(19) OFICINA ESPAÑOLA DE PATENTES Y MARCAS

ESPAÑA

(11) Número de publicación: **2 375 114**

(51) Int. CI.:

C07D 231/56 (2006.01)
C07D 401/06 (2006.01)
C07D 403/06 (2006.01)
A61P 31/00 (2006.01)
A61K 31/416 (2006.01)

(12) TRADUCCIÓN DE PATENTE EUROPEA T3

(96) Número de solicitud europea: **08758745 .7**
(96) Fecha de presentación: **23.05.2008**
(97) Número de publicación de la solicitud: **2155690**
(97) Fecha de publicación de la solicitud: **24.02.2010**

(54) Título: **DERIVADOS DE INDAZOLAMIDA.**

(30) Prioridad:
21.06.2007 DE 102007028521

(45) Fecha de publicación de la mención BOPI:
24.02.2012

(45) Fecha de la publicación del folleto de la patente:
24.02.2012

(73) Titular/es:
MERCK PATENT GMBH
FRANKFURTER STRASSE 250
64293 DARMSTADT, DE

(72) Inventor/es:
BUCHSTALLER, Hans-Peter;
EGGENWEILER, Hans-Michael y
SIRRENBERG, Christian

(74) Agente: **Carvajal y Urquijo, Isabel**

Aviso: En el plazo de nueve meses a contar desde la fecha de publicación en el Boletín europeo de patentes, de la mención de concesión de la patente europea, cualquier persona podrá oponerse ante la Oficina Europea de Patentes a la patente concedida. La oposición deberá formularse por escrito y estar motivada; sólo se considerará como formulada una vez que se haya realizado el pago de la tasa de oposición (art. 99.1 del Convenio sobre concesión de Patentes Europeas).

DESCRIPCIÓN

Derivados de indazolamida

Antecedentes de la invención

El objeto de la presente invención es encontrar nuevos compuestos con propiedades valiosas, principalmente aquellos que pueden usarse para la preparación de medicamentos.

La presente invención se refiere a compuestos en los que la inhibición, regulación y/o modulación de la HSP90 desempeña una función, además a composiciones farmacéuticas que contienen estos compuestos, así como a la utilización de los compuestos para el tratamiento de enfermedades en las que la HSP90 desempeña una función.

El plegado y la conformación correctos de las proteínas en células se garantizan mediante chaperonas moleculares y son críticas para la regulación del equilibrio entre síntesis de proteína y degradación. Las chaperonas son importantes para la regulación de muchas funciones centrales de células como, por ejemplo, la proliferación celular y la apoptosis (Jolly and Morimoto, 2000; Smith et al., 1998; Smith, 2001).

Proteínas de impacto térmico (heat shock proteins, HSPs)

Las células de un tejido reaccionan al estrés externo como, por ejemplo, calor, hipoxia, estrés por oxidación o tóxicos como metales pesados o alcoholes, con la activación de una serie de chaperonas que se conocen bajo la denominación de proeínas de impacto térmico, del inglés "heat shock proteins", (HSPs, por sus siglas en inglés). La activación de HSPs protege la célula contra lesiones provocadas por dichos factores de estrés, se acelera la recomposición del estado fisiológico y conduce a un estado de la célula tolerante del estrés. Además de este mecanismo de protección descubierto originalmente, proporcionado por HSPs en caso de estrés externo, en el transcurso del tiempo también se han descrito otras funciones importantes de chaperonas para HSPs individuales en condiciones normales, desprovistas de estrés. De esta manera, las distintas HSPs regulan, por ejemplo, el plegado correcto, la localización y función intracelular o la degradación regulada de una serie de proteínas biológicamente importantes de las células.

Las HSPs forman una familia de genes con productos génicos individuales, cuya expresión celular, función y localización se diferencia en células diferentes. La denominación y clasificación dentro de la familia se efectúa en base a su peso molecular, por ejemplo HSP27, HSP70, y HSP90.

Algunas enfermedades humanas se basan en un plegamiento incorrecto de la proteína (véase, por ejemplo, reseña Tytell et al., 2001; Smith et al., 1998). Por lo tanto, el desarrollo de terapias que intervienen en el mecanismo del plegamiento de proteína dependiente de las chaperonas podría ser útil en tales casos. Por ejemplo, en el caso de la enfermedad de Alzheimer, de las enfermedades priónicas o en el síndrome de Huntington, las proteínas desplegadas de manera incorrecta conducen a una agregación de proteína con evolución neurodegenerativa. Por el plegamiento incorrecto de proteína también puede generarse una pérdida de la función de tipo silvestre, lo que puede tener como consecuencia una función molecular y fisiológica mal regulada.

A las HSPs también se les atribuye una gran importancia en el caso de enfermedades tumorales. Hay indicios, por ejemplo, de que la expresión de determinadas HSPs se encuentra en conexión con el estadio del progreso de tumores (Martin et al., 2000; Conroy et al., 1996; Kawanishi et al., 1999; Jameel et al., 1992; Hoang et al., 2000; Lebeau et al., 1991).

El hecho de que HSP90 desempeña una función en varias rutas de señal oncogénicas centrales en la célula, y que se apunte a ciertos materiales naturales con actividad de HSP90 inhibidora de cáncer, condujo al concepto de que era conveniente una inhibición de la función de HSP90 en el tratamiento de enfermedades tumorales.

Un inhibidor de HSP90, 17- alilamino-17-demetoxigeldanamicina (17AAG), un derivado de geldanamicina, se encuentra actualmente en verificación clínica.

HSP90

La HSP90 representa aproximadamente un 1- 2% de toda la masa de proteína celular. Habitualmente, se presenta en la célula como dímero y está asociada con una gran cantidad de proteínas, llamadas co-chaperonas (véase por ejemplo Pratt, 1997). La HSP90 es esencial para la vitalidad de las células (Young et al., 2001) y desempeña un papel clave en la respuesta al estrés celular por interacción con muchas proteínas cuyo plegamiento original ha sido modificado por estrés externo, como por ejemplo impacto térmico, con el fin de recomponer el plegamiento original o impedir la agregación de la proteína. (Smith et al., 1998). También hay indicios de que la HSP90 tiene una

importancia contra los efectos de mutaciones, supuestamente por la corrección de un plegamiento incorrecto de las proteínas que se provocó por la mutación (Rutherford y Lindquist, 1998). Además, la HSP90 también tiene una importancia reguladora. En condiciones fisiológicas la HSP90 desempeña un rol en el presupuesto celular junto con su homólogo en el retículo endoplasmático, GRP94, con el fin de garantizar la estabilidad de la conformación y la maduración de distintas proteínas claves "clientes". Éstas pueden subdividirse en tres grupos: receptores para hormonas esteroides, las Ser/Thr o tirosinquinasas (por ejemplo ERBB2, RAF-1, CDK4 y LCK) y una colección de distintas proteínas como, por ejemplo, p53 mutada o la subunidad catalítica de la telomerasa hTERT. Cada una de estas proteínas adopta un papel clave en la regulación de procesos fisiológicos y bioquímicos de las células. La familia de la HSP90 conservada de los humanos está compuesta de cuatro genes, la HSP90α citosólica, la isoforma inducible HSP90β (Hickey et al., 1989), la GRP94 en el retículo endoplasmático (Argon et al., 1999) y el HSP75/TRAP1 en la matriz mitocondrial (Felts et al., 2000). Se supone que todos los miembros de la familia tienen una forma de acción similar, pero según su localización en la célula se enlazan con diversas proteínas "clientes". Por ejemplo, ERBB2 es una proteína "cliente" específica GRP94 (Argon et al., 1999), mientras que el receptor de tipo 1 del factor de necrosis tumoral (TNFR1) o la proteína de retinoblastoma (Rb) se detectaron como "clientes" deTRAP1 (Song et al., 1995; Chen et al., 1996). HSP90 participa en una serie de interacciones complejas con un gran número de proteínas "clientes" y proteínas reguladoras (Smith, 2001). Si bien aún no se han clarificado detalles moleculares precisos, en los últimos años, con ayuda de la cristalografía de rayos X, los experimentos e investigaciones bioquímicas han podido descifrar cada vez más detalles de la función chaperona de HSP90 (Prodromou et al., 1997; Stebbins et al., 1997). Conforme con esto, la HSP90 es una chaperona molecular dependiente de ATP (Prodromou et al, 1997), en cuyo caso la dimerización es importante para la hidrólisis de ATP. El enlace de ATP resulta en la formación de una estructura dimérica toroidal en la que ambos dominios N-terminales entran en estrecho contacto entre sí y producen un "switch" (conmutación) en la conformación. (Prodromou and Pearl, 2000).

Inhibidores conocidos de HSP90

La primera clase de inhibidores de HSP90 que fue descubierta fueron las ansamicinas de benzoquinona con los compuestos herbimicina A y geldanamicina. Originalmente se comprobó con ellas la reversión del fenotipo maligno en fibroblastos, la cual había sido inducida por la transformación con oncogén v-Src (Uehara et al., 1985).

Más tarde se mostró una fuerte actividad antitumoral in vitro (Schulte et al.,1998) e in vivo en modelos animales (Supko et al., 1995). Inmunoprecipitación y estudios de matrices de afinidad mostraron luego que el mecanismo de acción principal de la geldanamicina involucra un enlace con HSP90 (Whitesell et al., 1994; Schulte and Neckers, 1998). Además, mediante estudios de cristalografía de rayos X se mostró que geldanamicina compite por el sitio de enlace de ATP y se inhibe la actividad intrínseca a ATPasa por la HSP90 (Prodromou et al., 1997; Panaretou et al., 1998). De esta manera, se impide la generación de complejo de HSP90 multímero con su propiedad de fungir como chaperona para proteínas "clientes". Como consecuencia se degradan las proteínas "clientes" a través de la vía ubiquitina-proteasoma. El derivado de geldanamicina 17- alilamino-17-demetoxigeldanamicina (17AAG) mostró una propiedad inalterada en la inhibición de HSP90, en la degradación de proteínas "clientes" y actividad antitumoral en cultivos de células y modelos tumorales de xenoinjerto (Schulte et al, 1998; Kelland et al, 1999), pero tuvo una citotoxicidad hepática distintivamente más baja que la geldanamicina (Page et all 1997). En la actualidad se ensaya 17AAG en estudios clínicos de fase I/II. El Radicicol, un antibiótico macrocílico mostró también una revisión del fenotipo maligno de fibroplastos inducido por v-Src y v-Ha-Ras (Kwon et all 1992; Zhao et al, 1995). El Radicicol degrada un gran número de proteínas de señal como consecuencia de la inhibición de HSP90 (Schulte et al., 1998). Estudios cristalográficos de rayos X mostraron que el radicicol también se enlaza al dominio N-terminal de HSP90 e inhibe la actividad intrínseca de ATPasa (Roe et al., 1998).

Los antibióticos de tipo cumarina se enlazan de manera conocida al sitio de enlace de ATP del homólogo HSP90 del ADN girasa en bacterias. La cumarina, novobiocina, se enlaza al extremo carboxi-terminal de HSP90, es decir en otro sitio en HSP90 que la benzoquinona-ansamicina y radicicol, los cuales se enlazan al extremo N-terminal de HSP90. (Marcu et al., 2000b).

La inhibición de HSP90 por novobiocina resulta en la degradación de una gran cantidad de proteínas de señal dependientes de HSP90 (Marcu et al., 2000a).

Con PU3, un inhibidor de HSP90 derivado de purinas, pudo mostrarse la degradación de proteínas de señal, por ejemplo ERBB2. PU3 provoca la detención del ciclo celular y la diferenciación en las líneas celulares de cáncer de mama (Chiosis et al., 2001).

HSP90 como diana terapéutica

Mediante la participación de HSP90 en la regulación de una gran cantidad de vías de señal que tienen importancia decisiva en el fenotipo de un tumor, y el descubrimiento de que ciertas sustancias naturales ejercen su efecto biológico por inhibición de la actividad de la HSP90, en la actualidad se ensaya la HSP90 como nueva diana para el desarrollo de un agente terapéutico tumoral (Neckers et al., 1999).

El mecanismo principal de la forma de acción de la geldanamicina, 17AAG, y el radicicol comprende la inhibición del enlace de ATP al sitio de enlace de ATP en el extremo N-terminal de la proteína y la inhibición resultante de esta de la actividad intrínseca de ATPasa de la HSP90 (véase por ejemplo Prodromou et al., 1997; Stebbins et al., 1997; Panaretou et al., 1998). La inhibición de la actividad de ATPasa de la HSP90 impide la captación de co-chaperonas y favorece la formación de un heterocomplejo de HSP90 que lleva a las proteínas "clientes" por la vía de ubiquitina-proteasoma a la degradación (véase, por ejemplo Neckers et al., 1999; Kelland et al., 1999). El tratamiento de las células tumorales con inhibidores de la HSP90 conduce a la degradación selectiva de proteínas importantes con significado fundamental para procesos tales como proliferación celular, regulación del ciclo celular y apoptosis. Estos procesos son desregulados frecuentemente en los tumores (véase, por ejemplo, Hostein et al., 2001). Una justificación atractiva para el desarrollo de un inhibidor de HSP90 es que mediante degradación simultánea de varias proteínas que están relacionadas con el fenotipo transformado, puede lograrse un potente efecto terapéutico tumoral.

En particular, la presente invención se refiere a compuestos que inhiben, regulan y/o modulan HSP90, a composiciones que contienen estos compuestos, así como a métodos para su utilización para tratar enfermedades condicionadas por HSP90, como enfermedades tumorales, enfermedades virales como, por ejemplo, hepatitis B (Waxman, 2002); inmunosupresión en caso de trasplantes (Bijlmakers, 2000 and Yorgin, 2000); enfermedades condicionadas por inflamación (Bucci, 2000) como artritis reumatoide, asma, esclerosis múltiple, diabetes tipo 1, lupus erimatoso, psoriasis y enfermedad inflamatoria intestinal (Inflammatory Bowel Disease); fibrosis quística (Fuller, 2000); enfermedades relacionadas con angiogénesis (Hur, 2002 and Kurebayashi, 2001) tales como, por ejemplo, retinopatía diabética, hemangiomas, endometriosis y angiogénesis tumoral; enfermedades infecciosas; enfermedades autoinmunes; isquemia; estimulación de la regeneración nerviosa (Rosen et al., WO 02/09696; Degranco et al., WO 99/51223; Gold, US 6,210,974 B1); enfermedades fibrogenéticas tales como, por ejemplo, esclerodermia, polimiositis, lupus sistémico, cirrosis hepática, formación de queloides, nefritis intersticial y fibrosis pulmonar (Strehlow, WO 02/02123). La invención también hace referencia a la utilización de los compuestos de la invención para proteger células normales contra toxicidad causada por quimioterapia, así como a la utilización en caso de enfermedades, en cuyo caso el plegamiento incorrecto de proteína o la agregación es un factor causal principal tal como, por ejemplo, escrapia, la enfermedad de Creutzfeldt-Jakob, la enfermedad de Huntington o la enfermedad de Alzheimer (Sittler, Hum. Mol. Genet., 10, 1307, 2001; Tratzelt et al., Proc. Nat. Acad. Sci., 92, 2944, 1995; Winklhofer et al., J. Biol. Chem., 276, 45160, 2001). En la memoria WO01/72779 se describen compuestos de purina así como su utilización para tratar enfermedades condicionadas por GRP94 (homólogo o parálogo de HSP90), tales como enfermedades tumorales, en cuyo caso el tejido comprende un sarcoma o carcinoma, seleccionado del grupo compuesto de fibrosarcoma, mixosarcoma, liposarcoma, condrosarcoma, sarcoma osteogénico, cordoma, angiosarcoma, sarcoma de endotelio, linfangiosarcoma, linfangiosarcoma de endotelio, sinovioma, mesotelioma, tumor de Ewing, leiosarcoma, rabdomiosarcoma, carcinoma de colon, cáncer de páncreas, cáncer de mama, cáncer de ovario, cáncer de próstata, carcinoma de células escamosas, carcinoma basocelular, adenocarcinoma, carcinoma de glándulas sudoríparas, carcinoma de glándulas sebáceas, carcinoma papilar, adenocarcinomas papilares, cistadenocarcinomas, carcinoma de la médula ósea, carcinoma broncogénico, carcinoma de células renales, hepatoma, carcinoma del conducto biliar, carcinoma coriónico, seminoma, carcinoma embrionario, tumor de Wilms, cáncer cervical, tumor testicular, carcinoma de pulmón, carcinoma de pulmón de células pequeñas, carcinoma de vejiga, carcinoma epitelial, glioma, astrocitoma, meduloblastoma, craniofaringioma, ependimoma, pinealoma, hemangioblastoma, neuroma acústico, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leucemia, linfoma, mieloma múltiple, macroglobulinemia de Waldenstroms y enfermedad en cadena grave.

En la patente WO 01/72779 se revela además la utilización de los compuestos allí mencionados para el tratamiento de enfermedades virales, en cuyo caso el patógeno viral se selecciona del grupo compuesto por hepatitis tipo A, hepatitis tipo B, hepatitis tipo C, gripe, varicela, adenovirus, herpes Simplex tipo I (HSV-I), herpes Simplex tipo II (HSV-II), peste bovina, rinovirus, ecovirus, rotavirus, virus sincicial respiratorio (RSV), virus de papiloma, papovavirus, citomegalovirus, equinovirus, arbovirus, huntavirus, coxsackievirus, virus de paperas, virus de sarampión, virus de la rubeola, virus de poliomielitis, virus de inmunodeficiencia humana tipo I (VIH-I) y virus de inmunodeficiencia humana tipo II (VIH -II).

En la patente WO 01/72779 se describe además la utilización de los compuestos allí mencionados para la modulación de GRP94, en cuyo caso la actividad biológica modulada de GRP94 provoca una reacción inmune en un individuo, transporte de proteína del retículo endoplasmático, curación del estrés hipóxico/anóxico, curación de malnutrición, curación de estrés térmico o combinaciones de los mismas, y/o en cuyo caso el trastorno es un tipo de cáncer, una enfermedad infecciosa, un trastorno que se acompaña de un transporte interferido del retículo endoplasmático, un trastorno que se acompaña de isquemia/reperfusión, o combinaciones de los mismos, en cuyo caso el trastorno que se acompaña de isquemia / reperfusión es una consecuencia de paro cardiaco, asistolia y arritmias ventriculares retardadas, operación de corazón, operación cardiopulmonar de bypass, trasplante de órganos, lesión de la médula espinal, trauma cerebral, ataque apopléjico, ataque apopléjico tromboembólico, ataque hemorrágico, vaso-espasmo cerebral, hipotonía, hipoglicemia, status epilepticus (estado epiléptico), ataque epiléptico, angustia, esquizofrenia, trastorno neurodegenerativo, enfermedad de Alzheimer, corea de Huntington, esclerosis lateral amiotrófica (ALS) o estrés en el recién nacido.

En la patente WO 01/72779 se describe finalmente el uso de una cantidad eficaz de un modulador de la proteína GRP94 para la preparación de un medicamento para modificar una reacción celular posterior a un estado isquémico en un sitio del tejido en un individuo, mediante tratamiento de las células en el sitio del tejido con el modulador de la proteína GRP94, a fin de intensificar la actividad de GRP94 en células de forma tal que se modifique una ulterior reacción celular a un estado isquémico, en cuyo caso la condición isquémica posterior es preferentemente la consecuencia de paro cardíaco, asistolia y arritmias ventriculares retardadas, operación de corazón, operación cardiopulmonar de bypass, trasplante de órganos, lesión de la médula espinal, trauma cerebral, ataque apopléjico, ataque apopléjico tromboembólico, ataque apopléjico hemorrágico, vaso-espasmo cerebral, hipotonía, hipoglicemia, estado epiléptico, ataque epiléptico, angustia, esquizofrenia, un trastorno neurodegenerativo, enfermedad de Alzheimer, corea de Huntington, esclerosis lateral amiotrófica (ALS) o estrés en el recién nacido o, en cuyo caso, el sitio de tejido es el tejido para un trasplante.

A. Kamal et al. describen en Trends in Molecular Medicine, Vol. 10 No. 6, junio de 2004, aplicaciones terapéuticas y diagnósticas de la activación de la HSP90, entre otras, para el tratamiento de enfermedades del sistema nervioso central y de enfermedades cardiovasculares.

Por lo tanto, la identificación de pequeños compuestos que inhiben, regulan y/o modulan específicamente HSP90 es deseable y un objeto de la presente invención.

Se encontró que los compuestos de la invención y sus sales poseen propiedades farmacológicas muy valiosas al mismo tiempo que una buena tolerancia. Muestran principalmente propiedades inhibidoras de la HSP90.

Por esto son objeto de la presente invención los compuestos de acuerdo con la invención en calidad de medicamentos y/o principios activos de medicamentos en el tratamiento y/o la profilaxis de las enfermedades mencionadas y la utilización de compuestos de acuerdo con la invención para preparar un fármaco para el tratamiento y/o profilaxis de las enfermedades mencionadas.

El huésped o paciente puede pertenecer a cualquier especie de mamíferos como, por ejemplo, especies de primates, particularmente humanos; roedores, incluso ratones, ratas y hámsteres; conejos; equinos, bovinos, caninos, felinos, etc. Los modelos animales son de interés para investigaciones experimentales, en cuyo caso éstos ponen a disposición un modelo para el tratamiento de una enfermedad de los humanos.

ESTADO DE LA TÉCNICA

Los inhibidores de la indazol quinasa se describen en EP 1403255 A1, WO 02/10137 A2, WO 2004/022544 A1 y WO 2008/003396 A1. En la WO 00/53169 se describe la inhibición de HSP90 con cumarina o un derivado de cumarina. En la patenet WO 03/041643 A2 se revelan derivados de zearalanol inhibidores de HSP90.

Otros derivados de indazol inhibidores de HSP90 se conocen de WO 06/010595 y WO 02/083648.

Bibliografía adicional:

Argon Y and Simen BB. 1999 "Grp94, an ER chaperone with protein and peptide binding properties", Semin. Cell Dev. Biol., Vol. 10, pp. 495-505.

Bijlmakers M-JJE, Marsh M. 2000 "Hsp90 is essential for the synthesis and subsequent membrane association, but not the maintenance, of the Srckinase p56Ick", Mol. Biol. Cell, Vol. 11 (5), pp. 1585-1595.

Bucci M; Roviezzo F; Cicala C; Sessa WC, Cirino G. 2000 "Geldanamycin, an inhibitor of heat shock protein 90 (Hsp90) mediated signal transduction has anti-inflammatory effects and interacts with glucocorticoid receptor in vivo", Brit. J. Pharmacol., Vol 131 (1), pp. 13-16.

Carreras CW, Schirmer A, Zhong Z, Santi VS. 2003 "Filter binding assay for the geldanamycin-heat shock protein 90 interaction", Analytical Biochem., Vol 317, pp 40-46.

Chen C-F, Chen Y, Dai KD, Chen P-L, Riley DJ and Lee W-H. 1996 "A new member of the hsp90 family of molecular chaperones interacts with the retinoblastoma protein during mitosis and after heat shock", Mol. Cell. Biol., Vol. 16, pp. 4691-4699.

Chiosis G, Timaul MN, Lucas B, Munster PN, Zheng FF, Sepp-Lozenzino L and Rosen N. 2001 "A small molecule designed to bind to the adenine nucleotide pocket of HSP90 causes Her2 degradation and the growth arrest and differentiation of breast cancer cells", Chem. Biol., Vol. 8, pp. 289-299.

Chiosis G, Lucas B, Shtil A, Huezo H, Rosen N 2002 "Development of a purine-scaffold novel class of HSP90 binders that inhibit the proliferation of cancer cells and induce the degradation of her2 tyrosine kinase". Bioorganic Med. Chem., Vol 10, pp 3555-3564.

Conroy SE and Latchman DS. 1996 "Do heat shock proteins have a role in breast cancer?", Brit. J. Cancer, Vol. 74, pp. 717-721.

Felts SJ, Owen BAL, Nguyen P, Trepel J, Donner DB and Toft DO. 2000 "The HSP90-related protein TRAP1 is a mitochondrial protein with distinct functional properties", J. Biol. Chem., Vol. 5, pp. 3305-331 2.

Fuller W, Cuthbert AW. 2000 "Post-translational disruption of the delta F508 cystic fibrosis transmembrane conductance regulator (CFTR)-molecular Chaperone complex with geldanamycin stabilizes delta F508 CFTR in the rabbit reticulocyte lysate", J. Biol. Chem., Vol. 275(48), pp. 37462-37468.

Hickey E, Brandon SE, Smale G, Lloyd D and Weber LA. 1999 "Sequence and regulation of a gene encoding a human 89-kilodalton heat shock protein", Mol. Cell. Biol., Vol. 9, pp. 2615-2626.

Hoang AT, Huang J, Rudra-Gonguly N, Zheng J, Powell WC, Rabindron SK, Wu C and Roy-Burman P. 2000 "A novel association between the human heat shock transcription factor 1 (HSF1) and prostate adenocarcinoma, Am. J. Pathol., Vol. 156, pp. 857-864.

Hostein I, Robertson D, Di Stefano F, Workman P and Clarke PA. 2001 "Inhibition of signal transduction by the HSP90 inhibitor 17-allylamino-1 7-demethoxygeldanamycin results in cytostasis and apoptosis", Cancer Res., Vol. 61, pp. 4003-4009.

Hur E, Kim H-H, Choi SM, Kim JH, Yim S, Kwon HJ, Choi Y, Kim DK, Lee M-0, Park H. 2002 "Reduction of hypoxiainduced transcription through the repression of hypoxia-inducible factor-1α/aryl hydrocarbon receptor nuclear translocator DNA binding by the 90-kDa heat-shock protein inhibitor radicicol", Mol. Pharmacol., Vol 62(5), pp. 975-982.

Jameel A, Skilton RA, Campbell TA, Chander SK, Coombes RC and Luqmani YA. 1992 "Clinical Jolly C and Morimoto RI. 2000 "Role of the heat shock response and molecular chaperones in oncogenesis and cell death", J. Natl. Cancer Inst., Vol. 92, pp. 1564-1572.

Kawanishi K, Shiozaki H, Doki Y, Sakita I, Inoue M, Yano M, Tsujinata T,Shamma A and Monden M. 1999 "Prognostic significance of heat shock proteins 27 and 70 in patients with squamous cell carcinoma of the esophagus", Cancer, Vol. 85, pp. 1649-1657.

Kelland LR, Abel G, McKeage MJ, Jones M, Goddard PM, Valenti M, Murrer BA, and Harrap KR. 1993 "Preclinical antitumour evaluation of bisacetalo-amino-dichloro-cyclohexylamine platinum (IV): an orally active platinum drug", Cancer Research, Vol. 53, pp. 2581 - 2586.

Kelland LR, Sharp SY, Rogers PM, Myers TG and Workman P. 1999 "DT-diaphorase expression and tumor cell sensitivity to 17-allylamino,17-demetoxigeldanamycin, an inhibitor of heat shock protein 90", J. Natl. Cancer Inst., Vol. 91, pp. 1940-1949.

Kurebayashi J, Otsuki T, Kurosumi M, Soga S, Akinaga S, Sonoo, H. 2001 "A radicicol derivative, KF58333, inhibits expression of hypoxia-inducible factor-α and vascular endothelial growth factor, angiogenesis and growth of human breast cancer xenografts", Jap. J. Cancer Res., Vol. 92(12), 1342-1351.

Kwon HJ, Yoshida M, Abe K, Horinouchi S and Bepple T. 1992 "Radicicol, an agent inducing the reversal of transformed phentoype of srctransformed fibroblasts, Biosci., Biotechnol., Biochem., Vol. 56, pp. 538-539.

Lebeau J, Le Cholony C, Prosperi MT and Goubin G. 1991 "Constitutive overexpression of 89 kDa heat shock protein gene in the HBL100 mammary cell line converted to a tumorigenic phenotipe by the EJE24 Harvey-ras oncogene", Oncogene, Vol. 6, pp. 1125-1132.

Marcu MG, Chadli A, Bouhouche I, CatelliMand Neckers L. 2000a "The heat shock protein 90 antagonist novobiocin interacts with a previously unrecognized ATP-binding domain in the carboxyl terminus of the chaperone", J. Biol. Chem., Vol. 275, pp. 37181-37186.

Marcu MG, Schulte TW and Neckers L. 2000b "Novobiocin and related coumarins and depletion of heat shock protein 90-dependent signaling proteins", J. Natl. Cancer Inst., Vol. 92, pp. 242-248.

Martin KJ, Kritzman BM, Price LM, Koh B, Kwan CP, Zhang X, MacKay A, O'Hare MJ, Kaelin CM, Mutter GL, Pardee AB and Sager R. 2000 "Linking gene expression patterns to therapeutic groups in breast cancer", Cancer Res., Vol. 60, pp. 2232-2238.

Neckers L, Schulte TW and Momnaaugh E. 1999 "Geldanamycin as a potential anti-cancer agent: its molecular target and biochemical activity", Invest. New Druqs, Vol. 17, pp. 361-373.

Page J, Heath J, Fulton R, Yalkowsky E, Tabibi E, Tomaszewski J, Smith A and Rodman L. 1997 "Comparison of geldanamycin (NSC-122750) and 17-allylaminogeldanamycin (NSC-330507D) toxicity in rats", Proc. Am. Assoc. Cancer Res., Vol. 38, pp. 308.

Panaretou B, Prodromou C, Roe SM, OBrien R, Ladbury JE, Piper PW and Pearl LH. 1998 "ATP binding and hydrolysis are essential to the function of the HSP90 molecular chaperone in vivo", EMBOJ., Vol. 17, pp. 4829-4836.

Pratt WB. 1997 "The role of the HSP90-based chaperone system in signal transduction by nuclear receptors and receptors signalling via MAP kinase", Annu. Rev. Pharmacol. Toxicol., Vol. 37, pp. 297-326. Prodromou C, Roe SM, O'Brien R, Ladbury JE, Piper PW and Pearl LH. 1997 "Identification and structural characterization of the ATP/ADP-binding site in the HSP90 molecular chaperone", Cell, Vol. 90, pp. 65-75.

Prodromou C, Panaretou B, Chohan S, Siligardi G, O'Brien R, Ladbury JE, Roe SM, Piper PW and Pearl LH. 2000 "The ATPase cycle of HSP90 drives a molecular "clamp" via transient dimerization of the N-terminal domains", EMBO J., Vol. 19, pp. 4383-4392.

Roe SM, Prodromou C, O'Brien R, Ladbury JE, Piper PW and Pearl LH. 1999 "Structural basis for inhibition of the HSP90 molecular chaperone by the antitumour antibiotics radicicol and geldanamycin", J. Med. Chem., Vol. 42, pp. 260-266.

Rutherford SL and Lindquist S. 1998 "HSP90 as a capacitor for morphological evolution. Nature, Vol. 396, pp. 336-342.

Schulte TW, Akinaga S, Murakata T, Agatsuma T, Sugimoto S, Nakano H, Lee YS, Simen BB, Argon Y, Felts S, Toft DO, Neckers LM and Sharma SV. 1999 "Interaction of radicicol with members of the heat shock protein 90 family of molecular chaperones", Mol. Endocrinoloqy, Vol. 13, pp. 1435-1448.

Schulte TW, Akinaga S, Soga S, Sullivan W, Sensgard B, Toft D and Neckers LM. 1998 "Antibiotic radicicol binds to the N-terminal domain of HSP90 and shares important biologic activities with geldanamycin", Cell Stress and Chaperones, Vol. 3, pp. 100-108.

SchulteTW and Neckers LM. 1998 "The benzoquinone ansamycin 17-allylamino-17-demethoxygeldanamycin binds to HSP90 and shares important biologic activities with geldanamycin", Cancer Chemother. Pharmacol., Vol. 42, pp. 273-279.

Smith DF. 2001 "Chaperones in signal transduction", in: Molecular chaperones in the cell (P Ly, ed.; Oxford University Press, Oxford and NY), pp. 165-178.

Smith DF, Whitesell L and Katsanis E. 1998 "Molecular chaperones: Biology and prospects for pharmacological intervention", Pharmacological Reviews, Vol. 50, pp. 493-513.

Song HY, Dunbar JD, Zhang YX, Guo D and Donner DB. 1995 "Identification of a protein with homology to hsp90 that binds the type 1 tumour necrosis factor receptor", J. Biol. Chem., Vol. 270, pp. 3574-3581.

Stebbins CE, Russo A, Schneider C, Rosen N, Hartl FU and Pavletich NP. 1997 "Crystal structure of an HSP90-geldanamycin complex: targeting of a protein chaperone by an antitumor agent", Cell, Vol. 89, pp. 239-250.

Supko JG, Hickman RL, Grever MR and Malspeis L. 1995 "Preclinical pharmacologic evaluation of geldanamycin as an antitumour agent", Cancer Chemother. Pharmacol., Vol. 36, pp. 305-315.

Titell M and Hooper PL. 2001 "Heat shock proteins: new keys to the development of cytoprotective therapies", Emerging Therapeutic Tarqets, Vol. 5, pp. 267-287.

Uehara U, Hori M, Takeuchi T and Umezawa H. 1986 "Phenotypic change from transformed to normal induced by benzoquinoid ansamycins accompanies inactivation of p6Osrc in rat kidney cells infected with Rous sarcoma virus", Mol. Cell. Biol., Vol. 6, pp. 21 98-2206.

Waxman, Lloyd H. Inhibiting hepatitis C virus processing and replication. (Merck & Co., Inc., USA). PCT Int. Appl. (2002), WO 0207761 Whitesell L, Mimnaugh EG, De Costa B, Miers CE and Neckers LM. 1994 "Inhibition of heat shock protein HSP90-pp60v-src heteroprotein complex formation by benzoquinone ansamycins: essential role for stress proteins in oncogenic transformation", Proc. Natl. Acad. Sci. USA., Vol. 91, pp. 8324-8328.

Yorgin et al. 2000 "Effects of geldanamycin, a heat-shock protein 90-binding agent, on T cell function and T cell nonreceptor protein tirosine kinases", J. Immunol., Vol 164(6), pp. 2915-2923.

Young JC, Moarefi I y Hartl FU. 2001 "HSP90: a specialized but essential protein-folding tool", J. Cell. Biol., Vol. 154, pp. 267-273.

Zhao JF, Nakano H and Sharma S. 1995 "Suppression of RAS and MOS transformation by radicicol", Oncoqene, Vol. 11, pp. 161 -173.

RESUMEN DE LA INVENCIÓN

La invención hace referencia a los compuestos de la reivindicación 1 de la patente.

También son objeto de la invención los estereoisómeros (isómeros E, Z) así como los hidratos y solvatos de estos compuestos. Por solvatos de los compuestos se entienden adiciones de moléculas inertes de solventes a los compuestos, las cuales se forman debido a su fuerza de atracción mutua. Solvatos son, por ejemplo, mono- o dihidratos o alcóxidos.

La expresión "cantidad eficaz" significa la cantidad de un medicamento o de un principio activo farmacéutico que provoca una respuesta biológica o medicinal en un tejido, sistema, animal o humano, que se busca o se pretende por parte de un investigador o un médico. Además, la expresión "cantidad terapéuticamente eficaz" significa una cantidad que, en comparación con un sujeto correspondiente que no haya obtenido esta cantidad, tiene como consecuencia lo siguiente: tratamiento curativo mejorado, curación, prevención o remisión de una enfermedad, un cuadro patológico, un estado patológico, un mal, un trastorno o de efectos secundarios o también la reducción del progreso de una enfermedad, un mal o un trastorno. La denominación "cantidad terapéuticamente eficaz" también abarca las cantidades que son eficaces para elevar la función fisiológica normal.

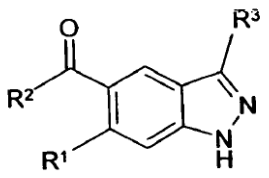
También son objeto de la invención mezclas de los compuestos de la fórmula I de acuerdo con la invención, por ejemplo mezclas de dos diastereomeros, por ejemplo en proporción 1:1, 1:2, 1:3, 1:4, 1:5, 1:10, 1:100 o 1:1000. Particularmente se prefieren en este caso mezclas de compuestos estereoisómeros.

Los compuestos de la invención y también las materias primas de partida para su preparación se preparan, por lo demás, según métodos conocidos, tal como se describen en la bibliografía (por ejemplo, las obras estándar como Houben-Weil, Methoden der organischen Chemie (Métodos de la Química Orgánica), Georg-Thieme-Verlag editorial, Stuttgart), y son ciertamente adecuados para las reacciones mencionadas en condiciones de reacción. Aquí también puede hacerse uso de variantes conocidas que no se han mencionado en la presente.

Si se desea, las materias primas de partida pueden formarse in situ, de tal modo que no se aíslen de la mezcla de reacción sino se hagan reaccionar inmediatamente para formar los compuestos de la invención.

Los compuestos de partida son conocidos por lo regular. Si son nuevos pueden no obstante prepararse según métodos conocidos.

Se revelan compuestos de la fórmula I



I

donde

R^1 significa H, OH, OCH_3, OCF_3, $OCHF_2$, OBzl, OAc, p-metoxi- benciloxi, SH, $S(O)_mCH_3$, SO_2NH_2, Hal, CF_3 o CH_3,

Preferentemente, pueden obtenerse compuestos de la fórmula I haciendo reaccionar un compuesto de la fórmula II con un heterociclo R^2. En los compuestos de la fórmula II L significa preferentemente F, Cl, Br, I o un grupo OH transformado reactivamente como, por ejemplo, un éster activado, un imidazolida o alquilsulfoniloxi con 1-6 átomos de C (preferible metilsulfoniloxi o trifluorometilsulfoniloxi) o arilsulfoniloxi con 6-10 átomos de C (preferible fenil- o p-tolilsulfoniloxi). En los compuestos de la fórmula II, L significa preferentemente Cl.

R^2 significa heterociclo mono o bicíclico, insustituido o sustituido una, dos o tres veces por R^4 y/o R^5, saturado o insaturado, con 1 a 4 átomos de N, O y/o S, el cual contiene al menos un átomo de N y en cuyo caso el átomo de N está enlazado directamente al grupo carbonilo adyacente,

R^3 significa H, Hal, A, OA, AlkOH, COOA, COA, COHet, $CONH_2$, CONHA, CONAA', CONHAr, CONH(AlkAr), CONAAr, CONA(AlkAr), CONHHet, CONH(AlkHet), CONAHet, CONA(AlkHet), AlkCOOA, AlkCONHA, AlkCONAA', $AlkNHCONH_2$, AlkNHCONHA, AlkNHCONAA', AlkNHCOA, AlkNHCOAr, $AlkNHSO_2A$, $AlkNHSO_2Ar$, $AlkNASO_2Ar$, $AlkNHSO_2CH_2Ar$, $AlkNASO_2CH_2Ar$, AlkAr, AlkHet, NHAr, NHA, NAA', NAAr, NAHet o NHHet,

R^4 significa H, A, Ar, $(CH_2)_nHet$, Hal, CN, NO_2, NH_2, OH, OA, OAr, OAlkAr, OAlkHet, OAHet, SH, SA, SAr, SAlkAr, SHet, SAlkHet, COA, COAr, COHet, $S(O)_mA$, $S(O)_mAr$, $S(O)_mAAr$, $S(O)_mHet$, $S(O)_mAHet$, NHA, NHAr, NHHet, NAA', NAAr, NAHet, COOH, COOA, $CONH_2$, CONHA, CONAA', $CONH(CH_2)_nAr$, $CONA(CH_2)Ar$, $CONH(CH_2)_nHet$, $CONA(CH_2)_nHet$, SO_2NH_2, SO_2NHA, SO_2NAA', $SO_2NH(CH_2)_nAr$, $SO_2NA(CH_2)_nAr$, $SO_2NH(CH_2)_nHet$, $SO_2NA(CH_2)_nHet$, NHCOA, NACOA', $NHCO(CH_2)_nAr$, $NACO(CH_2)_nAr$, $NHCO(CH_2)_nHet$, $NACO(CH_2)_nHet$, $NHSO_2A$, $NASO_2A'$, $NHSO_2(CH_2)_nAr$, $NASO_2(CH_2)_nAr$, $NHSO_2(CH_2)_nHet$, $NASO_2(CH_2)_nHet$, NHCOOA, NHCOOAr, NHCOOHet, NHCONHA, NHCONHAr, NHCONHHet, =O (oxígeno de carbonilo), $OAlkNH_2$, OAlkNHA, OAlkNAA', OAlkOH, OAlkOA, OAlkCN, $CONHAlkNH_2$, CONHAlkNHA, CONHAlkNAA', $COAlkNH_2$, COAlkNHA o COAlkNAA',

R^5 significa H, A, Ar, Het, AlkAr, AlkHet, COA, $CO(CH_2)_nAr$, $CO(CH_2)_nHet$, SO_2A, $SO_2(CH_2)_nAr$, $SO_2(CH_2)_nHet$, COOA, COOAr, COOHet, CONHA, CONHAr o CONHHet,

Ar significa fenilo insustituido o mono-, di-, tri-, tetra- o penta-sustituido por A, OA, OH, SH, $S(O)_mA$, Hal, NO_2, CN, COA, COOH, COOA, $CONR^6R^7$, $SO_2NR^6R^7$, NR^6R^7, $OCONR^6R^7$, NR^6COR^7, $NR^6SO_2R^7$, $NR^6CONR^6R^7$, $(CH_2)_nNHSO_2A$, $O(CH_2)_pCN$, SO_2Het^1, $O(CH_2)_pNR^6R^7$ y/o $(CH_2)_mHet^1$, naftilo o bifenilo,

A, A' significan respectivamente entre sí alquilo no ramificado o ramificado con 1-10 átomos de C, donde 1-3 grupos CH_2 pueden reemplazarse por O, S, SO, SO_2, NH, NMe o NEt y/o también 1-5 átomos de H pueden estar reemplazados por F y/o CI, Alk^1 o alquilo cíclico con 3-8 átomos de C,

Alk^1 significa alquenilo o alquinilo con 2-6 átomos de C,

Alk significa alquileno no ramificado o ramificado con 1-8 átomos de C donde 1-7 átomos de H que pueden estar reemplazados por OH, F, Cl y/o Br, y/o donde uno o dos grupos CH_2 pueden estar reemplazados por O,

Het significa un heterociclo mono o binuclear, saturado, insaturado o aromático con 1 a 4 átomos de N, O y/o S, el cual puede estar insustituido o mono-, di- o tri-sustituido por A, OA, OH, SH, $S(O)_mA$, Hal, NO_2, CN, COA, COOA, $CONR^6R^7$, $SO_2NR^6R^7$, NR^6R^7, $OCONR^6R^7$, NR^6COR^7, $NR^6SO_2R^7$, $NR^6CONR^6R^7$, =S, =NH, =NA y/o =O (oxígeno de carbonilo),

Het^1 significa un heterociclo mononuclear saturado con 1 a 3 átomos de N y/o de O el cual puede estar insustituido o mono-, di- o tri-sustituido por A, OA, OH y/o =O (oxígeno de carbonilo),

R^6, R^7 significan respectivamente independientemente entre sí H o alquilo con 1-6 átomos de C, donde 1-3 grupos de CH_2 pueden estar reemplazados por O, S, SO, SO_2, NH, NMe, o NEt y/o también 1-5 átomos de H pueden estar reemplazados por F y/o CI,

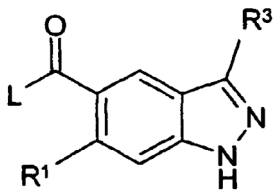
Hal significa F, Cl, Br o I,

m significa 0, 1 o 2,

n significa 0, 1, 2, 3 o 4,

p significa 1, 2, 3 o 4.

Además, se revela un compuesto de la fórmula II



II

donde

R^1 y R^3 tienen los significados indicados en la reivindicación 1, y L significa F, Cl, Br, I o un grupo OH libre o transformado reactivamente.

La reacción se efectúa según métodos que son conocidos para el experto en la materia. Primero la reacción se efectúa en un solvente adecuado. Como solvente son adecuados, por ejemplo, hidrocarburos como hexano, éter de petróleo, benceno, tolueno o xileno; hidrocarburos clorados como tricloroetileno, 1,2-dicloroetano, tetracloruro de carbono, cloroformo o diclorometano; alcoholes como metanol, etanol, isopropanol, n-propanol, n-butanol o terc.-butanol; éteres como éter de dietilo, éter de diisopropilo, tetrahidrofurano (THF) o dioxano; éteres de glicol como éter de etilenglicolmonometilo o etilenglicolmonoetilo (metilglicol o etilglicol), éter de etilenglicoldimetilo (diglima); cetonas como acetona o butanona; amidas como acetamida, dimetilacetamida o dimetilformamida (DMF); nitrilos como acetonitrilo; sulfóxidos como dimetilsulfóxido (DMSO); disulfuro de carbono; ácidos carboxílicos como ácido fórmico o ácido acético; nitrocompuestos como nitrometano o nitrobenceno; ésteres como acetato de etilo o mezclas de los solventes mencionados. Como solvente particularmente se prefiere THF.

El tiempo de reacción se encuentra según las condiciones aplicadas entre algunos minutos y 14 días, la temperatura de reacción se encuentra entre aproximadamente 0 C° y 150 C°, normalmente entre 15C° y 120C°, particularmente preferible entre 50 C° y 100 C°.

Sales farmacéuticas y otras formas

Los compuestos mencionados según la invención pueden usarse en su forma no salina definitiva. Por otra parte, la presente invención también comprende la utilización de estos compuestos en forma de sus sales farmacéuticas que pueden derivarse de diferentes ácidos y bases, orgánicos e inorgánicos, de acuerdo con procedimientos conocidos en el campo de la especialidad. Las sales farmacéuticas de los compuestos de la invención se preparan en su mayor parte de manera convencional. Siempre que el compuesto de la invención contiene un grupo de ácido carboxílico, puede formarse una de sus sales adecuadas haciendo reaccionar el compuesto con una base adecuada para llegar a una correspondiente sal de adición de base. Tales sales son, por ejemplo, hidróxidos de metales alcalinos, entre ellos hidróxido de potasio, hidróxido de sodio e hidróxido de litio; hidróxidos de metal alcalino-térreo como hidróxido de bario e hidróxido de calcio; alcóxidos de metal alcalino, por ejemplo etóxido de potasio y propóxido de sodio; así como diversas bases orgánicas como piperidina, dietanolamina y N-metilglutamina. Las sales de aluminio de los compuestos de la fórmula I también se cuentan entre éstas. En caso de determinados compuestos de la fórmula I pueden formarse sales de adición de ácido tratando estos compuestos con ácidos orgánicos e inorgánicos farmacéuticos, por ejemplo ácidos halohídricos como ácido clorhídrico, ácido bromhídrico o ácido yodhídrico, otras sales minerales y sus sales correspondientes como sulfato, nitrato o fosfato y similares como sulfonatos de arilo y monoarilo como sulfonato de etano, sulfonato de tolueno y sulfonato de benceno, así como otros ácidos orgánicos y sus sales correspondientes como acetato, trifluoracetato, tartrato, maleato, succinato, citrato, benzoato, salicilato, ascorbato y similares. De conformidad con esto entre las sales de adición de ácido farmacéuticas de los compuestos de la fórmula I se cuentan los siguientes: acetato, adipato, alginato, arginato, aspartato, benzoato, sulfonato de benceno (besilato), bisulfato, bisulfito, bromuro, butirato, alcanforato, sulfonato de alcánfor, caprilato, cloruro, benzoato de cloro, citrato, propionato de ciclopentano, digluconato, dihidrofosfato, dinitrobenzoato, dodecilsulfato, sulfonato de etano, fumarato, galacterato (de ácido múcico), galacturonato, glucoheptanoato, gluconato, glutamato, glicerofosfato, hemisuccinato, hemisulfato, heptanoato, hexanoato, hipurato, hidrocloruro, hidrobromuro, hidroyoduro, sulfonato de 2-hidroxietano, yoduro, isetionato, isobutirato, lactato, lactobionato, malato, maleato, malonato, mandelato, metafosfato, sulfonato de metano, benzoato de metilo, monohidrofosfato, sulfonato de 2-naftalina, nicotinato, nitrato, oxalato, oleato, palmoato, pectinato, persulfato, acetato de fenilo, propionato de 3-fenilo, fosfato, fosfonato, ftalato, lo cual no representa restricción alguna.

Además, entre las sales de bases de los compuestos de la invención se cuentan las sales de aluminio, amonio, calcio, cobre, hierro (III), hierro (II), litio, magnesio, manganeso (III), manganeso (II), potasio, sodio y cinc, lo cual sin embargo no debe representar restricción alguna. Entre las sales mencionadas arriba se prefieren las de amonio; las sales de metal alcalino de sodio y potasio, así como las sales de metal alcalino-térreo de calcio y magnesio. Entre las sales de los compuestos de la invención que se derivan de bases orgánicas, farmacéuticas, no tóxicas, se cuentan sales de aminas primarias, secundarias y terciarias, de aminas sustituidas, entre ellas también aminas

sustituidas de procedencia natural, aminas cíclicas así como de resinas básicas de intercambio iónico, por ejemplo arginina, betaína, cafeína, cloroprocaína, colina, N,N'-dibenciletilendiamina (benzatina), diciclohexilamina, dietanolamina, dietilamina, 2-dietilaminoetanol, 2-dimetilaminoetanol, etanolamina, etilendiamina, N-etilmorfolina, N-etilpiperidina, glucamina, glucosamina, histidina, hidrabamina, iso-propilamina, lidocaína, lisina, meglumina, N-metil-D-glucamina, morfolina, piperazina, piperidina, resinas de poliamina, procaína, purina, teobromina, trietanolamina, trietilamina, trimetilamina, tripropilamina y tris-(hidroximetil)-metilamina (trometamina), lo cual no debe representar restricción alguna.

Compuestos de la presente invención que contienen grupos básicos que contienen nitrógeno, pueden cuaternizarse con agentes como alquil(de C_1-C_4) haluros, por ejemplo cloruro, bromuro y yoduro de metilo, etilo, isopropilo y terc.-butilo; sulfatos de dialquilo (de C_1-C_4), por ejemplo sulfato de dimetilo, de dietilo y de diamilo; haloalquilos de (C_{10}-C_{18}), por ejemplo cloruro, bromuro y yoduro de decilo, dodecilo, laurilo, miristilo y estearilo; así como halo aril-alquil(de C_1-C_4), por ejemplo cloruro de bencilo y bromuro de fenetilo. Con tales sales pueden prepararse compuestos de la invención solubles tanto en agua como en aceite.

Entre las sales farmacéuticas mencionadas que se prefieren se cuentan acetato, trifluoracetato, besilato, citrato, fumarato, gluconato, hemisuccinato, hipurato, hidrocloruro, hidrobromuro, isetionato, mandelato, meglumina, nitrato, oleato, fosfonato, pivalato, fosfato de sodio, estearato, sulfato, sulfosalicilato, tartrato, tiomalato, tosilato y trometamina, lo cual sin embargo no representa restricción alguna.

Las sales de adición de ácido de compuestos básicos de la invención se preparan poniendo en contacto la forma básica libre con una cantidad suficiente del ácido deseado, por lo cual se obtiene la sal de manera usual. La base libre puede regenerarse de manera usual poniendo en contacto la forma salina con una base y aislando la base libre. Las formas básicas libres se diferencian en cierto sentido de sus correspondientes formas salinas respecto de determinadas propiedades físicas como solubilidad en solventes polares. En el contexto de la invención las sales corresponden, sin embargo, a sus respectivas formas básicas libres.

Tal como se ha mencionado, se forman sales farmacéuticas de adición de bases de los compuestos de la invención con metales o aminas, como metales alcalinos y metales alcalino-térreos o aminas orgánicas. Metales preferidos son sodio, potasio, magnesio y calcio. Aminas orgánicas preferidas son N,N'-dibenciletilendiamina, cloroprocaína, colina, dietanolamina, etilendiamina, N-metil-D-glucamina y procaína.

Las sales de adición de bases de compuestos ácidos de la invención se preparan poniendo en contacto la forma ácida libre con una cantidad suficiente de la base deseada, por lo cual se obtiene la sal de manera usual. El ácido libre puede regenerarse poniendo en contacto la forma salina con un ácido y aislando el ácido libre de manera usual. Las formas ácidas libres se diferencian en cierto sentido de sus formas salinas correspondientes respecto de determinadas propiedades físicas, tal como solubilidad en solventes polares; sin embargo, en el contexto de la invención, las sales corresponden de otra manera a las formas ácidas libres respectivas.

Si un compuesto de la invención contiene más de un grupo que puede formar sales farmacéuticas, entonces la invención también comprende sales múltiples. Entre las formas salinas múltiples típicas se encuentran, por ejemplo, bitartrato, diacetato, difumarato, dimeglumina, difosfato, disodio y trihidrocloruro, lo cual no debe representar restricción alguna. Teniendo en cuenta lo dicho con anterioridad se ve que bajo la expresión "sal farmacéutica" ha de entenderse en el presente contexto un principio activo que contiene un compuesto de la invención en la forma de una de sus sales, principalmente cuando esta forma salina le confiere al principio activo propiedades farmacocinéticas mejoradas, en comparación con la forma libre del principio activo u otra forma salina del principio activo que se utilizó con anterioridad. La forma salina farmacéutica del principio activo también puede conferir a este principio activo solo una propiedad farmacocinética deseada de la cual no disponía antes, y puede influir positivamente en la farmacodinámica de este principio activo respecto a su efectividad terapéutica en el cuerpo.

Los compuestos de la invención pueden ser quirales debido a su estructura molecular y, de conformidad con esto, pueden presentarse en varias formas enantioméricas. Por esto también pueden presentarse en forma racémica o en forma ópticamente activa.

Puesto que la actividad farmacéutica de los racematos o de los estereoisómeros de los compuestos de la invención puede diferenciarse, puede ser deseable usar los enantiómeros. En estos casos, el producto final o incluso los productos intermedios pueden separarse en compuestos enantioméricos mediante medidas químicas o físicas conocidas por el experto en la materia, o incluso emplearse como tales en la síntesis.

En el caso de aminas racémicas, de la mezcla se forman diaestereómeros mediante reacción con un agente de resolución ópticamente activo. Como agente de resolución son adecuados, por ejemplo, ácidos ópticamente activos, como las formas R y S de ácido tartárico, ácido diacetiltartárico, ácido dibenzoiltartárico, ácido mandélico, ácido málico, ácido láctico, aminoácidos adecuadamente N-protegidos (por ejemplo, N-benzoilprolina o N-bencenosulfonilprolina) o los diferentes ácidos alcanforsulfónicos ópticamente activos. También es ventajosa una

resolución cromatográfica de enantiómeros con ayuda de un agente de resolución ópticamente activo (por ejemplo dinitrobenzoilfenilglicina, triacetato de celulosa un otros derivados de carbohidratos o polímeros de metacrilato derivatizados quiralmente, fijados sobre gel de sílice). Como eluyentes son adecuados para esto mezclas de solventes acuosas o alcohólicas tales como, por ejemplo, hexano/isopropanol/acetonitrilo, por ejemplo en proporción de 82:15:3.

También es objeto de la invención la utilización de los compuestos y/o de sus sales fisiológicas inocuas para la preparación de un medicamento (preparación farmacéutica), principalmente por una vía no química. En este caso pueden llevarse a una forma de dosificación apropiada junto con al menos un excipiente o coadyuvante sólido, líquido y/o semilíquido y opcionalmente en combinación con uno o varios otros ingredientes activos.

Además, son objeto de la invención medicamentos que contienen al menos un compuesto de la invención y/o sus sales, solvatos y estereoisómeros utilizables en farmacia, incluso sus mezclas en todas las proporciones y de manera opcional excipientes y/o adyuvantes.

Las formulaciones farmacéuticas pueden administrarse en forma de unidades de dosis que contienen una cantidad predeterminada de principio activo por unidad de dosis. Una unidad tal puede contener, por ejemplo, 0,1 mg a 3 g, preferentemente 1 mg a 700 mg, particularmente preferible 5 mg a 100 mg de un compuesto de la invención, según el estado patológico tratado, la vía de administración y la edad, peso y estado del paciente, o pueden administrarse formulaciones farmacéuticas en forma de unidades de dosis que contienen una cantidad predeterminada de principio activo por unidad de dosis. Las formulaciones de unidad de dosis son aquellas que contienen una dosis diaria o una dosis parcial, tal como se indica arriba, o una fracción correspondiente de la misma de un principio activo. Además, pueden prepararse tales formulaciones farmacéuticas según un método conocido generalmente en el campo de la especialidad farmacéutica.

Las formulaciones farmacéuticas pueden adaptarse para administrarse por cualquier vía adecuada, por ejemplo, por vías oral (incluso bucal o sublingual), rectal, nasal, tópica (incluso bucal, sublingual o transdérmica), vaginal o parenteral (incluso subcutánea, intramuscular, intravenosa o intradérmica). Tales formulaciones pueden prepararse según todos los métodos conocidos en el campo de la especialidad farmacéutica. Por ejemplo, poniendo en contacto el principio activo con el o los excipientes y con el o los adyuvantes.

Las formulaciones farmacéuticas adaptadas a la administración oral pueden administrarse como unidades separadas como, por ejemplo, cápsulas o comprimidos; polvos o granulados; soluciones o suspensiones en líquidos acuosos o no acuosos; espumas comestibles o mousses; o emulsiones líquidas aceite en agua o emulsiones líquidas agua en aceite.

De esta manera, en el caso de la administración oral en forma de una tableta o de una cápsula, los componentes de principio activo pueden combinarse, por ejemplo, con un excipiente oral, no tóxico e inerte farmacéutico, como por ejemplo etanol, glicerina, agua, entre otros. Se preparan polvos triturando el compuesto hasta un tamaño fino adecuado y mezclándolo con un excipiente farmacéutico triturado de igual manera como, por ejemplo un carbohidrato comestible tal como, por ejemplo, almidón o manitol. También puede estar presente un saborizante, un conservante, un dispersante y un colorante.

Las cápsulas se obtienen preparando una mezcla en polvo tal como se ha descrito con anterioridad y llenando con ésta vainas de gelatina moldeadas. Pueden adicionarse lubricantes y agentes de deslizamiento tales como, por ejemplo, ácido silícico altamente disperso, talco, estearato de magnesio, estearato de calcio o polietilenglicol en forma sólida, antes del proceso de llenado. Asimismo, puede adicionarse un desintegrante o un solubilizante como, por ejemplo, agar-agar, carbonato de calcio o carbonato de sodio, a fin de mejorar la disponibilidad del medicamento después de la ingesta de la cápsula.

Además, en caso de desearse o requerirse, pueden incorporarse a la mezcla aglutinantes, lubricantes y desintegrante adecuados, así como colorantes. Los aglutinantes adecuados incluyen almidón, gelatina, azúcares naturales como, por ejemplo, glucosa o beta-lactosa, edulcorantes de maíz, goma natural y sintética como, por ejemplo, acacia, tragacanto o alginato de sodio, carboximetilcelulosa, polietilenglicol, ceras, entre otras. Los lubricantes usados en estas formas de dosis incluyen oleato de sodio, estearato de sodio, estearato de magnesio, benzoato de sodio, acetato de sodio, cloruro de sodio, entre otras. Los desintegrantes incluyen, sin estar restringido a éstos, almidón, metilcelulosa, agar, bentonita, goma xantano, entre otros. Las tabletas se formulan, por ejemplo, preparando una mezcla pulverulenta, granulándola o comprimiéndola en seco, agregando un lubricante y un desintegrante y comprimiendo todo en tabletas. Una mezcla pulverulenta se prepara mezclando un compuesto triturado de una manera adecuada con un diluyente o una base, tal como se describió arriba, y opcionalmente con un aglutinante tal como, por ejemplo, carboximetilcelulosa, un alginato, gelatina o polivinilpirrolidona, un retardante de solución como, por ejemplo, parafina, un acelerante de resorción como, por ejemplo, una sal cuaternaria y/o un agente de absorción como, por ejemplo, bentonita, caolín o fosfato dicálcico. La mezcla en polvo puede granularse humectándola con un aglutinante como, por ejemplo, jarabe, pasta de almidón, pasta, mucílago de acadia o

soluciones de materiales celulósicos o poliméricos y presionándola a través de un tamiz. Como alternativa para la granulación puede dejarse pasar la mezcla en polvo a través de una máquina para hacer tabletas, en cuyo caso se generan grumos moldeados que se quiebran en gránulos. Los gránulos pueden lubricarse mediante adición de ácido esteárico, una sal de estearato, talco o aceite mineral, con el fin de evitar que se peguen a los moldes de tabletas. La mezcla lubricada se comprime entonces para formar tabletas. Los compuestos de la invención también pueden combinarse con un excipiente inerte que fluye libremente y luego comprimirse directamente para formar tabletas sin la realización de etapas de granulación o compresión en seco. También puede estar presente una capa protectora transparente u opaca que se compone de un sellamiento de goma laca, una capa de azúcar o de material polimérico y de una capa brillante de cera. A estos recubrimientos pueden adicionarse colorantes con el fin de poder diferenciar las diversas unidades de dosis.

Los líquidos orales como, por ejemplo, soluciones, jarabes y elíxires, pueden prepararse en forma de unidades de dosis de tal modo que una cantidad dada contenga una cantidad predeterminada de compuesto. Los jarabes pueden prepararse disolviendo el compuesto en una solución acuosa con sabor adecuado, mientras que los elíxires se preparan usando un vehículo alcohólico no tóxico. Las suspensiones pueden formularse por dispersión del compuesto en un vehículo no tóxico. Asimismo, pueden adicionarse solubilizantes y emulsionantes como, por ejemplo, alcoholes isoestearílicos etoxilados y éteres de polioxietilensorbitol, conservantes, aditivos saborizantes como, por ejemplo, aceite de menta o endulzantes naturales o sacarina u otros edulcorantes artificiales, entre otros.

Las formulaciones de unidades de dosis para la administración oral pueden incluirse opcionalmente en microcápsulas. La formulación también puede prepararse de tal manera que la liberación se prolongue o se retrase; por ejemplo, mediante recubrimiento o incrustación de material en forma de partículas a polímeros, cera, entre otros.

Los polímeros de la invención, así como sus sales y solvatos también pueden administrarse en forma de sistemas de introducción de liposomas como, por ejemplo, vesículas pequeñas unilaminares, vesículas grandes unilaminares y vesículas multilaminares. Los liposomas pueden formarse a partir de diversos fosfolípidos como, por ejemplo, colesterol, estearilamina o fosfatidilcolinas.

Los compuestos de acuerdo con la invención, así como las sales y solvatos, también pueden introducirse utilizando anticuerpos monoclonales como portadores individuales a los que se acoplan las moléculas de compuesto. Los compuestos también pueden acoplarse con polímeros solubles como excipientes de medicamento dirigidos a una diana. Tales polímeros pueden abarcar polivinilpirrolidona, copolímero de pirano, fenol de polihidroxipropilmetacrilamida, fenol de polihidroxietilaspartamida o polietilenoxidpolilisina, sustituida con residuos de palmitoilo. Además, los compuestos pueden estar acoplados a una clase de polímeros biodegradables que son adecuados para lograr una liberación controlada de un medicamento, por ejemplo poli(ácido láctico), poliepsilon-caprolactona, poli(ácido hidroxibutírico), poliortoésteres, poliacetales, polidihidroxipiranos, policianoacrilatos y copolímeros en bloques reticulados o anfipáticos de hidrogeles.

Las formulaciones farmacéuticas a la administración transdérmica pueden administrarse como parches autónomos para un contacto estrecho prolongado con la epidermis del receptor. De esta manera, el principio activo puede introducirse desde el parche, por ejemplo, por medio de iontoforesis, como se describe de manera general en Pharmaceutical Research, 3(6), 318 (1986).

Los compuestos farmacéuticos adaptados a la administración tópica pueden estar formulados en forma de ungüentos, cremas, suspensiones, lociones, polvos, soluciones, pastas, geles, esprays, aerosoles o aceites.

Para tratamientos del ojo o de otros tejidos externo, por ejemplo la boca y la piel, las formulaciones se aplican preferentemente como ungüento o crema tópicos. En caso de la formulación para un ungüento, el principio activo puede emplearse ya sea como una base de crema parafínica o una miscible con agua. De manera alternativa, el principio activo puede formularse para una crema con una base cremosa de aceite de agua o una base de agua en aceite.

A las formulaciones farmacéuticas adaptadas a la aplicación tópica en el ojo pertenecen las gotas oftálmicas, en cuyo caso el principio activo se disuelve o se suspende en un vehículo adecuado, principalmente un solvente acuoso.

Las formulaciones farmacéuticas adaptadas a la aplicación tópica en la boca comprenden tabletas para chupar, pastillas y enjuagues bucales.

Las formulaciones farmacéuticas adaptadas a la administración rectal pueden administrarse en forma de supositorios o enemas.

Las formulaciones farmacéuticas adaptadas a la administración nasal en los que la sustancia soporte es un sólido, contienen un polvo grueso con un tamaño de partícula en el rango de 20-500 micrómetros, por ejemplo, que se

administra de la manera como se aspira el rapé; es decir, inhalando rápidamente por las vías nasales desde un recipiente con el polvo sostenido cerca de la nariz. Las formulaciones adecuadas para administrarse como espray nasal o gotas nasales con un líquido como sustancia soporte comprenden soluciones de principio activo en agua o aceite.

Las formulaciones farmacéuticas adaptadas a la administración por inhalación comprenden polvos de partículas finas o neblinas que pueden generarse por medio de distintos tipos de dosificadores a presión con aerosoles, nebulizadores o insufladores.

Las formulaciones farmacéuticas adaptadas a la administración vaginal pueden administrarse como pesarios, tampones, cremas, geles, pastas, espumas o formulaciones en espray.

A las formulaciones farmacéuticas adaptadas a la administración parenteral pertenecen las soluciones inyectables estériles acuosas o no acuosas que contienen antioxidantes, búferes, bacteriostáticos y solutos, a través de los cuales la formulación se vuelve isotónica con la sangre del receptor a ser tratado; así como suspensiones estériles acuosas y no acuosas que pueden contener agentes de suspensión y espesantes. Las formulaciones pueden ofrecerse en recipientes de dosis únicas o múltiples, por ejemplo ampollas selladas y viales y almacenarse en estado seco por congelamiento (liofilizado) de tal manera que solo se requiera la adición del vehículo líquido, por ejemplo agua, para fines inyectables y las soluciones preparadas según la receta pueden prepararse a partir de polvos, gránulos y tabletas estériles.

Se entiende que las formulaciones, además de los componentes mencionados de manera particular con anterioridad, pueden contener otros agentes usuales en el campo especializado respecto del correspondiente tipo de la formulación; de esta manera, por ejemplo para la administración oral, las formulaciones adecuadas pueden contener sustancias saborizantes.

Una cantidad terapéuticamente eficaz de un compuesto de la presente invención depende de un serie de factores, incluso, por ejemplo, la edad y el peso de la persona o animal, del estado patológico exacto que requiere de tratamiento, así como de su gravedad, de la naturaleza de la formulación así como de la vía de administración, y en definitiva se establece por parte del médico o veterinario tratante. No obstante, una cantidad eficaz de un compuesto de la invención para el tratamiento se encuentra generalmente en el rango de 0,1 a 100 mg/kg de peso corporal del receptor (mamífero) por día y de manera particularmente típica en el rango de 1 a 10 mg/kg de peso corporal por día. De esta manera, para un mamífero adulto de 70 kg de peso, la cantidad real por día estaría usualmente entre 70 y 700 mg, en cuyo caso esta cantidad puede darse como dosis única por día o más usual en una serie de dosis parciales (como, por ejemplo, dos, tres, cuatro, cinco o seis) por día, de tal modo que la dosis diaria total sea la misma. Una cantidad eficaz de una sal o de un solvato o de un derivado fisiológicamente funcional de los mismos puede determinarse per se como fracción de la cantidad eficaz del compuesto de la invención. Puede suponerse que para el tratamiento de los otros estados patológicos mencionados anteriormente son adecuadas dosis similares.

Además, son objeto de la invención los medicamentos que contienen al menos un compuesto de acuerdo con la invención y/o sus sales, solvatos y estereoisómeros que puedan usarse en farmacia, incluso sus mezclas en todas las proporciones, y al menos otro principio activo de medicamento.

Como otros principios activos medicamentosos se prefieren quimioterapéuticos, principalmente aquellos que inhiben la angiogénesis y de esta manera el crecimiento y la propagación de células tumorales; en este caso se prefieren los inhibidores de los receptores de VEGF que contienen robozimas y antisentido dirigidas a los receptores de VEGF, así como angiostatina y endostatina,

Ejemplos de agentes antineoplásicos que pueden utilizarse en combinación con los compuestos de la invención contienen en general agentes alquilantes; antimetabólicos; epidofilotoxina; una enzima antineoplásica; un inhibidor de la topoisomerasa; procarbazina; mitoxantrona o complejos de coordinación de platino.

Los agentes antineoplásicos se seleccionan preferentemente de las siguientes clases: antraciclinas, fármacos vinca, mitomicina, bleomicina, nucleósidos citotóxicos, epotilonas, discomolidas, pteridinas, diinenos y podofilotoxinas. En las clases mencionadas se prefieren particularmente, por ejemplo, carminomicina, daunorrubicina, aminopterina, metotrexato, metopterina, diclormetotrexato, mitomicina C, porfiromicina, 5 fluoruracilo, 6-mercaptopurina, gemcitabina, citosinarabinósido, podofilotoxina o derivados de podofilotoxinda, tales como, por ejemplo, etopósidos, fosfato etopósidos o tenipósido, melfalano, vinblastina, vincristina, leurosidina, vindesina, leurosina y paclitaxel. Otros agentes neoplásicos preferidos se seleccionan del grupo de estramustina, carboplatino, ciclofosfamida, bleomicina, gemcitabina, ifosamida, melfalano, hexametilmelamina, tiotepa, citarabina, idatrexato, trimetrexato, dacarbazina, L-asparaginasa, camptotecina, CPT-11, topotecano, arabinosil-citosina, bicalutamida, flutamida, leuprolida, derivados de piridobenzoindol, tnterferones e interleuquinas.

También es objeto de la invención un kit que consiste en paquetes separados de

(a) una cantidad eficaz de un compuesto de la invención y/o sus sales, solvatos y estereoisómeros utilizables farmacéuticamente, incluso sus mezclas en todas las proporciones,

y

(b) una cantidad eficaz de otro principio activo de medicamento.

El kit contiene recipientes adecuados como cajas o cartones, frascos, sachets o ampollas individuales.

El kit también puede contener, por ejemplo, ampollas separadas en las cuales se presenta una cantidad eficaz de un compuesto de la invención y/o de sus sales, solvatos y estereoisómeros farmacéuticamente utilizables, incluso sus mezclas en todas las proporciones y una cantidad eficaz de otro principio activo de medicamento disuelto o en forma liofilizada.

UTILIZACIÓN

Los presentes compuestos son adecuados como principios activos farmacéuticos para mamíferos, principalmente para el ser humano, en el tratamiento de enfermedades en las que la HSP90 desempeña un papel. De esta manera, es objeto de la invención la utilización de los compuestos de la invención, así como de sus sales, solvatos y estereoisómeros utilizables en farmacia, incluso sus mezclas en todas las proporciones, para la preparación de un medicamento para tratar enfermedades en las que la inhibición, regulación y/o modulación de la HSP90 desempeña un papel.

La presente invención comprende la utilización de los compuestos de la invención y/o de sus sales y solvatos fisiológicamente inocuas para la preparación de un medicamento para tratar enfermedades tumorales como, por ejemplo, fibrosarcoma, mixosarcoma, liposarcoma, condrosarcoma, sarcoma osteogénico, cordoma, angiosarcoma, sarcoma de endotelio, linfangiosarcoma, linfangiosarcoma de endotelio, sinovioma, mesotelioma, tumor de Ewing, leiosarcoma, rabdomiosarcoma, carcinoma de colon, cáncer de páncreas, cáncer de mama, cáncer de ovarios, cáncer de próstata, carcinoma de células escamosas, carcinoma basocelular, adenocarcinoma, carcinoma de glándulas sudoríparas, carcinoma de glándulas sebáceas, carcinoma papilar, adenocarcinomas papilares, cistadenocarcinomas, carcinoma de la médula ósea, carcinoma broncogénico, carcinoma de células renales, hepatoma, carcinoma del conducto biliar, carcinoma coriónico, seminoma, carcinoma embrionario, tumor de Wilms, cáncer cervical, tumor testicular, carcinoma de pulmón, carcinoma de pulmón de células pequeñas, carcinoma de vejiga, carcinoma epitelial, glioma, astrocitoma, meduloblastoma, craniofaringioma, ependimoma, pinealoma, hemangioblastoma, neuroma acústica, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leucemia, linfoma, mieloma múltiple, macroglobulinemia de Waldenstroms y enfermedad en cadena grave; enfermedades virales, en cuyo caso el patógeno viral se selecciona del grupo compuesto por hepatitis tipo A, hepatitis tipo B, hepatitis tipo C, gripe, varicela, adenovirus, herpes Simplex tipo 1 (HSV-I), herpes Simplex tipo II (HSV-II), peste bovina, rinovirus, ecovirus, rotavirus, virus sincicial respiratorio (RSV), virus papiloma, papovavirus, citomegalovirus, equinovirus, arbovirus, hantavirus, coxsackievirus, virus de las paperas, virus del sarampión, virus de la rubeola, virus de la polio, virus de inmunodeficiencia humana tipo I (HIV-I) y virus de inmunodeficiencia humana tipo II (HIV-II);

Para la inmunosupresión en caso de trasplantes; enfermedades causadas por inflamación, tales como artritis reumatoide, asma, esclerosis múltiple, diabetes de tipo 1, lupus eritematoso, psoriasis y Inflammatory Bowel Disease (enfermedad del intestino inflamado); fibrosis cística; enfermedades relacionadas con angiogénesis como, por ejemplo, retinopatía diabética, hemangiomas, endometriosis, angiogénesis tumorales; enfermedades infecciosas; enfermedades autoinmunes; isquemia; estimulación de la regeneración nerviosa; enfermedades fibrogenéticas como, por ejemplo, esclerodermia, polimiositis, lupus sistémico, cirrosis hepática, formación de queloides, nefritis intersticial y fibrosis pulmonar;

Los compuestos de la invención pueden inhibir principalmente el crecimiento de cáncer, células tumorales y metástasis tumorales y, por esto, son adecuados para la terapia tumoral.

La presente invención comprende la utilización de los compuestos de la invención y/o sus sales y solvatos fisiológicamente inocuos para la preparación de un medicamento para proteger células normales contra toxicidad que se causa por quimioterapia, así como para el tratamiento de enfermedades en las que el plegamiento incorrecto de proteínas o la agregación es un factor causal principal como, por ejemplo, escrapia, enfermedad de Creutzfeldt-Jakob, de Huntington o de Alzheimer.

La enfermedad también hace referencia a la utilización de los compuestos de la invención y/o sus sales y solvatos fisiológicamente inocuos para la preparación de un medicamento para tratar enfermedades del sistema nervioso central, de enfermedades cardiocirculatorias y caquexia.

En otra forma de realización, la invención también hace referencia a la utilización de los compuestos de la invención y/o sus sales y solvatos fisiológicamente inocuos para preparar un medicamento para la modulación de HSP90, en cuyo caso la actividad biológica modulada de HSP90 provoca una reacción inmune en un individuo, el transporte de proteínas del retículo endoplasmático, la curación del estrés hipóxico/anóxico, la curación de la desnutrición, la curación del estrés por calor, o combinaciones de ellos, y/o en cuyo caso el trastorno es un tipo de cáncer, una enfermedad infecciosa, un trastorno que está acompañado de un transporte de proteínas alterado del retículo endoplasmático, un trastorno que está acompañado de isquemia / reperfusión, o combinaciones de ellos, en cuyo caso el trastorno acompañado de de isquemia / reperfusión es una consecuencia de paro cardiaco, asistolia y arritmias ventriculares retrasadas, operación de corazón, operación cardiopulmonar de bypass, trasplantes de órganos, lesión de la médula espinal, trauma cerebral, ataque apopléjico, ataque apopléjico tromboembólico, ataque apopléjico hemorrágico, vasoespasmo cerebral, hipotonía, hipoglicemia, estado epiléptico, un ataque epiléptico, angustia, esquizofrenia, un trastorno neurodegenerativo, enfermedad de Alzheimer, corea de Huntington, esclerosis lateral amiotrófica (ALS) o estrés en el recién nacido.

En otra forma de realización la invención también hace referencia a la utilización de los compuestos de la invención y/o sus sales y solvatos fisiológicamente inocuos para preparar un medicamento para el tratamiento de isquemia como consecuencia de paro cardiaco, asistolia y arritmias ventriculares retardadas, operación de corazón, operación cardiopulmonar de bypass, trasplante de órganos, lesión de la médula espinal, trauma cerebral, ataque apopléjico, ataque apopléjico tromboembólico, ataque apopléjico hemorrágico, vasoespasmo cerebral, hipotonía, hipoglicemia, estado epiléptico, un ataque epiléptico, angustia, esquizofrenia, un trastorno neurodegenerativo, enfermedad de Alzheimer, corea de Huntington, esclerosis lateral amiotrófica (ALS) o estrés en el recién nacido.

Método de ensayo para la medición de inhibidores de la HSP90

El enlace de geldanamicina o 17- alilamino-17-demetoxigeldanamicina (17AAG) y su inhibición competitiva en HSP90 puede utilizarse a fin de determinar la actividad inhibitoria de los compuestos de la invención (Carreras et al. 2003, Chiosis et al. 2002). En un caso especial, se usa un ensayo de enlace en filtro a radioligando. En tal caso, como radioligando se usa 17-alilamino-geldanamicina marcada con tritio, [3H]17AAG. Este ensayo de enlace en filtro permite una búsqueda dirigida de inhibidores que interfieren con el sitio de enlace con ATP.

Material

HSP90α humano recombinante (expresa E. coli, 95% de pureza); [3H]17AAG (17-alilamino-geldanamicina, [alilamino-2,3-^{3}H. Actividad específica: 1,11x1012 Bq/mmol (Moravek, MT-1717); búfer de filtro HEPES (50 mM de HEPES, pH 7,0, $MgCl_2$ de 5mM, BSA 0.01 %), placa filtrante Multiscreen-FB (1 μm) (Millipore, MAFBNOB 50).

Método

Las placas filtrantes de microtitulación de 96 cavidades primero se mojan y se recubren con polietienimina de 0,1%.

El ensayo se realiza en las siguientes condiciones:

Temperatura de reacción 22 C°

Tiempo de reacción: 30 min., agitar a 800 rpm

Volumen de ensayo: 50 ml

Concentraciones finales: HEPES-HCl de 50 mM, pH 7,0, $MgCl_2$ de 5 mM, 0,01 % (p/v) BSA

HSP90: 1,5 mg/ensayo

[3H]17AAG: 0,08 mM.

Al final de la reacción se filtra el sobrenadante por succión en la placa de filtro con ayuda de un colector (manifold) al vacío (Multiscreen Separation System, Millipore) y el filtro se lava dos veces. Las placas filtrantes se miden luego con un contador beta (Microbeta, Wallac) con un centelleador (Microscint 20, Packard).

De los valores "counts per minutes" (conteos por minutos) se determina el "% del control" y a partir de allí se calcula el valor de IC_{50} de un compuesto.

Tabla 1

Inhibición de HSP90 por algunos compuestos de la fórmula I representativos de la invención	
Compuesto de la fórmula I	IC_{50}
"A1"	A
"A2"	A
"A3"	A
"A4"	A
"A5"	A
"A6"	A
"A7"	A
"A8"	A
"A9"	B
"A10"	A
"A11"	A
"A14"	B
"A15"	A
"A16"	A
"A17"	A
"A18"	A
"A19"	A
"A20"	A
"A26"	A
"A27"	A
"A28"	A
"A29"	A
"A30"	A
"A31"	A
"A32"	A
"A33"	A
"A34"	A
"A35"	A
"A36"	A
"A37"	A
"A38"	A
"A39"	A
"A40"	A
"A41	A
"A43"	A
"A47"	A
"A48"	B
"A49"	A
"A50"	A

IC_{50}: 10 nM - 1 μM = A

1 μM - 10 μM = B

> 10 μM = C

Previa y posteriormente, todas las temperaturas se indican en °C. En los ejemplos que figuran a continuación, "procesamiento convencional" significa que, si se requiere, se adiciona agua, si se requiere se ajusta según la composición del producto final a valores de pH entre 2 y 10, se extrae con acetato de etilo o diclorometano, se separa, se seca la fase orgánica sobre sulfato de sodio, se evapora y se purifica por cromatografía en gel de sílice y/o por cristalización. Valores de Rf en gel de sílice; eluyente: acetato de etilo / metanol 9:1.

Condiciones de LC-MS y HPLC

Los datos M+H+ indicados en los siguientes ejemplos son los resultados de medición de LC-MS:

Sistema Hewlett Packard de la serie HP 1100 con las siguientes características: fuente de iones: electronebulización (modo positivo); barrido: 100-1000 m/z; tensión de fragmentación: 60 V; temperatura de gas: 300°C, DAD: 220 nm. Velocidad de flujo: 2.4 ml/min. La columna de fraccionamiento redujo según DAD la velocidad de flujo para la MS a 0,75ml/min.

Columna: Chromolith SpeedROD RP-18e 50-4.6

Solvente: calidad LiChrosolv de la empresa Merck KGaA

Solvente A: H_2O (0.01 % de TFA)

Solvente B: ACN (0.008% de TFA)

Los tiempos de retención indicados en los ejemplos siguientes Rt [min] son los resultados de las mediciones de HPLC:

Gradiente P:

5.5 min; flujo: 2,75 ml / min de 99:1 a 0:100 de agua / acetonitrilo agua + TFA (0.01 % en volumen); acetonitrilo + TFA (0.01 % en volumen)

Columna: Chromolith SpeedROD RP 18e 50-4.6

Longitud de onda: 220 nm

Gradiente N:

5.5 min; flujo: 2,75 ml / min de 90:10 a 0:100 de agua / acetonitrilo agua + TFA (0.01 % en volumen); Acetonitril +

TFA (0.01 % en volumen)

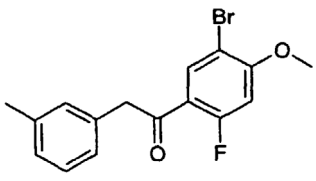
Columna: Chromolith SpeedROD RP 18e 50-4.6

Longitud de onda: 220 nm

Ejemplo 1

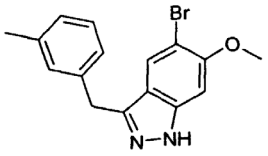
Preparación de 5-(1,3-dihidro-isoindol-2-il-carbonil)-3-(3-metil-benzil)-6-hidroxi-1H-indazol ("A1")

1.1 A 3,25 g de cloruro de aluminio se adicionan bajo argón 12 ml de diclormetano y se enfría revolviendo a -55°C. A esta temperatura se adiciona a gotas una solución de 2,5 g de 2-bromo-5-fluor-anisol y 2,47 g de m-tolil-acetilcloruro en 8 ml de diclormetano. Se revuelve aún por 10 minutos y se deja calentar lentamente a 0°C y se hidroliza luego con HCl de 1N. Se sigue revolviendo por 15 minutos, se diluye con diclormetano y se procesa de manera usual. El residuo obtenido se digiere con éter de petróleo / éter dietílico (8:2), se filtra por succión y se lava con éter de petróleo. Después de secar se obtienen 1,85 g "1 a"



"1a"

1.2 Una suspensión de 1,85 g de "1a" en 10 ml de dioxano se mezcla con 0,74 ml de hidróxido de hidrazinio y se calienta por 2,5 horas bajo reflujo. Se enfría, se mezcla con acetato de etilo y HCl de 1 N y se procesa de la manera usual. El residuo se cromatografía en gel de sílice, Se obtienen 1,24 g de 5-bromo-6-metoxi-3-(3-metil-benzil)-1H-indazol ("1b")



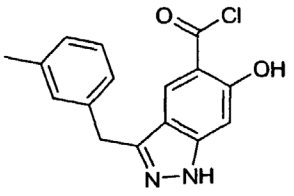
"1b"

1.3 1,24 g de "1b" se disuelven bajo argón en 12 ml de diclorometano y se enfría a 0°C. Se adicionan a gotas 3,45 ml de tribromuro de boro y se revuelve por 16 horas a temperatura ambiente. Se procesa de la manera usual y se cromatografía el residuo para una purificación adicional por una columna de gel de sílice de 120 g de RP18. Se obtienen 578 mg de 5-bromo-6-hidroxi-3-(3-metilbenzil)-1H-indazol ("1c").

1.4 Reacción en autoclaves a 100°/4-6 bar/22 horas: 578 mg de "1c", 25 ml de metanol, 300 mg de trietilamina, 25 ml de tolueno se cargan y se desgasifican. Luego se adicionan 15 mg (1,1'-bis(difenilfosfino)-ferrocen)dicloropaladio(II). El autoclave se distensiona, se presiona CO a 4 bar y se calienta a 100°. Después de remover el solvente se obtiene 5-metoxicarbonil-6-hidroxi-3-(3-metil-bencil)-1H-indazol ("1 d").

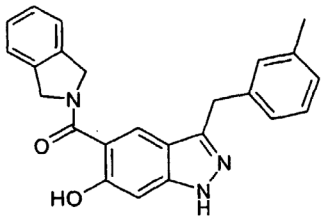
1.5 Una solución de 523 mg de "4d" en 10 ml de dioxano se mezcla con 4,23 ml de NaOH de 2N y se calienta por 1,5 horas bajo reflujo. Se procesa de la manera usual y se obtienen 386 mg de 5-carboxi-6-hidroxi-3-(3-metil-bencil)-1H-indazol ("1e").

1.6 A una suspensión de 50 mg de "1e" en 2 ml de THF se adicionan 25 ml de cloruro de tionilo y se revuelve por una hora. Se adicionan 2 ml de tolueno, el solvente se retira a 30° y se obtiene 5-cloro-carbonil-6-hidroxi-3-(3-metilbencil)-1H-indazol ("1f")



"1f"

1.7 1f" se disuelve en 1,5 ml de THF y se adicionan a gotas a una solución de 25,3 mg de isoindolina y 90,3 µl de N-etildiisopropilamina en 0,5 ml de THF. Se revuelve por una hora. Se procesa de la manera usual y se obtienen 31,5 mg de "A1", $M+H^+$ 384;

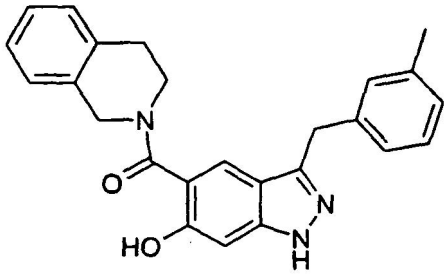
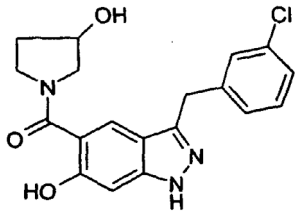
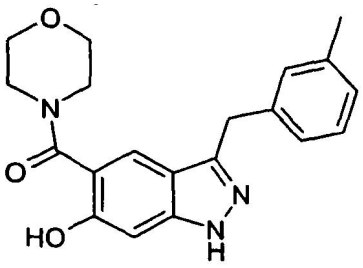


"A1"

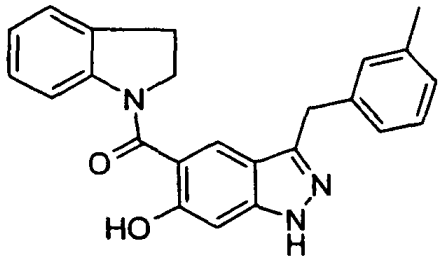
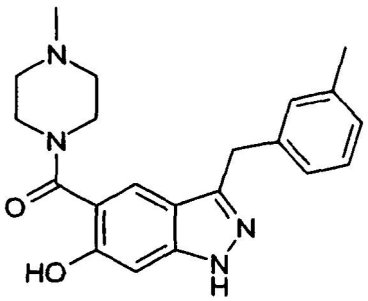
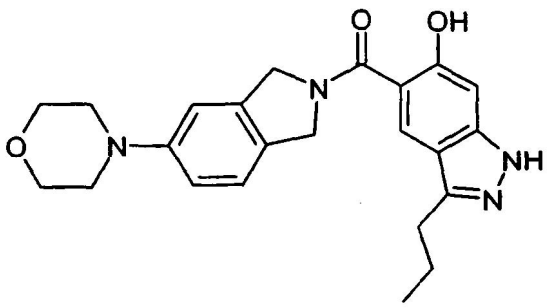
;

^{1}H-NMR (DMSO-d_6, 80°C): δ [ppm] 12.41 (s, 1H, ancho), 10.1 (s, 1H), 7.52 (s, 1H), 7.38 (d, 1H), 7.38-7.18 (m, 3H), 7.18-7.06 (m, 3H), 6.97 (s, 1H), 6.86 (s, 1H), 4.81 (s, 2H), 4.56 (s, 2H), 4.15 (s, 2H), 2.22 (s, 3H).

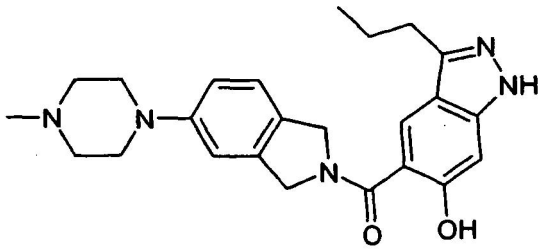
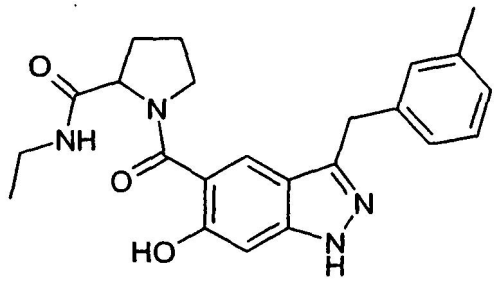
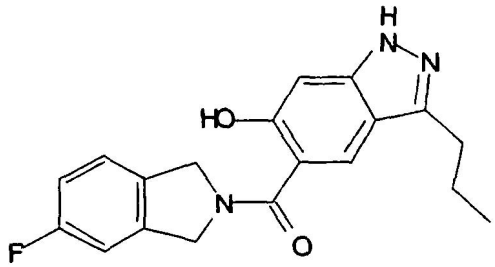
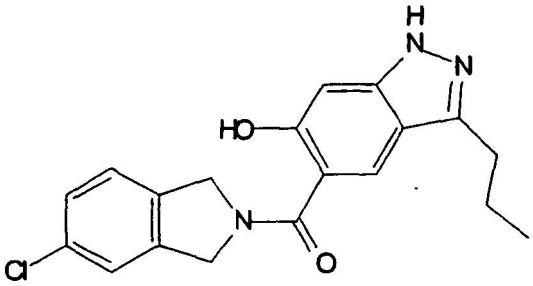
De manera análoga se obtienen los siguientes compuestos

Compuesto	Estructura y/o nombre	RT [min] (HPLC) (Gradiente)	M+H+
"A2"		2,37 (N)	398
"A3"	5-(1,3-Dihidro-isoindol-2-yl-carbonil)-3-(3-metoxi-bencil)-6-hidroxi-1*H*-indazol	2,17 (N)	400
"A4"	5-(1,3-Dihidro-isoindol-2-il-carbonil)-3-butil-6-hidroxi-1*H*-indazol	2,07 (N)	336
"A5"	 5-(3-Hidroxi-pirrolidin-1-il-carbonil)-3-(3-cloro-bencil)-6-hidroxi-1H-indazol	1,47 (N)	372
"A6"	5-(3-Hidroxi-pirrolidin-1-il-carbonil)-3-(3-metil-bencil)-6-hidroxi-1H-indazol	1,49 (N)	352
"A7"	5-((R)-3-Hidroxi-pirrolidin-1-il-carbonil)-3-(3-cloro-bencil)-6-hidroxi-1H-indazol	1,54 (N)	372
"A8"	5-((R)-3-Hidroxi-pirrolidin-1-il-carbonil)-3-(3-metil-bencil)-6-hidroxi-1H-indazol	1,49 (N)	352
"A9"	5-((S)-3-Hidroxi-pirrolidin-1-il-carbonil)-3-(3-metil-bencil)-6-hidroxi-1H-indazol	1,47 (N)	352
"A10"		1,67 (N)	352

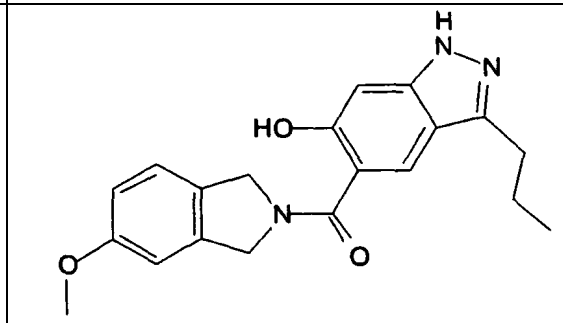
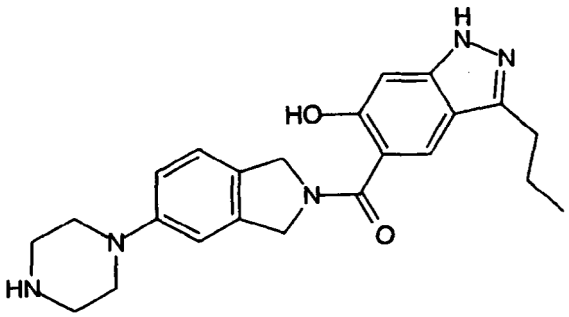
(continuación)

Compuesto	Estructura y/o nombre	RT [min] (HPLC) (Gradiente)	M+H+
"A11"		2,41 (N)	384
"A12"	5-(5-Metoxi-1,3-dihidro-isoindol-2-il-carbonil)-3-(3-metil-bencil)-6-hidroxi-1H-indazol		
"A13"	5-(1,3-Dihidro-isoindol-2-il-carbonil)-3-propil-6-hidroxi-1H-indazol	1,88 (N)	322
^{1}H-NMR (DMSO-d_6, 80°C): δ [ppm] 12.26 (s, 1H, ancho), 10.03 (s, 1H), 7.62 (s, 1H), 7.44-7.19 (m, 4H), 6.85 (s, 1H), 4.82 (s, 2H), 4.63 (s, 2H), 2.80 (t, 2H), 1.76-1.66 (m, 2H), 0.93 (t, 3H)			
"A14"	5-(5-Brom-1,3-dihidro-isoindol-2-il-carbonil)-3-butil-6-hidroxi-1*H*-indazol	2,35 (N)	415
"A15"	5-(5-Brom-1,3-dihidro-isoindol-2-il-carbonil)-3-propil-6-hidroxi-1*H*-indazol	2,15 (N)	401
"A16"	5-(Pirrolidin-1-il-carbonil)-3-(3-metil-bencil)-6-hidroxi-1H-indazol	1,93 (N)	336
^{1}H-NMR (DMSO-d_6, 80°C): δ [ppm] 12.2 (s, 1H, ancho), 10.22 (s, 1H), 7.46 (s, 1H), 7.16-7.04 (m, 3H), 6.96 (d, 1H), 6.78 (s, 1H), 4.14 (s, 2H), 3.45-3.28 (m, 4H), 2.24 (s, 3H), 1.88-1.76 (m, 4H)			
"A17"		2,34 (P)	365
^{1}H-NMR 7.27 (s, (DMSO-d_6, 80°C): δ [ppm] 12.18 (s, 1H, ancho), 7.27 (s, 1H), 7.15-7.02 (m, 3H), 6.96 (d, 1H), 6.8 (s, 1H), 4.13 (s, 2H), 3.44-3.29 (m, 4H), 2.33-2.16 (m, 10H)			
"A18"	5-(1,3-Dihidro-isoindol-2-il-carbonil)-3-cyclopentilmetil-6-hidroxi-1*H*-indazol	2,19 (N)	362
^{1}H-NMR (DMSO-d_6, 80°C): δ [ppm] 12.32 (s, 1H, ancho), 10.09 (s, 1H), 7.67 (s, 1H), 7.44 (d, 1H), 7.39-7.25 (m, 3H), 6.91 (s, 1H), 4.88 (s, 2H), 4.69 (s, 2H), 2.86 (d, 2H), 2.39-2.27 (m, 1H), 1.79-1.47 (m, 5H), 1.37-1.23 (m, 3H)			
"A19"		1,56 (N)	407
^{1}H-NMR (DMSO-d_6, 80°C): δ [ppm] 12.13 (s, 1H, ancho), 9.88 (s, 1H), 7.66 (s, 1H), 7.24-7.13 (m, 1H), 6.94-6.86 (m, 3H), 4.89-4.64 (m, 4H), 3.76 (t, 4H), 3.11 (t, 4H), 2.86 (t, 2H), 1.83-1.74 (m, 2H), 0.99 (t, 3H)			

(continuación)

Compuesto	Estructura y/o nombre	RT [min] (HPLC) (Gradiente)	M+H+
"A20"		2,33 (P)	420
^{1}H-NMR (DMSO-d_6, 80°C): δ [ppm] 12.12 (s, 1H, ancho), 9.86 (s, 1H), 7.64 (s, 1H), 7.19-7.09 (m, 1H), 6.91-6.84 (m, 3H), 4.78-4.62 (m, 4H), 3.13 (t, 4H), 2.84 (t, 2H), 2.47 (t, 4H), 2.24 (s, 3H), 1.82-1.71 (m, 2H), 0.97 (t, 3H)			
"A21"		1,63 (N)	407
"A22"			
"A23"			

(continuación)

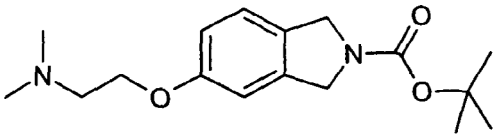
Compuesto	Estructura y/o nombre	RT [min] (HPLC) (Gradiente)	M+H+
"A24"			
"A25"			

Ejemplo 2

Preparación de [5-(2-dimetilamino-etoxi)-1,3-dihidro-isoindol-2-il]-(6-hidroxi-3-propil-1H-indazol-5-il)-metanona ("A26")

2.1 Una solución de 20,4 g de 5-hidroxi-isoindol-1,3-diona en 300 ml de THF seco se enfría bajo una atmósfera de nitrógeno hasta -5°. Después se adicionan a gotas 750,3 ml de complejo borano/THF (solución de 1 M). Se calienta hasta temperatura ambiente y luego se calienta por 16 horas bajo reflujo. Se enfría a 0°, se mezcla lentamente con 100 ml de metanol y luego con 100 ml de HCl de 2M. Luego se calienta la mezcla por 3 horas bajo reflujo. Se enfría, se concentra el volumen a 200 ml y se mezcla con 100 ml de agua. Se extrae tres veces con diclormetano y cuidadosamente se alcaliniza la fase acuosa (contiene el producto) con carbonato de sodio. Se adicionan 27,3 g de dicarbonato de di-ter.-butilo a la fase acuosa y se revuelve por 30 minutos. Se extrae con diclorometano, se procesa de la manera usual y se obtienen 12,2 g de éster ter.-butílico de ácido 5-hidroxi-1,3-dihidro-isoindol-2-carboxílico.

2.2 A una suspensión de 1 g de éster ter.-butílico de ácido 5-hidroxi-1,3-dihidro-isoindol-2-carboxílico y 0,6 ml de 2-(dimetilamino)-etanol en 50 ml de THF se adicionan 3,4 g de trifenilfosfina enlazada a polímero. A esta solución se adicionan 1,61 g de azadicarboxilato de di-ter.-butilo y se revuelve por 18 a temperatura ambiente. Se filtra a través de kieselgur (diatomita), se lava con THF y se concentra la solución. El residuo se cromatografía por flash RP (Isco Companion®). Se procesa de la manera usual y se obtienen 650 mg de éster ter.-butílico de 5-(2-dimetilamino-etoxi)-1,3-dihidro-isoindol-2-carboxílico.



2.3 631 mg de éster ter.-butílico de ácido 5-(2-dimetilamino-etoxi)-1,3-dihidro-isoindol-2-carboxílico se mezclan con 5 ml de HCl de 4M en dioxano y se revuelve por 1 h a temperatura ambiente. Después se remueve el solvente. Después de secar se obtienen 631 mg de clorhidrato de [2-(2,3-dihidro-1H-isoindol-5-iloxi)-etil]-dimetilamina (aceite).

2.4 Una suspensión de 75 mg de ácido 6-hidroxi-3-propil-1H-indazol-5-carboxílico en 2 ml de THF se mezcla con 48,3 ml de cloruro de tionilo y se revuelve por 10 minutos. Se adicionan 2 ml de tolueno y se retira el solvente en el rotavapor a 45°.

El residuo se suspende en 2 ml de THF. La suspensión se adiciona a una solución de 0,121 g de clorhidrato de [2-(2,3-dihidro-1H-isoindol-5-iloxi)-etil]-dimetilamina y 0,34 ml de N-etildiisopropilamina en 1 ml de THF. La mezcla se revuelve por 45 minutos a temperatura ambiente. Se adiciona además 1 ml de DMF y se revuelve por 2 horas. La mezcla de reacción se transfiere a un embudo de separación, se diluye con agua y se extrae tres veces con acetato de etilo. Las fases orgánicas unidas se lavan con agua, se secan sobre sulfato de sodio, se filtra y luego se retira el solvente. El producto crudo se cromatografía mediante HPLC preparativa.

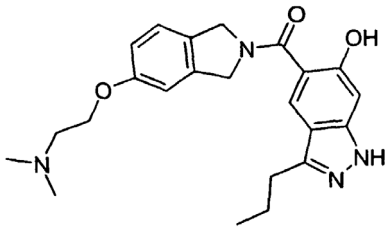
Método de HPLC: Gradiente: 5,5 min / Fl.: 2,75 ml/min 90:10 - 0:100

Agua + 0,01% TFA : acetonitrilo + 0,01% TFA

Columna: Chromolith SpeedROD RP18e 50-4.6

Longitud de onda: 220 nm

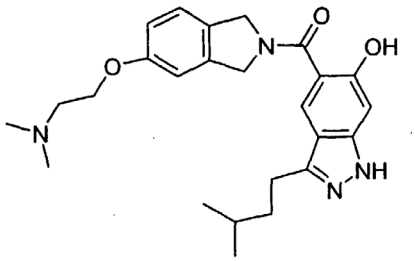
Las fracciones 1-11 se juntan, se retira el acetonitrilo, el residuo acuoso se mezcla con solución saturada de bicarbonato y se re-extrae el producto con acetato de etilo. El solvente se retira, se disuelve en una mezcla 1:1 de metanol y agua y después se liofiliza. Se obtienen 27,7 mg de "A26"



"A26" ;

^{1}H-NMR (DMSO-d_6, 80°C): δ [ppm] 12.08 (s, 1H, ancho), 9.84 (s, 1H, ancho), 7.62 (s, 1H), 7.25-7.12 (m, 1H, ancho), 6.94-6.78 (m, 3H), 4.81-4.59 (m, 4H, ancho), 4.04 (t, 2H), 2.83 (t, 2H), 2.62 (t, 2H), 2.25 (s, 6H), 1.75 (m, 2H), 0.9 (t, 3H).

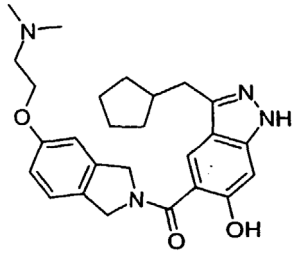
De manera análoga al ejemplo 2.4, mediante reacción de clorhidrato de [2-(2,3-dihidro-1H-isoindol-5-iloxi)-etil]-dimetilamina y ácido 6-hidroxi-3-(3-metil-butil)-1H-indazol-5-carboxílico se obtiene el compuesto [5-(2-dimetilaminoetoxi)-1,3-dihidro-isoindol-2-il]-[6-hidroxi-3-(3-metilbutil)-1H-indazol-5-il]-metanona ("A27")



"A27" ;

^{1}H-NMR (DMSO-d_6, 90°C): δ = 12.03 (s, 1H, ancho), 9.79 (s, 1H), 7.62 (s, 1H), 7.23-7.13 (m, 1H), 6.92-6.8 (m, 3H), 4.72 (s, 2H), 4.68 (s, 2H), 4.05 (t, 2H), 2.85 (t, 2H), 2.65 (t, 2H), 1.67-1.57 (m, 3H), 0.93 (d, 6H).

De manera análoga mediante reacción de clorhidrato de [2-(2,3-dihidro-1H-isoindol-5-iloxi)-etil]-dimetilamina y de ácido 6-hidroxi-3-ciclopentilmetil-1H-indazol-5-carboxílico se obtiene el compuesto (3-ciclopentilmetil-6-hidroxi-1Hindazol-5-il)-[5-(2-dimetilamino-etoxi)-1,3-dihidro-isoindol-2-il]-metanona ("A28")



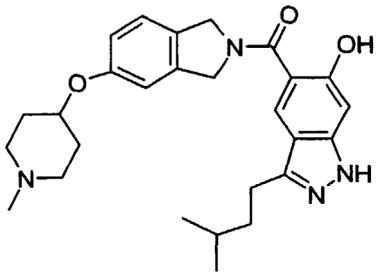
"A28" ;

^{1}H-NMR (DMSO-d_6, 90°C): δ = 11.95 (s, 1H, ancho), 9.7 (s, 1H), 7.64 (s, 1H), 7.19 (d, 1H), 6.95-6.8 (m, 3H), 4.74 (s, 2H), 4.71 (s, 2H), 4.1 (t, 2H), 3.05-2.65 (m, 3H, H2O), 2.41-2.25 (m, 7H), 1.77-1.43 (m, 6H), 1.35-1.2 (m, 3H).

De manera análoga se obtiene el compuesto (3-ciclohexilmetil-6-hidroxi-1H-indazol-5-il)-[5-(2-dimetilaminoetoxi)-1,3-dihidro-isoindol-2-il]-metanona ("A29");

^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 12.07 (s, 1H, ancho), 9.8 (s, 1H), 7.61 (s, 1H), 7.22-7.13 (m, 1H), 6.93-6.8 (m, 3H), 4.72 (s, 2H, ancho), 4.68 (s, 2H, ancho), 4.03 (t, 2H), 2.72 (d, 2H), 2.62 (t, 2H), 2.22 (s, 6H), 1.79-1.54 (m, 6H), 1.29-0.9 (m, 8H).

De manera análoga al ejemplo 2.4 mediante reacción de clorhidrato de 5-(1-metilpiperidin-4-iloxi)-2,3-dihidro-1H-isoindol y ácido 6-hidroxi-3-(3-metil-butil)-1H-indazol-5-carboxílico se obtiene el compuesto [6-hidroxi-3-(3-metil-butil)-1H-indazol-5-il]-[5-(1-metil-piperidin-4-iloxi)-1,3-dihidro-isoindol-2-il]-metanona ("A30")



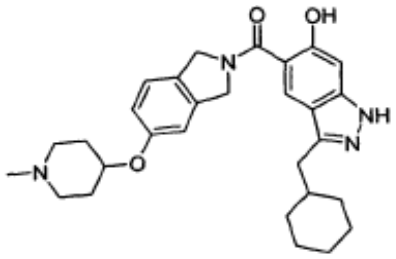
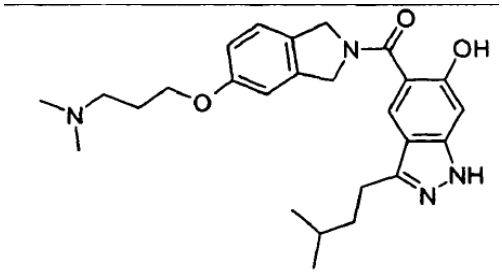
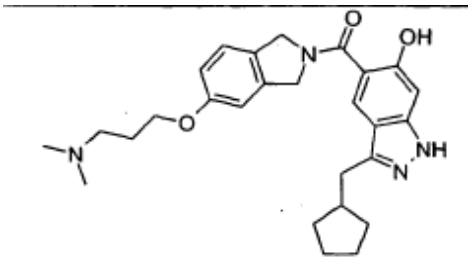
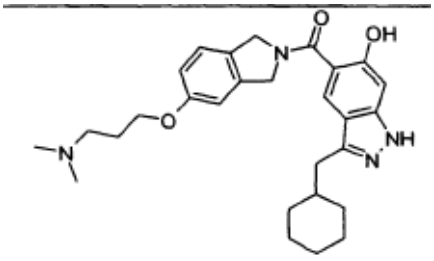
"A30" ;

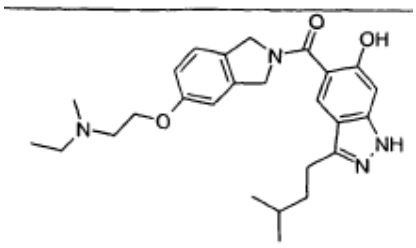
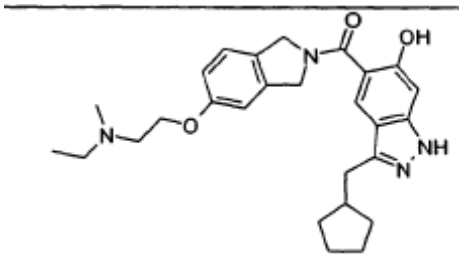
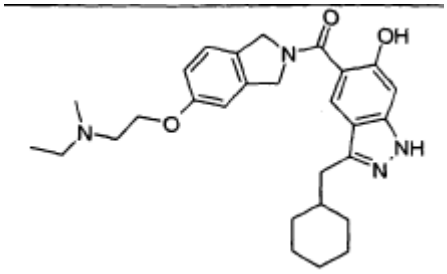
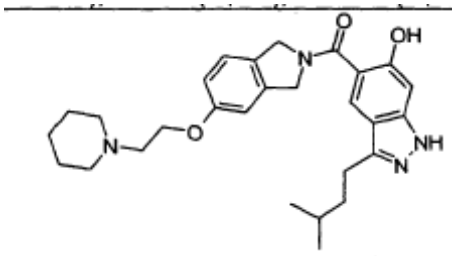
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 12.1 (s, 1H, ancho), 9.85 (s, 1H), 7.65 (s, 1H), 7.25-7.17 (m, 1H, ancho), 6.98-6.85 (m, 3H), 4.76 (s, 2H, ancho), 4.72 (s, 2H, ancho), 4.36-4.29 (m, 1H), 2.89 (t, 2H), 2.66-2.61 (m, 2H), 2.25 (s, 3H), 1.98-1.9 (m, 2H), 1.74-1.62 (m, 7H), 0.98 (d, 6H).

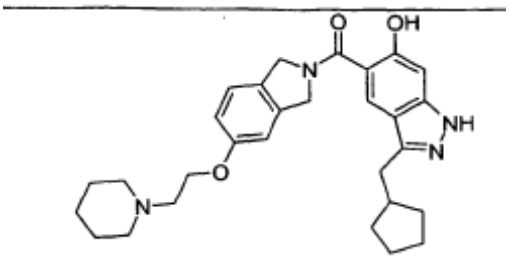
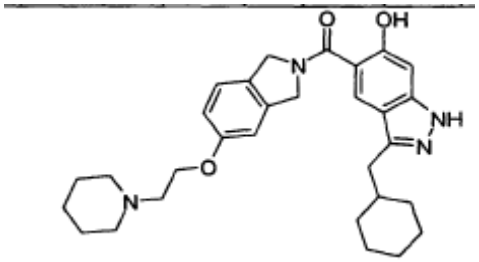
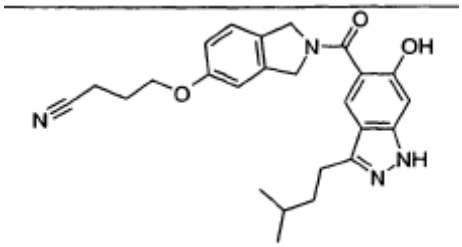
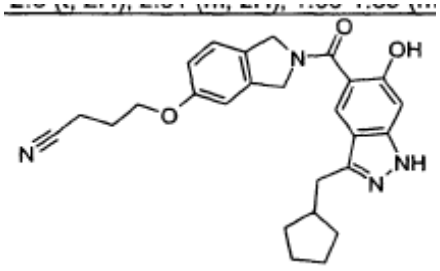
[0108] De manera análoga se obtiene el compuesto (3-ciclopentilmetil-6-hidroxi-1H-indazol-5-il)-[5-(1-metil-piperidin-4-iloxi)-1,3-dihidro-isoindol-2-il]-metanona ("A31 ");

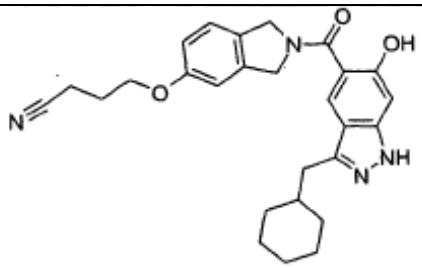
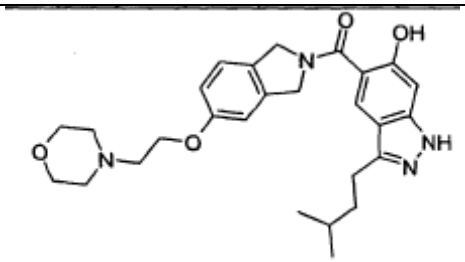
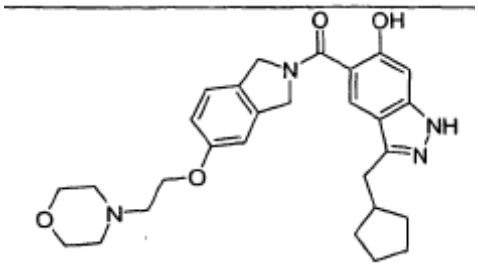
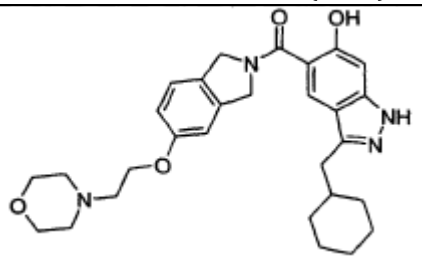
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 12.07 (s, 1H, ancho), 9.8 (s, 1H), 7.62 (s, 1H), 7.22-7.1 (m, 1H, ancho), 6.92-6.81 (m, 3H), 4.72 (s, 2H, ancho), 4.68 (s, 2H, ancho), 4.31-4.24 (m, 1H), 2.82 (d, 2H), 2.64-2.55 (m, 2H), 2.36-2.26 (m, 1H), 2.17 (s, 3H), 1.93-1.85 (m, 2H), 1.73-1.44 (m, 9H), 1.32-1.22 (m, 3H).

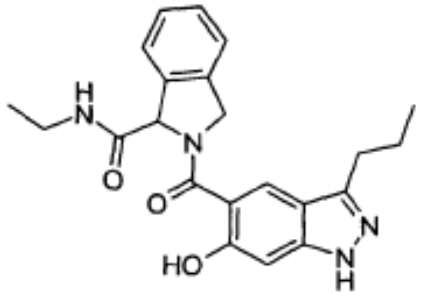
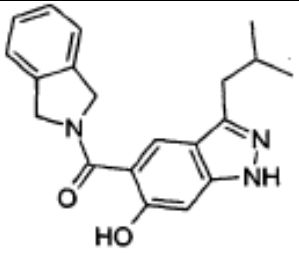
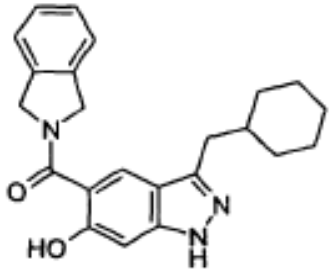
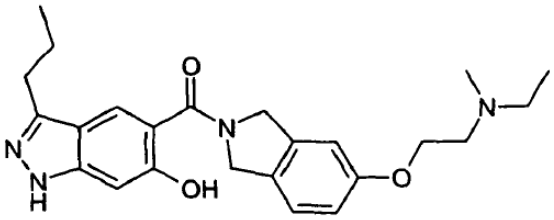
De manera análoga se obtienen los siguientes compuestos

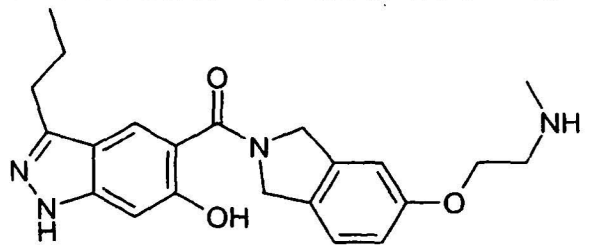
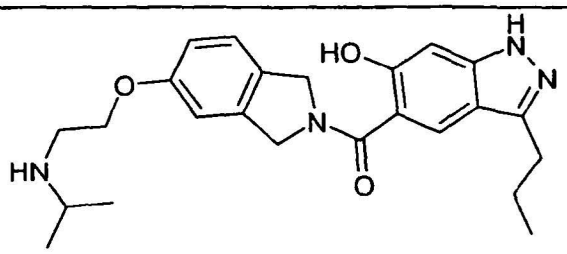
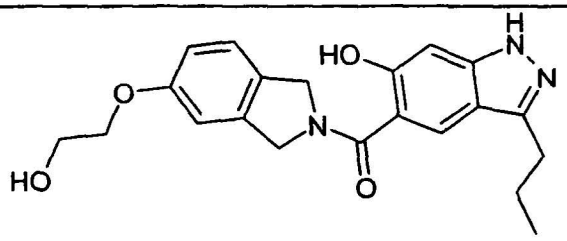
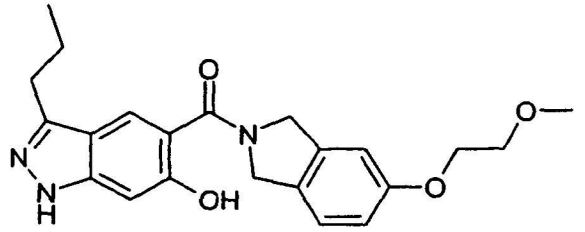
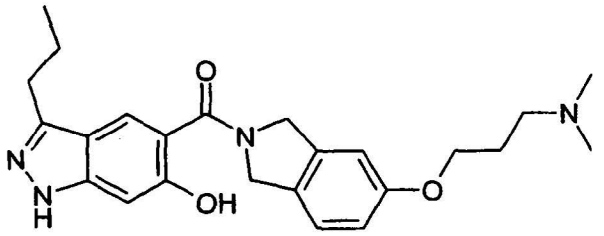
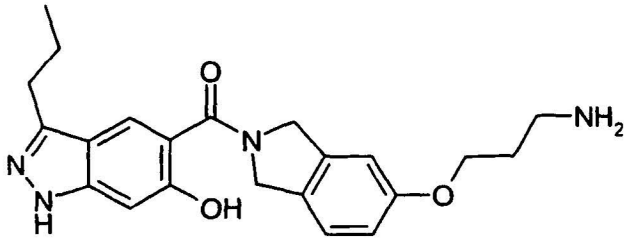
Compuesto	Estructura y/o nombre	RT [min] (HPLC) (Gradiente)	M+H+
"A32"	 (3-ciclohexilmetil-6-hidroxi-1H-indazol-5-il)-[5-(1-metil-piperidin-4-iloxi)-1,3-dihidro-isoindol-2-il]-metanona	2,86 (P)	489
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 12.1 (s, 1H, ancho), 9.83 (s, 1H), 7.63 (s, 1H), 7.24–7.14 (m, 1H, ancho), 6.95-6.85 (m, 3H), 4.74 (s, 2H, ancho), 4.7 (s, 2H, ancho), 4.34-4.27 (m, 1H), 2.75 (d, 2H), 2.67-2.61 (m, 2H), 2.23 (s, 3H), 1.96-1.88 (m, 2H), 1.8-1.56 (m, 9H), 1.29-0.97 (m, 6H)			
"A33"	 [5-(3-dimetilamino-propoxi)-1,3.dihidro-isoindol-2-il]-[6-hidroxi-3-(3-metil-butil)-1H-indazol-5-il]-metanona	2,72 (P)	451
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 12.0 (s, 1H, ancho), 9.75 (s, 1H), 7.65 (s, 1H), 7.2 (d, 1H), 6.93-6.8 (m, 3H), 4.77 (s, 2H), 4.73 (s, 2H), 4.08 (t, 2H), 2.89 (t, 2H), 2.2 (s, 6H), 1.8 (m, 2H), 1.72-1.62 (m, 3H), 0.95 (d, 6H)			
"A34"		2,77 (P)	463
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 11.96 (s, 1H, ancho), 9.7 (s, 1H), 7.63 (s, 1H), 7.17 (d, 1H), 6.9-6.78 (m, 3H), 4.74 (s, 2H), 4.7 (s, 2H), 3.99 (t, 2H), 2.84 (d, 2H), 2.41-2.26 (m, 3H), 1.82 (m, 2H), 1.75-1.44 (m, 6H), 1.33-1.22 (m, 2H)			
"A35"	 (3-ciclohexilmetil-6-hidroxi-1H-indazol-5-il)-[5-(3-dimetilamino-propoxi)-1,3-dihidro-isoindol-2-il]-metanona	2,83 (P)	477

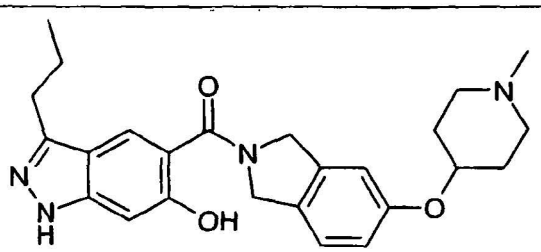
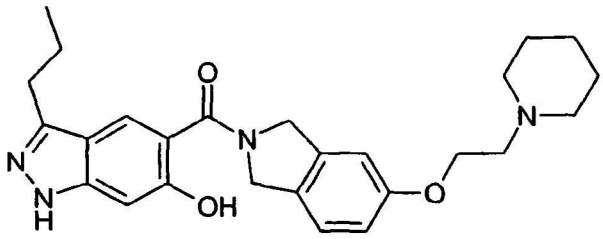
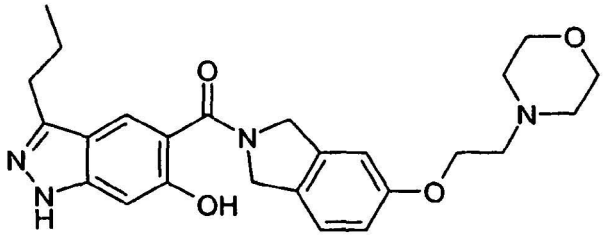
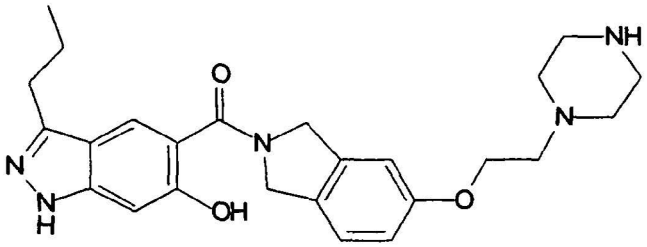
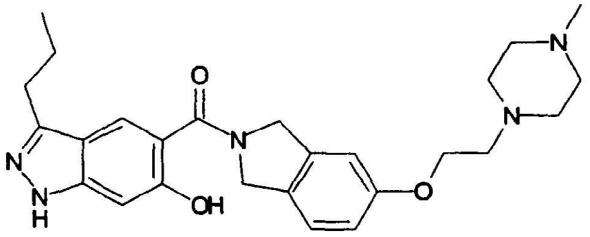
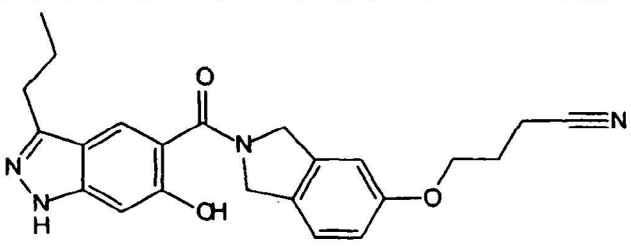
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 11.97 (s, 1H, ancho), 9.72 (s, 1H), 7.62 (s, 1H), 7.16 (d, 1H), 6.89-6.78 (m, 3H), 4.74 (s, 2H), 4.70 (s, 2H), 4.01 (t, 2H), 2.75 (d, 2H), 2.40 (t, 2H), 2.17 (s, 6H), 1.82 (m, 2H), 1.75-1.53 (m, 6H), 1.30-0.95 (m, 5H)			
"A36"	 (5-[2-(etil-metil-amino)-etoxi]-1,3-dihidro-isoindol-2-il)-[6-hidroxi-3-(3-metil-butil)-1H-indazol-5-il]-metanona	2,59 (P)	451
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 12.0 (s, 1H, ancho), 9.75 (s, 1H), 7.66 (s, 1H), 7.21 (d, 1H), 6.95-6.83 (m, 3H), 4.77 (s, 2H), 4.73 (s, 2H), 4.07 (t, 2H), 2.97-2.8 (m, 4H), 2.75 (t, 2H), 2.28 (s, 3H), 1.72-1.63 (m, 3H), 1.02 (t, 3H), 0.91 (d, 6H)			
"A37"	 (3-ciclopentilmetil-6-hidroxi-1H-indazol-5-il)-(5-[2-(etil-metil-amino)-etoxi]-1,3-dihidro-isoindol-2-il)-metanona	2,59 (P)	463
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] = 12.0 (s, 1H, ancho), 9.75 (s, 1H), 7.67 (s, 1H), 7.21 (d, 1H), 6.94-6.84 (m, 3H), 4.77 (s, 2H), 4.73 (s, 2H), 4.08 (t, 2H), 2.87 (d, 2H), 2.75 (T, 2H), 2.47-2.55 (m, 2H, DMSO), 2.36 (m, 1H), 2.28 (s, 3H), 1.78-1.48 (m, 5H), 1.37-1.26 (m, 3H), 1.02 (t, 3H)			
"A38"	 (3-ciclohexilmetil-6-hidroxi-1H-indazol-5-il)- {5-[2-(etil-metil-amino)-etoxi]-1,3-dihidro-isoindol-2-il}-metanona	2,69 (P)	477
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 12.01 (s, 1H, ancho), 9.8 (s, 1H), 7.6 (s, 1H), 7.32-7.12 (m, 1H), 6.97-6.77 (m, 3H), 4.72 (s, 2H, ancho), 4.67 (s, 2H, ancho), 4.08 (t, 2H), 2.9-2.76 (m, 2H), 2.72 (d, 2H), 2.65-2.52 (m, 2H), 2.32 (s, 3H), 1.8-1.5 (m, 6H), 1.29-09 (m, 8H)			
"A39"	 [6-hidroxi-3-(3-metil-butil)-1H-indazol-5-il]-[5-(2-piperidin-1-il-etoxi)-1.3-dihidro-isoindol-2-il]-metanona	2,53 (P)	477

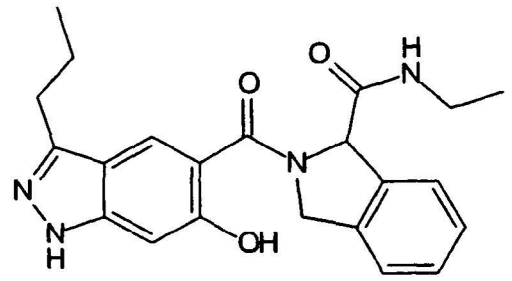
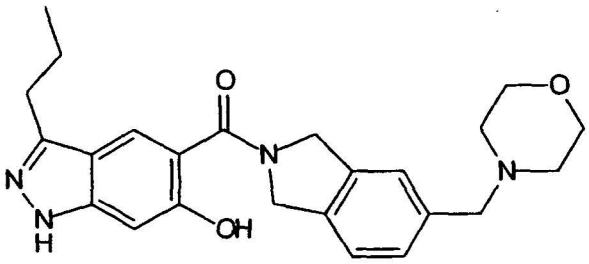
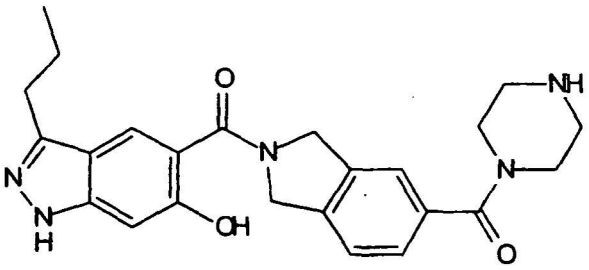
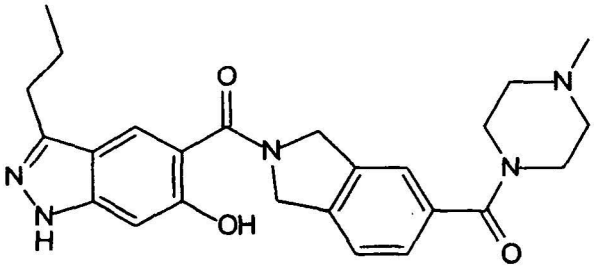
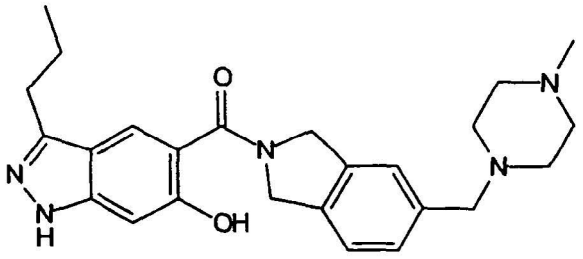
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 12.05 (s, 1H, ancho), 9.8 (s, 1H, ancho), 7.61 (s, 1H), 7.1-7.25 (m, 1H), 6.95-6.75 (m, 3H), 4.72 (s, 2H, ancho), 4.67 (s, 2H, ancho), 4.05 (t, 2H), 2.65 (t, 2H), 2.38-2.46 (m, 4H), 1.7-1.32 (m, 9H), 0.93 (s, 6H)			
"A40"	 (3-ciclopentilmetil-6hidroxi-1H-indazol-5il)-[5-(2-piperidin-1-il-etoxi)-1,3-dihidro-isoindol-2-il]-metanona	2,55 (P)	489
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 11.98 (s, 1H, ancho), 9.73 (s, 1H), 7.63 (s, 1H), 7.17 (s, 1H), 6.95-6.8 (m, 3H), 4,73 (s, 2H), 4.68 (s, 2H), 4.05 (t, 2H), 2.84 (s, 2H), 2.65 (t, 2H), 2.44 (t, 4H), 2.32 (m, 1H), 1.75-1.20 (m, 14H)			
"A41"	 (3-ciclohexilmetil-6hidroxi-1H-indazol-5il)-[5-(2-piperidin-1-il-etoxi)-1,3-dihidro-isoindol-2-il]-metanona	2,71 (P)	503
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] = 12.02 (s, 1H, ancho), 9.76 (s, 1H), 7.65 (s, 1H), 7.2 (d, 1H), 6.98-681 (m, 3H), 4.76 (s, 2H), 4.72 (s, 2H), 4.08 (t, 2H), 2.77 (d, 2H), 2.70 (t, 2H), 2.6-2.42 (m, 4H, DMSO), 1.86-0.99 (m, 17H)			
"A42"	 4-(2-[6-hidroxi-3-(3-metil-butil)-1H-indazol-5-carbonil]-23-dihidro-1H-isoindol-5-iloxi)-butironitrilo	3,16 (P)	433
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 11.98 (s, 1H, ancho), 9.74 (s, 1H), 7.63 (s, 1H), 7.2 (d, 1H), 6.94-6.81 (m, 3H), 4.74 (s, 2H), 4.69 (s, 2H), 4.05 (t, 2H), 2.85 (t, 2H), 2.6 (t, 2H), 2.01 (m, 2H), 1.68-1.59 (m, 3H), 0.93 (d, 6H)			
"A43"	 4-[2-(3-ciclopentilmetil-6hidroxi-1H-indazol-5-carbonil)-2,3-dihidro-1H-isoindol-5- iloxi]-butironitrilo	3,13 (P)	445

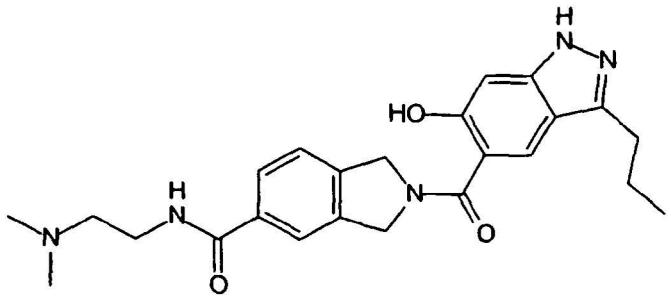
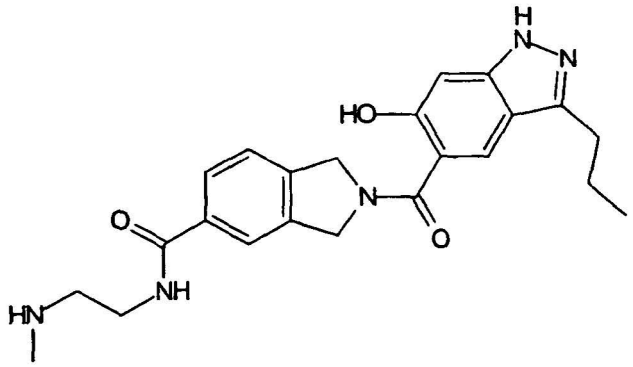
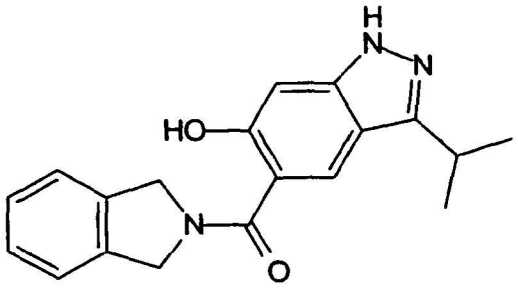
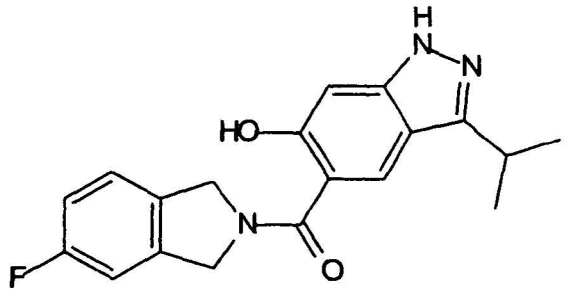
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 12.02 (s, 1H, ancho), 9.74 (s, 1H, ancho), 7.67 (s, 1H), 7.22 (d, 1H), 6.95-6.85 (m, 3H), 4.78 (s, 2H), 4.08 (t, 2H), 2.88 (d, 2H), 2.63 (t, 2H), 2.36 (m, 1H), 2.05 (m, 2H), 1.79-1.25 (m, 8H)			
"A44"	 4-[2-(3-ciclohexilmetil-6-hidroxi-1H-indazol-5-carbonil)-2,3-dihidro-1H-isoindol-5-iloxi]-butironitrilo	3,26 (P)	459
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] 12.02 (s, 1H, ancho), 9.75 (s, 1H, ancho), 7.61 (s, 1H), 7.2)d, 1H), 6.95-6.82 (m, 3H), 4.73 (s, 2H), 4.69 (s, 2H), 4.04 (t, 2H), 2,74 (d, 2H), 2.6 (t, 2H), 2.0 (m, 2H), 1.81-1.53 (m, 5H), 1.31-0.96 (m, 6H)			
"A45"	 [6-hidroxi-3-(3-metil-butil)-1H-indazol-5-il]-[5-(2-morfolin-4-il-etoxi)-1,3-dihidro-isoindol-2-il]-metanona	2,71 (P)	479
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] = 11.95 (s, 1H, ancho), 9.71 (s, 1H), 7.61 (s, 1H), 7.16 (d, 1H), 6.9 -6.8 (m, 3H), 4.72 (s, 2H), 4.68 (s, 2H), 4.06 (t, 2H), 3.55 (t, 4H), 2.85 (t, 2H), 2.5-2.42 (m, 4H, DMSO), 1.66-1.57 (m, 3H), 0.92 (d, 6H)			
"A46"	 (3-ciclopentilmetil-6-hidroxi-1H-indazol-5-il)-[5-(2-morfolin-4-il-etoxi)-1,3 dihidro-isoindol-2-il]-metanona	2,75 (P)	491
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] = 12.03 (s, 1H, ancho), 9.76 (s, 1H), 7.66 (s, 1H), 7.21 (d, 1H), 6.95-6.84 (m, 3H), 4.77 (s, 2H), 4.73 (s, 2H), 4.11 (t, 2H), 3.6 (t, 4H), 2.88 (d, 2H), 2.74 (t, 2H), 2.47-2.55 (m, 4H, DMSO), 2.35 (m, 1H), 1.8-1.25 (m, 8H)			
"A47"	 (3-ciclohexilmetil-6-hidroxi-1H-indazol-5-il)-[5-(2-morfolin-4-il-etoxi)-1,3-dihidro-isoindol-2-il]-metanona	2,65 (P)	505
^{1}H-NMR (DMSO-d_6, 90°C): δ [ppm] = 12.05 (s, 1H, ancho), 9.78 (s, 1H), 7.65 (s, 1H), 7.21 (d, 1H), 6.97-6.84 (m, 3H), 4.76 (s, 2H), 4.72 (s, 2H), 4.12 (t, 2H), 3.6 (t, 4H), 2.82-2.70 (m, 4H), 2.6-2.44 (m, 4H, DMSO), 1.86-0.95 (m, 11H)			

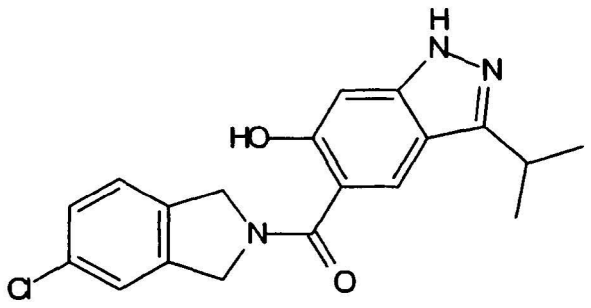
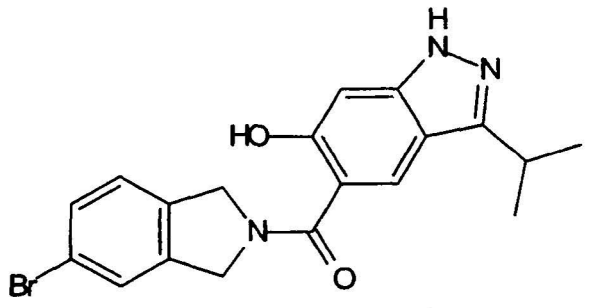
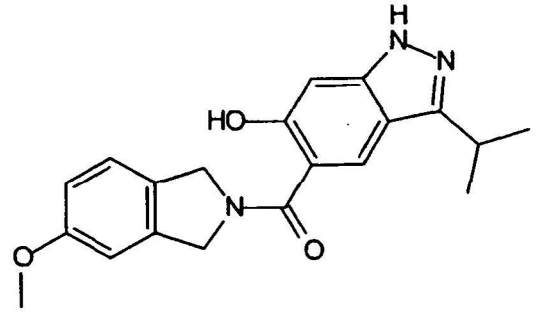
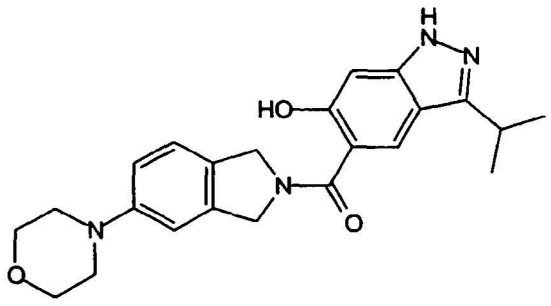
"A48"	 Etilamida de ácido 2-(6-hidroxi-3-propil-1H-indazol-5-carbonil)-2,3-dihidro-1H-isoindol-1-carboxílico	1,96 (N)	393
"A49"	 (1,3-dihidro-isoindol-2-il)-(6-hidroxi-3-isobutil-1H-indazol-5-il)-metanona	1,89 (N)	336
"A50"	 (3-ciclohexilmetil-6-hidroxi-1H-indazol-5-il)-(1,3-dihidro-isoindol-2-il)-metanona		
"A51"			

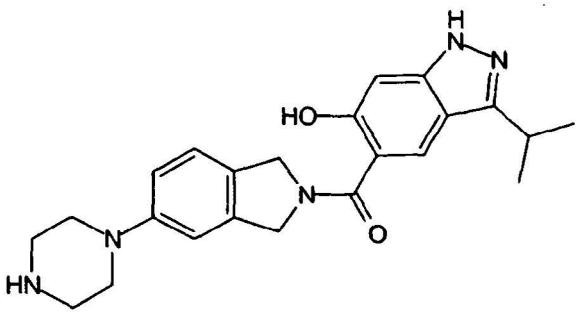
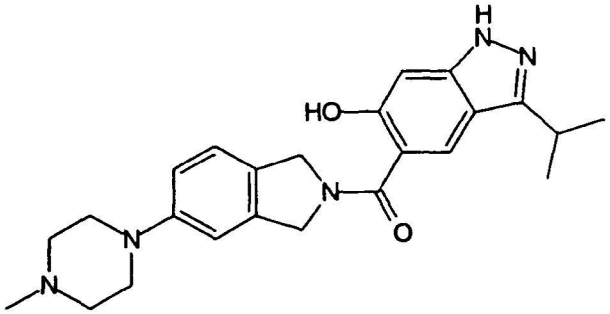
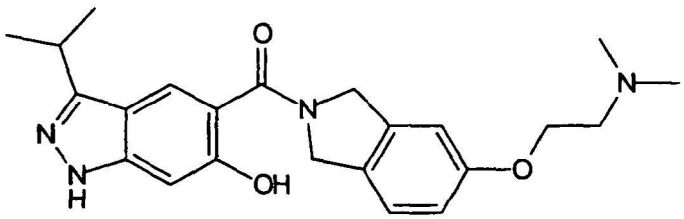
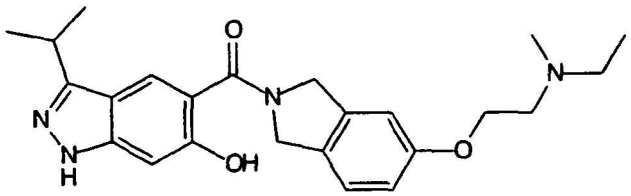
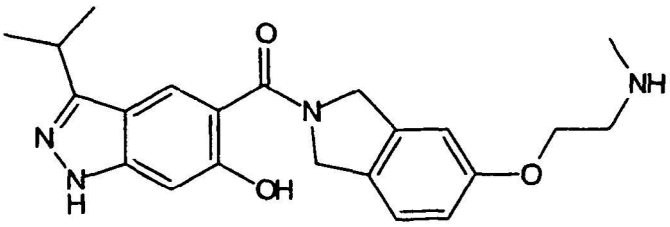
"A52"			
"A53"			
"A54"			
"A55"			
"A56"			
"A57"			

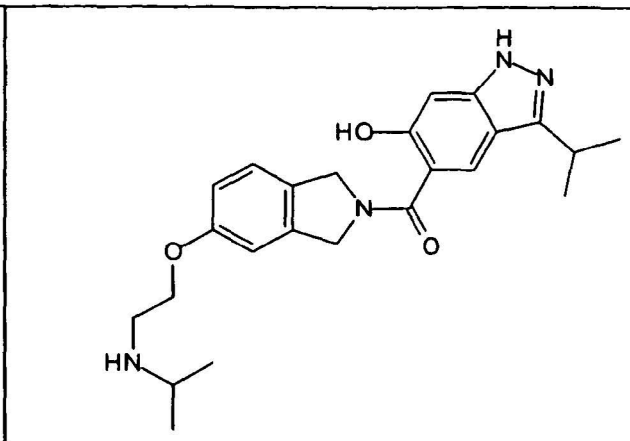
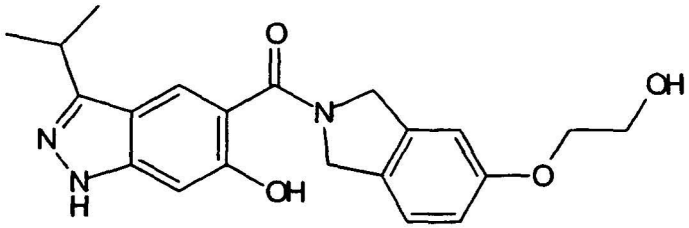
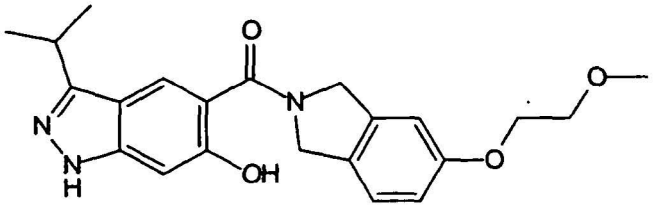
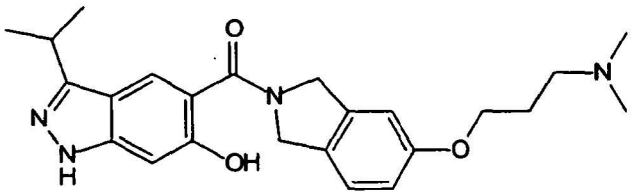
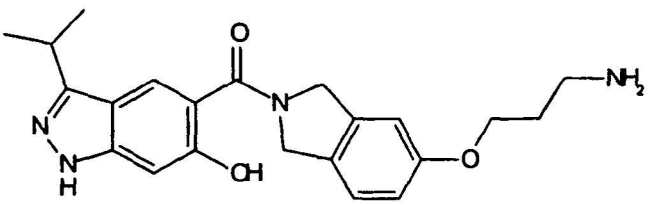
"A58"			
"A59"			
"A60"			
"A61"			
"A62"			
"A63"			

