July 18, 2017

Vertex Announces Positive Phase 1 & Phase 2 Data from Three Different Triple Combination Regimens in People with Cystic Fibrosis Who Have One F508del Mutation and One Minimal Function Mutation (F508del/Min)

-Phase 2 data showed mean absolute improvements in ppFEV$_1$ of 9.7 and 12.0 percentage points for VX-152 and VX-440, respectively, in triple combination with tezacaftor and ivacaftor in F508del/Min patients; Initial data from Phase 1 study showed mean absolute improvement in ppFEV$_1$ of 9.6 percentage points with VX-659 triple combination in F508del/Min patients-

-First data to demonstrate the potential to treat the underlying cause of CF in people with F508del/Min mutations, a severe and difficult-to-treat type of the disease-

-Initial Phase 2 data also showed mean absolute improvements in ppFEV$_1$ of 7.3 and 9.5 percentage points when VX-152 or VX-440 was added in people with two copies of the F508del mutation (F508del/F508del), who were already receiving tezacaftor and ivacaftor-

-All 3 triple combination regimens were generally well tolerated across the studies-

BOSTON--(BUSINESS WIRE)-- Vertex Pharmaceuticals Incorporated (Nasdaq: VRTX) today announced positive data from Phase 1 and Phase 2 studies of three different triple combination regimens in people with cystic fibrosis (CF) who have one *F508del* mutation and one minimal function mutation (*F508del*/Min). These are the first data to demonstrate the potential to treat the underlying cause of CF in these patients, who have a severe and difficult-to-treat type of the disease. Data from the Phase 2 studies in these patients showed mean absolute improvements in percent predicted forced expiratory volume in one second (ppFEV$_1$) of 9.7 and 12.0 percentage points from baseline for the triple combination regimens with VX-152 (200mg q12h) or VX-440 (600mg q12h), respectively. Initial data from a Phase 1 study showed a mean absolute improvement in ppFEV$_1$ of 9.6 percentage points from baseline for the triple combination regimen of VX-659, tezacaftor and ivacaftor in people with one *F508del* mutation and one minimal function mutation. The company also announced today initial data showing improvements in mean absolute ppFEV$_1$ of 7.3 and 9.5 percentage points when VX-152 or VX-440 was added in people with two copies of the *F508del* mutation, who were already receiving tezacaftor and ivacaftor. Vertex will host a conference call for investors today, July 18, 2017 at 5:00 p.m. EDT, to discuss these results.

The triple combination regimens were generally well tolerated across all three studies, and the majority of adverse events were mild to moderate in severity. Across the studies, the discontinuation rate due to adverse events was low.

"These safety and efficacy data are clear and compelling, indicating significant potential benefit for people with CF from each of these three different triple combination regimens," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex. "We will be collecting and evaluating additional data from these and other studies and will make a decision on which regimen(s) to take forward into pivotal program(s), which we expect to begin in the first half of 2018."

Vertex has established a Steering Committee of global CF experts and clinical trial investigators to support the design, conduct and execution of the triple combination pivotal study program. This committee is co-chaired by Steven M. Rowe, M.D., M.S.P.H., Professor of Medicine, Pediatrics, and Cell, Developmental and Integrative Biology, Director of the Gregory Fleming James Cystic Fibrosis Research Center, Nancy and Eugene Gwaltney Endowed Chair for Medical Research, University of Alabama at Birmingham, and Jennifer Taylor-Cousar, M.D., Associate Professor, Departments of Medicine and Pediatrics, Pulmonary Divisions, Medical Director of Clinical Research Services and Co-Director and Director of the CF Therapeutics Development Network, Adult CF Program, National Jewish Health, Colorado.

"Patients with minimal function mutations have been waiting for a medicine to treat the underlying cause of their disease, which makes these data showing pronounced improvements in lung function particularly important," said Dr. Rowe. "It's also encouraging to see that the addition of a next-generation corrector may lead to substantial additional benefits for patients with two copies of the *F508del* mutation, who were already receiving tezacaftor and ivacaftor."

Next Steps

Vertex has advanced four next-generation correctors in parallel with the goal of developing the best triple combination regimen or regimens for people living with CF.

Vertex has accelerated the development programs for VX-445 and VX-659. A VX-445 Phase 2 study is underway and a VX-659 Phase 2 study will begin in early August. VX-445 and VX-659 will be evaluated in triple combination with tezacaftor and ivacaftor in people with one *F508del* mutation and one minimal function mutation and will be evaluated in people with two copies of the *F508del* mutation who are already receiving tezacaftor and ivacaftor. Data from both of these Phase 2 studies are expected in early 2018.

Pending additional data from these Phase 2 studies and the ongoing studies of VX-152 and VX-440 and discussions with regulatory agencies and the Steering Committee, Vertex plans to initiate pivotal development of one or more triple combination regimens in the first half of 2018.

About the VX-440 Phase 2 Study

This randomized, double-blind Phase 2 study is evaluating VX-440 (200mg and 600mg q12h) in combination with tezacaftor and ivacaftor in two different groups of people with CF ages 18 and older - those who have one *F508del* mutation and one minimal function mutation, and in those who have two copies of the *F508del* mutation. Minimal function mutations are those that result in little-to-no functioning CFTR protein and are not responsive to ivacaftor, tezacaftor or the combination of ivacaftor and tezacaftor. The primary objectives for the study are safety, tolerability and efficacy as assessed by mean absolute change in ppFEV$_1$ from baseline. Secondary endpoints include change in sweat chloride and Cystic Fibrosis Questionnaire-Revised (CFQ-R).

Overall Safety Data: In the study, the triple combination regimen was generally well tolerated. The majority of adverse events were mild or moderate. The most common adverse events (> 10%), regardless of treatment group, were infective pulmonary exacerbation, cough, sputum increased and diarrhea. There was one discontinuation due to an adverse event in the triple combination treatment groups (elevated liver enzymes > 5x upper limit of normal in the VX-440 600mg group) and one in the control groups (respiration abnormal and sputum increased). One additional patient treated with the triple combination had elevated liver enzymes (> 8x upper limit of normal in the VX-440 600mg group), which were observed on the final day of dosing. In both patients, the elevated liver enzymes returned to normal after treatment discontinuation or completion.

4-Week Efficacy Data in *F508del*/Min Patients: Part 1 of the study evaluated the triple combination for four weeks in 47 patients who have one *F508del* mutation and one minimal function mutation (11 in placebo, 18 in VX-440 200mg and 18 in VX-440 600mg). A summary of the within-group lung function and sweat chloride data is provided below:

VX-440 in *F508del*/Min Patients		
Mean Absolute Within-Group Change From Baseline Through Day 29*	**Mean Absolute Within-Group Change in ppFEV$_1$ (percentage points)**	**Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)**
Triple placebo	+1.4 (p=0.4908)	+1.6 (p=0.6800)
VX-440 (200mg q12h) + tezacaftor (50mg q12h or 100mg QD) + ivacaftor (150mg q12h)	+10.0 (p < 0.0001)	-20.7 (p < 0.0001)
VX-440 (600mg q12h) + tezacaftor (50mg q12h) + ivacaftor (300mg q12h)	+12.0 (p < 0.0001)	-33.1 (p < 0.0001)

** all p-values are within group p-values based on mixed effect models; values expressed as 'Through Day 29' are the average of Day 15 and Day 29 measures*

A secondary endpoint in the study measured mean absolute change in the respiratory domain of CFQ-R, a validated patient-reported outcome tool, at Day 29. In this study, the mean absolute improvements for patients with a minimal function mutation who received the triple combination were 18.3 points (VX-440 200mg) and 20.7 points (VX-440 600mg). The improvement for those who received placebo was 2.2 points.

4-Week Efficacy Data in *F508del*/*F508del* Patients: Part 2 of the study is ongoing to evaluate the addition of VX-440 for four weeks in 26 patients who have two copies of the *F508del* mutation, who were already receiving the combination of

tezacaftor and ivacaftor (6 in placebo and 20 in VX-440 600mg). In this part of the study, all participants received four weeks of treatment with tezacaftor and ivacaftor and were then randomized to the addition of VX-440 or placebo for four additional weeks. A summary of the within-group lung function and sweat chloride data for the triple combination treatment period, from baseline (end of the 4-week tezacaftor/ivacaftor run-in period), is provided below:

VX-440 in *F508del*/*F508del* Patients		
Mean Absolute Within-Group Change From Baseline Through Day 29*	**Mean Absolute Within-Group Change in ppFEV$_1$ (percentage points)**	**Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)**
Placebo + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	-2.5 (p=0.2755)	+2.1 (p=0.7385)
VX-440 (600mg q12h) + tezacaftor (50mg q12h) + ivacaftor (300mg q12h)	+9.5 (p < 0.0001)	-31.3 (p < 0.0001)
** all p-values are within group p-values based on mixed effect models; values expressed as 'Through Day 29' are the average of Day 15 and Day 29 measures*		

The safety follow-up portion of the study in patients with two copies of the *F508del* mutation is ongoing.

About the VX-152 Phase 2 Study

This ongoing Phase 2 randomized, double-blind study is evaluating VX-152 (100mg, 200mg and 300mg q12h) in combination with tezacaftor and ivacaftor in people with CF ages 18 and older who have one *F508del* mutation and one minimal function mutation and in people who have two copies of the *F508del* mutation. The primary objective is safety and tolerability. Secondary endpoints include mean absolute change in ppFEV$_1$ and change in sweat chloride. Data reported today are from the 100mg and 200mg arms of the study in people who have one *F508del* mutation and one minimal function mutation and from the 200mg arm in people who have two copies of the *F508del* mutation.

Overall Safety Data: In the study, the triple combination regimen was generally well tolerated. The majority of adverse events were mild or moderate. The most common adverse events (> 10%), regardless of treatment group, were cough, sputum increased, infective pulmonary exacerbation, productive cough, diarrhea and fatigue. There was one discontinuation due to an adverse event in the triple combination treatment groups (pneumonia in the VX-152 200mg group) and none in the control groups.

2-Week Initial Efficacy Data in *F508del*/Min Patients: In Part 1 of the study, the triple combination was evaluated for two weeks in 21 patients ages 18 and older who have one *F508del* mutation and one minimal function mutation (5 in combined placebo, 6 in VX-152 100mg and 10 in VX-152 200mg). A summary of the initial within-group lung function and sweat chloride data (secondary endpoints) from the VX-152 100mg and 200mg dose groups is provided below:

VX-152 in *F508del*/Min Patients		
Observed Mean Absolute Within-Group Change from Baseline at Day 15*	**Observed Mean Absolute Within-Group Change in ppFEV$_1$ (percentage points)**	**Observed Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)**
Triple placebo	-0.9 (p=0.6245)	+1.0 (p=0.5659)
VX-152 (100mg q12h) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+5.6 (p=0.0135)	-19.6 (p=0.0004)
VX-152 (200mg q12h) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+9.7 (p=0.0017)	-14.1 (p=0.0219)
** p-values presented are within-group p-values based on 1 sample t-test; an efficacy analysis using mixed effect models will be conducted following completion of an additional cohort of patients currently being treated in the study*		

This part of the study is ongoing to evaluate the triple combination of VX-152 (300mg q12h), tezacaftor and ivacaftor in patients with one *F508del* mutation and one minimal function mutation. These data are expected later in 2017.

2-Week Initial Efficacy Data in *F508del*/*F508del* Patients: Part 2 of the study is ongoing to evaluate the addition of VX-152 for two weeks in 14 patients ages 18 and older who have two copies of the *F508del* mutation, who were already

receiving the combination of tezacaftor and ivacaftor (4 in placebo and 10 in VX-152 200mg). A summary of the initial within-group lung function and sweat chloride data (secondary endpoints) for the triple combination treatment period, from baseline (end of the 4-week tezacaftor/ivacaftor run-in period), is provided below:

VX-152 in *F508del/F508del* Patients		
Observed Mean Absolute Within-Group Change from Baseline at Day 15*	**Observed Mean Absolute Within-Group Change in ppFEV$_1$ (percentage points)**	**Observed Mean Absolute Within-Group Change in Sweat Chloride (mmol/L)**
Placebo + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	-1.4 (p=0.2773)	+3.4 (p=0.1212)
VX-152 (200mg q12h) + tezacaftor (100mg QD) + ivacaftor (150mg q12h)	+7.3 (p=0.0354)	-20.9 (p=0.0010)
** p-values presented are within-group p-values based on 1 sample t-test; an efficacy analysis using mixed effect models will be conducted following completion of an additional cohort of patients currently being treated in the study*		

This part of the study is ongoing to evaluate the addition of VX-152 (300mg q12h) for four weeks in patients with two *F508del* mutations, who are already receiving the combination of tezacaftor and ivacaftor. These data are expected in early 2018.

About the VX-659 Phase 1 Study

This Phase 1 randomized, double-blind, placebo-controlled study evaluated the safety and tolerability of single and multiple ascending doses of VX-659 alone and in triple combination with tezacaftor and ivacaftor in healthy volunteers. It also evaluated the safety and tolerability of VX-659 as part of a triple combination for two weeks in 12 people with CF ages 18 and older who have one *F508del* mutation and one minimal function mutation (3 in placebo and 9 in VX-659 120mg). In this part of the study, sweat chloride was evaluated as an additional endpoint, and the absolute change in ppFEV$_1$ was evaluated as part of the safety analysis.

In CF patients, VX-659 was generally well tolerated in triple combination with tezacaftor and ivacaftor. The majority of adverse events were mild or moderate. The most common adverse events (> 10%), regardless of treatment group, were cough, infective pulmonary exacerbation and productive cough. There were no discontinuations due to adverse events in either group.

At Day 15, there was a mean absolute improvement in ppFEV$_1$ of +9.6 percentage points from baseline in those receiving the triple combination regimen of VX-659 (120mg q12h), tezacaftor and ivacaftor and a mean decrease in sweat chloride of -41.6 mmol/L. For those receiving placebo, there was a mean absolute decrease in ppFEV$_1$ of -0.4 percentage points and a mean decrease in sweat chloride of -11.0 mmol/L.

Preclinical Toxicology Data

In the Phase 2 study of VX-440, women of childbearing potential were required to use pre-specified, non-hormonal methods of contraception based on results from previous preclinical reproductive toxicology studies. Preclinical reproductive toxicology studies of VX-152, VX-659 and VX-445 are complete with no adverse findings of note.

About CF

CF is a rare, life-shortening genetic disease affecting approximately 75,000 people in North America, Europe and Australia.

CF is caused by a defective or missing CFTR protein resulting from mutations in the CFTR gene. Children must inherit two defective *CFTR* genes — one from each parent — to have CF. There are approximately 2,000 known mutations in the *CFTR* gene. Some of these mutations, which can be determined by a genetic test, or genotyping test, lead to CF by creating non-working or too few CFTR proteins at the cell surface. The defective function or absence of CFTR protein results in poor flow of salt and water into and out of the cell in a number of organs. In the lungs, this leads to the buildup of abnormally thick, sticky mucus that can cause chronic lung infections and progressive lung damage in many patients that eventually leads to death. The median age of death is in the mid-to-late 20s.

About Vertex

Vertex is a global biotechnology company that aims to discover, develop and commercialize innovative medicines so people with serious diseases can lead better lives. In addition to our clinical development programs focused on cystic fibrosis, Vertex has more than a dozen ongoing research programs aimed at other serious and life-threatening diseases.

Founded in 1989 in Cambridge, Mass., Vertex today has research and development sites and commercial offices in the United States, Europe, Canada and Australia. For seven years in a row, *Science* magazine has named Vertex one of its Top Employers in the life sciences. For additional information and the latest updates from the company, please visit www.vrtx.com.

Collaborative History with Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT)

Vertex initiated its CF research program in 2000 as part of a collaboration with CFFT, the nonprofit drug discovery and development affiliate of the Cystic Fibrosis Foundation. KALYDECO® (ivacaftor), ORKAMBI® (lumacaftor/ivacaftor), tezacaftor, VX-440, VX-152, VX-659 and VX-445 were discovered by Vertex as part of this collaboration.

Special Note Regarding Forward-looking Statements

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, including, without limitation, Dr. Chodakewitz's statements in the third paragraph, and the information provided regarding Vertex's plans to initiate pivotal development of one or more triple combination regimens in the first half of 2018. While Vertex believes the forward-looking statements contained in this press release are accurate, these forward-looking statements represent the company's beliefs only as of the date of this press release, and there are a number of factors that could cause actual events or results to differ materially from those indicated by such forward-looking statements. Those risks and uncertainties include, among other things, (i) that Vertex could experience unforeseen delays in conducting its development programs relating to triple combination treatments and in submitting related regulatory filings, (ii) that the initial results set forth in this press release may differ from the final results from these ongoing studies, (iii) that regulatory authorities may not approve, or approve on a timely basis, triple combination treatments due to safety, efficacy or other reasons, and (iv) and other risks listed under Risk Factors in Vertex's annual report and quarterly reports filed with the Securities and Exchange Commission and available through the company's website at www.vrtx.com. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

(VRTX-GEN)

Conference Call and Webcast

The company will host a conference call and webcast today at 5:00 p.m. EDT to discuss these results. To access the call, please dial (866) 501-1537 (U.S.) or +1 (720) 545-0001 (International). The conference call will be webcast live, and a link to the webcast may be accessed through Vertex's website at www.vrtx.com in the "Investors" section under "Events and Presentations." To ensure a timely connection, it is recommended that users register at least 10 minutes prior to the scheduled webcast. An archived webcast will be available on the company's website.

