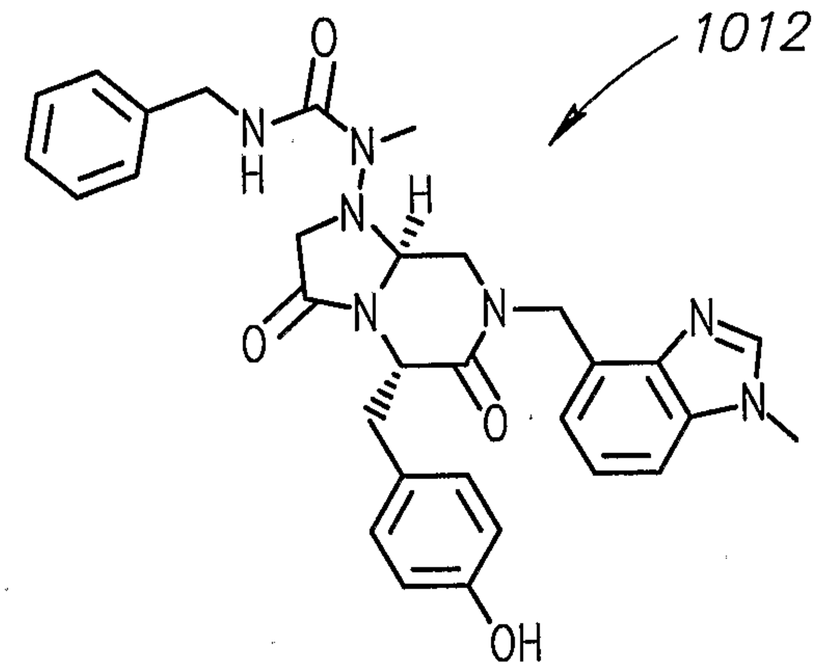


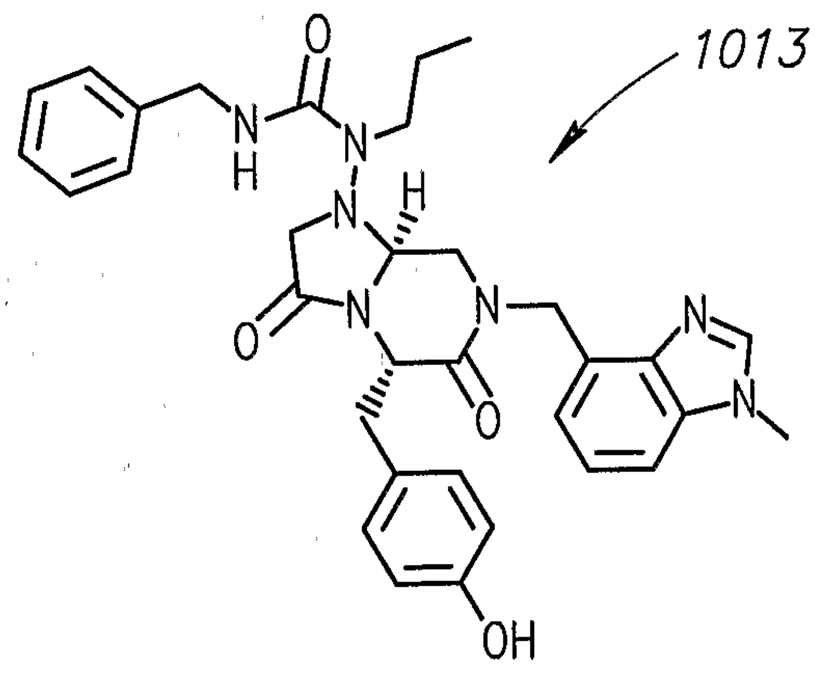
FIG.6A

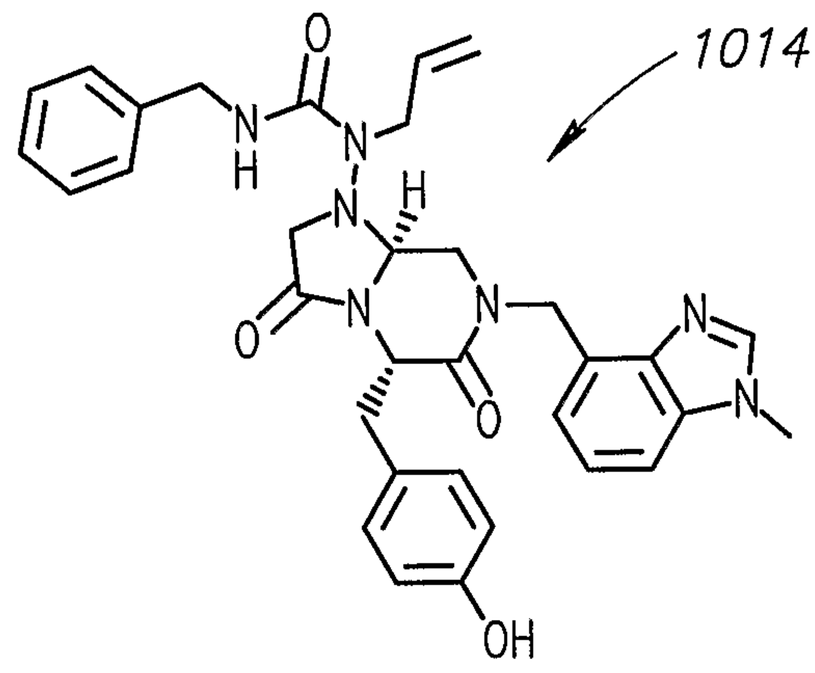


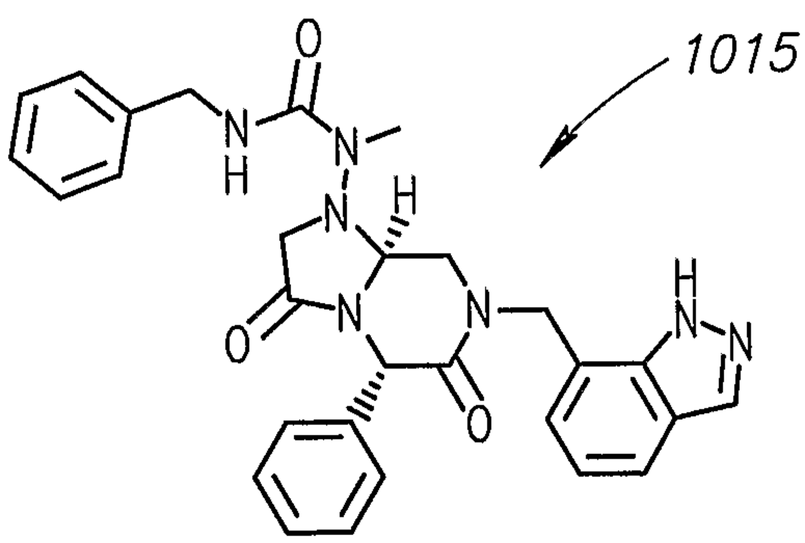












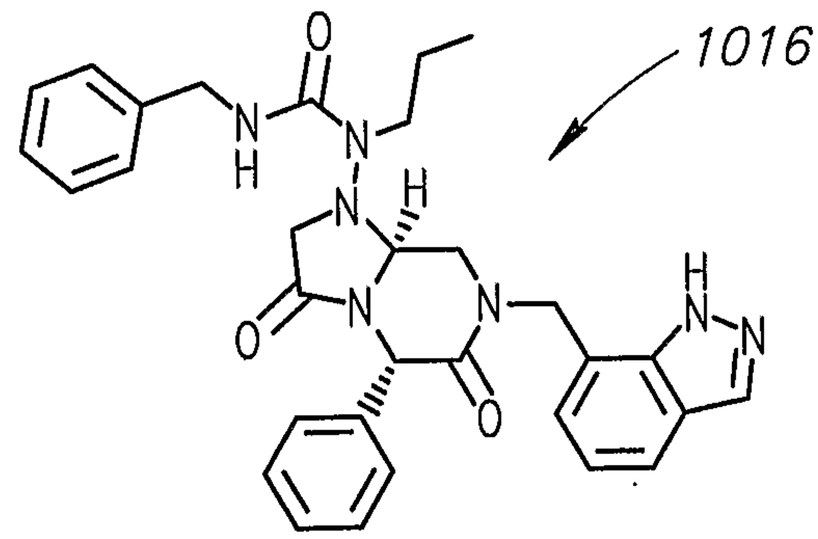
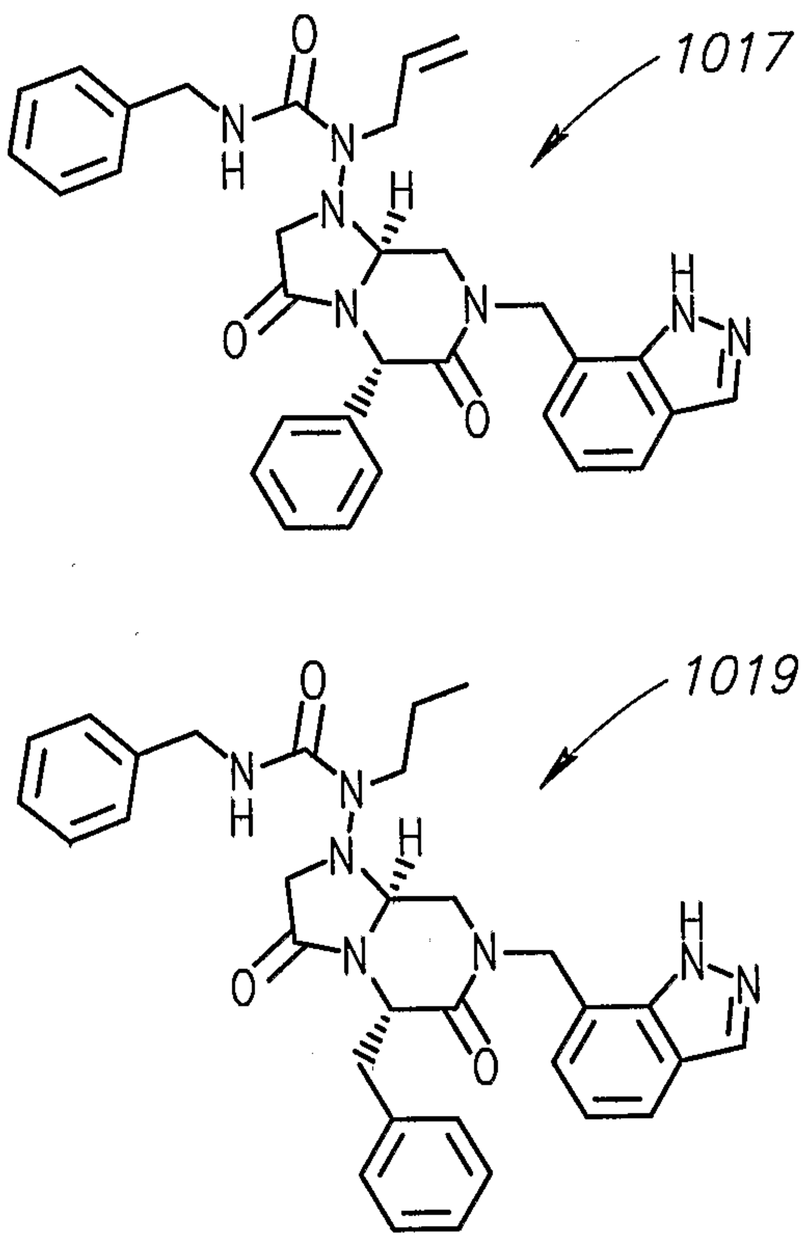
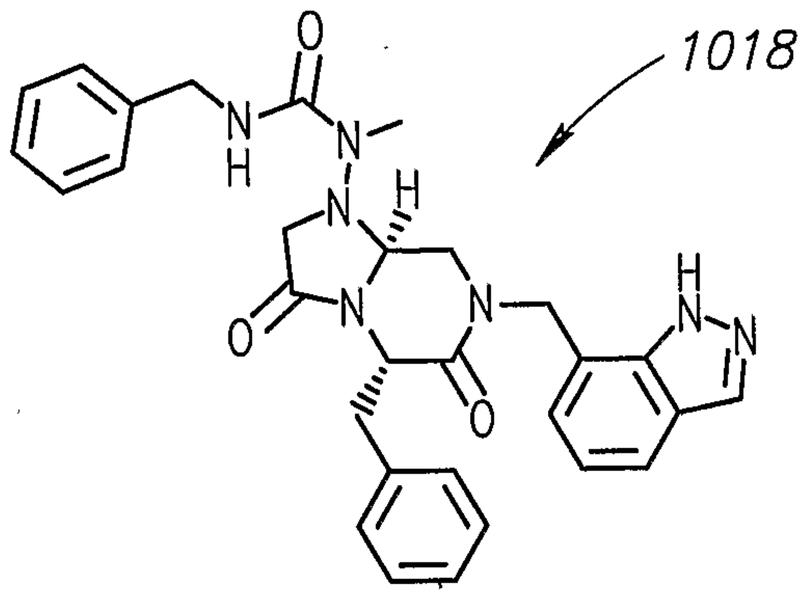
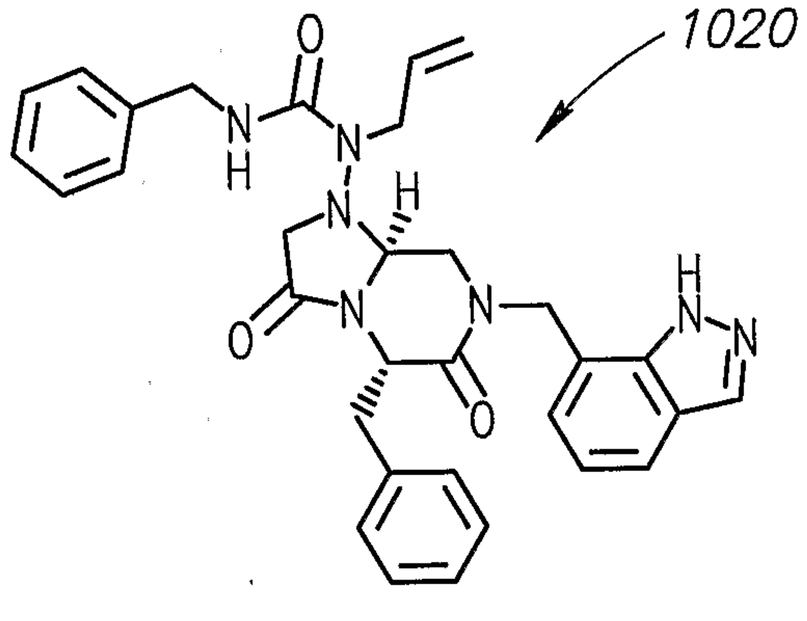
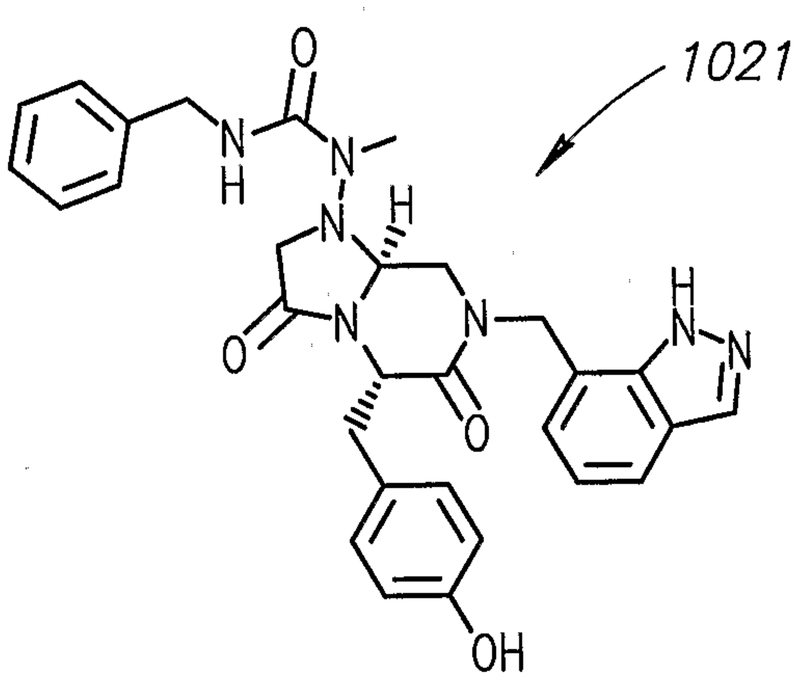


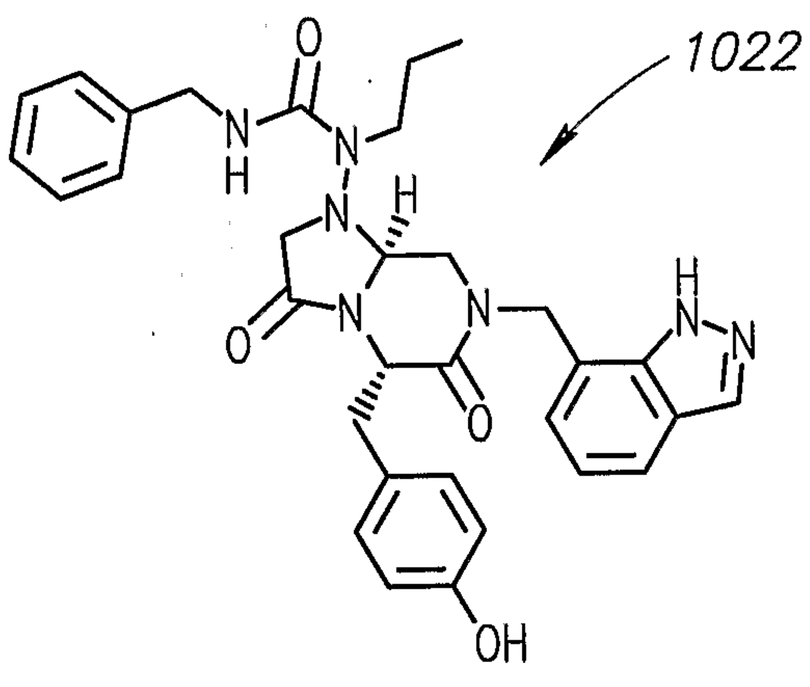
FIG.6B

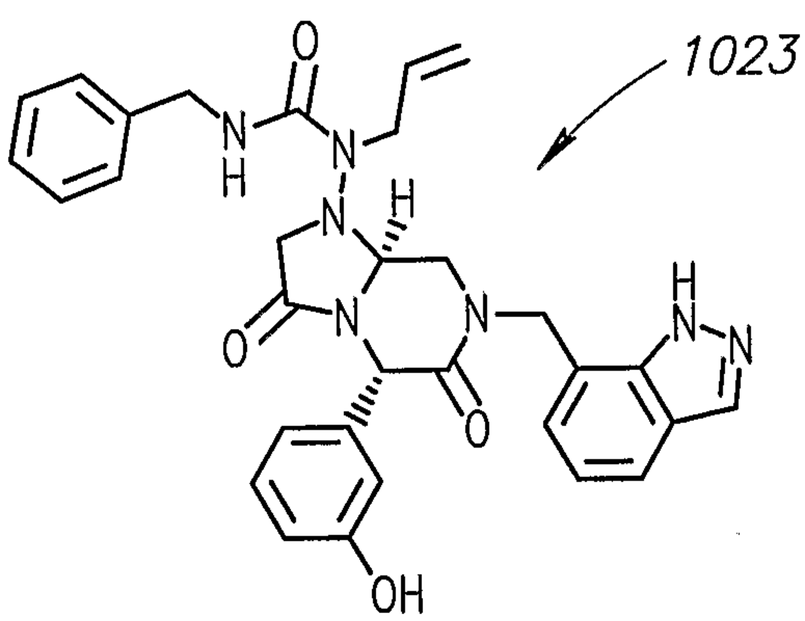












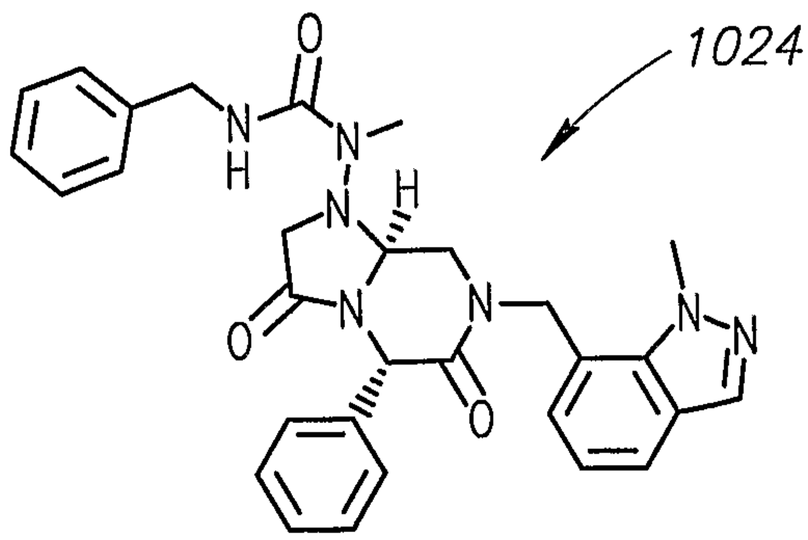
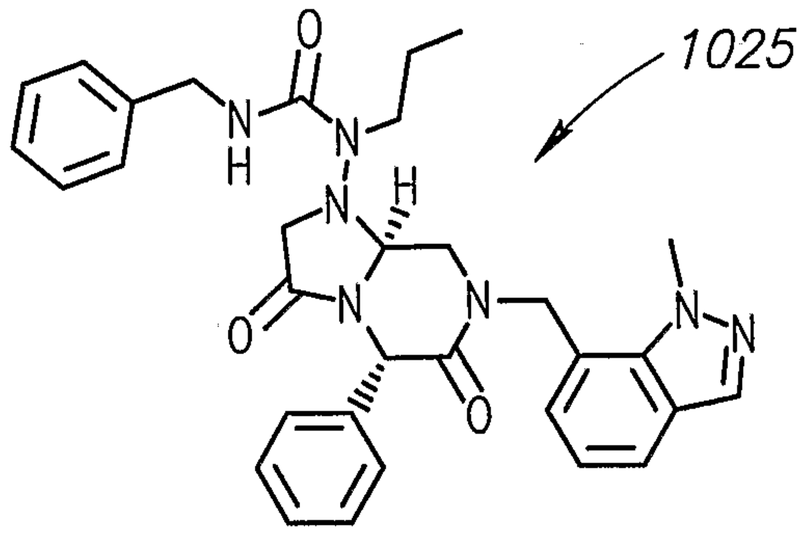
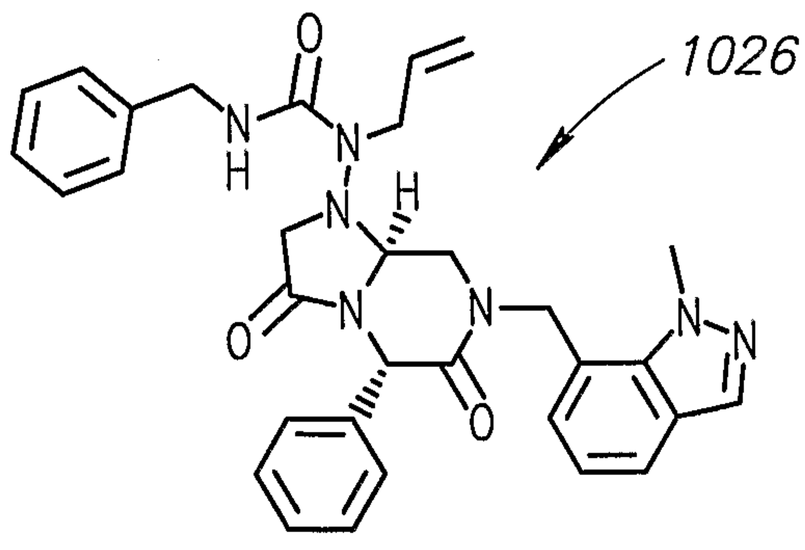
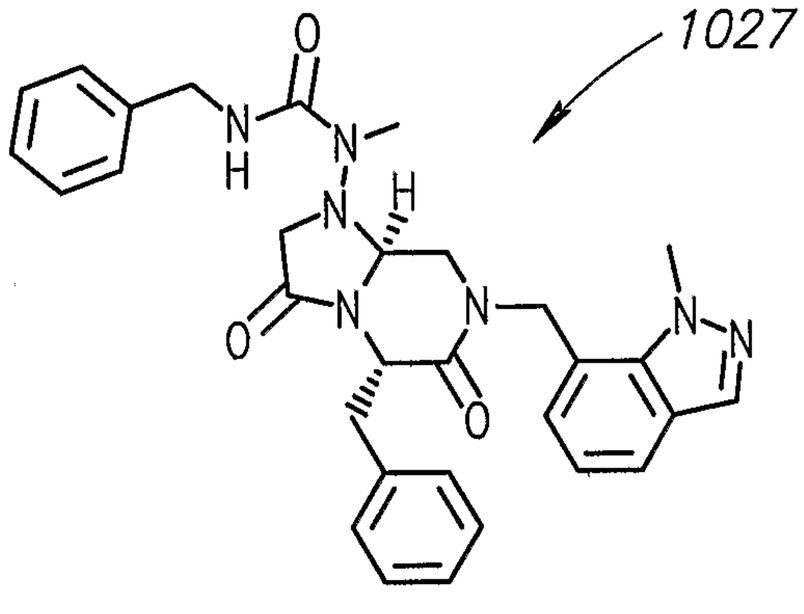
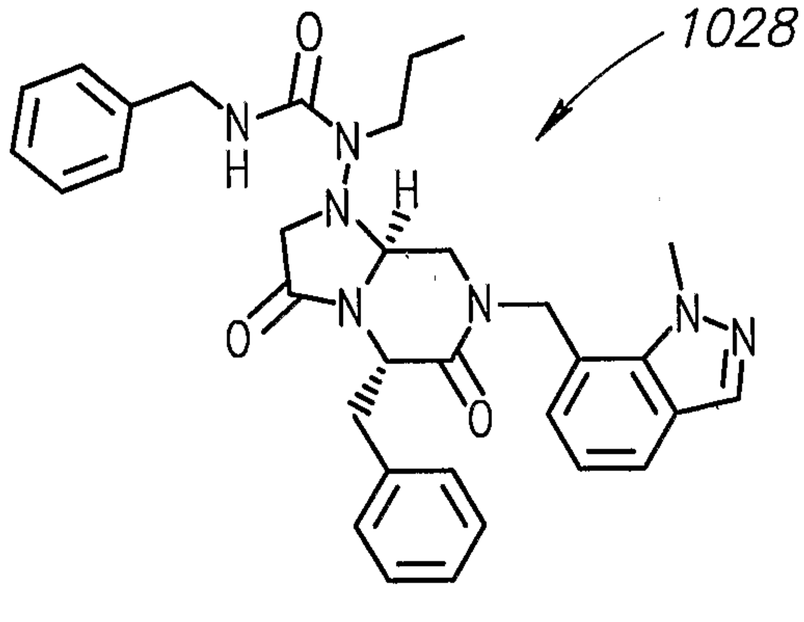


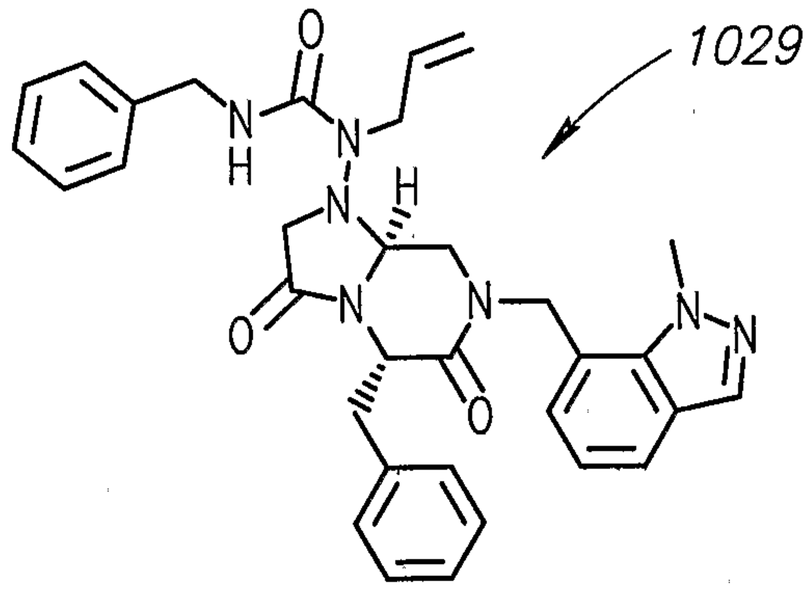
FIG.6C











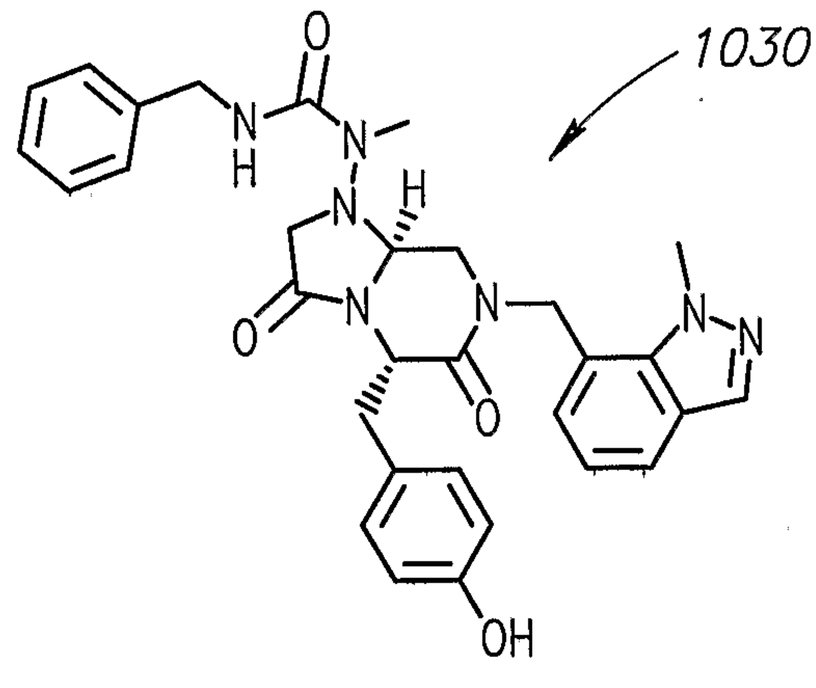
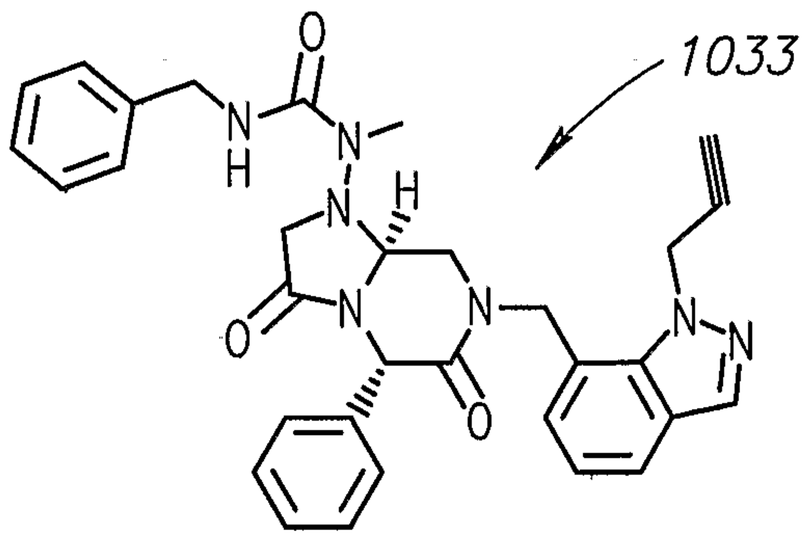
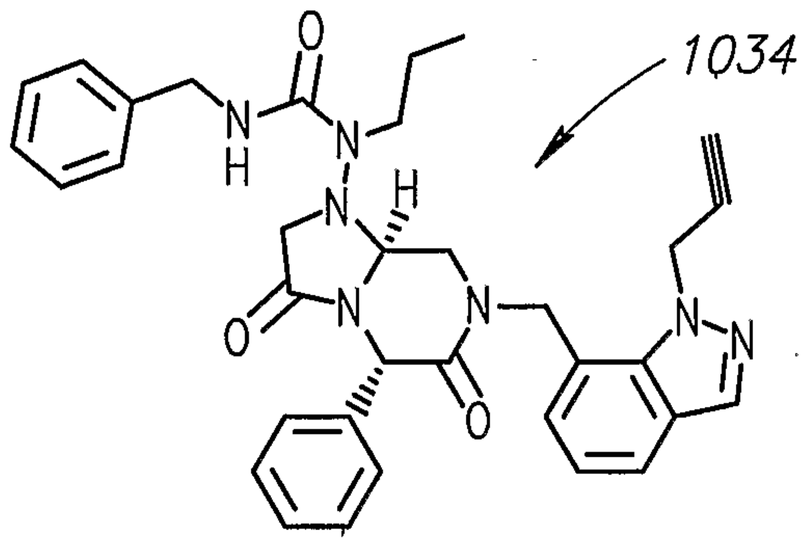
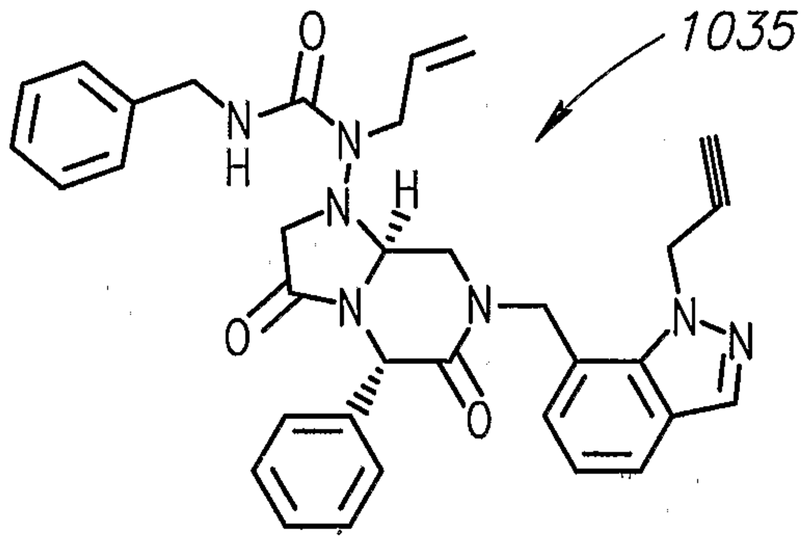
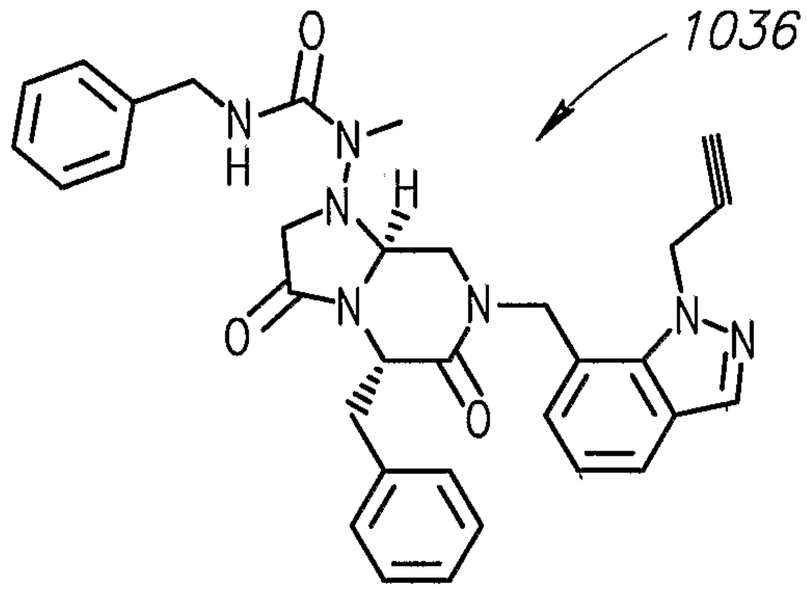


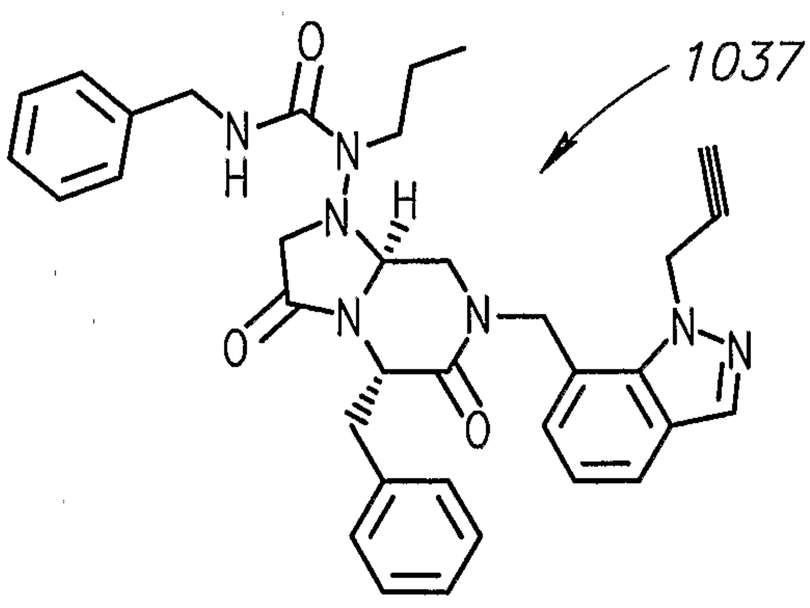
FIG.6D

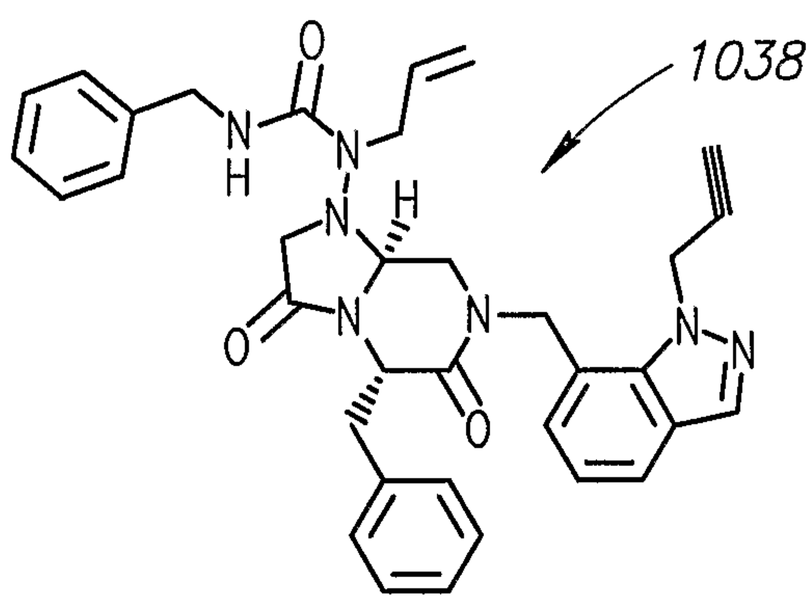


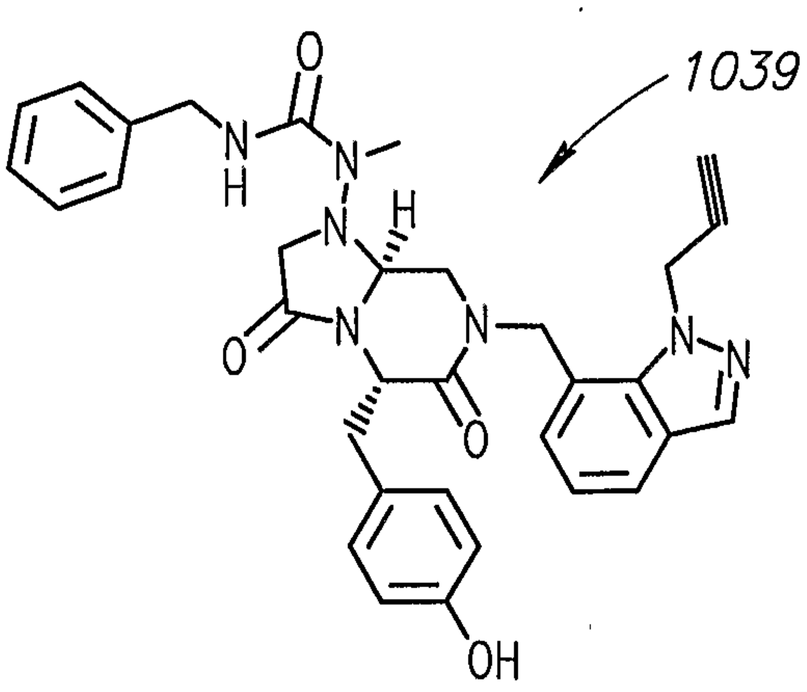












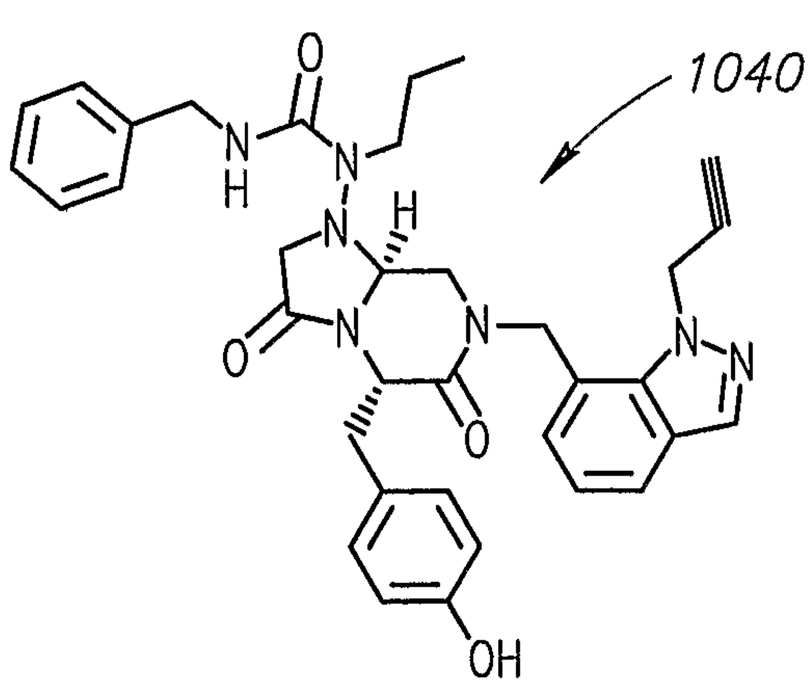


FIG.6E

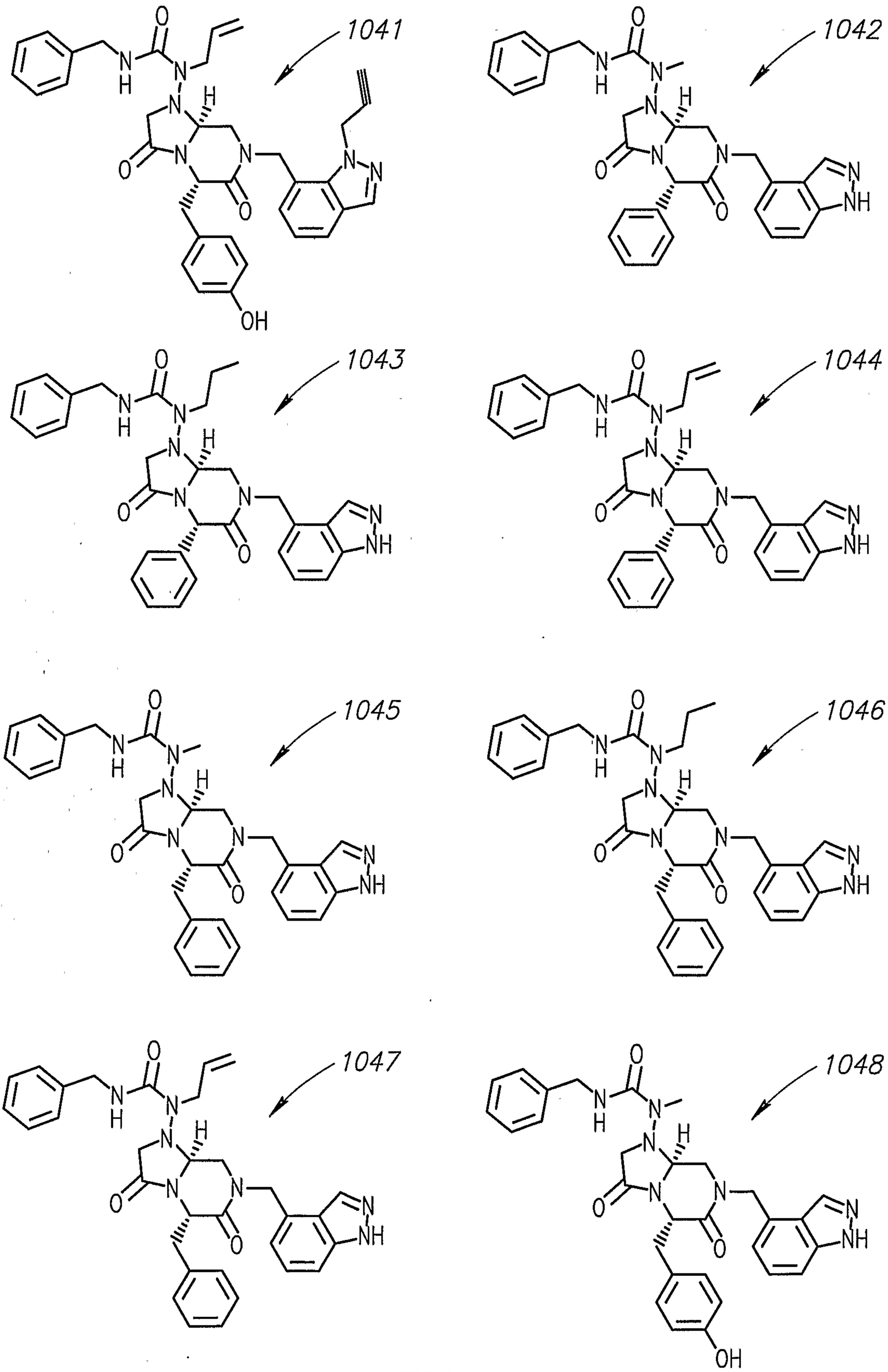
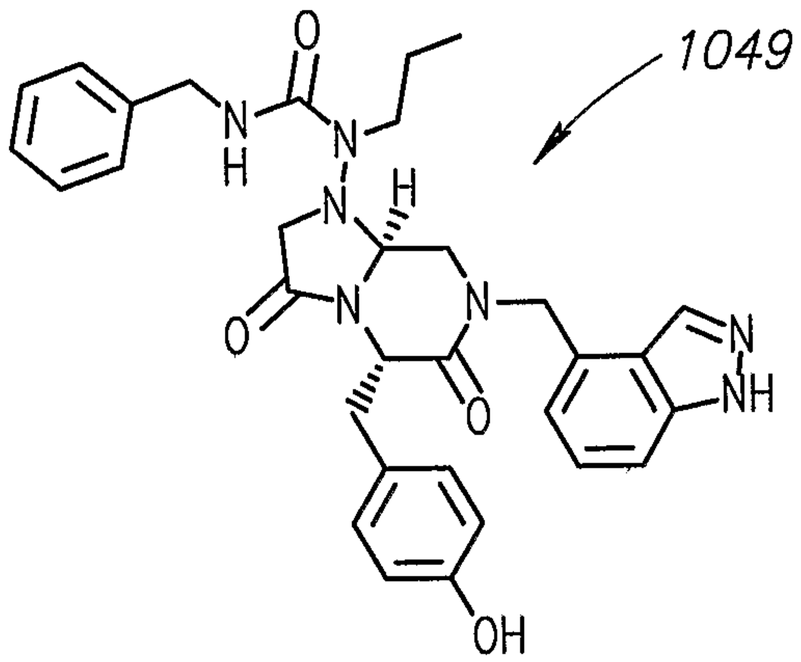
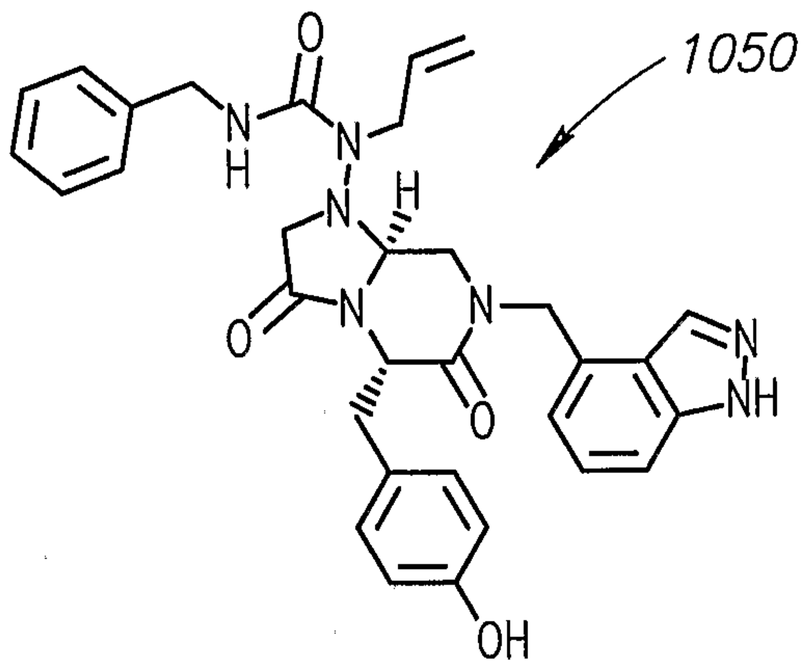
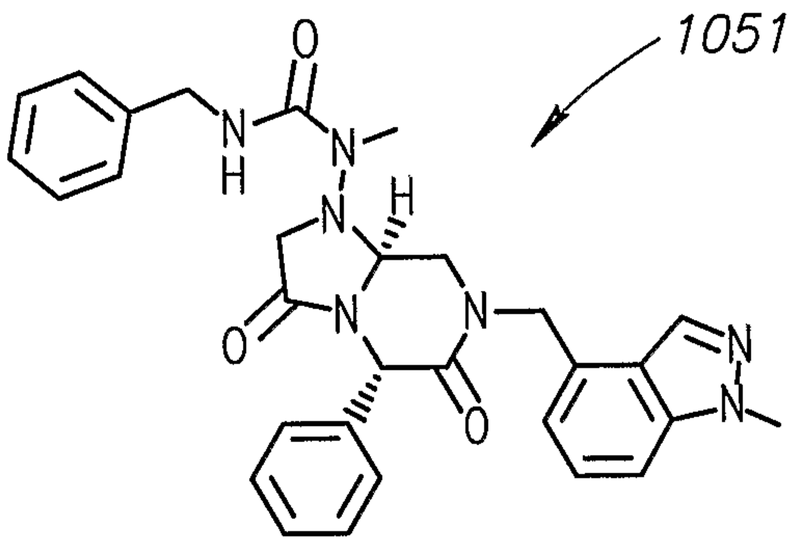
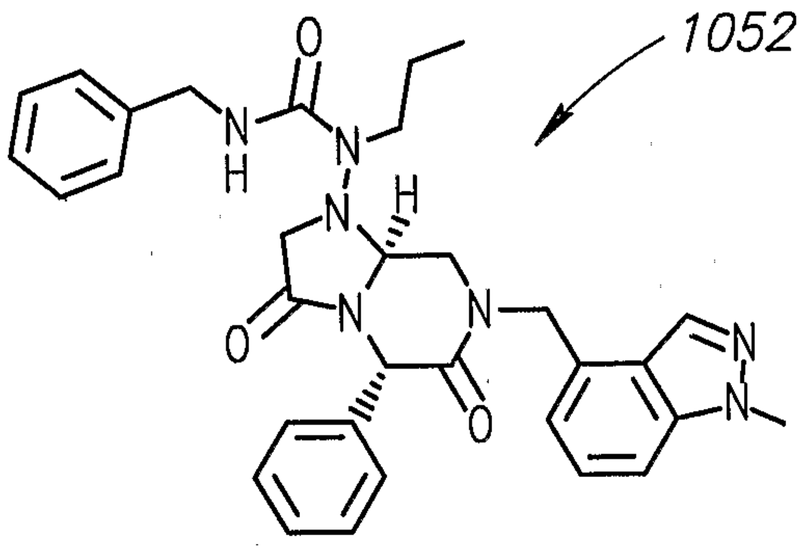


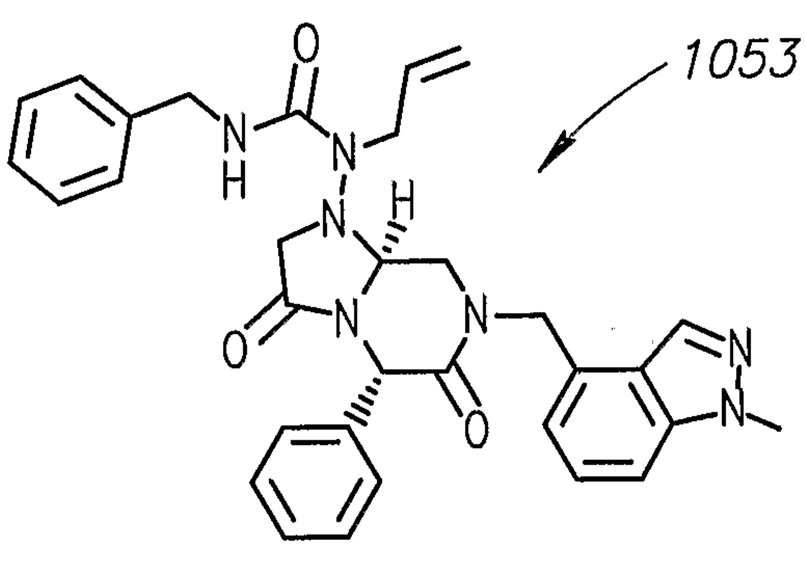
FIG.6F

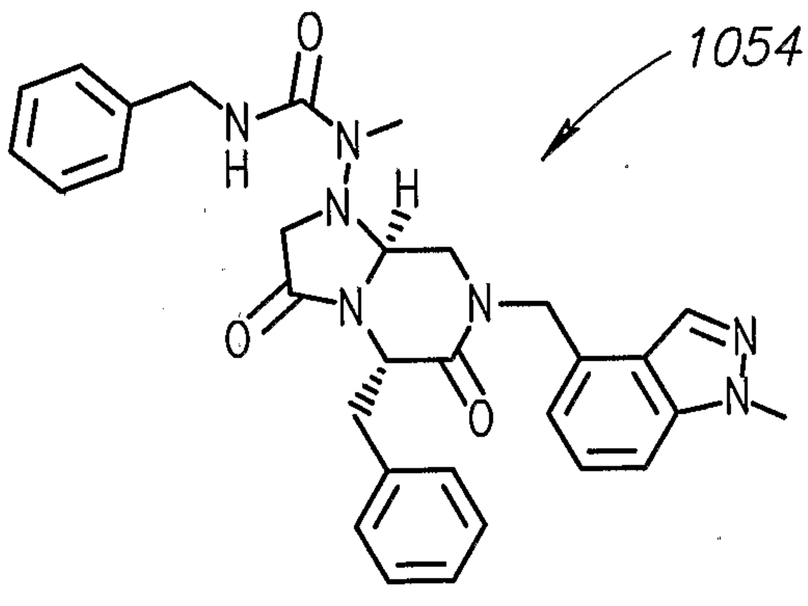


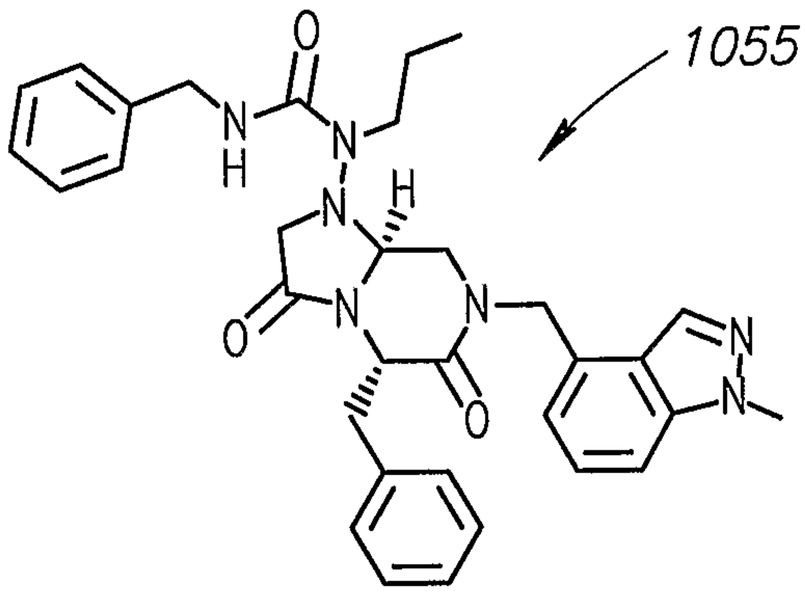












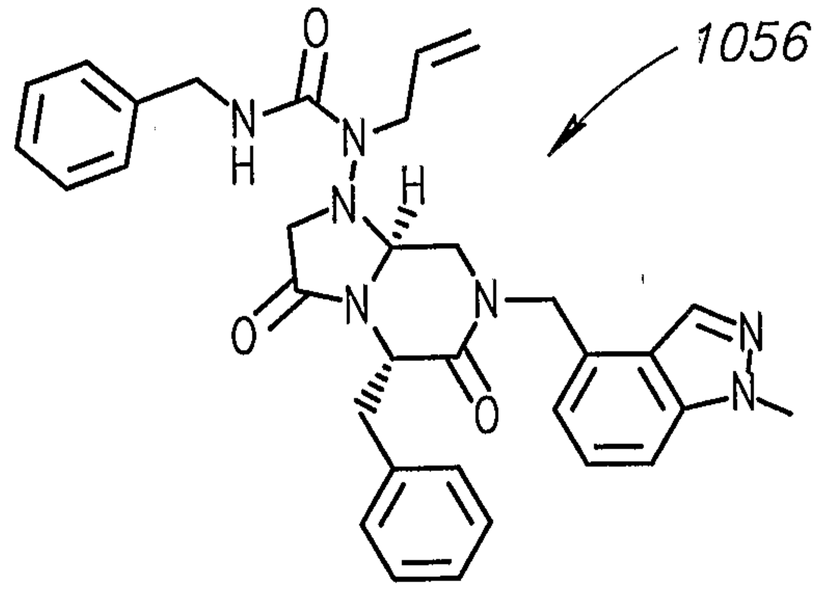


FIG.6G

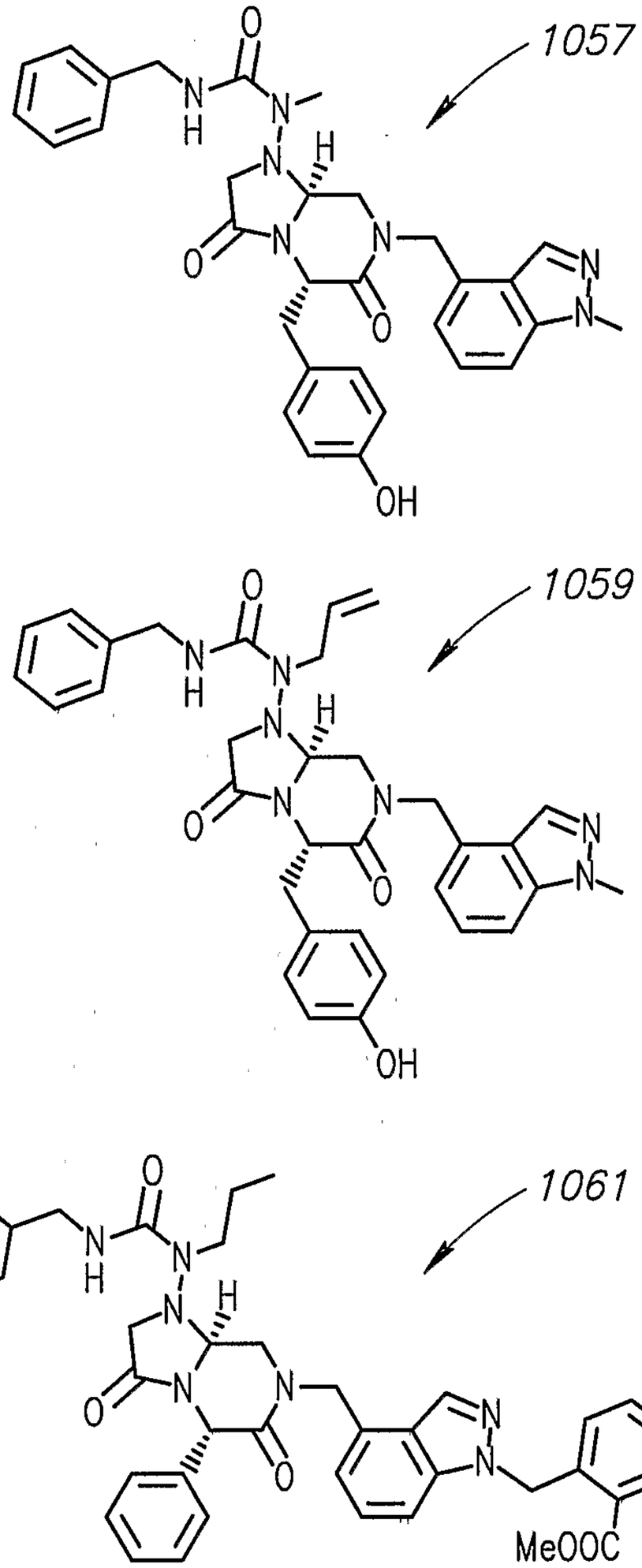
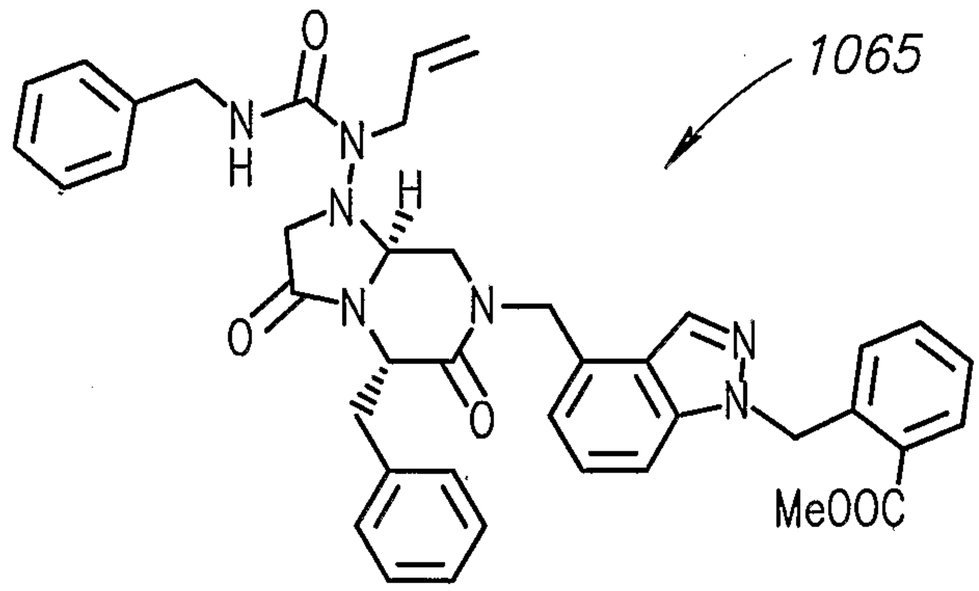


FIG.6H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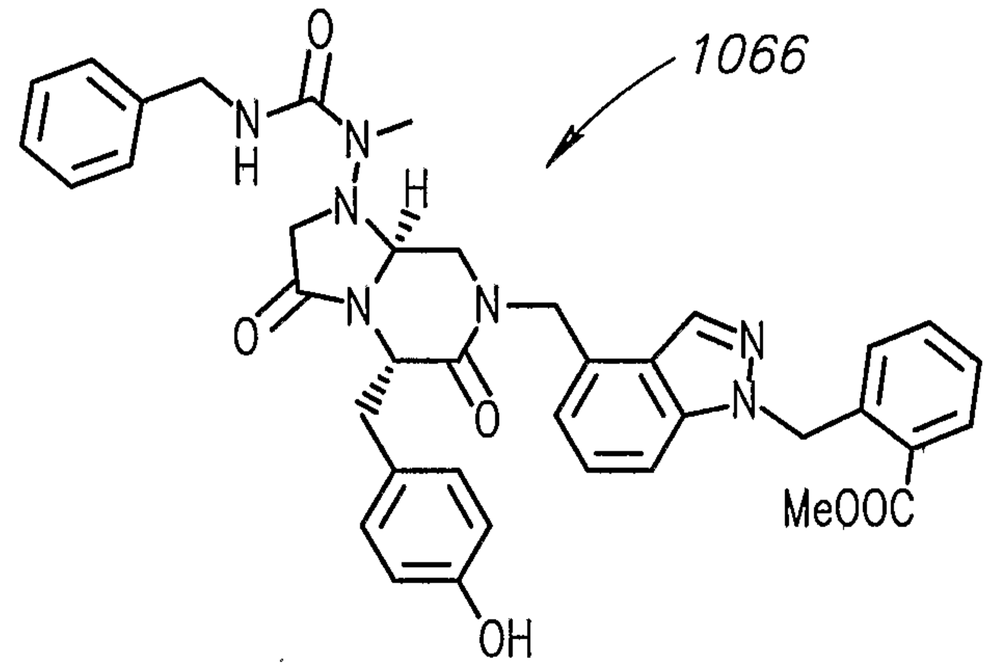
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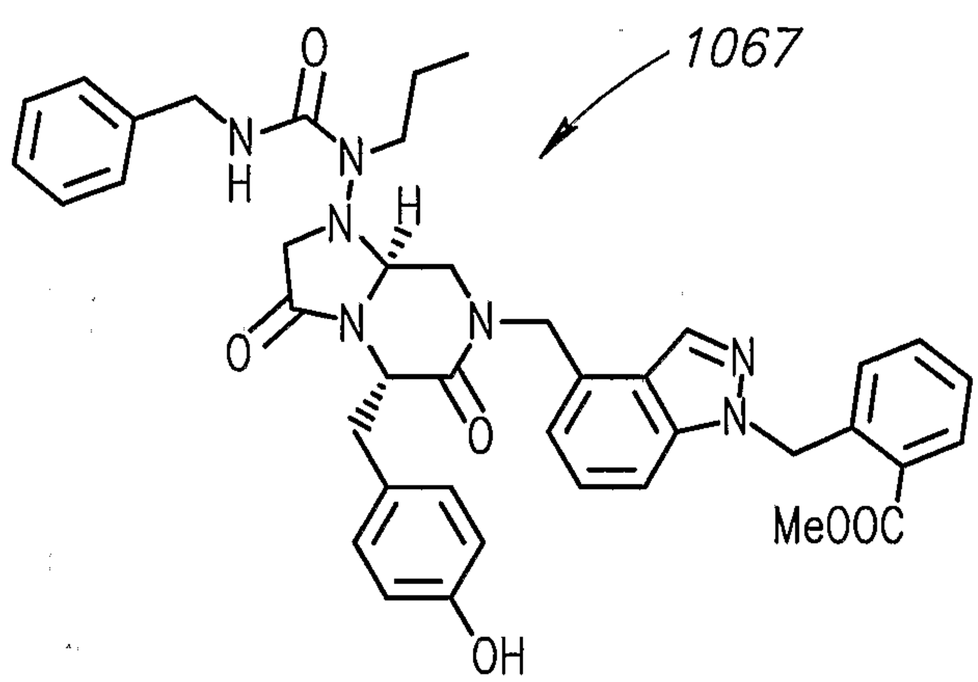
OH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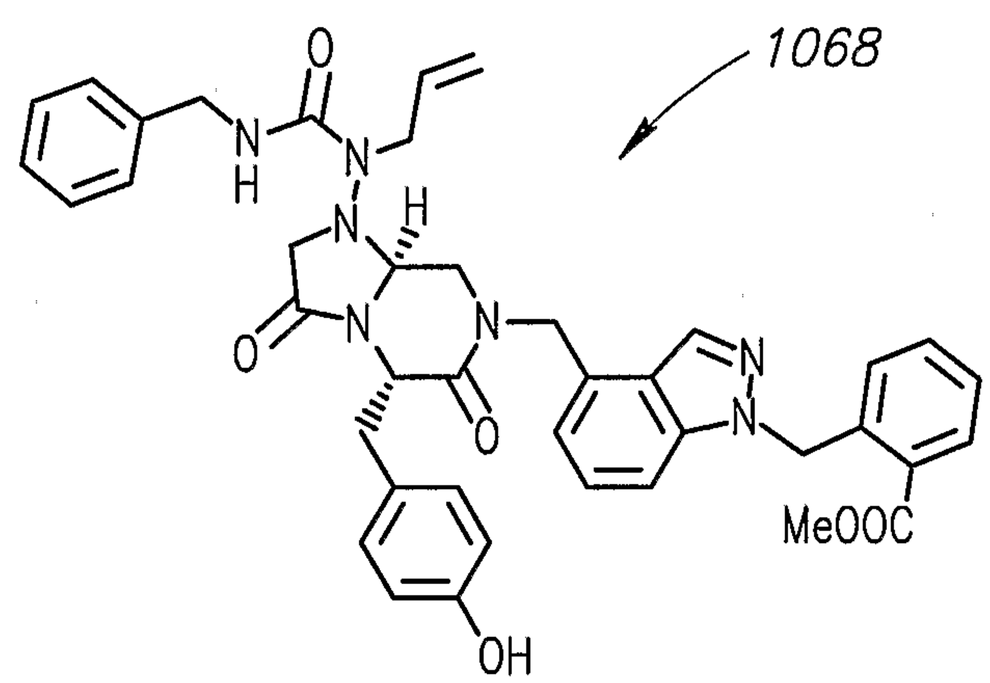
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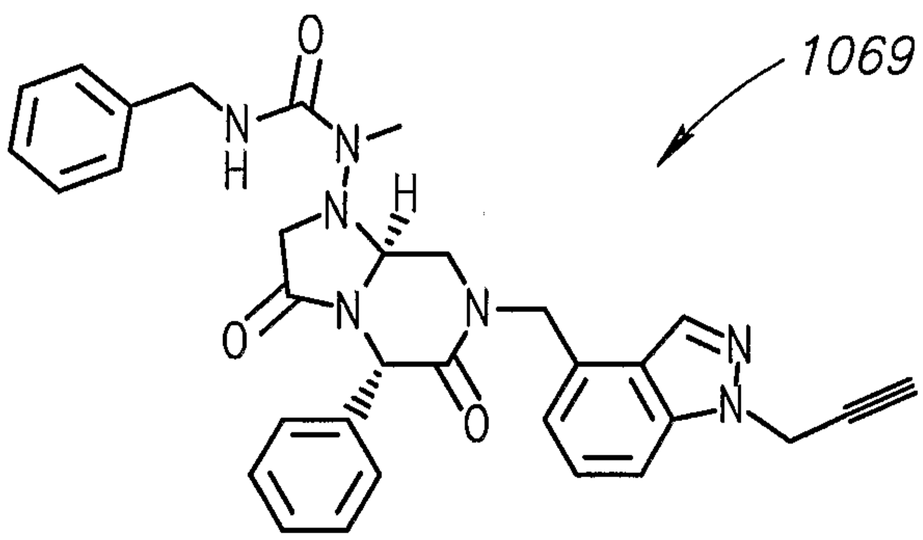
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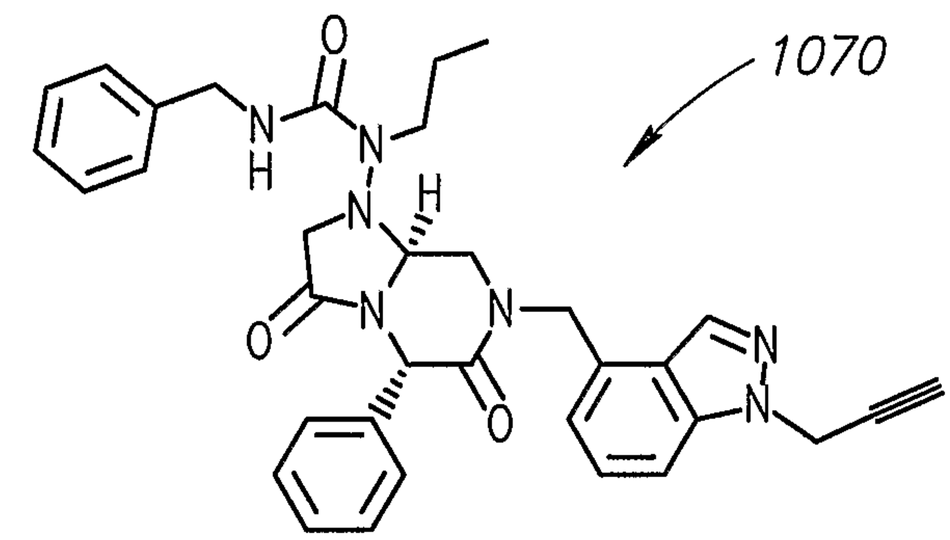
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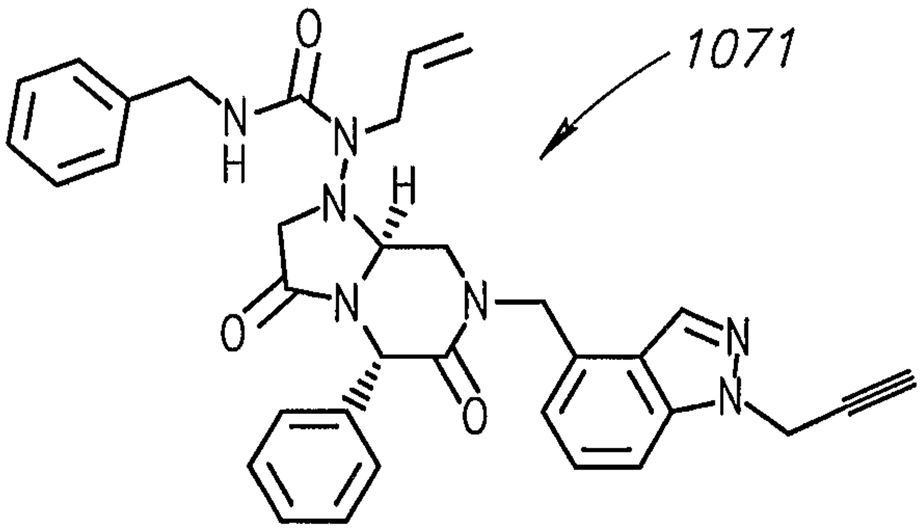
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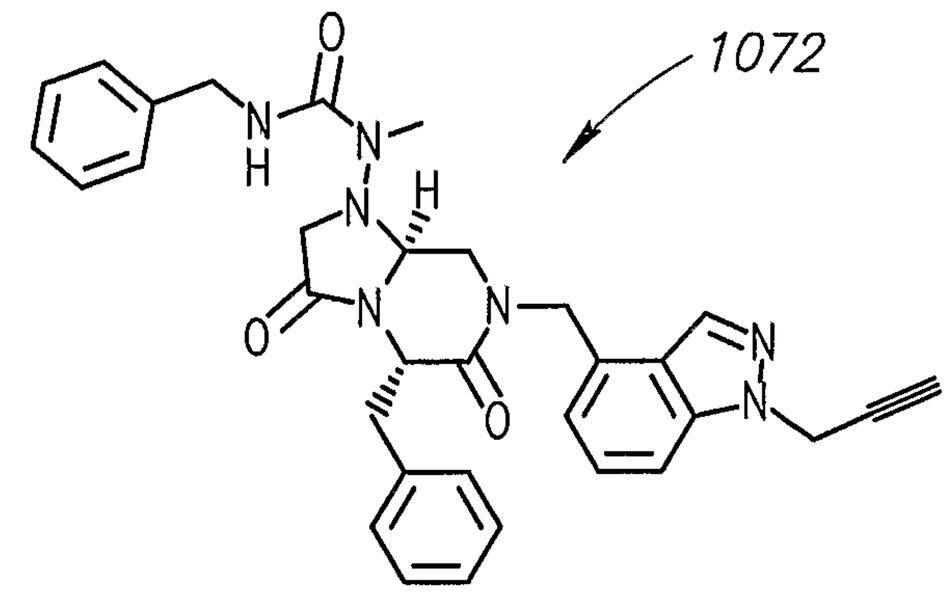
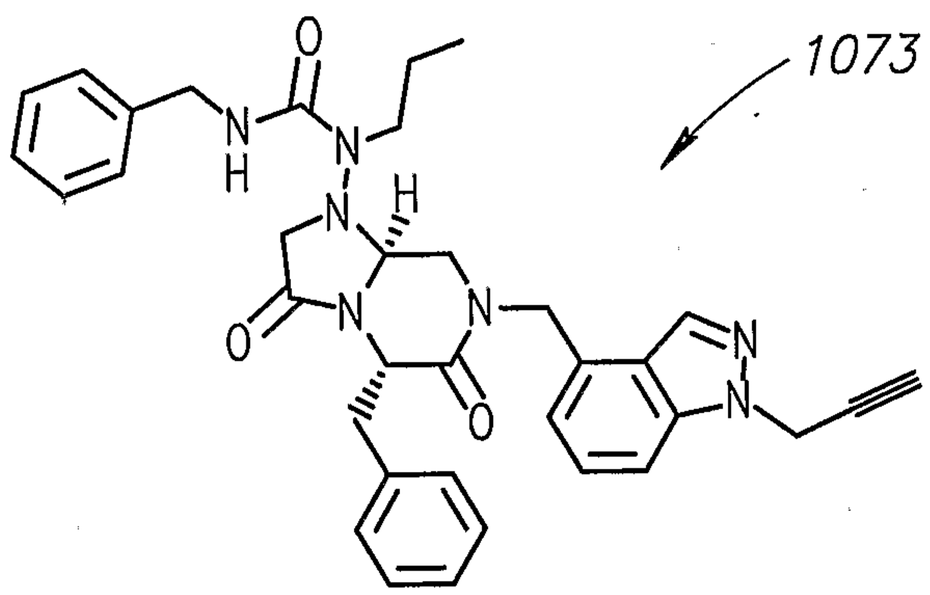
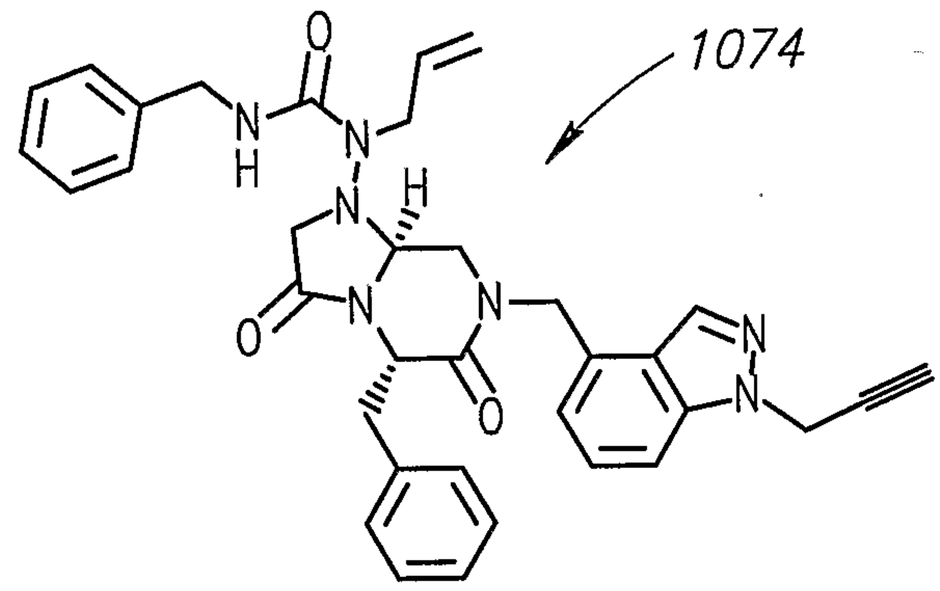
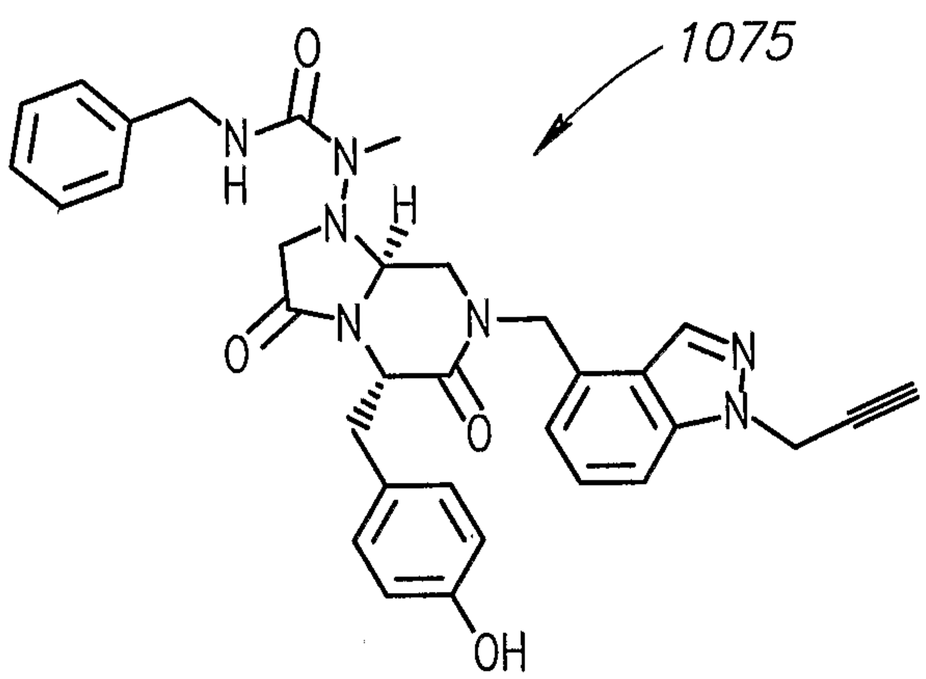
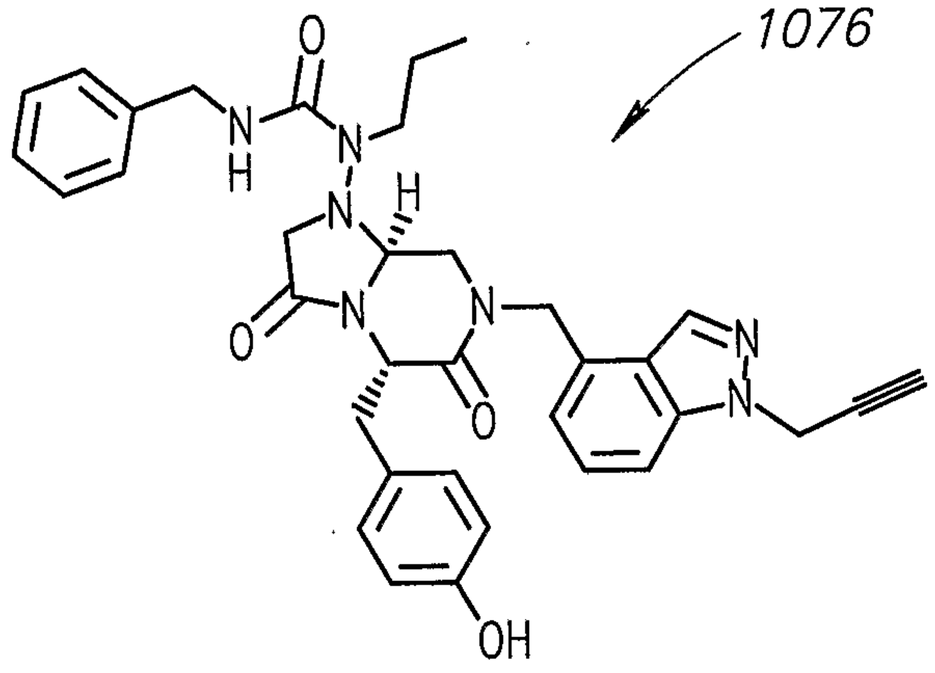

1072

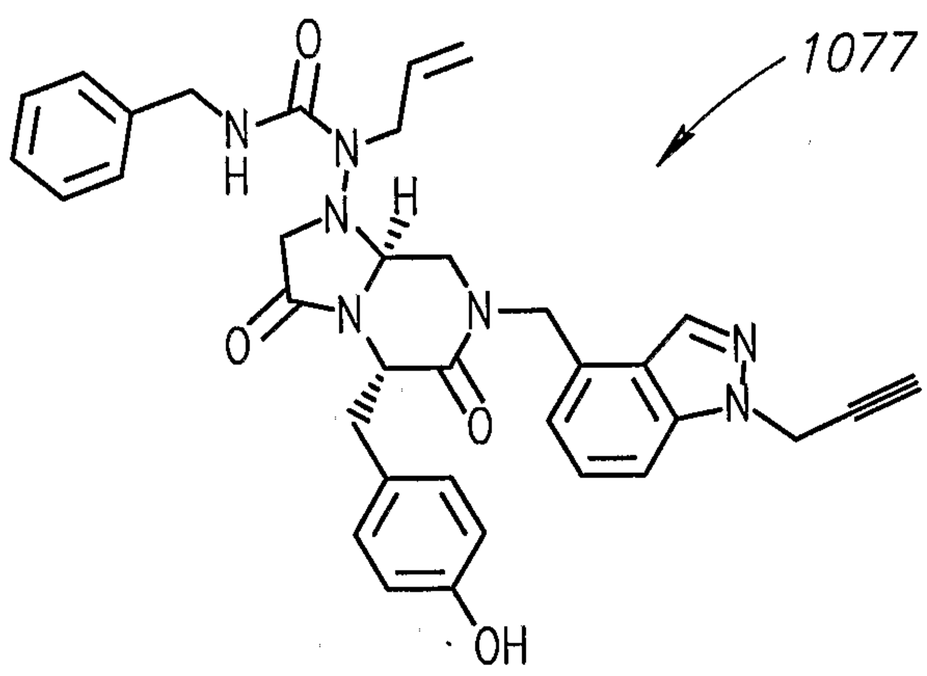
FIG.6I

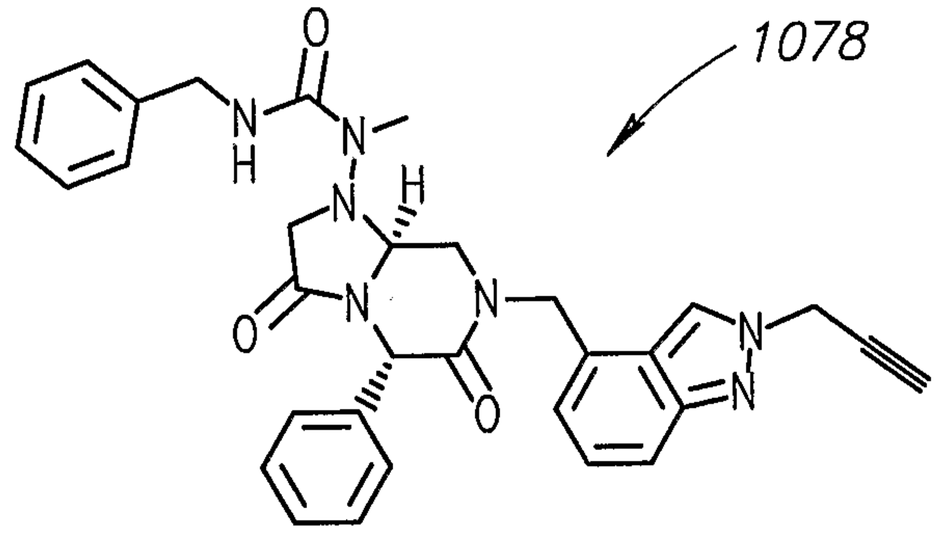


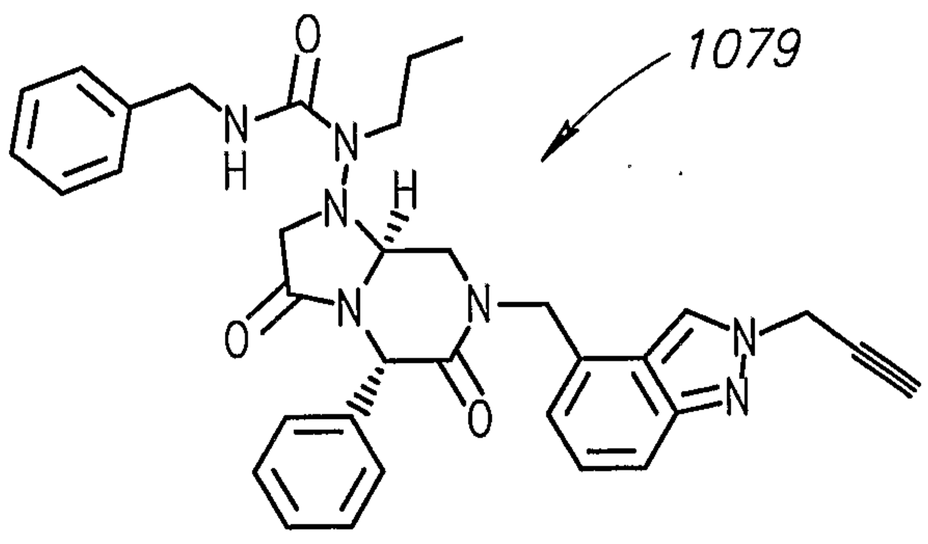












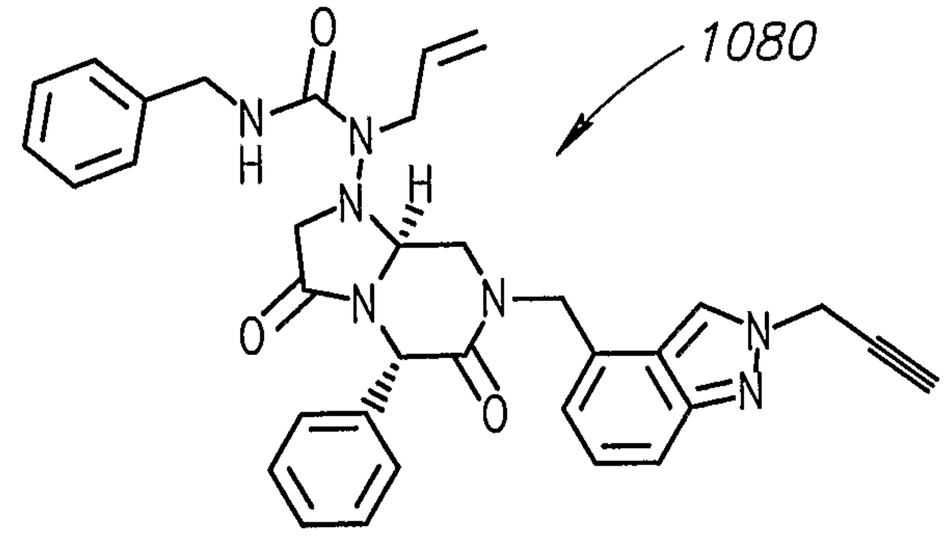


FIG.6J

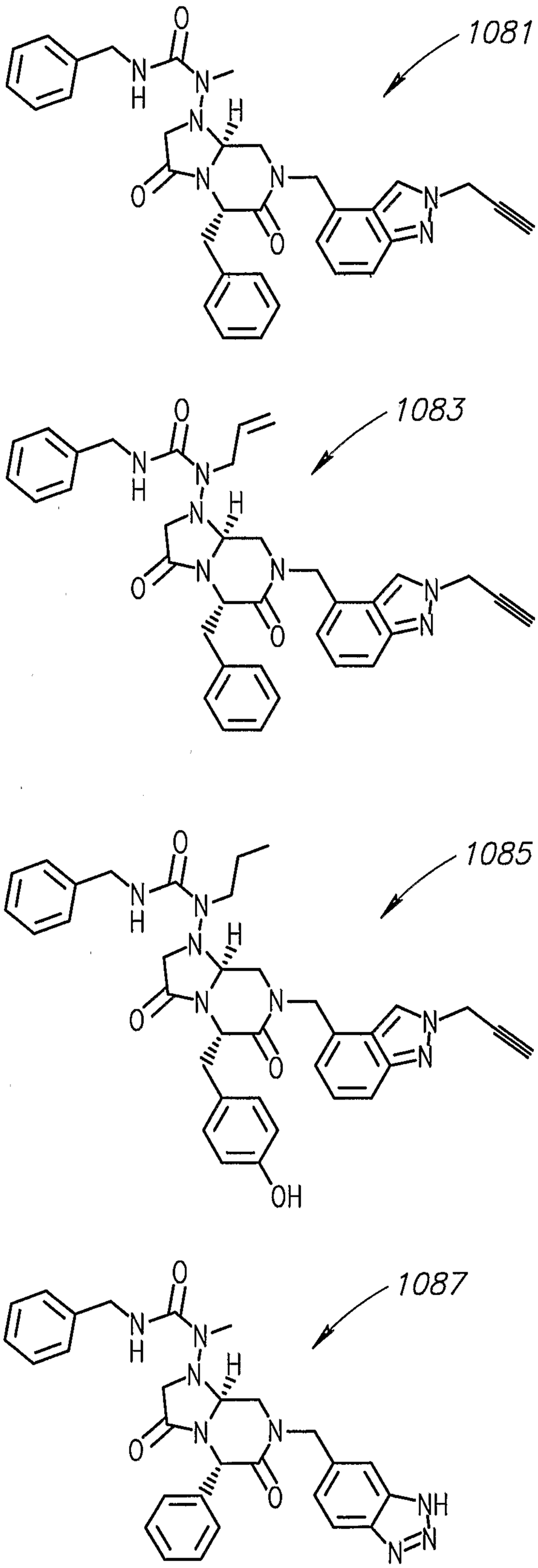
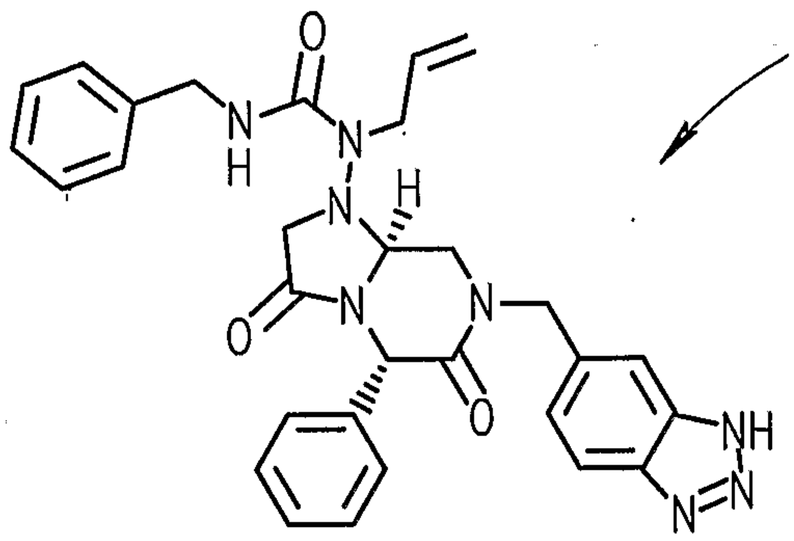
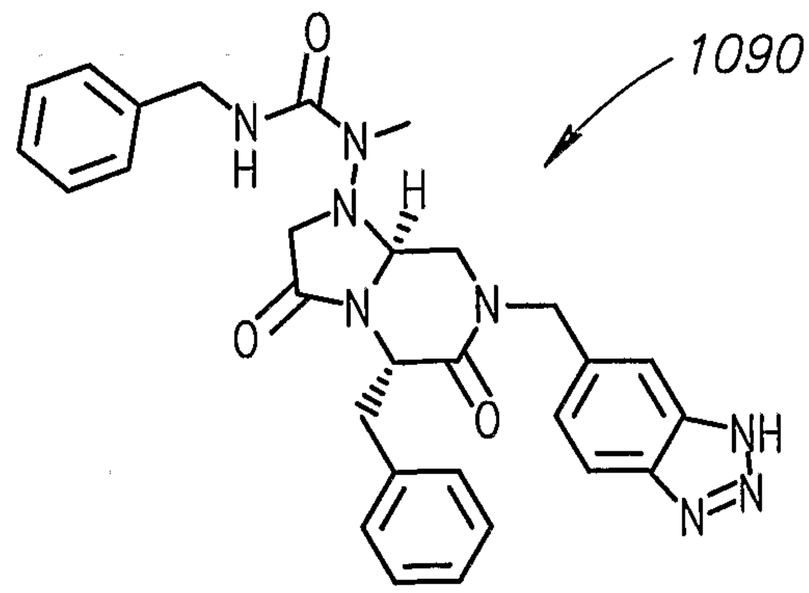
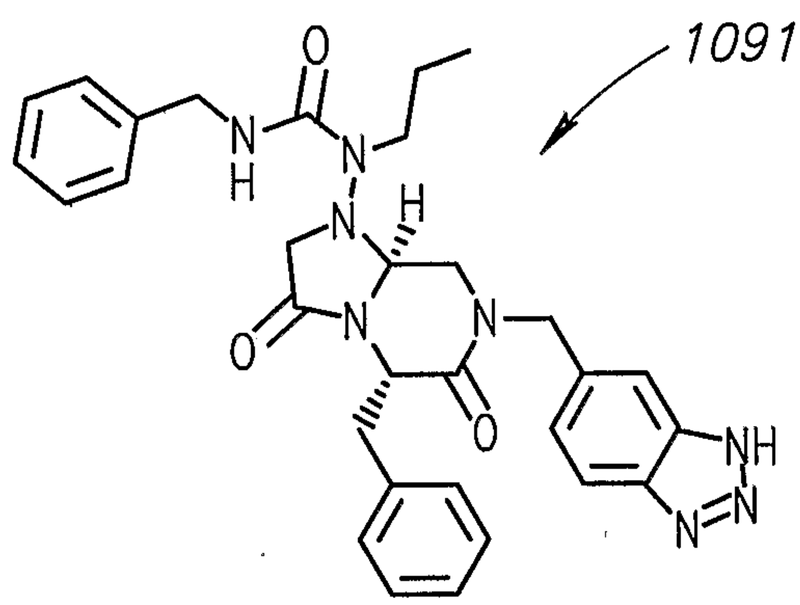
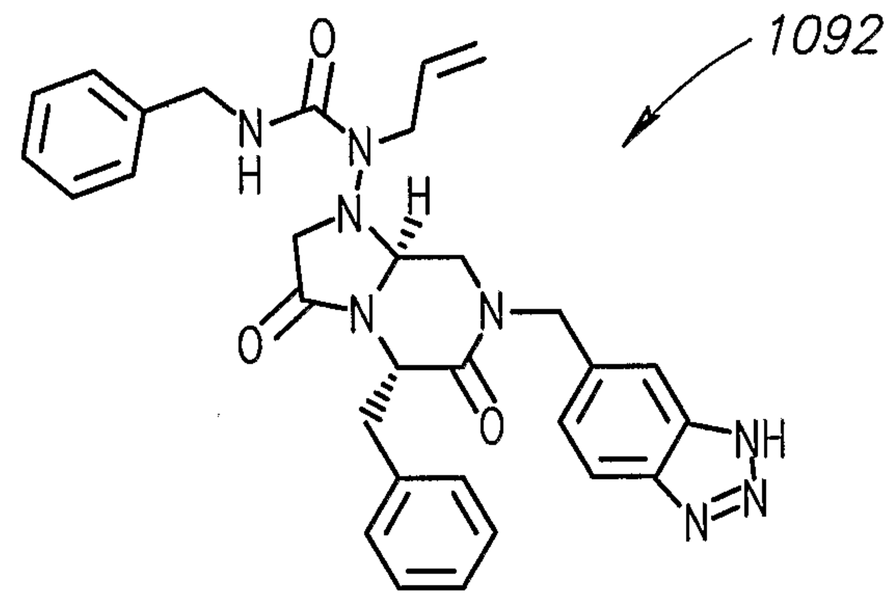


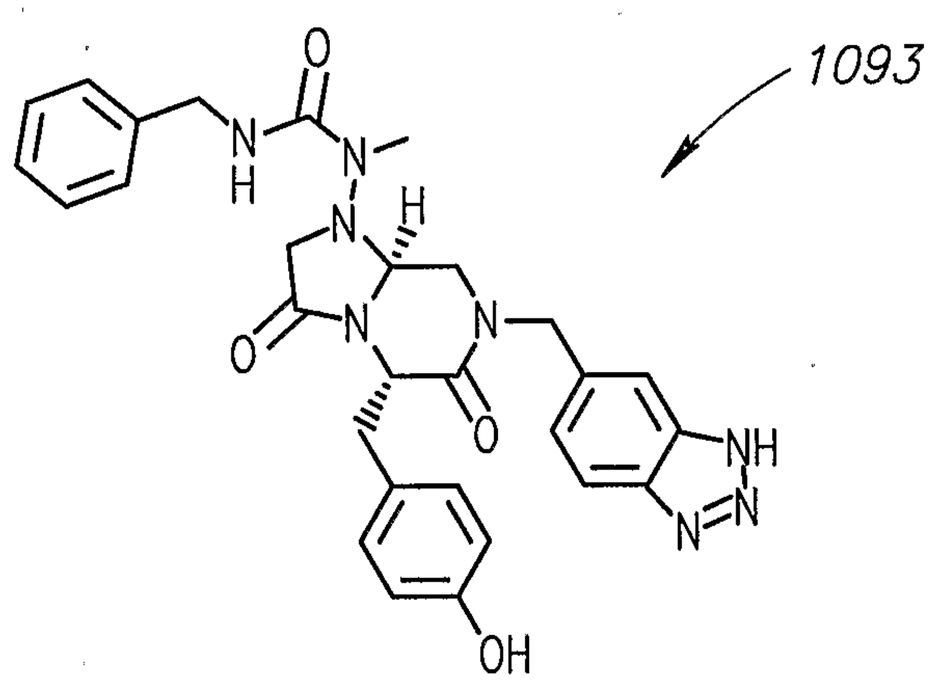
FIG.6K

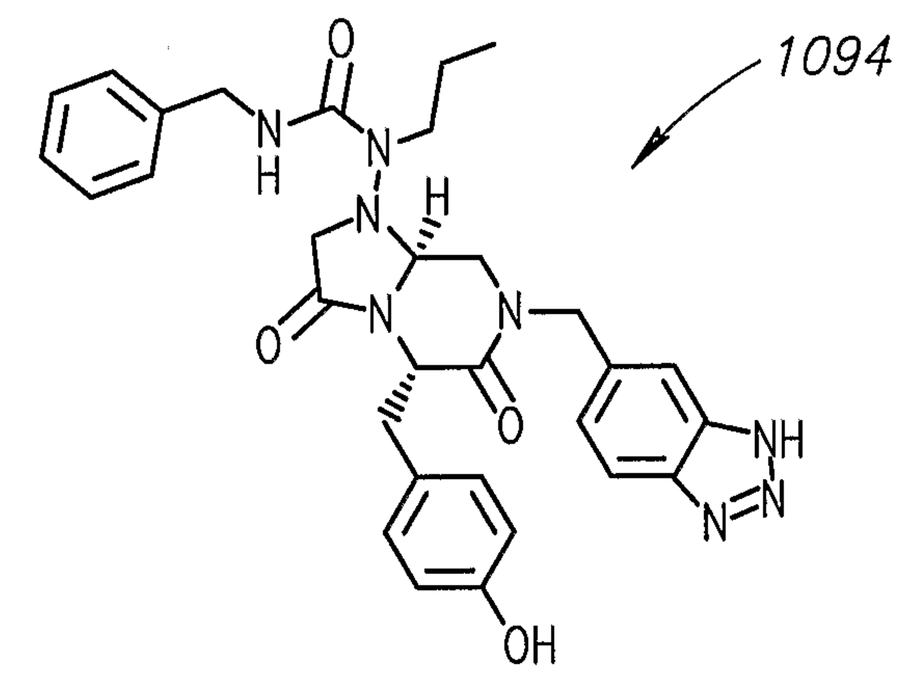


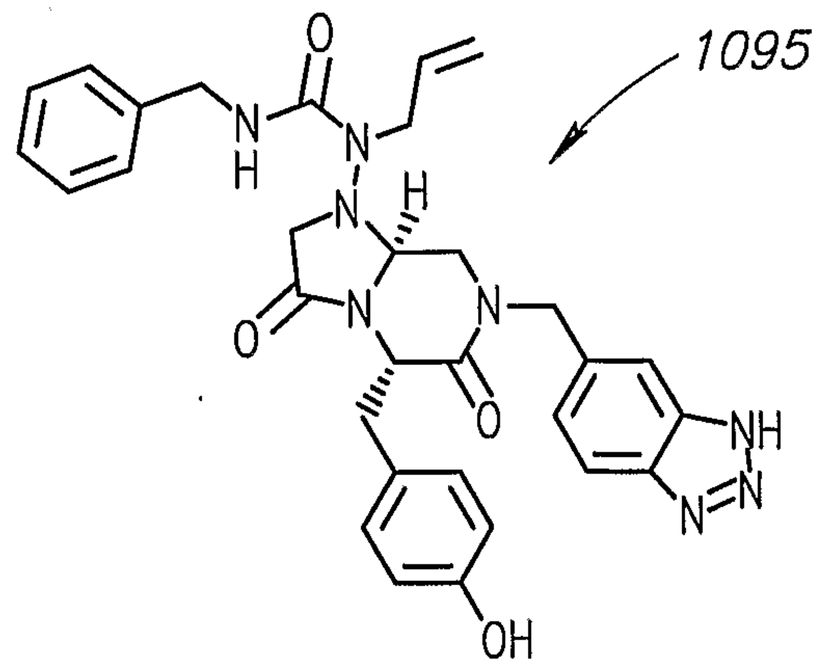












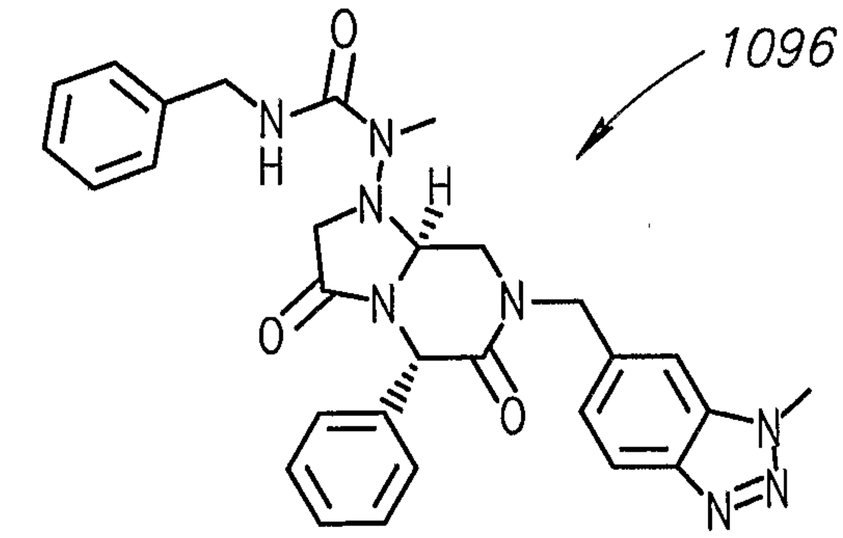
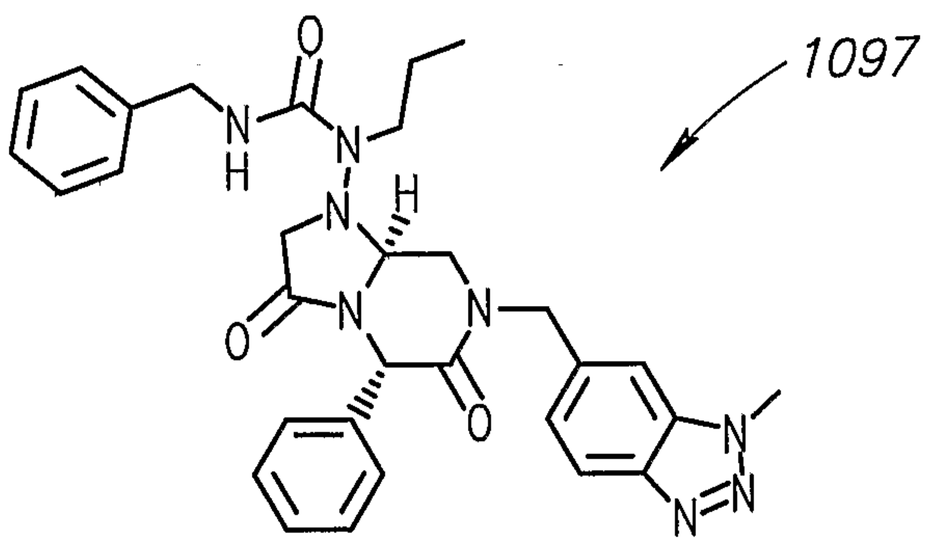
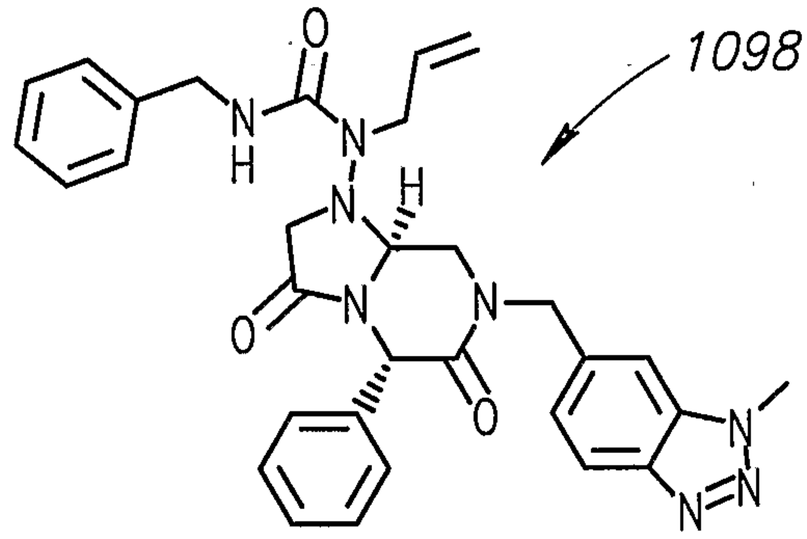
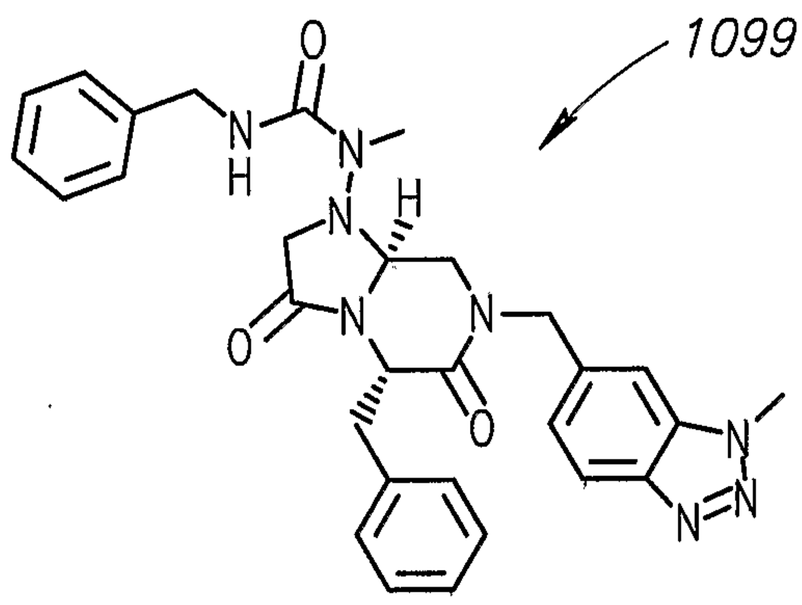
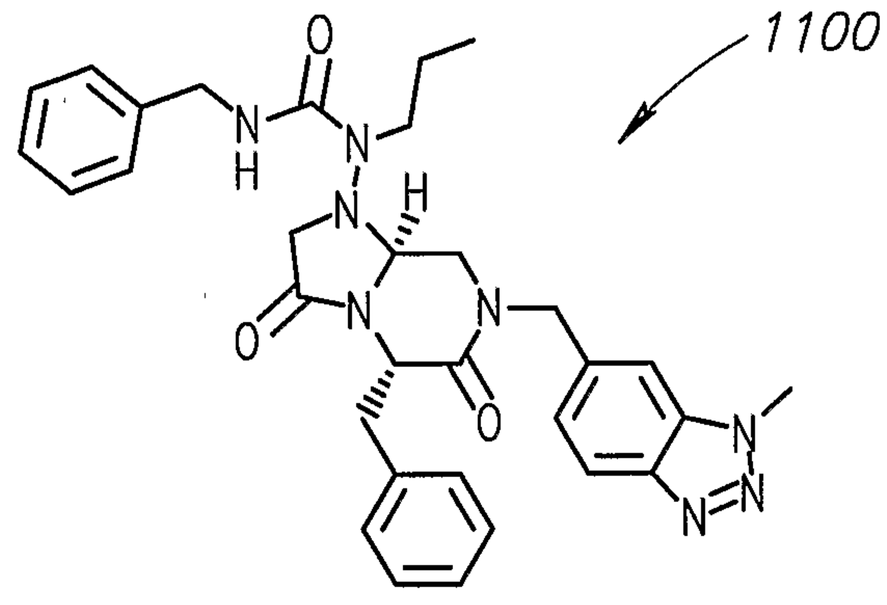


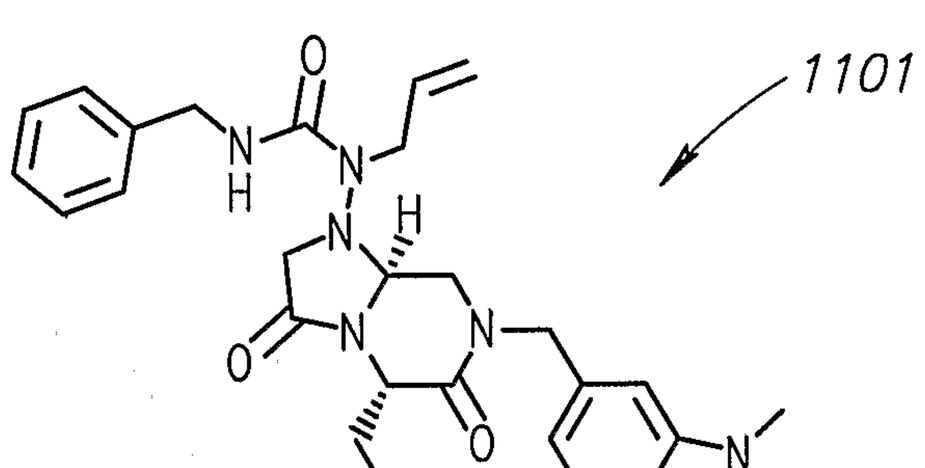
FIG.6L











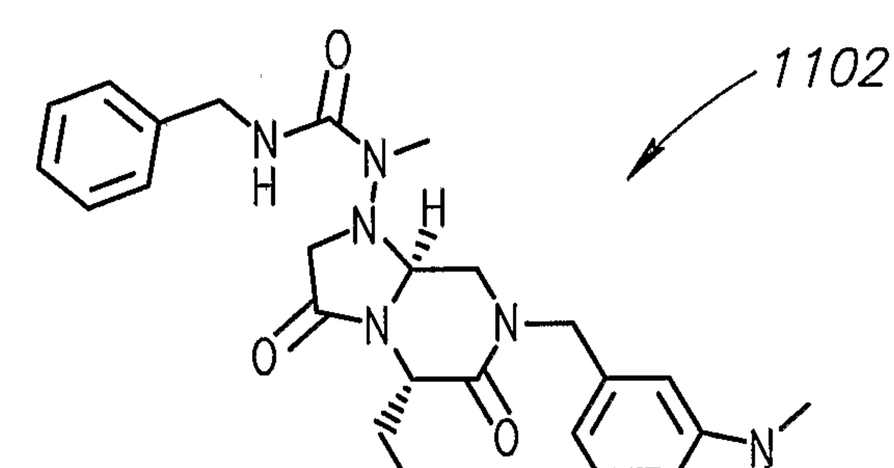
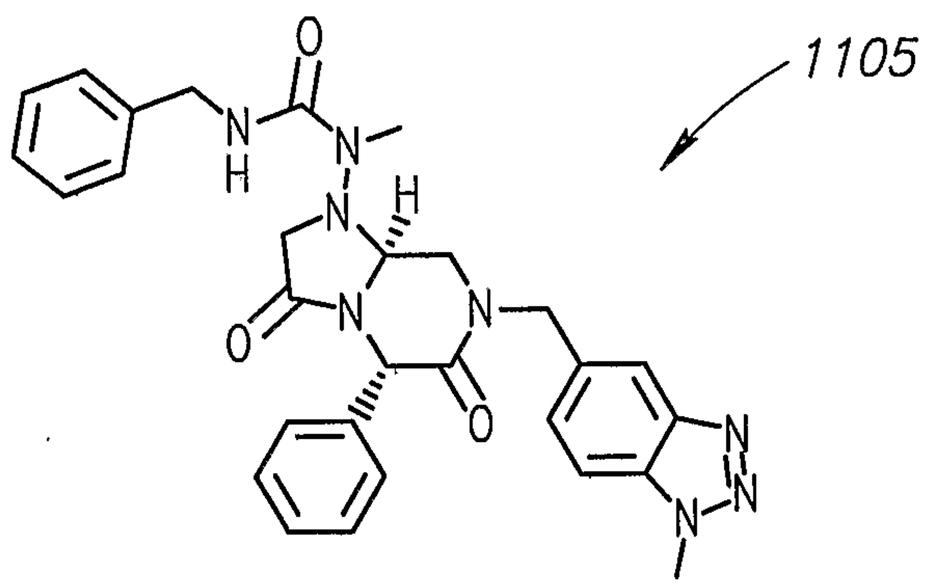
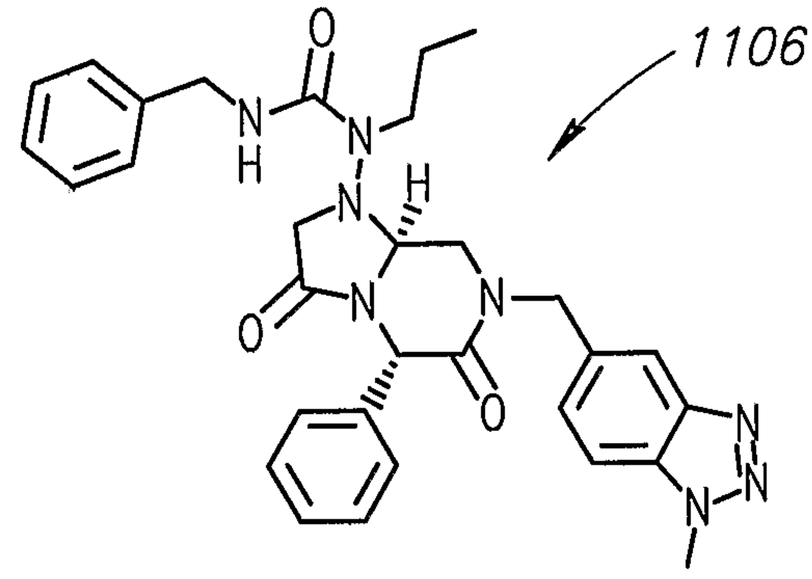
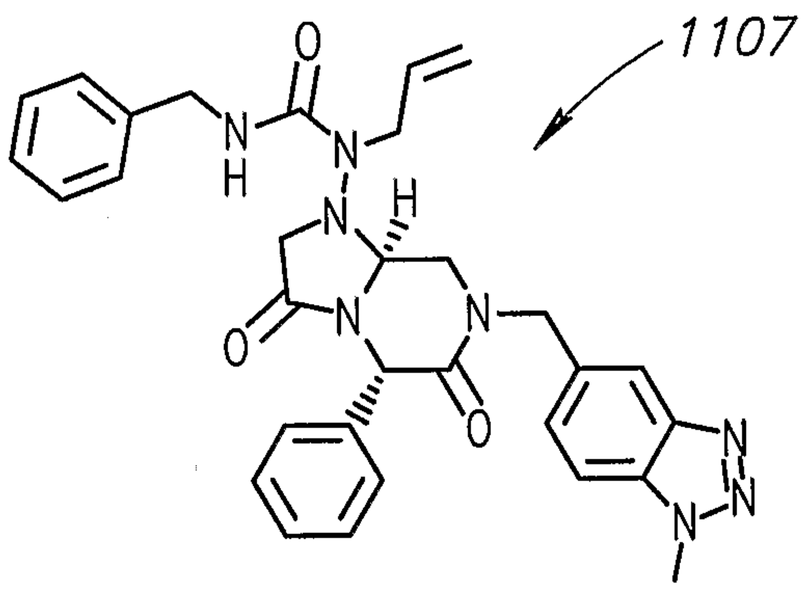
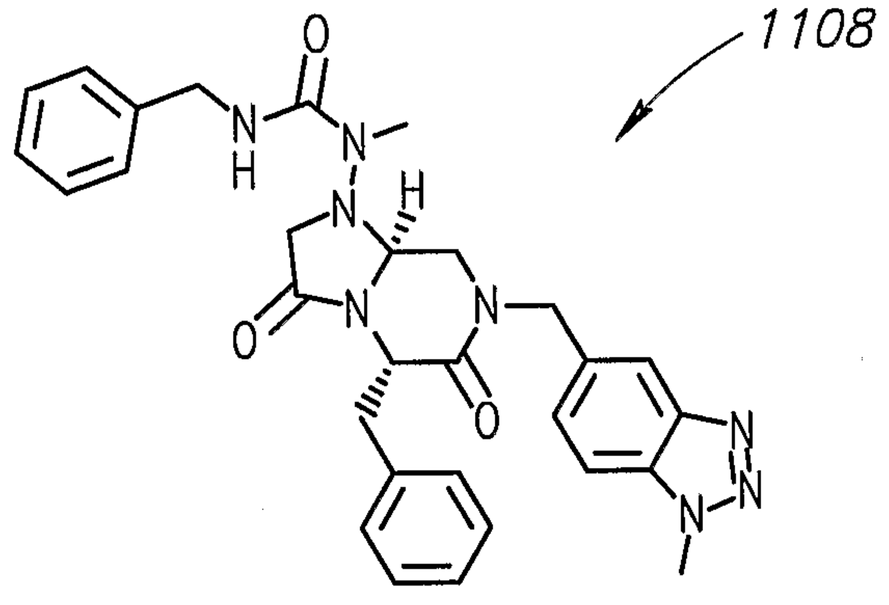


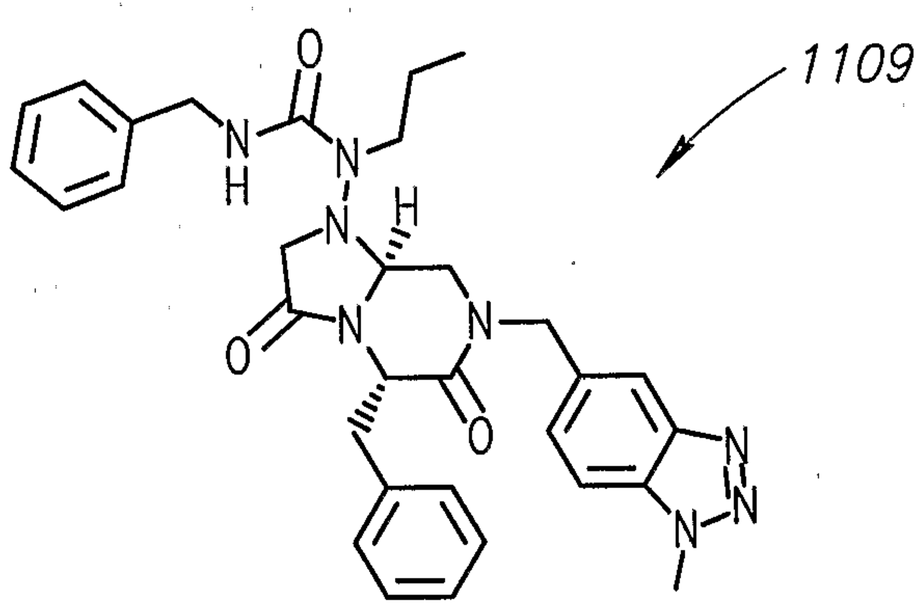
FIG.6M

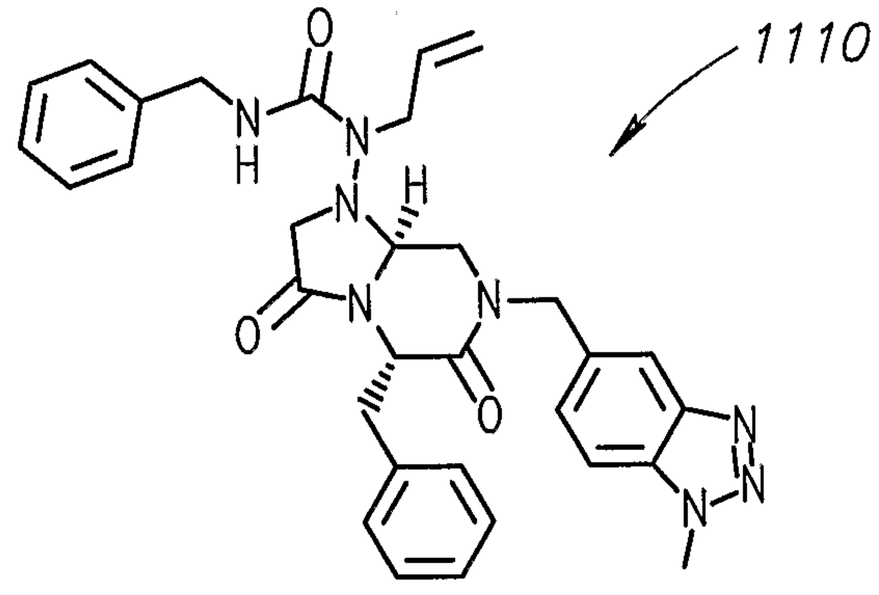


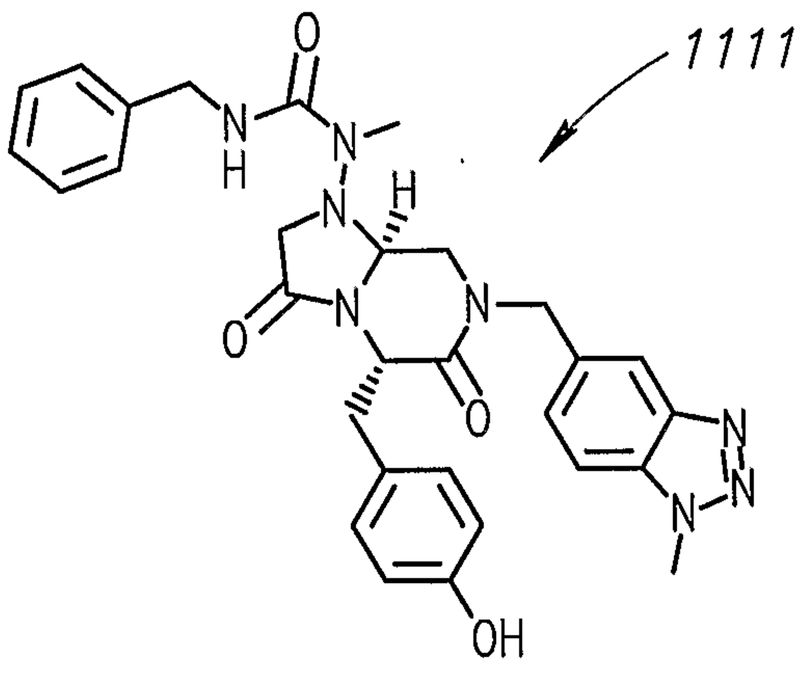












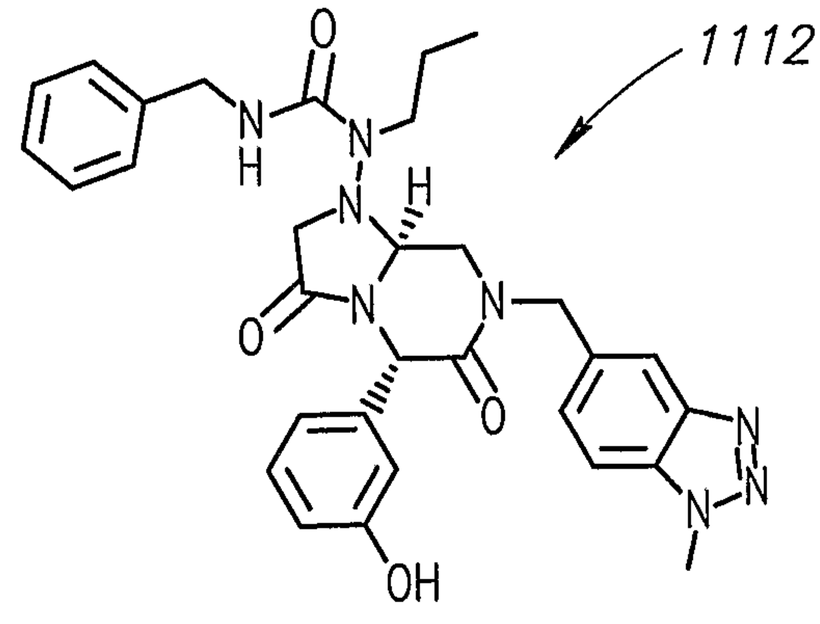
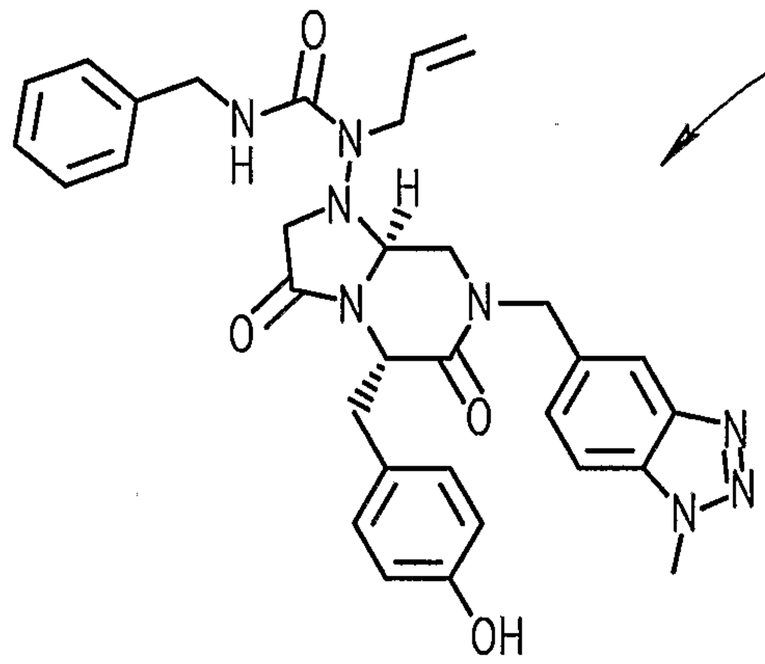
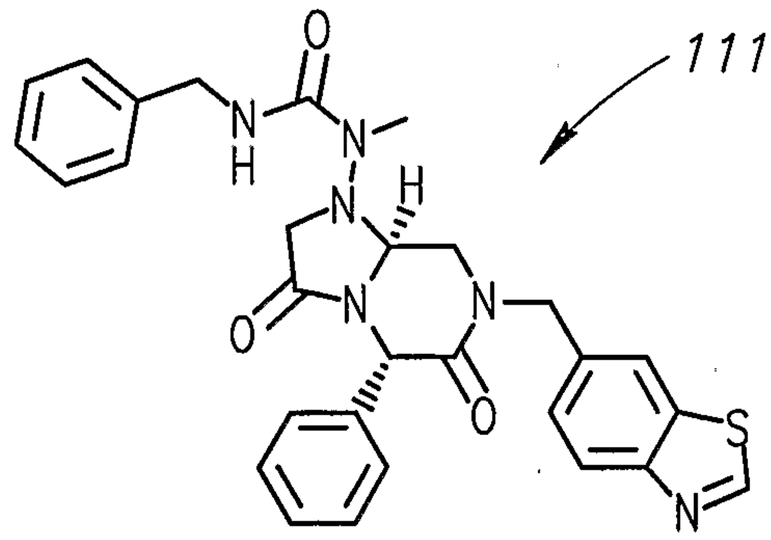
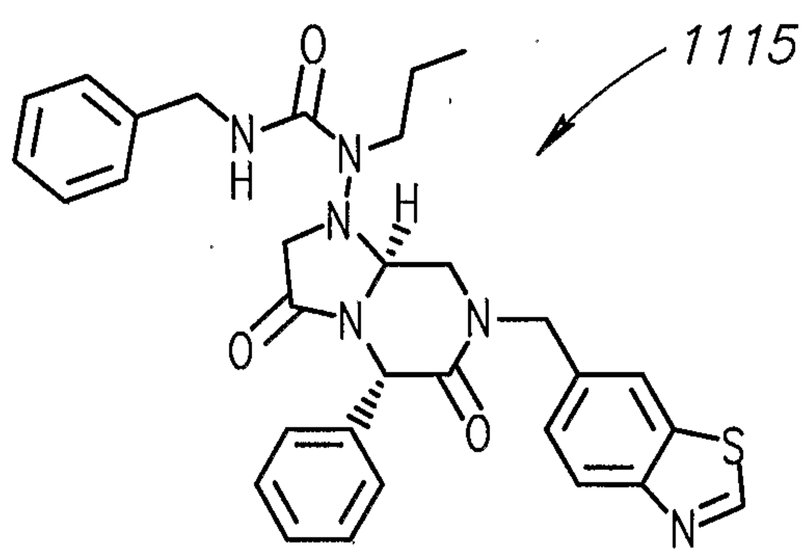
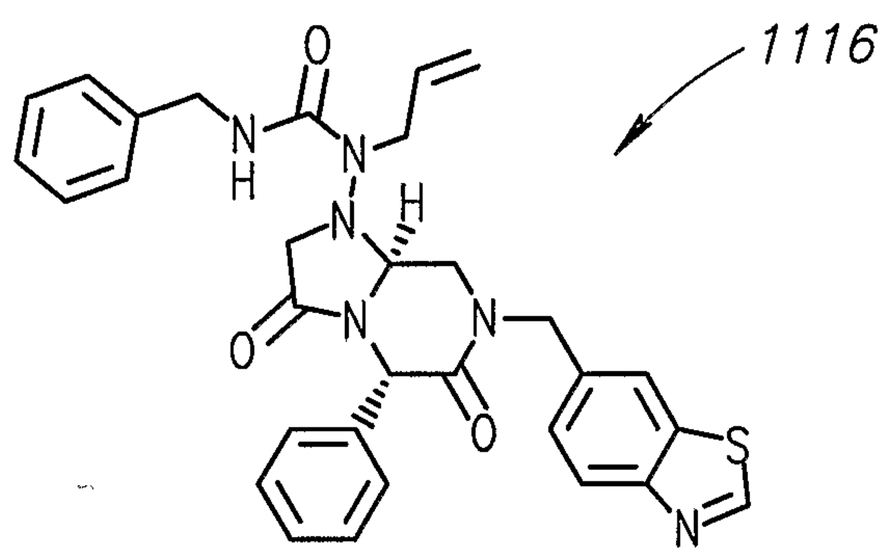


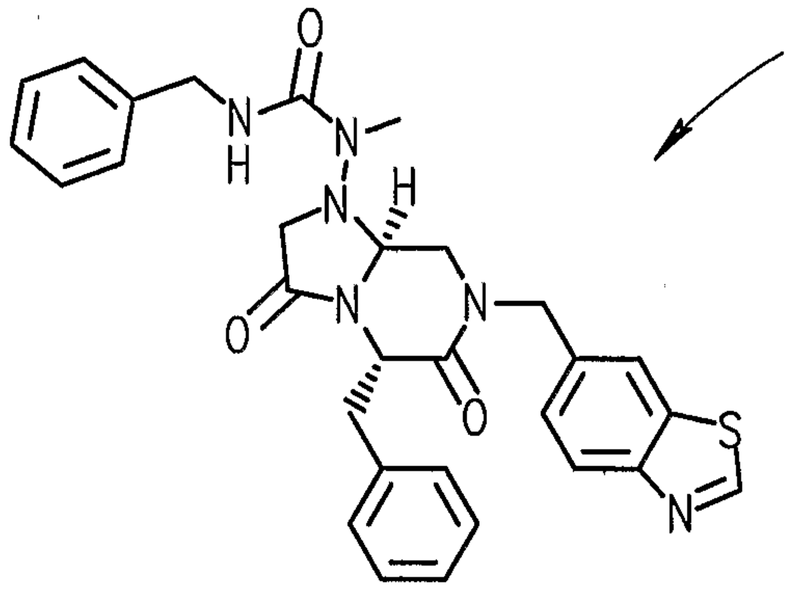
FIG.6N

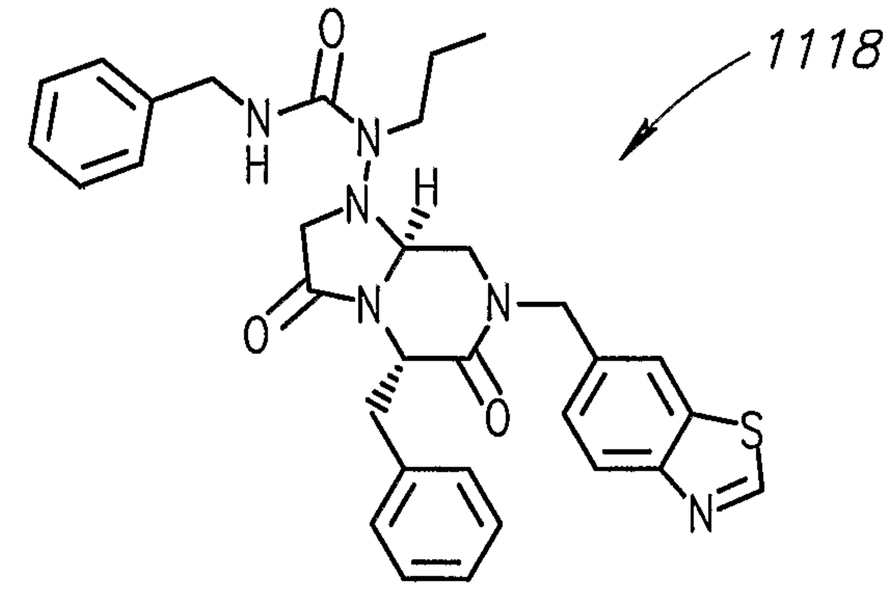


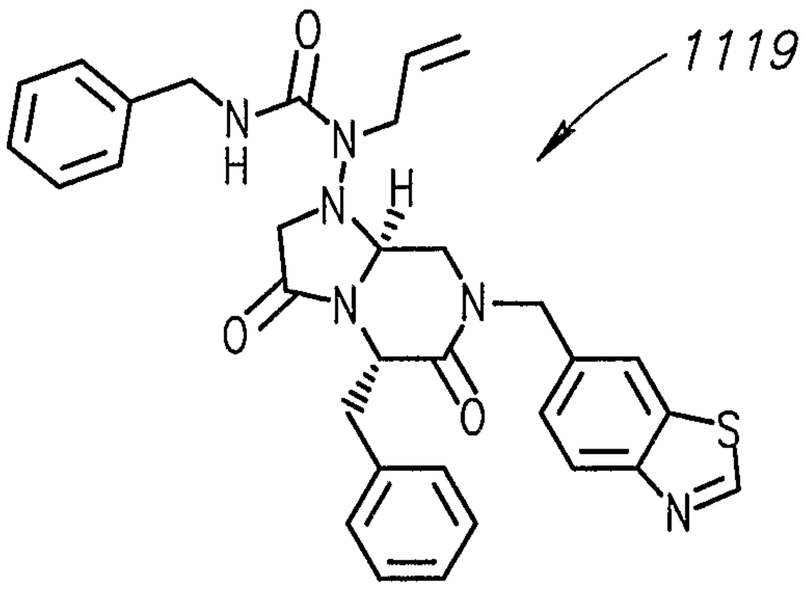












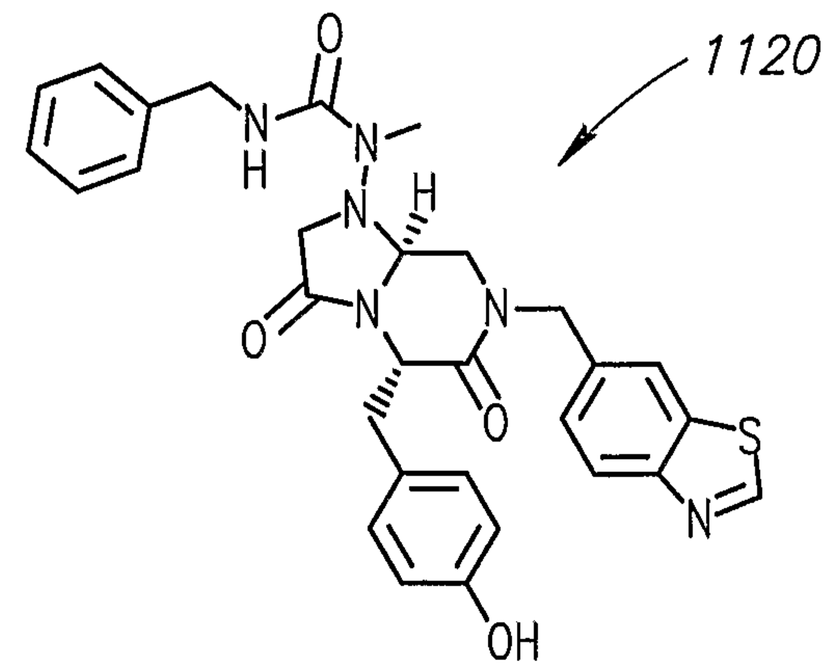
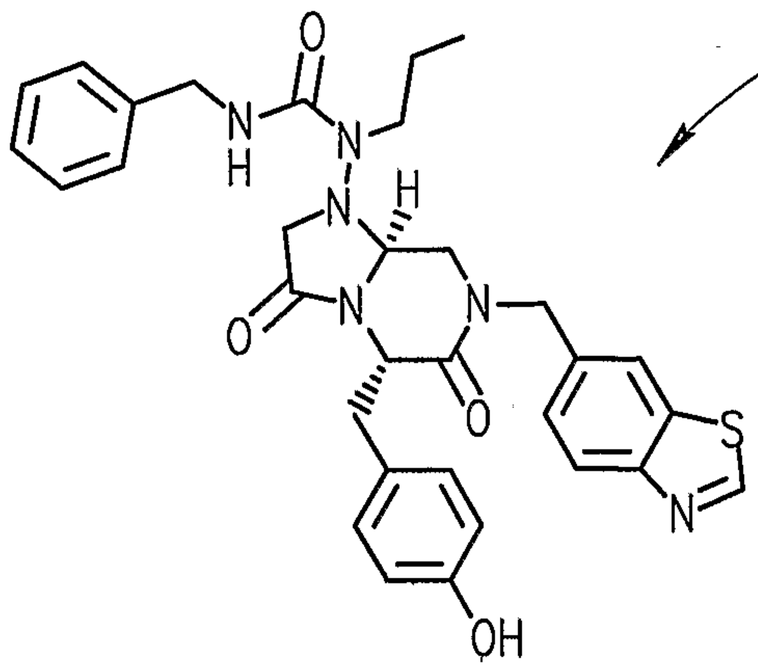
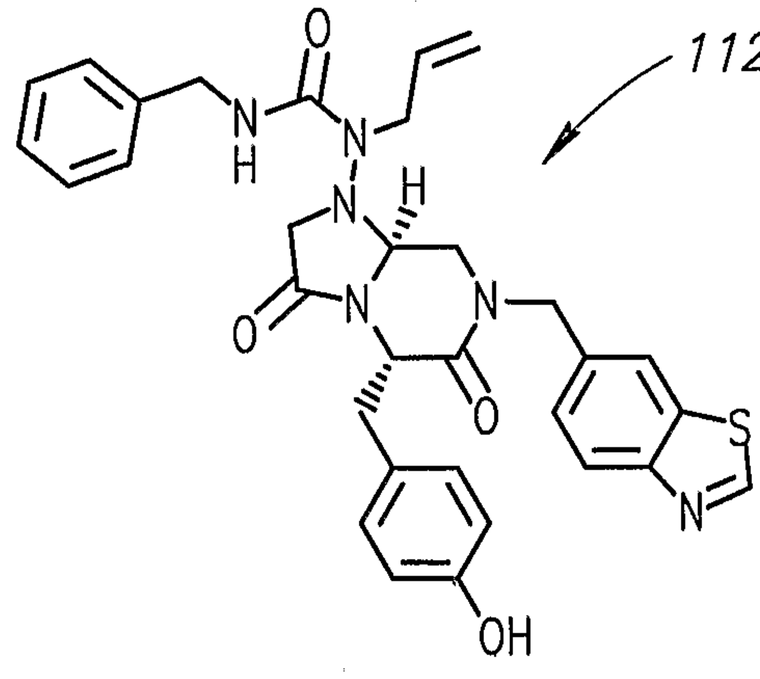
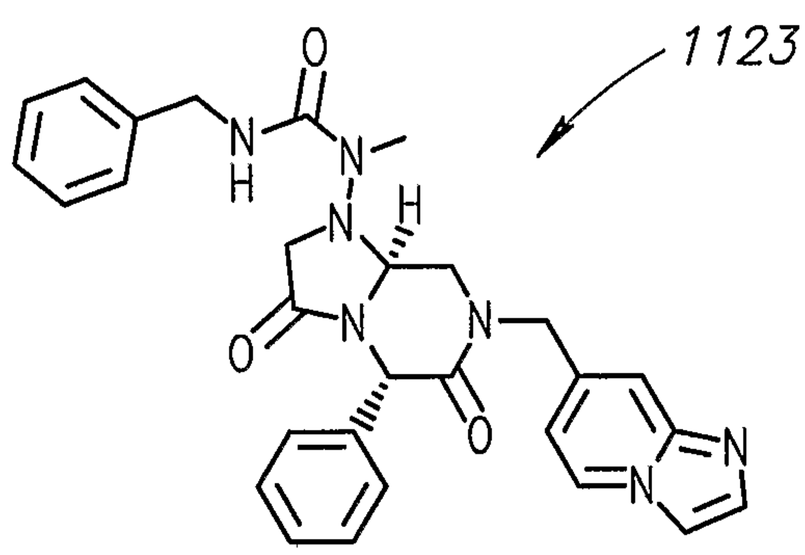
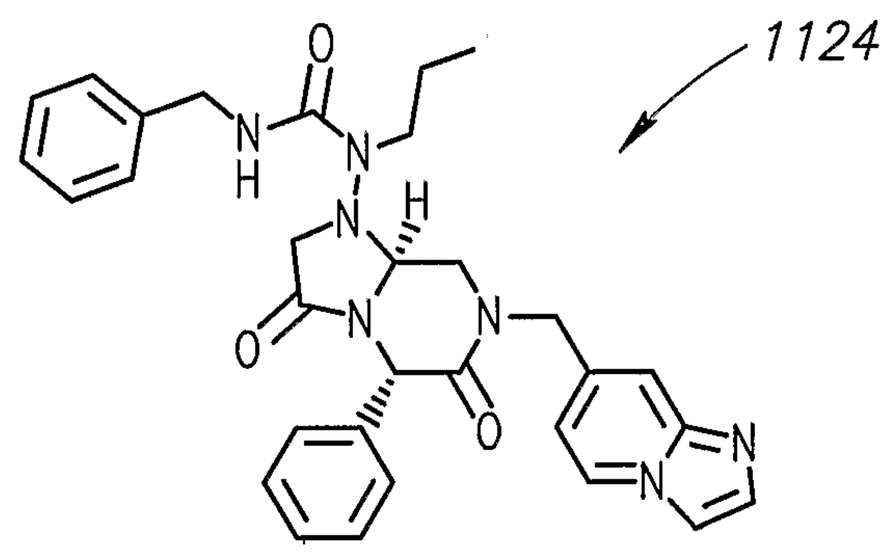


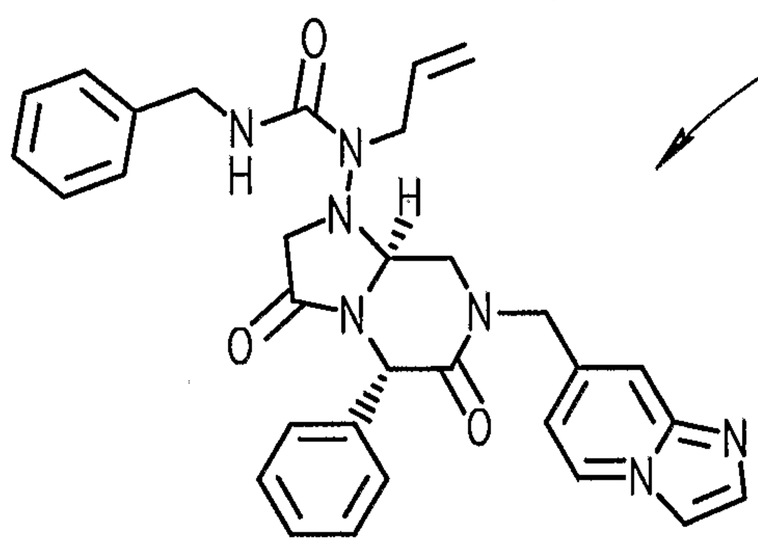
FIG.60

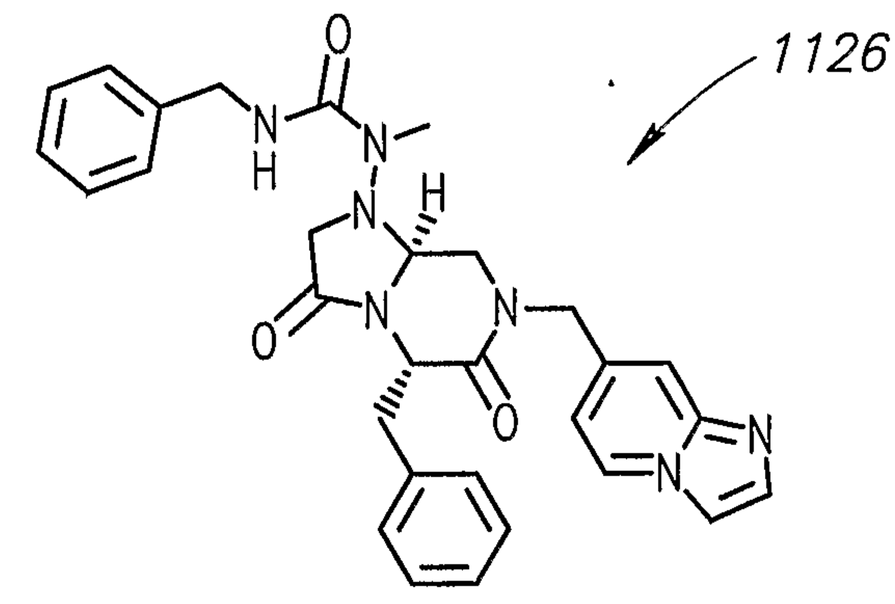


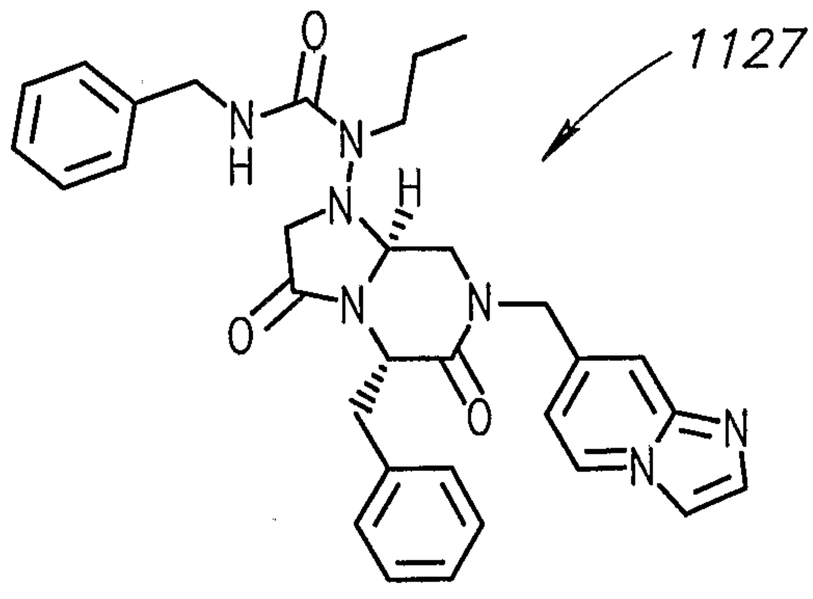












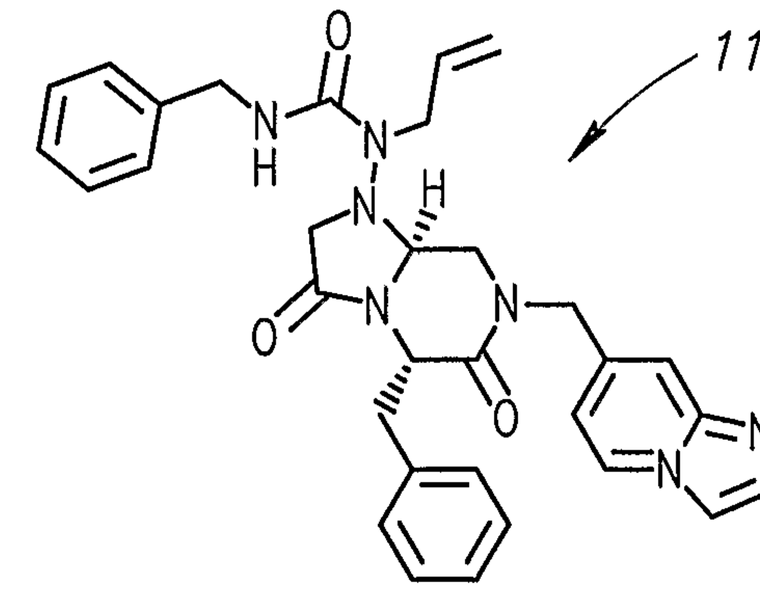
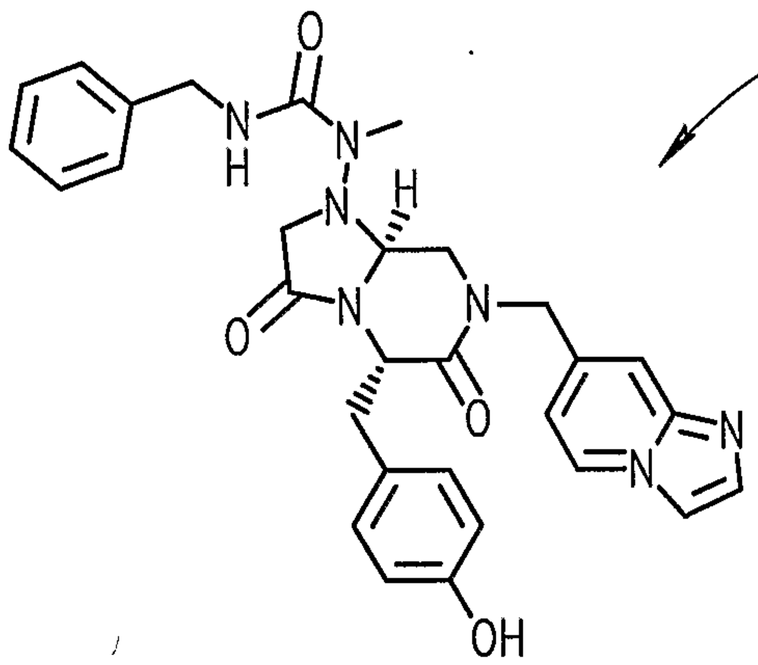
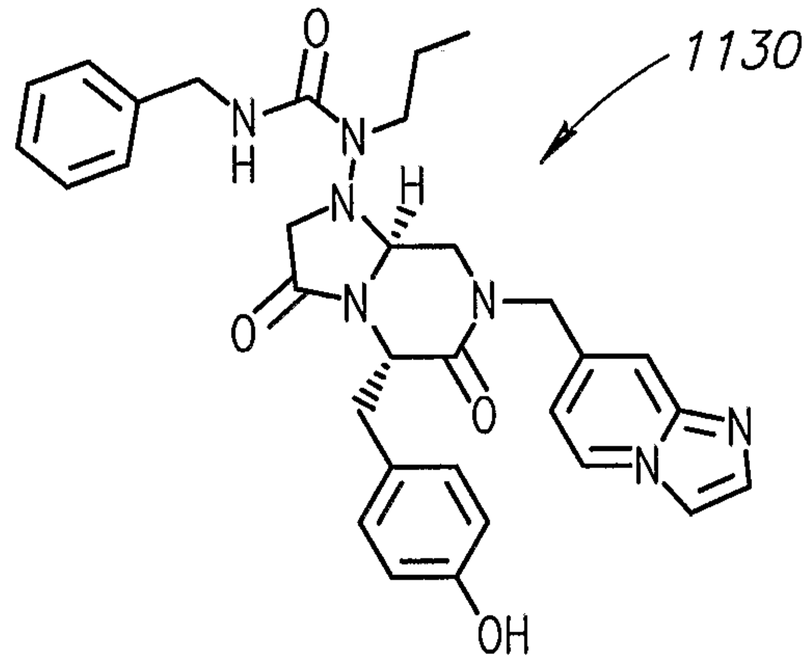
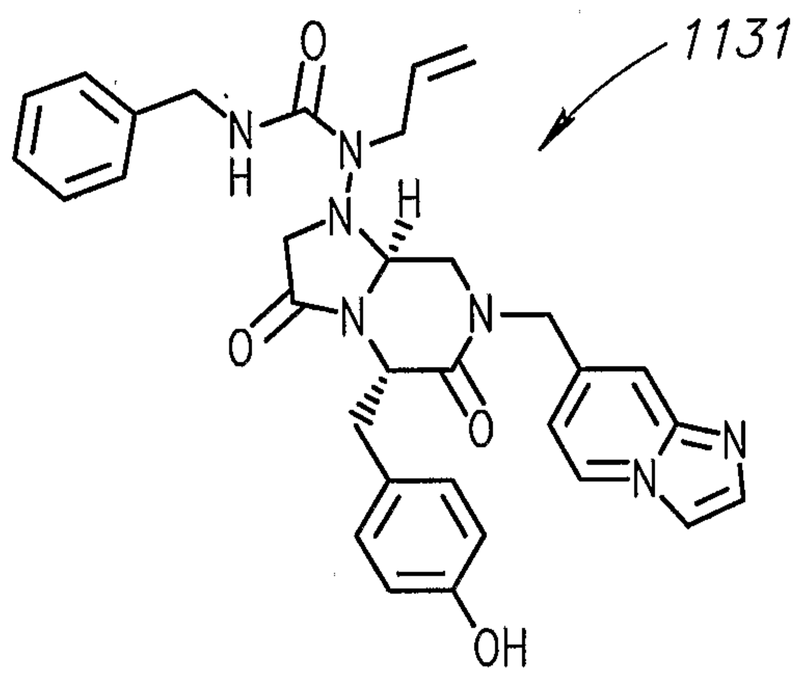
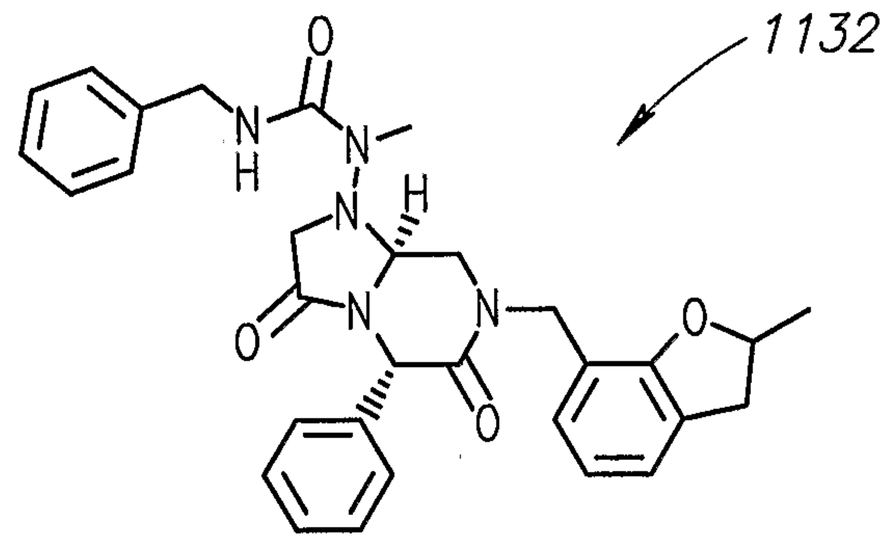


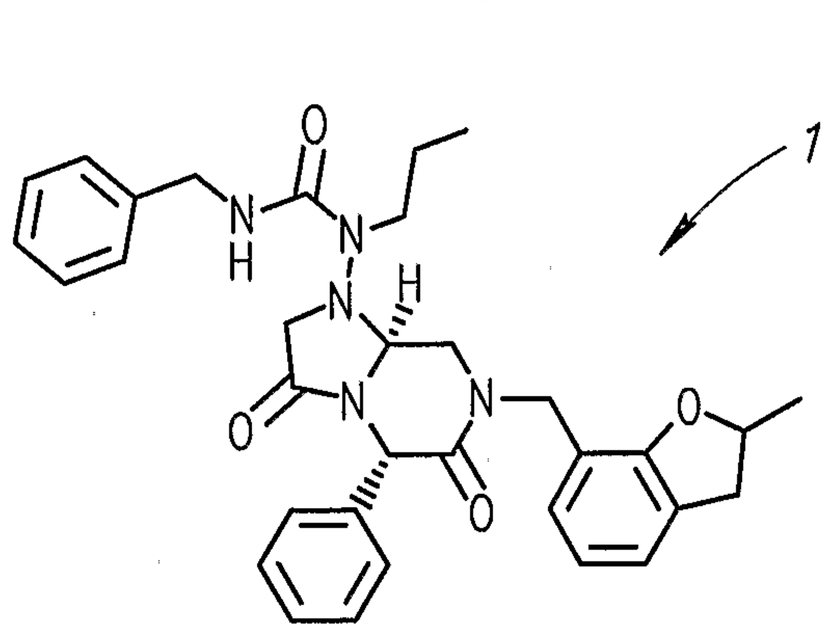
FIG.6P











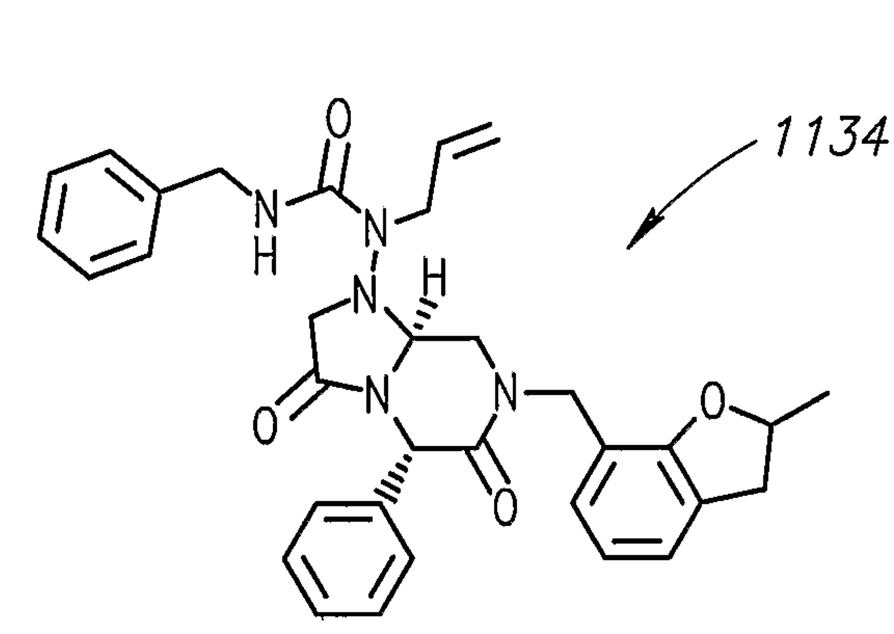
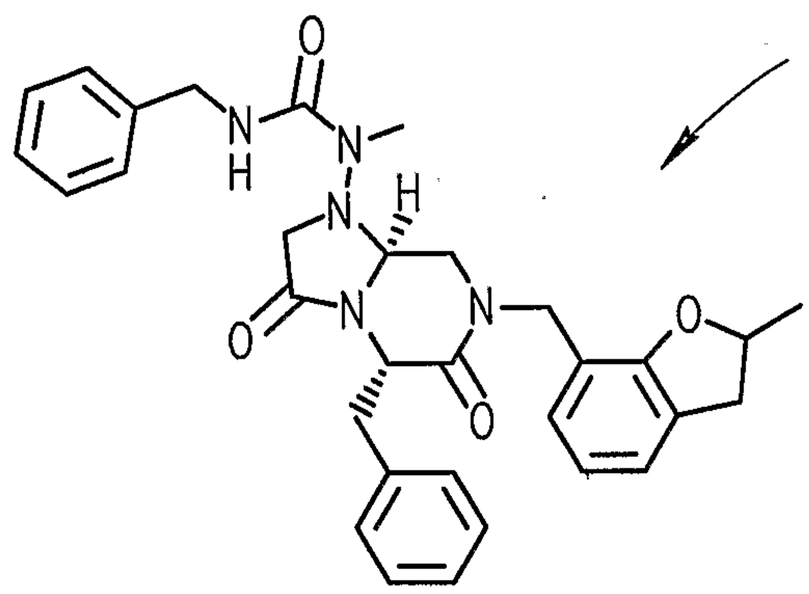
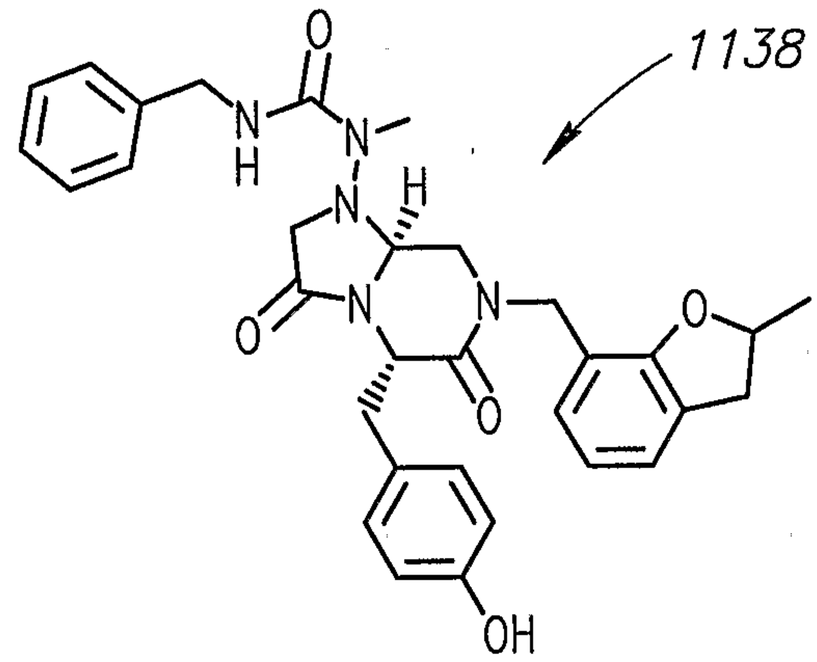
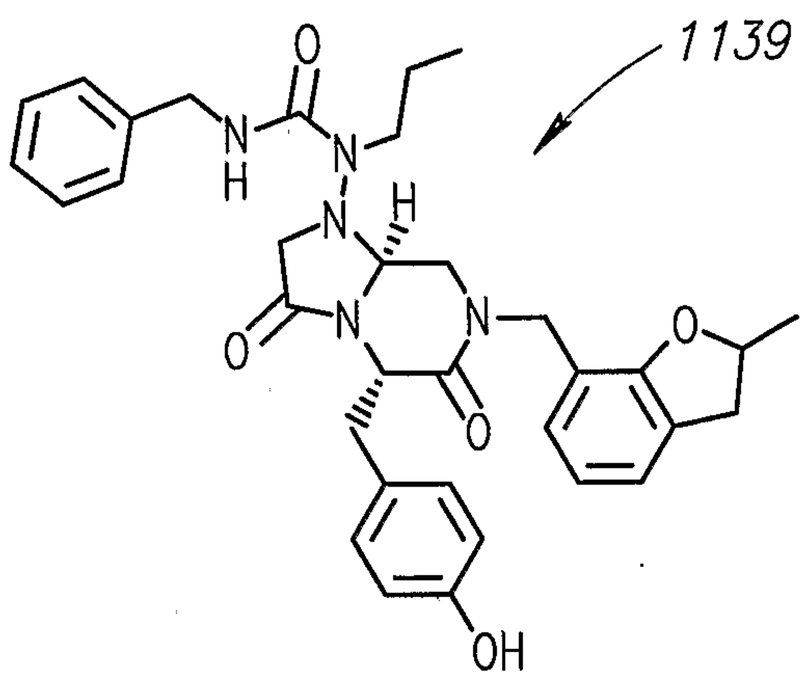
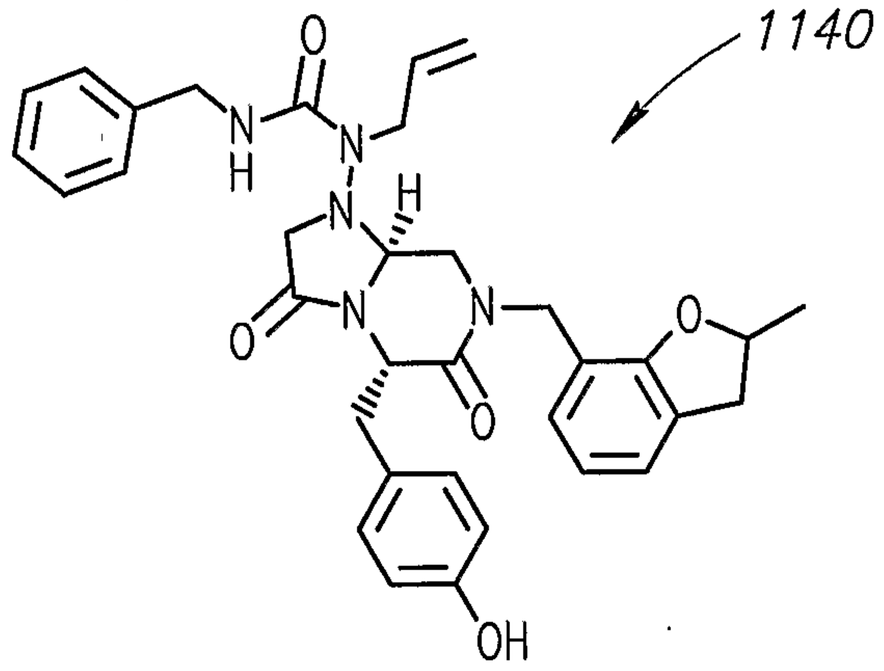


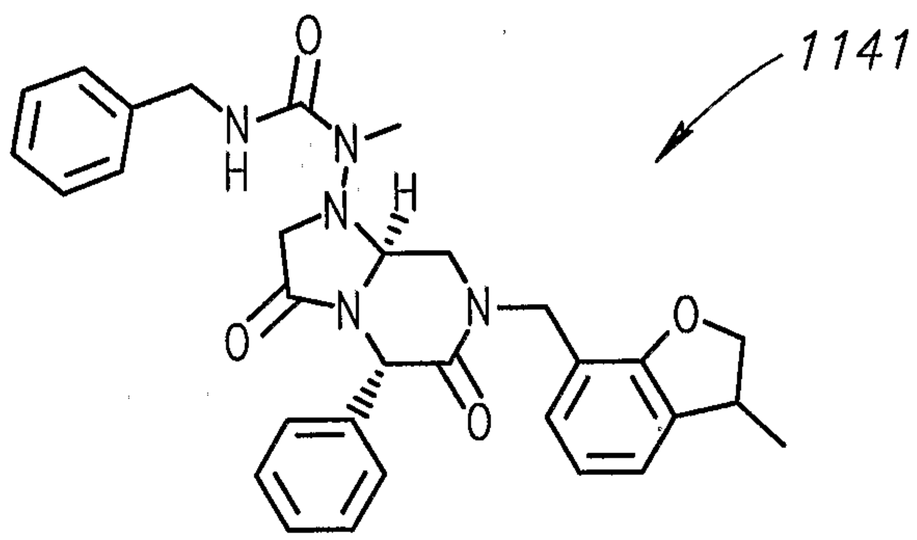
FIG.6Q

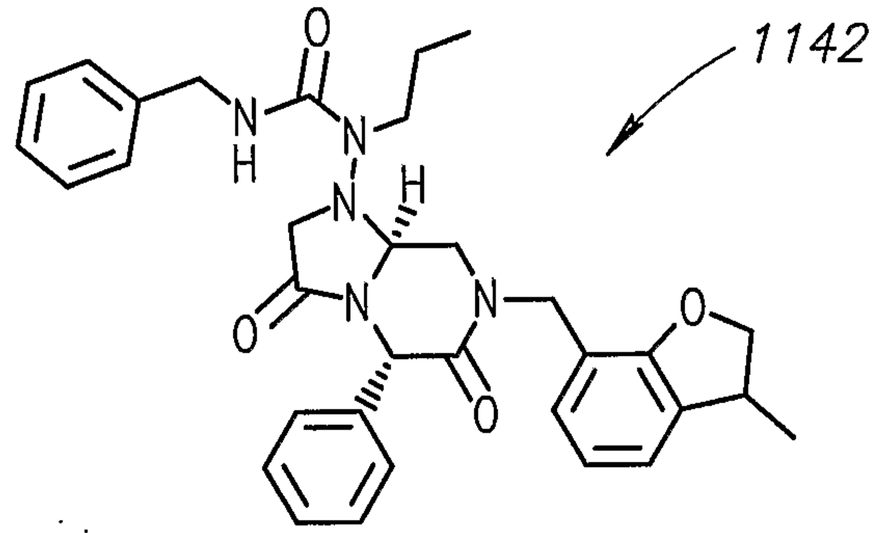


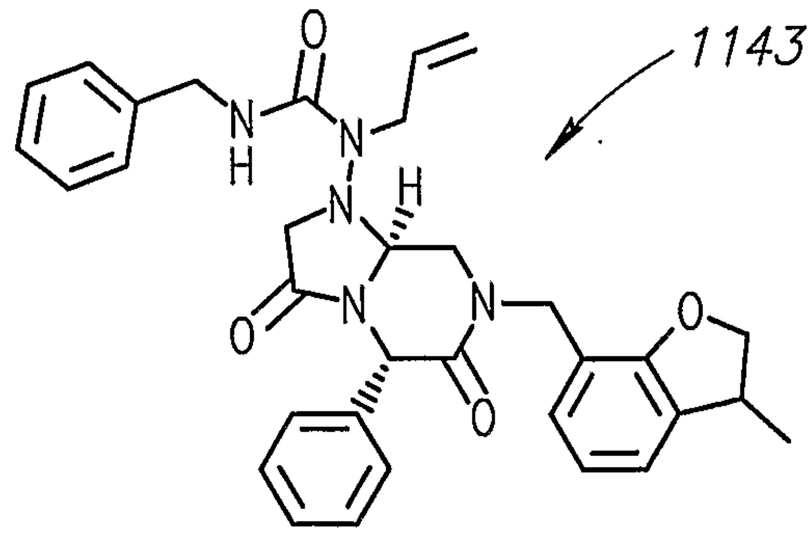












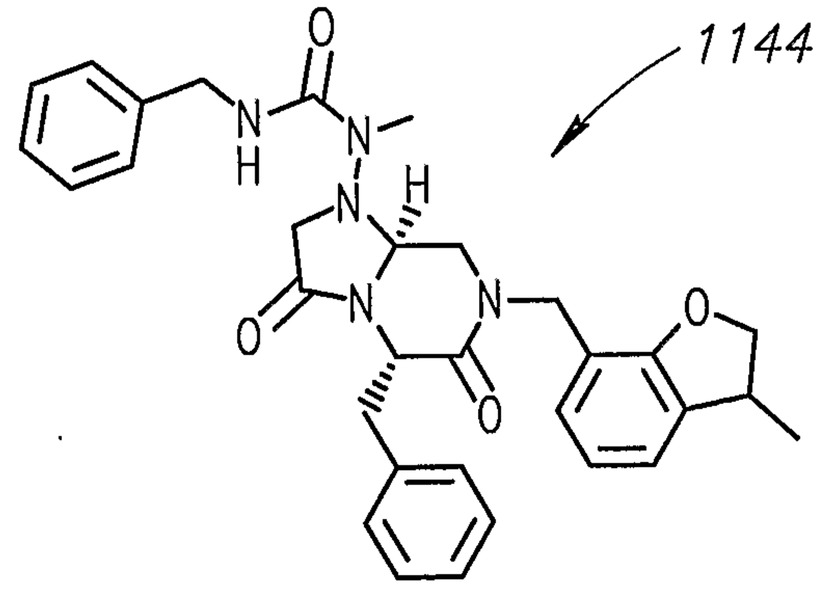
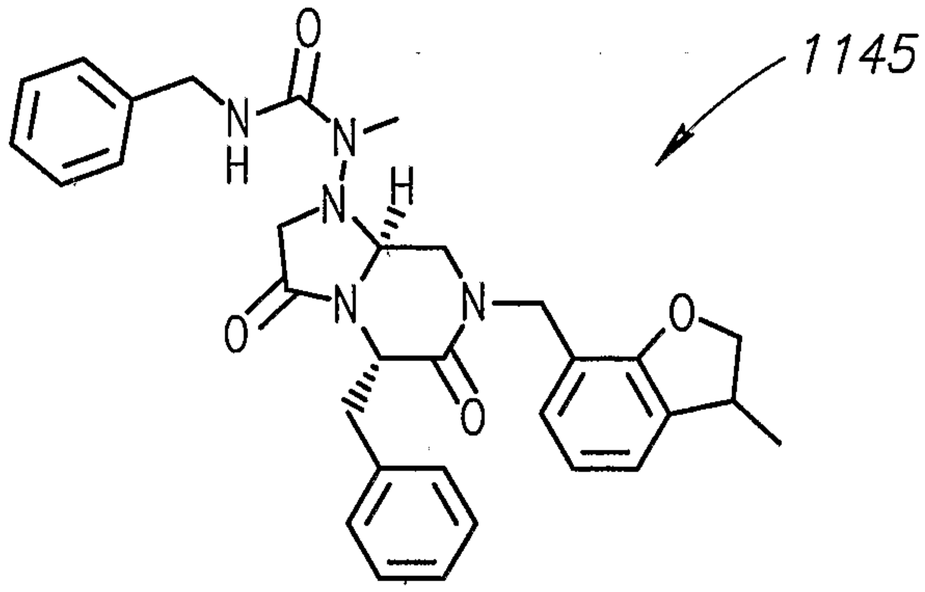
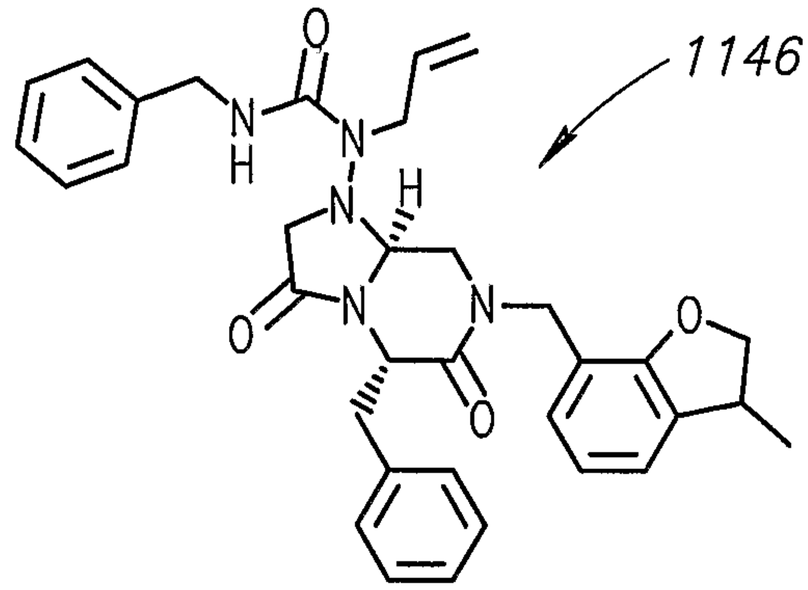
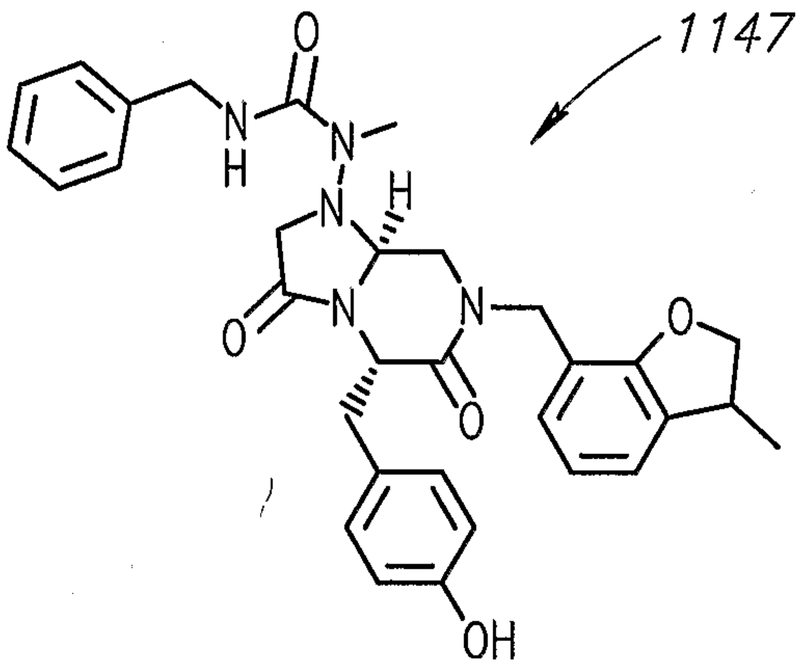
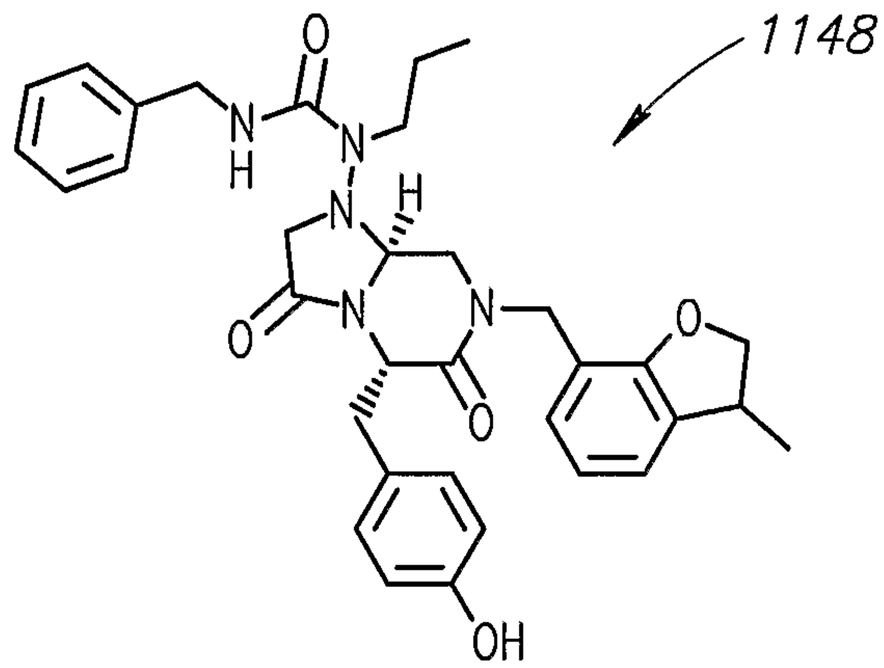


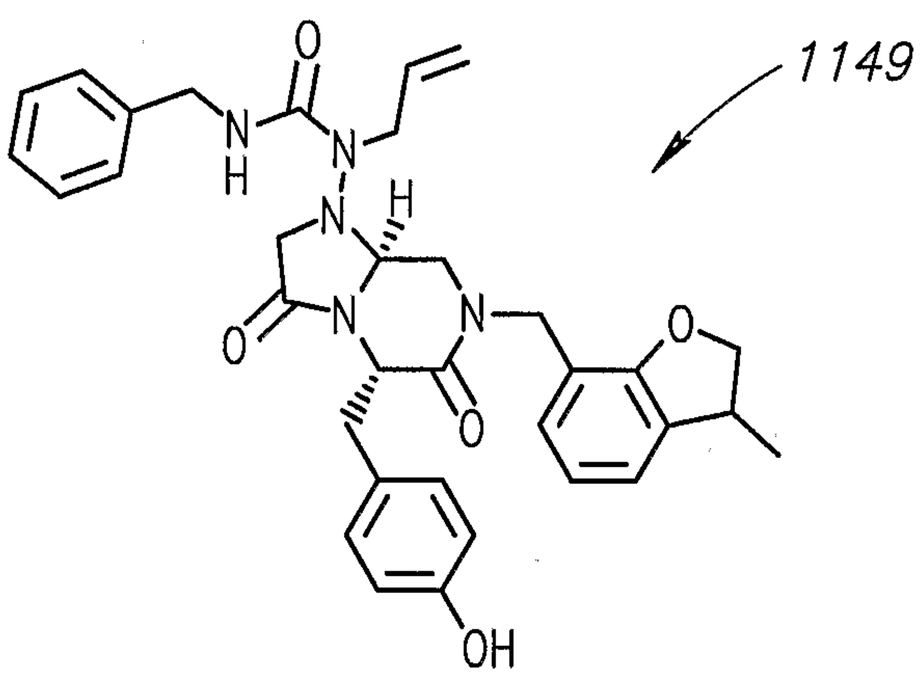
FIG.6R

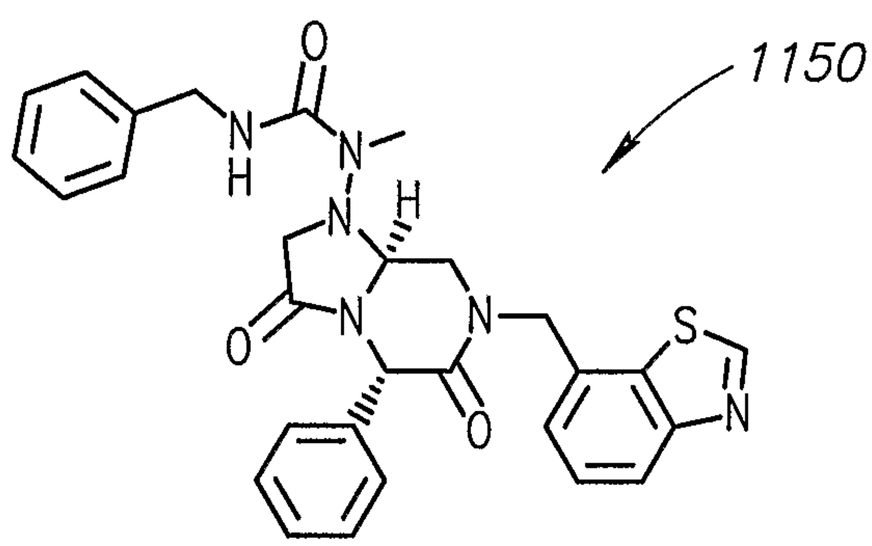


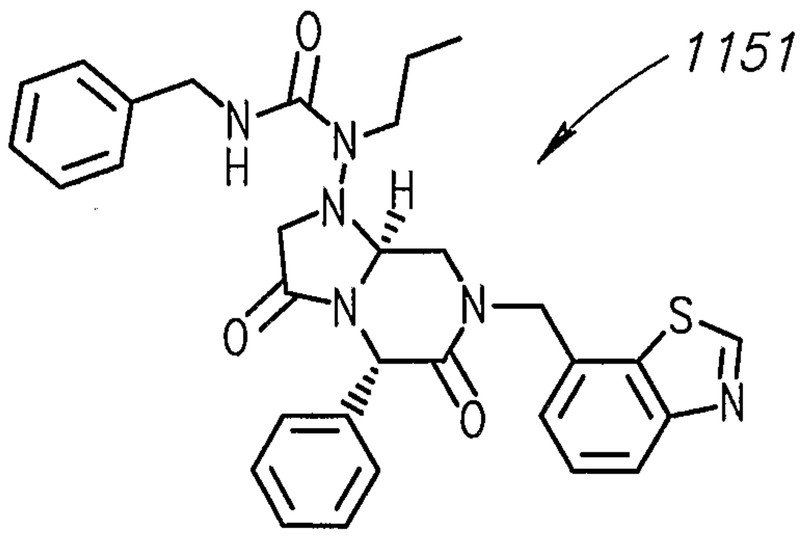












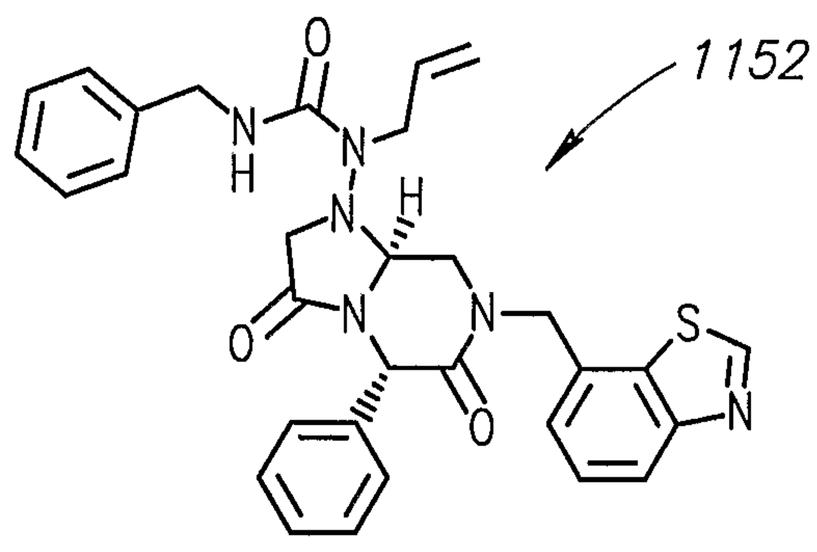
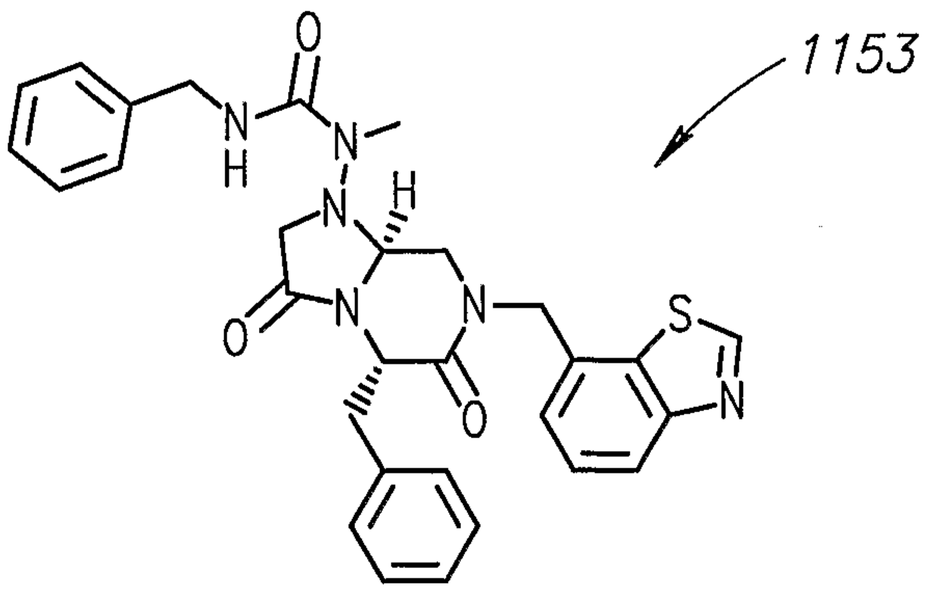
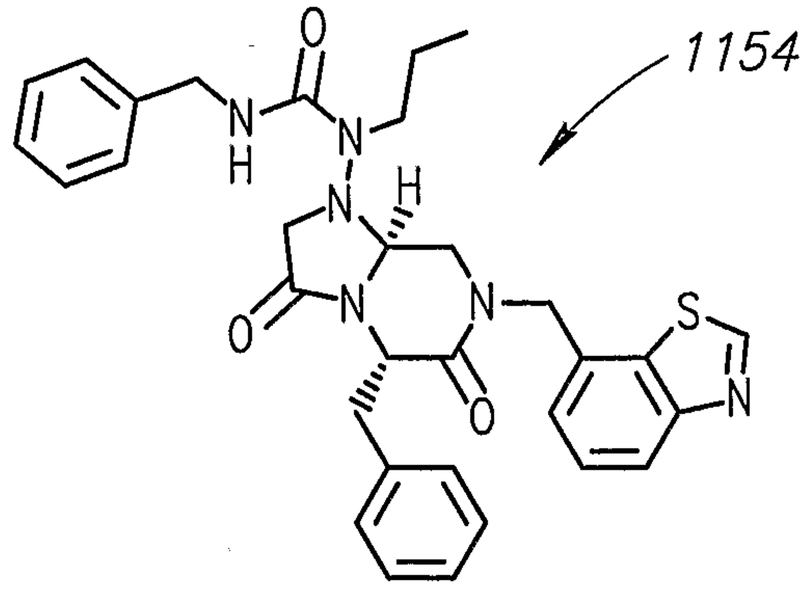
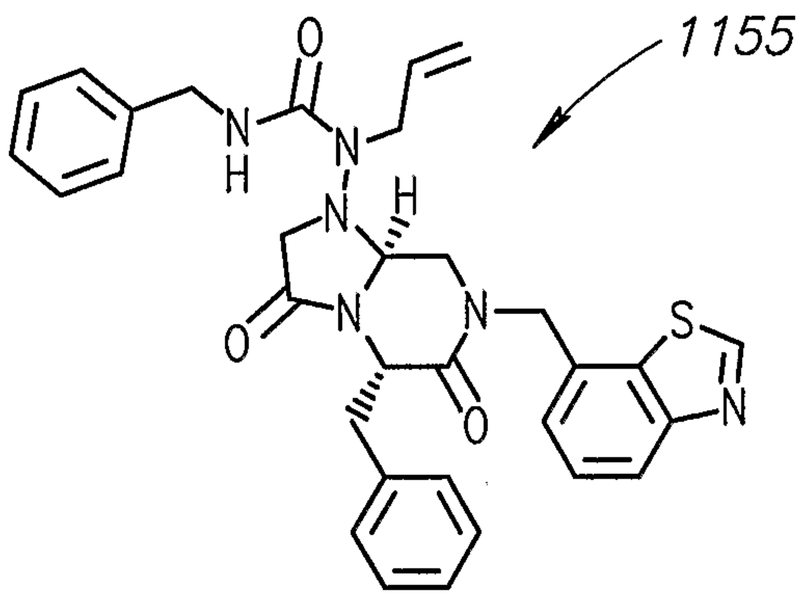
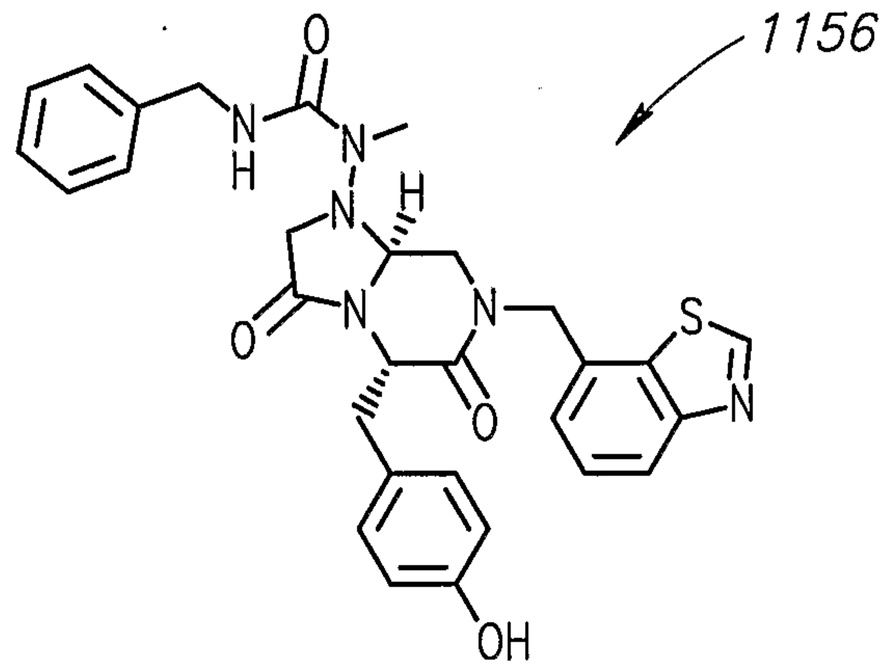


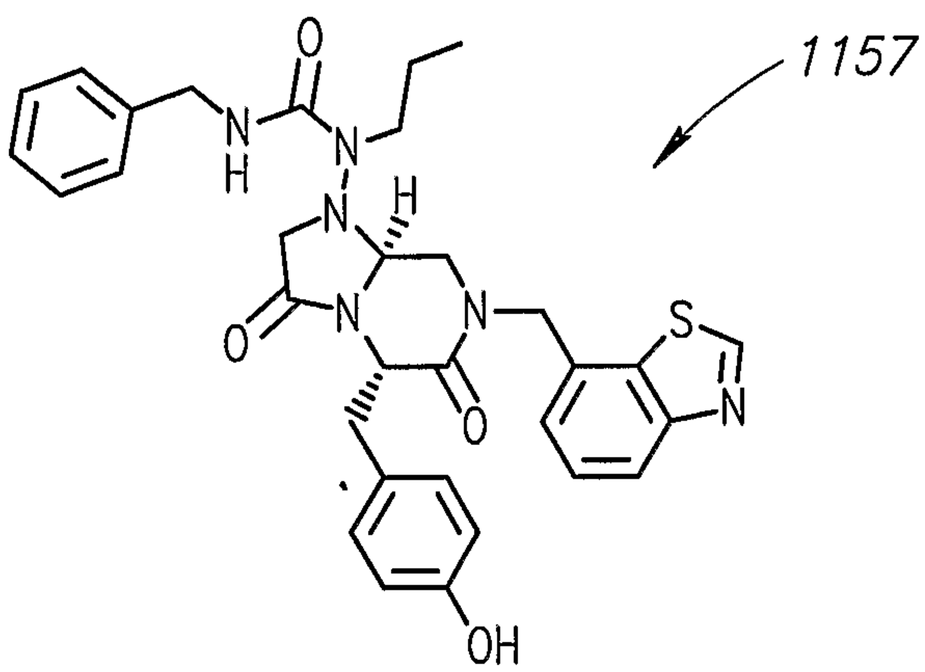
FIG.6S

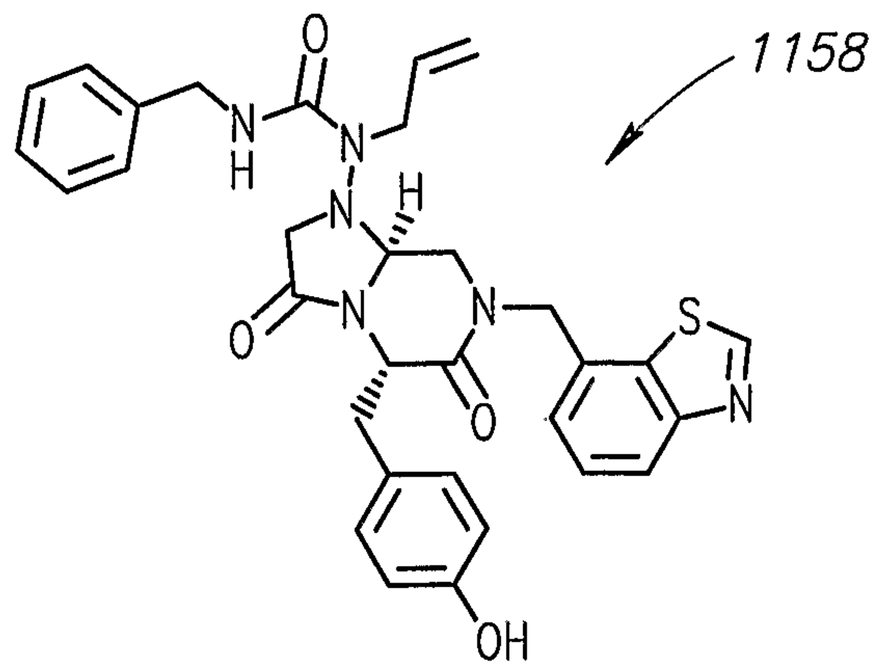


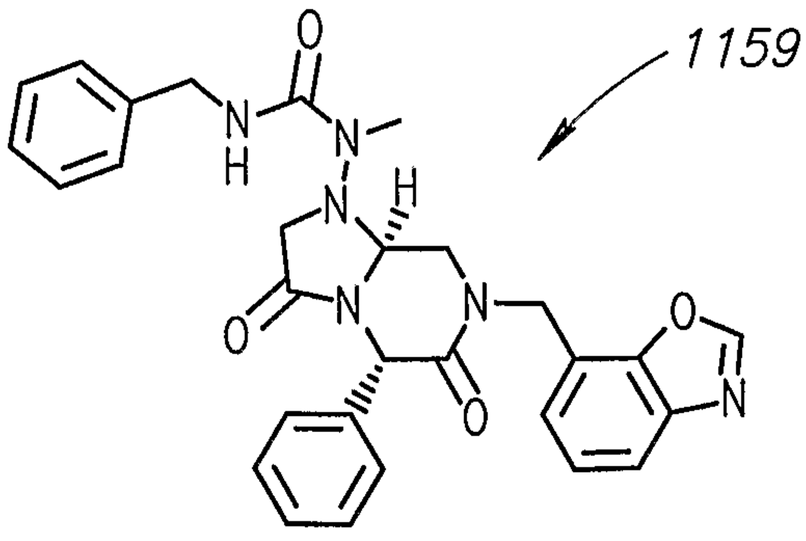












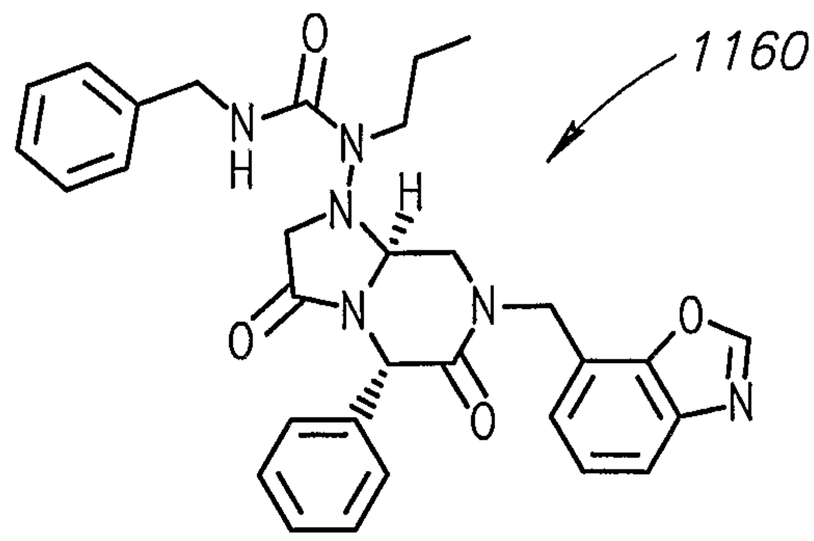
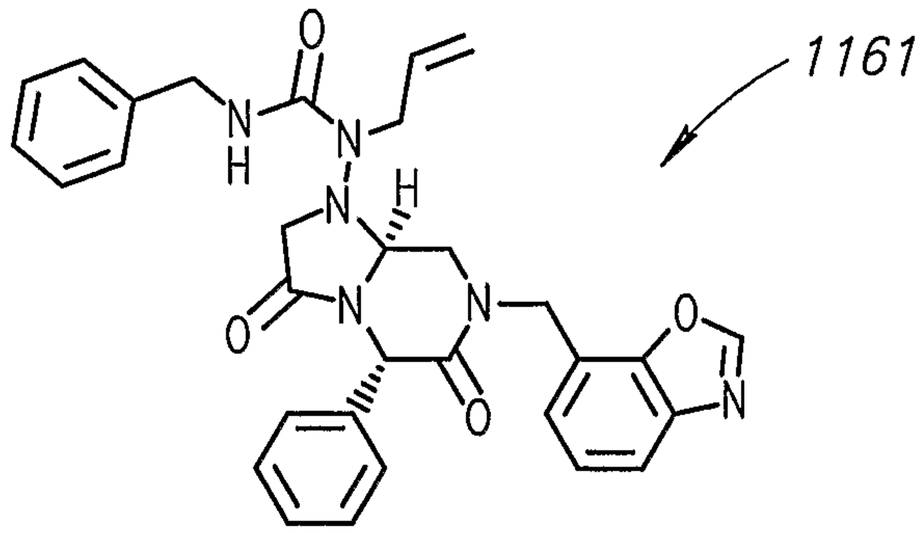
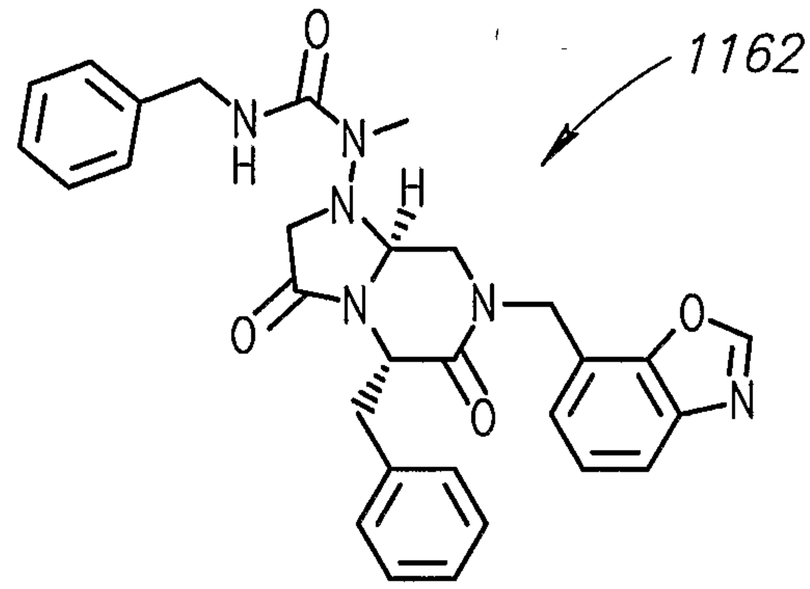
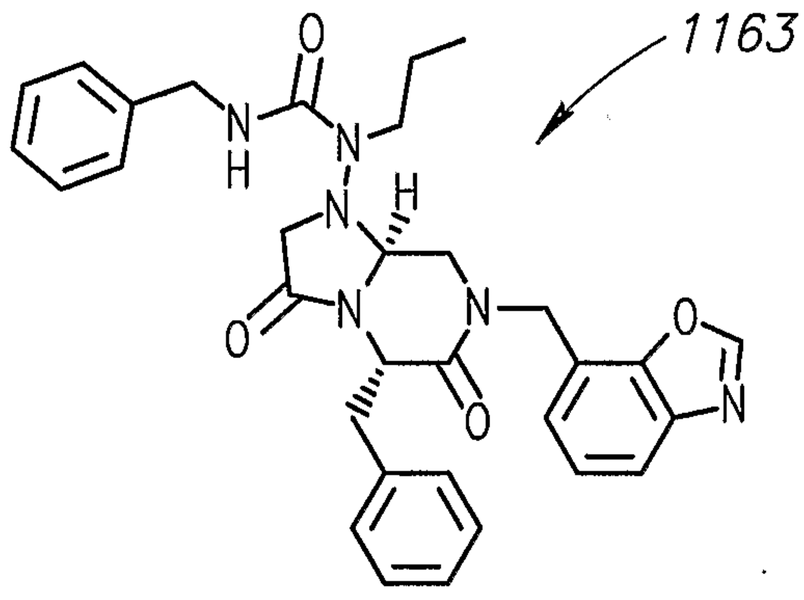
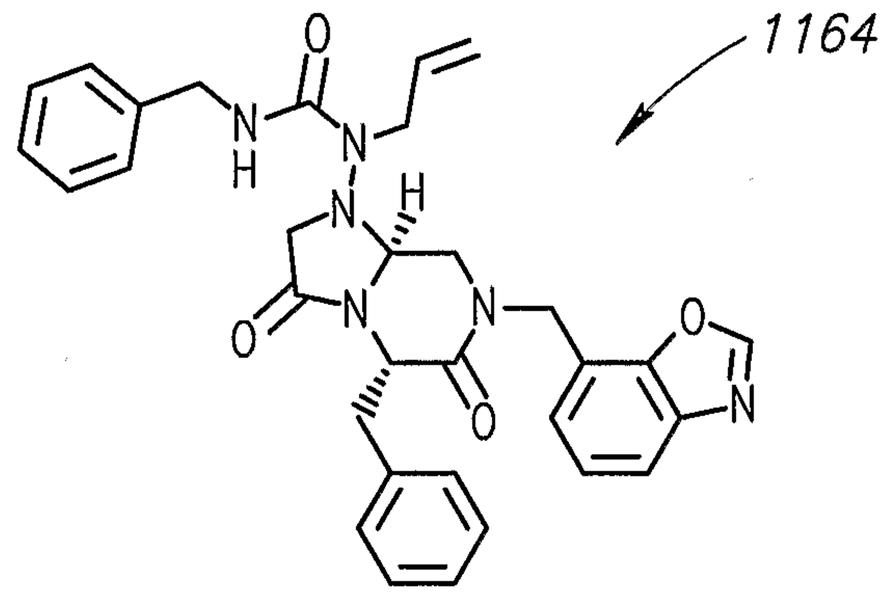


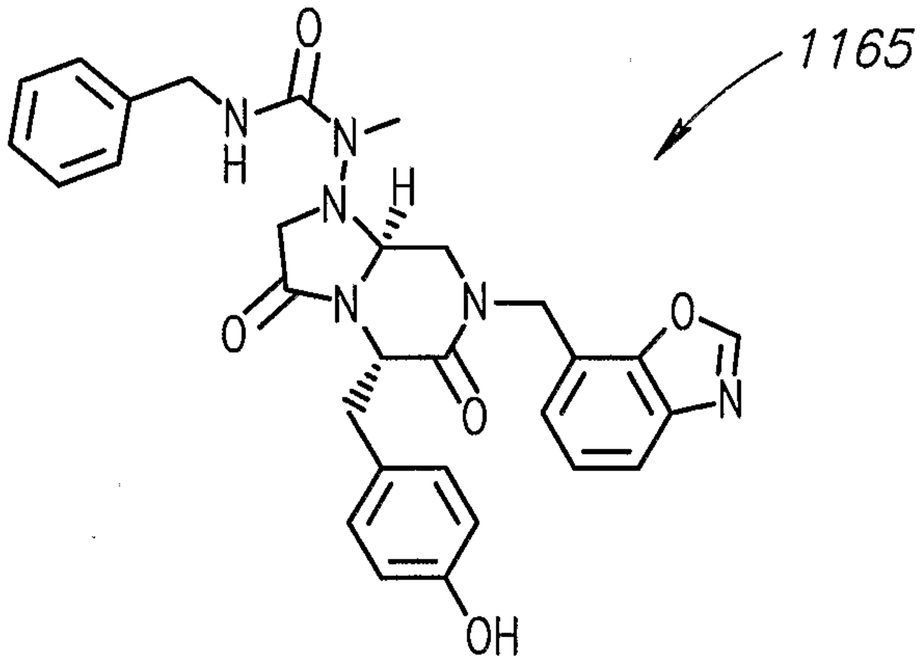
FIG.6T

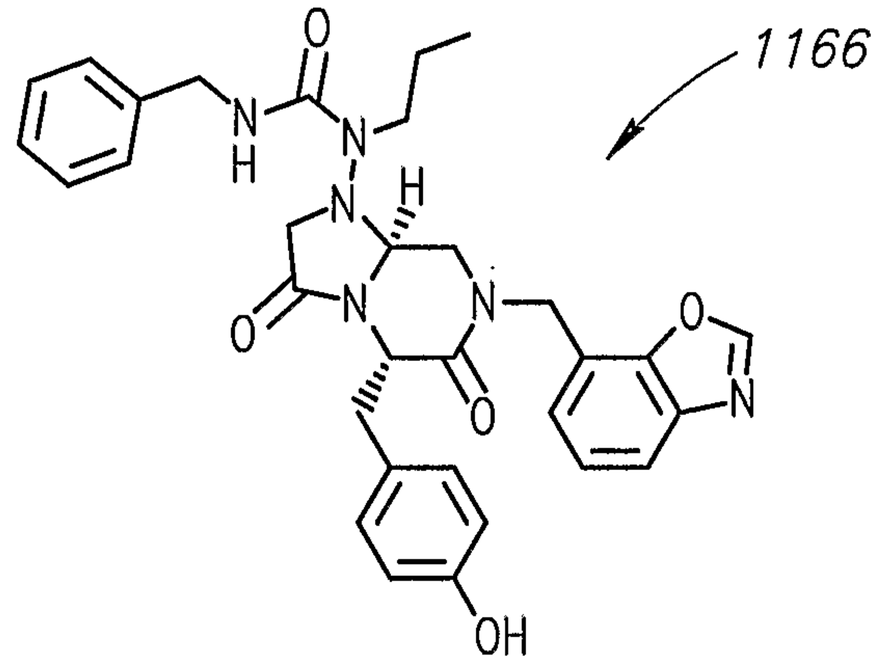


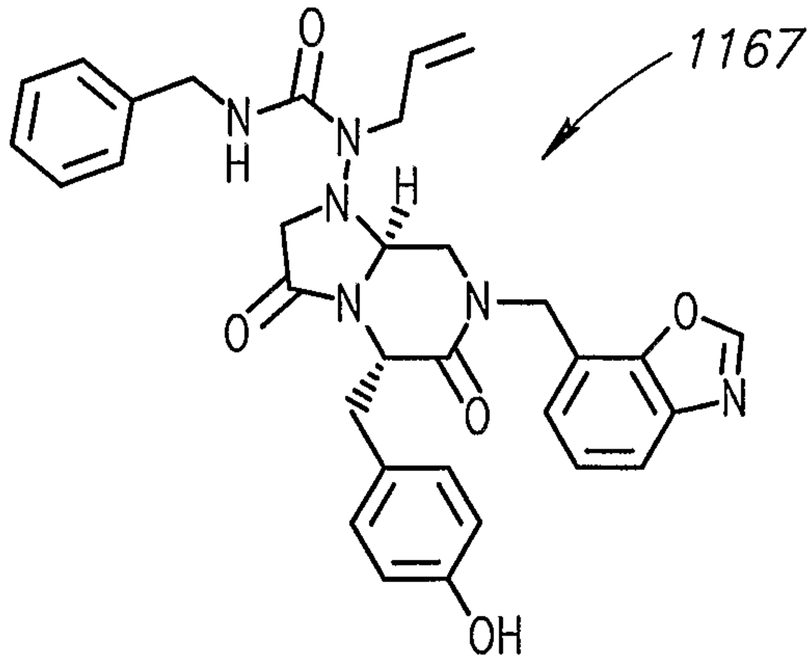












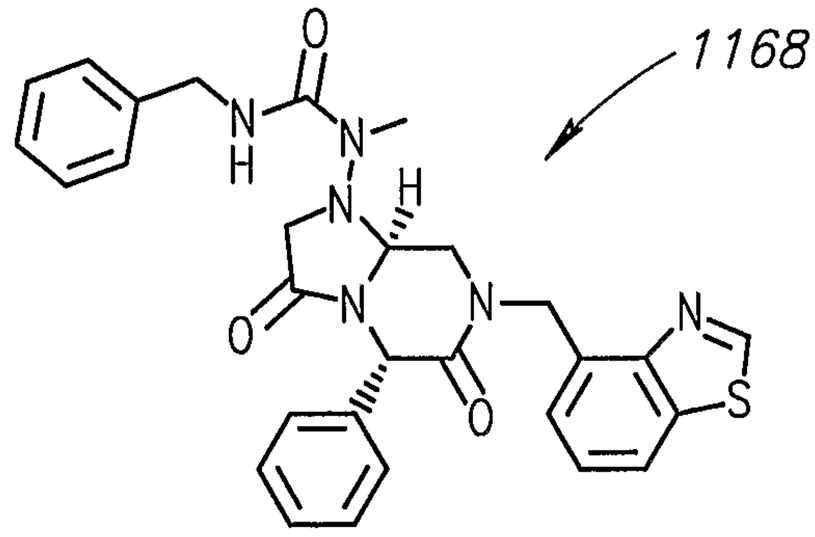
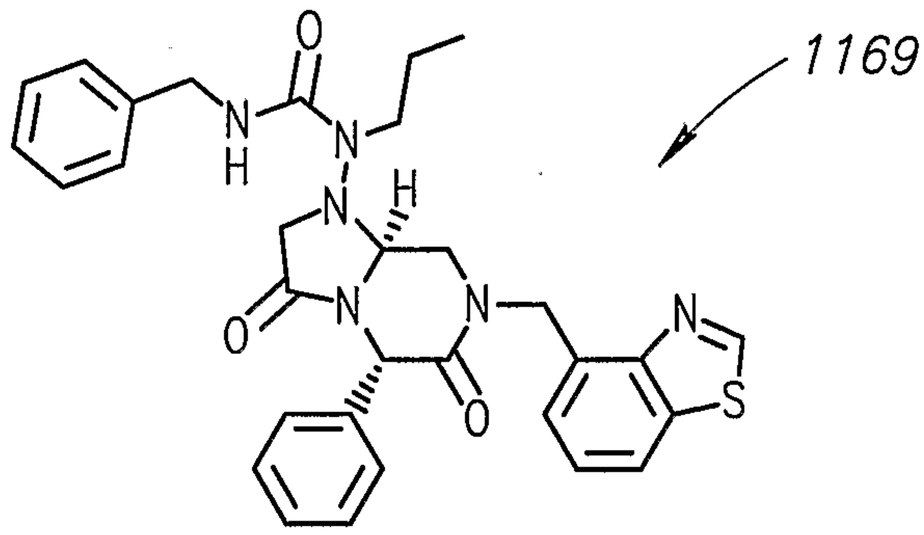
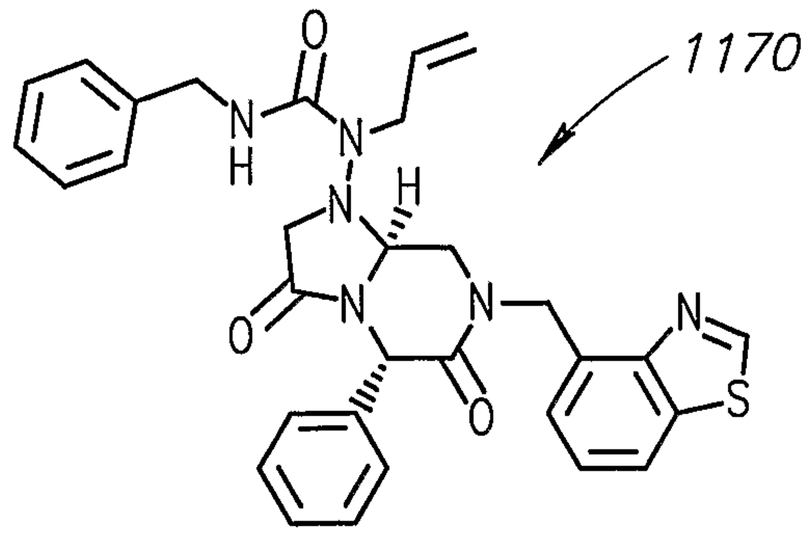
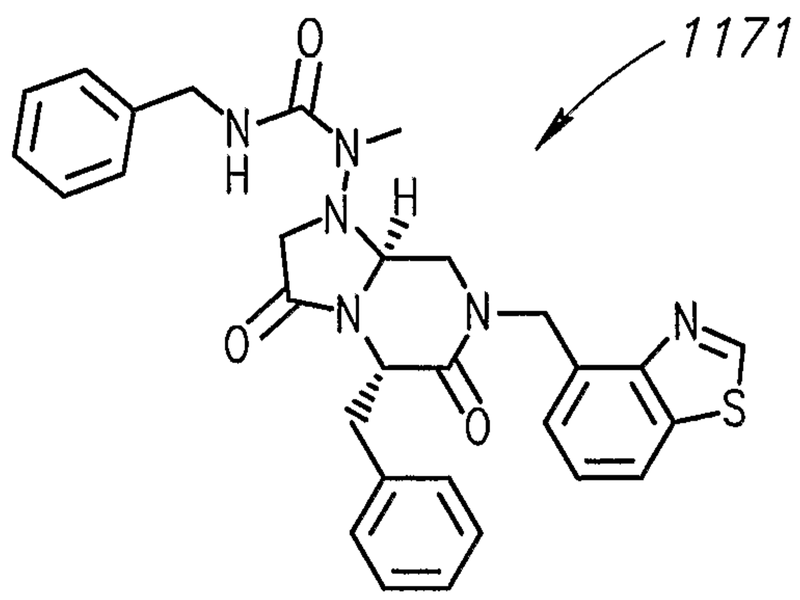
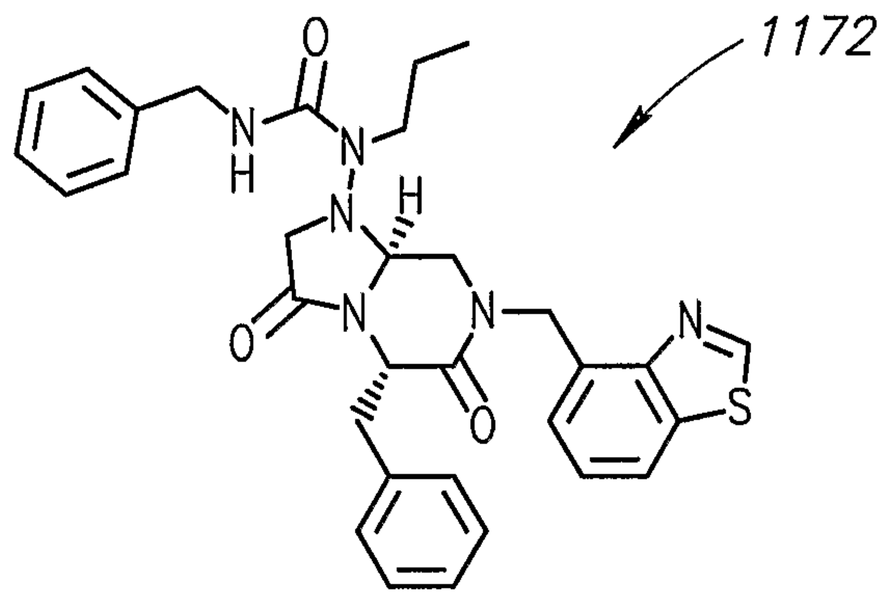


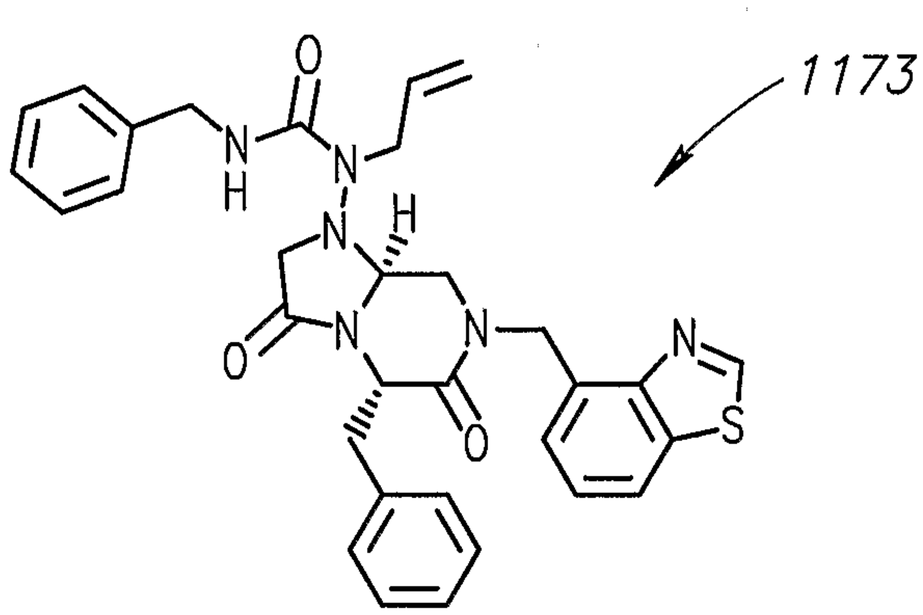
FIG.6U

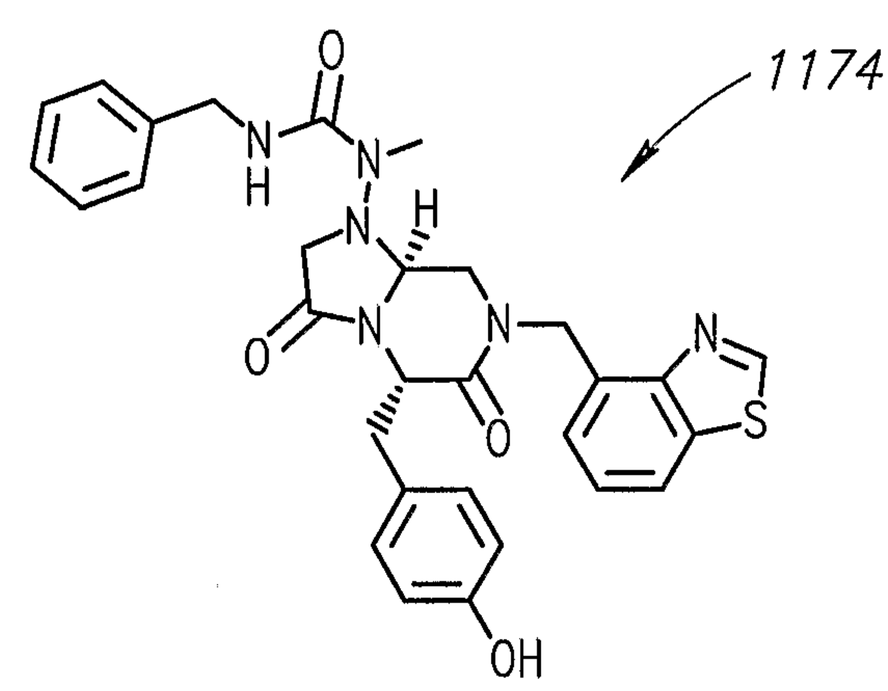


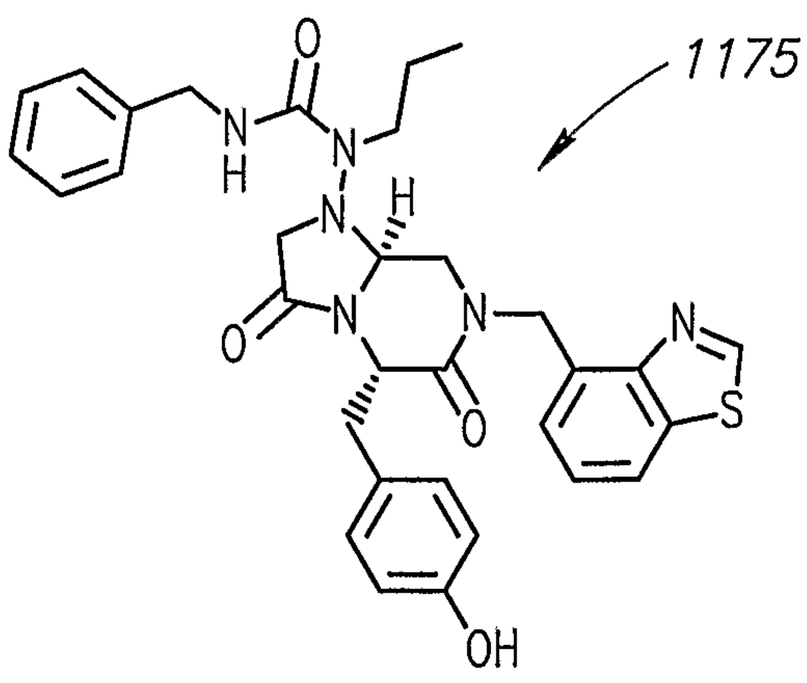












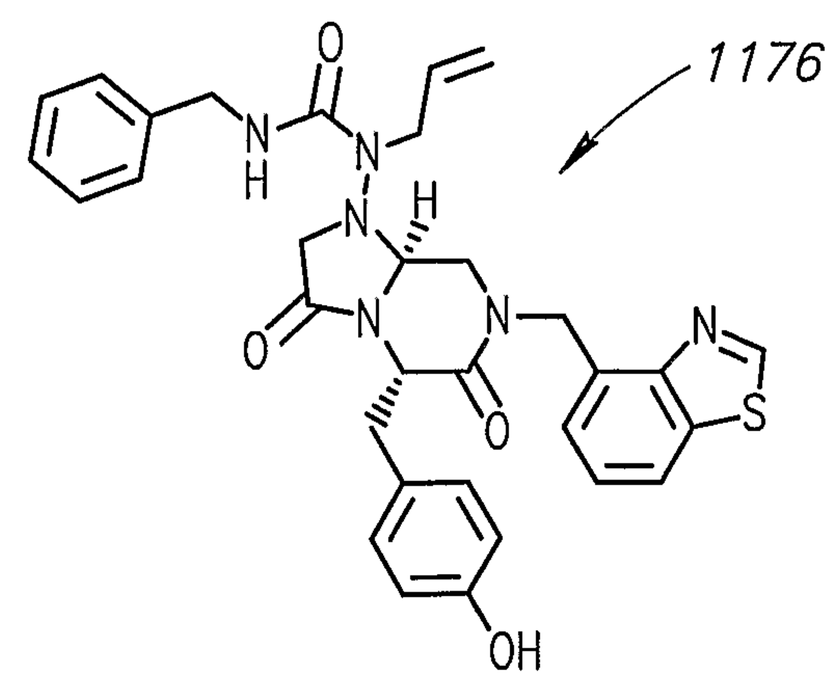
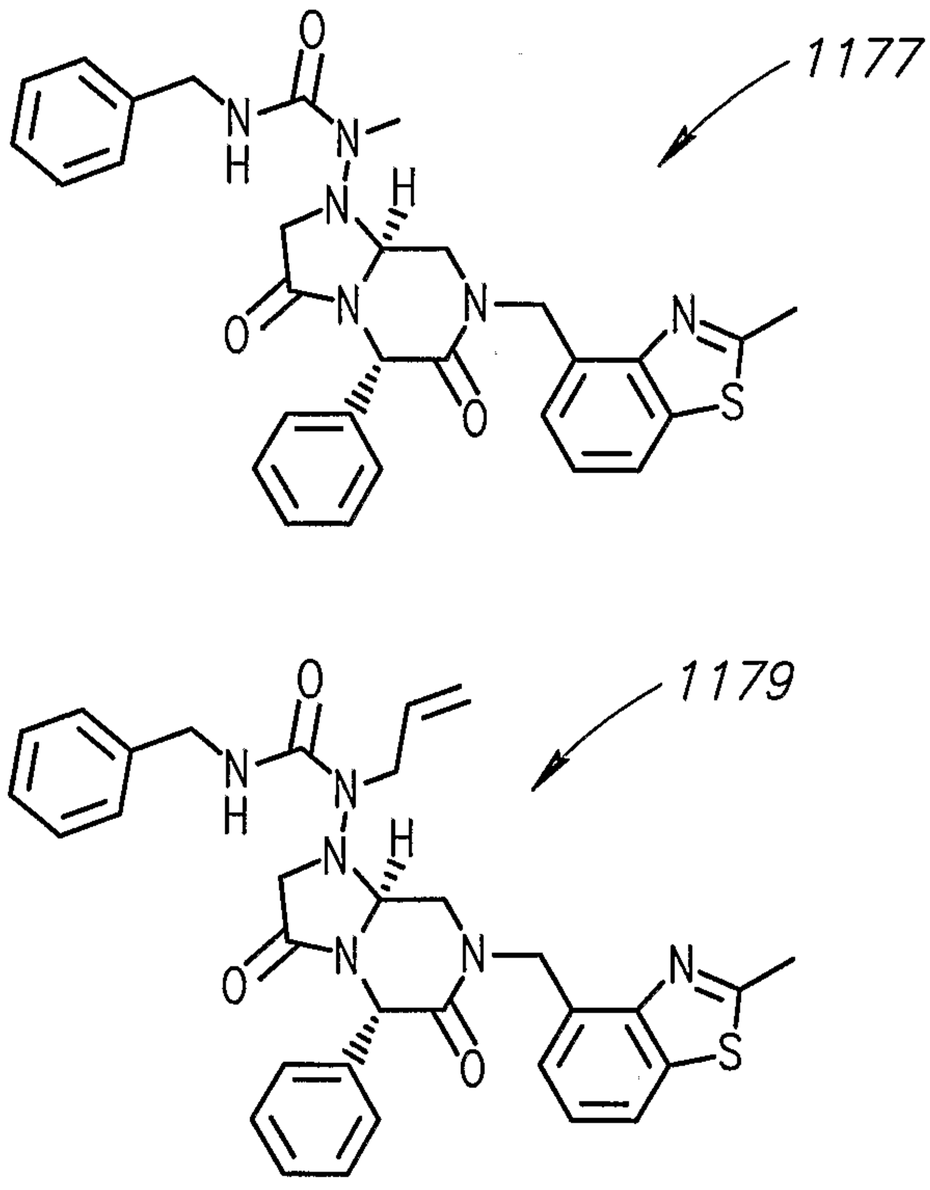
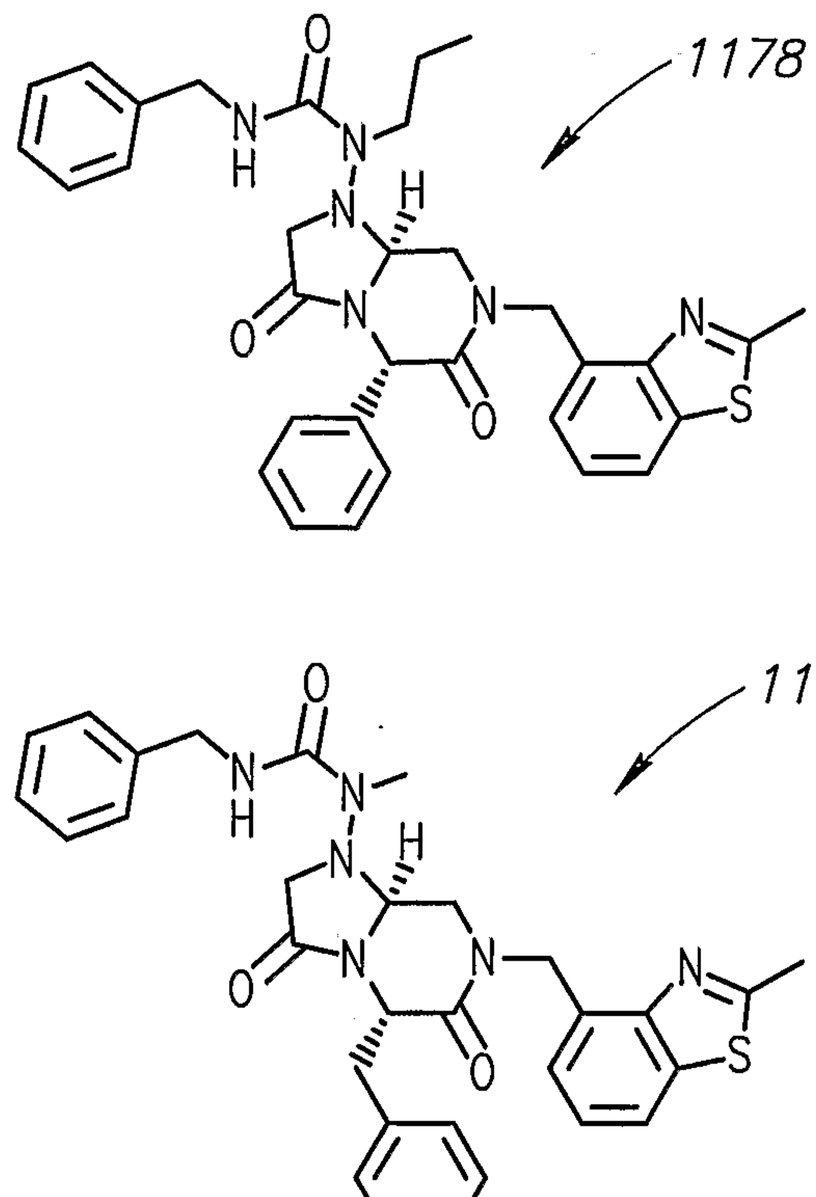
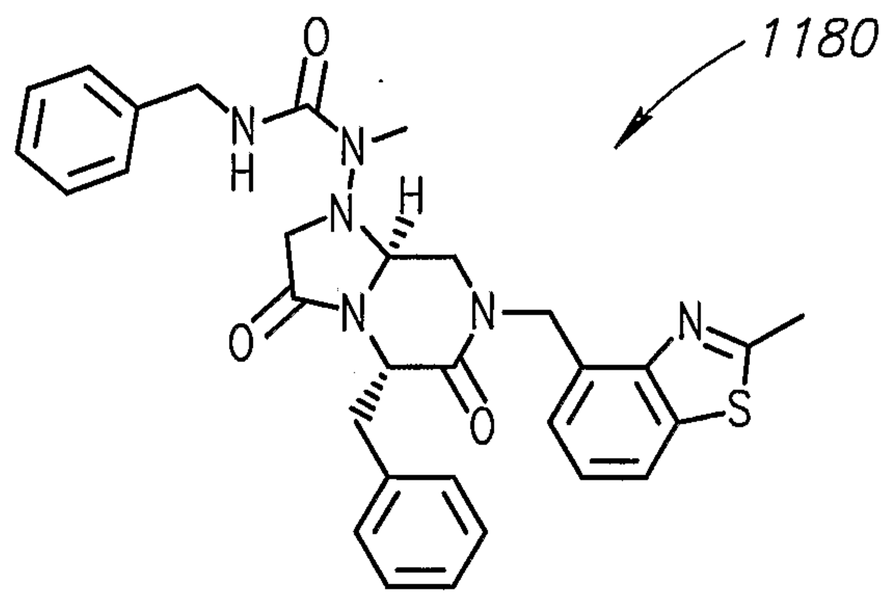
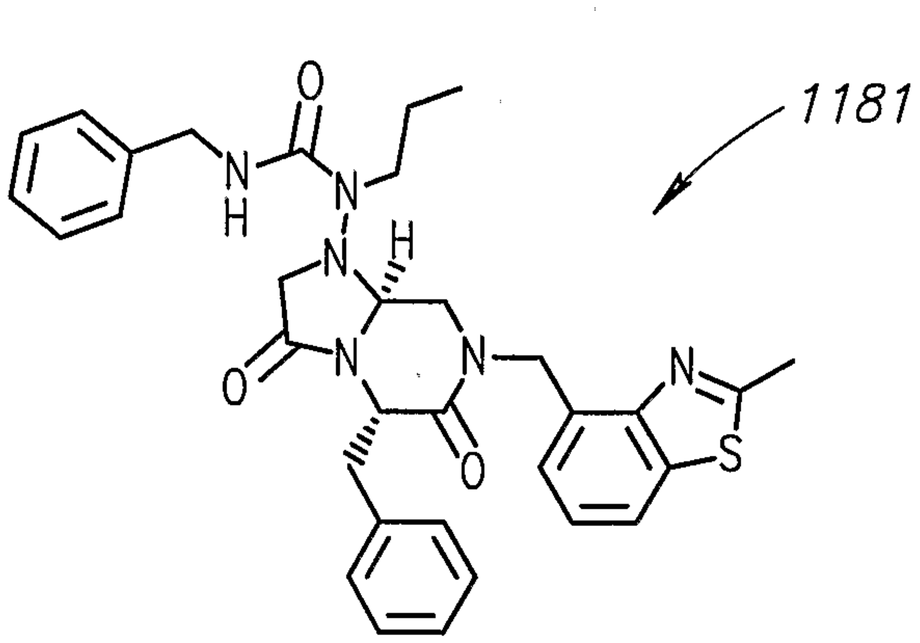


FIG.6V









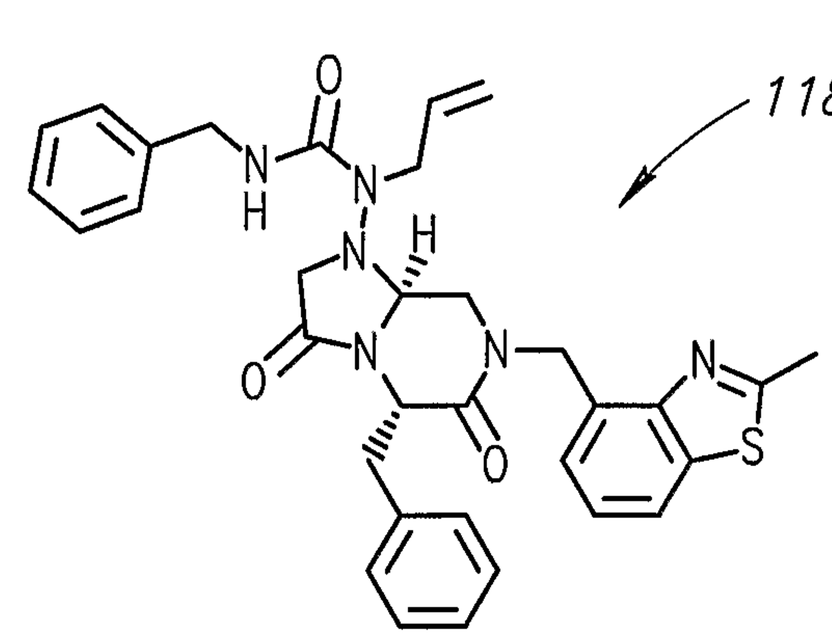


FIG.6W

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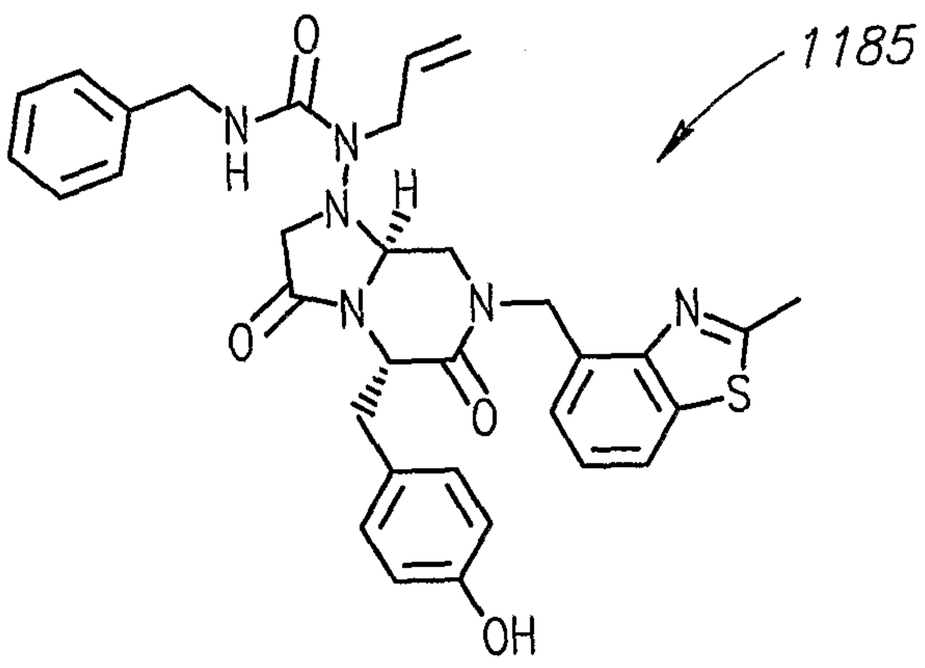

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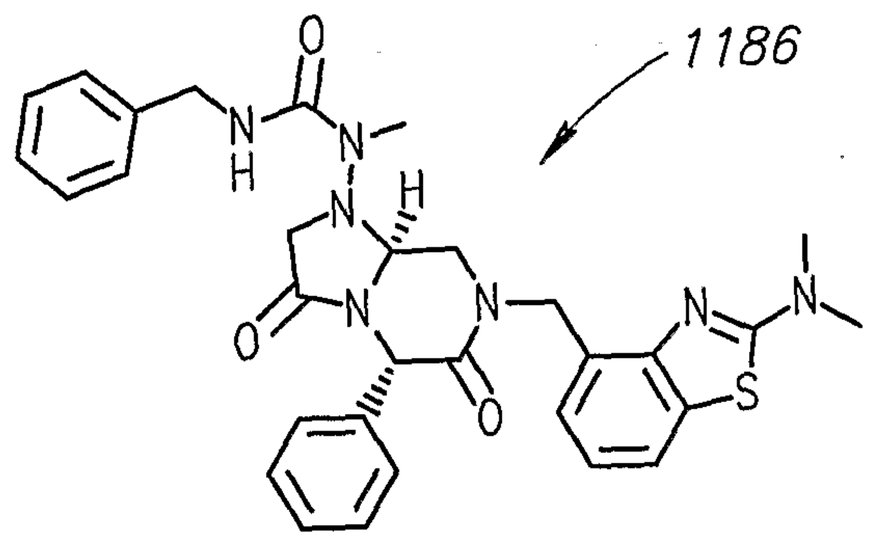

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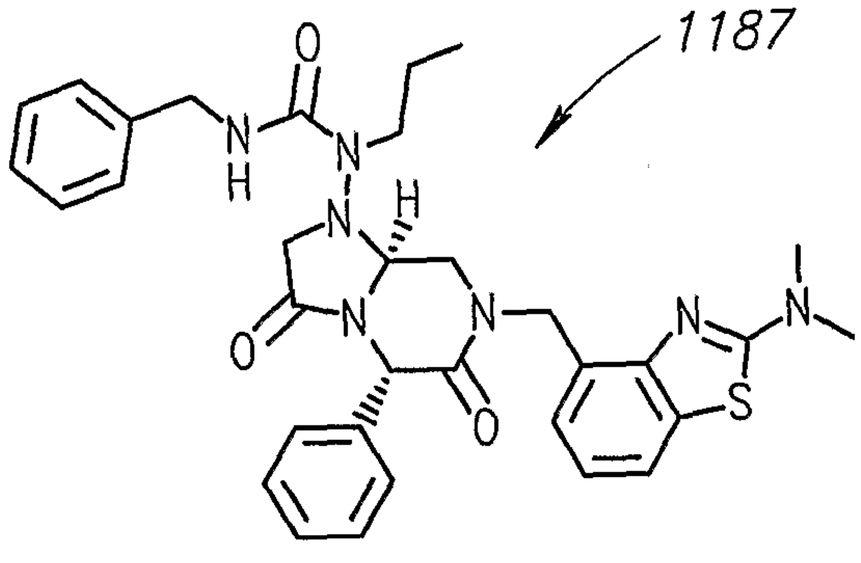

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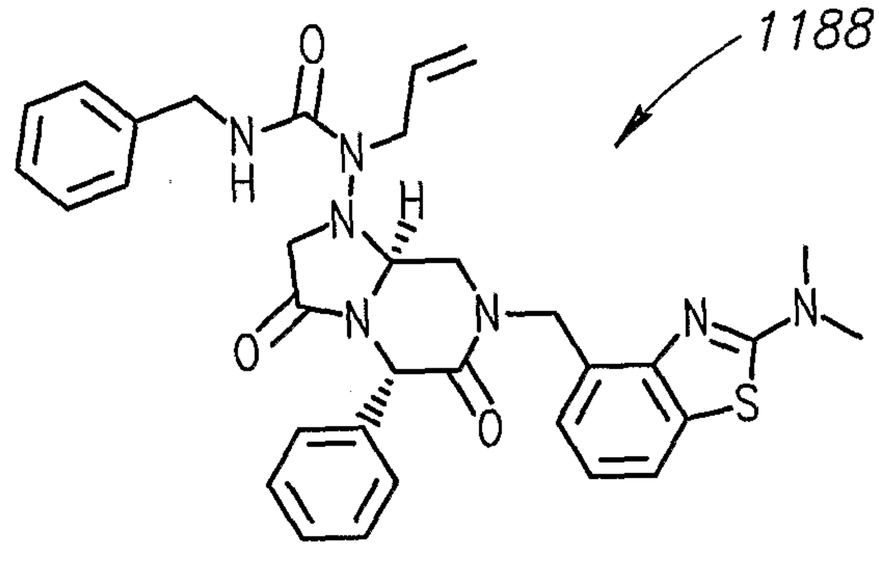

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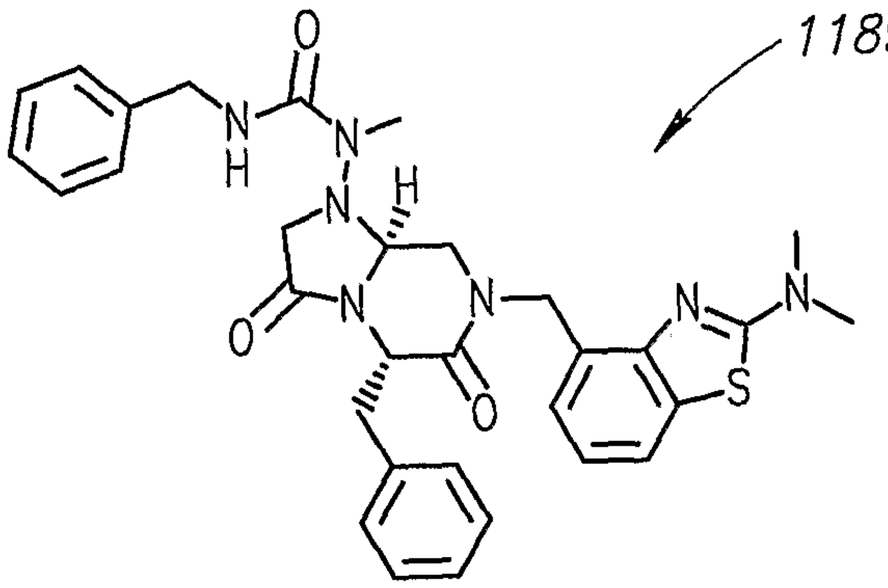

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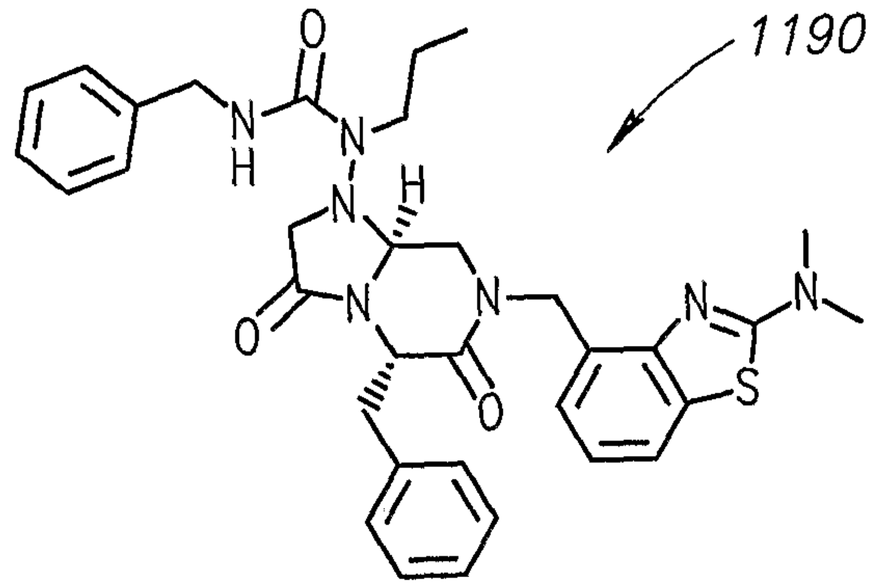

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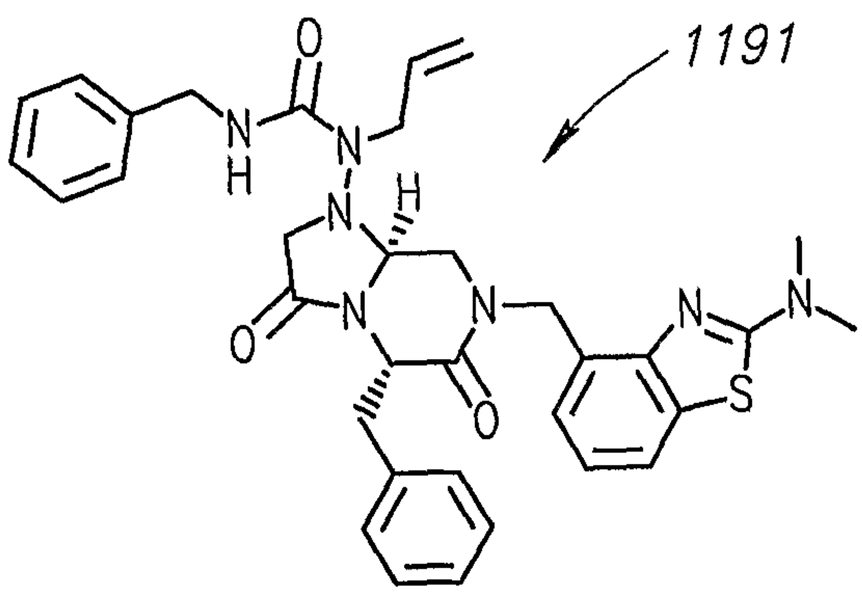

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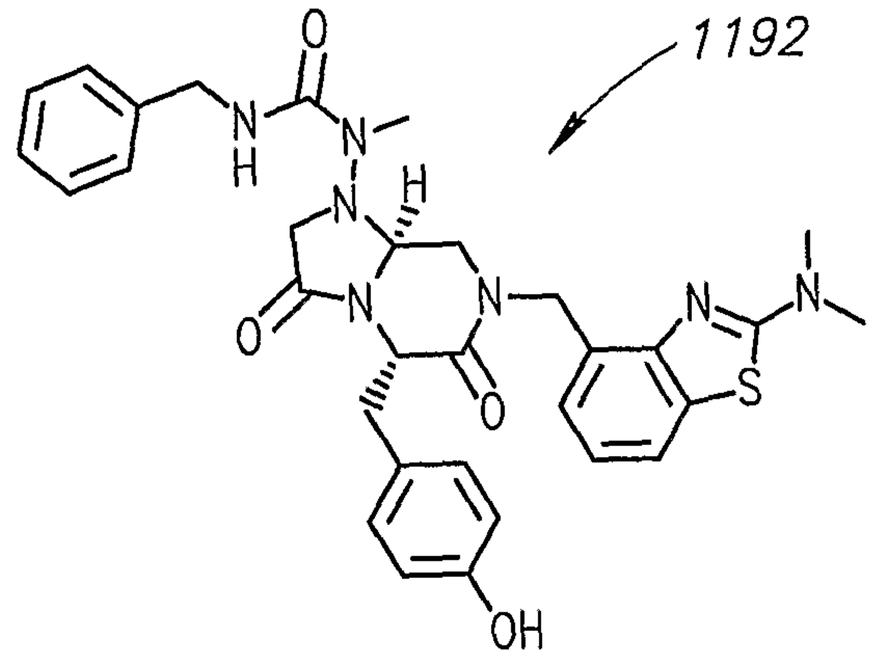
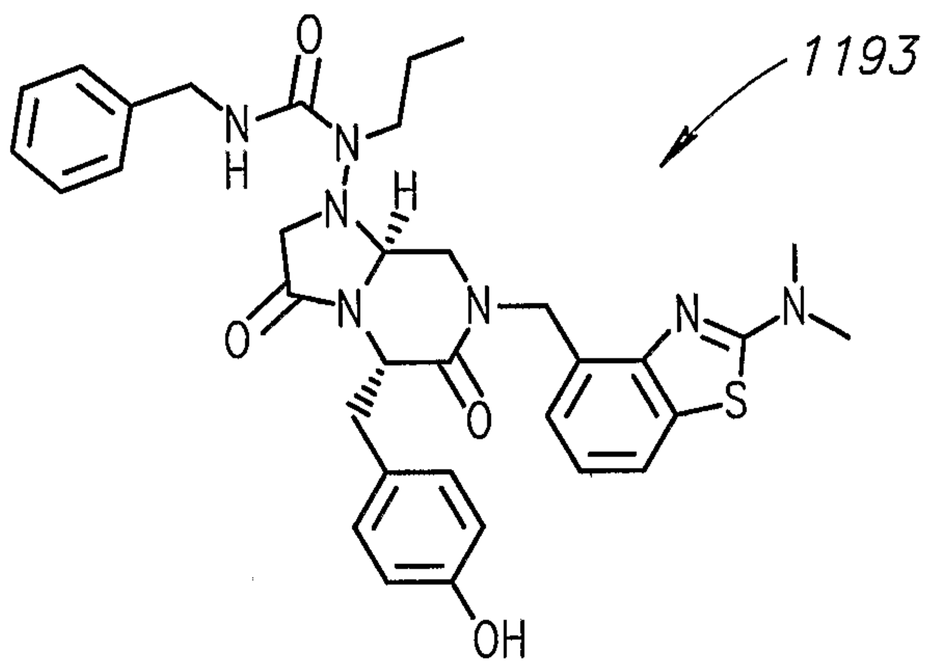
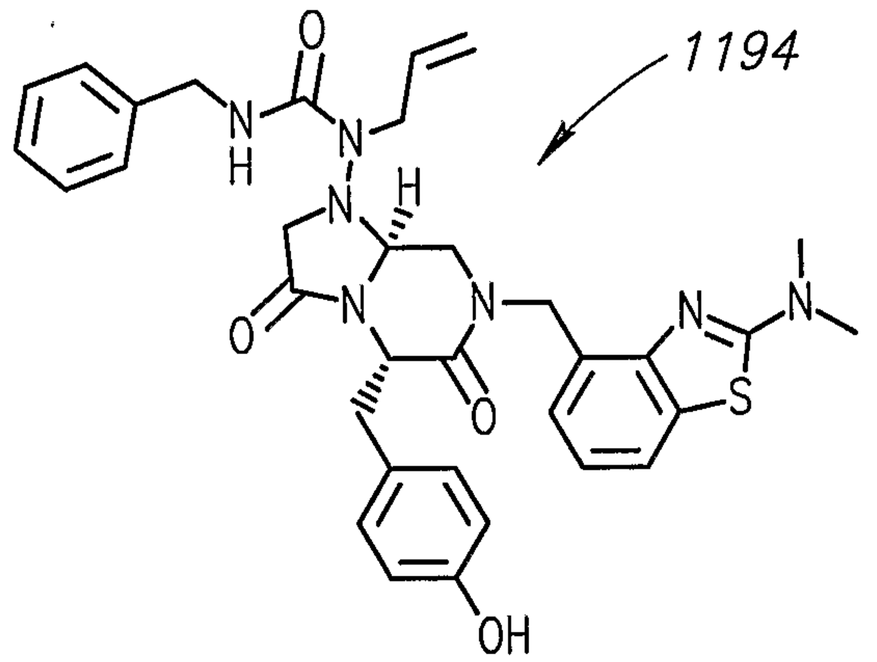
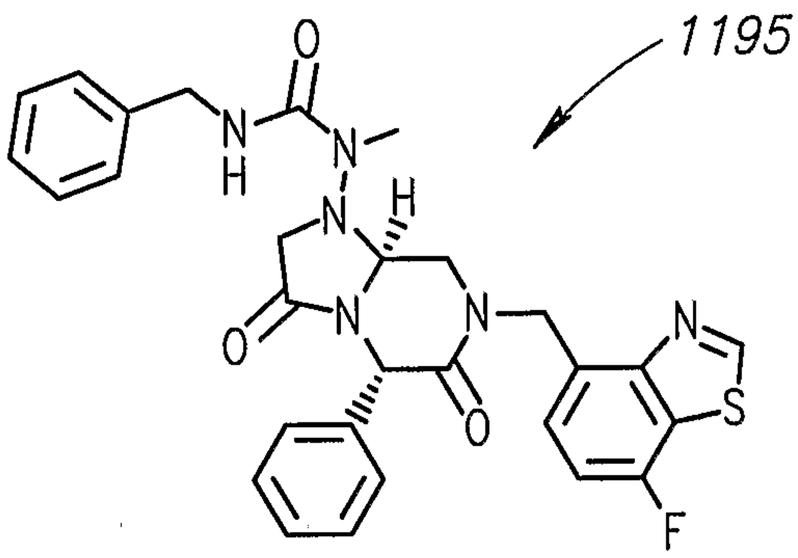
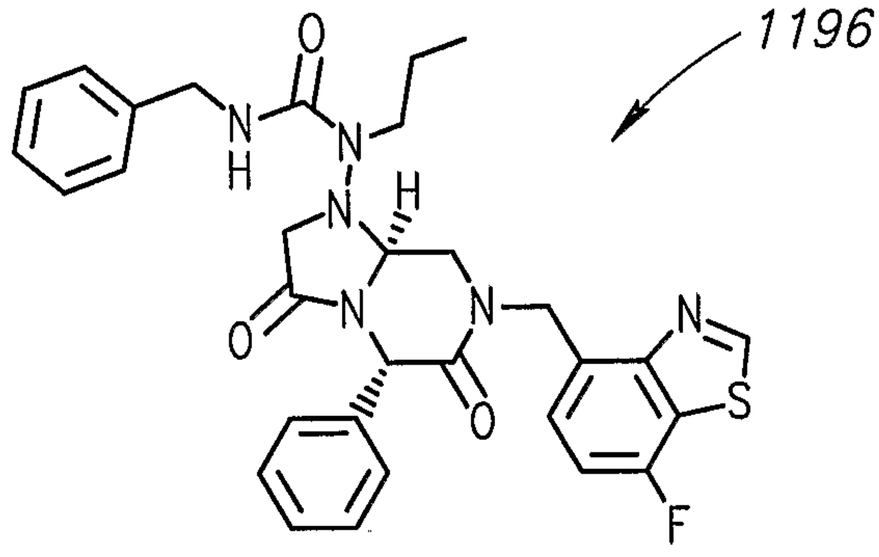


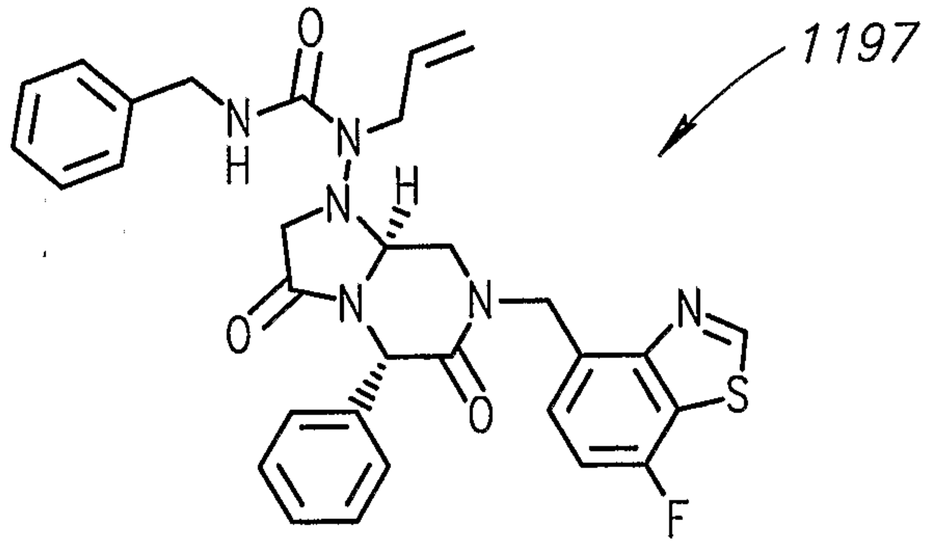
FIG.6X

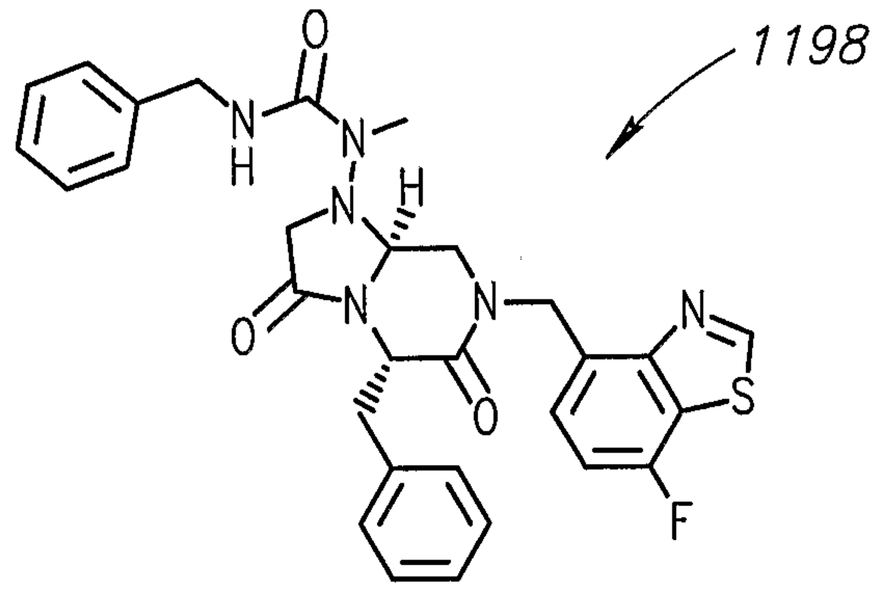


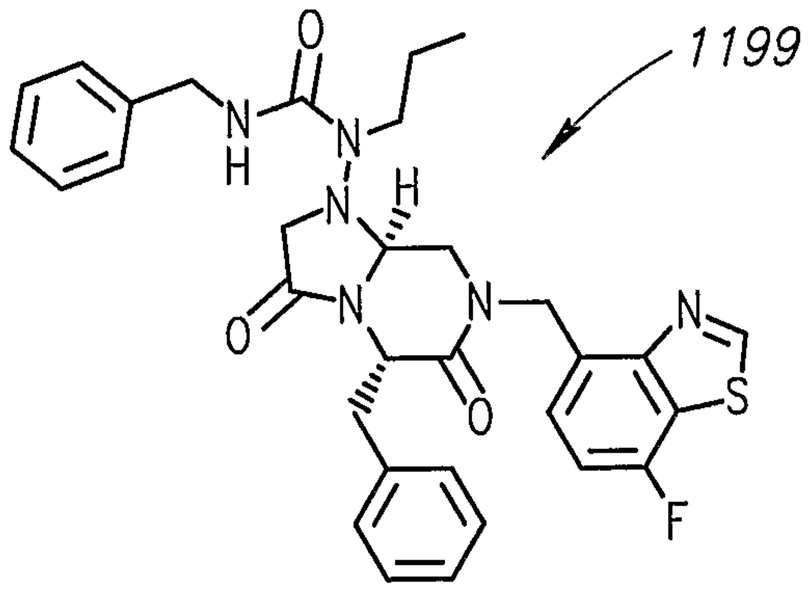












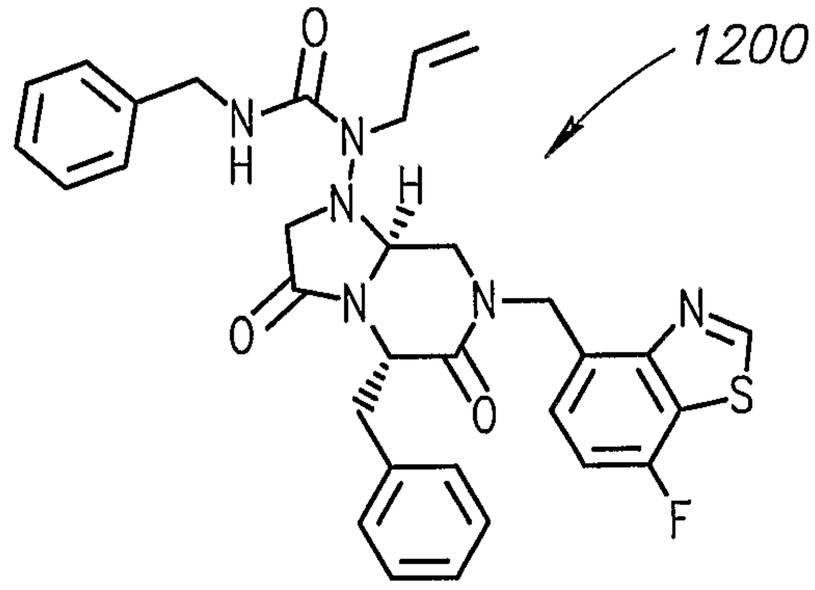


FIG.6Y

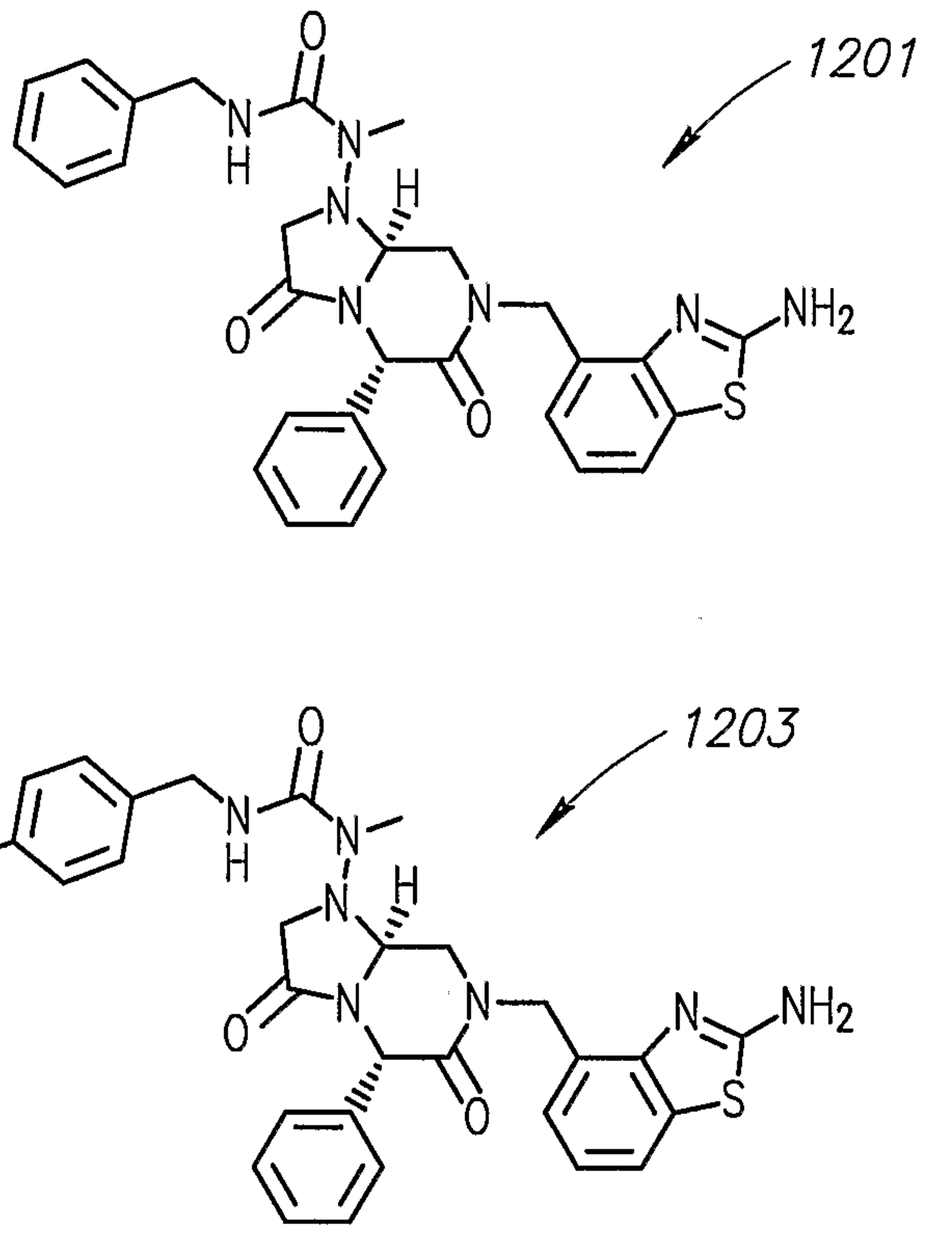
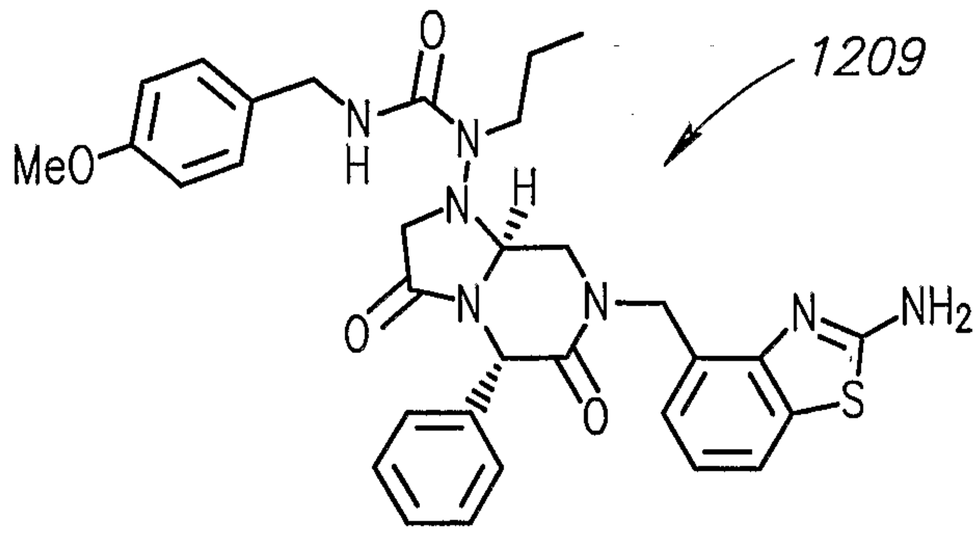