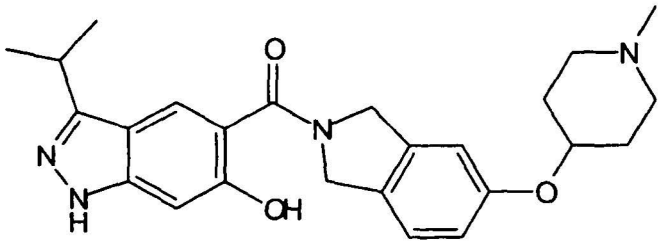
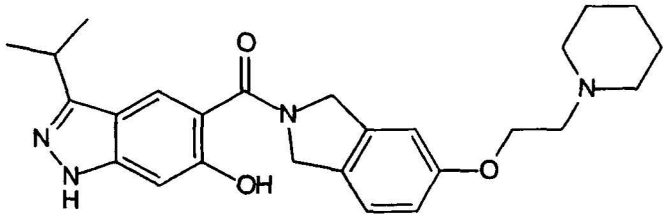
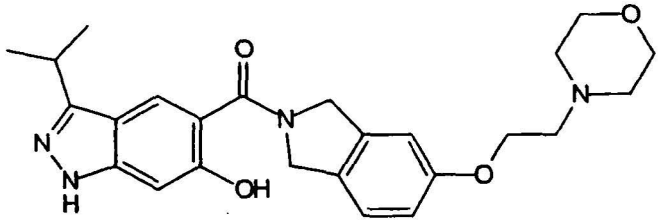
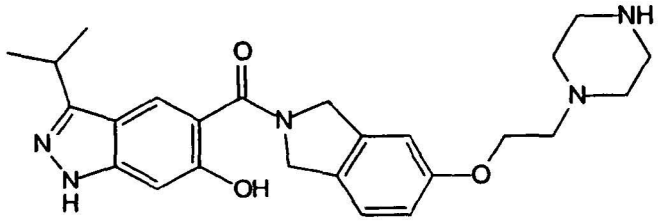
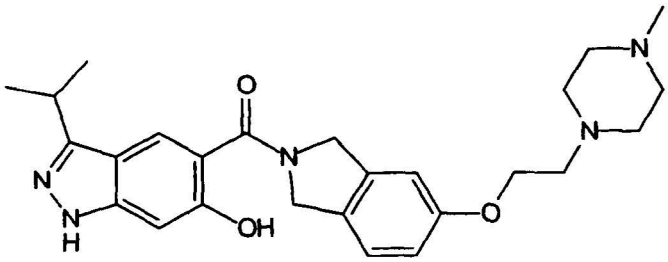
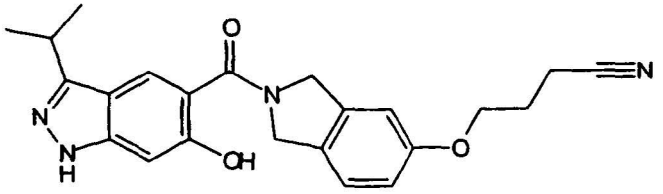
"A64"			
"A65"			
"A66"			
"A67"			
"A68"			

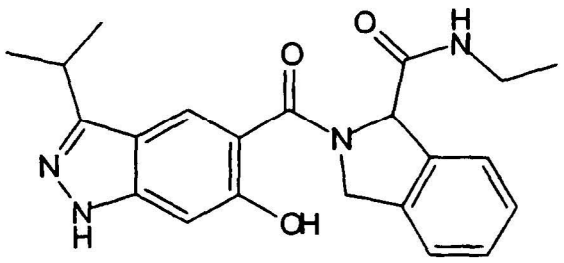
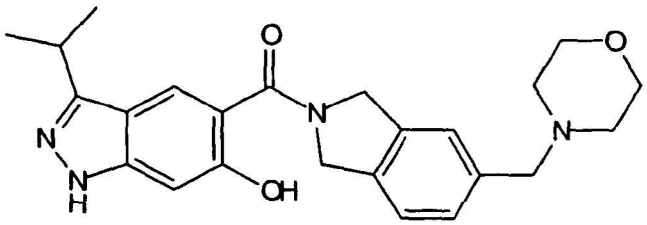
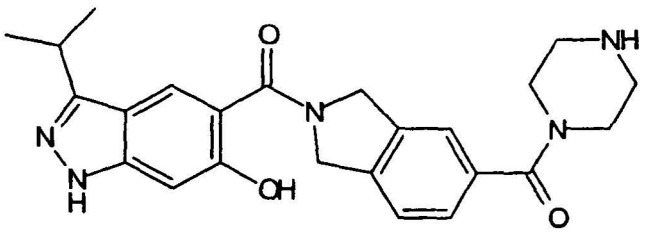
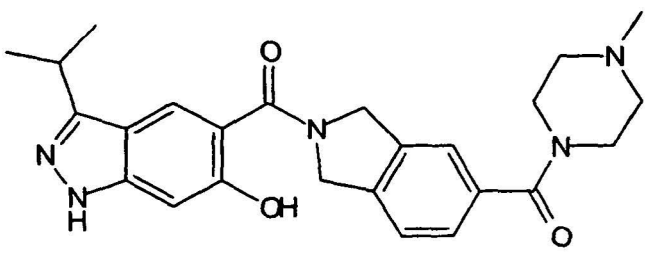
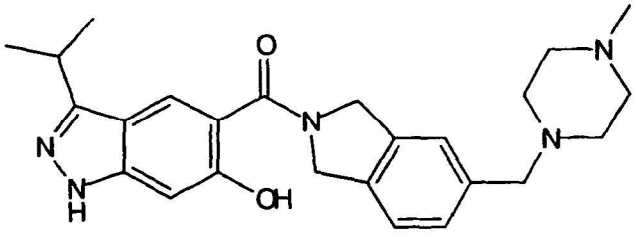
"A69"			
"A70"			
"A71"			
"A72"			

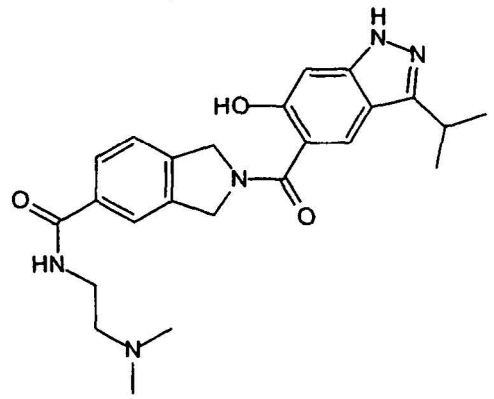
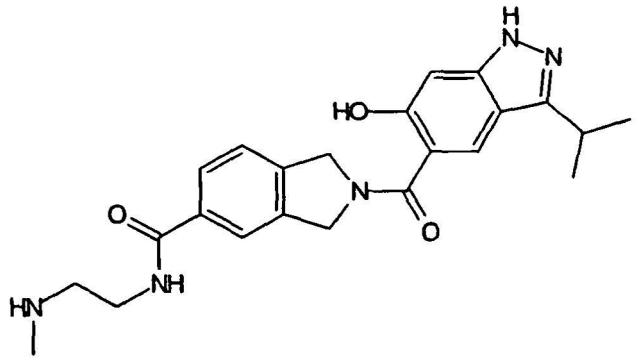
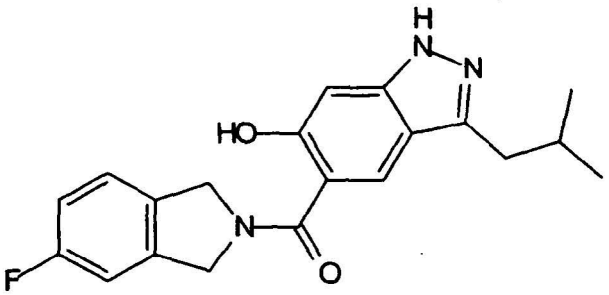
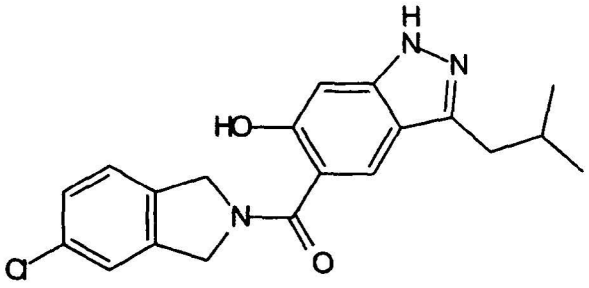
"A73"			
"A74"			
"A75"			
"A76"			

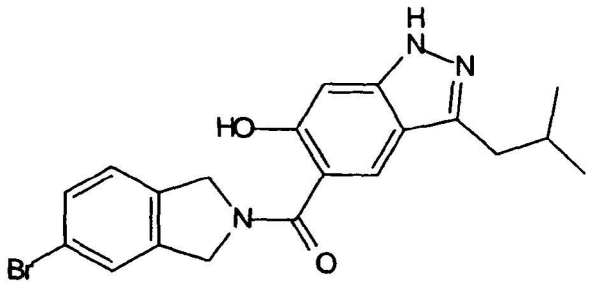
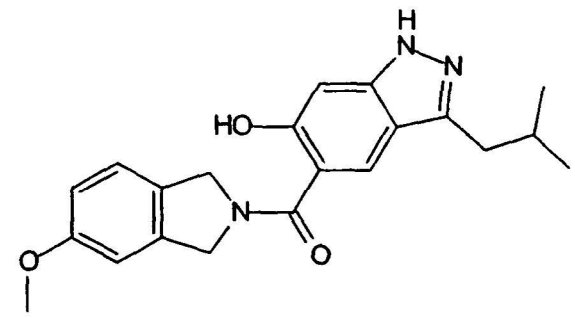
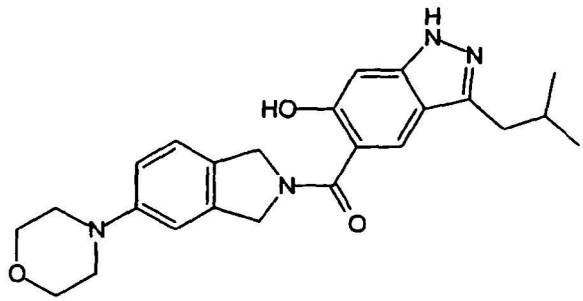
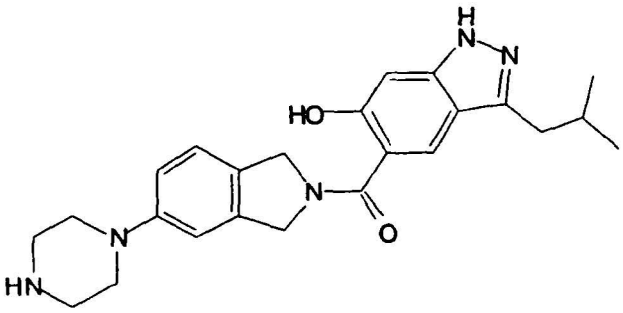
"A77"			
"A78"			
"A79"			
"A80"			
"A81"			

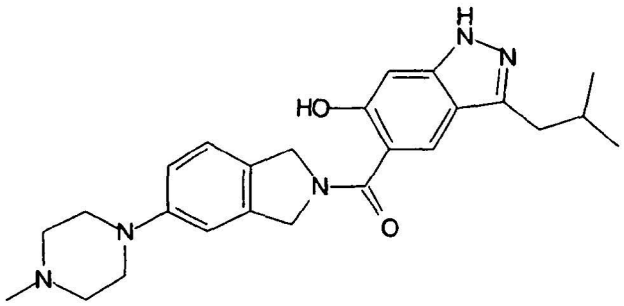
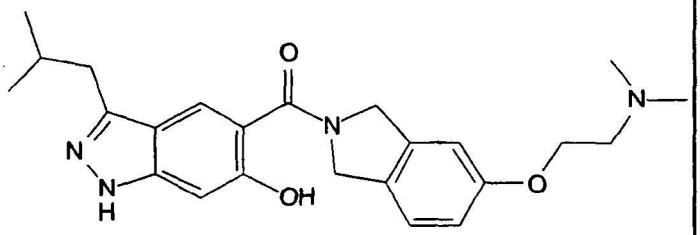
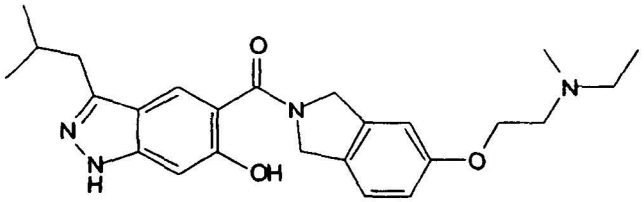
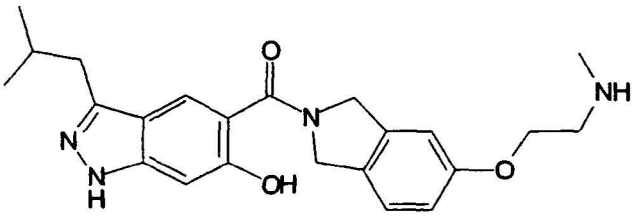
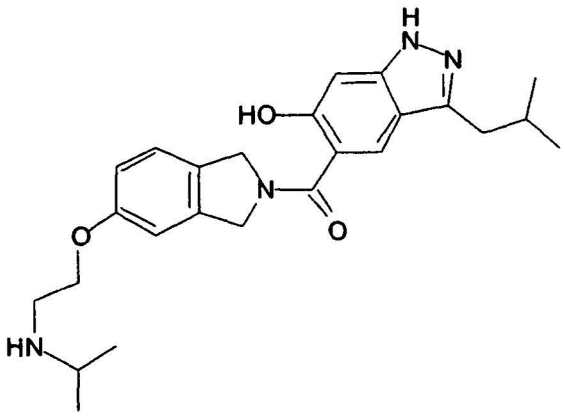
"A82"			
"A83"			
"A84"			
"A85"			
"A86"			

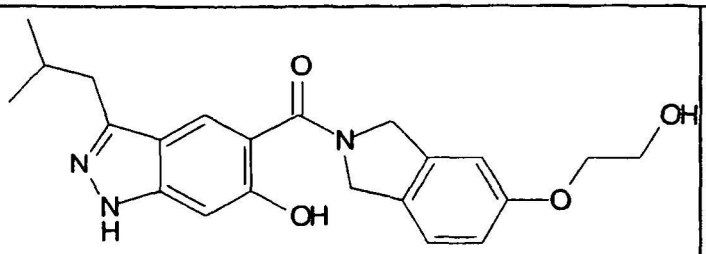
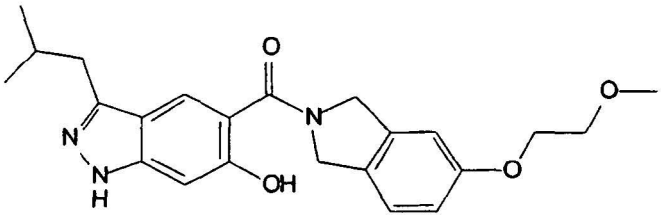
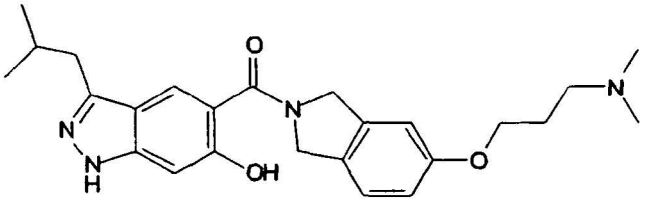
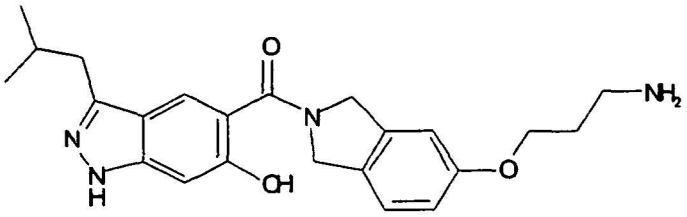
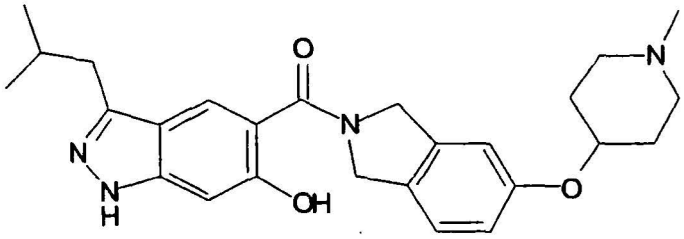
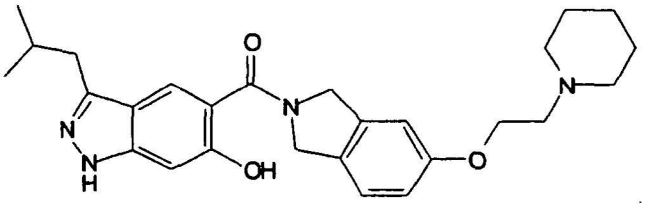
"A87"			
"A88"			
"A89"			
"A90"			
"A91"			
"A92"			

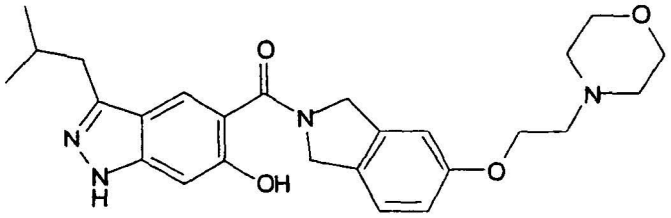
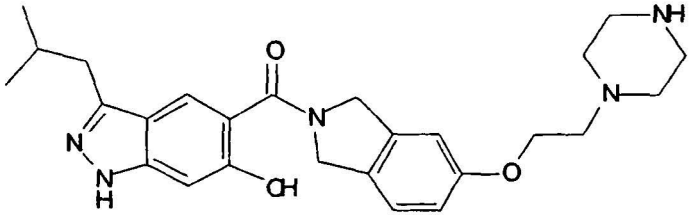
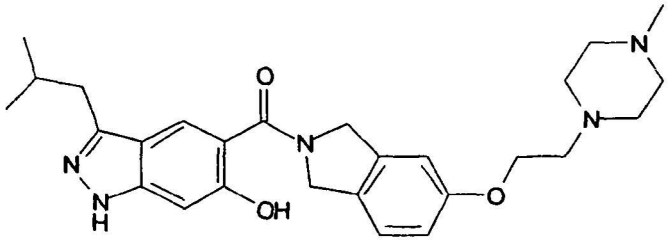
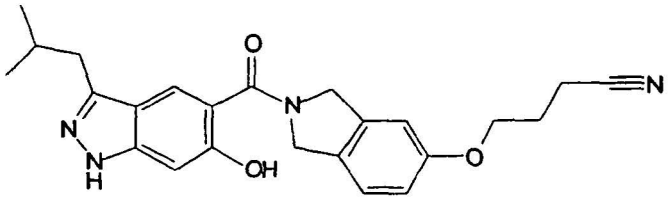
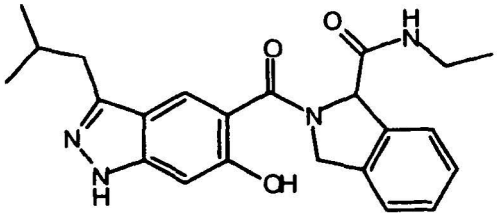
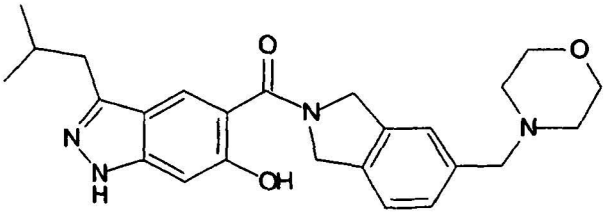
"A93"			
"A94"			
"A95"			
"A96"			
"A97"			

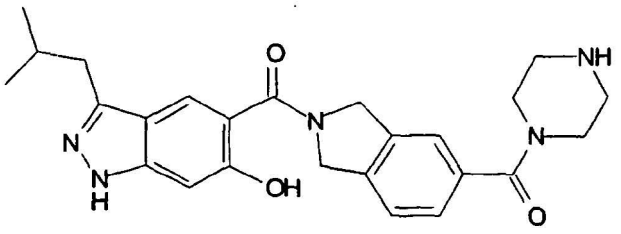
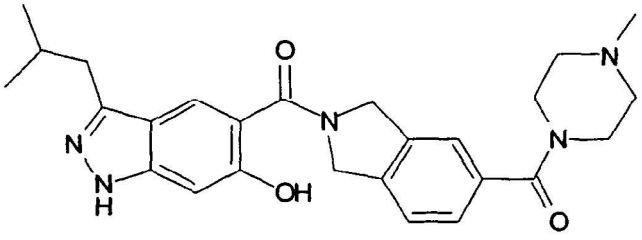
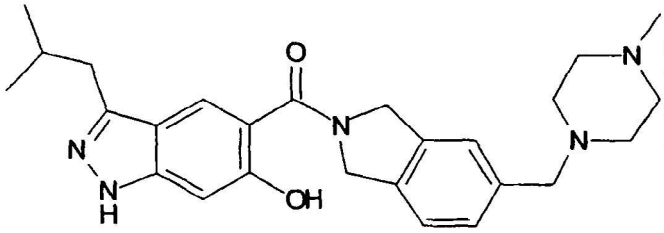
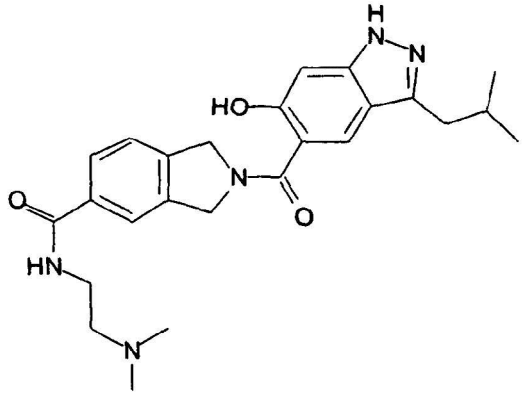
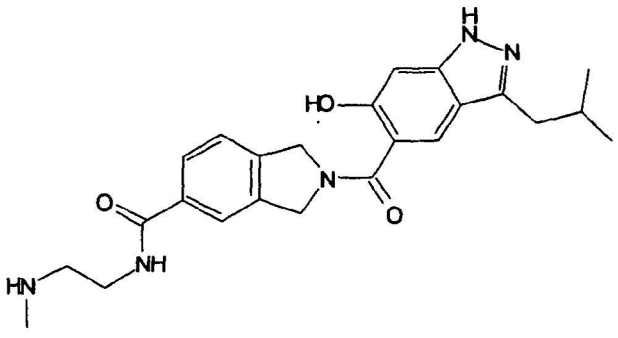
"A98"			
"A99"			
"A100"			
"A101"			

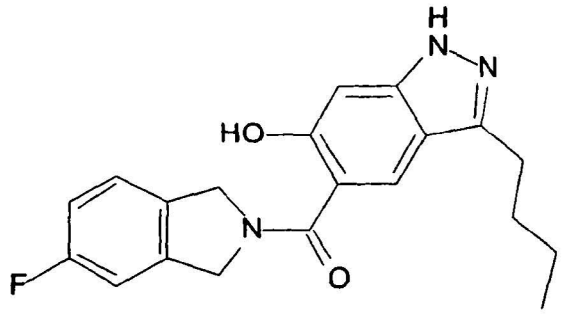
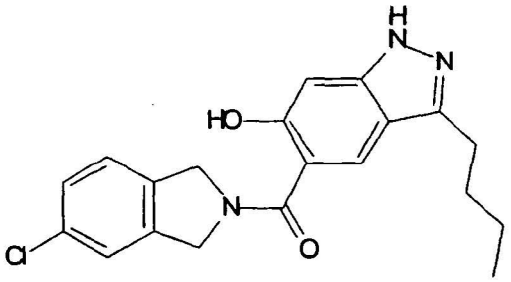
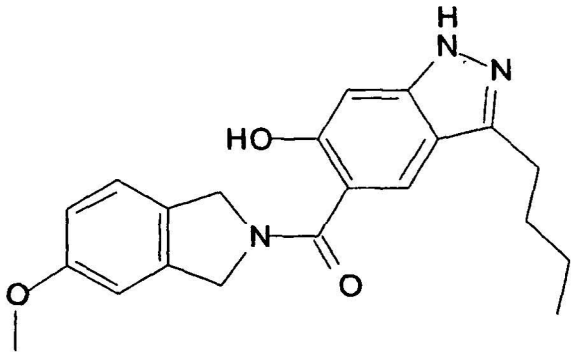
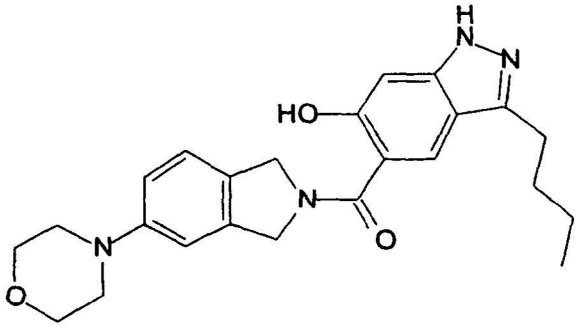
"A102"			
"A103"			
"A104"			
"A105"			

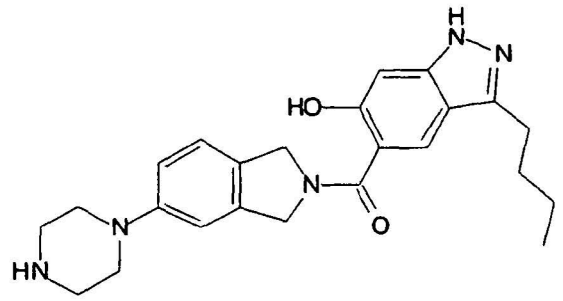
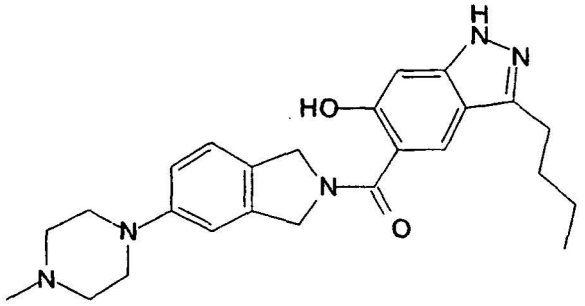
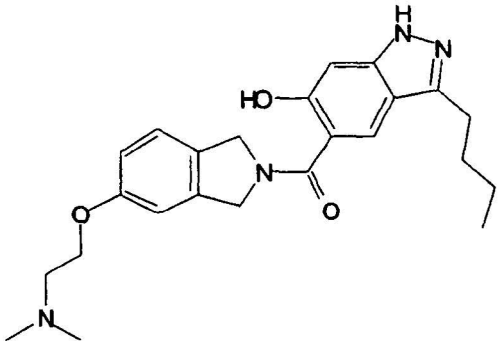
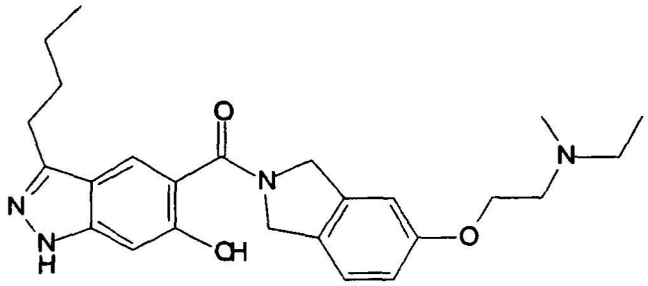
"A106"			
"A107"			
"A108"			
"A109"			
"A110"			

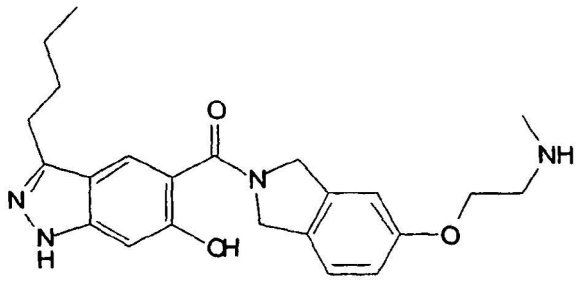
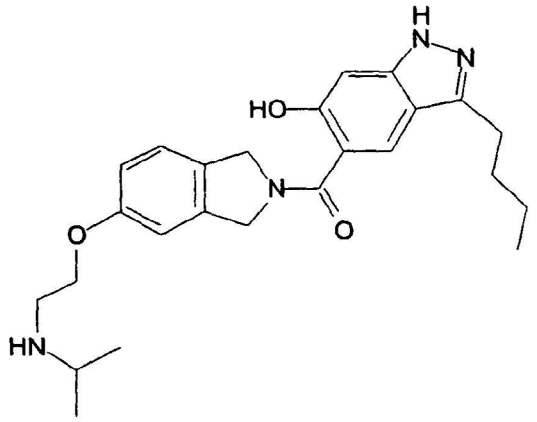
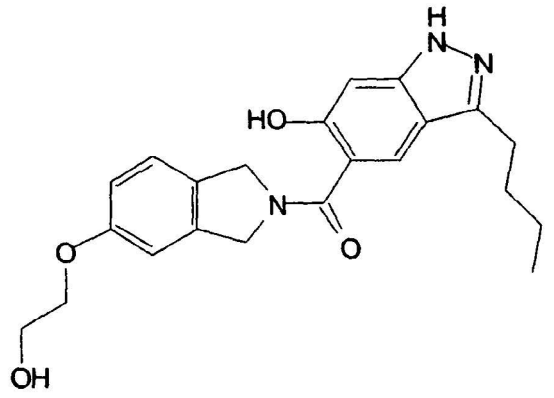
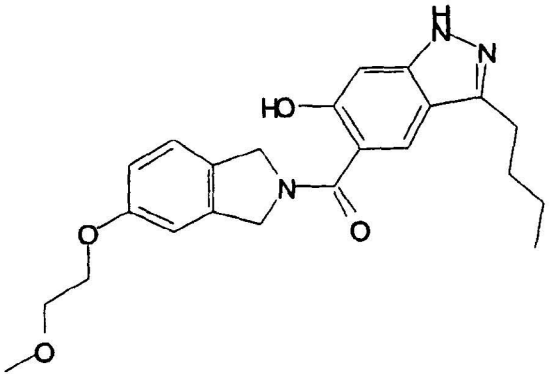
"A111"			
"A112"			
"A113"			
"A114"			
"A115"			
"A116"			

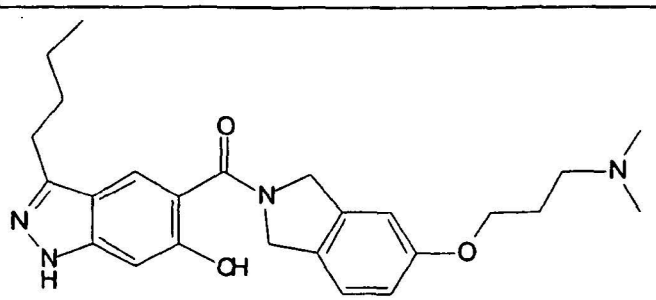
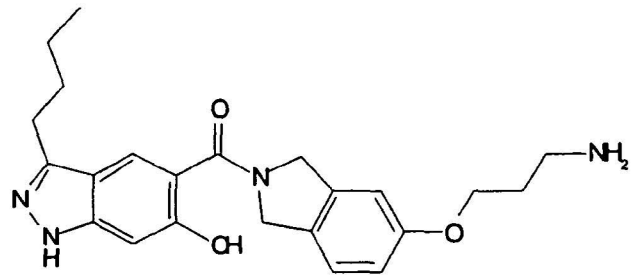
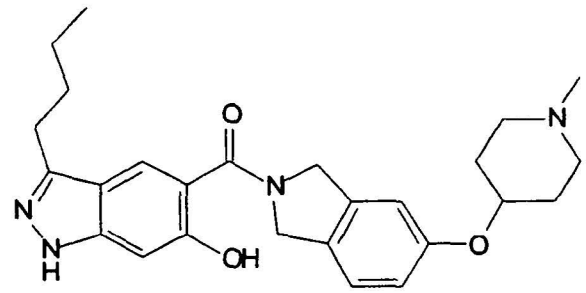
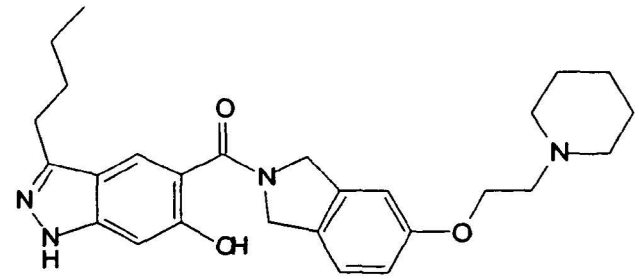
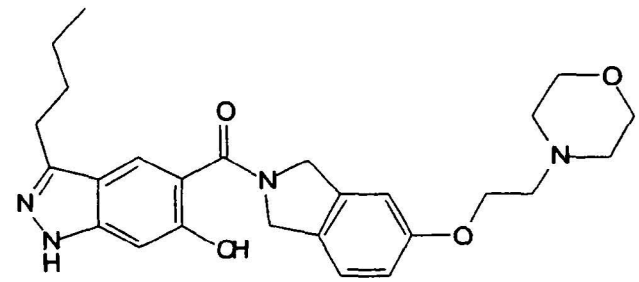
"A117"			
"A118"			
"A119"			
"A120"			
"A121"			
"A122"			

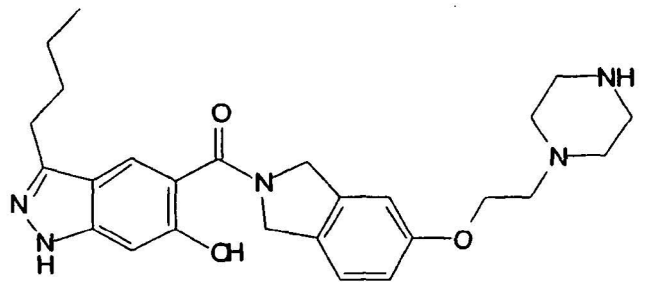
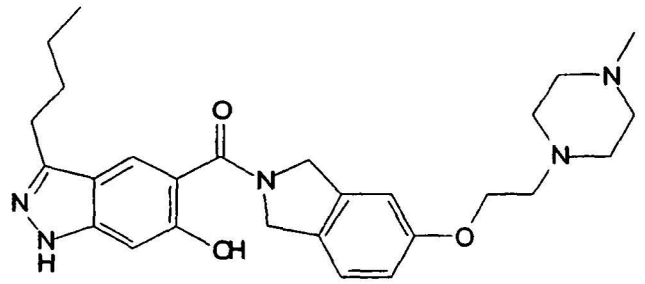
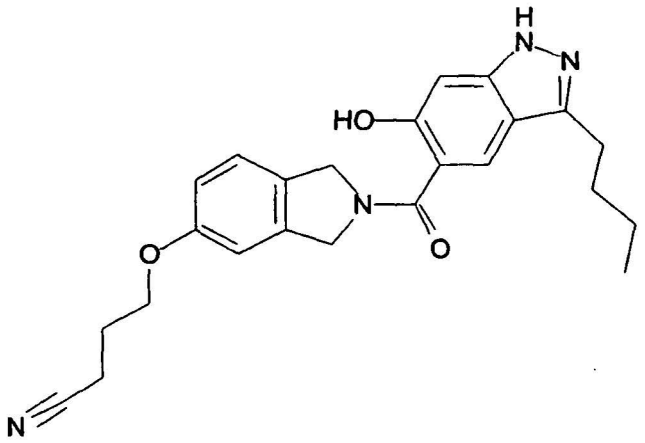
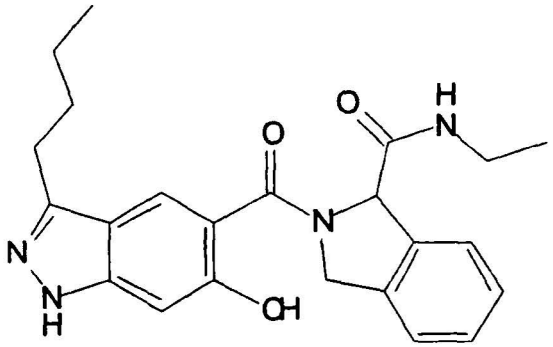
"A123"			
"A124"			
"A125"			
"A126"			
"A127"			

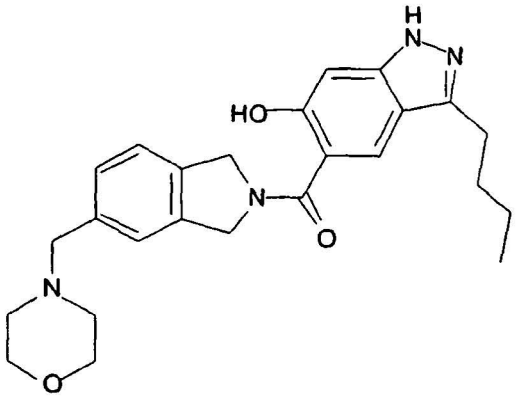
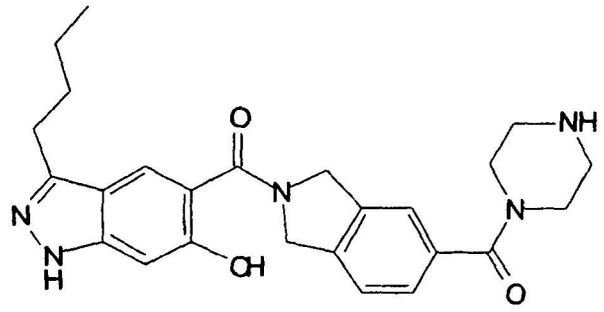
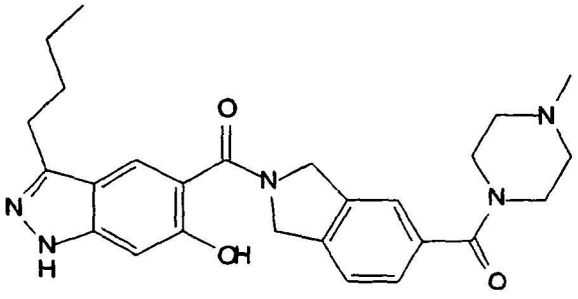
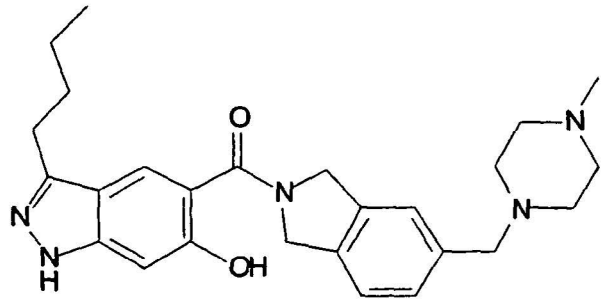
"A128"			
"A129"			
"A130"			
"A131"			

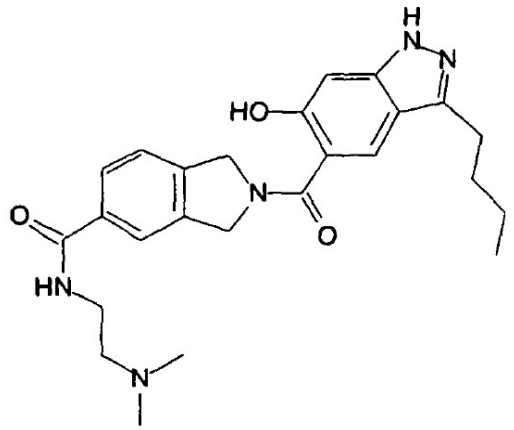
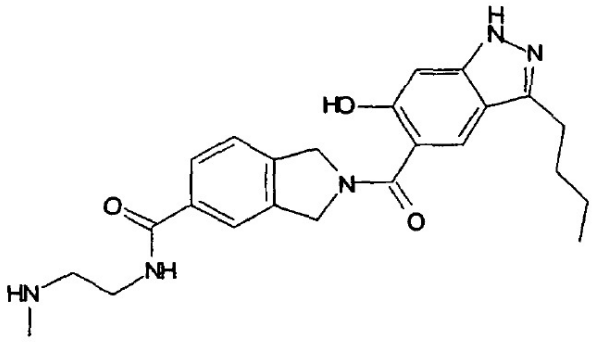
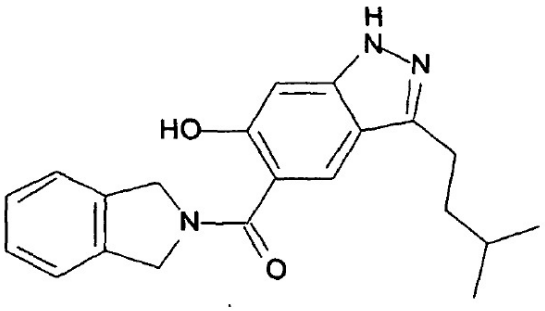
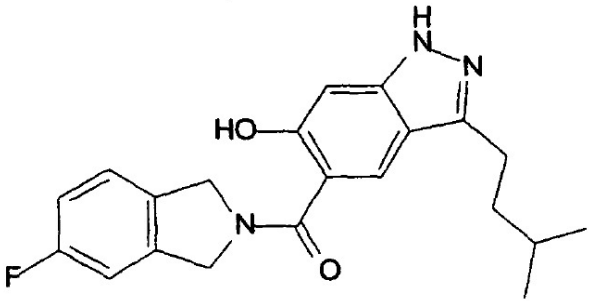
"A132"			
"A133"			
"A134"			
"A135"			

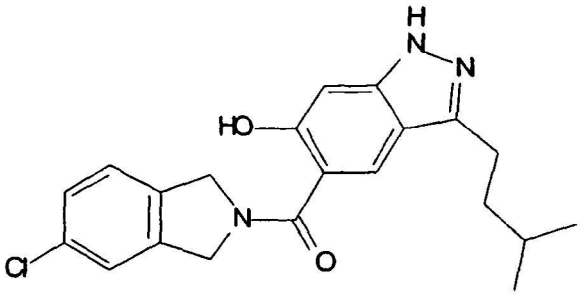
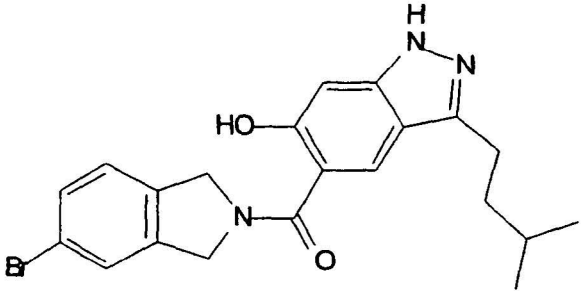
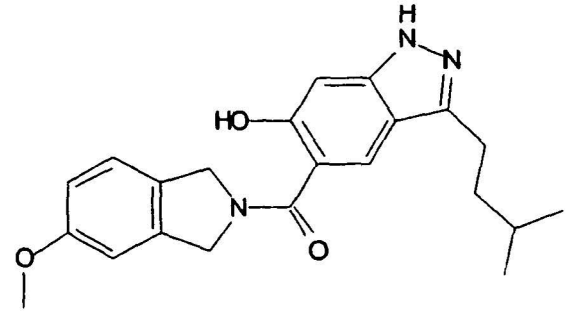
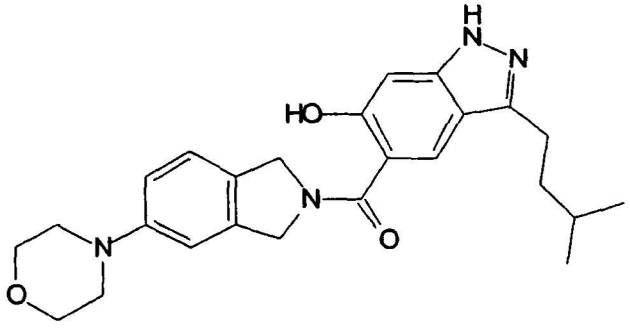
"A136"			
"A137"			
"A138"			
"A139"			

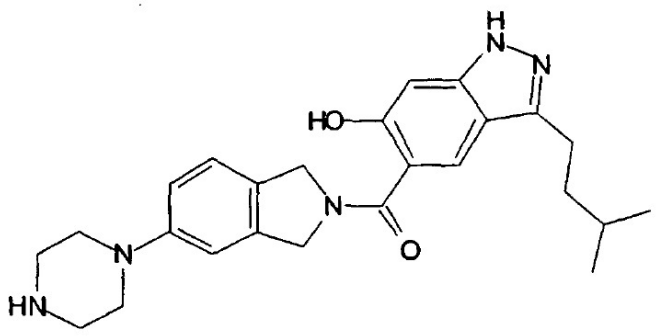
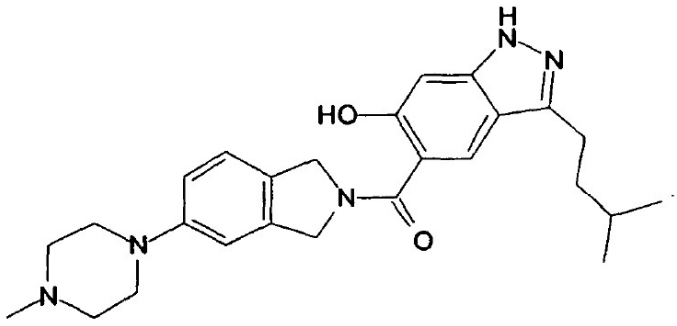
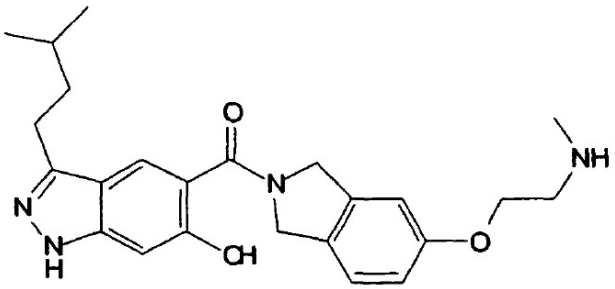
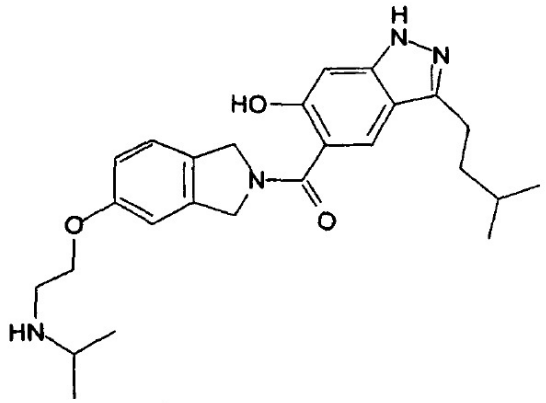
"A140"			
"A141"			
"A142"			
"A143"			
"A144"			

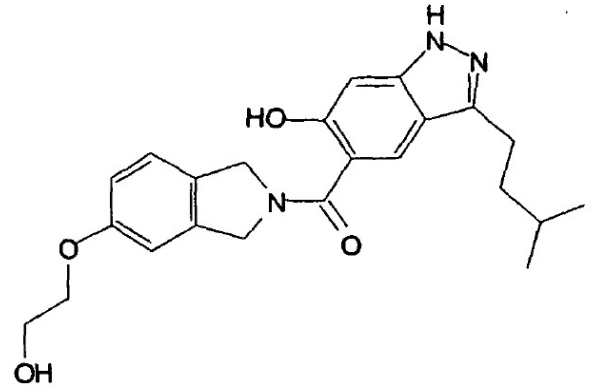
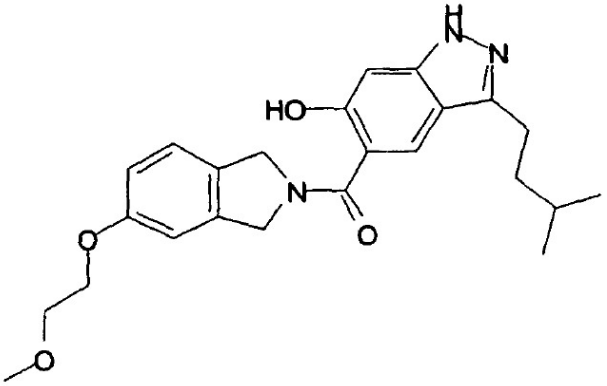
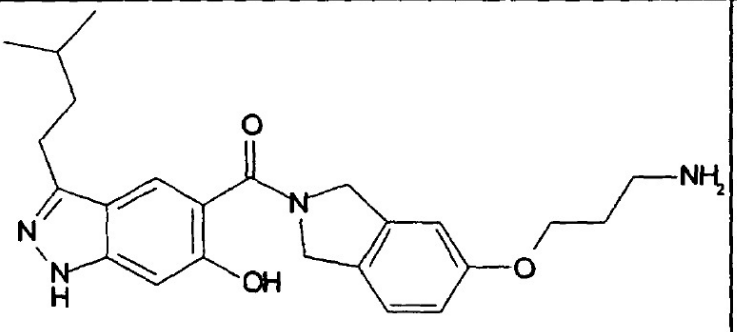
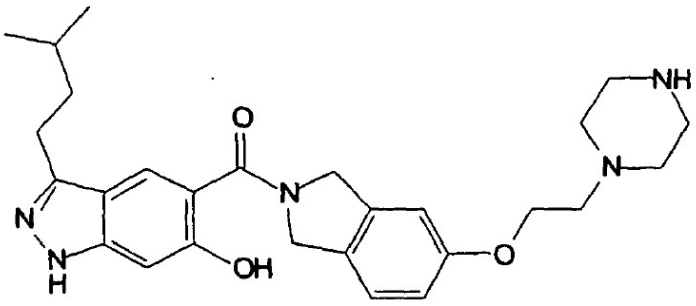
"A145"			
"A146"			
"A147"			
"A148"			

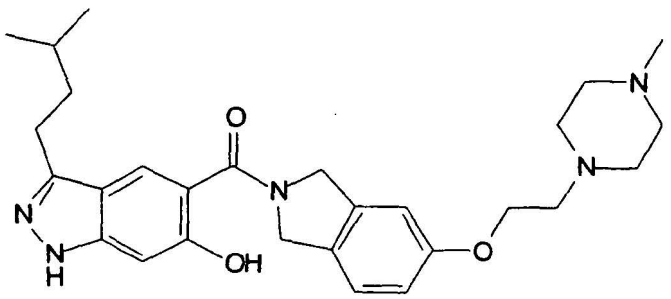
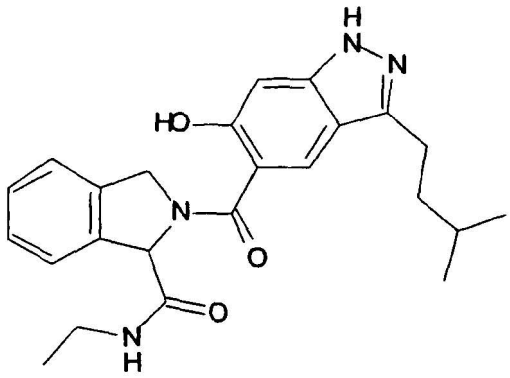
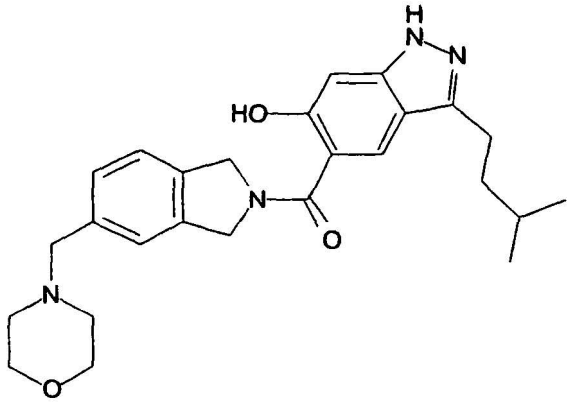
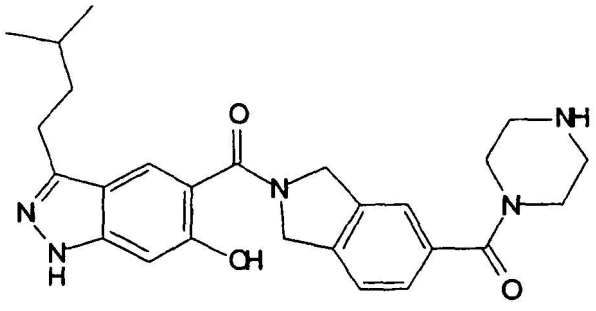
"A149"			
"A150"			
"A151"			
"A152"			

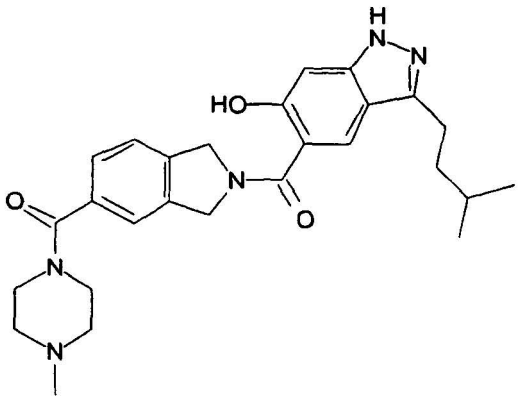
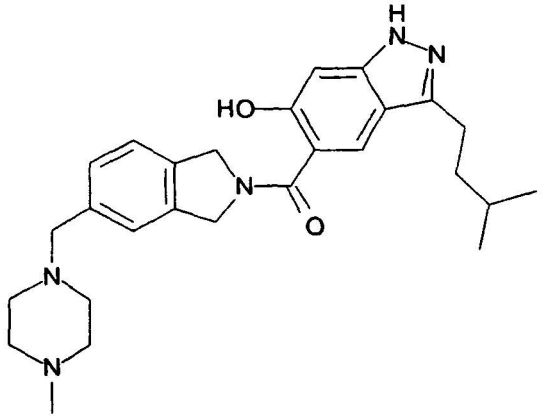
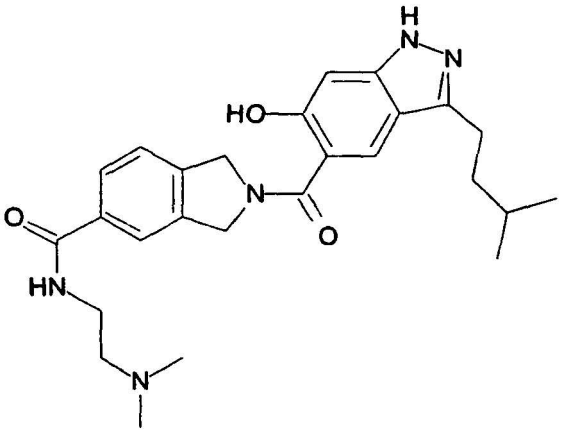
"A153"			
"A154"			
"A155"			
^{1}H-NMR (DMSO-d6, 90°C): [ppm] = 11.9 (s, 1H, ancho), 9.73 (s, 1H), 7.64 (s, 1H), 7.32-7.22 (m, 4H), 6.86 (s, 1H), 4.79 (s, 4H), 2.0-2.8 (m, 2H, H2O), 1.68-1.60 (m, 3H), 0.93 (d, 6H)			
"A156"			

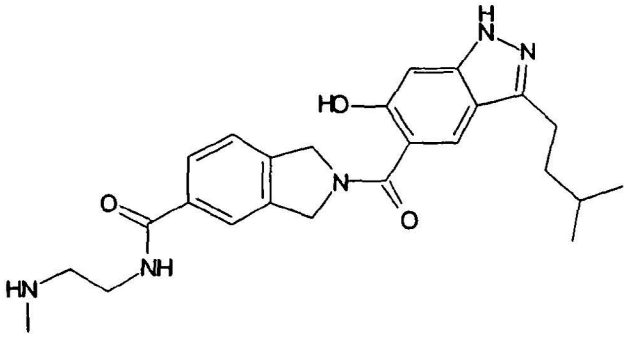
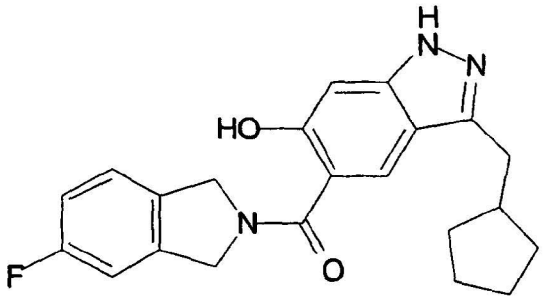
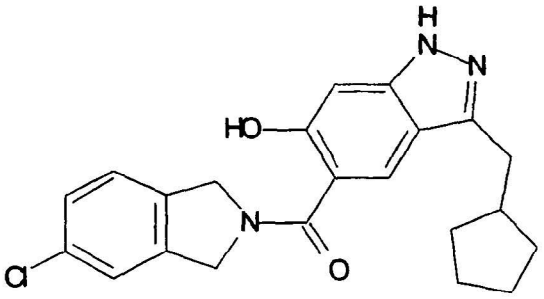
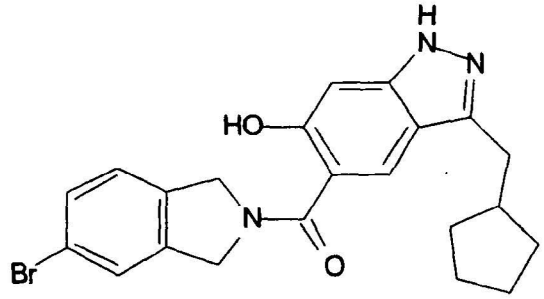
"A157"			
"A158"			
"A159"			
"A160"			

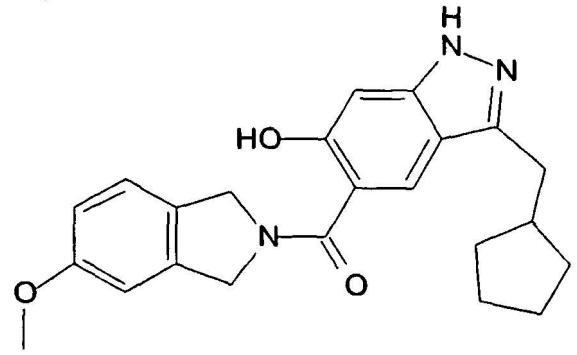
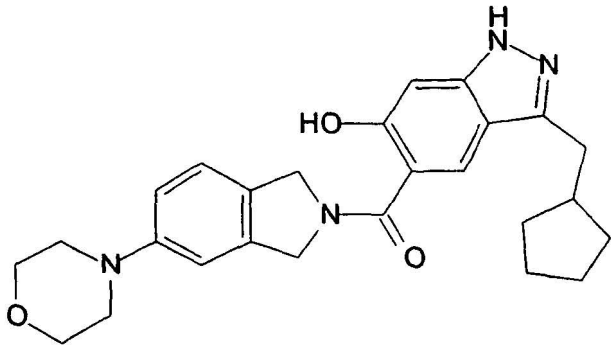
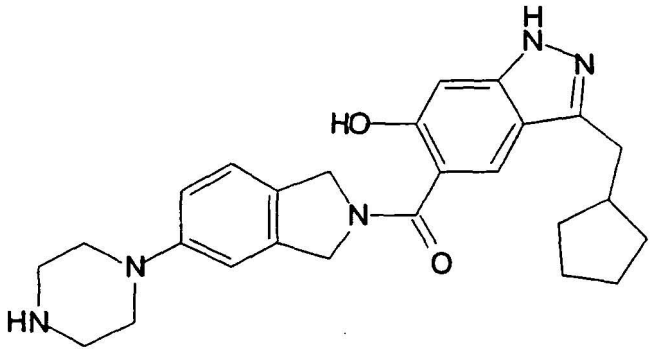
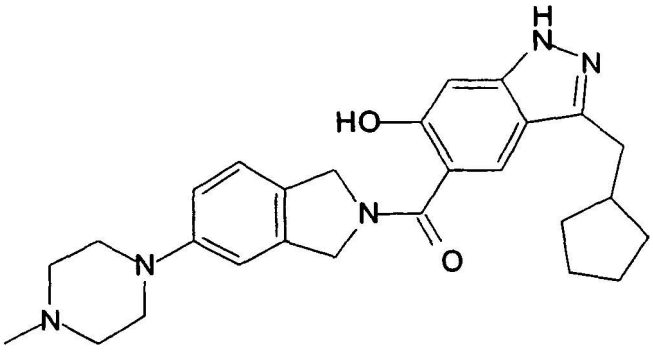
"A161"			
"A162"			
"A163"			
^{1}H-NMR (DMSO-d6, 90°C): [ppm] = 12.0 (s, 1H, ancho), 7.62 (s, 1H), 7.18 (d, 1H), 6.94-6.79 (m, 3H), 4.74 (s, 2H, ancho), 4.69 (s, 2H, ancho), 4.08-4.0 (m, 2H), 3.25-2.75 (m, 4H, H2O), 2.41 (s, 3H), 1.67-1.60 (m, 3H), 0.93 (d, 6H)			
"A164"			

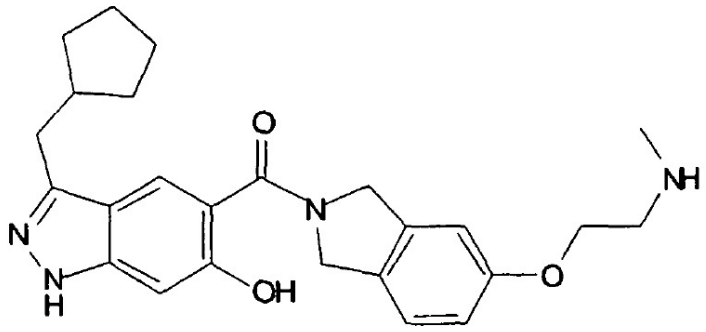
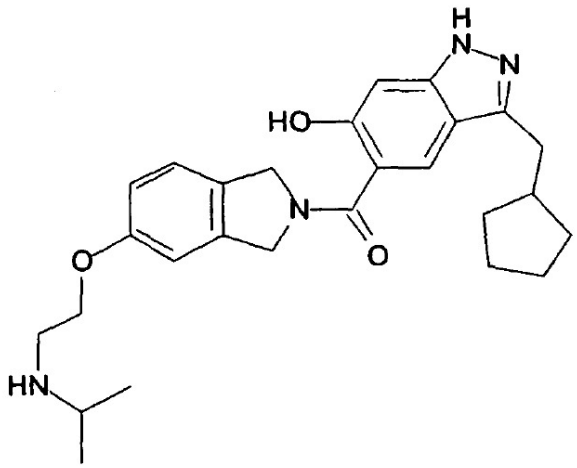
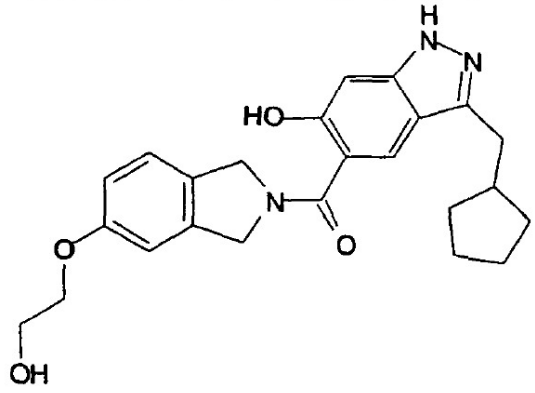
"A165"			
^{1}H-NMR (DMSO-d6, 90°C): [ppm] = 12.04 (s, 1H, ancho), 9.79 (s, 1H, ancho), 7.65 (s, 1H), 7.21 (d, 1H), 6.94-6.84 (m, 3H), 4.76 (s, 2H, ancho), 4.72 (s, 2H, ancho), 4.02 (t, 2H), 3.74 (t, 2H), 1.71-1.63 (m, 3H), 0.96 (d, 6H)			
"A166"			
"A167"			
"A168"			

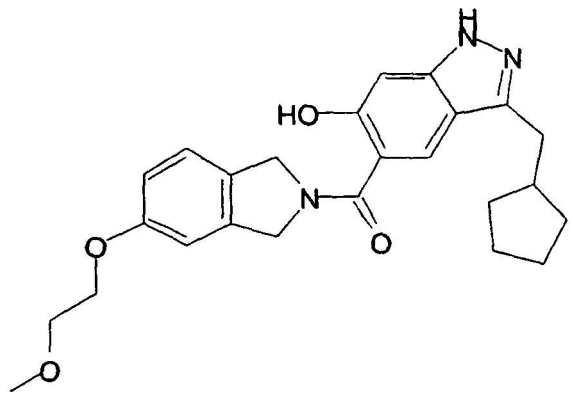
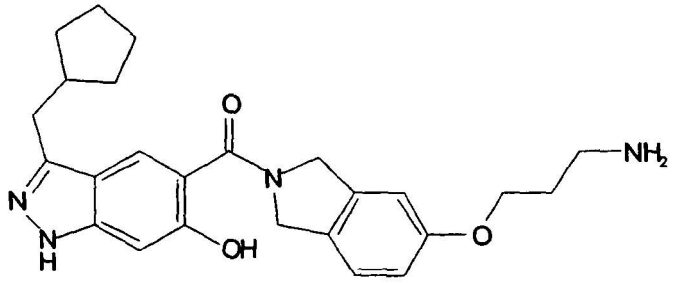
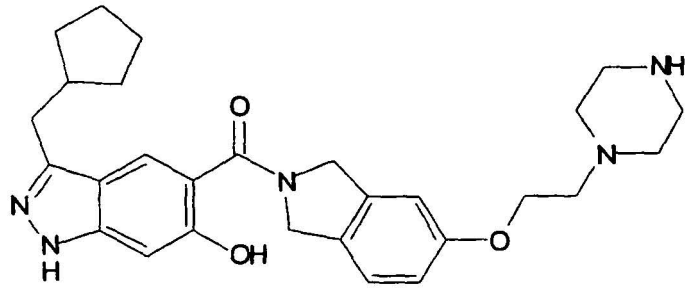
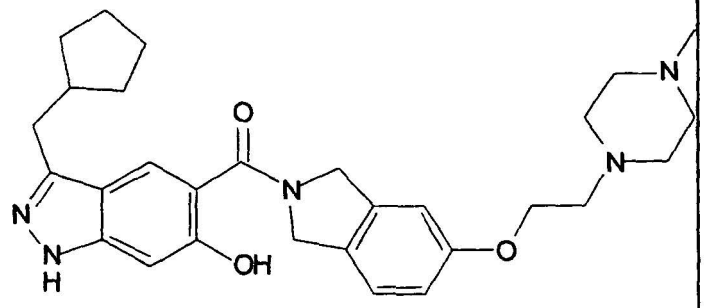
"A169"			
"A170"			
"A171"			
"A172"			

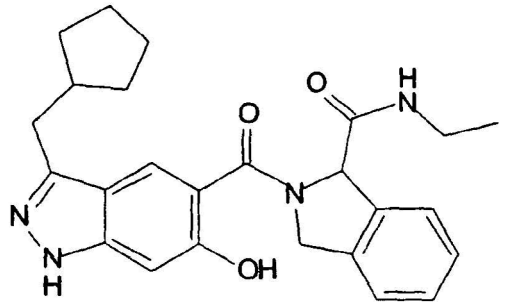
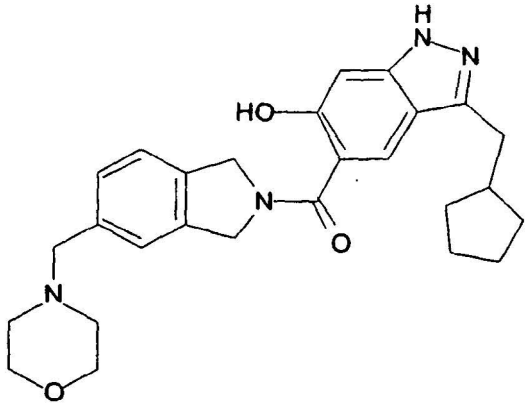
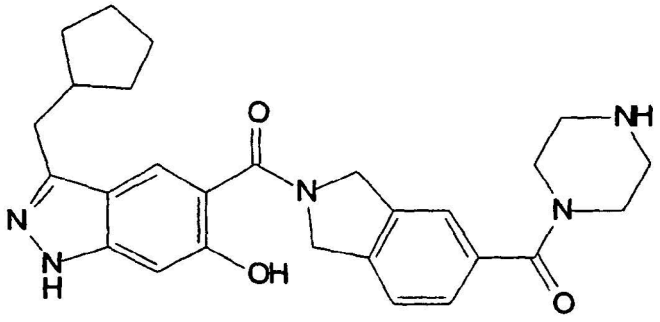
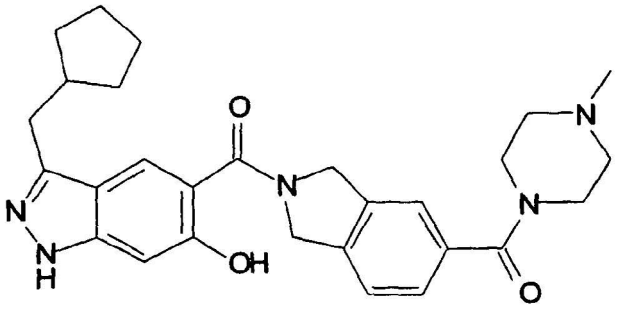
"A173"			
"A174"			
"A175"			

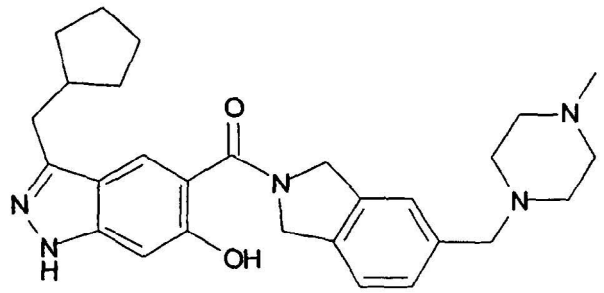
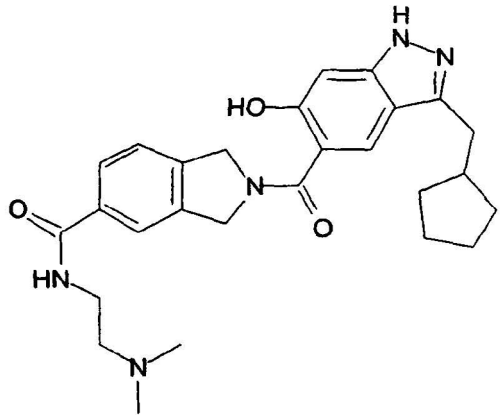
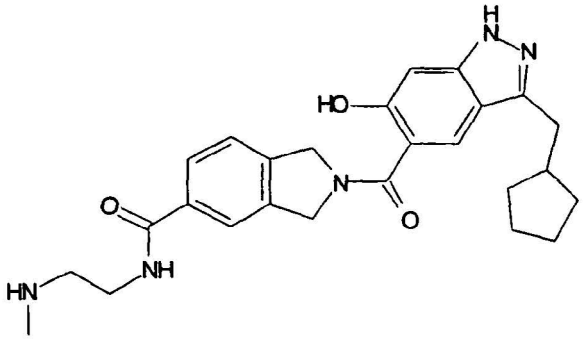
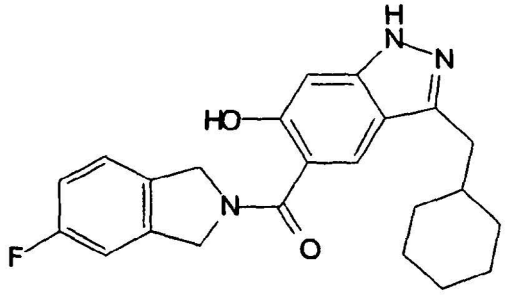
"A176"			
"A177"			
"A178"			
"A179"			

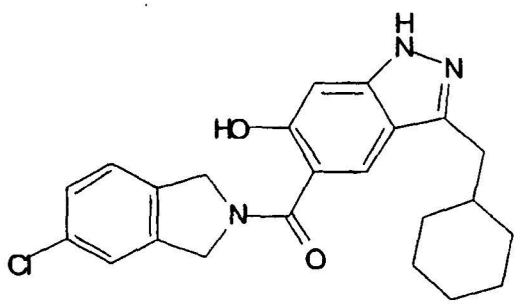
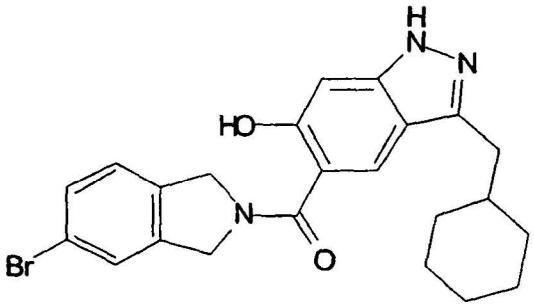
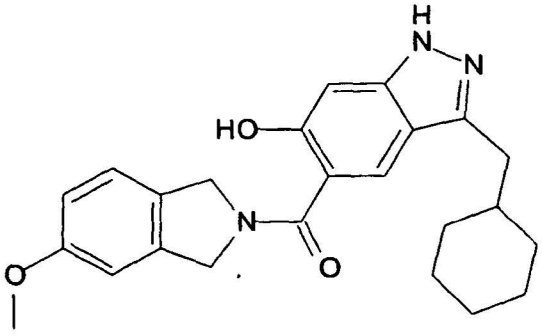
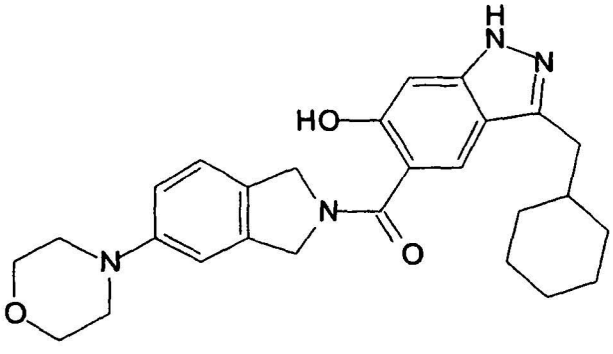
"A180"			
"A181"			
"A182"			
"A183"			

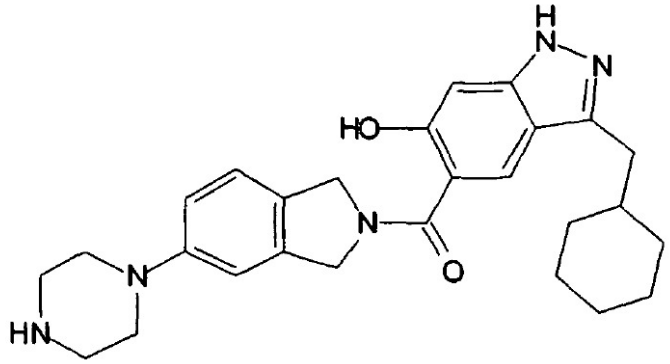
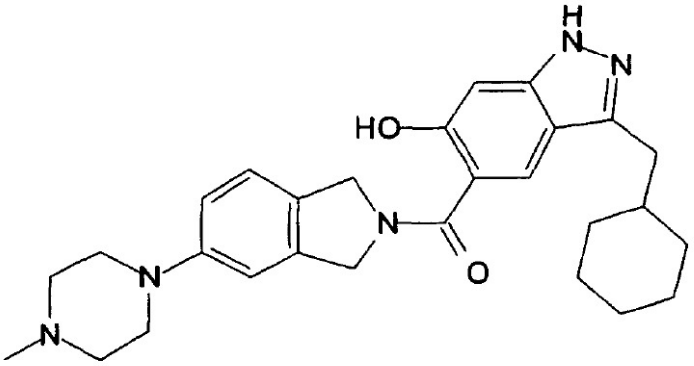
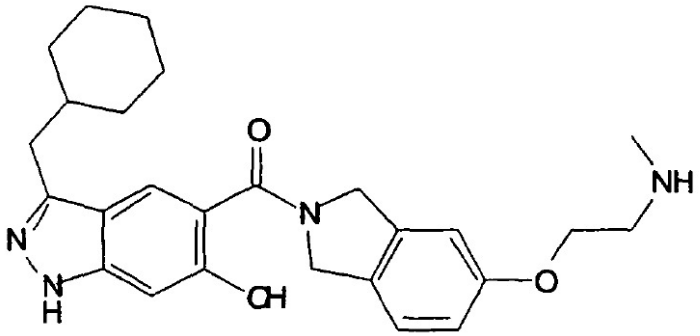
"A184"			
^{1}H-NMR (DMSO-d6, 90°C): [ppm] = 12.02 (s, 1H, ancho), 7.63 (s, 1H), 7.18 (d, 1H), 6.94-6.8 (m, 3H), 4.74 (s, 2H, ancho), 4.69 (s, 2H, ancho), 4.06-3.96 (m, 2H), 3.15-2.75 (m, 4H, H2O), 2.42-2.26 (m, 4H), 1.75-1.23 (m, 8H)			
"A185"			
"A186"			
^{1}H-NMR (DMSO-d6, 90°C): [ppm] = 12.03 (s, 1H, ancho), 9.76 (s, 1H, ancho), 7.67 (s, 1H), 7.2 (d, 1H), 6.96-6.85 (m, 3H), 4.77 (s, 2H, ancho), 4.73 (s, 2H, ancho), 4.02 (t, 2H), 3. 74 (t, 2H), 2.88 (d, 2H), 2.43-2.29 (m, 8H)			

"A187"			
"A188"			
"A189"			
"A190"			

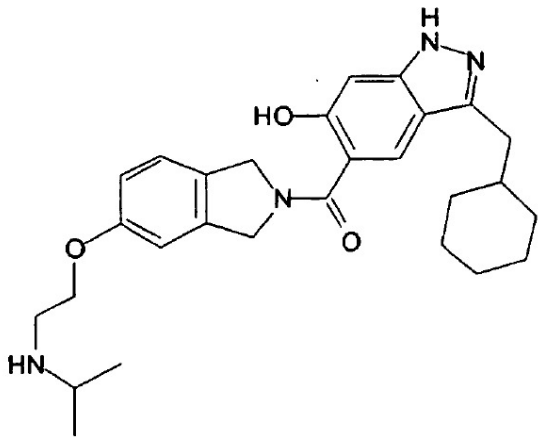
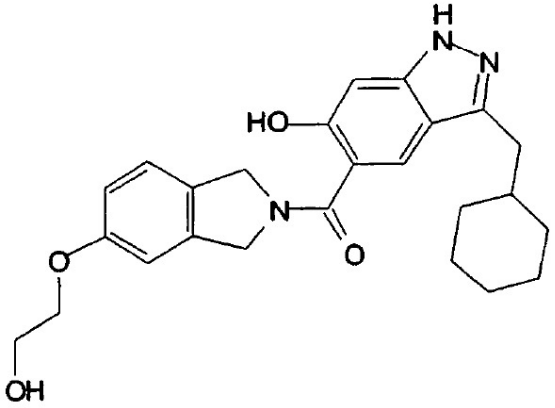
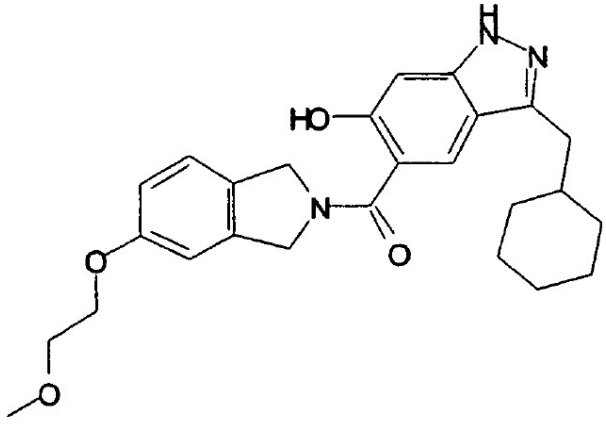
"A191"			
"A192"			
"A193"			
"A194"			

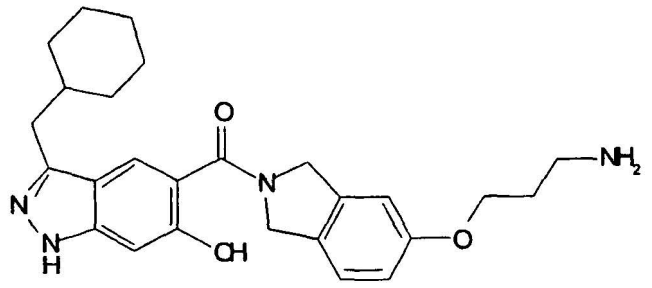
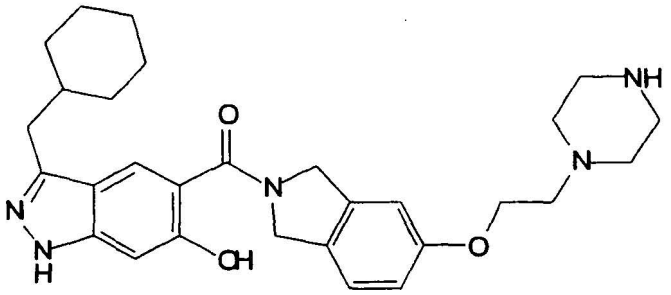
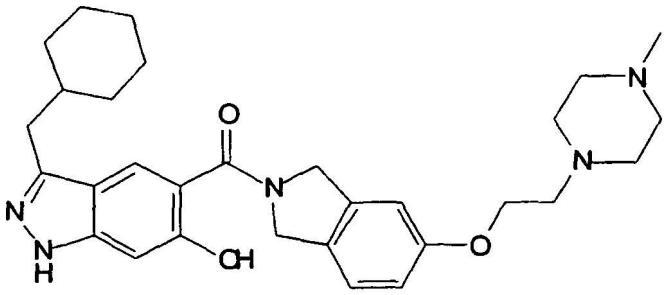
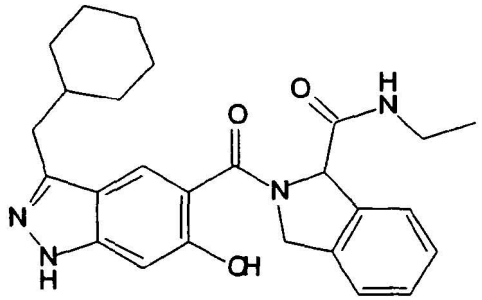
"A195"			
"A196"			
"A197"			
"A198"			

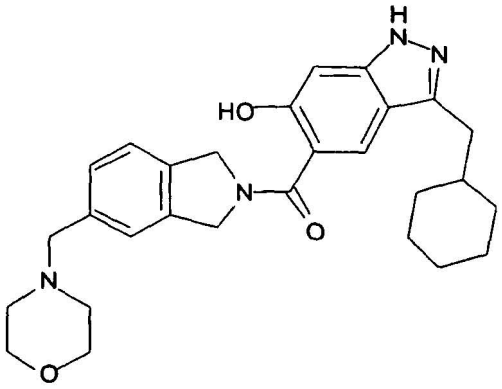
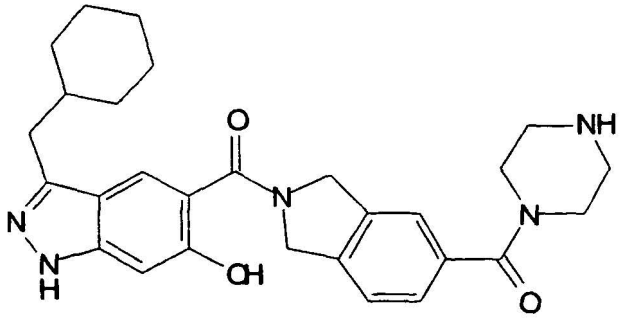
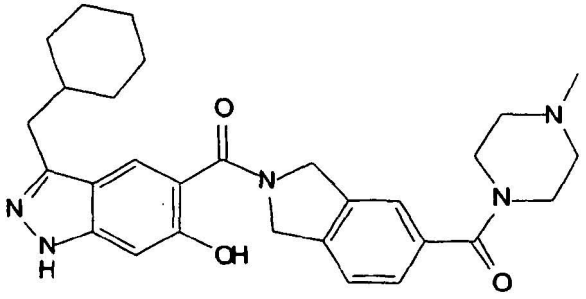
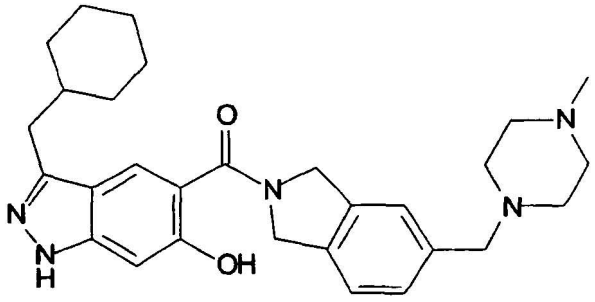
"A199"			
"A200"			
"A201"			
"A202"			

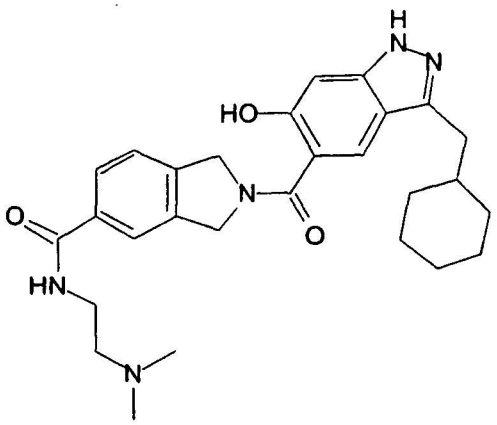
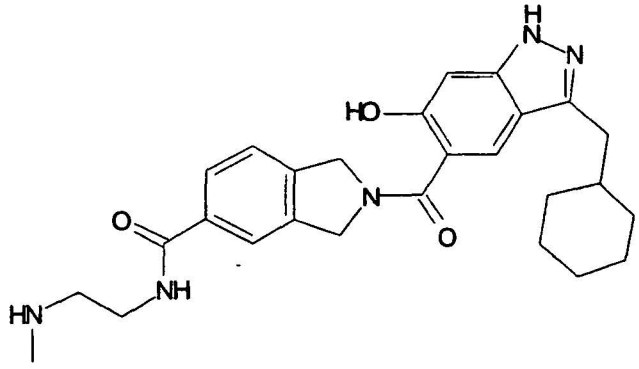
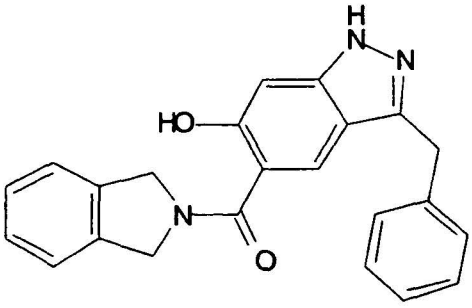
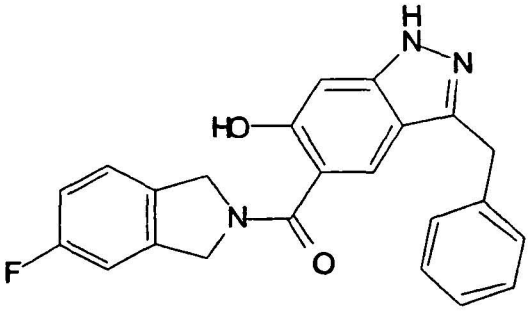
"A203"			
"A204"			
"A205"			

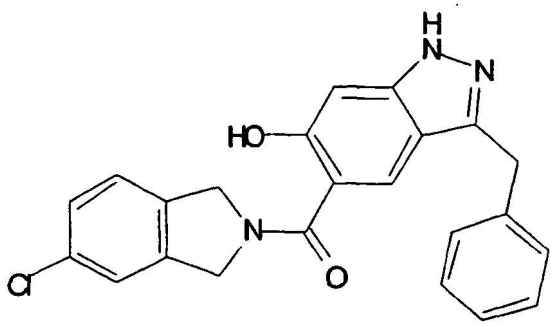
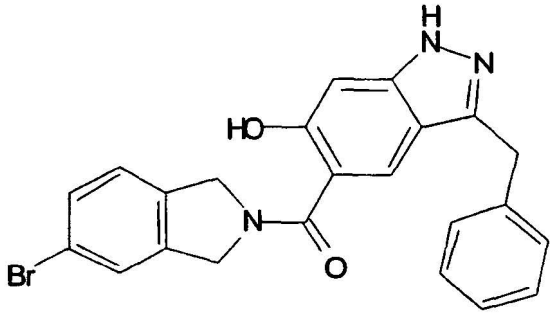
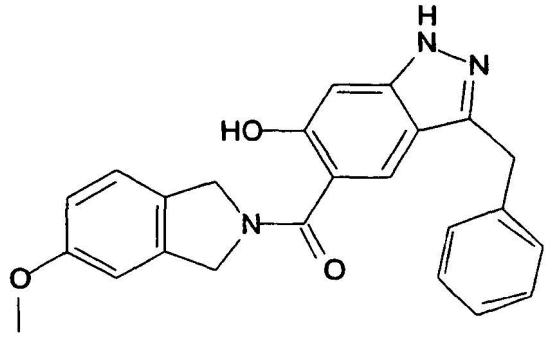
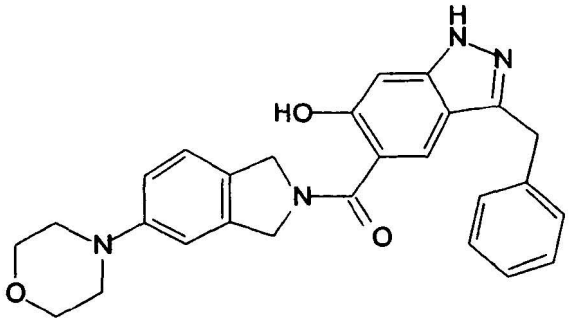
^{1}H-NMR (DMSO-d6, 90°C): [ppm] = 12.04 (s, 1H, ancho), 7.61 (s, 1H), 7.24-7.11 (m, 1H), 6.95-6.79 (m, 3H), 4.74 (s, 2H, ancho), 4.69 (s, 2H, ancho), 4.09-3.98 (m, 2H), 3.2-2.8 (m, 2H, H2O), 2.77-2.68 (m, 2H), 2.39 (s, 3H), 1.8-1.54 (m, 6H), 1.28-0.98 (m, 5H)

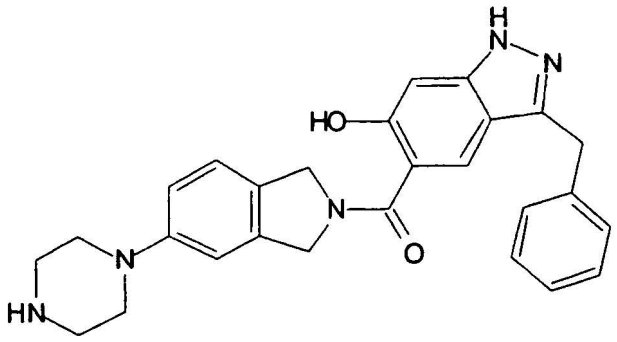
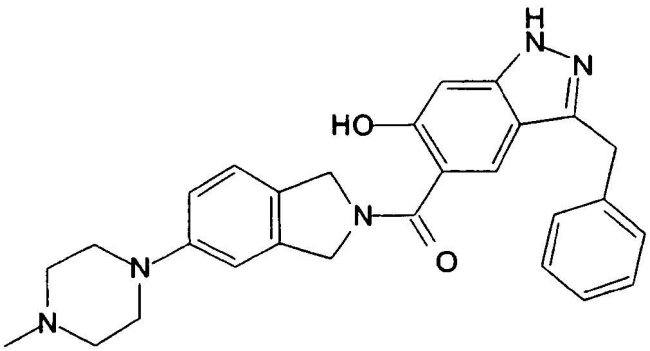
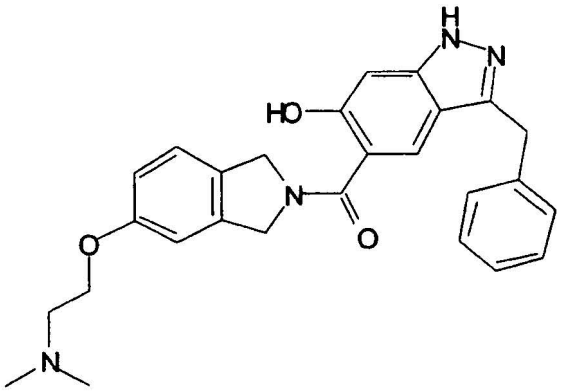
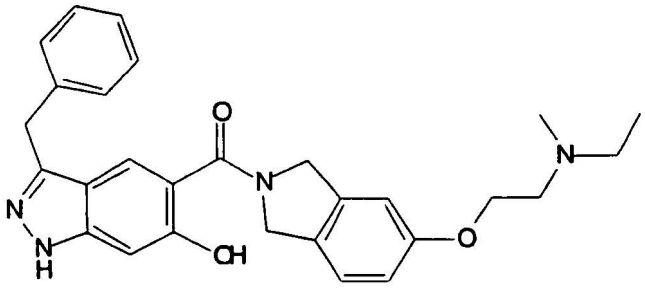
"A206"			
"A207"			
^{1}H-NMR (DMSO-d6, 90°C): [ppm] = 12.0 (s, 1H, ancho), 9.72 (s, 1H), 7.62 (s, 1H), 7.17 (d, 1H), 6.87-6.82 (m, 3H), 4.74 (s, 2H, ancho), 4.7 (s, 2H, ancho), 4.41-4.34 (m, 1H), 3.99 (t, 2H), 3.74-3.65 (m, 2H), 2.74 (d, 2H), 1.8-1.54 (m, 6H), 1.29-0.97 (m, 5H)			
"A208"			

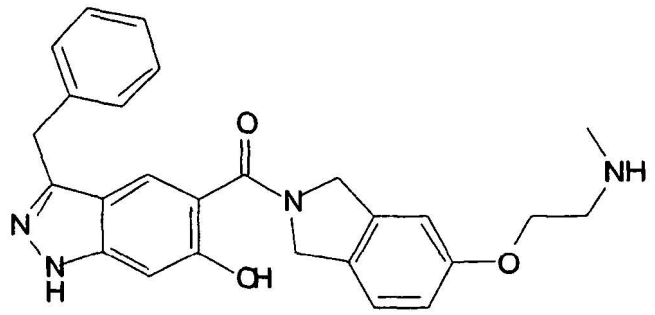
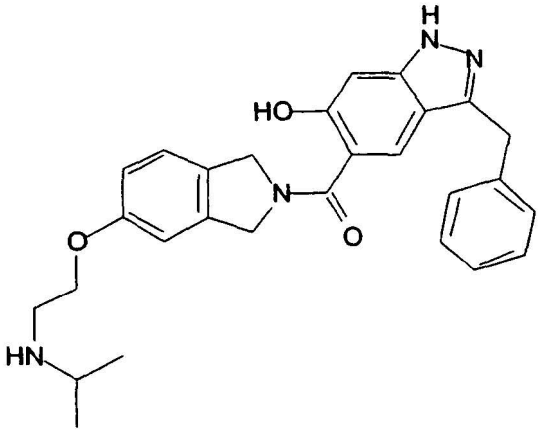
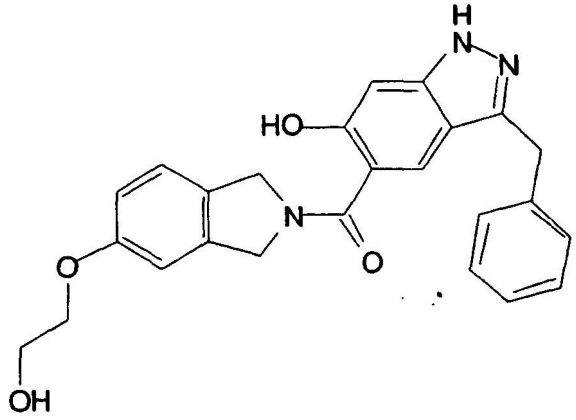
"A209"			
"A210"			
"A211"			
"A212"			

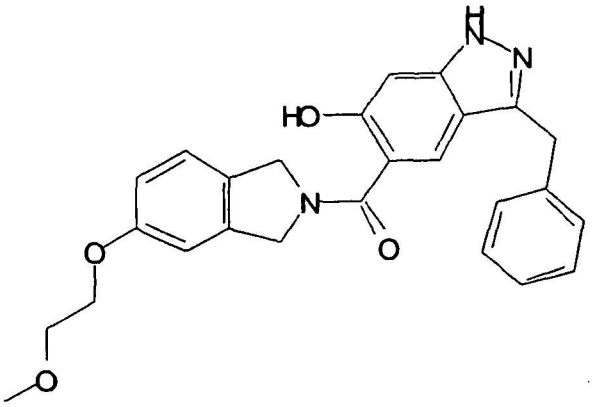
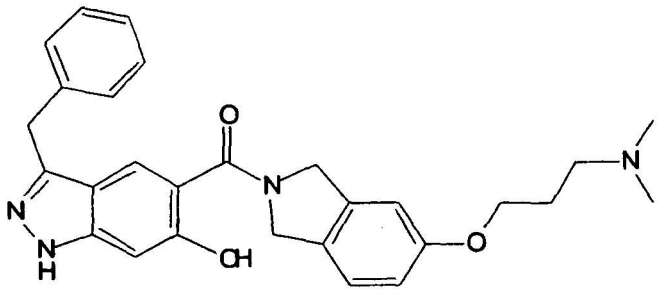
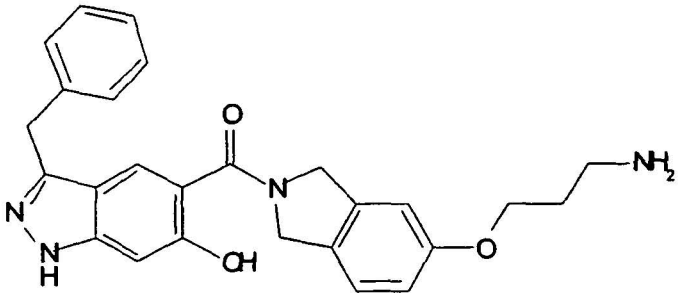
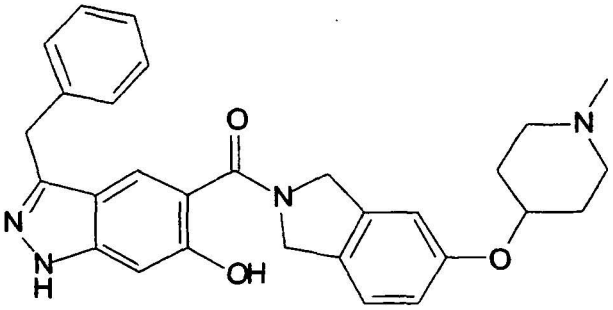
"A213"			
"A214"			
"A215"			
"A216"			

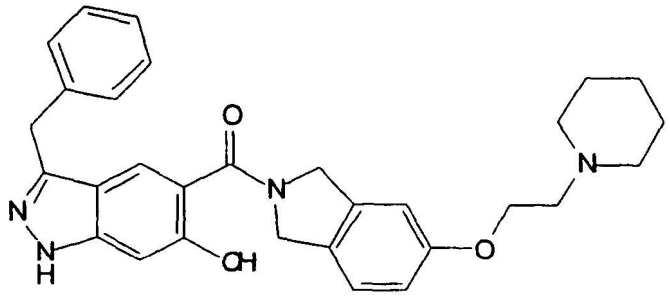
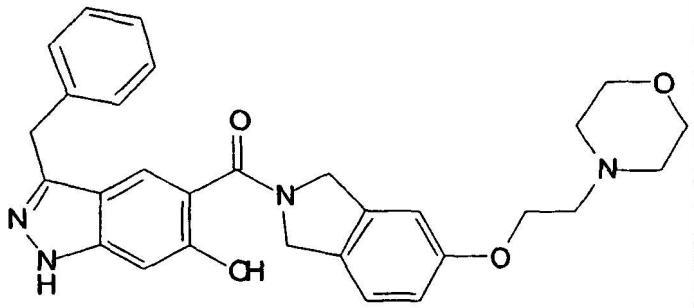
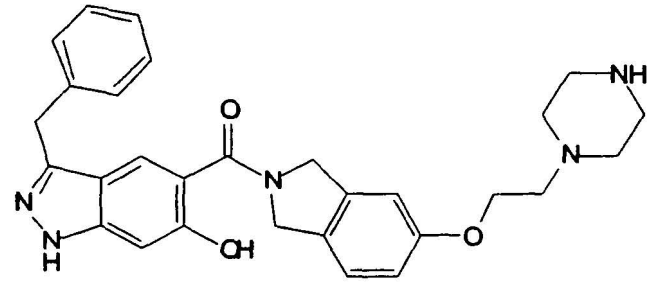
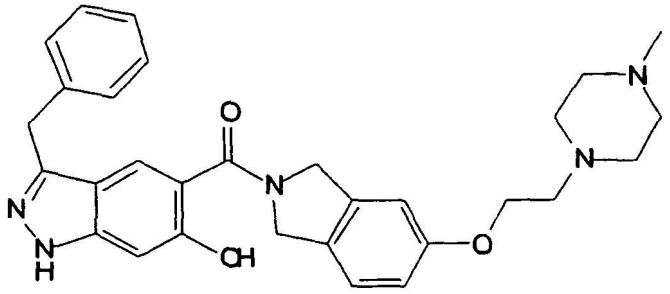
"A217"			
"A218"			
"A219"			
"A220"			

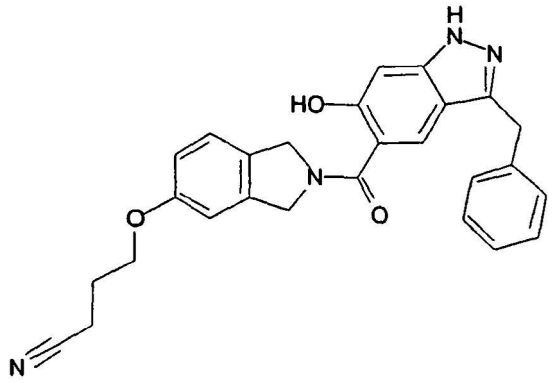
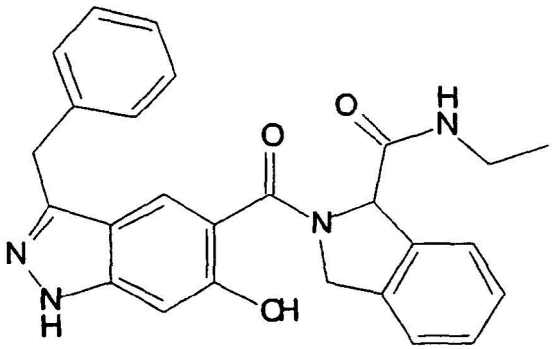
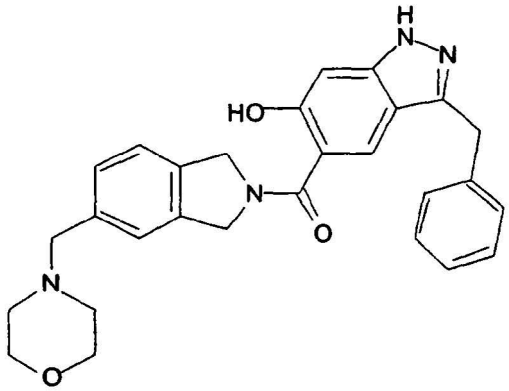
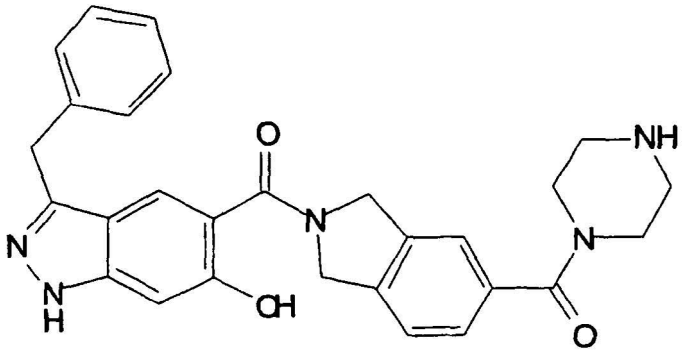
"A221"			
"A222"			
"A223"			
"A224"			

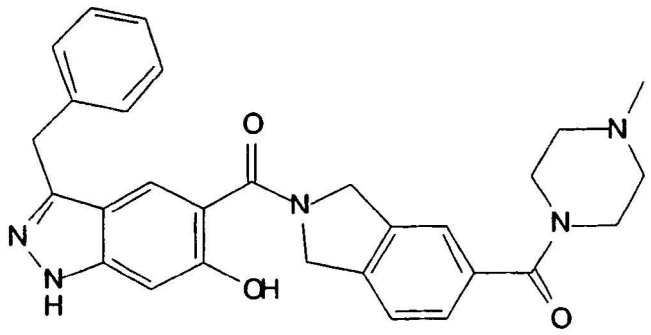
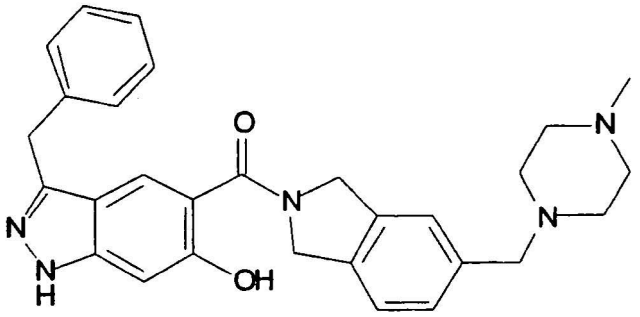
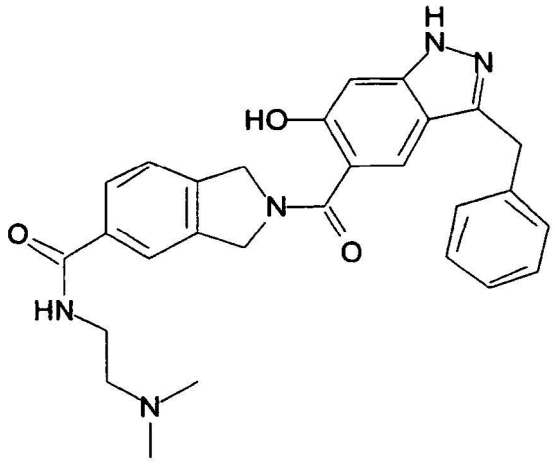
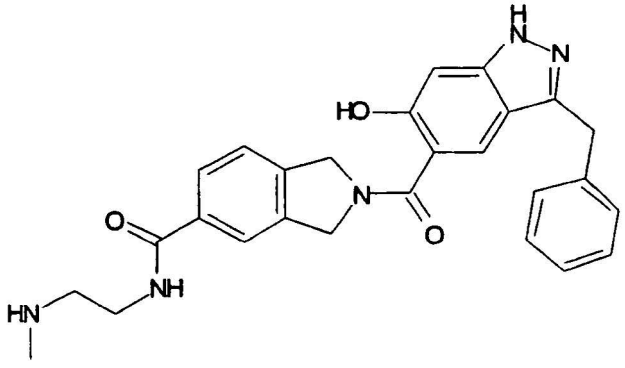
"A225"			
"A226"			
"A227"			
"A228"			

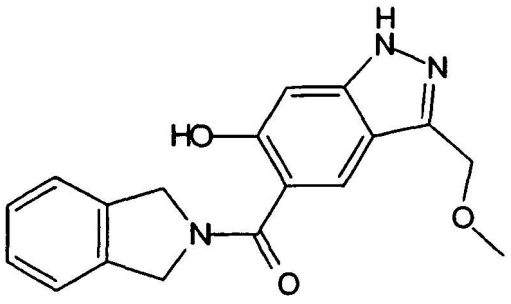
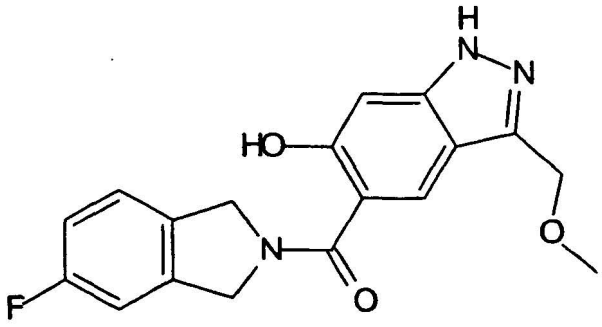
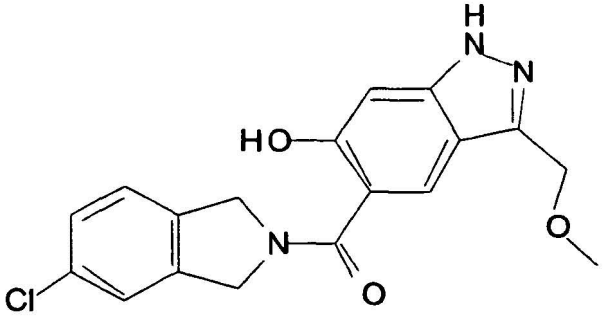
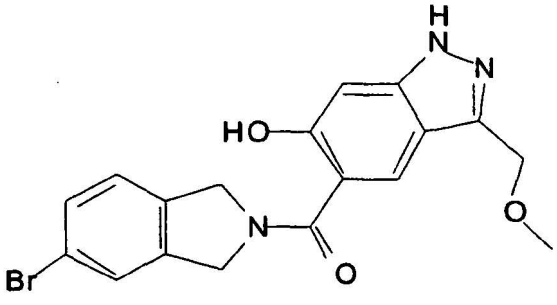
"A229"			
"A230"			
"A231"			

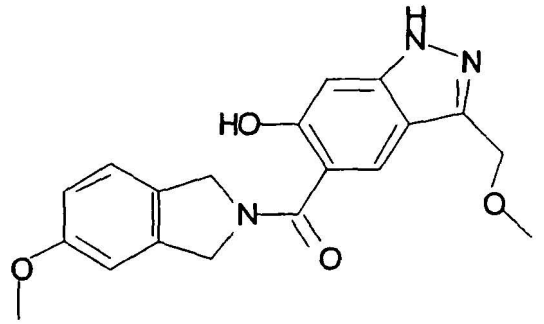
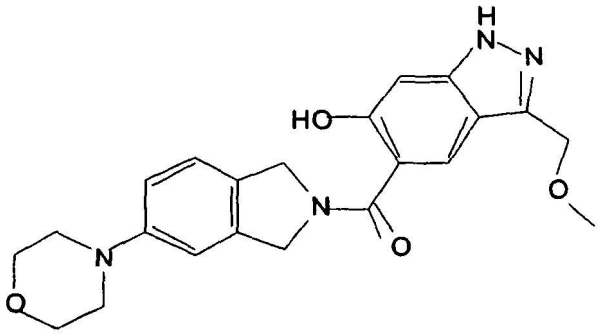
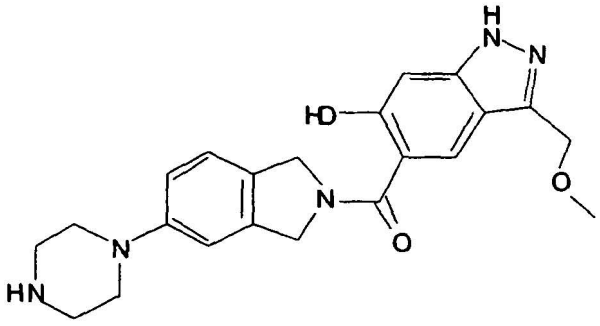
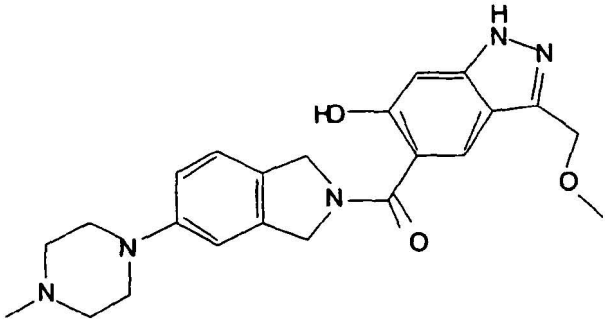
"A232"			
"A233"			
"A234"			
"A235"			

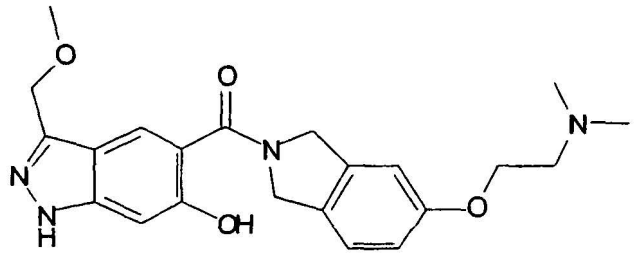
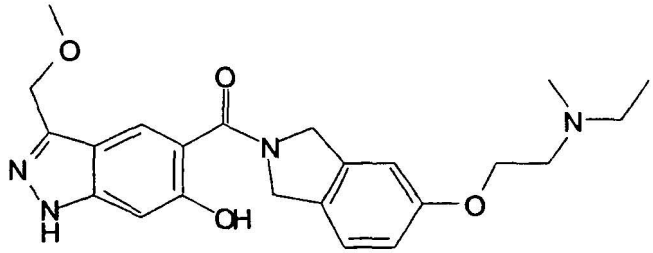
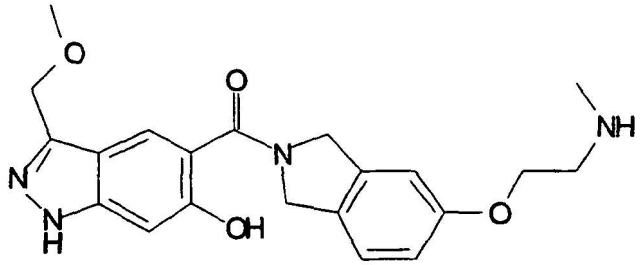
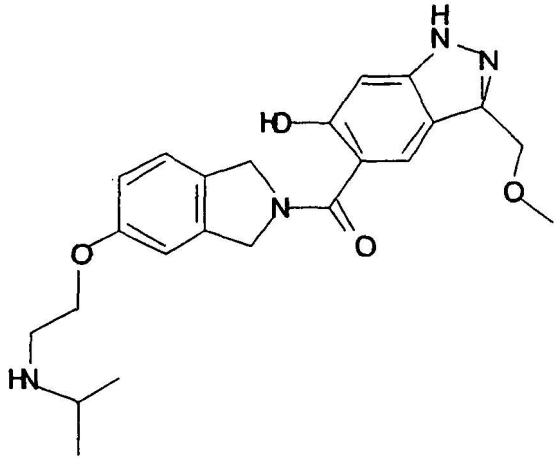
"A236"			
"A237"			
"A238"			
"A239"			

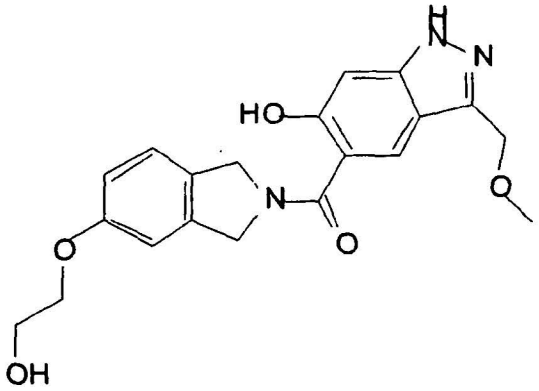
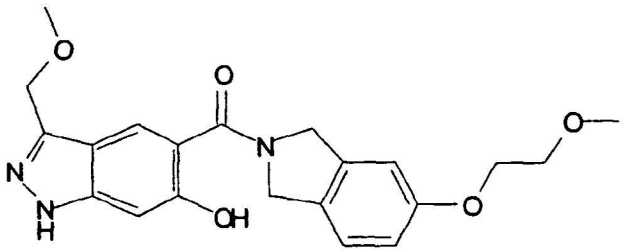
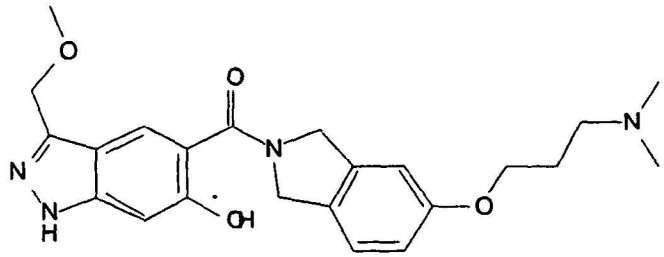
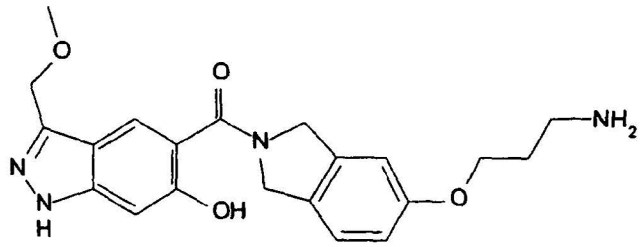
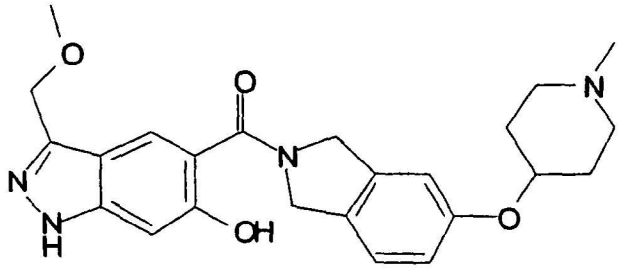
"A240"			
"A241"			
"A242"			
"A243"			

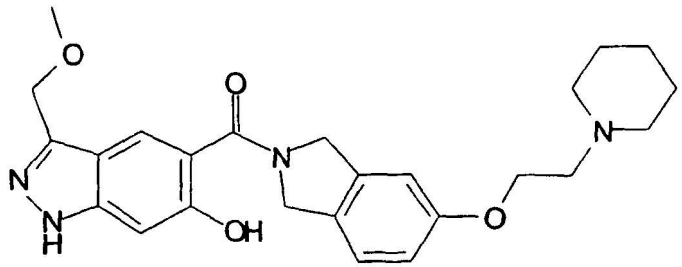
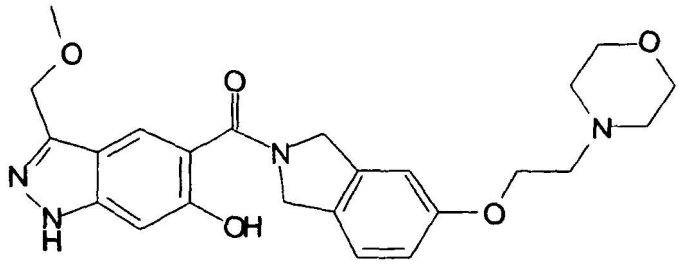
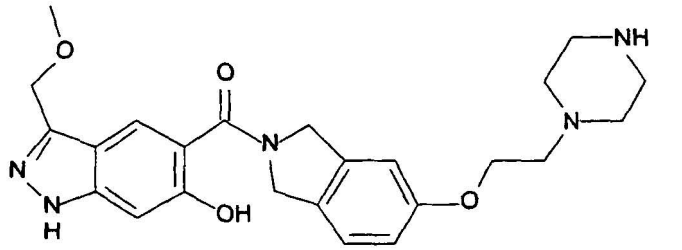
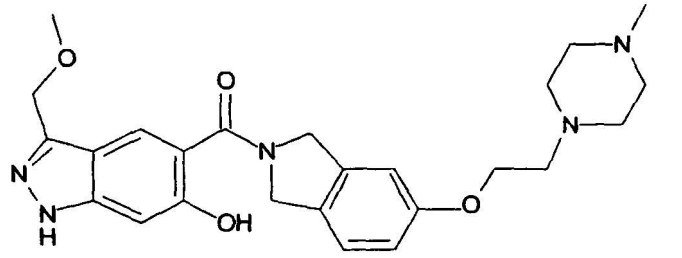
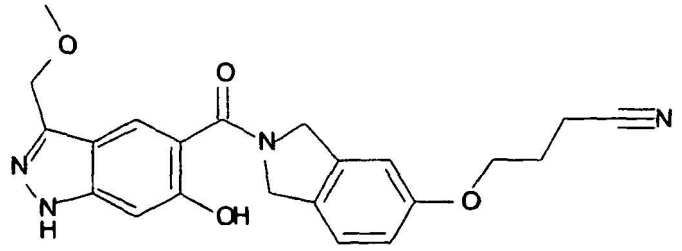
"A244"			
"A245"			
"A246"			
"A247"			

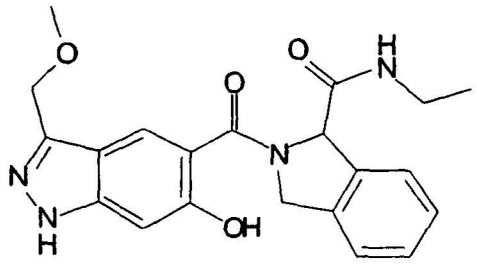
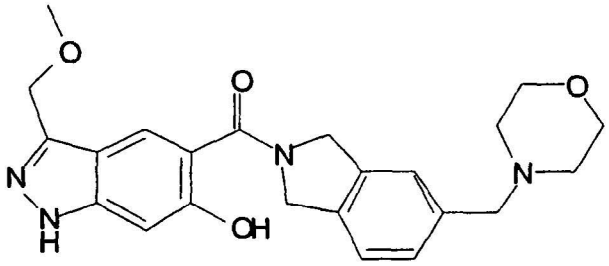
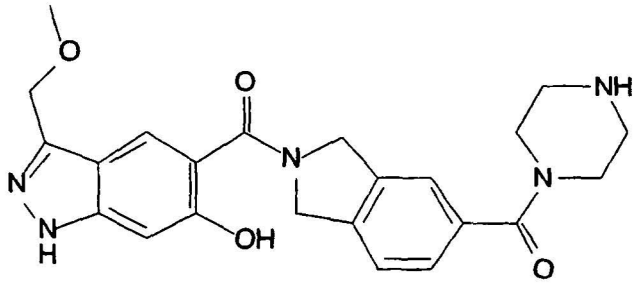
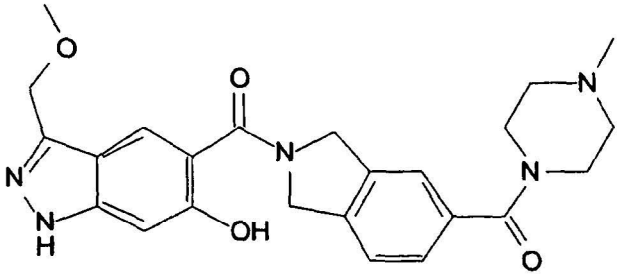
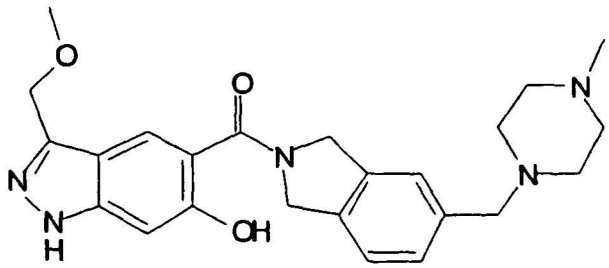
"A248"			
"A249"			
"A250"			
"A251"			

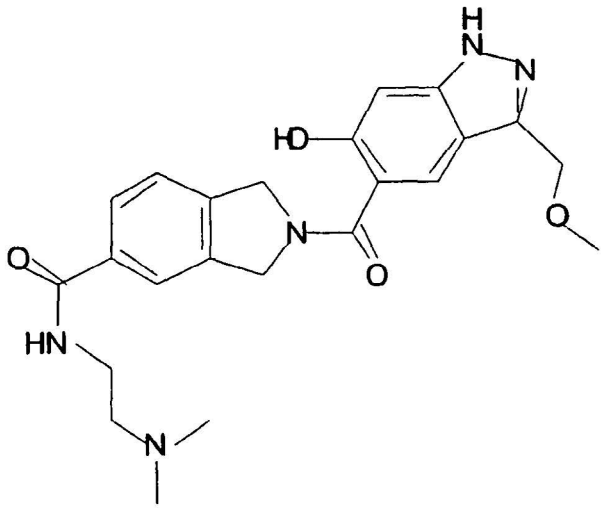
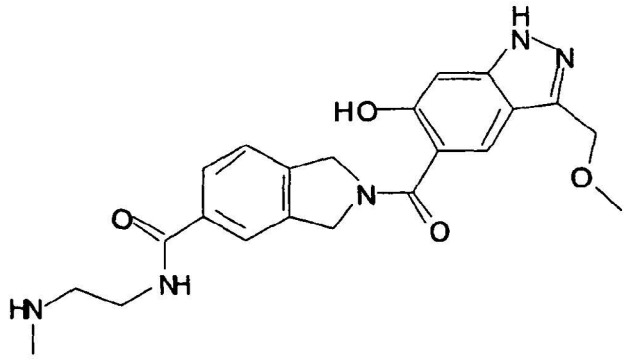
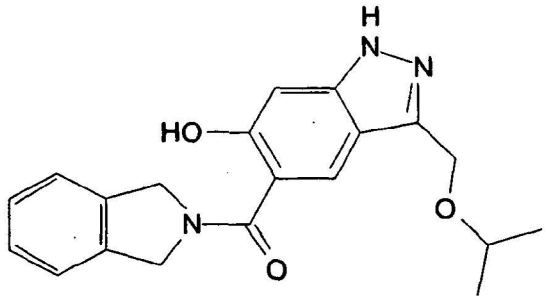
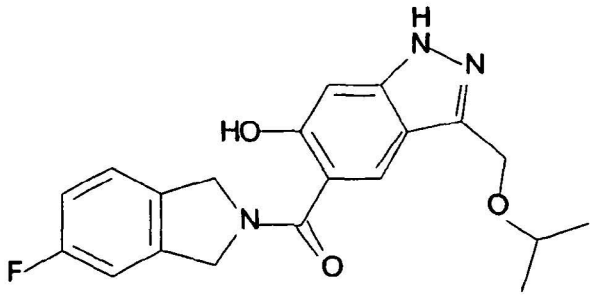
"A252"			
"A253"			
"A254"			
"A255"			

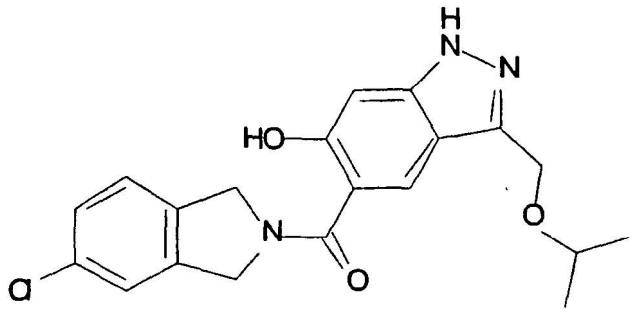
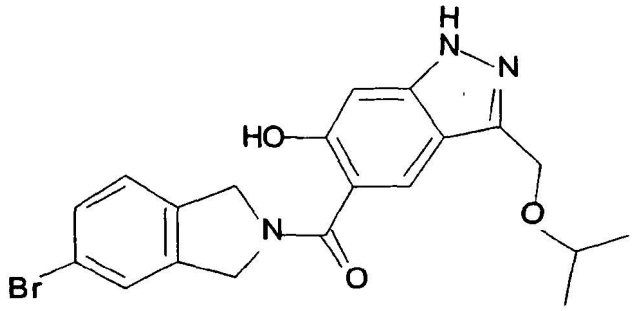
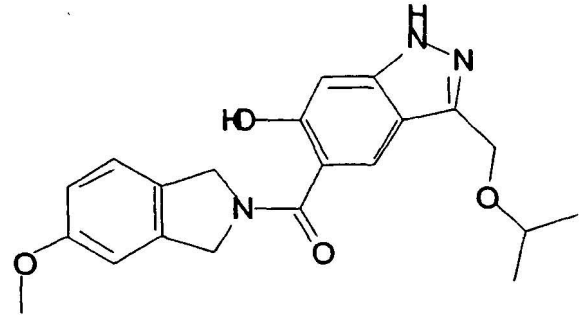
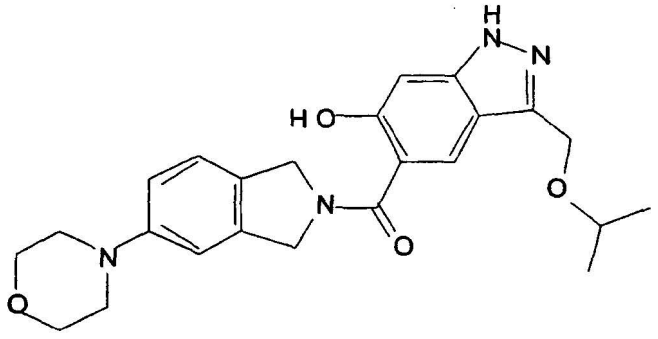
"A256"			
"A257"			
"A258"			
"A259"			

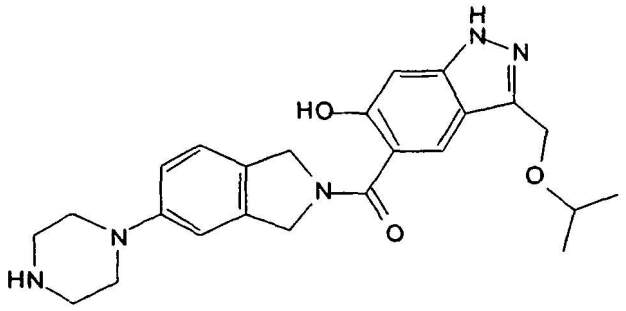
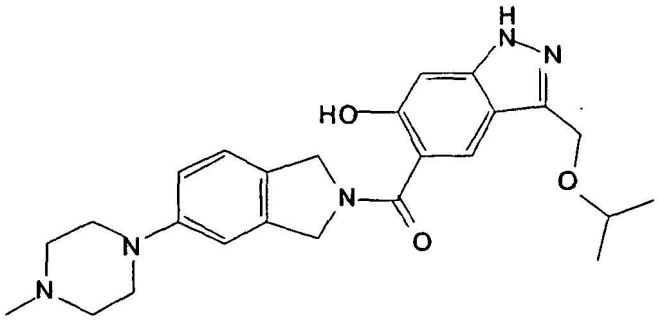
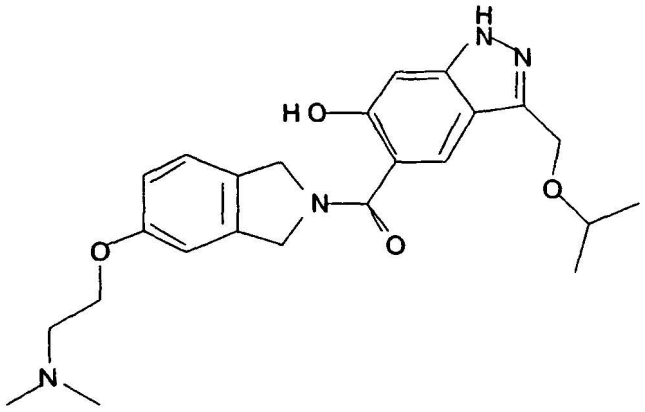
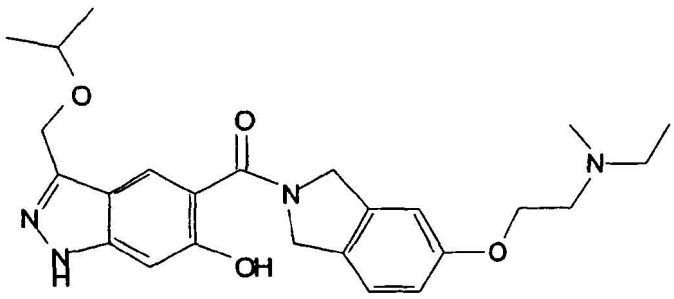
"A260"			
"A261"			
"A262"			
"A263"			
"A264"			

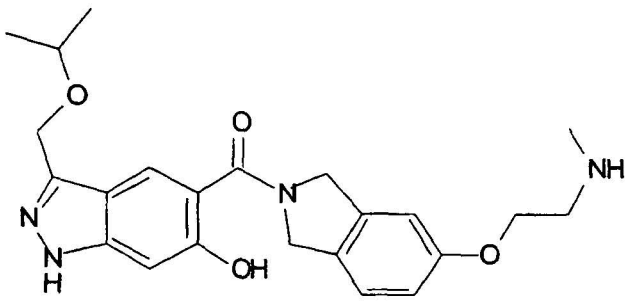
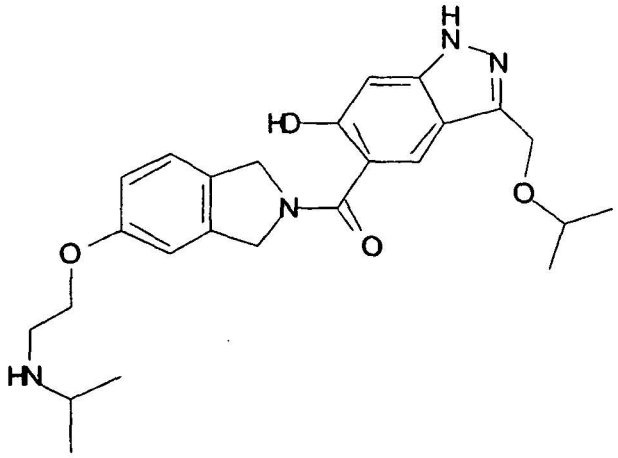
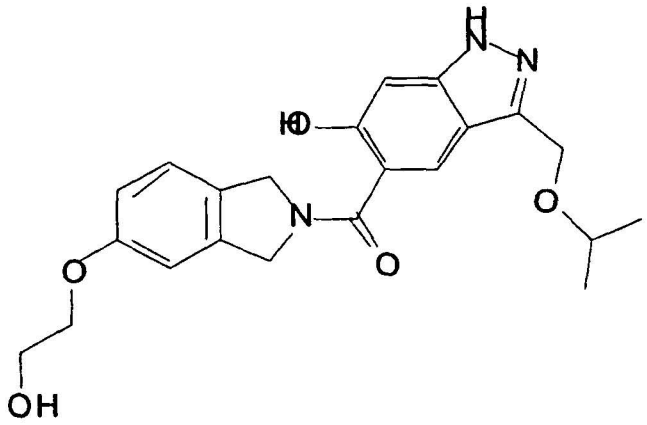
"A265"			
"A266"			
"A267"			
"A268"			
"A269"			

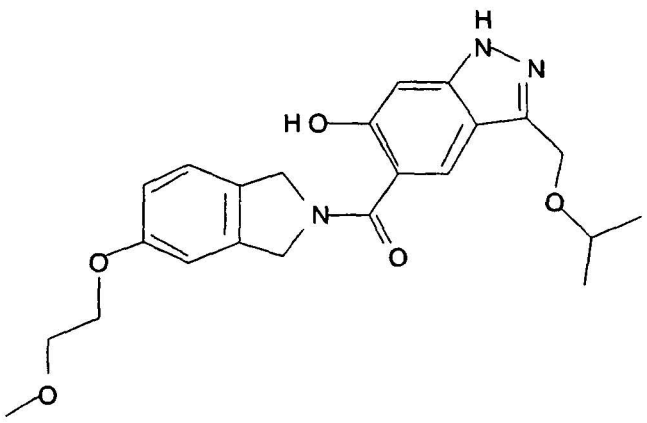
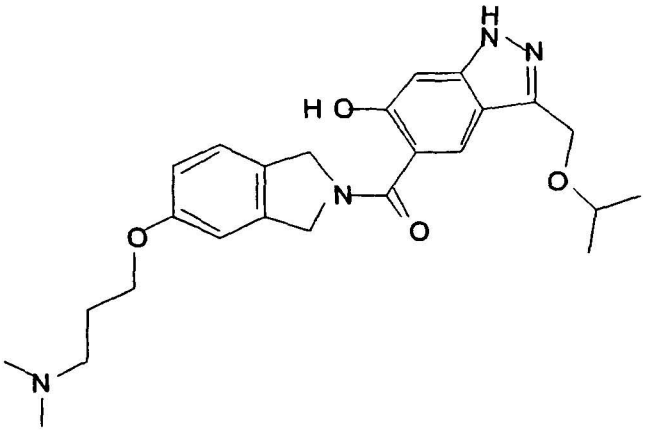
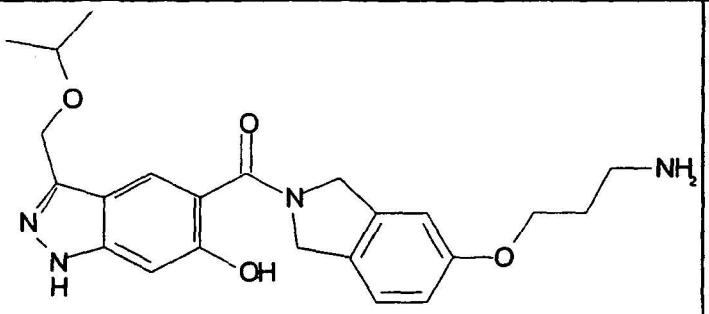
"A270"			
"A271"			
"A272"			
"A273"			
"A274"			

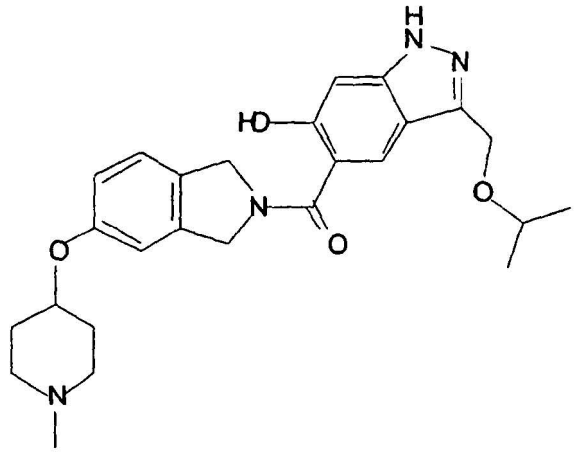
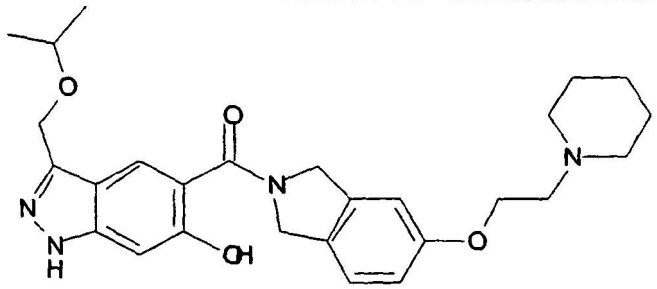
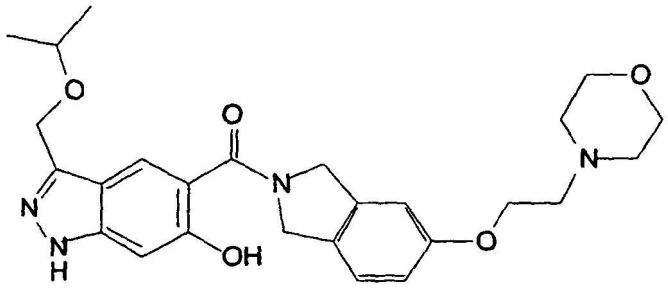
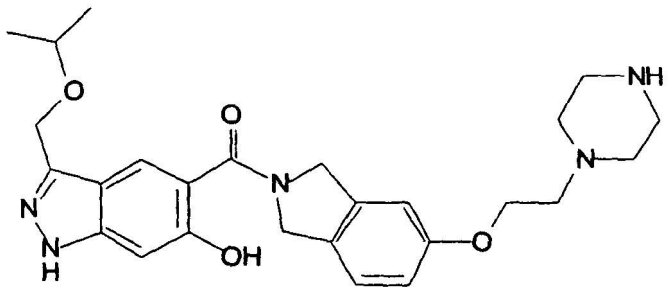
"A275"			
"A276"			
"A277"			
"A278"			

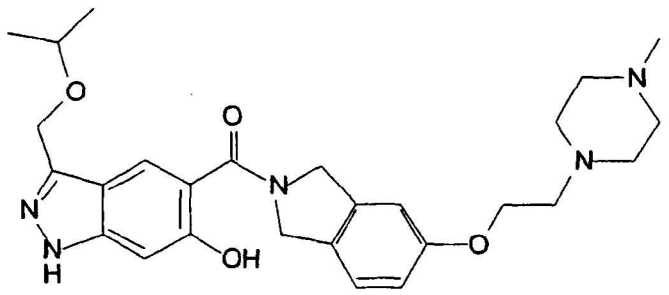
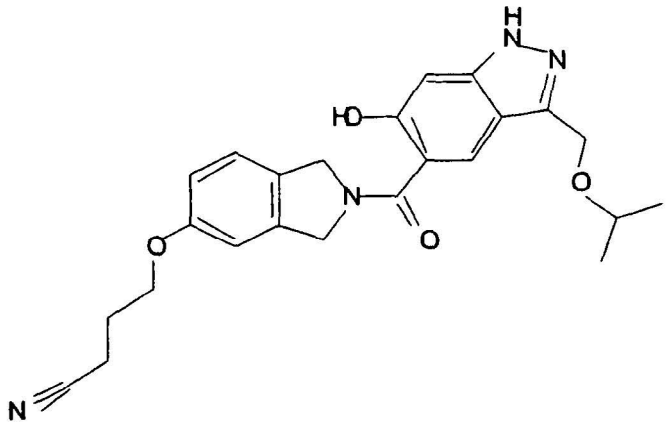
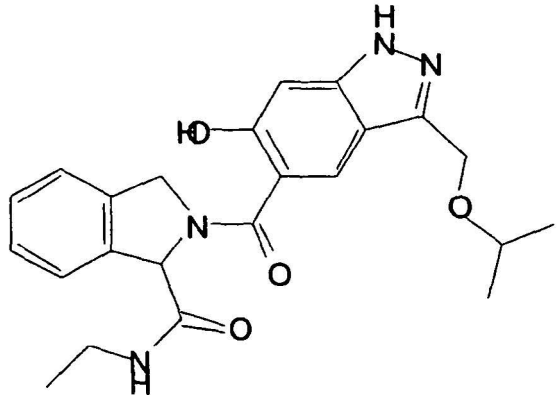
"A279"			
"A280"			
"A281"			
"A282"			

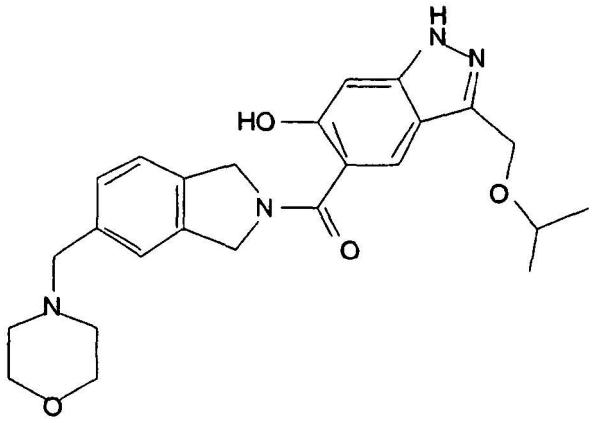
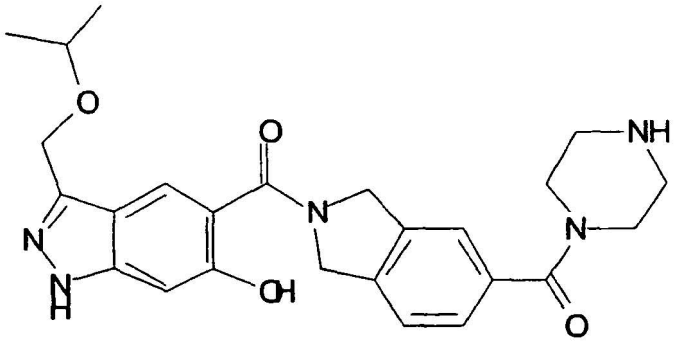
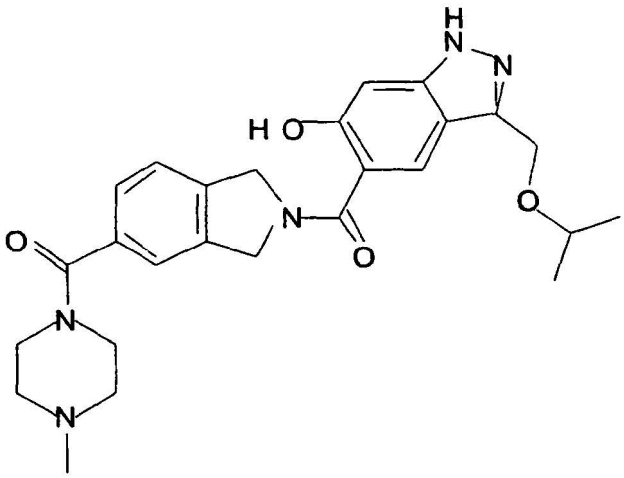
"A283"			
"A284"			
"A285"			
"A286"			