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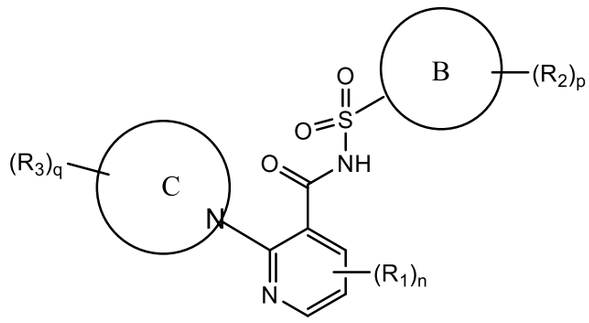
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CAPÍTULO REIVINDICATORIO MODIFICADO

(Primer Examen de Fondo)

1. Un compuesto de Fórmula Ib-iii:



Ib-iii

o una de sus sales farmacéuticamente aceptables, en donde:

Anillo B es un anillo arilo C_6-C_{10} o anillo heteroarilo o heterocíclico C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR;

Anillo C es un anillo heteroarilo o heterocíclico C_3-C_{14}, en donde cualquiera de 1 a 4 átomos del anillo son independientemente N, O o S y, en donde un nitrógeno en el Anillo C es el punto de unión con el anillo piridina;

y en donde, independientemente para cada aparición:

R_1 es halo; CN; F_5S; SiR_3; OH; NRR; alquilo o fluoroalquilo C_1-C_6; alcoxi o fluoroalcoxi C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; (alquilen C_1-C_9)-R_4, en donde hasta cuatro unidades de CH_2 son reemplazadas independientemente con O, CO, S, SO, SO_2 o NR; arilo C_6-C_{10}; anillo heteroarilo o heterocíclico C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR; o cicloalquilo C_3-C_{10};

R_2 es halo; OH; NRR; azida; CN; CO_2R; alquilo o fluoroalquilo C_1-C_6; alcoxi o fluoroalcoxi C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; arilo C_6-C_{10}; anillo heteroarilo o heterocíclico C_3-C_{13}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente, O, S, N o NR; cicloalquilo C_3-C_{10}; o un (alquilen C_1-C_9)-R_4, en donde hasta cuatro unidades de CH_2 son reemplazadas independientemente con O, CO, S, SO, SO_2 o NR; o dos grupos R_2 juntos pueden formar un grupo $=CH_2$ u =O;

R_3 es halo; CN; CO_2R; alquilo o fluoroalquilo C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; alcoxi o fluoroalcoxi C_1-C_6; o arilo C_6-C_{10}; anillo heteroarilo o heterocíclico C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR; cicloalquilo C_3-C_{10}; o un (alquilen C_1-C_9)-R_4, en donde hasta cuatro unidades de CH_2 son reemplazadas independientemente con O, CO, S, SO, SO_2 o NR; o dos grupos R_3 juntos pueden formar un grupo $=CH_2$ u =O;

R_4 es H; azida; CF_3; CHF_2; OR; CCH; CO_2R; OH; arilo C_6-C_{10}, heteroarilo o heterocicloalquilo C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR; cicloalquilo C_3-C_{10}; NRR, NRCOR, CONRR, CN, halo o SO_2R;

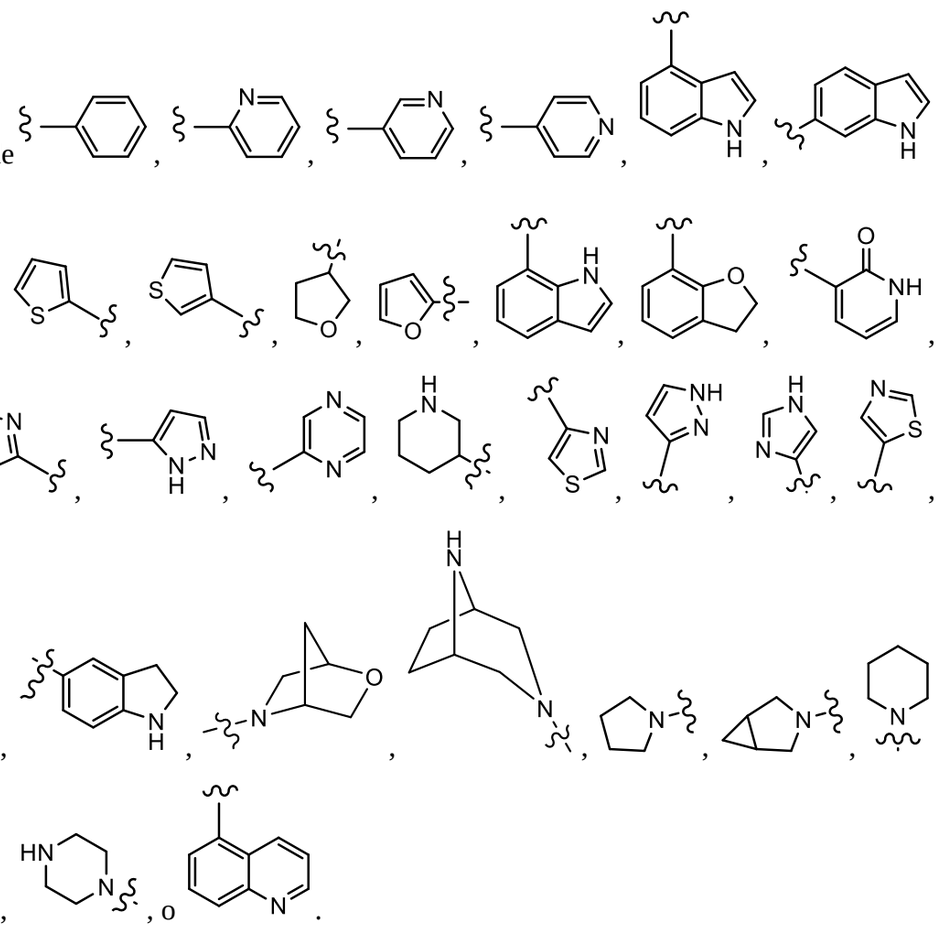
R es independiente, H; OH; CO_2H; CO_2alquilo C_1-C_6; alquilo C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; arilo C_6-C_{10}; heteroarilo o heterocicloalquilo C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR; o cicloalquilo C_3-C_{10};

n es 0, 1, 2 o 3;

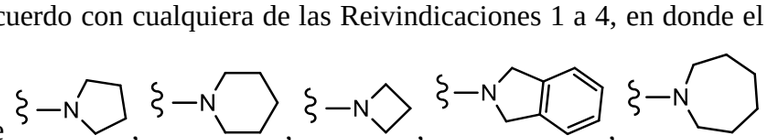
p es 0, 1, 2 o 3; y

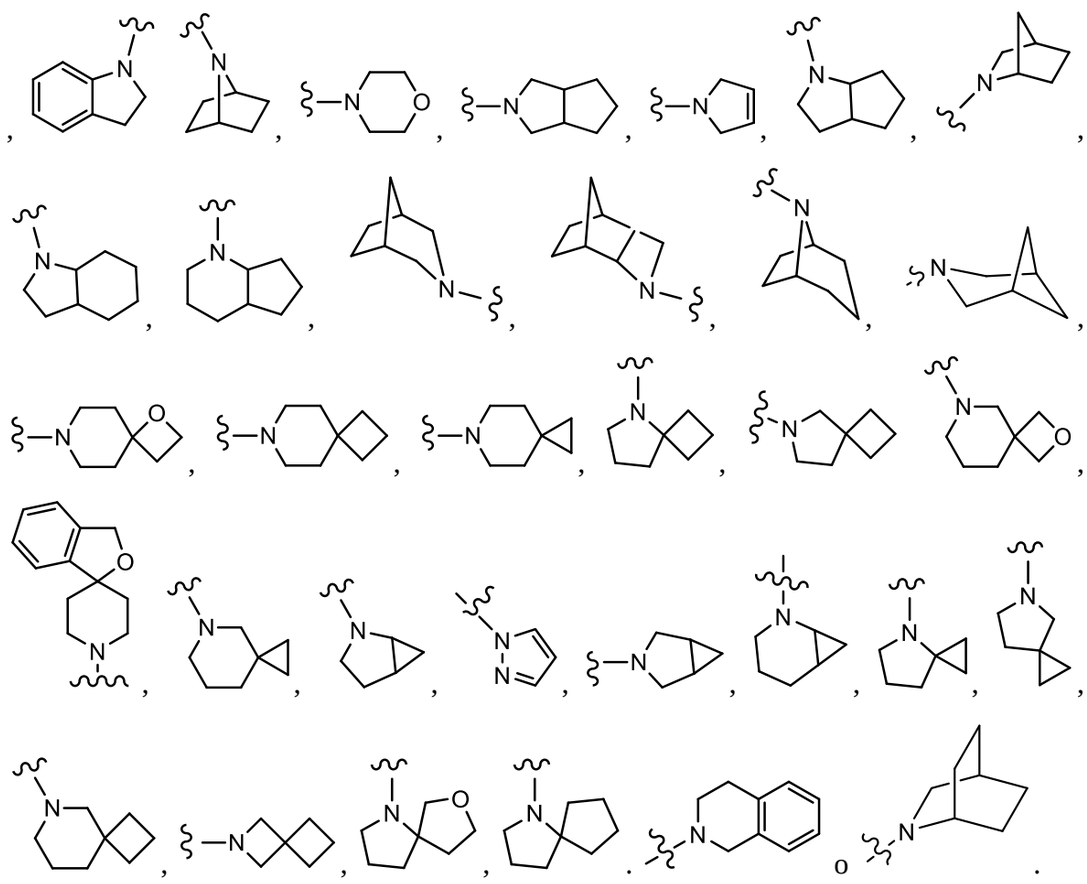
q es 0, 1, 2, 3, 4 o 5.

2. El compuesto de acuerdo con la Reivindicación 1, en donde el anillo B es fenilo, piridilo, piridin-2(1*H*)-ona, pirazol, indol, aza-indol, tiofeno, dihidrobenzofurano o quinolina.

3. El compuesto de acuerdo con la Reivindicación 1 o 2, en donde el anillo B se selecciona de  , o .

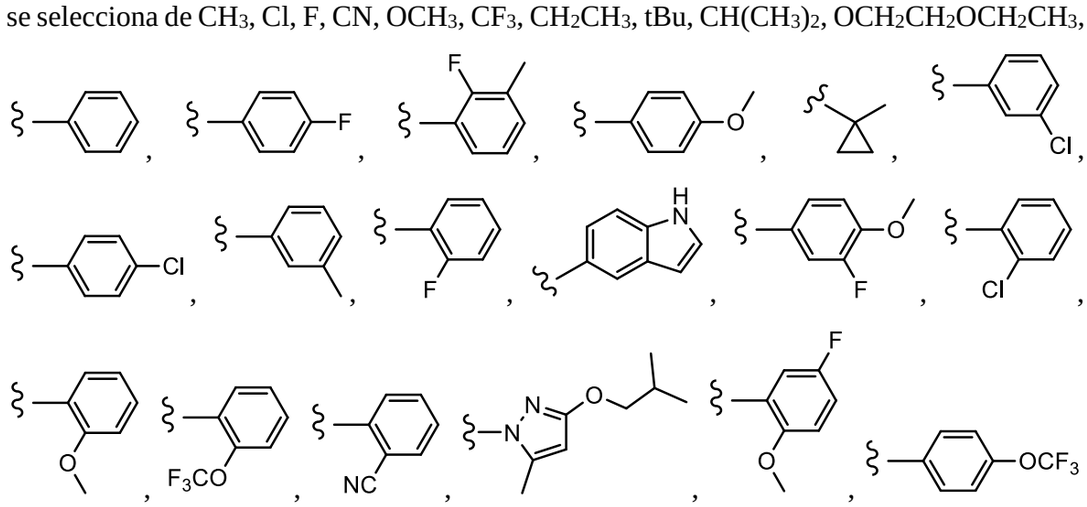
4. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 3, en donde el anillo C se selecciona entre indol, piperidina, azepano, azetadina, indolina, isoindolina o pirrolidina.

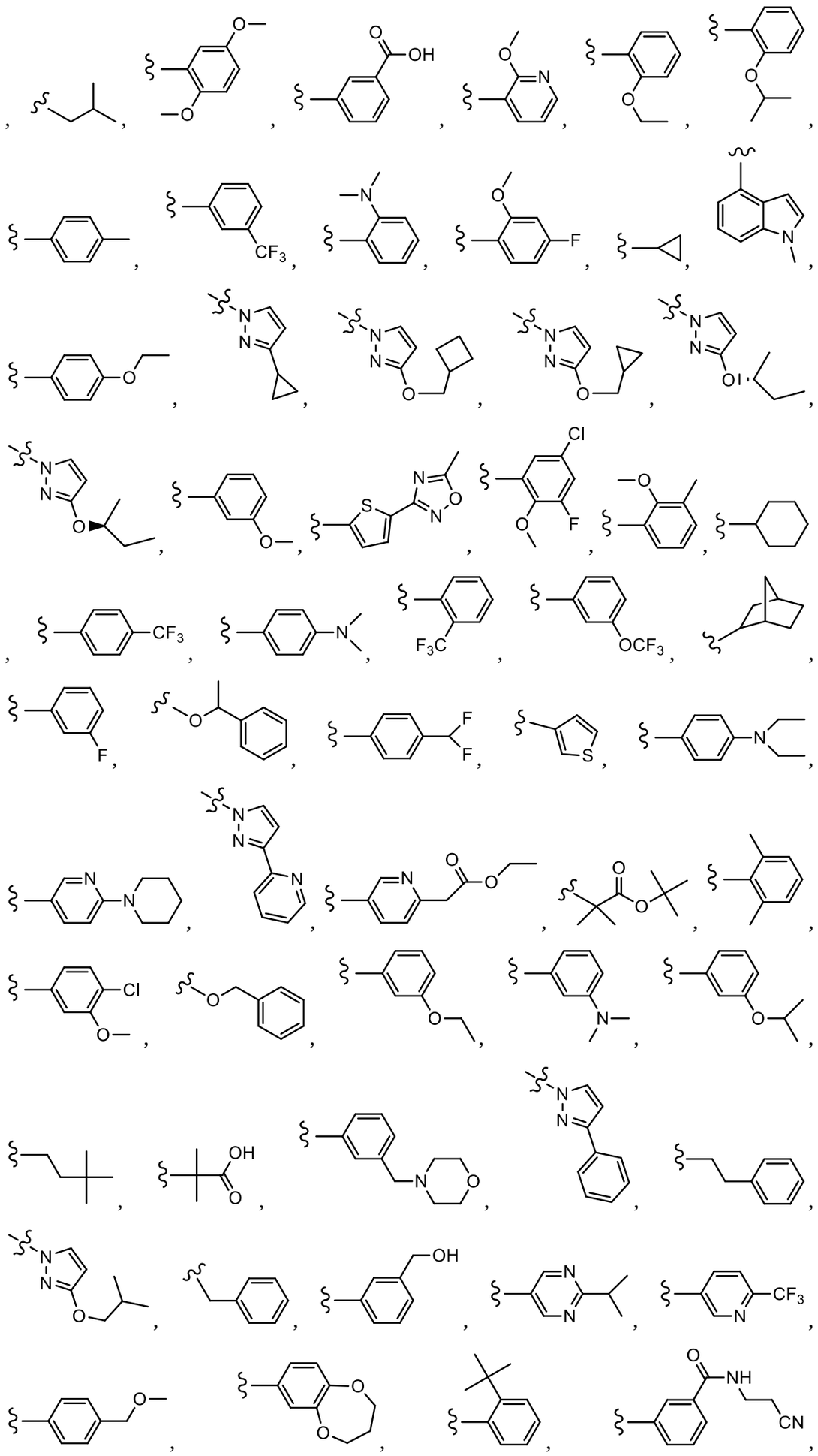
5. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 4, en donde el anillo C se selecciona entre  ,

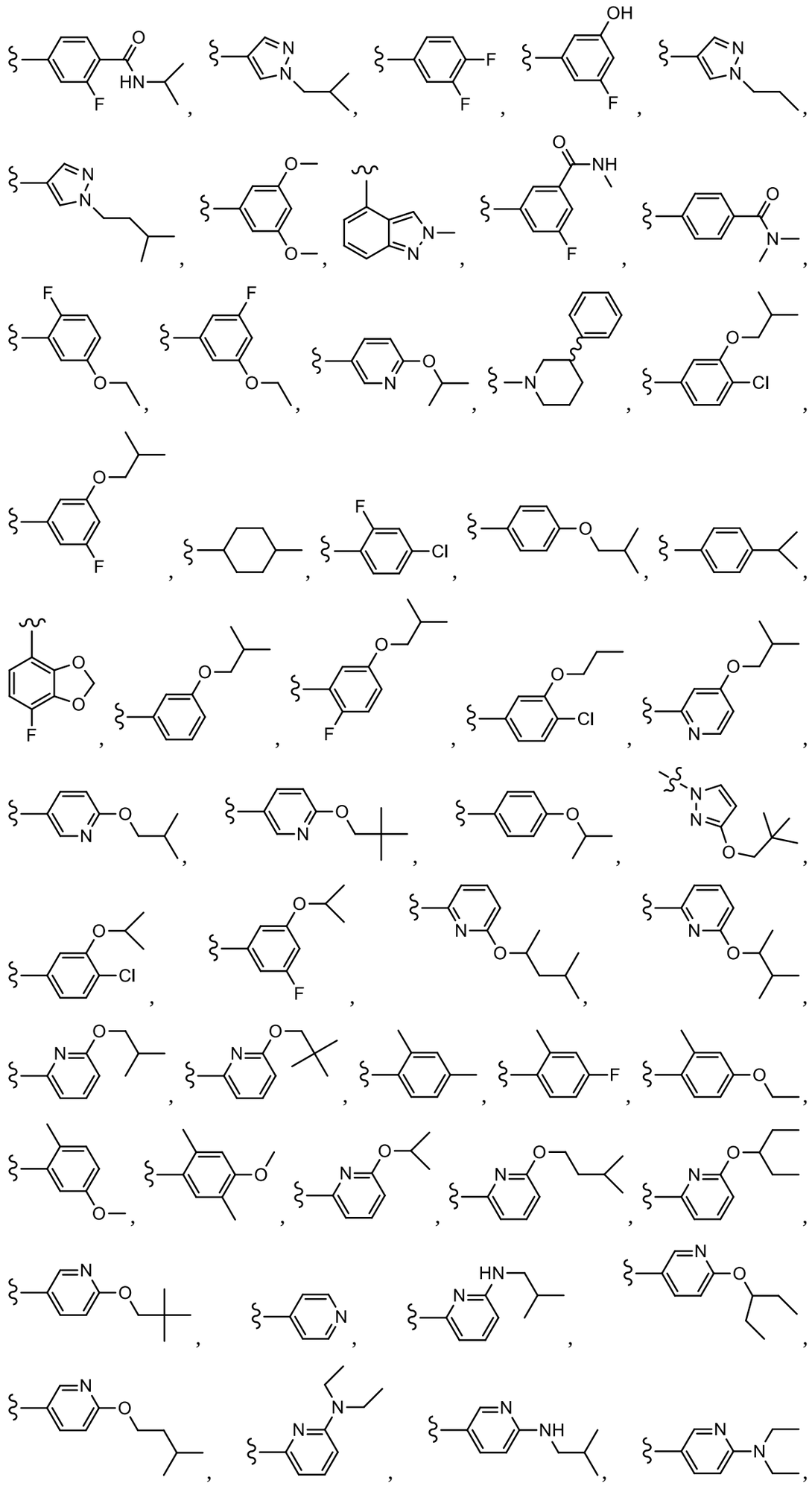


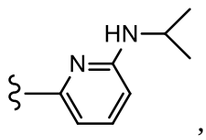
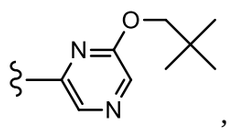
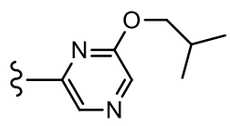
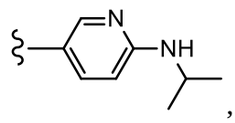
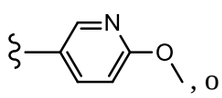
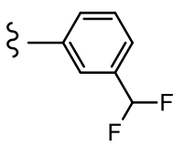
6. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 5, en donde R_1 es halo, CN, alquilo C_1-C_6, alcoxi C_1-C_6, cicloalquilo C_3-C_8 o un anillo fenilo, piridilo, pirimidina, indol, aza-indol, pirazol o tiofeno, o un (alquilen C_1-C_9)-R_4 en donde hasta cuatro unidades de CH_2 son reemplazadas independientemente con O, CO, S, SO, SO_2 o NR, en donde todos los anillos están opcionalmente sustituidos con uno o más grupos seleccionados de halo, alquilo C_1-C_6, alcoxi C_1-C_6, fluoroalquilo C_1-C_6, fluoroalcoxi C_1-C_6, OH, CH_2OH, CH_2OCH_3, CN, CO_2H, amino, amido, heteroarilo C_3-C_{10} y heterocicloalquilo C_3-C_{10}.

7. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 6, en donde R_1 se selecciona de CH_3, Cl, F, CN, OCH_3, CF_3, CH_2CH_3, tBu, $CH(CH_3)_2$, $OCH_2CH_2OCH_2CH_3$,

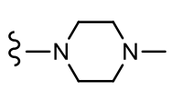
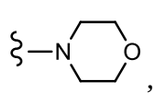
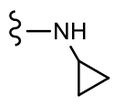
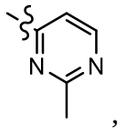
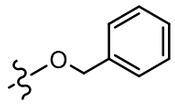
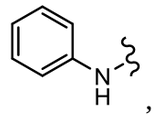
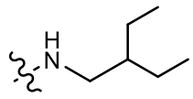
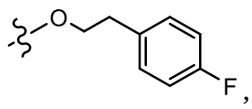
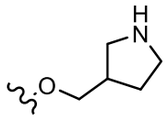
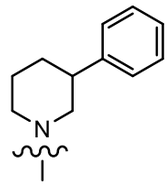
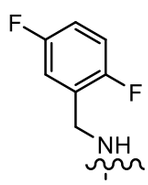
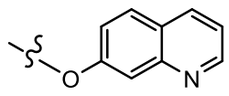
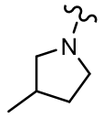
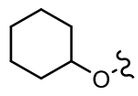
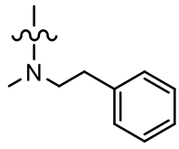
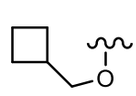
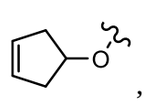
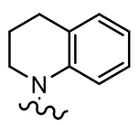
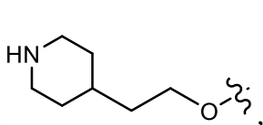
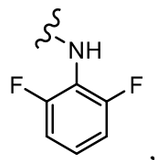
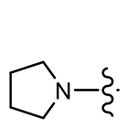
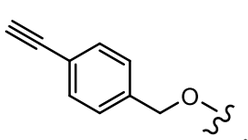
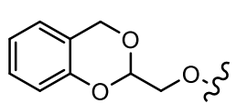
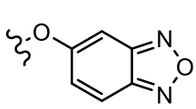
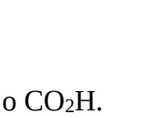






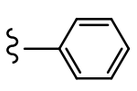
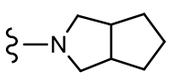
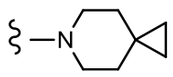
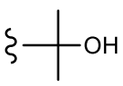
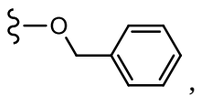
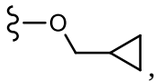
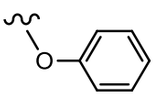
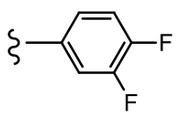
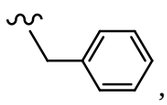
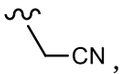
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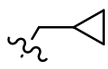
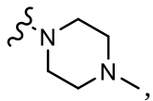
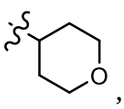
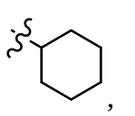
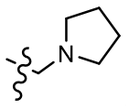
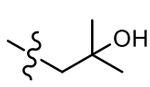
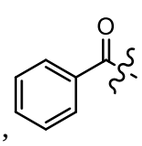
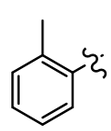
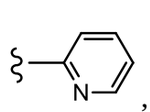
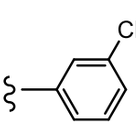
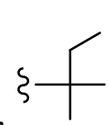
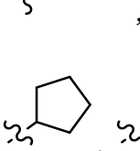
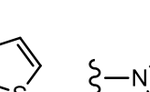
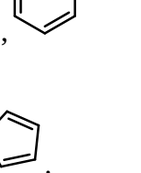
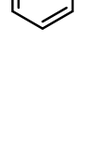
8. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 7, en donde R_2 se selecciona de halo, OH, CN, azida, amino, alquilo o fluoroalquilo C_1-C_6, alcoxi o fluoroalcoxi C_1-C_6, heterocíclico C_3-C_{10}, en donde hasta 4 átomos del anillo son independientemente O, S, N o NR; o un (alquileno C_1-C_9)-R_4, en donde hasta cuatro unidades de CH_2 son reemplazadas independientemente con O, CO, S, SO, SO_2 o NR.

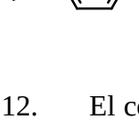
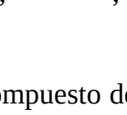
9. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 8, en donde R_2 se selecciona de Cl, F, OH, CN, N_3, NH_2, $NH(CH_3)$, $N(CH_3)_2$, $N(CH_3)CH_2CH_2CH_3$, $N(CH_3)CH_2CH_2CH_2CH_3$, CH_3, CH_2OH, CH_2CH_3, $CH_2CH_2CH_3$, =O, CH_3SO_2, CH_3SO_2NH, CF_3CONH, CH_3CONH, $CH_3CON(CH_3)$, tBuOCONH, $(CH_3)_2CHOCONH$, $CH(CH_3)_2$, CHF_2, OCH_3, OCH_2CH_3, $OCH_2CH_2CH_3$, $OCH_2CH_2CH(CH_3)_2$, OCF_3, $OCHF_2$, $OC(CH_3)_3$, OCH_2CH_2tBu, $NHCH(CH_3)(CH_2CH_2CH_3)$, $OCH(CH_3)_2$, $NH(CH_2)_2O(CH_2)_2CH_3$, $C(O)CH_3$, CH_2CH_2OH, CH_2NH_2, $NH(CH_2)_2OH$, $N(CH_3)CH_2CH_2CH_2OCH_3$, $NHCH_2CH_2COOH$, $NH(CH_2)_2N(CH_3)_2$, $NH(CH_2)_2NH_2$, $NH(CH_2)_3NH_2$, $NH(CH_2)_2OCH_3$, $NHCH(CH_3)_2$,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  ,  , o CO_2H.

10. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 9, en donde R_3 se selecciona de halo, CN, alquilo o fluoroalquilo C_1-C_6, alcoxi C_1-C_6 o heteroarilo C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR.

11. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 10, en donde R_3 se selecciona de Cl, I, deuterio, F, CN, CH_3, OH, OCH_3, CF_3, CH_2CH_3, CH_2CF_3, $CH_2CH_2CH_3$, $OCH_2CH(CH_3)_2$, $OCH(CH_3)_2$, CO_2H, CO_2NH_2, OCH_2CH_3, CH_2OCH_3, $CH(CH_3)_2$, CCH, CH_2CONH_2, CO_2CH_3, $-CH_2N(CH_3)_2$, CO_2tBu, tBu, $=CH_2$, =O,


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12. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 11, en donde n es 0.

13. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 11, en donde n es 1.

14. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 11, en donde n es 2.

15. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 14, en donde p es 0.

16. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 14, en donde p es 1.

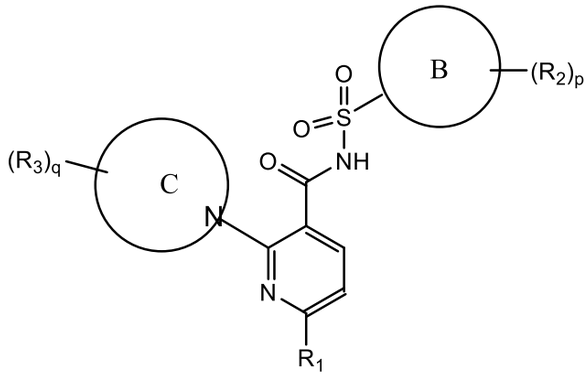
17. El compuesto de acuerdo con cualquiera de las Reivindicaciones 1 a 14, en donde p es 2.

18. El compuesto de acuerdo con la Reivindicación 1, en donde R_1 es fenilo, piridina o pirazol, y n es 1.

19. El compuesto de acuerdo con la Reivindicación 1, en donde R_1 es fenilo, piridina o pirazol, n es 1, R_2 es amino o alquilo y p es 0 o 1.

20. El compuesto de acuerdo con la Reivindicación 1, en donde R_1 es fenilo, piridina o pirazol, n es 1, R_3 es alquilo y q es 1, 2, 3 o 4.

21. Un compuesto de Fórmula Ib-iv:



Ib-iv

o una de sus sales farmacéuticamente aceptables, en donde, independientemente para cada aparición:

Anillo B es un anillo arilo C_6-C_{10} o anillo heteroarilo o heterocíclico C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR;

Anillo C es un anillo heteroarilo o heterocíclico C_3-C_{14}, en donde cualquiera de 1 a 4 átomos del anillo son independientemente N, O o S y, en donde un nitrógeno en el Anillo C es el punto de unión con el anillo piridina;

R_1 es arilo C_6-C_{10} o heteroarilo C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR;

R_2 es halo; OH; NRR; azida; CN; CO_2R; alquilo o fluoroalquilo C_1-C_6; alcoxi o fluoroalcoxi C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; arilo C_6-C_{10}; anillo heteroarilo o heterocíclico C_3-C_{13}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR; cicloalquilo C_3-C_{10}; o un (alquilen C_1-C_9)-R_4, en donde hasta cuatro unidades de CH_2 son reemplazadas independientemente con O, CO, S, SO, SO_2 o NR; o dos grupos R_2 juntos pueden formar un grupo $=CH_2$ u =O;

R_3 es halo; CN; CO_2R; alquilo o fluoroalquilo C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; alcoxi o fluoroalcoxi C_1-C_6; o arilo C_6-C_{10}; anillo heteroarilo o heterocíclico C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente, O, S, N o NR; cicloalquilo C_3-C_{10}; o un (alquilen C_1-C_9)-R_4, en donde hasta cuatro unidades de CH_2 son reemplazadas independientemente con O, CO, S, SO, SO_2 o NR; o dos grupos R_3 juntos pueden formar un grupo $=CH_2$ u =O;

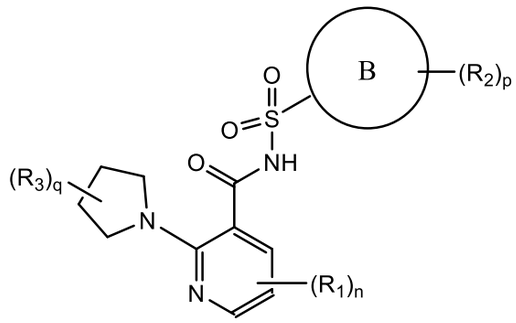
R_4 es H; azida; CF_3; CHF_2; OR; CCH; CO_2R; OH; arilo C_6-C_{10}, heteroarilo o heterocicloalquilo C_3-C_{10} o, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR; cicloalquilo C_3-C_{10}; NRR, NRCOR, CONRR, CN, halo o SO_2R;

R es independientemente H; OH; CO_2H; CO_2alquilo C_1-C_6; alquilo C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; arilo C_6-C_{10}; heteroarilo o heterocicloalquilo C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR; o cicloalquilo C_3-C_{10};

p es 0, 1, 2 o 3; y

q es 0, 1, 2, 3, 4 o 5.

22. Un compuesto de Fórmula Ib-v:



Ib-v

o una de sus sales farmacéuticamente aceptables, en donde, independientemente para cada aparición:

Anillo B es un anillo arilo C_6-C_{10} o anillo heteroarilo o heterocíclico C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR;

R_1 es halo; CN; F_5S; SiR^3; OH; NRR; alquilo o fluoroalquilo C_1-C_6; alcoxi o fluoroalcoxi C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; (alquilen C_1-C_9)-R^4, en donde hasta cuatro unidades de CH_2 son reemplazadas independientemente con O, CO, S, SO, SO_2 o NR; arilo C_6-C_{10}; anillo heteroarilo o heterocíclico C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR; o cicloalquilo C_3-C_{10};

R_2 es halo; OH; NRR; azida; CN; CO_2R; alquilo o fluoroalquilo C_1-C_6; alcoxi o fluoroalcoxi C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; arilo C_6-C_{10}; anillo heteroarilo o heterocíclico C_3-C_{12}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR; cicloalquilo C_3-C_{10}; o un (alquilen C_1-C_9)-R^4, en donde hasta cuatro unidades de CH_2 son reemplazadas independientemente con O, CO, S, SO, SO_2 o NR; o dos grupos R_2 juntos pueden formar un grupo $=CH_2$ u =O;

R_3 es halo; CN; CO_2R; alquilo o fluoroalquilo C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; alcoxi o fluoroalcoxi C_1-C_6; o arilo C_6-C_{10}; anillo heteroarilo o heterocíclico C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR; cicloalquilo C_3-C_{10}; o un (alquilen C_1-C_9)-R^4, en donde hasta cuatro unidades de CH_2 son reemplazadas independientemente con O, CO, S, SO, SO_2 o NR; o dos R_3 juntos pueden formar un grupo $=CH_2$ u =O;

R_4 es H; azida; CF_3; CHF_2; OR; CCH; CO_2R; OH; arilo C_6-C_{10}, heteroarilo o heterocicloalquilo C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR; cicloalquilo C_3-C_{10}; NRR, NRCOR, CONRR, CN, halo o SO_2R;

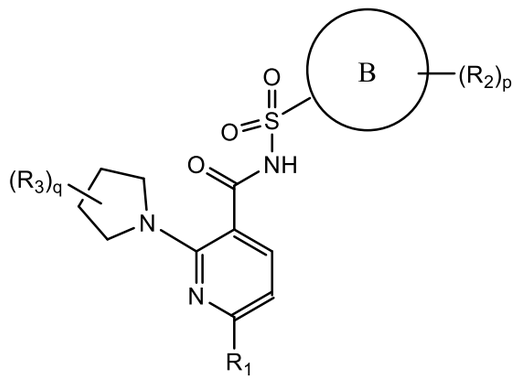
R es independientemente H; OH; CO_2H; CO_2alquilo C_1-C_6; alquilo C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; arilo C_6-C_{10}; heteroarilo o heterocicloalquilo C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR; o cicloalquilo C_3-C_{10};

n es 0, 1, 2 o 3;

p es 0, 1, 2 o 3; y

q es 0, 1, 2, 3, 4 o 5.

23. Un compuesto de Fórmula Ib-vi:



Ib-vi

o una de sus sales farmacéuticamente aceptables, en donde independientemente para cada aparición:

Anillo B es un anillo arilo C_6-C_{10} o anillo heteroarilo o heterocíclico C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR;

R_1 es arilo C_6-C_{10} o heteroarilo C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR;

R_2 es halo; OH; NRR; azida; CN; CO_2R; alquilo o fluoroalquilo C_1-C_6; alcoxi o fluoroalcoxi C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; arilo C_6-C_{10}; anillo heteroarilo o heterocíclico C_3-C_{13}, en donde cualquiera de 1 a 4 átomos de anillo son independiente O, S, N o NR; cicloalquilo C_3-C_{10}; o un (alquilen C_1-C_9)-R_4, en donde hasta cuatro unidades de CH_2 son reemplazadas independientemente con O, CO, S, SO, SO_2 o NR; o dos grupos R_2 juntos pueden formar un grupo $=CH_2$ u =O;

R_3 es halo; CN; CO_2R; alquilo o fluoroalquilo C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; alcoxi o fluoroalcoxi C_1-C_6; o arilo C_6-C_{10}; anillo heteroarilo o heterocíclico C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR; cicloalquilo C_3-C_{10}; o un (alquilen C_1-C_9)-R_4, en donde hasta cuatro unidades de CH_2 son reemplazadas independiente con O, CO, S, SO, SO_2 o NR; o dos grupos R_3 juntos pueden formar un grupo $=CH_2$ u =O;