FIG.7A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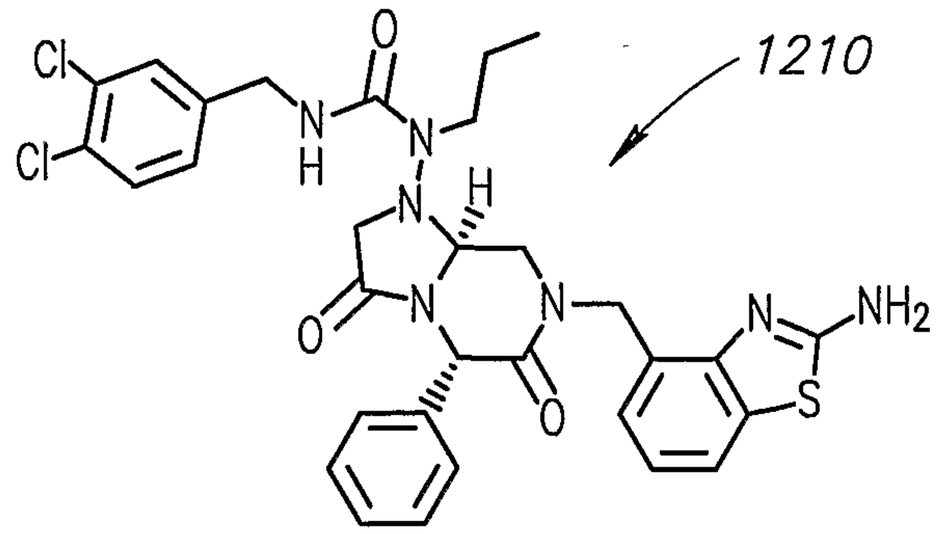
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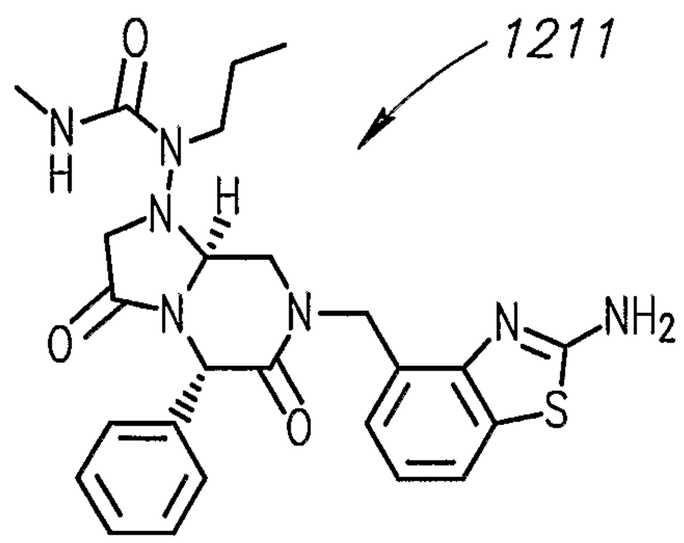
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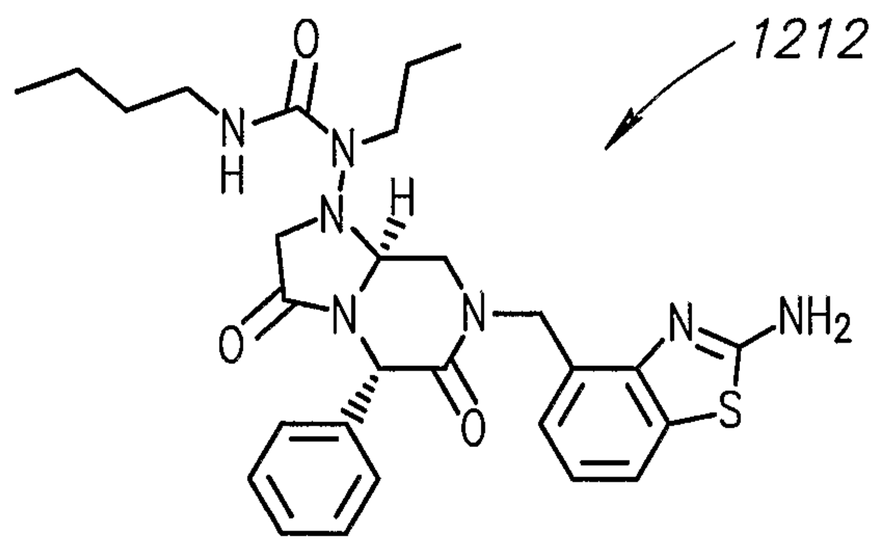
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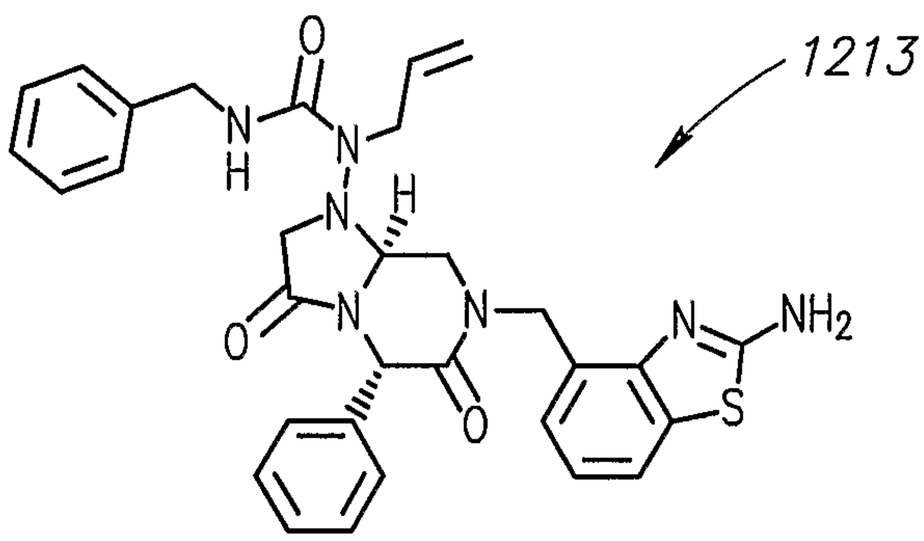
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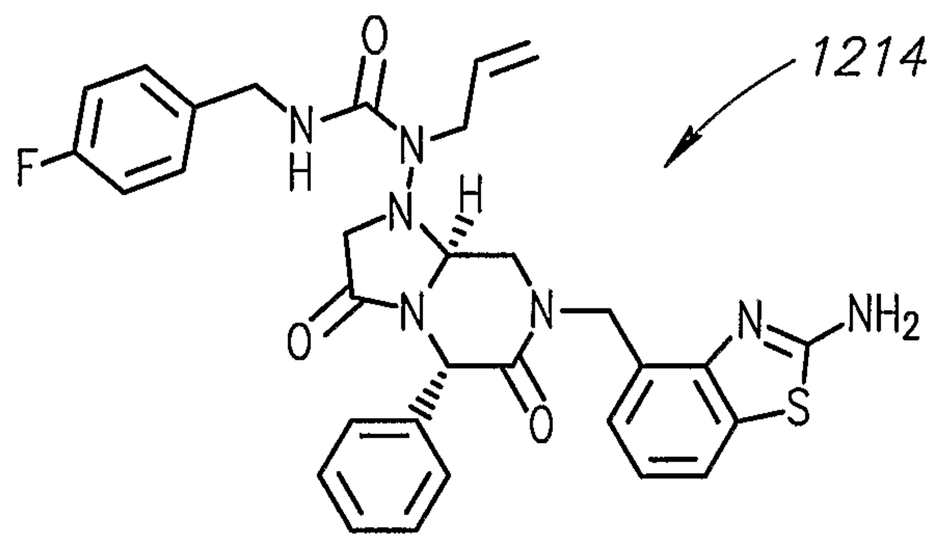
1214
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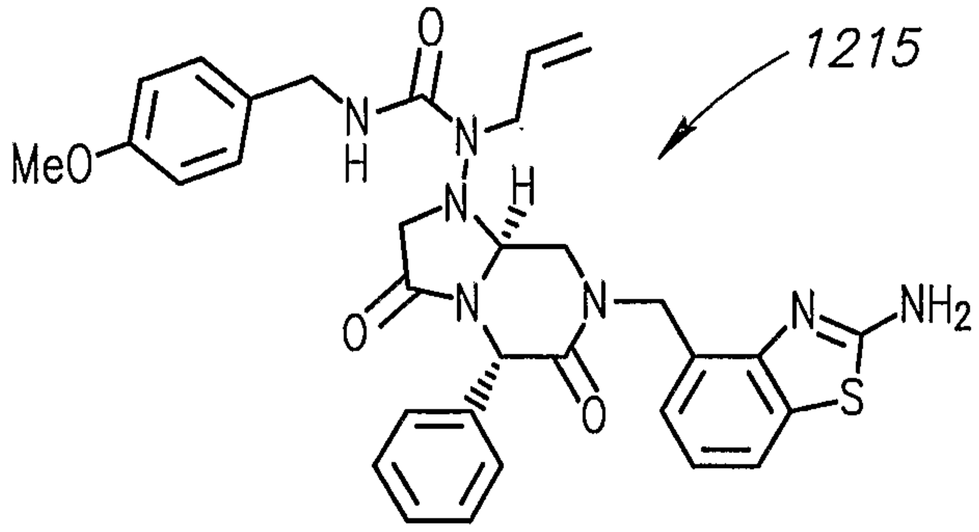
S
NH2


1215
MeO
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2

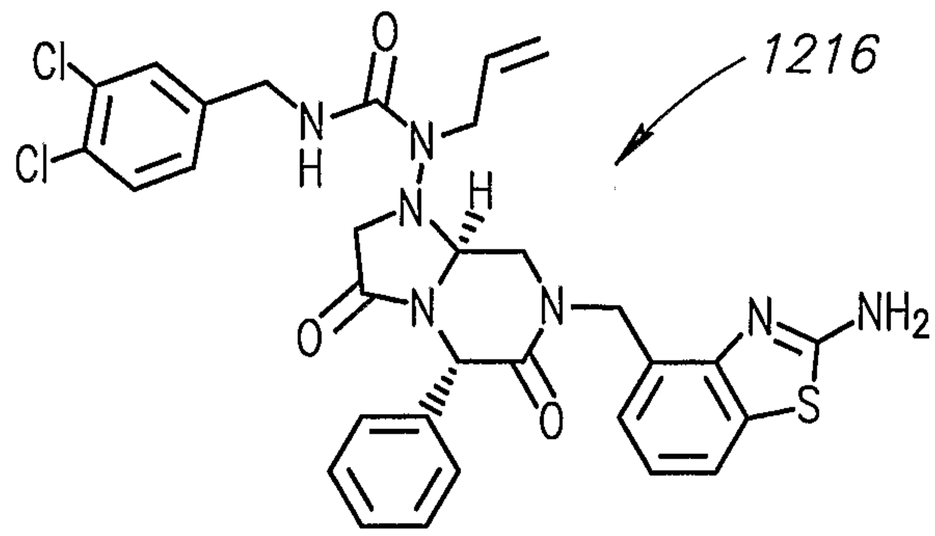
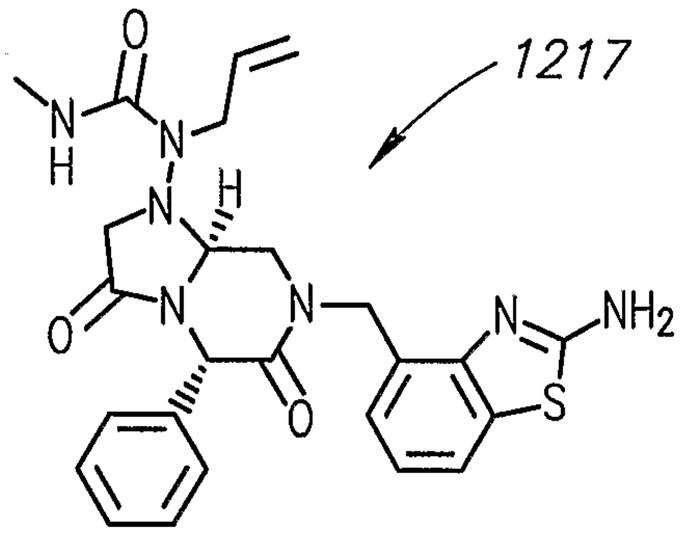
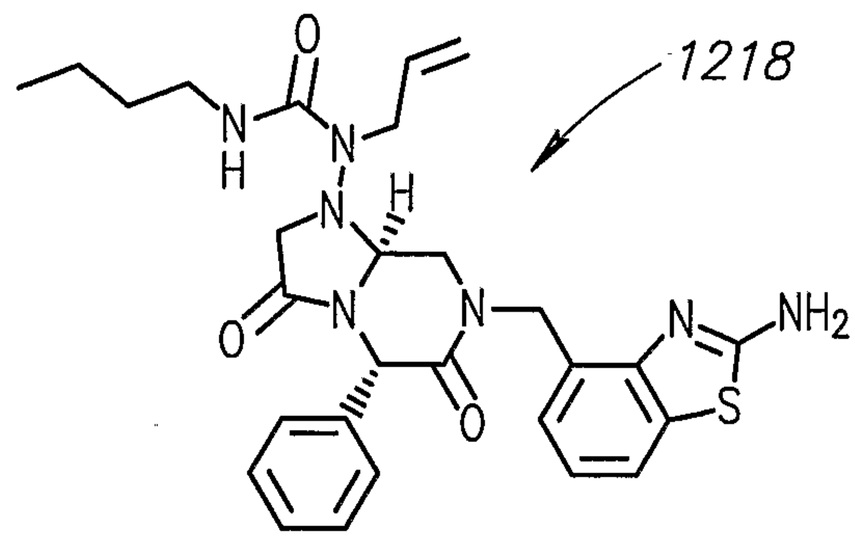
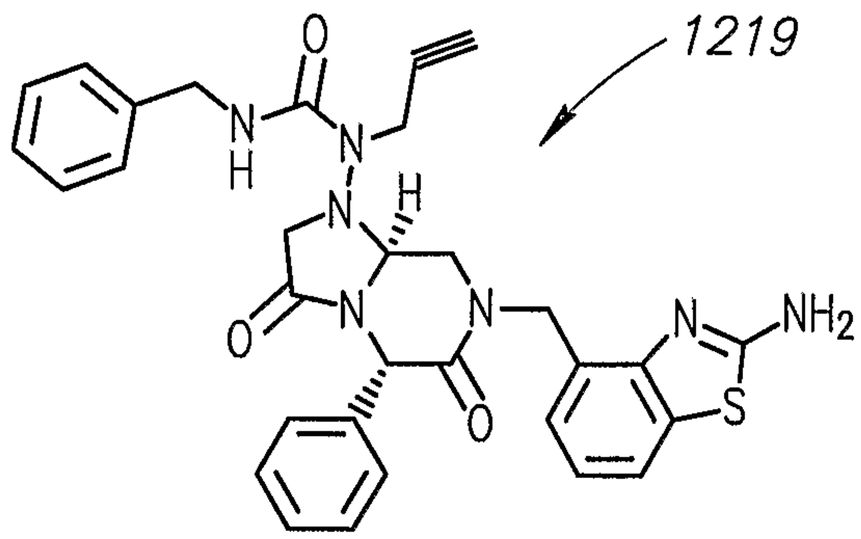
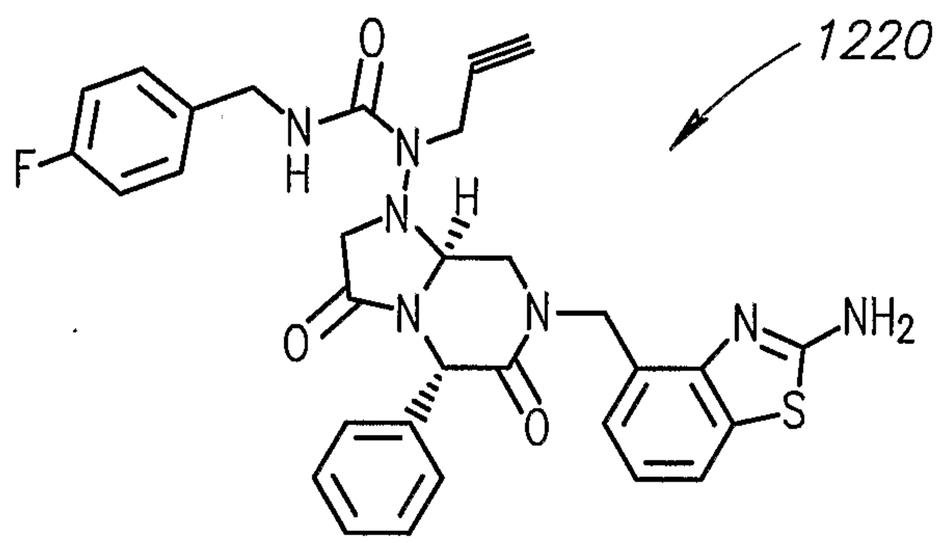

1216
Cl
Cl
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2

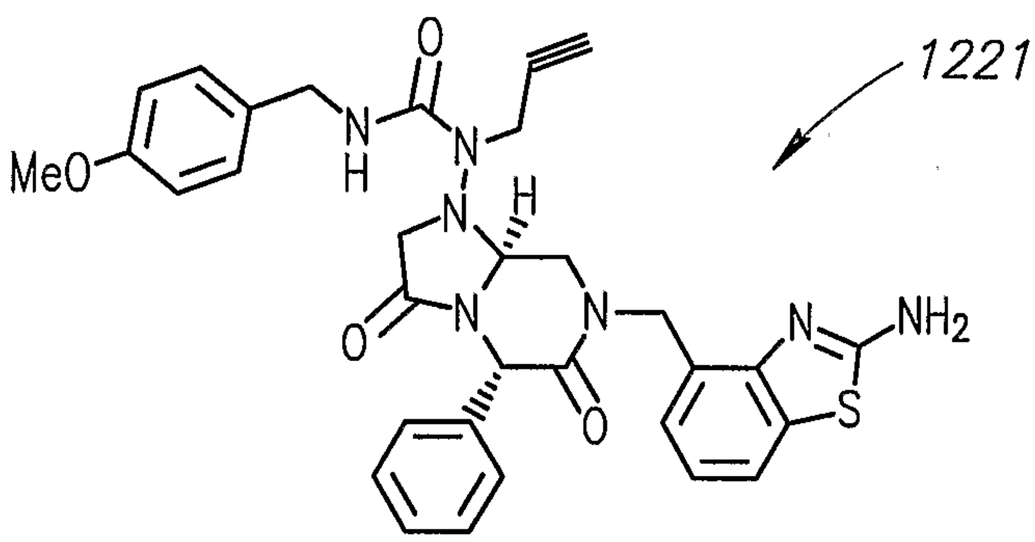
FIG.7B

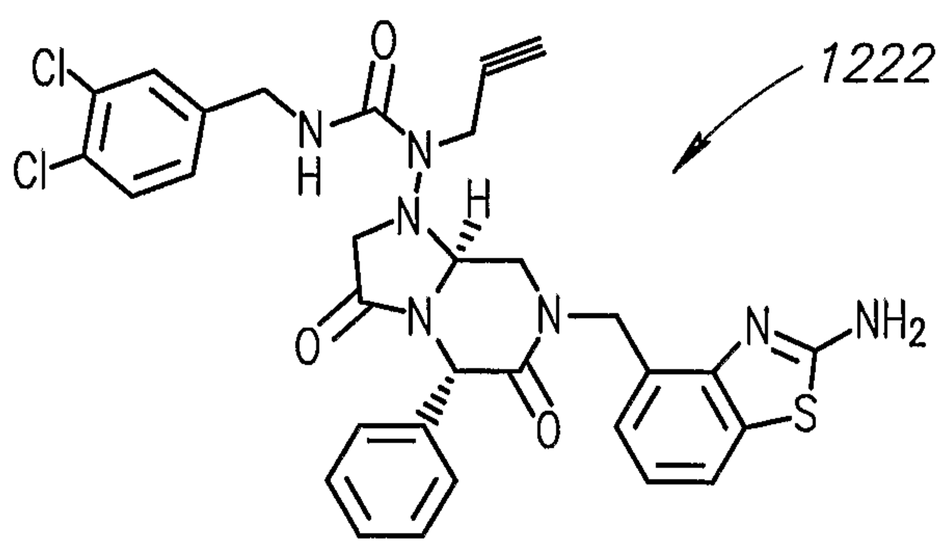


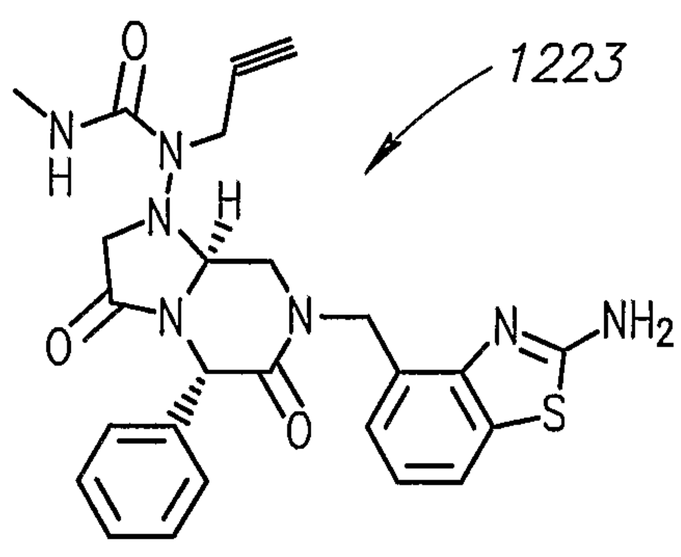












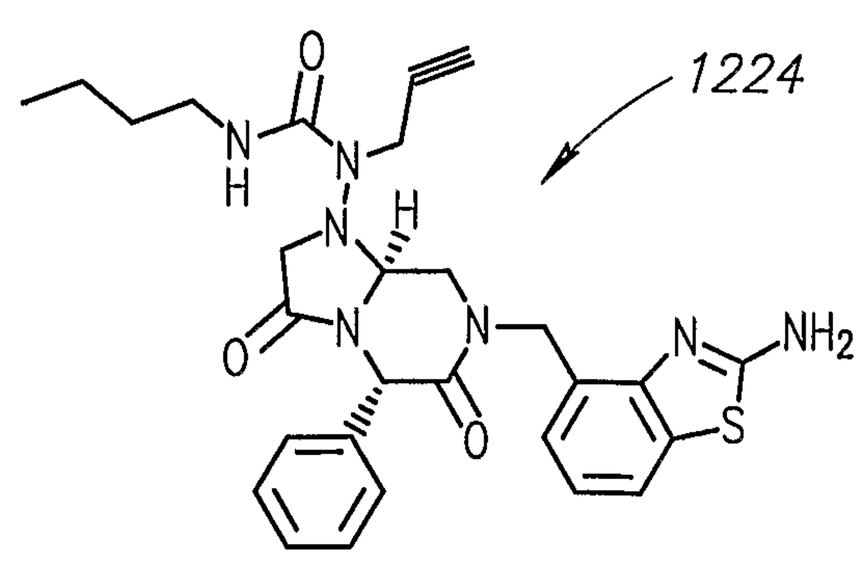
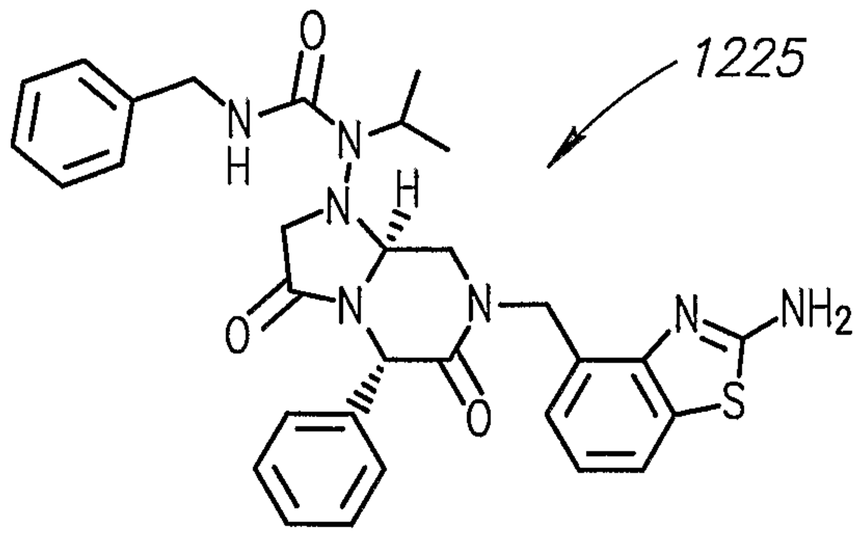
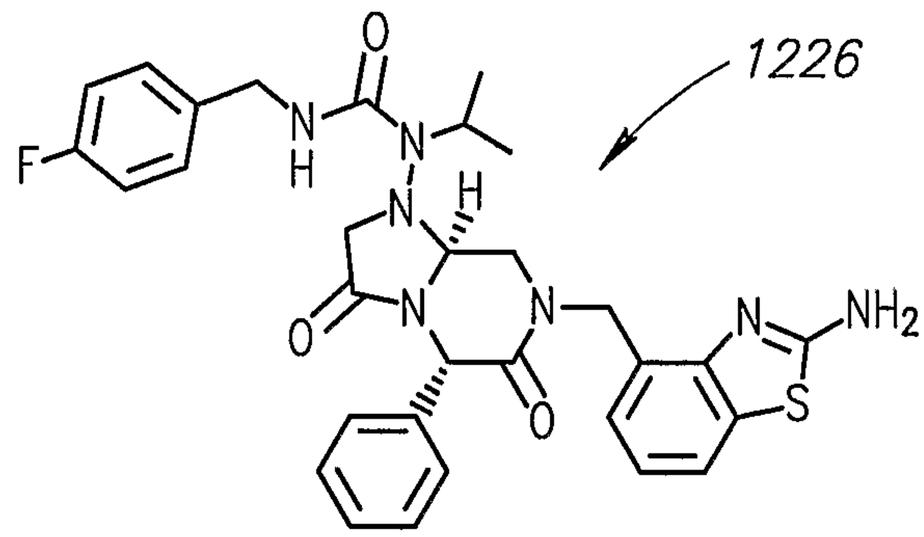
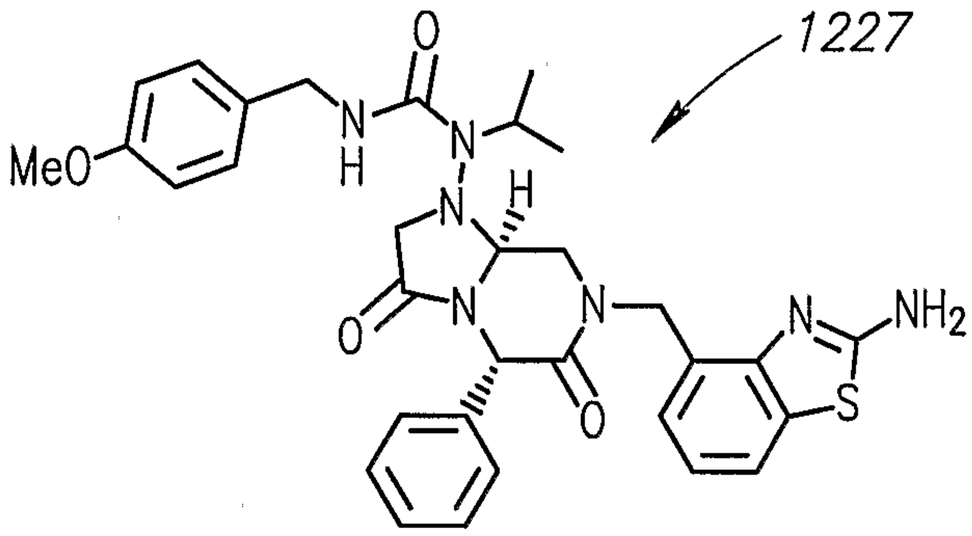
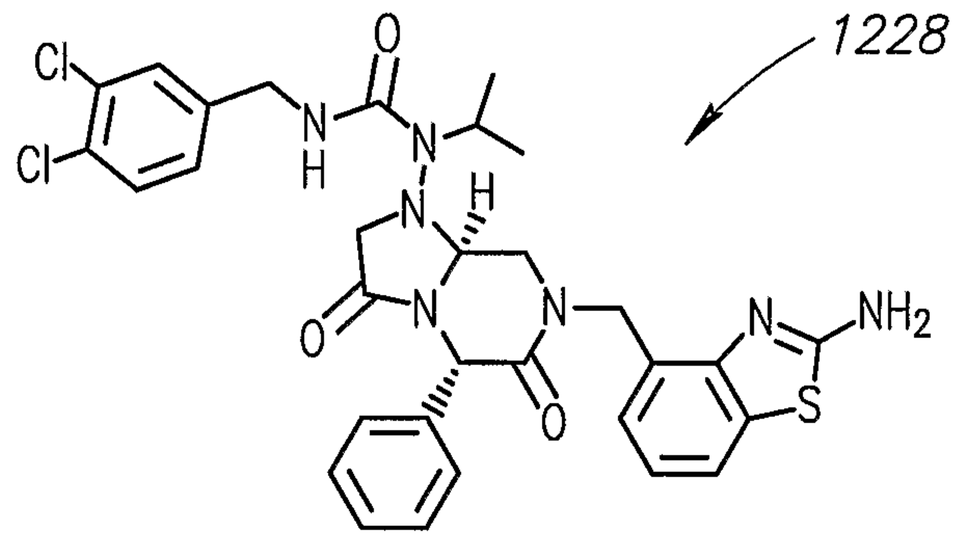


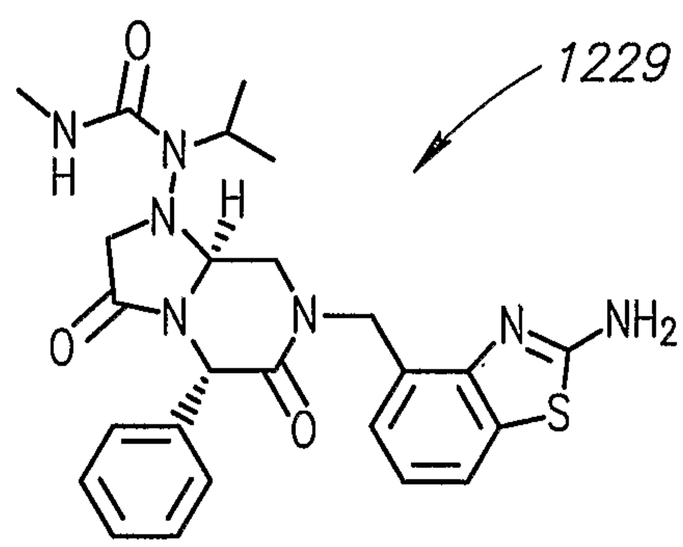
FIG.7C

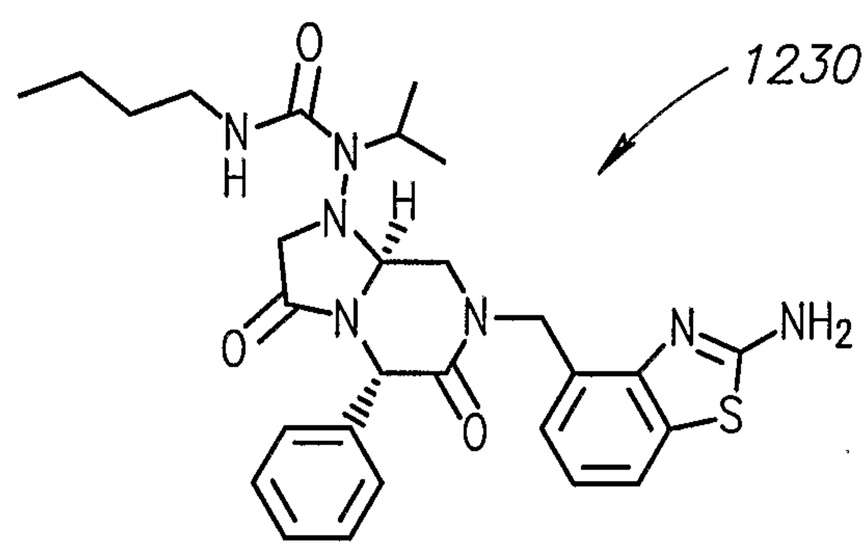


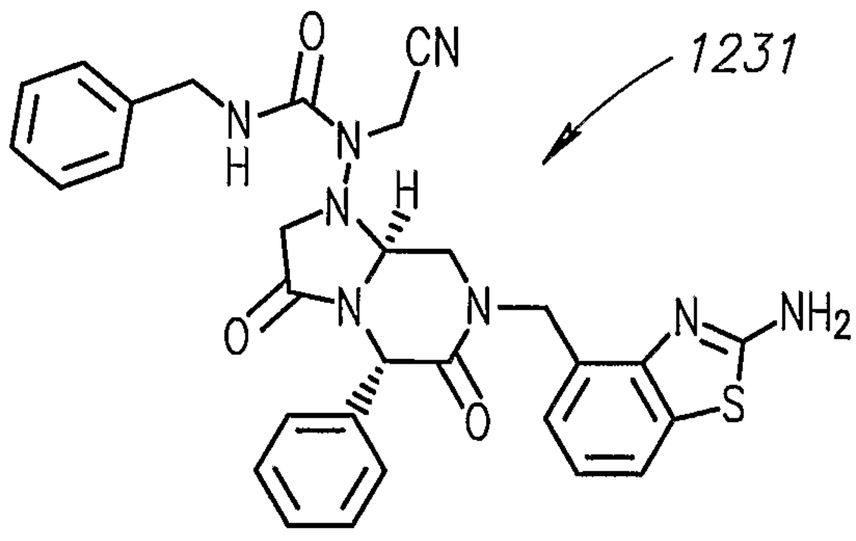












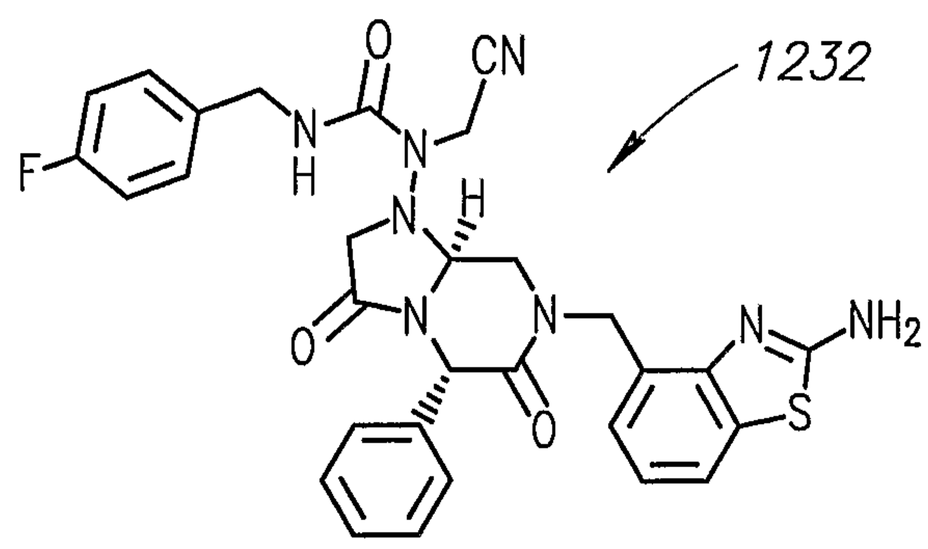
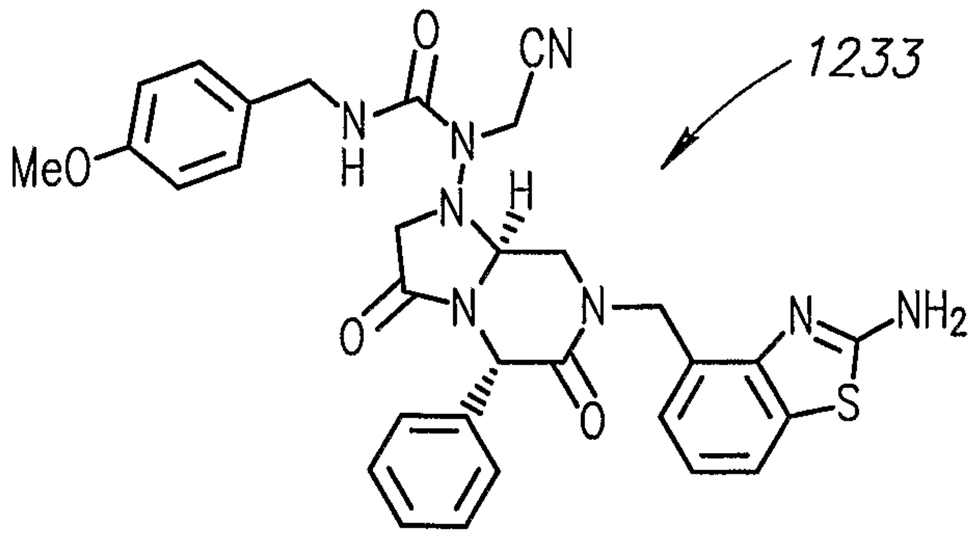


FIG.7D


1233
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CN
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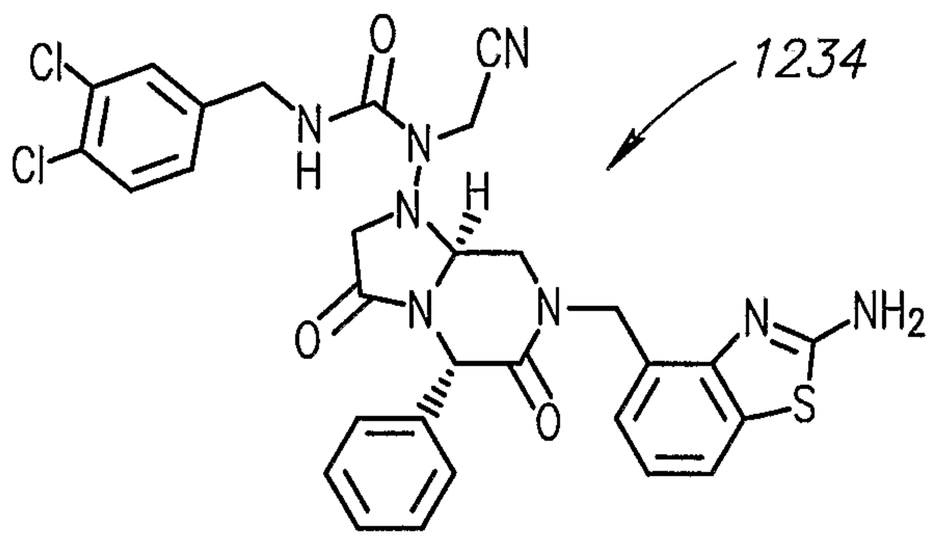
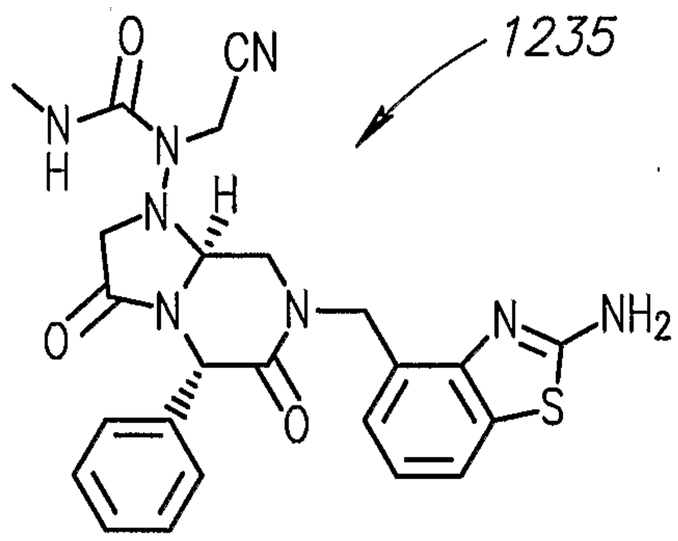
N
H
NH2
S


1234
Cl
Cl
CN
O
N
H
NH2
S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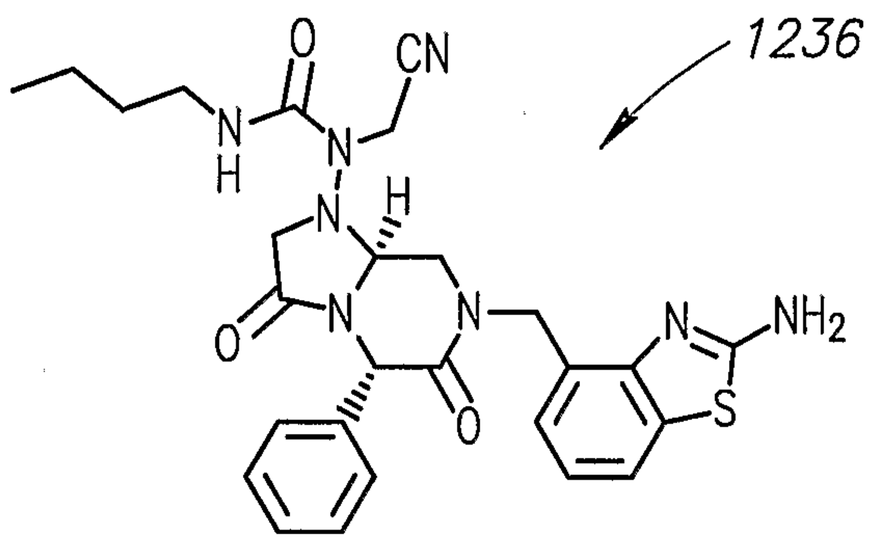
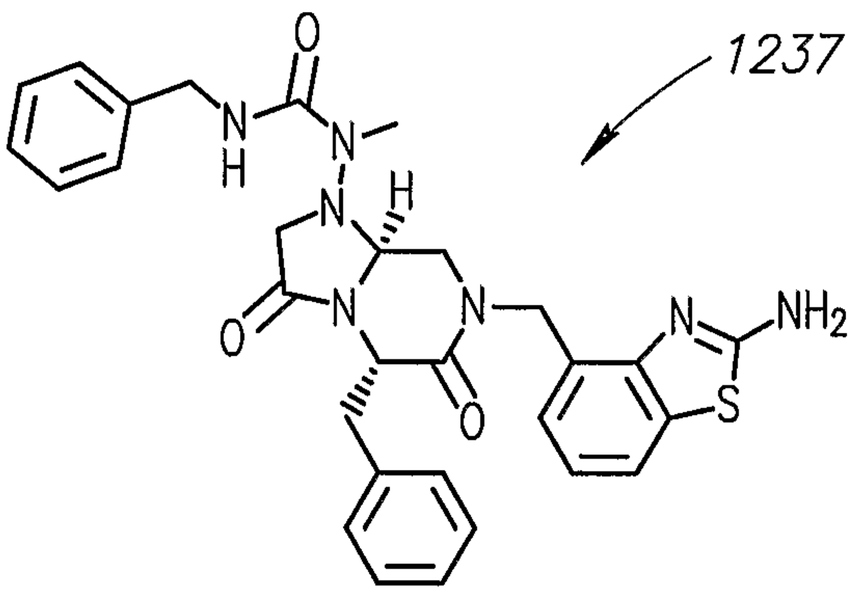
H
NH2
S


1236
CN
O
N
H
NH2
S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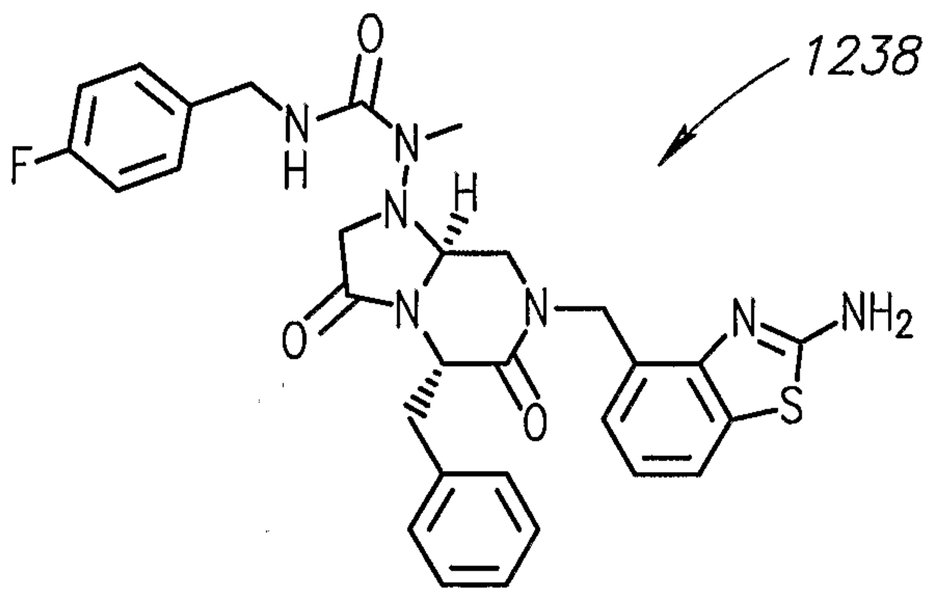
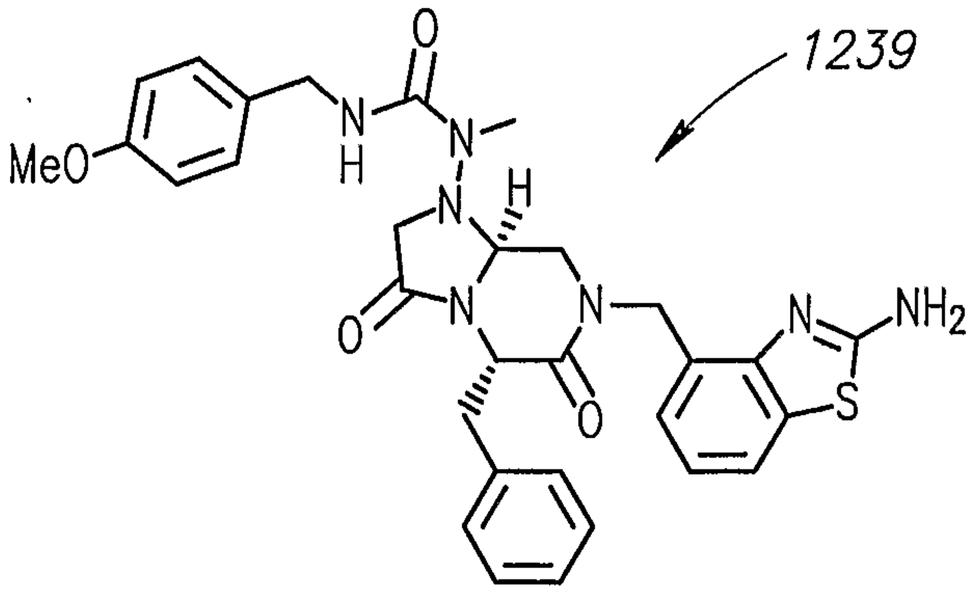
O
N
H
NH2
S


1238
F
O
N
H
NH2
S


1239
MeO
O
N
H
NH2
S

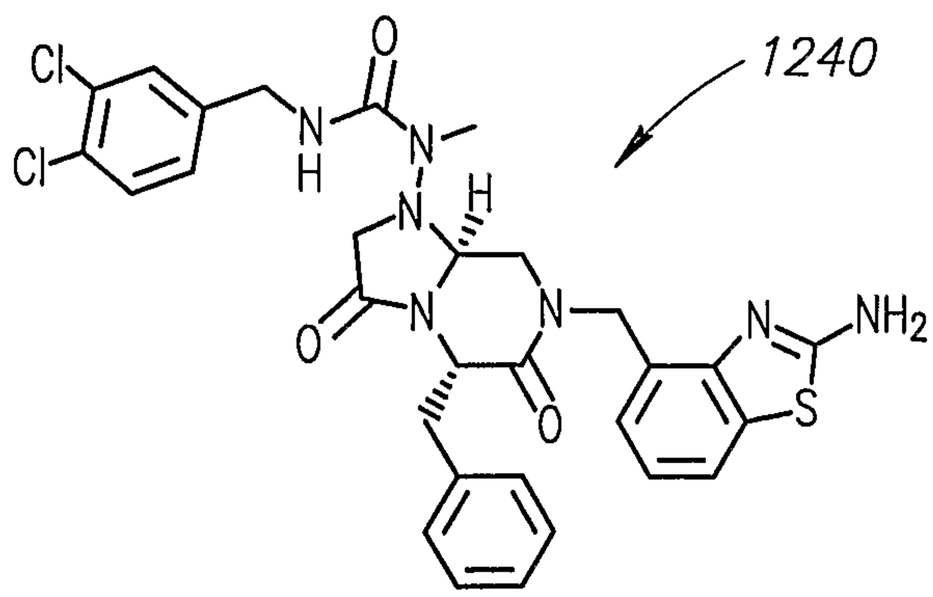
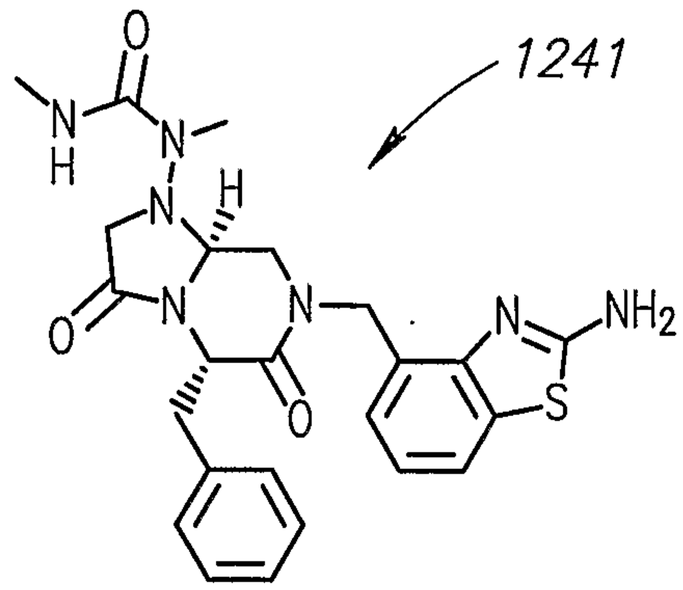
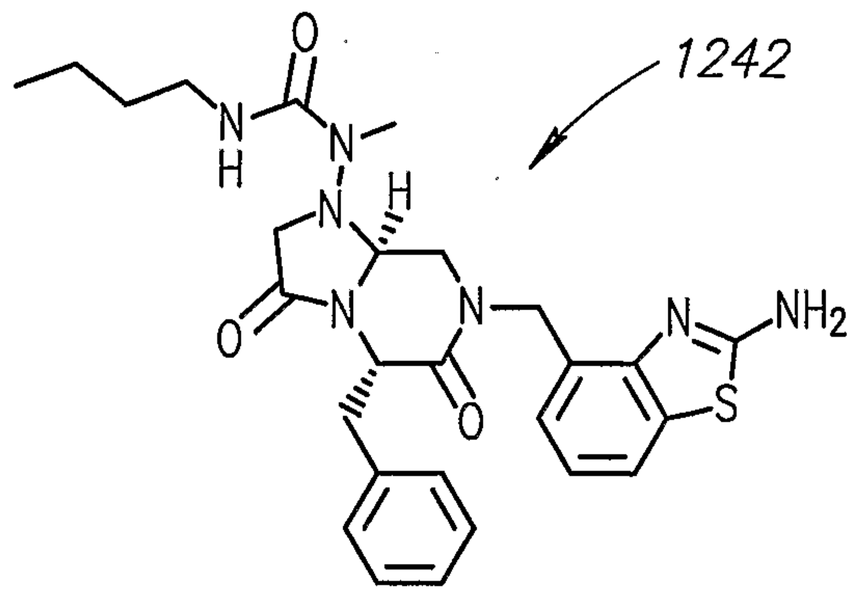
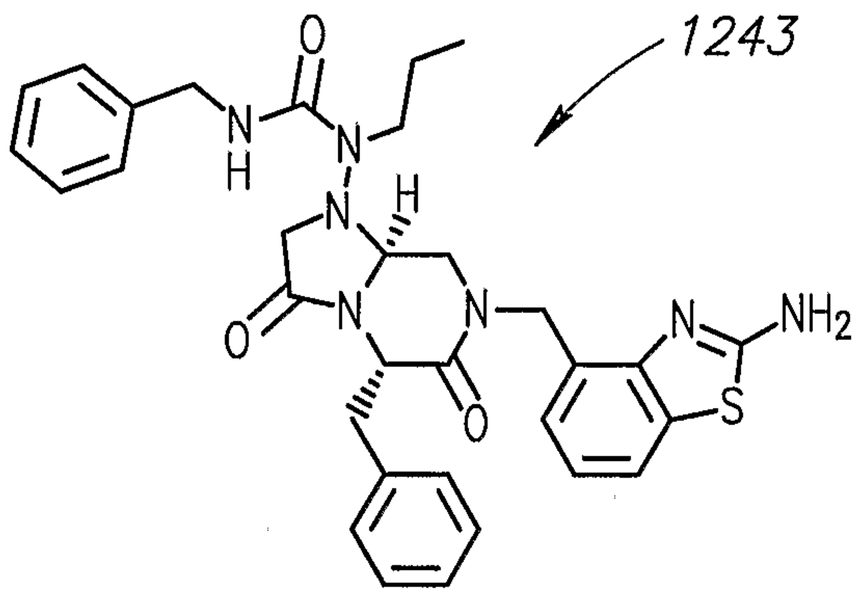
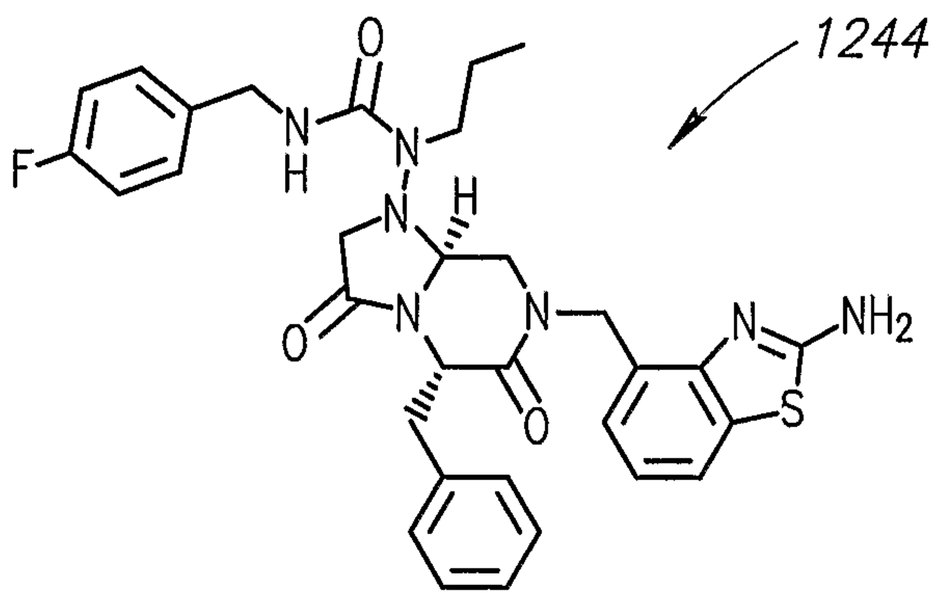

1240
Cl
Cl
O
N
H
NH2
S

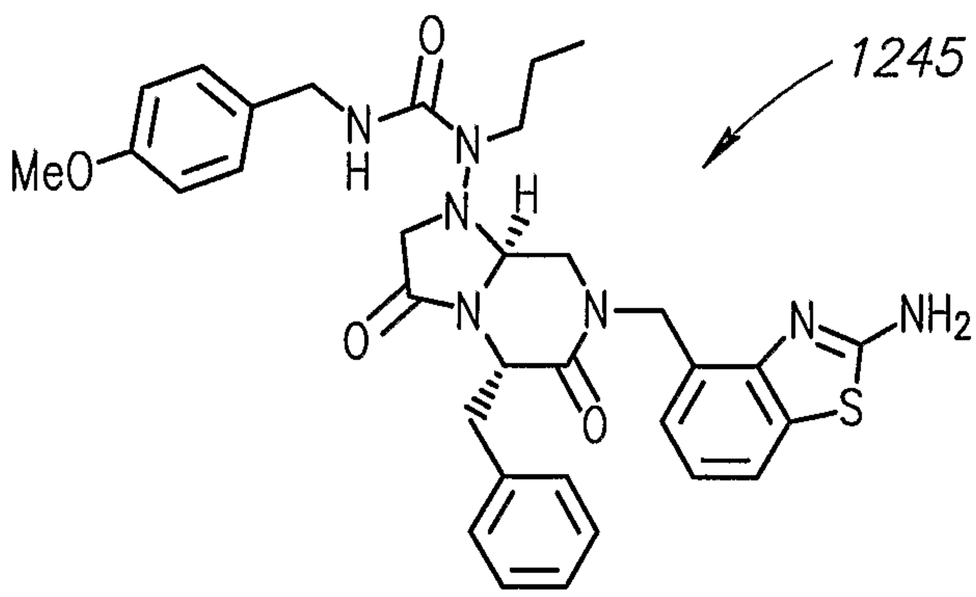
FIG.7E

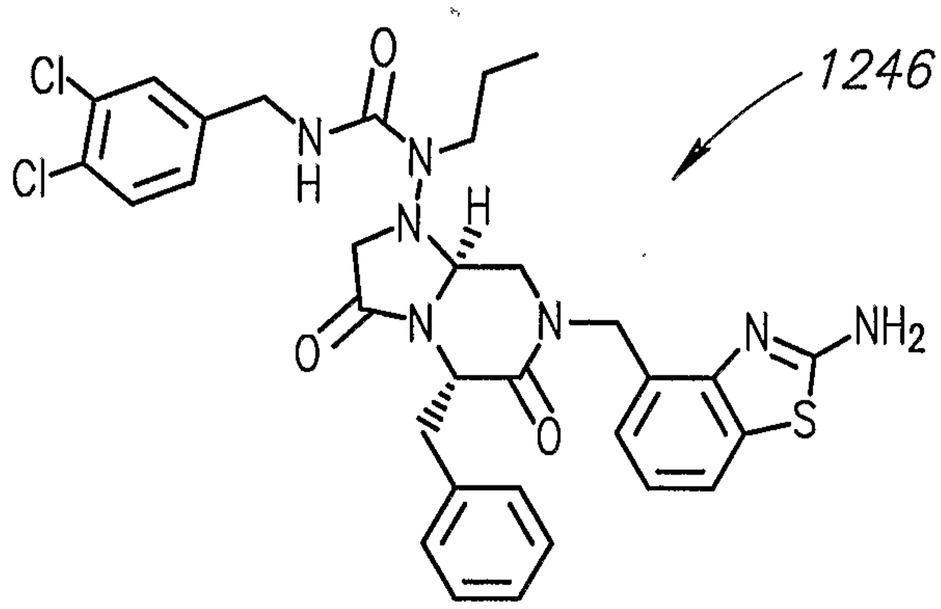


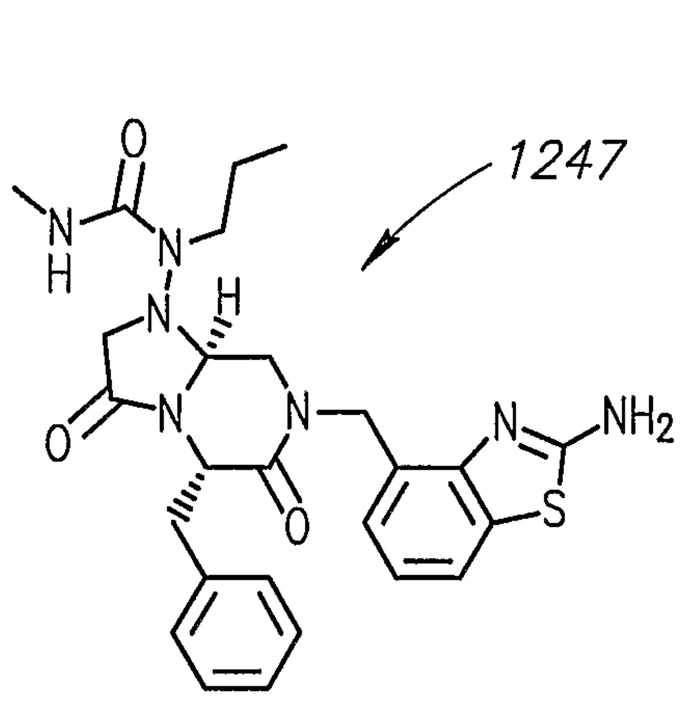












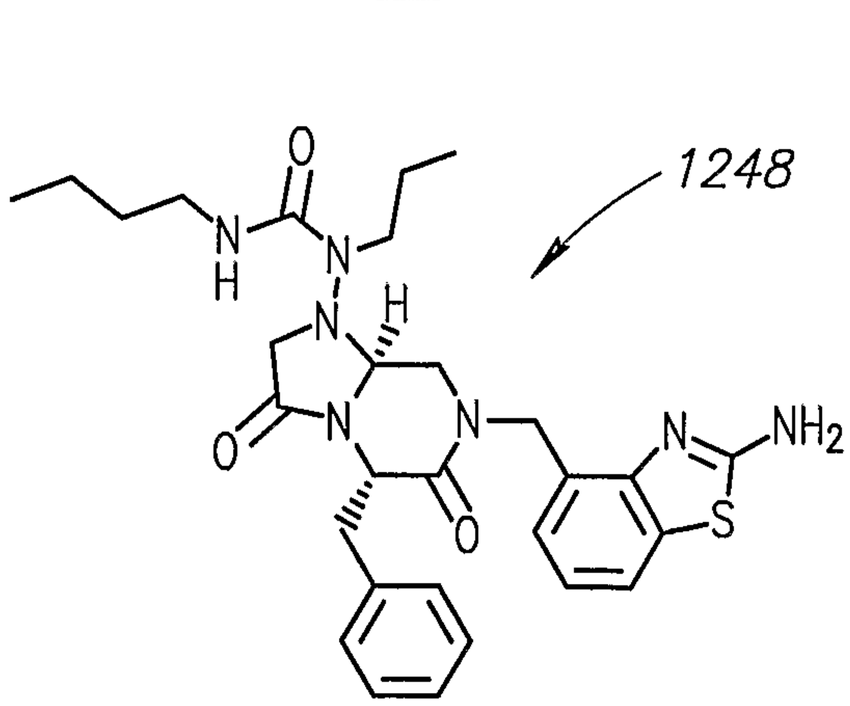
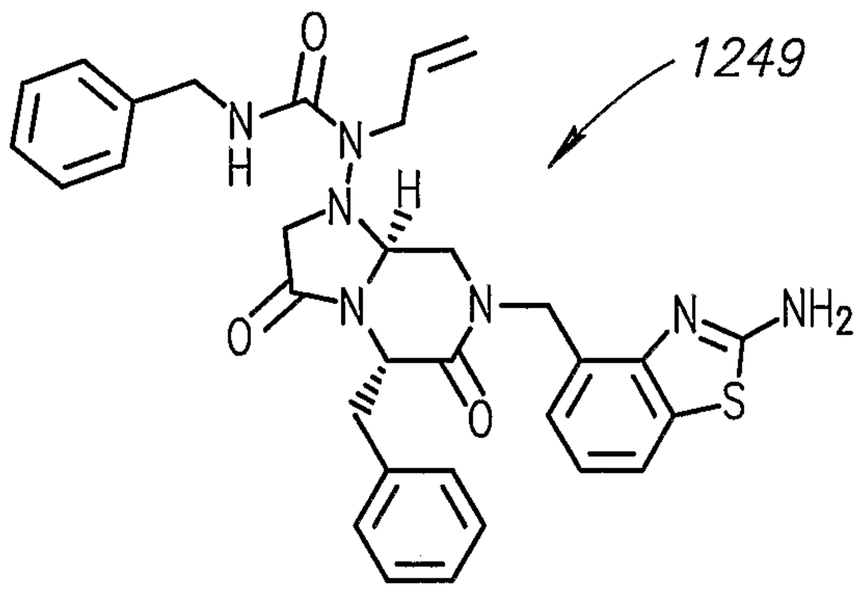
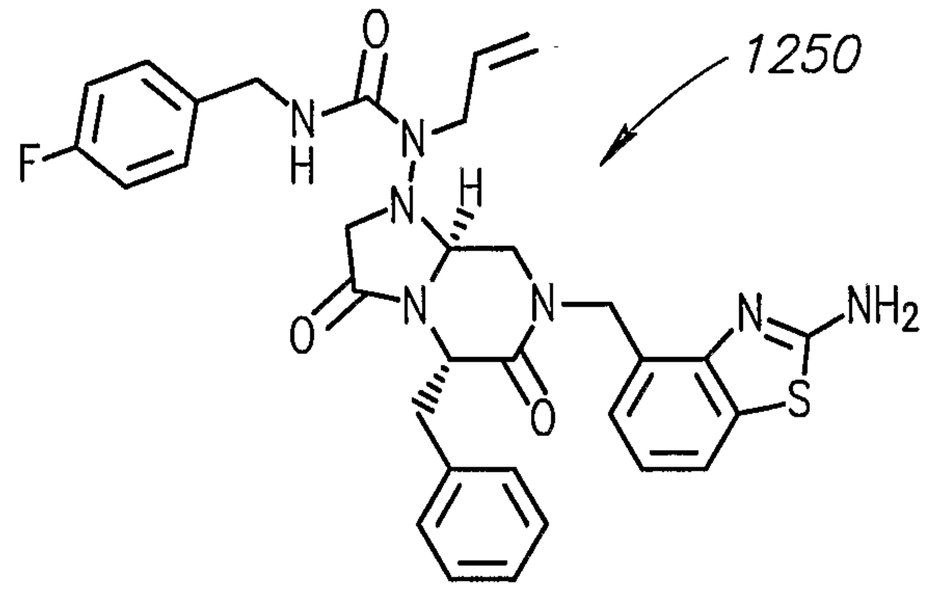
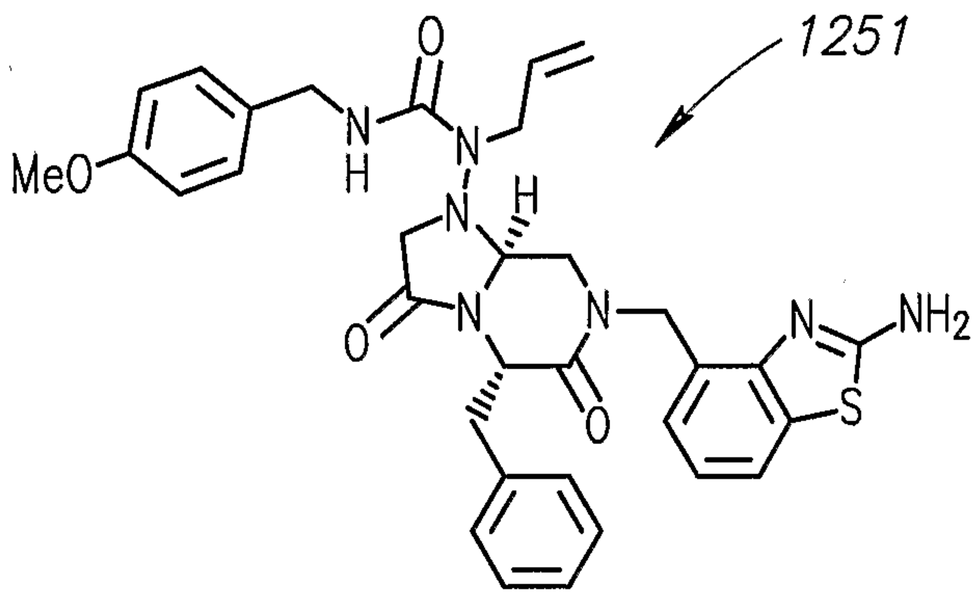
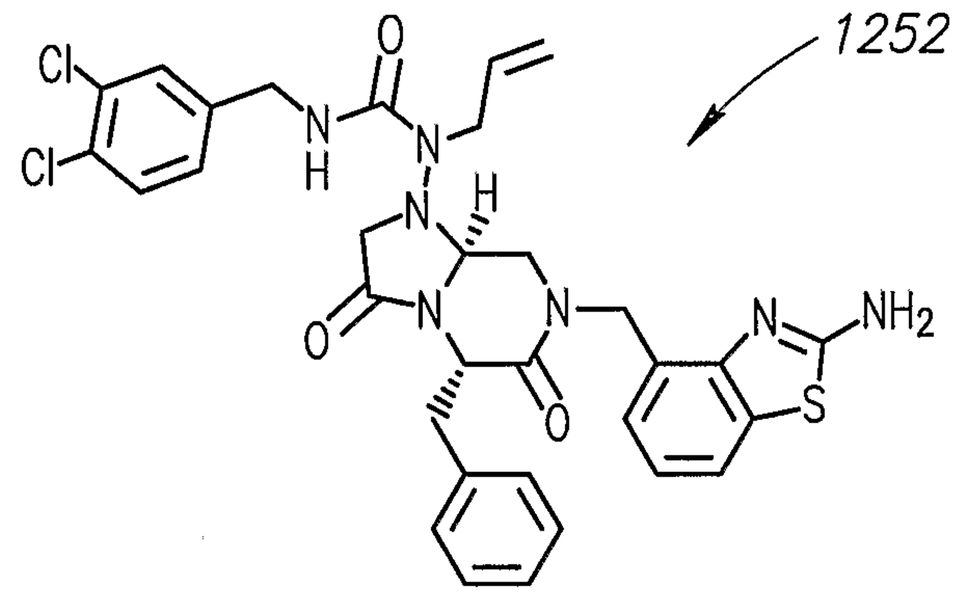


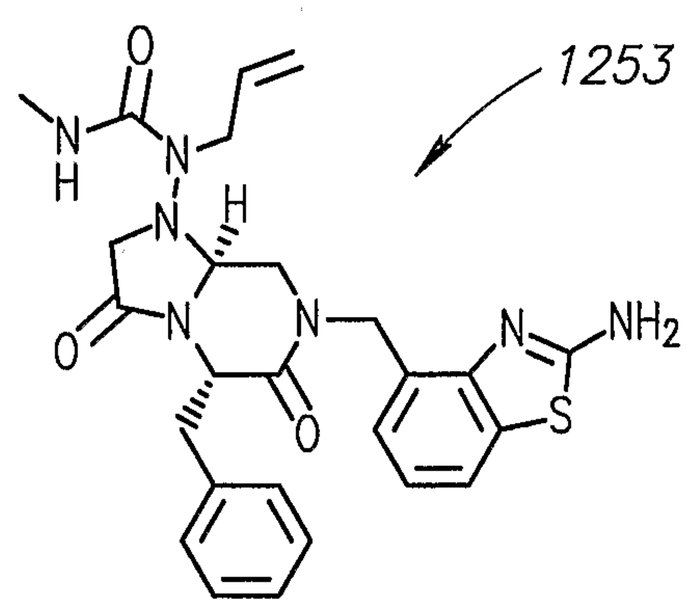
FIG.7F











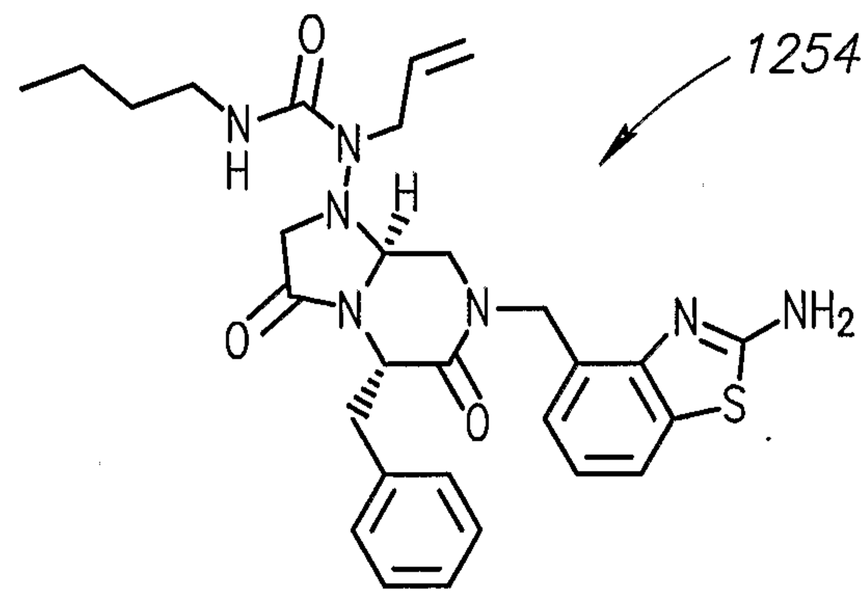
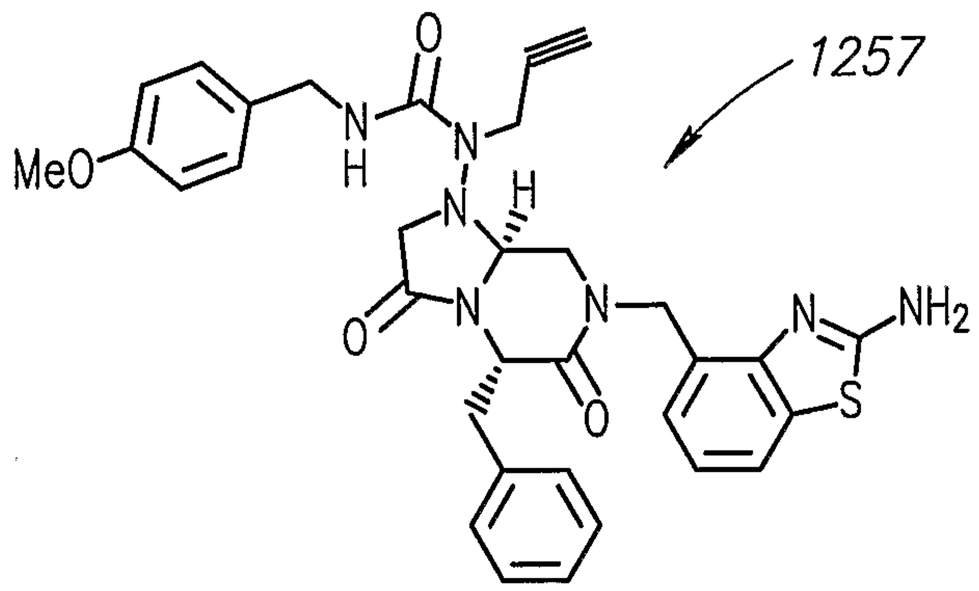
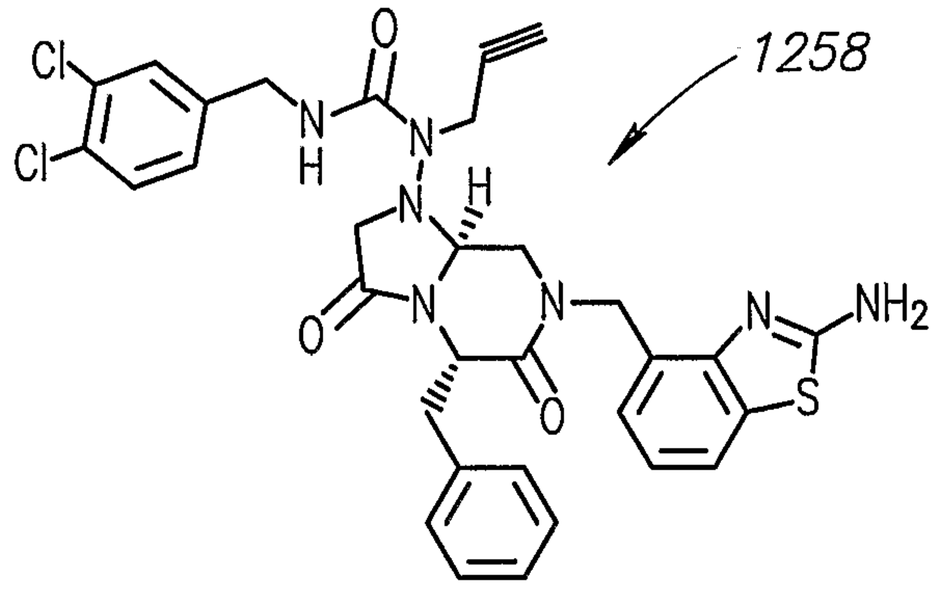
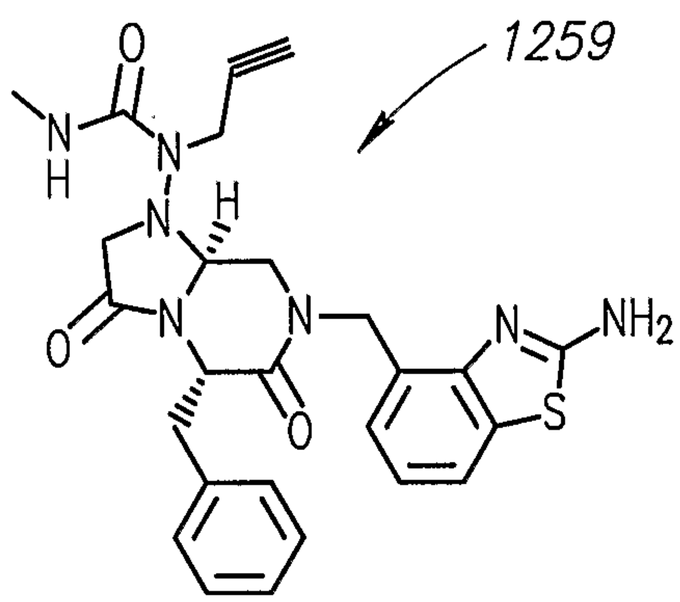
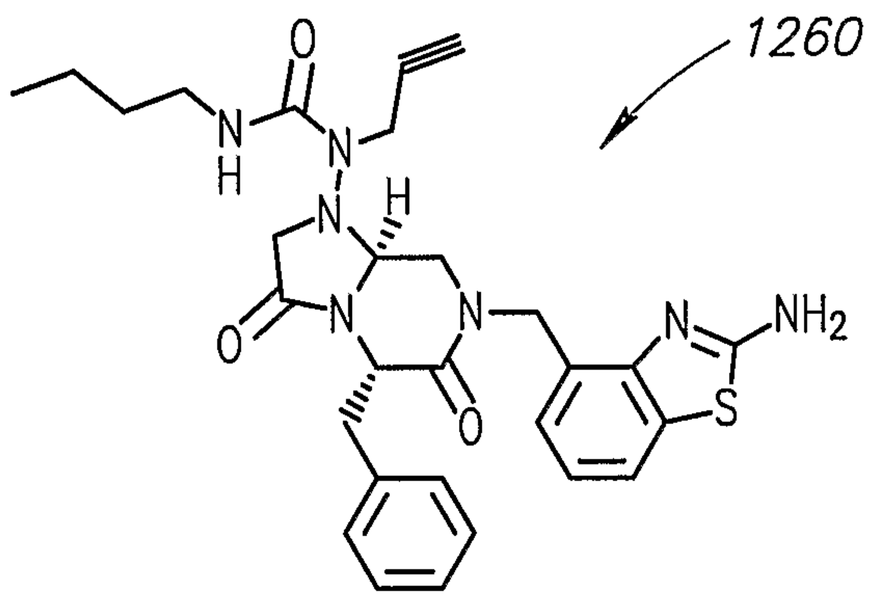


FIG.7G


1257
MeO
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2


1258
Cl
Cl
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2


1259
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2


1260
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N
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N
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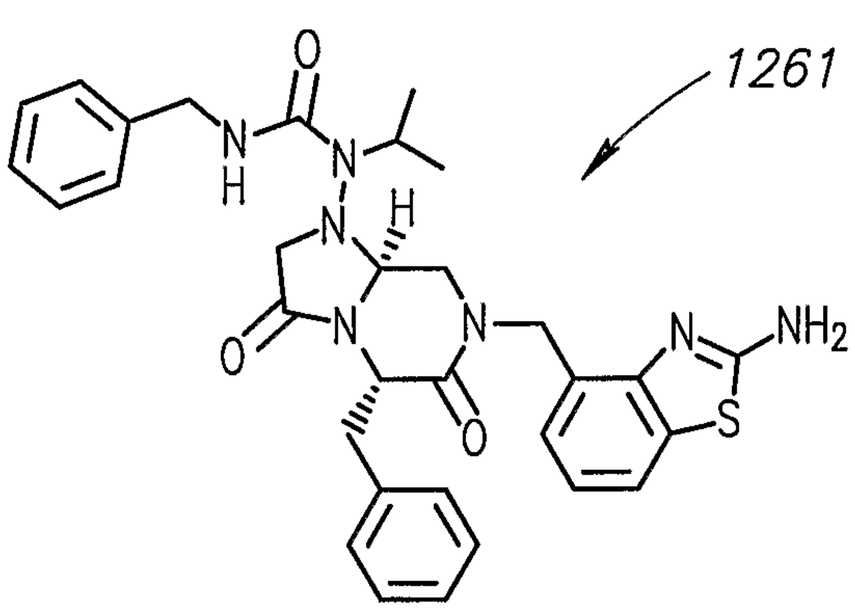
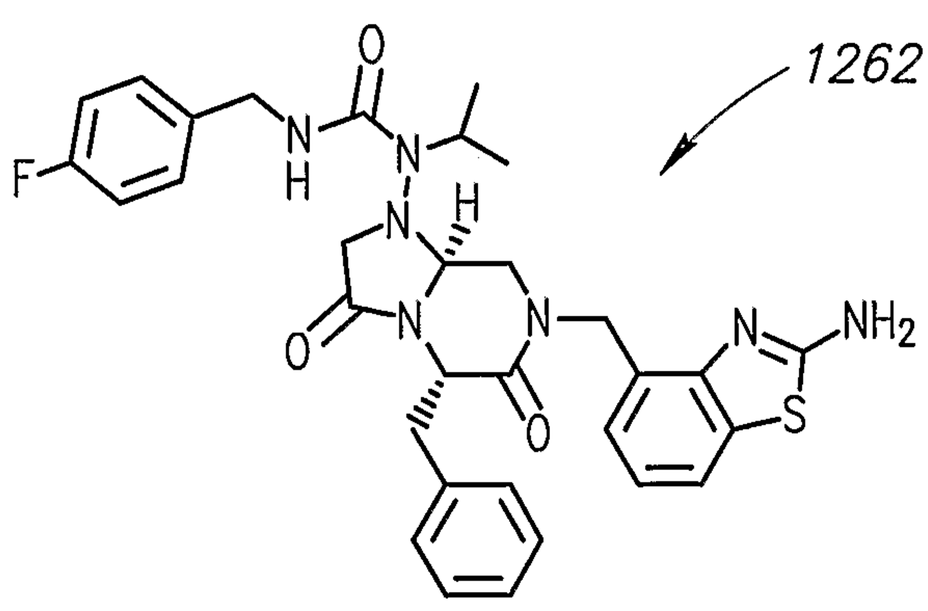
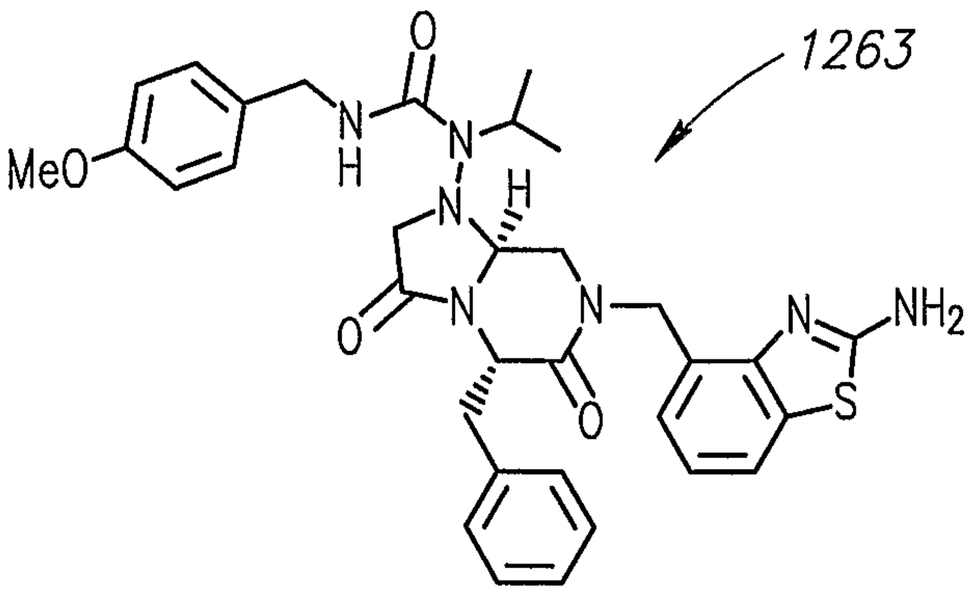
H
O
N
N
O
N
N
S
NH2


1261
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2


1262
F
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2


1263
MeO
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2

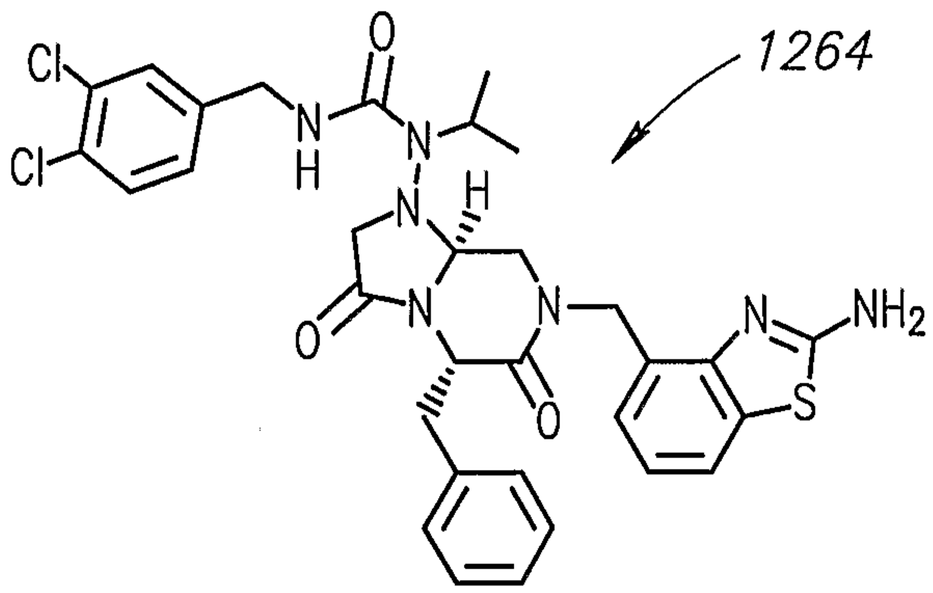
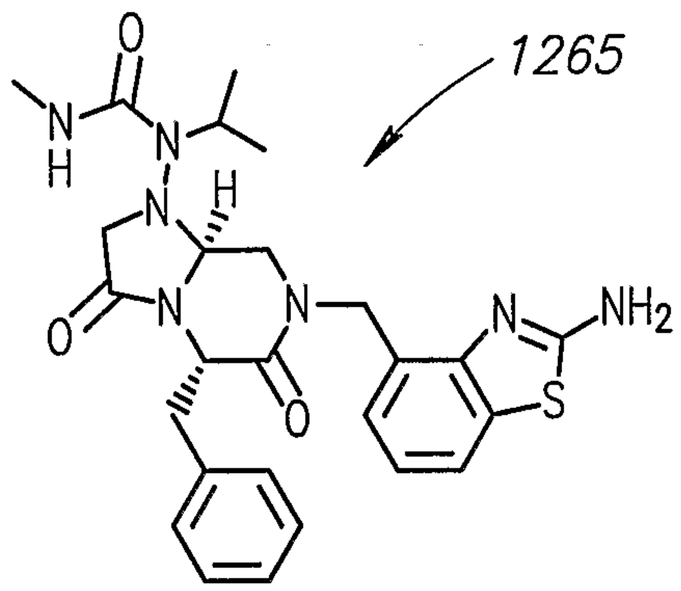
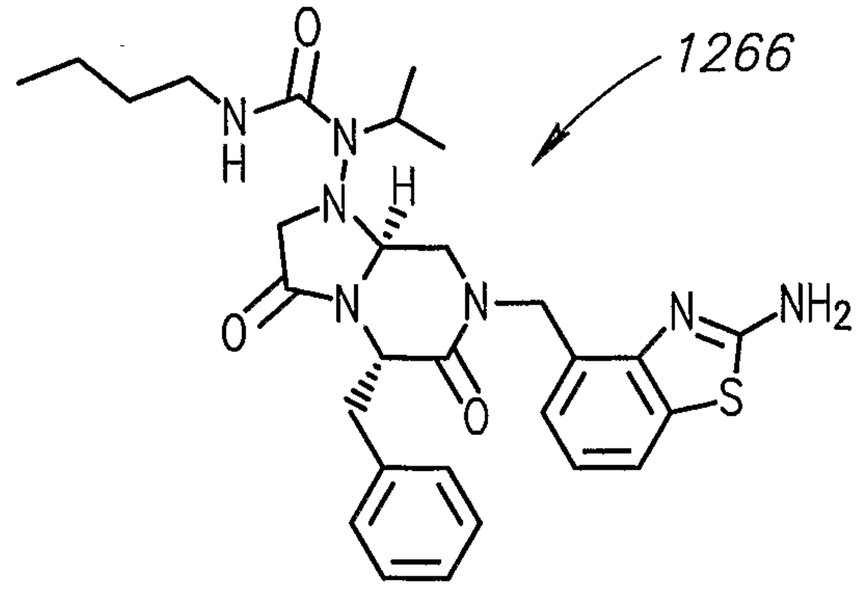
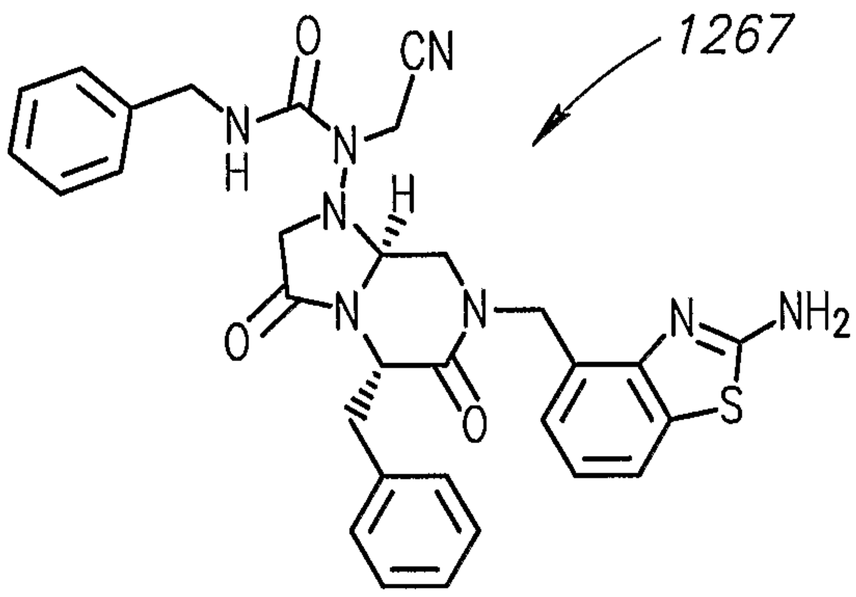
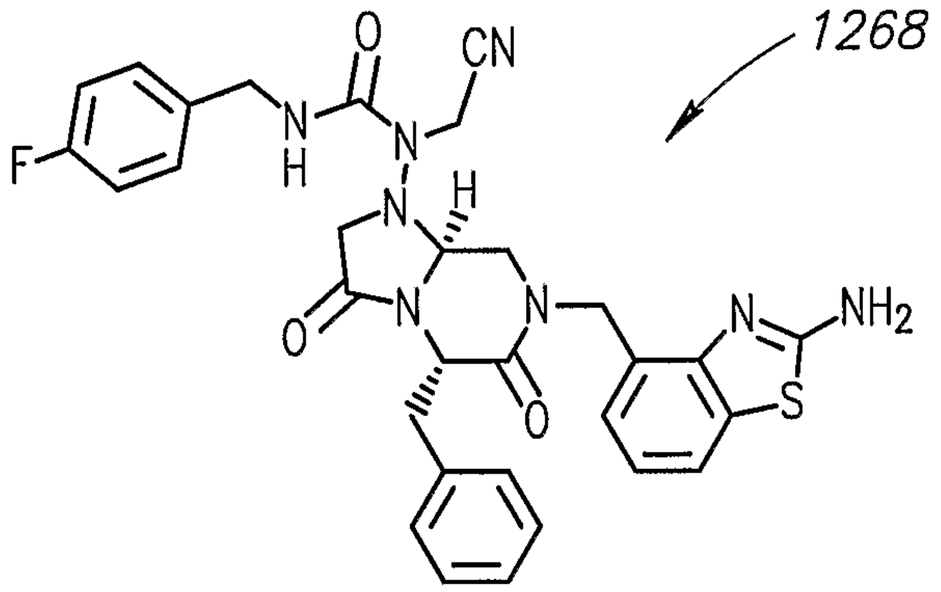

1264
Cl
Cl
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2

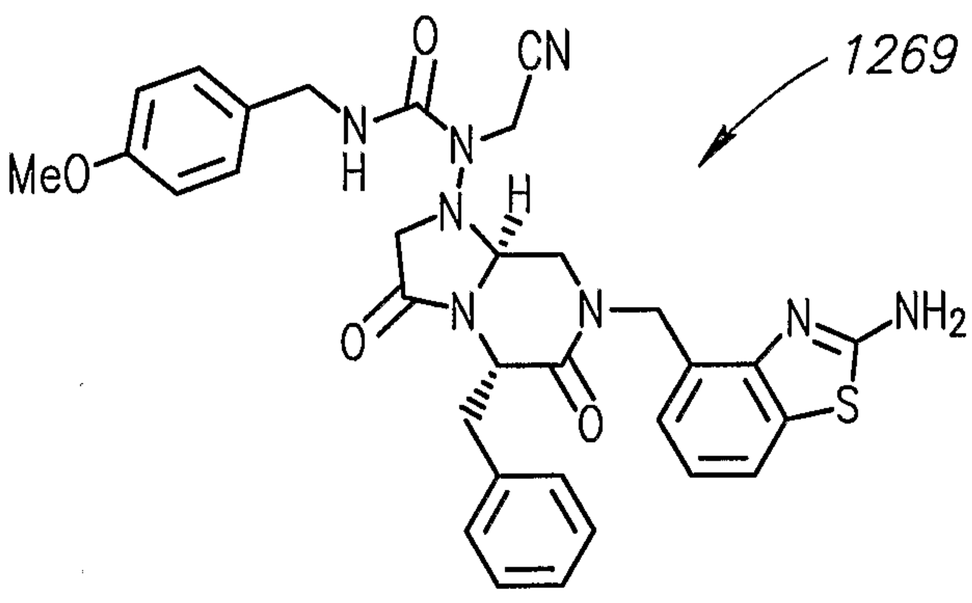
FIG.7H

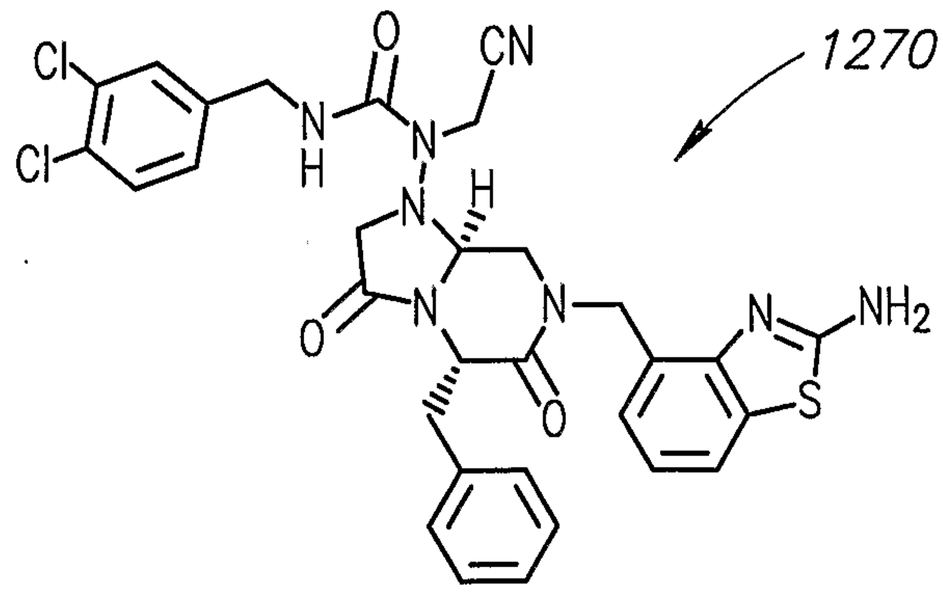


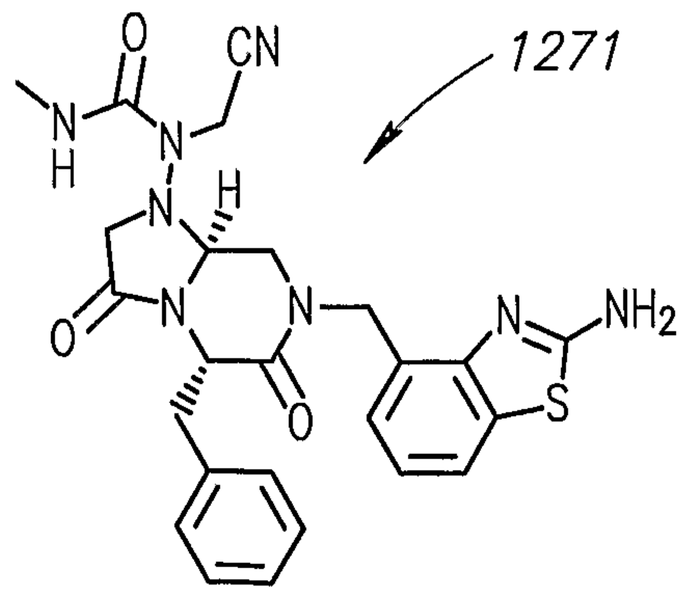












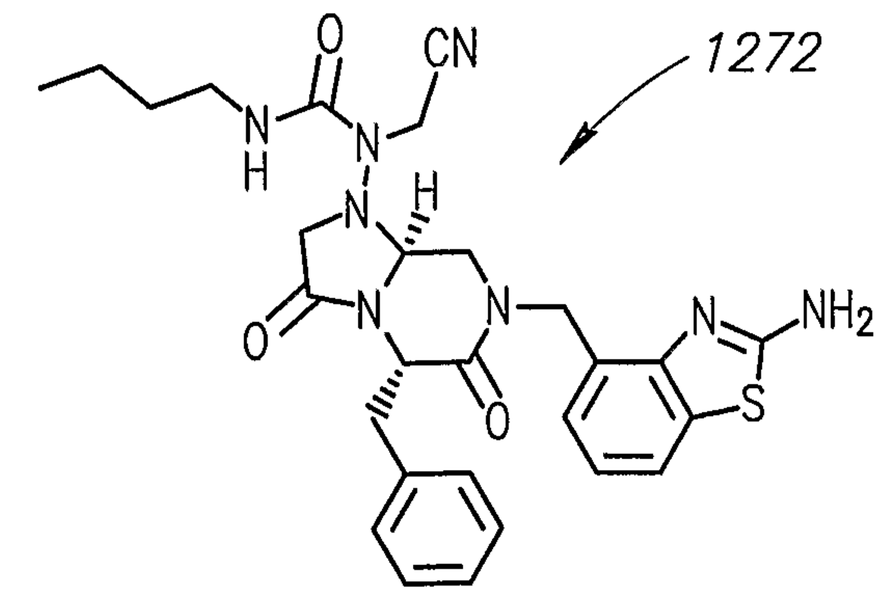
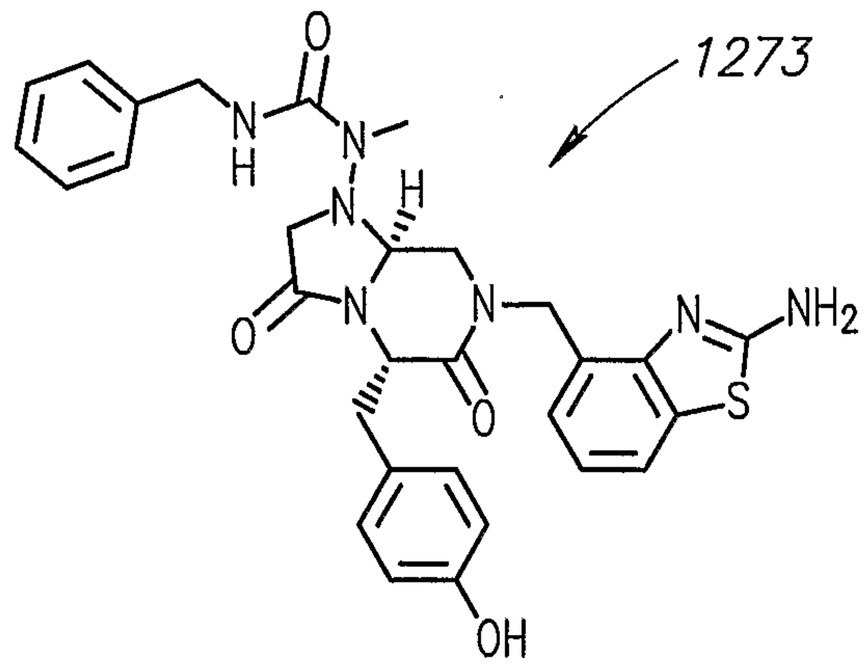
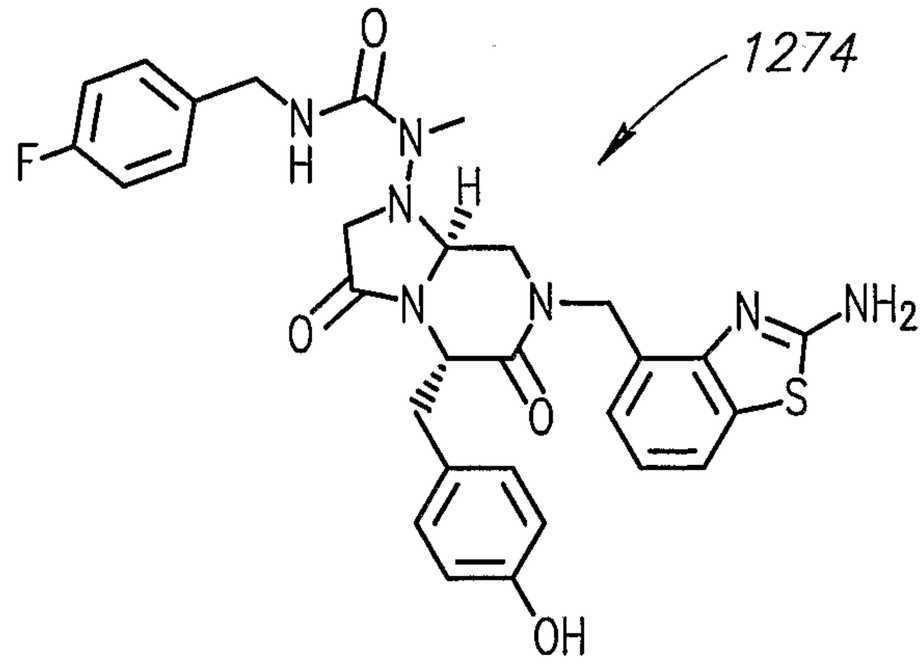
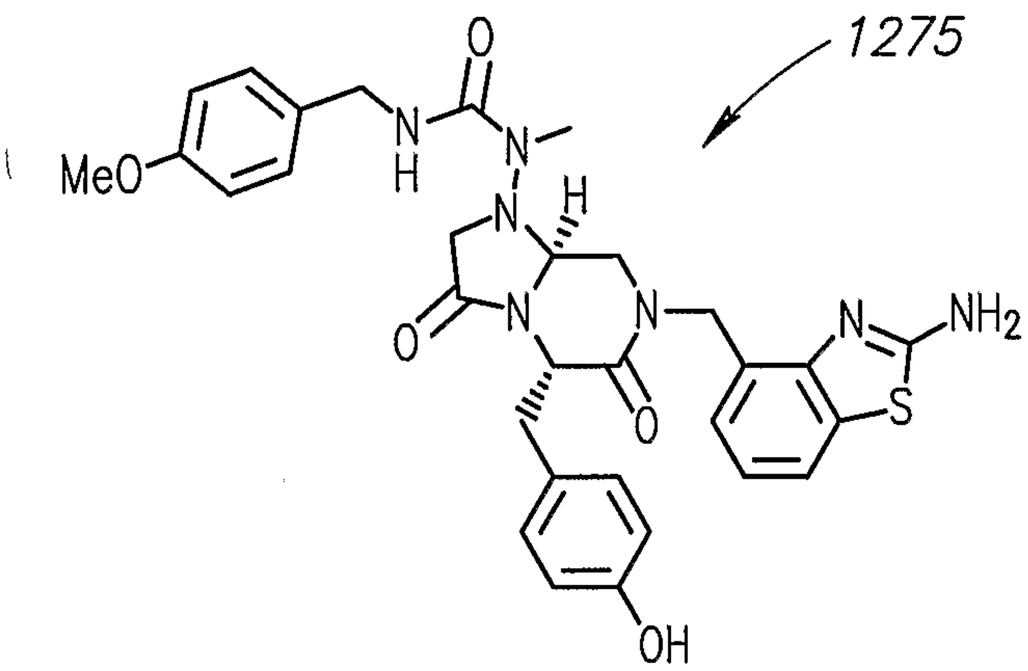
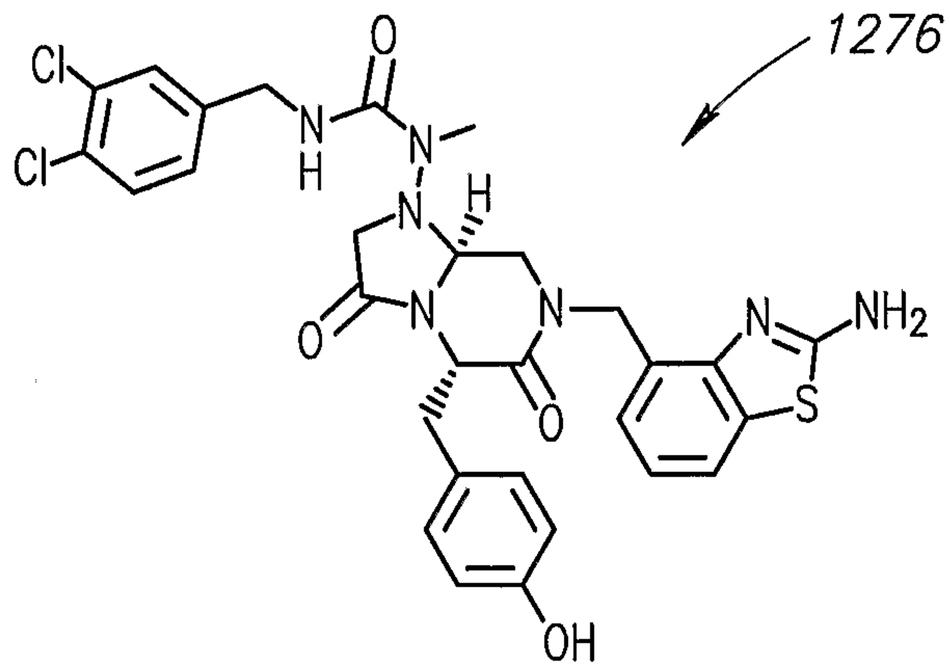


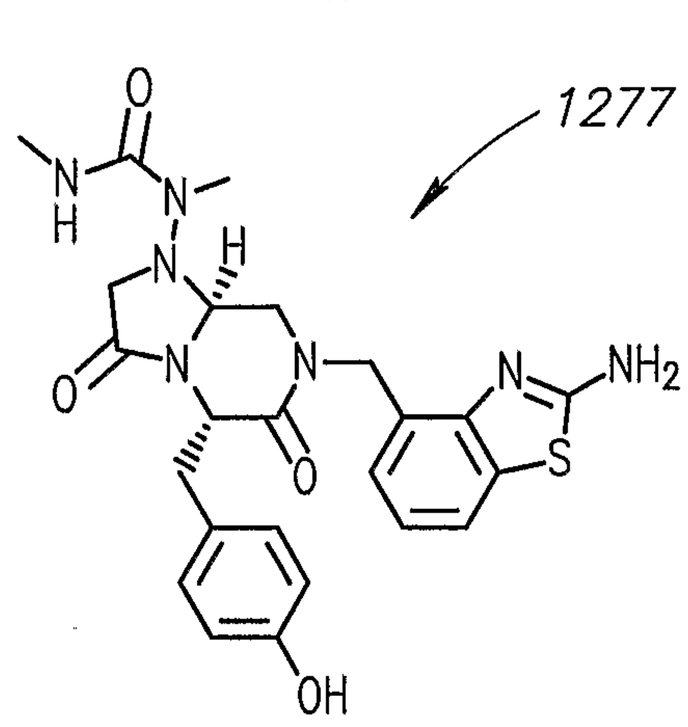
FIG.7I











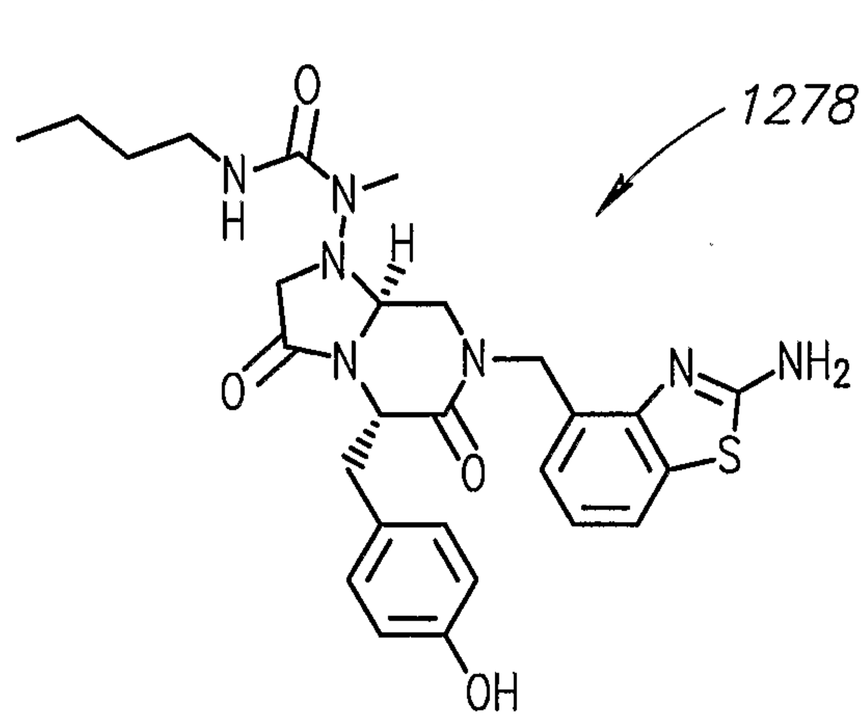
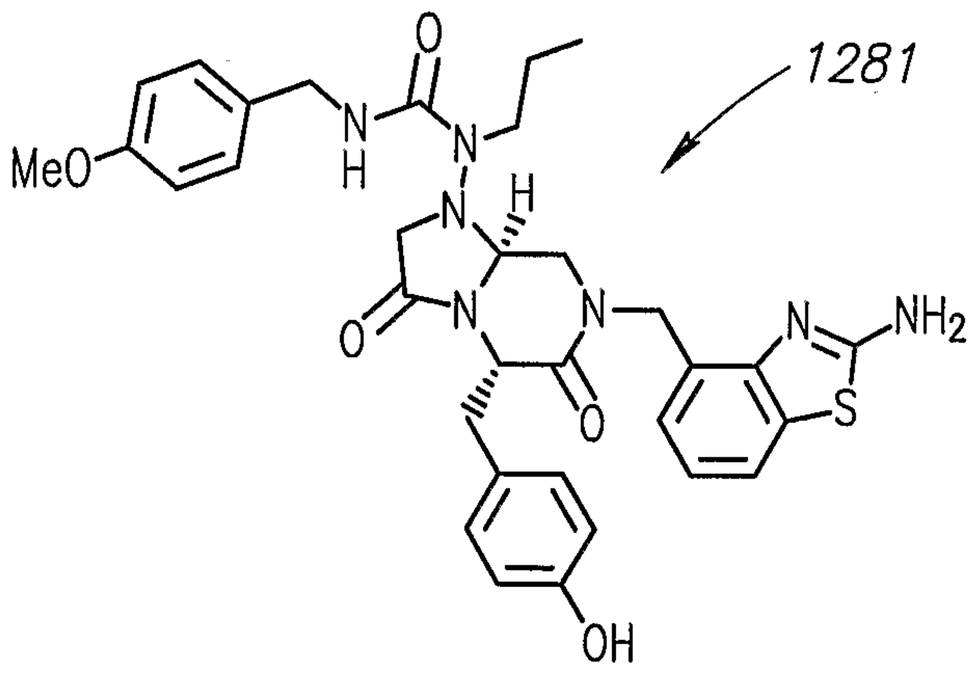


FIG.7J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NH2
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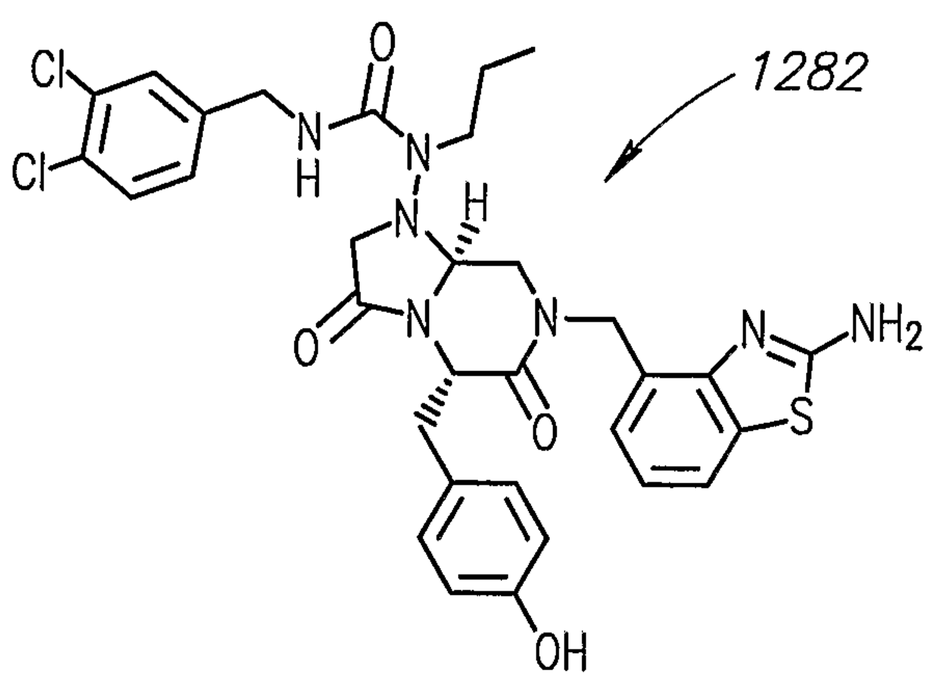
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NH2
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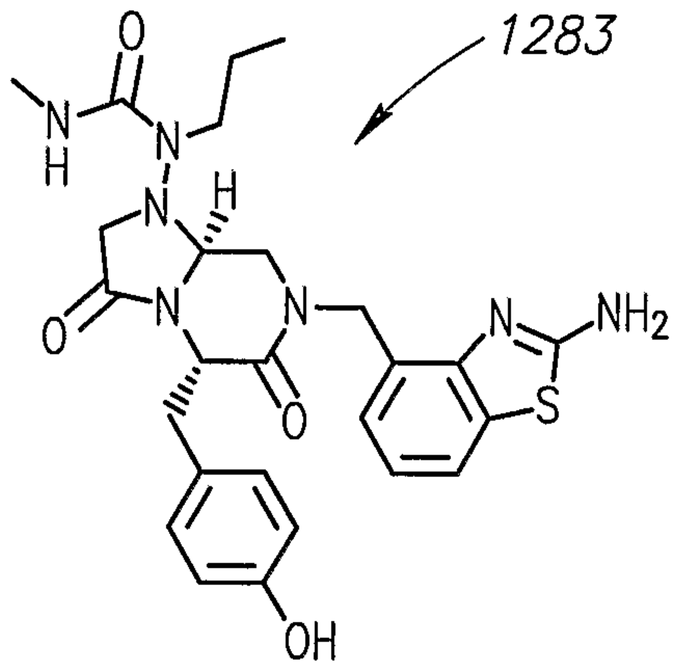
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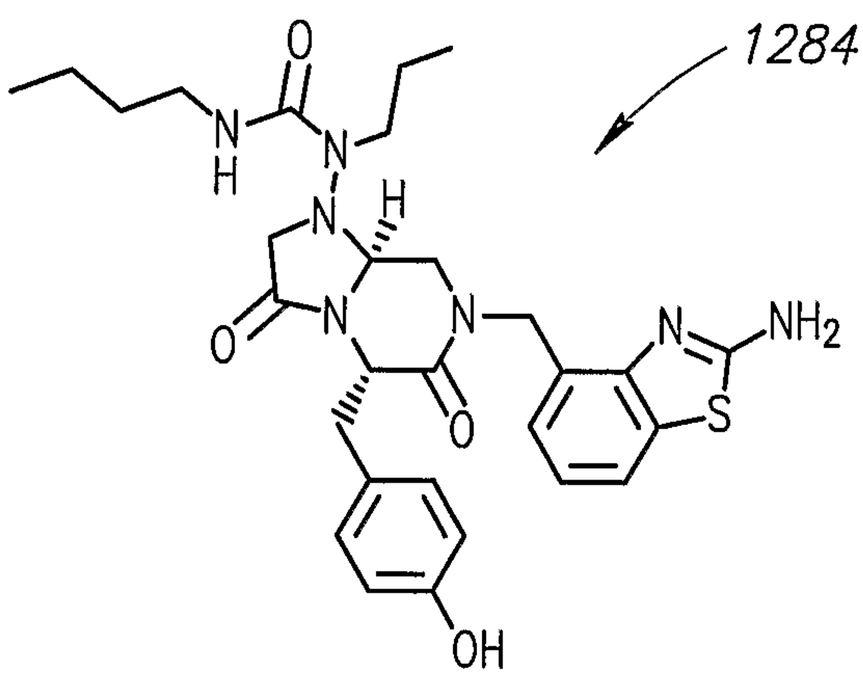
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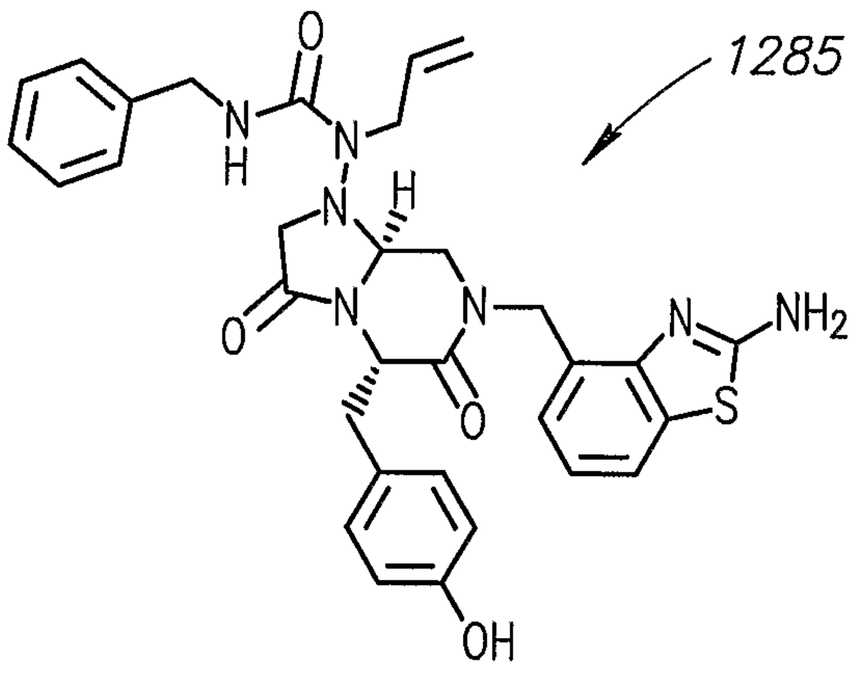
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NH2
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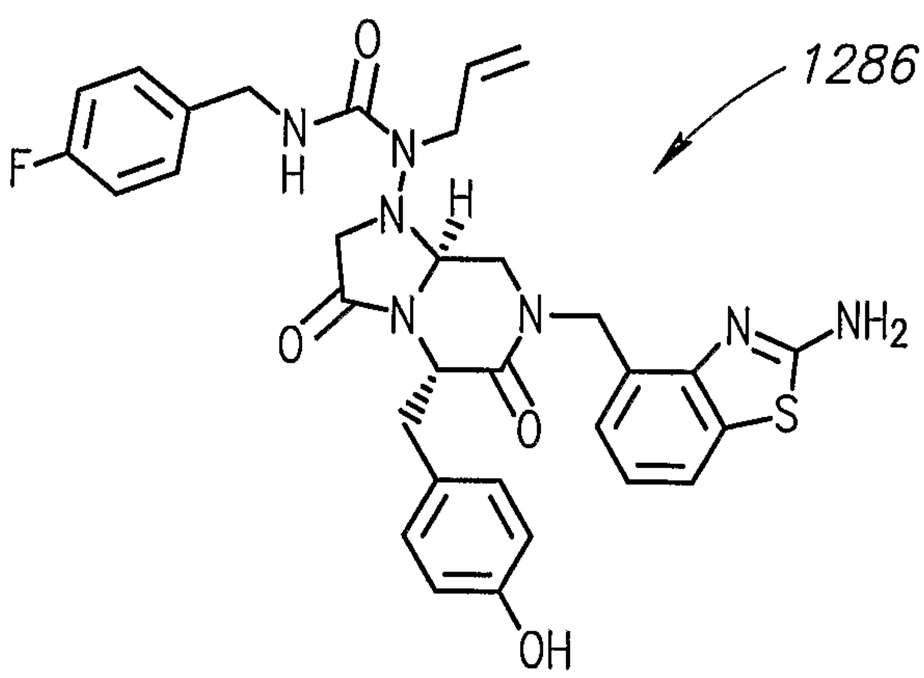
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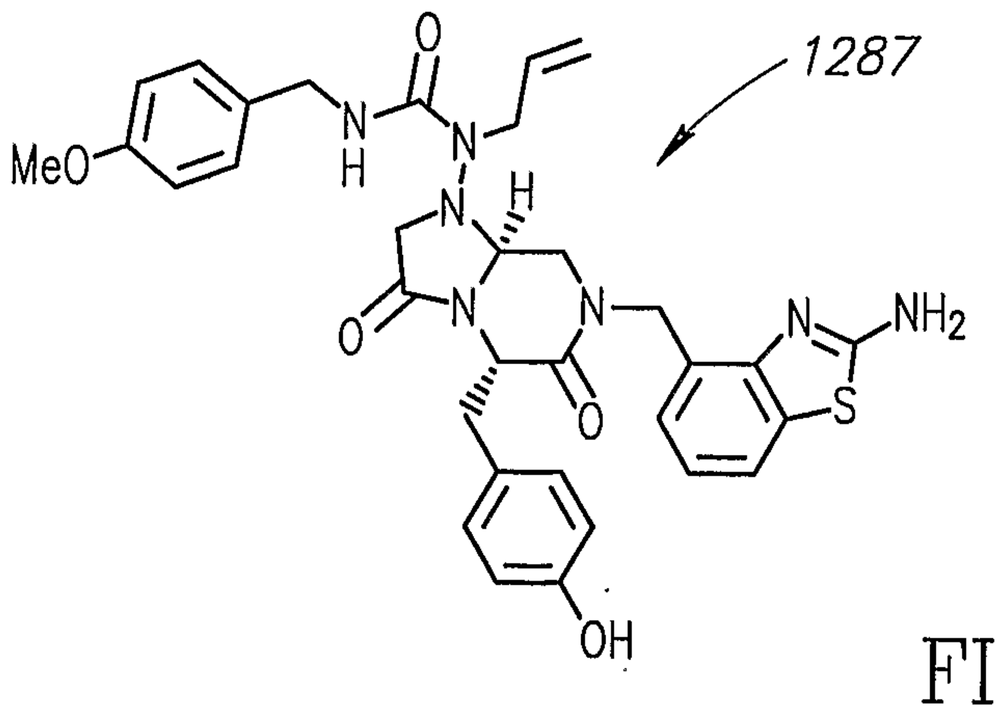
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NH2
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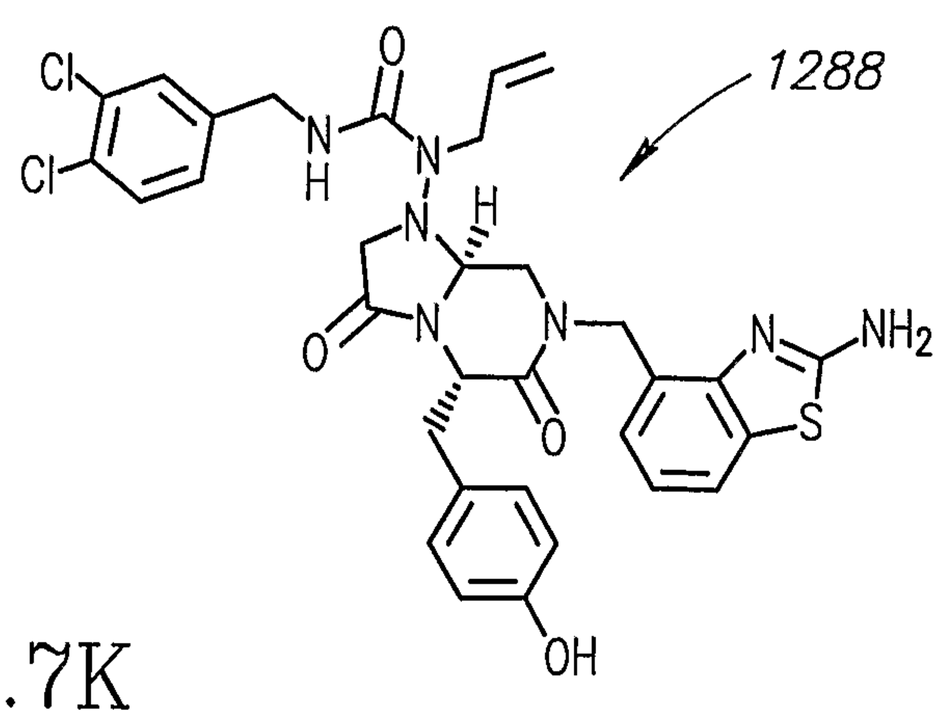
1288
Cl
Cl
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N
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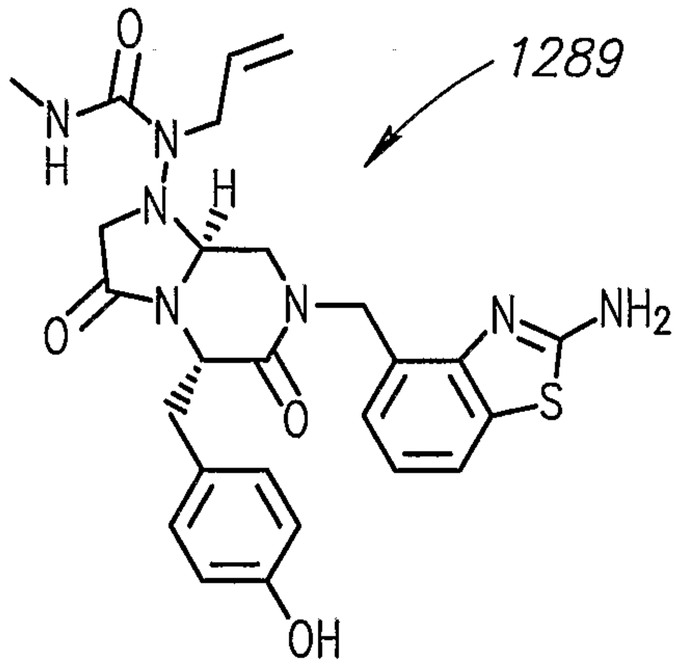
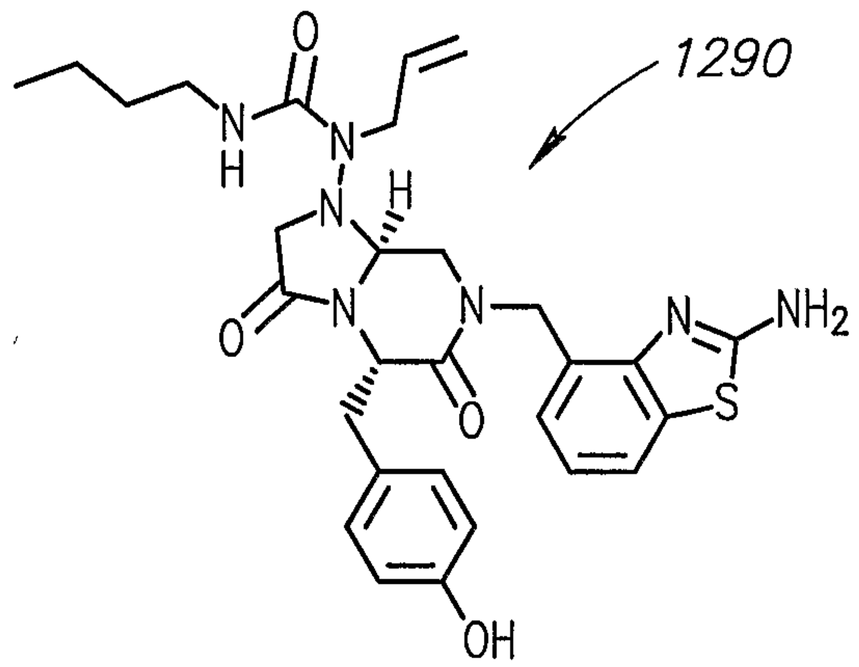
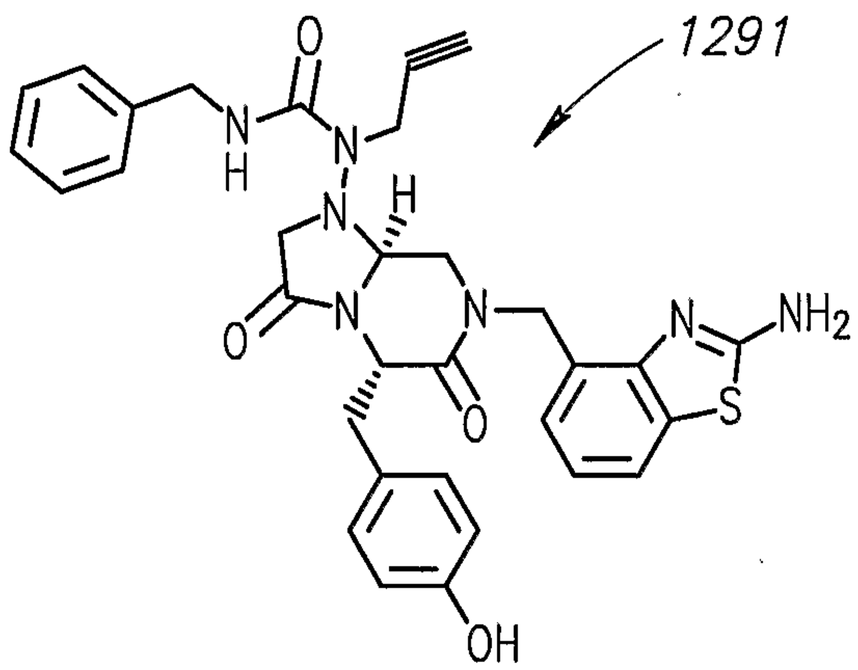
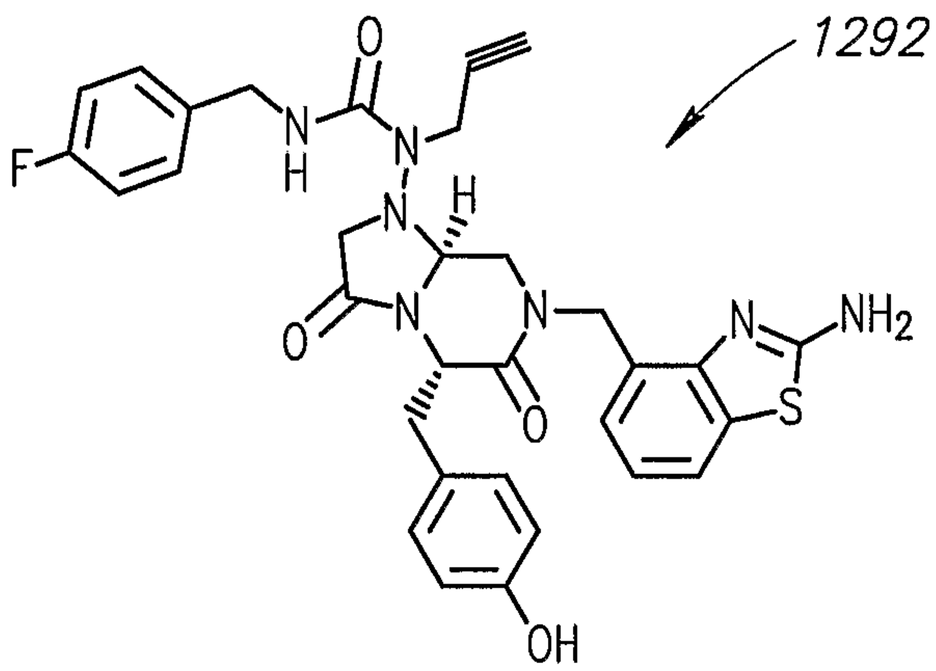
N
H
O
N
N
O
N
N
S
NH2
OH

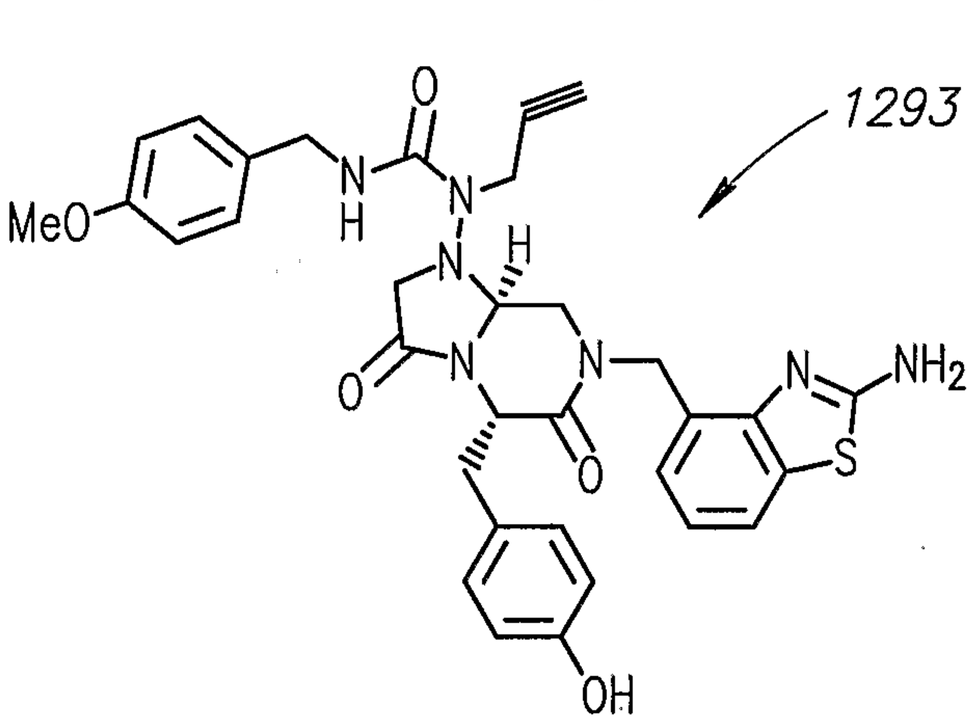
FIG.7K











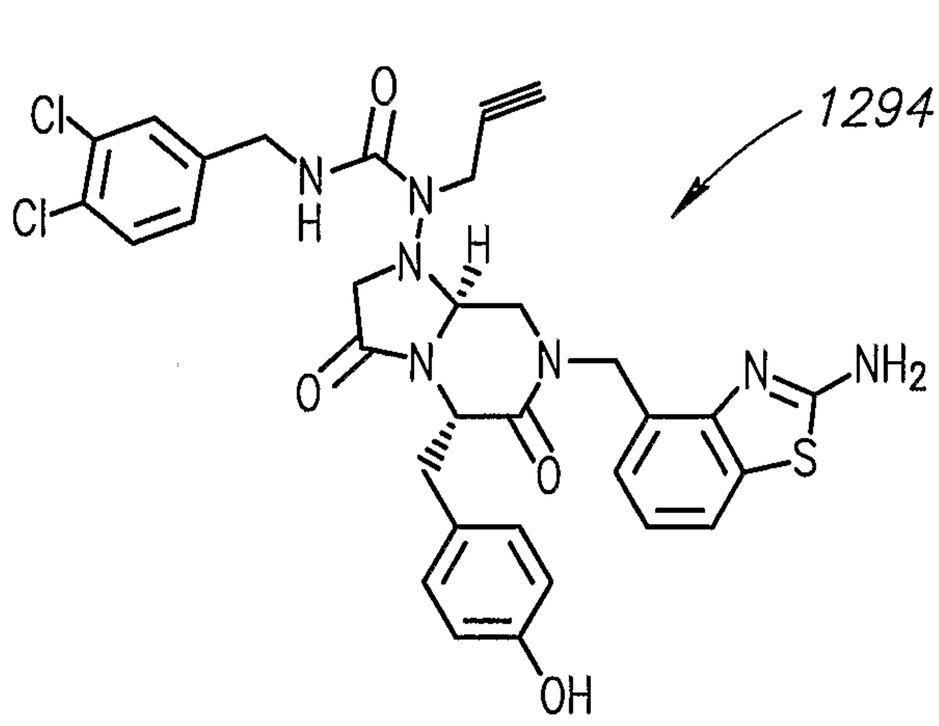
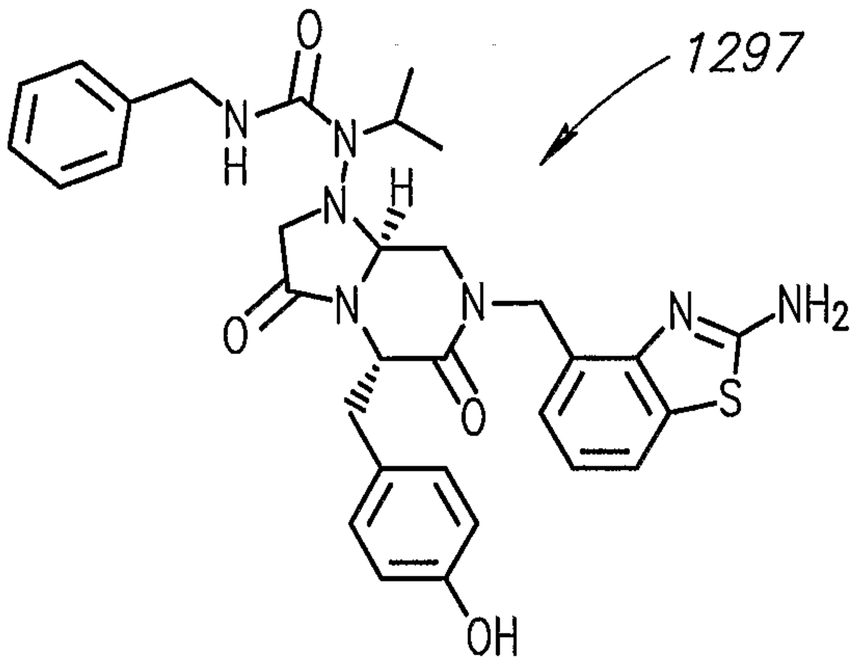
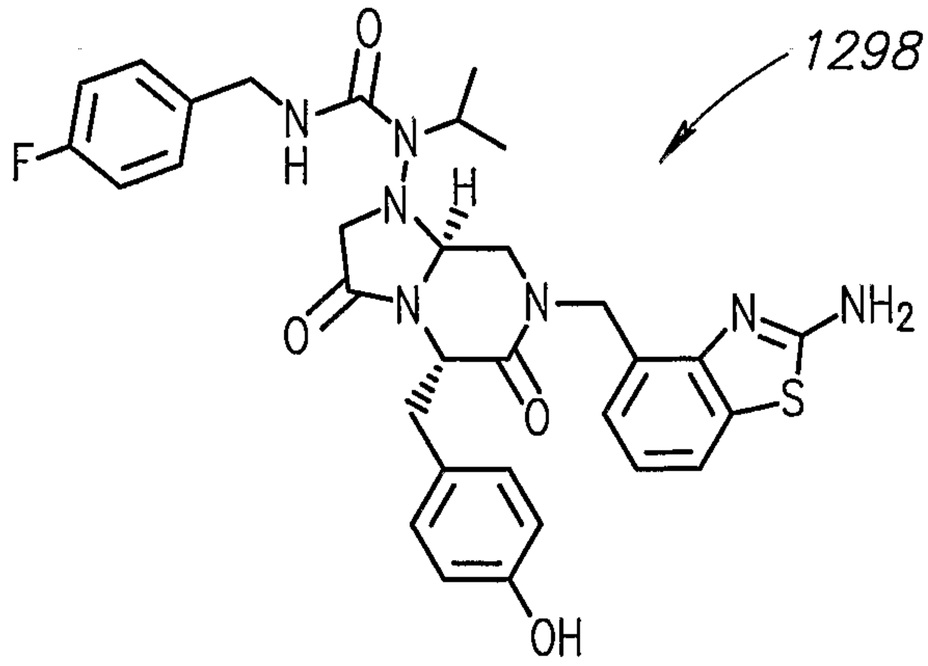
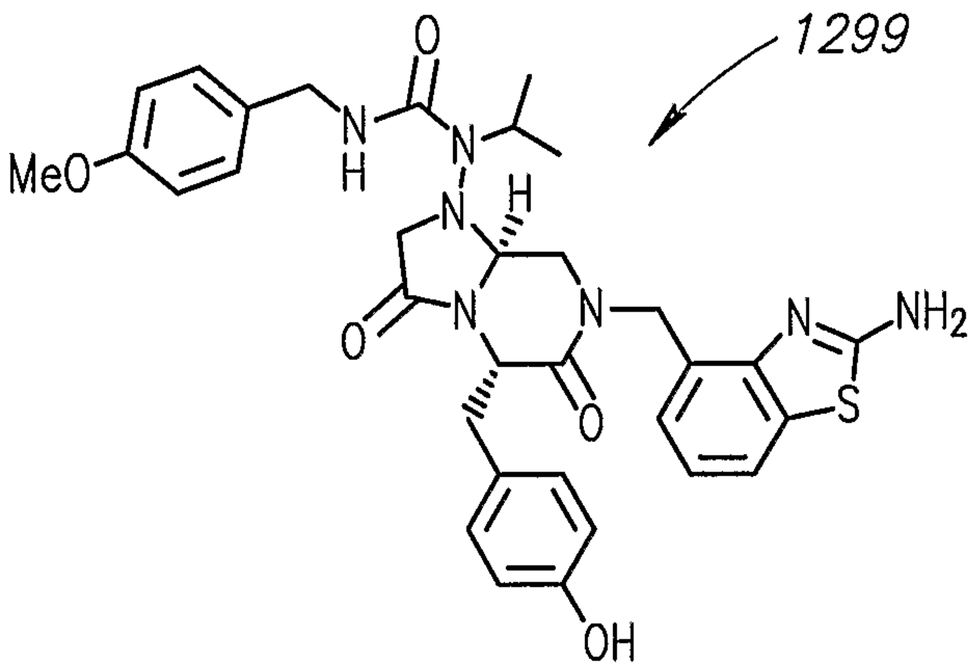
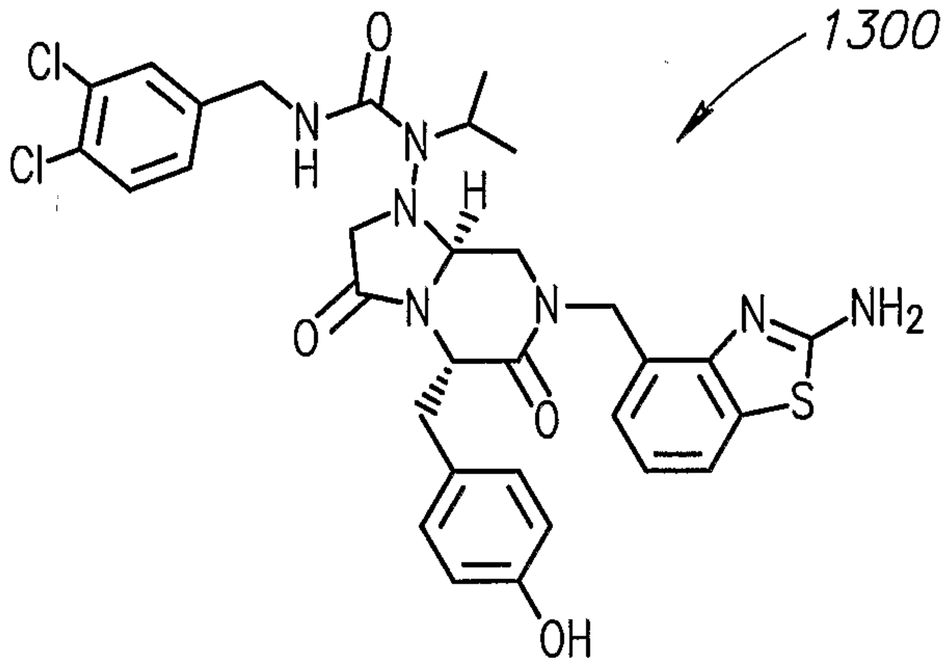


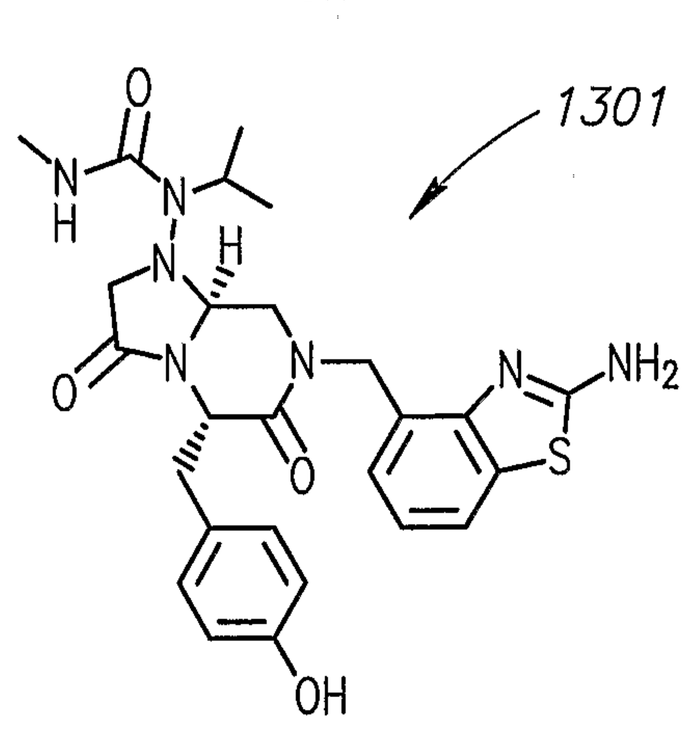
FIG.7L

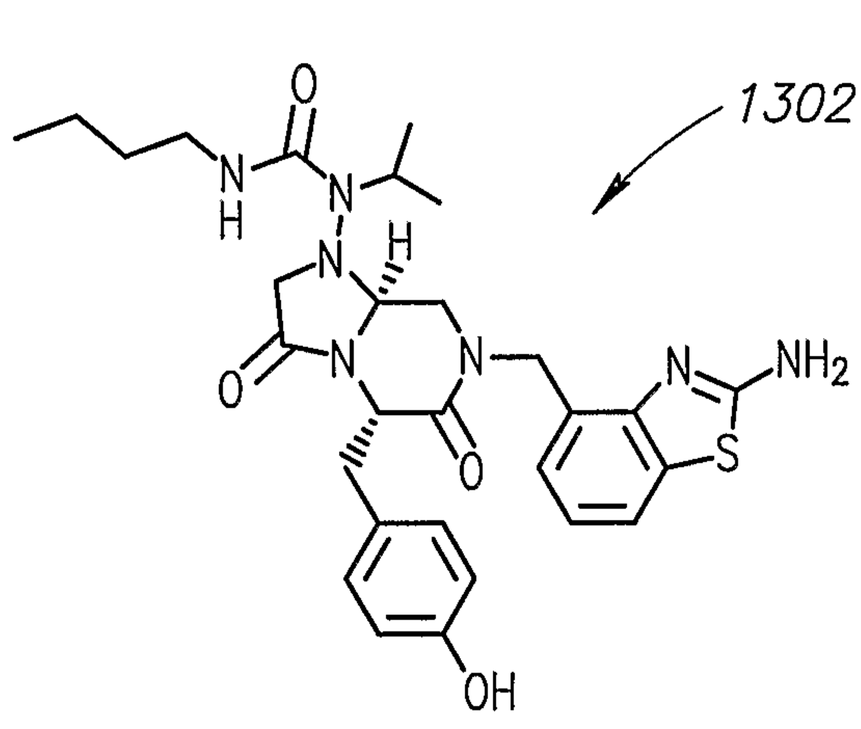


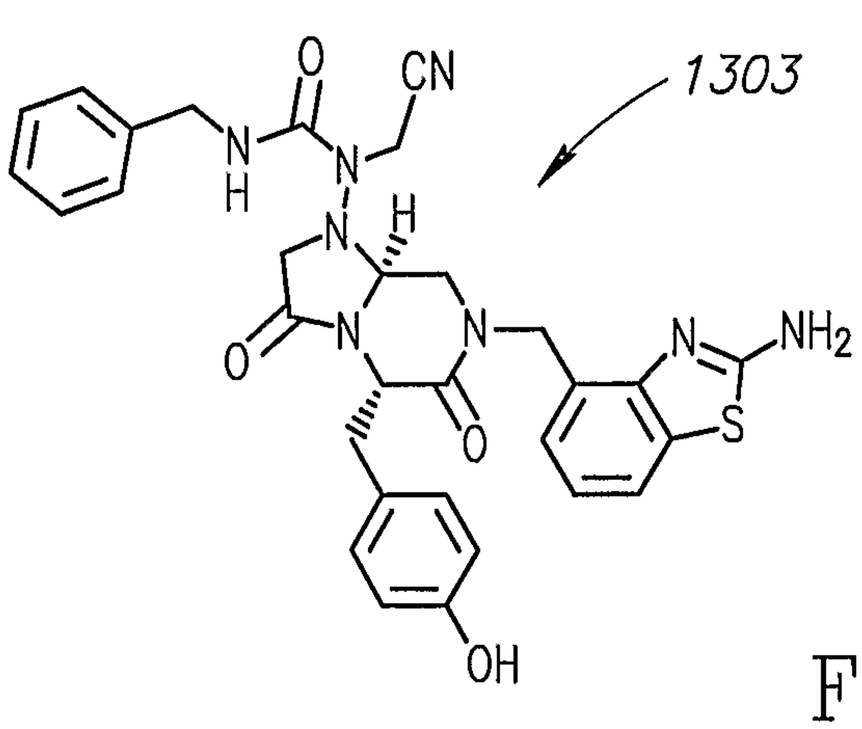












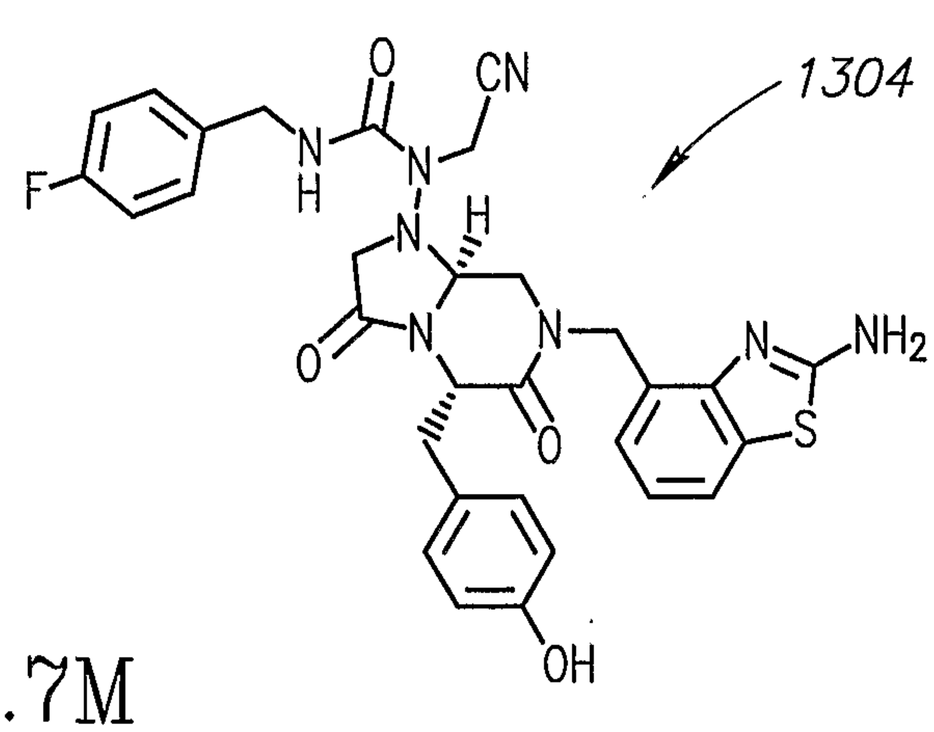
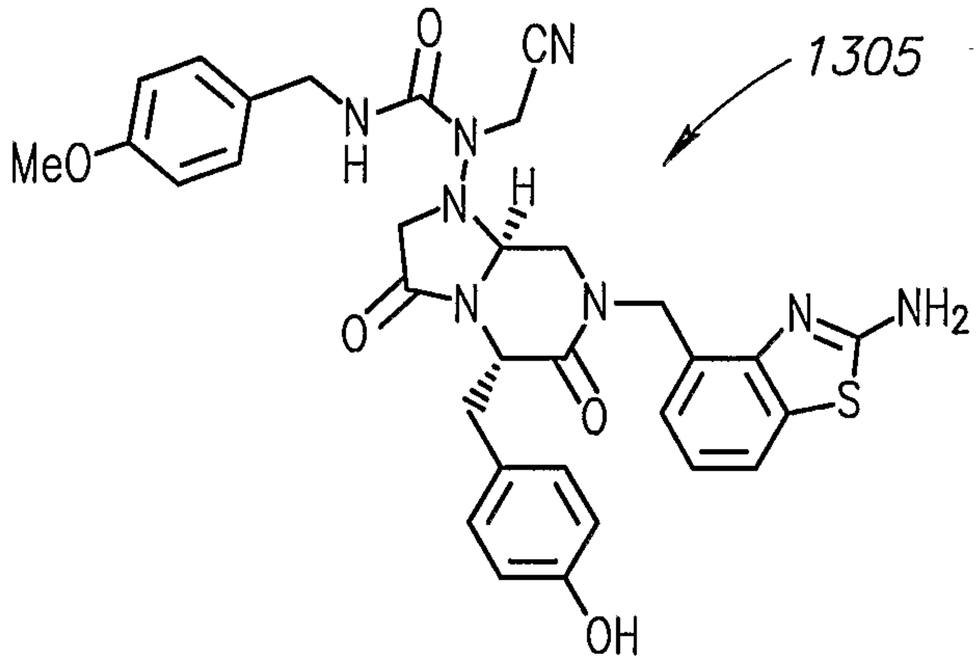


FIG.7M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H
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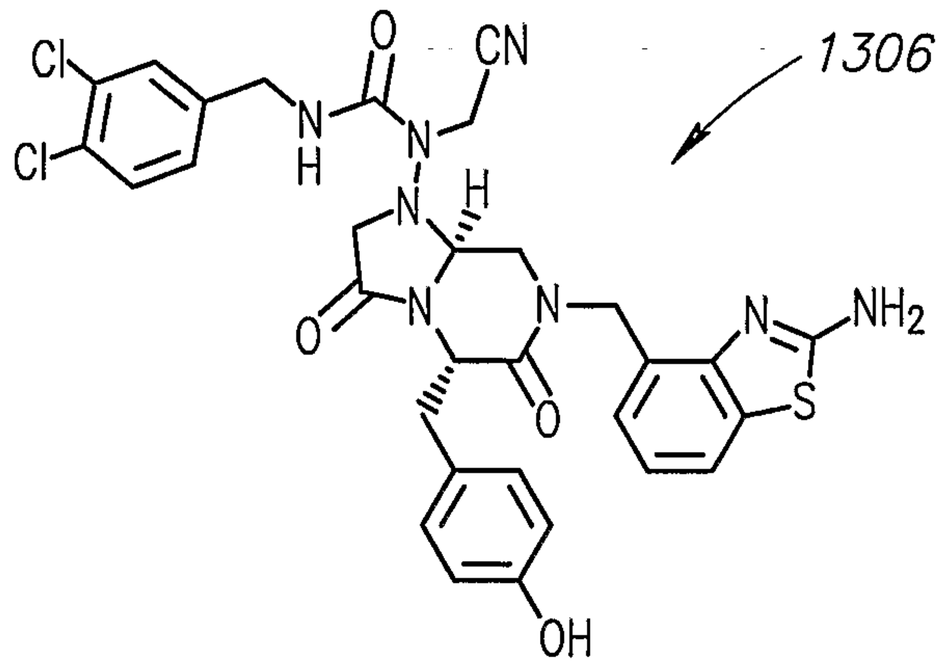
H
N
O
N
O
N
N
NH2
S
OH


1306
Cl
Cl
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CN
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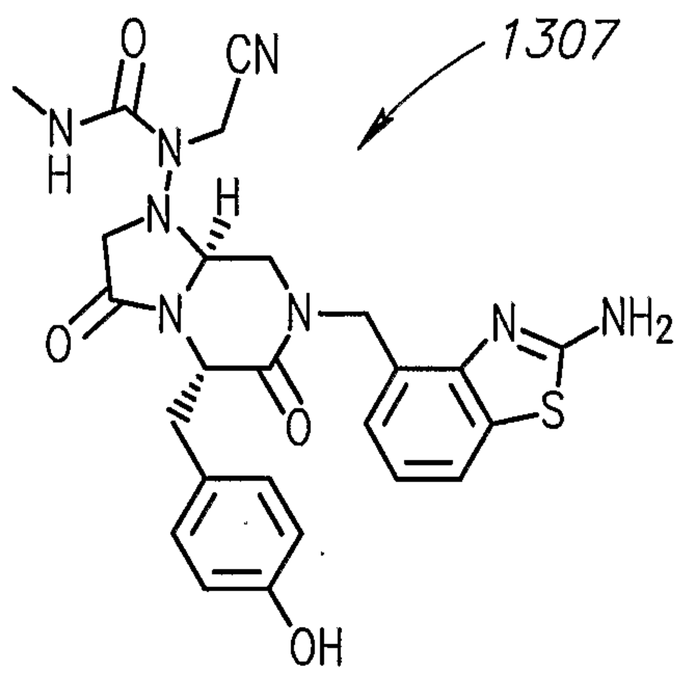
H
N
H
N
O
N
O
N
N
NH2
S
OH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H
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H
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O
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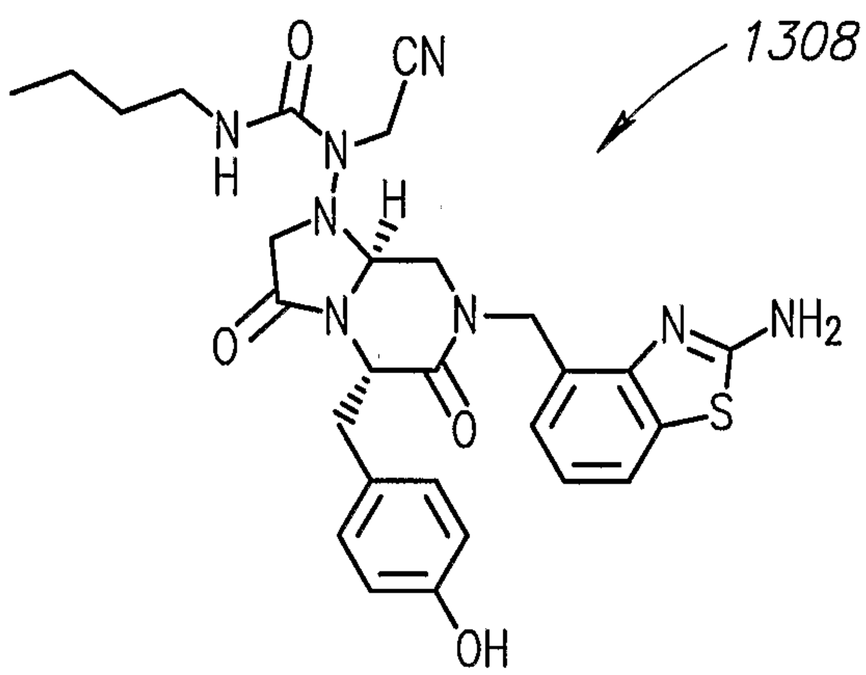
O
N
N
NH2
S
OH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O
N
O
N
N
NH2
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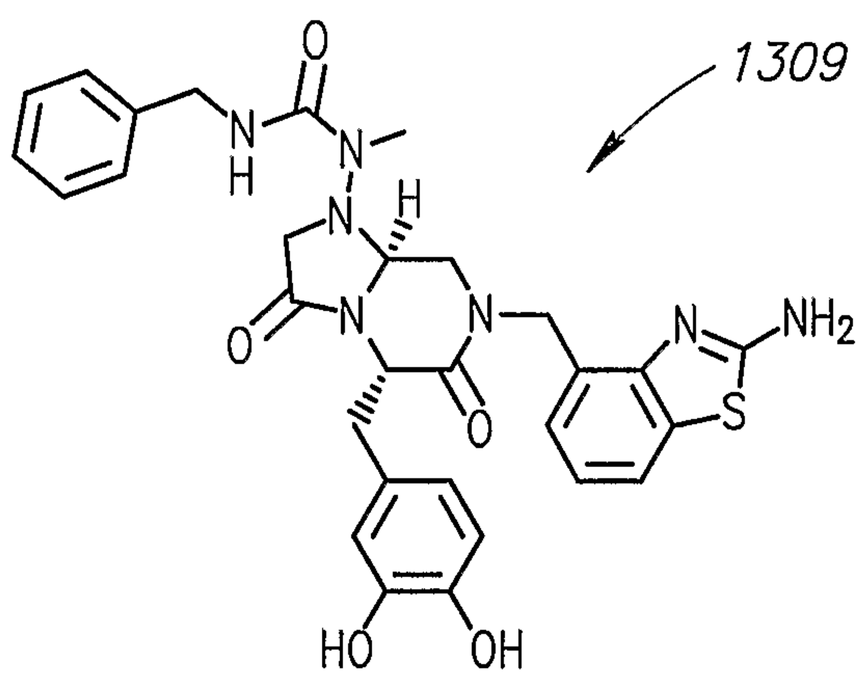
OH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N
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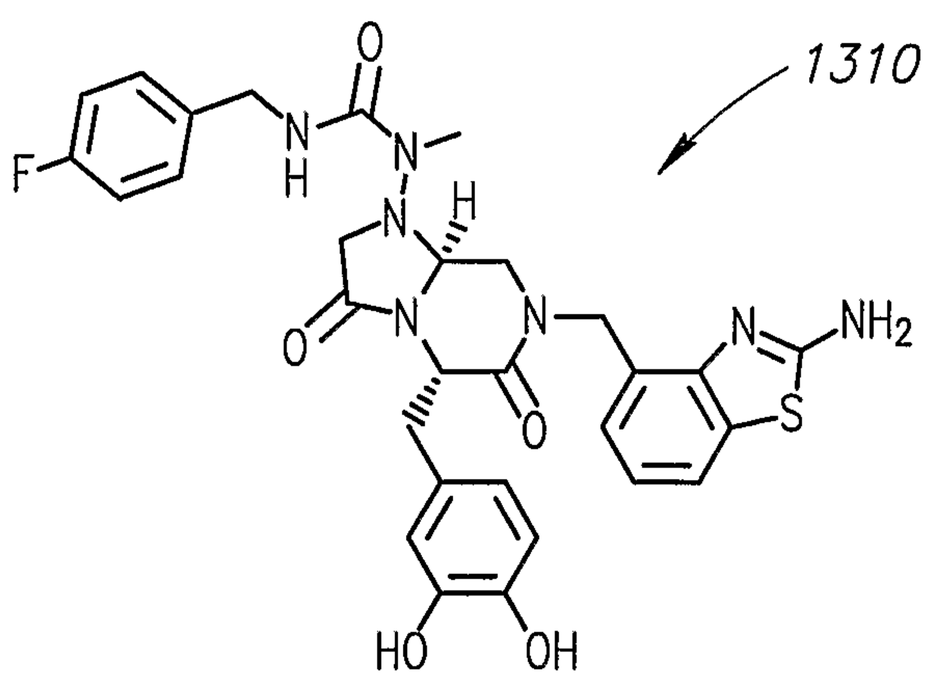
N
O
N
O
N
N
NH2
S
HO
OH


1310
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N
H
N
H
N
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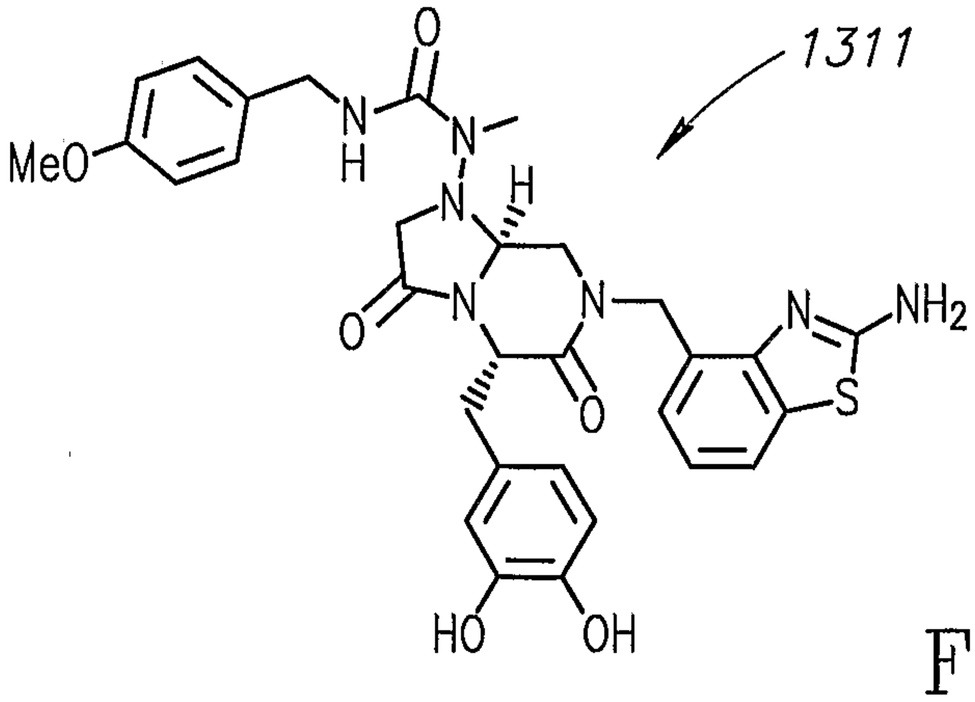
N
N
NH2
S
HO
OH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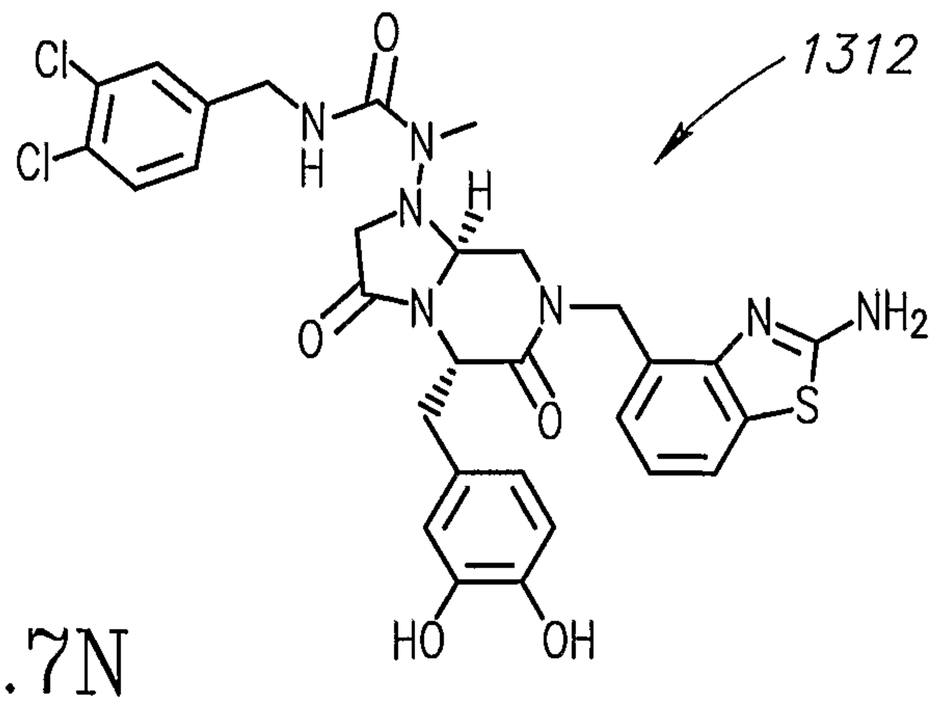
HO
OH


1312
Cl
Cl
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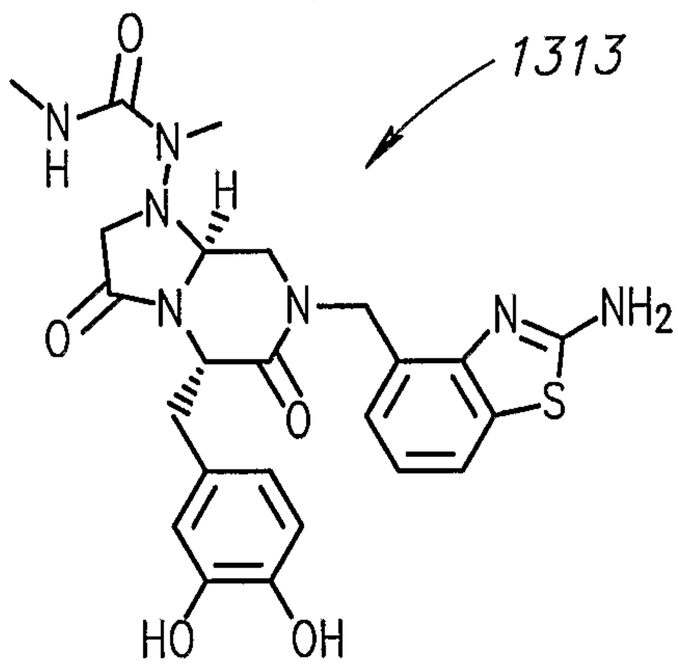
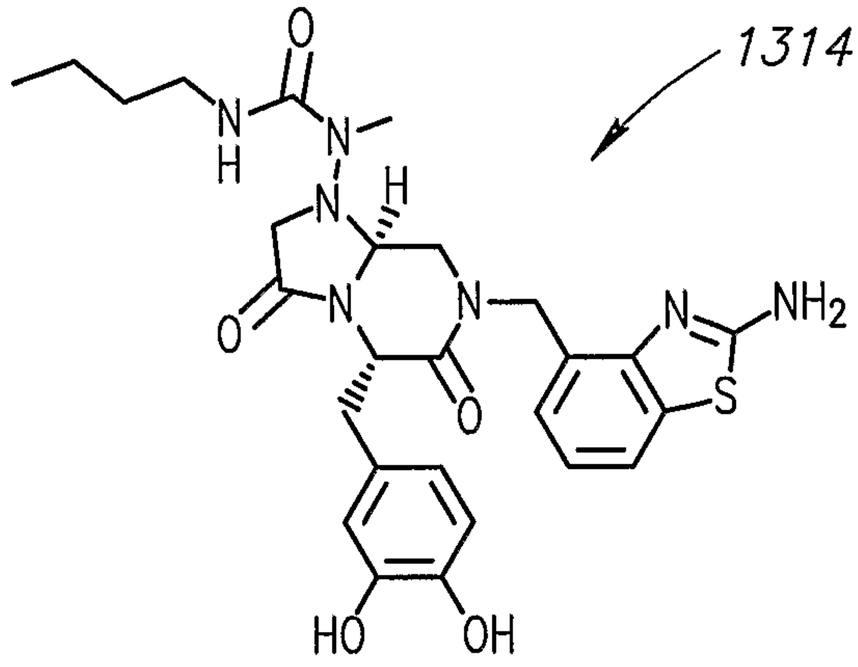
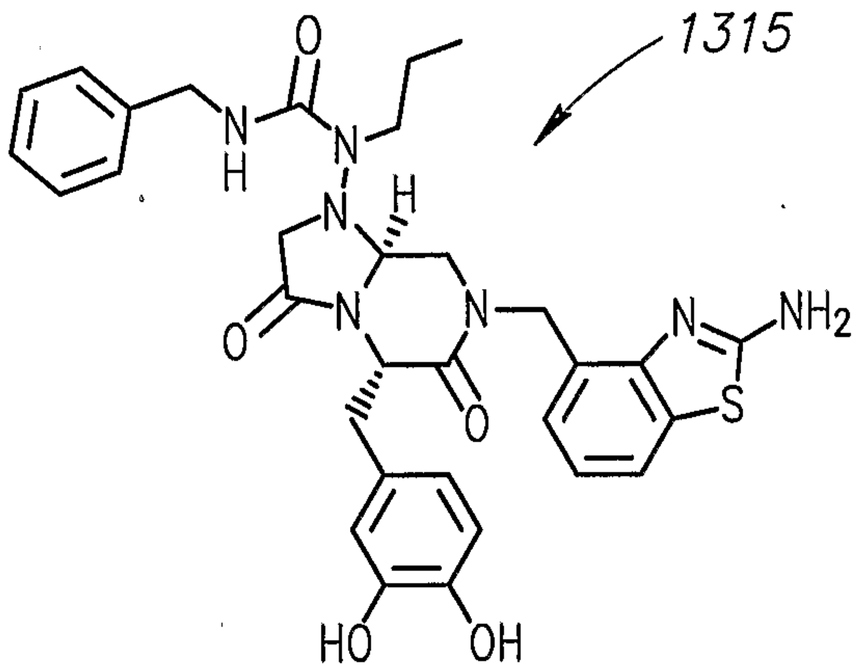
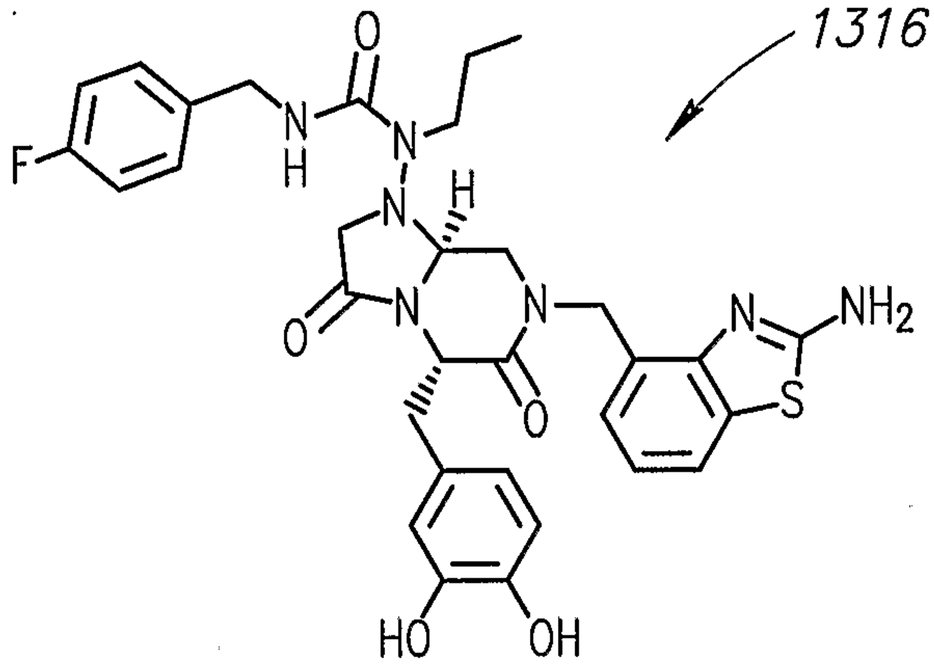
N
H
N
H
N
O
N
O
N
N
NH2
S
HO
OH

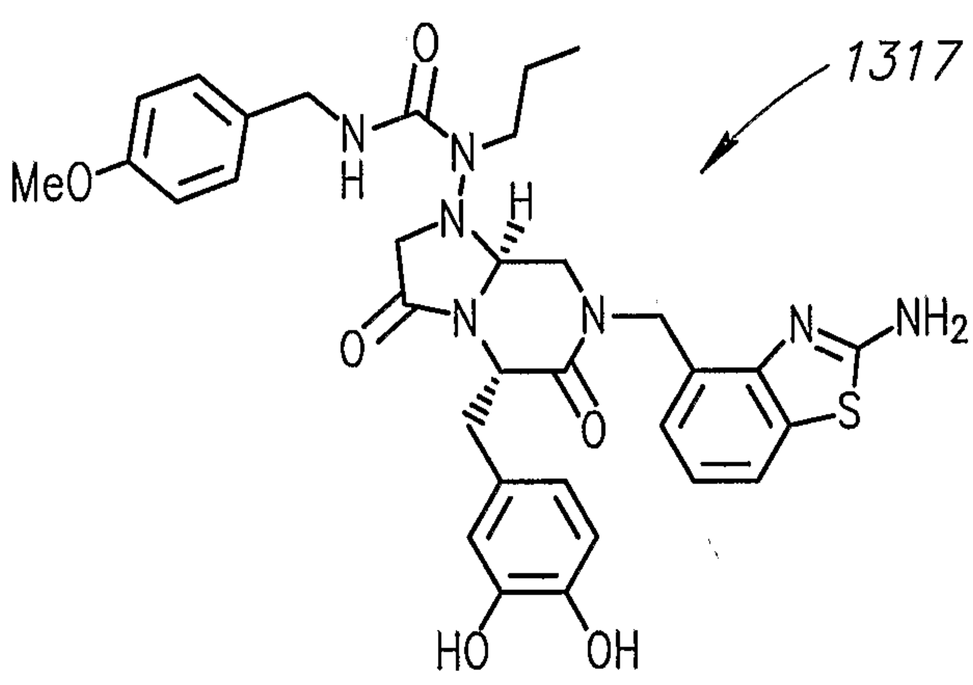
FIG.7N











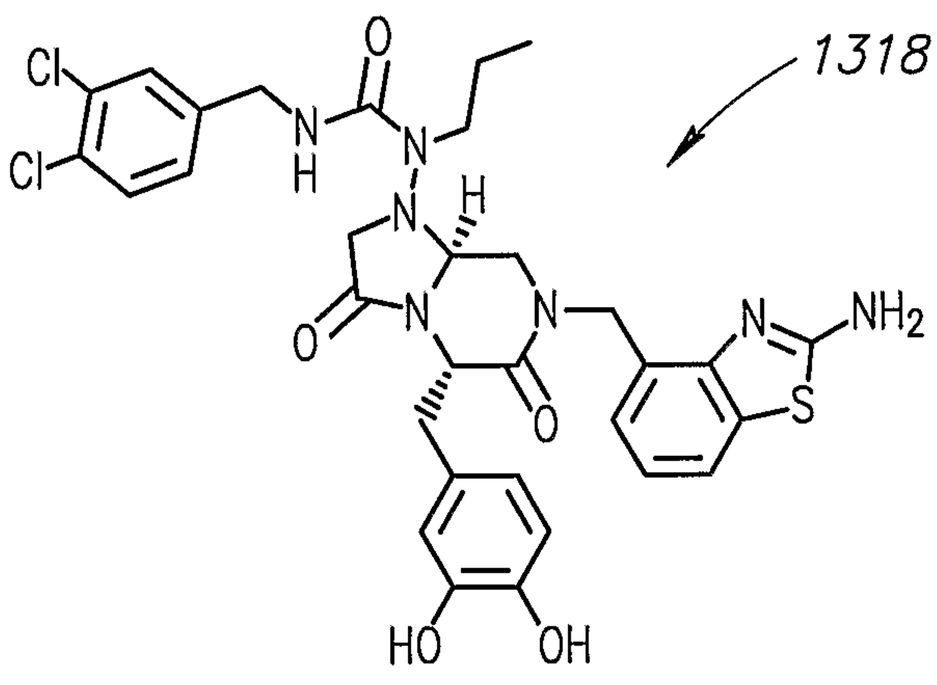
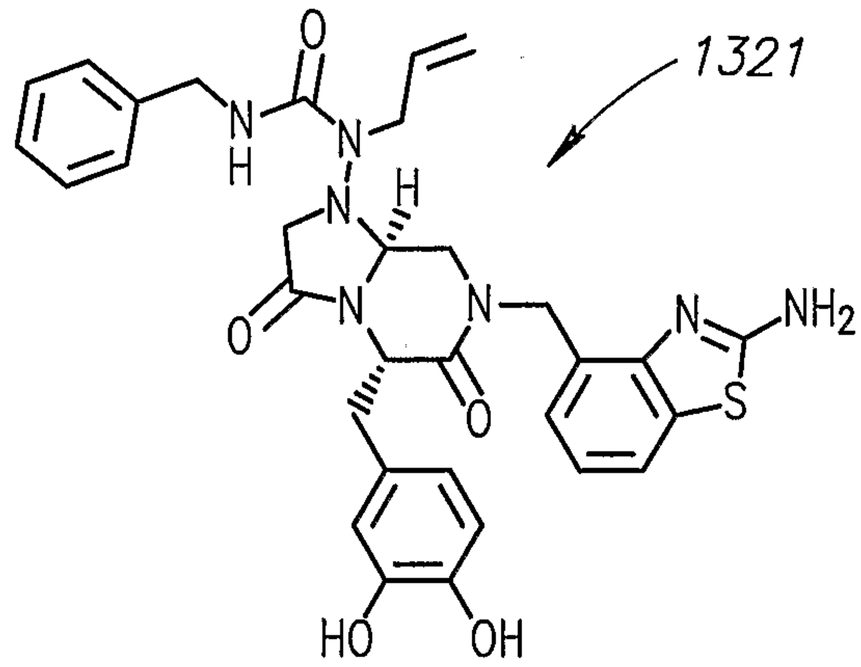


FIG.70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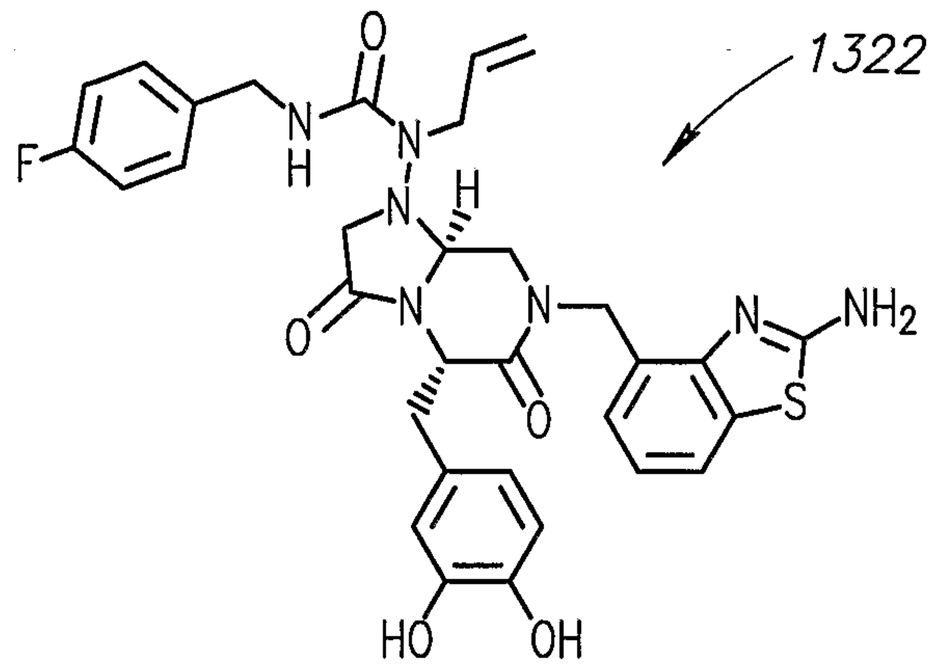
H
O
N
N
O
N
N
S
NH2
HO
OH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NH2
HO
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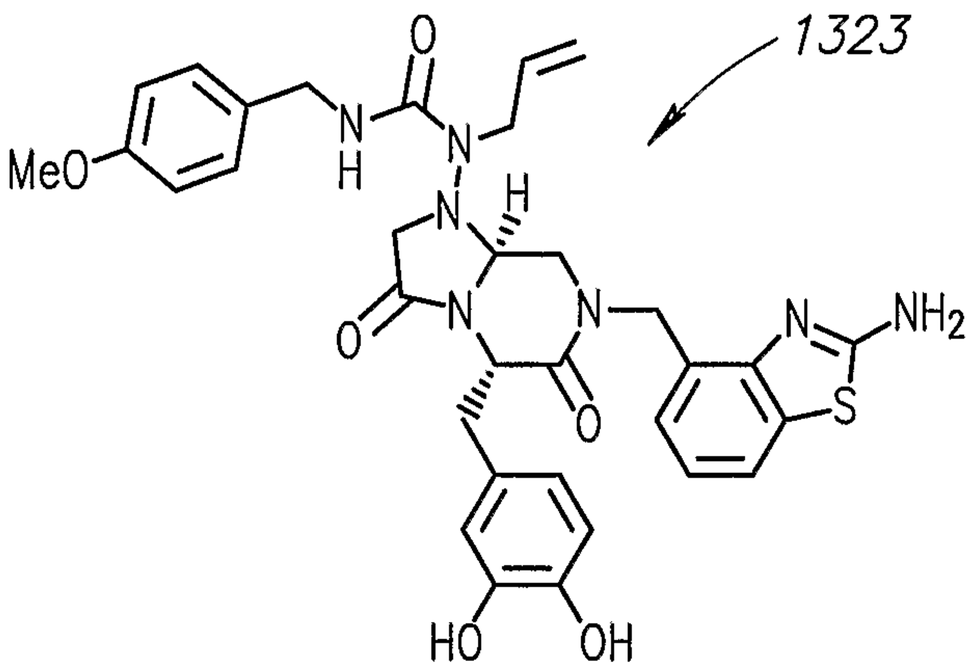
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NH2
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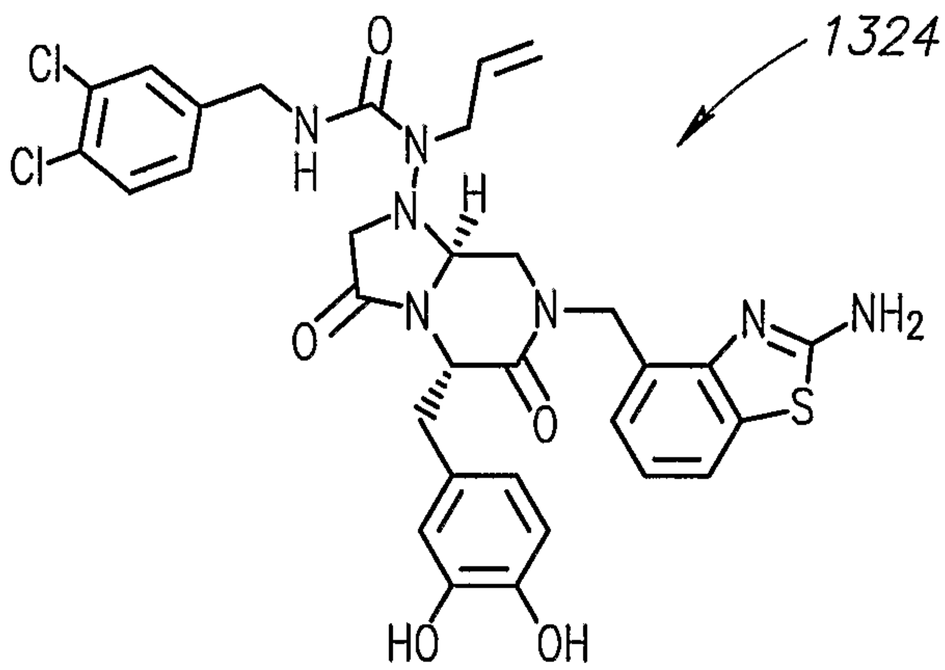
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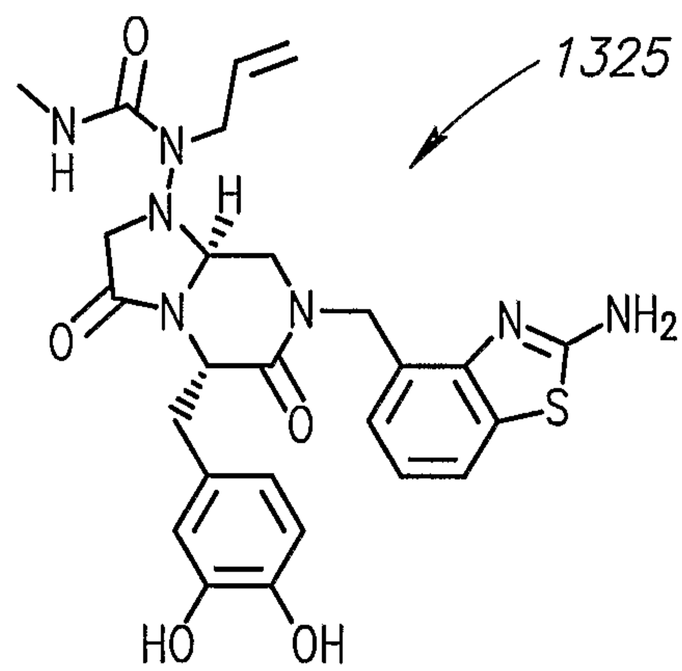
S
NH2
HO
OH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NH2
HO
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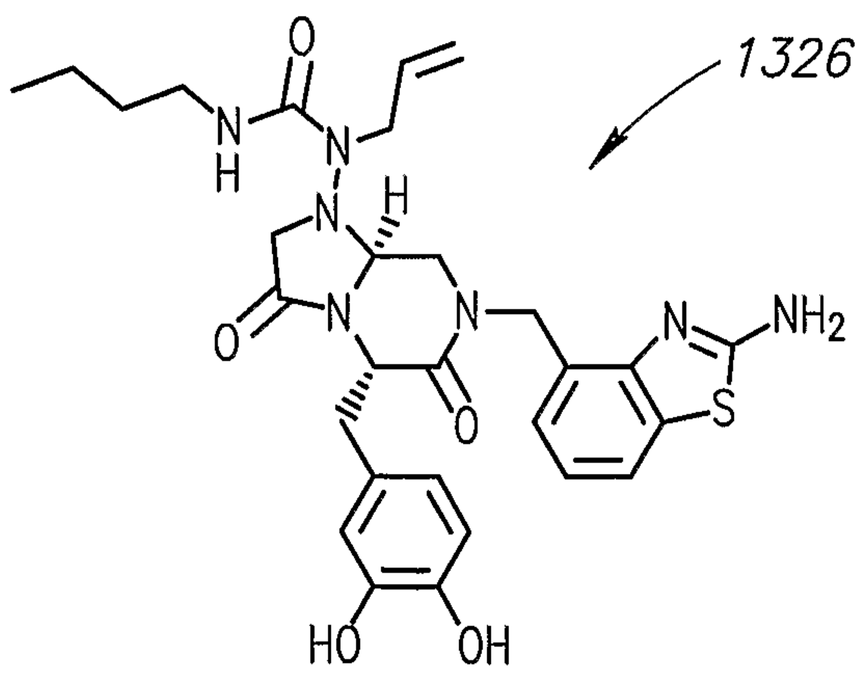
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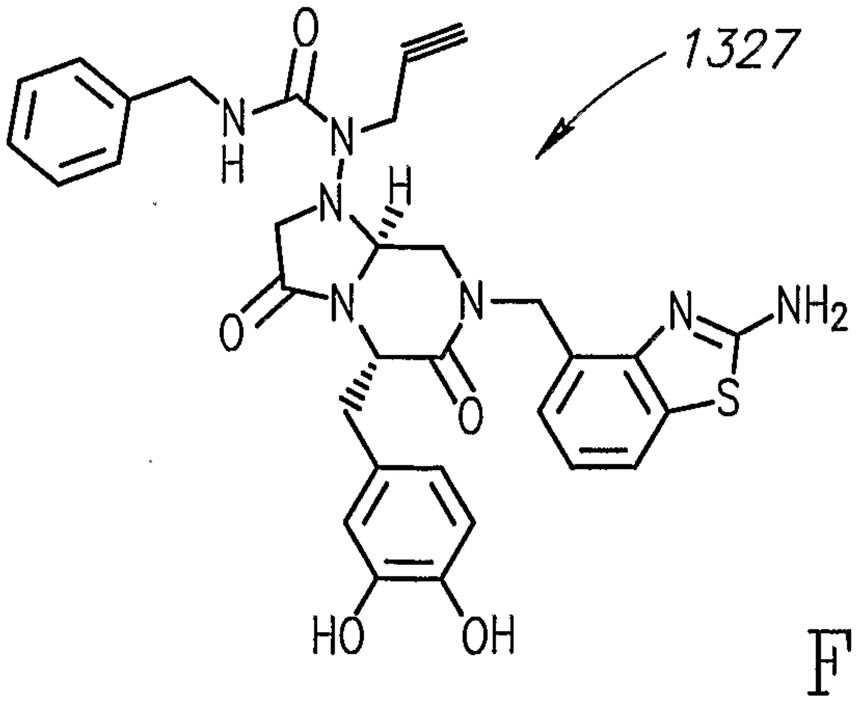
N
N
S
NH2
HO
OH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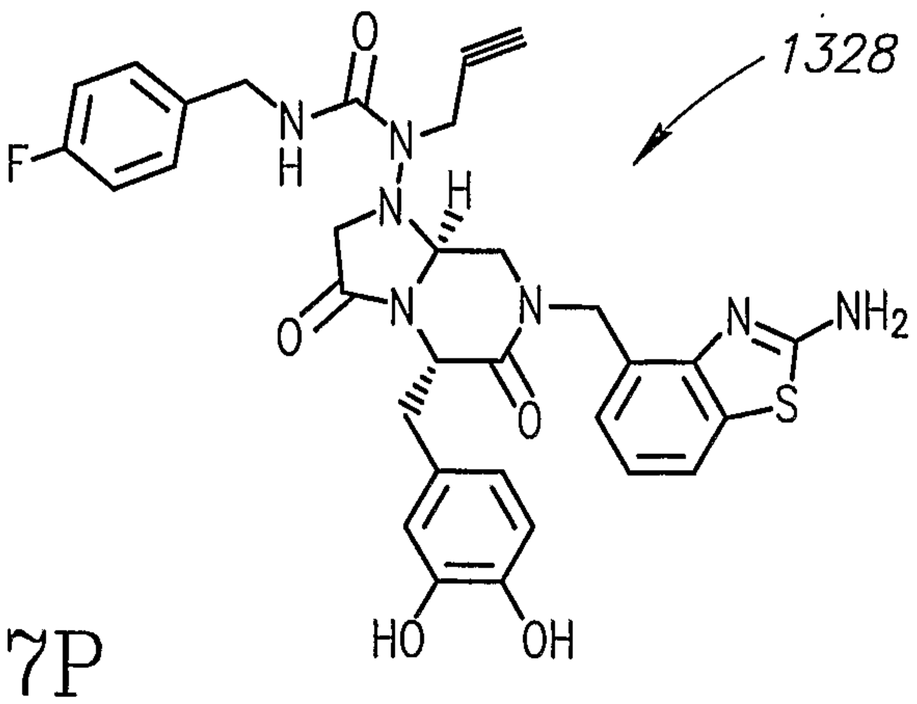
S
NH2
HO
OH


1328
F
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H
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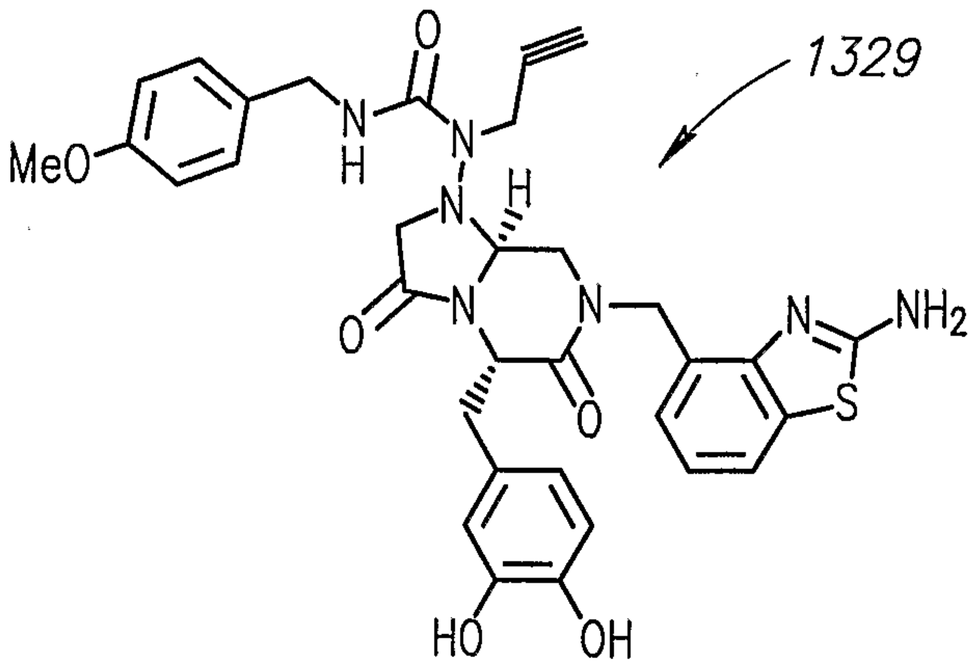
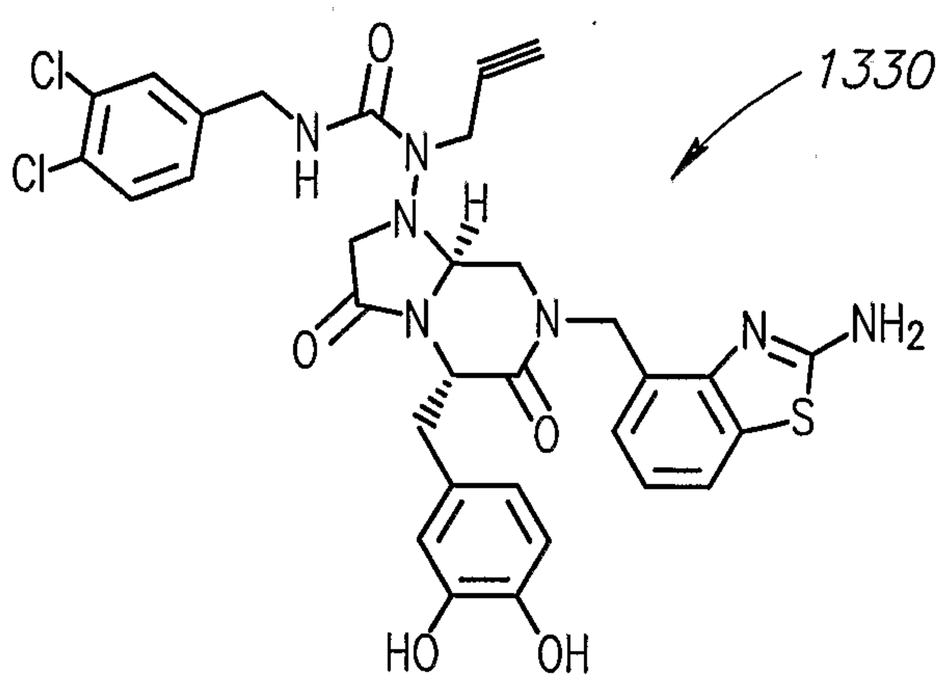
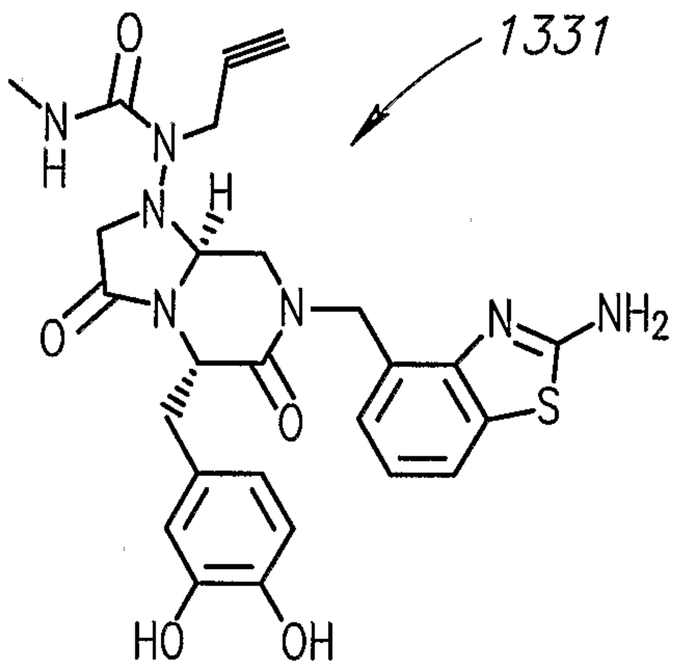
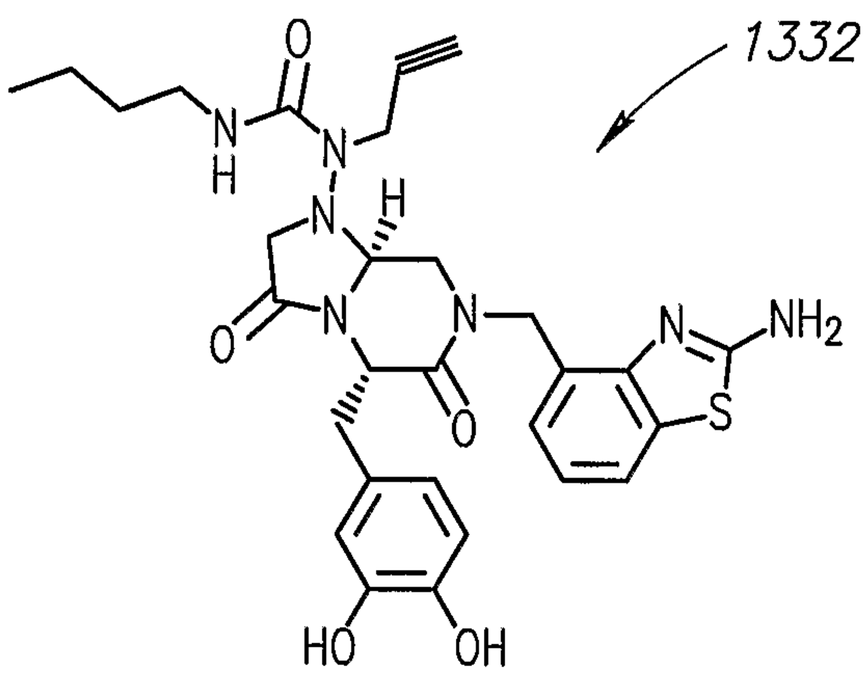
N
H
O
N
N
O
N
N
S
NH2
HO
OH

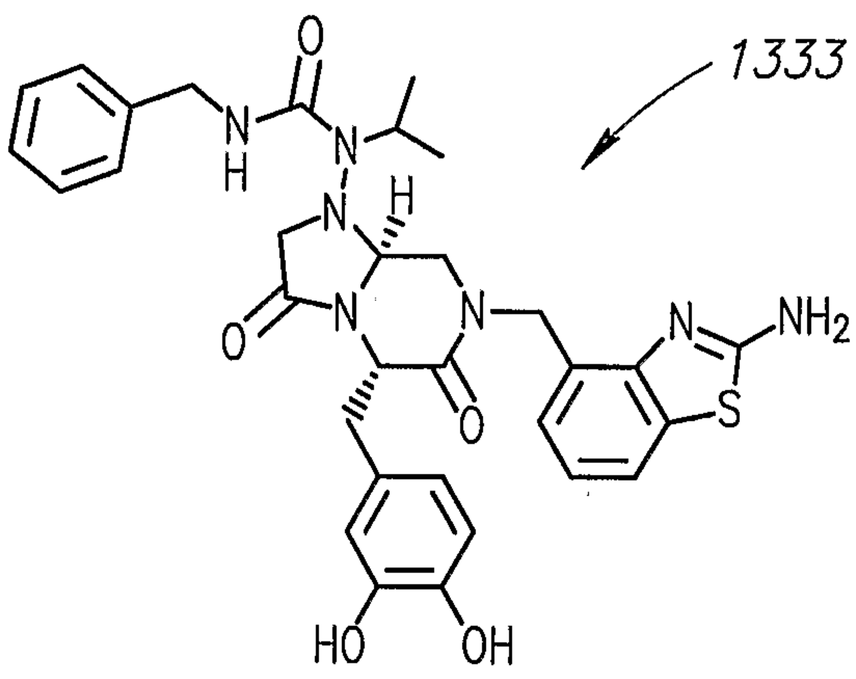
FIG.7P

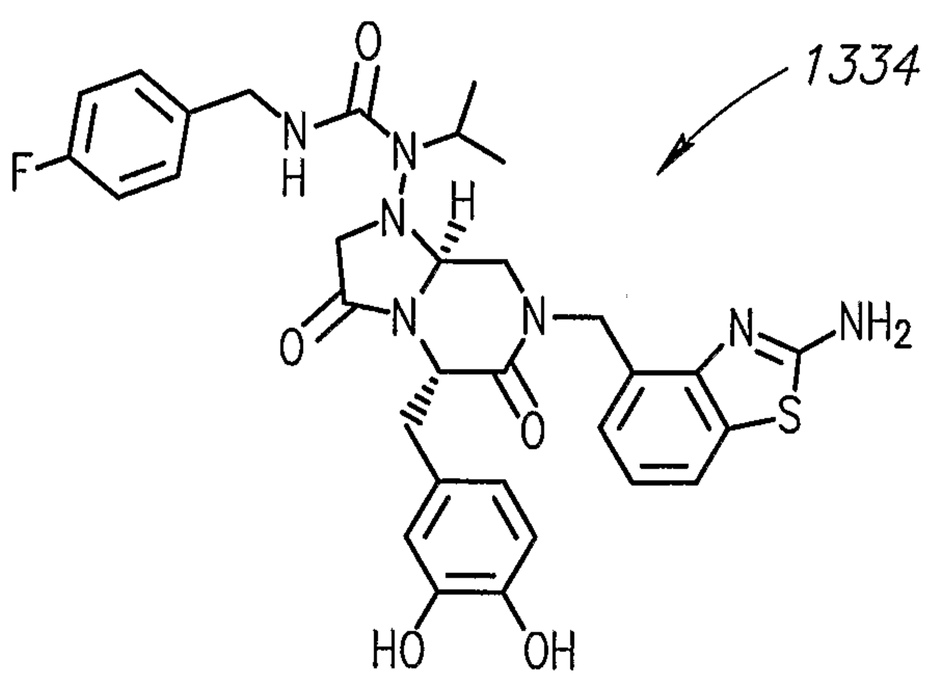

1329
MeO
HO
OH
NH2

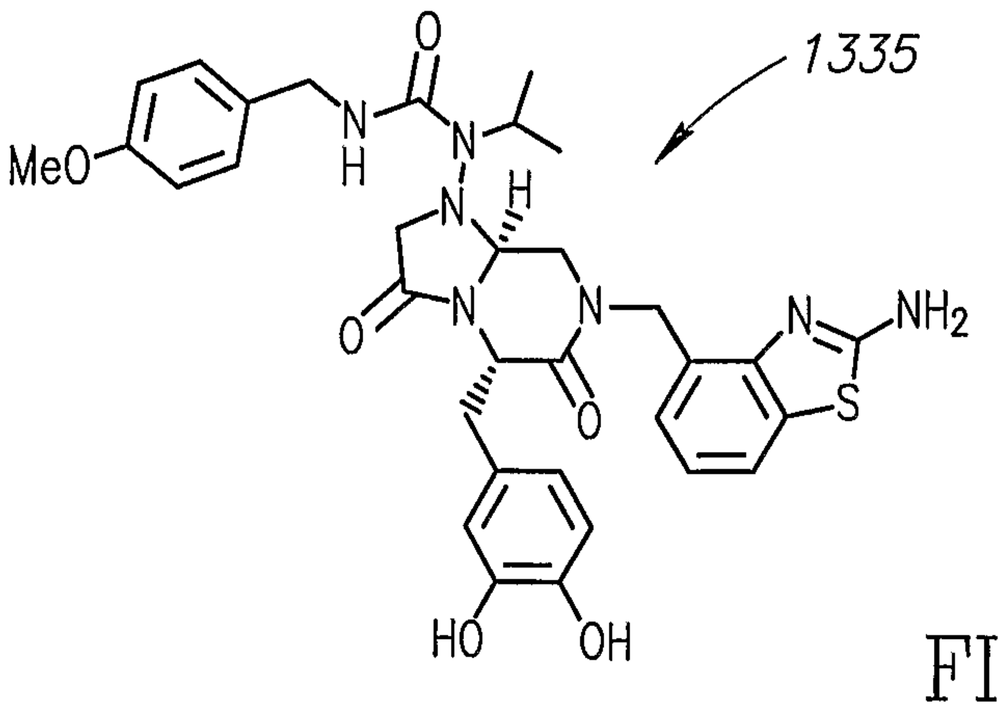

1330
Cl
Cl
HO
OH
NH2


1331
HO
OH
NH2


1332
HO
OH
NH2


1333
HO
OH
NH2


1334
F
HO
OH
NH2


1335
MeO
HO
OH
NH2

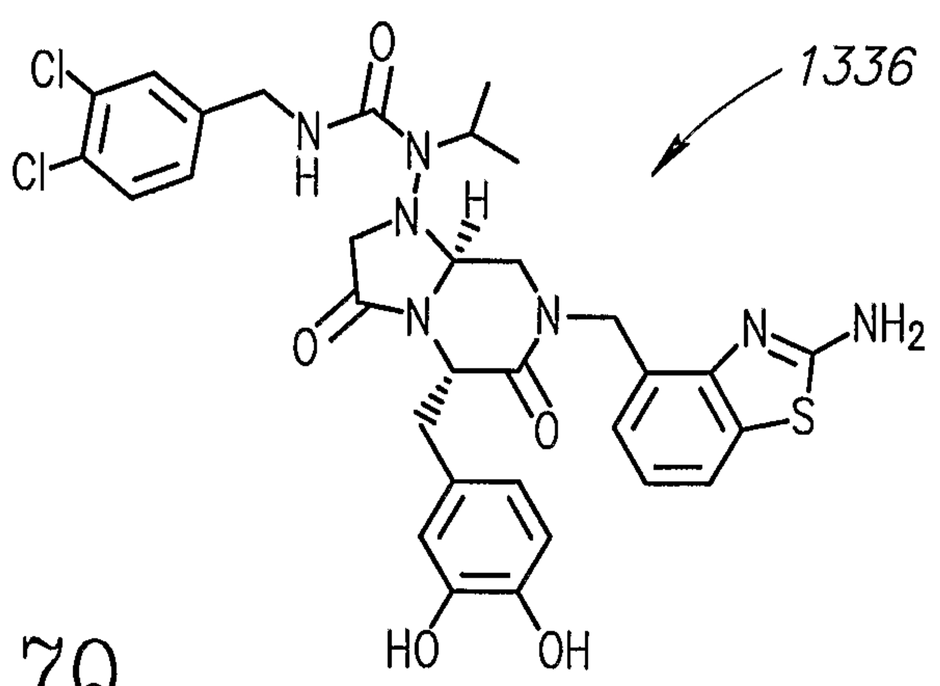
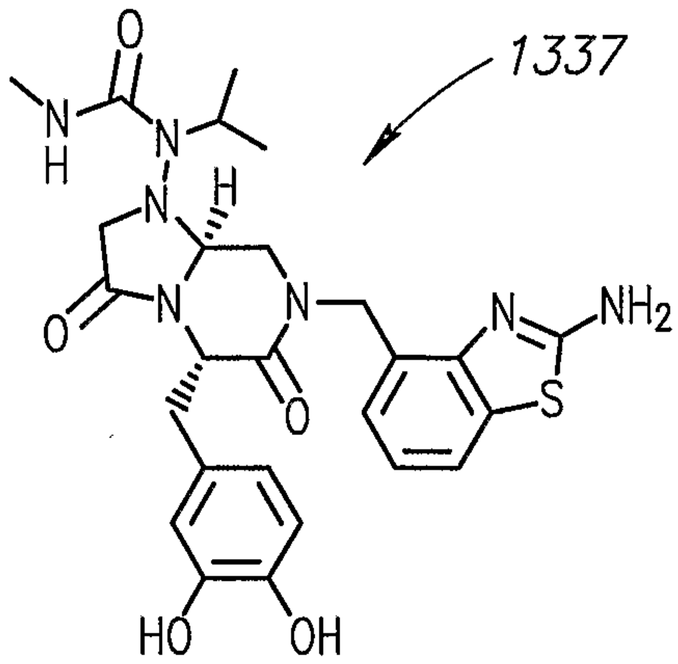
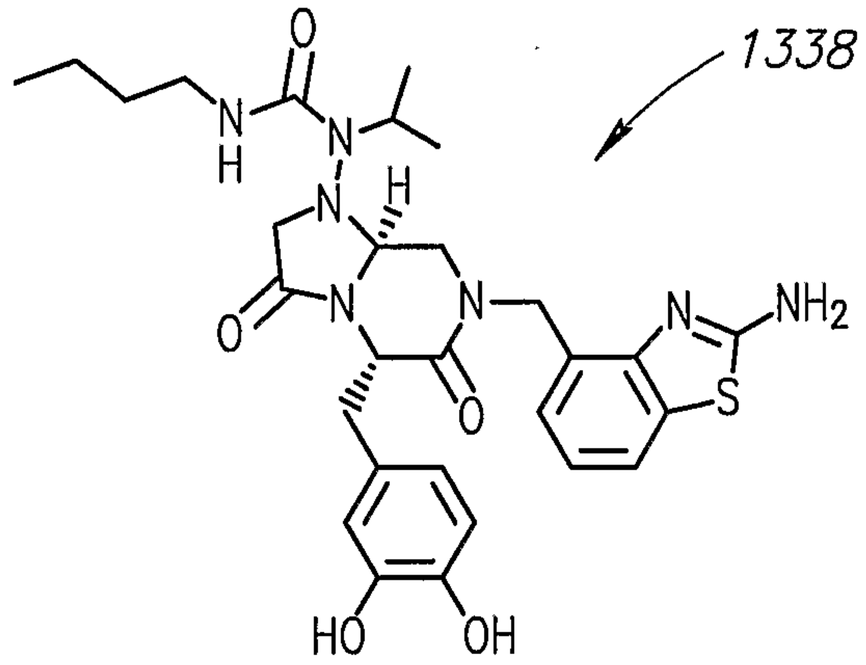
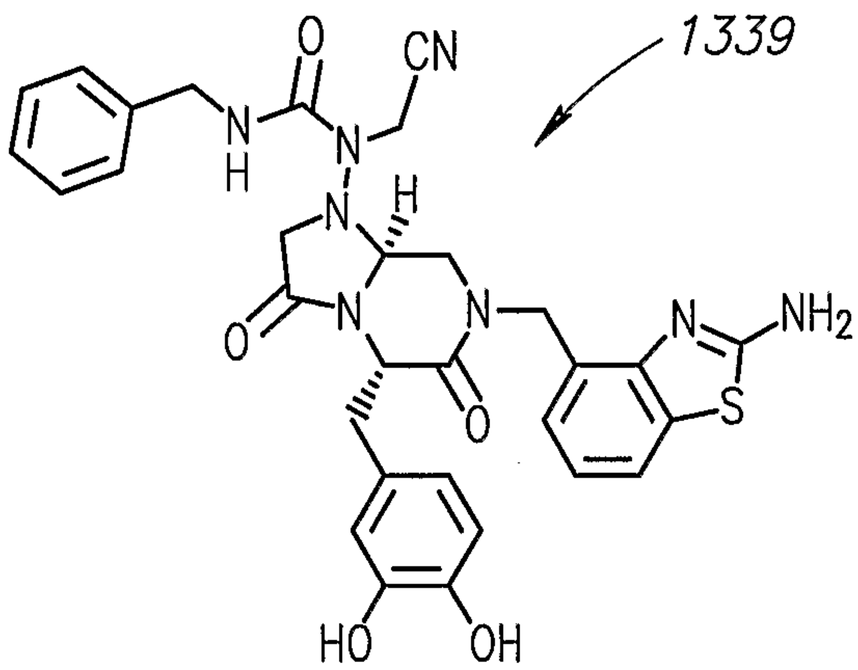
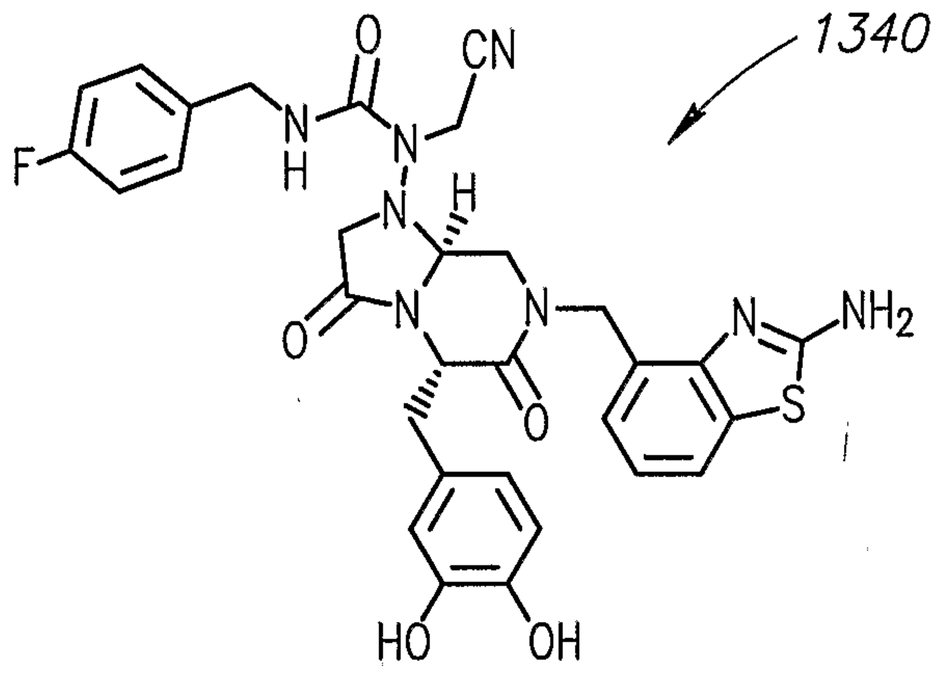

1336
Cl
Cl
HO
OH
NH2

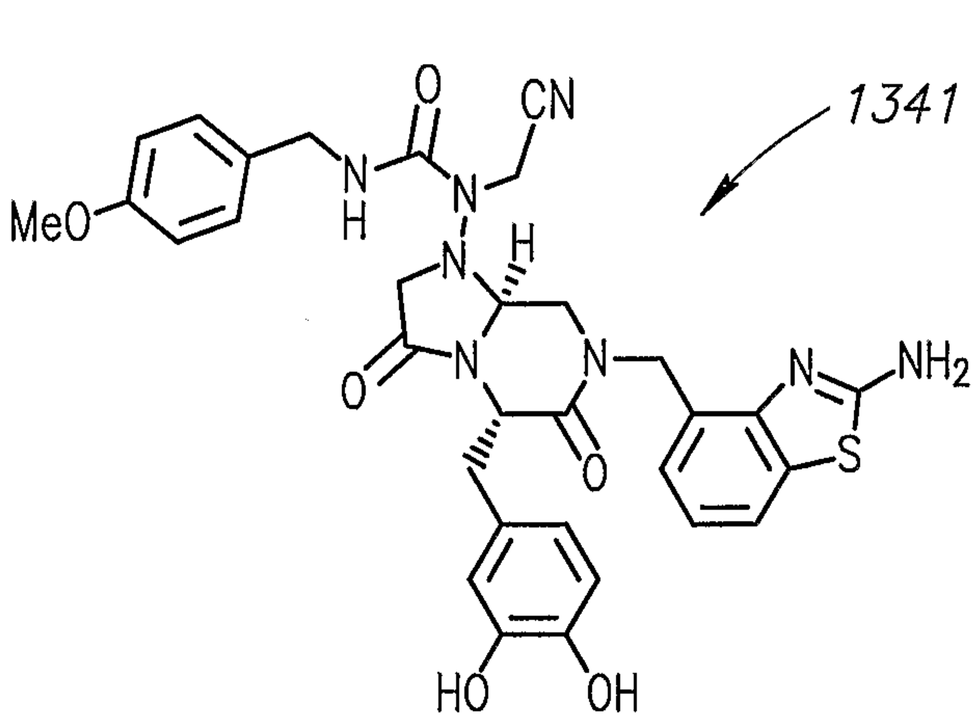
FIG.7Q

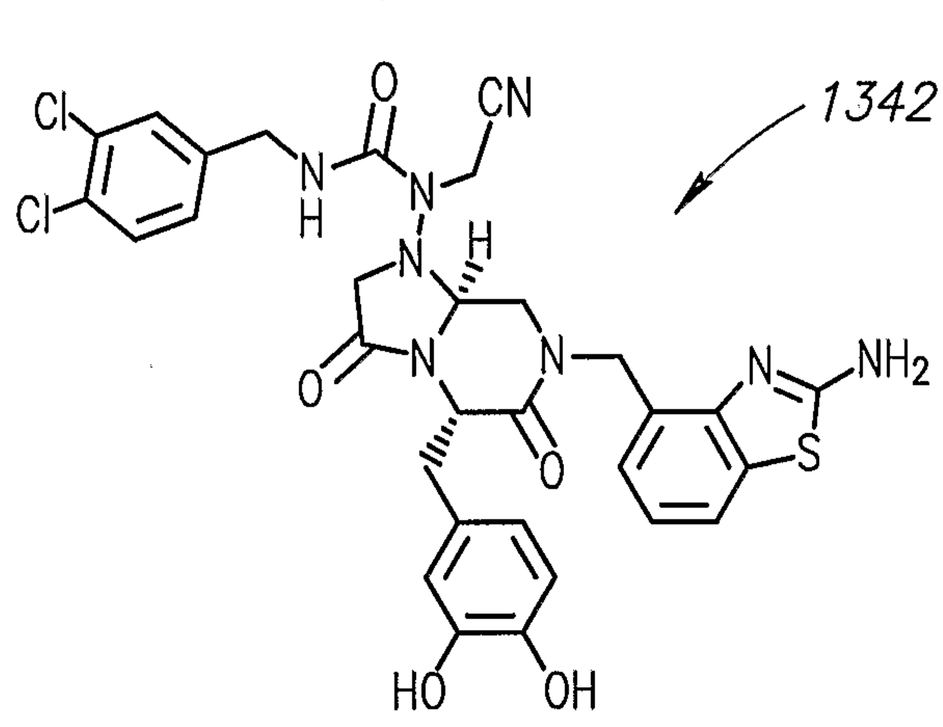


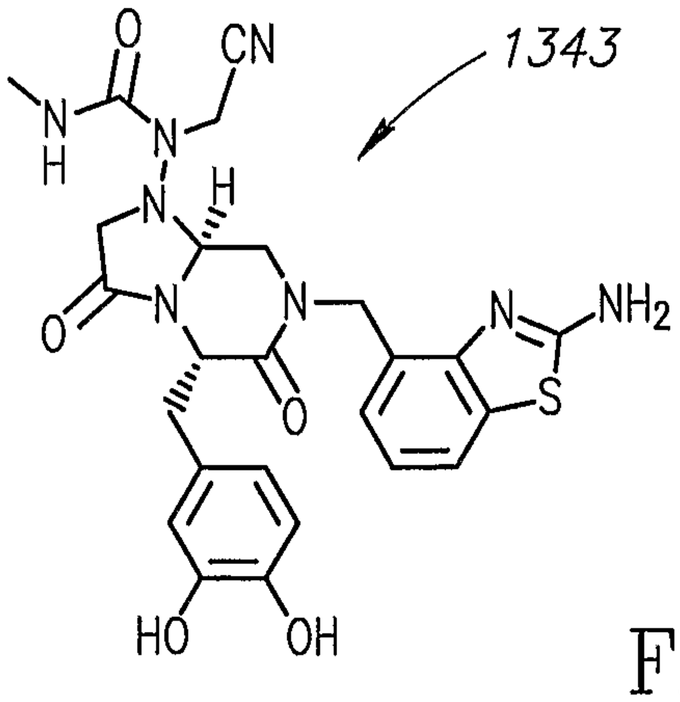












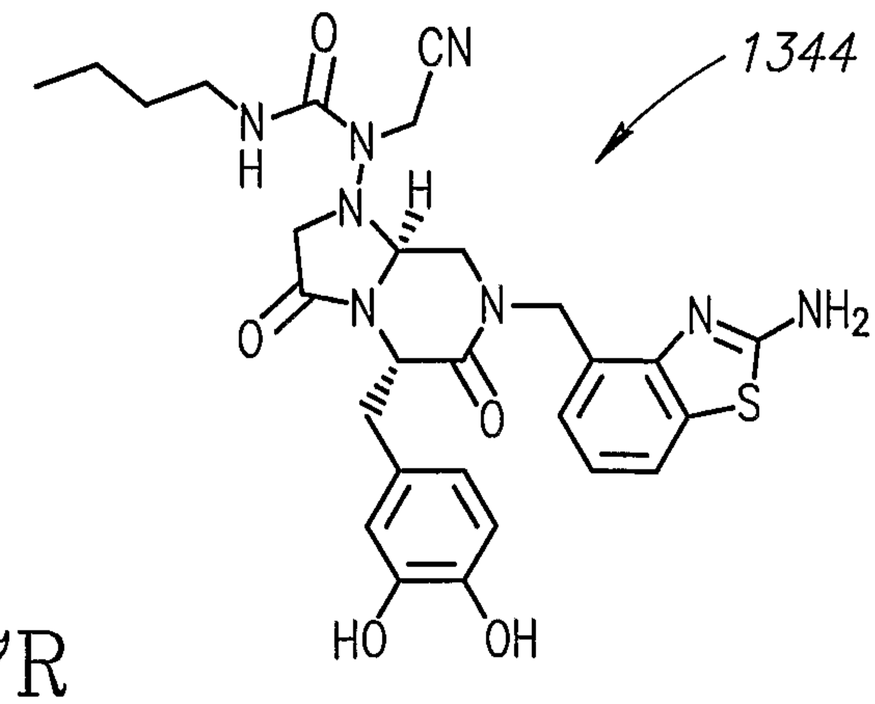
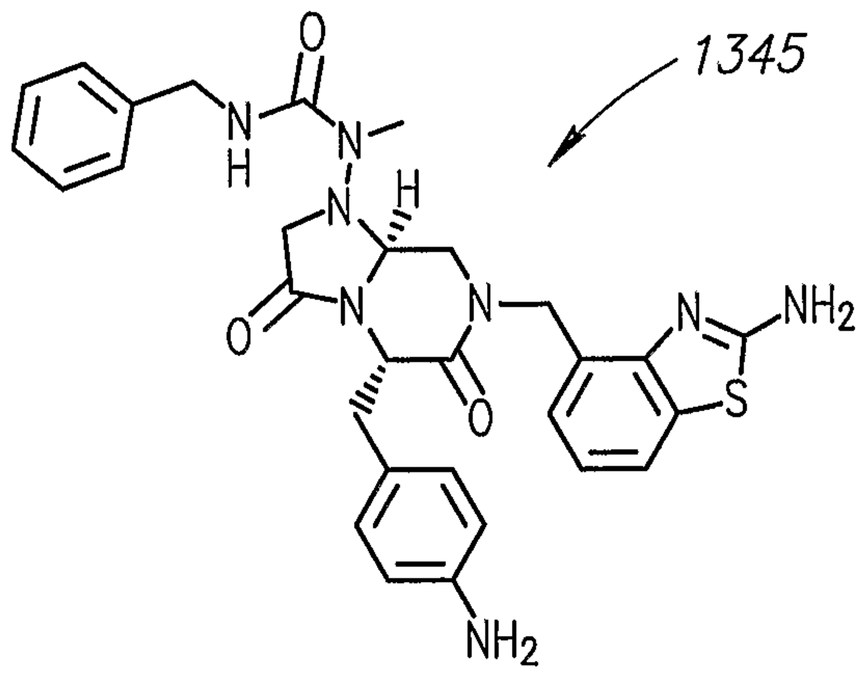
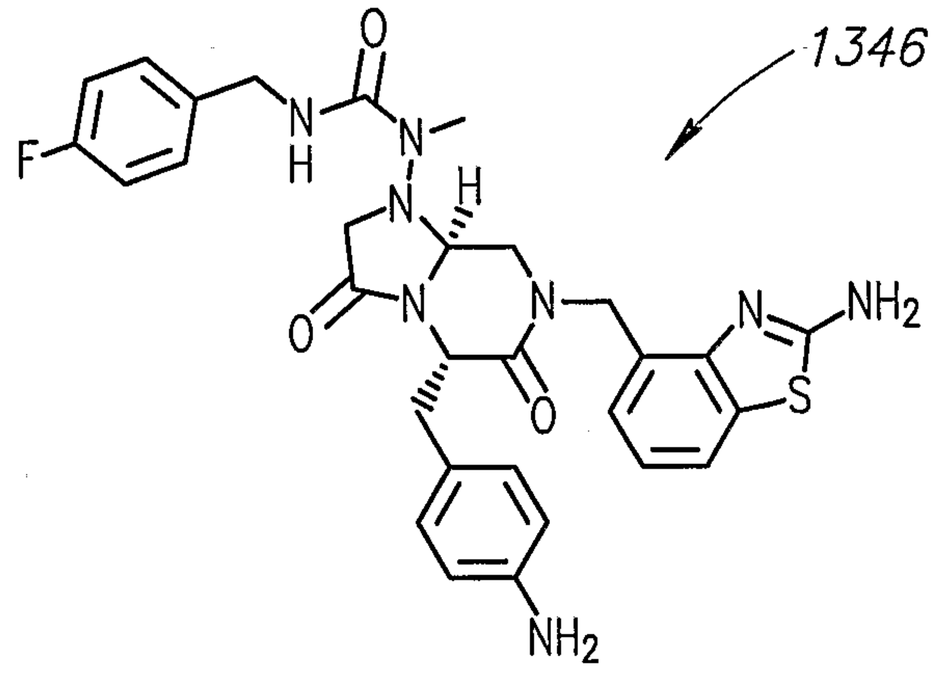
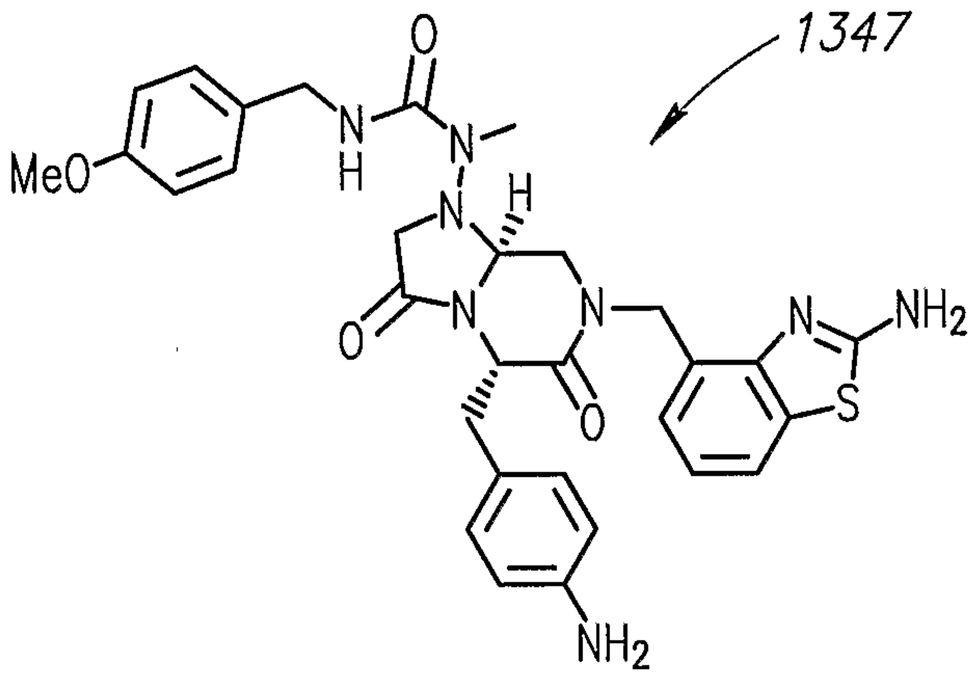
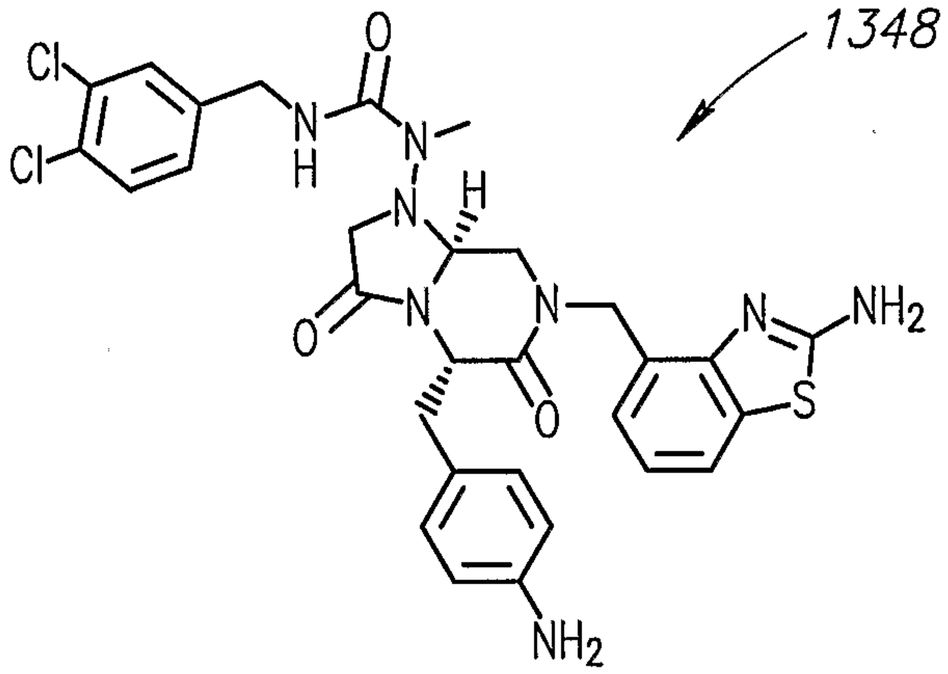


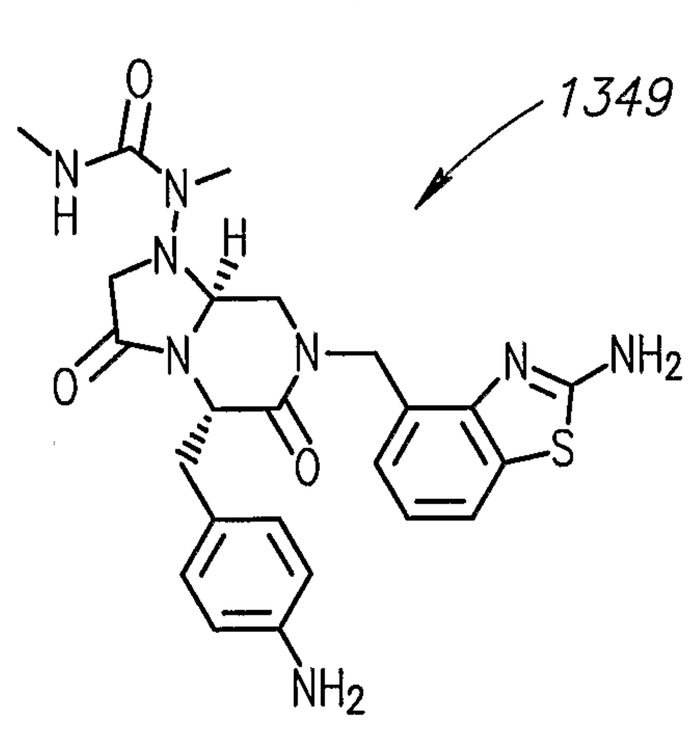
FIG.7R

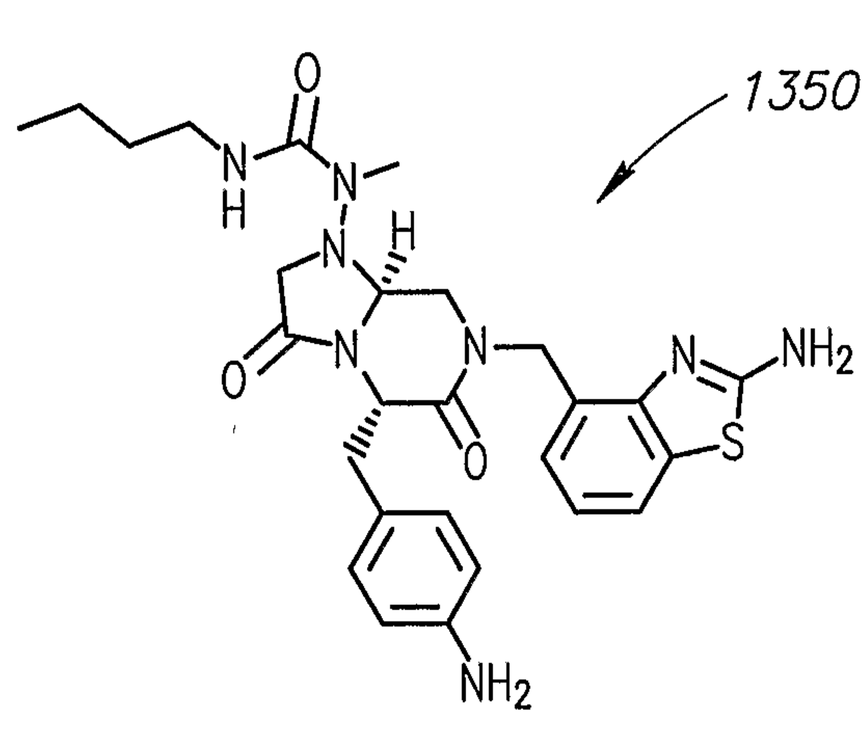


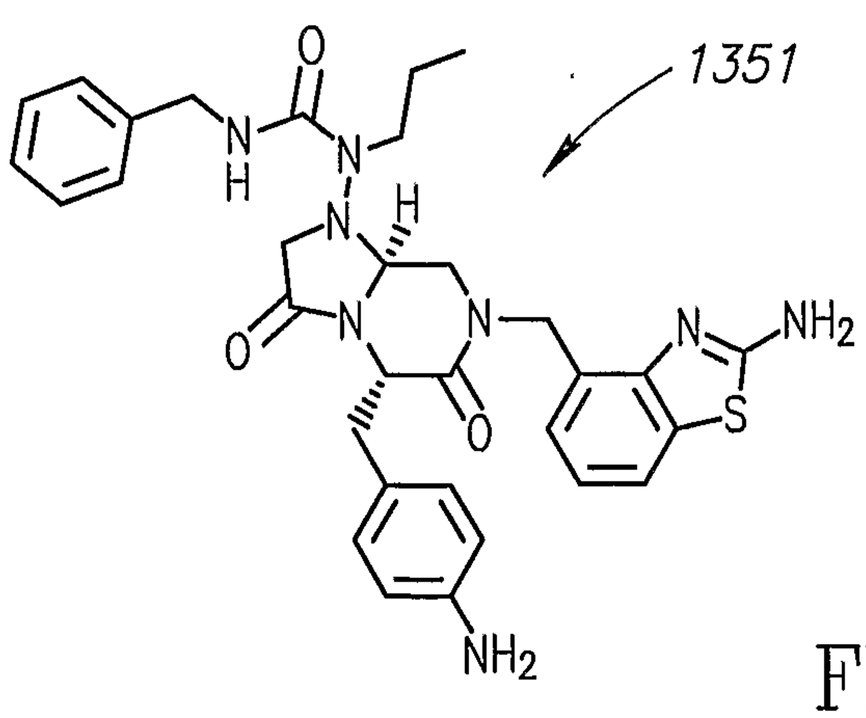












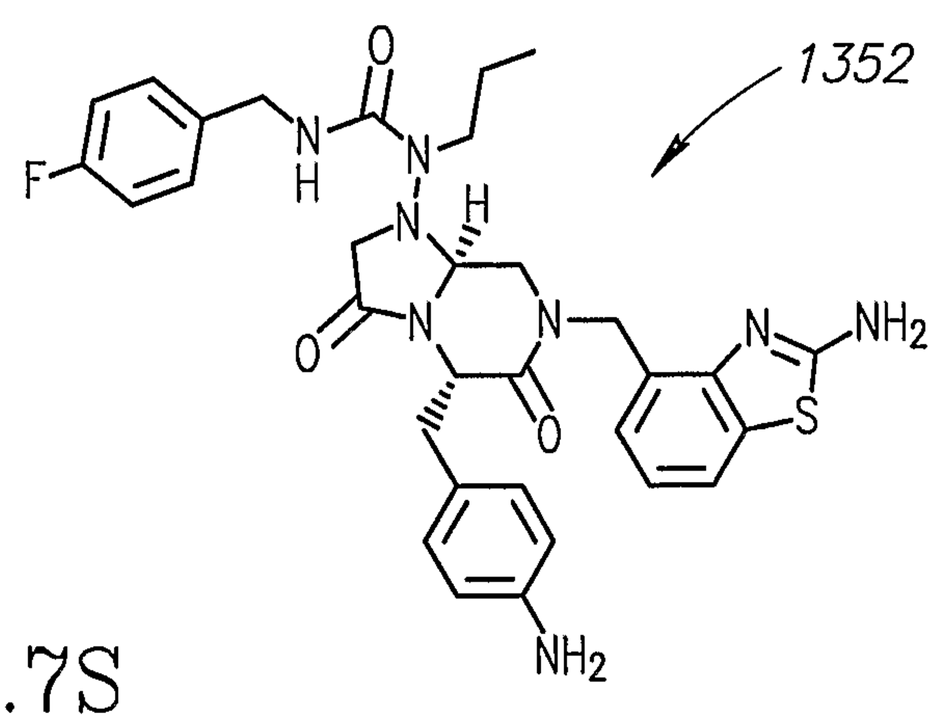
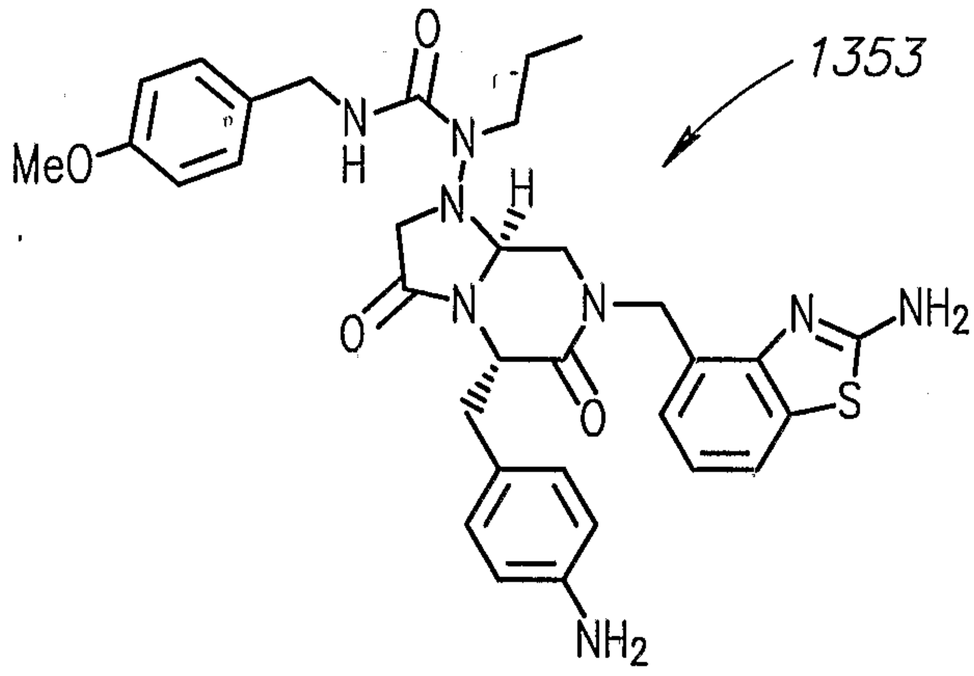
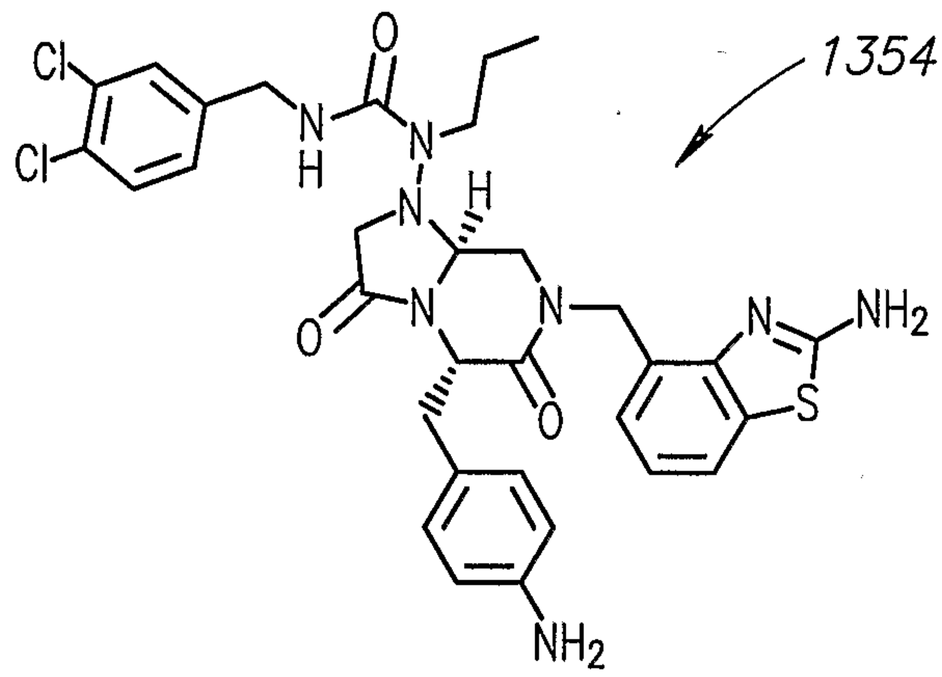
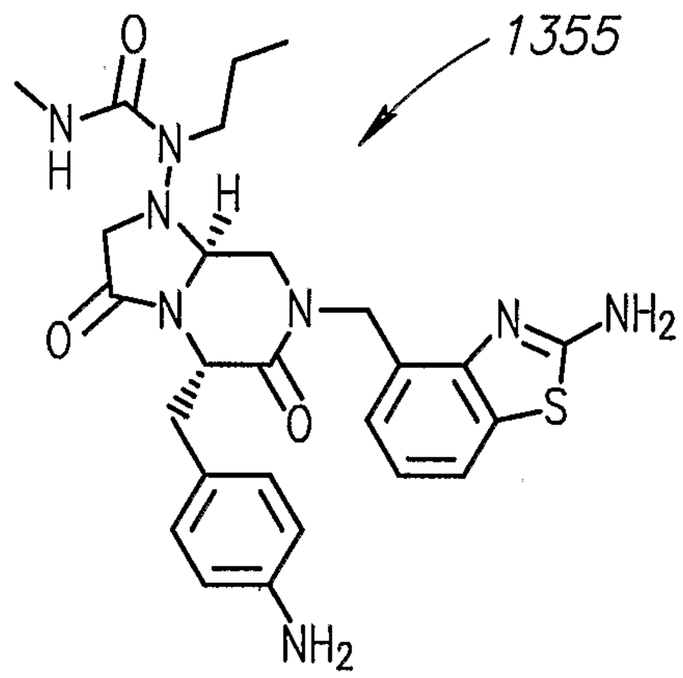
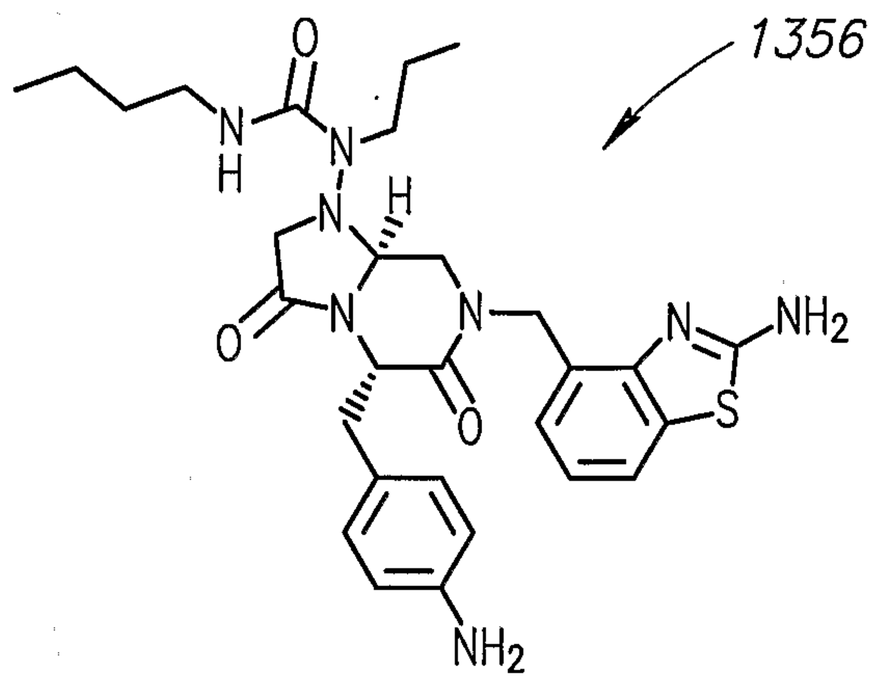


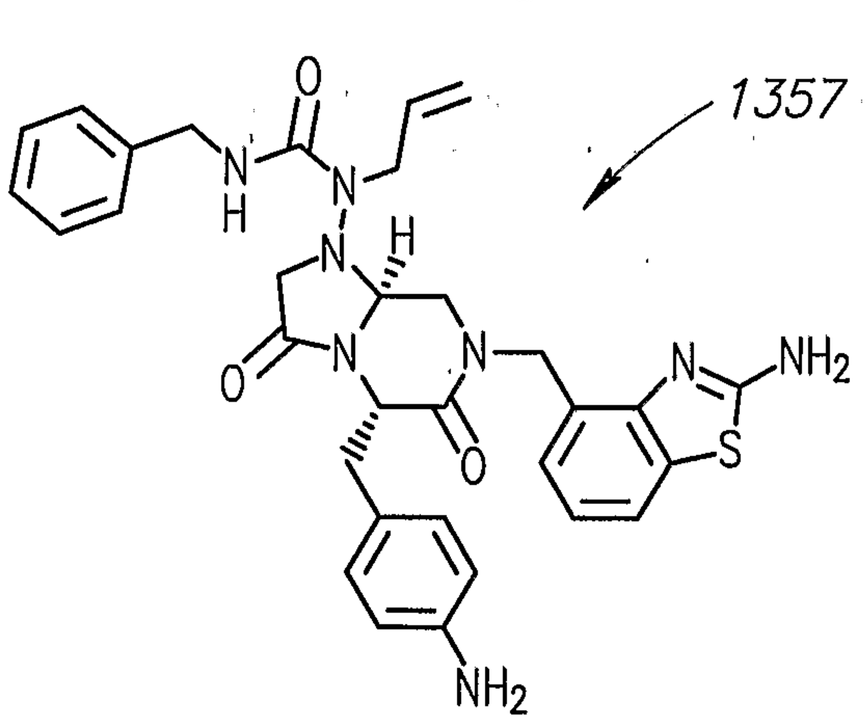
FIG.7S

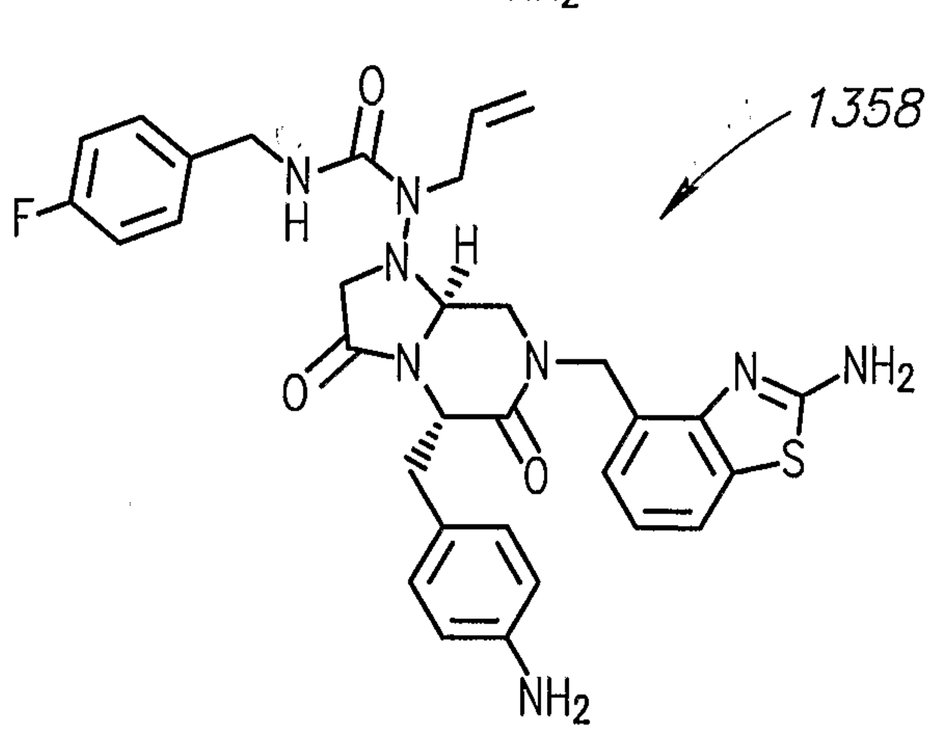

1353
MeO
NH2

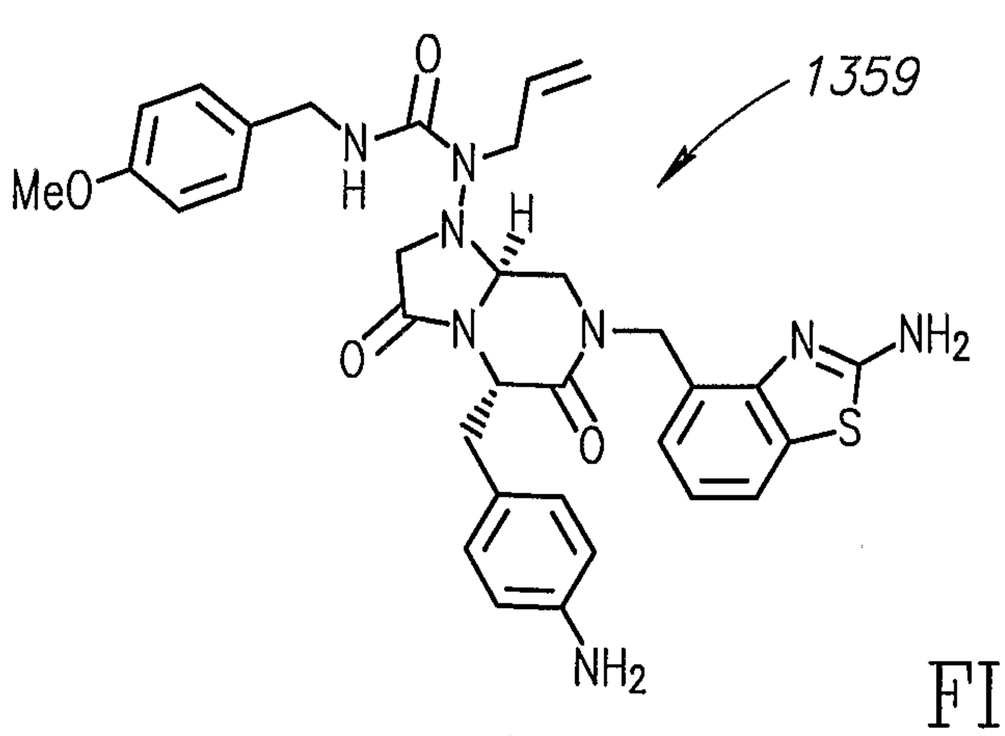

1354
Cl
Cl
NH2


1355
NH2


1356
NH2


1357
NH2


1358
F
NH2


1359
MeO
NH2

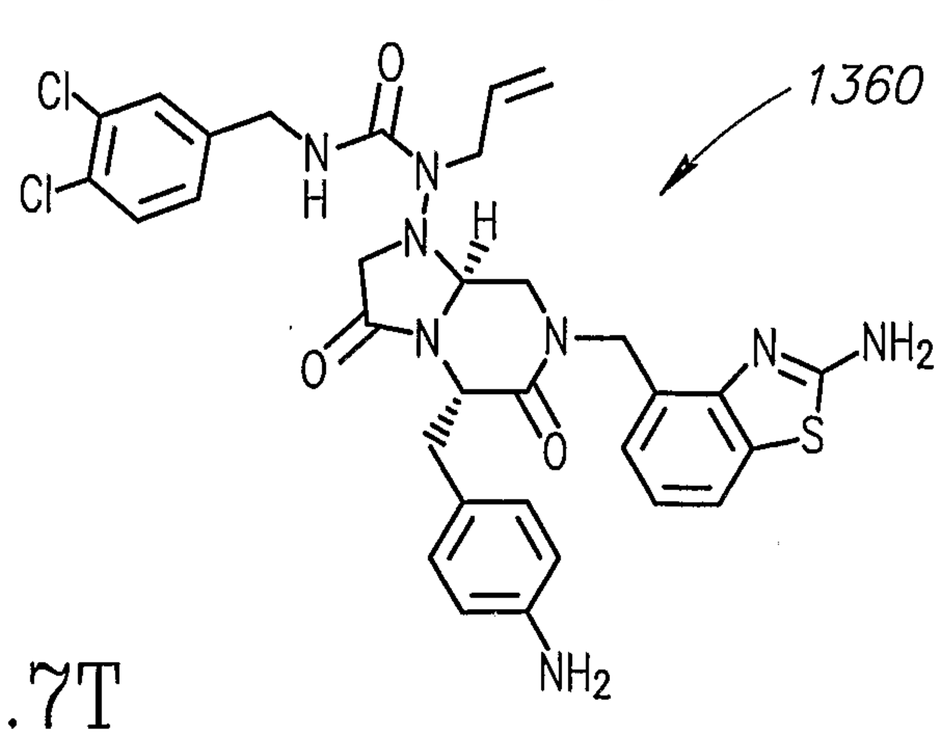
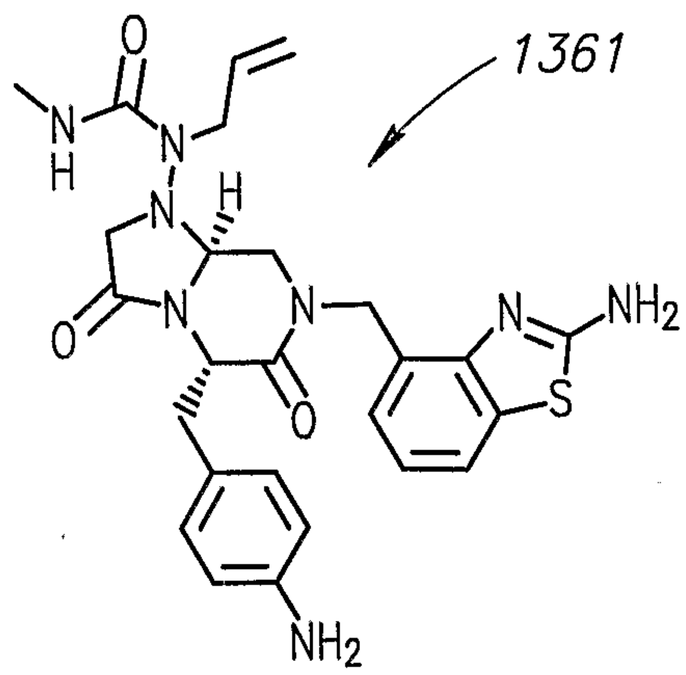
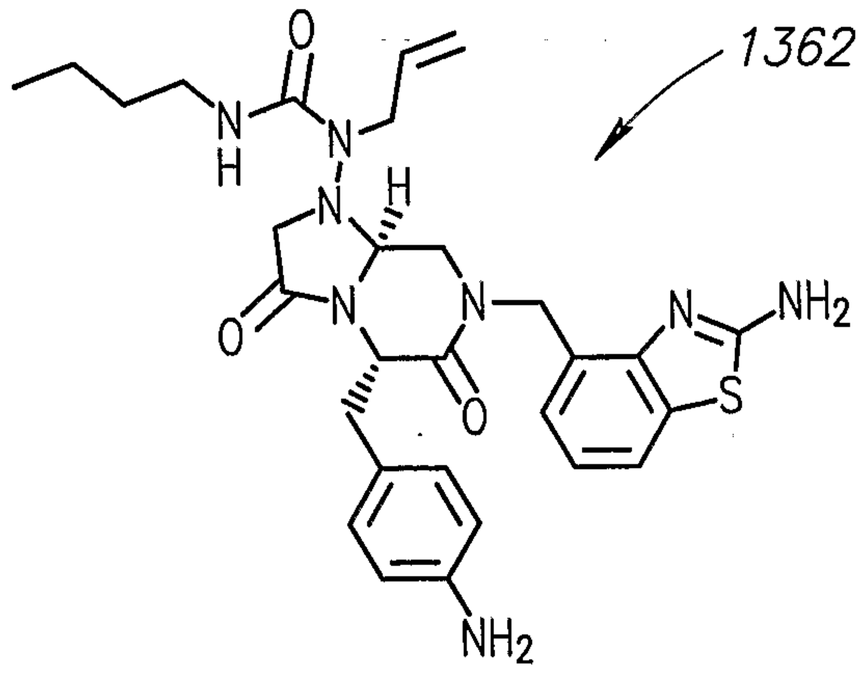
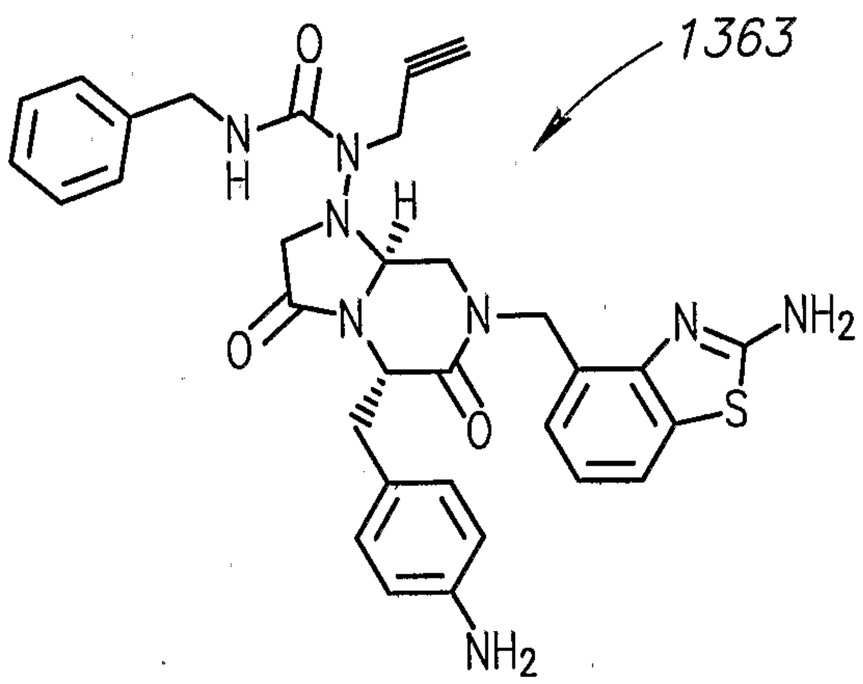
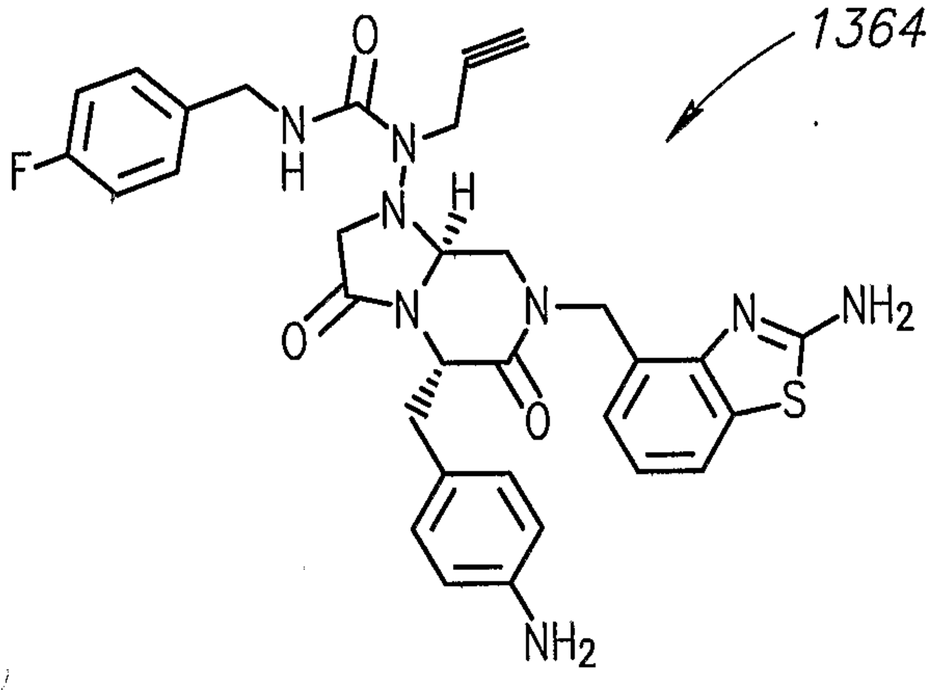