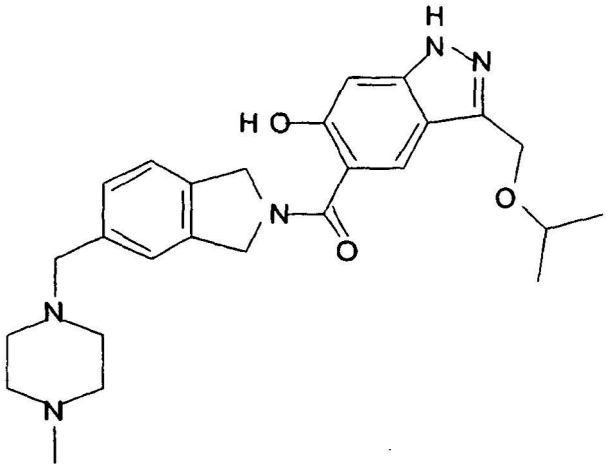
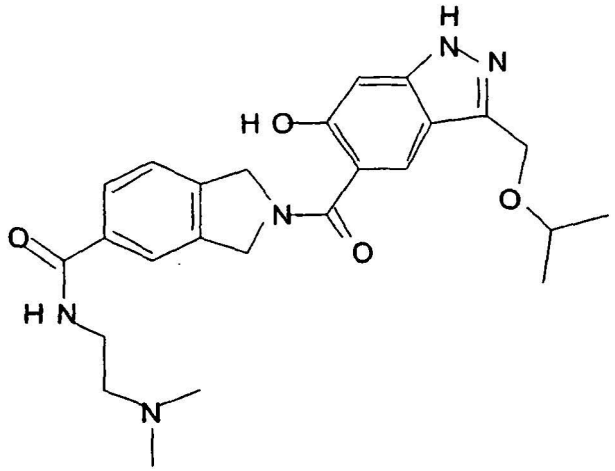
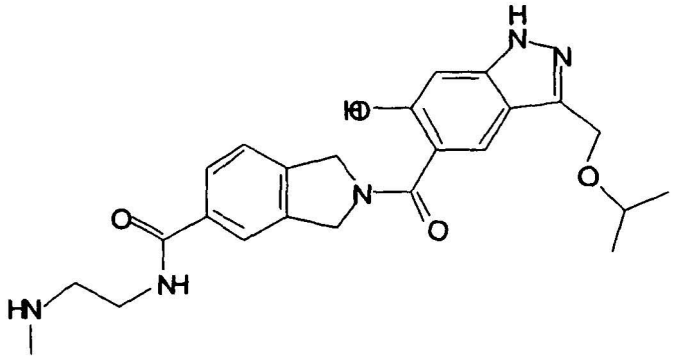
"A287"			
"A288"			
"A289"			

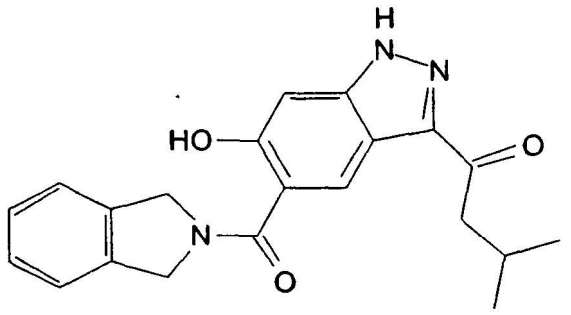
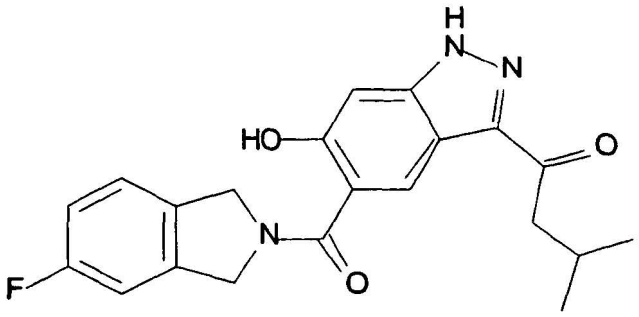
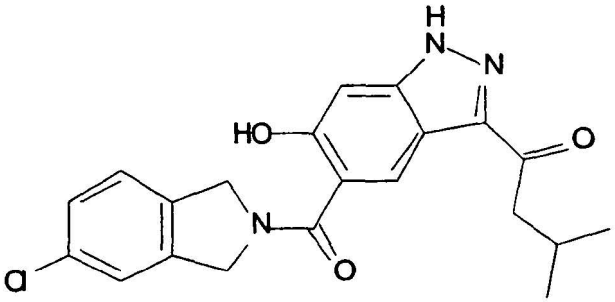
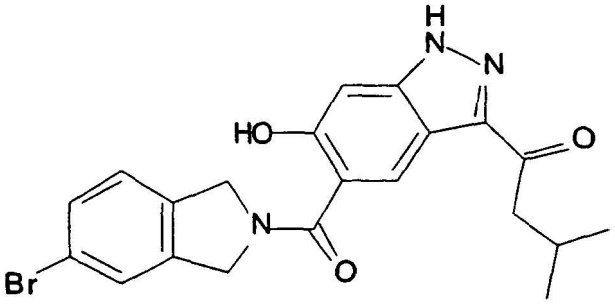
"A290"			
"A291"			
"A292"			

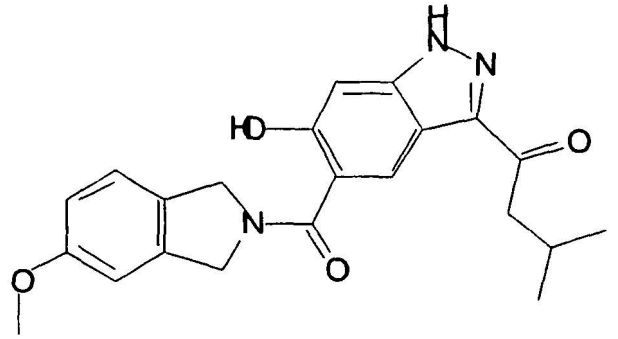
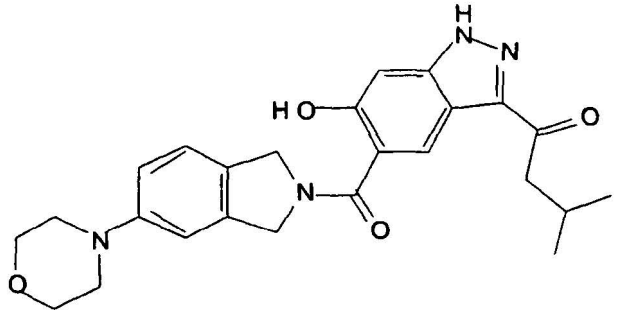
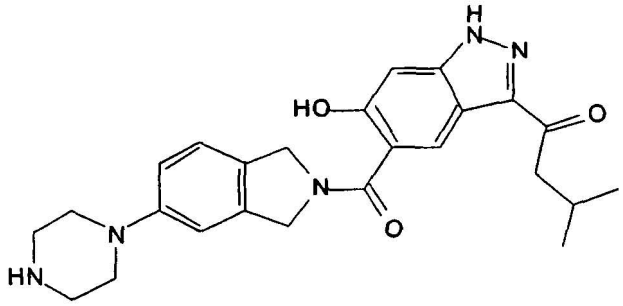
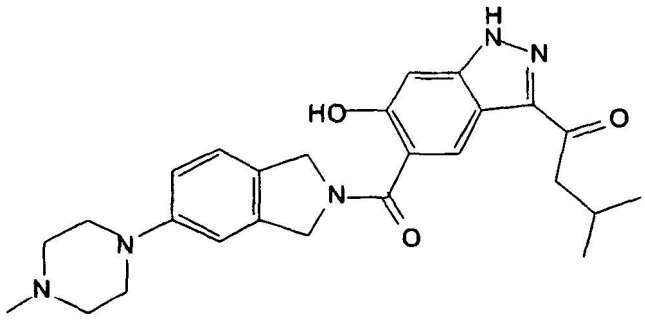
"A293"			
"A294"			
"A295"			
"A296"			

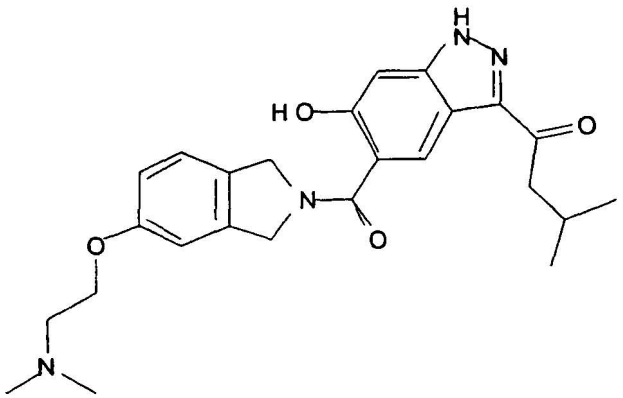
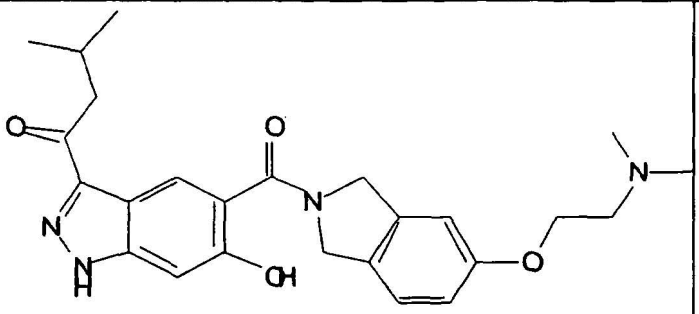
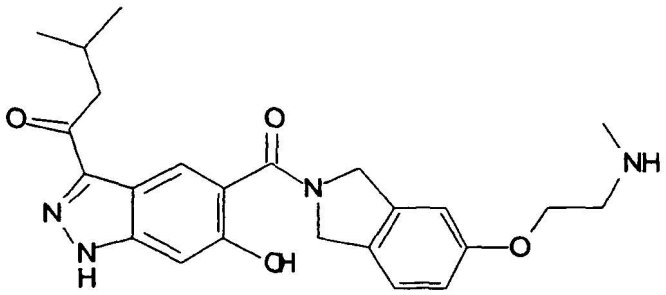
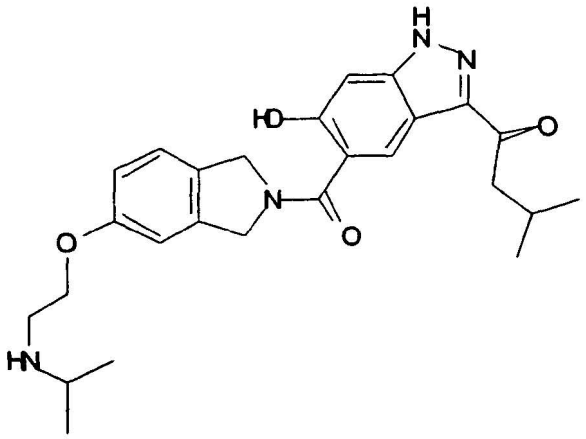
"A297"			
"A298"			
"A299"			

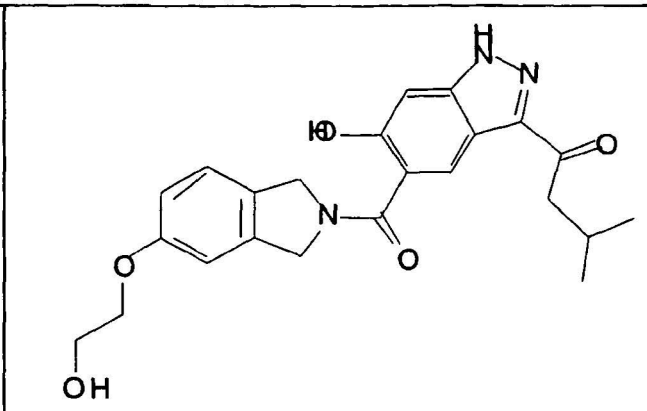
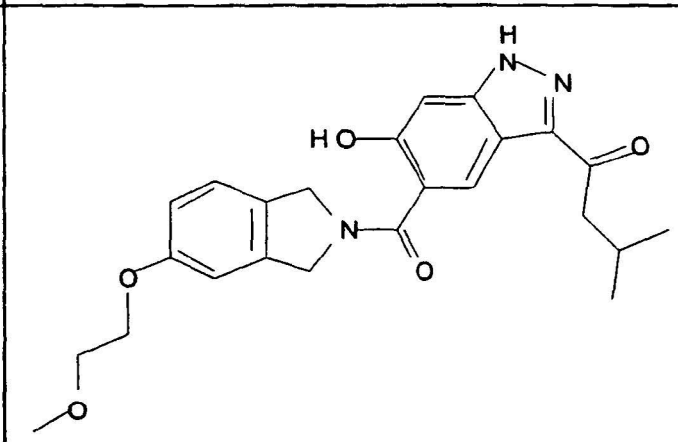
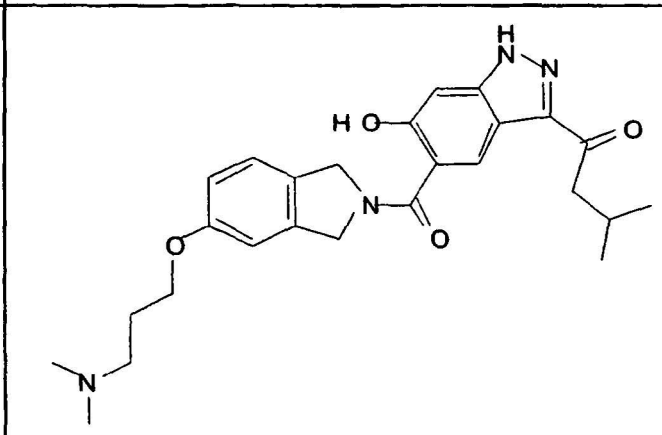
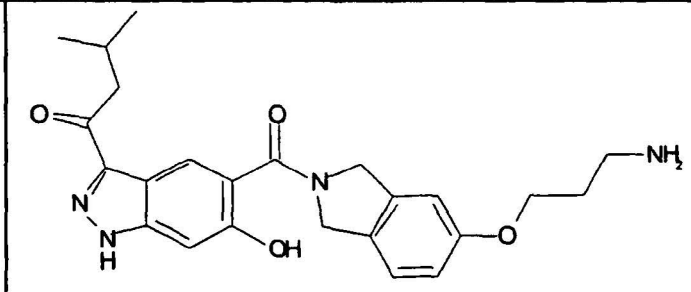
"A300"			
"A301"			
"A302"			

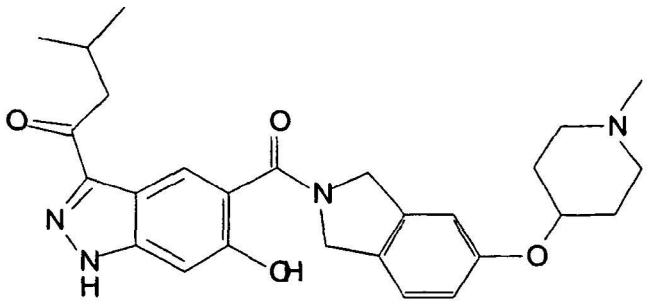
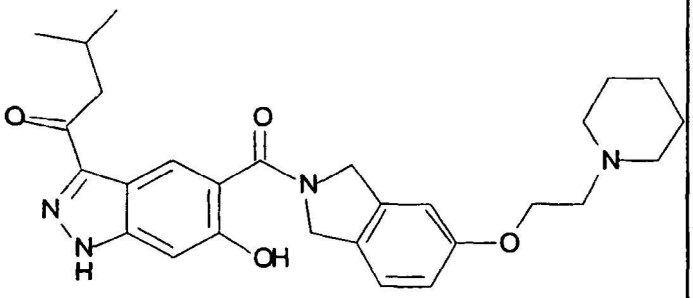
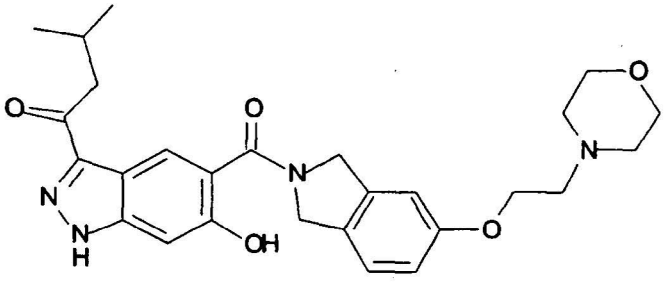
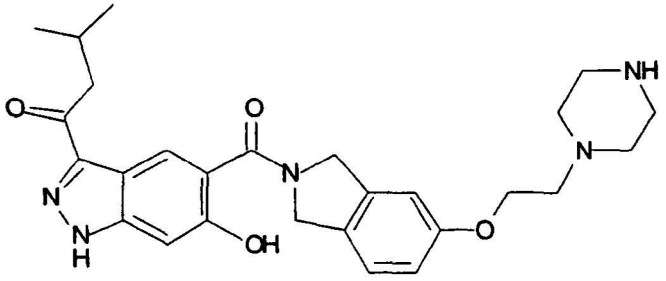
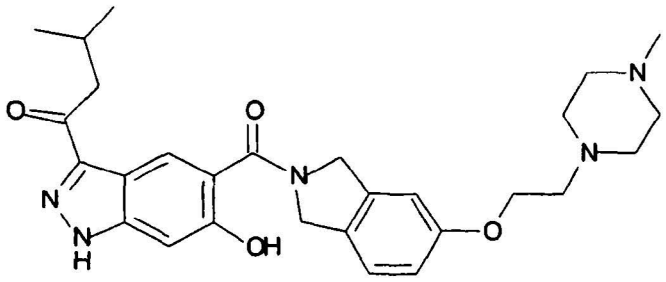
"A303"			
"A304"			
"A305"			

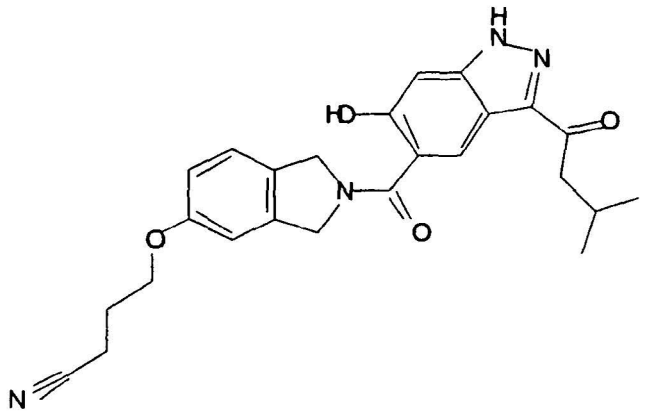
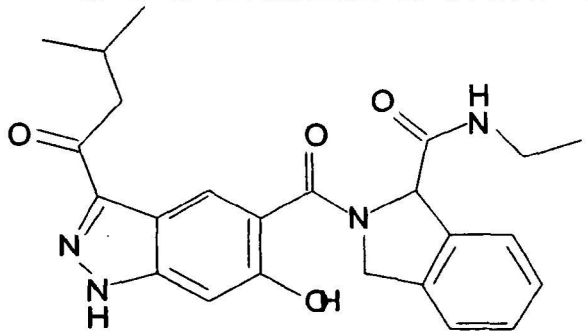
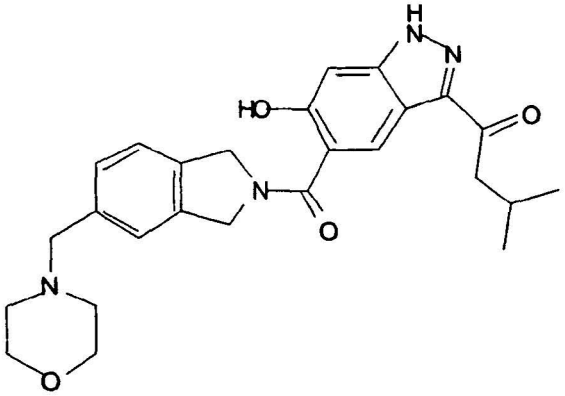
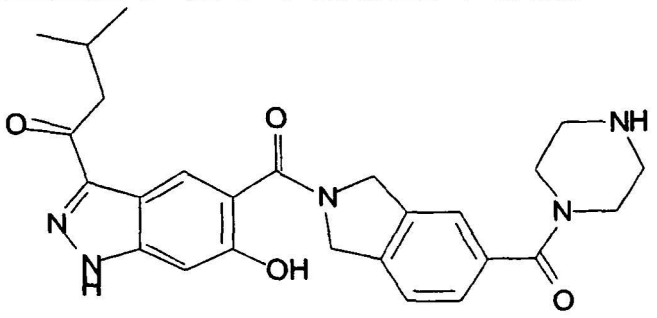
"A306"			
"A307"			
"A308"			
"A309"			

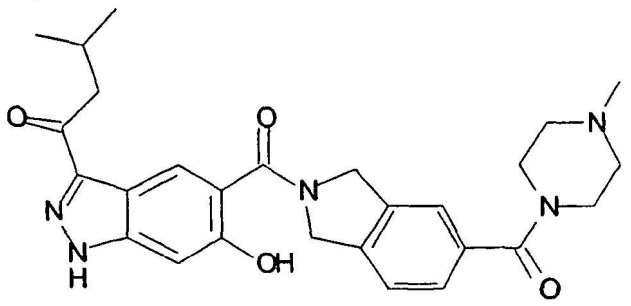
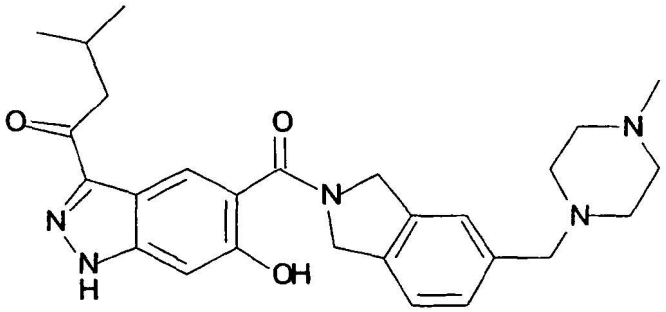
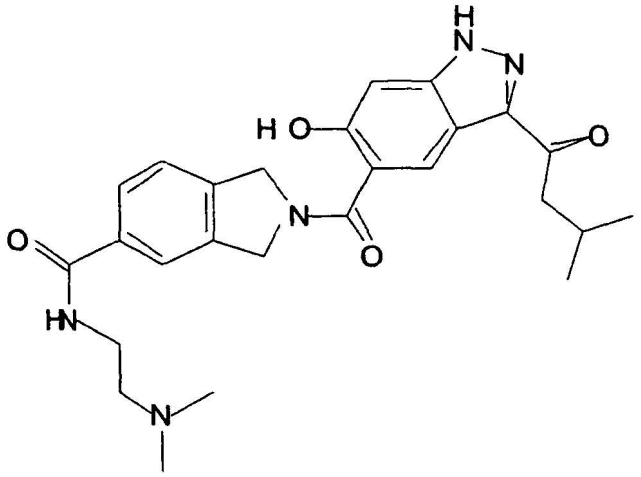
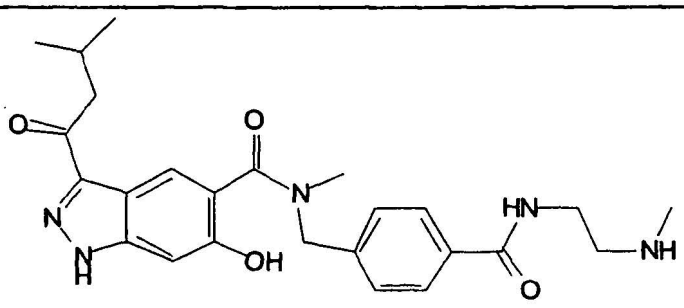
"A310"			
"A311"			
"A312"			
"A313"			

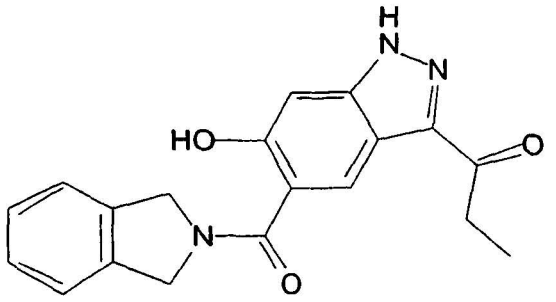
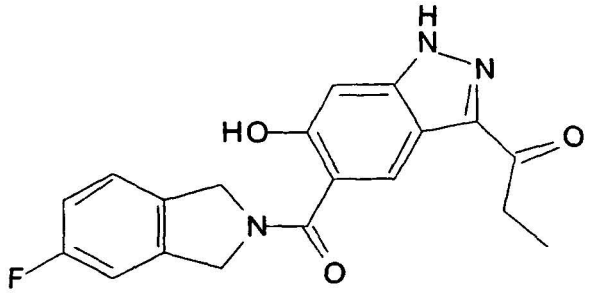
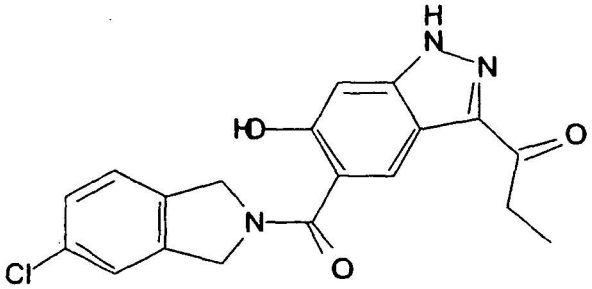
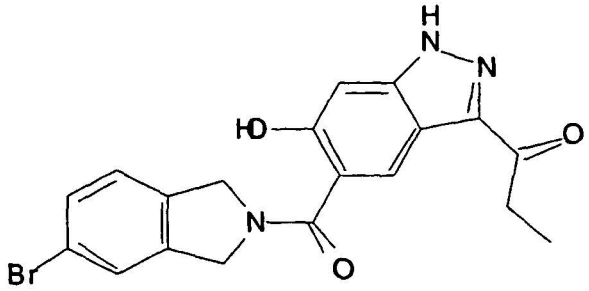
"A314"			
"A315"			
"A316"			
"A317"			

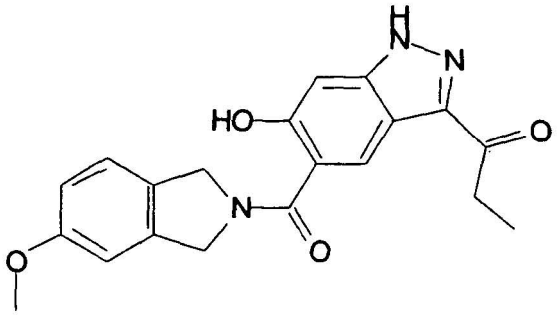
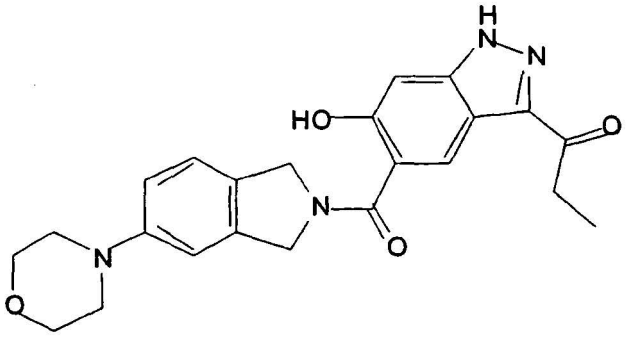
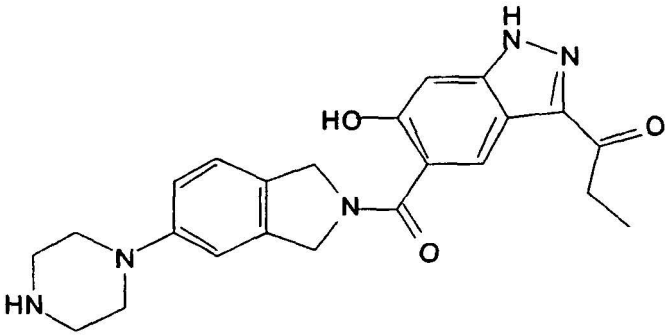
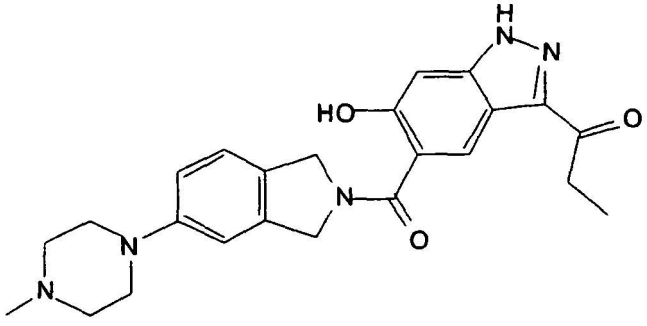
"A318"			
"A319"			
"A320"			
"A321"			

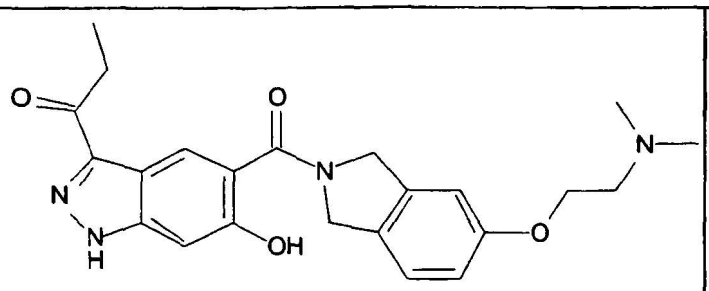
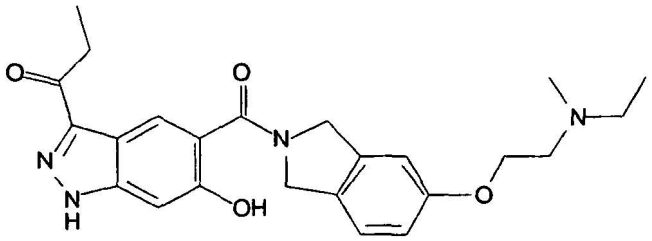
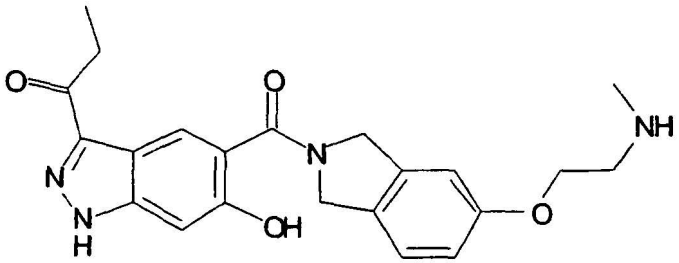
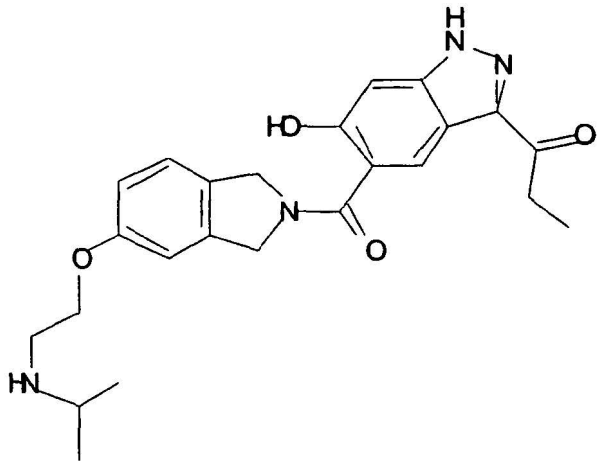
"A322"			
"A323"			
"A324"			
"A325"			
"A326"			

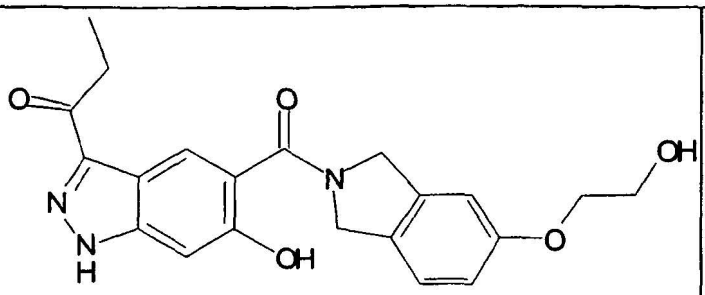
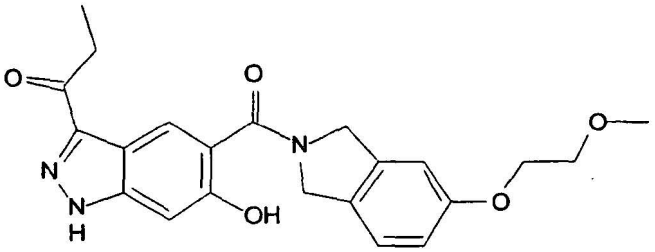
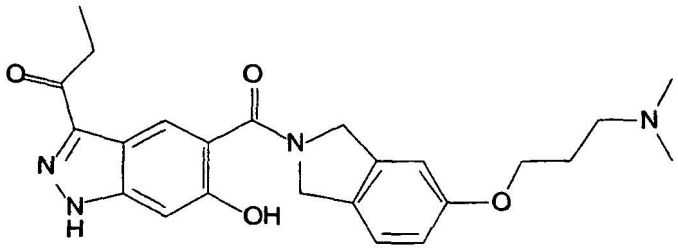
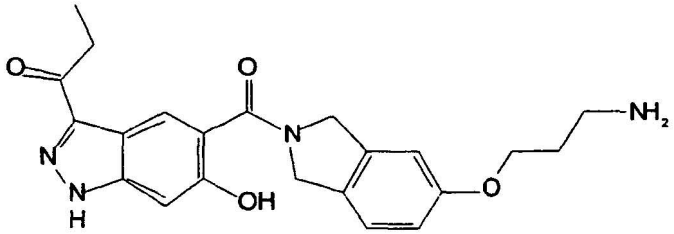
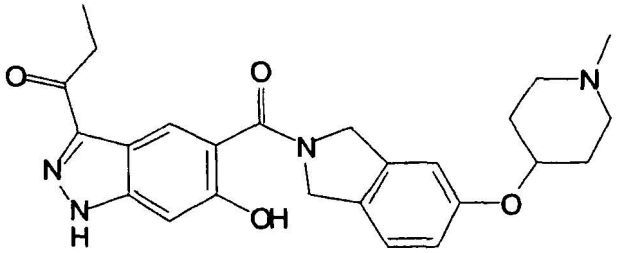
"A327"			
"A328"			
"A329"			
"A330"			

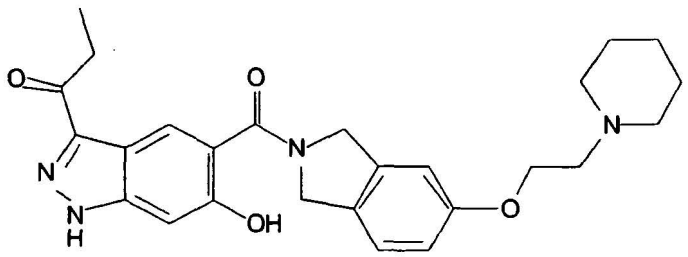
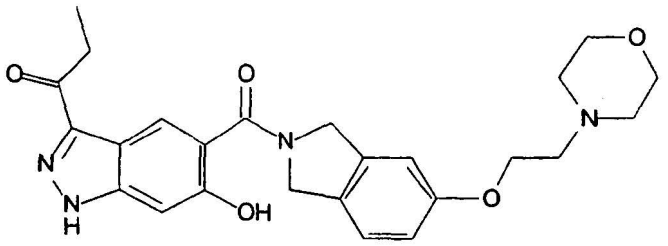
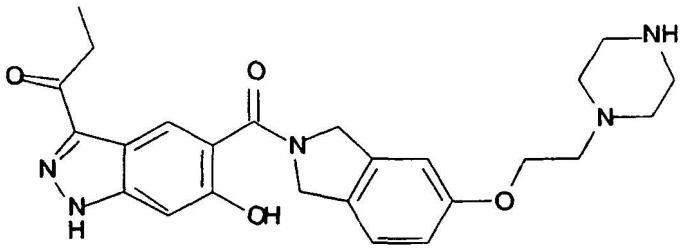
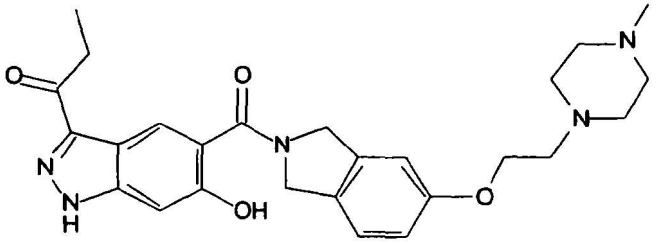
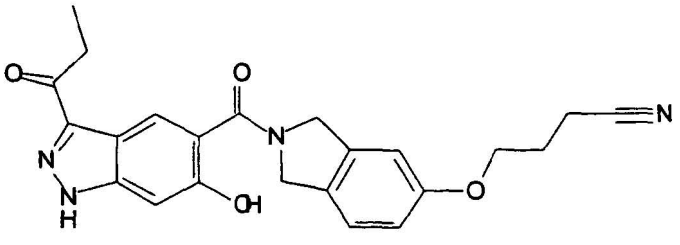
"A331"			
"A332"			
"A333"			
"A334"			

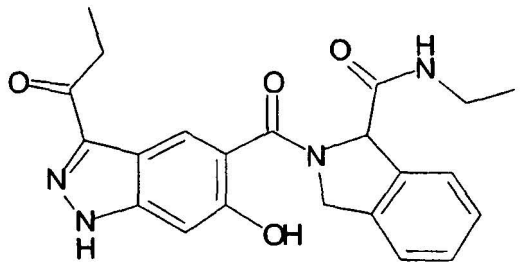
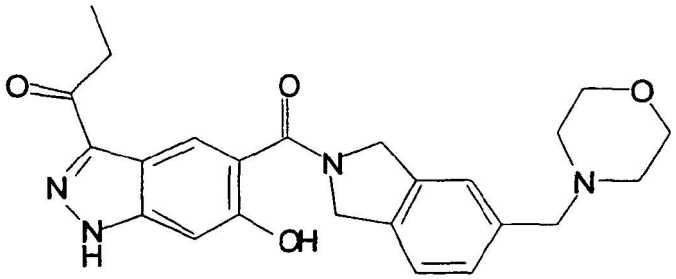
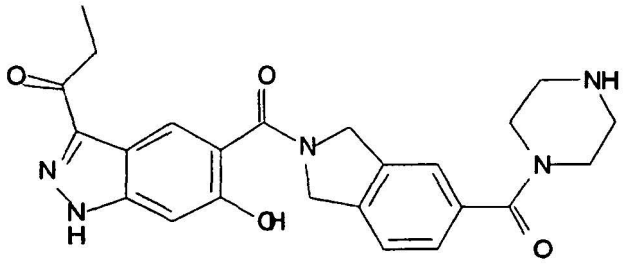
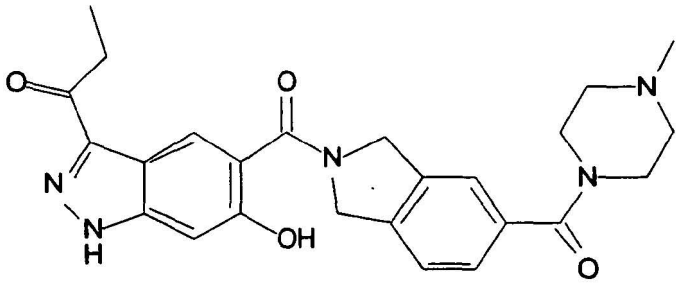
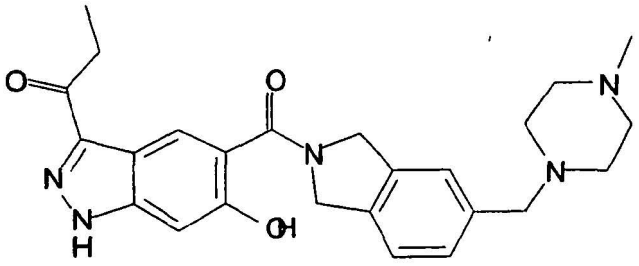
"A335"			
"A336"			
"A337"			
"A338"			

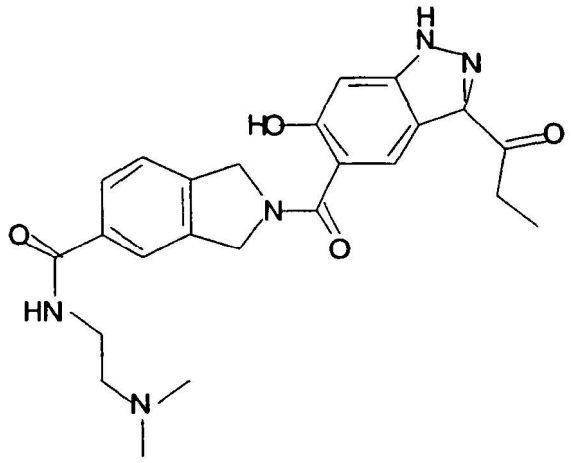
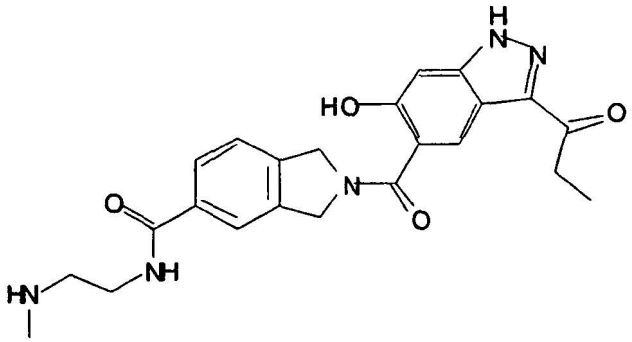
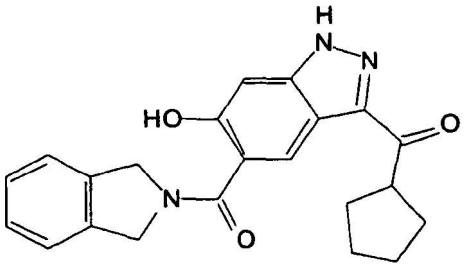
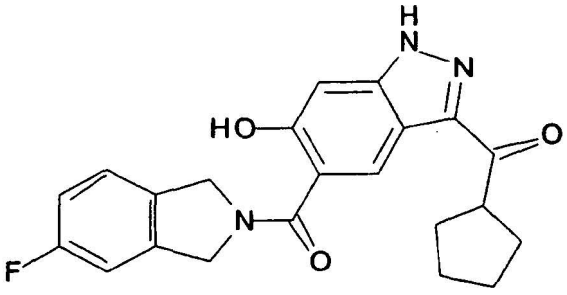
"A339"			
"A340"			
"A341"			
"A342"			

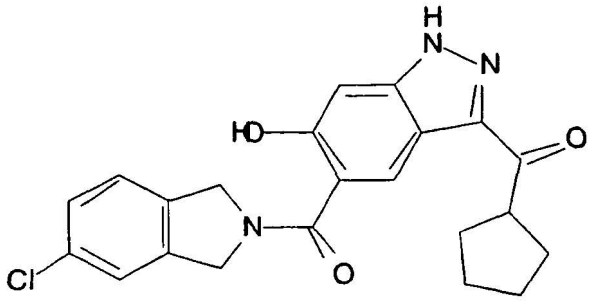
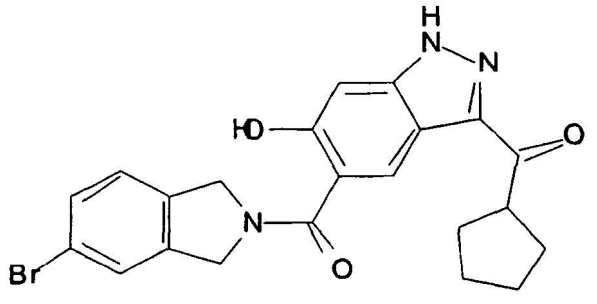
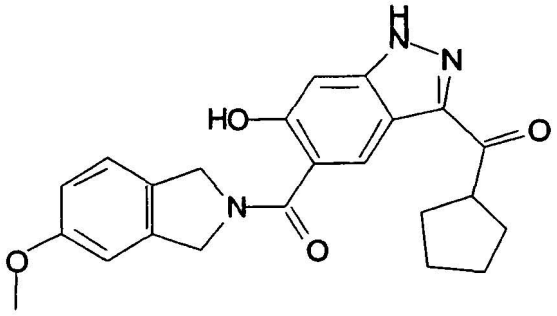
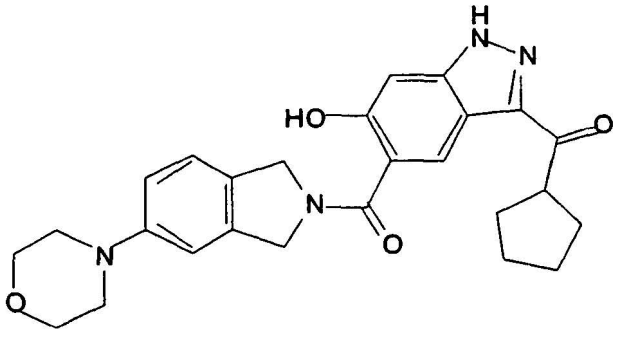
"A343"			
"A344"			
"A345"			
"A346"			

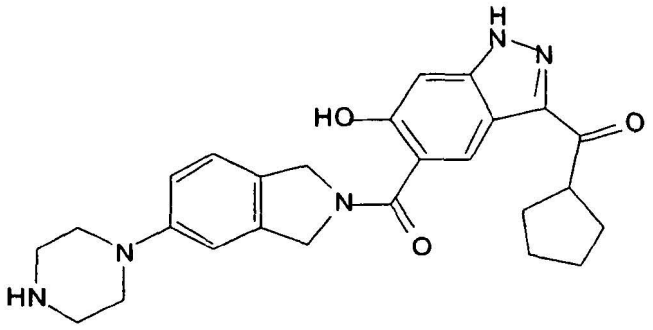
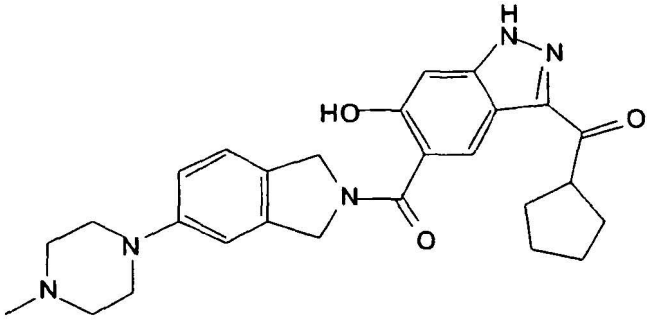
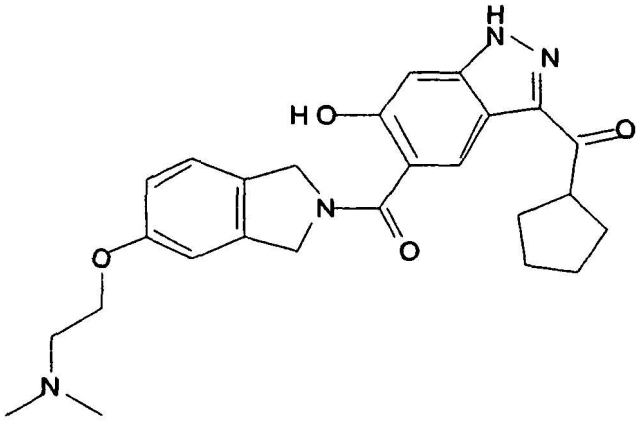
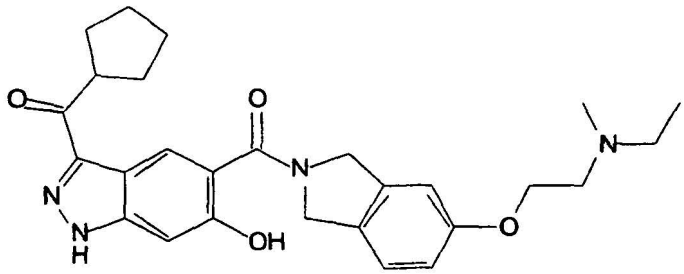
"A347"			
"A348"			
"A349"			
"A350"			
"A351"			

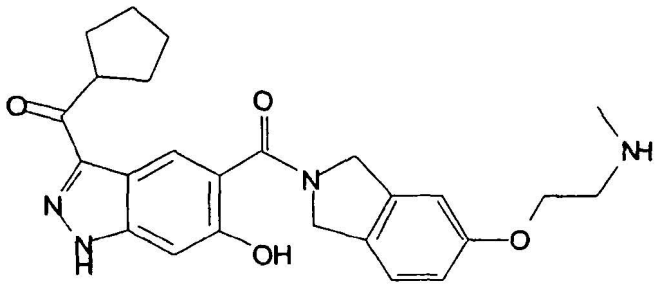
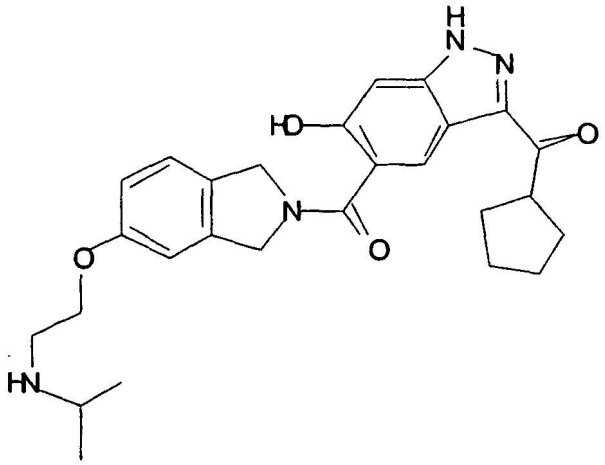
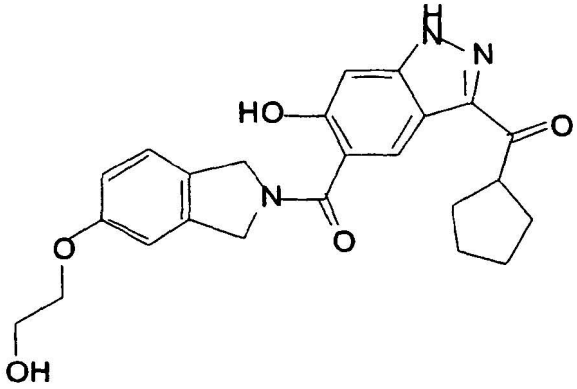
"A352"			
"A353"			
"A354"			
"A355"			
"A356"			

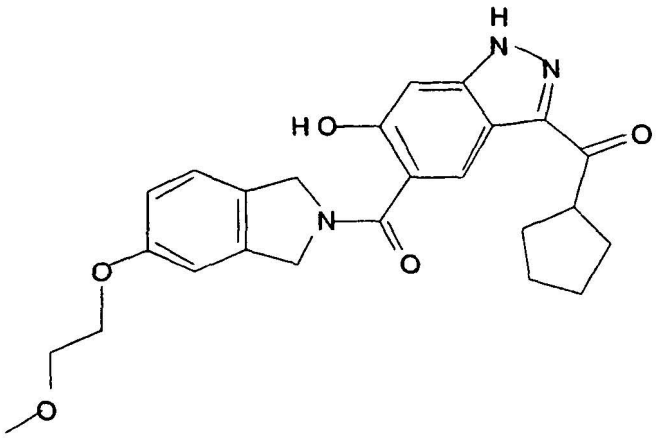
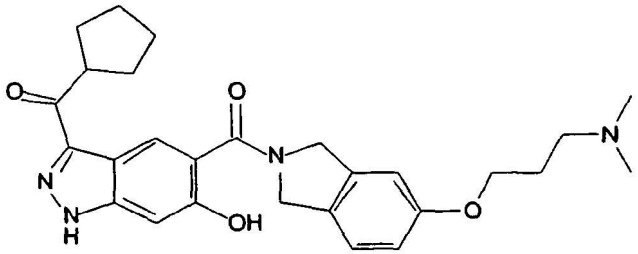
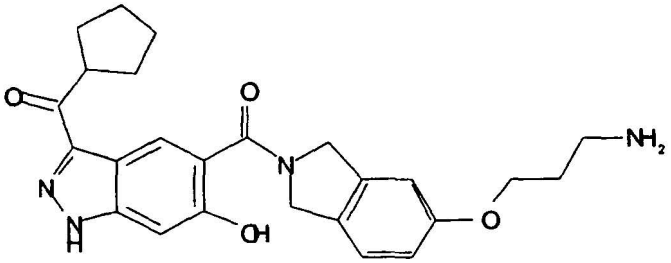
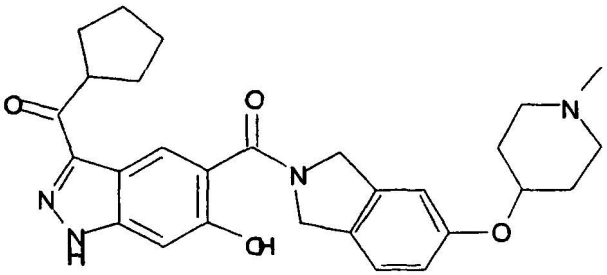
"A357"			
"A358"			
"A359"			
"A360"			
"A361"			

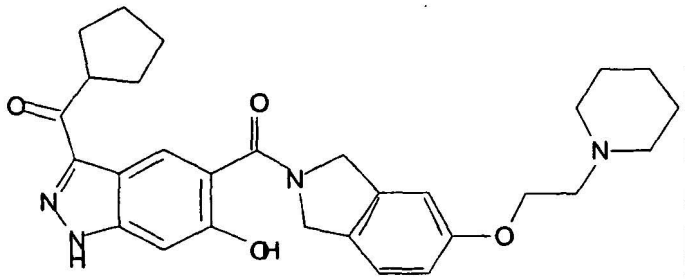
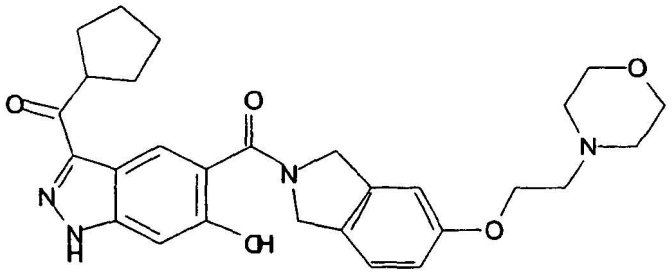
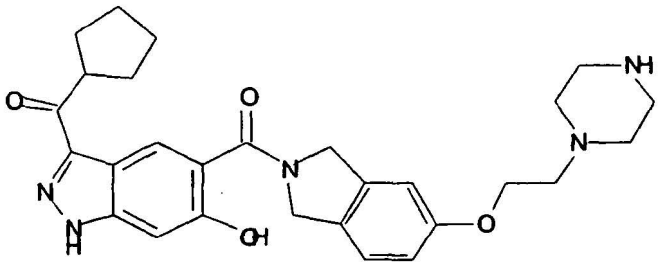
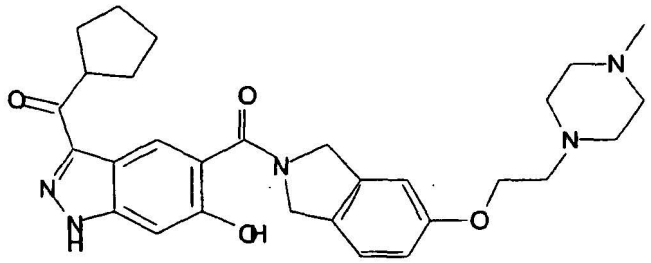
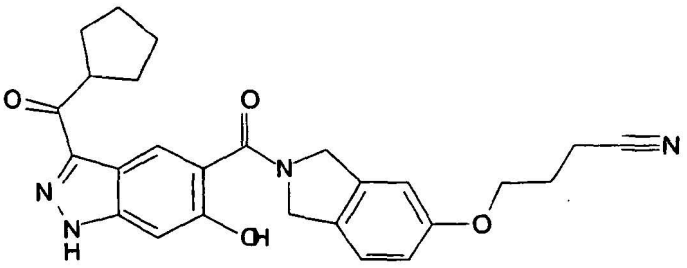
"A362"			
"A363"			
"A364"			
"A365"			

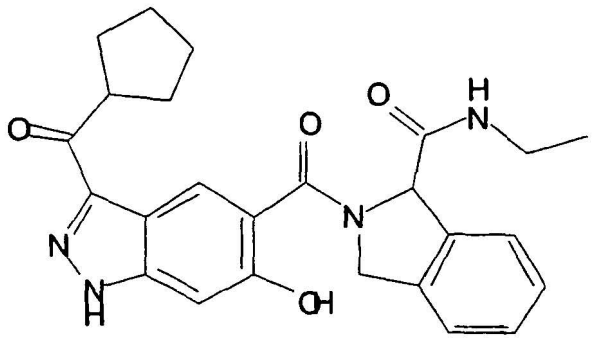
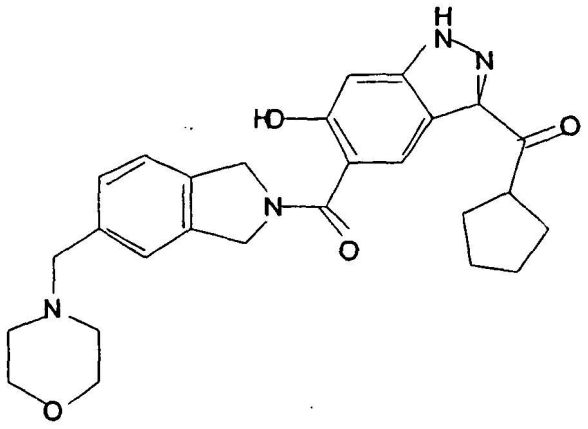
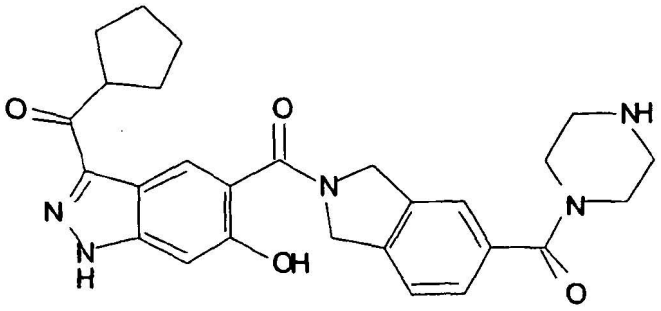
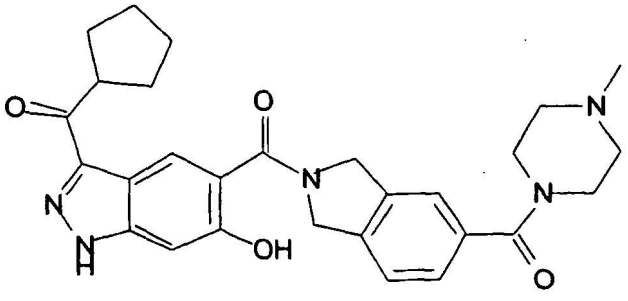
"A366"			
"A367"			
"A368"			
"A369"			

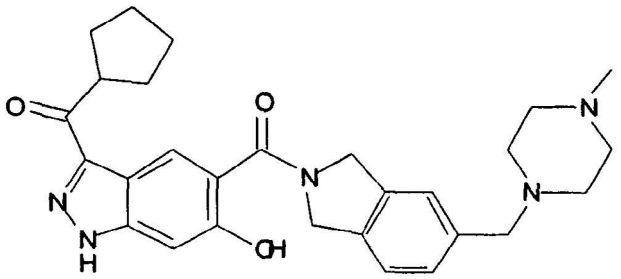
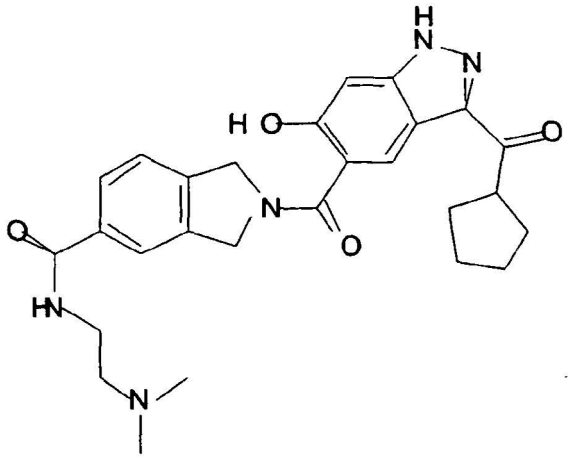
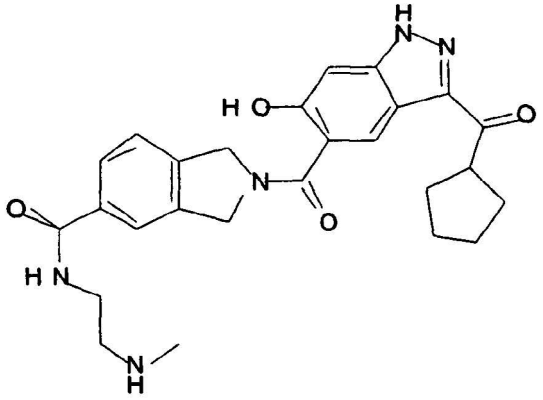
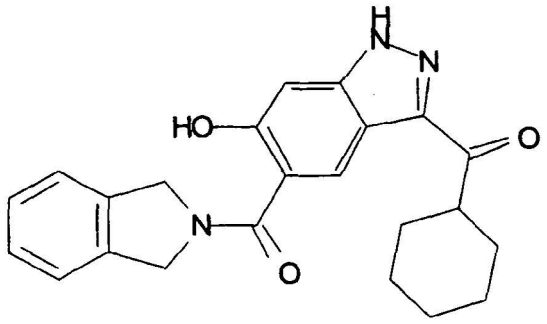
"A370"			
"A371"			
"A372"			
"A373"			

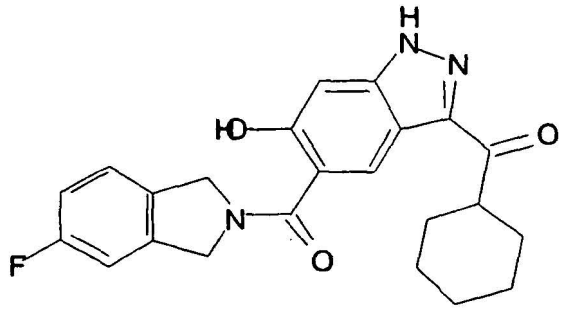
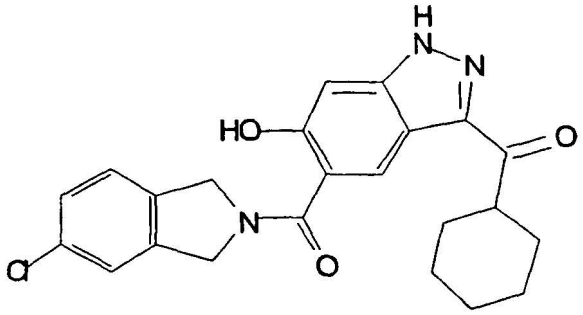
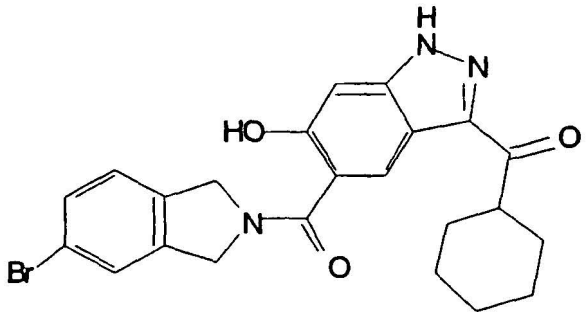
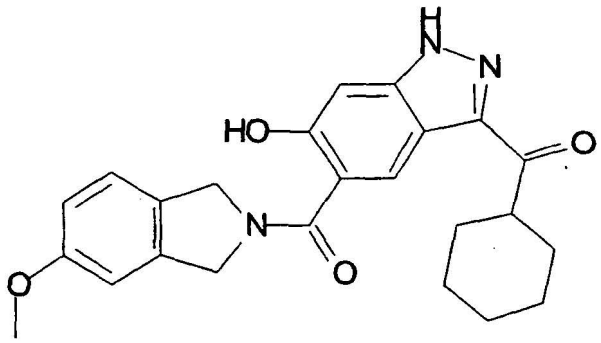
"A374"			
"A375"			
"A376"			

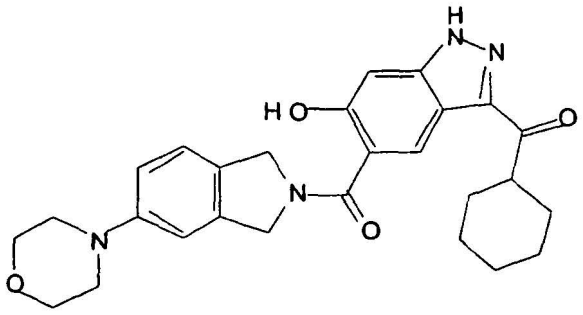
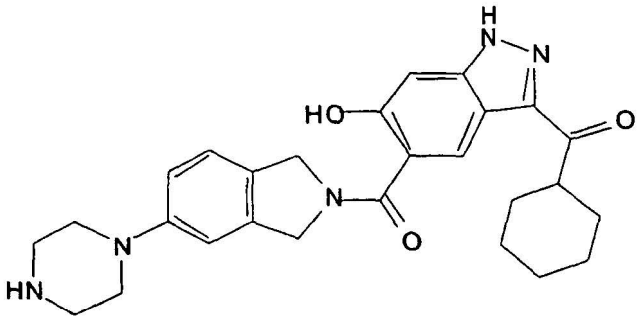
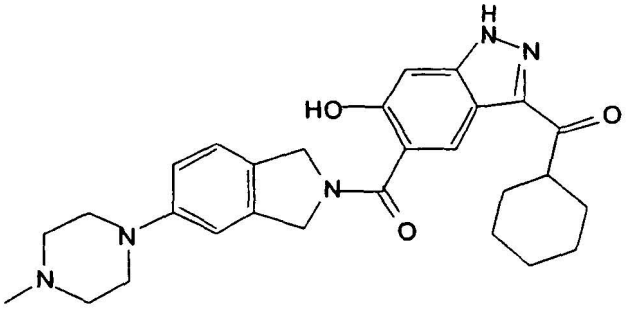
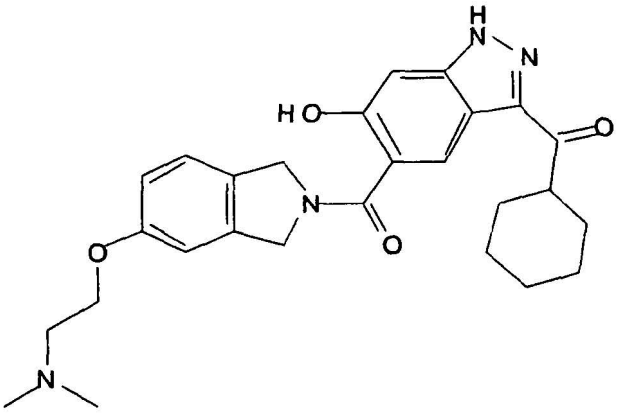
"A377"			
"A378"			
"A379"			
"A380"			

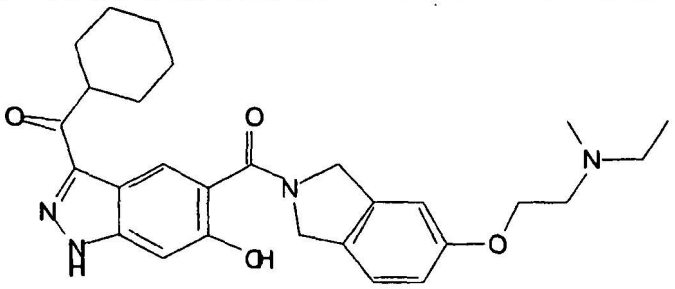
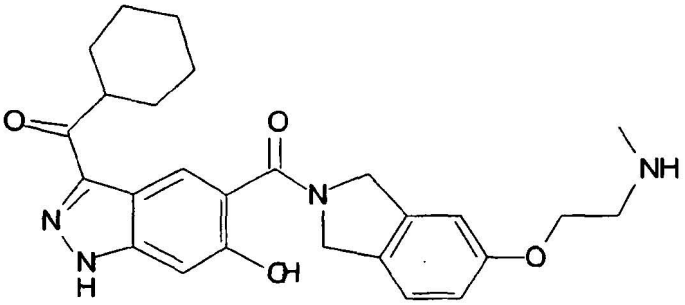
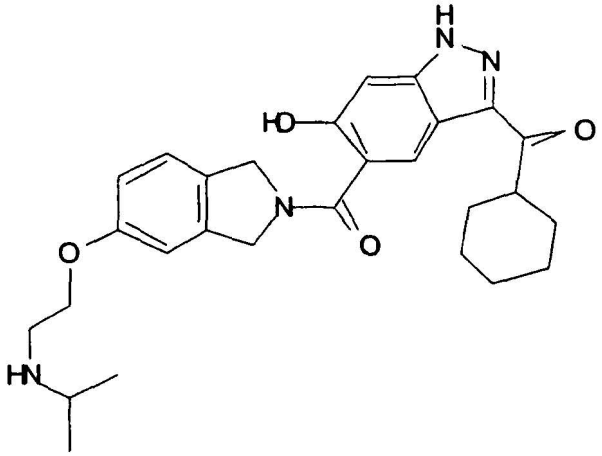
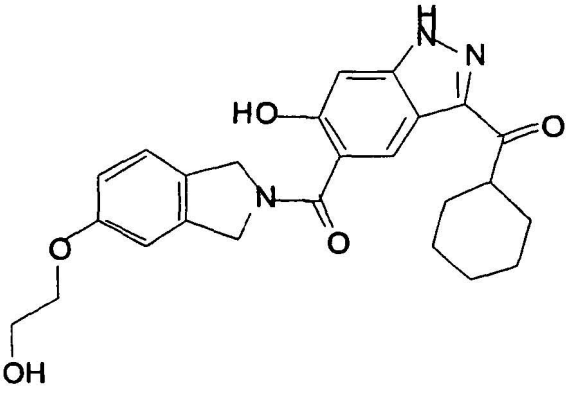
"A381"			
"A382"			
"A383"			
"A384"			
"A385"			

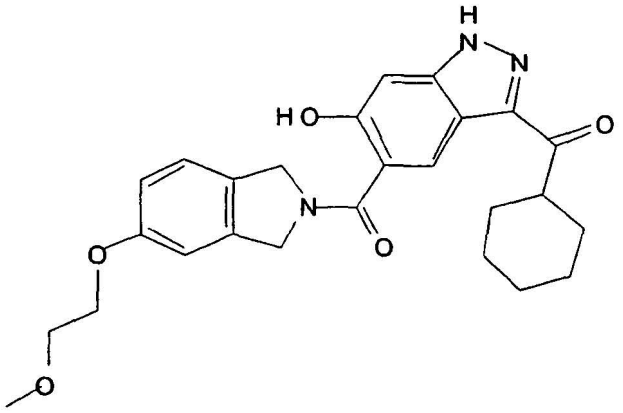
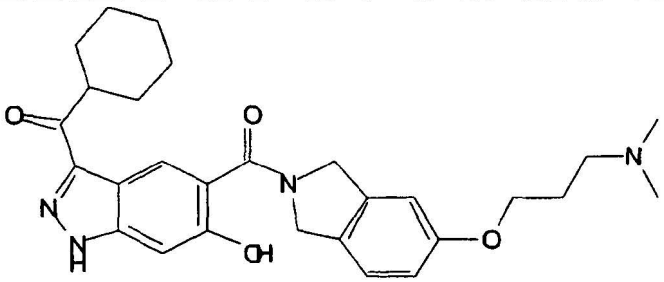
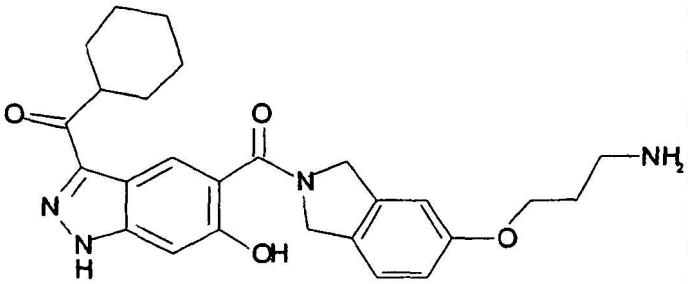
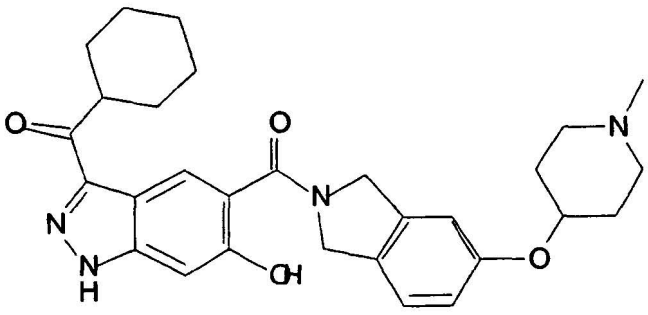
"A386"			
"A387"			
"A388"			
"A389"			

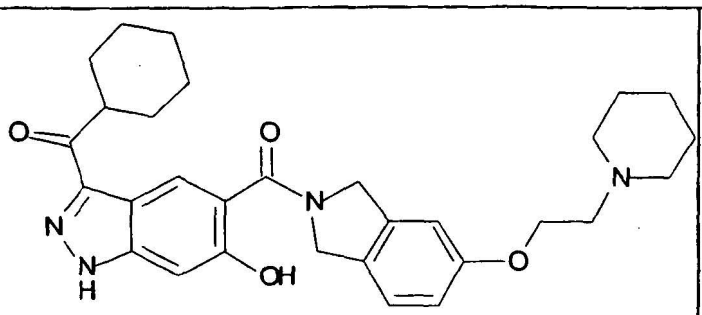
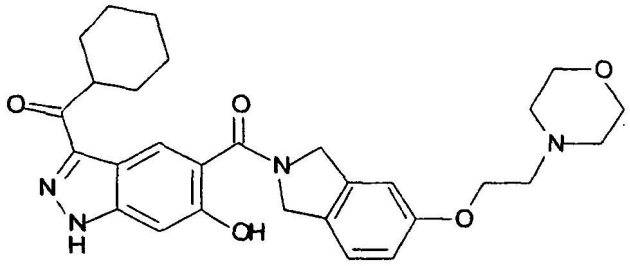
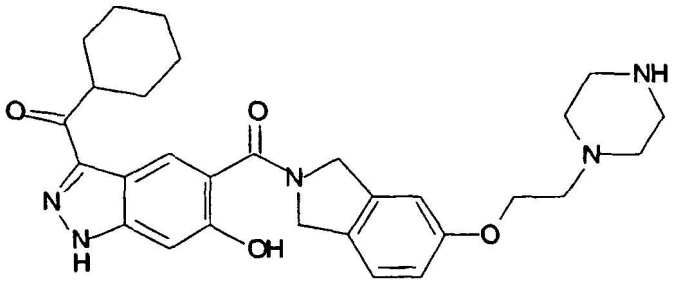
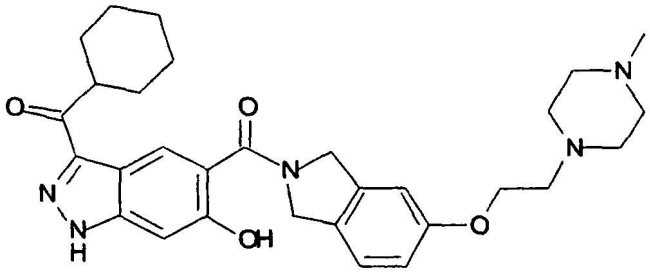
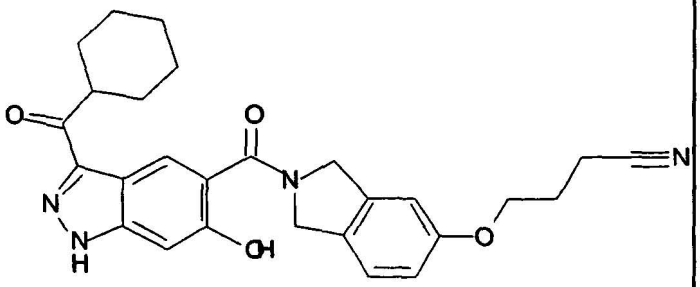
"A390"			
"A391"			
"A392"			
"A393"			

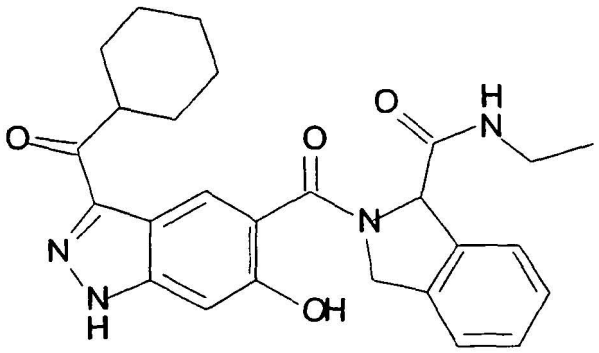
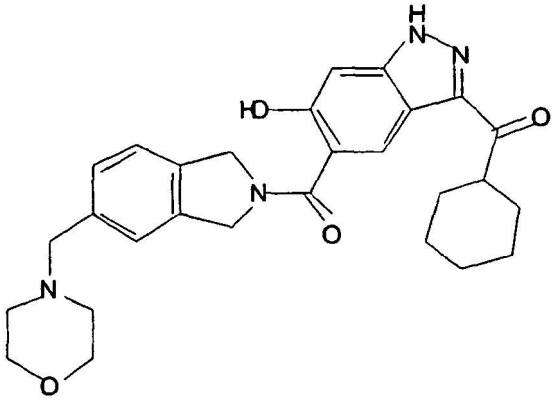
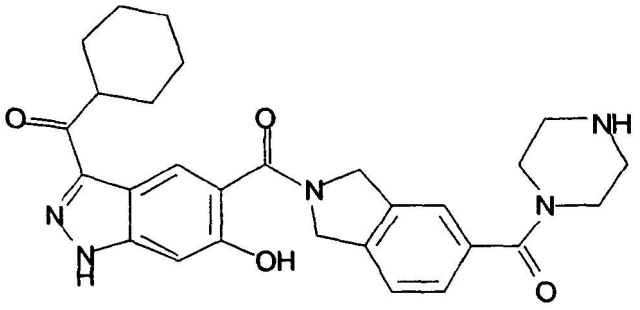
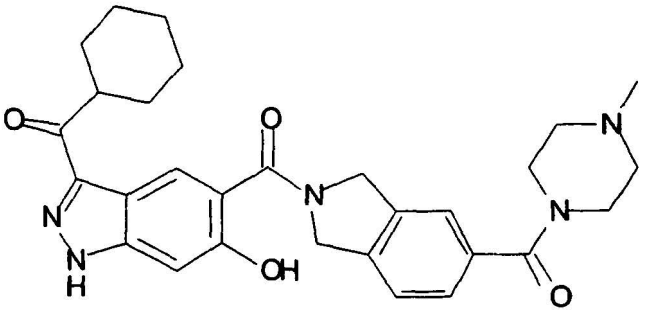
"A394"			
"A395"			
"A396"			
"A397"			

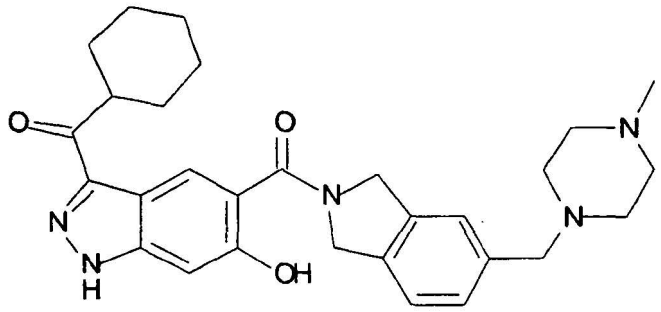
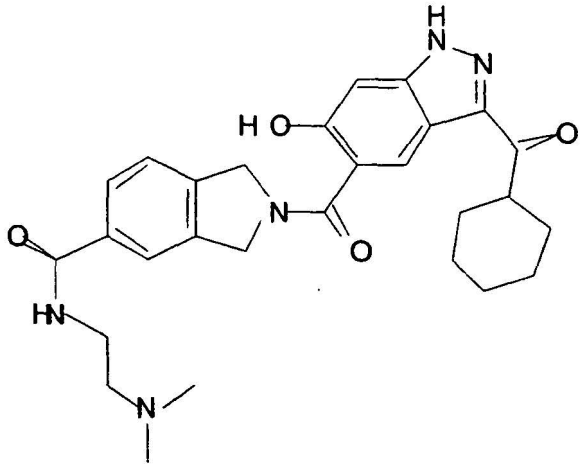
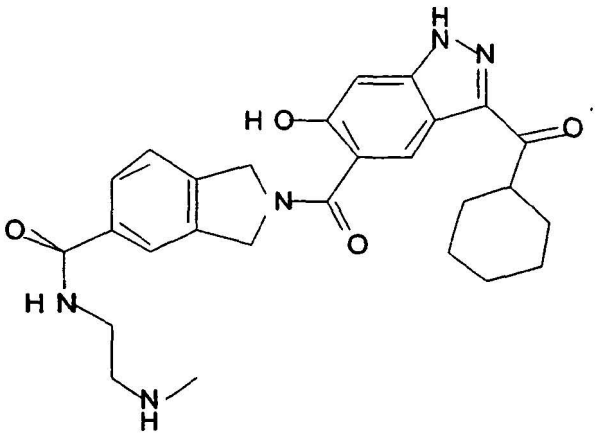
"A398"			
"A399"			
"A400"			
"A401"			

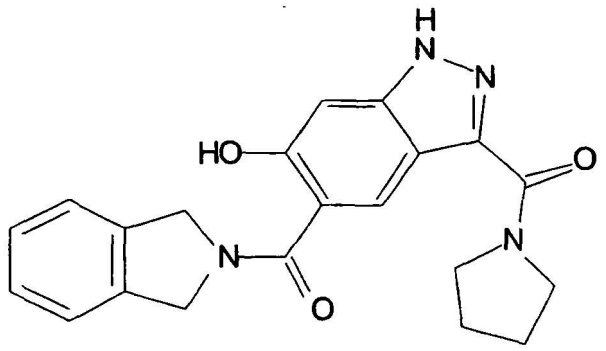
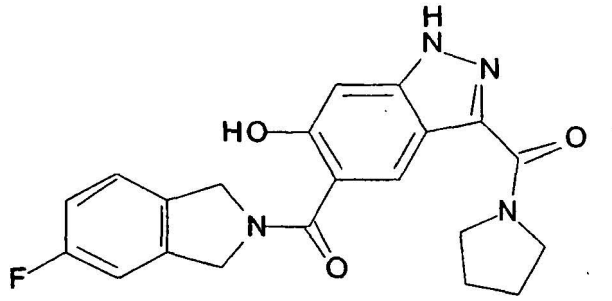
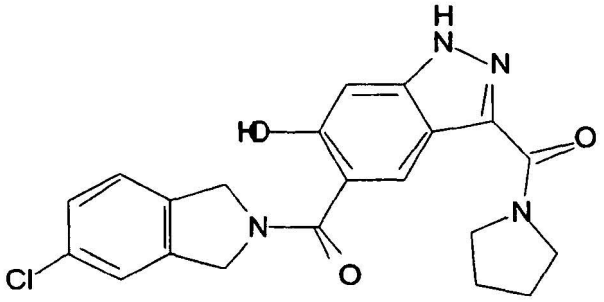
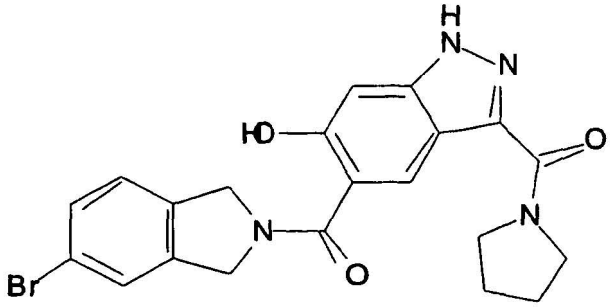
"A402"			
"A403"			
"A404"			
"A405"			

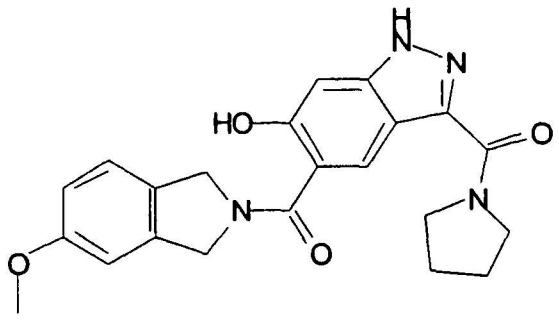
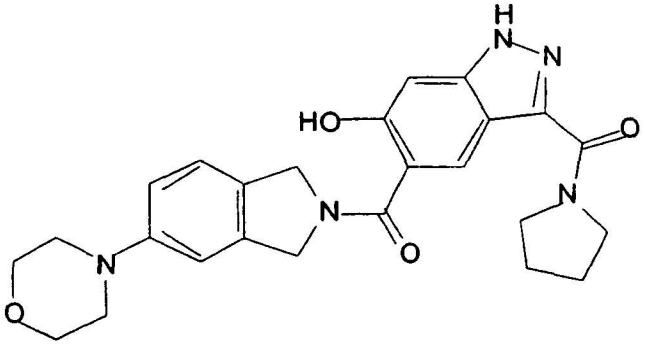
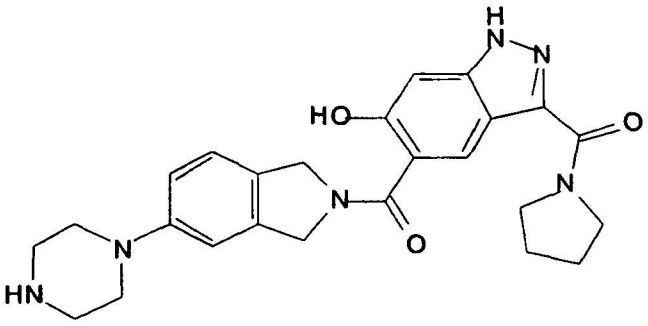
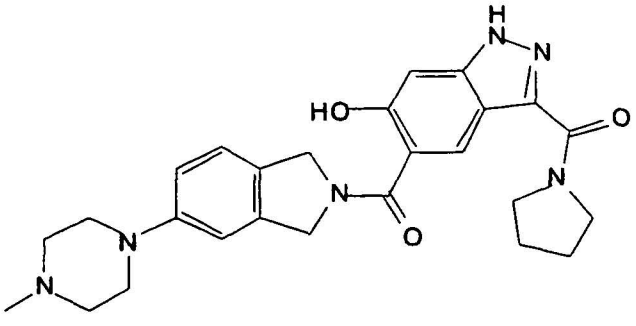
"A406"			
"A407"			
"A408"			
"A409"			

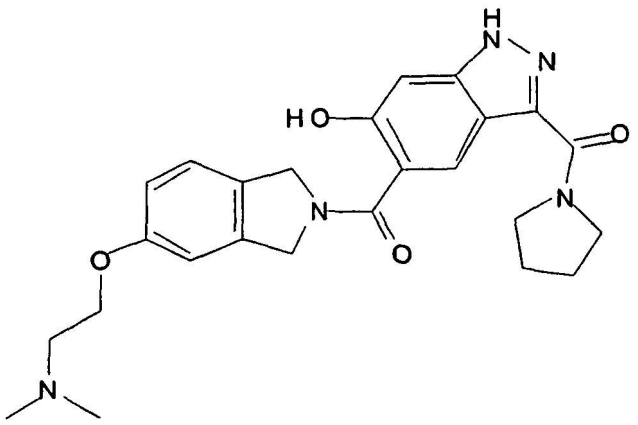
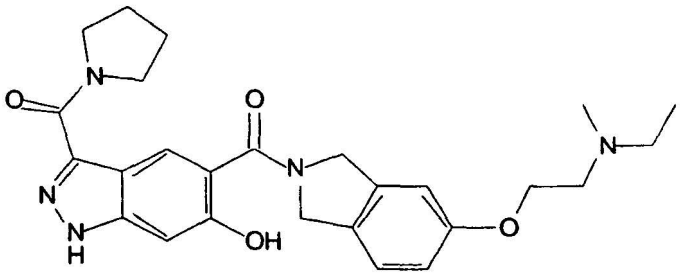
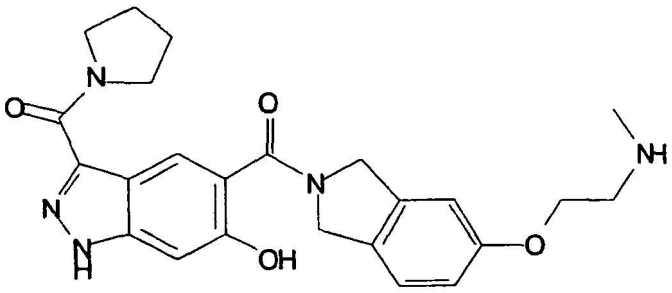
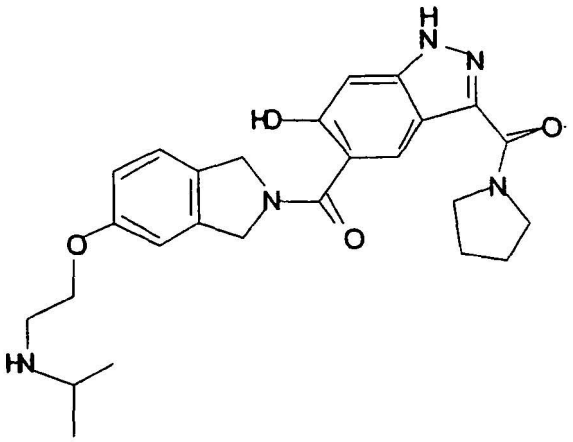
"A410"			
"A411"			
"A412"			
"A413"			
"A414"			

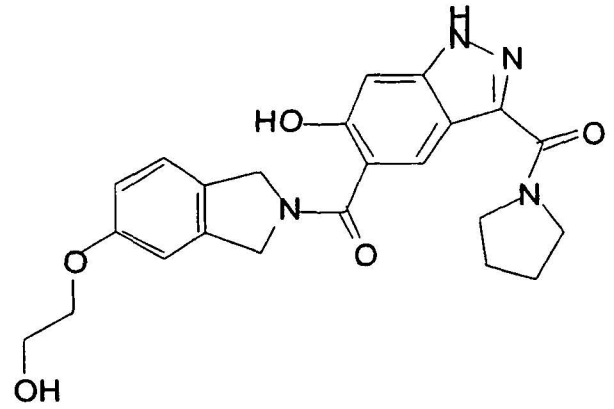
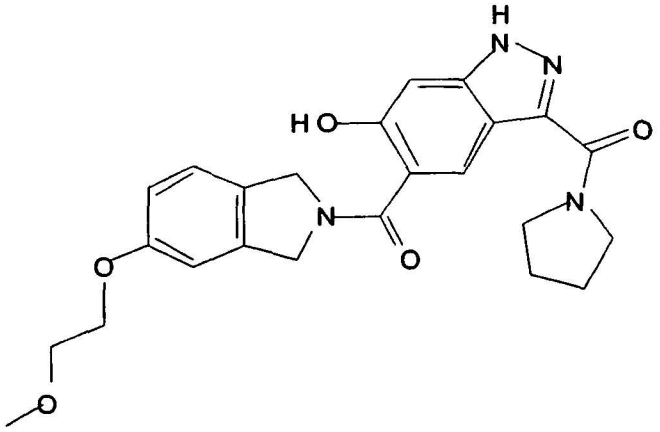
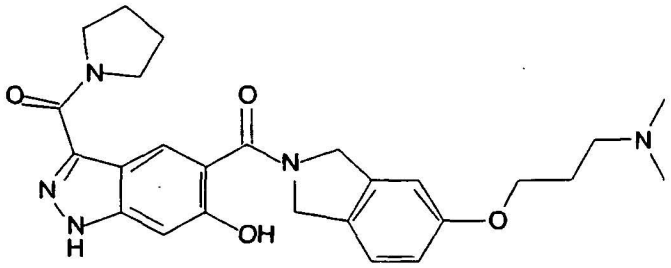
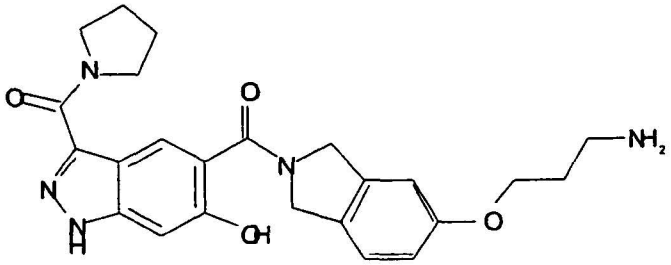
"A415"			
"A416"			
"A417"			
"A418"			

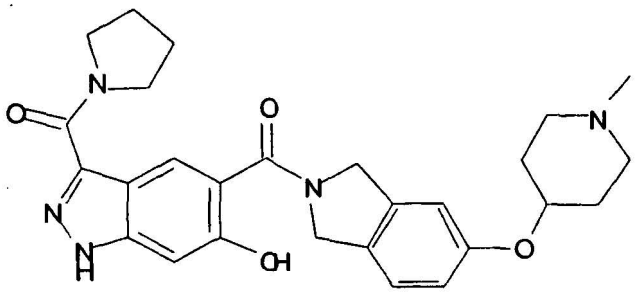
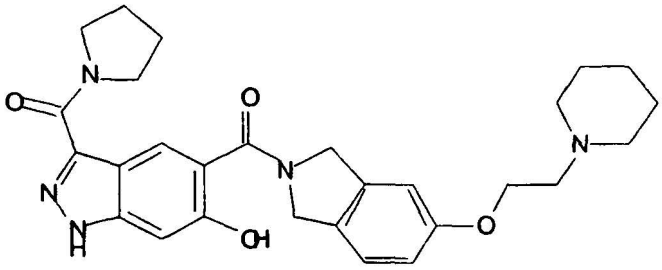
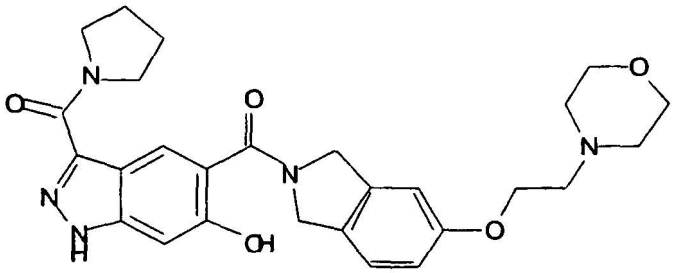
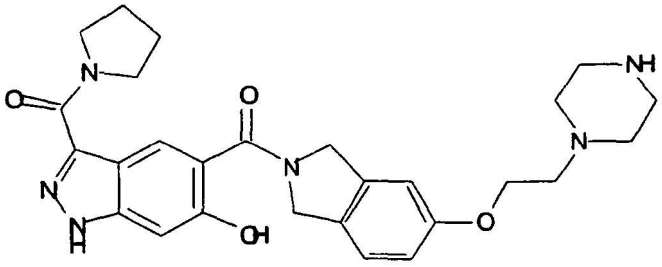
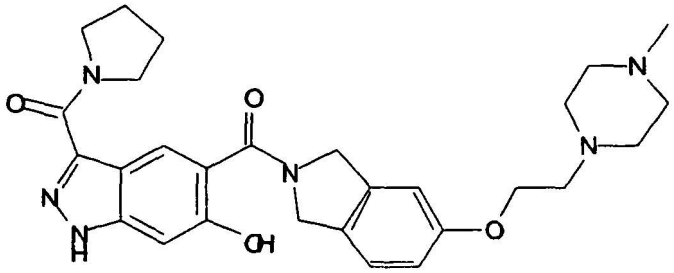
"A419"			
"A420"			
"A421"			

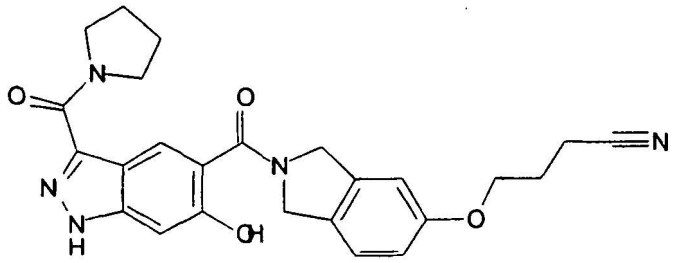
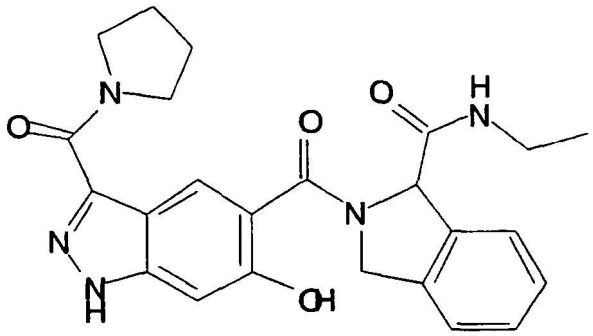
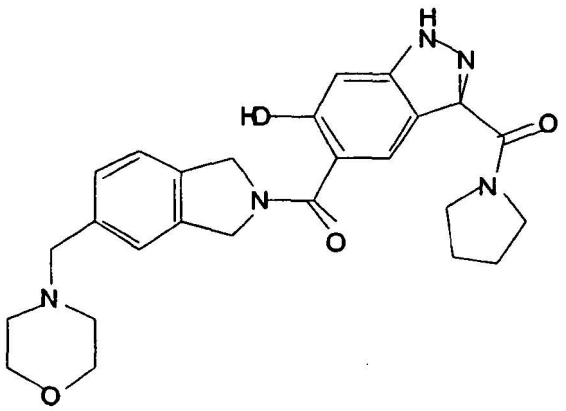
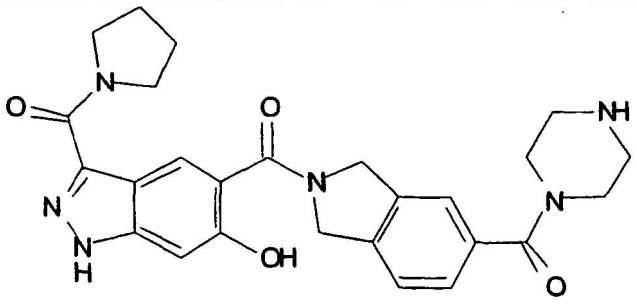
"A422"			
"A423"			
"A424"			
"A425"			

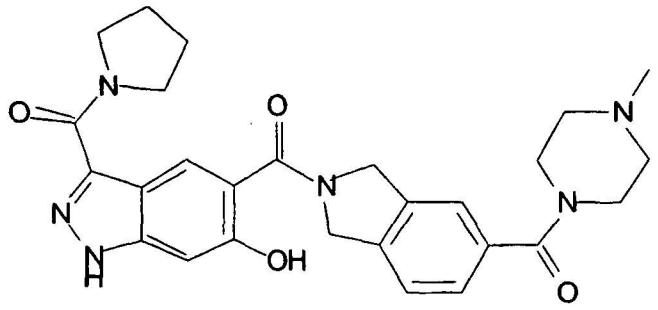
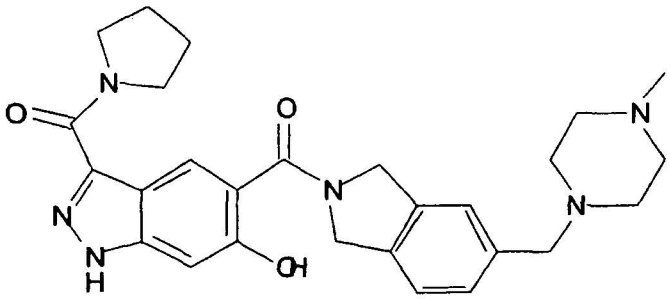
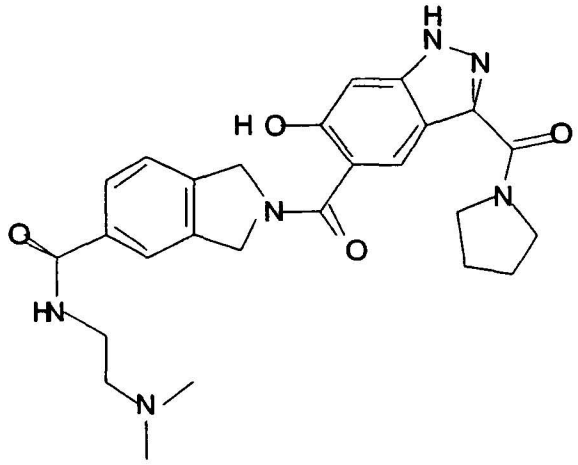
"A426"			
"A427"			
"A428"			
"A429"			

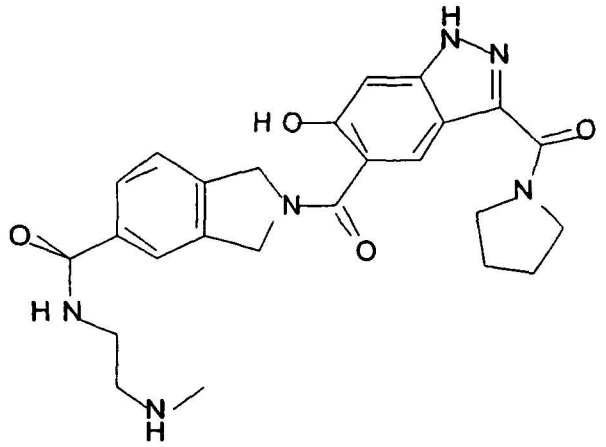
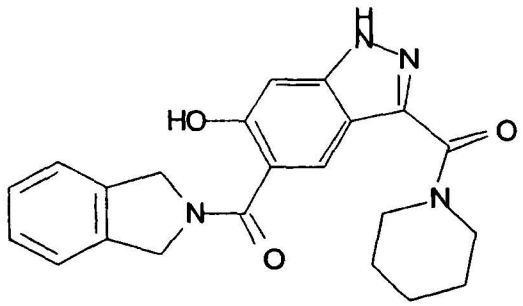
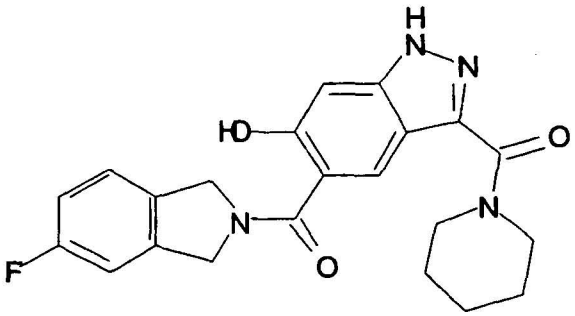
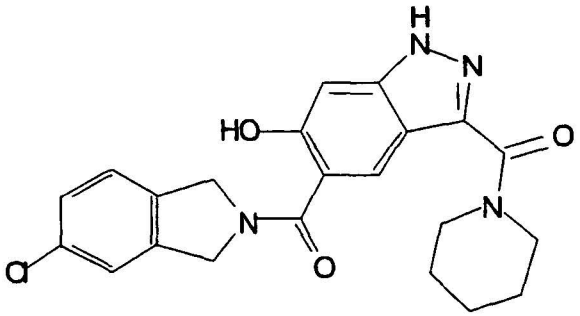
"A430"			
"A431"			
"A432"			
"A433"			

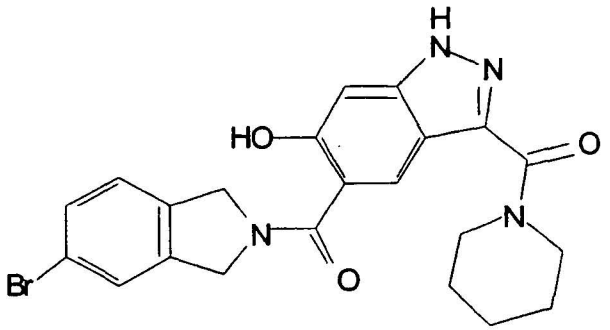
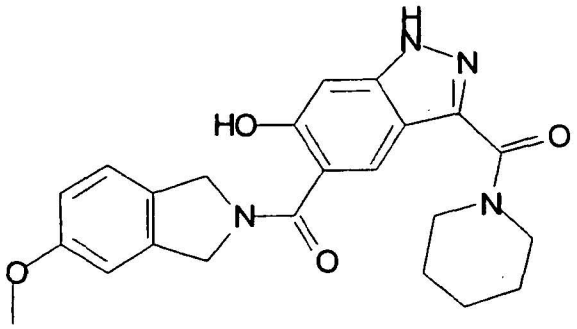
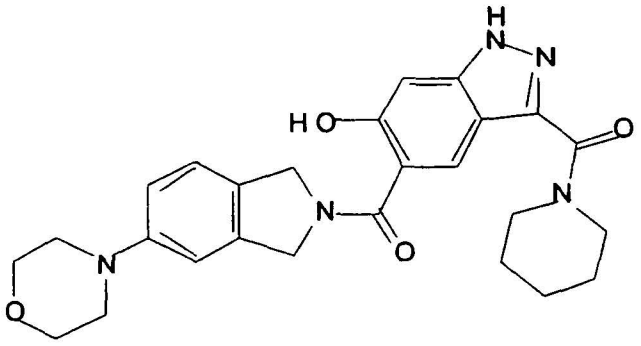
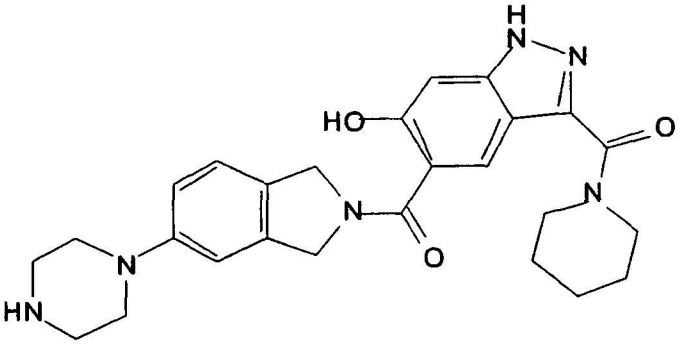
"A434"			
"A435"			
"A436"			
"A437"			

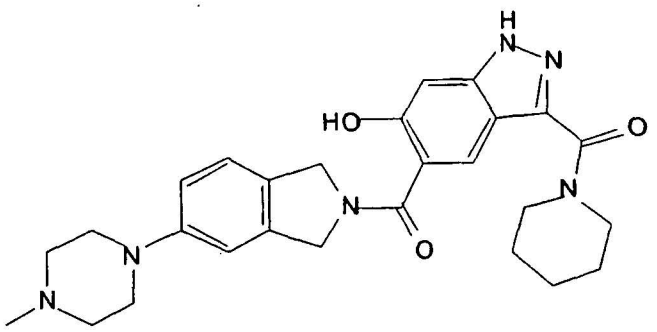
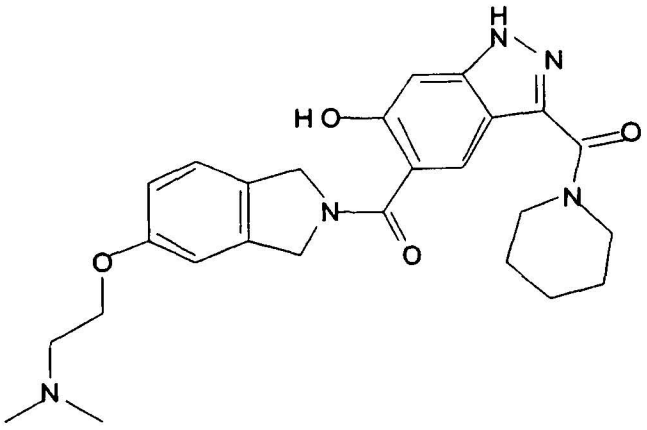
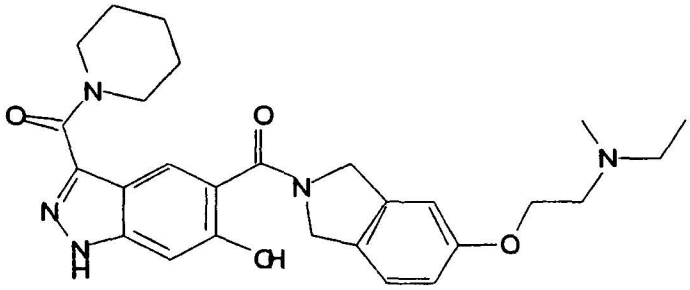
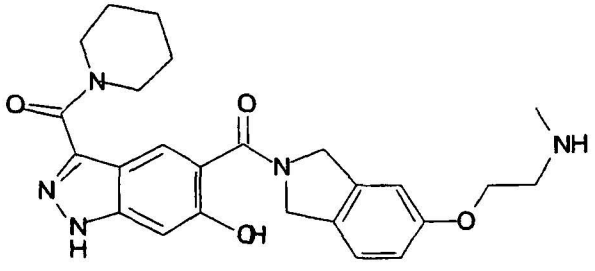
"A438"			
"A439"			
"A440"			
"A441"			
"A442"			

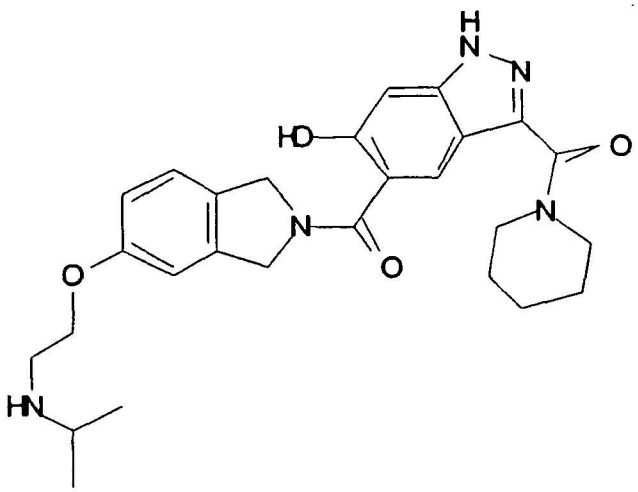
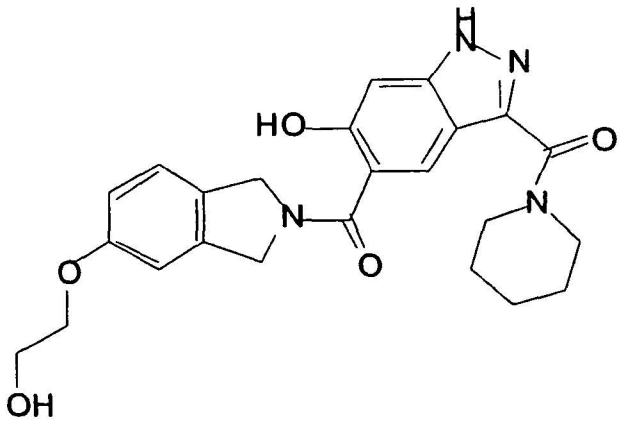
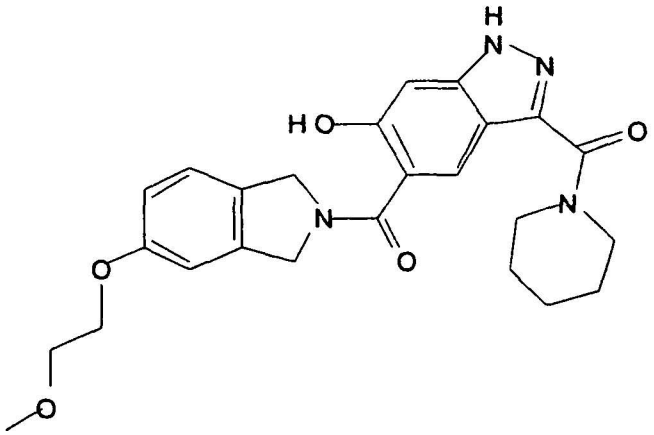
"A443"			
"A444"			
"A445"			
"A446"			

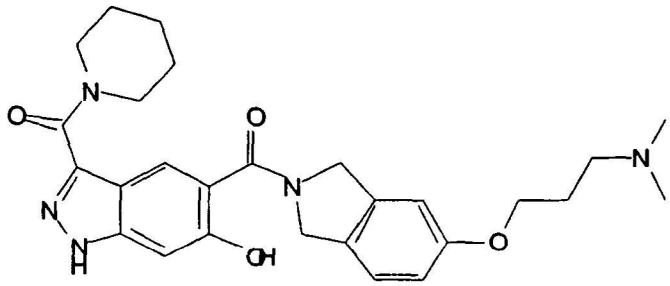
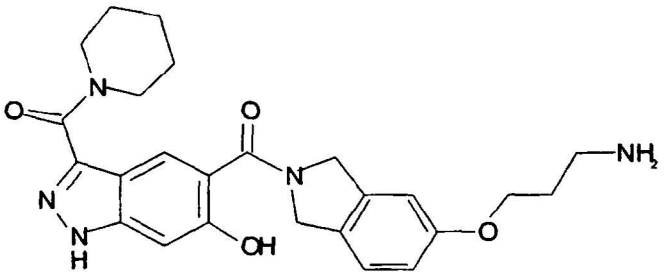
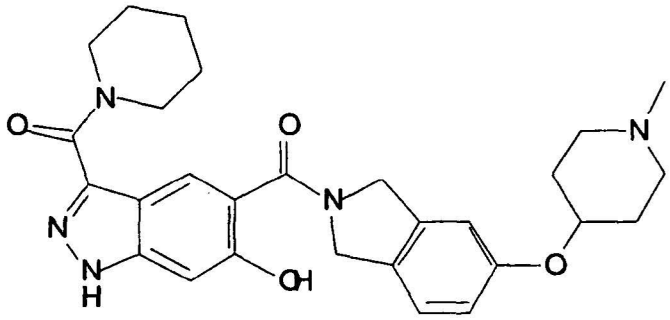
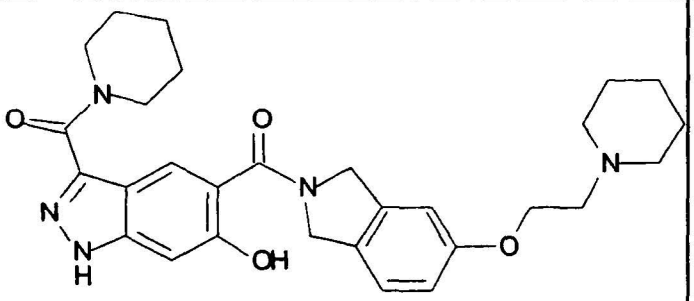
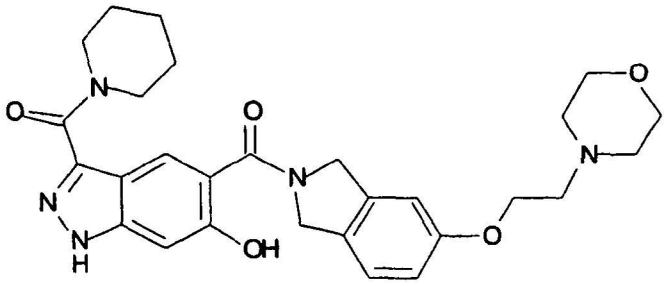
"A447"			
"A448"			
"A449"			

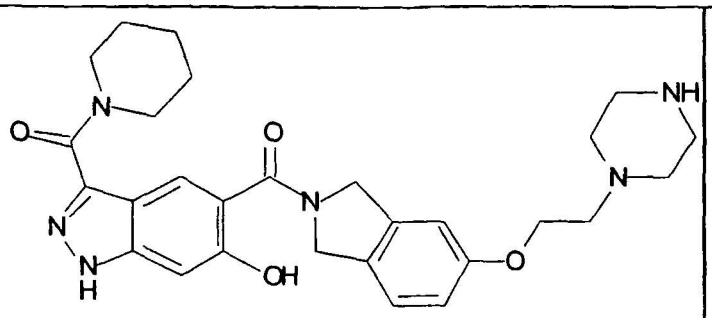
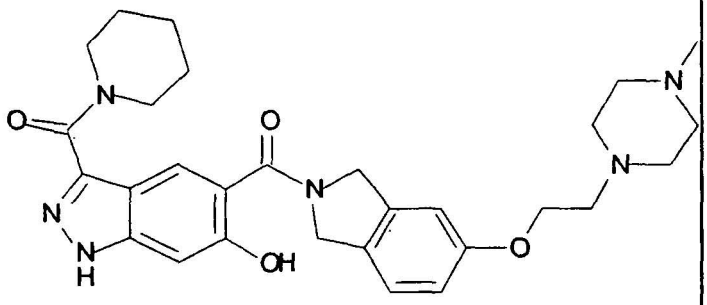
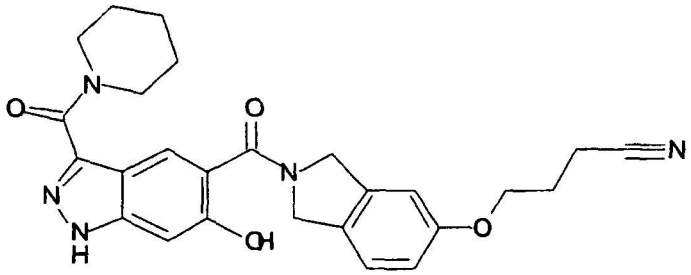
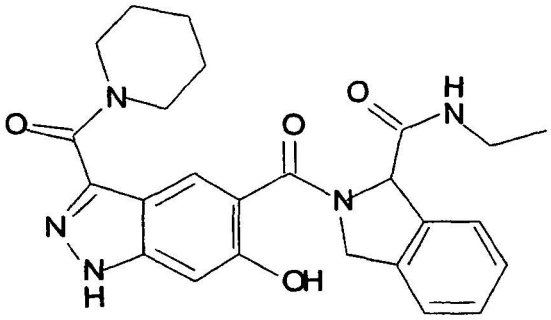
"A450"			
"A451"			
"A452"			
"A453"			

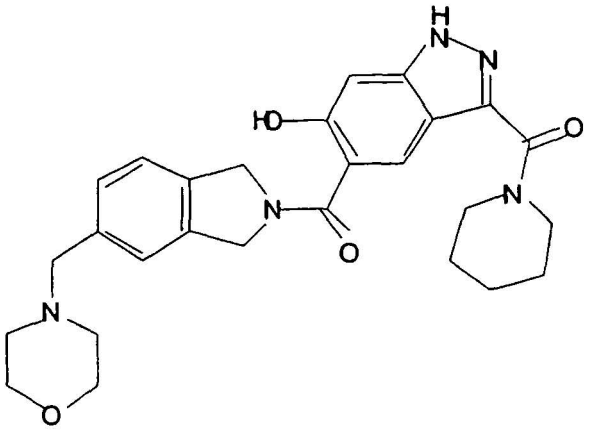
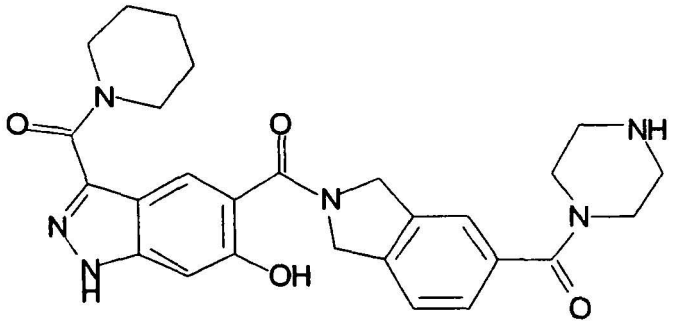
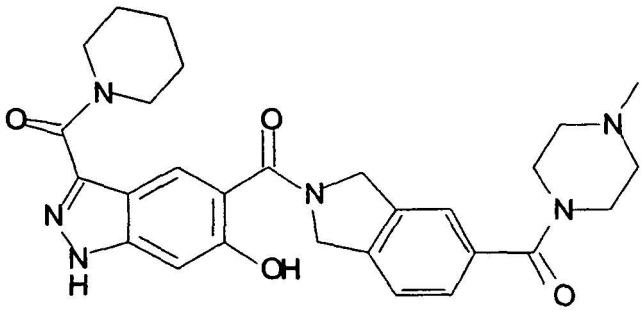
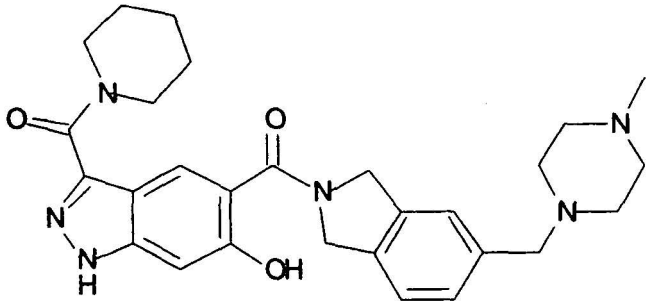
"A454"			
"A455"			
"A456"			
"A457"			

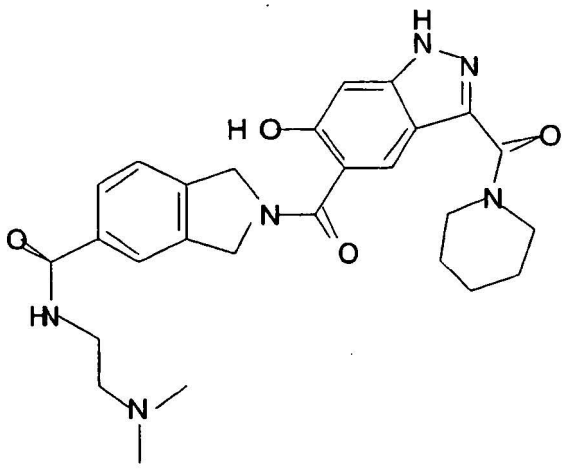
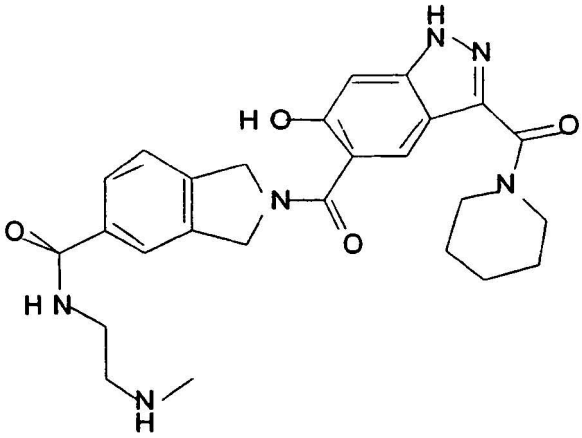
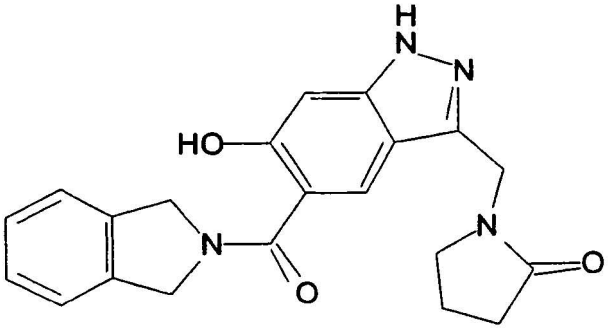
"A458"			
"A459"			
"A460"			
"A461"			

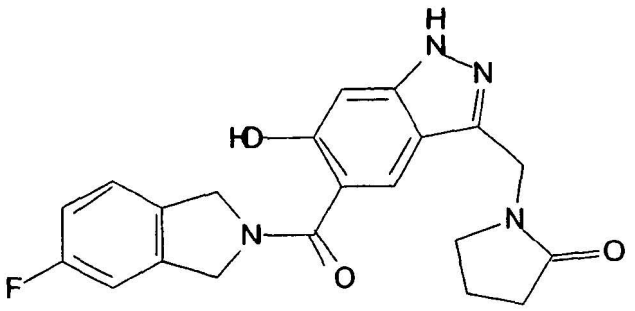
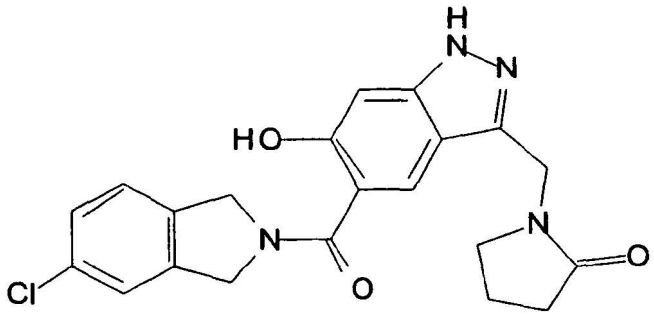
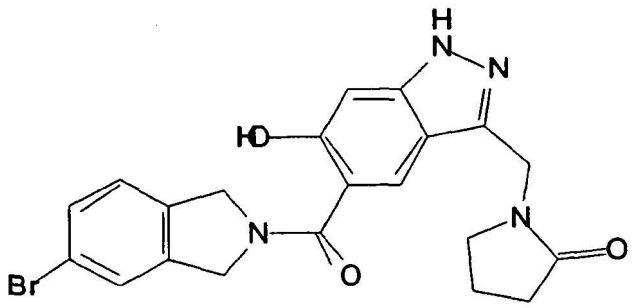
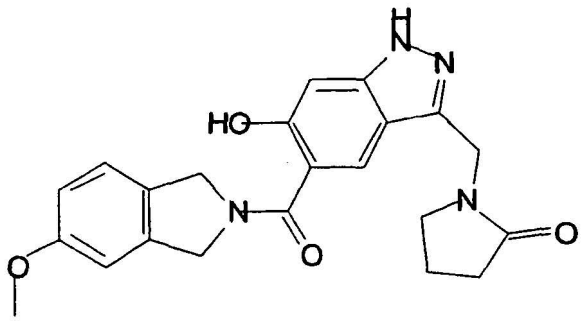
"A462"			
"A463"			
"A464"			

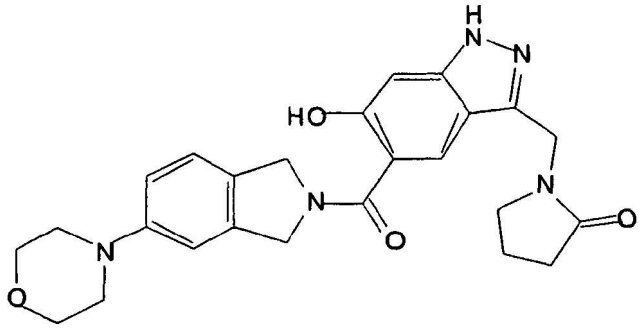
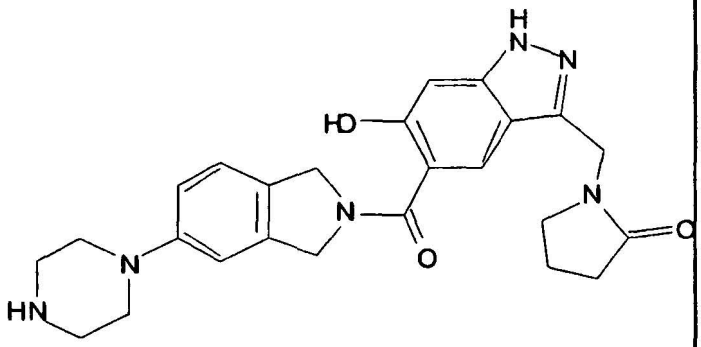
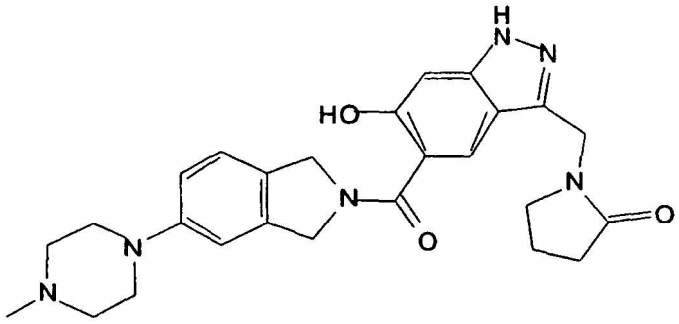
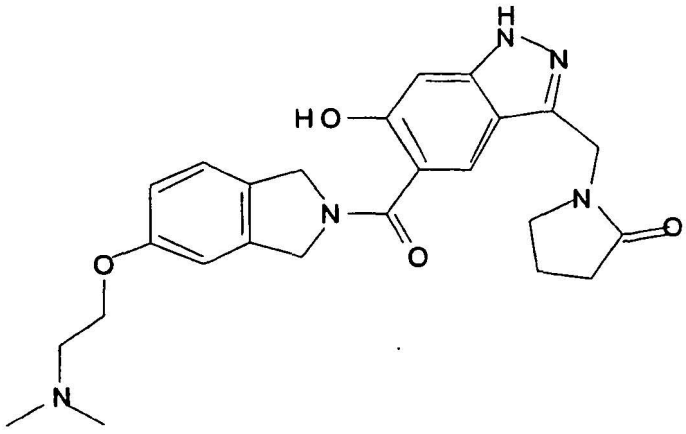
"A465"			
"A466"			
"A467"			
"A468"			
"A469"			

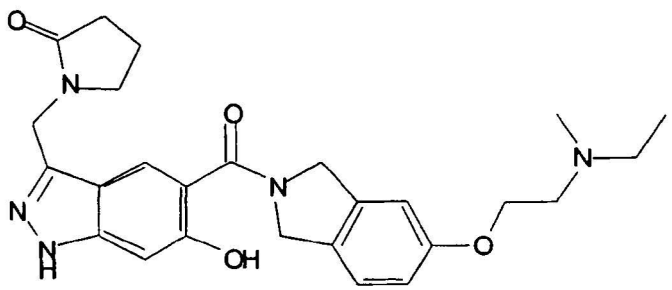
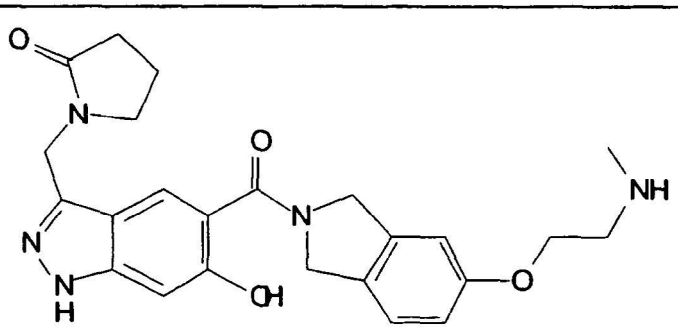
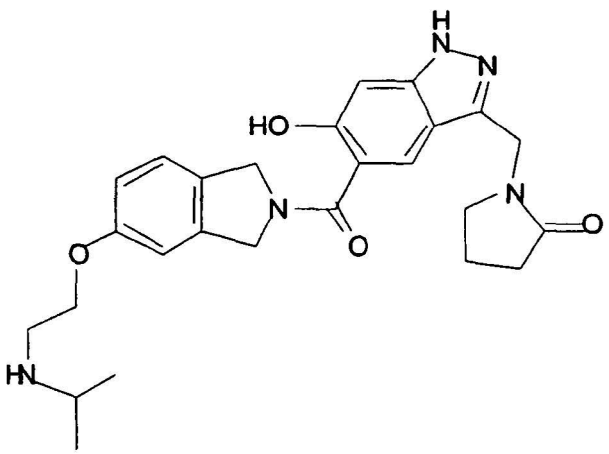
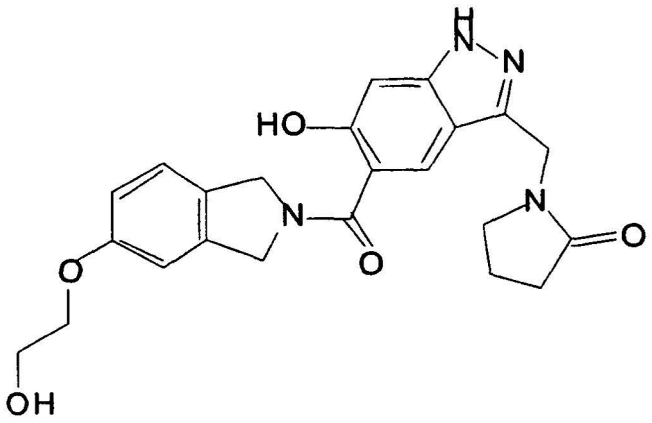
"A470"			
"A471"			
"A472"			
"A473"			

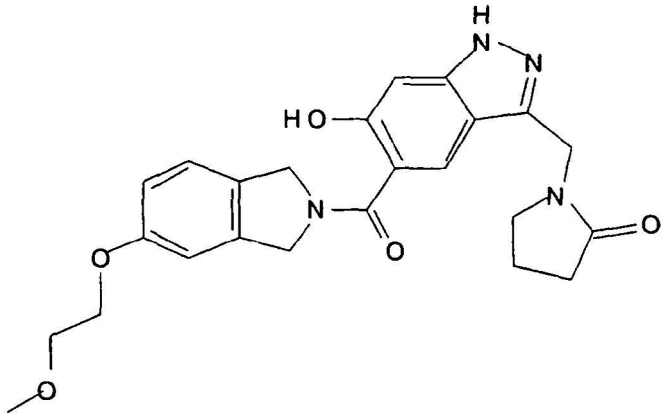
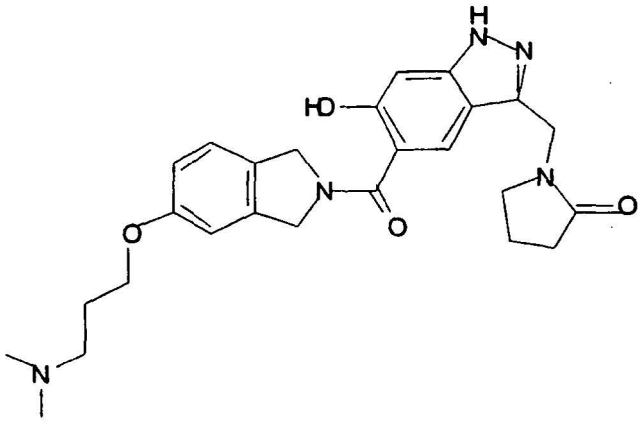
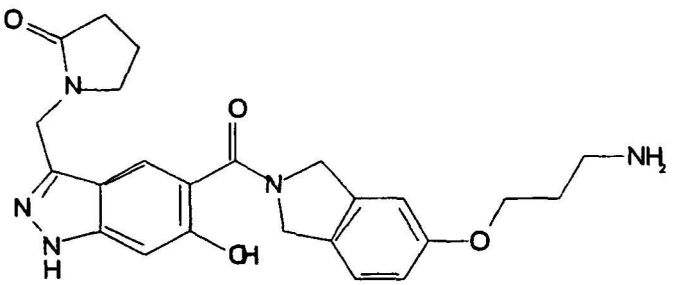
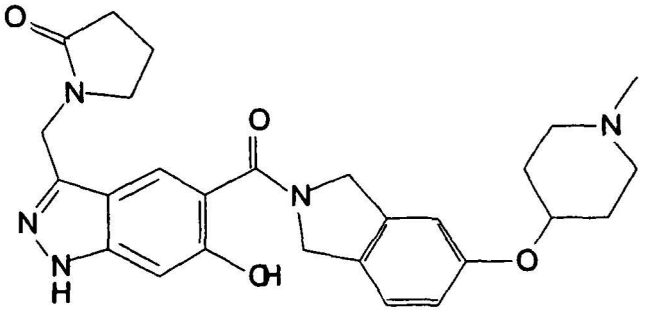
"A474"			
"A475"			
"A476"			
"A477"			

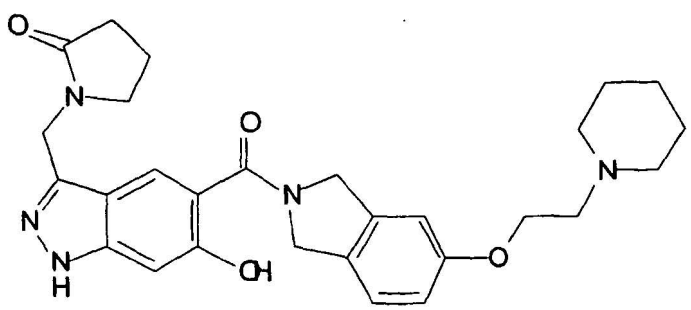
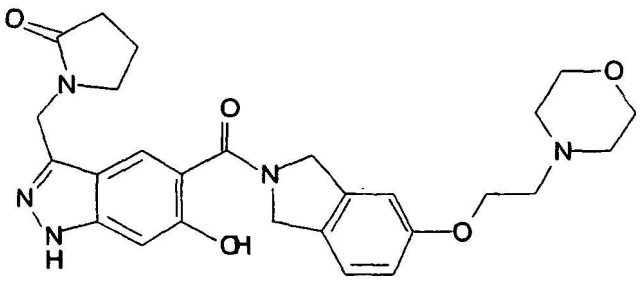
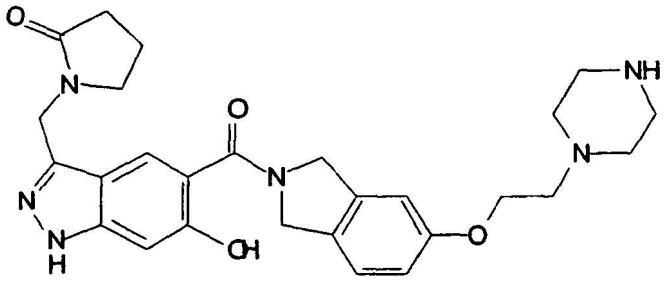
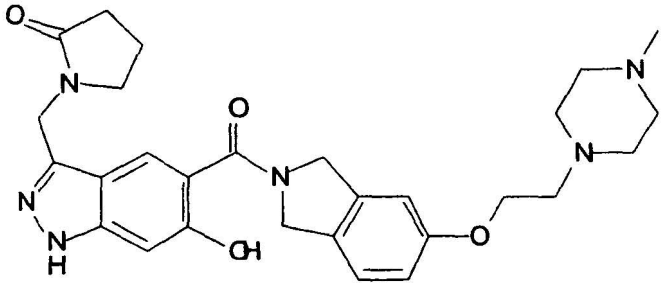
"A478"			
"A479"			
"A480"			

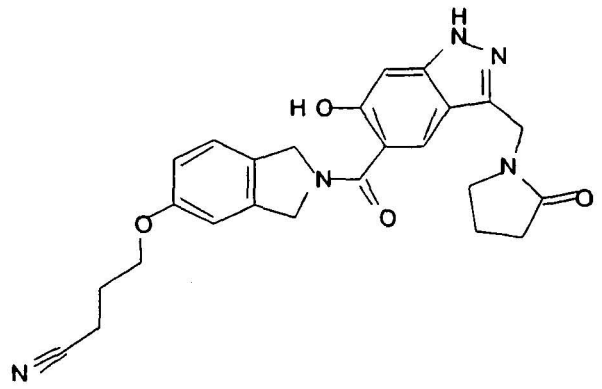
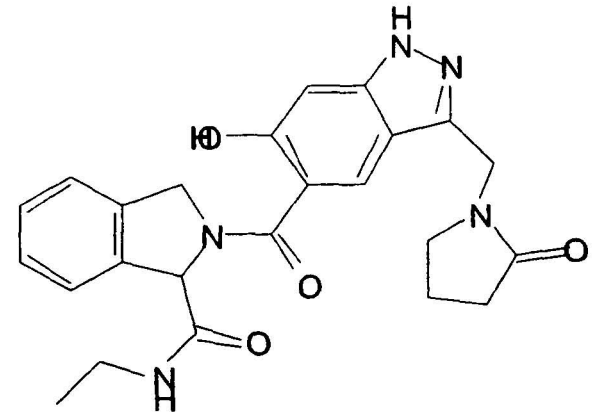
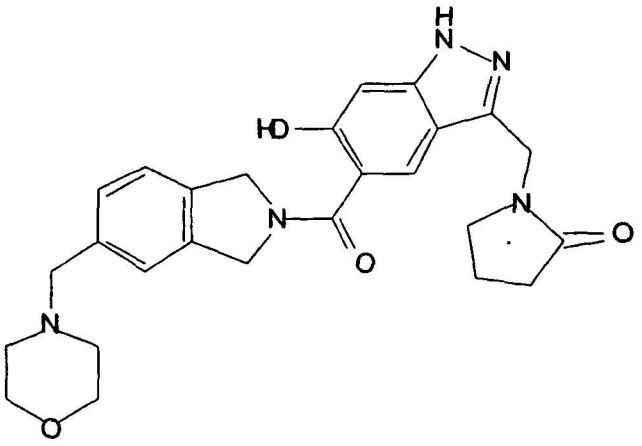
"A481"			
"A482"			
"A483"			
"A484"			

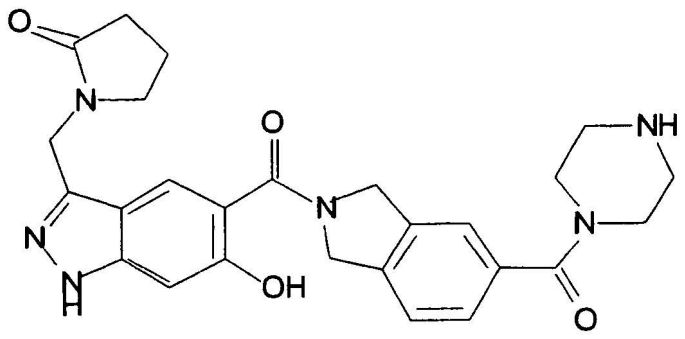
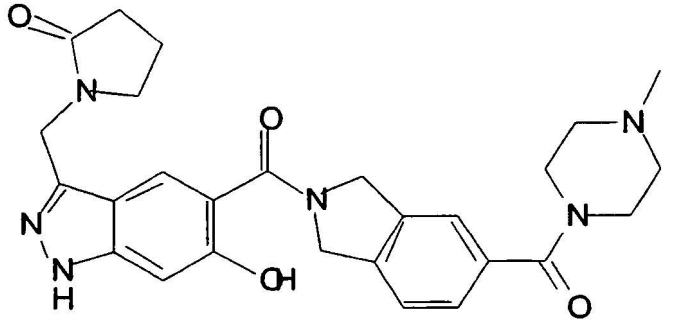
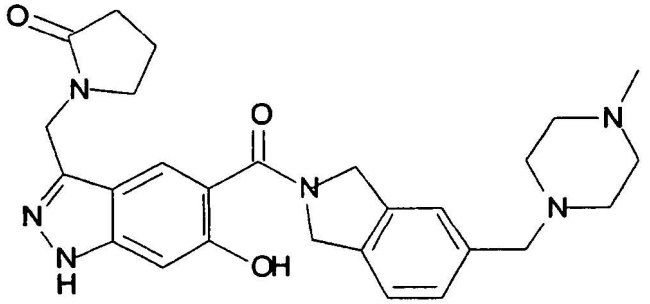
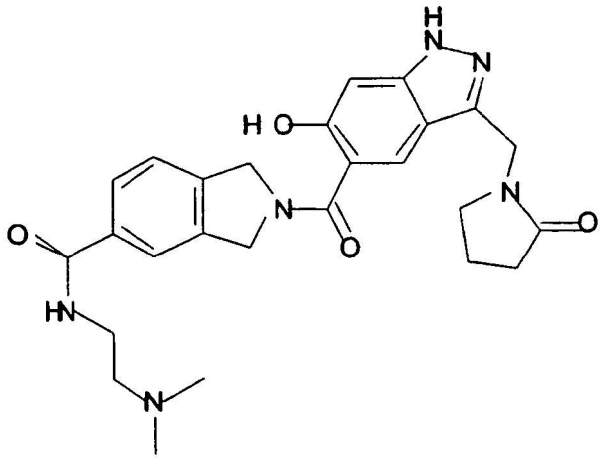
"A485"			
"A486"			
"A487"			
"A488"			

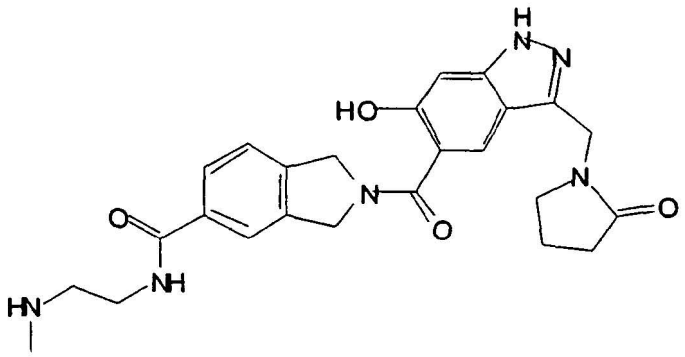
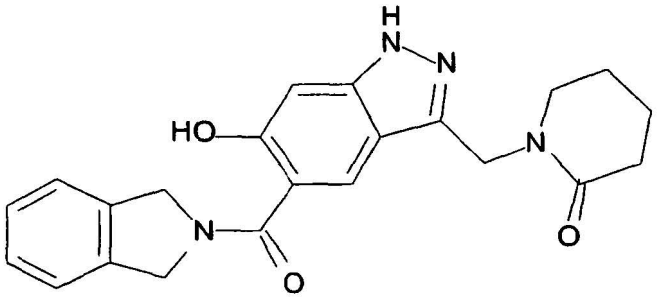
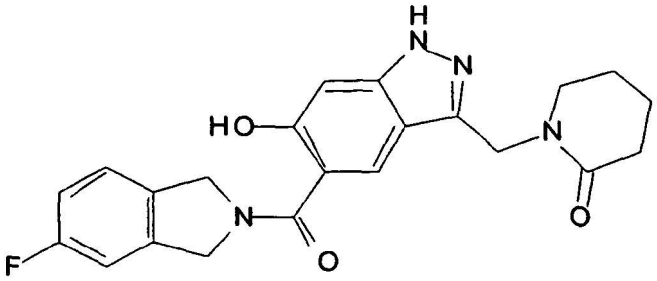
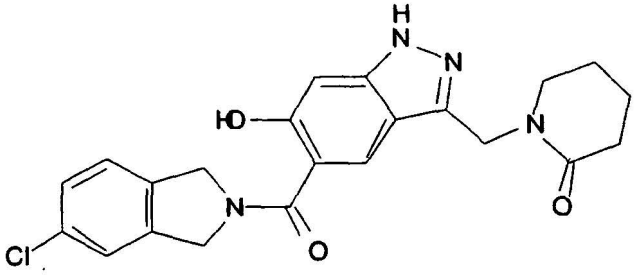
"A489"			
"A490"			
"A491"			
"A492"			