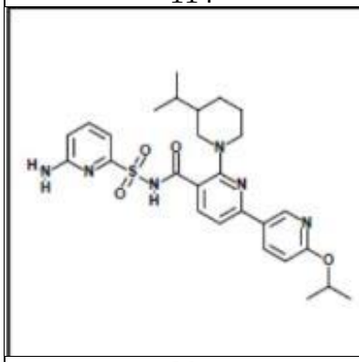
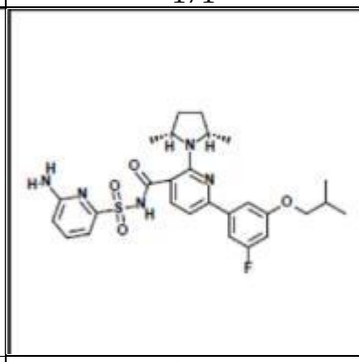
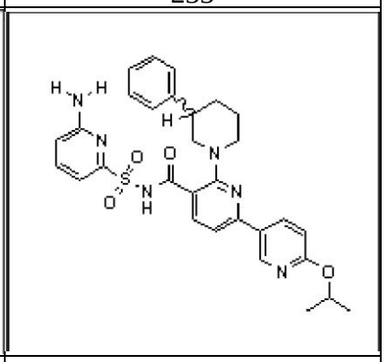
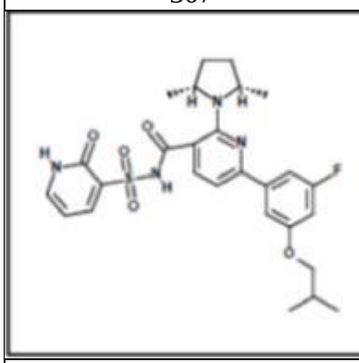
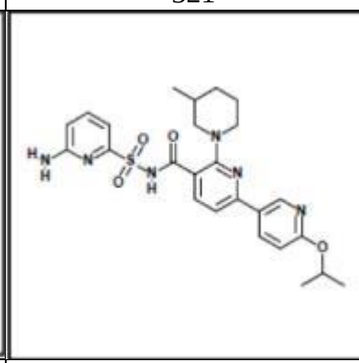
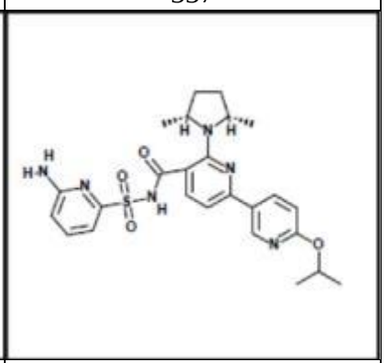
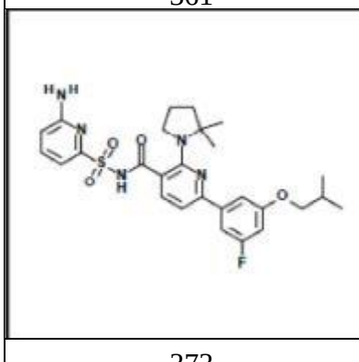
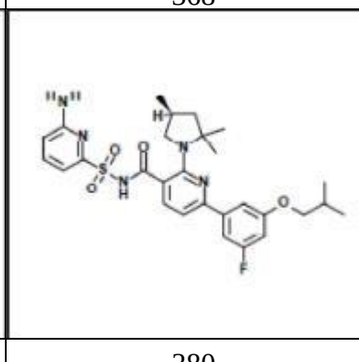
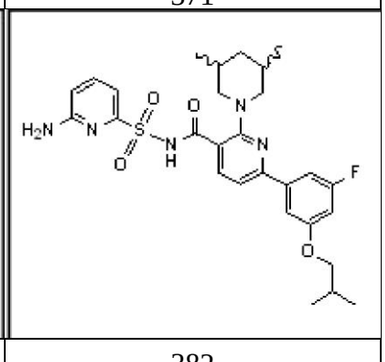
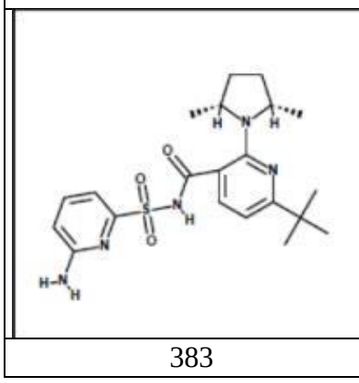
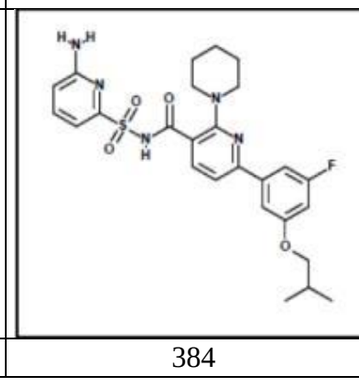
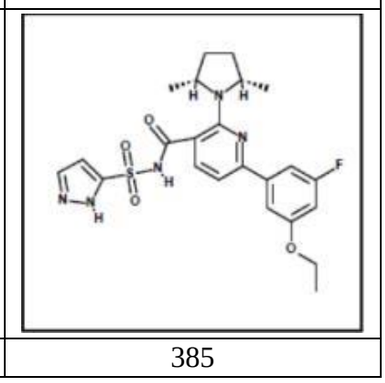
R_4 es H; azida; CF_3; CHF_2; OR; CCH; CO_2R; OH; arilo C_6-C_{10}, heteroarilo o heterocicloalquilo C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente, O, S, N o NR; cicloalquilo C_3-C_{10}; NRR, NRCOR, CONRR, CN, halo o SO_2R;

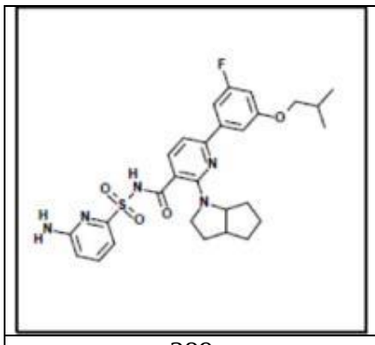
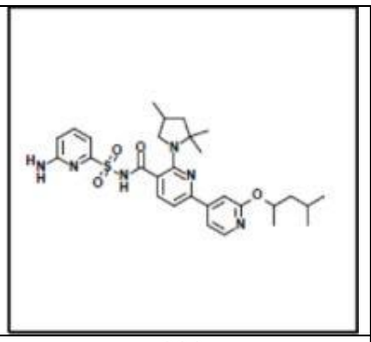
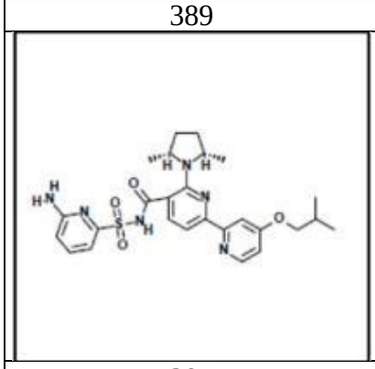
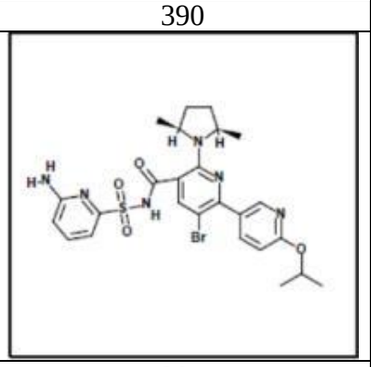
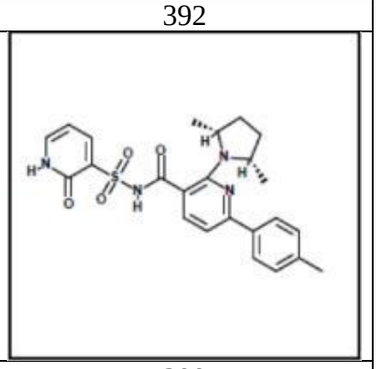
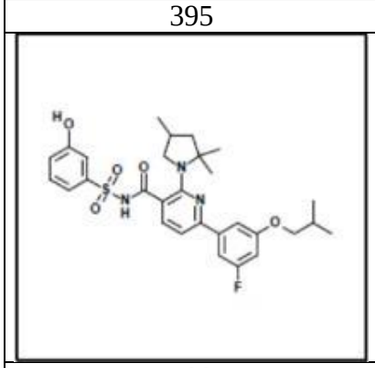
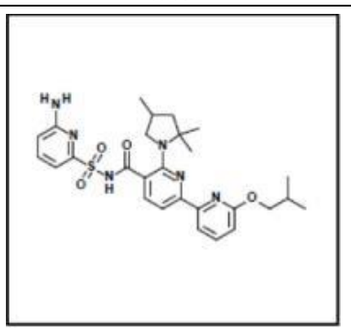
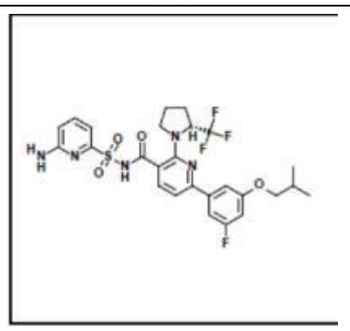
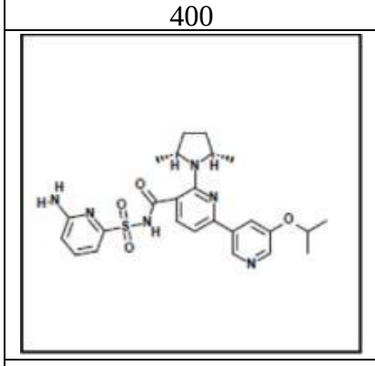
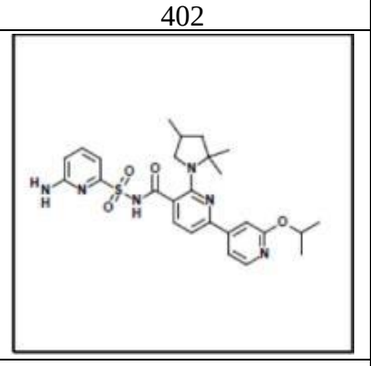
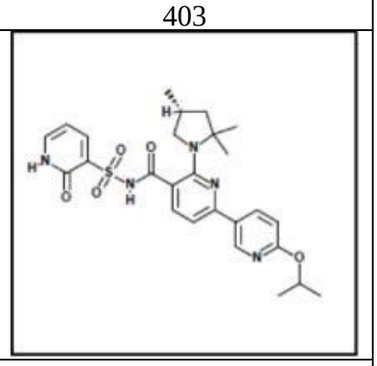
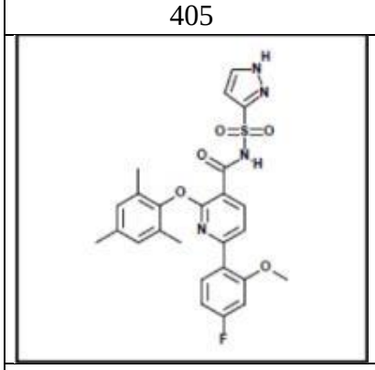
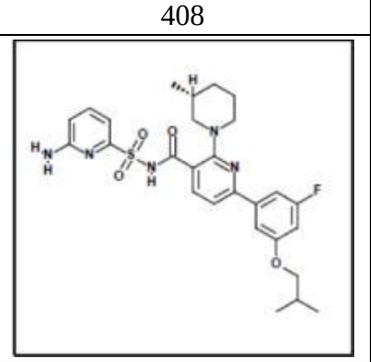
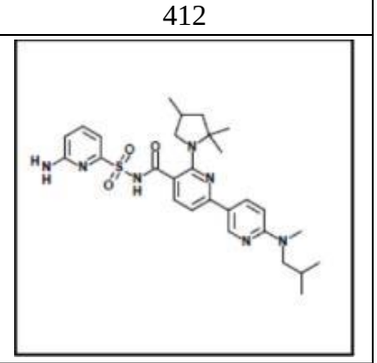
R es independientemente H; OH; CO_2H; CO_2alquilo C_1-C_6; alquilo C_1-C_6; alquenilo C_1-C_6; alquinilo C_1-C_6; arilo C_6-C_{10}; heteroarilo o heterocicloalquilo C_3-C_{10}, en donde cualquiera de 1 a 4 átomos de anillo son independientemente, O, S, N o NR; o cicloalquilo C_3-C_{10};

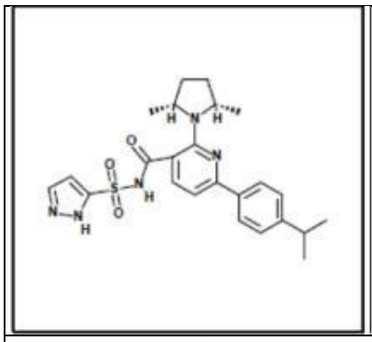
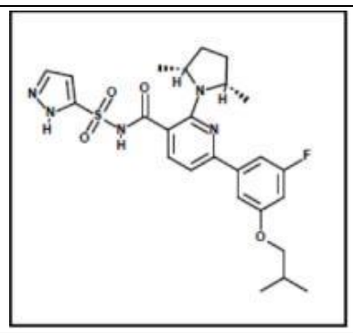
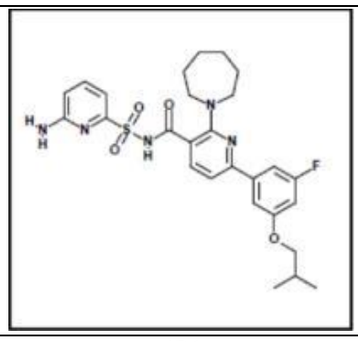
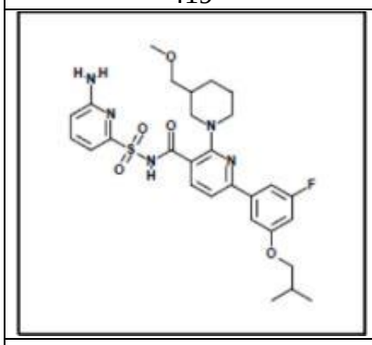
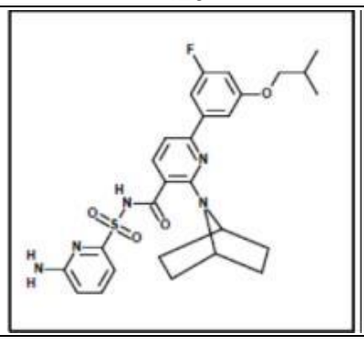
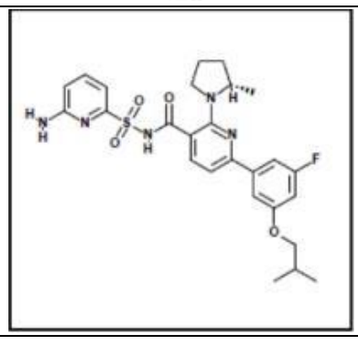
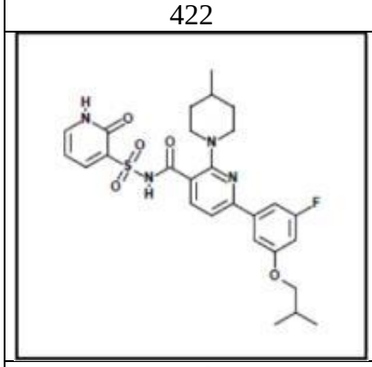
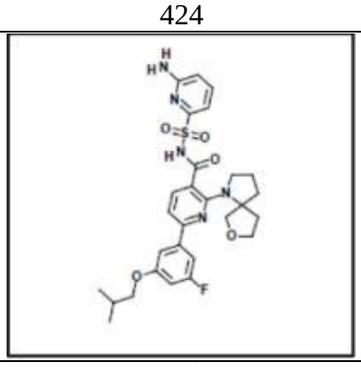
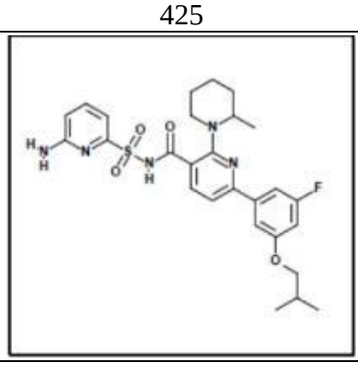
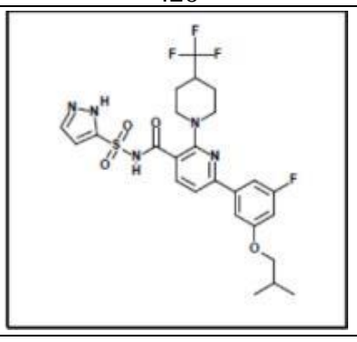
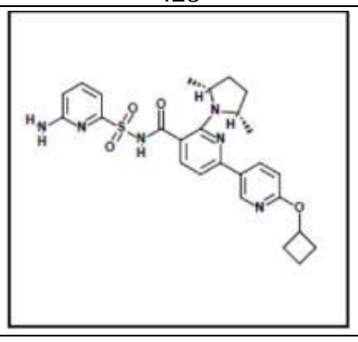
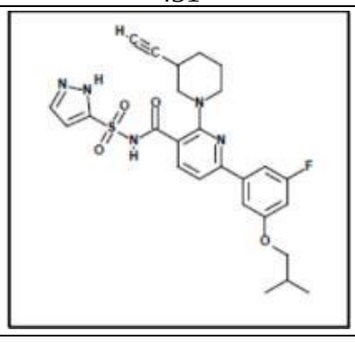
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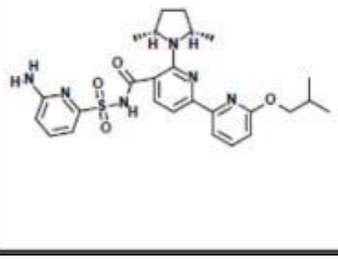
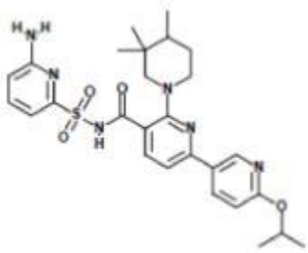
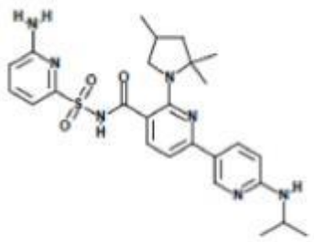
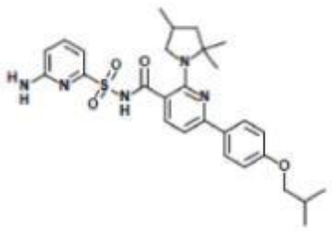
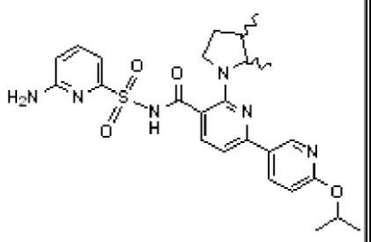
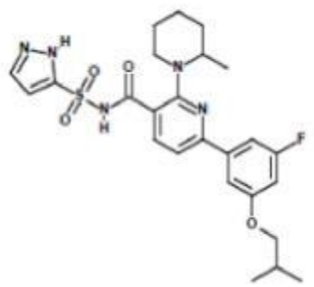
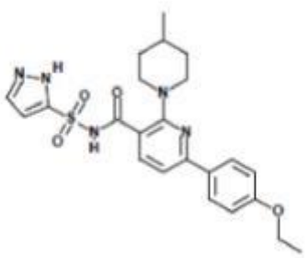
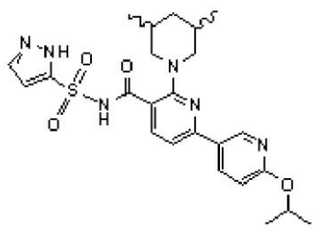
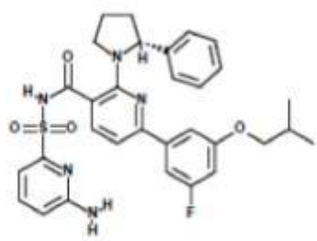
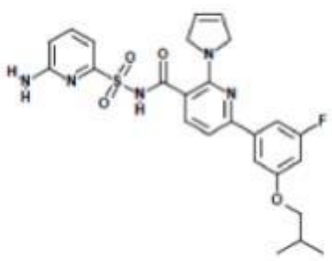
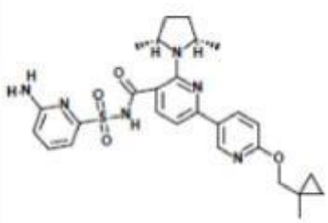
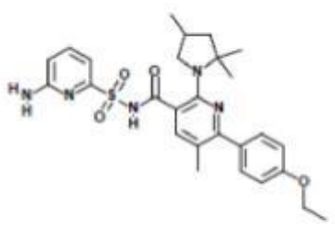
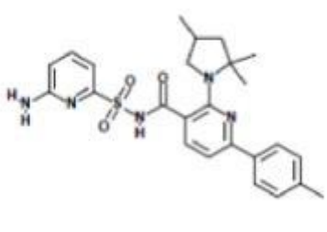
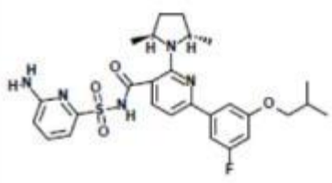
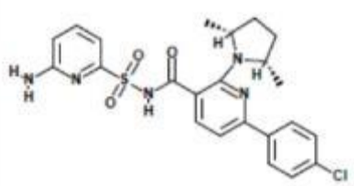
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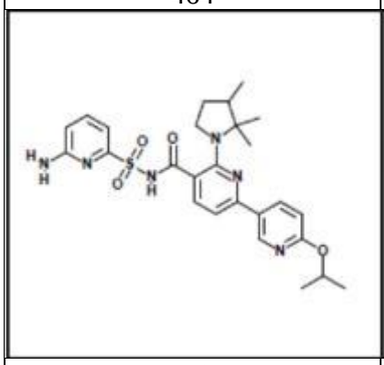
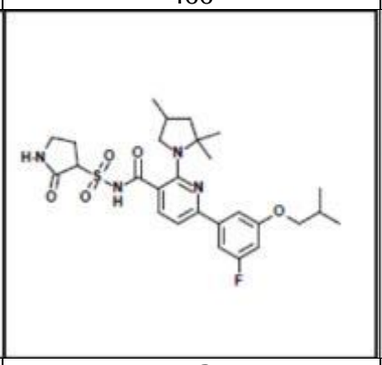
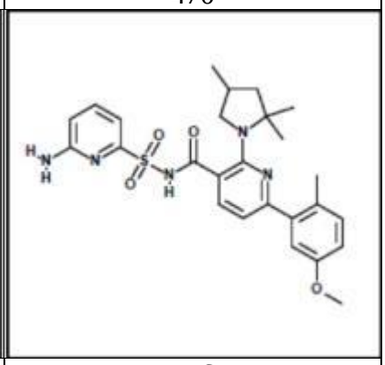
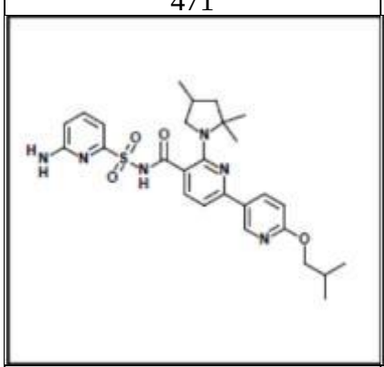
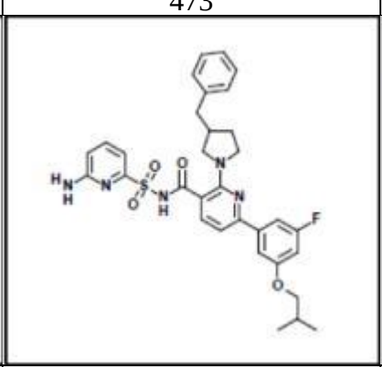
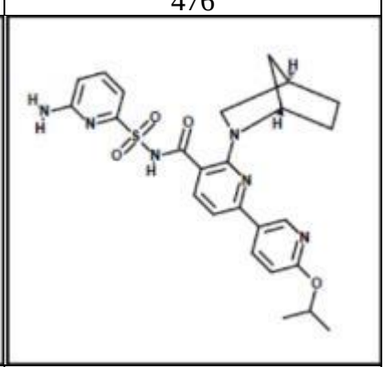
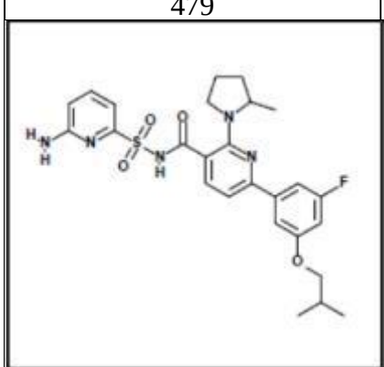
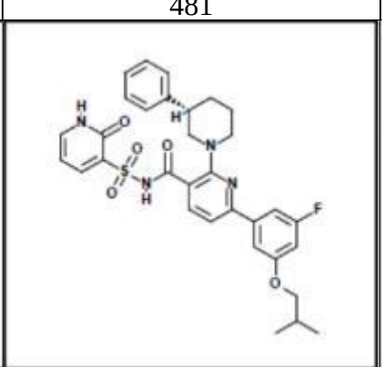
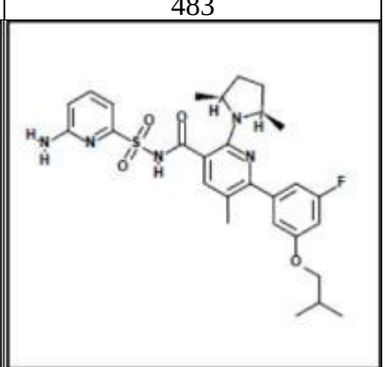
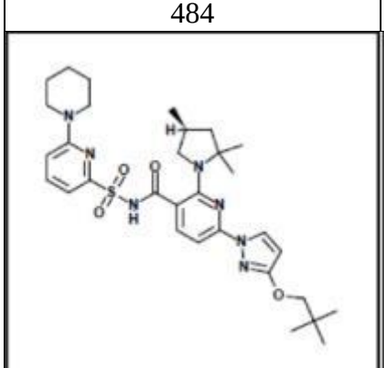
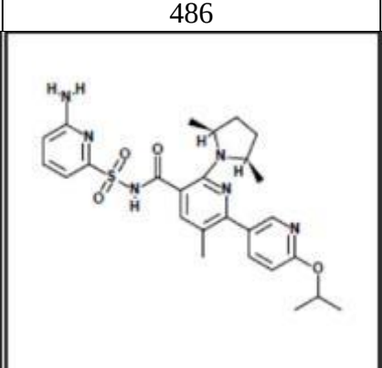
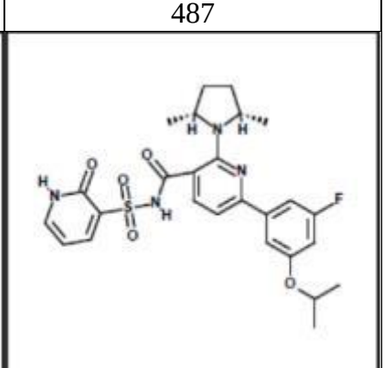
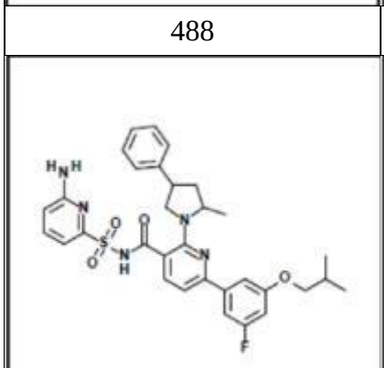
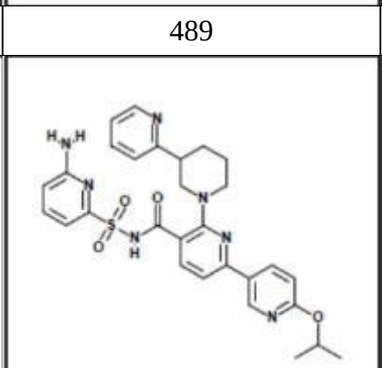
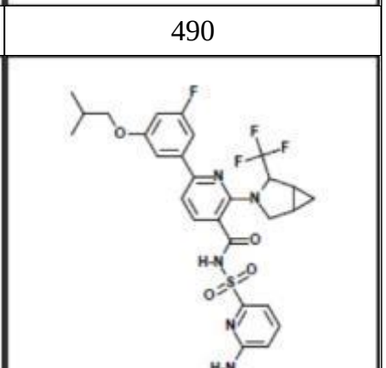
24. El compuesto de acuerdo con la Reivindicación 1, o una sal farmacéuticamente aceptable del mismo, en donde el compuesto se selecciona entre:

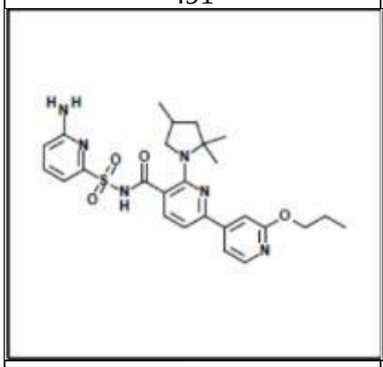
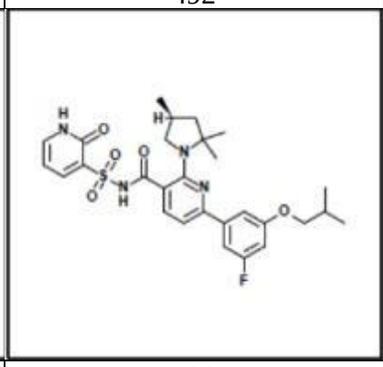
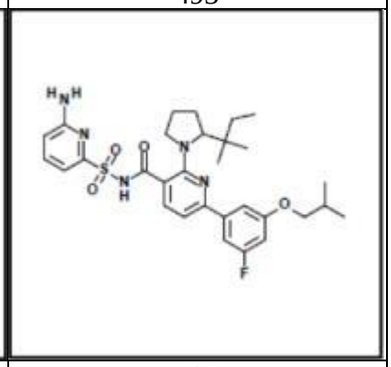
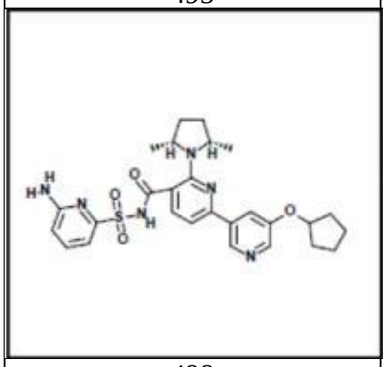
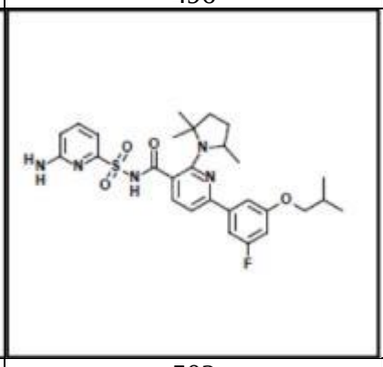
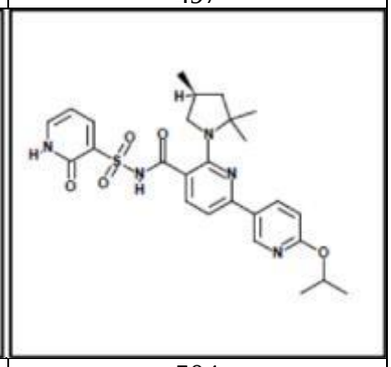
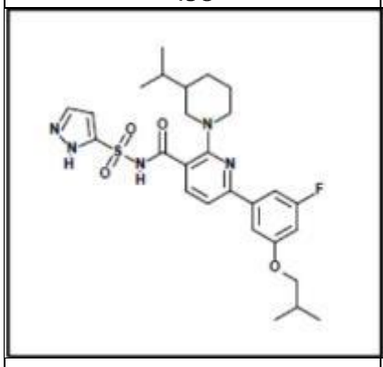
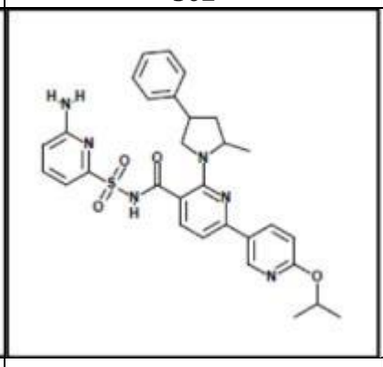
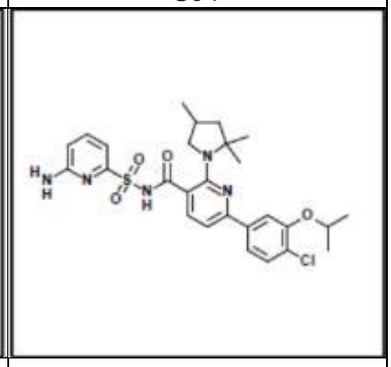
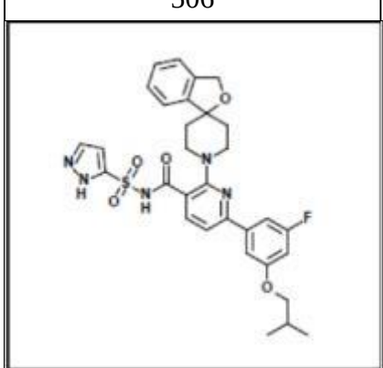
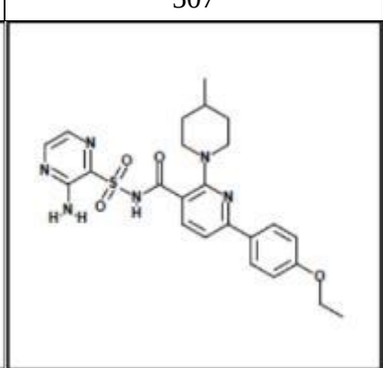
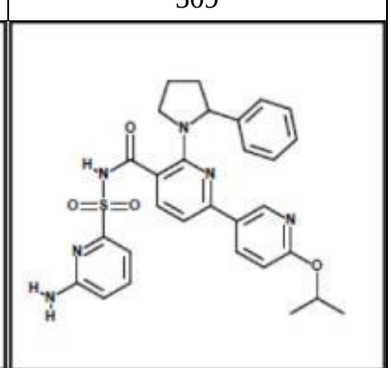
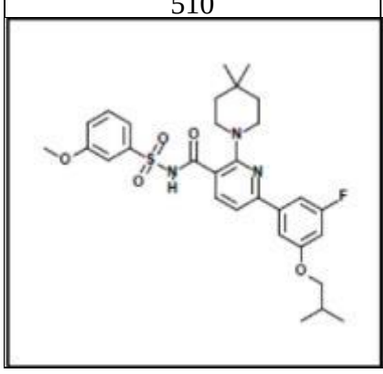
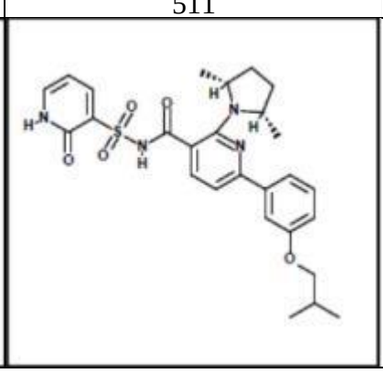
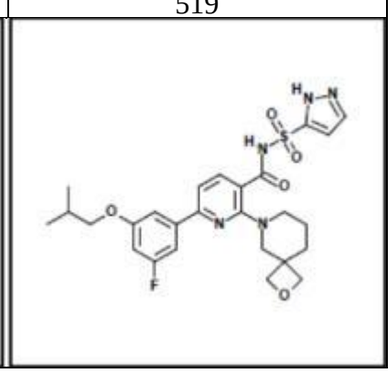
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307	321	337
		
361	368	371
		
373	380	382
		
383	384	385

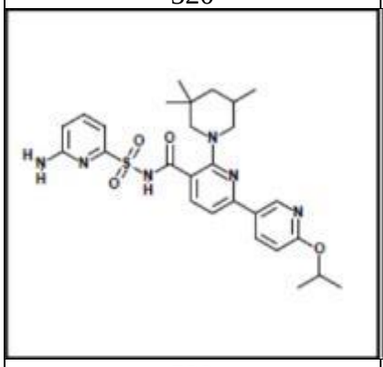
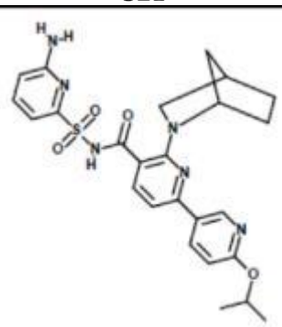
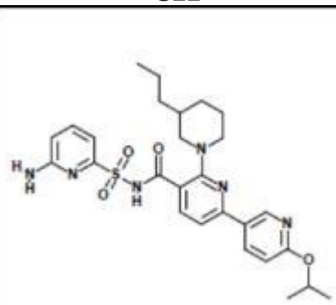
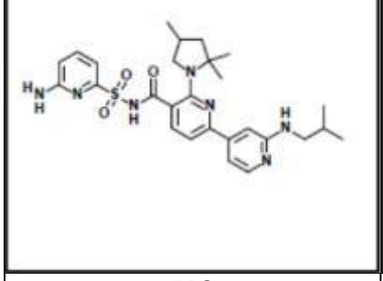
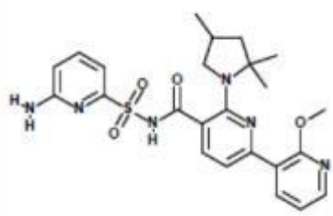
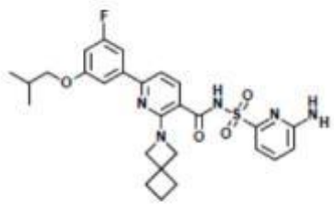
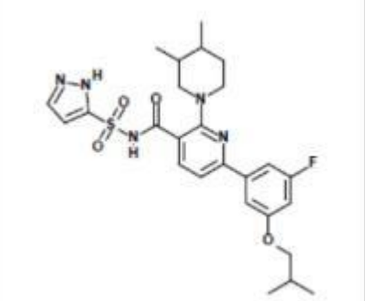
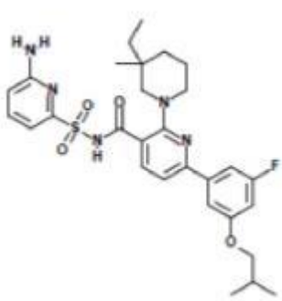
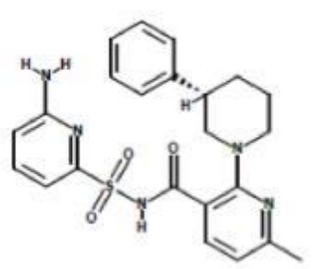
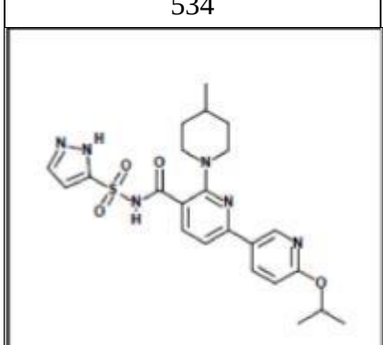
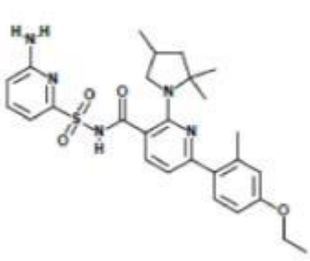
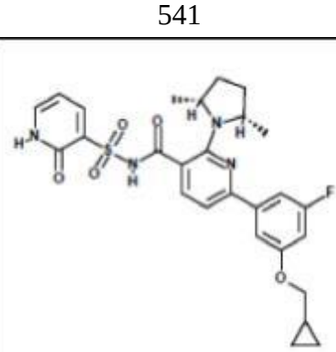
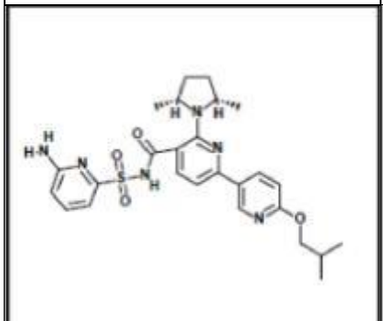
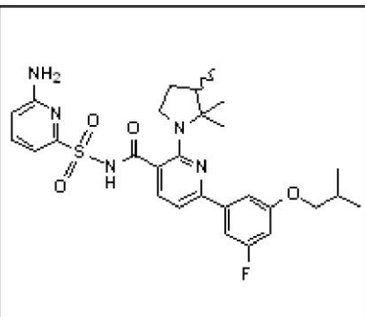
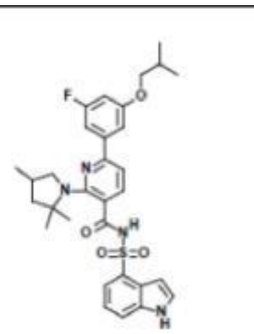
		