1360
Cl
Cl
NH2

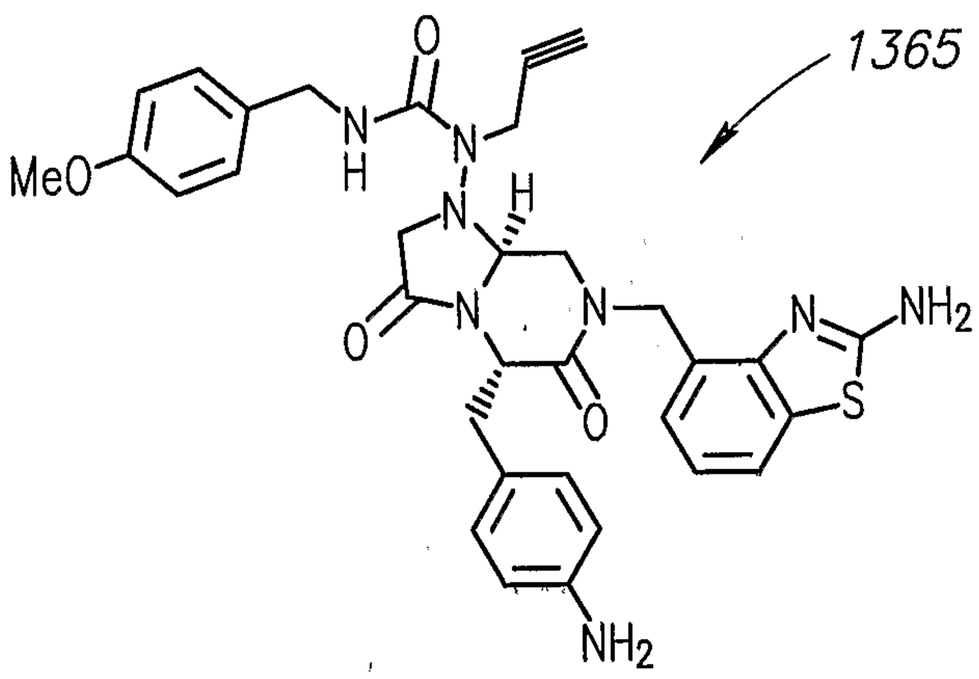
FIG.7T

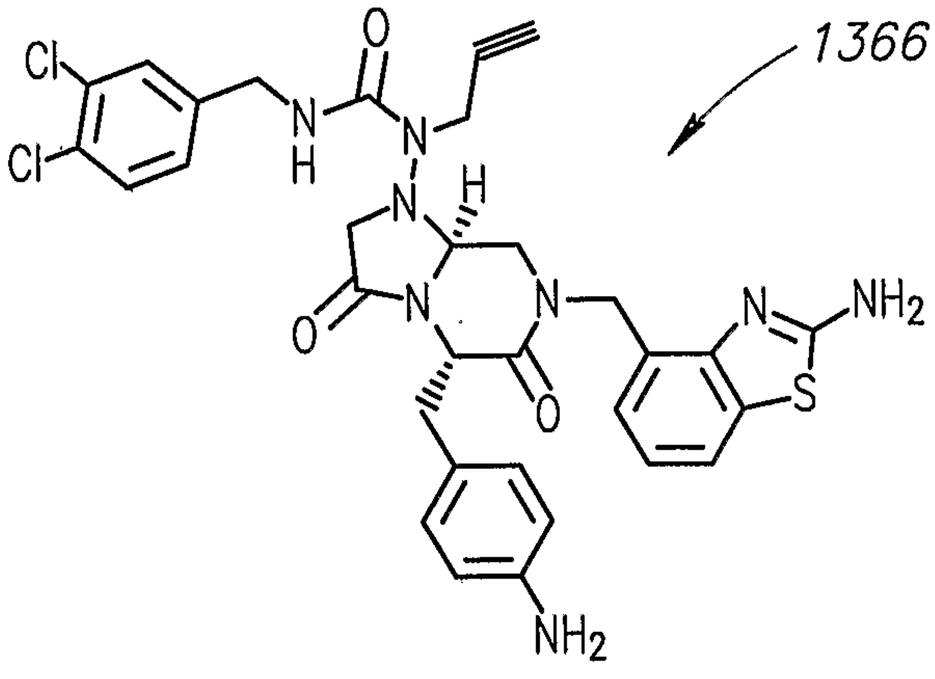


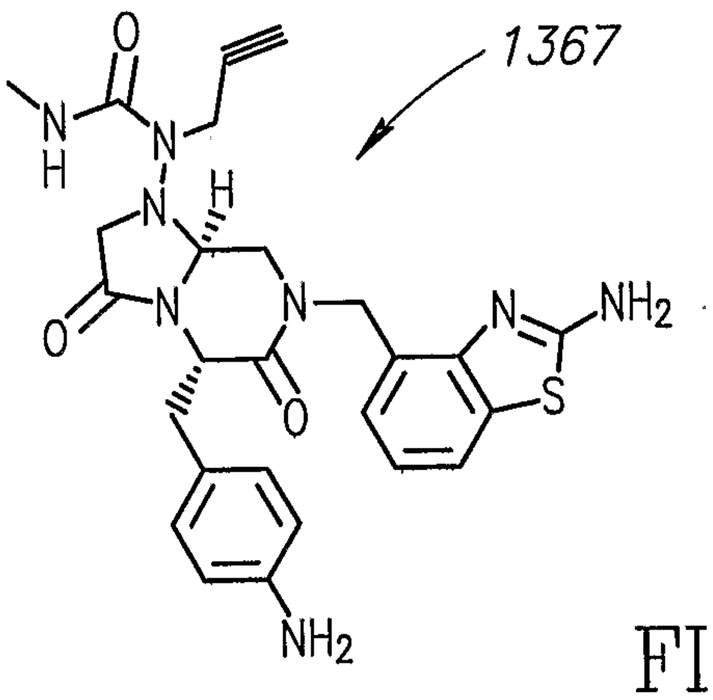












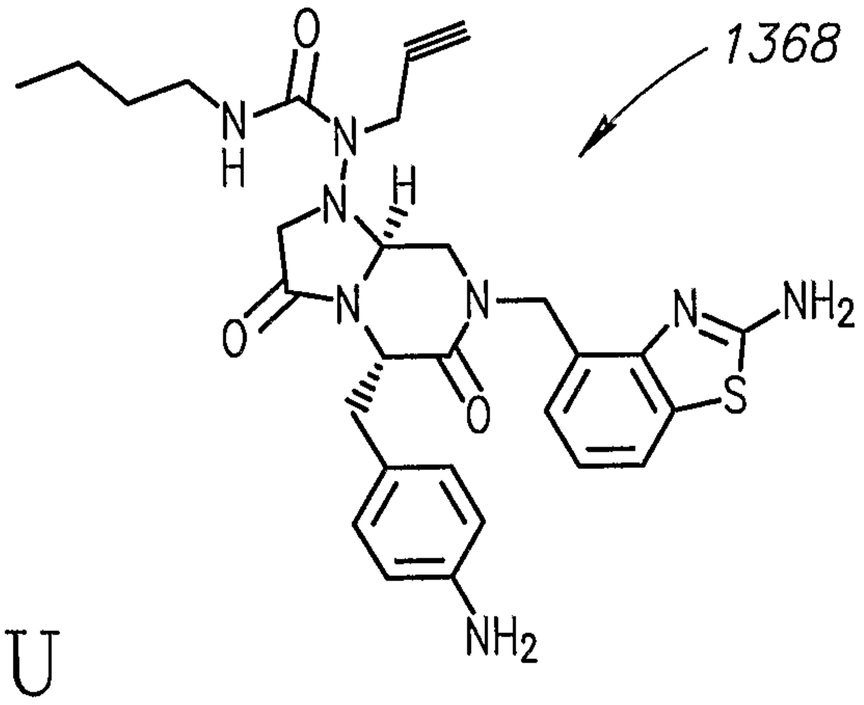
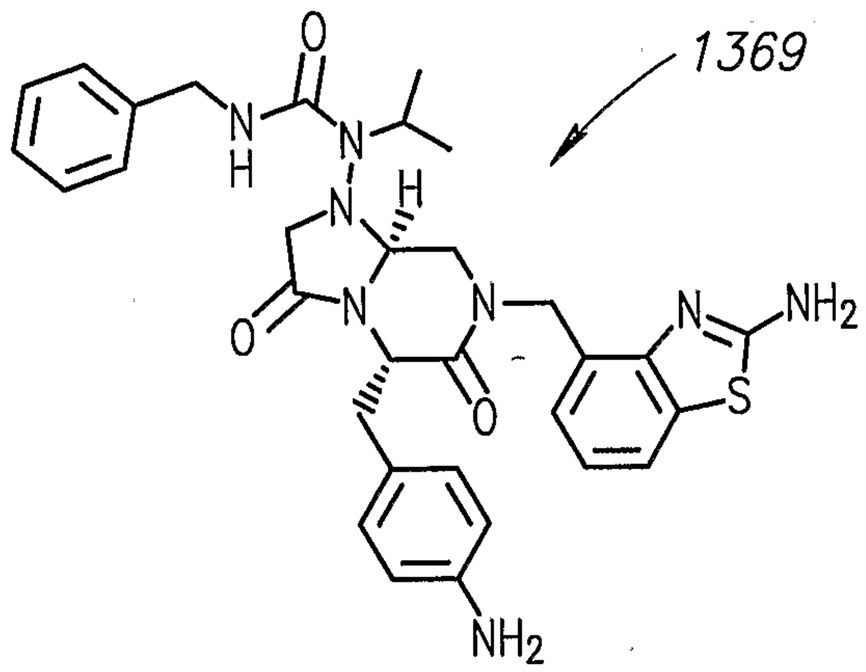
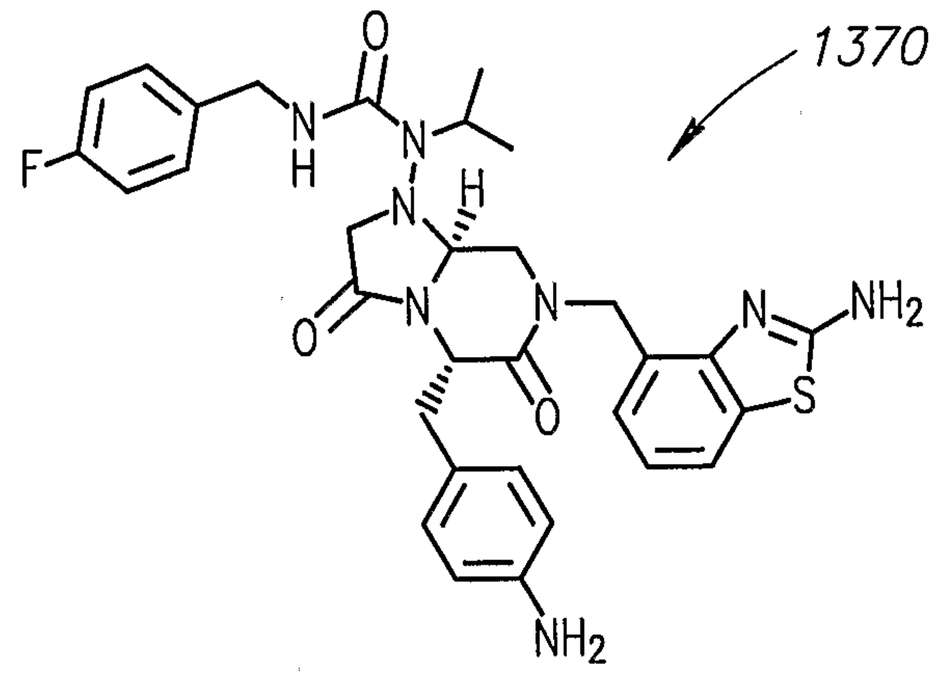
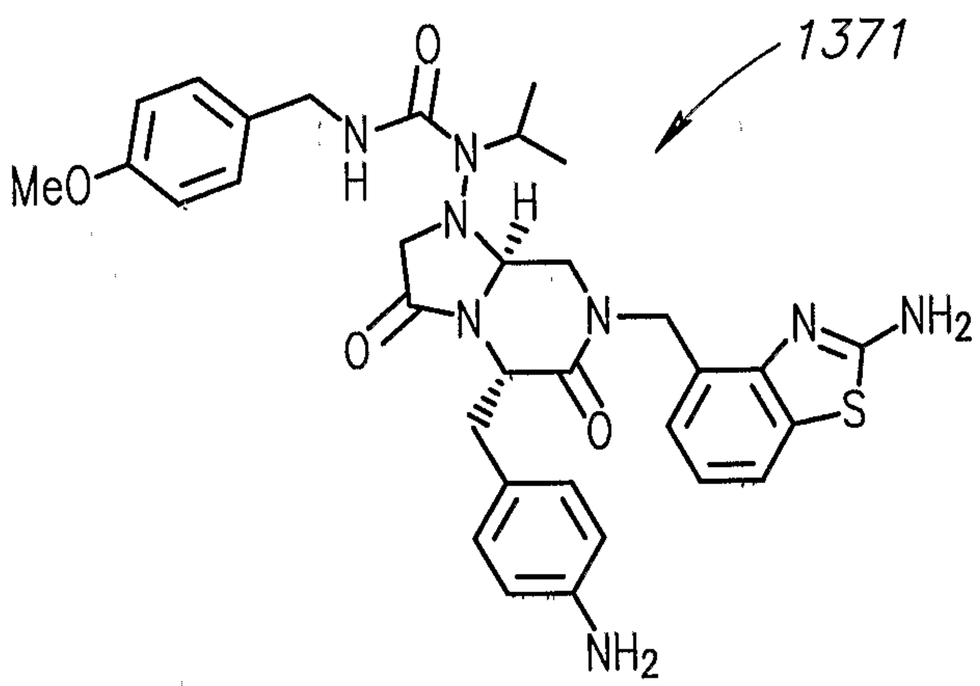
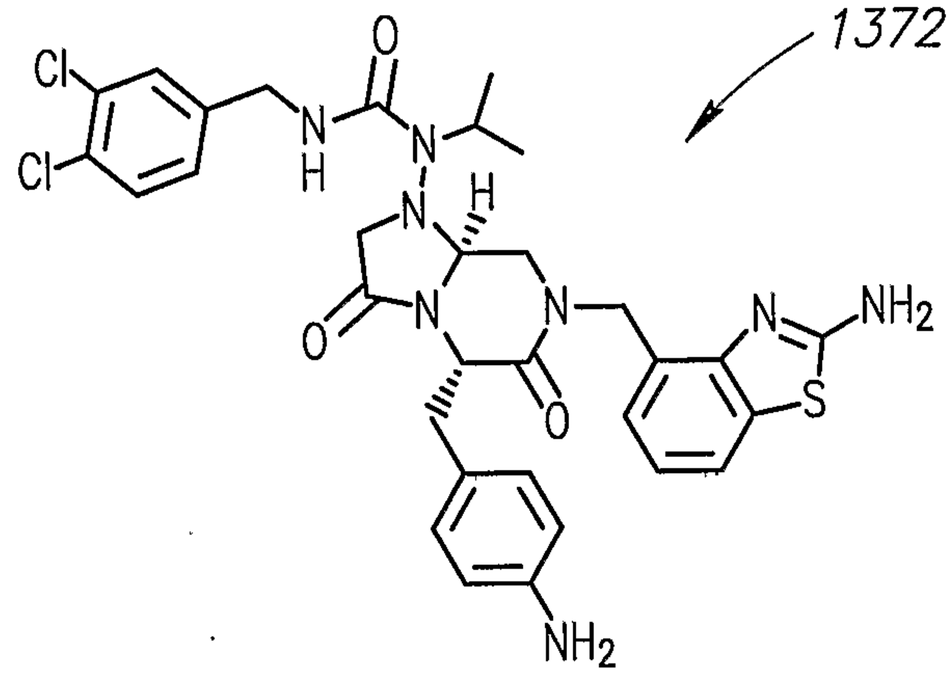


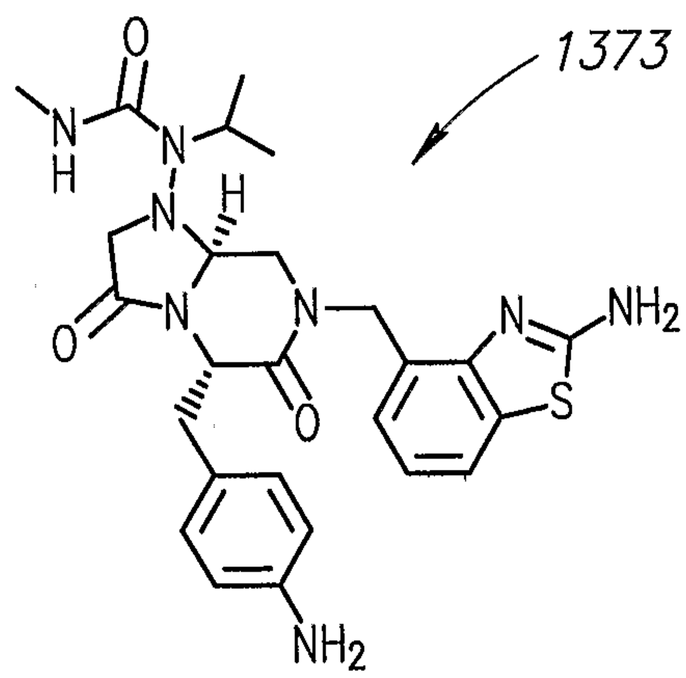
FIG.7U

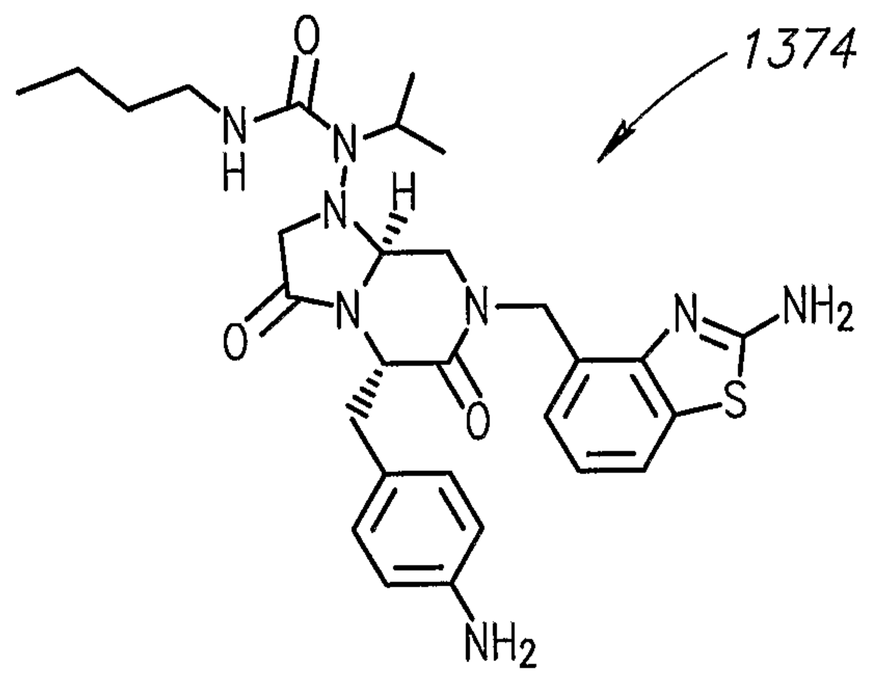


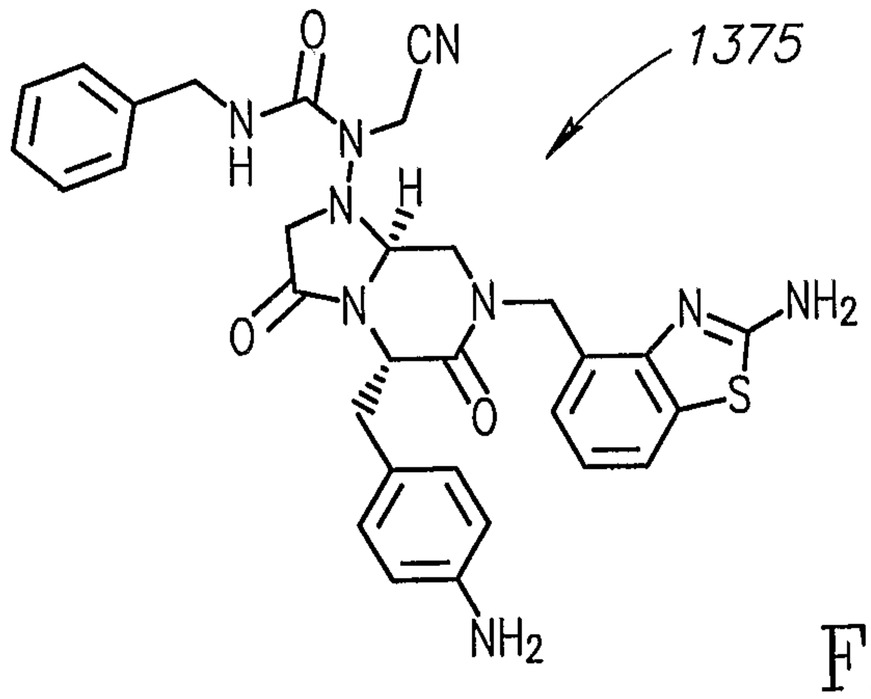












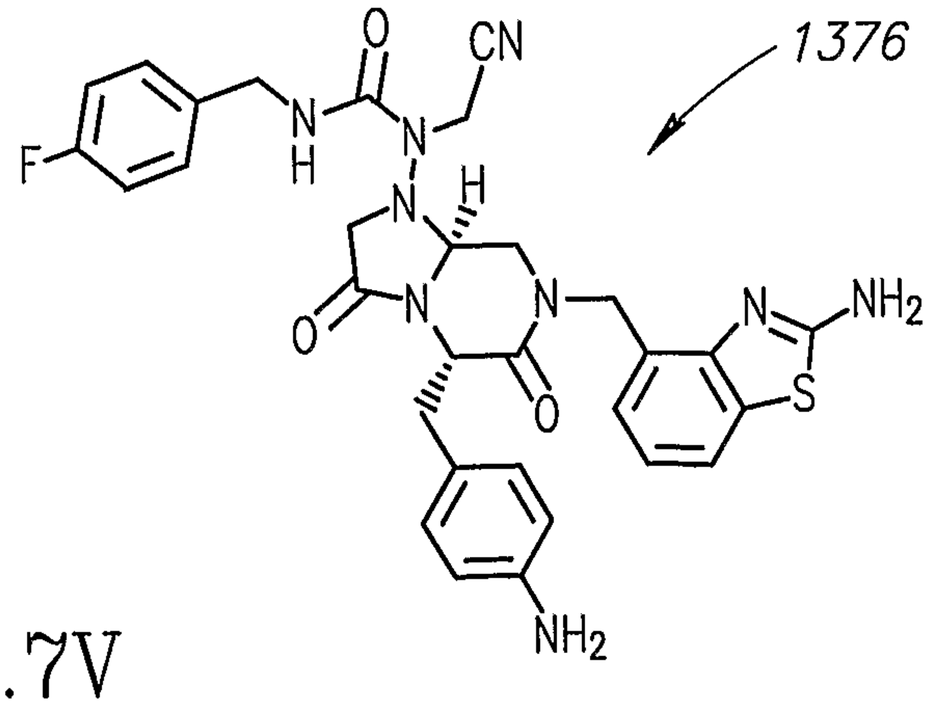


FIG.7V

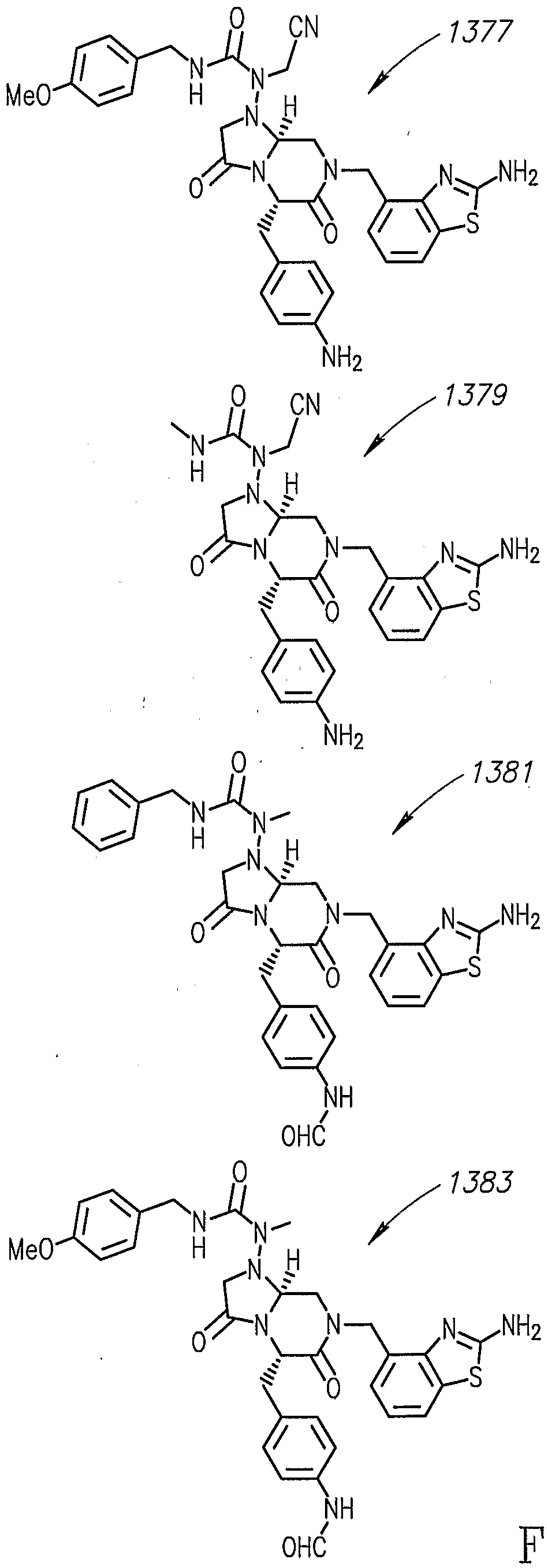
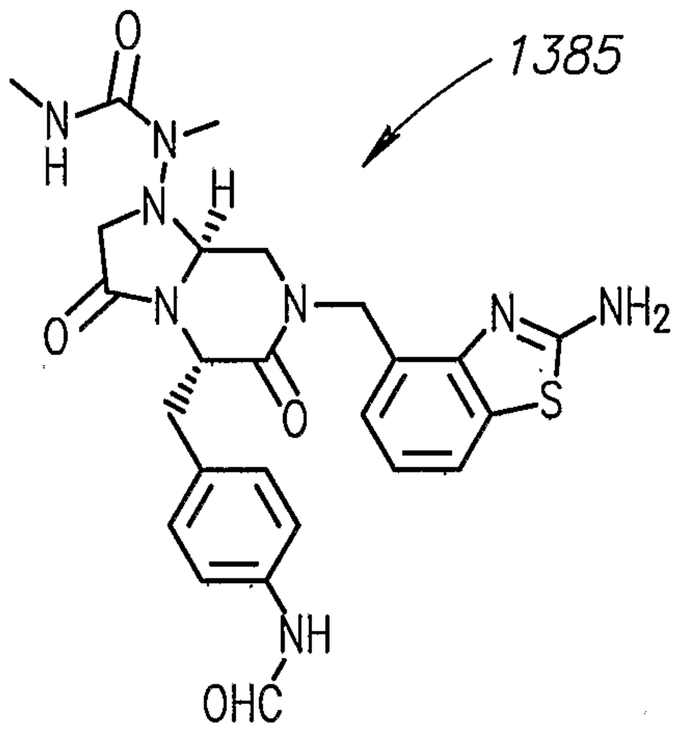
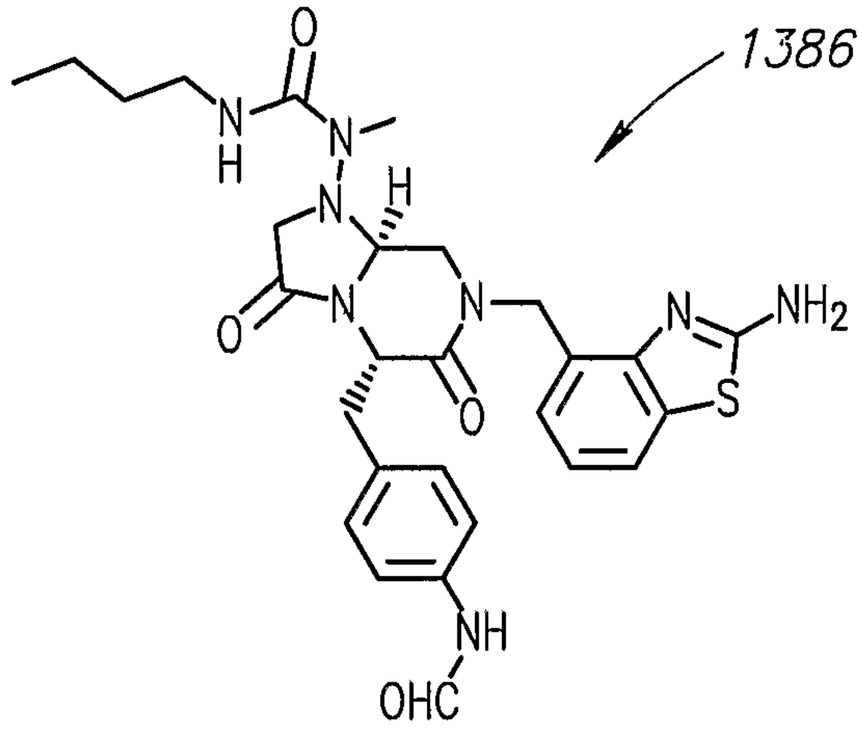
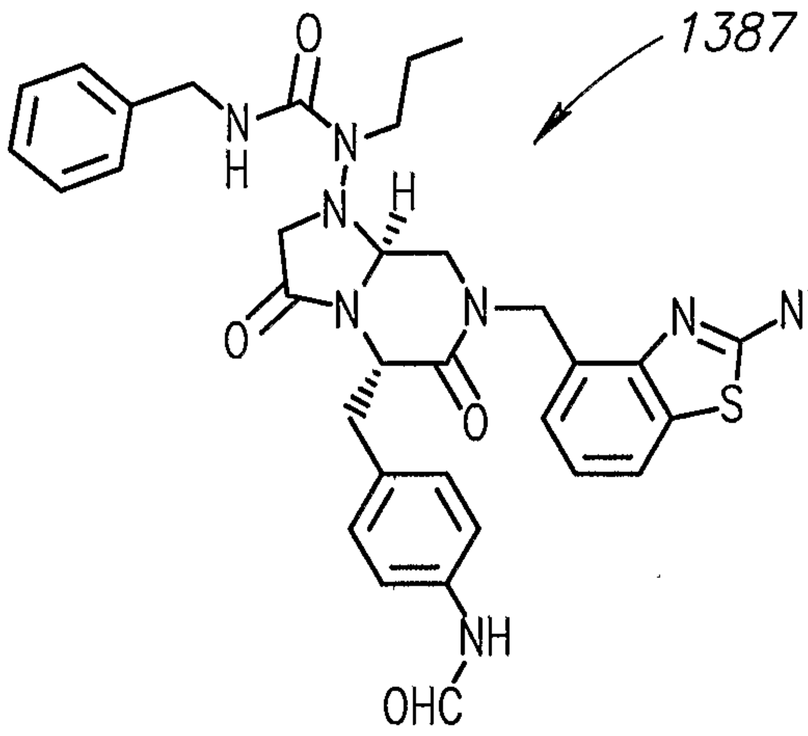
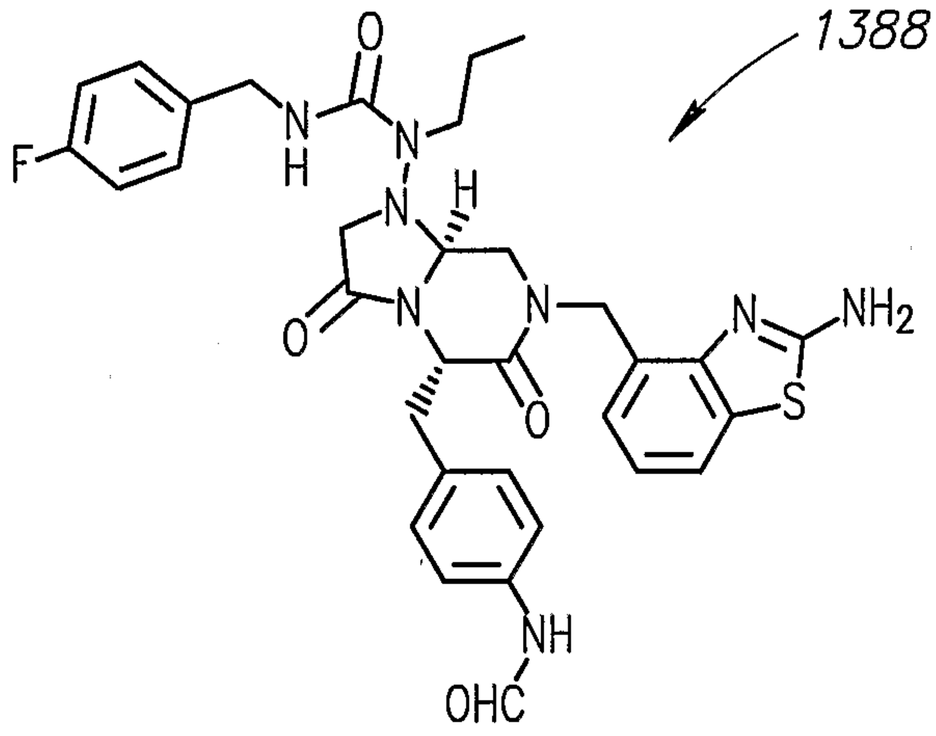

1377
MeO
O
CN
N
H
N
H
N
O
N
O
N
N
S
NH2
NH2
1378
Cl
Cl
1379
1380
1381
1382
F
NH
OHC
1383
1384

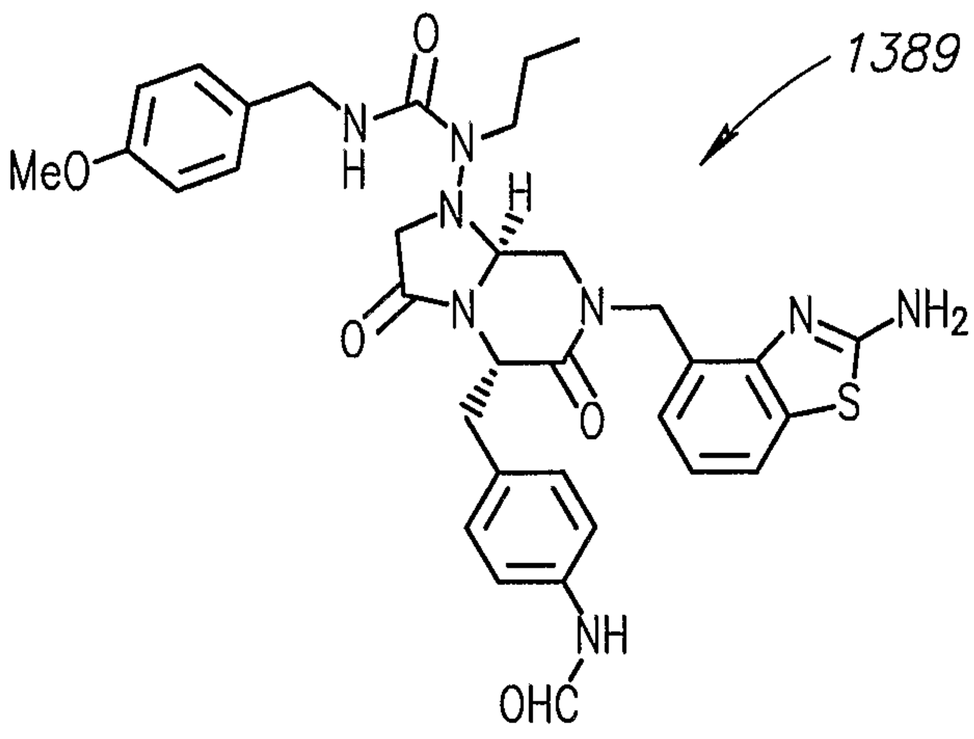
FIG.7W











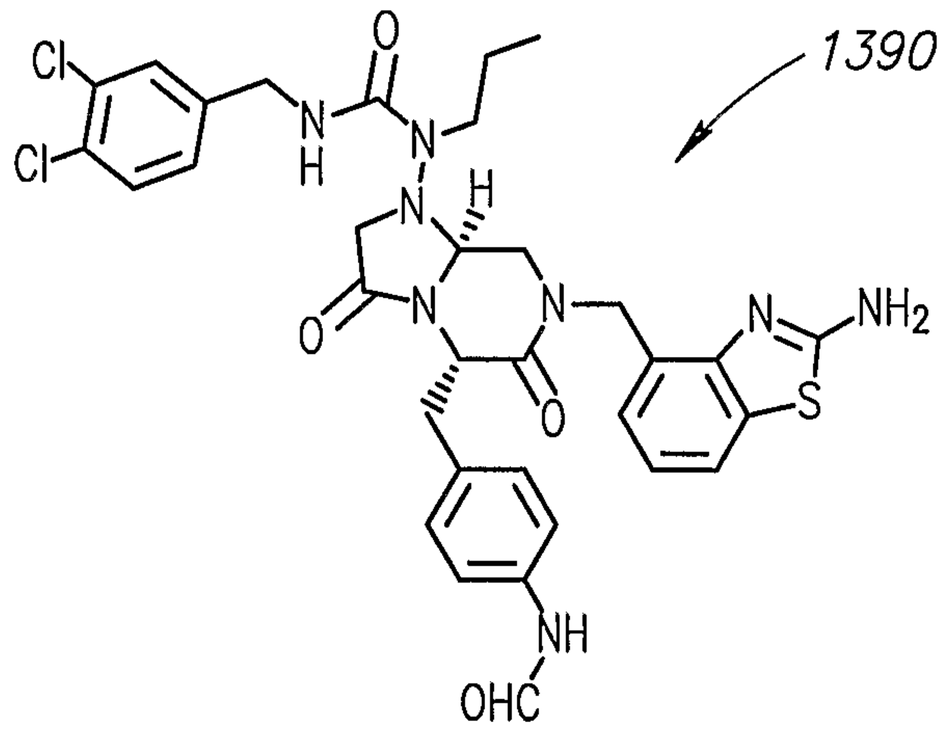
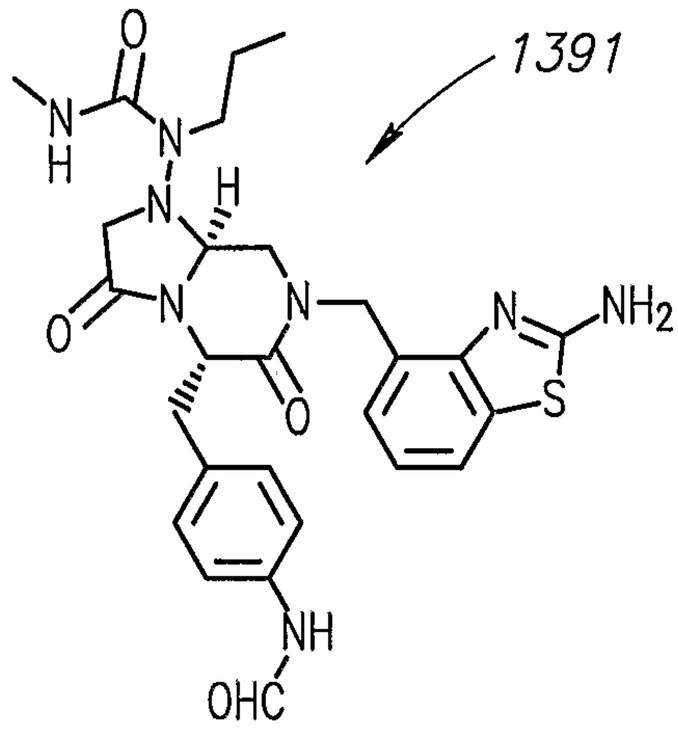
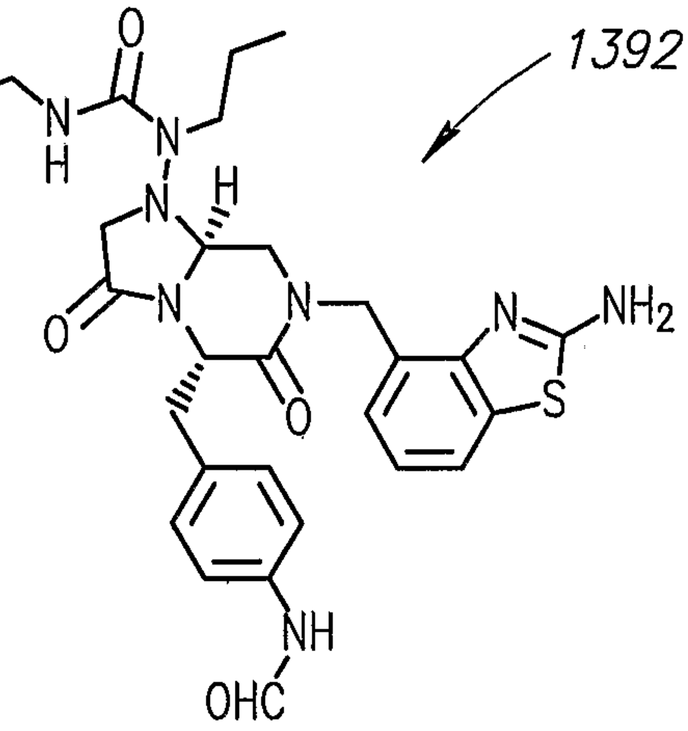
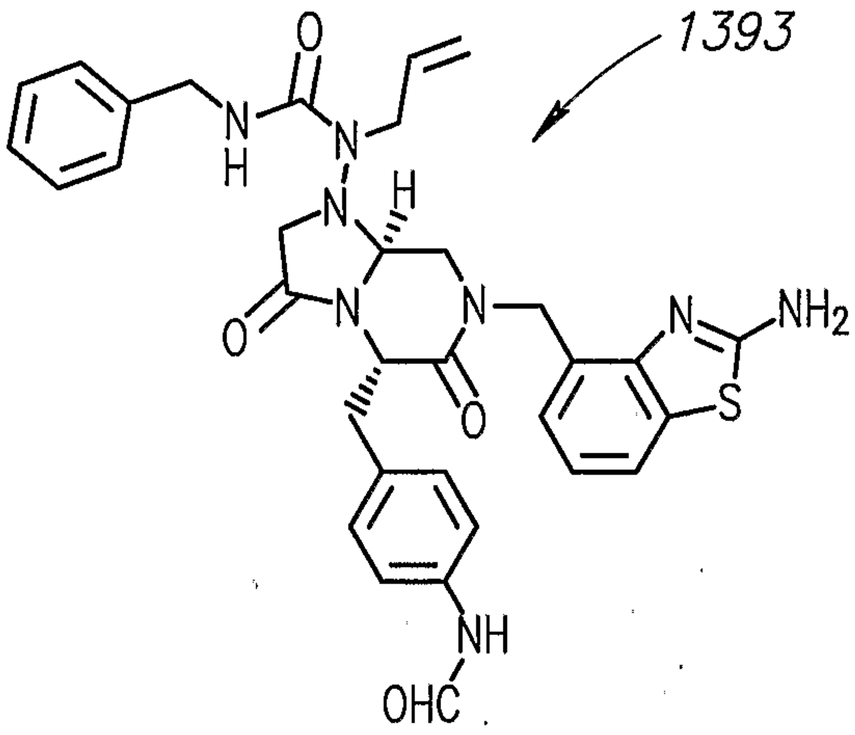
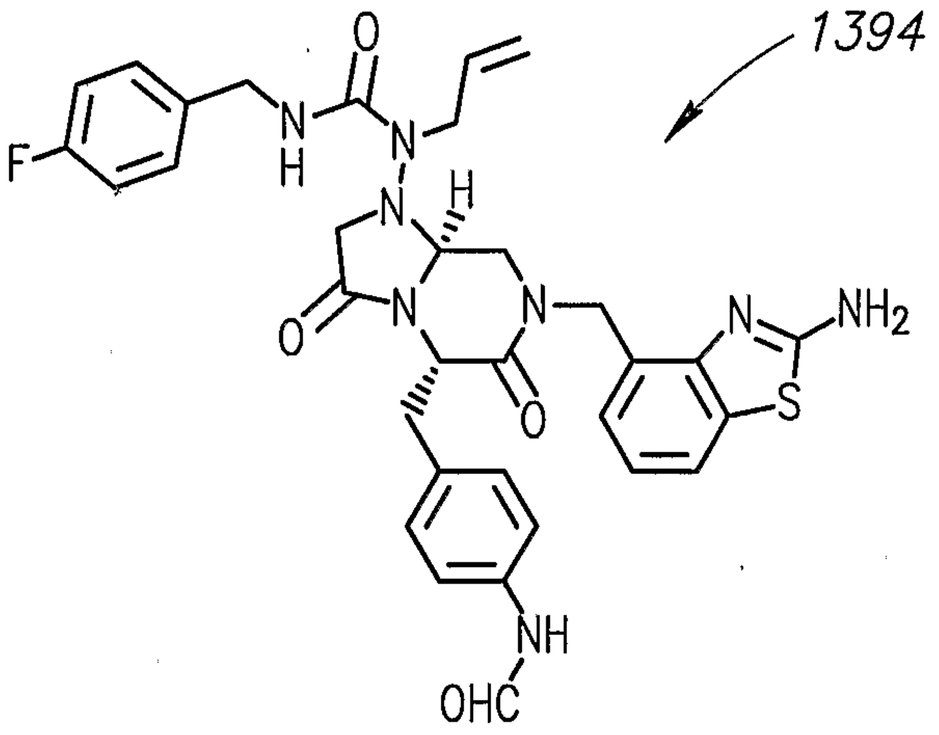


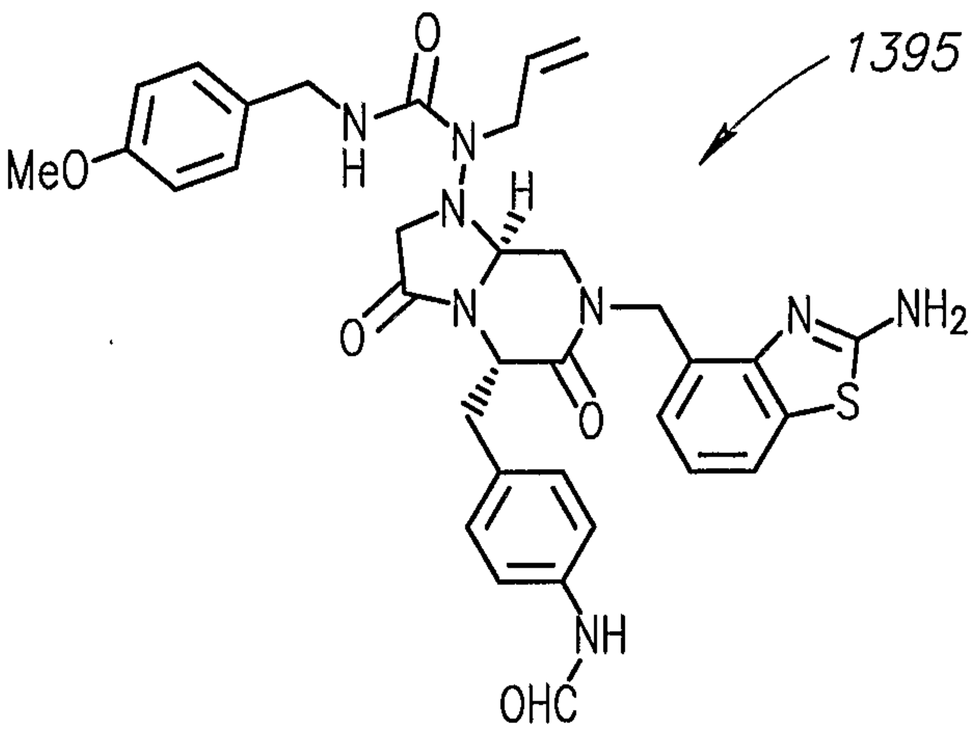
FIG.7X











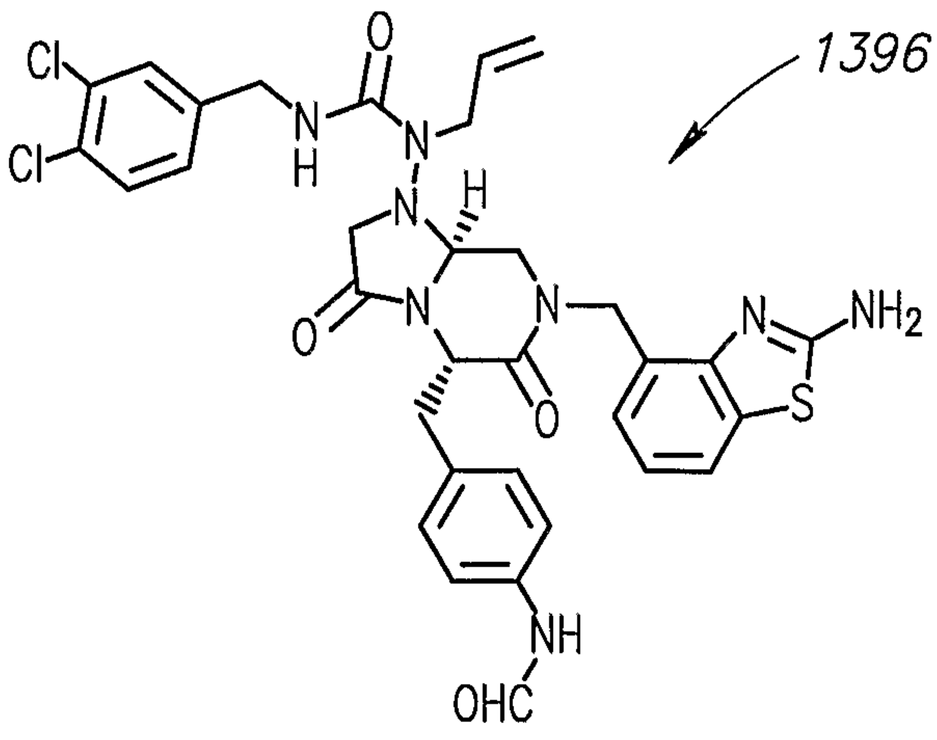
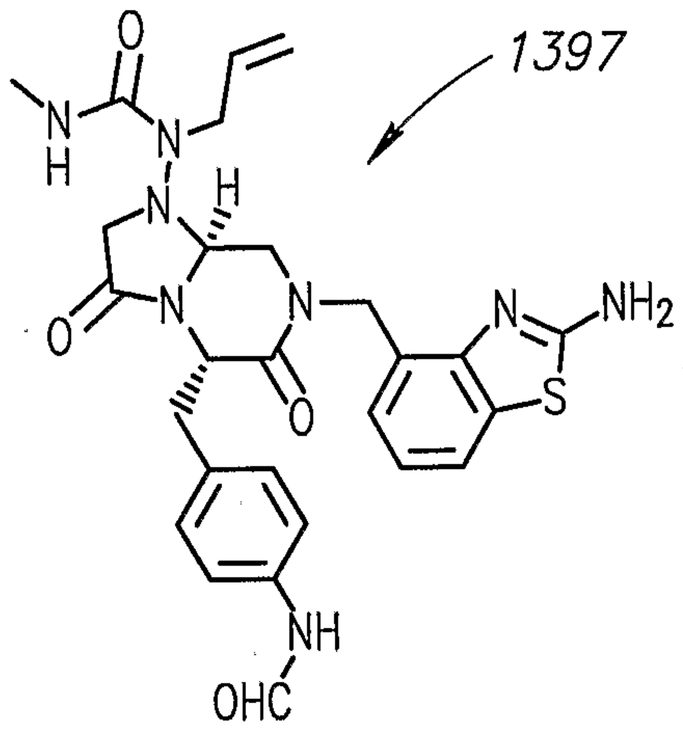
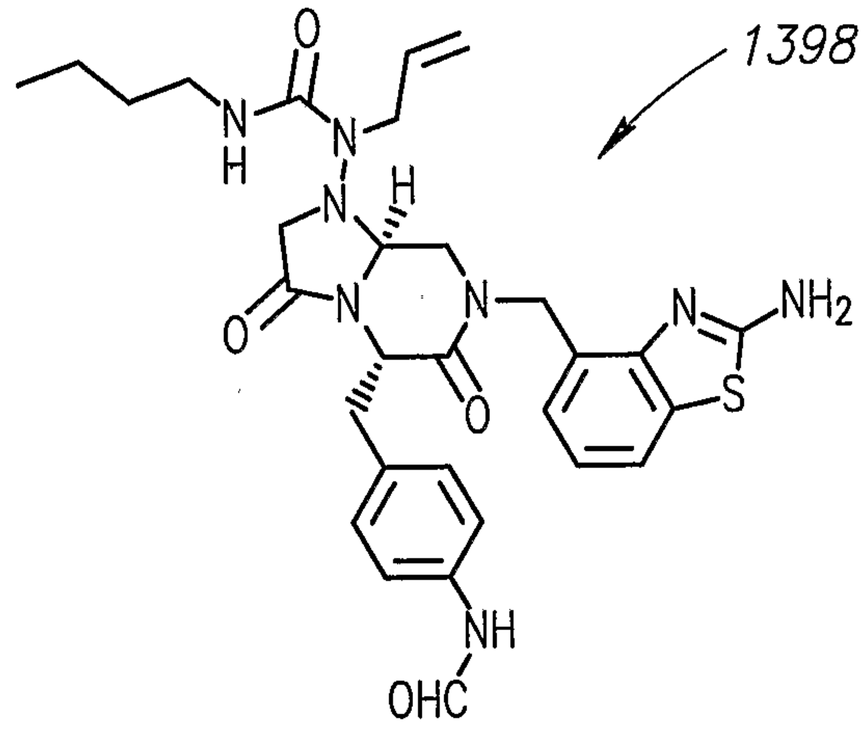
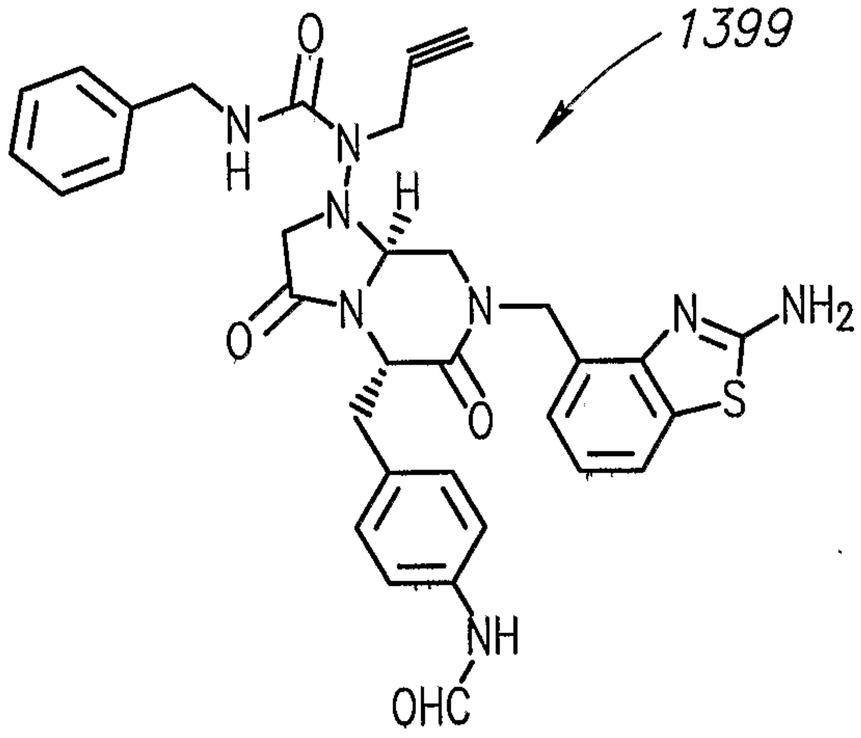


FIG.7Y


1397
O
N
H
N
N
H
O
N
O
N
N
NH2
S
NH
OHC


1398
O
N
H
N
N
H
O
N
O
N
N
NH2
S
NH
OHC


1399
O
N
H
N
N
H
O
N
O
N
N
NH2
S
NH
OHC

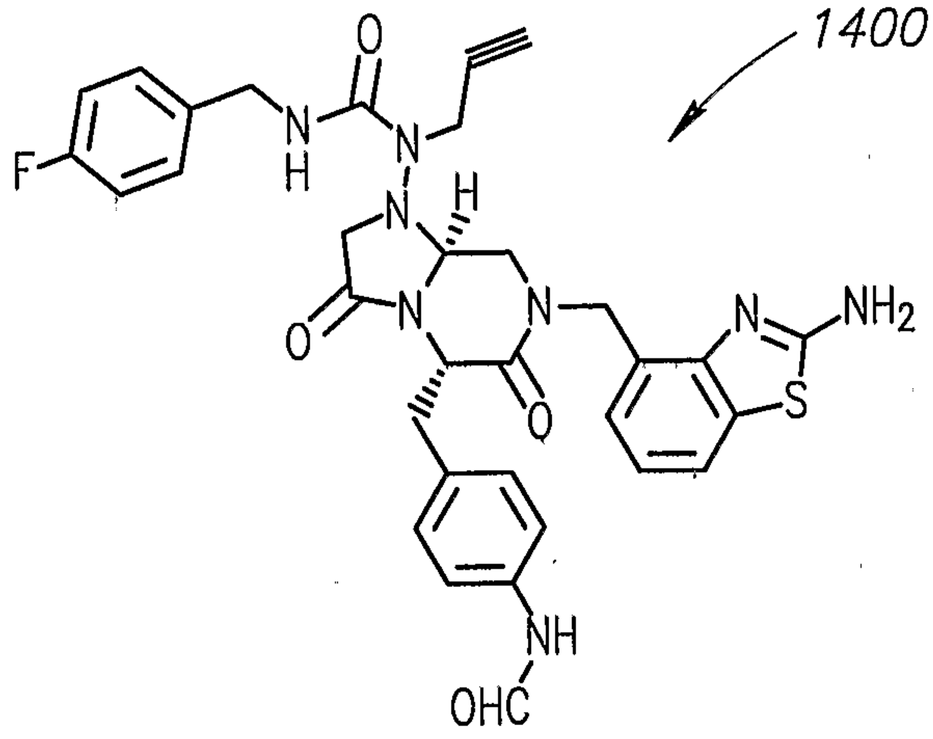
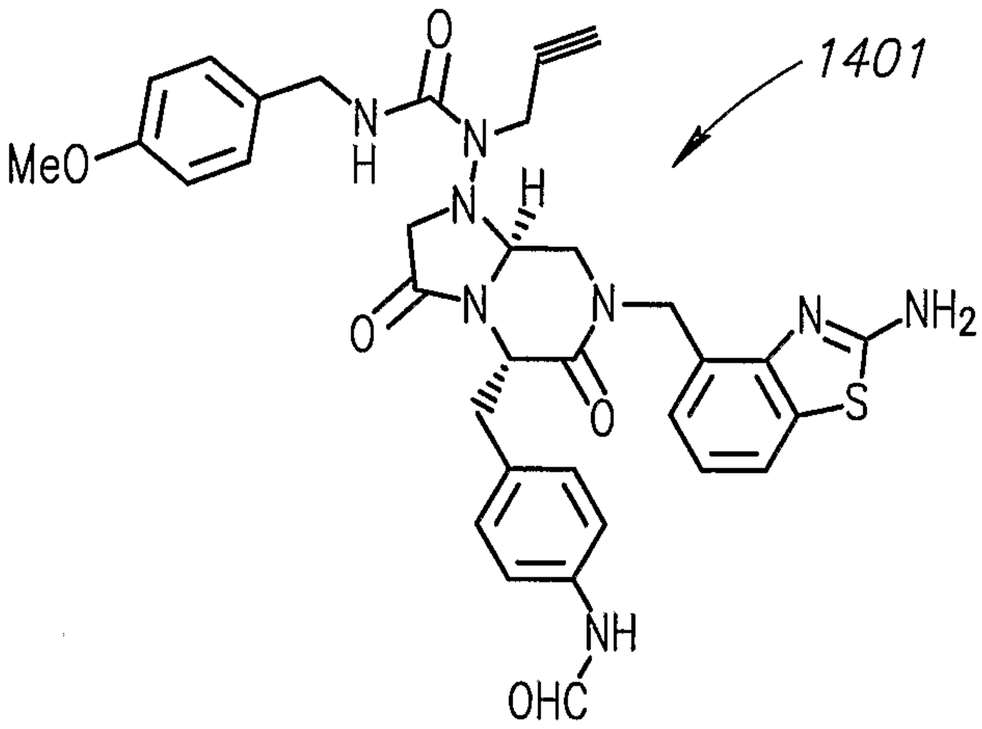
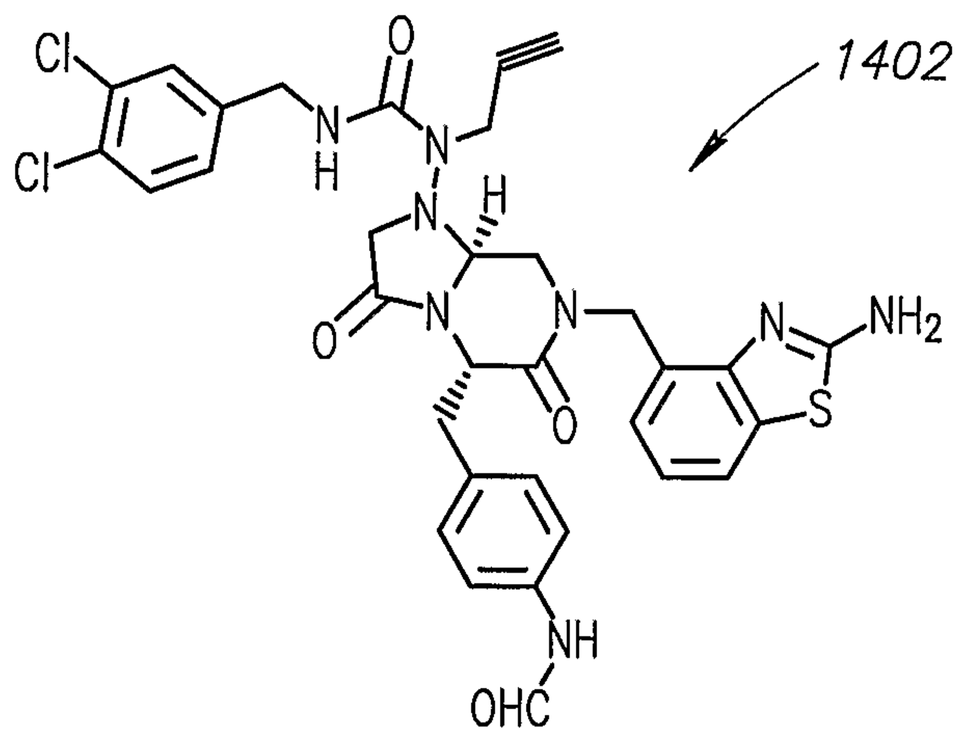
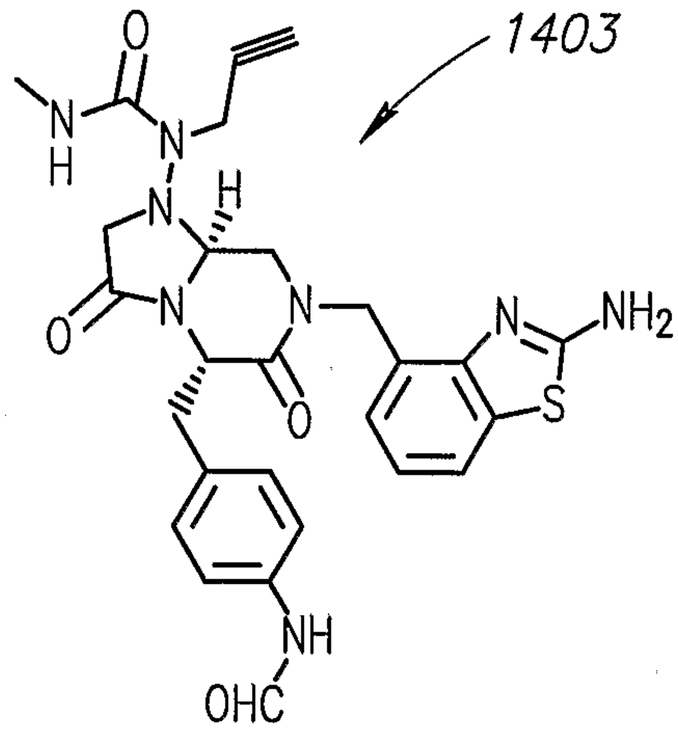
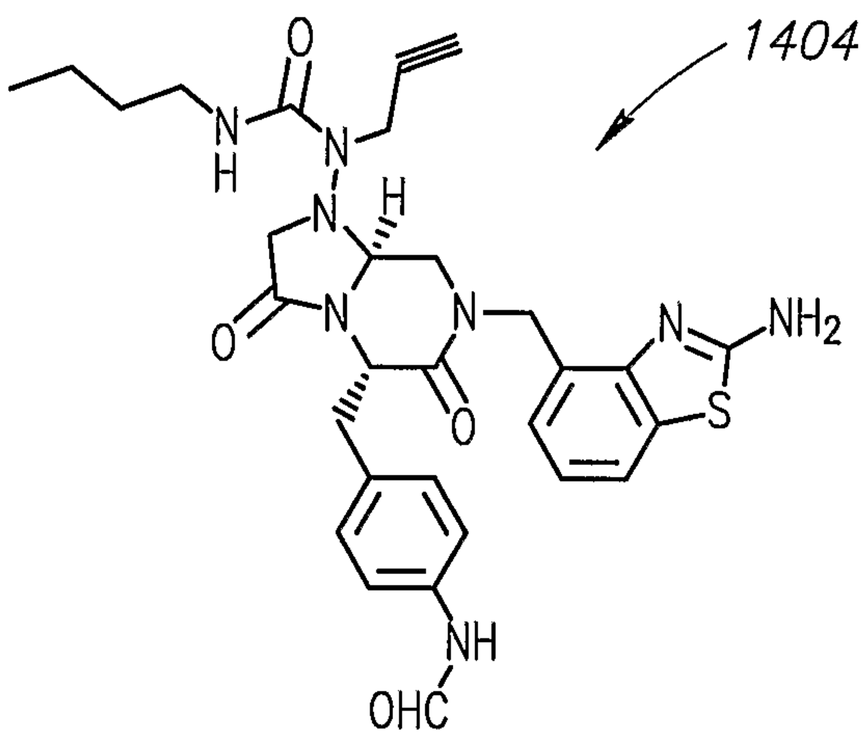

1400
F
O
N
H
N
N
H
O
N
O
N
N
NH2
S
NH
OHC

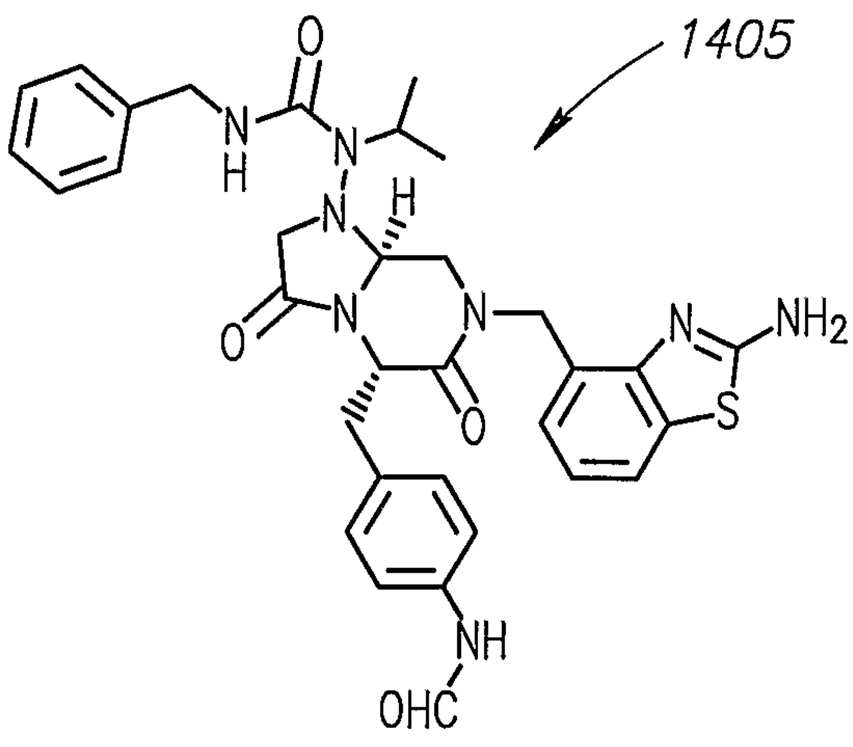
FIG.7Z


1401
MeO
N
H
O
N
N
H
O
N
N
O
N
S
NH2
NH
OHC


1402
Cl
Cl
N
H
O
N
N
H
O
N
N
O
N
S
NH2
NH
OHC


1403
N
H
O
N
N
H
O
N
N
O
N
S
NH2
NH
OHC


1404
N
H
O
N
N
H
O
N
N
O
N
S
NH2
NH
OHC


1405
N
H
O
N
N
H
O
N
N
O
N
S
NH2
NH
OHC

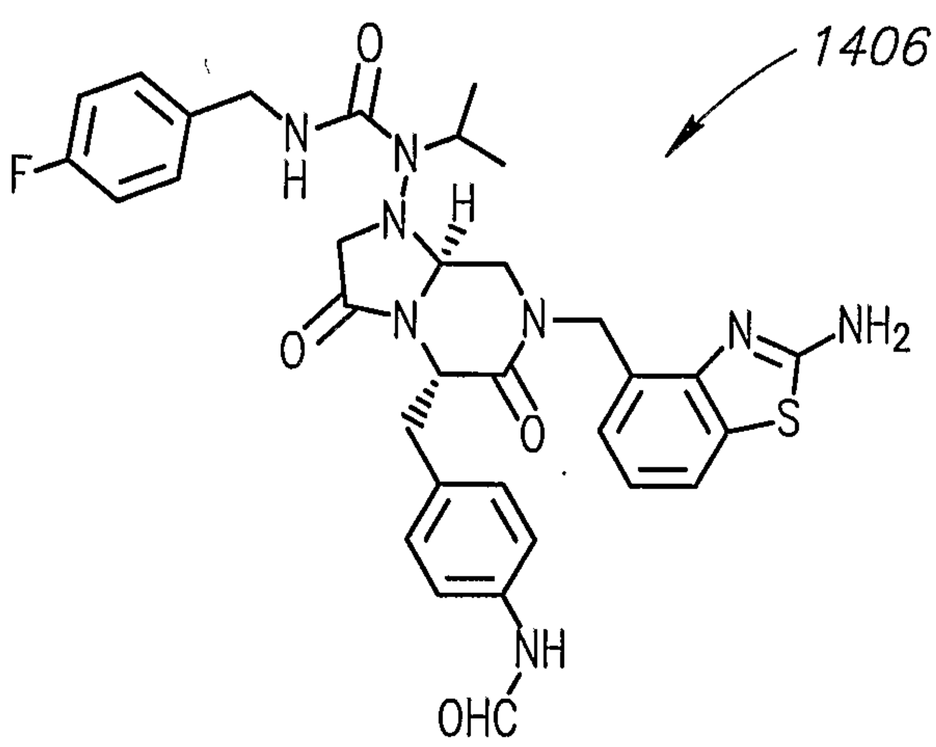
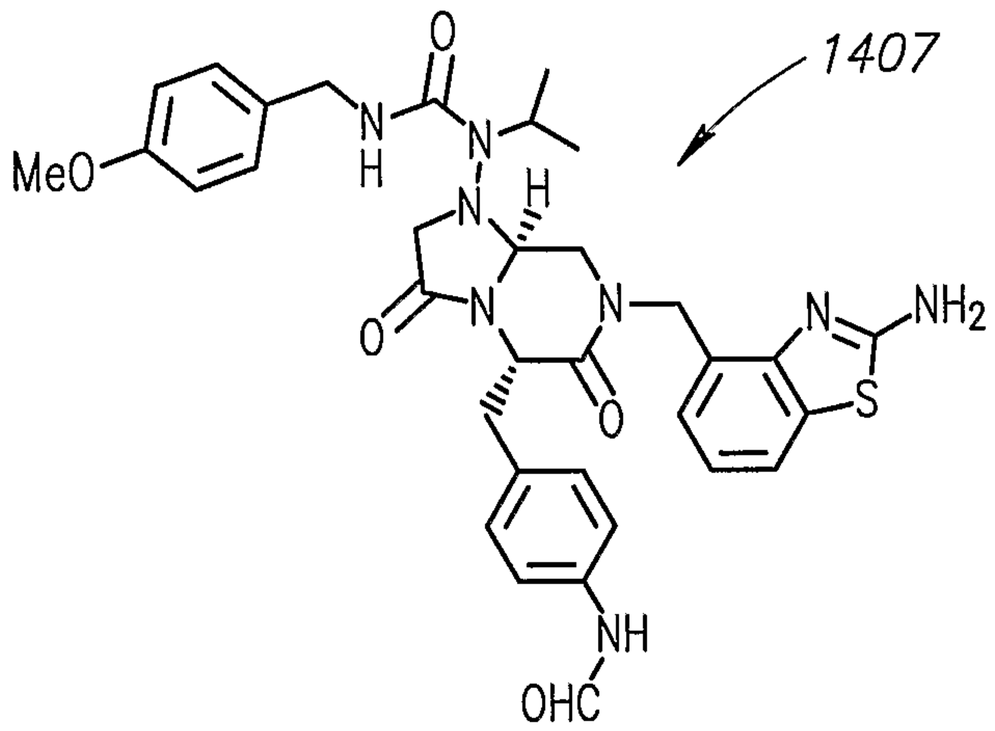
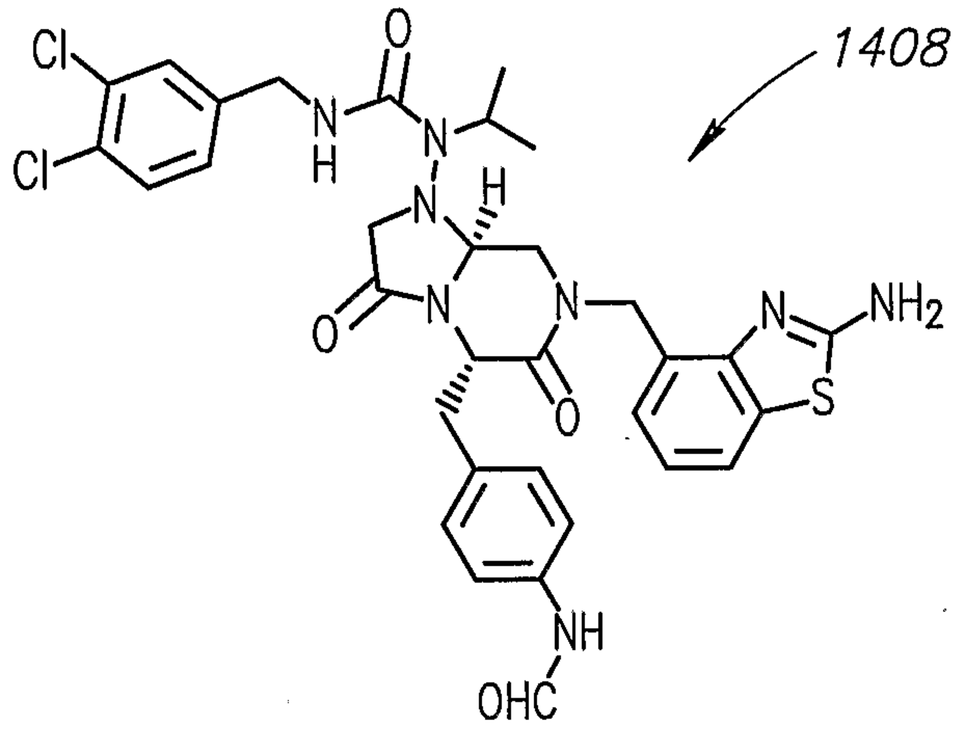

1406
F
N
H
O
N
N
H
O
N
N
O
N
S
NH2
NH
OHC

FIG.8A

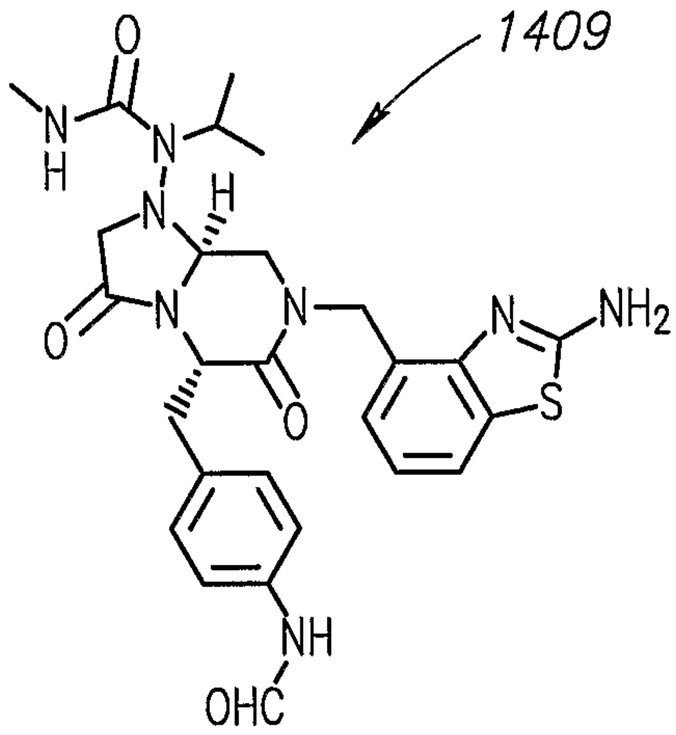
1407



1408



1409



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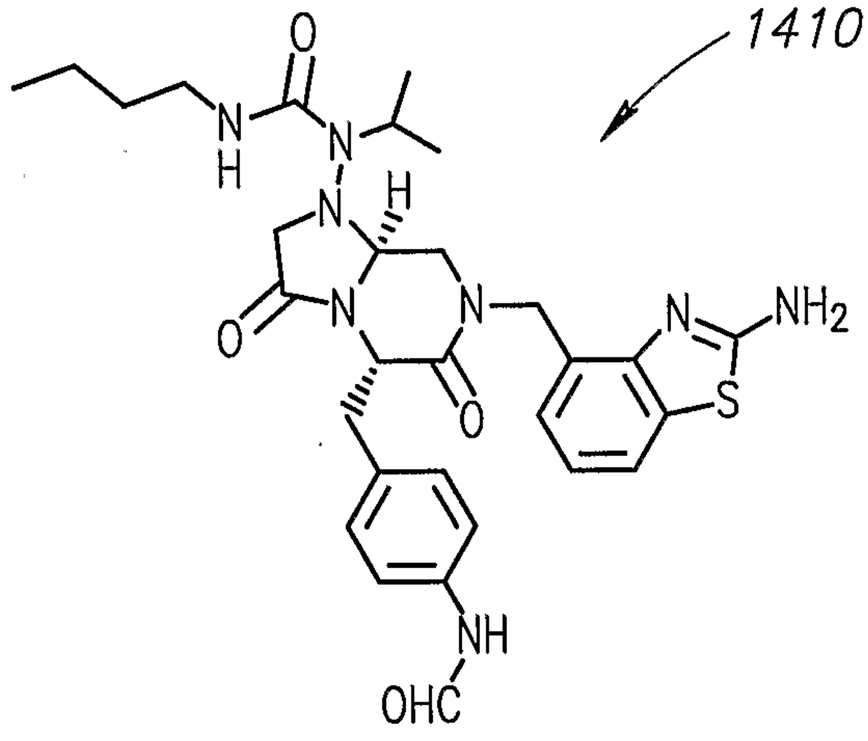
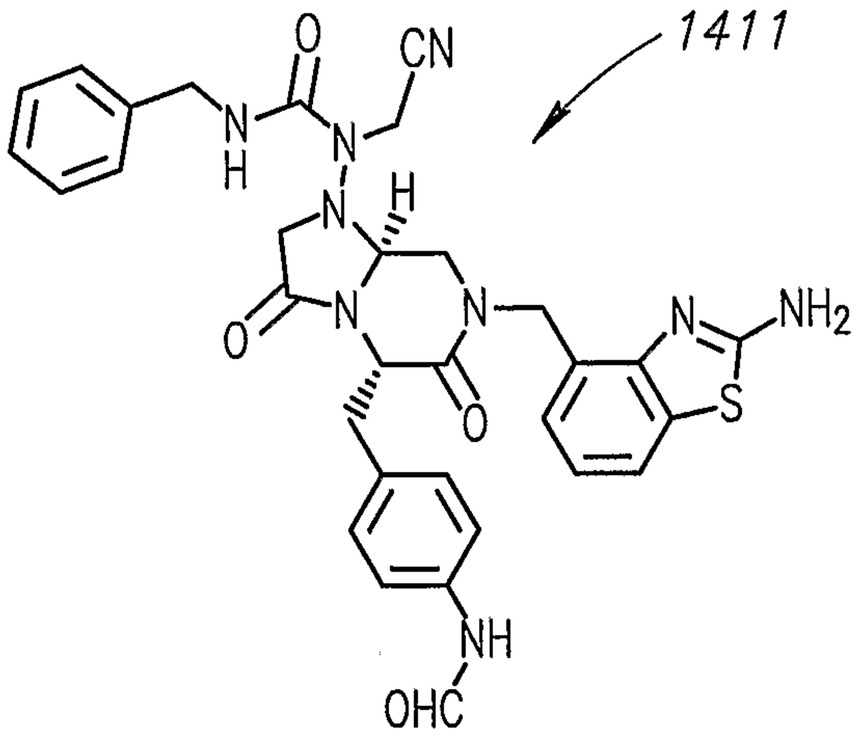


1411



1412

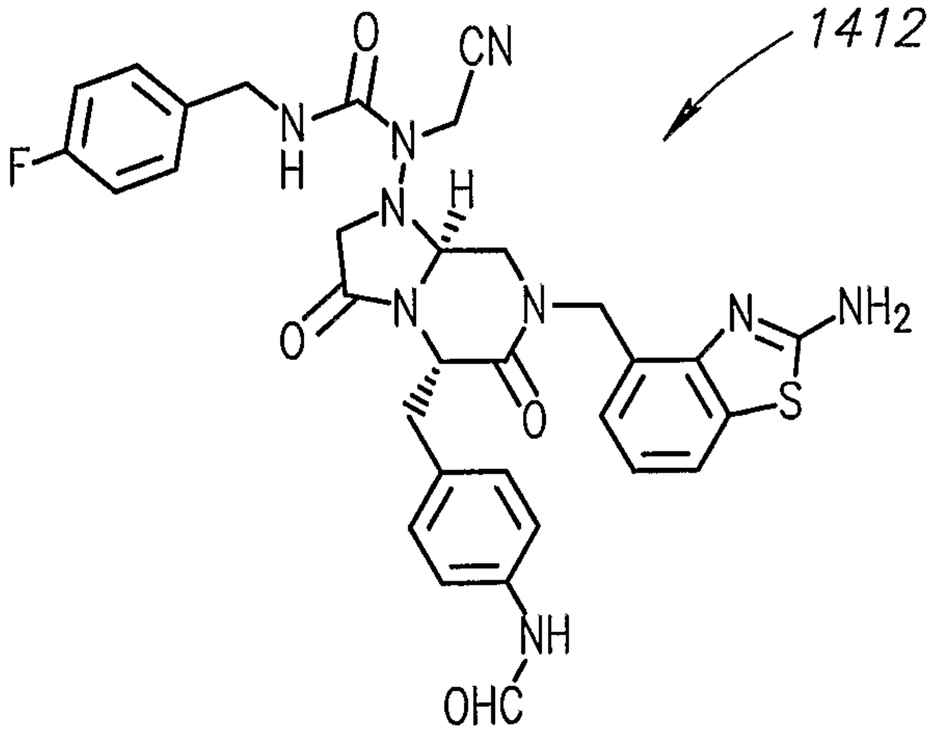
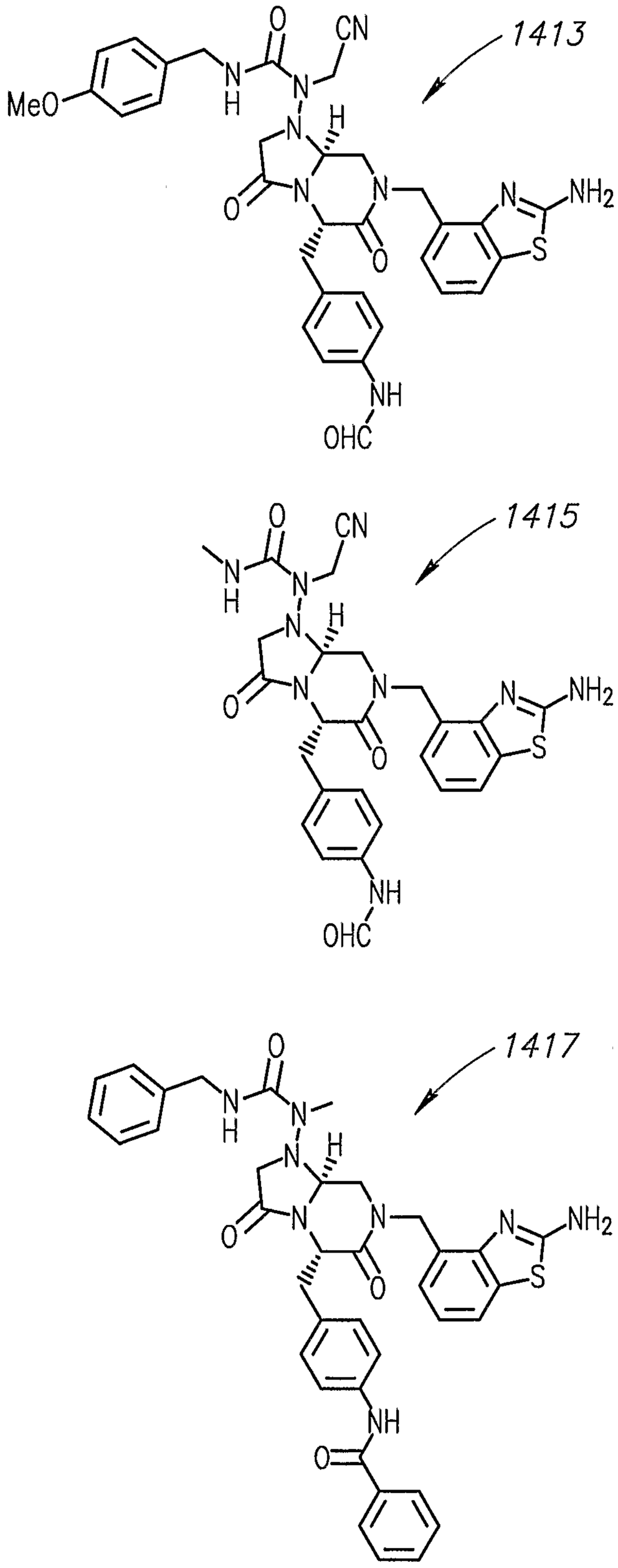
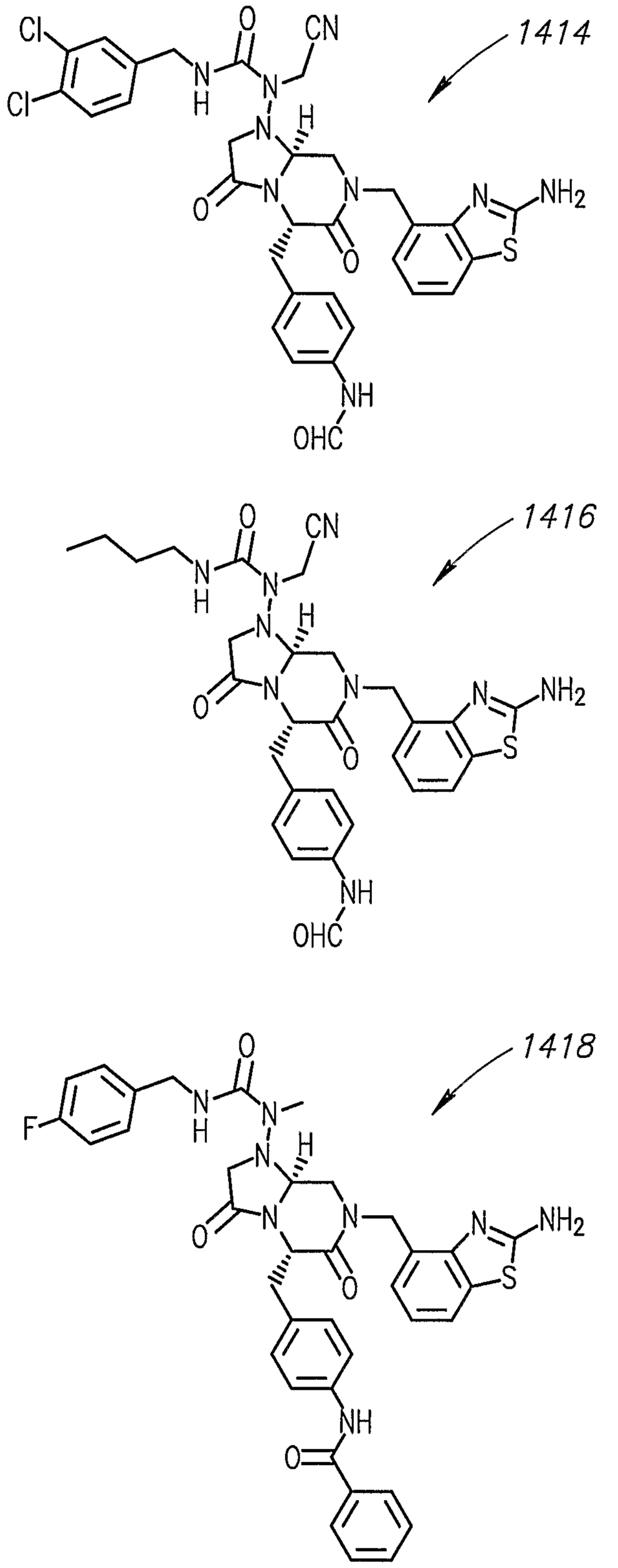


FIG.8B


1413
MeO
O
CN
N
H
N
H
N
O
N
N
O
N
S
NH2
NH
OHC


1414
Cl
Cl
O
CN
N
H
N
H
N
O
N
N
O
N
S
NH2
NH
OHC

1415
O
CN
N
H
N
H
N
O
N
N
O
N
S
NH2
NH
OHC

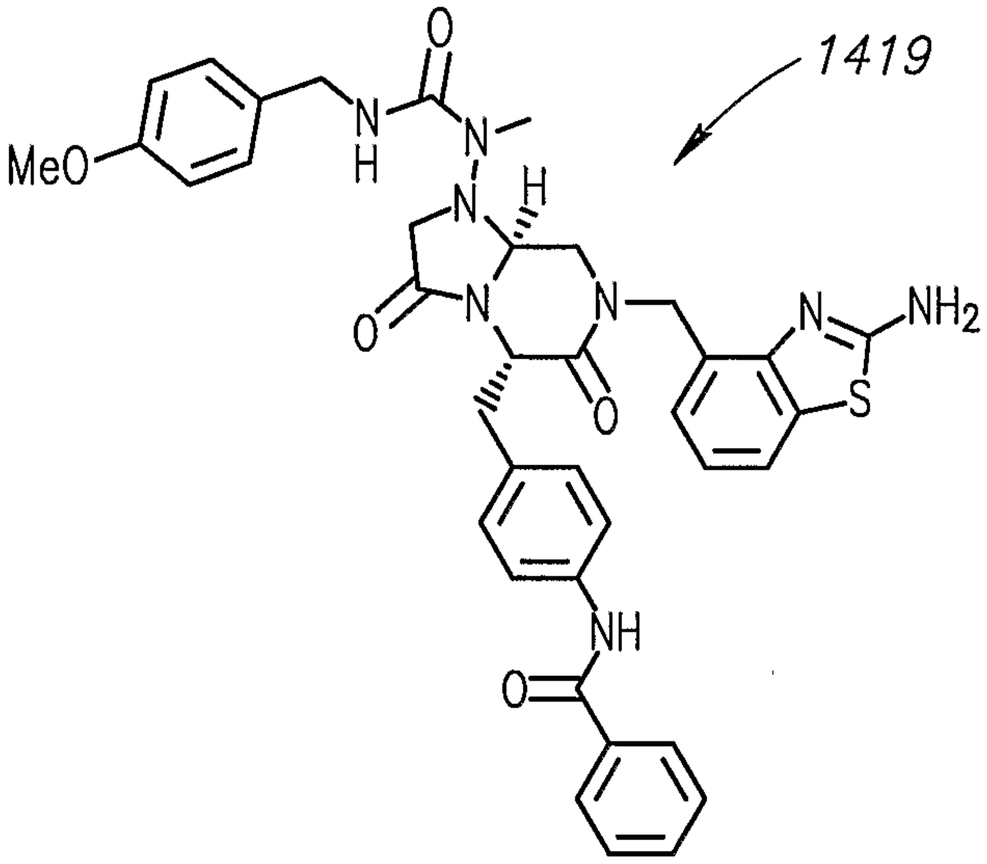
1416
O
CN
N
H
N
H
N
O
N
N
O
N
S
NH2
NH
OHC

1417
O
N
H
N
H
N
O
N
N
O
N
S
NH2
NH
O

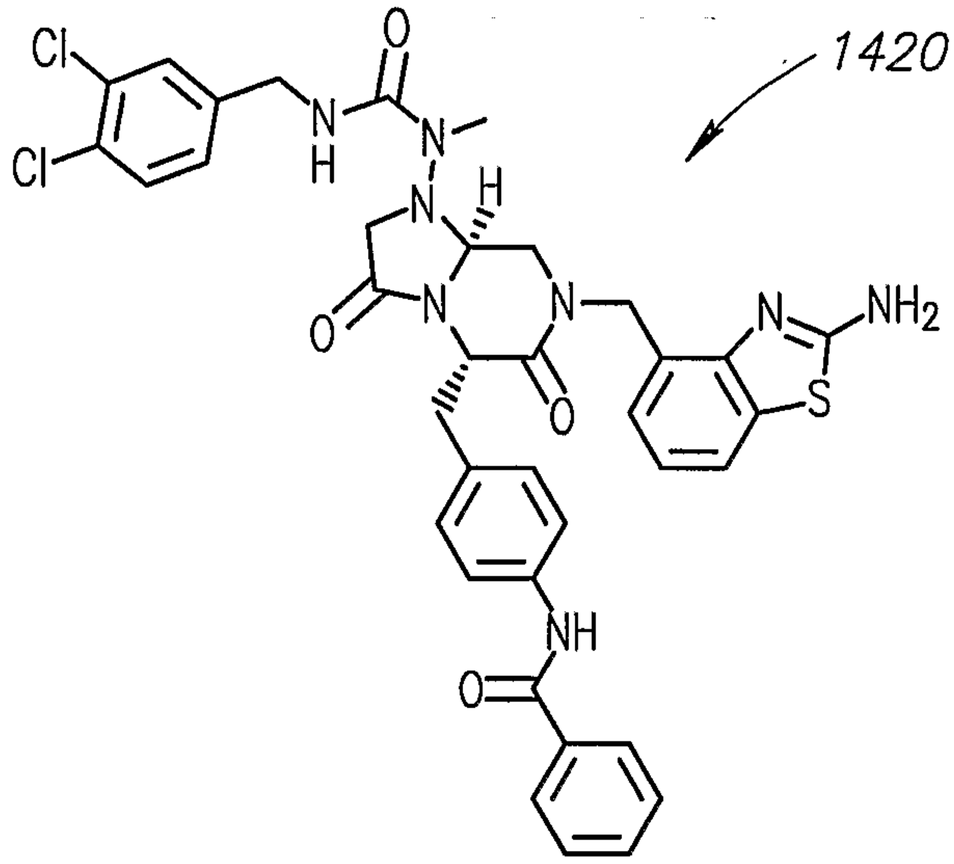
1418
F
O
N
H
N
H
N
O
N
N
O
N
S
NH2
NH
O

FIG.8C

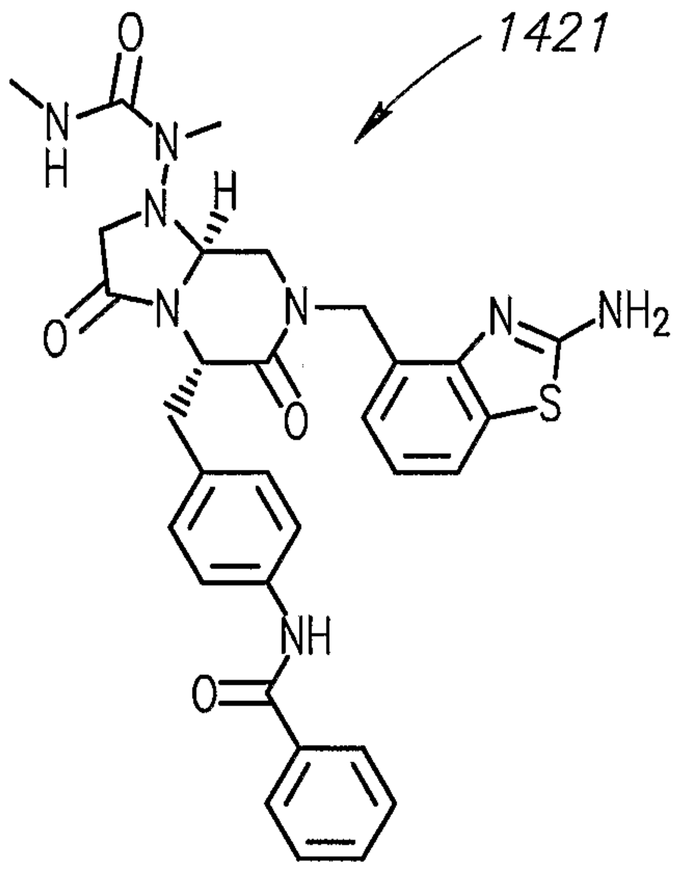
1419



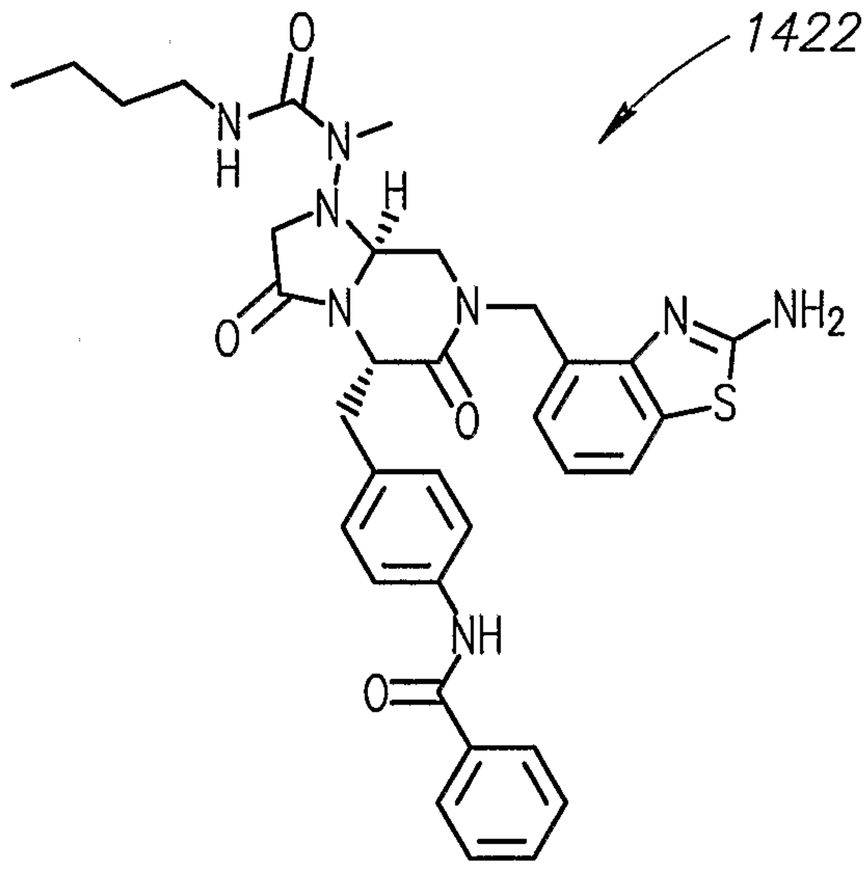
1420



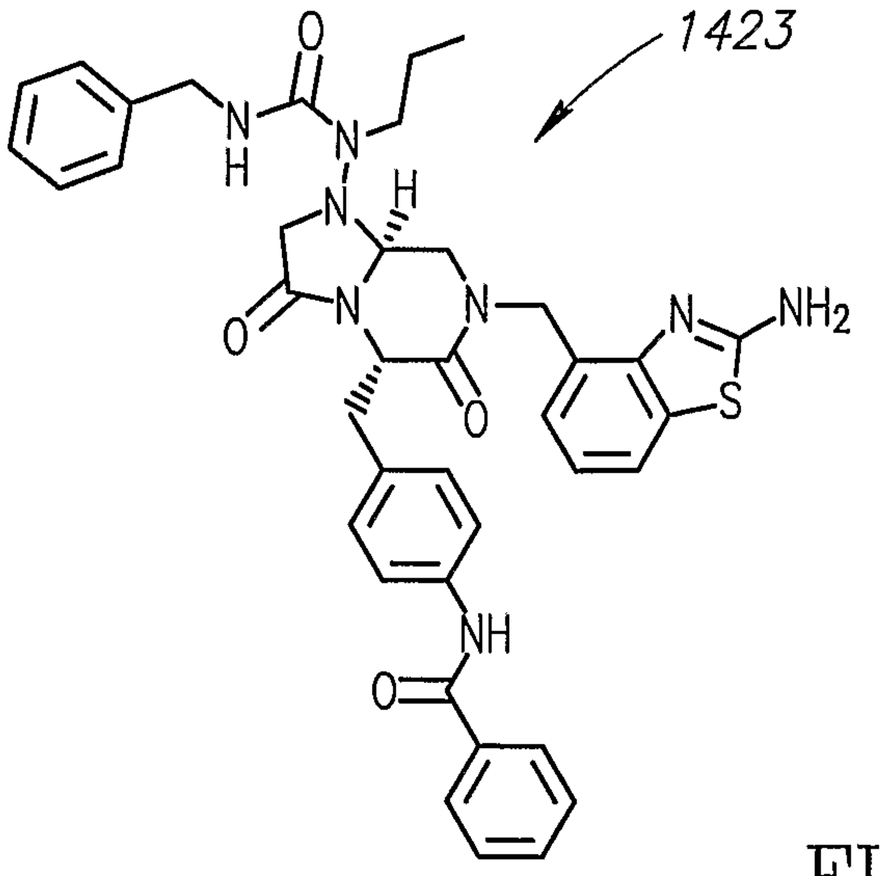
1421



1422



1423



1424

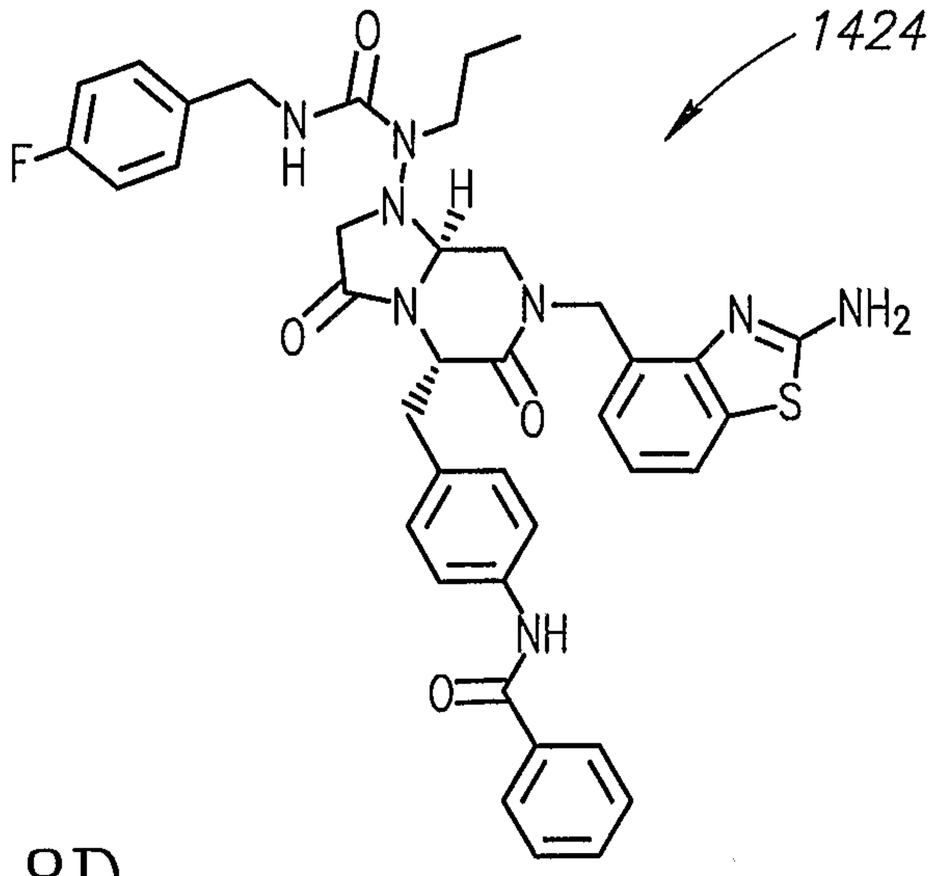
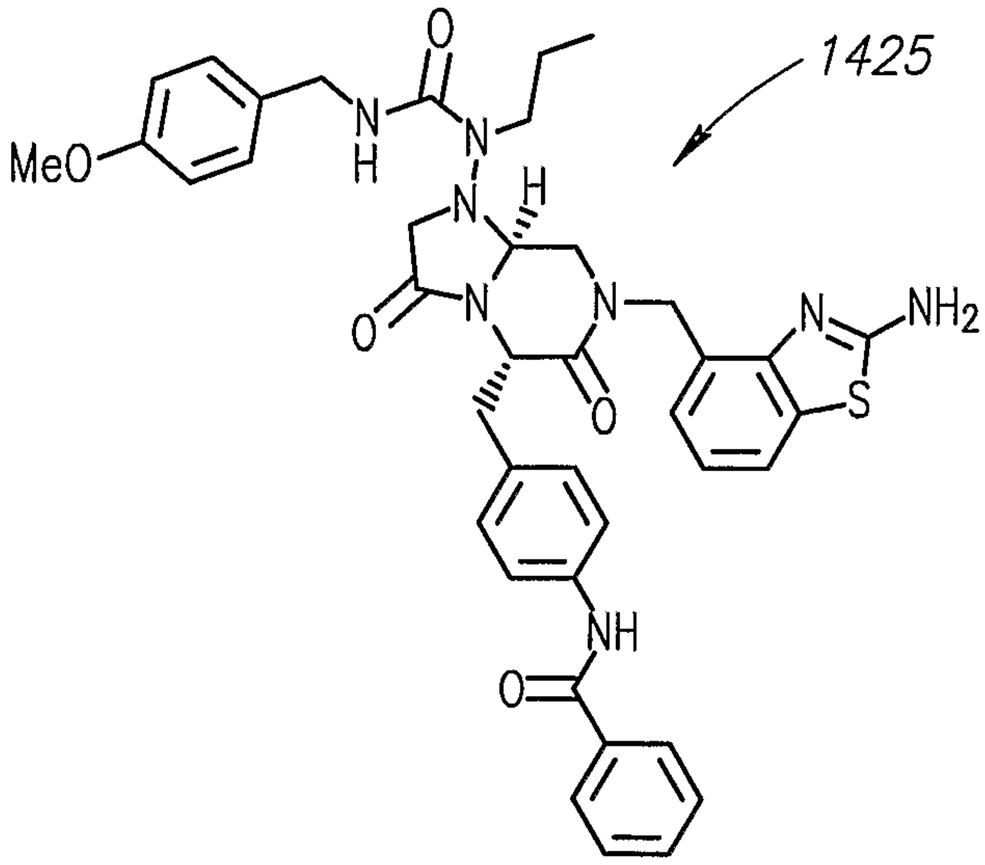
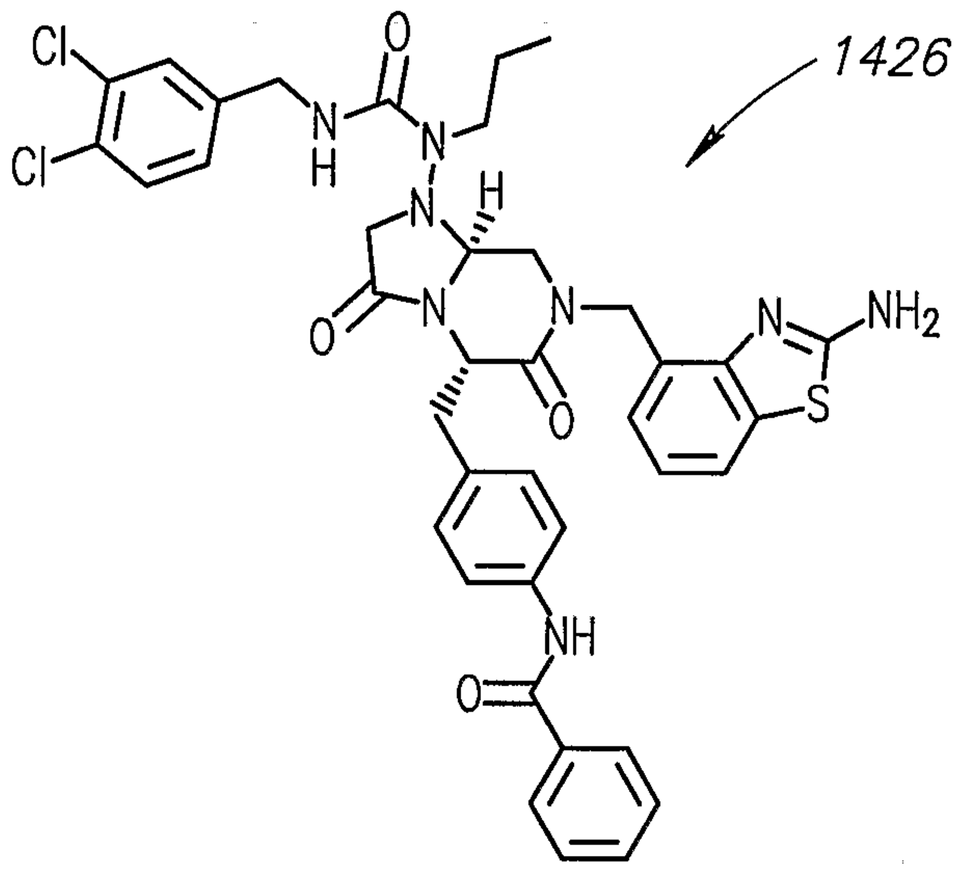


FIG.8D

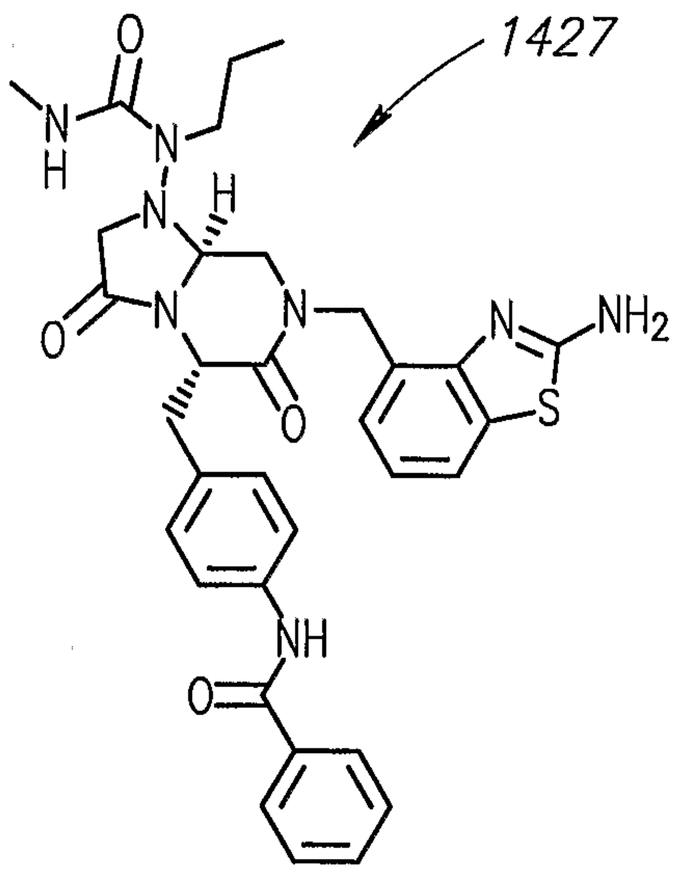
1425



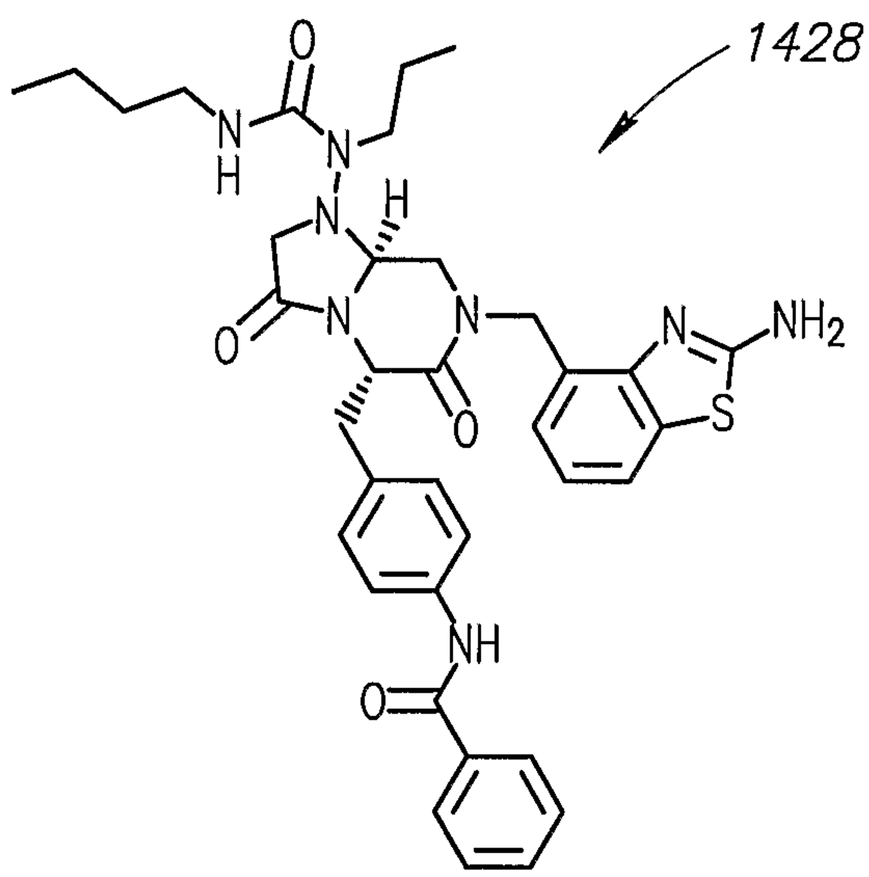
1426



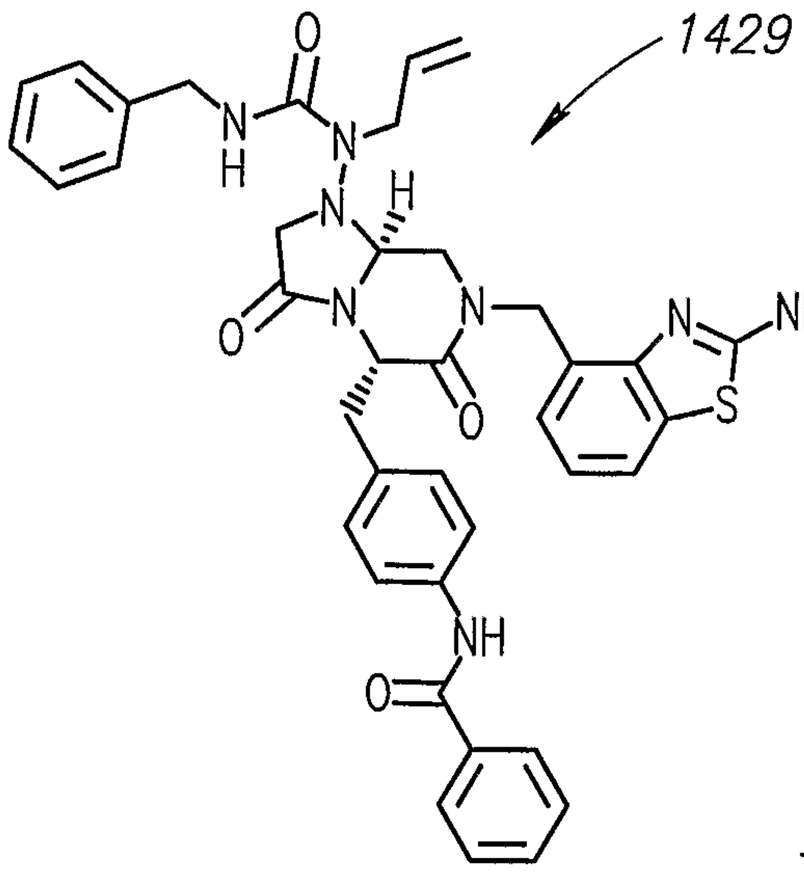
1427



1428



1429



1430

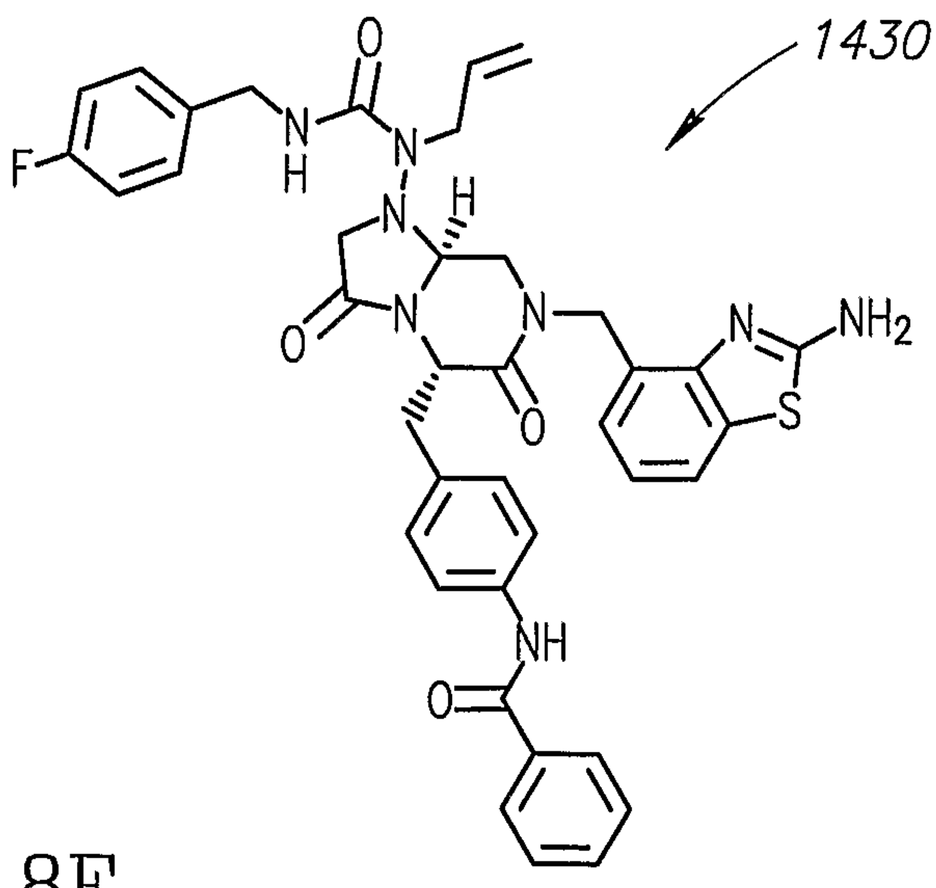
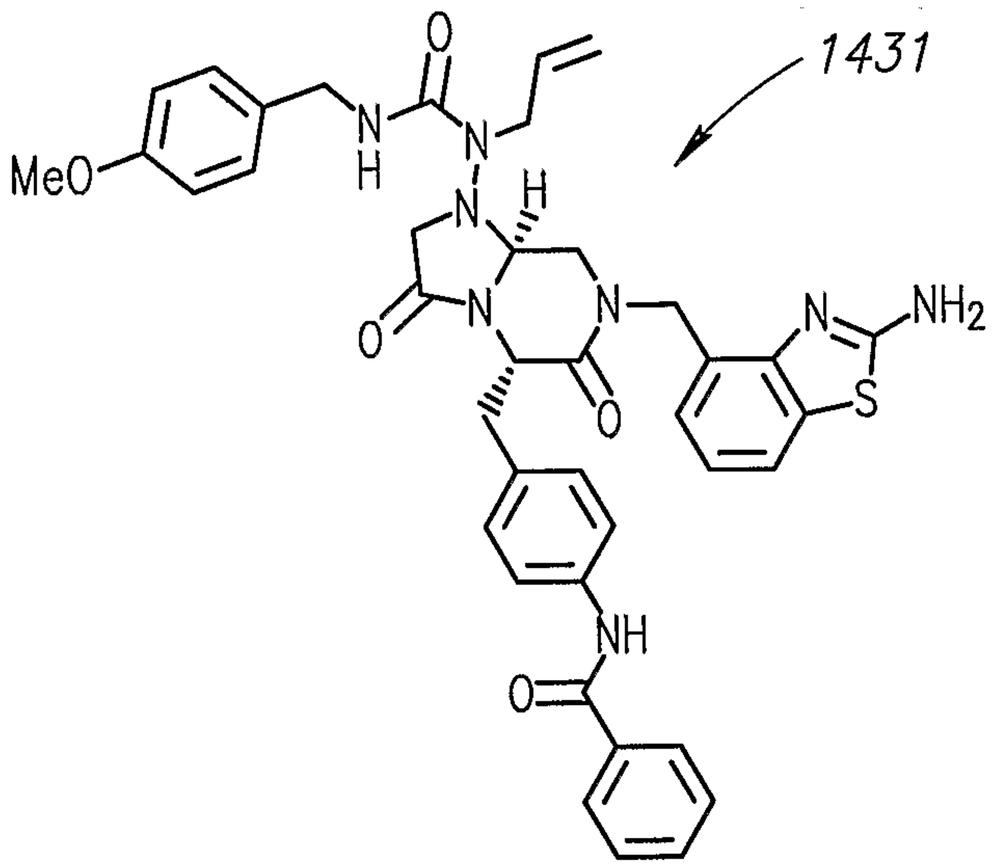
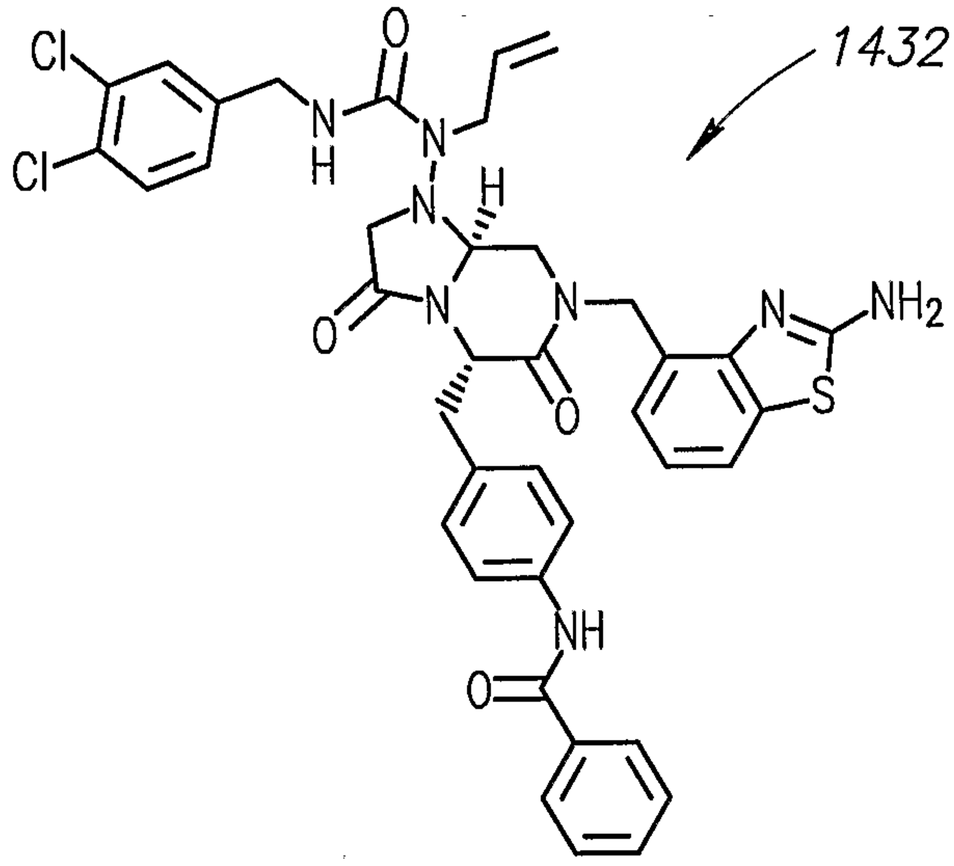
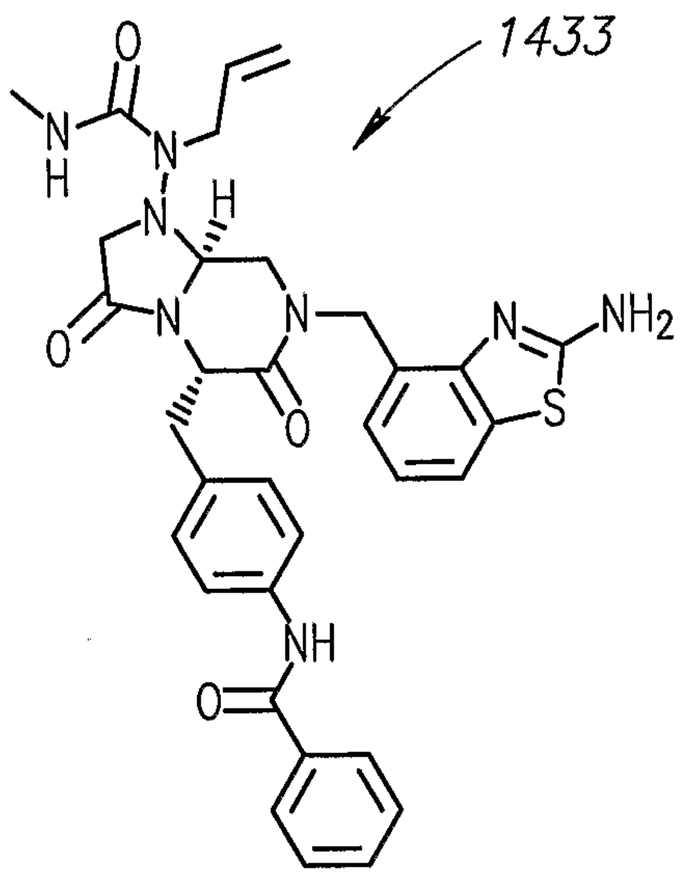
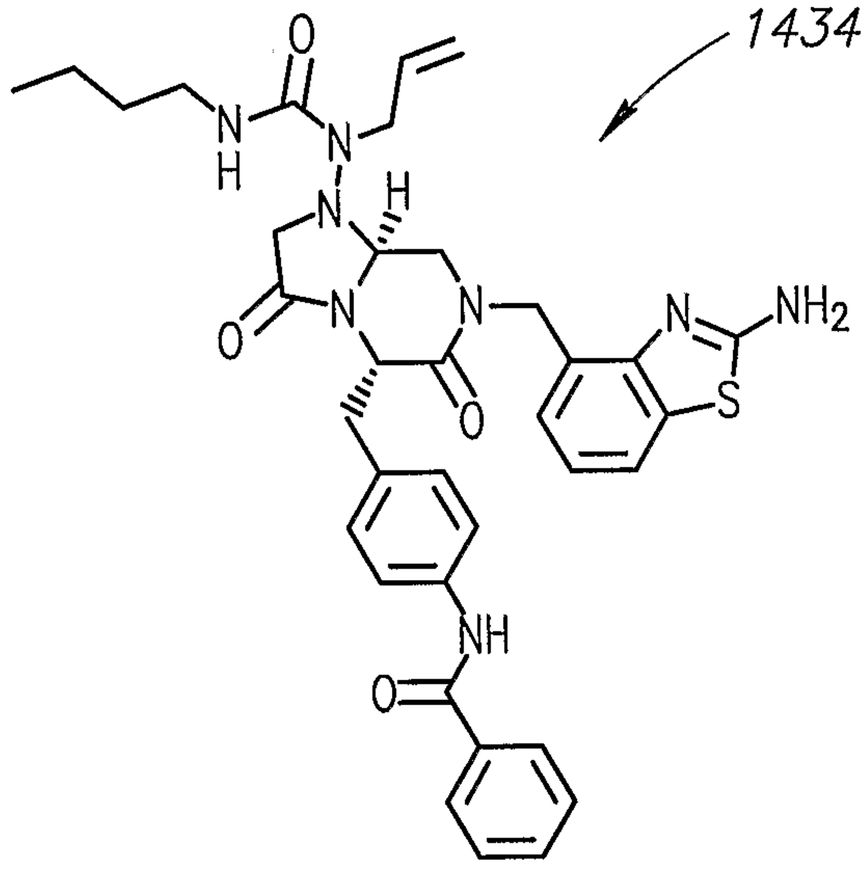


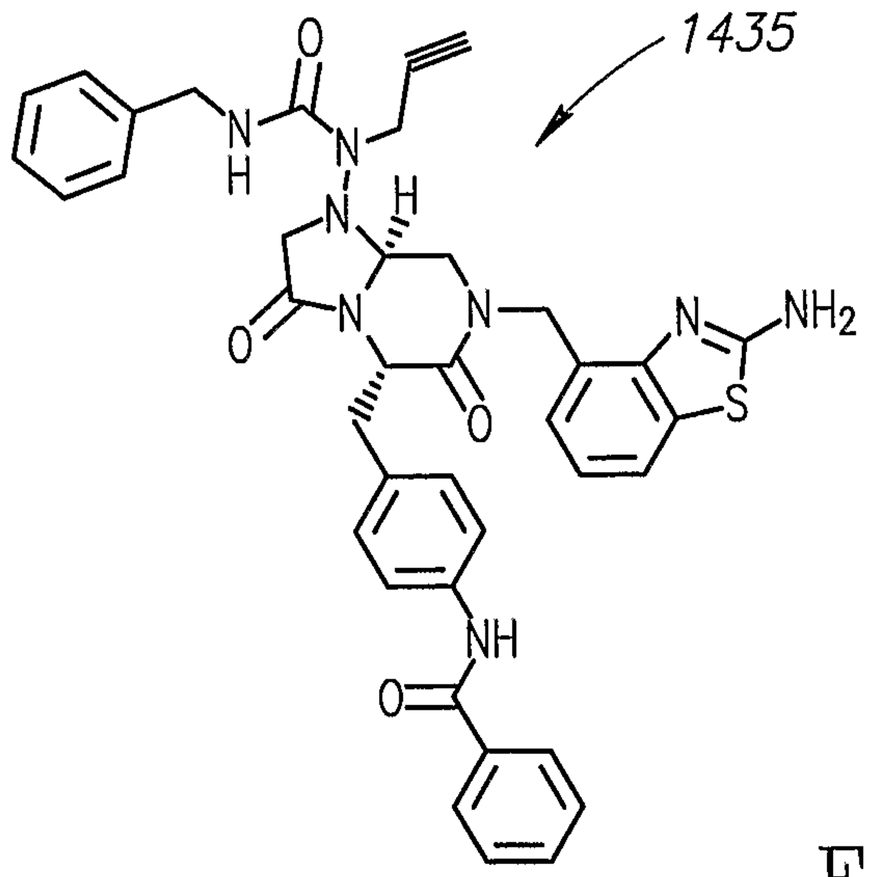
FIG.8E


1431
MeO
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
NH
O


1432
Cl
Cl
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
NH
O


1433
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
NH
O


1434
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
NH
O


1435
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
NH
O

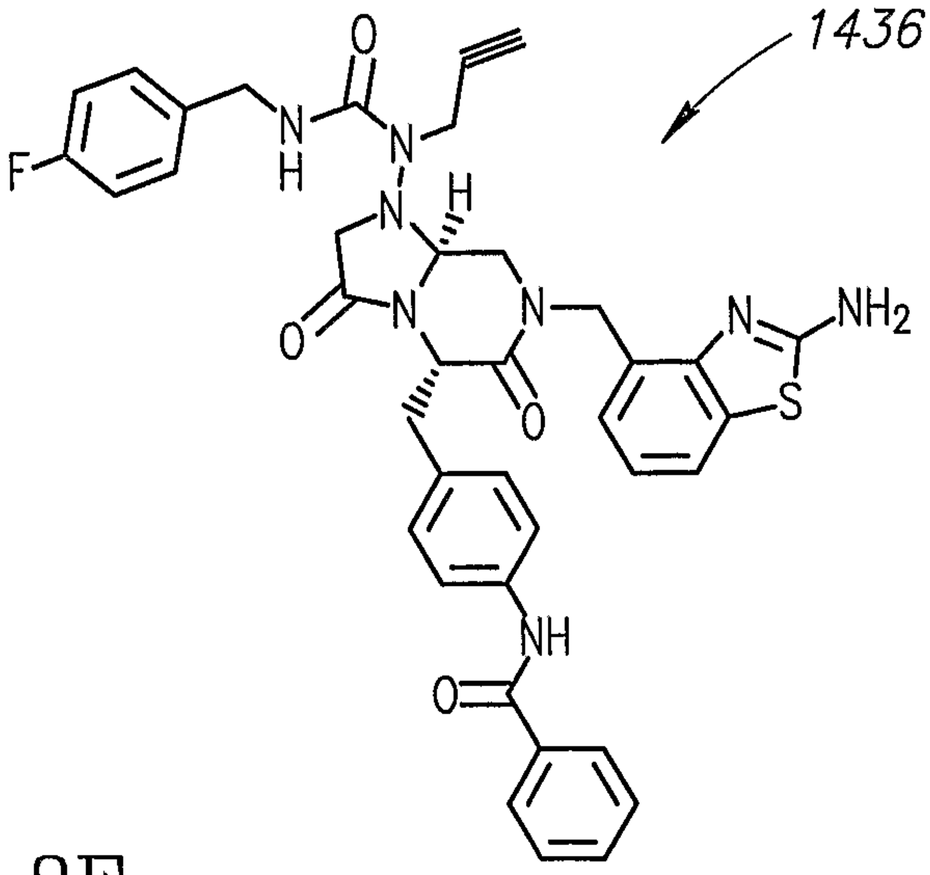
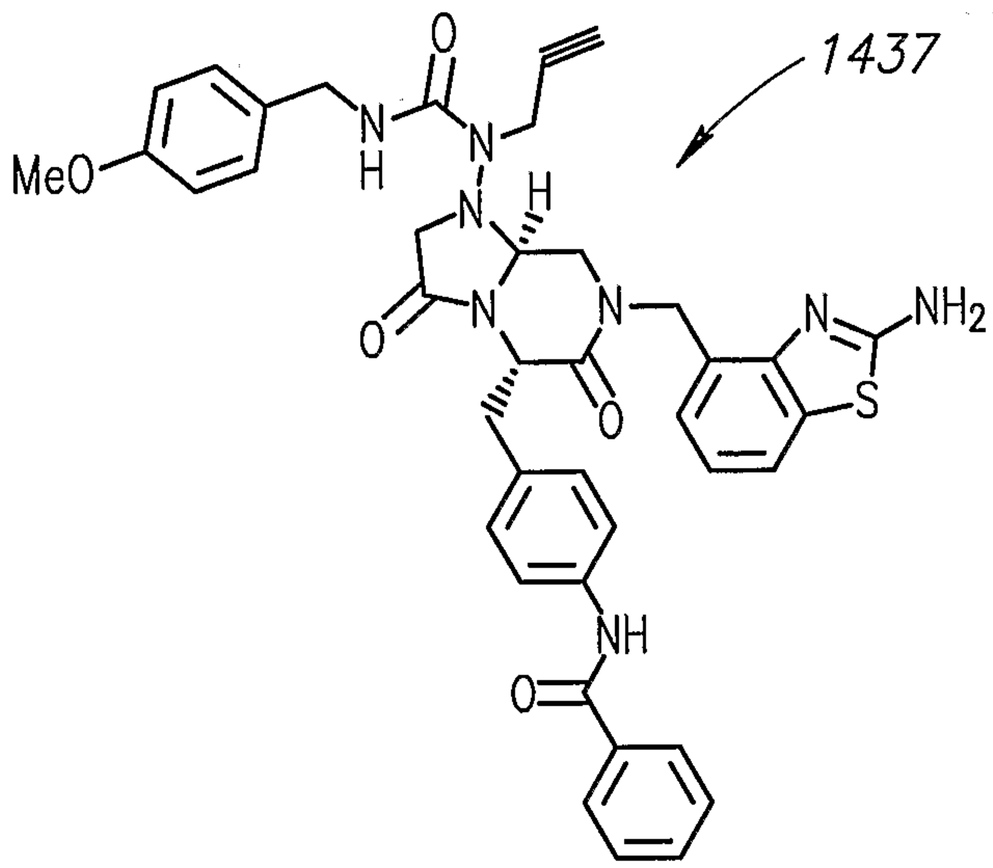
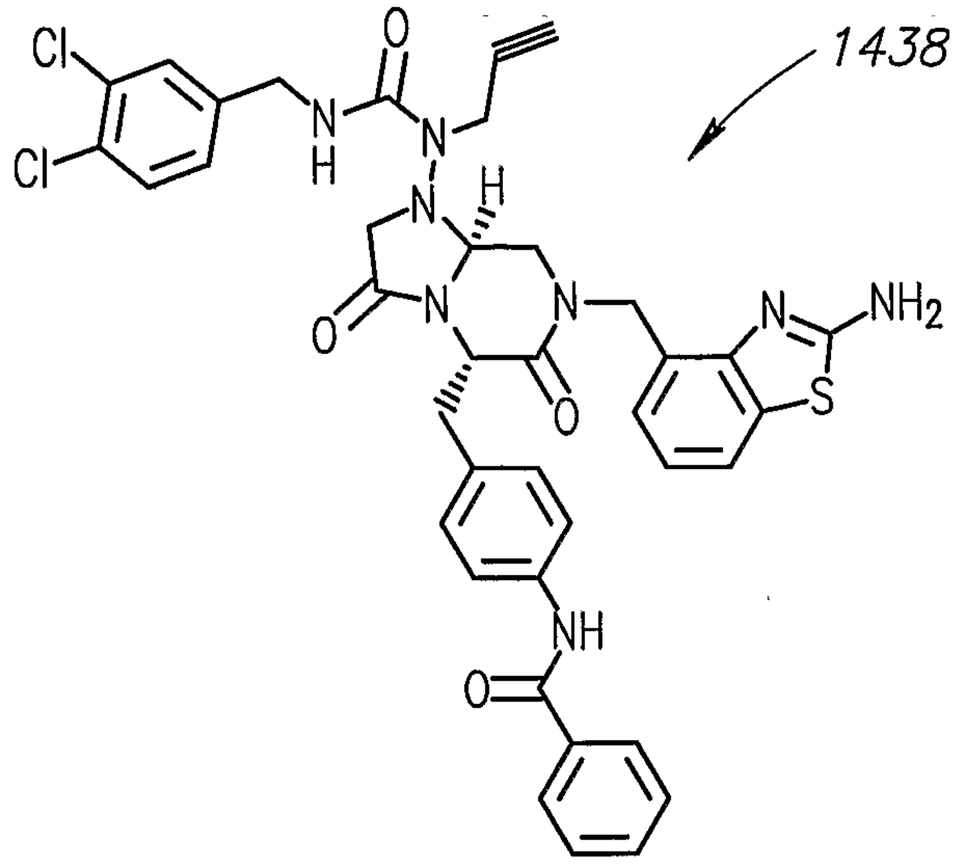

1436
F
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
NH
O

FIG.8F

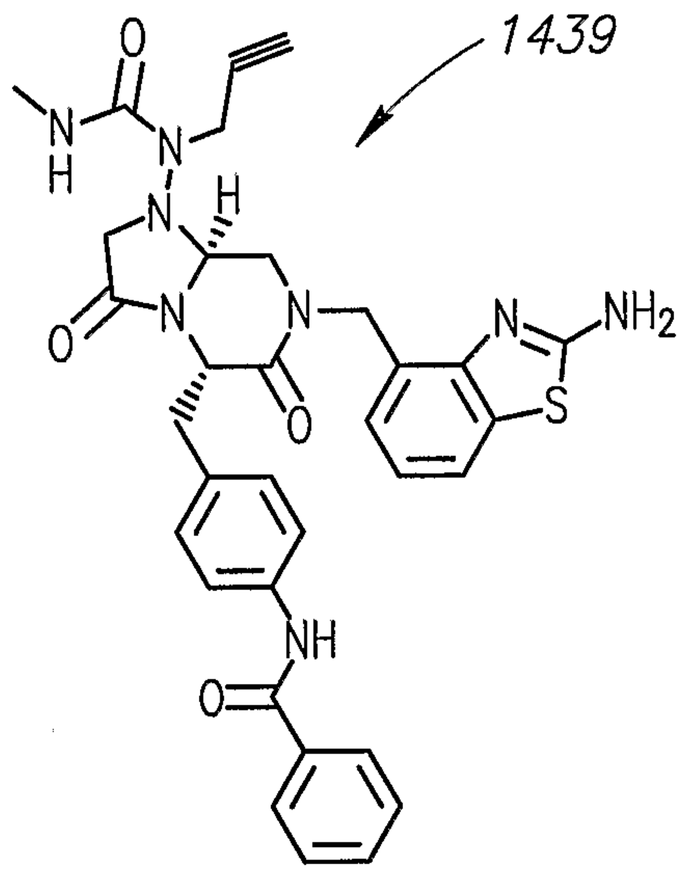
1437



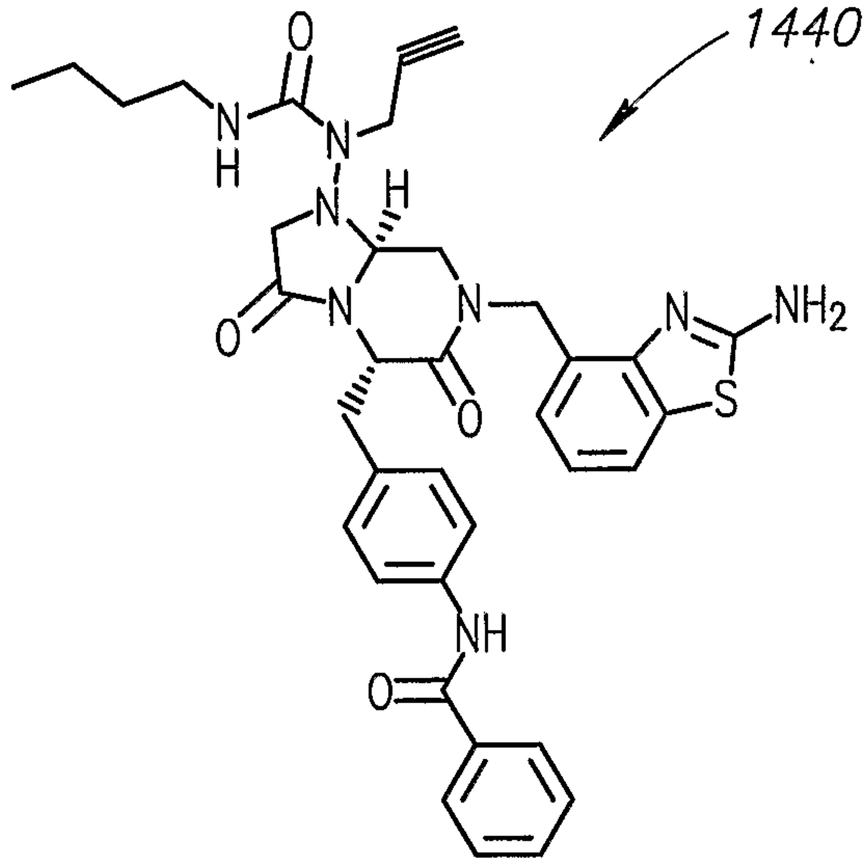
1438



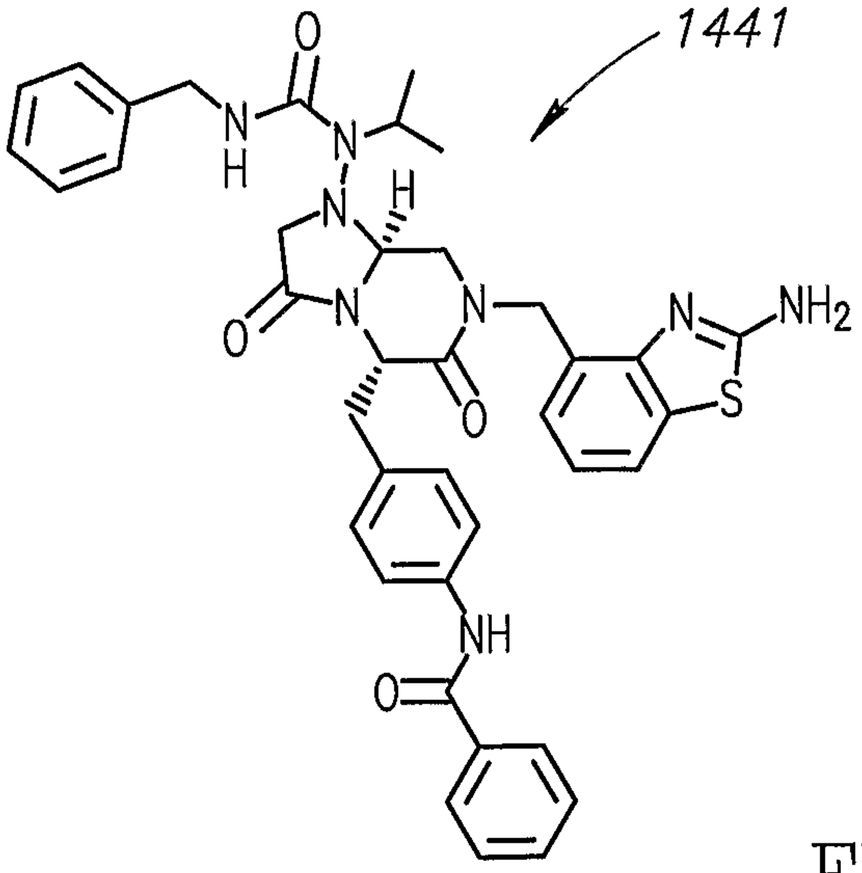
1439



1440



1441



1442

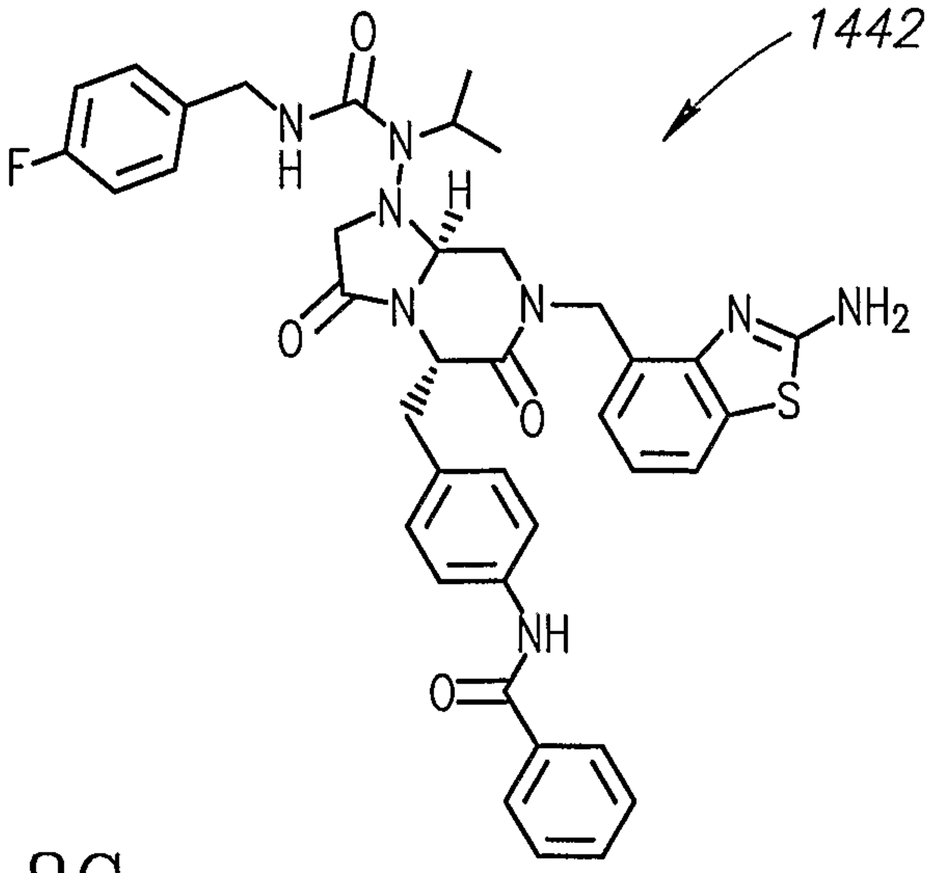
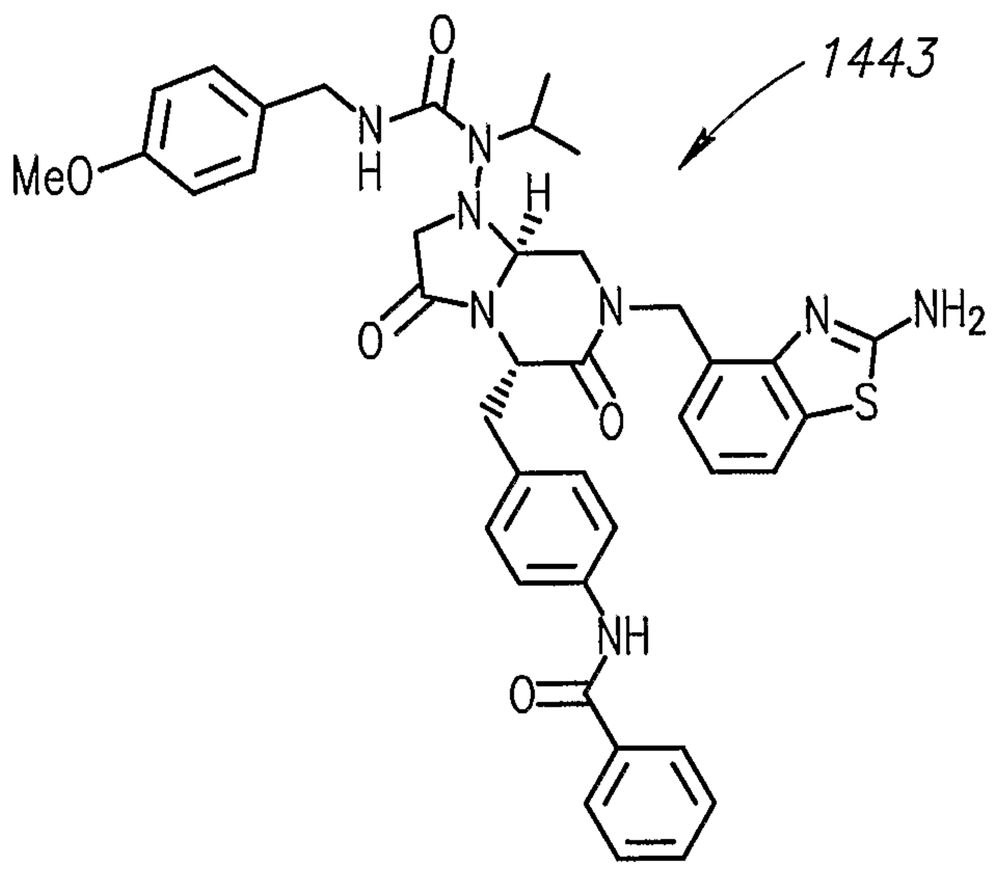
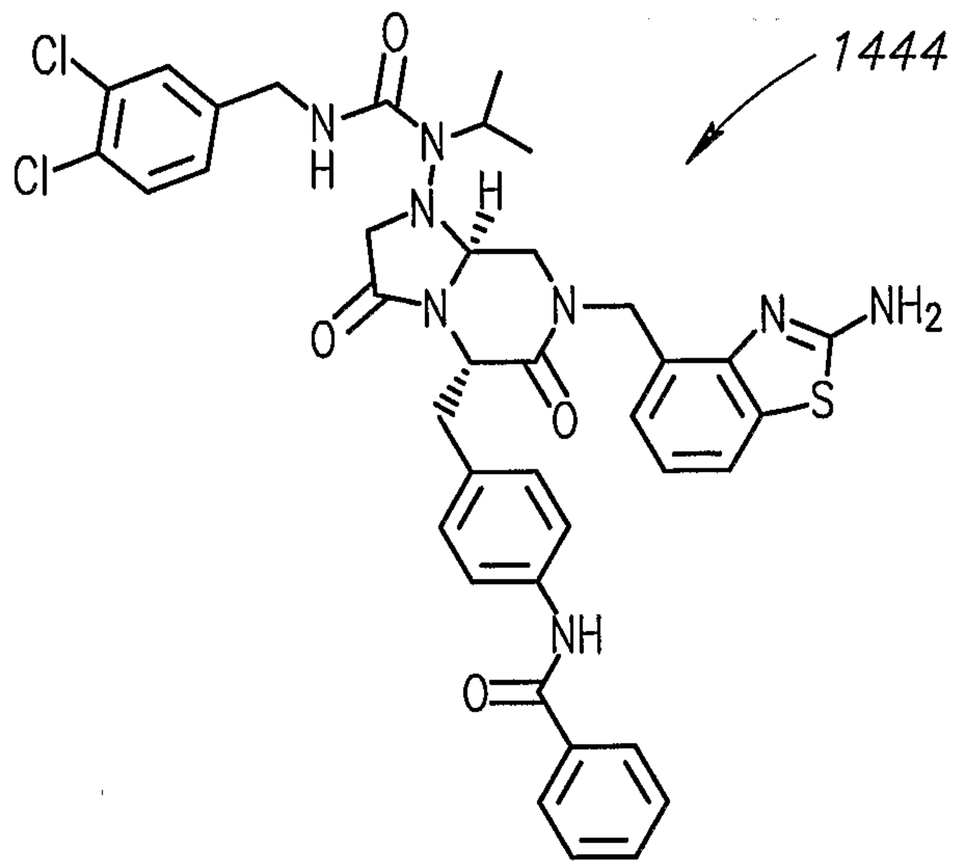


FIG.8G

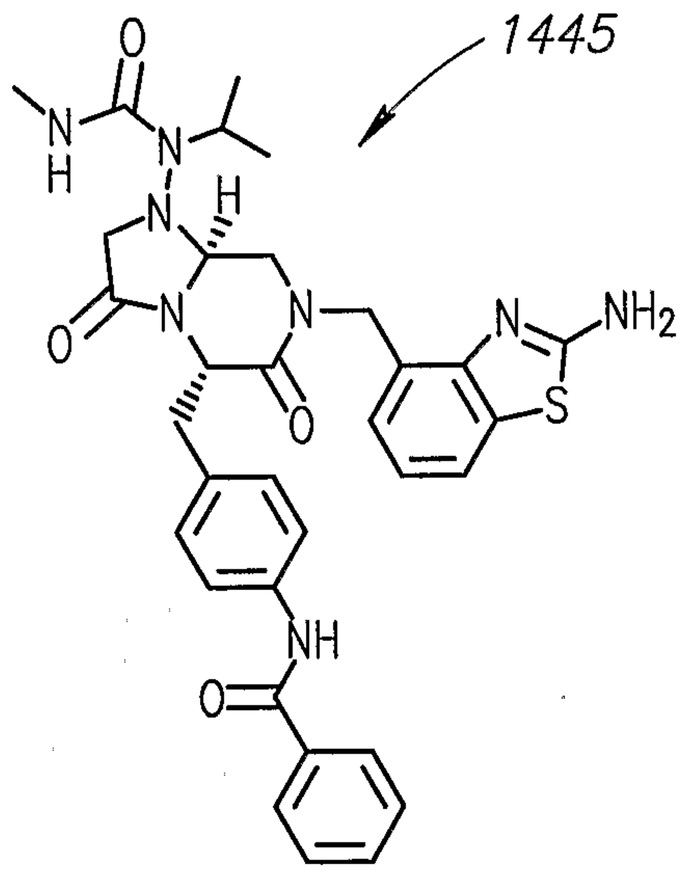
1443



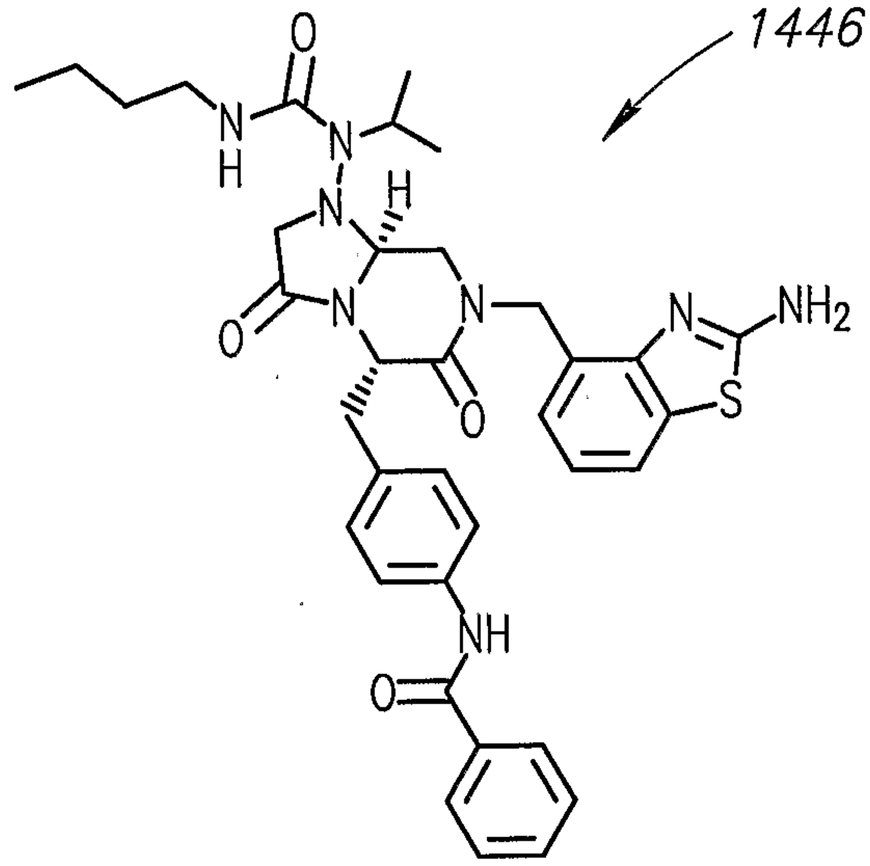
1444



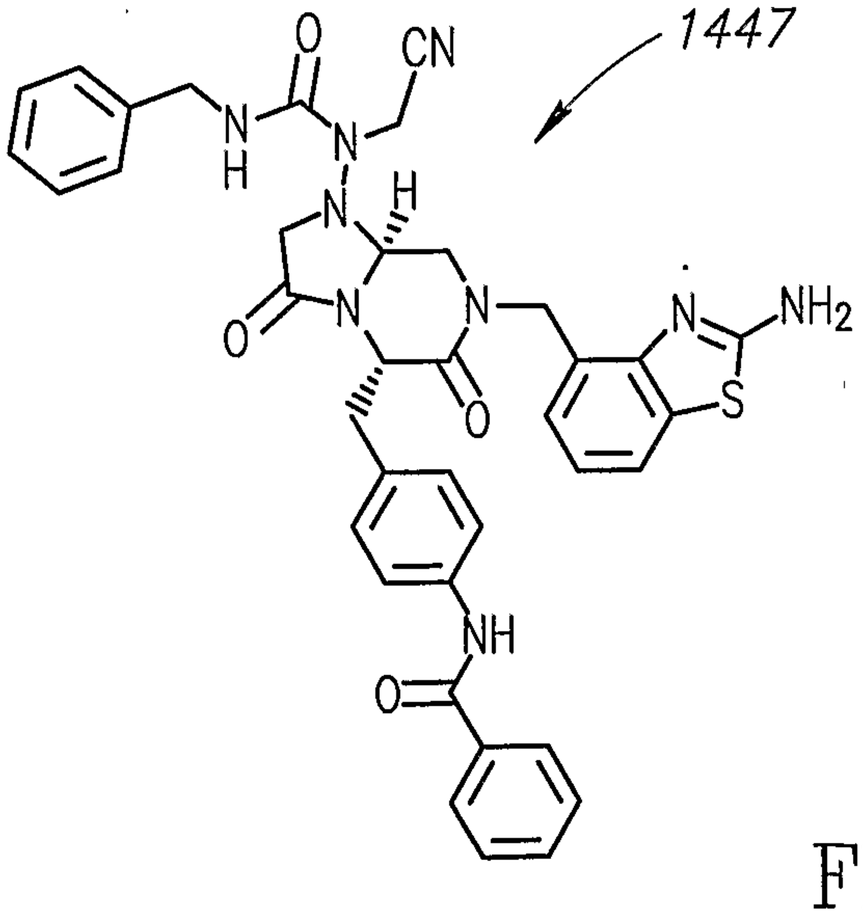
1445



1446



1447



1448

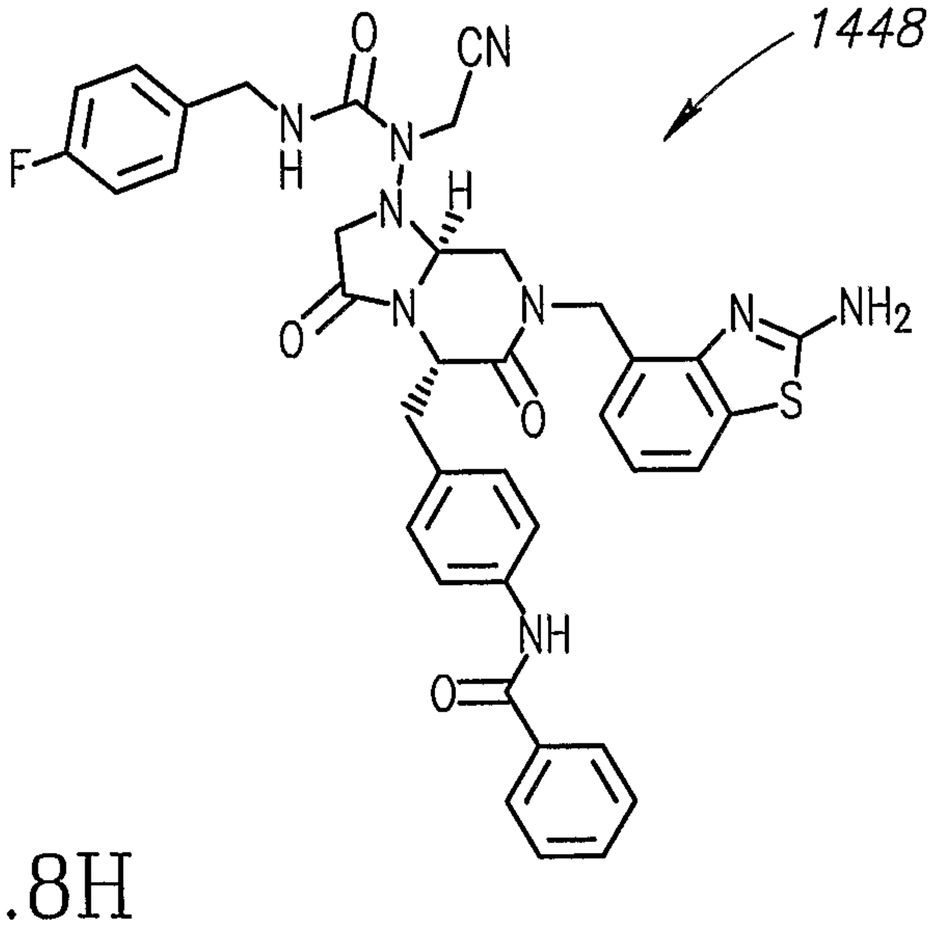
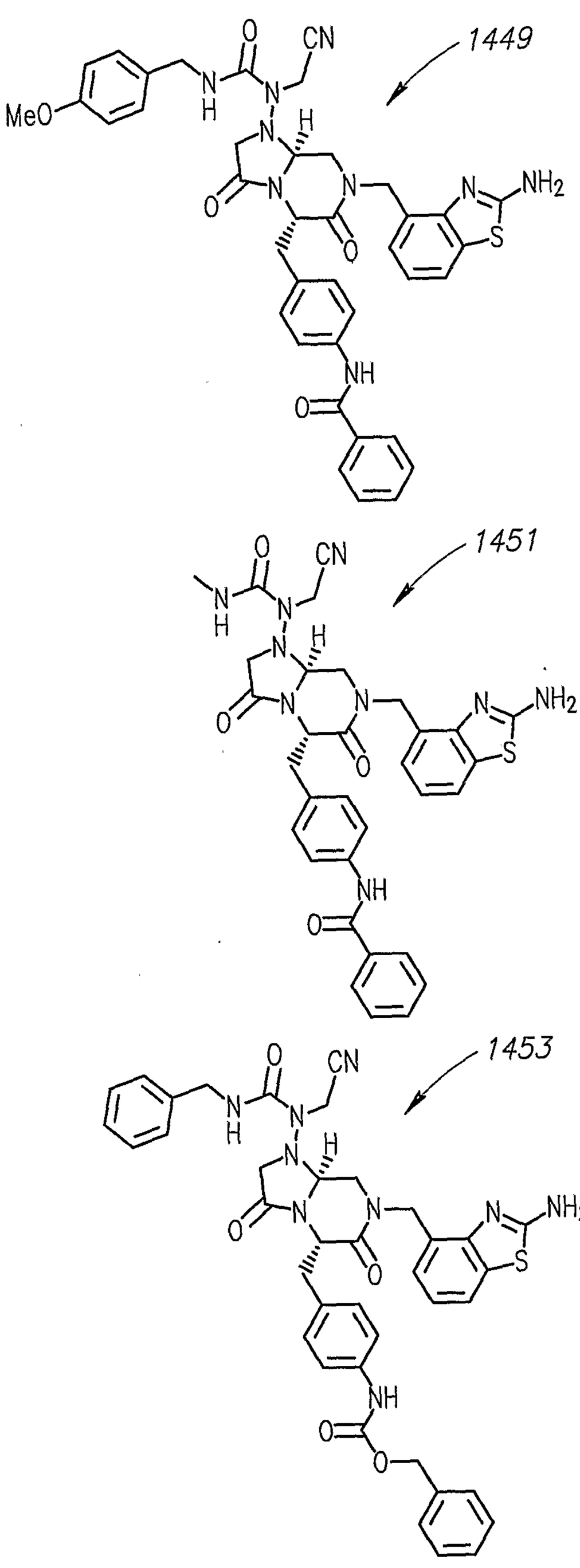
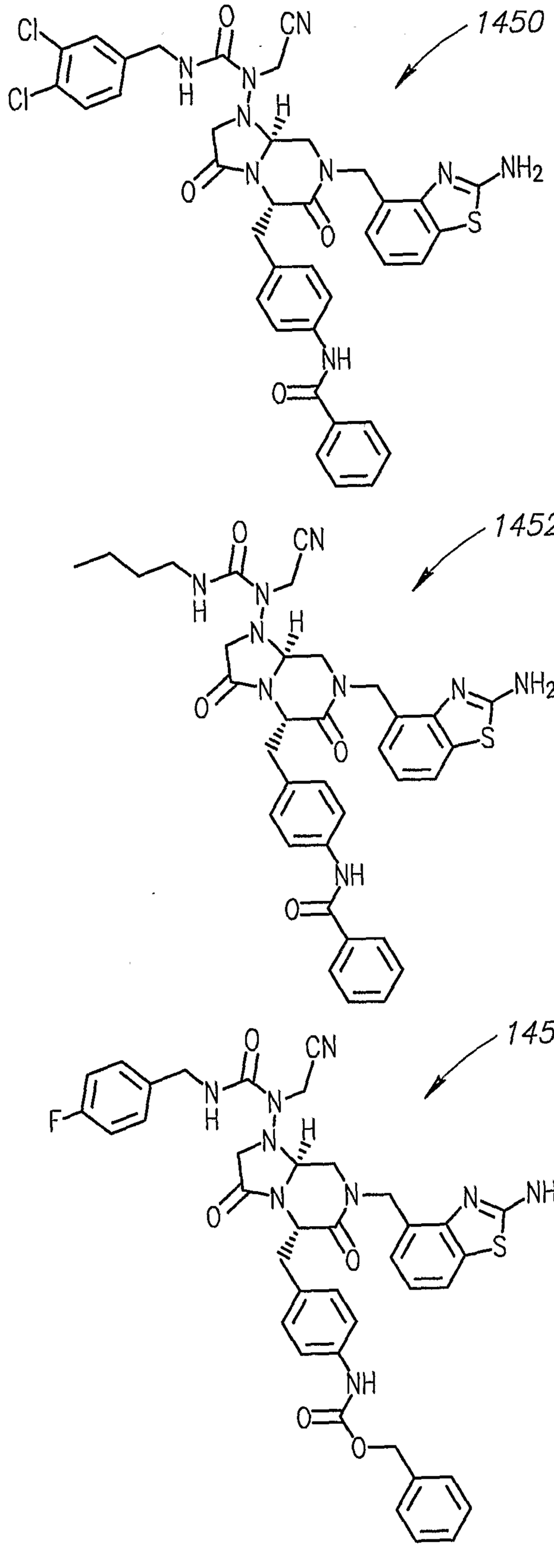


FIG.8H


1449
MeO
O
CN
N
H
N
N
O
N
O
N
S
NH2
NH
O


1450
Cl
Cl
O
CN
N
H
N
N
O
N
O
N
S
NH2
NH
O

1451
O
CN
N
H
N
N
O
N
O
N
S
NH2
NH
O

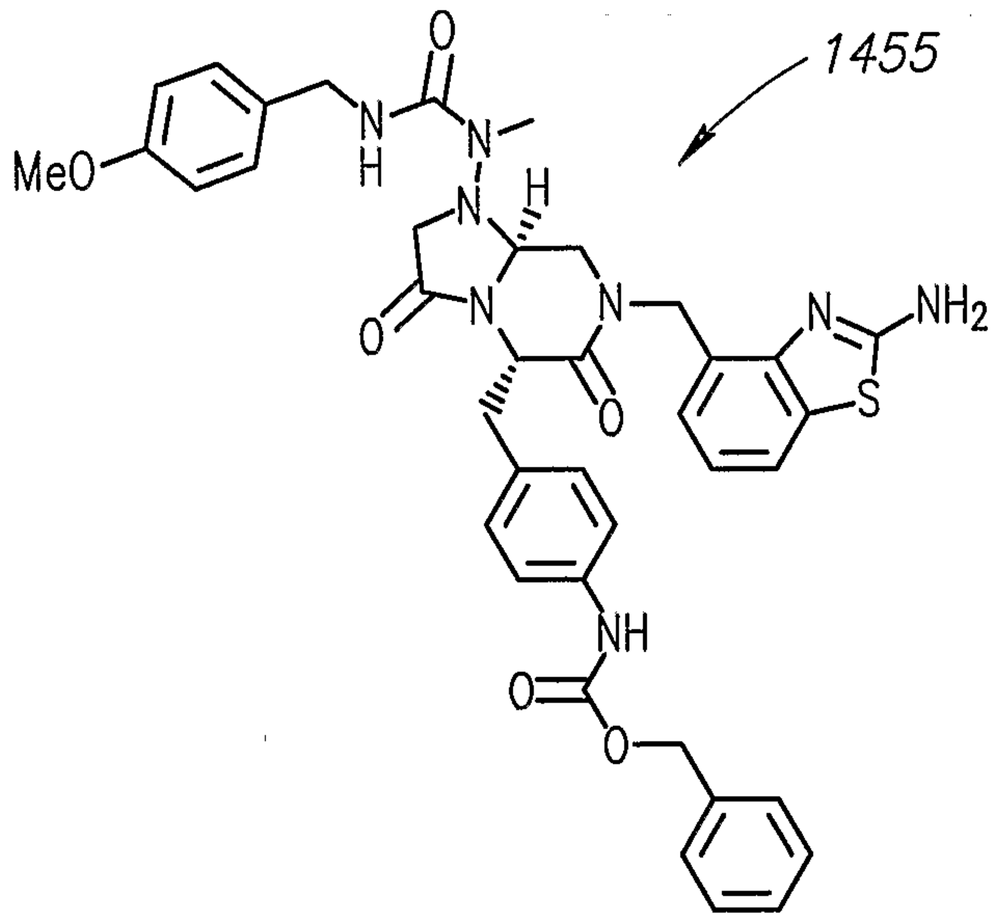
1452
O
CN
N
H
N
N
O
N
O
N
S
NH2
NH
O

1453
O
CN
N
H
N
N
O
N
O
N
S
NH2
NH
O
O

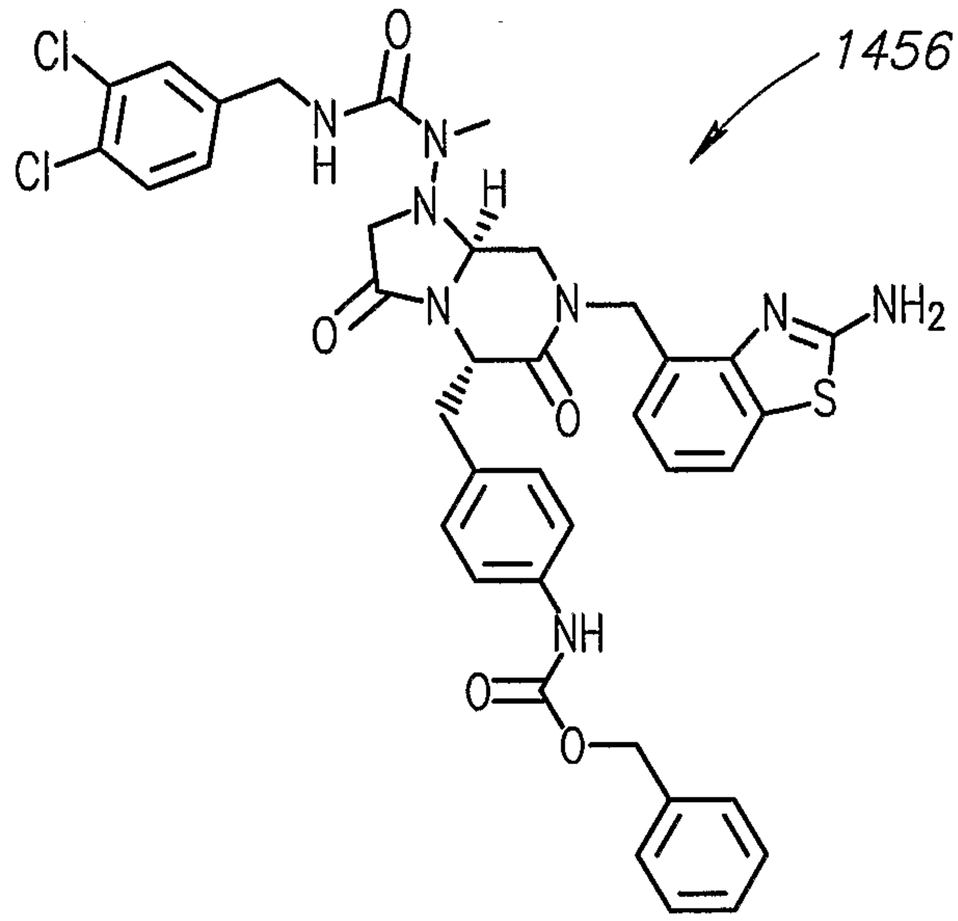
1454
F
O
CN
N
H
N
N
O
N
O
N
S
NH2
NH
O
O

FIG.8I

1455



1456



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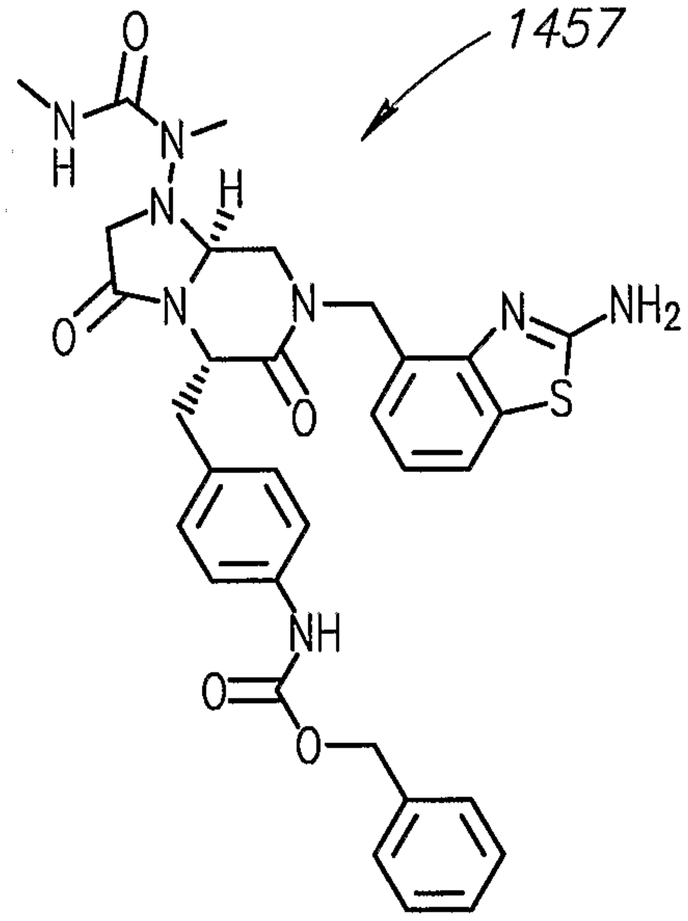

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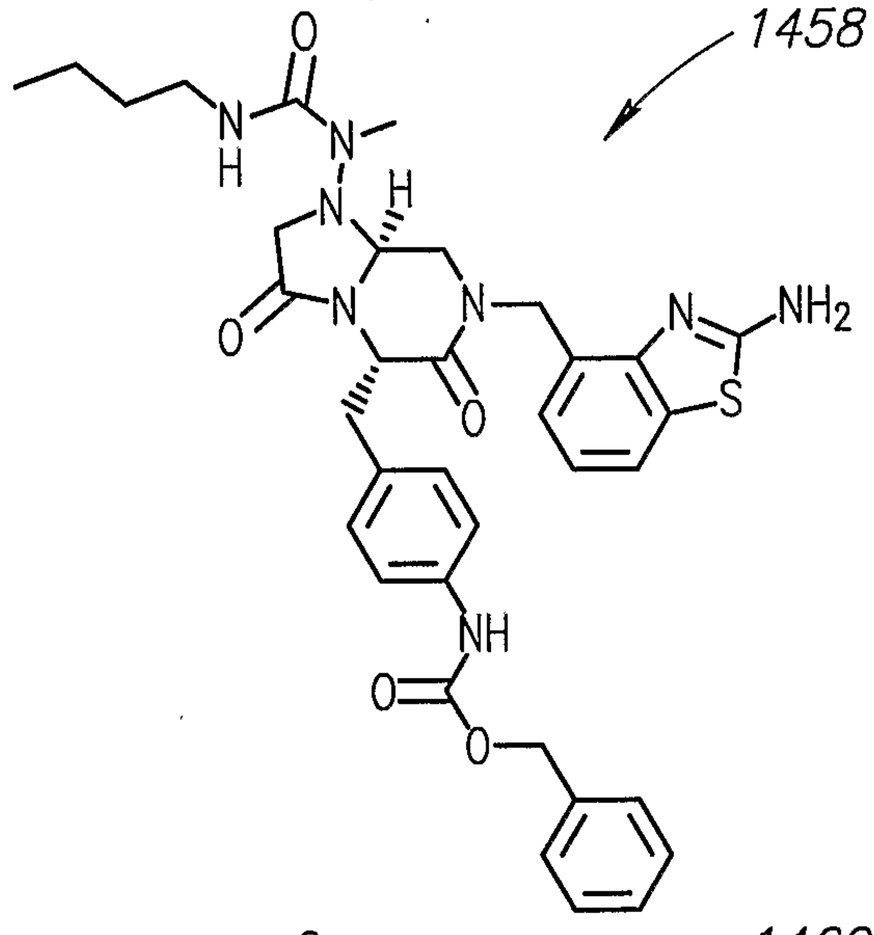

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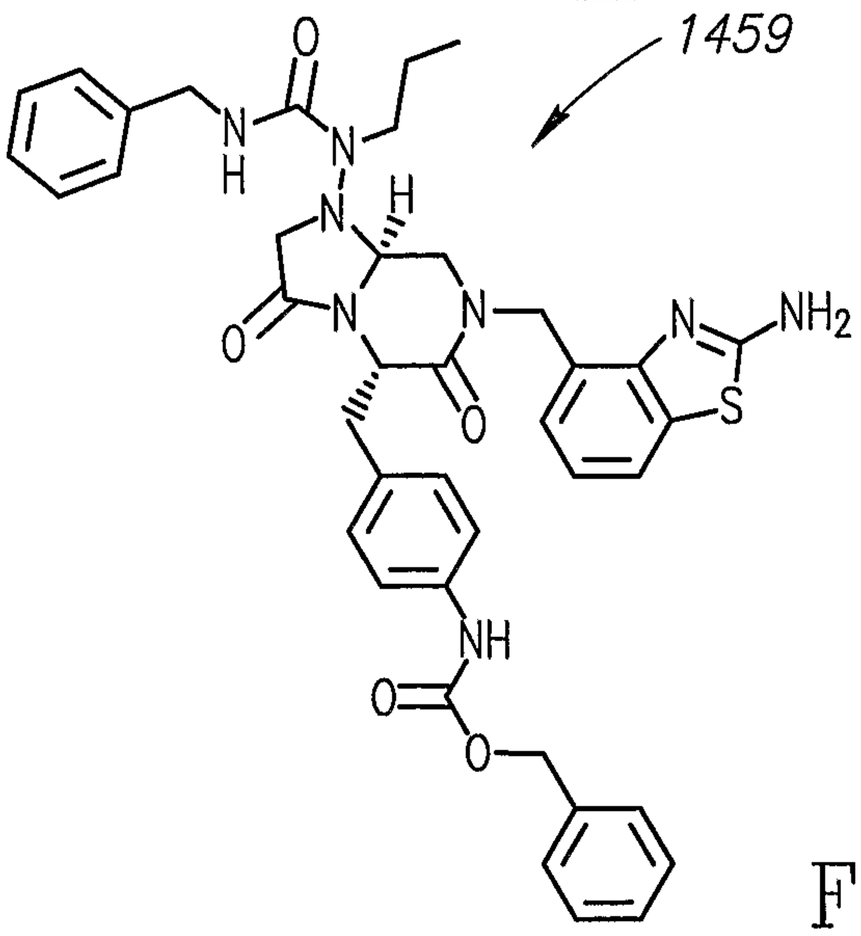

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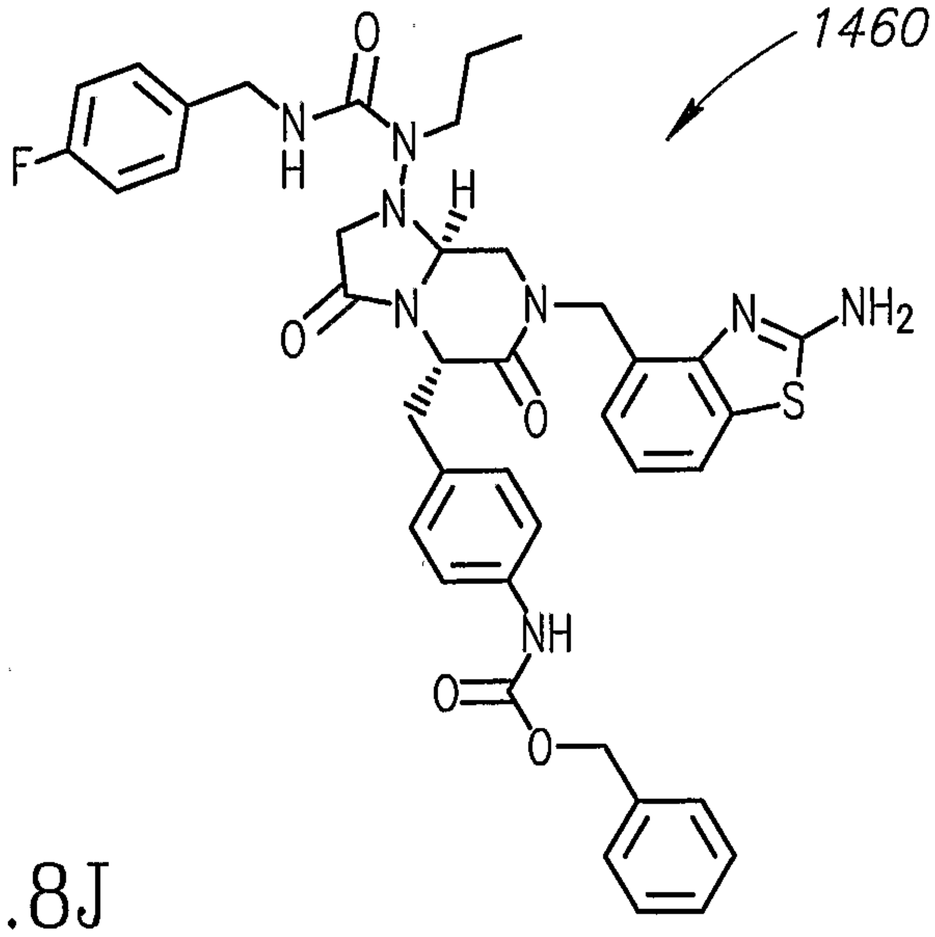
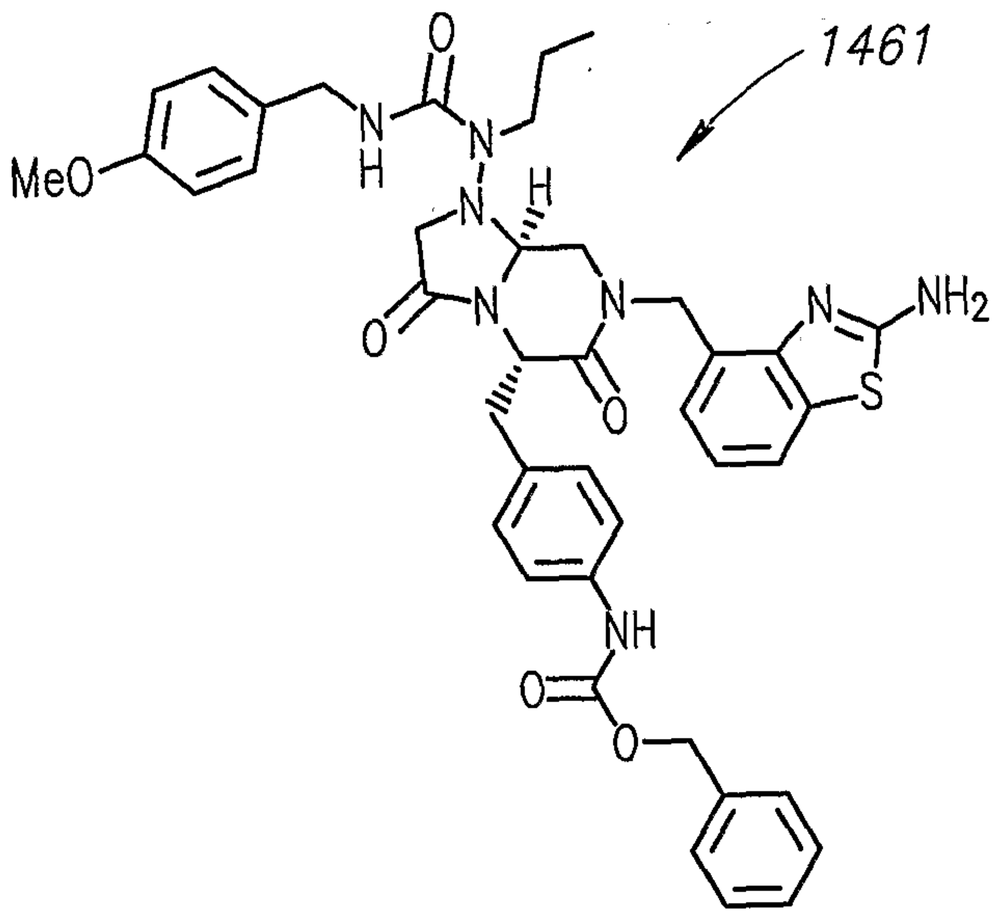


FIG.8J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MeO
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N
H
N
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N
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N
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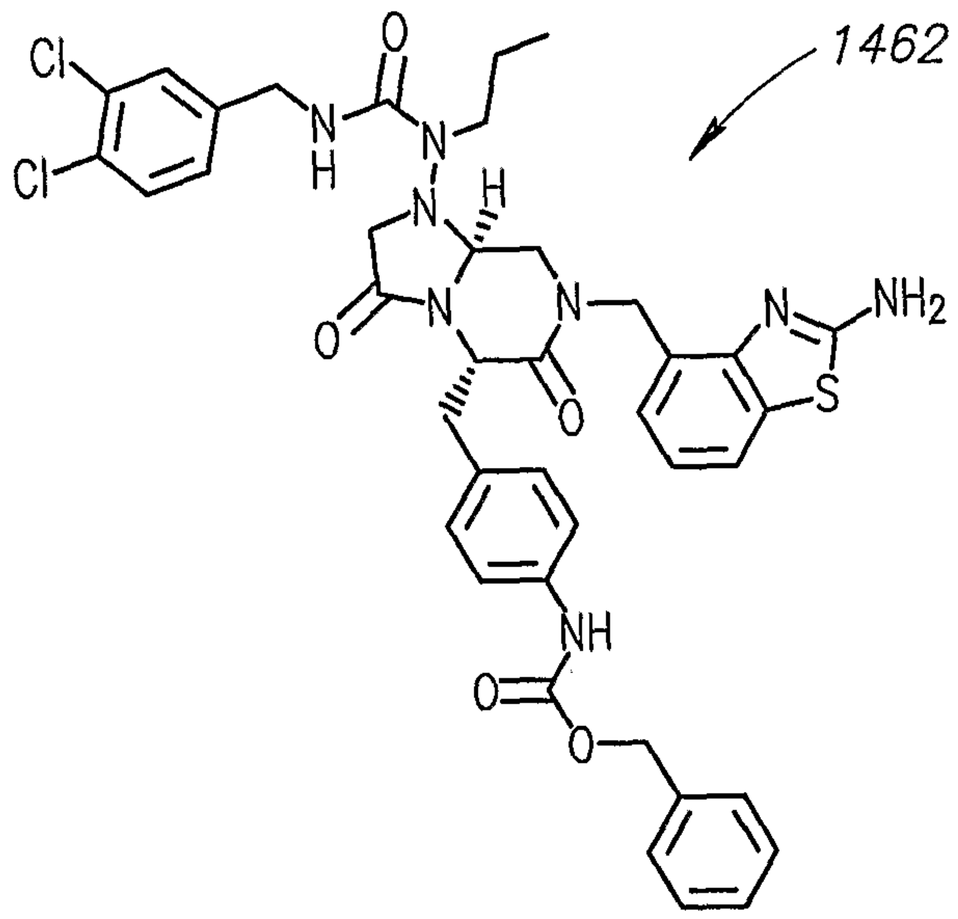
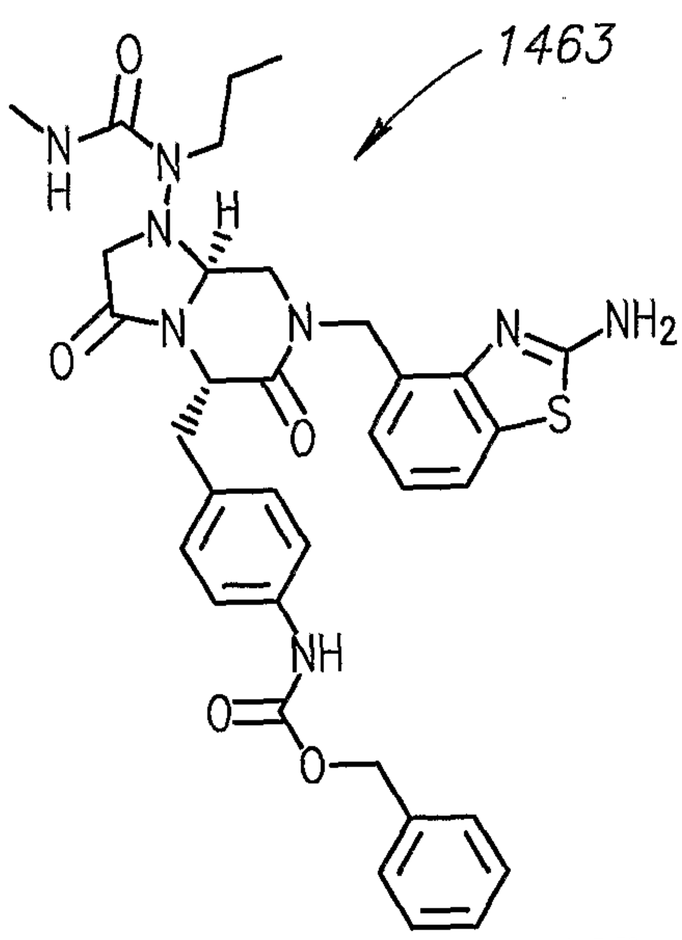
N
N
S
NH2
NH
O
O
O


1462
Cl
Cl
O
N
H
N
H
N
O
N
O
N
N
S
NH2
NH
O
O
O


1463
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N
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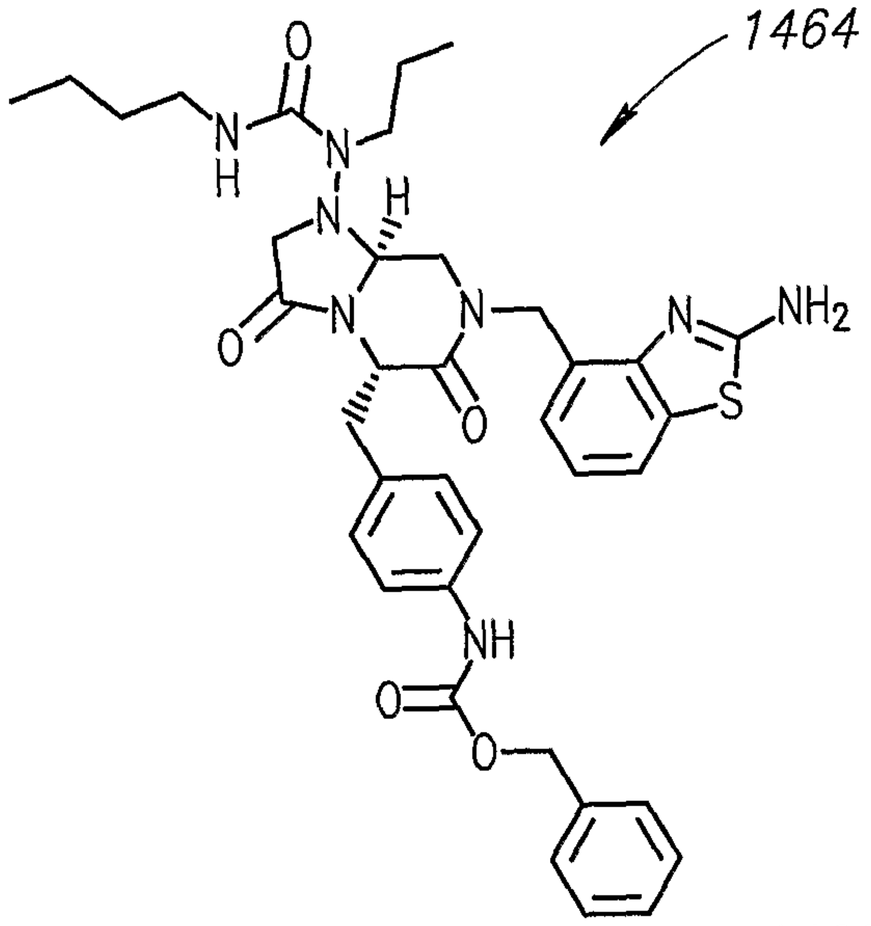
N
O
N
O
N
N
S
NH2
NH
O
O
O


1464
O
N
H
N
H
N
O
N
O
N
N
S
NH2
NH
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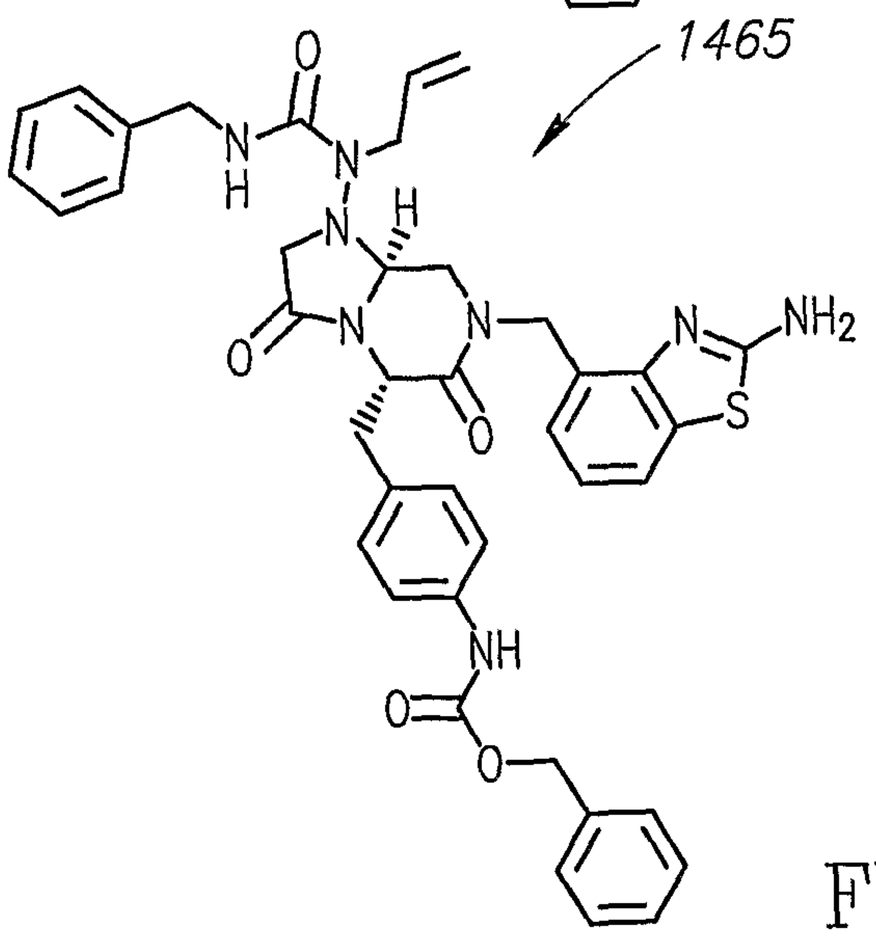
O
O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N
H
N
H
N
O
N
O
N
N
S
NH2
NH
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O
O

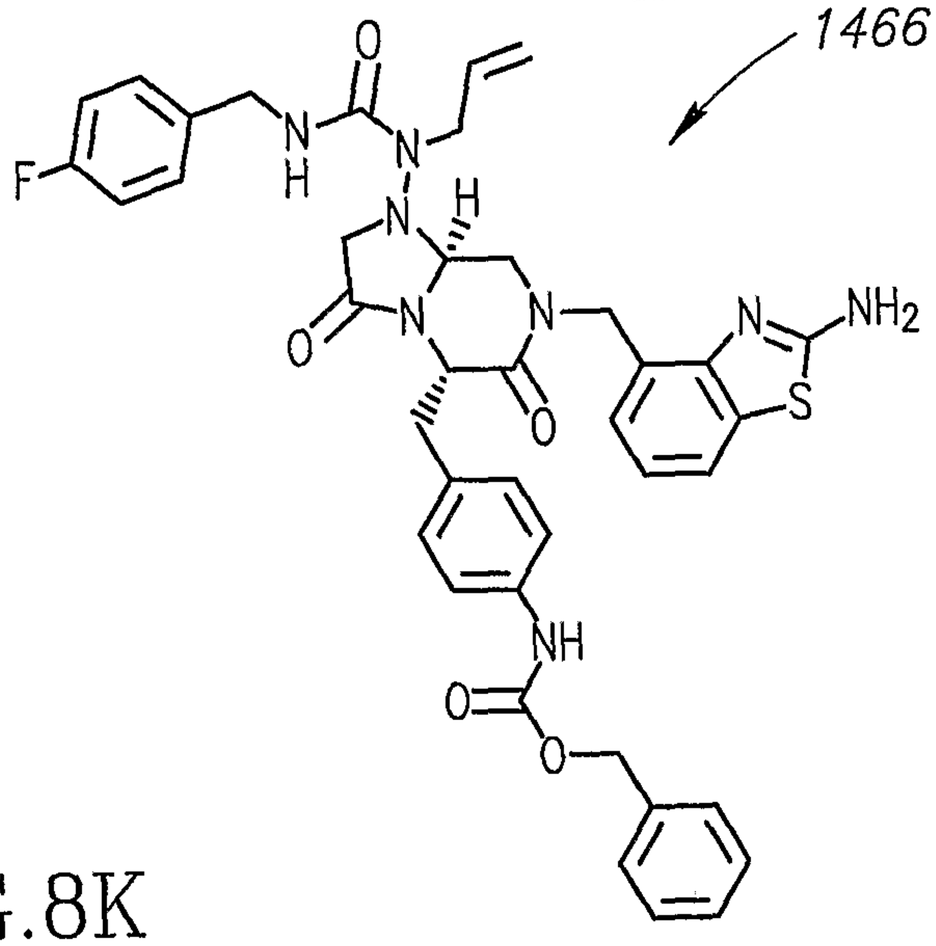
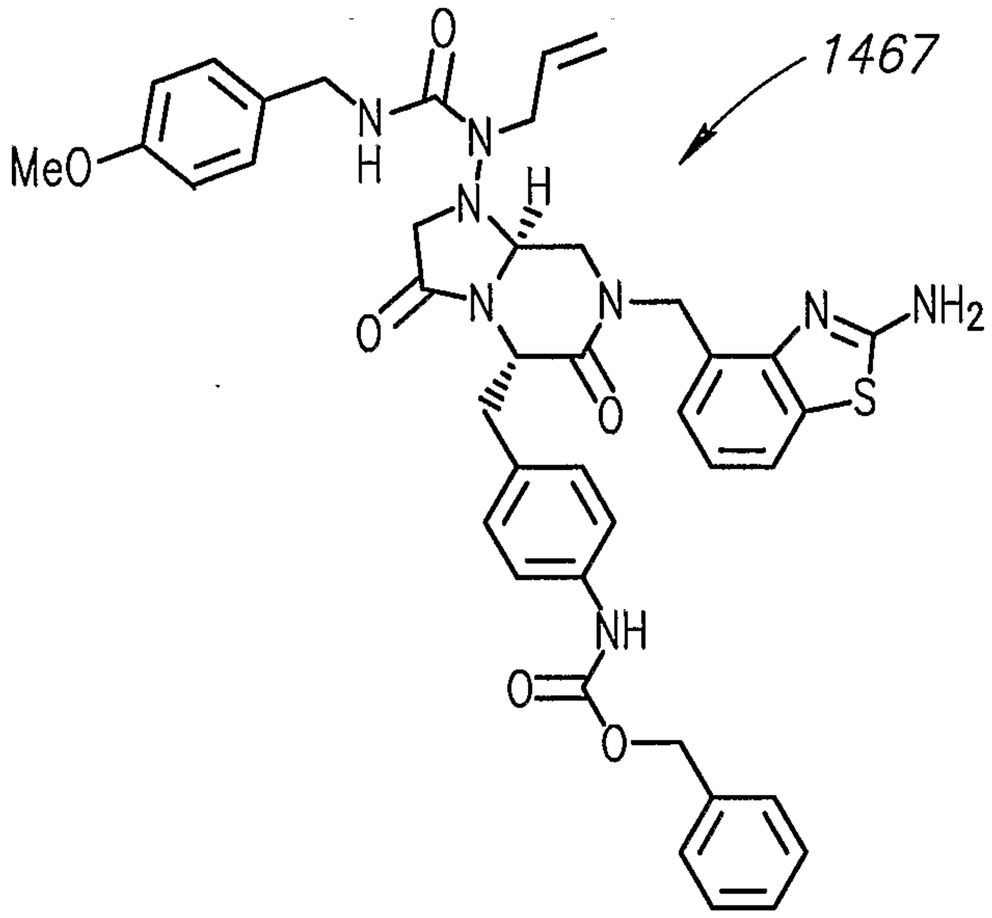

1466
F
O
N
H
N
H
N
O
N
O
N
N
S
NH2
NH
O
O
O

FIG.8K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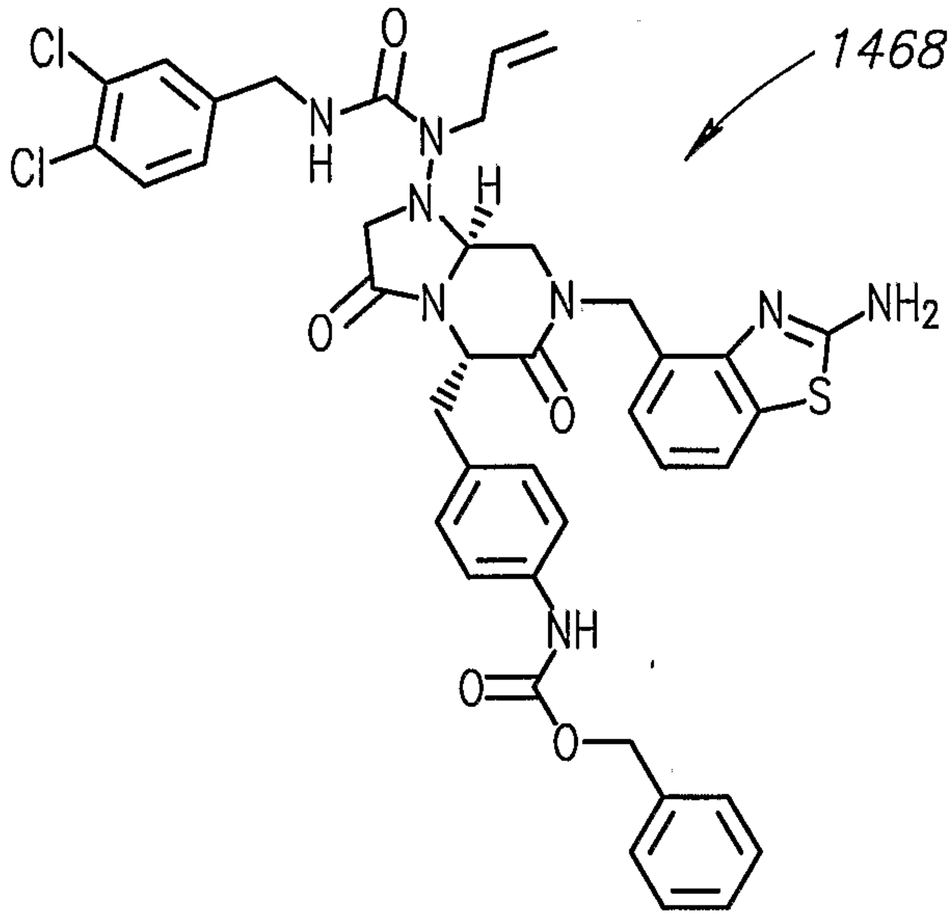
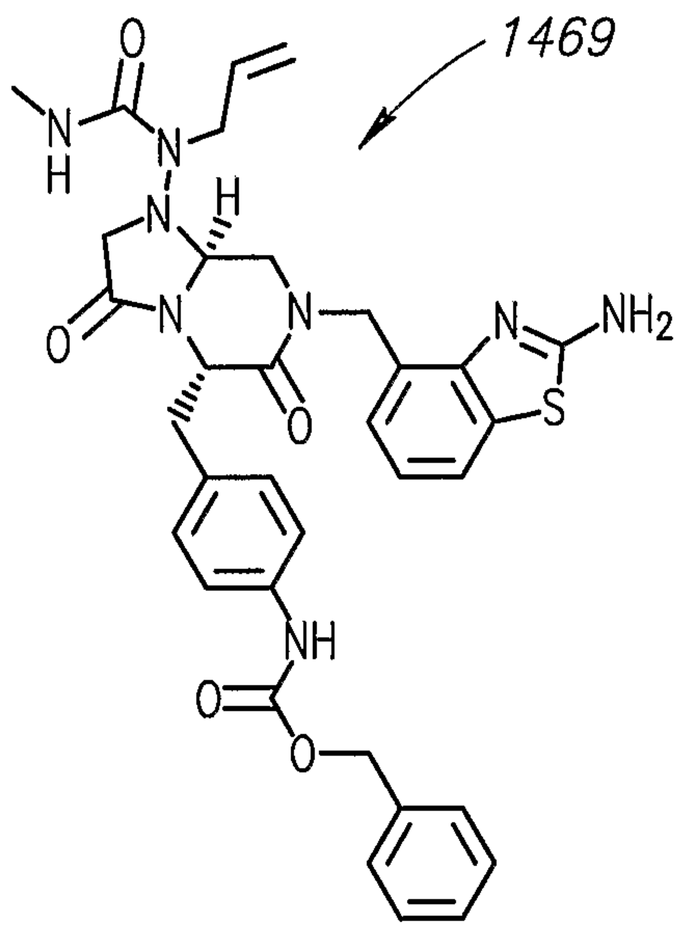
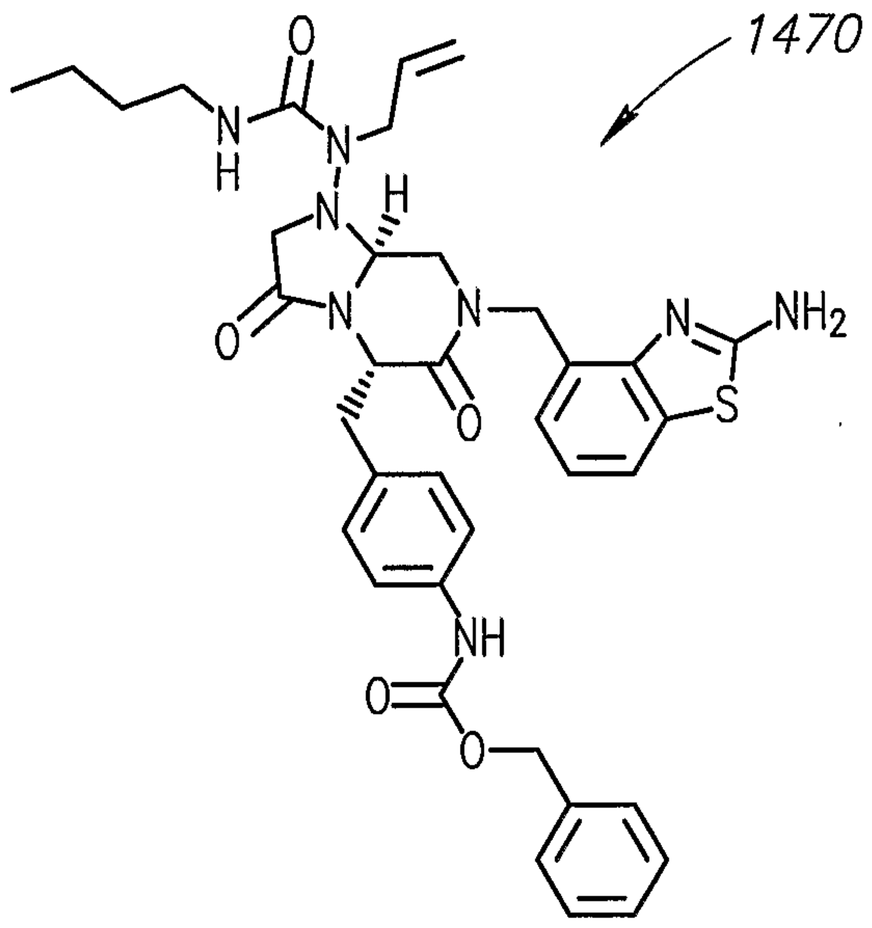
MeO
O
N
H
N
H
O
N
N
O
N
N
S
NH2
NH
O
O


1468
Cl
Cl
O
N
H
N
H
O
N
N
O
N
N
S
NH2
NH
O
O


1469
O
N
H
N
H
O
N
N
O
N
N
S
NH2
NH
O
O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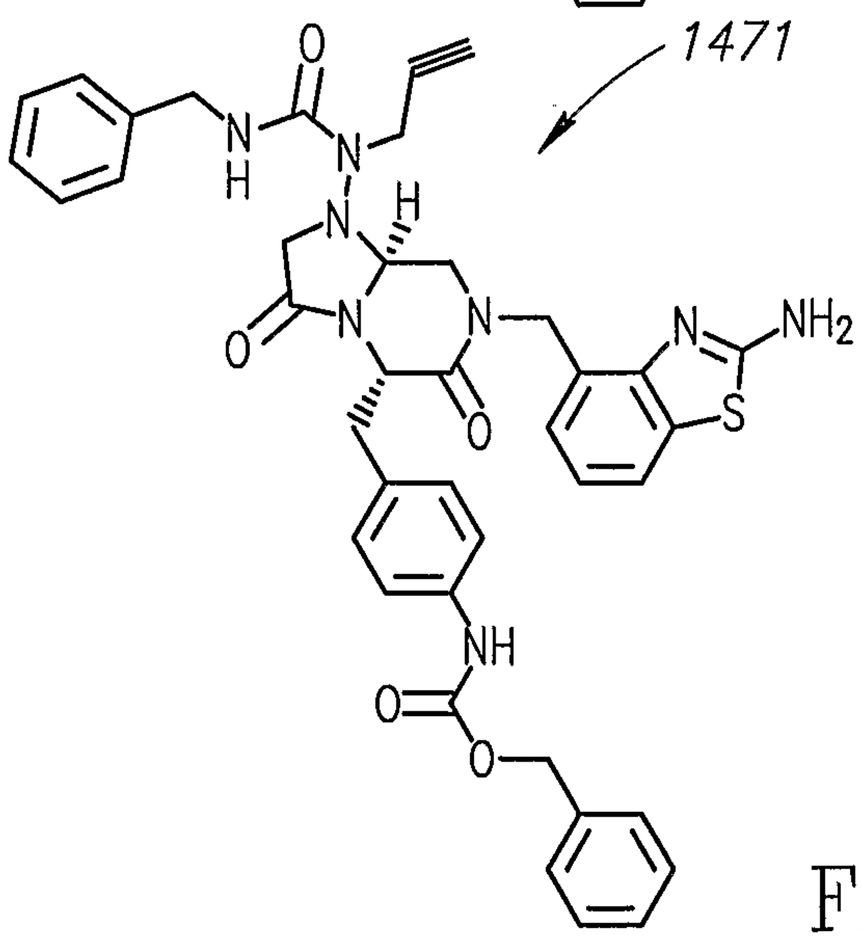
O
N
H
N
H
O
N
N
O
N
N
S
NH2
NH
O
O


1471
O
N
H
N
H
O
N
N
O
N
N
S
NH2
NH
O
O

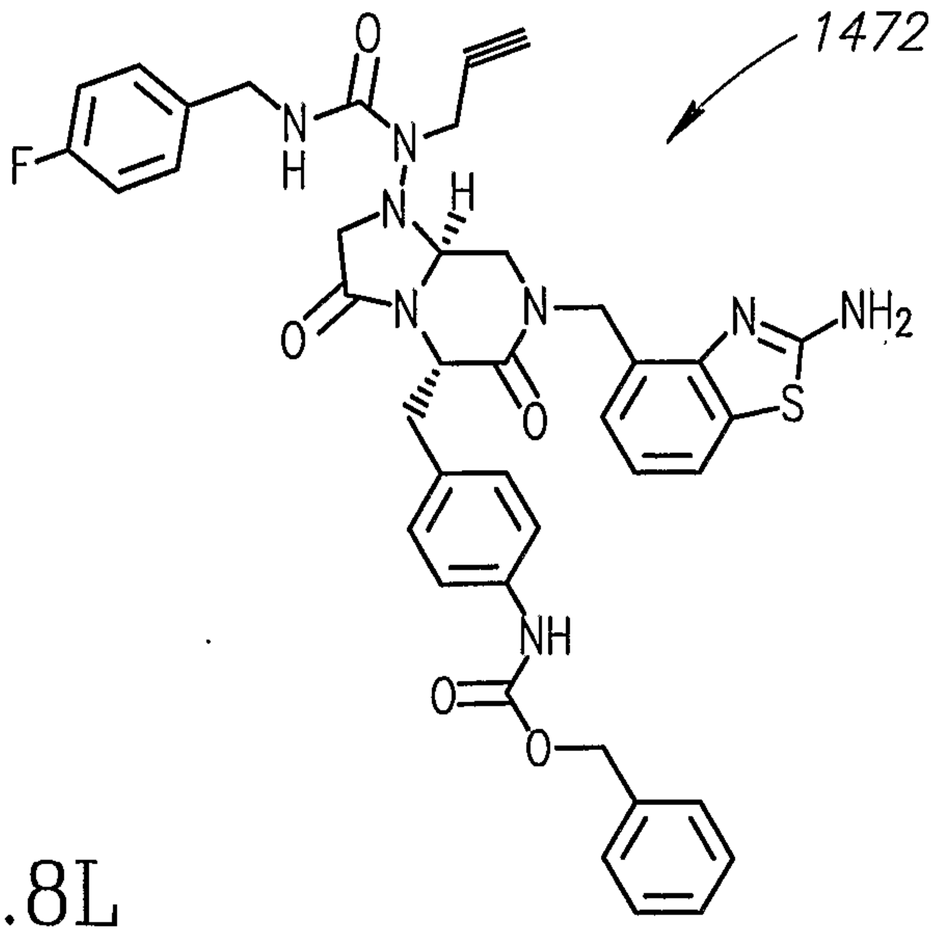
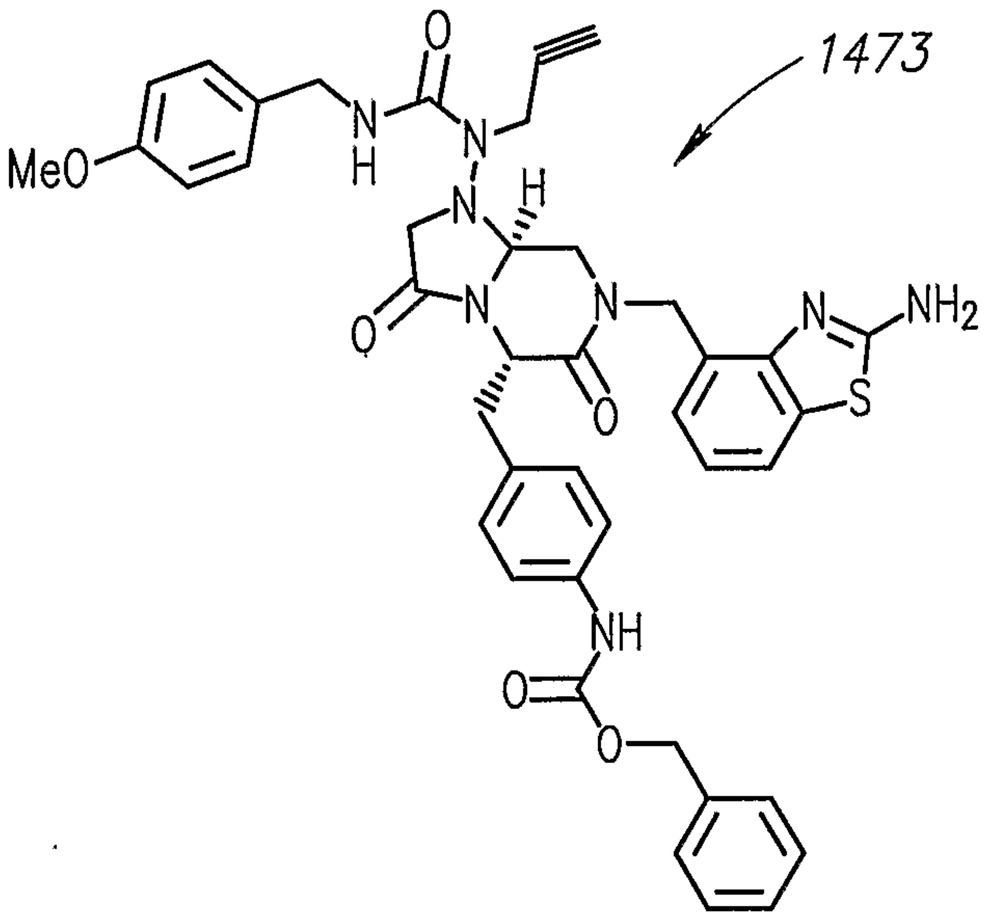
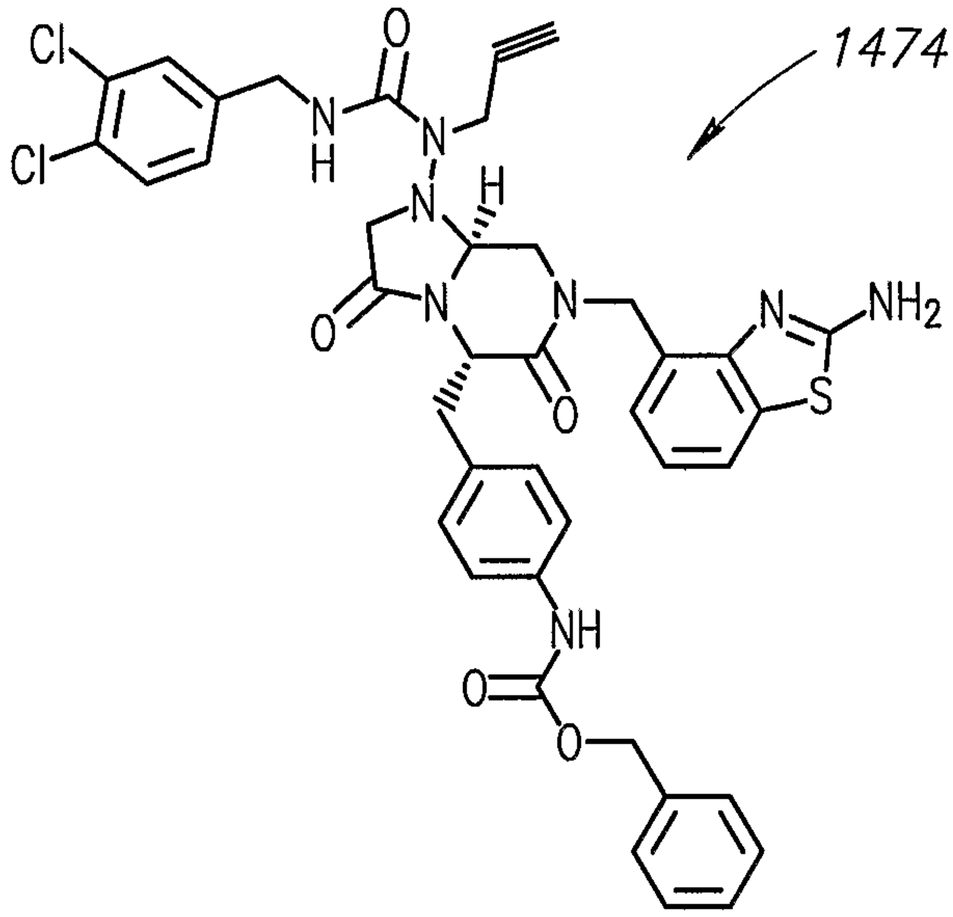
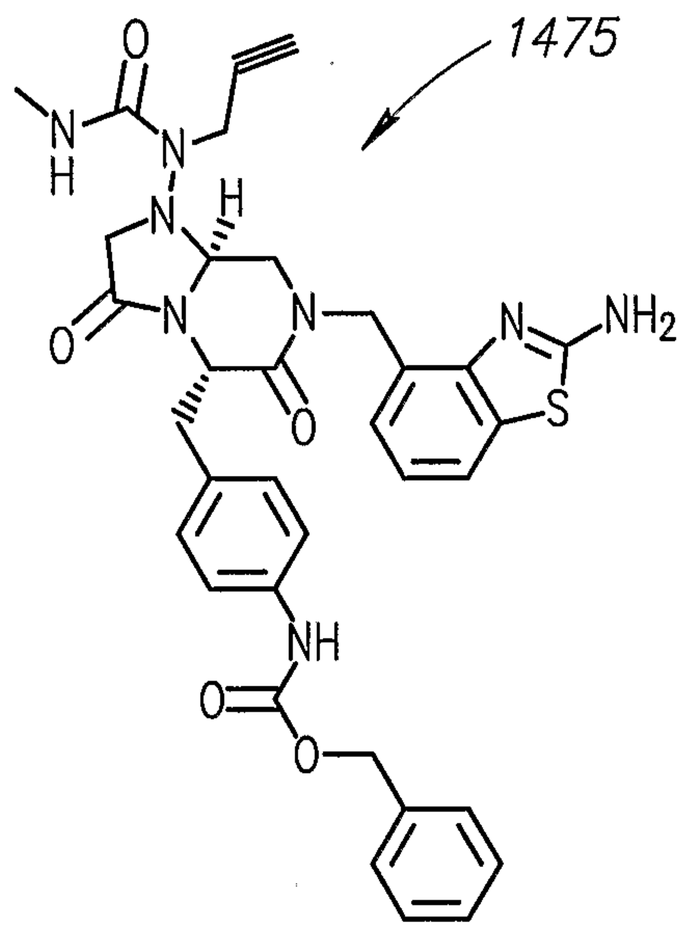

1472
F
O
N
H
N
H
O
N
N
O
N
N
S
NH2
NH
O
O

FIG.8L


1473
MeO
O
N
H
N
O
O
NH
O
O
N
S
NH2


1474
Cl
Cl
O
N
H
N
O
O
NH
O
O
N
S
NH2


1475
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N
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N
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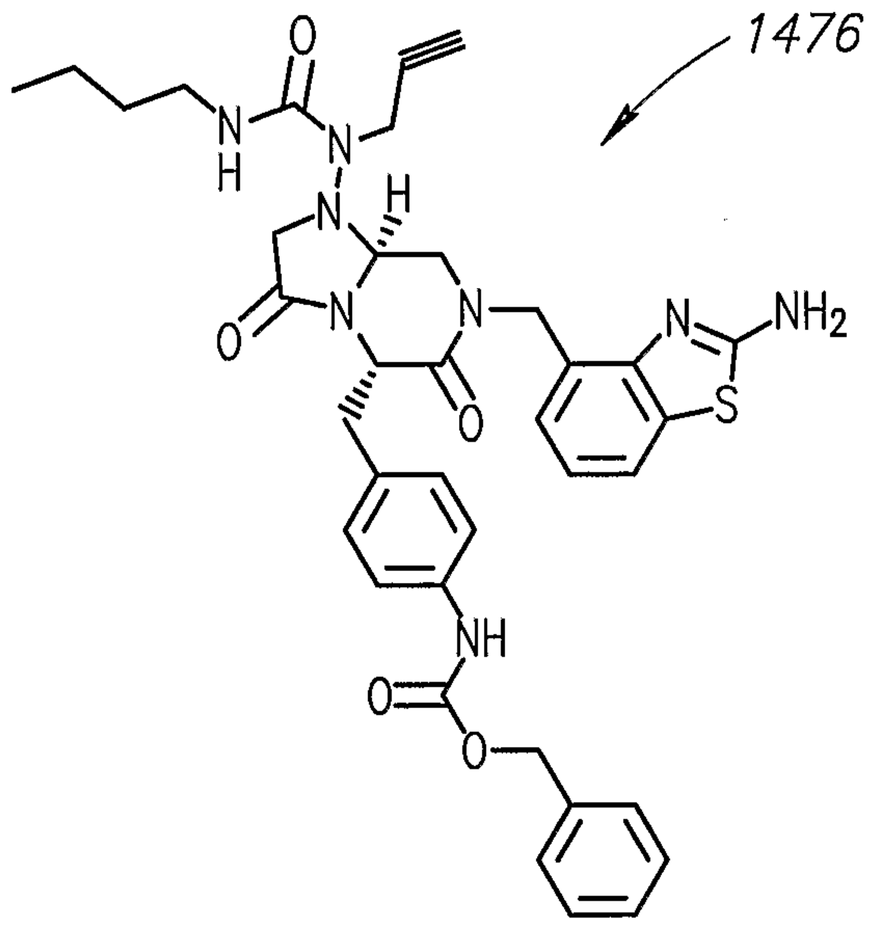
NH
O
O
N
S
NH2


1476
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O
N
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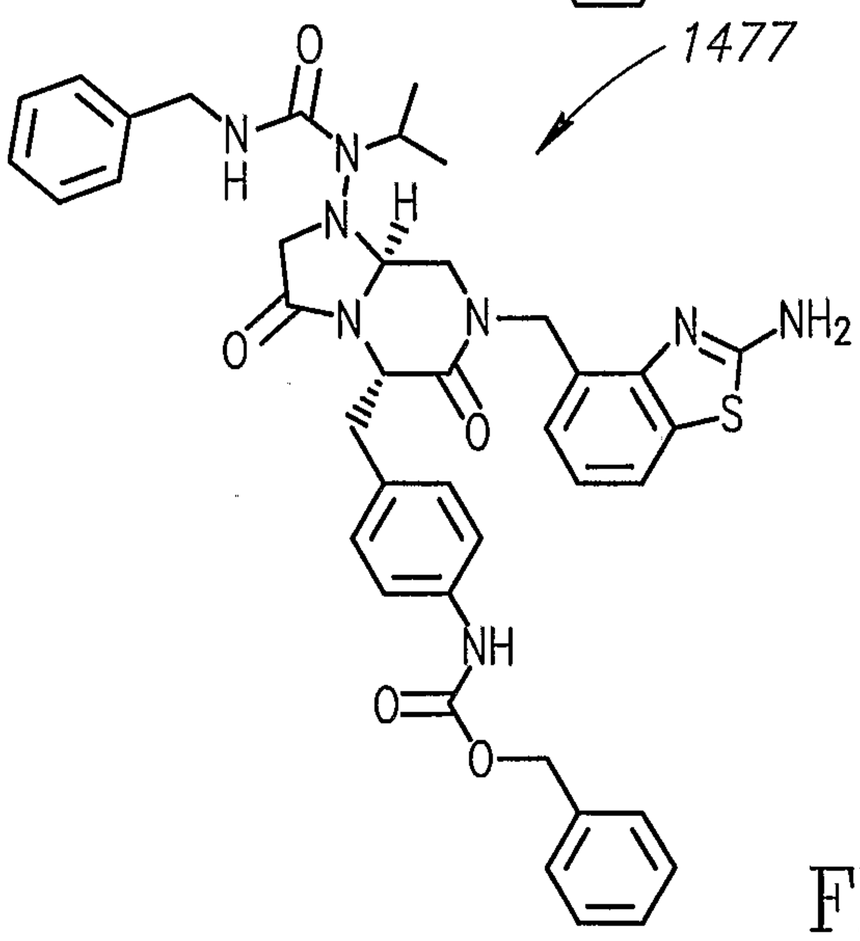
NH2


1477
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N
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O
N
S
NH2

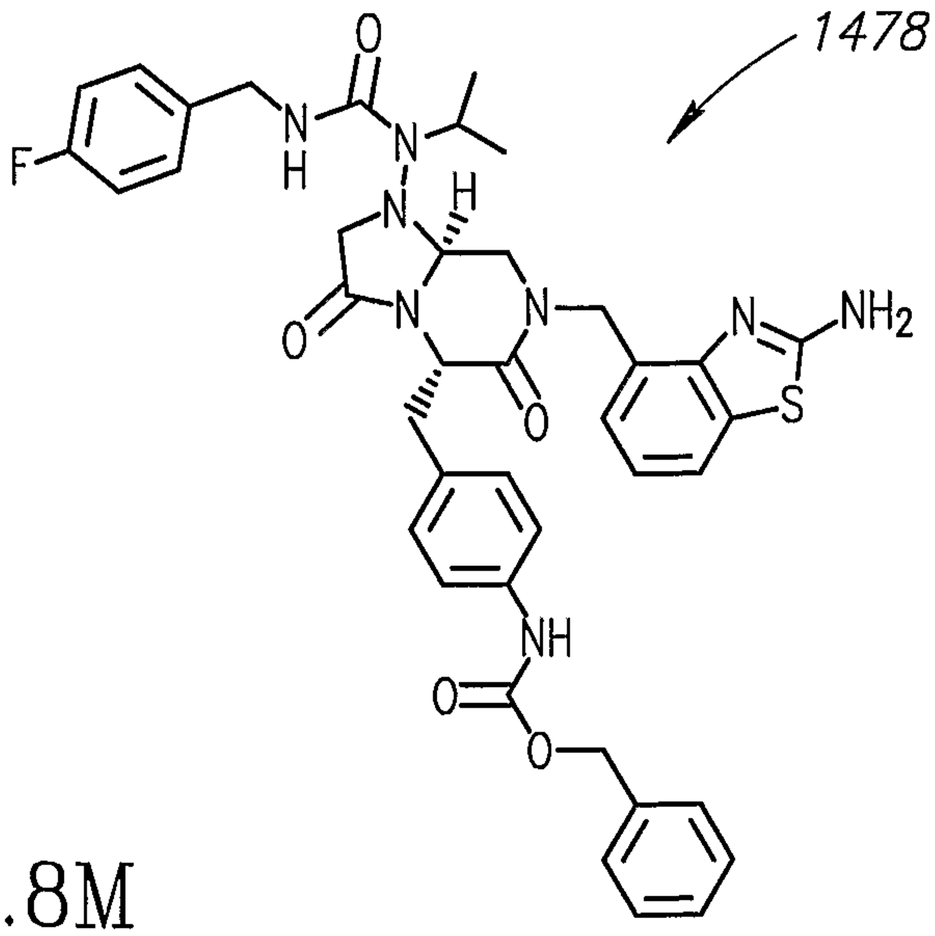
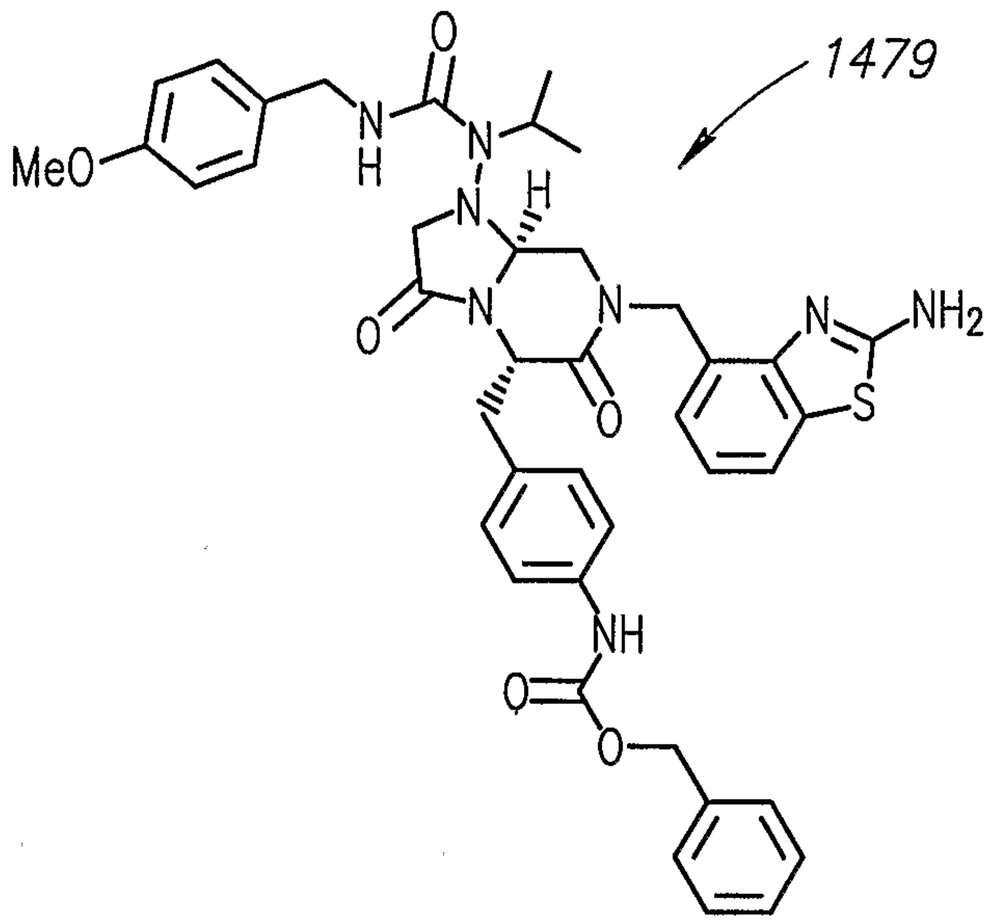

1478
F
O
N
H
N
O
O
NH
O
O
N
S
NH2

FIG.8M


1479
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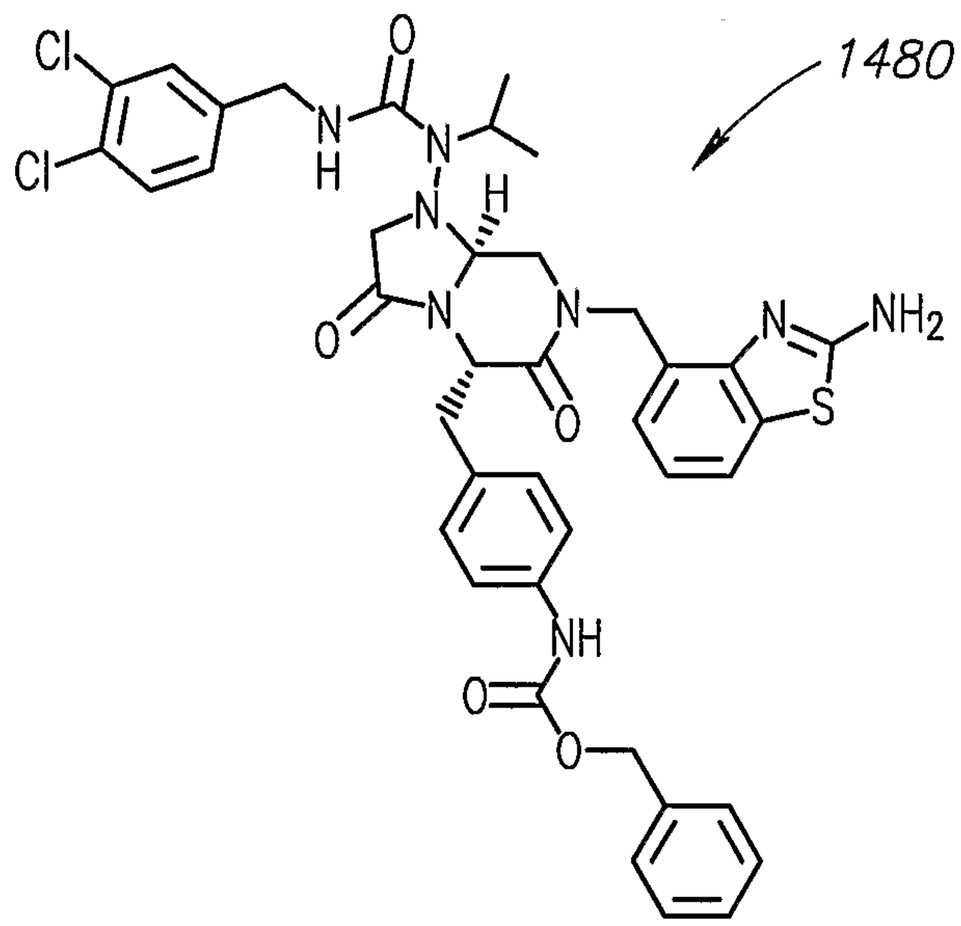
N
H
N
H
N
O
N
O
N
N
S
NH2
NH
O
O


1480
Cl
Cl
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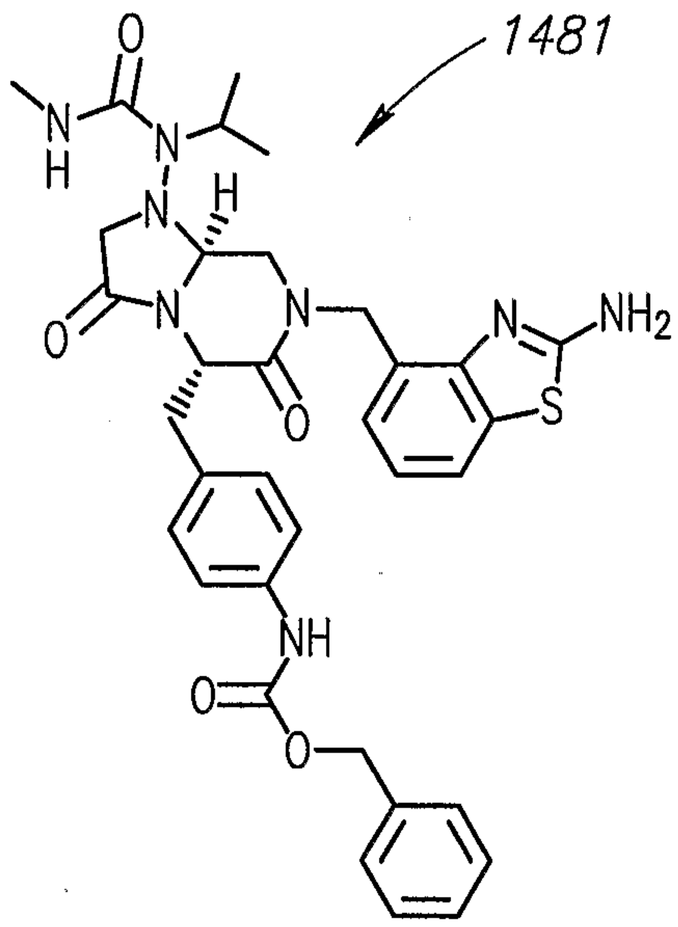
N
H
N
H
N
O
N
O
N
N
S
NH2
NH
O
O


1481
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N
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O
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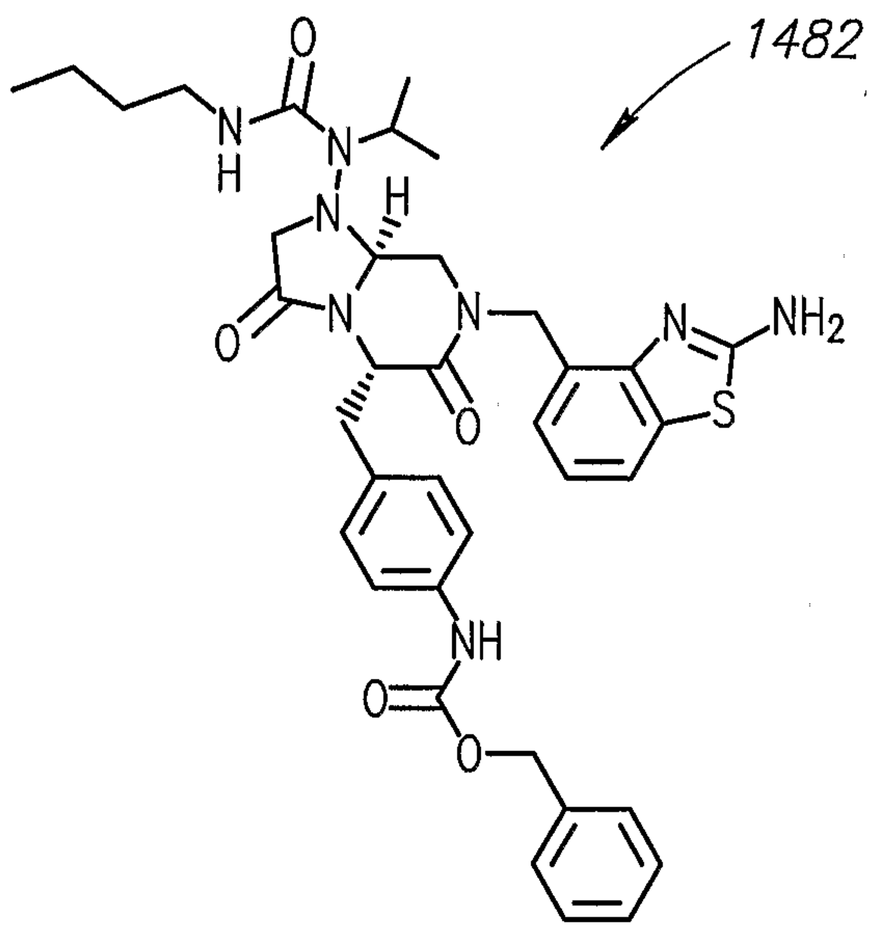
O
N
N
S
NH2
NH
O
O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N
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N
H
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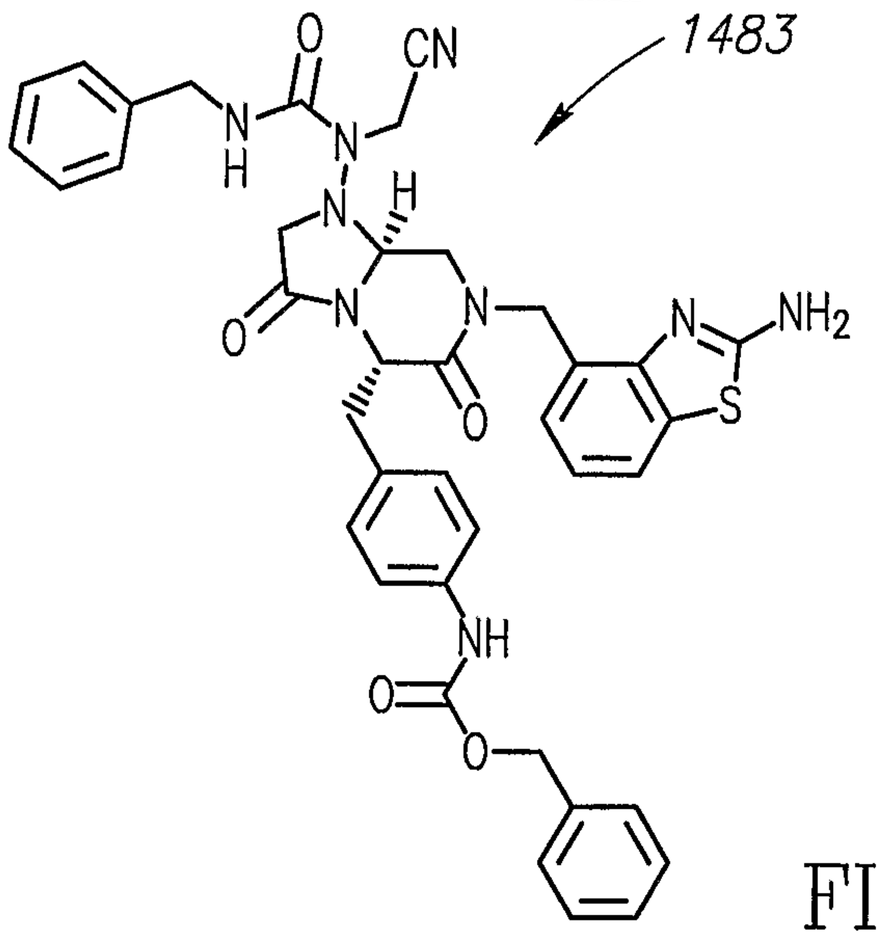
O
N
O
N
N
S
NH2
NH
O
O


1483
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N
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N
O
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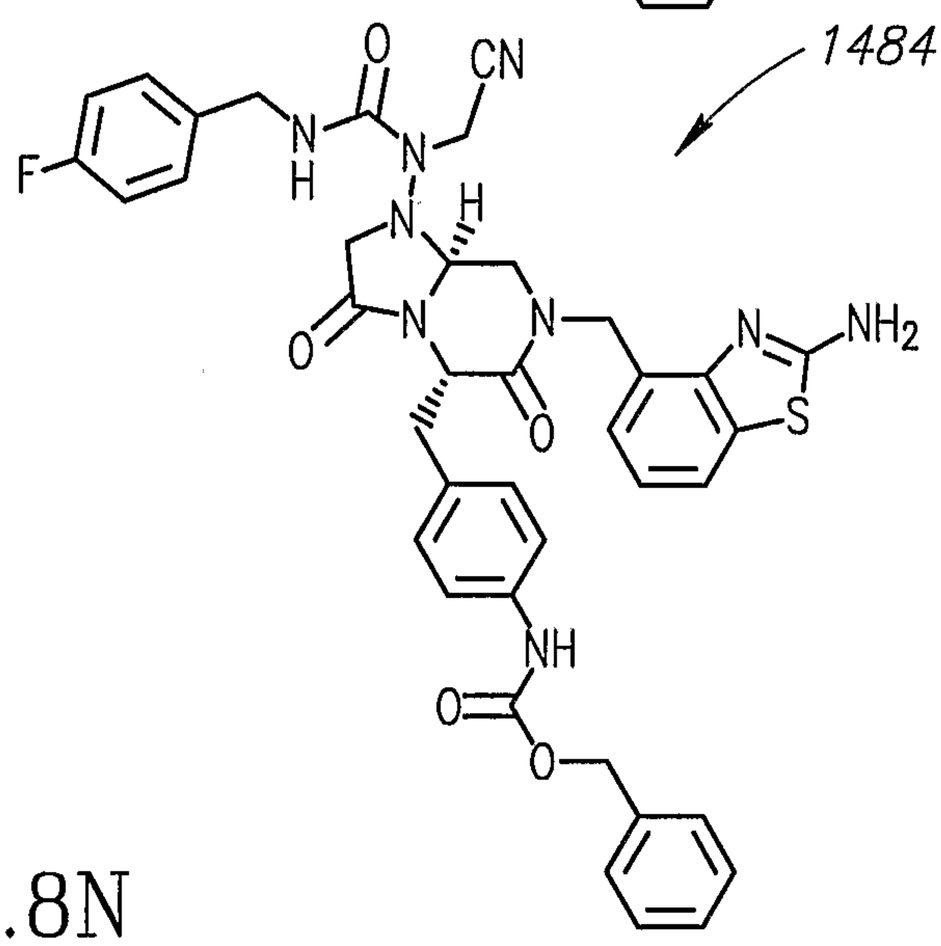
O
N
N
S
NH2
NH
O
O


1484
F
O
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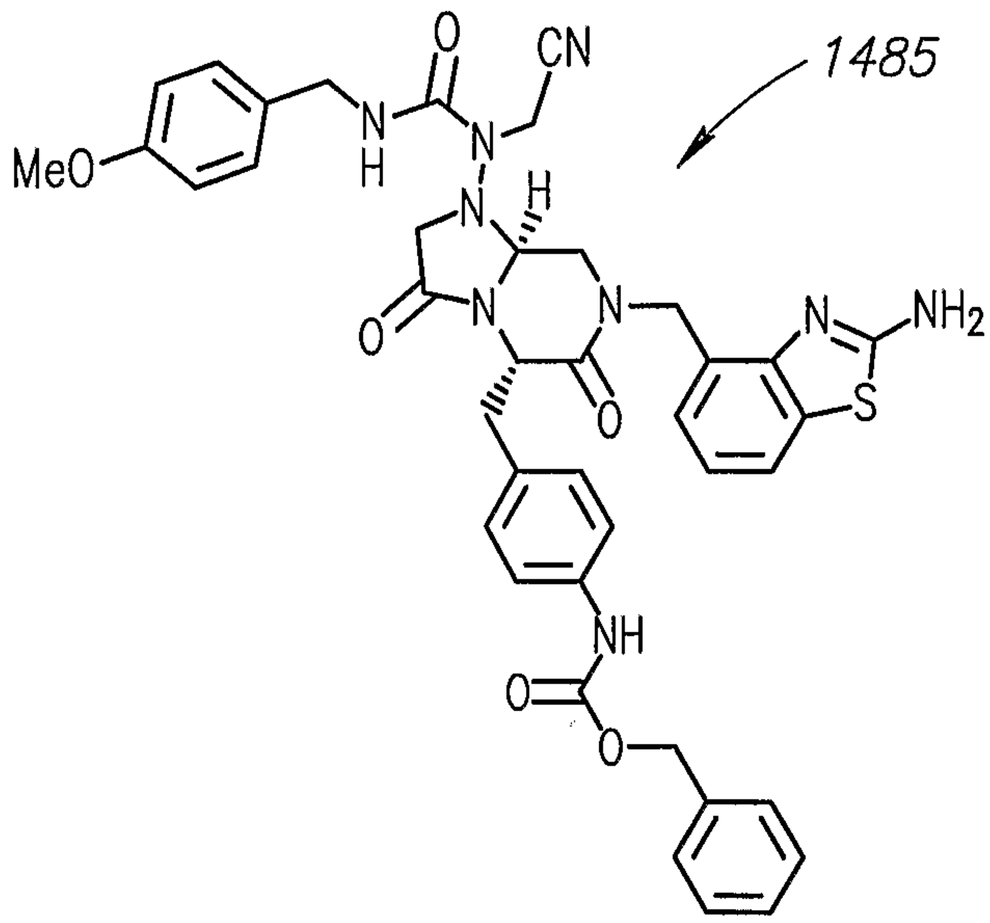
H
N
H
N
O
N
O
N
N
S
NH2
NH
O
O

FIG.8N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N
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H
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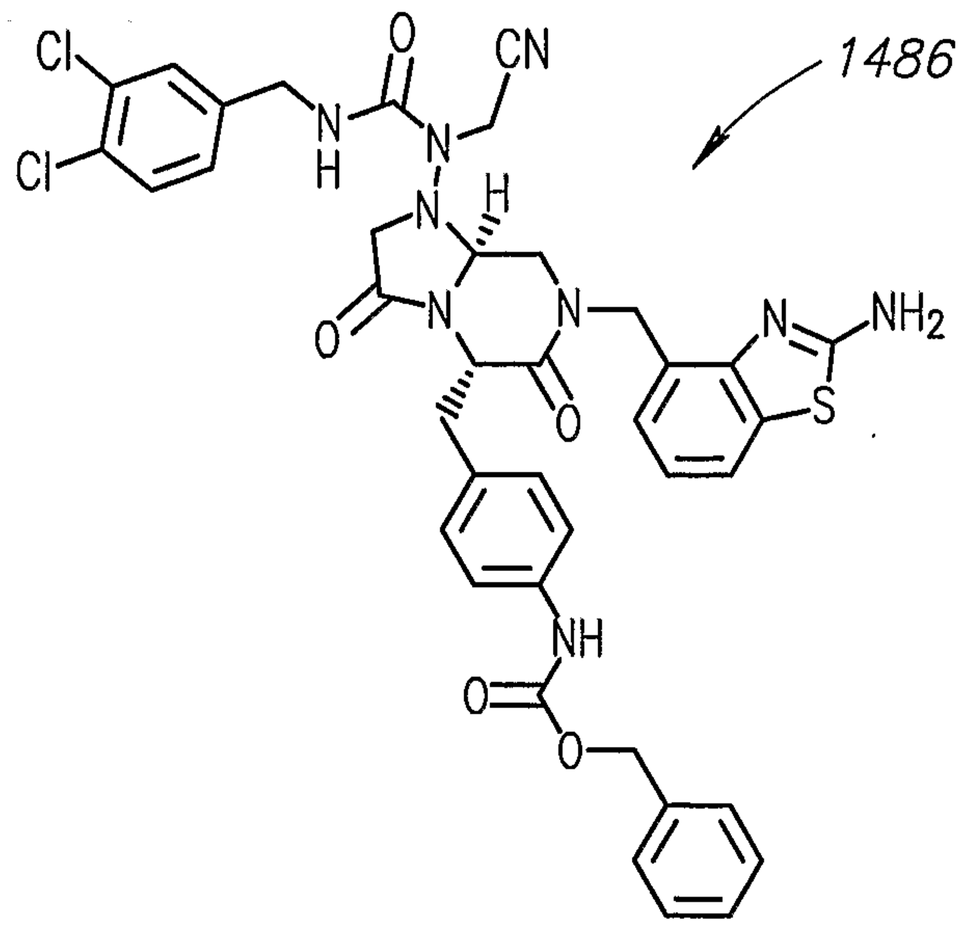
N
O
N
S
NH2
NH
O
O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CN
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H
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O
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N
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NH2
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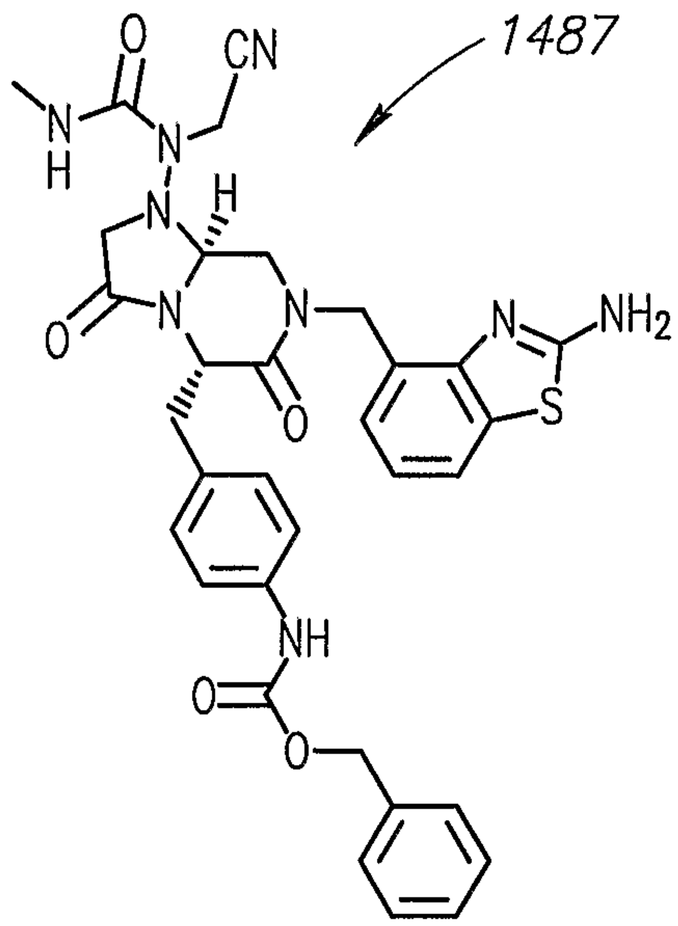
O
O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O
N
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NH2
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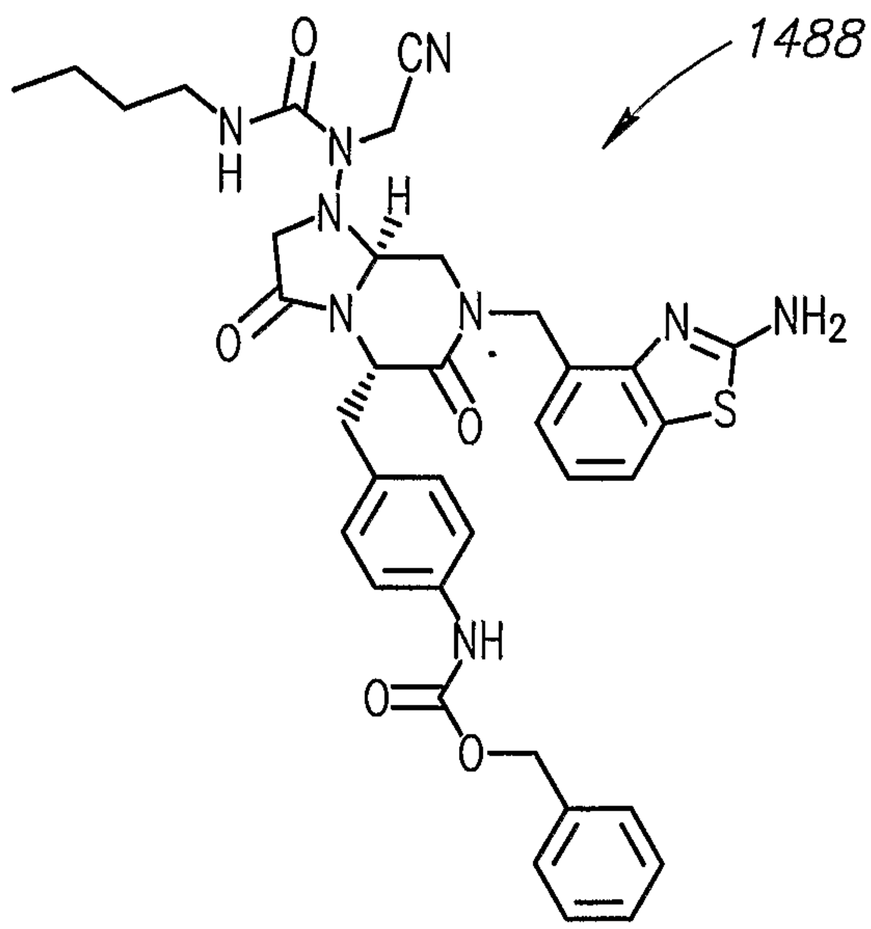
O
O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CN
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O
N
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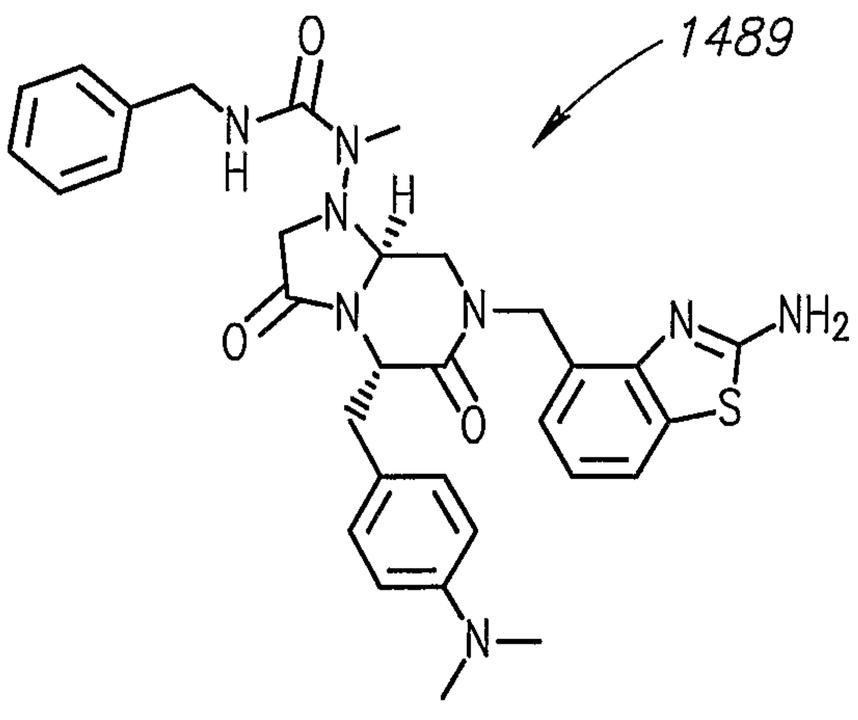
NH2
NH
O
O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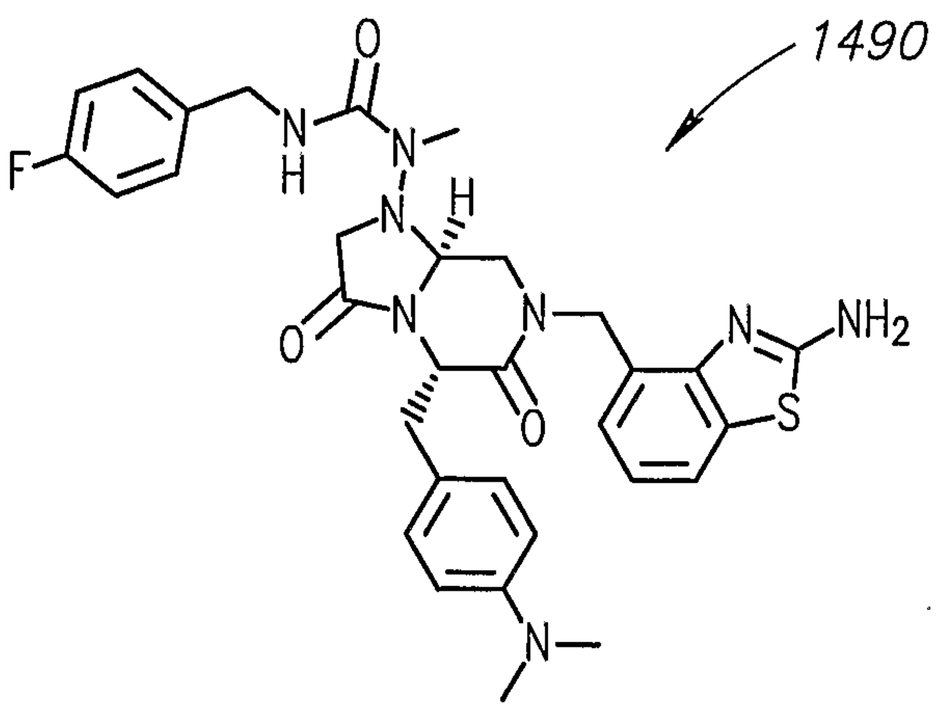
N
S
NH2
N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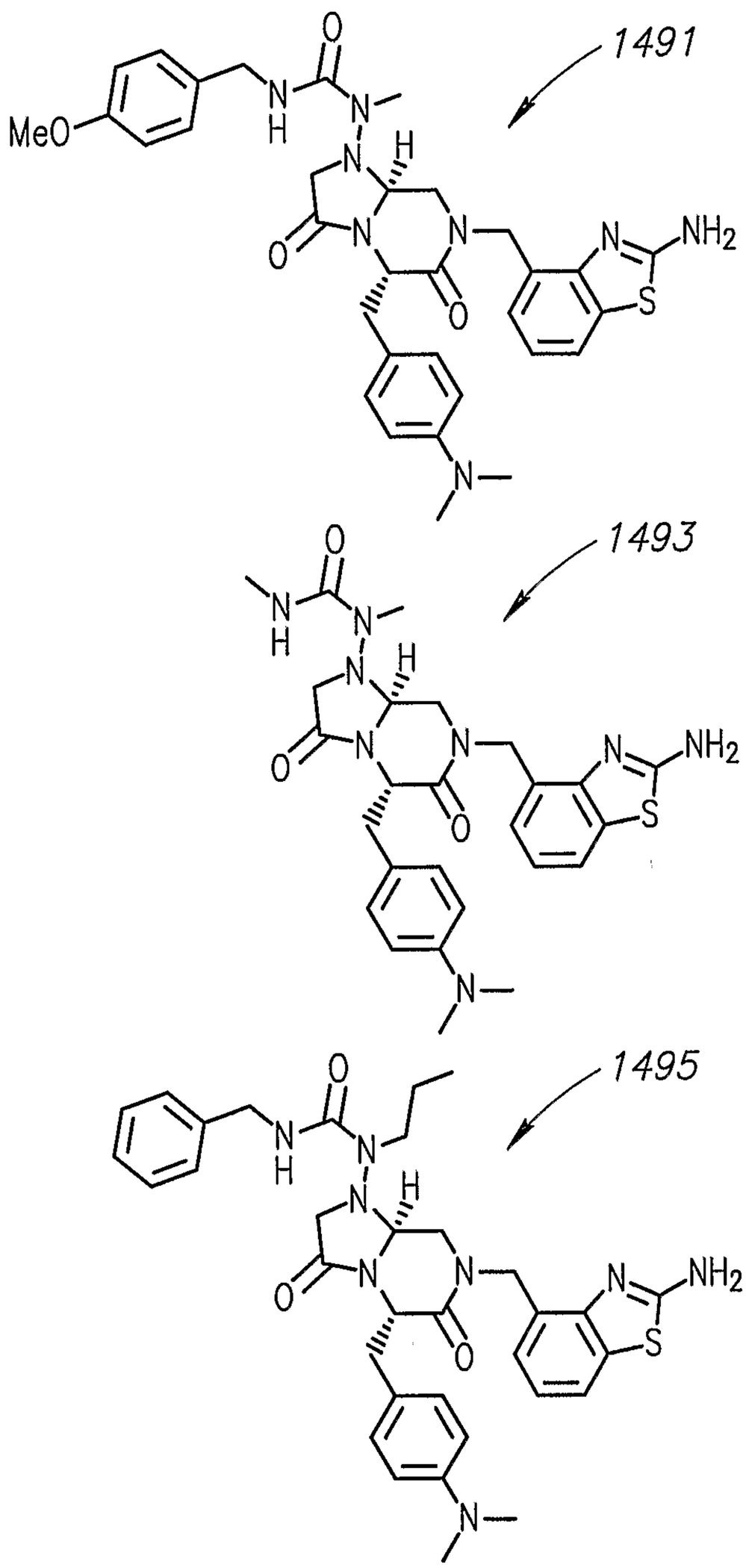
O
N
S
NH2
N

FIG.80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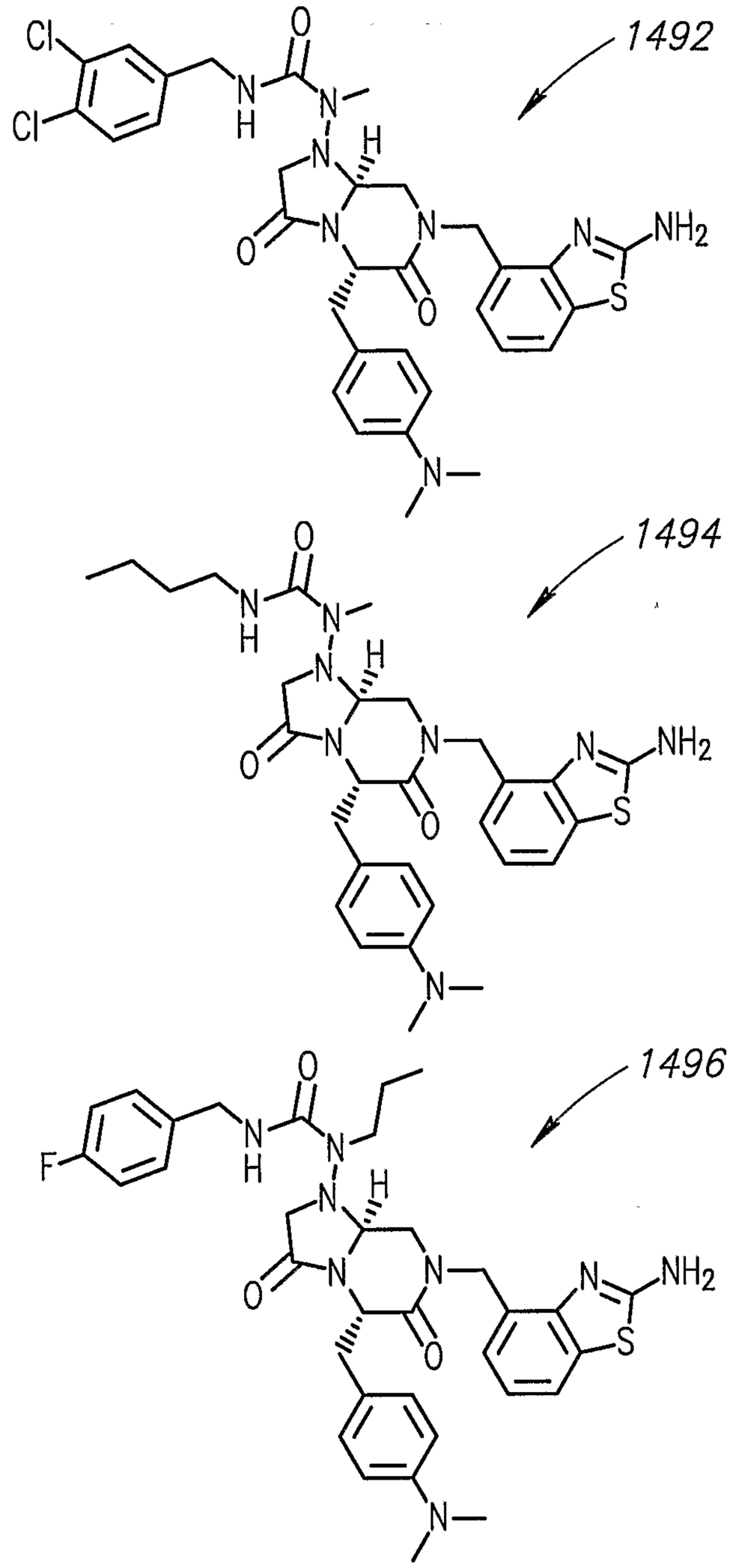
N
O
N
N
S
NH2
N


1492
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N
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H
O
N
O
N
N
S
NH2
N

1493
O
N
H
N
N
H
O
N
O
N
N
S
NH2
N

1494
O
N
H
N
N
H
O
N
O
N
N
S
NH2
N

1495
O
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H
N
N
H
O
N
O
N
N
S
NH2
N

1496
F
O
N
H
N
N
H
O
N
O
N
N
S
NH2
N

1497
MeO
O
N
H
N
N
H
O
N
O
N
N
S
NH2
N

1498
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O
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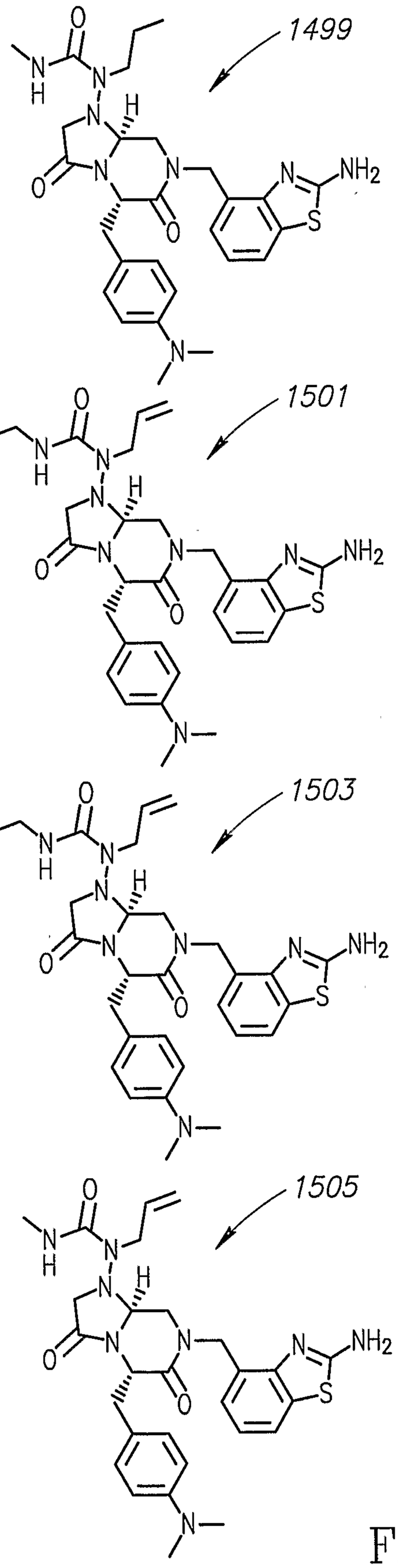
O
N
N
S
NH2
N