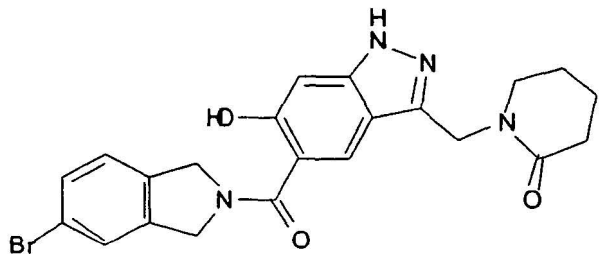
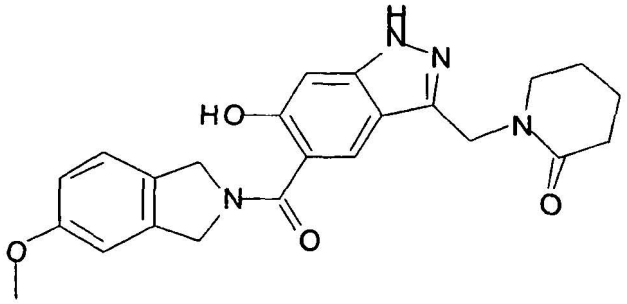
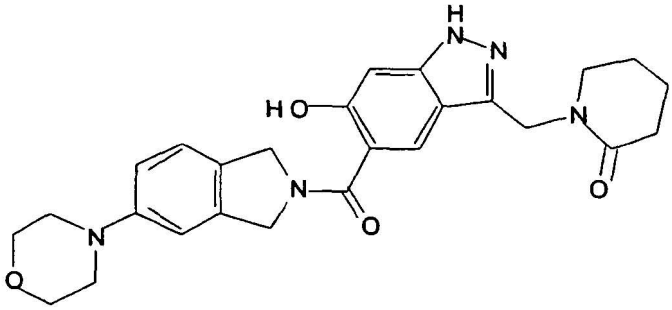
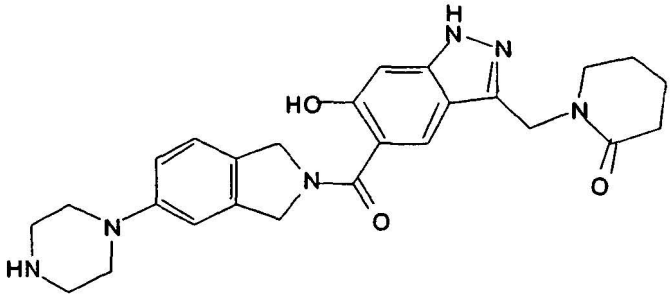
"A493"			
"A494"			
"A495"			
"A496"			

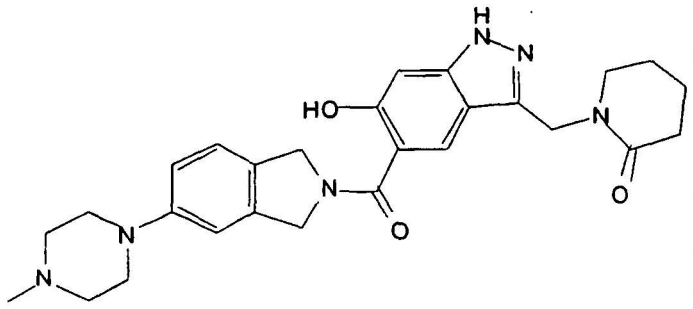
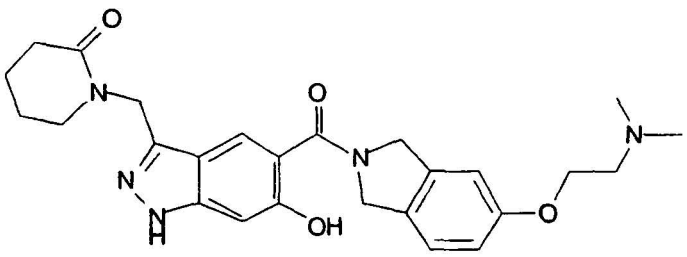
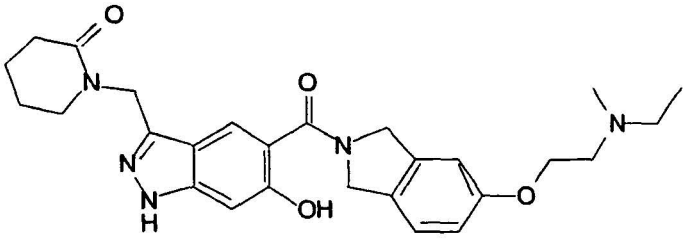
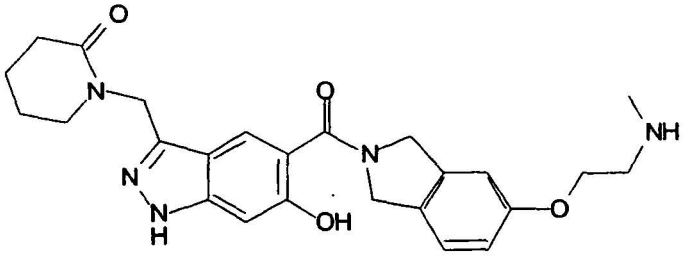
"A497"			
"A498"			
"A499"			
"A500"			

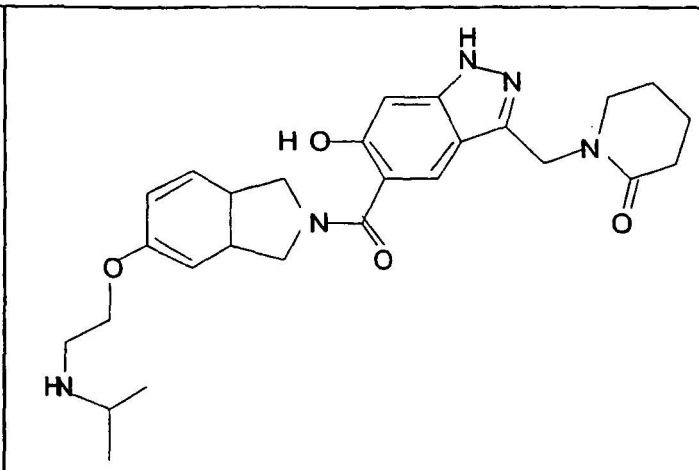
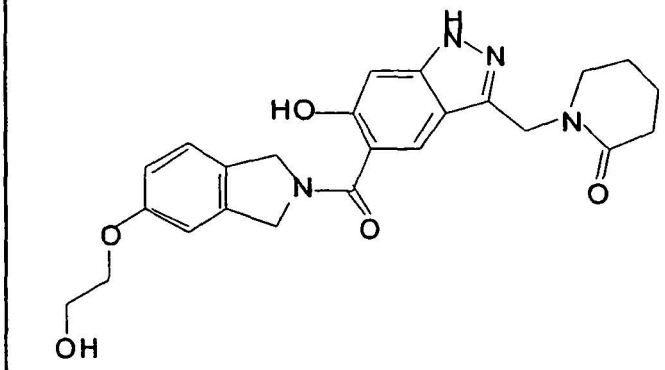
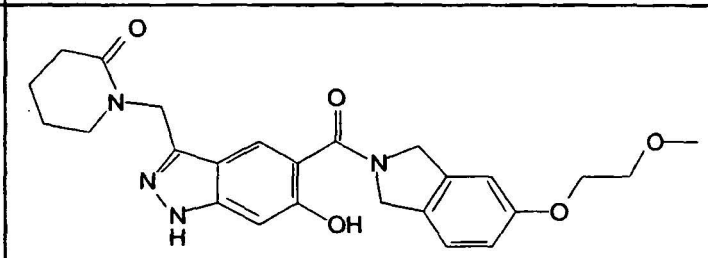
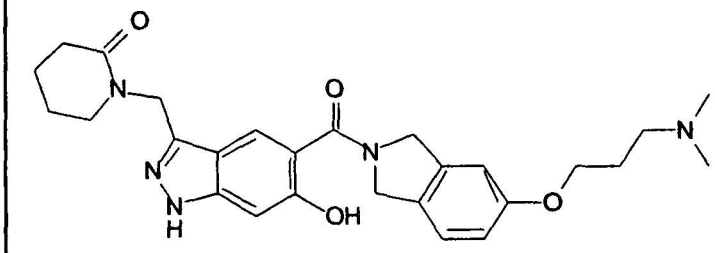
"A501"			
"A502"			
"A503"			

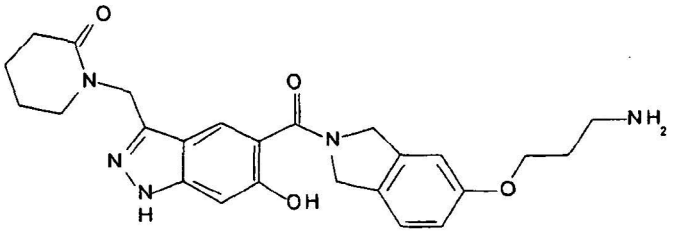
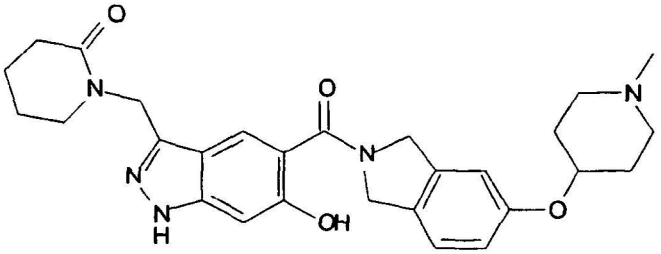
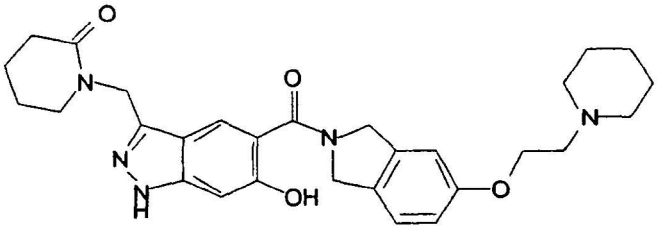
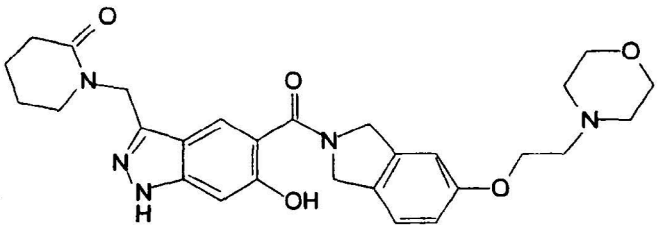
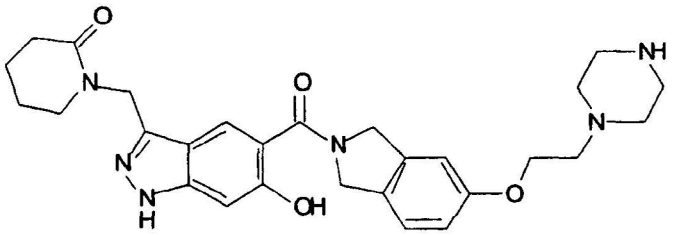
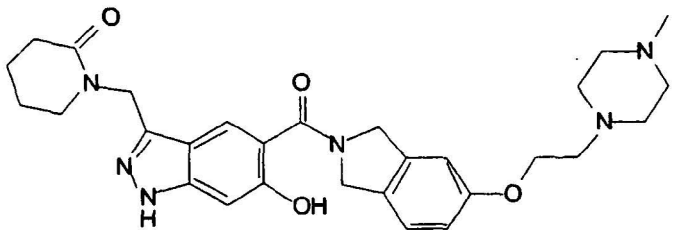
"A504"			
"A505"			
"A506"			
"A507"			

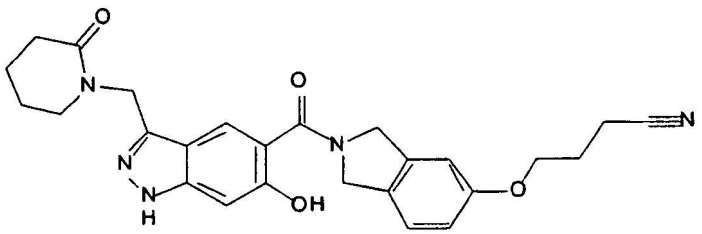
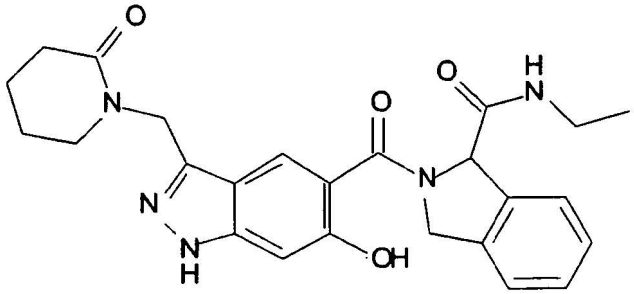
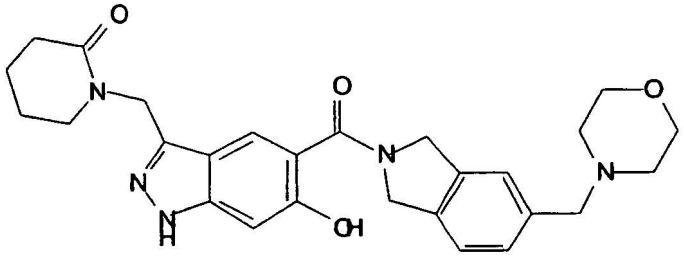
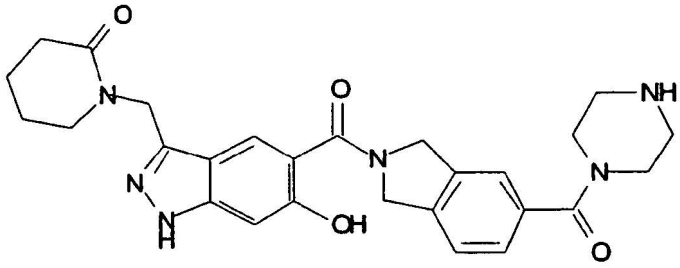
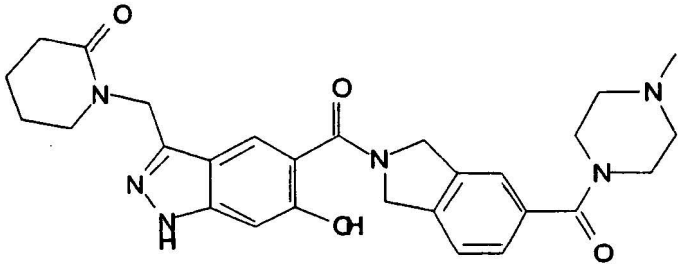
"A508"			
"A509"			
"A510"			
"A511"			

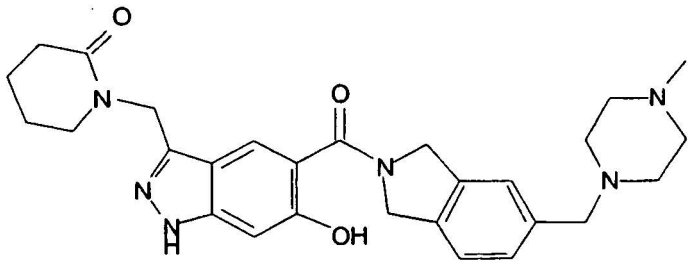
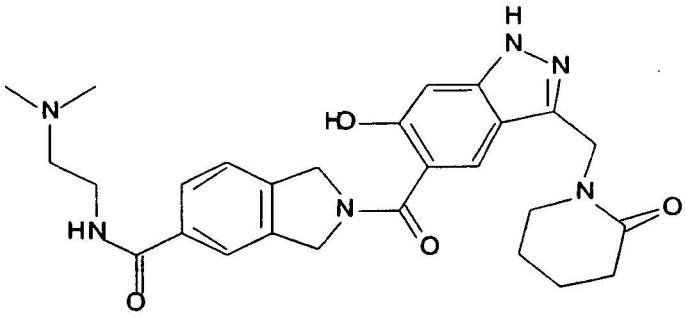
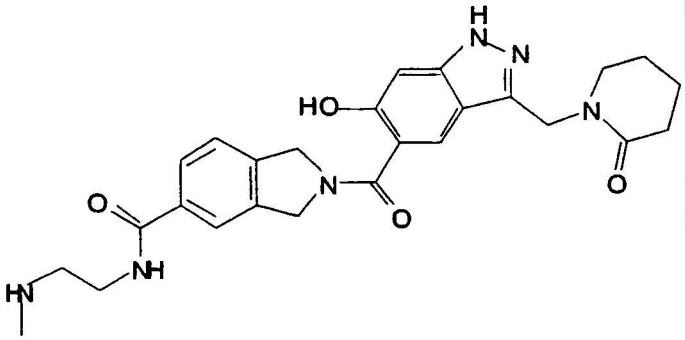
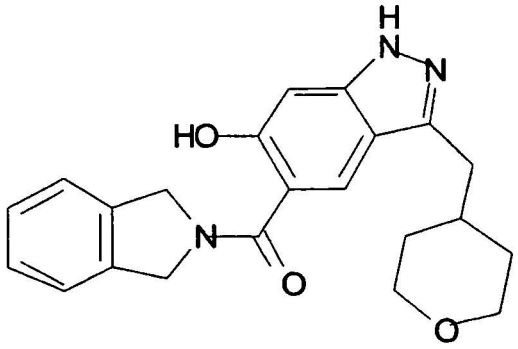
"A512"			
"A513"			
"A514"			
"A515"			

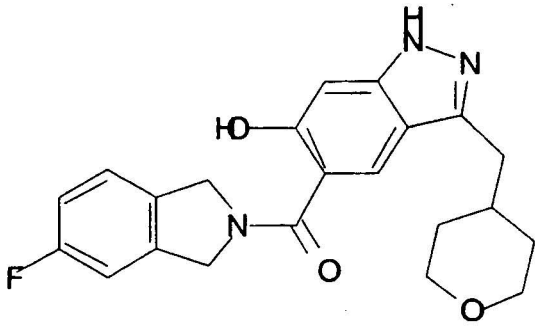
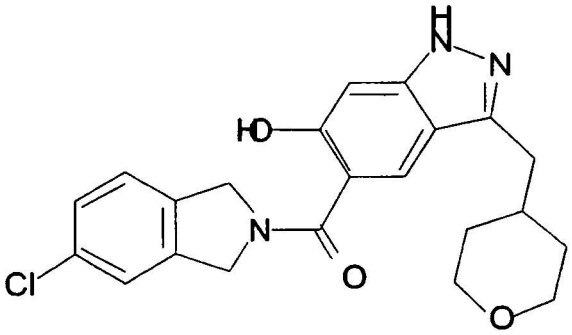
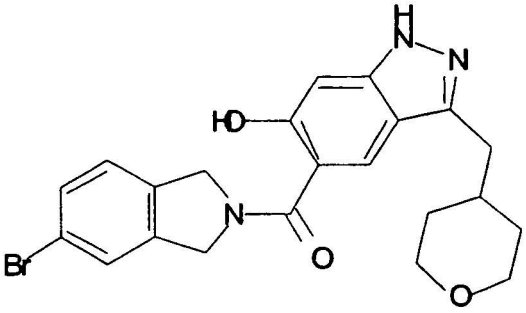
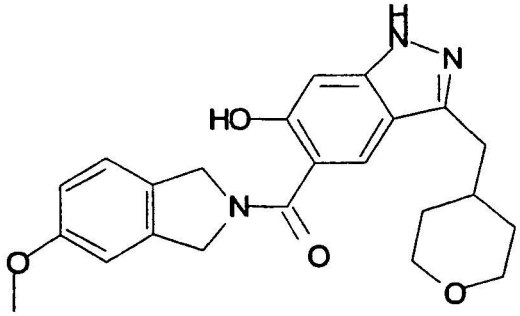
"A516"			
"A517"			
"A518"			
"A519"			

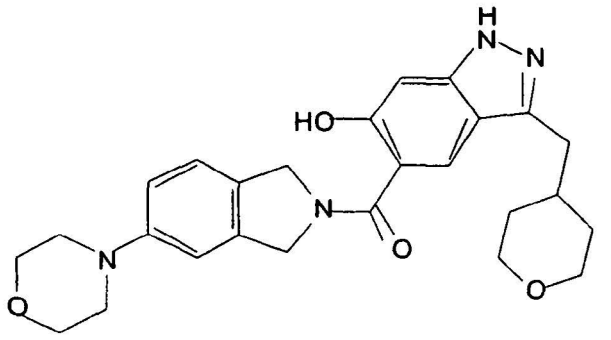
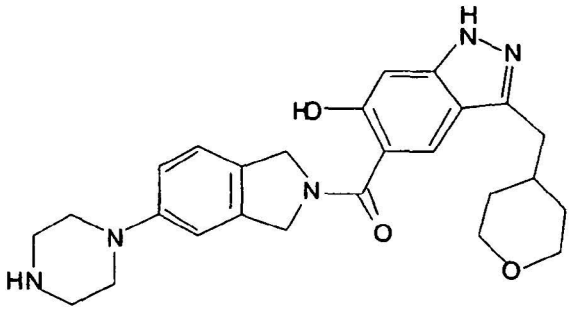
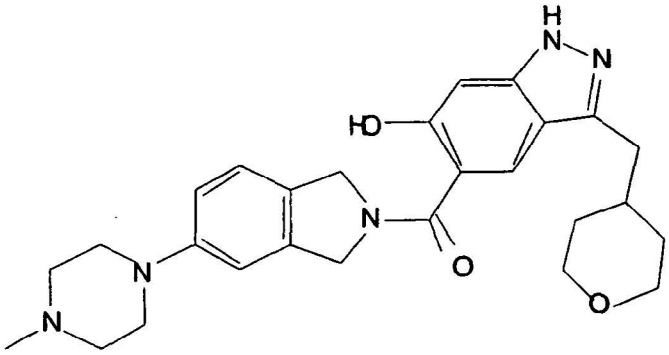
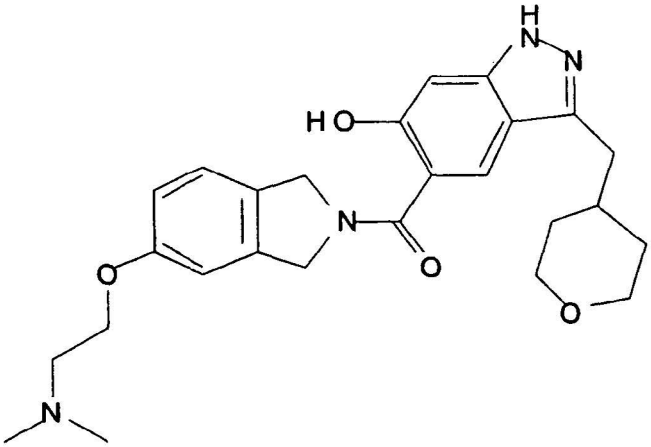
"A520"			
"A521"			
"A522"			
"A523"			

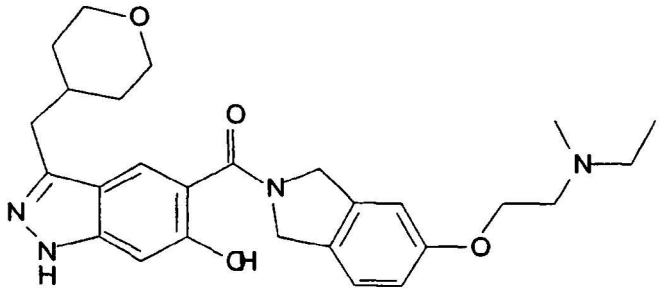
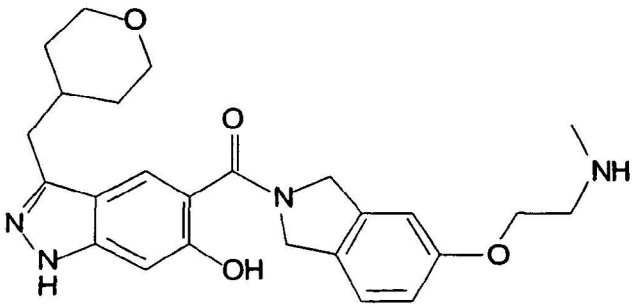
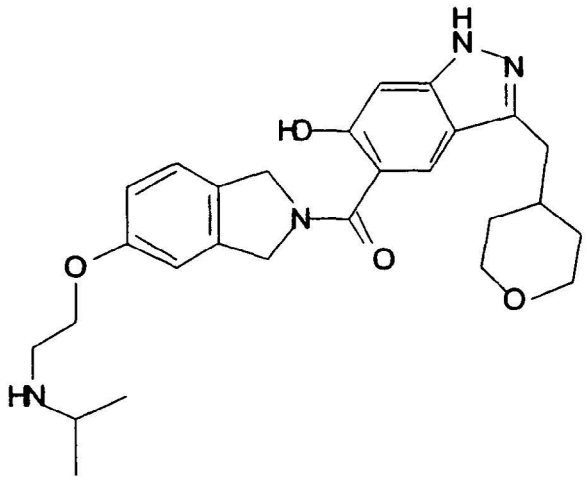
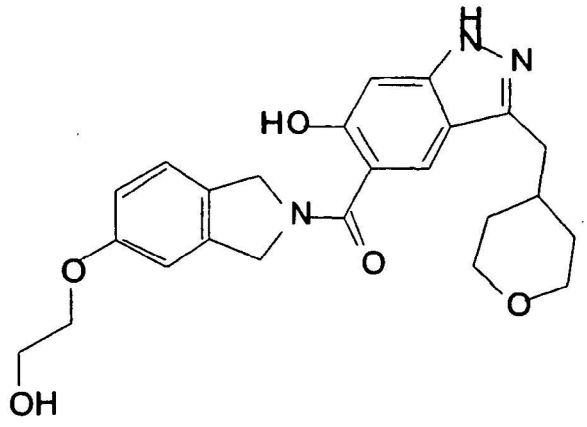
"A524"			
"A525"			
"A526"			
"A527"			
"A528"			
"A529"			

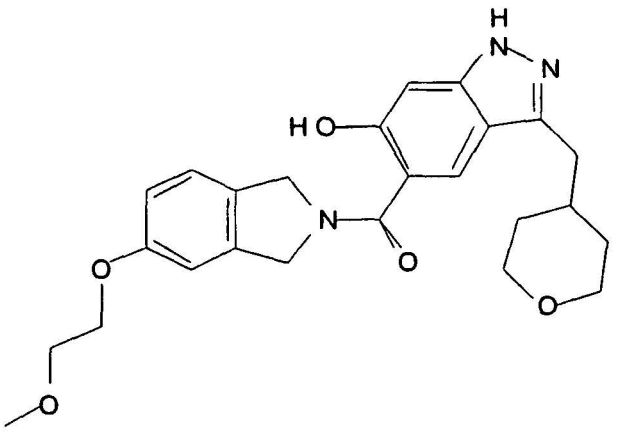
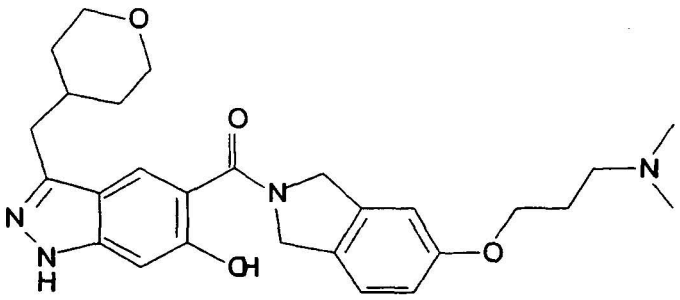
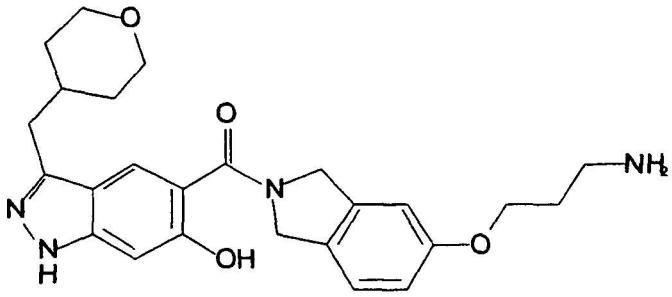
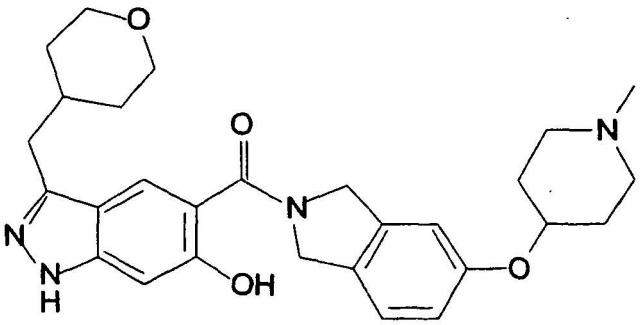
"A530"			
"A531"			
"A532"			
"A533"			
"A534"			

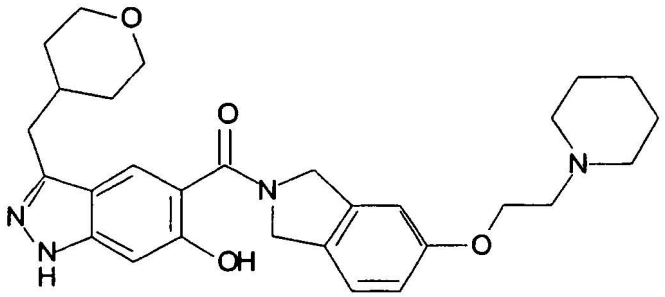
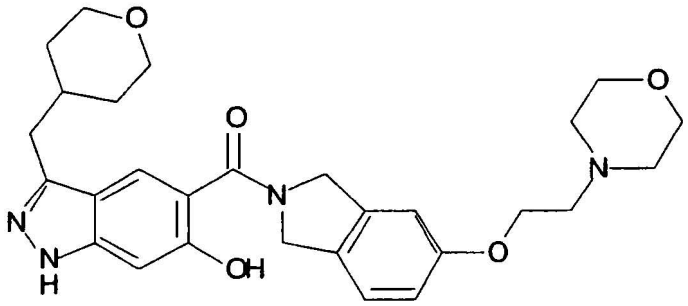
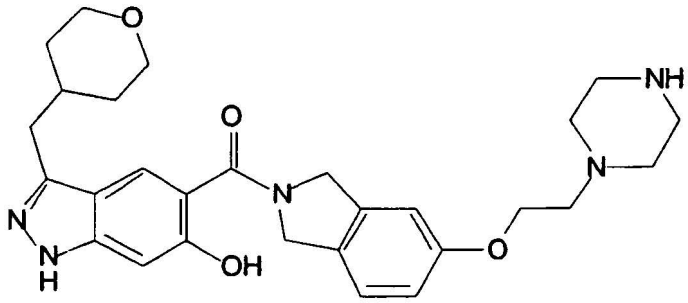
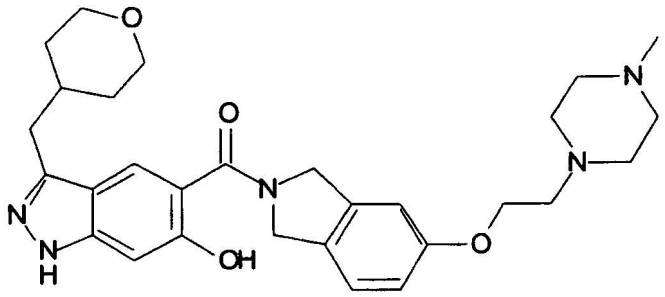
"A535"			
"A536"			
"A537"			
"A538"			

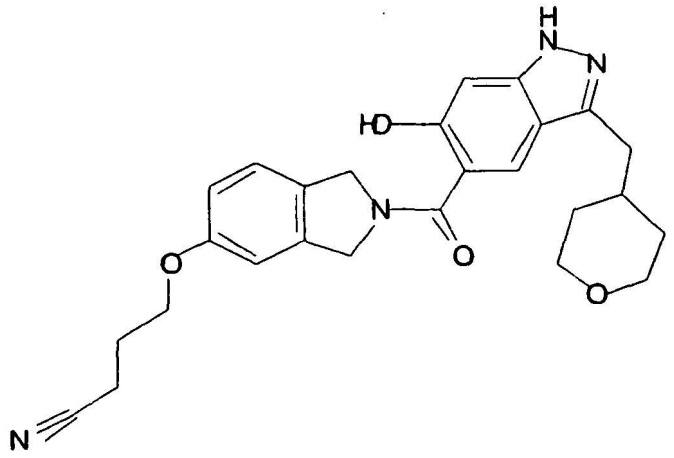
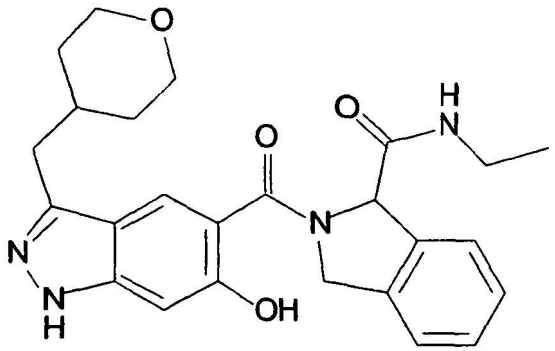
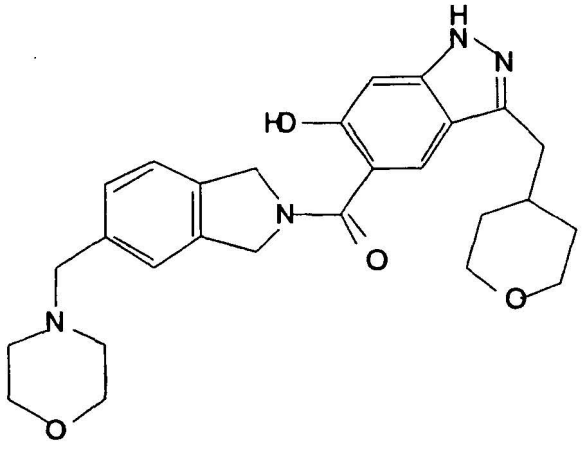
"A539"			
"A540"			
"A541"			
"A542"			

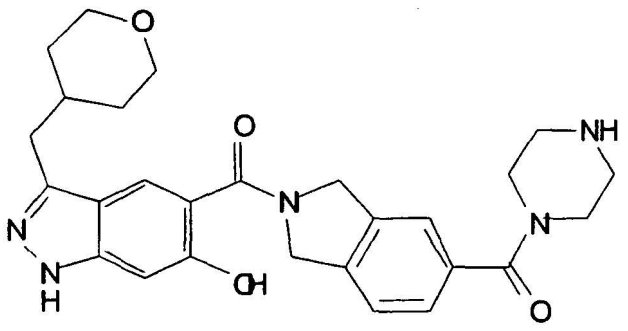
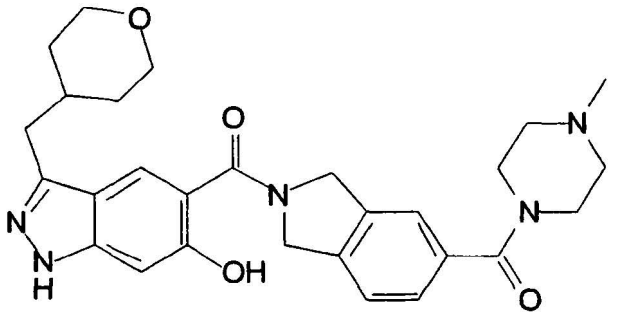
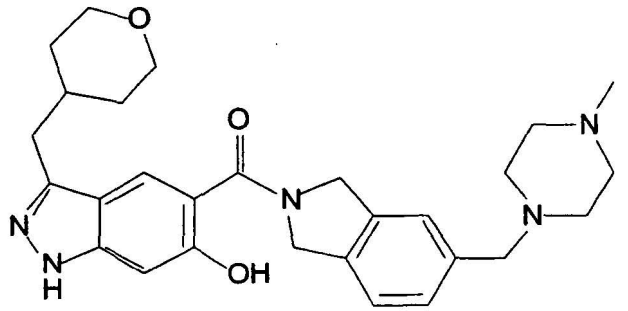
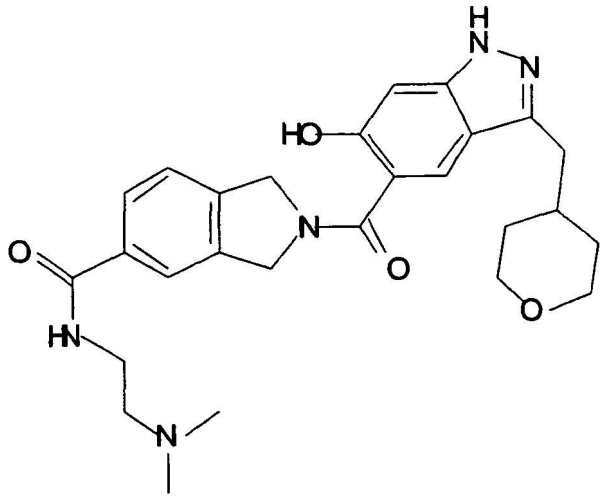
"A543"			
"A544"			
"A545"			
"A546"			

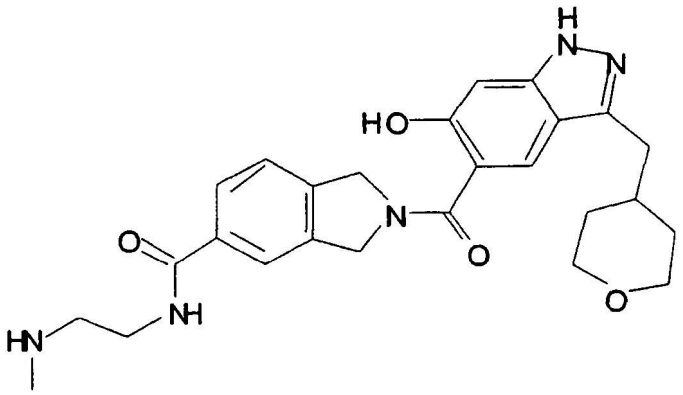
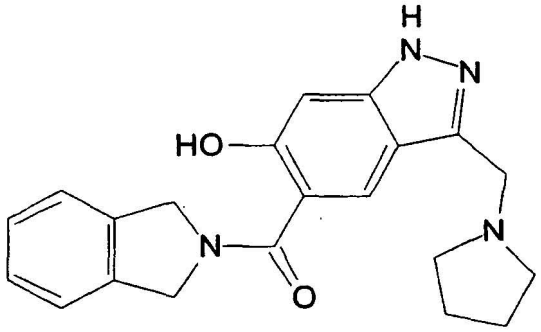
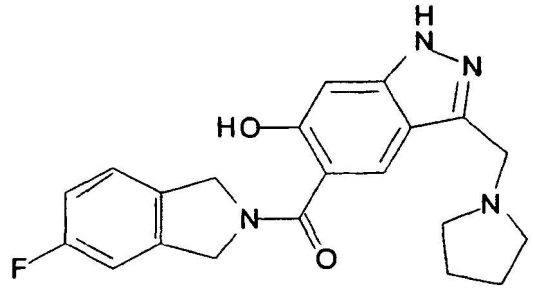
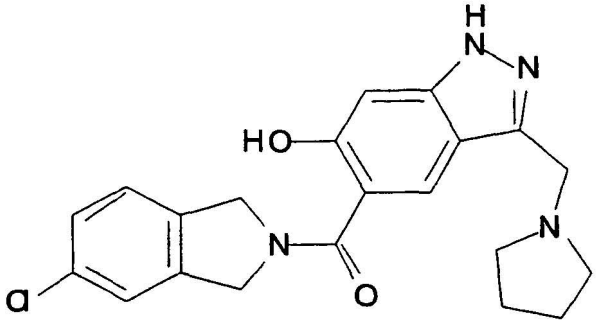
"A547"			
"A548"			
"A549"			
"A550"			

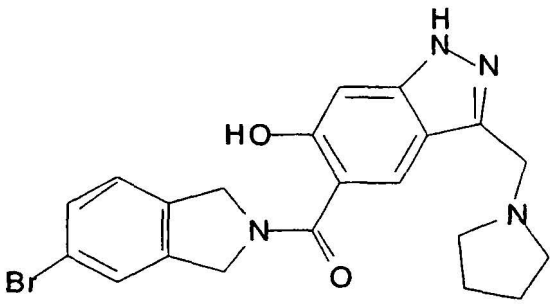
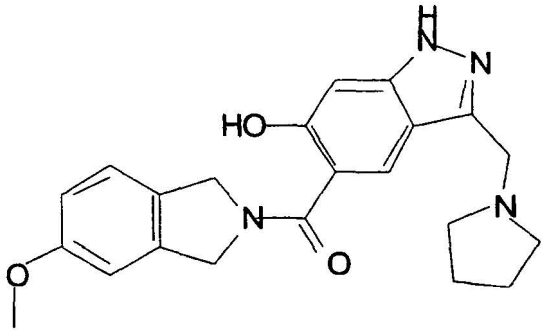
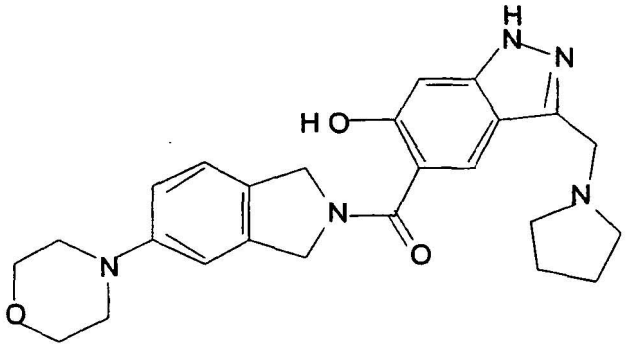
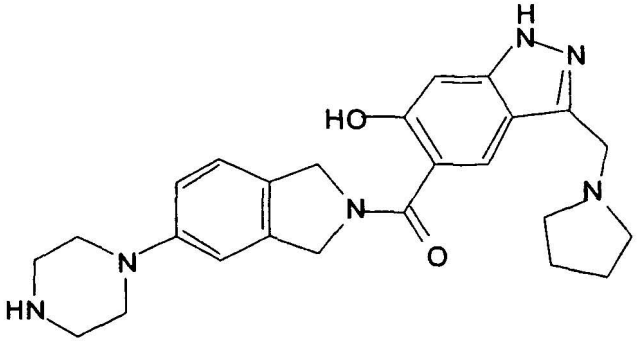
"A551"			
"A552"			
"A553"			
"A554"			

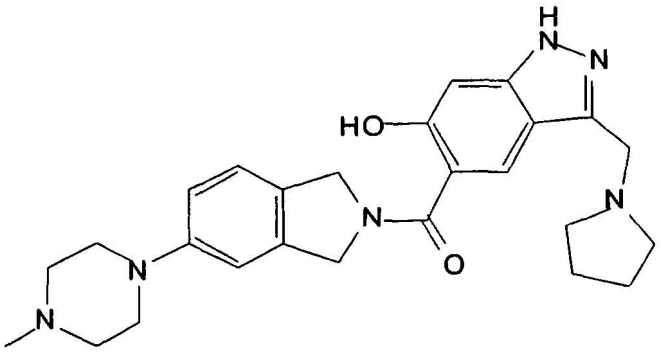
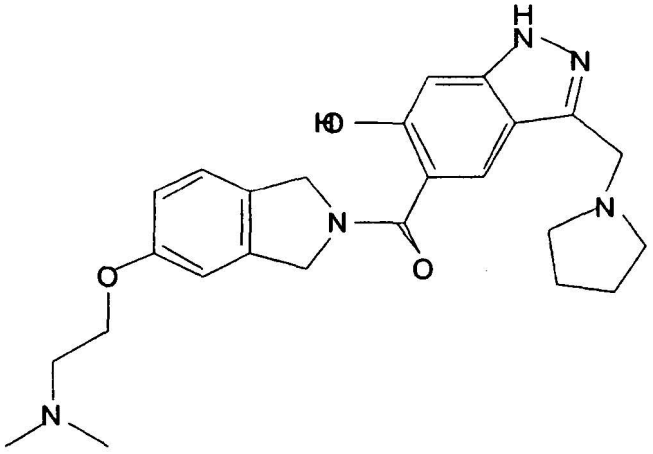
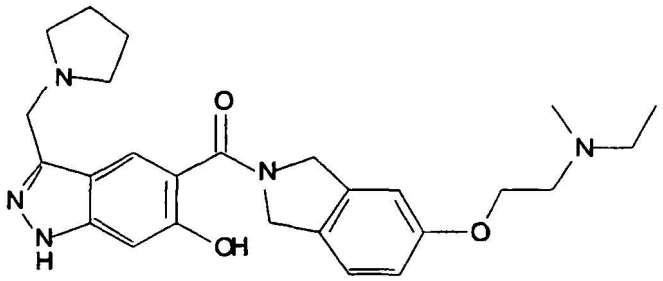
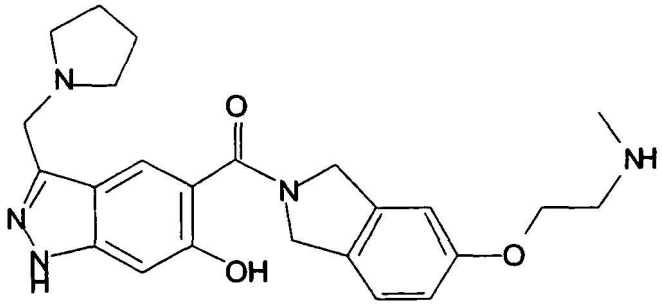
"A555"			
"A556"			
"A557"			
"A558"			

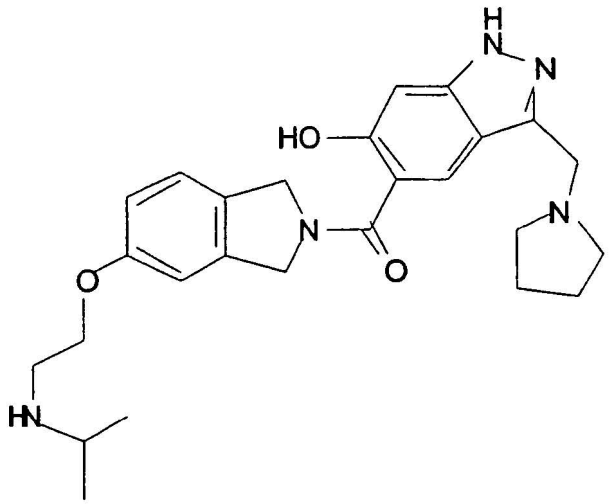
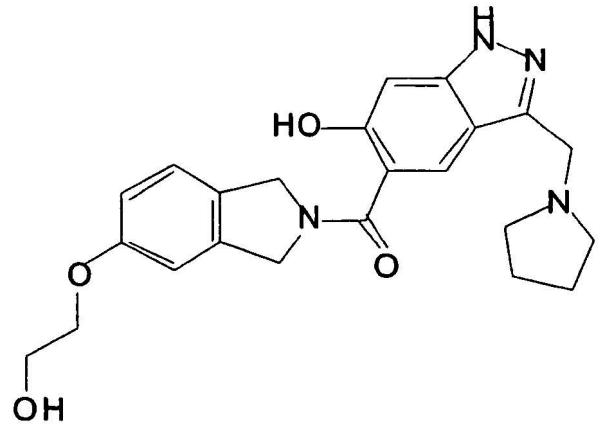
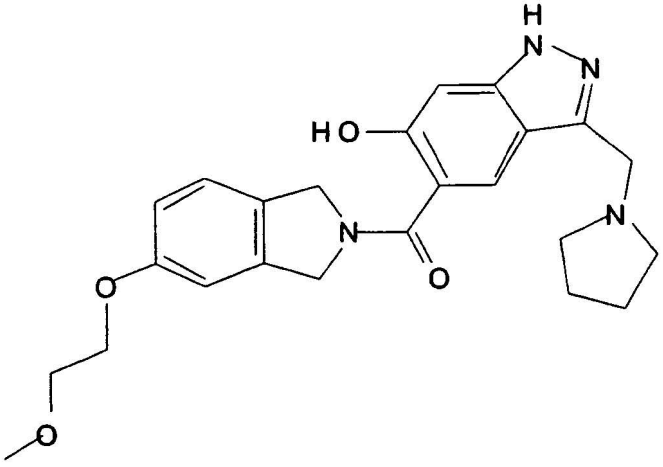
"A559"			
"A560"			
"A561"			

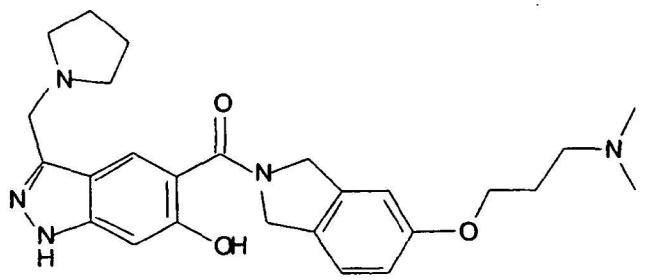
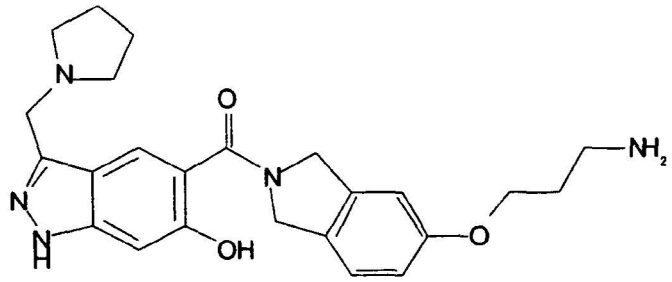
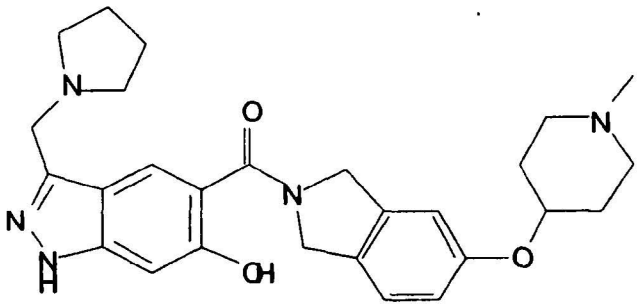
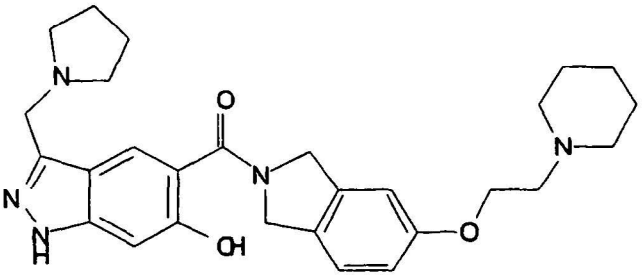
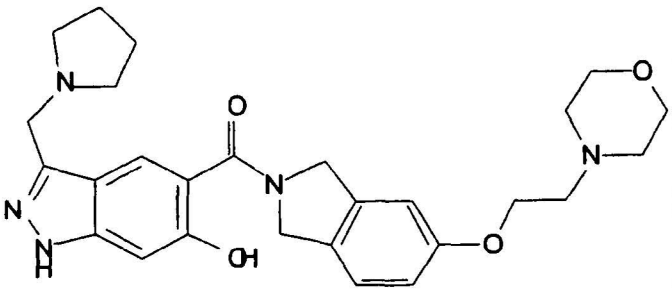
"A562"			
"A563"			
"A564"			
"A565"			

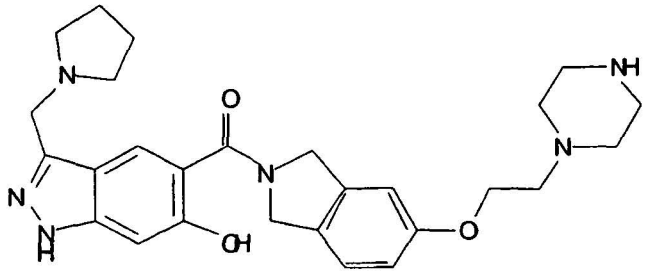
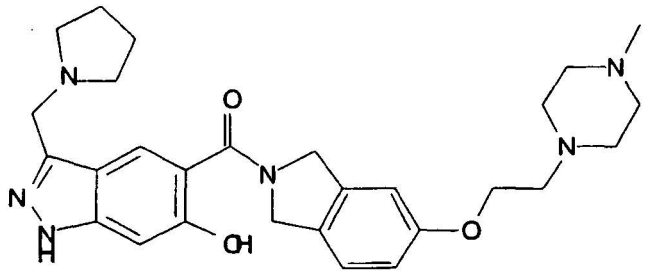
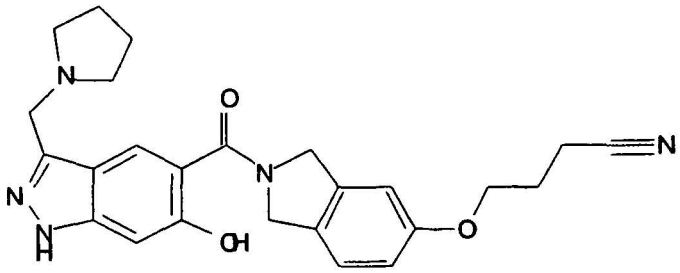
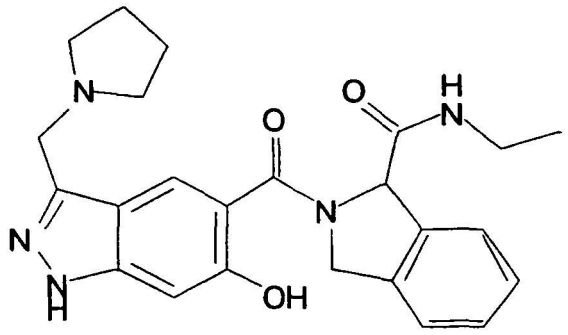
"A566"			
"A567"			
"A568"			
"A569"			

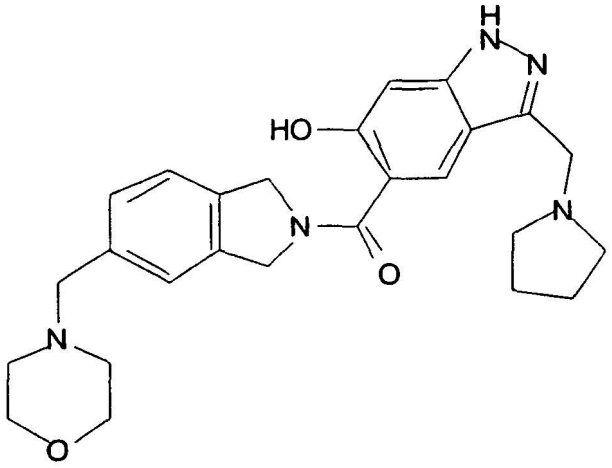
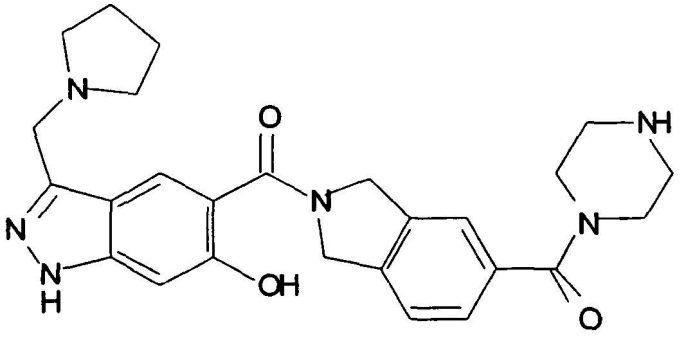
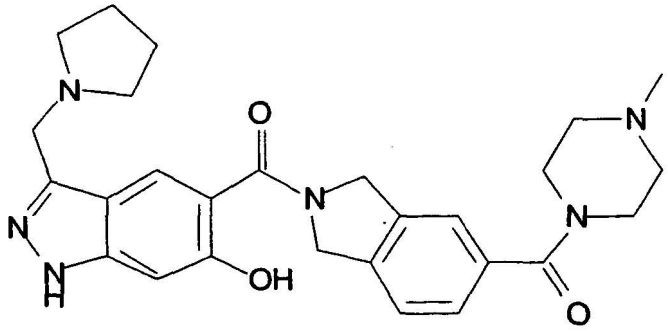
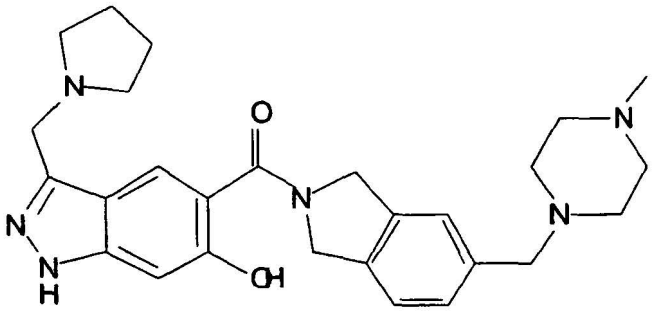
"A570"			
"A571"			
"A572"			
"A573"			

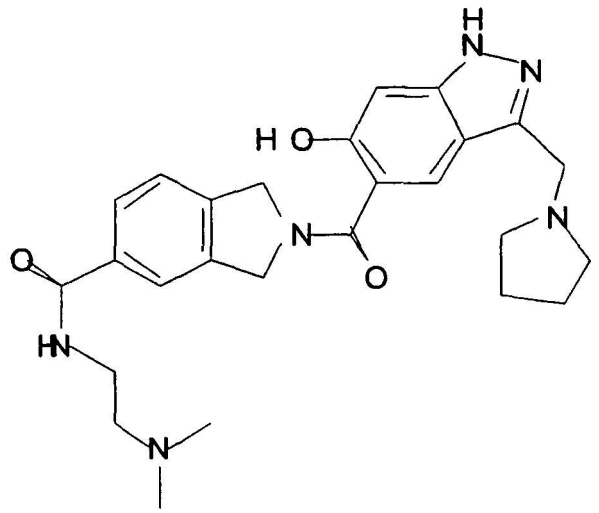
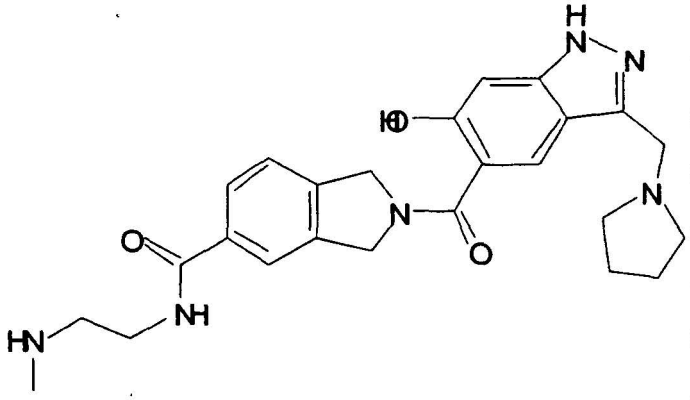
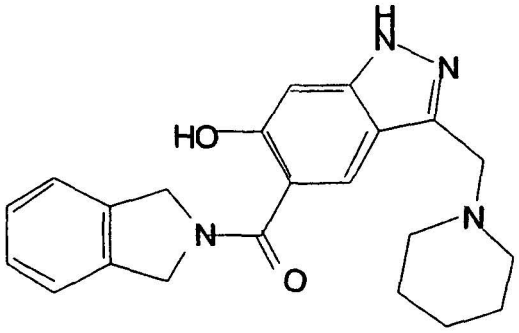
"A574"			
"A575"			
"A576"			
"A577"			

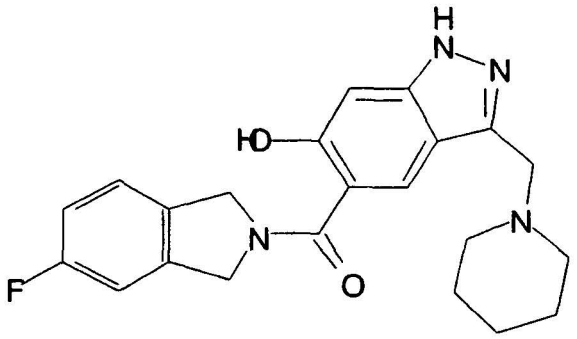
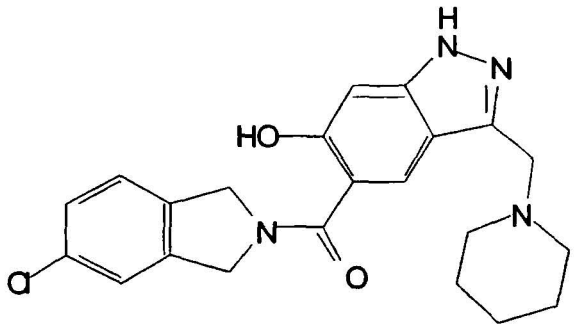
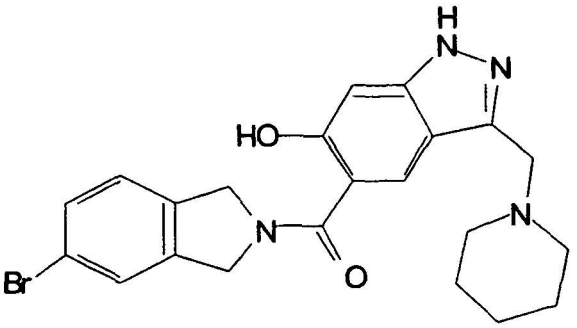
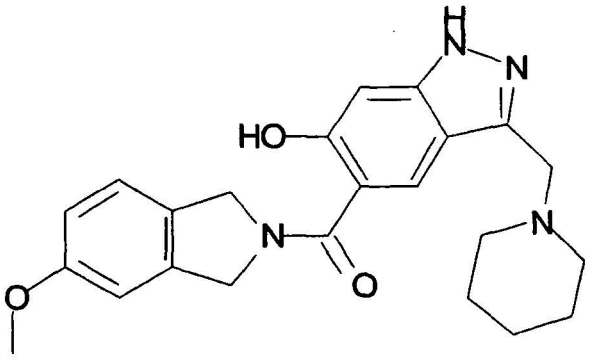
"A578"			
"A579"			
"A580"			

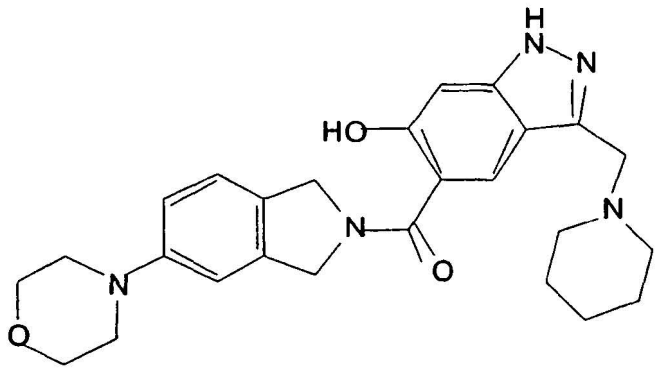
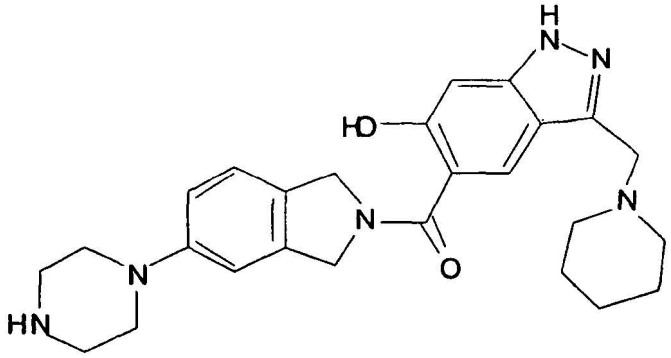
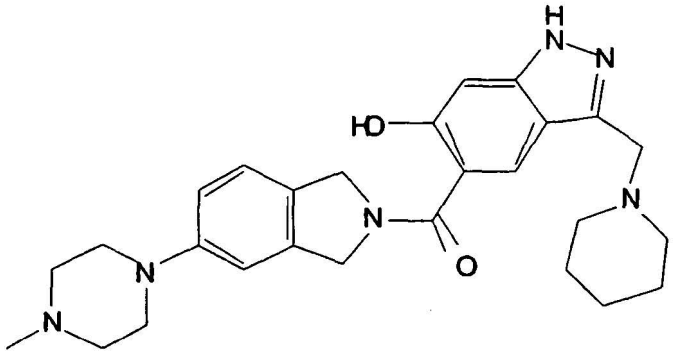
"A581"			
"A582"			
"A583"			
"A584"			
"A585"			

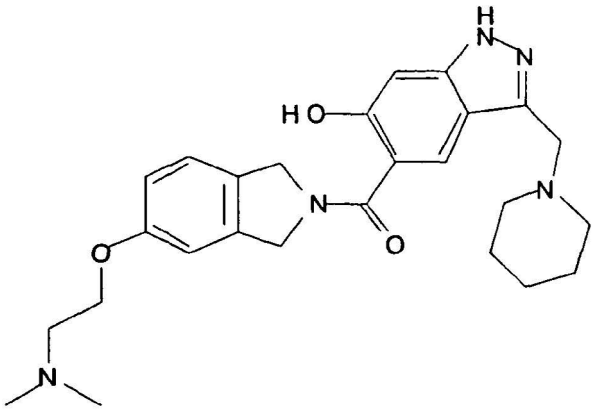
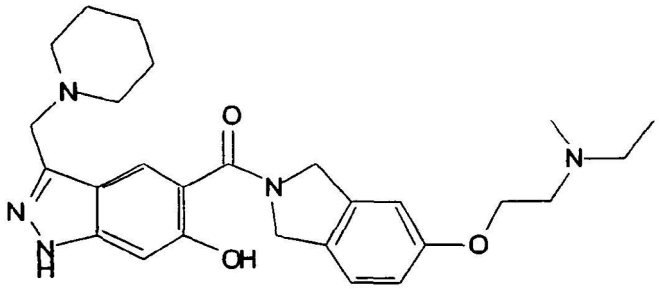
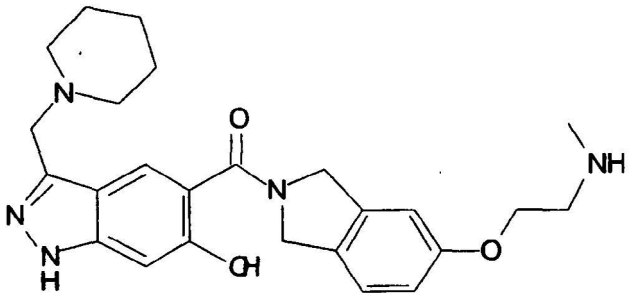
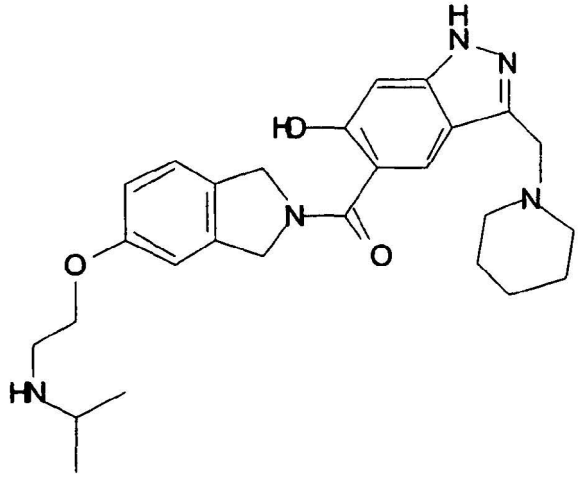
"A586"			
"A587"			
"A588"			
"A589"			

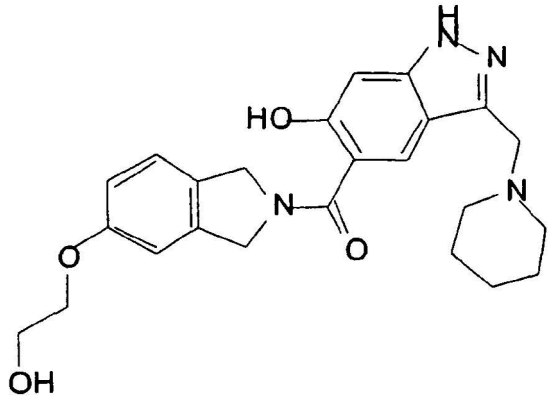
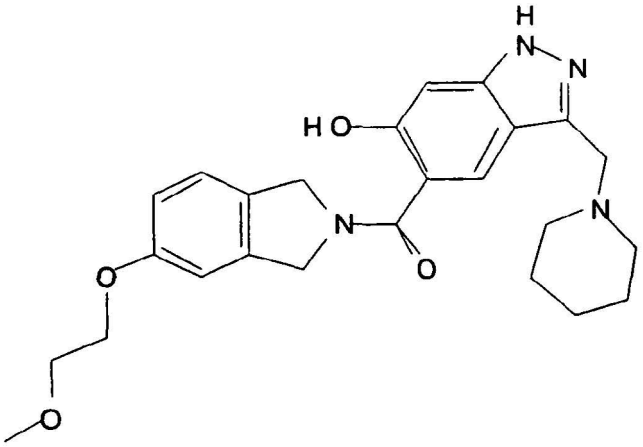
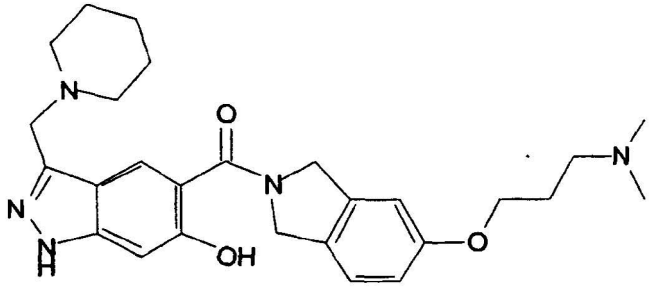
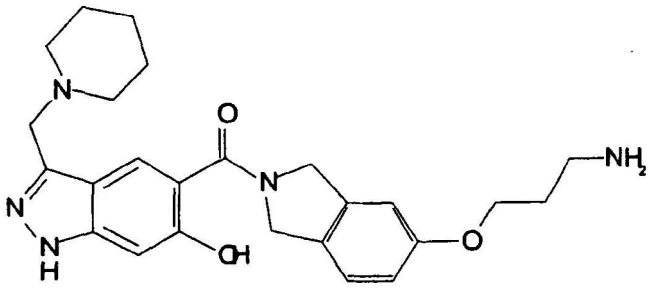
"A590"			
"A591"			
"A592"			
"A593"			

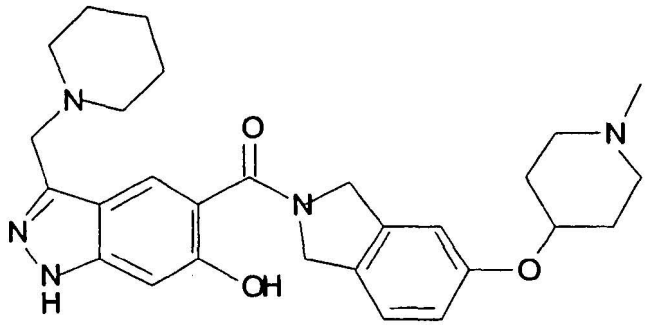
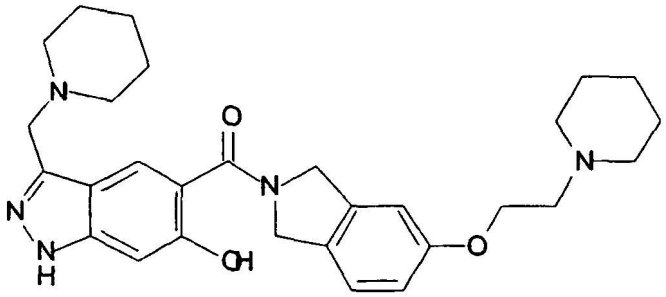
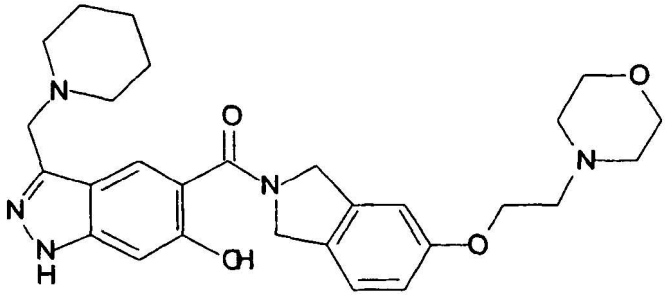
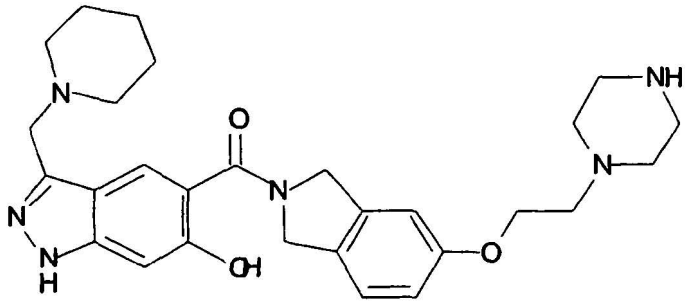
"A594"			
"A595"			
"A596"			

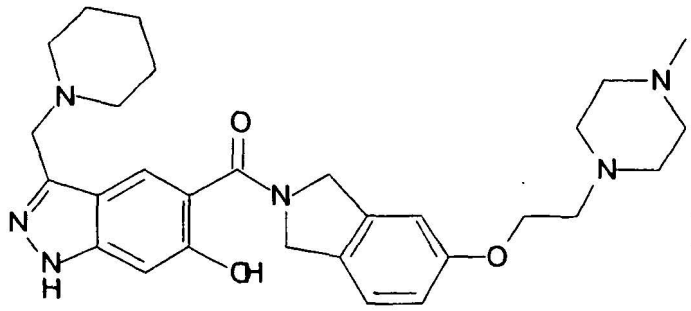
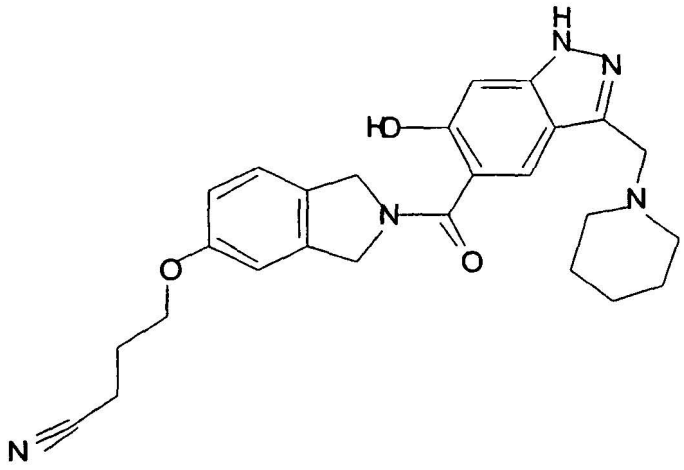
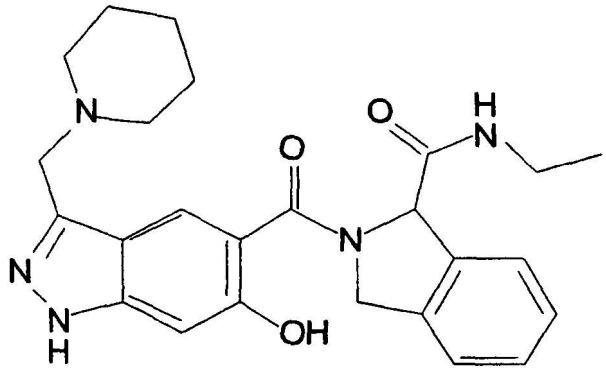
"A597"			
"A598"			
"A599"			
"A600"			

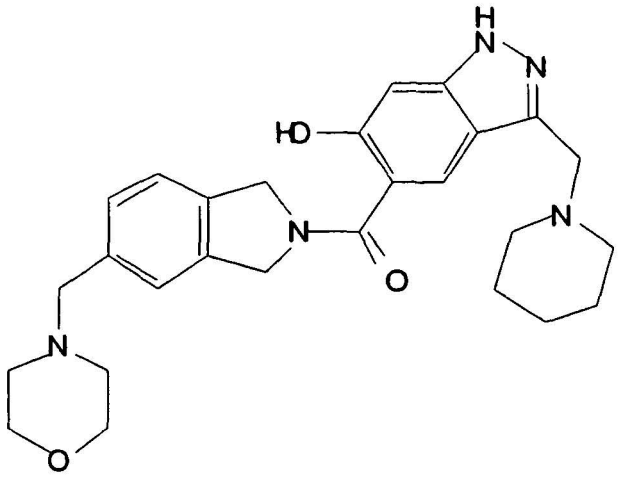
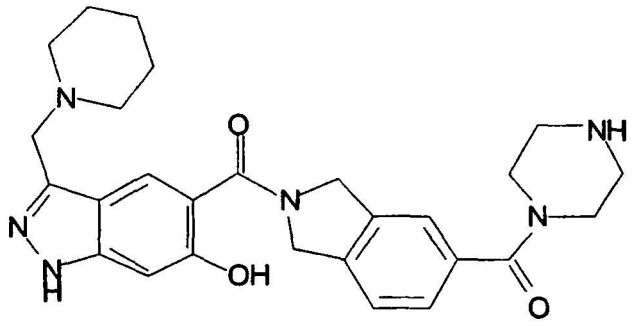
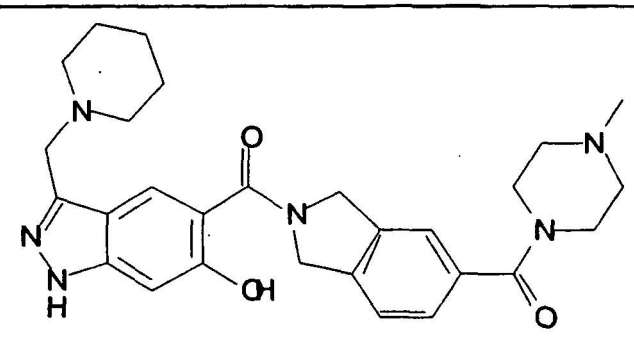
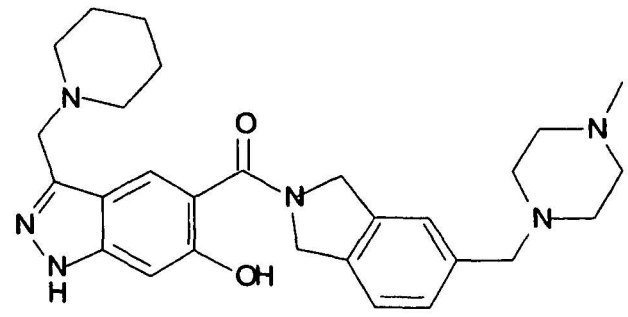
"A601"			
"A602"			
"A603"			

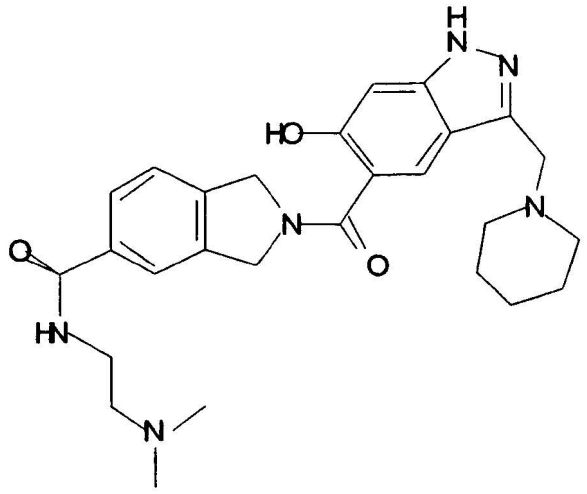
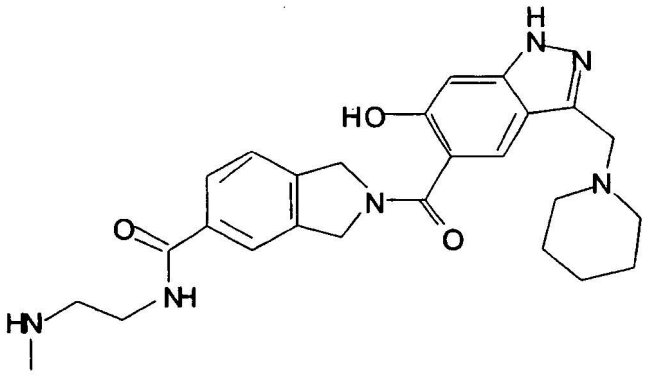
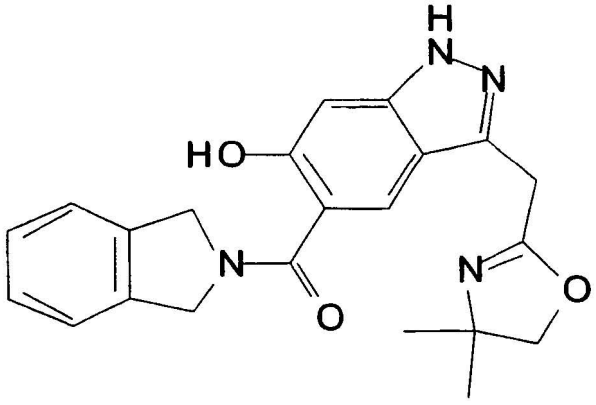
"A604"			
"A605"			
"A606"			
"A607"			

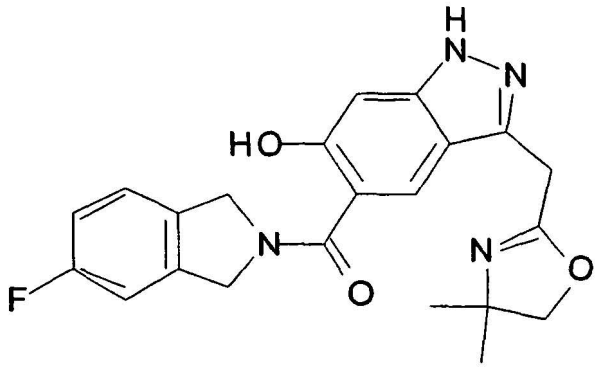
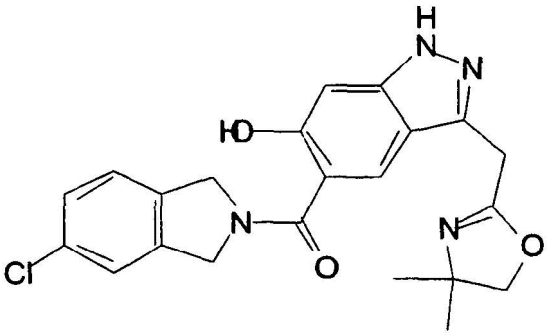
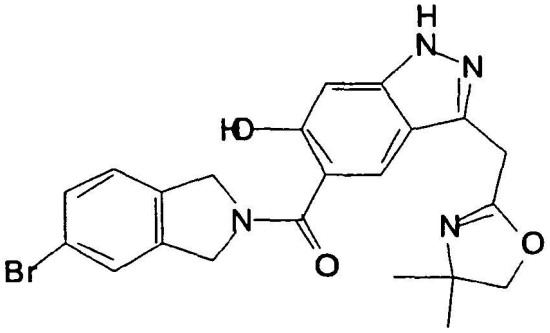
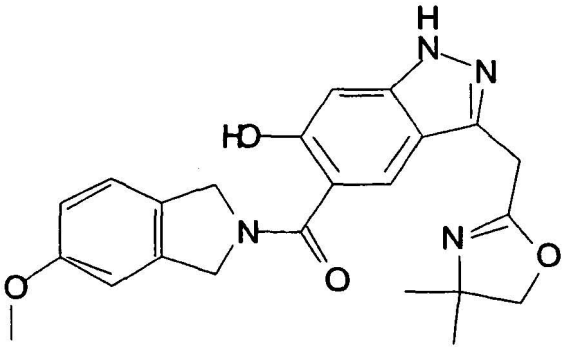
"A608"			
"A609"			
"A610"			
"A611"			

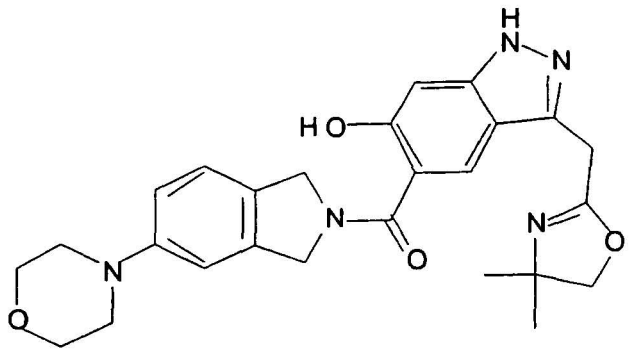
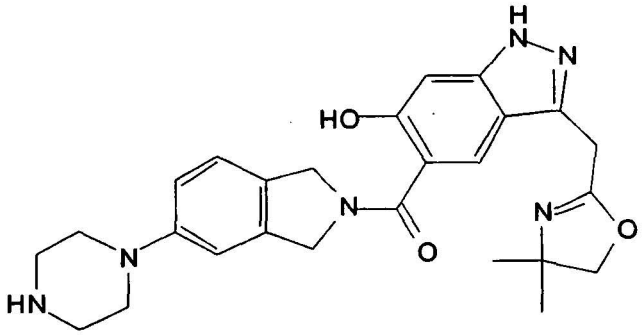
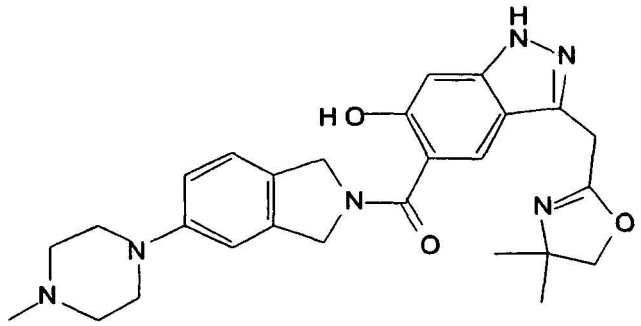
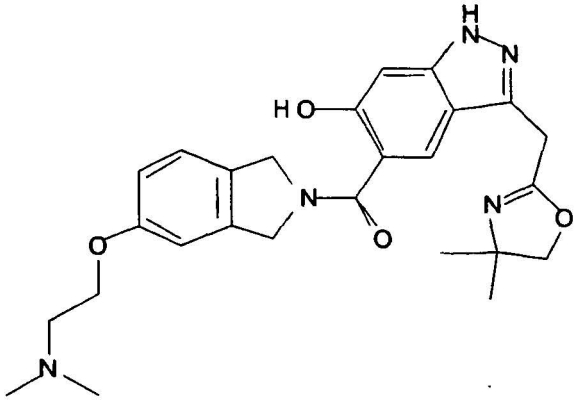
"A612"			
"A613"			
"A614"			
"A615"			

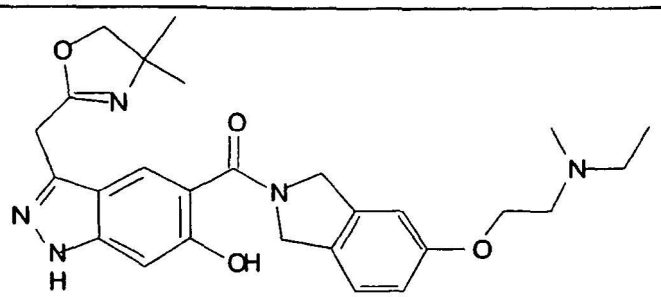
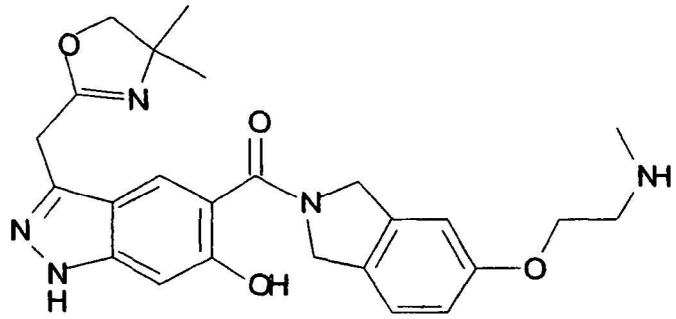
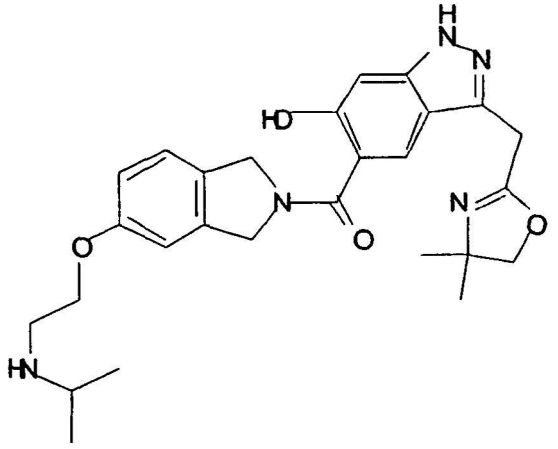
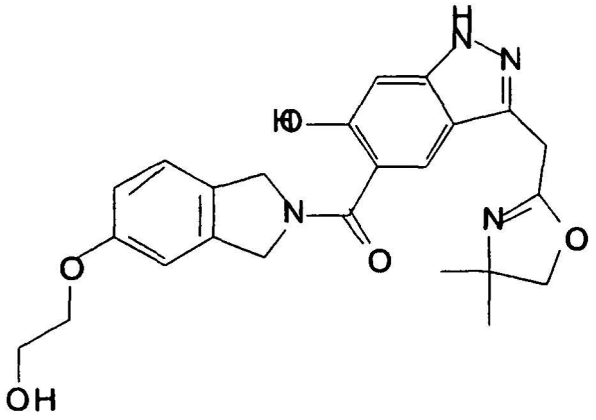
"A616"			
"A617"			
"A618"			

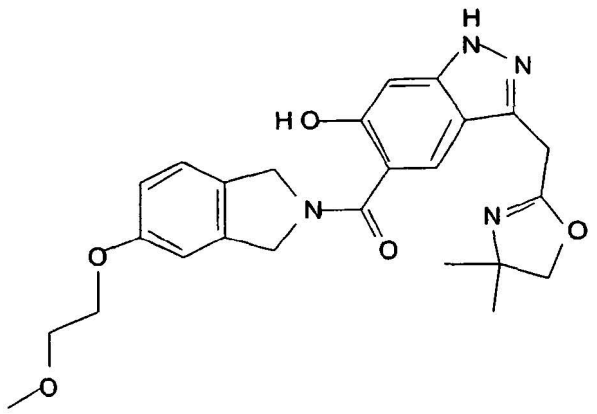
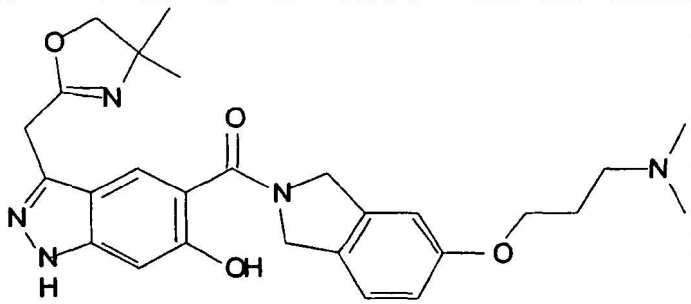
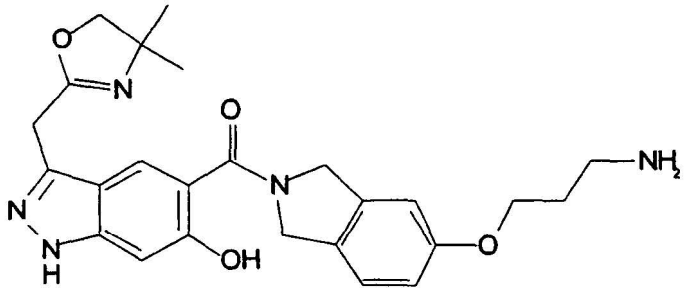
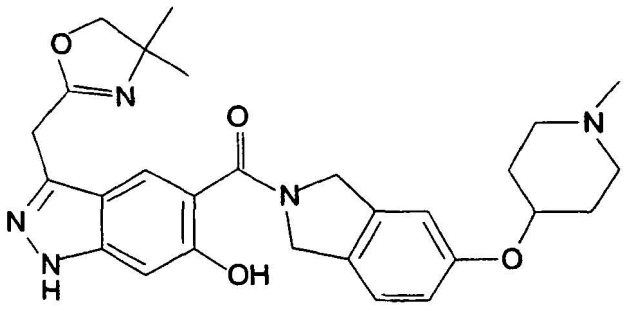
"A619"			
"A620"			
"A621"			
"A622"			

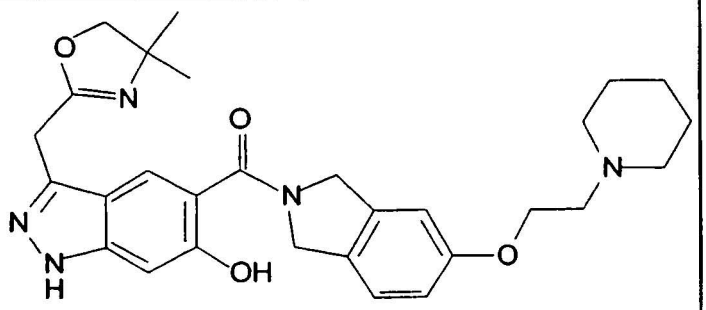
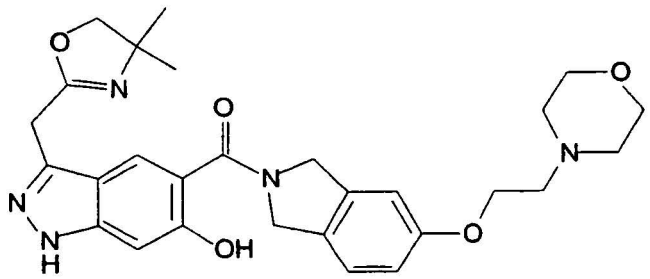
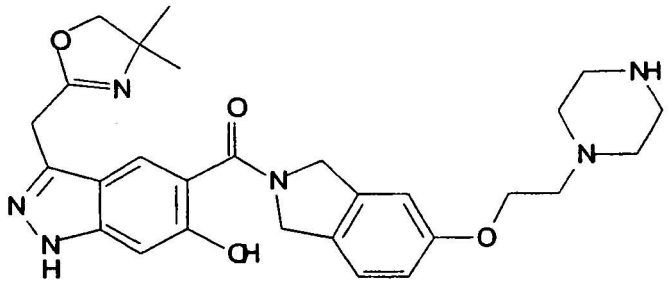
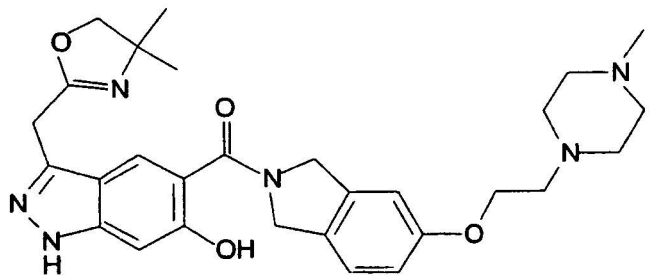
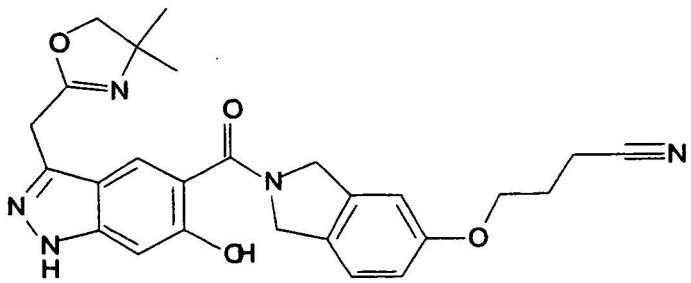
"A623"			
"A624"			
"A625"			

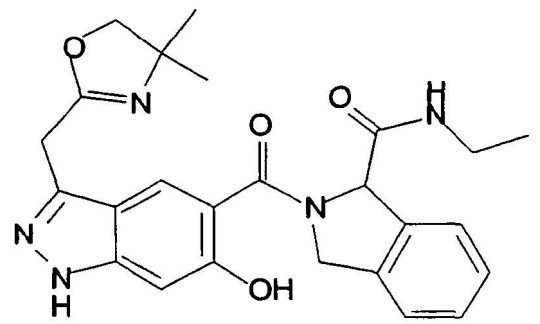
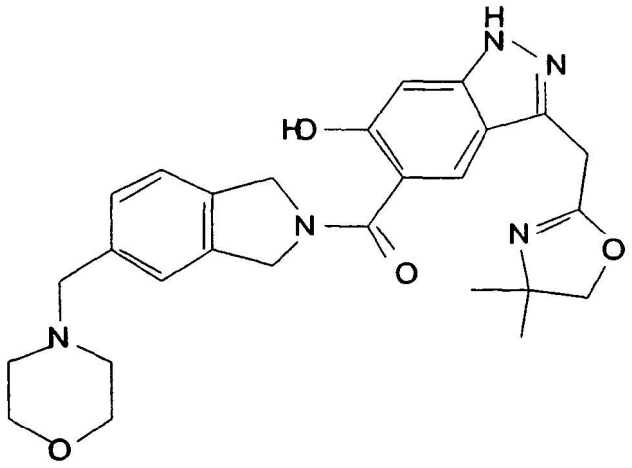
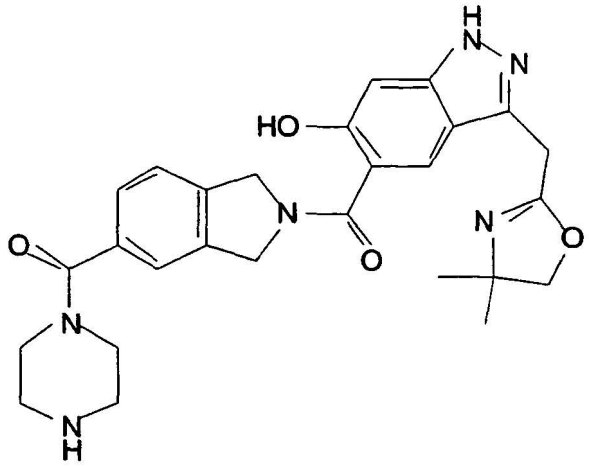
"A626"			
"A627"			
"A628"			
"A629"			

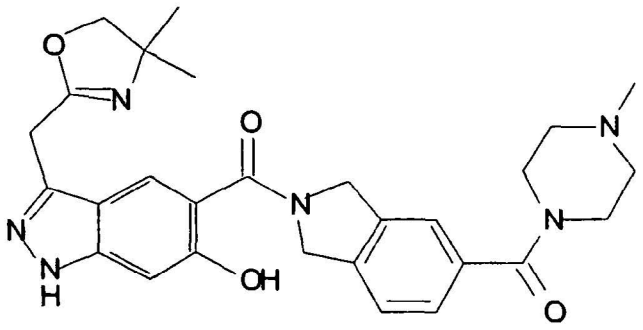
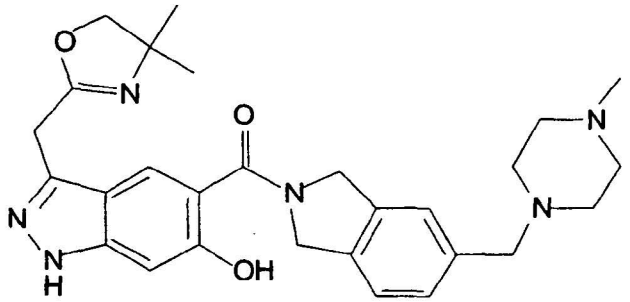
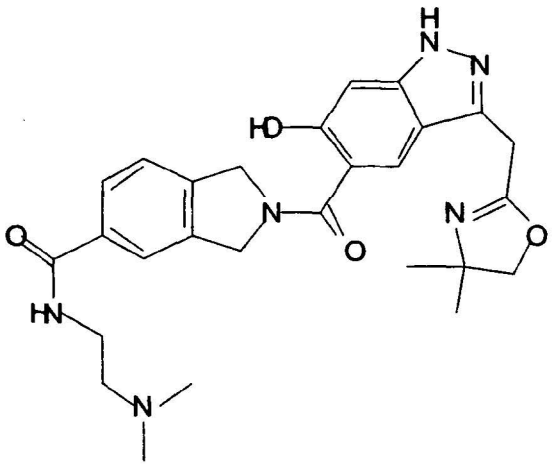
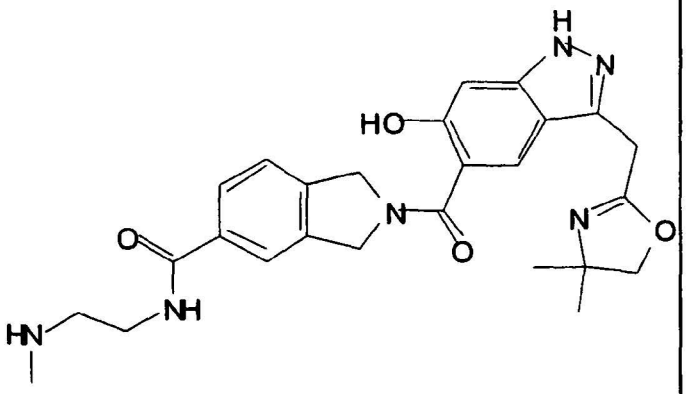
"A630"			
"A631"			
"A632"			
"A633"			

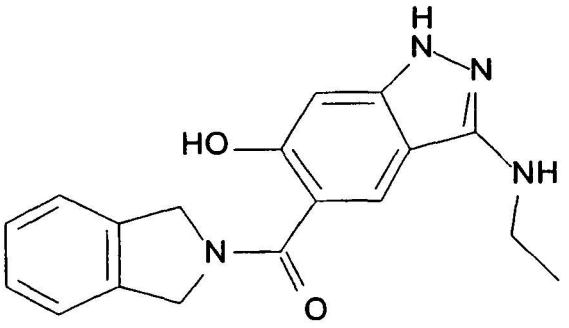
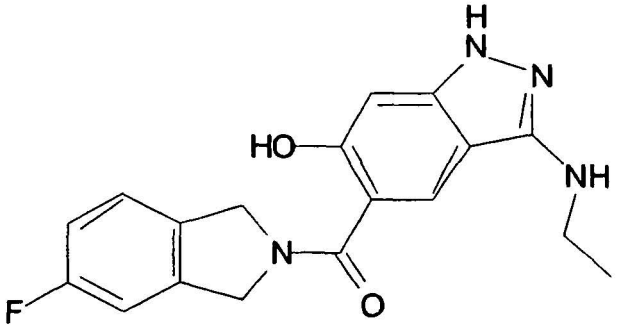
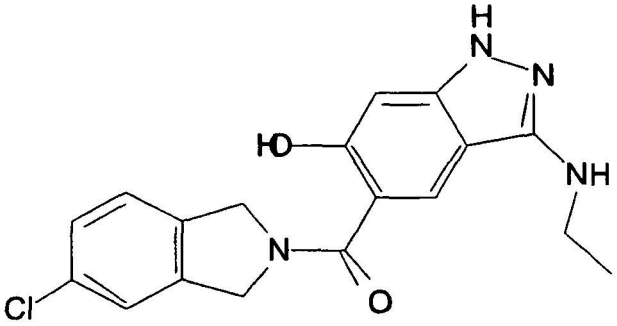
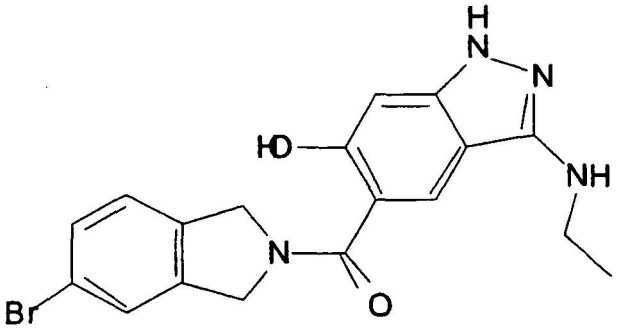
"A634"			
"A635"			
"A636"			
"A637"			

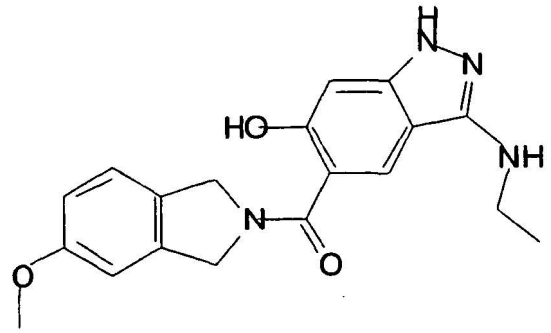
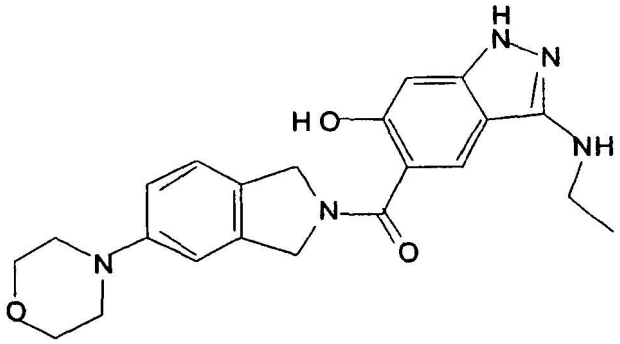
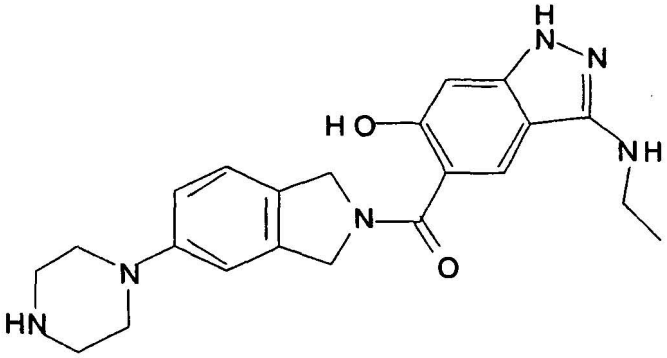
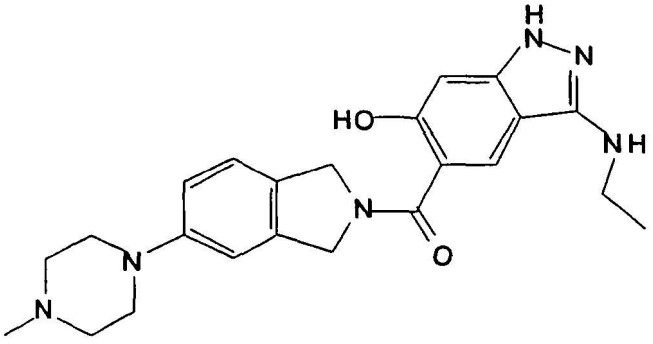
"A638"			
"A639"			
"A640"			
"A641"			

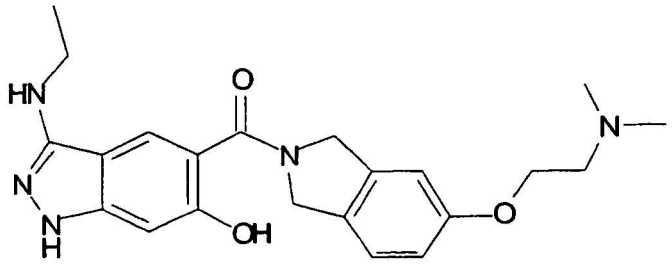
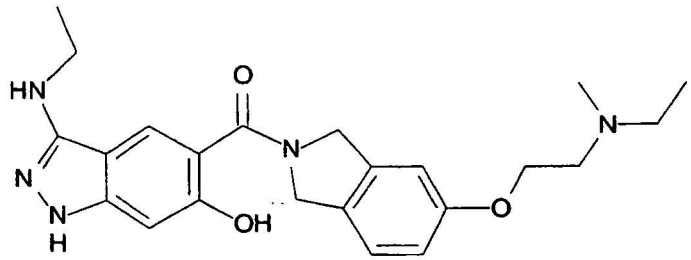
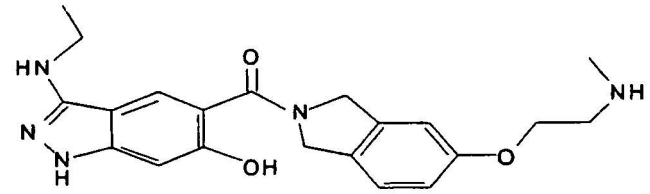
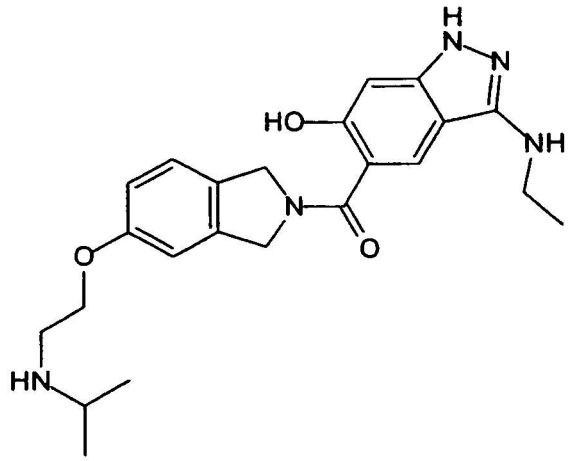
"A642"			
"A643"			
"A644"			
"A645"			
"A646"			

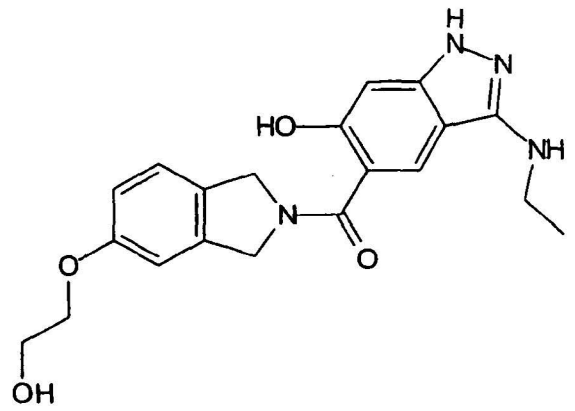
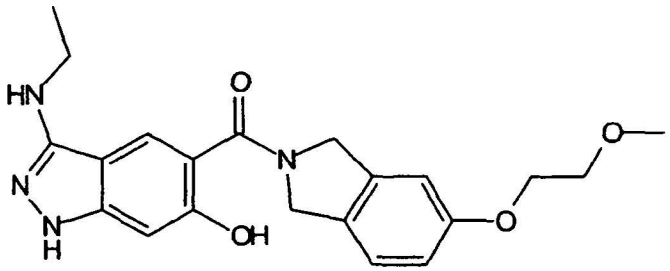
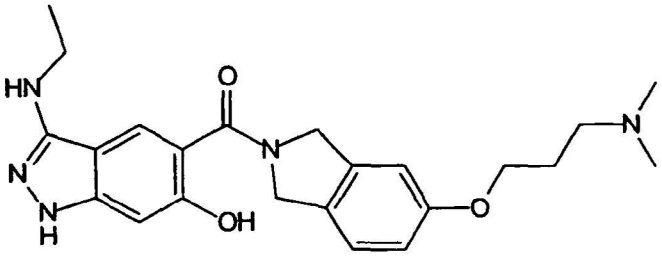
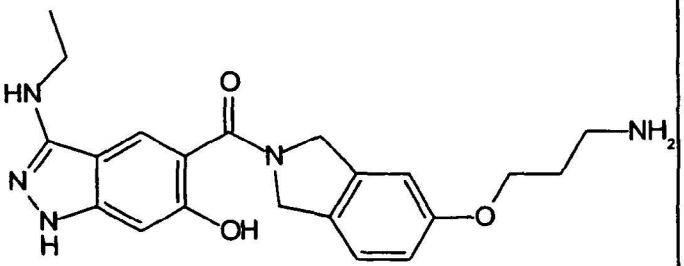
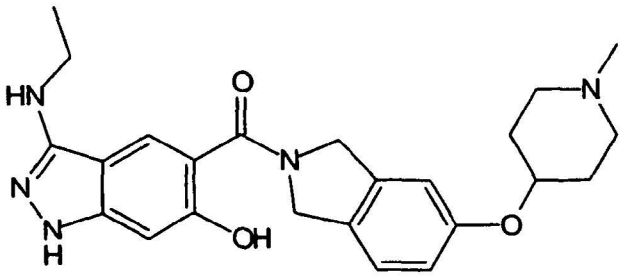
"A647"			
"A648"			
"A649"			

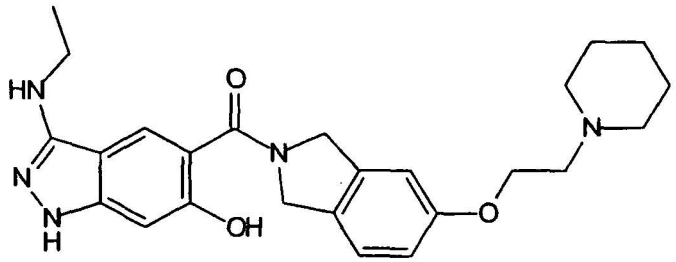
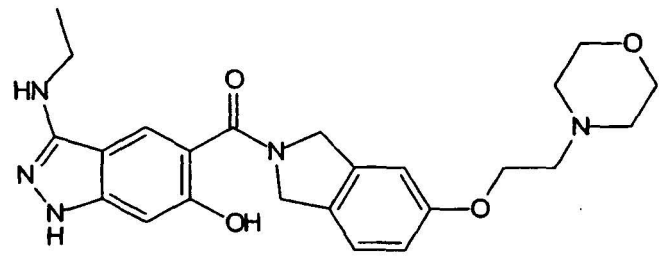
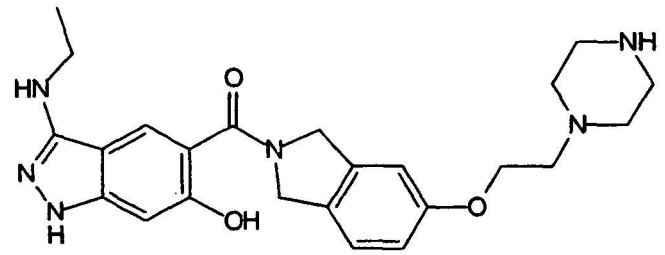
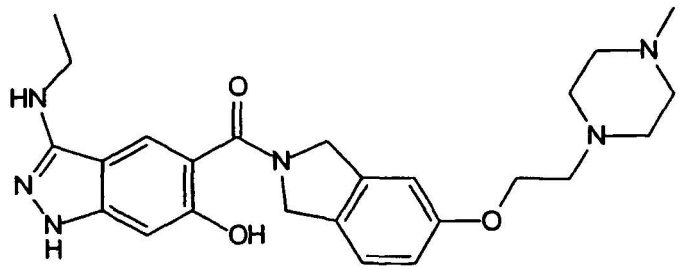
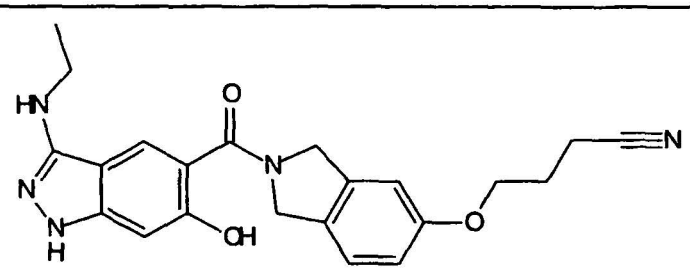
"A650"			
"A651"			
"A652"			
"A653"			

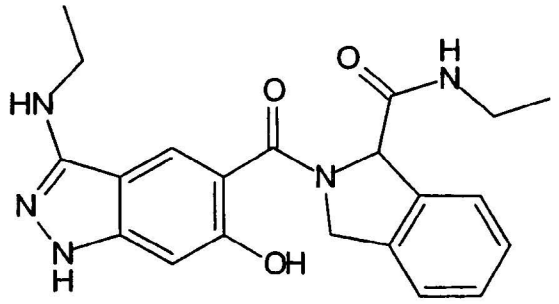
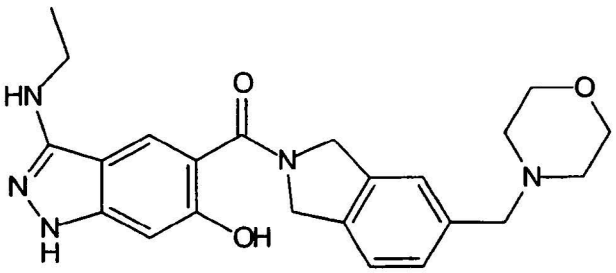
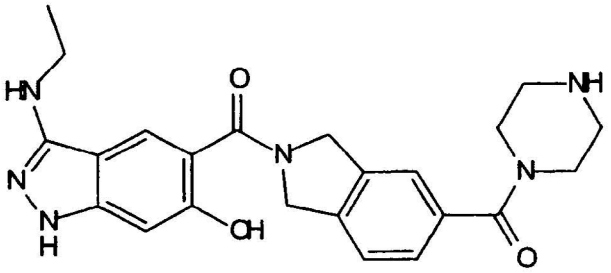
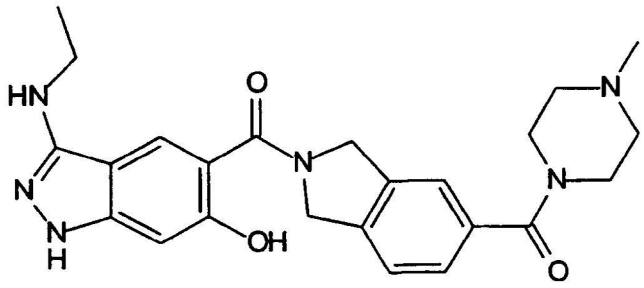
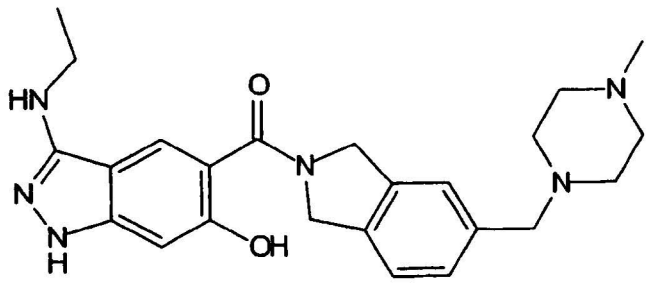
"A654"			
"A655"			
"A656"			
"A657"			

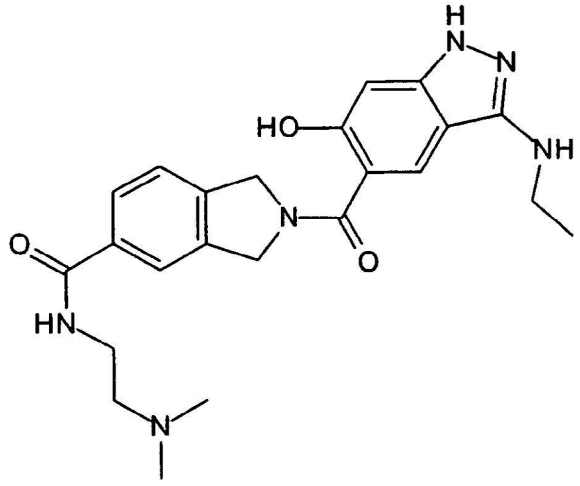
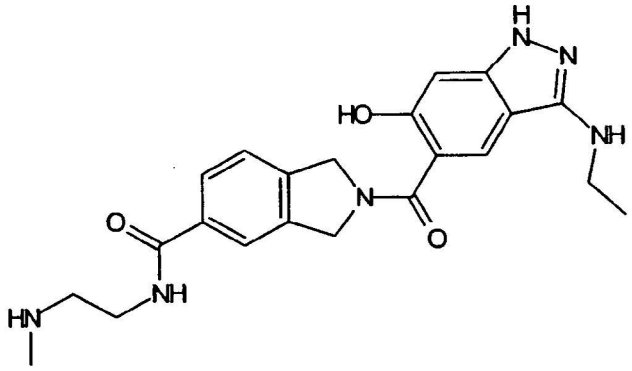
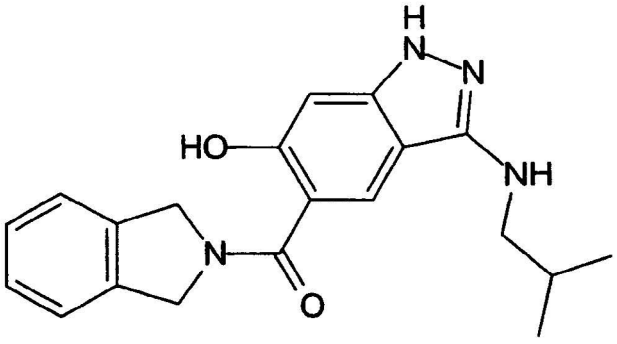
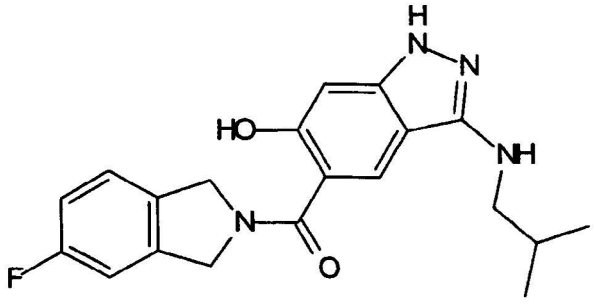
"A658"			
"A659"			
"A660"			
"A661"			

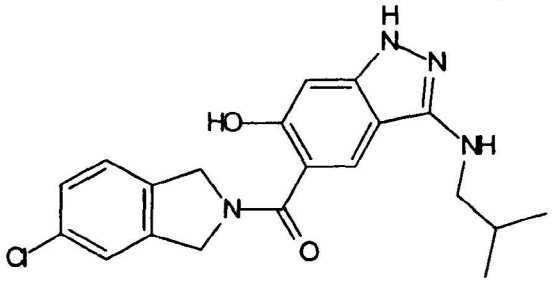
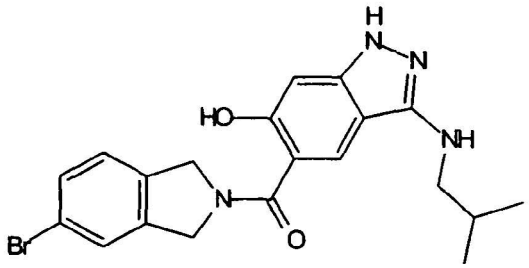
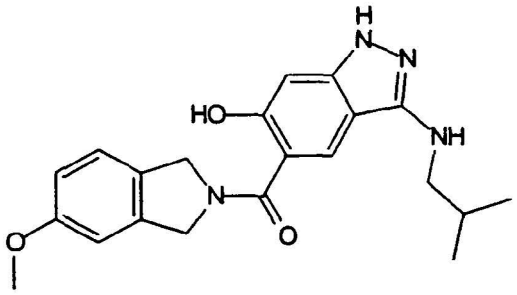
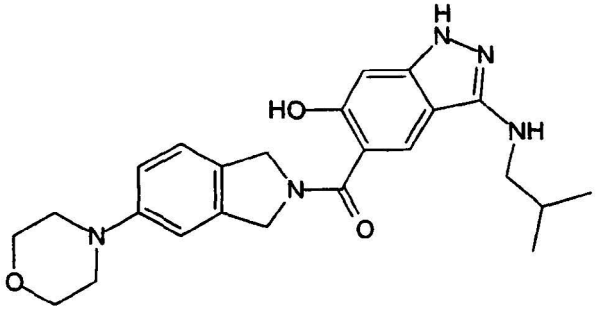
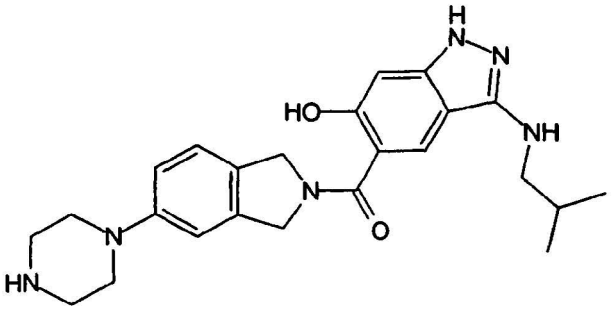
"A662"			
"A663"			
"A664"			
"A665"			

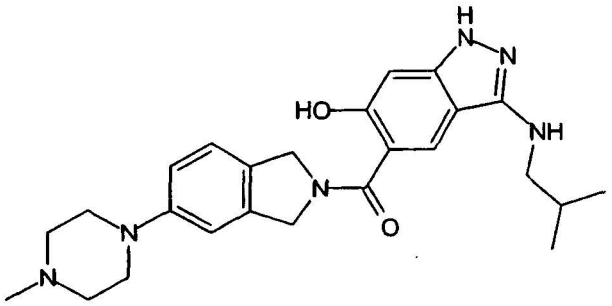
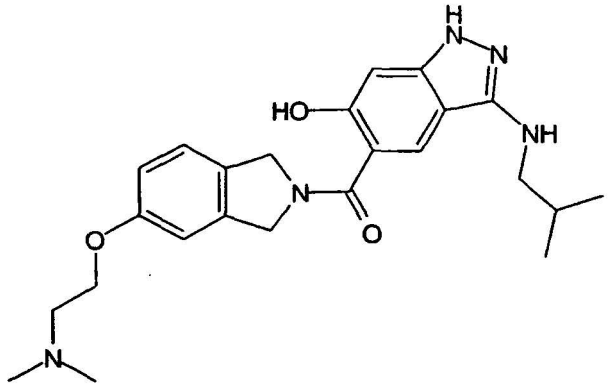
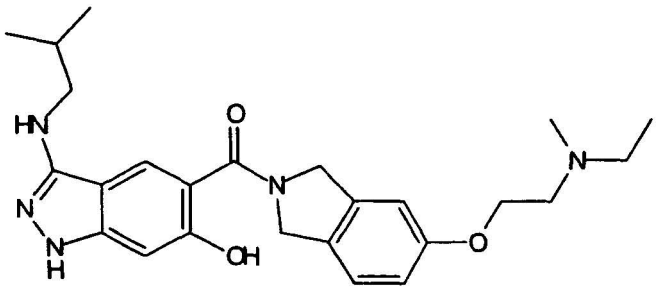
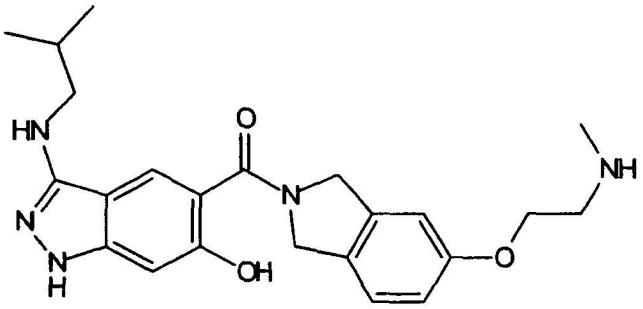
"A666"			
"A667"			
"A668"			
"A669"			
"A670"			

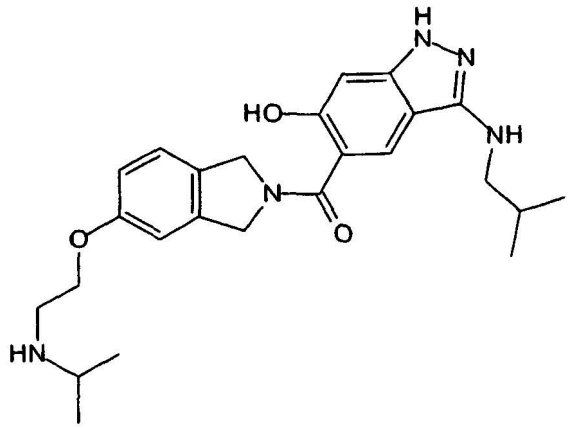
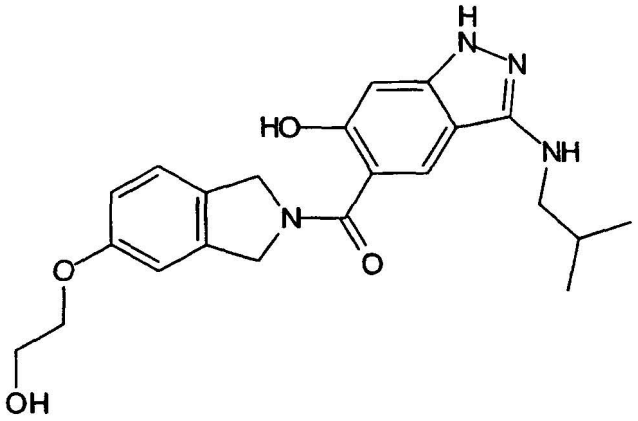
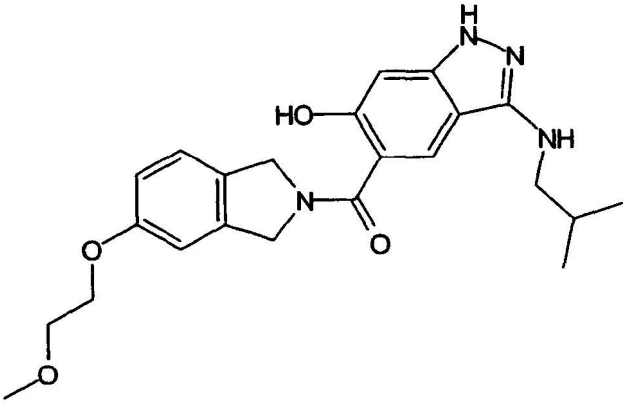
"A671"			
"A672"			
"A673"			
"A674"			
"A675"			

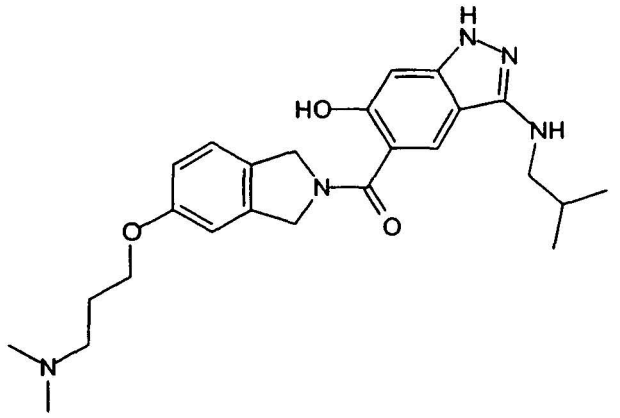
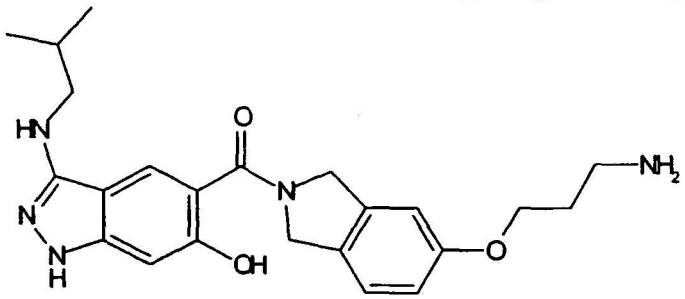
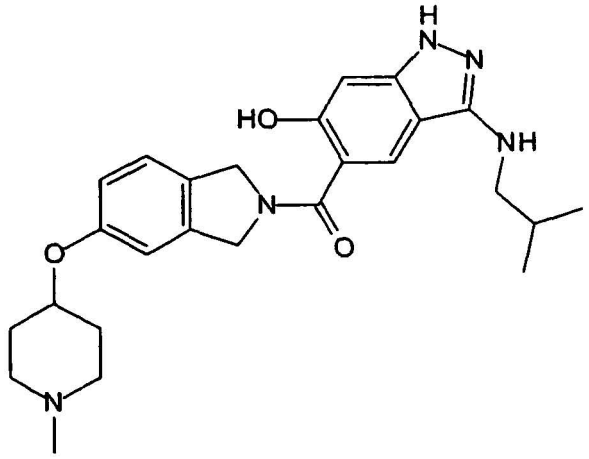
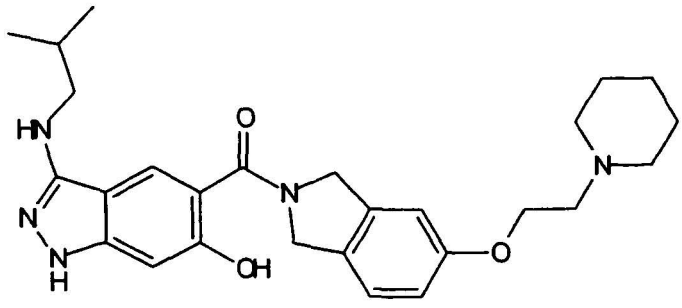
"A676"			
"A677"			
"A678"			
"A679"			
"A680"			

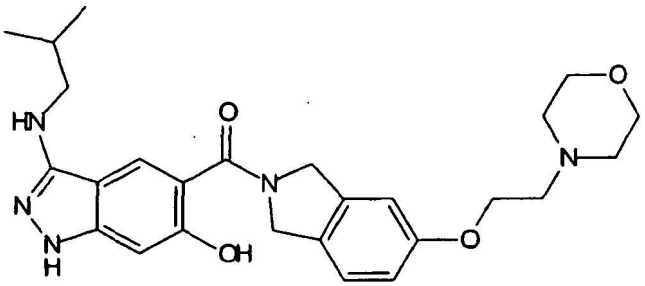
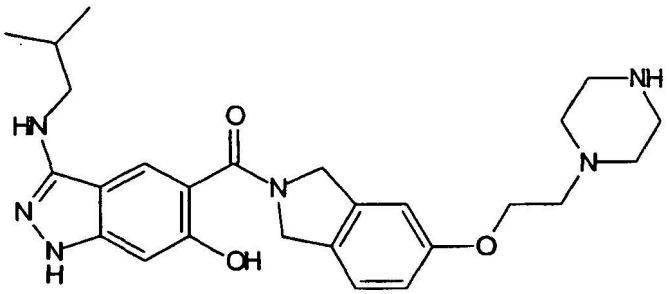
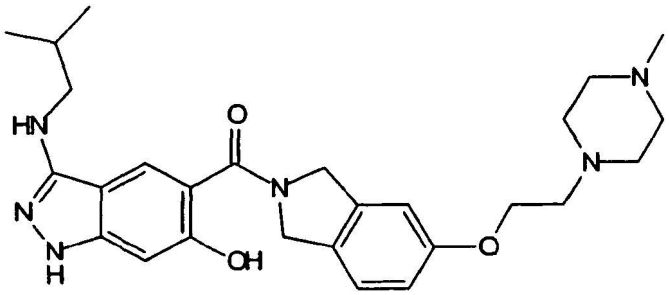
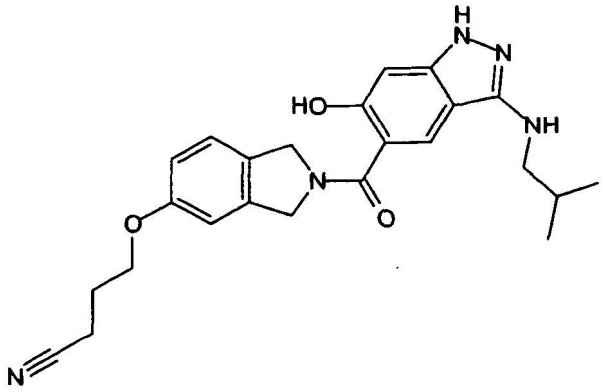
"A681"			
"A682"			
"A683"			
"A684"			

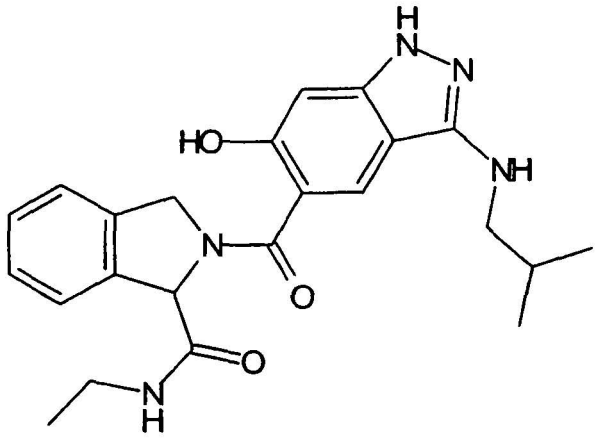
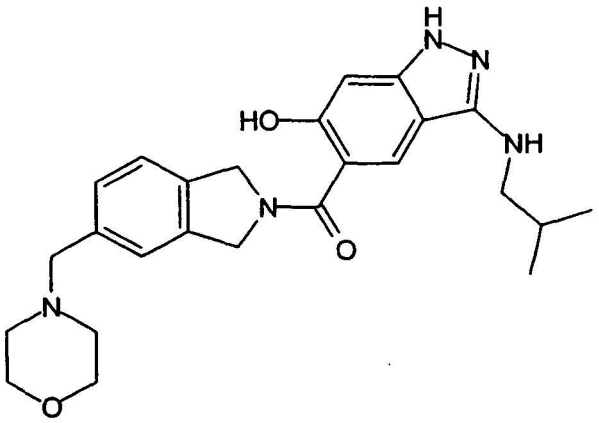
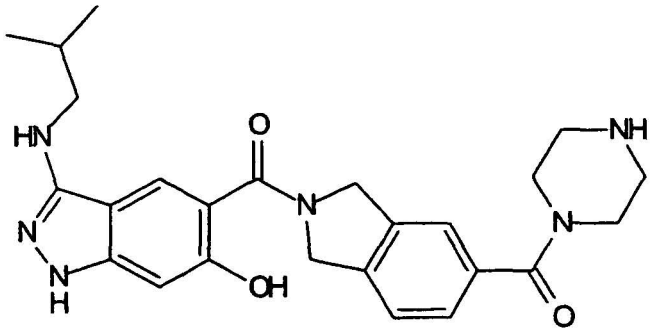
"A685"			
"A686"			
"A687"			
"A688"			
"A689"			

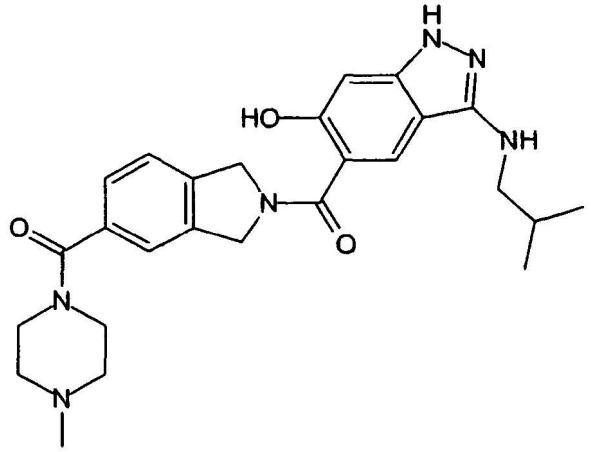
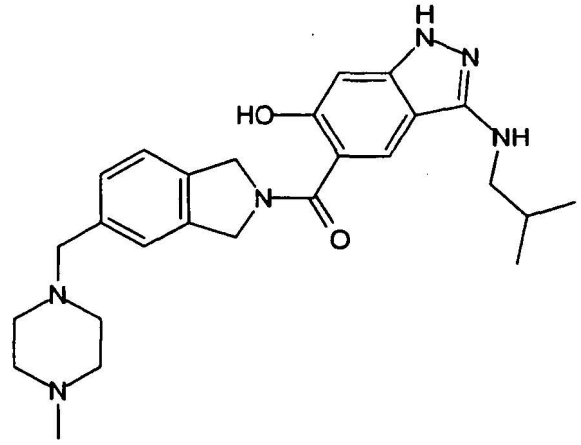
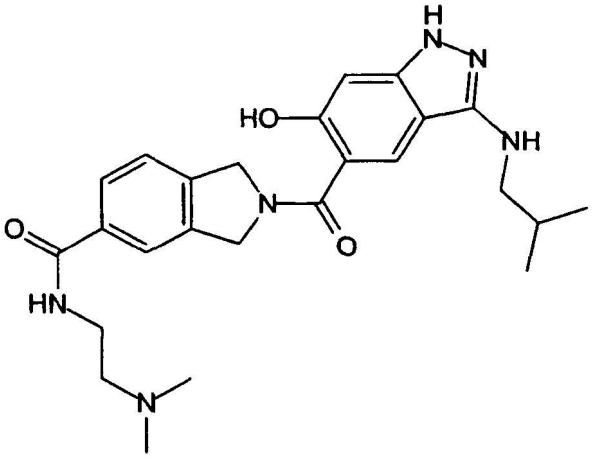
"A690"			
"A691"			
"A692"			
"A693"			

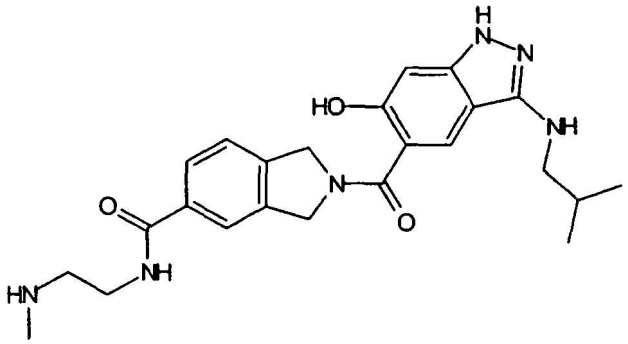
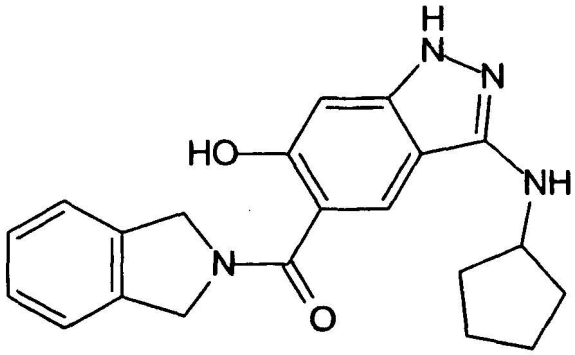
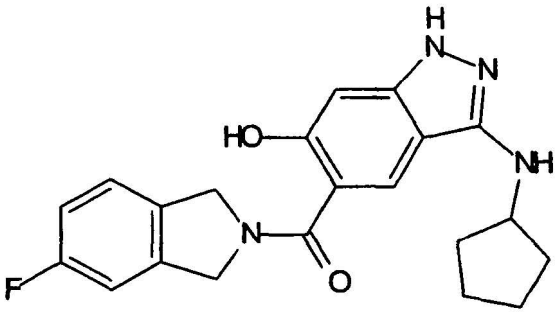
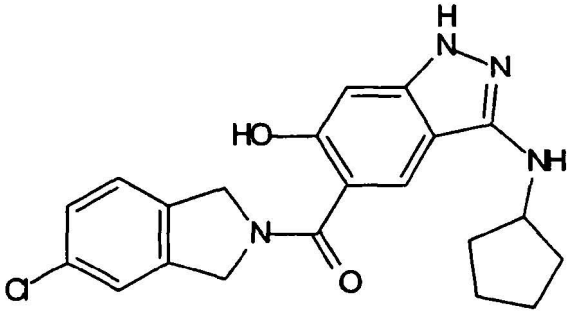
"A694"			
"A695"			
"A696"			

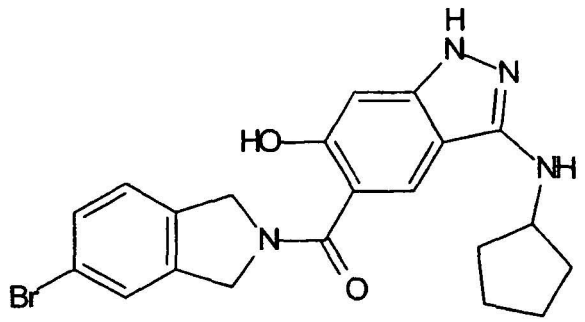
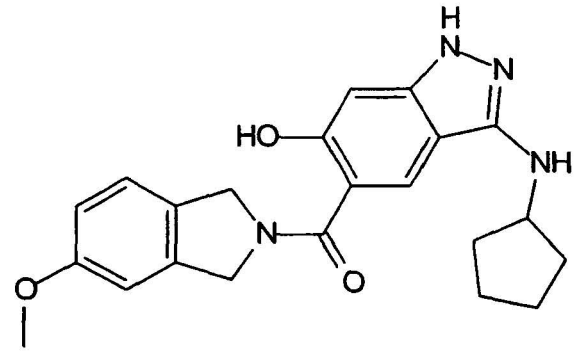
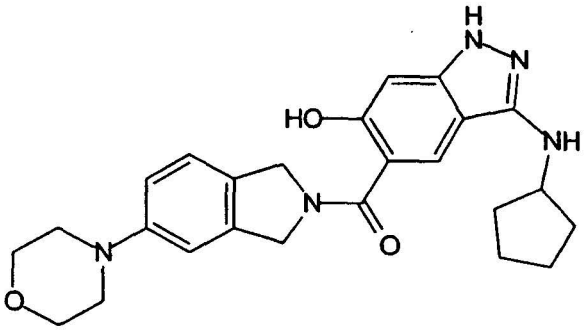
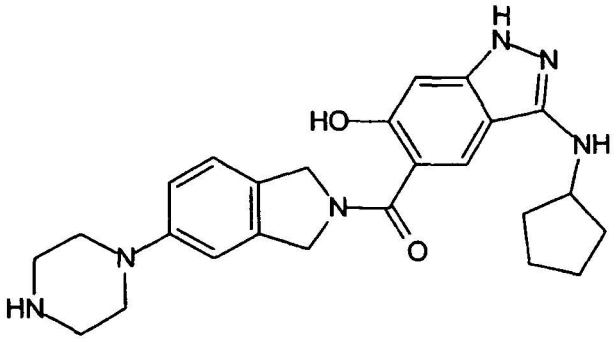
"A697"			
"A698"			
"A699"			
"A700"			