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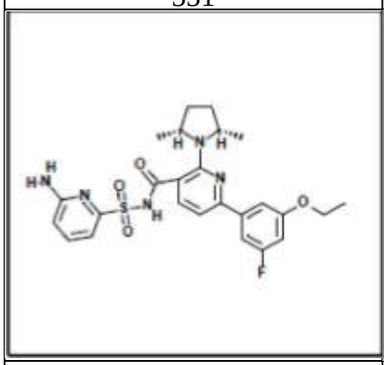
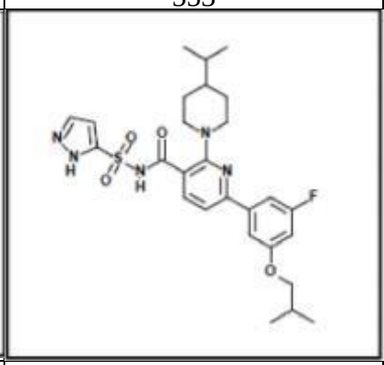
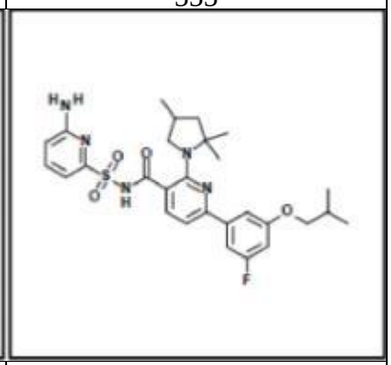
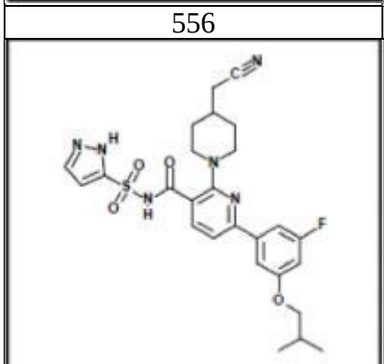
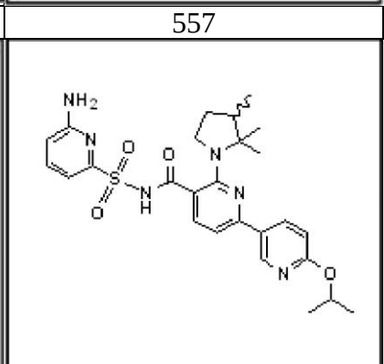
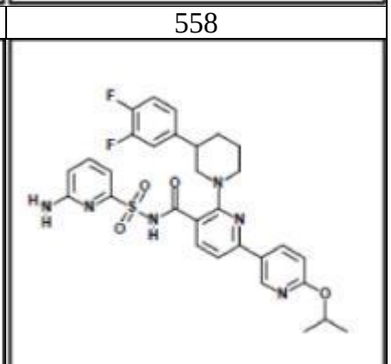
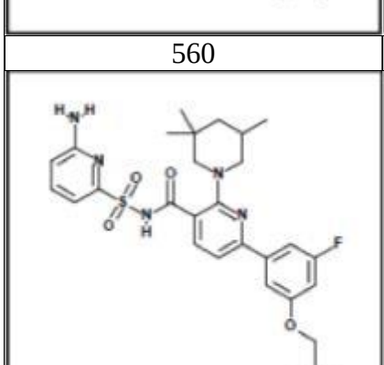
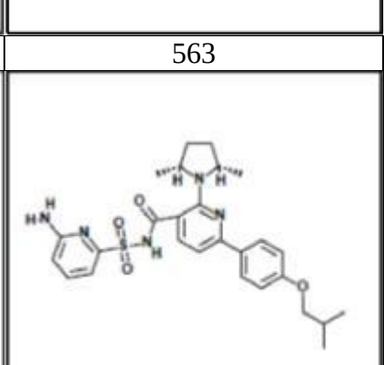
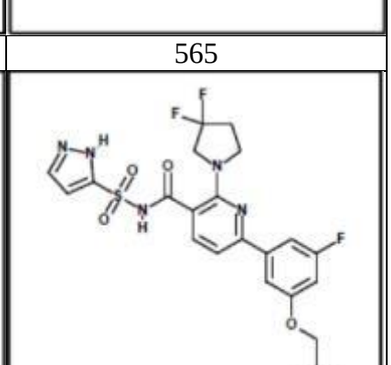
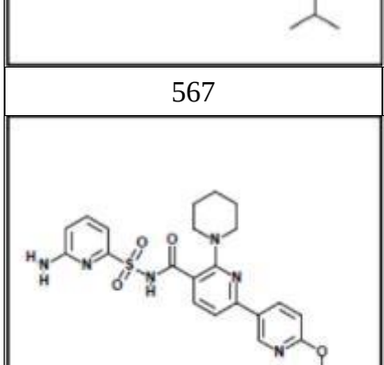
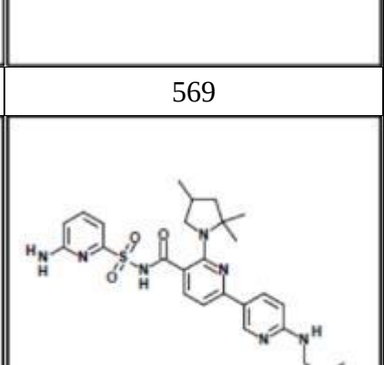
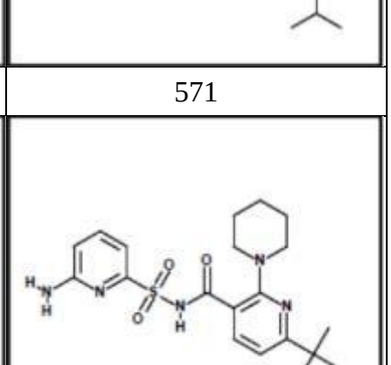
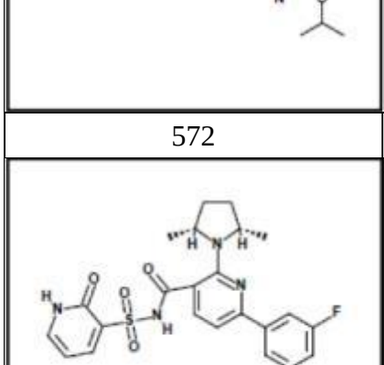
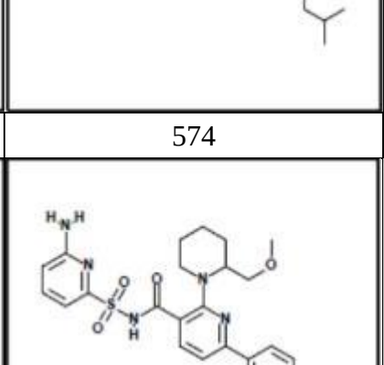
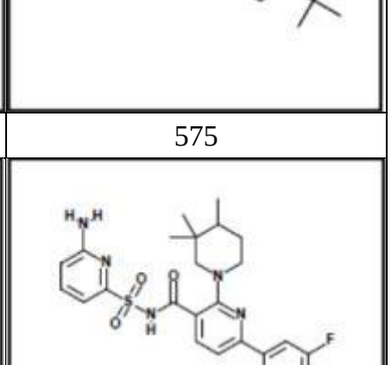
		