FIG.8P



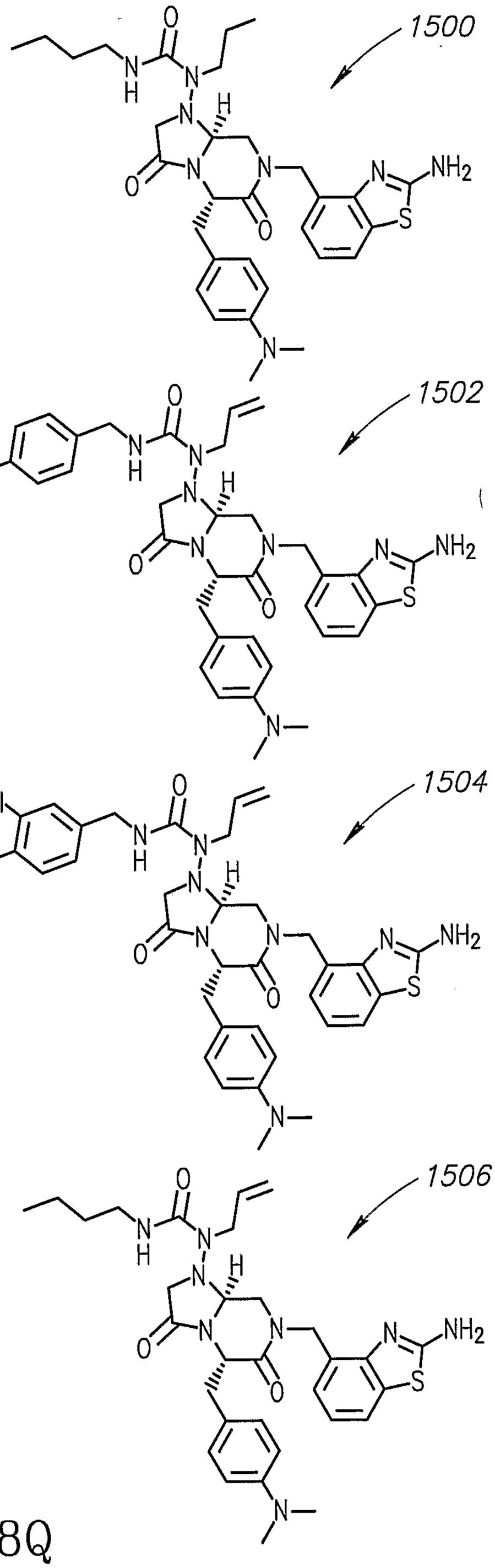


FIG.8Q

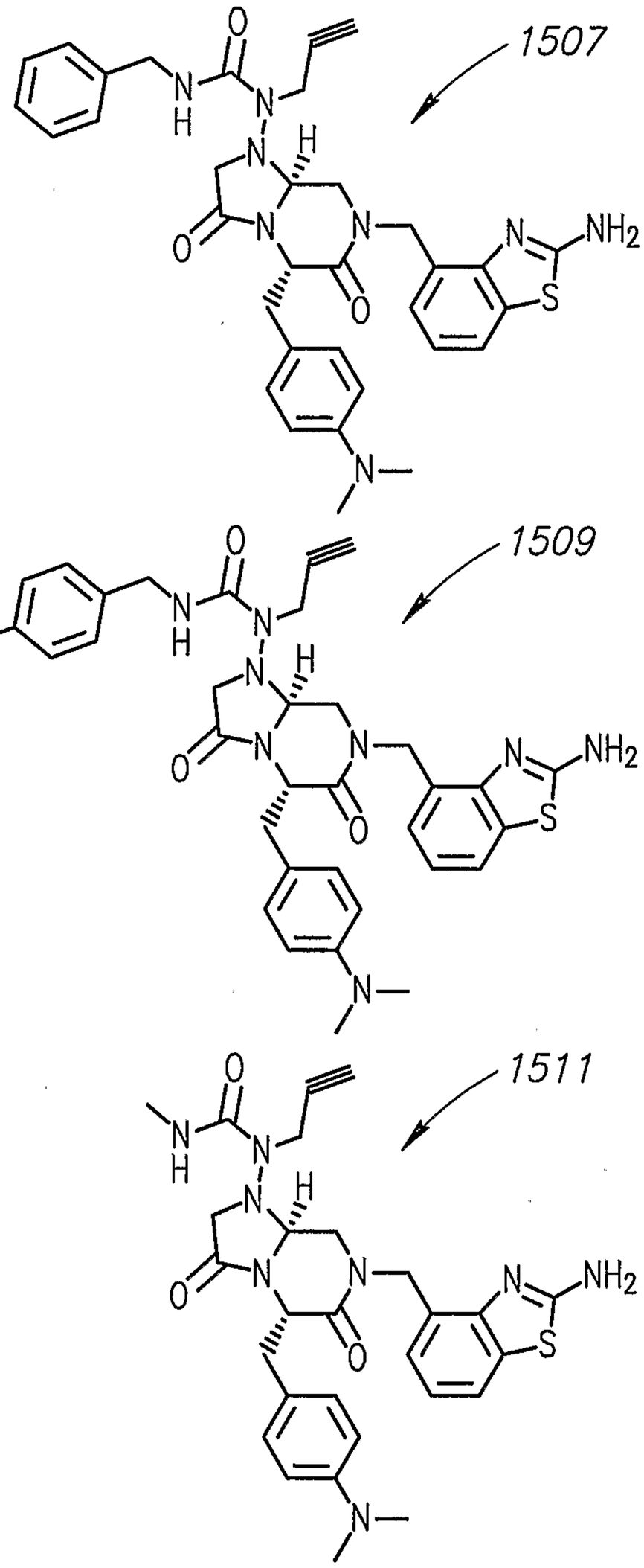
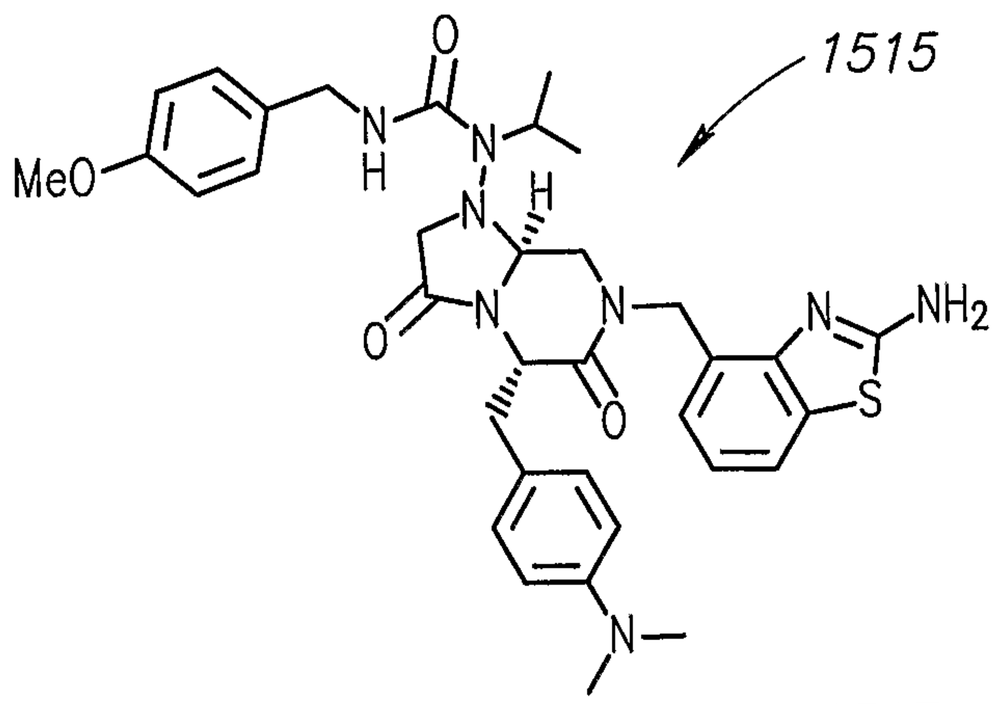
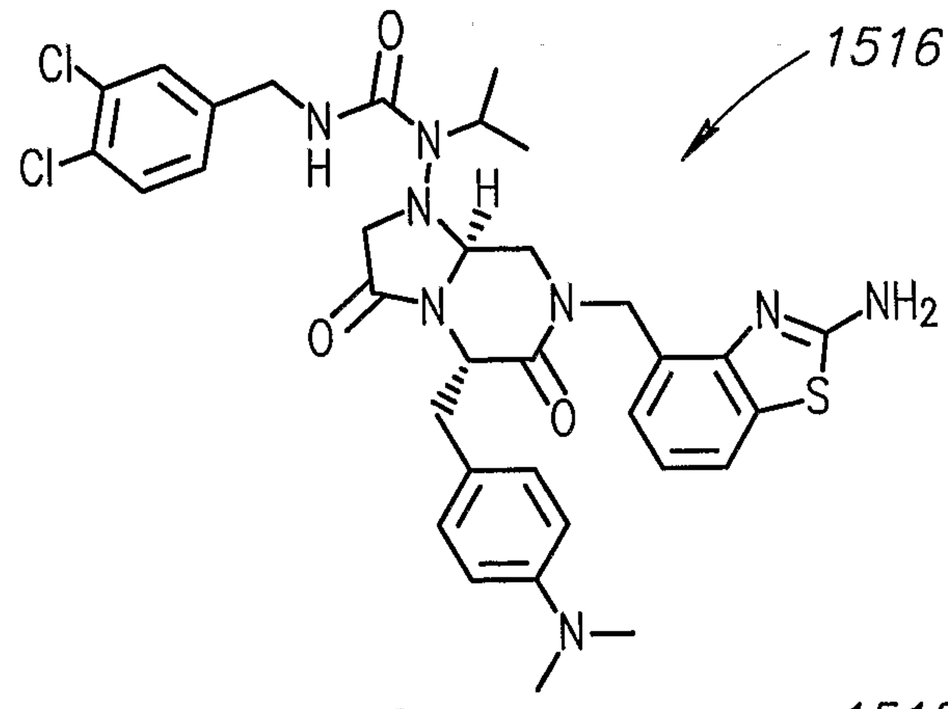
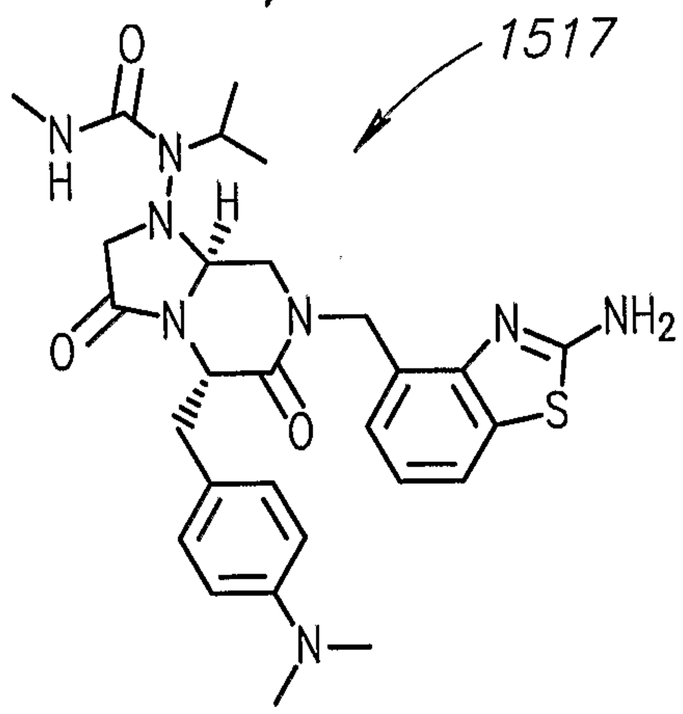
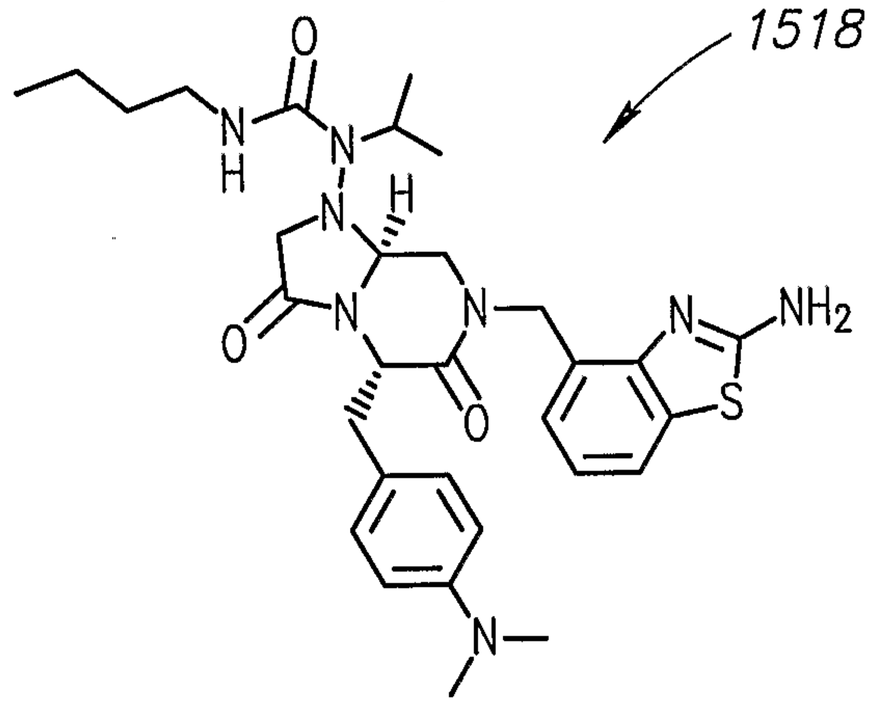


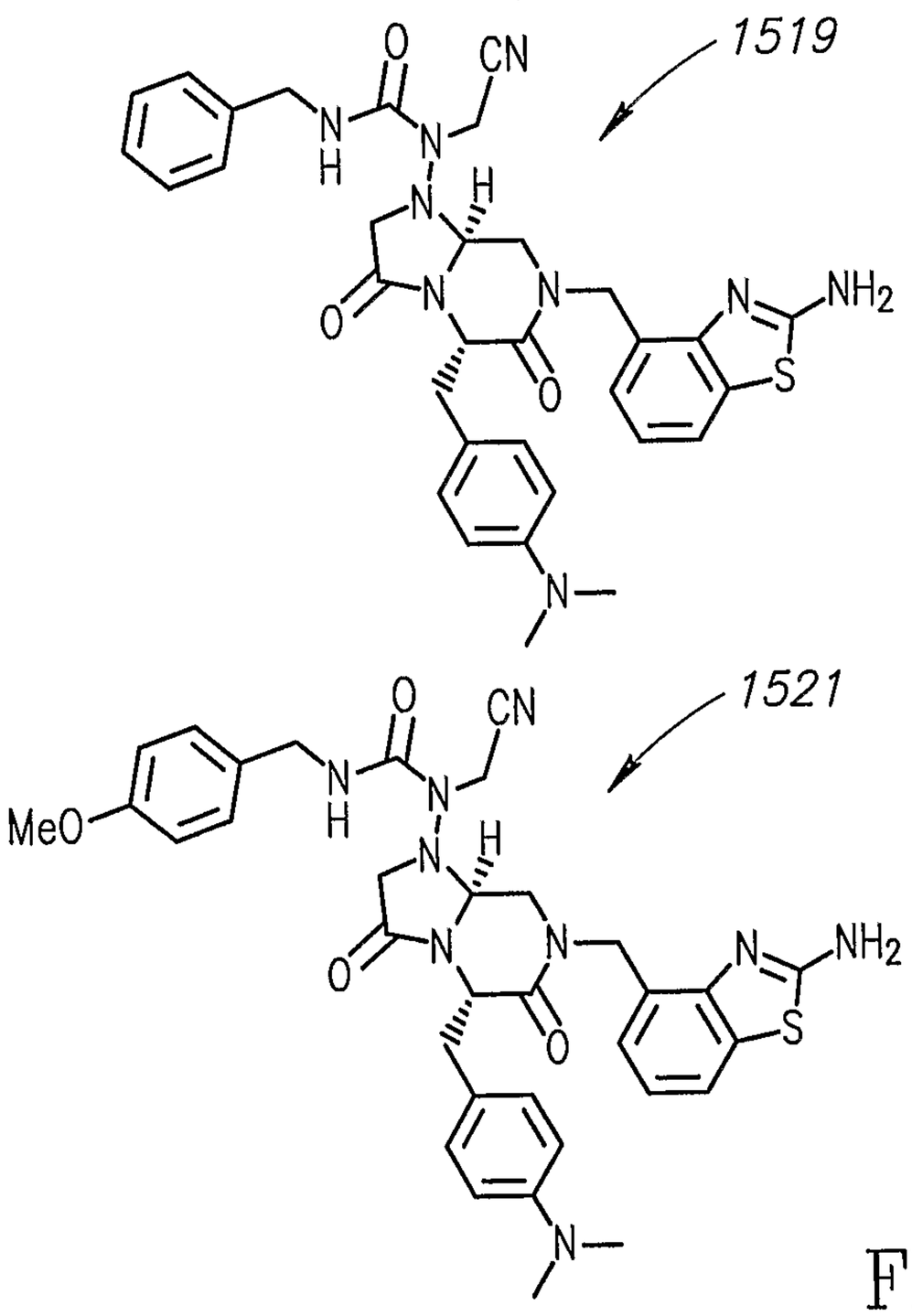
FIG.8R











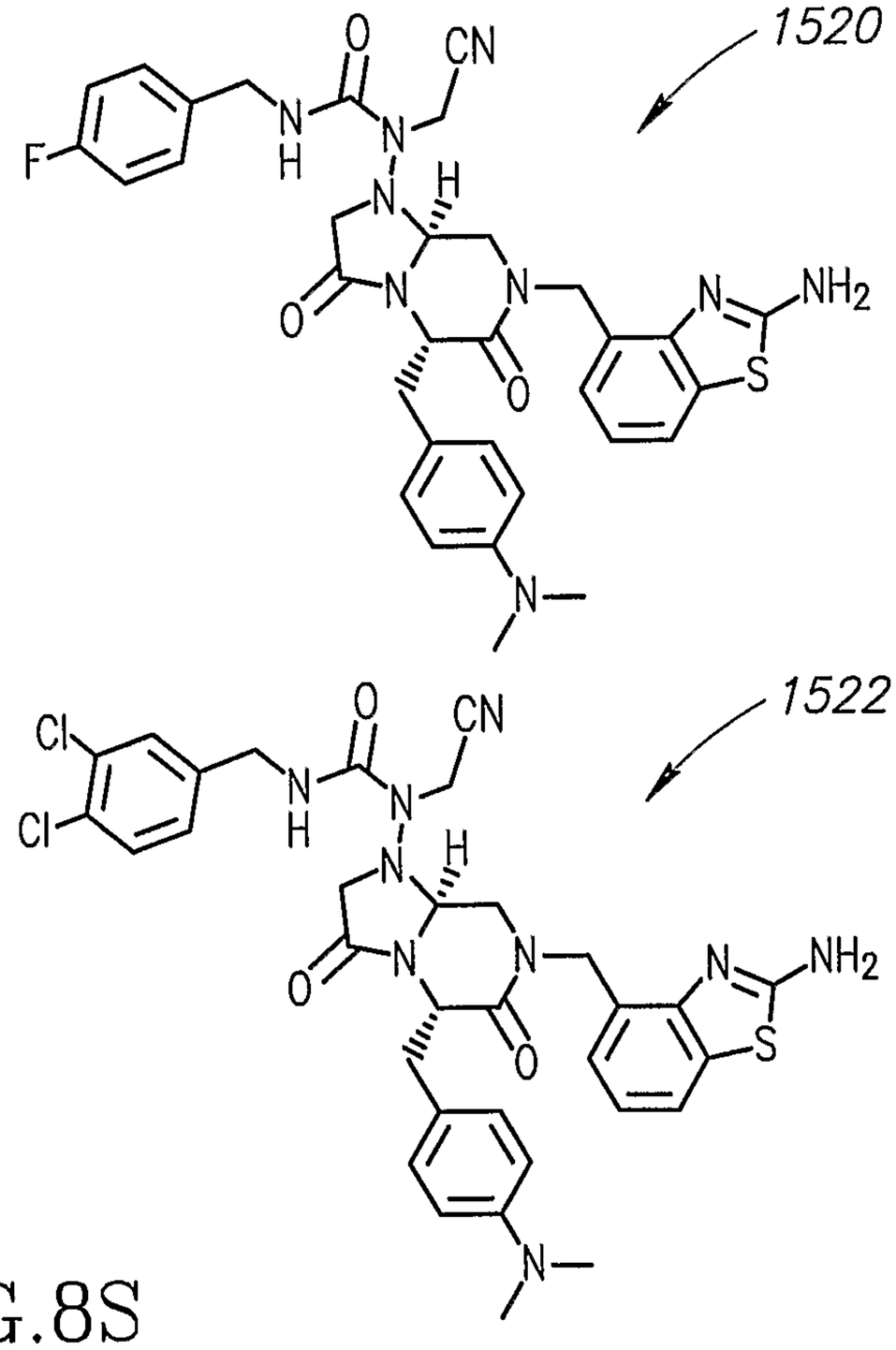
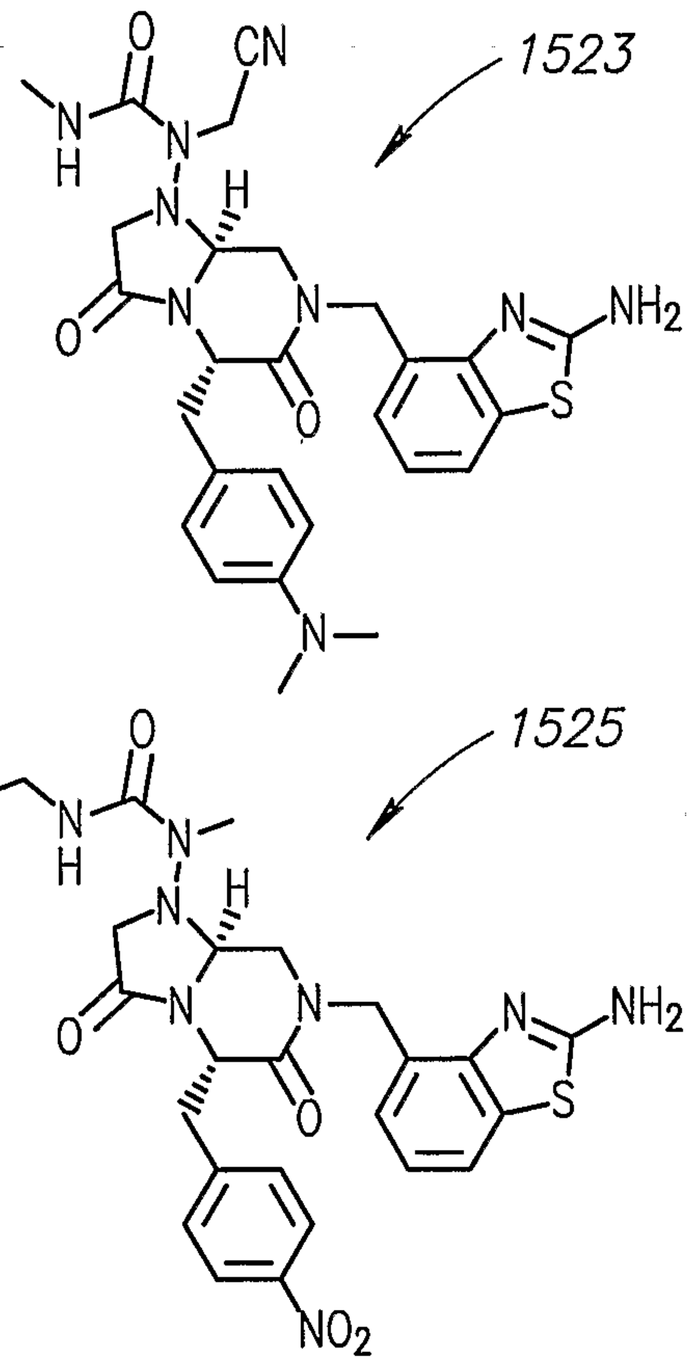
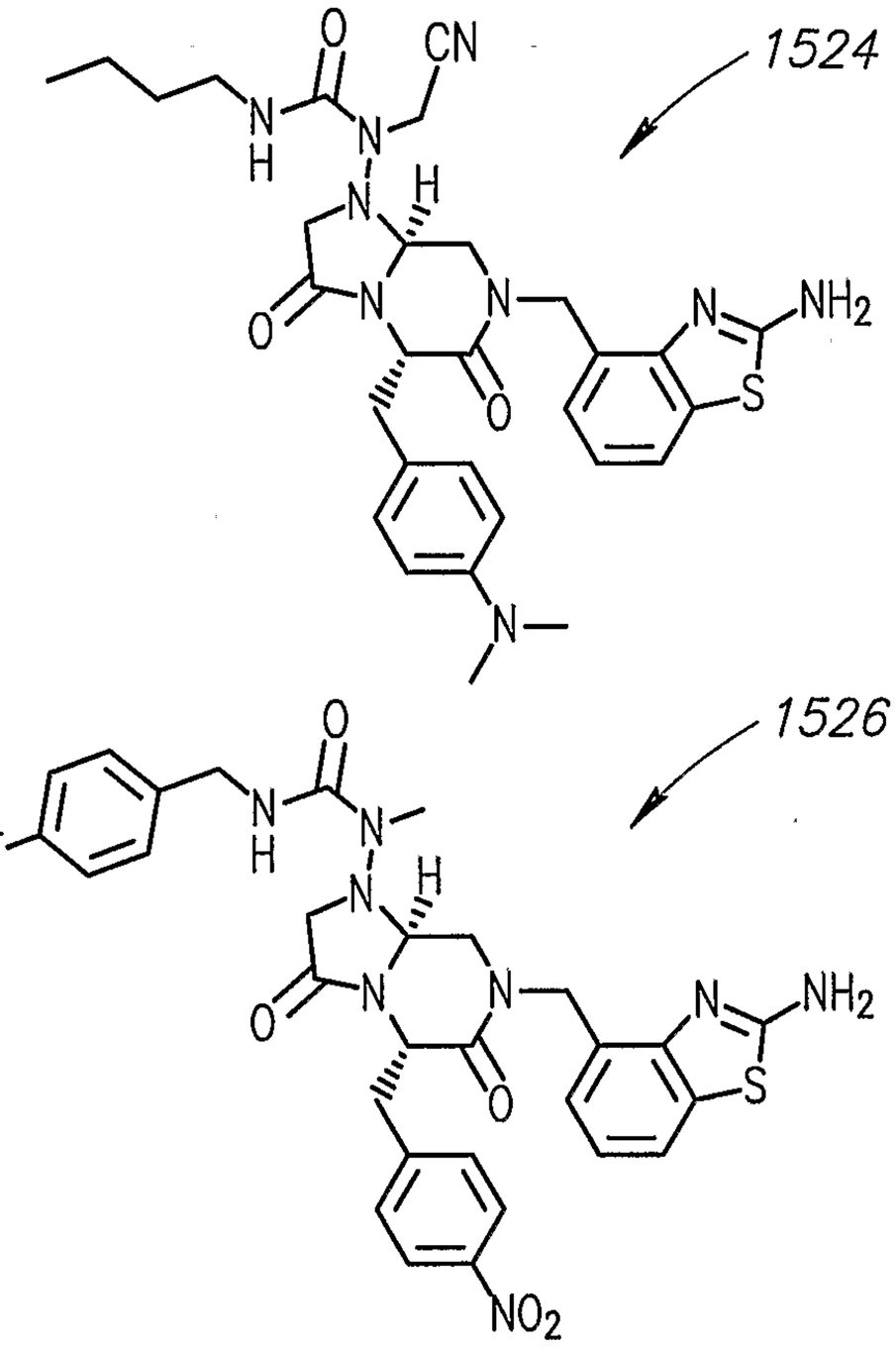
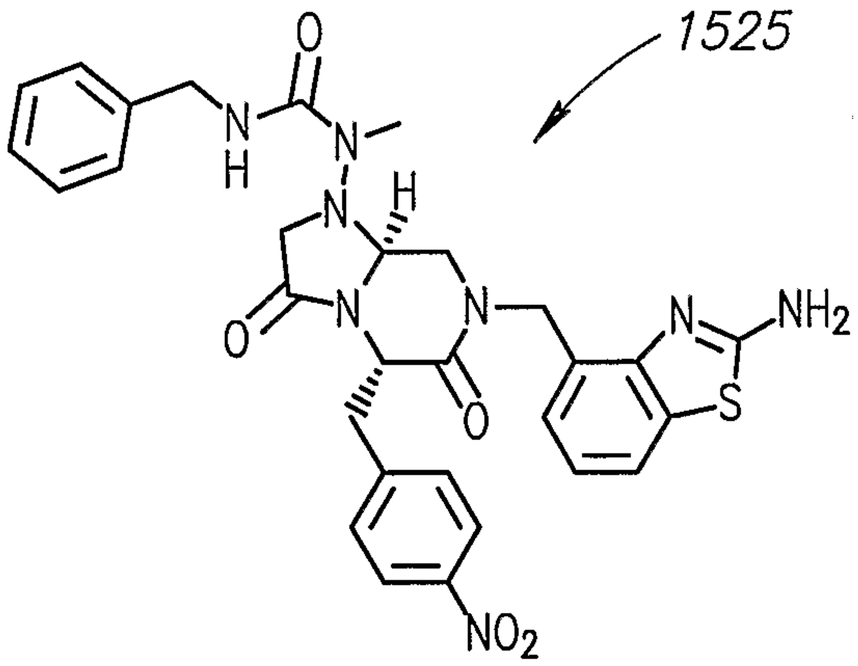
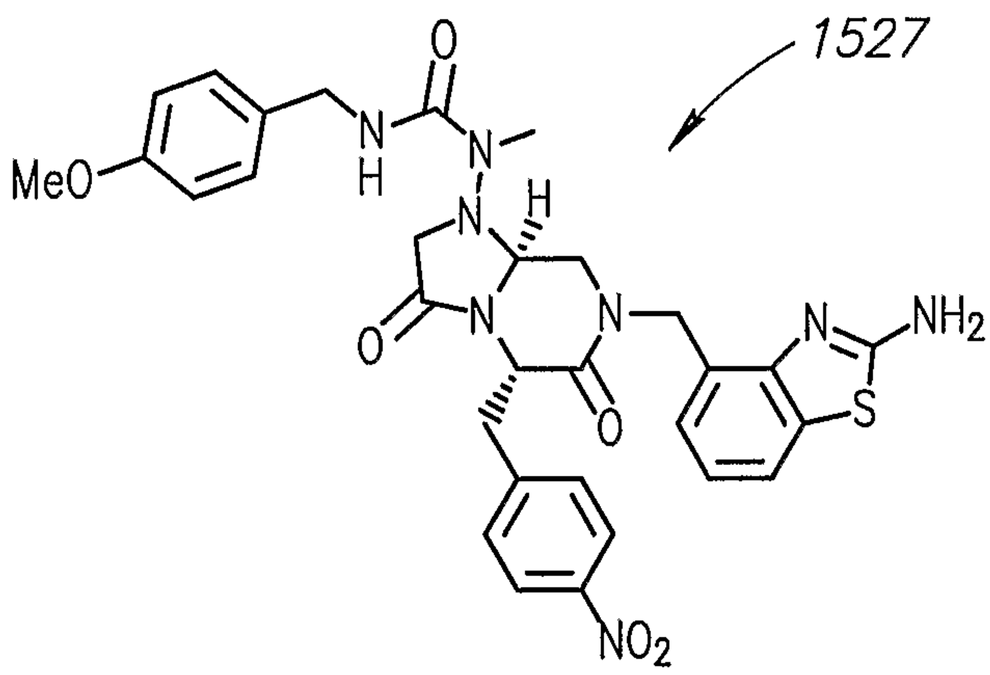


FIG.8S









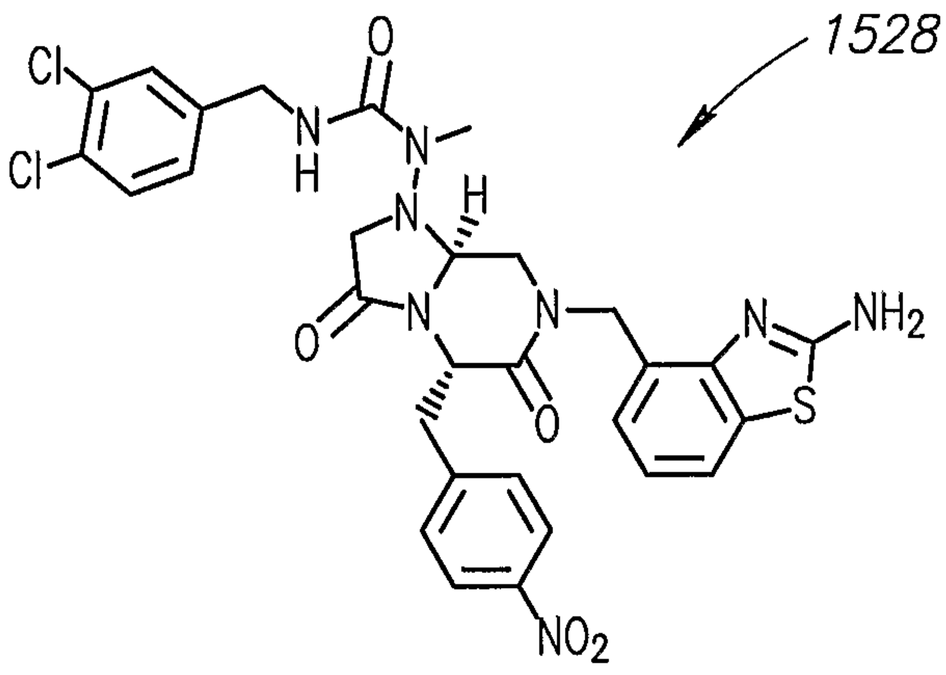
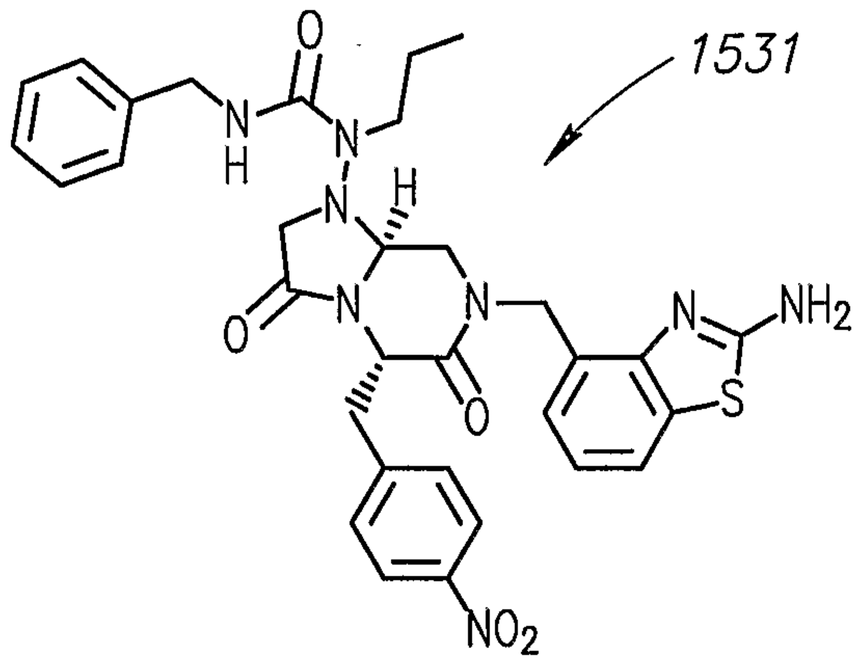


FIG.8T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N
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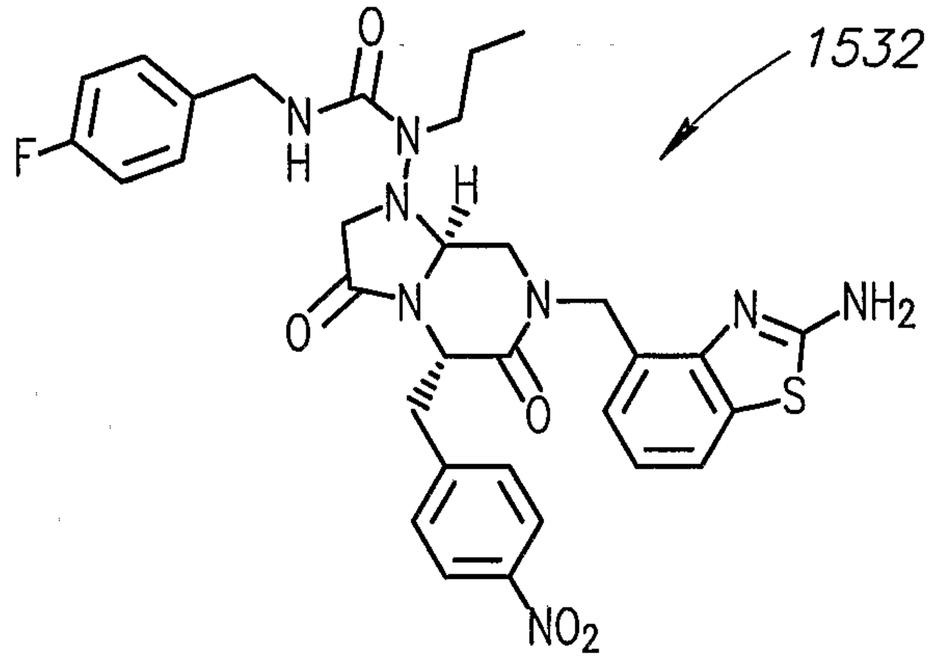
N
NH2
S
NO2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N
H
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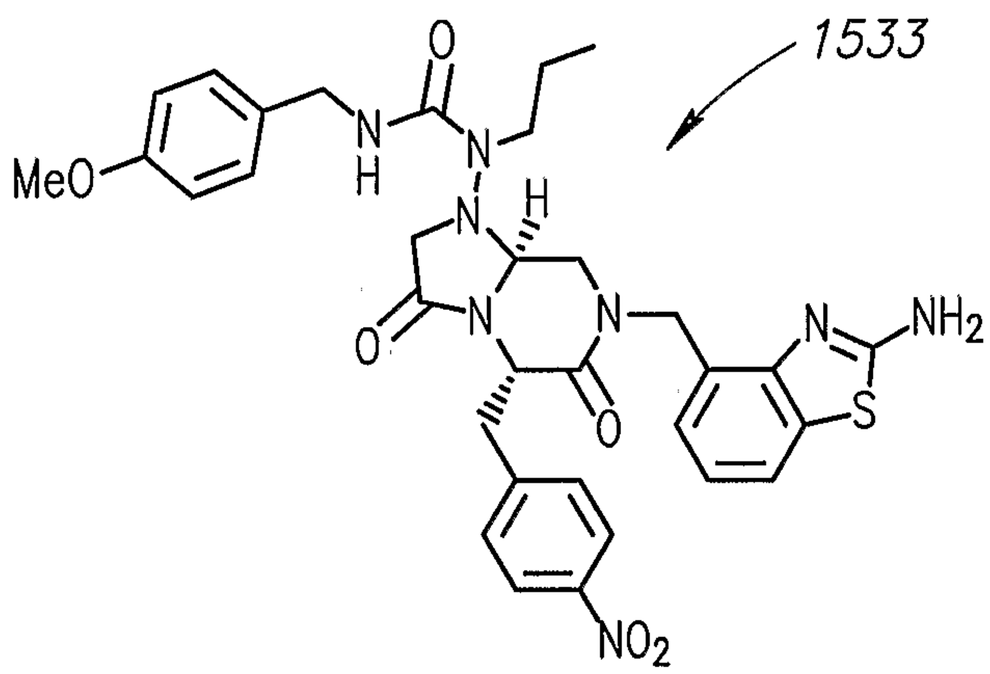
N
H
O
N
N
O
N
N
NH2
S
NO2


1533
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O
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H
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N
N
O
N
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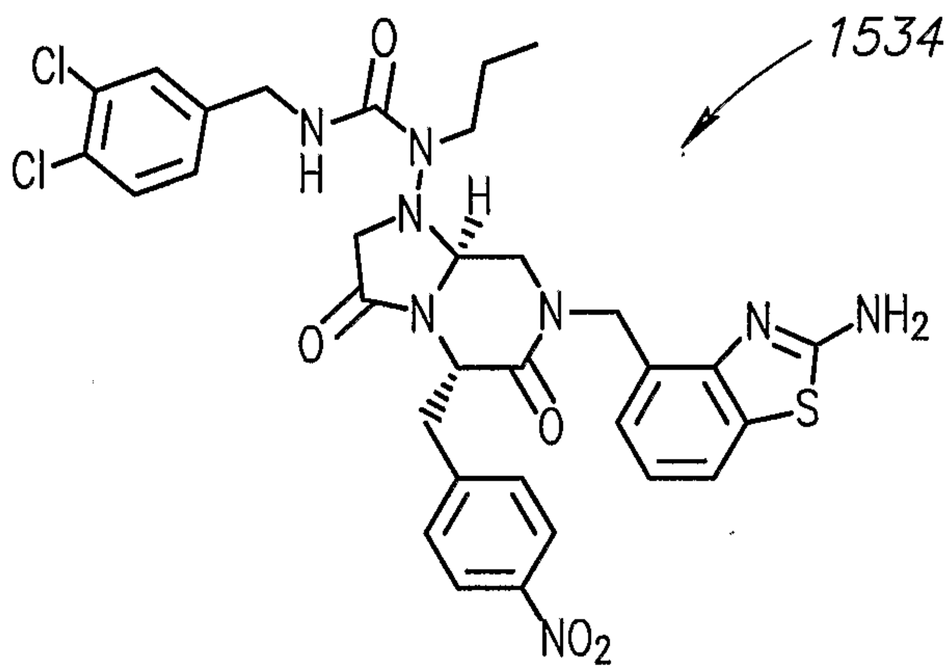
NH2
S
NO2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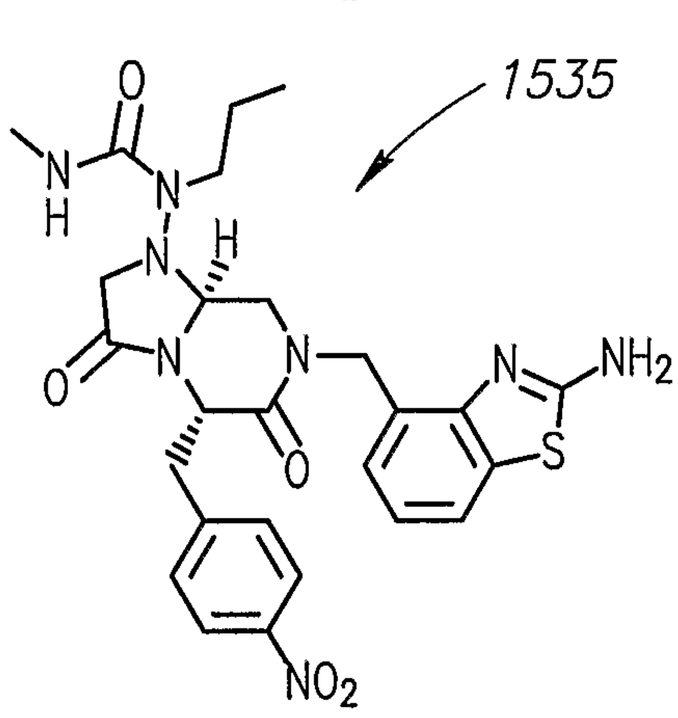
H
O
N
N
O
N
N
NH2
S
NO2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N
N
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N
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N
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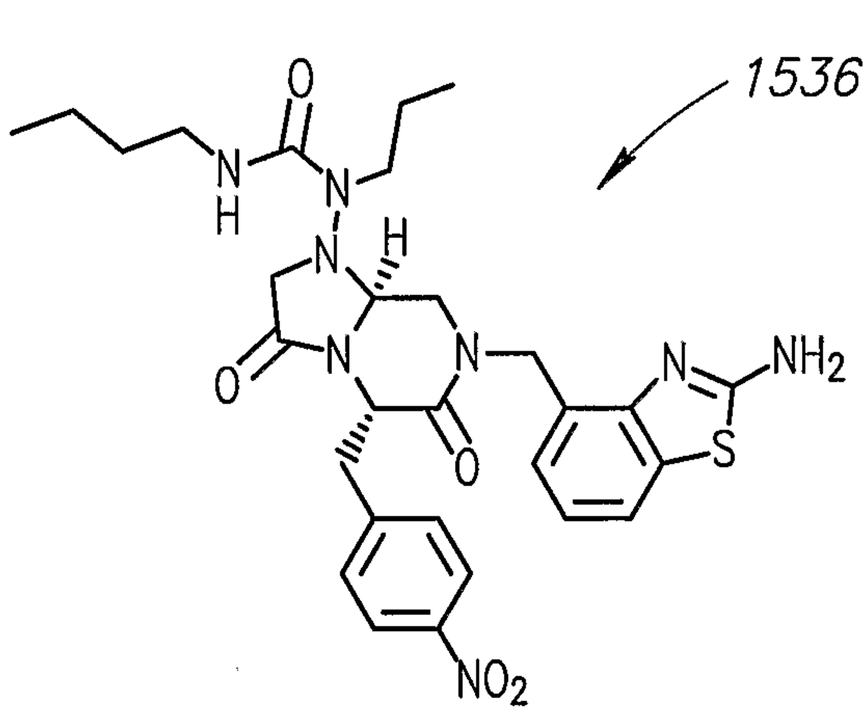
S
NO2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N
NH2
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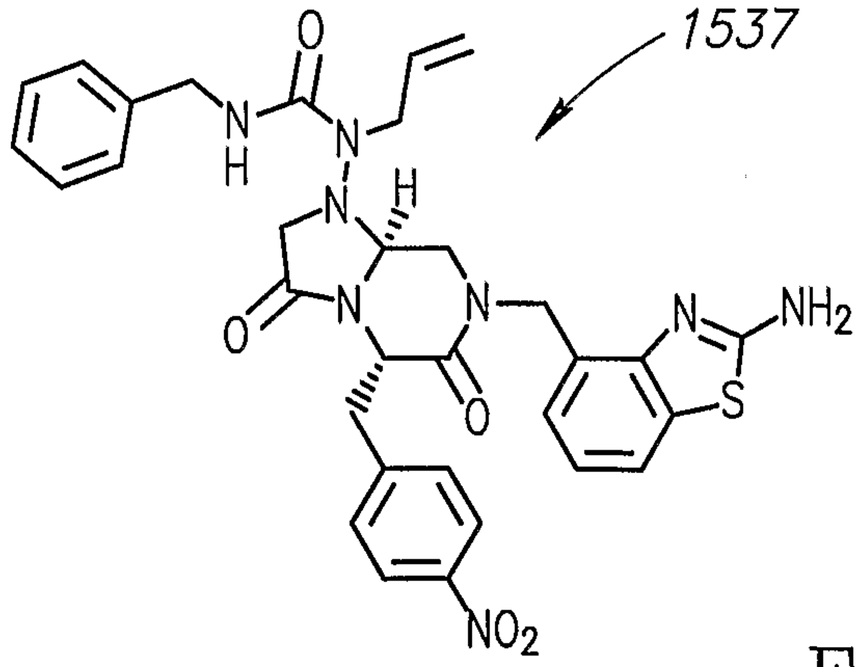
NO2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N
N
O
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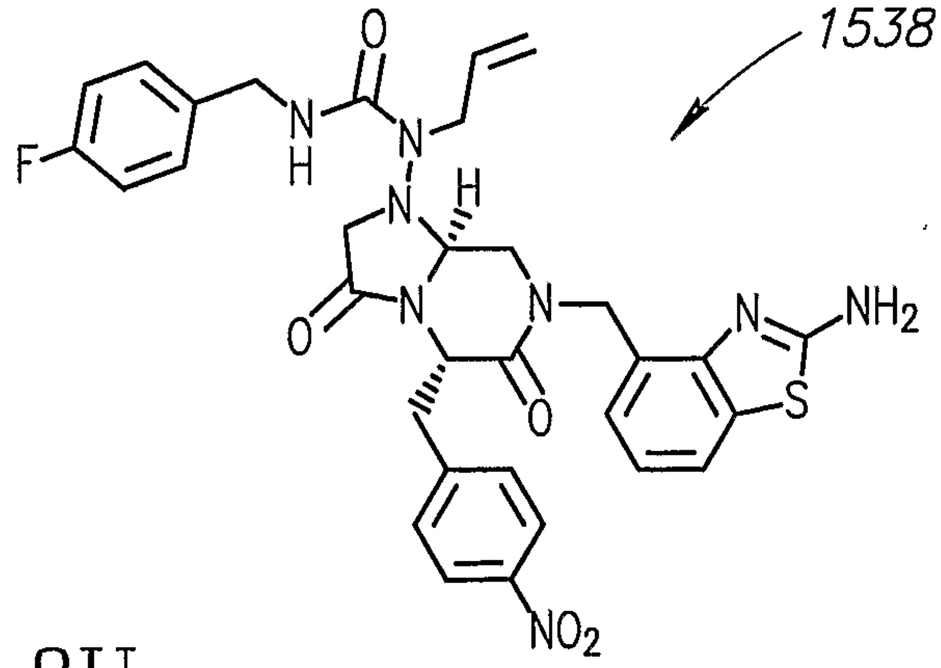
N
NH2
S
NO2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F
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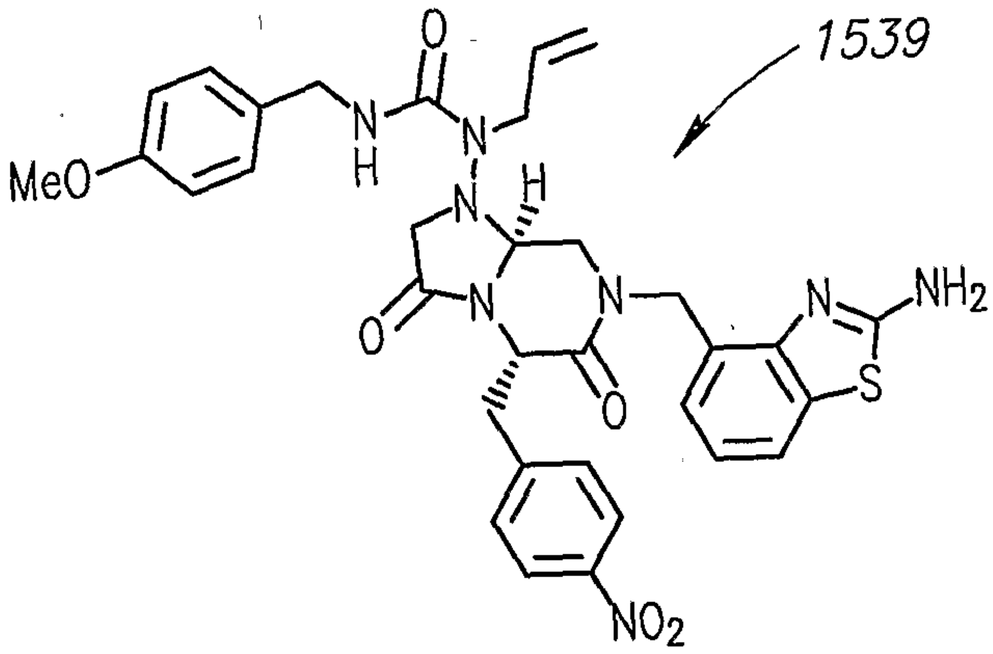
H
N
N
H
O
N
N
O
N
N
NH2
S
NO2

FIG.8U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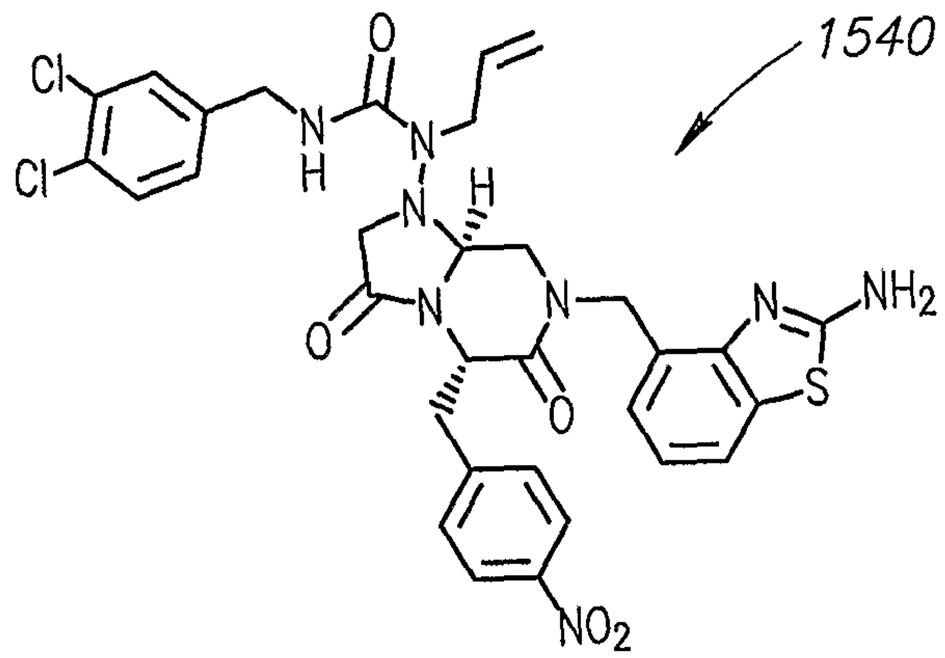
N
H
N
N
H
N
O
N
O
N
S
NH2
NO2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H
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O
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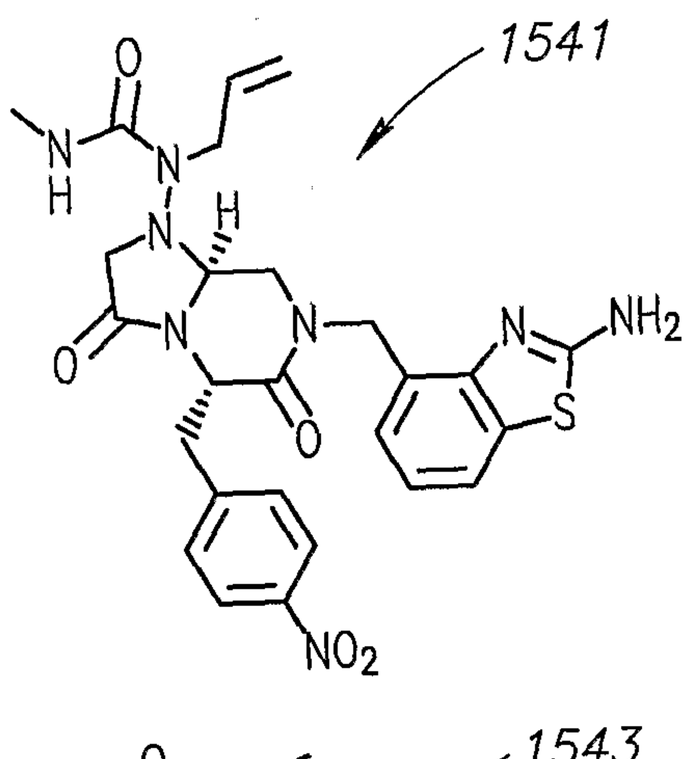
O
N
S
NH2
NO2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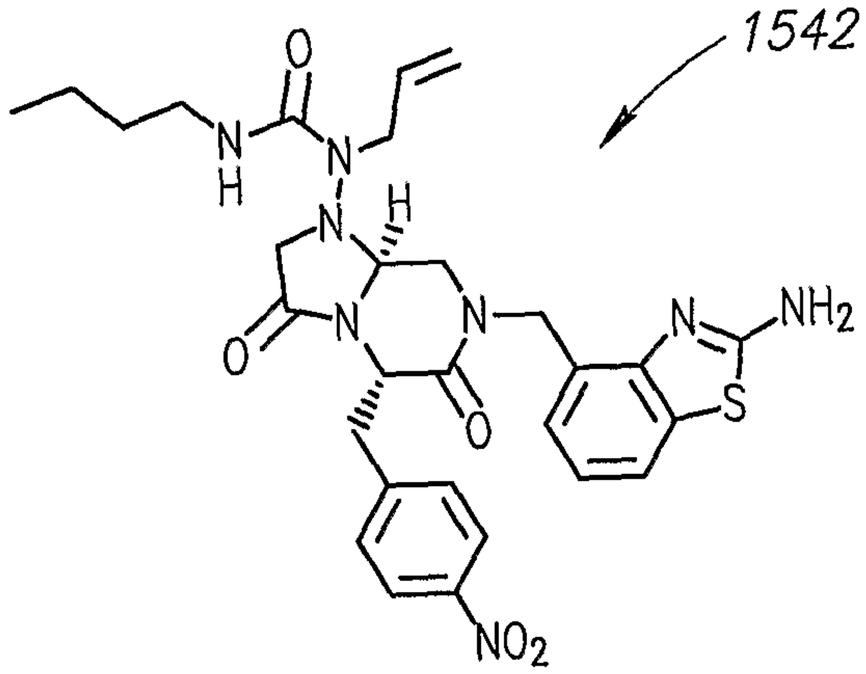
N
N
H
N
O
N
O
N
S
NH2
NO2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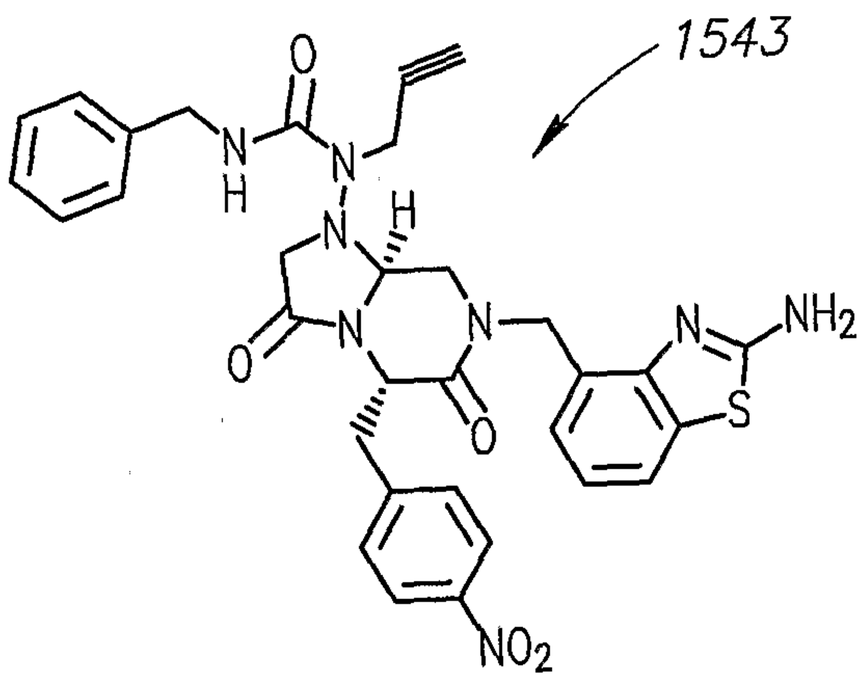
N
S
NH2
NO2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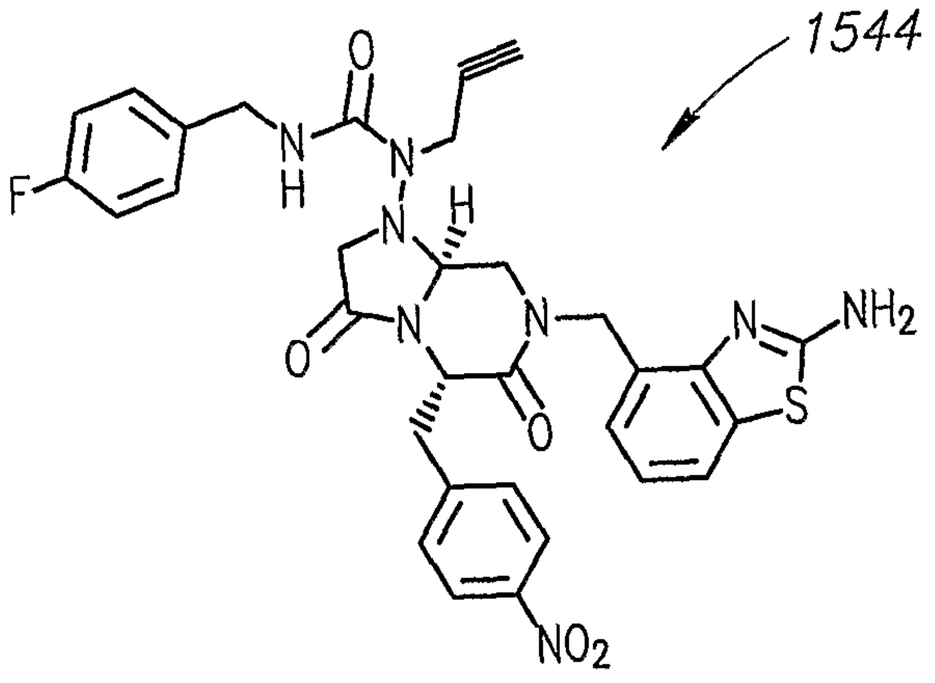
N
H
N
N
H
N
O
N
O
N
S
NH2
NO2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N
H
N
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H
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O
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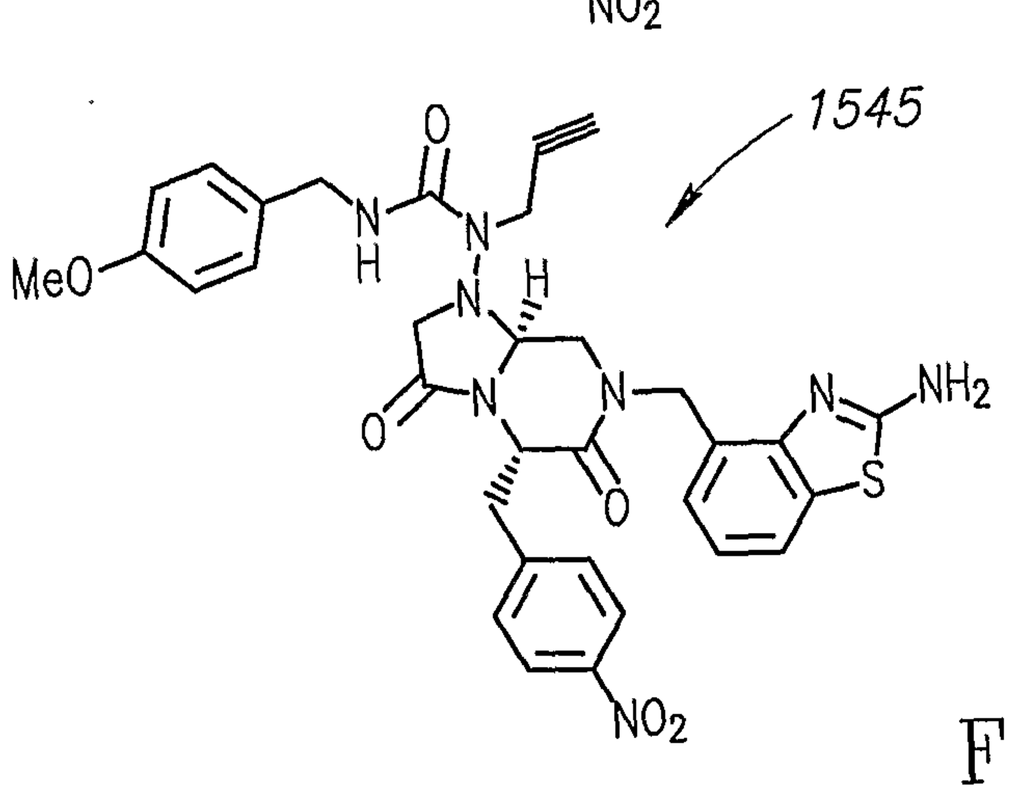
N
S
NH2
NO2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N
N
H
N
O
N
O
N
S
NH2
NO2

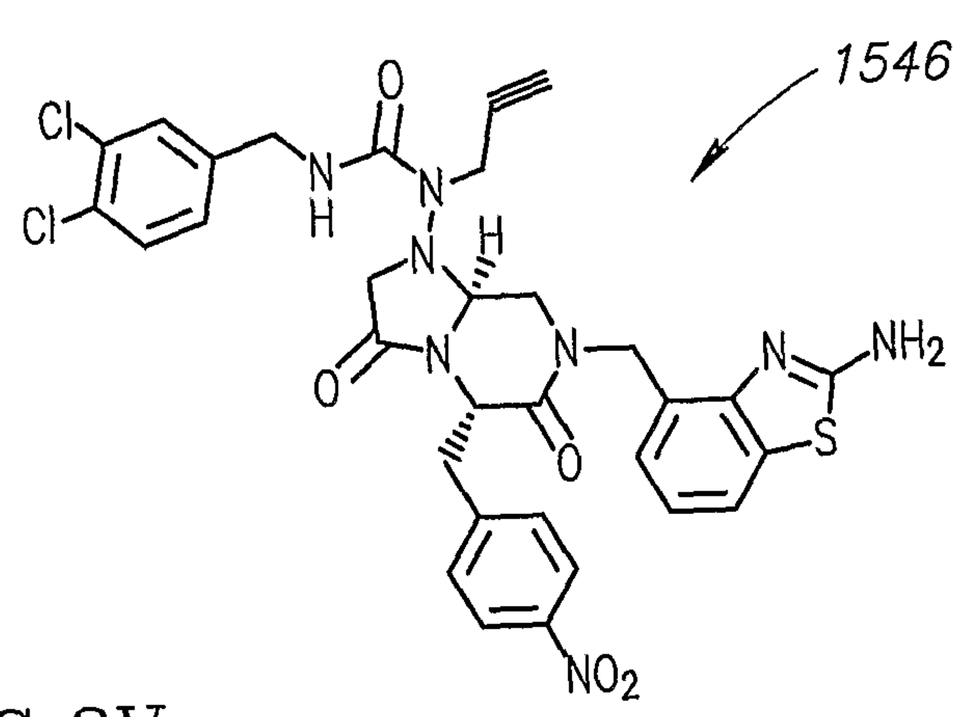
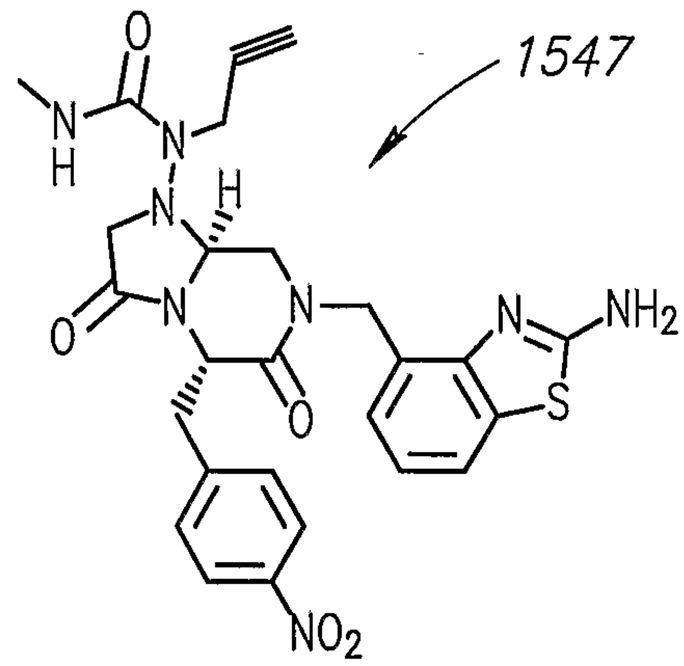
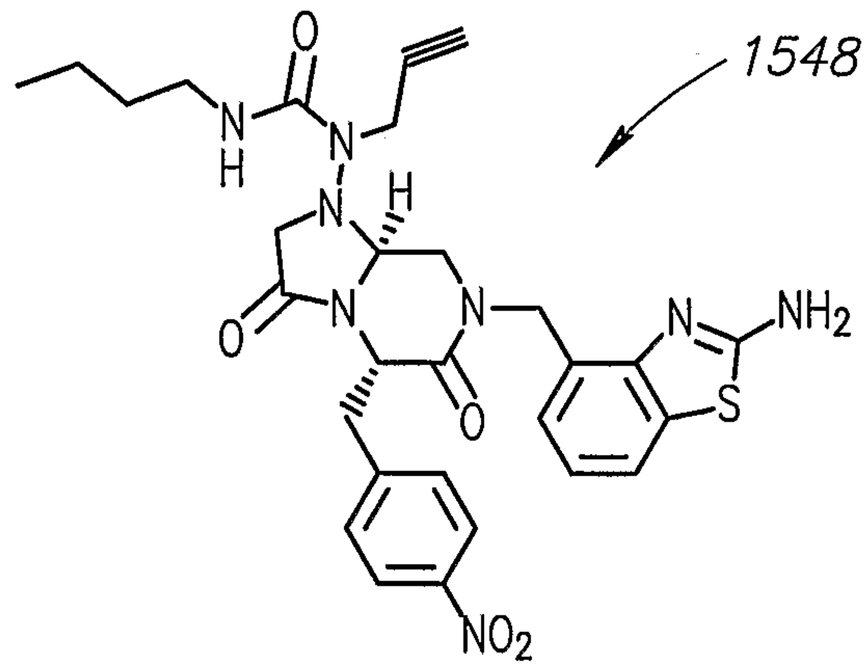
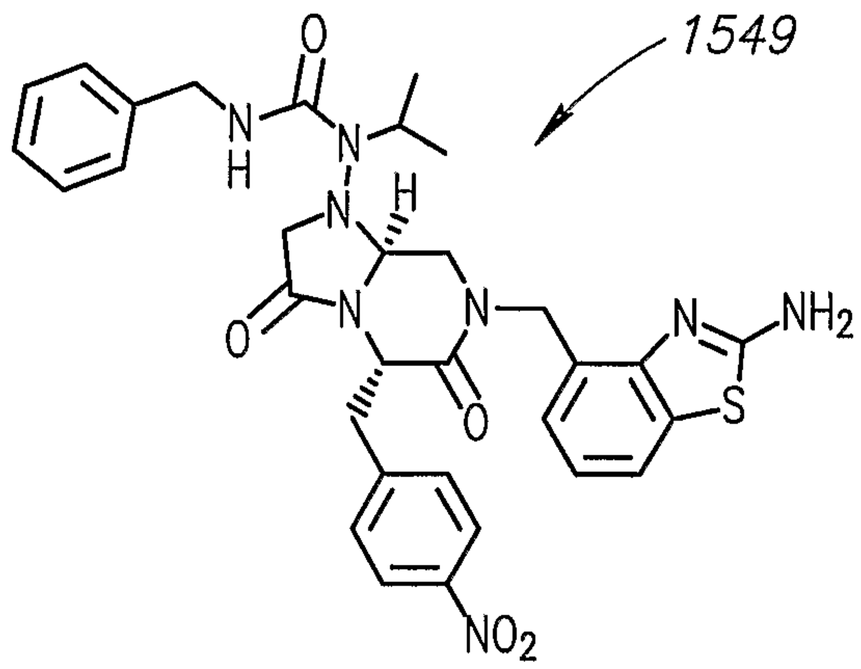
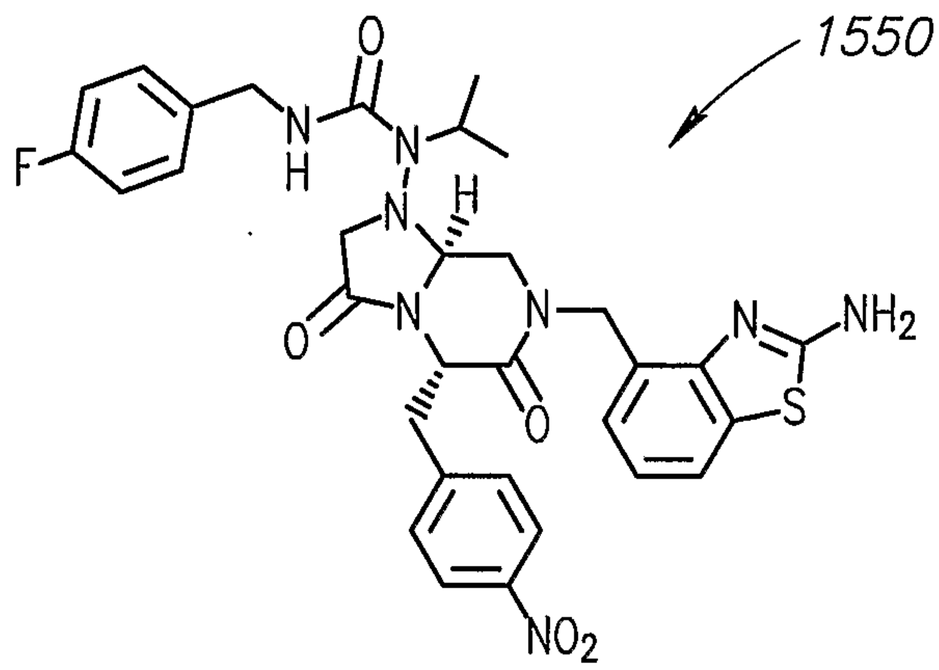

1546
Cl
Cl
O
N
H
N
N
H
N
O
N
O
N
S
NH2
NO2

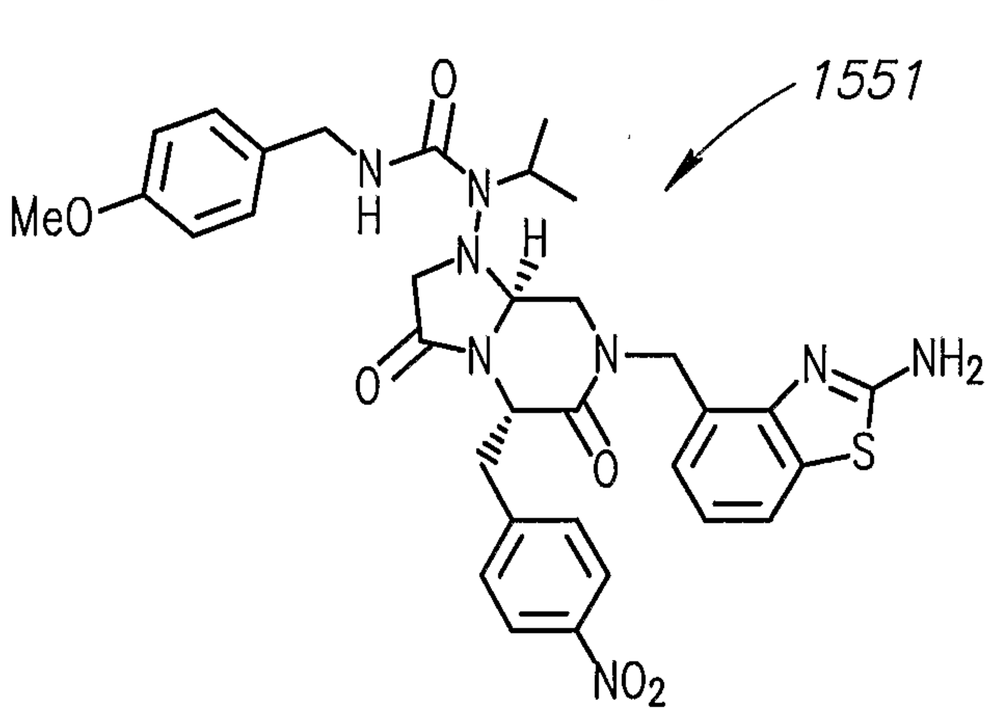
FIG.8V











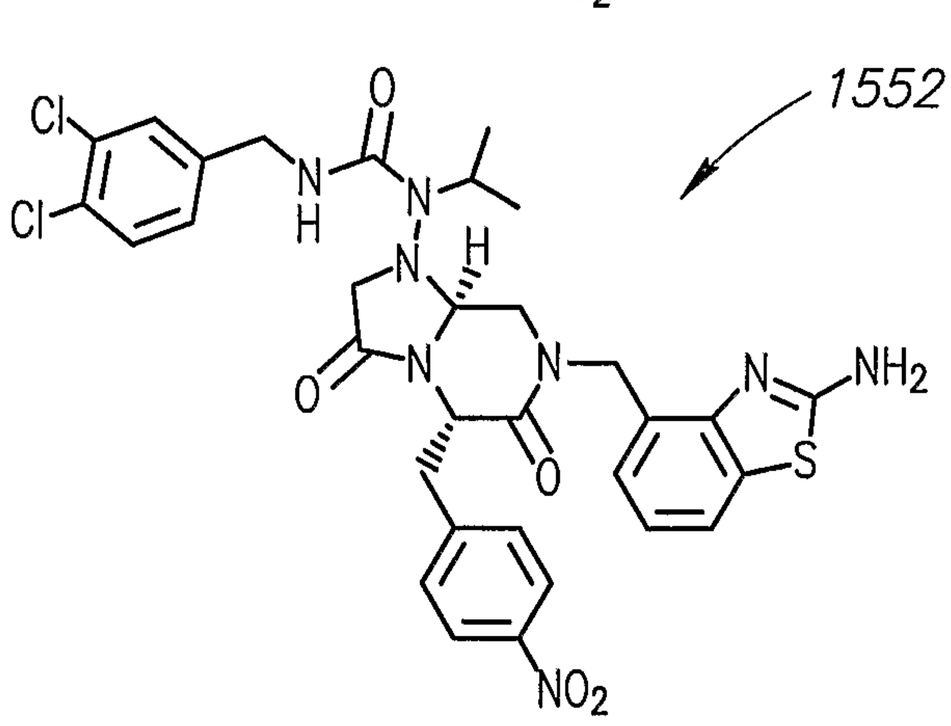
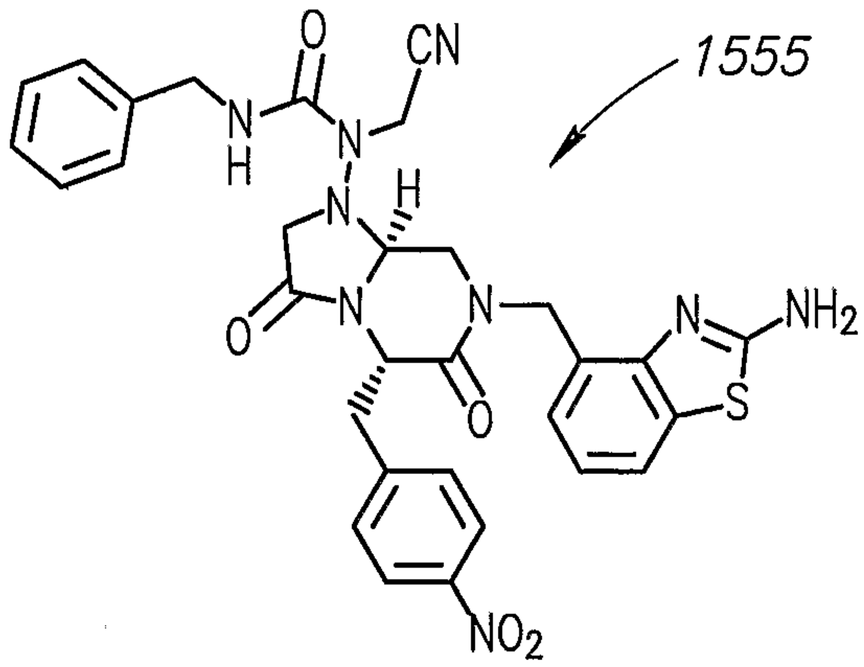


FIG.8W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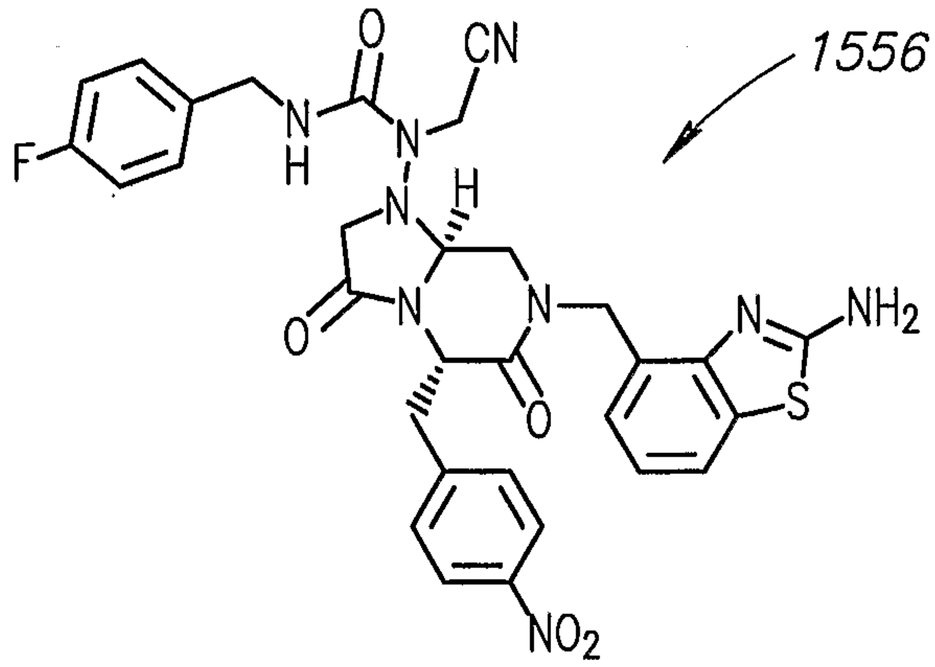
CN
N
H
N
H
N
O
N
O
N
N
S
NH2
NO2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N
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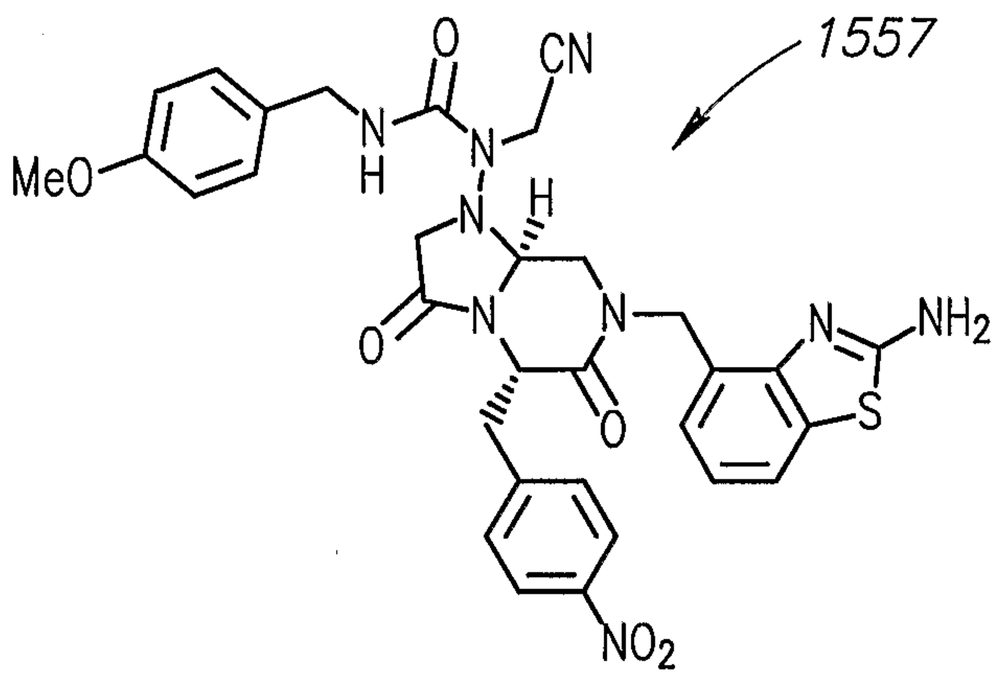
N
H
N
O
N
O
N
N
S
NH2
NO2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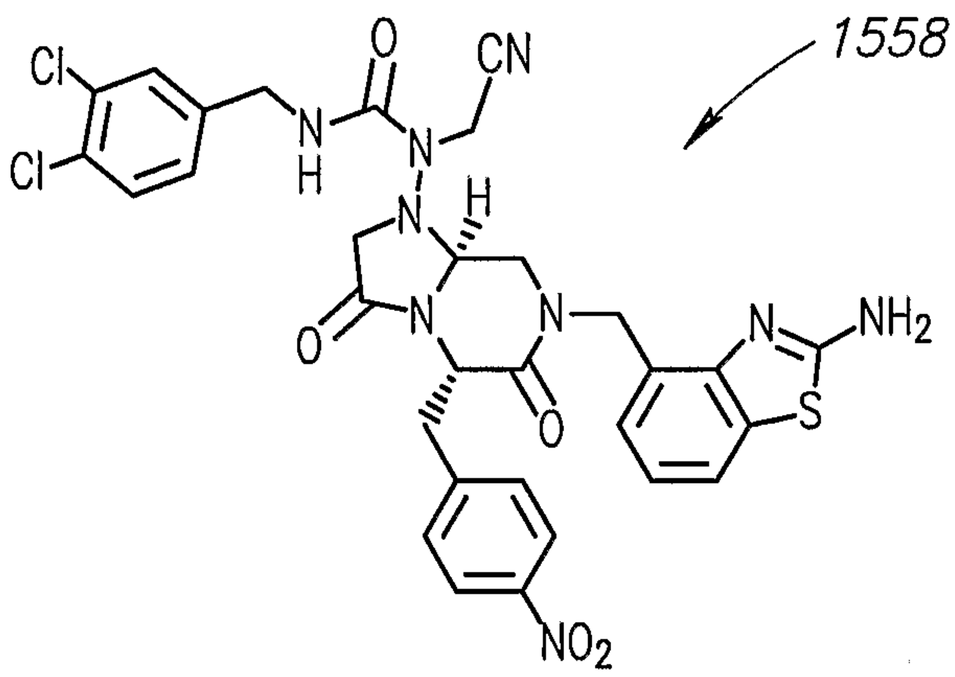
N
H
N
H
N
O
N
O
N
N
S
NH2
NO2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Cl
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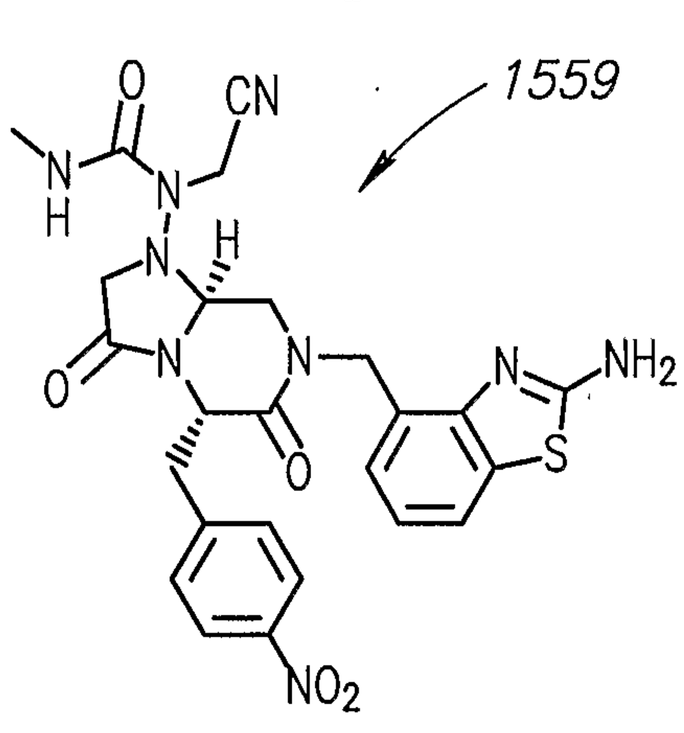
CN
N
H
N
H
N
O
N
O
N
N
S
NH2
NO2


1559
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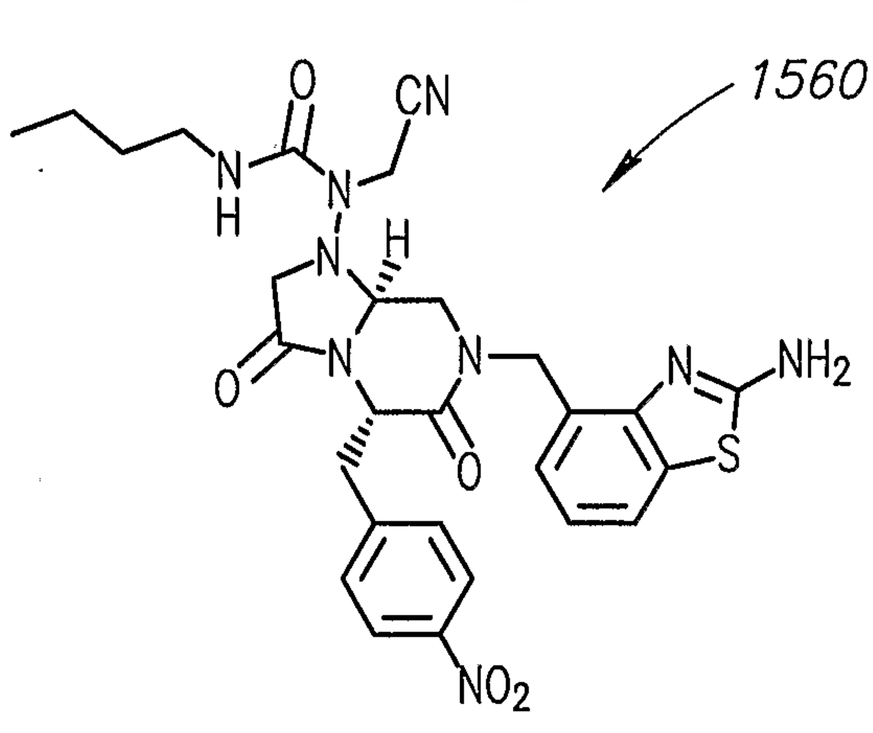
CN
N
H
N
H
N
O
N
O
N
N
S
NH2
NO2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CN
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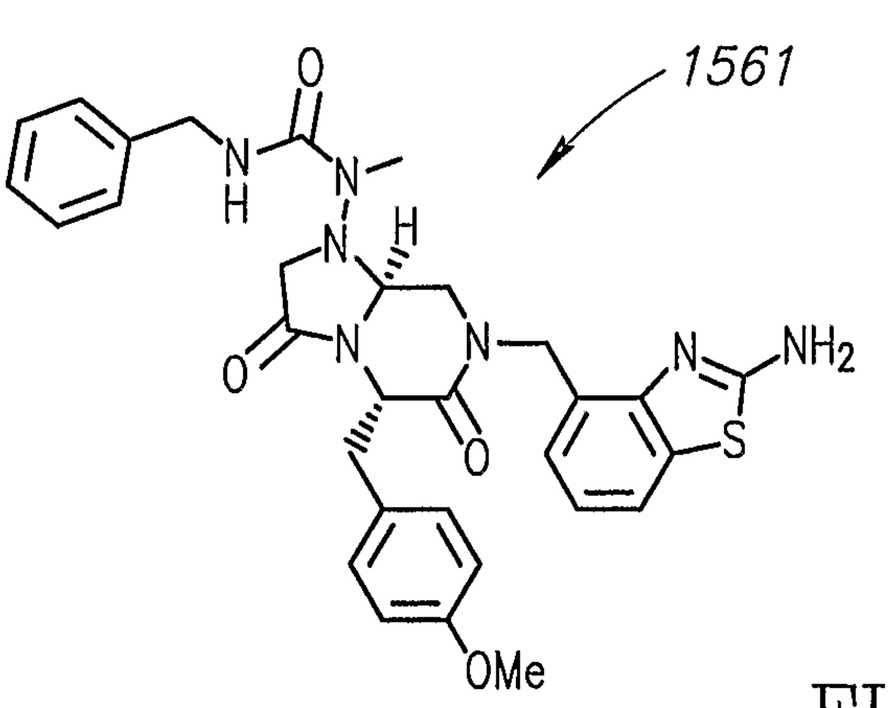
H
N
H
N
O
N
O
N
N
S
NH2
NO2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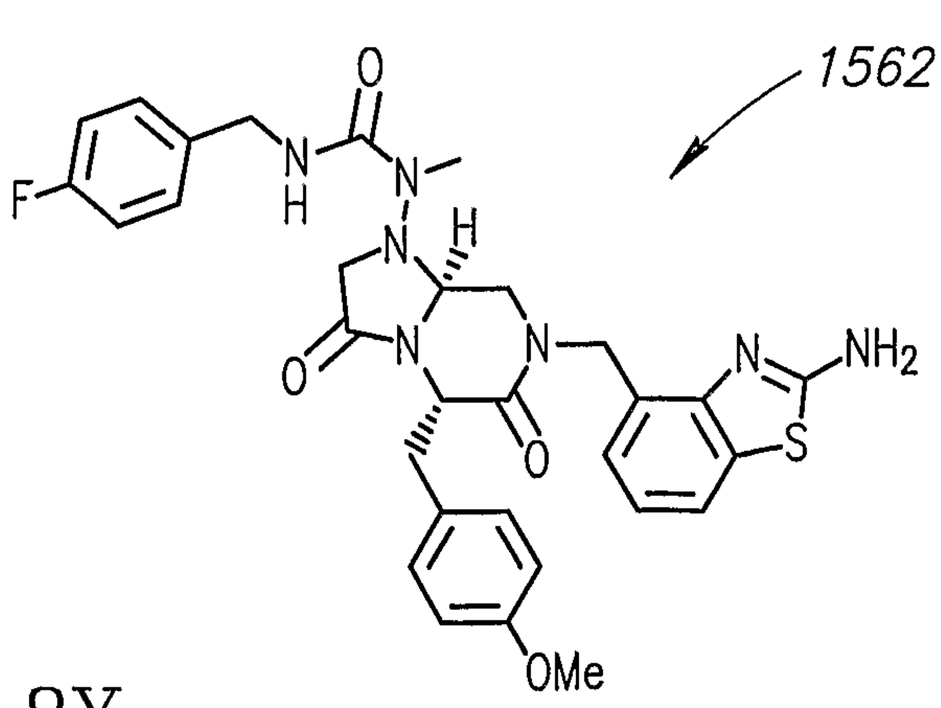
N
H
N
H
N
O
N
O
N
N
S
NH2
OMe


1562
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N
H
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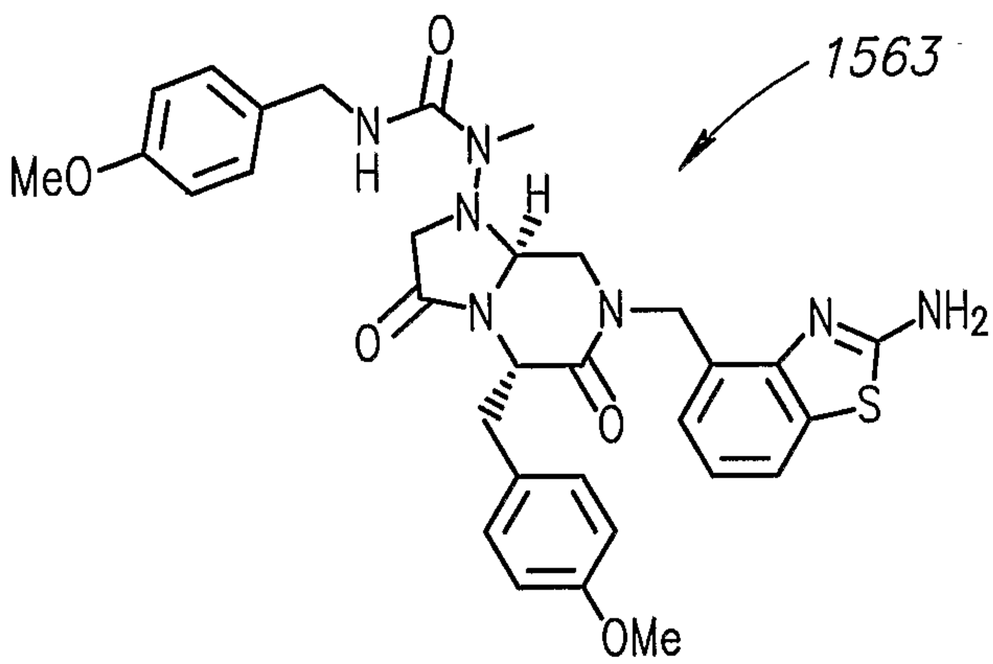
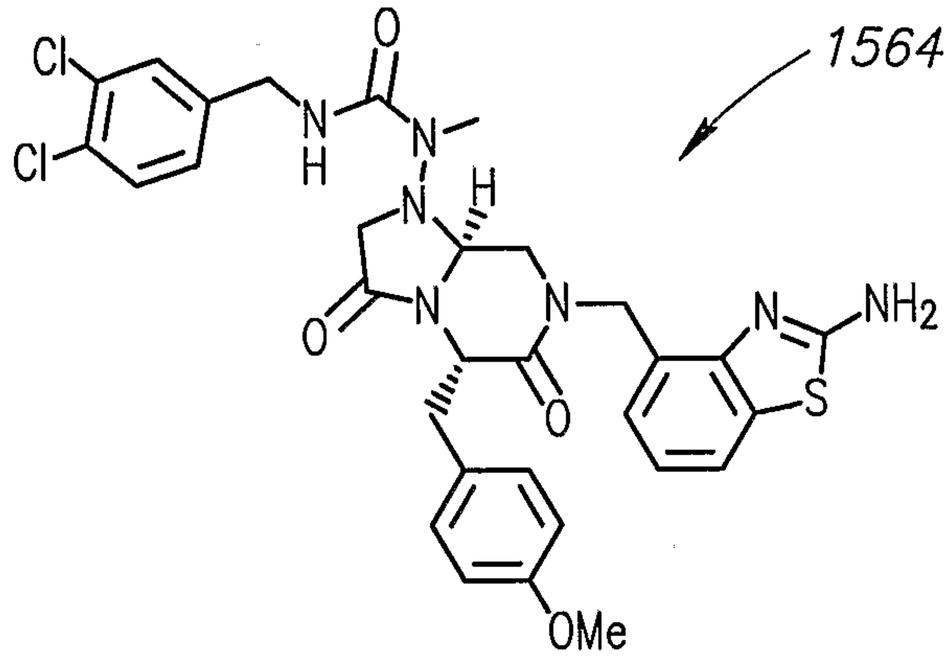
H
N
O
N
O
N
N
S
NH2
OMe

FIG.8X


1563
MeO
OMe


1564
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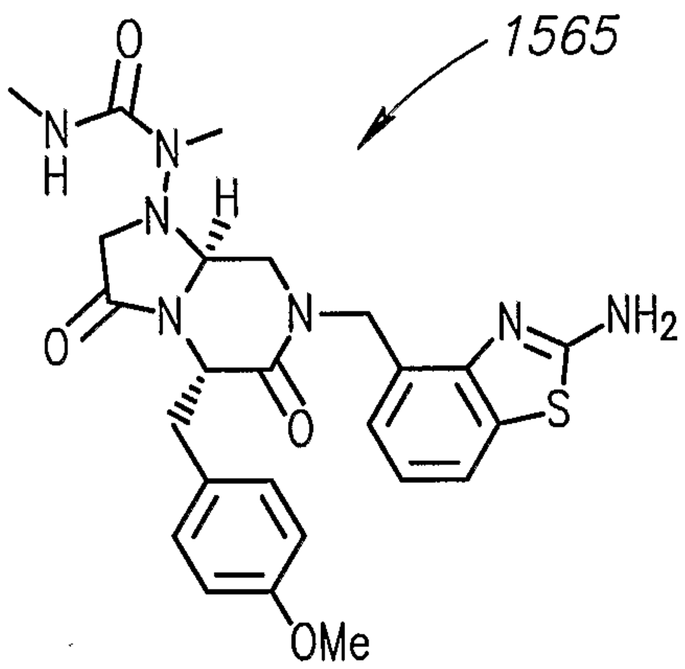
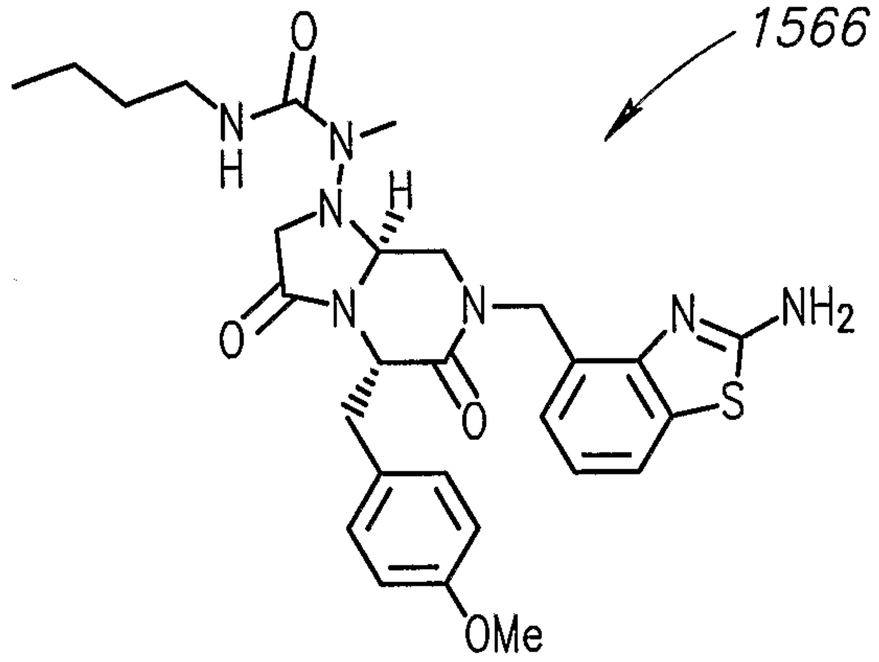
Cl
OMe


1565
OMe


1566
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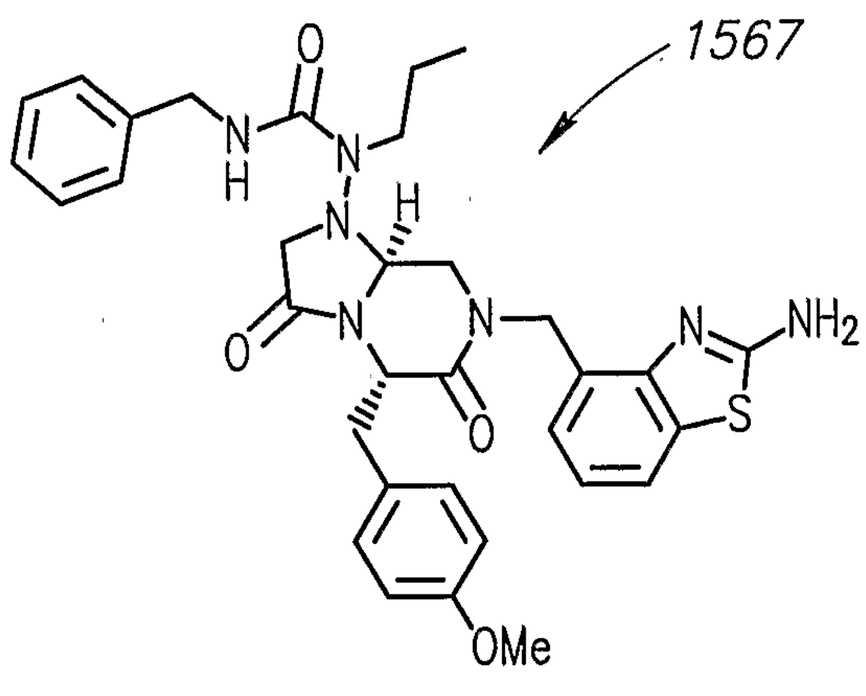
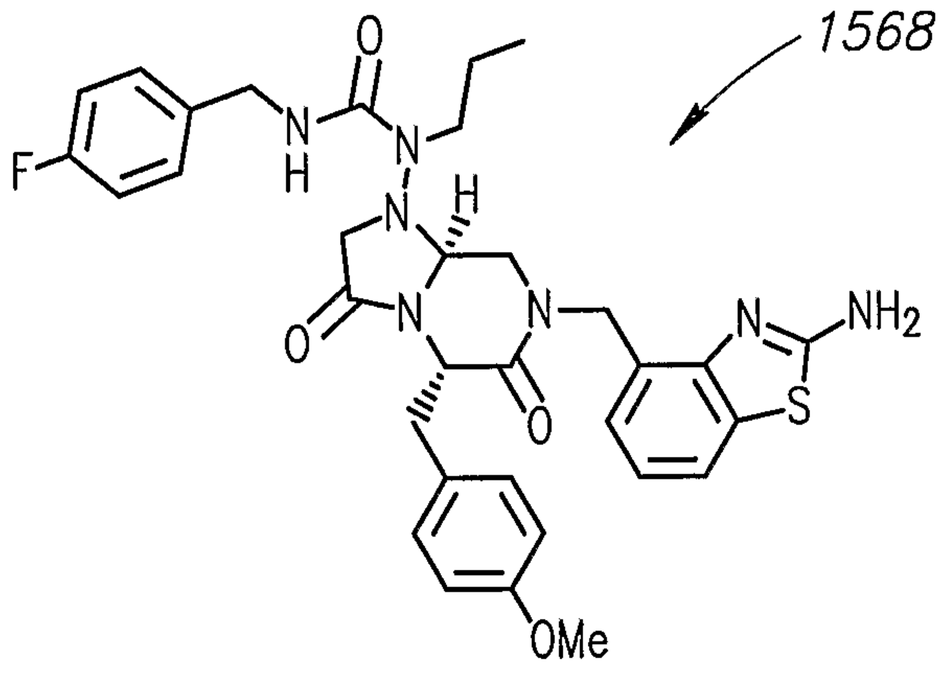
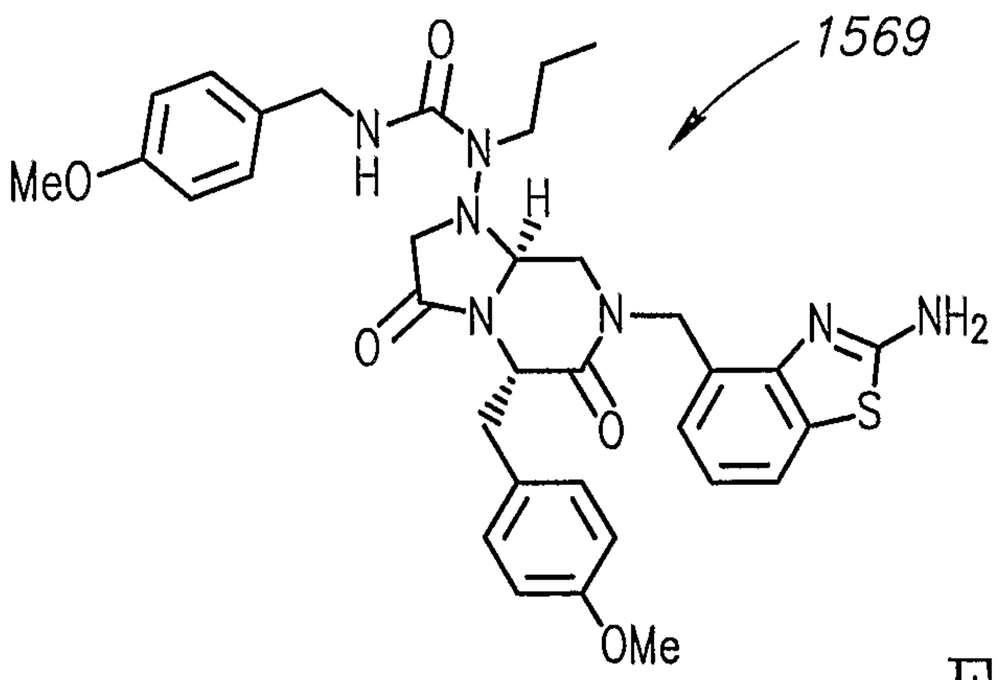

1567
OMe


1568
F
OMe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MeO
OMe

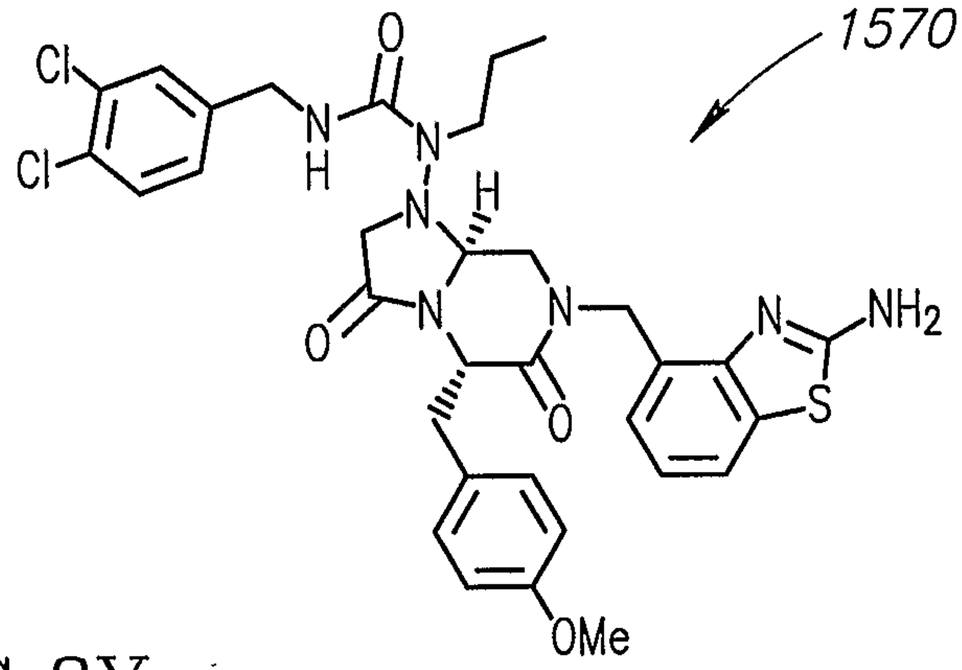
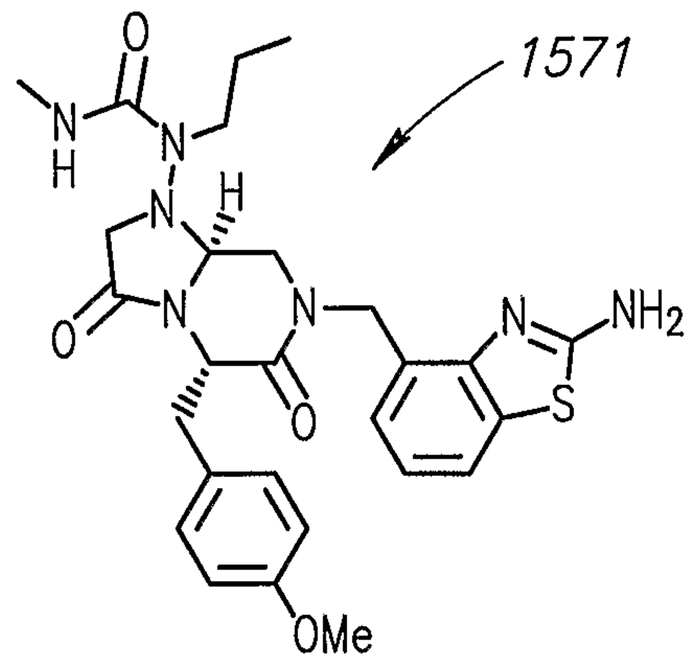

1570
Cl
Cl
OMe

FIG.8Y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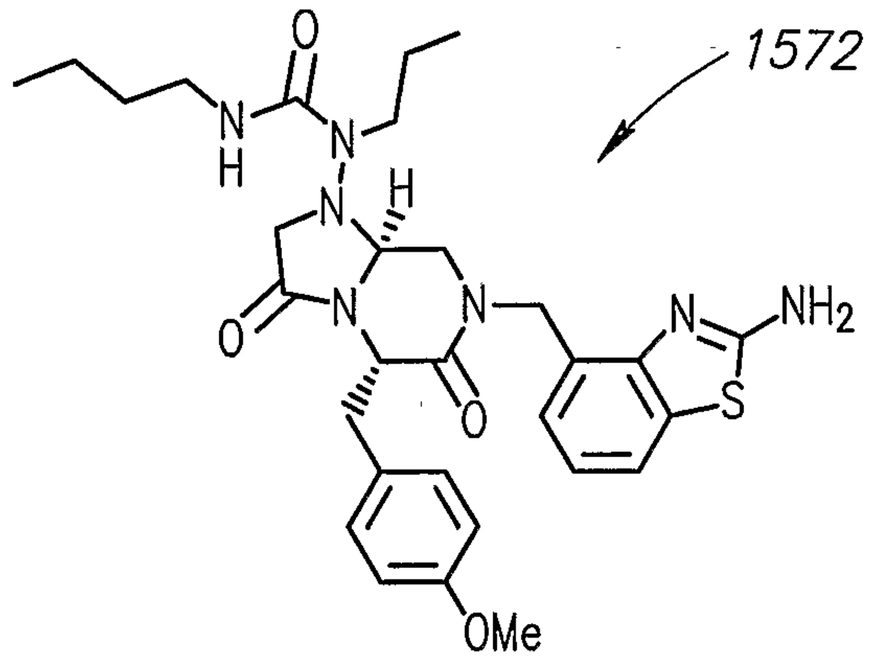
N
N
H
O
N
N
N
NH2
S
O
OMe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N
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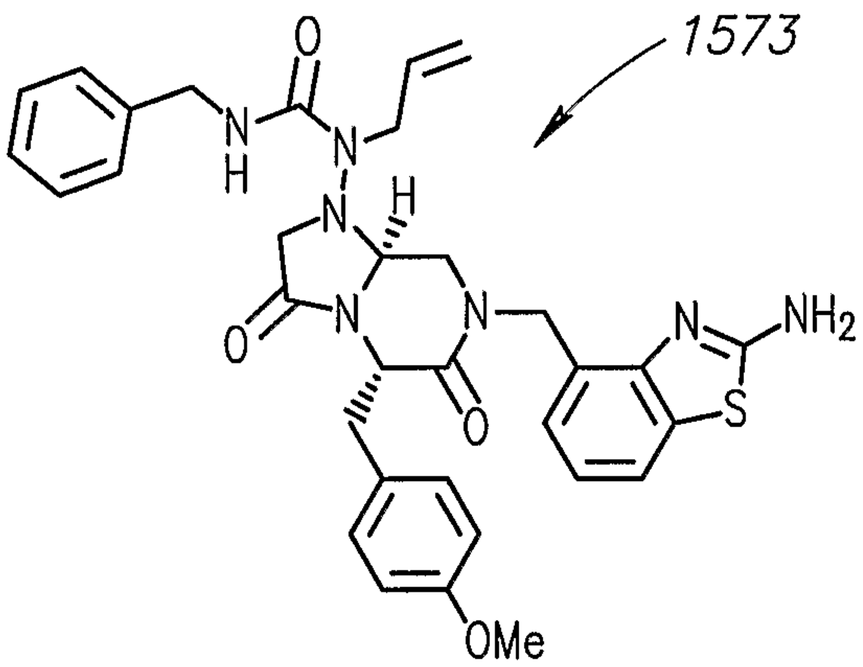
NH2
S
O
OMe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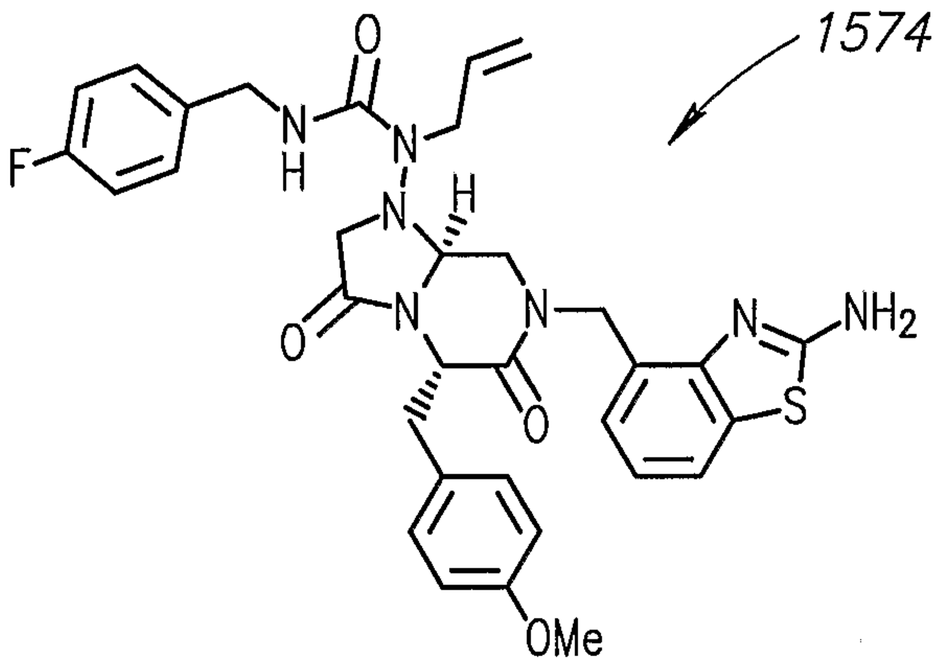
NH2
S
O
OMe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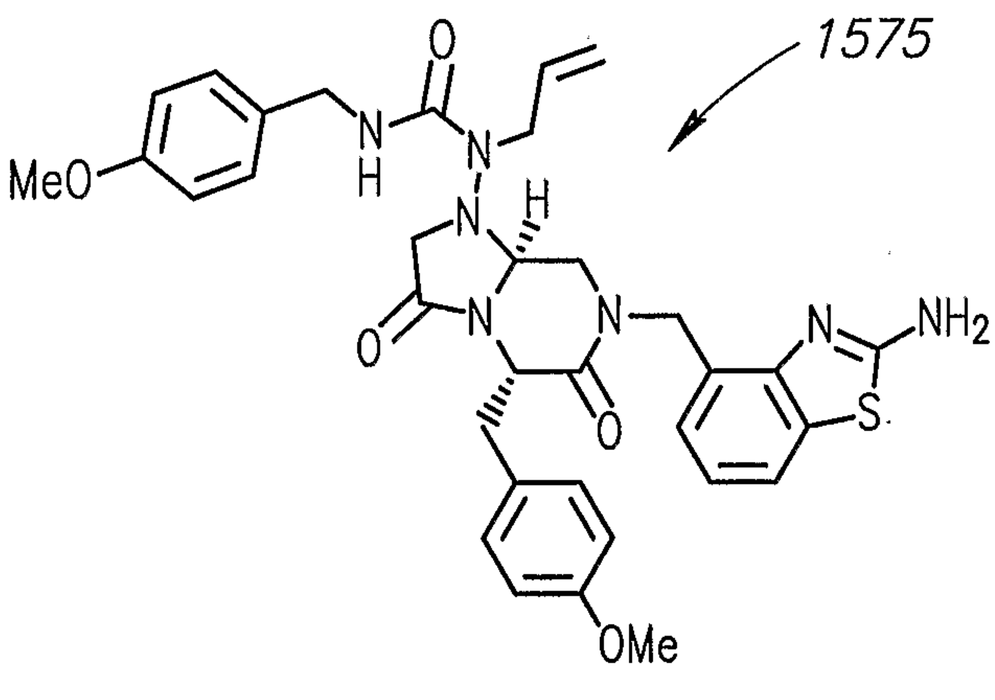
NH2
S
O
OMe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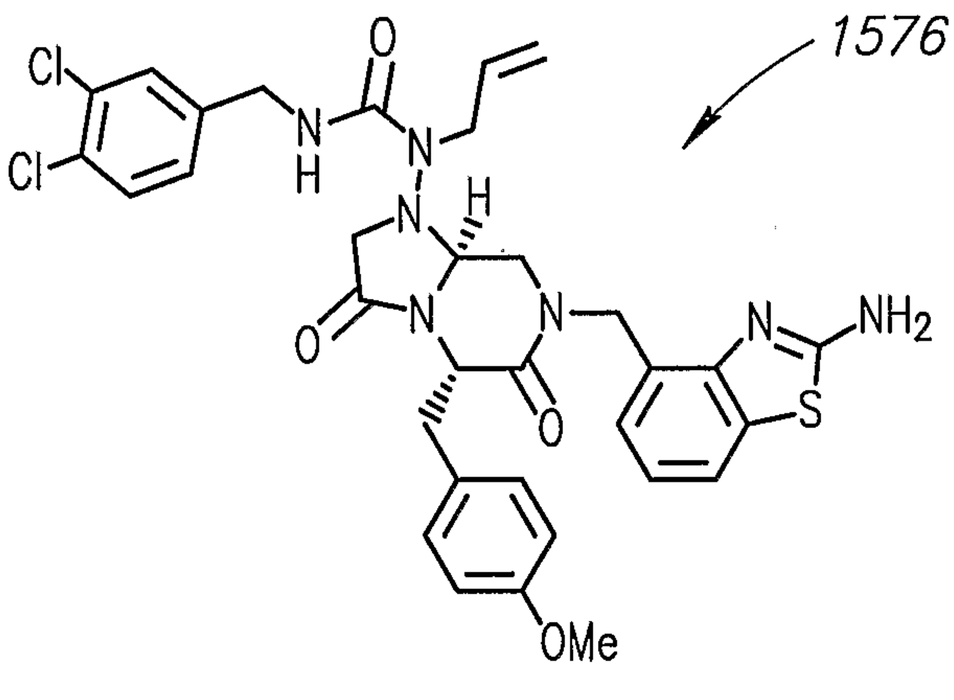
MeO
O
N
H
N
N
H
O
N
N
N
NH2
S
O
OMe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Cl
Cl
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N
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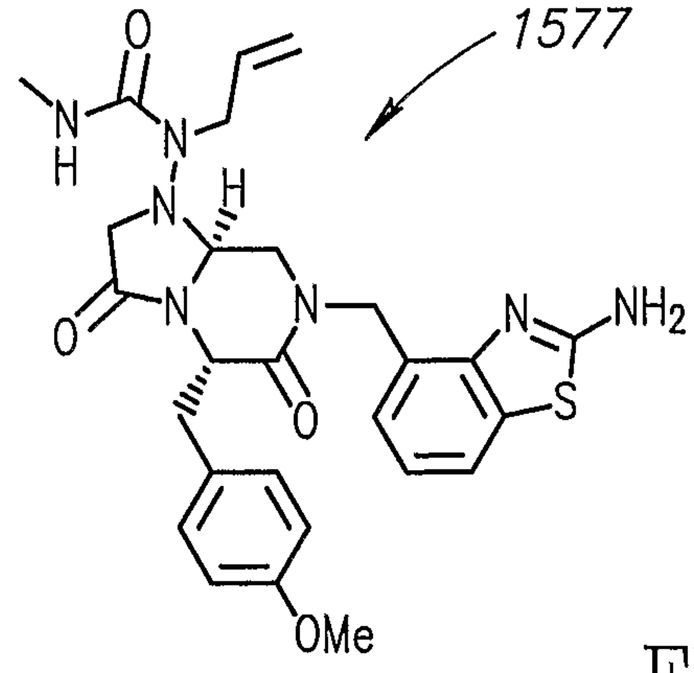
N
H
O
N
N
N
NH2
S
O
OMe


1577
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N
N
H
O
N
N
N
NH2
S
O
OMe

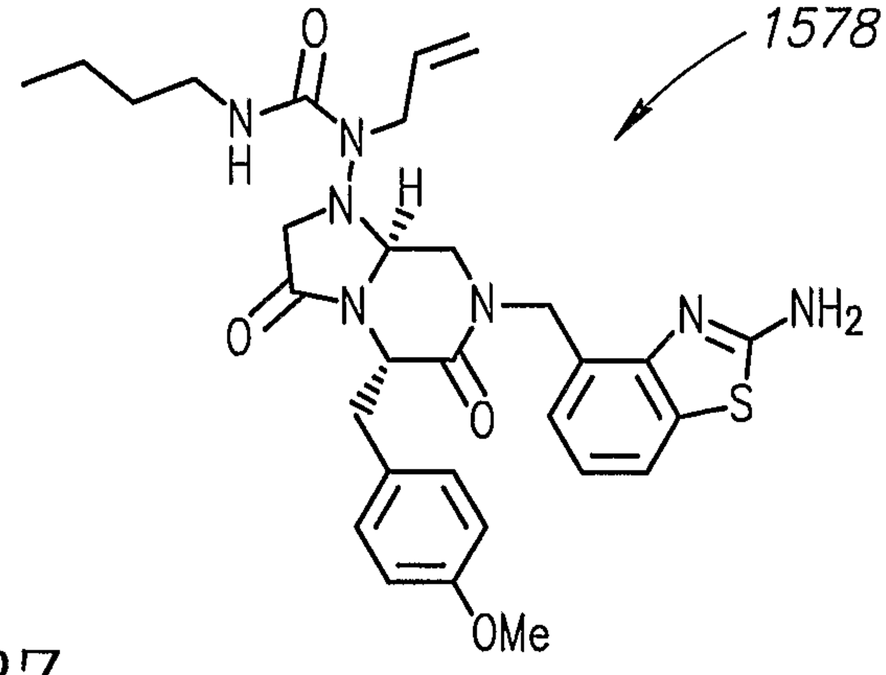
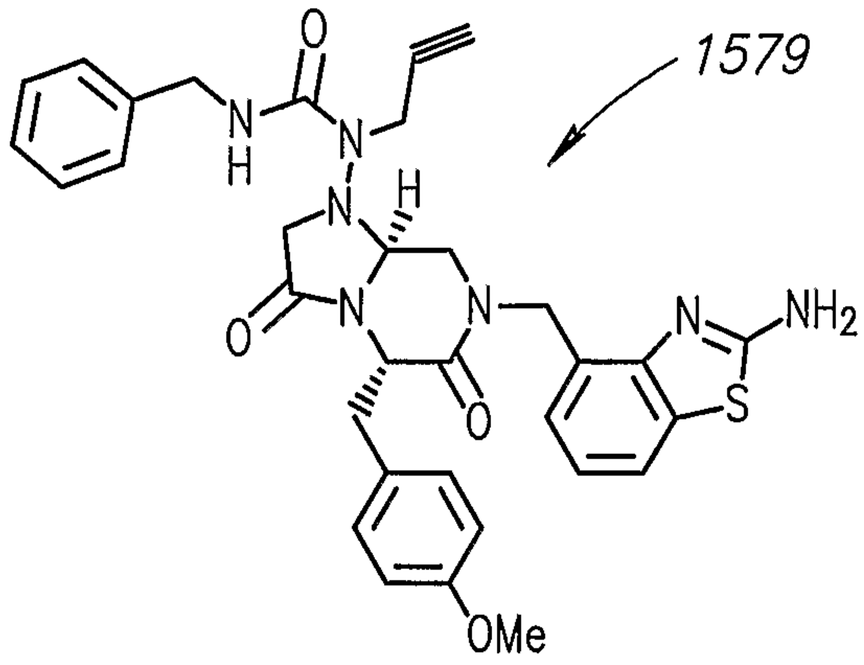

1578
O
N
H
N
N
H
O
N
N
N
NH2
S
O
OMe

FIG.8Z


1579
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N
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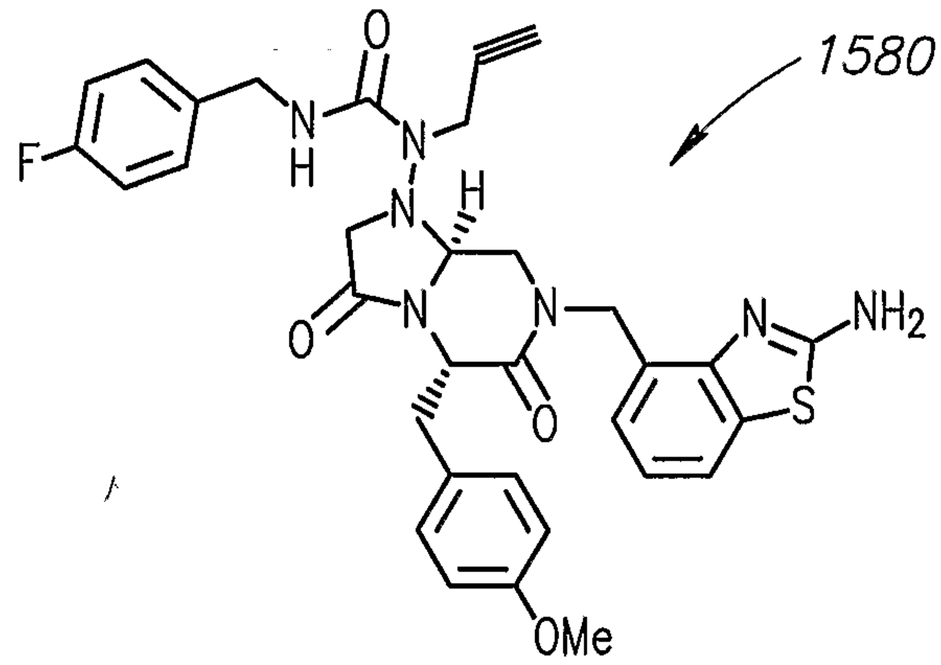
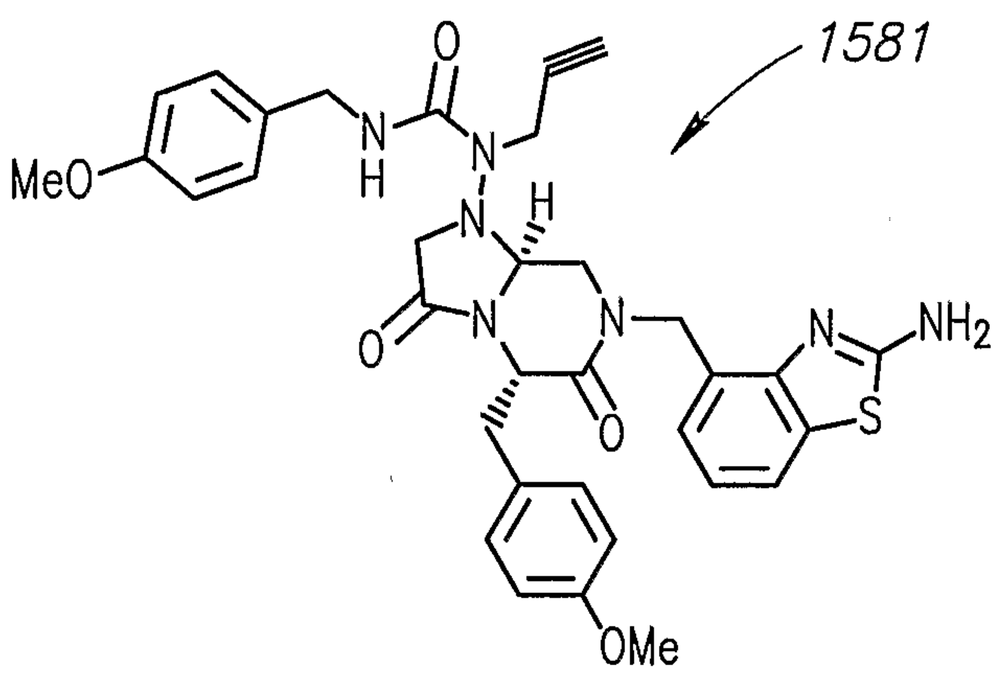
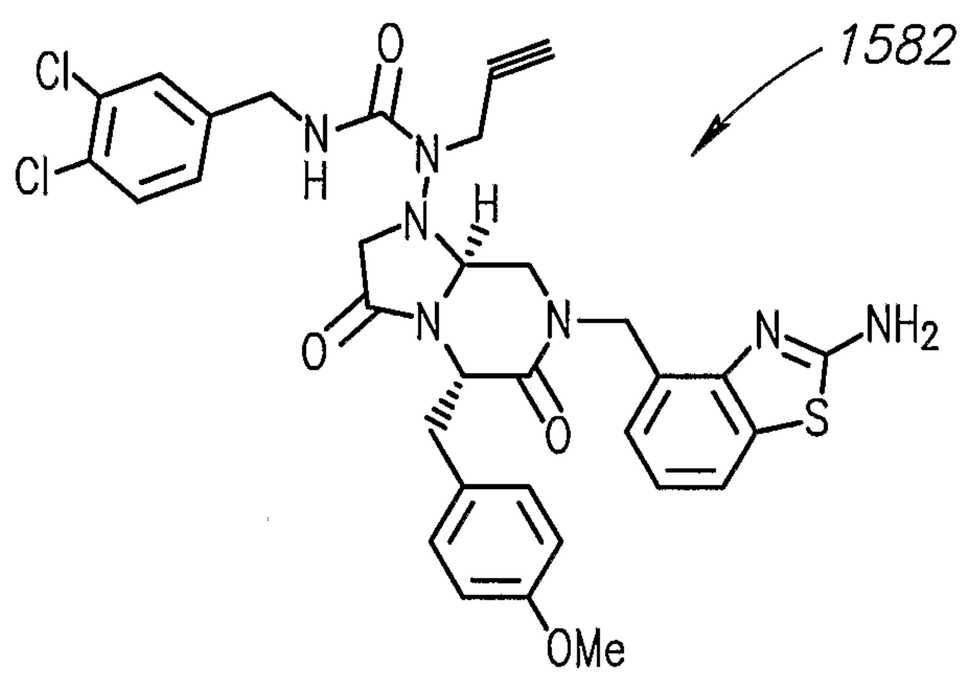
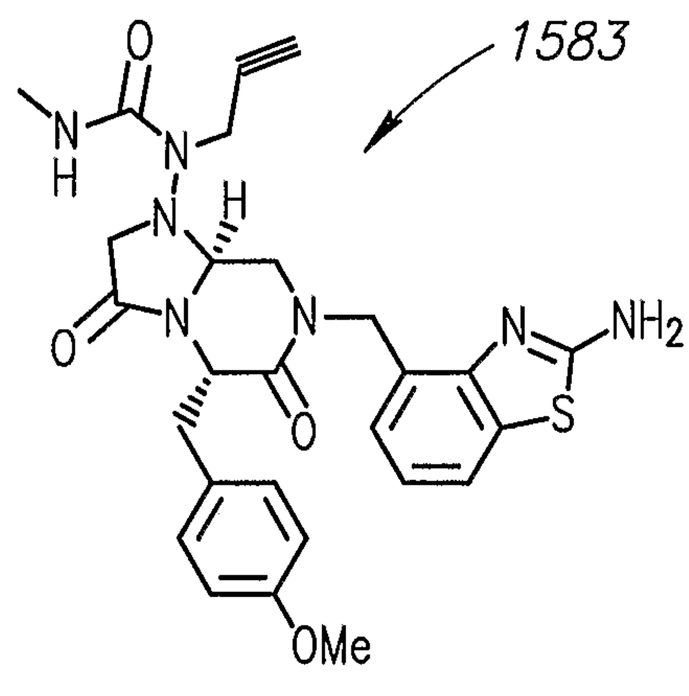
N
N
H
O
N
N
O
N
N
S
NH2
OMe


1580
F
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
OMe


1581
MeO
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
OMe


1582
Cl
Cl
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
OMe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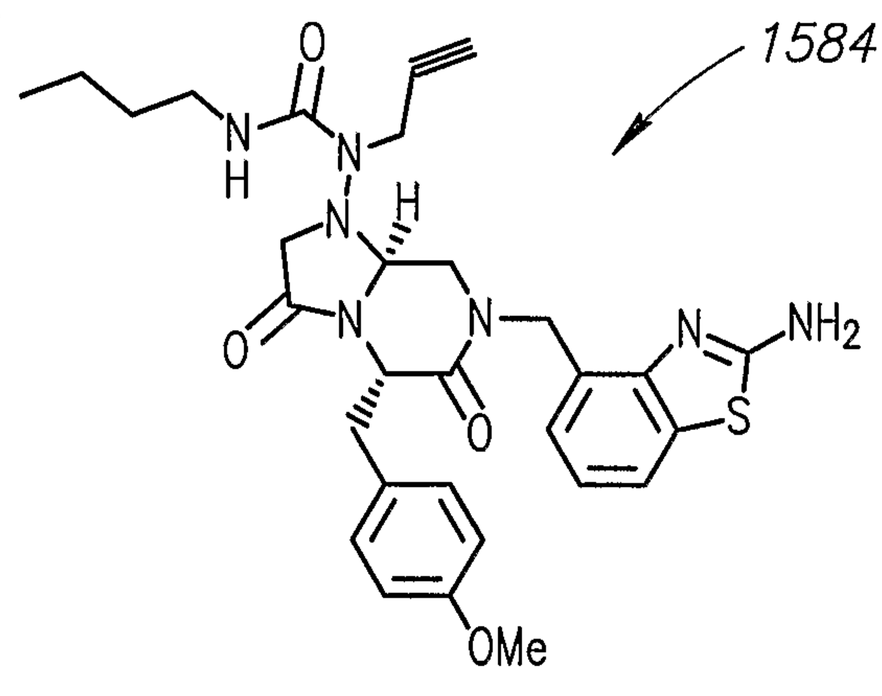
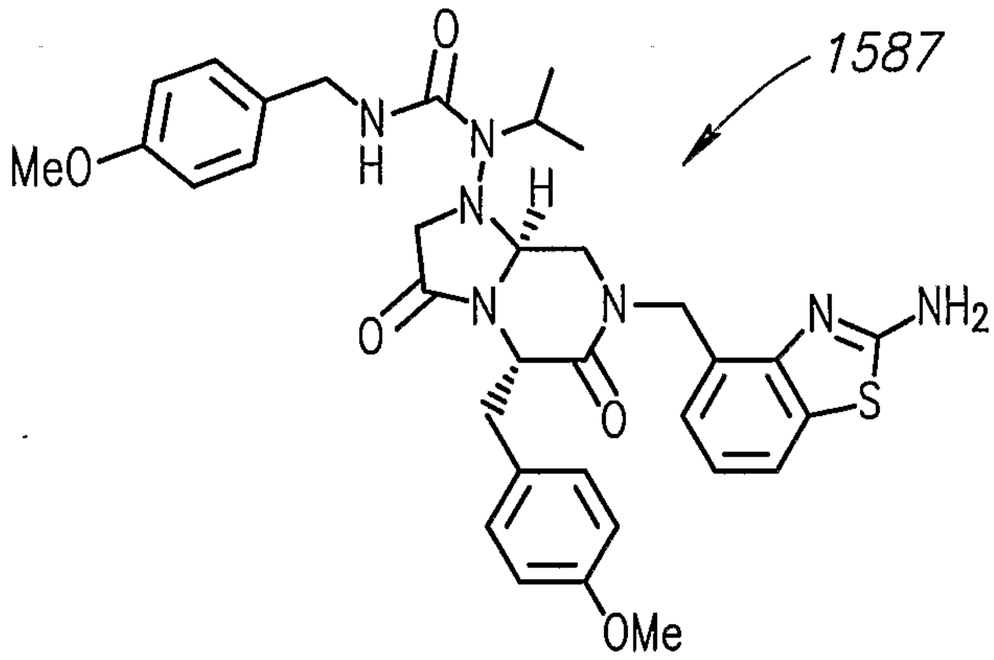
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
OMe


1584
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
OMe

1585
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
OMe

1586
F
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
OMe

FIG.8AA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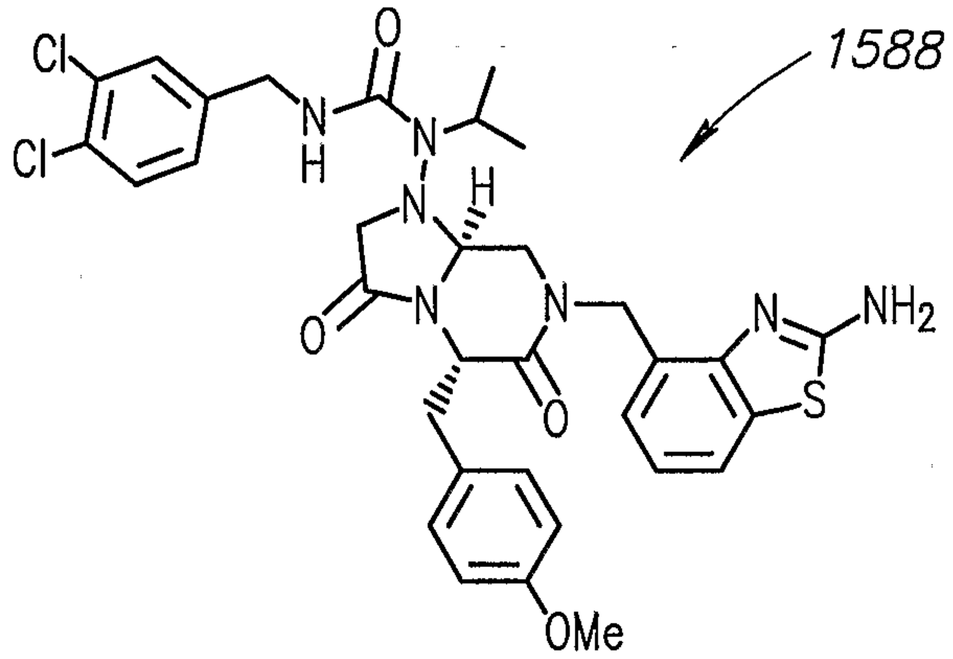
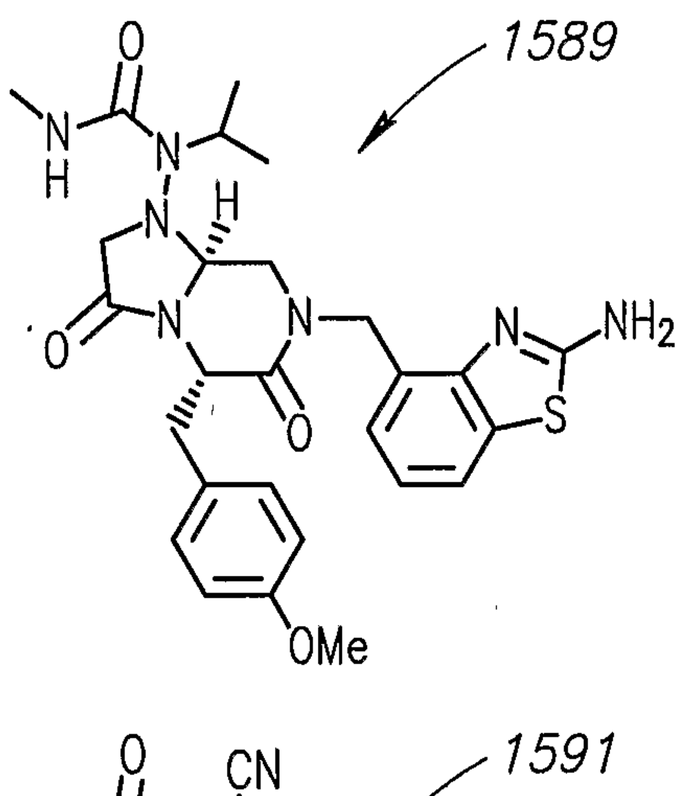
O
N
H
N
N
H
O
N
N
O
O
N
N
S
NH2
OMe


1588
Cl
Cl
O
N
H
N
N
H
O
N
N
O
O
N
N
S
NH2
OMe


1589
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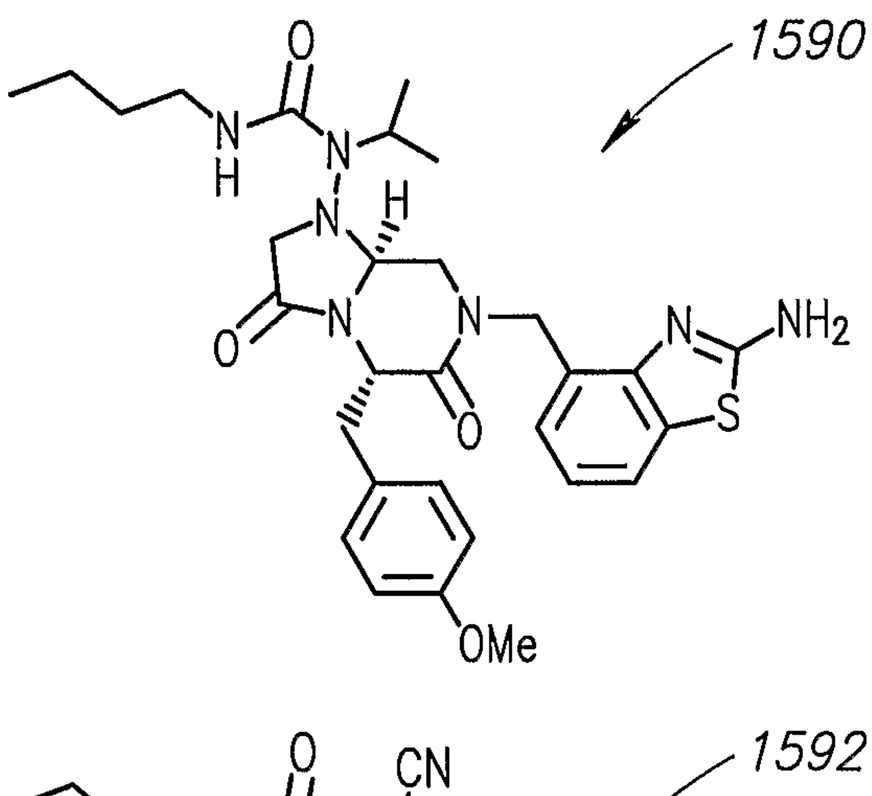
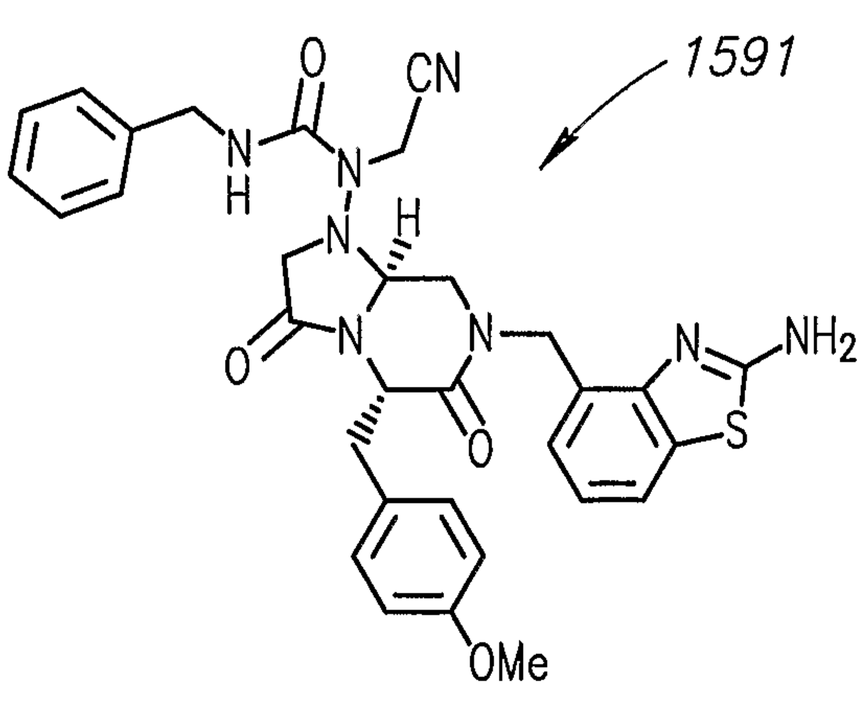
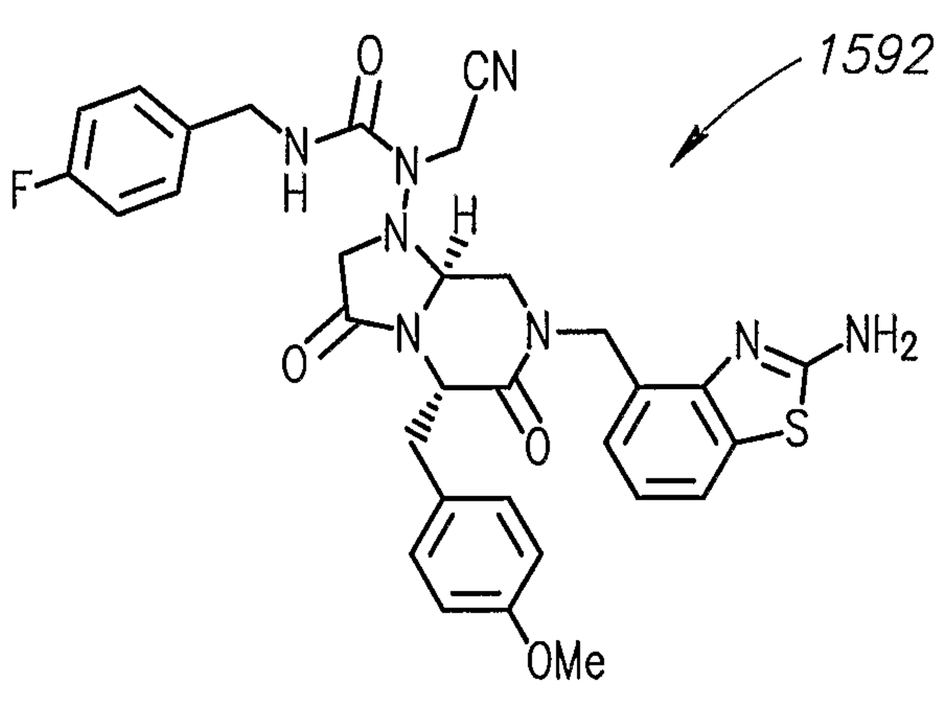
N
H
O
N
N
H
O
N
N
O
O
N
N
S
NH2
OMe


1590
O
N
H
O
N
N
H
O
N
N
O
O
N
N
S
NH2
OMe


1591
O
CN
N
H
O
N
N
H
O
N
N
O
O
N
N
S
NH2
OMe


1592
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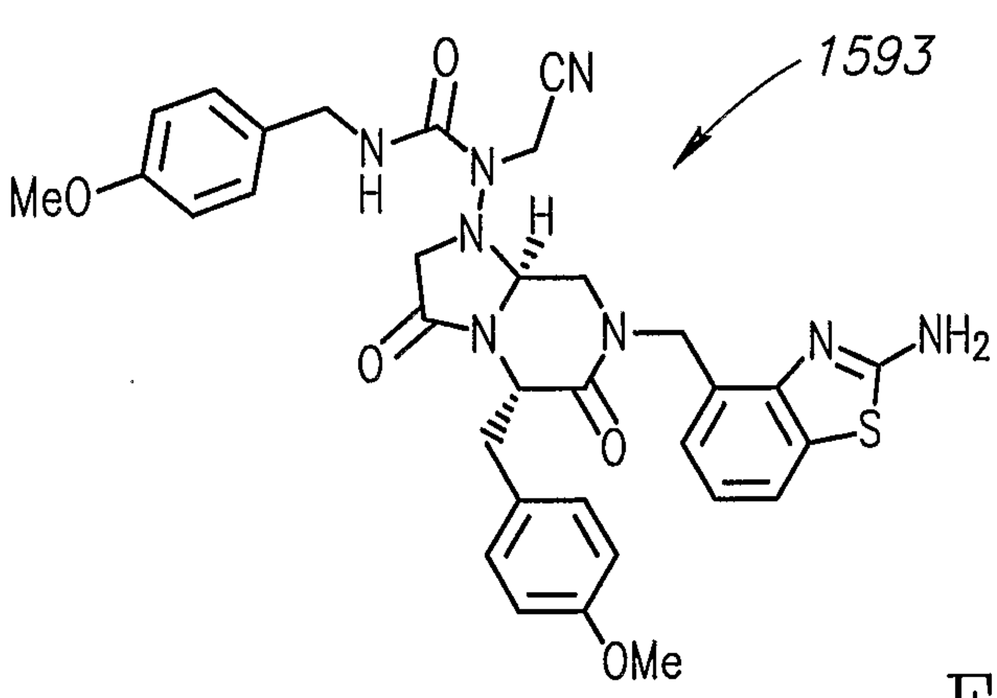
O
CN
N
H
O
N
N
H
O
N
N
O
O
N
N
S
NH2
OMe


1593
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O
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N
H
O
N
N
H
O
N
N
O
O
N
N
S
NH2
OMe

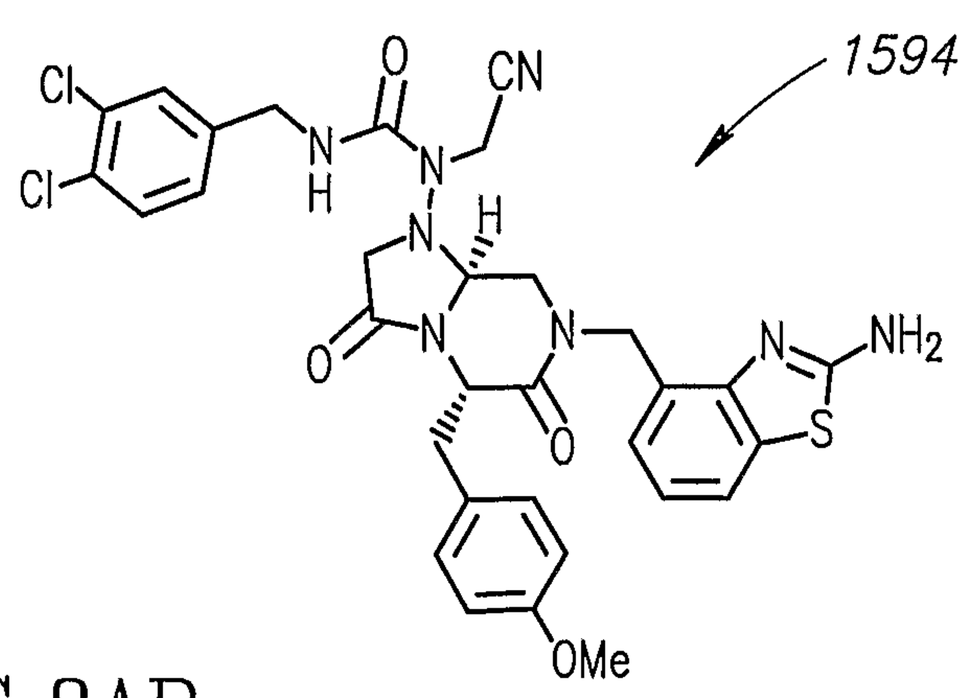
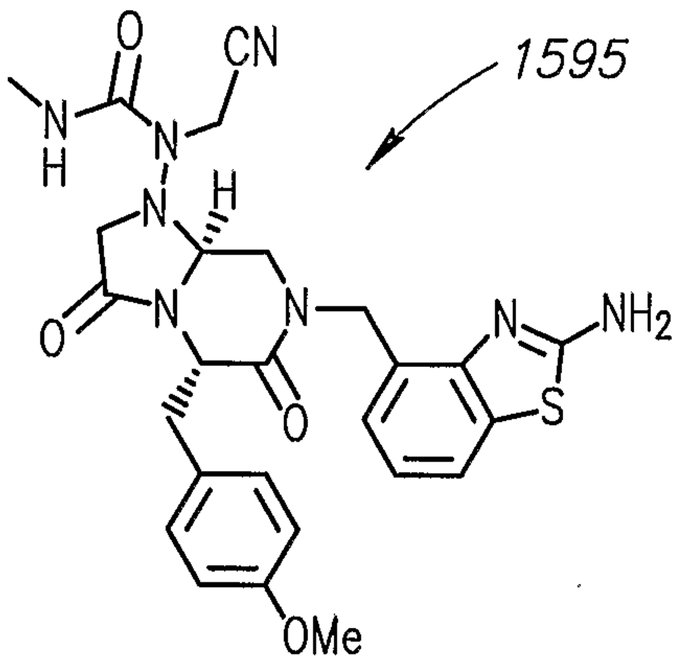
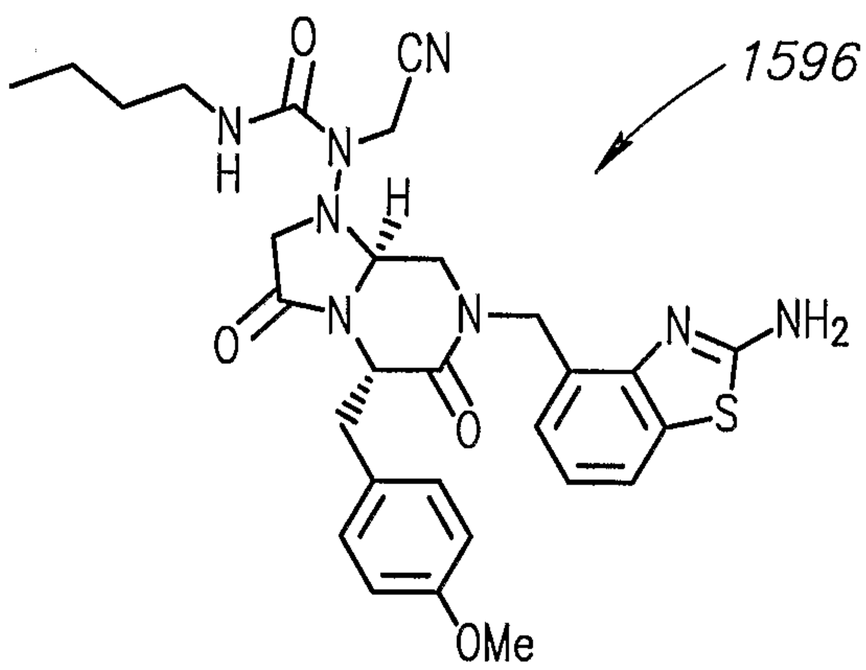
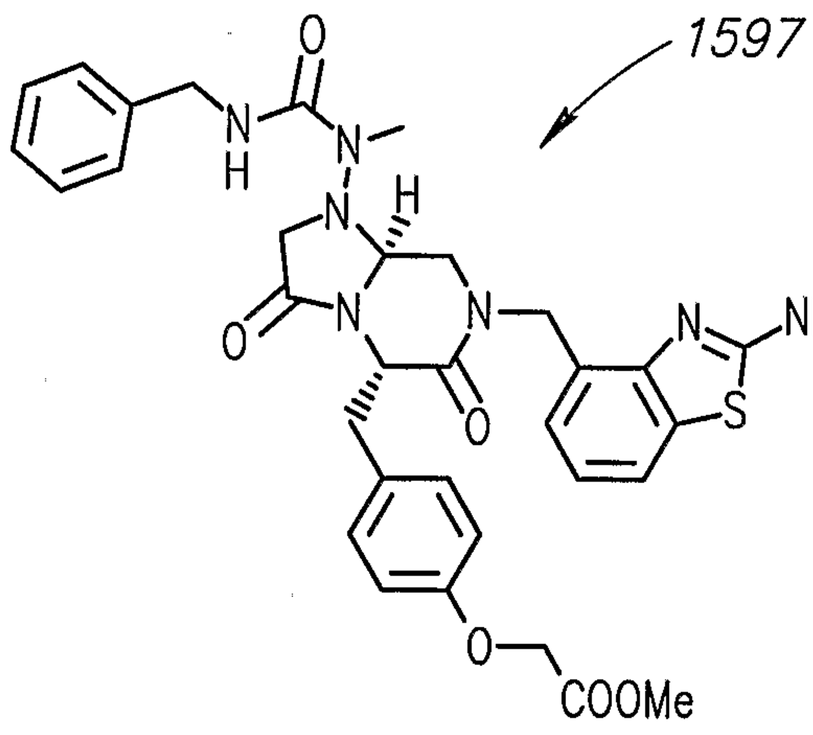
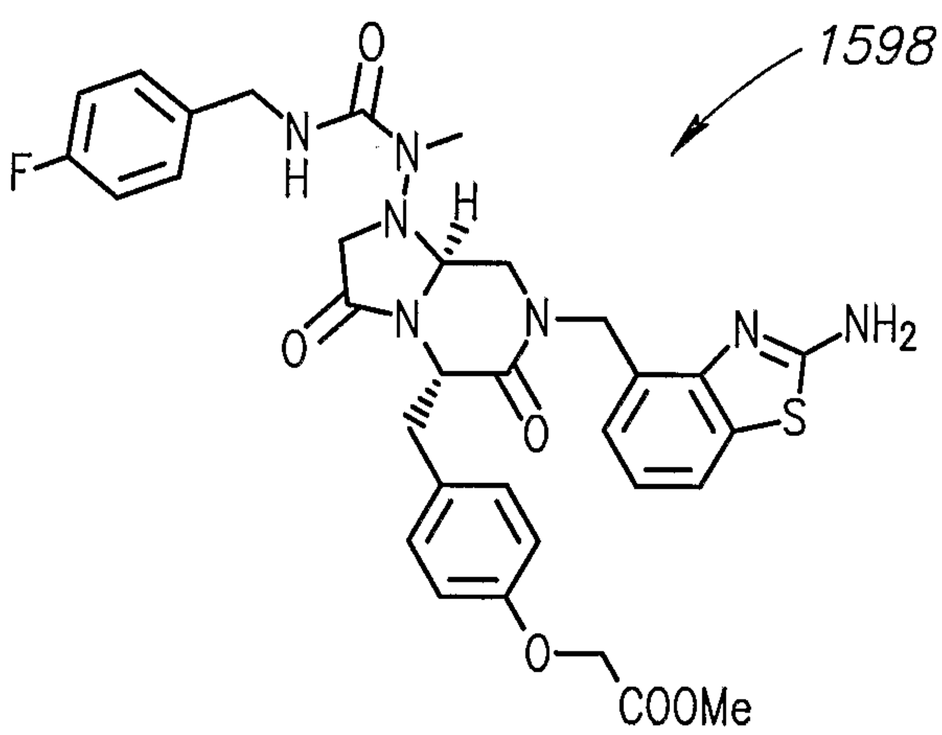

1594
Cl
Cl
O
CN
N
H
O
N
N
H
O
N
N
O
O
N
N
S
NH2
OMe

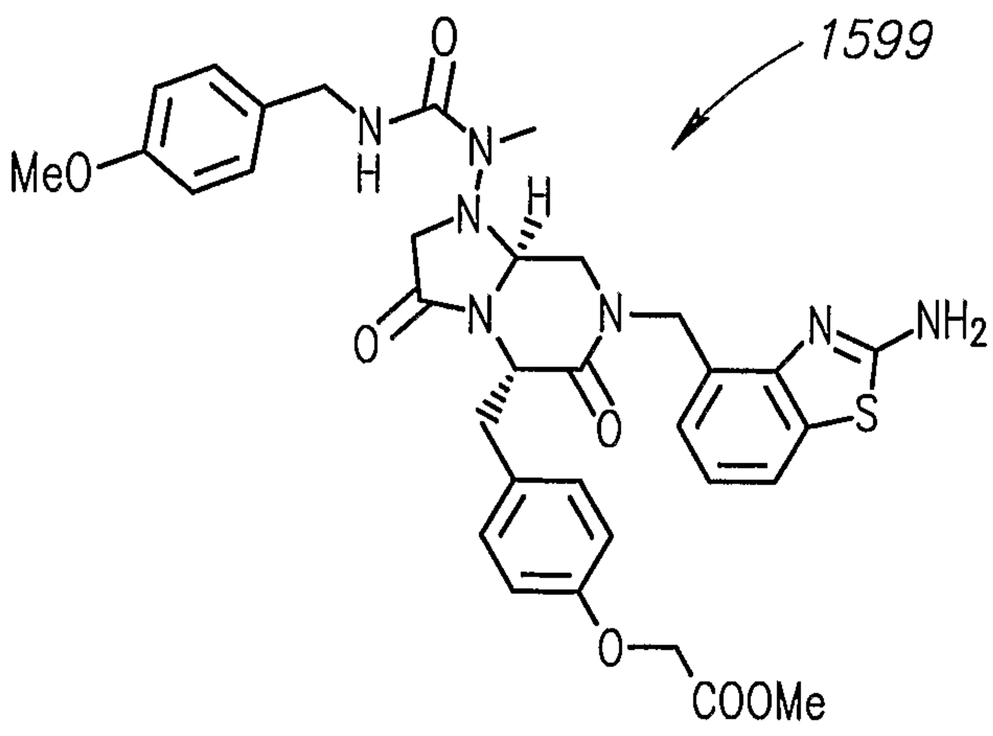
FIG.8AB


1595
O
CN
N
H
N
N
H
O
N
N
N
NH2
S
O
OMe


1596
O
CN
N
H
N
N
H
O
N
N
N
NH2
S
O
OMe


1597
O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe


1598
F
O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe


1599
MeO
O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe

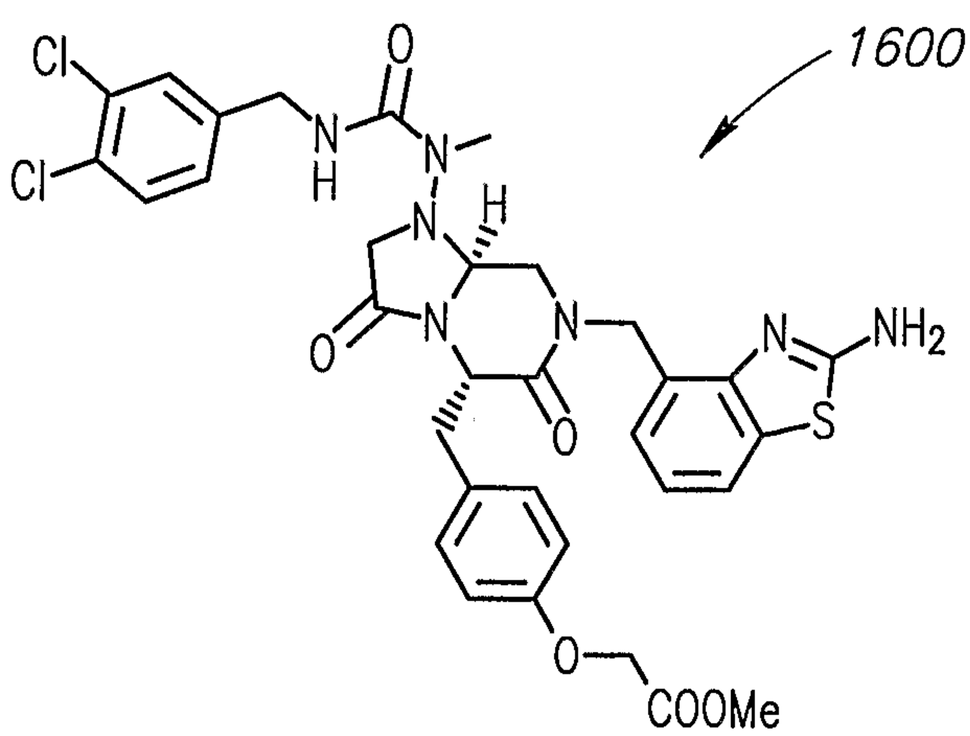
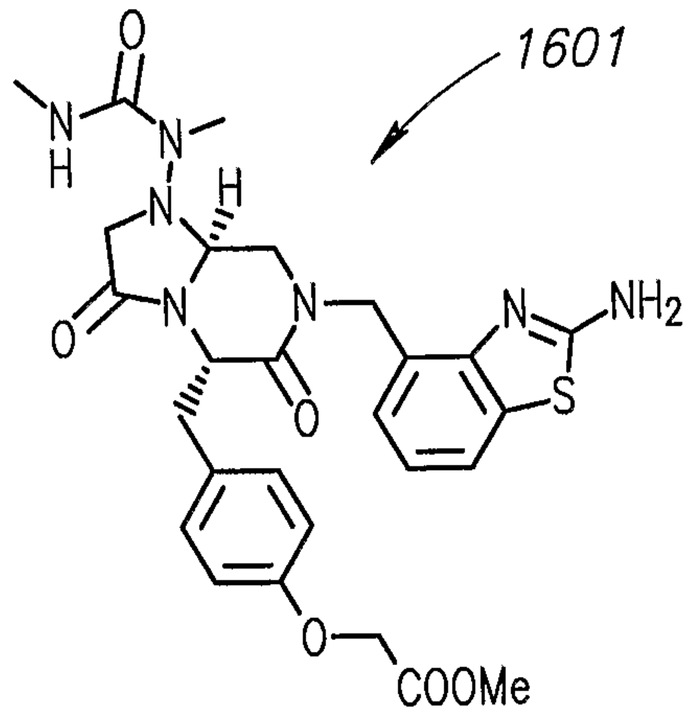
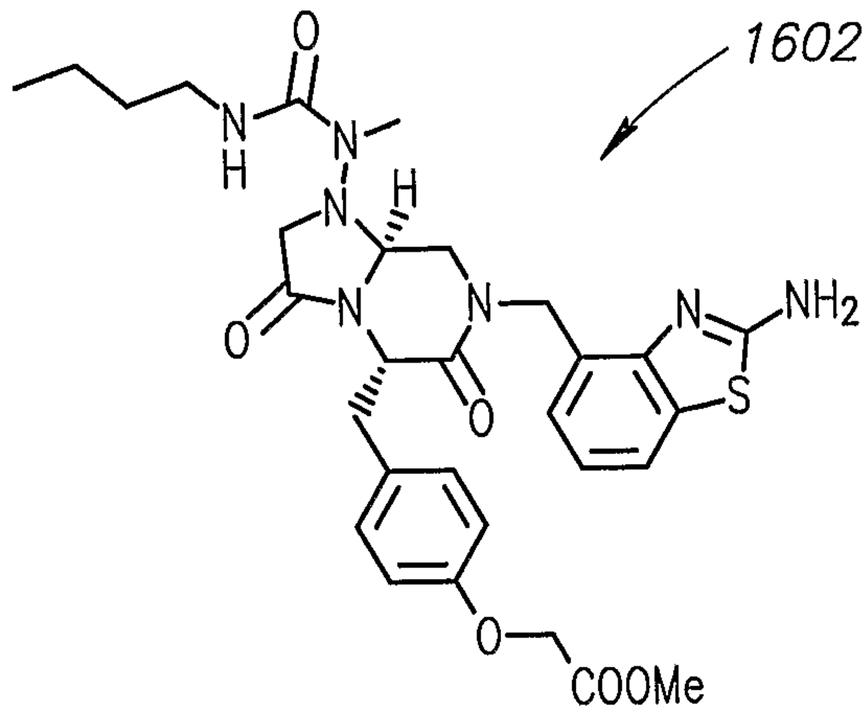

1600
Cl
Cl
O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe

FIG.8AC

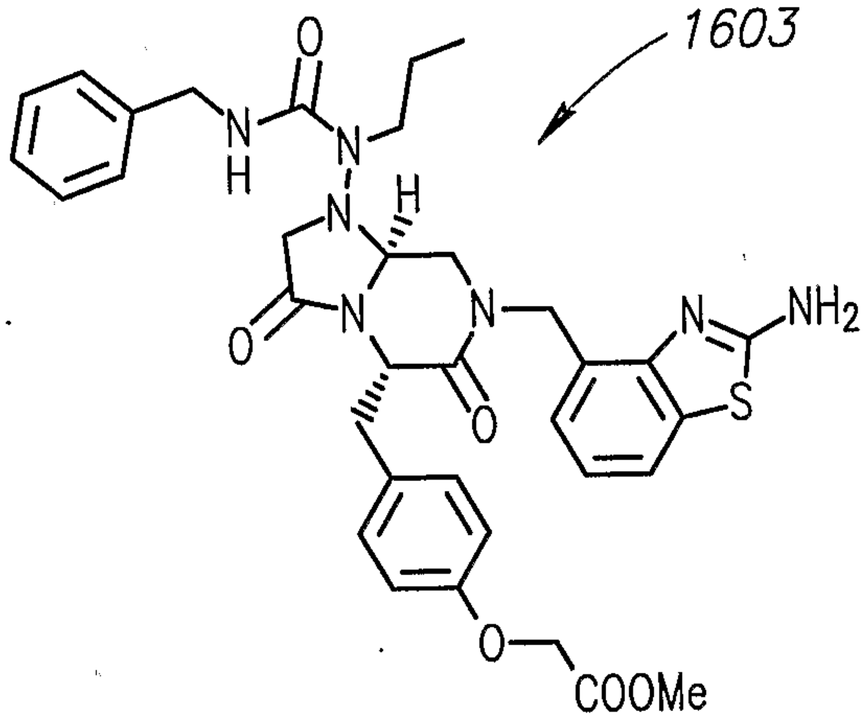
1601



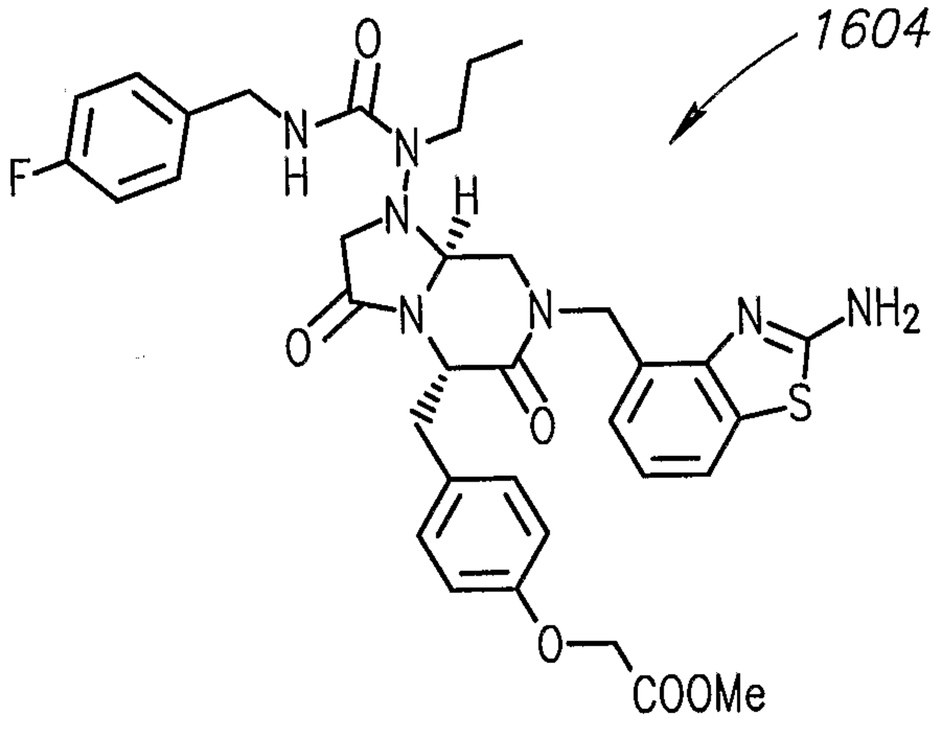
1602



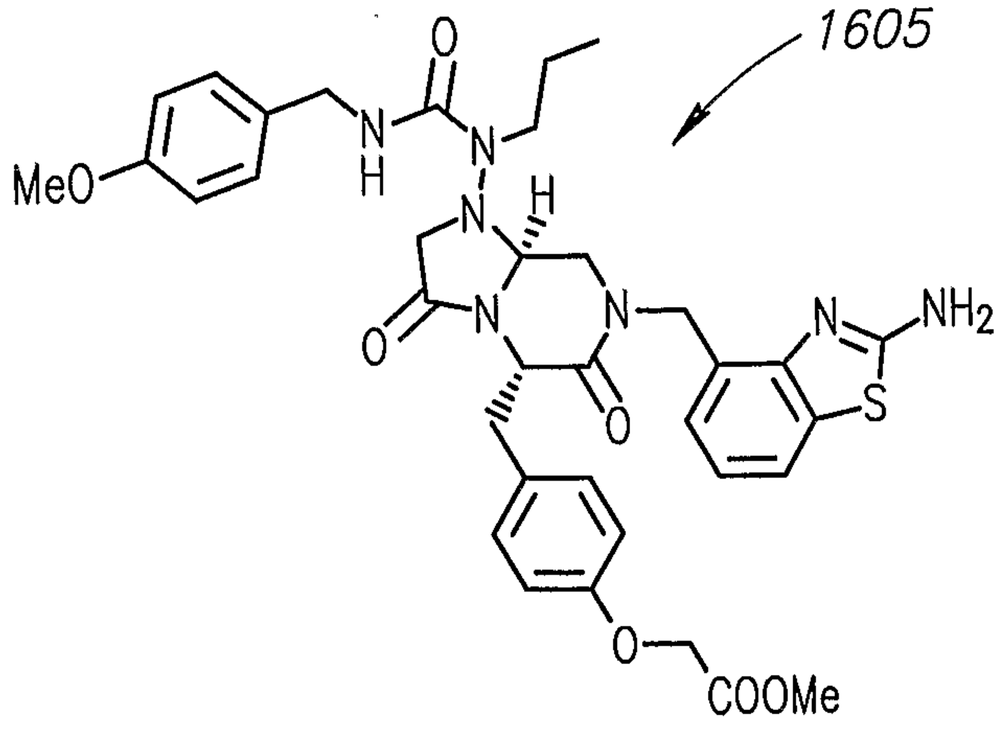
1603



1604



1605



1606

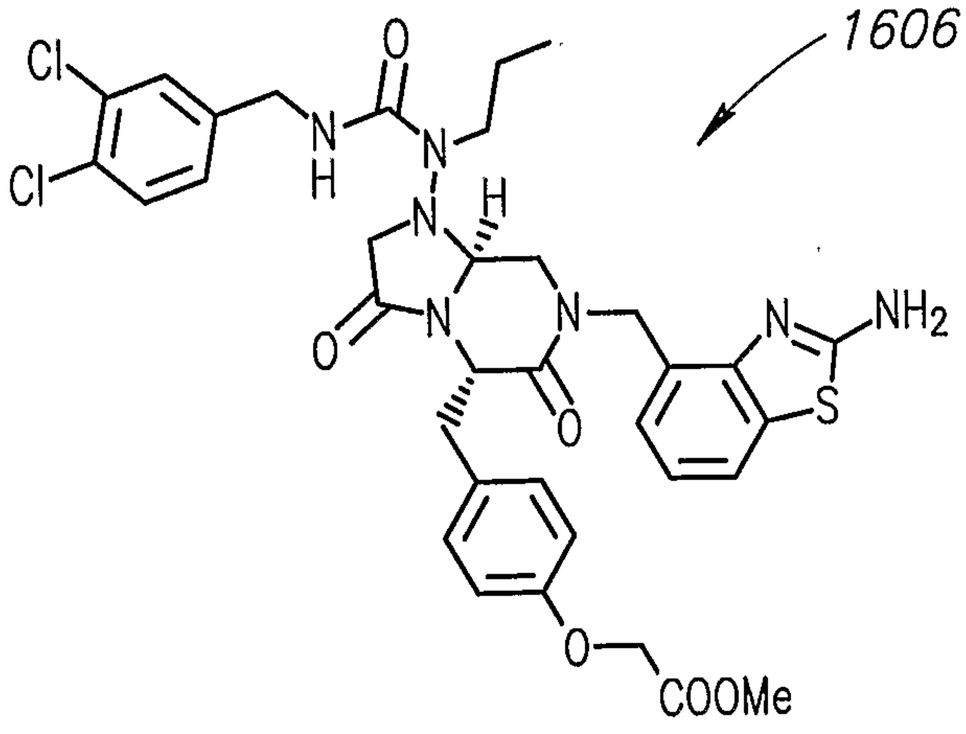
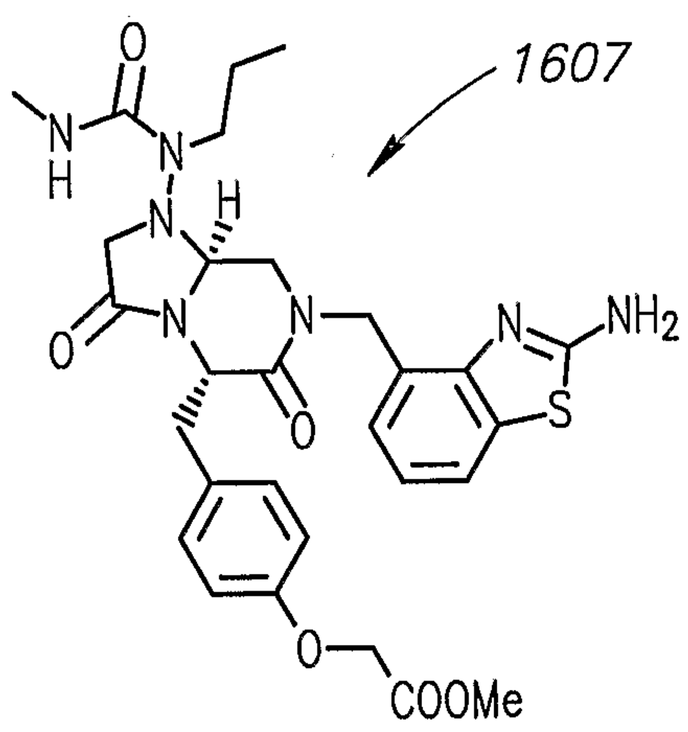
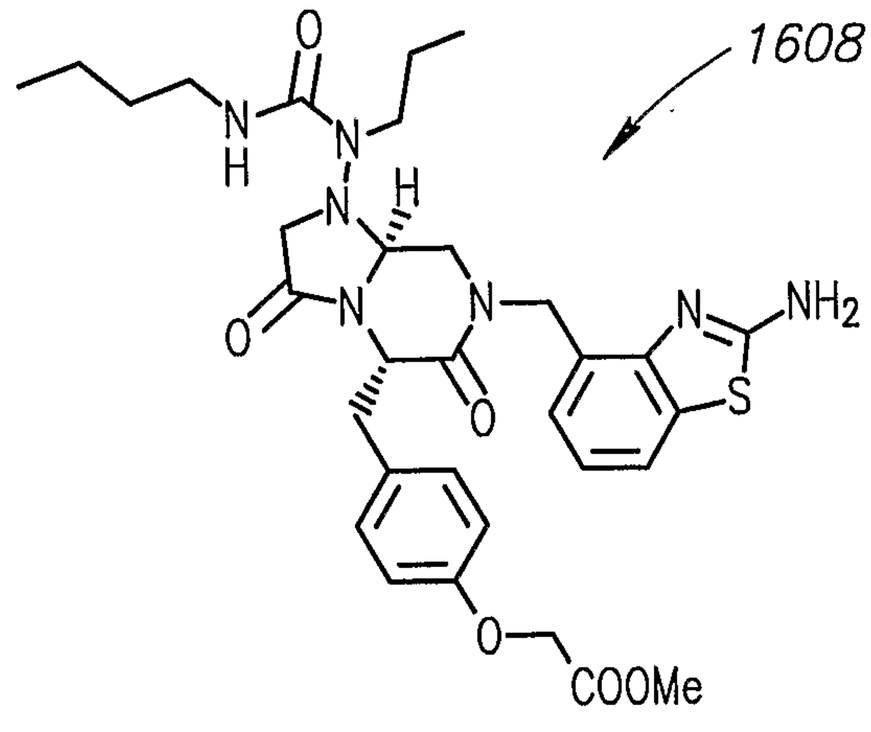
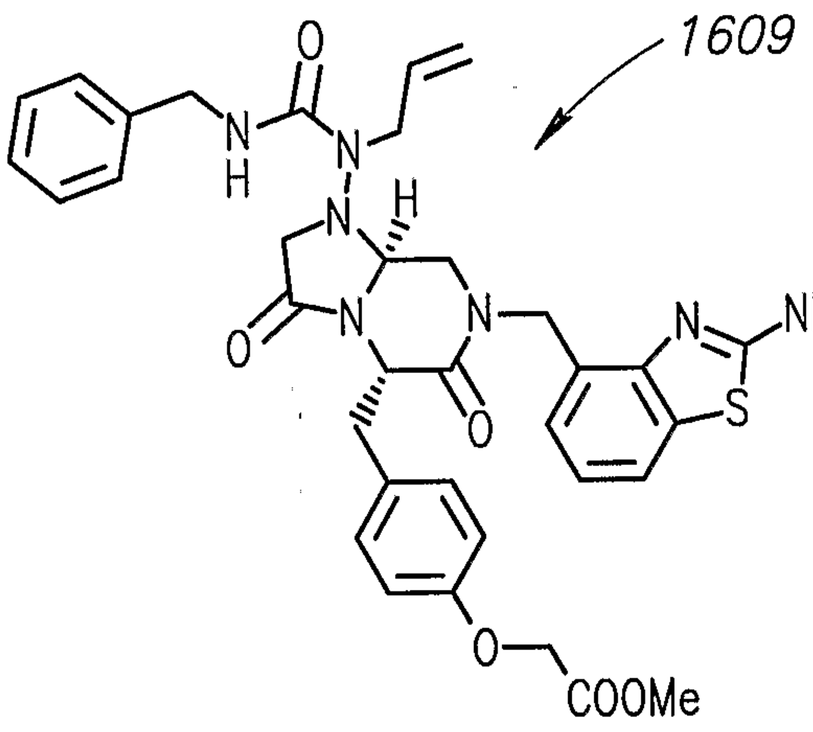
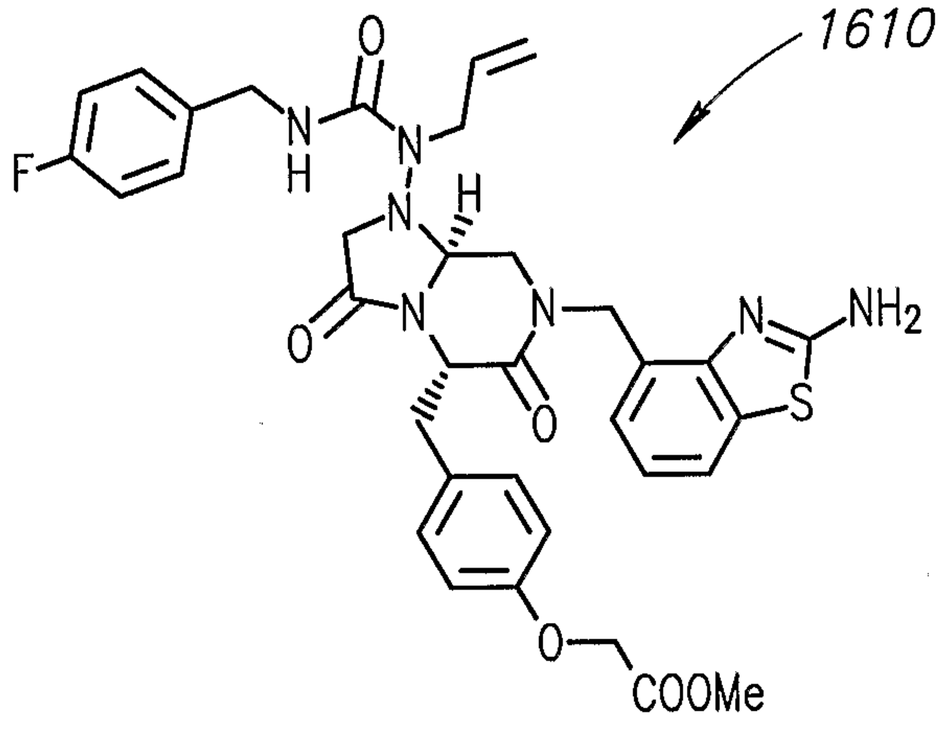


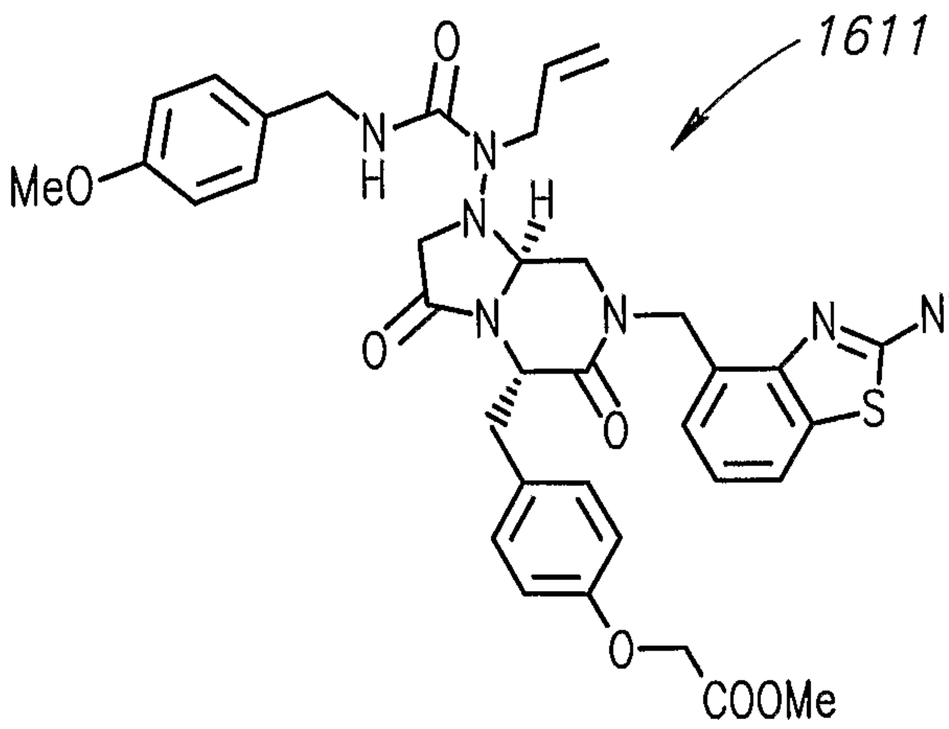
FIG.9A


1607
O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe


1608
O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe


1609
O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe


1610
F
O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe


1611
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O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe

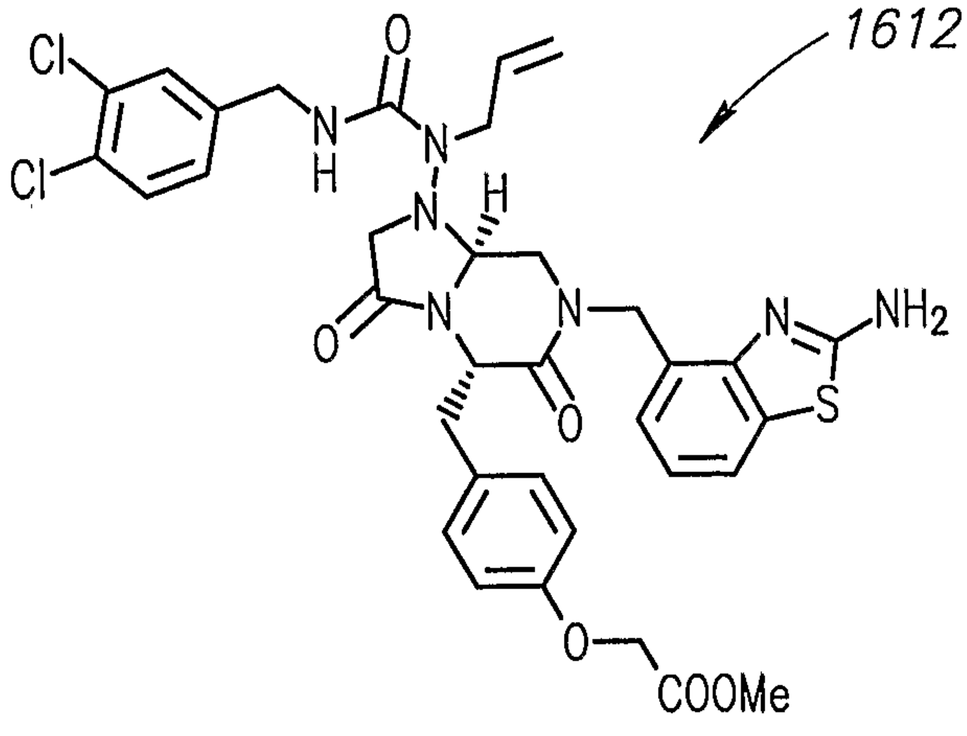
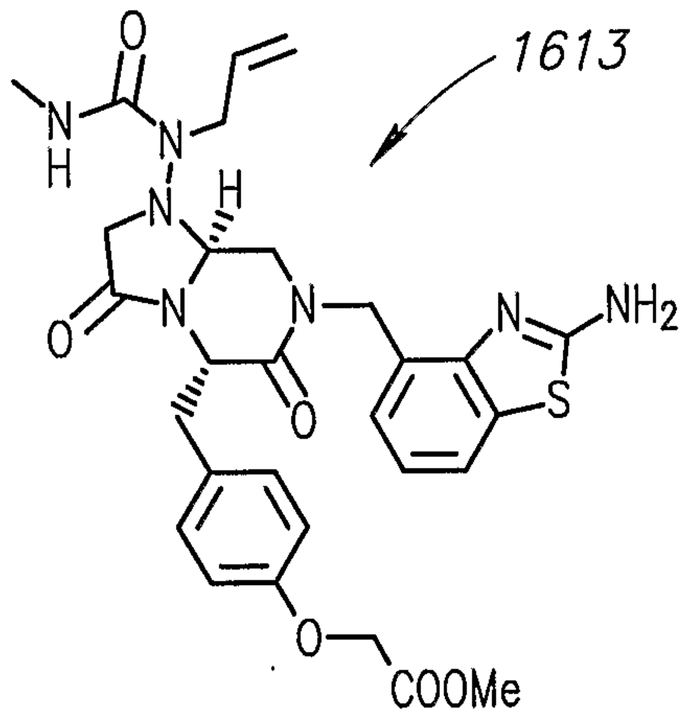
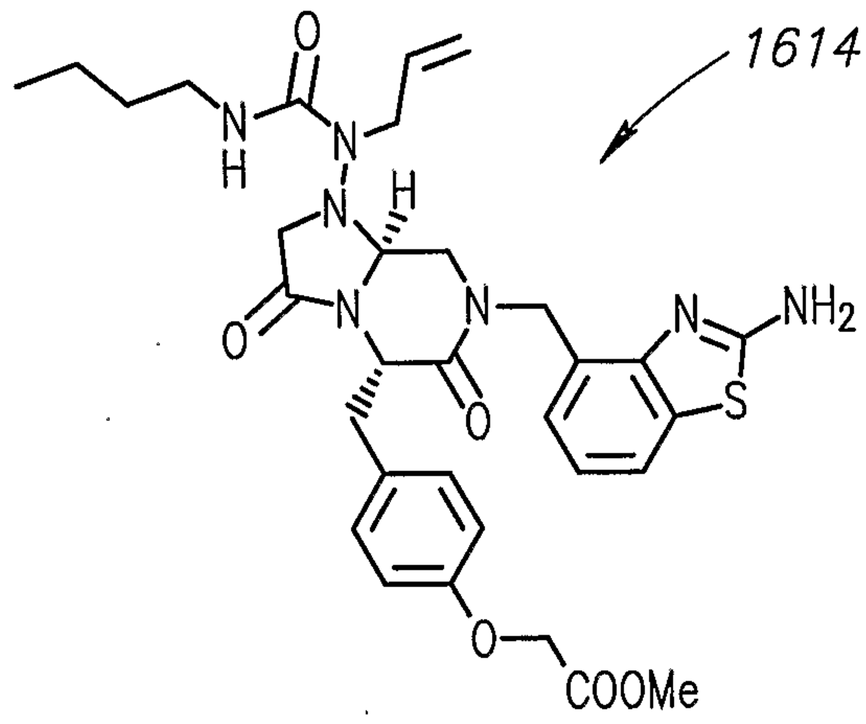
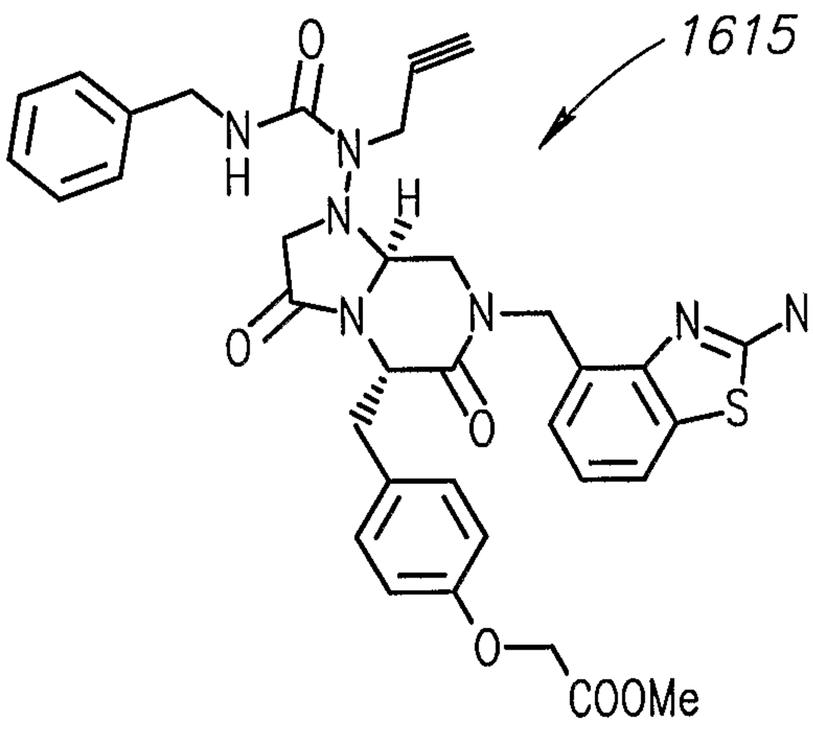
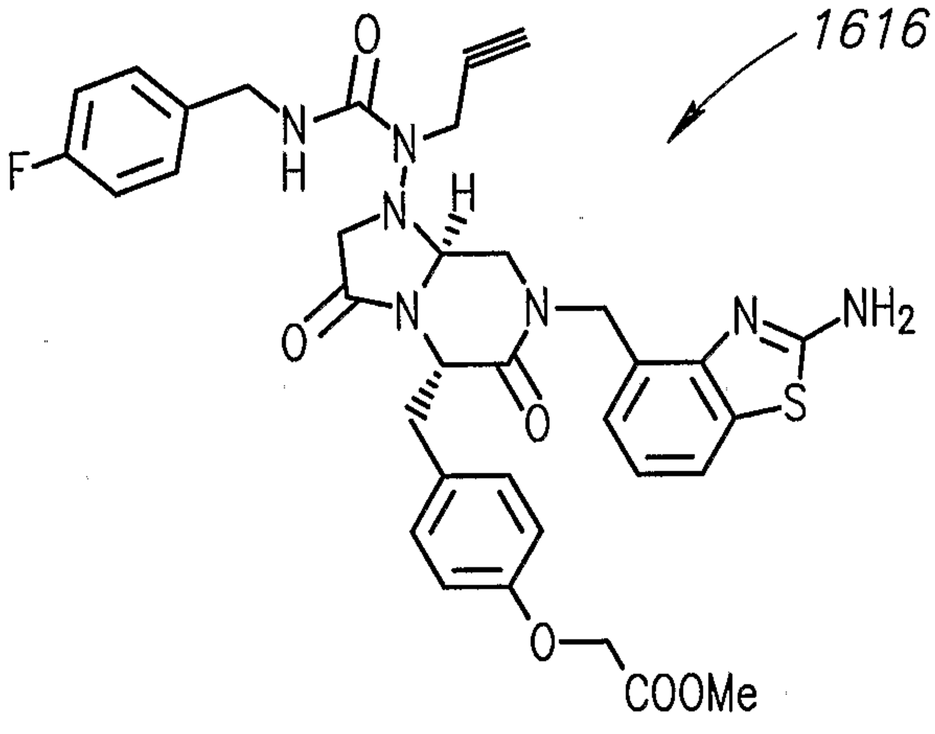

1612
Cl
Cl
O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe

FIG.9B


1613
O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe


1614
O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe


1615
O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe


1616
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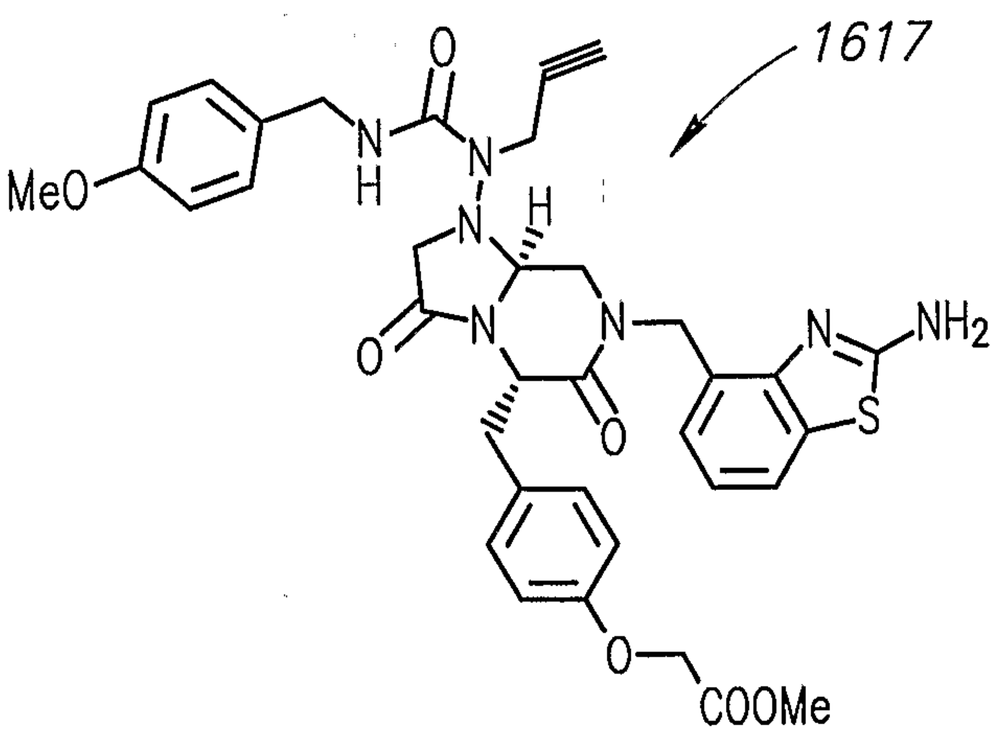
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe


1617
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N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe

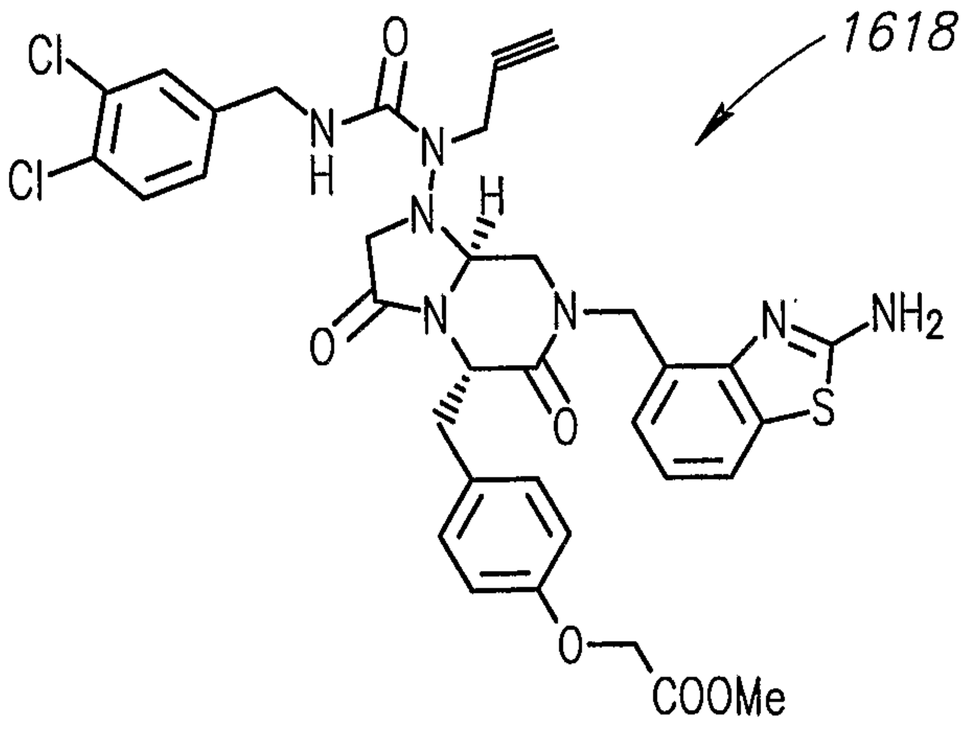
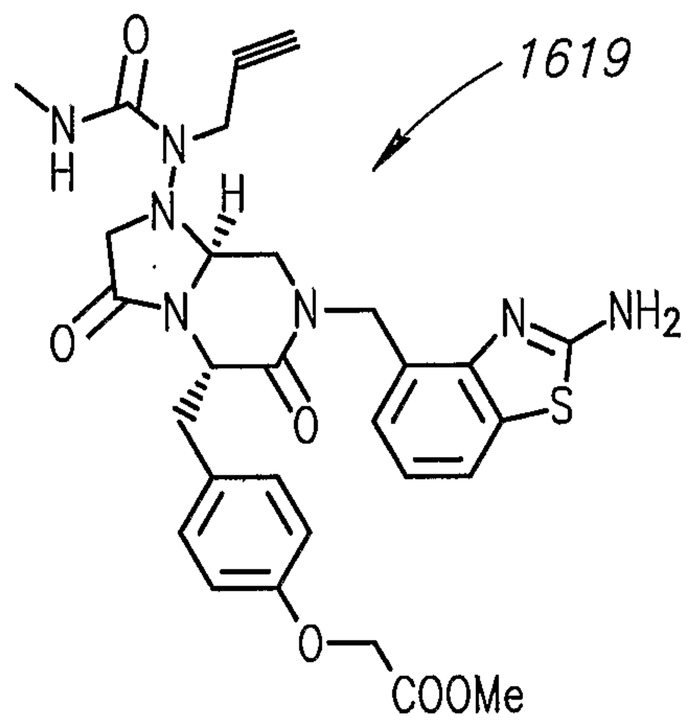
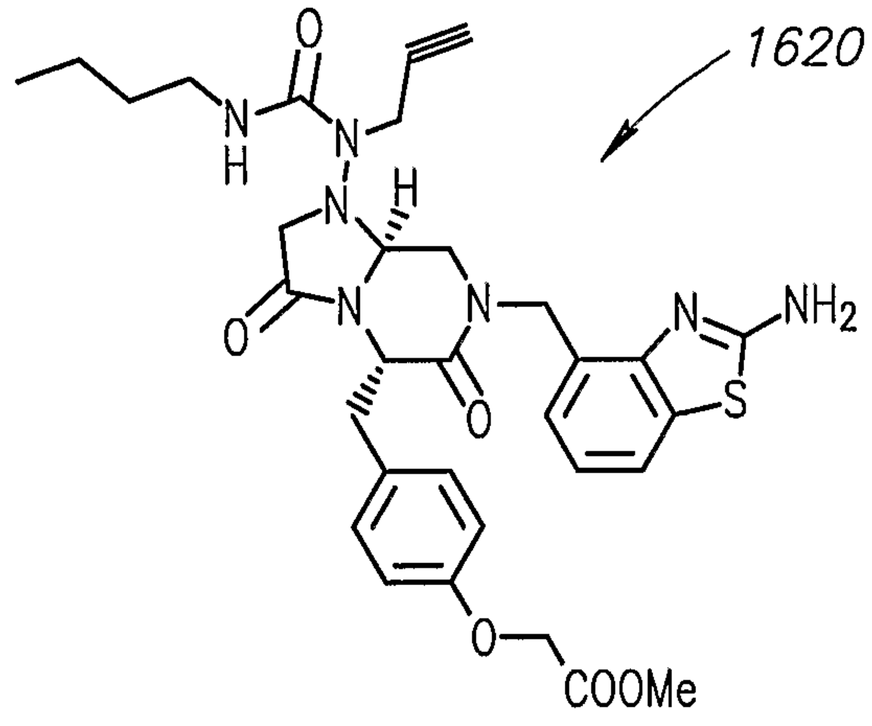

1618
Cl
Cl
O
N
H
N
N
H
O
N
N
N
NH2
S
O
O
COOMe

FIG.9C


1619
O
N
H
N
N
H
O
N
N
O
N
N
NH2
S
O
COOMe


1620
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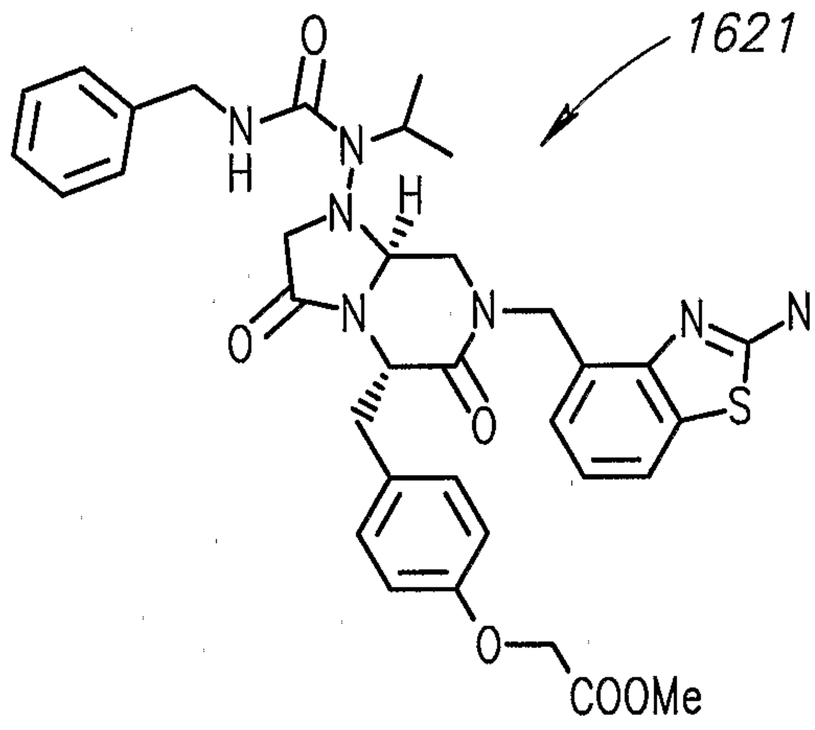
N
N
H
O
N
N
O
N
N
NH2
S
O
COOMe


1621
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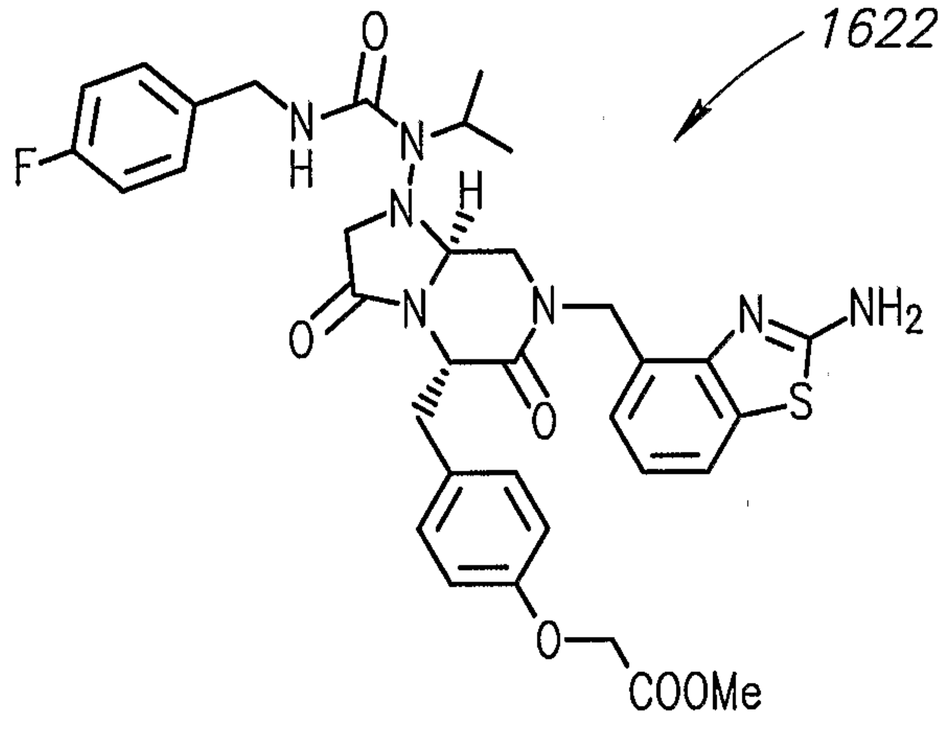
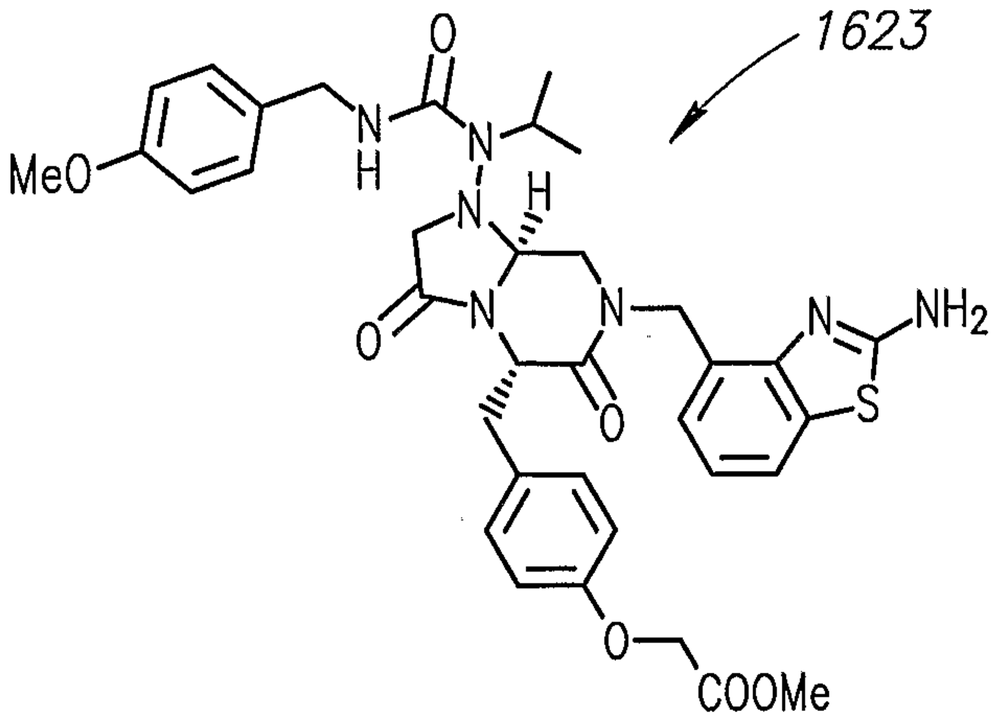
N
H
N
N
H
O
N
N
O
N
N
NH2
S
O
COOMe


1622
F
O
N
H
N
N
H
O
N
N
O
N
N
NH2
S
O
COOMe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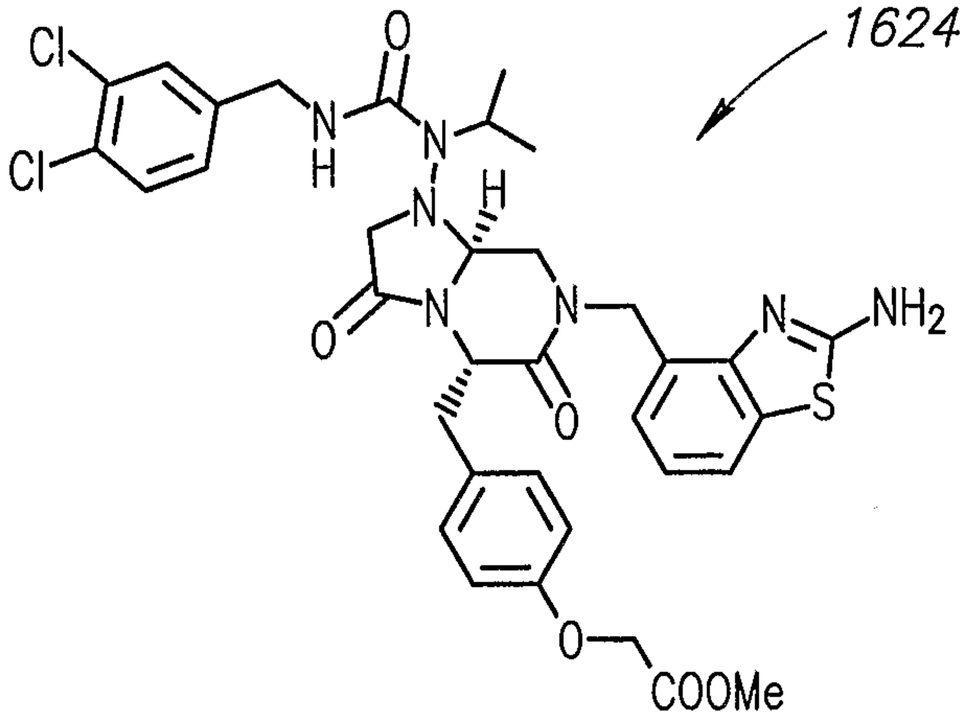
1624
Cl
Cl
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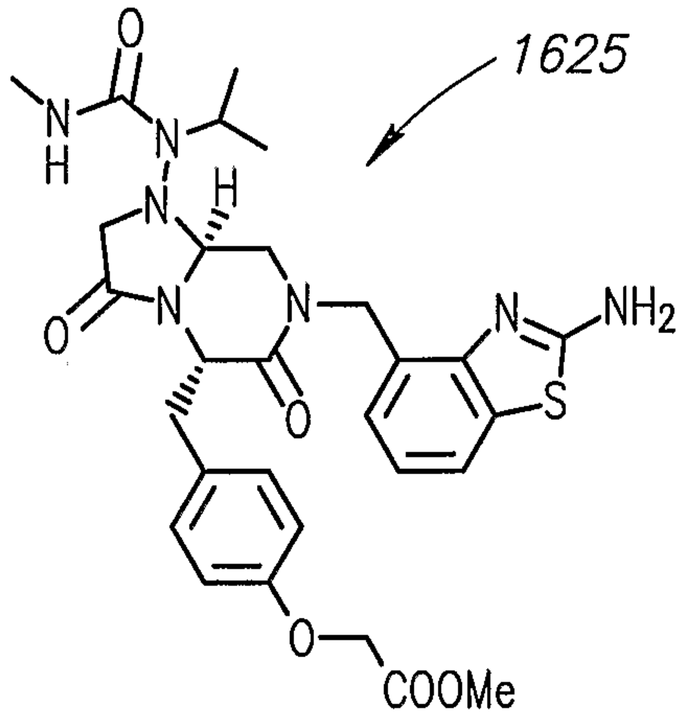
O
N
N
NH2
S
O
COOMe

FIG.9D

1625



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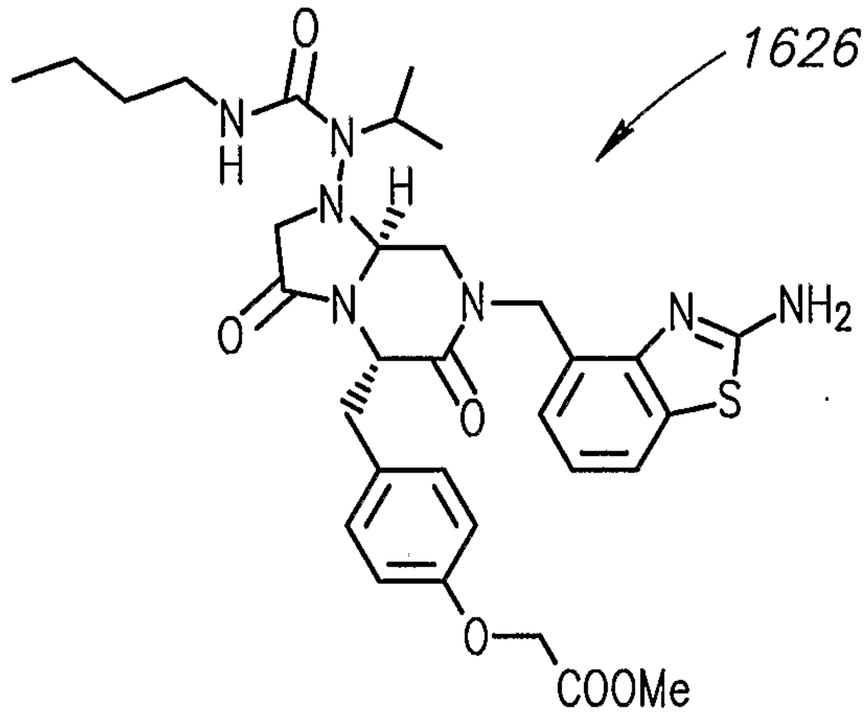

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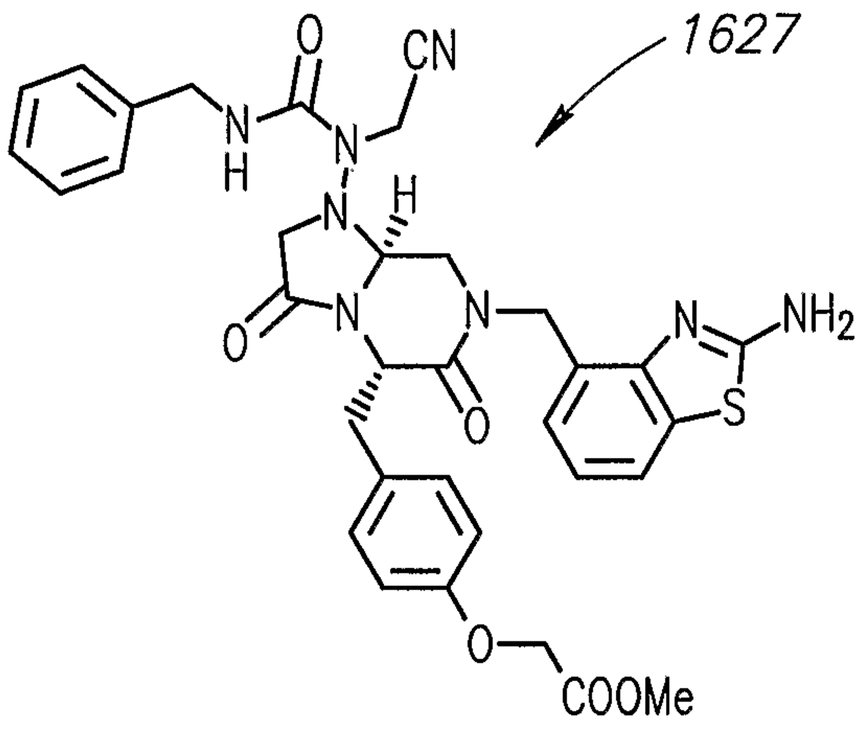

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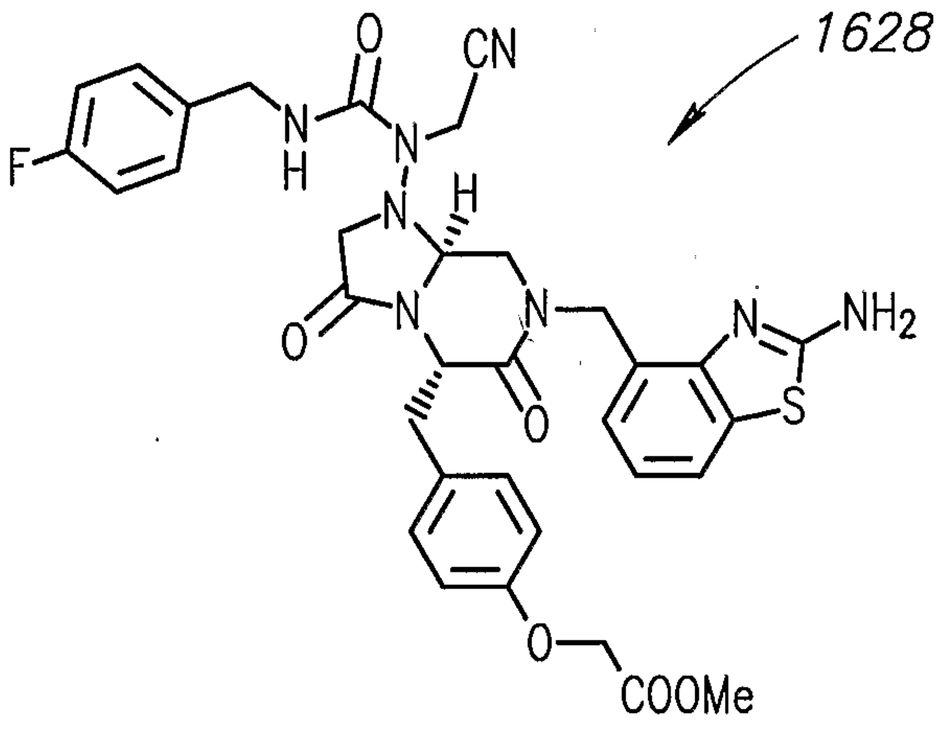

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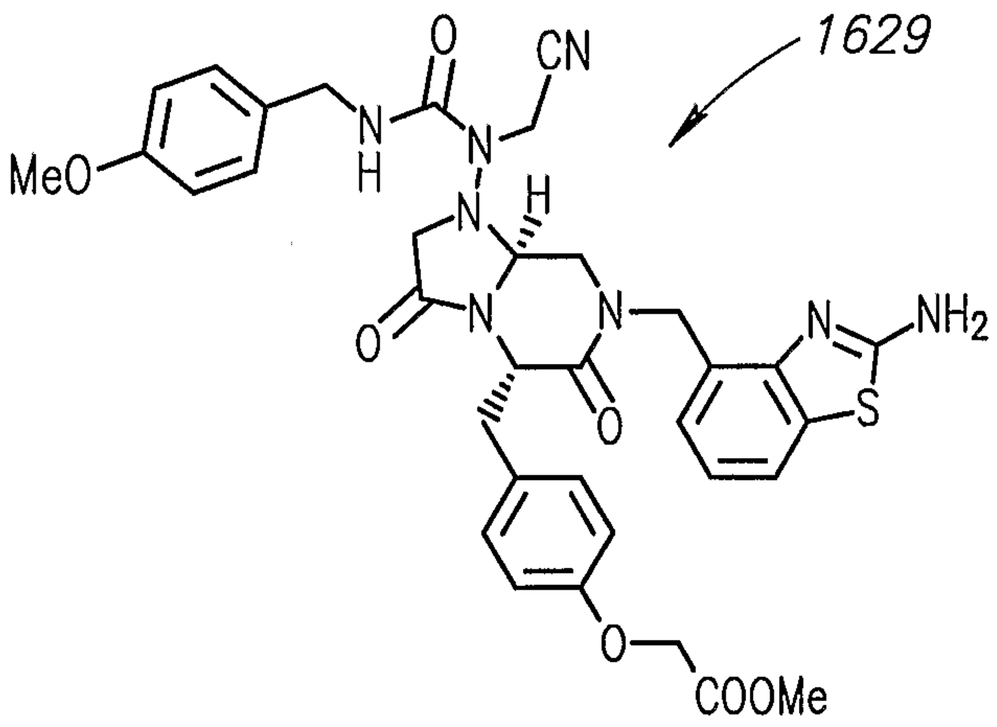

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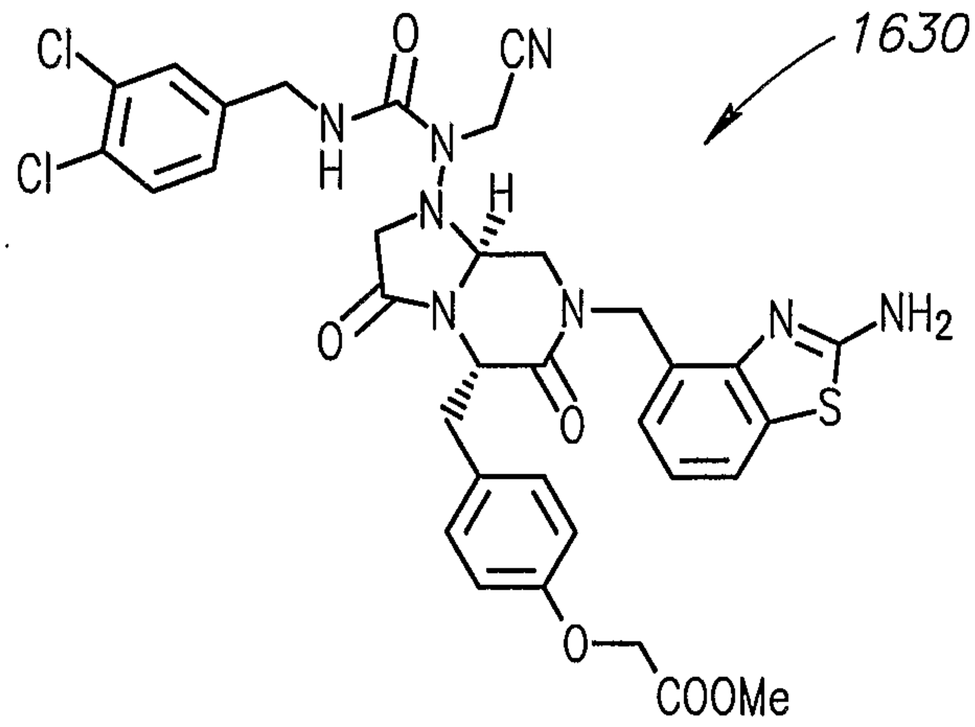


FIG.9E

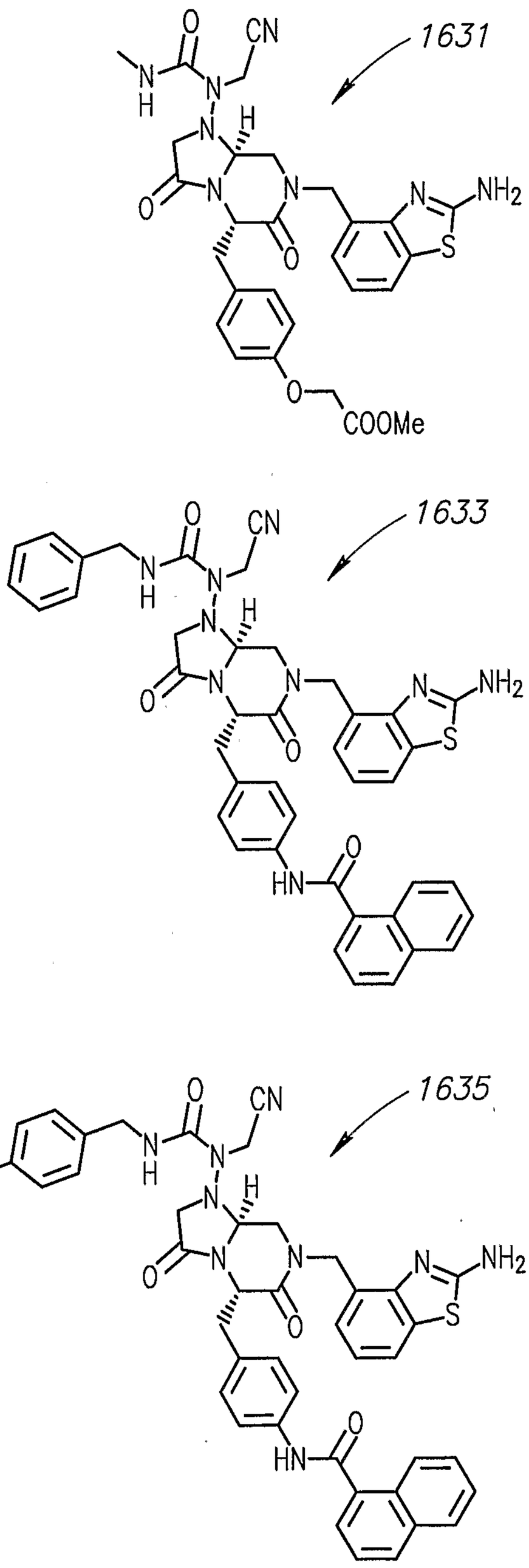
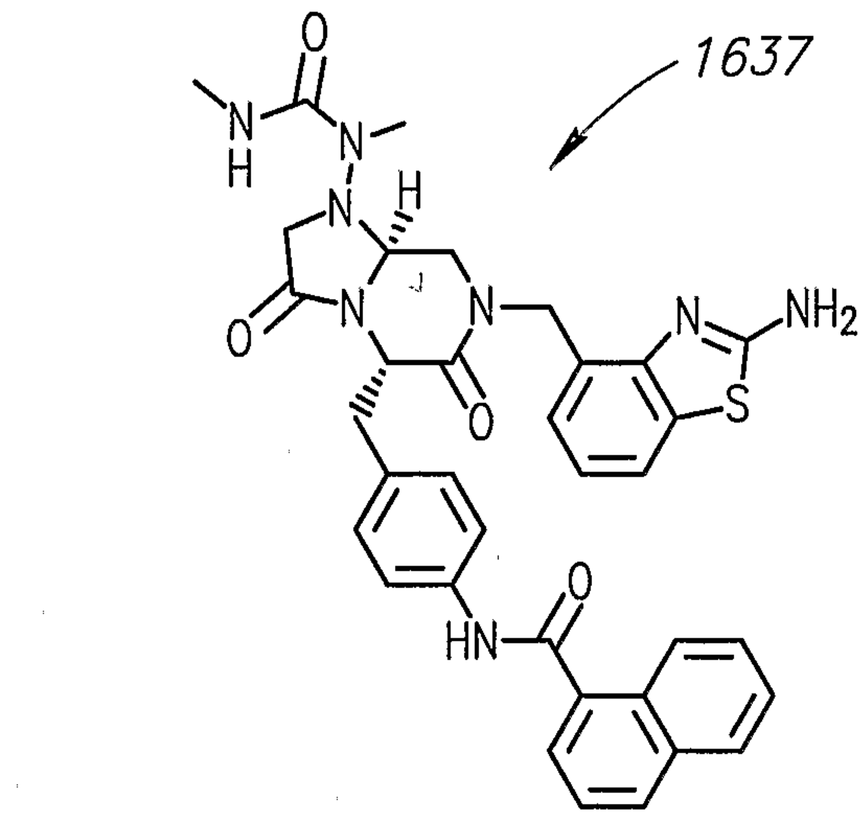
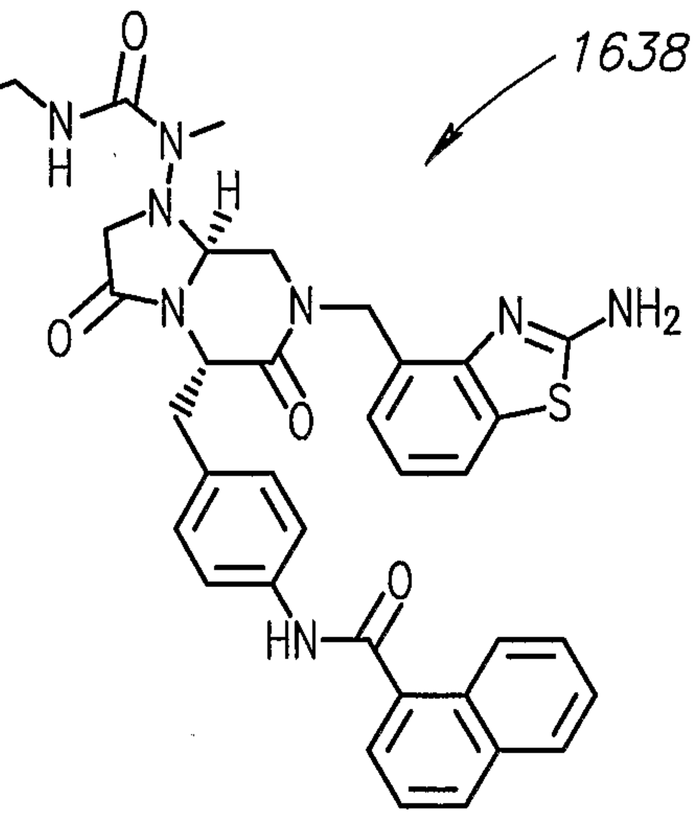
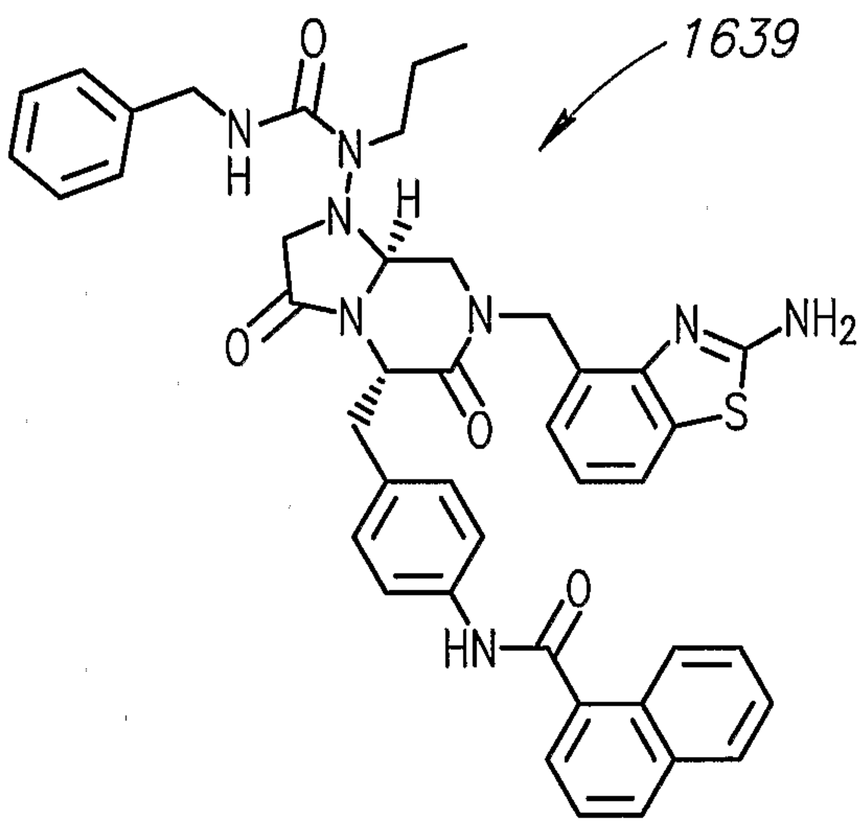
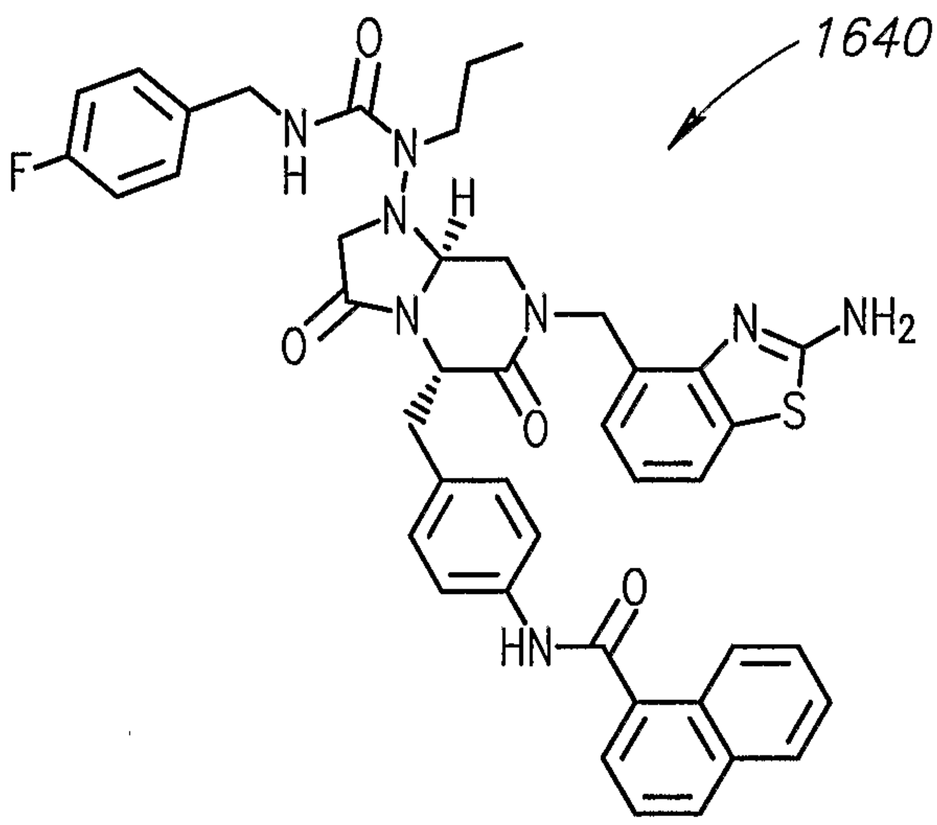


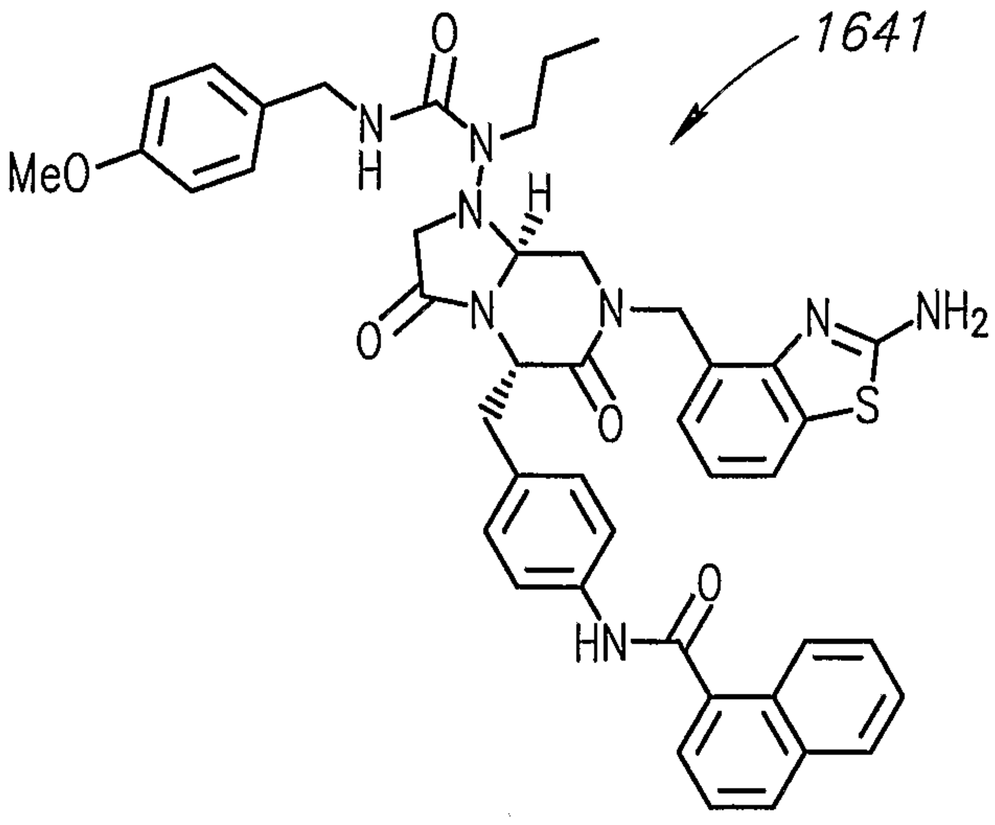
FIG.9F











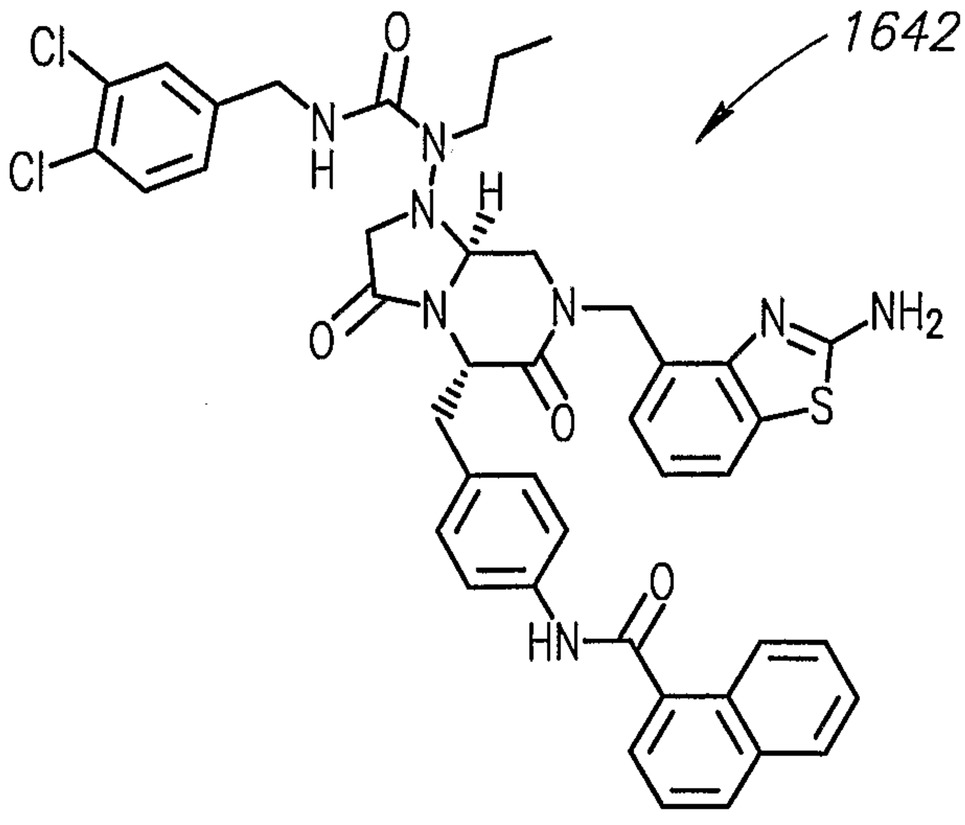
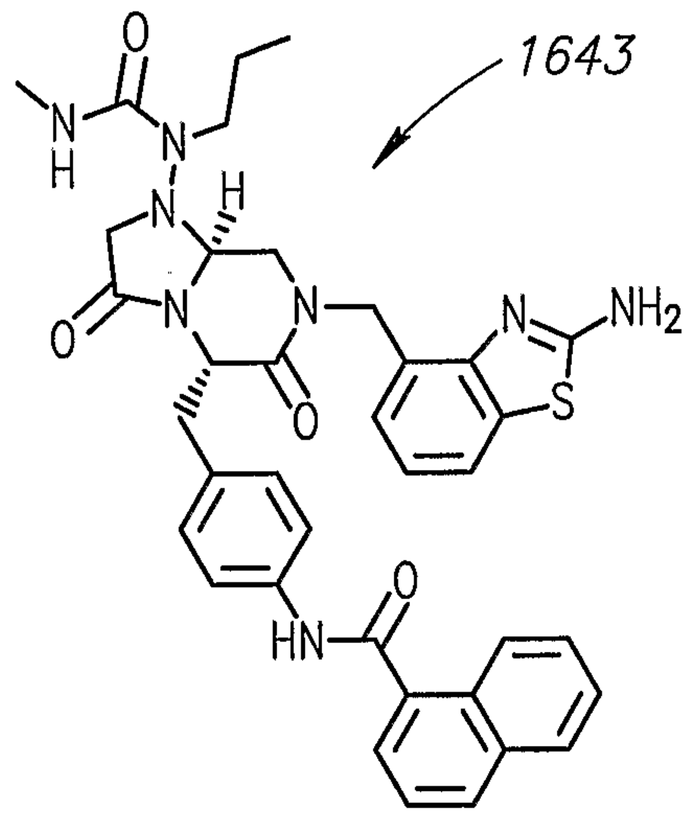
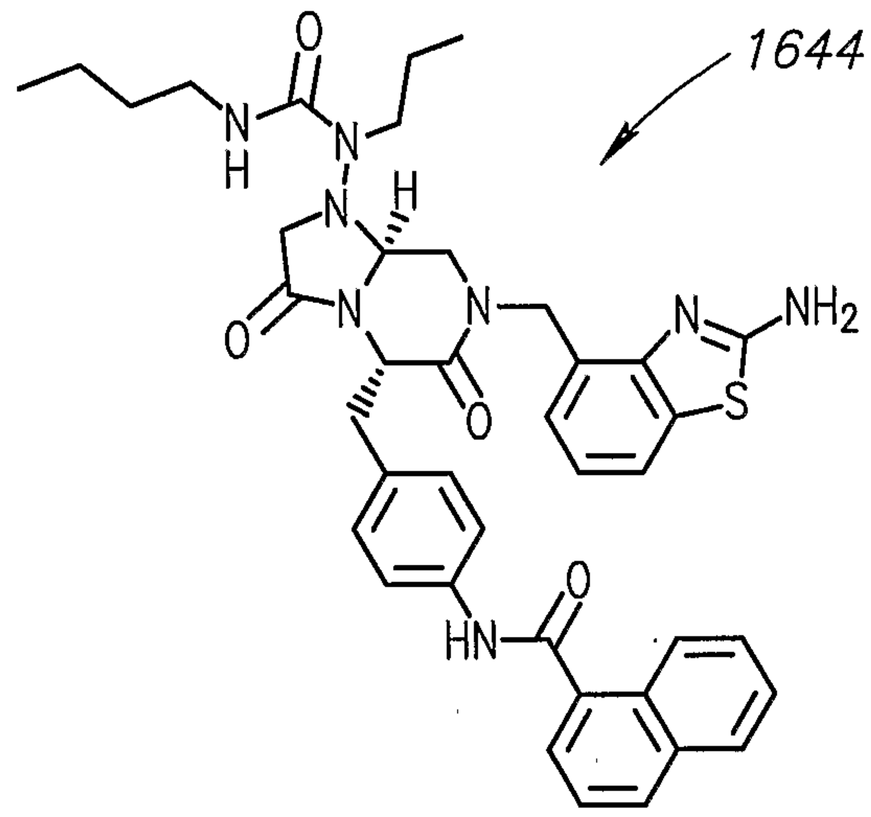
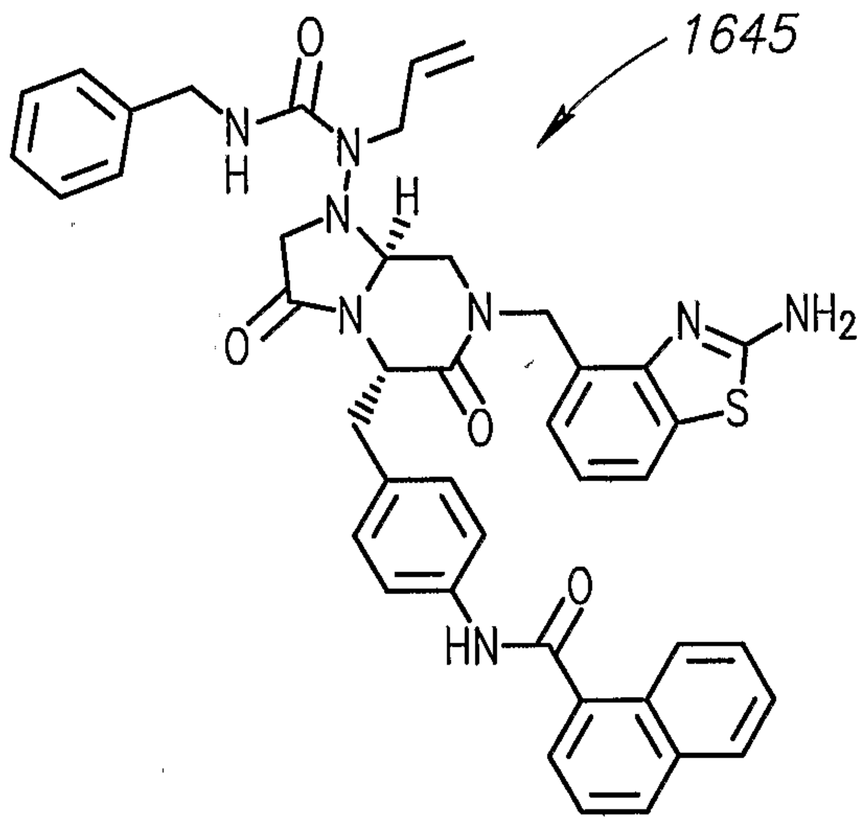
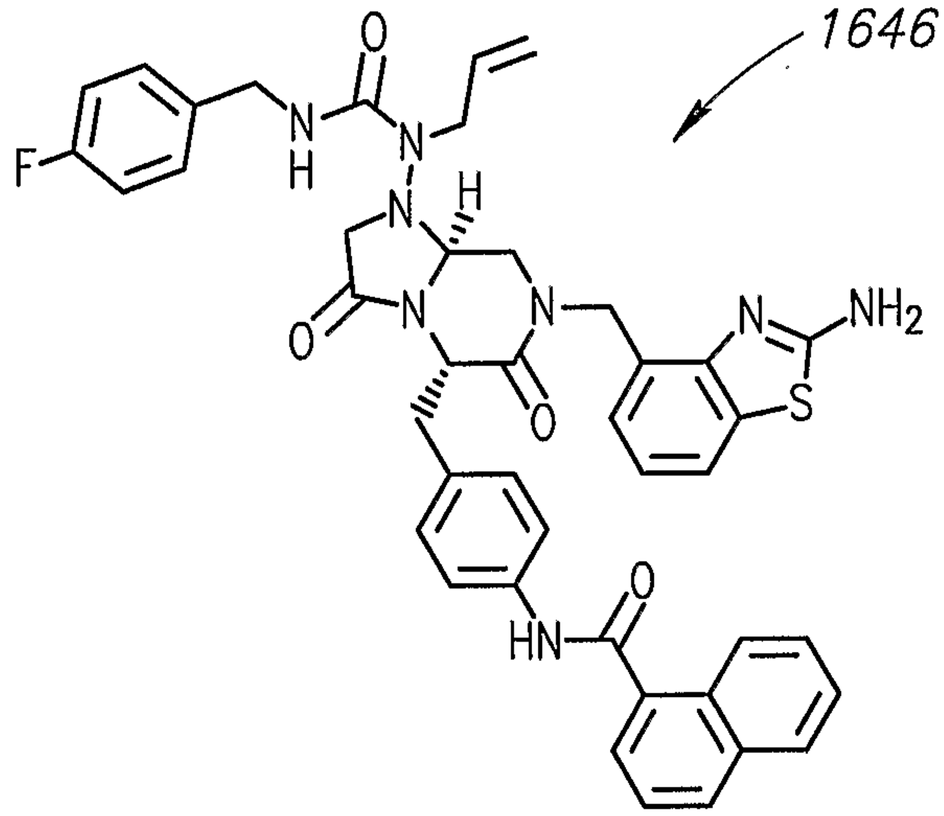


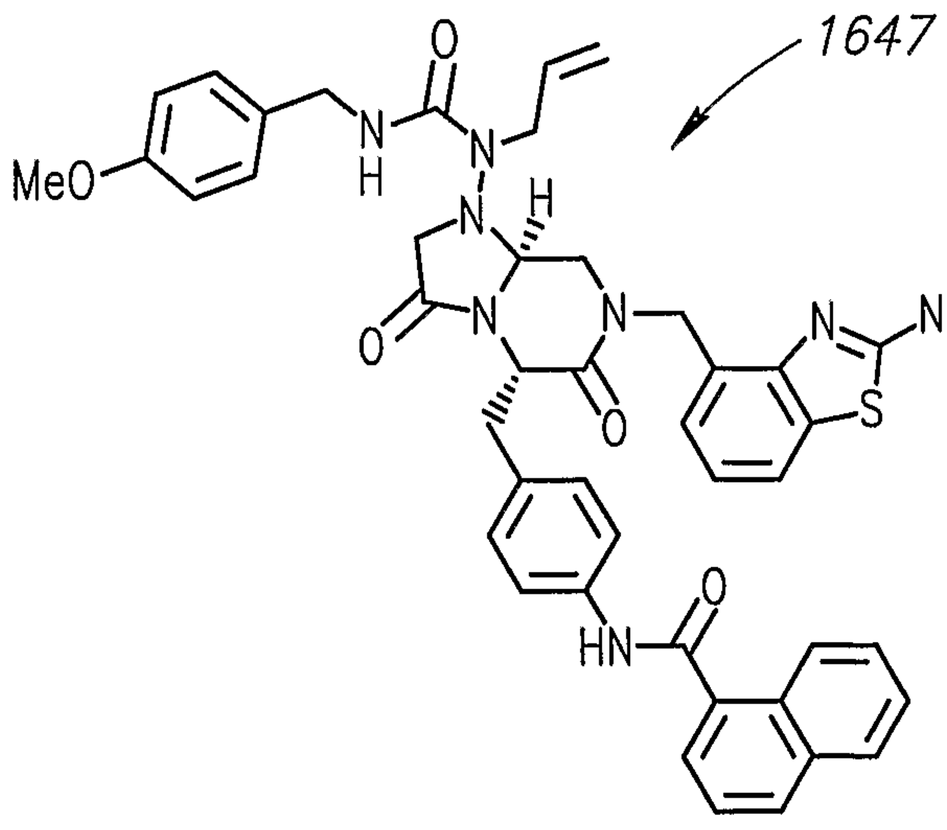
FIG.9G











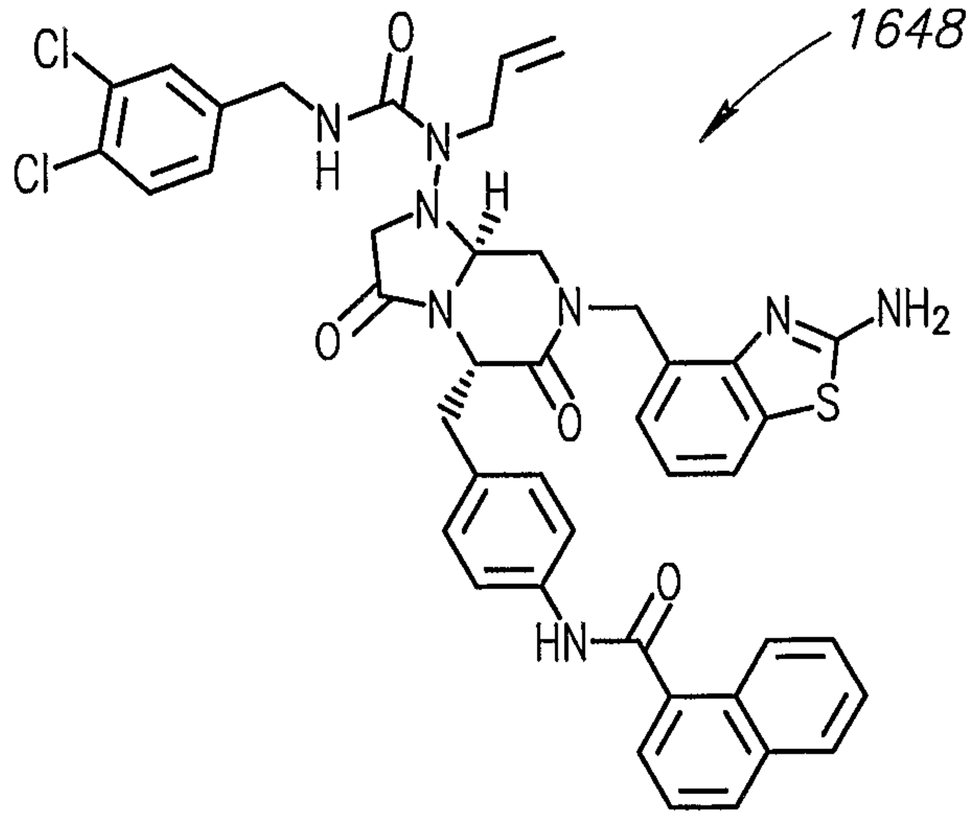
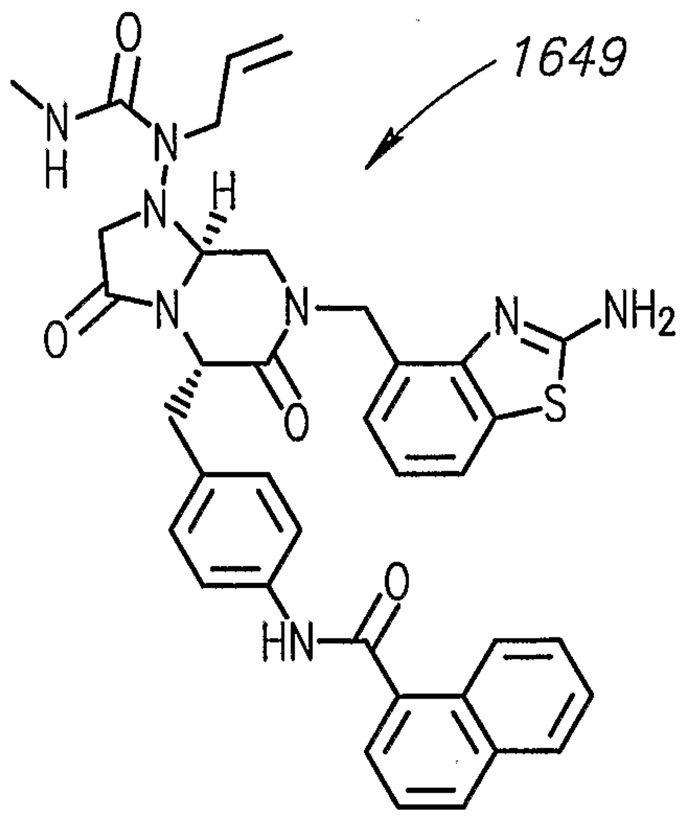
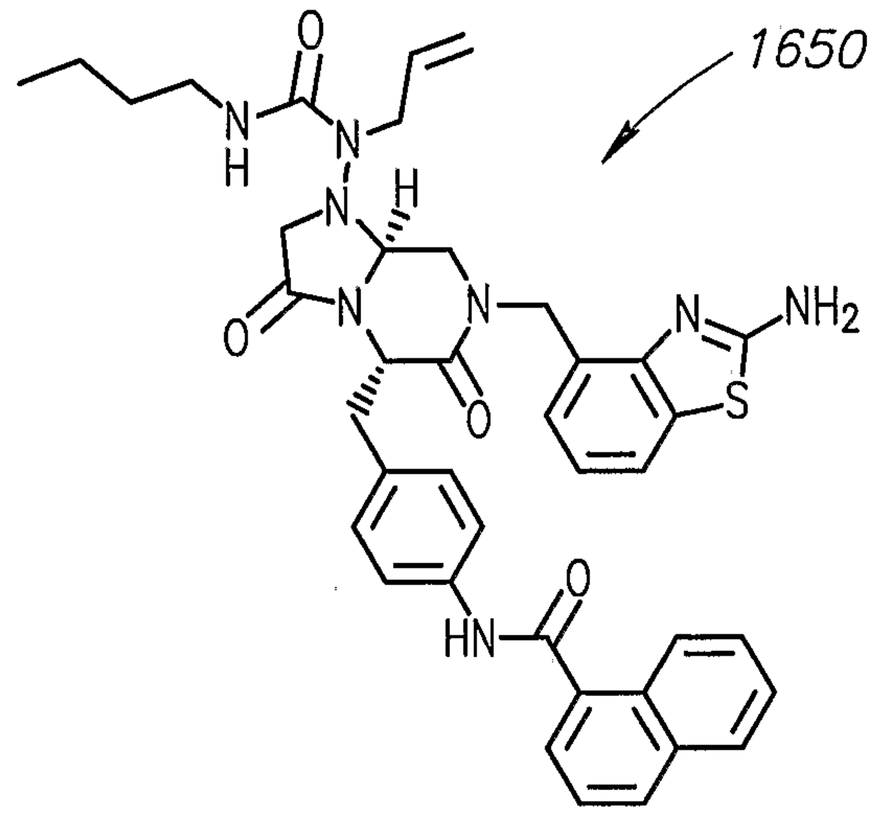
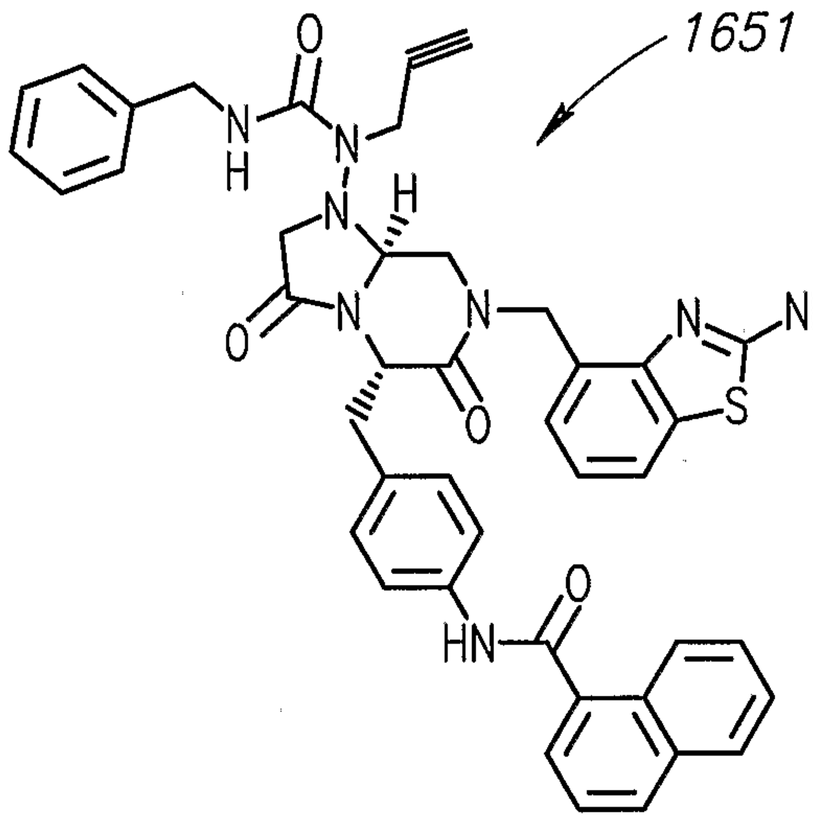
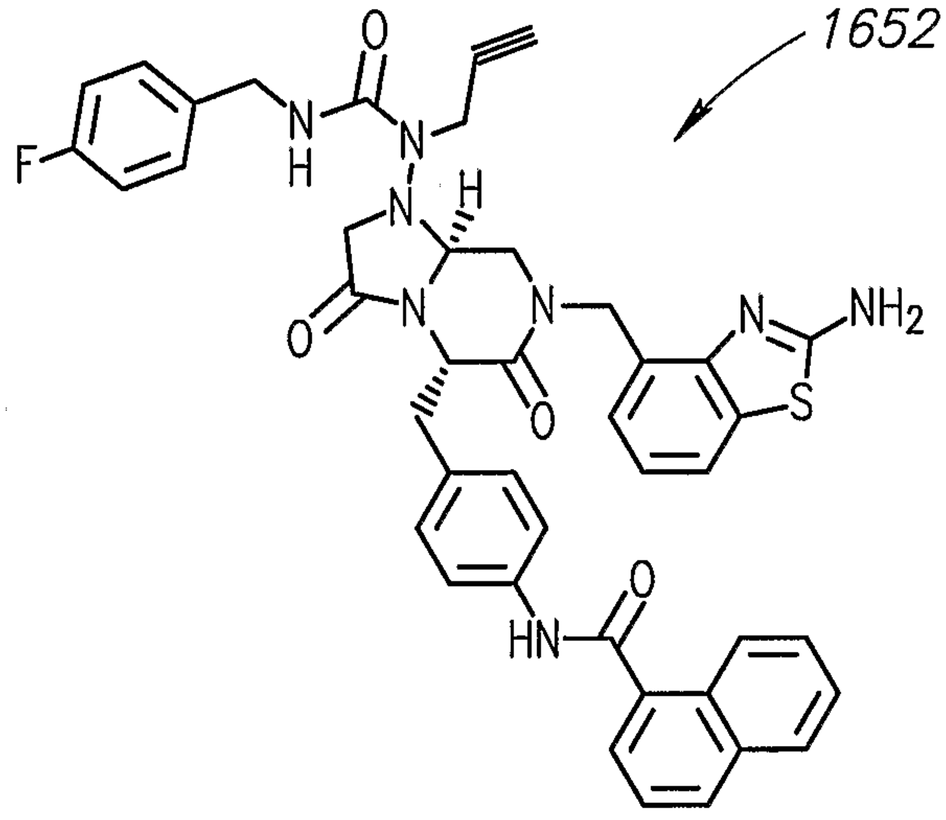


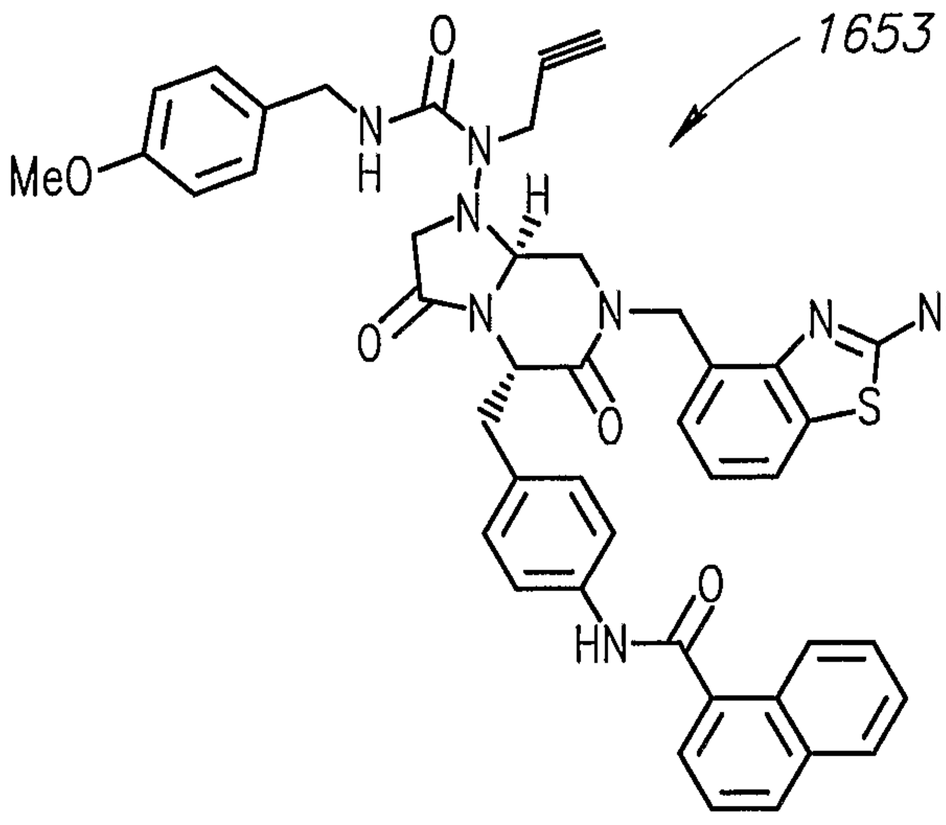
FIG.9H











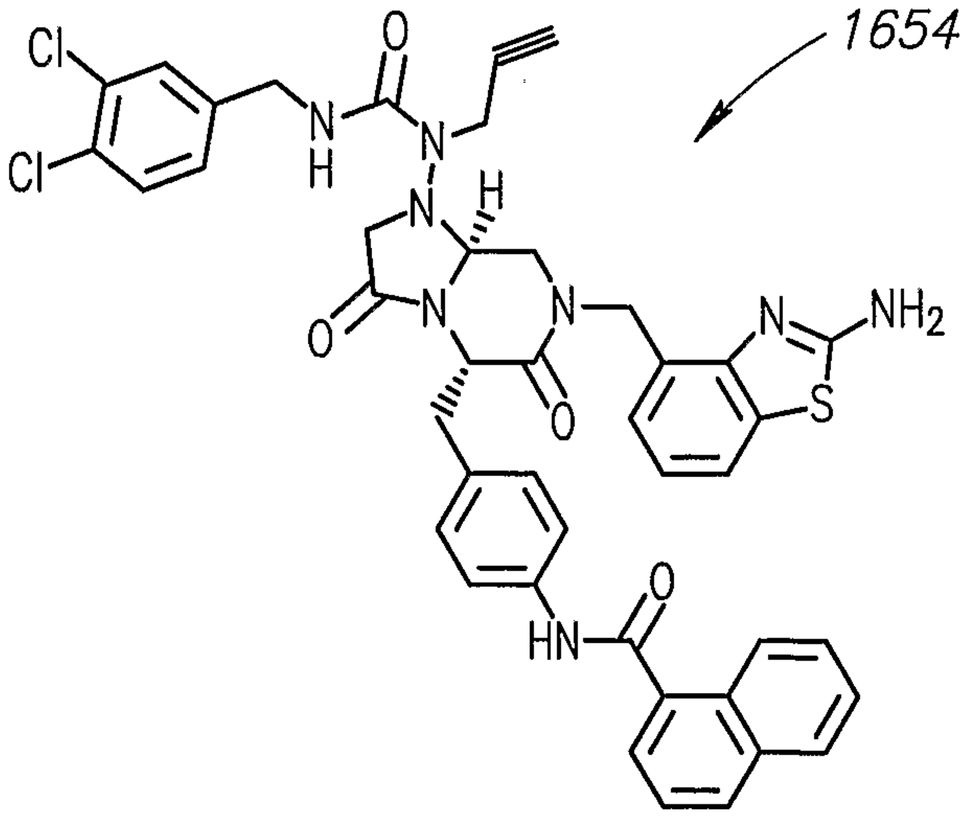
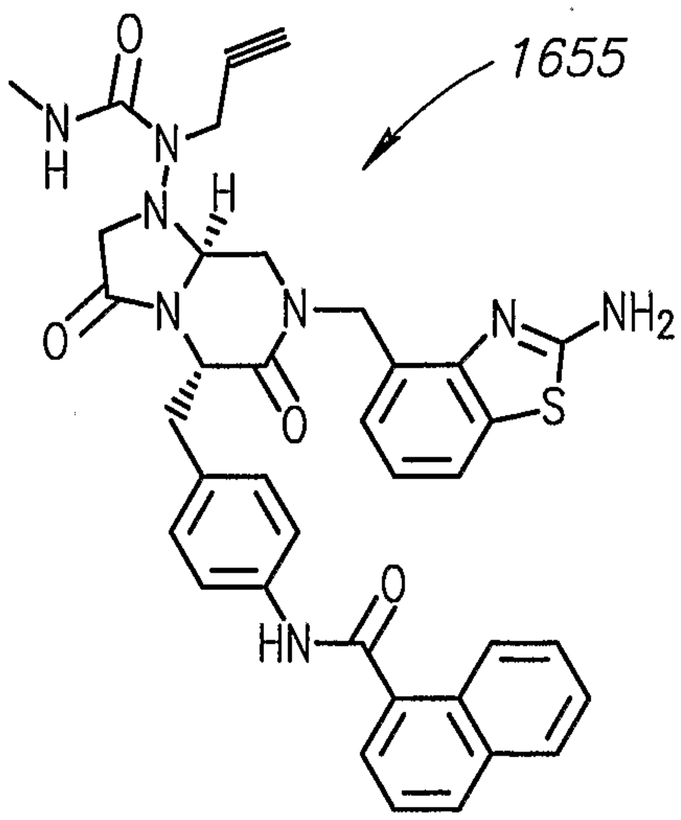


FIG.9I

1655



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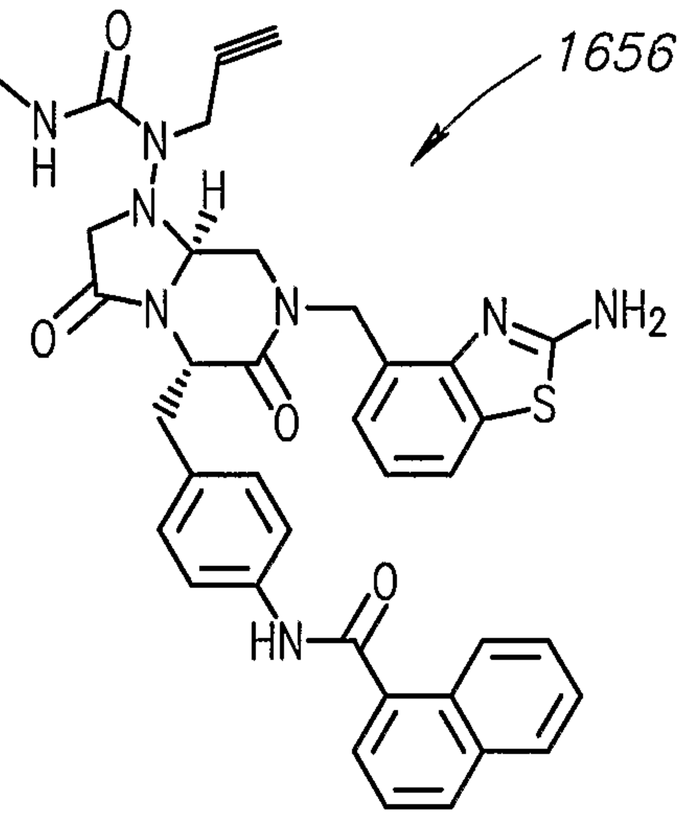