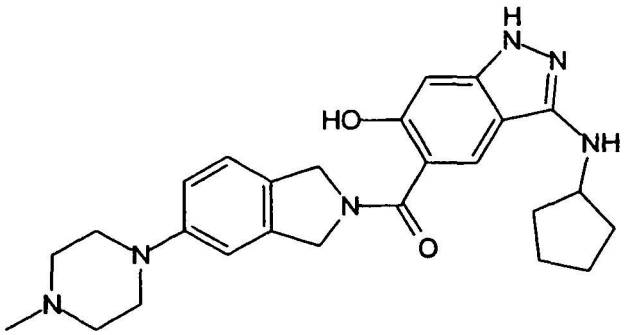
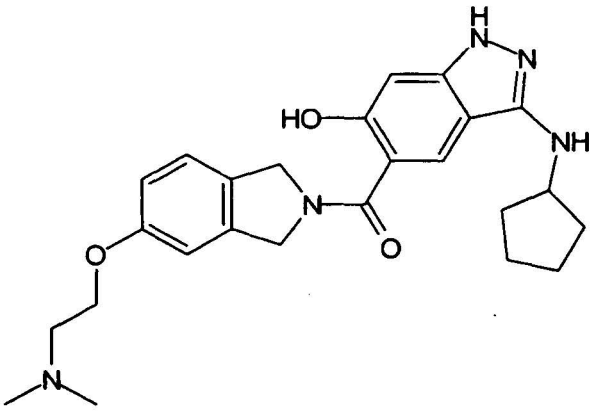
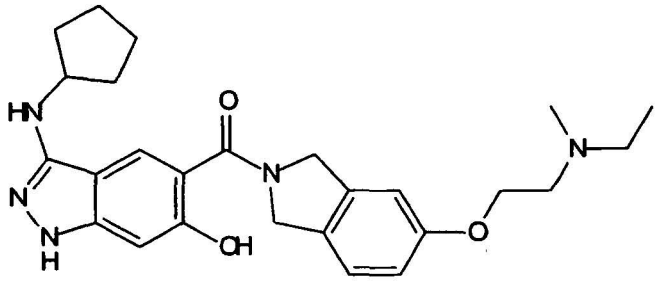
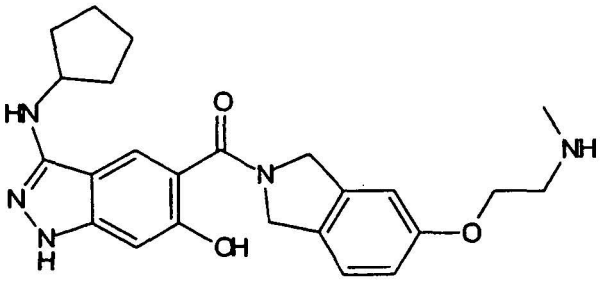
"A701"			
"A702"			
"A703"			
"A704"			

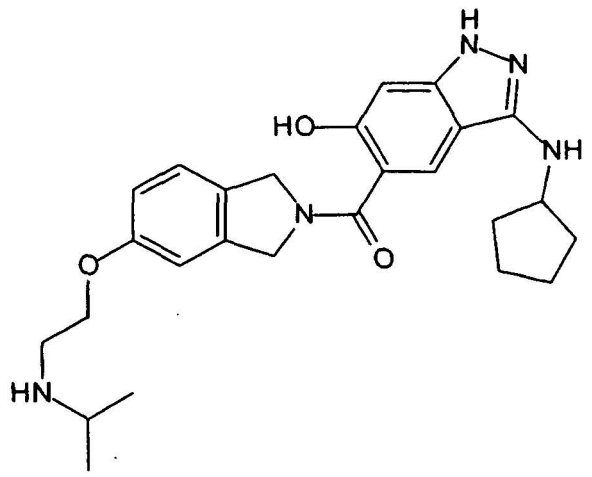
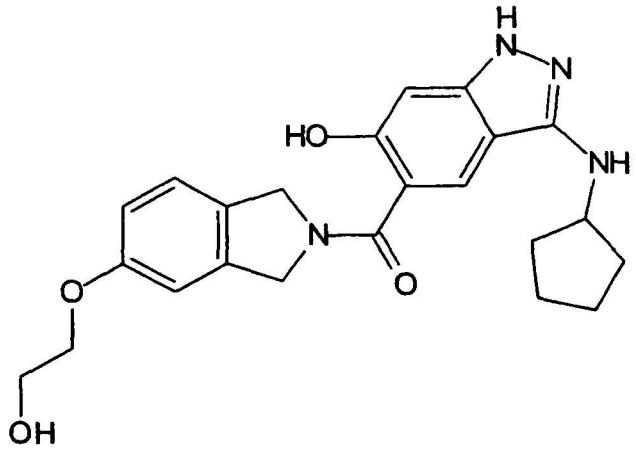
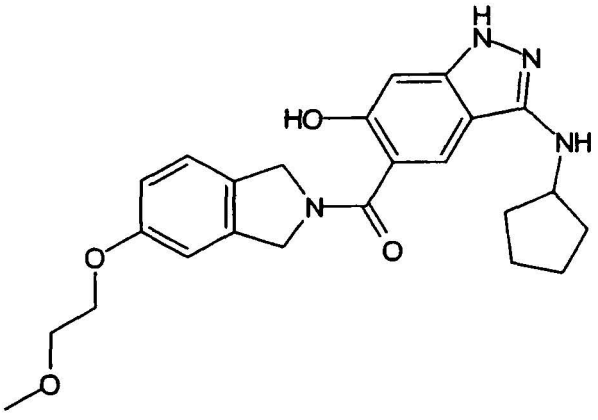
"A705"			
"A706"			
"A707"			

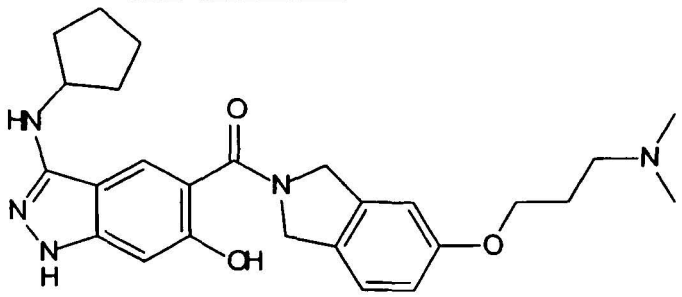
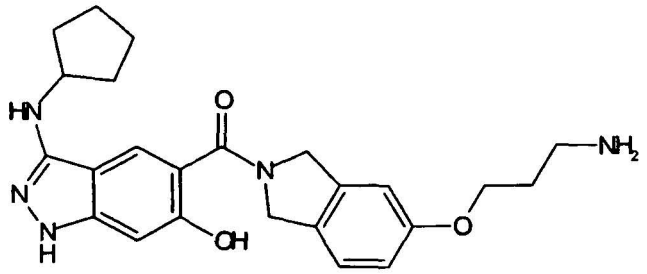
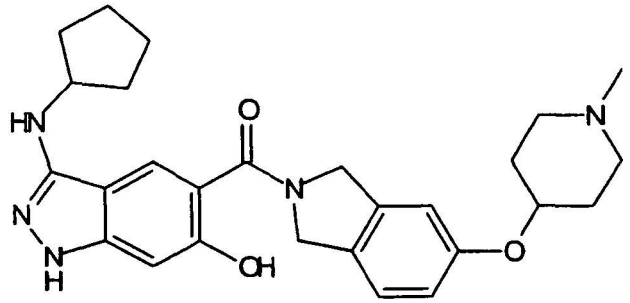
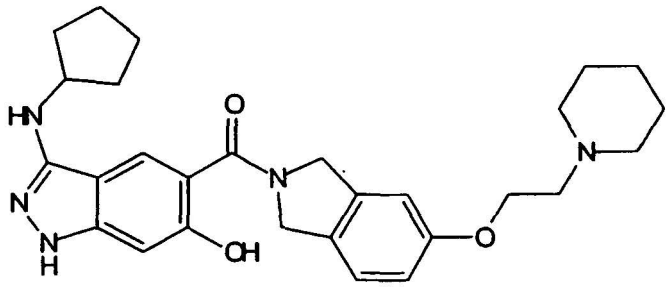
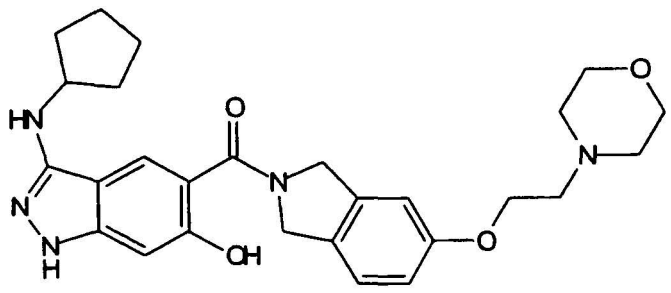
"A708"			
"A709"			
"A710"			

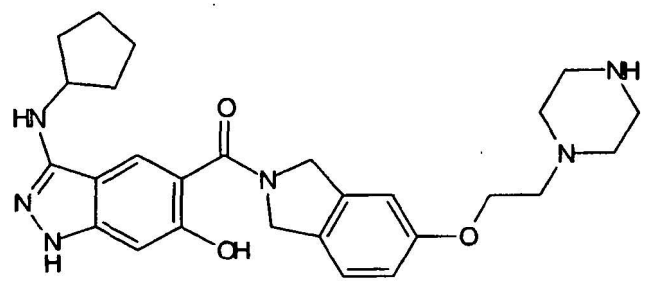
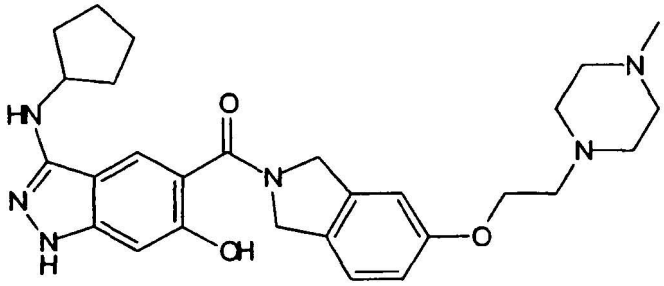
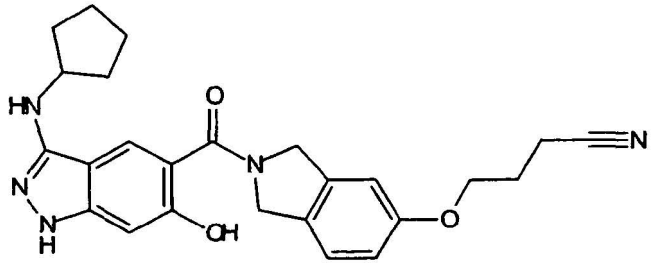
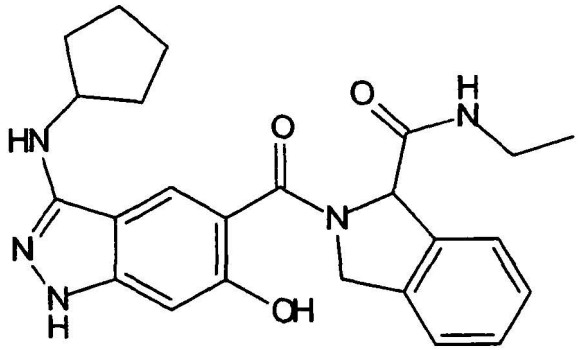
"A711"			
"A712"			
"A713"			
"A714"			

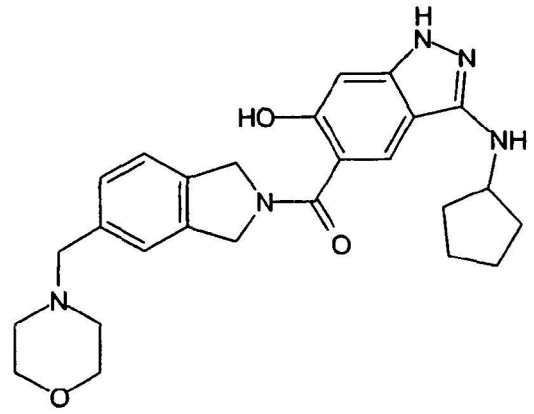
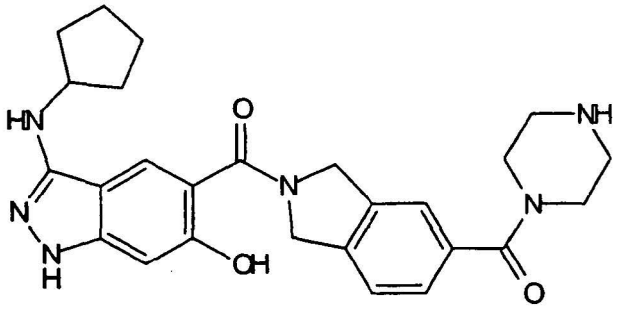
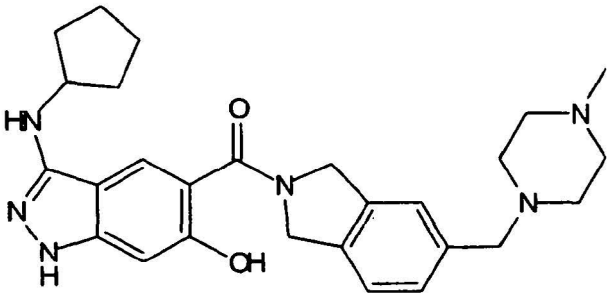
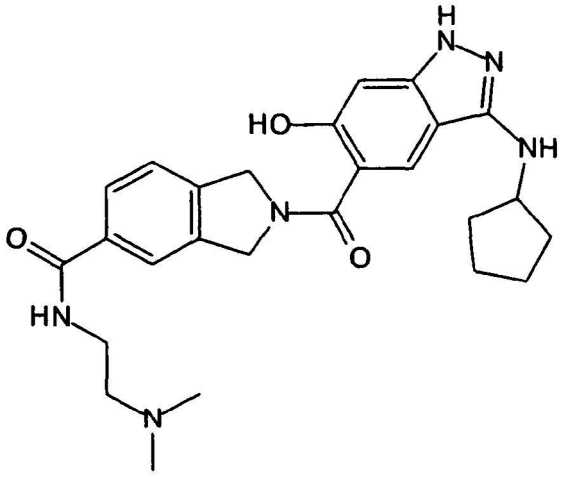
"A715"			
"A716"			
"A717"			
"A718"			

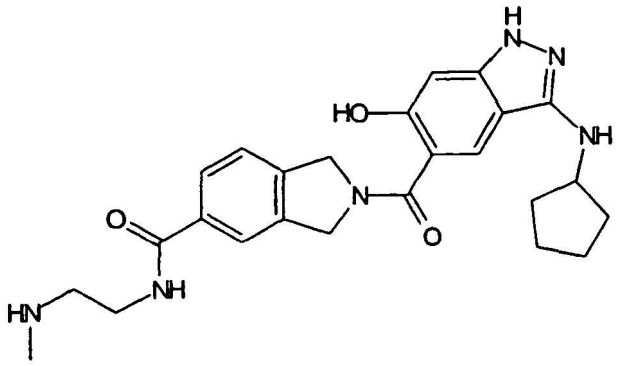
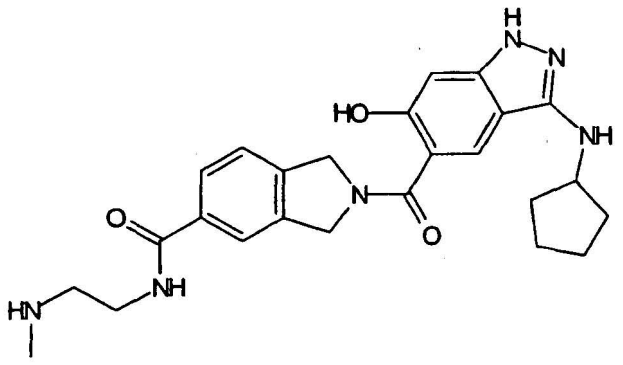
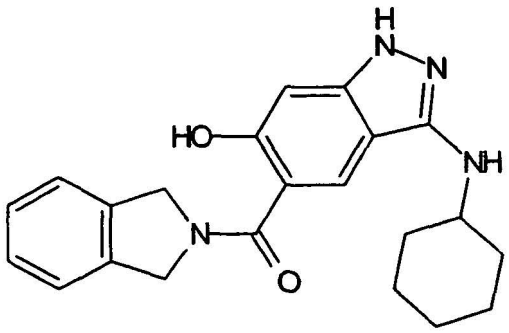
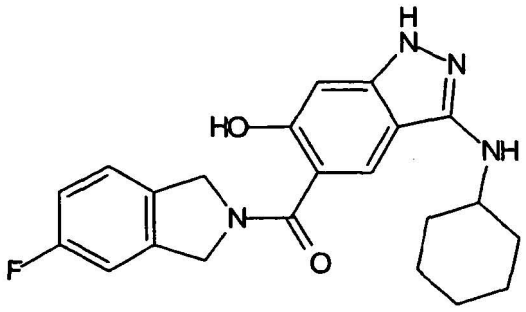
"A719"			
"A720"			
"A721"			
"A722"			

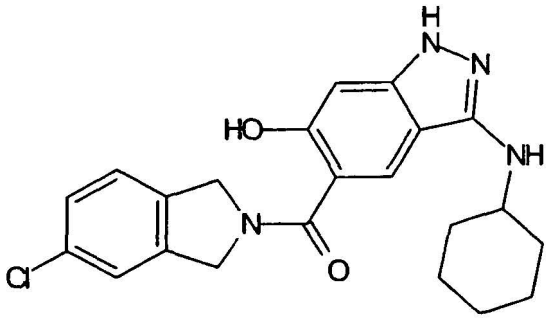
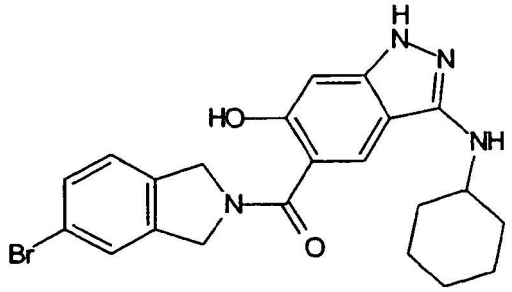
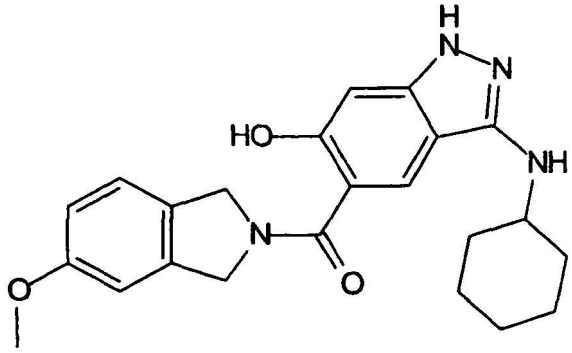
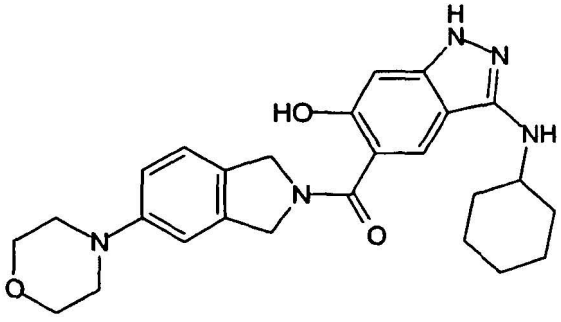
"A723"			
"A724"			
"A725"			

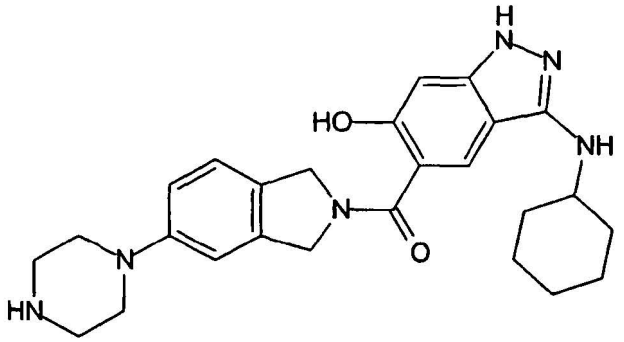
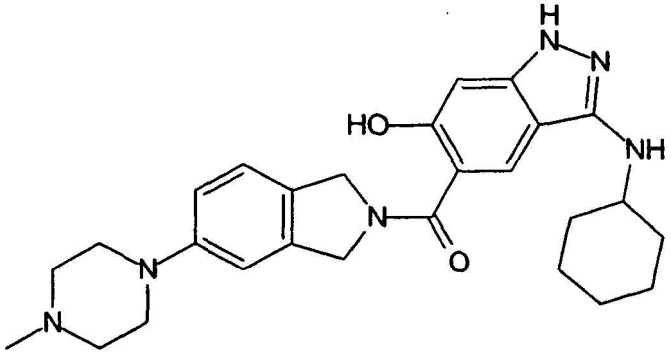
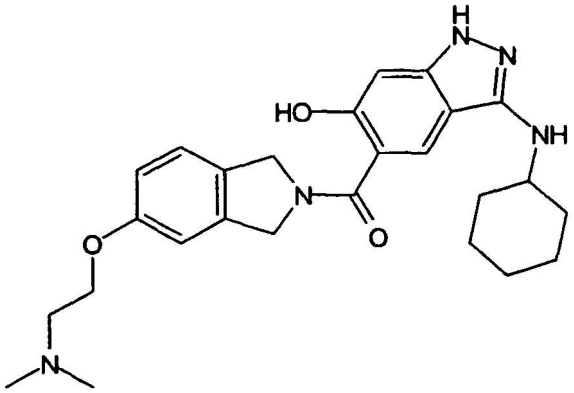
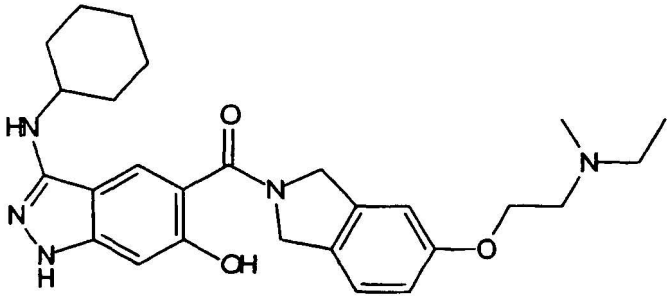
"A726"			
"A727"			
"A728"			
"A729"			
"A730"			

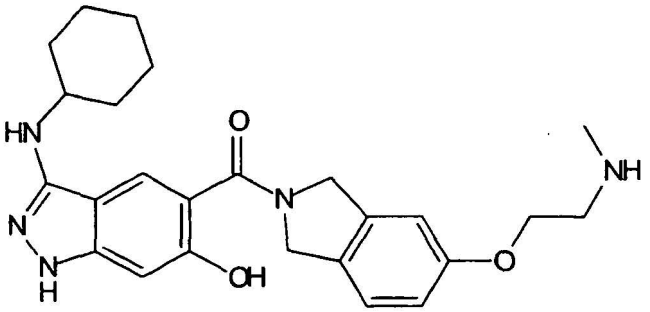
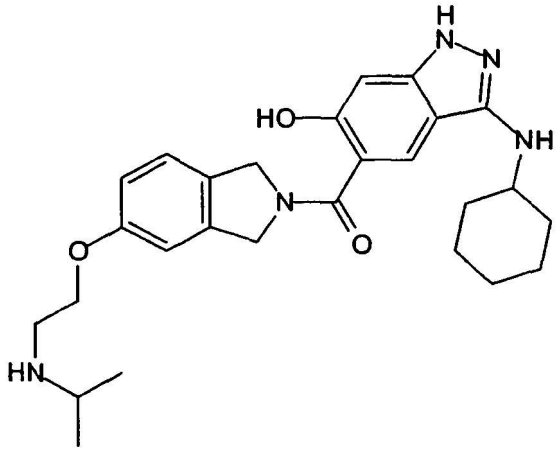
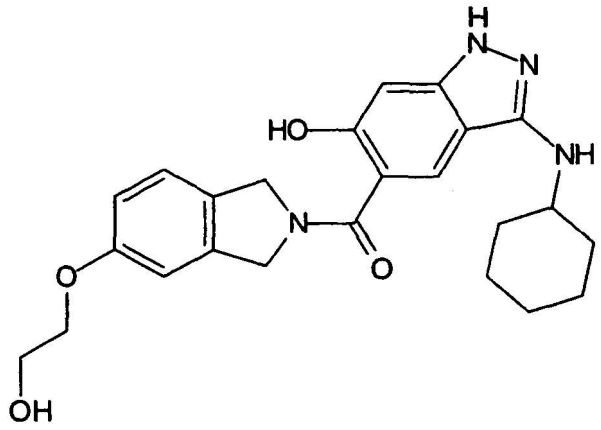
"A731"			
"A732"			
"A733"			
"A734"			

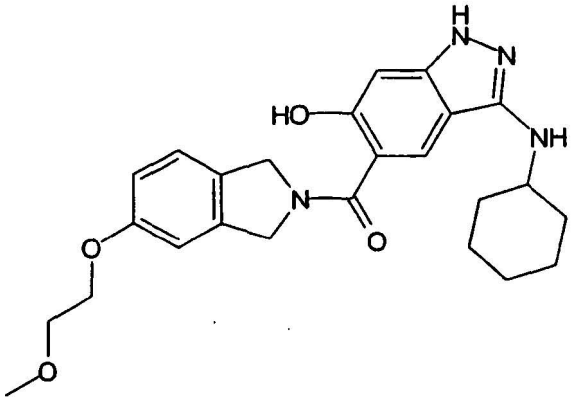
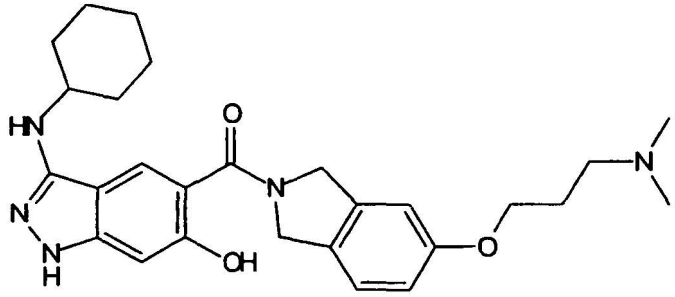
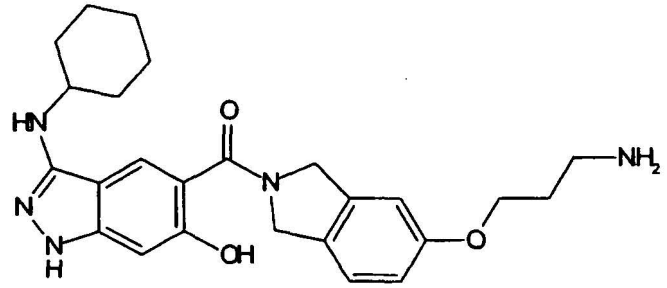
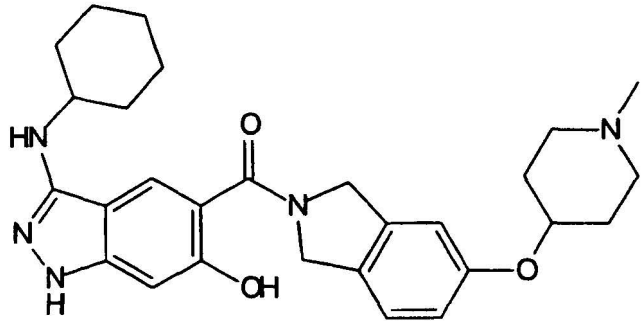
"A735"			
"A736"			
"A737"			
"A738"			

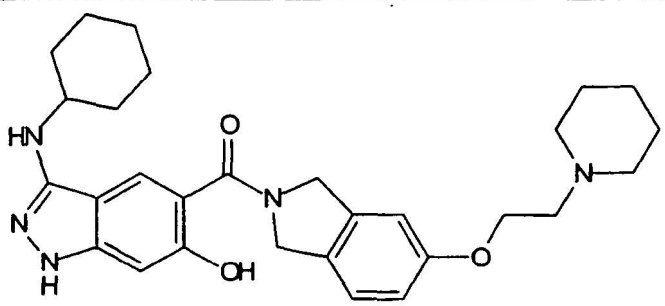
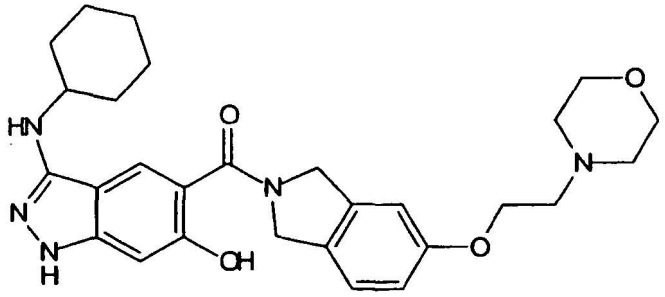
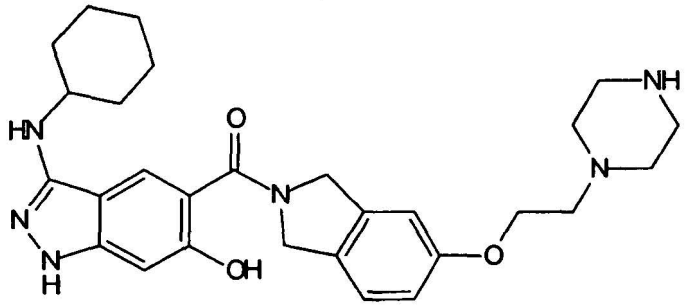
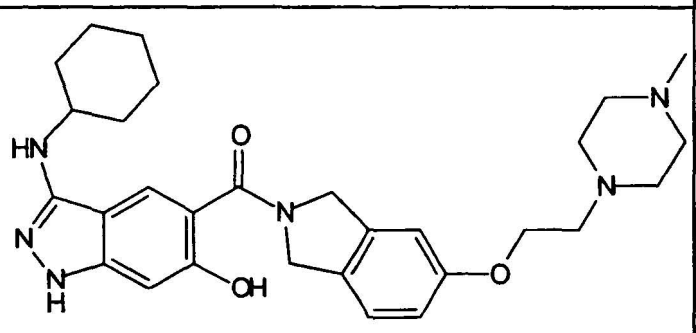
"A739"			
"A740"			
"A741"			
"A742"			

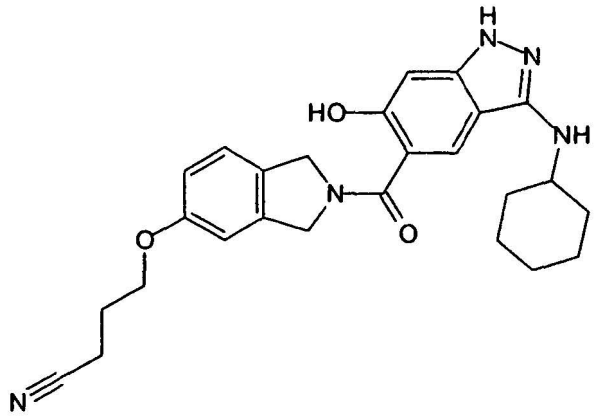
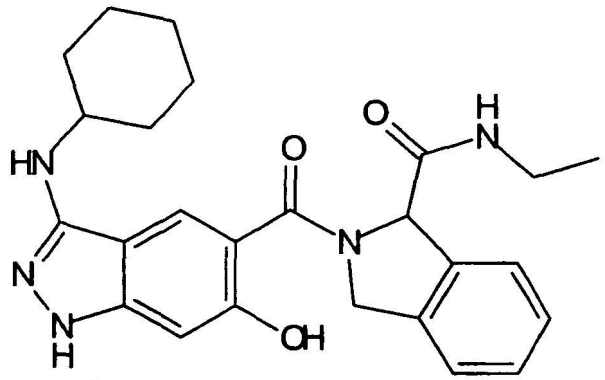
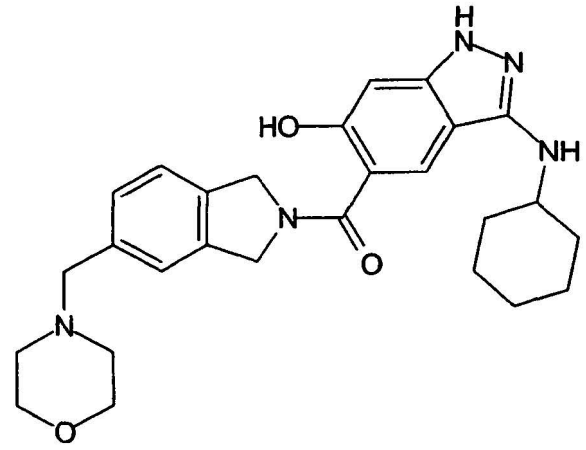
"A743"			
"A744"			
"A745"			
"A746"			

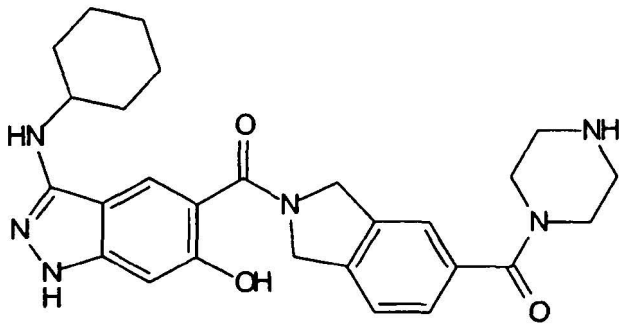
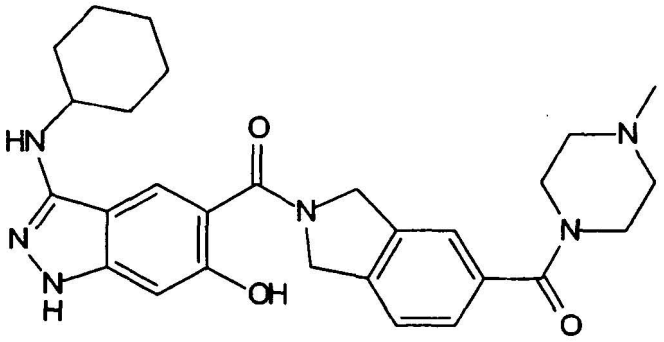
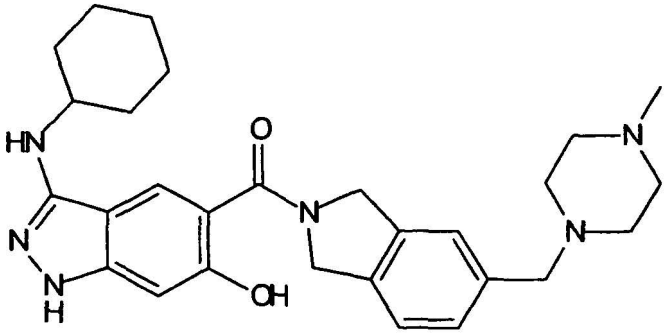
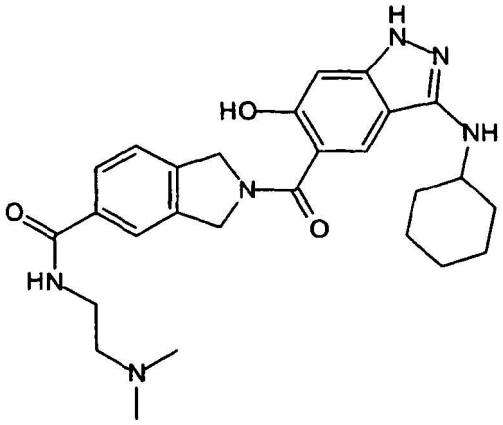
"A747"			
"A748"			
"A749"			
"A750"			

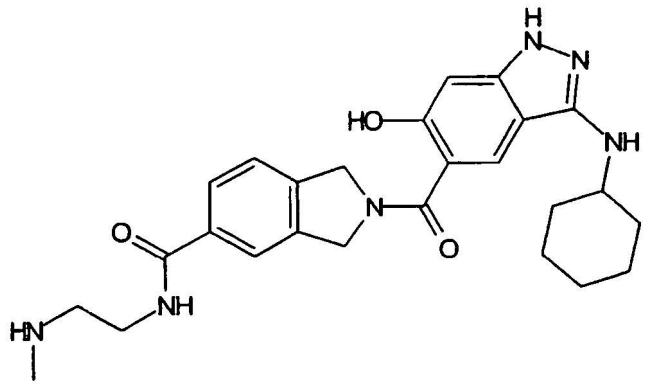
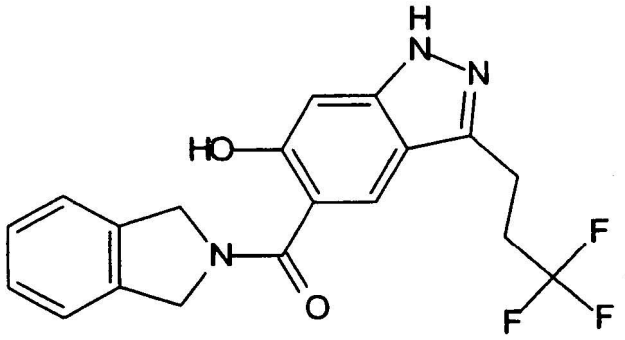
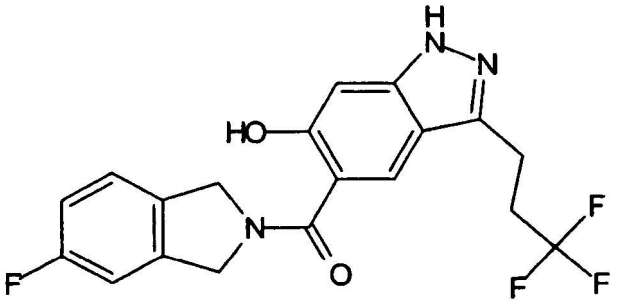
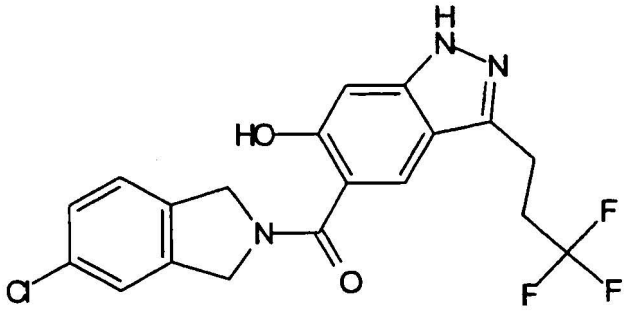
"A751"			
"A752"			
"A753"			

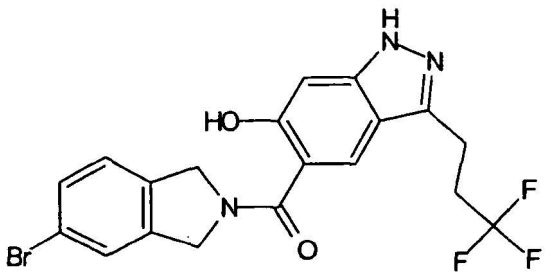
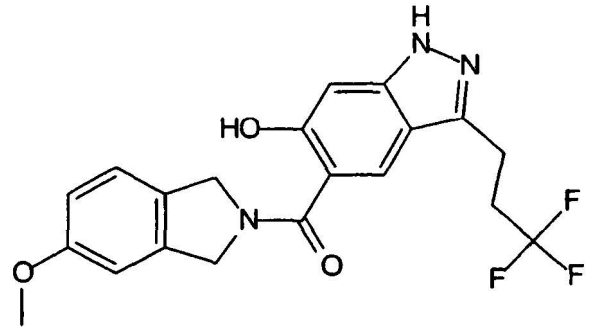
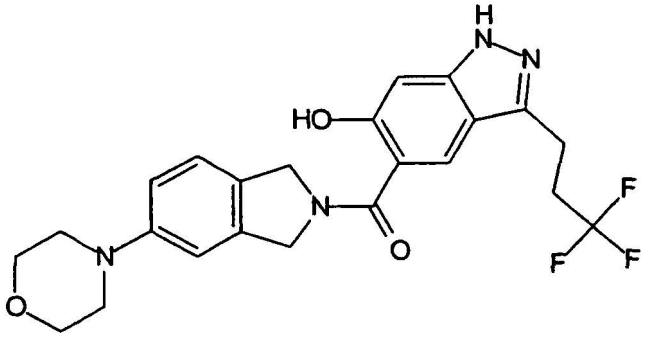
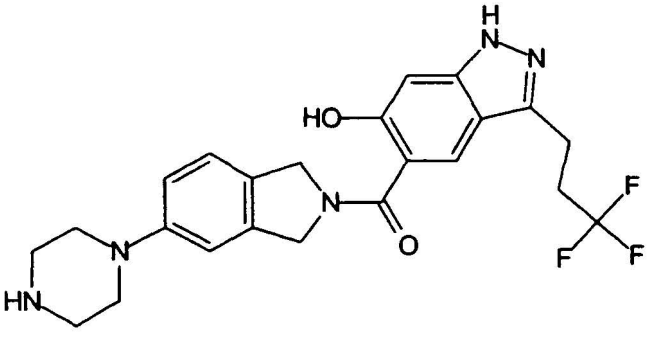
"A754"			
"A755"			
"A756"			
"A757"			

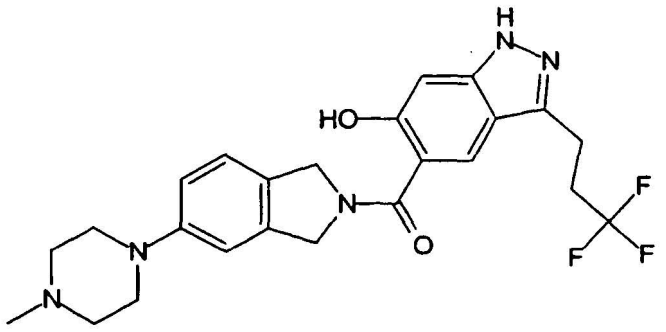
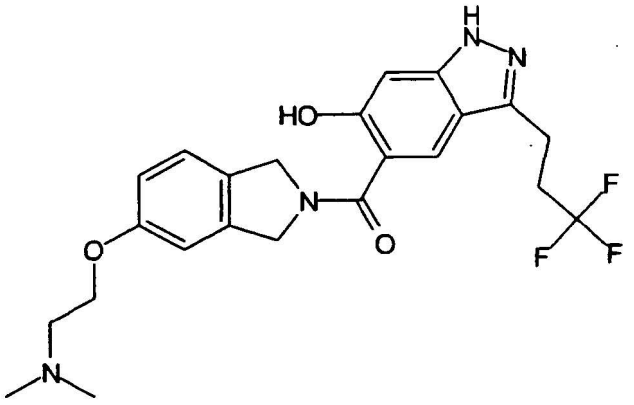
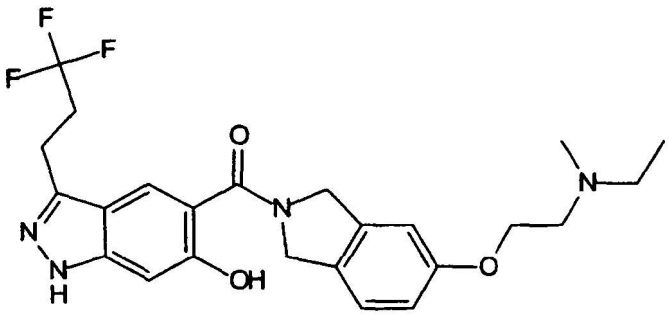
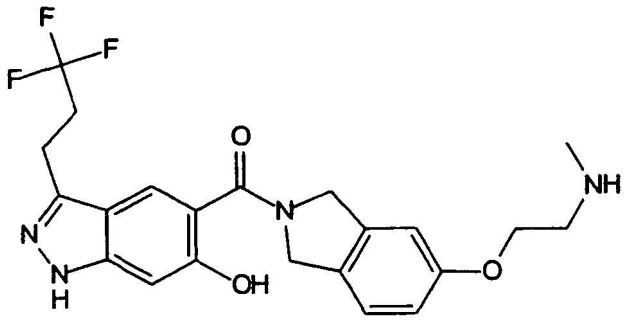
"A758"			
"A759"			
"A760"			
"A761"			

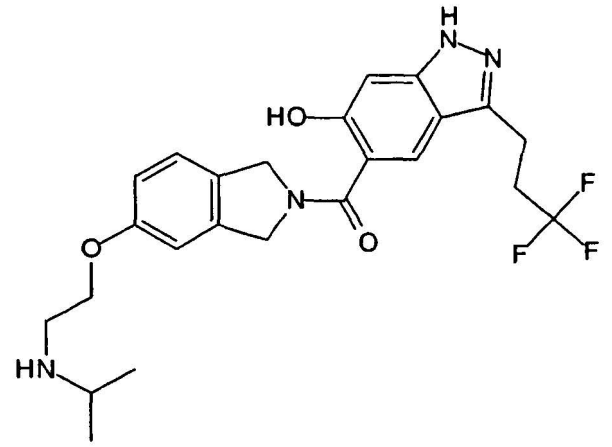
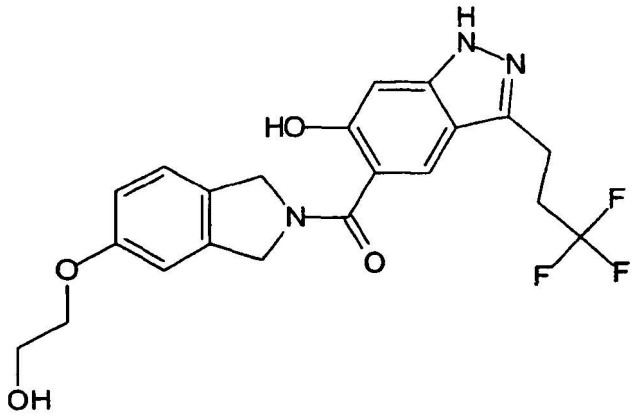
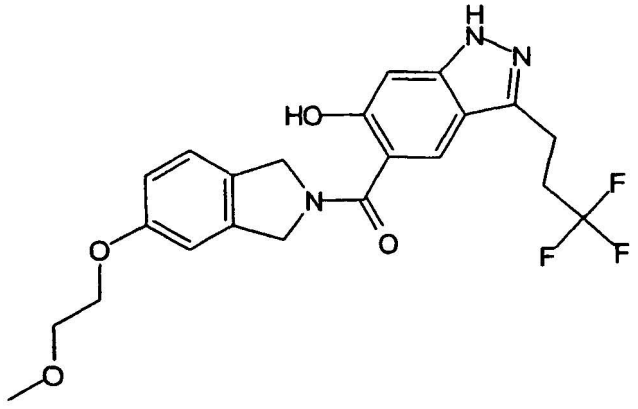
"A762"			
"A763"			
"A764"			

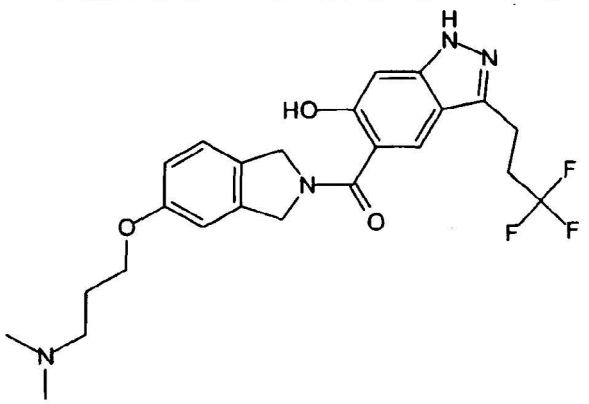
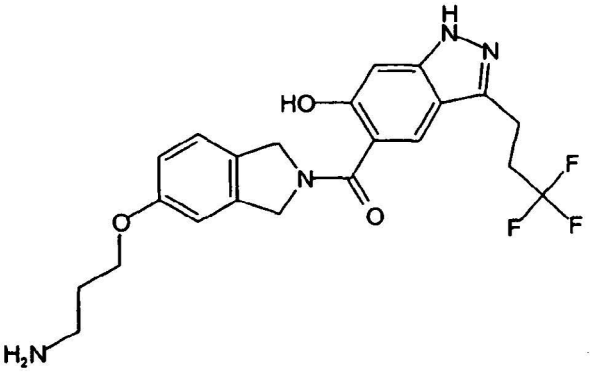
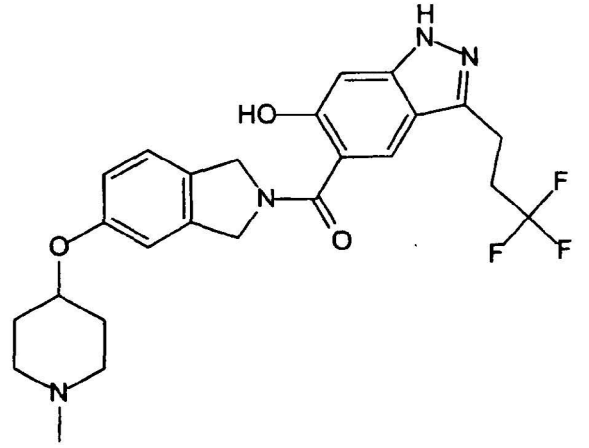
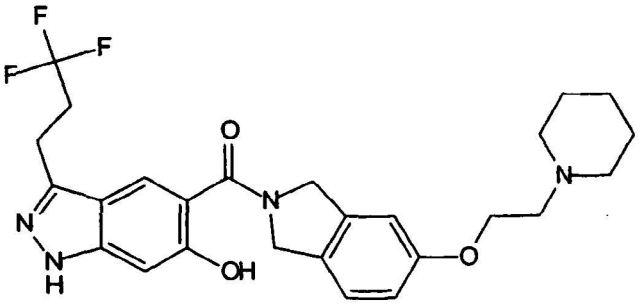
"A765"			
"A766"			
"A767"			
"A768"			

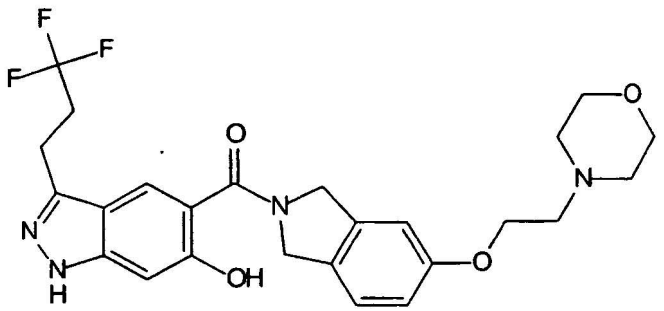
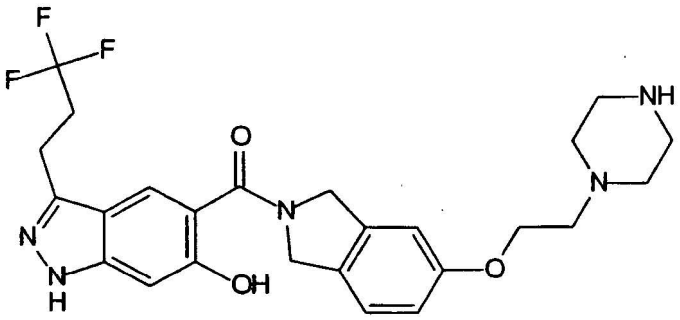
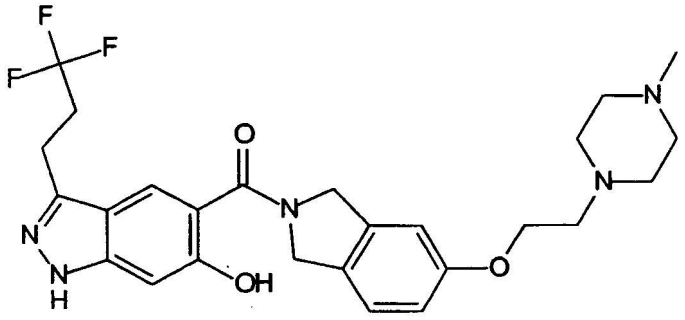
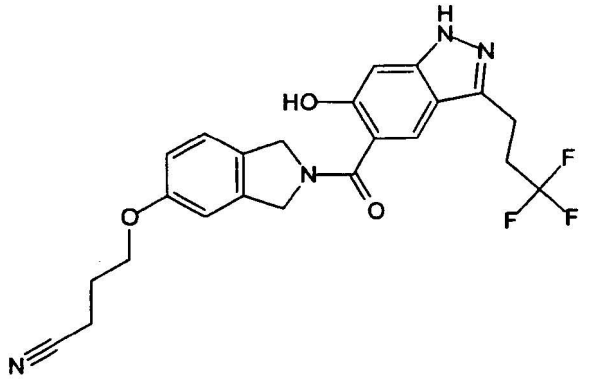
"A769"			
"A770"			
"A771"			
"A772"			

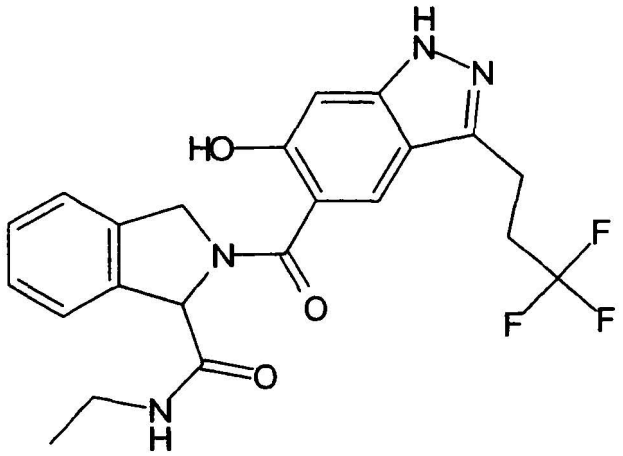
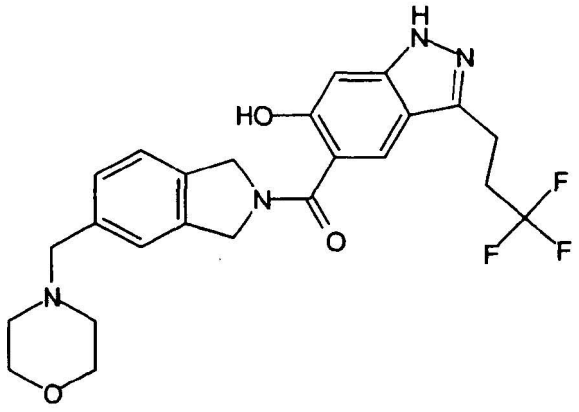
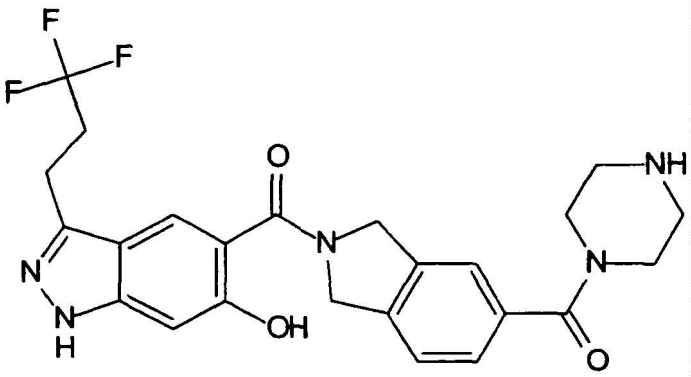
"A773"			
"A774"			
"A775"			
"A776"			

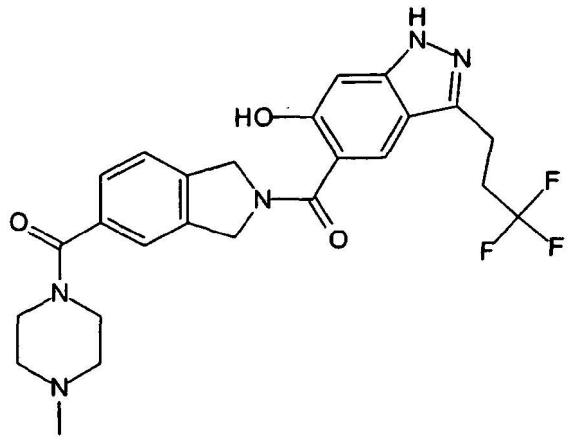
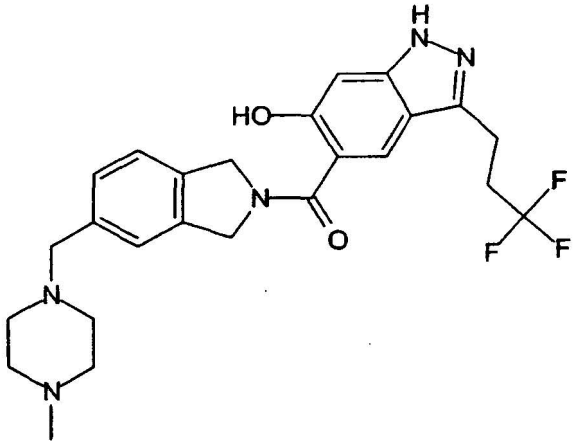
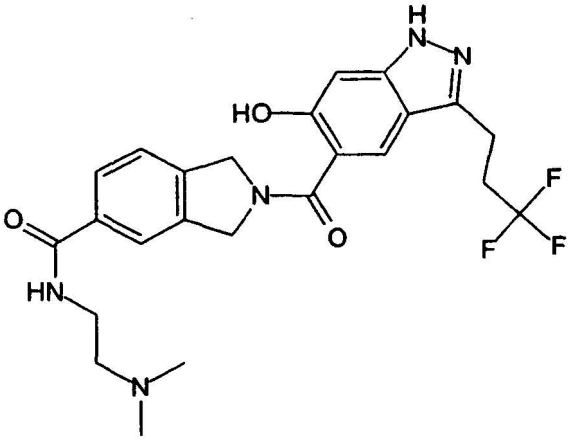
"A777"			
"A778"			
"A779"			
"A780"			

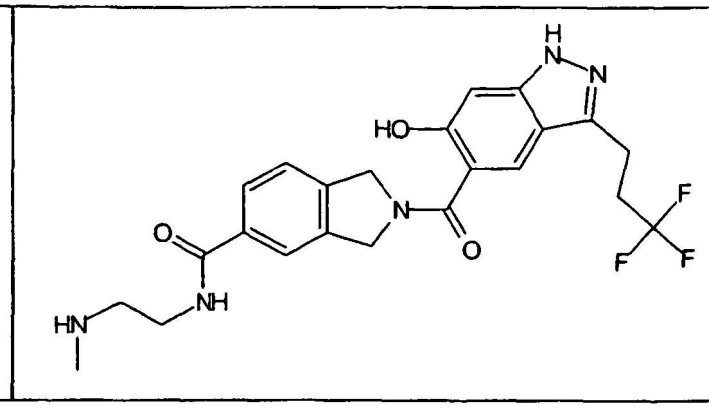
"A781"			
"A782"			
"A783"			

"A784"			
"A785"			
"A786"			
"A787"			

"A788"			
"A789"			
"A790"			
"A791"			

"A792"			
"A793"			
"A794"			

"A795"			
"A796"			
"A797"			

"A798"			

Los siguientes ejemplos se refieren a preparaciones farmacéuticas:

Ejemplo A: Frascos para inyectables

Una solución de 100 g de un principio activo de la invención y 5 g de hidrofosfato disódico en 3 l de agua bidestilada se ajusta a un pH de 6,5 con ácido clorhídrico de 2 N, se filtra en forma estéril, se envasa en frascos para inyectables, se liofiliza en condiciones estériles y se sella de manera estéril. Cada frasco para inyectables contiene 5 mg de principio activo.

Ejemplo B: Supositorios

Se funde una mezcla de 20 g de un principio activo de la invención con 100 g de lecitina de soya y 1400 g de manteca de cacao, se vierte en moldes y se deja enfriar. Cada supositorio contiene 20 mg de principio activo.

Ejemplo C: Solución

Se prepara una solución a partir de 1 g de un principio activo de la invención, 9,38 g de $NaH_2PO_4 \cdot 2\ H_2O$, 28,48 g de $Na_2HPO_4 \cdot 12\ H_2O$ y 0,1 g de cloruro de benzalconio en 940 ml de agua bidestilada. Se ajusta a un pH de 6,8, se completa a 1 l y se esteriliza mediante radiación. Esta solución puede usarse en forma de gotas oftálmicas.

Ejemplo D: Ungüentos

Se mezclan 500 mg de un principio activo de la invención con 99,5 g de vaselina en condiciones de asepsia.

Ejemplo E: Tabletas

Una mezcla de 1 kg de principio activo, 4 kg de lactosa, 1,2 kg de almidón de patata, 0,2 kg de talco y 0,1 kg de estearato de magnesio se comprimen en tabletas de manera usual, de tal modo que cada tableta contiene 10 mg de principio activo.

Ejemplo F: Grageas

De manera análoga al ejemplo E se comprimen tabletas que después se recubren de manera usual con un revestimiento de sacarosa, almidón de patata, talco, tragacanto y colorante.

Ejemplo G: Cápsulas

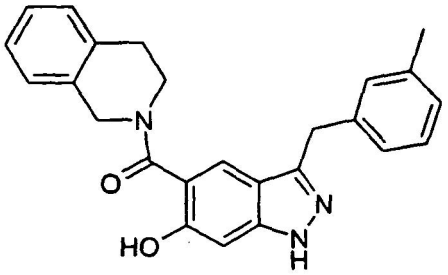
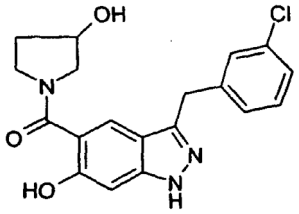
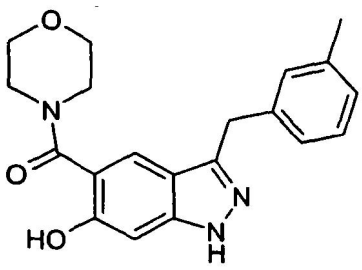
2 kg de principio activo se envasan de manera usual en cápsulas de gelatina dura de modo que cada cápsula contenga 20 mg del principio activo.

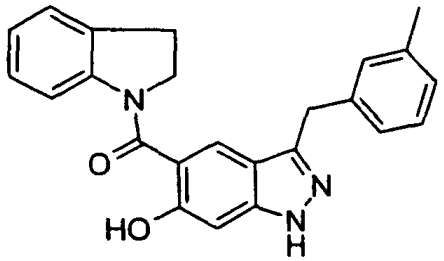
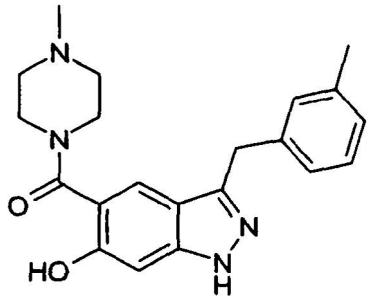
Ejemplo H: Ampollas

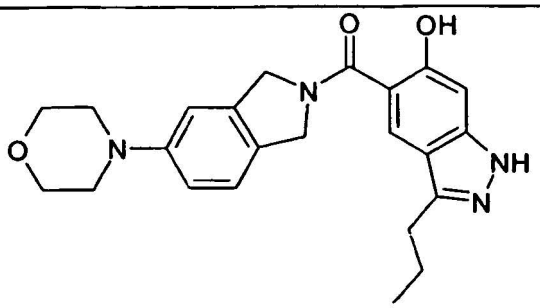
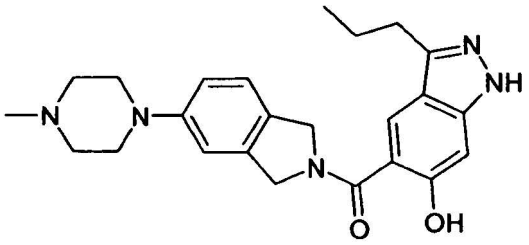
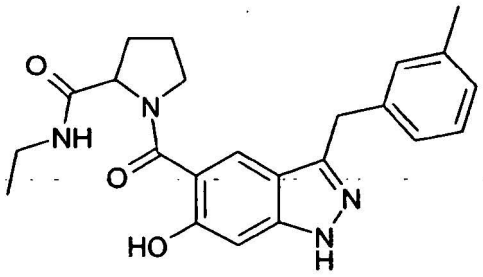
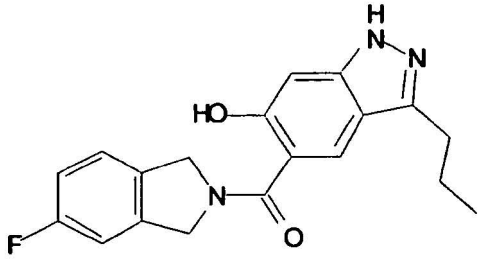
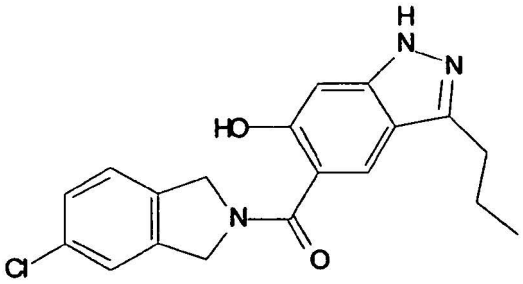
Una solución de 1 kg de un principio activo de la invención en 60 l de agua bidestilada se filtra de manera estéril, se envasa en ampollas, se liofiliza en condiciones estériles y se sellan de manera estéril. Cada ampolla contiene 10 mg de principio activo.

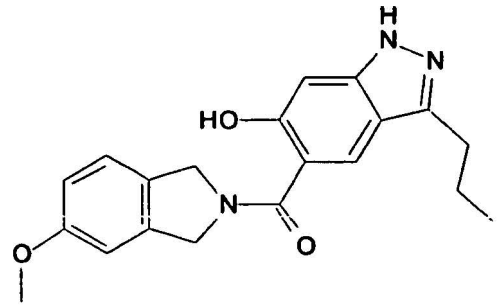
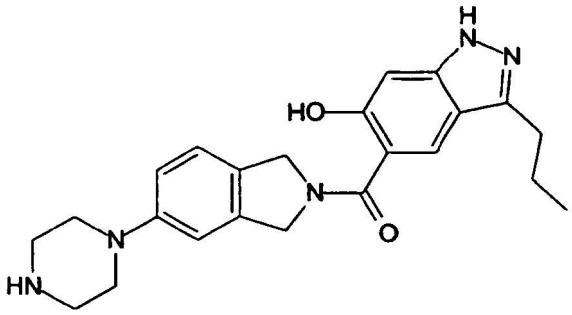
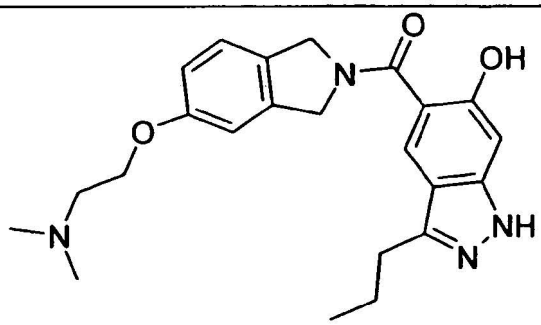
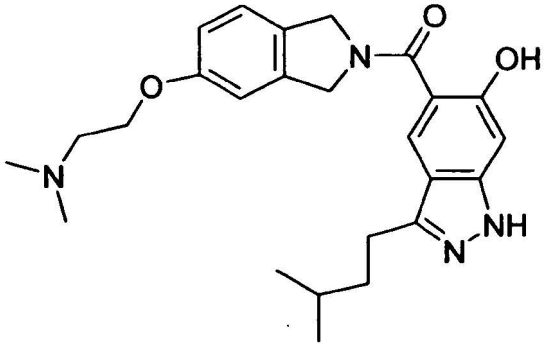
REIVINDICACIONES

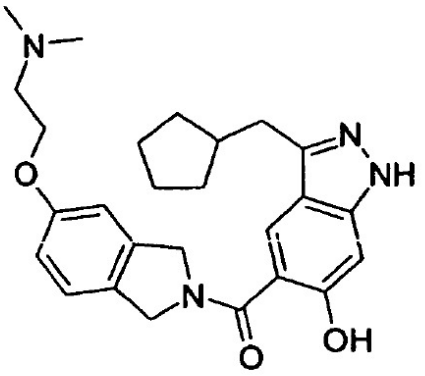
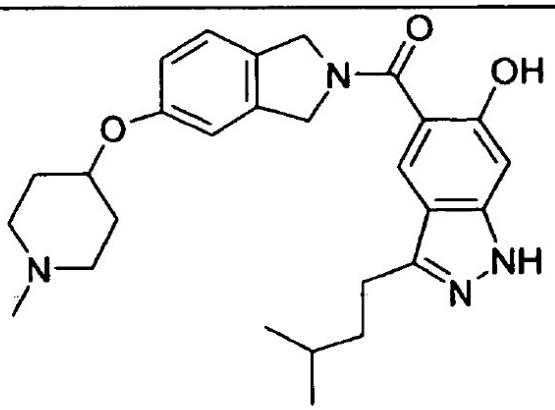
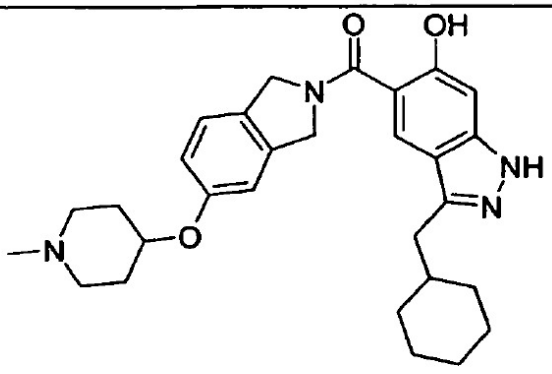
1. Compuestos seleccionados del grupo de

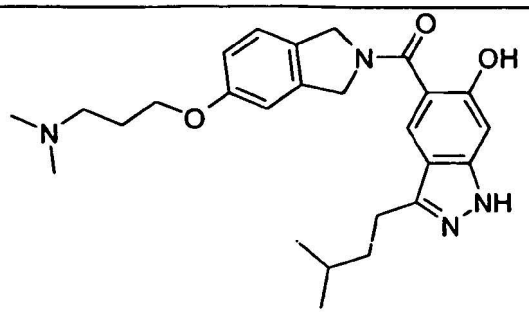
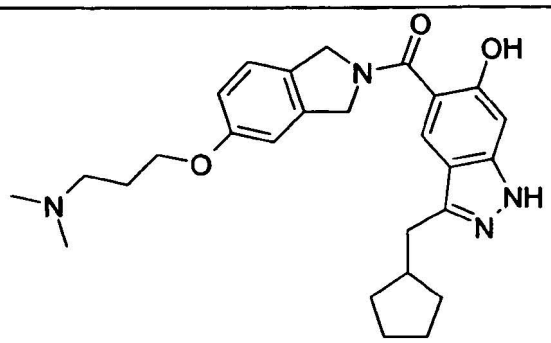
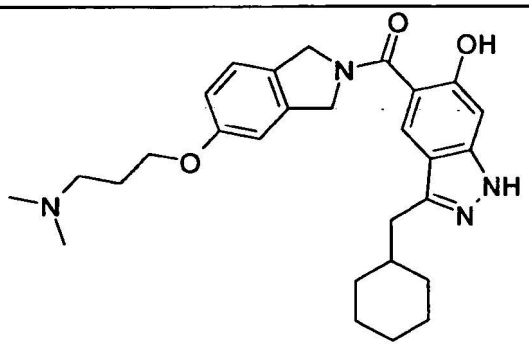
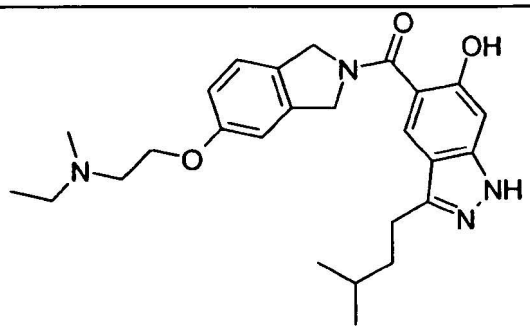
Compuesto	Estructura y/o nombre
"A1"	5-(1,3-dihidro-isoindol-2-il-carbonil)-3-(3-metil-bencil)-6-hidroxi-1H-indazol
"A2"	
"A3"	5-(1,3-Dihidro-isoindol-2-yl-carbonil)-3-(3-metoxi-bencil)-6-hidroxi-1*H*-indazol
"A4"	5-(1,3-Dihidro-isoindol-2-il-carbonil)-3-butil-6-hidroxi-1*H*-indazol
"A5"	 5-(3-Hidroxi-pirrolidin-1-il-carbonil)-3-(3-cloro-bencil)-6-hidroxi-1H-indazol
"A6"	5-(3-Hidroxi-pirrolidin-1-il-carbonil)-3-(3-metil-bencil)-6-hidroxi-1H-indazol
"A7"	5-((R)-3-Hidroxi-pirrolidin-1-il-carbonil)-3-(3-cloro-bencil)-6-hidroxi-1H-indazol
"A8"	5-((R)-3-Hidroxi-pirrolidin-1-il-carbonil)-3-(3-metil-bencil)-6-hidroxi-1H-indazol
"A9"	5-((S)-3-Hidroxi-pirrolidin-1-il-carbonil)-3-(3-metil-bencil)-6-hidroxi-1H-indazol
"A10"	

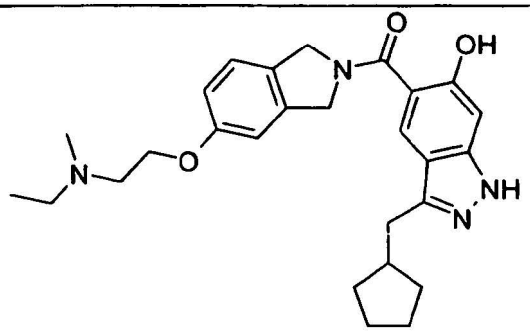
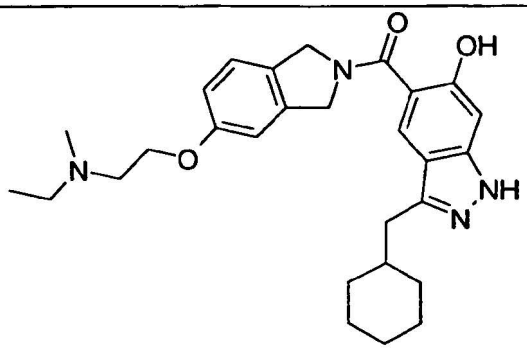
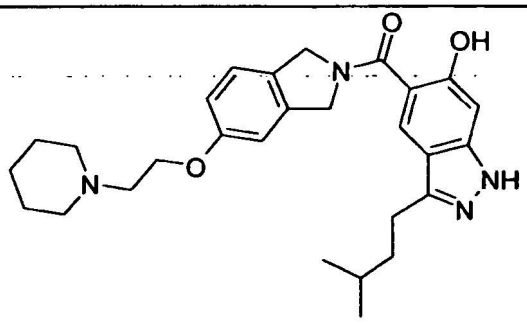
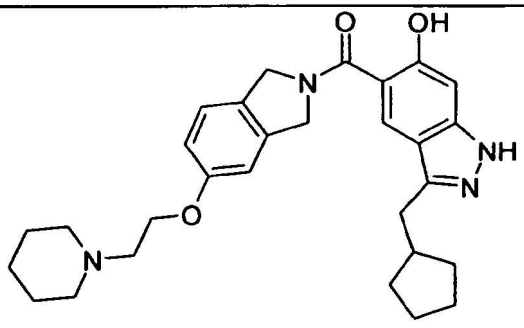
Compuesto	Estructura y/o nombre
"A11"	
"A12"	5-(5-Metoxi-1,3-dihidro-isoindol-2-il-carbonil)-3-(3-metil-bencil)-6-hidroxi-1H-indazol
"A13"	5-(1,3-Dihidro-isoindol-2-il-carbonil)-3-propil-6-hidroxi-1H-indazol
"A14"	5-(5-Brom-1,3-dihidro-isoindol-2-il-carbonil)-3-butil-6-hidroxi-1*H*-indazol
"A15"	5-(5-Brom-1,3-dihidro-isoindol-2-il-carbonil)-3-propil-6-hidroxi-1*H*-indazol
"A16"	5-(Pirrolidin-1-il-carbonil)-3-(3-metil-bencil)-6-hidroxi-1H-indazol
"A17"	
"A18"	5-(1,3-Dihidro-isoindol-2-il-carbonil)-3-cyclopentilmetil-6-hidroxi-1*H*-indazol

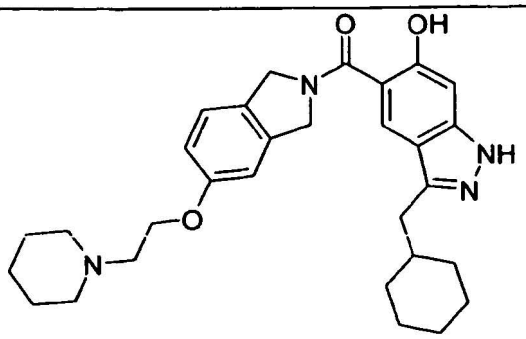
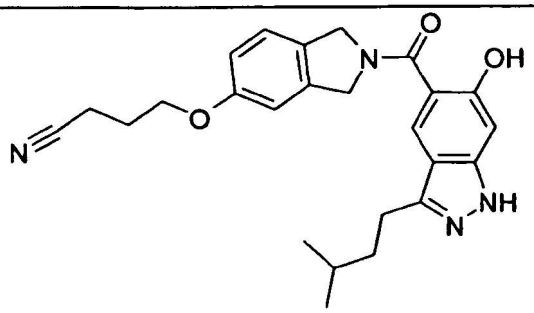
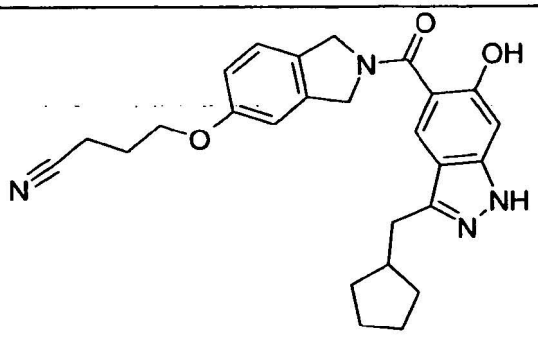
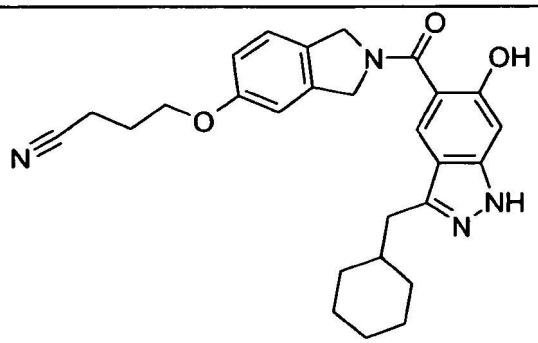
"A19"	
"A20"	
"A21"	
"A22"	
"A23"	

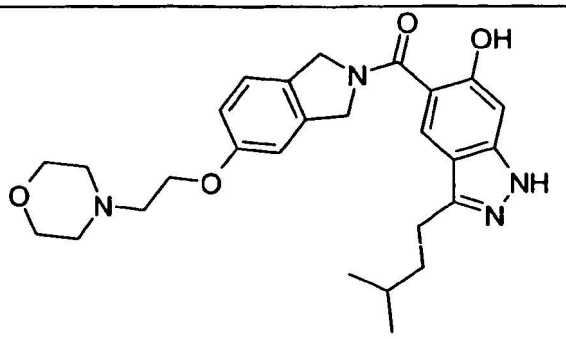
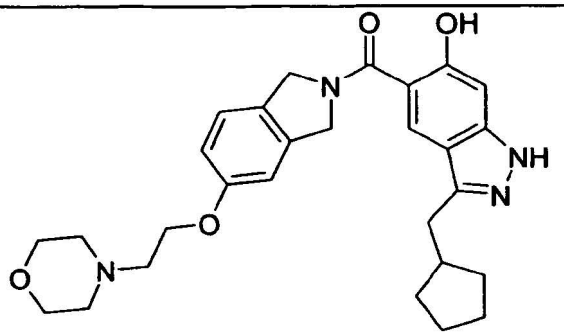
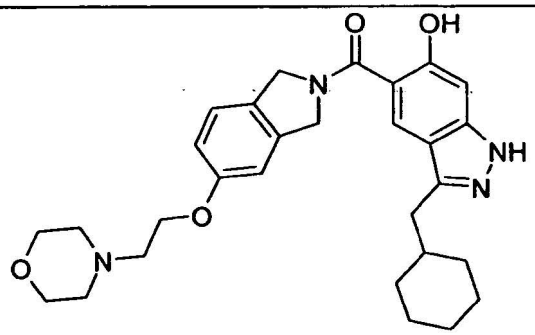
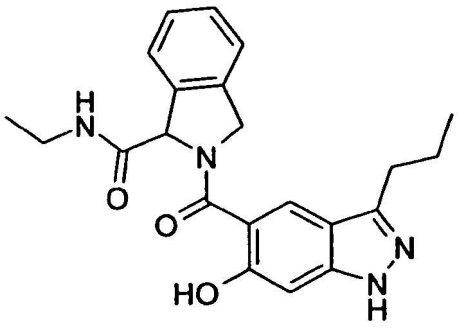
"A24"	
"A25"	
"A26"	
"A27"	

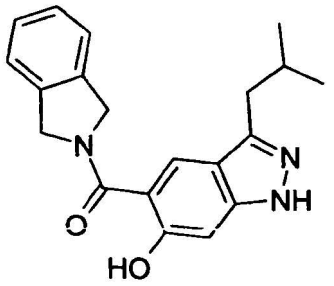
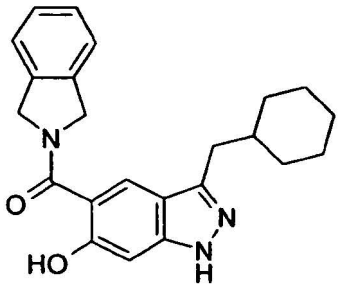
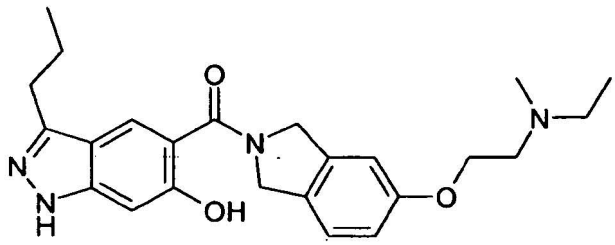
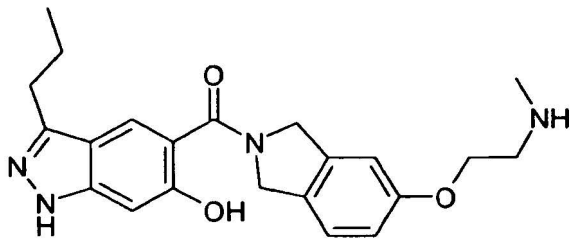
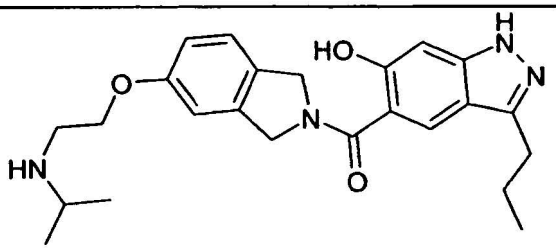
"A28"	
"A29"	(3-ciclohexilmetil-6-hidroxi-1H-indazol-5-il)-[5-(2-dimetilamino-etoxi) -1,3-dihidro-isoindol-2-il]-metanona
"A30"	
"A31"	(3-ciclopentilmetil-6-hidroxi-1H-indazol-5-il)-[5-(1-metil- piperidin -4-iloxi)-1,3-dihidro-isoindol-2-il]-metanona
"A32"	

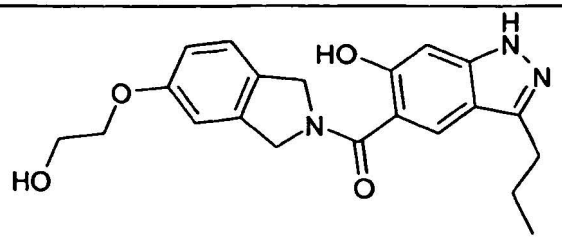
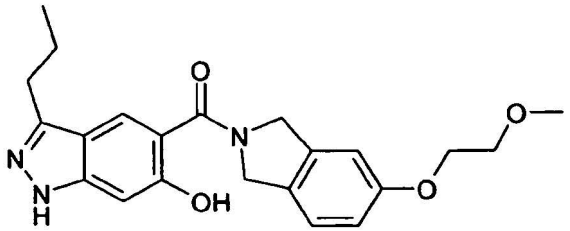
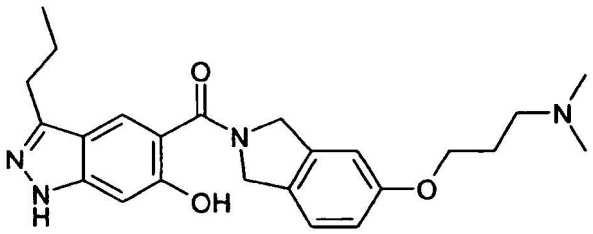
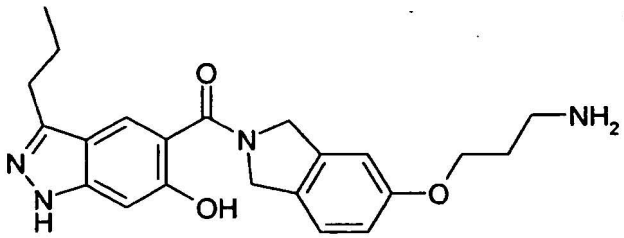
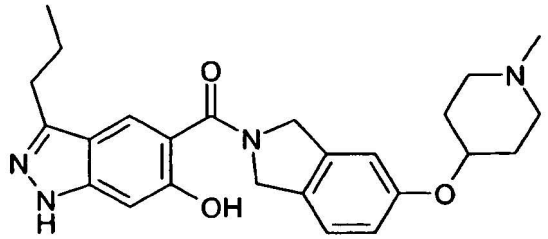
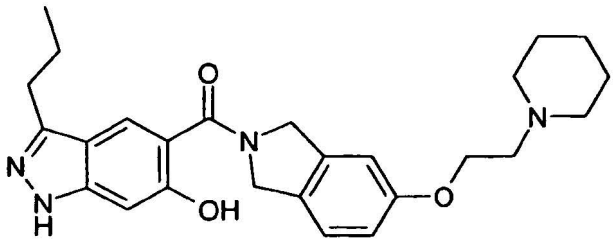
"A33"	
"A34"	
"A35"	
"A36"	

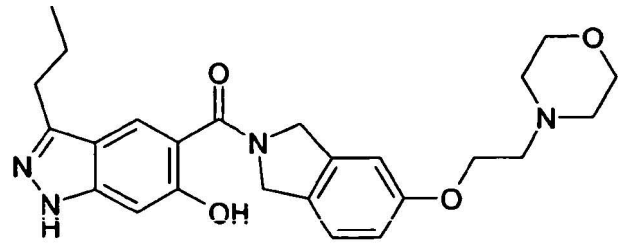
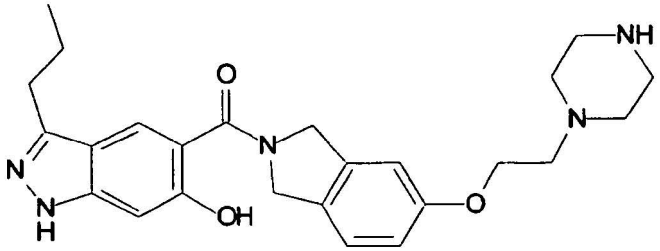
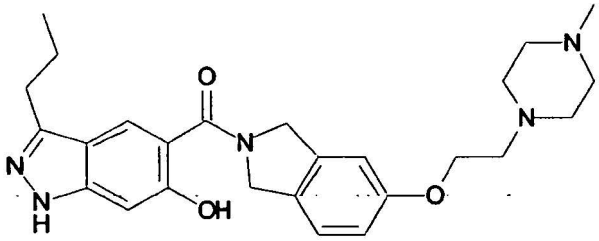
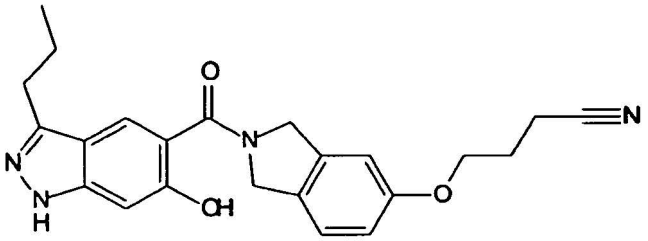
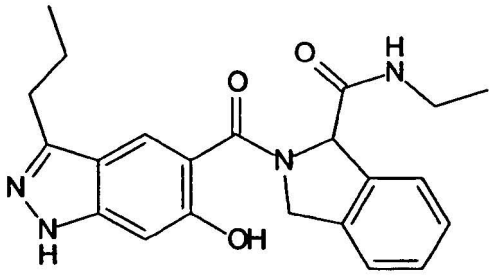
"A37"	
"A38"	
"A39"	
"A40"	

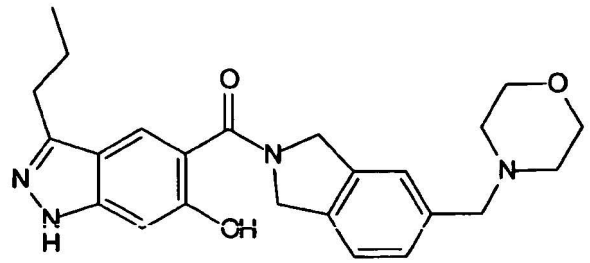
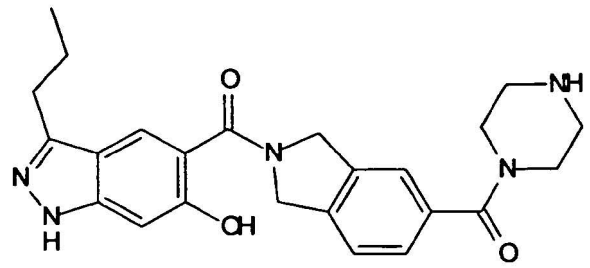
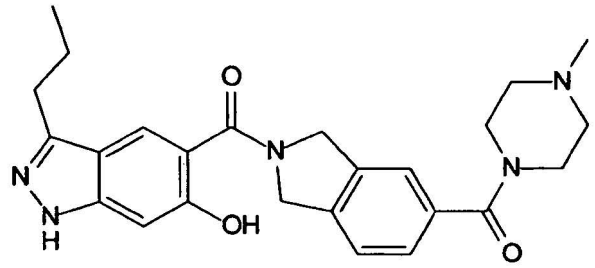
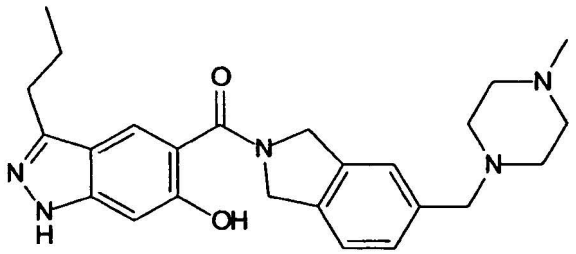
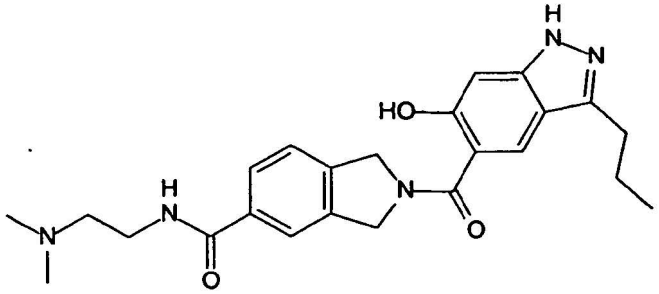
"A41"	
"A42"	
"A43"	
"A44"	

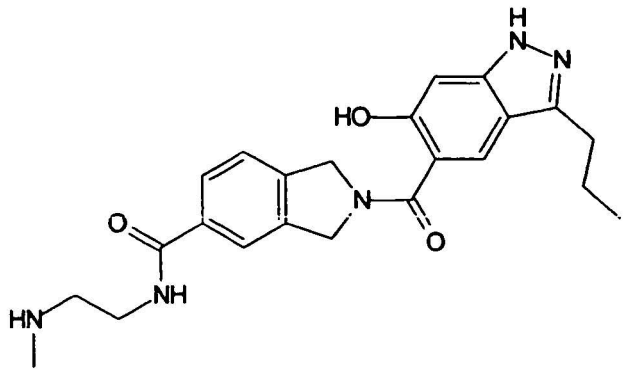
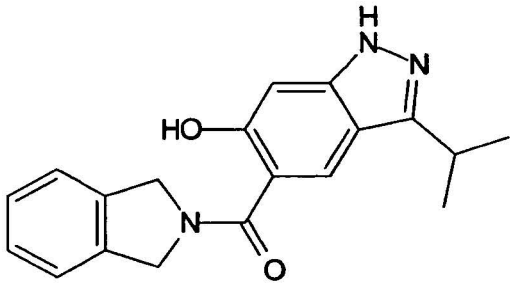
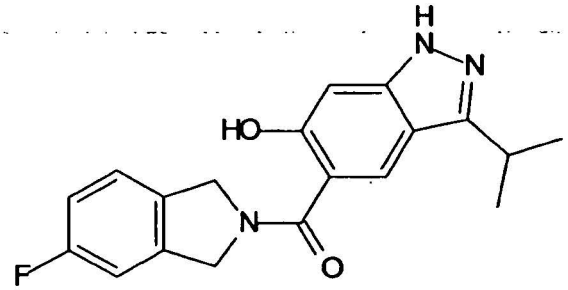
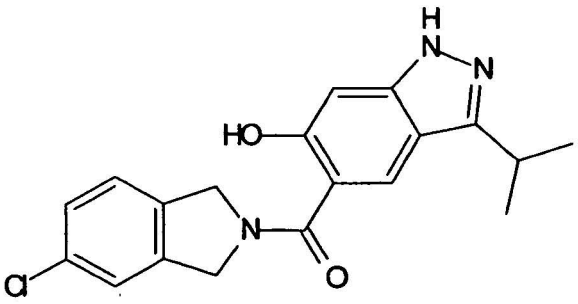
"A45"	
"A46"	
"A47"	
"A48"	

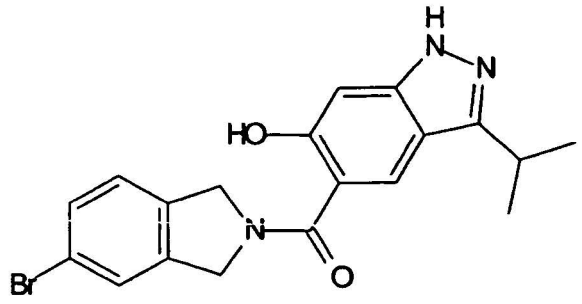
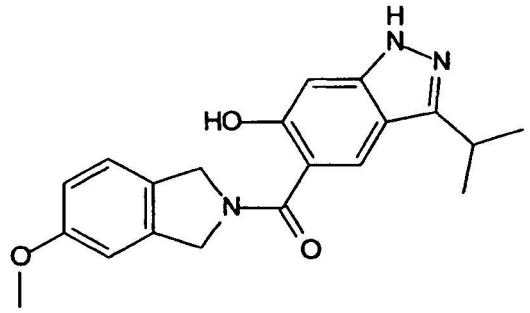
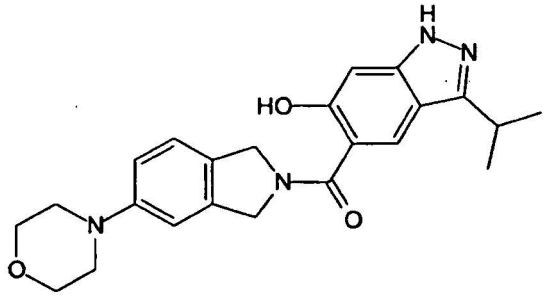
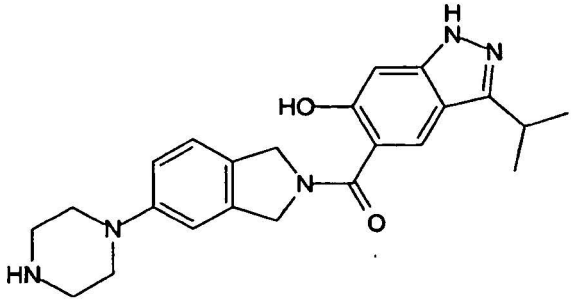
"A49"	
"A50"	
"A51"	
"A52"	
"A53"	

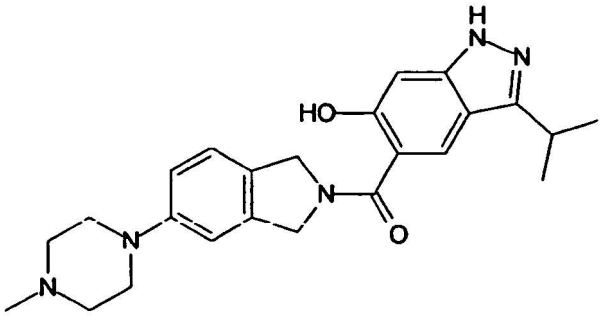
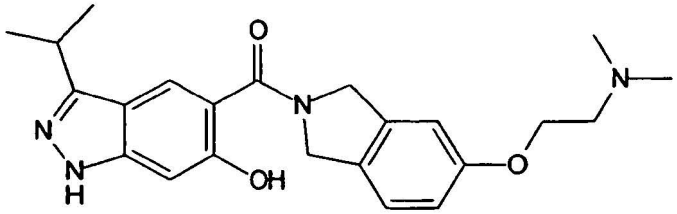
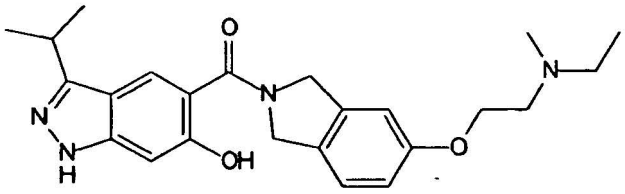
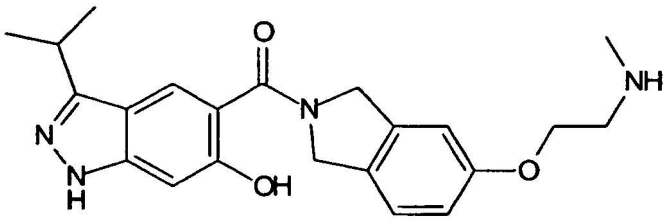
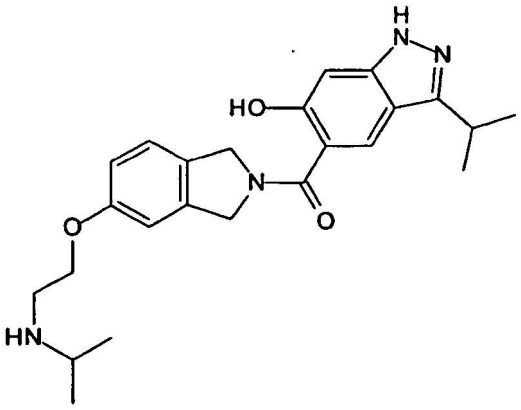
"A54"	
"A55"	
"A56"	
"A57"	
"A58"	
"A59"	

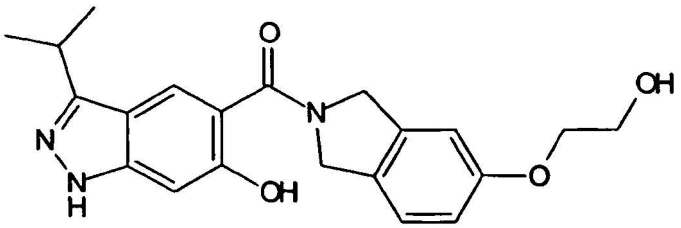
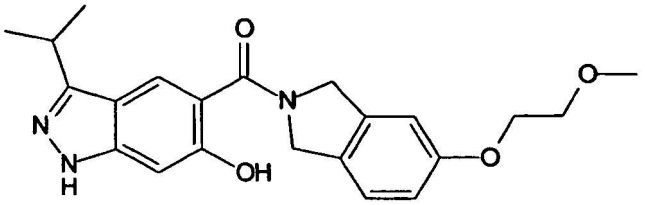
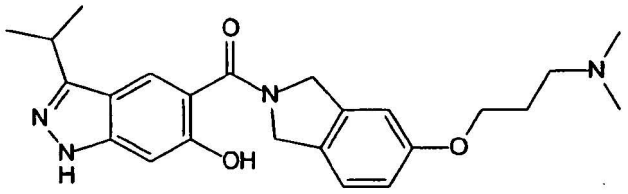
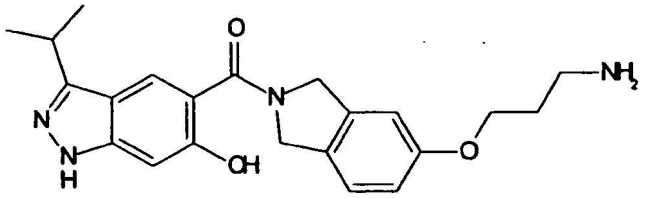
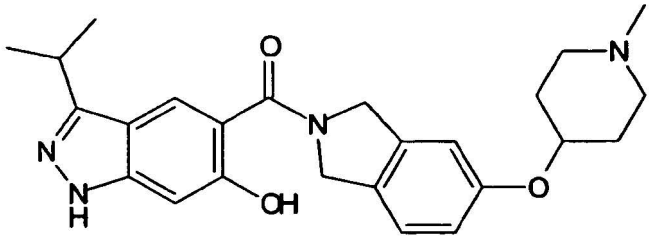
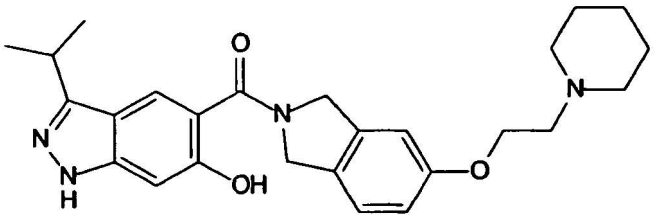
"A60"	
"A61"	
"A62"	
"A63"	
"A64"	

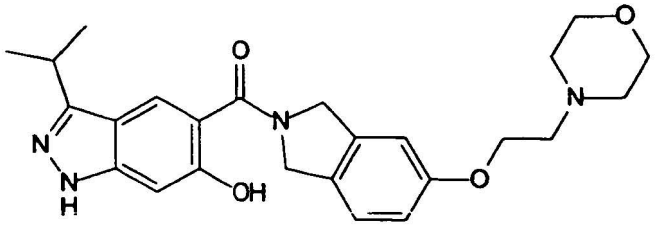
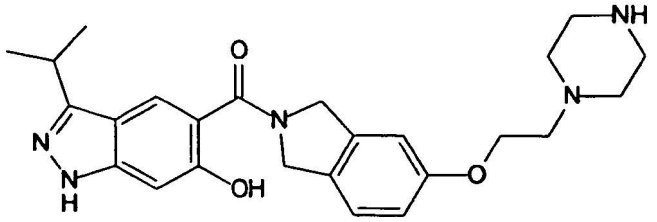
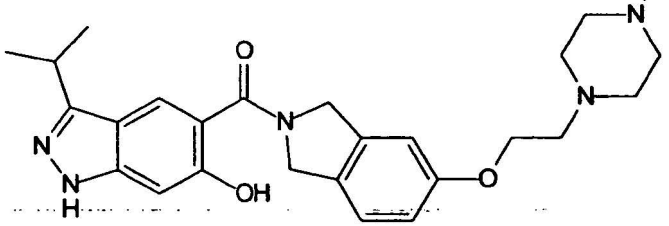
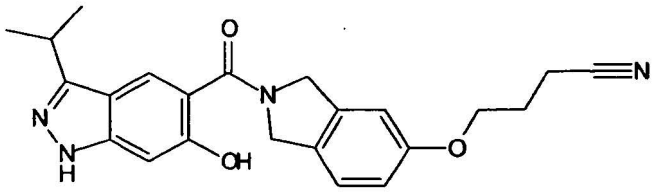
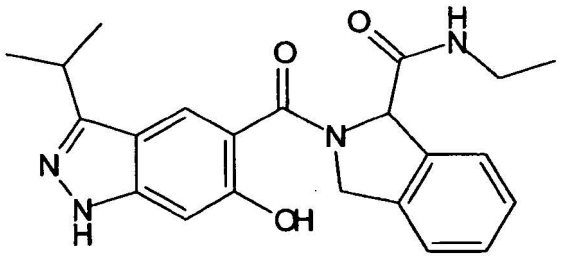
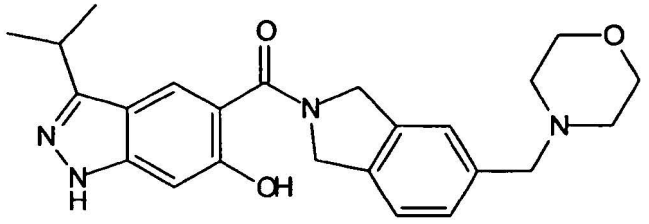
"A65"	
"A66"	
"A67"	
"A68"	
"A69"	

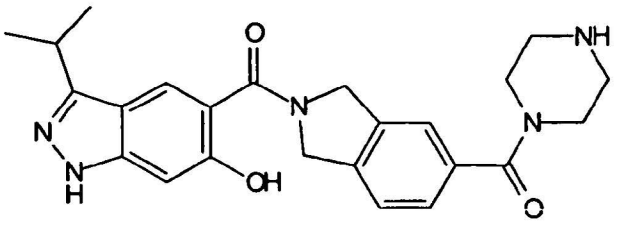
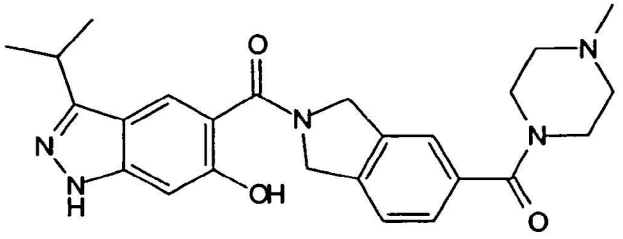
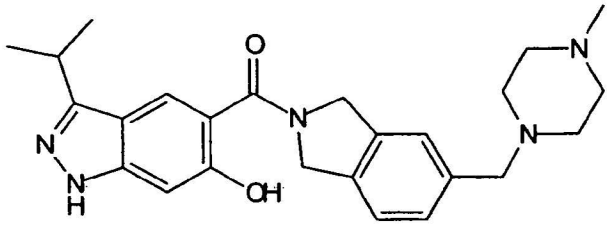
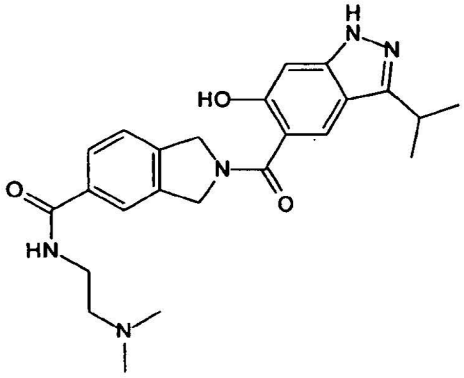
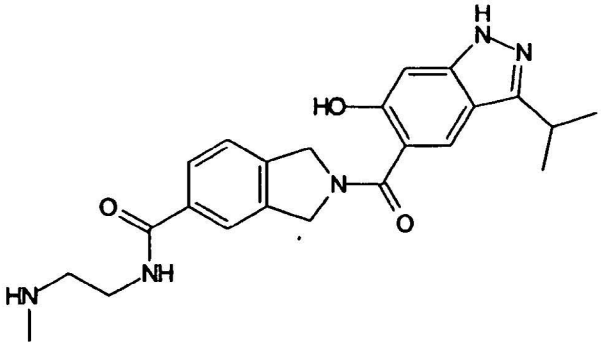
"A70"	
"A71"	
"A72"	
"A73"	

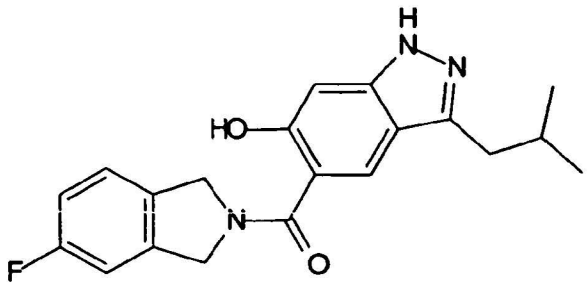
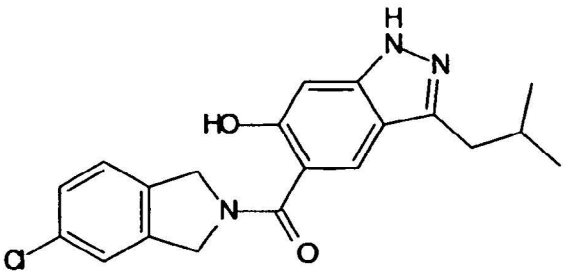
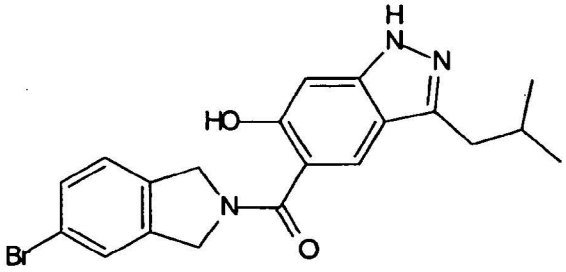
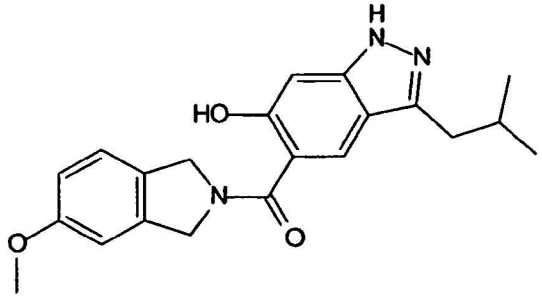
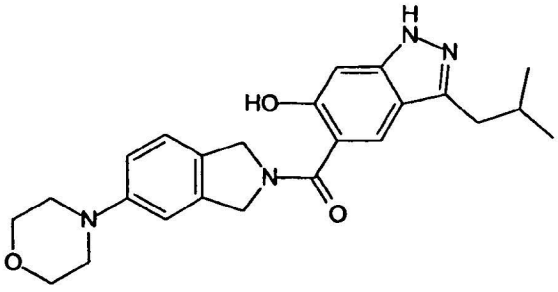
"A74"	
"A75"	
"A76"	
"A77"	

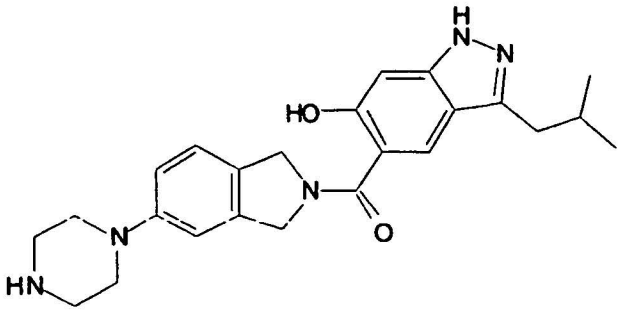
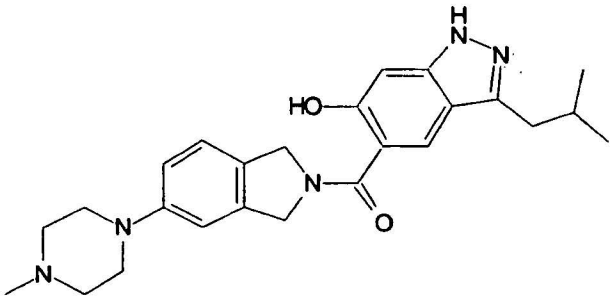
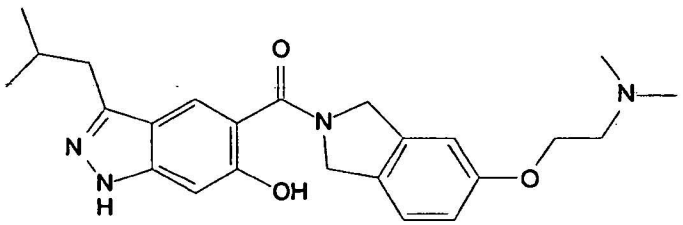
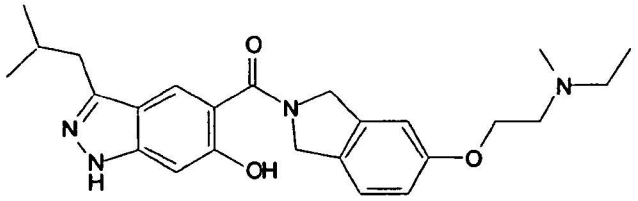
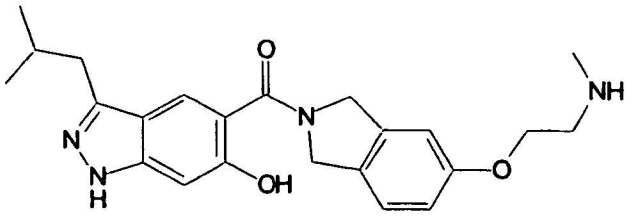
"A78"	
"A79"	
"A80"	
"A81"	
"A82"	

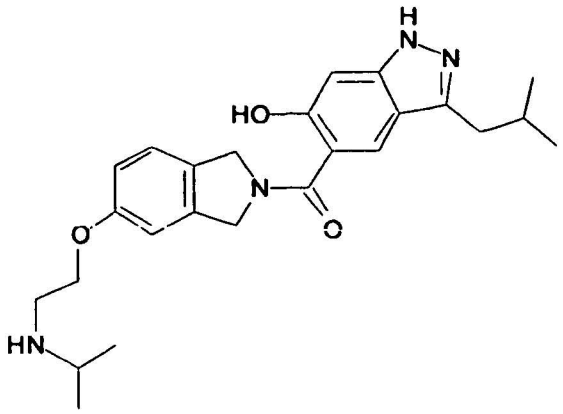
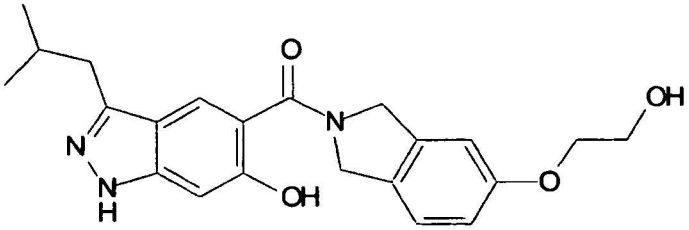
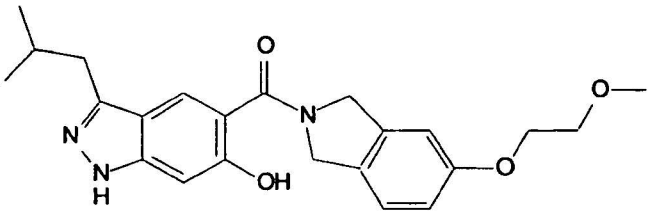
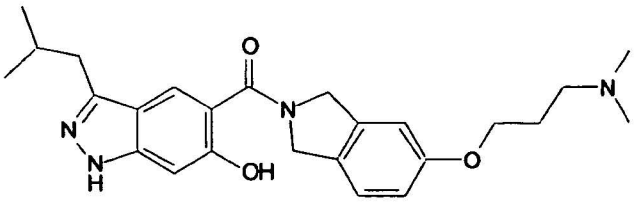
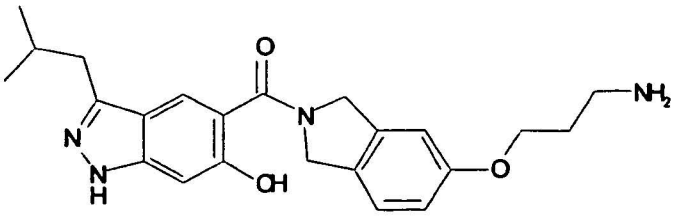
"A83"	
"A84"	
"A85"	
"A86"	
"A87"	
"A88"	

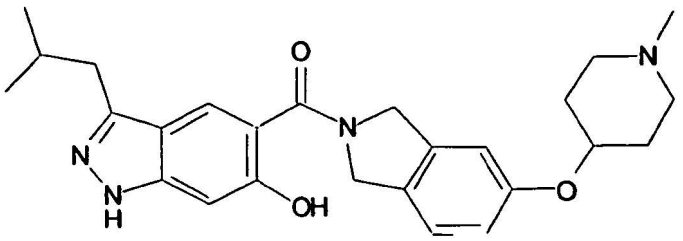
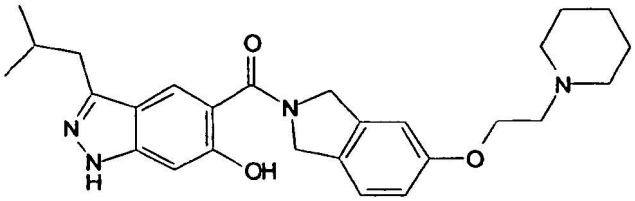
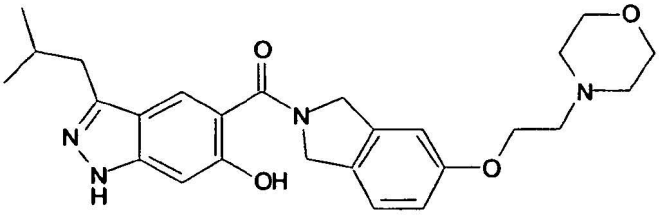
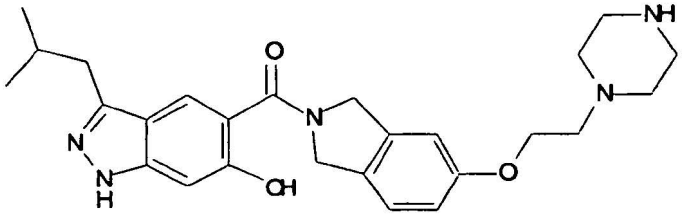
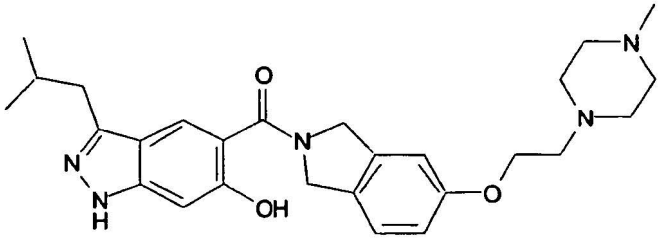
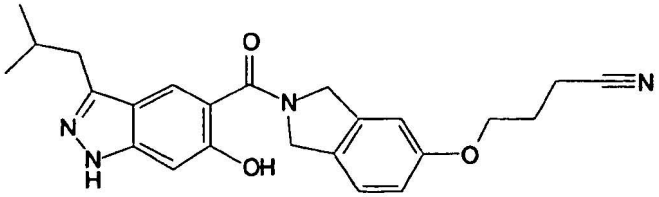
"A89"	
"A90"	
"A91"	
"A92"	
"A93"	
"A94"	

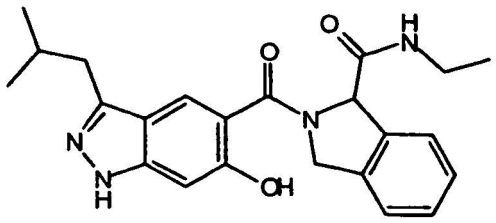
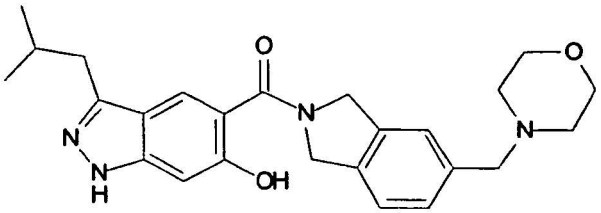
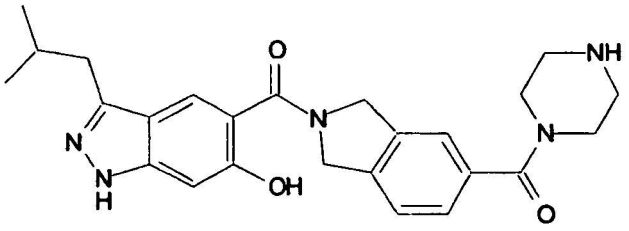
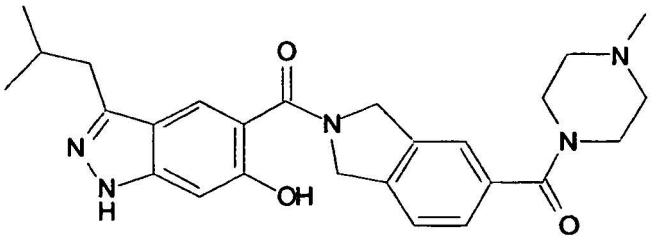
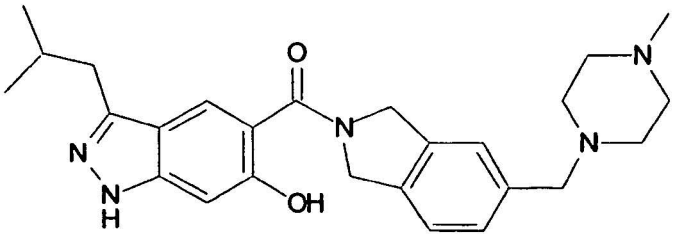
"A95"	
"A96"	
"A97"	
"A98"	
"A99"	

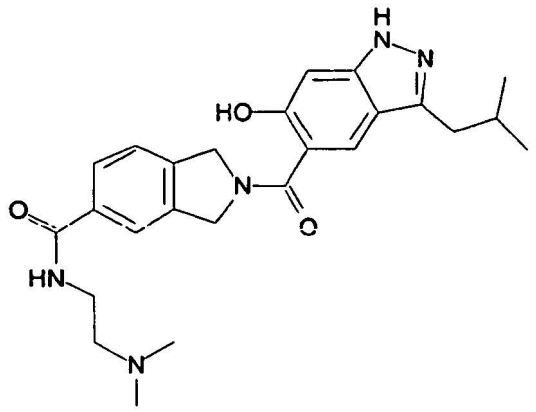
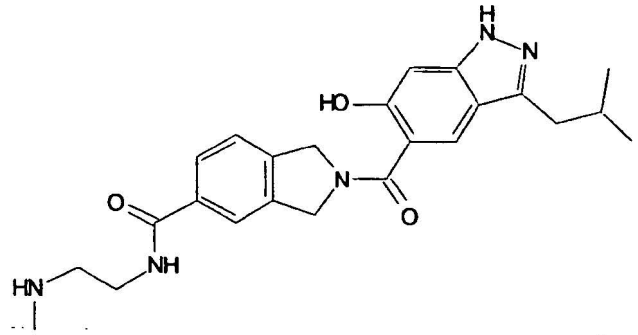
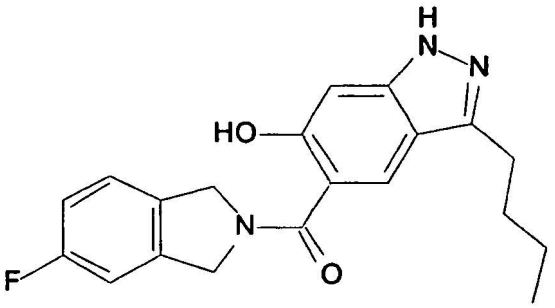
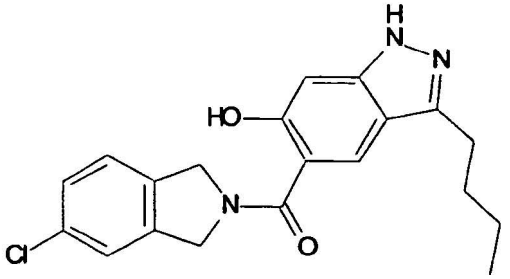
"A100"	
"A101"	
"A102"	
"A103"	
"A104"	

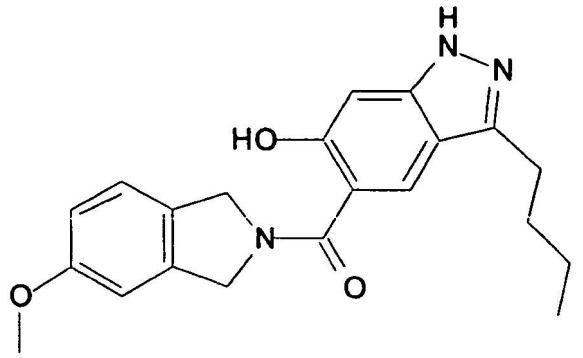
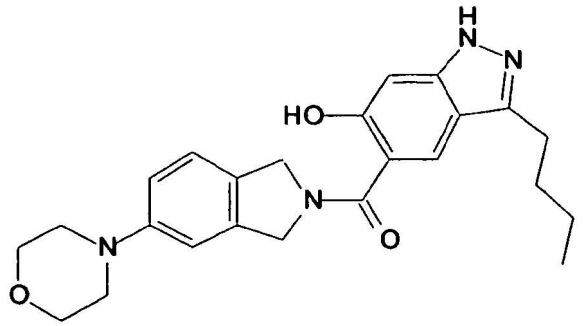
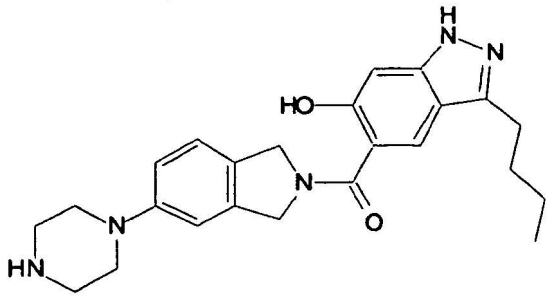
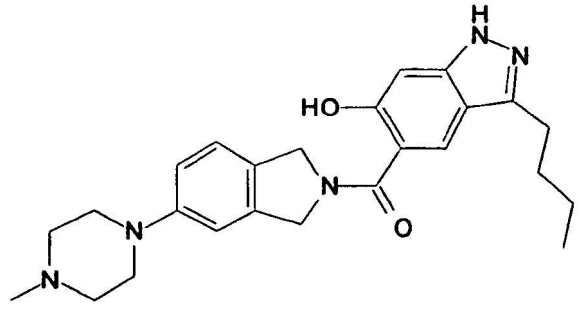
"A105"	
"A106"	
"A107"	
"A108"	
"A109"	

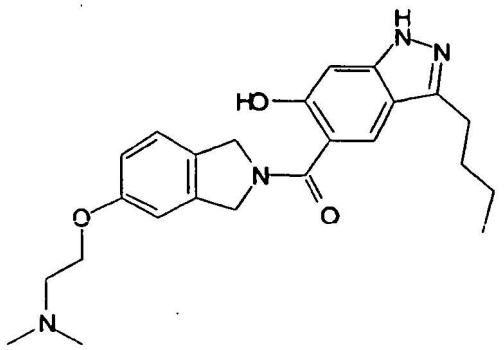
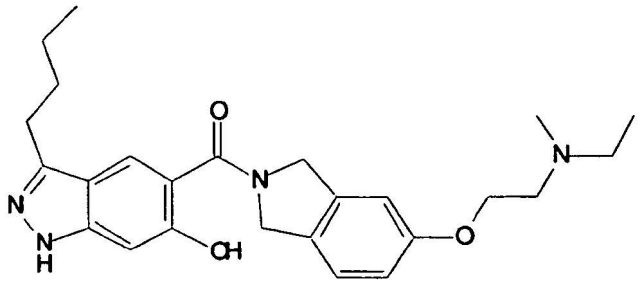
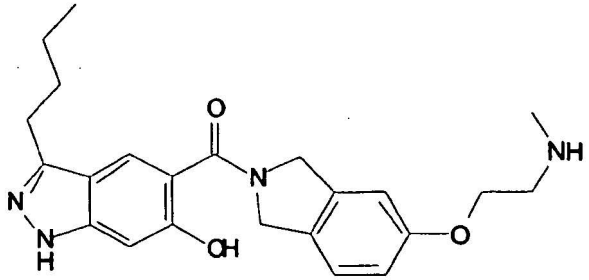
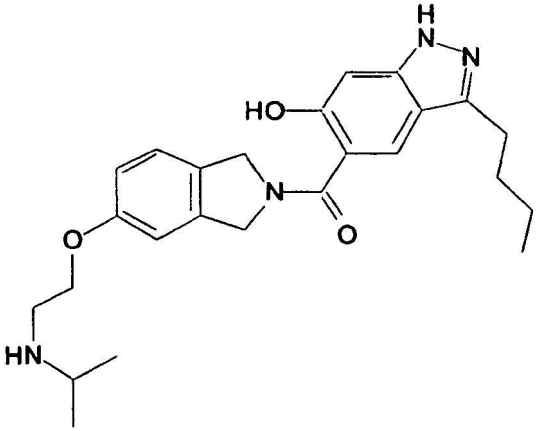
"A110"	
"A111"	
"A112"	
"A113"	
"A114"	

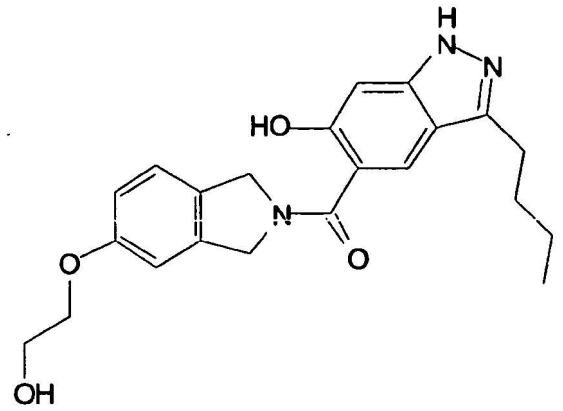
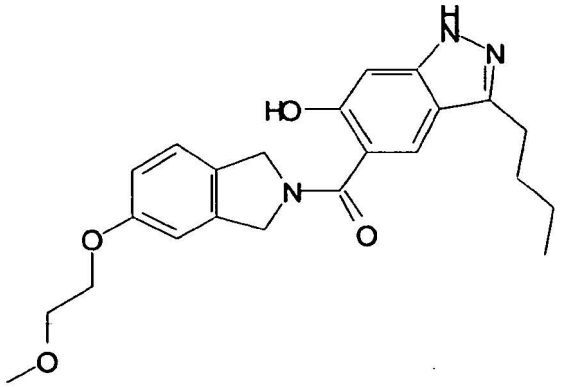
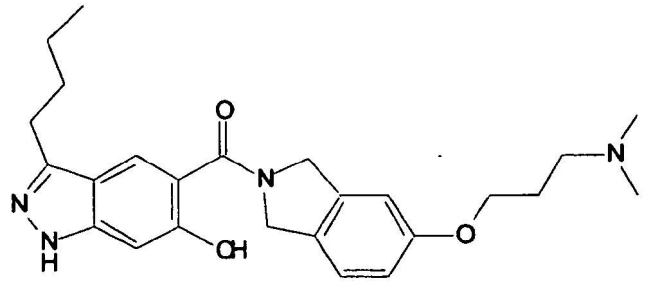
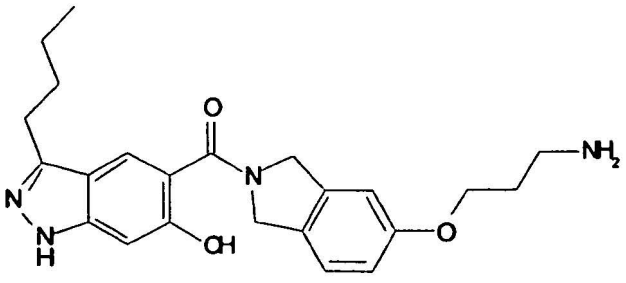
"A115"	
"A116"	
"A117"	
"A118"	
"A119"	
"A120"	

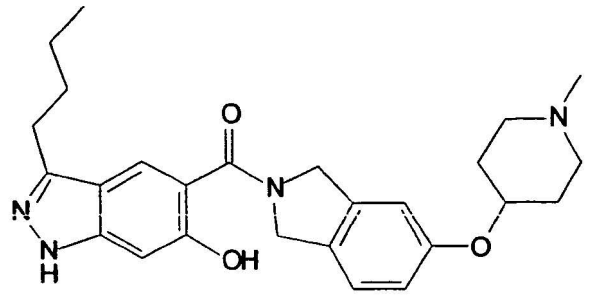
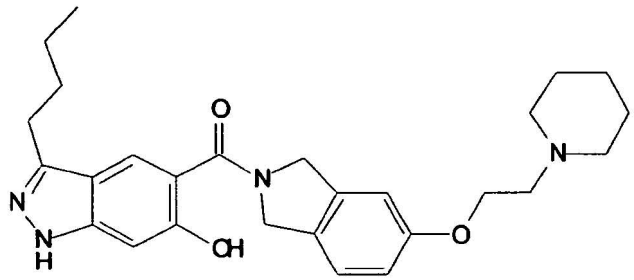
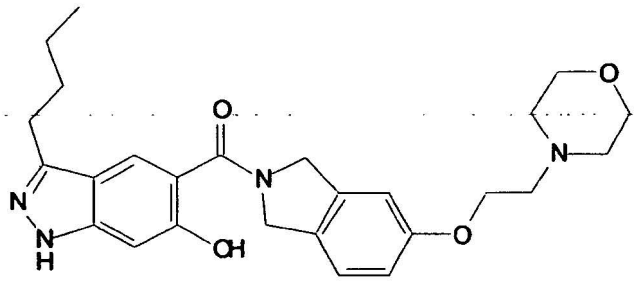
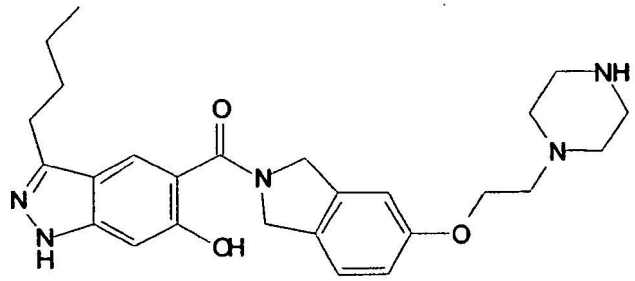
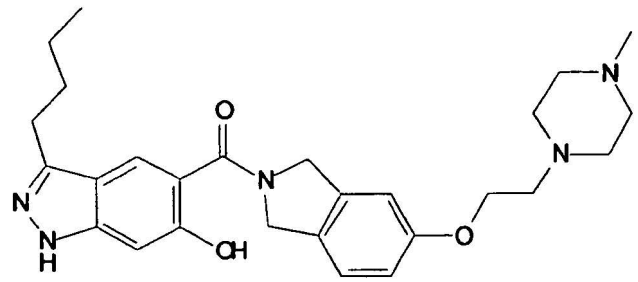
"A121"	
"A122"	
"A123"	
"A124"	
"A125"	

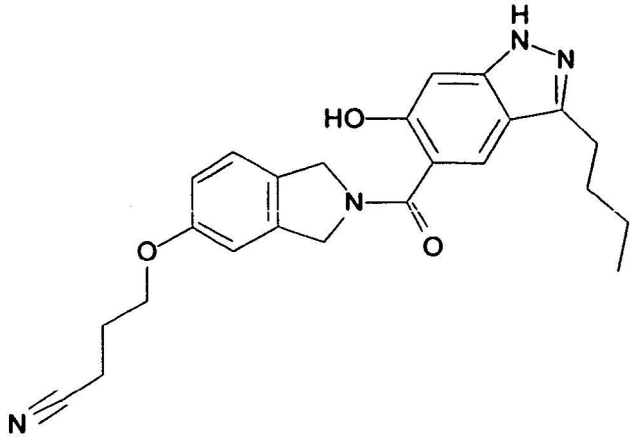
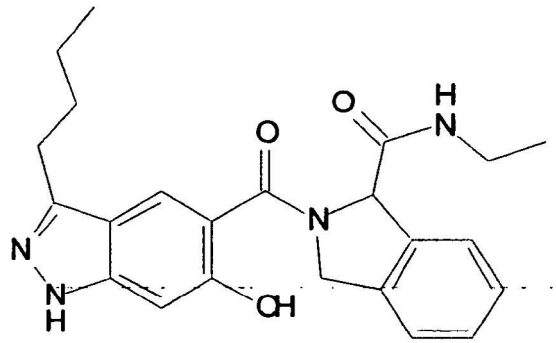
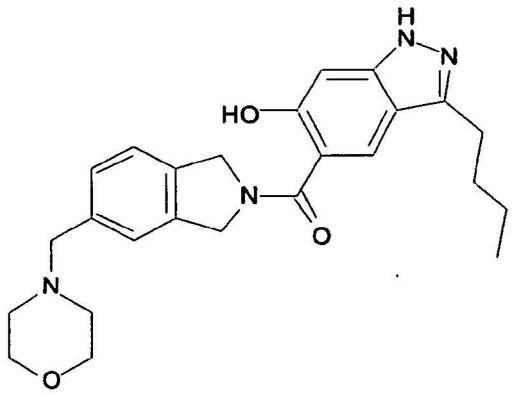
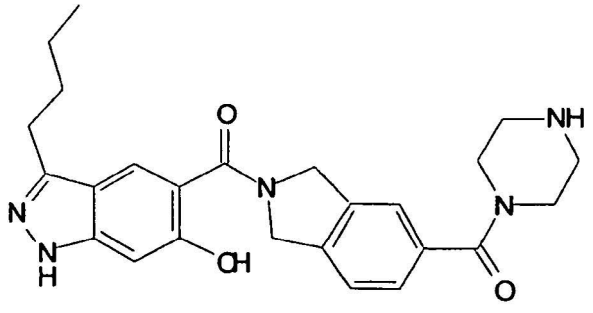
"A126"	
"A127"	
"A128"	
"A129"	

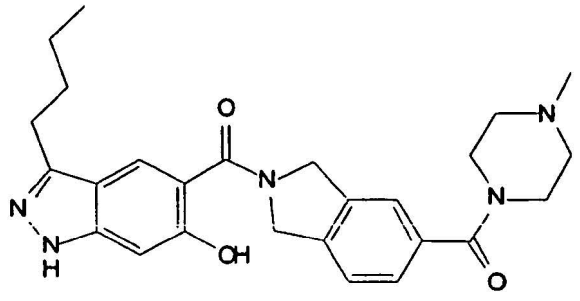
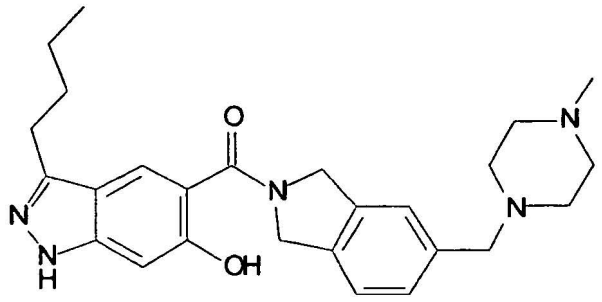
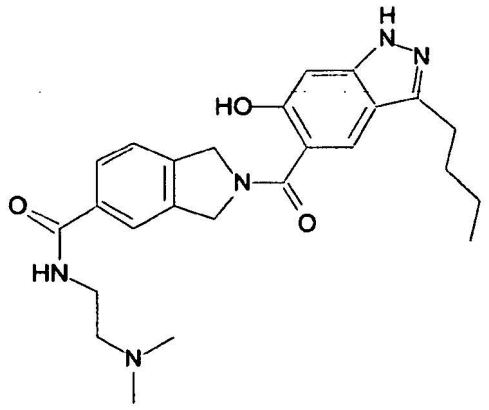
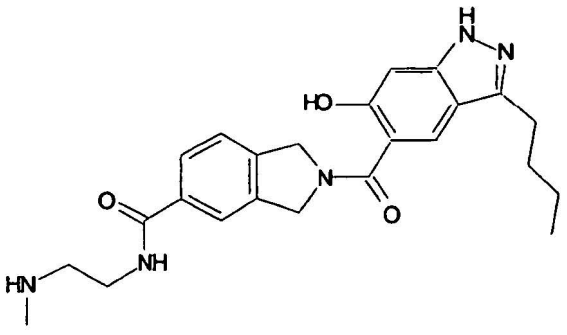
"A130"	
"A131"	
"A132"	
"A133"	

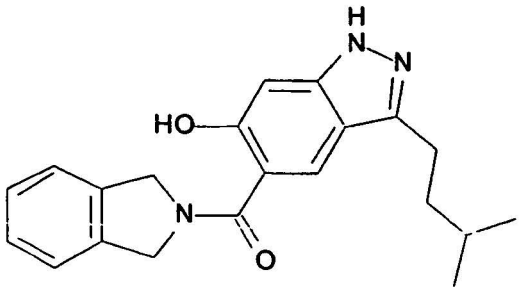
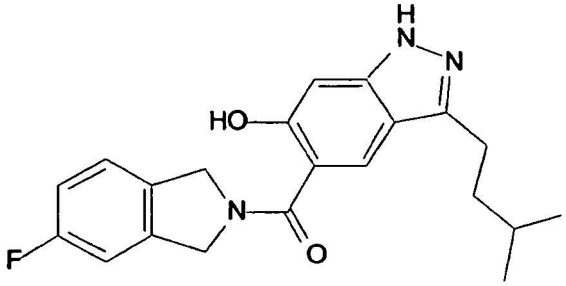
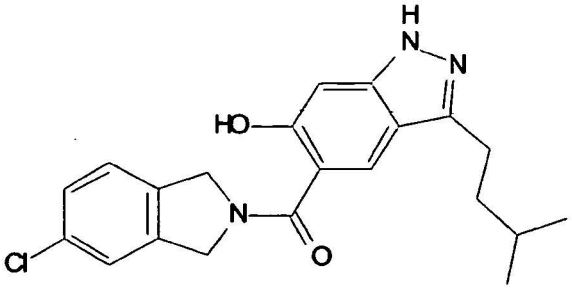
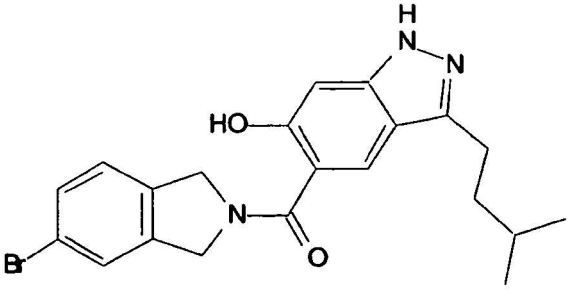
"A134"	
"A135"	
"A136"	
"A137"	

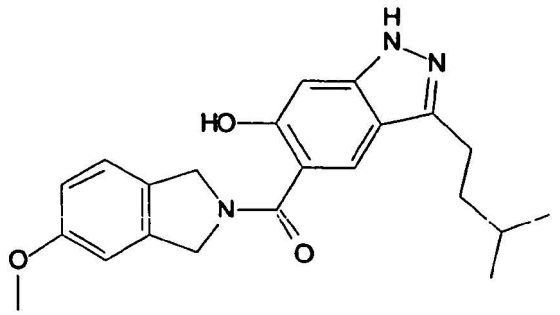
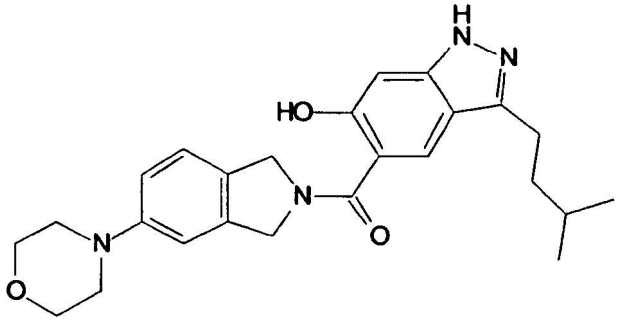
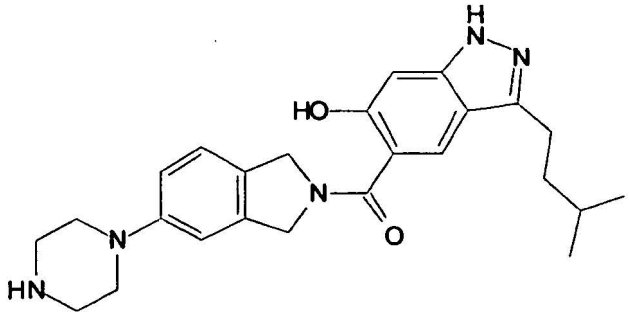
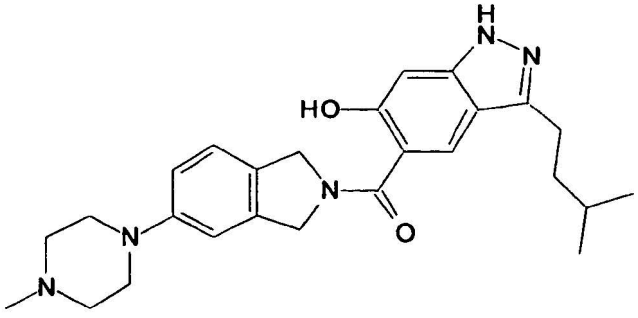
"A138"	
"A139"	
"A140"	
"A141"	