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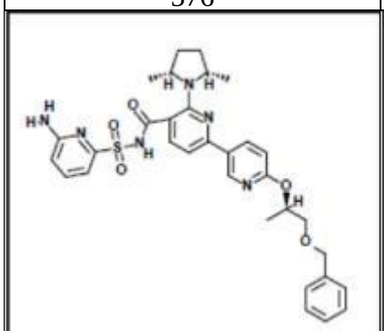
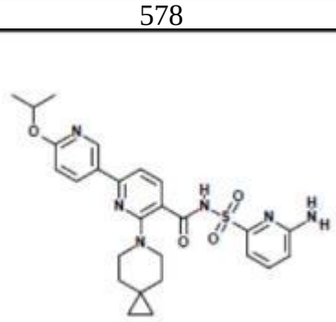
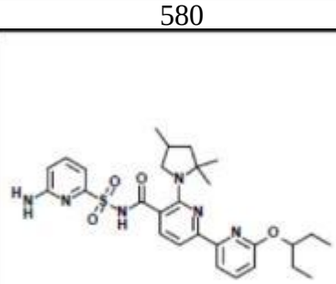
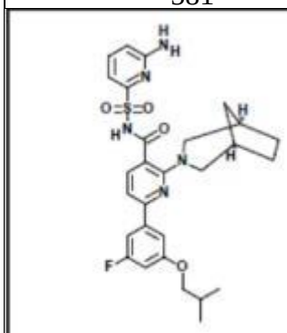
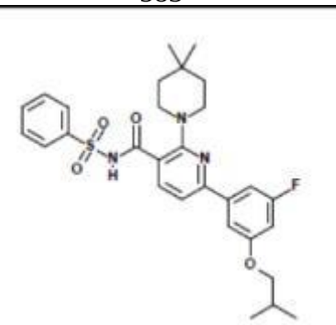
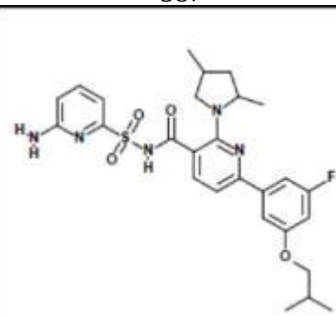
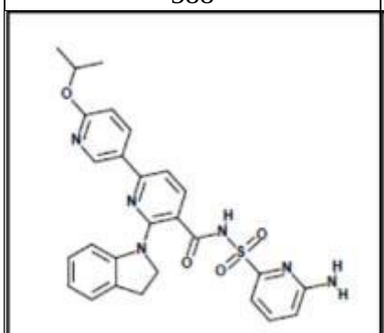
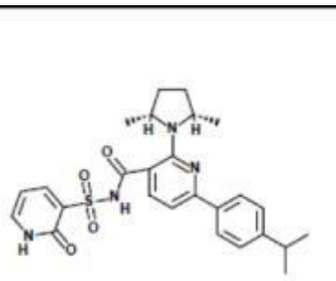
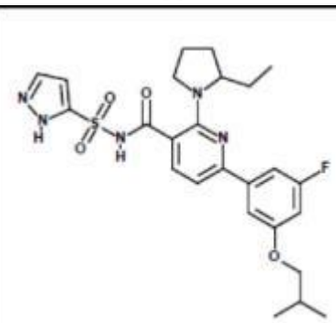
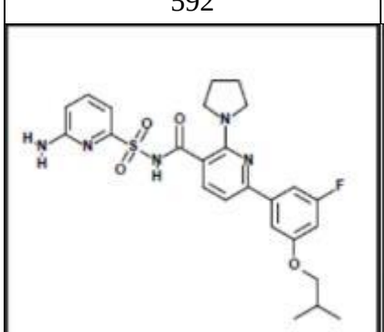
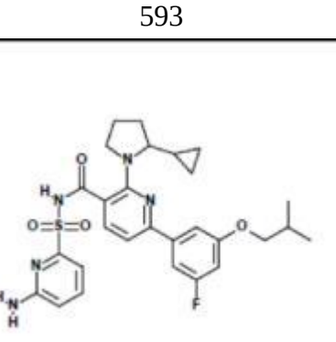
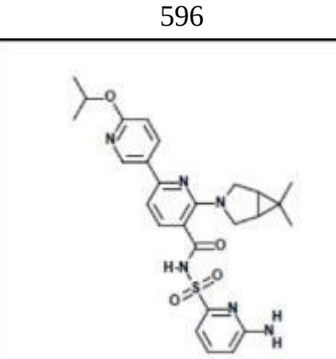
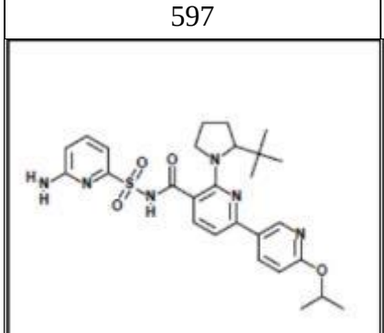
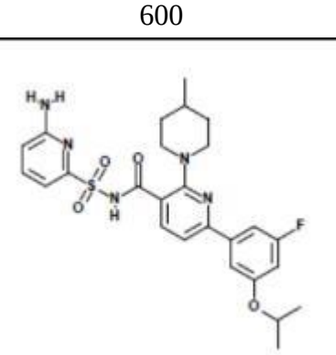
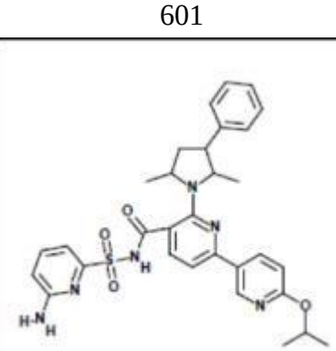
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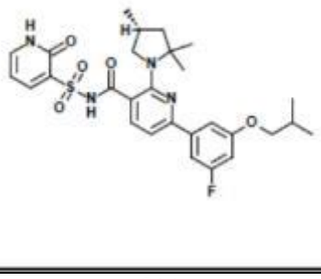
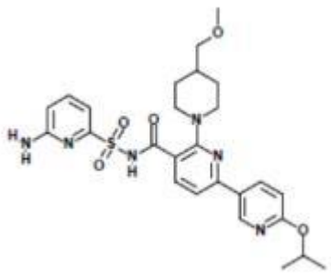
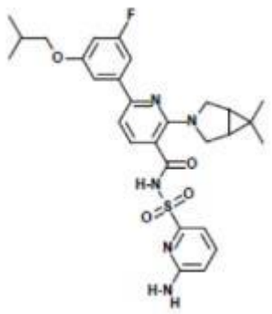
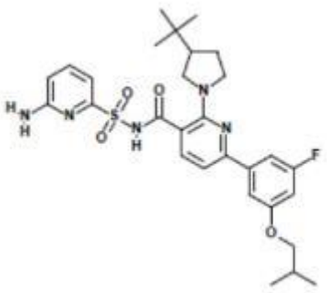
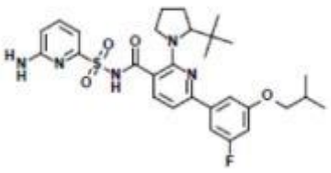
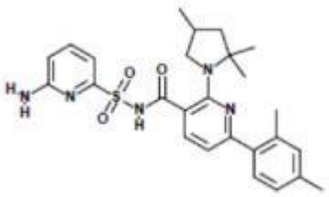
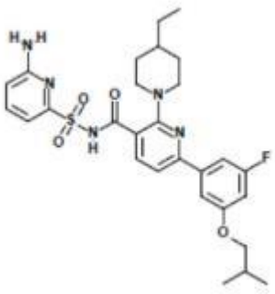
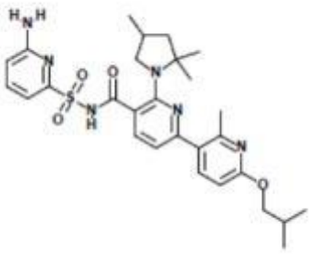
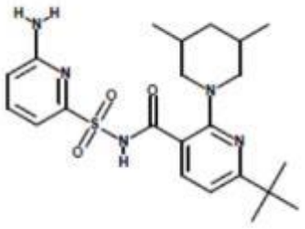
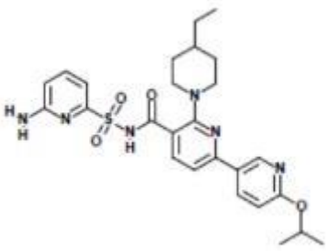
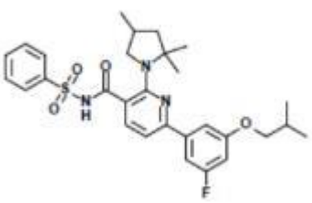
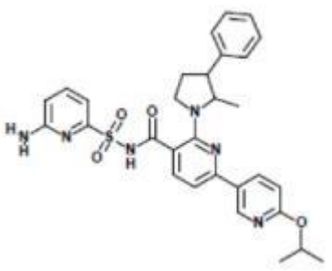
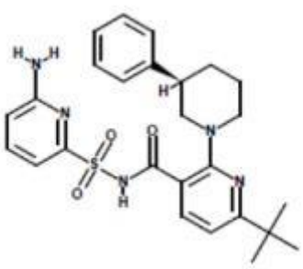
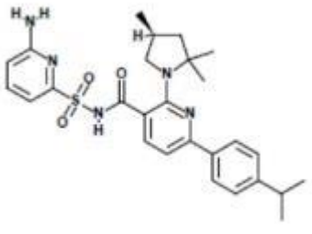
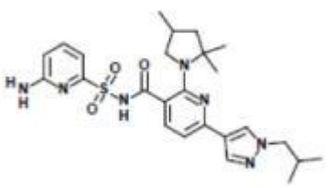
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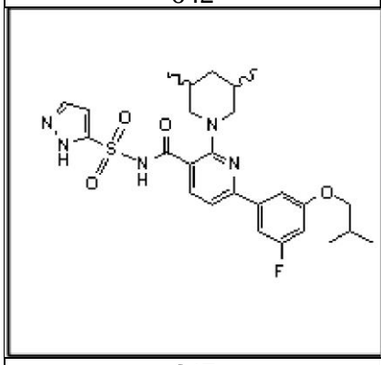
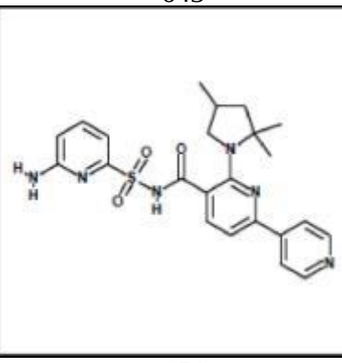
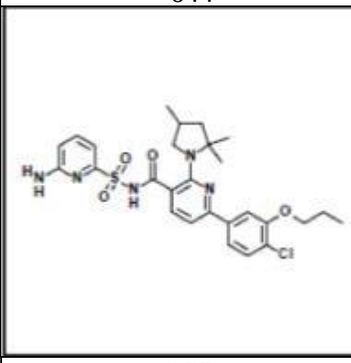
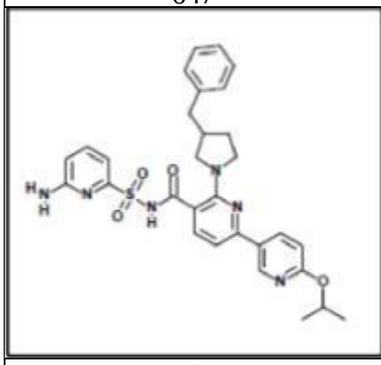
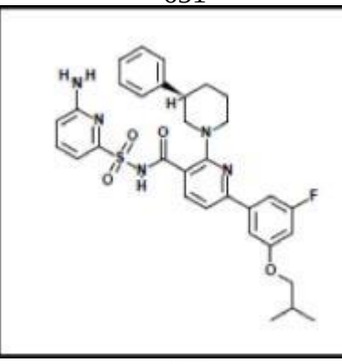
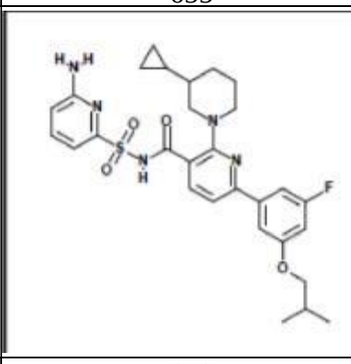
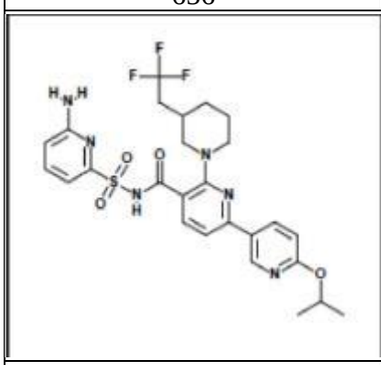
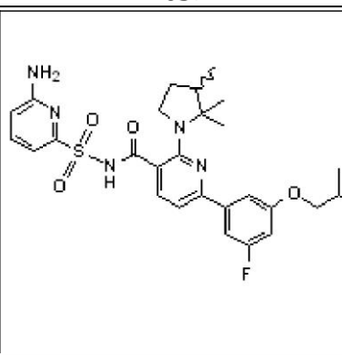
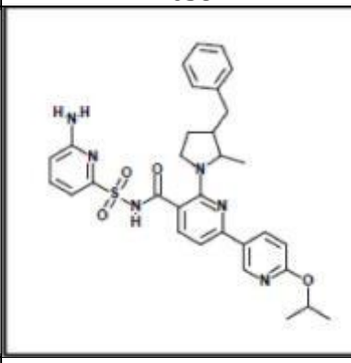
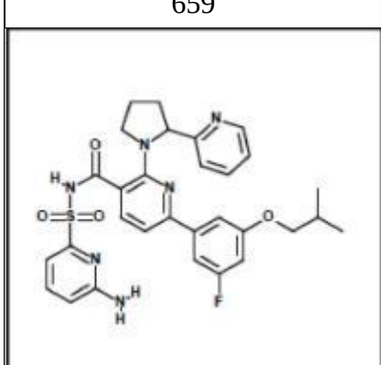
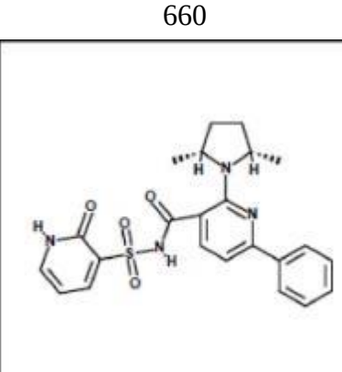
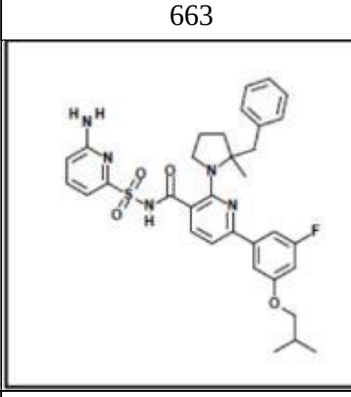
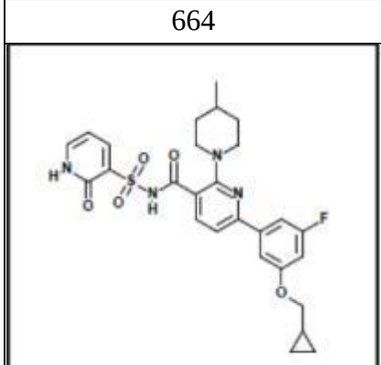
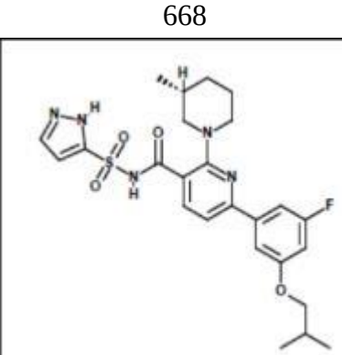
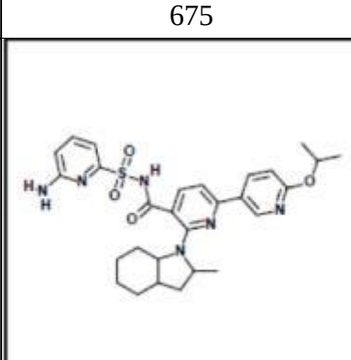
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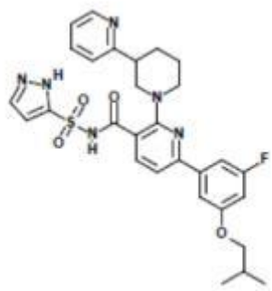
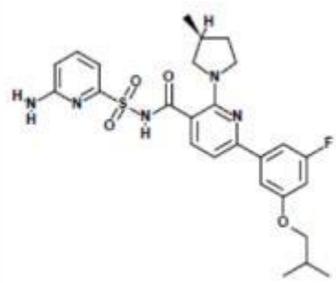
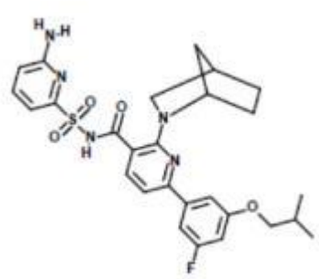
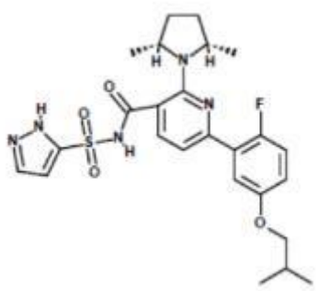
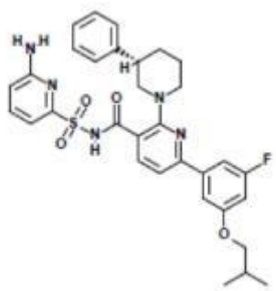
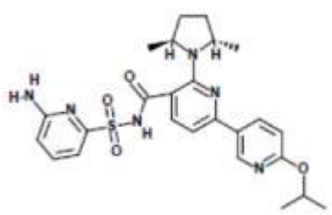
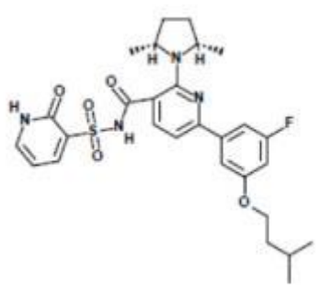
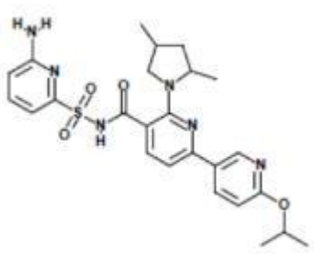
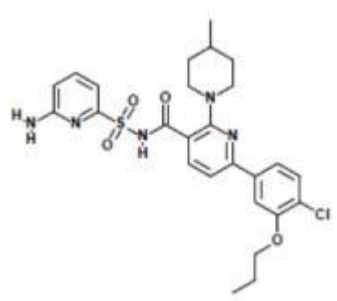
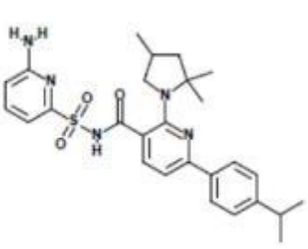
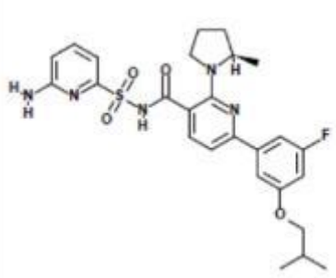
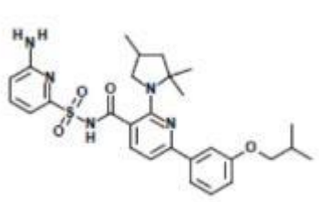
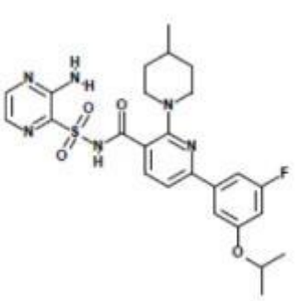
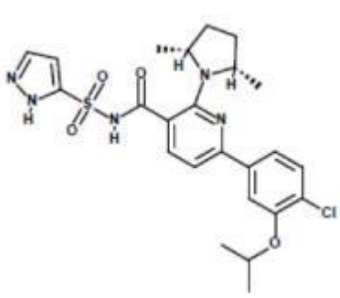
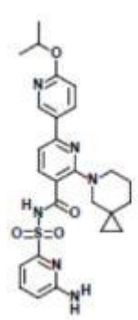
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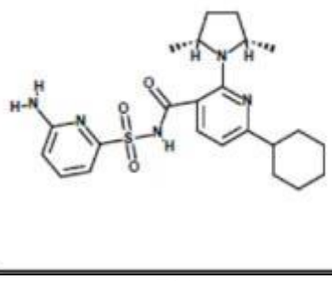
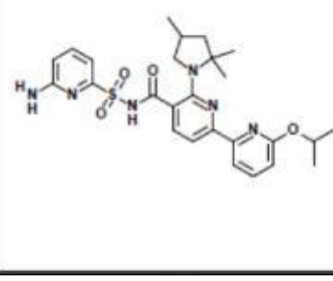
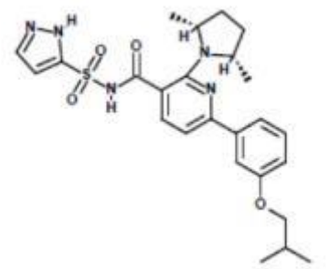
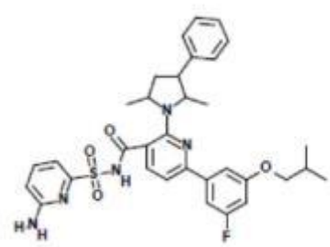
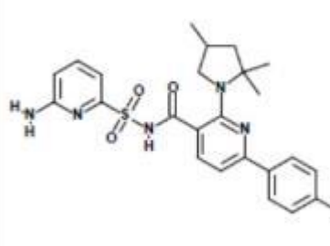