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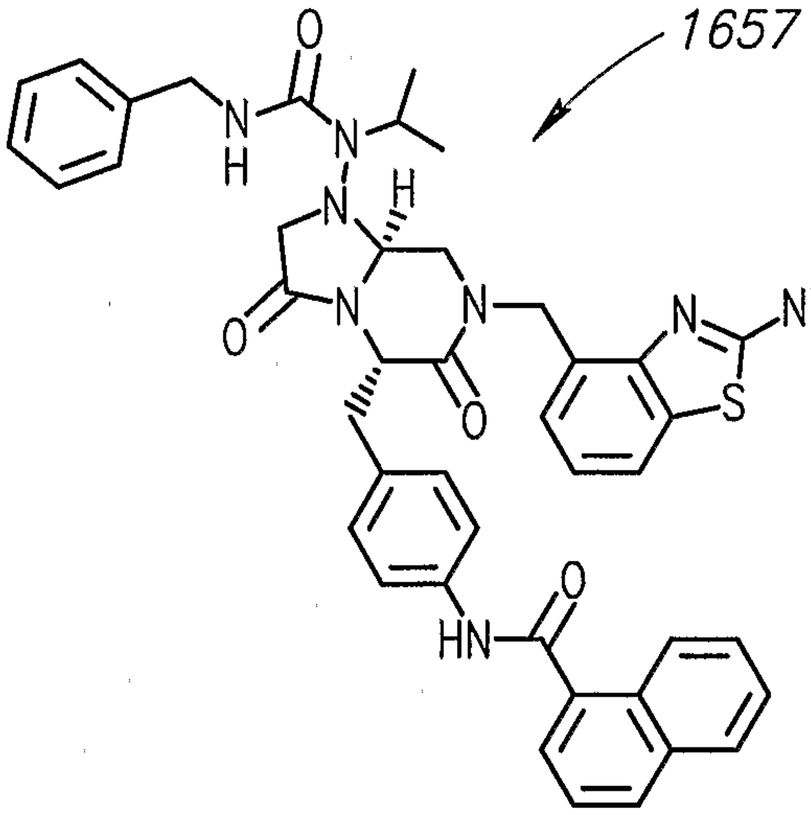

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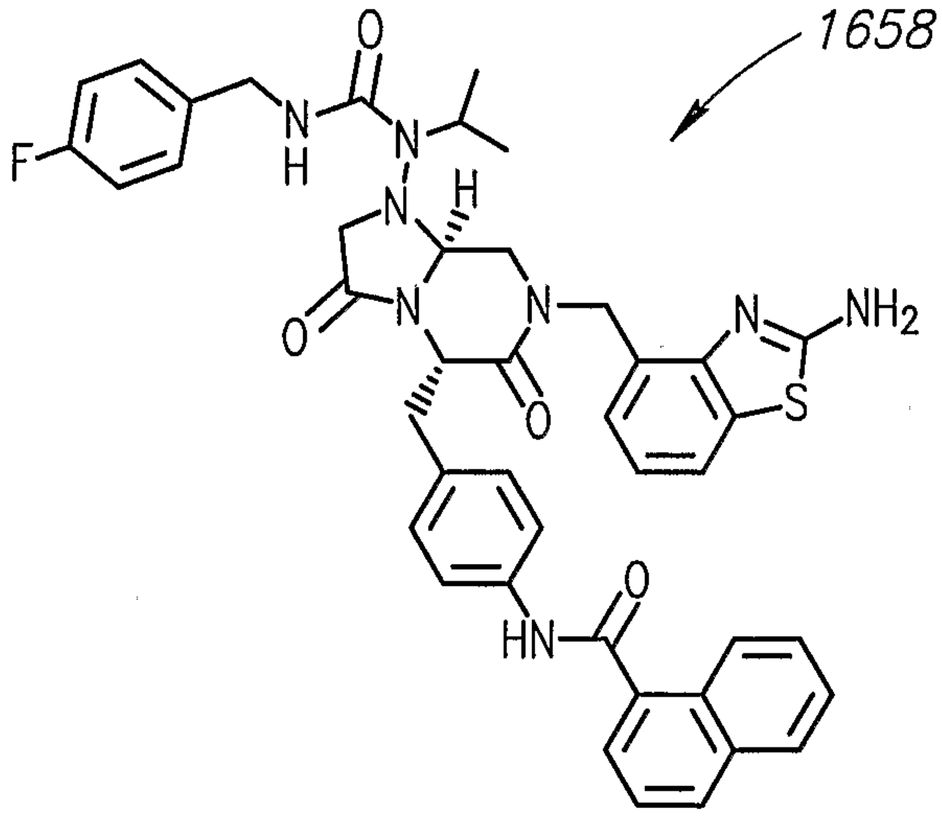

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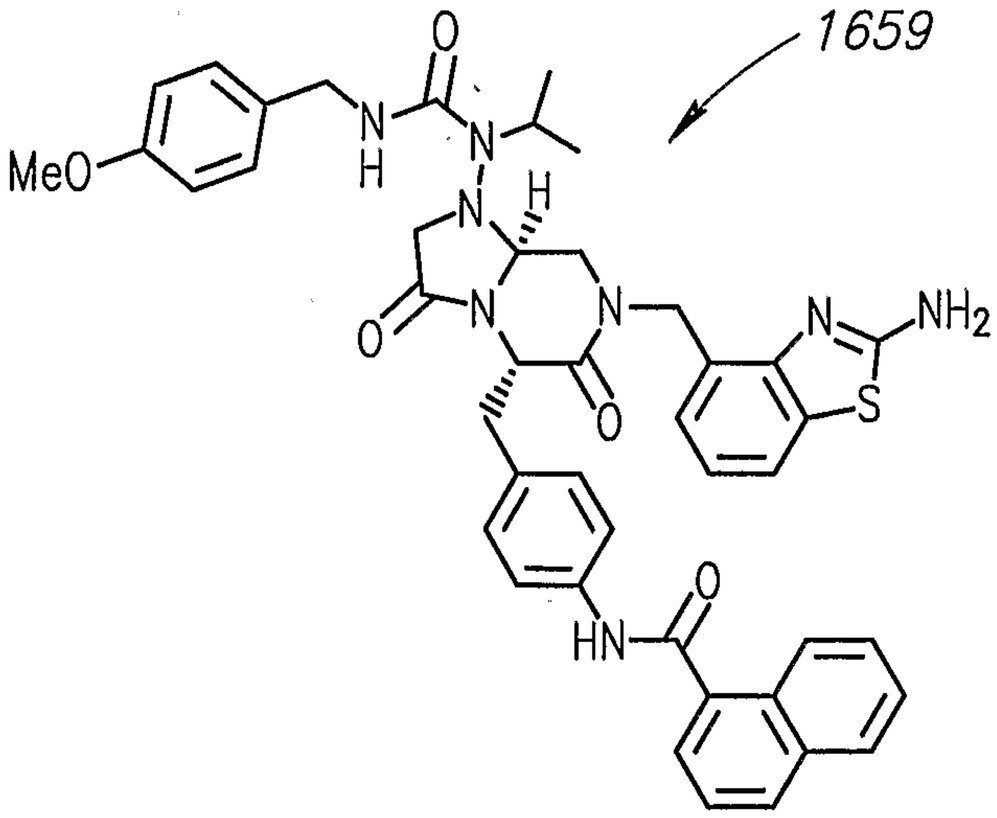

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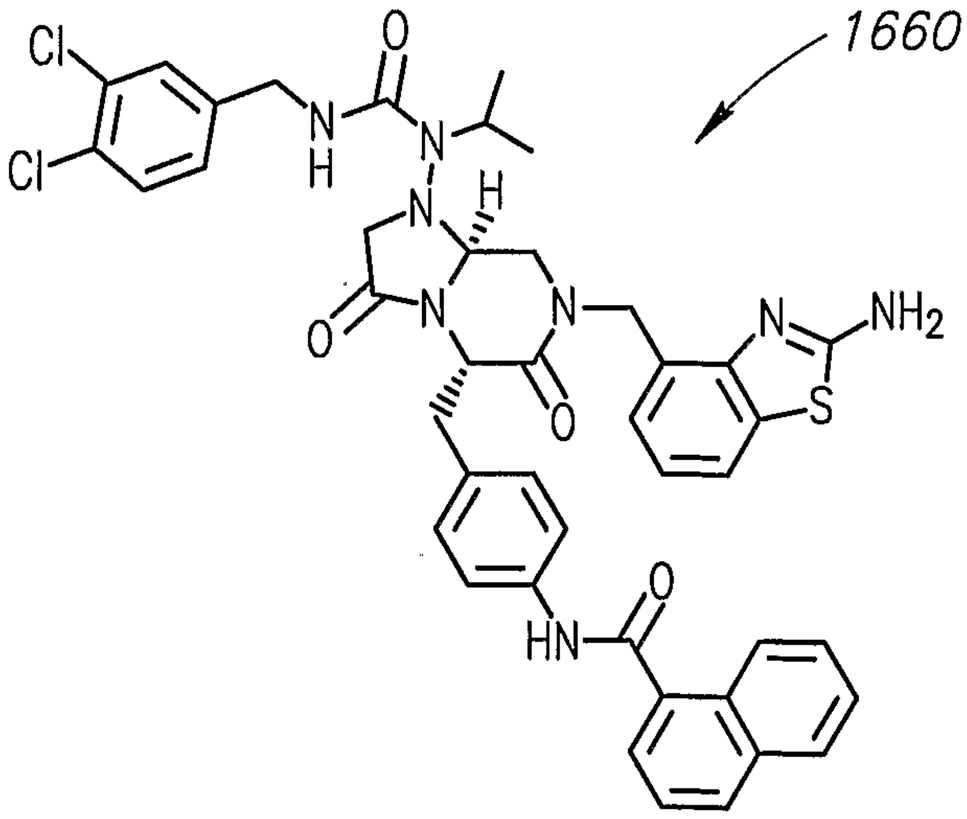
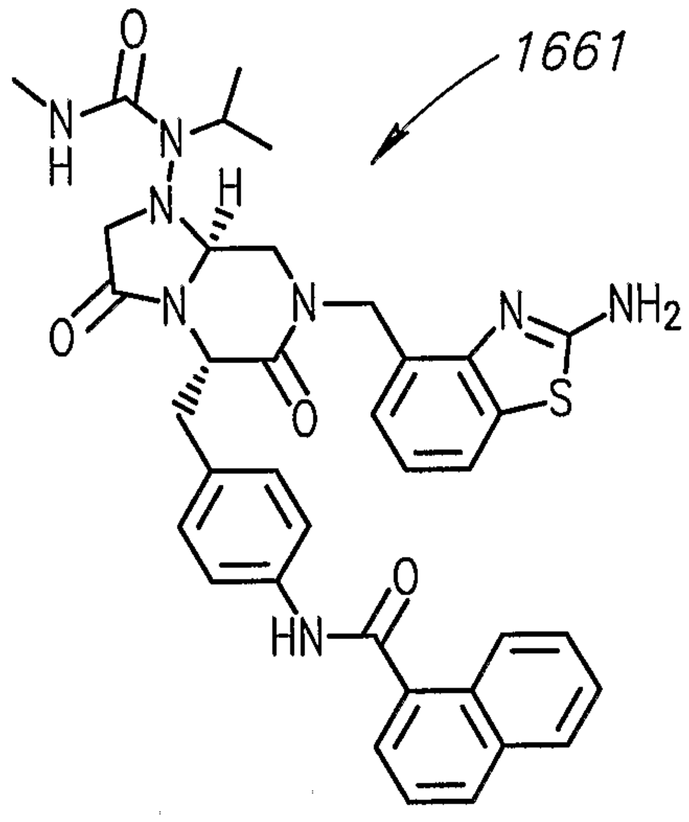


FIG.9J

1661



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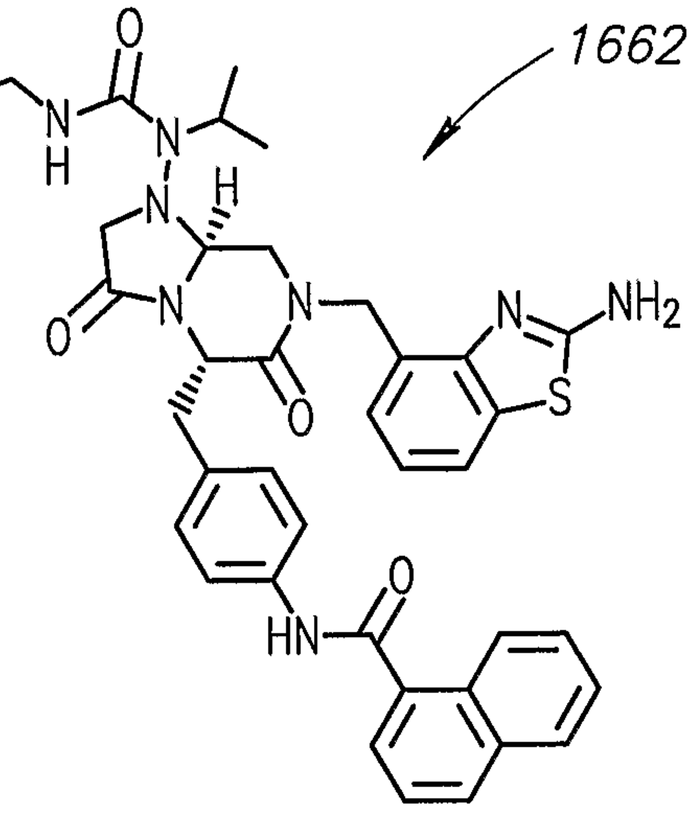

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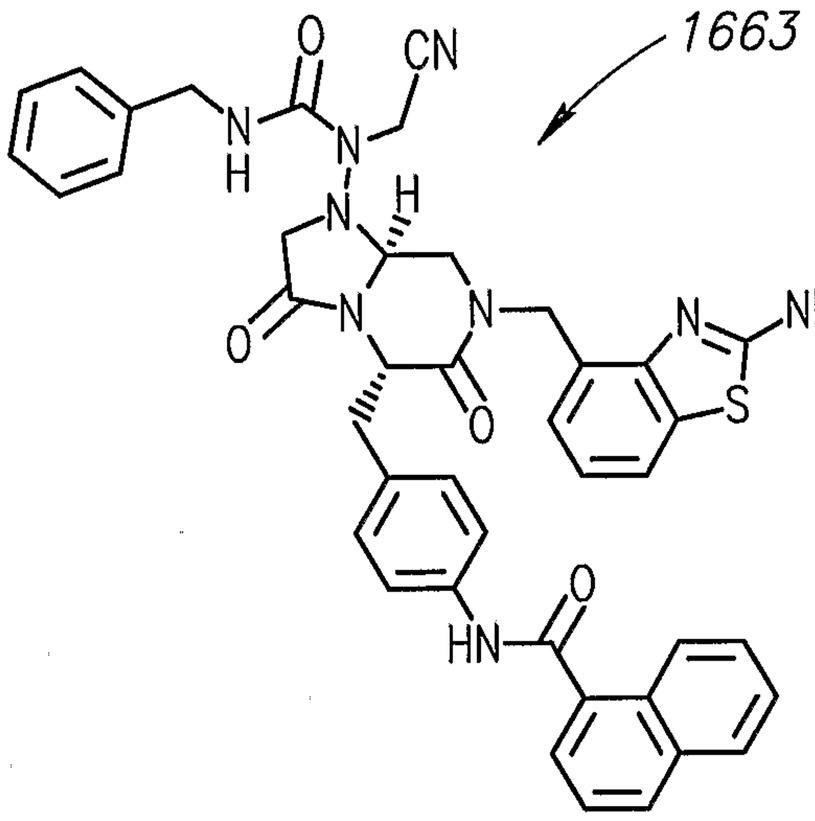

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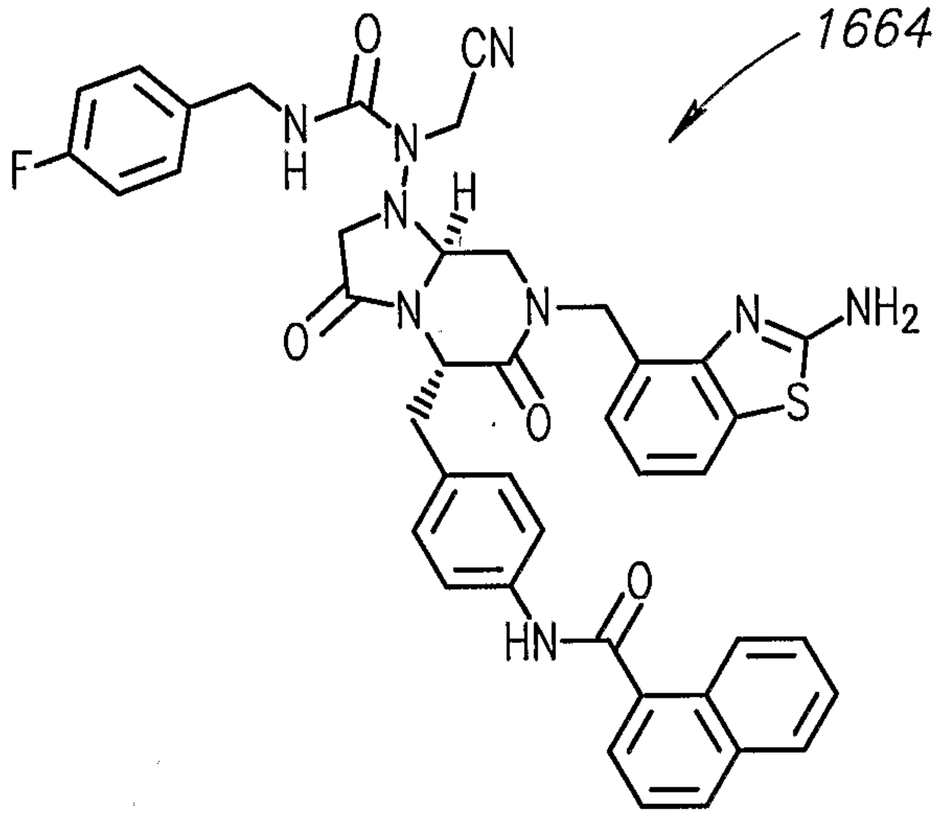

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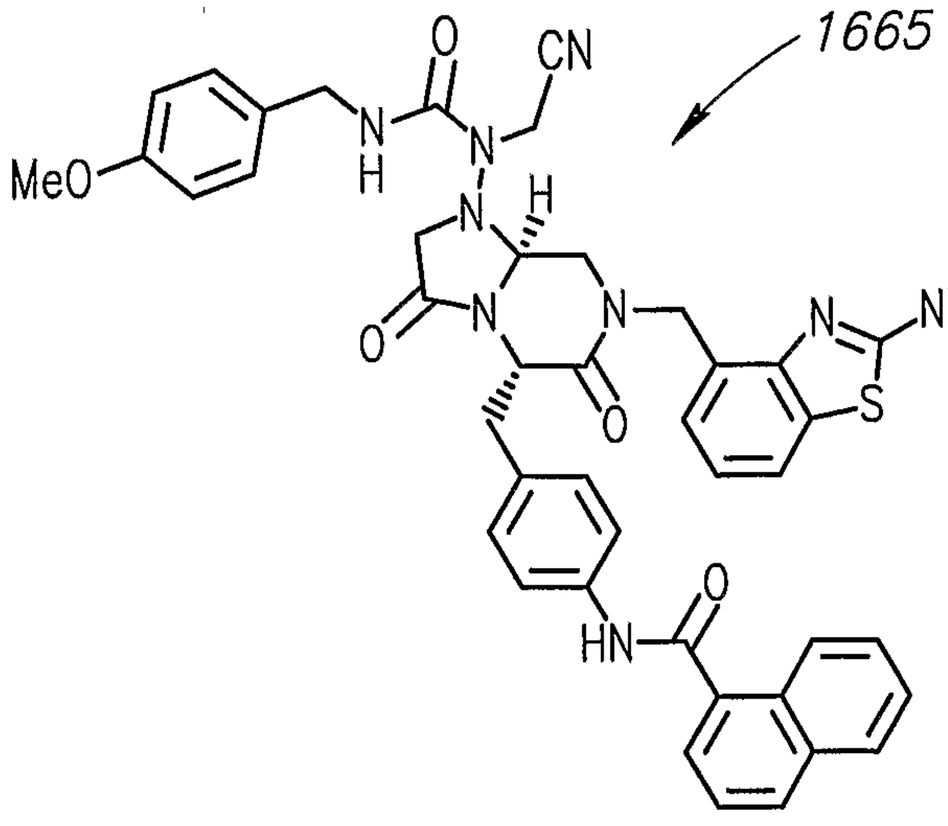

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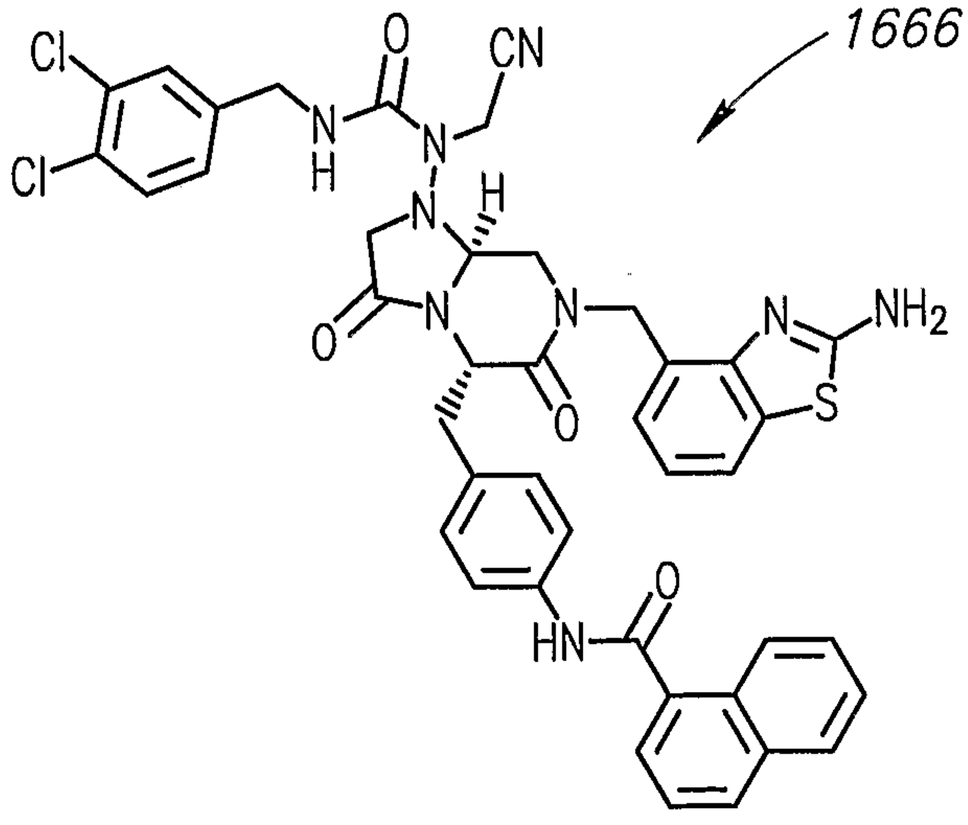
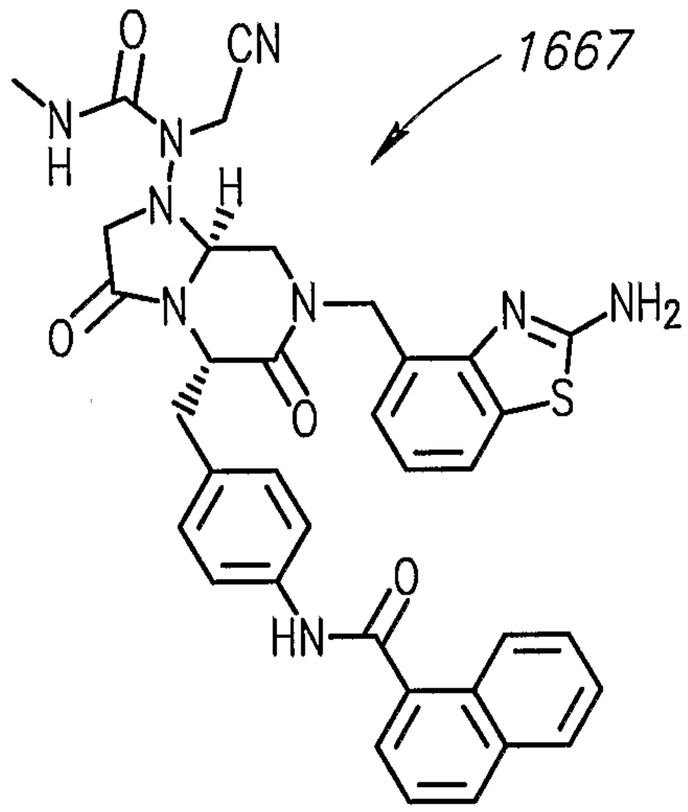


FIG.9K

1667



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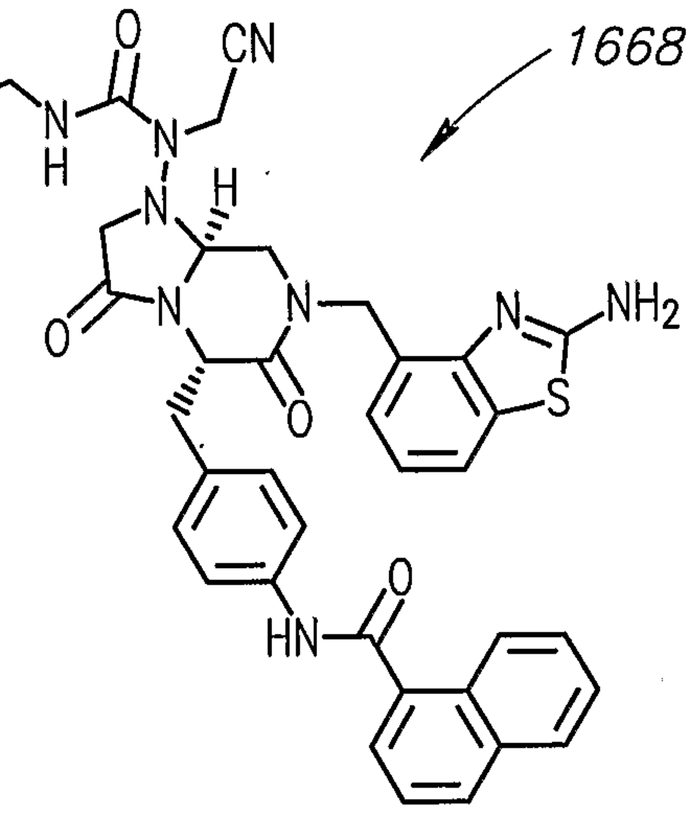

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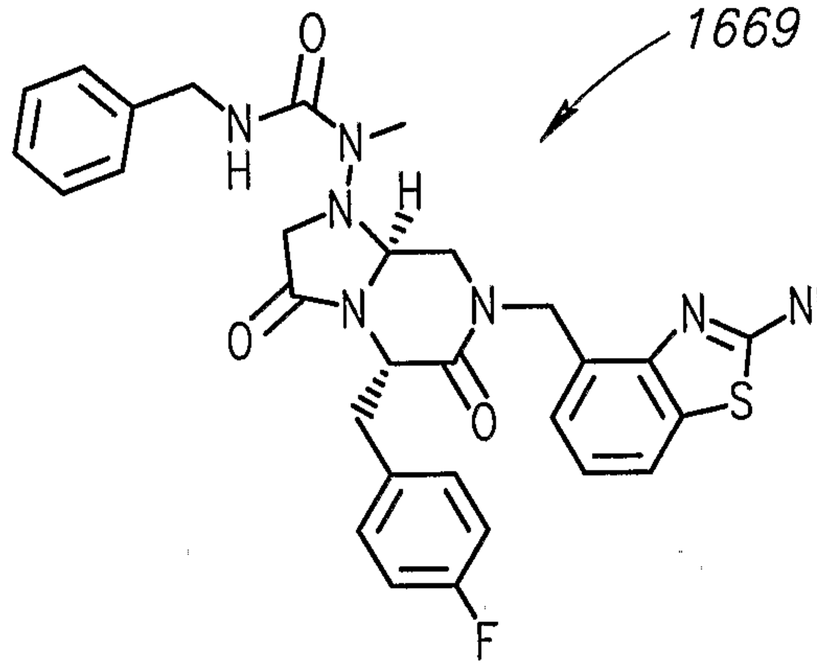

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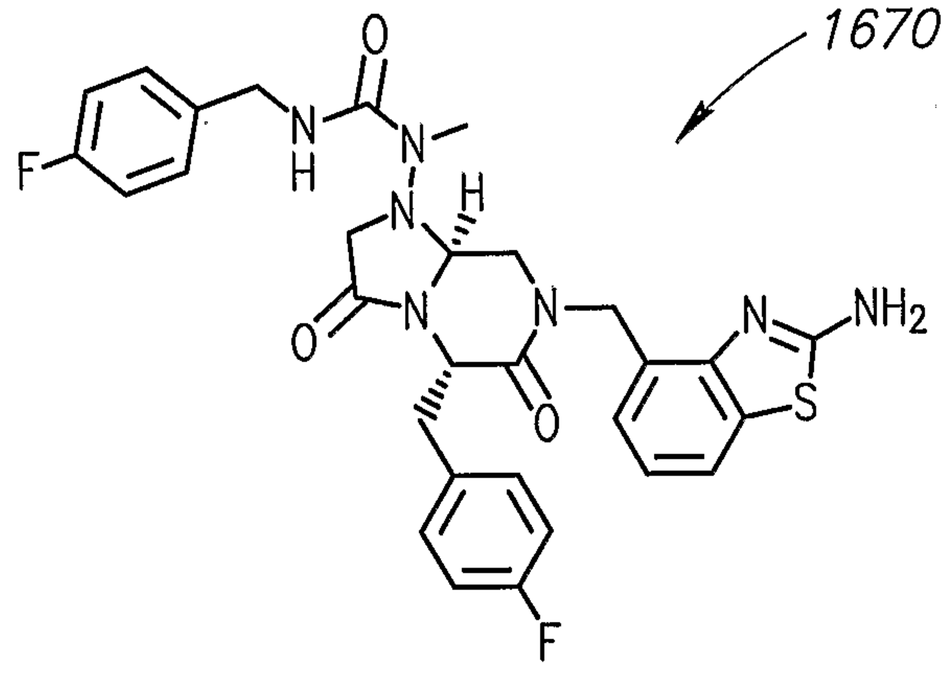

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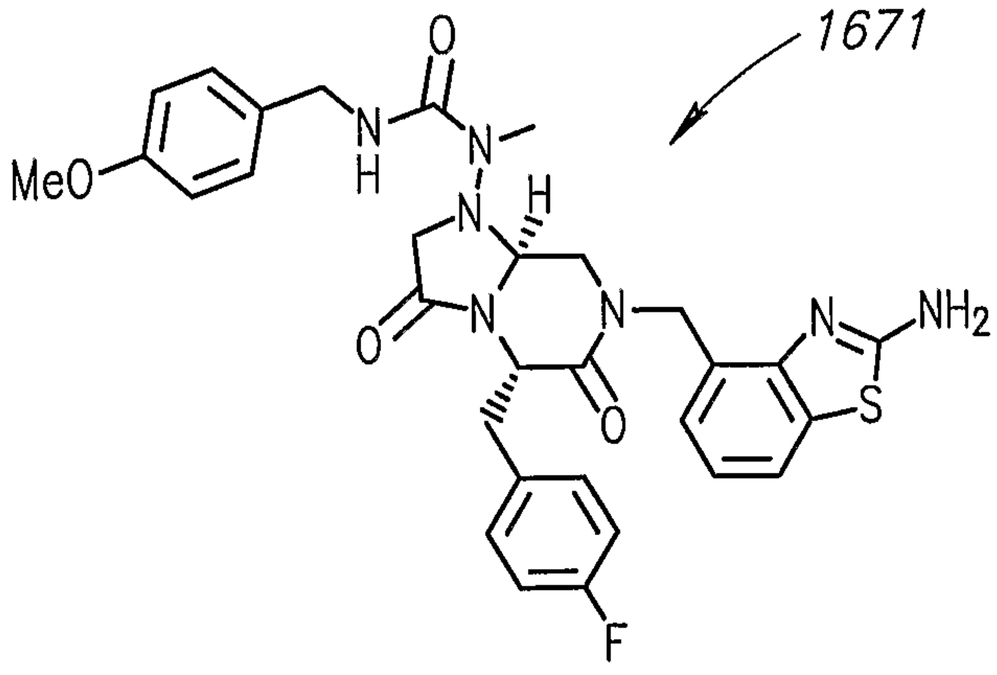

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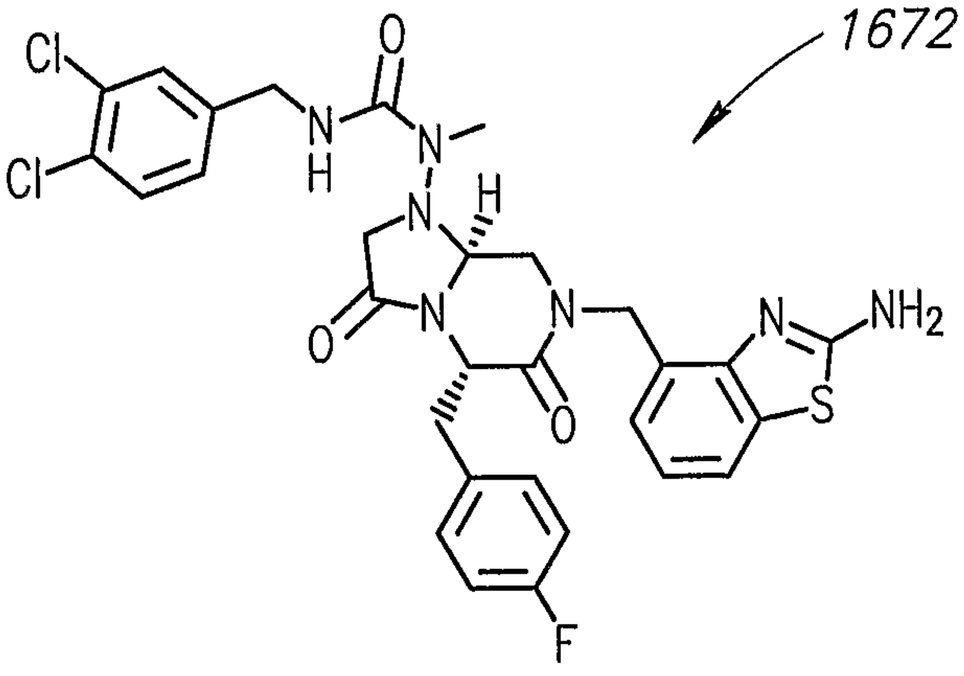
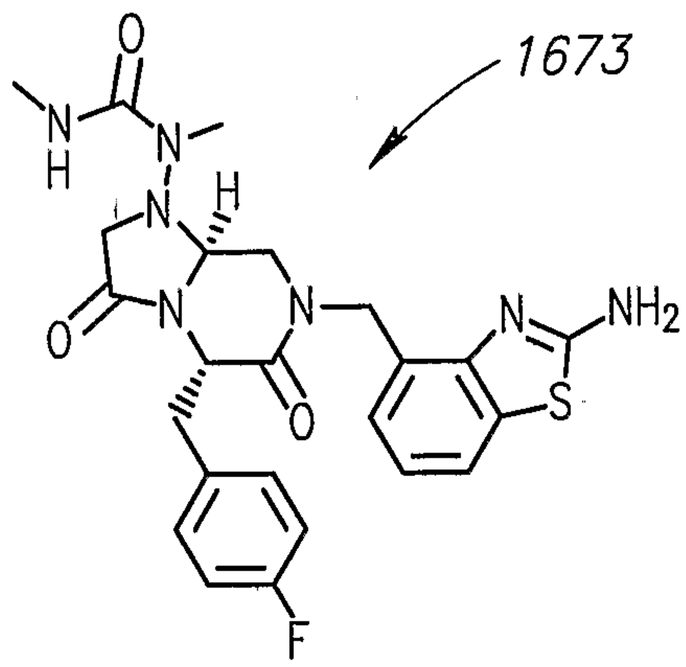
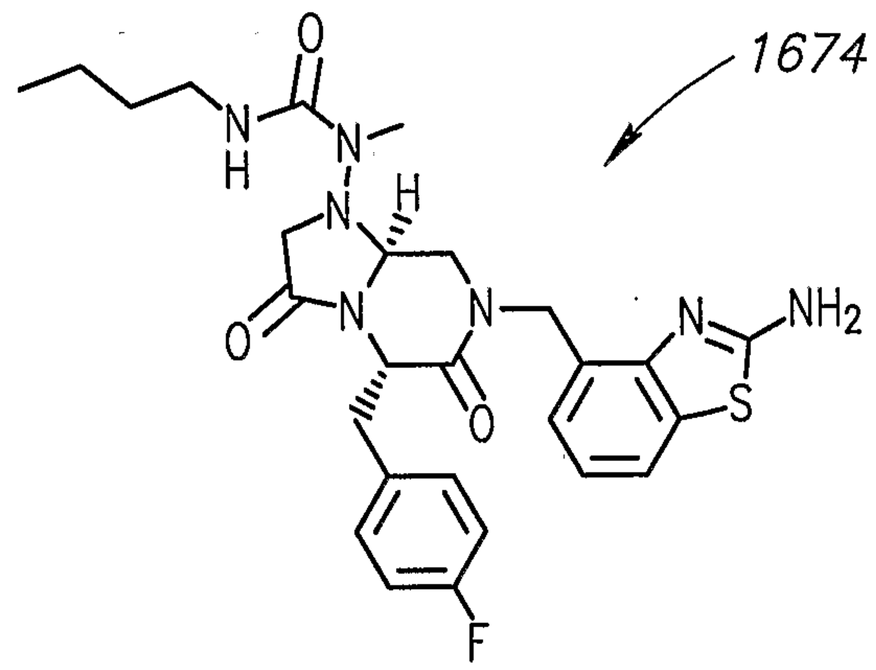
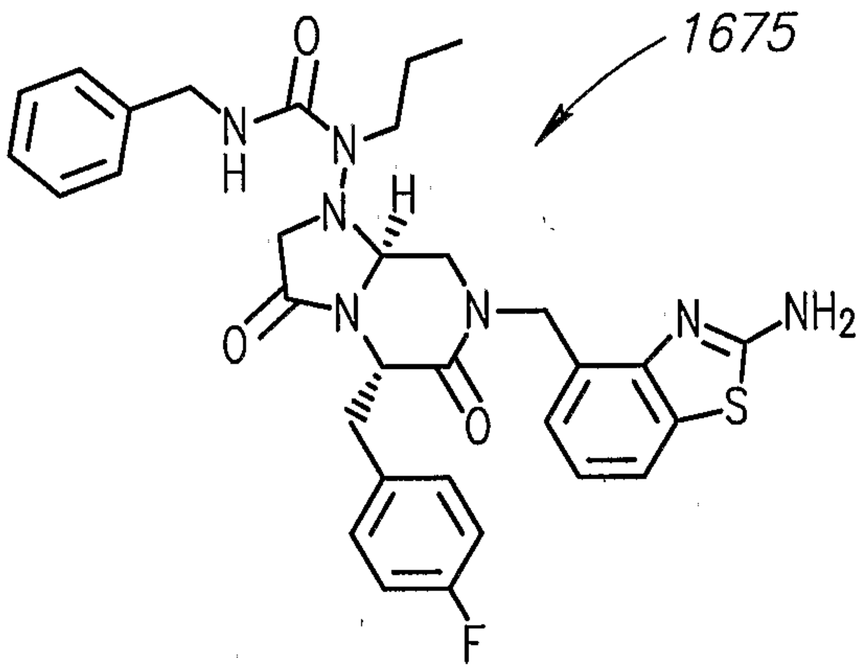
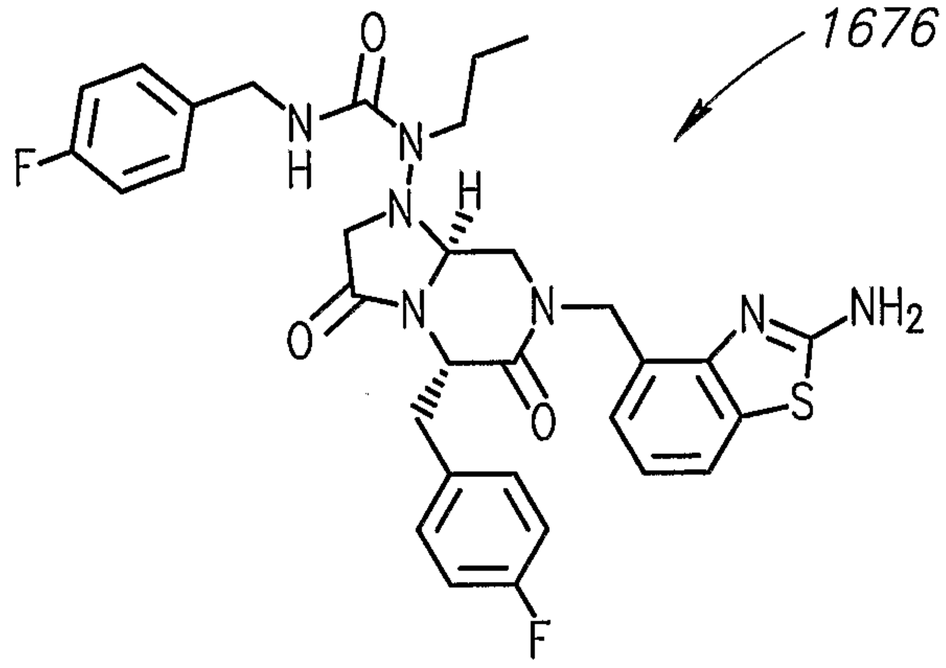


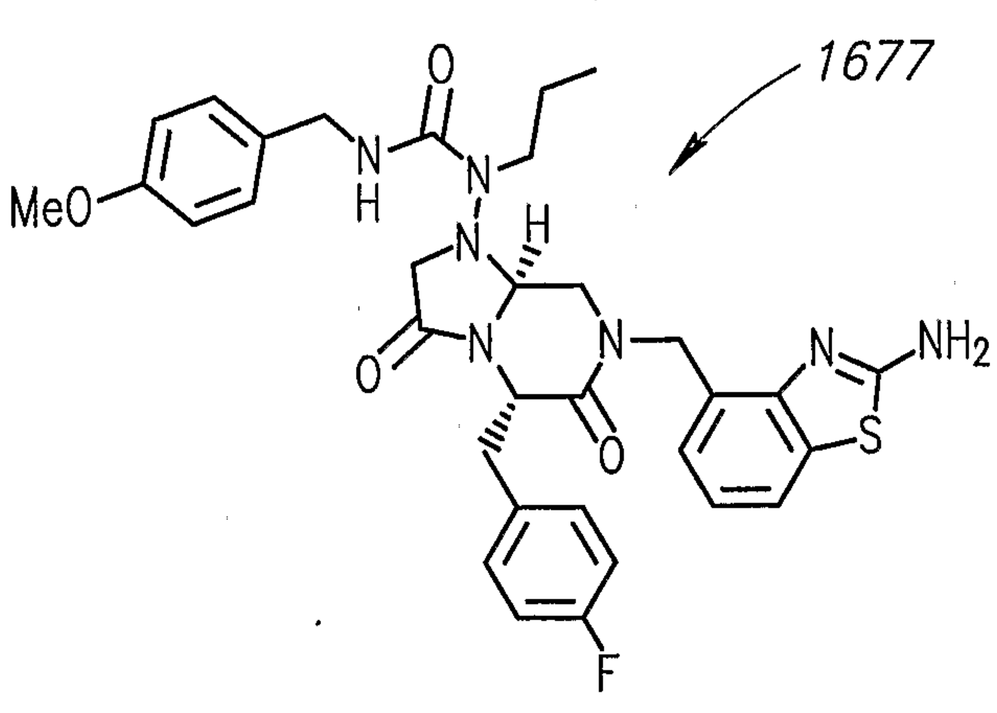
FIG.9L











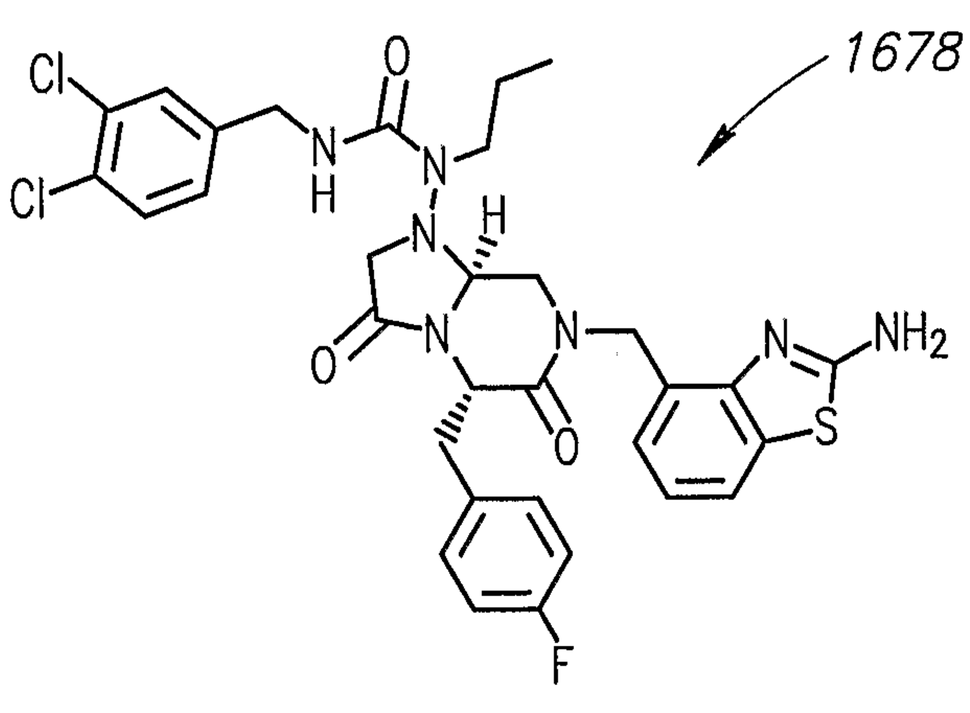
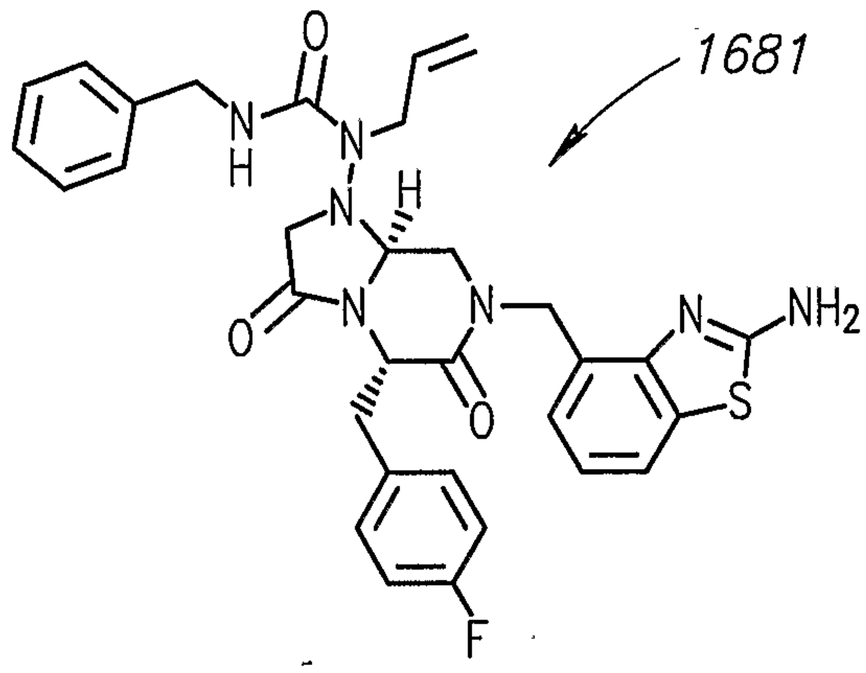
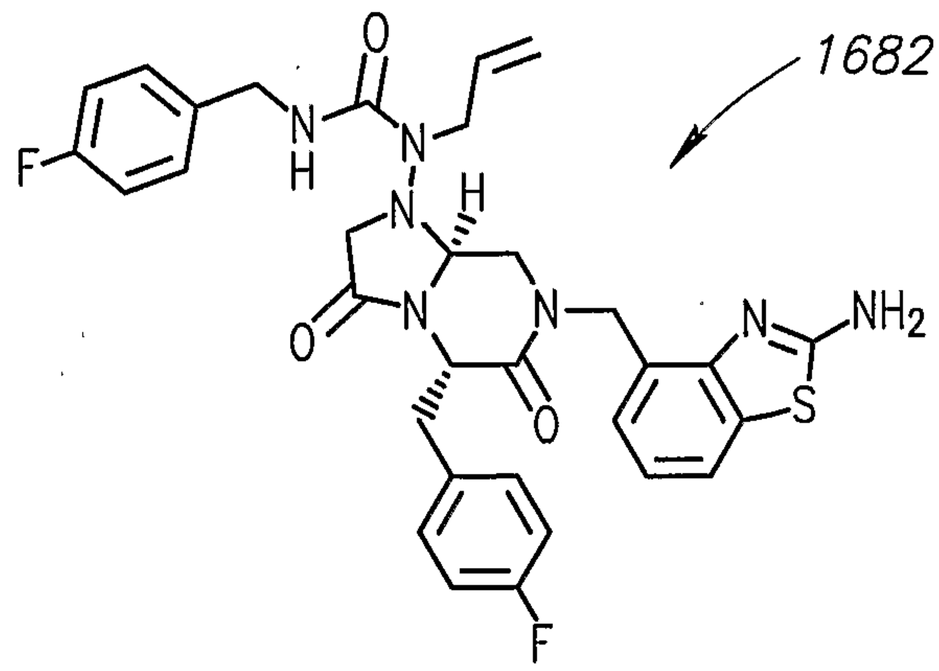
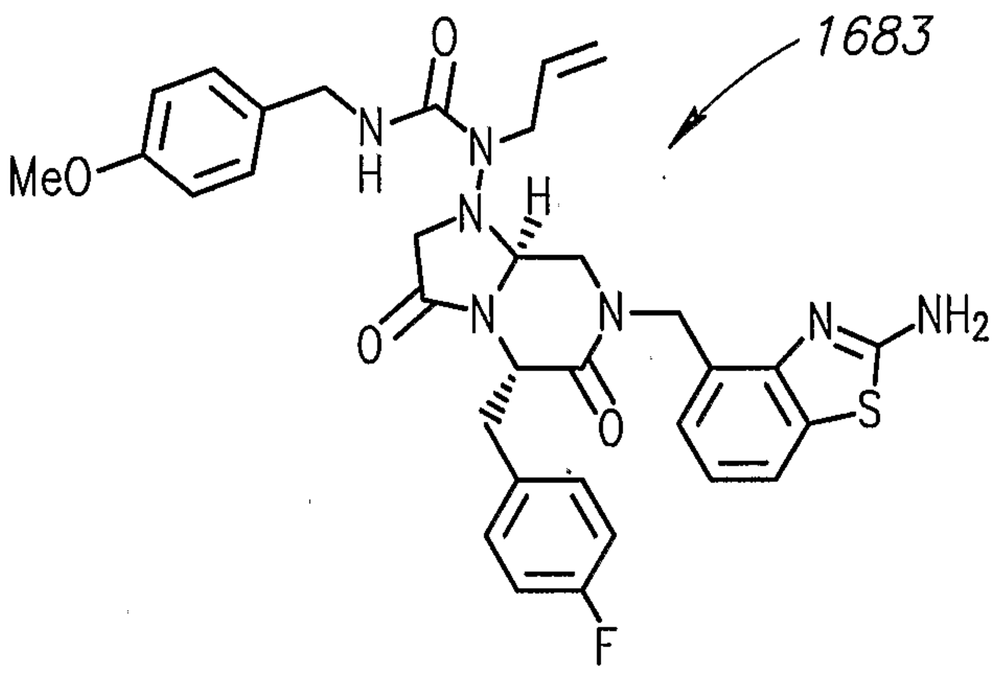
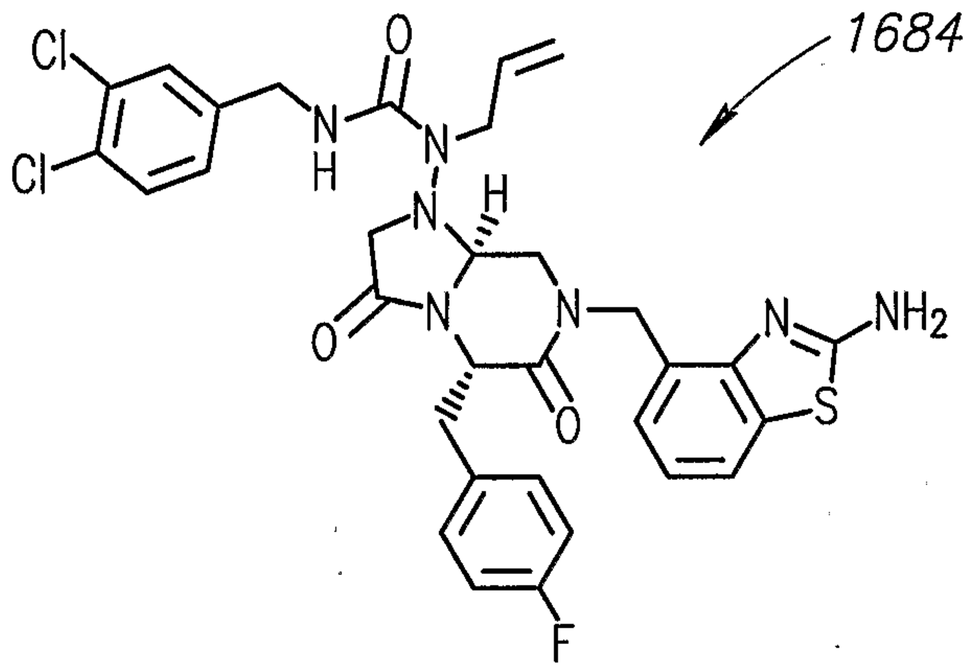


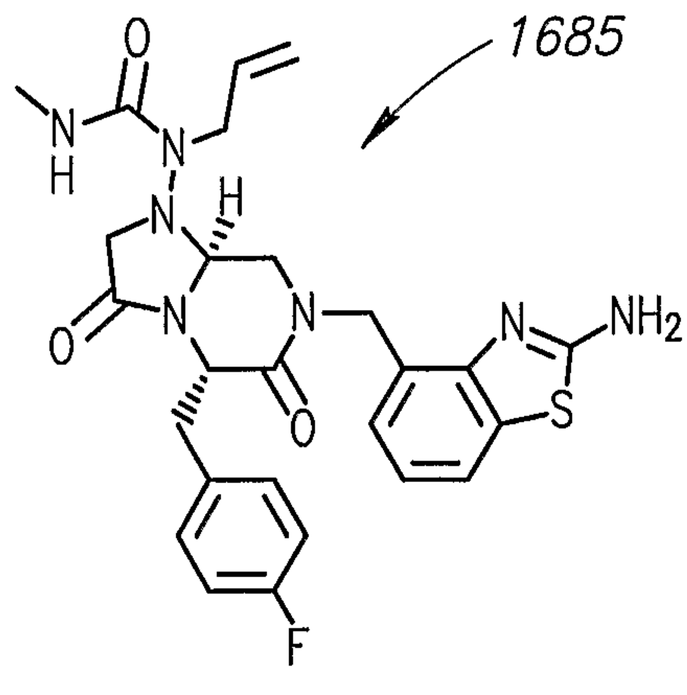
FIG.9M











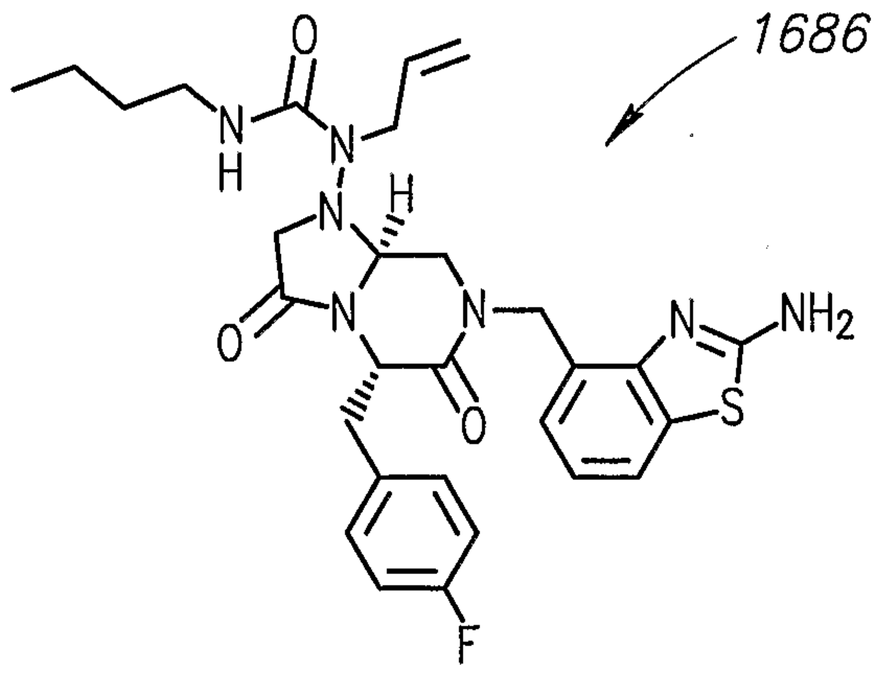
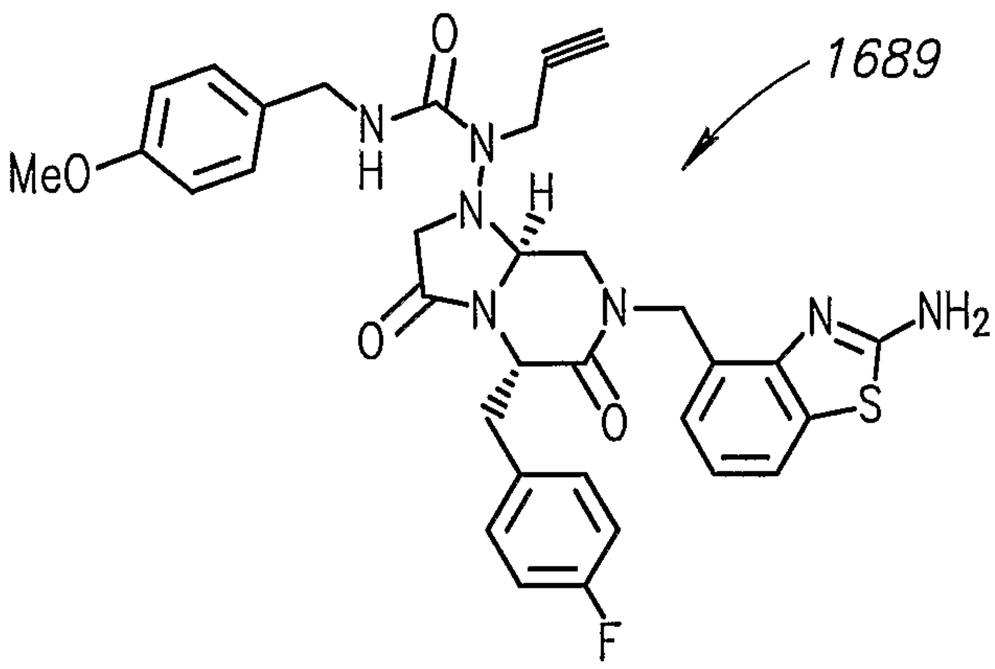


FIG.9N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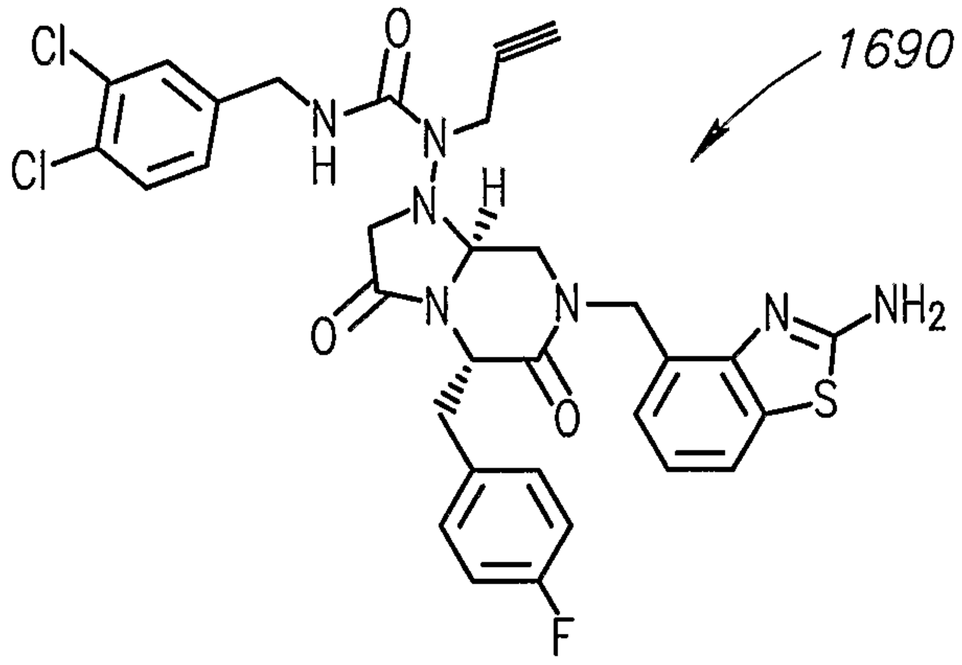
1690
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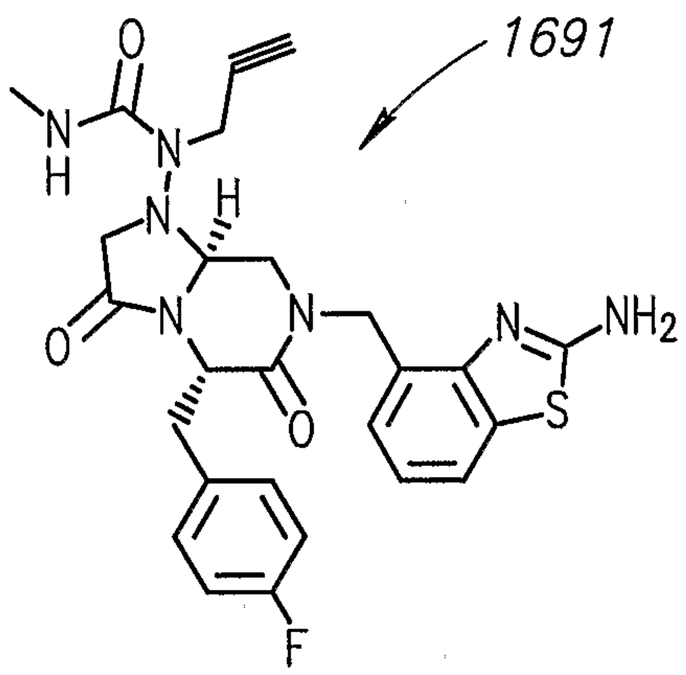
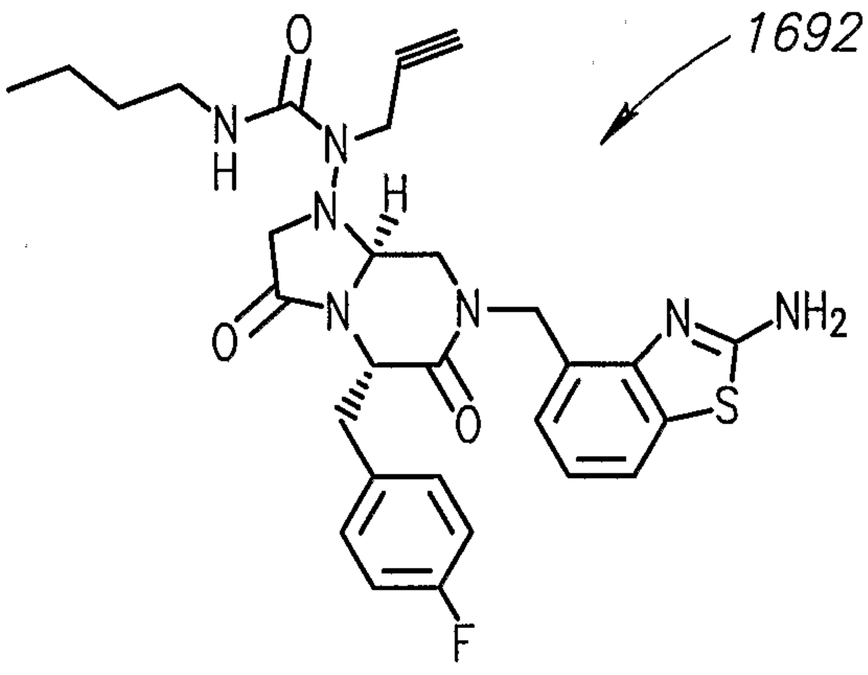
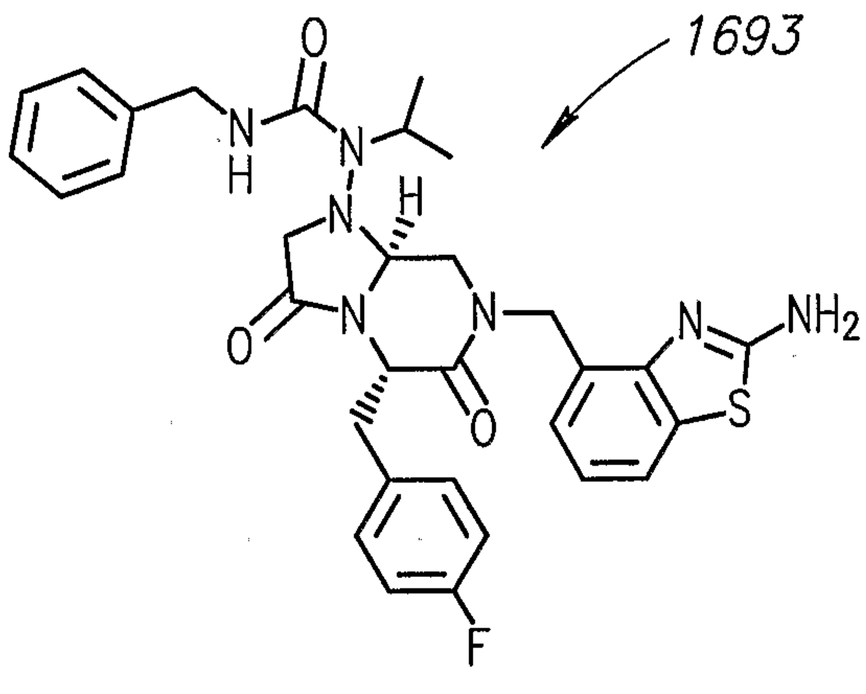
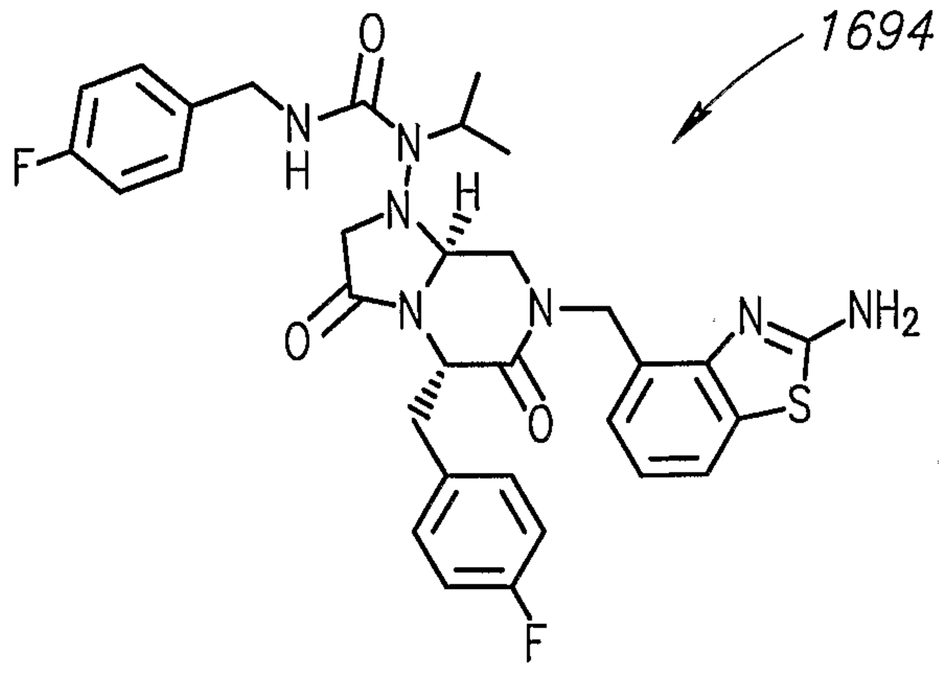
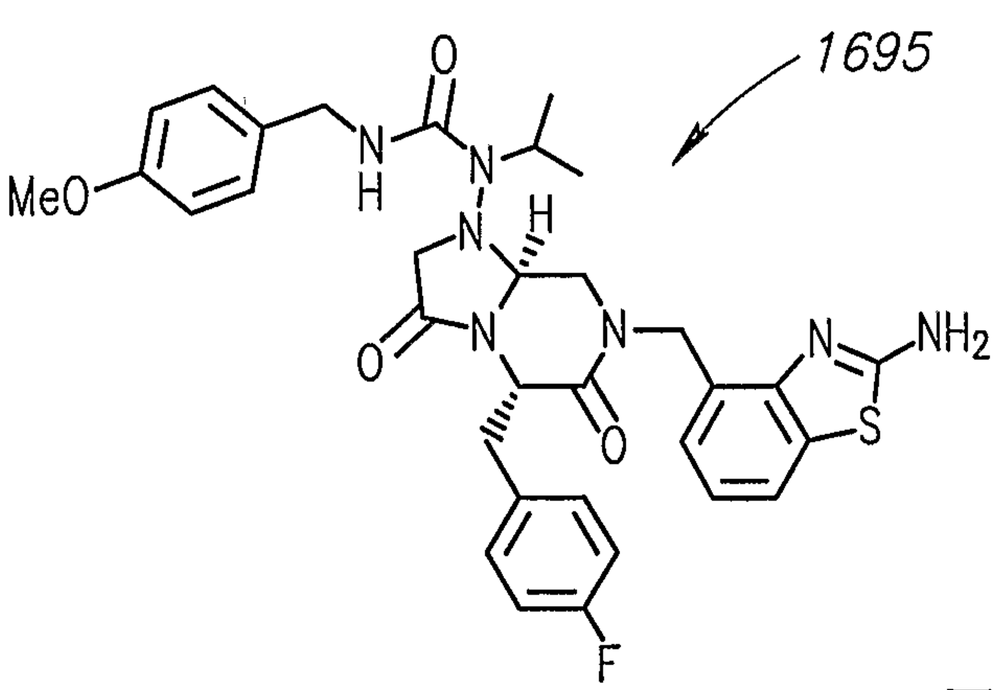
NH2
F


1691
O
N
H
N
N
H
O
N
O
N
N
S
NH2
F


1692
O
N
H
N
N
H
O
N
O
N
N
S
NH2
F


1693
O
N
H
N
N
H
O
N
O
N
N
S
NH2
F


1694
F
O
N
H
N
N
H
O
N
O
N
N
S
NH2
F


1695
MeO
O
N
H
N
N
H
O
N
O
N
N
S
NH2
F

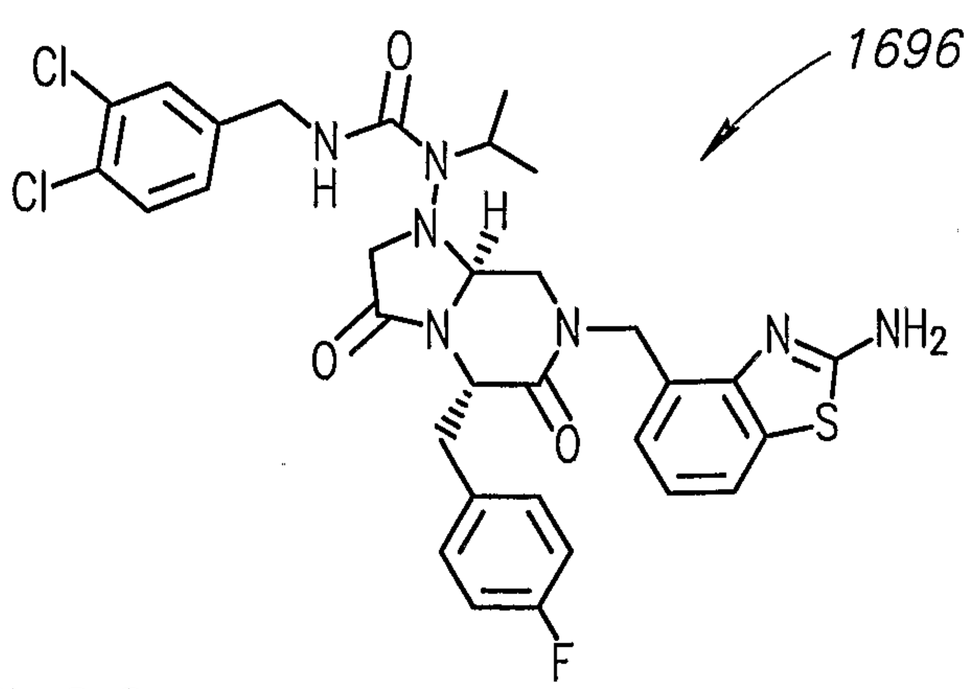
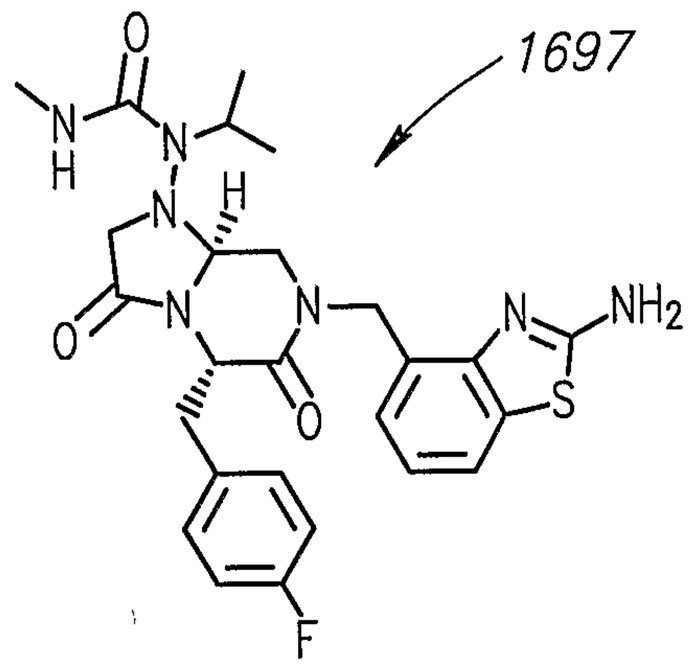
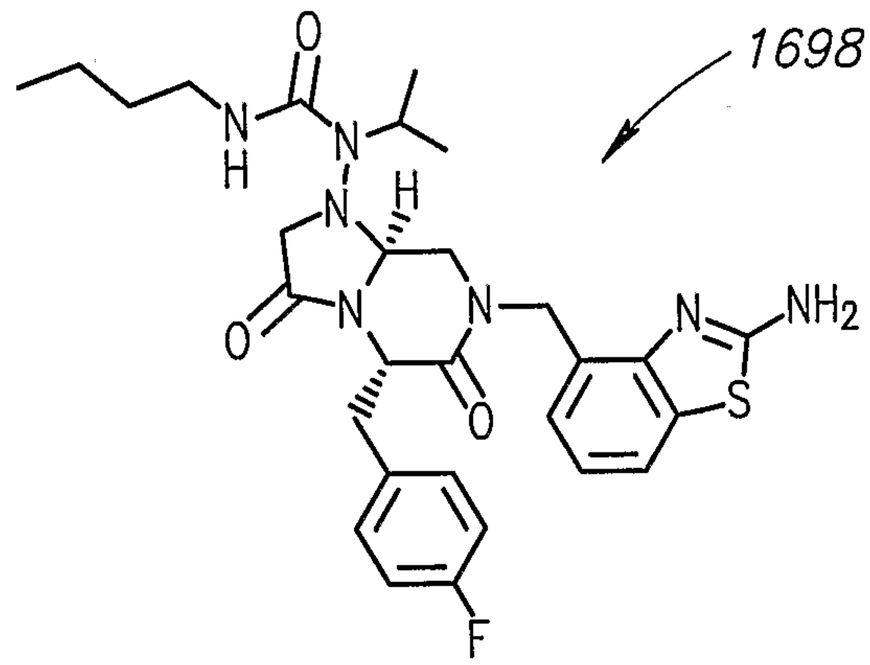
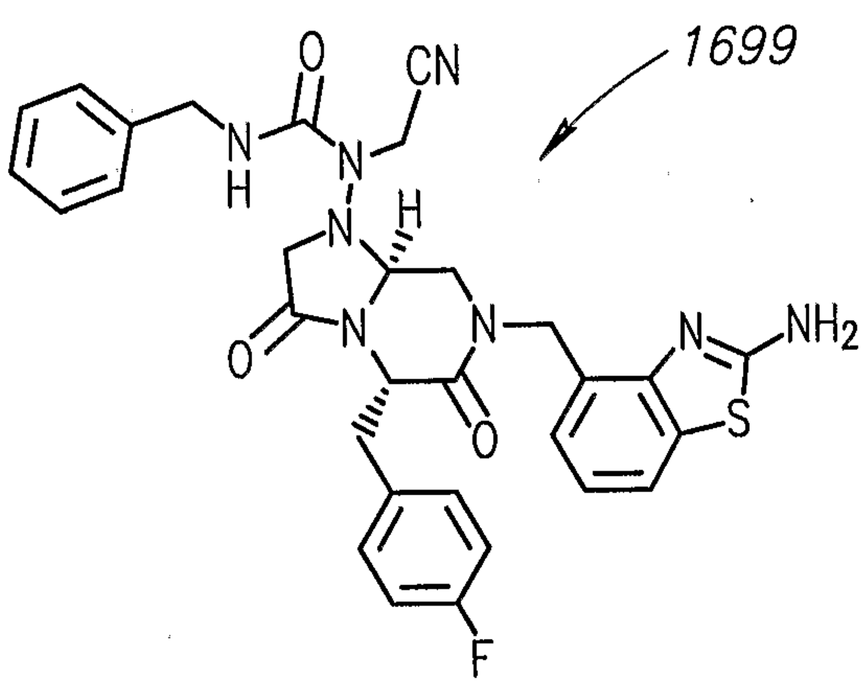
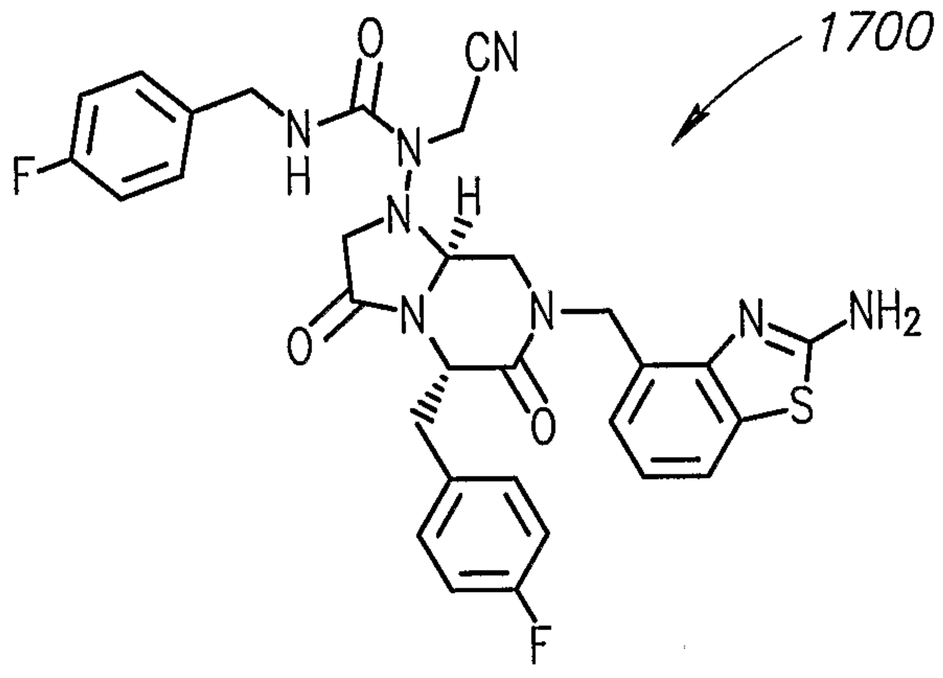

1696
Cl
Cl
O
N
H
N
N
H
O
N
O
N
N
S
NH2
F

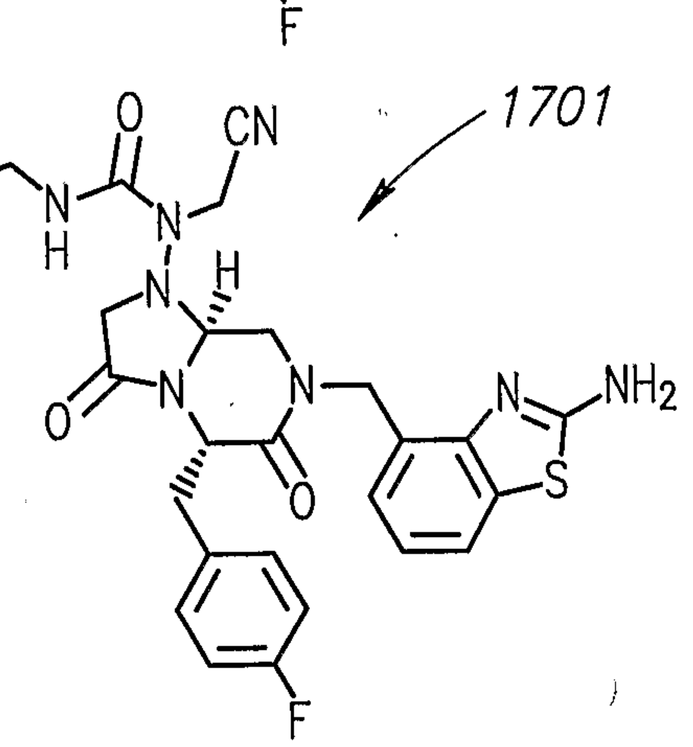
FIG.90











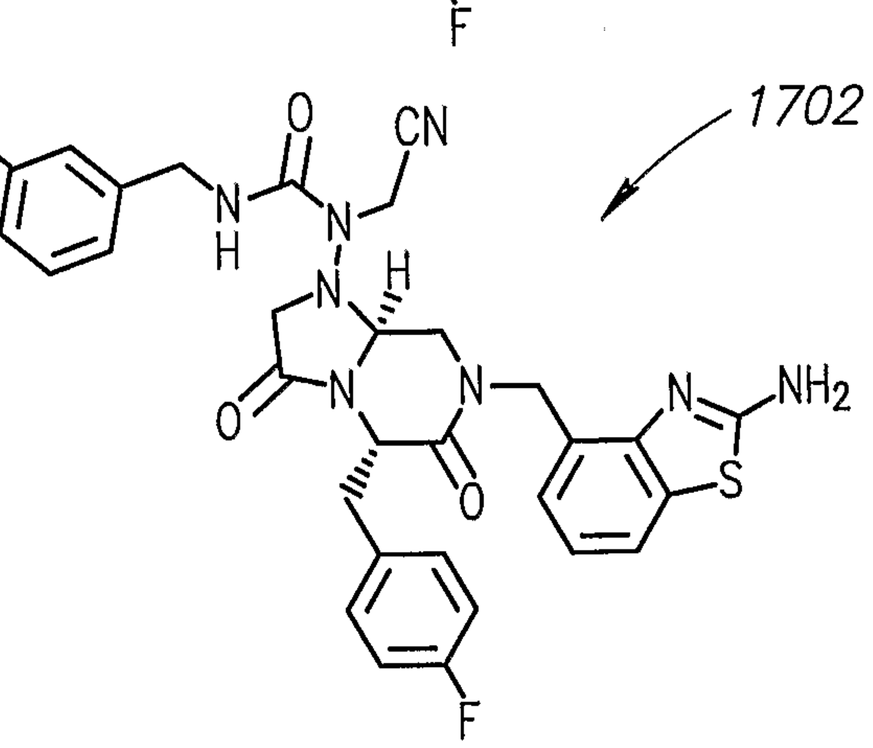


FIG.9P

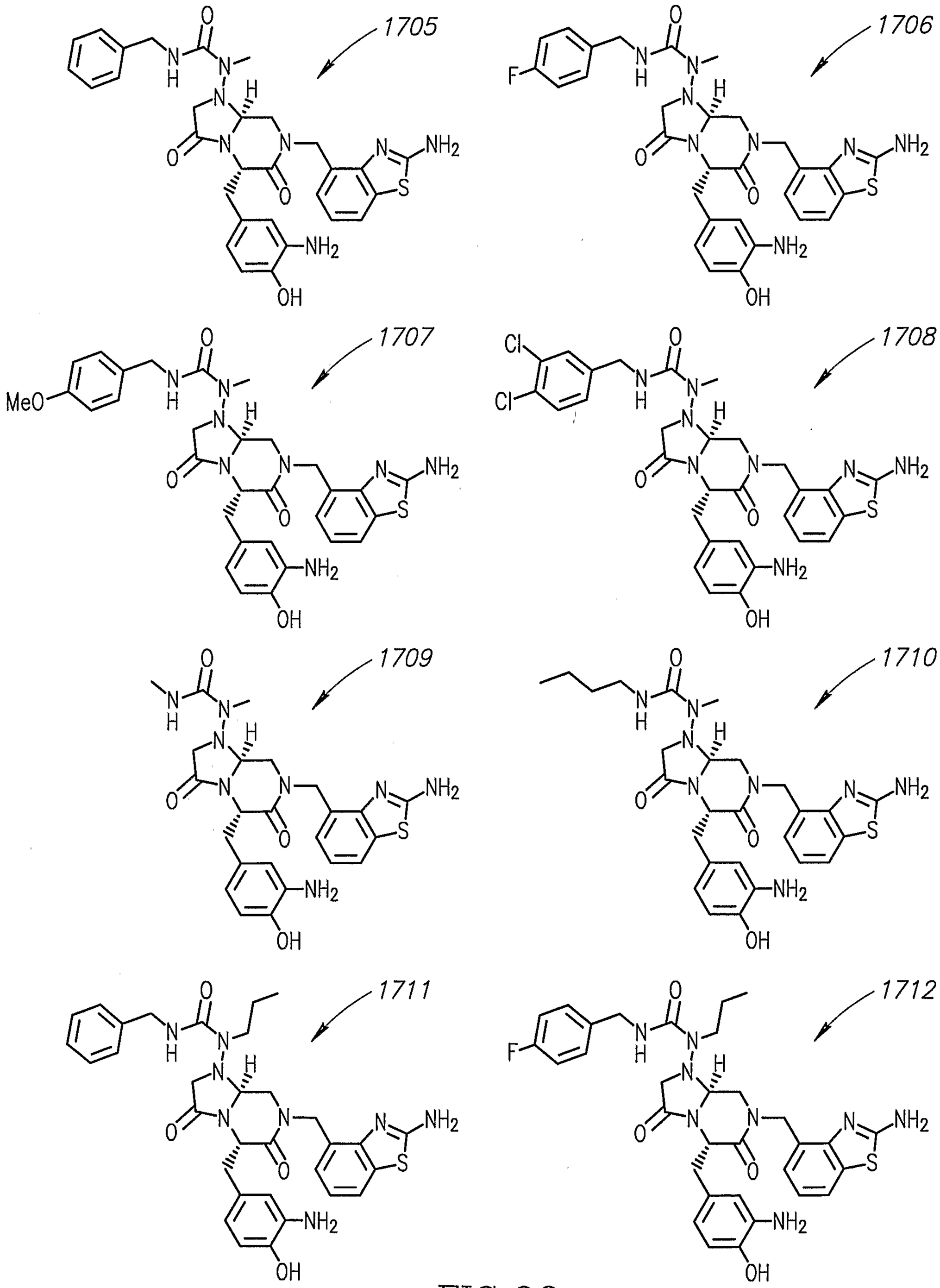


FIG.9Q

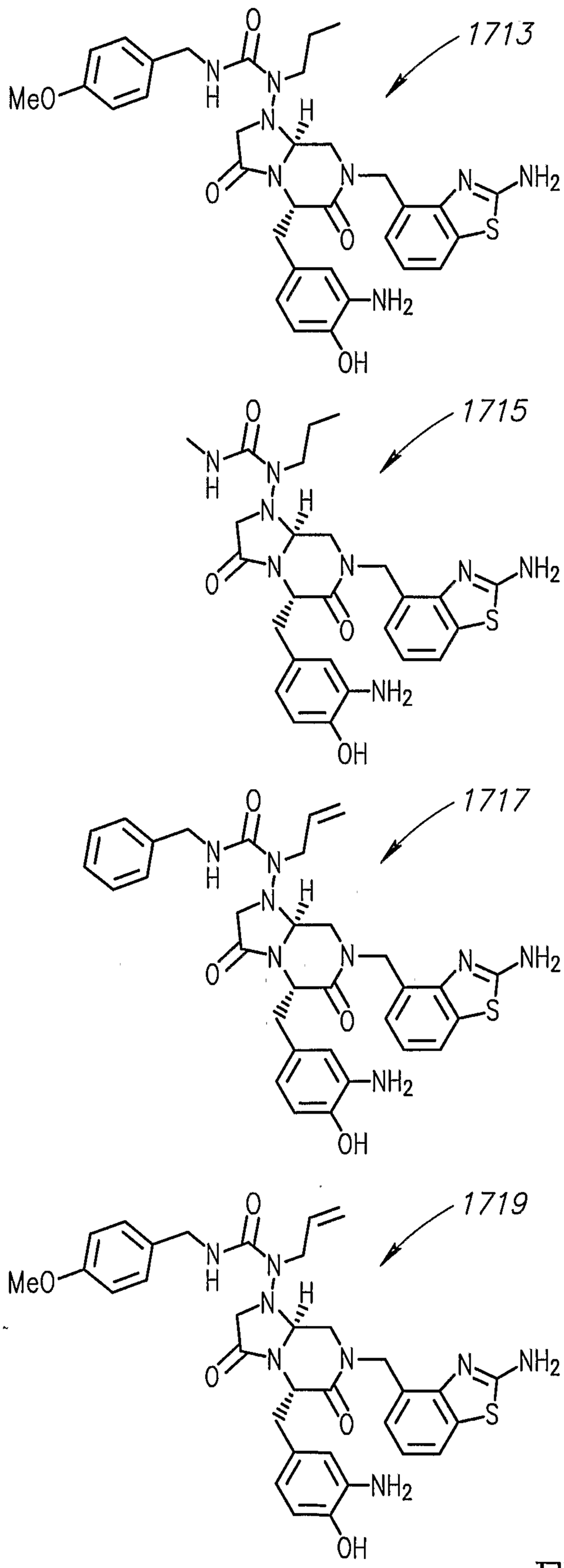
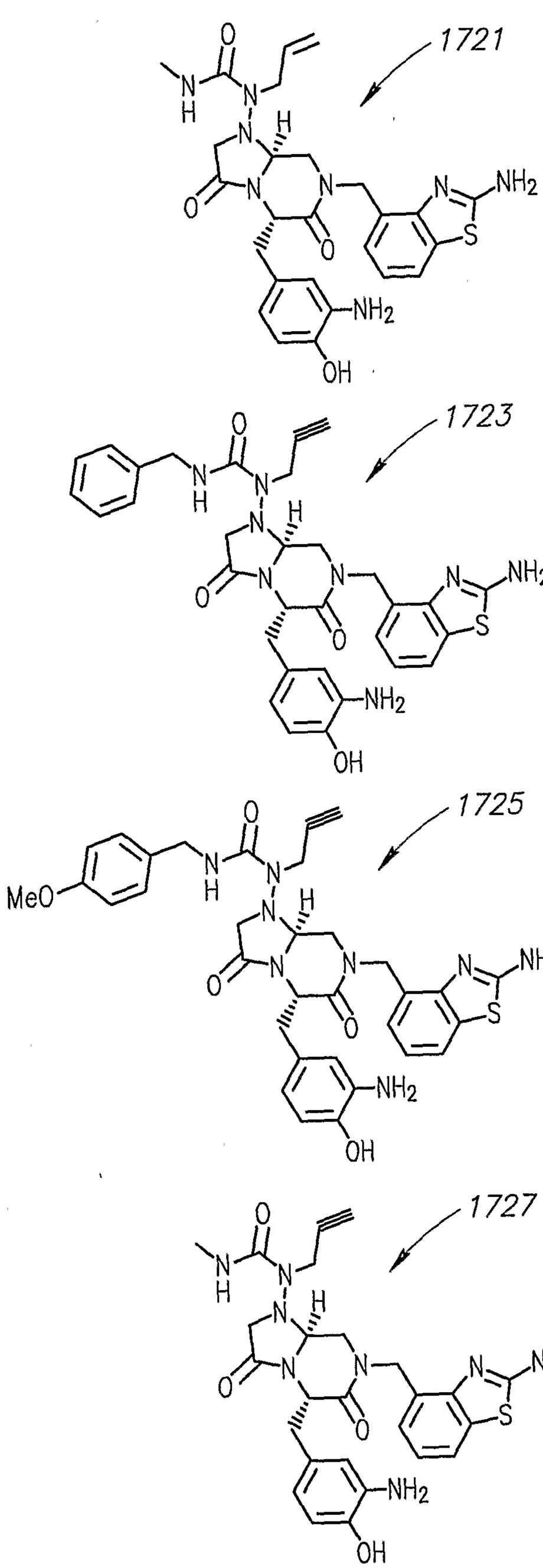


FIG.9R



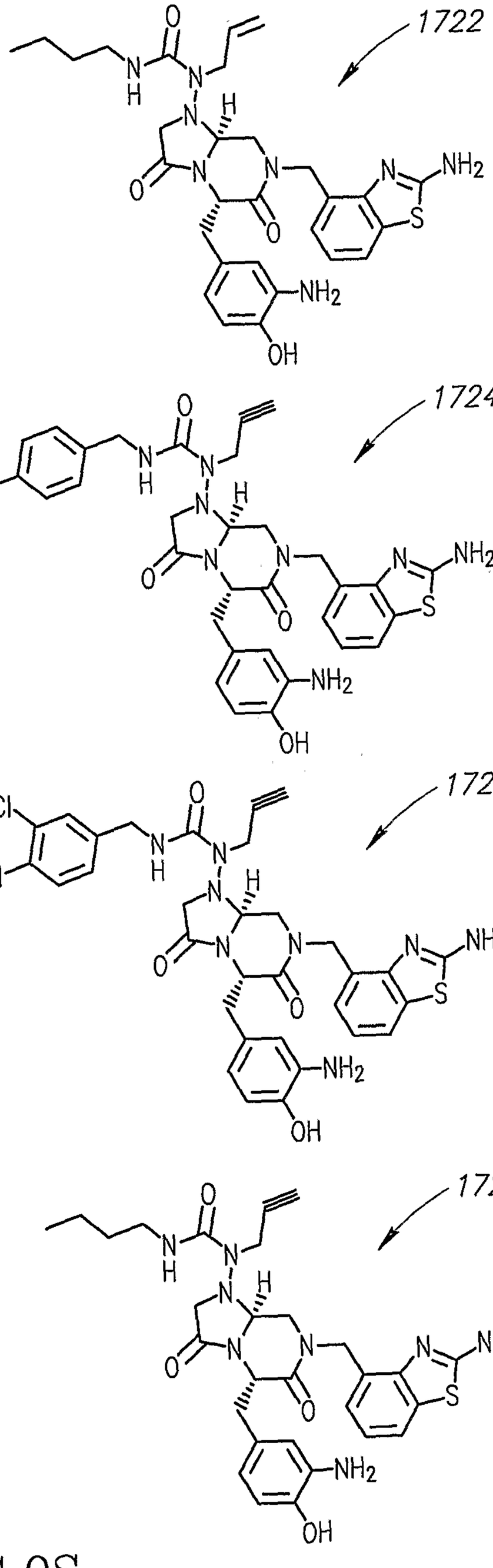
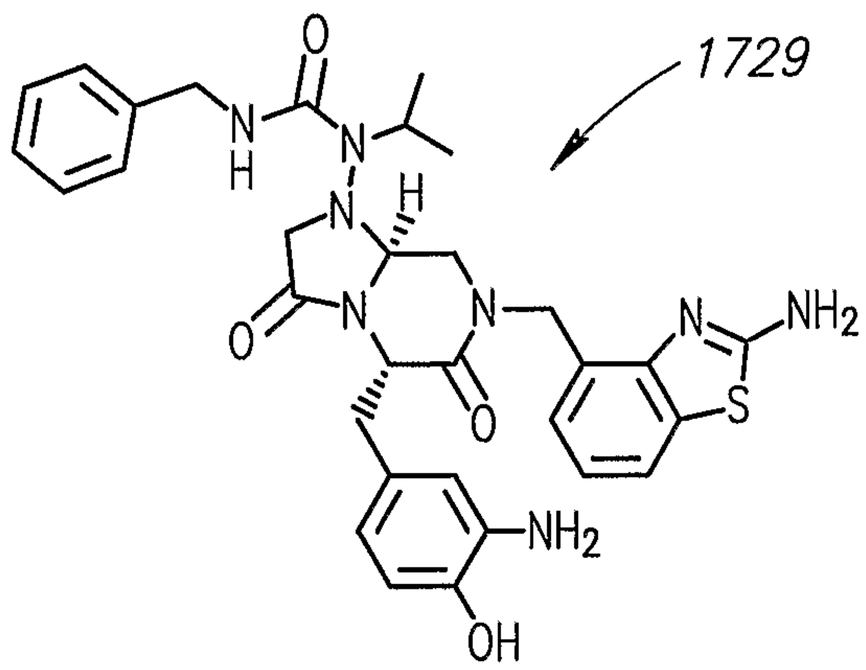
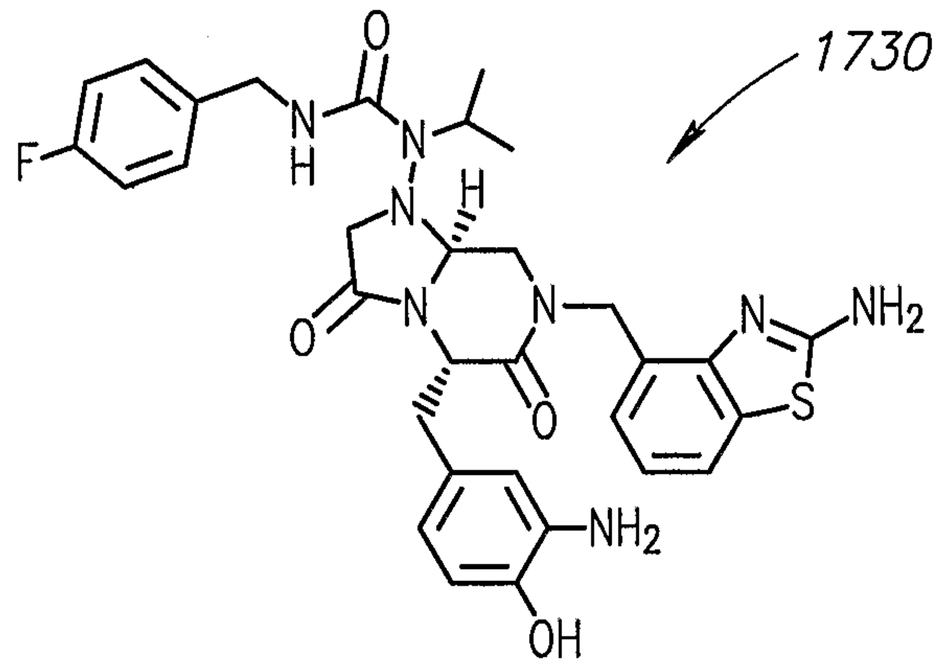


FIG.9S


1729
O
N
H
N
O
N
H
N
O
N
N
S
NH2
NH2
OH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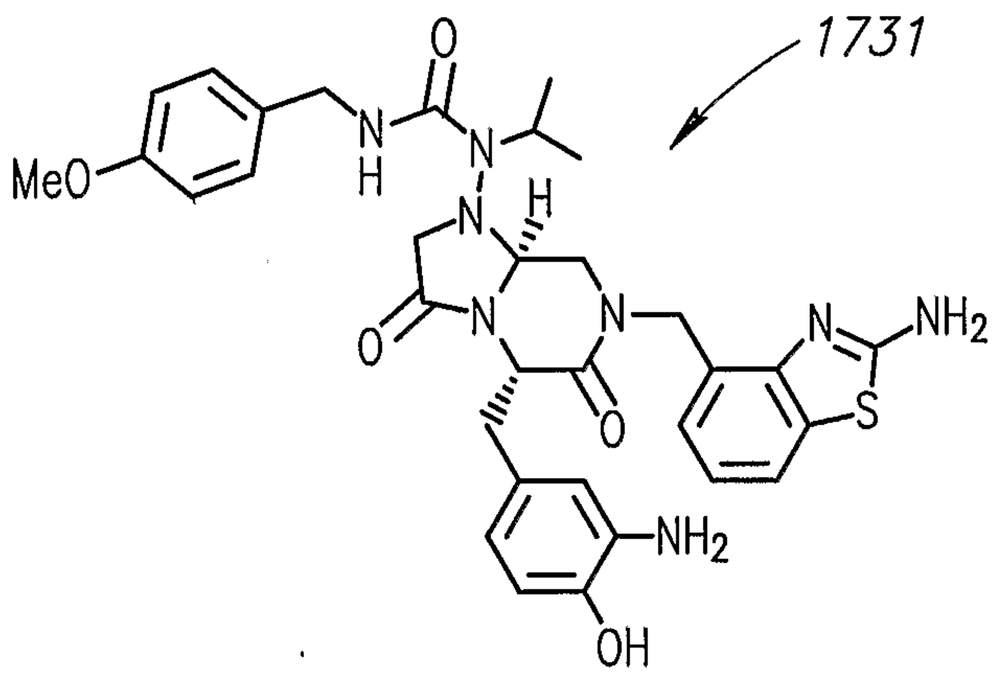
F
O
N
H
N
O
N
H
N
O
N
N
S
NH2
NH2
OH


1731
MeO
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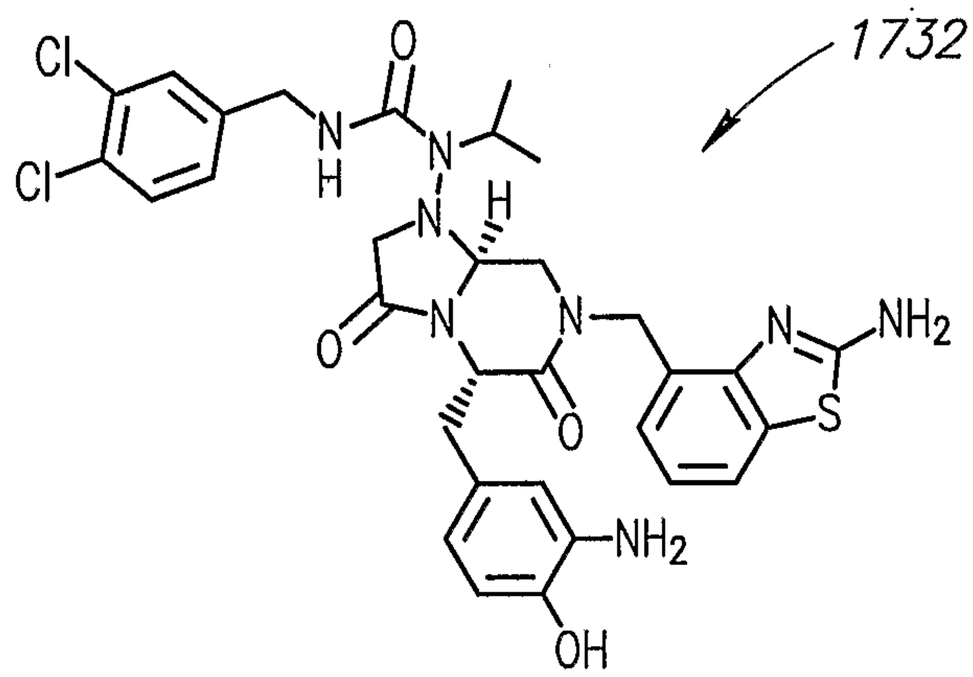
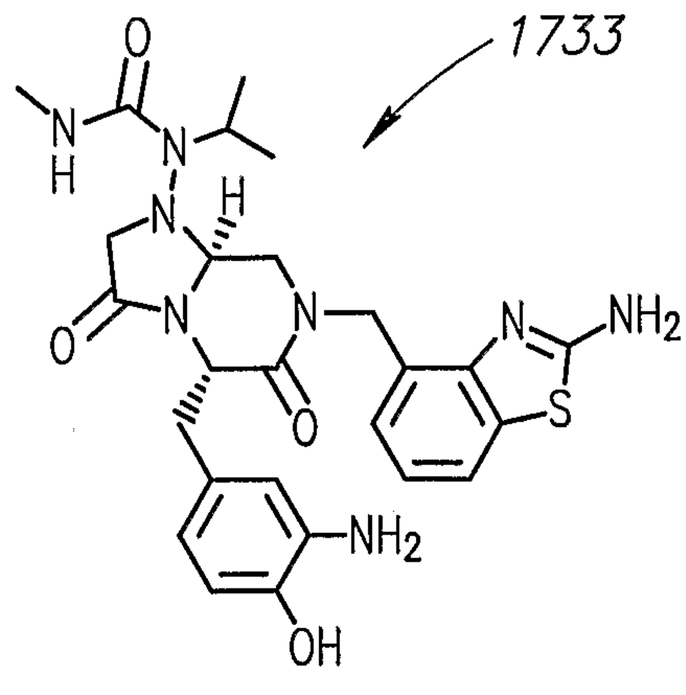
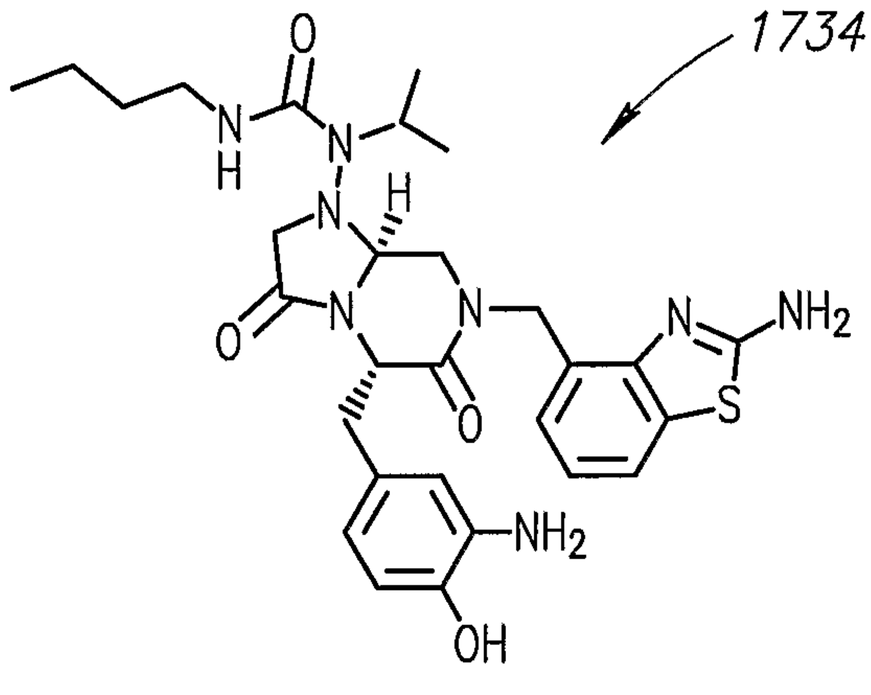
N
H
N
O
N
H
N
O
N
N
S
NH2
NH2
OH


1732
Cl
Cl
O
N
H
N
O
N
H
N
O
N
N
S
NH2
NH2
OH


1733
O
N
H
N
O
N
H
N
O
N
N
S
NH2
NH2
OH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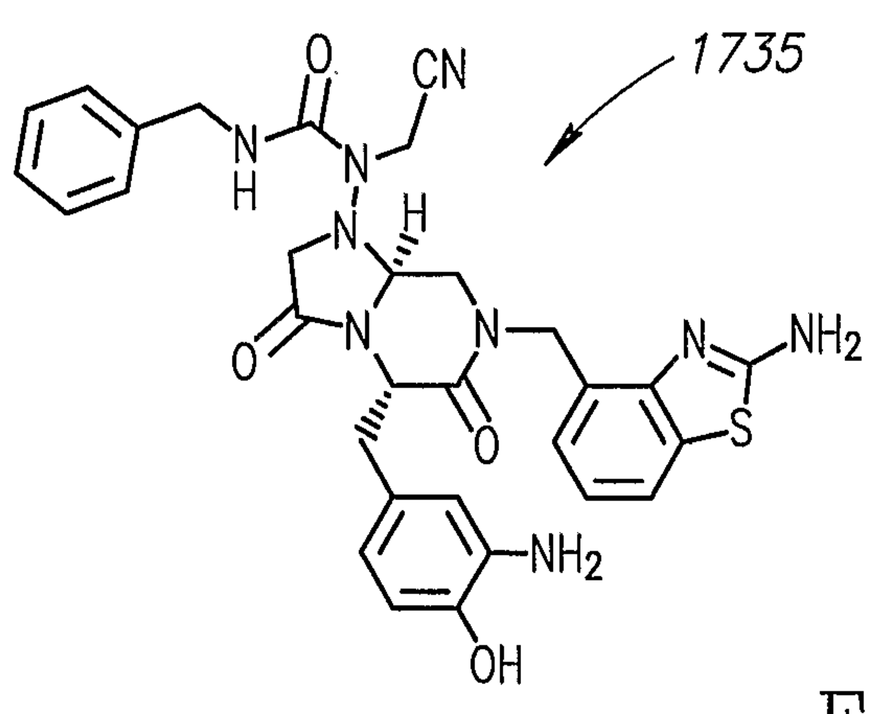
N
H
N
O
N
H
N
O
N
N
S
NH2
NH2
OH


1735
O
CN
N
H
N
O
N
H
N
O
N
N
S
NH2
NH2
OH

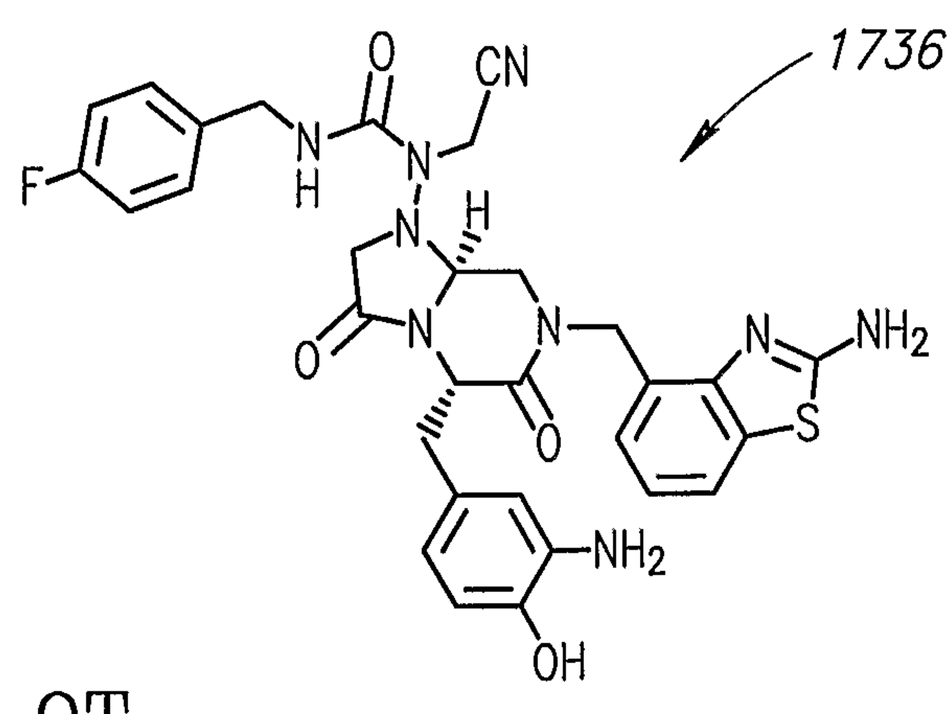
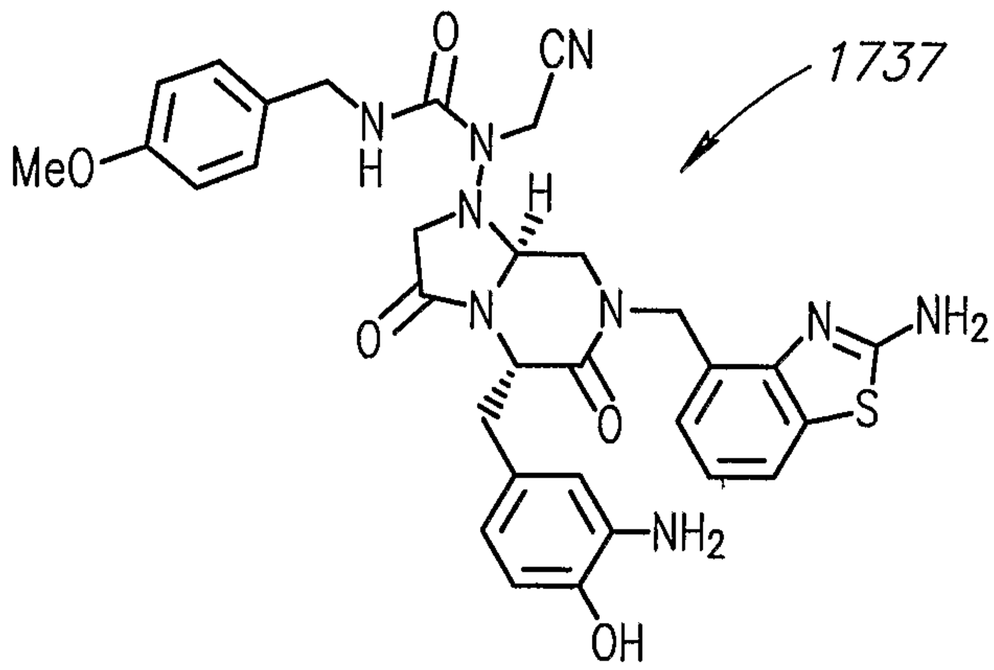
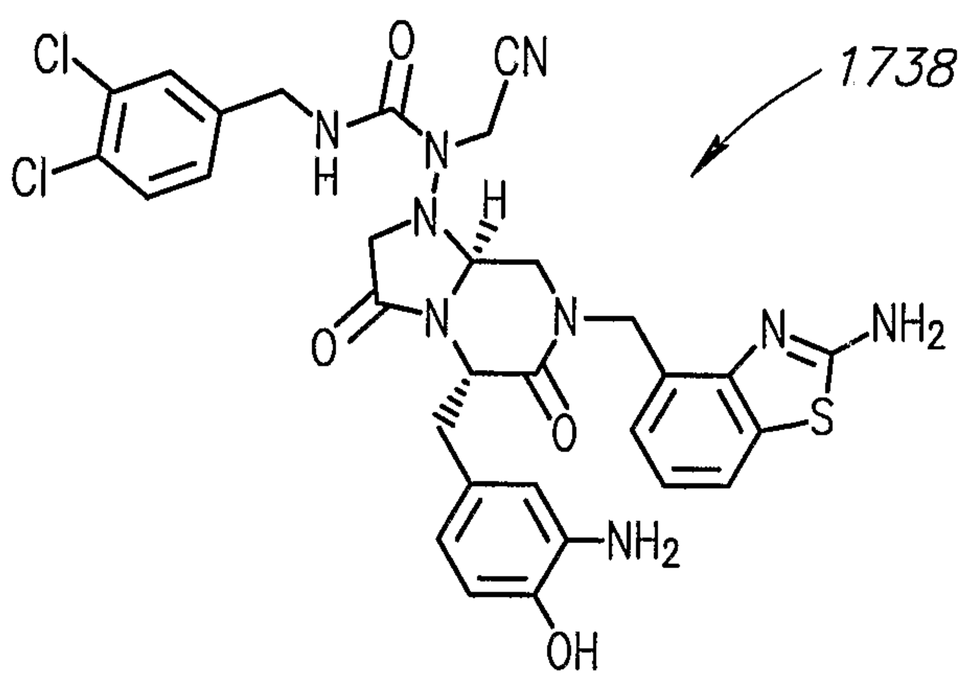
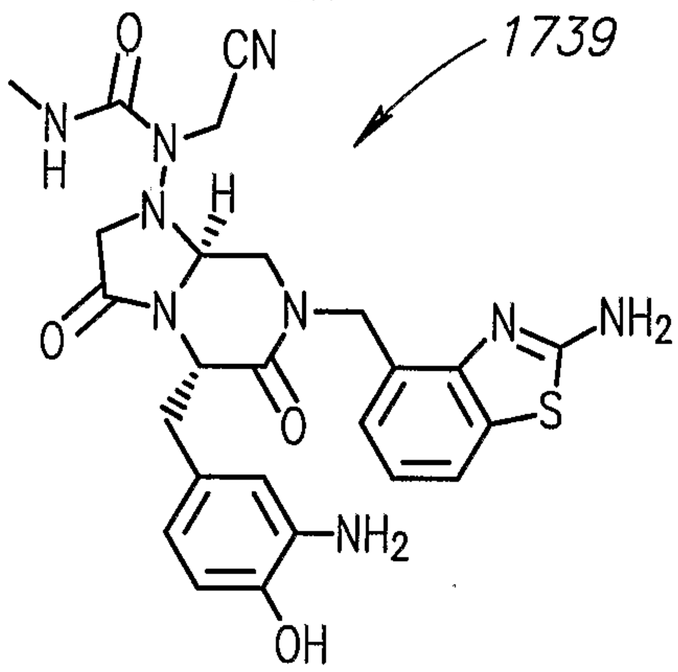
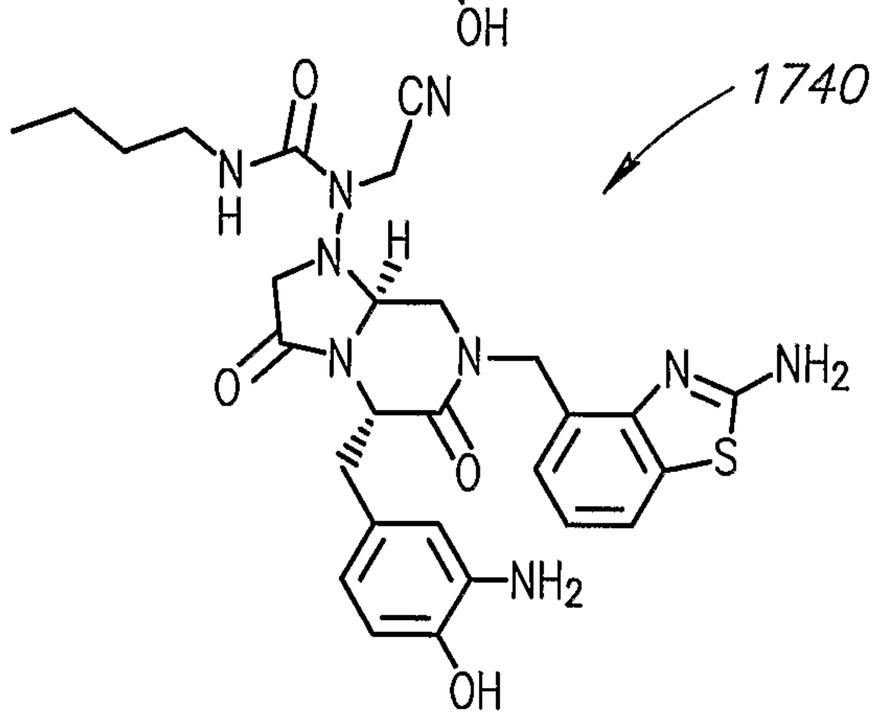

1736
F
O
CN
N
H
N
O
N
H
N
O
N
N
S
NH2
NH2
OH

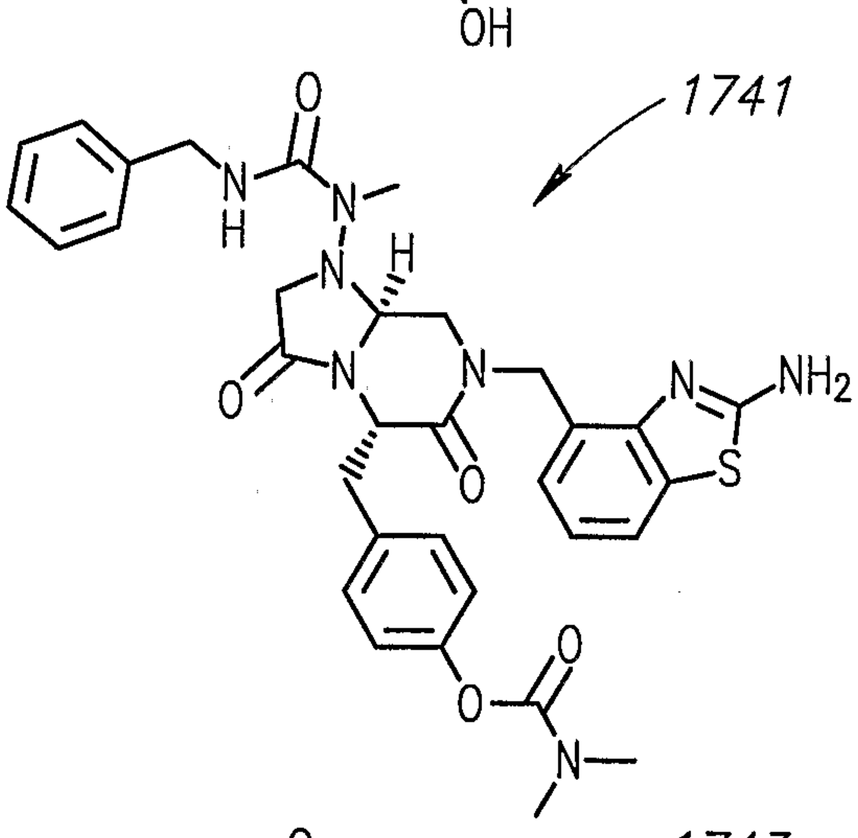
FIG.9T

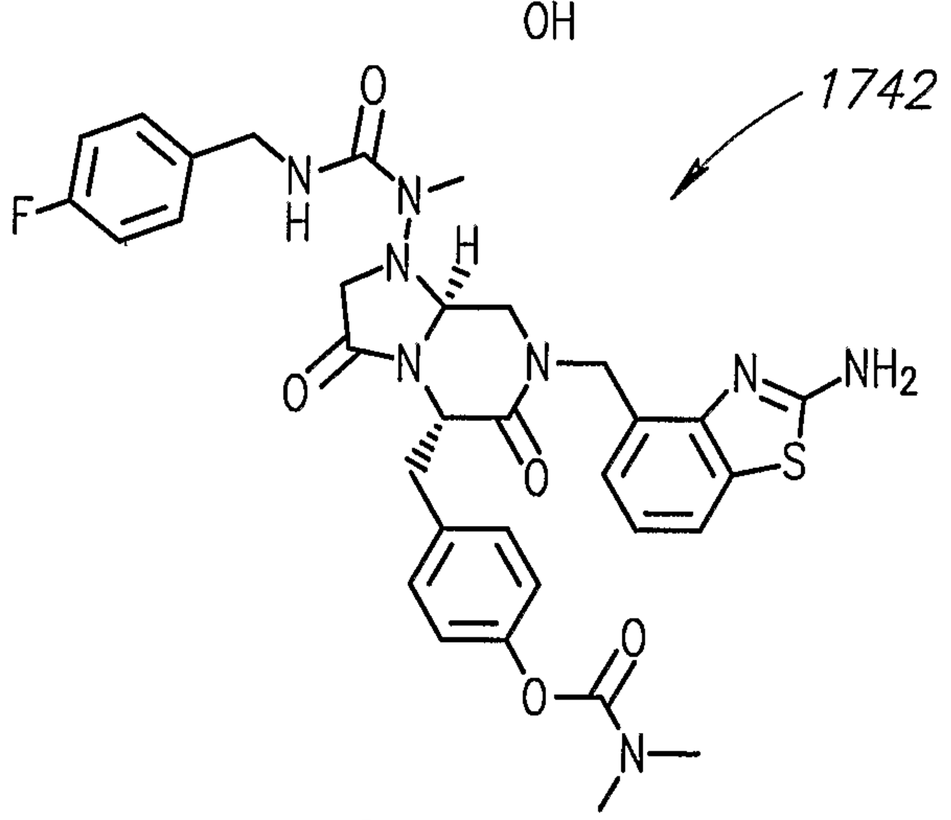

1737
MeO
O
CN
N
H
N
O
N
O
N
N
S
NH2
NH2
OH


1738
Cl
Cl
O
CN
N
H
N
O
N
O
N
N
S
NH2
NH2
OH


1739
O
CN
N
H
N
O
N
O
N
N
S
NH2
NH2
OH


1740
O
CN
N
H
N
O
N
O
N
N
S
NH2
NH2
OH


1741
O
N
H
N
N
O
N
O
N
N
S
NH2
O
O
N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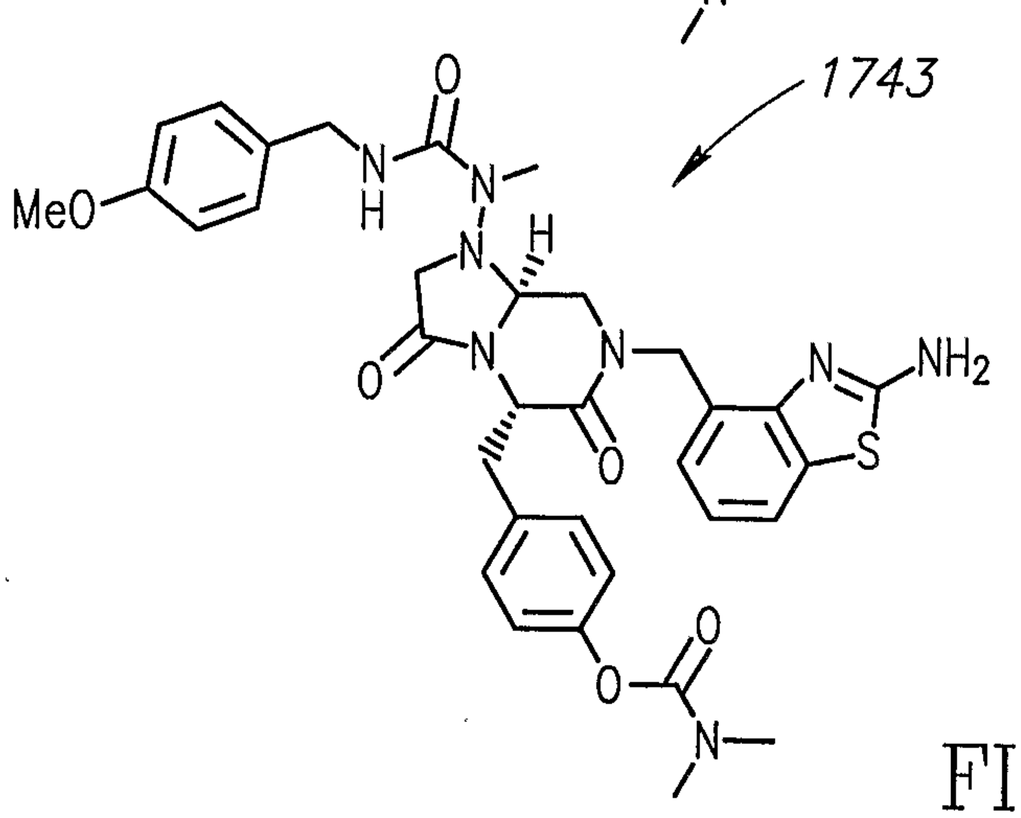
F
O
N
H
N
N
O
N
O
N
N
S
NH2
O
O
N


1743
MeO
O
N
H
N
N
O
N
O
N
N
S
NH2
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O
N

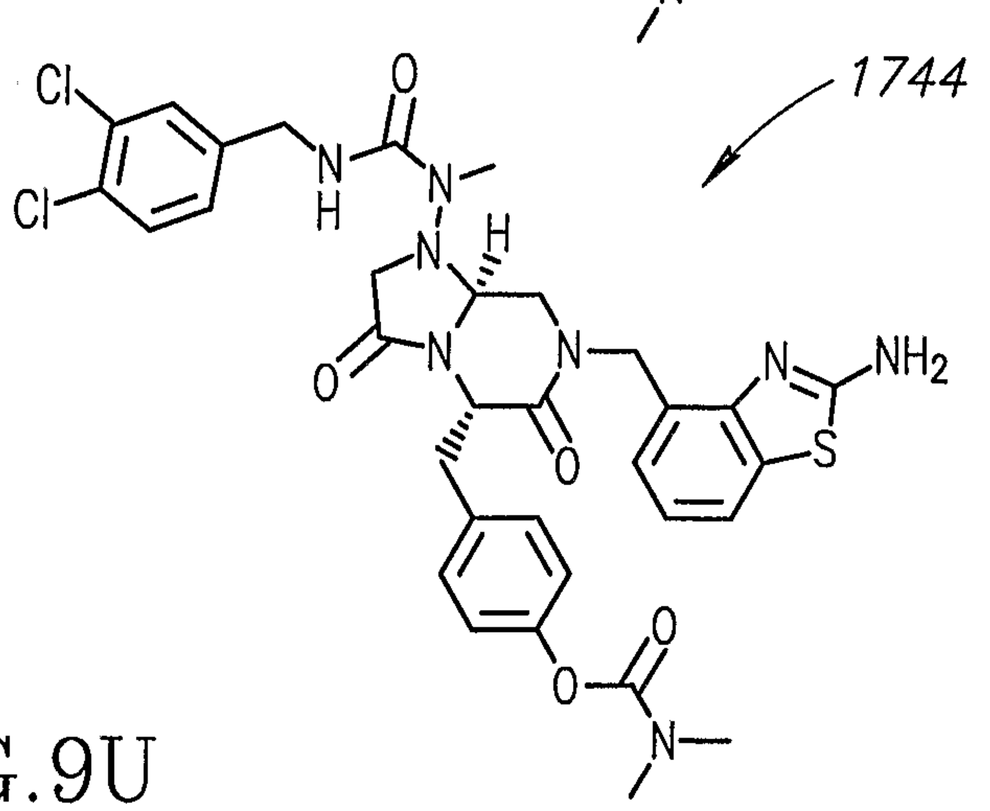
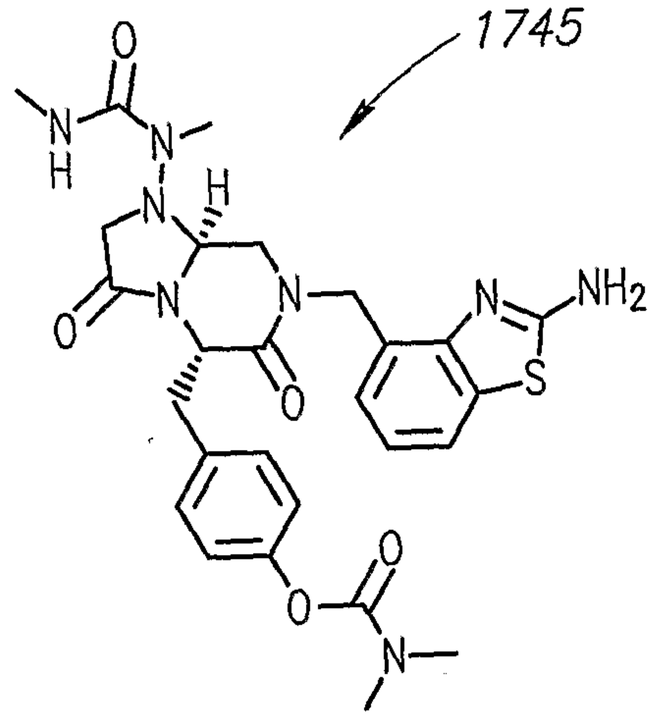
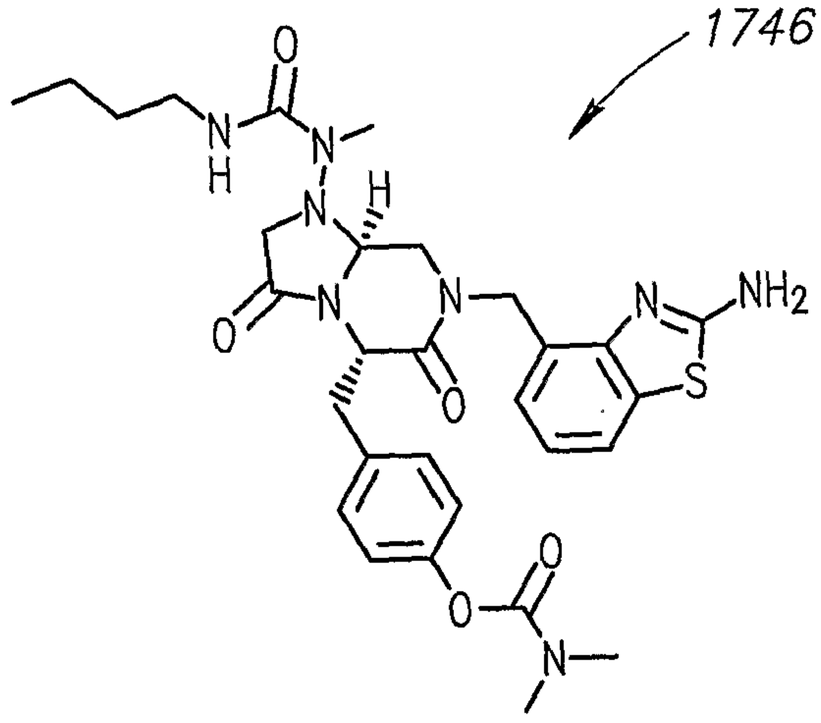

1744
Cl
Cl
O
N
H
N
N
O
N
O
N
N
S
NH2
O
O
N

FIG.9U

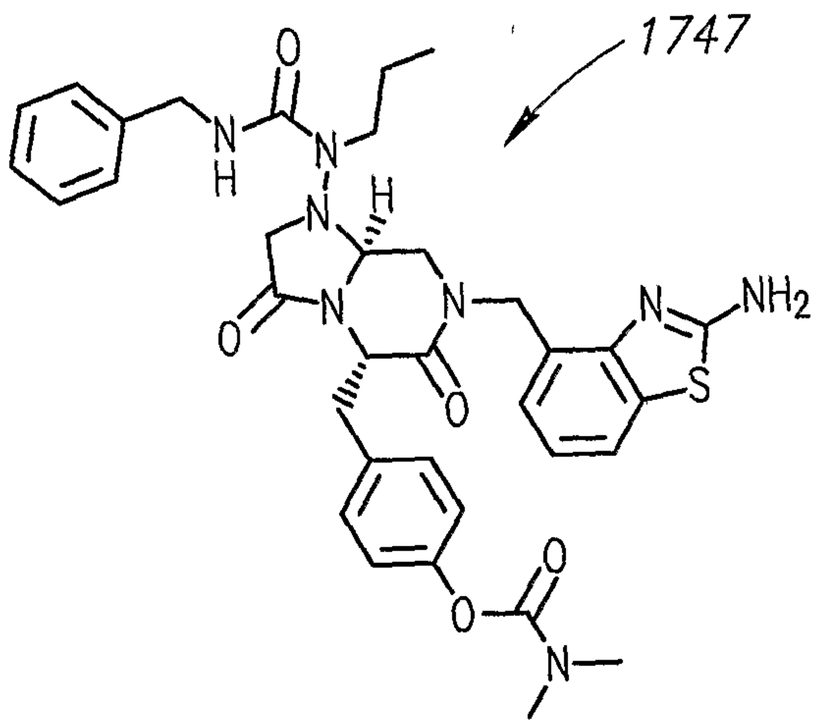
1745



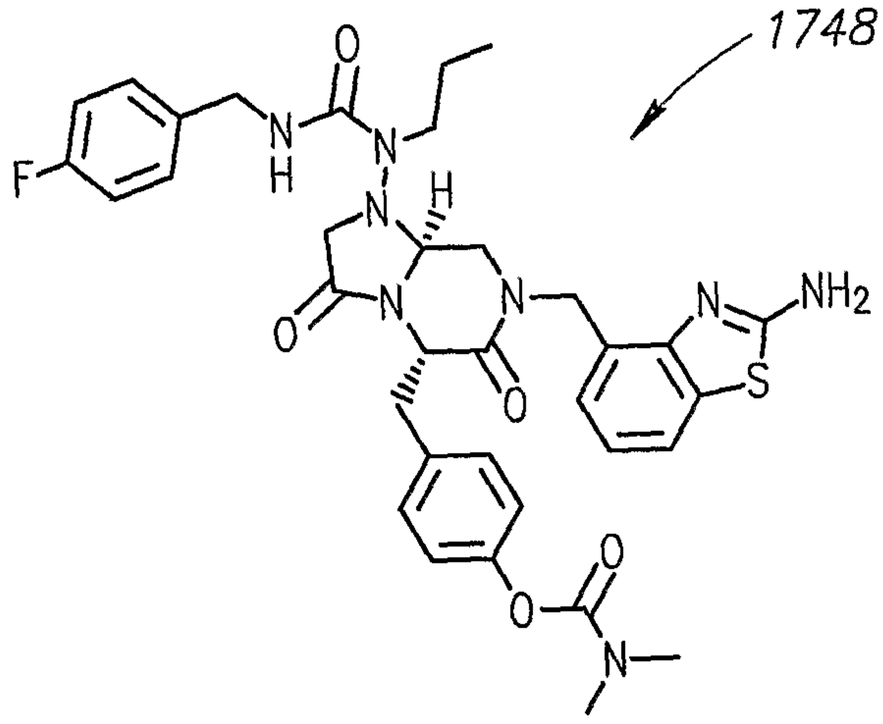
1746



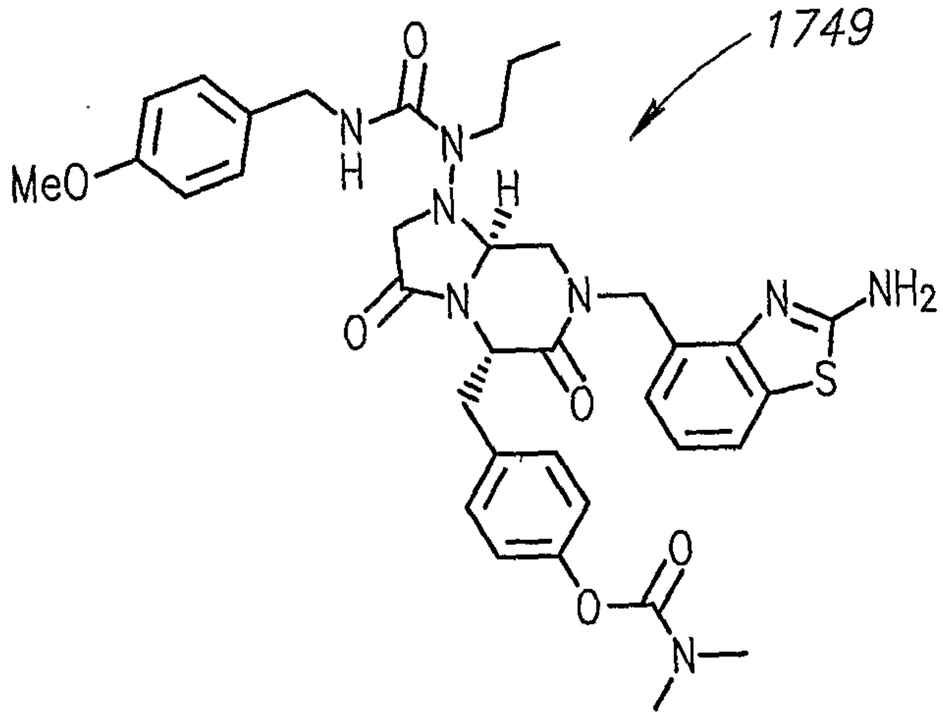
1747



1748



1749



1750

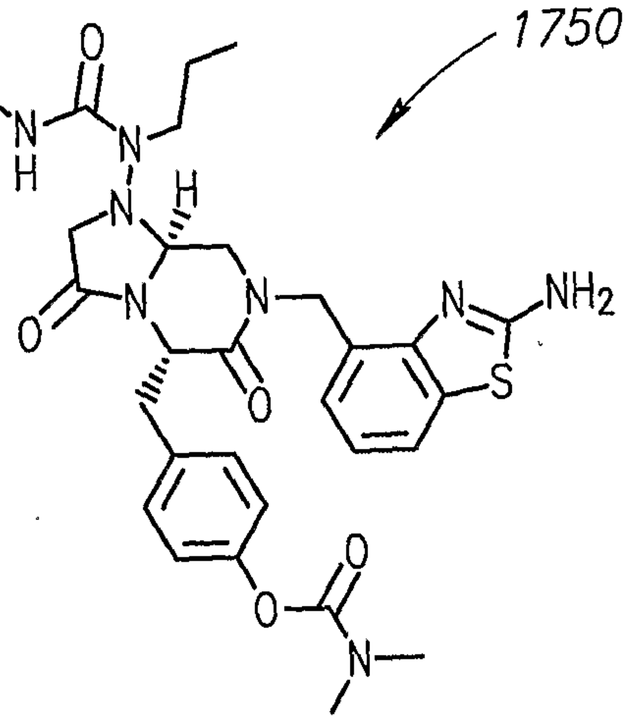
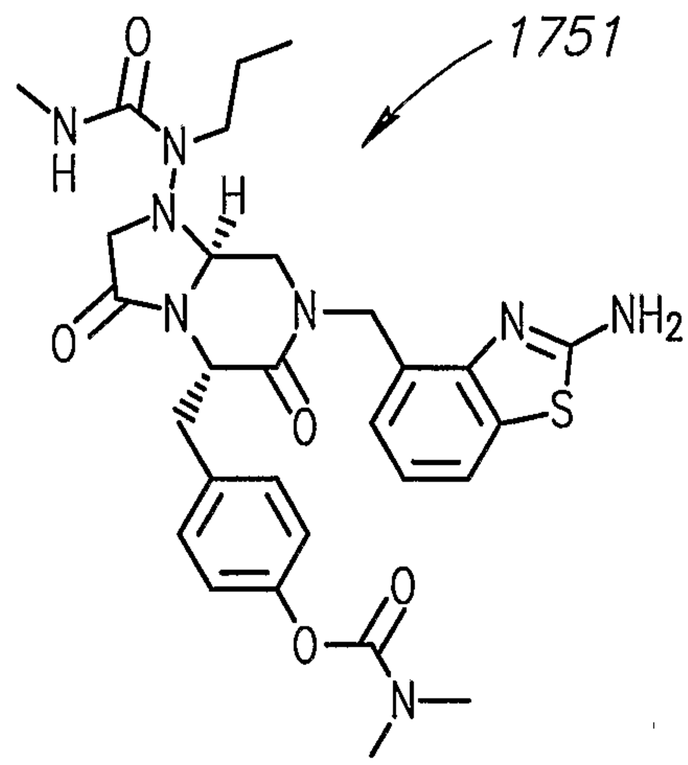
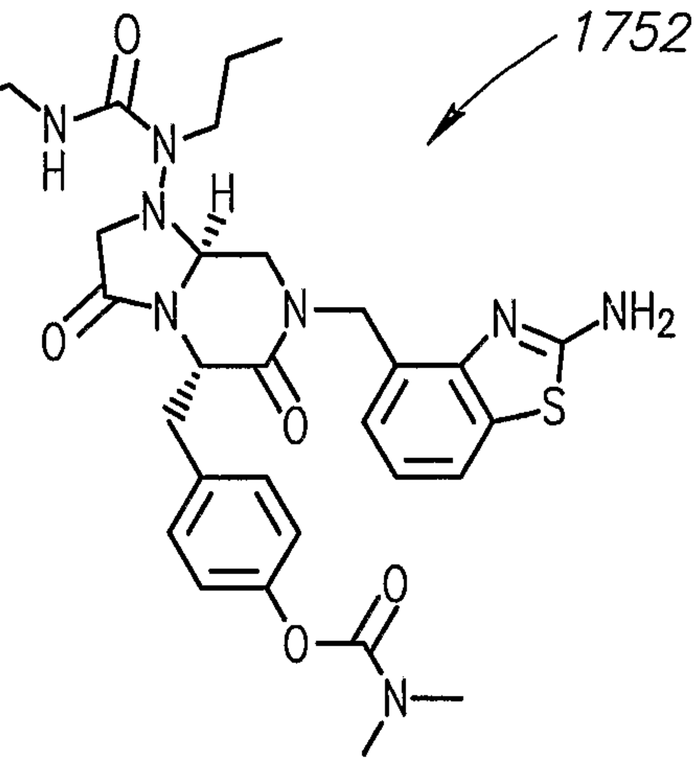
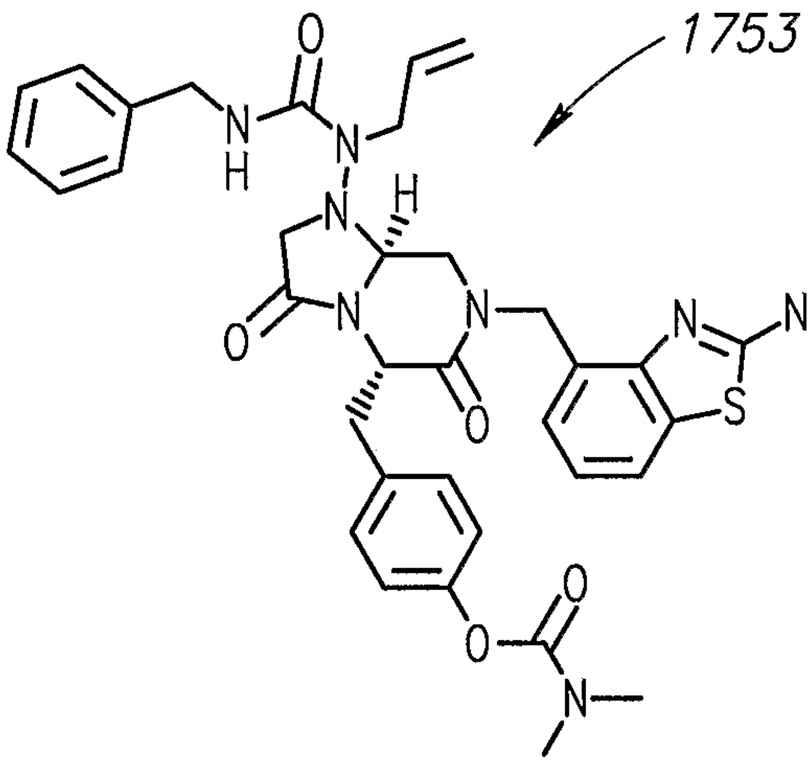
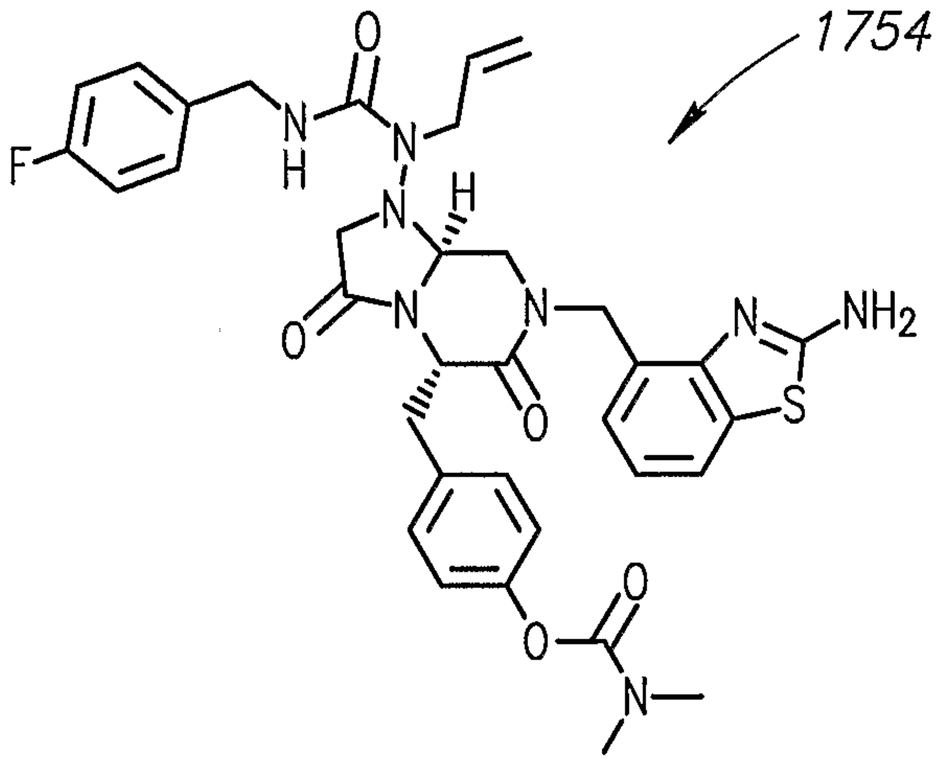


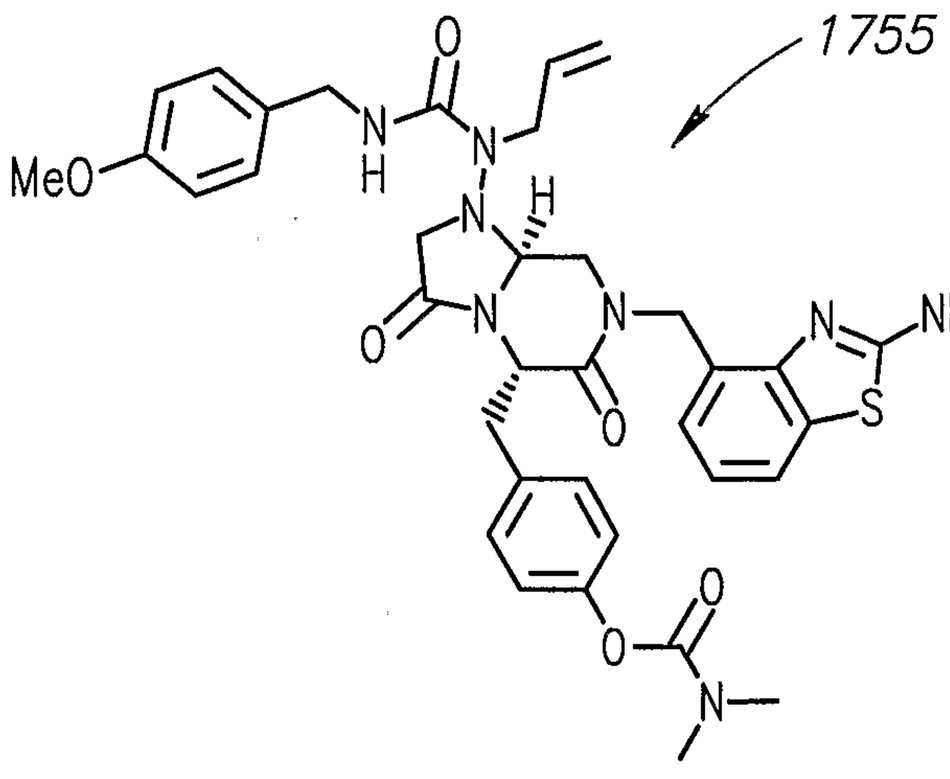
FIG.9V











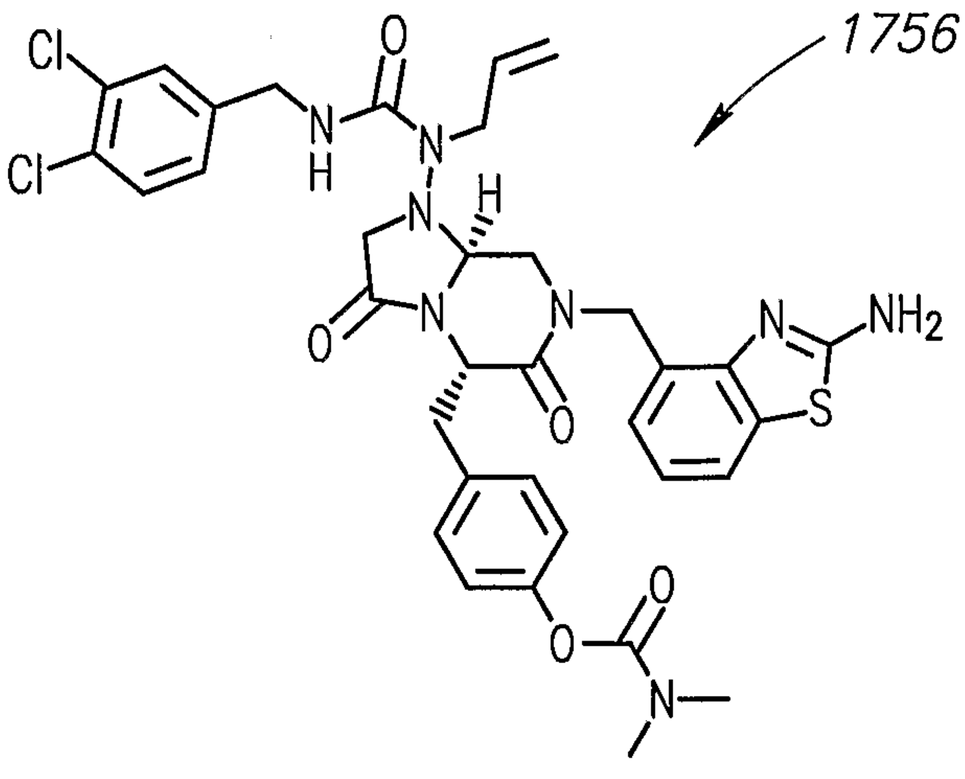
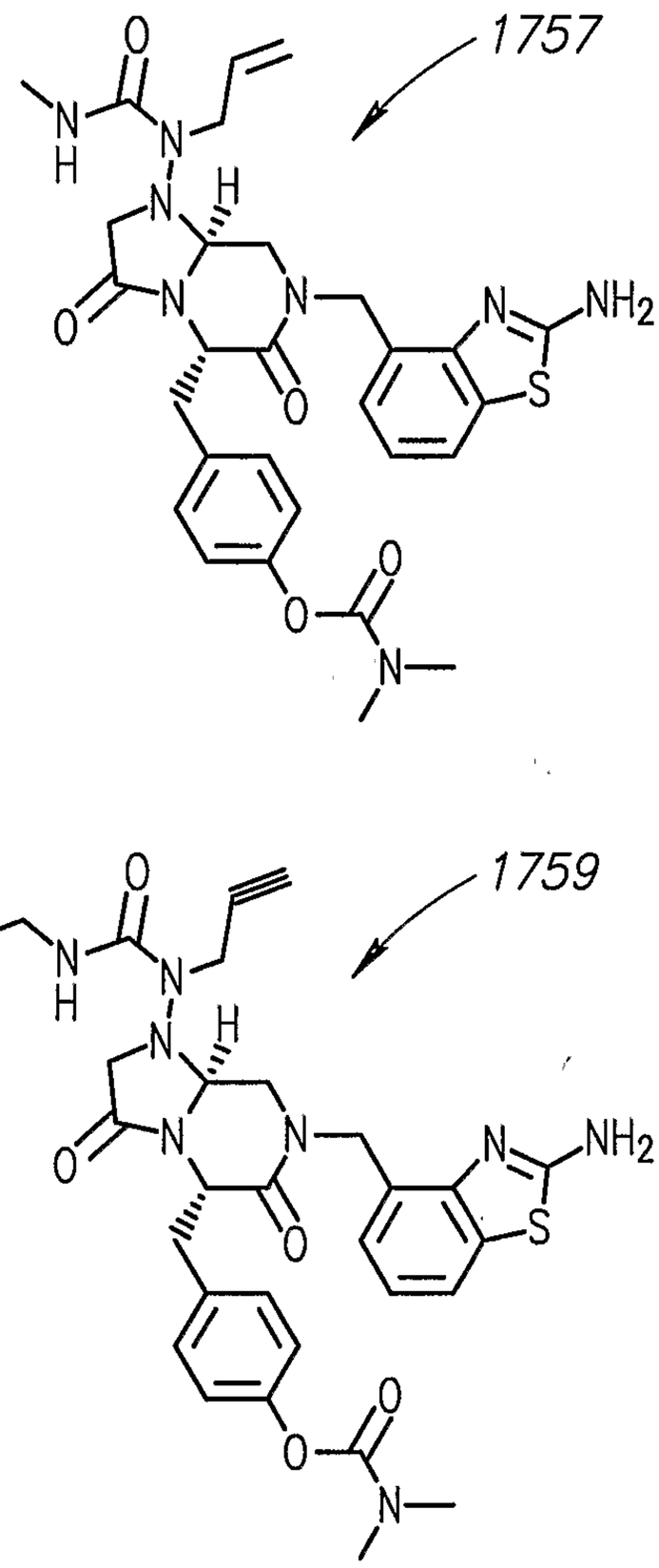
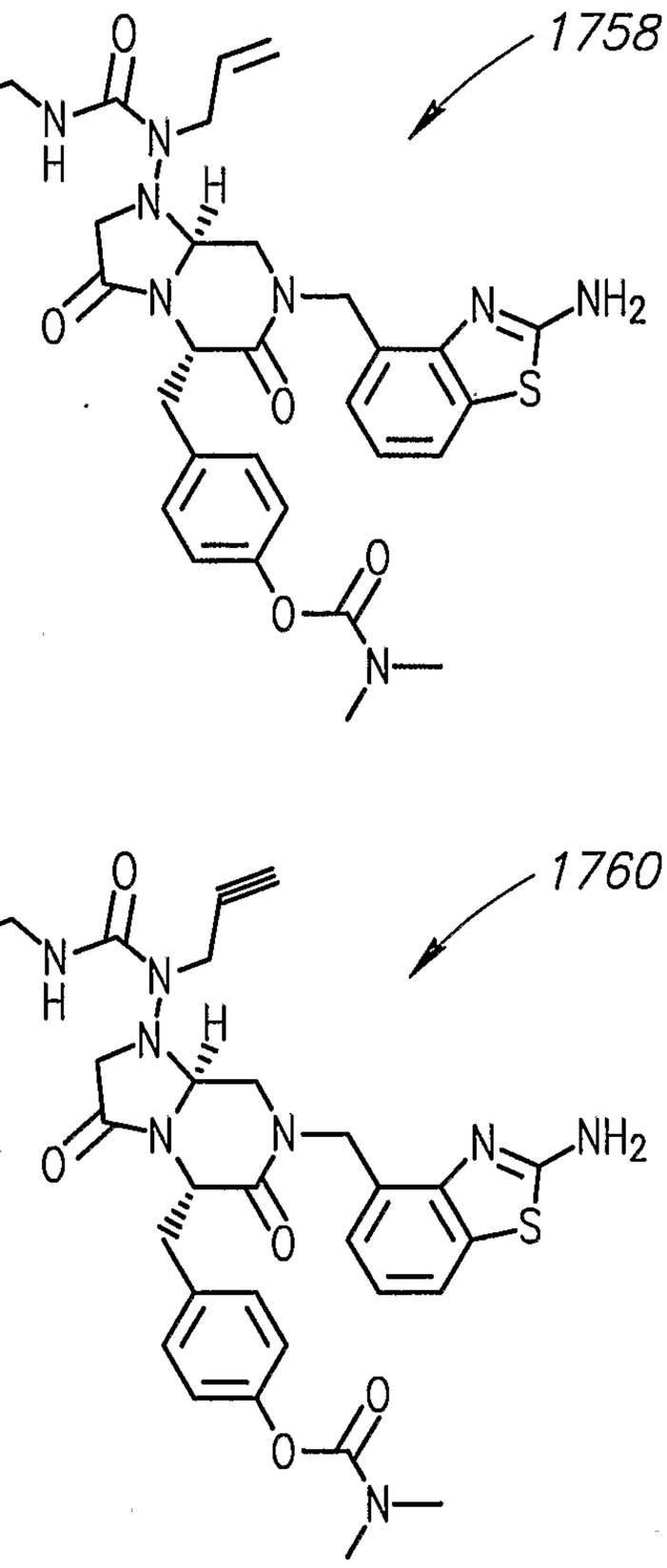
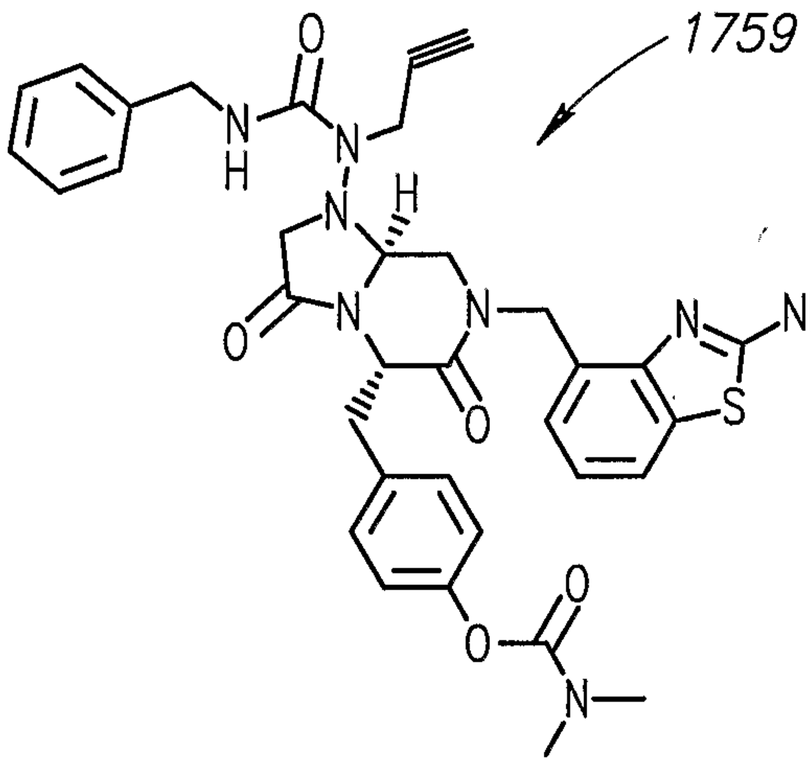
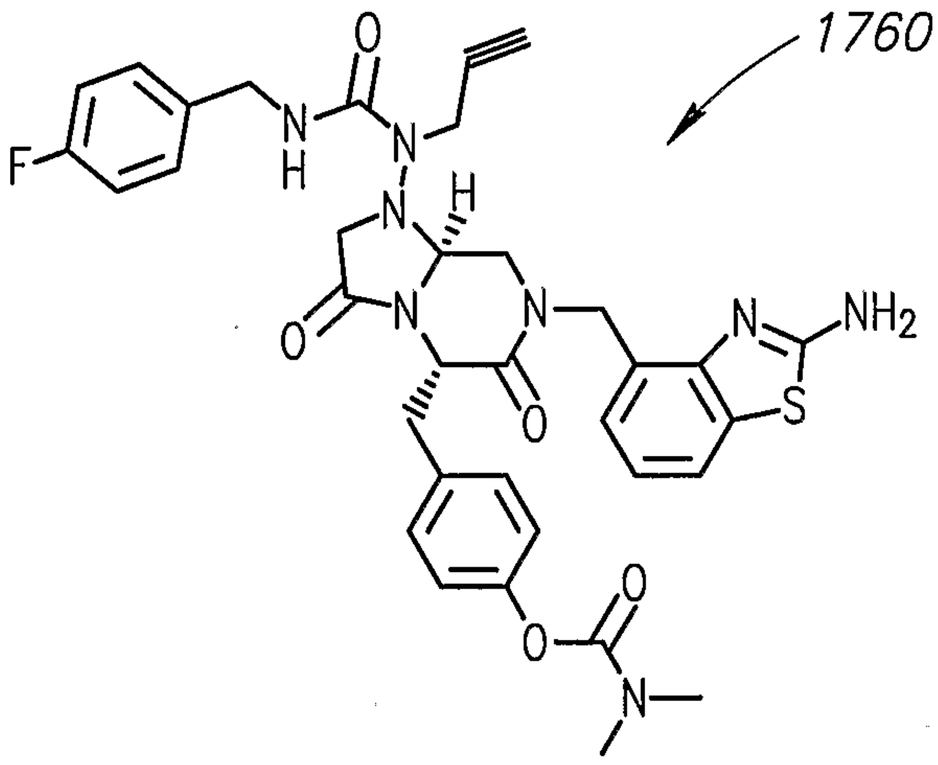


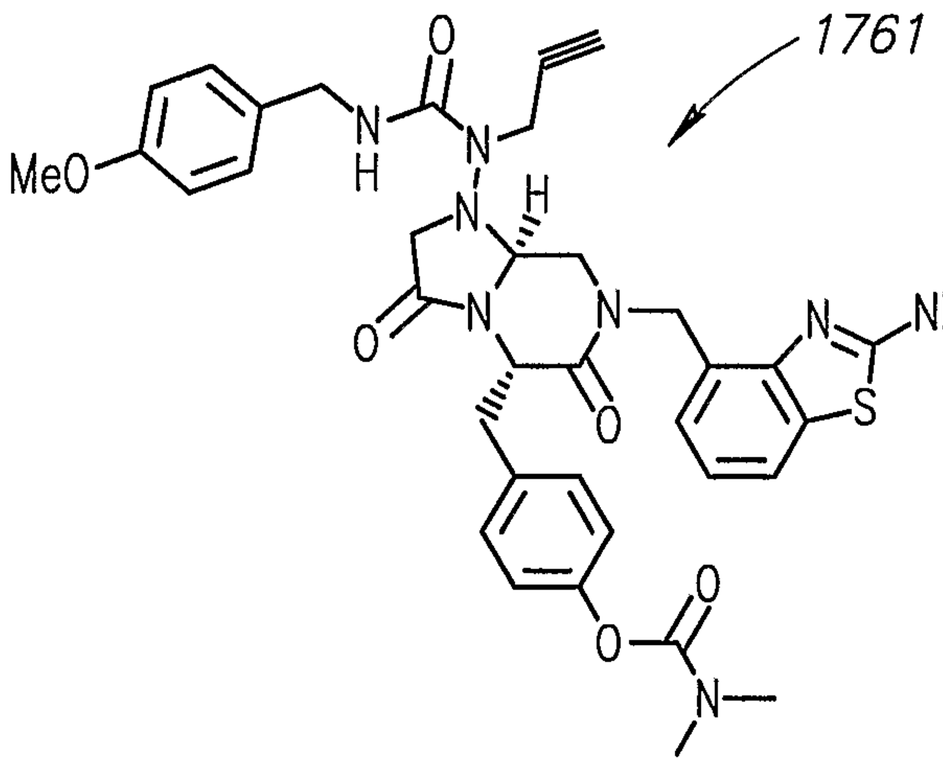
FIG.9W











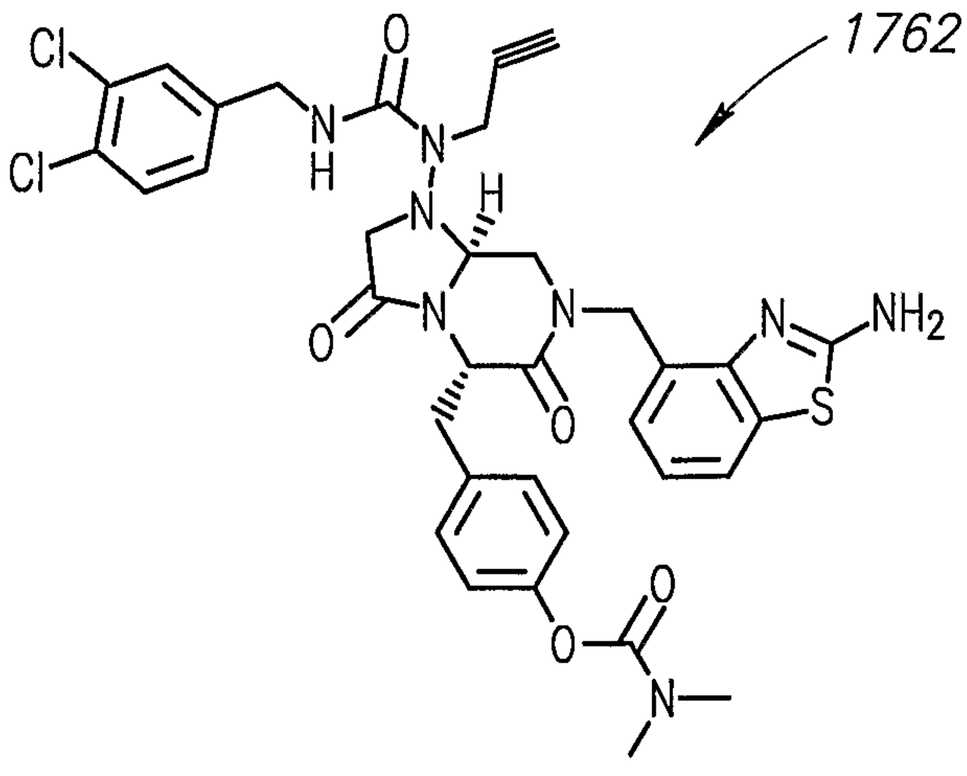
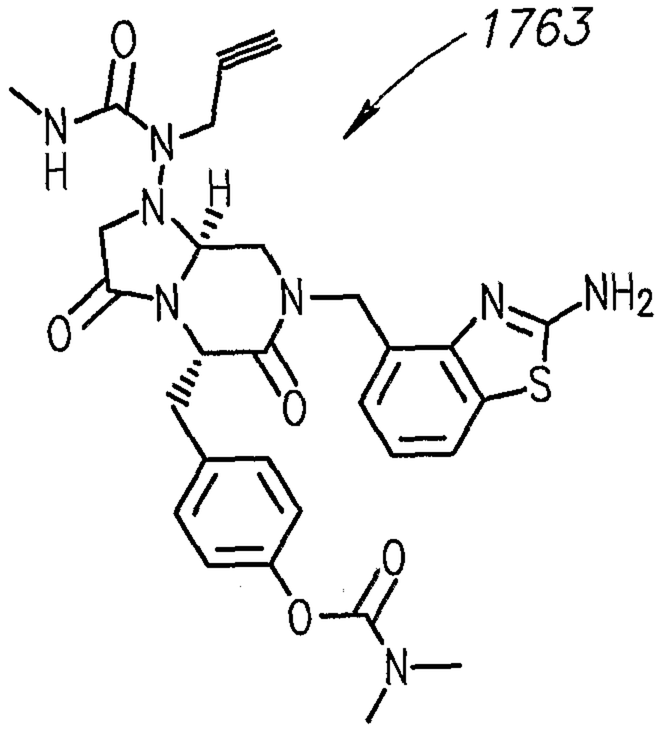
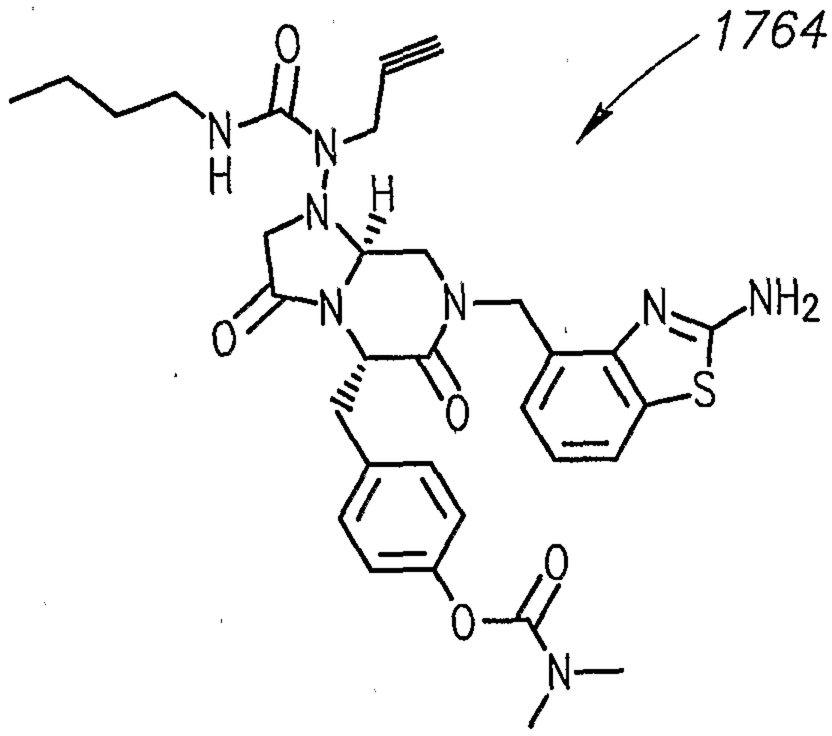


FIG.9X

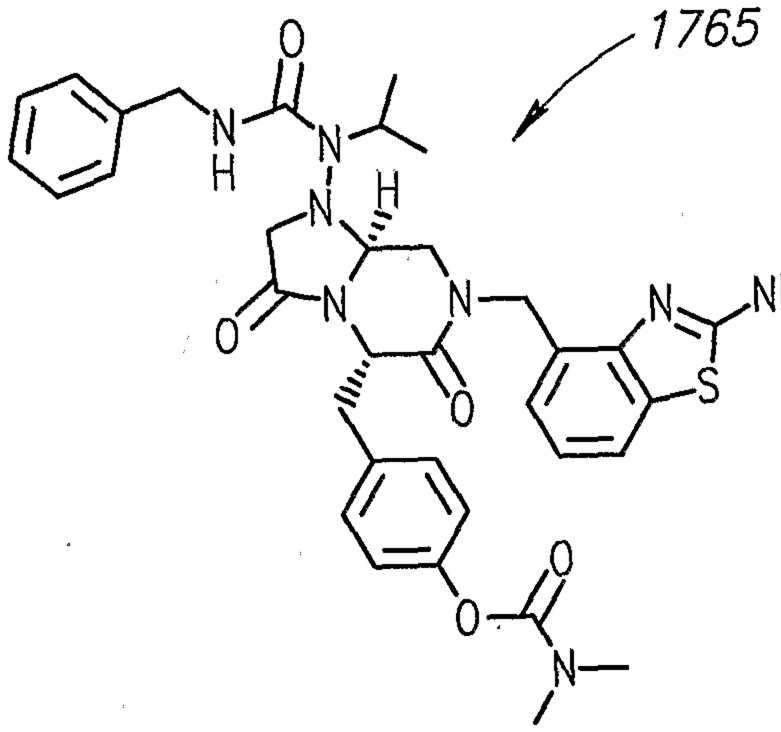
1763



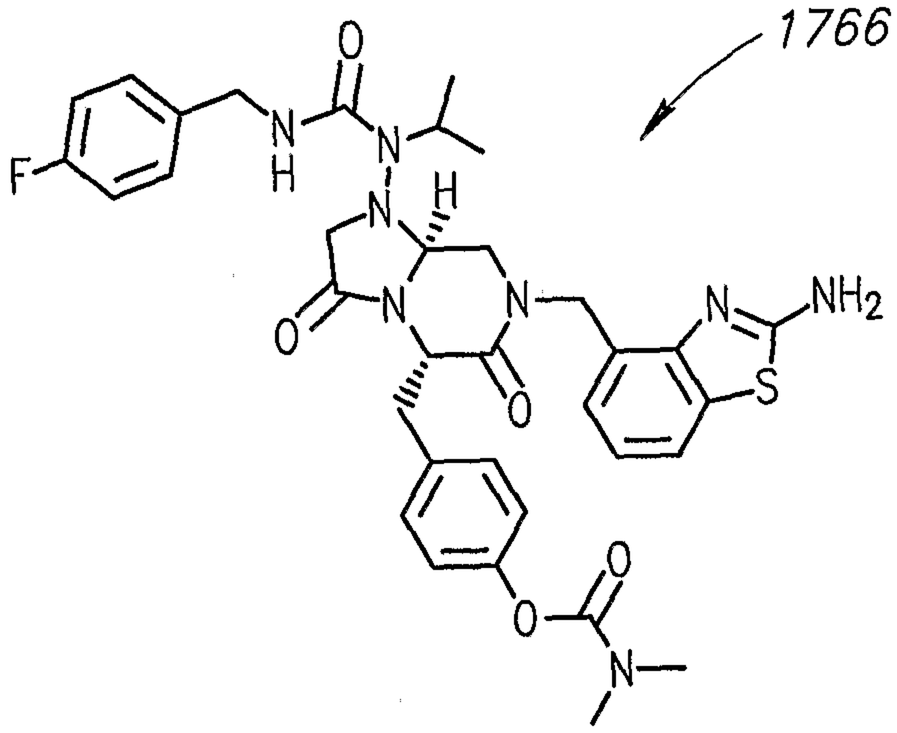
1764



1765



1766



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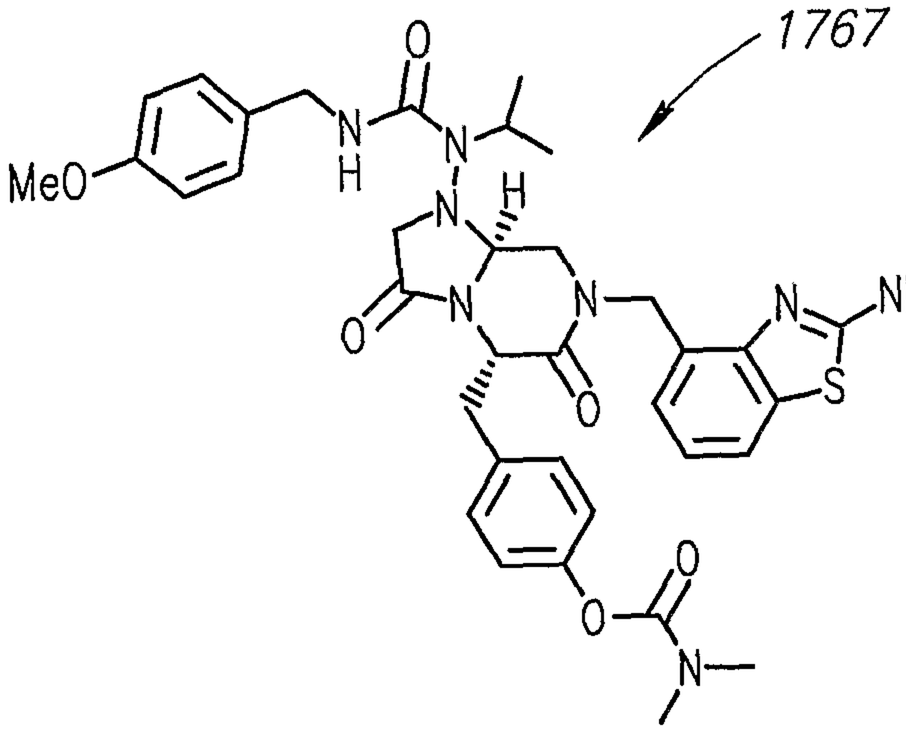

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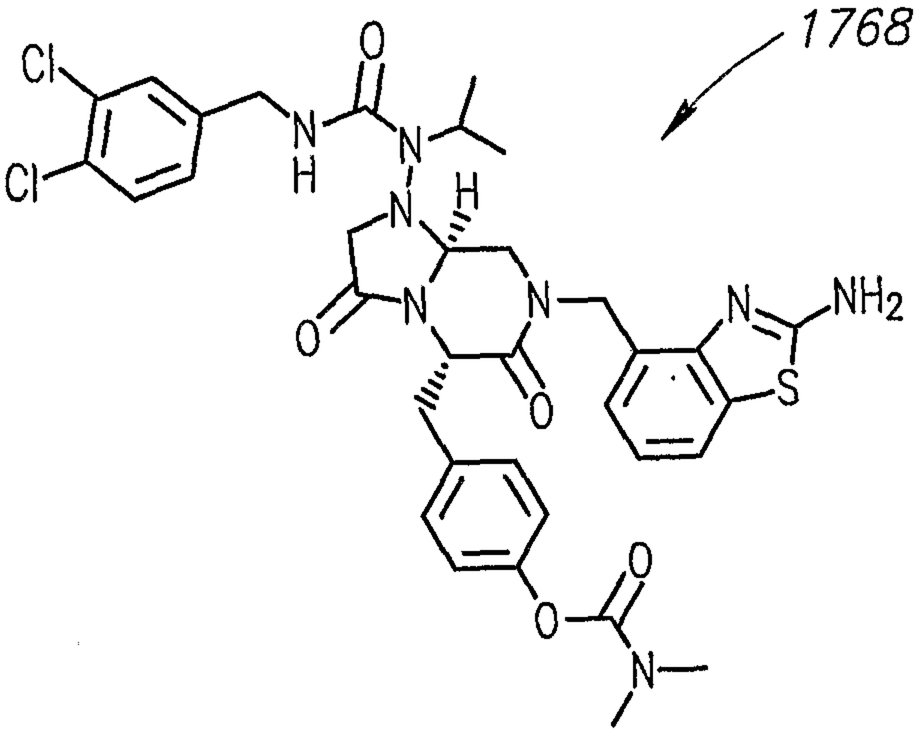
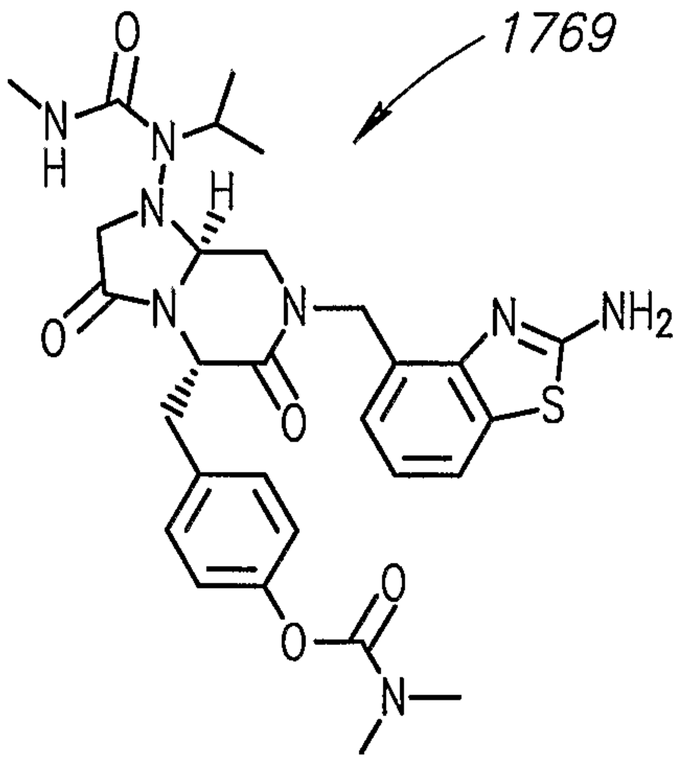


FIG.9Y

1769



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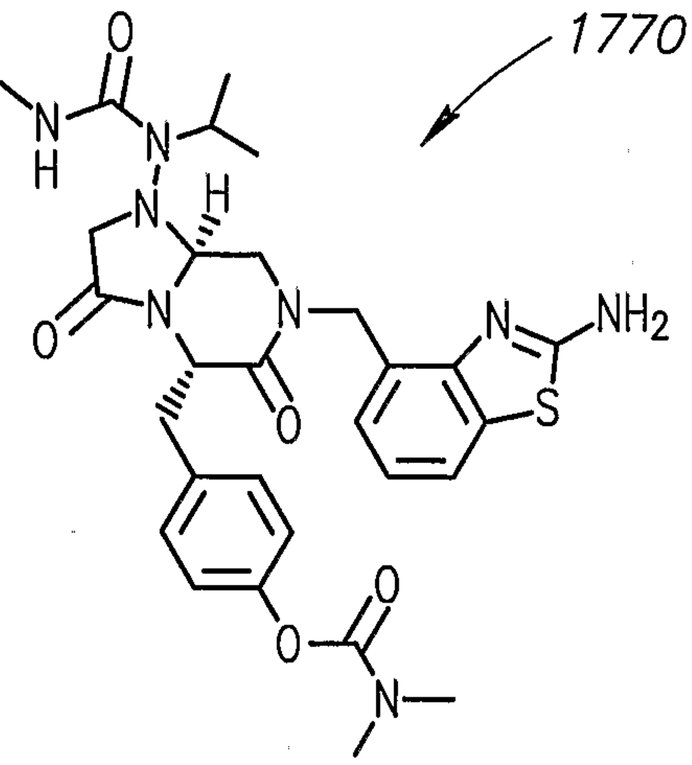

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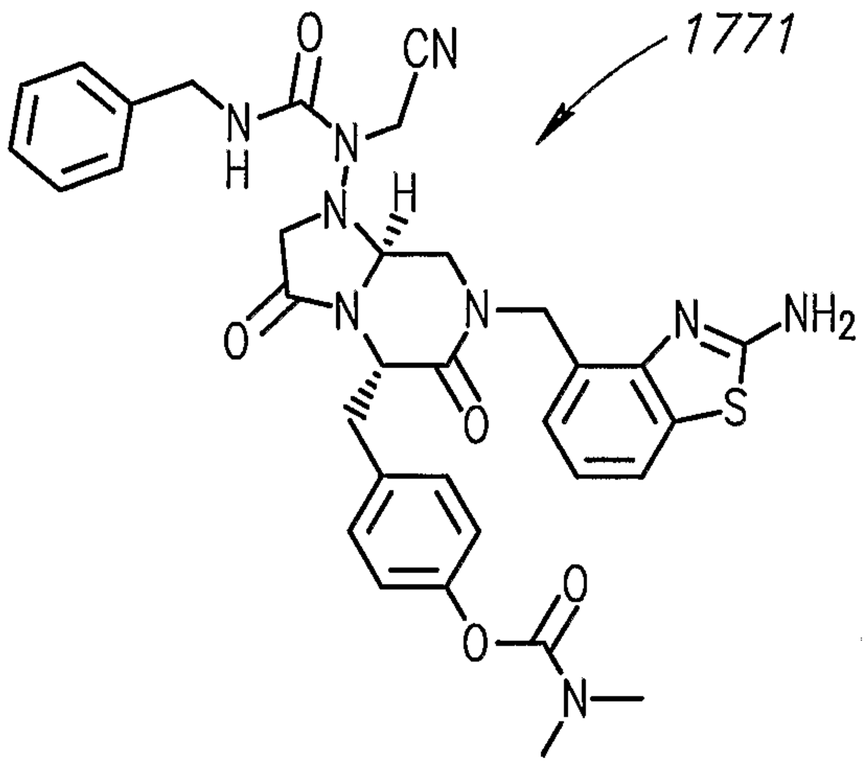

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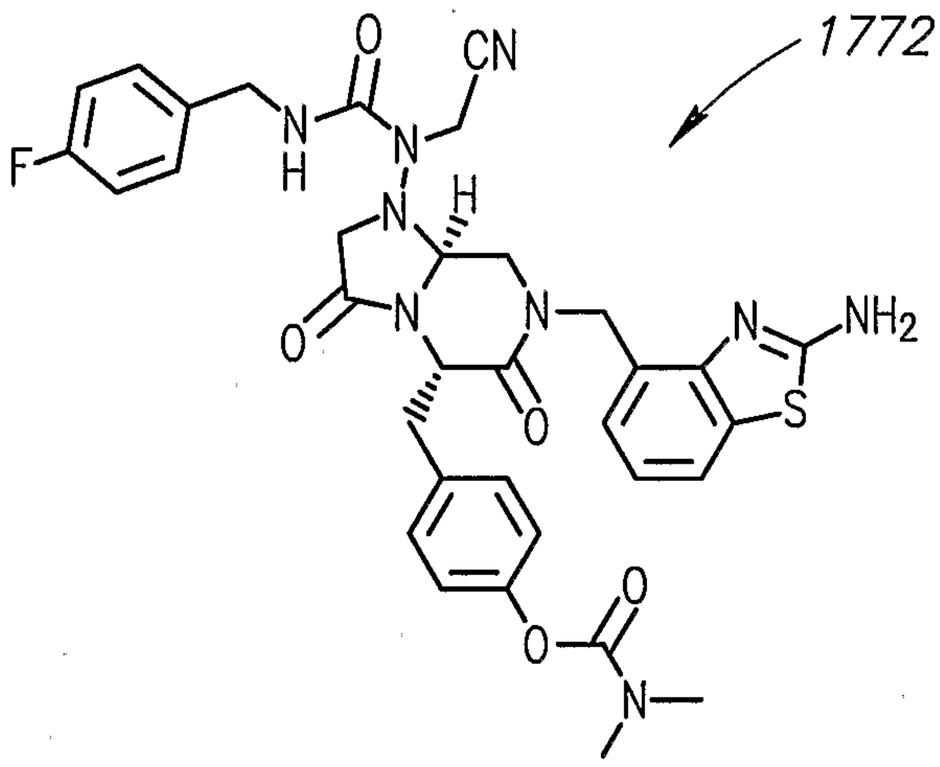

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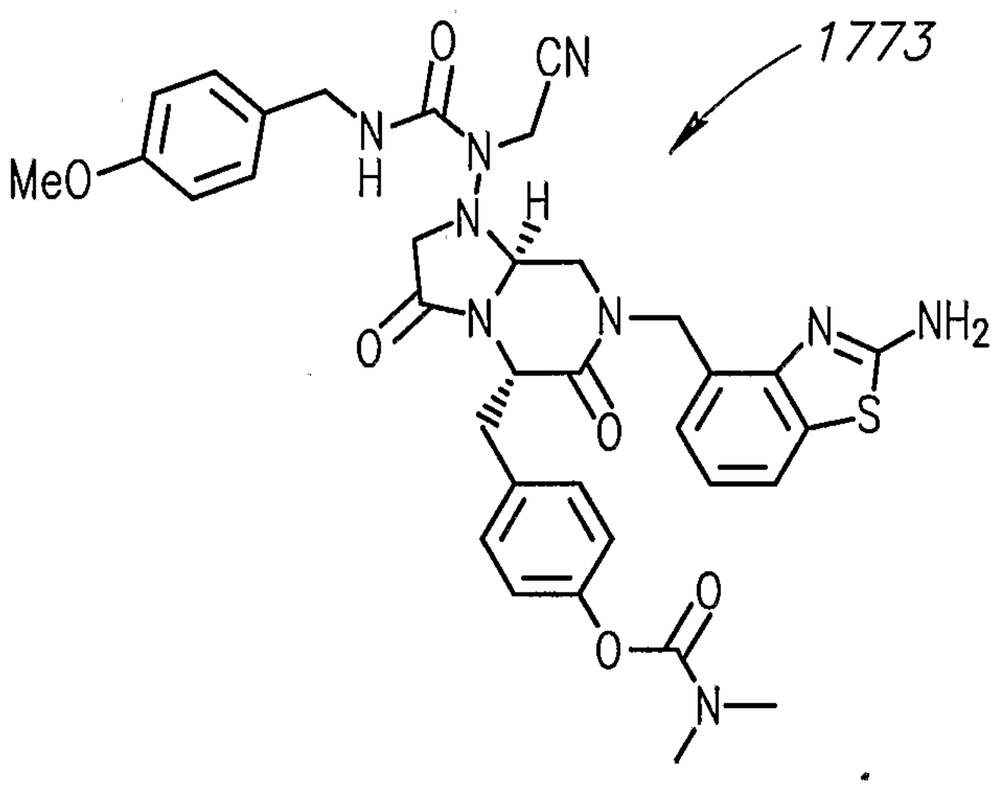

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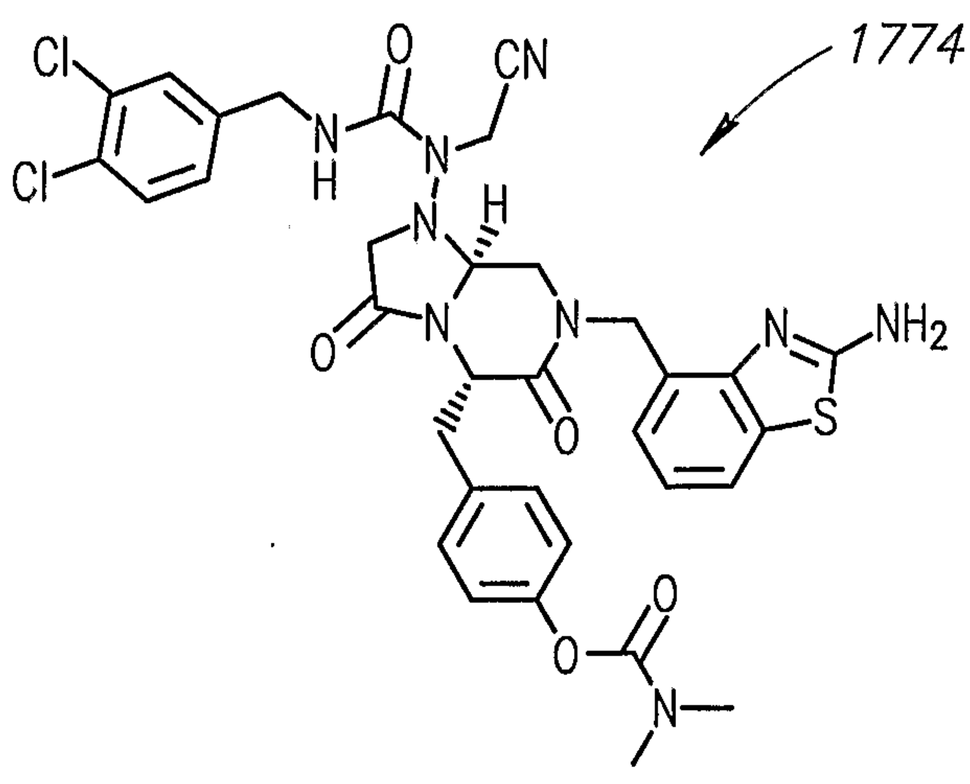
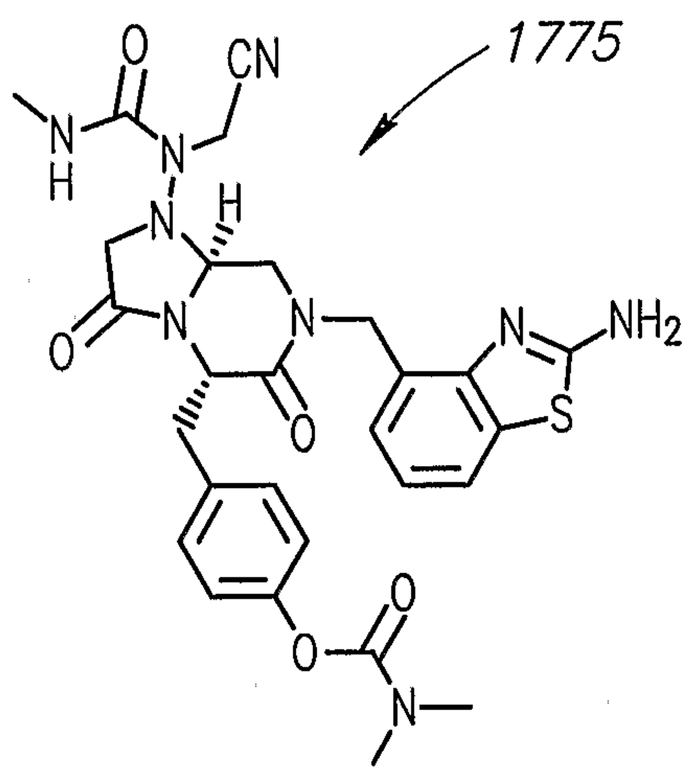
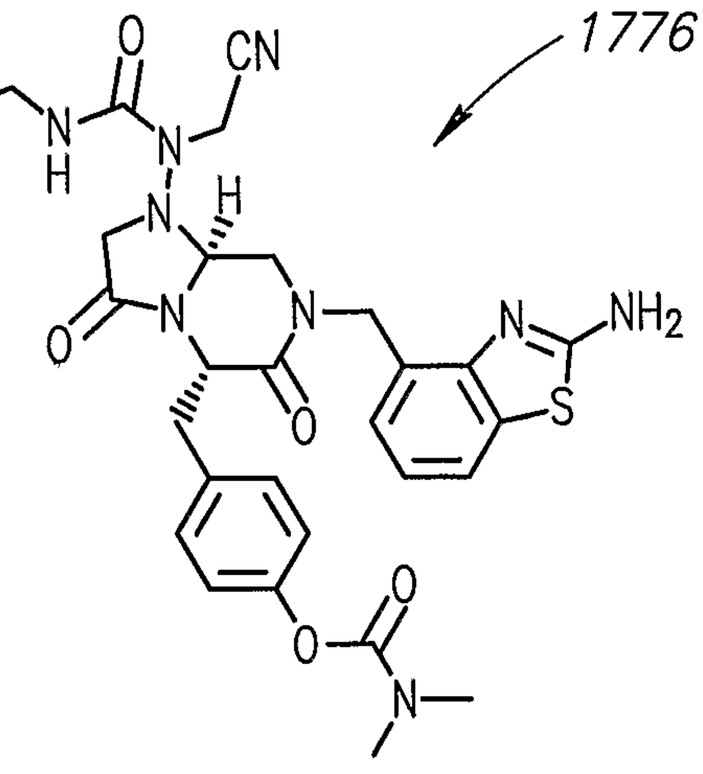
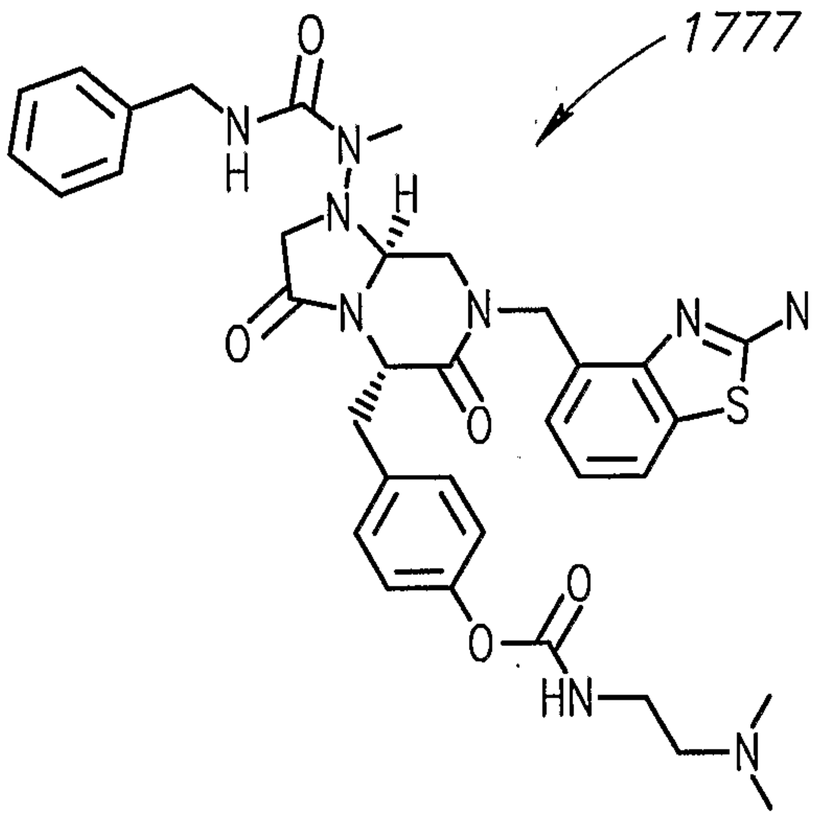
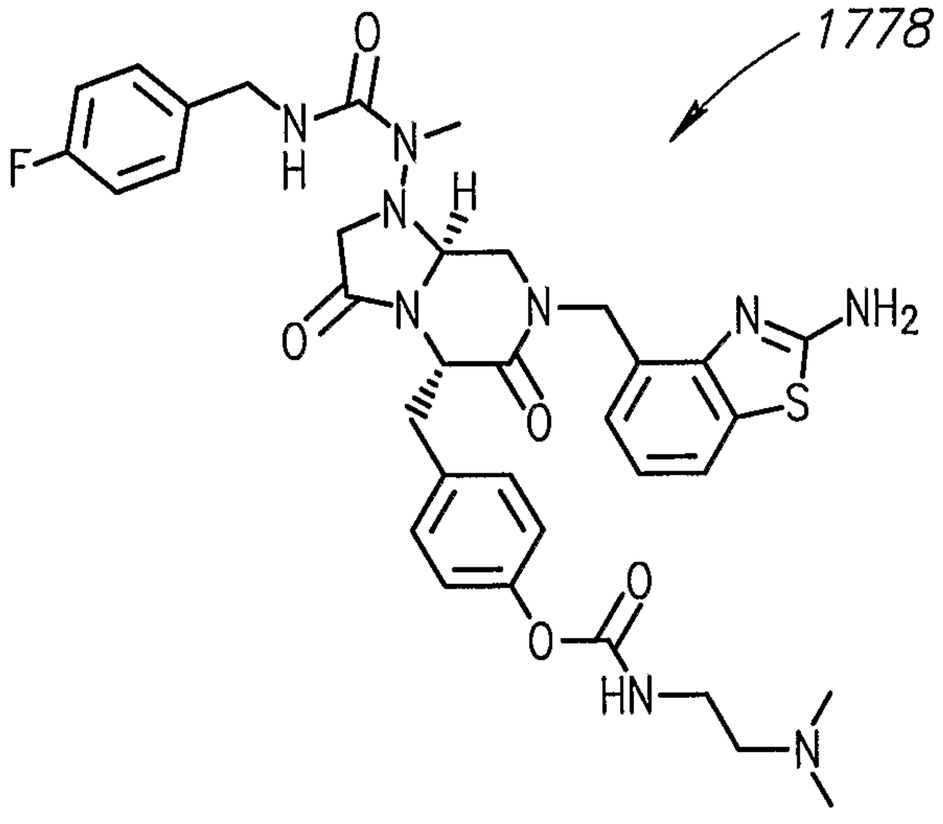


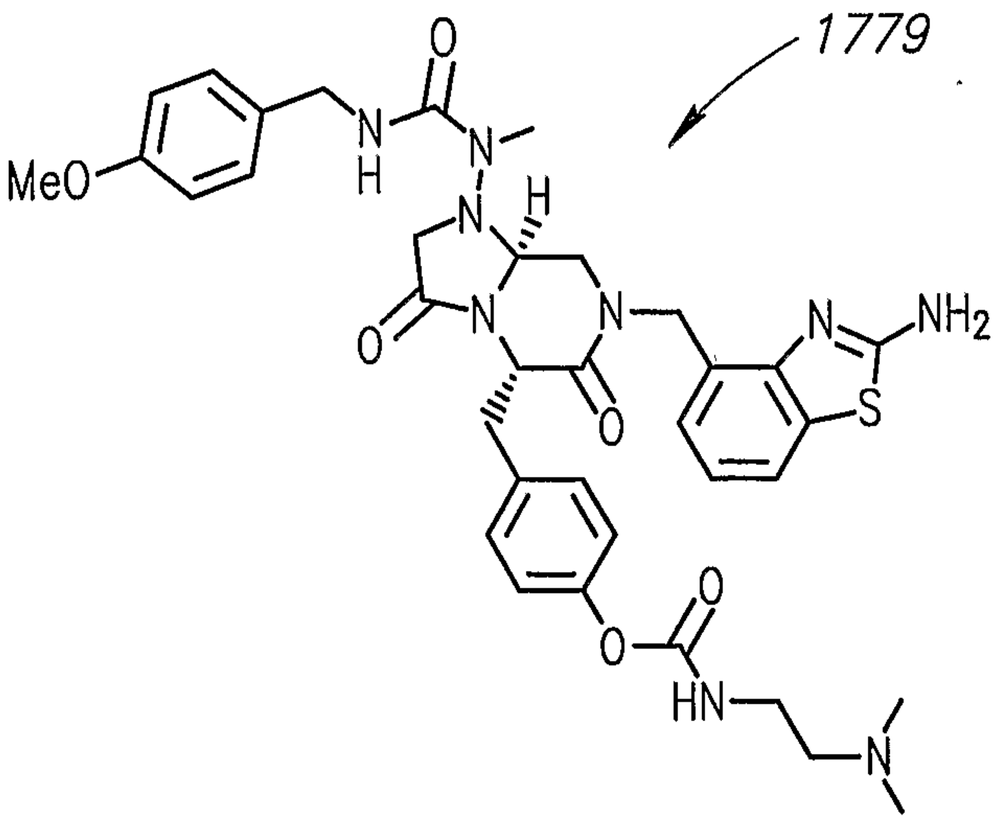
FIG.9Z











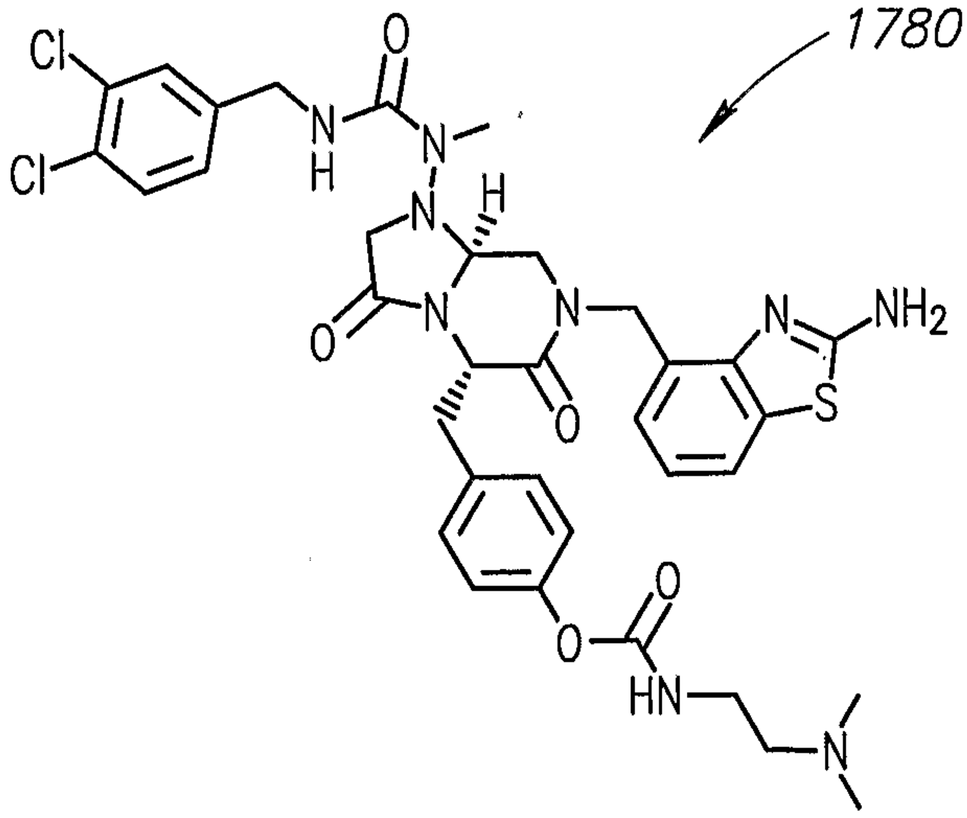
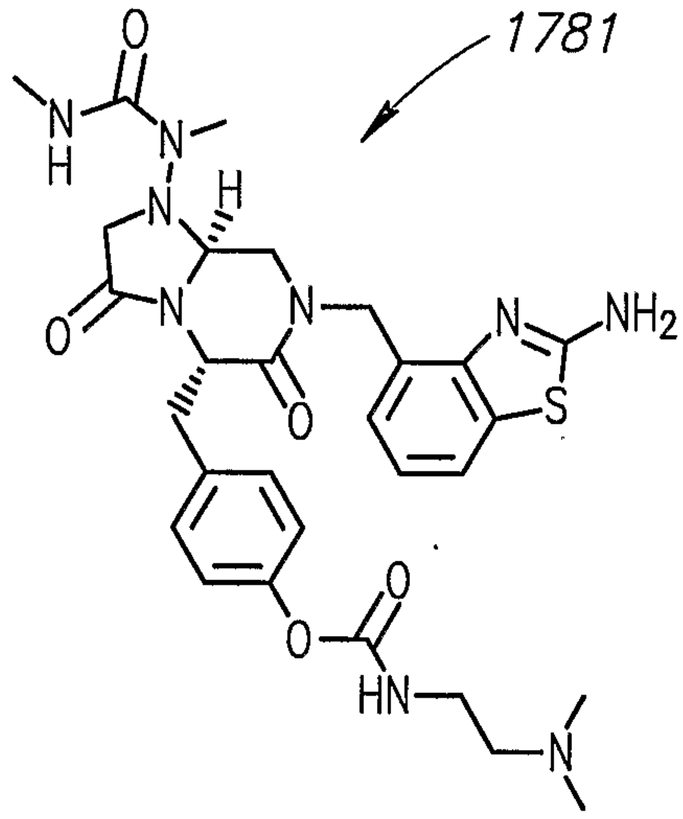


FIG.9AA

1781



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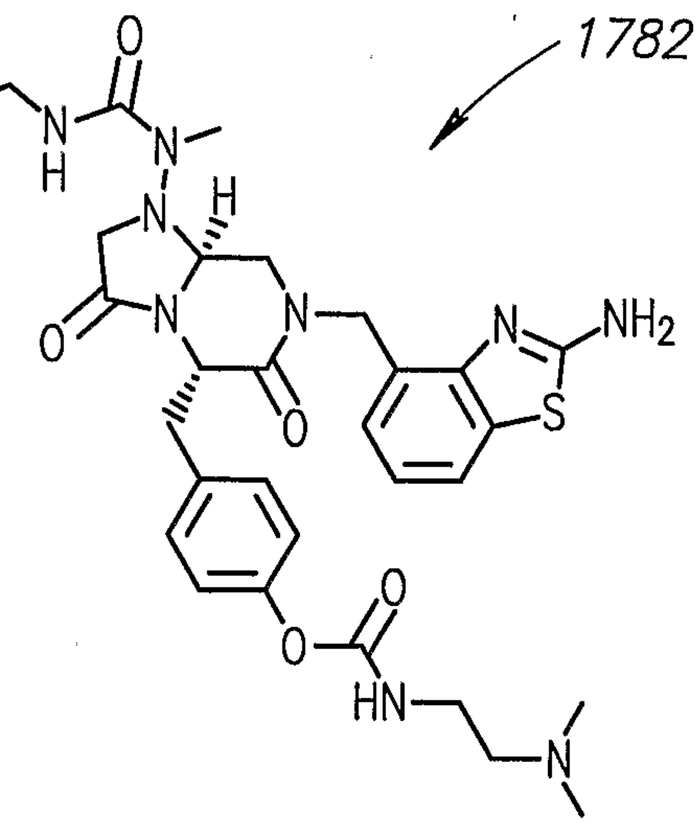

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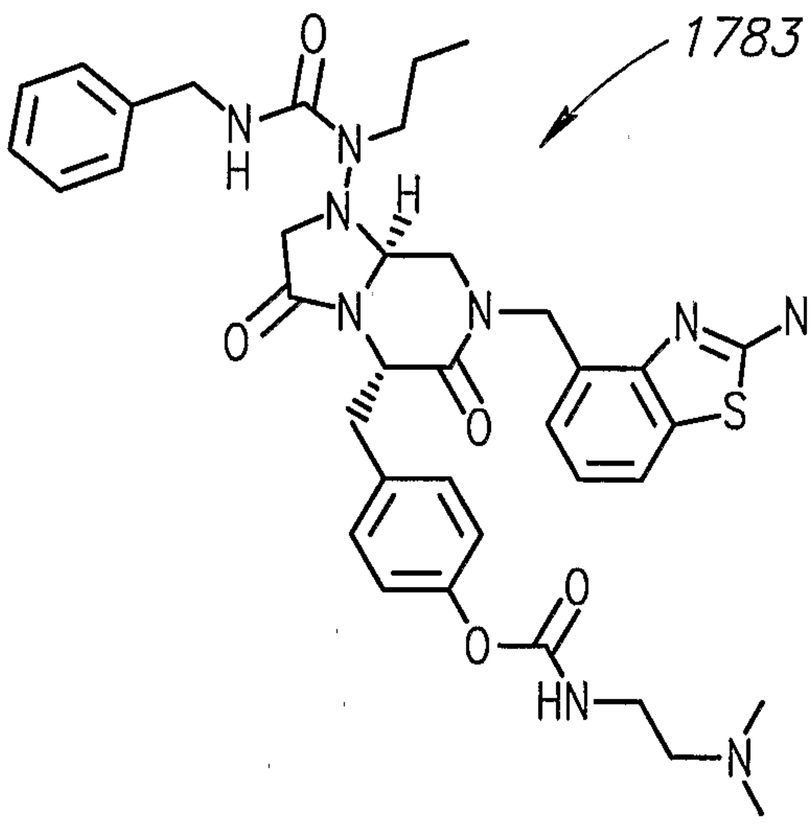

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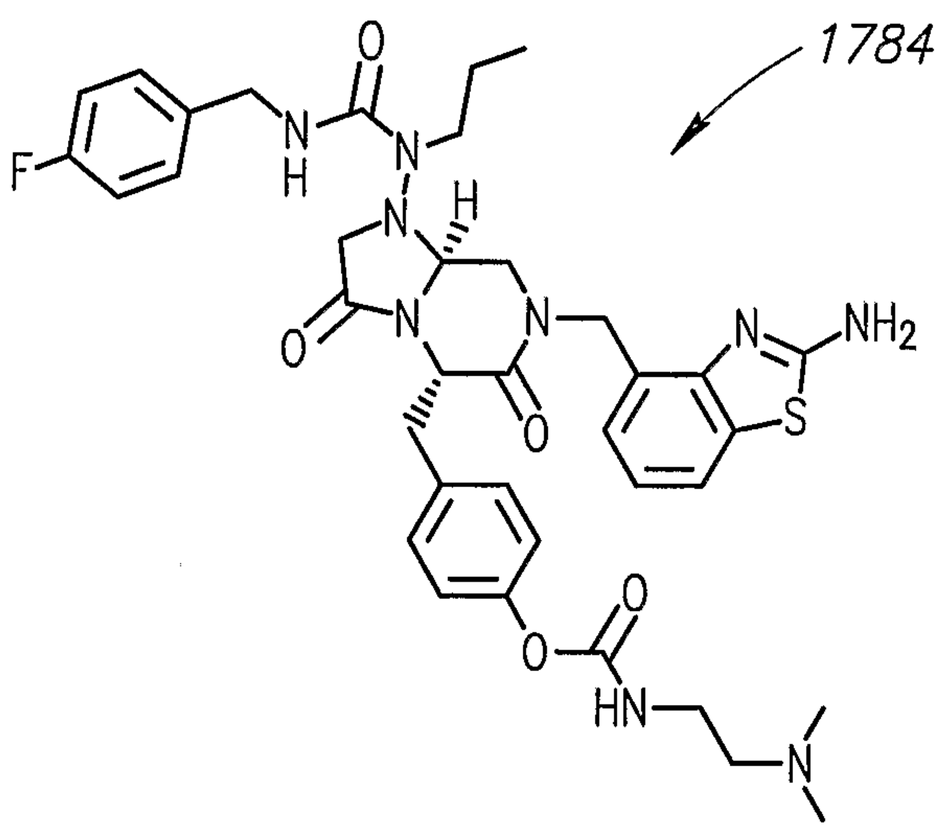

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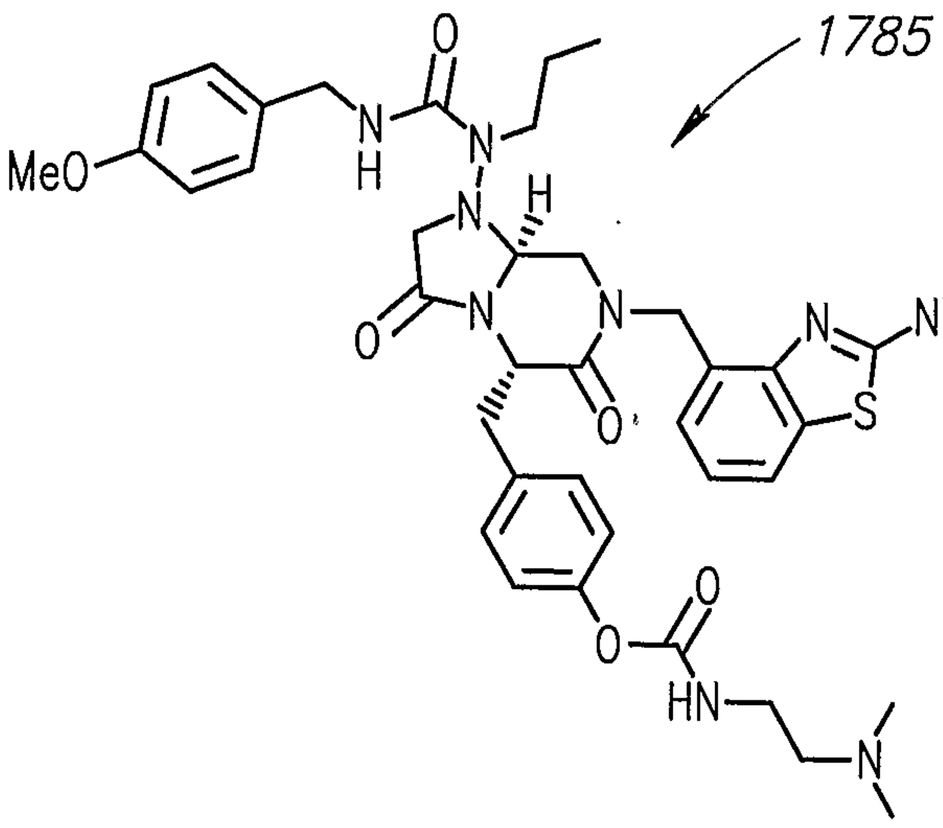

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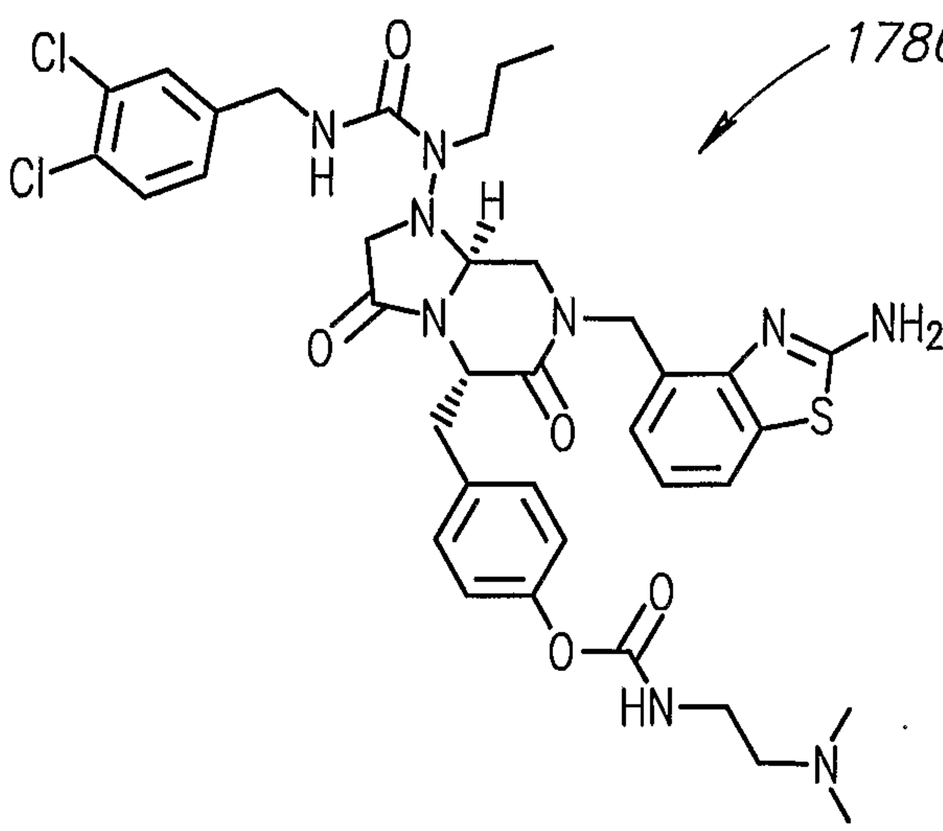
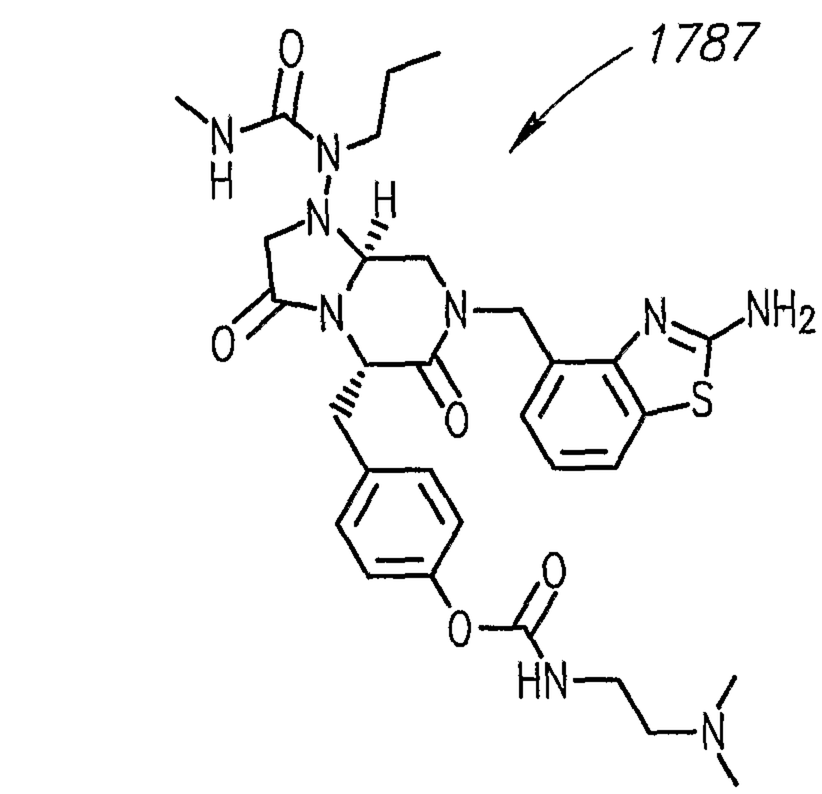
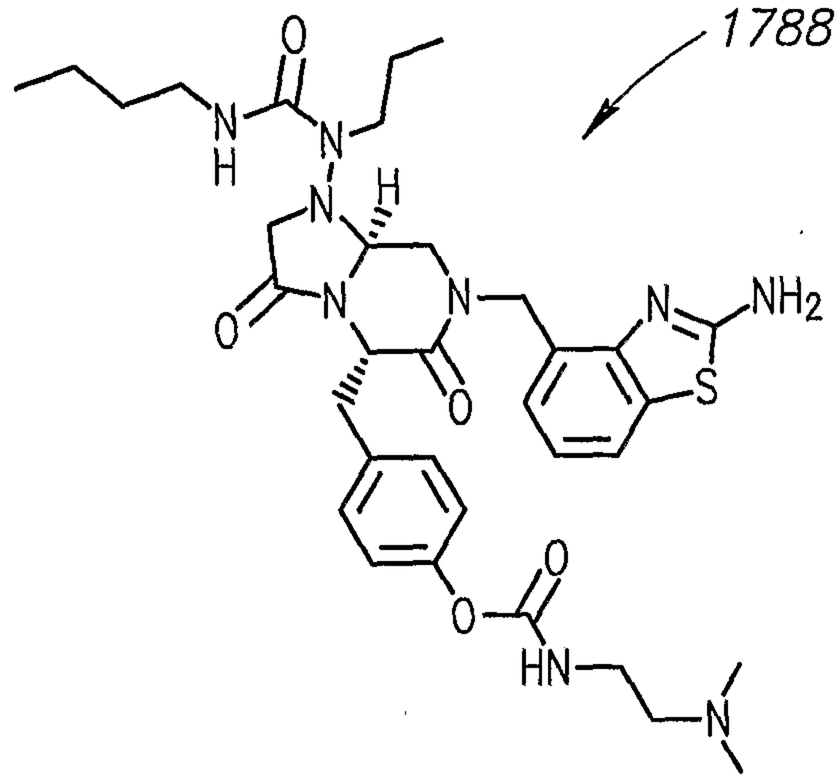
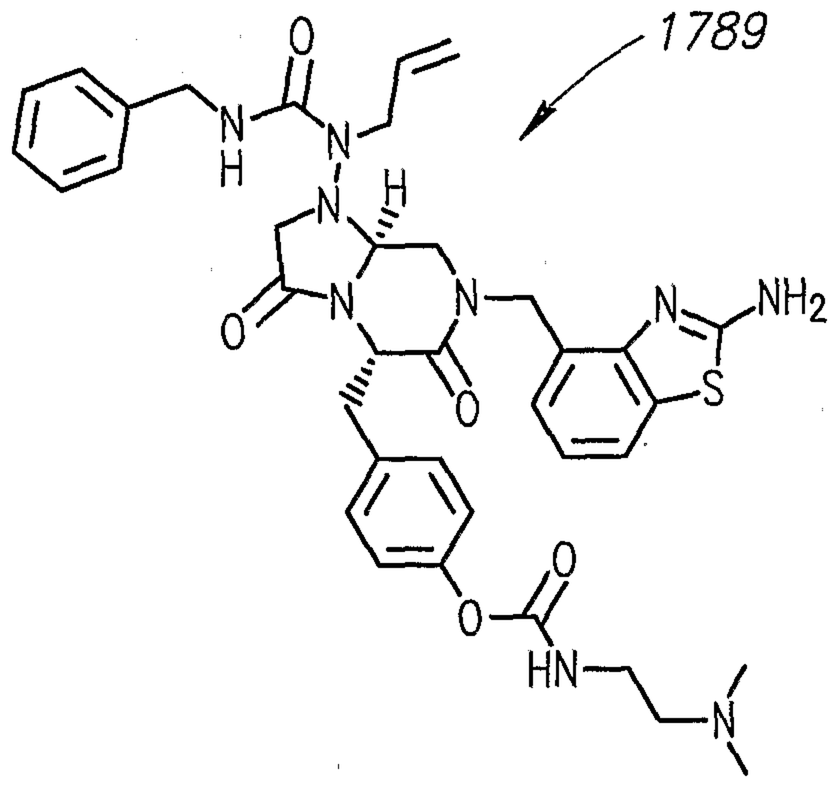
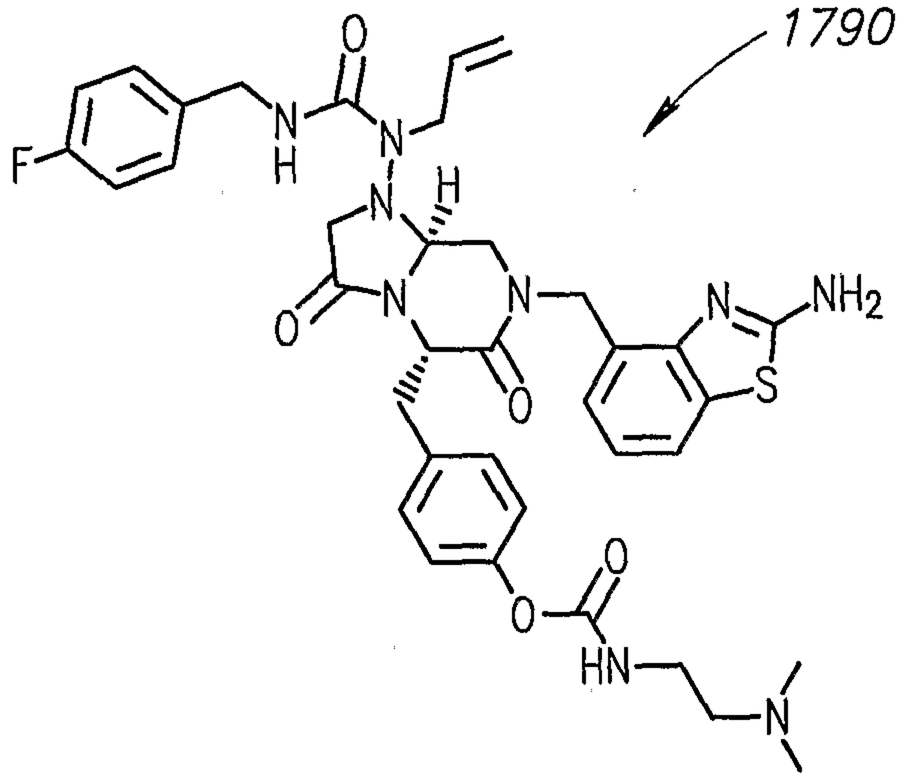


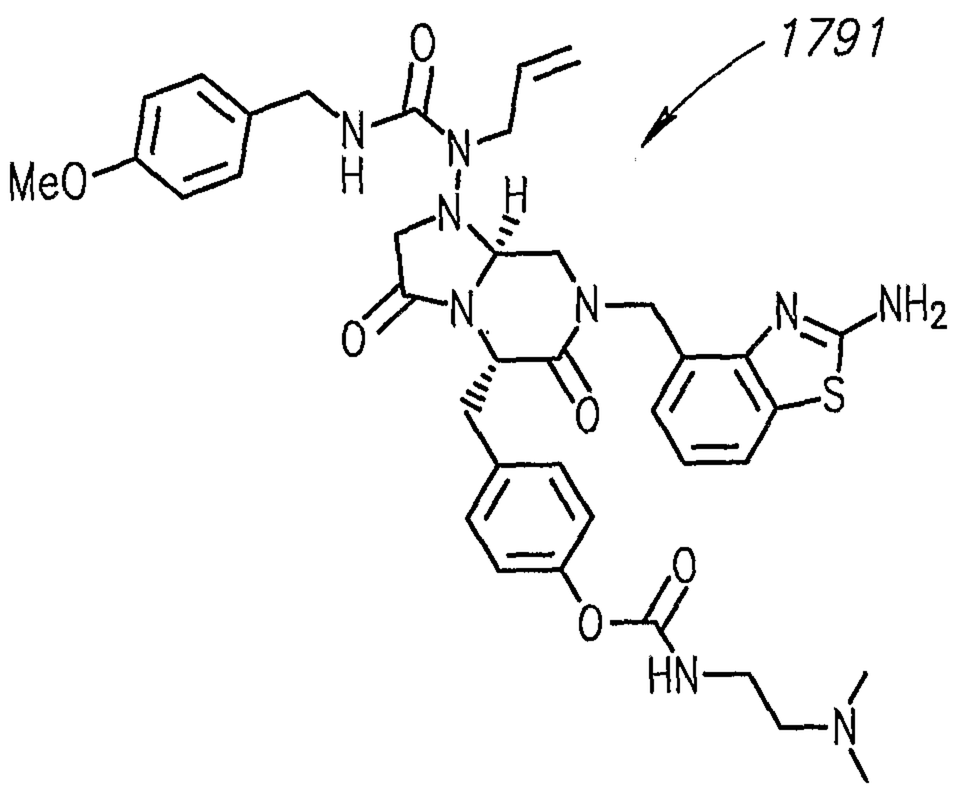
FIG.9AB











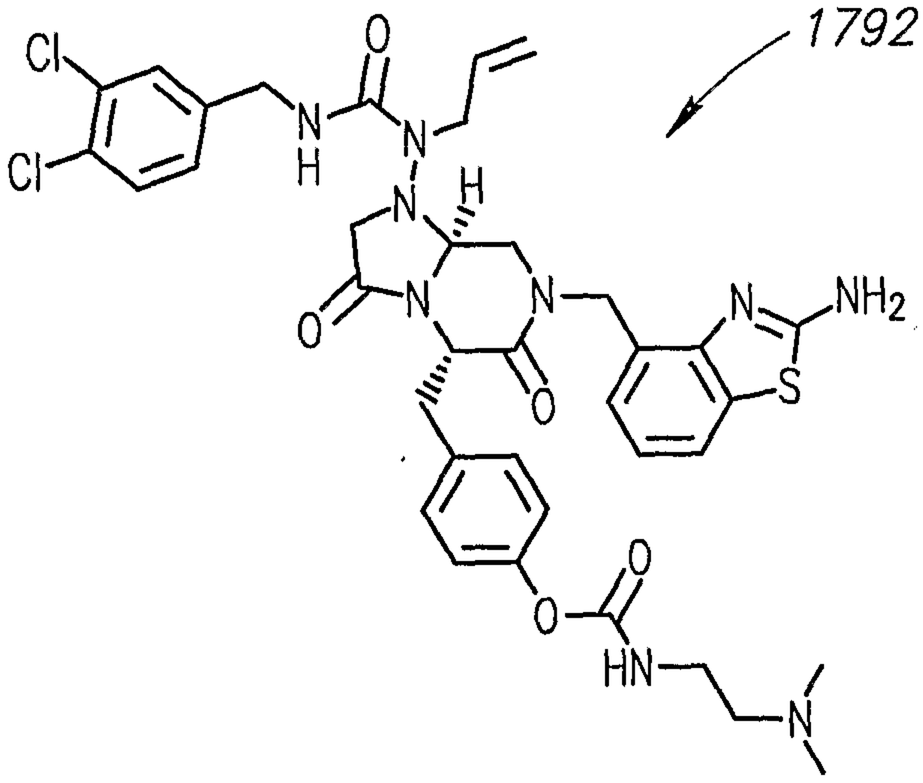


FIG.9AC

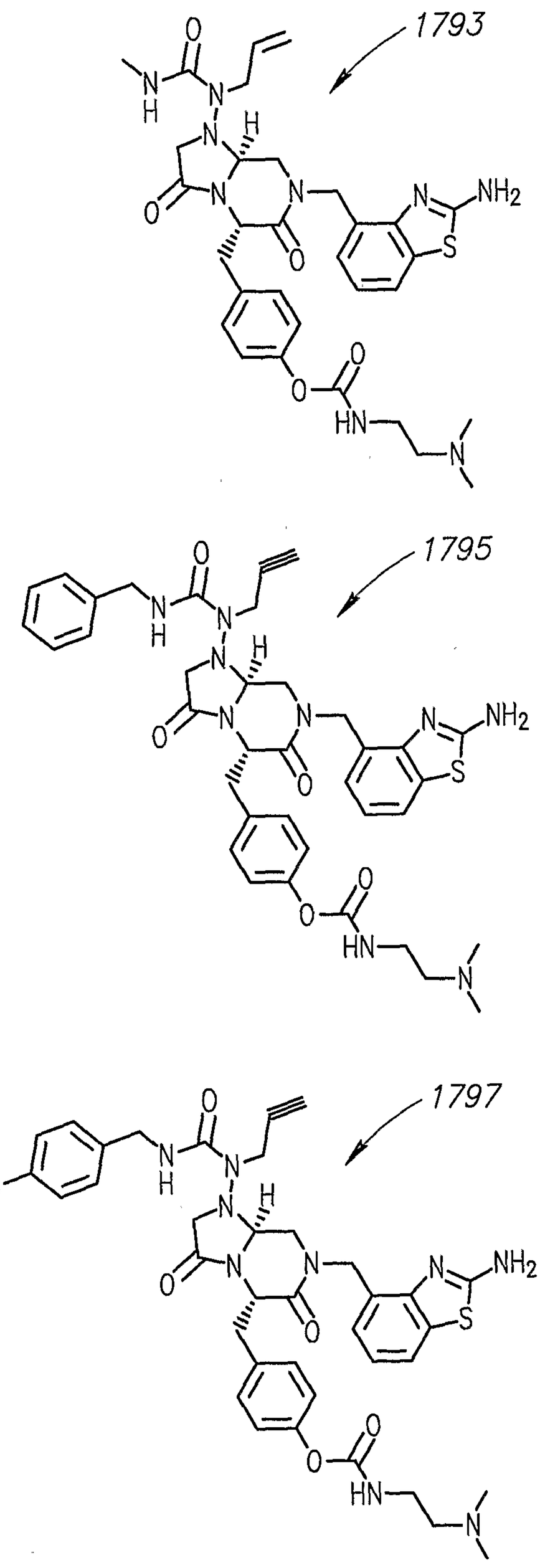
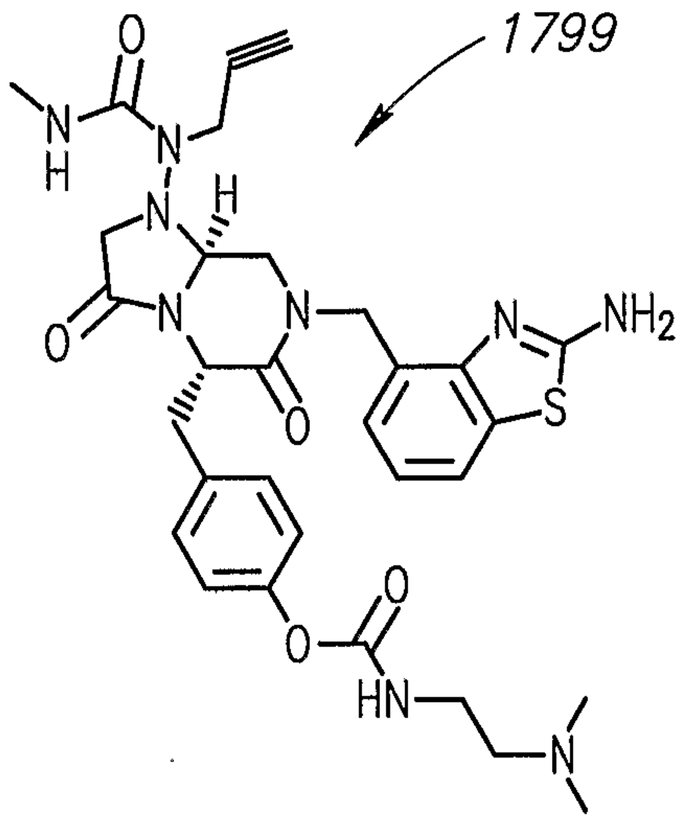


FIG.9AD



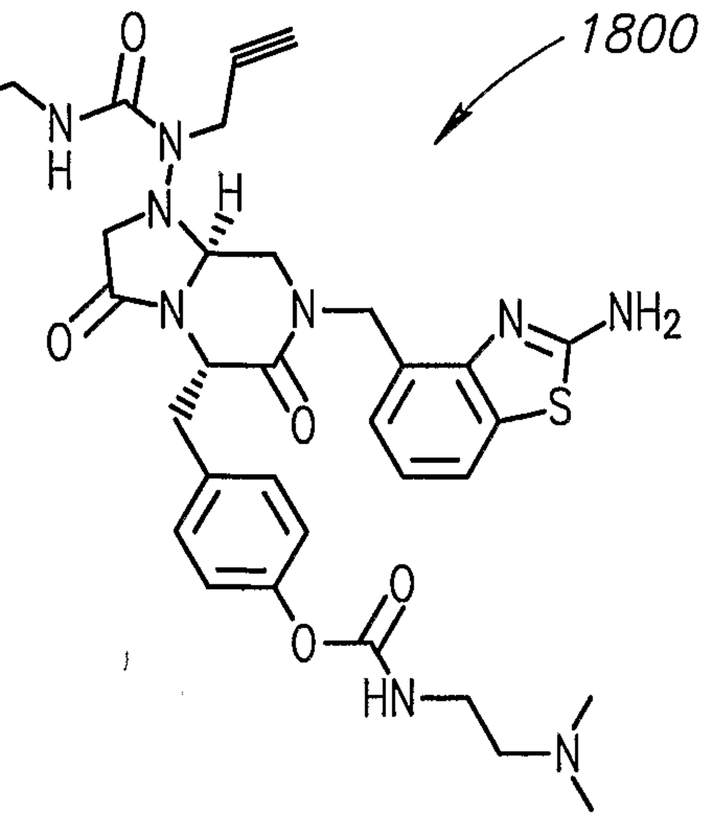
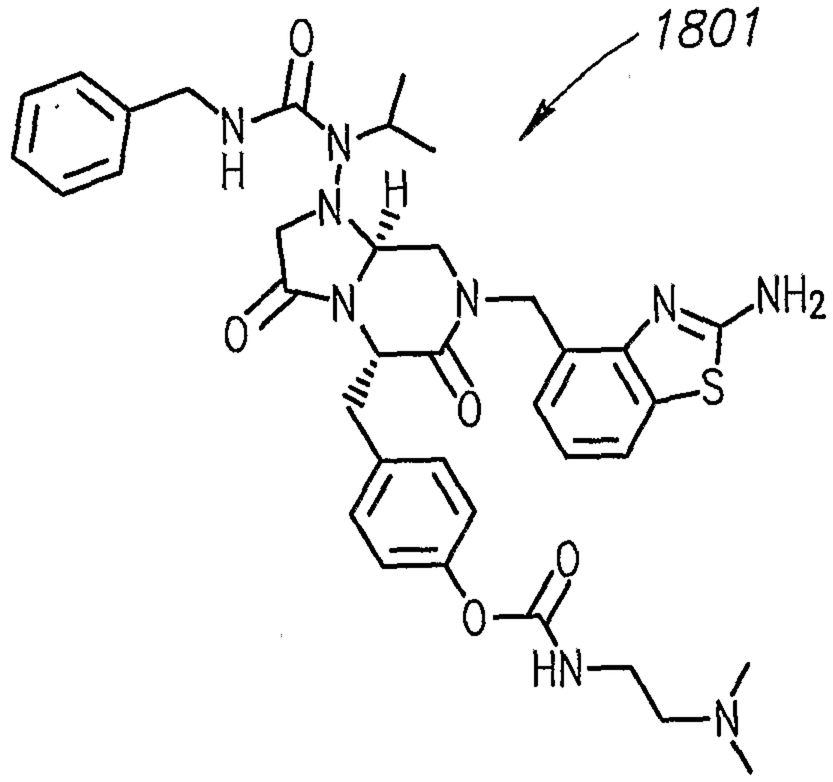


FIG.9AE

1801



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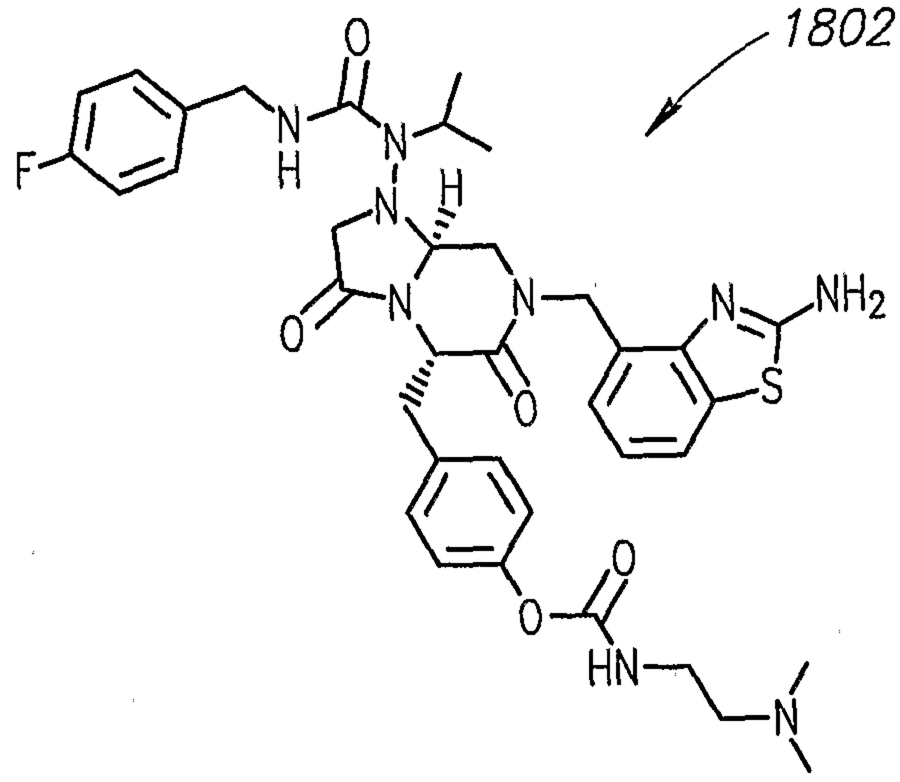

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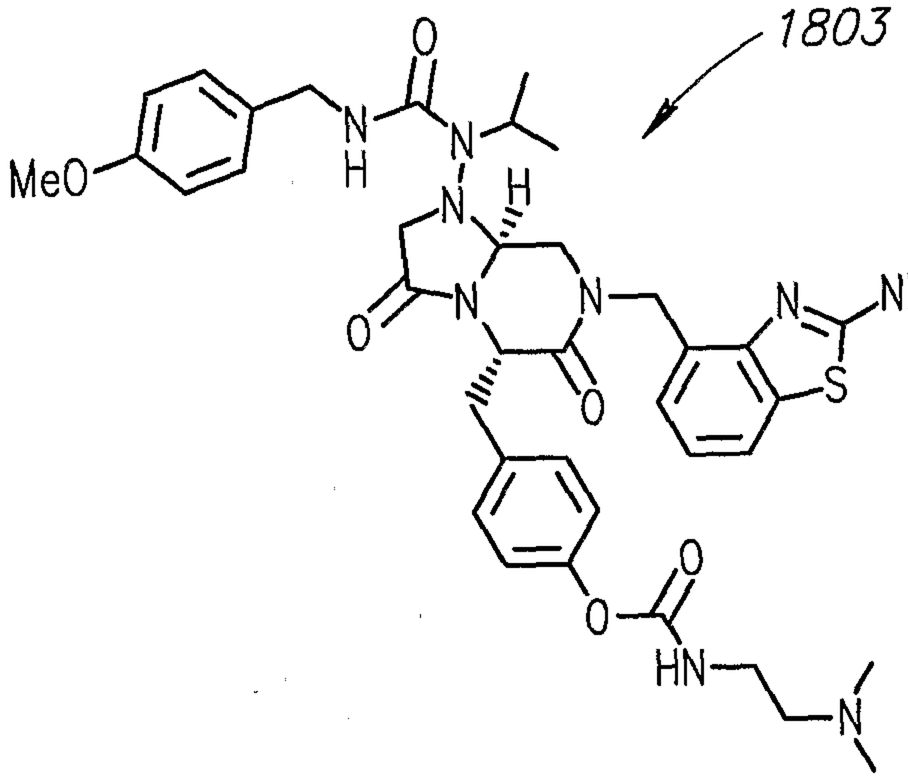

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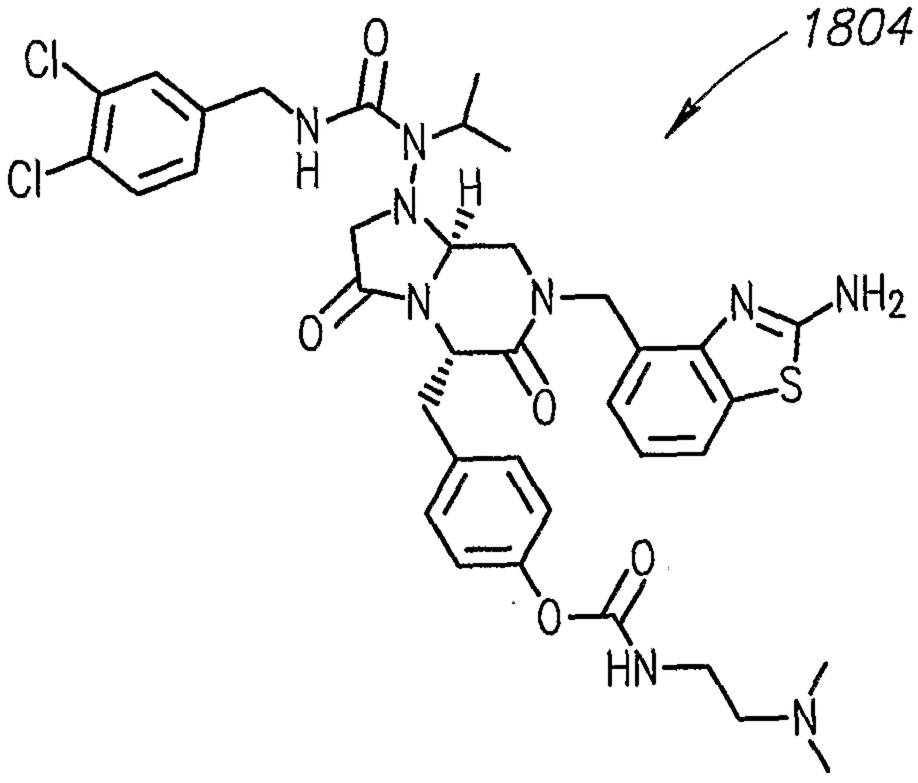

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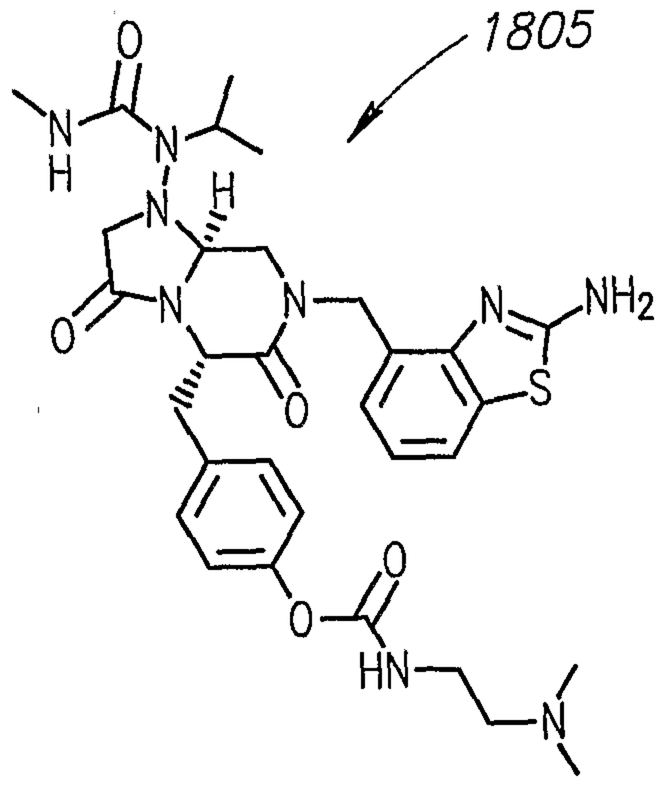

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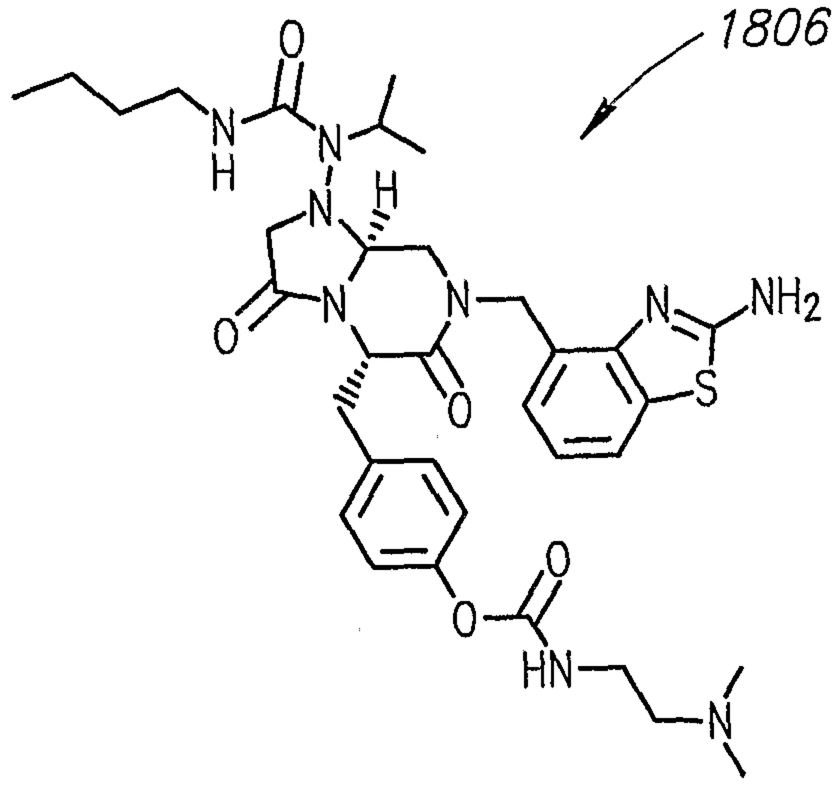
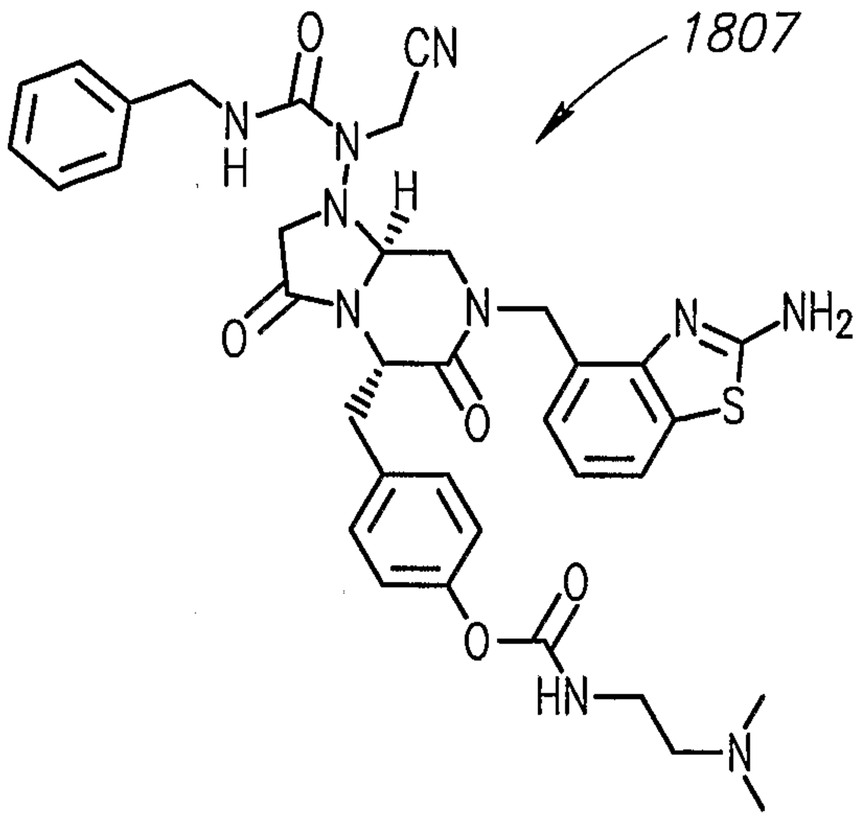


FIG.10A

1807



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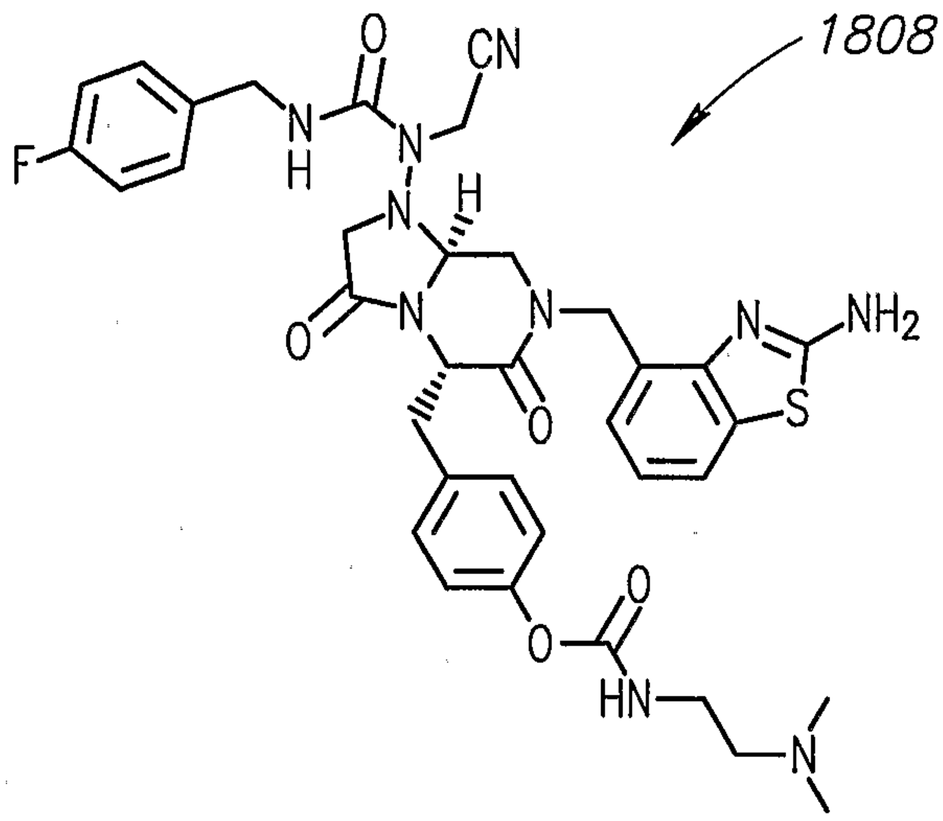

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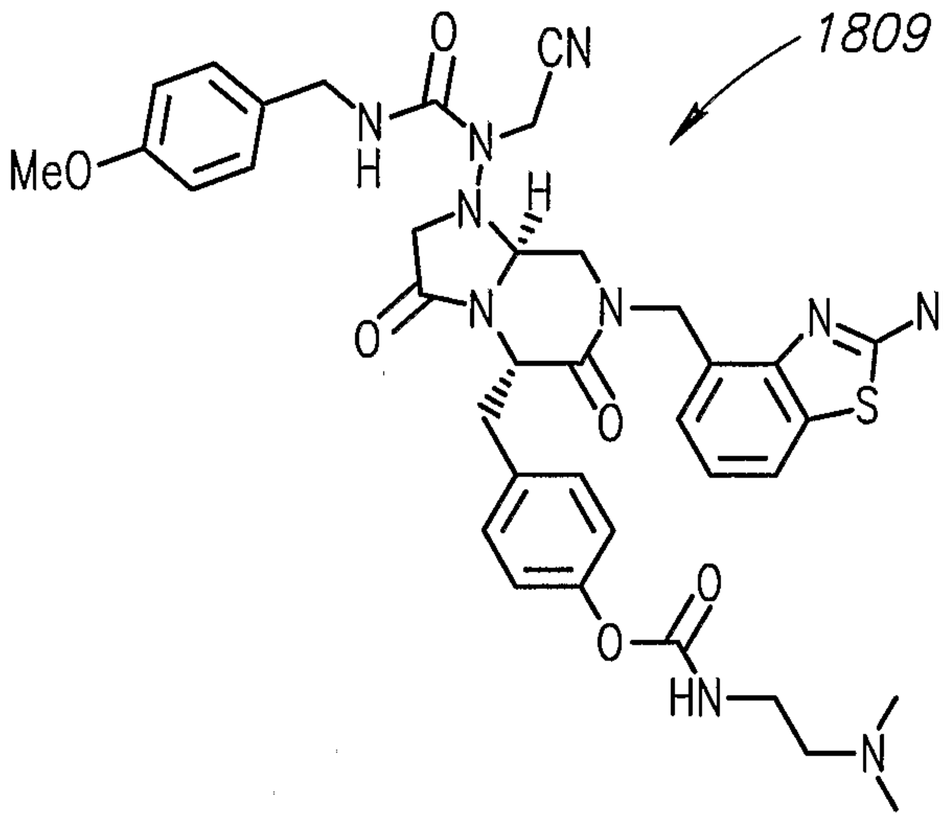

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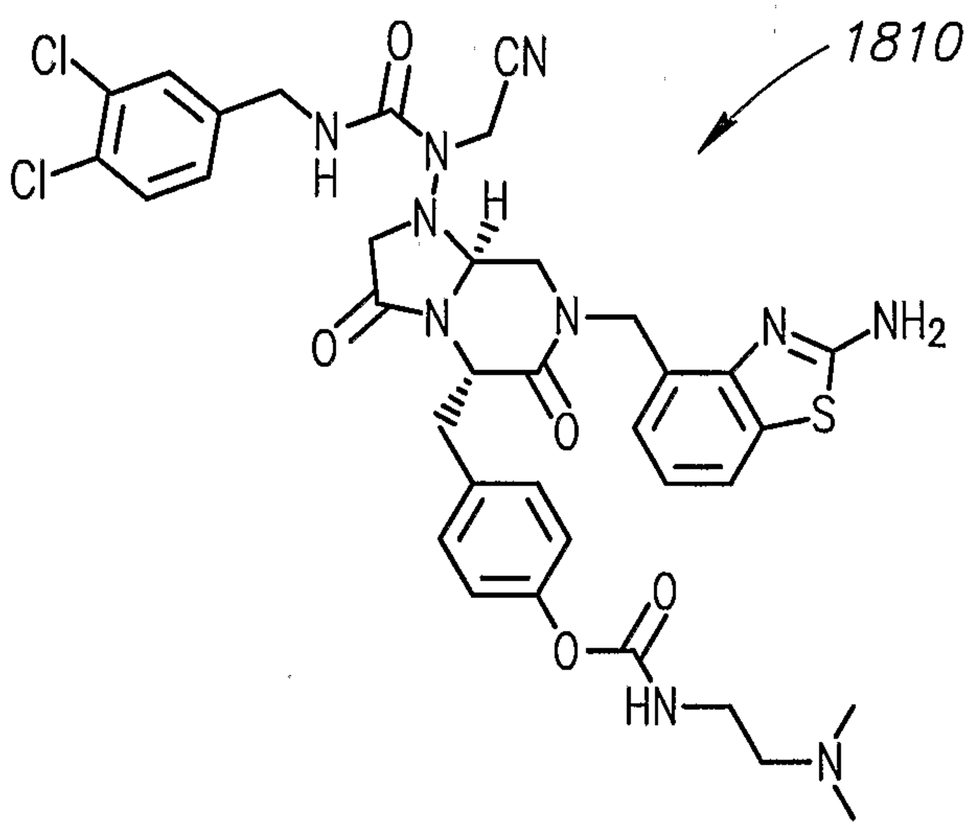

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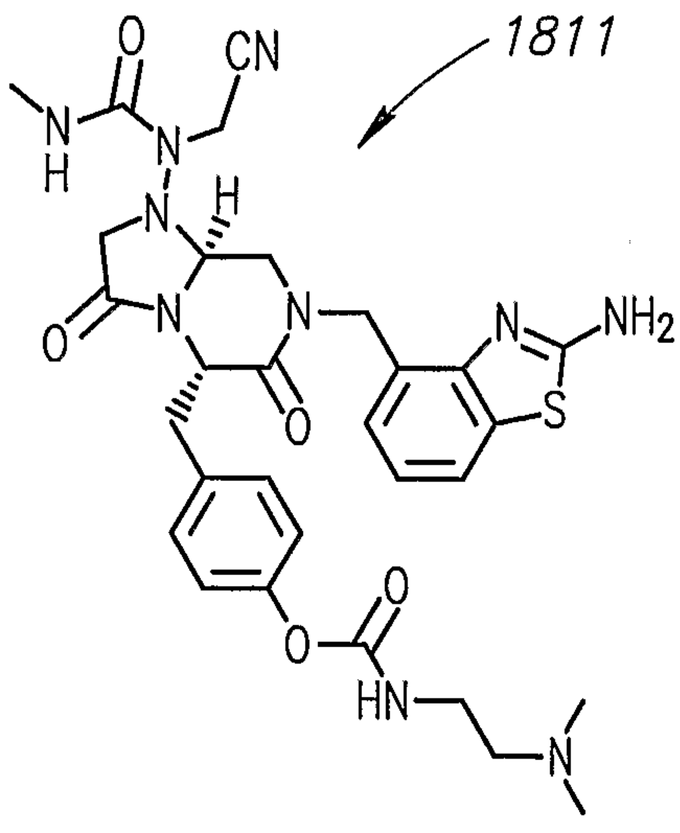

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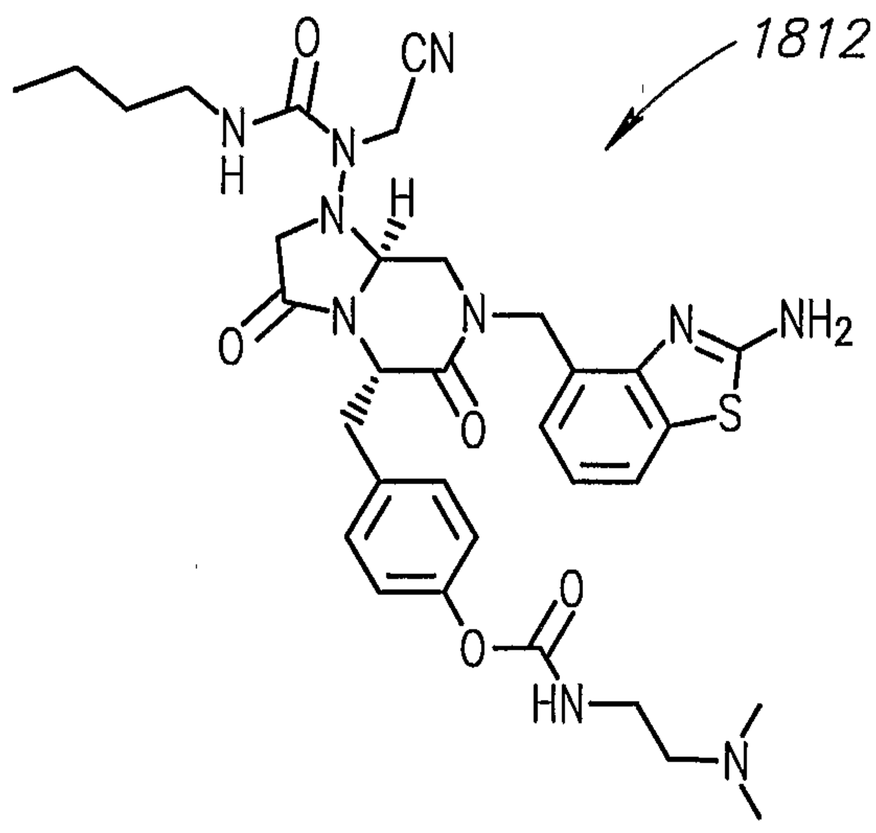
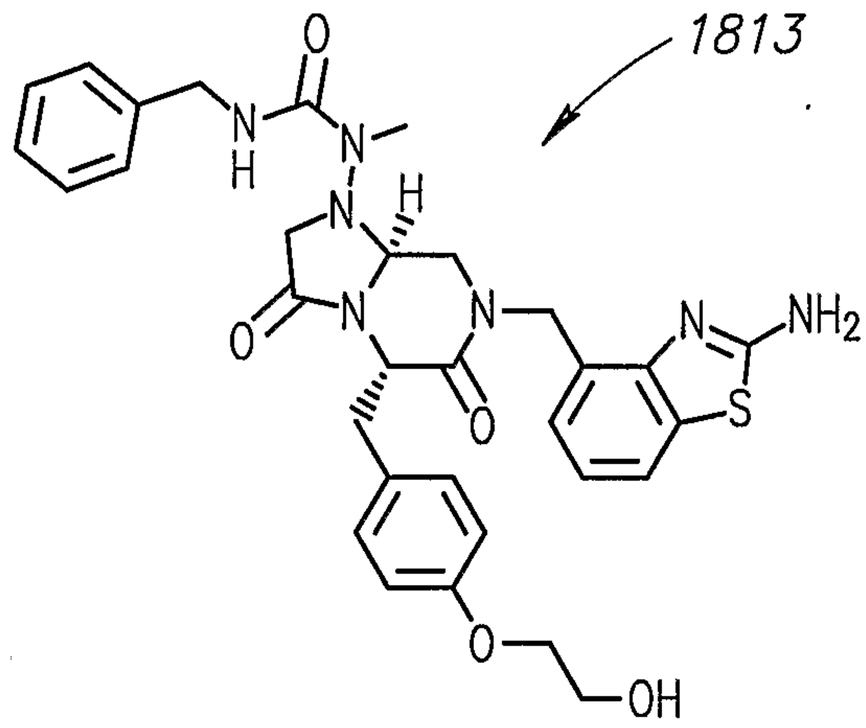


FIG.10B

1813



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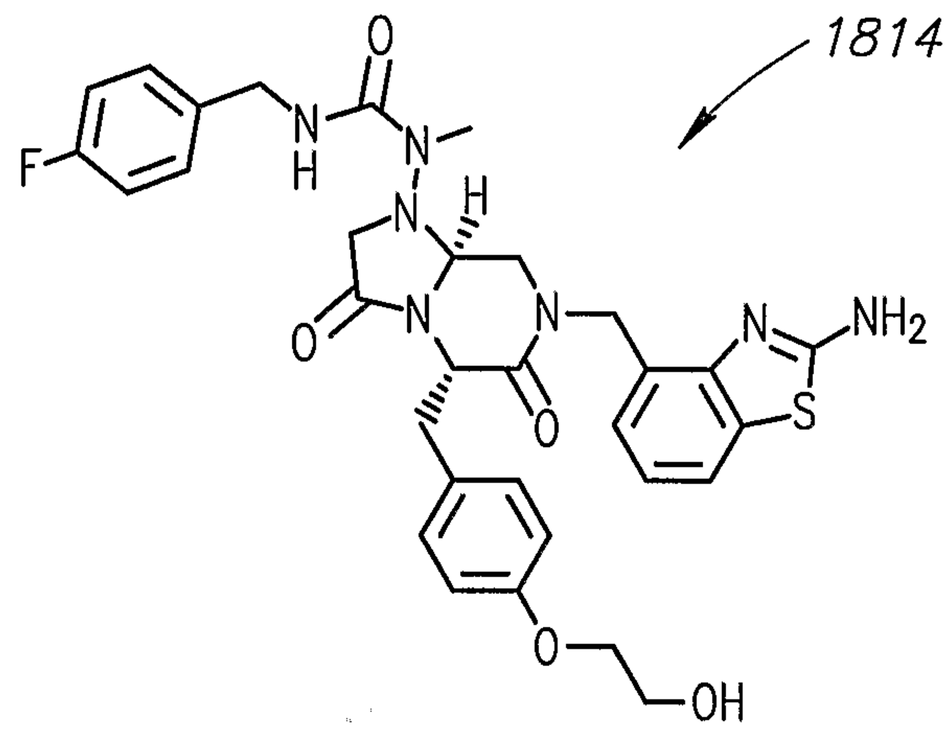

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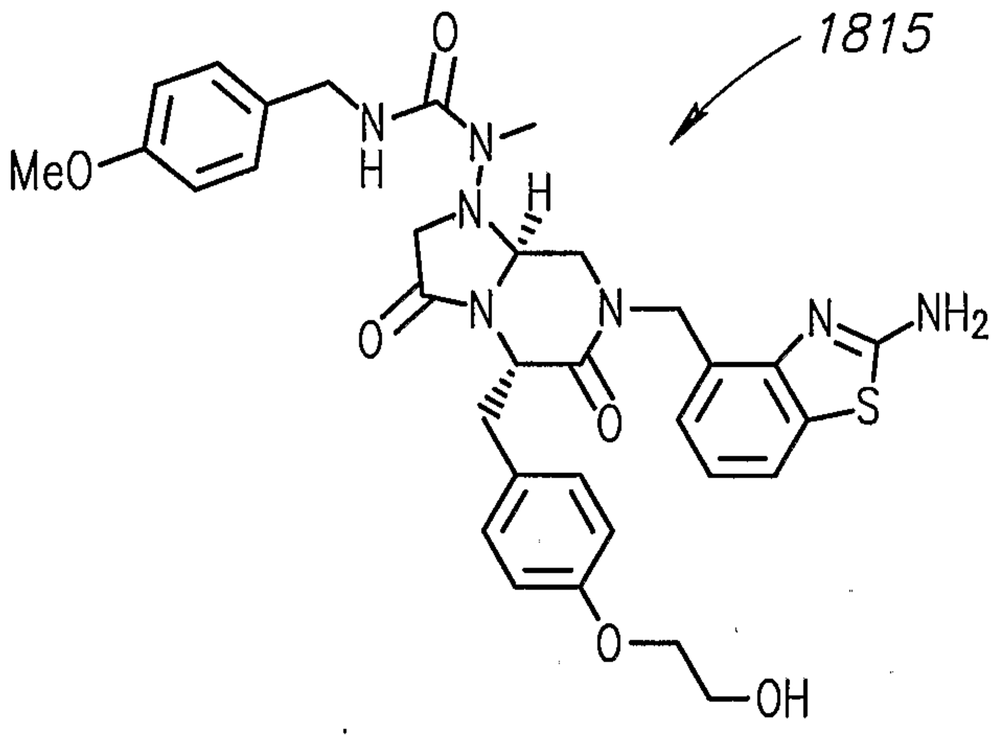