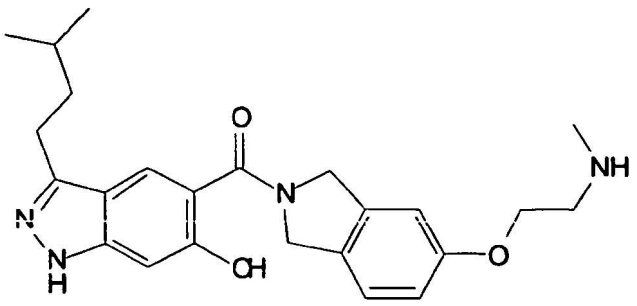
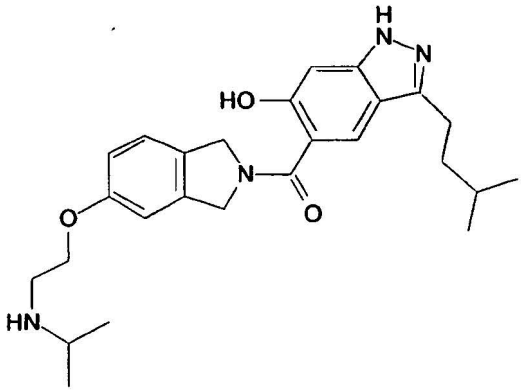
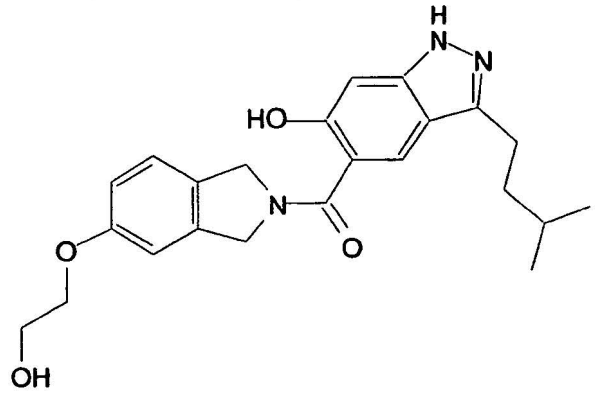
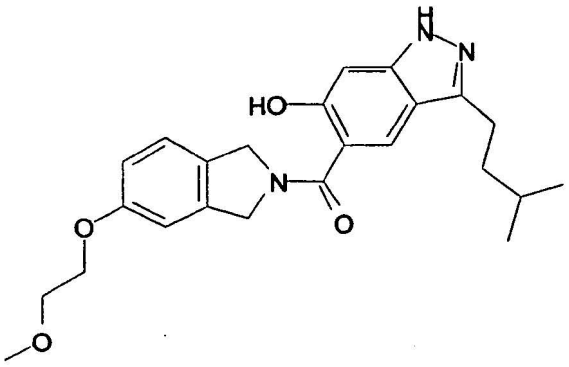
"A142"	
"A143"	
"A144"	
"A145"	
"A146"	

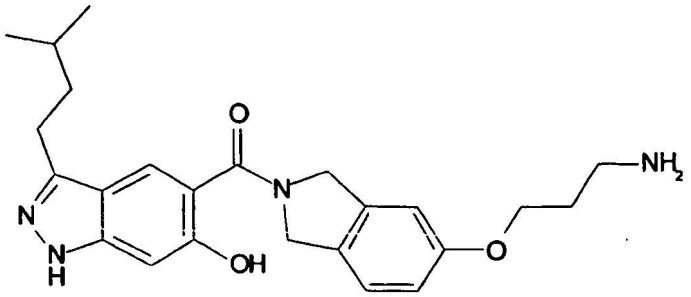
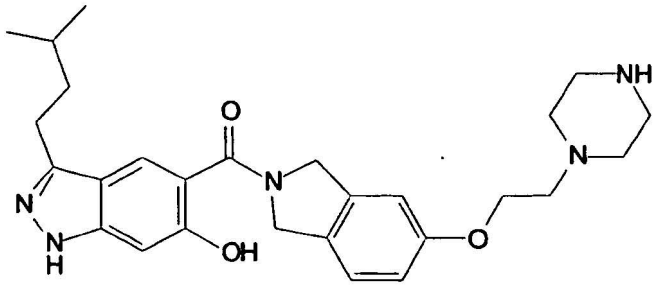
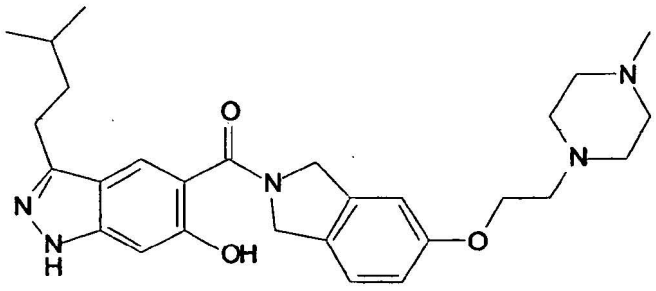
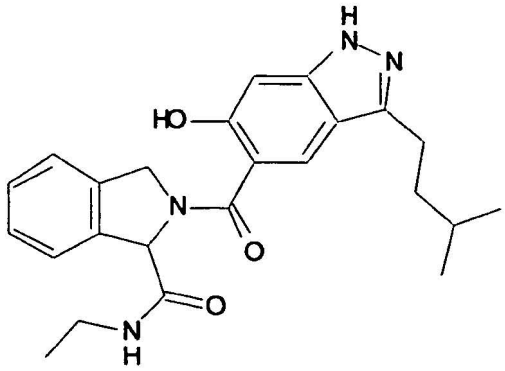
"A147"	
"A148"	
"A149"	
"A150"	

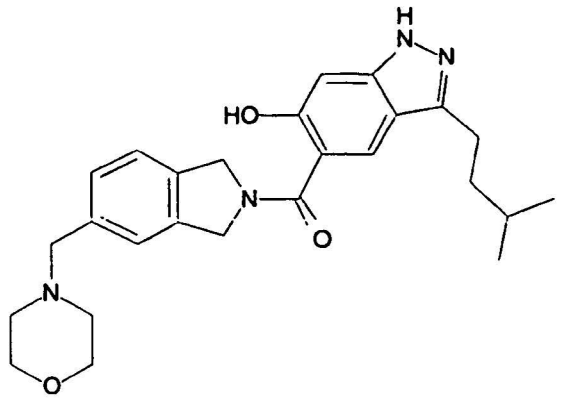
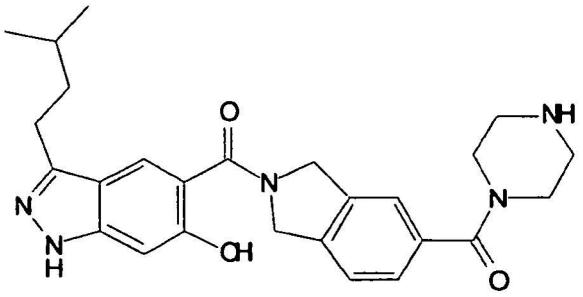
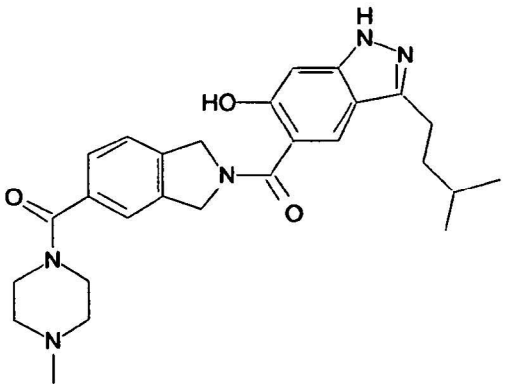
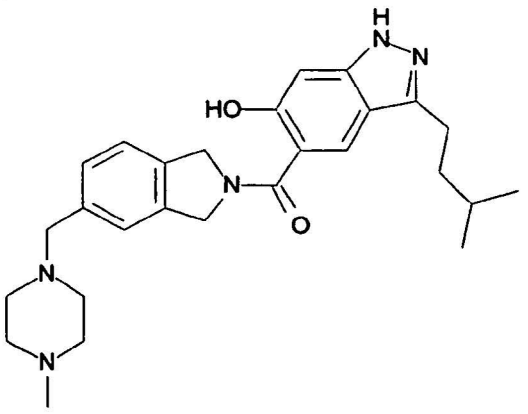
"A151"	
"A152"	
"A153"	
"A154"	

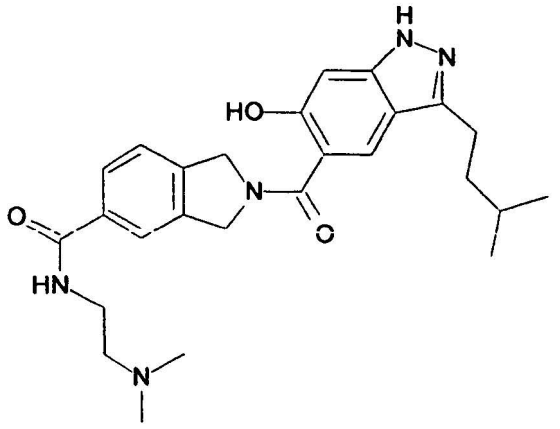
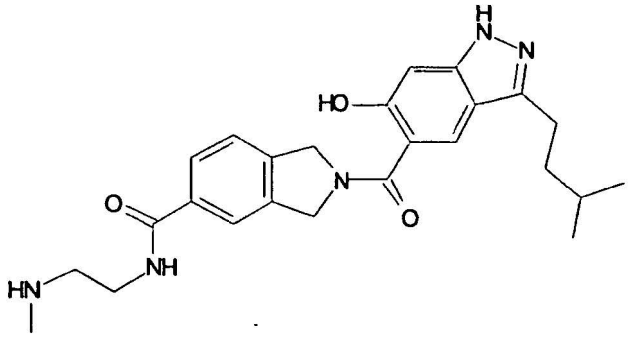
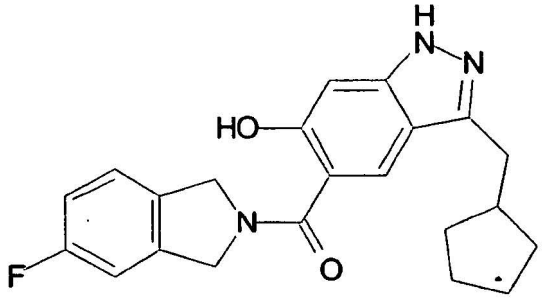
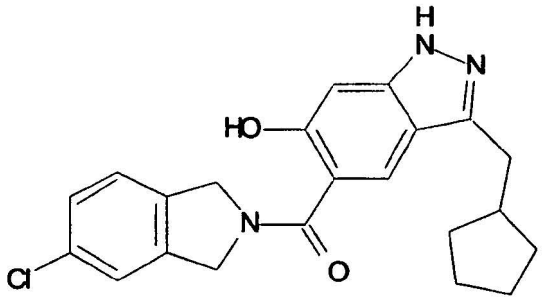
"A155"	
"A156"	
"A157"	
"A158"	

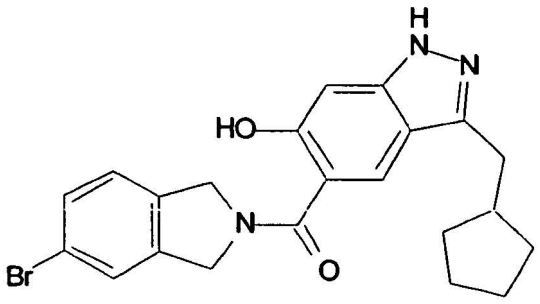
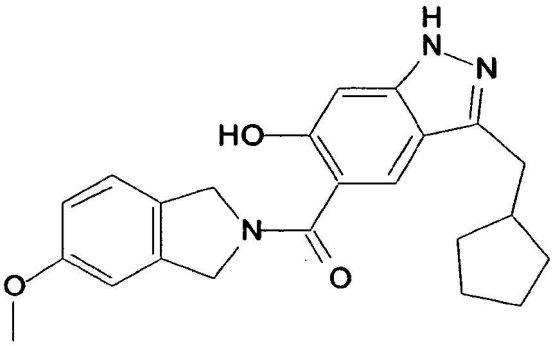
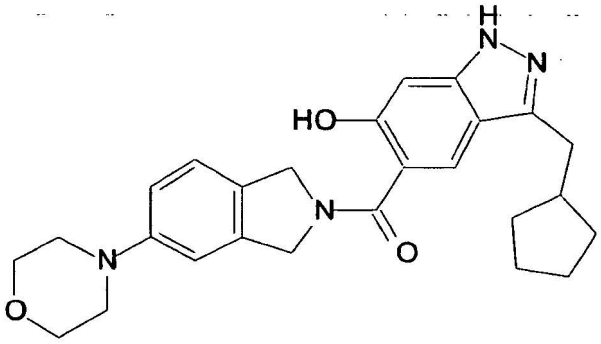
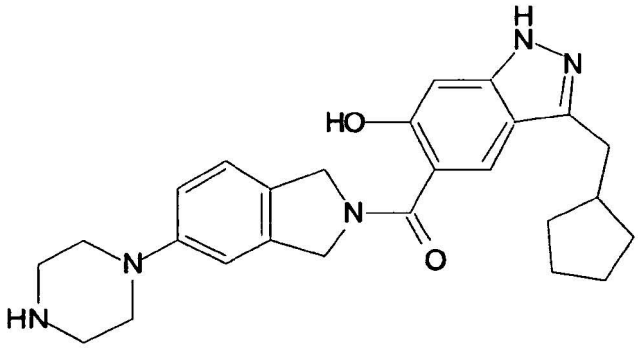
"A159"	
"A160"	
"A161"	
"A162"	

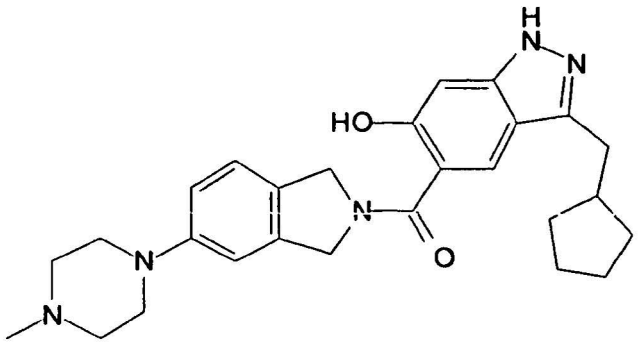
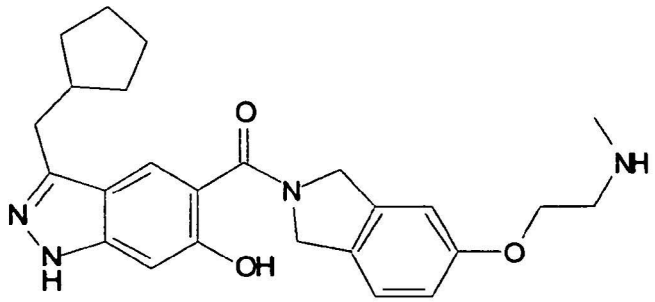
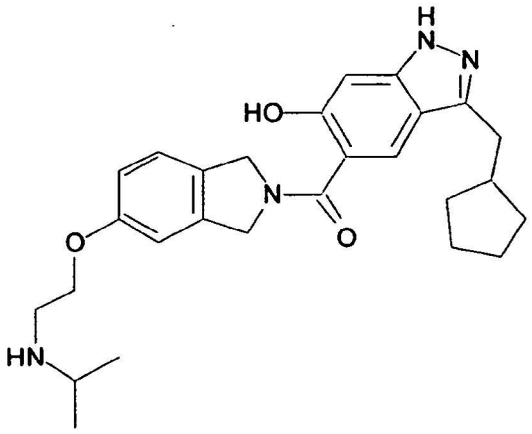
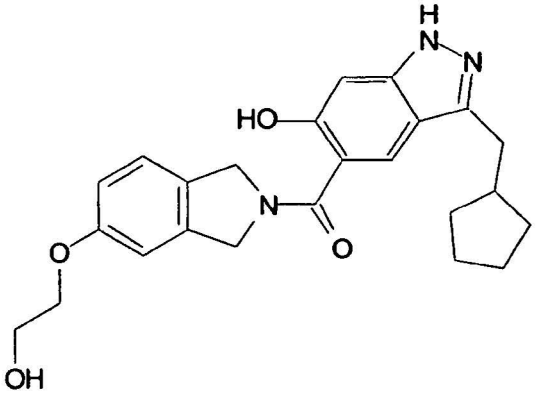
"A163"	
"A164"	
"A165"	
"A166"	

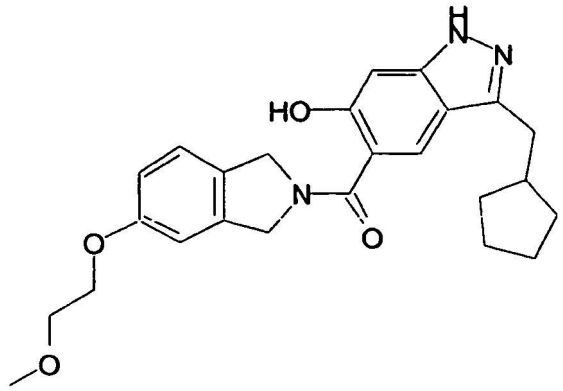
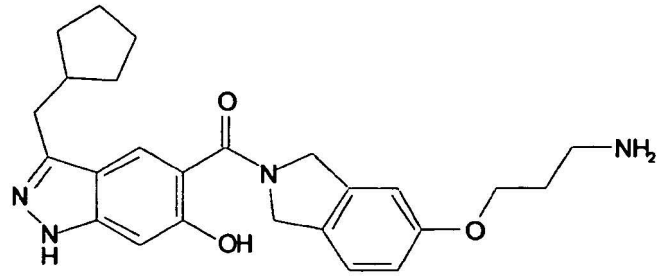
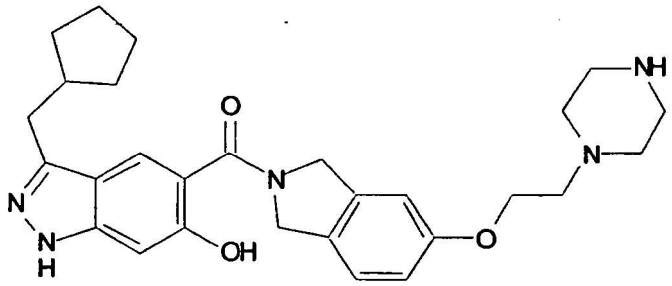
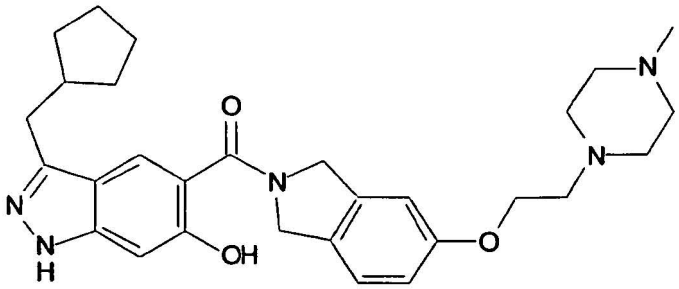
"A167"	
"A168"	
"A169"	
"A170"	

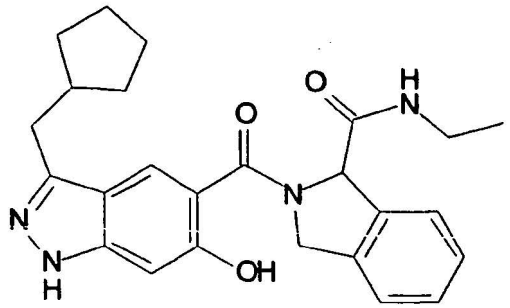
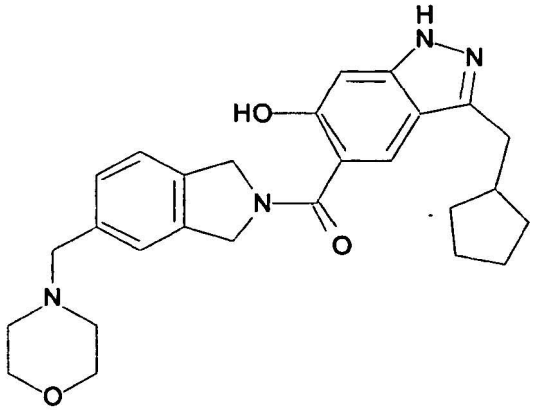
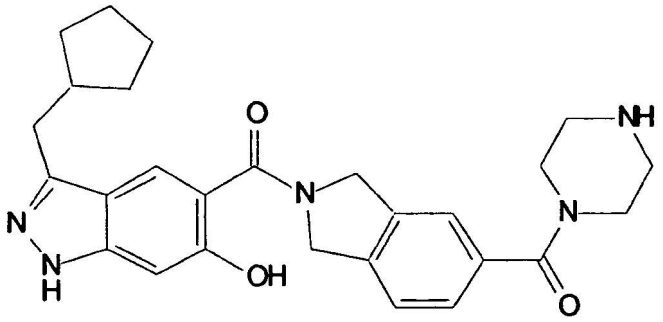
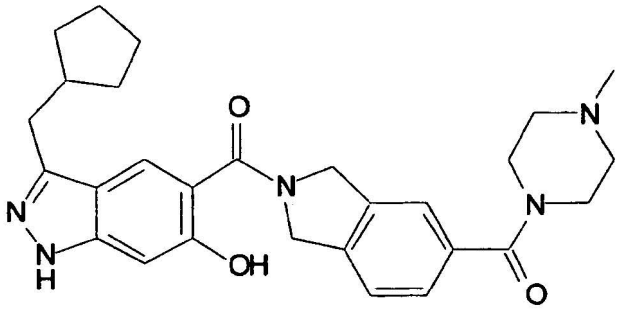
"A171"	
"A172"	
"A173"	
"A174"	

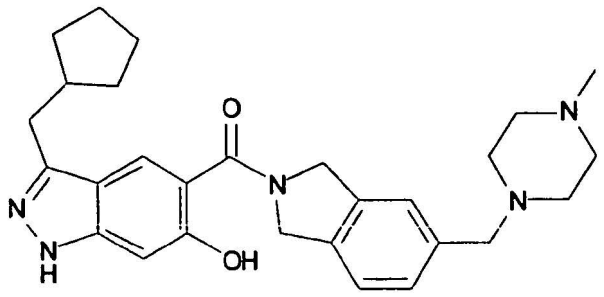
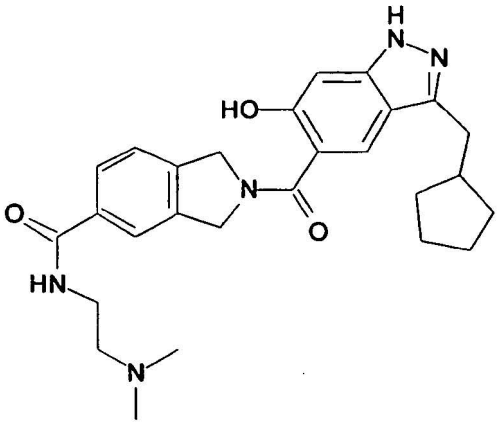
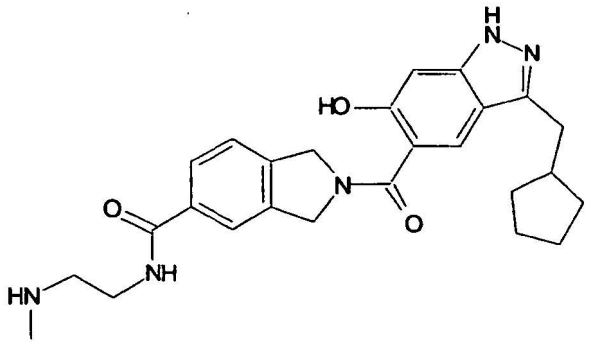
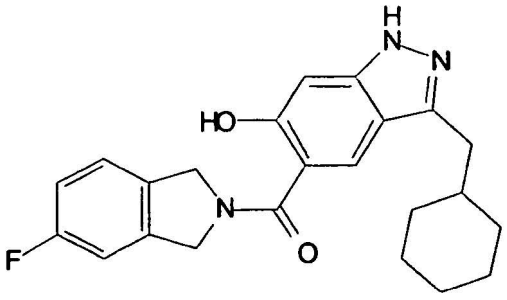
"A175"	
"A176"	
"A177"	
"A178"	

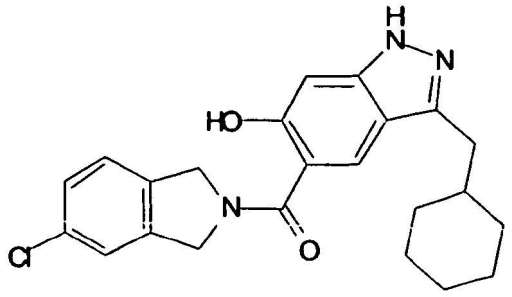
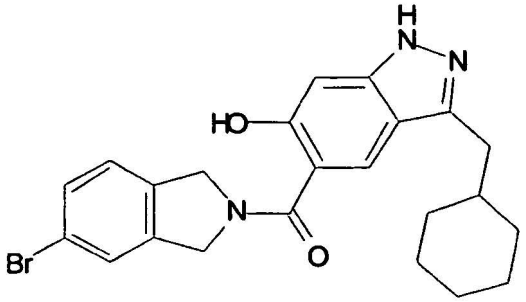
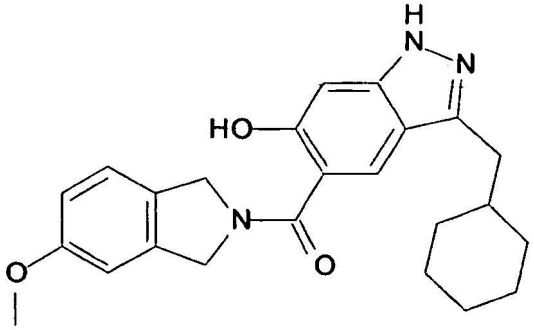
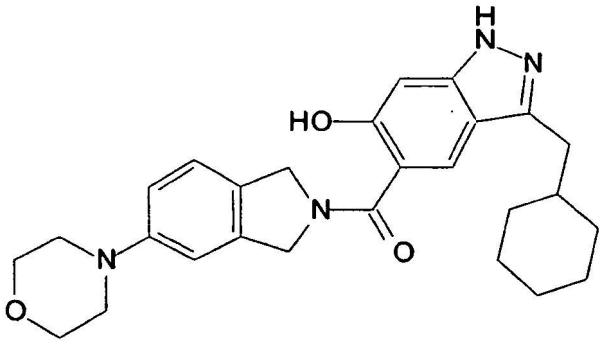
"A179"	
"A180"	
"A181"	
"A182"	

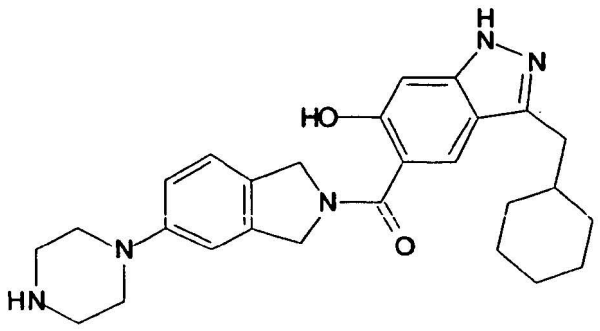
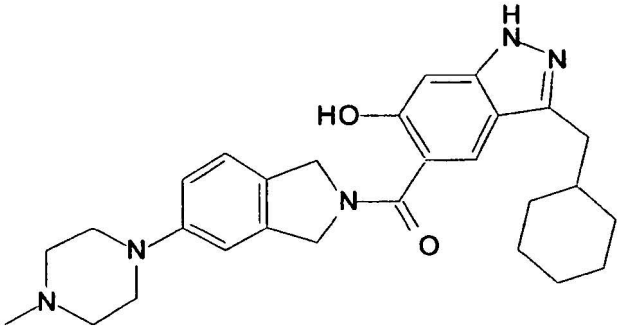
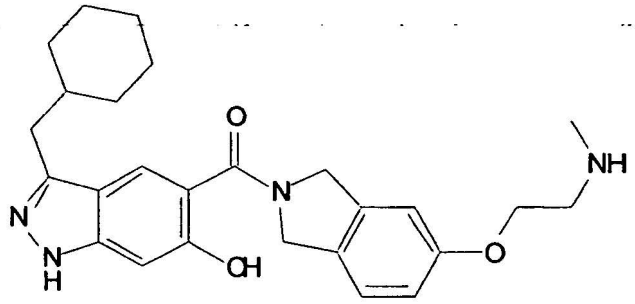
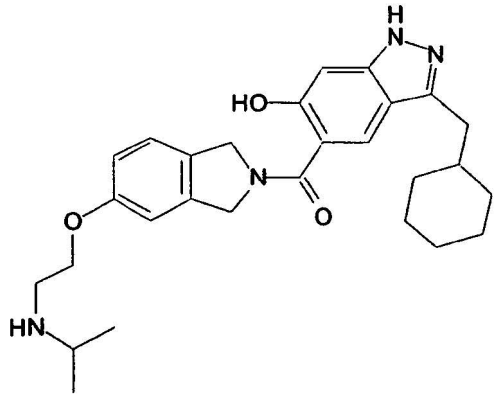
"A183"	
"A184"	
"A185"	
"A186"	

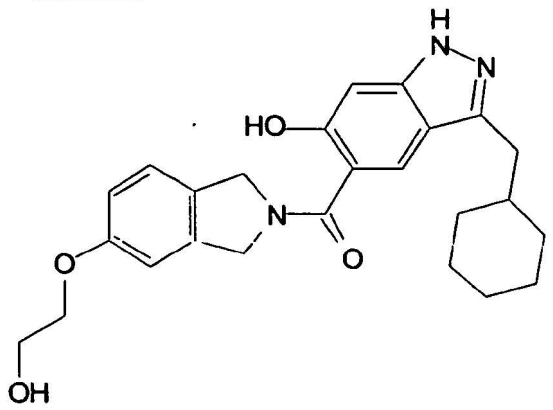
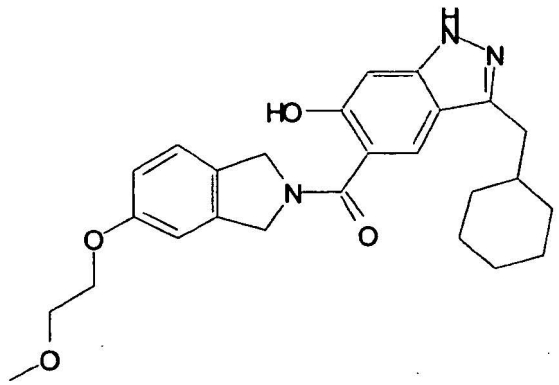
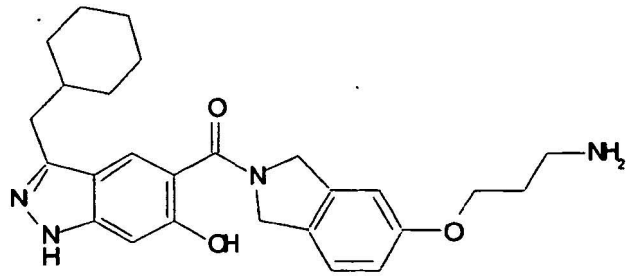
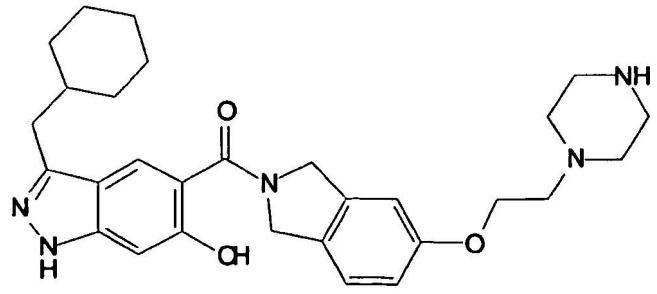
"A187"	
"A188"	
"A189"	
"A190"	

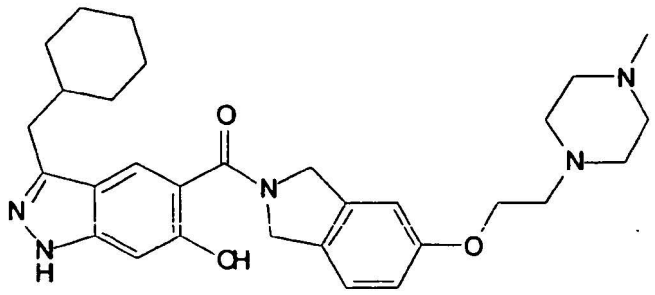
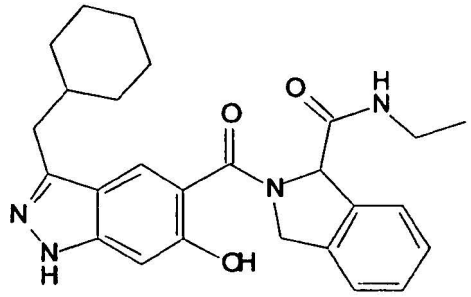
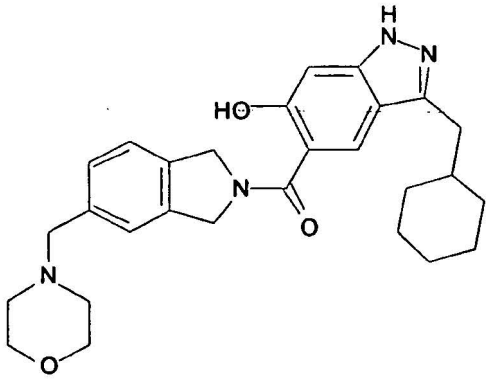
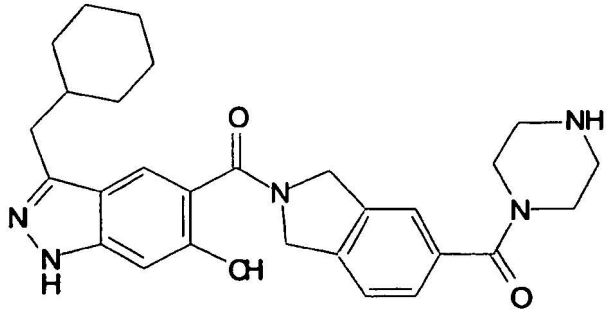
"A191"	
"A192"	
"A193"	
"A194"	

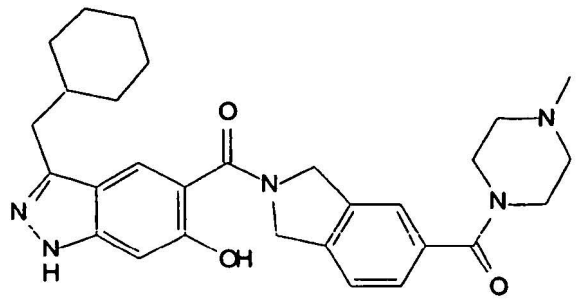
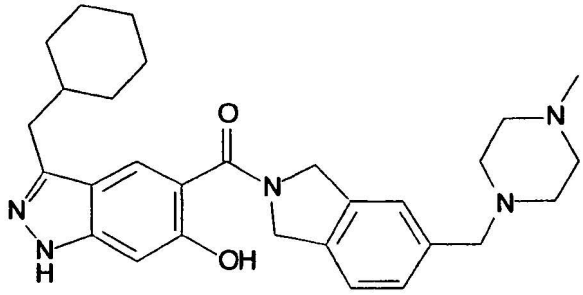
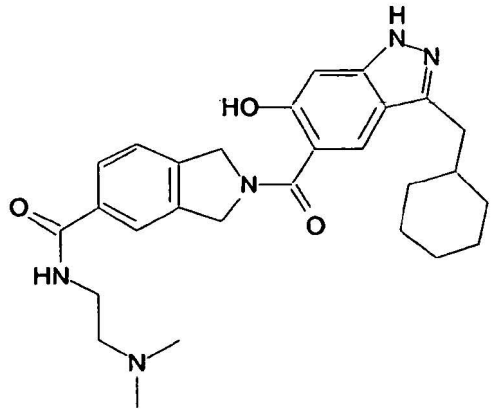
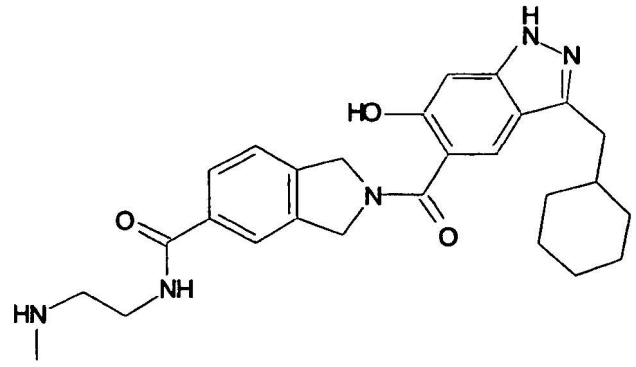
"A195"	
"A196"	
"A197"	
"A198"	

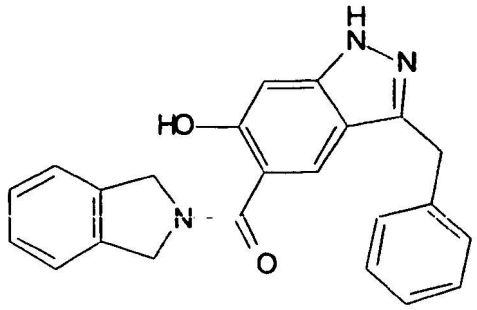
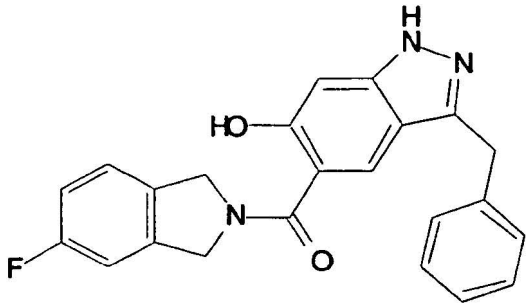
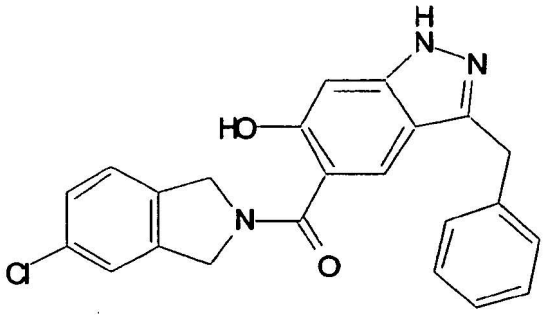
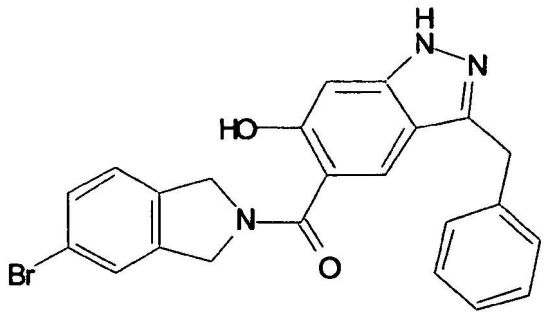
"A199"	
"A200"	
"A201"	
"A202"	

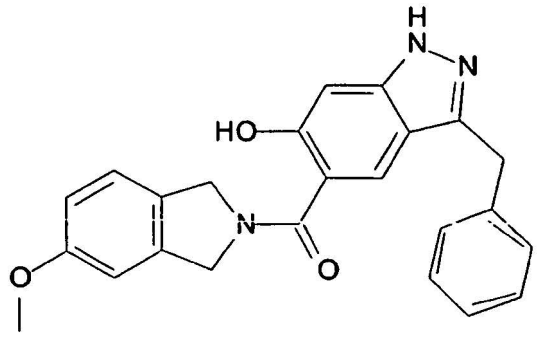
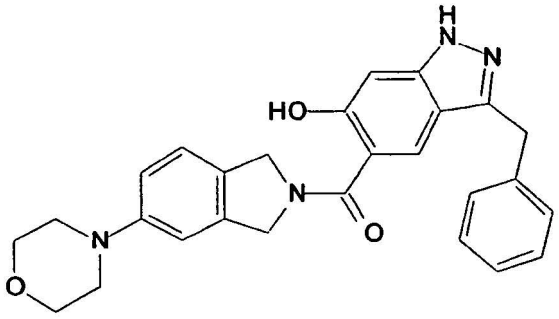
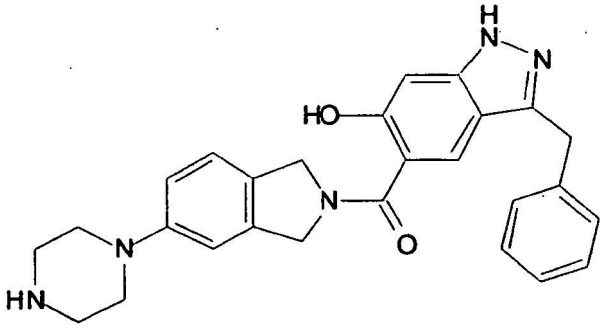
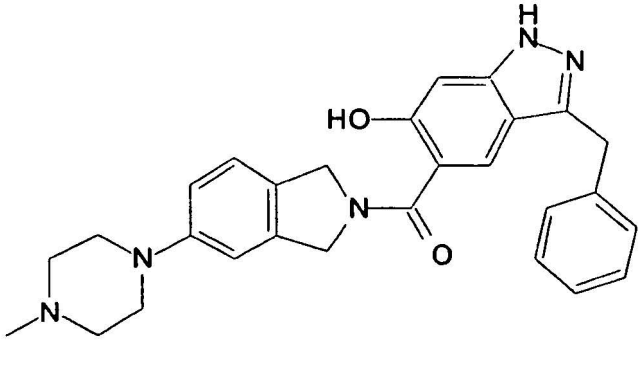
"A203"	
"A204"	
"A205"	
"A206"	

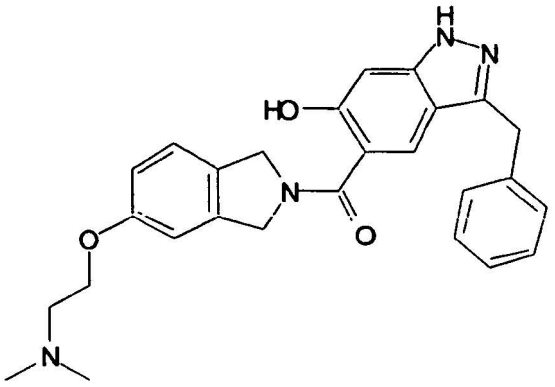
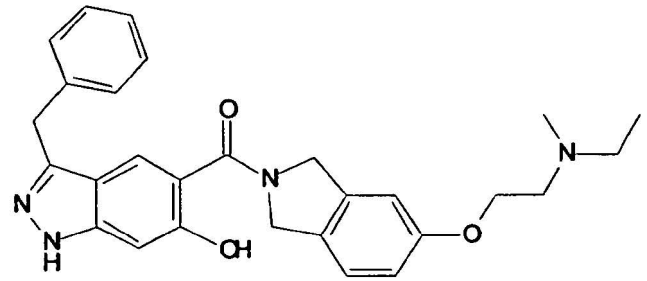
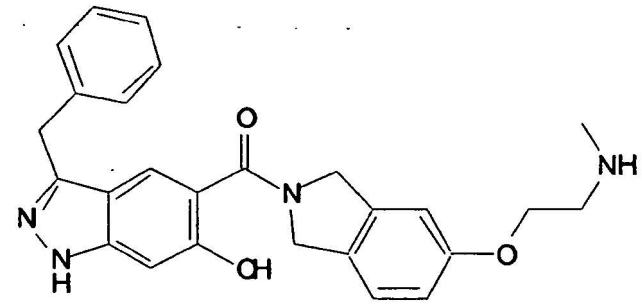
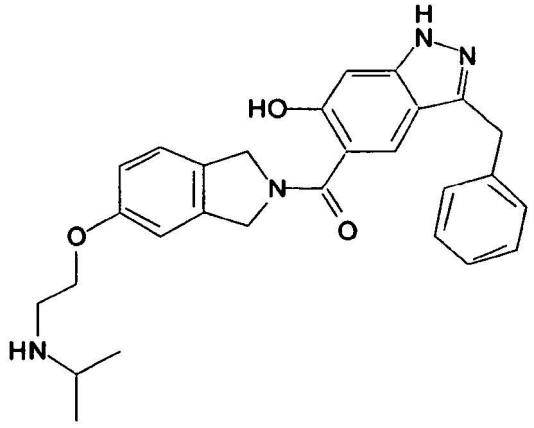
"A207"	
"A208"	
"A209"	
"A210"	

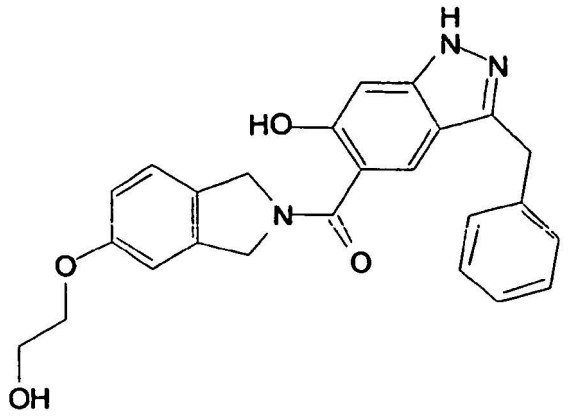
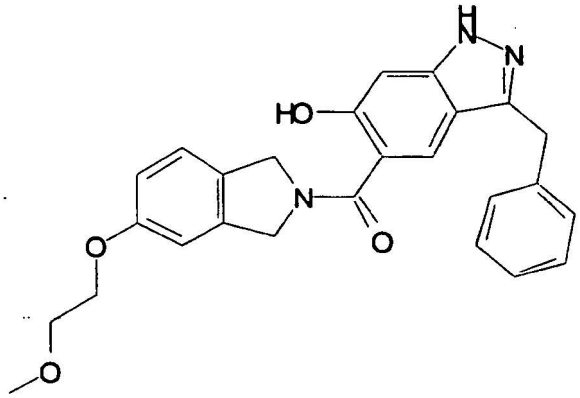
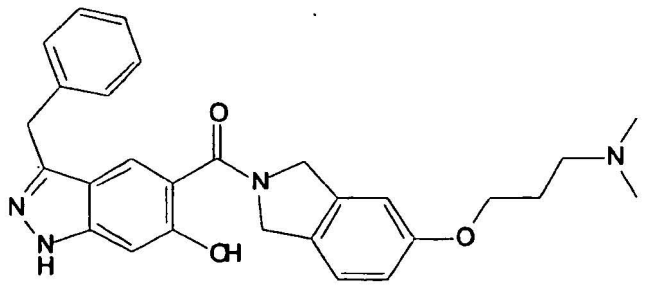
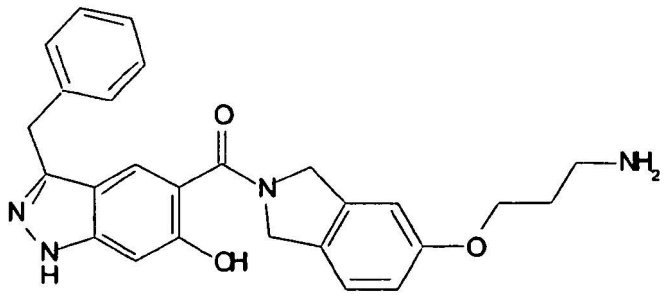
"A211"	
"A212"	
"A213"	
"A214"	

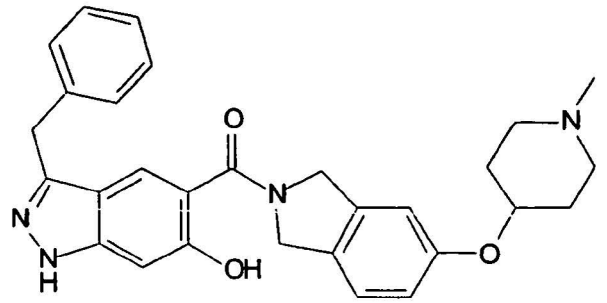
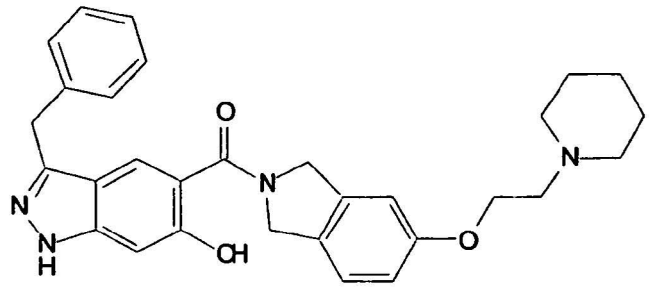
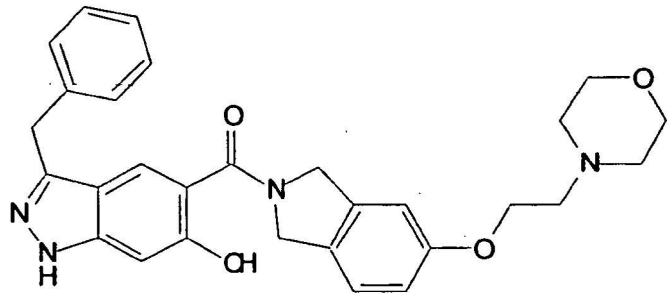
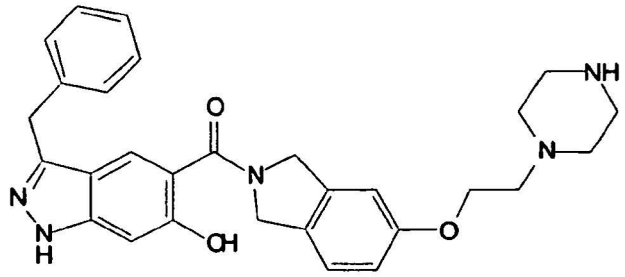
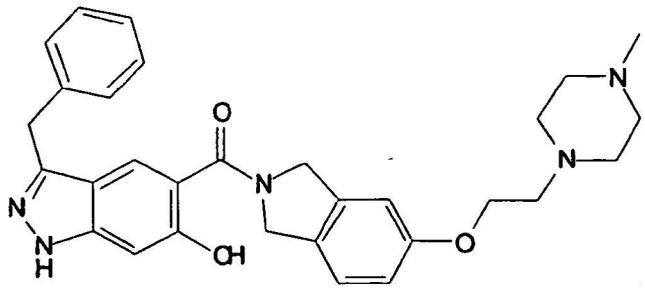
"A215"	
"A216"	
"A217"	
"A218"	

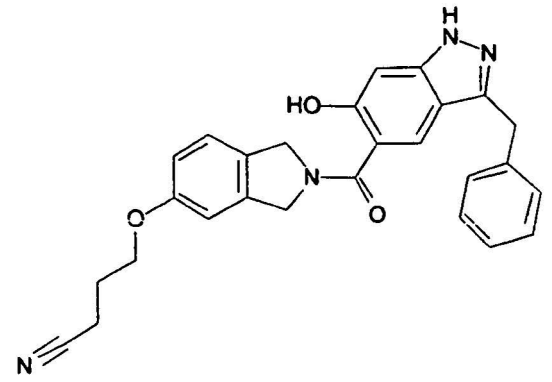
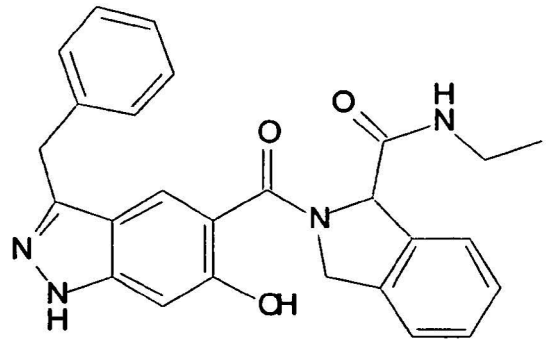
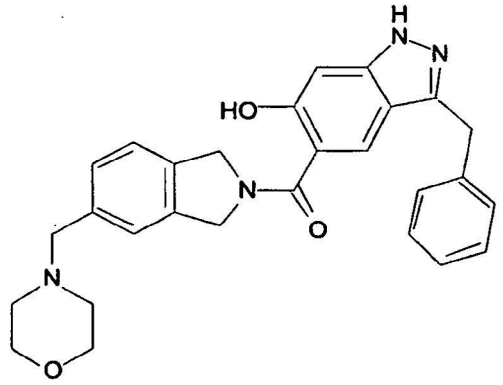
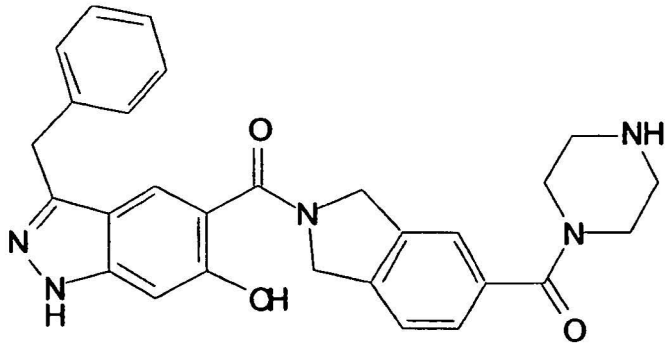
"A219"	
"A220"	
"A221"	
"A222"	

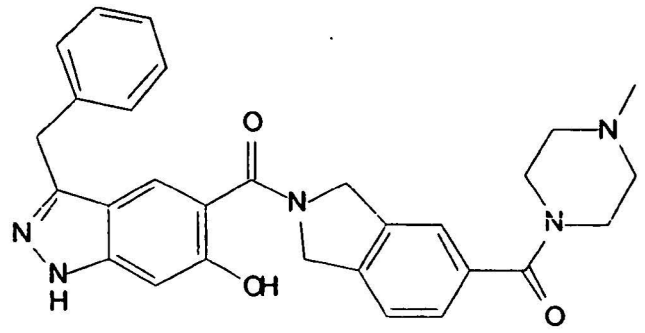
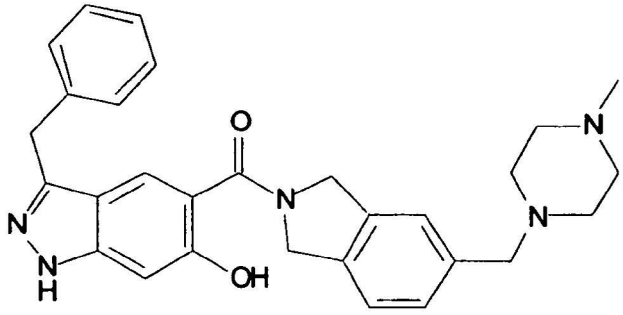
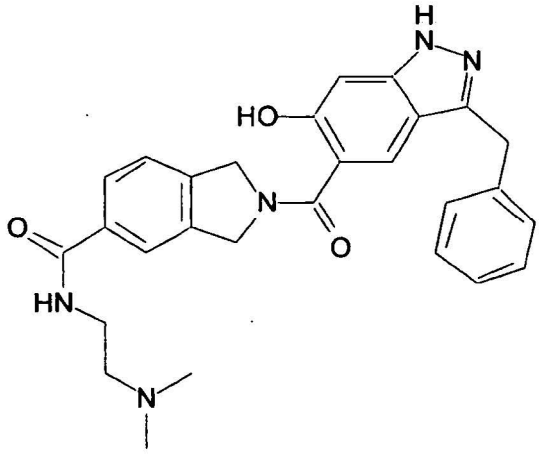
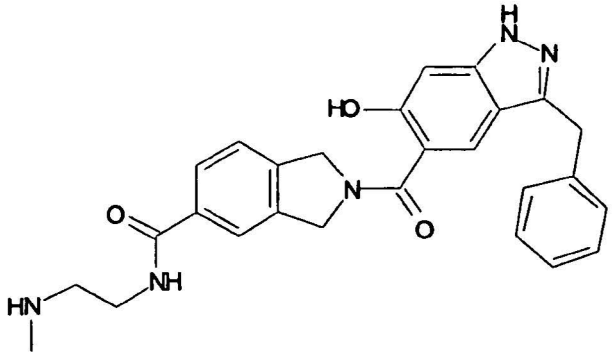
"A223"	
"A224"	
"A225"	
"A226"	

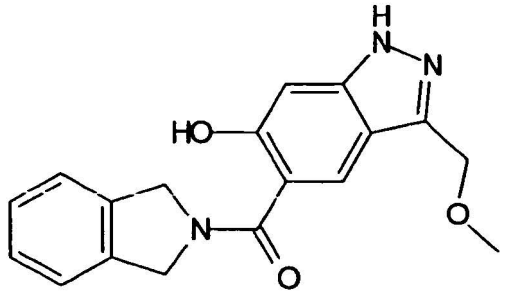
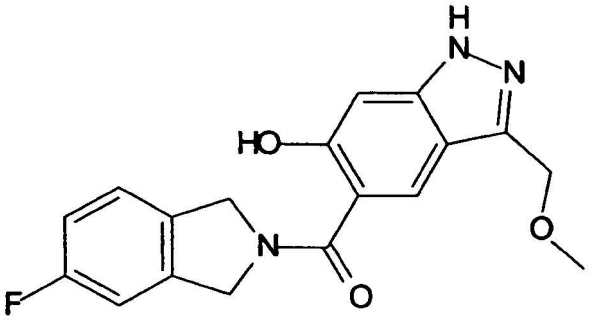
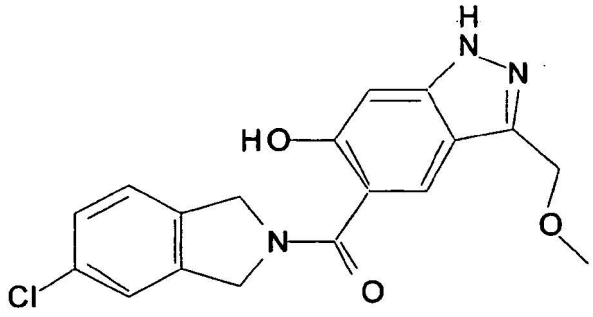
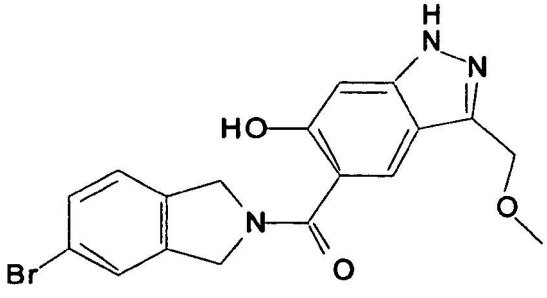
"A227"	
"A228"	
"A229"	
"A230"	

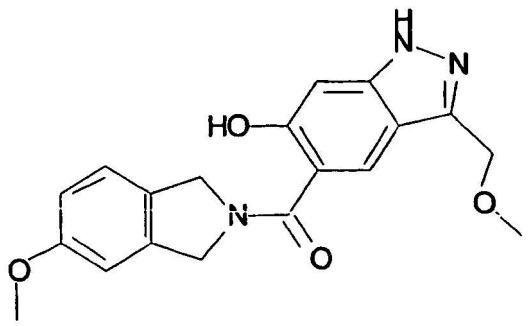
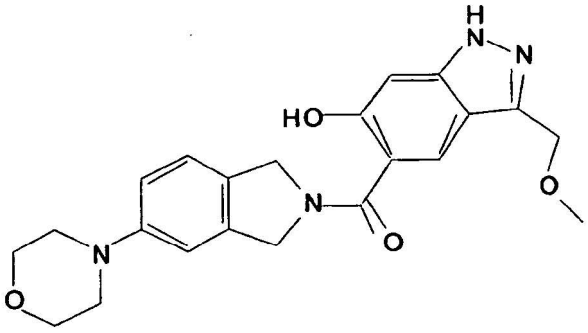
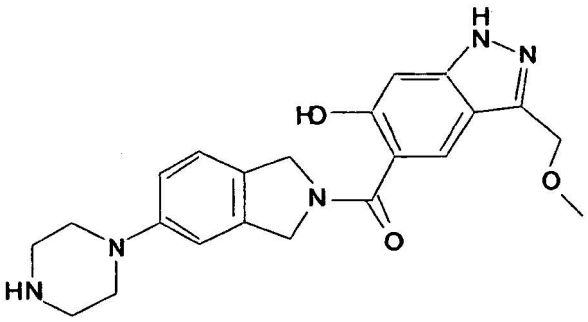
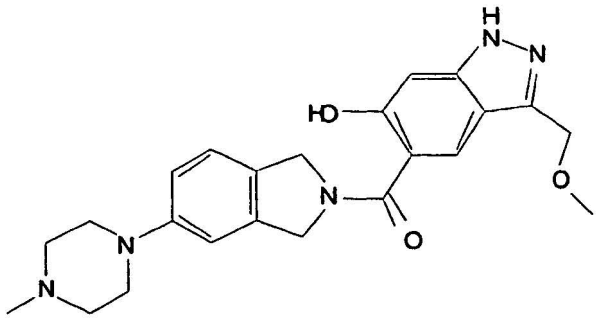
"A231"	
"A232"	
"A233"	
"A234"	

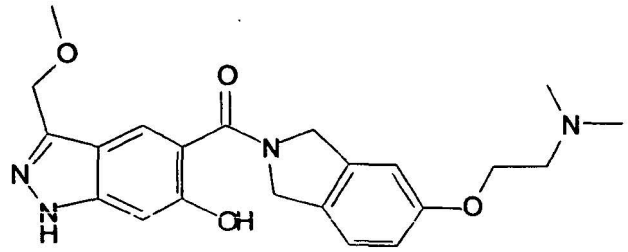
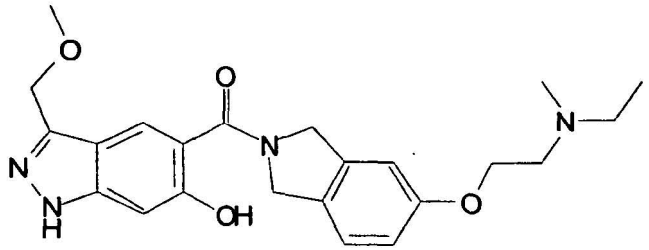
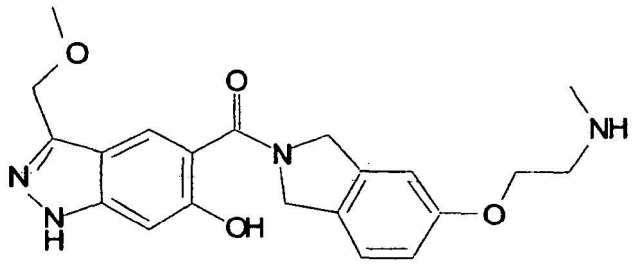
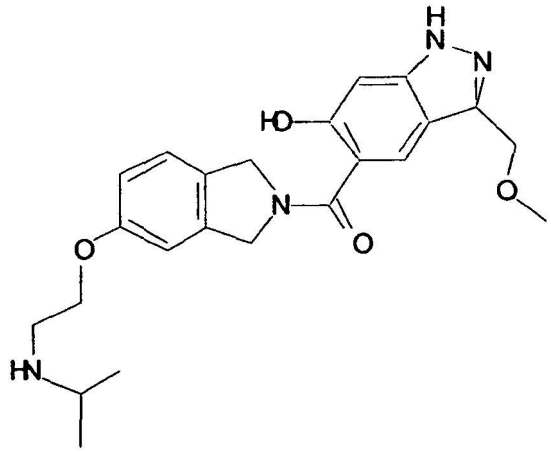
"A235"	
"A236"	
"A237"	
"A238"	
"A239"	

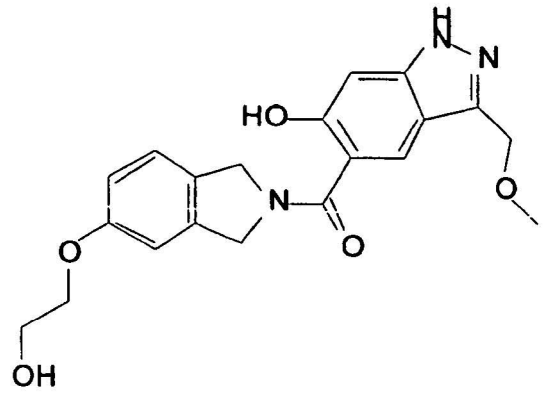
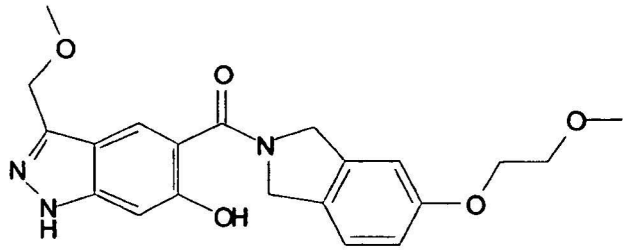
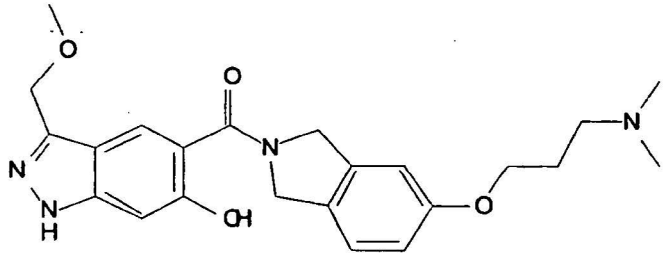
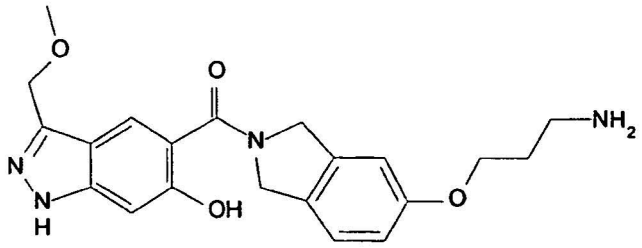
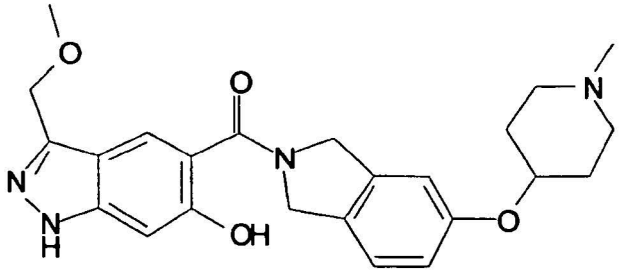
"A240"	
"A241"	
"A242"	
"A243"	

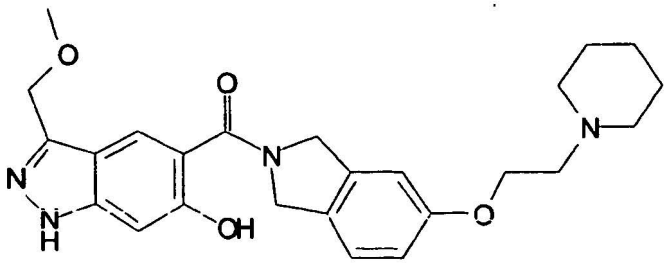
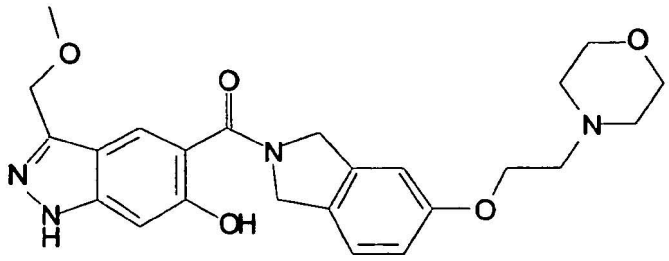
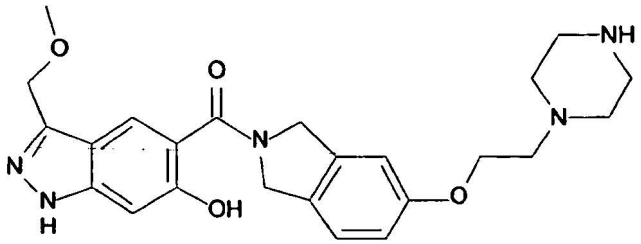
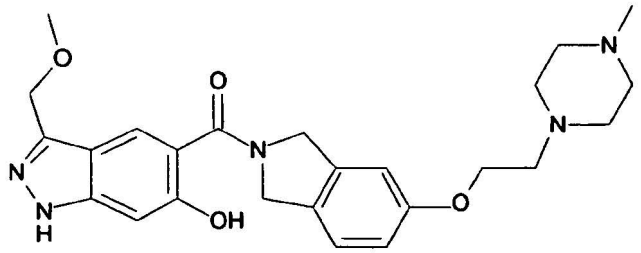
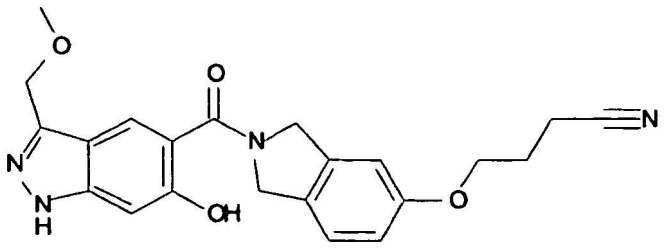
"A244"	
"A245"	
"A246"	
"A247"	

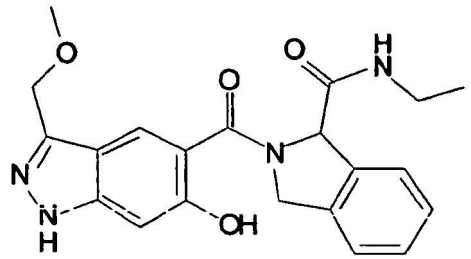
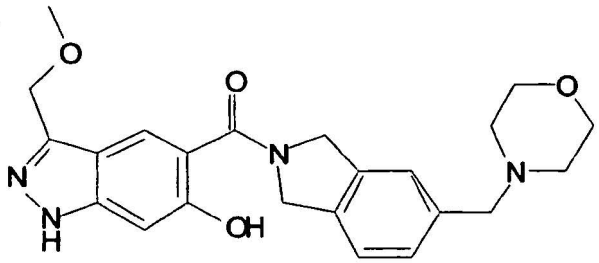
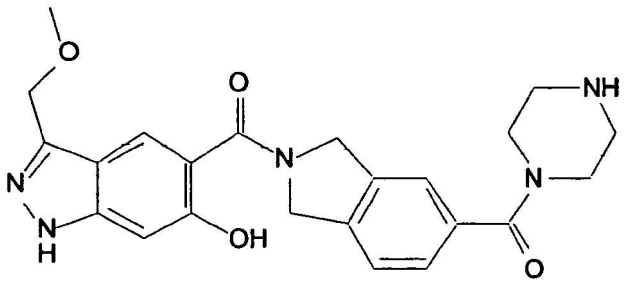
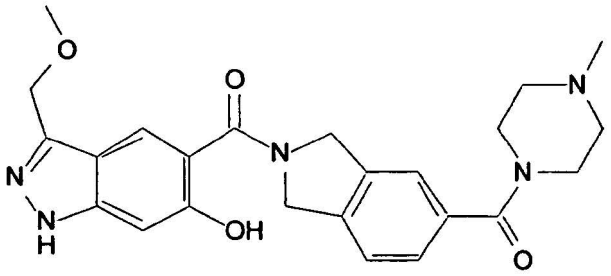
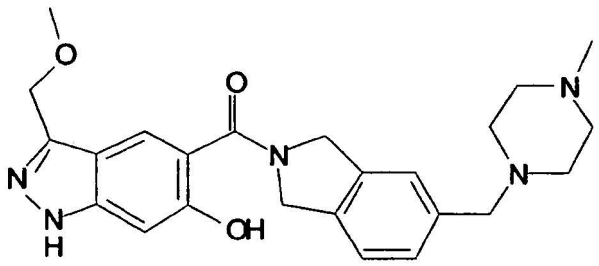
"A248"	
"A249"	
"A250"	
"A251"	

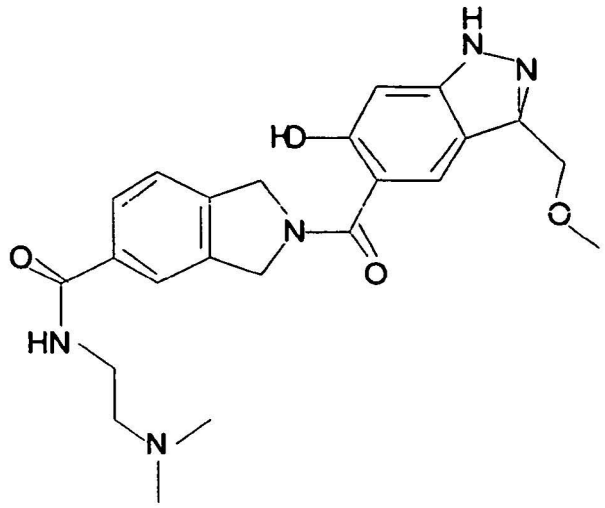
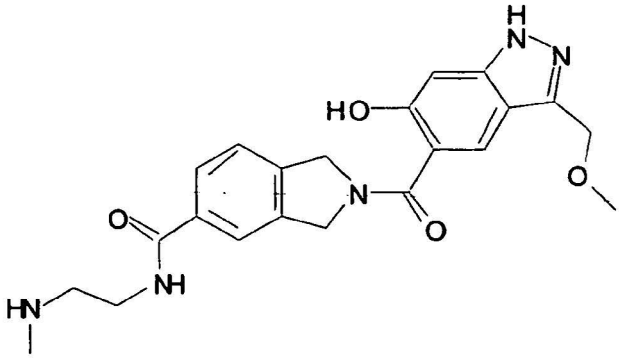
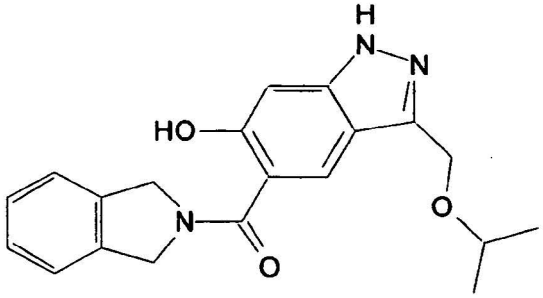
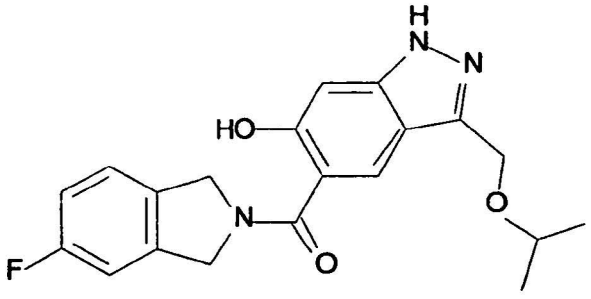
"A252"	
"A253"	
"A254"	
"A255"	

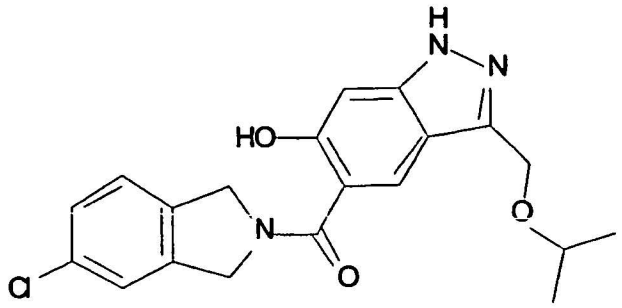
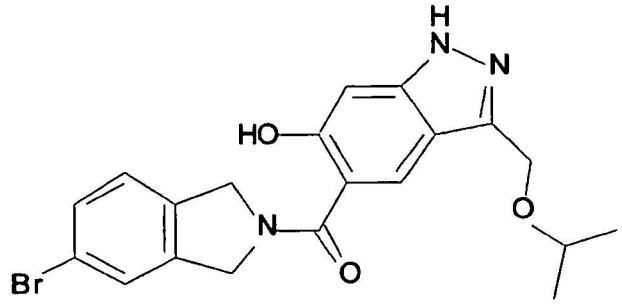
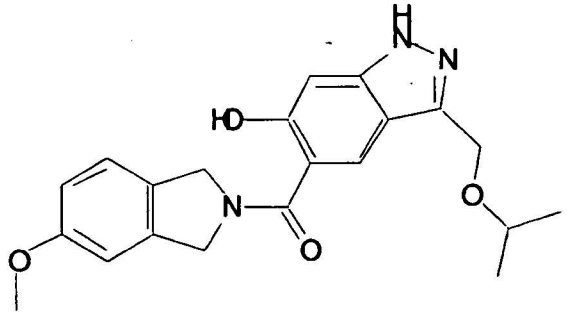
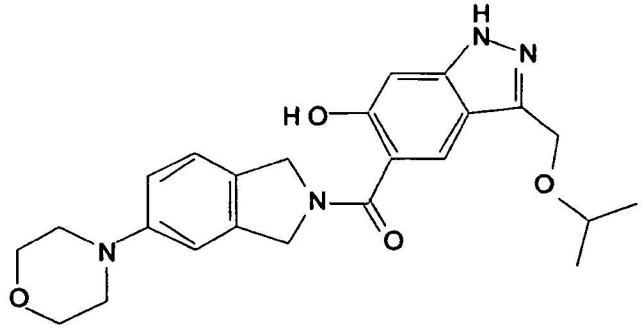
"A256"	
"A257"	
"A258"	
"A259"	

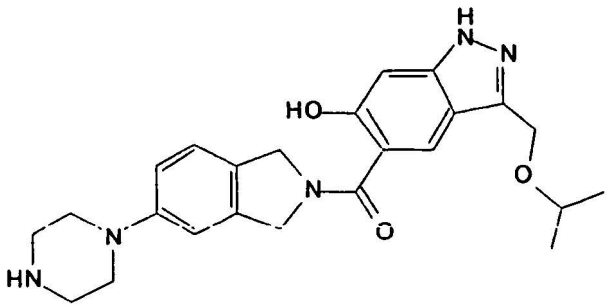
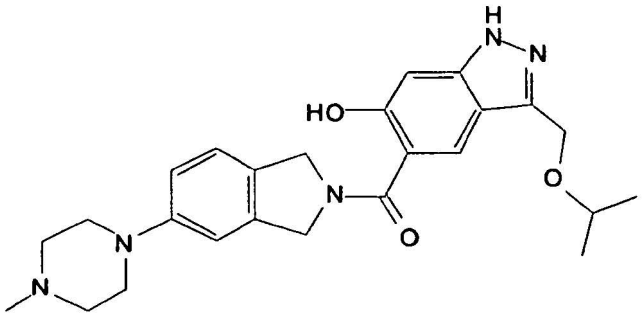
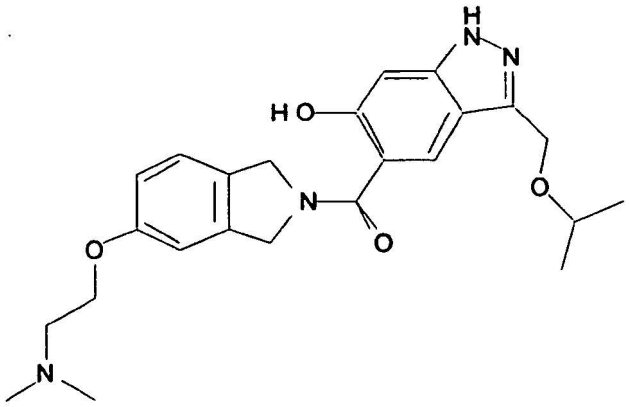
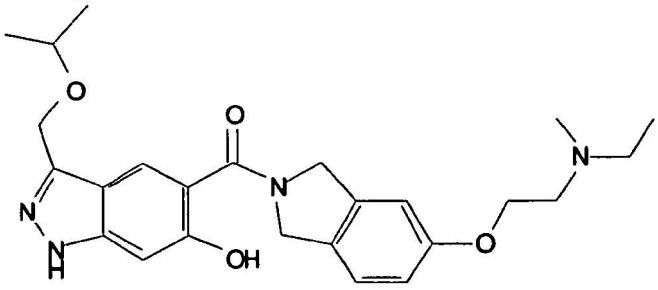
"A260"	
"A261"	
"A262"	
"A263"	
"A264"	

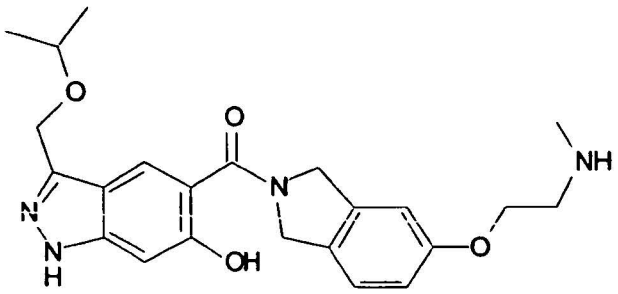
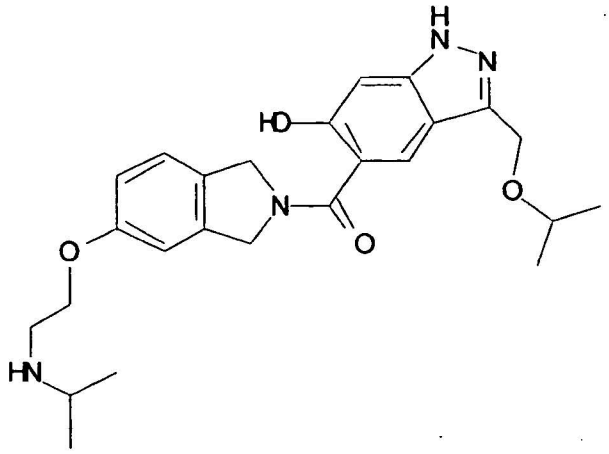
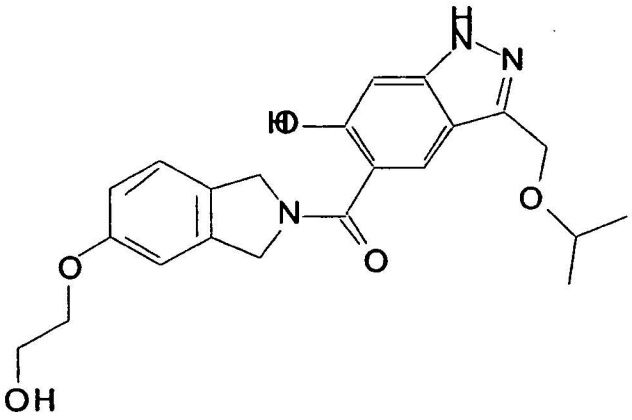
"A265"	
"A266"	
"A267"	
"A268"	
"A269"	

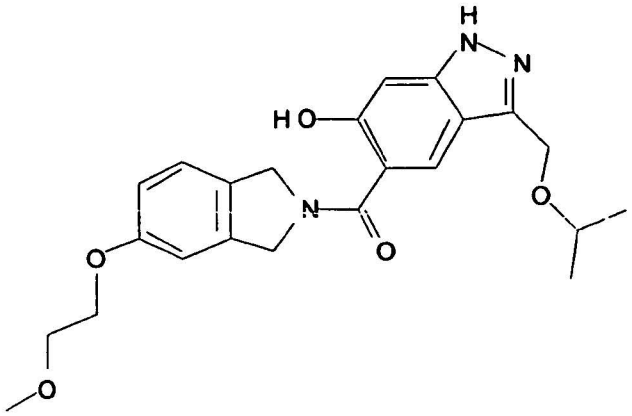
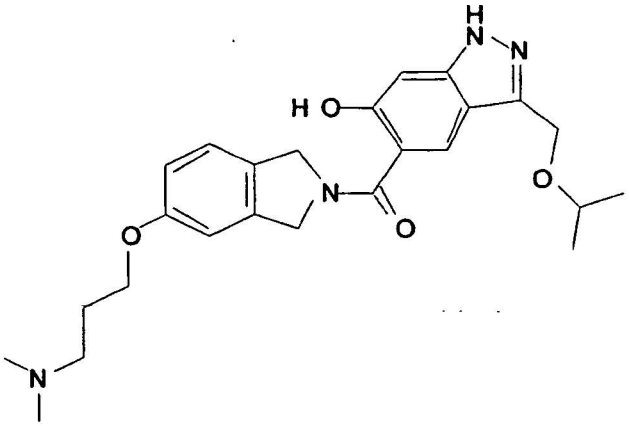
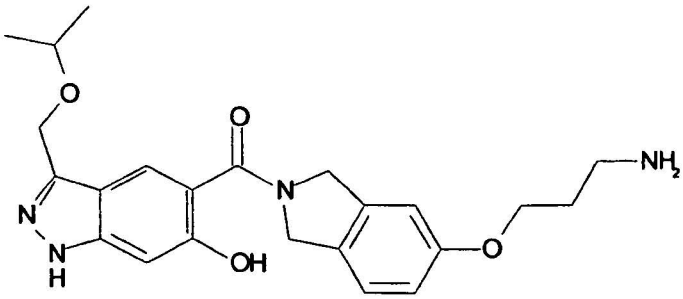
"A270"	
"A271"	
"A272"	
"A273"	
"A274"	

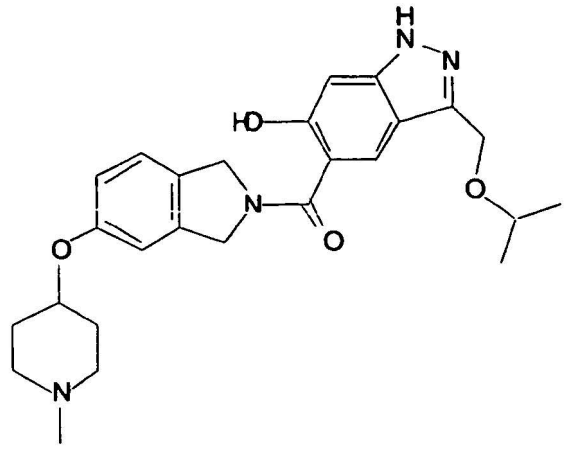
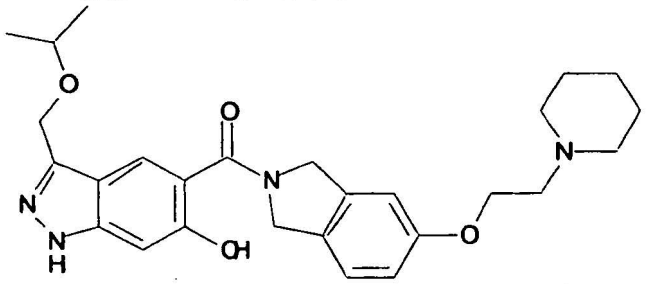
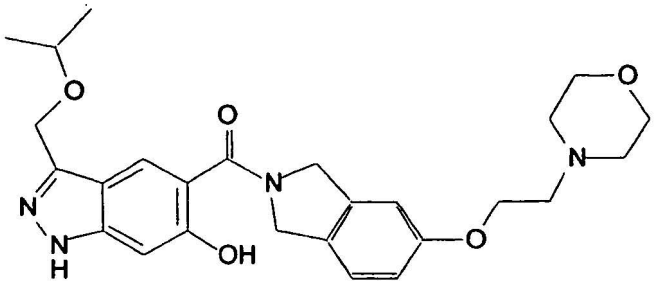
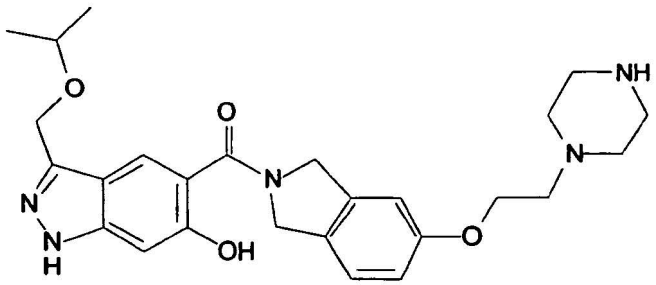
"A275"	
"A276"	
"A277"	
"A278"	

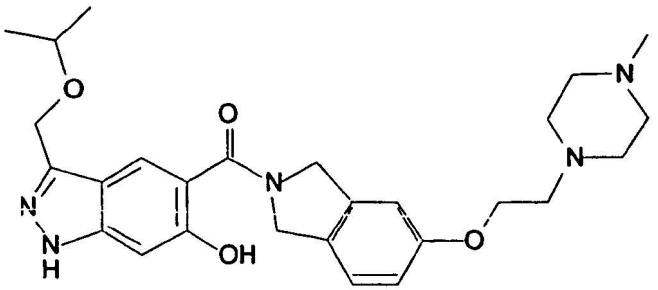
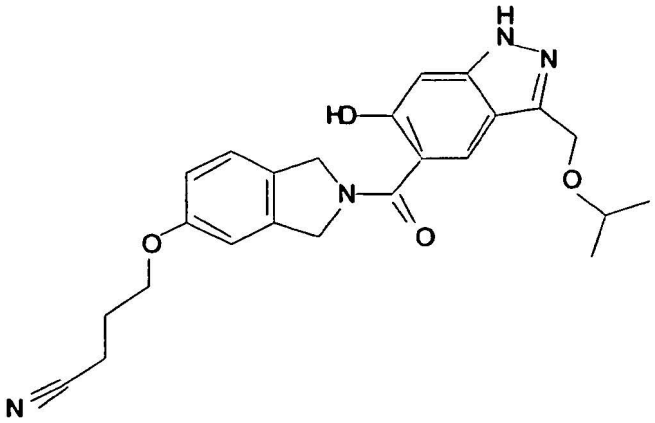
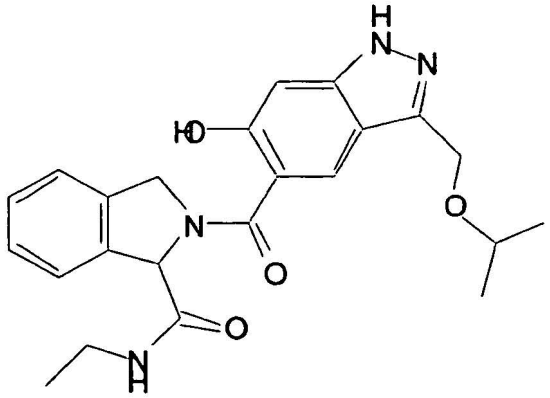
"A279"	
"A280"	
"A281"	
"A282"	

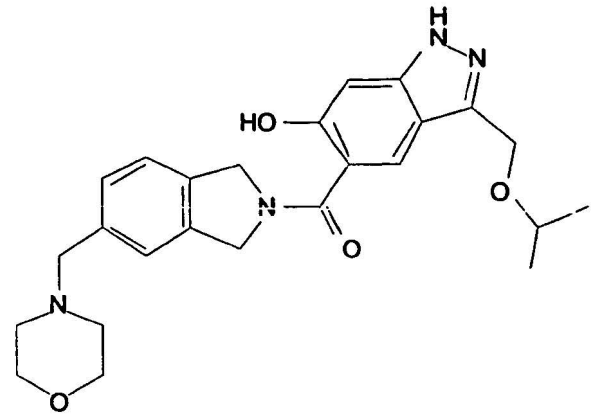
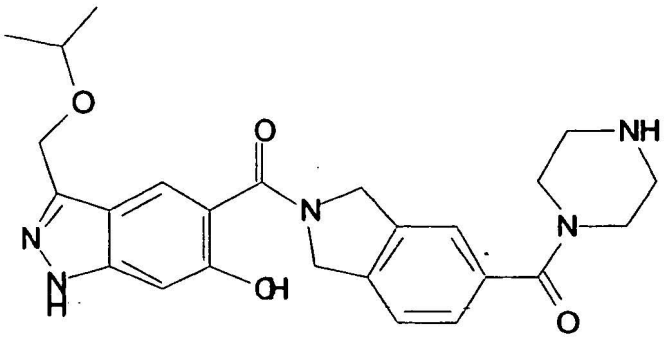
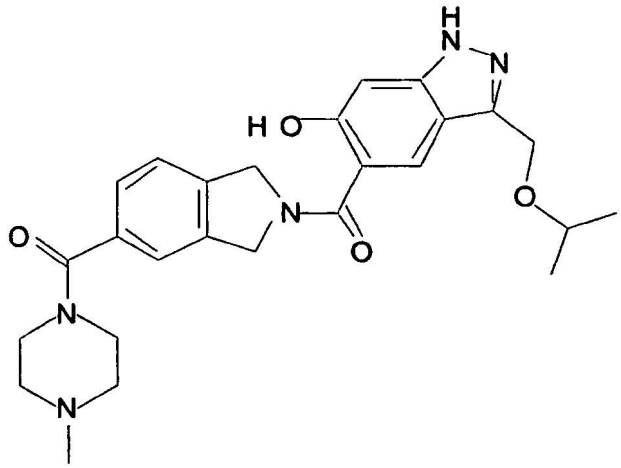
"A283"	
"A284"	
"A285"	
"A286"	

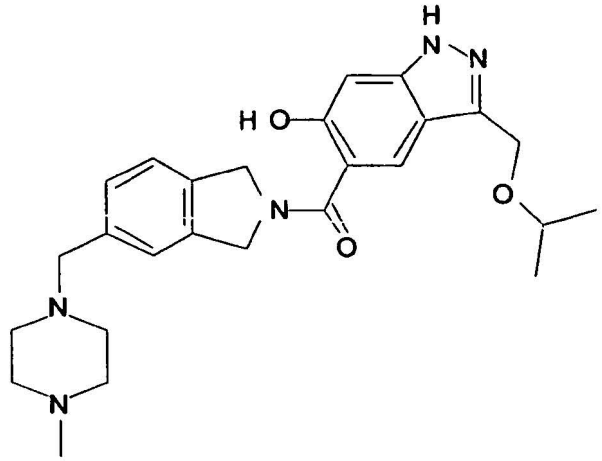
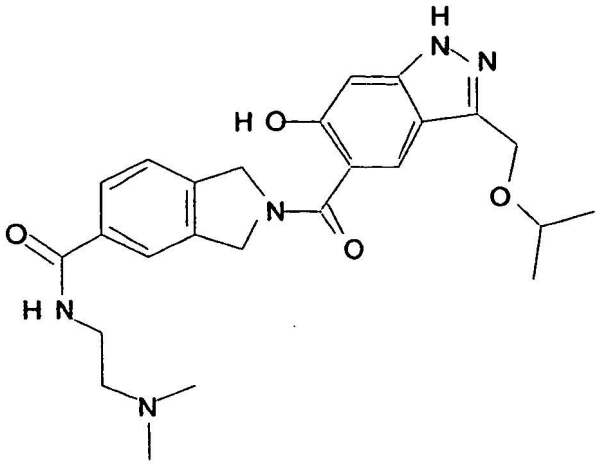
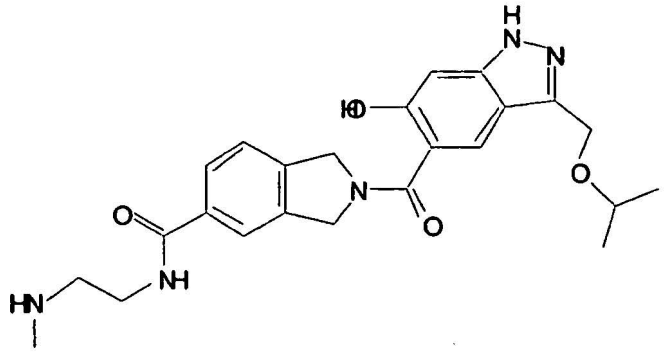
"A287"	
"A288"	
"A289"	

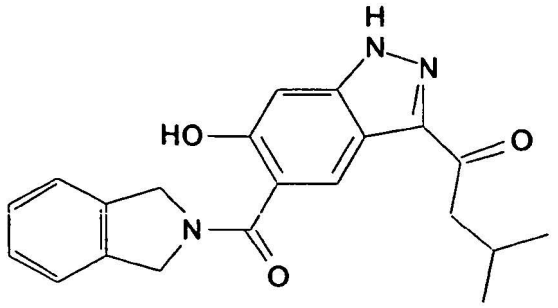
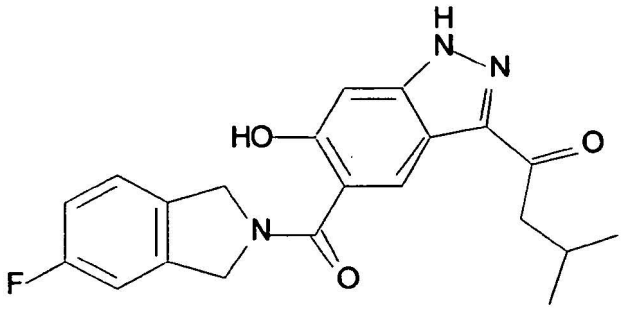
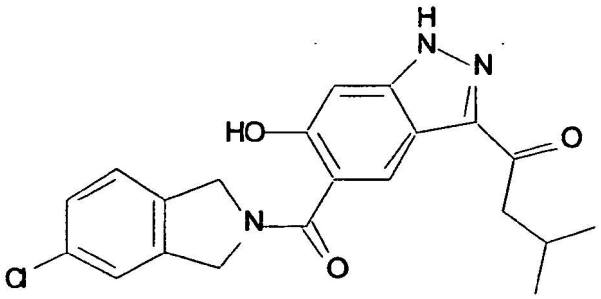
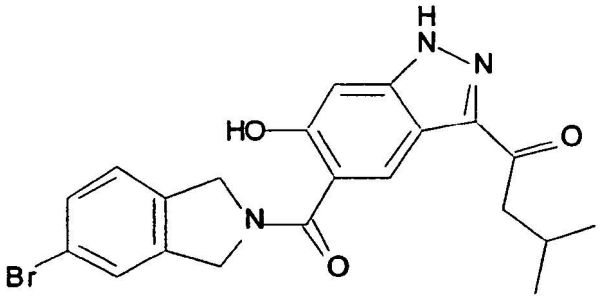
"A290"	
"A291"	
"A292"	

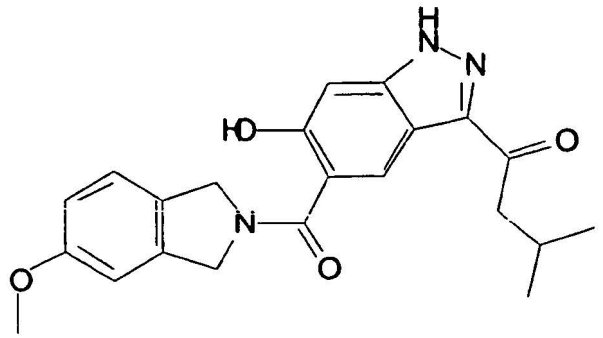
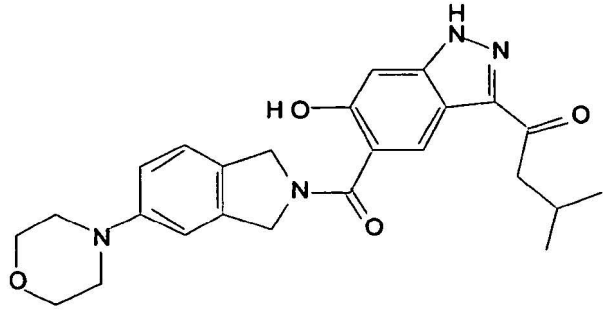
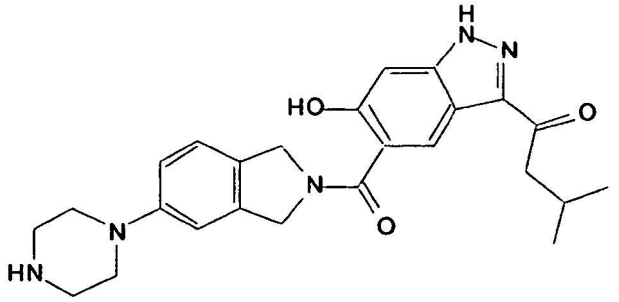
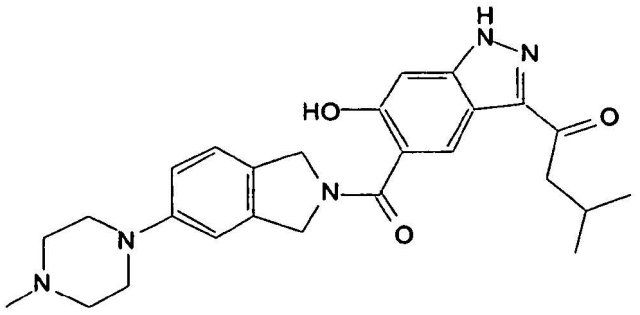
"A293"	
"A294"	
"A295"	
"A296"	

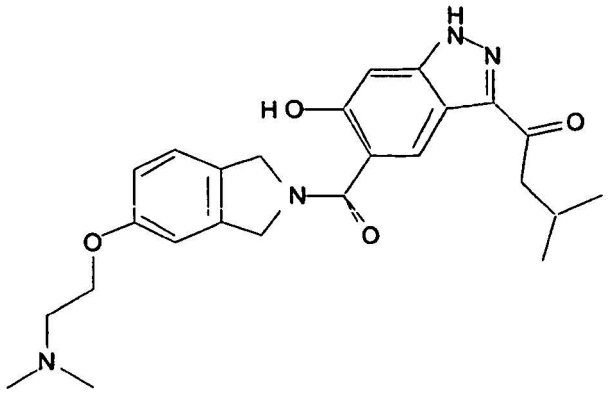
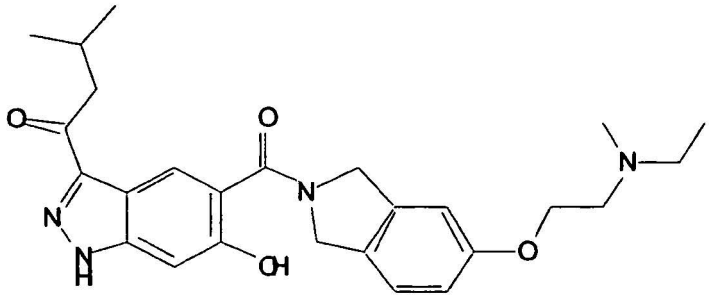
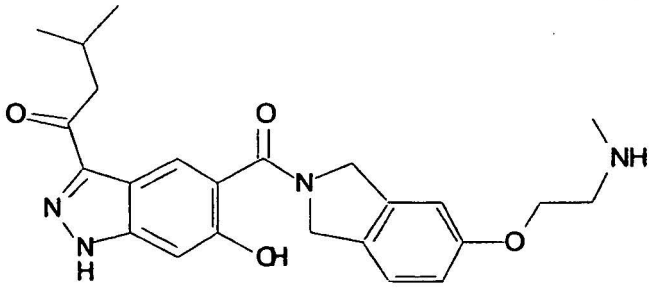
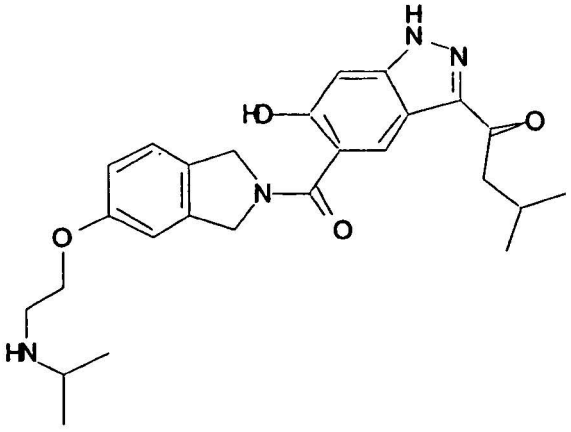
"A297"	
"A298"	
"A299"	

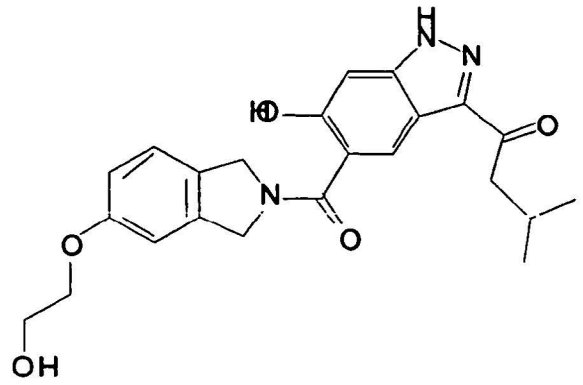
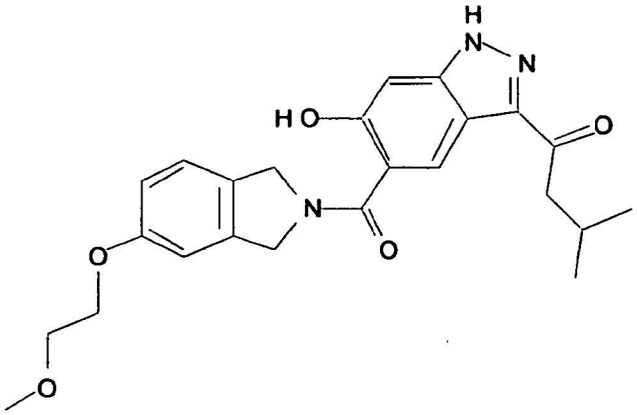
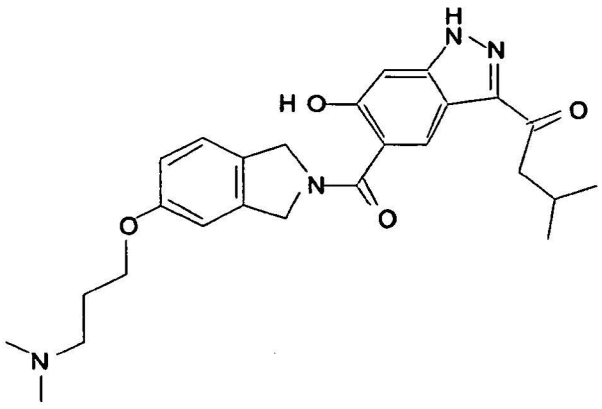
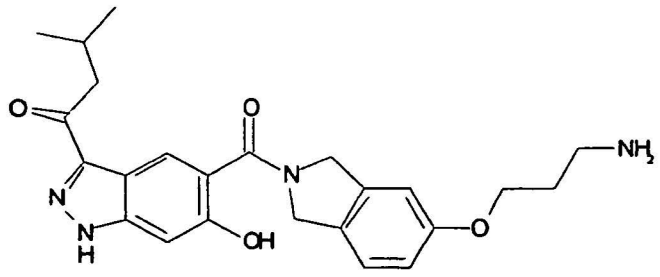
"A300"	
"A301"	
"A302"	

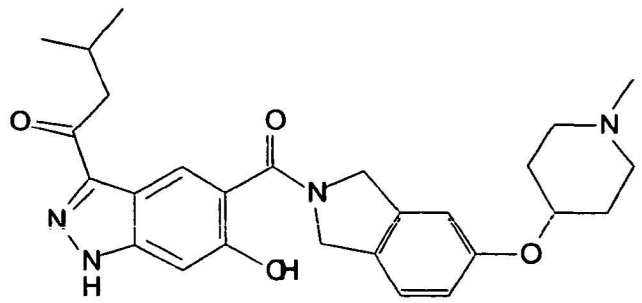
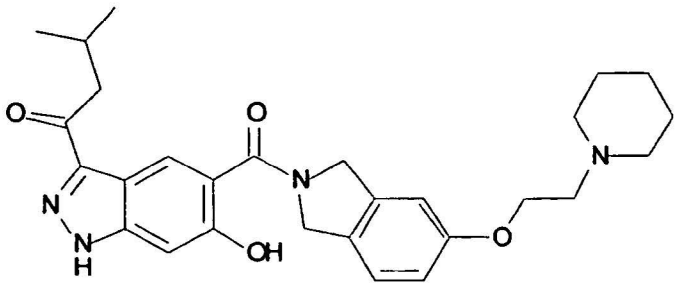
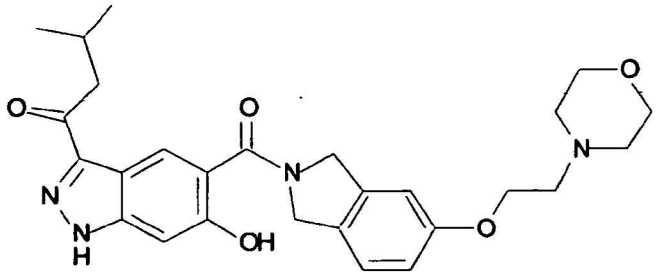
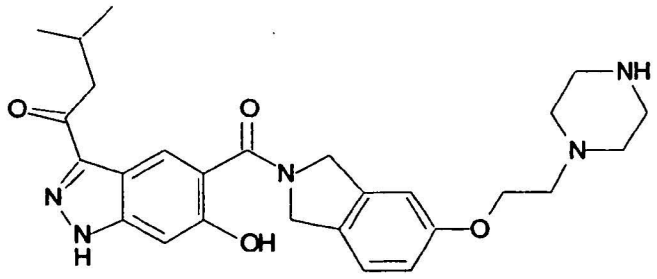
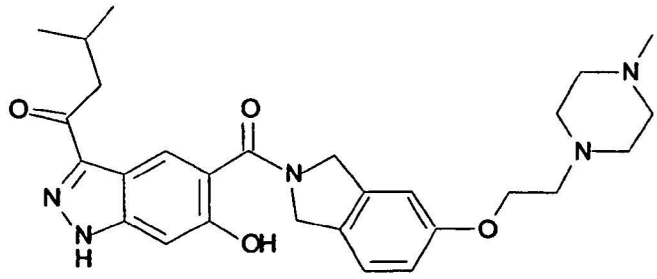
"A303"	
"A304"	
"A305"	

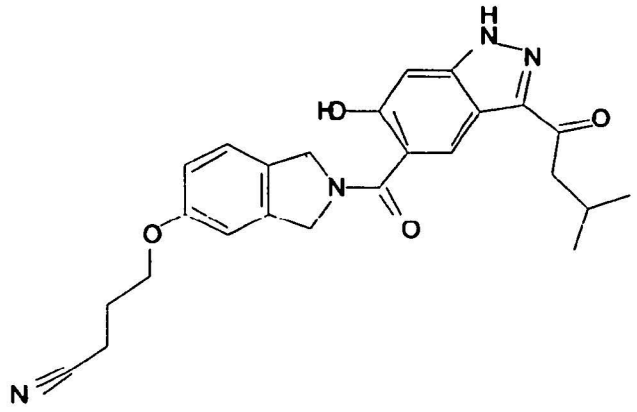
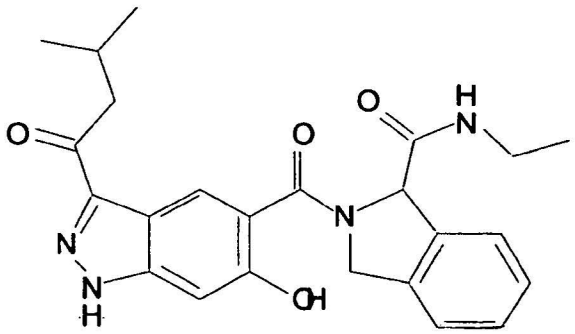
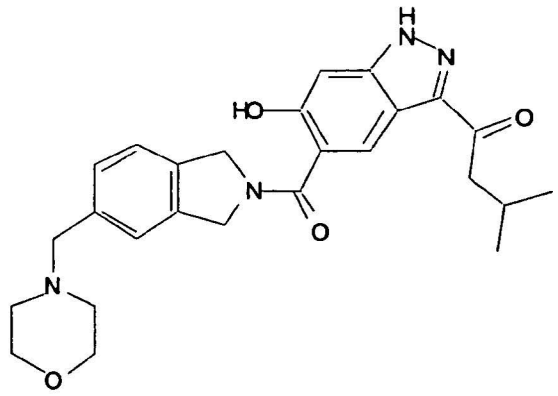
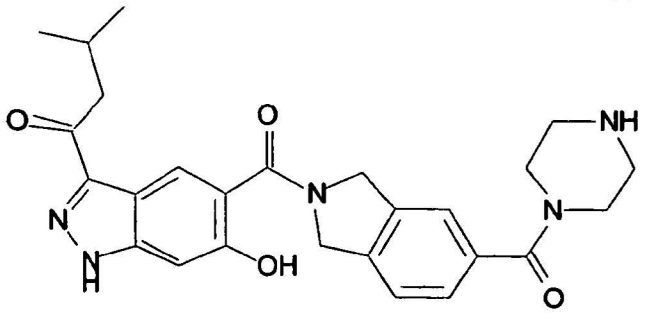
"A306"	
"A307"	
"A308"	
"A309"	

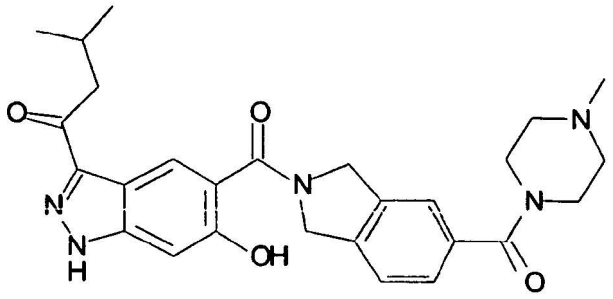
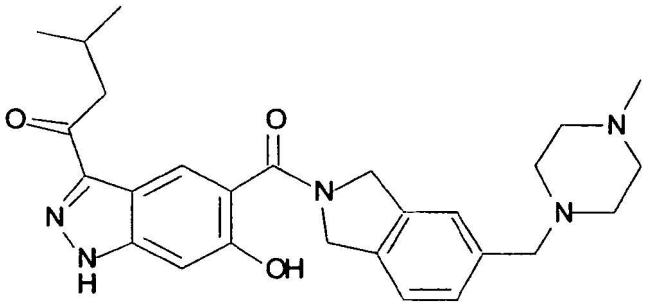
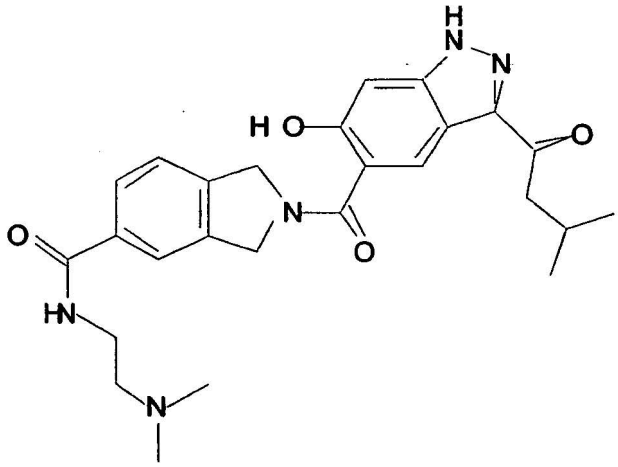
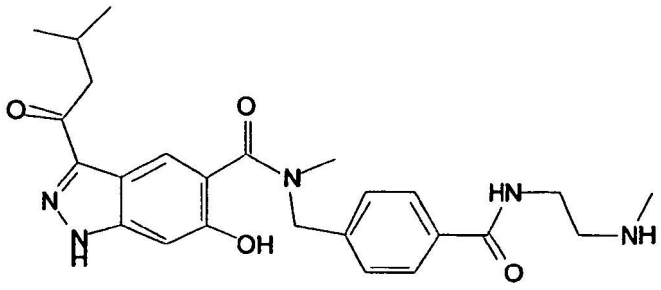
"A310"	
"A311"	
"A312"	
"A313"	

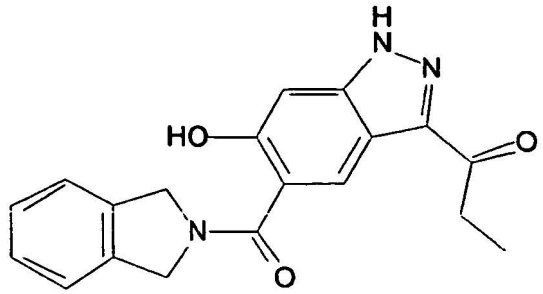
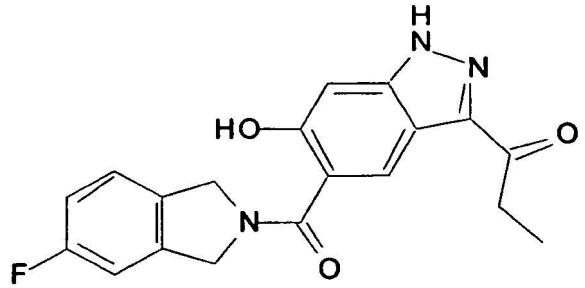
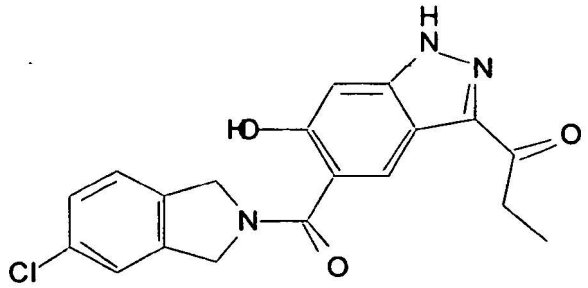
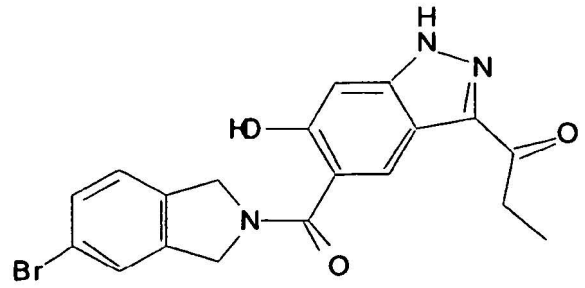
"A314"	
"A315"	
"A316"	
"A317"	

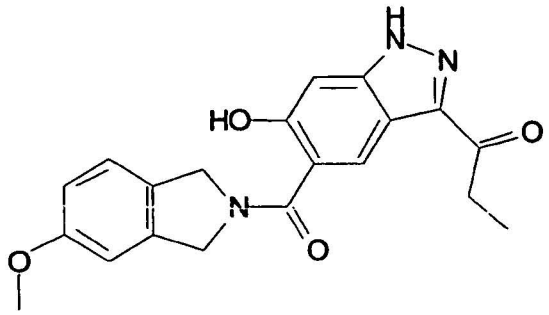
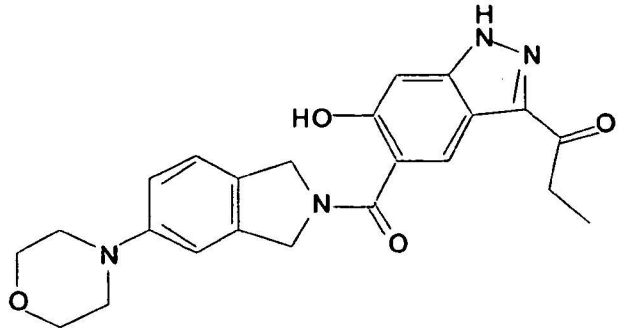
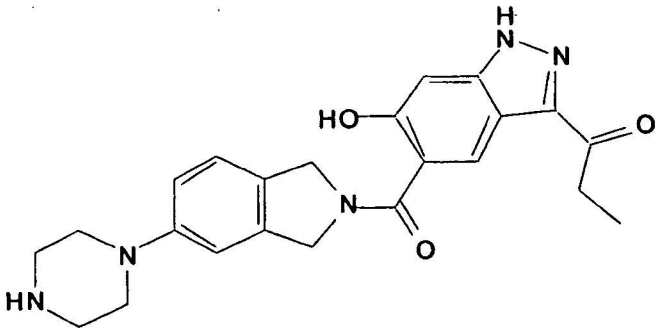
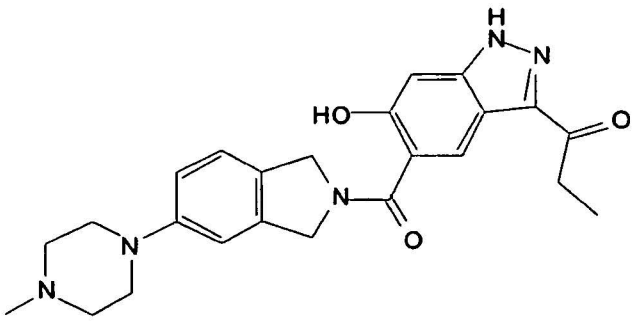
"A318"	
"A319"	
"A320"	
"A321"	

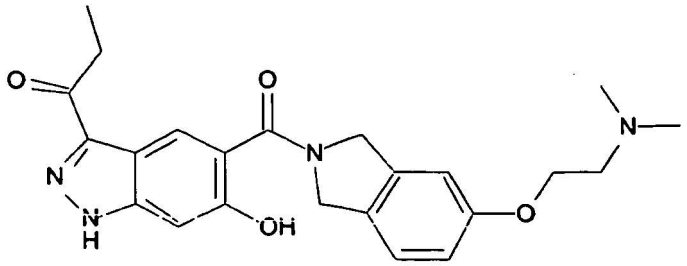
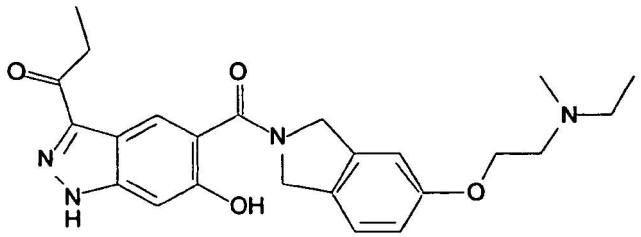
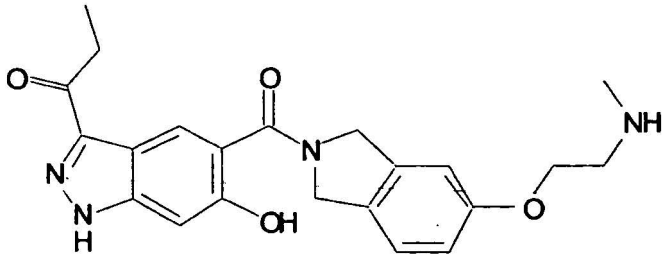
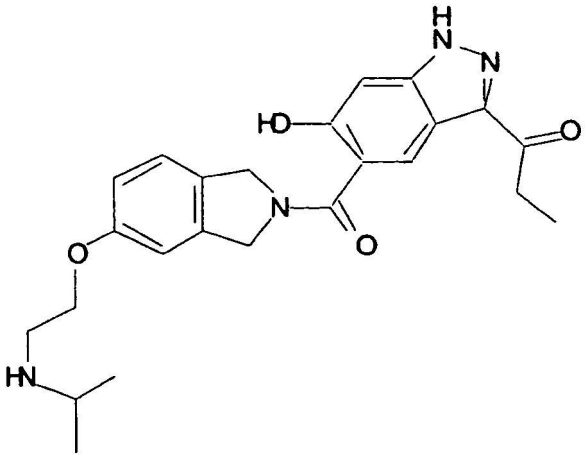
"A322"	
"A323"	
"A324"	
"A325"	
"A326"	

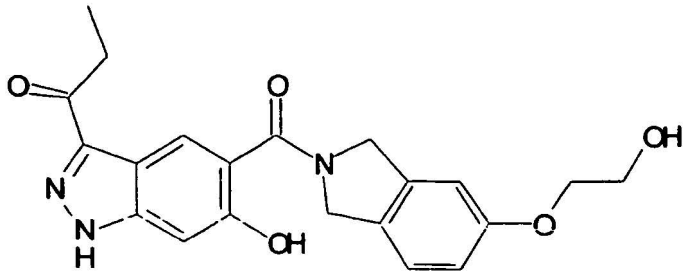
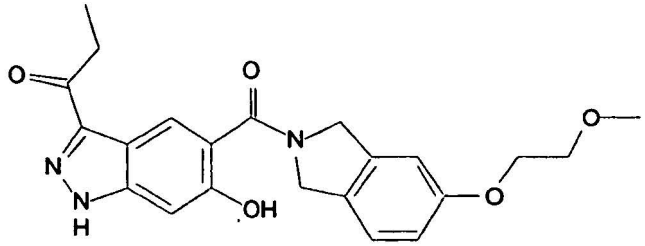
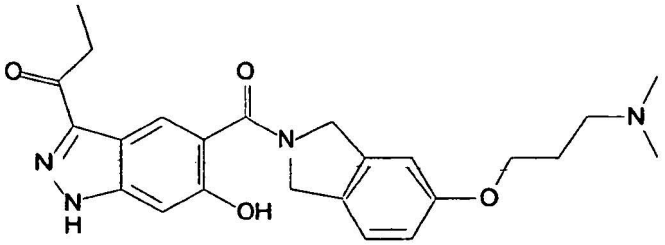
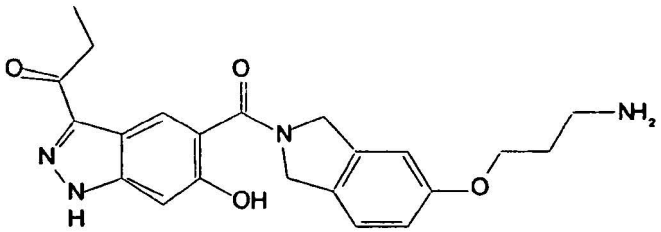
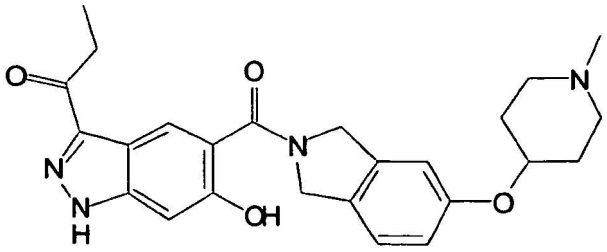
"A327"	
"A328"	
"A329"	
"A330"	

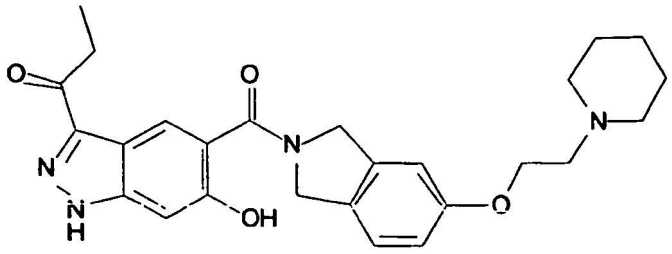
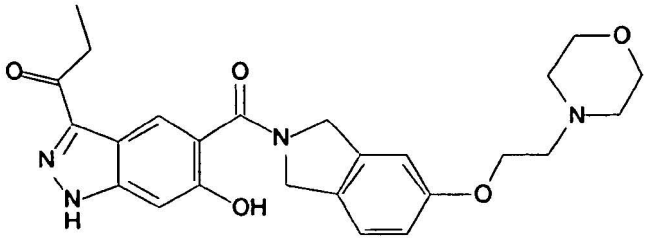
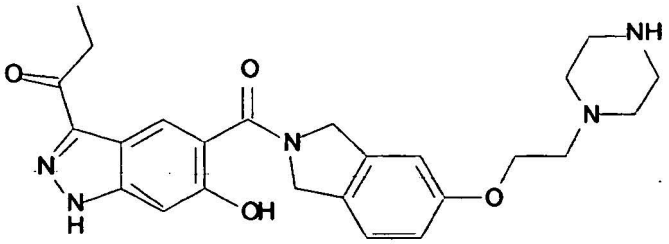
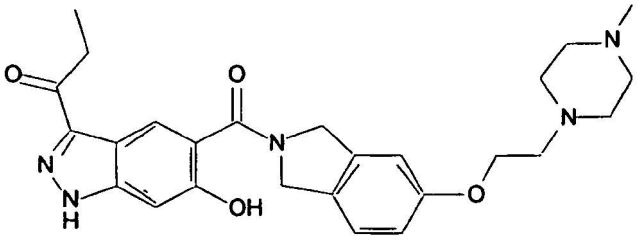
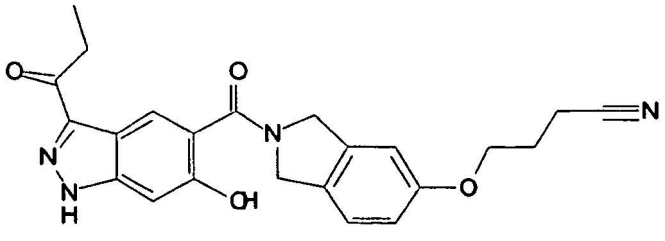
"A331"	
"A332"	
"A333"	
"A334"	

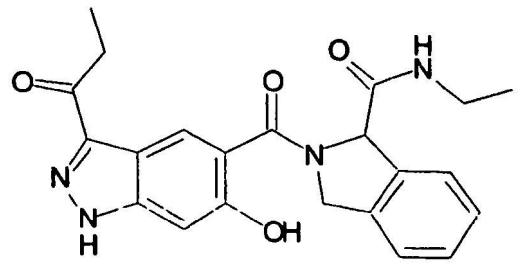
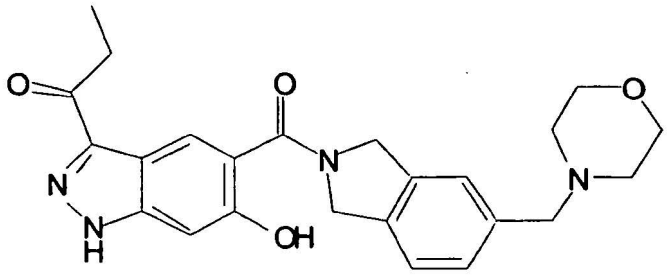
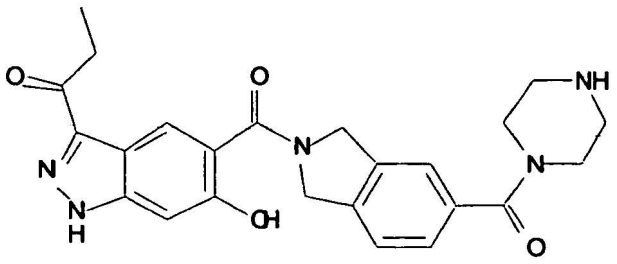
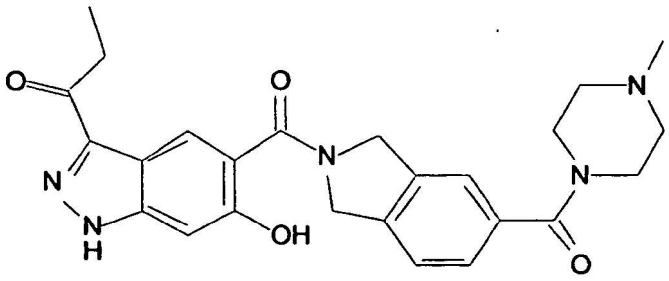
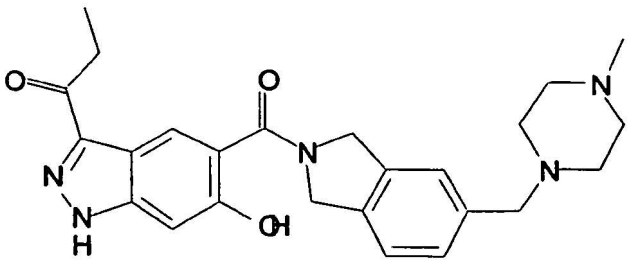
"A335"	
"A336"	
"A337"	
"A338"	

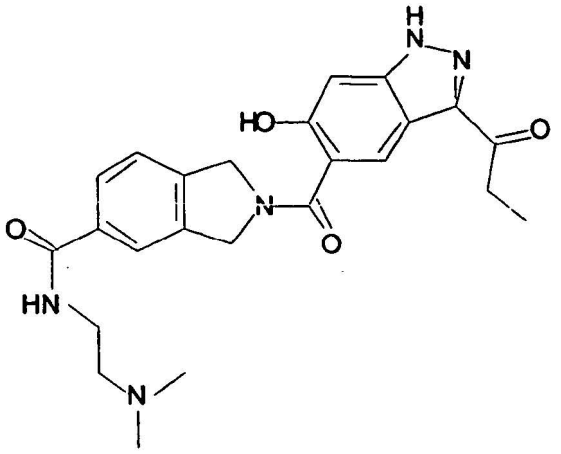
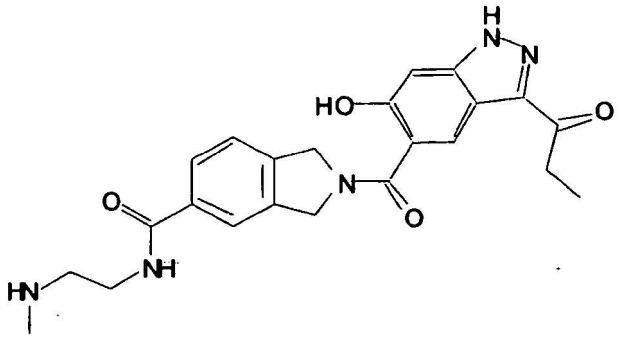
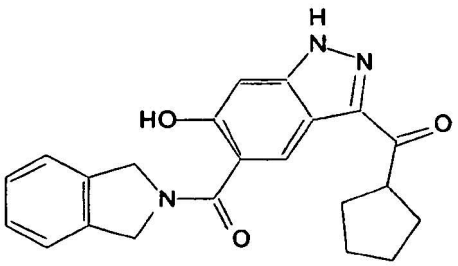
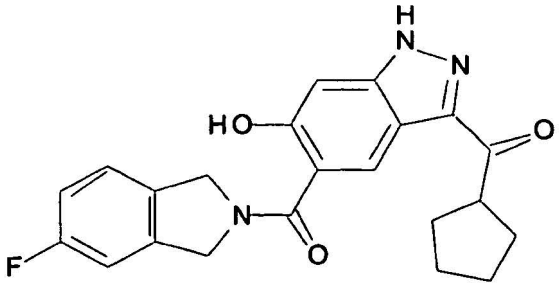
"A339"	
"A340"	
"A341"	
"A342"	

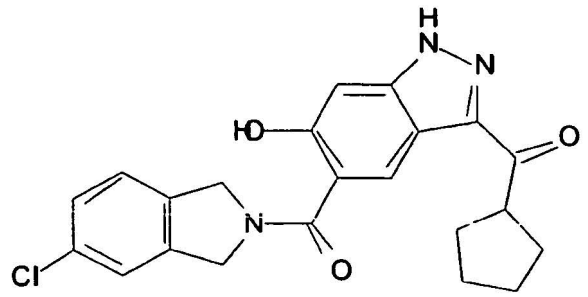
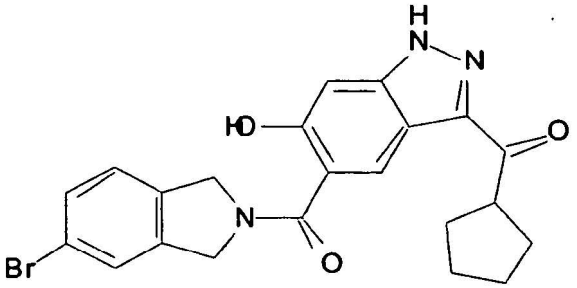
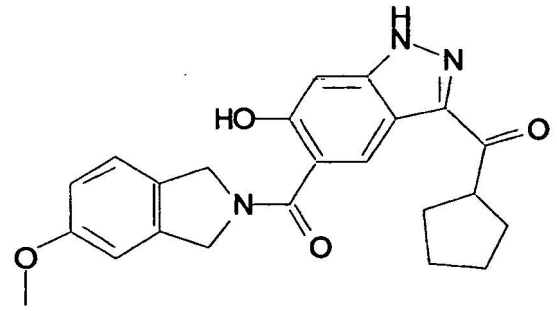
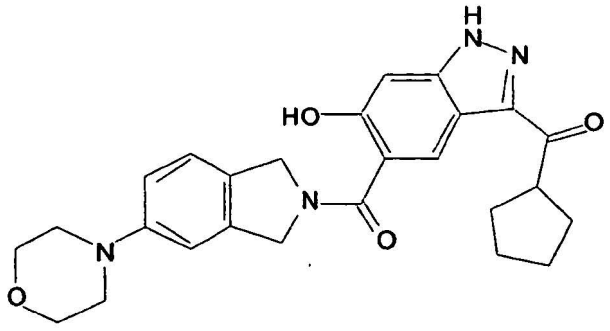
"A343"	
"A344"	
"A345"	
"A346"	

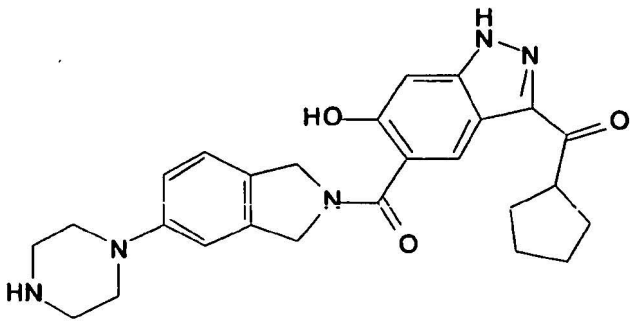
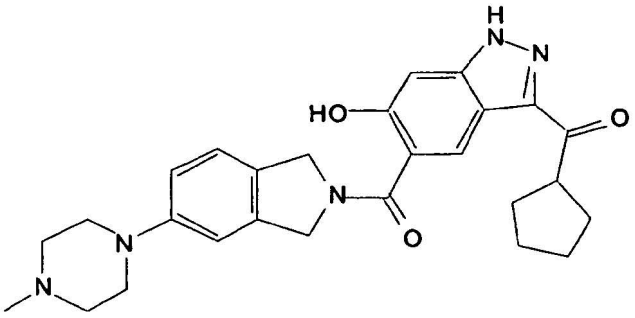
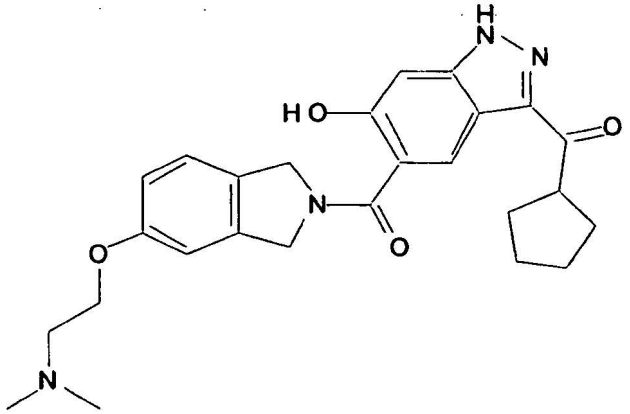
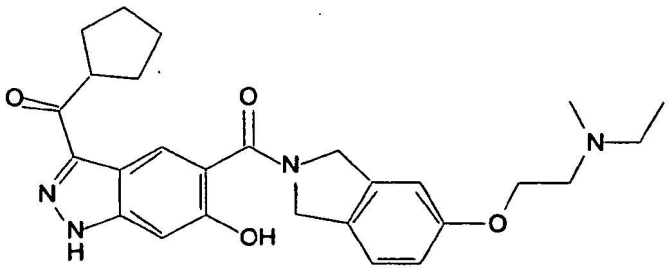
"A347"	
"A348"	
"A349"	
"A350"	
"A351"	

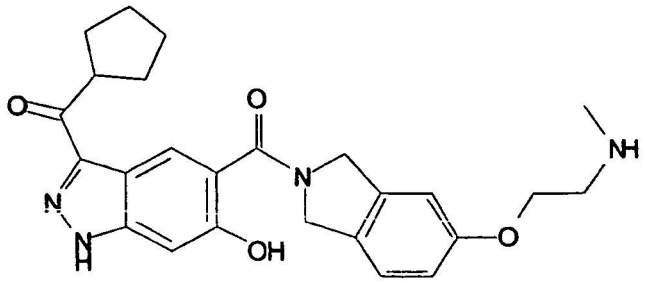
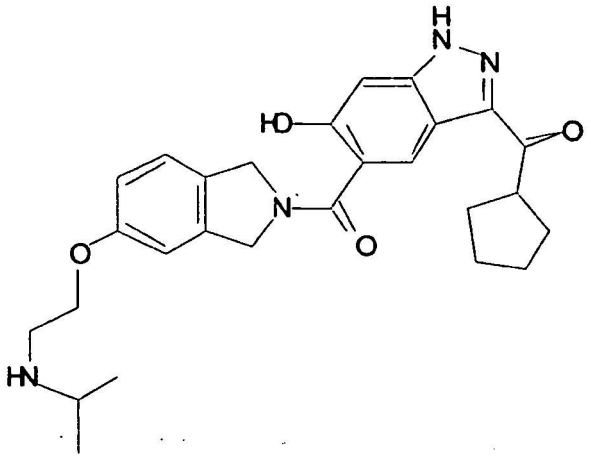
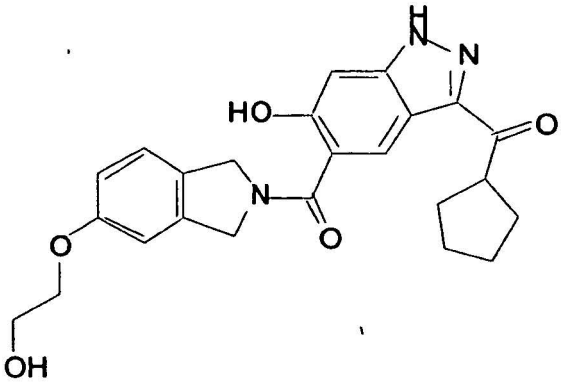
"A352"	
"A353"	
"A354"	
"A355"	
"A356"	

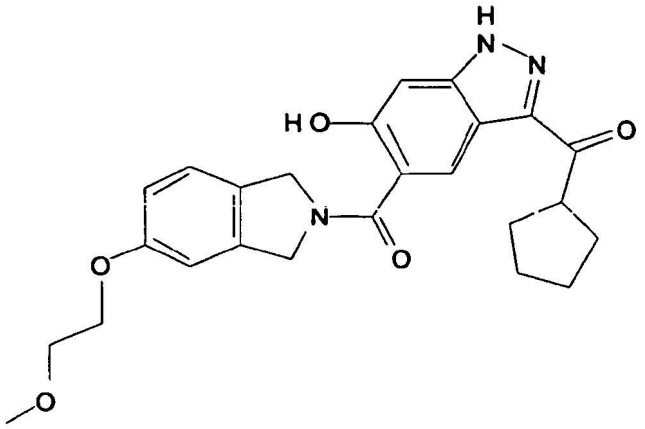
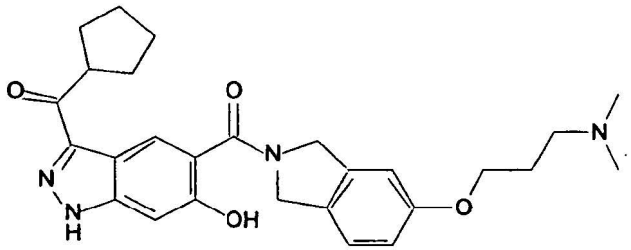
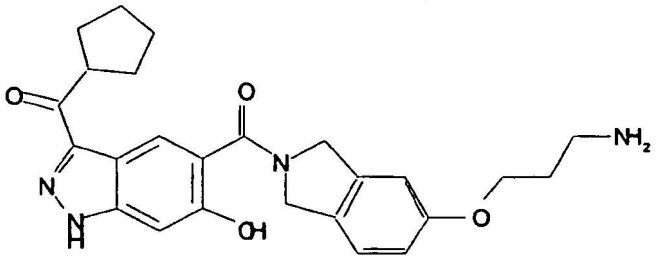
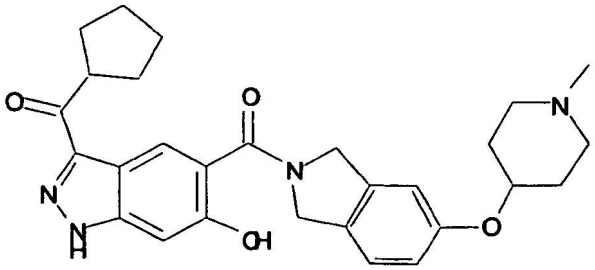
"A357"	
"A358"	
"A359"	
"A360"	
"A361"	

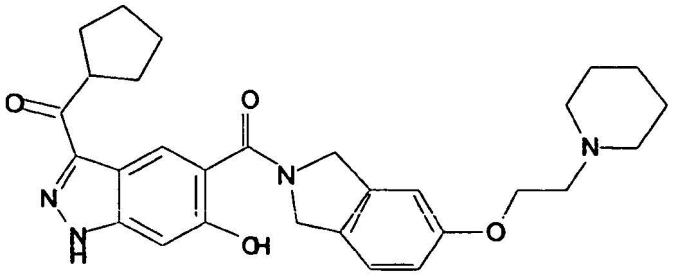
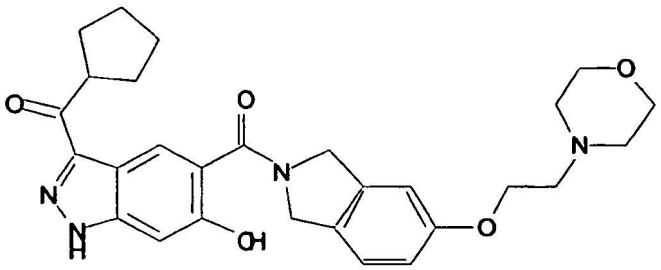
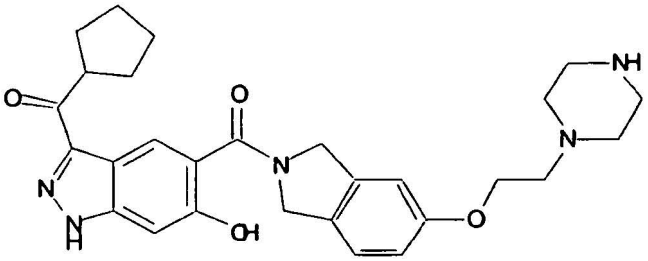
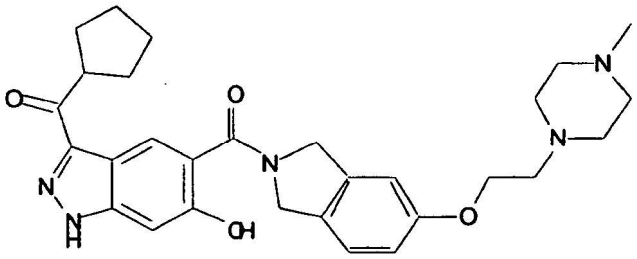
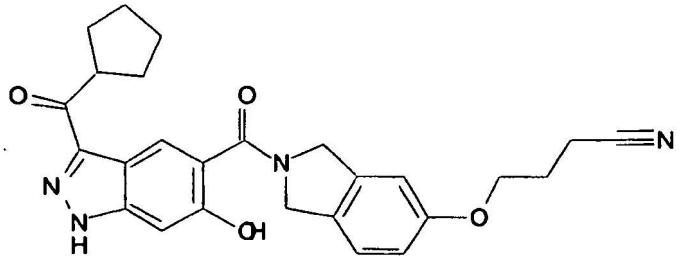
"A362"	
"A363"	
"A364"	
"A365"	