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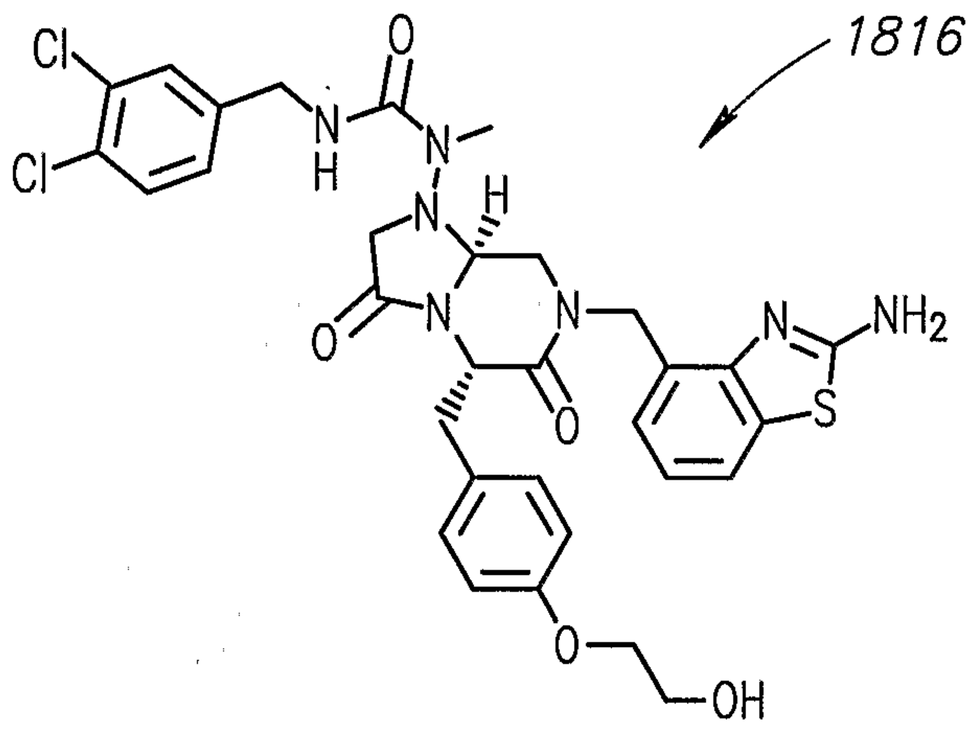

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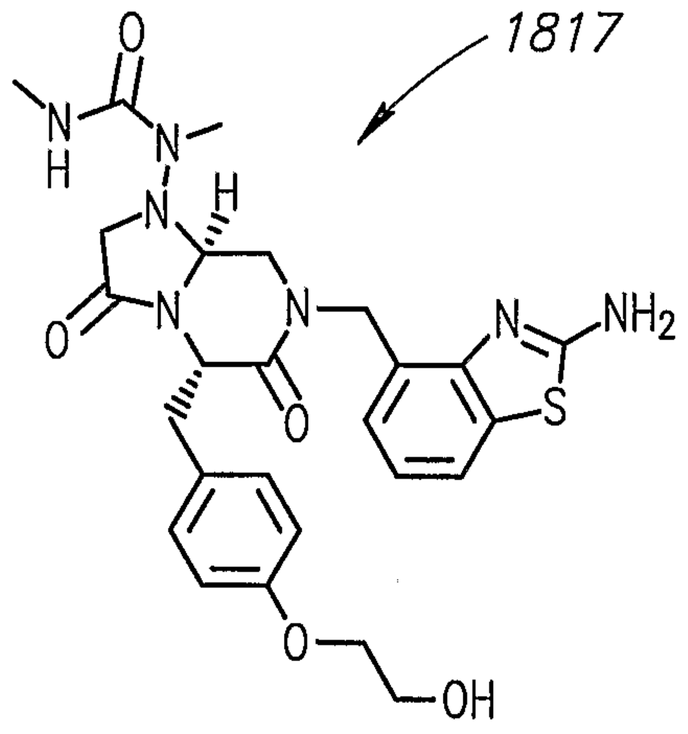

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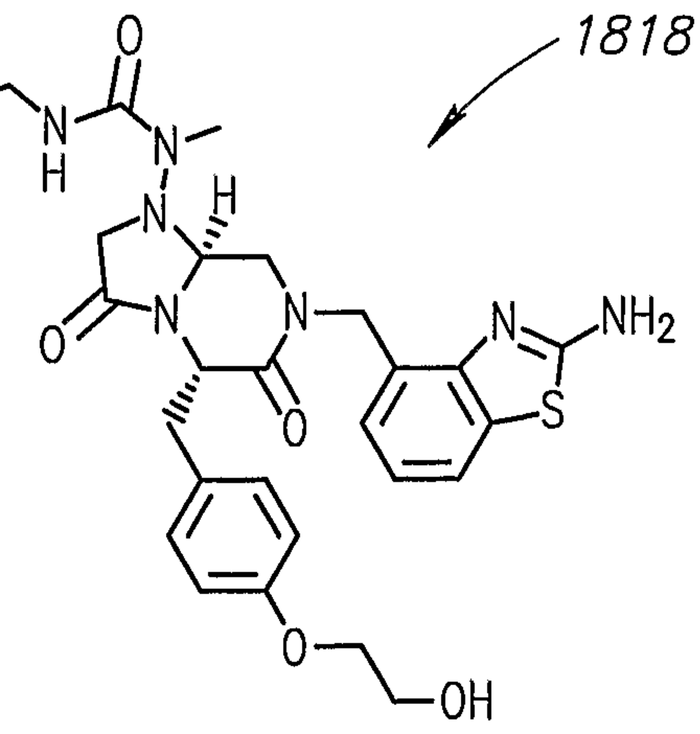
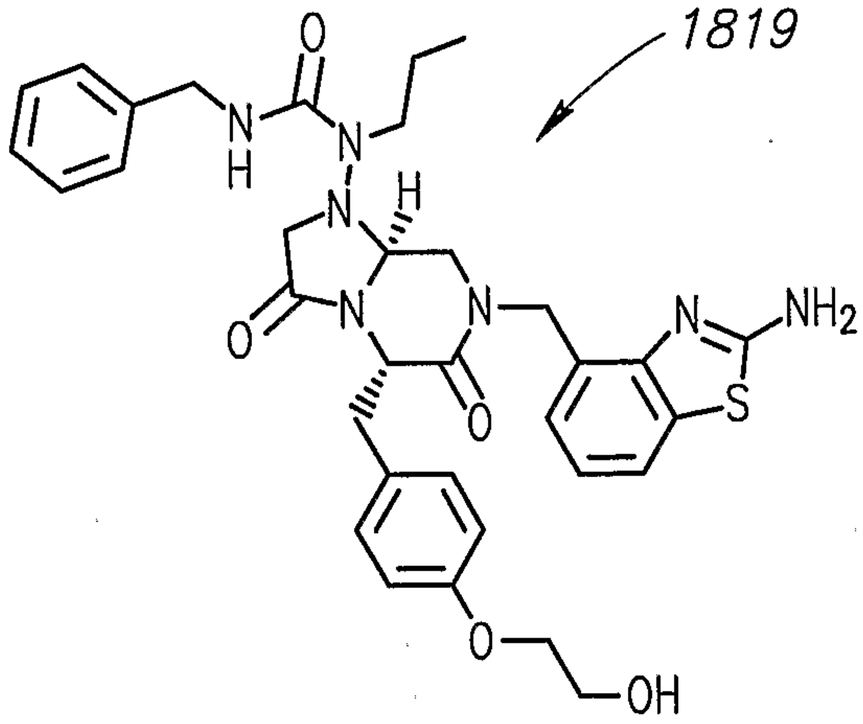


FIG.10C

1819



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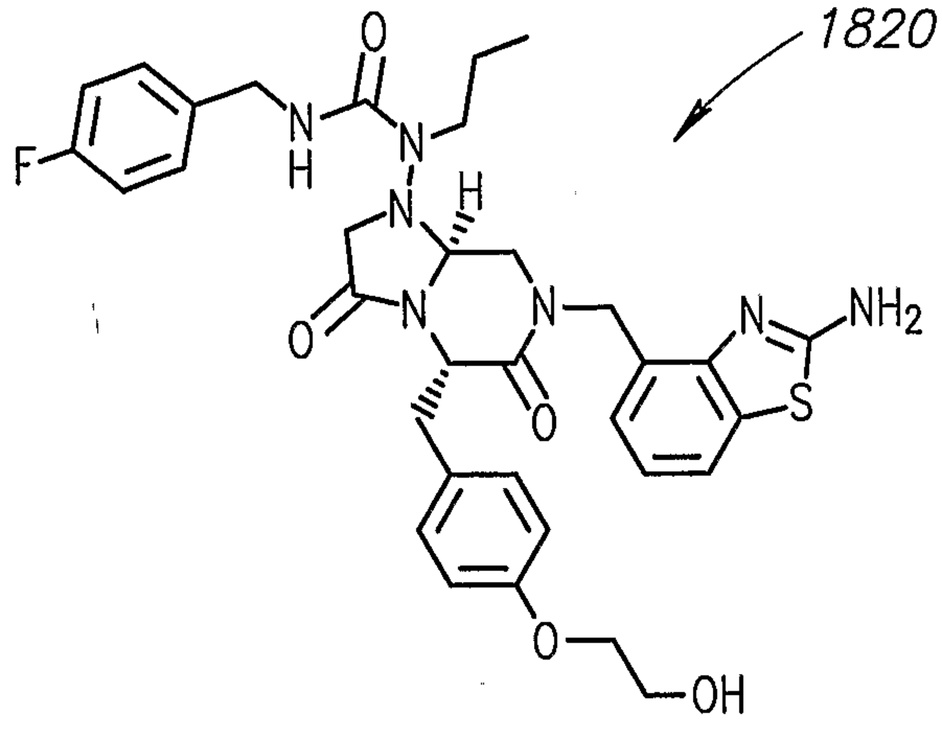

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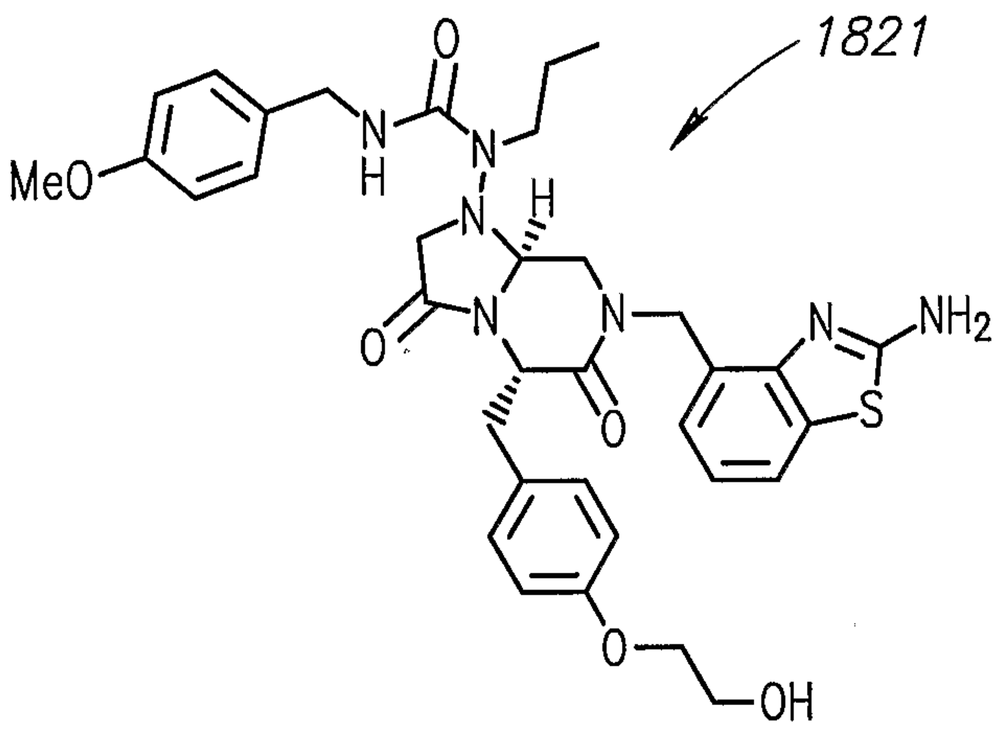

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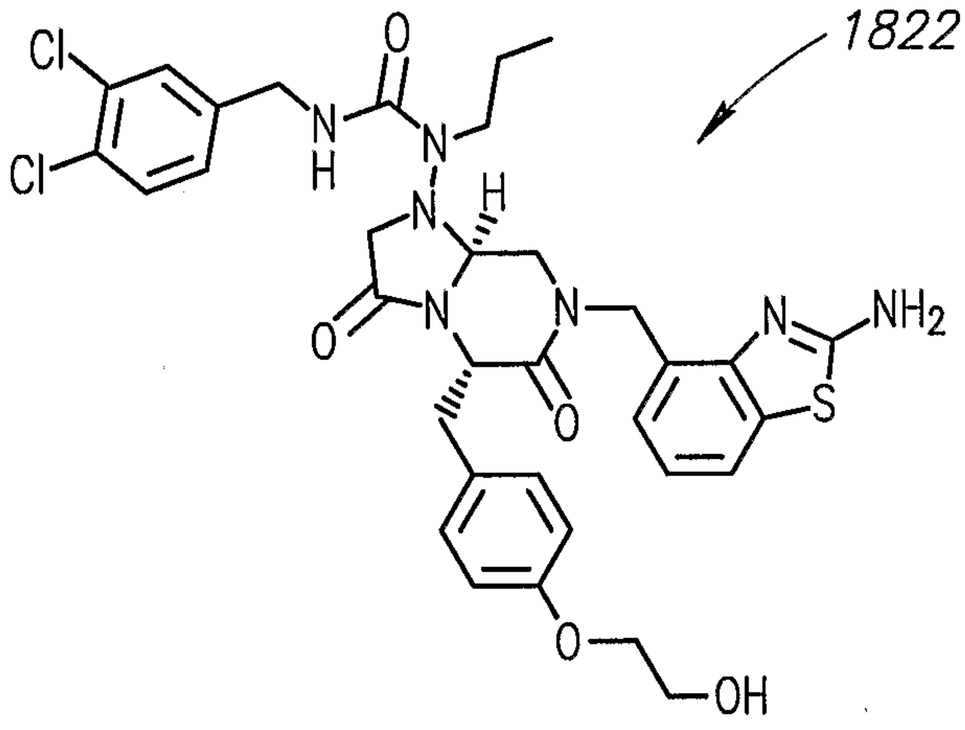

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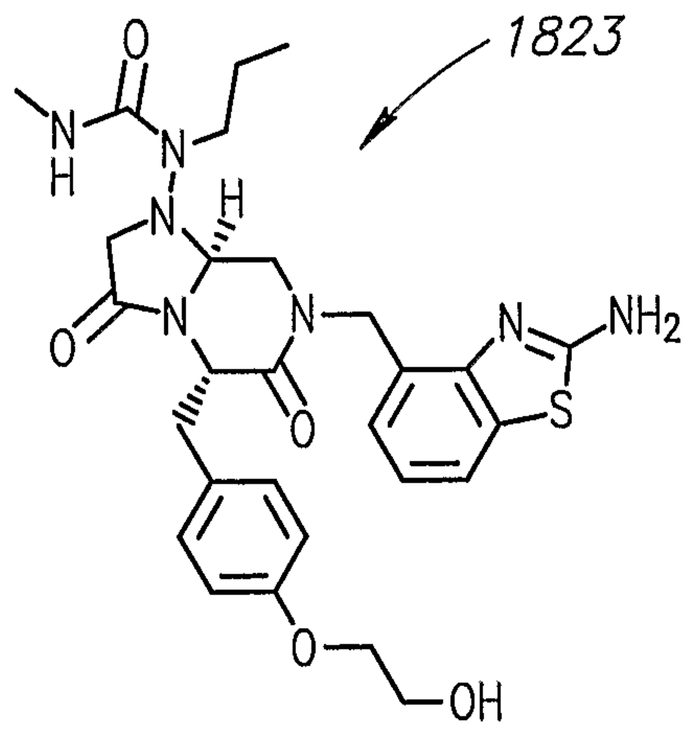

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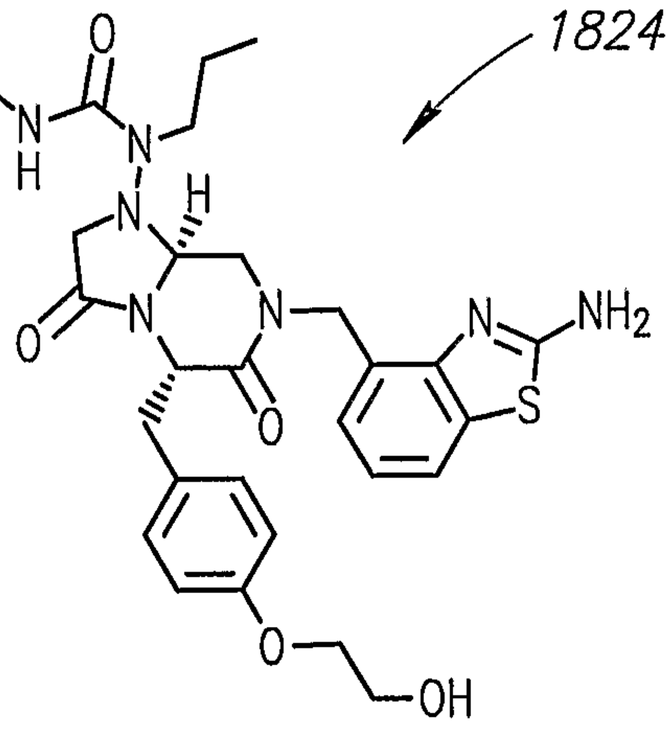
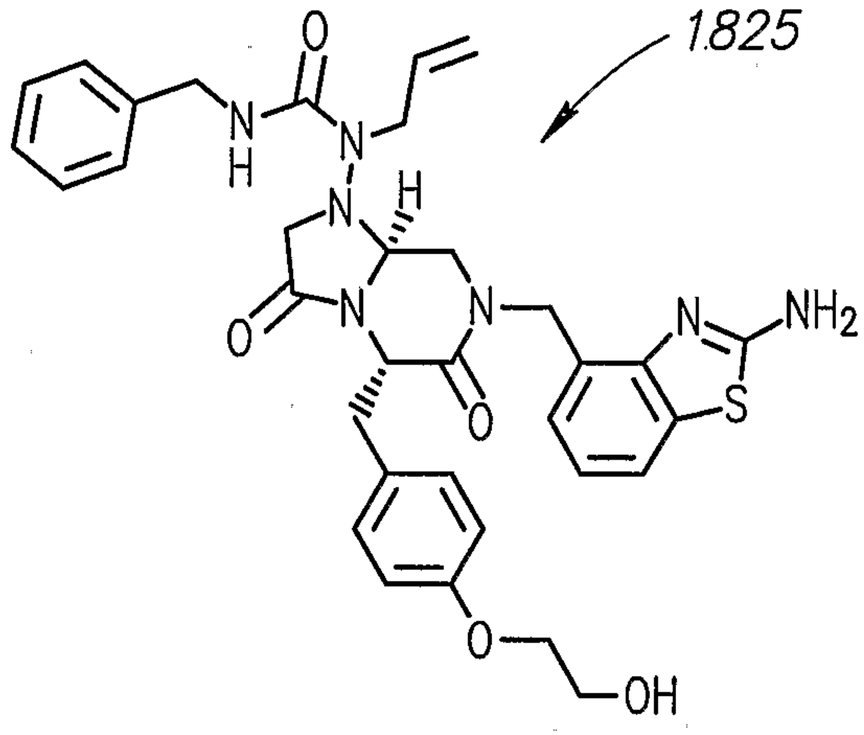


FIG.10D

1825



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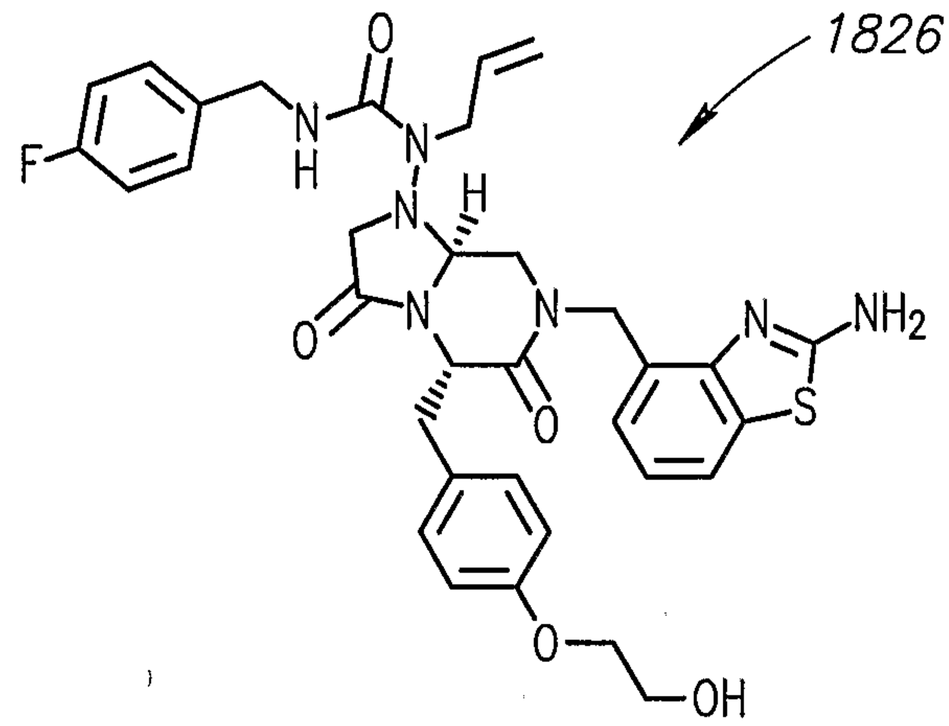

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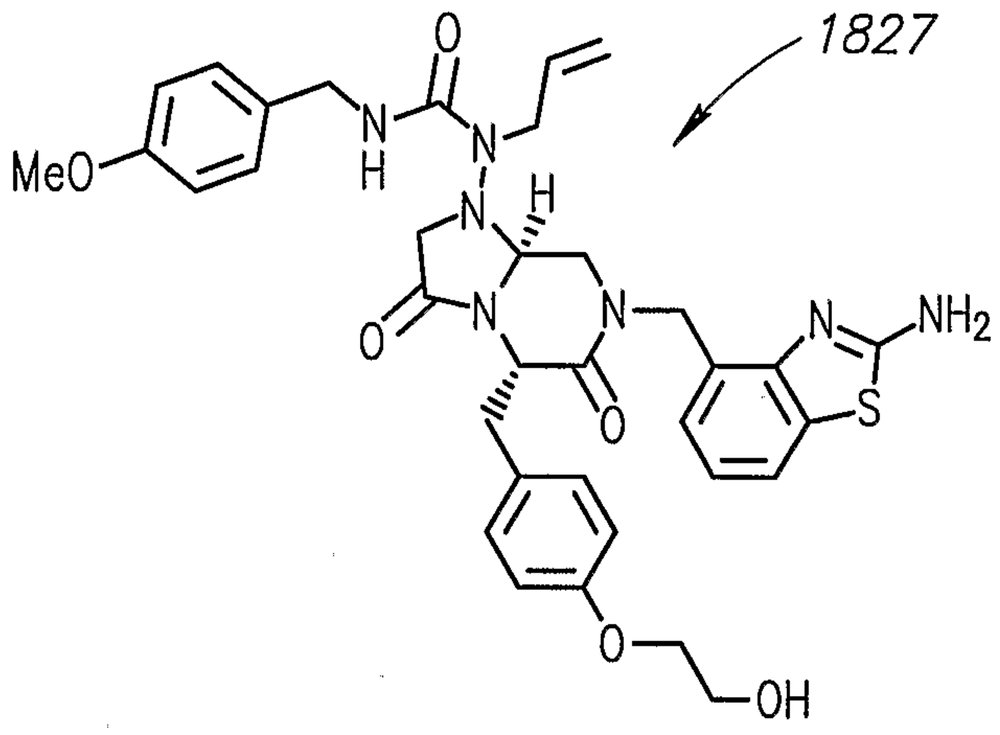

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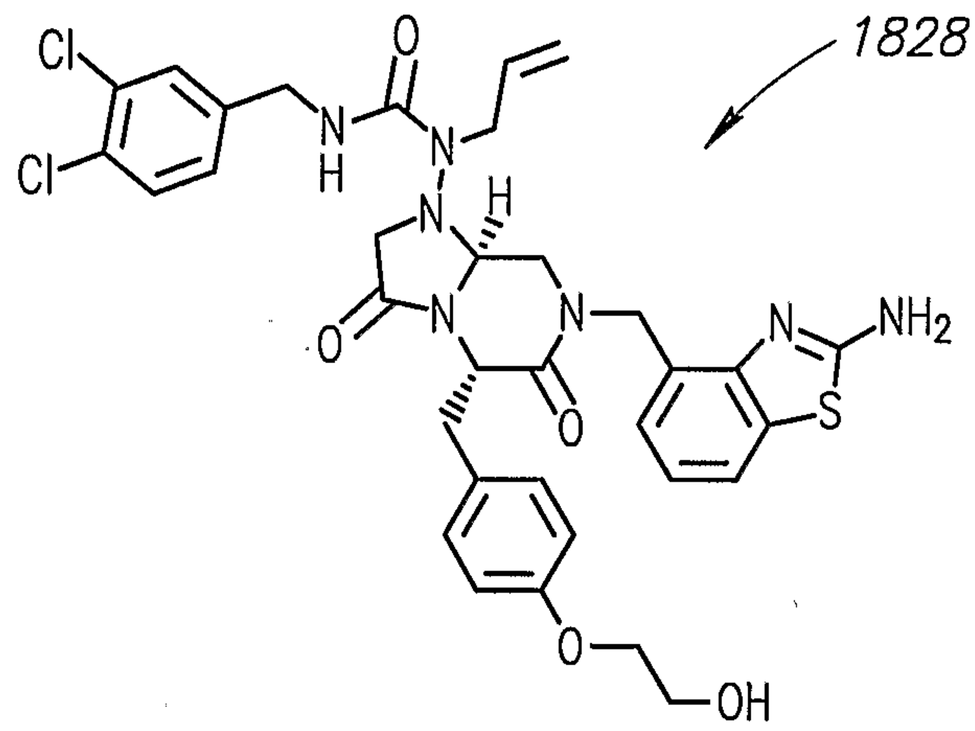

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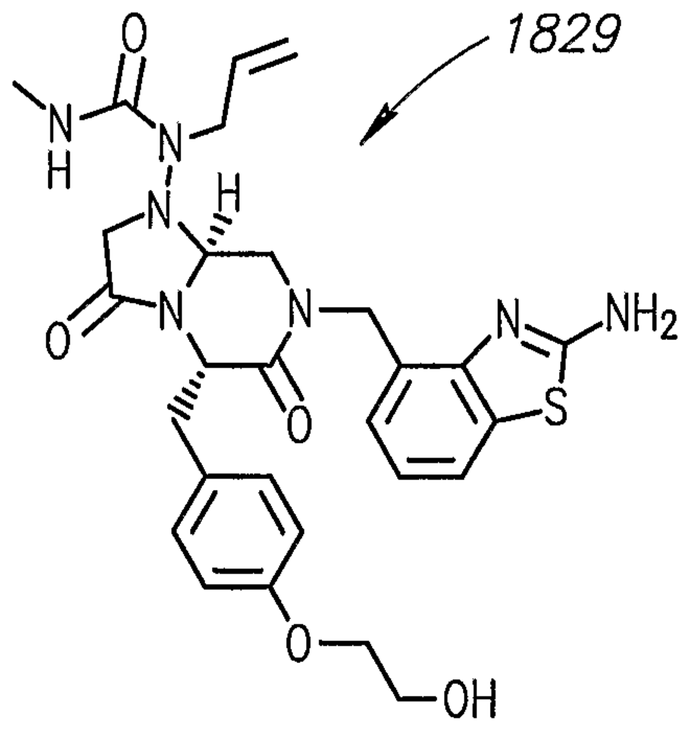


1830

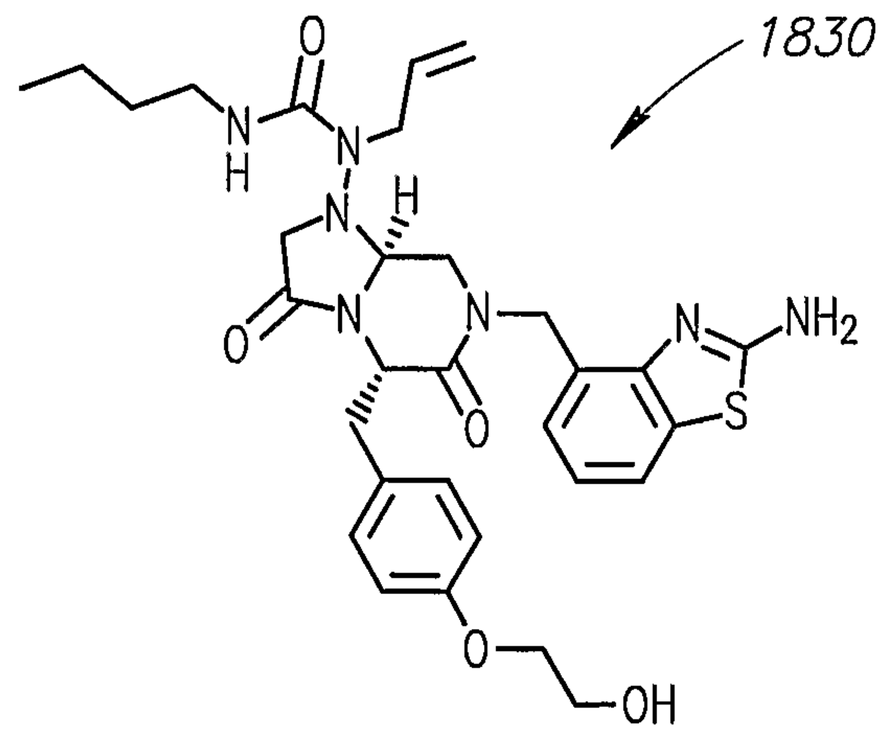
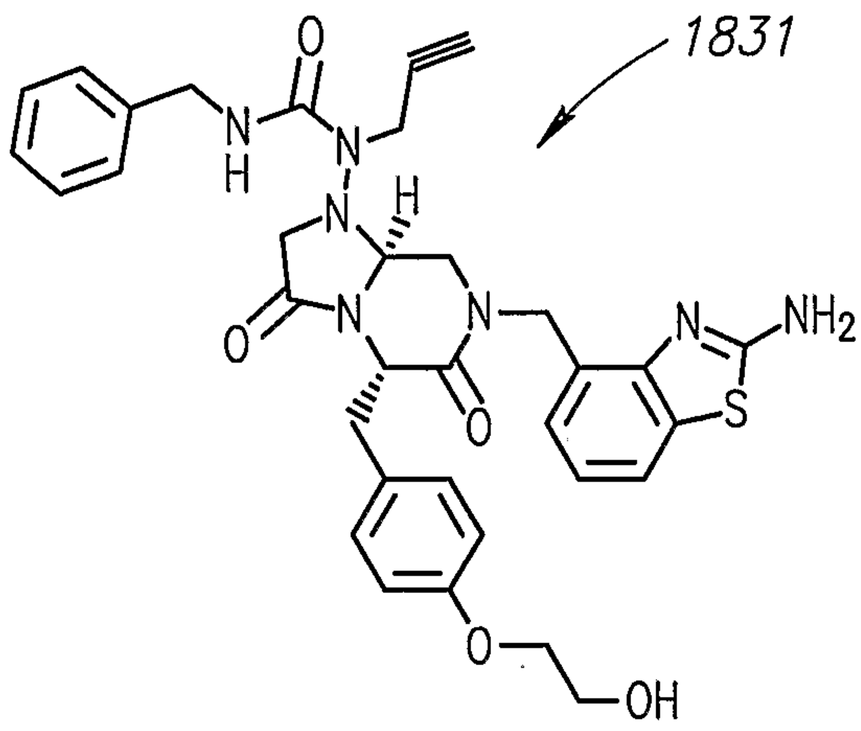
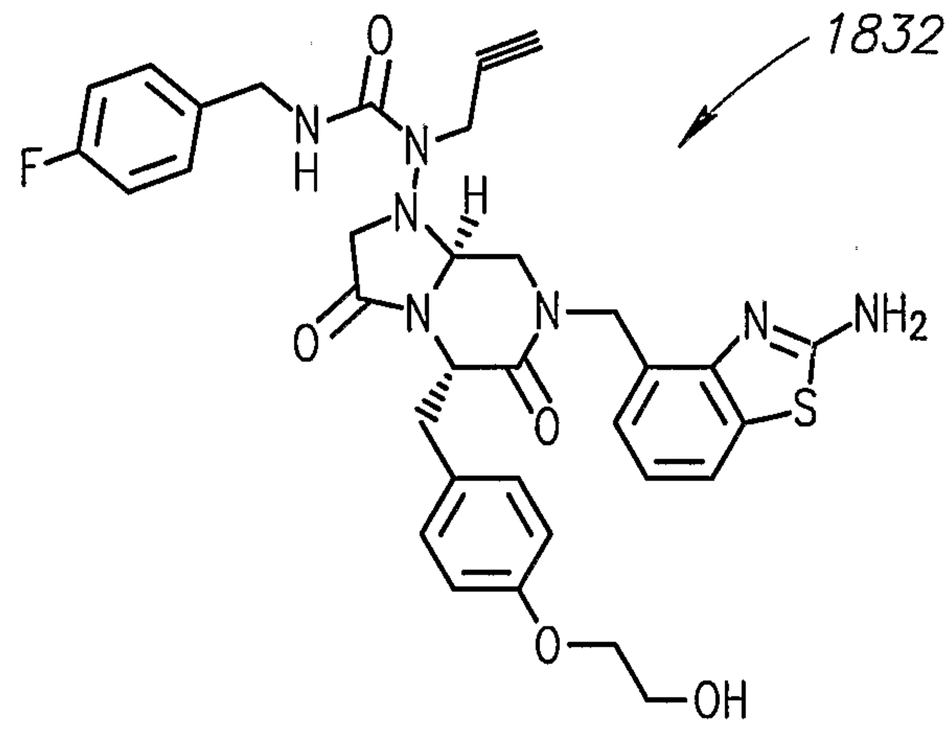
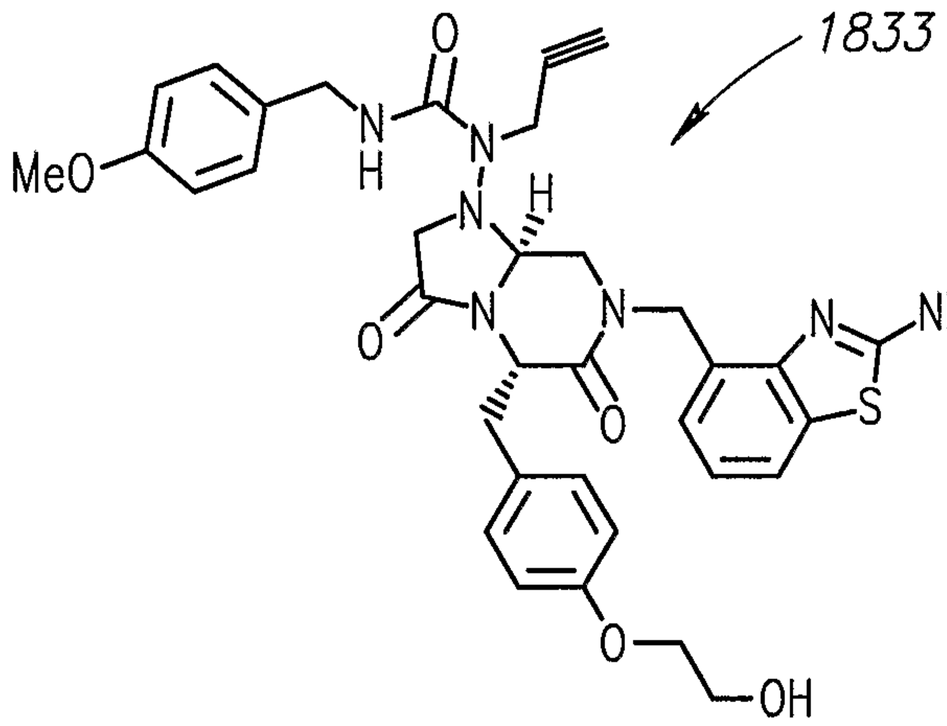
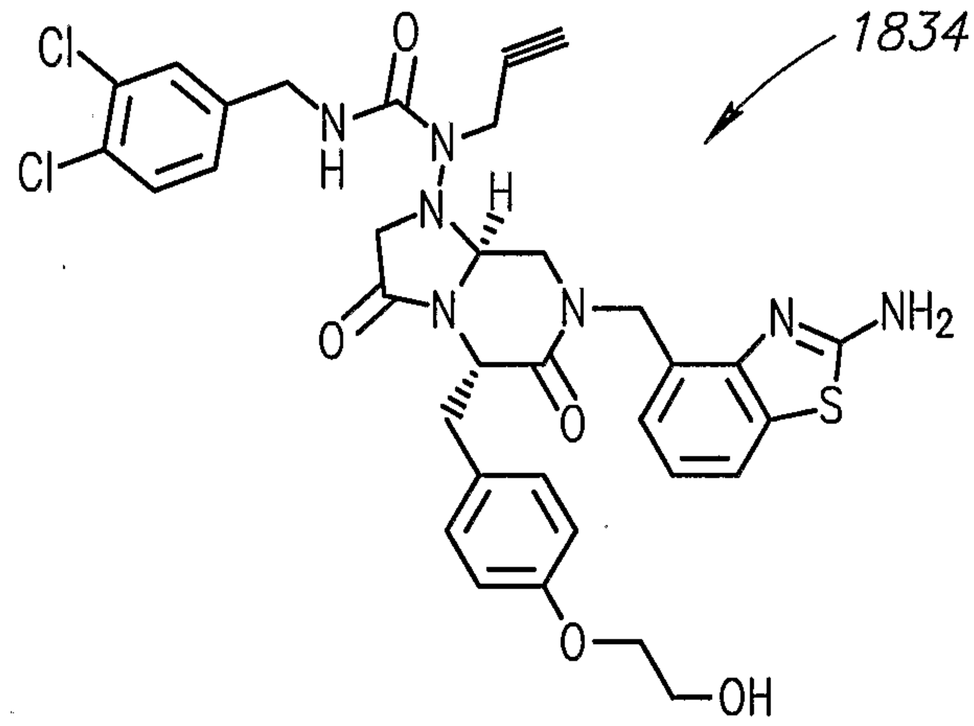


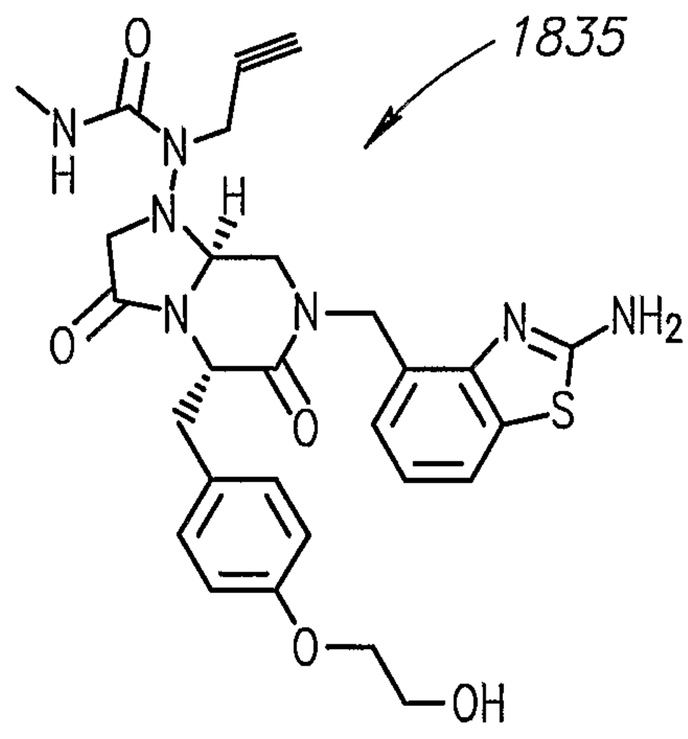
FIG.10E











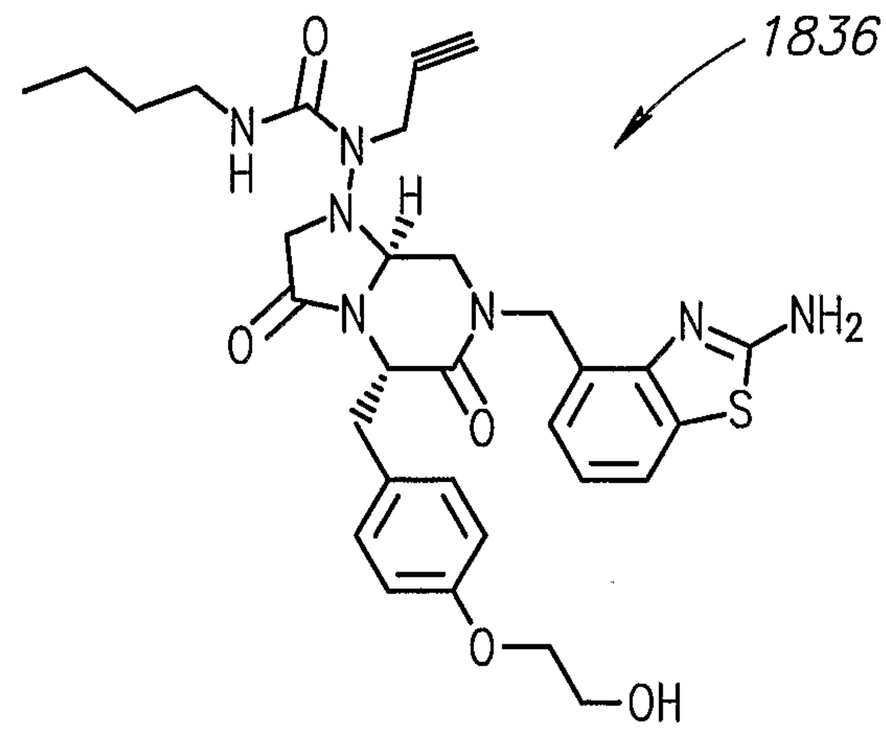
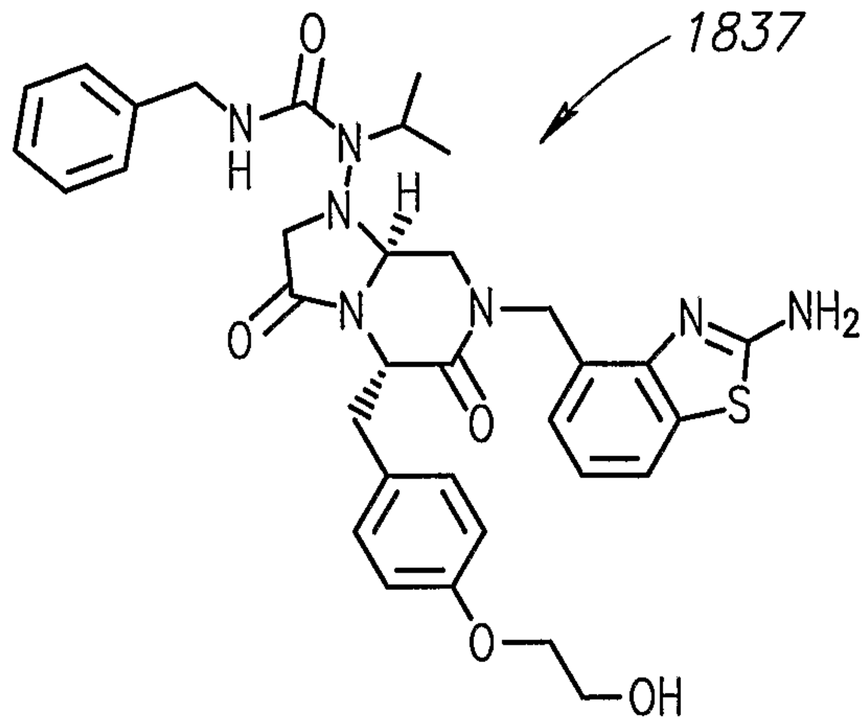


FIG.10F

1837



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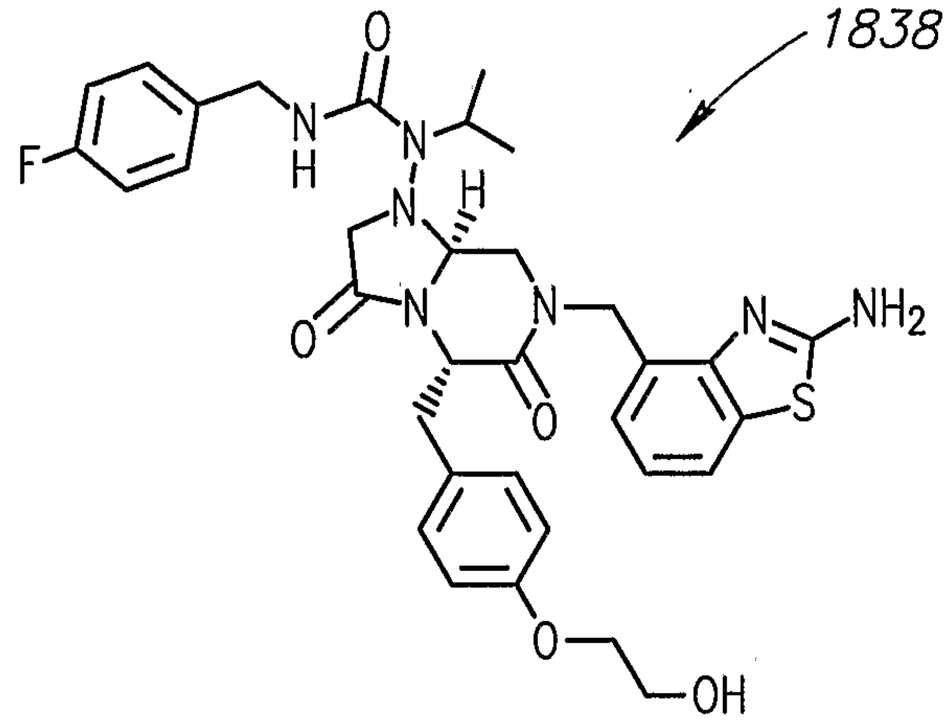

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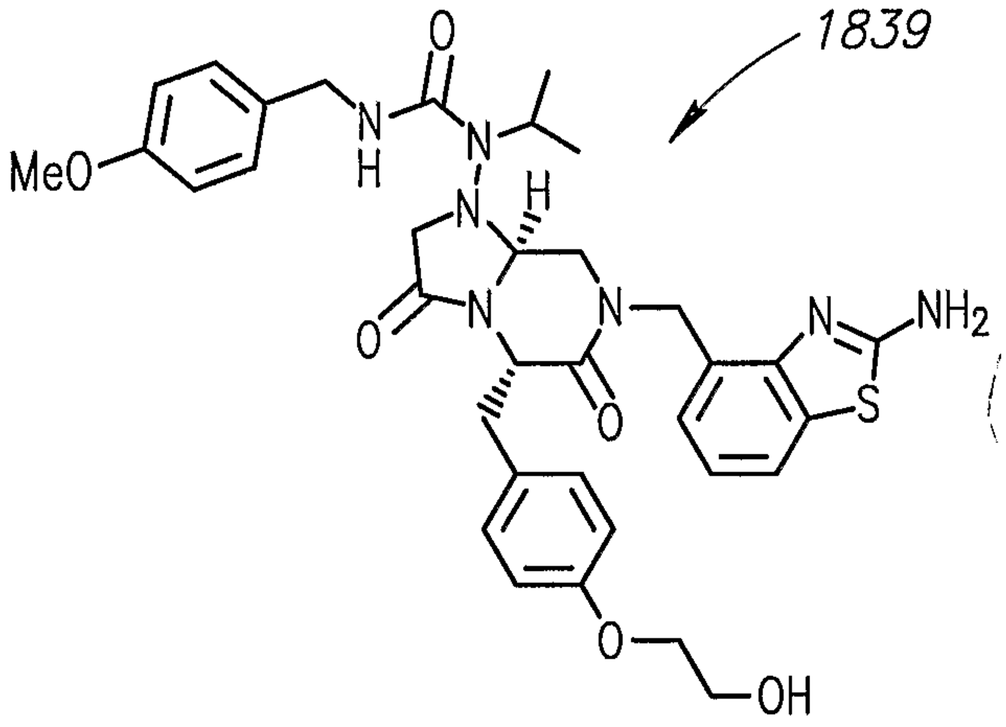

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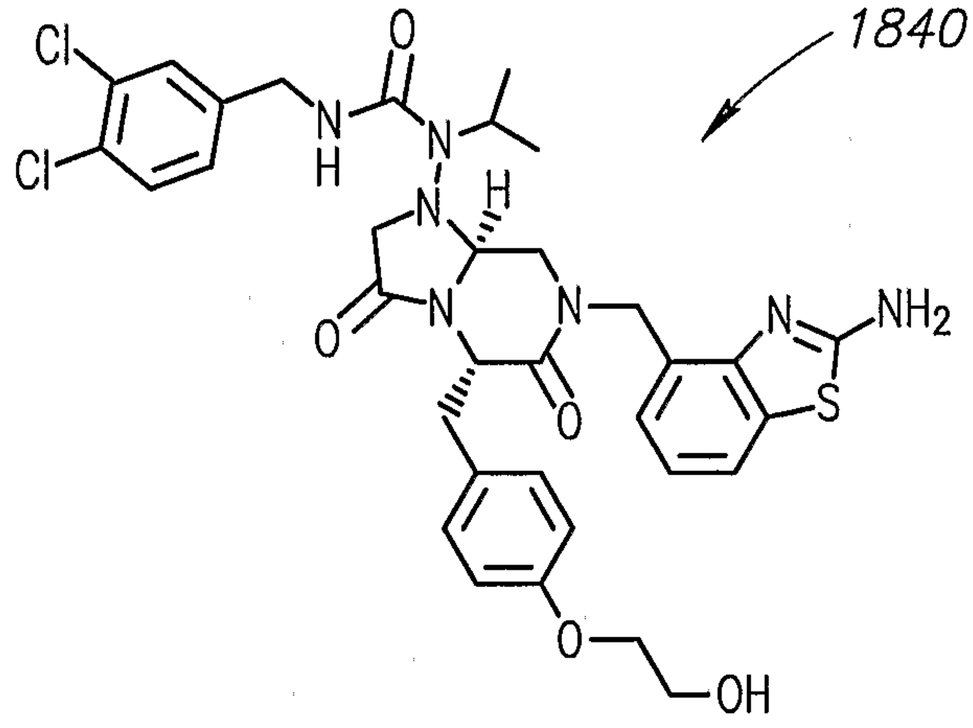

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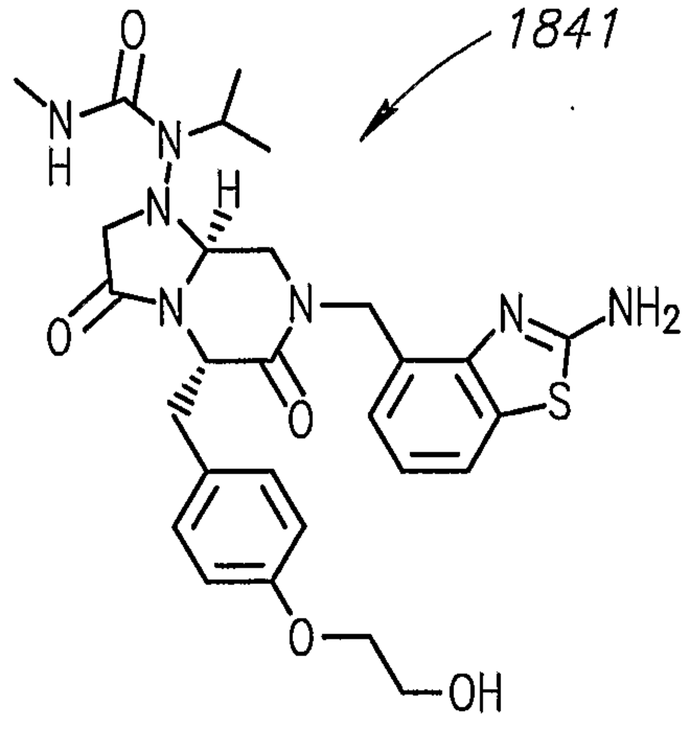

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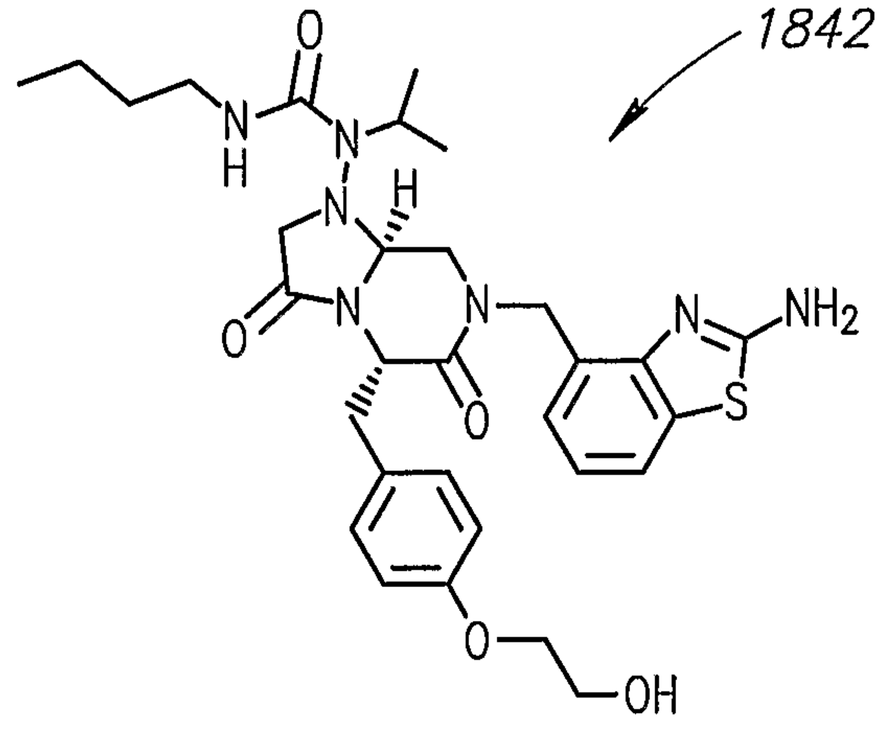
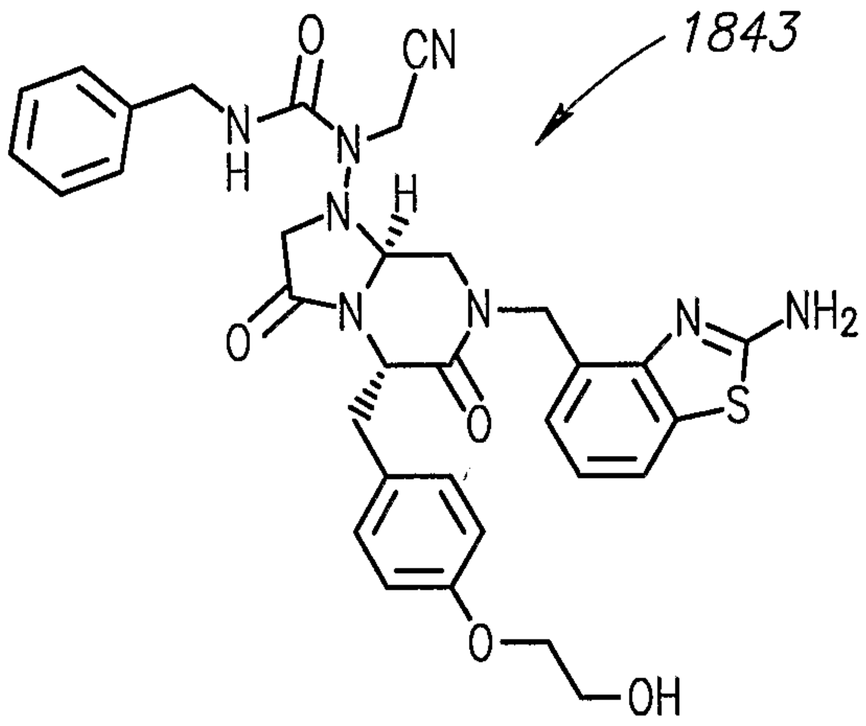


FIG.10G

1843



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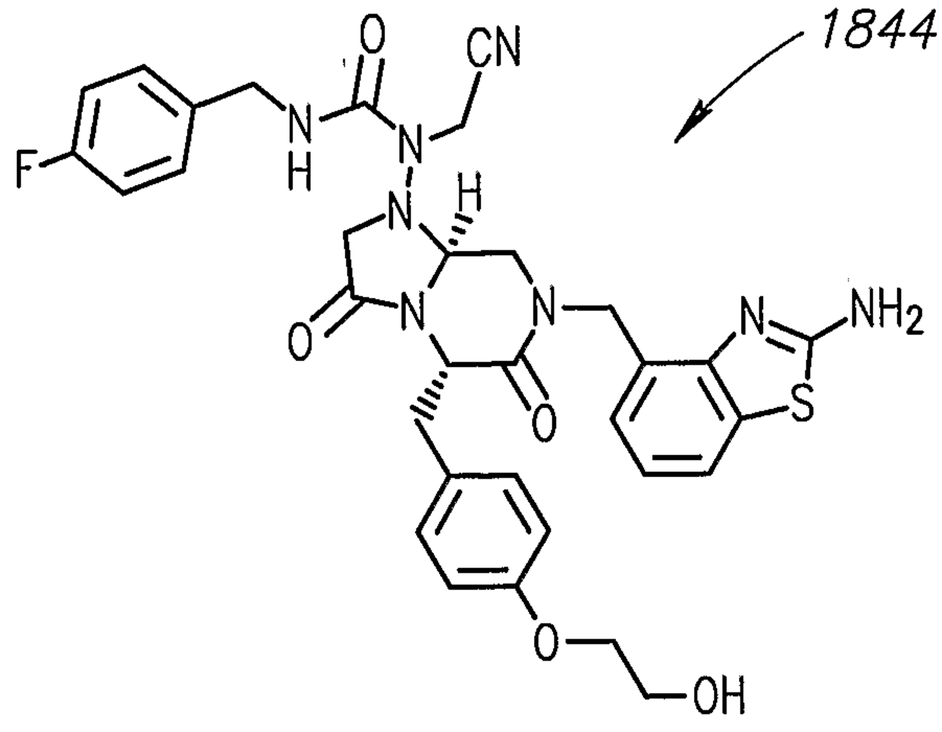

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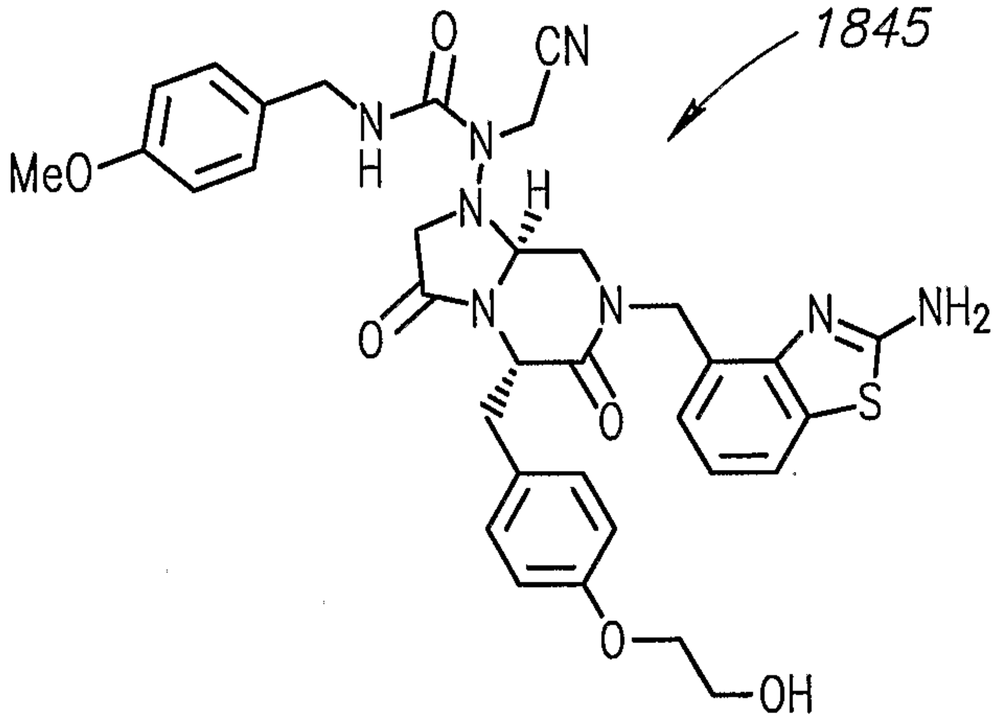

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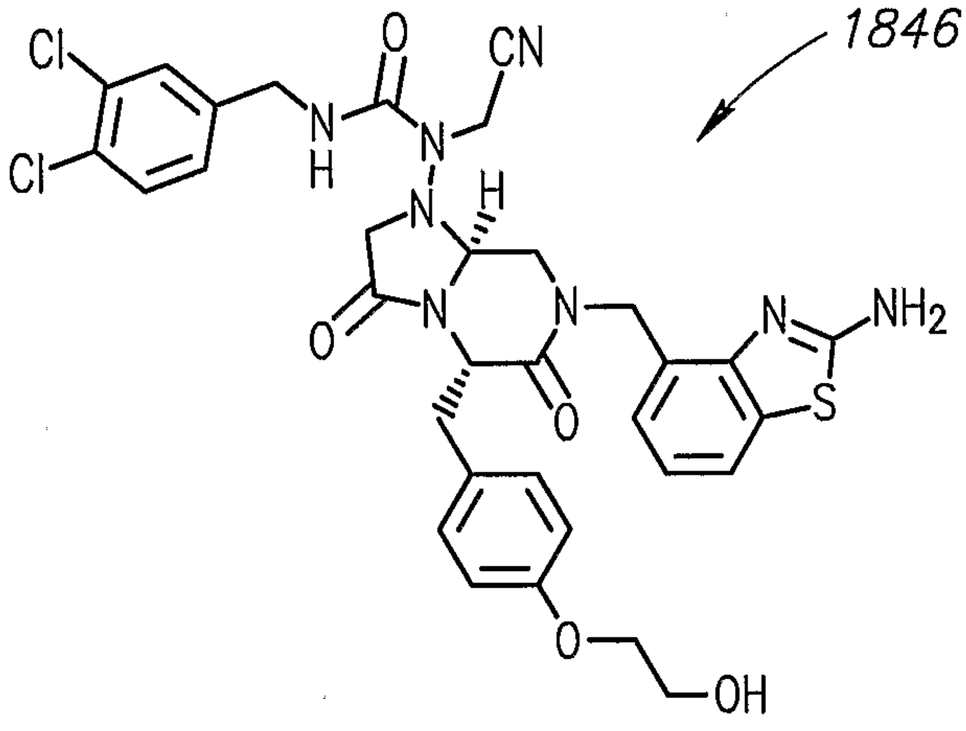

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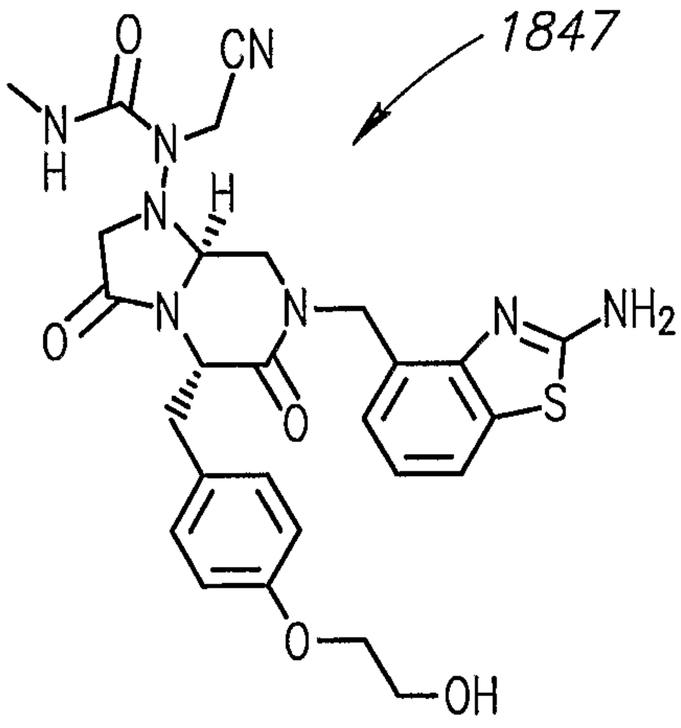

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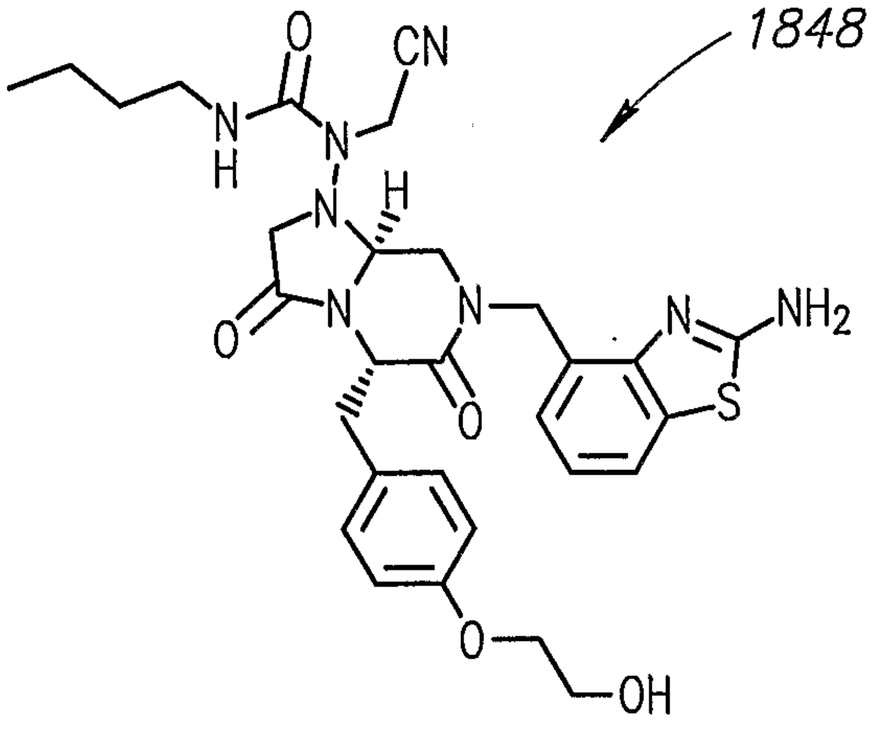
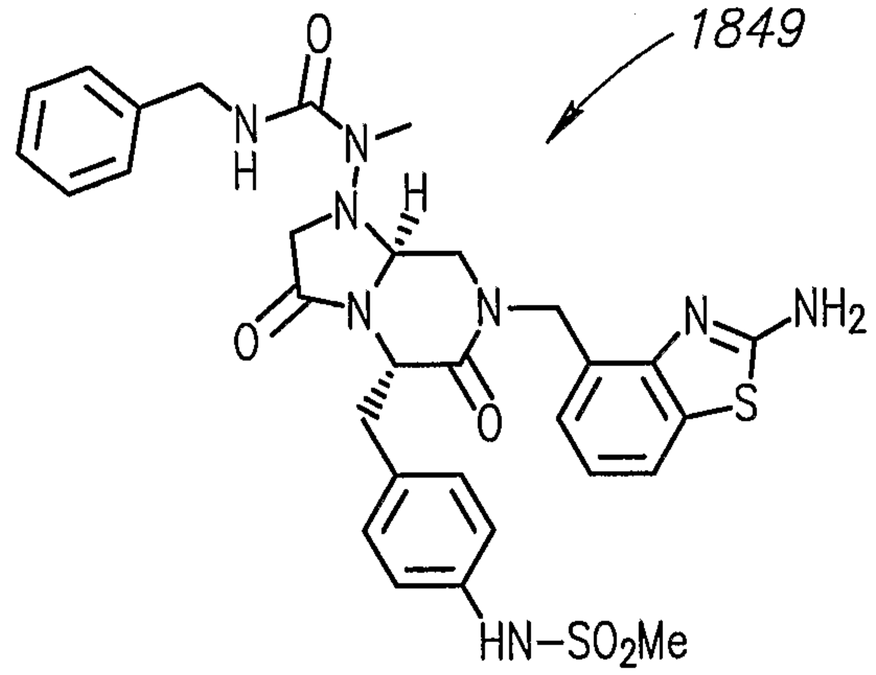


FIG.10H

1849



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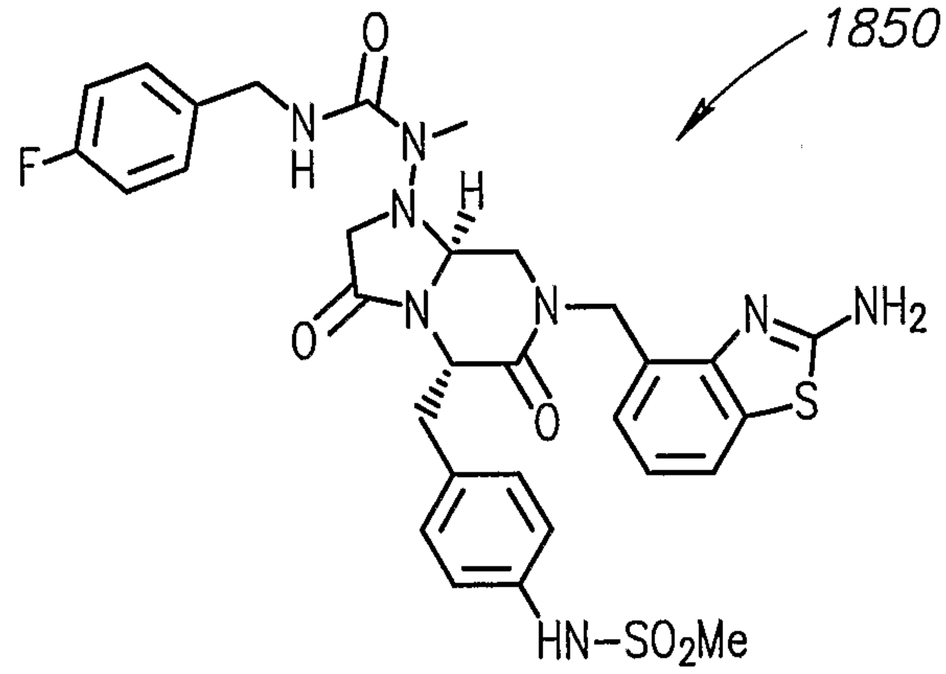

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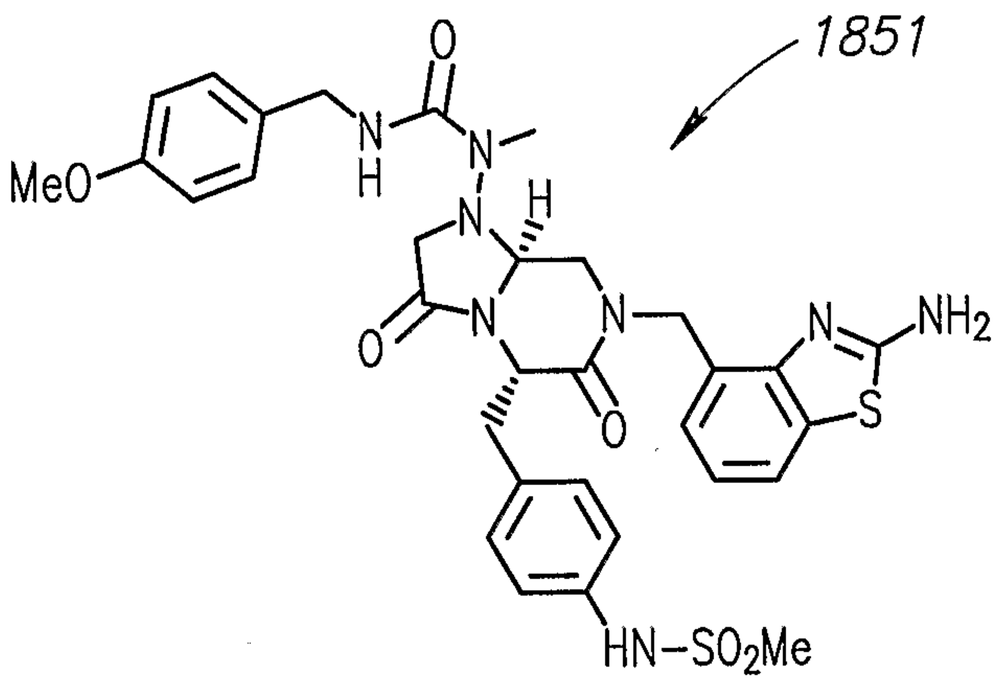

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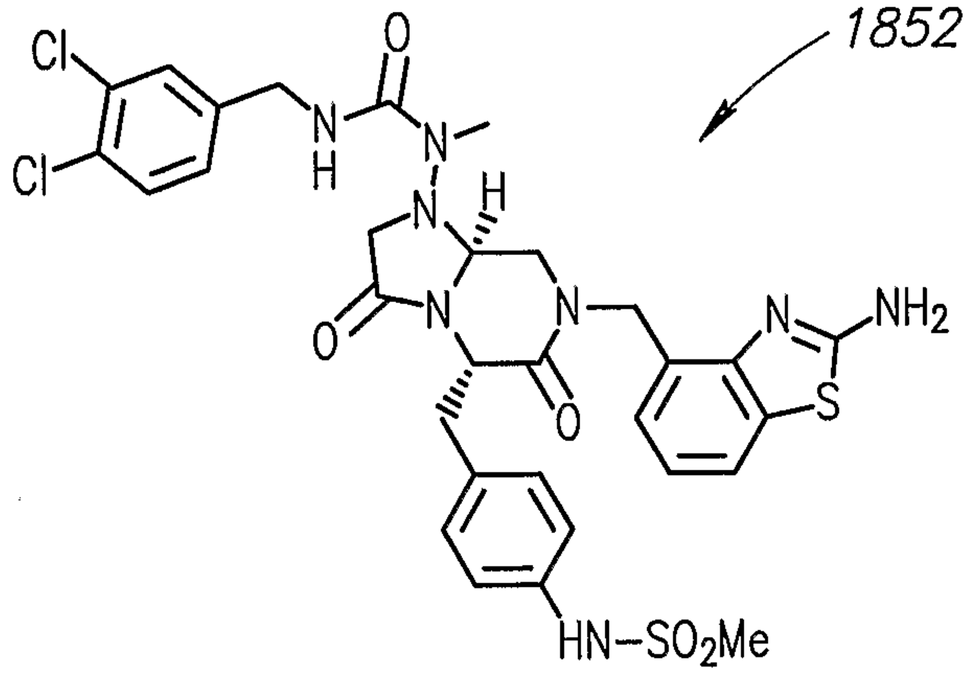

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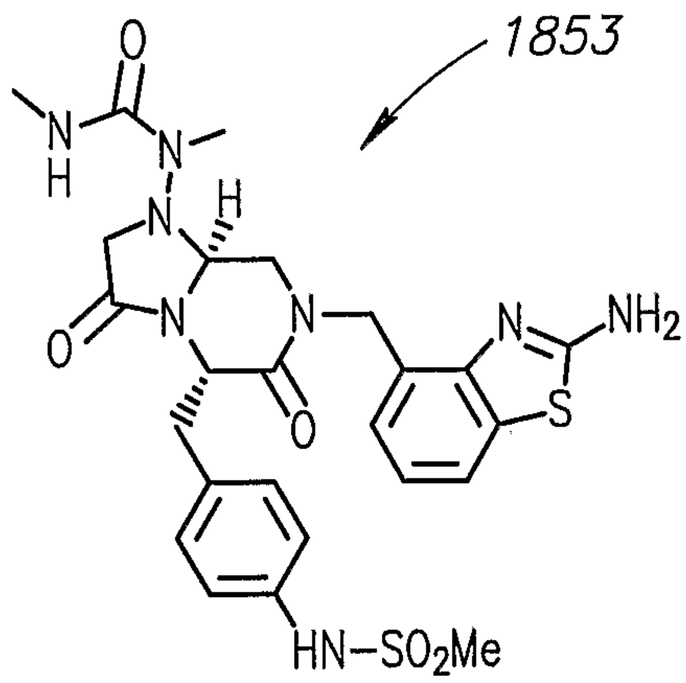

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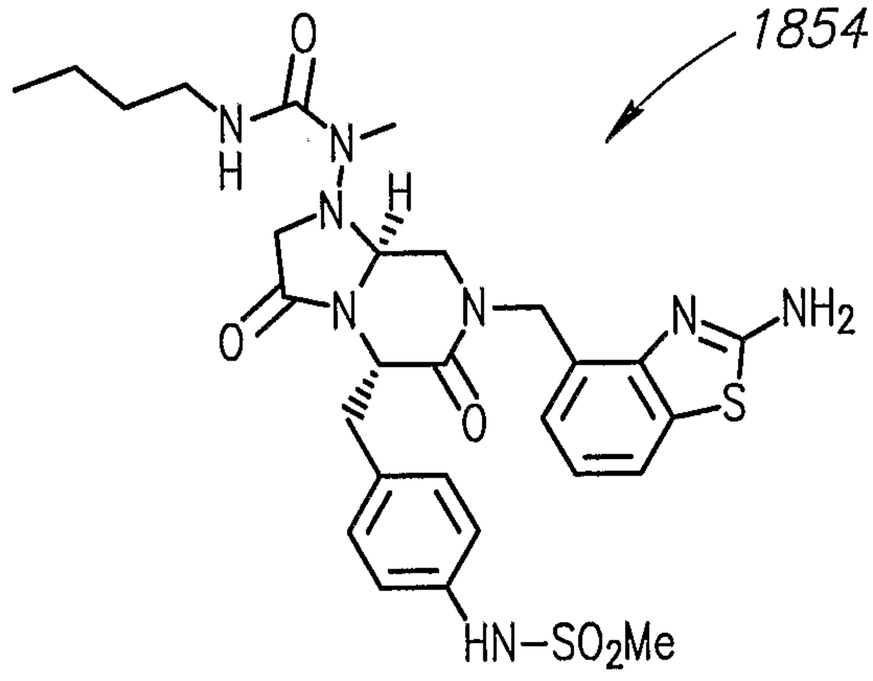
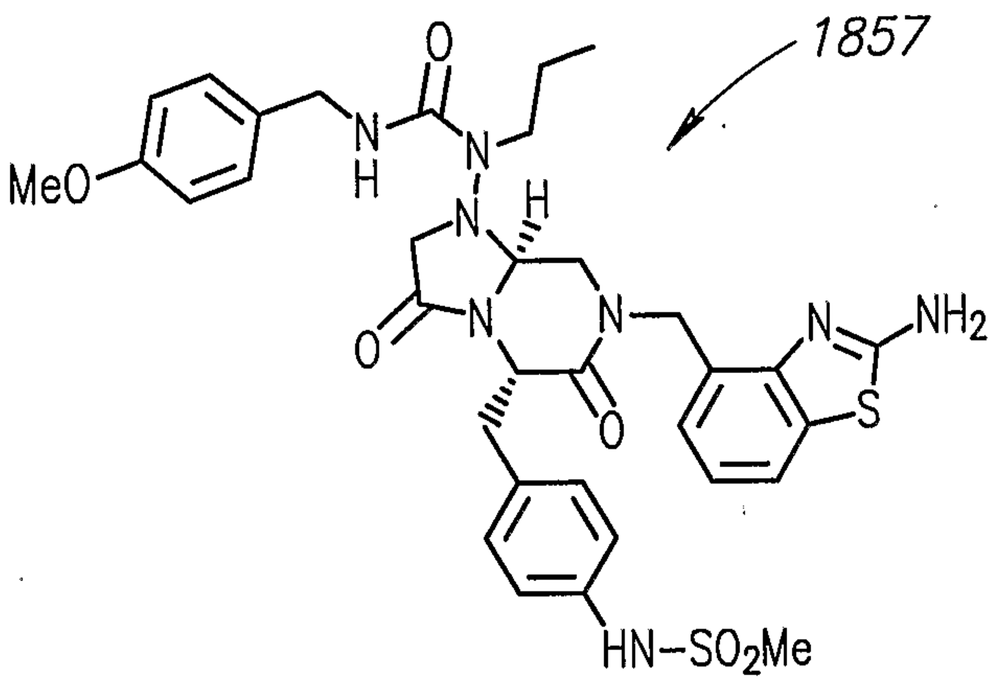
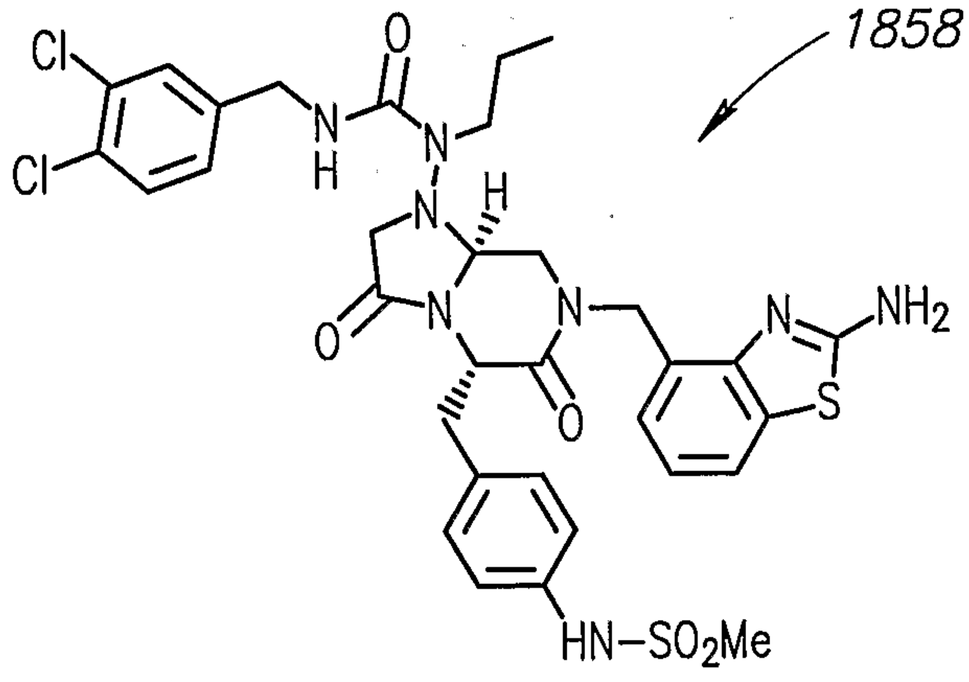


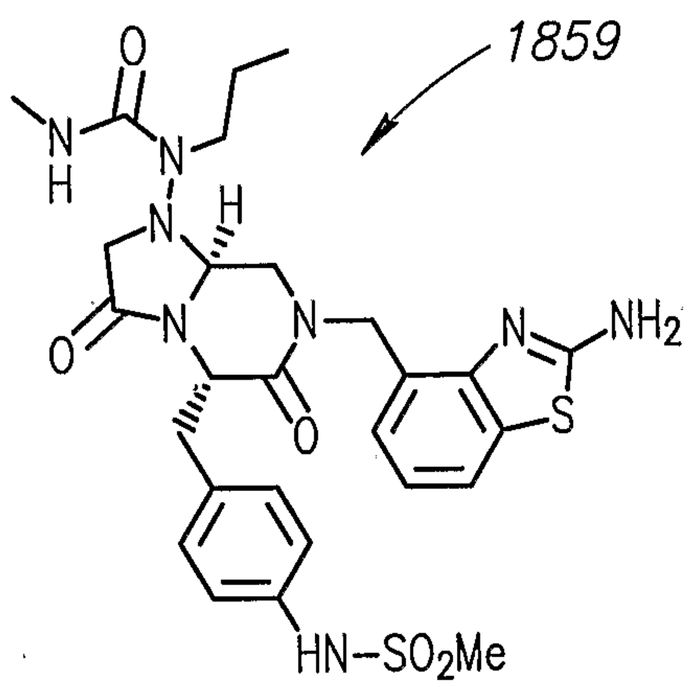
1855

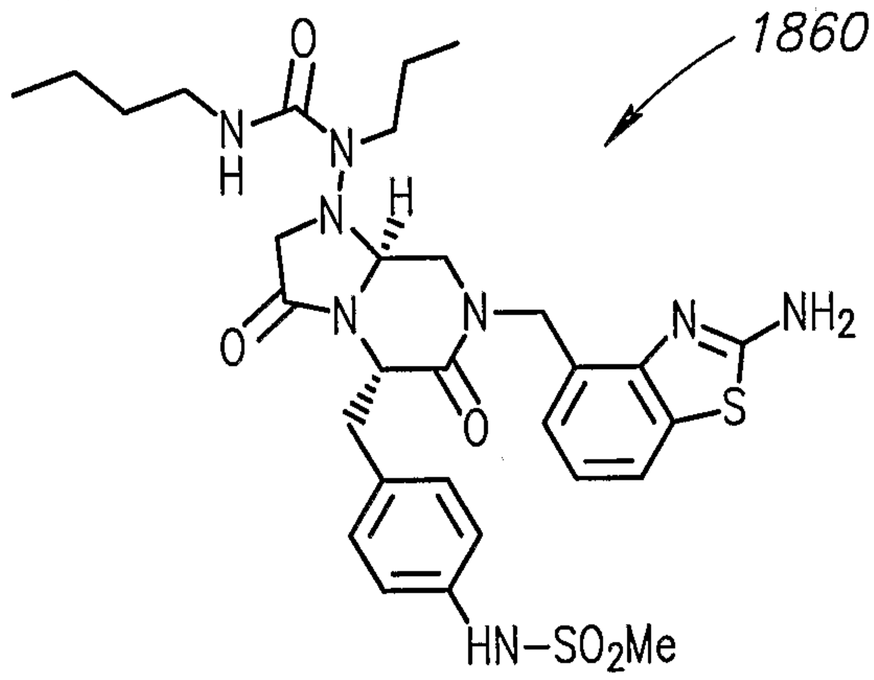
1856

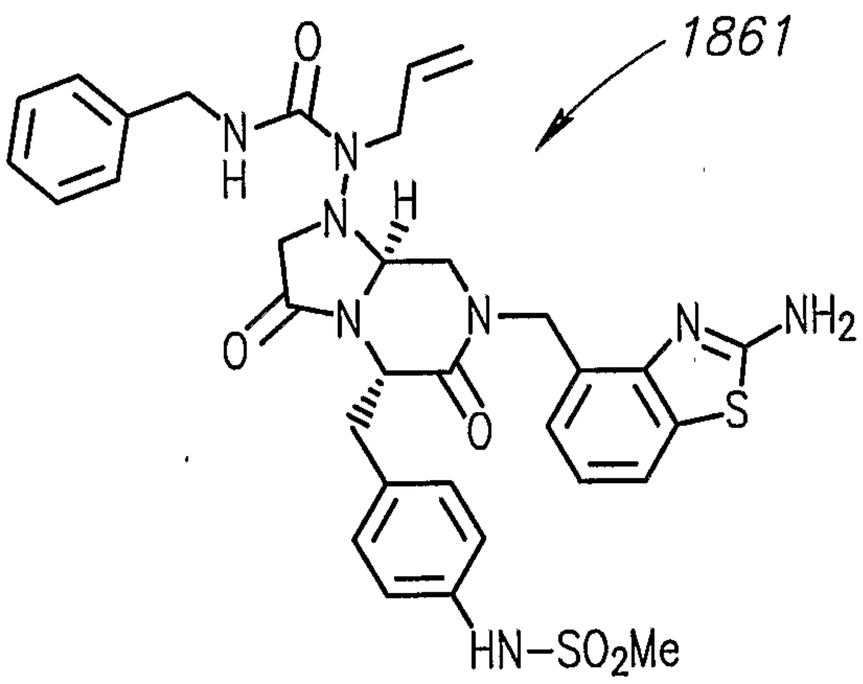
FIG.10I

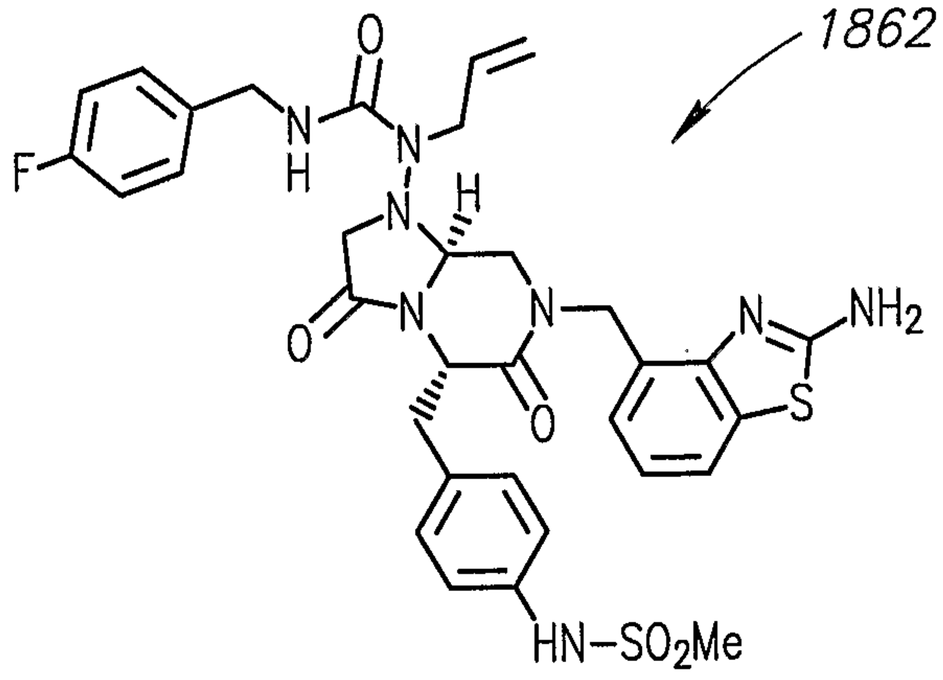

1857
MeO
HN–SO2Me

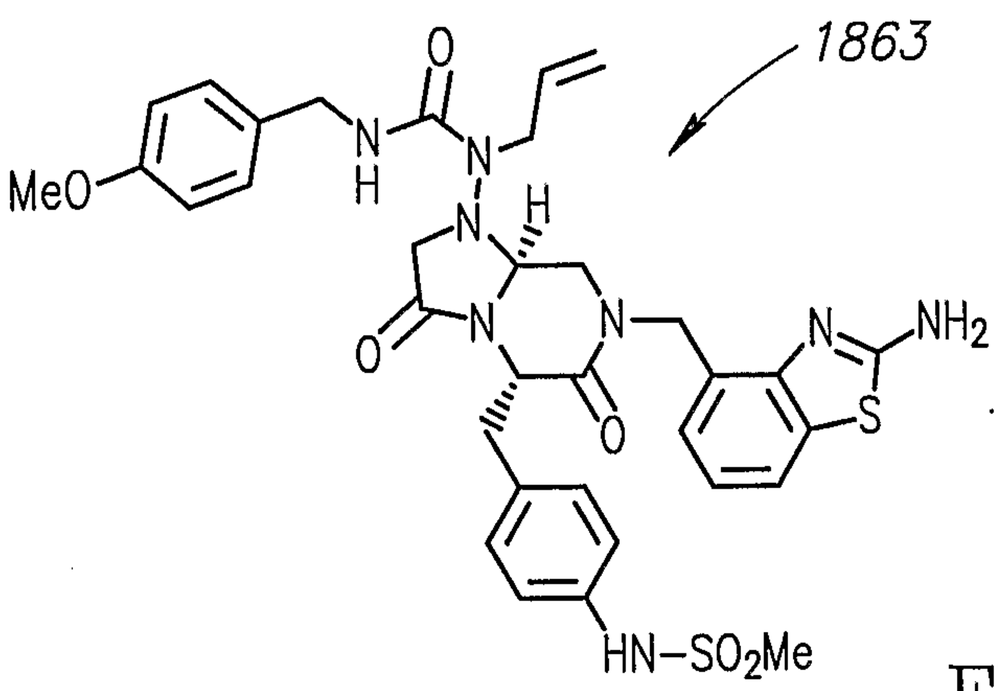

1858
Cl
Cl
HN–SO2Me


1859
HN–SO2Me


1860
HN–SO2Me


1861
HN–SO2Me


1862
F
HN–SO2Me


1863
MeO
HN–SO2Me

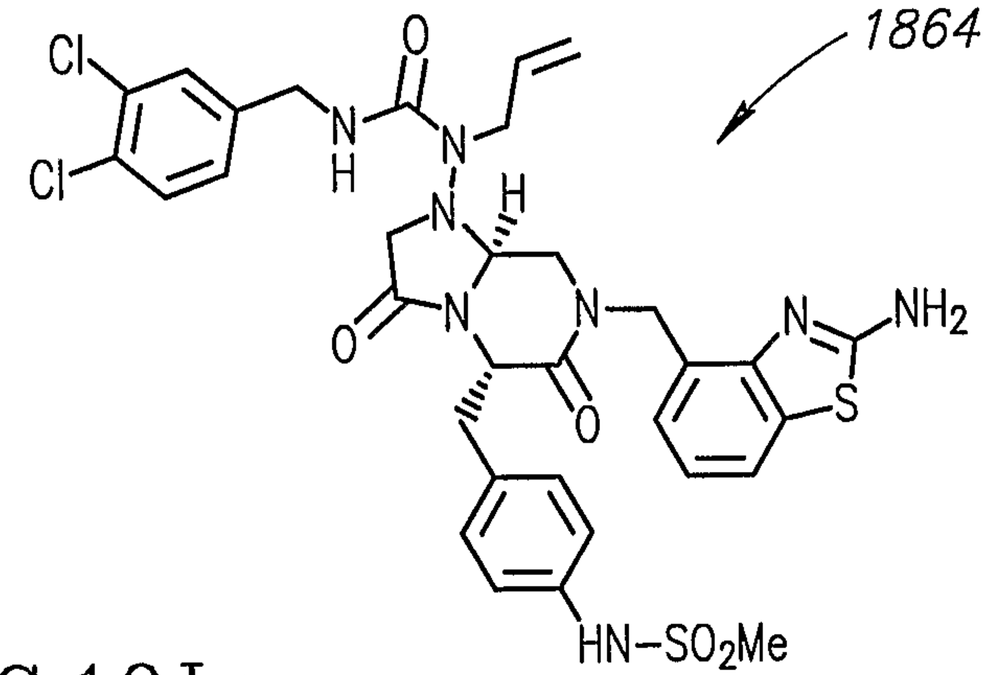
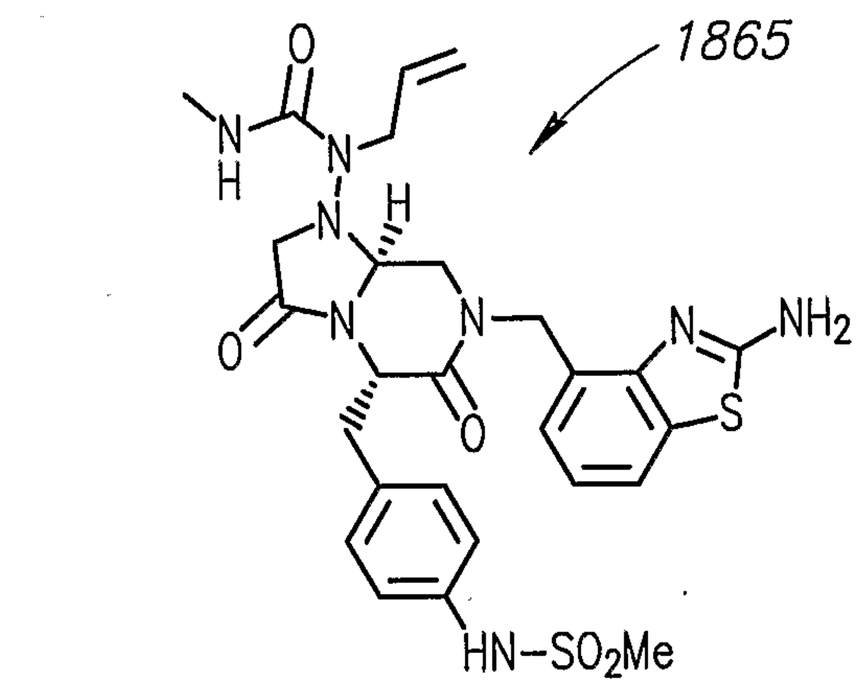
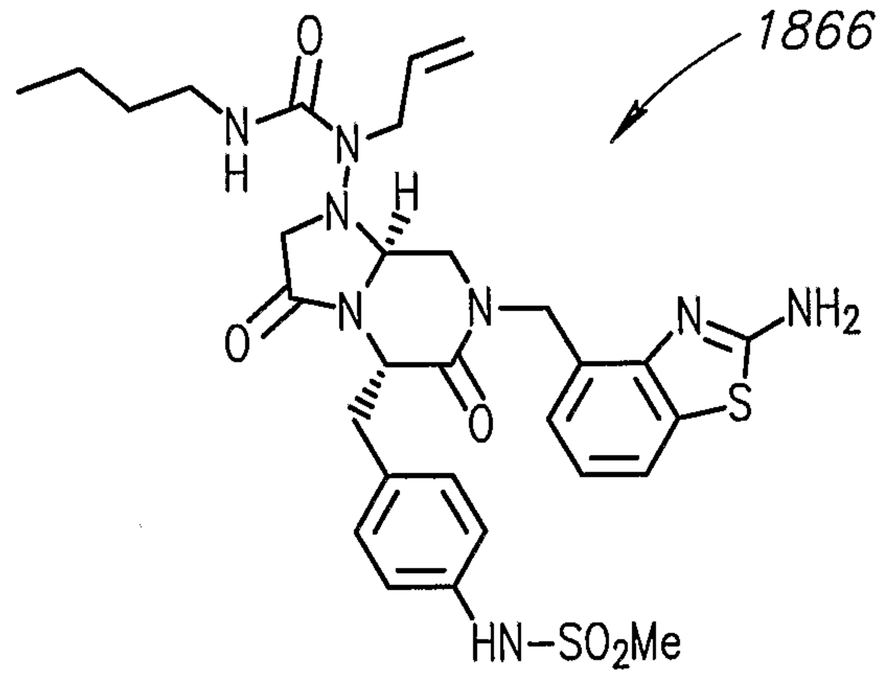
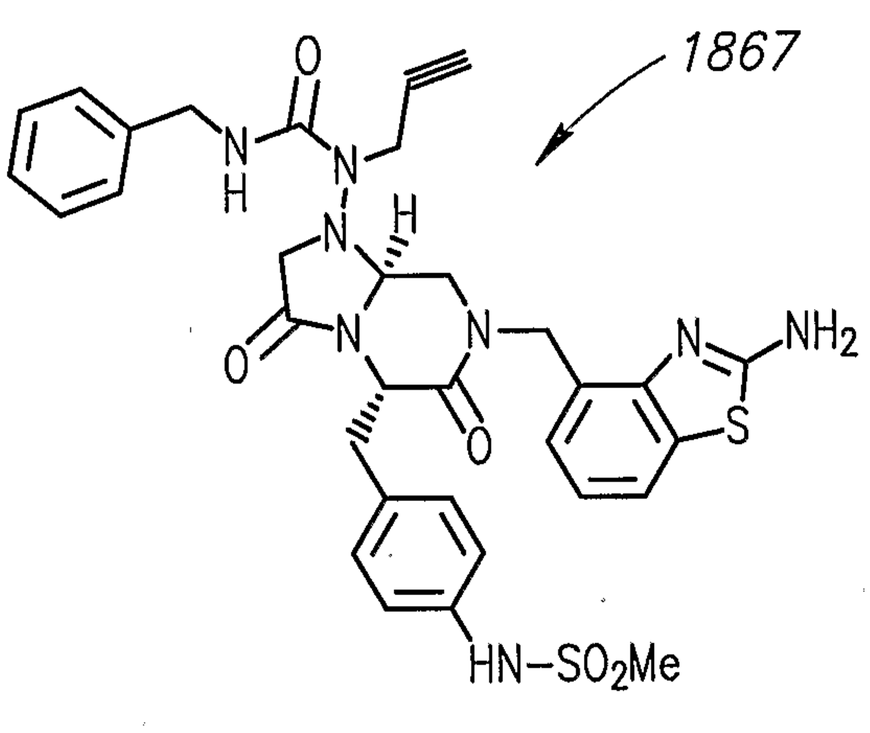
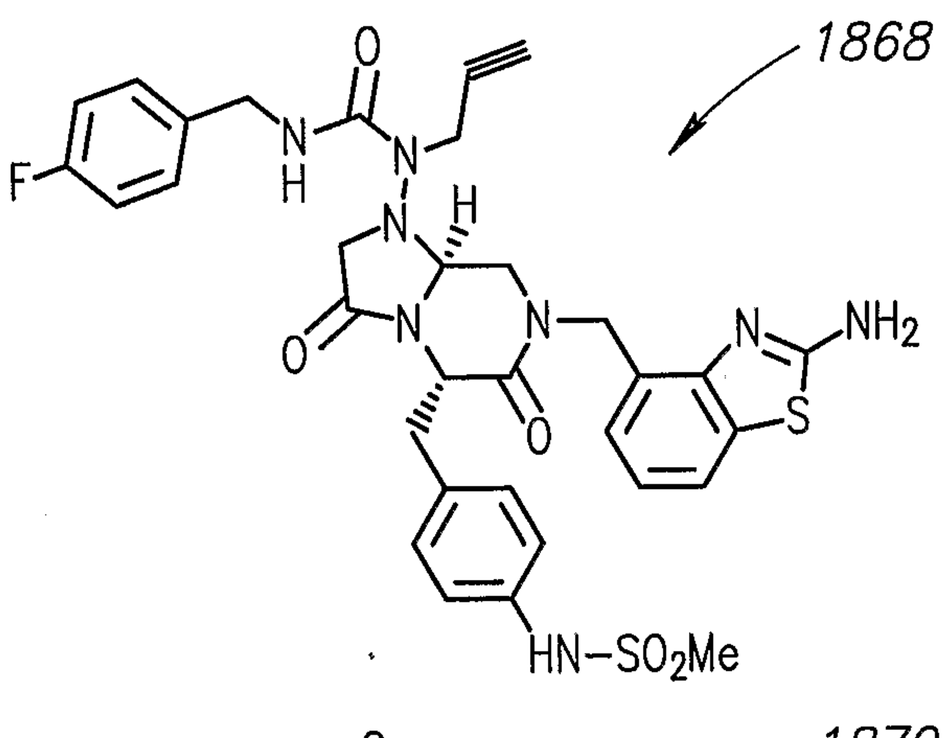

1864
Cl
Cl
HN–SO2Me

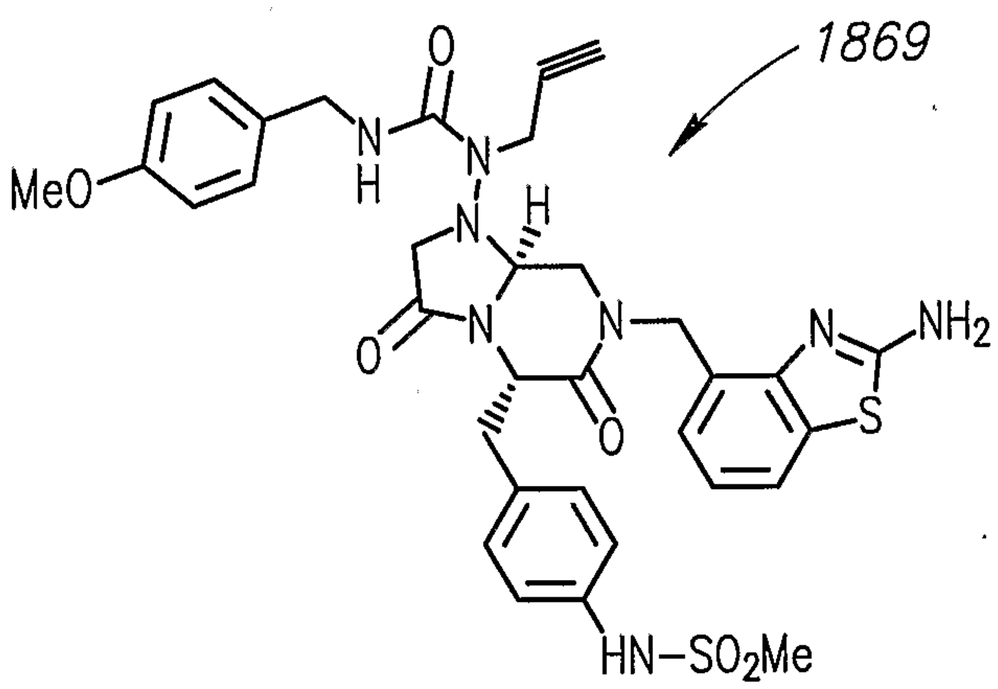
FIG.10J

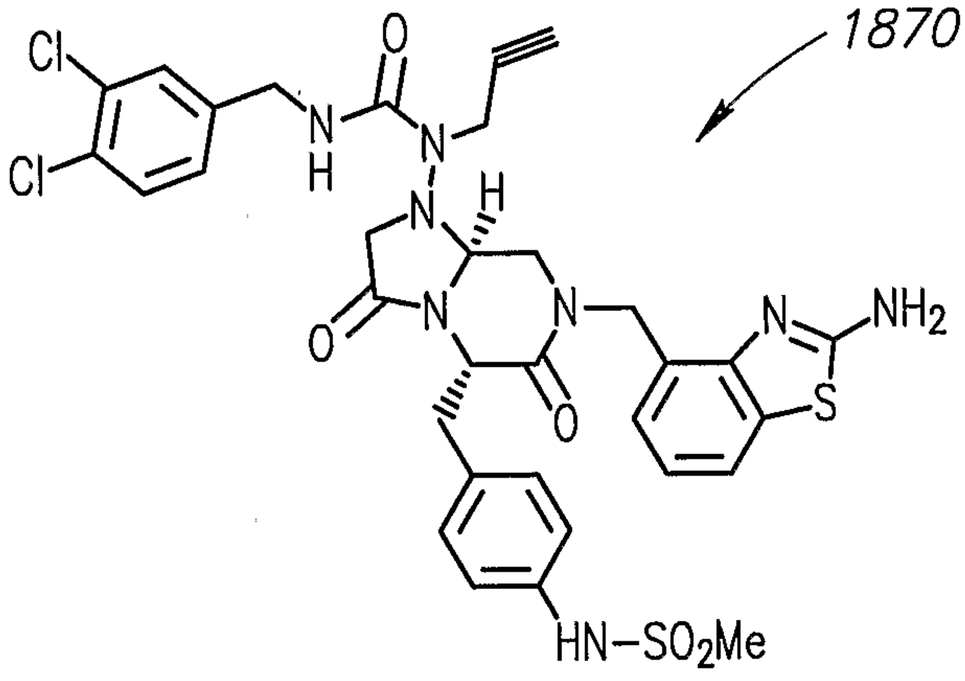

1865
O
N
H
N
N
H
O
N
O
N
N
S
NH2
HN–SO2Me

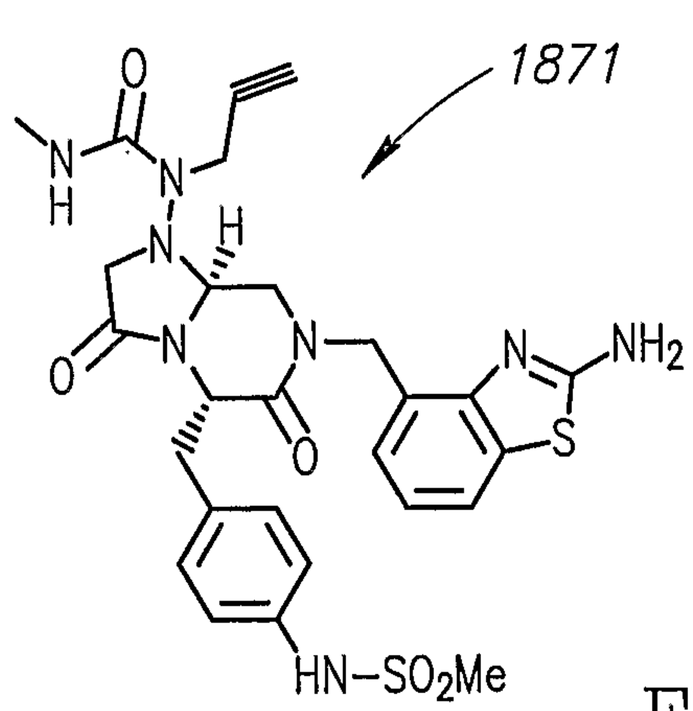

1866
O
N
H
N
N
H
O
N
O
N
N
S
NH2
HN–SO2Me


1867
O
N
H
N
N
H
O
N
O
N
N
S
NH2
HN–SO2Me


1868
F
O
N
H
N
N
H
O
N
O
N
N
S
NH2
HN–SO2Me


1869
MeO
O
N
H
N
N
H
O
N
O
N
N
S
NH2
HN–SO2Me


1870
Cl
Cl
O
N
H
N
N
H
O
N
O
N
N
S
NH2
HN–SO2Me


1871
O
N
H
N
N
H
O
N
O
N
N
S
NH2
HN–SO2Me

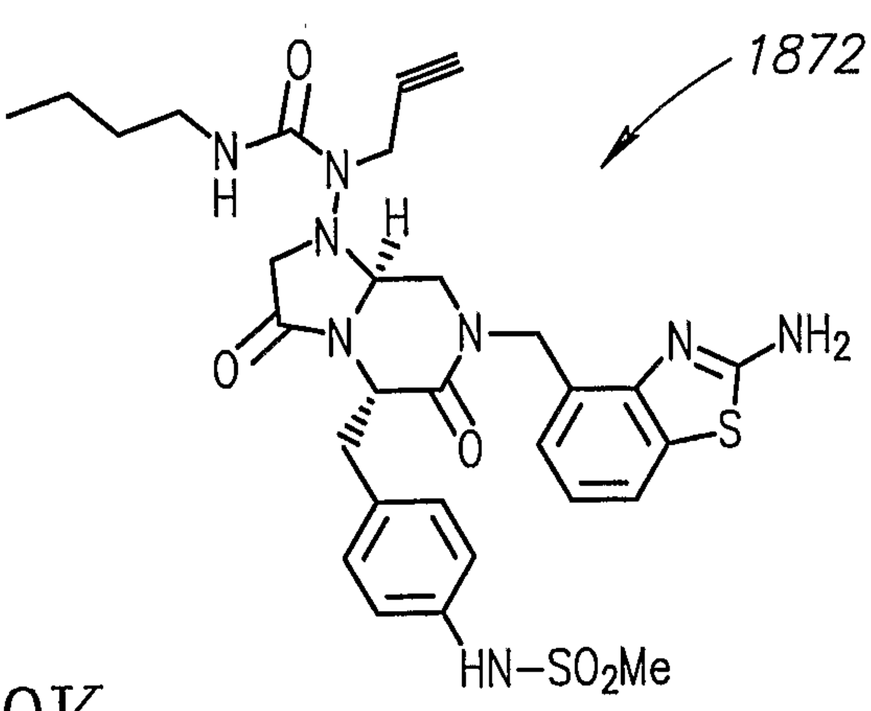
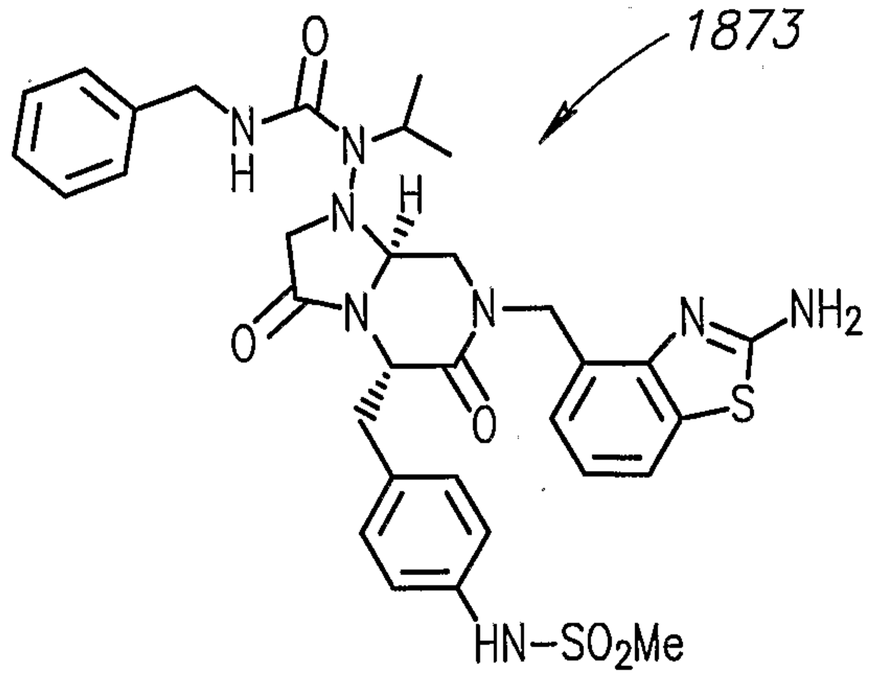
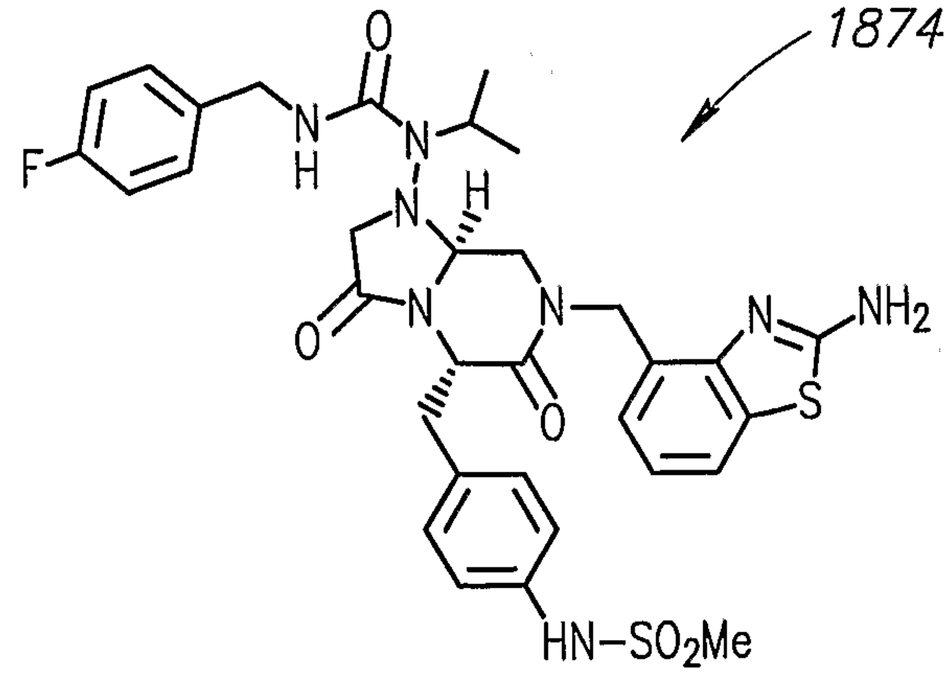

1872
O
N
H
N
N
H
O
N
O
N
N
S
NH2
HN–SO2Me

FIG.10K

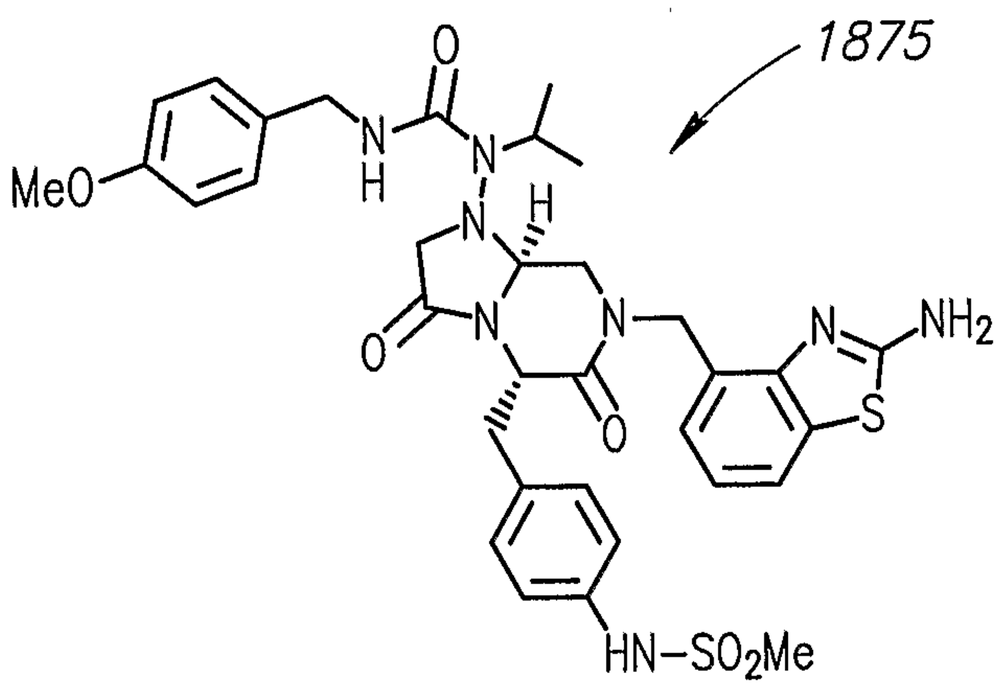
1873



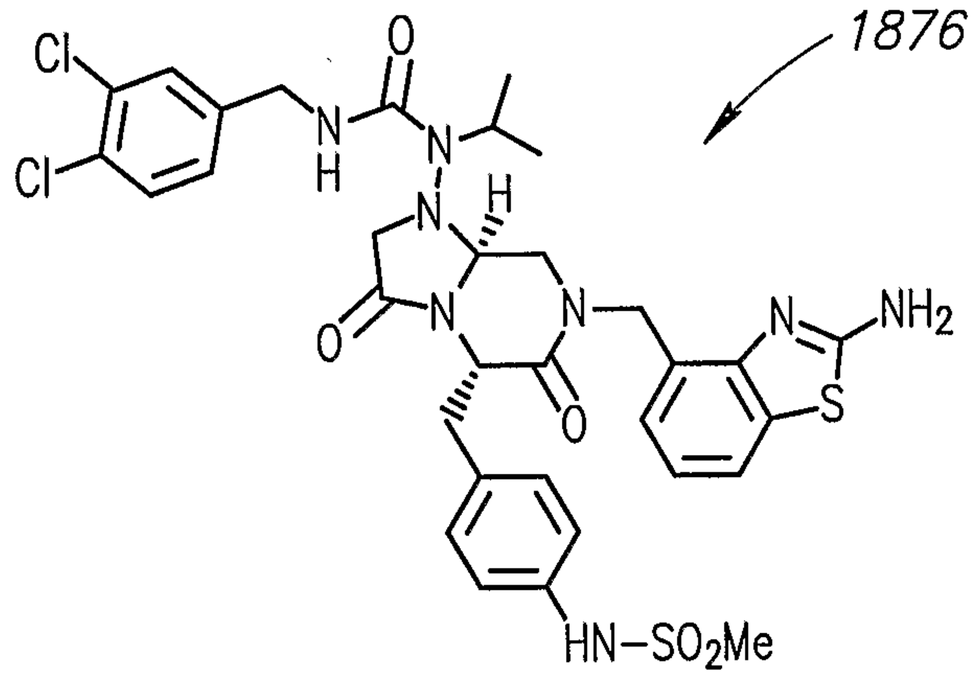
1874



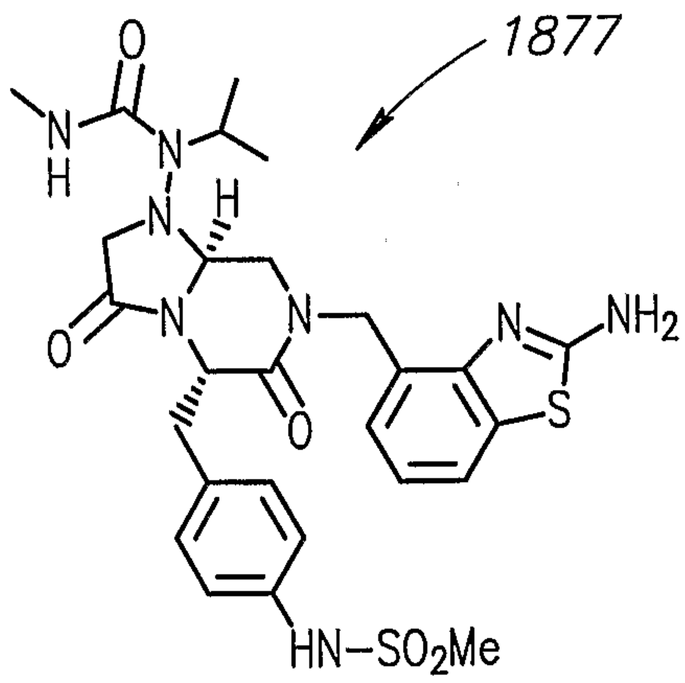
1875



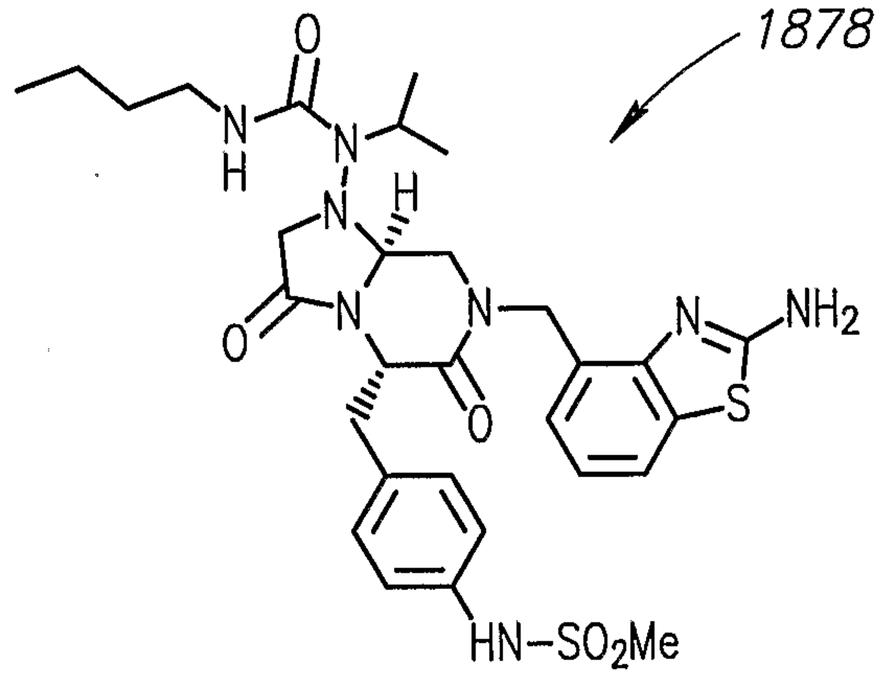
1876



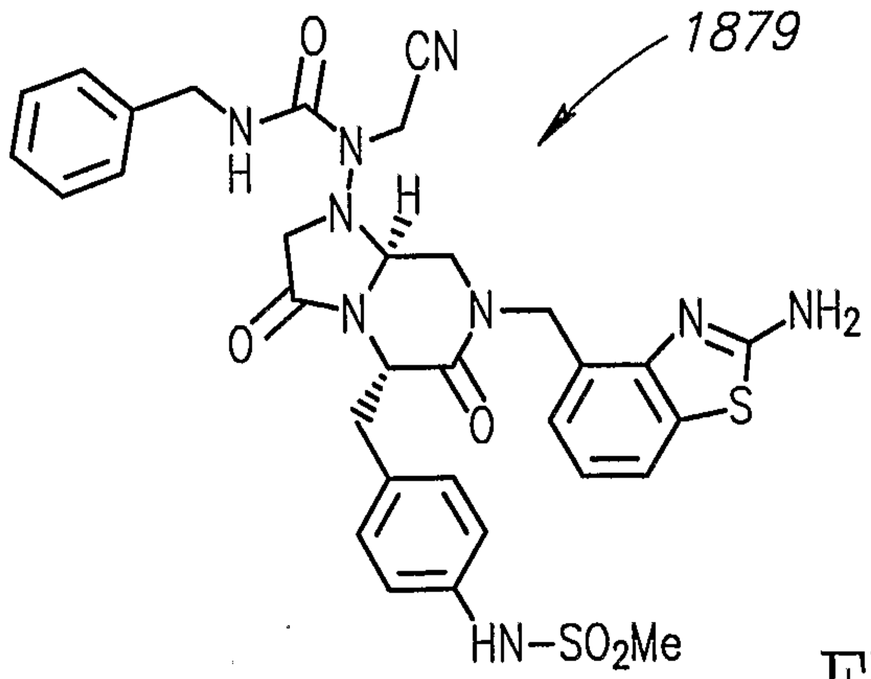
1877



1878



1879



1880

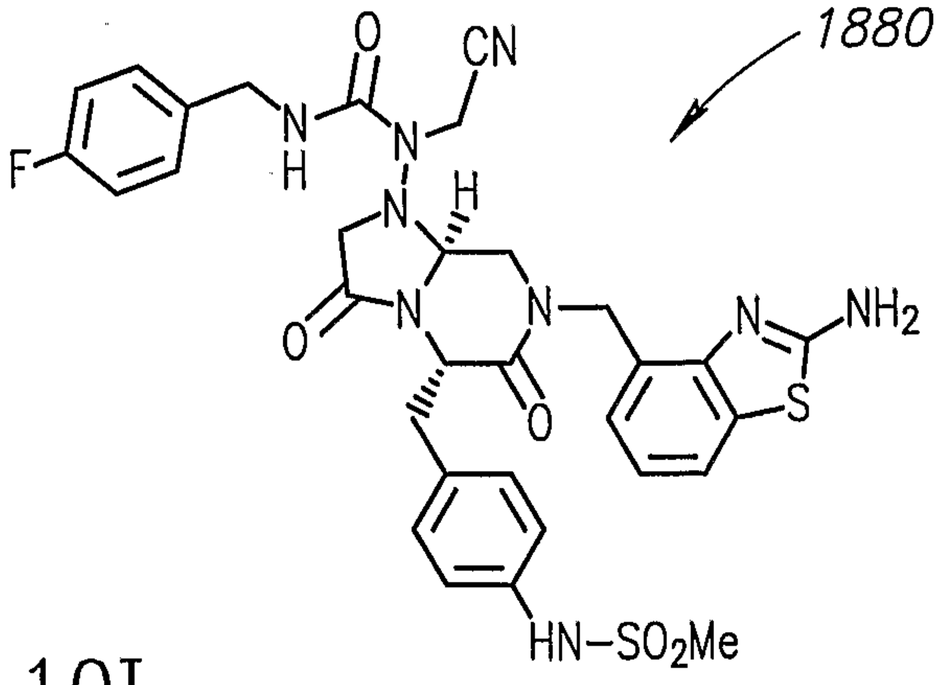
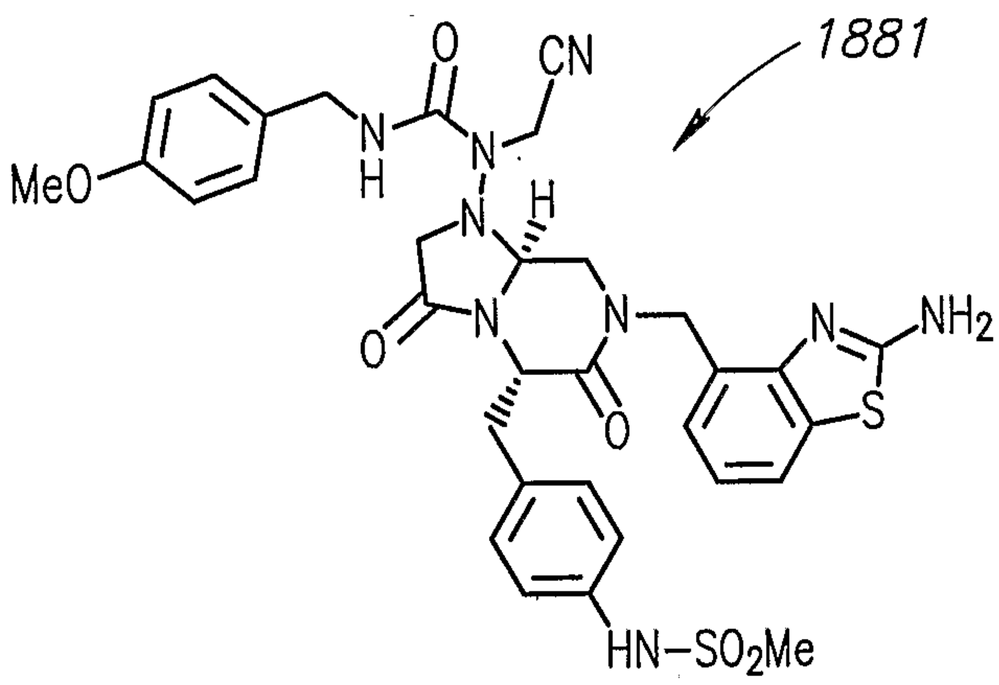
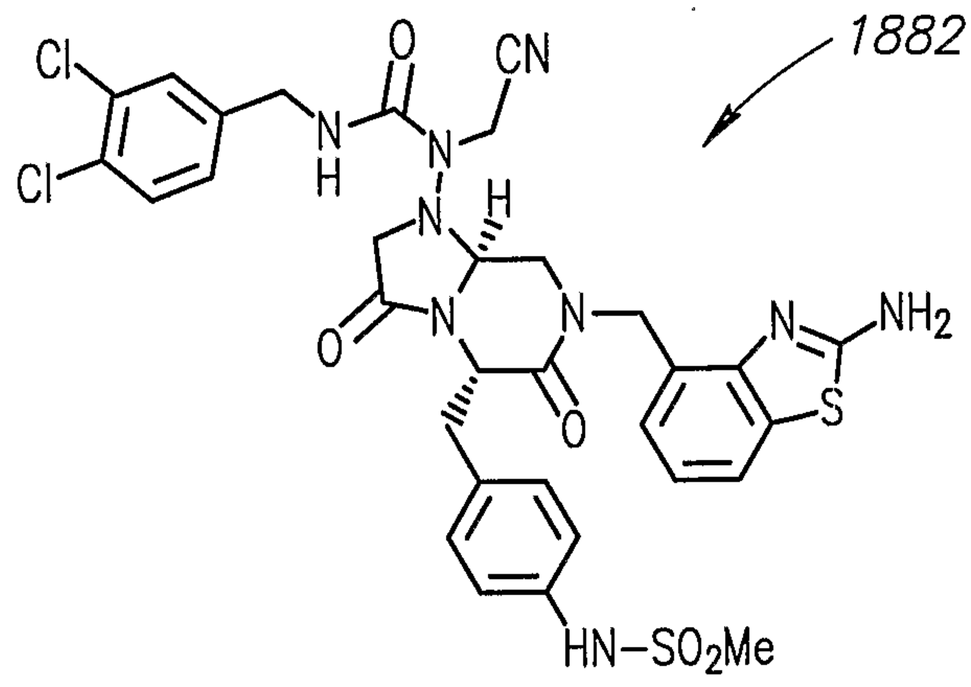
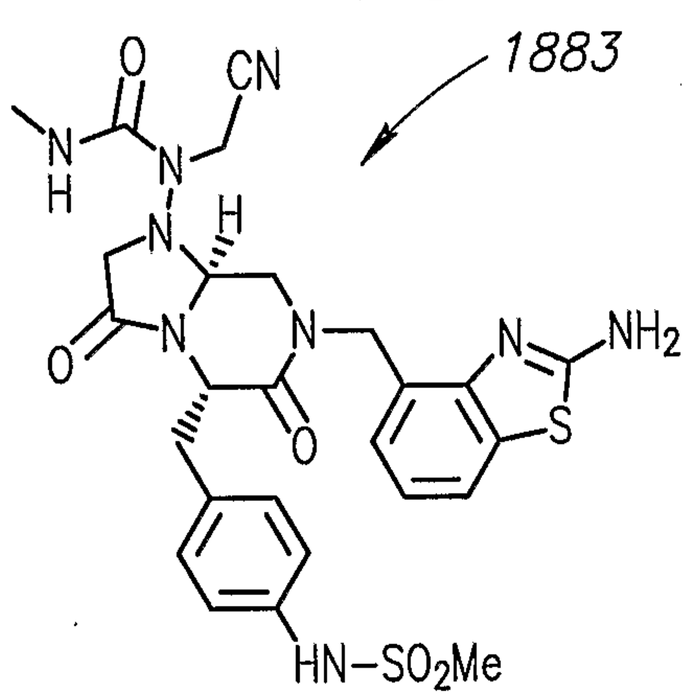
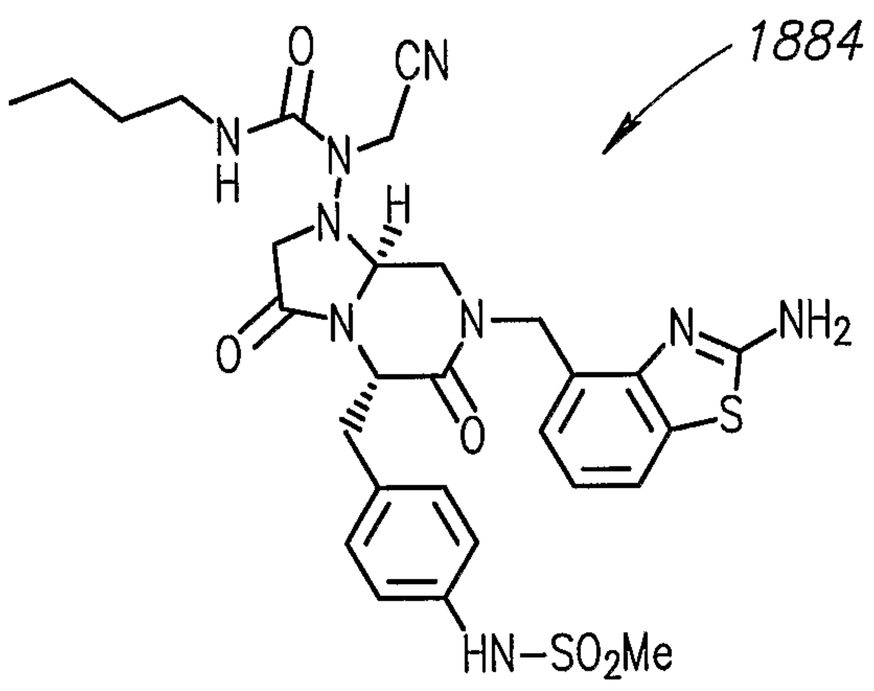


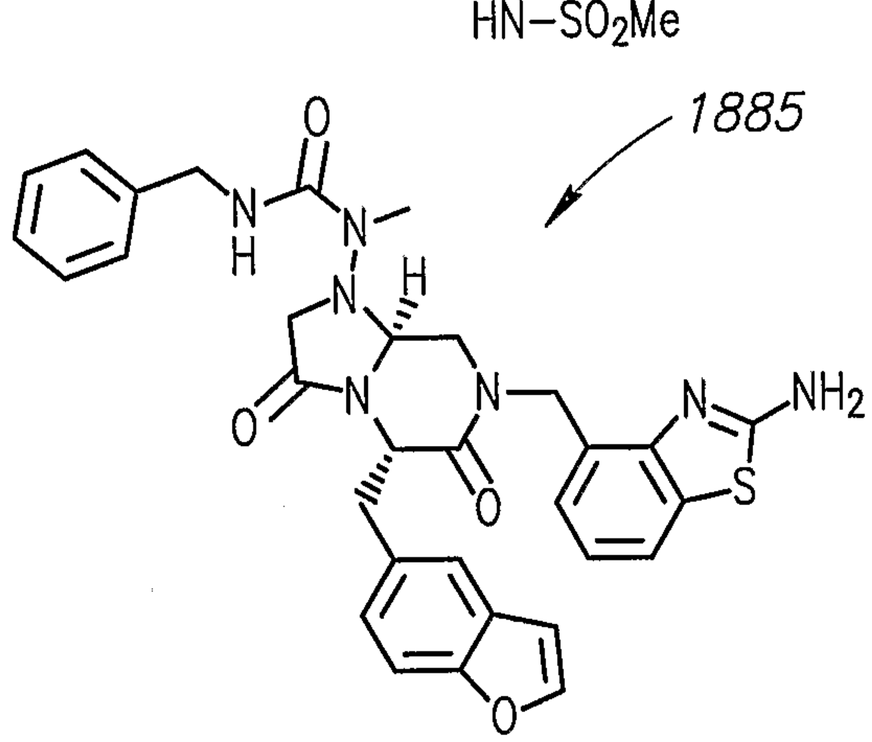
FIG.10L

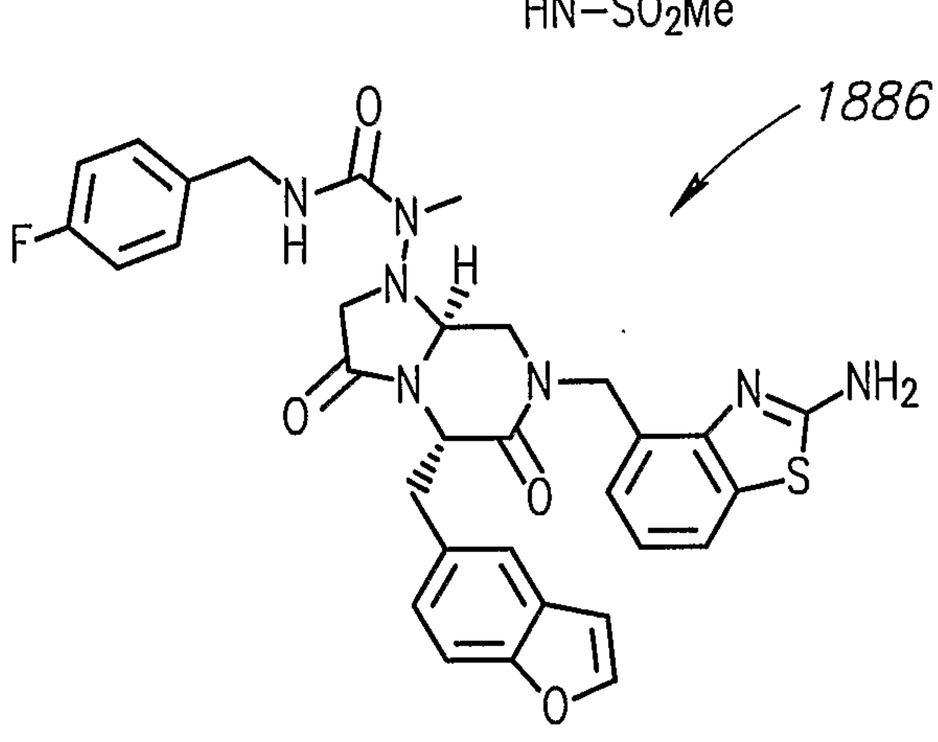

1881
MeO
O
CN
N
H
N
H
N
O
N
O
N
N
NH2
S
HN–SO2Me


1882
Cl
Cl
O
CN
N
H
N
H
N
O
N
O
N
N
NH2
S
HN–SO2Me


1883
O
CN
N
H
N
H
N
O
N
O
N
N
NH2
S
HN–SO2Me


1884
O
CN
N
H
N
H
N
O
N
O
N
N
NH2
S
HN–SO2Me


1885
O
N
H
N
H
N
O
N
O
N
N
NH2
S
O

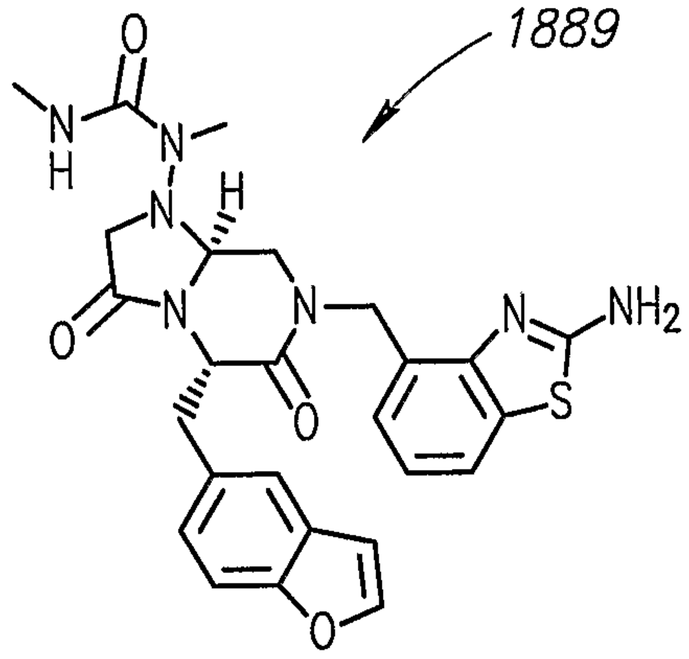

1886
F
O
N
H
N
H
N
O
N
O
N
N
NH2
S
O

1887
MeO
O
N
H
N
H
N
O
N
O
N
N
NH2
S
O

1888
Cl
Cl
O
N
H
N
H
N
O
N
O
N
N
NH2
S
O

FIG.10M

1889



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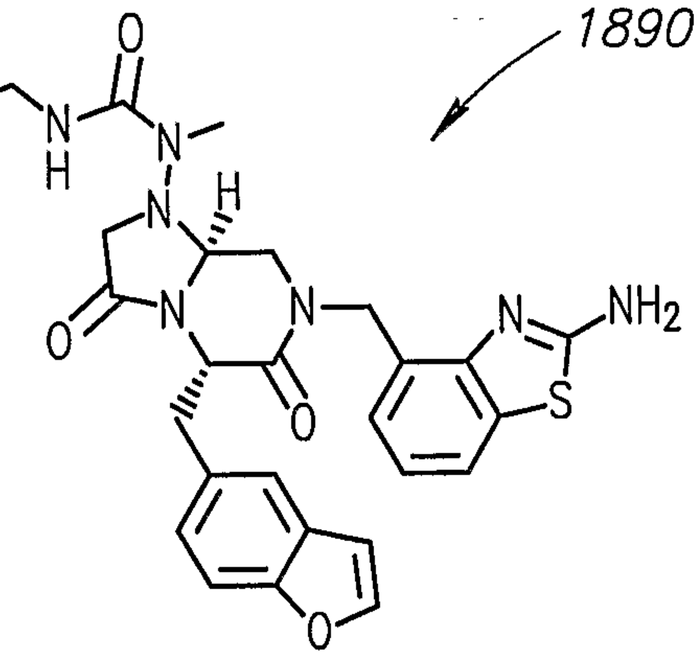

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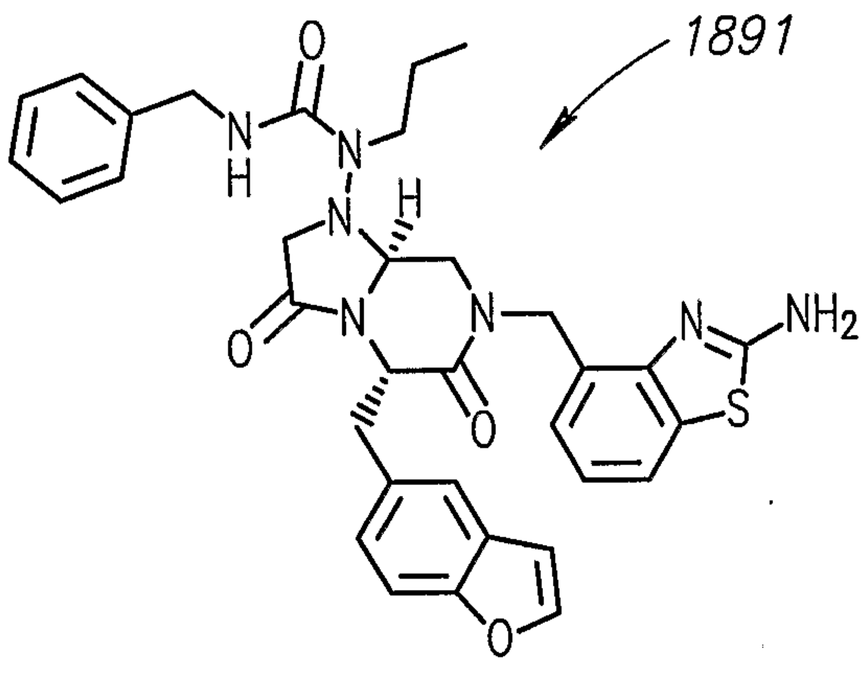

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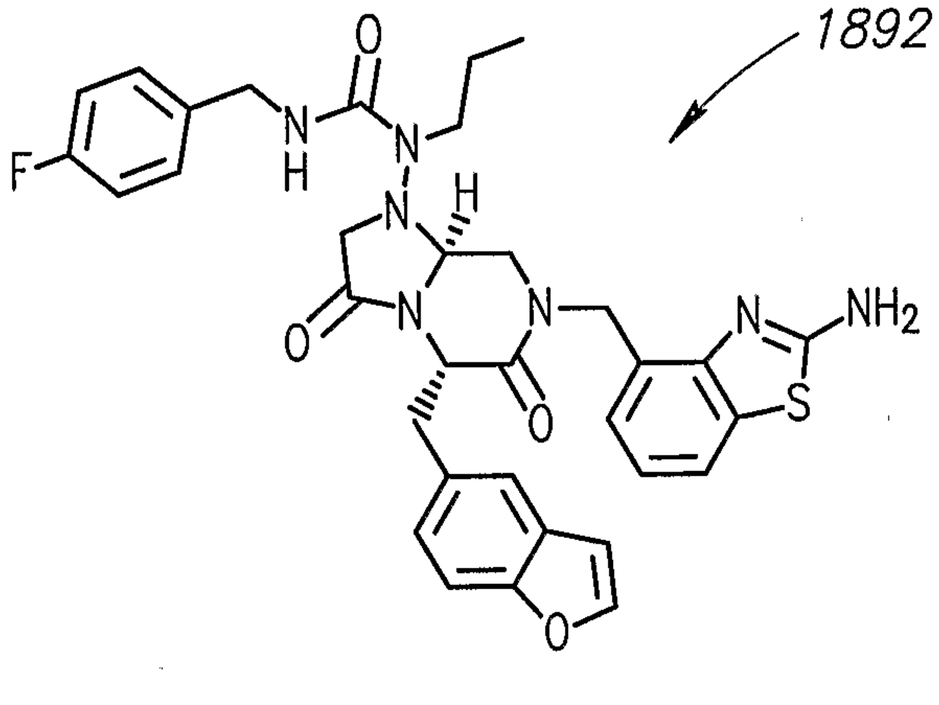

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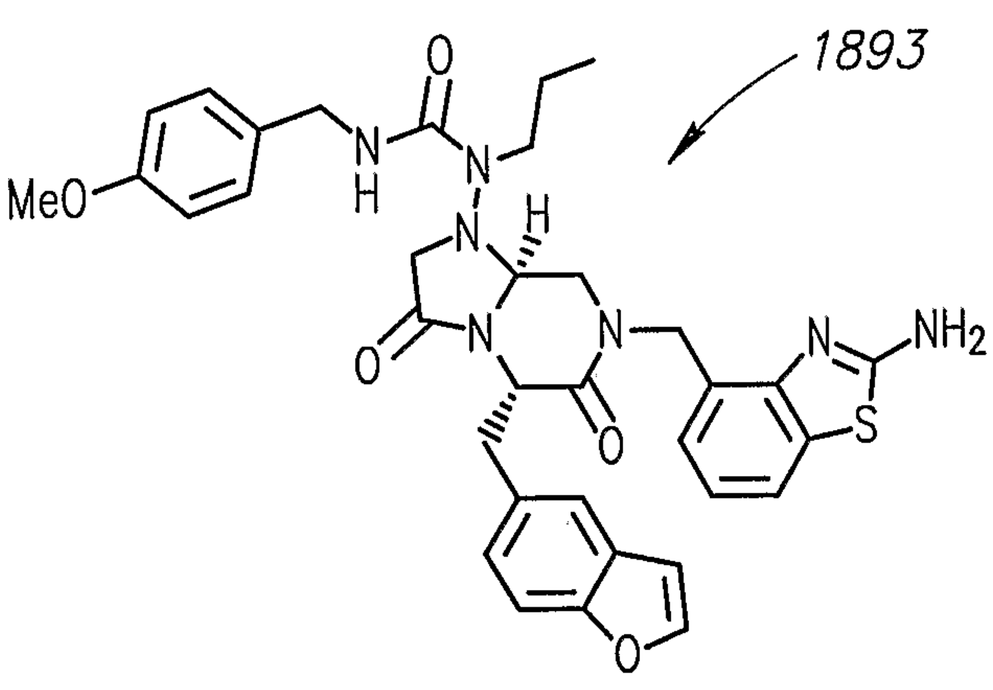

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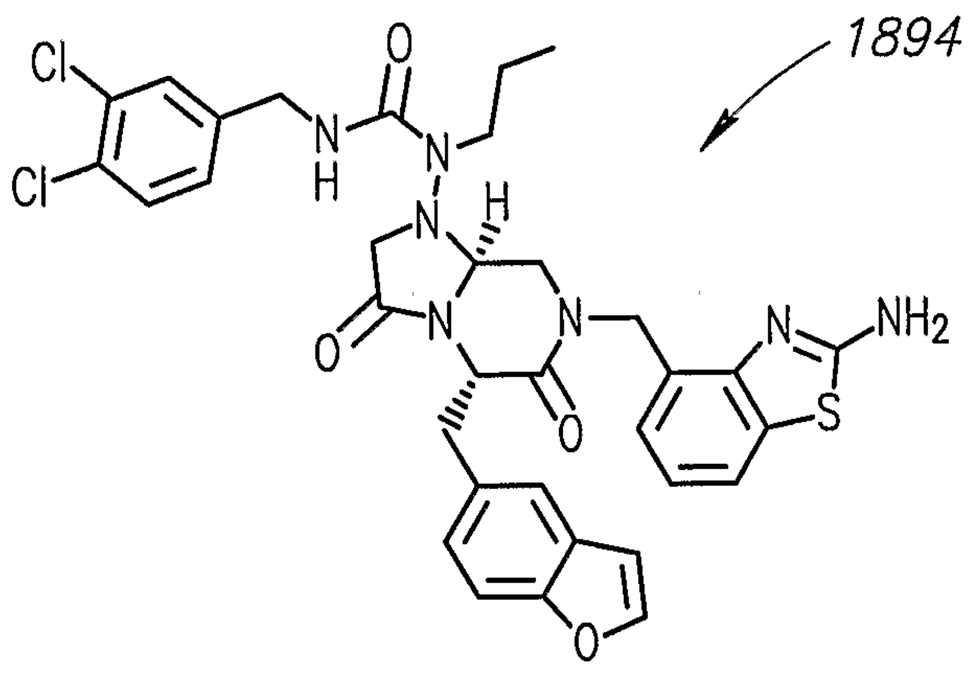
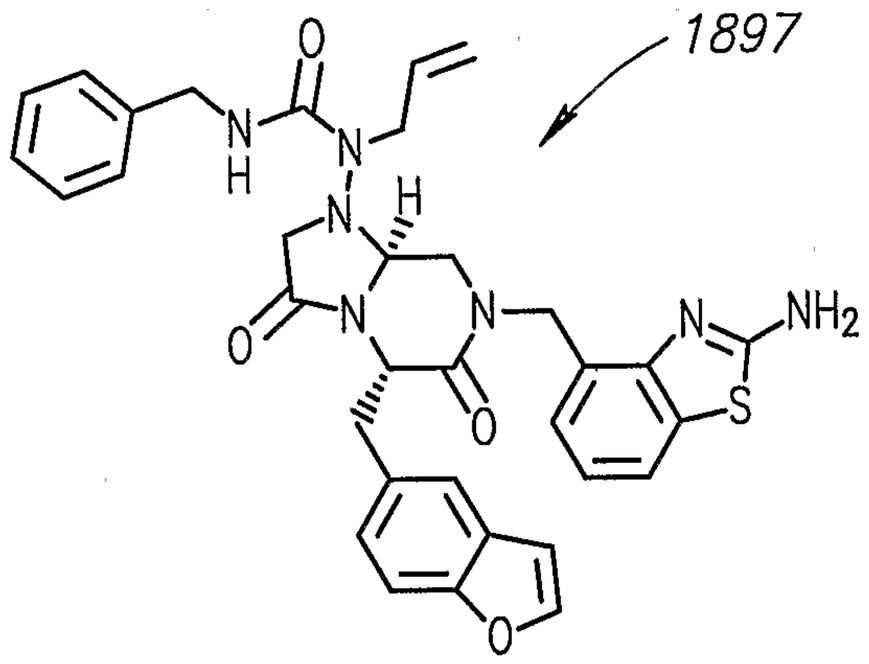


1895

1896

FIG.10N

1897



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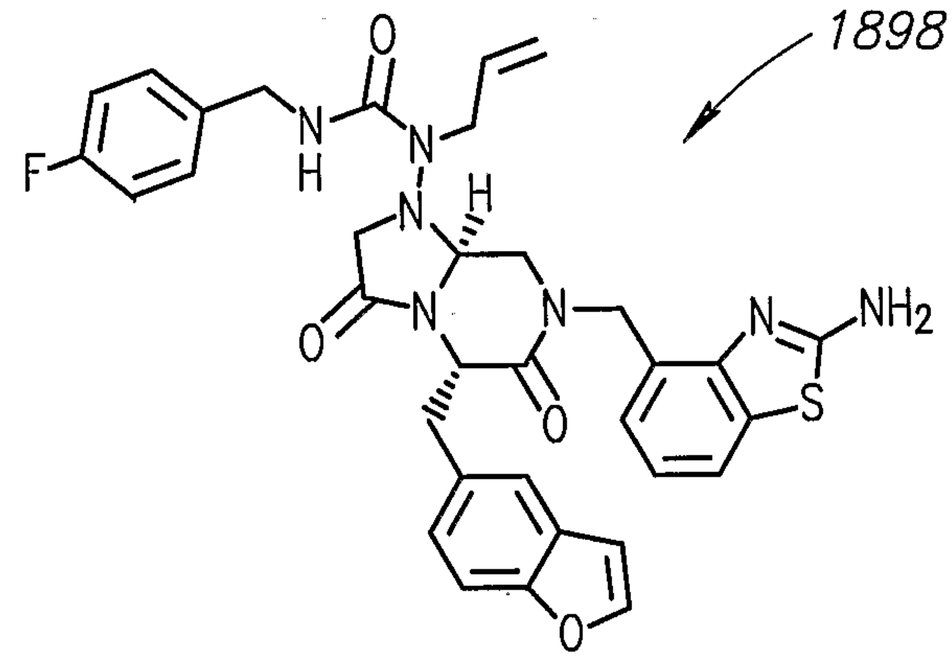

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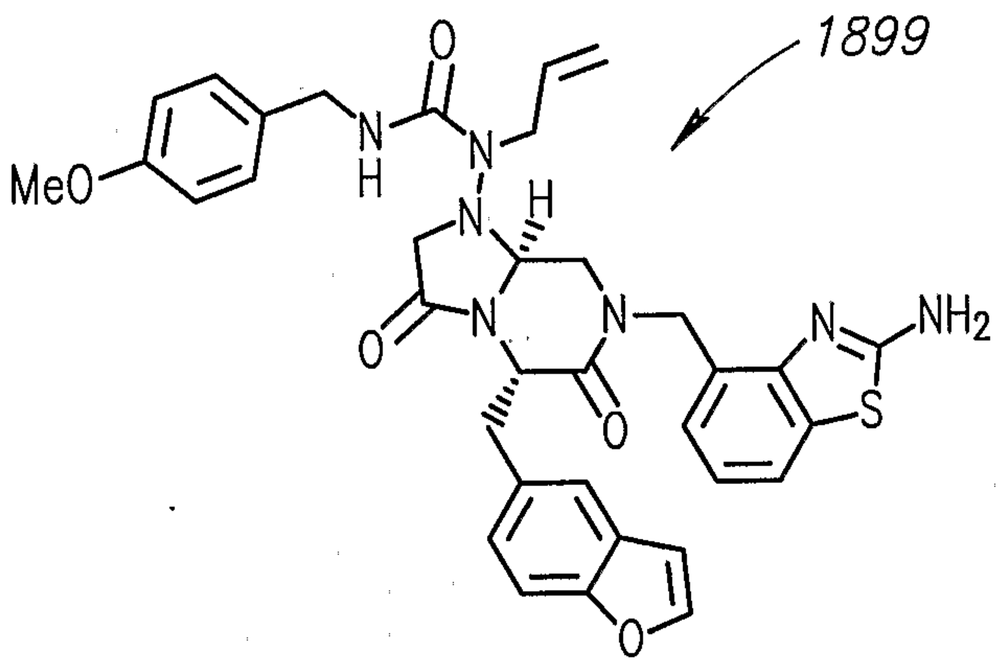

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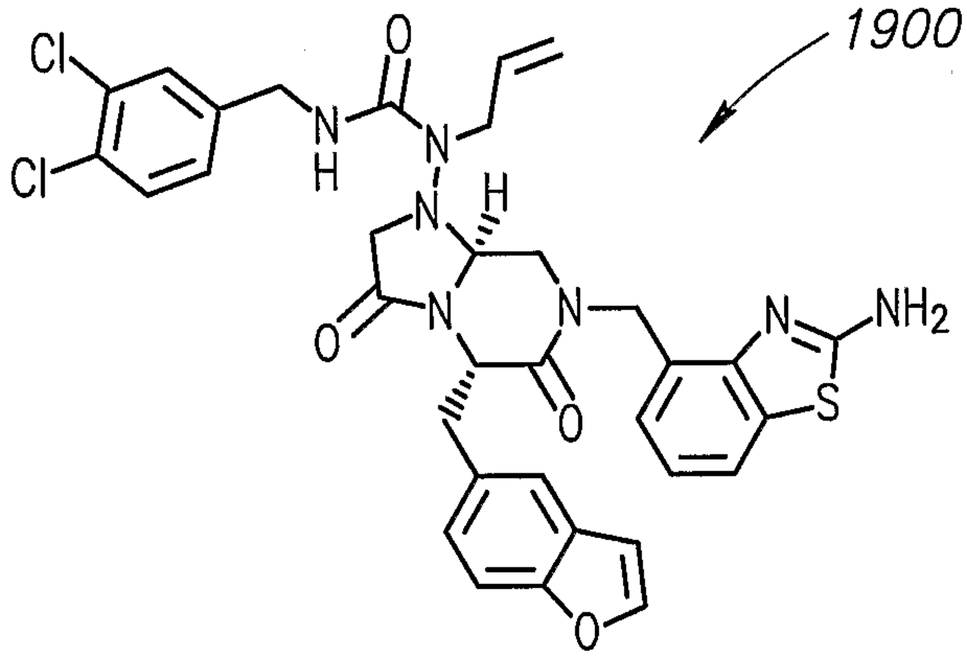

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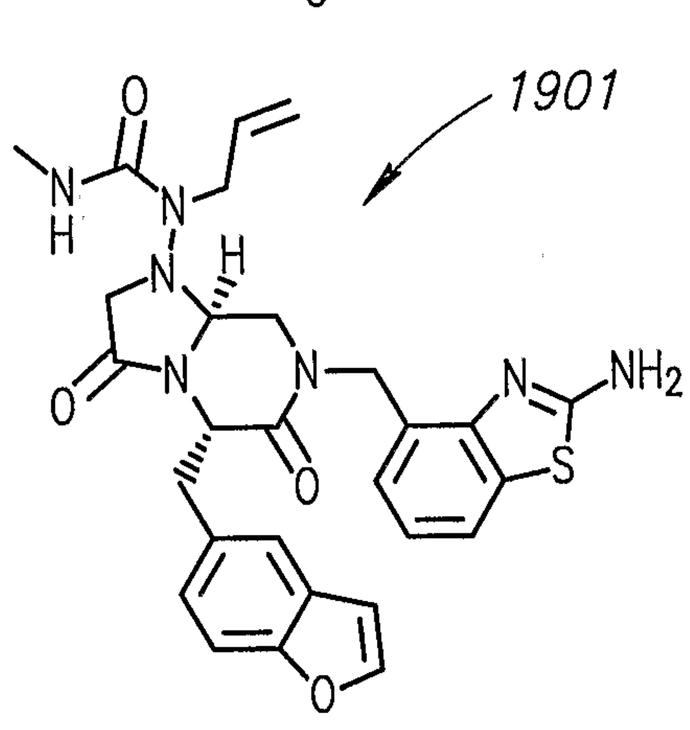

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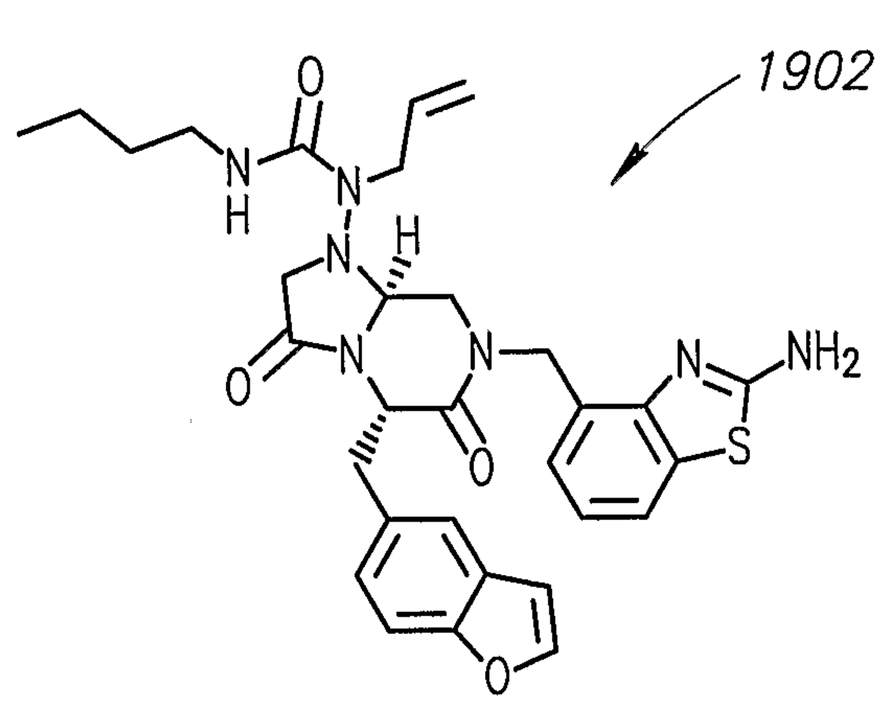
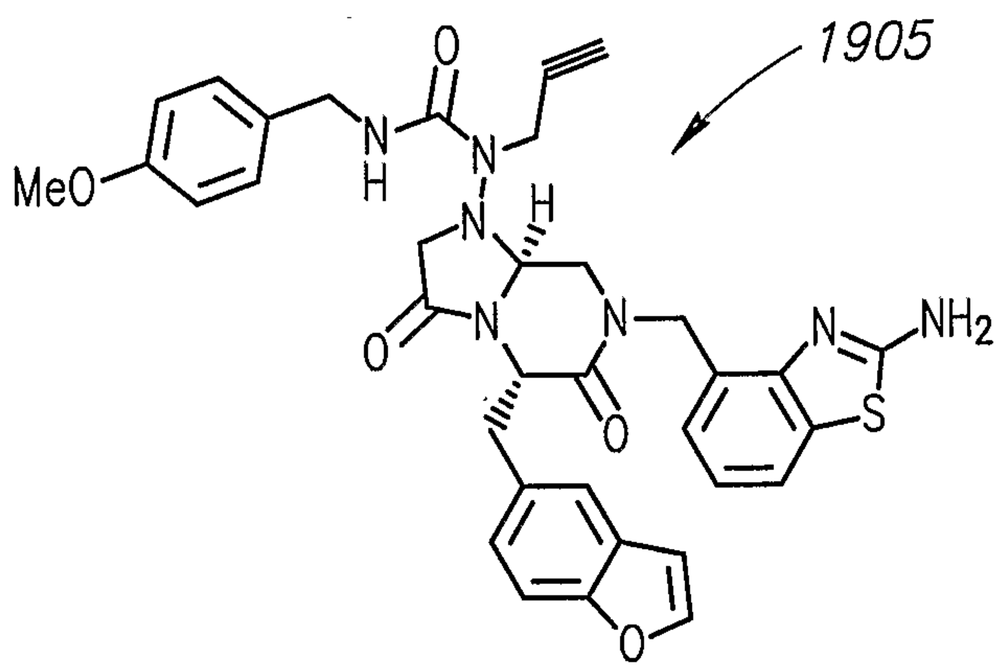


1903

1904

FIG.100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H
N
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N
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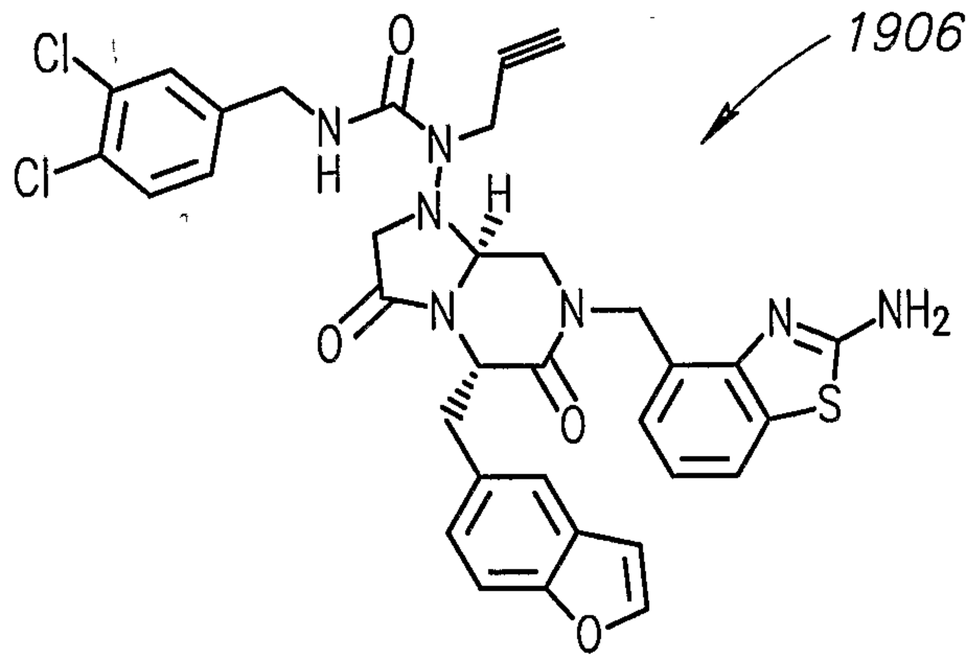
N
N
S
NH2
O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Cl
Cl
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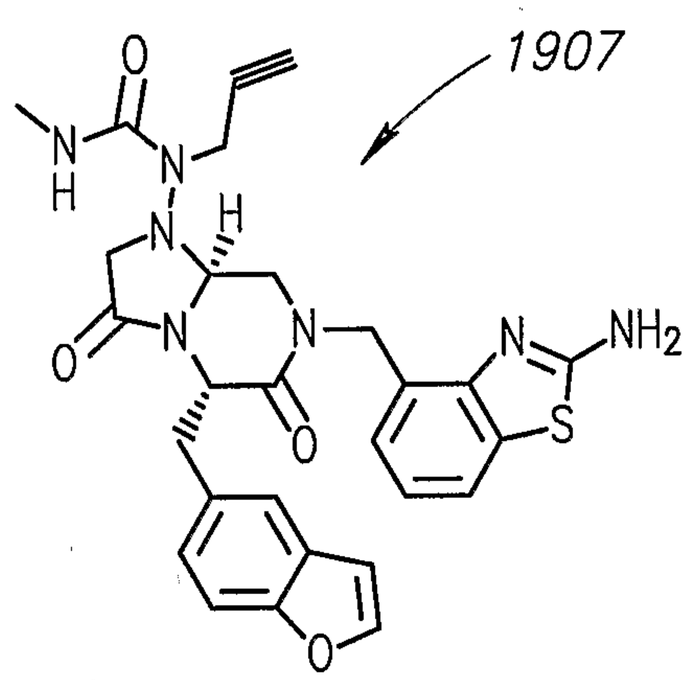
N
H
N
H
N
O
N
O
N
N
S
NH2
O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N
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N
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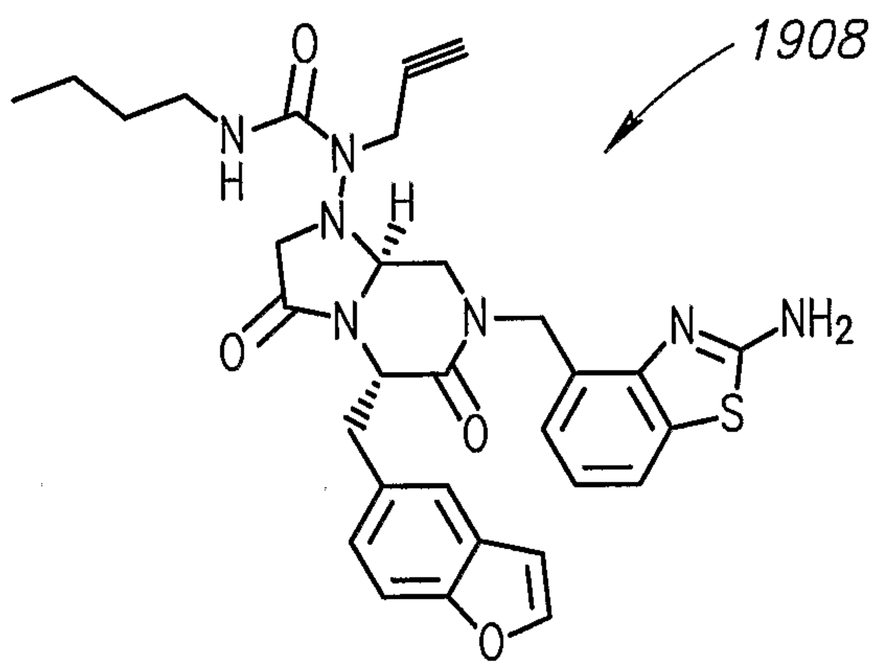
S
NH2
O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N
H
N
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N
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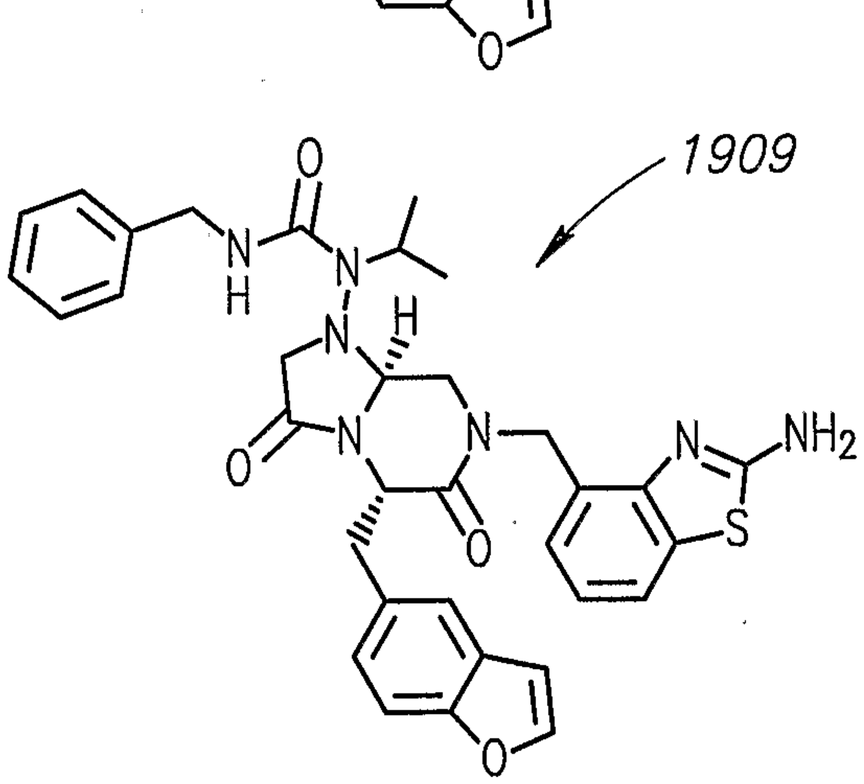
N
N
S
NH2
O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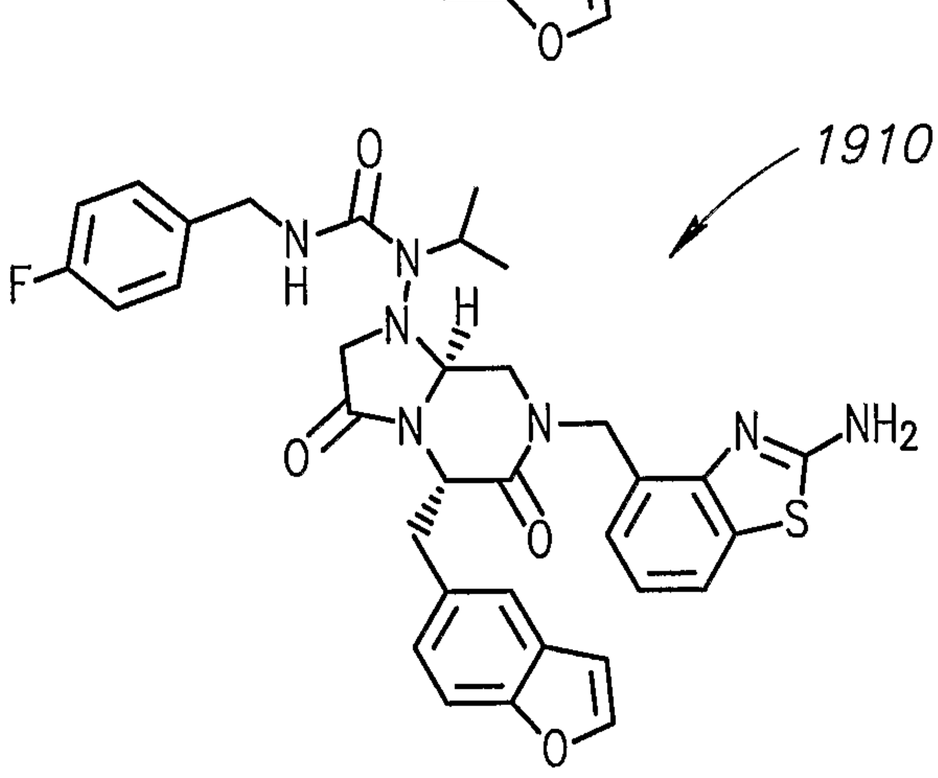
N
S
NH2
O


1910
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H
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H
N
O
N
O
N
N
S
NH2
O

1911
MeO
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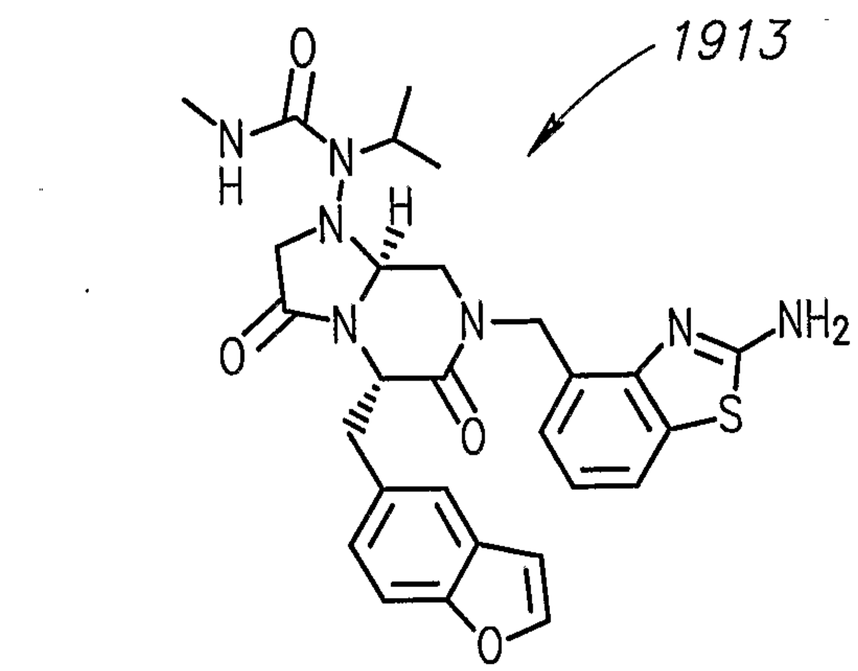
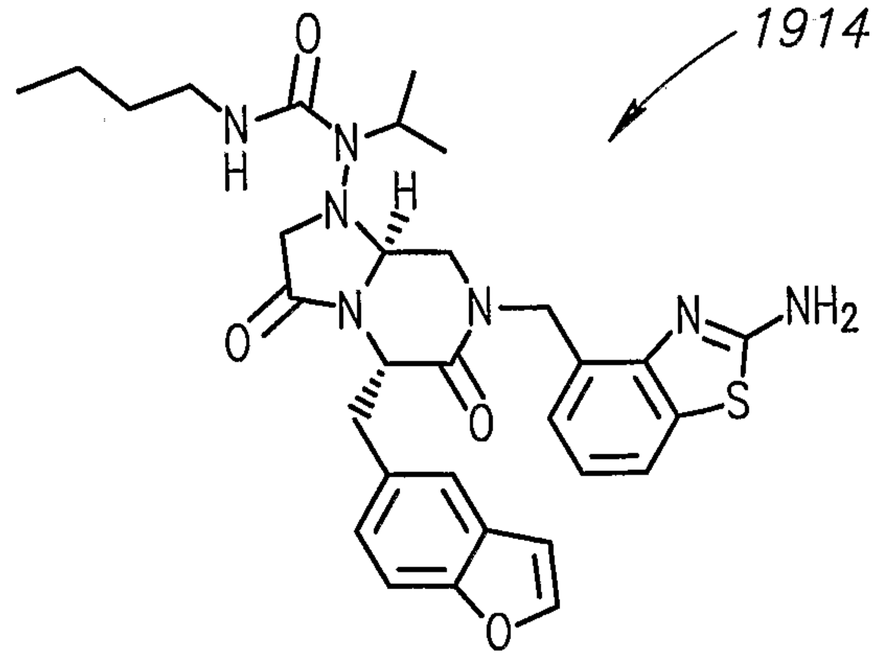
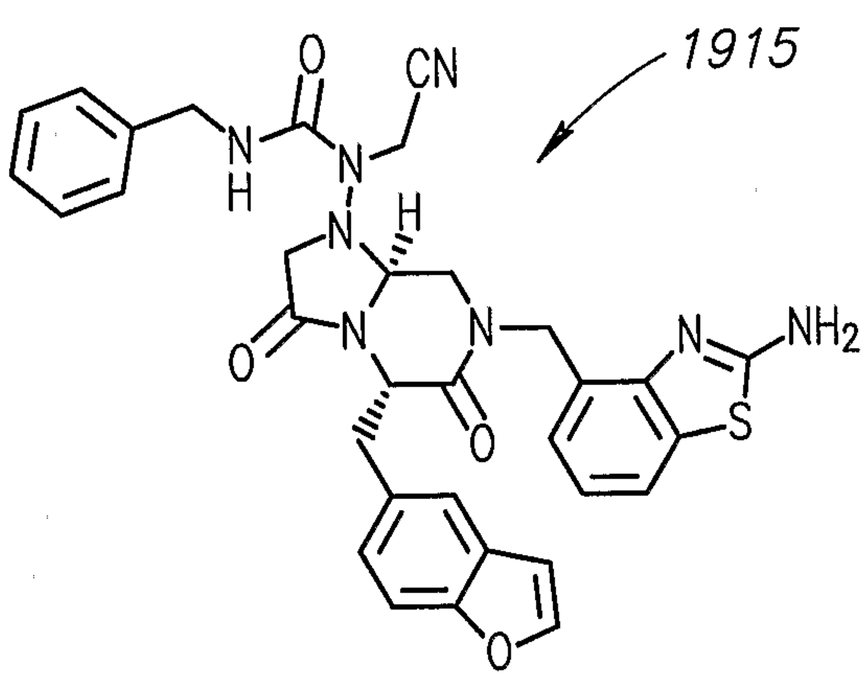
N
H
N
H
N
O
N
O
N
N
S
NH2
O

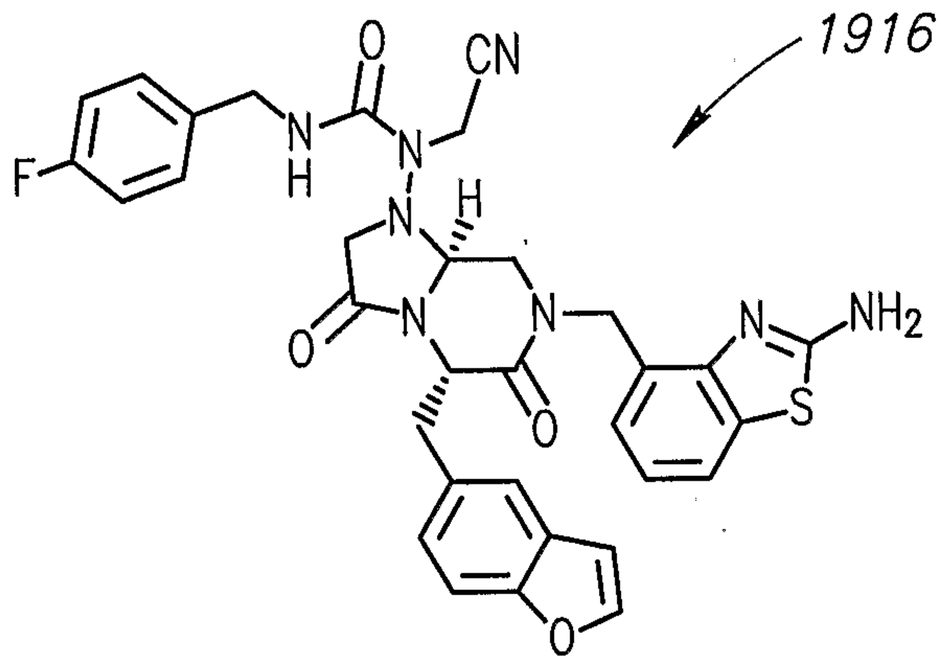
1912
Cl
Cl
O
N
H
N
H
N
O
N
O
N
N
S
NH2
O

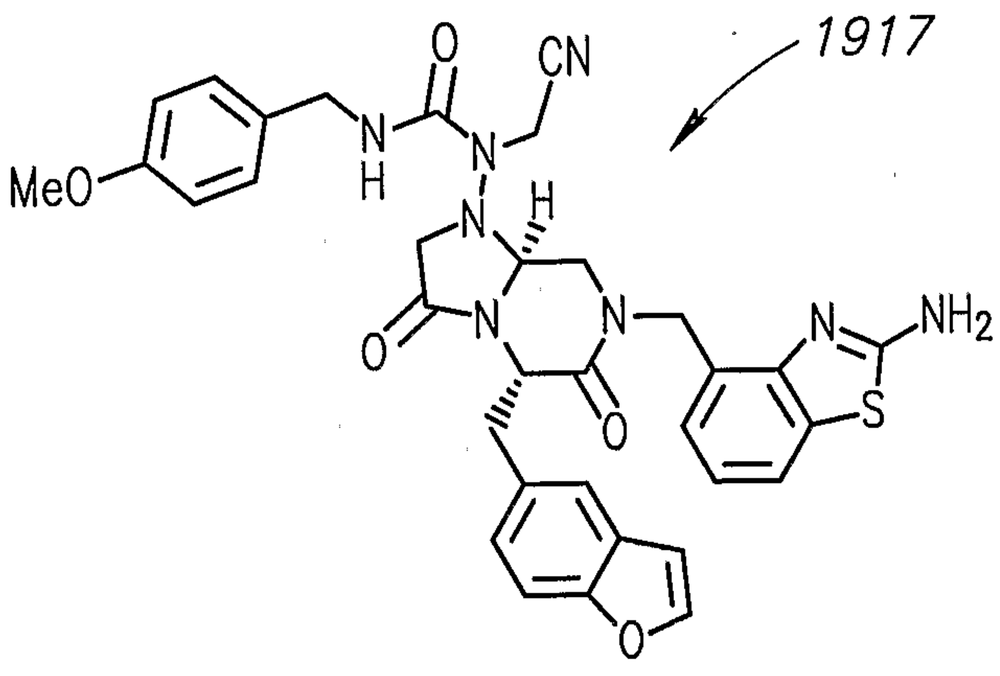
FIG.10P

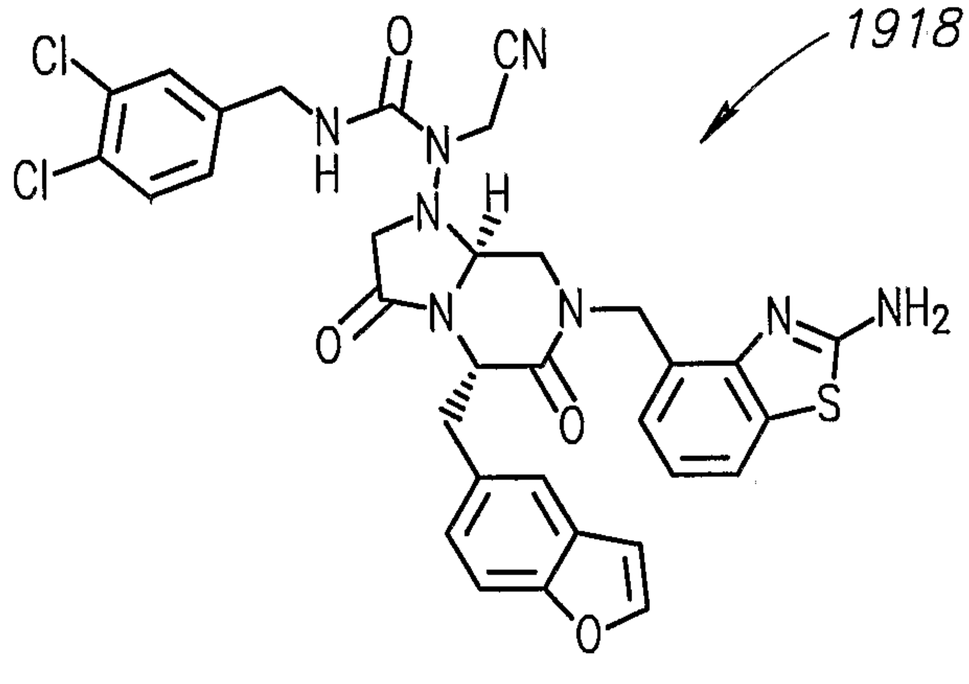


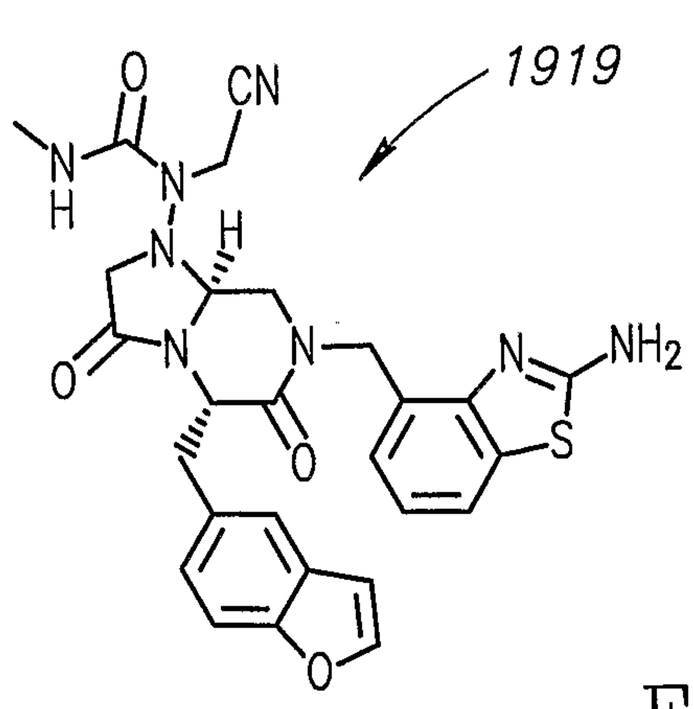












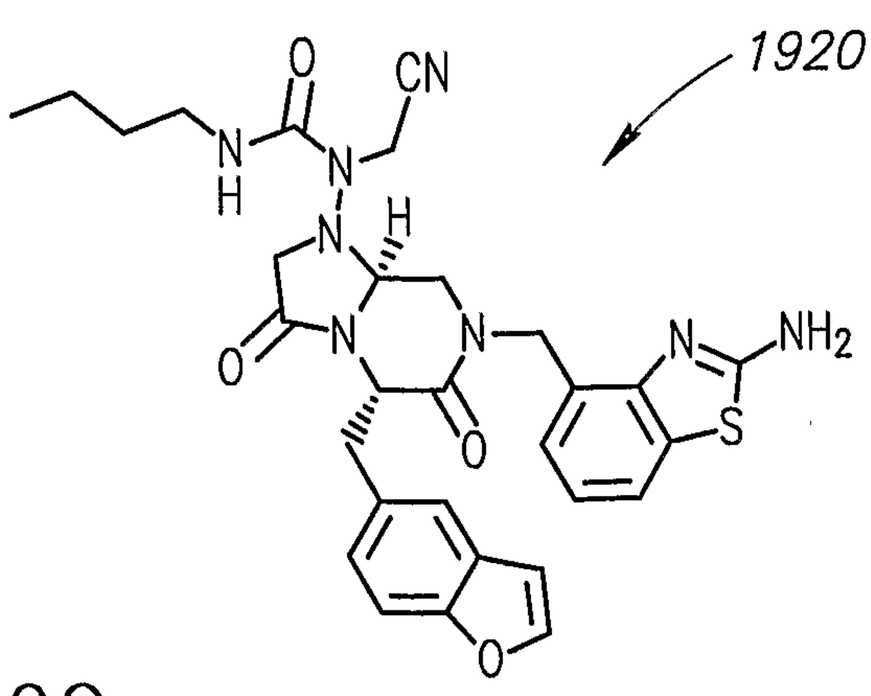
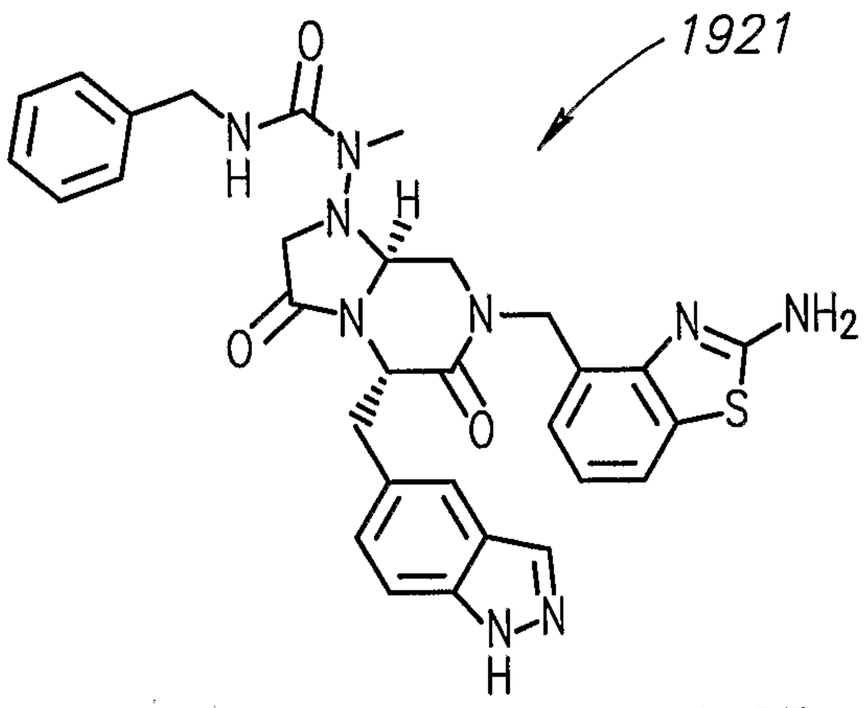
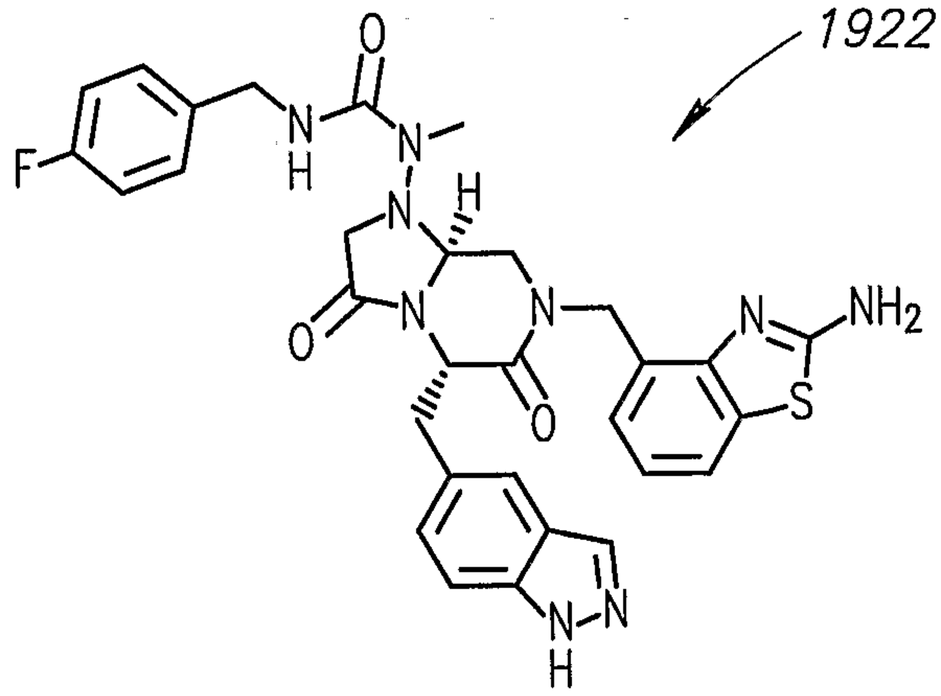
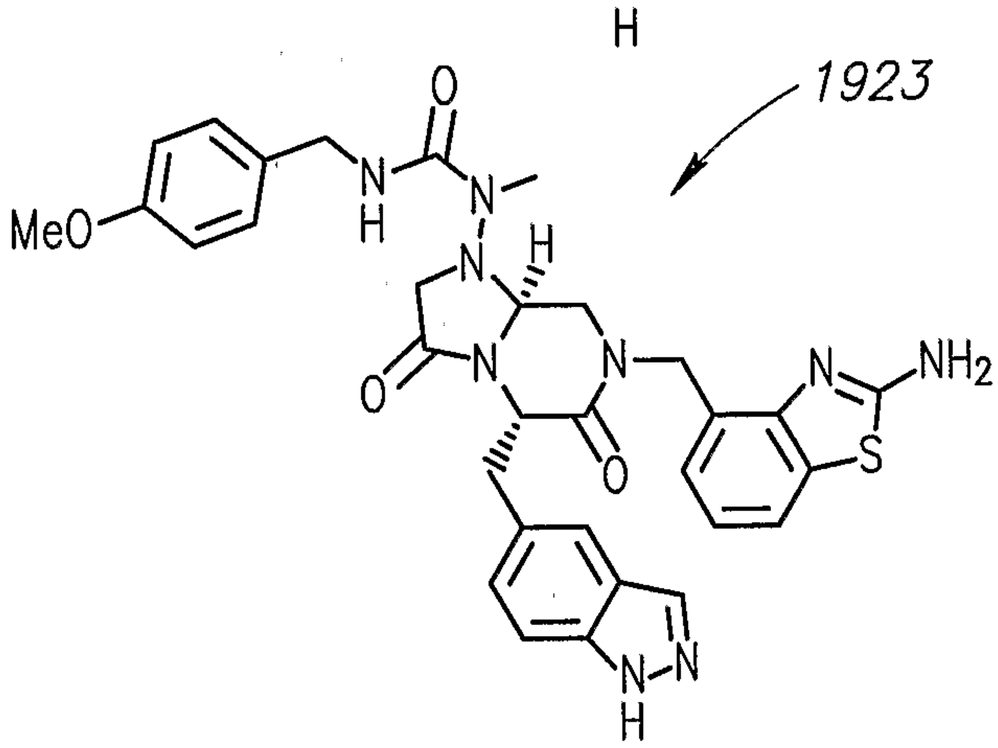
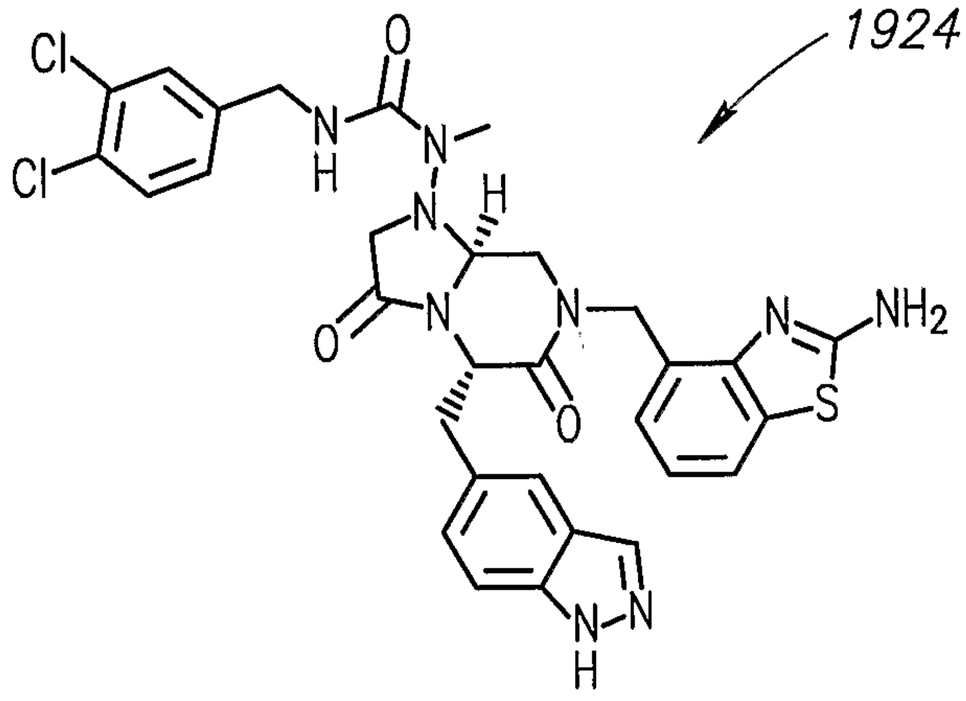


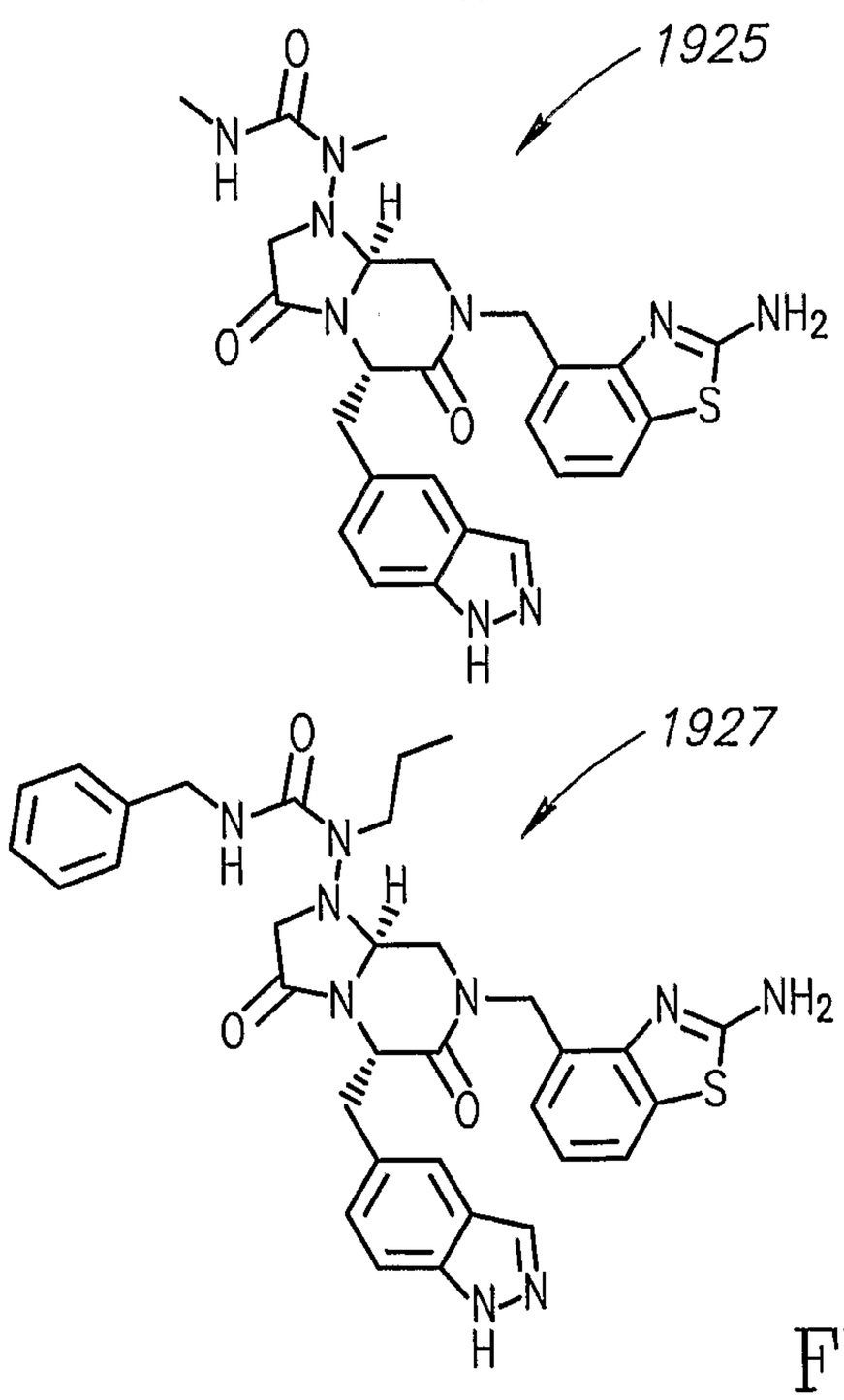
FIG.10Q











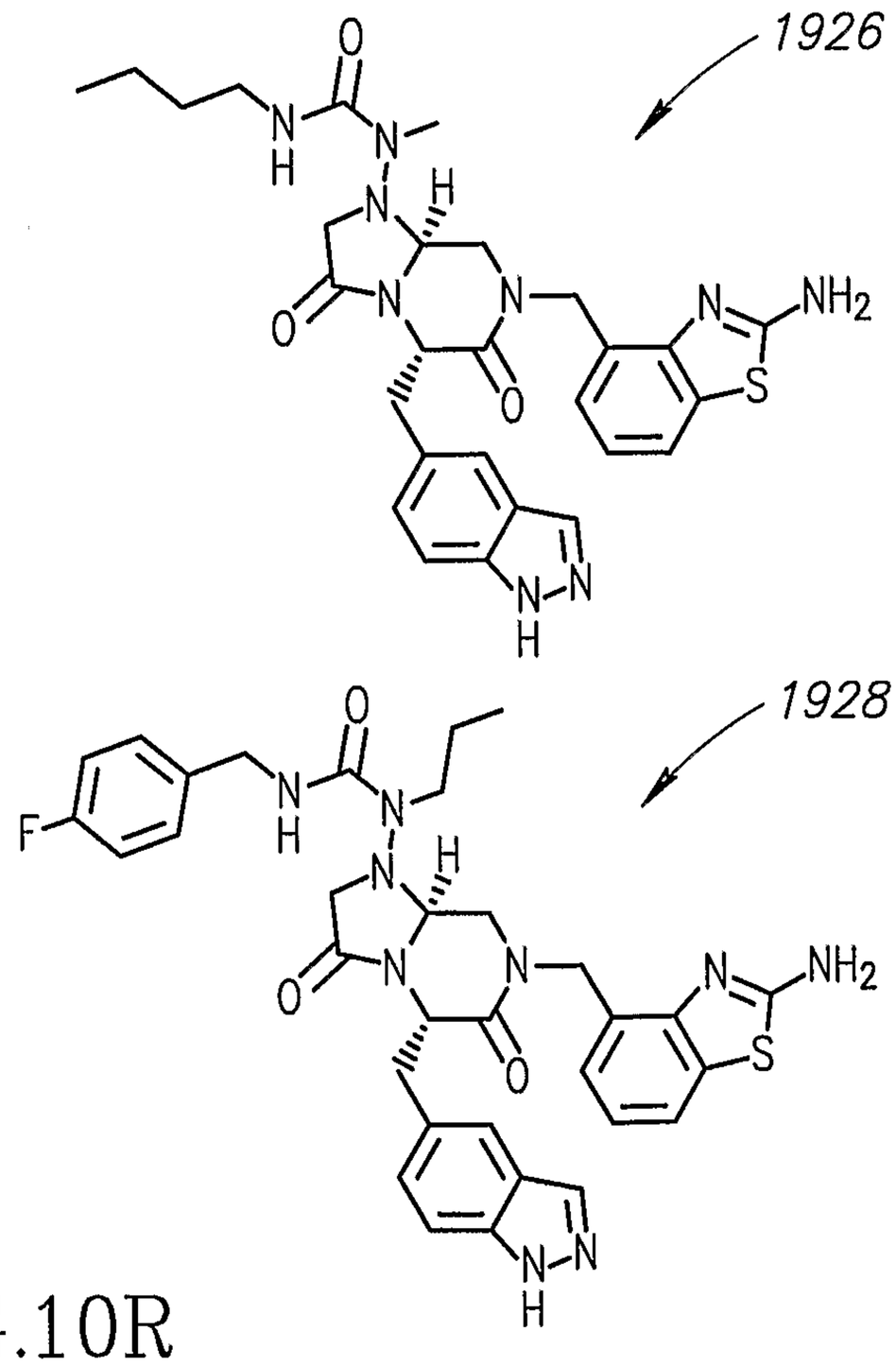
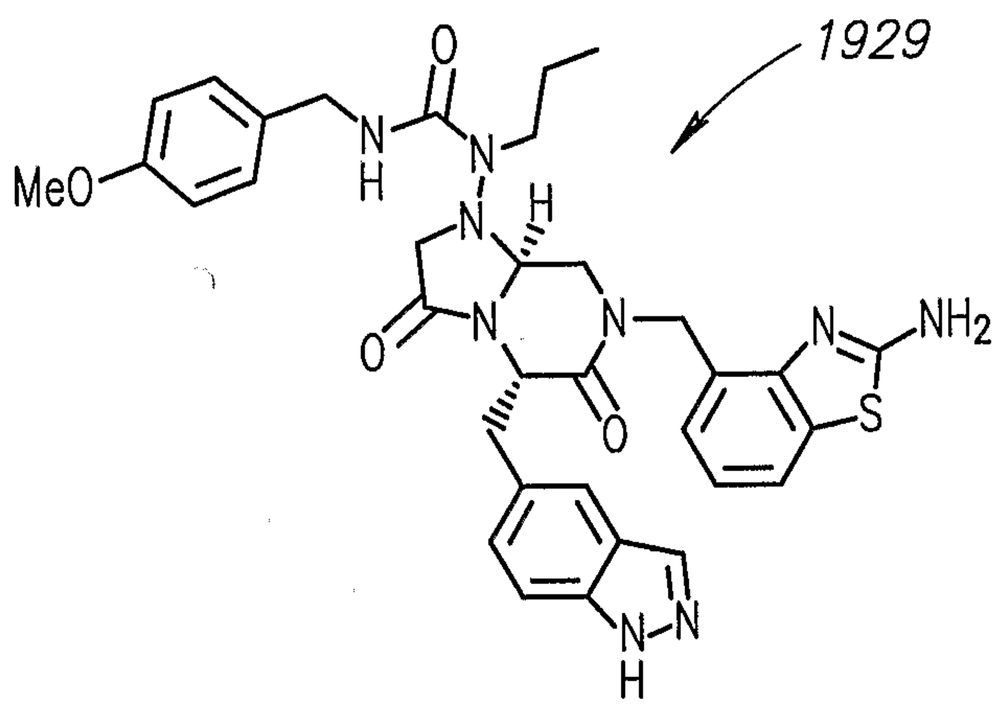


FIG.10R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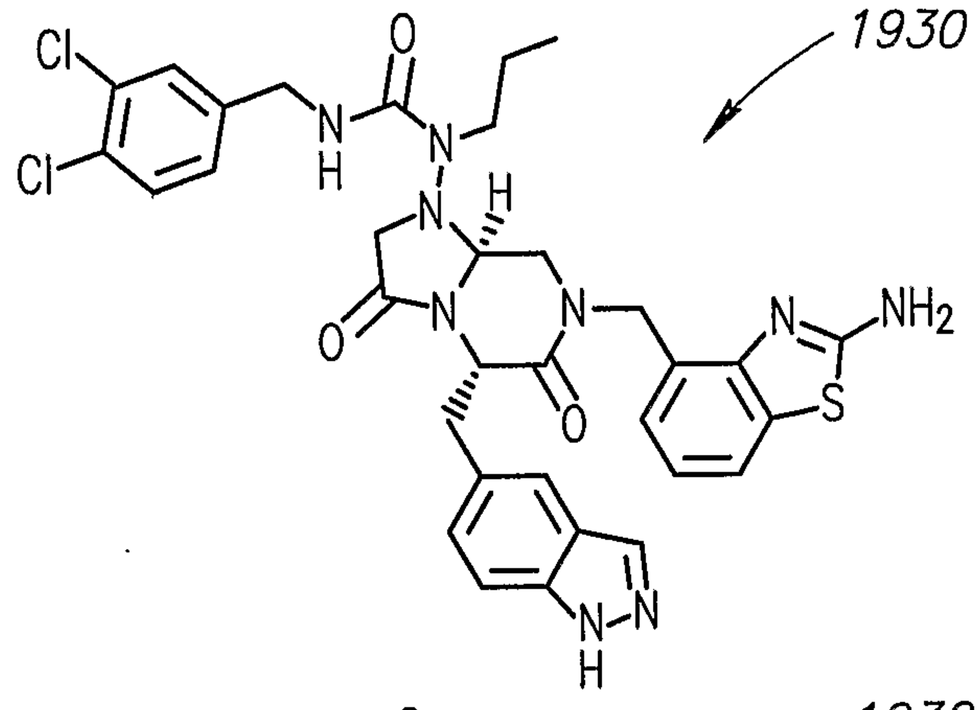
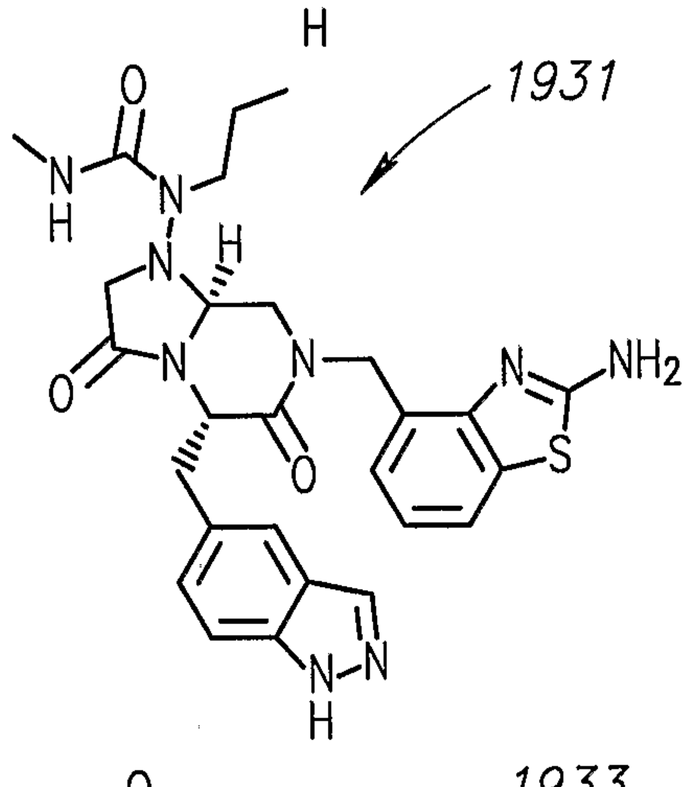
MeO
O
N
H
N
H
O
O
N
N
N
S
NH2
N
N
H


1930
Cl
Cl
O
N
H
N
H
O
O
N
N
N
S
NH2
N
N
H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N
N
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NH2
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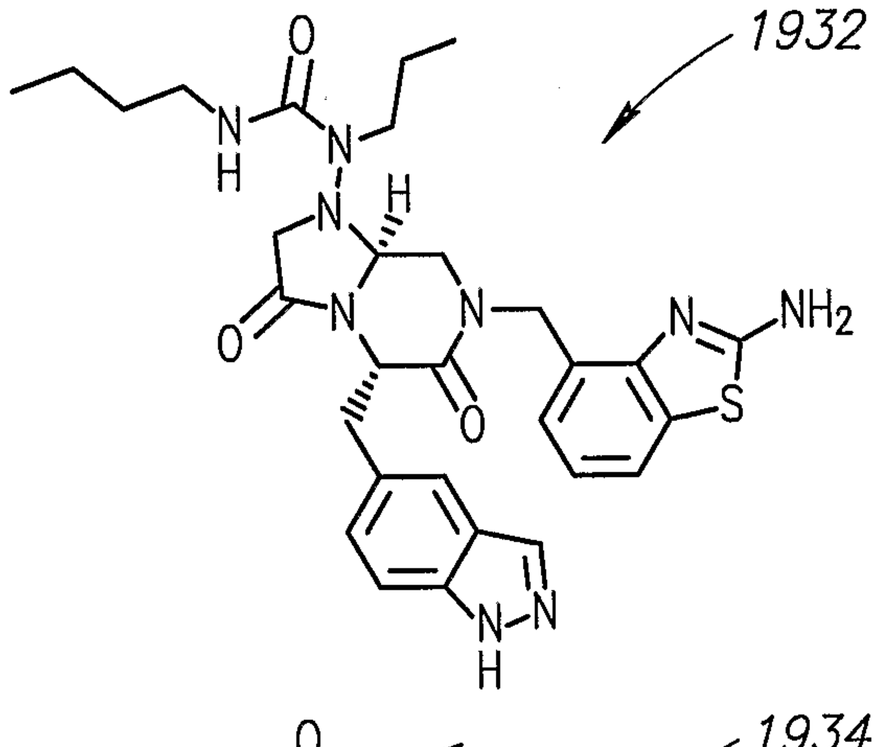
N
H


1932
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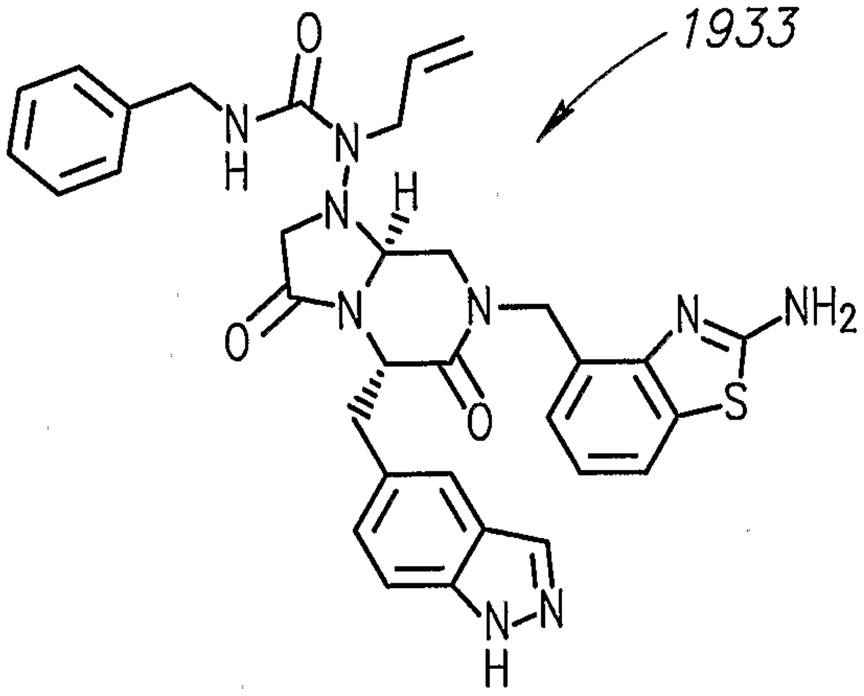
H
N
H
O
O
N
N
N
S
NH2
N
N
H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N
H
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N
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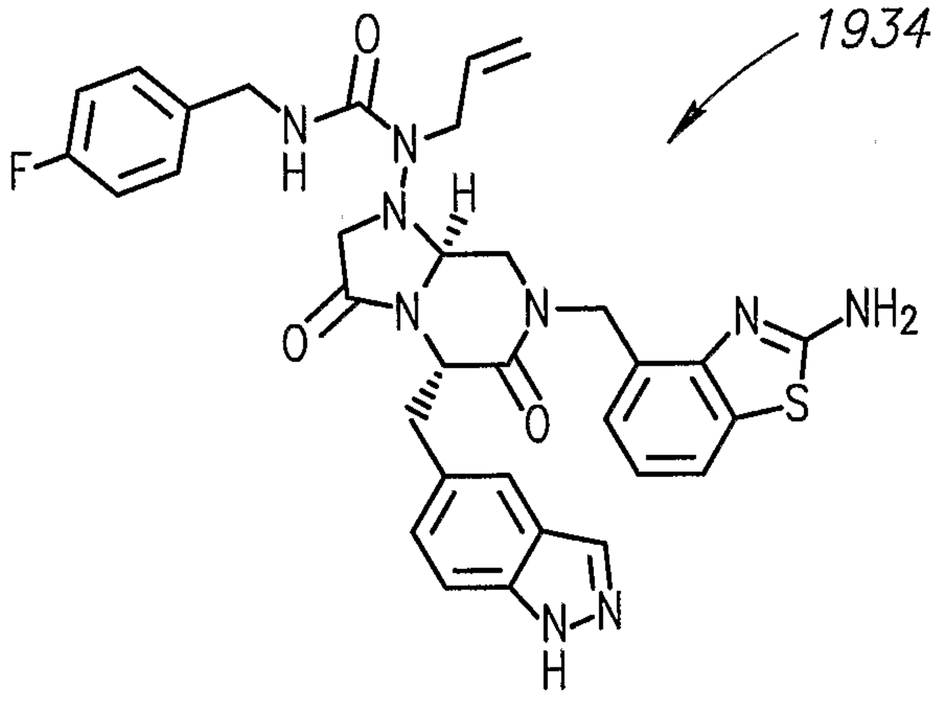
NH2
N
N
H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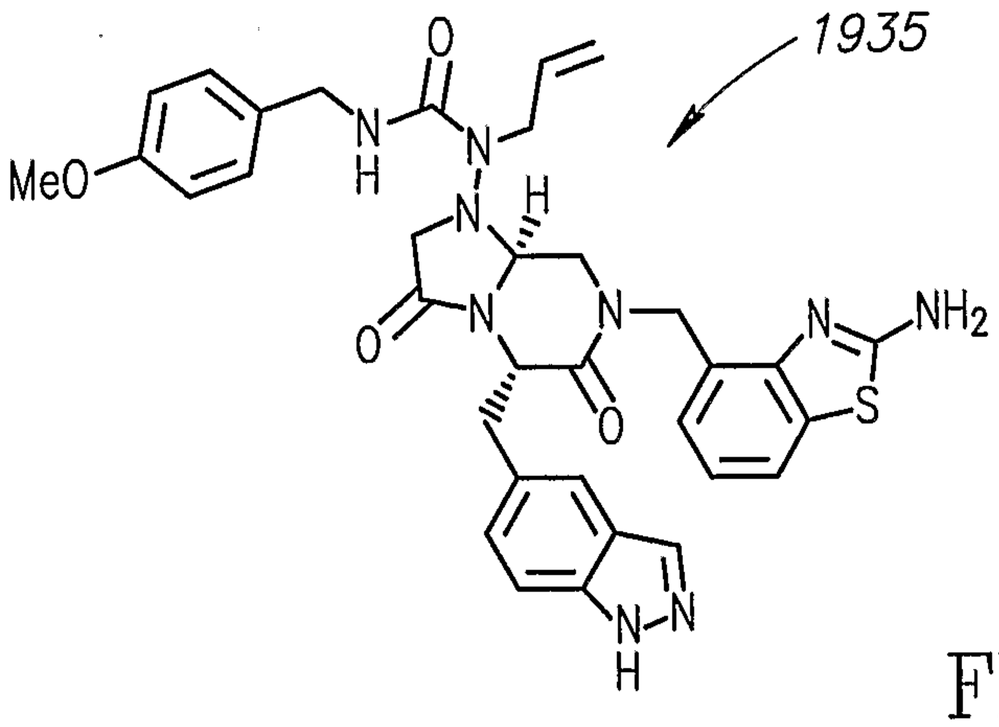
O
N
H
N
H
O
O
N
N
N
S
NH2
N
N
H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H
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H
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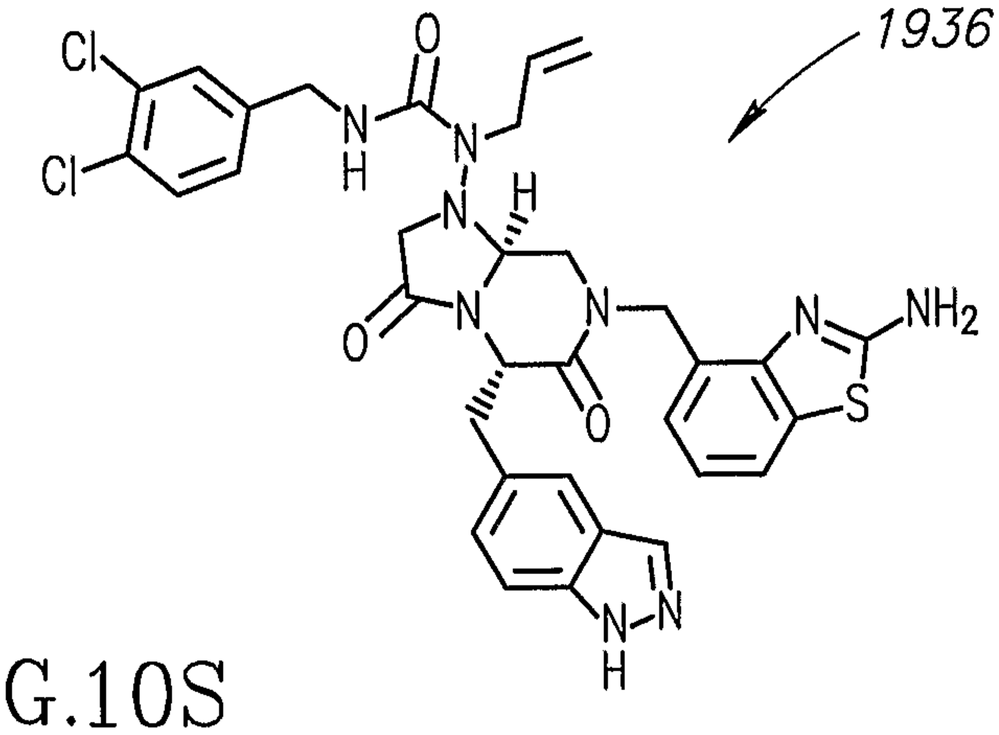
N
N
N
S
NH2
N
N
H


1936
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Cl
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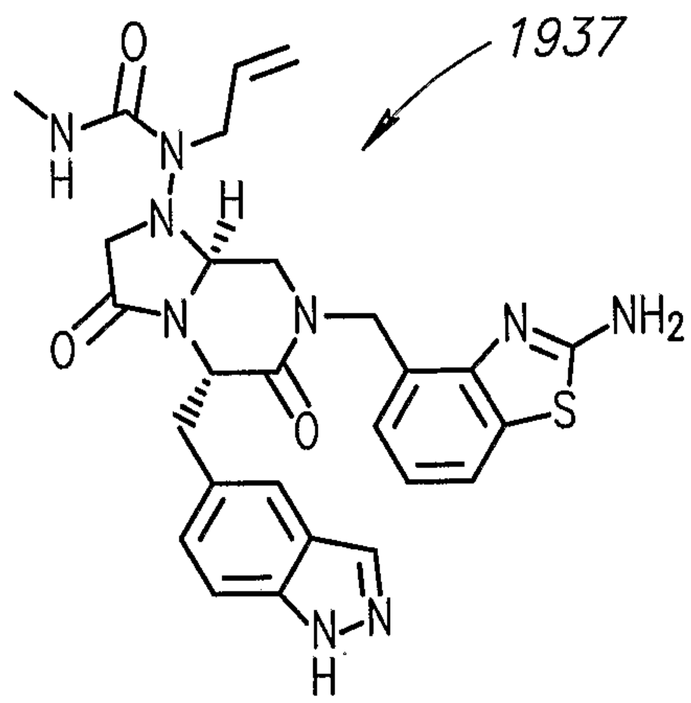
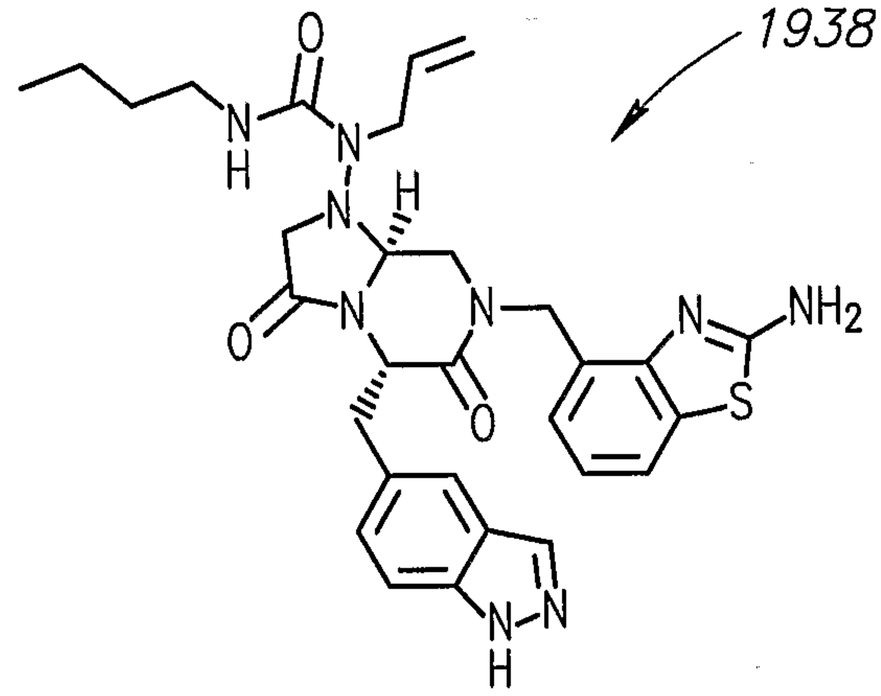
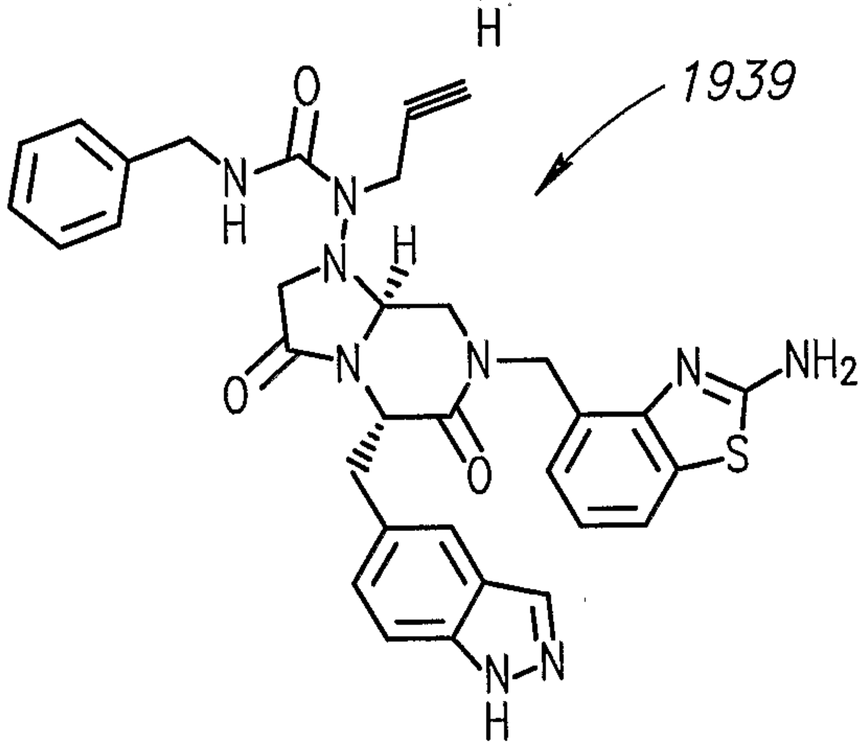
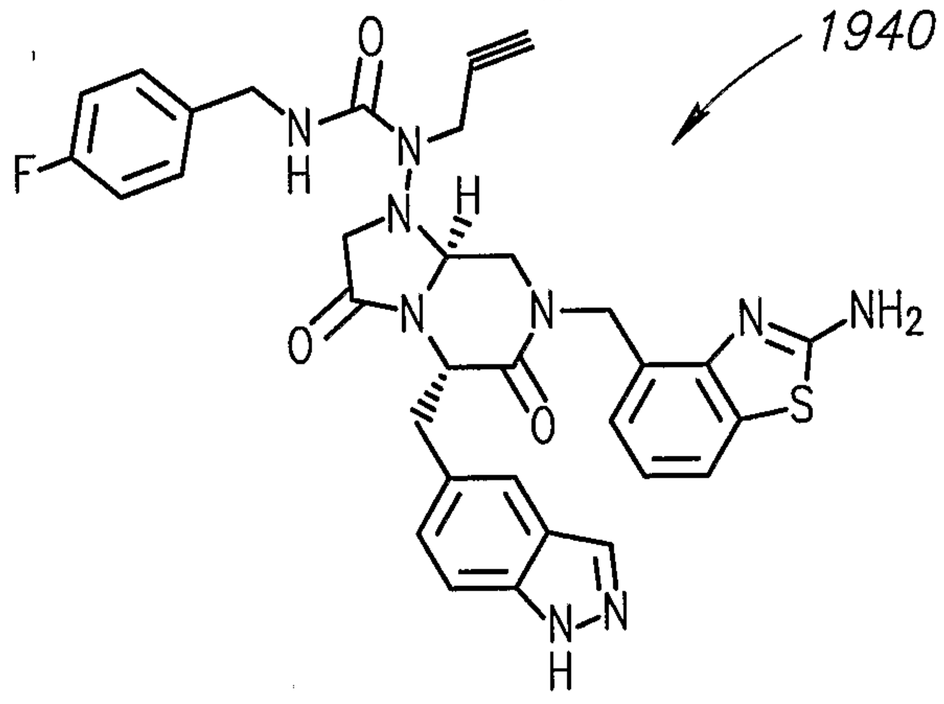
N
H
N
H
O
O
N
N
N
S
NH2
N
N
H

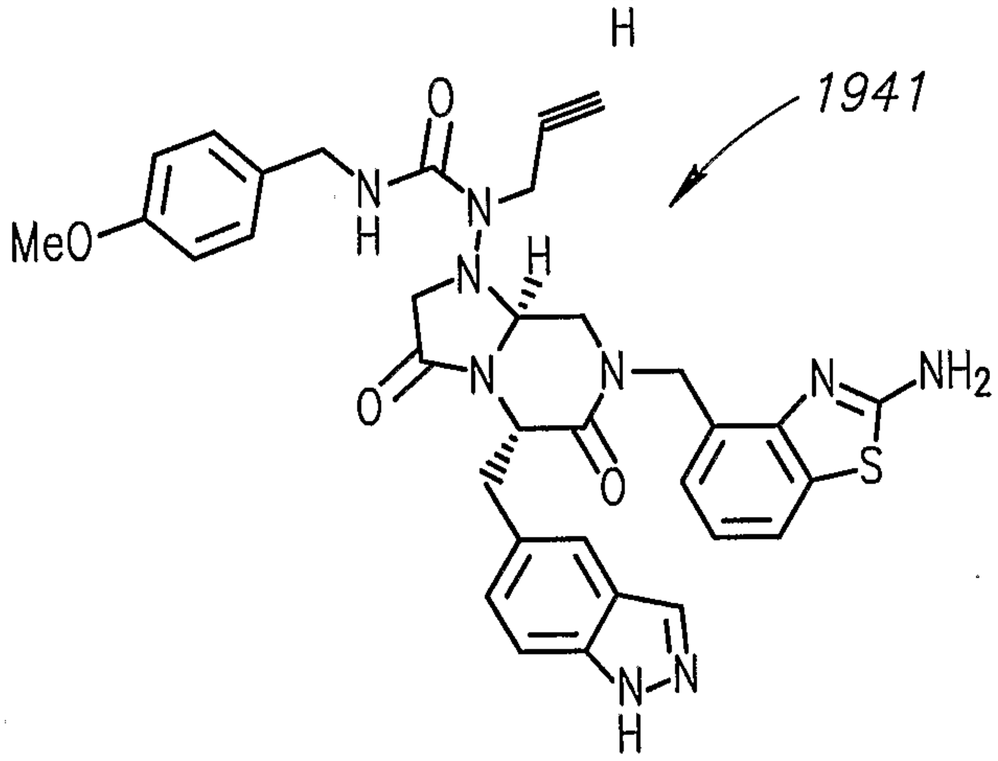
FIG.10S

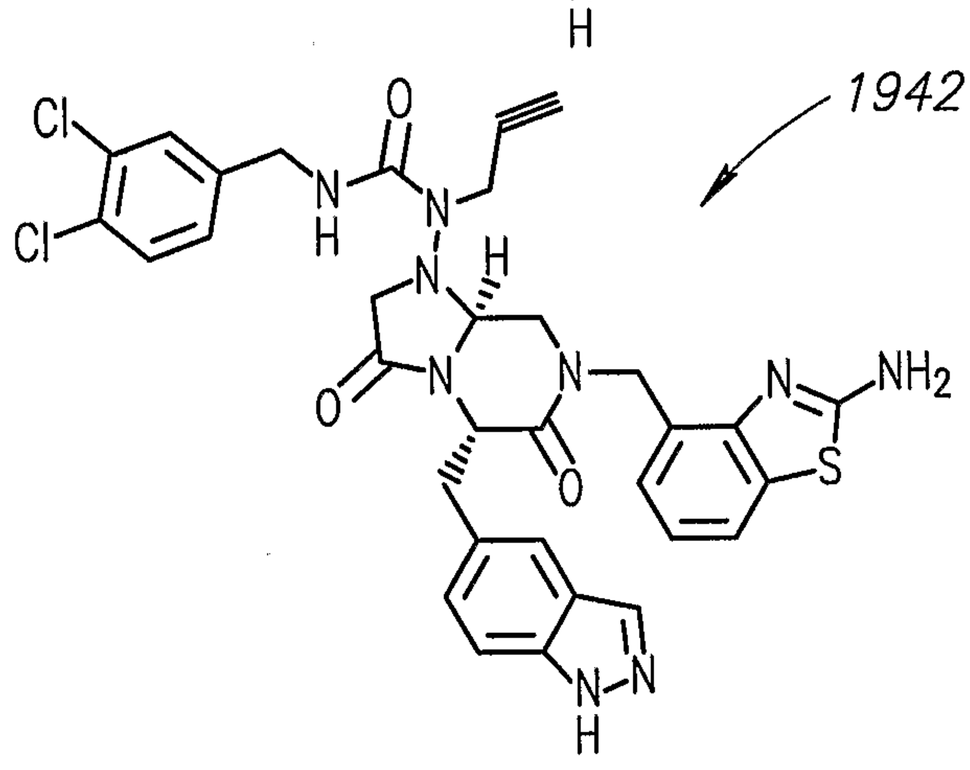


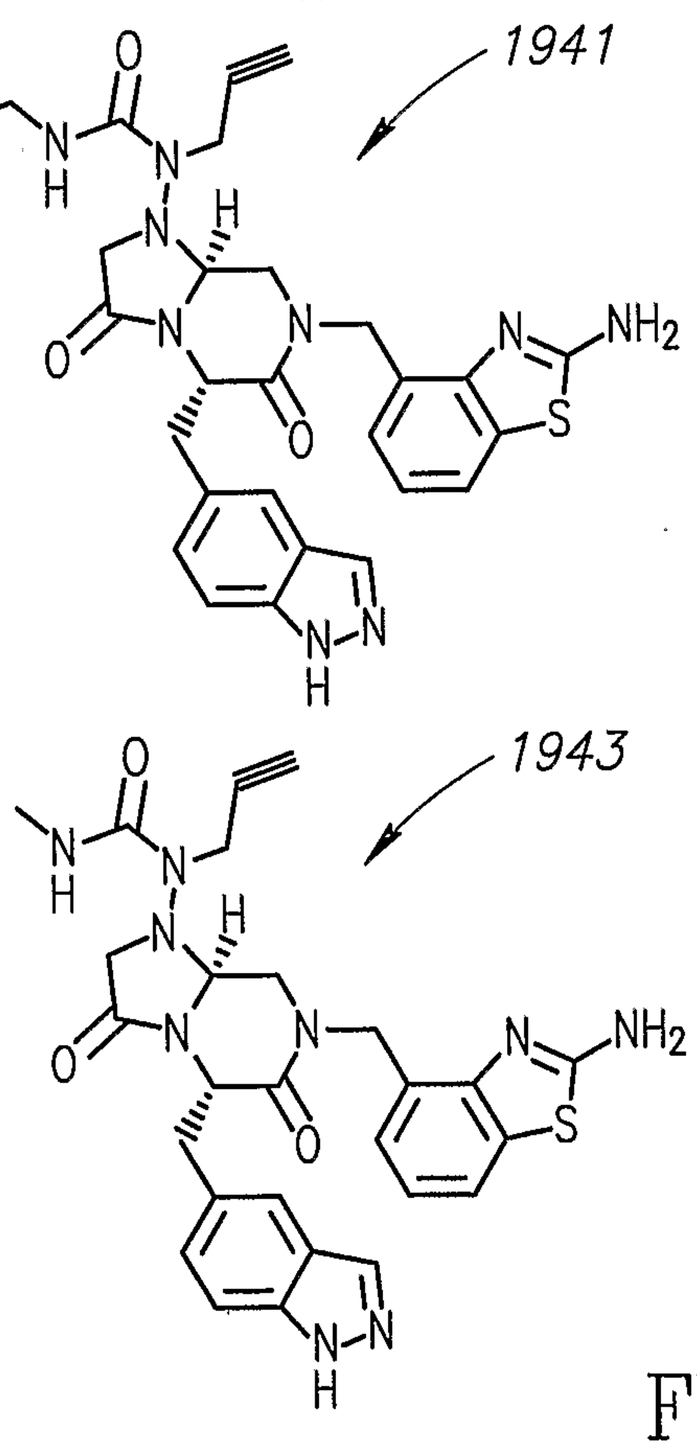












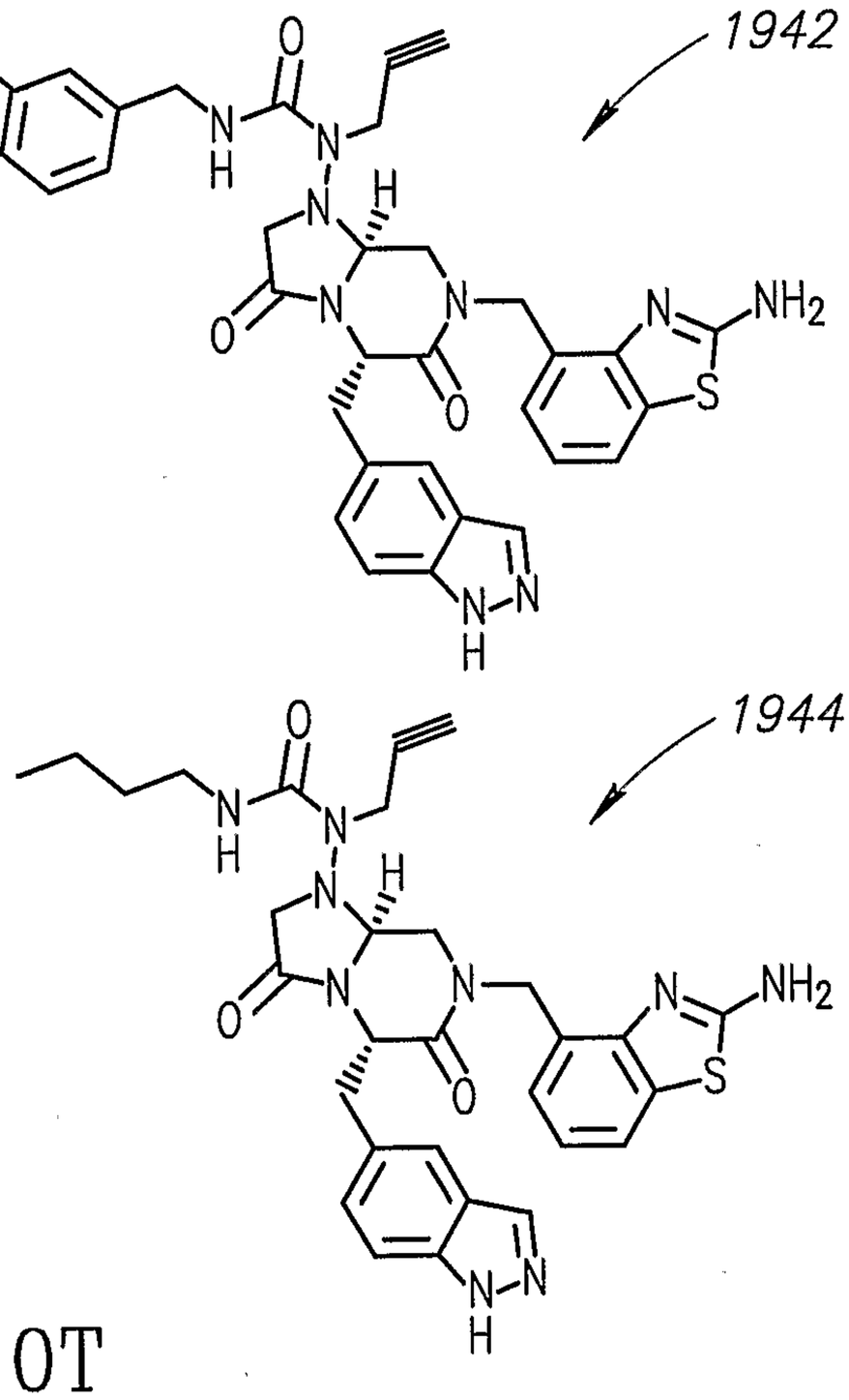
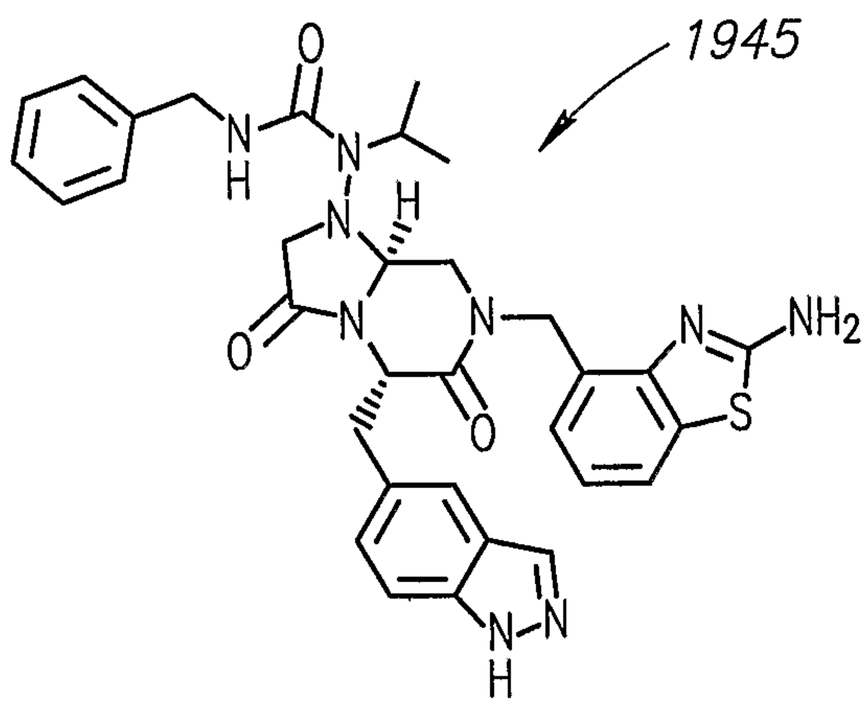
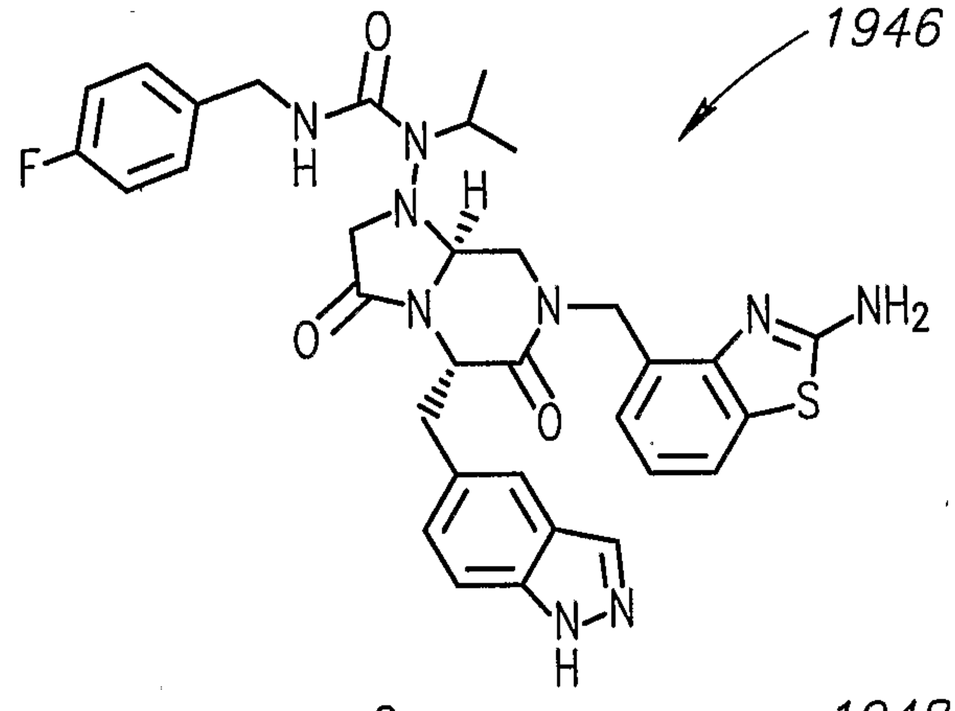
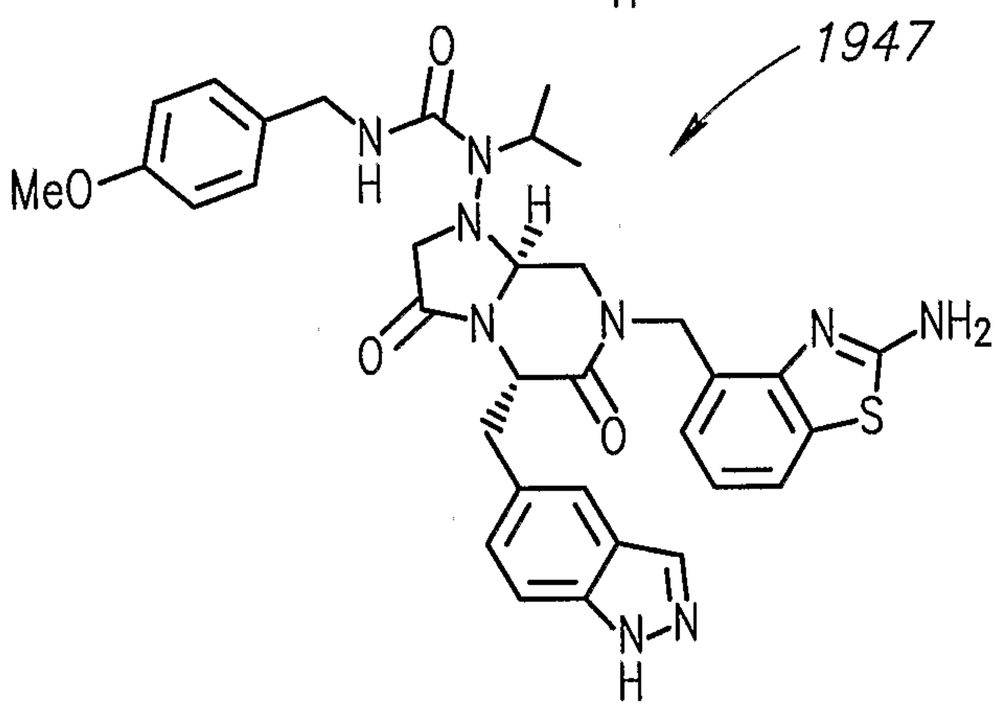
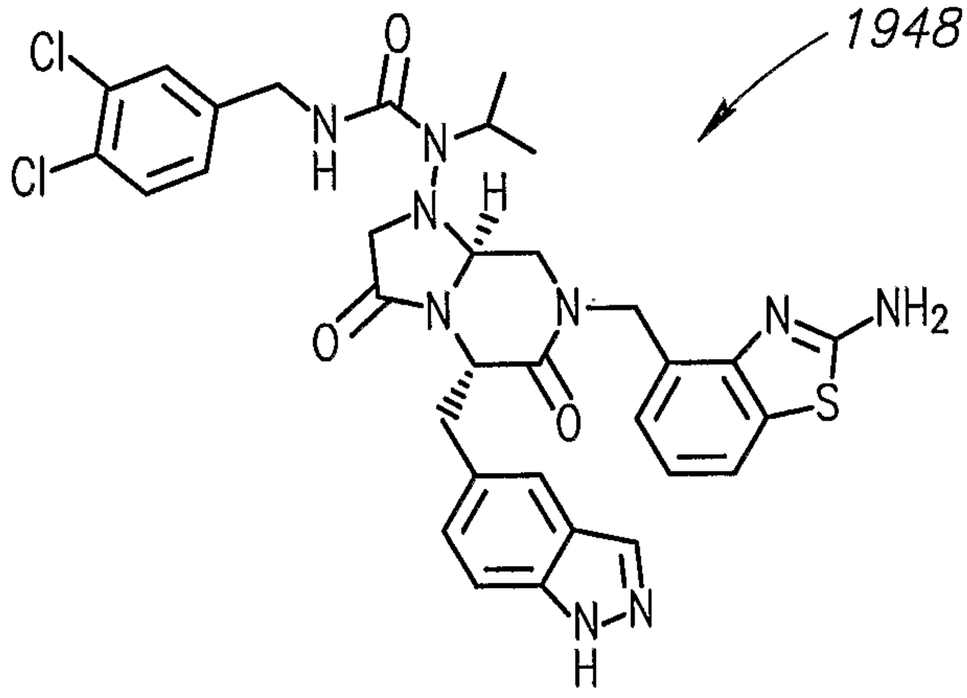


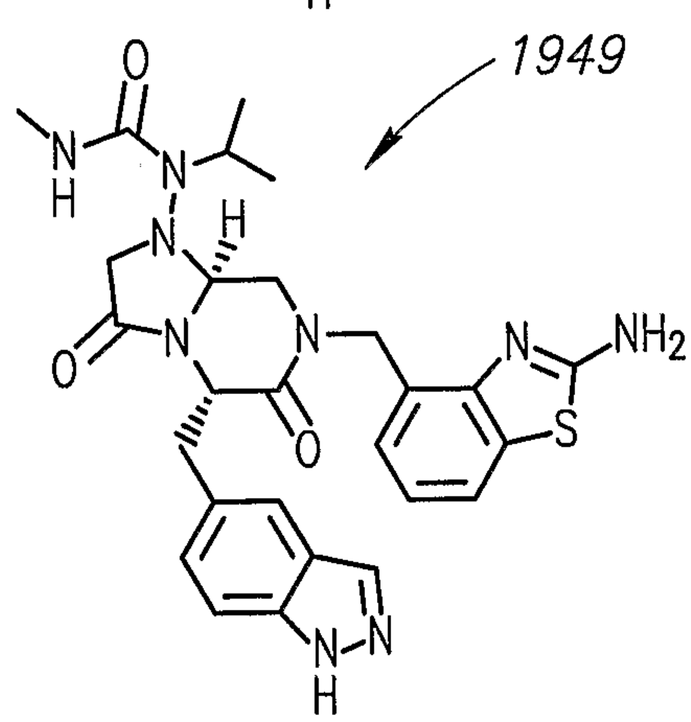
FIG.10T











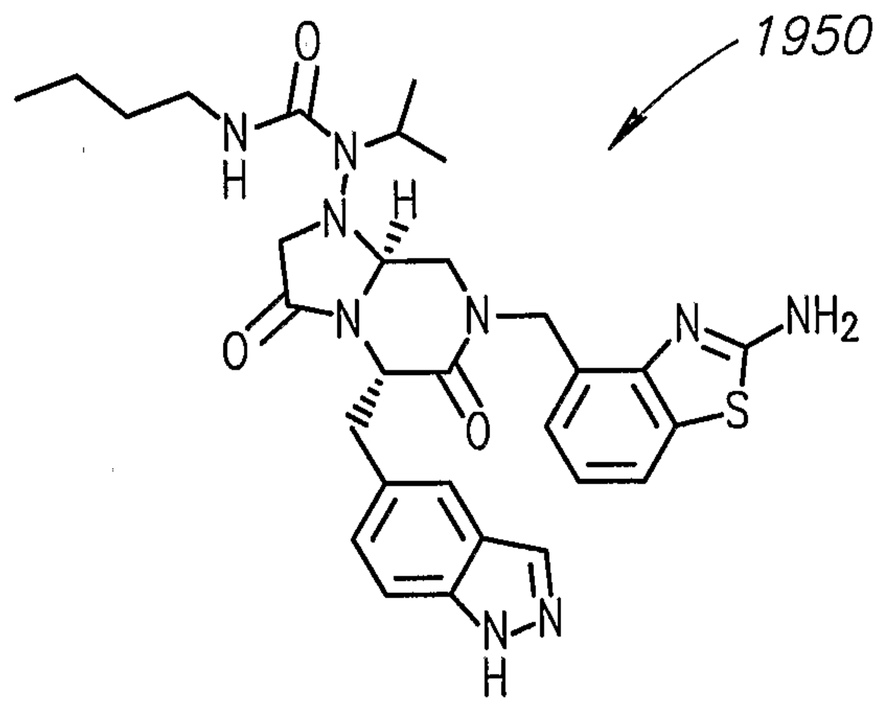
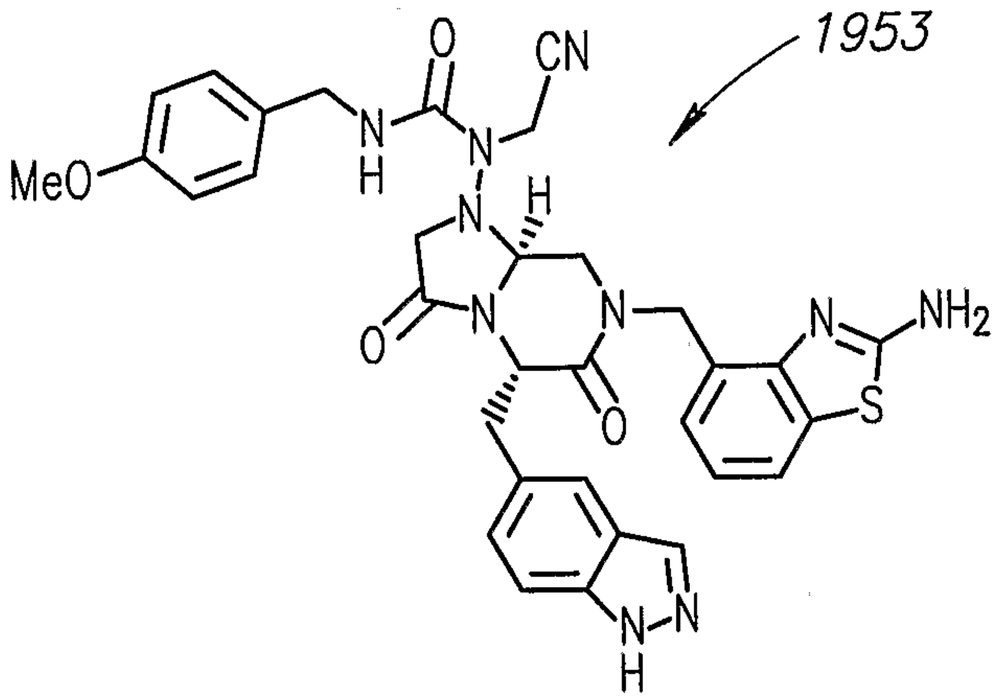
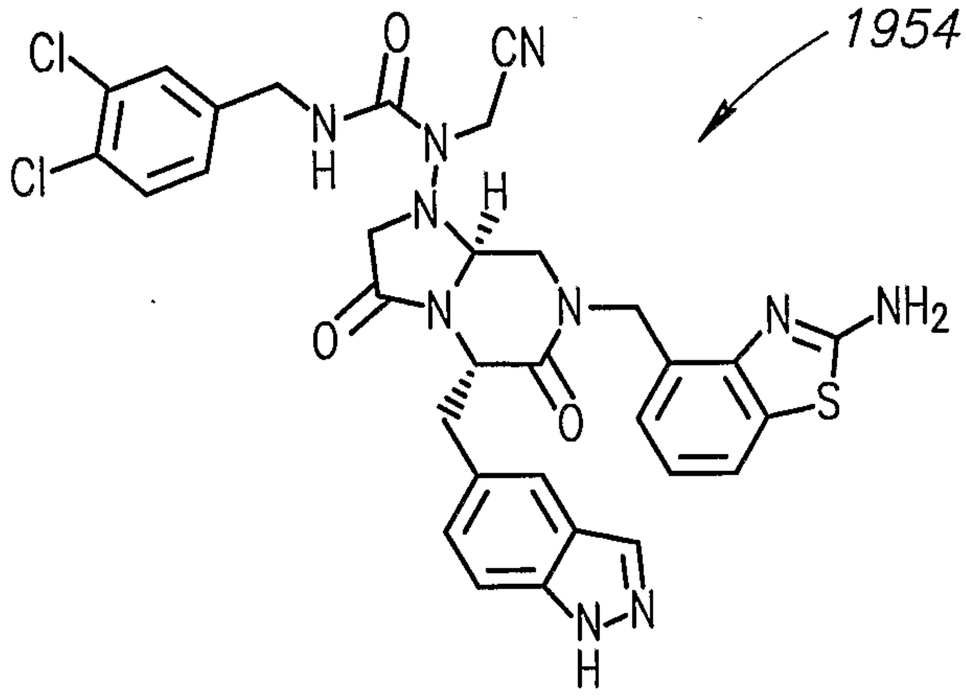


FIG.10U

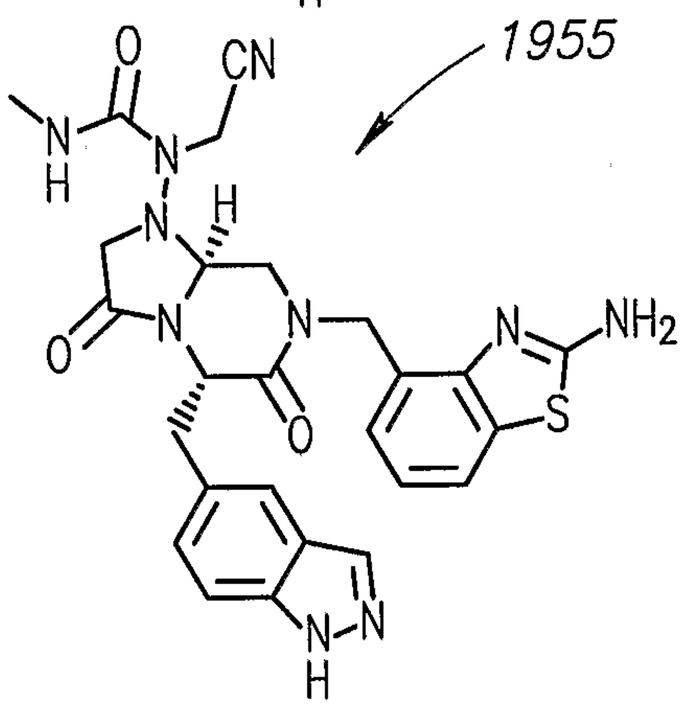
1953



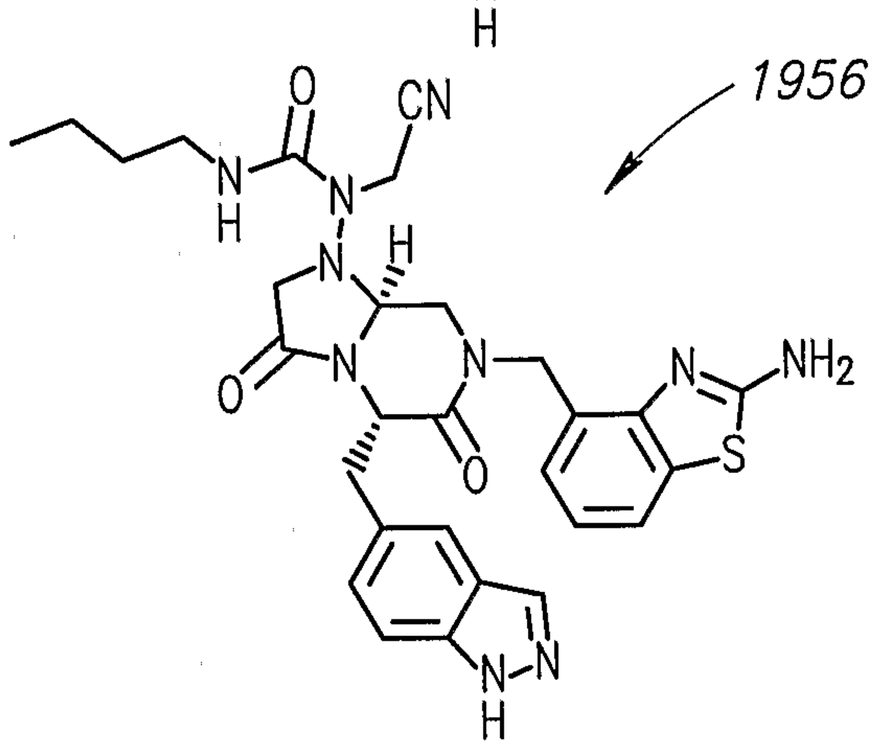
1954



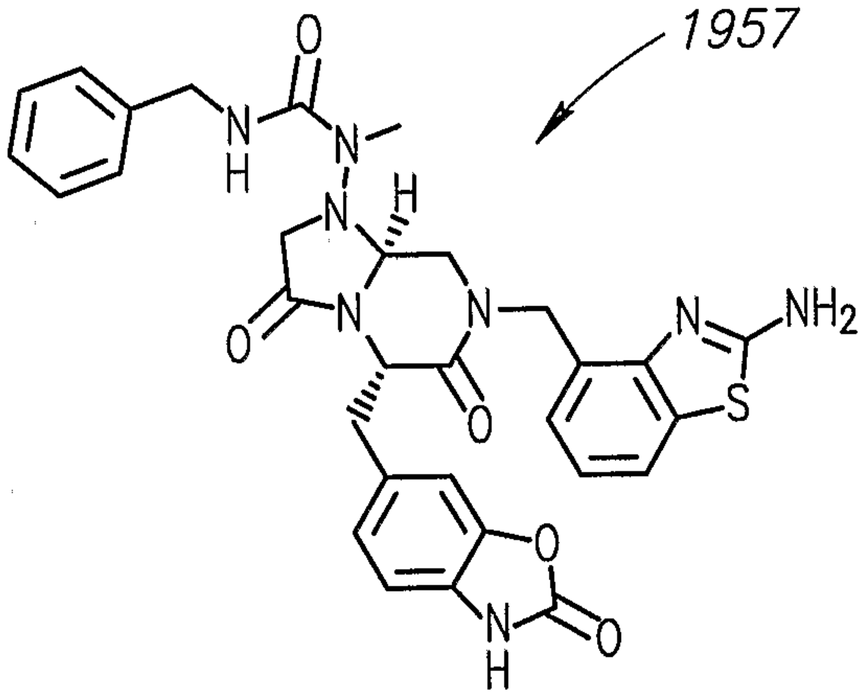
1955



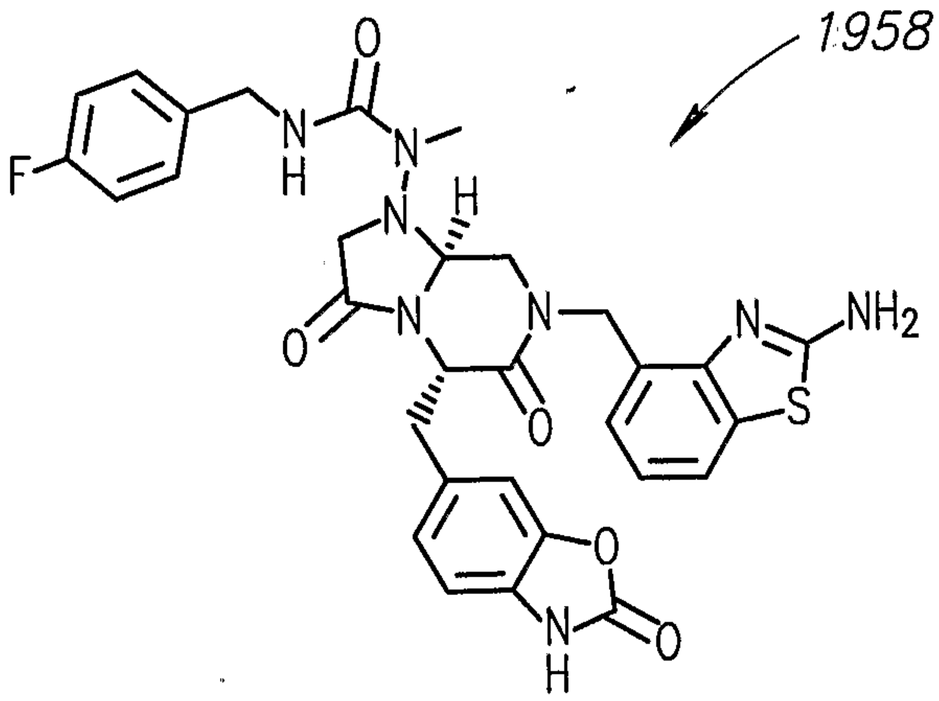
1956



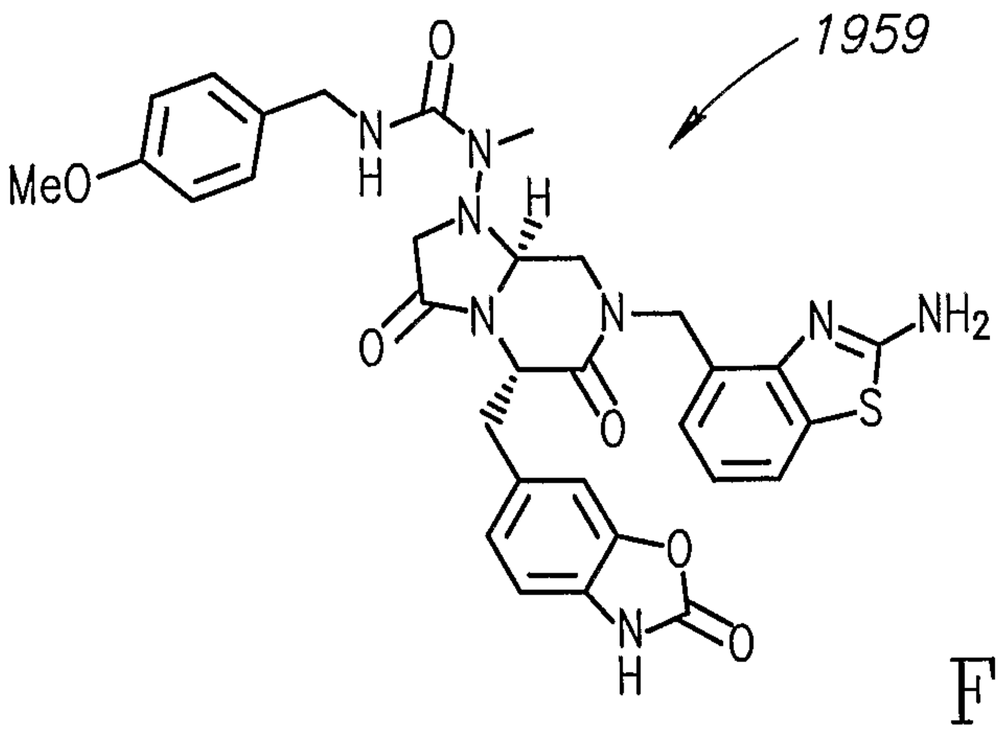
1957



1958



1959



1960

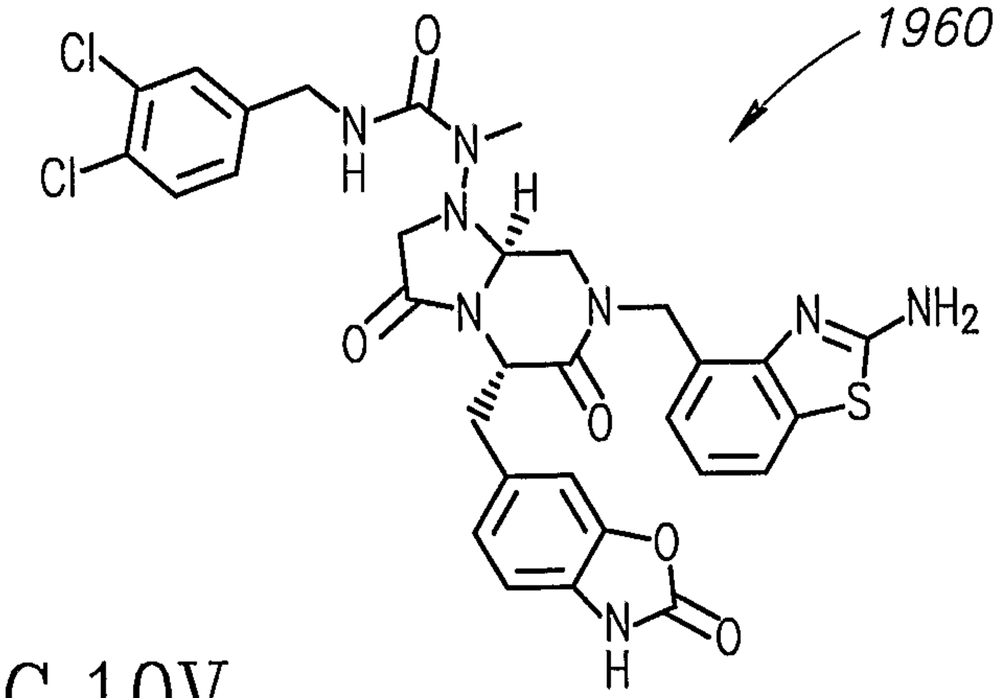
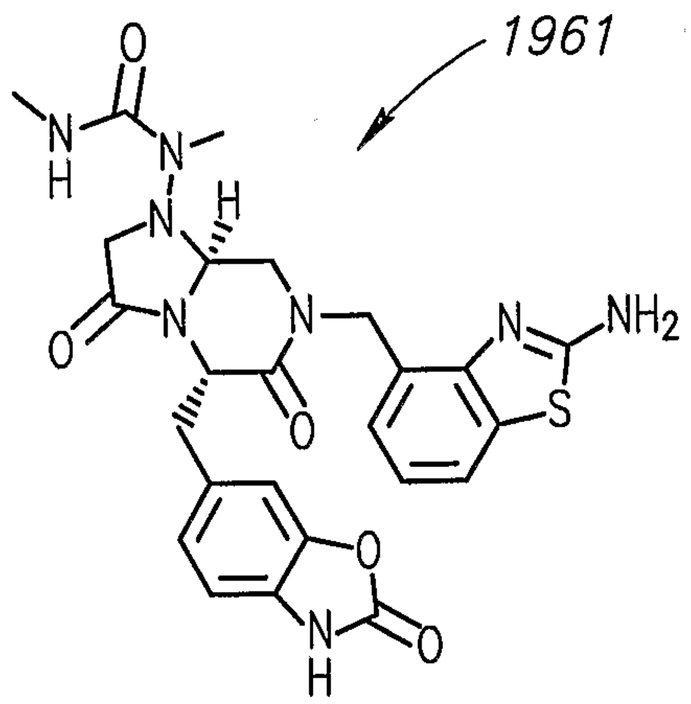
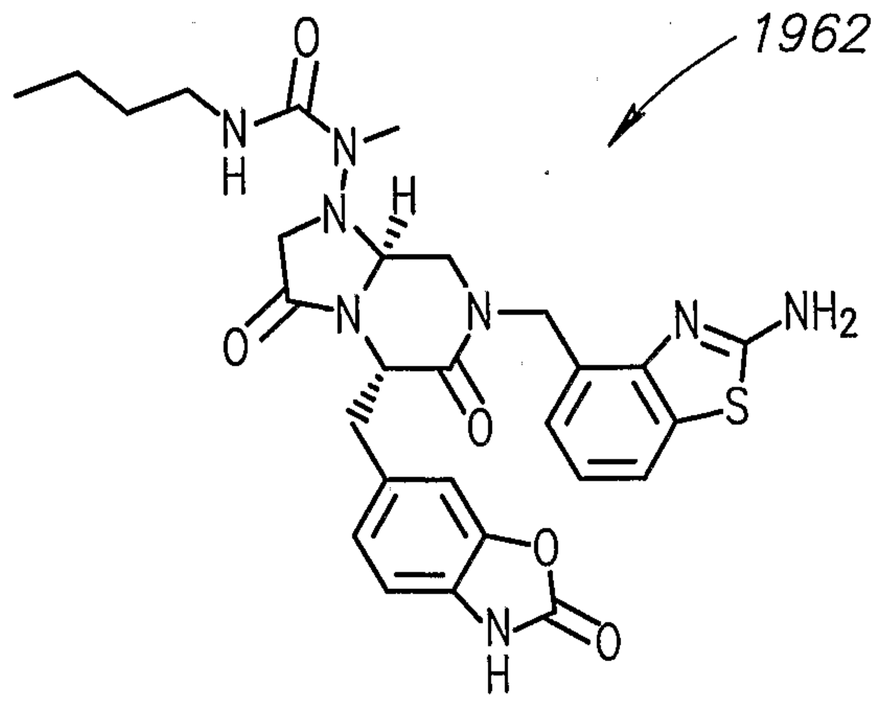
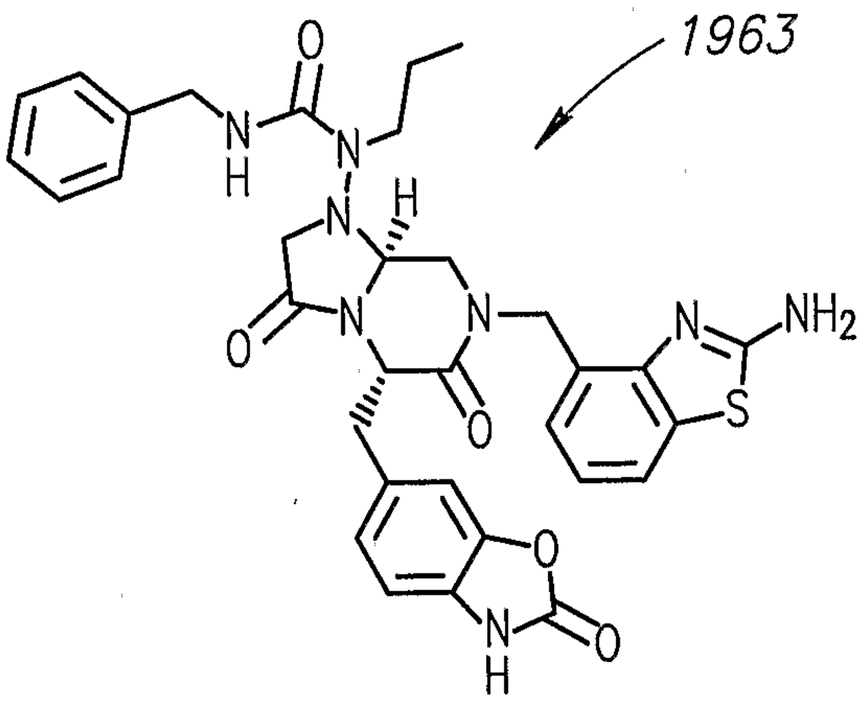
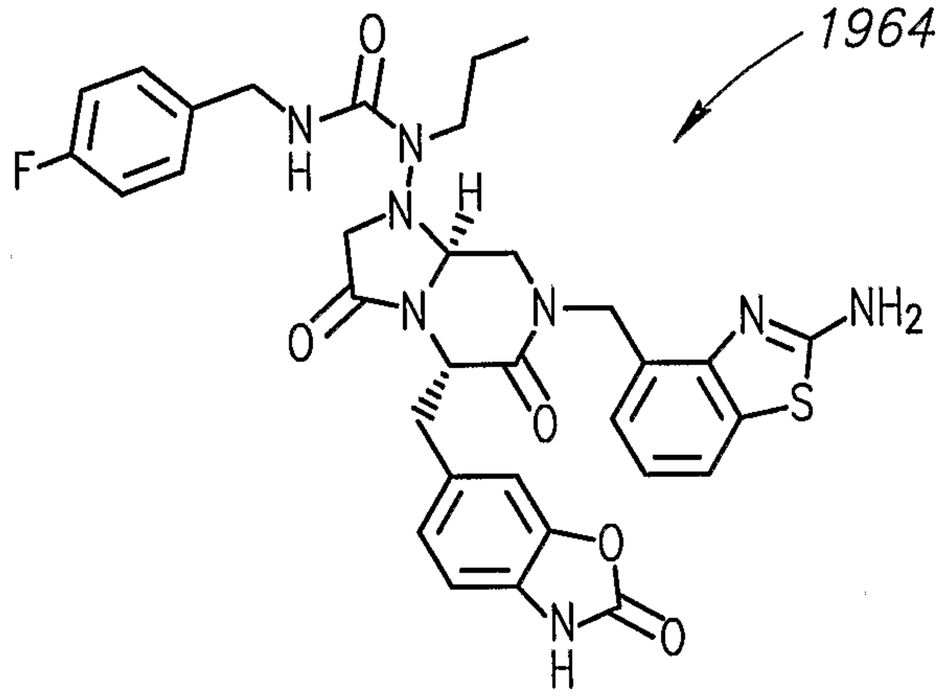


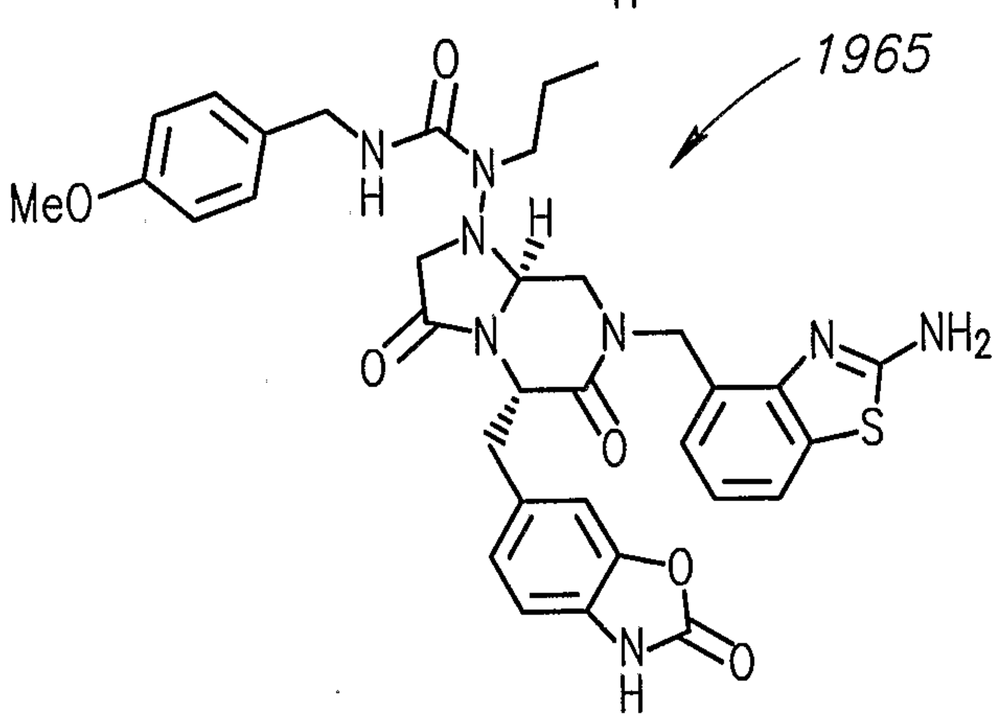
FIG.10V











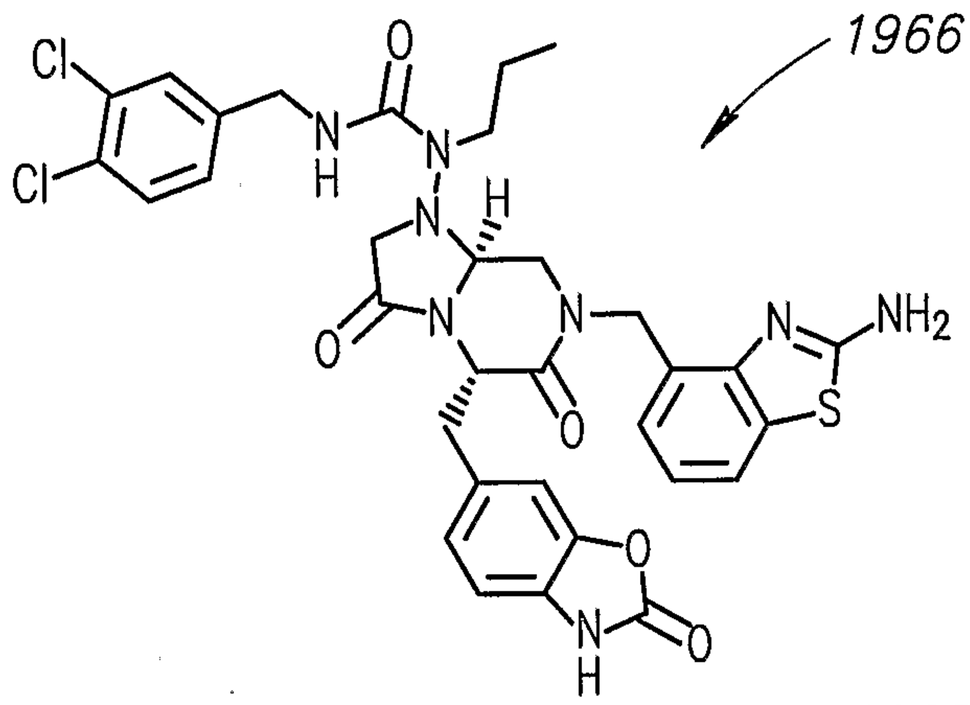
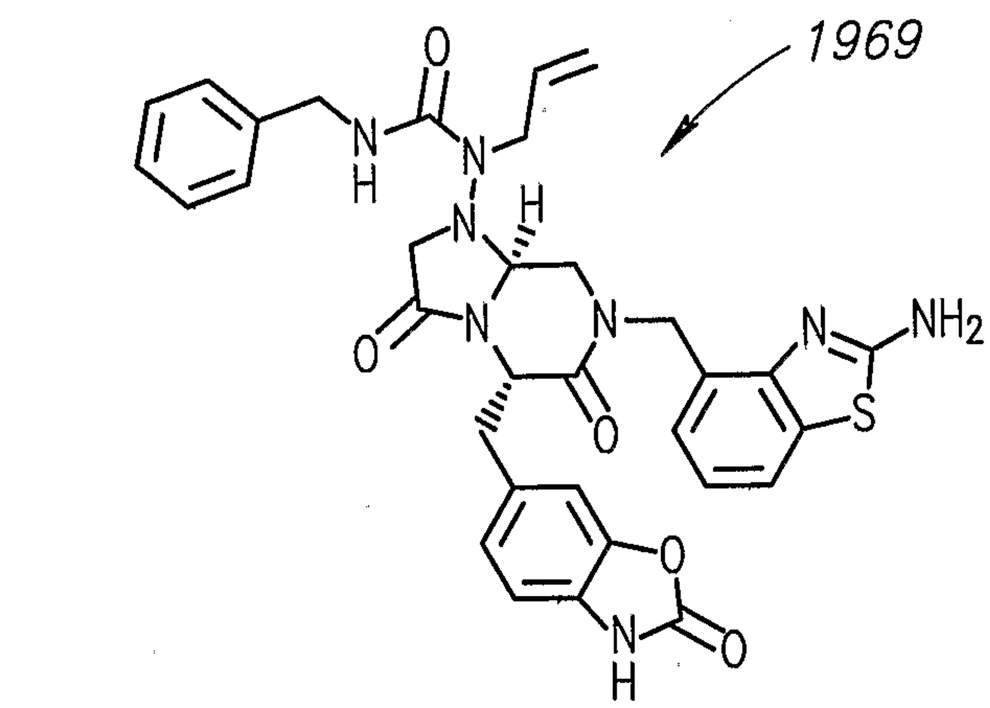
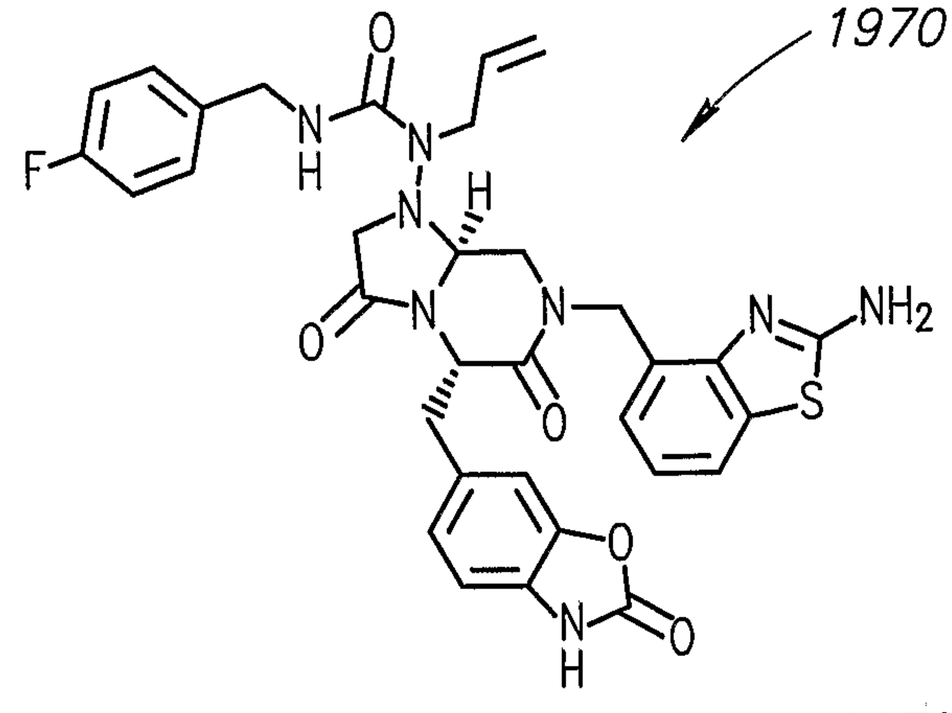
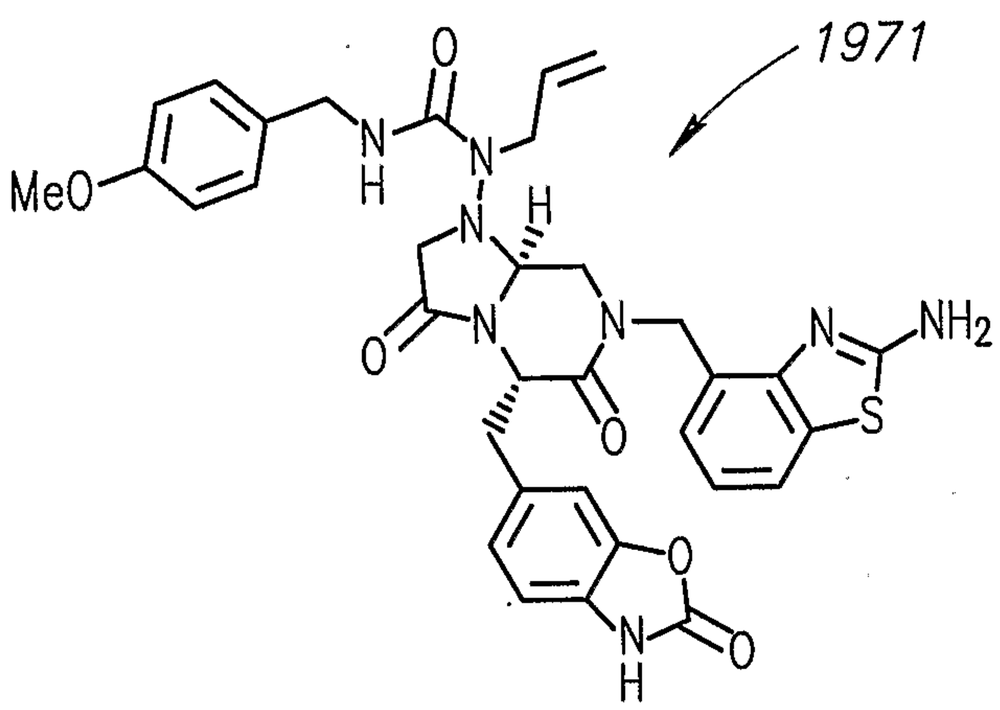
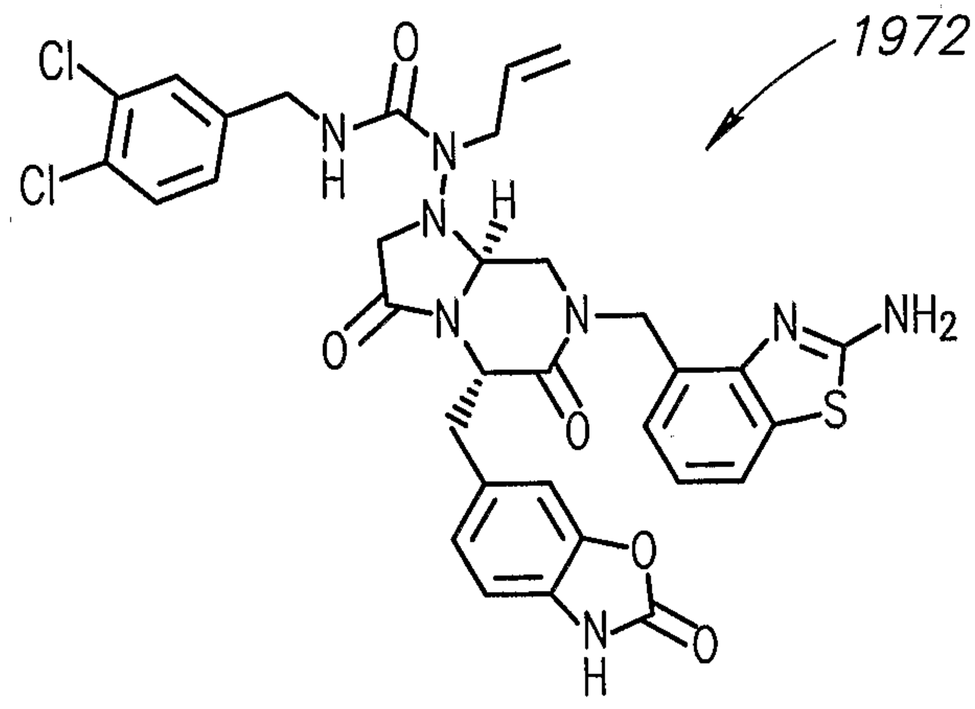


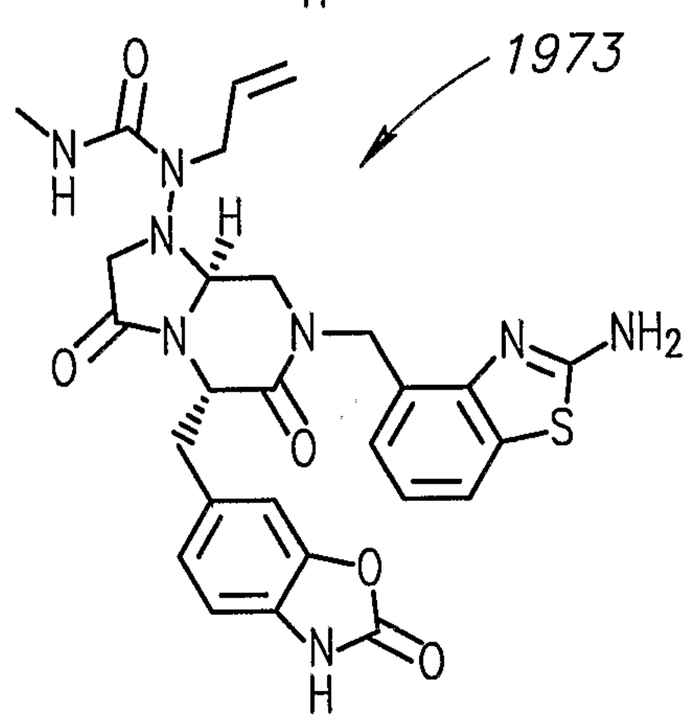
FIG.10W

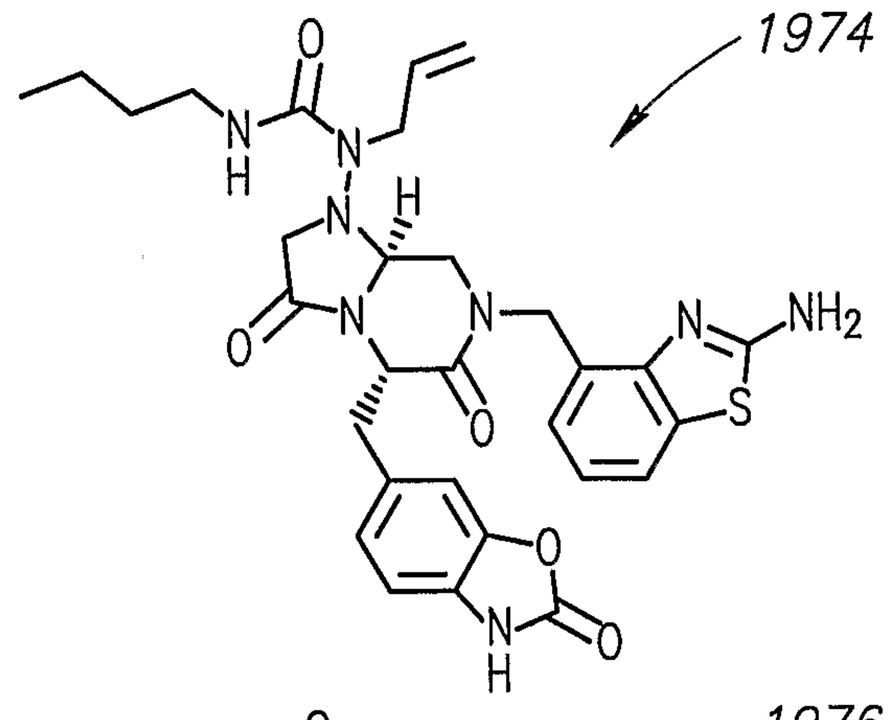


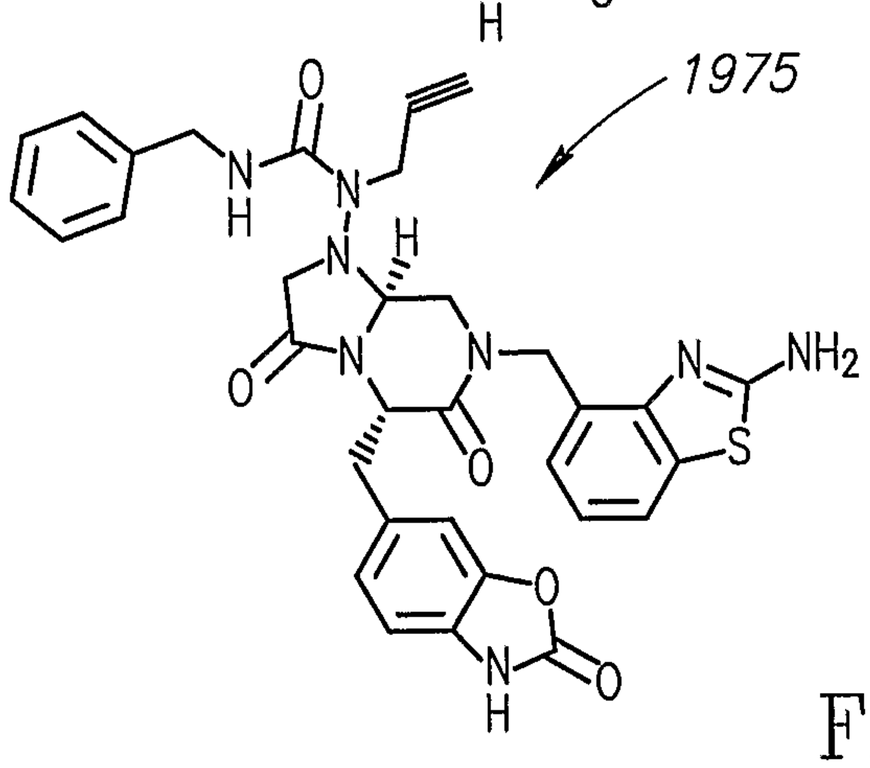












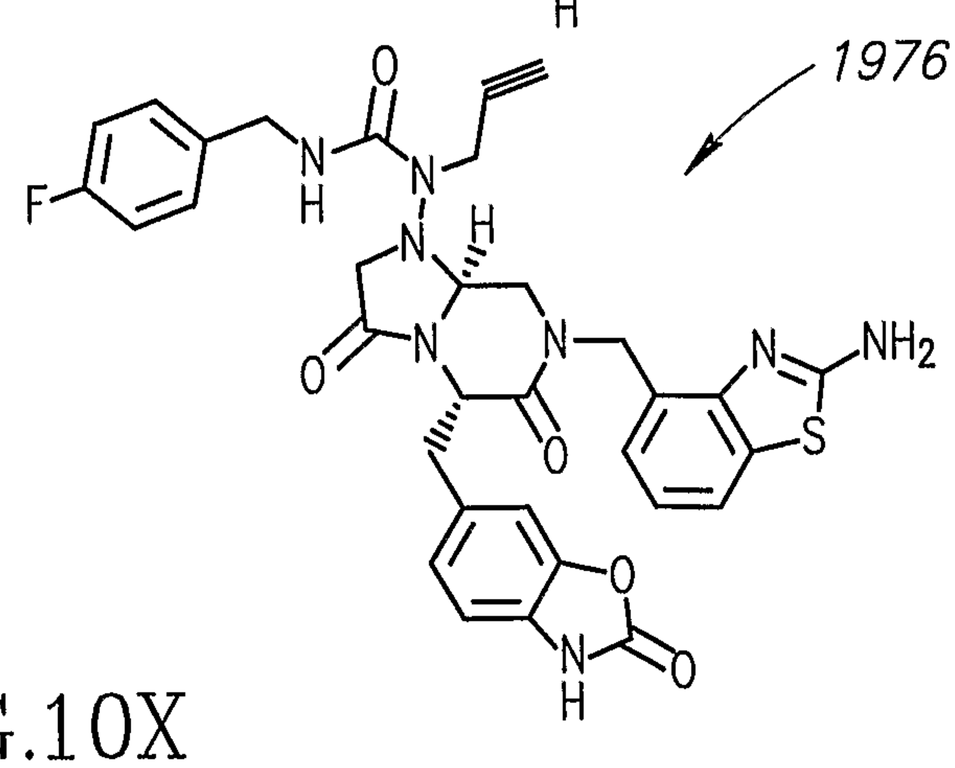
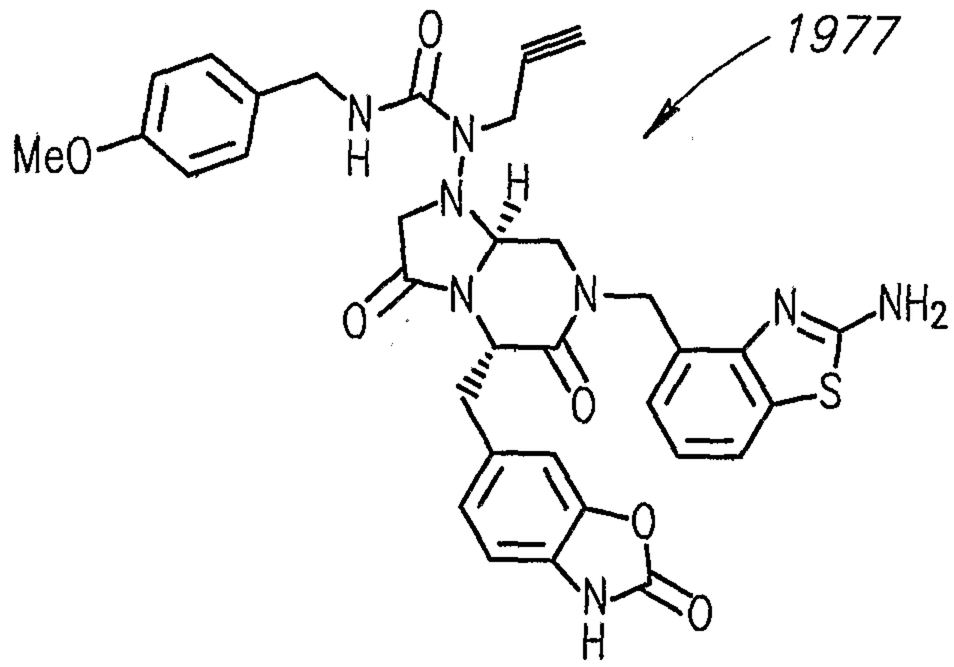
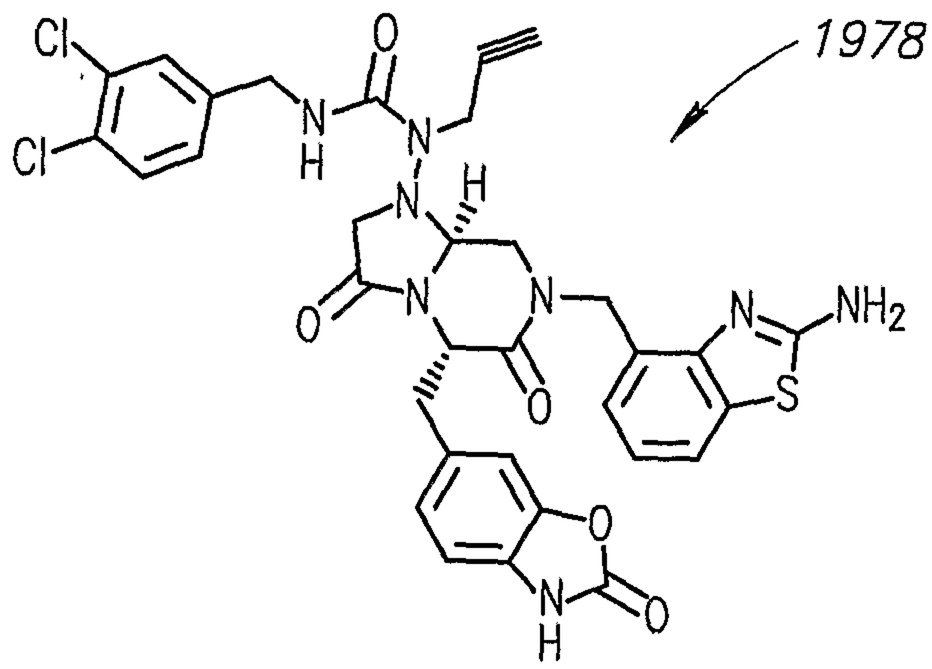
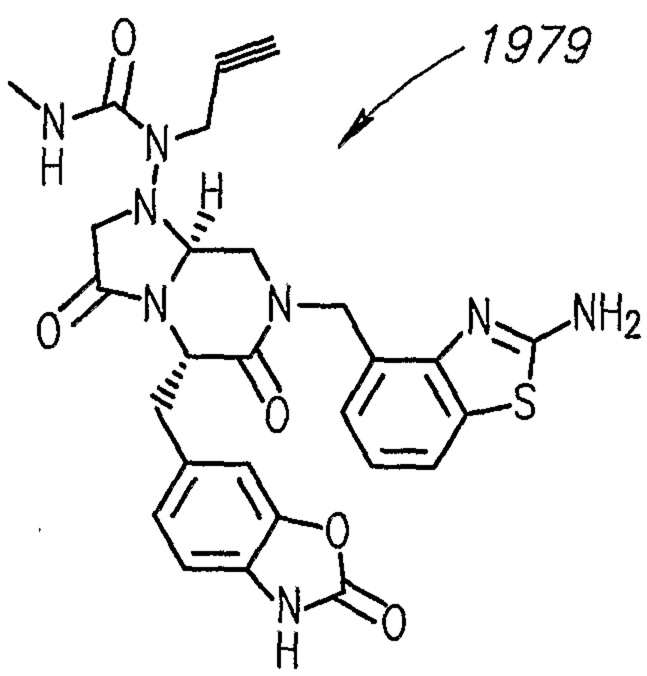
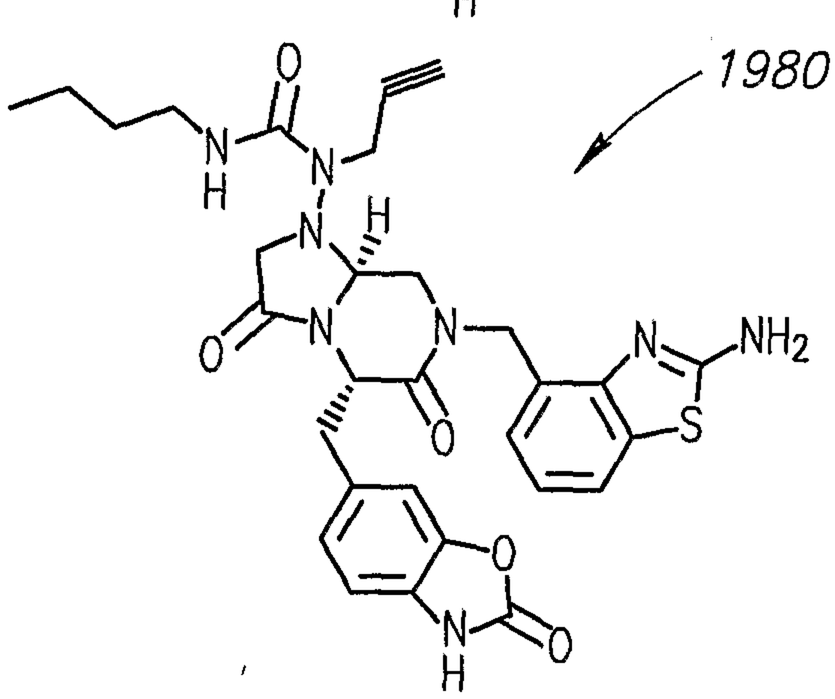


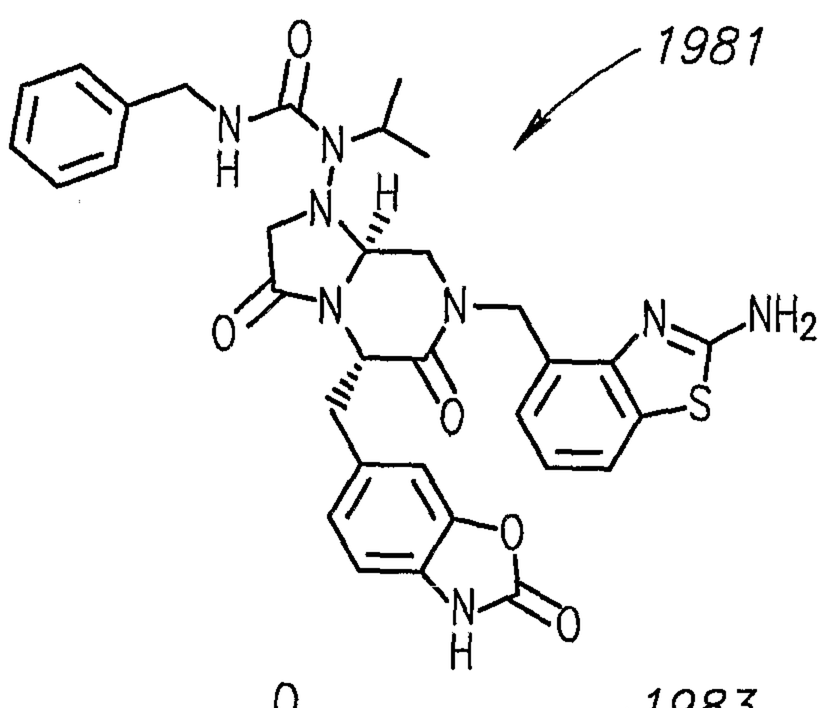
FIG.10X

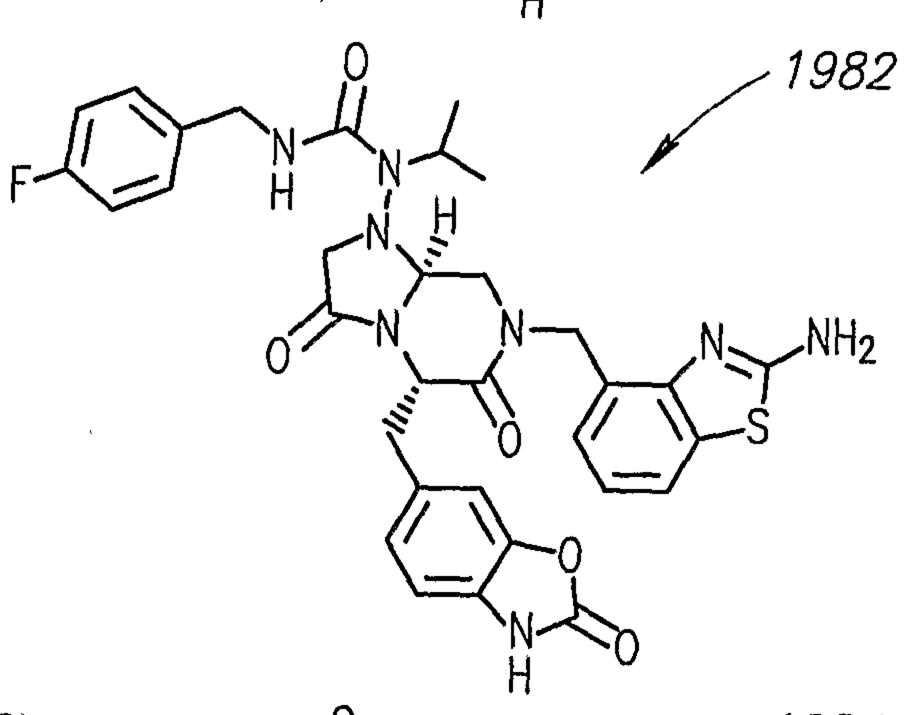

1977
MeO
O
N
H
N
O
NH2
S

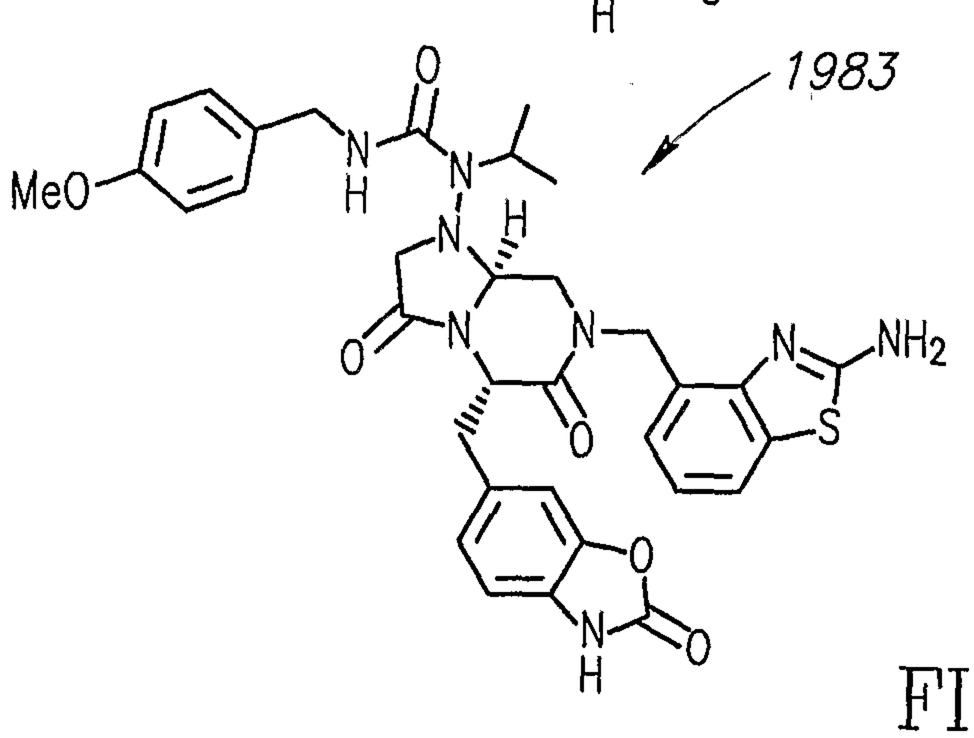

1978
Cl
Cl
O
N
H
N
O
NH2
S


1979
O
N
H
N
O
NH2
S


1980
O
N
H
N
O
NH2
S


1981
O
N
H
N
O
NH2
S


1982
F
O
N
H
N
O
NH2
S


1983
MeO
O
N
H
N
O
NH2
S

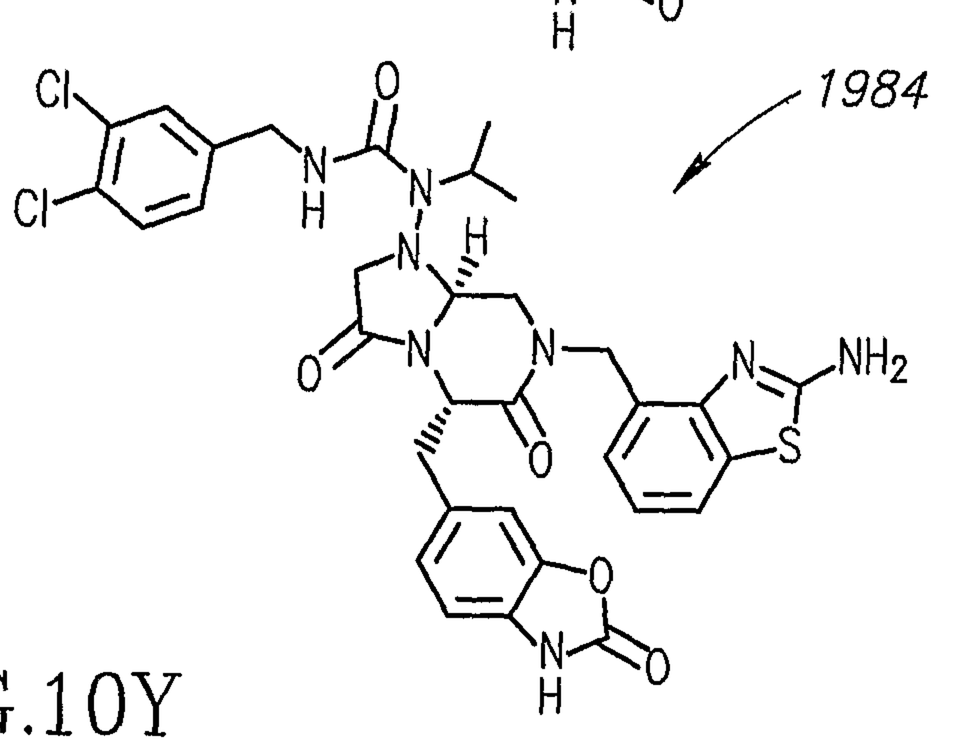
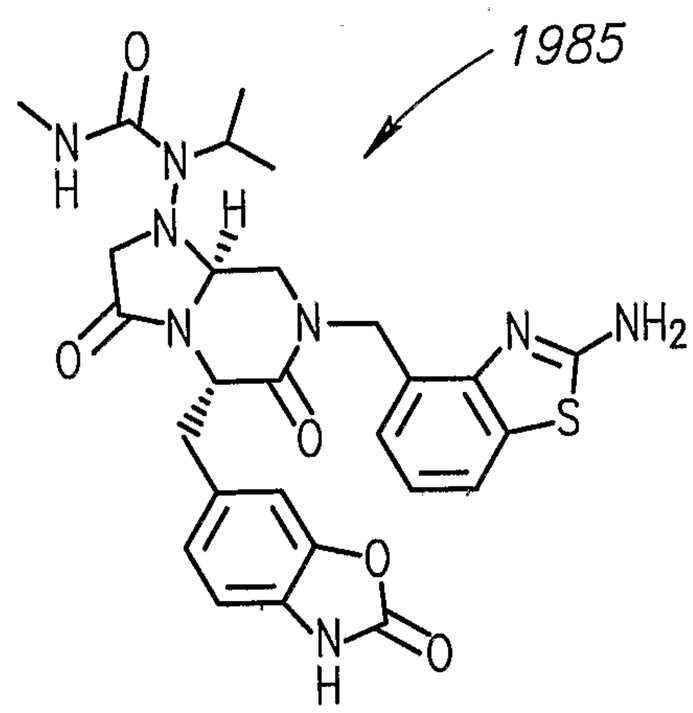
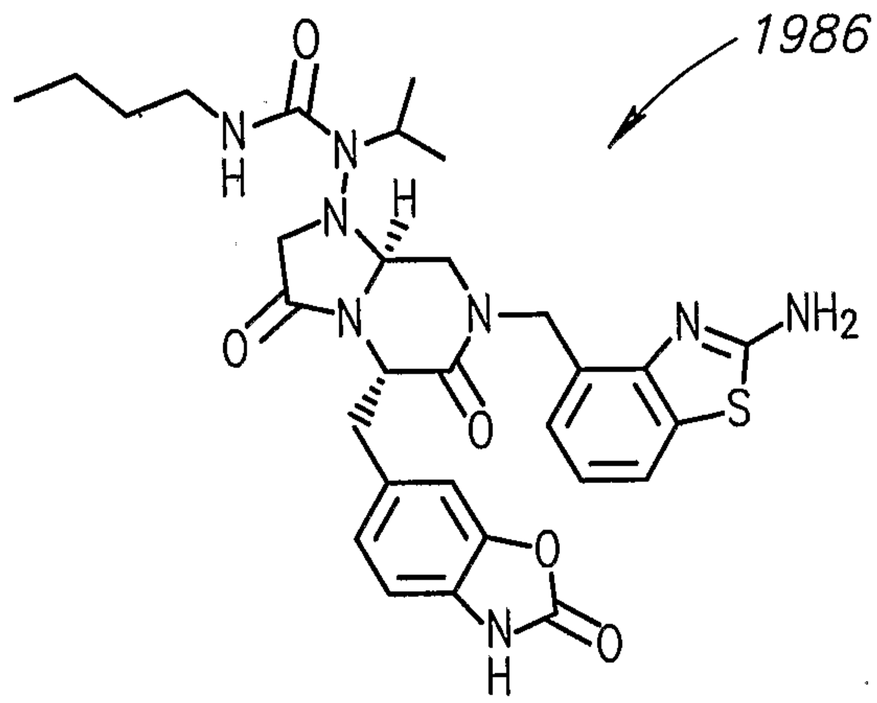
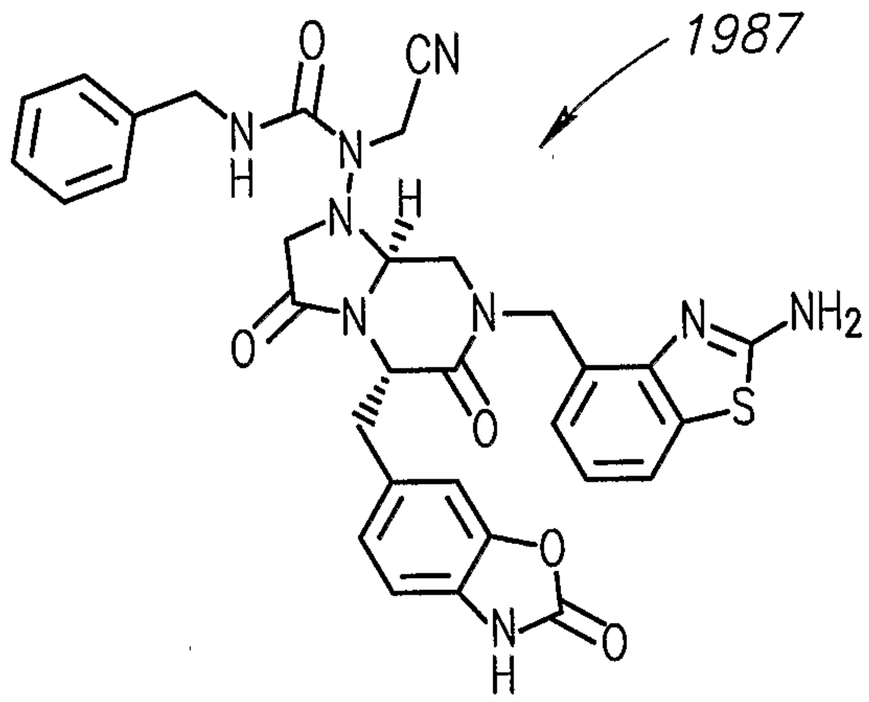
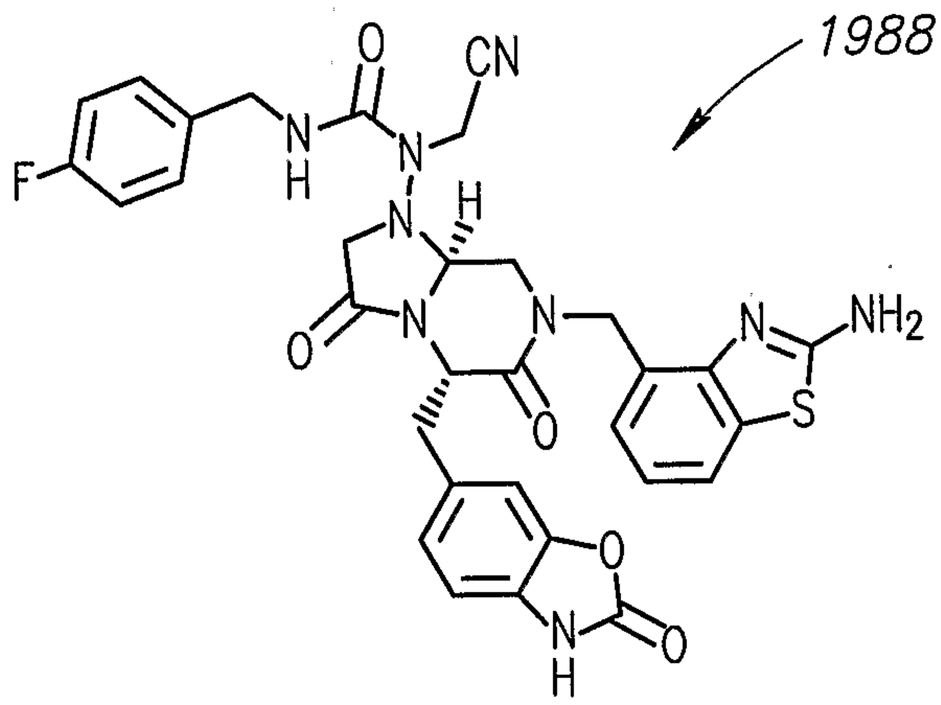

1984
Cl
Cl
O
N
H
N
O
NH2
S

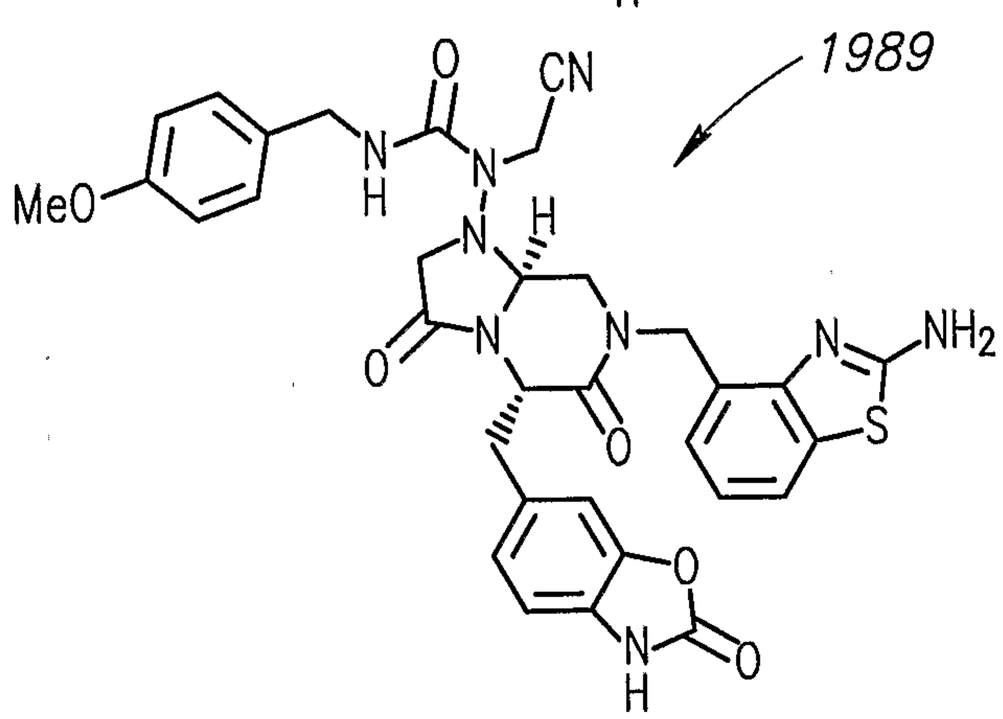
FIG.10Y











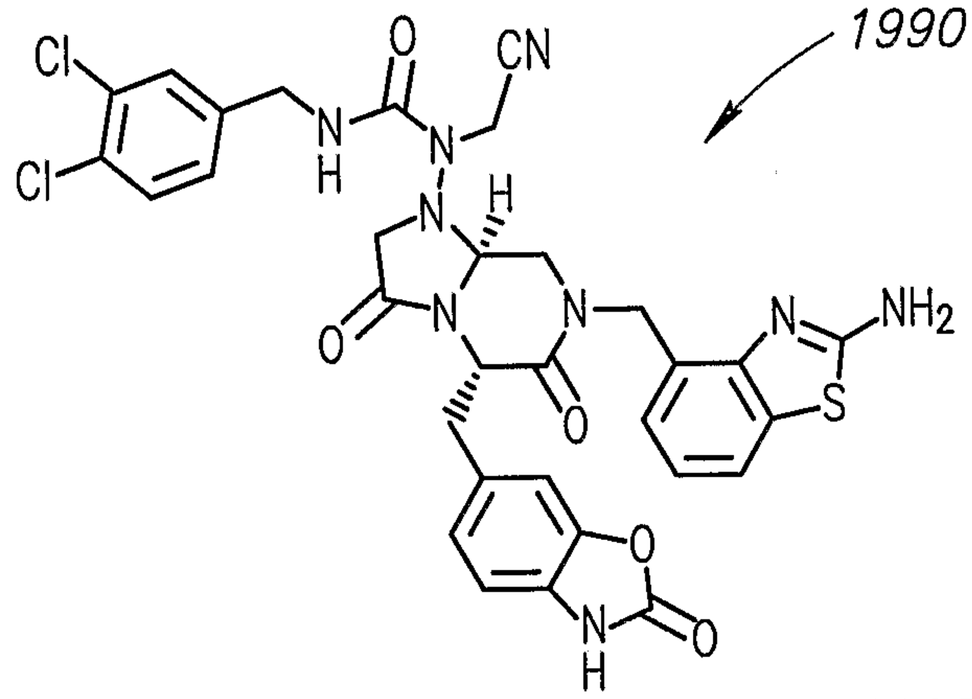
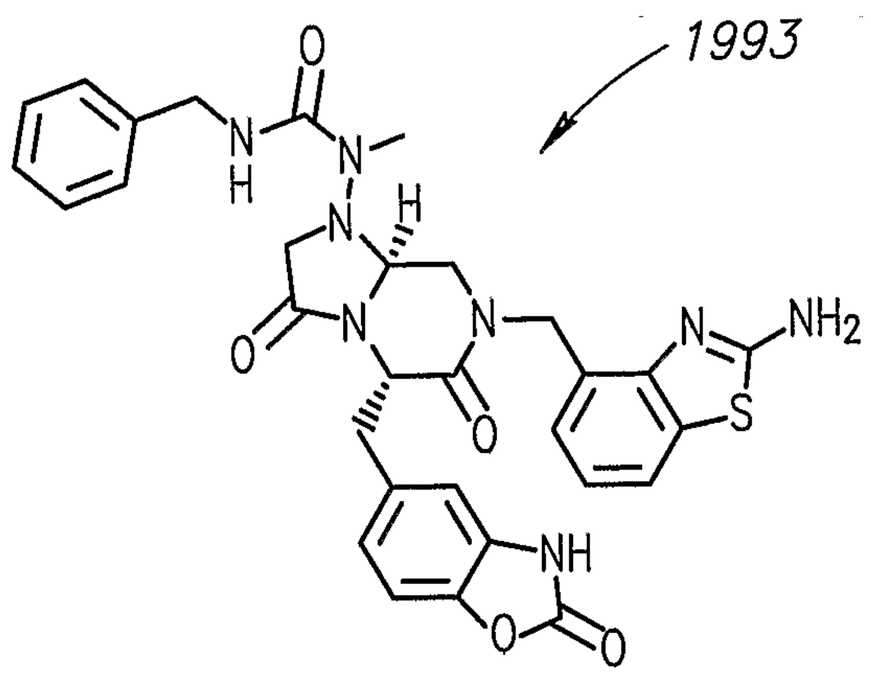
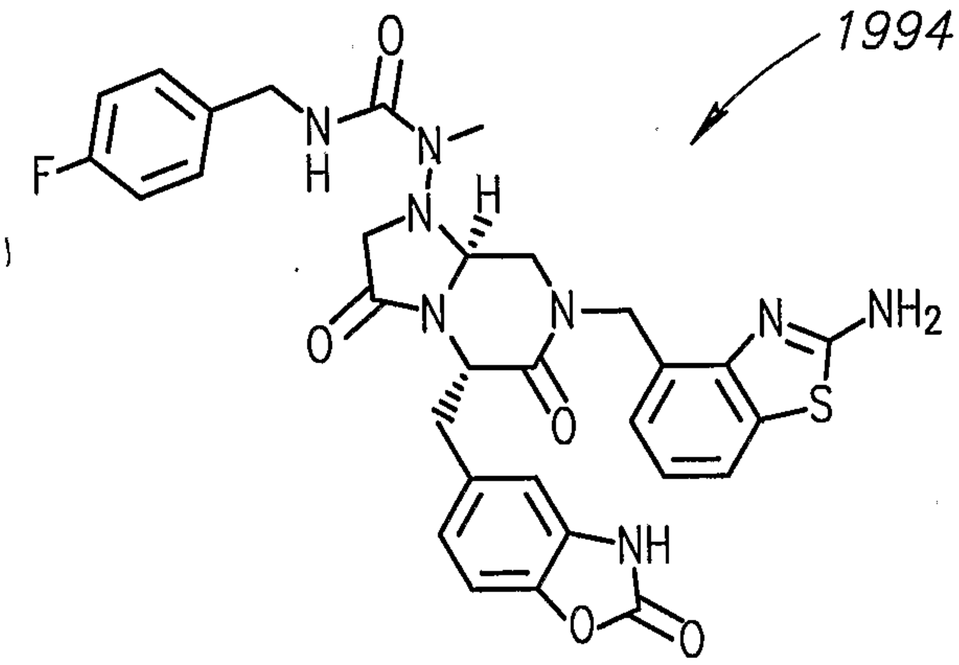
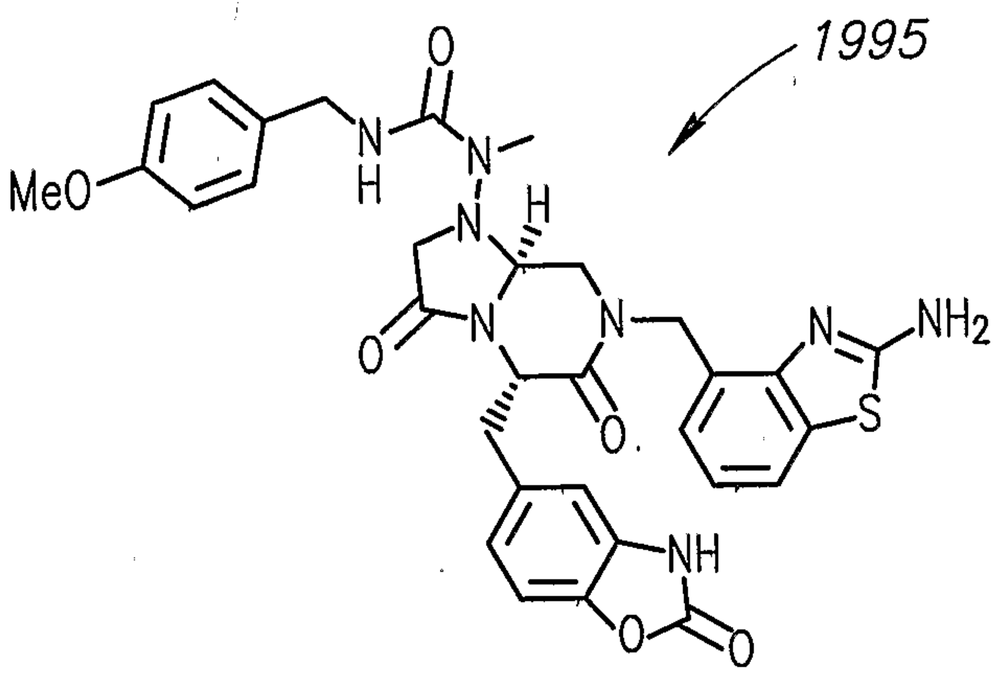
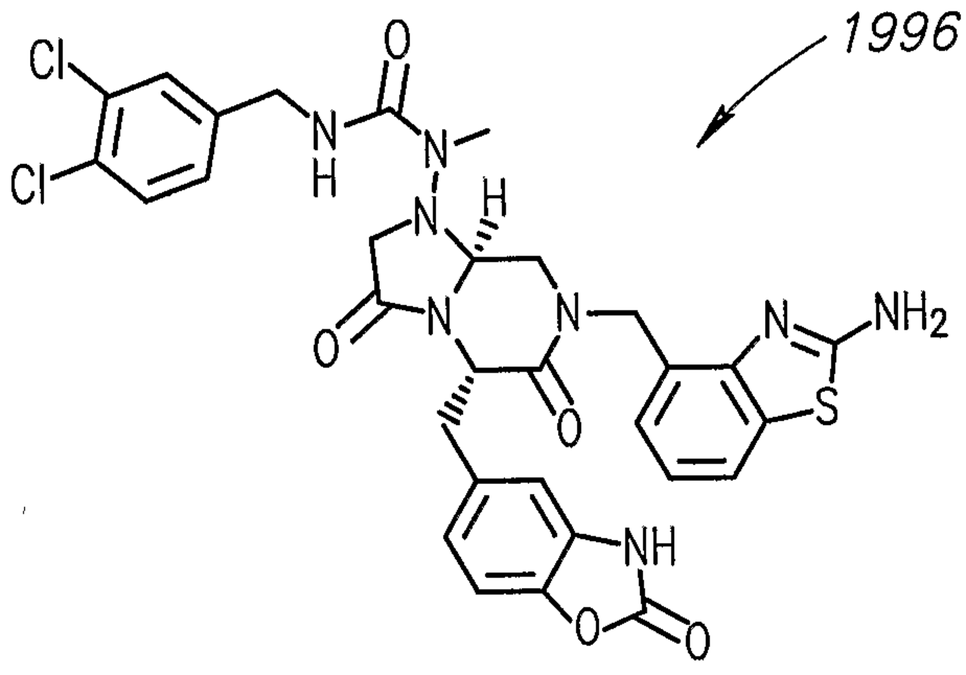


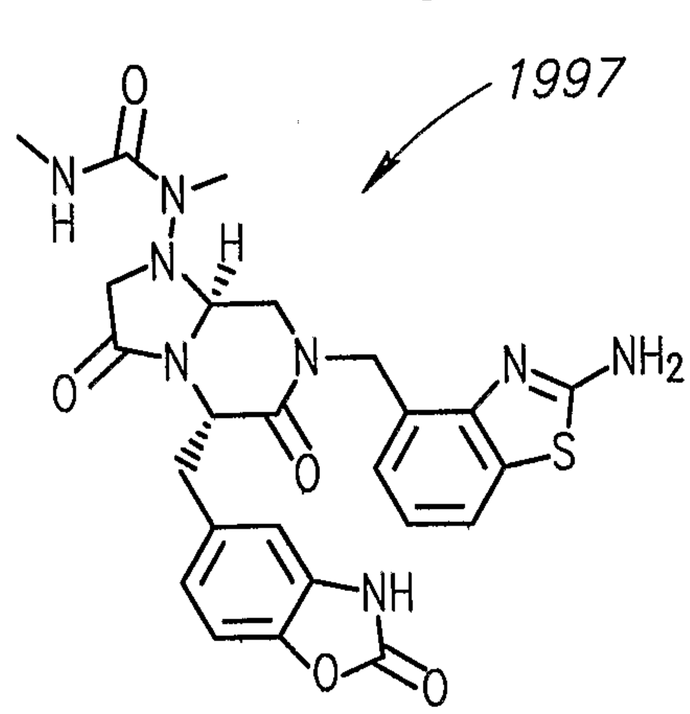
FIG.10Z











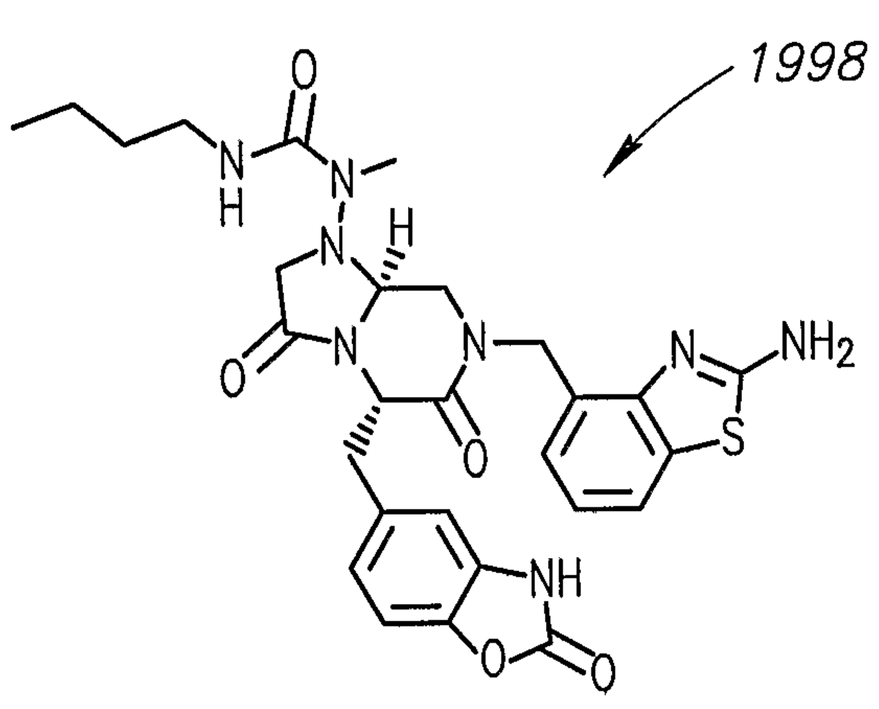
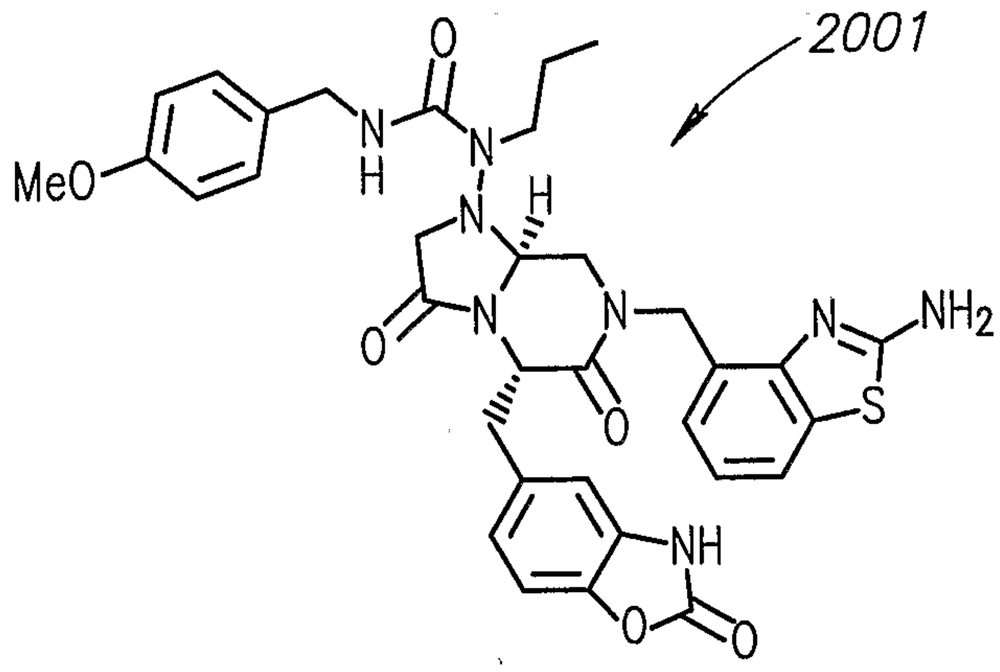
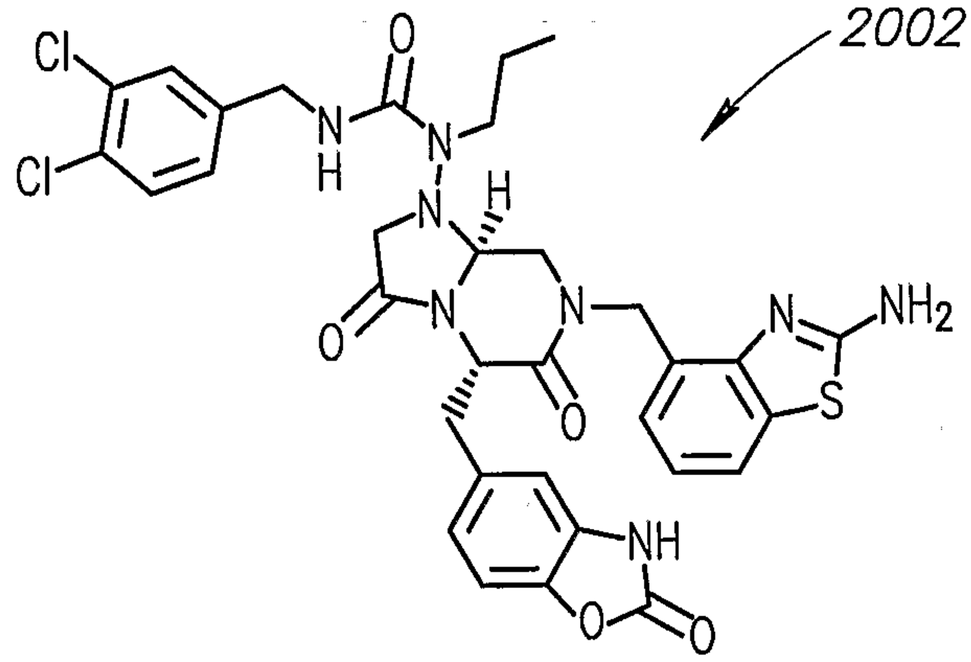


FIG.10AA

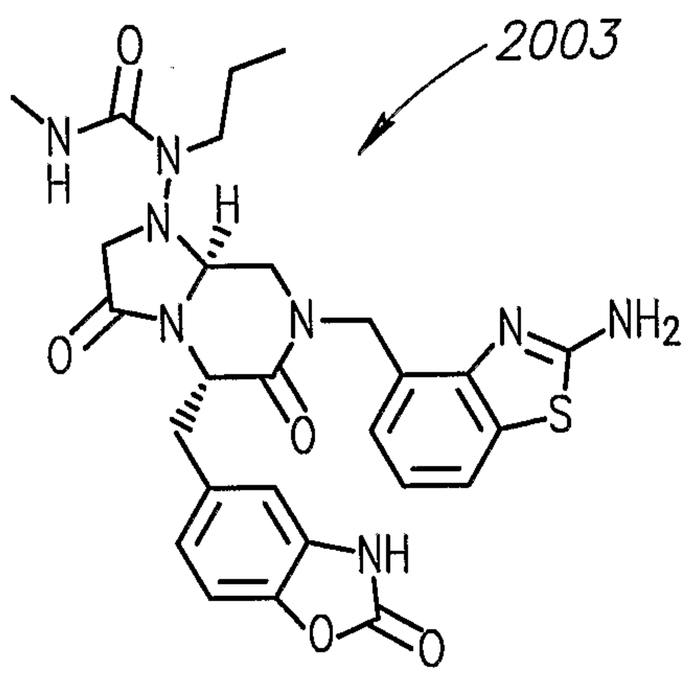
2001



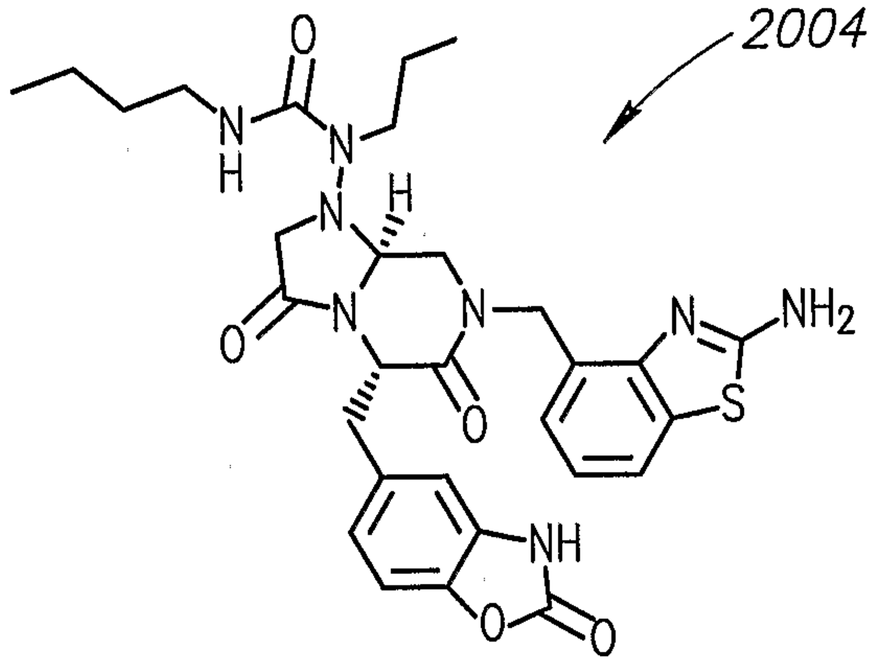
2002



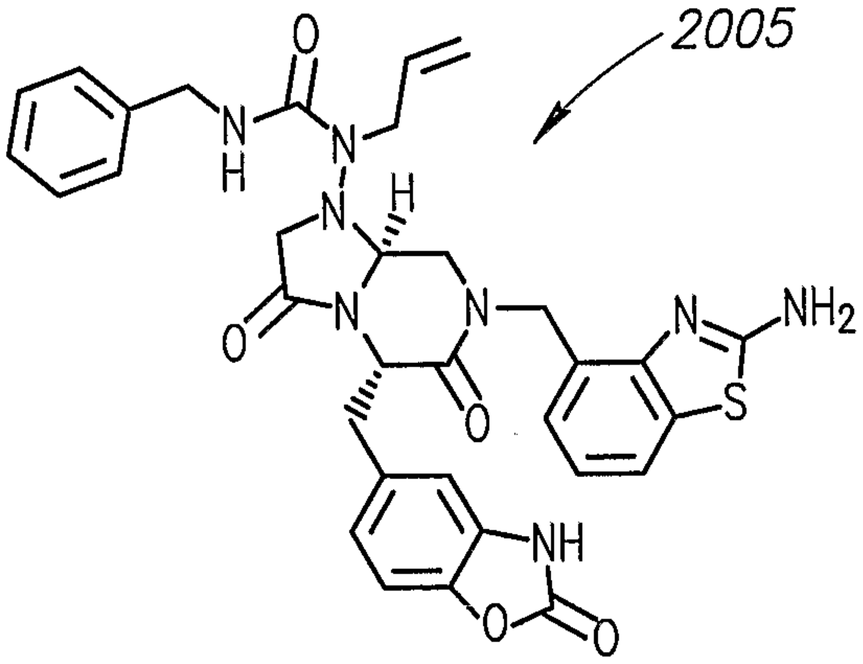
2003



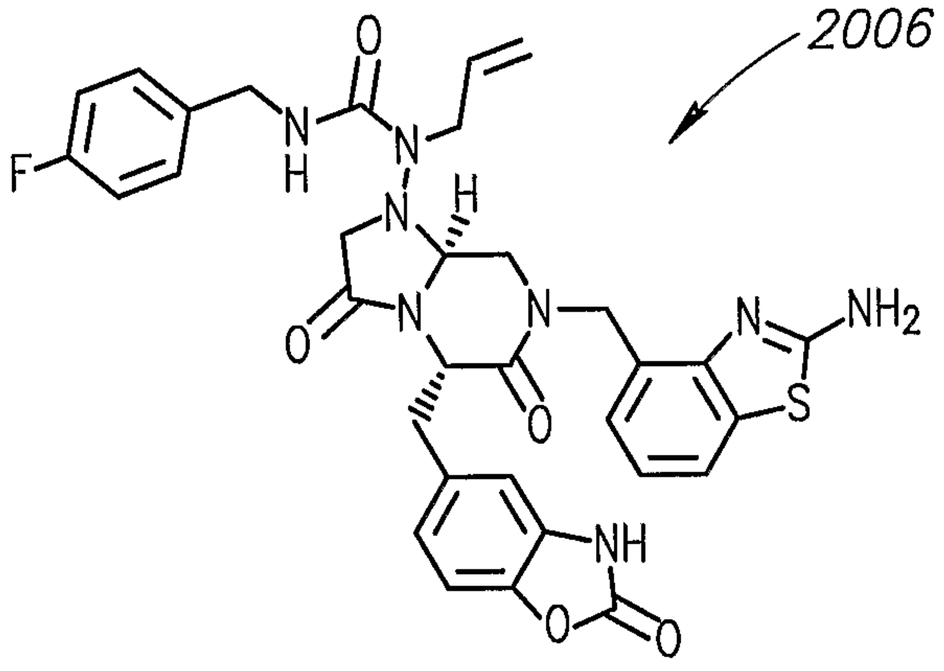
2004



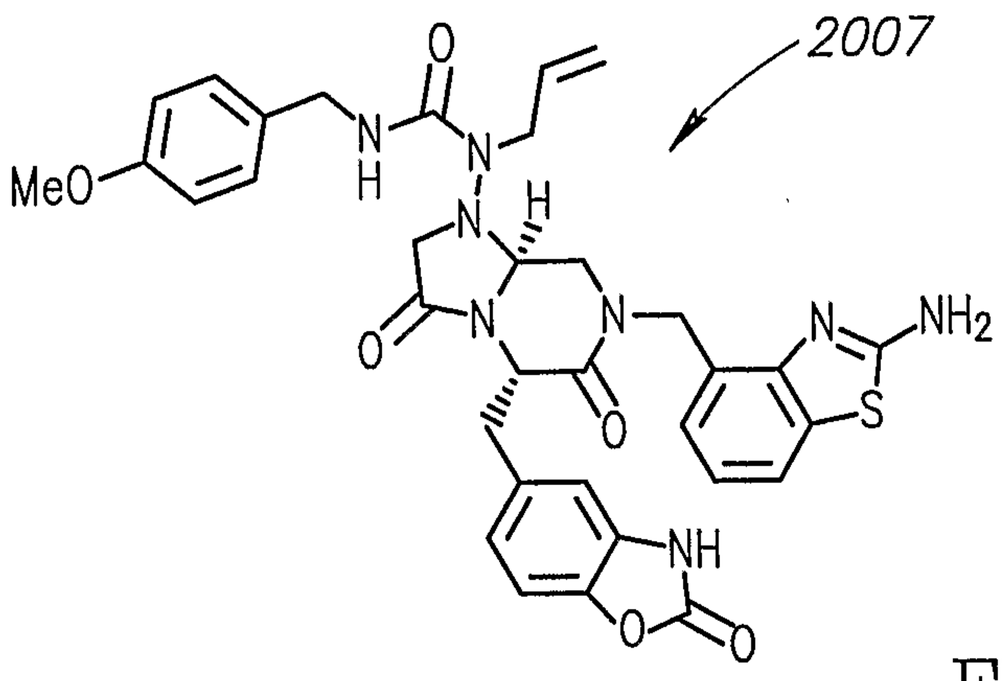
2005



2006



2007



2008

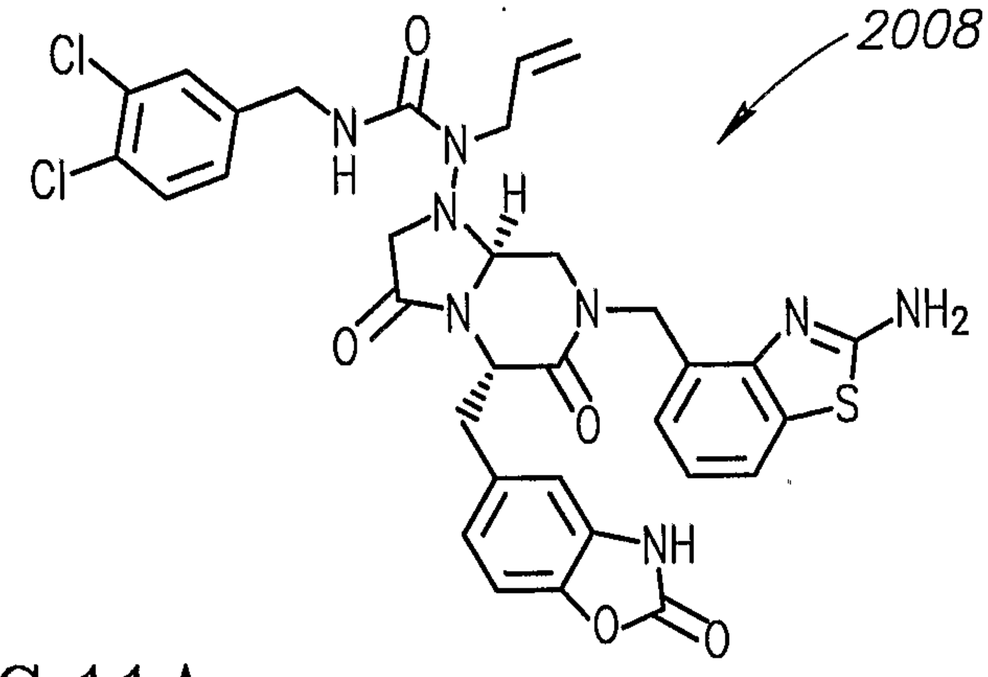
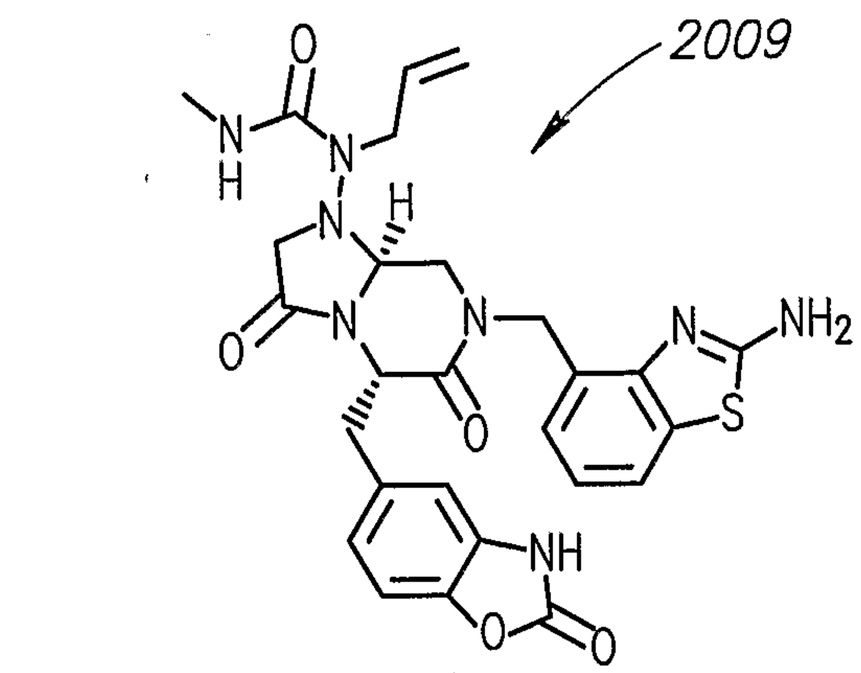
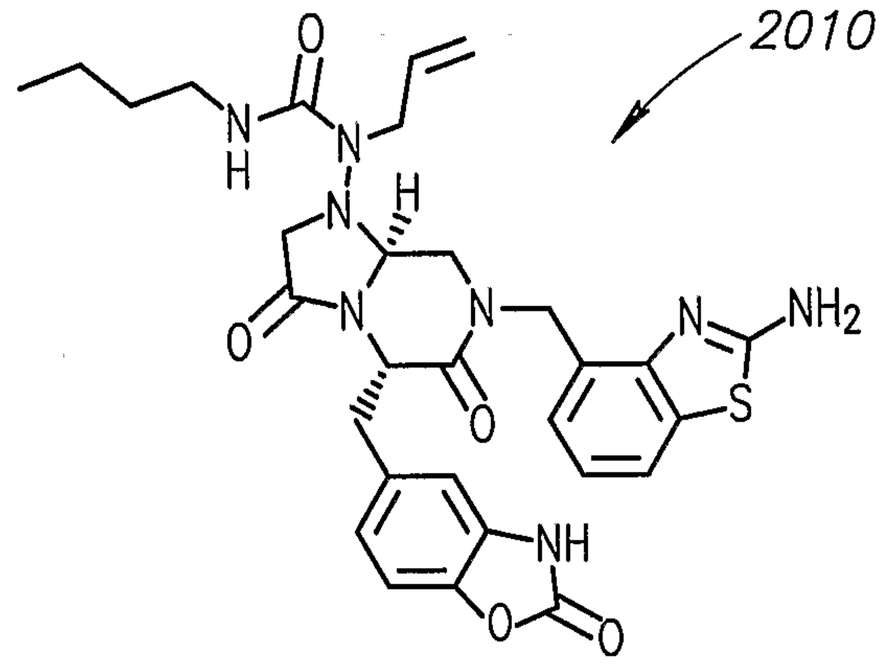
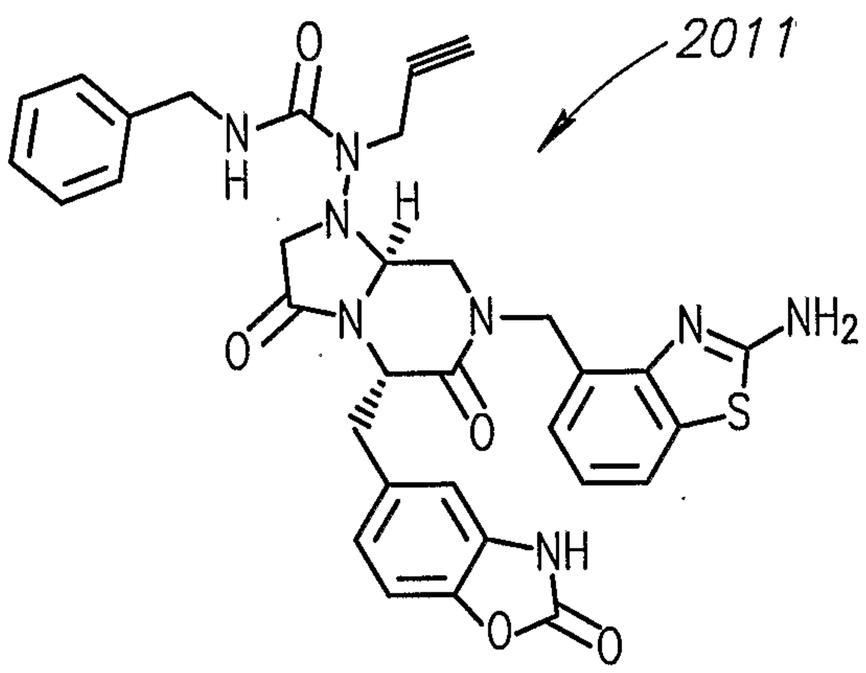
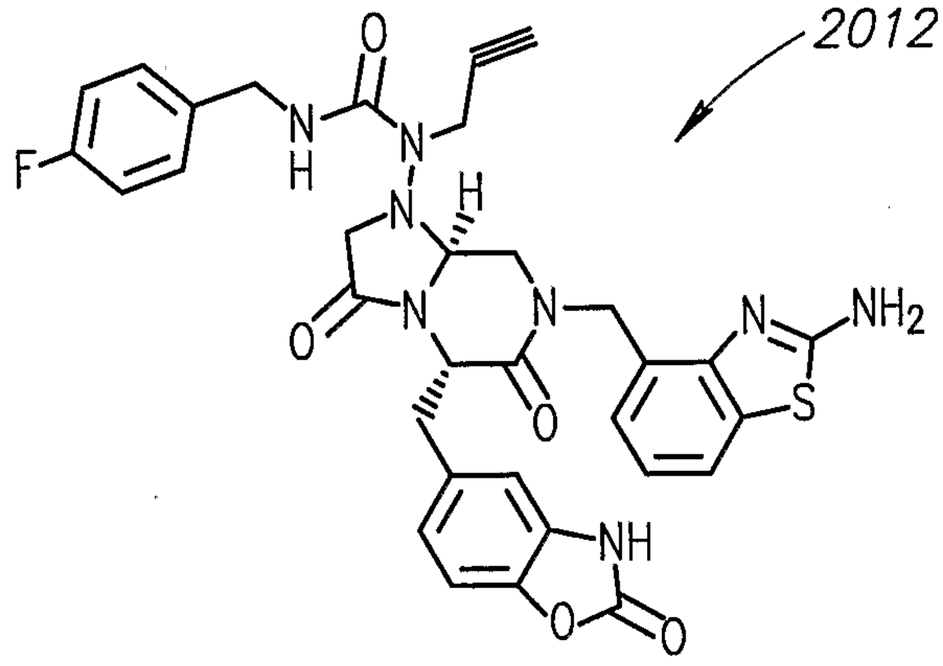


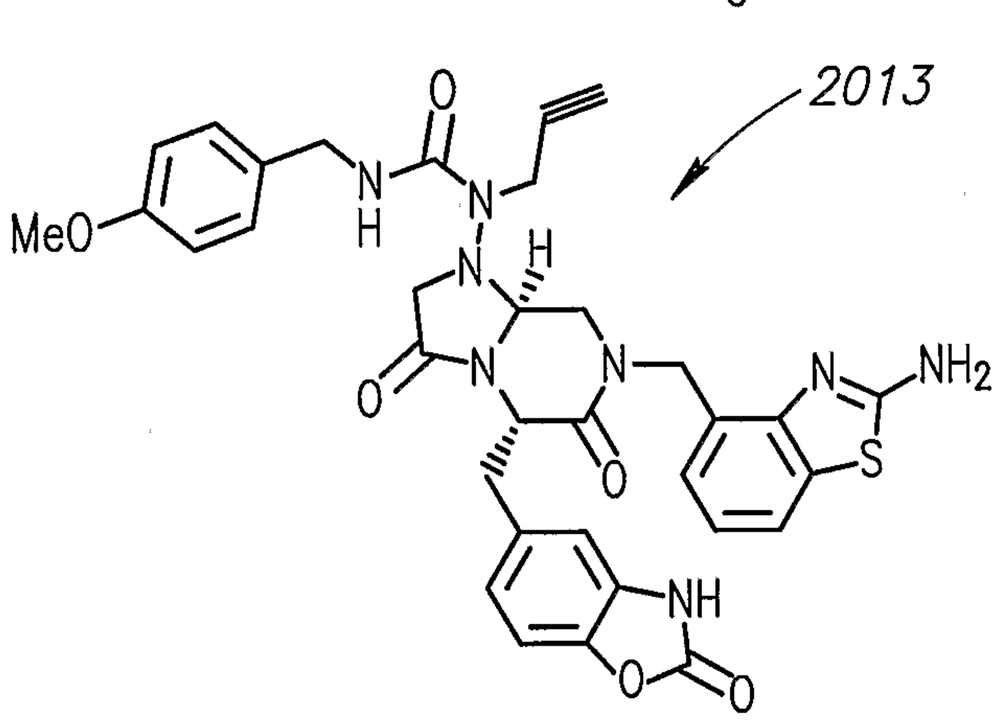
FIG.11A











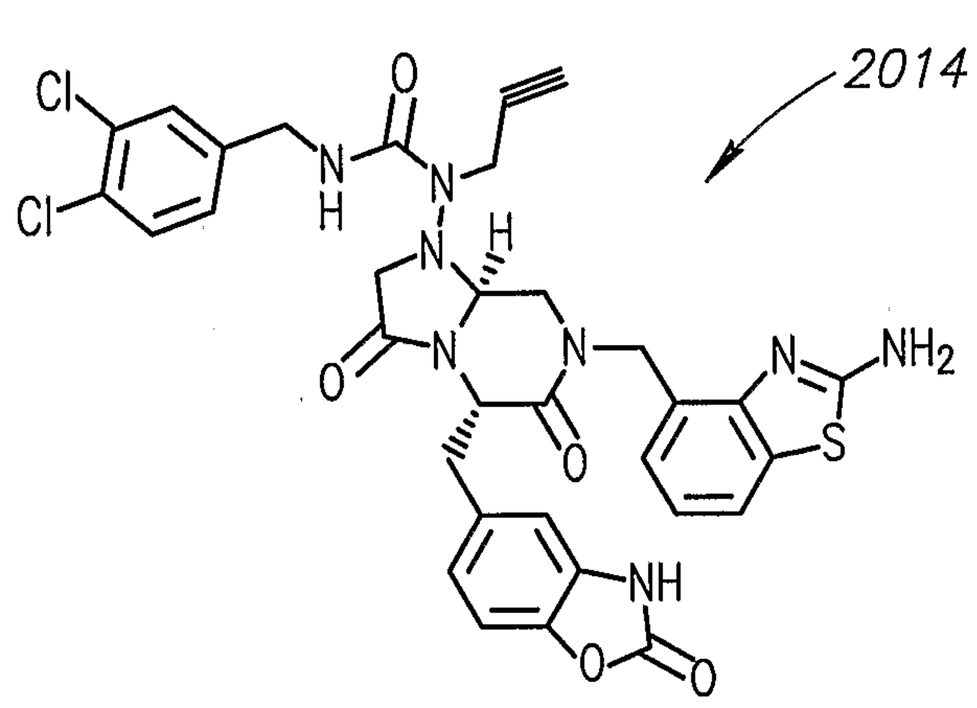
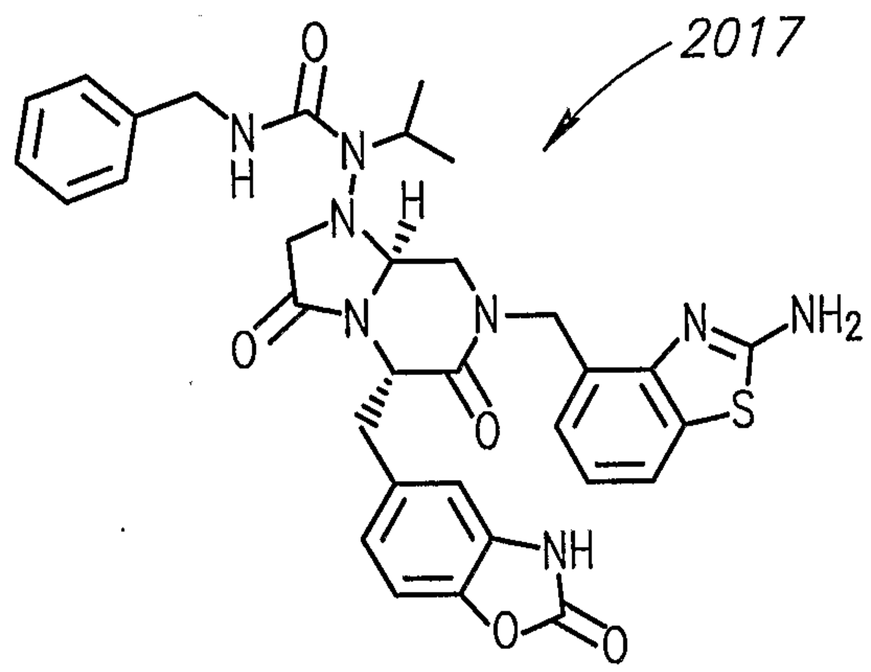
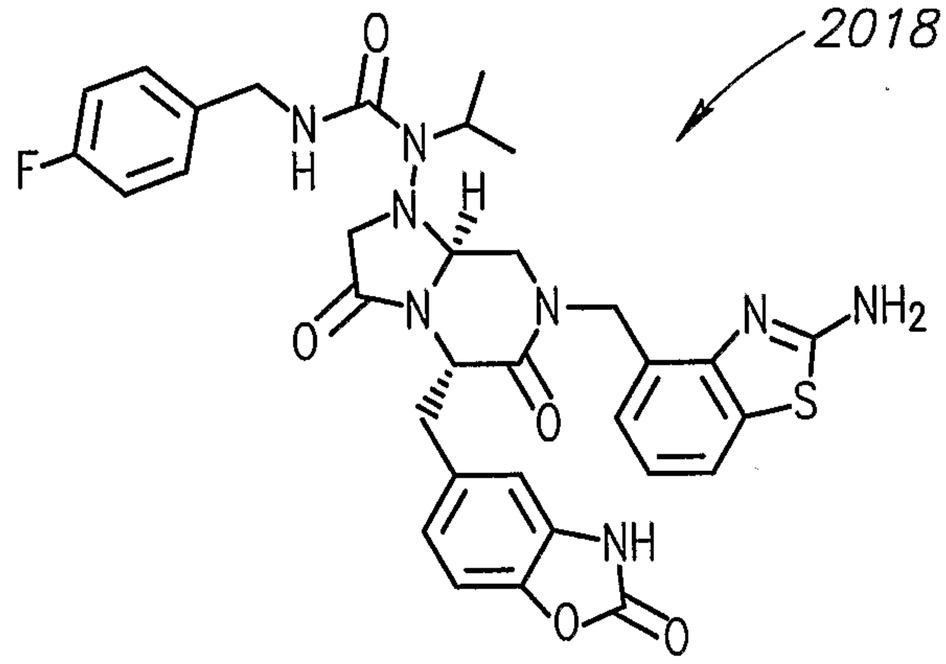
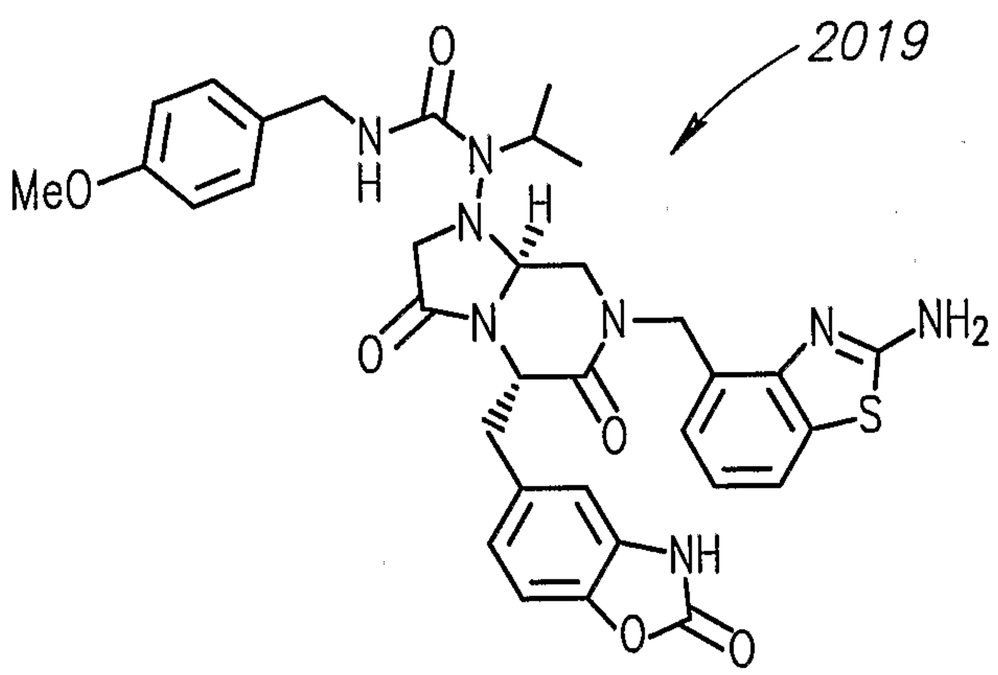
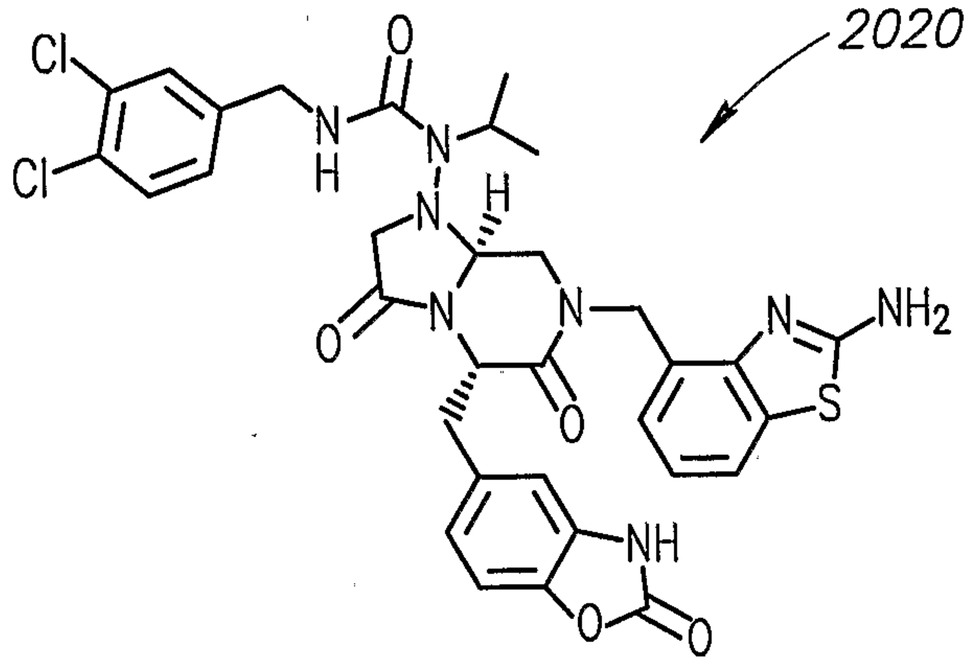


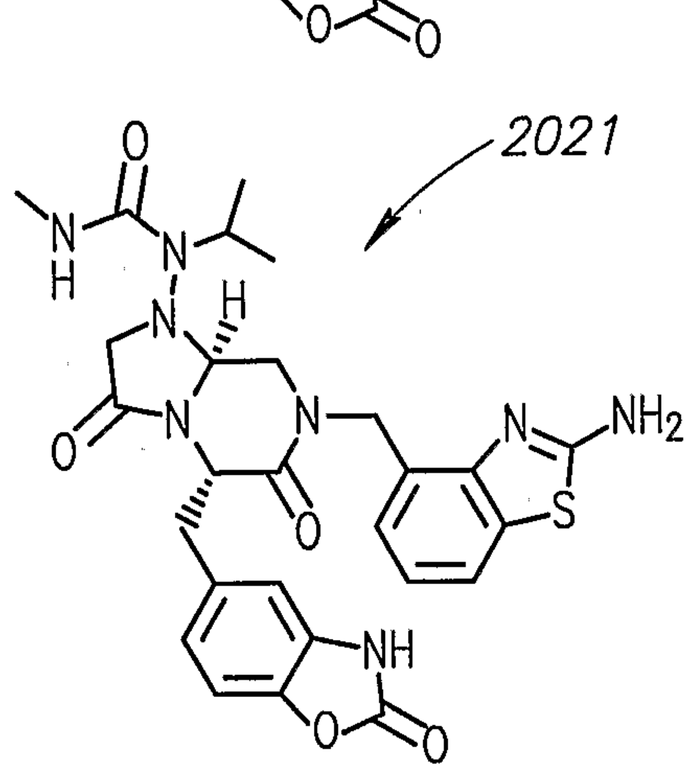
FIG.11B











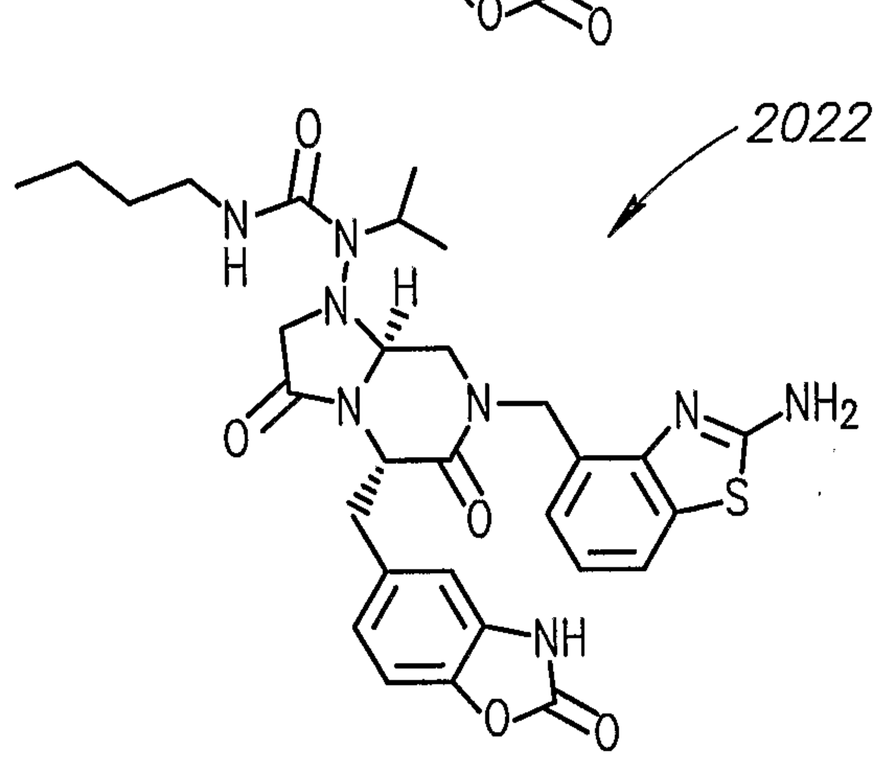
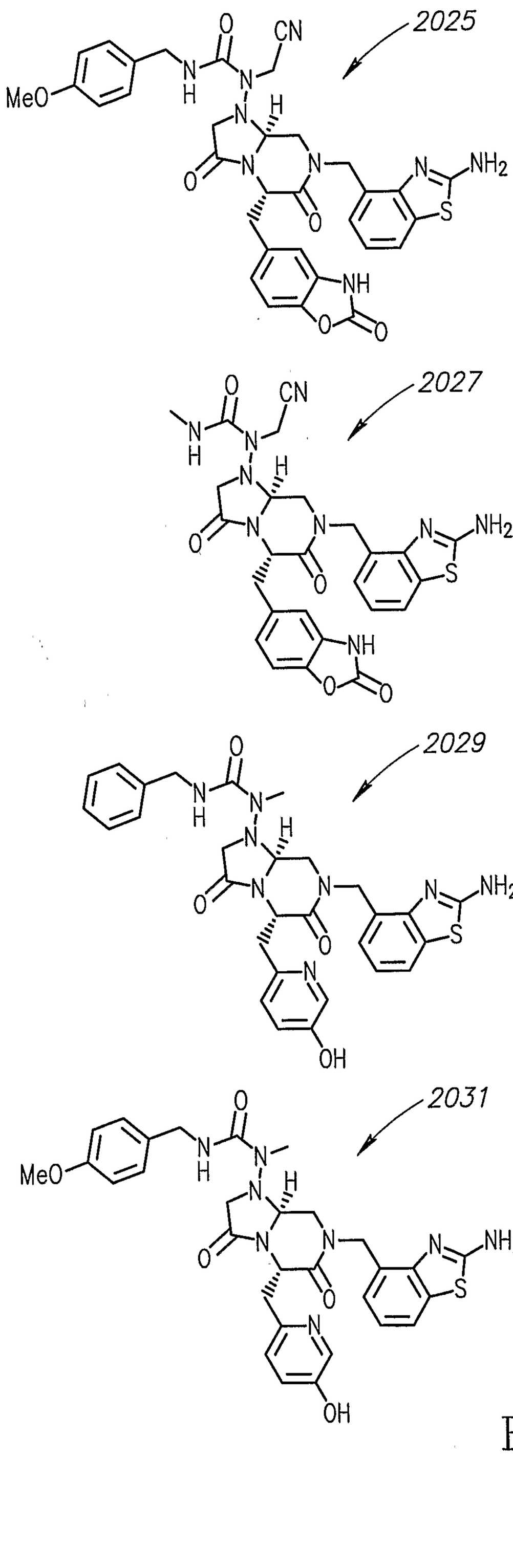
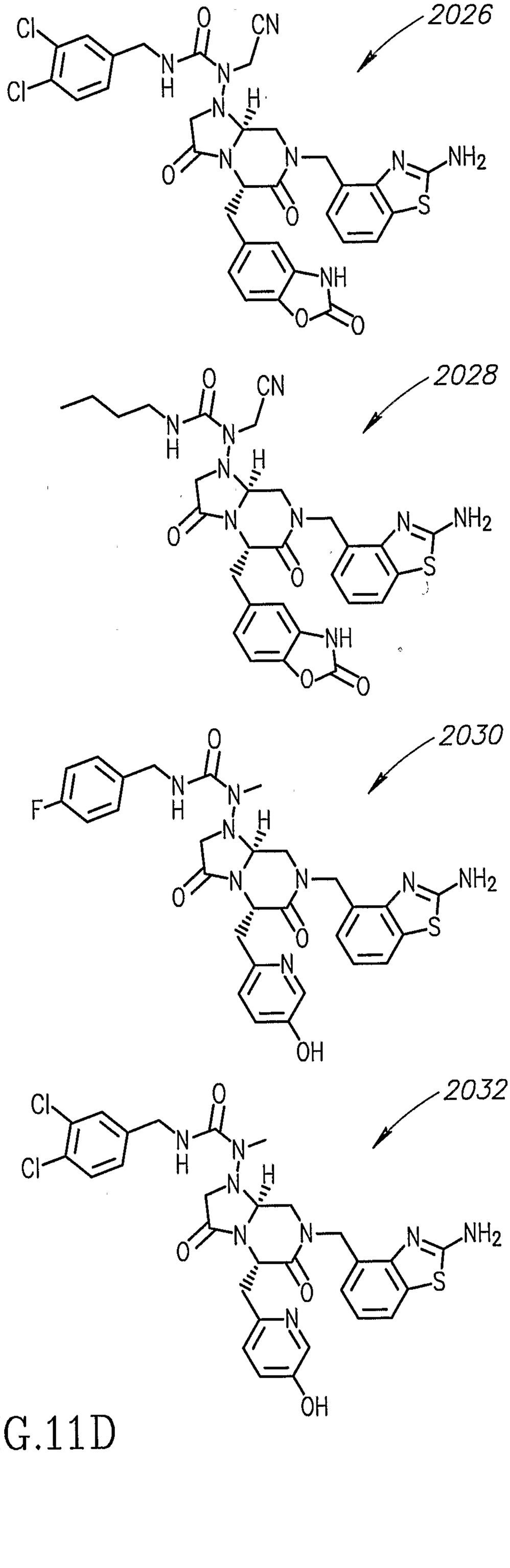


FIG.11C


2025
MeO
O
CN
N
H
NH2
S
NH


2026
Cl
Cl
O
CN
N
H
NH2
S
NH

2027
O
CN
N
H
NH2
S
NH

2028
O
CN
N
H
NH2
S
NH

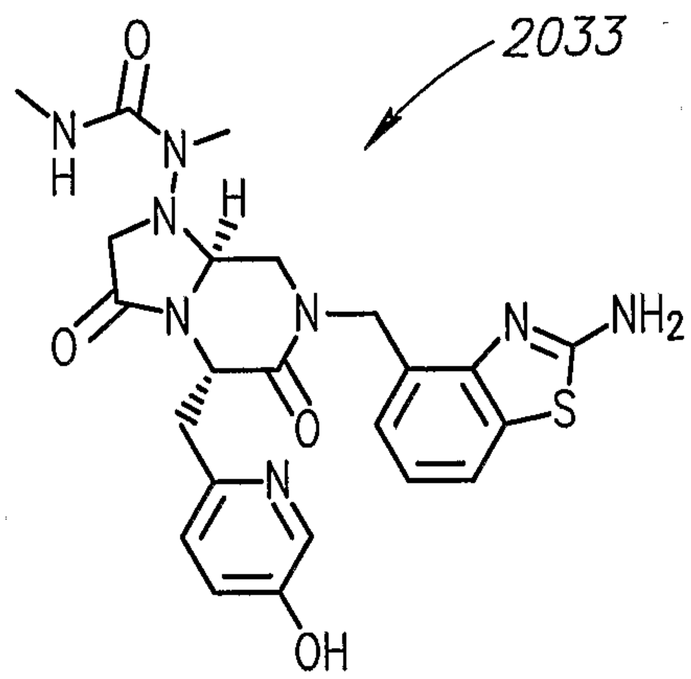
2029
O
N
H
NH2
S
OH

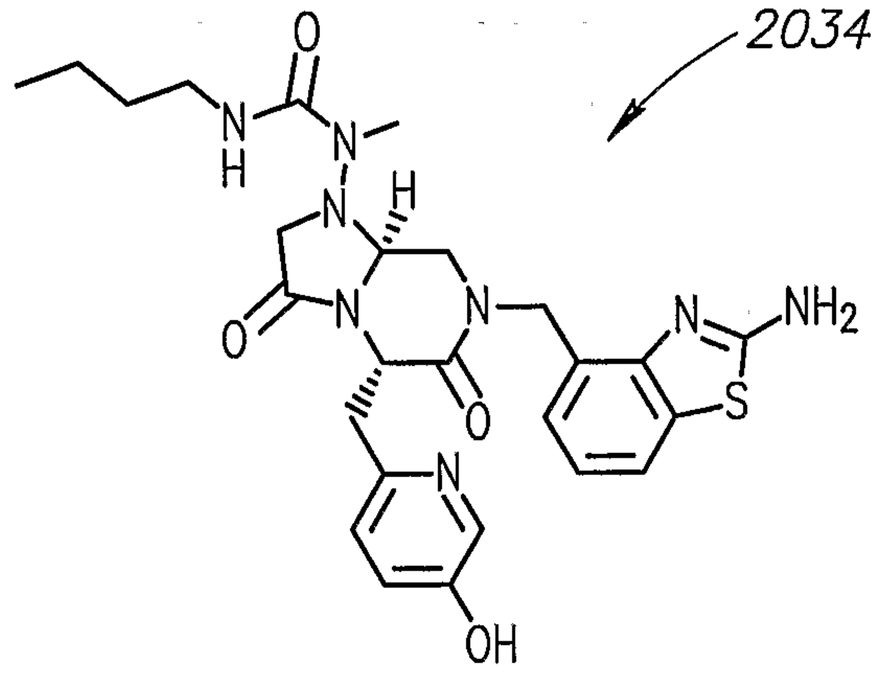
2030
F
O
N
H
NH2
S
OH

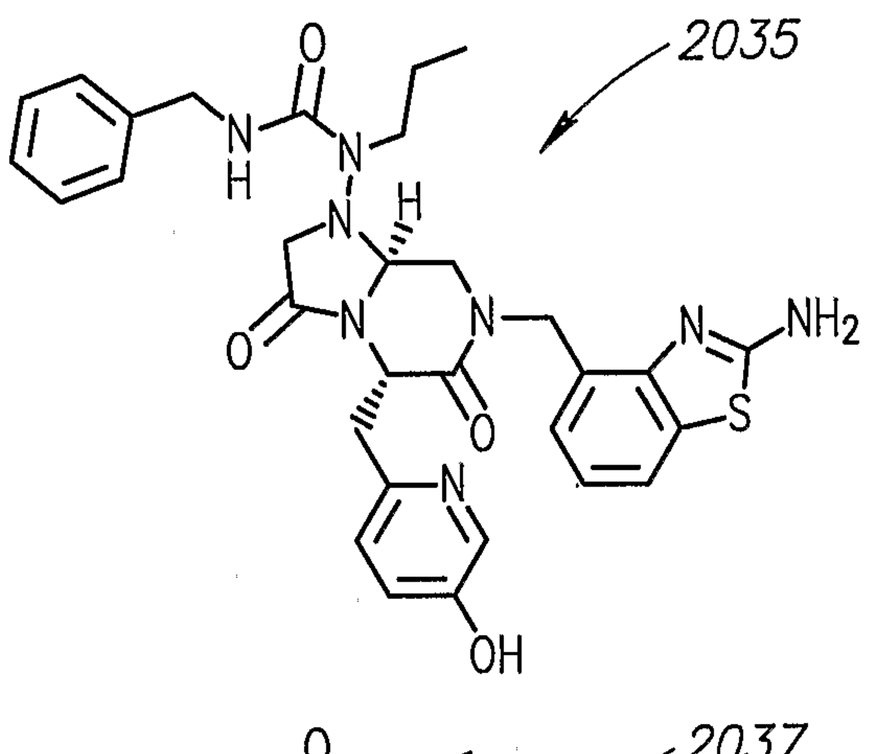
2031
MeO
O
N
H
NH2
S
OH

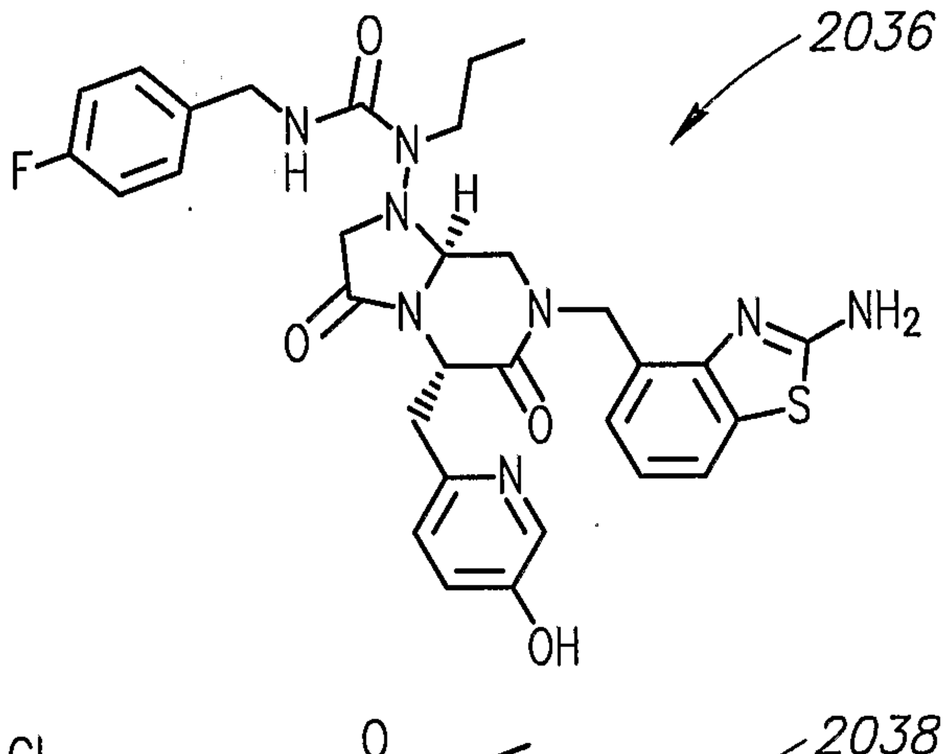
2032
Cl
Cl
O
N
H
NH2
S
OH

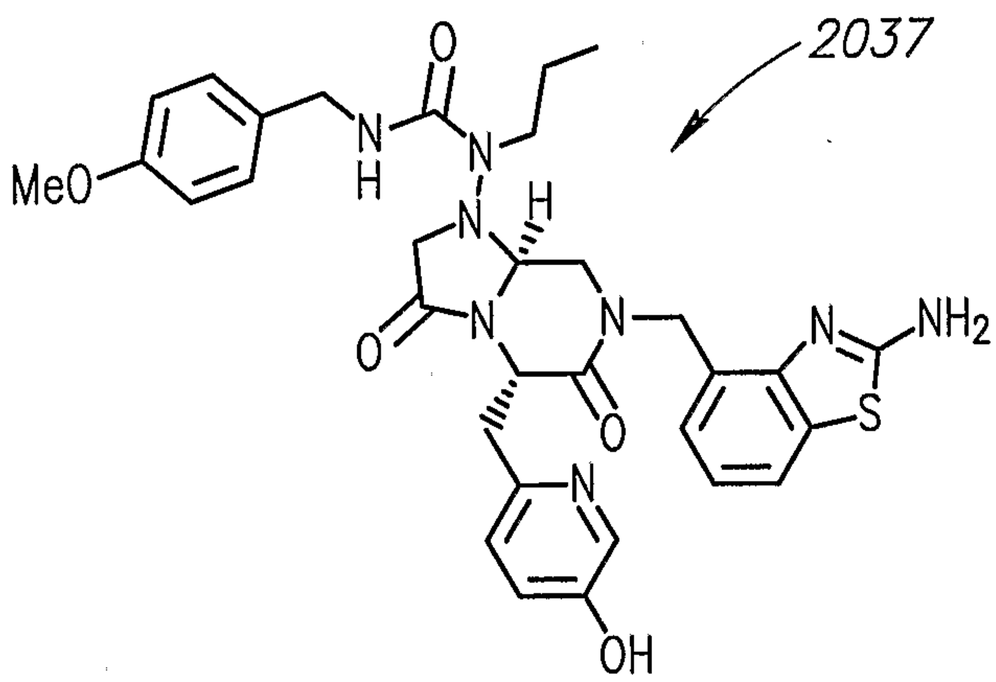
FIG.11D

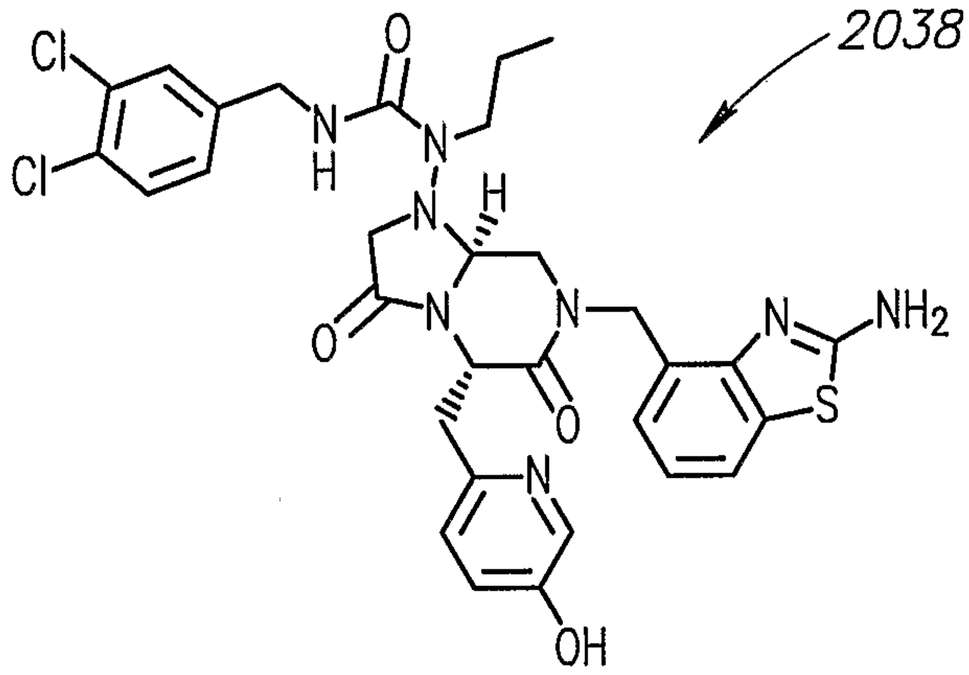


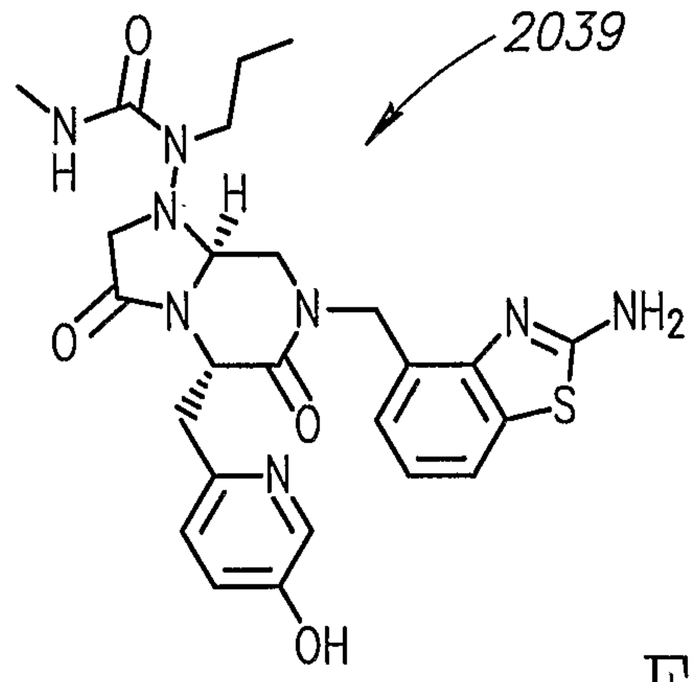












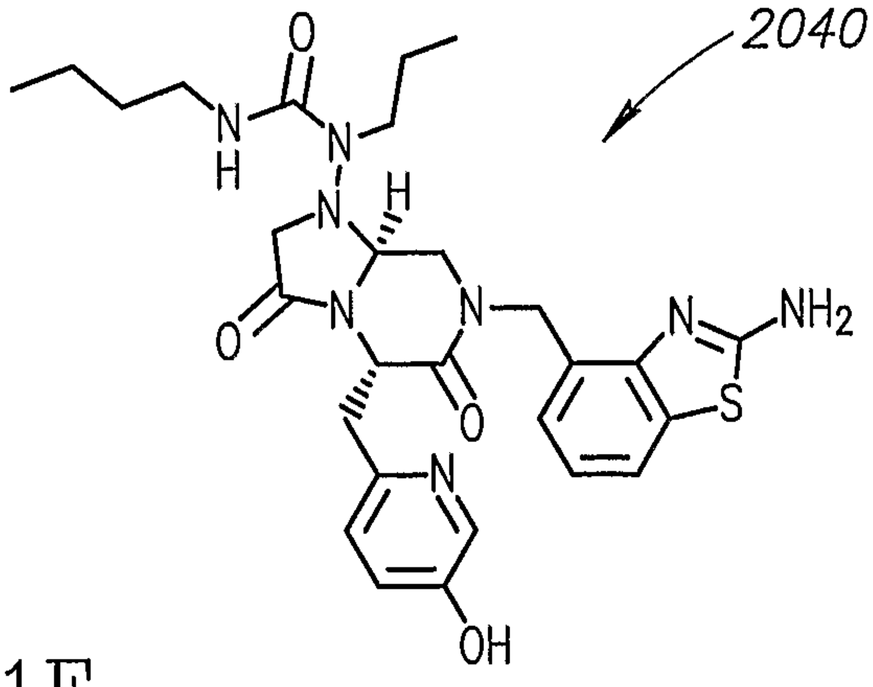
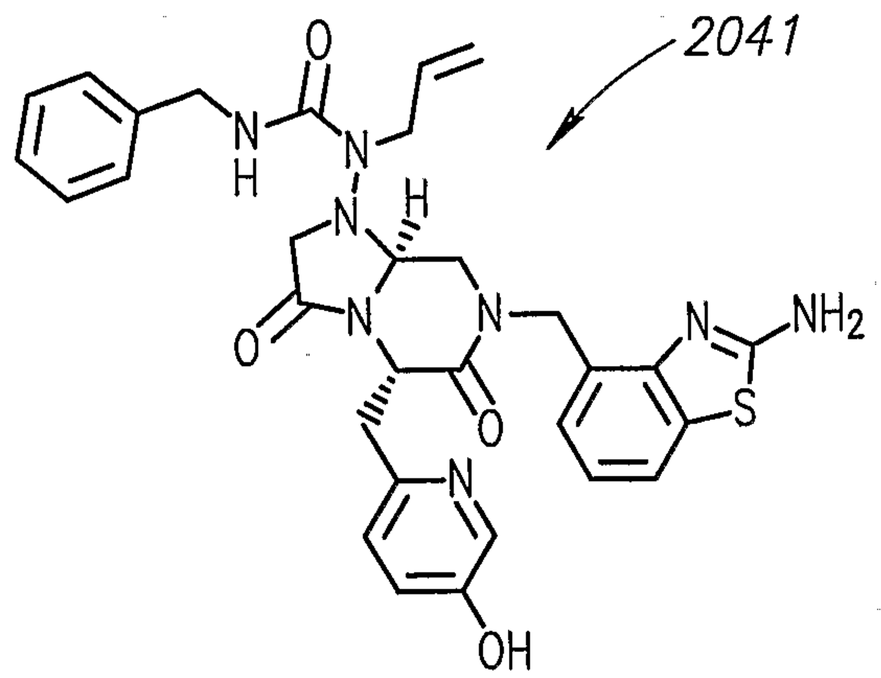
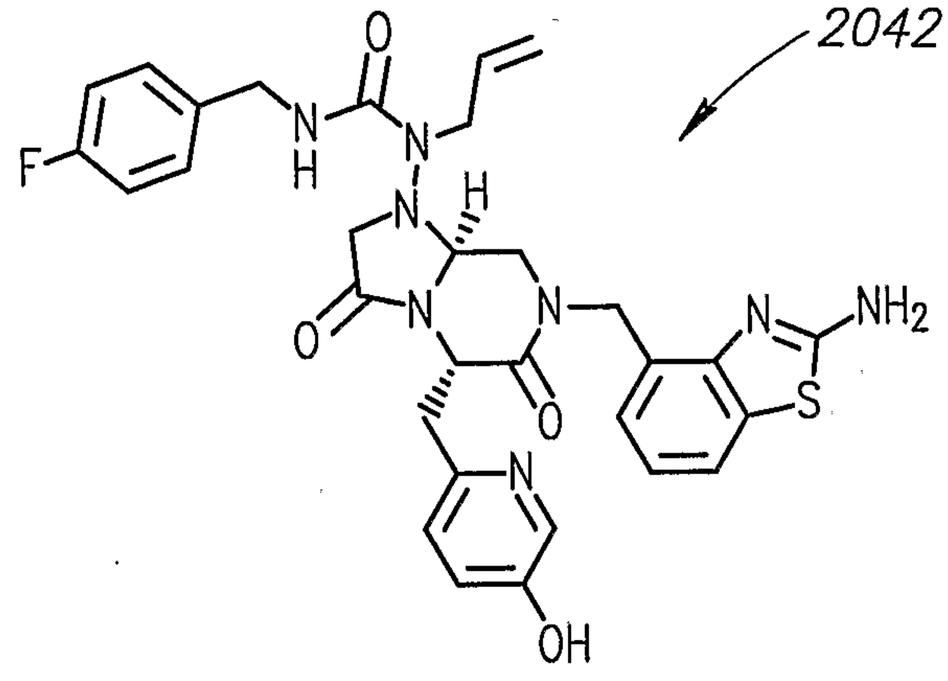
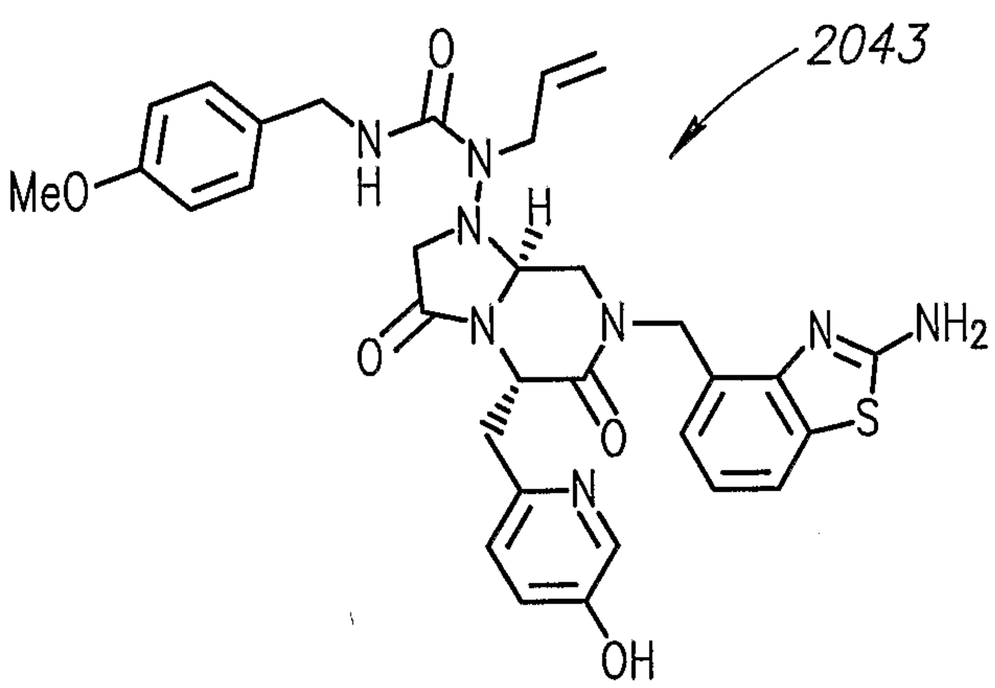
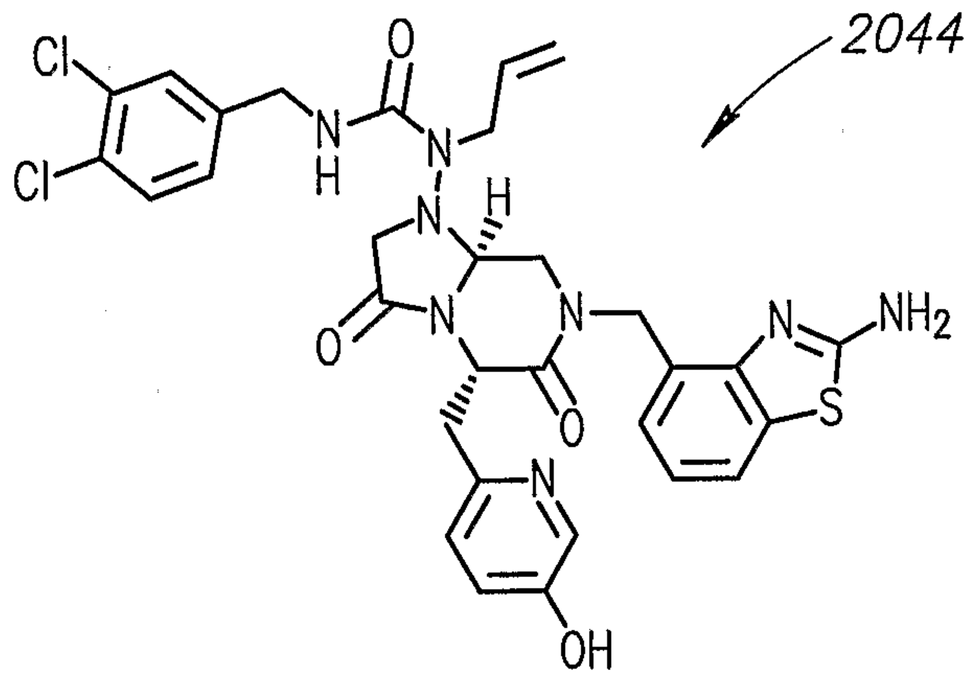


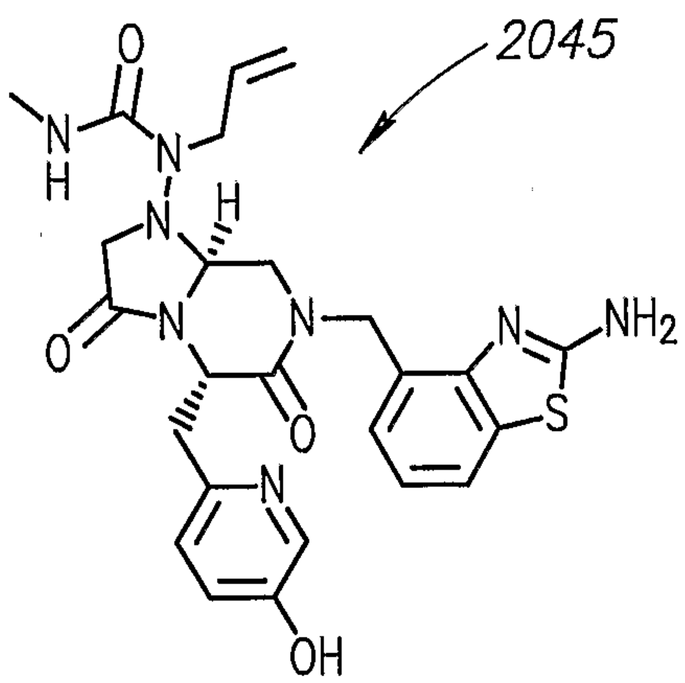
FIG.11E

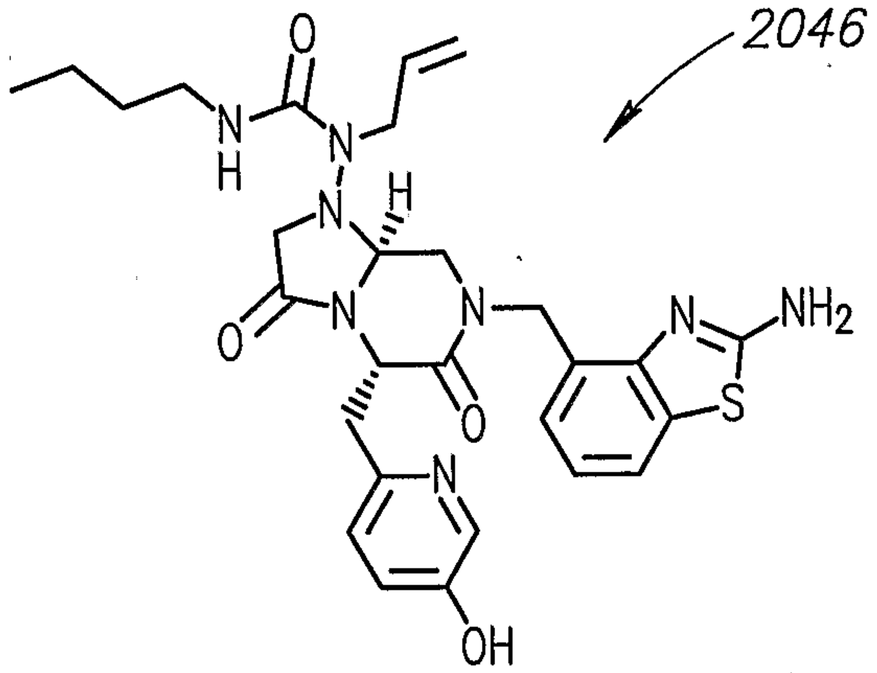

2041
O
N
H
N
N
H
O
N
O
N
N
S
NH2
N
OH

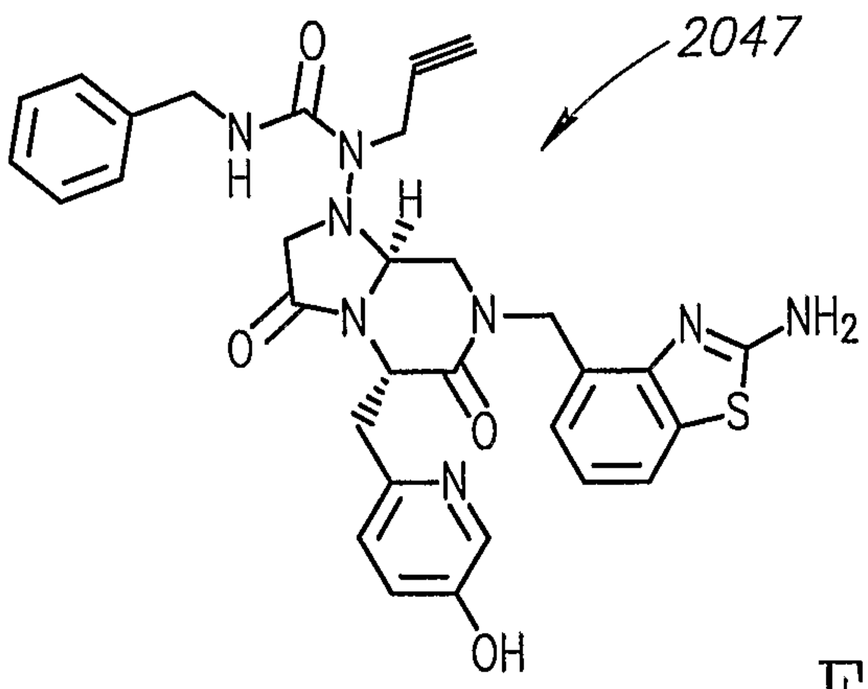

2042
F
O
N
H
N
N
H
O
N
O
N
N
S
NH2
N
OH


2043
MeO
O
N
H
N
N
H
O
N
O
N
N
S
NH2
N
OH


2044
Cl
Cl
O
N
H
N
N
H
O
N
O
N
N
S
NH2
N
OH


2045
O
N
H
N
N
H
O
N
O
N
N
S
NH2
N
OH


2046
O
N
H
N
N
H
O
N
O
N
N
S
NH2
N
OH


2047
O
N
H
N
N
H
O
N
O
N
N
S
NH2
N
OH

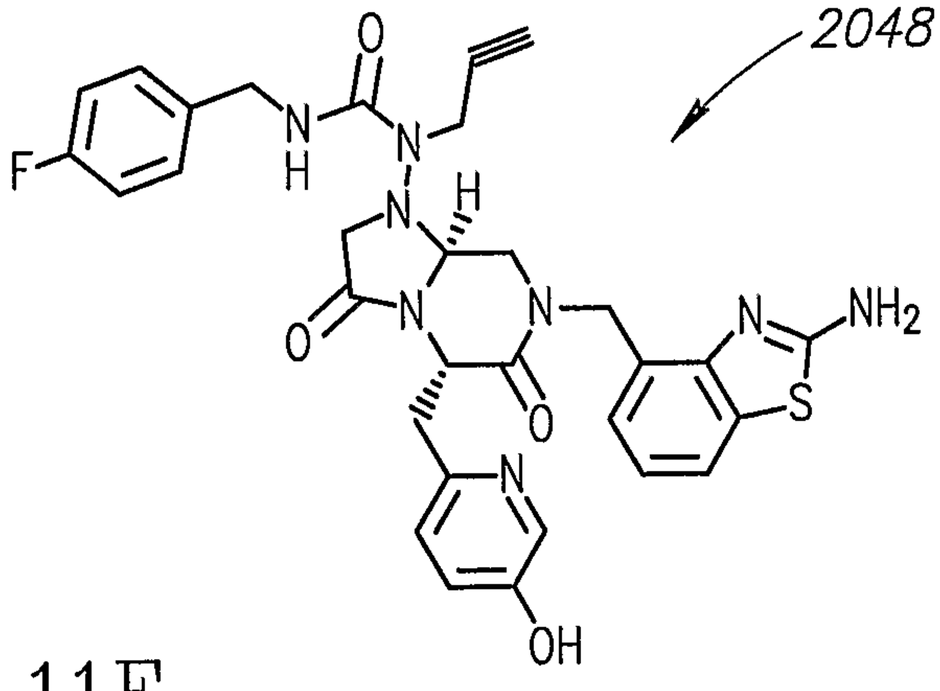
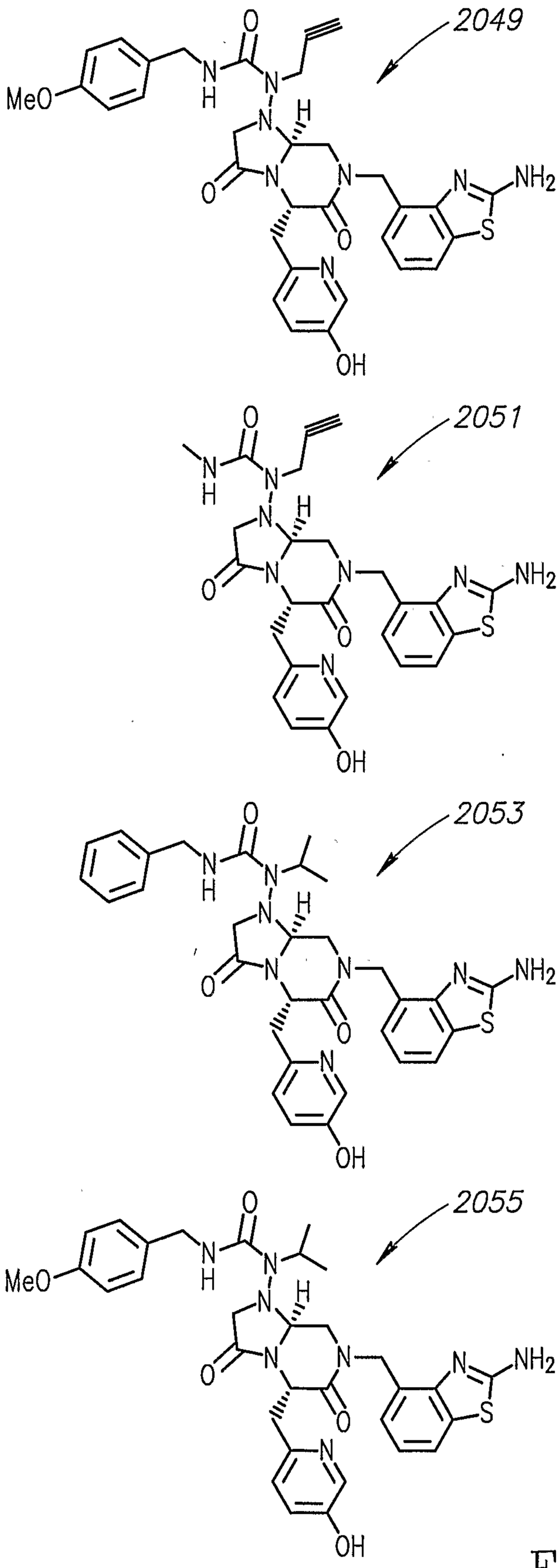
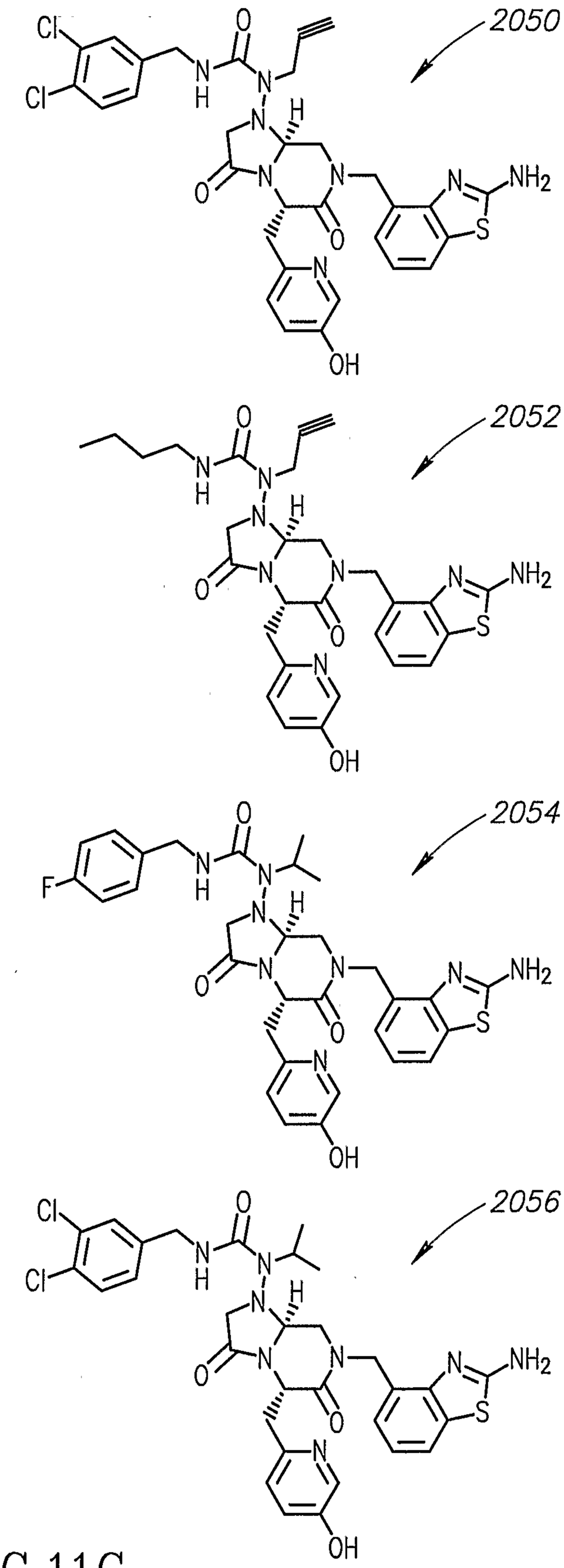

2048
F
O
N
H
N
N
H
O
N
O
N
N
S
NH2
N
OH

FIG.11F


2049
MeO
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
O
N
OH


2050
Cl
Cl
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
O
N
OH

2051
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
O
N
OH

2052
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
O
N
OH

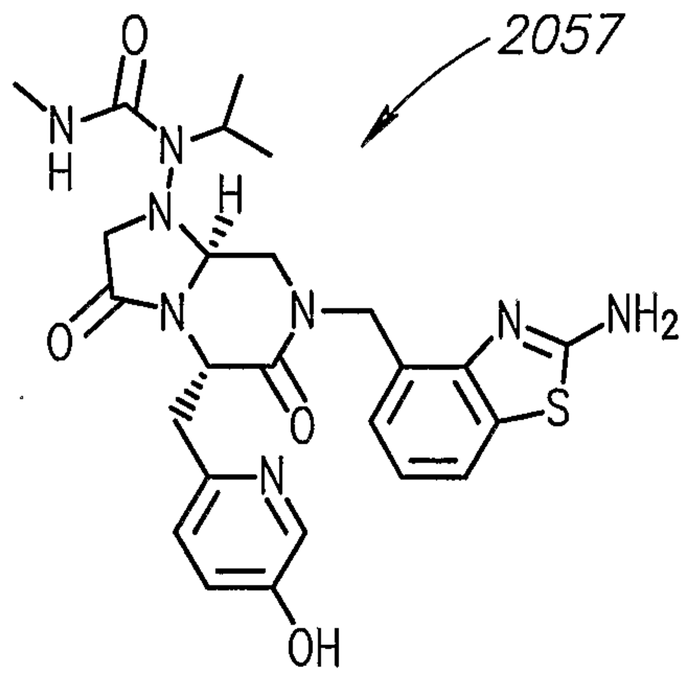
2053
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
O
N
OH

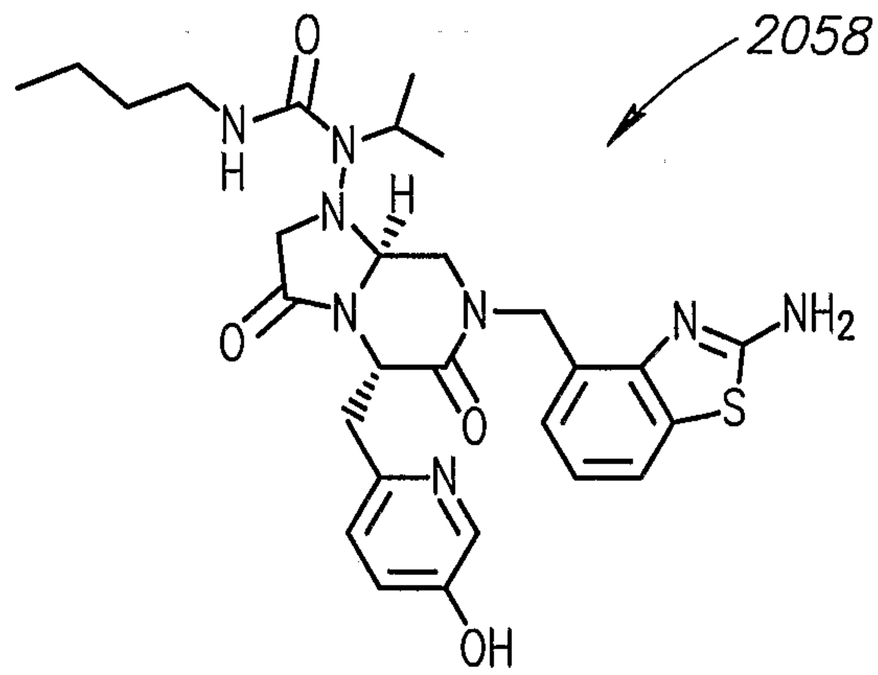
2054
F
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
O
N
OH

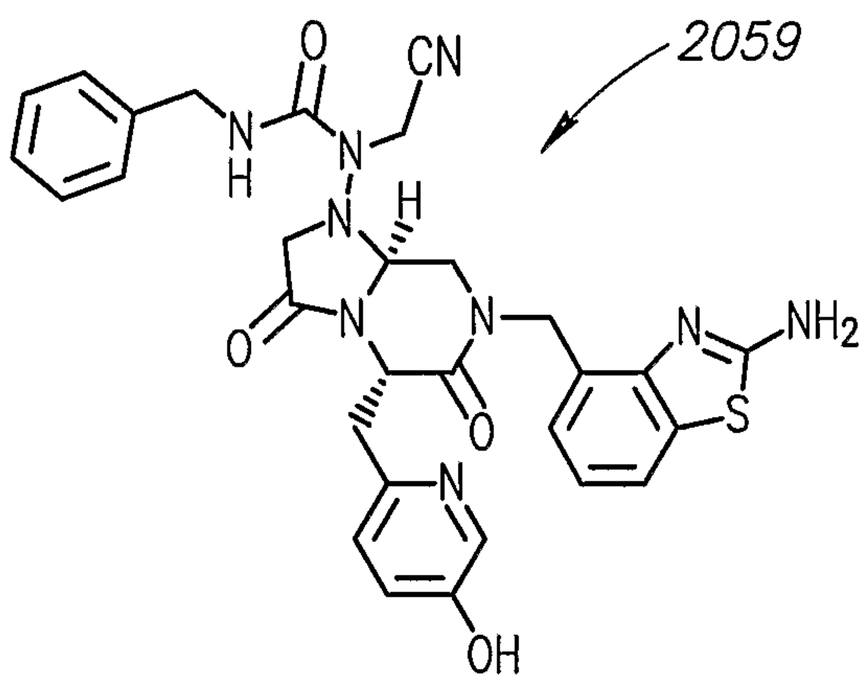
2055
MeO
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
O
N
OH

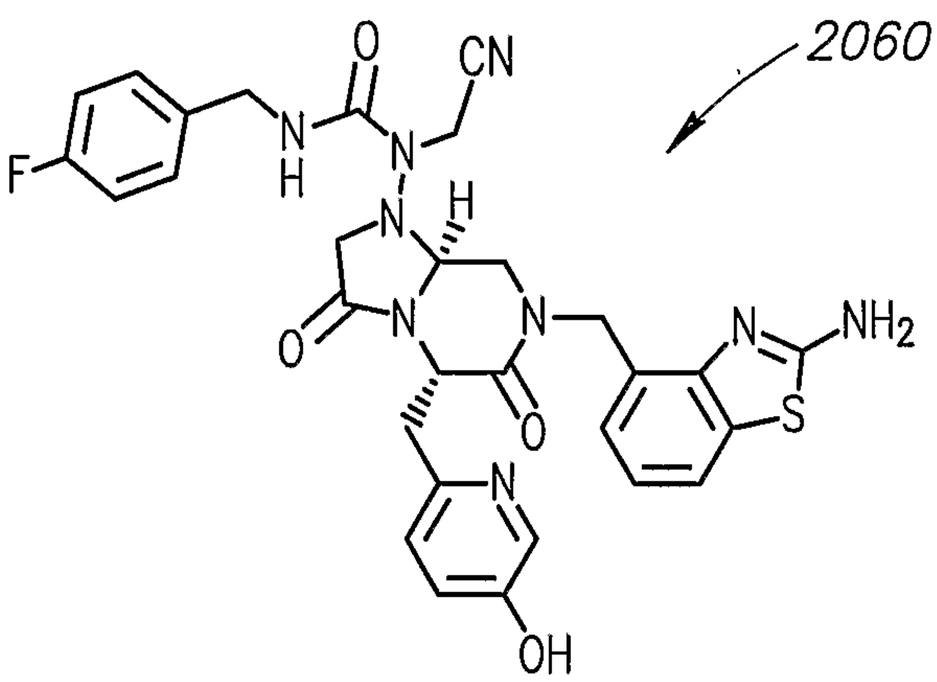
2056
Cl
Cl
O
N
H
N
N
H
O
N
N
O
N
N
S
NH2
O
N
OH

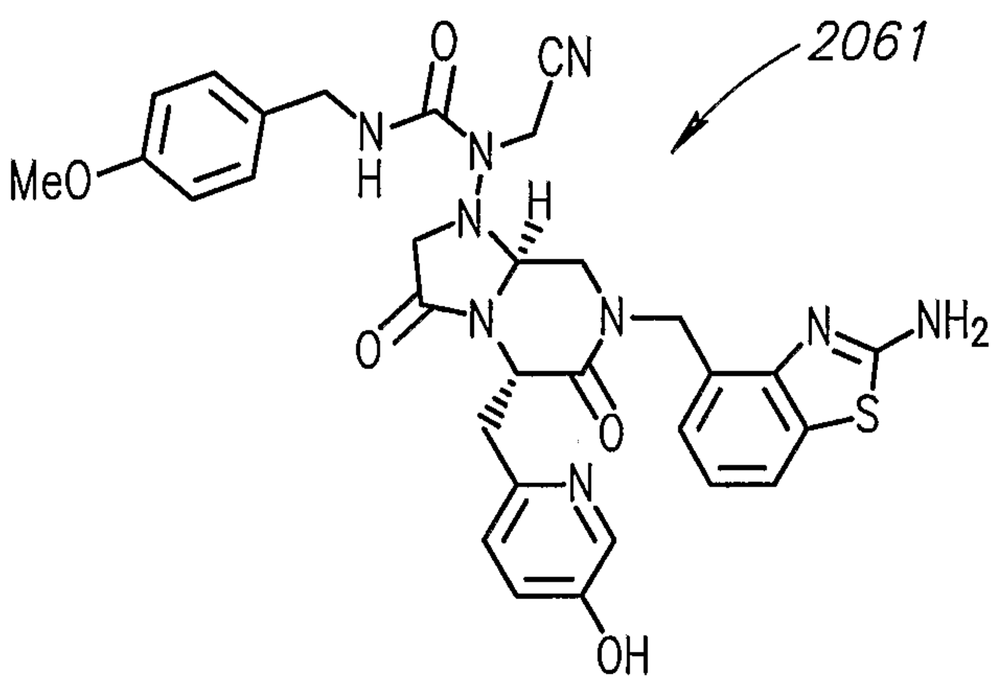
FIG.11G

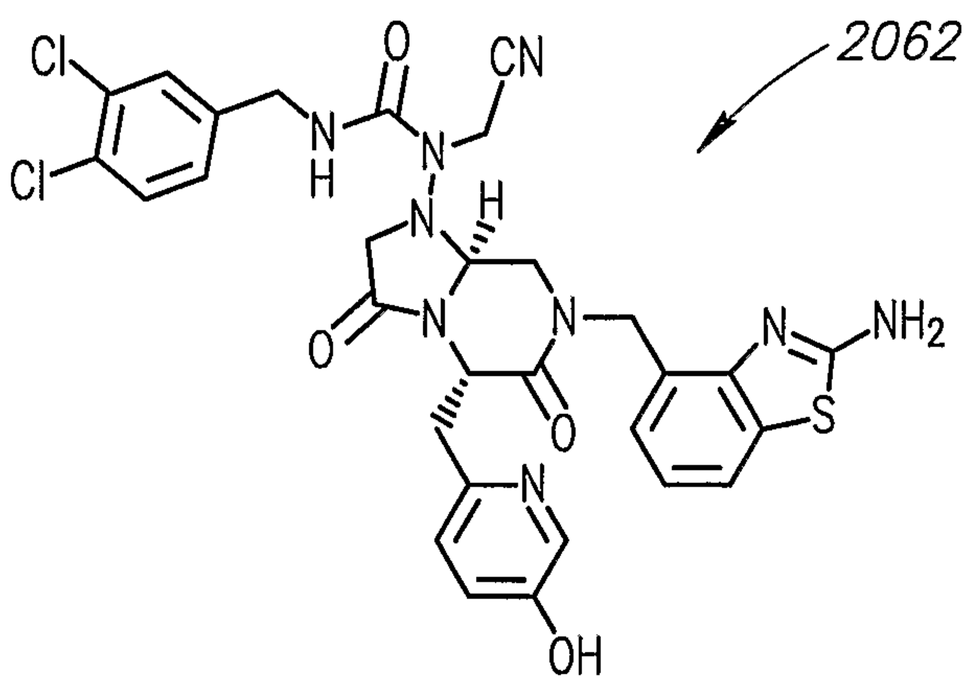

2057
O
N
H
N
N
H
O
N
N
N
NH2
S
O
N
OH

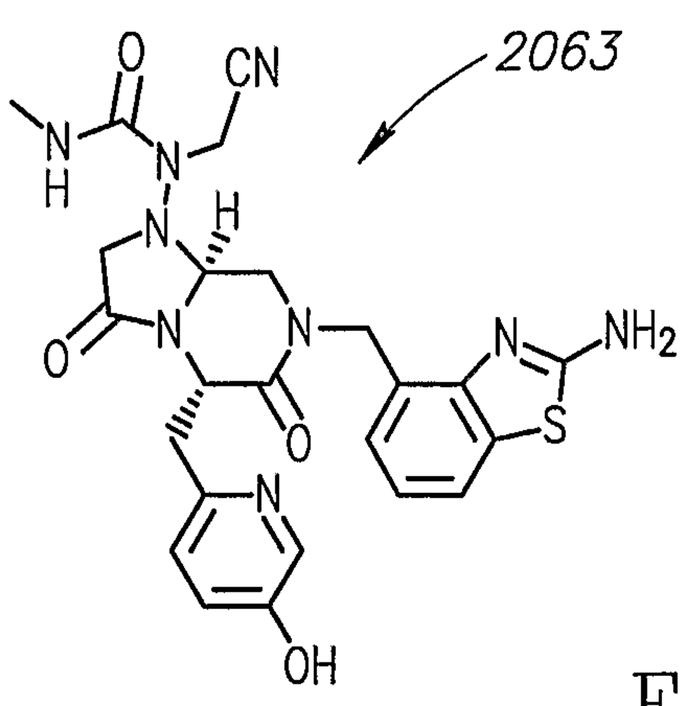

2058
O
N
H
N
N
H
O
N
N
N
NH2
S
O
N
OH


2059
O
CN
N
H
N
N
H
O
N
N
N
NH2
S
O
N
OH


2060
F
O
CN
N
H
N
N
H
O
N
N
N
NH2
S
O
N
OH


2061
MeO
O
CN
N
H
N
N
H
O
N
N
N
NH2
S
O
N
OH


2062
Cl
Cl
O
CN
N
H
N
N
H
O
N
N
N
NH2
S
O
N
OH


2063
O
CN
N
H
N
N
H
O
N
N
N
NH2
S
O
N
OH

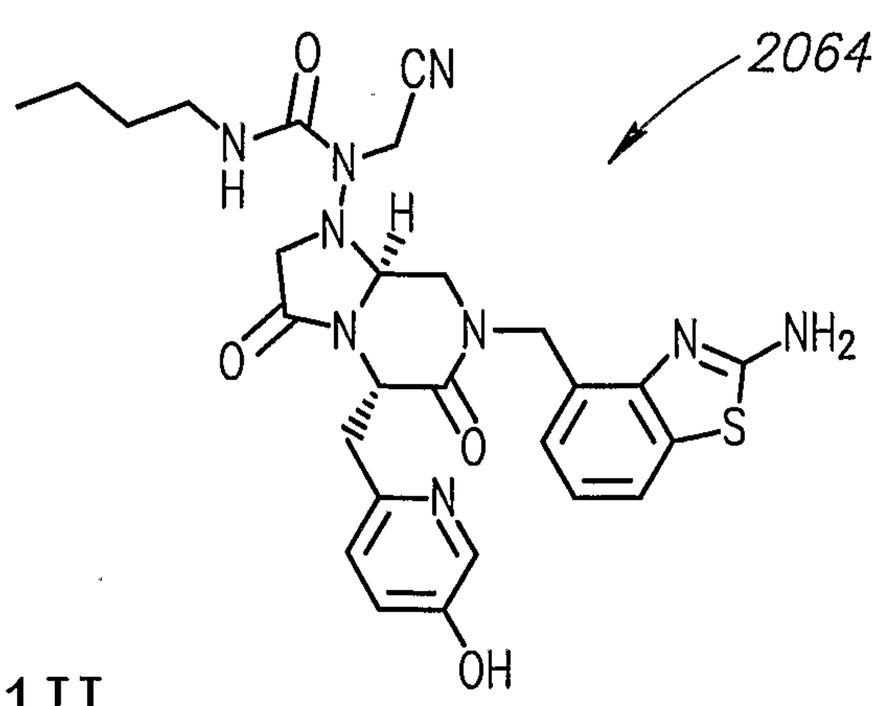

2064
O
CN
N
H
N
N
H
O
N
N
N
NH2
S
O
N
OH

FIG.11H

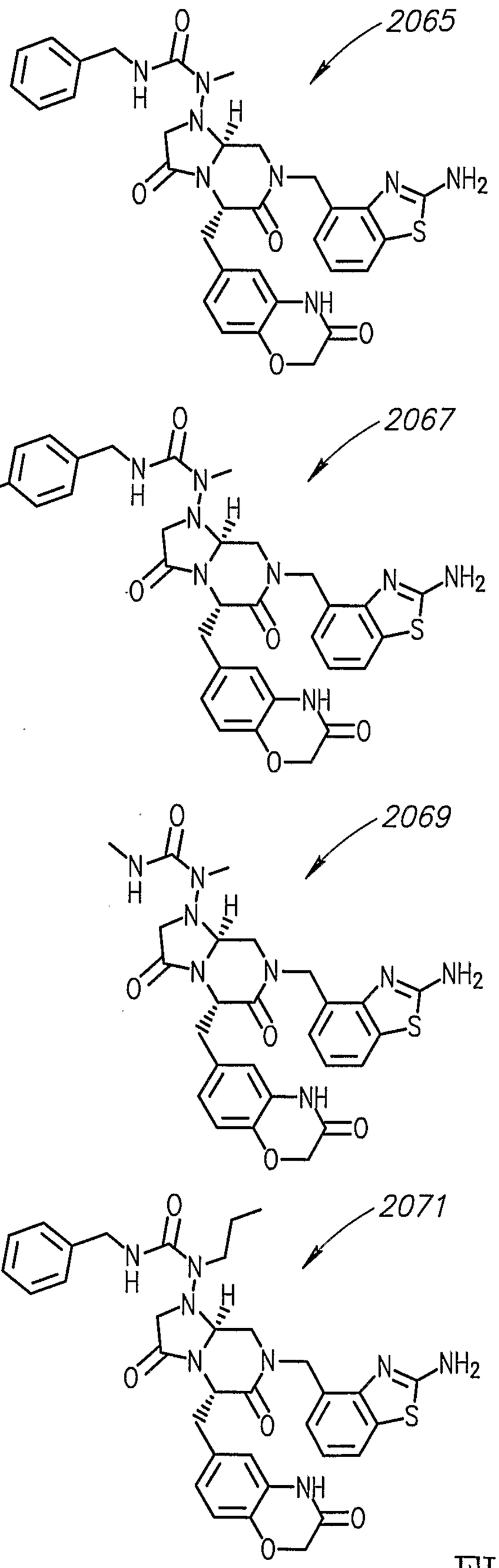
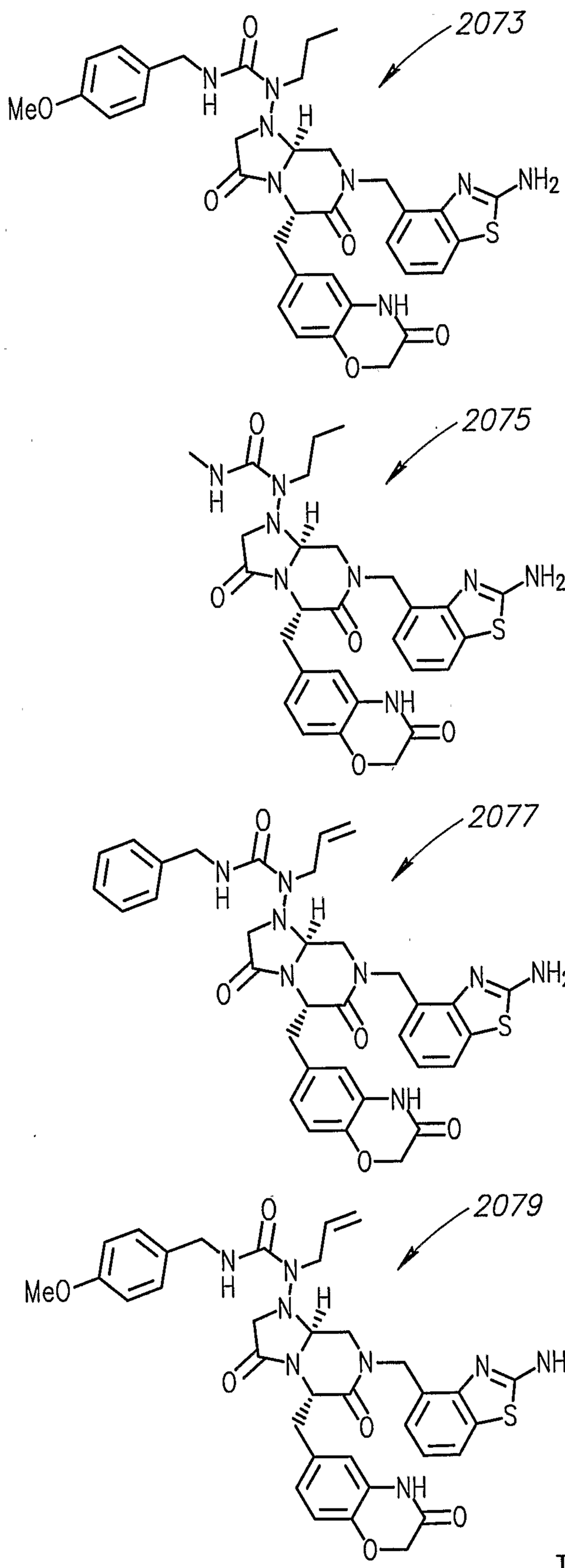
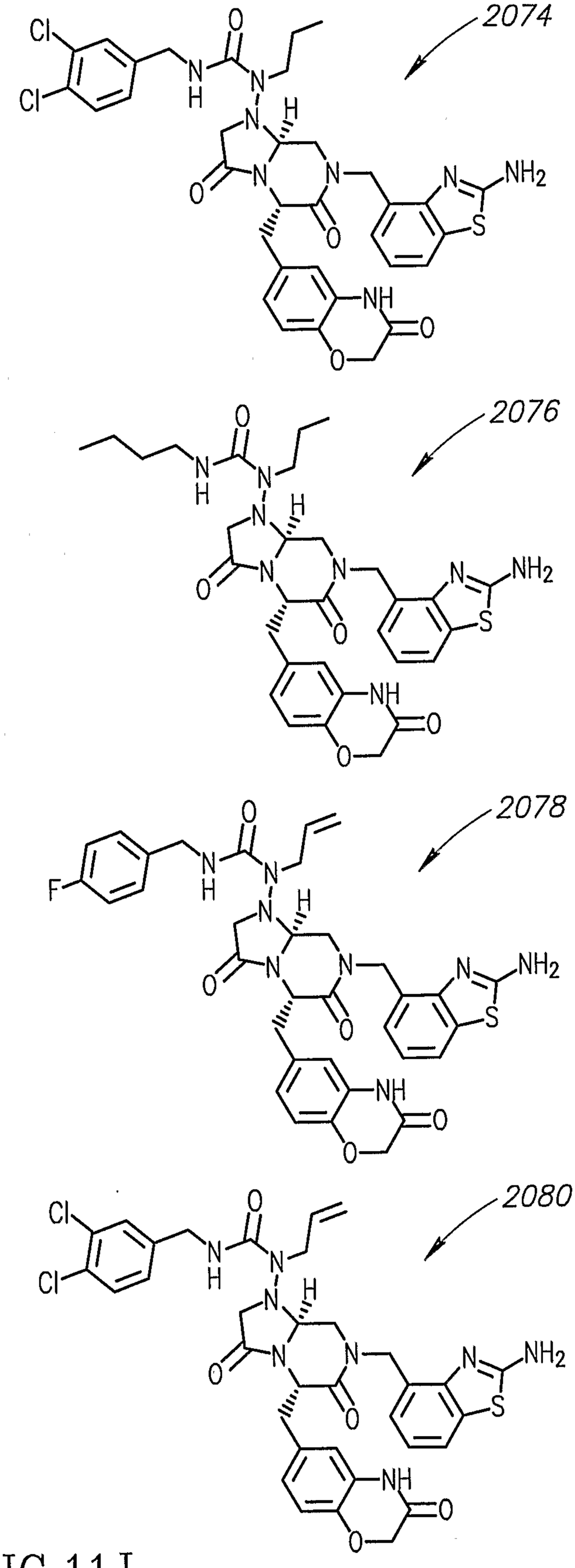


FIG.11I


2073
MeO
N
H
O
N
H
N
N
O
O
N
N
S
NH2
NH
O
O


2074
Cl
Cl
N
H
O
N
H
N
N
O
O
N
N
S
NH2
NH
O
O

2075
N
H
O
N
H
N
N
O
O
N
N
S
NH2
NH
O
O

2076
N
H
O
N
H
N
N
O
O
N
N
S
NH2
NH
O
O

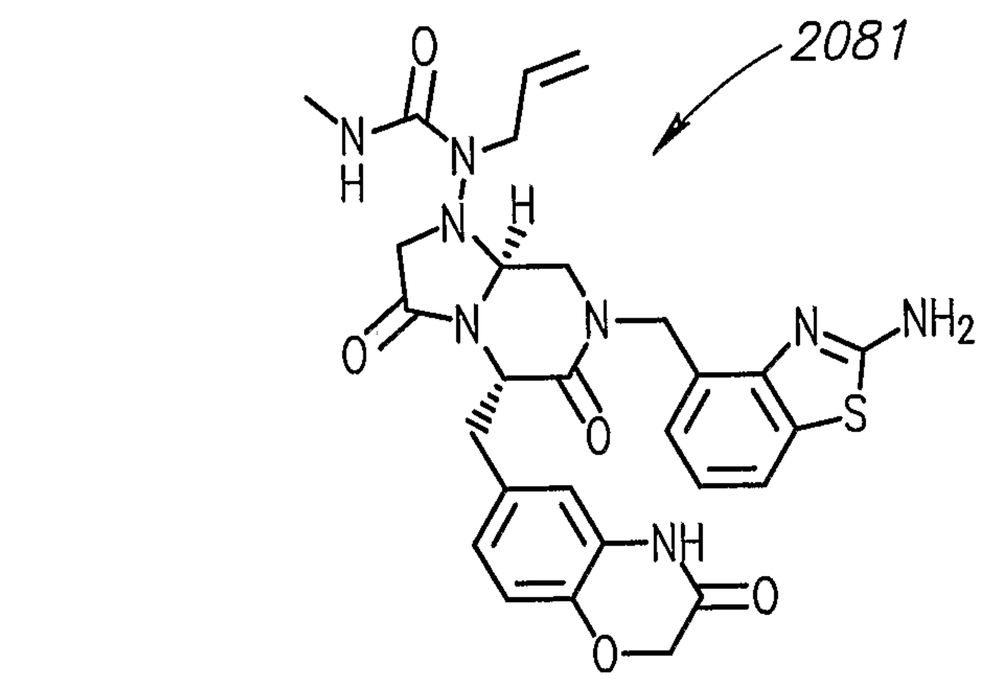
2077
N
H
O
N
H
N
N
O
O
N
N
S
NH2
NH
O
O

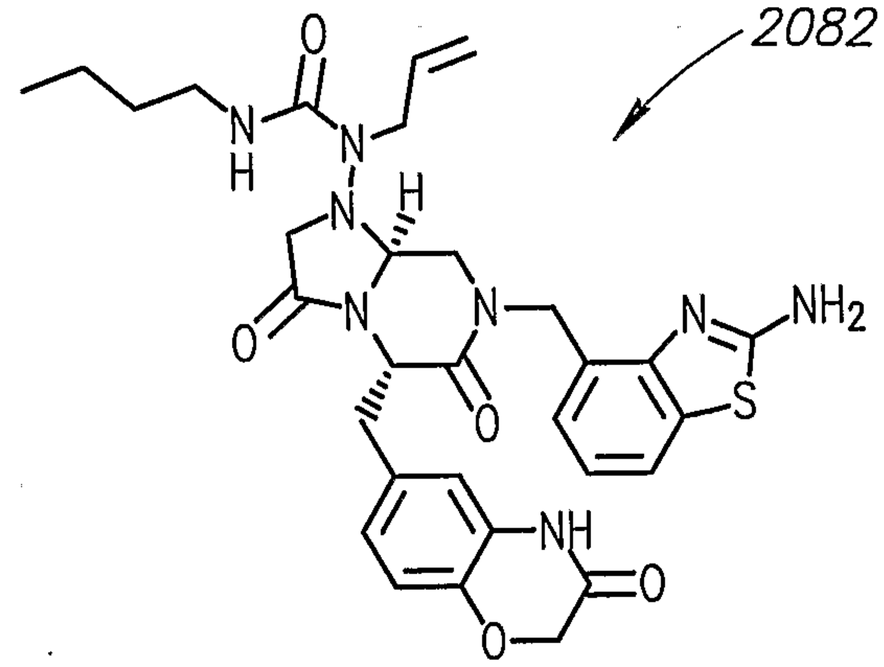
2078
F
N
H
O
N
H
N
N
O
O
N
N
S
NH2
NH
O
O

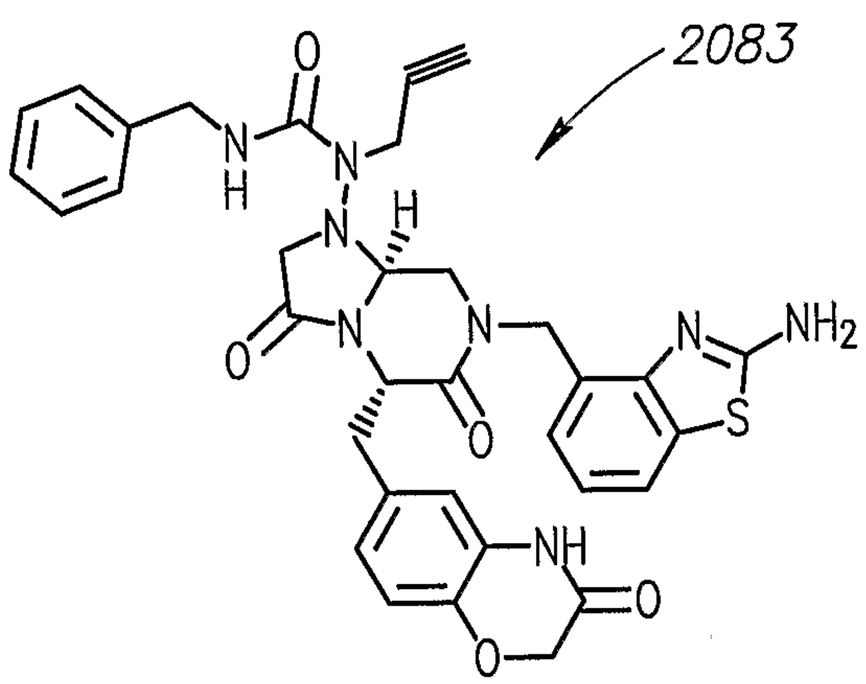
2079
MeO
N
H
O
N
H
N
N
O
O
N
N
S
NH2
NH
O
O

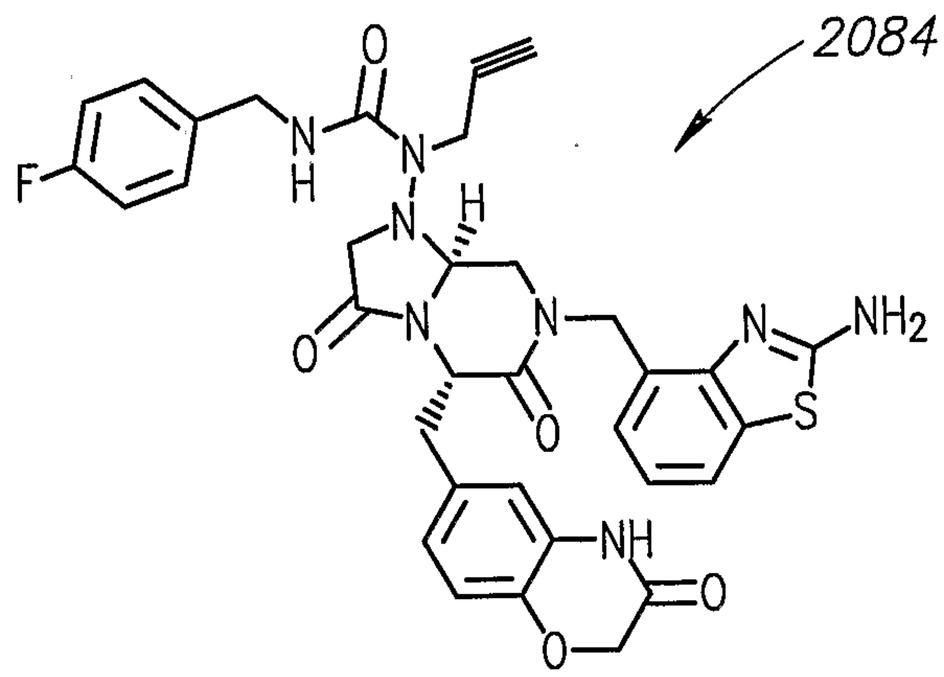
2080
Cl
Cl
N
H
O
N
H
N
N
O
O
N
N
S
NH2
NH
O
O

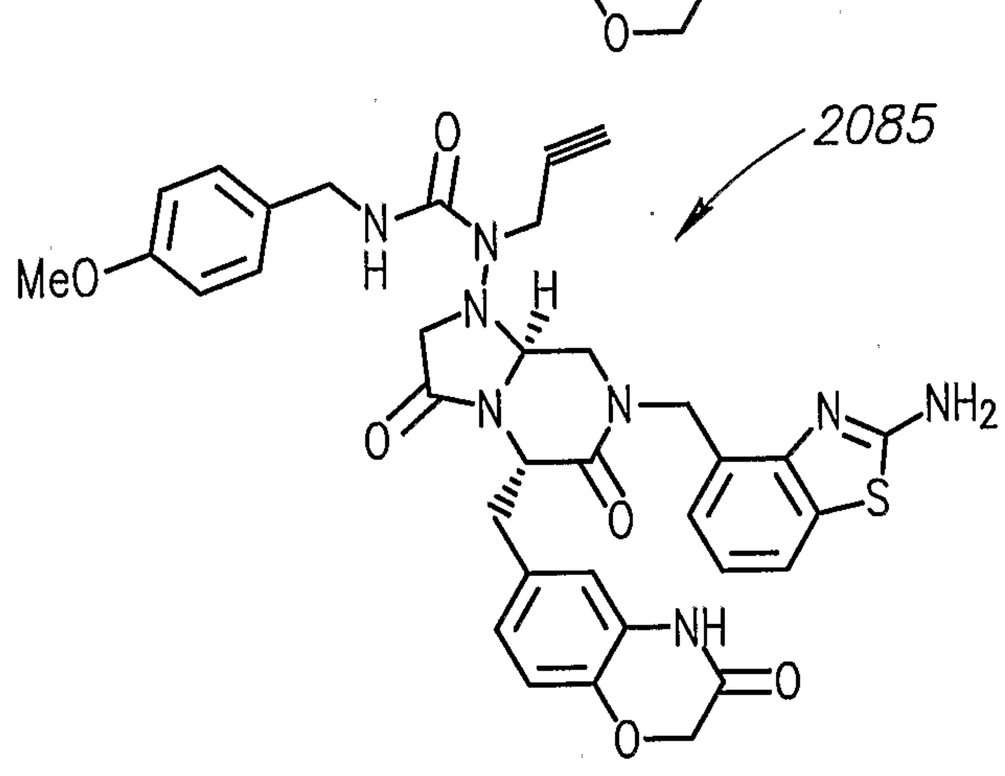
FIG.11J











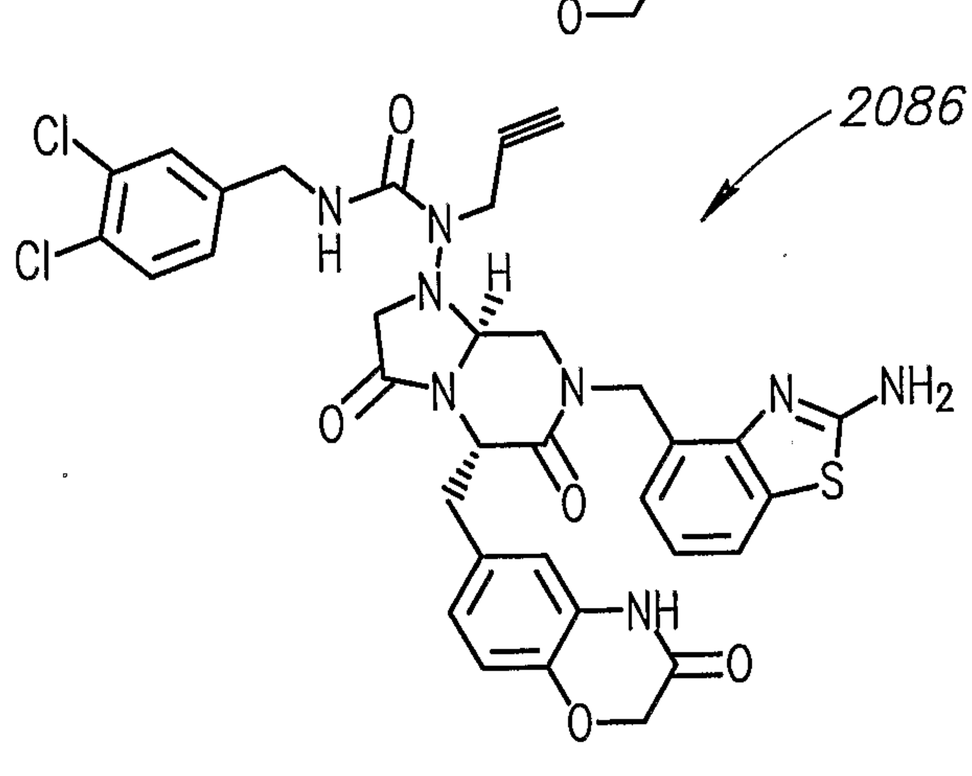
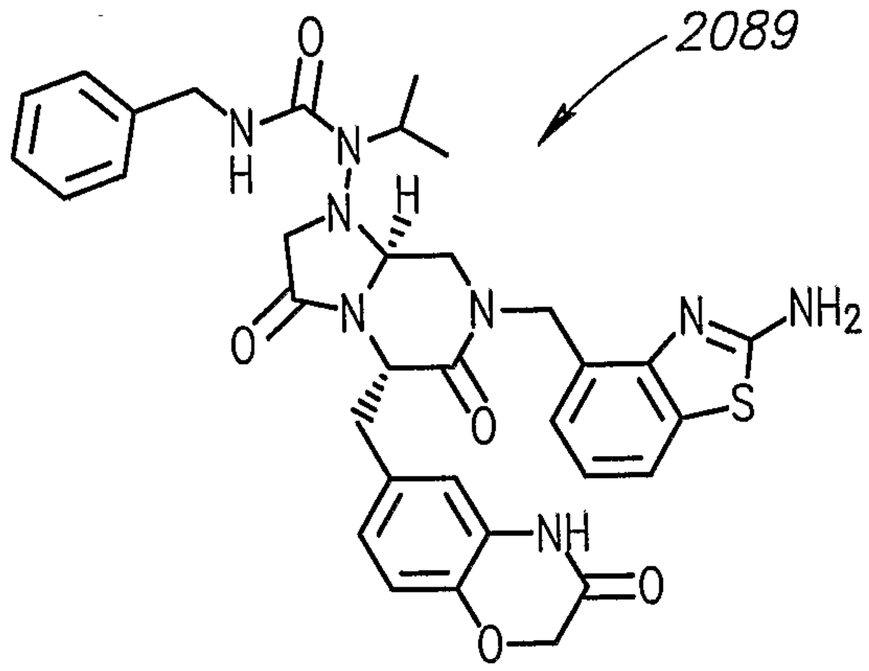
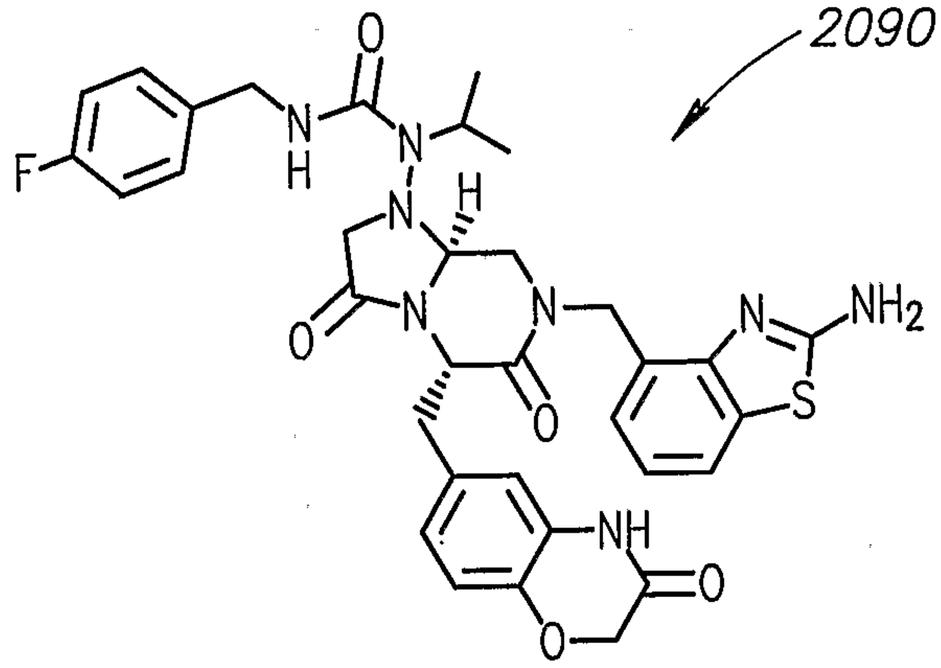


FIG.11K

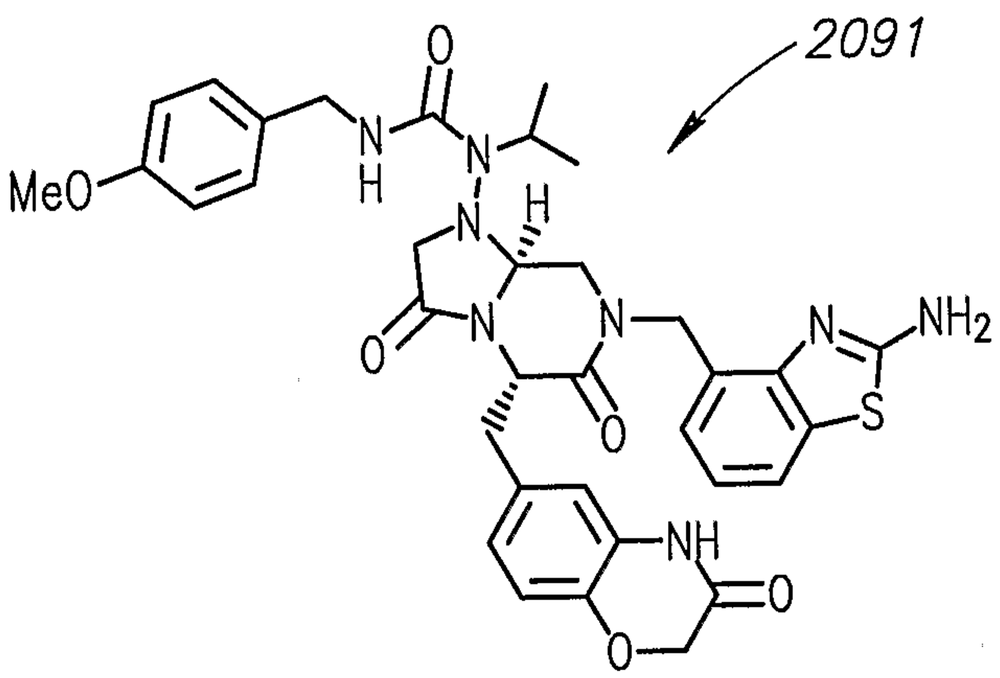
2089



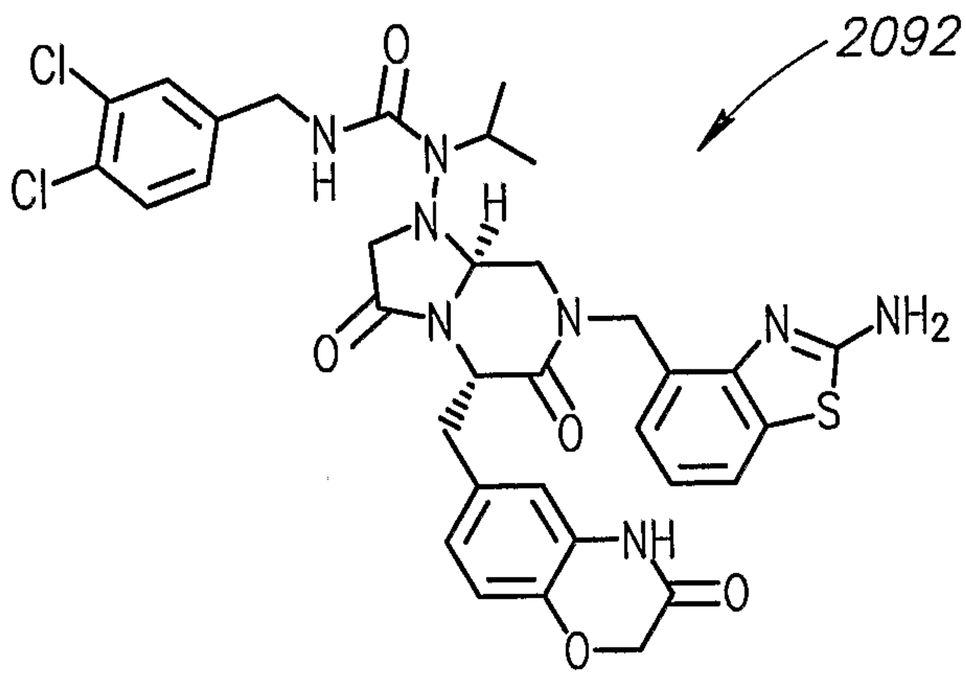
2090



2091



2092



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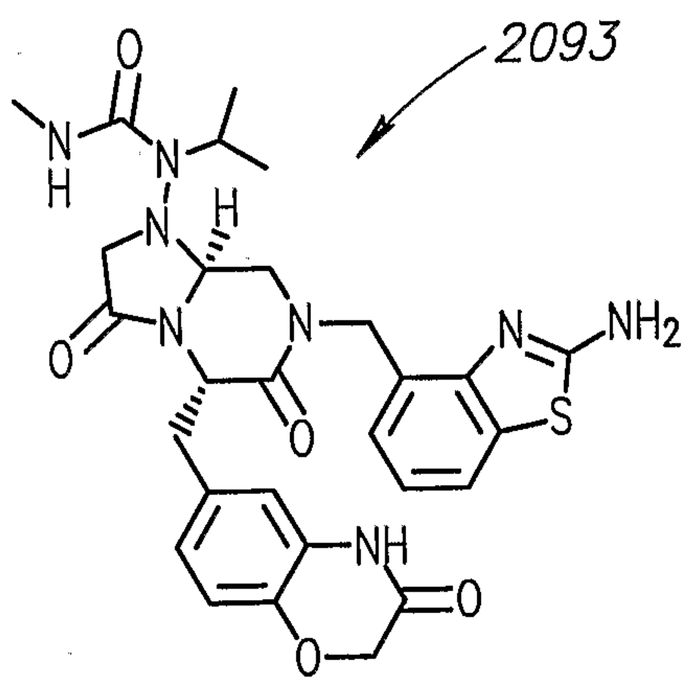

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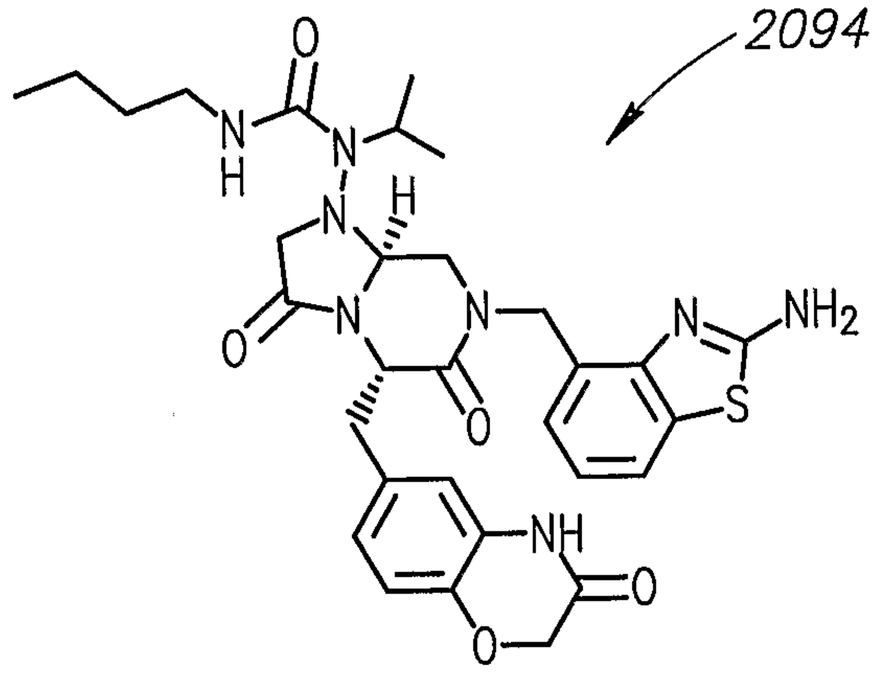

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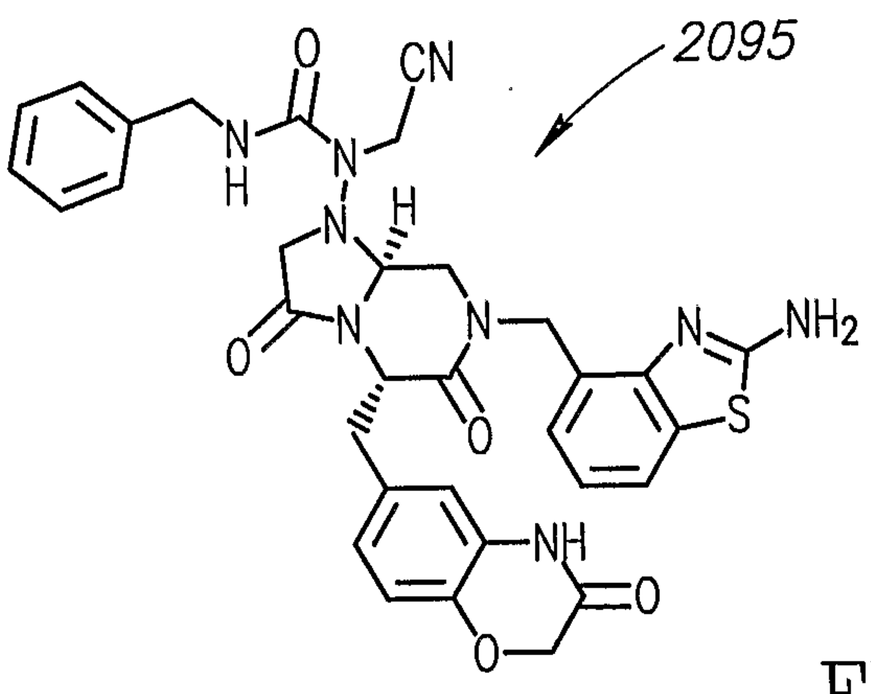

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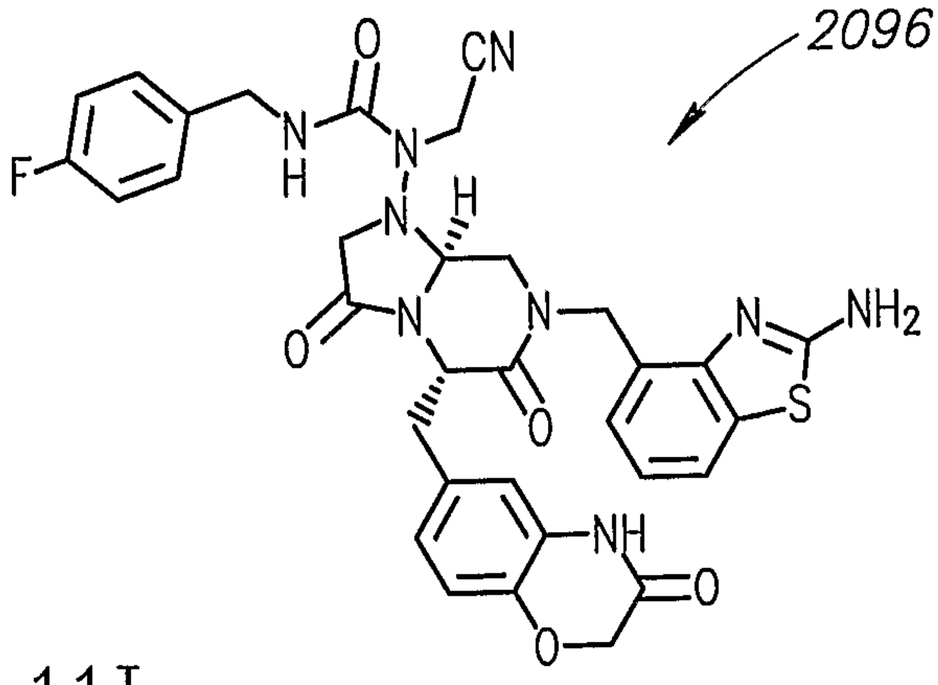
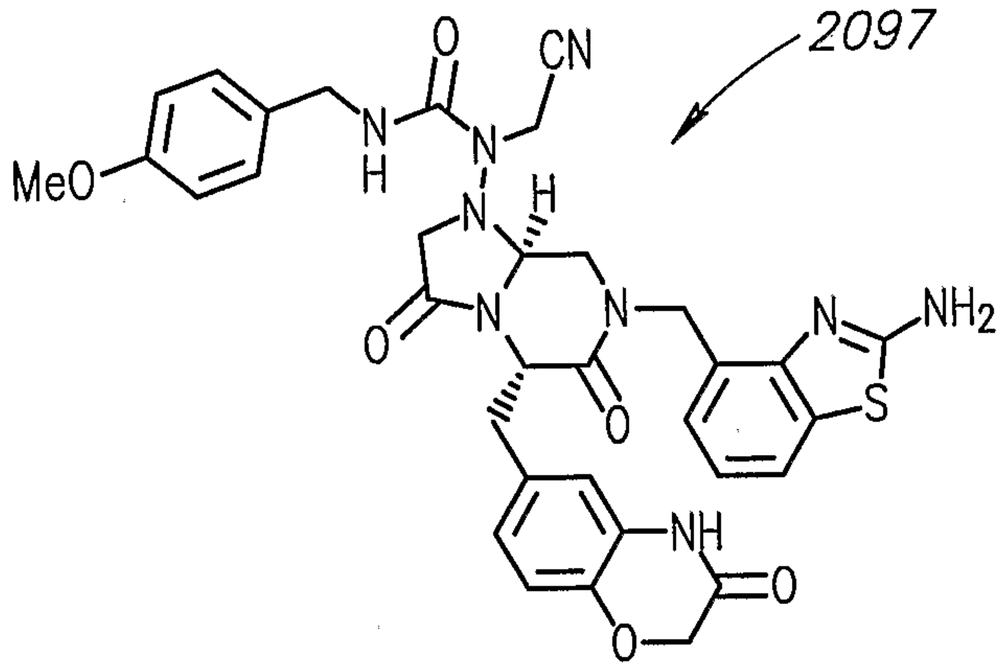


FIG.11L

2097



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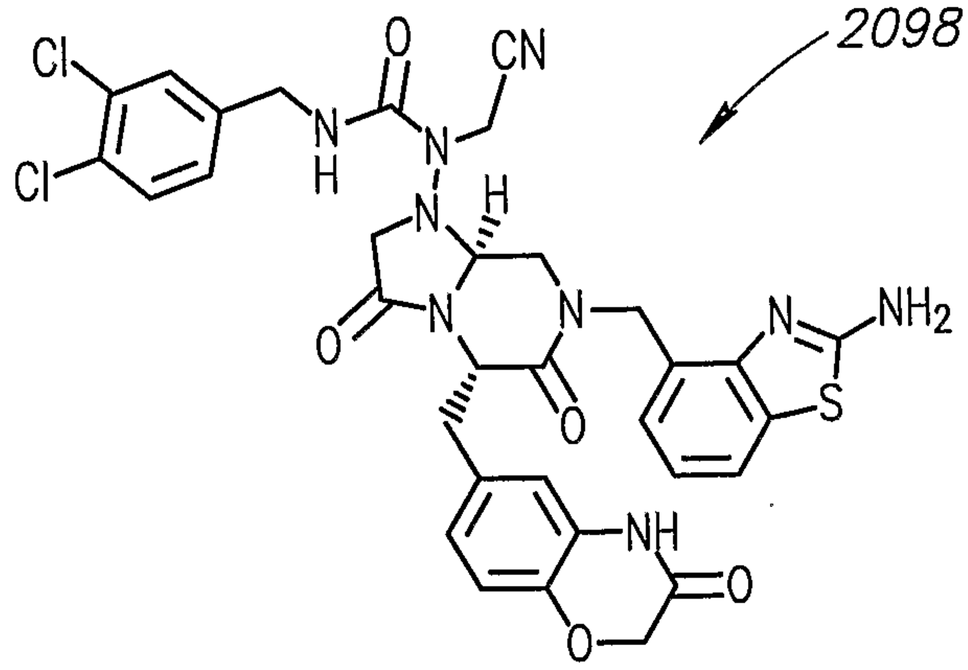

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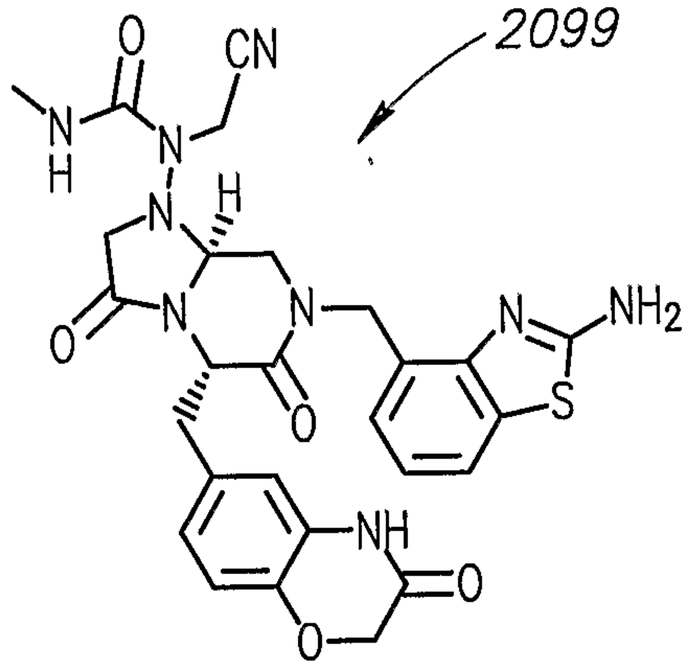

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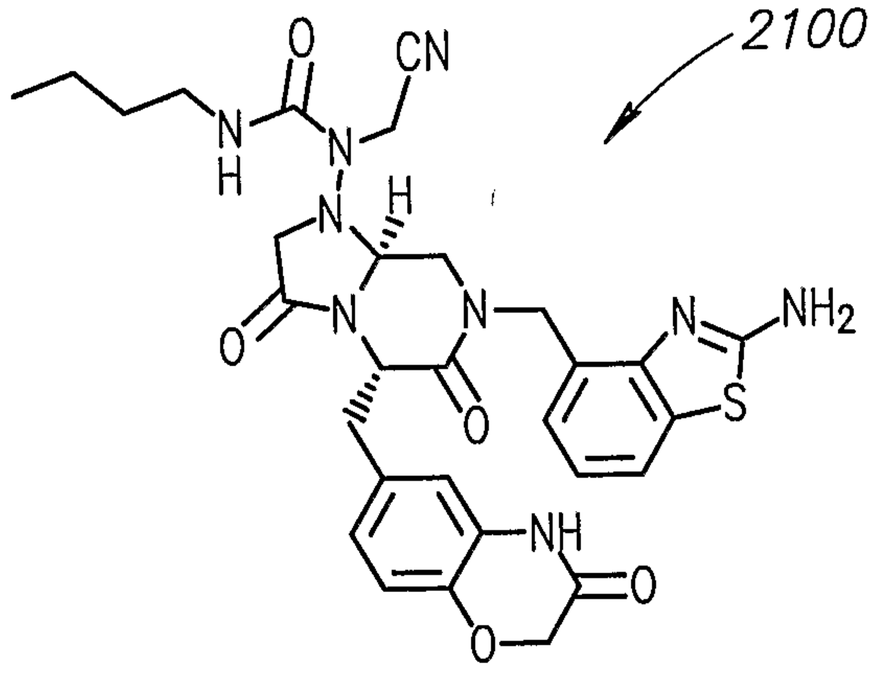

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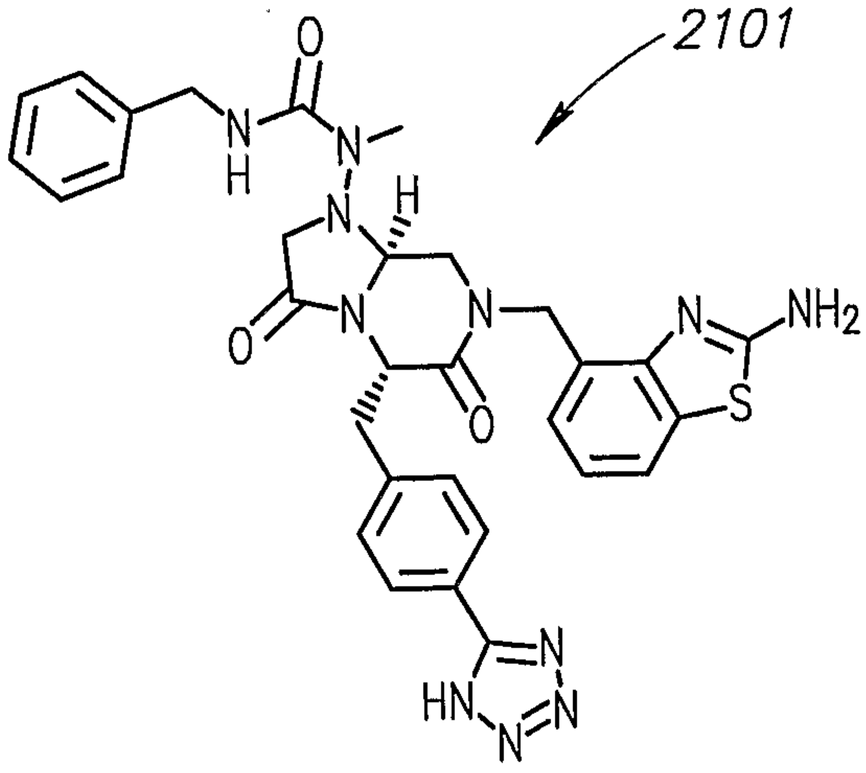

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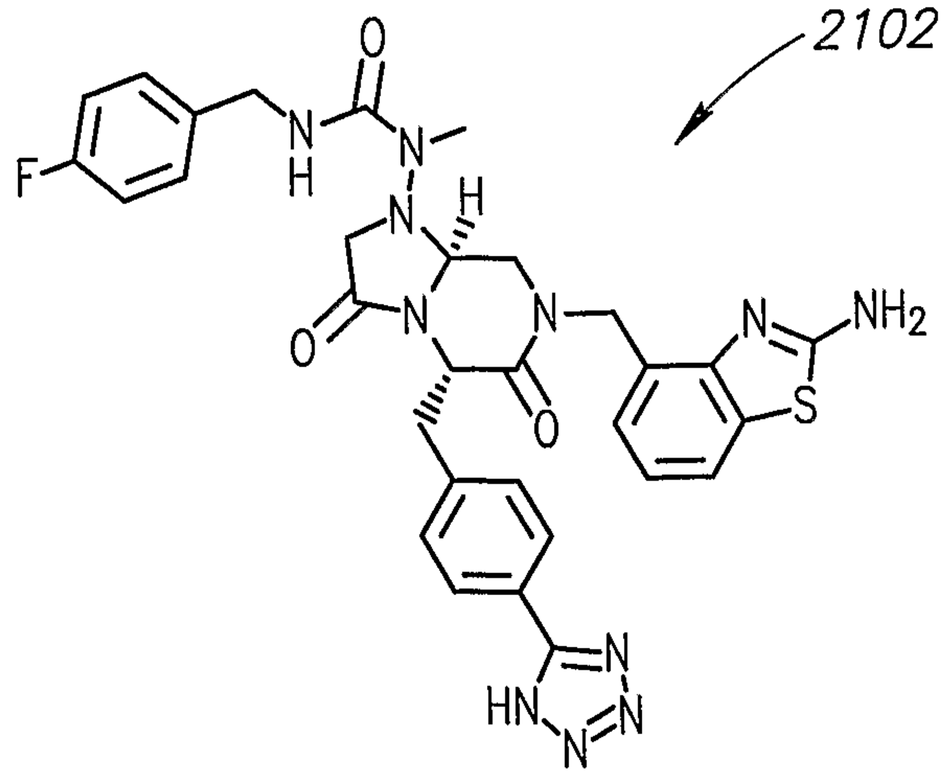
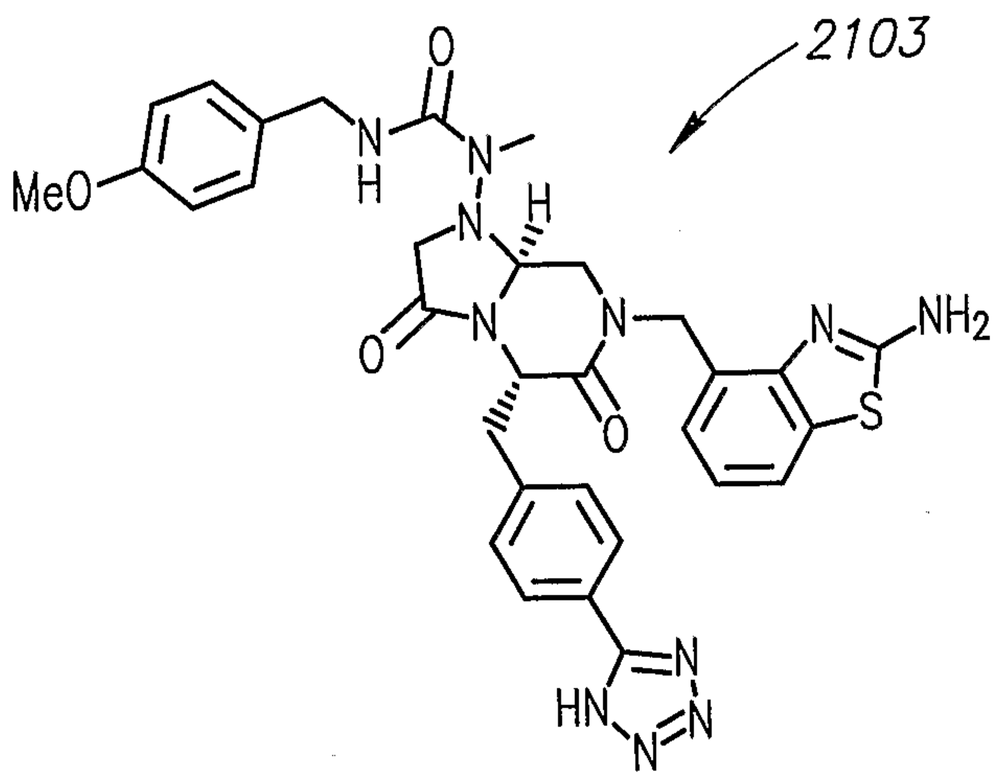


FIG.11M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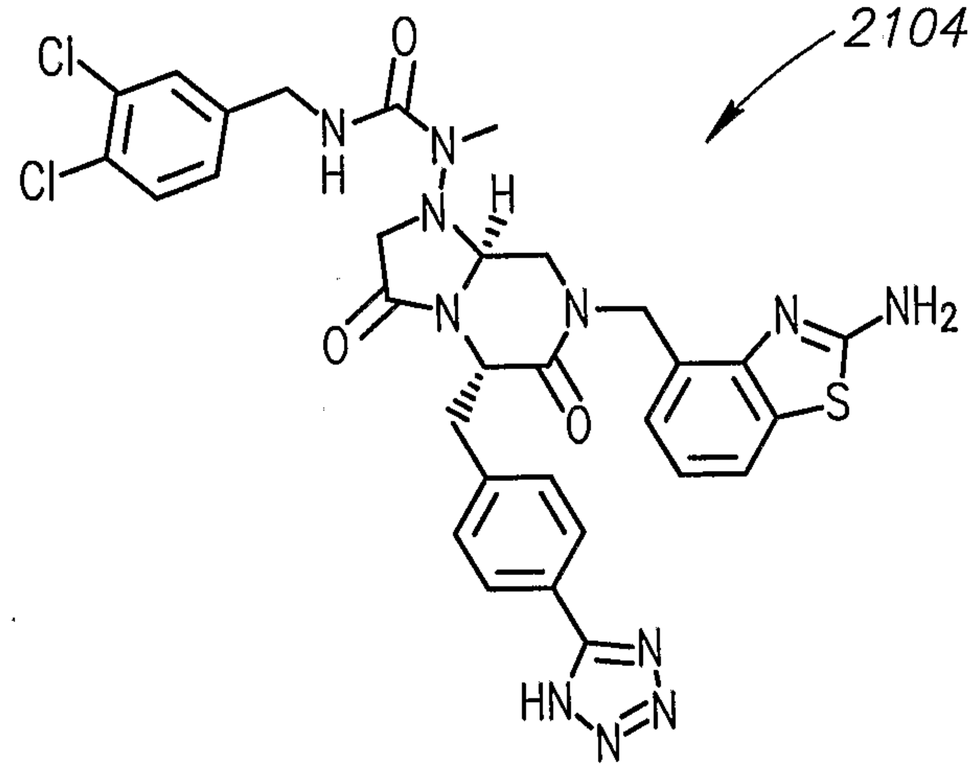
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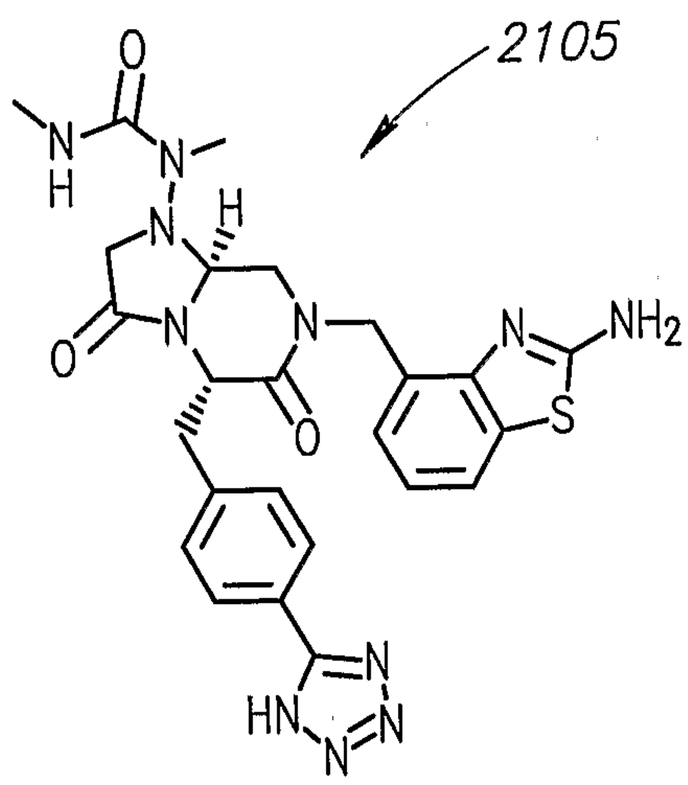
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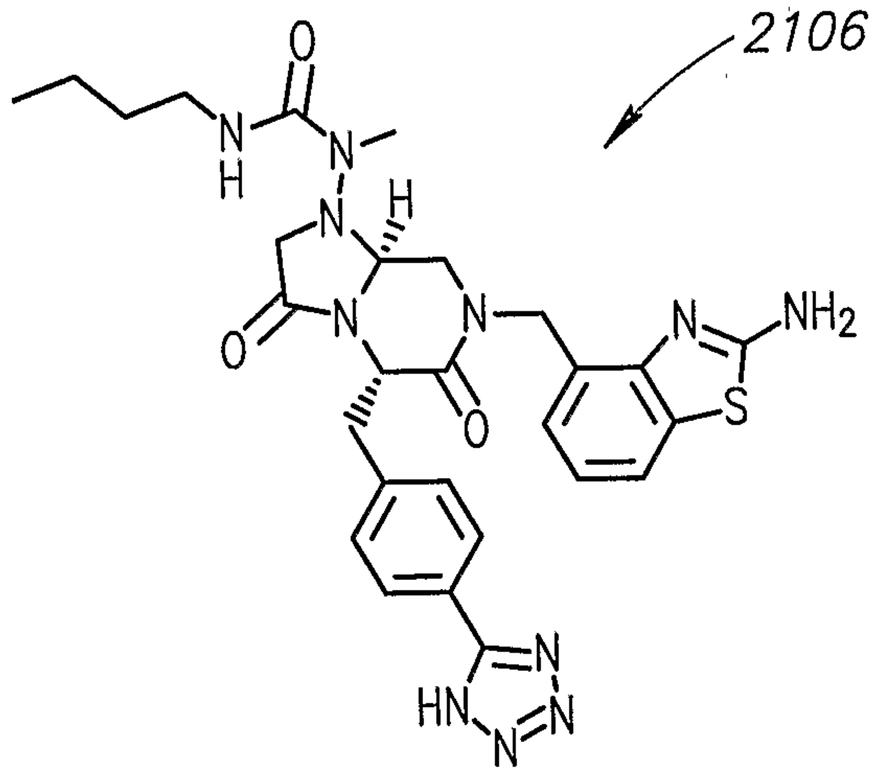
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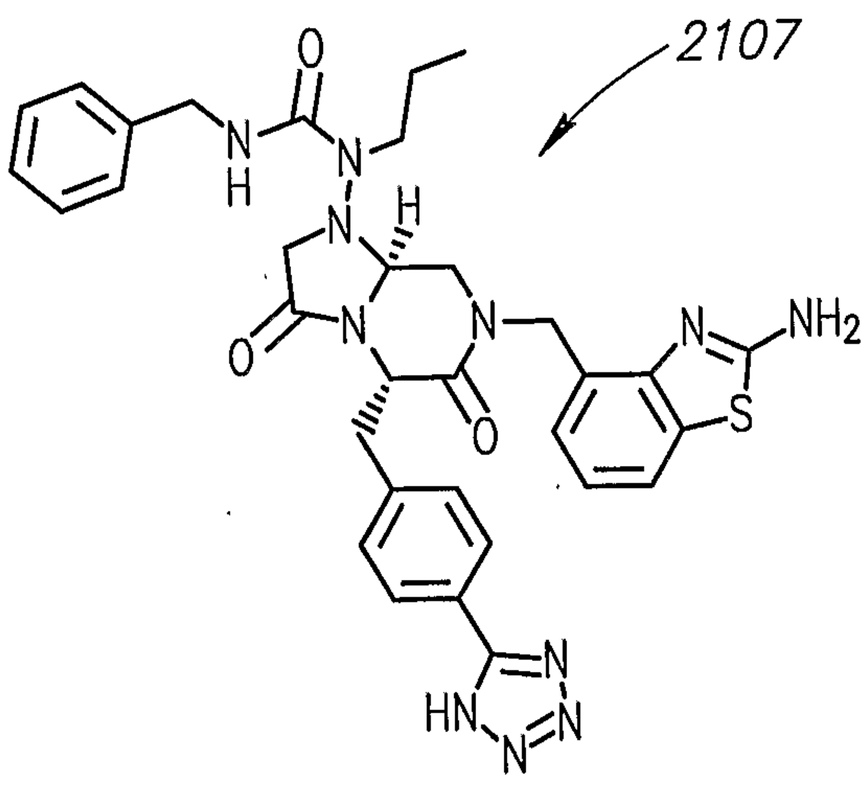
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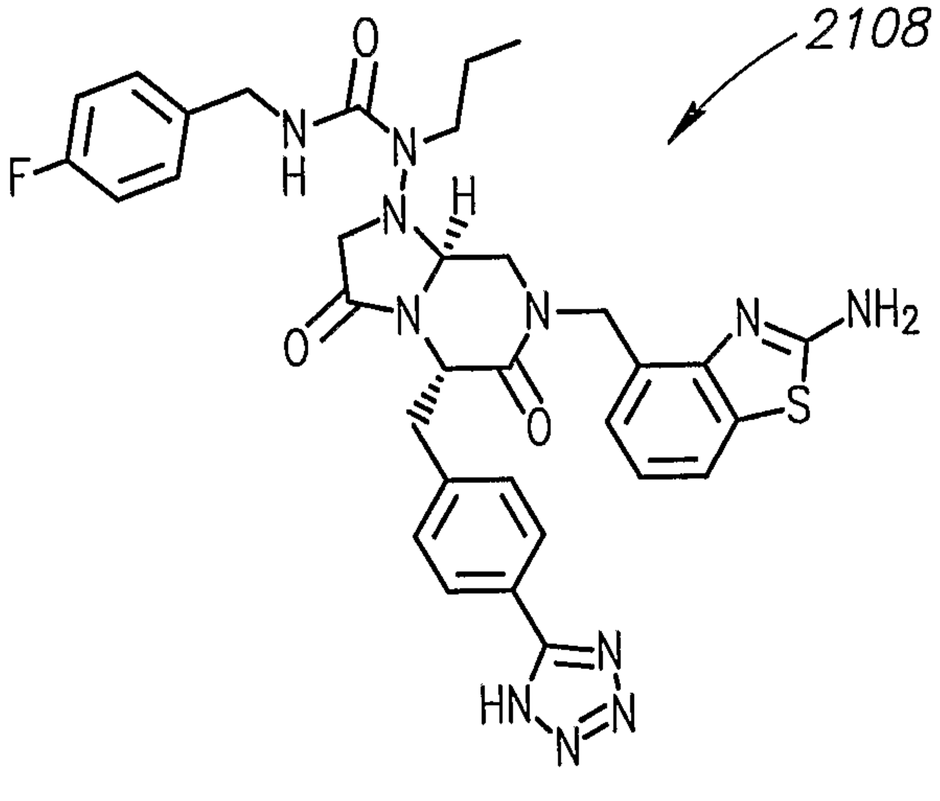
2108
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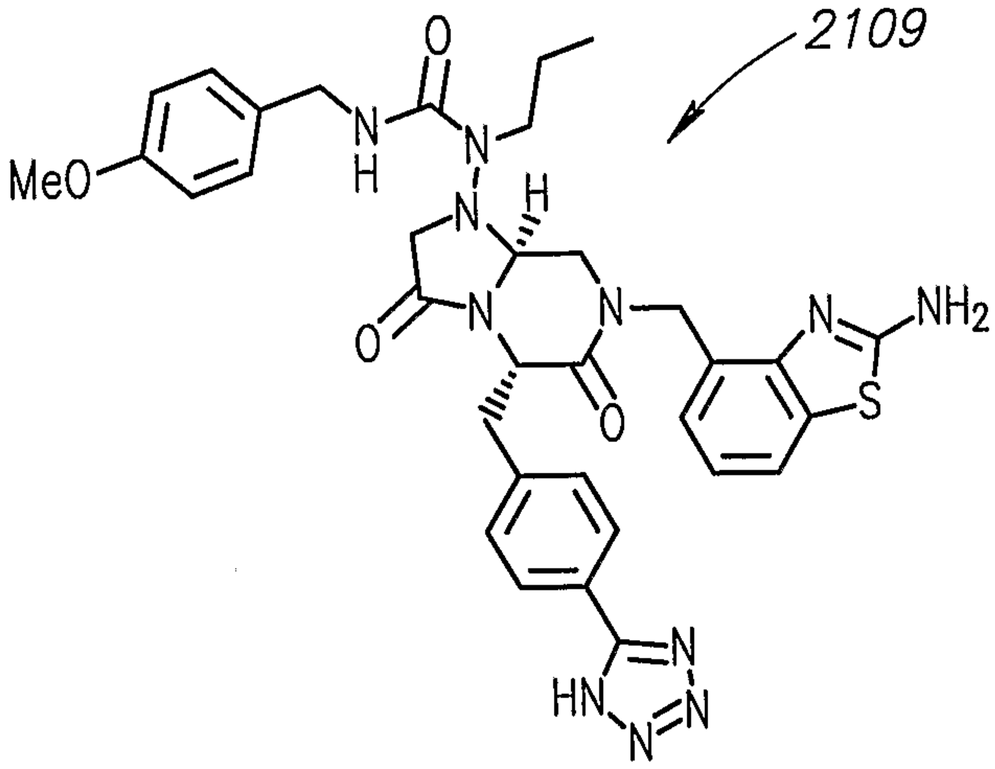
FIG.11N

2109



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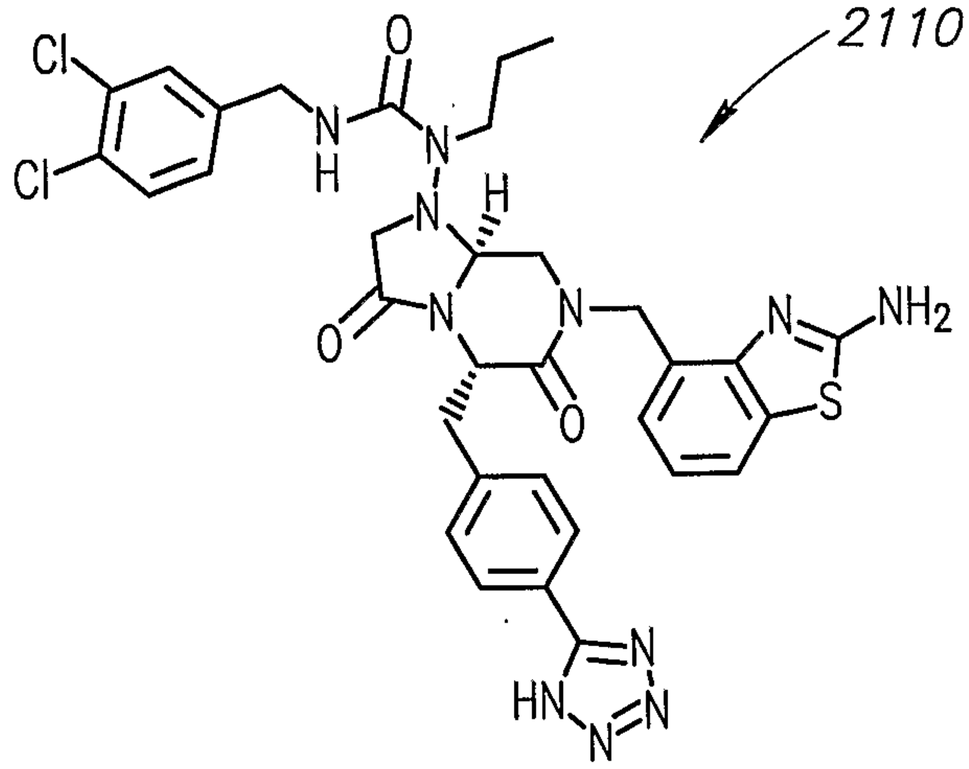

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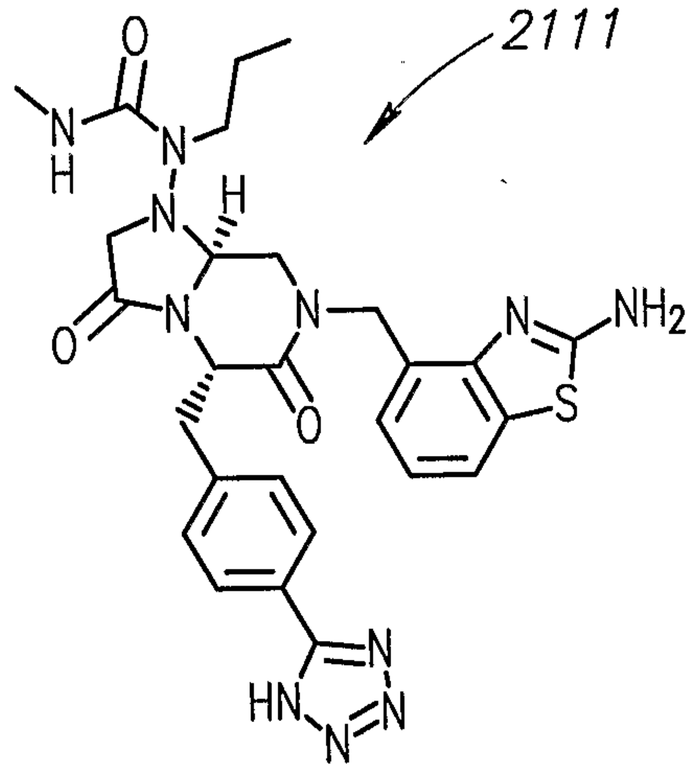

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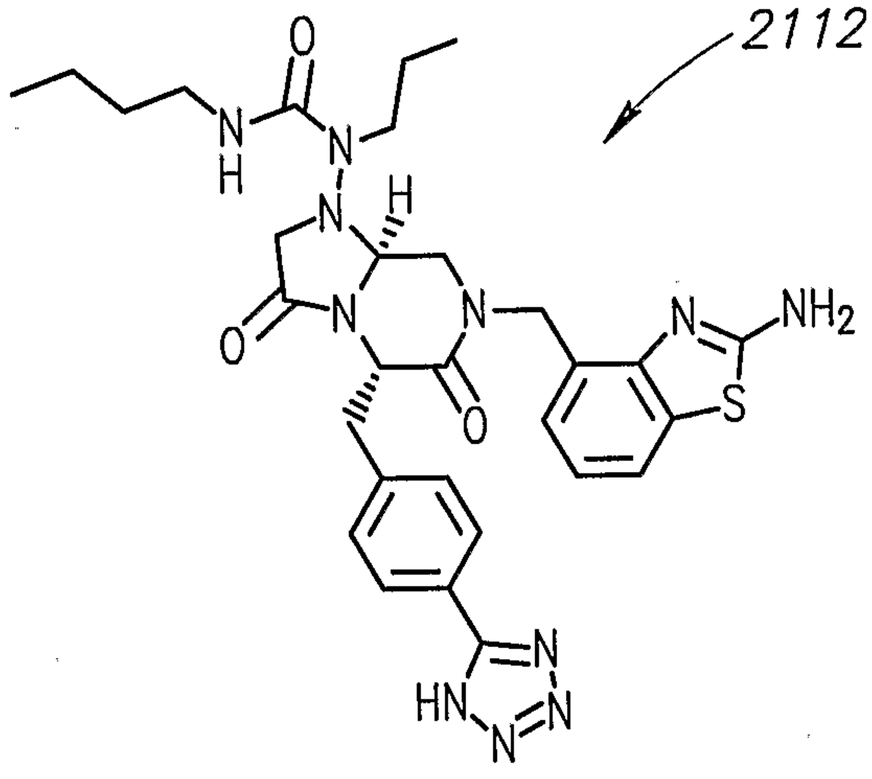

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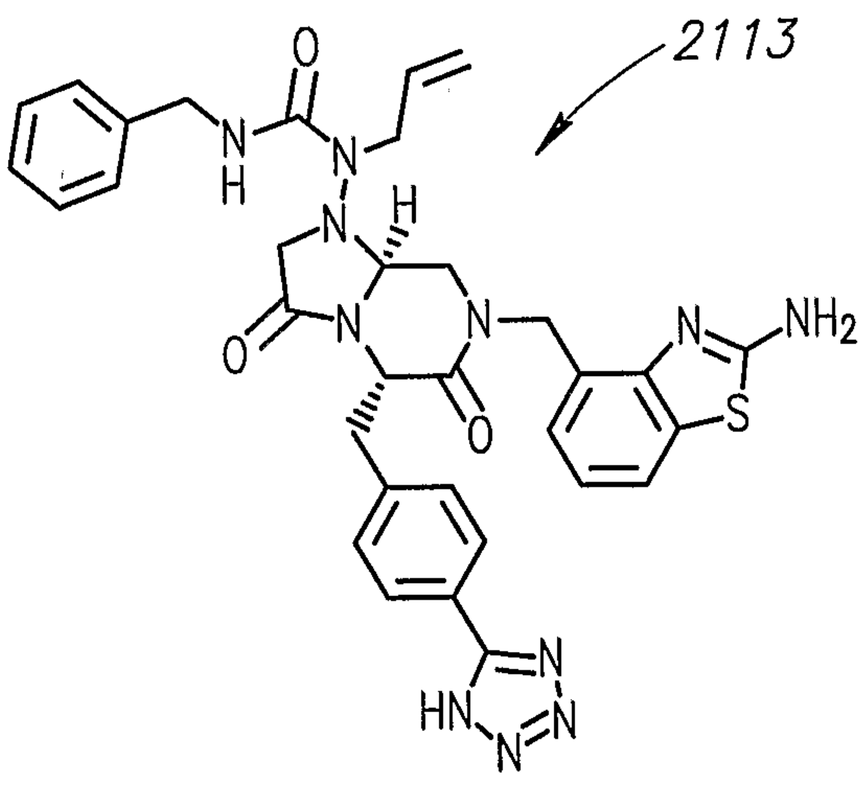

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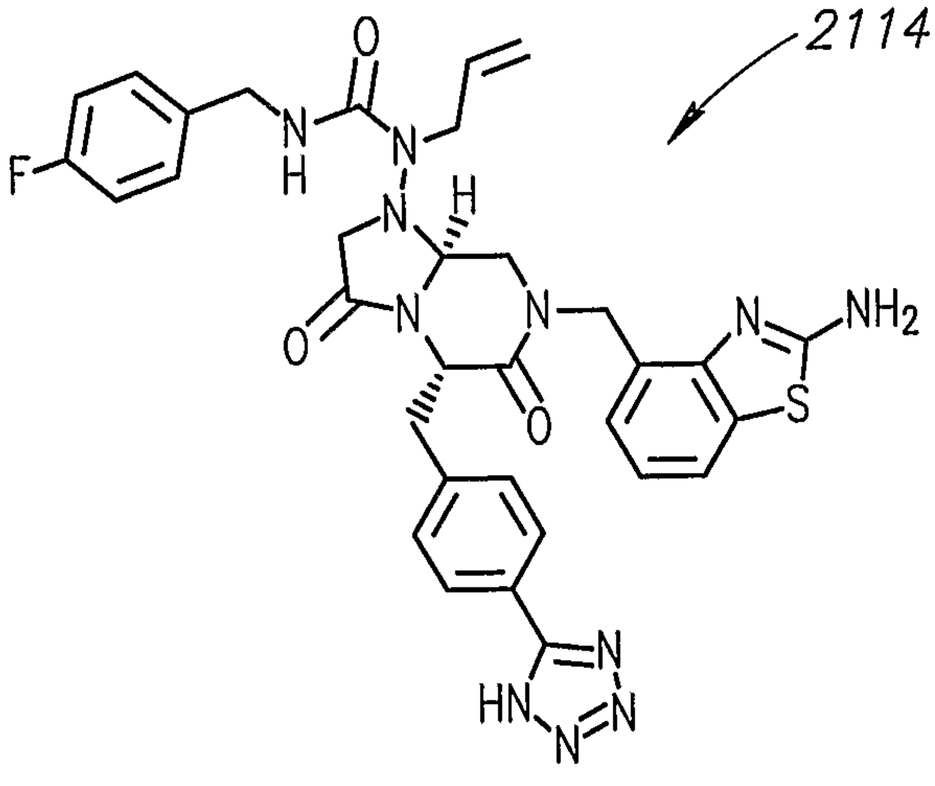
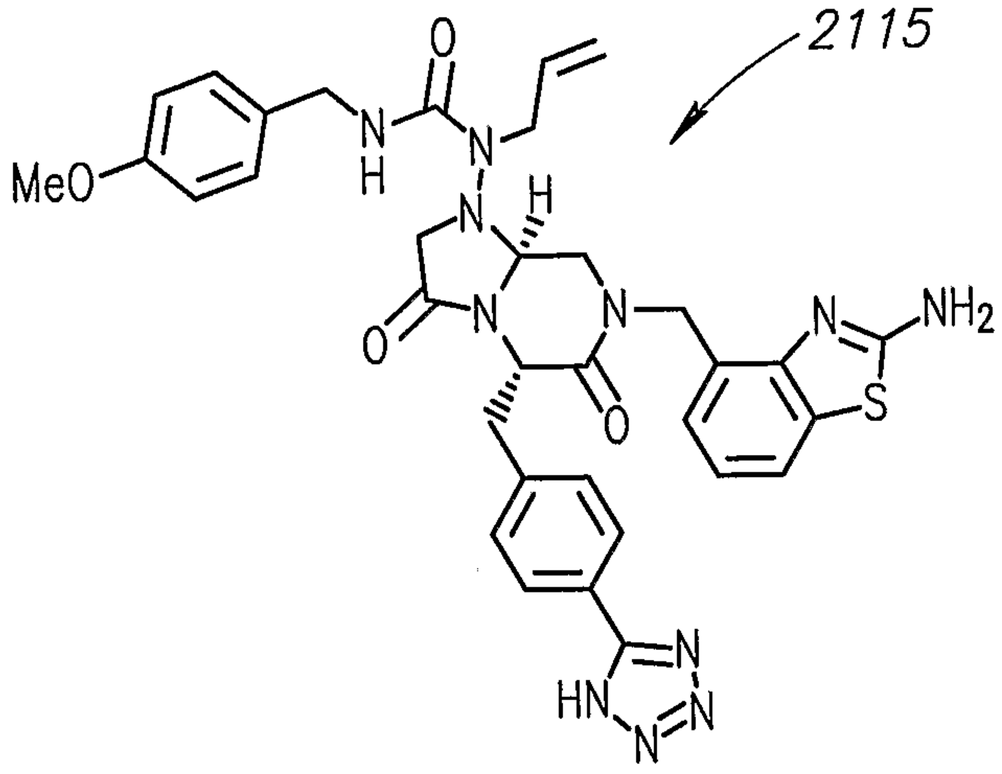


FIG.110

2115



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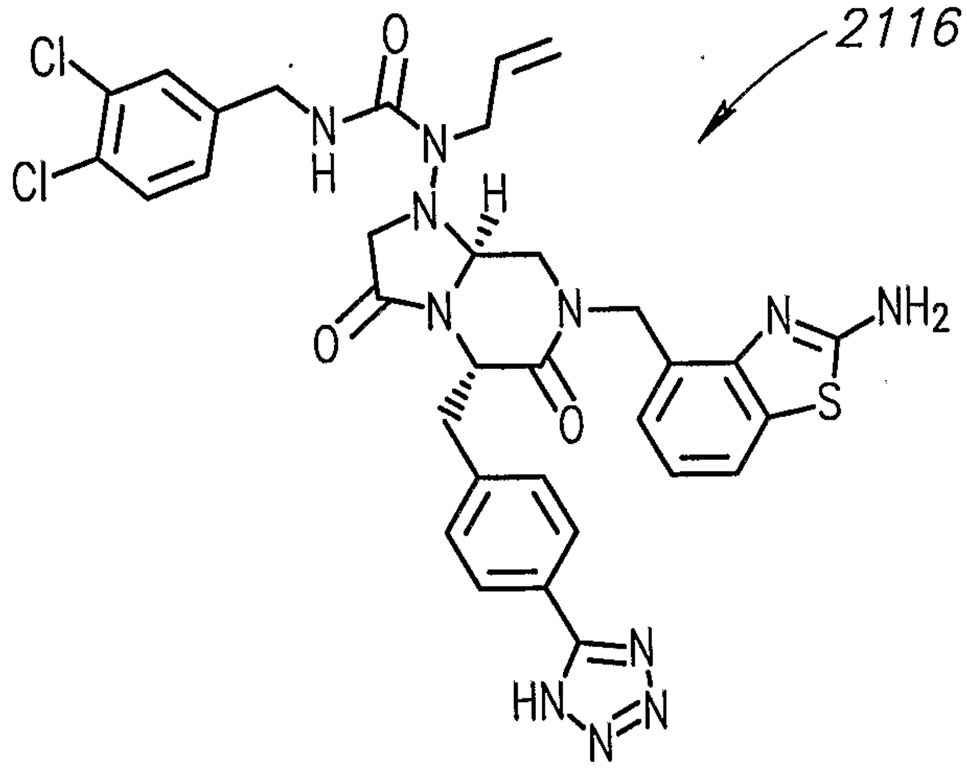

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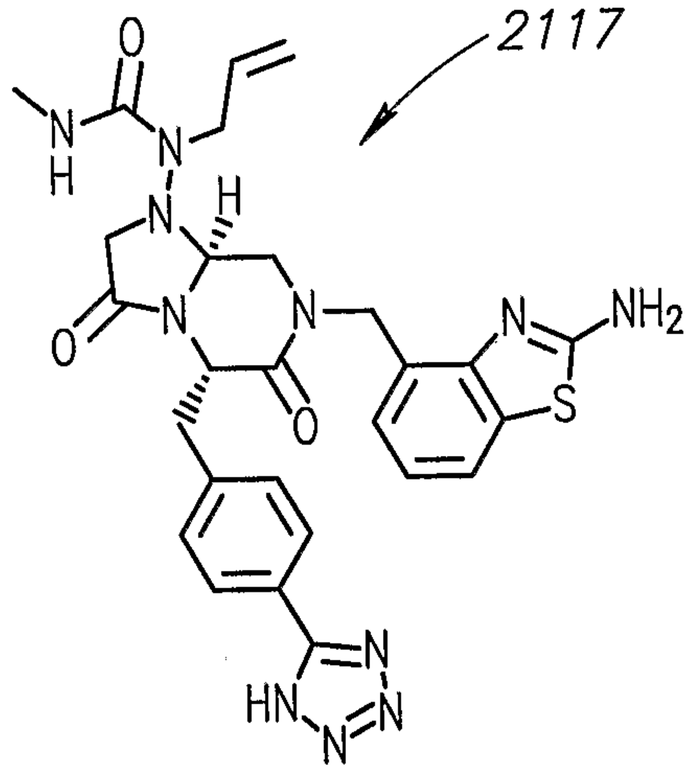

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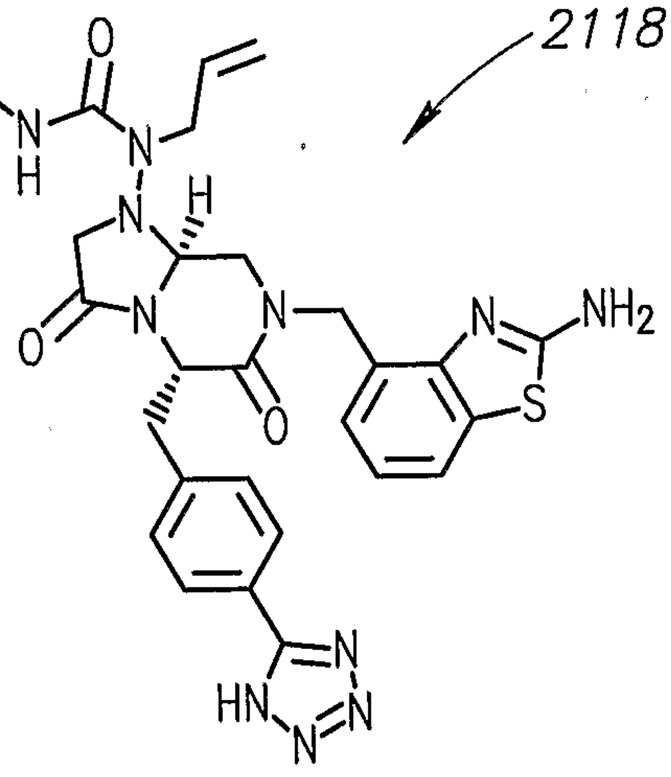

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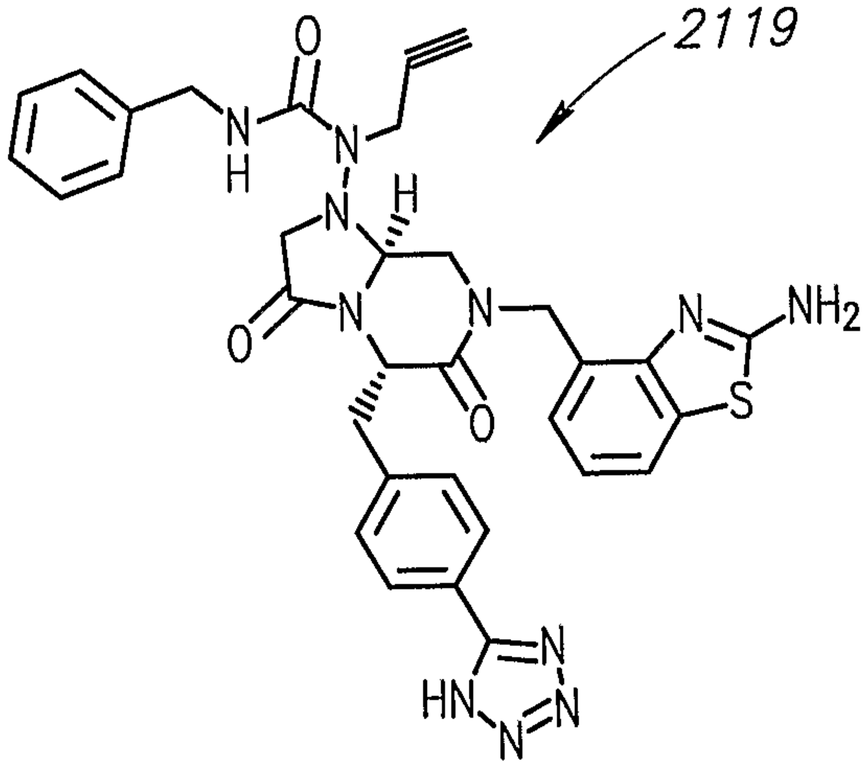

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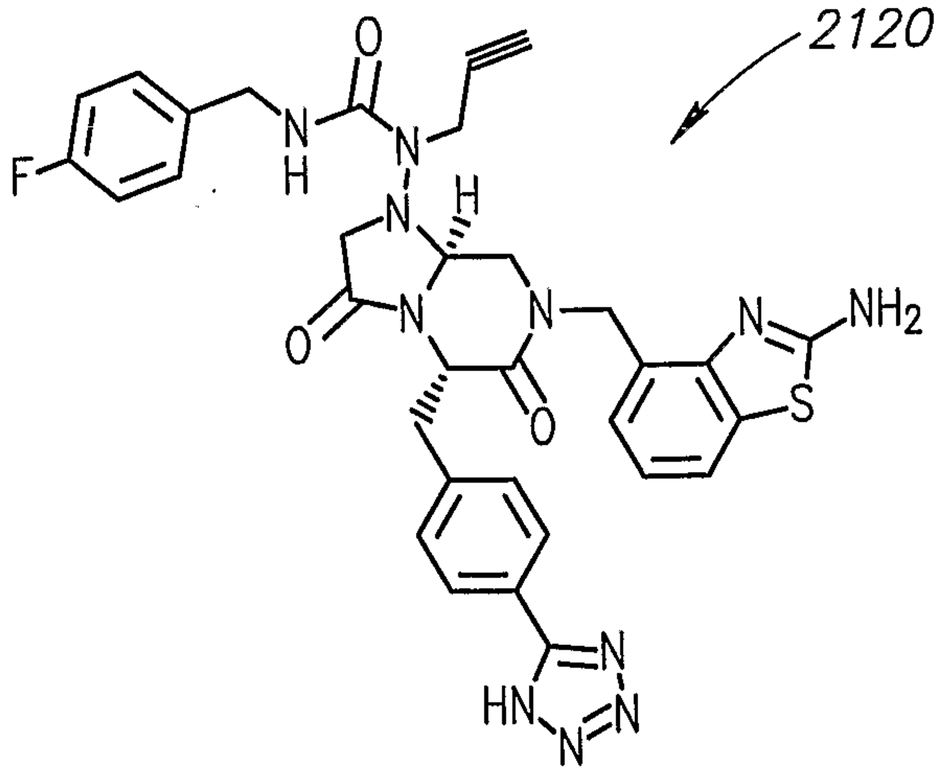
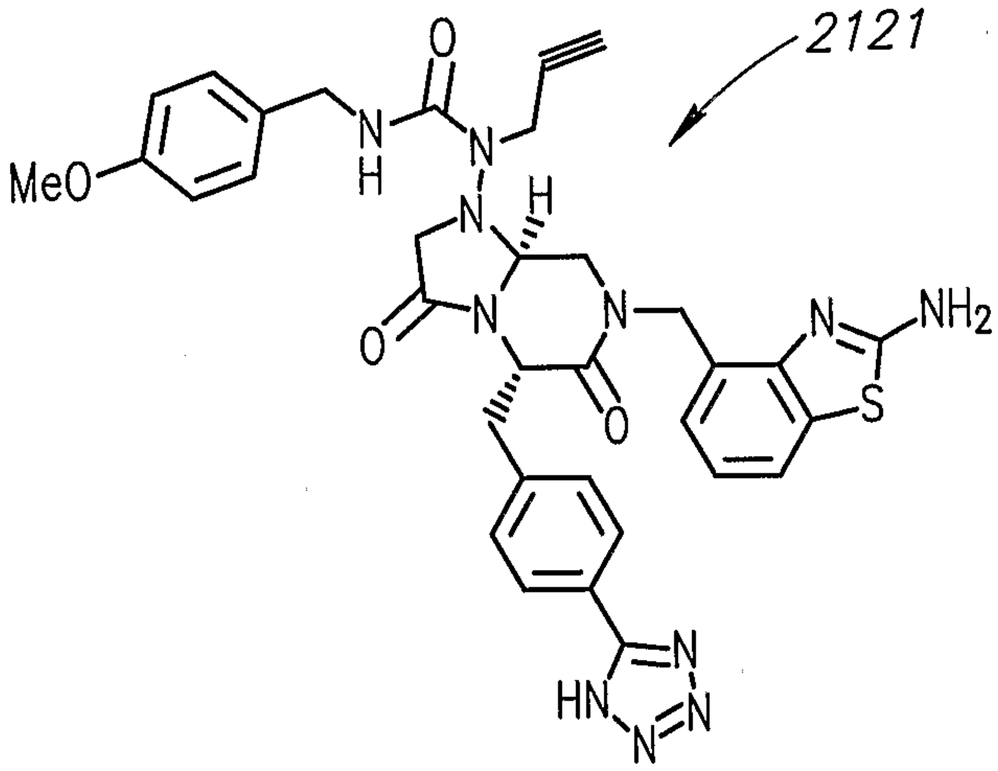


FIG.11P

2121



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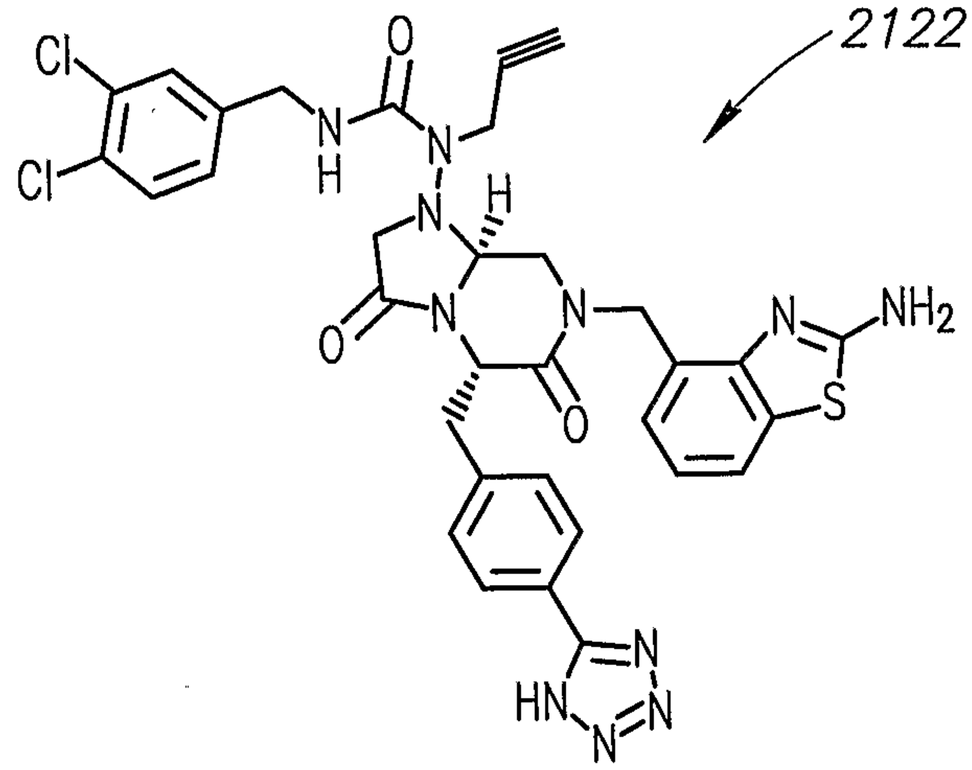

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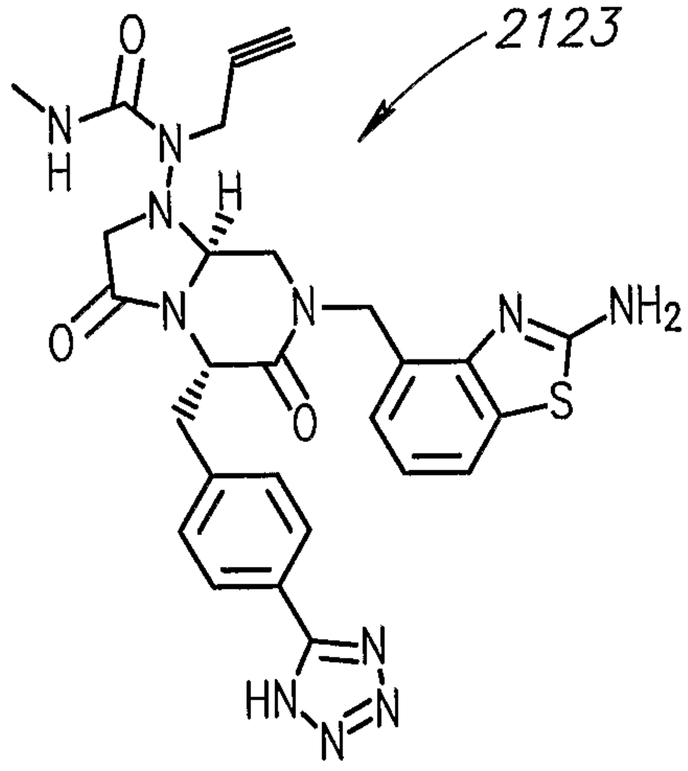

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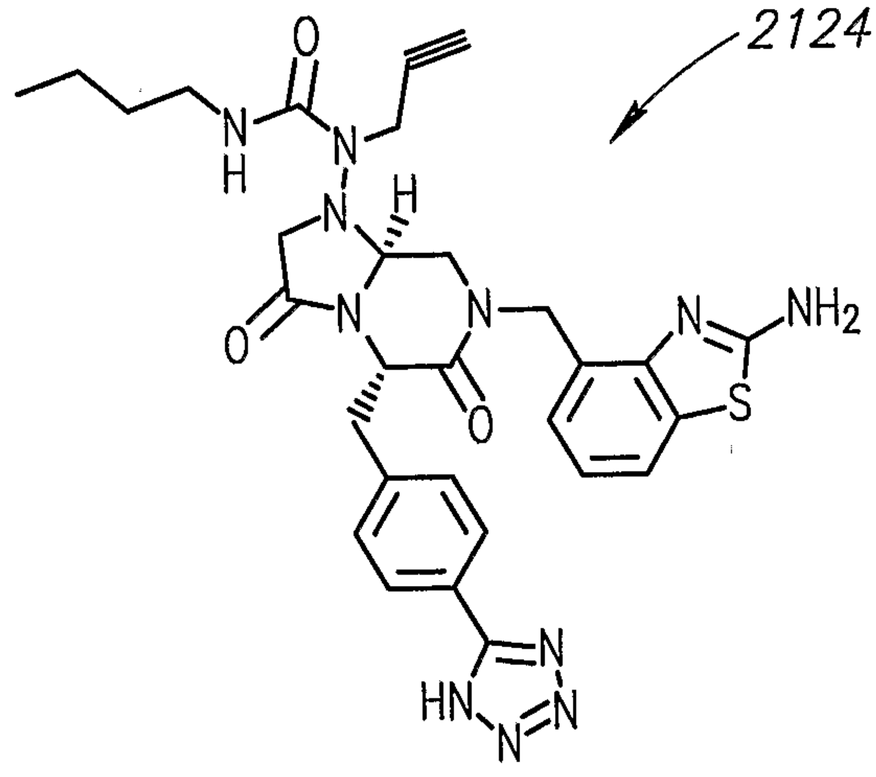

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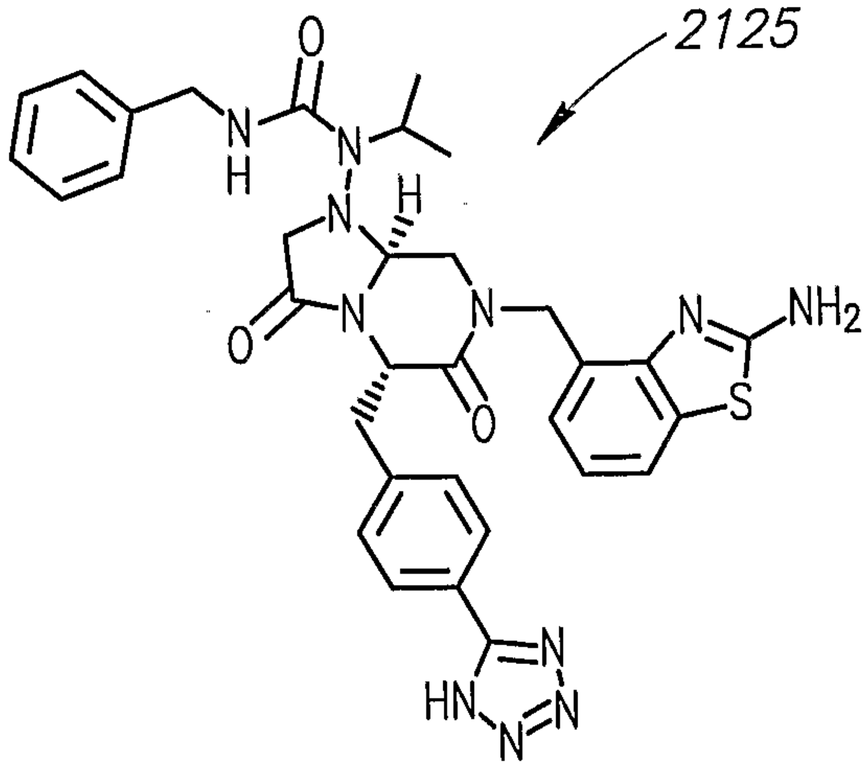

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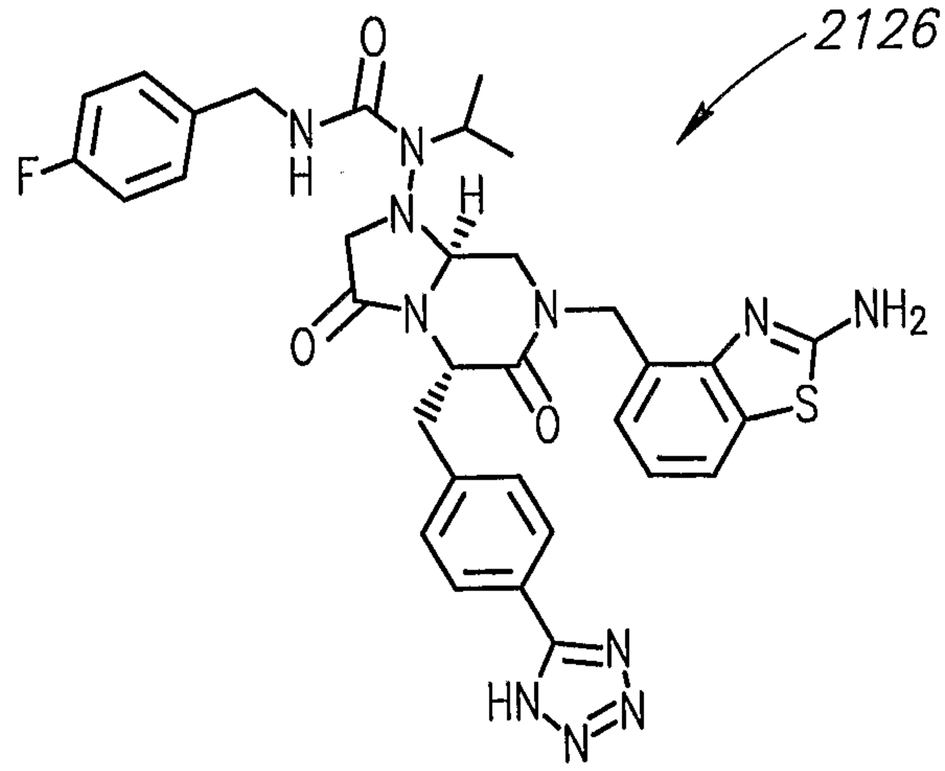
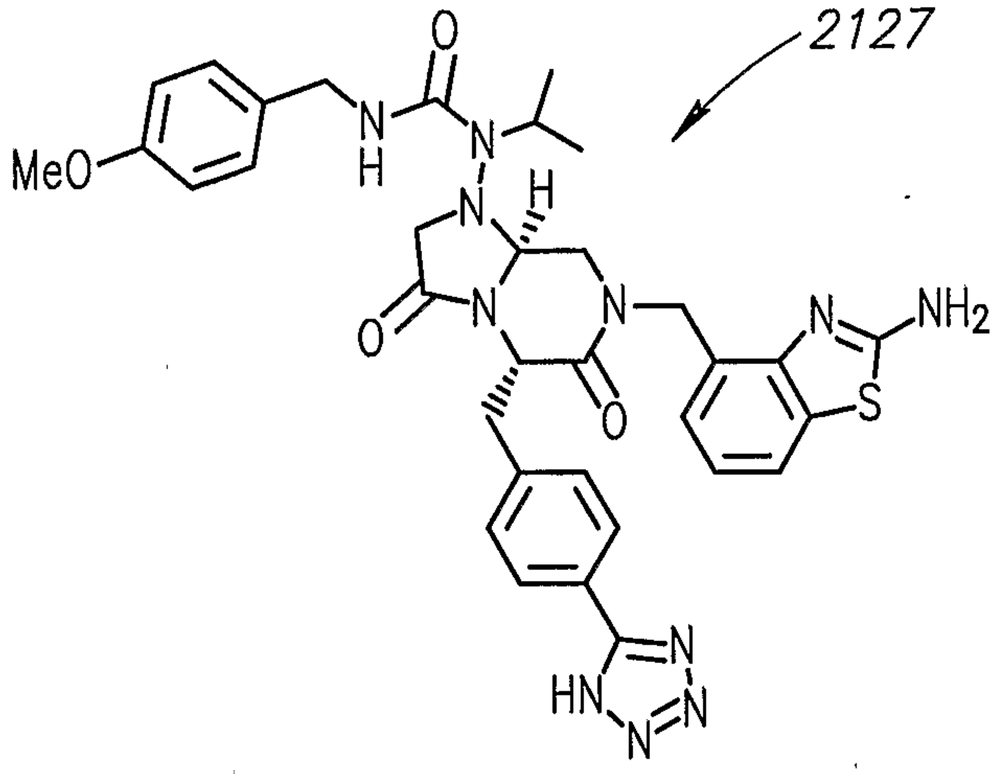


FIG.11Q

2127



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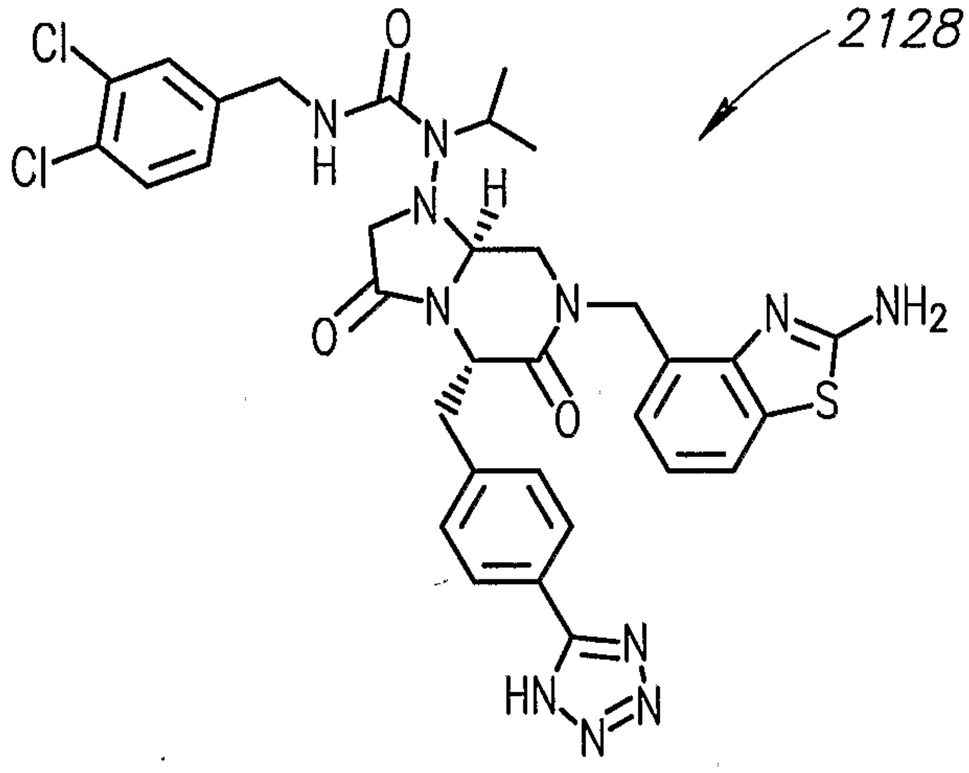

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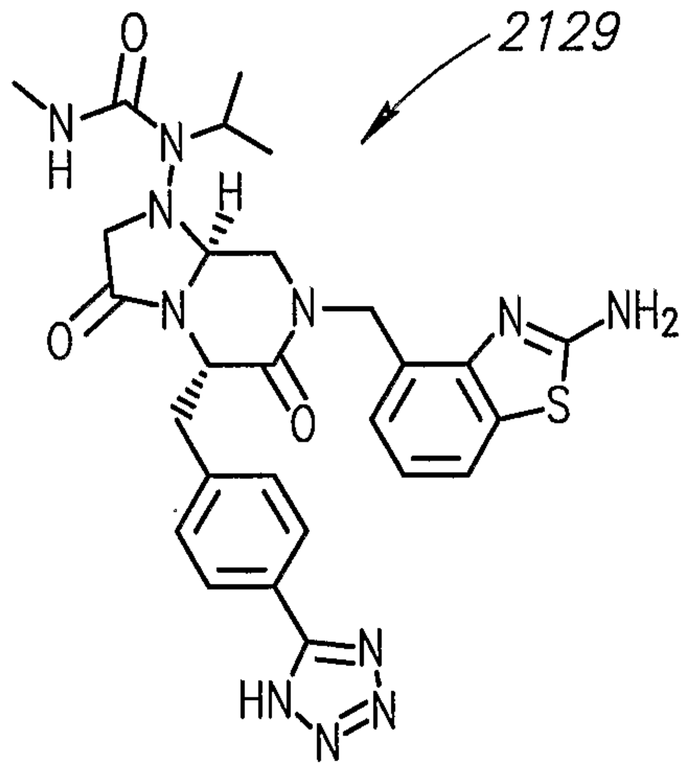