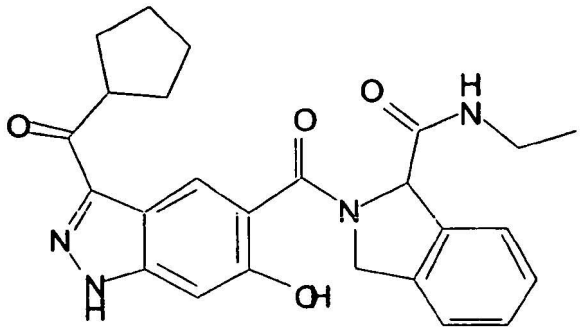
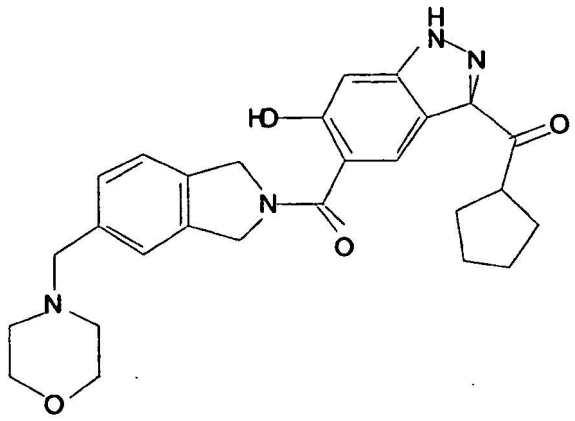
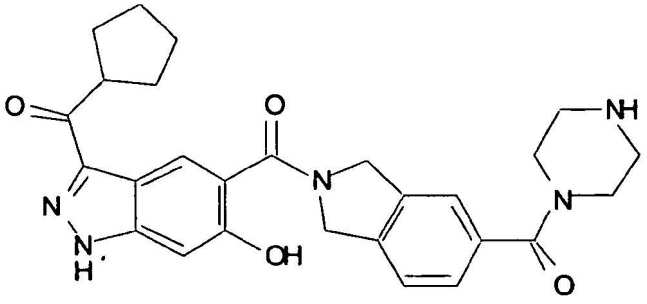
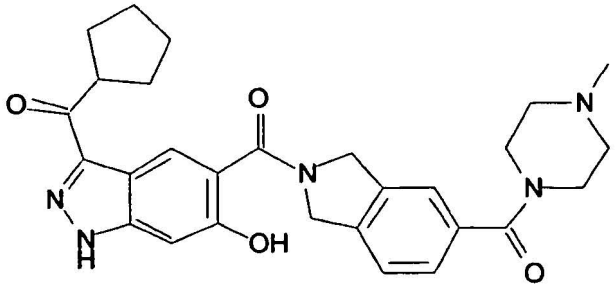
"A366"	
"A367"	
"A368"	
"A369"	

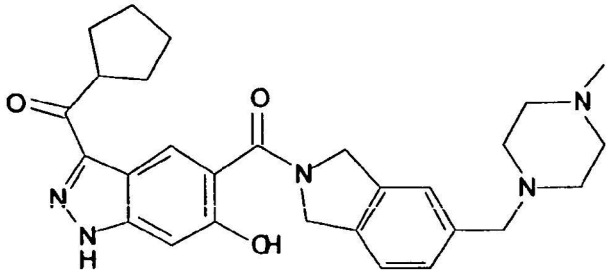
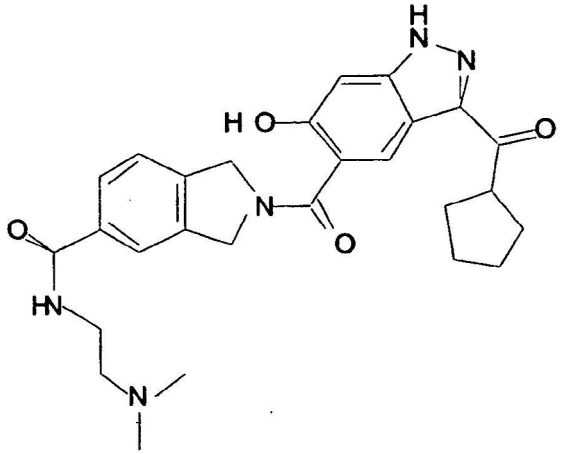
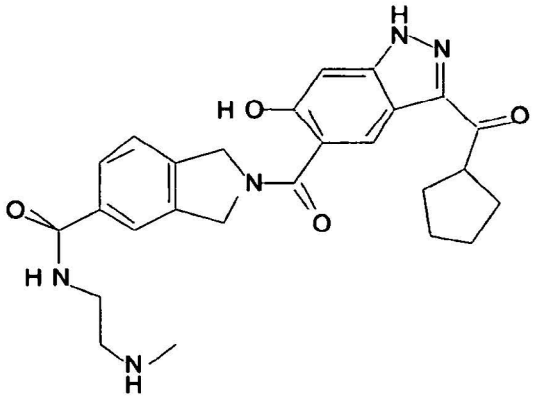
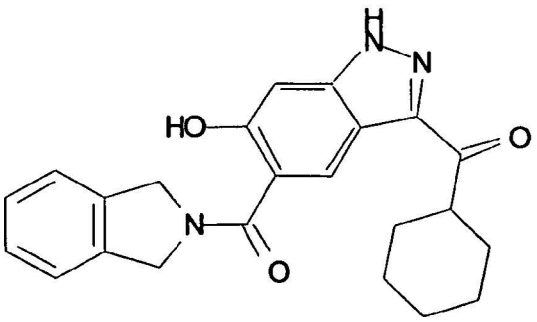
"A370"	
"A371"	
"A372"	
"A373"	

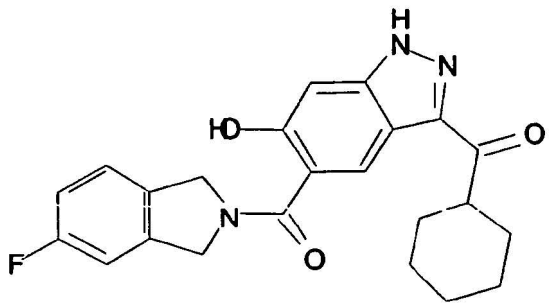
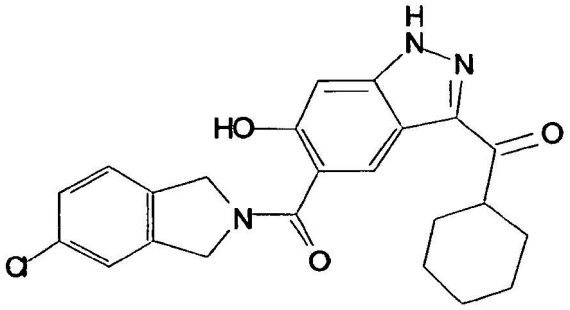
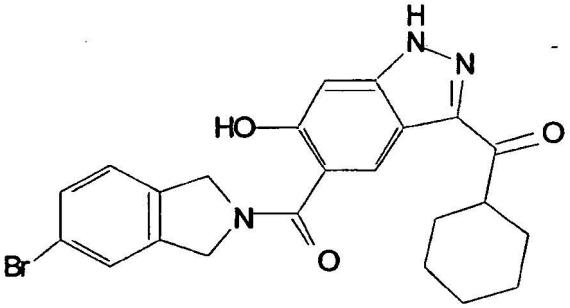
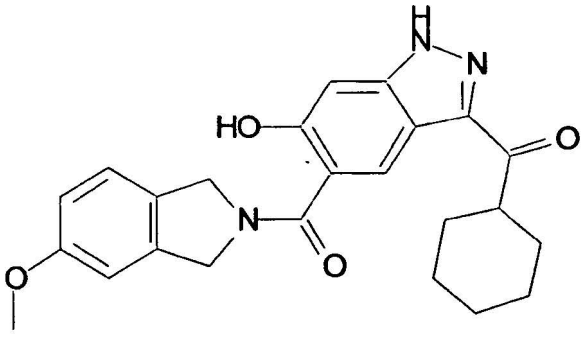
"A374"	
"A375"	
"A376"	

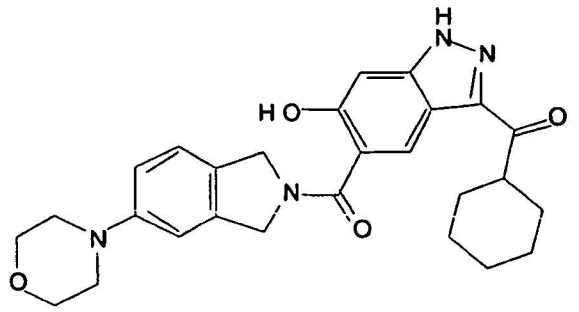
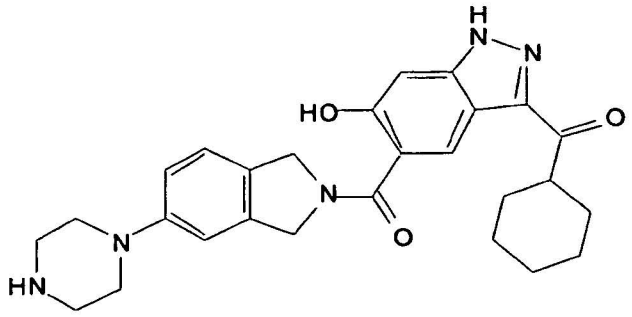
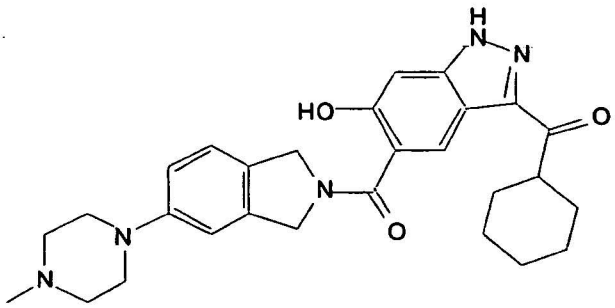
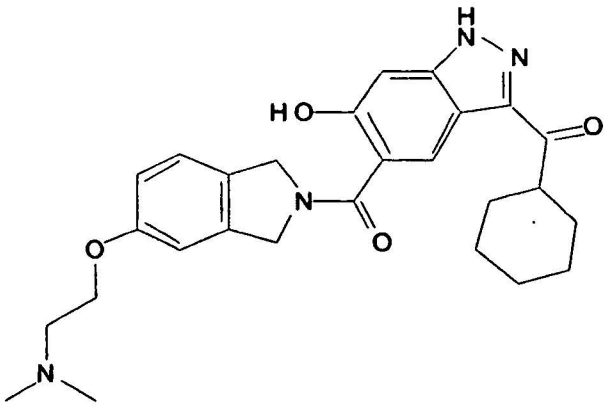
"A377"	
"A378"	
"A379"	
"A380"	

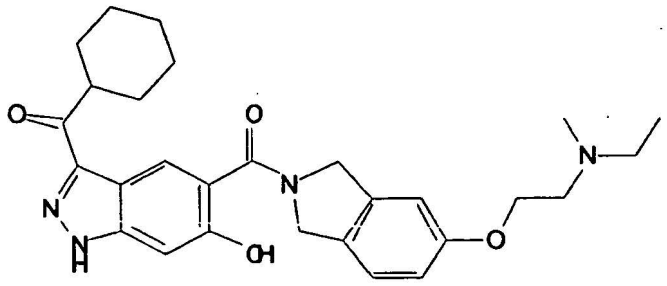
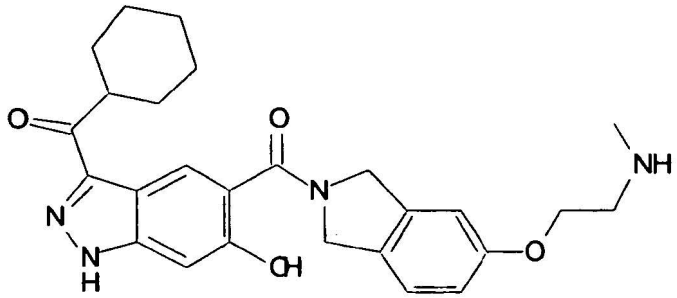
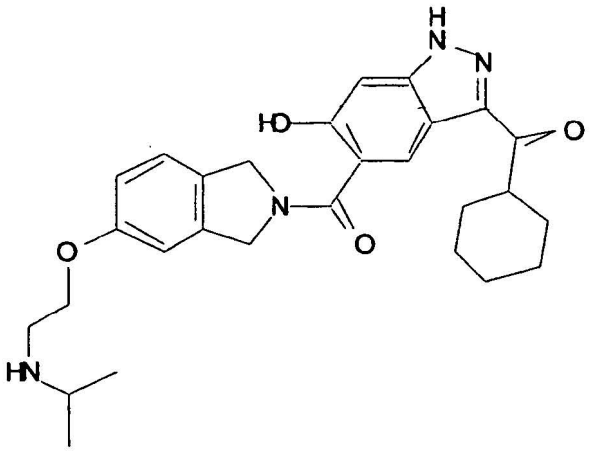
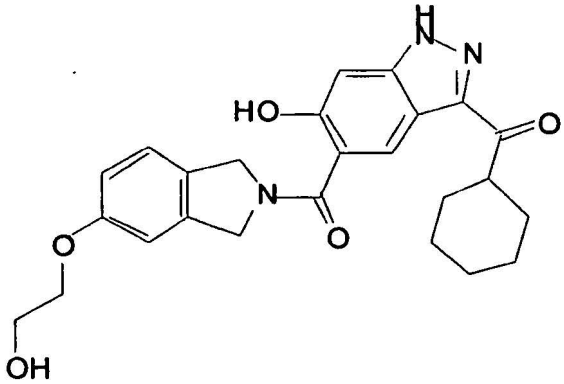
"A381"	
"A382"	
"A383"	
"A384"	
"A385"	

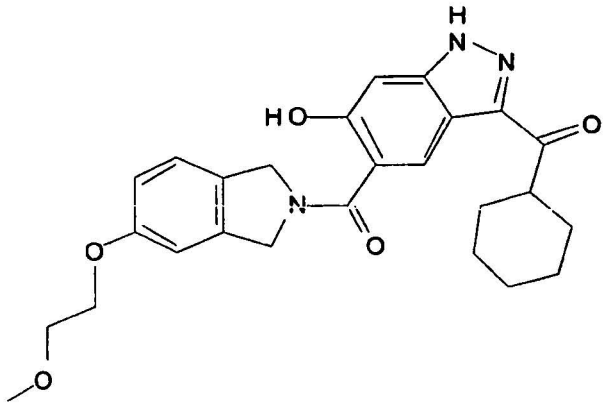
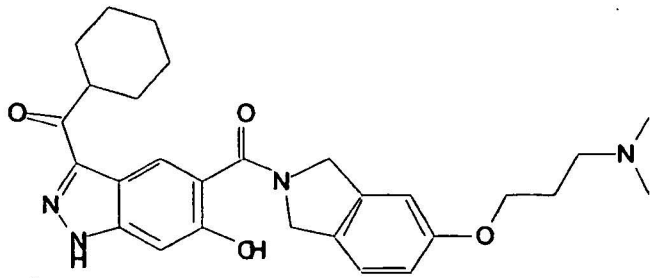
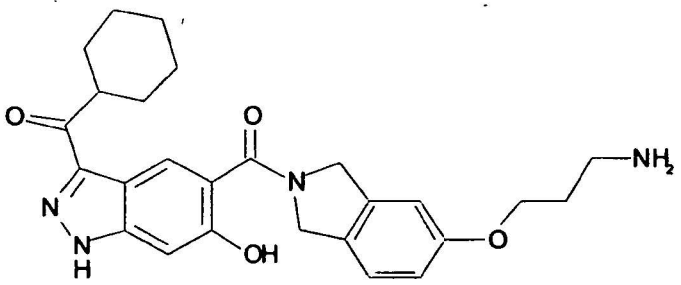
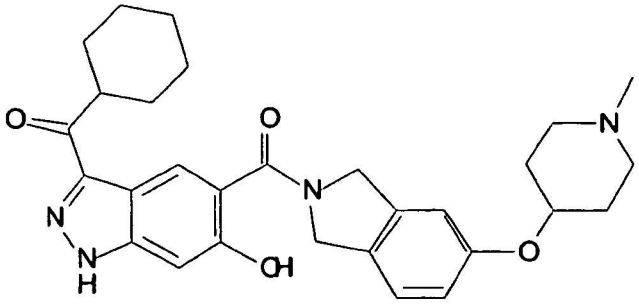
"A386"	
"A387"	
"A388"	
"A389"	

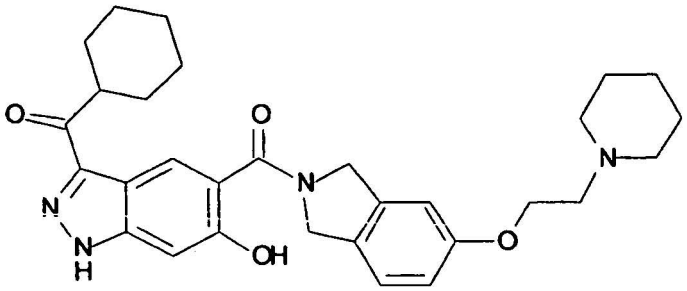
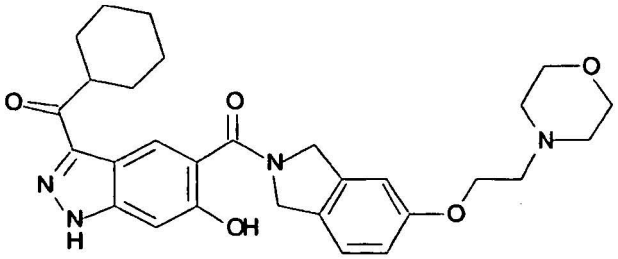
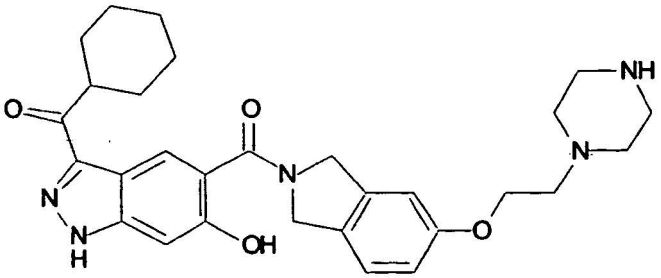
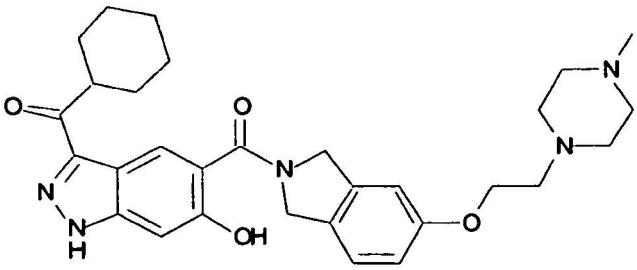
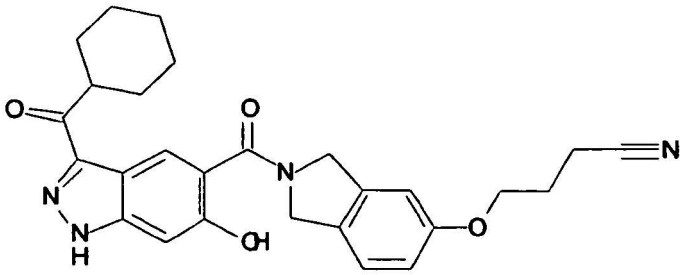
"A390"	
"A391"	
"A392"	
"A393"	

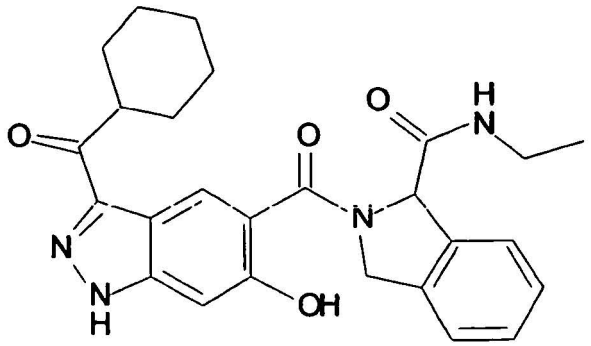
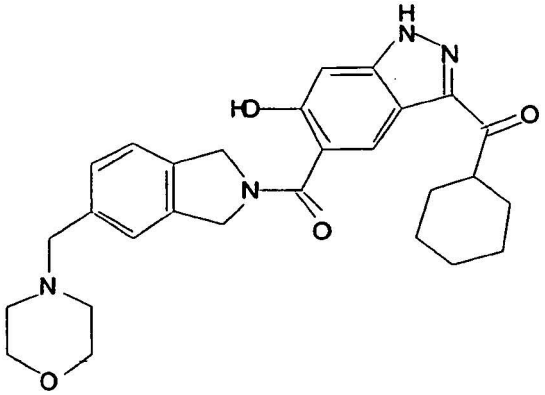
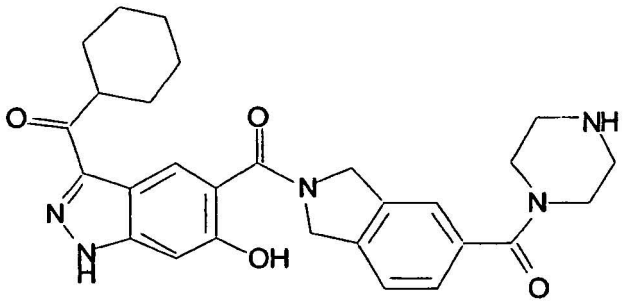
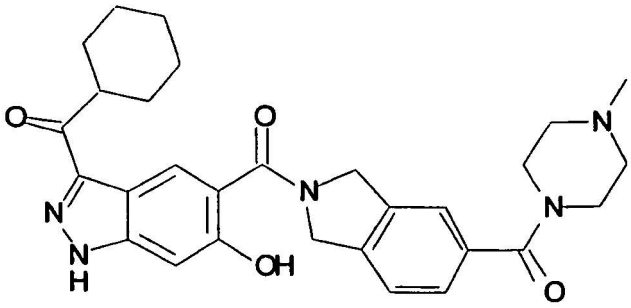
"A394"	
"A395"	
"A396"	
"A397"	

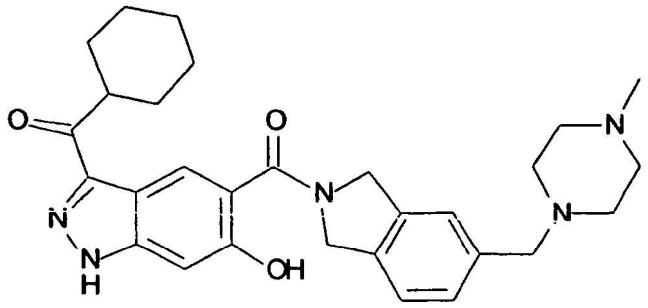
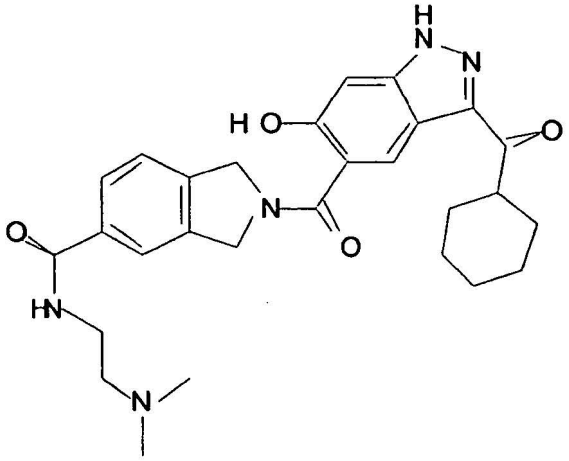
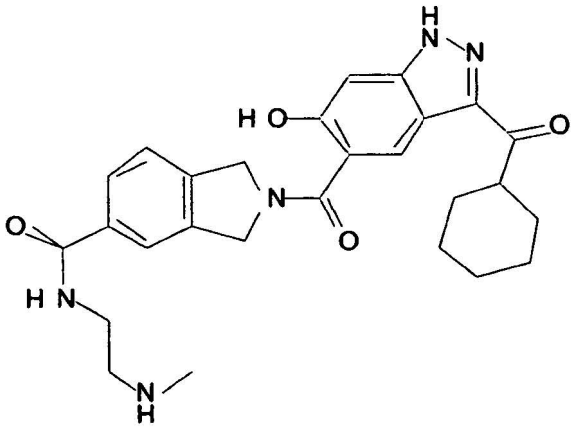
"A398"	
"A399"	
"A400"	
"A401"	

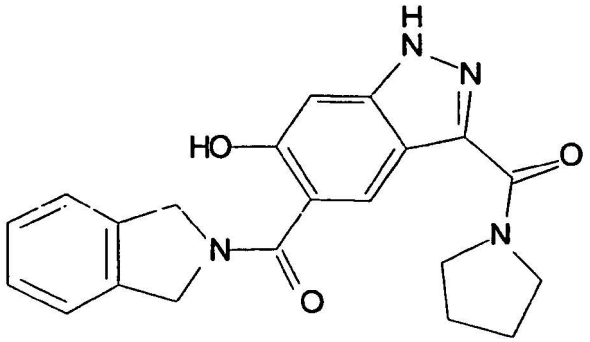
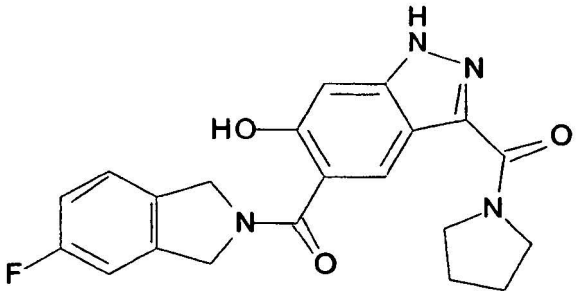
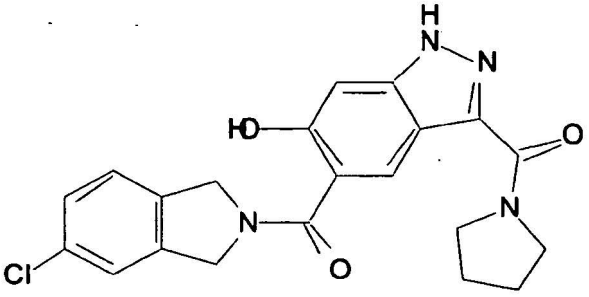
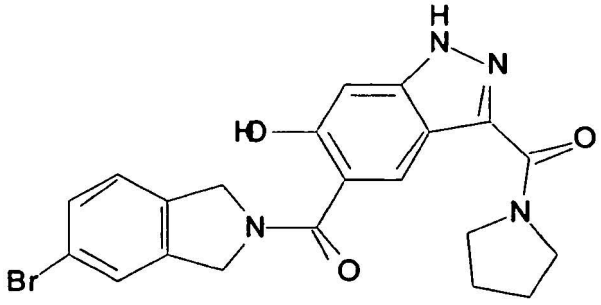
"A402"	
"A403"	
"A404"	
"A405"	

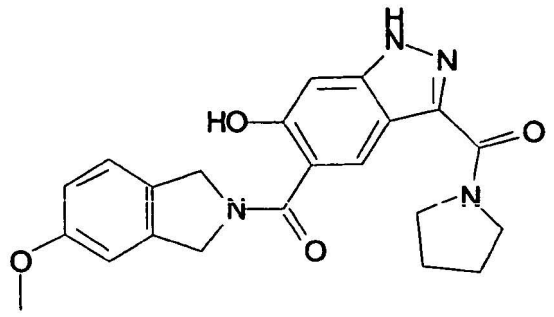
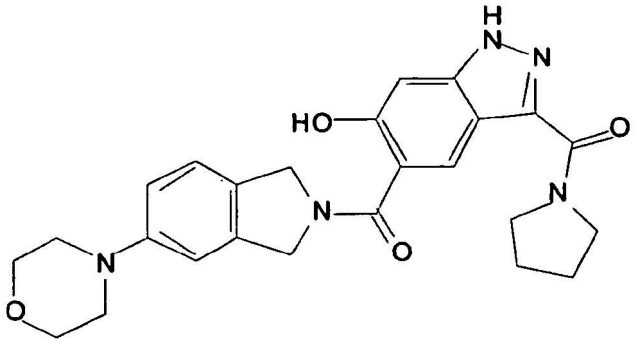
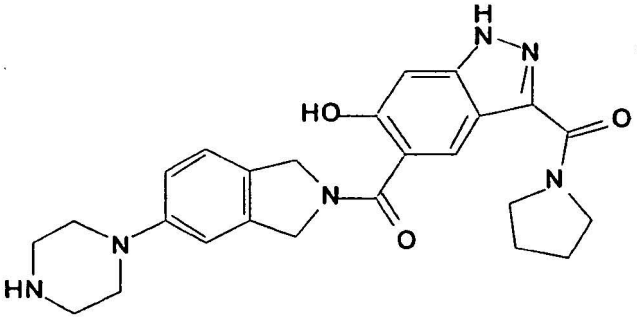
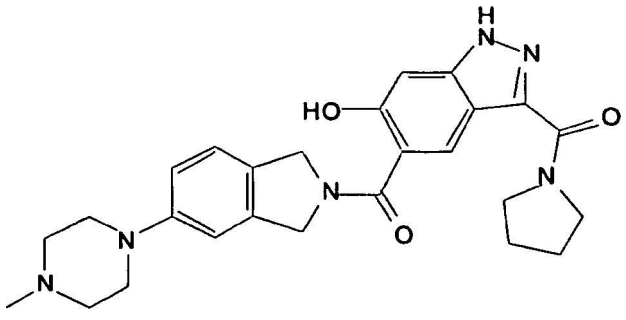
"A406"	
"A407"	
"A408"	
"A409"	

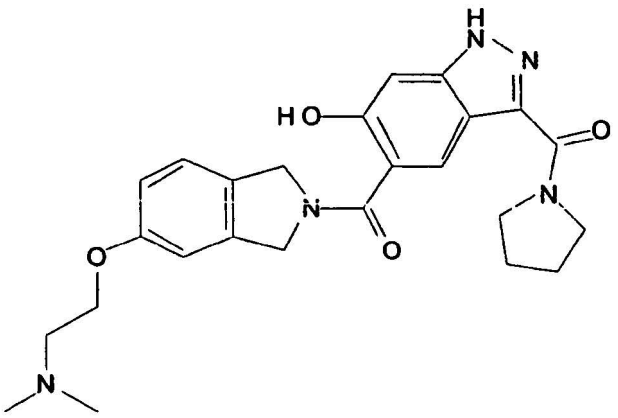
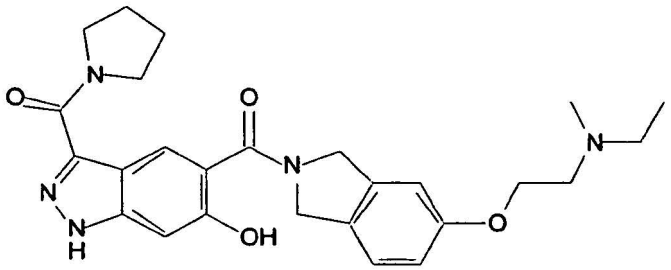
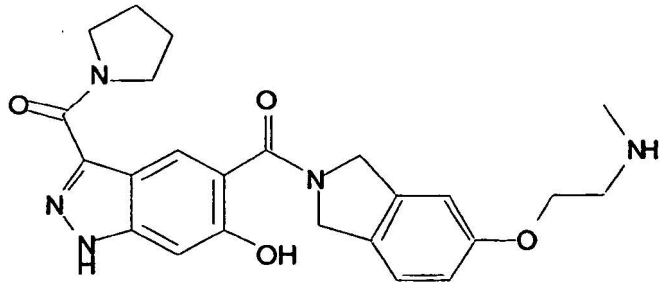
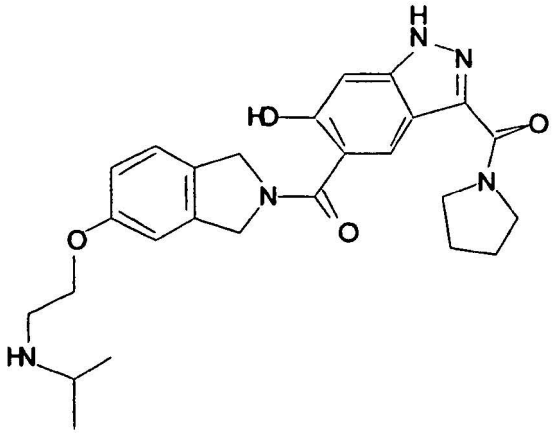
"A410"	
"A411"	
"A412"	
"A413"	
"A414"	

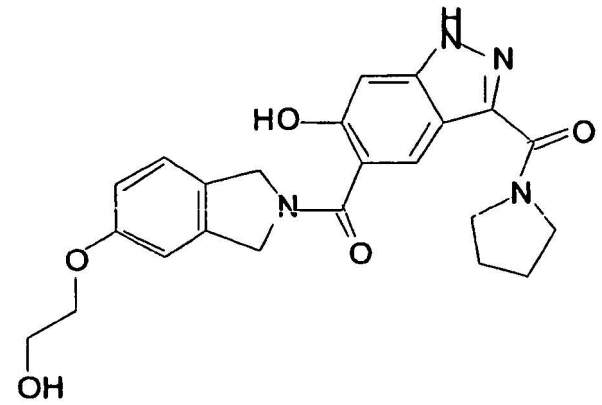
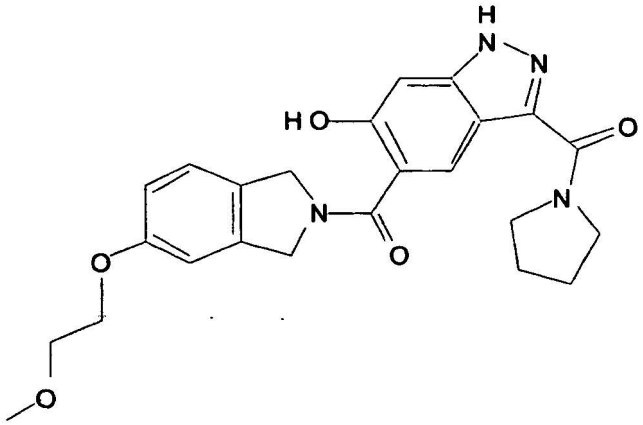
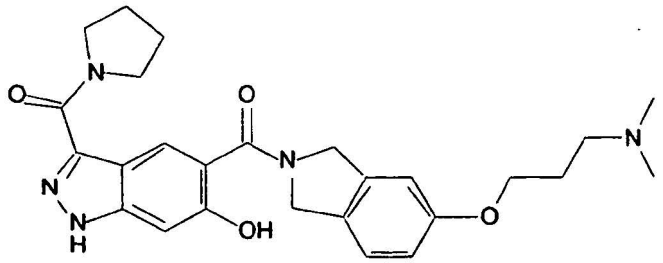
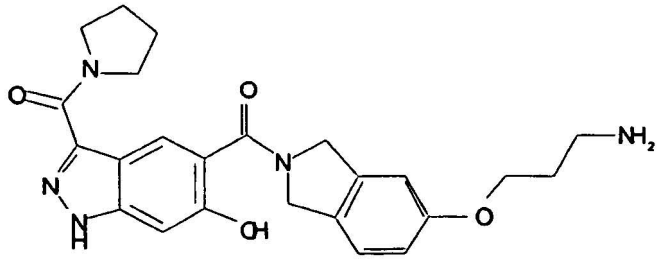
"A415"	
"A416"	
"A417"	
"A418"	

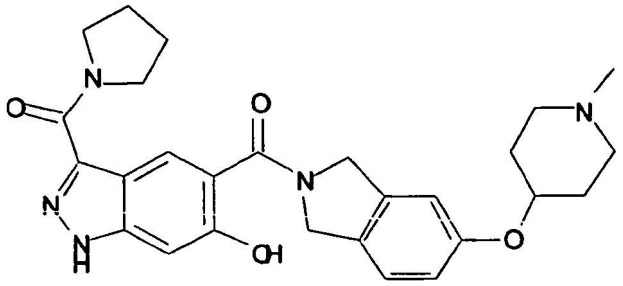
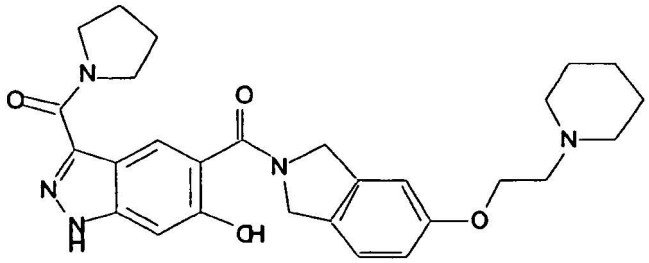
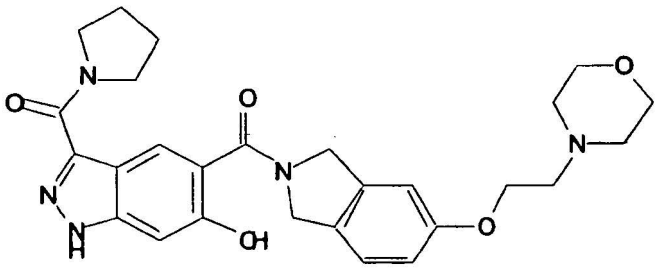
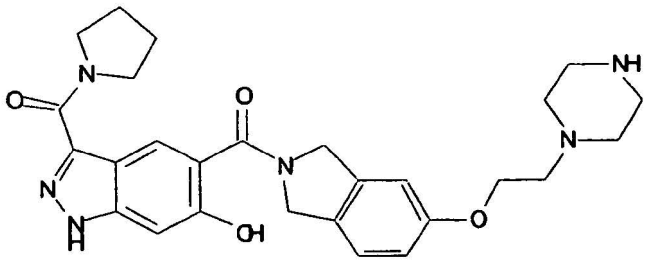
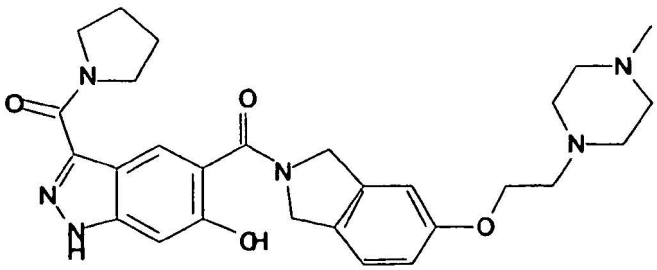
"A419"	
"A420"	
"A421"	

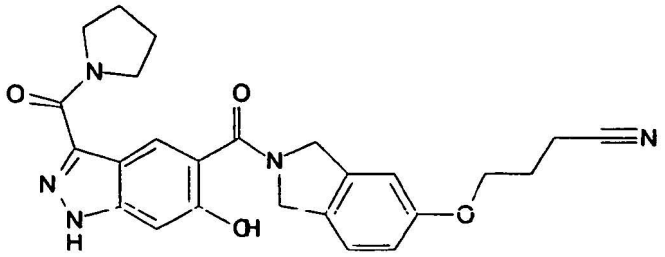
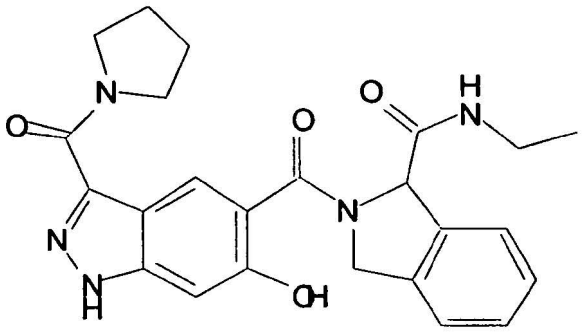
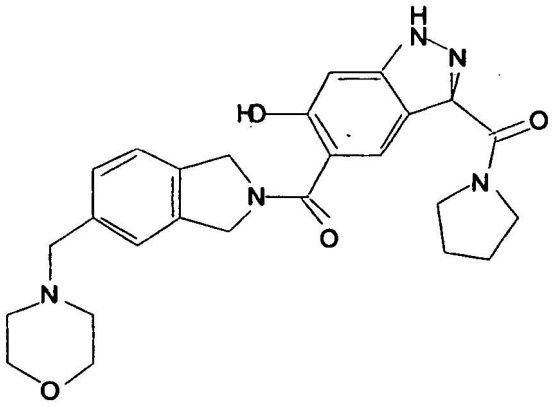
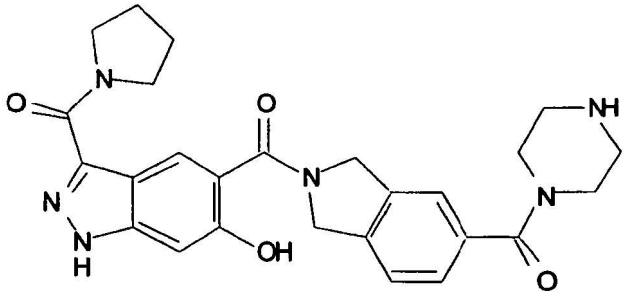
"A422"	
"A423"	
"A424"	
"A425"	

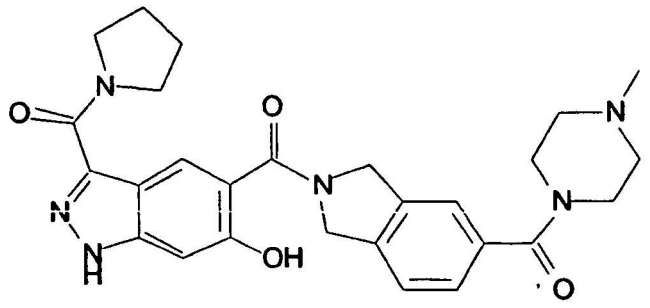
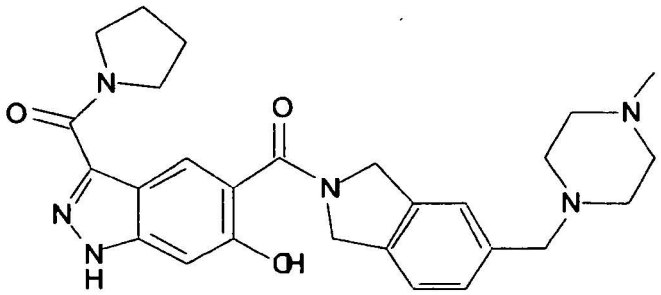
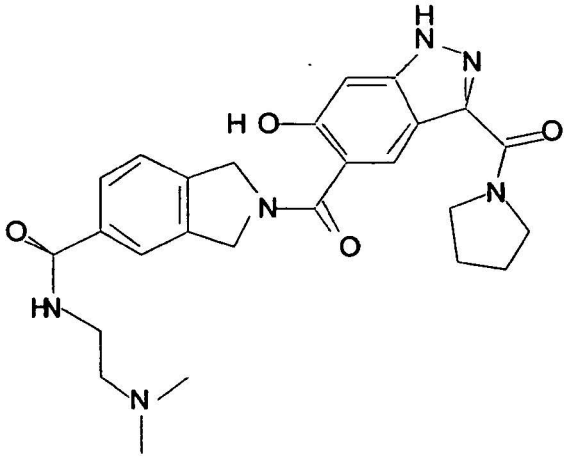
"A426"	
"A427"	
"A428"	
"A429"	

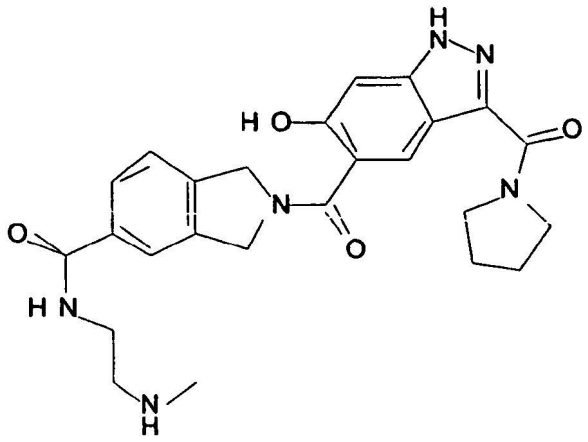
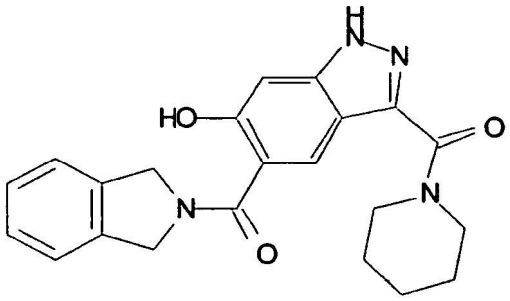
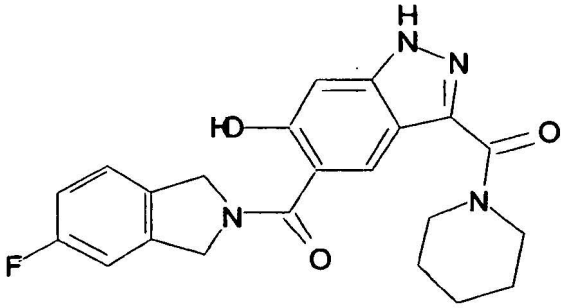
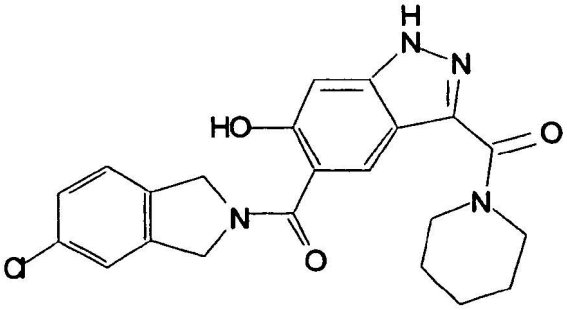
"A430"	
"A431"	
"A432"	
"A433"	

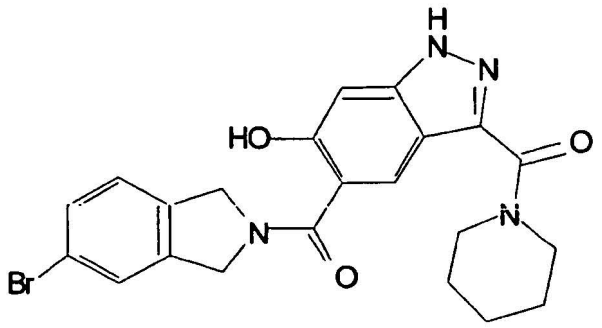
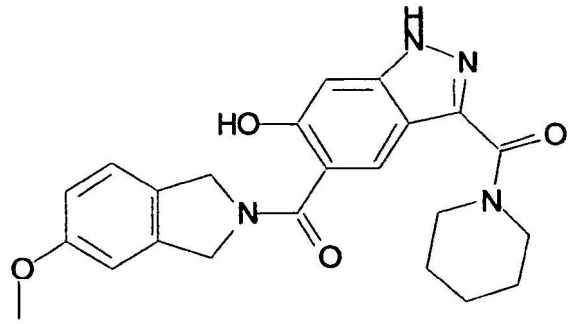
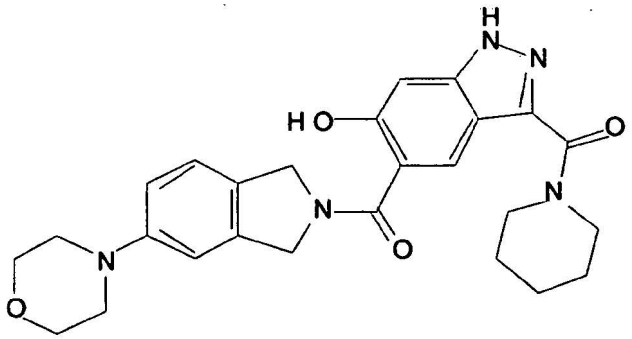
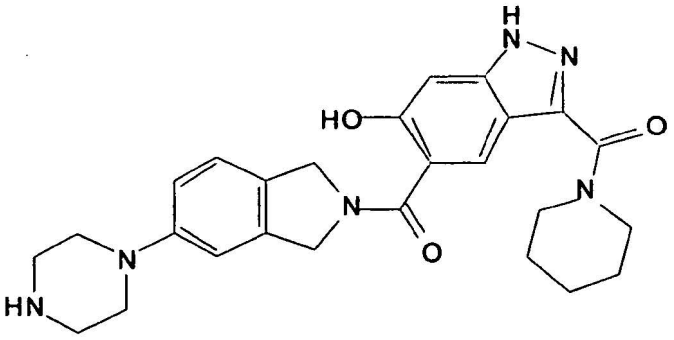
"A434"	
"A435"	
"A436"	
"A437"	

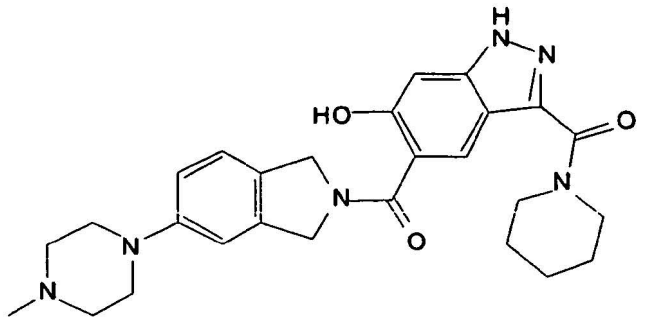
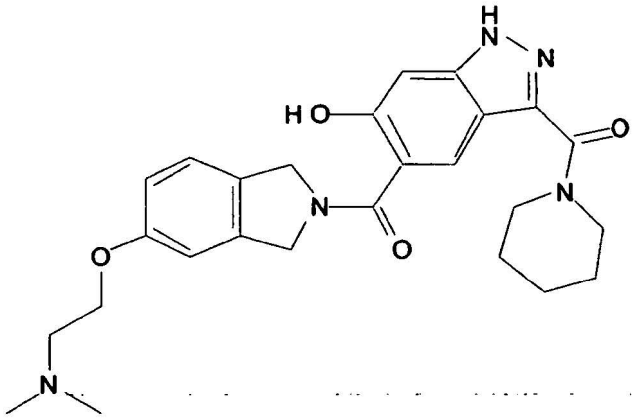
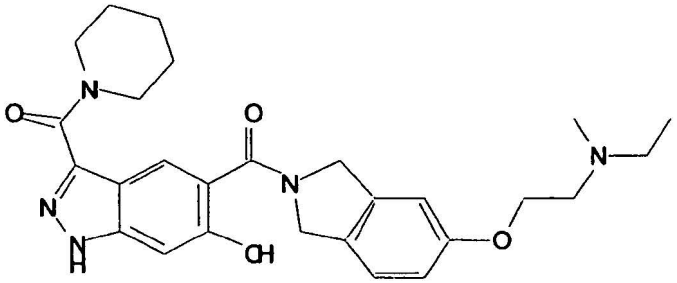
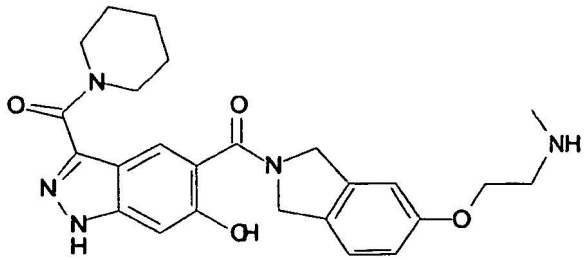
"A438"	
"A439"	
"A440"	
"A441"	
"A442"	

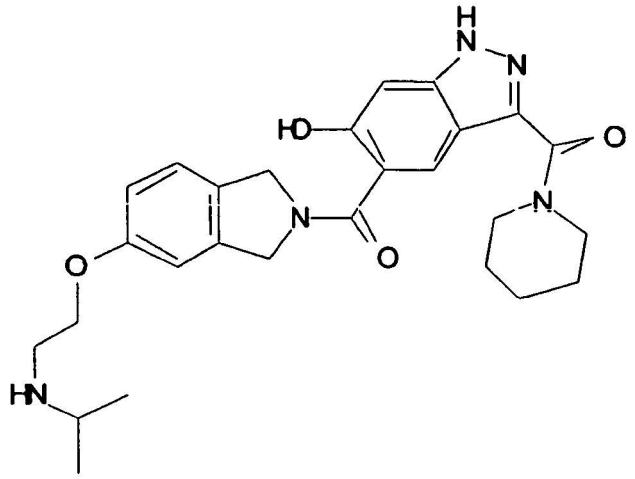
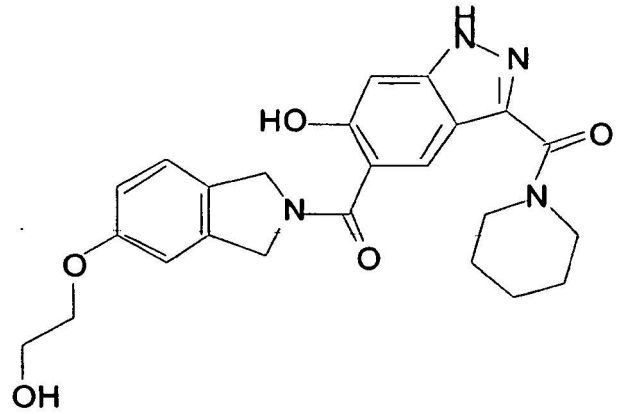
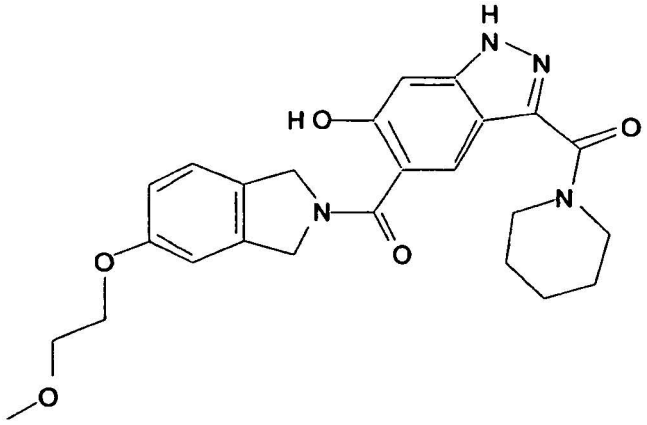
"A443"	
"A444"	
"A445"	
"A446"	

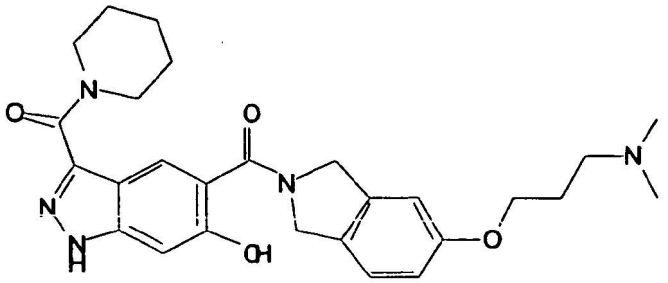
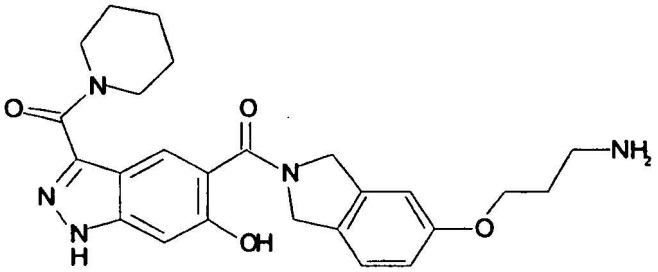
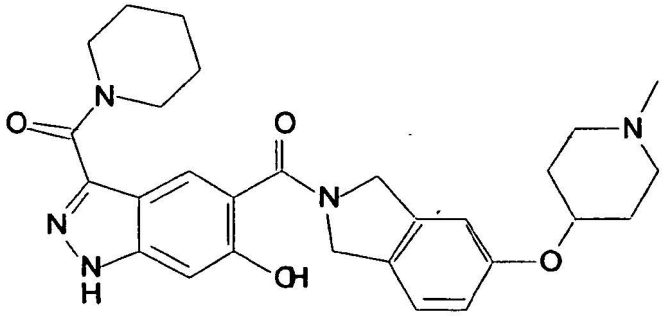
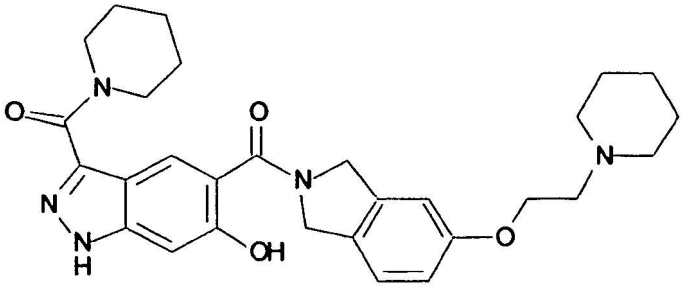
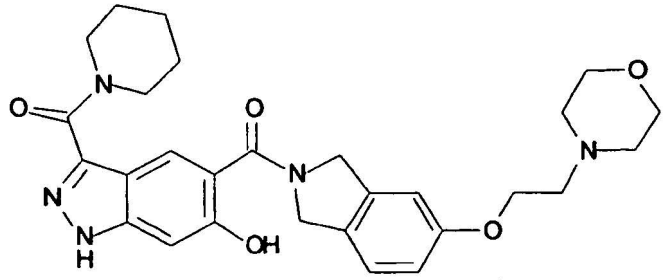
"A447"	
"A448"	
"A449"	

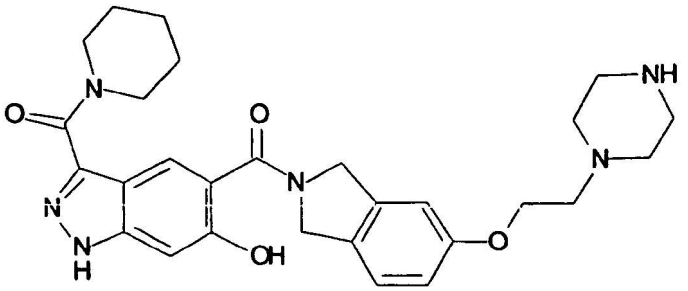
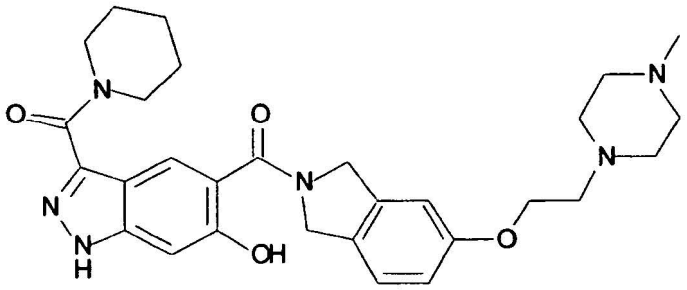
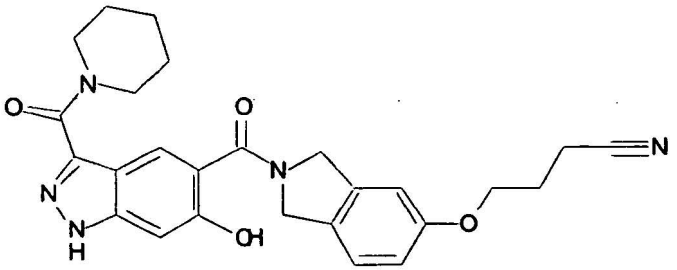
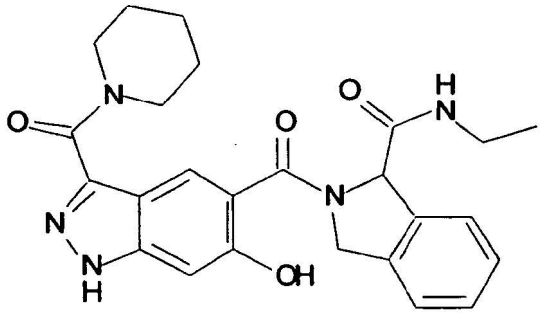
"A450"	
"A451"	
"A452"	
"A453"	

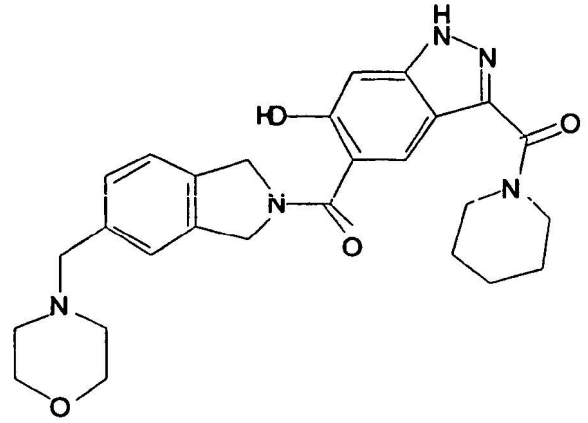
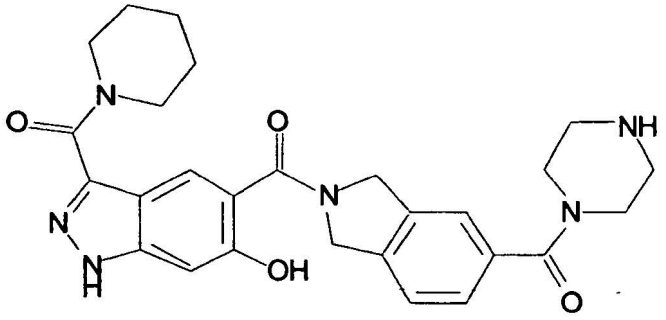
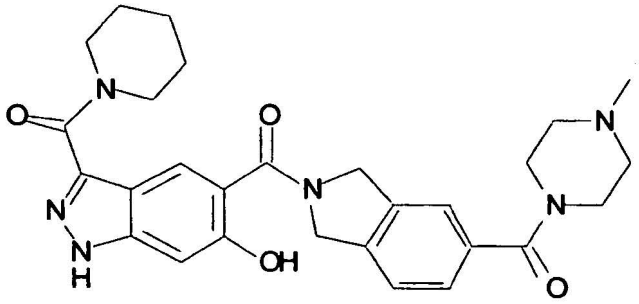
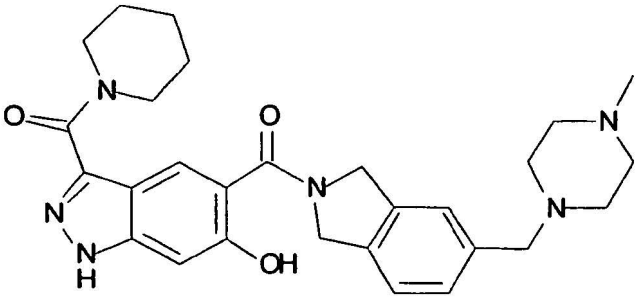
"A454"	
"A455"	
"A456"	
"A457"	

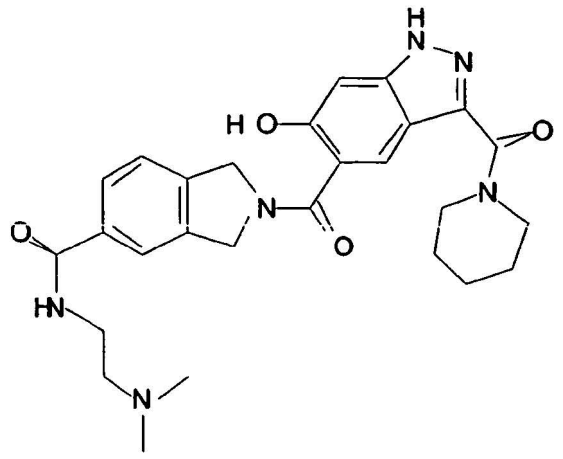
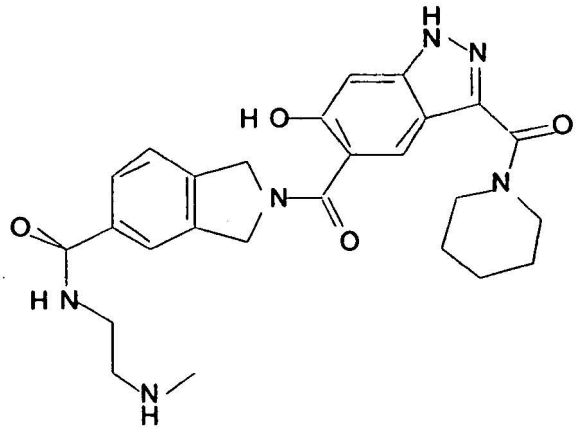
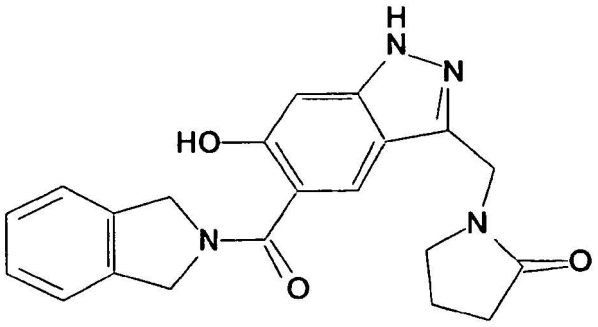
"A458"	
"A459"	
"A460"	
"A461"	

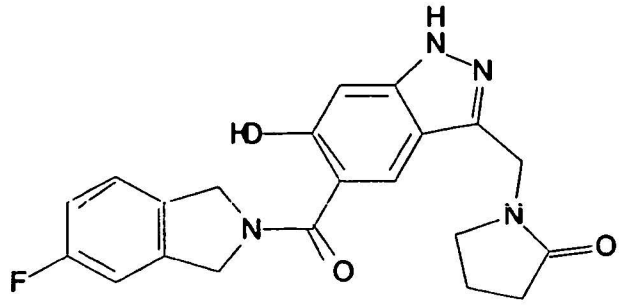
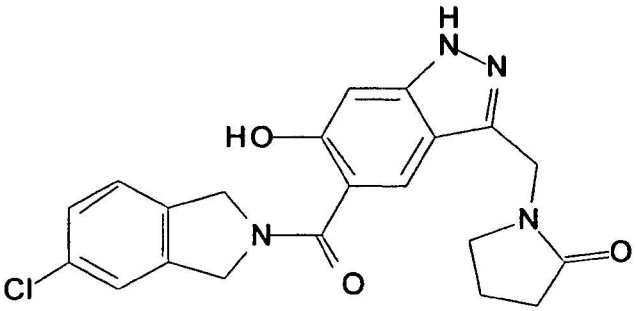
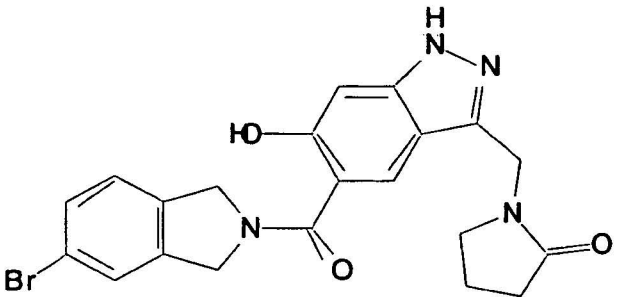
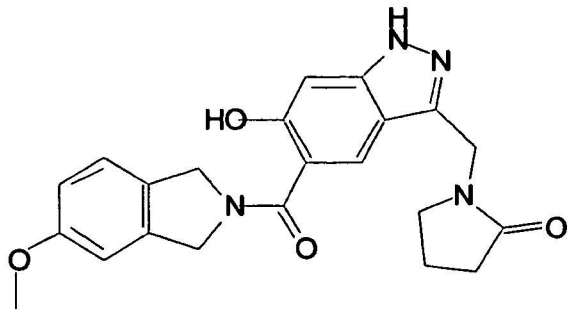
"A462"	
"A463"	
"A464"	

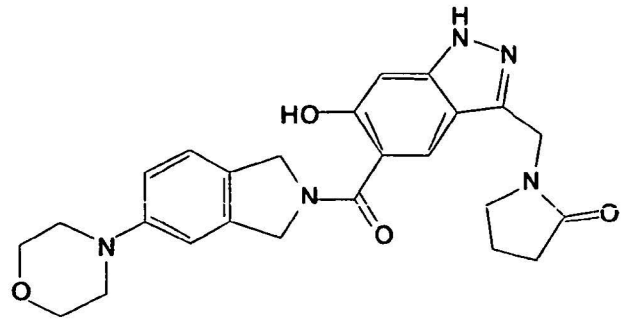
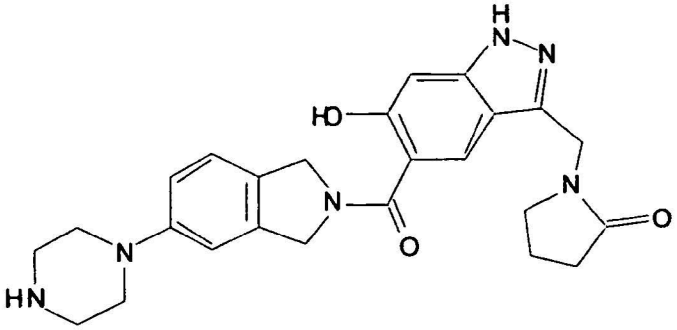
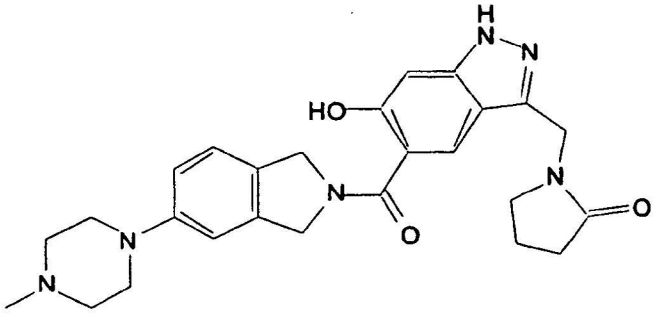
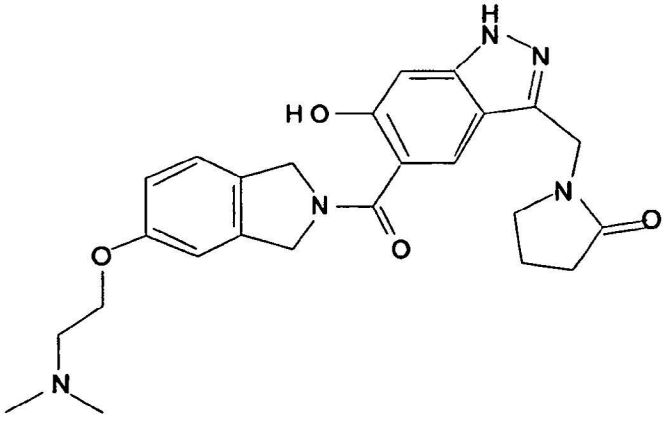
"A465"	
"A466"	
"A467"	
"A468"	
"A469"	

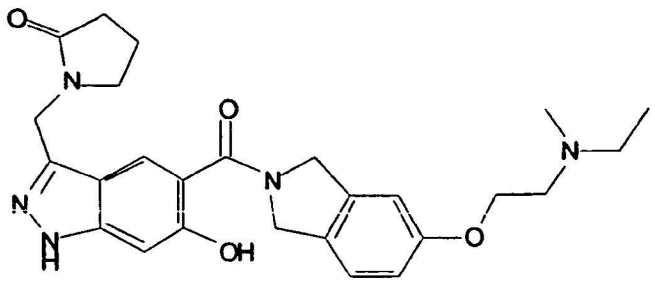
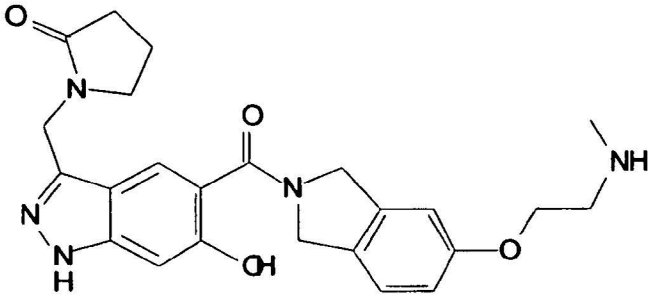
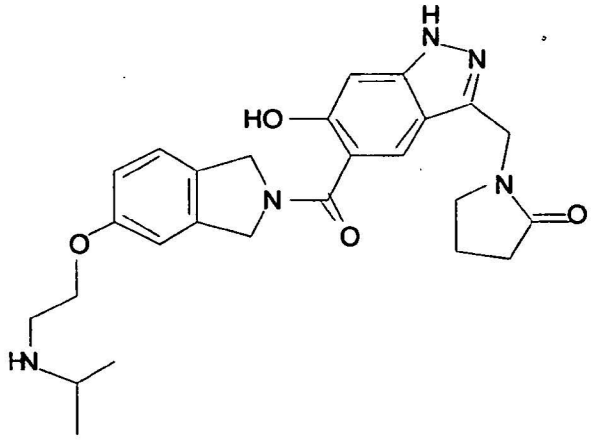
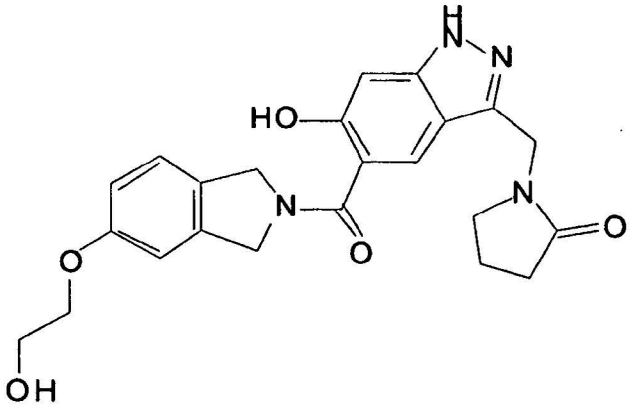
"A470"	
"A471"	
"A472"	
"A473"	

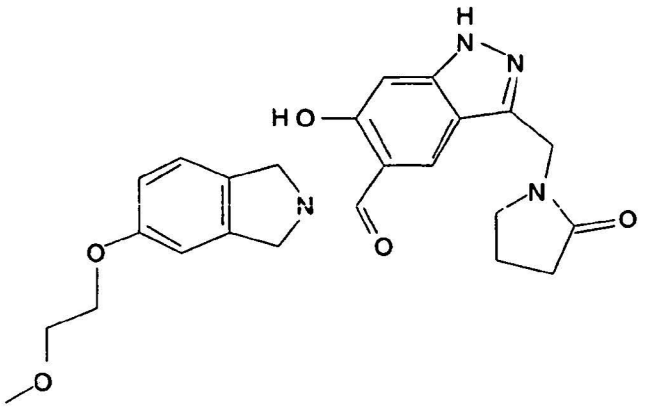
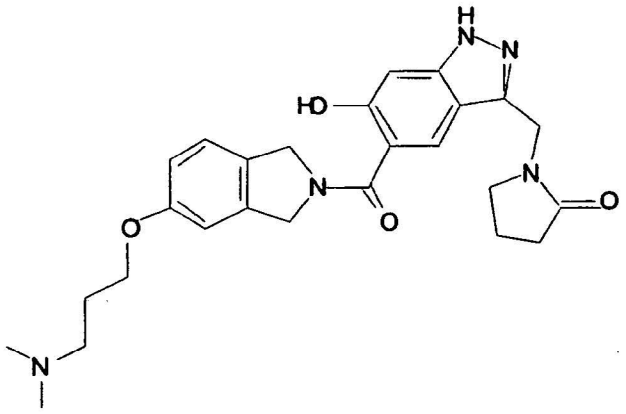
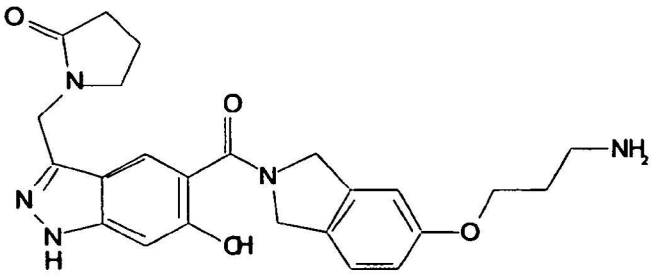
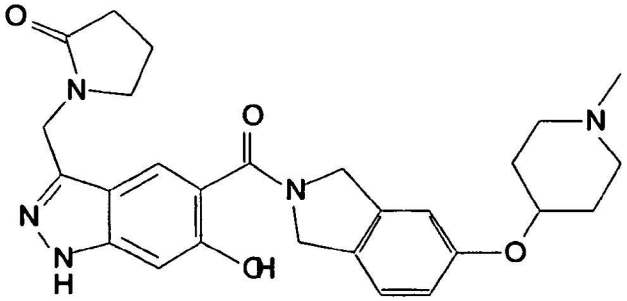
"A474"	
"A475"	
"A476"	
"A477"	

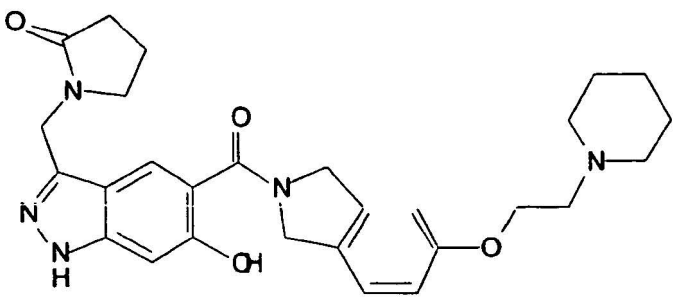
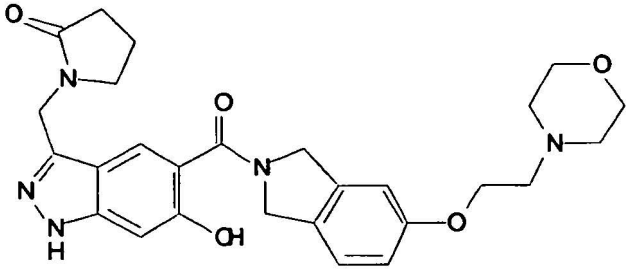
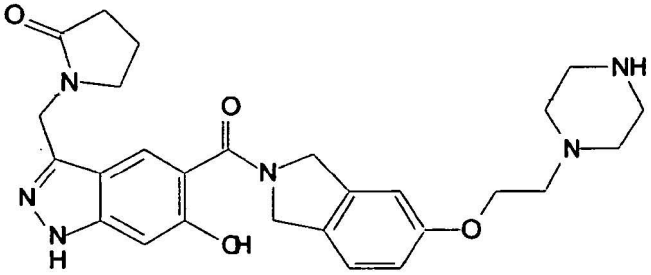
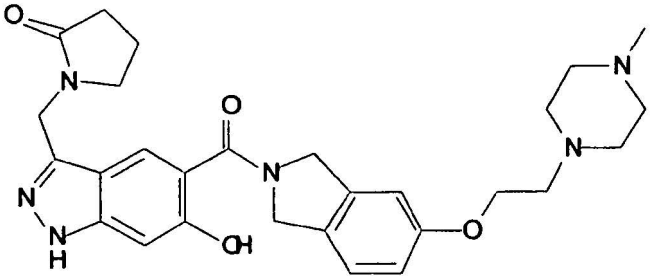
"A478"	
"A479"	
"A480"	

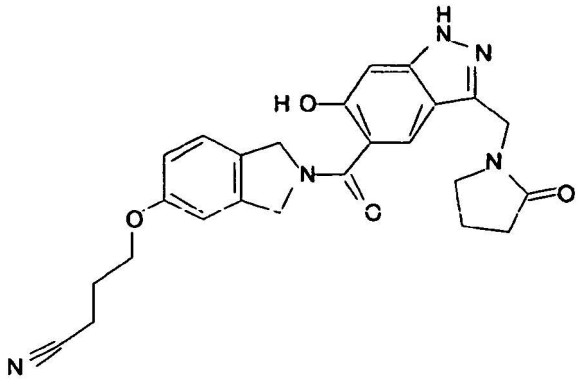
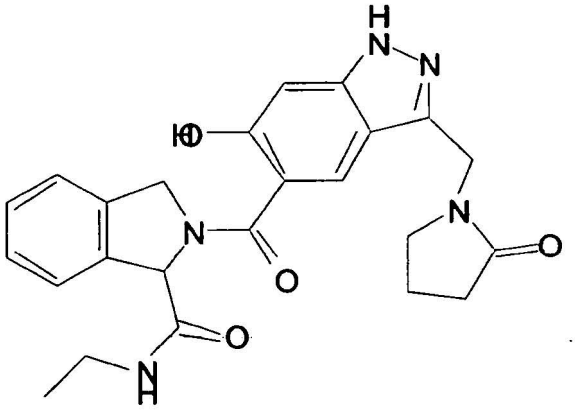
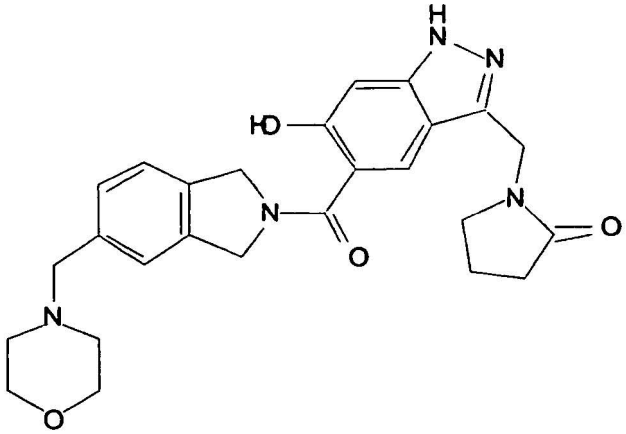
"A481"	
"A482"	
"A483"	
"A484"	

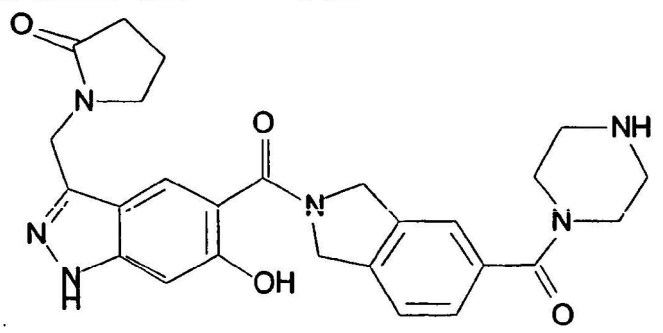
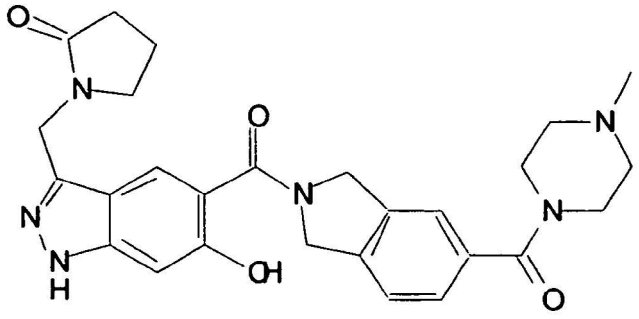
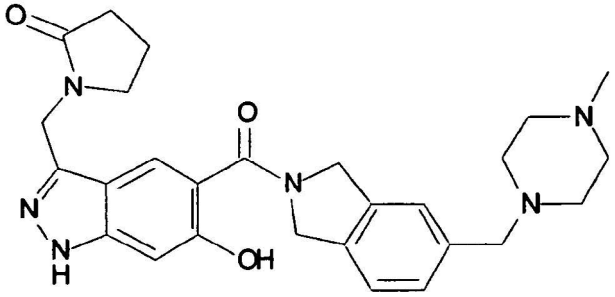
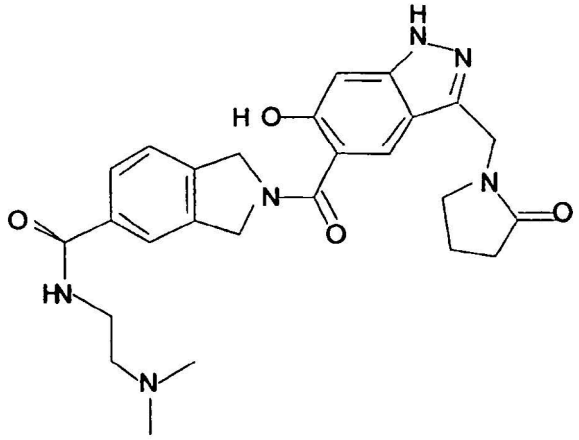
"A485"	
"A486"	
"A487"	
"A488"	

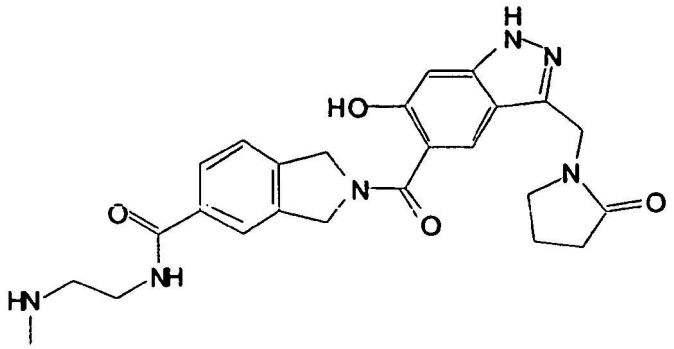
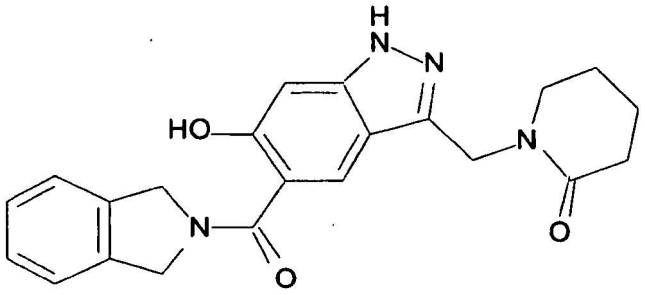
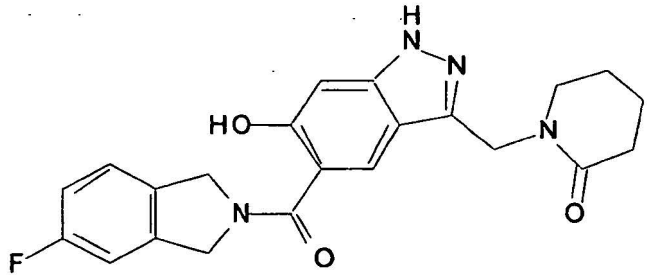
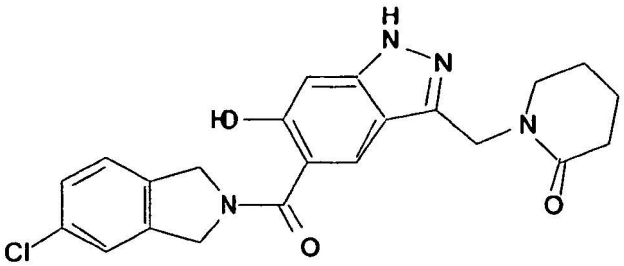
"A489"	
"A490"	
"A491"	
"A492"	

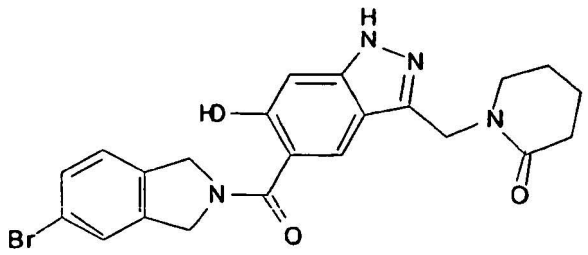
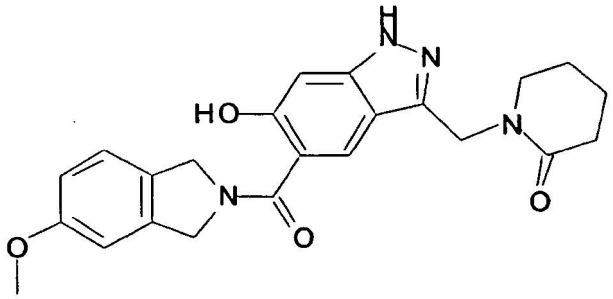
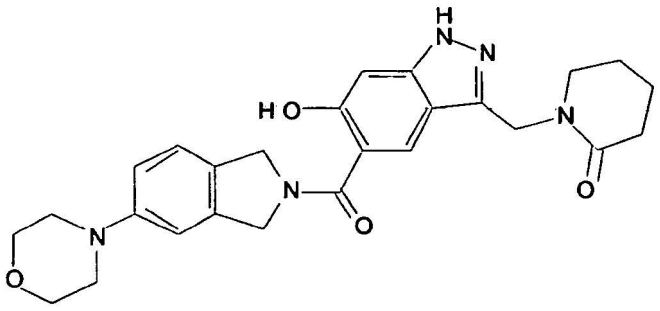
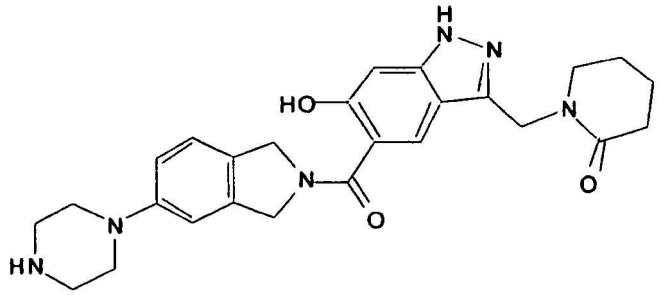
"A493"	
"A494"	
"A495"	
"A496"	

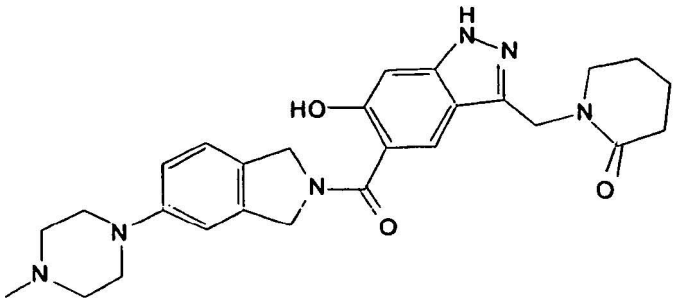
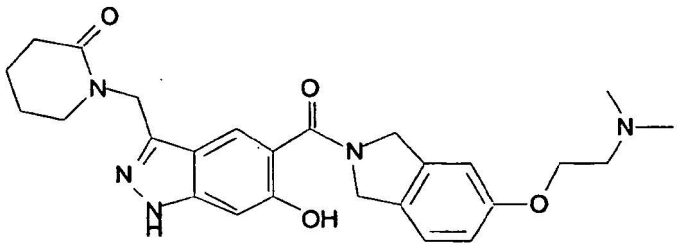
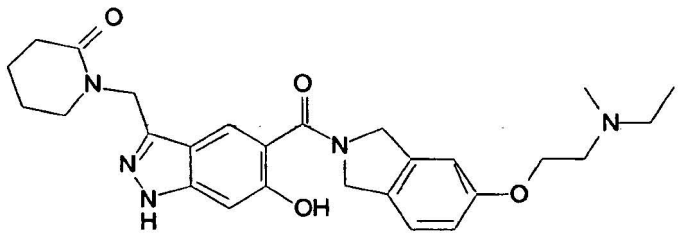
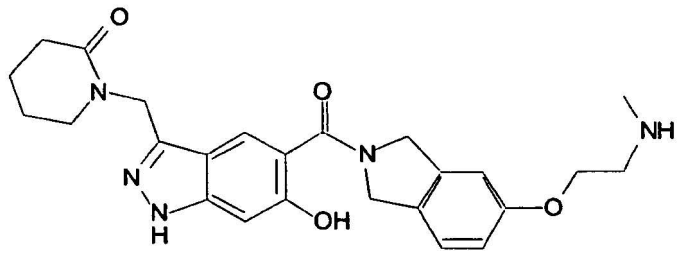
"A497"	
"A498"	
"A499"	
"A500"	

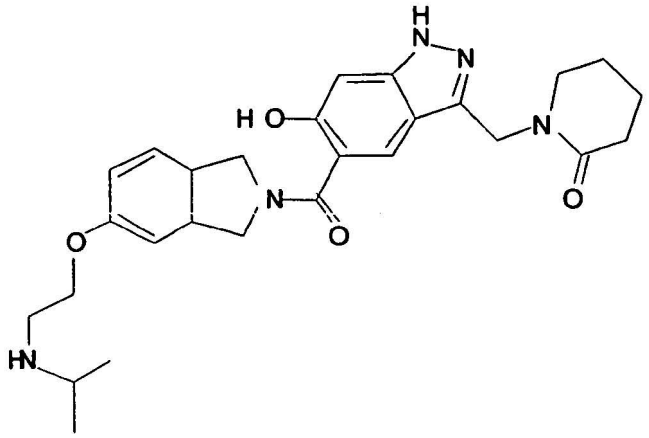
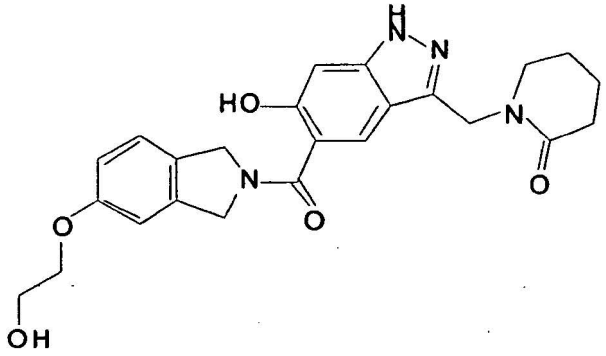
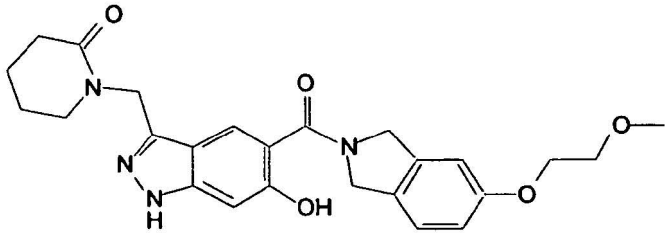
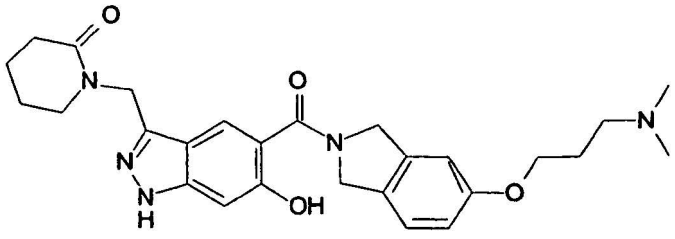
"A501"	
"A502"	
"A503"	

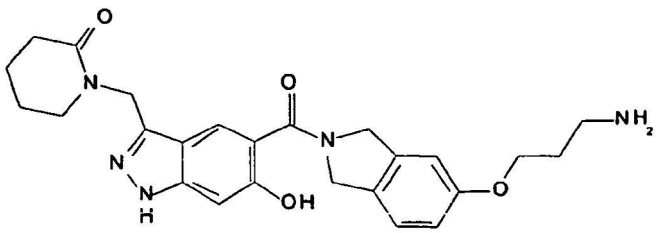
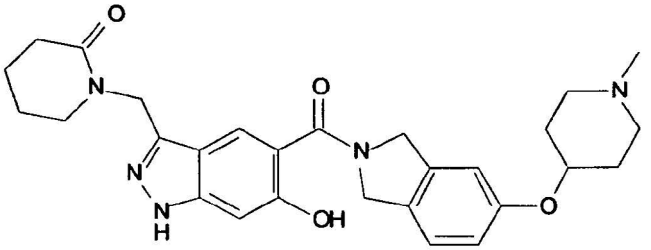
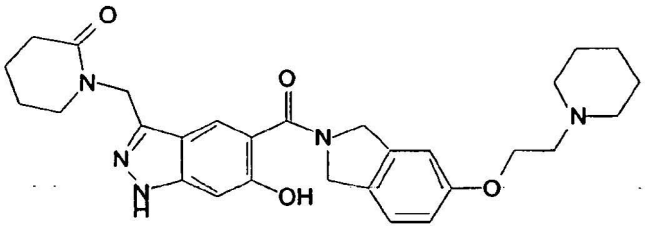
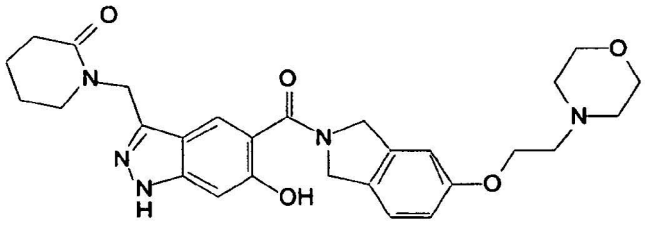
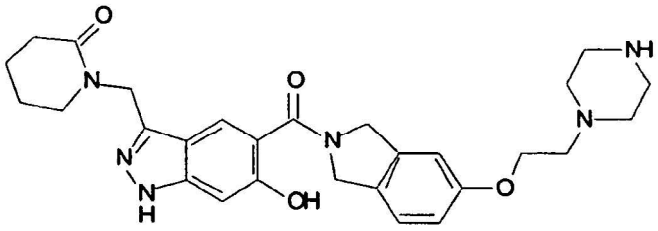
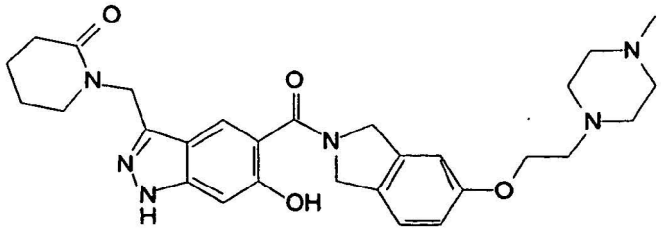
"A504"	
"A505"	
"A506"	
"A507"	

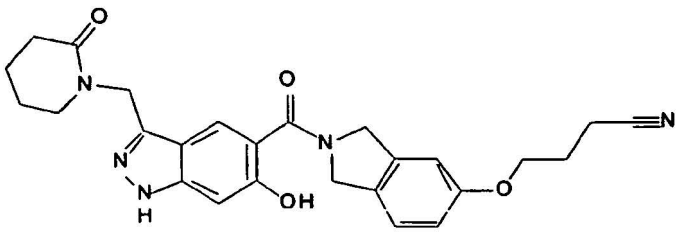
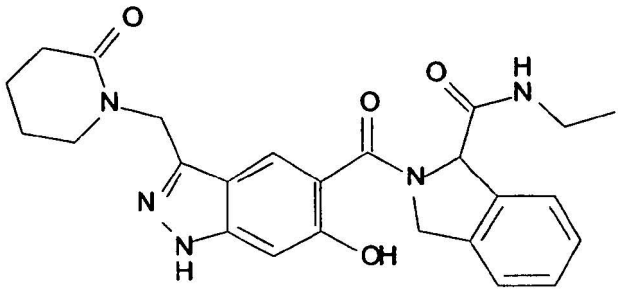
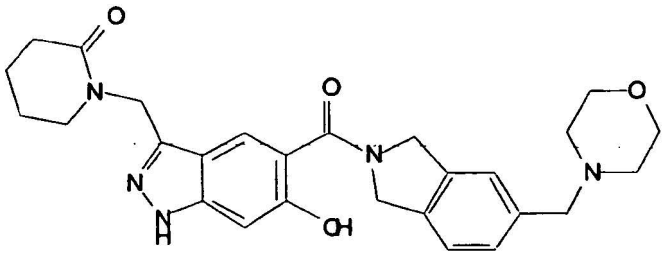
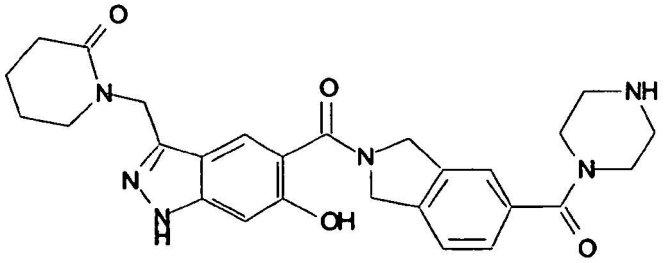
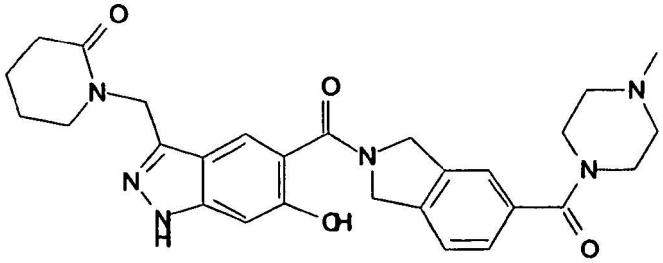
"A508"	
"A509"	
"A510"	
"A511"	

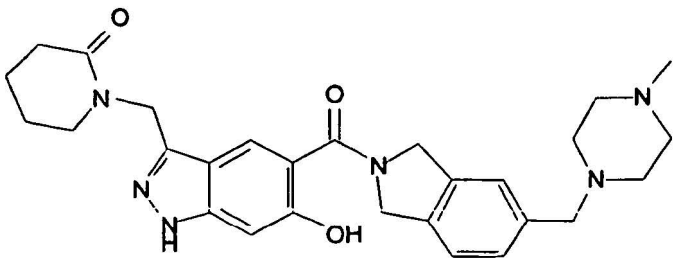
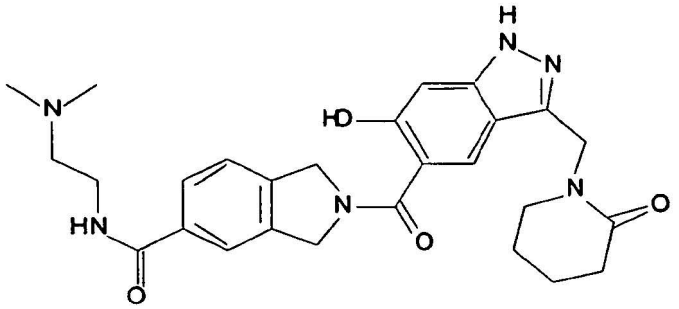
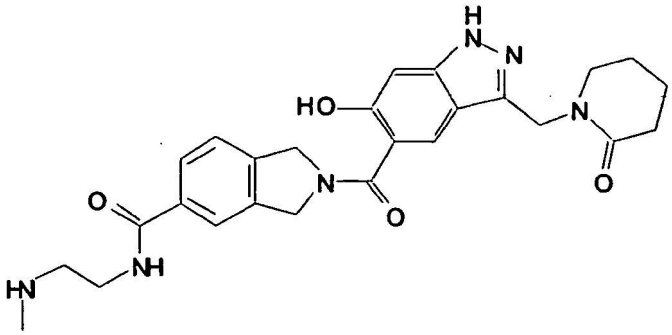
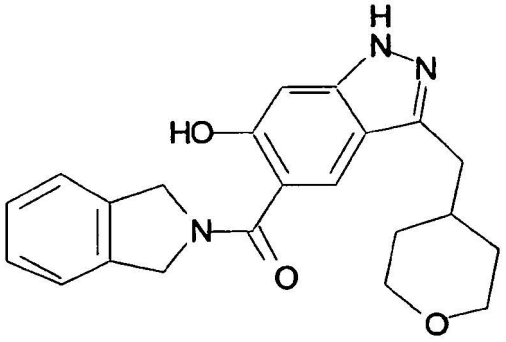
"A512"	
"A513"	
"A514"	
"A515"	

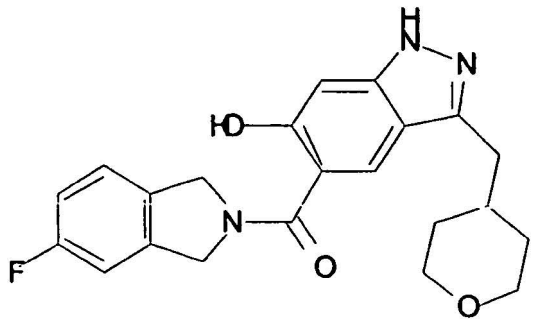
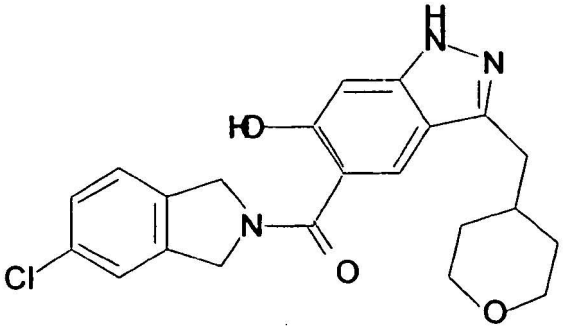
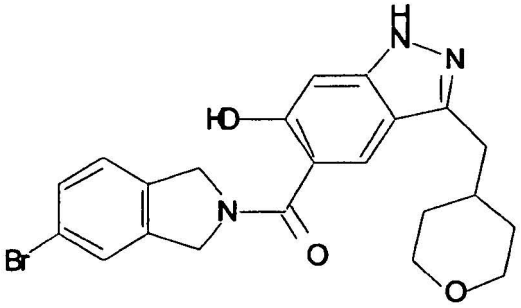
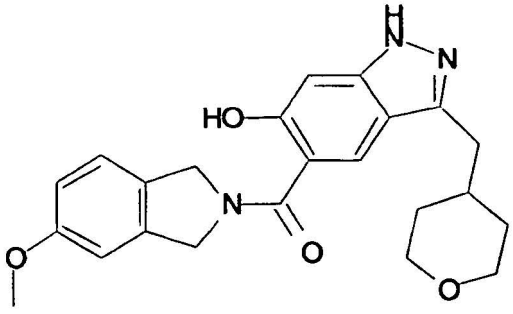
"A516"	
"A517"	
"A518"	
"A519"	

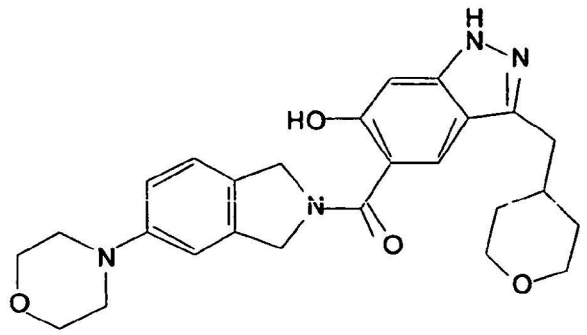
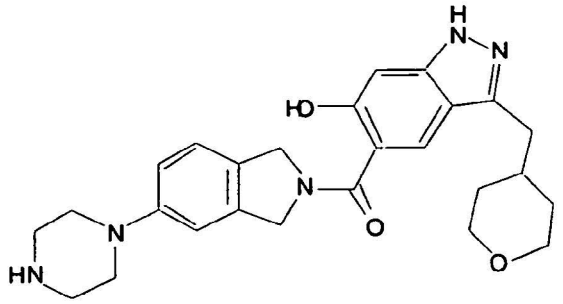
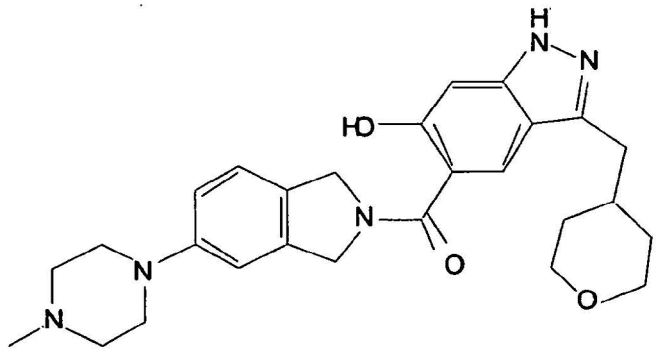
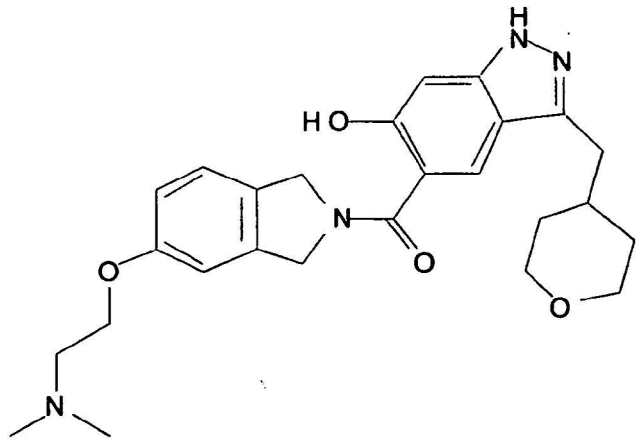
"A520"	
"A521"	
"A522"	
"A523"	

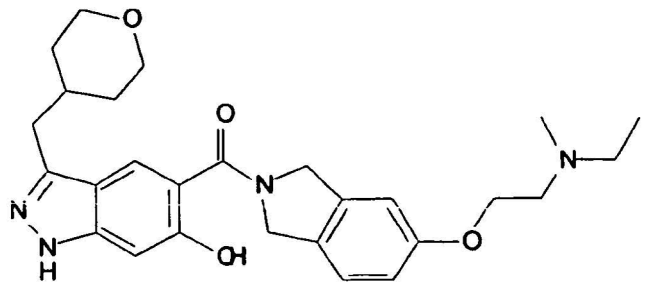
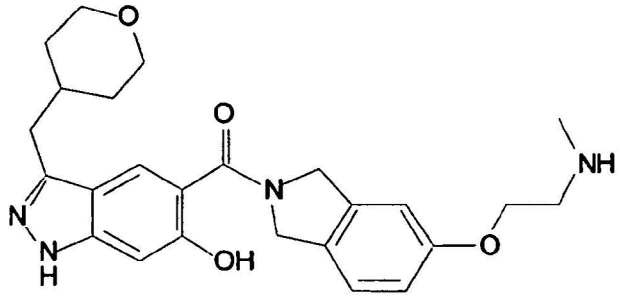
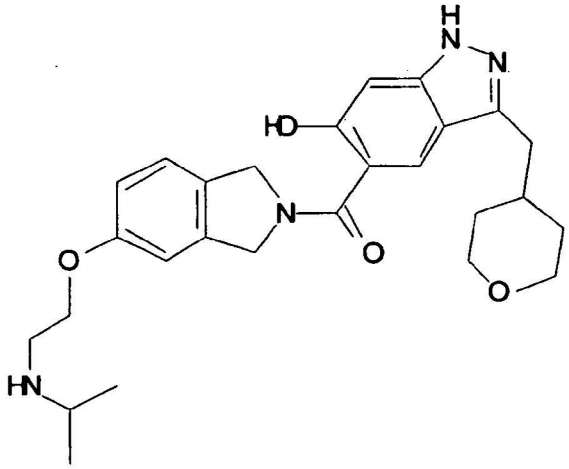
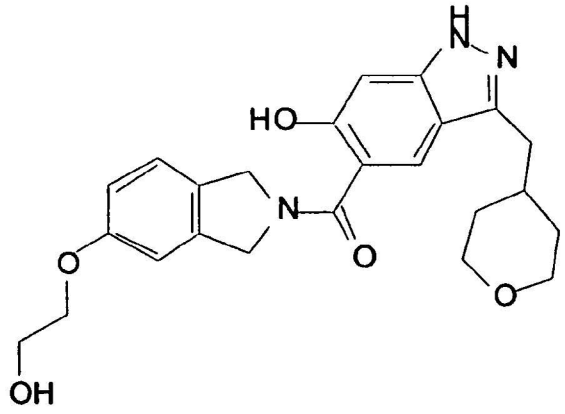
"A524"	
"A525"	
"A526"	
"A527"	
"A528"	
"A529"	

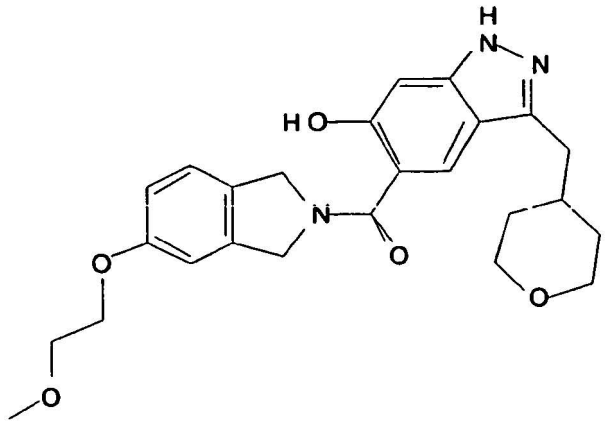
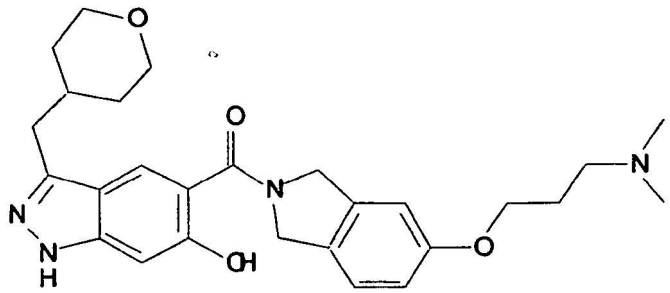
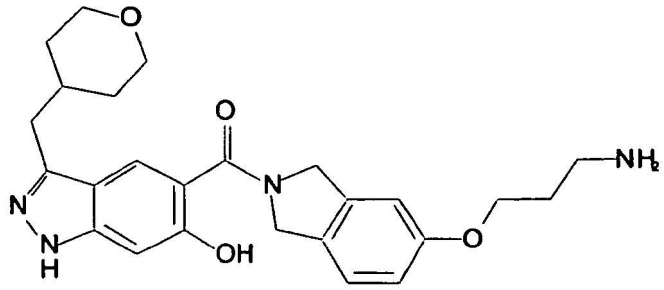
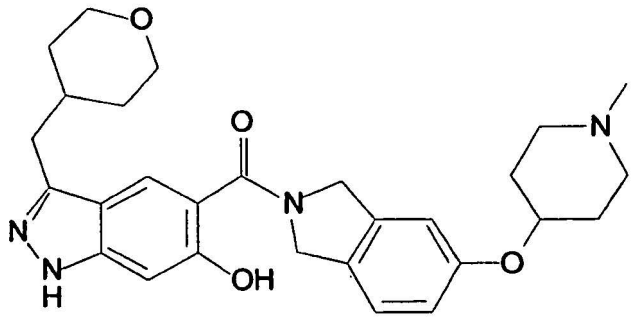
"A530"	
"A531"	
"A532"	
"A533"	
"A534"	

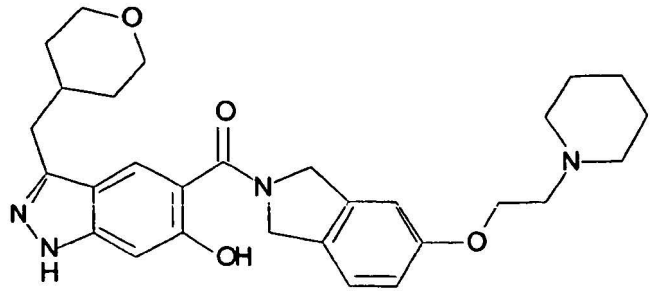
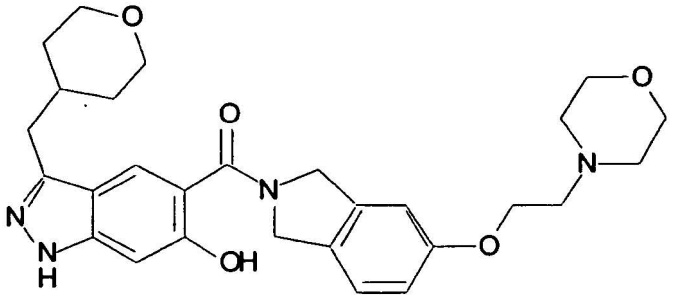
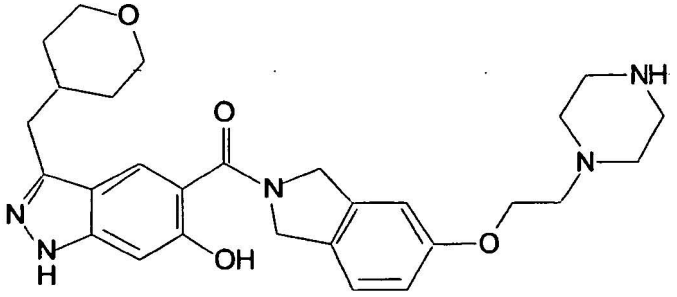
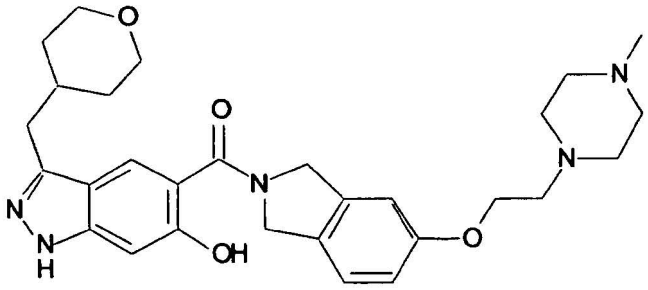
"A535"	
"A536"	
"A537"	
"A538"	

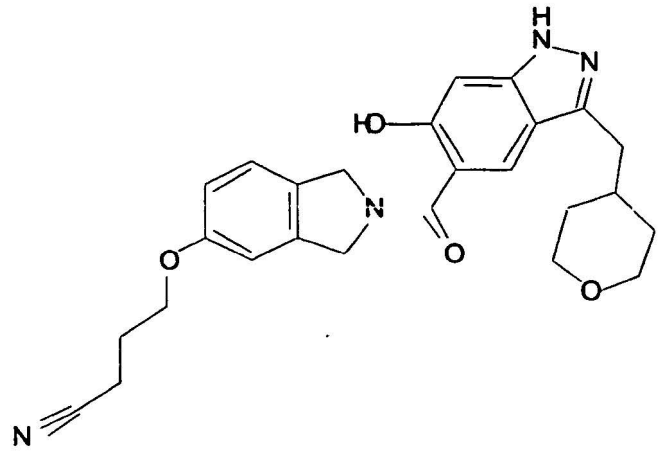
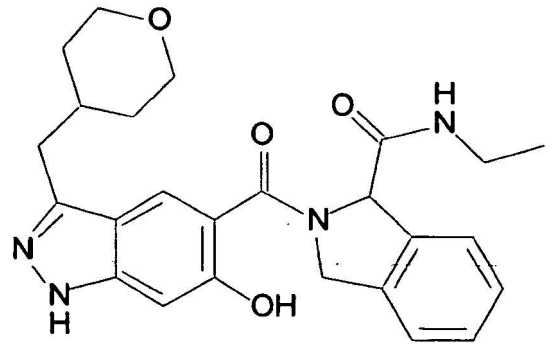
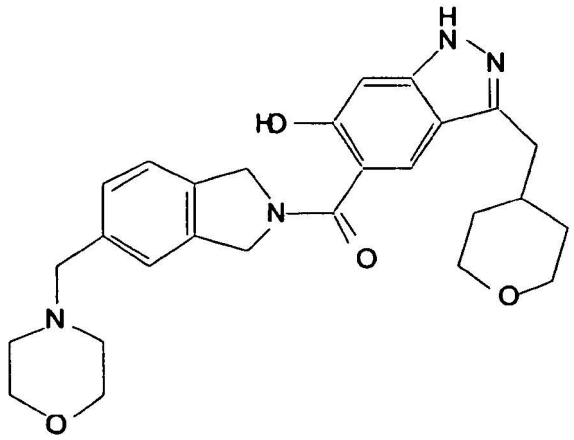
"A539"	
"A540"	
"A541"	
"A542"	

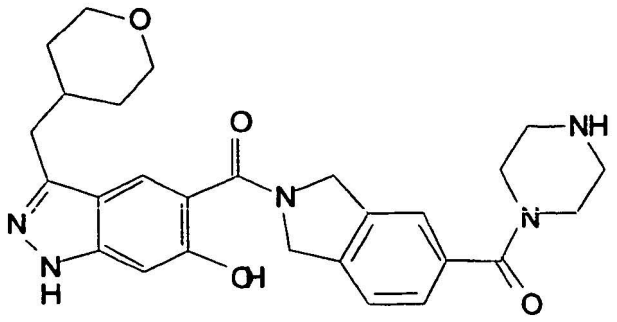
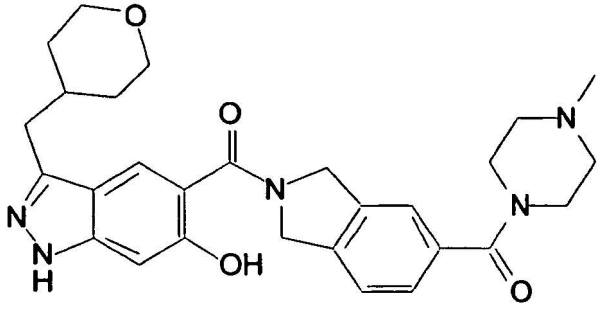
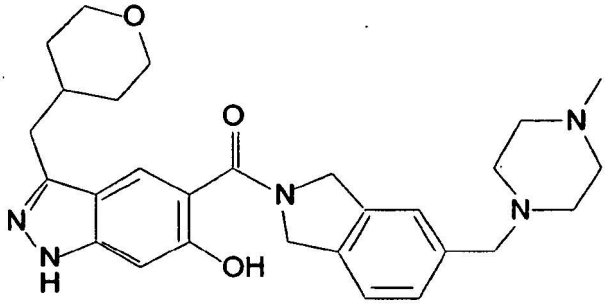
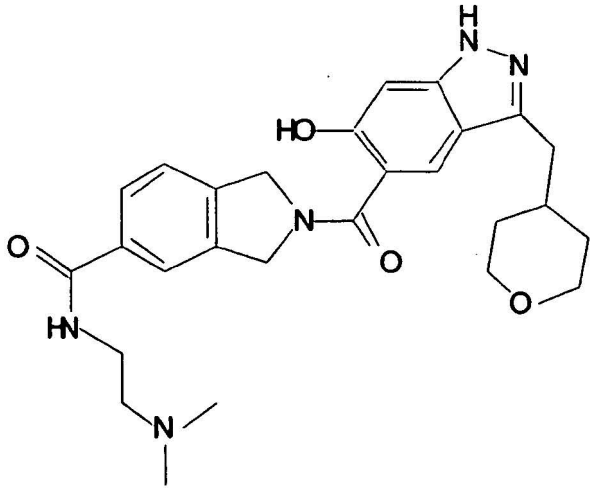
"A543"	
"A544"	
"A545"	
"A546"	

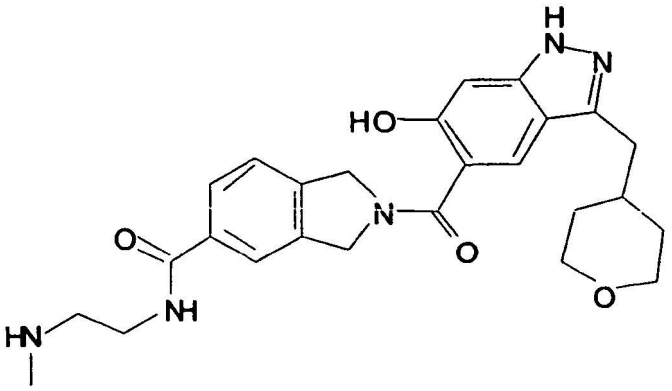
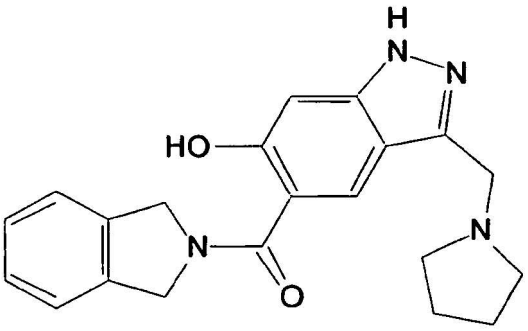
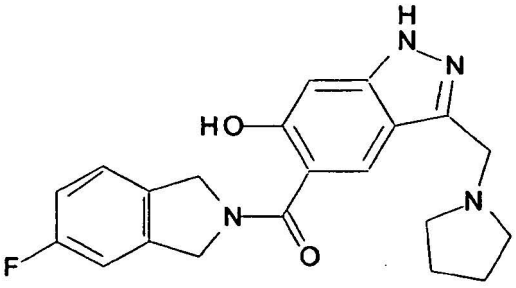
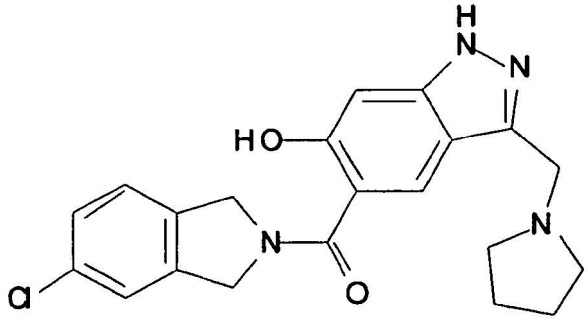
"A547"	
"A548"	
"A549"	
"A550"	

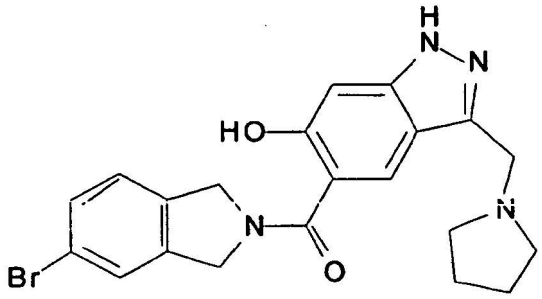
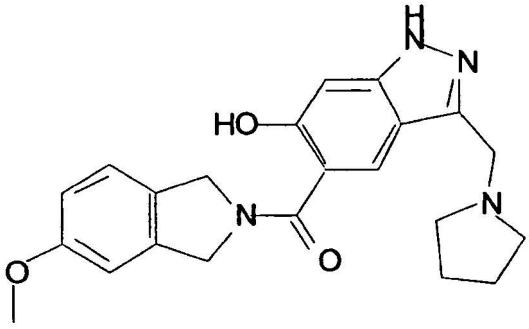
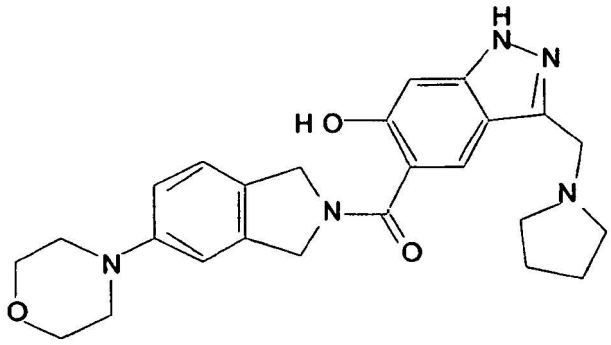
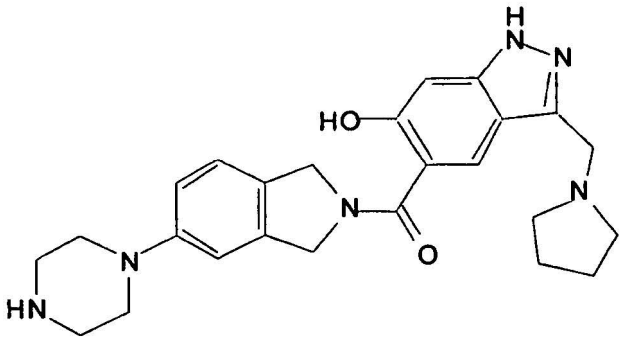
"A551"	
"A552"	
"A553"	
"A554"	

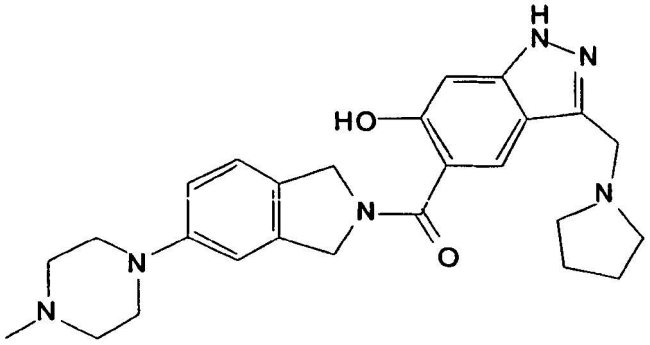
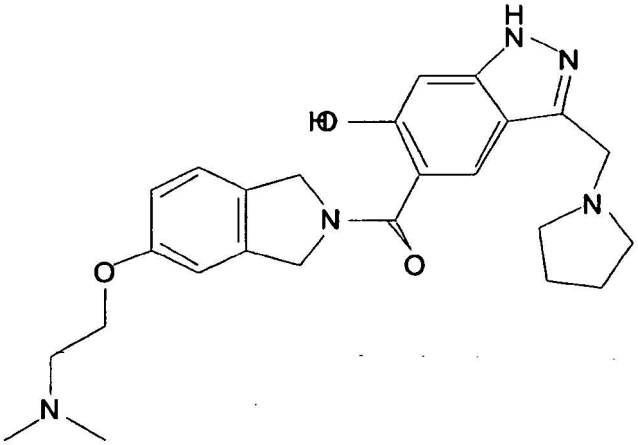
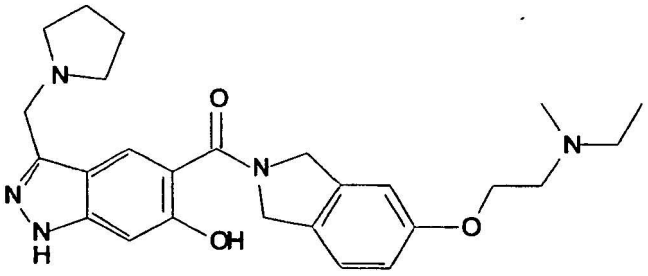
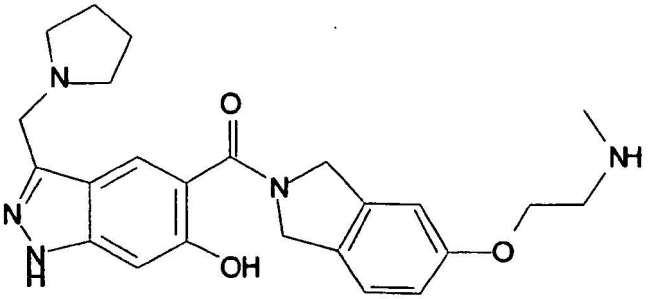
"A555"	
"A556"	
"A557"	
"A558"	

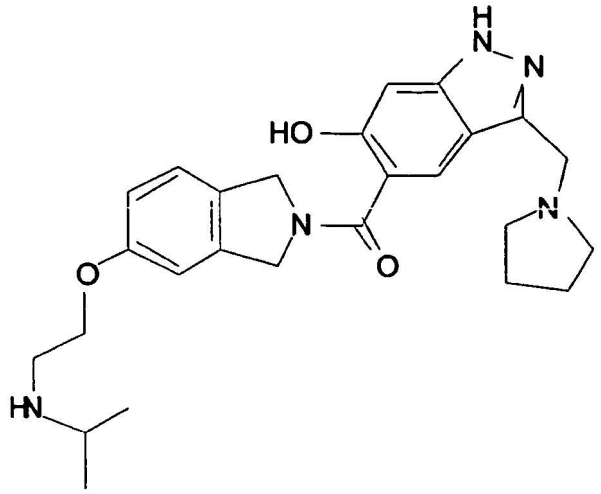
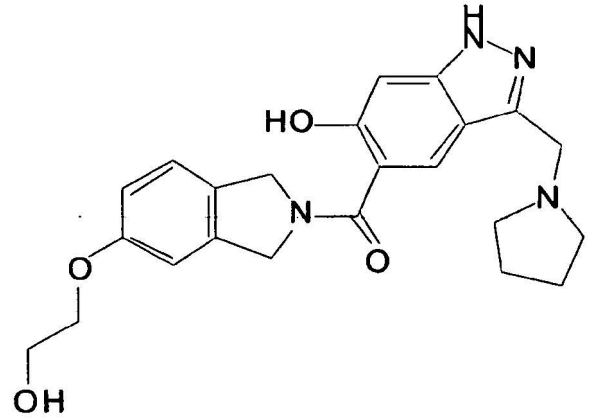
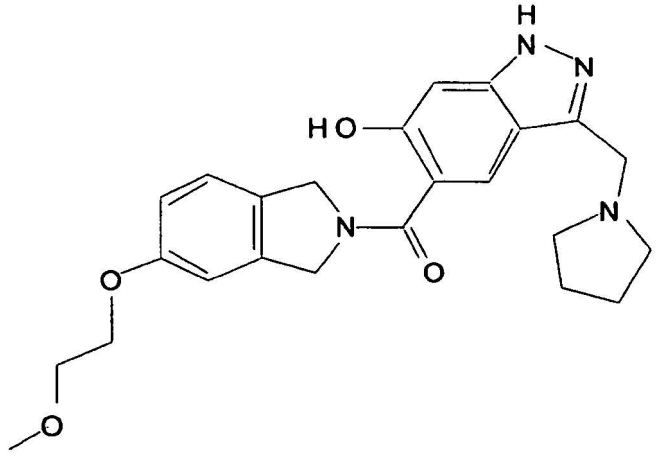
"A559"	
"A560"	
"A561"	

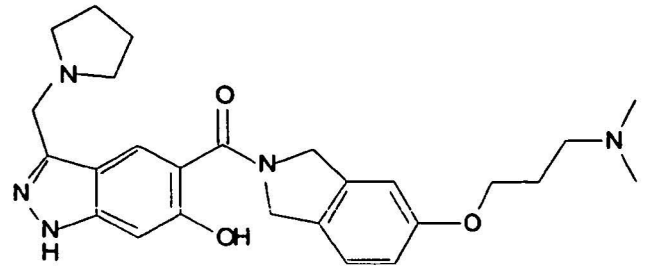
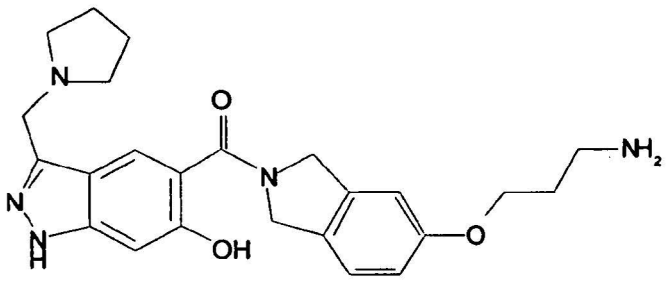
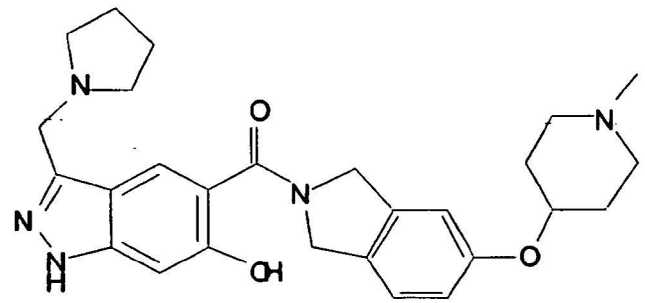
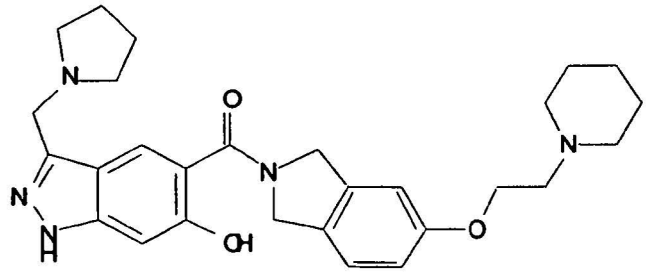
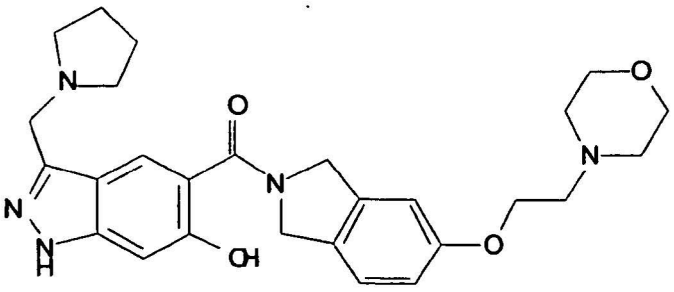
"A562"	
"A563"	
"A564"	
"A565"	

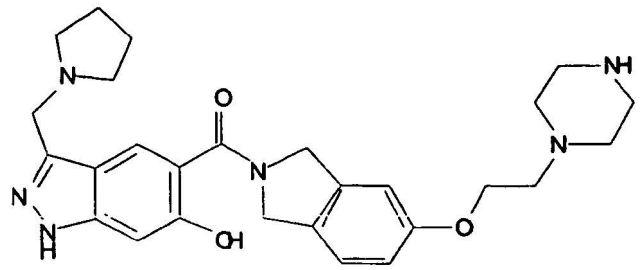
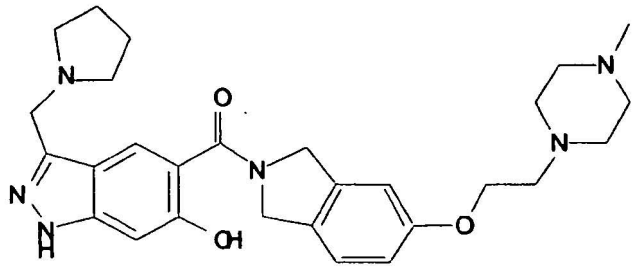
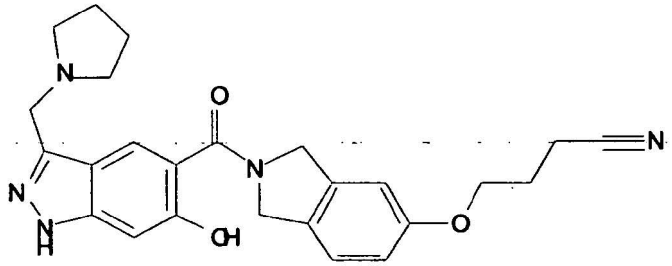
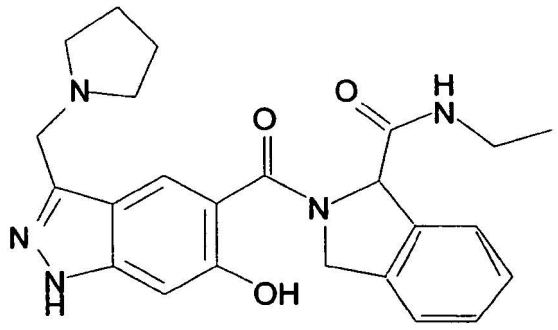
"A566"	
"A567"	
"A568"	
"A569"	

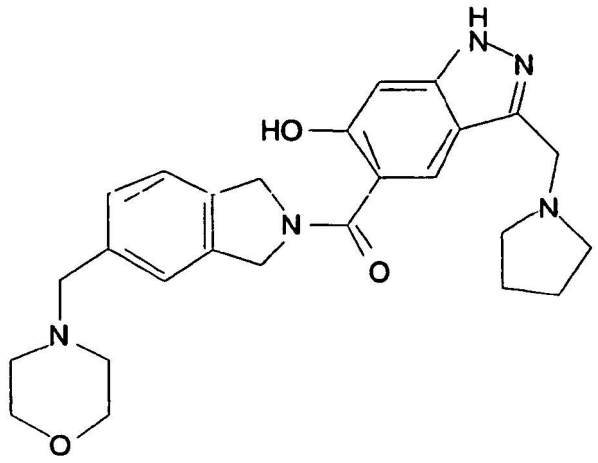
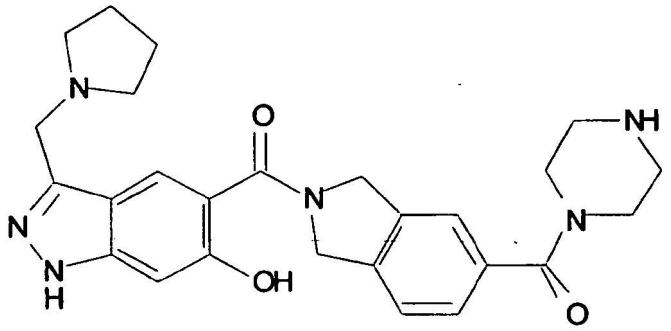
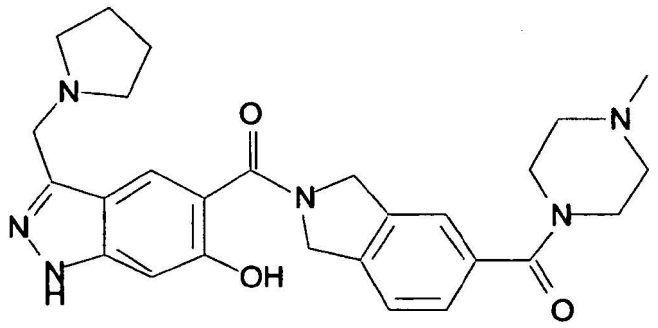
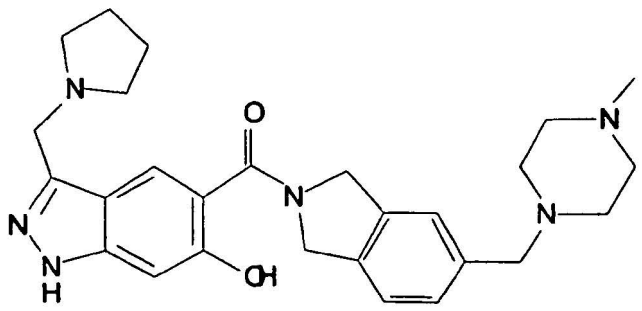
"A570"	
"A571"	
"A572"	
"A573"	

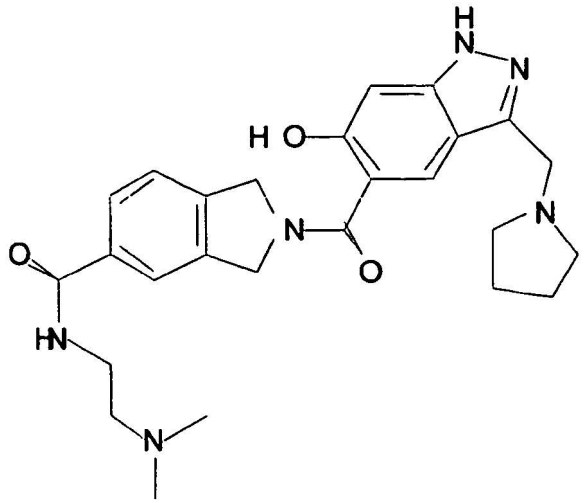
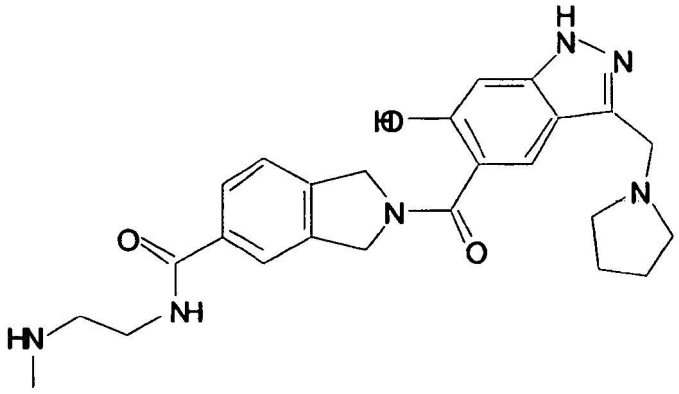
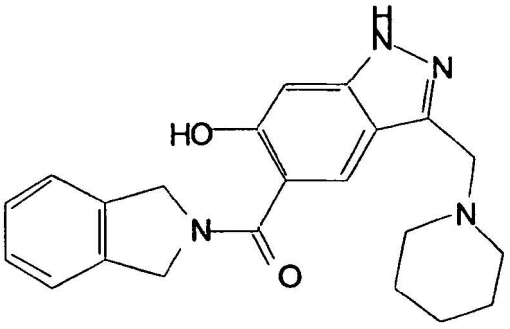
"A574"	
"A575"	
"A576"	
"A577"	