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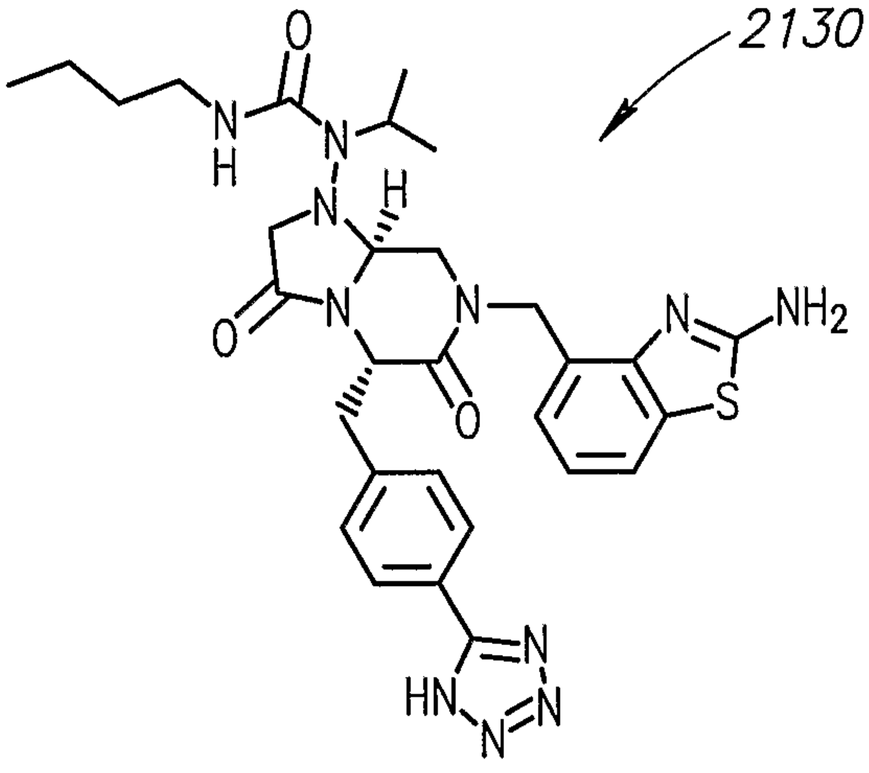

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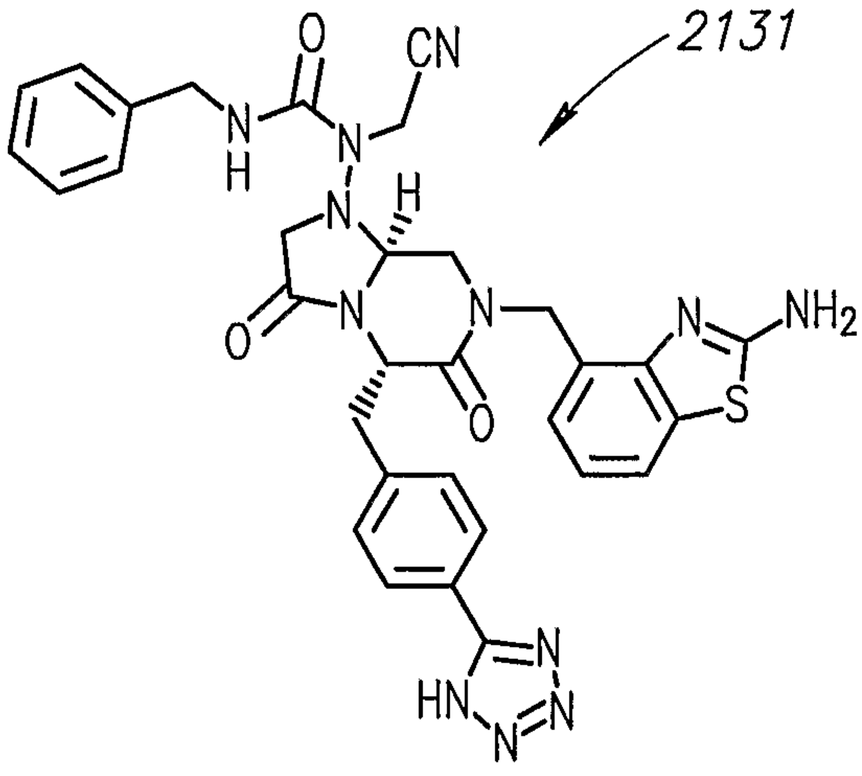

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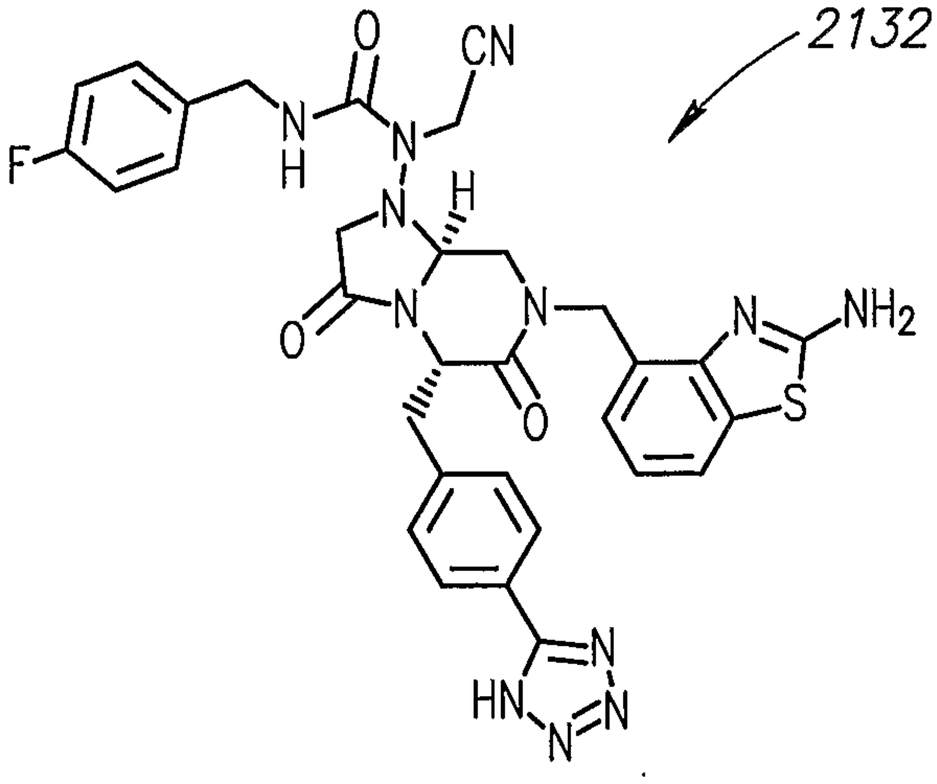
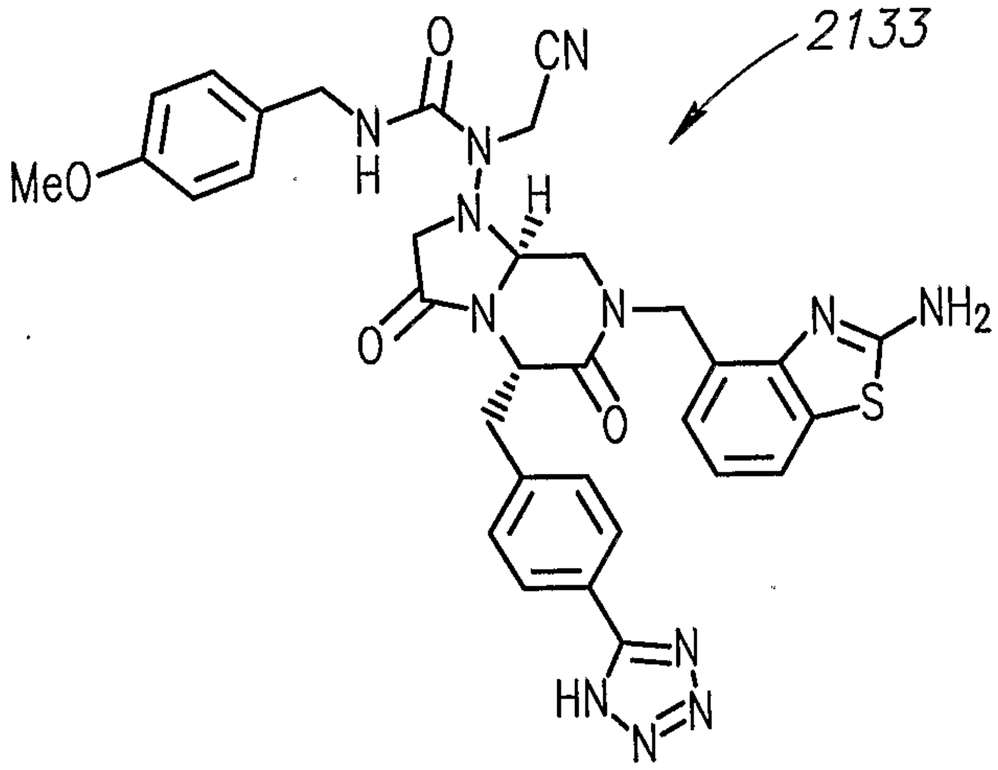


FIG.11R

2133



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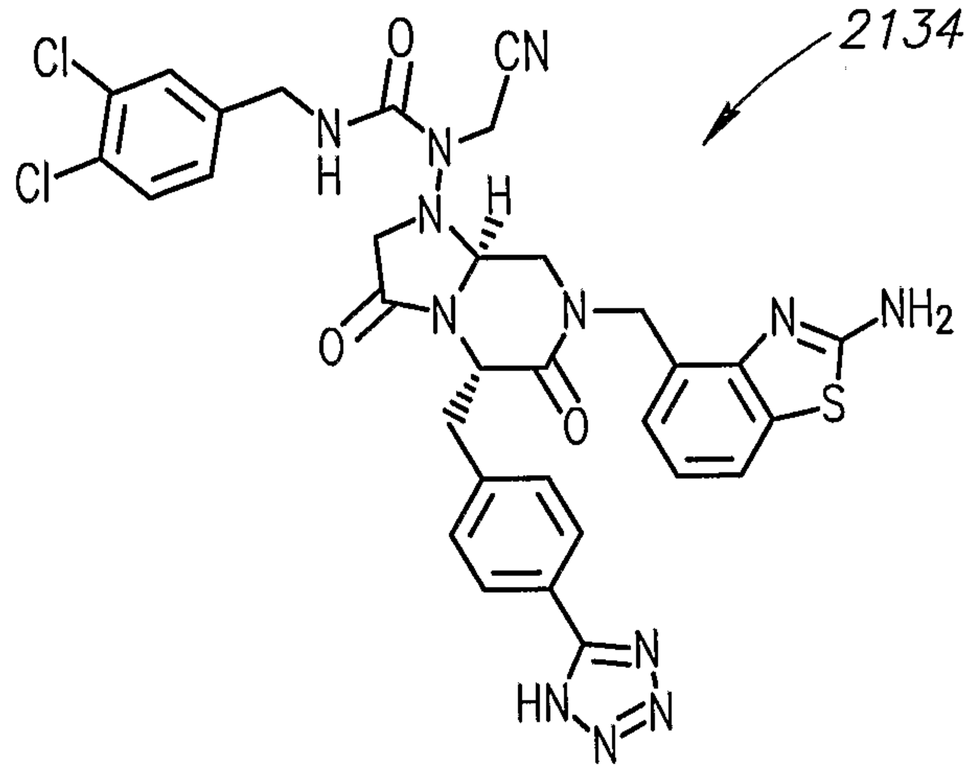

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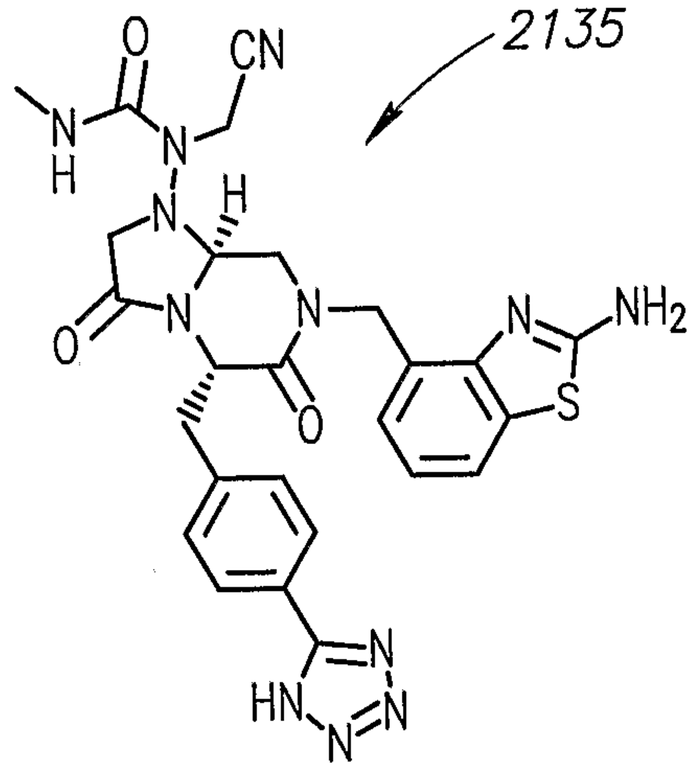

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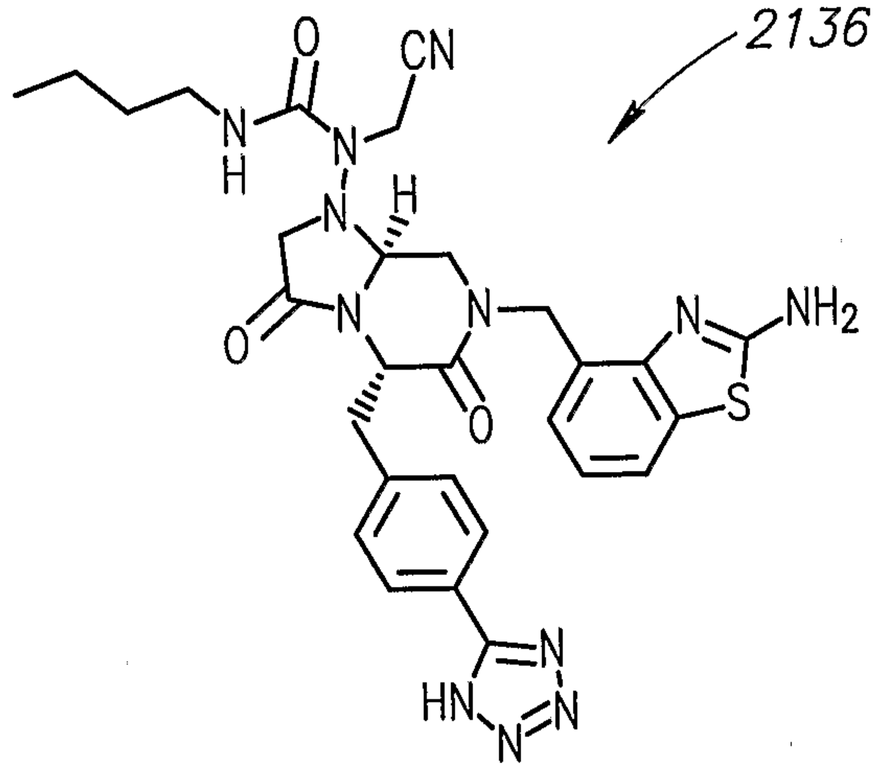

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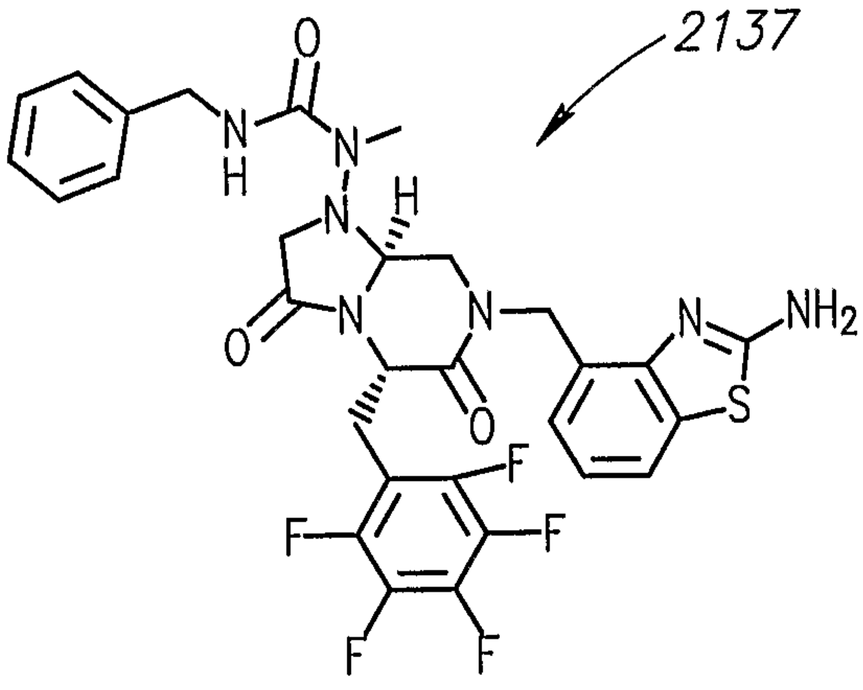

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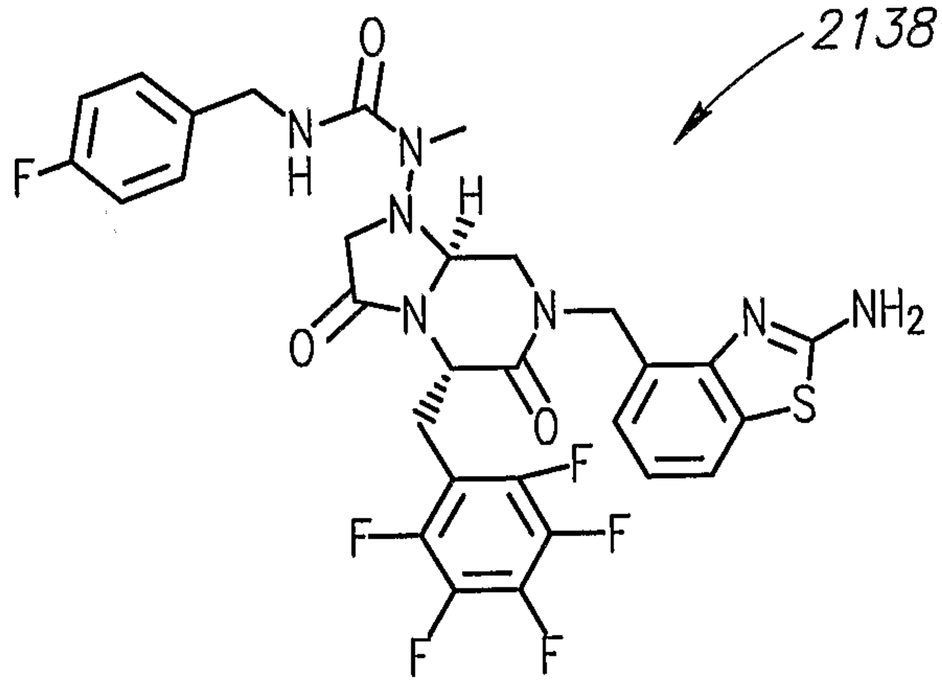
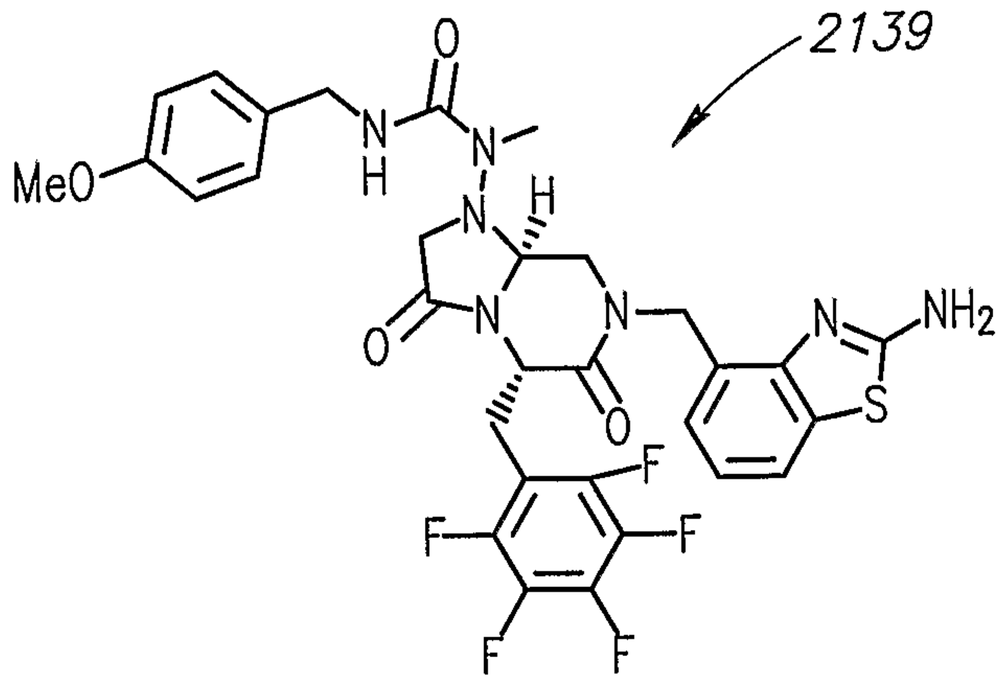


FIG.11S

2139



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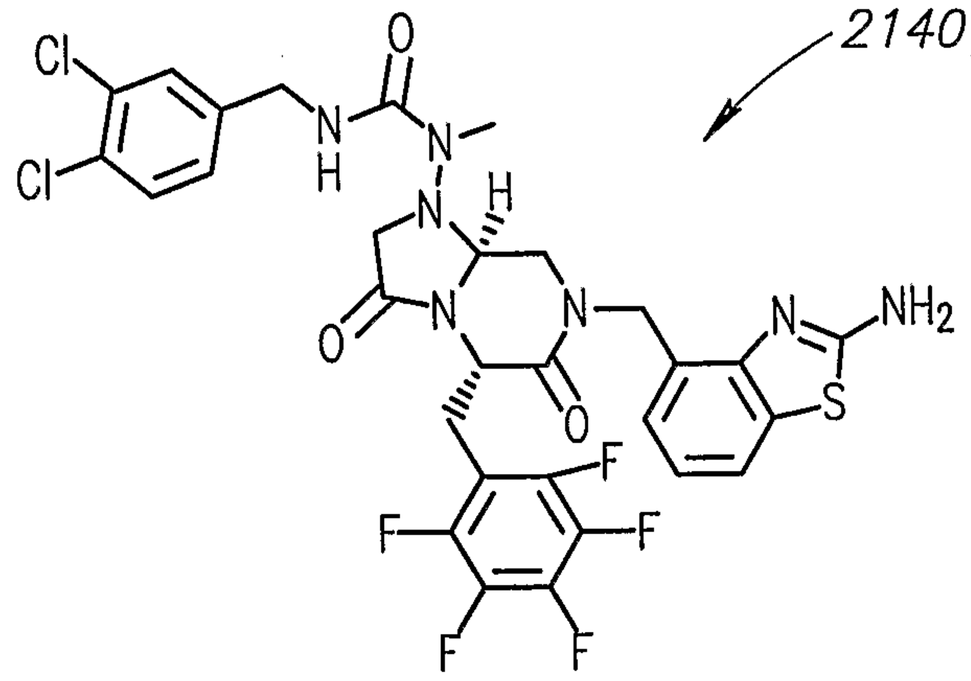

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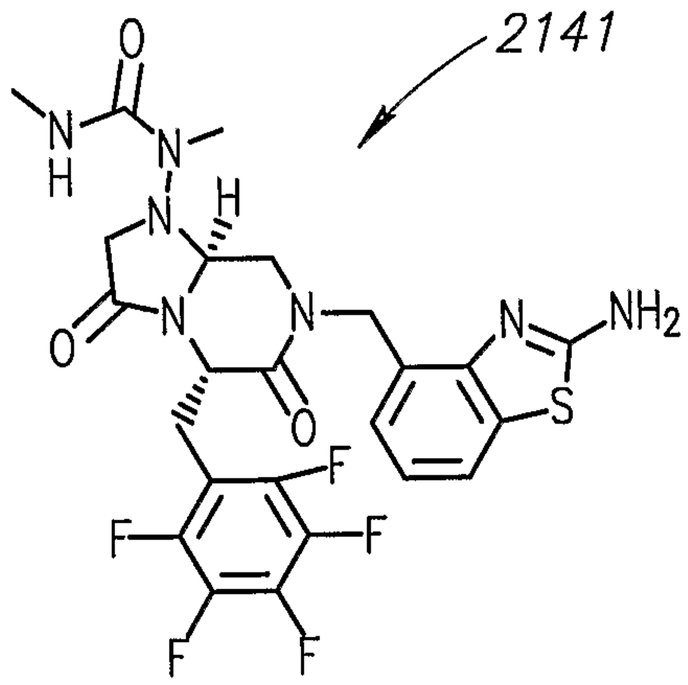

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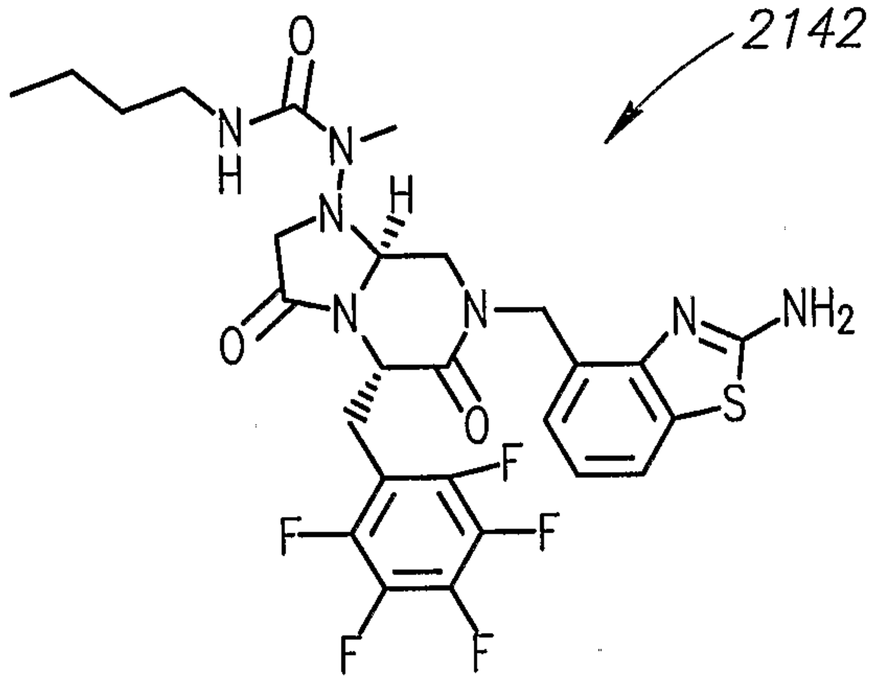

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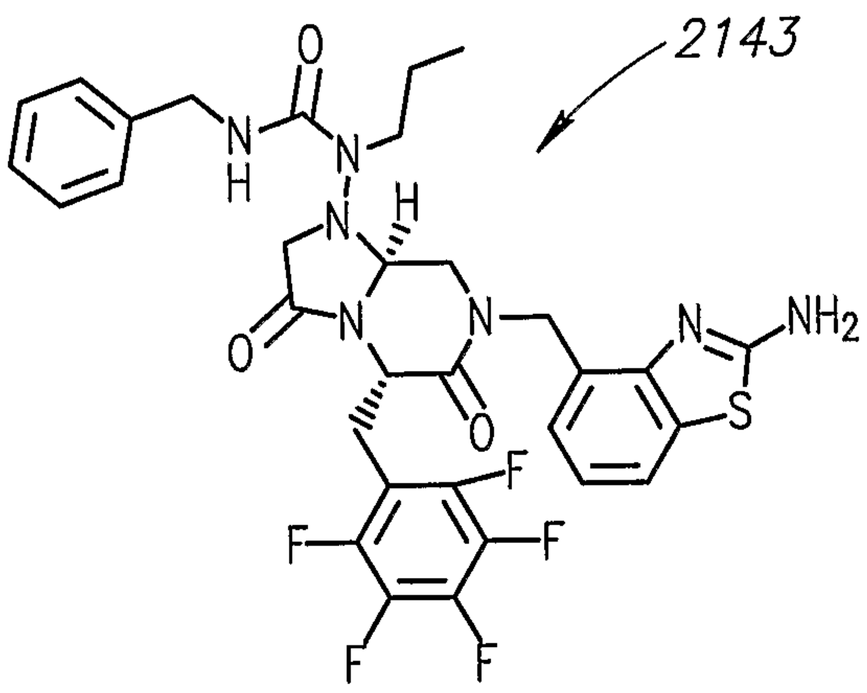

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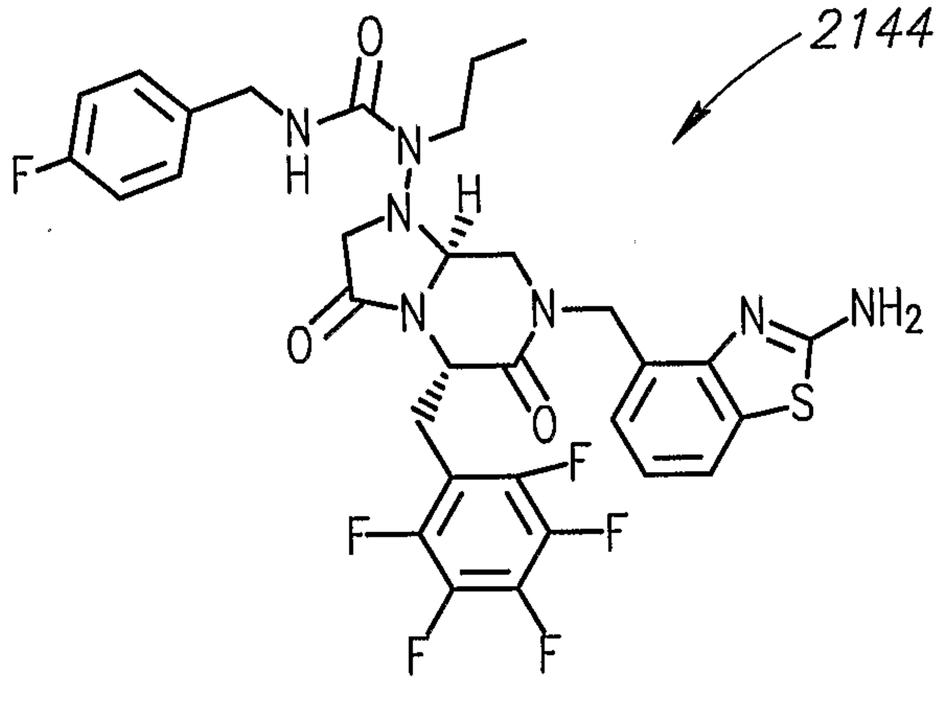

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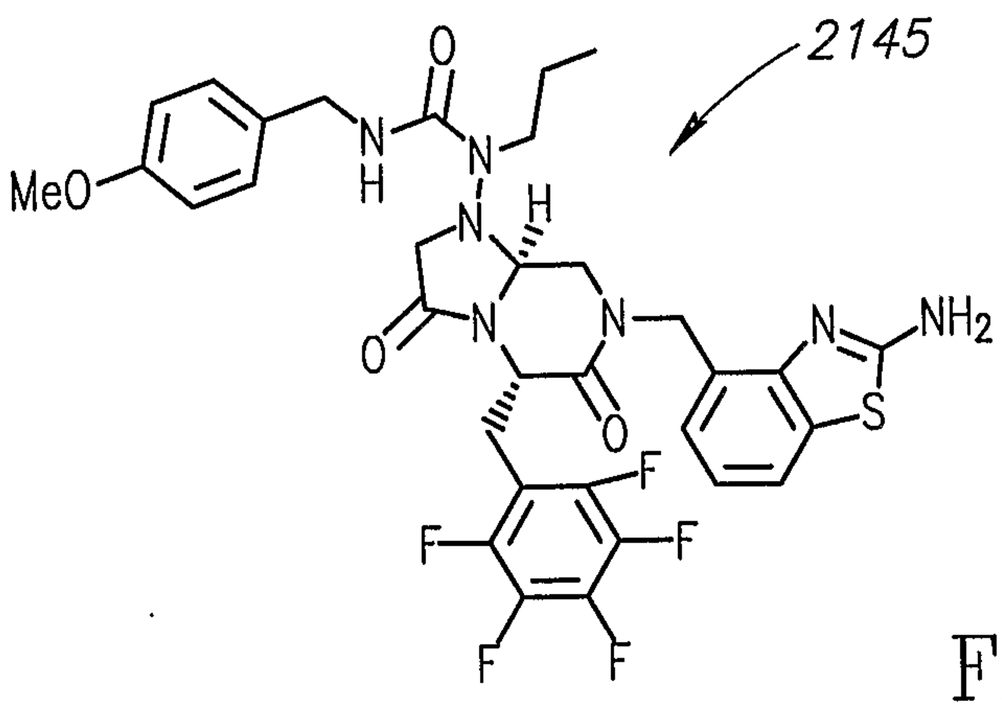

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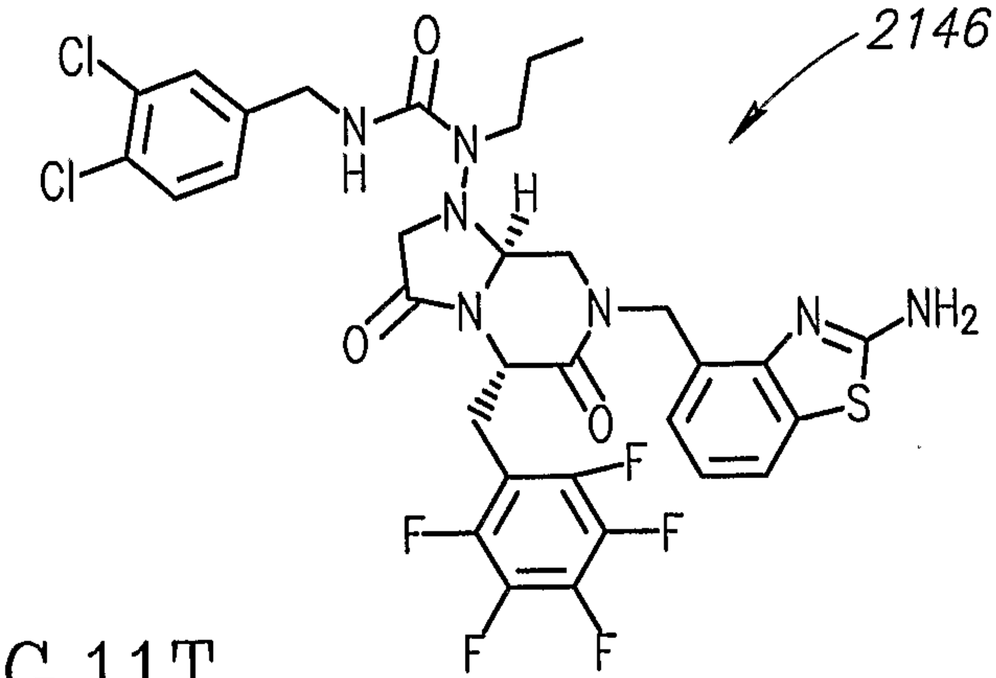
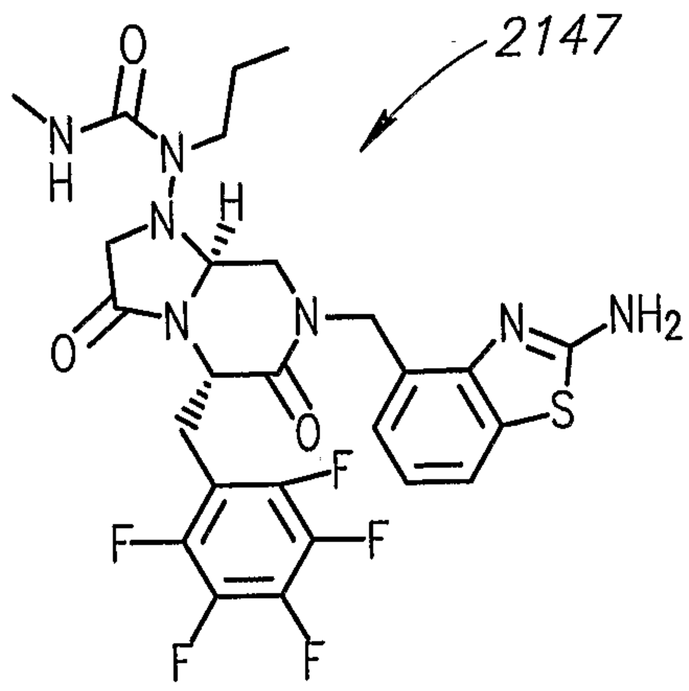
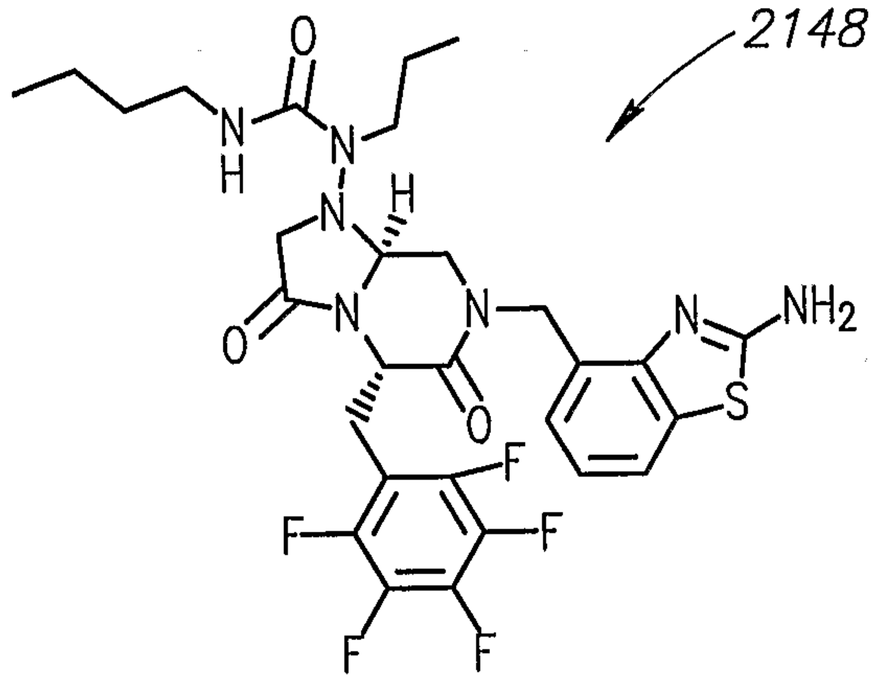
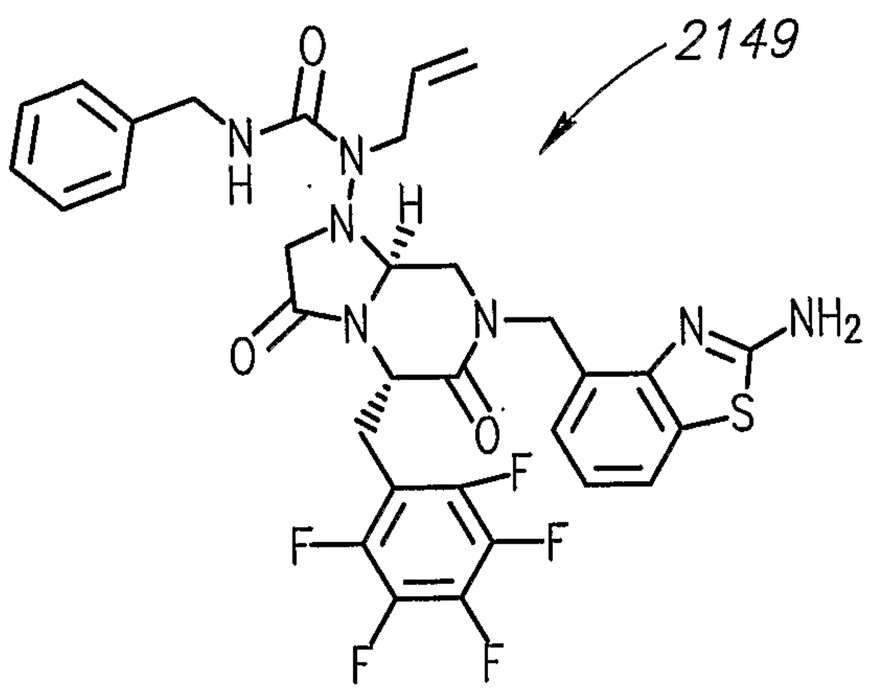
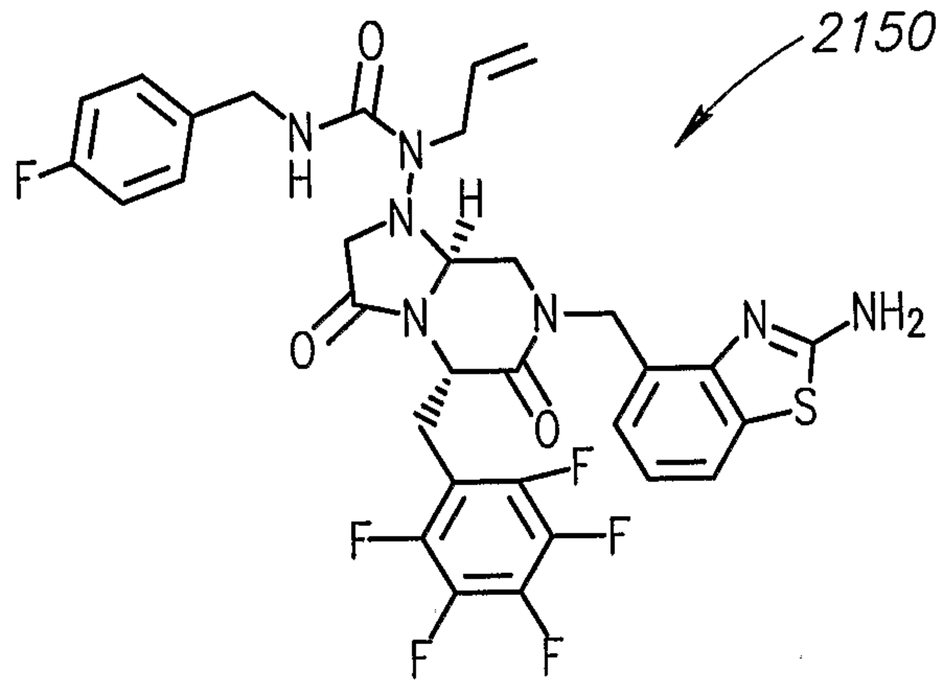


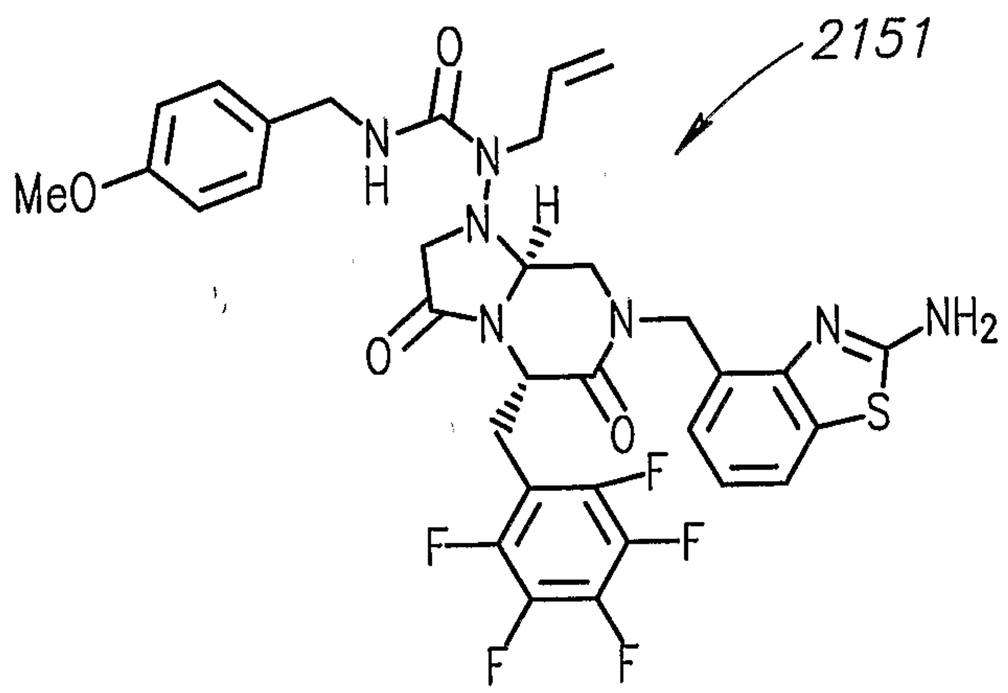
FIG.11T

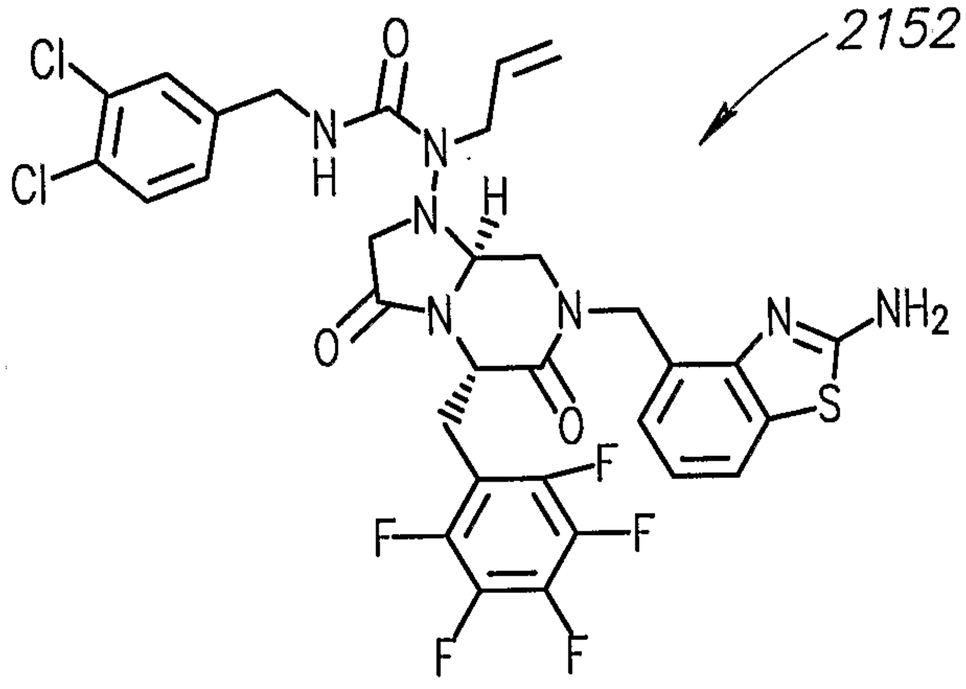


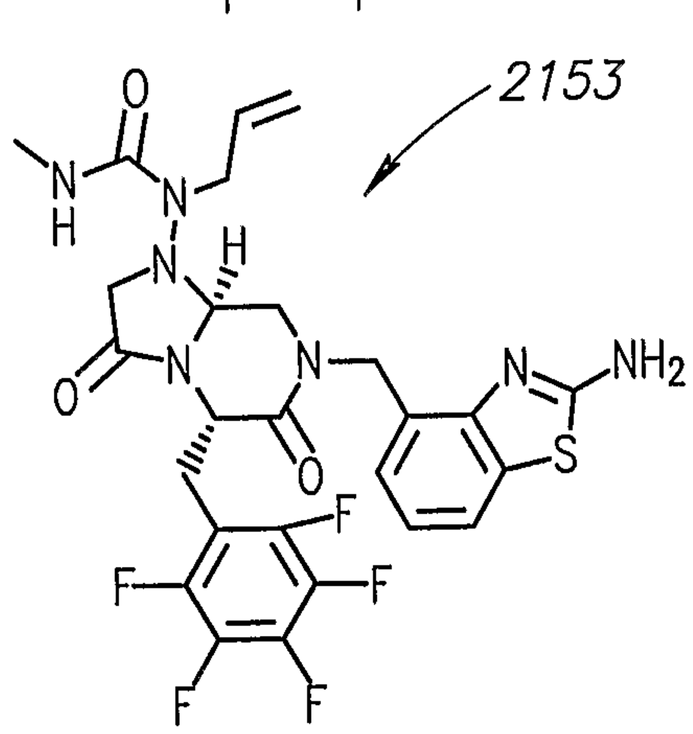












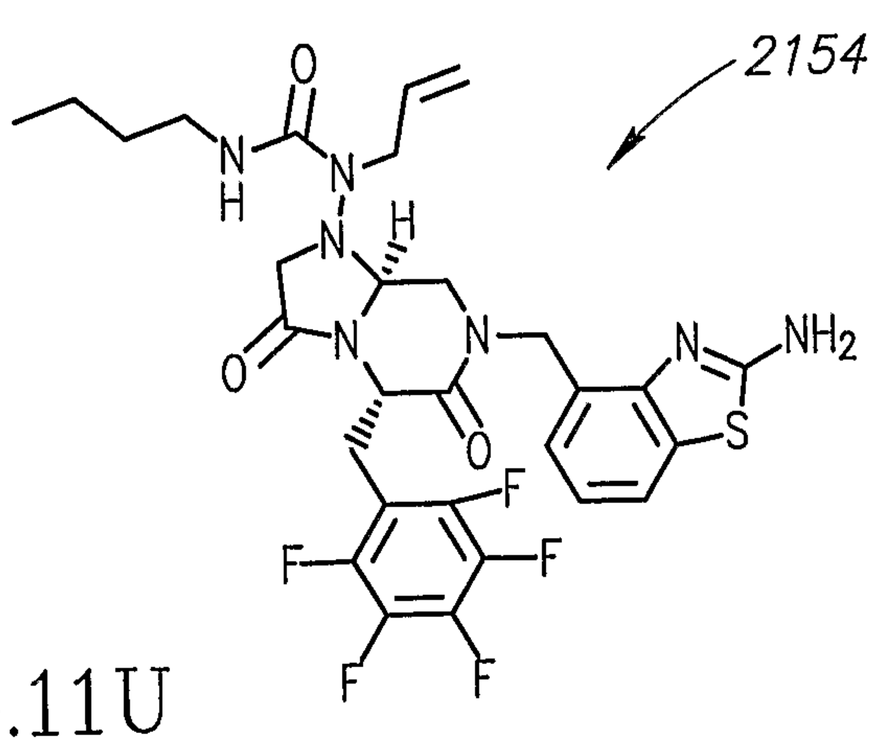
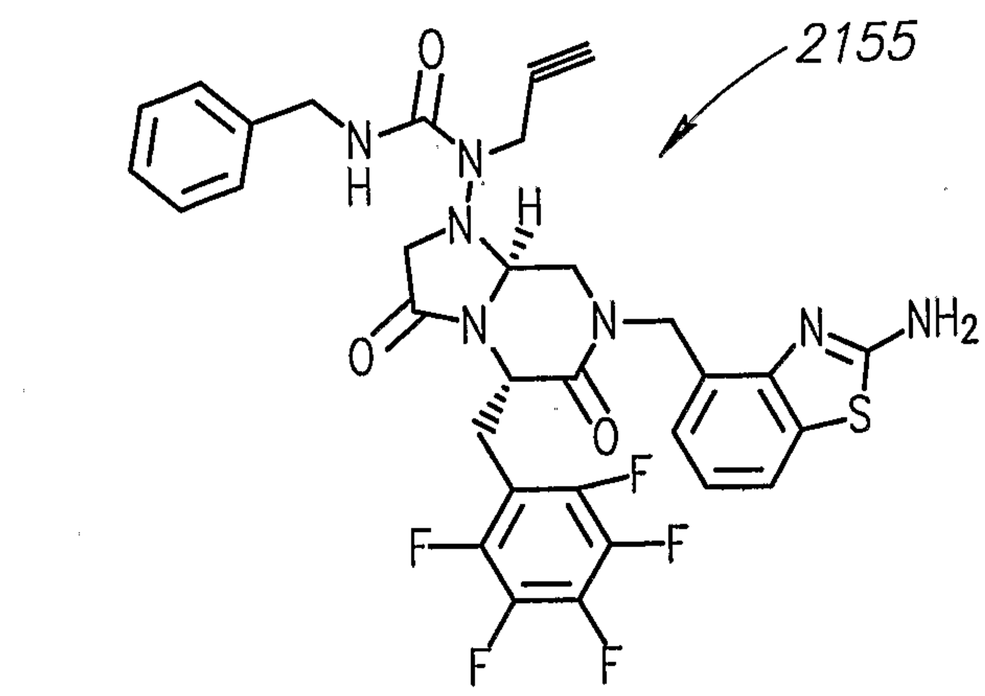
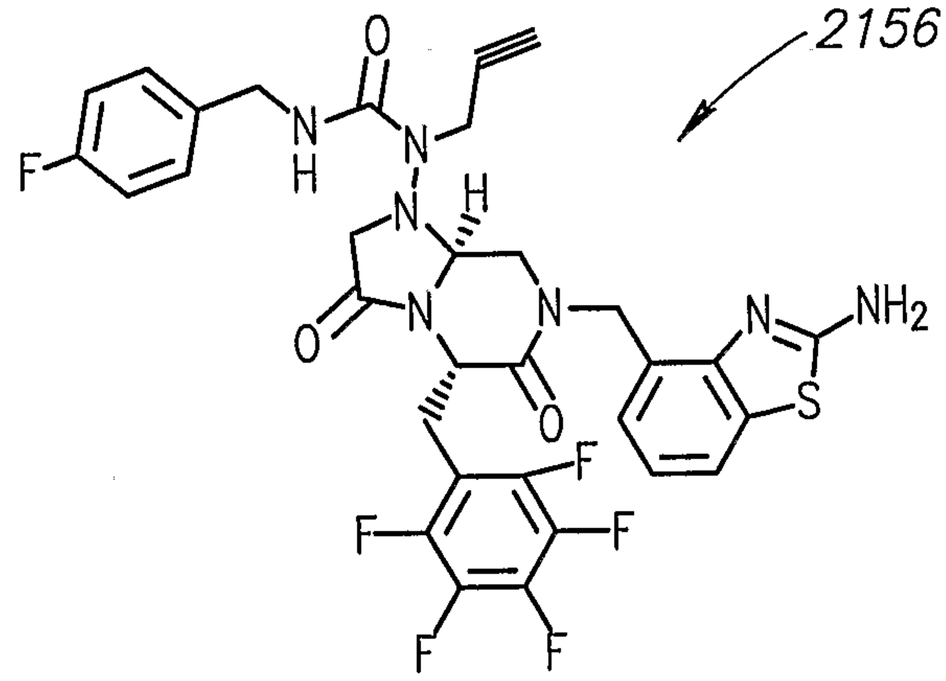
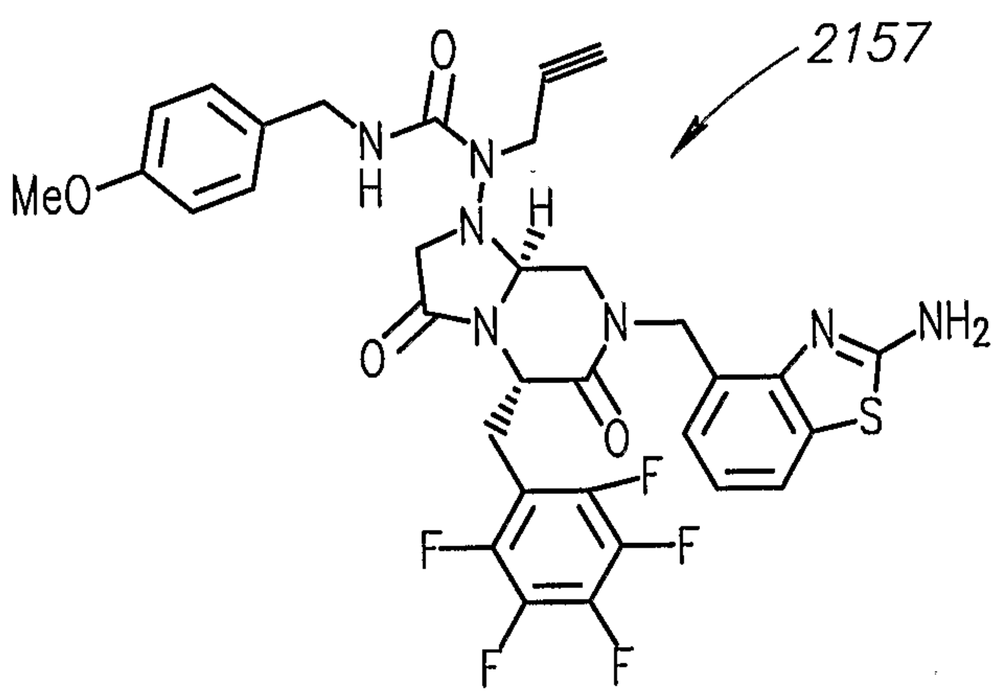
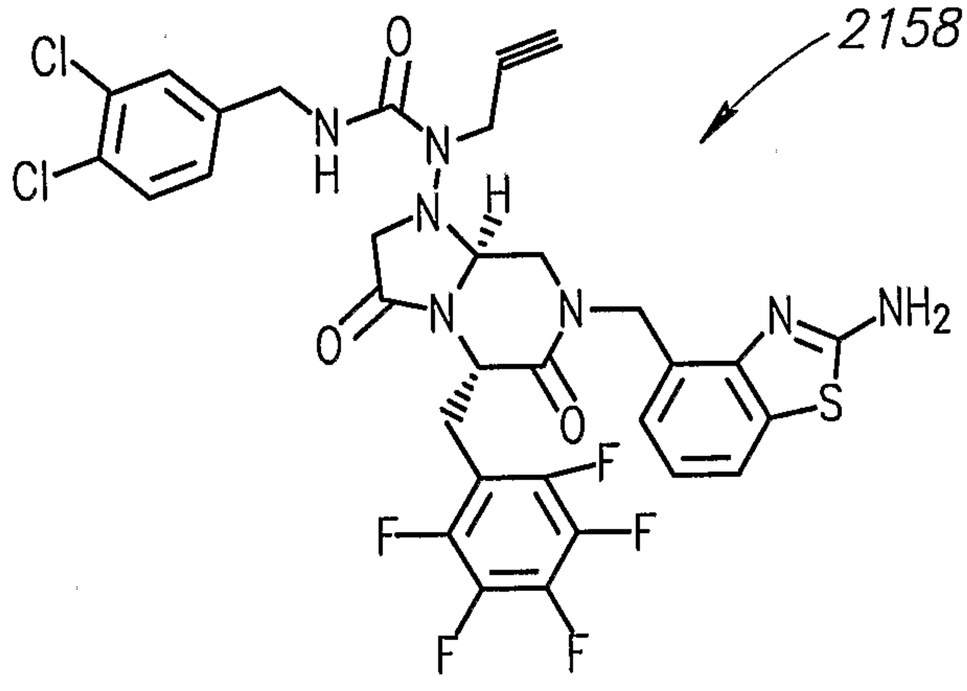


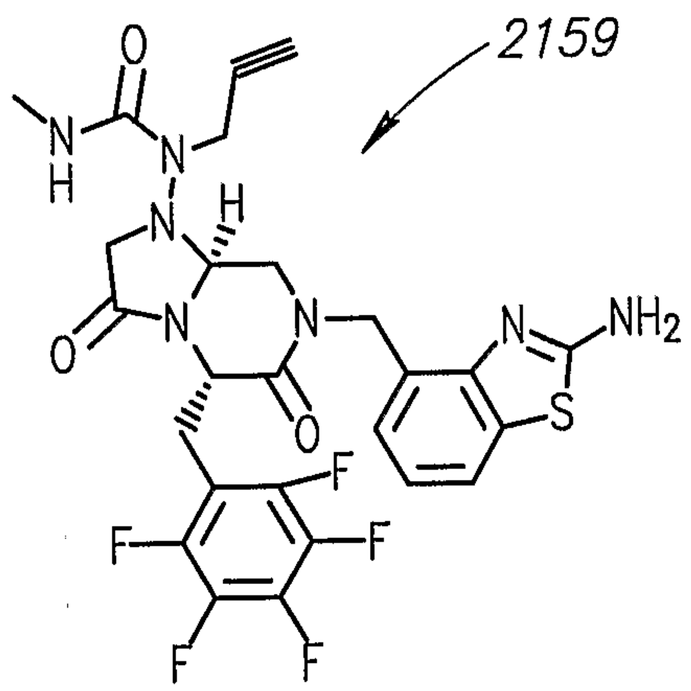
FIG.11U

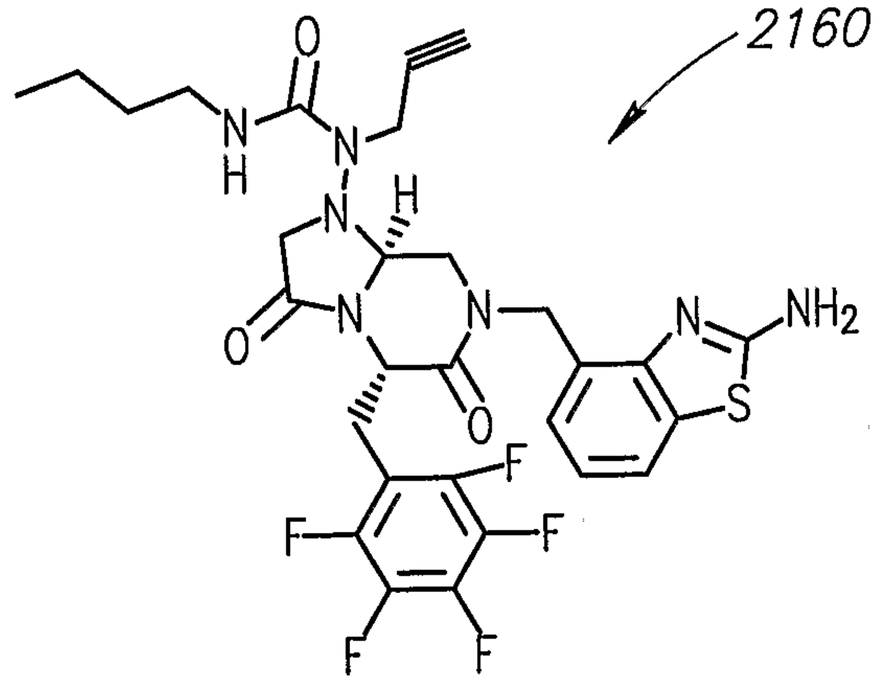


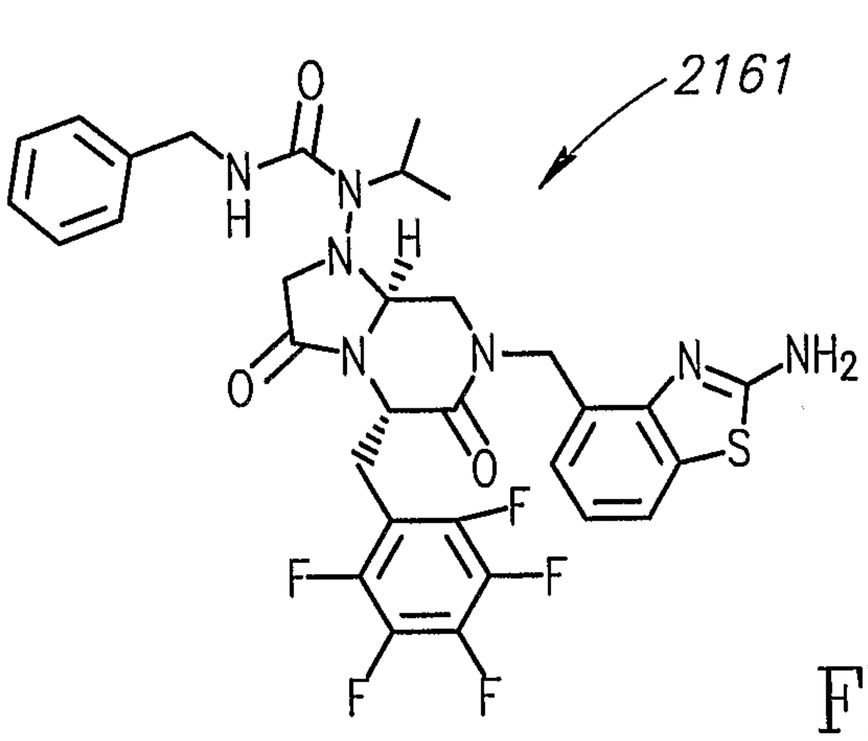












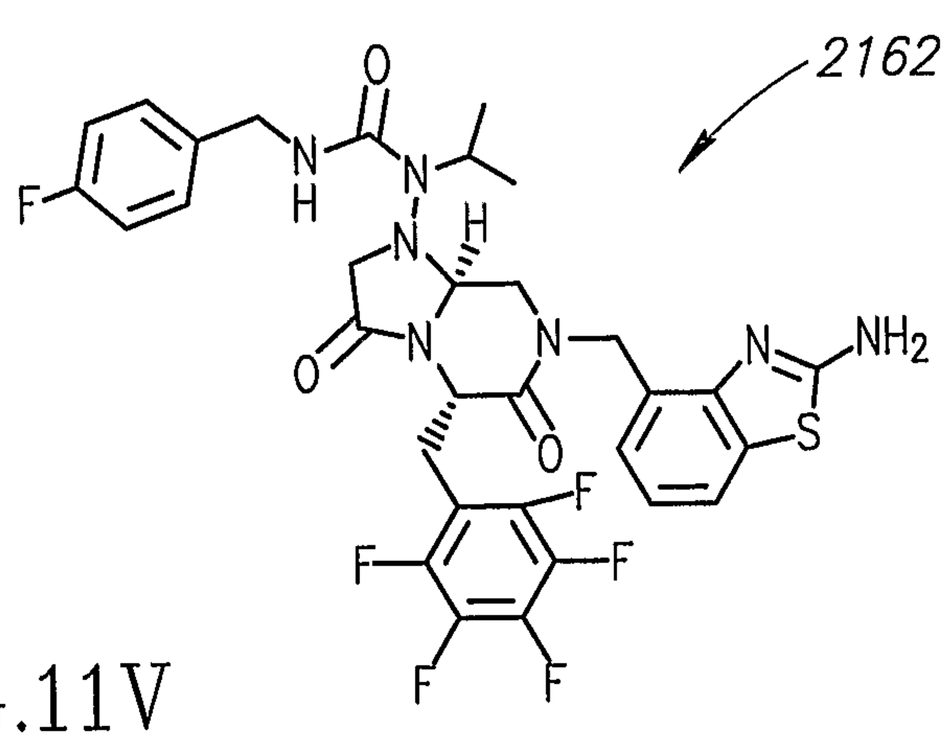
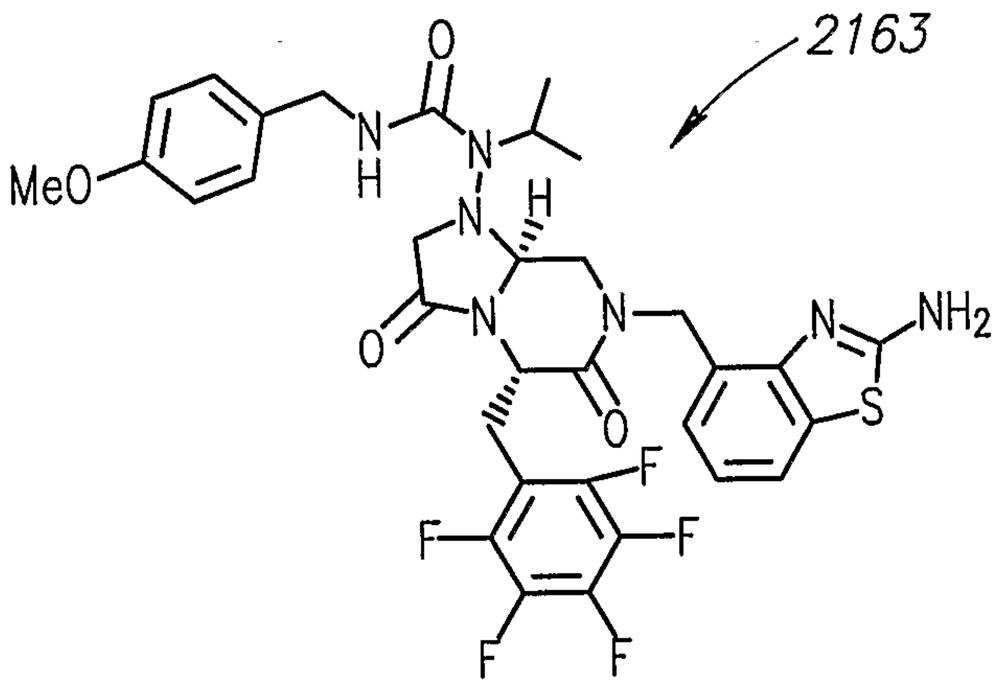


FIG.11V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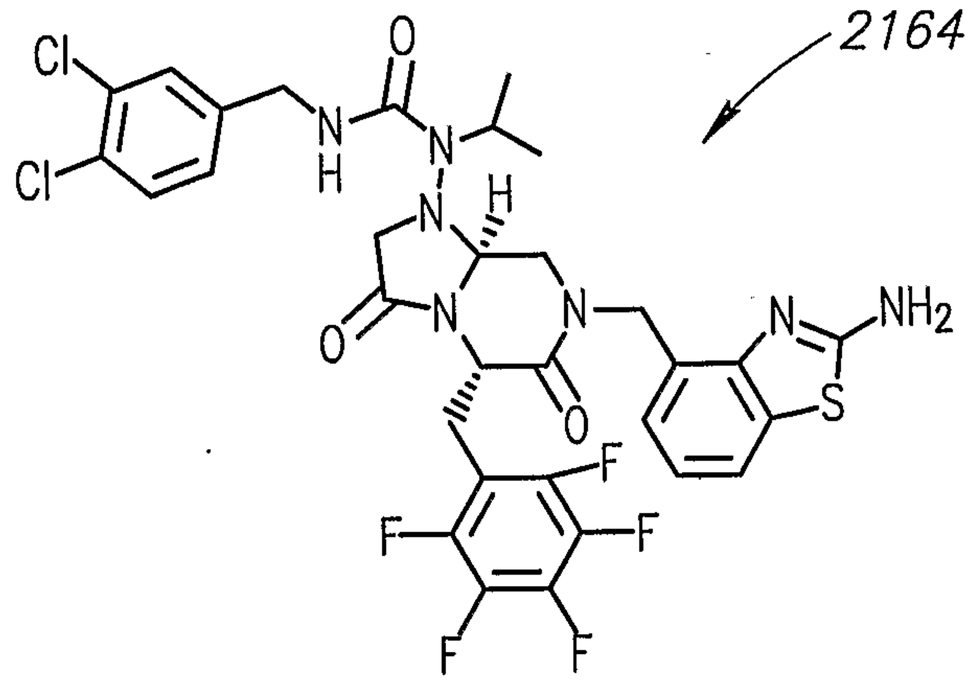
2164
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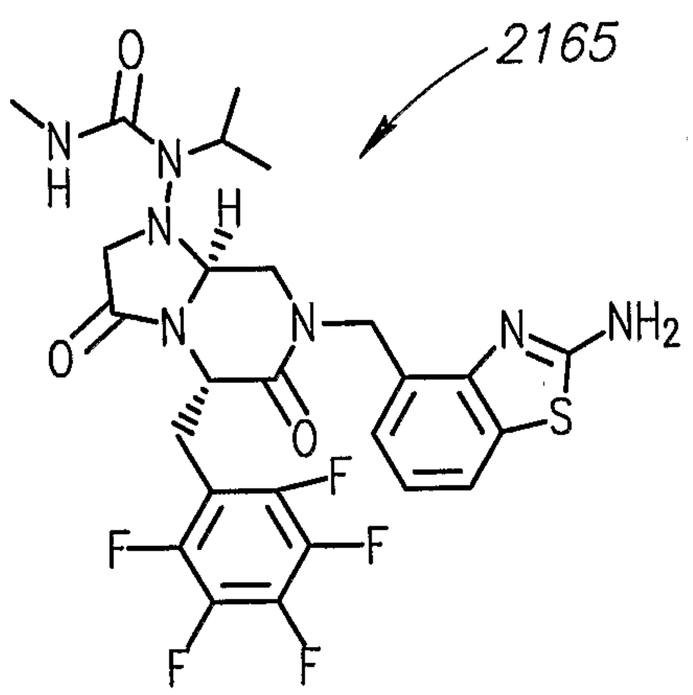
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NH2
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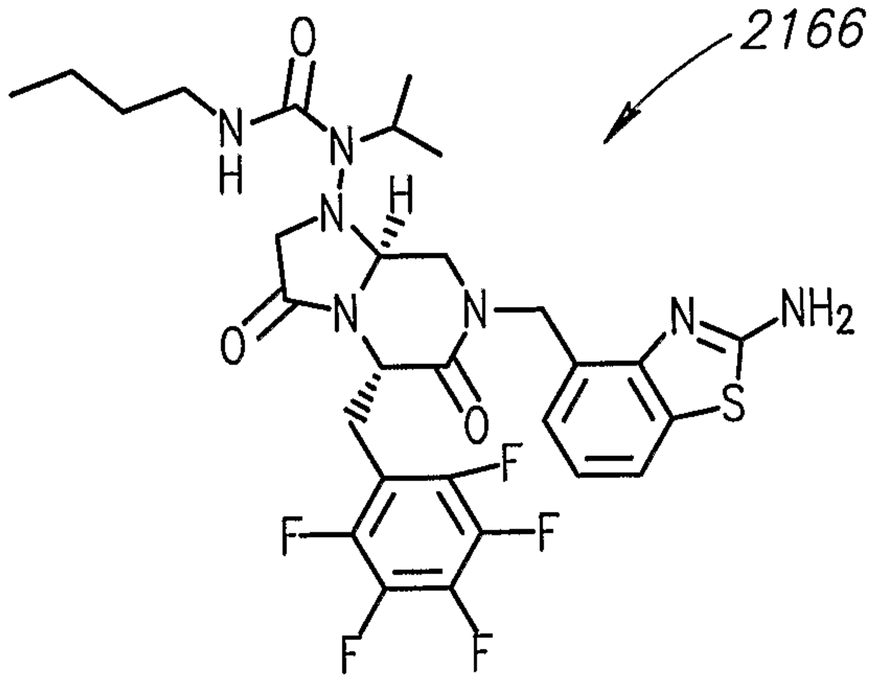
F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NH2
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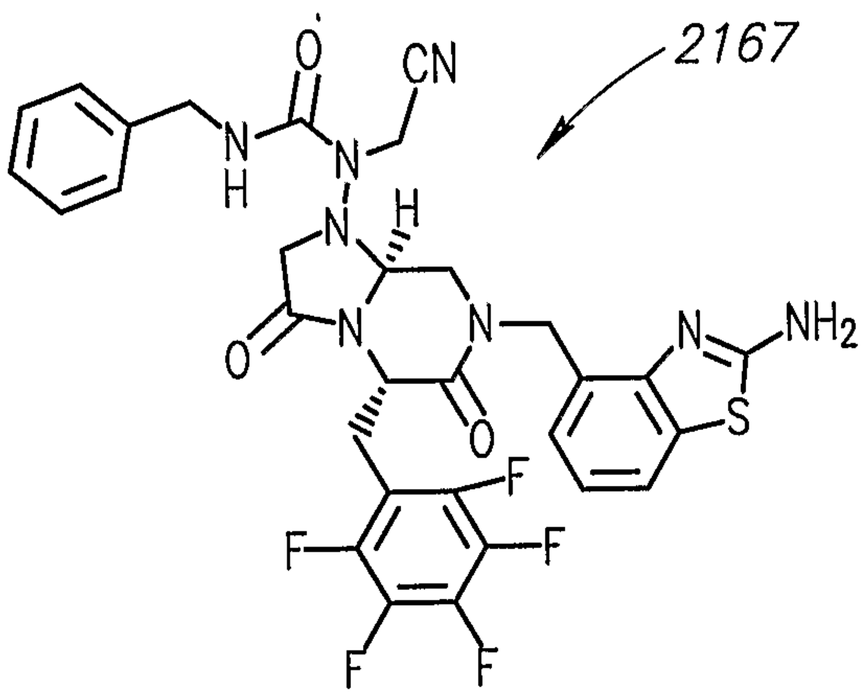
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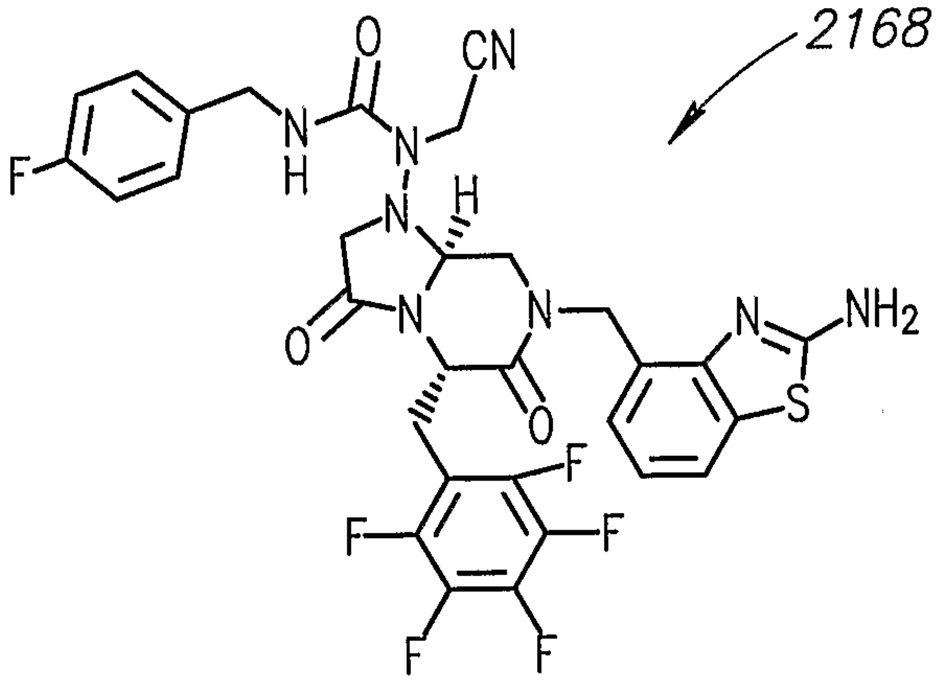
2168
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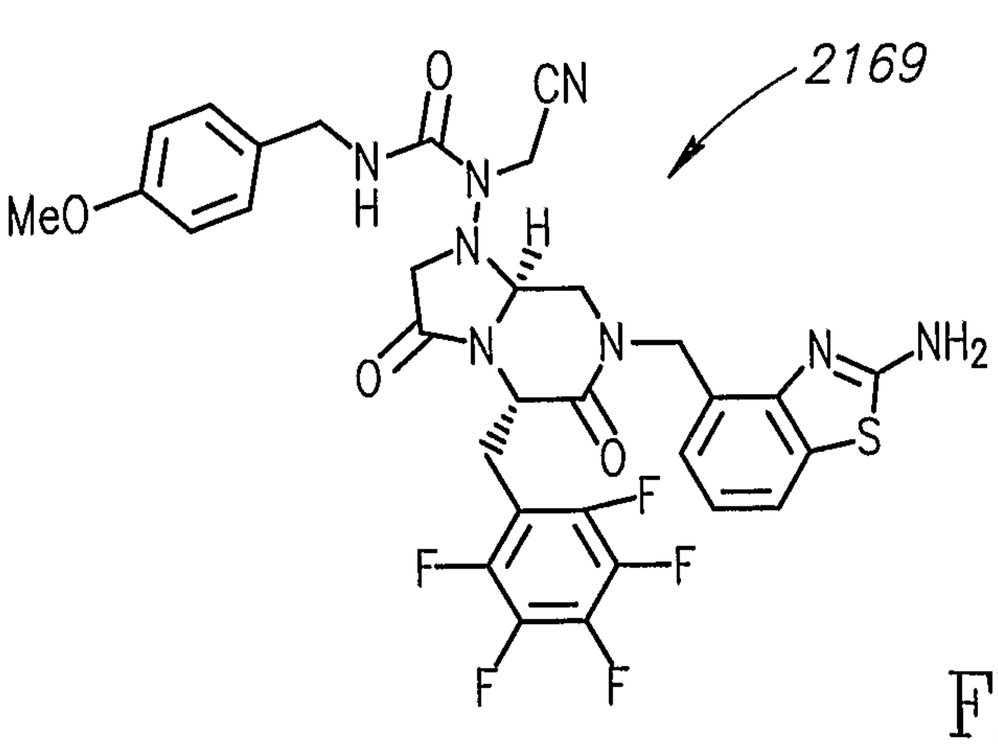
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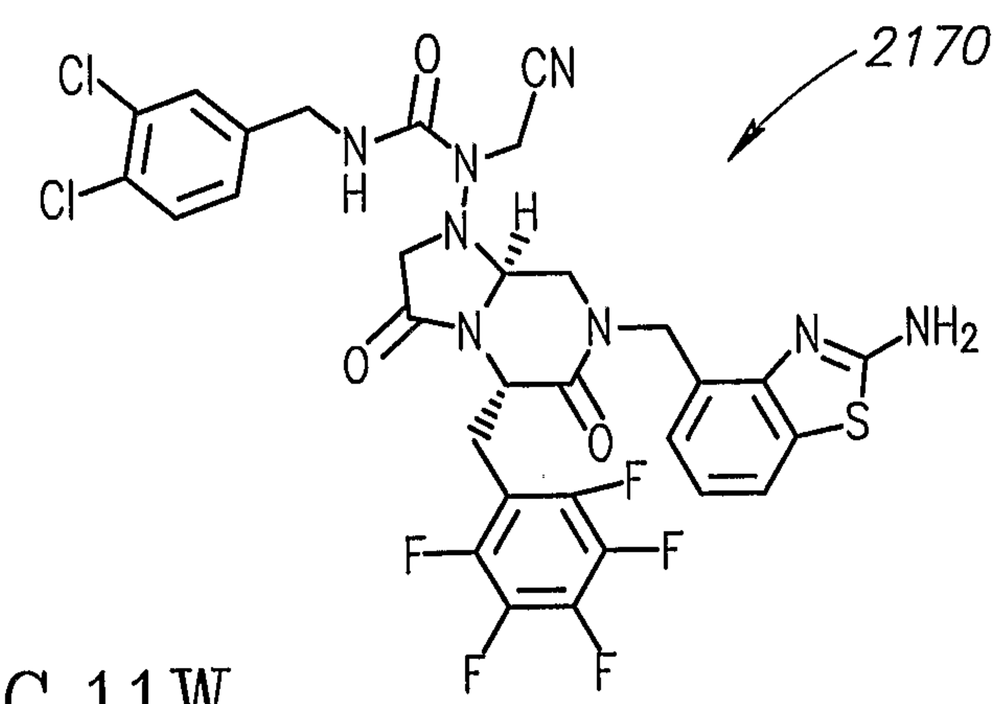
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NH2
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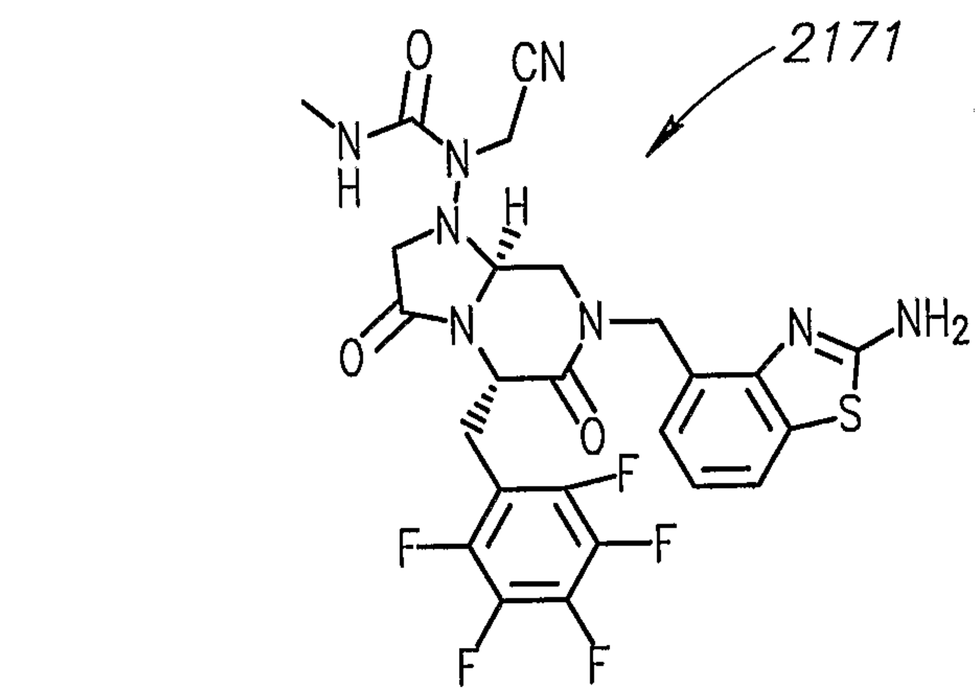
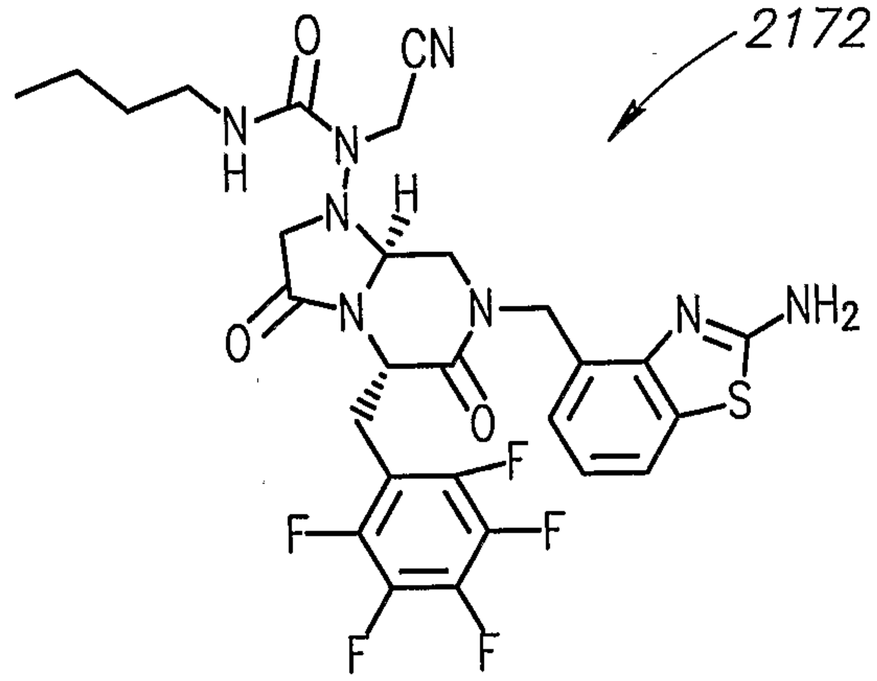
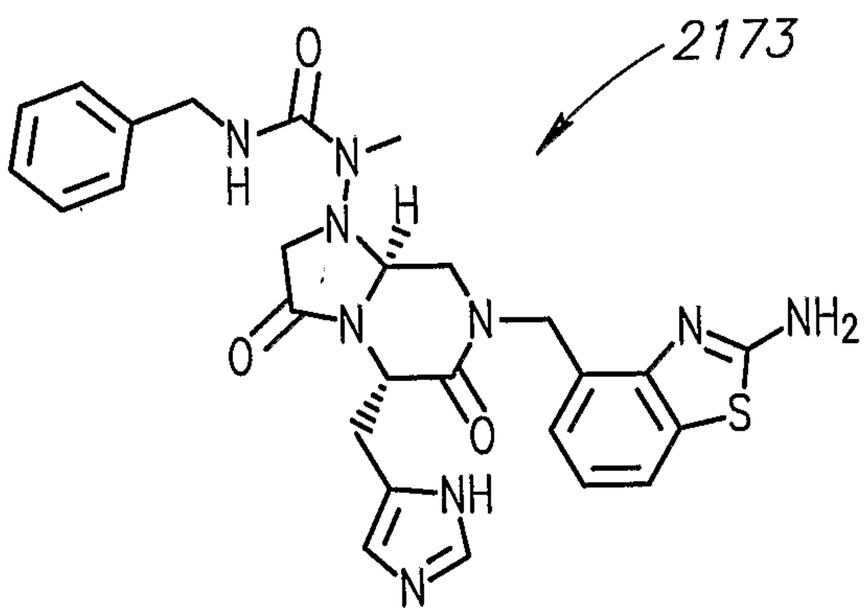
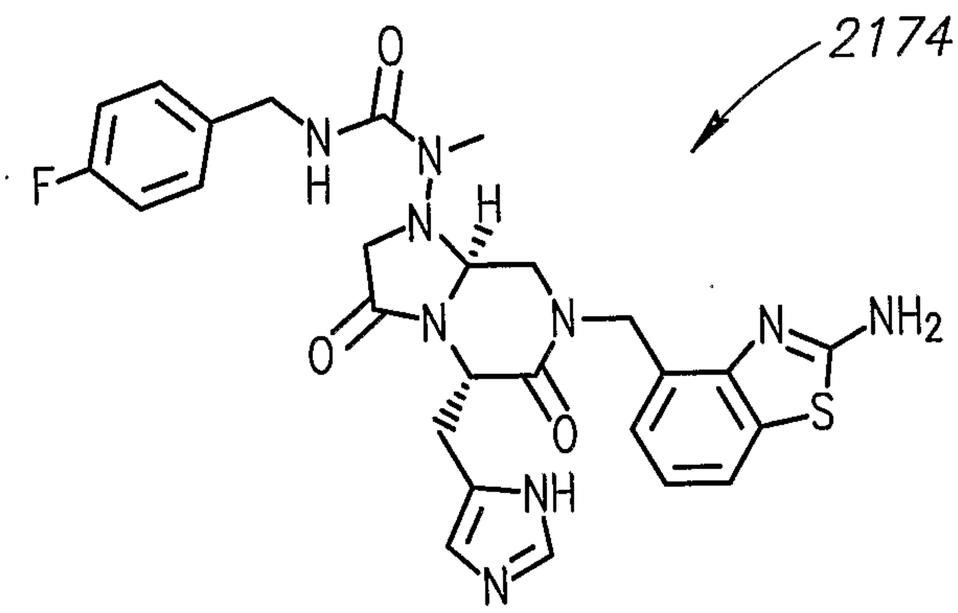
F
F

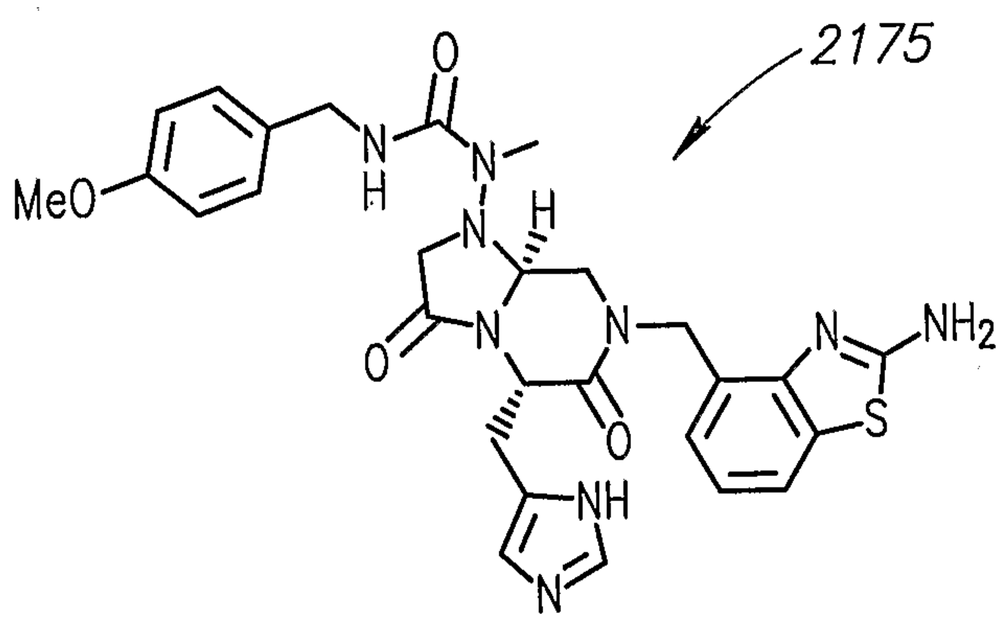
FIG.11W

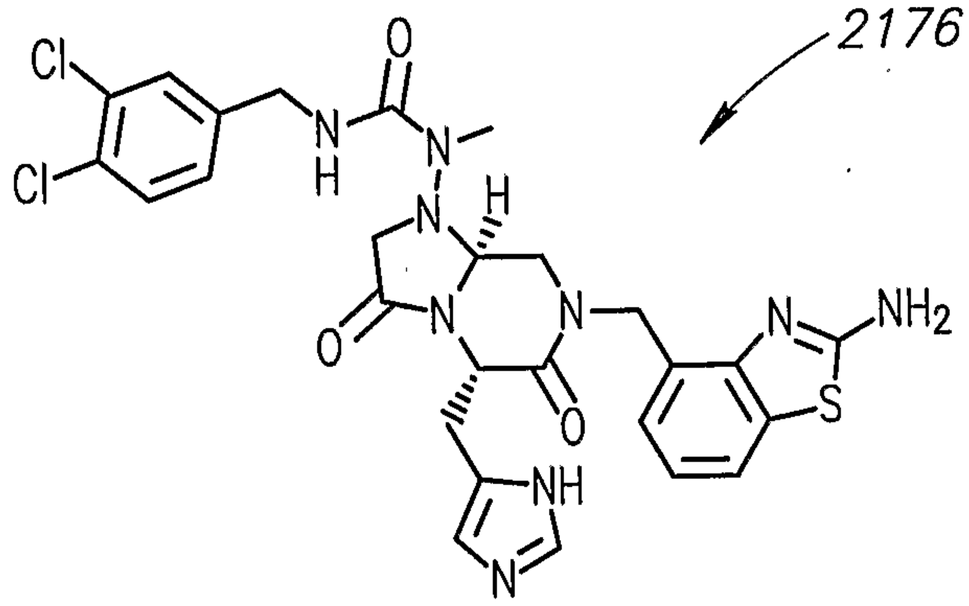


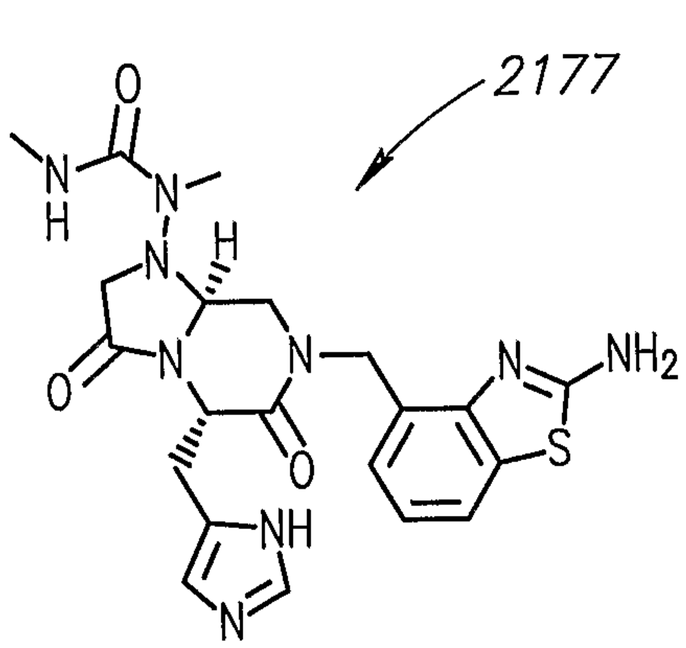












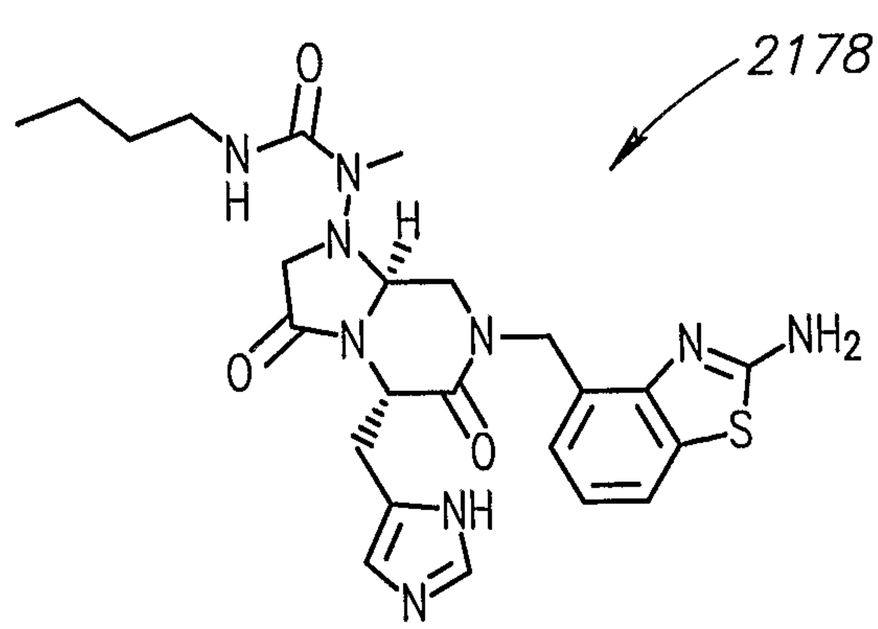
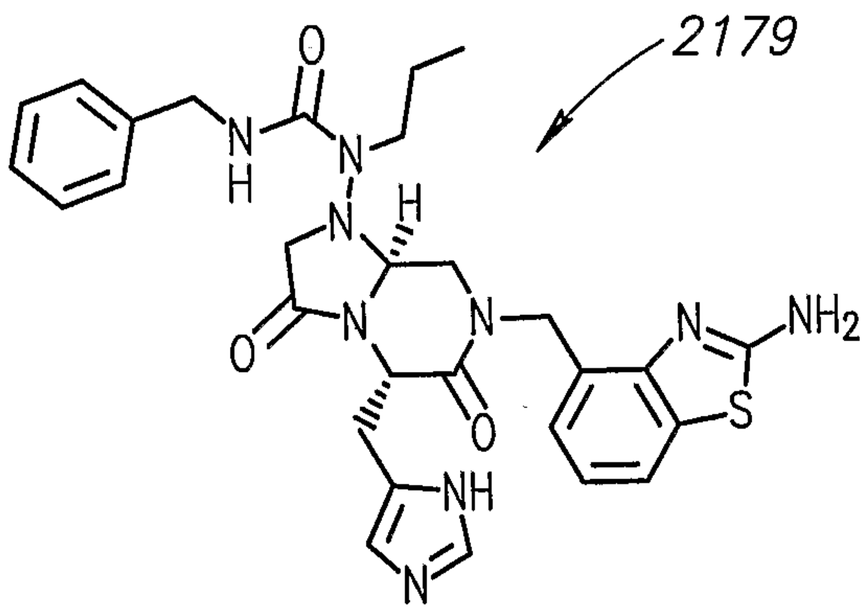
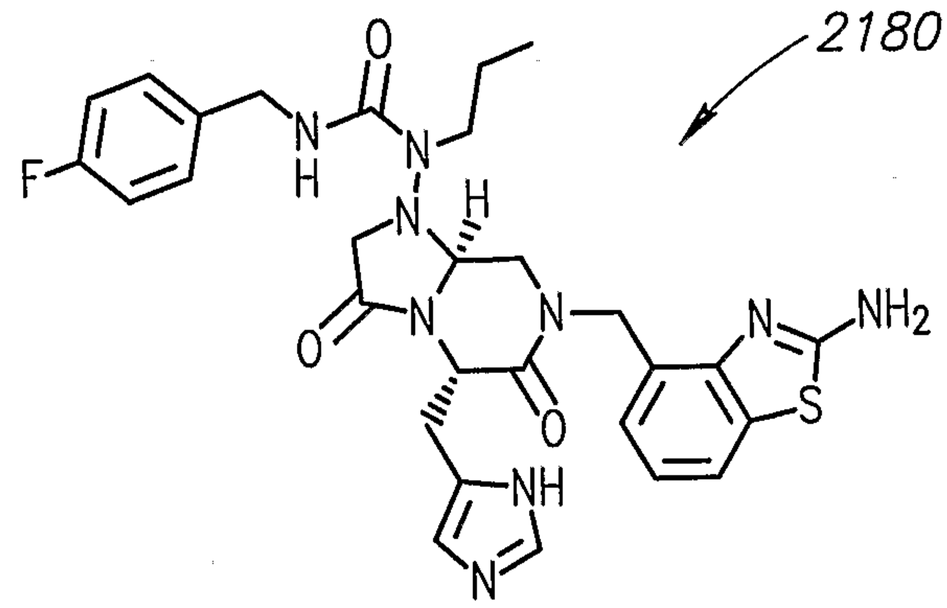
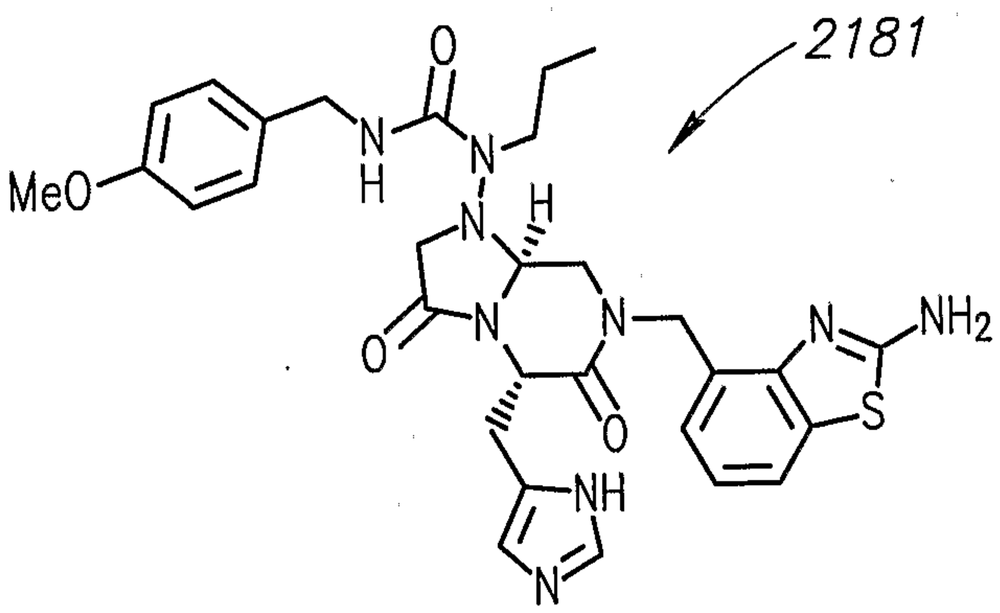
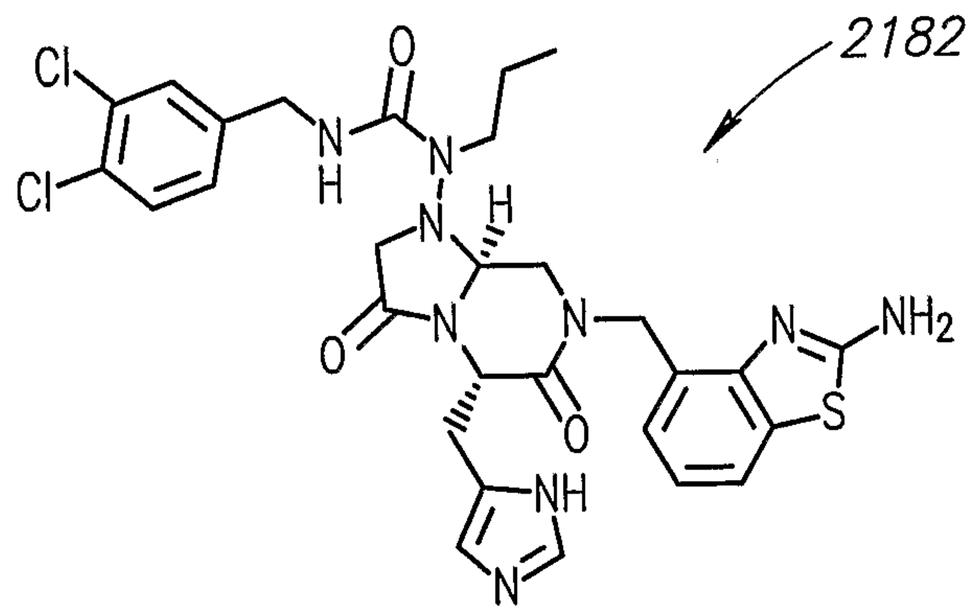


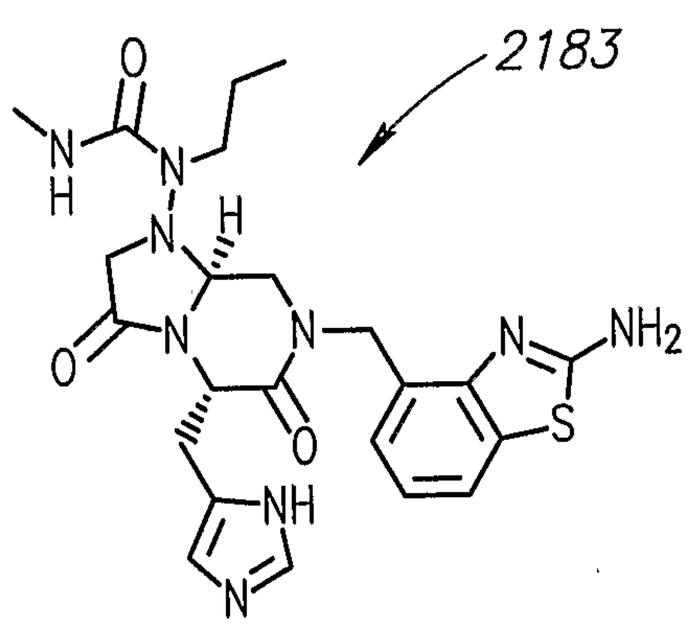
FIG.11X

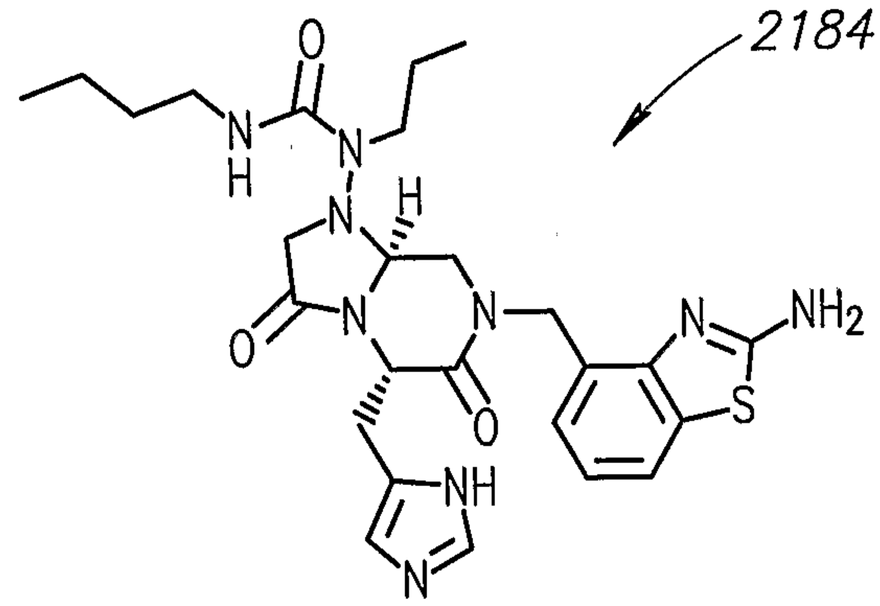


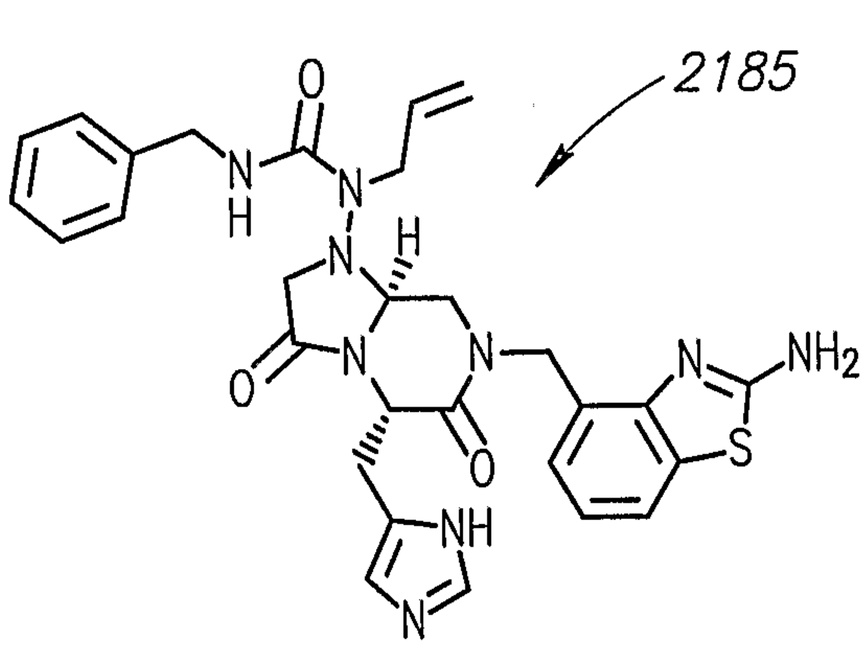












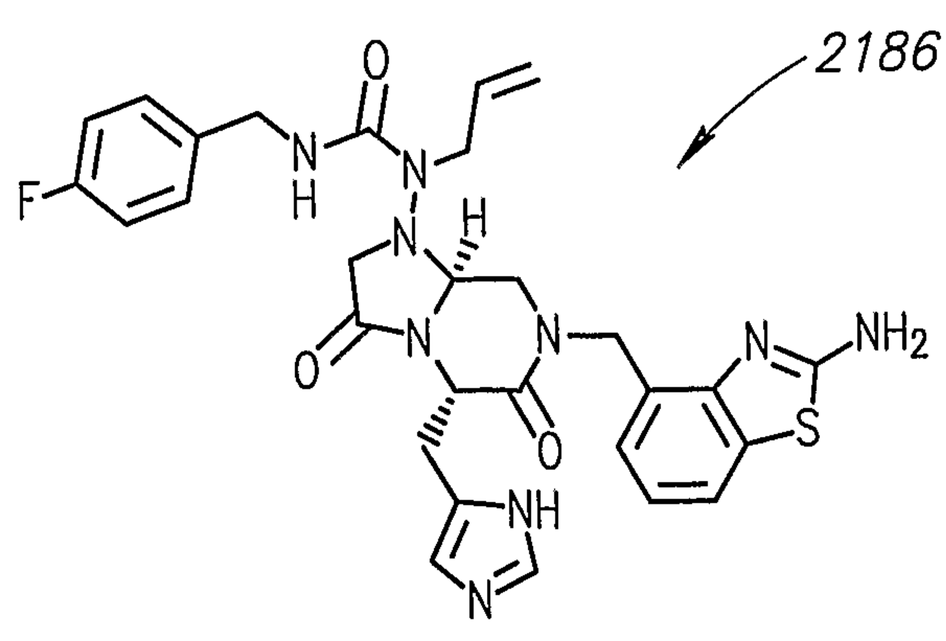
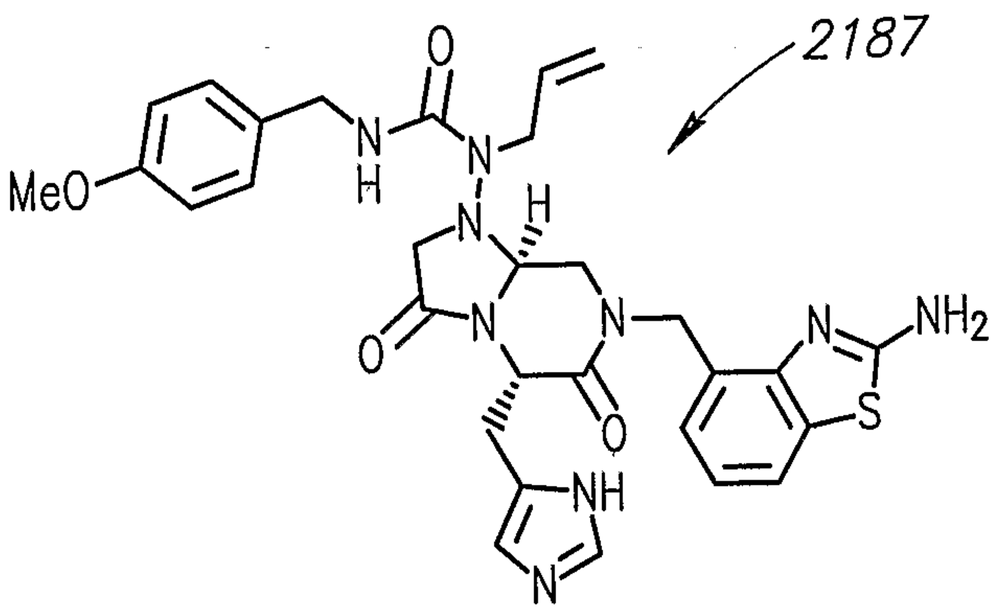


FIG.11Y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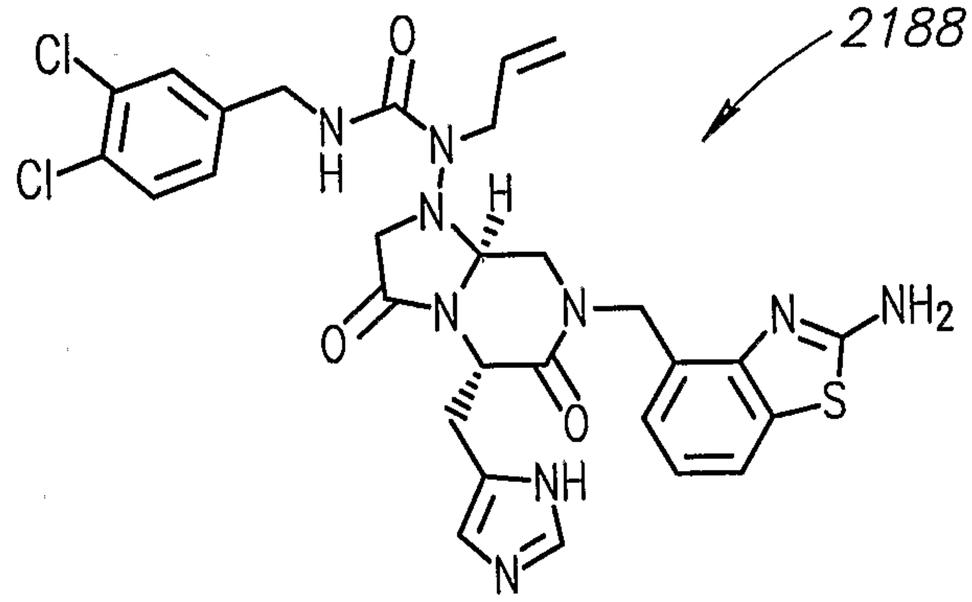
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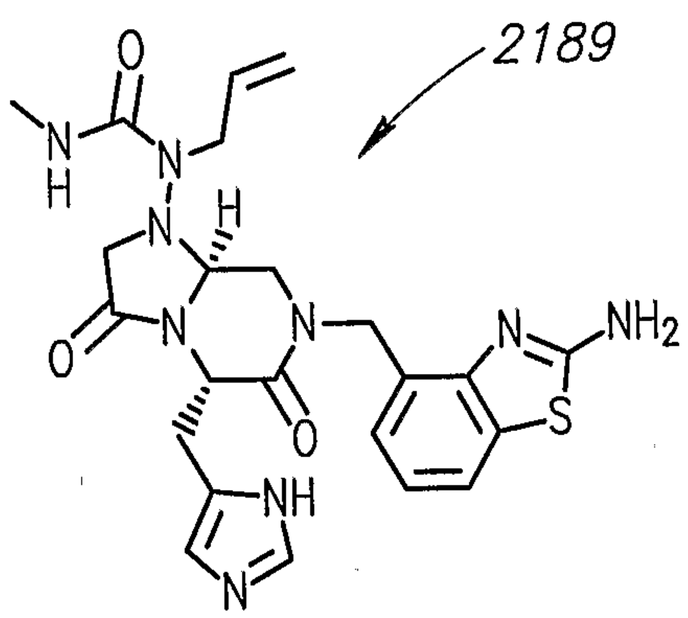
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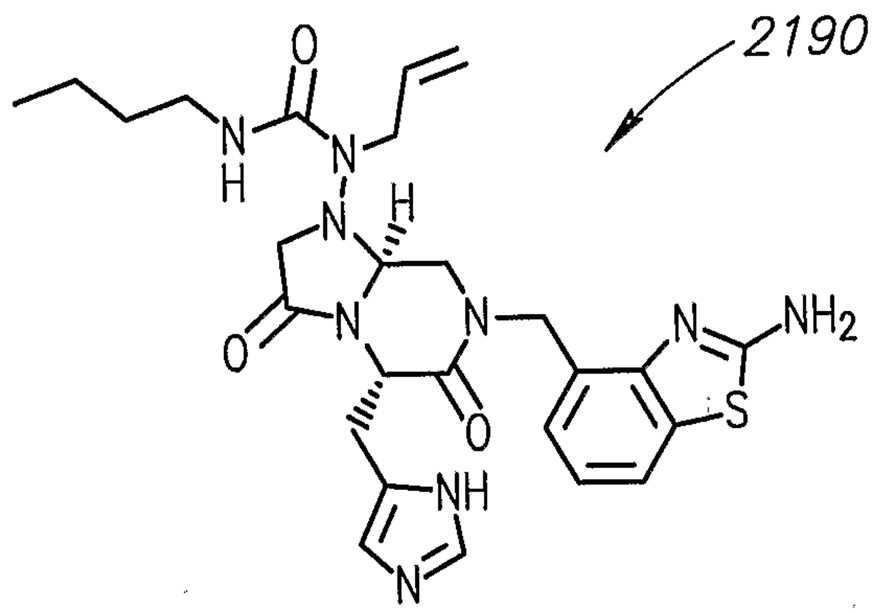
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NH2
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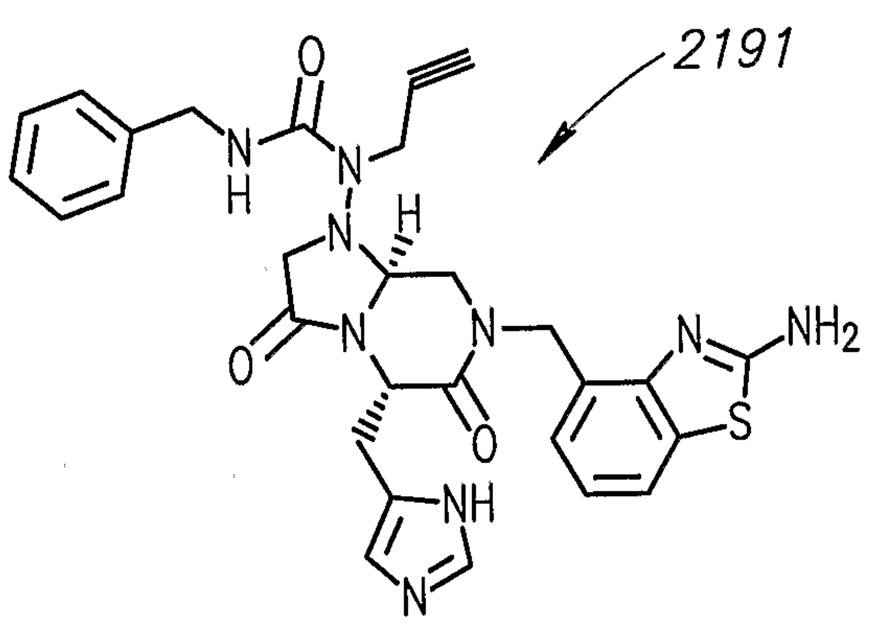
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NH
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NH2
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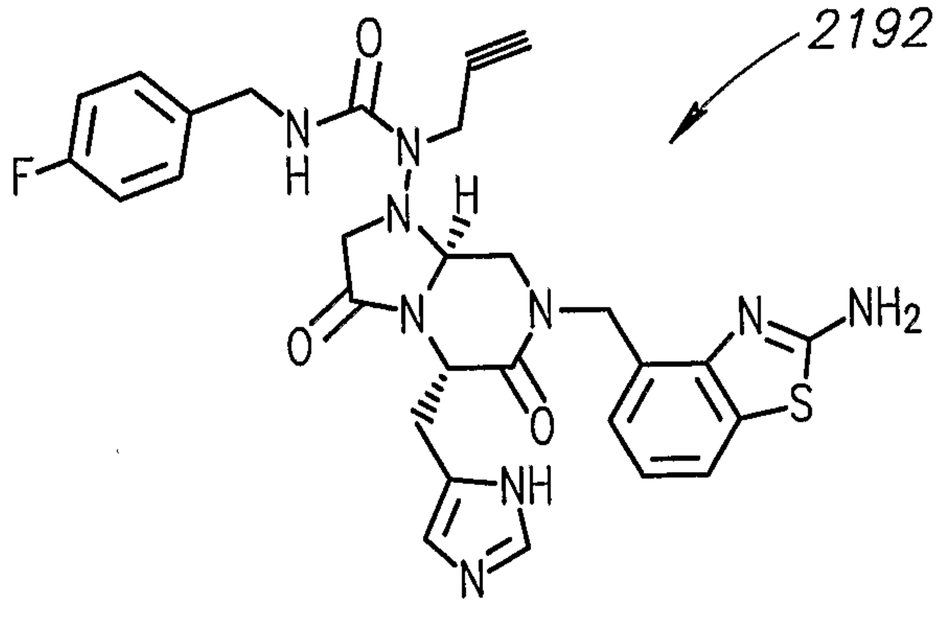
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NH2
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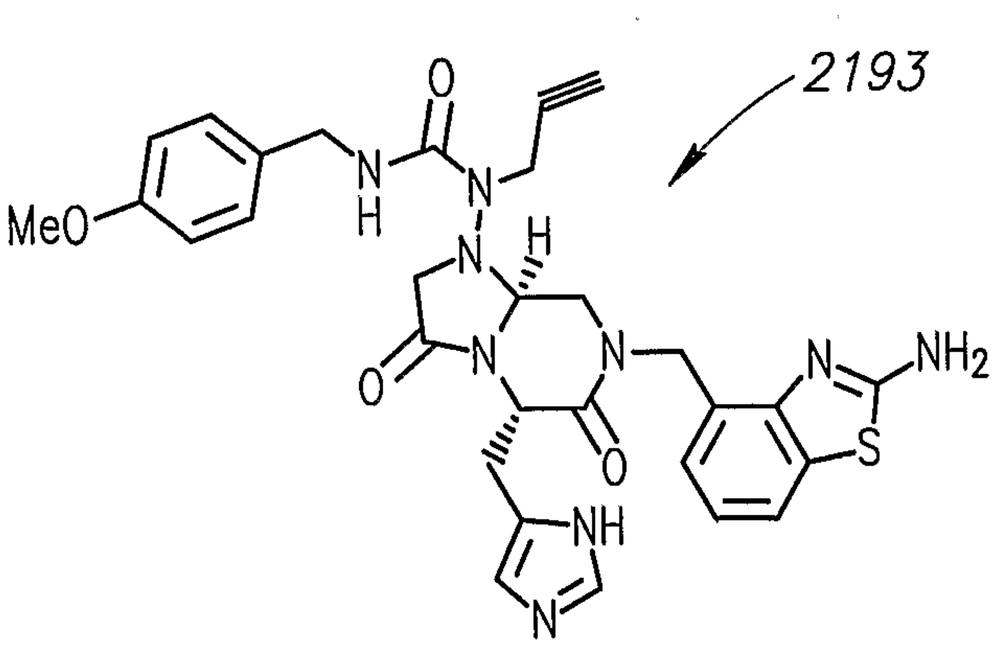
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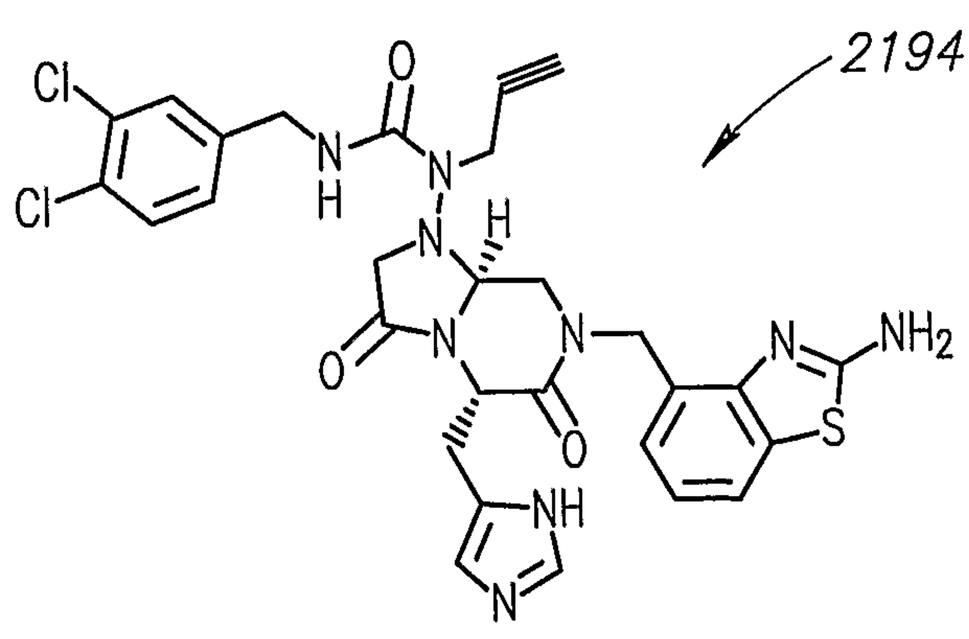
N
N
NH2
S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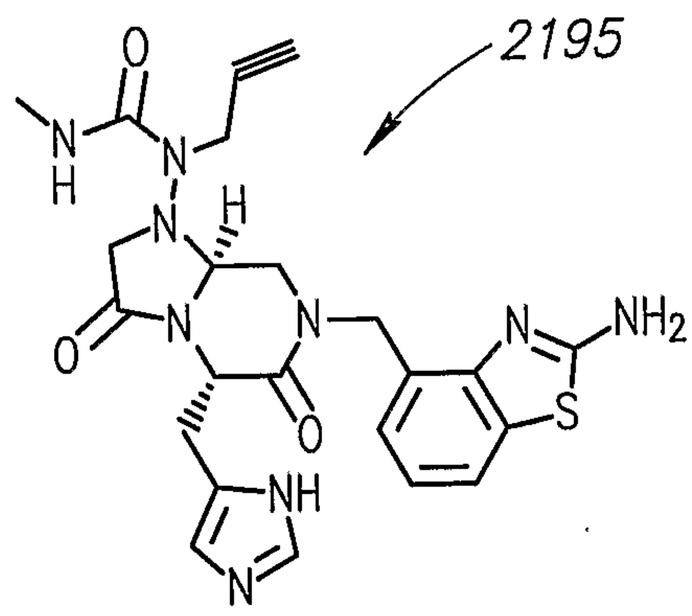
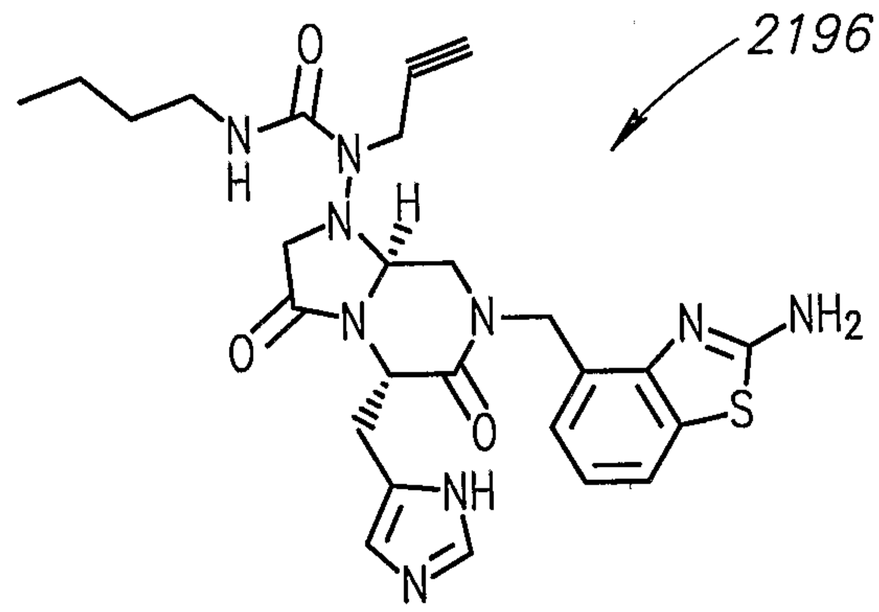
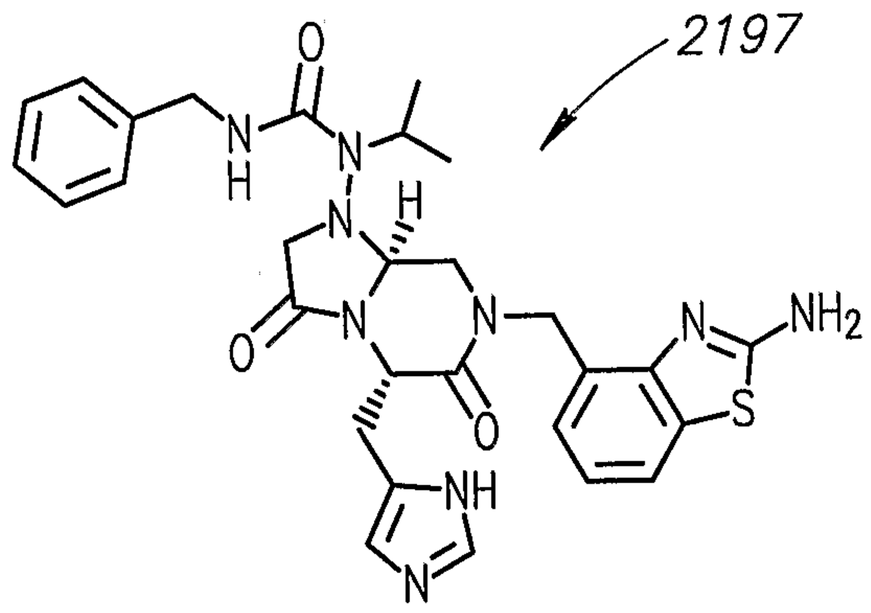
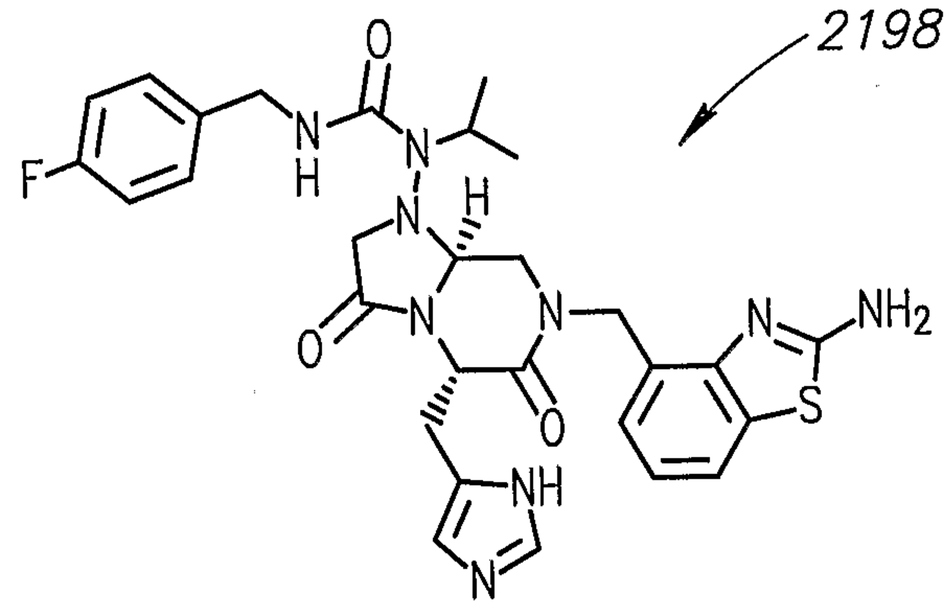
H
O
N
O
N
NH
N
N
NH2
S

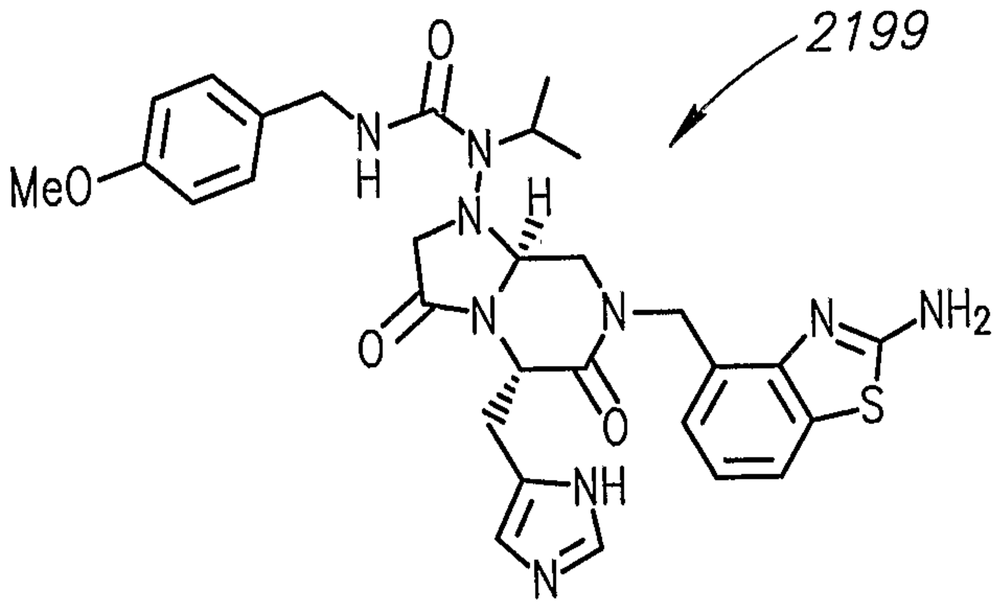
FIG.11Z











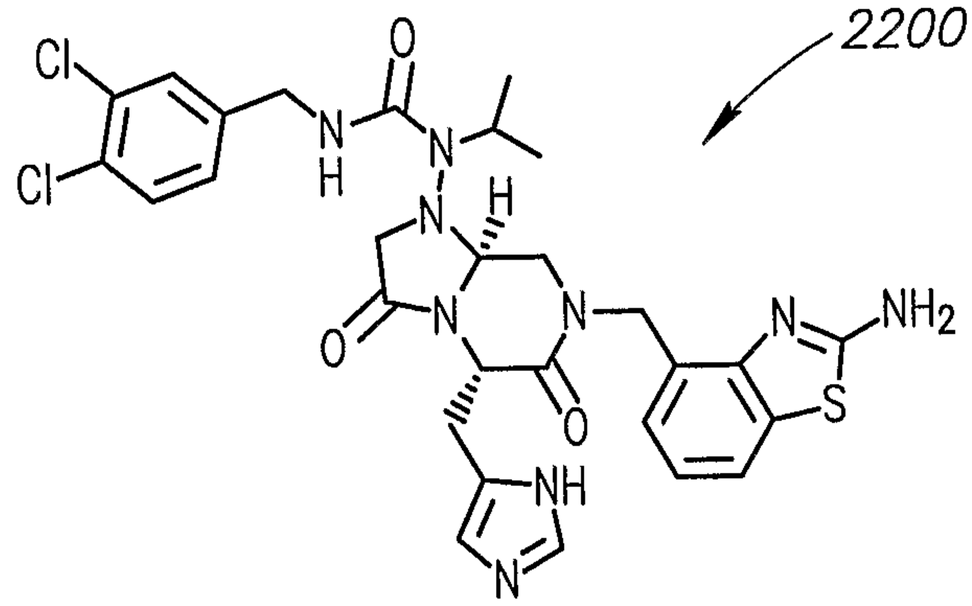
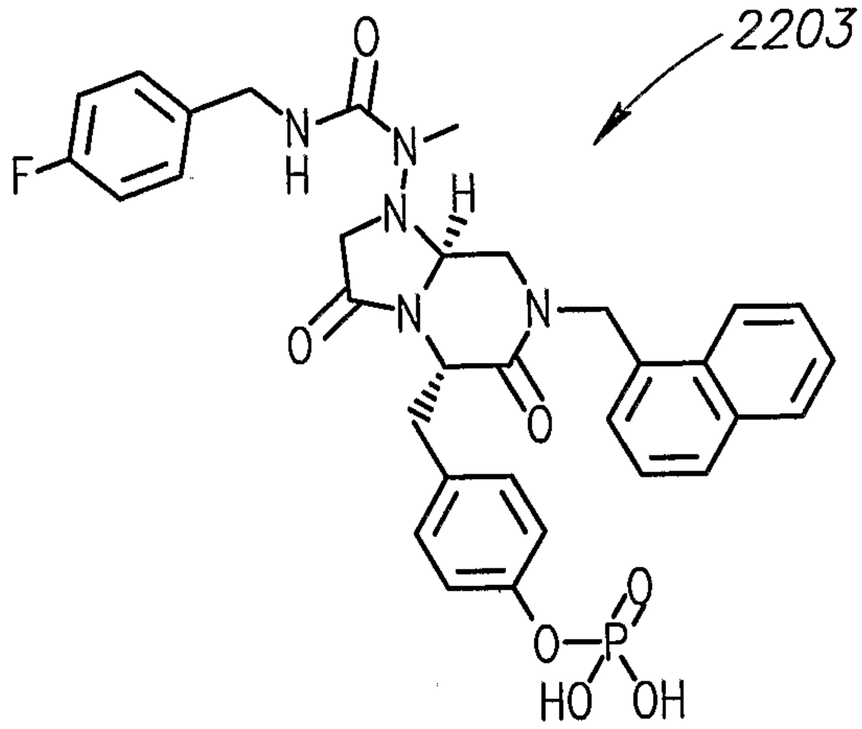
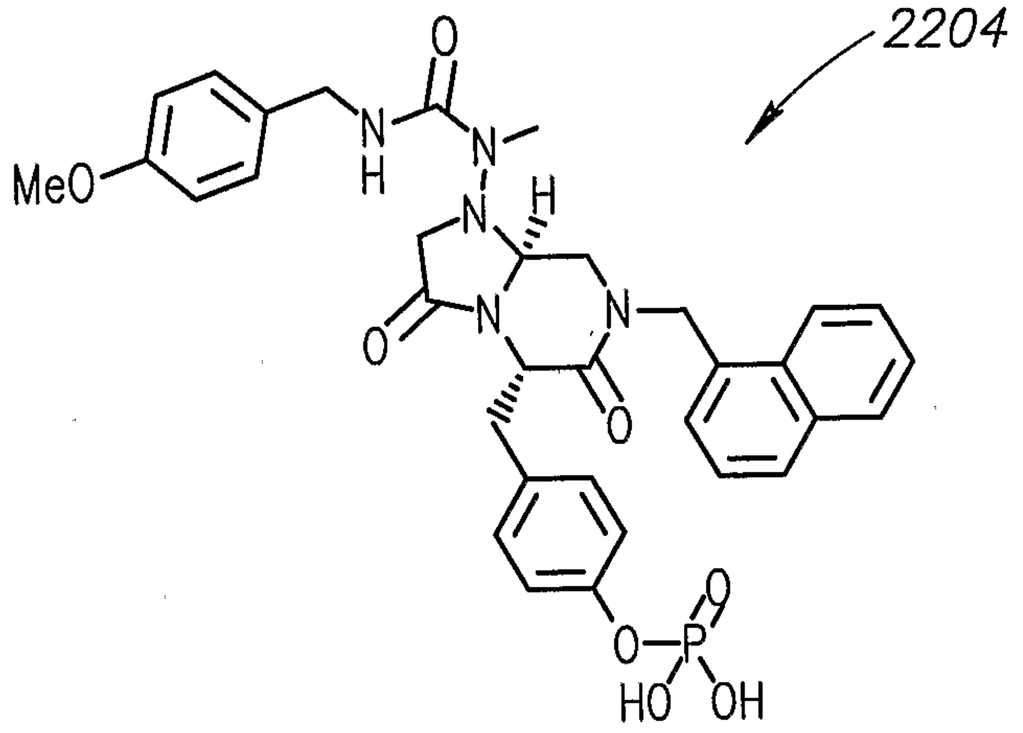


FIG.11AA

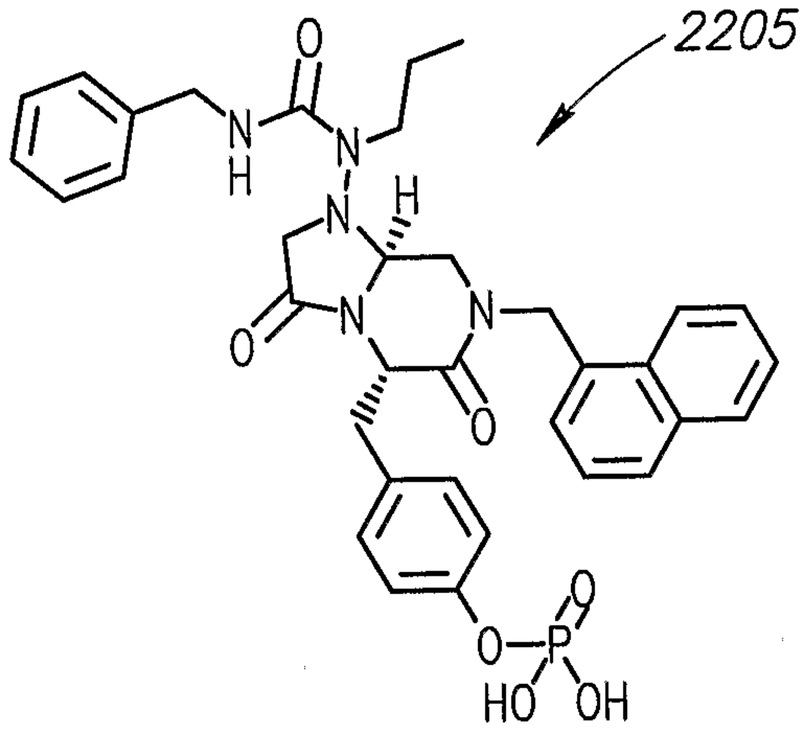
2203



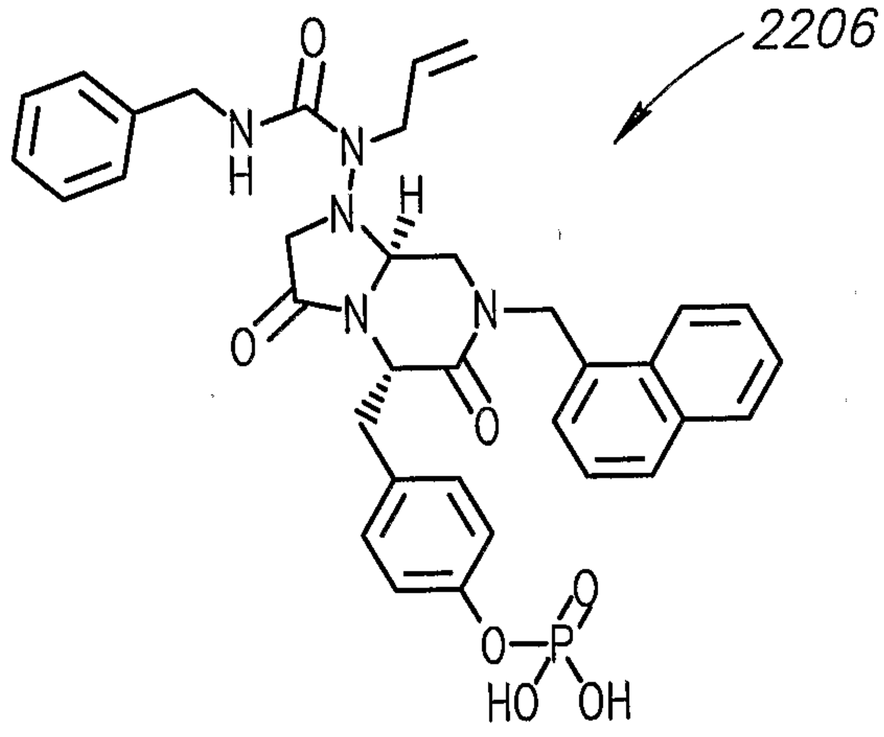
2204



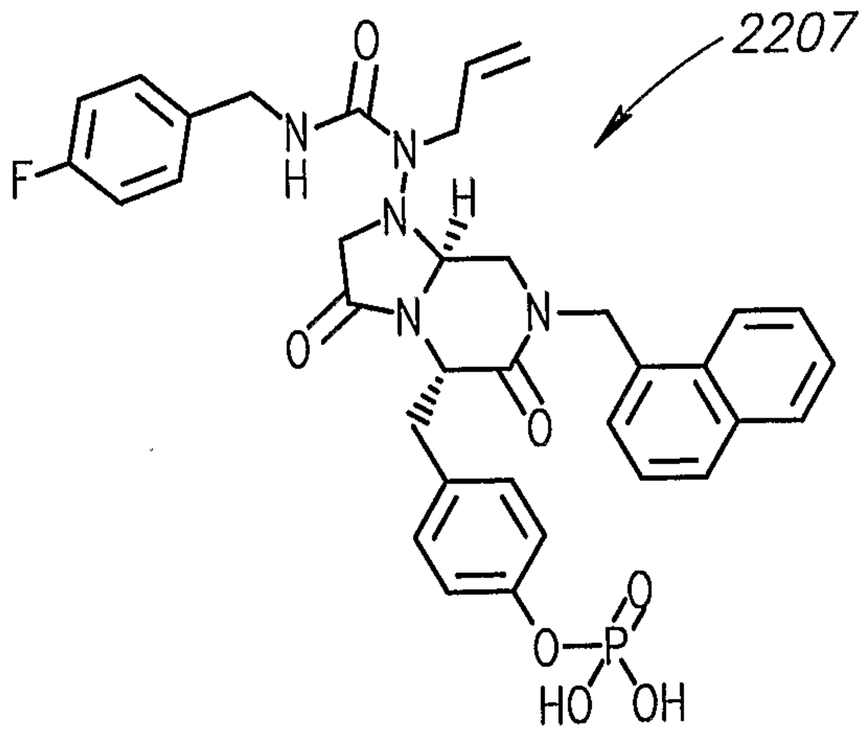
2205



2206



2207



2208

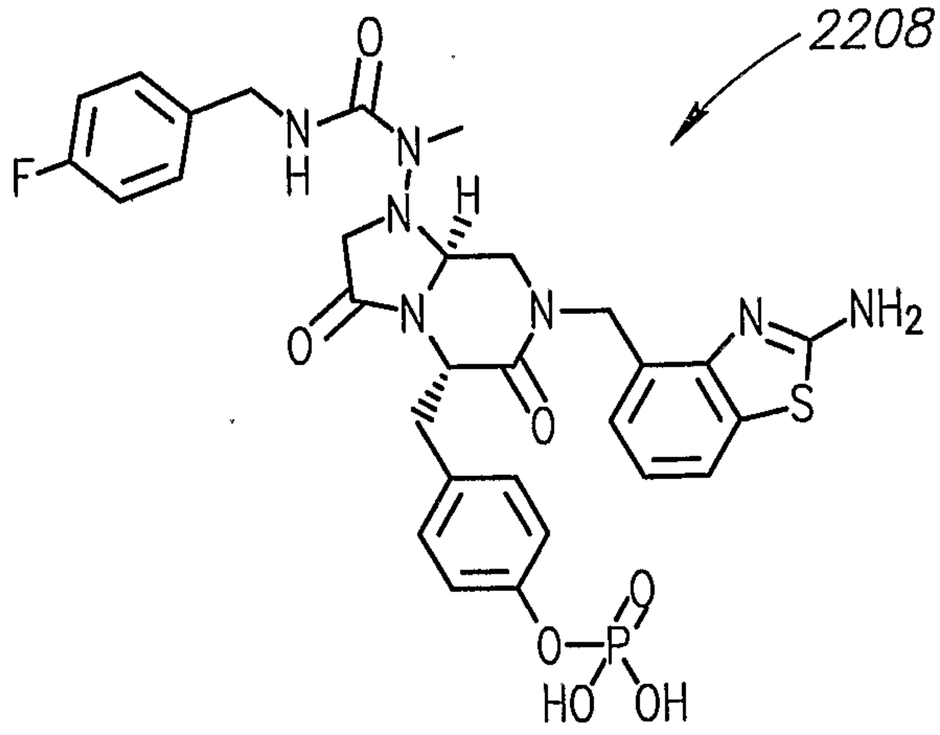
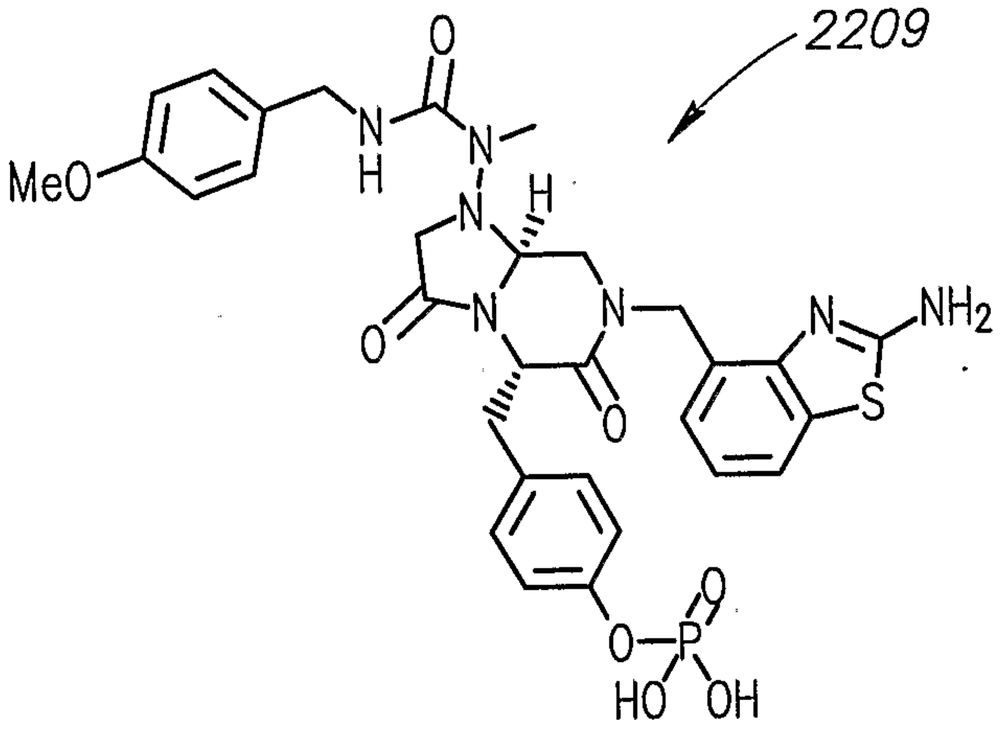
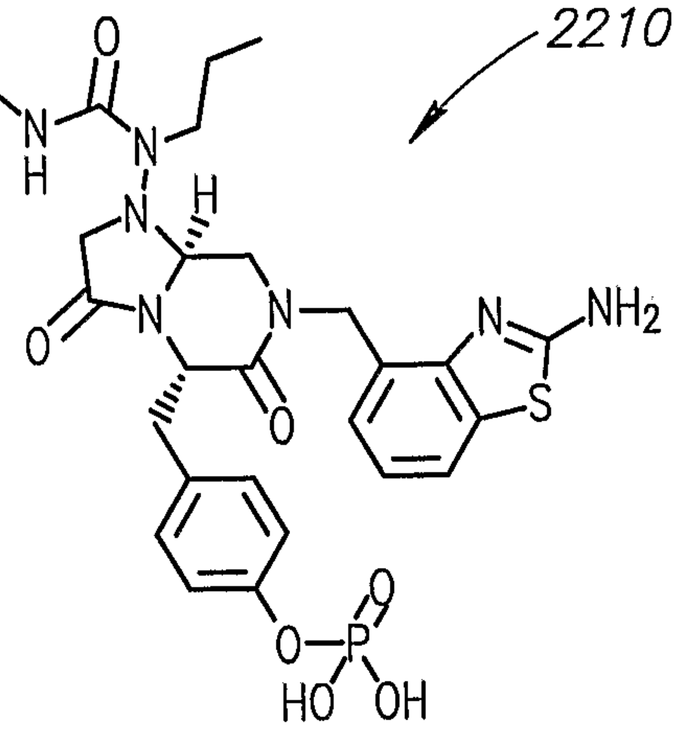


FIG.12A

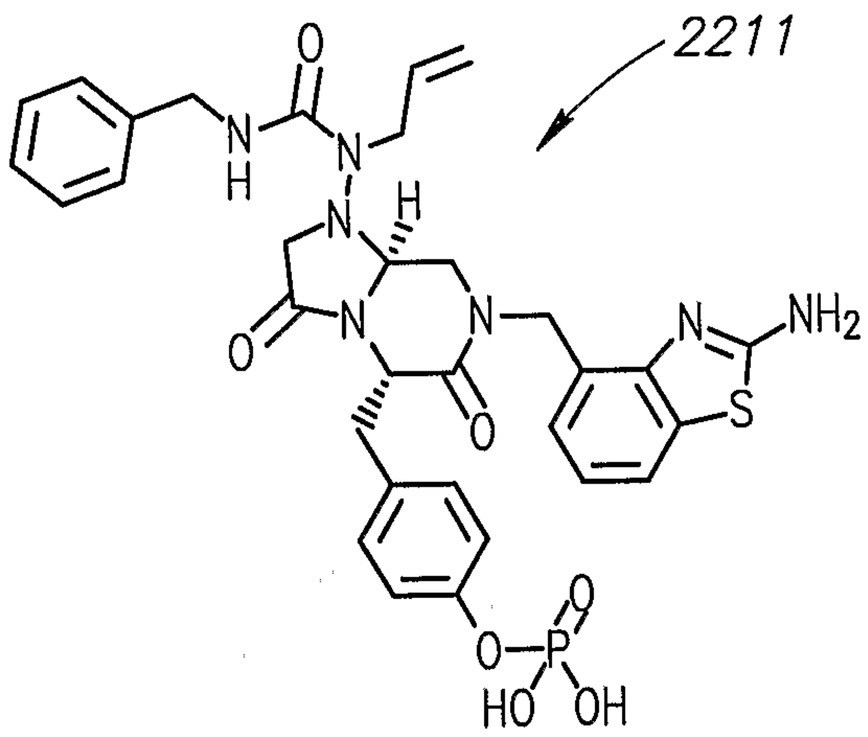
2209



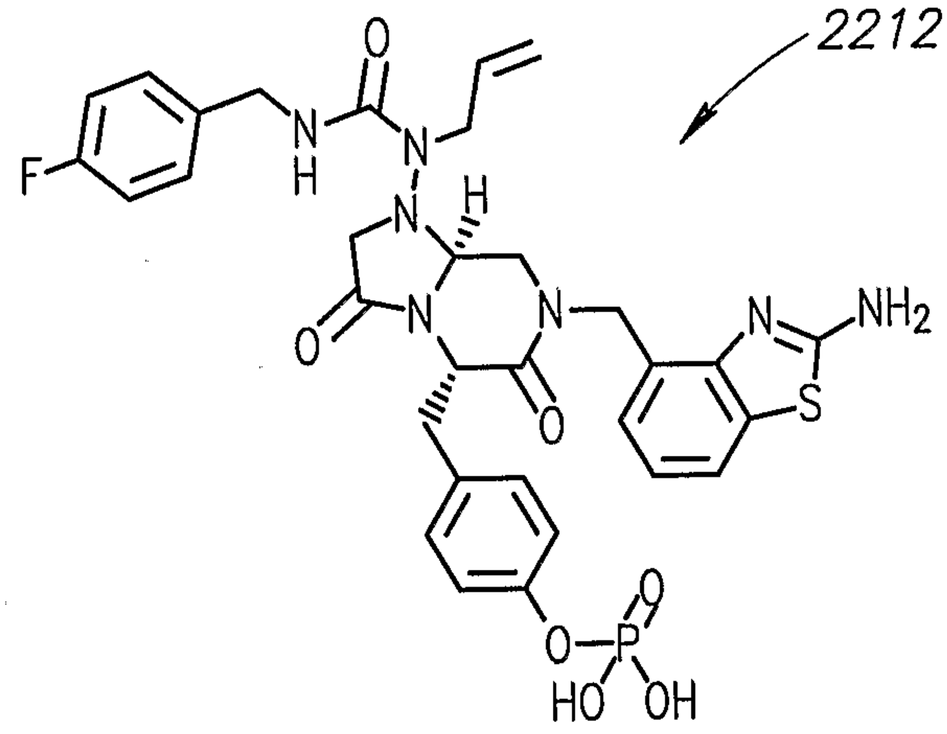
2210



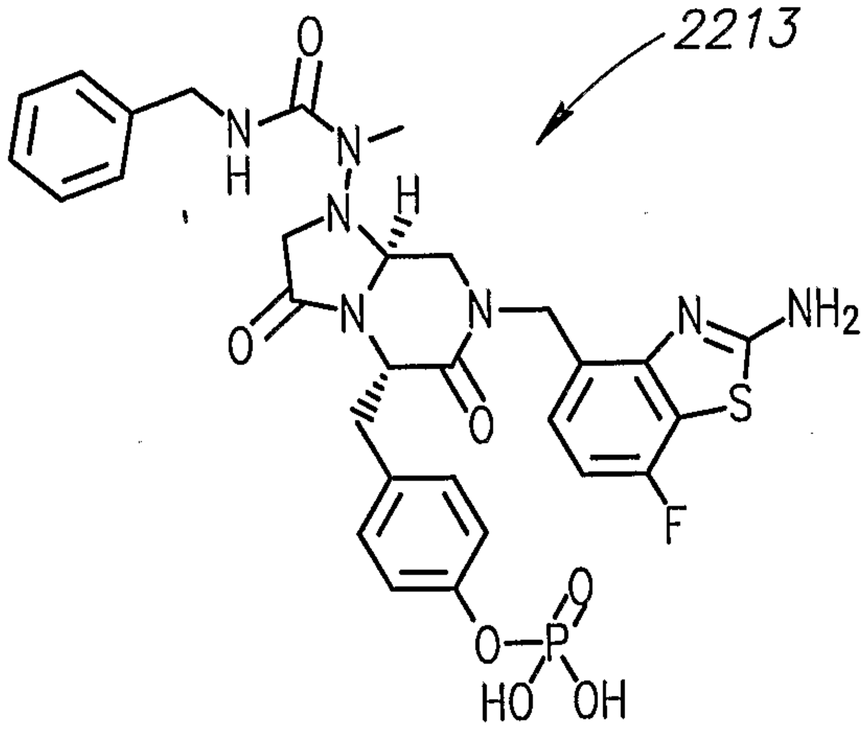
2211



2212



2213



2214

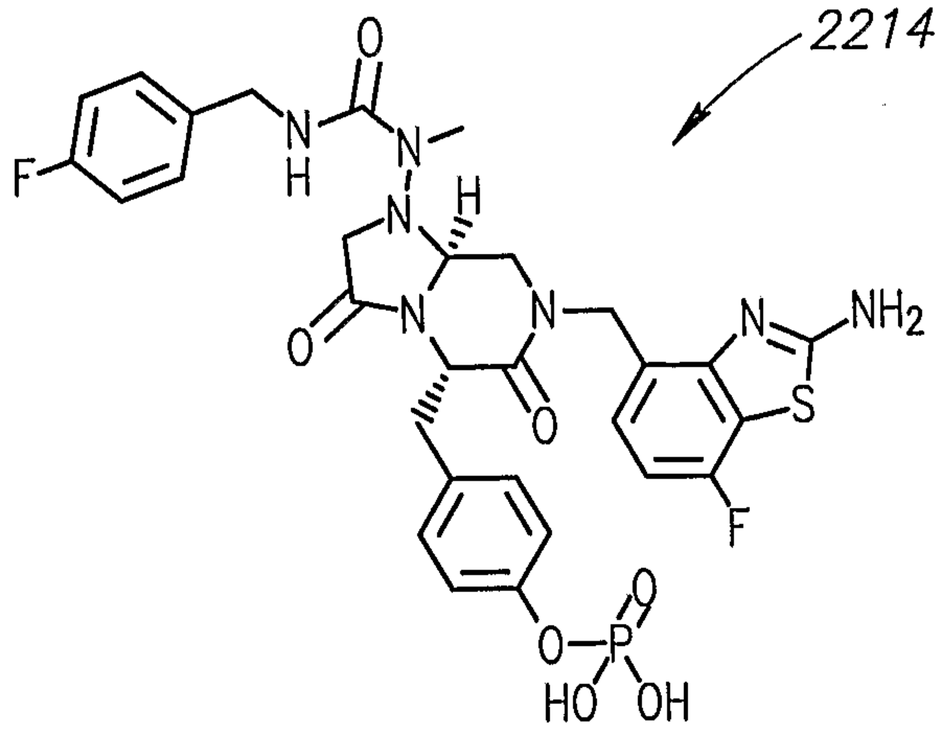
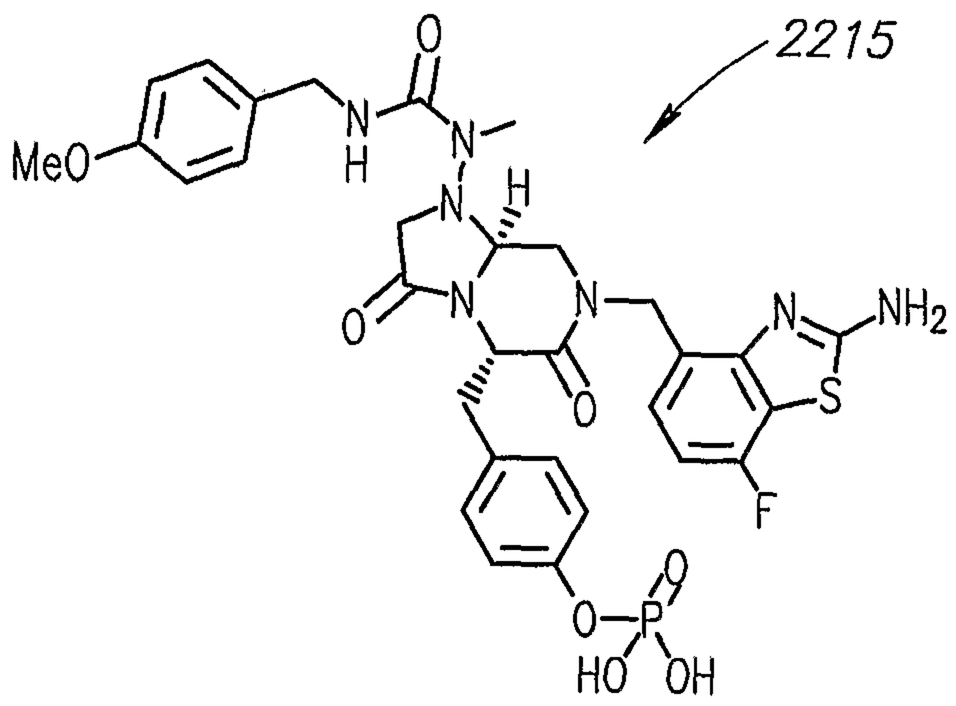
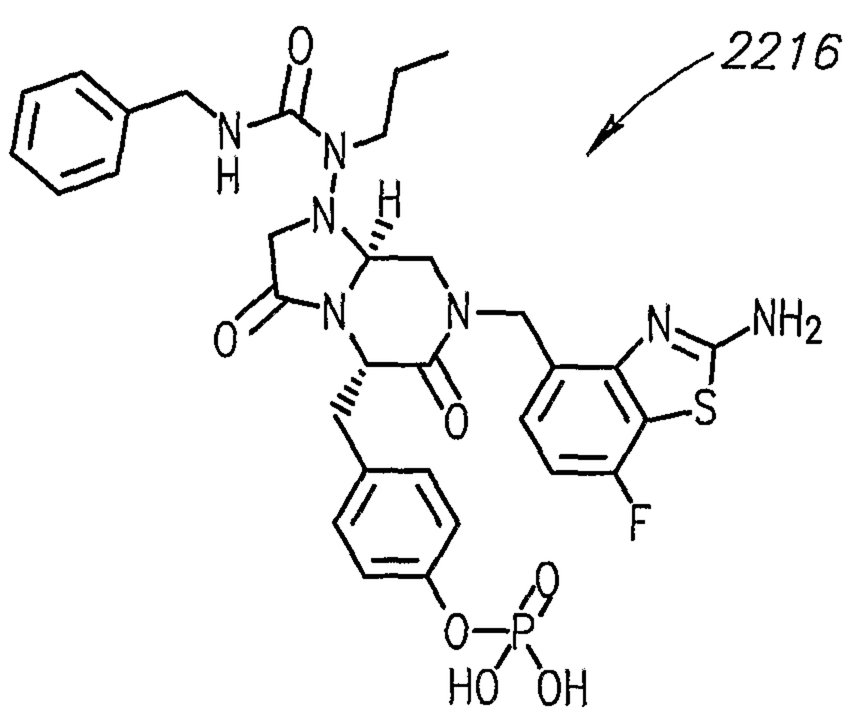


FIG.12B


2215
MeO
O
N
H
N
H
N
O
N
O
N
N
NH2
S
F
O
P
HO
OH


2216
O
N
H
N
H
N
O
N
O
N
N
NH2
S
F
O
P
HO
OH

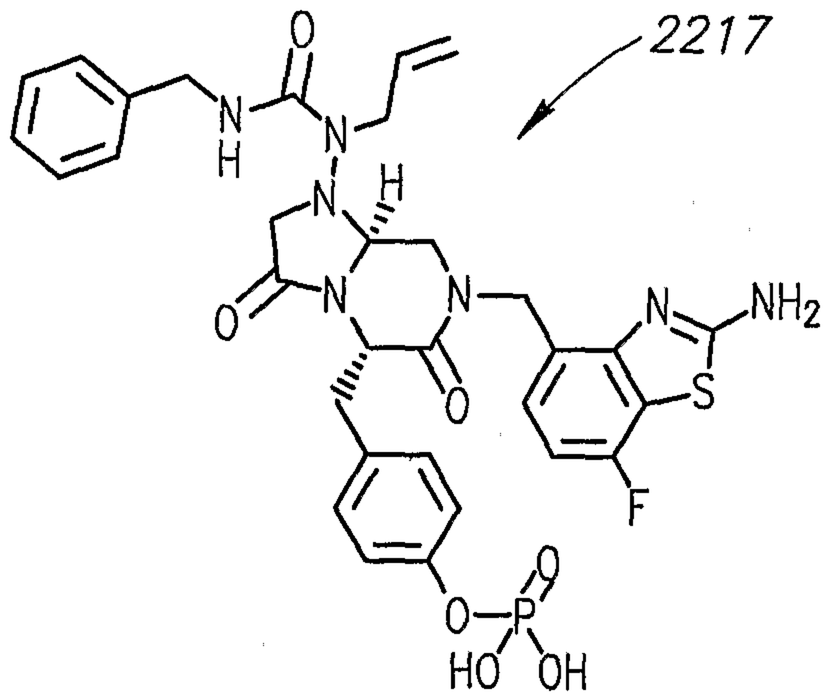
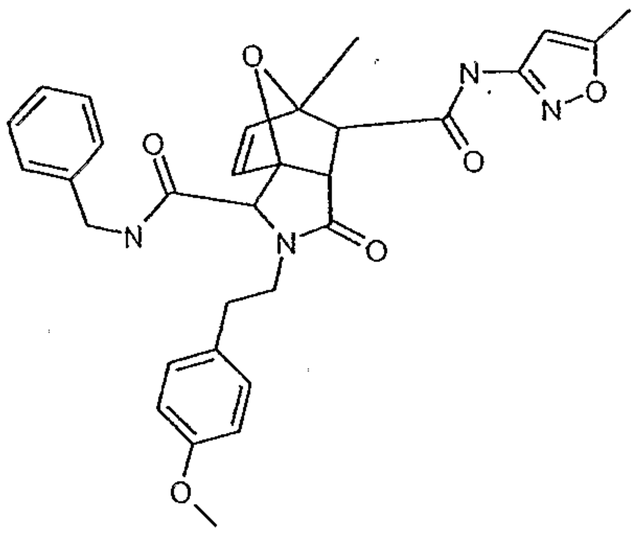

2217
O
N
H
N
H
N
O
N
O
N
N
NH2
S
F
O
P
HO
OH

FIG.12C

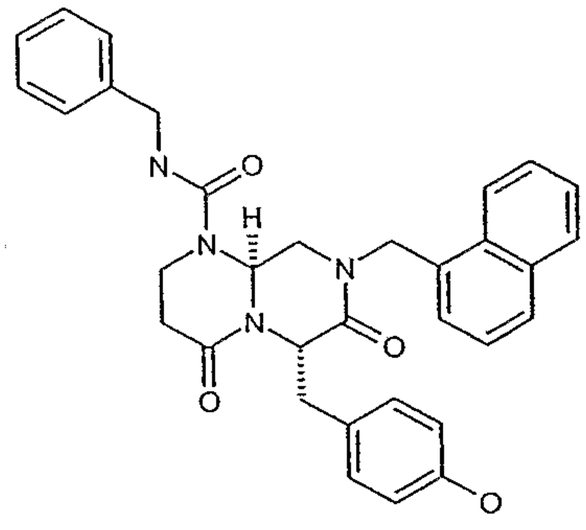
FIGURE 13

A.



ASN 06387747

B.



ICG001

C.

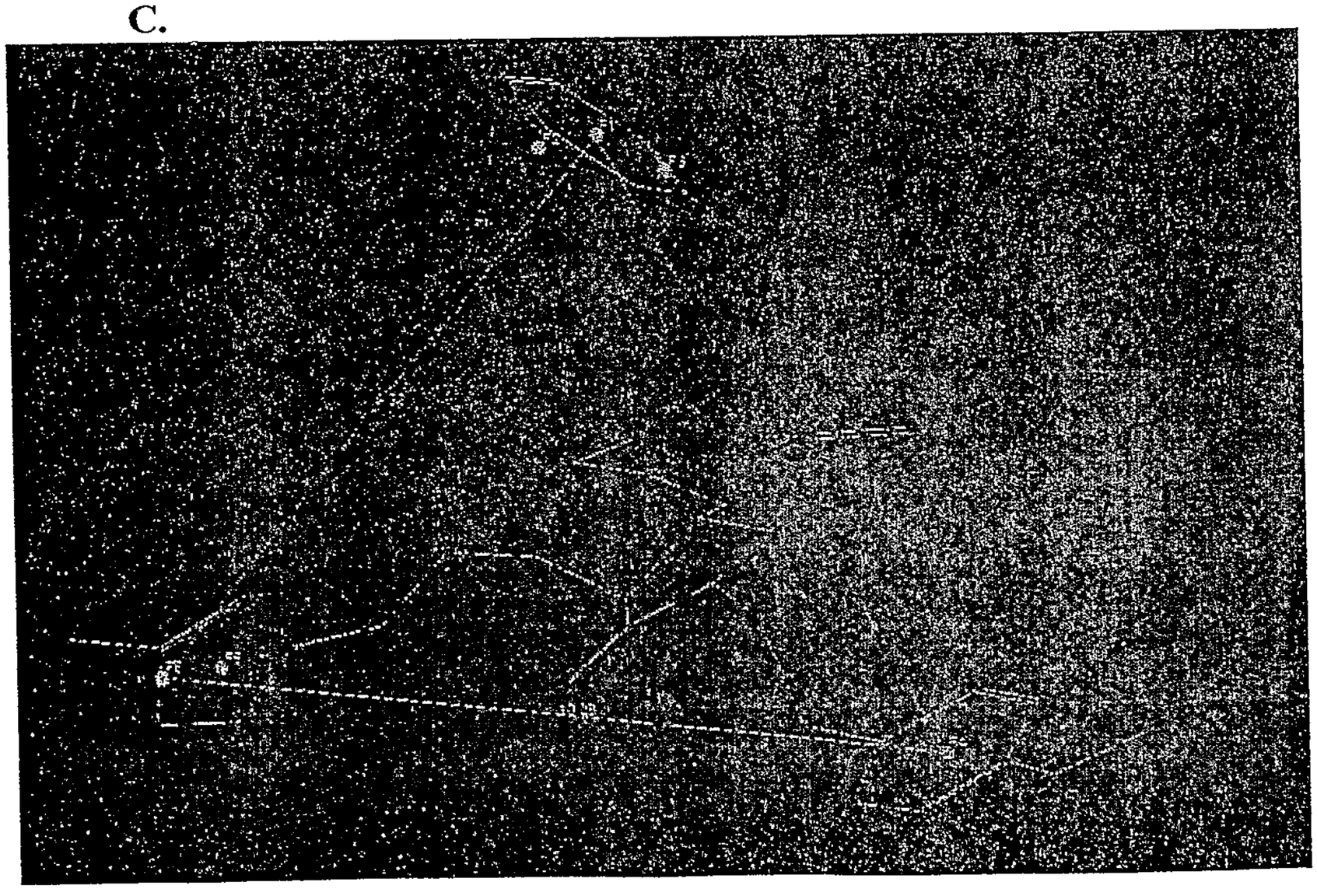


FIGURE 14

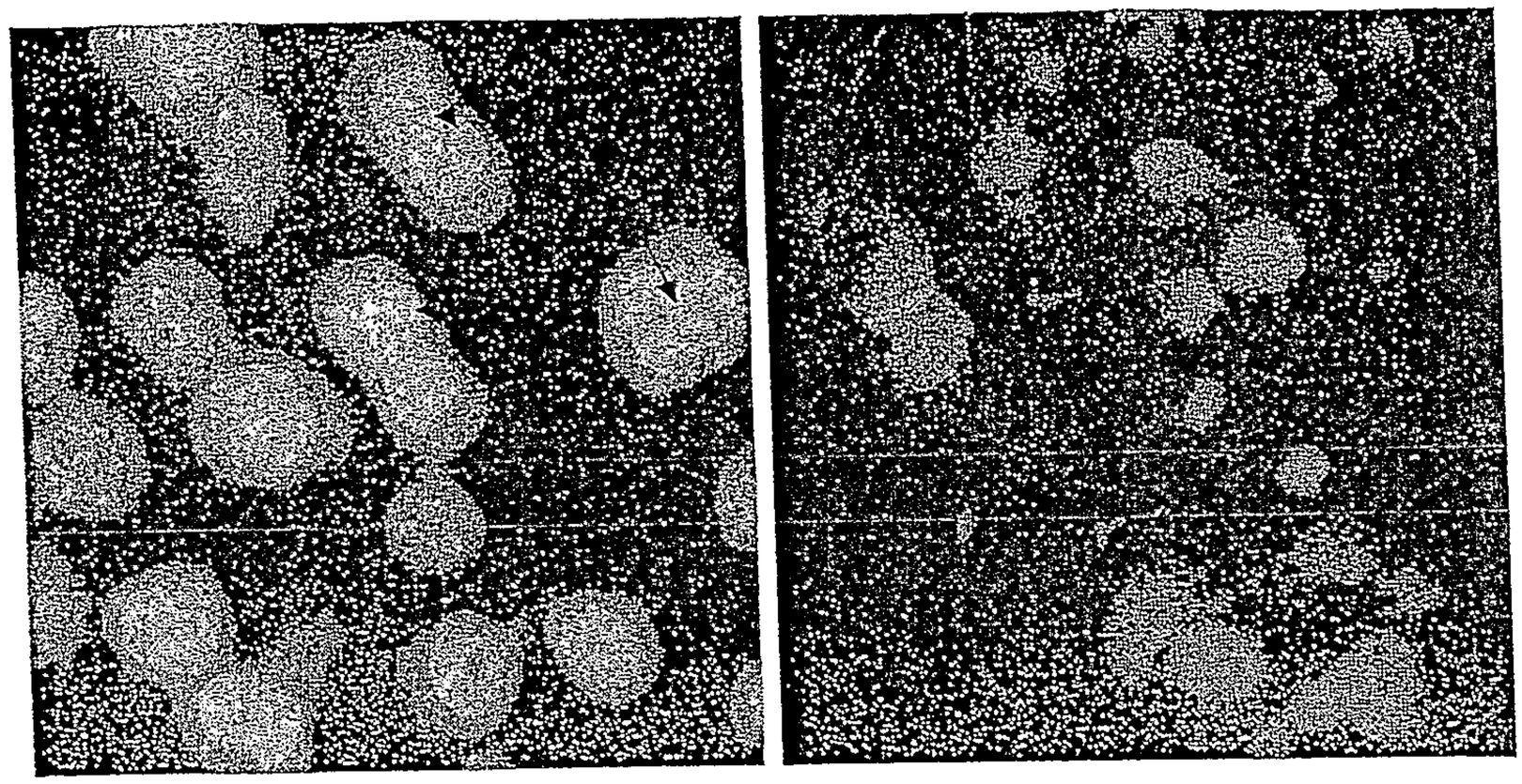
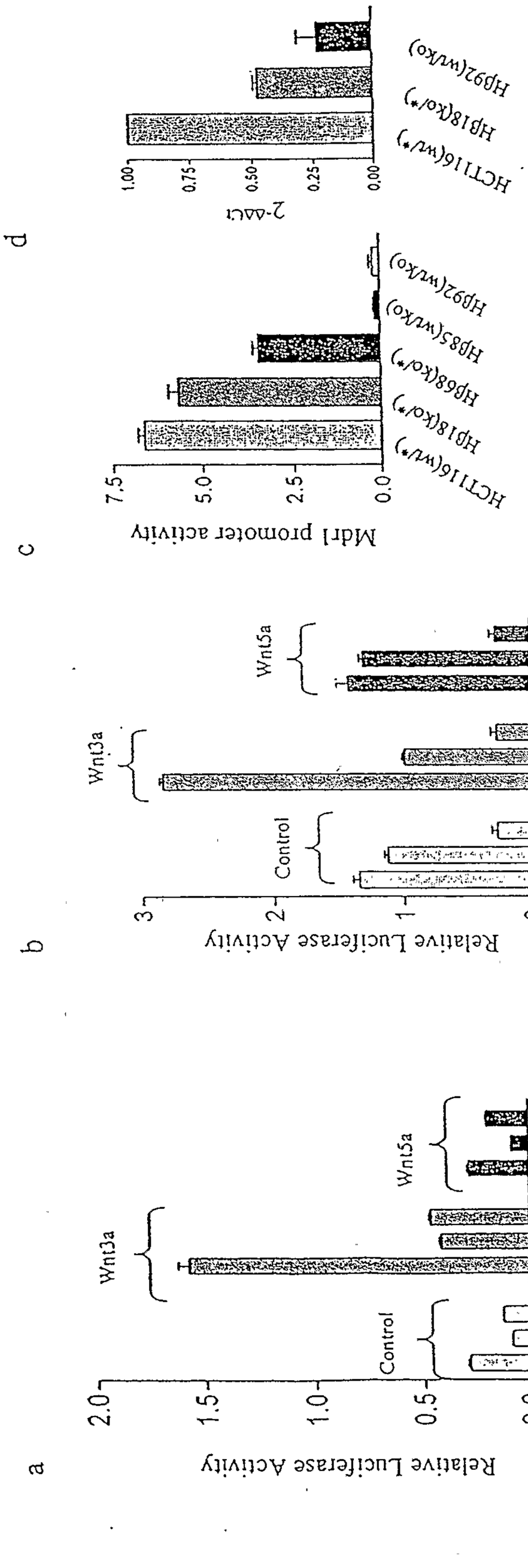

b
S
N
C
β-catenin
β-Actin
1 2 3 4
K562
a
S
N
C
β-catenin
β-Actin
1 2 3 4
Mes-sa
c
Mes-sa R
Mes-sa S
Relative Luciferase Activity
1000
750
500
250
0
1 2 3 4 5 6
TOPFLASH
TOPFLASH+dnTCF4
FOPFLASH

FIGURE 15


a
Relative Luciferase Activity
2.0
1.5
1.0
0.5
0.0
Wnt3a
Control
Wnt5a
TOPFLASH
dnTCF4
FOPFLASH
1 2 3 4 5 6 7 8 9
b
Relative Luciferase Activity
3
2
1
0
Wnt3a
Control
Wnt5a
Pgl3b-mdr1
dnTCF4
PgL3-basic
1 2 3 4 5 6 7 8 9
c
Mdr1 promoter activity
7.5
5.0
2.5
0.0
HCT116(wt/*)
HP18(Ko/*)
HP68(Ko/*)
HP85(wt/Ko)
HP92(wt/Ko)
d
2-ΔΔCt
1.00
0.75
0.50
0.25
0.00
HCT116(wt/*)
HP18(Ko/*)
HP92(wt/Ko)
e
Input
Rabbit IgG
AcH3
TCF4
β-catenin
Mdr1
M
1 2 3 4 5 6 7 8 9 10 11

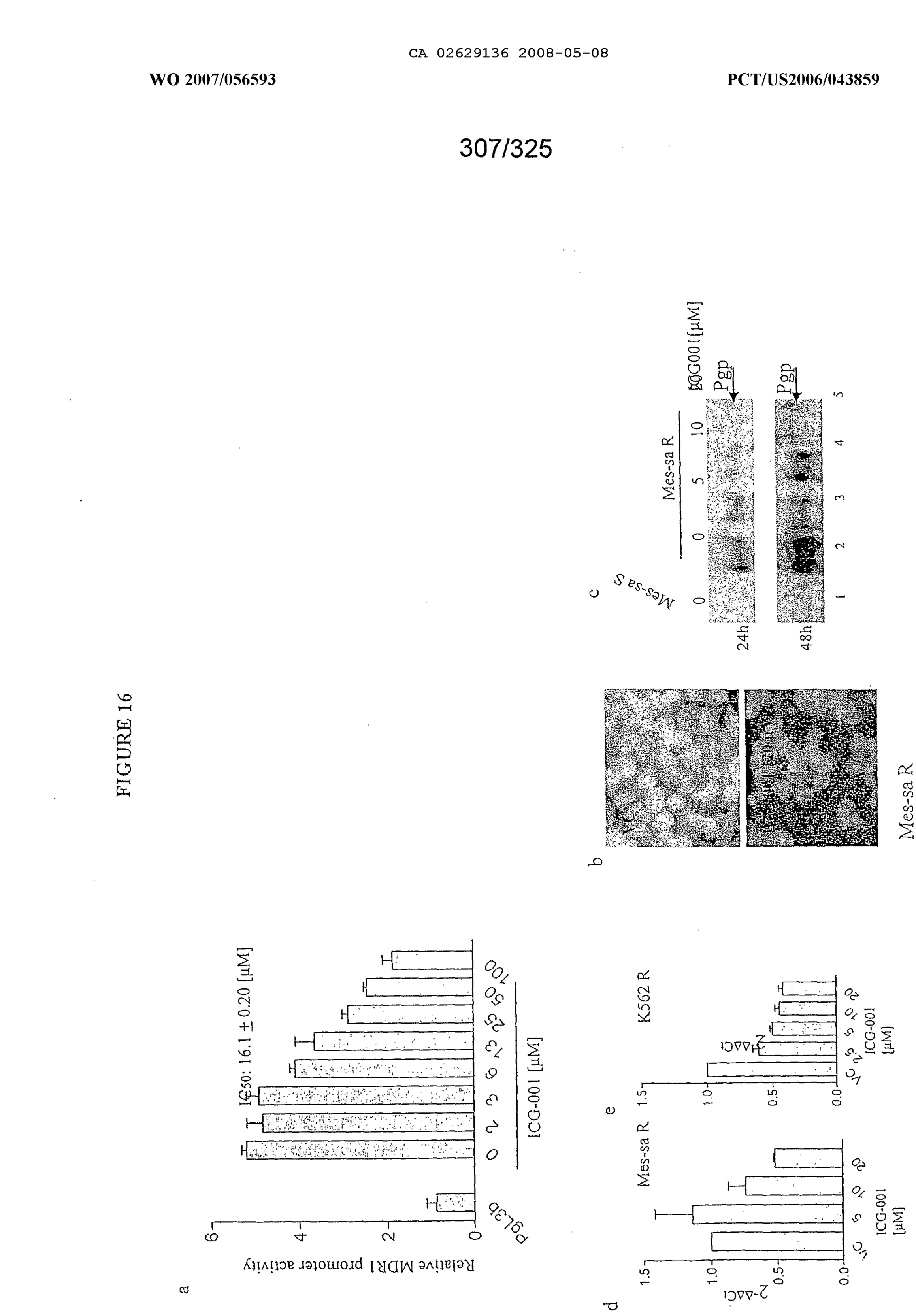

a
Relative MDR1 promoter activity
pGL3b
ICG-001 [μM]
IC50: 16.1 ± 0.20 [μM]
b
Mes-sa R
c
Mes-sa S
Mes-sa R
ICG-001 [μM]
Pgp
24h
48h
d
Mes-sa R
2-ΔΔCt
e
K562 R
2-ΔΔCt
ICG-001 [μM]

FIGURE 16

FIGURE 17

a
HCT116 (wt/*)
Hβ18 (ko/*)
Hβ92 (wt/ko)
Mdr1 promoter reporter activity
15
10
5
0
pCMV-pTβ-catenin - + + + - + + +
pCMV-CBP - + - - - + - -
pCMV-p300 - - + - - - + -
1 2 3 4 5 6 7 8 9 10 11 12
b
HCT116 (wt/*)
Hβ18 (ko/*)
Hβ92 (wt/ko)
Mdr1 promoter reporter activity
100
75
50
25
0
ICG-001 [μM] VC 1 5 10 15 30 VC 1 5 10 15 30 VC 1 5 10 15 30 VC 1 5 10 15 30
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
c
A
ICG-001(μM) 0 0 10 25
Input
Rabbit IgG
0 0 10 25
1 2 3 4 5 1 2 3 4 5 6 7 8 9
Mdr1
B
ICG-001[μM] 0 0 10 25
Ac Histone H3
CBP
0 0 10 25
1 2 4 1 2 3 4 6 7 8 9
Mdr1
p300

FIGURE 18

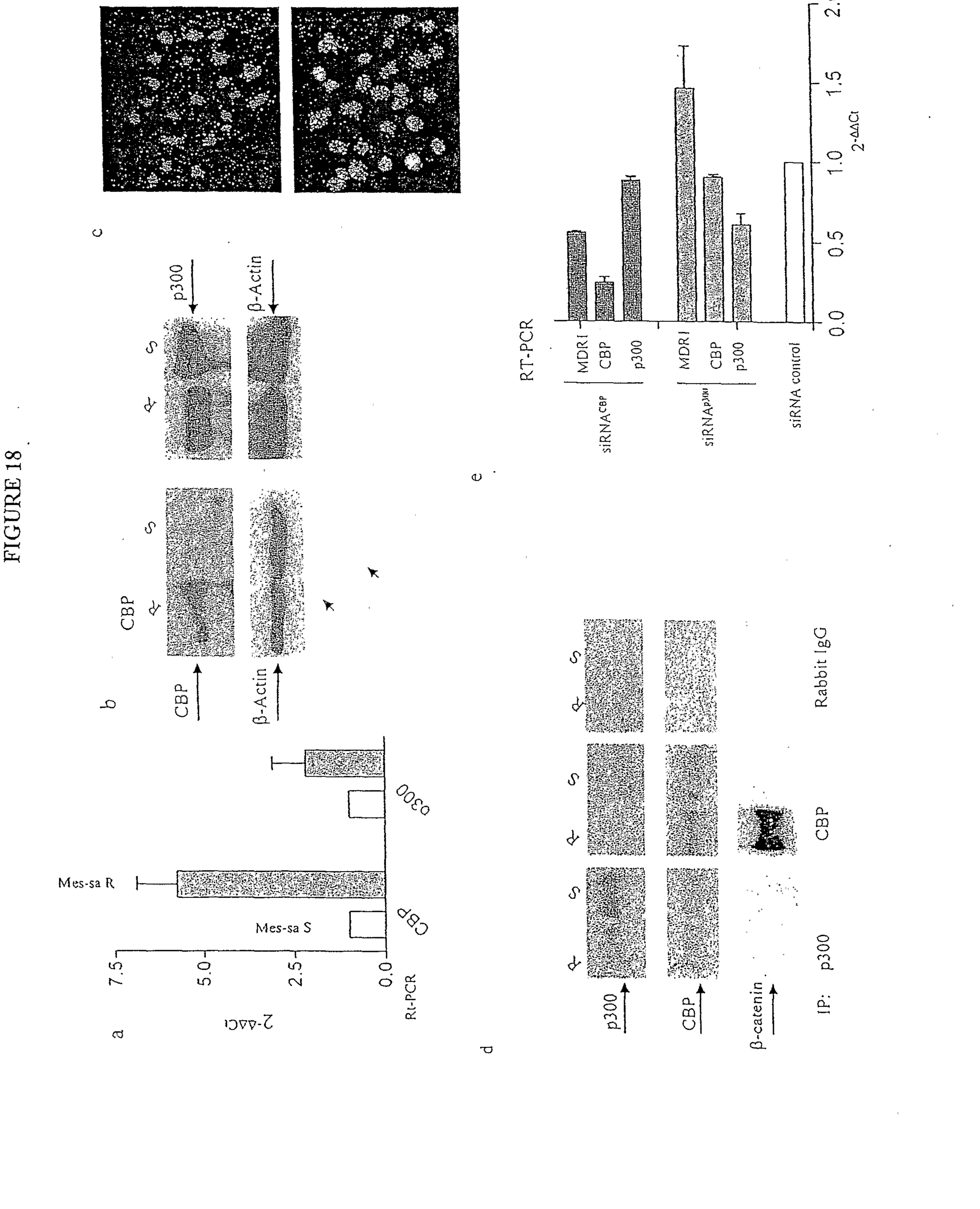

a
2-ΔΔCt
7.5
5.0
2.5
0.0
Mes-sa R
Mes-sa S
RT-PCR
CBP
p300
b
CBP
R
S
CBP
β-Actin
c
R
S
p300
β-Actin
d
RT-PCR
siRNA CBP
siRNA p300
MDR1
CBP
p300
MDR1
CBP
p300
siRNA control
0.0
0.5
1.0
1.5
2-ΔΔCt
e
R
S
R
S
p300
CBP
β-catenin
CBP
Rabbit IgG
IP: p300

FIGURE 19

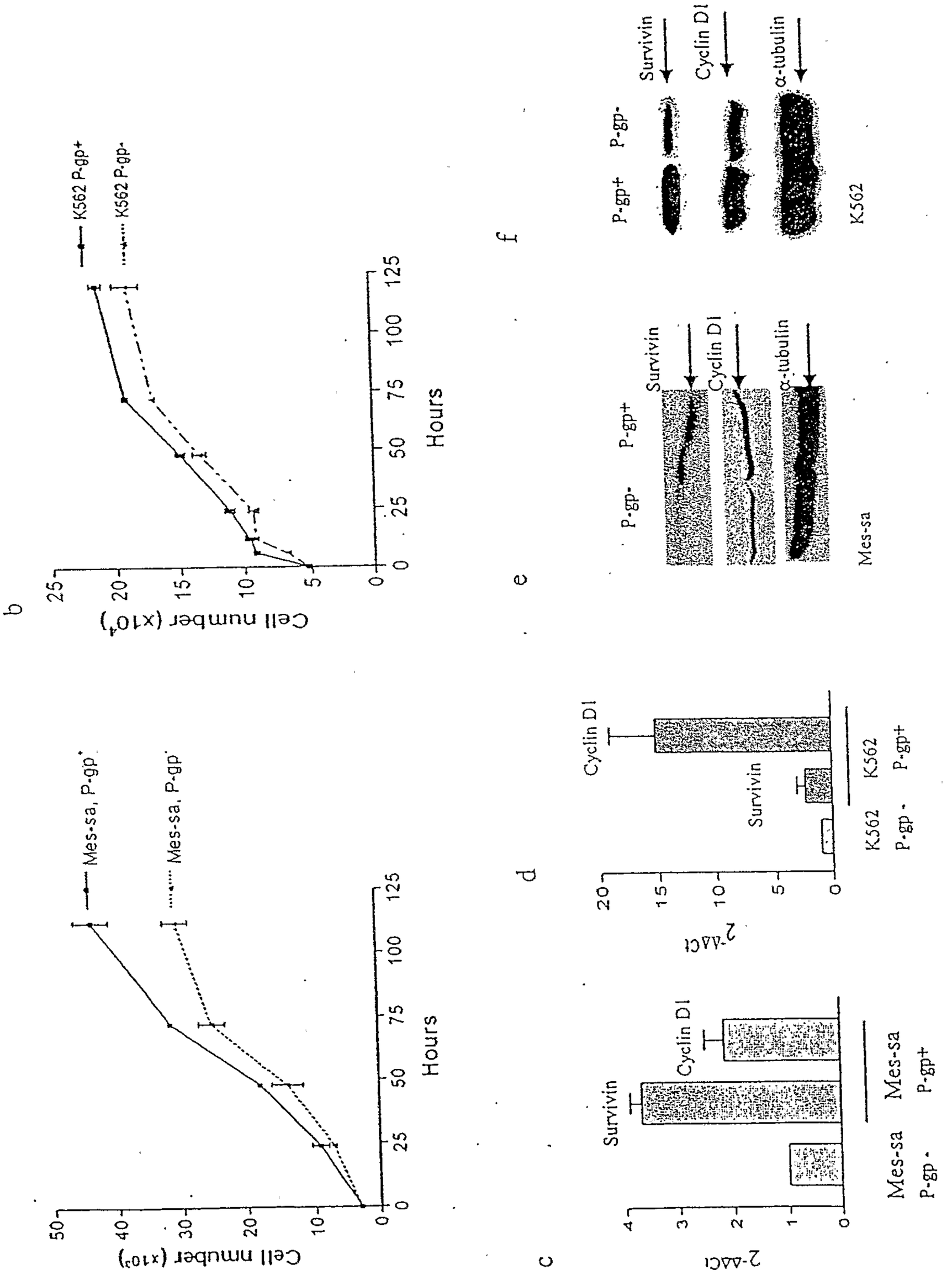

a
Cell number (x10³)
Hours
Mes-sa, P-gp+
Mes-sa, P-gp-
b
Cell number (x10⁴)
Hours
K562 P-gp+
K562 P-gp-
c
2-ΔΔCt
Survivin
Cyclin D1
Mes-sa
P-gp+
d
2-ΔΔCt
Cyclin D1
Survivin
K562
P-gp+
e
P-gp-
P-gp+
Survivin
Cyclin D1
α-tubulin
Mes-sa
f
P-gp+
P-gp-
Survivin
Cyclin D1
α-tubulin
K562

FIGURE 2

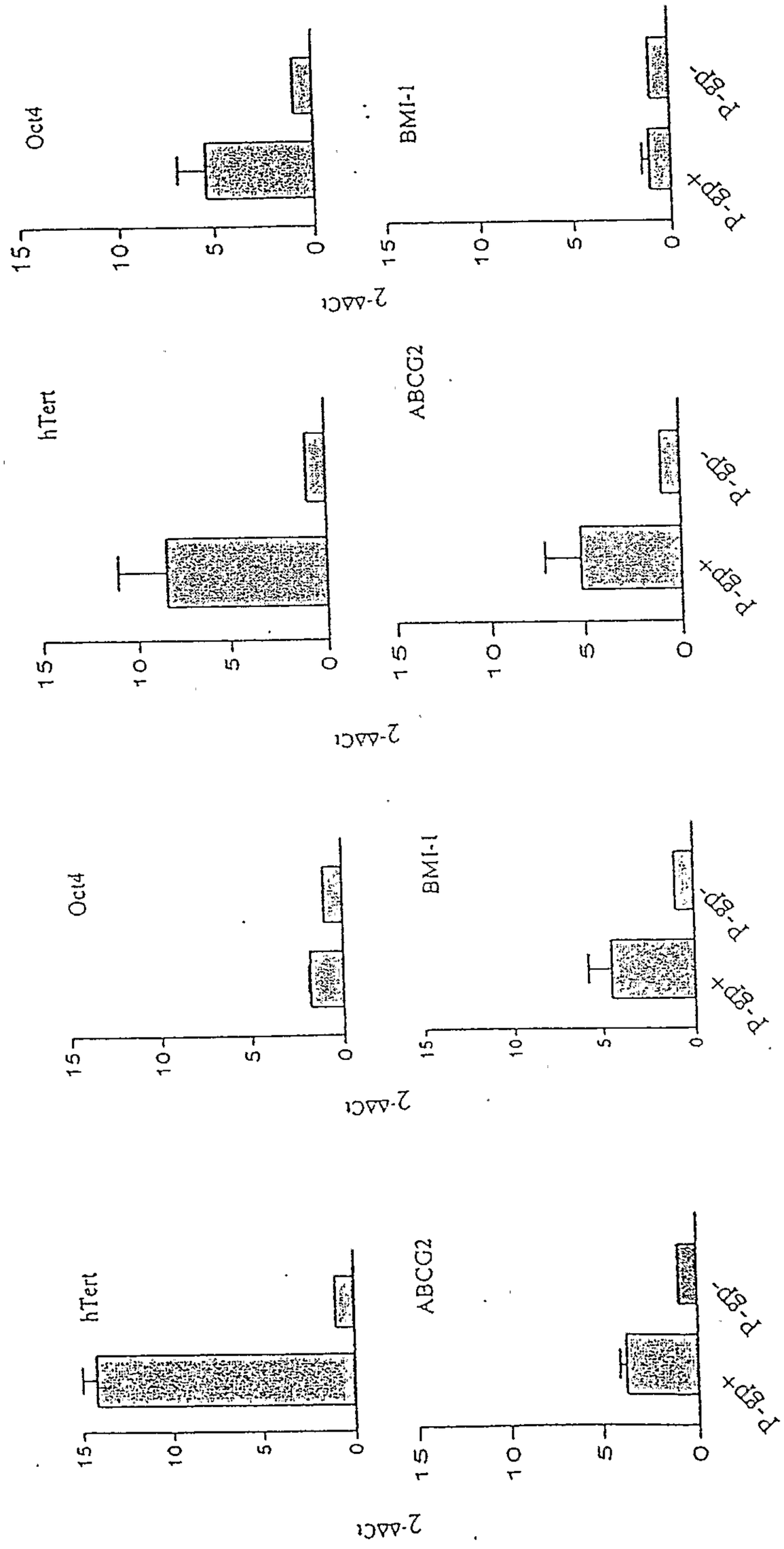
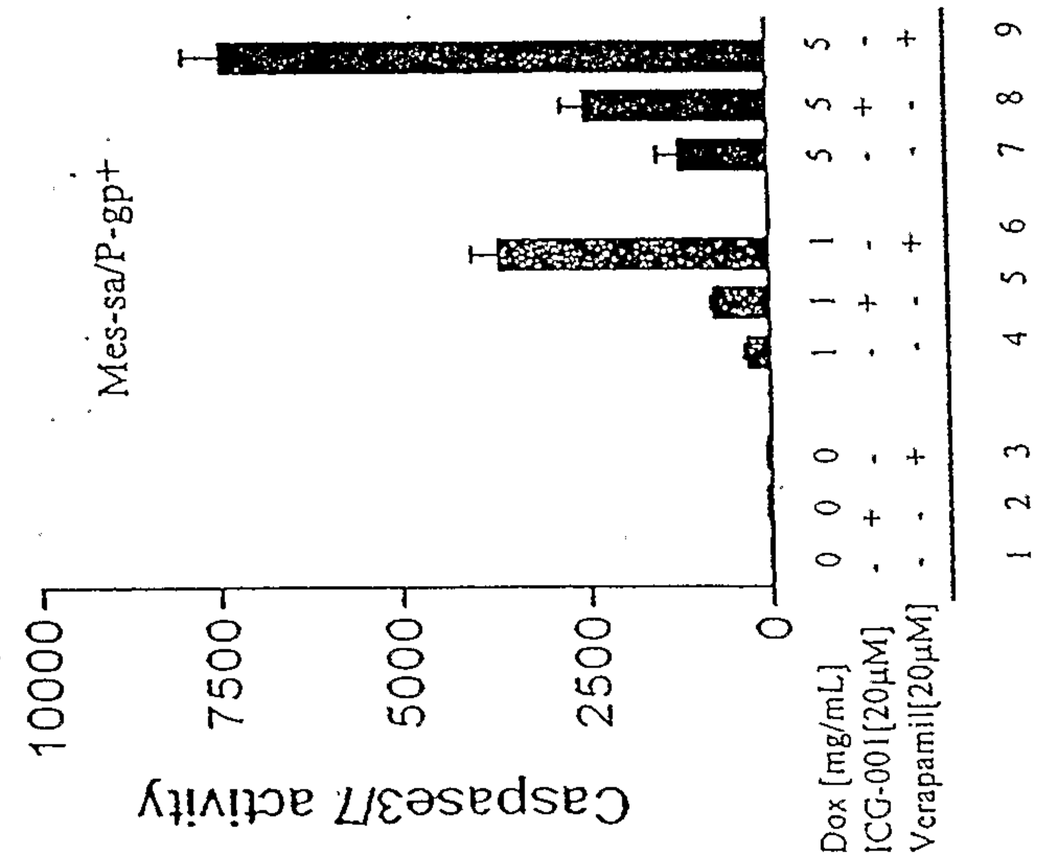
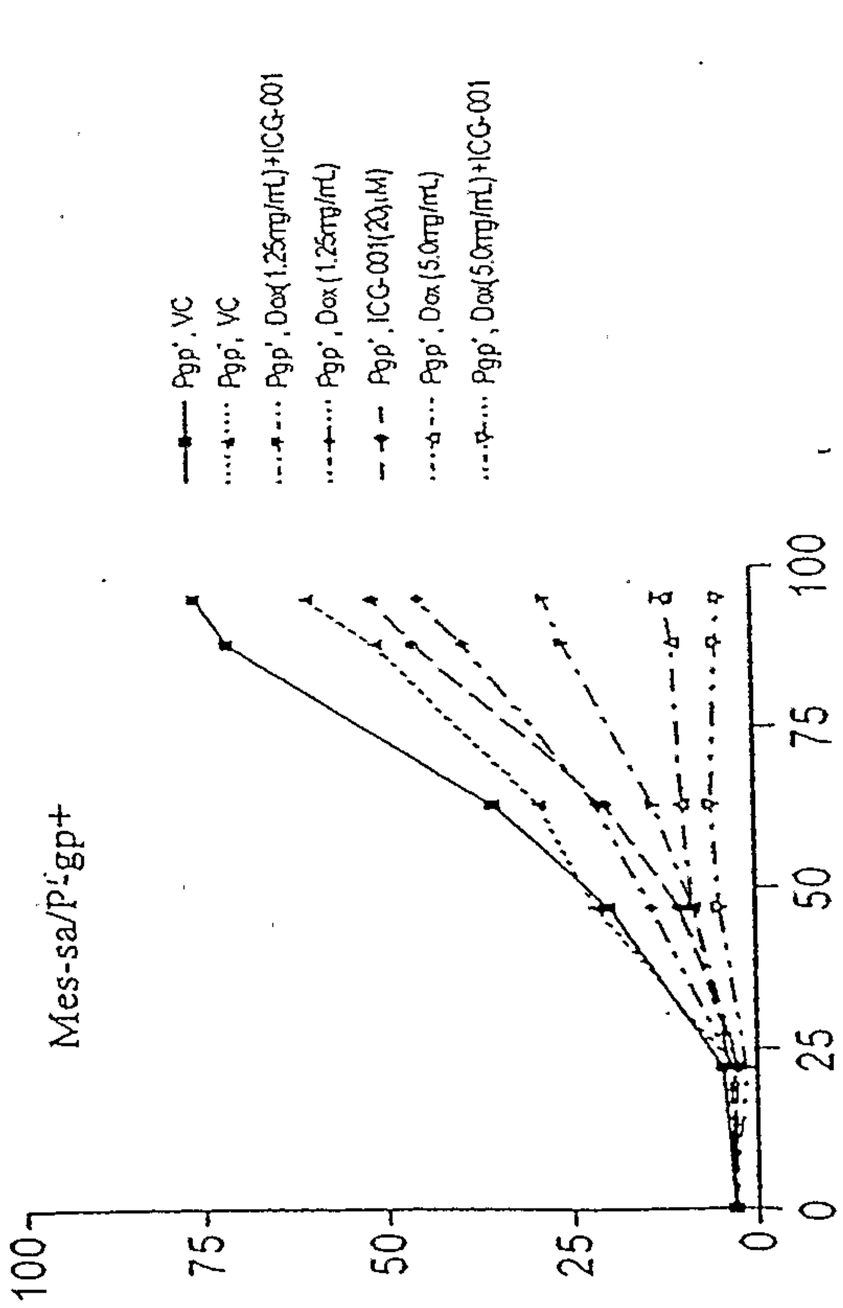

Oct4
BMI-1
hTert
ABCG2
2-ΔΔCt
15
10
5
0
P-gp+
P-gp-
P-gp+
P-gp-
Oct4
CD133
α-tubulin
K562
P-gp-
CD133
α-tubulin
P-gp+
Mes-sa

FIGURE 21A


Mes-sa/P-gp+
Caspase3/7 activity
10000
7500
5000
2500
0
Dox [mg/mL] 0 0 0 1 1 1 5 5 5
ICG-001[20μM] - + - - + - - + -
Verapamil[20μM] - - + - - + - - +
1 2 3 4 5 6 7 8 9


Mes-sa/P-gp+
Cell number (x1000)
100
75
50
25
0
0
25
50
75
100
Hours
Pgp', VC
Pgp', VC
Pgp', Dox(1.25mg/mL)+ICG-001
Pgp', Dox(1.25mg/mL)
Pgp', ICG-001(20μM)
Pgp', Dox(5.0mg/mL)
Pgp', Dox(5.0mg/mL)+ICG-001

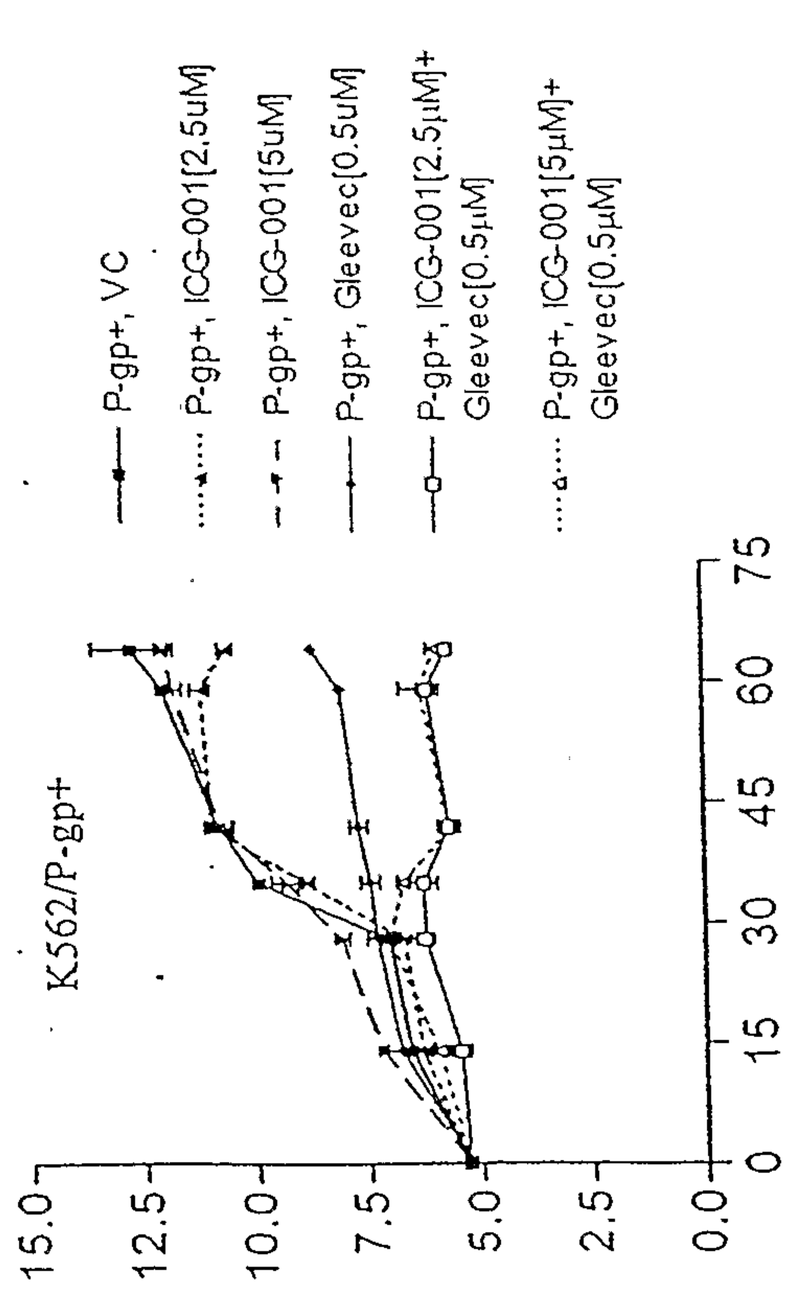
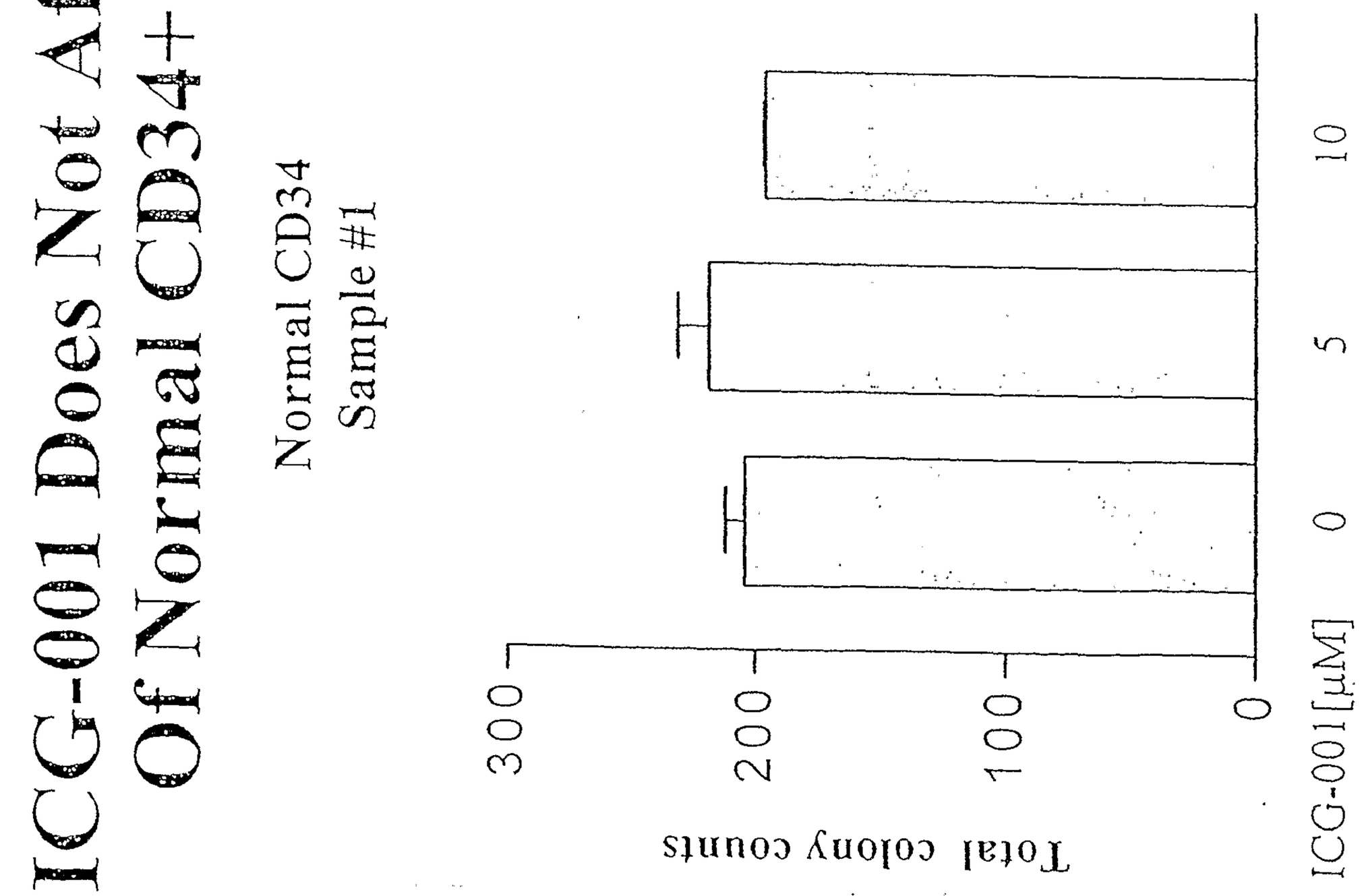

K562/P-gp+
Cell Number (x10^5)
15.0
12.5
10.0
7.5
5.0
2.5
0.0
0
15
30
45
60
75
Hours
P-gp+, VC
P-gp+, ICG-001[2.5uM]
P-gp+, ICG-001[5uM]
P-gp+, Gleevec[0.5uM]
P-gp+, ICG-001[2.5μM]+ Gleevec[0.5μM]
P-gp+, ICG-001[5μM]+ Gleevec[0.5μM]

FIGURE 21B

ICG-001 Does Not Affect Colony Formation Of Normal CD34+ Hematopoietic Cells

Normal CD34
Sample #1



Normal CD34
Sample #2

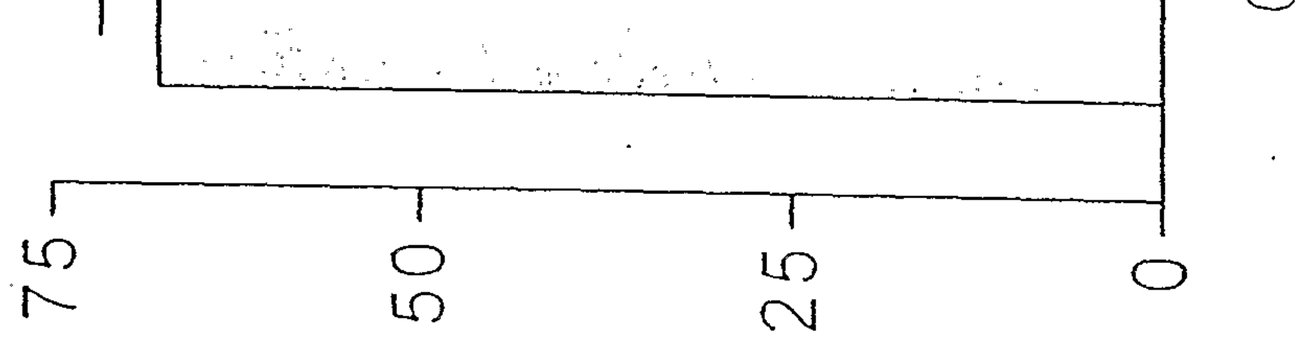


FIGURE 21C

ICG-001 Compounds Target Cancer Stem Cells in CML

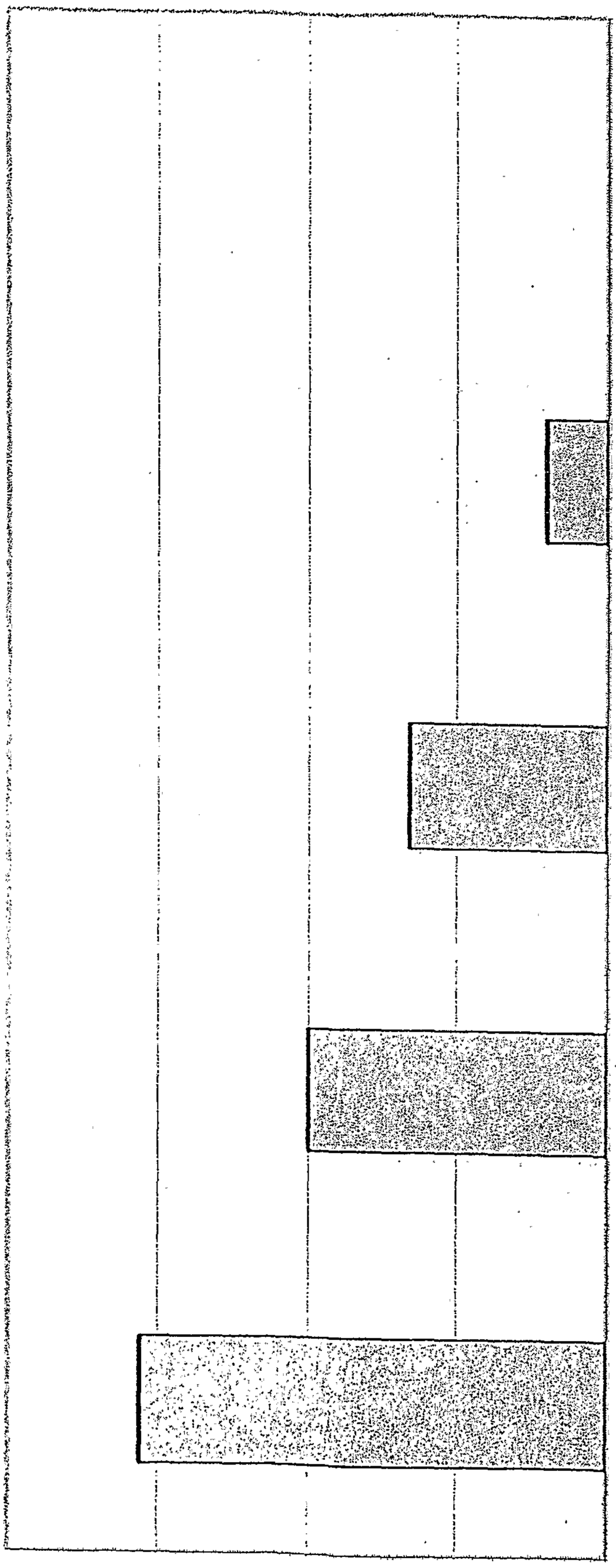
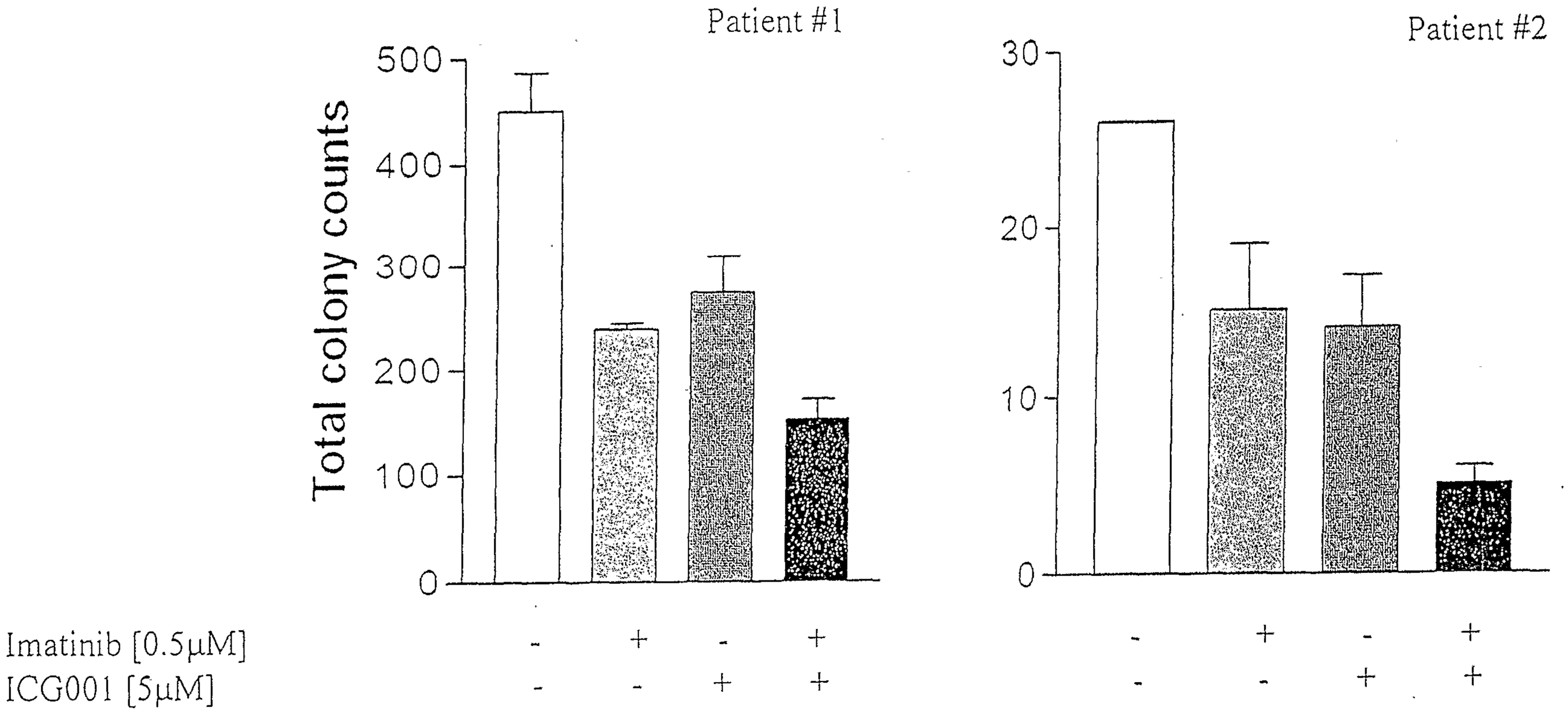


FIGURE 21D

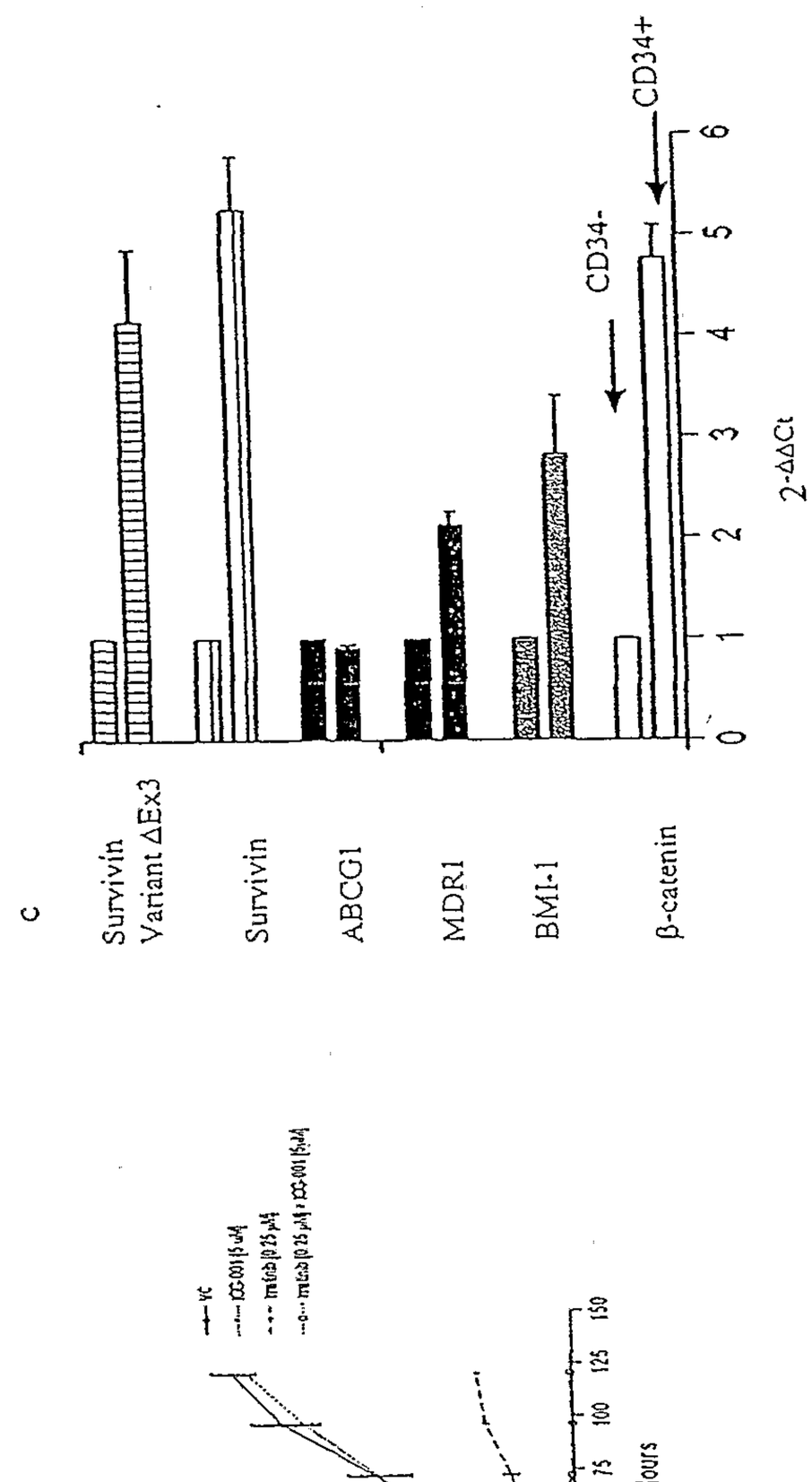
Colony Counts For 2 CML Patients



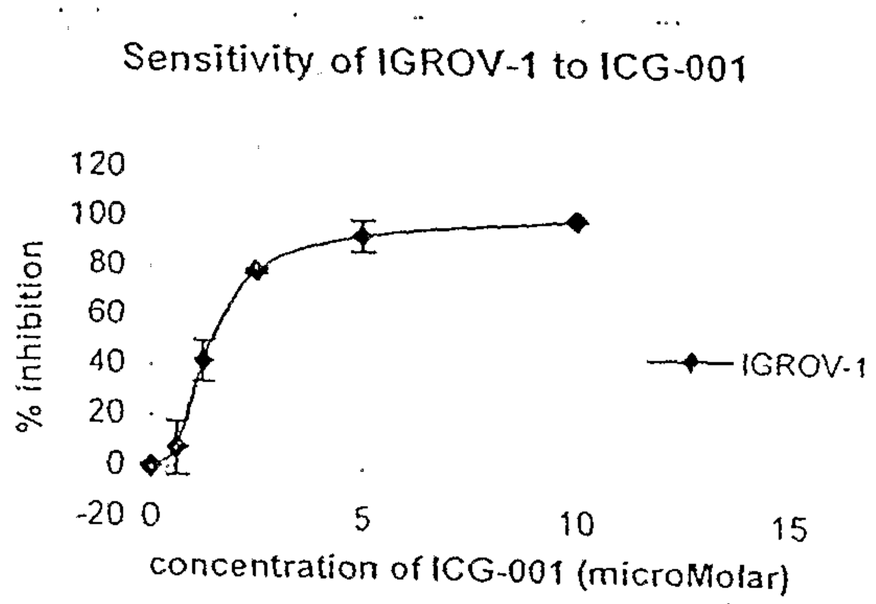
Patient 1 – Late Chronic Phase, off IM for 6 months
Patient 2 – Blast Crisis Patient on Imatinib

WO 2007/056593
PCT/US2006/043859
315/325
CA 2629136 2008-05-08

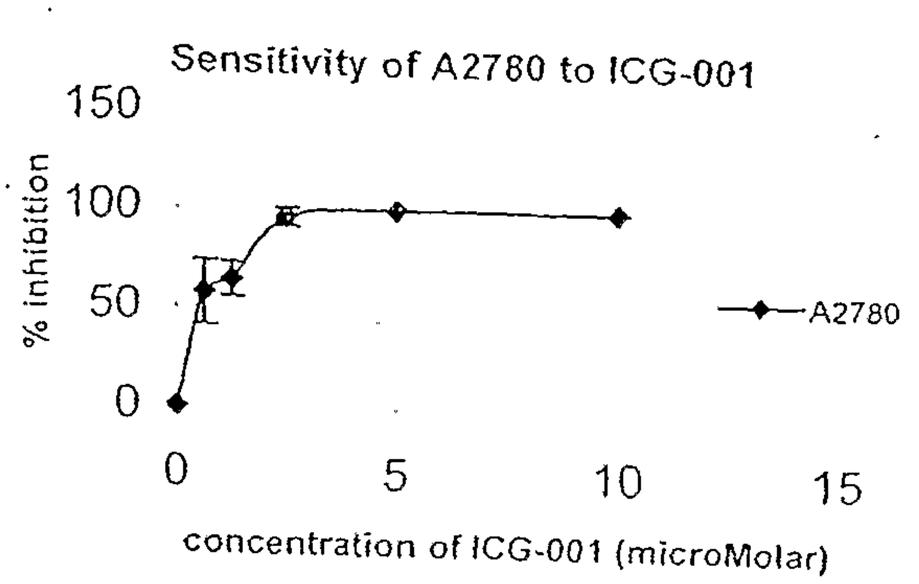
FIGURE 22


a
Cell number (x10³)
Hours
b
Cell Number (x10³)
Hours
vc
ICG-001(5μM)
Gx(2mM)
Gx(2mM)+ICG-001(5μM)
c
Survivin Variant ΔEx3
Survivin
ABCG1
MDR1
BMI-1
β-catenin
CD34+
CD34-
2-ΔΔCt
d
VC
ICG-001
+imatinib

A



B



C

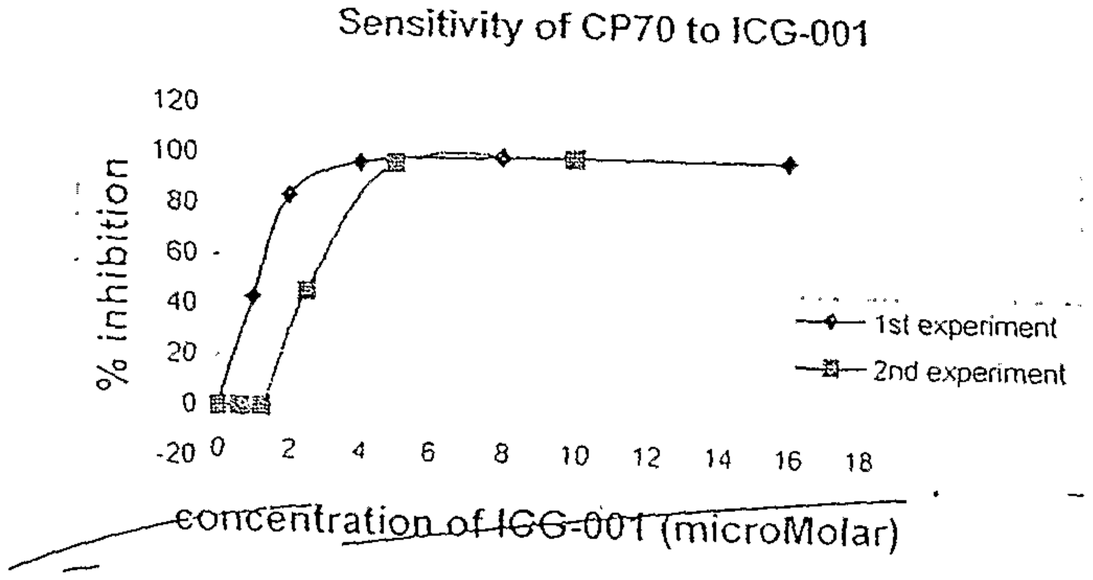
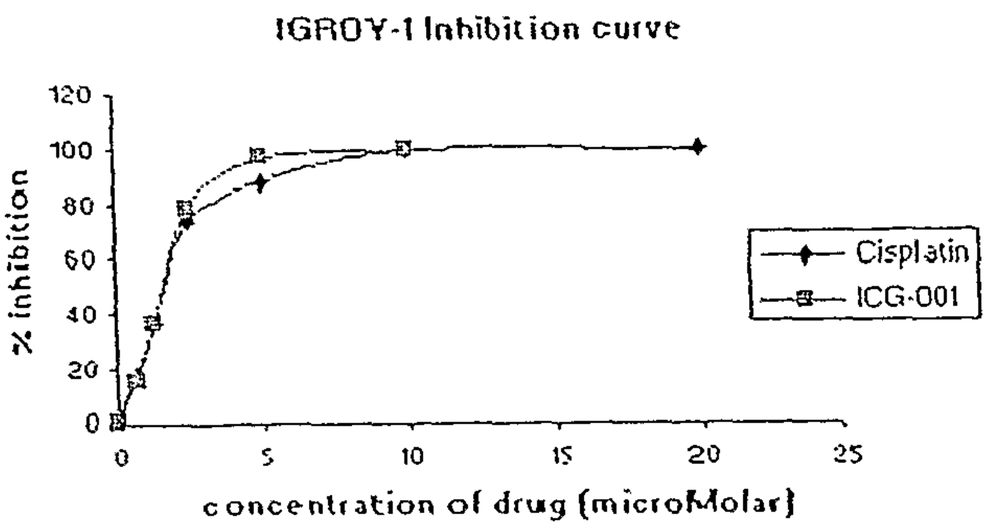
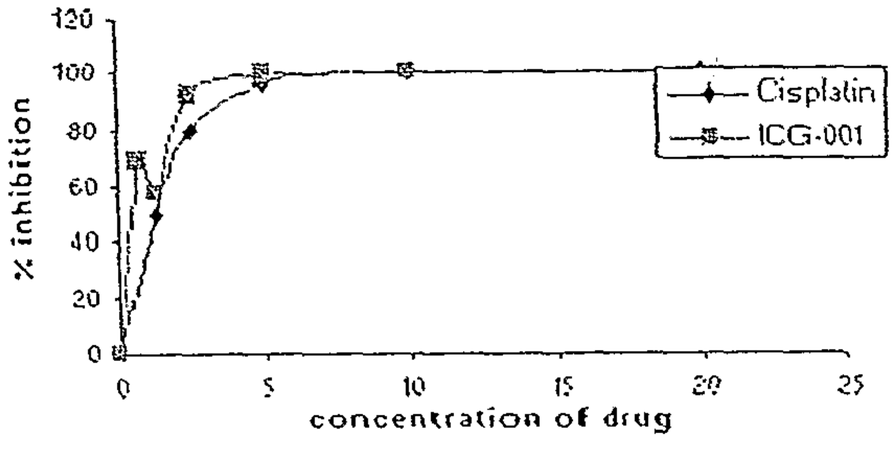
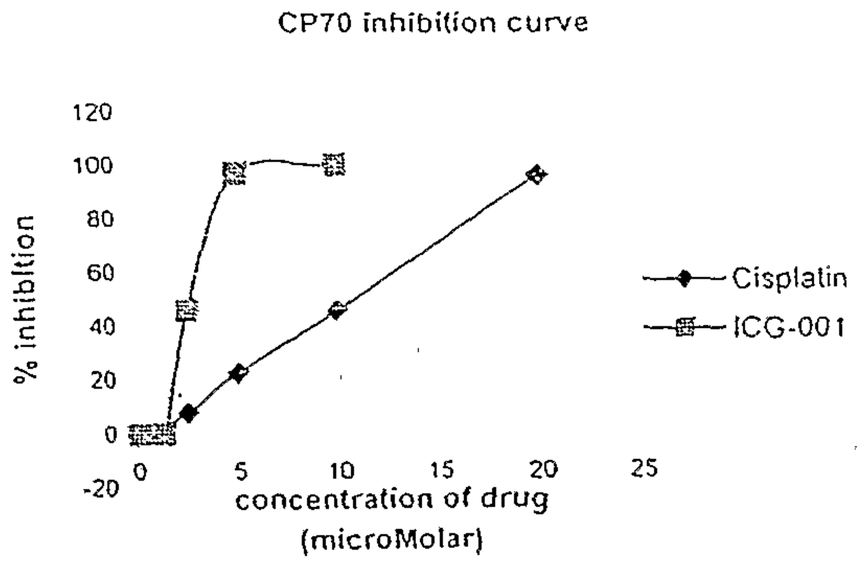


FIGURE 23





C



Sensitivity of A2780 and its cisplatin-resistant variant, CP70, to cisplatin and ICG-001.

FIGURE 24

FIGURE 25

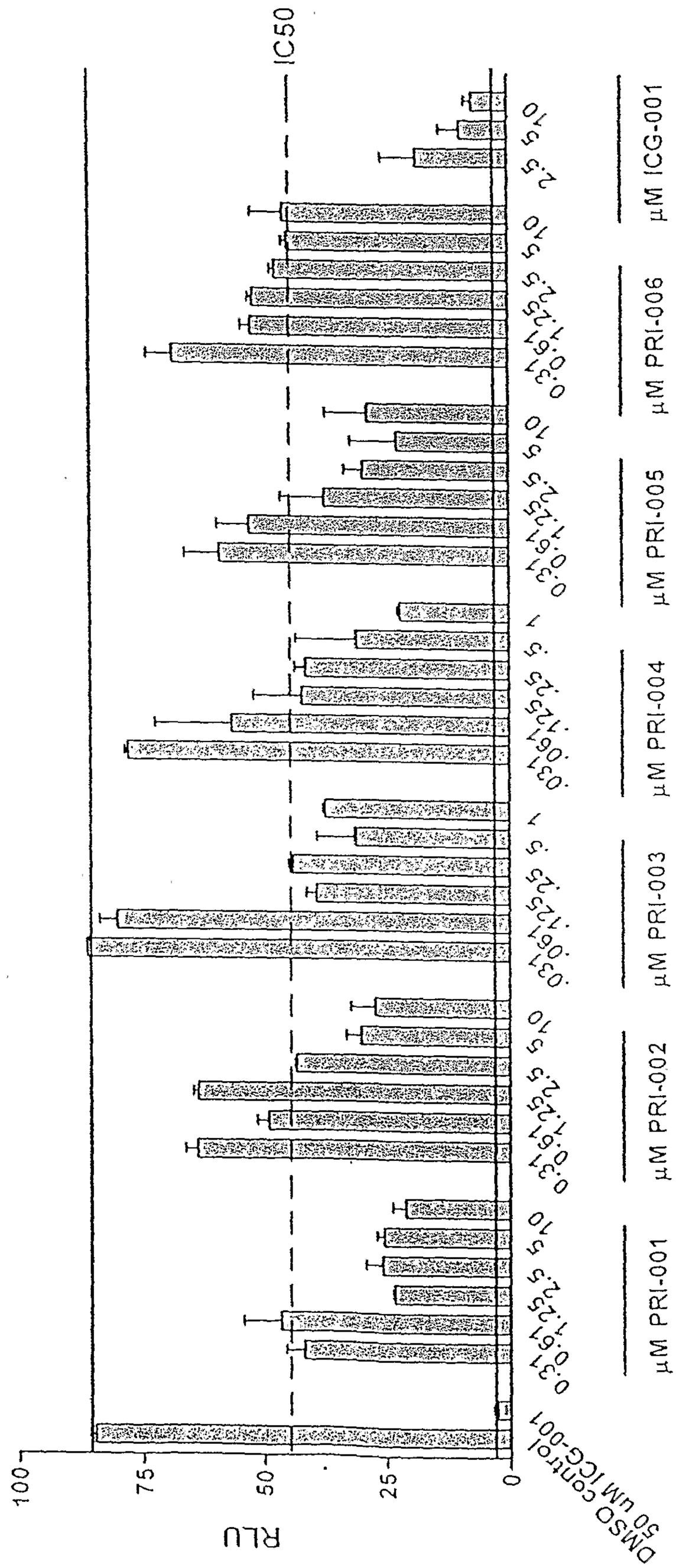

TOPFLASH in SW480 Cells
RLU
100
75
50
25
0
DMSO control
50 uM ICG-001
0.3
0.6
1.25
2.5
5
10
μM PRI-001
μM PRI-002
μM PRI-003
μM PRI-004
μM PRI-005
μM PRI-006
μM ICG-001

FIGURE 26

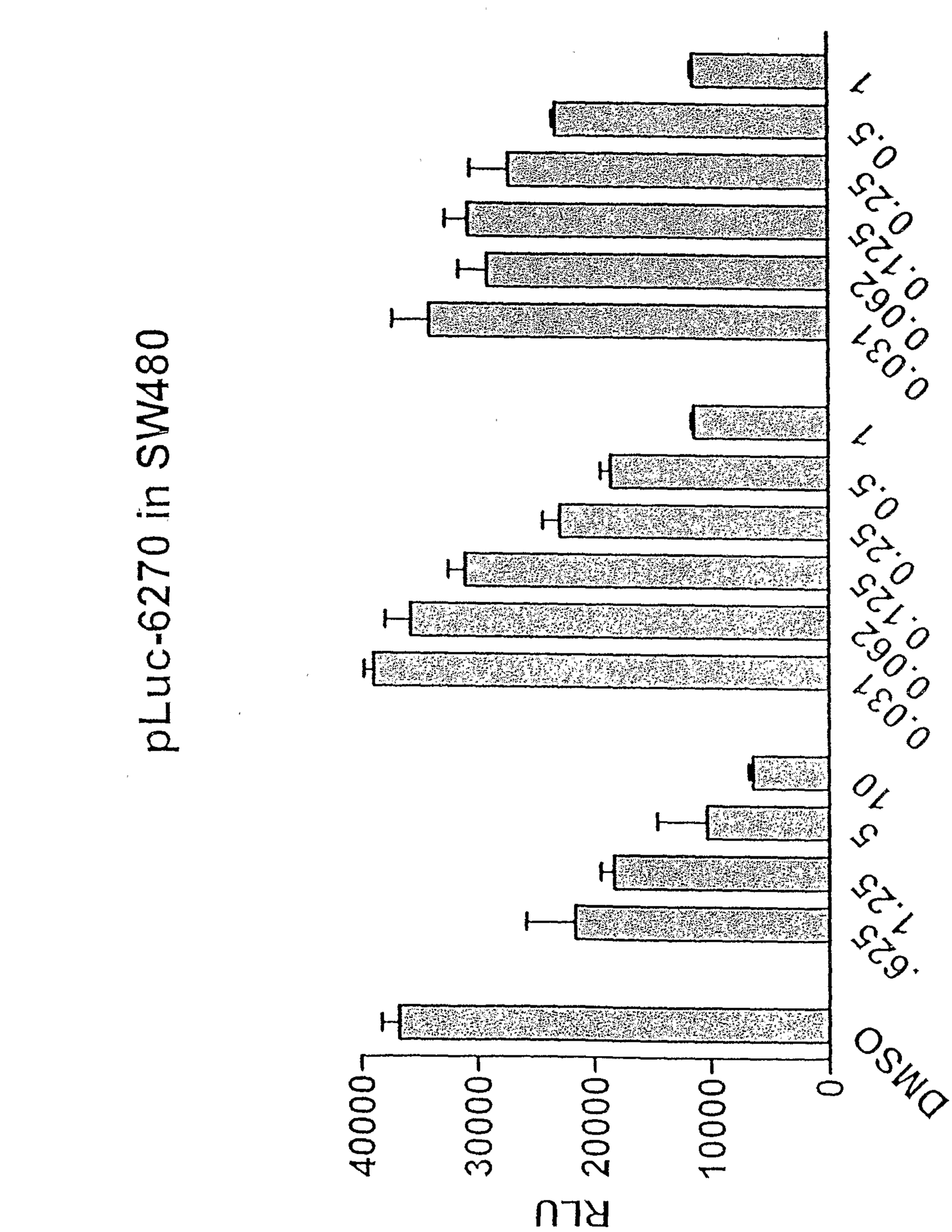

pLuc-6270 in SW480
RLU
40000
30000
20000
10000
0
DMSO
0.625
1.25
5
10
μM ICG-001
0
0.03125
0.0625
0.125
0.25
0.5
1
μM PRI-003
0
0.03125
0.0625
0.125
0.25
0.5
1
μM PRI-004

FIGURE 27A

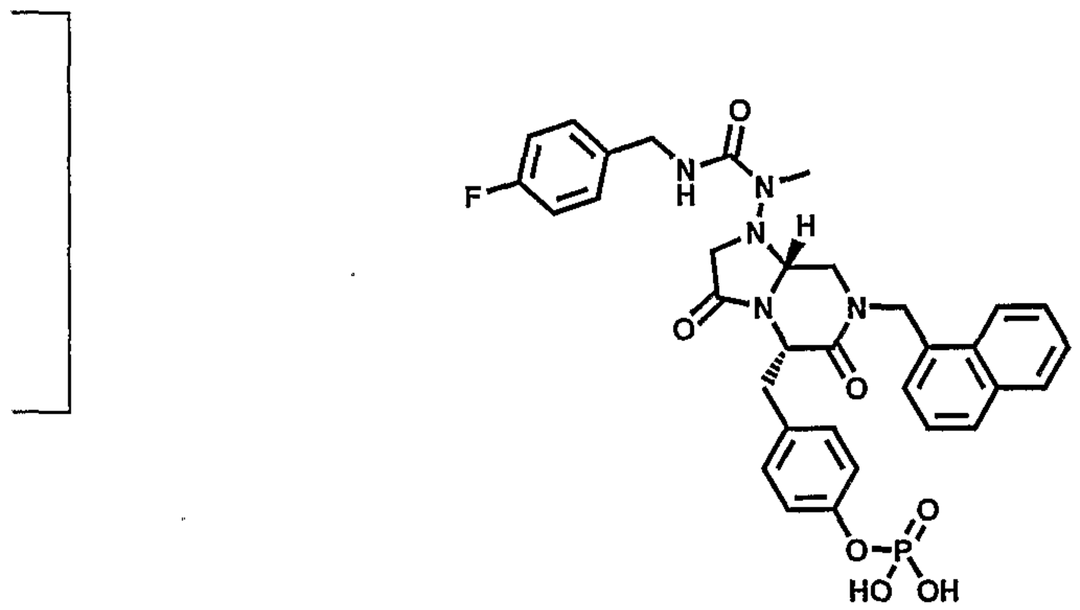
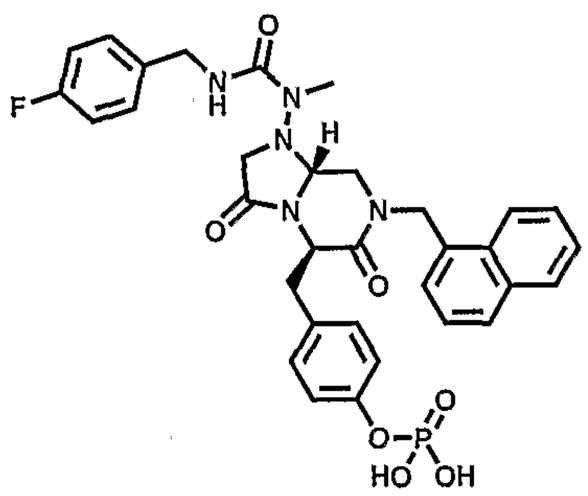
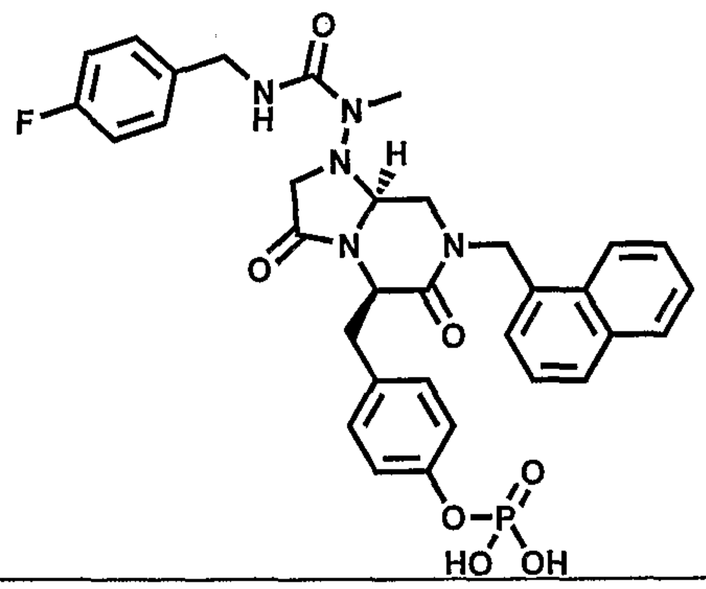
2203	
2204	
2205	

FIGURE 27B

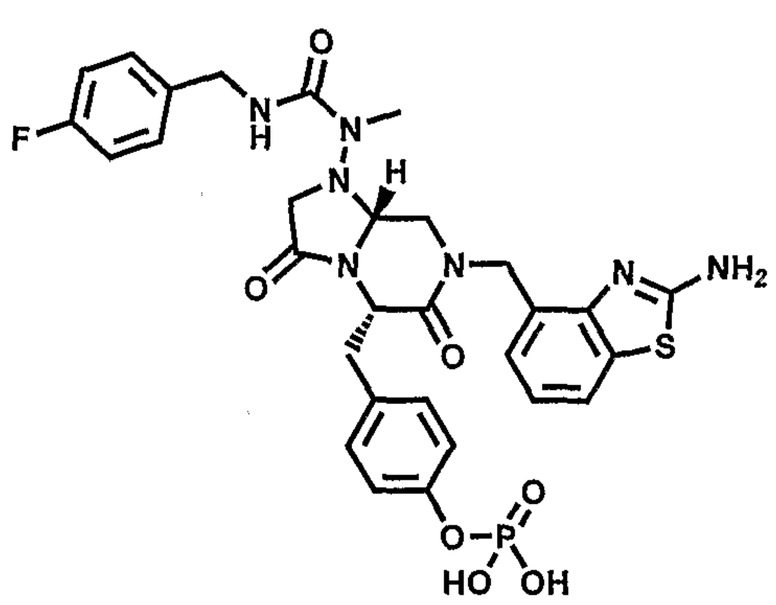
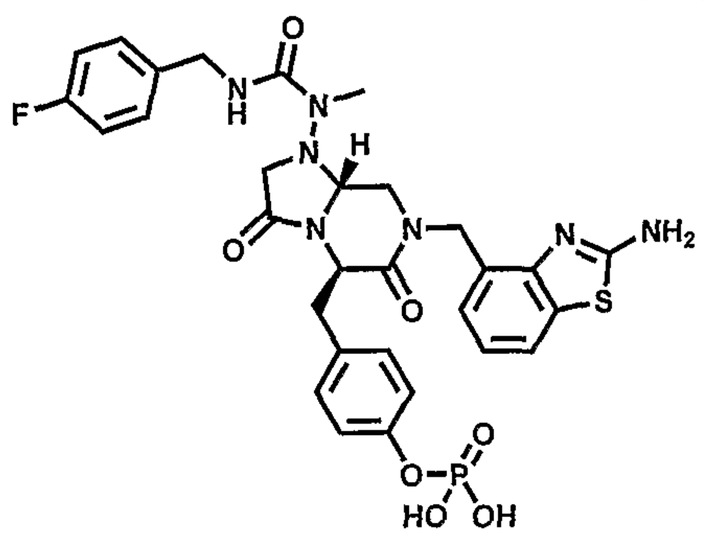
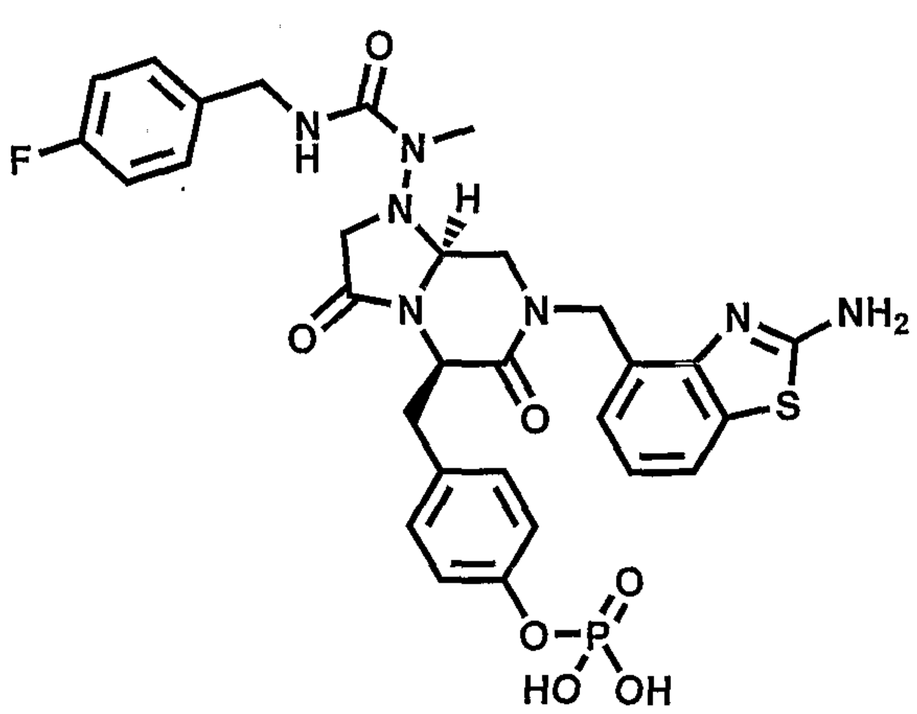
2206	
2207	
2208	

FIGURE 27C

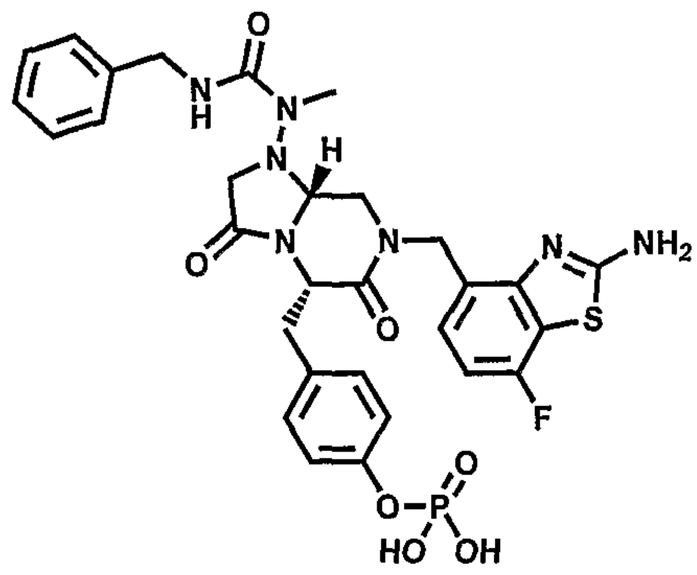
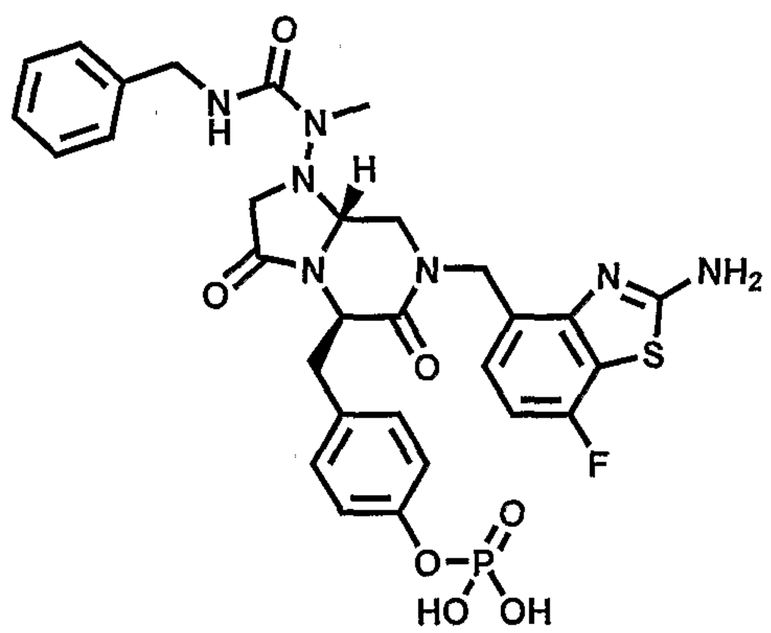
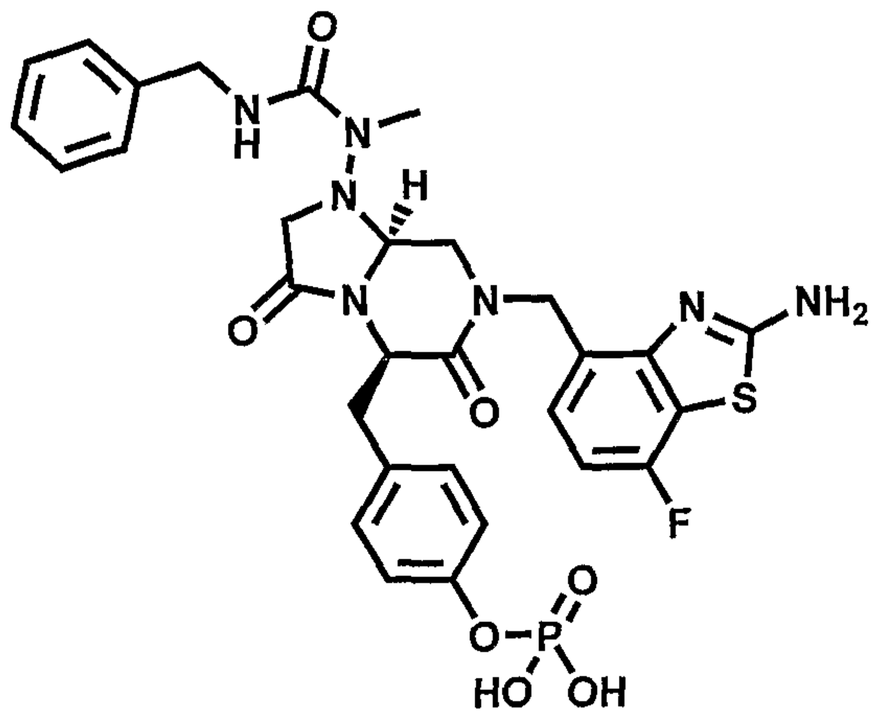
2209	
2210	
2211	

FIGURE 27D

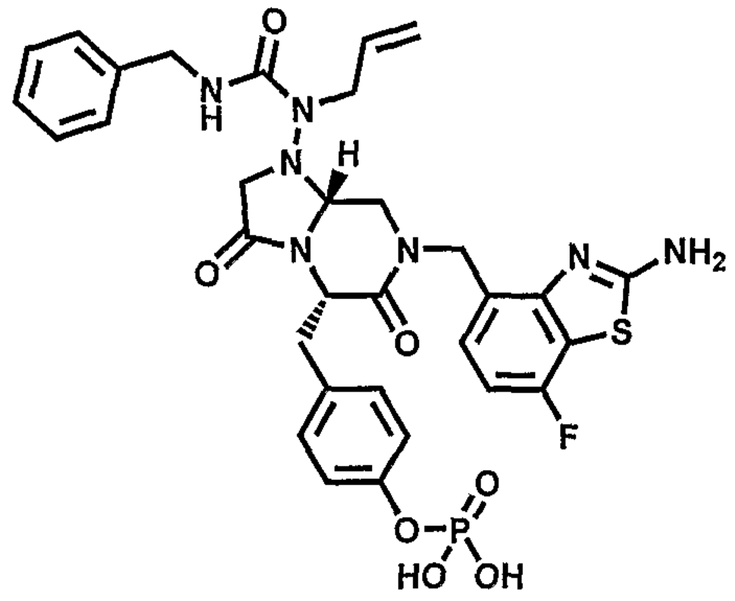
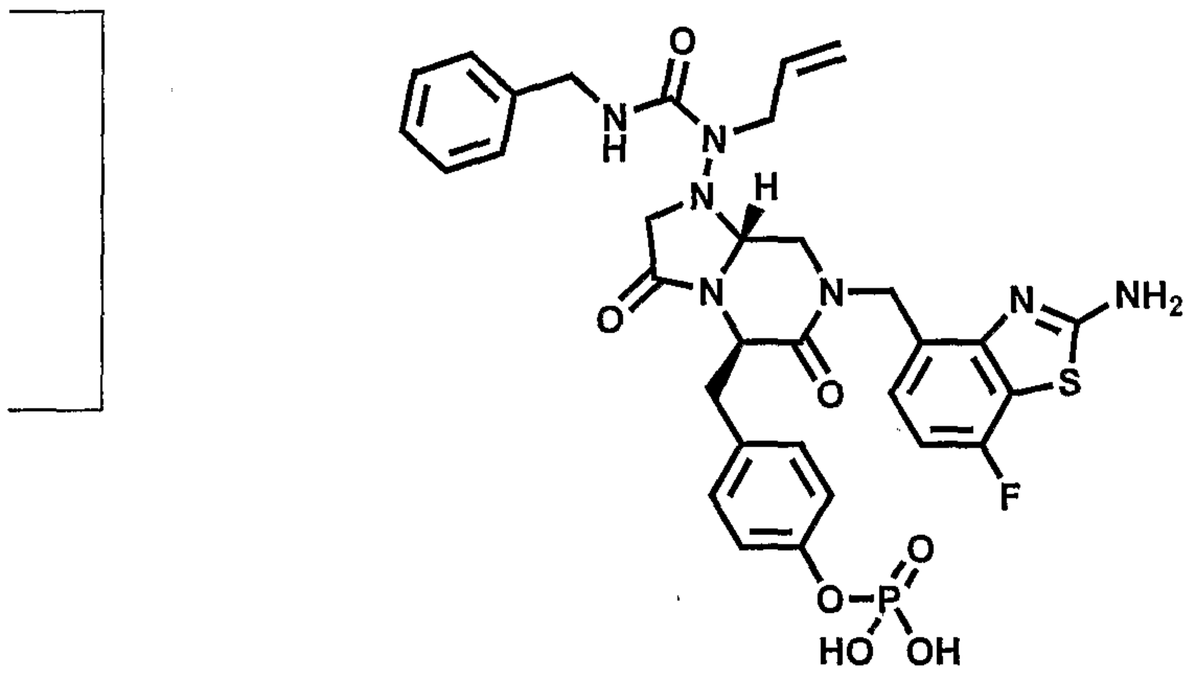
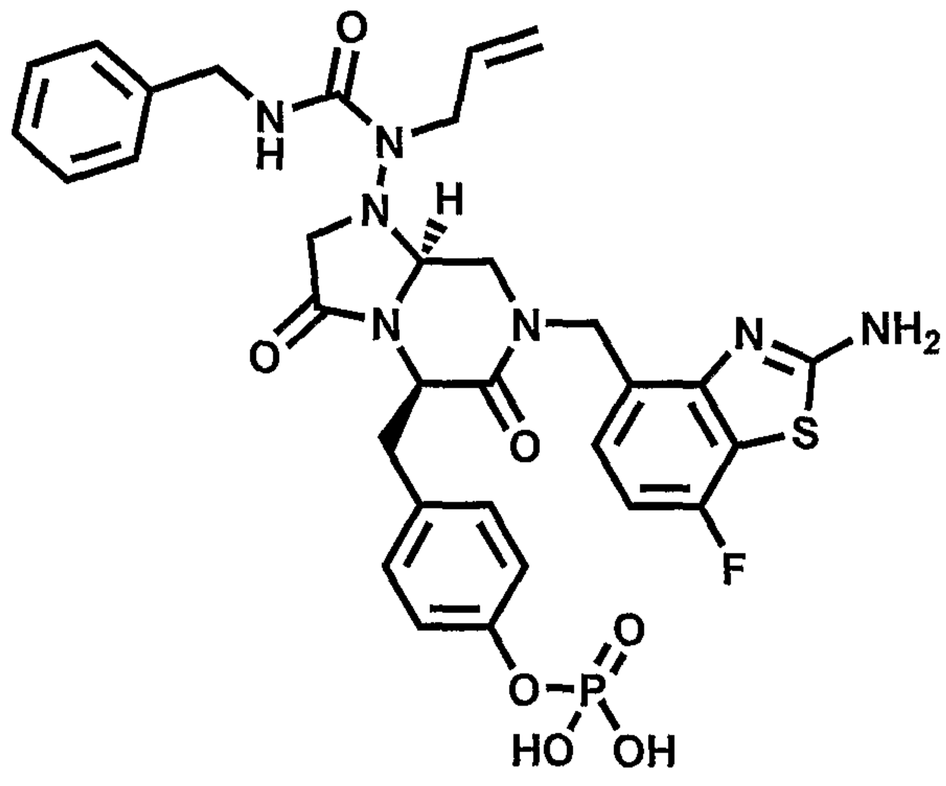
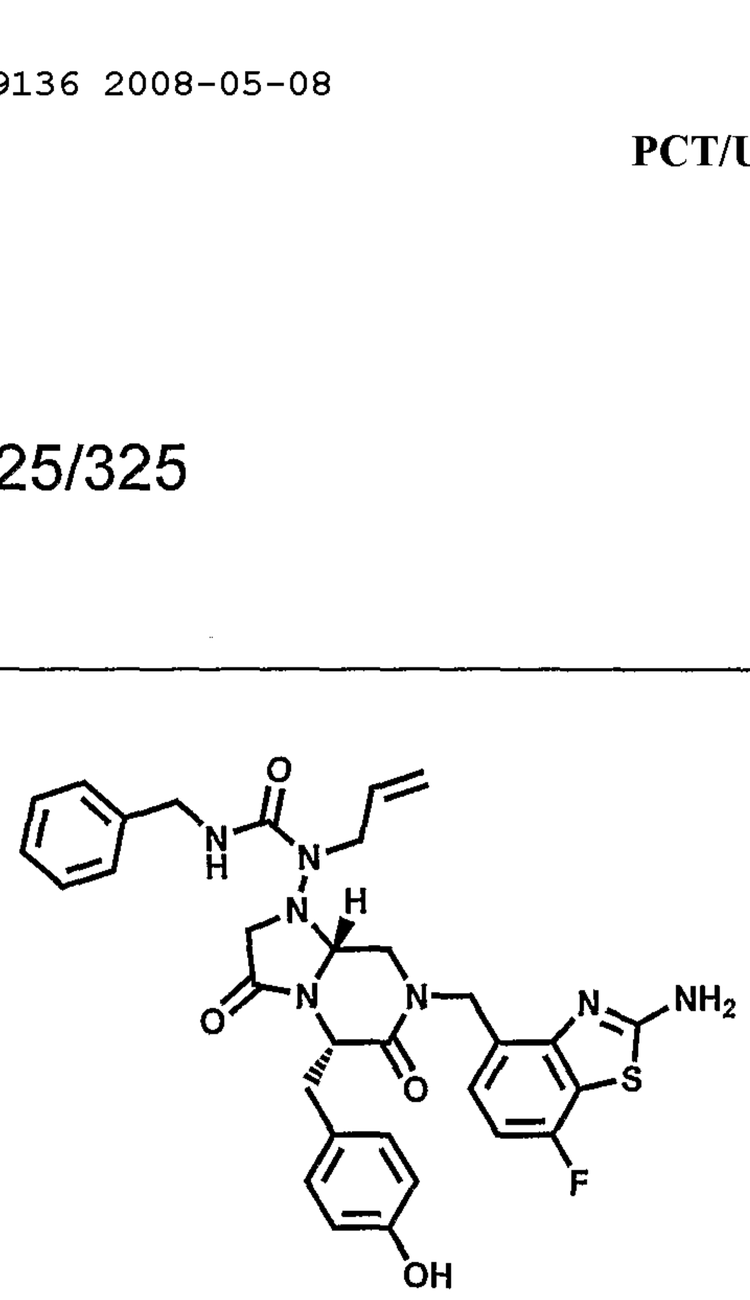
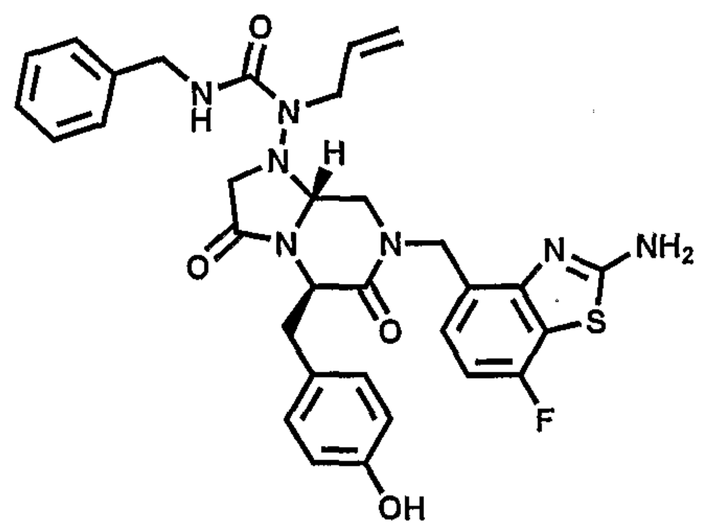
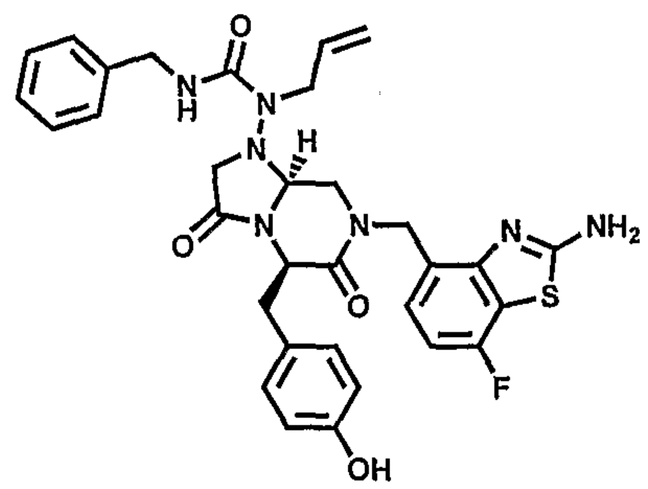
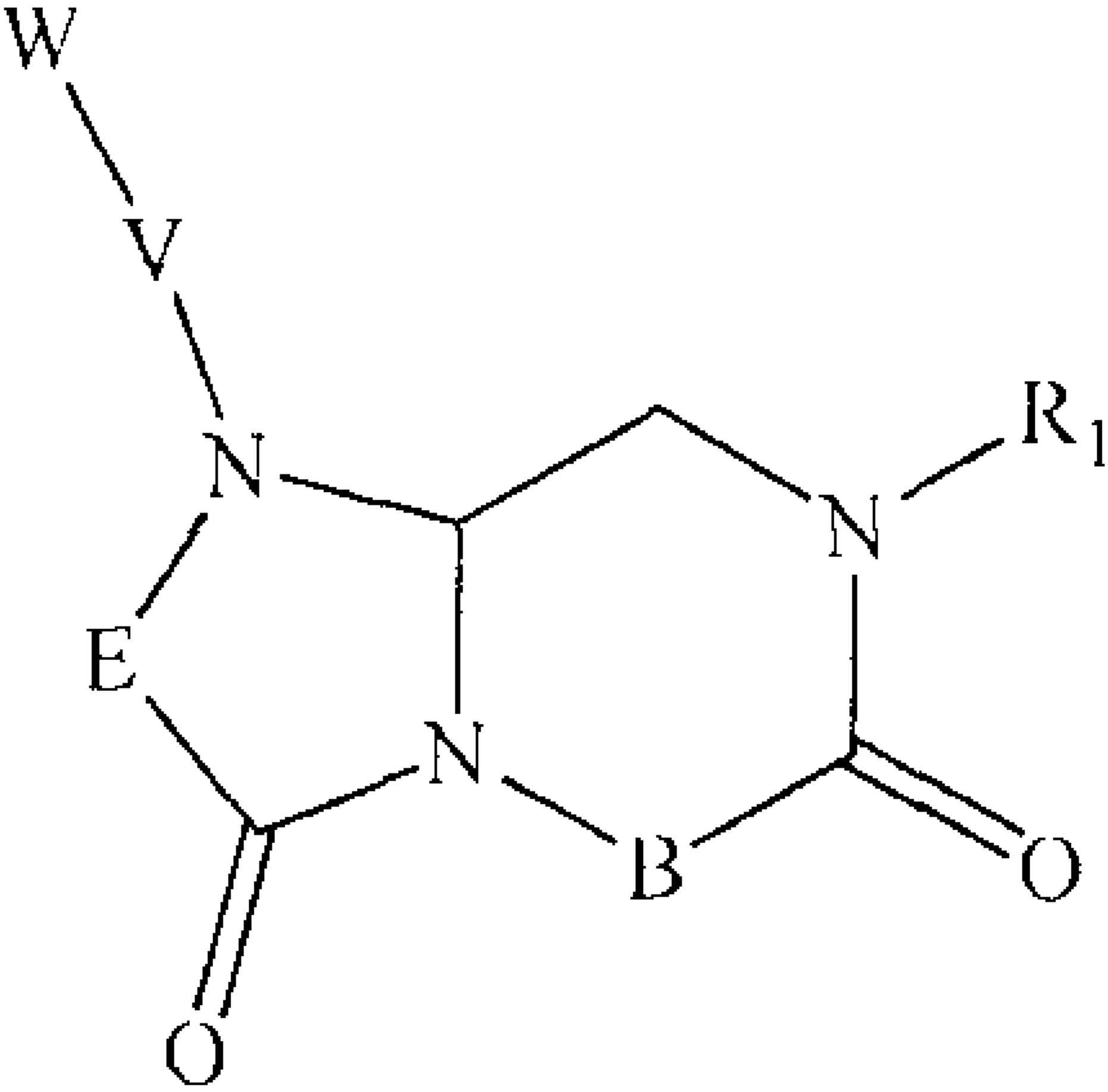
2212	
2213	
2214	

FIGURE 27E

2215	
2216	
2217	



(VI)