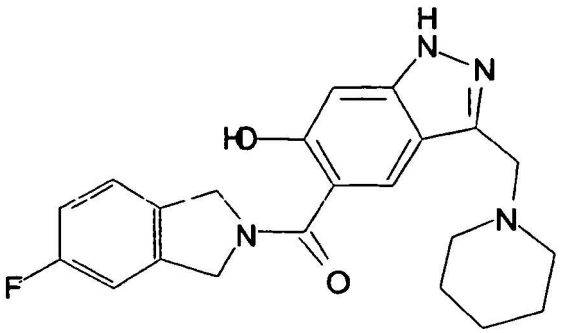
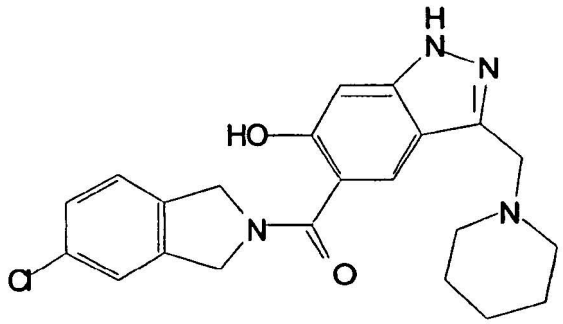
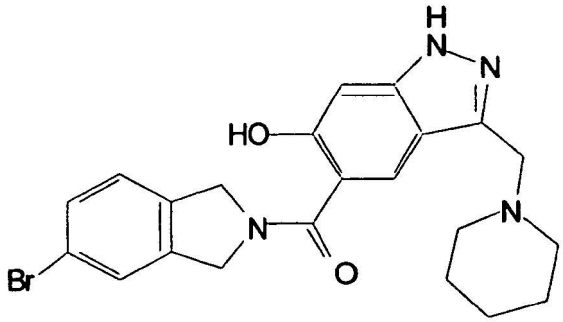
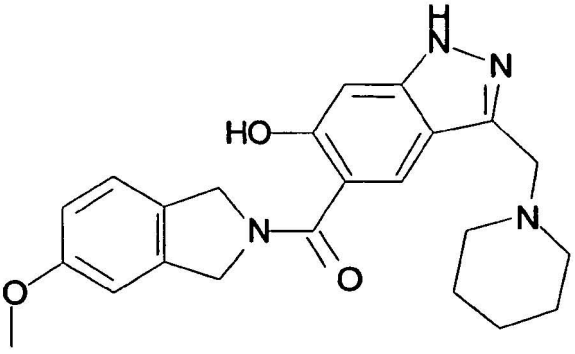
"A578"	
"A579"	
"A580"	

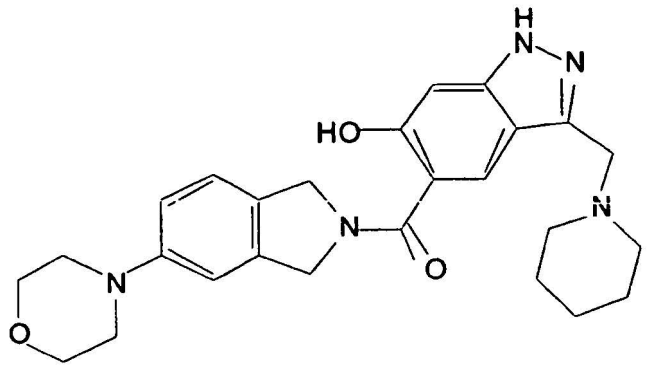
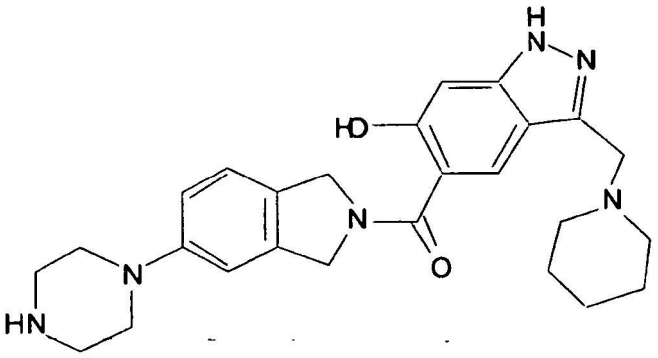
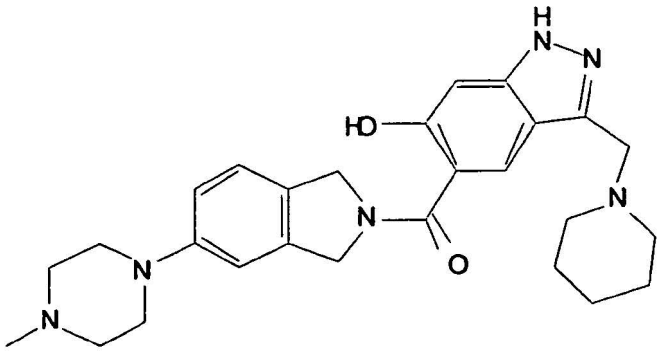
"A581"	
"A582"	
"A583"	
"A584"	
"A585"	

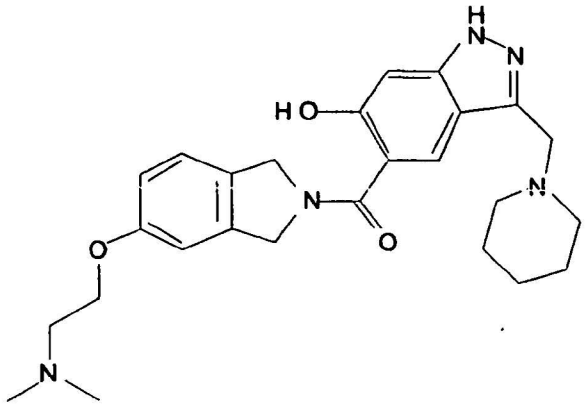
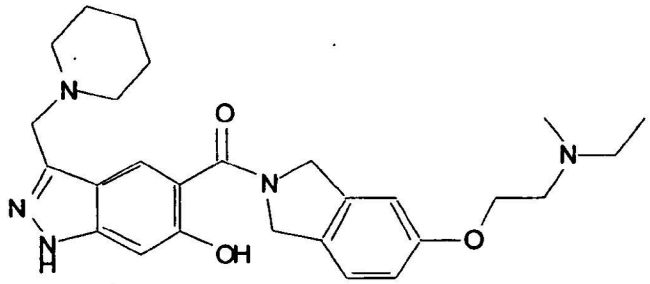
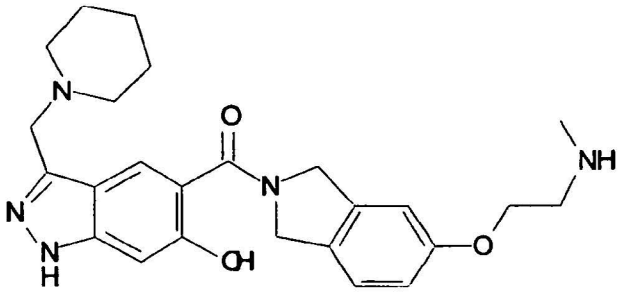
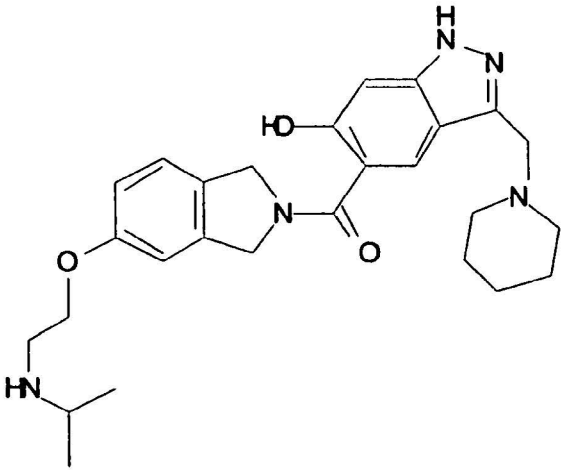
"A586"	
"A587"	
"A588"	
"A589"	

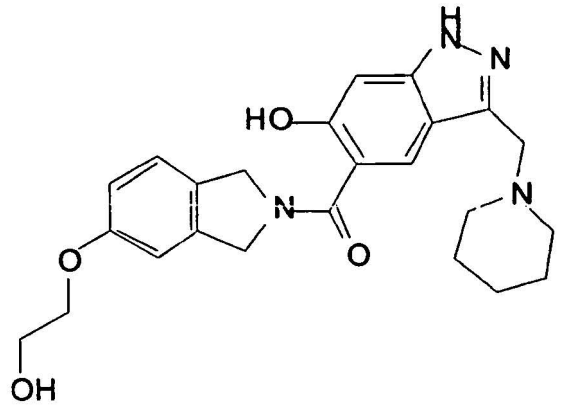
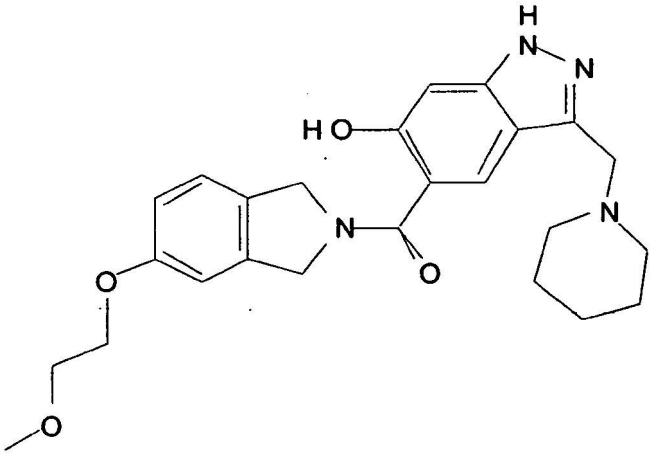
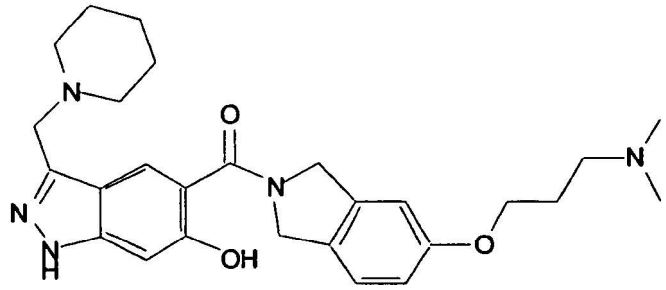
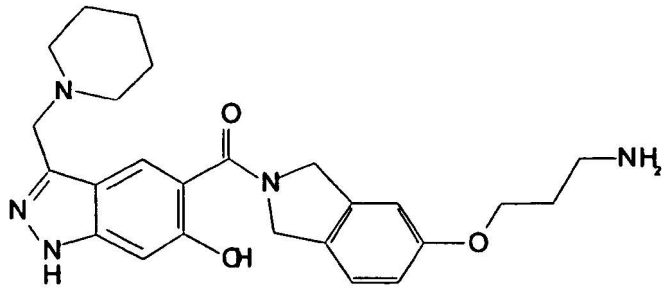
"A590"	
"A591"	
"A592"	
"A593"	

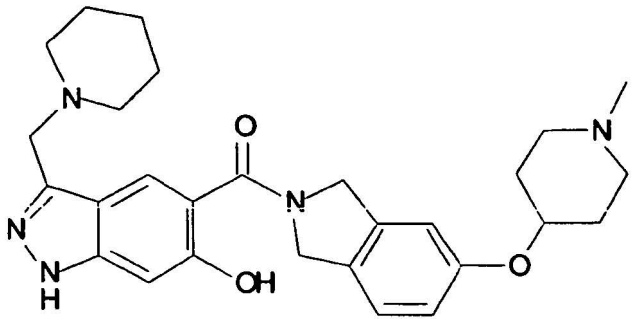
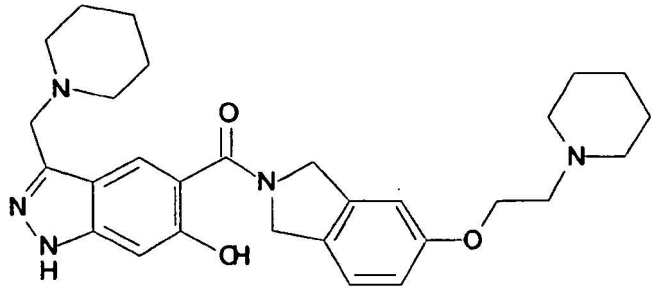
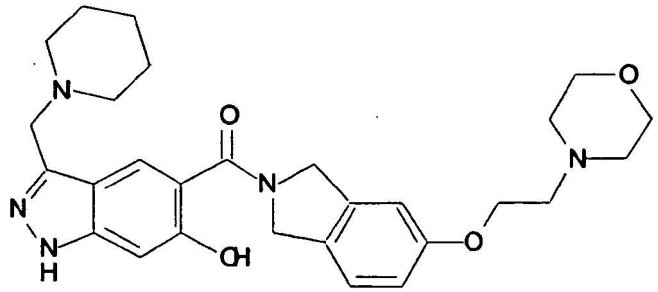
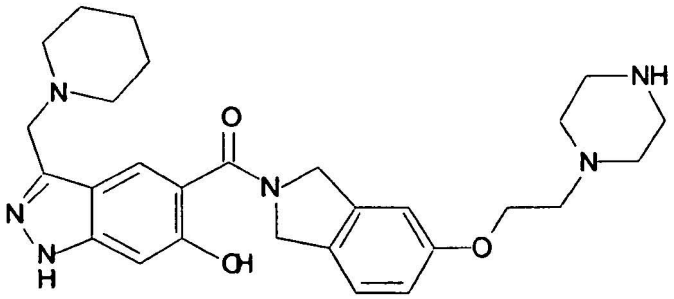
"A594"	
"A595"	
"A596"	

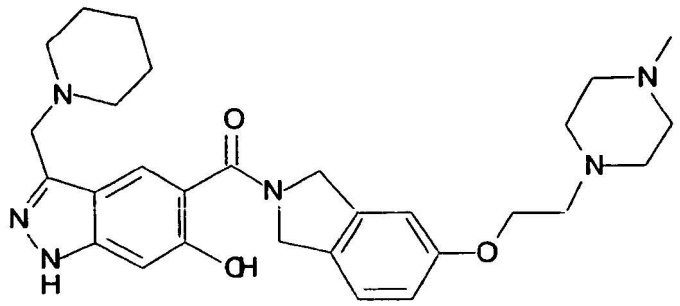
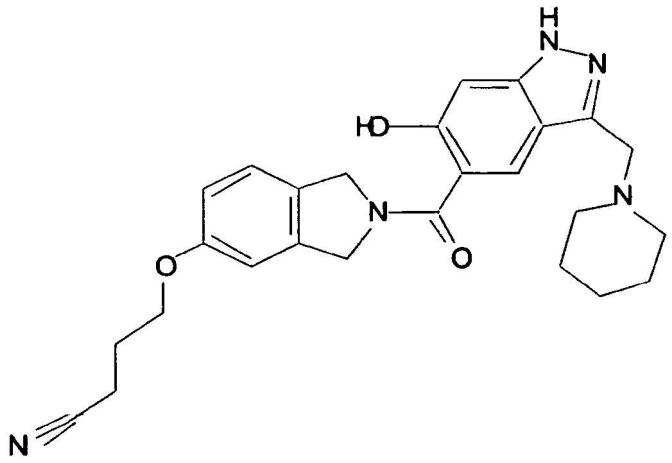
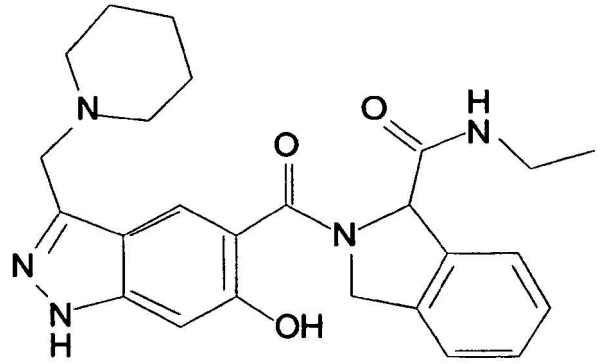
"A597"	
"A598"	
"A599"	
"A600"	

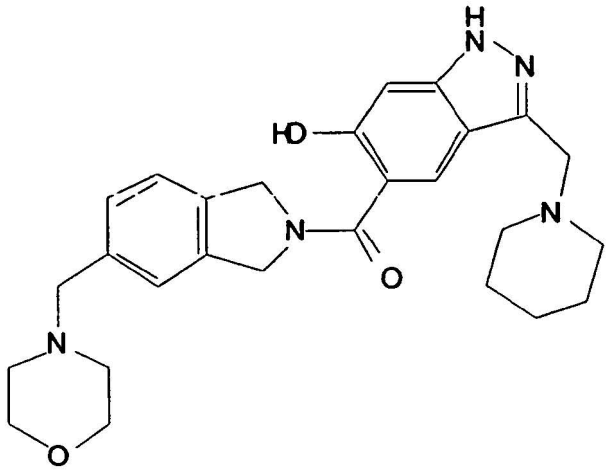
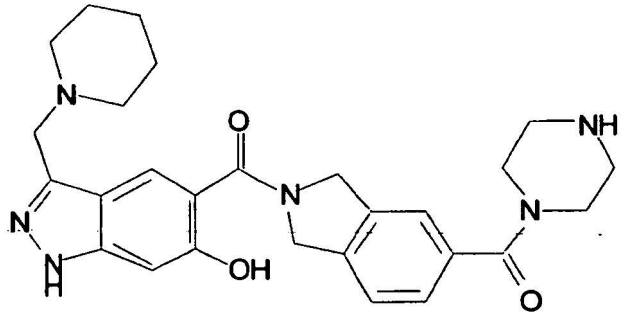
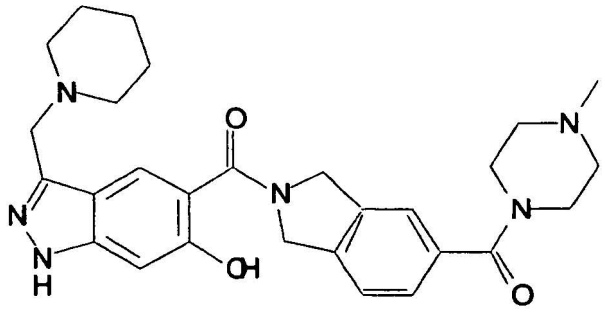
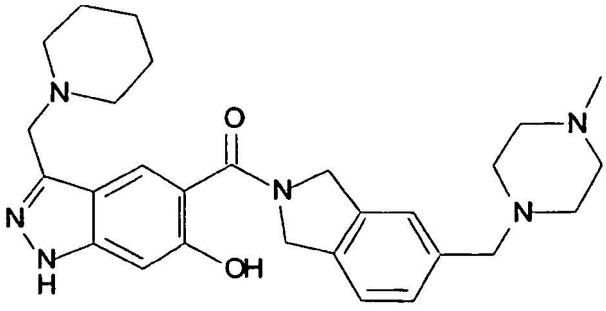
"A601"	
"A602"	
"A603"	

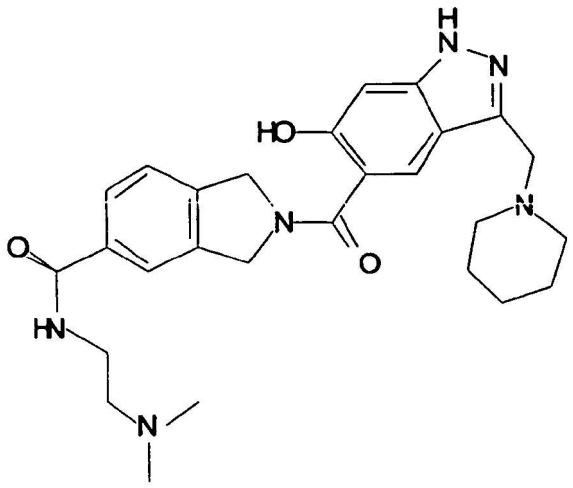
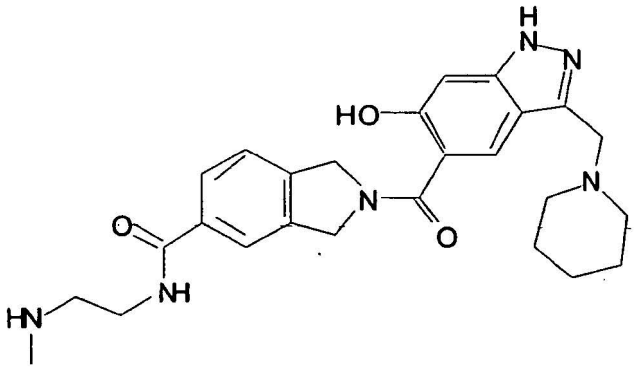
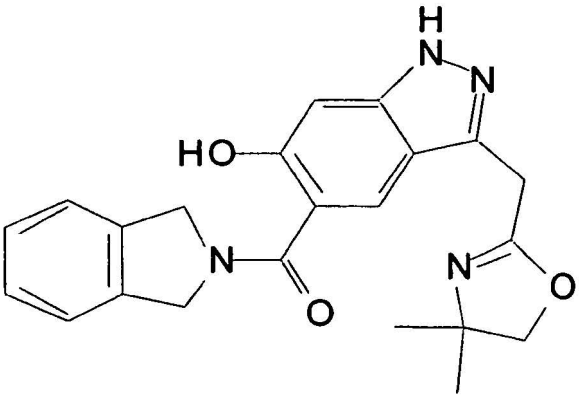
"A604"	
"A605"	
"A606"	
"A607"	

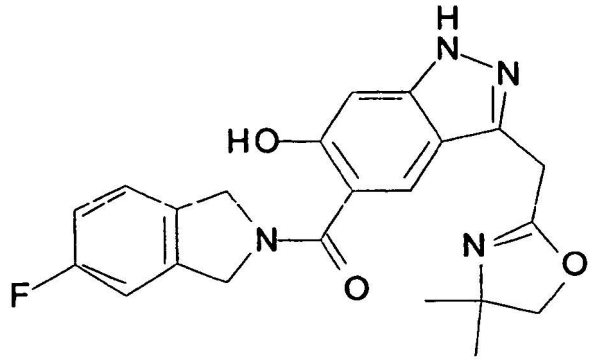
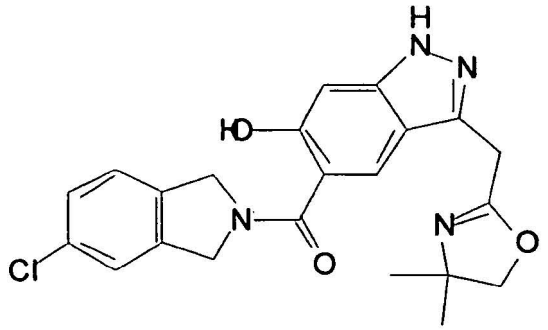
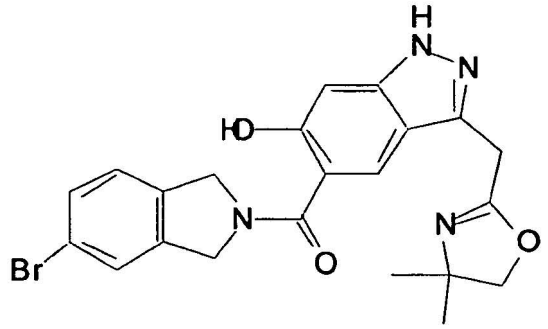
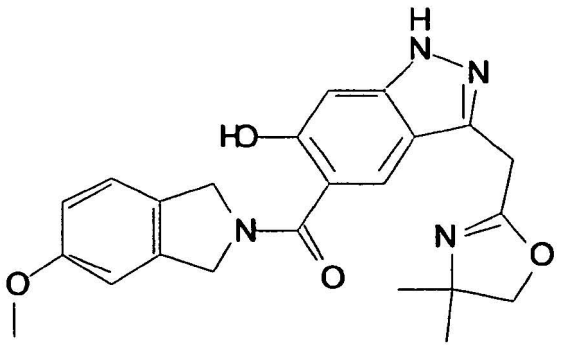
"A608"	
"A609"	
"A610"	
"A611"	

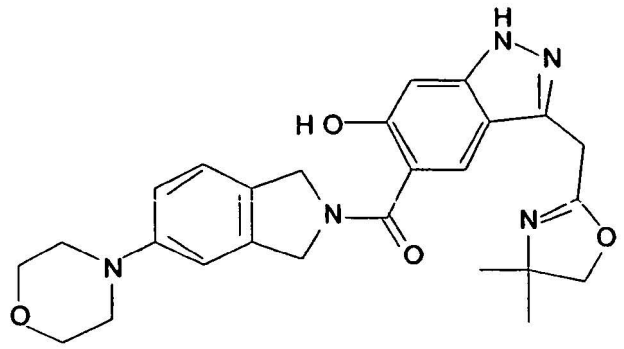
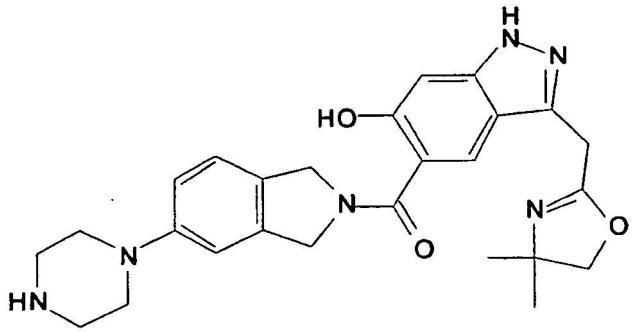
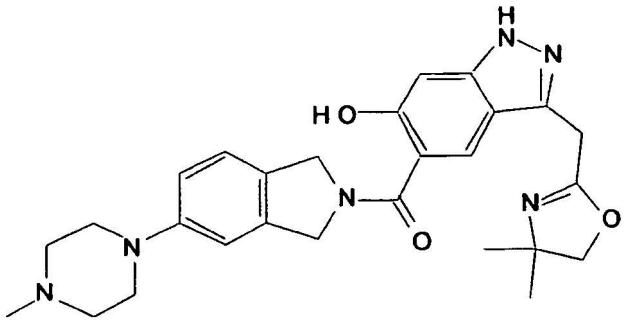
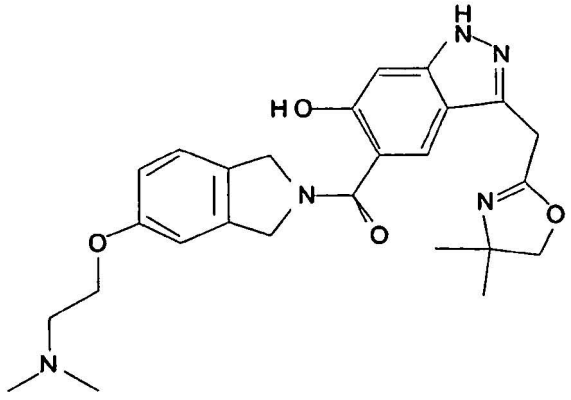
"A612"	
"A613"	
"A614"	
"A615"	

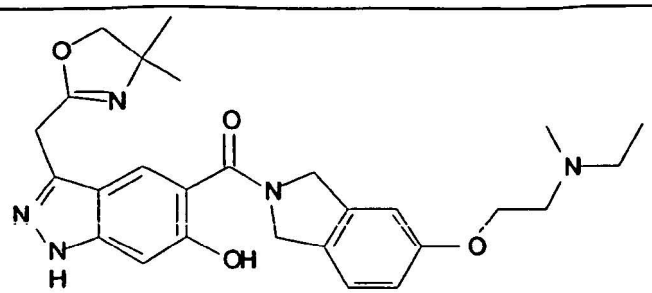
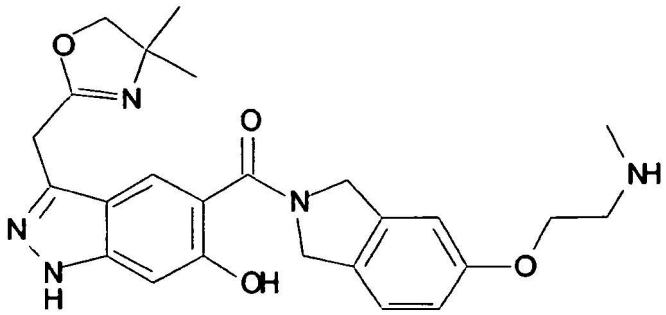
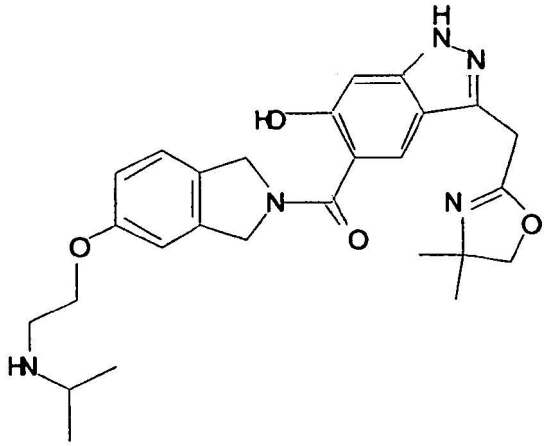
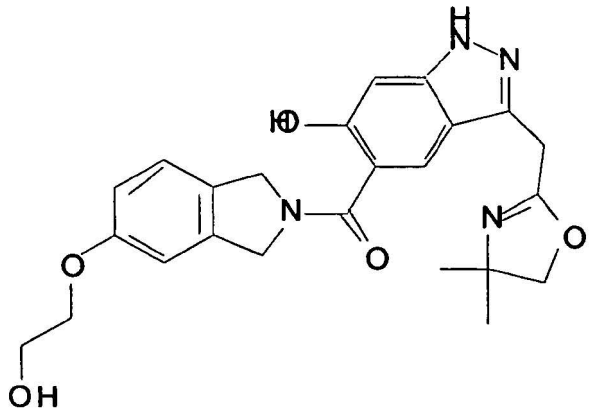
"A616"	
"A617"	
"A618"	

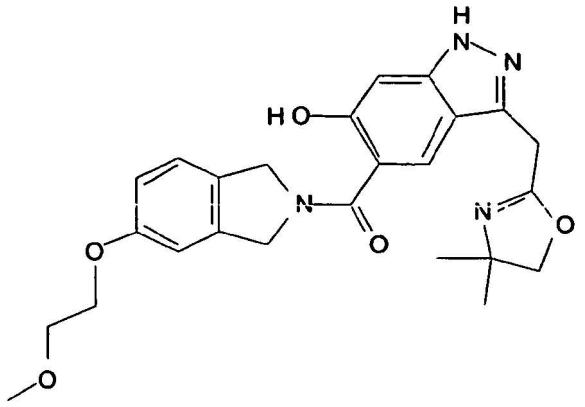
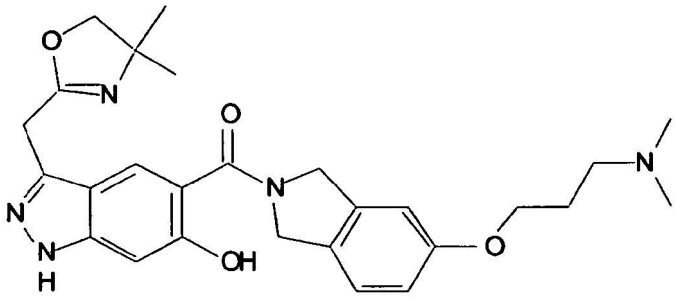
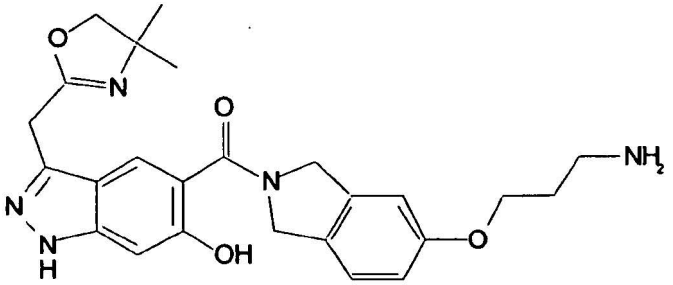
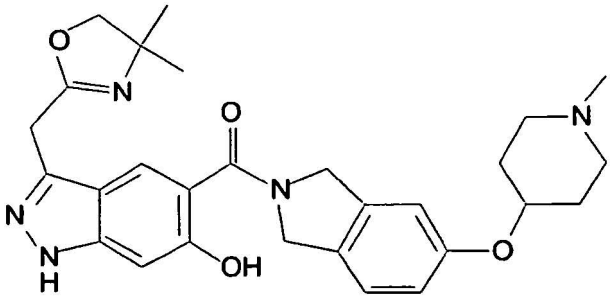
"A619"	
"A620"	
"A621"	
"A622"	

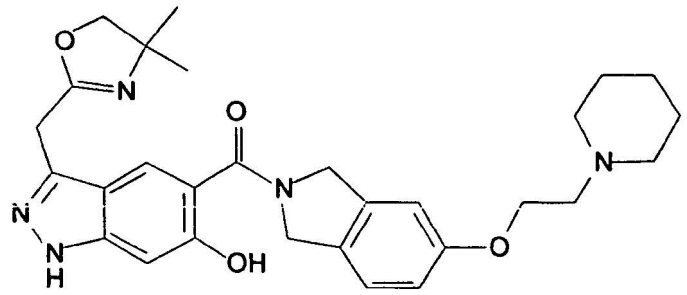
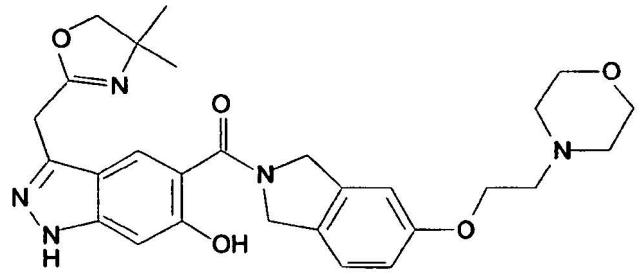
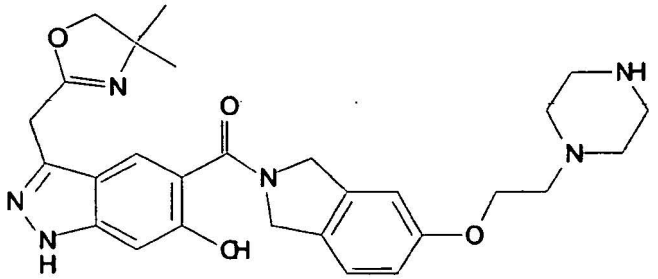
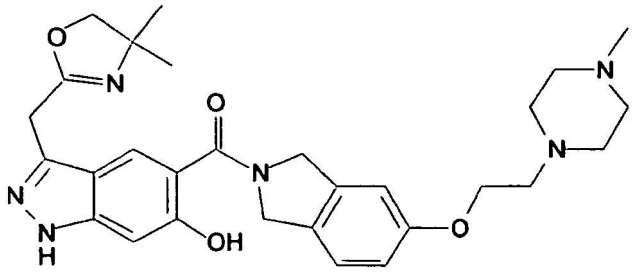
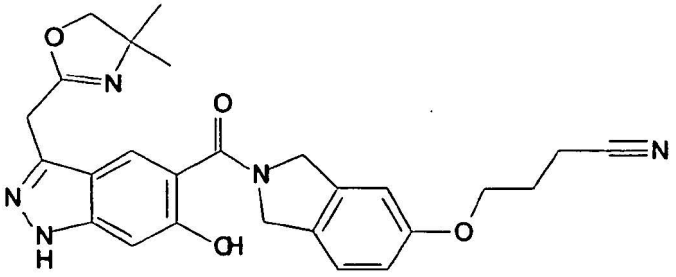
"A623"	
"A624"	
"A625"	

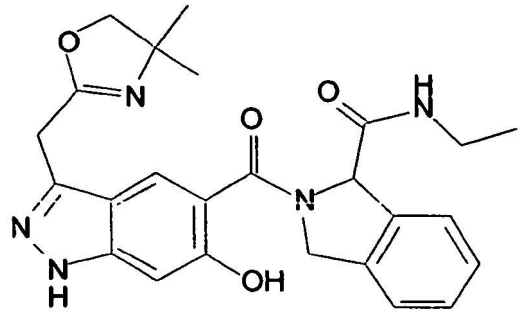
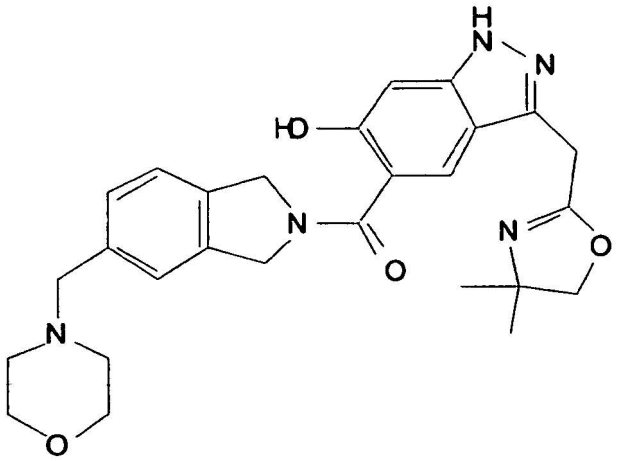
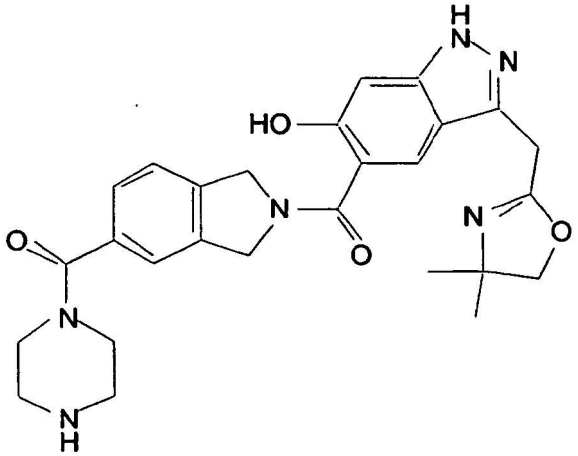
"A626"	
"A627"	
"A628"	
"A629"	

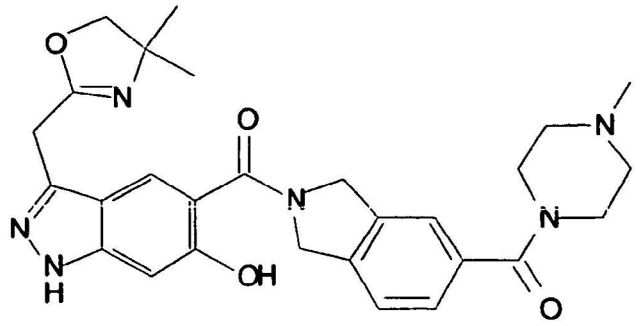
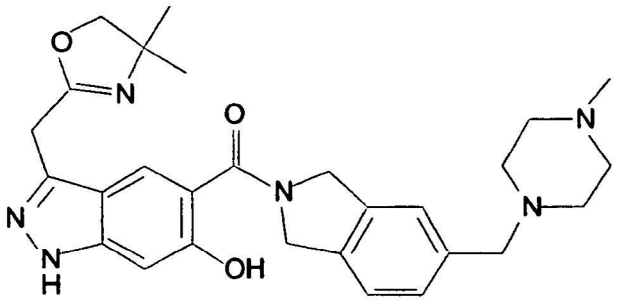
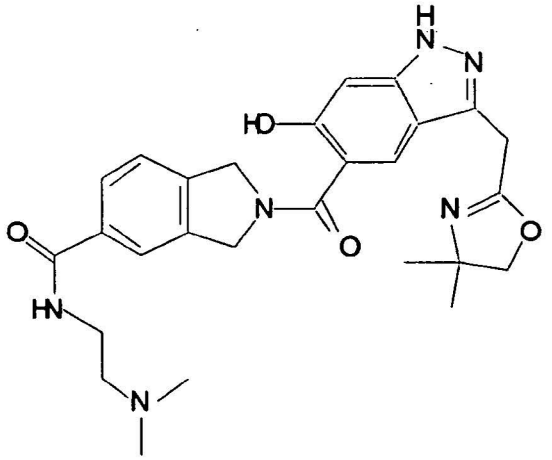
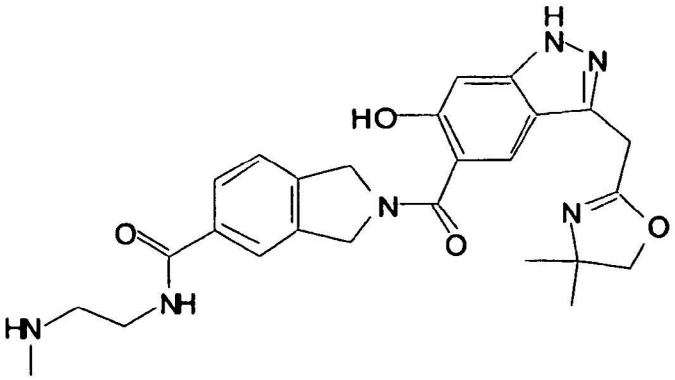
"A630"	
"A631"	
"A632"	
"A633"	

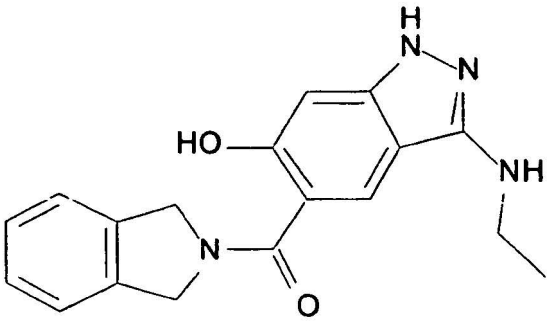
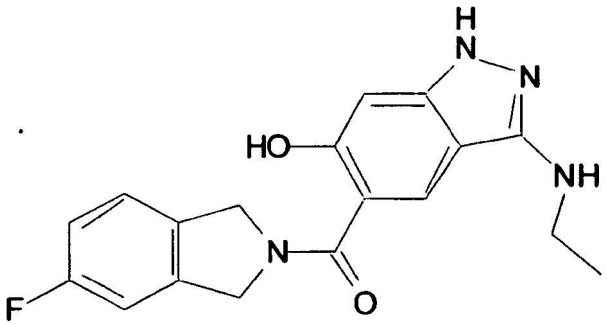
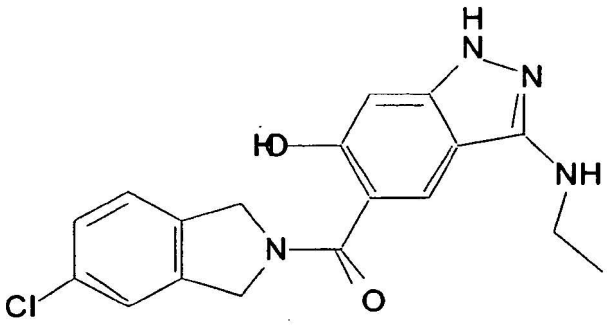
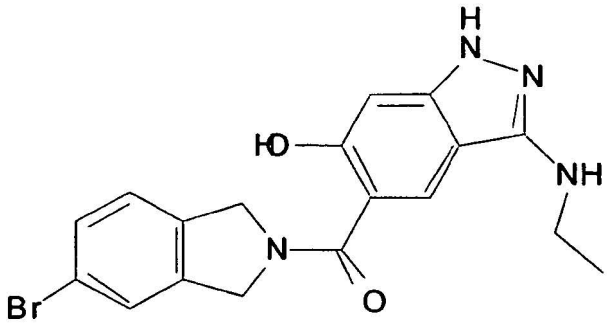
"A634"	
"A635"	
"A636"	
"A637"	

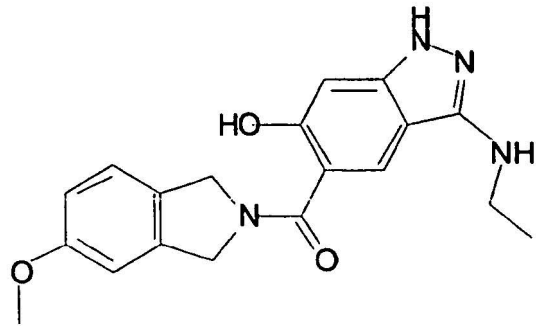
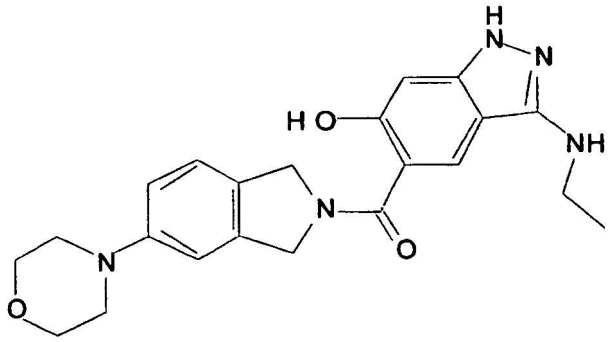
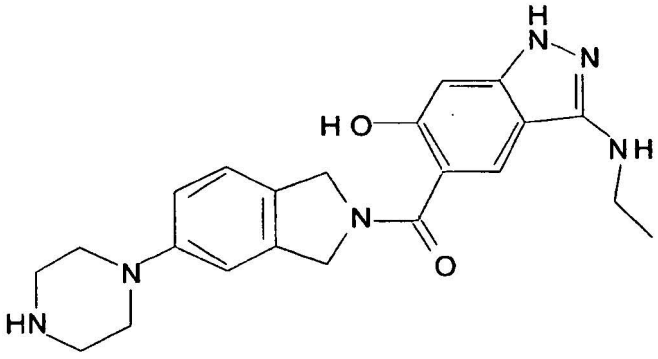
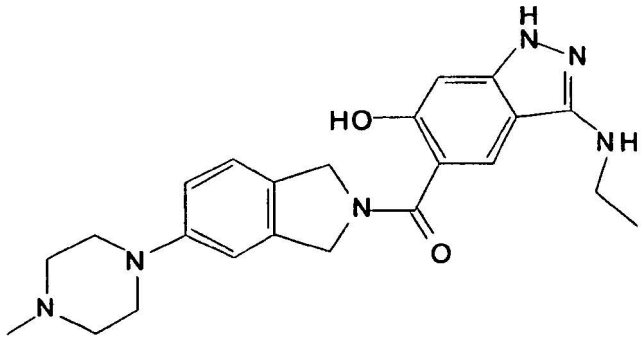
"A638"	
"A639"	
"A640"	
"A641"	

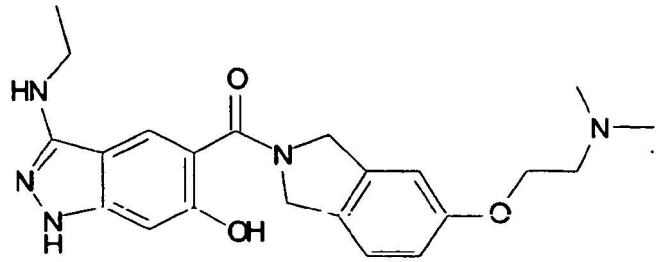
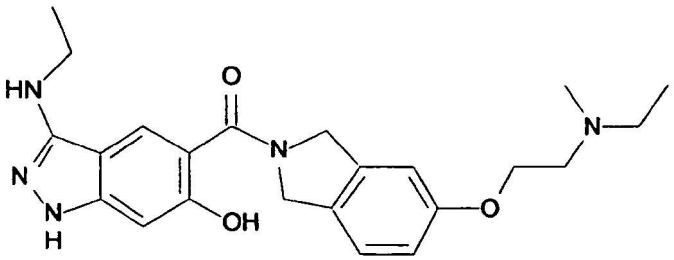
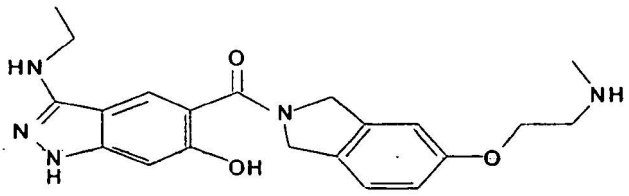
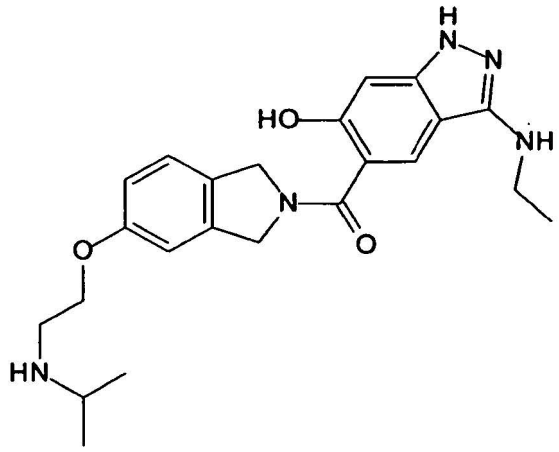
"A642"	
"A643"	
"A644"	
"A645"	
"A646"	

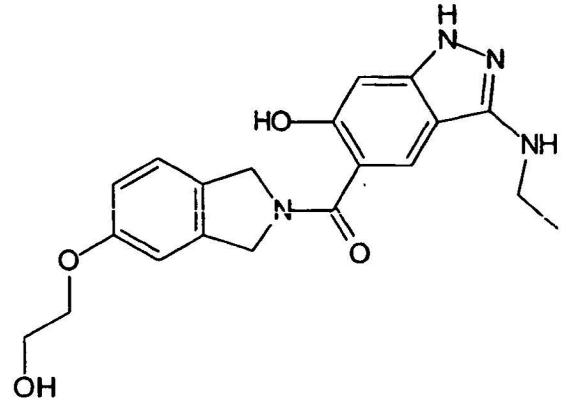
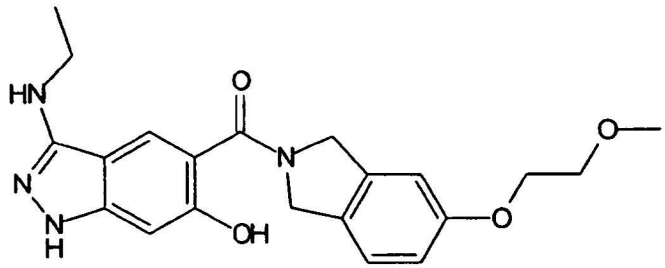
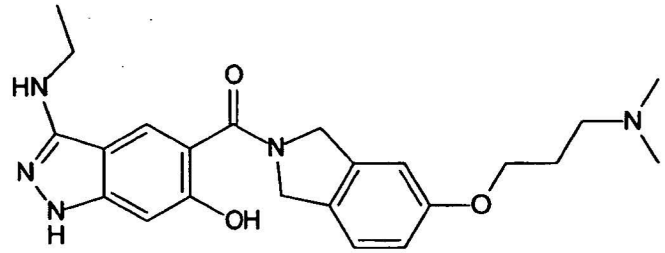
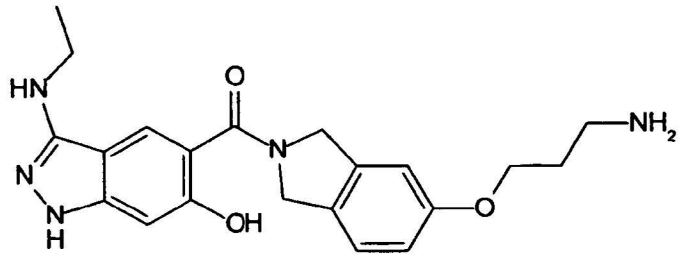
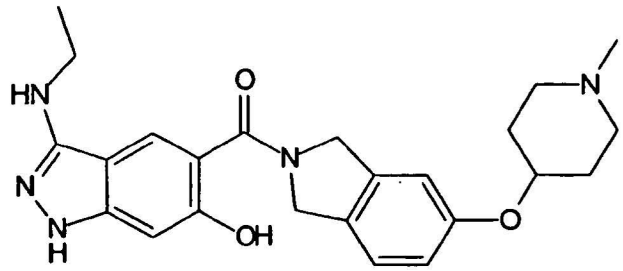
"A647"	
"A648"	
"A649"	

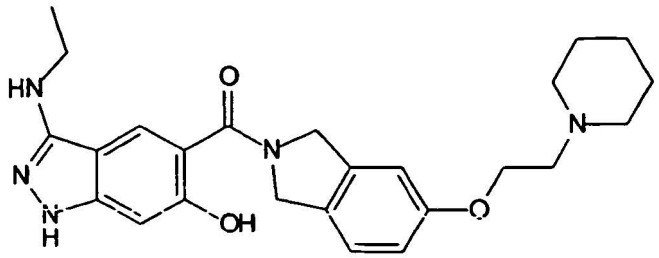
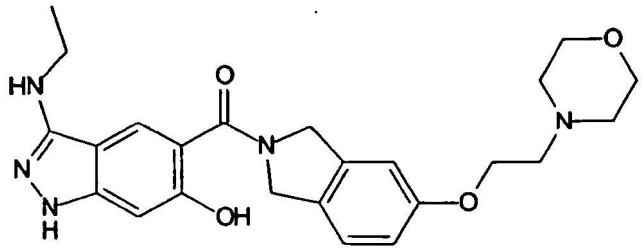
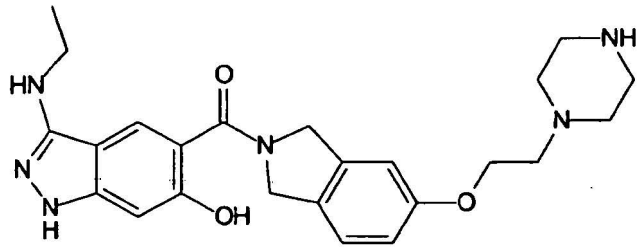
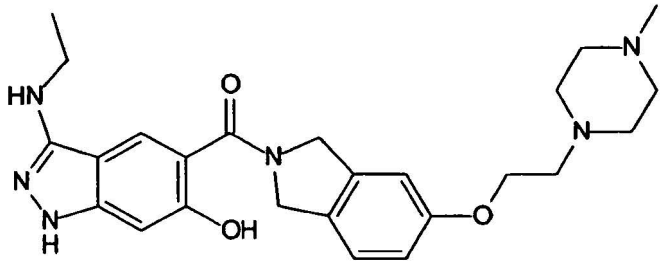
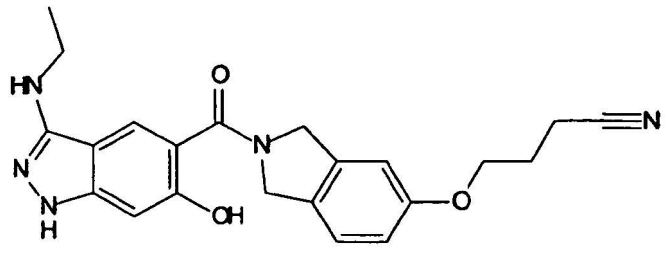
"A650"	
"A651"	
"A652"	
"A653"	

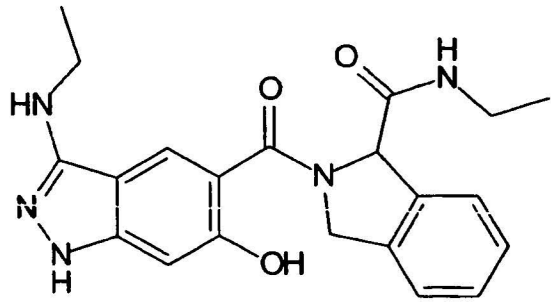
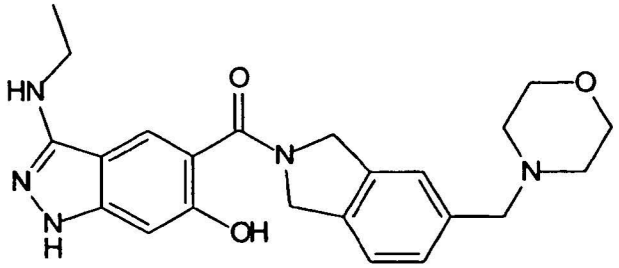
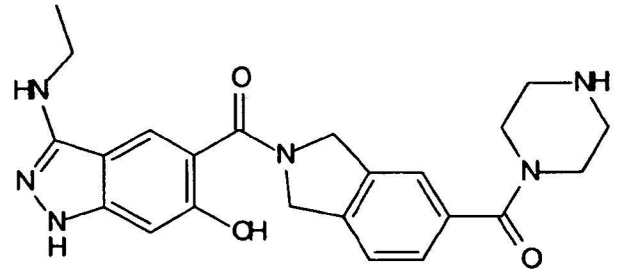
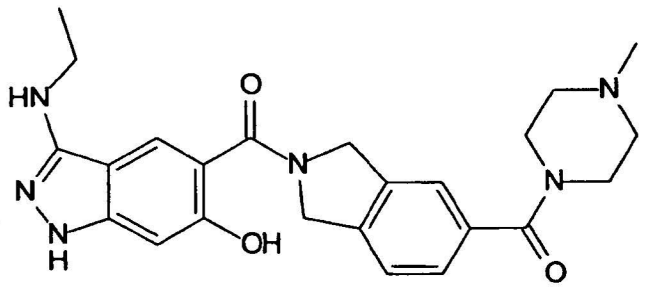
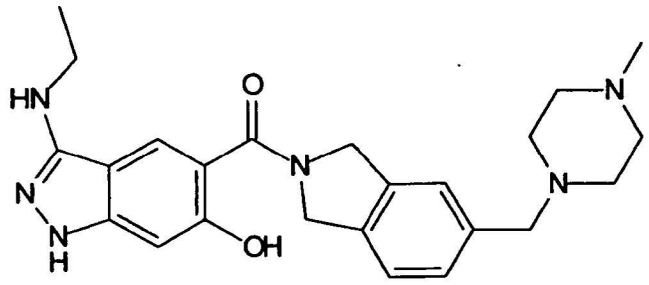
"A654"	
"A655"	
"A656"	
"A657"	

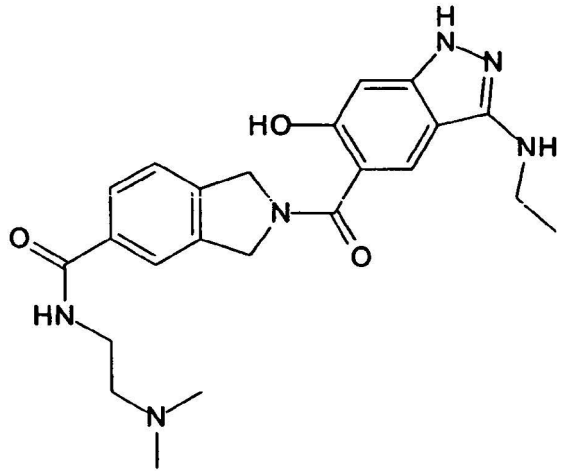
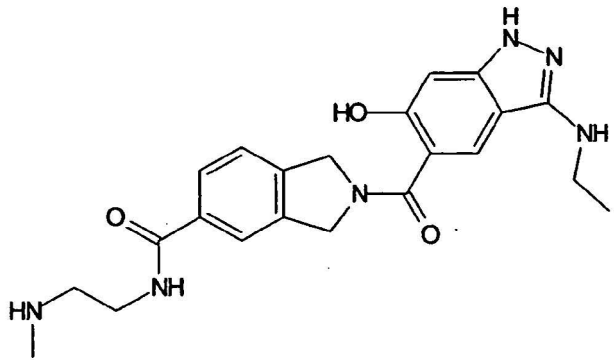
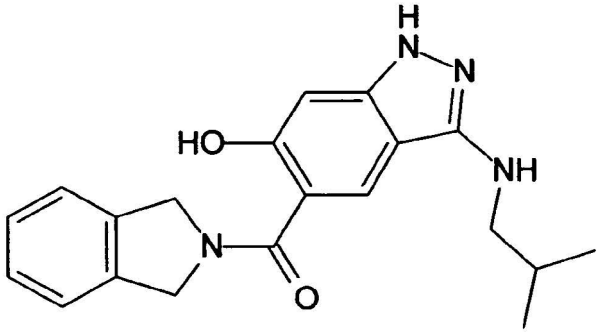
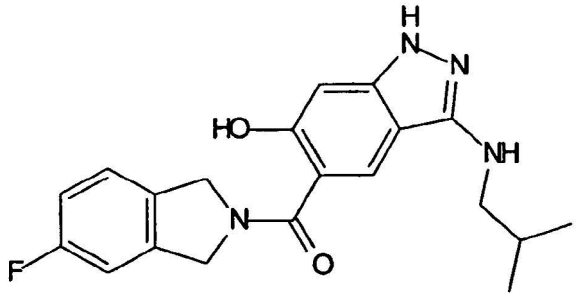
"A658"	
"A659"	
"A660"	
"A661"	

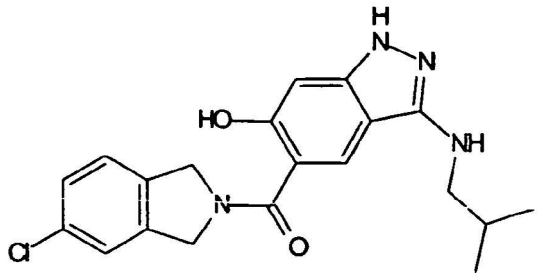
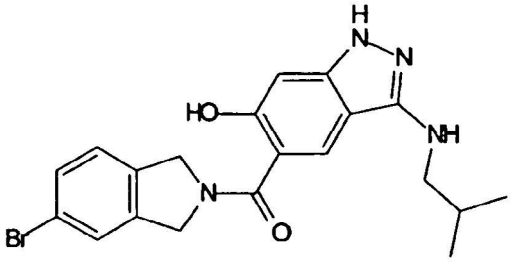
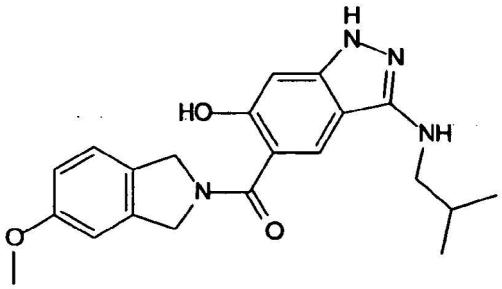
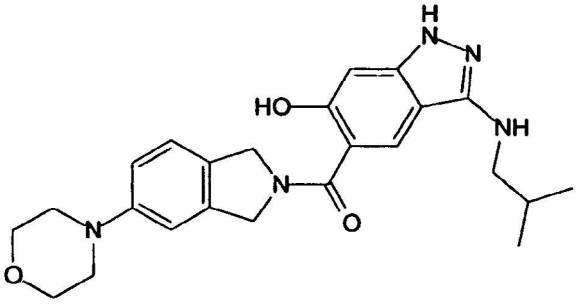
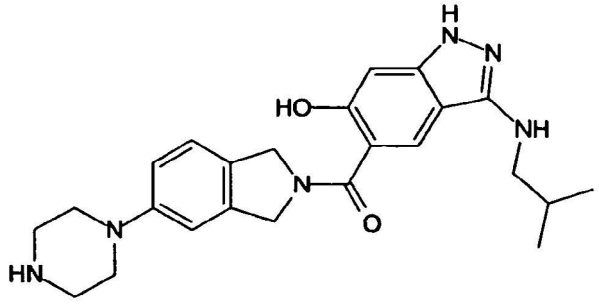
"A662"	
"A663"	
"A664"	
"A665"	

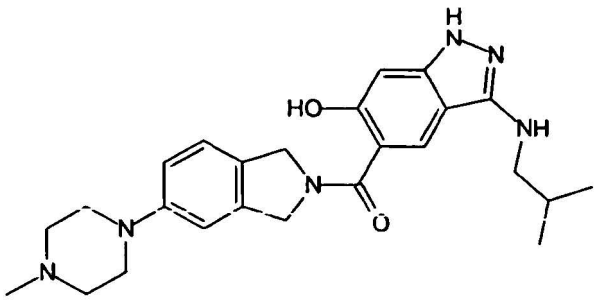
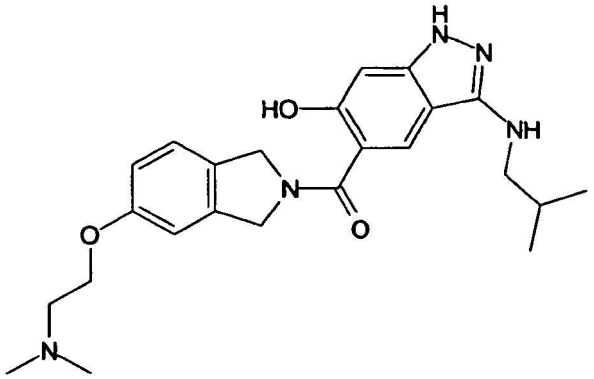
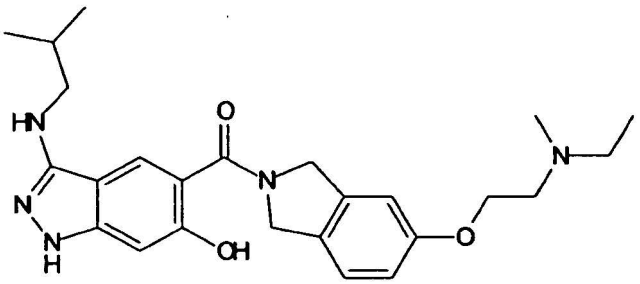
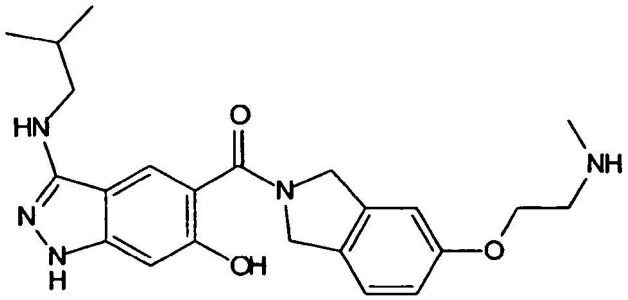
"A666"	
"A667"	
"A668"	
"A669"	
"A670"	

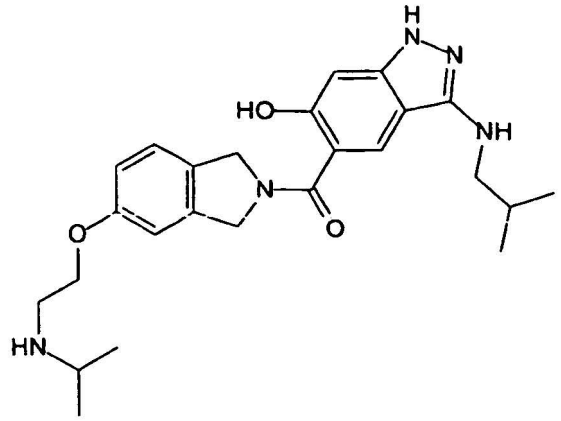
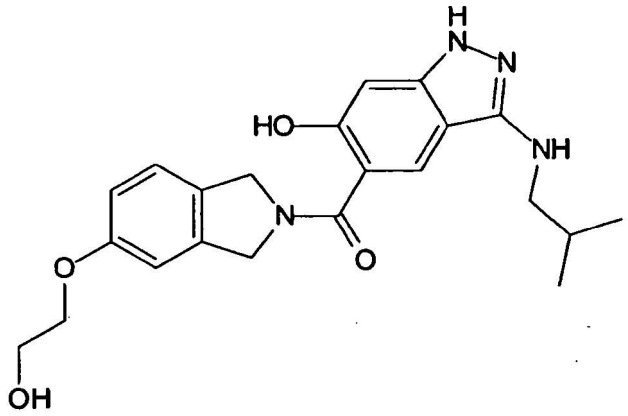
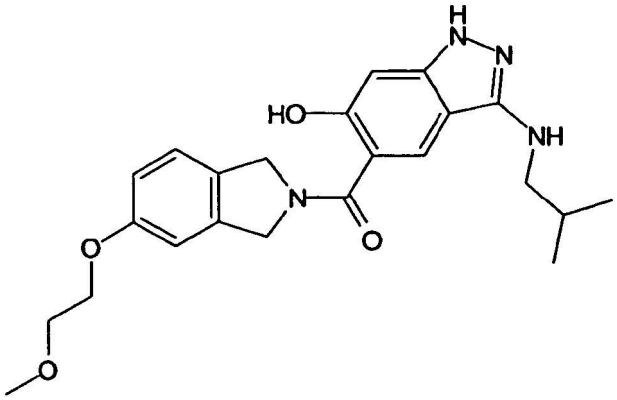
"A671"	
"A672"	
"A673"	
"A674"	
"A675"	

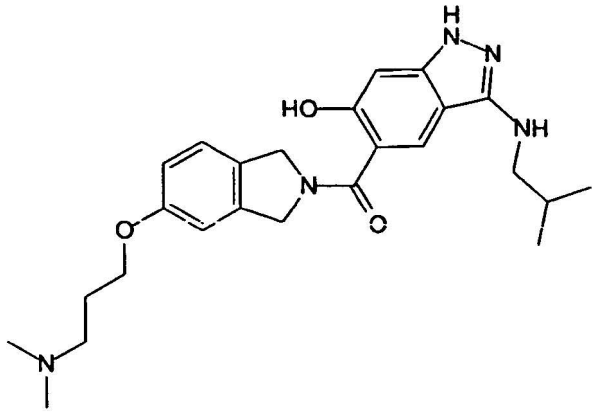
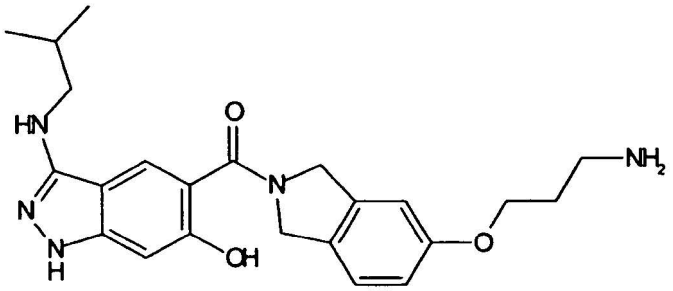
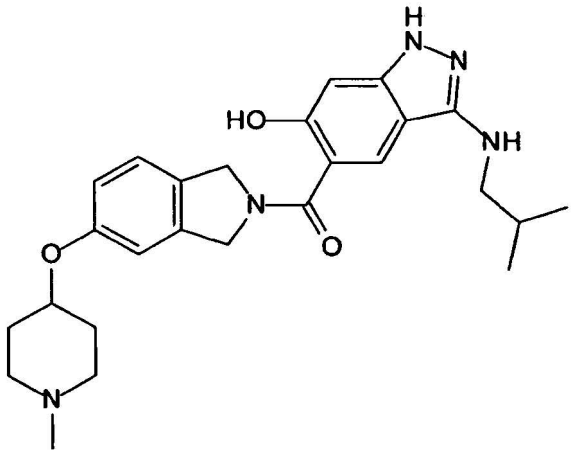
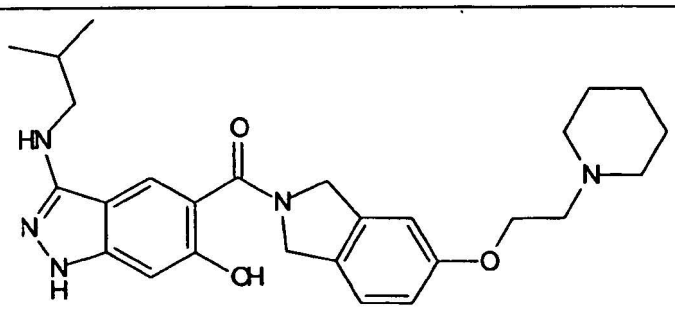
"A676"	
"A677"	
"A678"	
"A679"	
"A680"	

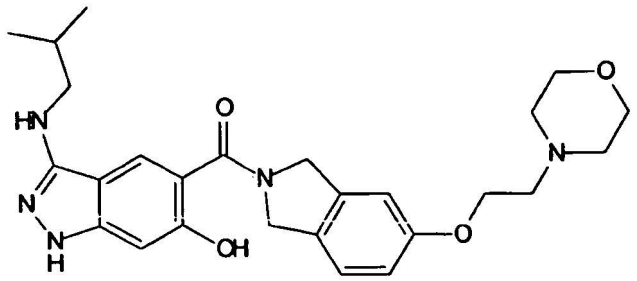
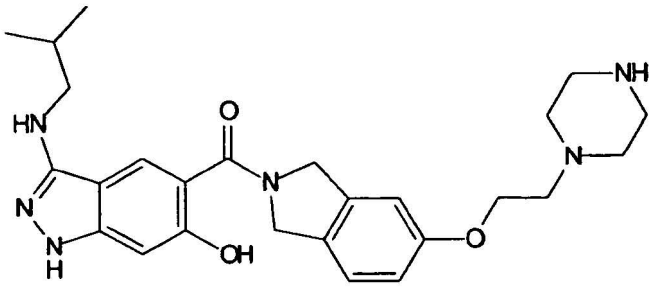
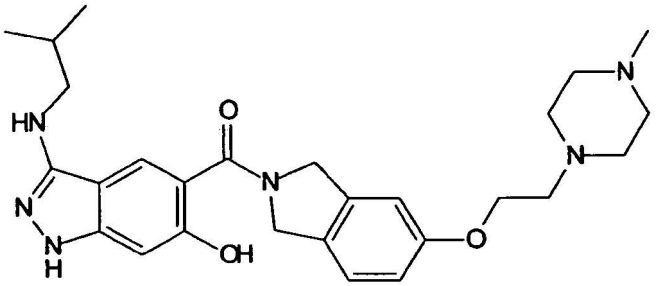
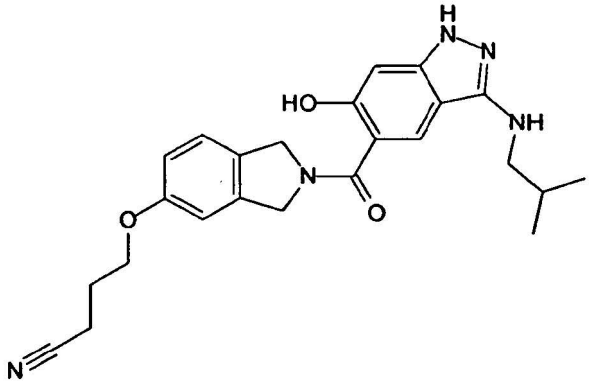
"A681"	
"A682"	
"A683"	
"A684"	

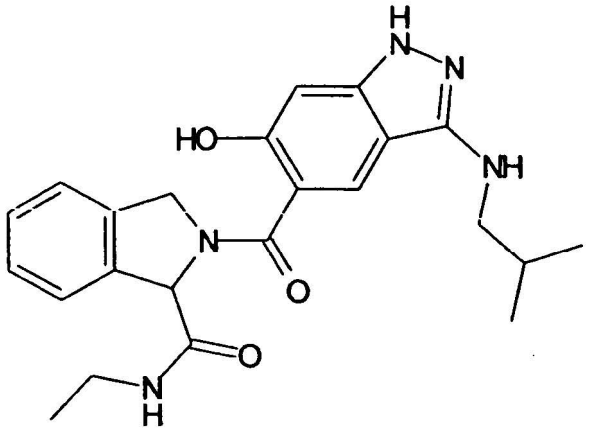
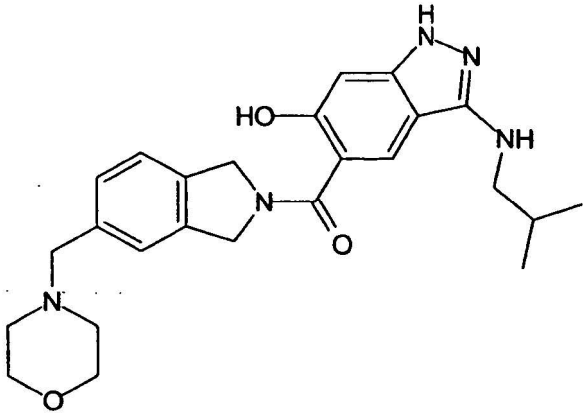
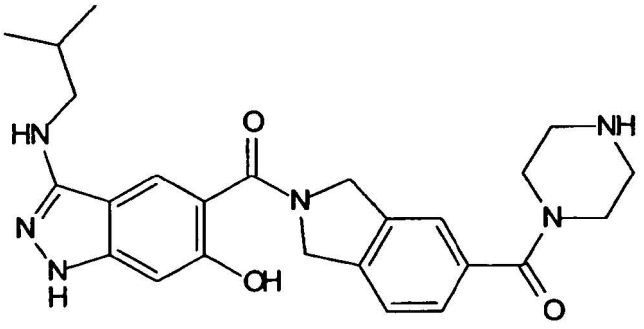
"A685"	
"A686"	
"A687"	
"A688"	
"A689"	

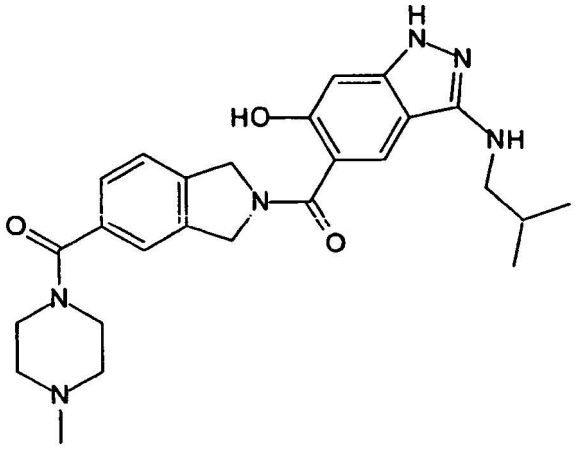
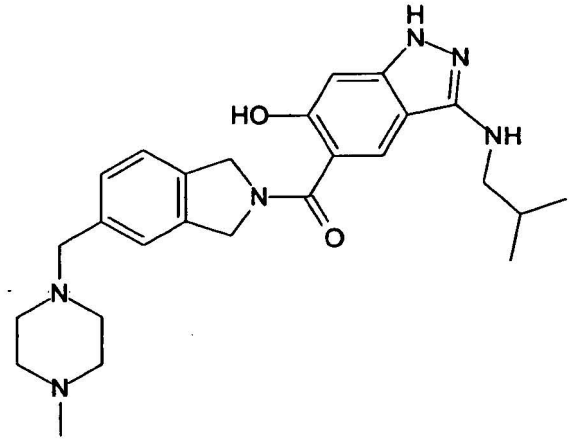
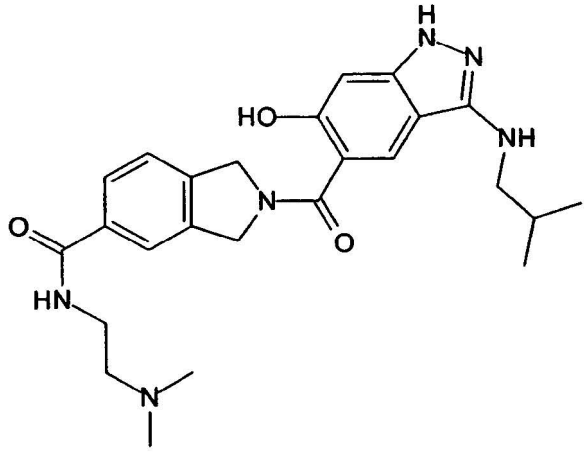
"A690"	
"A691"	
"A692"	
"A693"	

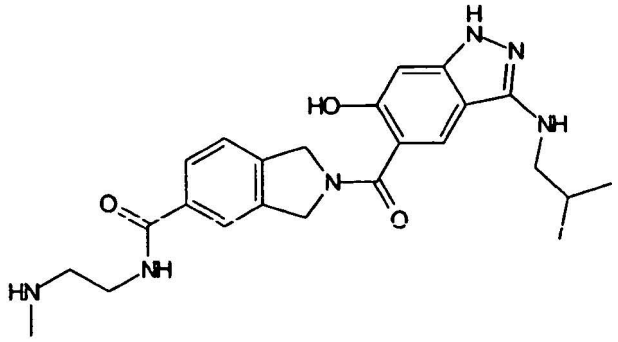
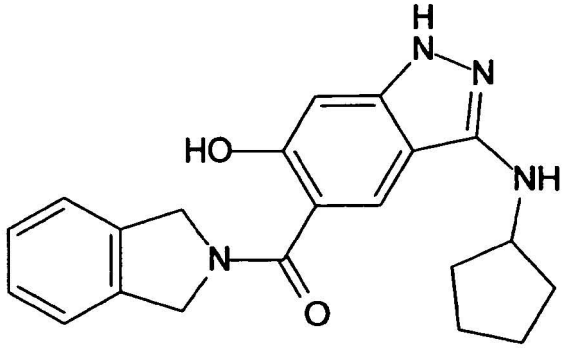
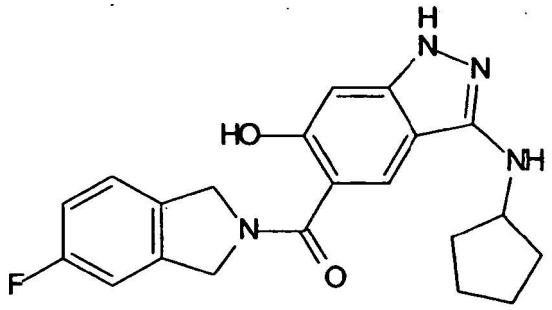
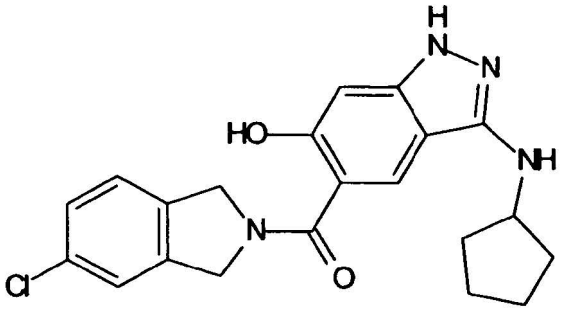
"A694"	
"A695"	
"A696"	

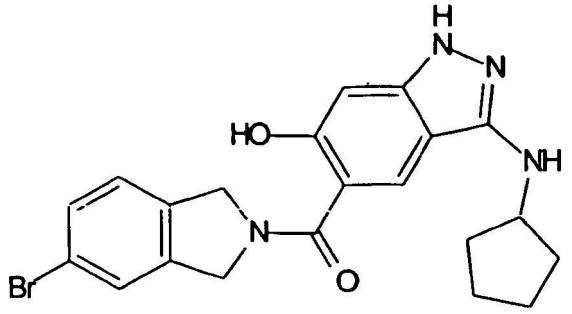
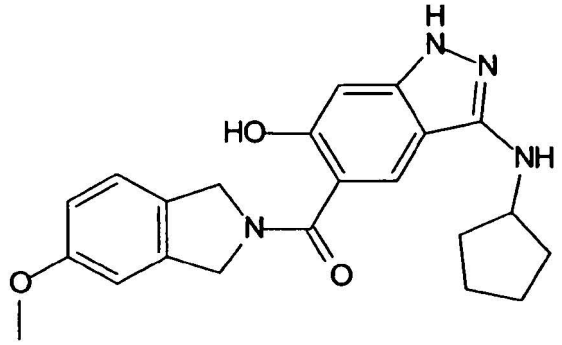
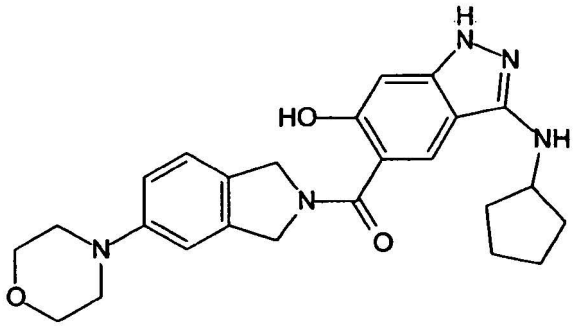
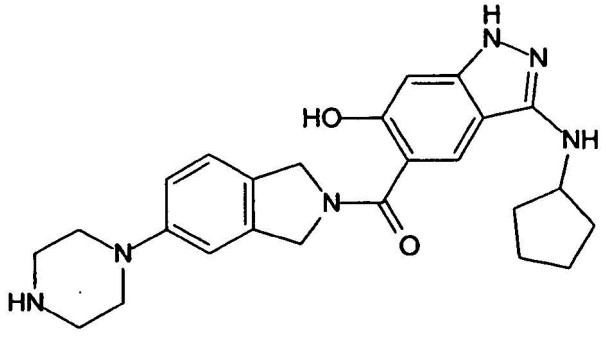
"A697"	
"A698"	
"A699"	
"A700"	

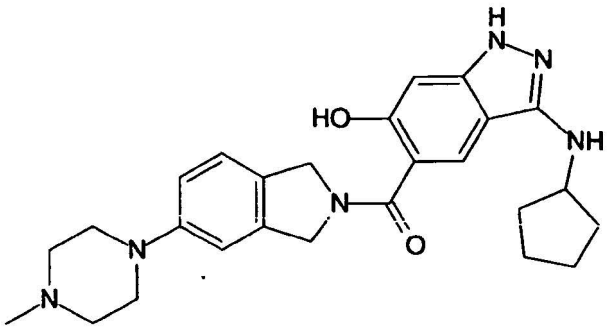
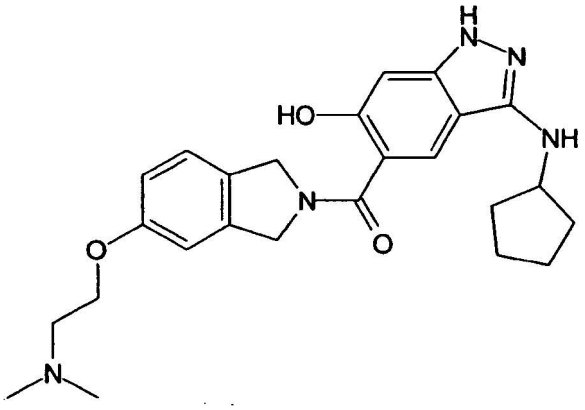
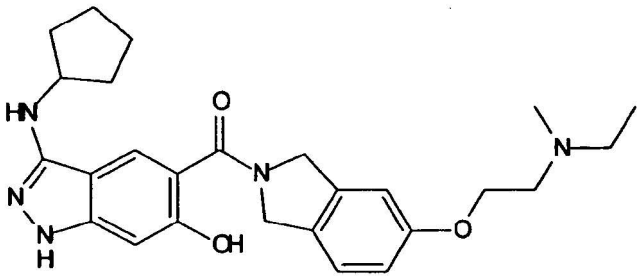
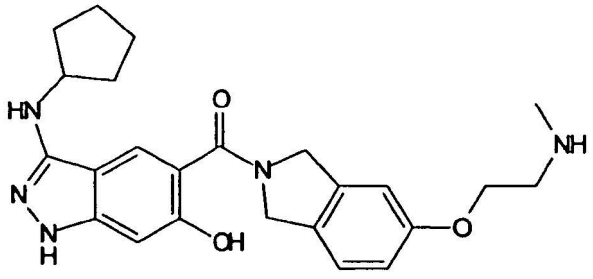
"A701"	
"A702"	
"A703"	
"A704"	

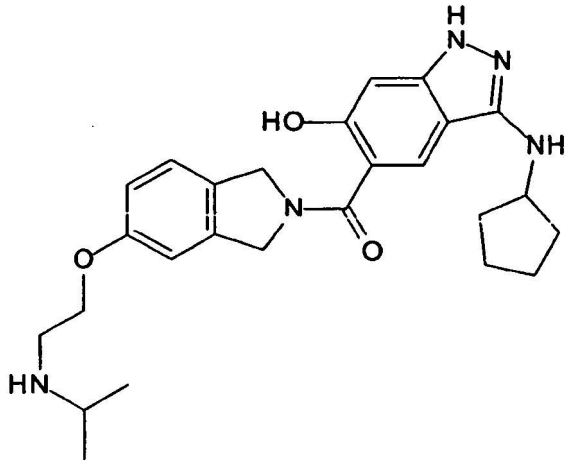
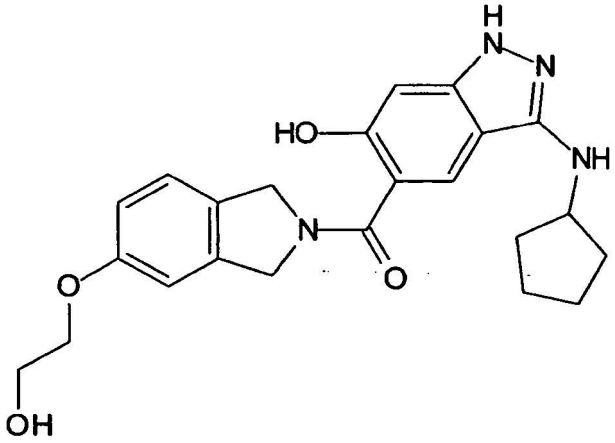
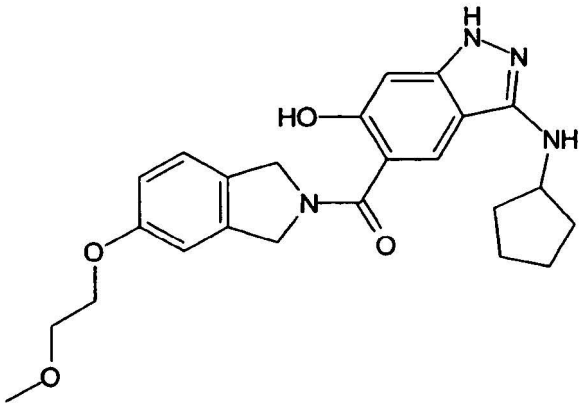
"A705"	
"A706"	
"A707"	

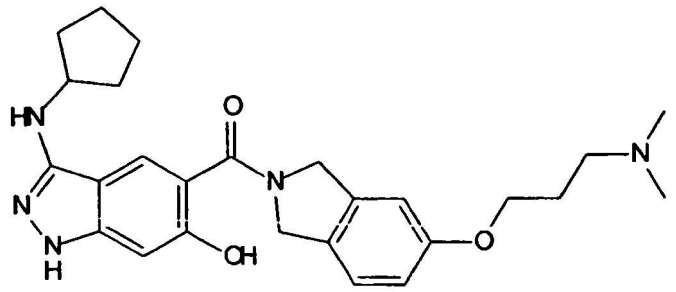
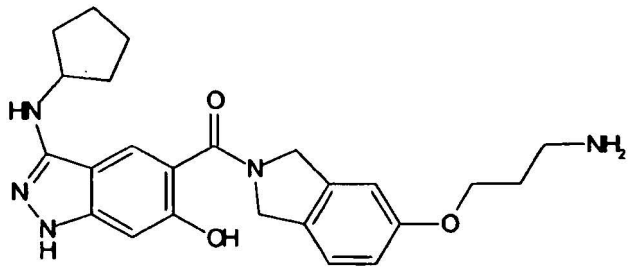
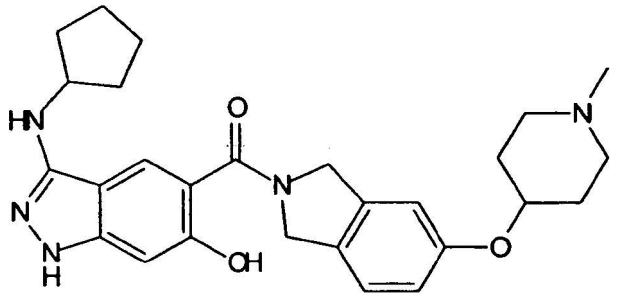
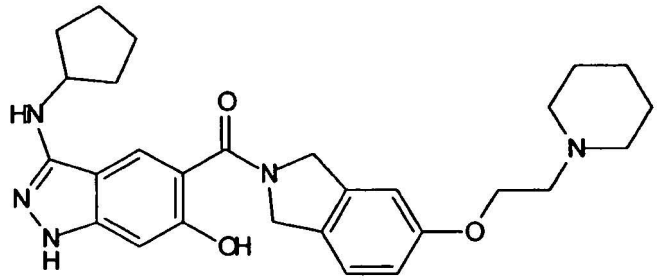
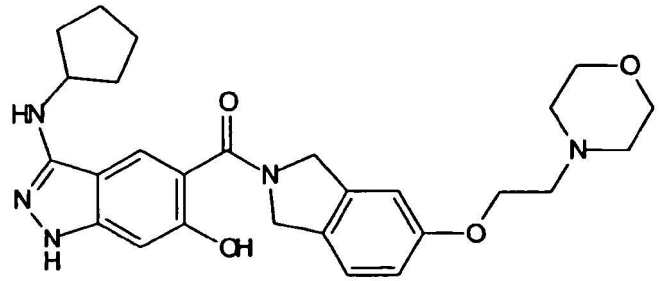
"A708"	
"A709"	
"A710"	

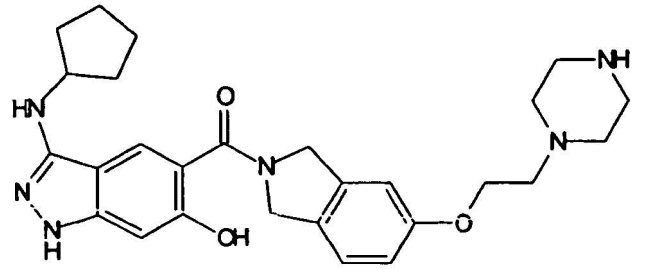
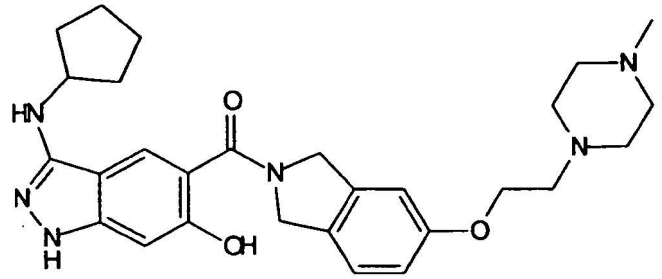
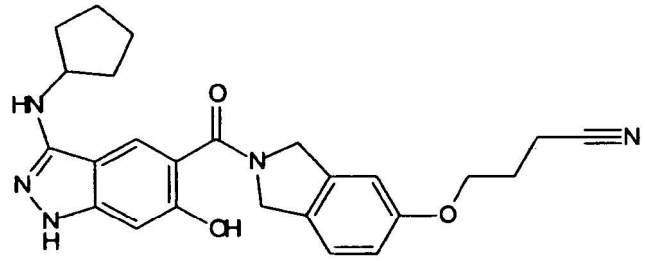
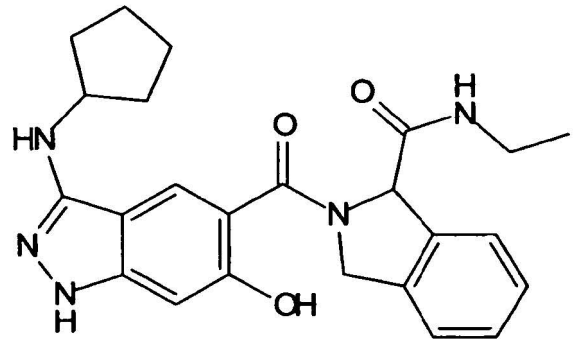
"A711"	
"A712"	
"A713"	
"A714"	

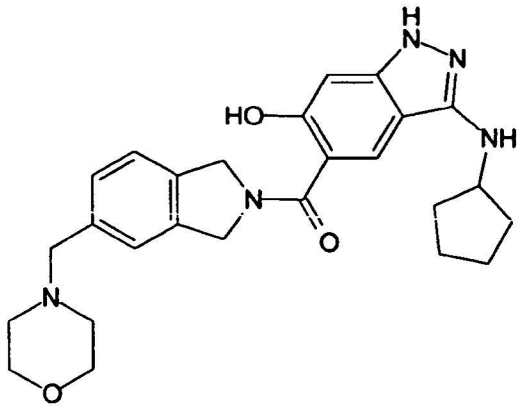
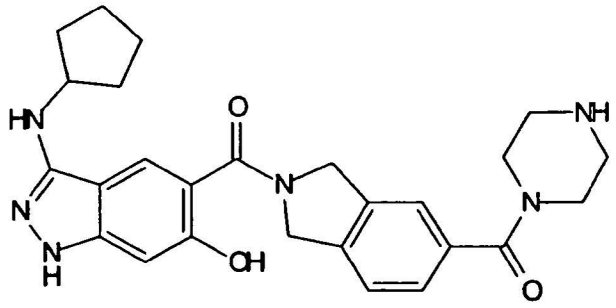
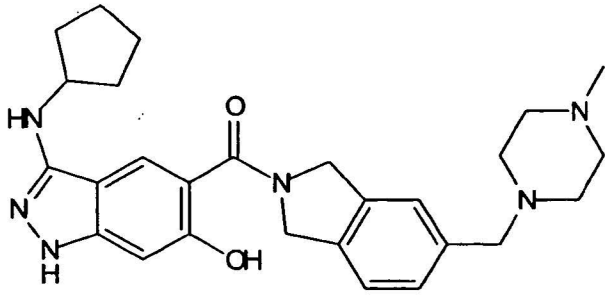
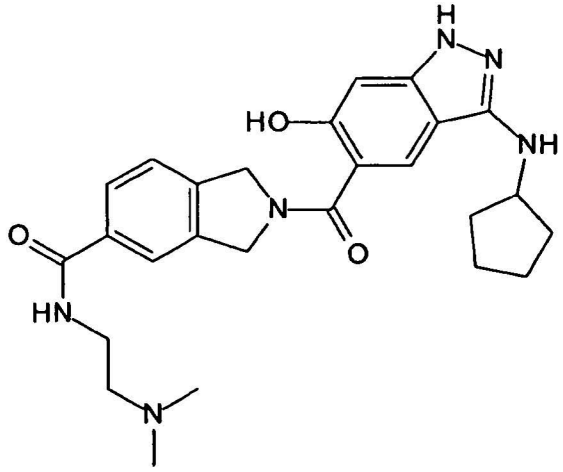
"A715"	
"A716"	
"A717"	
"A718"	

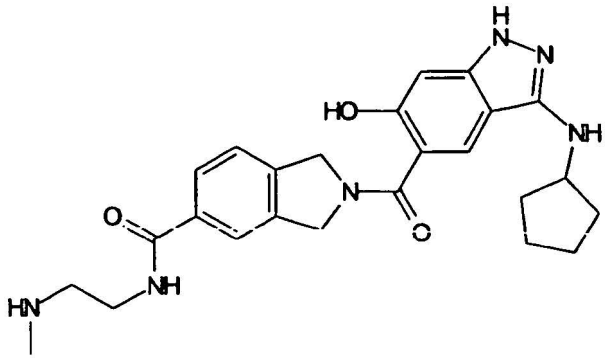
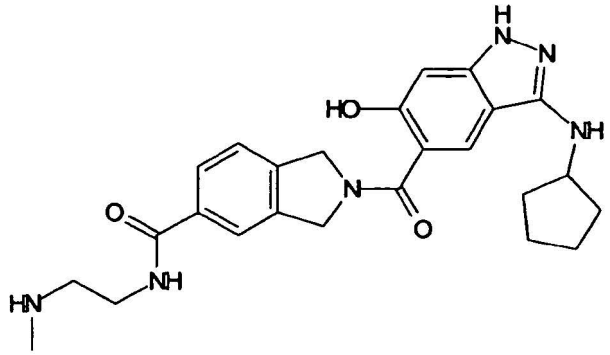
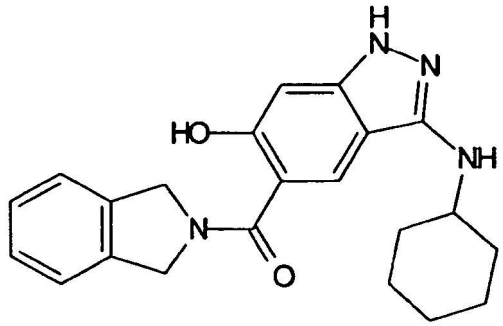
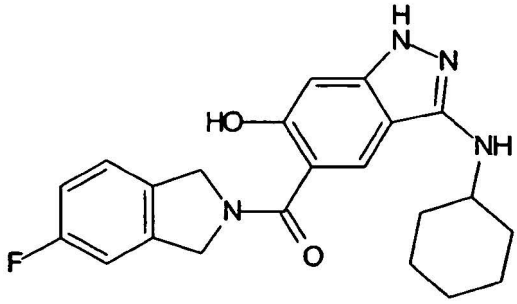
"A719"	
"A720"	
"A721"	
"A722"	

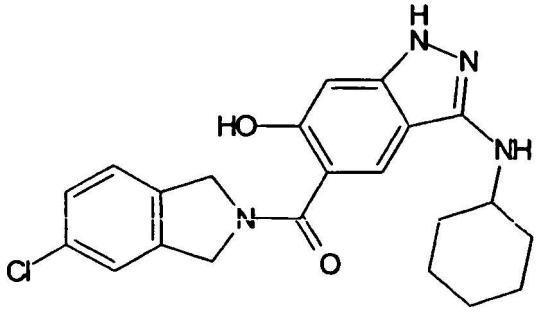
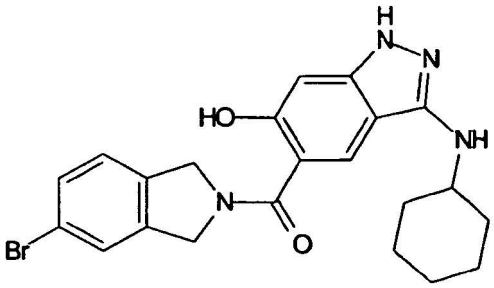
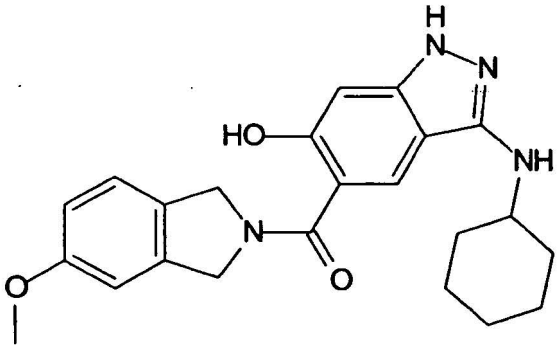
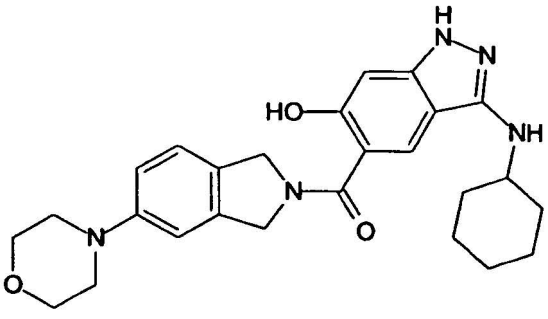
"A723"	
"A724"	
"A725"	

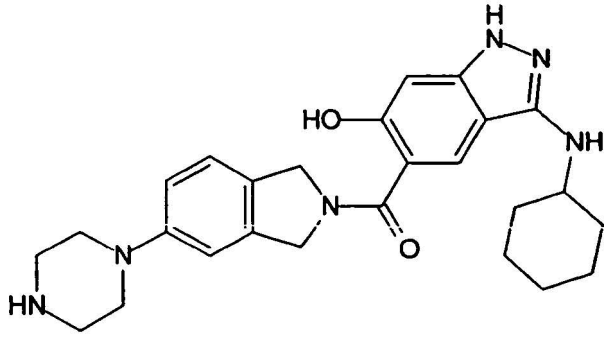
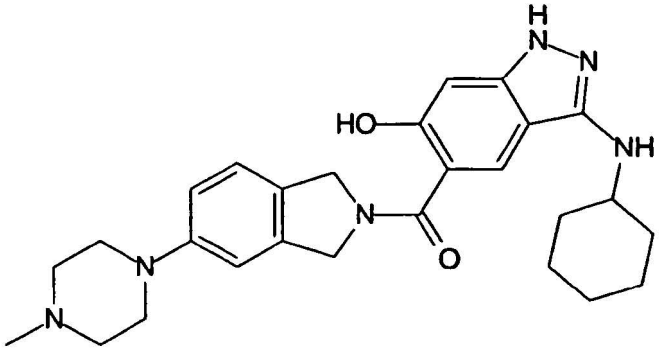
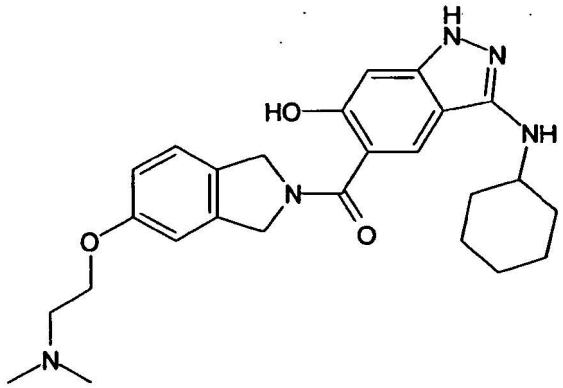
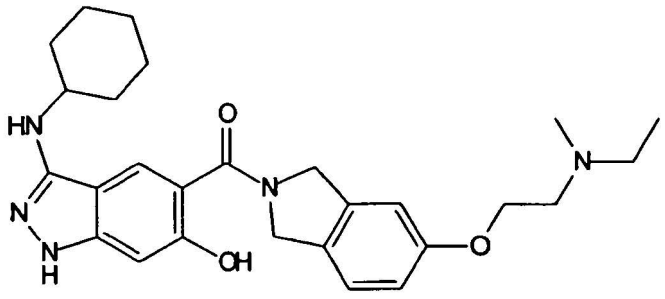
"A726"	
"A727"	
"A728"	
"A729"	
"A730"	

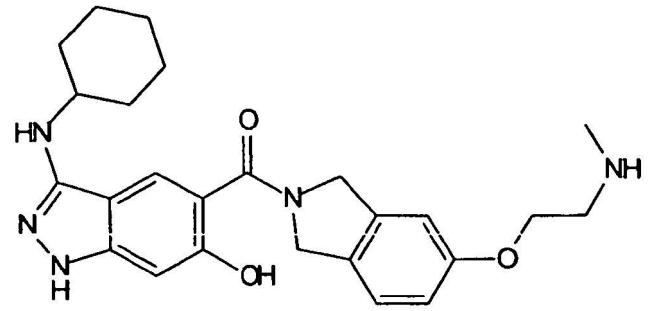
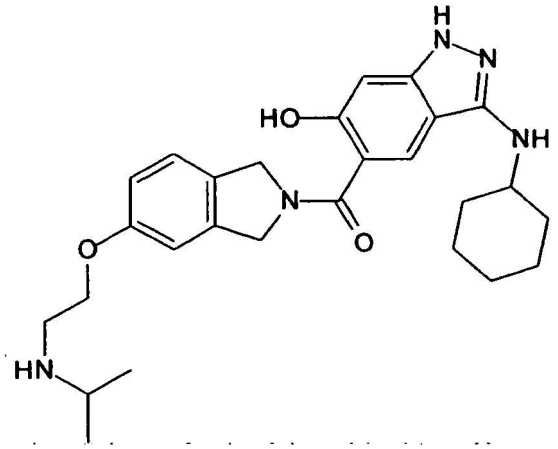
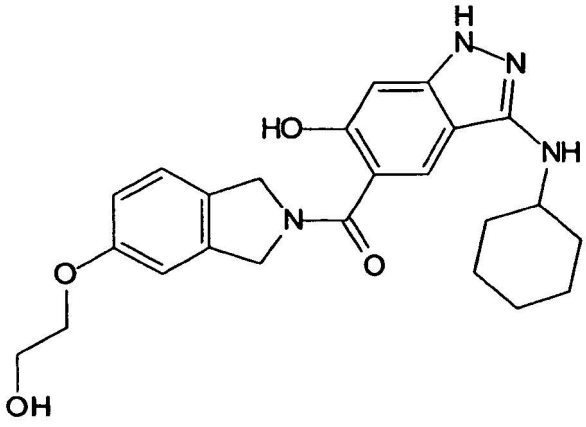
"A731"	
"A732"	
"A733"	
"A734"	

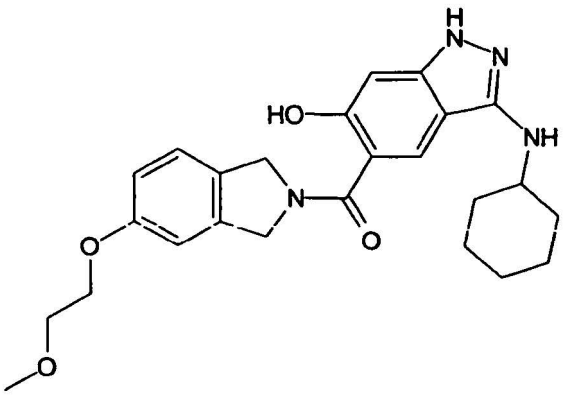
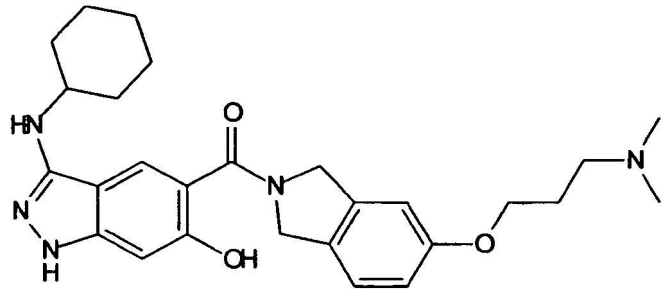
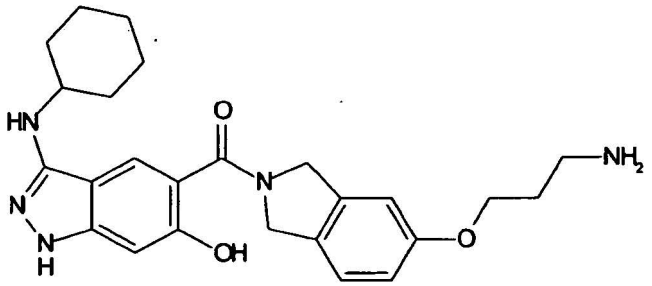
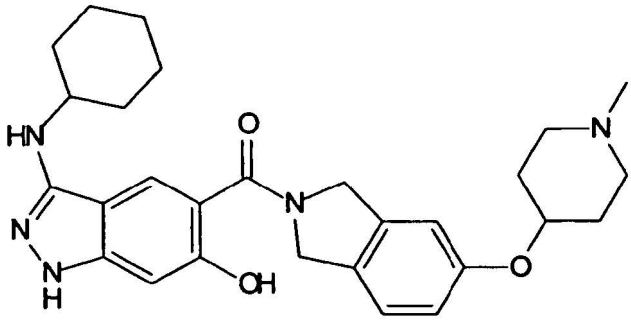
"A735"	
"A736"	
"A737"	
"A738"	

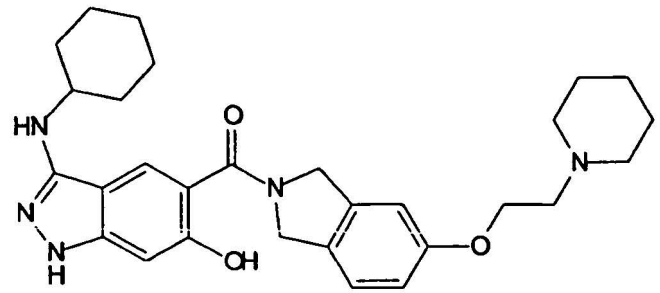
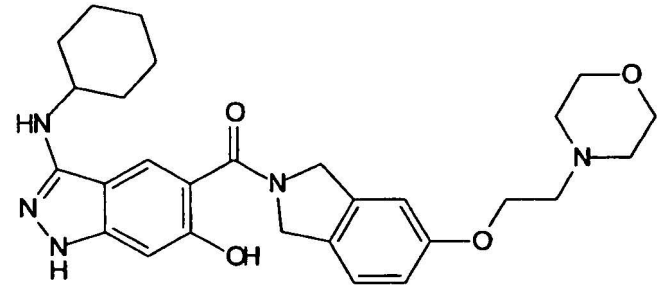
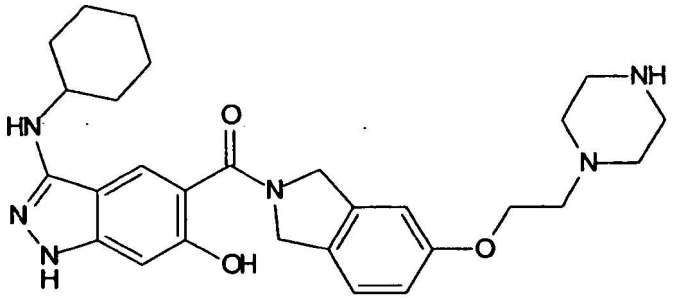
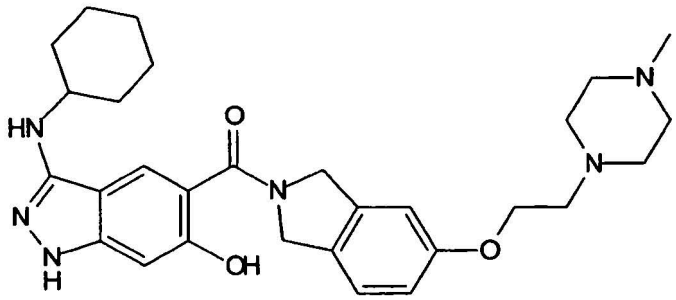
"A739"	
"A740"	
"A741"	
"A742"	

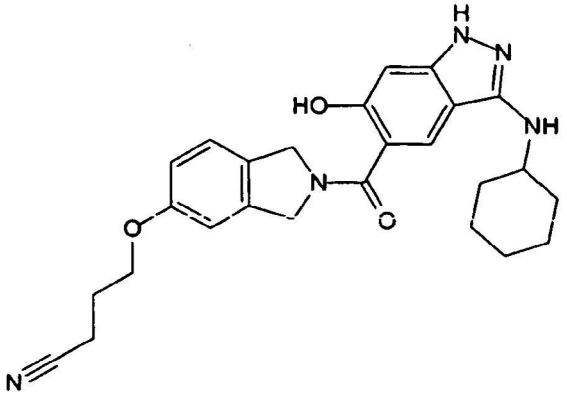
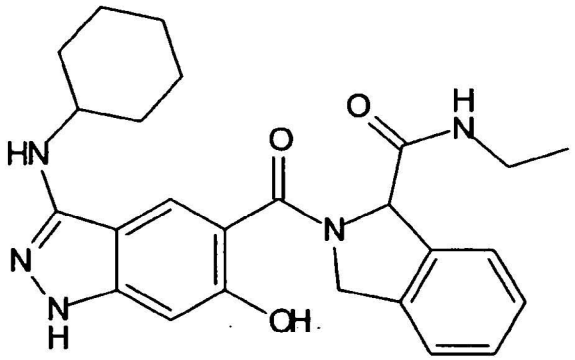
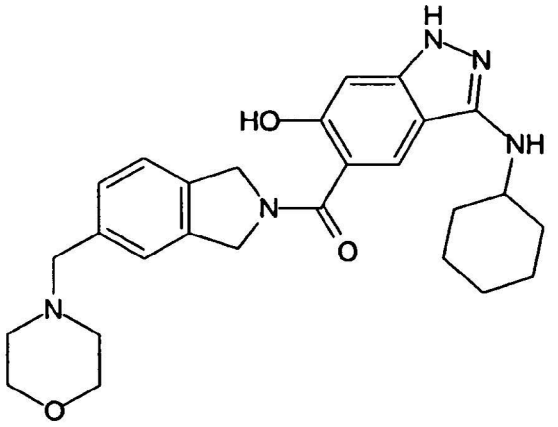
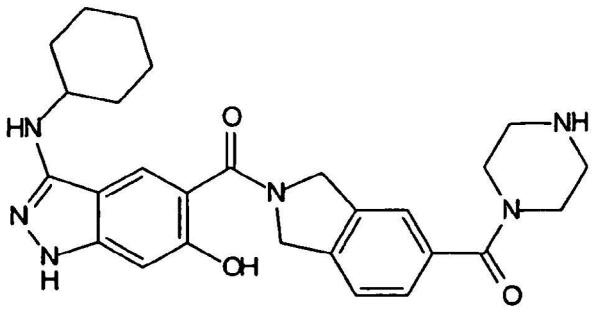
"A743"	
"A744"	
"A745"	
"A746"	

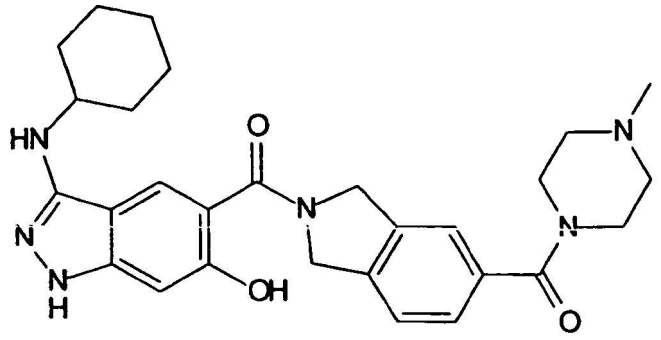
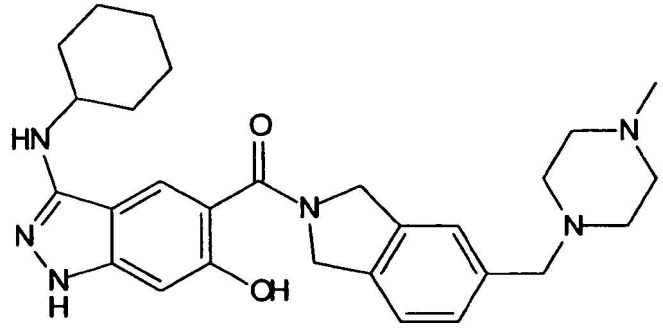
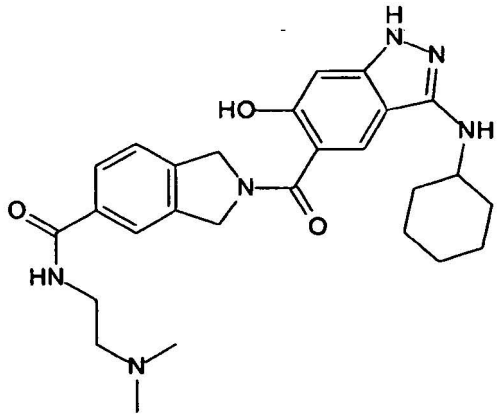
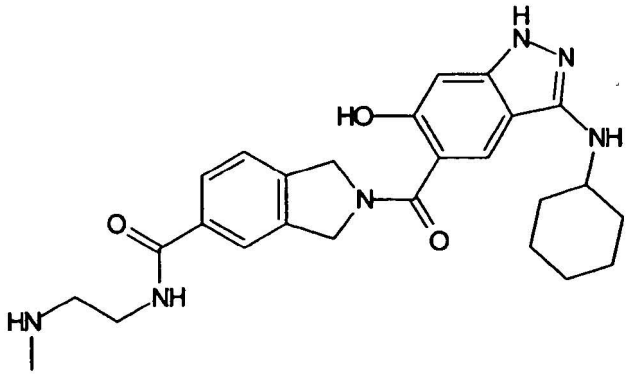
"A747"	
"A748"	
"A749"	
"A750"	

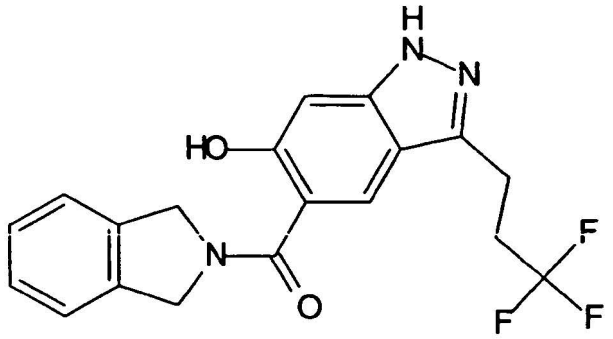
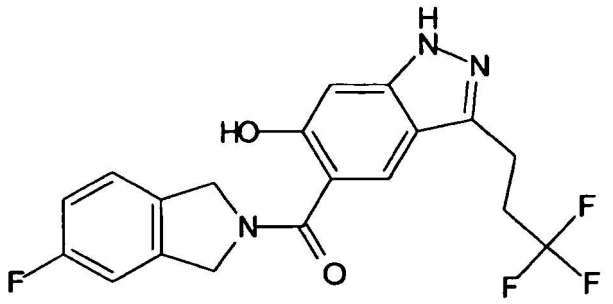
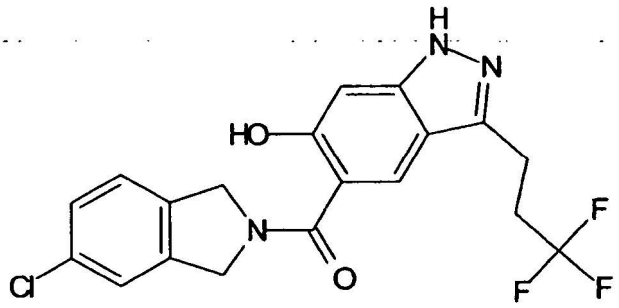
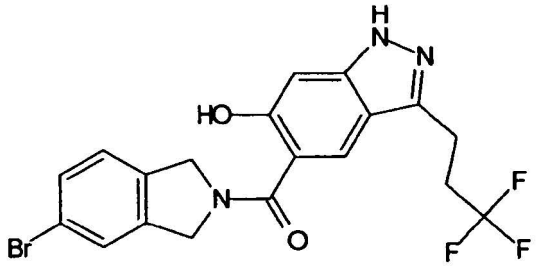
"A751"	
"A752"	
"A753"	

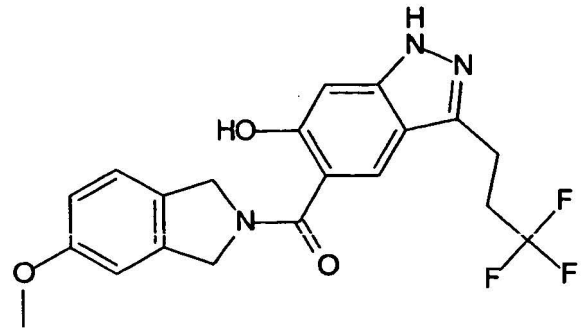
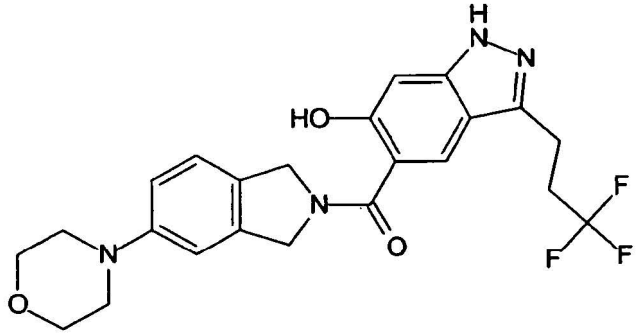
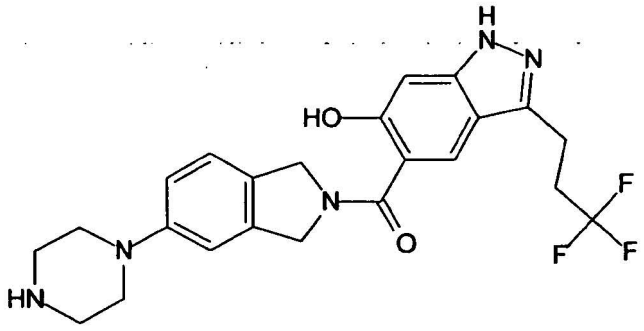
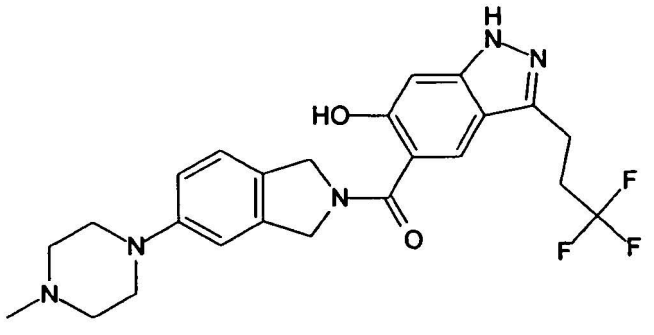
"A754"	
"A755"	
"A756"	
"A757"	

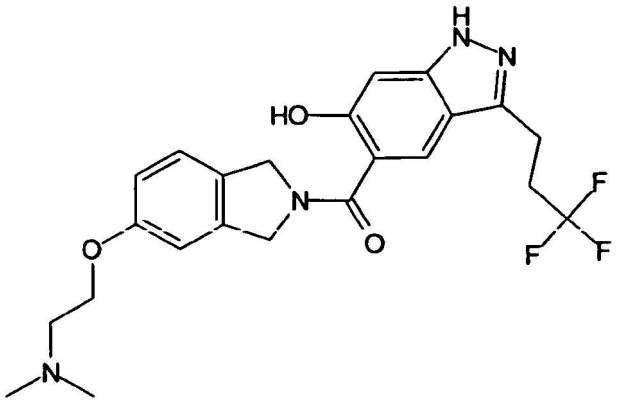
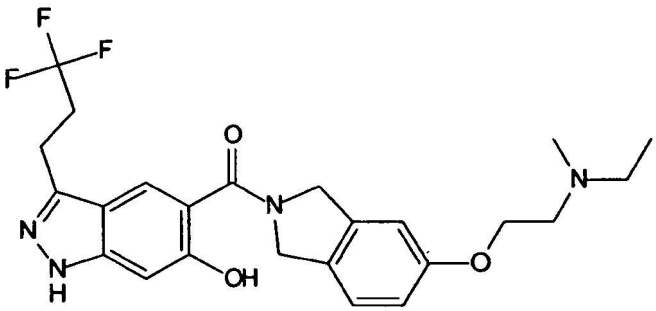
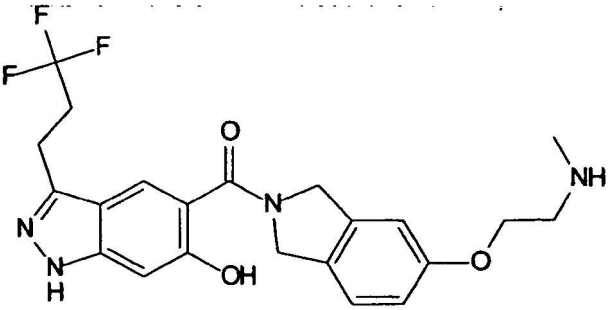
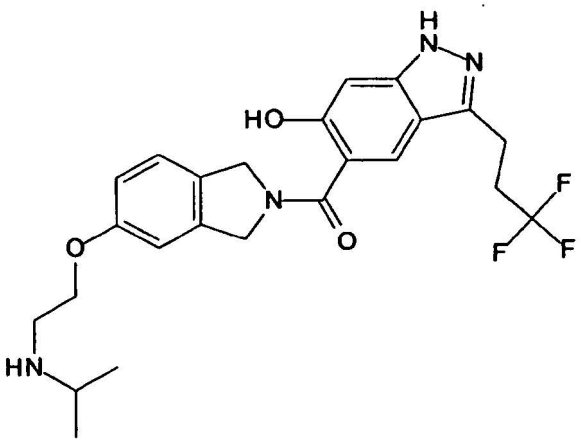
"A758"	
"A759"	
"A760"	
"A761"	

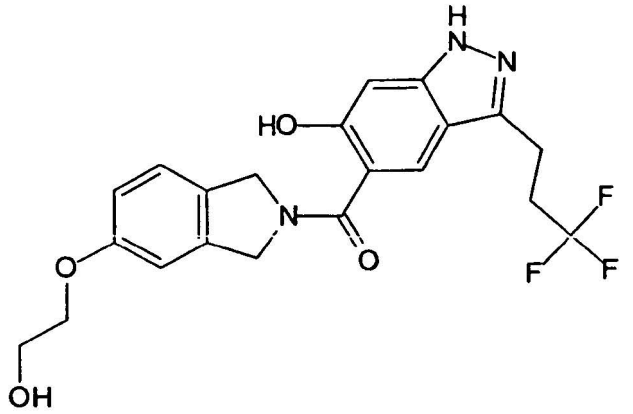
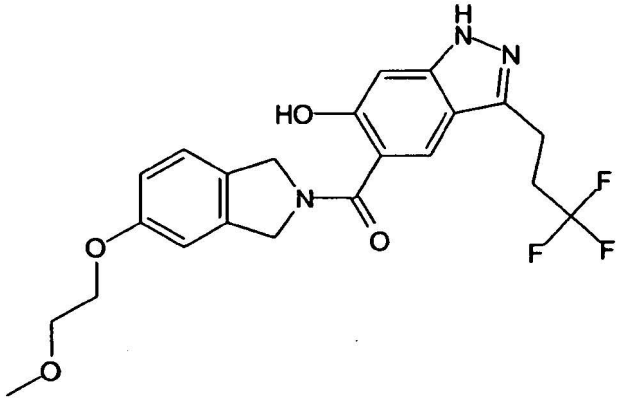
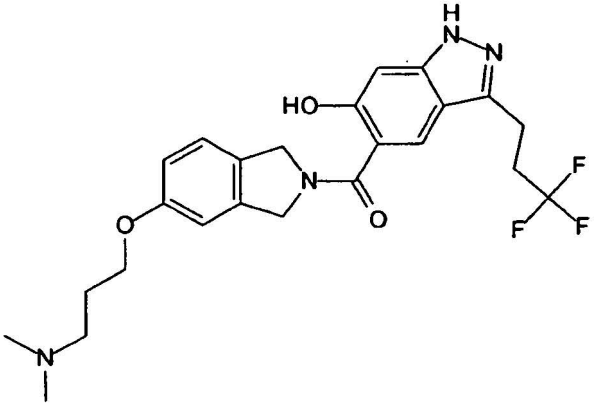
"A762"	
"A763"	
"A764"	
"A765"	

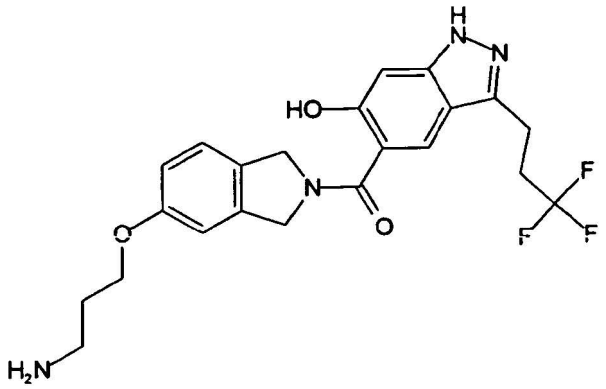
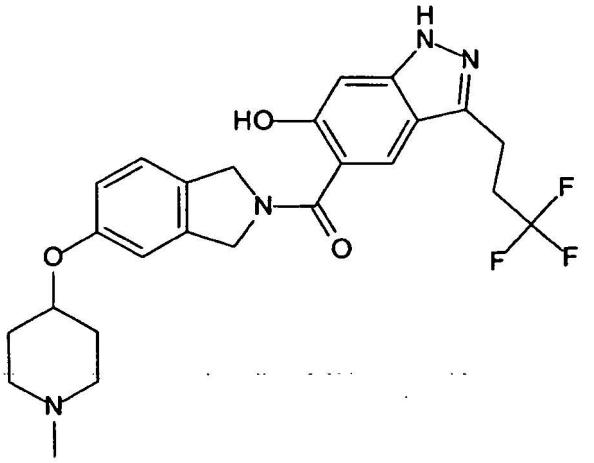
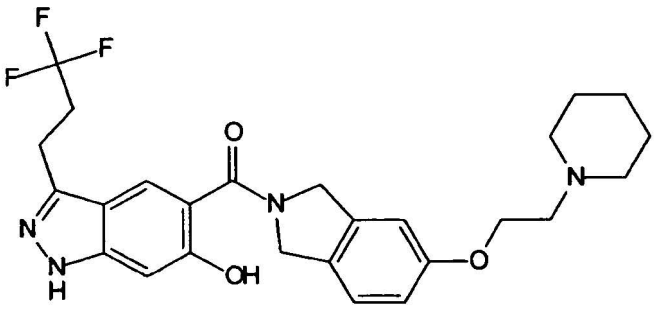
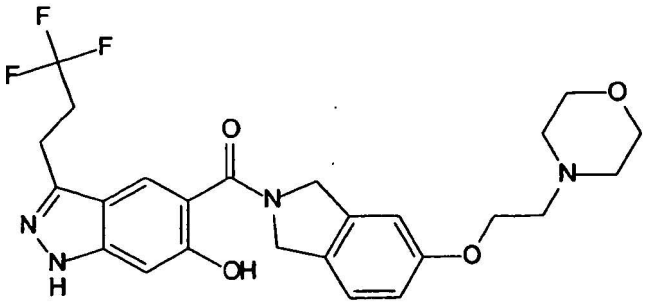
"A766"	
"A767"	
"A768"	
"A769"	

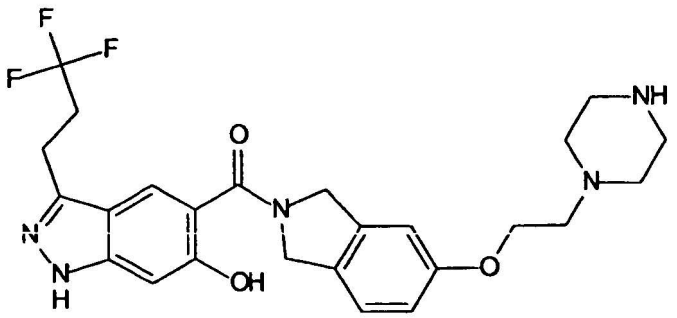
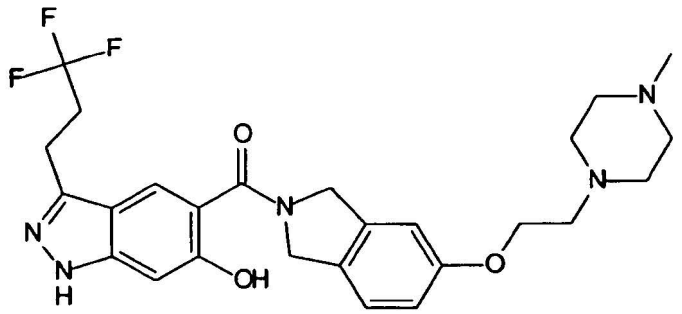
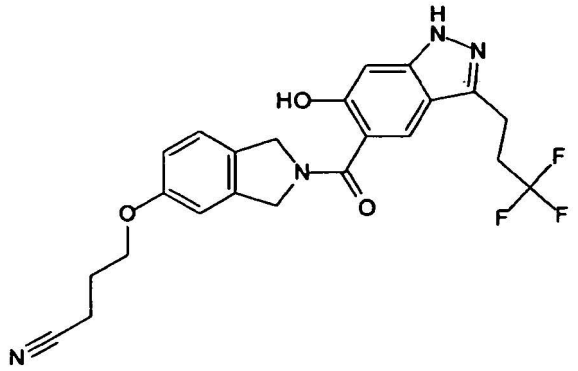
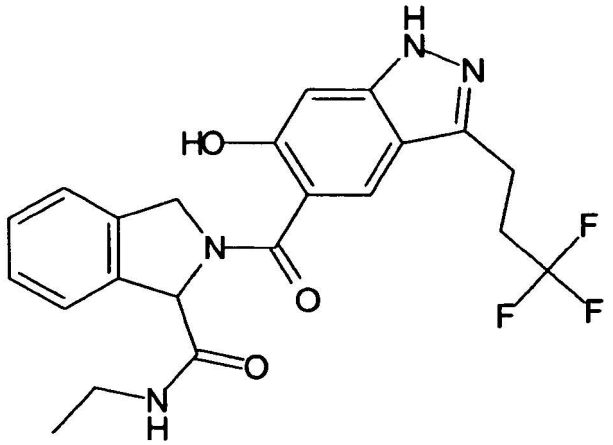
"A770"	
"A771"	
"A772"	
"A773"	

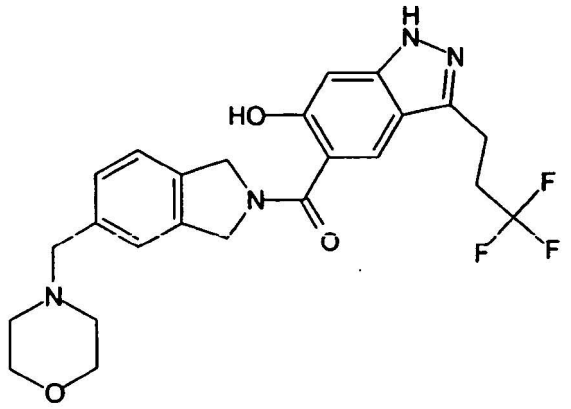
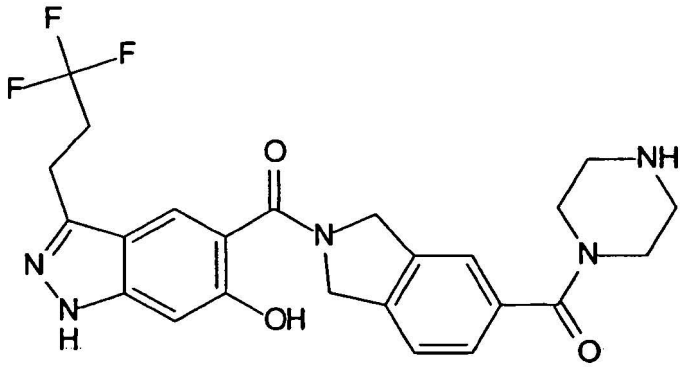
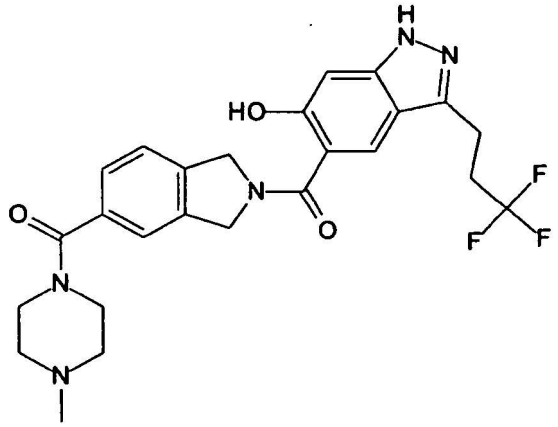
"A774"	
"A775"	
"A776"	
"A777"	

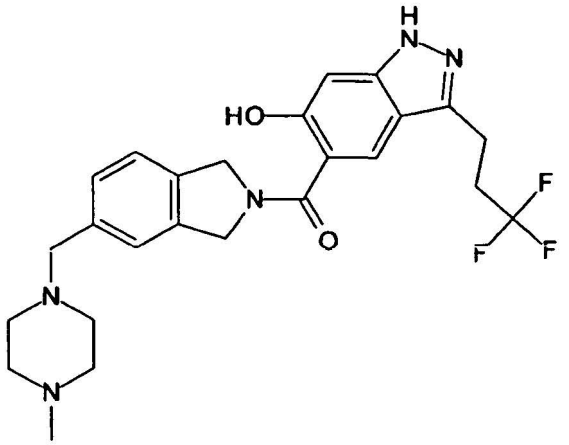
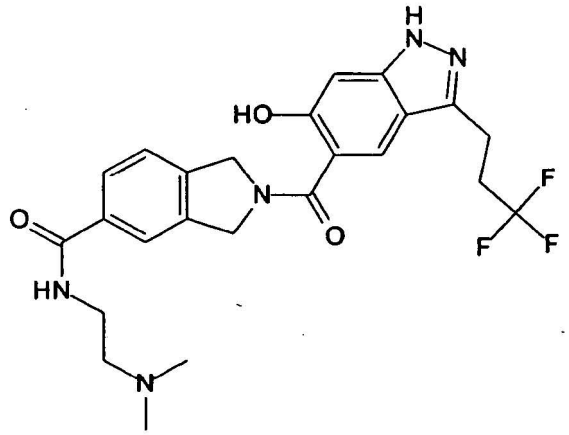
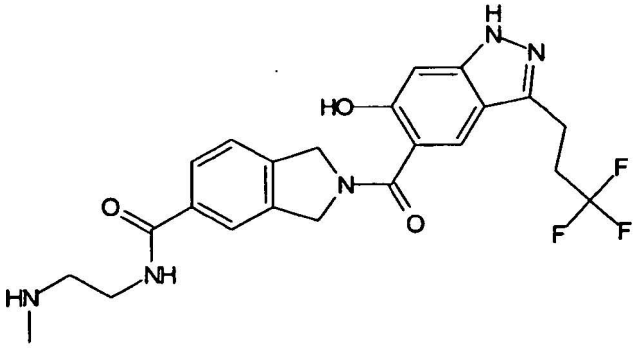
"A778"	
"A779"	
"A780"	
"A781"	

"A782"	
"A783"	
"A784"	

"A785"	
"A786"	
"A787"	
"A788"	

"A789"	
"A790"	
"A791"	
"A792"	

"A793"	
"A794"	
"A795"	

"A796"	
"A797"	
"A798"	

Así como sus sales, solvatos y estereoisómeros farmacéuticamente utilizables, incluso sus mezclas en todas las proporciones.

2. Medicamentos que contienen al menos un compuesto según la reivindicación 1 y/o sus sales, solvatos y estereoisómeros utilizables farmacéuticamente, incluso sus mezclas en todas las proporciones, así como opcionalmente vehículos y/o adyuvantes.

3. Utilización de compuestos según la reivindicación 1, así como sus sales, solvatos y estereoisómeros utilizables farmacéuticamente, incluso sus mezclas en todas las proporciones, para la preparación un medicamento para el tratamiento o la prevención de enfermedades tumorales, enfermedades virales, para la inmunodepresión en caso de trasplantes, enfermedades condicionadas por inflamación, fibrosis cística, enfermedades relacionadas con angiogénesis, enfermedades infecciosas, enfermedades autoinmunes, isquemia, enfermedades fibrogenéticas, para la estimulación de la regeneración nerviosa, para inhibir el crecimiento del cáncer, células tumorales y metástasis tumorales, para la protección de células normales contra la toxicidad que se ocasiona por quimioterapia, para el

tratamiento de enfermedades en las que el plegamiento incorrecto de proteínas o la agregación es un factor causal principal.

4. Utilización según la reivindicación 3, en cuyo caso las enfermedades tumorales son fibrosarcoma, mixosarcoma, liposarcoma, condrosarcoma, sarcoma osteogénica, cordoma, angiosarcoma, sarcoma de endotelio, linfangiosarcoma, linfangiosarcoma de endotelio, sinovioma, mesotelioma, tumor de Ewing, leiosarcoma, rabdomiosarcoma, carcinoma de colon, cáncer de páncreas, cáncer de mama, cáncer de ovarios, cáncer de próstata, carcinoma de células escamosas, carcinoma basocelular, adenocarcinoma, carcinoma de glándulas sudoríparas, carcinoma de glándulas sebáceas, carcinoma papilar, adenocarcinomas papilares, cistadenocarcinomas, carcinoma de la médula ósea, carcinoma broncogénico, carcinoma de células renales, hepatoma, carcinoma del conducto biliar, carcinoma coriónico, seminoma, carcinoma embrionario, tumor de Wilms, cáncer cervical, tumor testicular, carcinoma de pulmón, carcinoma de pulmón de células pequeñas, carcinoma de vejiga, carcinoma epitelial, glioma, astrocitoma, meduloblastoma, craniofaringioma, ependimoma, pinealoma, hemangioblastoma, neuroma acústico, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leucemia, linfoma, mieloma múltiple, macroglobulinemia de Waldenstroms y enfermedad en cadena grave.

5. Utilización según la reivindicación 3, en cuyo caso el patógeno viral de las enfermedades virales se selecciona del grupo que se compone de hepatitis tipo A, hepatitis tipo B, hepatitis tipo C, gripe, varicela, adenovirus, herpes Simplex tipo I (HSV-I), herpes Simplex tipo II (HSV-II), peste bovina, rinovirus, ecovirus, rotavirus, virus sincicial respiratorio (RSV), virus de papiloma, papovavirus, citomegalovirus, equinovirus, arbovirus, huntavirus, coxsackievirus, virus de paperas, virus de sarampión, virus de la rubeola, virus de poliomielitis, virus de inmunodeficiencia humana tipo I (VIH-I) y virus de inmunodeficiencia humana tipo II (VIH -II).

6. Utilización según la reivindicación 3, en cuyo caso las enfermedades condicionadas por inflamación son artritis reumatoide, asma, esclerosis múltiple, diabetes tipo 1, lupus eritematoso, psoriasis y Inflammatory Bowel Disease (Enfermedad inflamatoria de intestino).

7. Utilización según la reivindicación 3, en cuyo caso las enfermedades relacionadas con angiogénesis son retinopatía diabética, hemangioma, endometriosis y angiogénesis tumorales.

8. Utilización según la reivindicación 3, en cuyo caso las enfermedades fibrogenéticas son esclerodermis, polimiositis, lupus sistémico, cirrosis hepática, formación de queloides, nefritis intersticial y fibrosis pulmonar.

9. Utilización según la reivindicación 3, en cuyo caso las enfermedades en las que el plegamiento incorrecto de proteína o la agregación es un factor causal principal es escrapia, enfermedad de Creutzfeldt-Jakob, de Huntington o de Alzheimer.

10. Medicamento que contiene al menos un compuesto según la reivindicación 1 y/o sus sales, solvatos y estereoisómeros utilizables farmacéuticamente, incluso sus mezclas en todas las proporciones, y al menos otro principio activo de medicamento.

11. Kit que se compone de paquetes separados de

(a) una cantidad eficaz de un compuesto según la reivindicación 1 y/o de sus sales, solvatos y estereoisómeros utilizables farmacéuticamente, incluso sus mezclas en todas las proporciones,

y

(b) una cantidad eficaz de otro principio activo de medicamento.