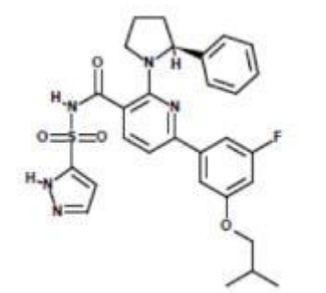
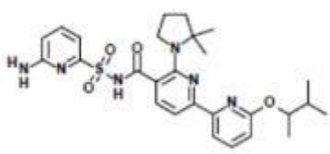
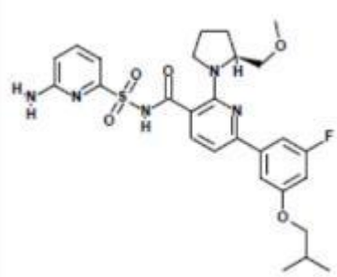
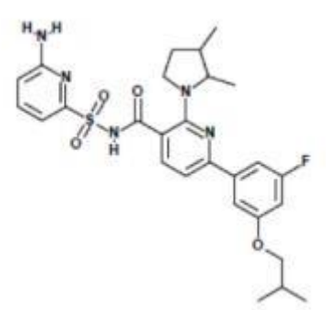
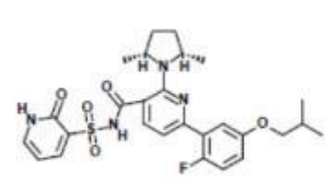
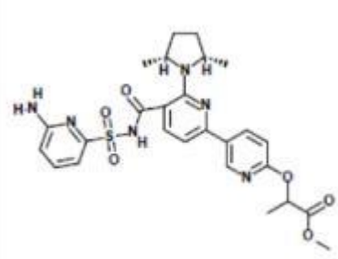
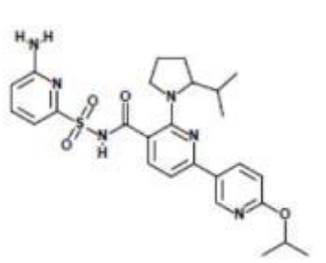
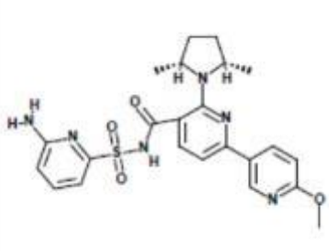
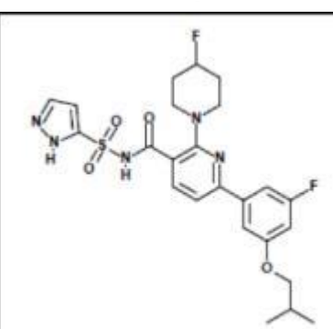
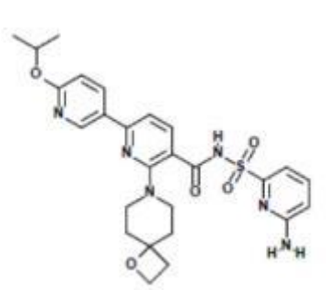
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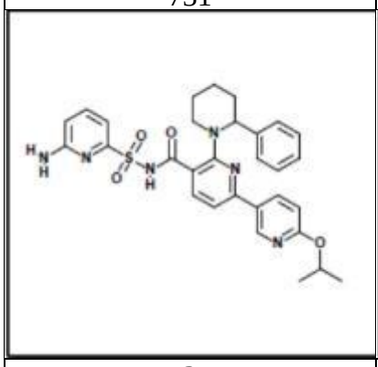
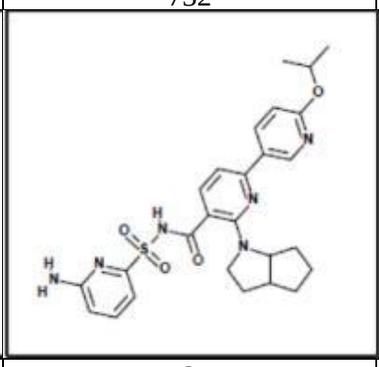
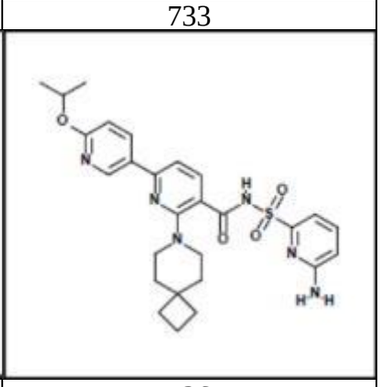
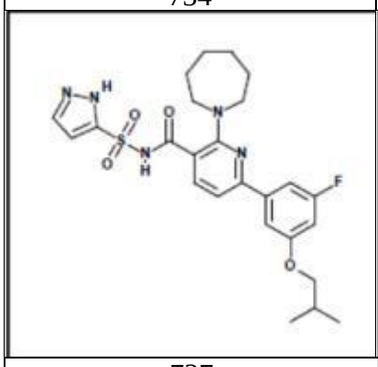
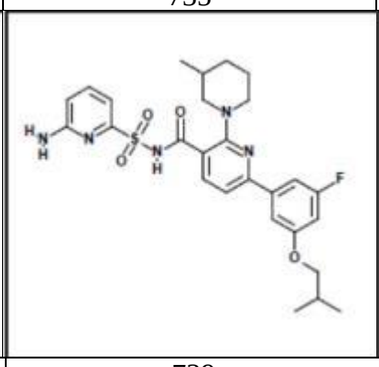
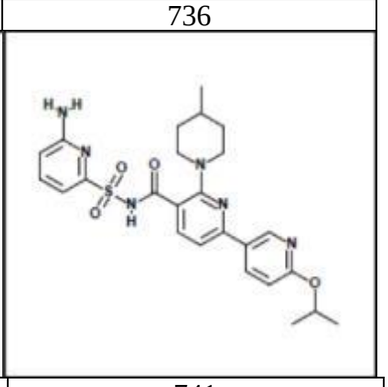
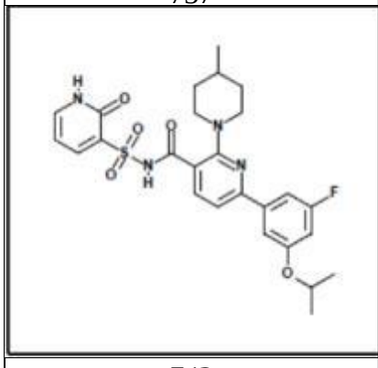
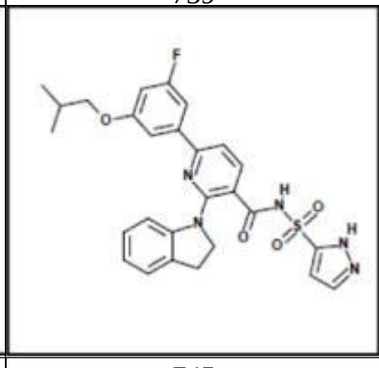
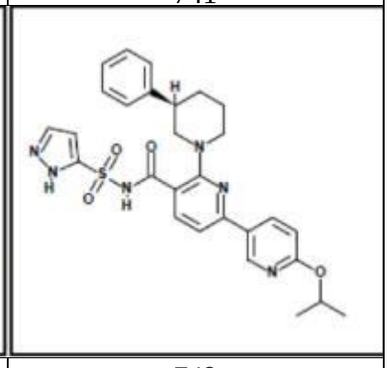
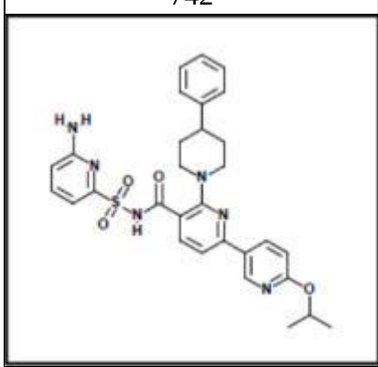
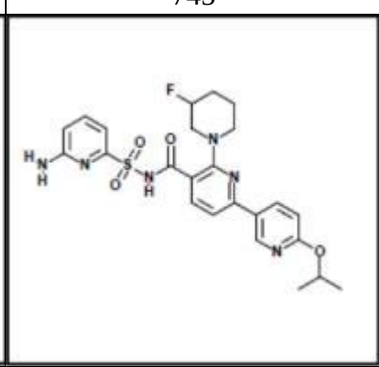
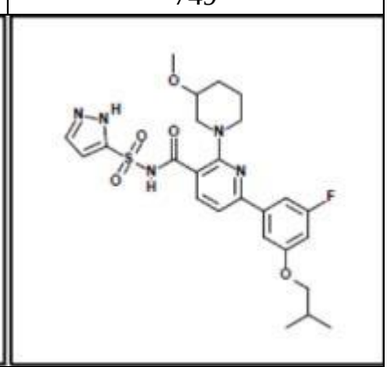
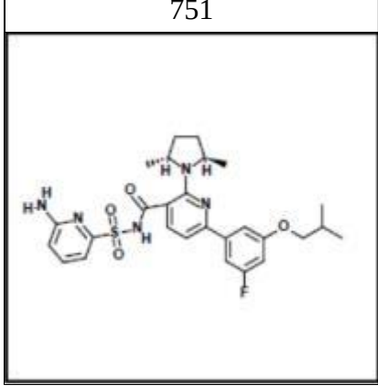
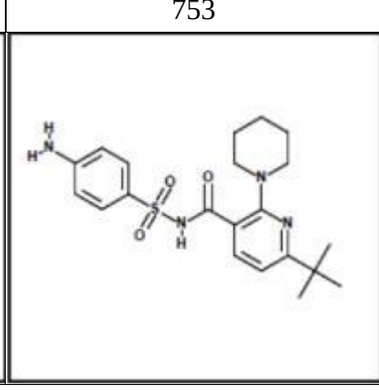
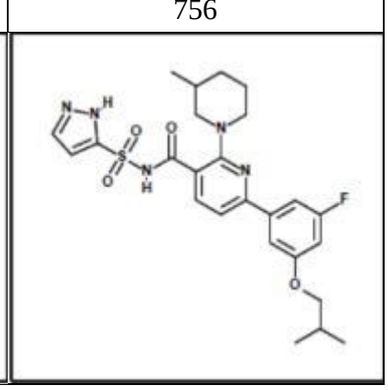
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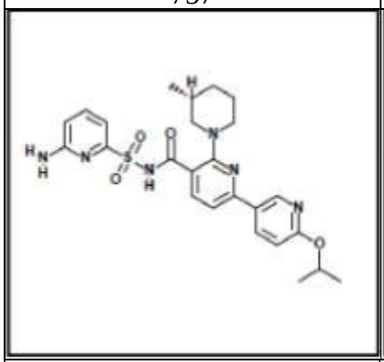
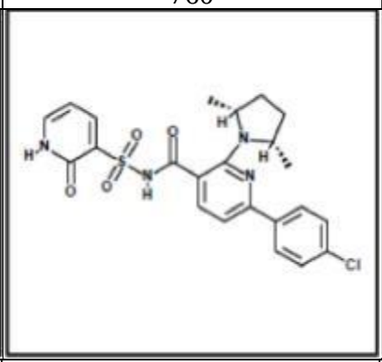
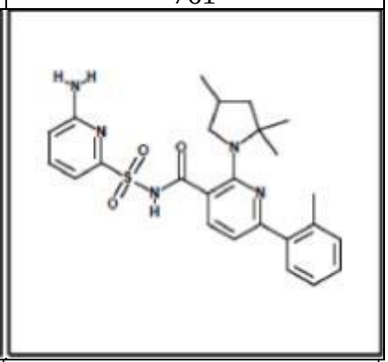
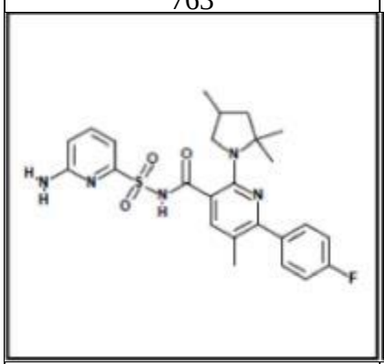
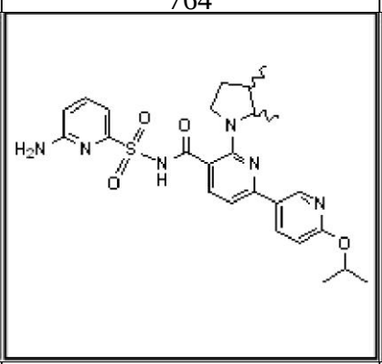
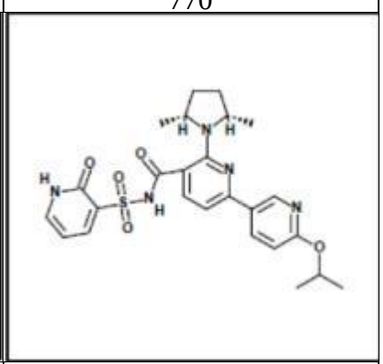
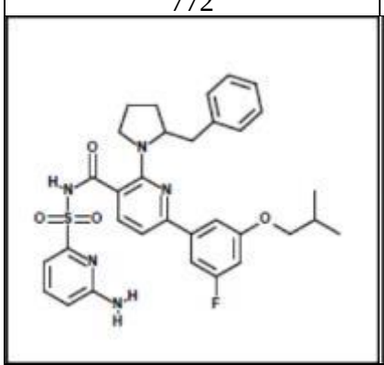
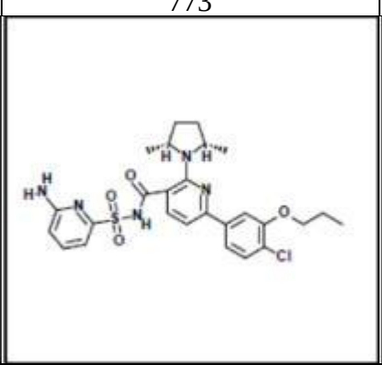
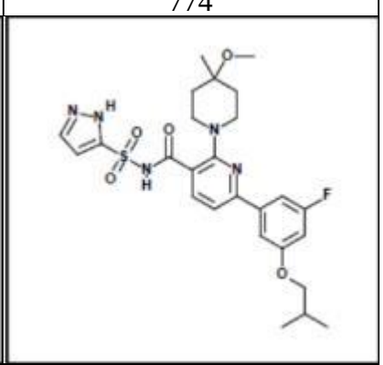
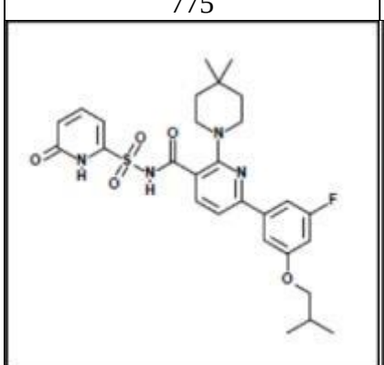
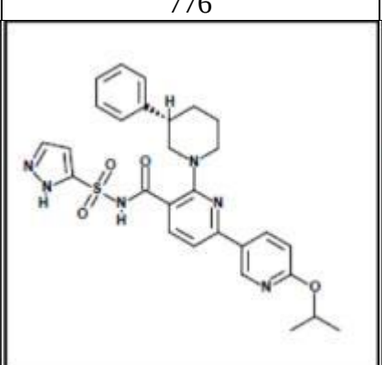
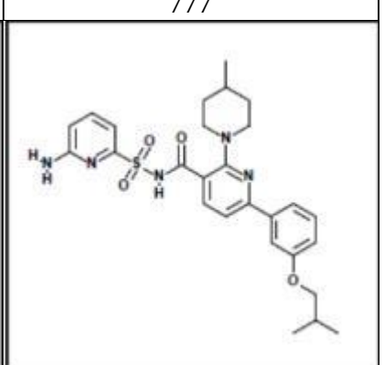
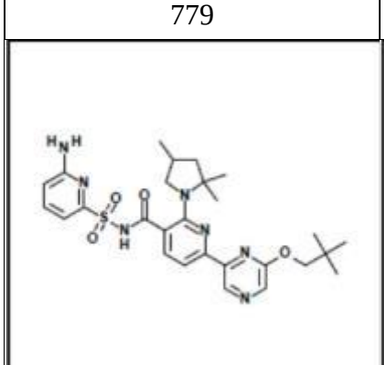
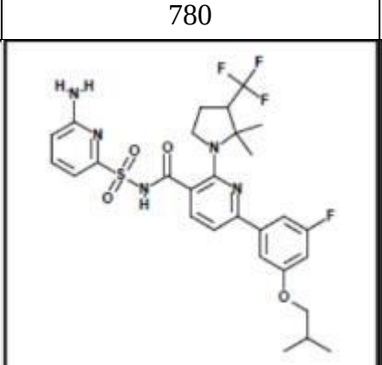
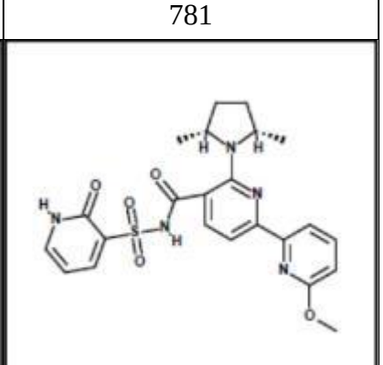
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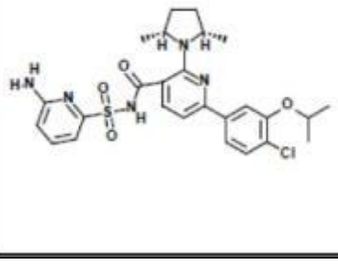
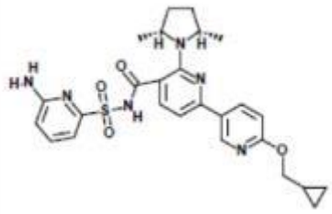
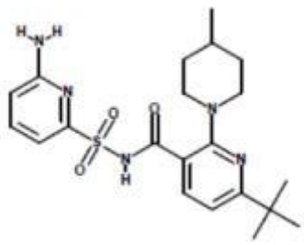
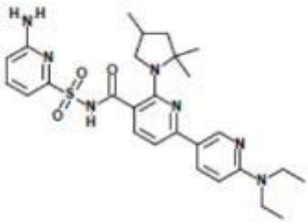
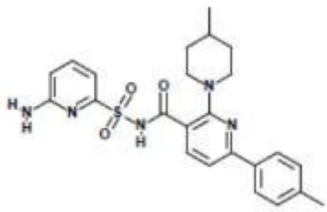
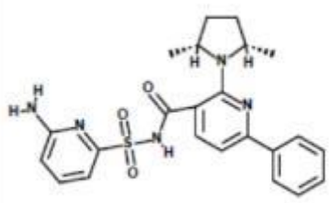
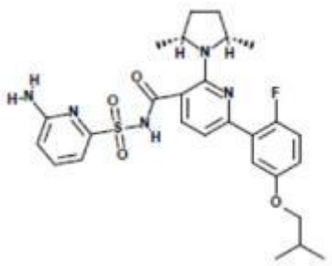
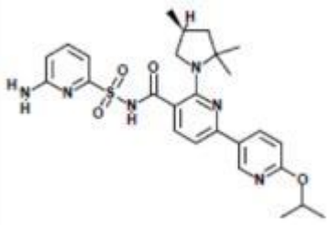
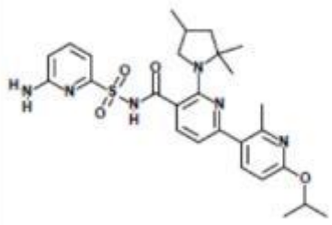
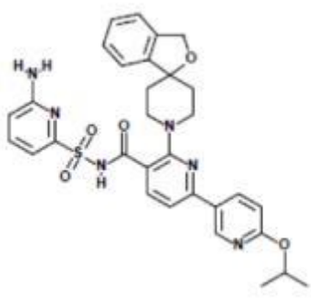
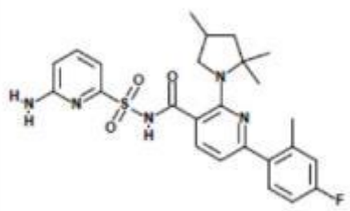
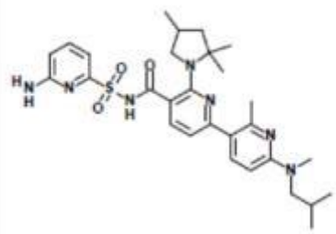
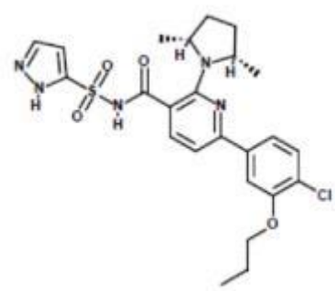
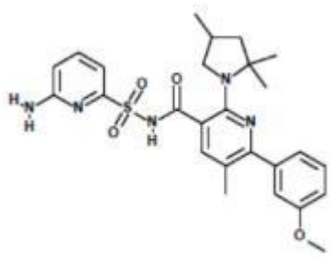
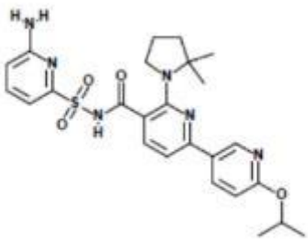
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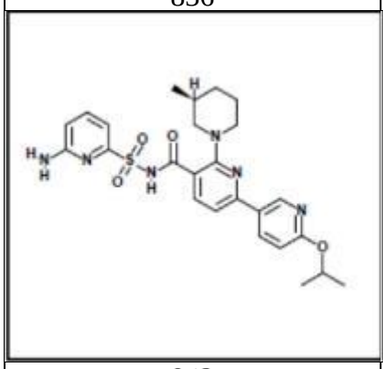
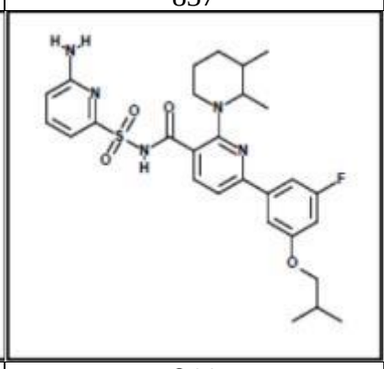
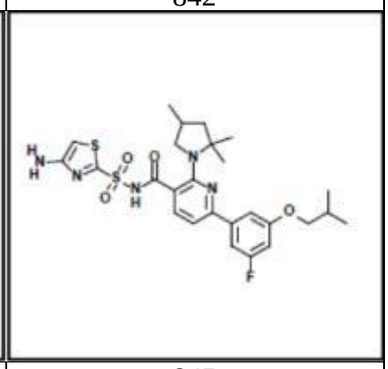
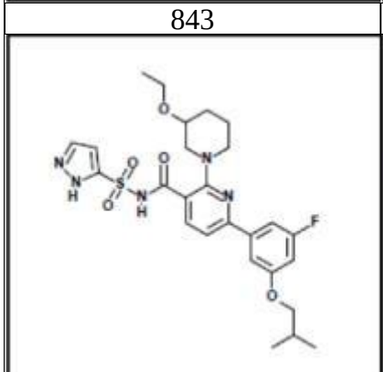
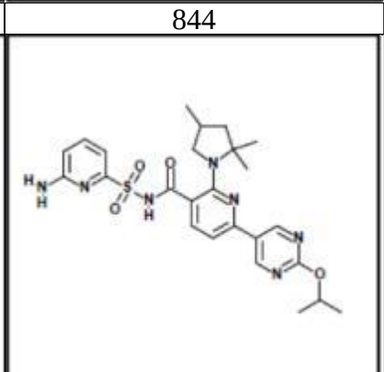
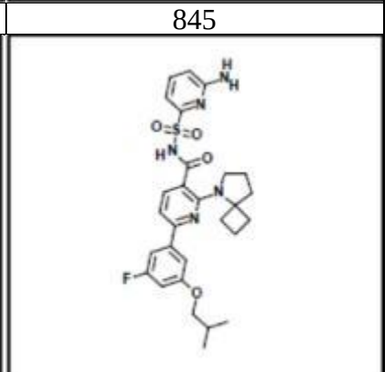
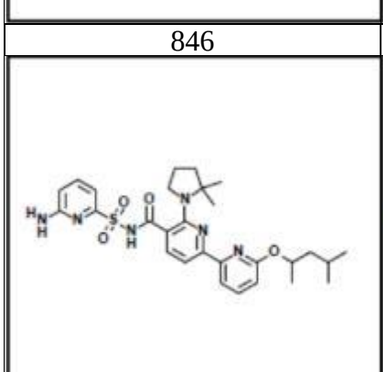
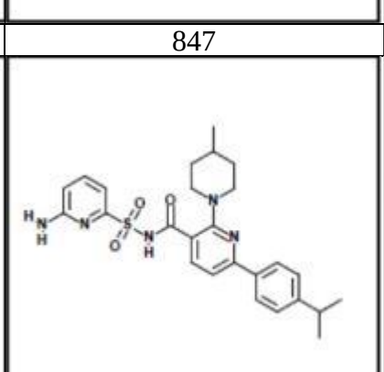
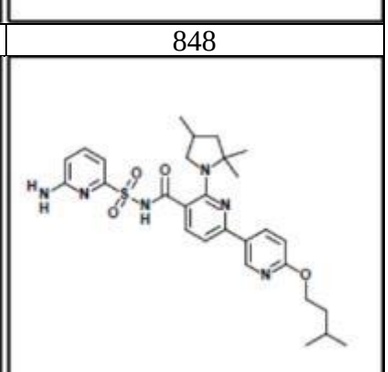
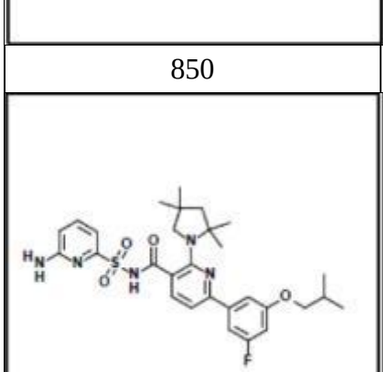
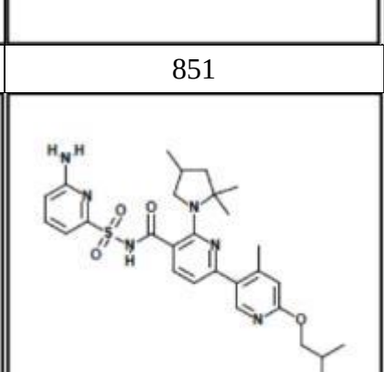
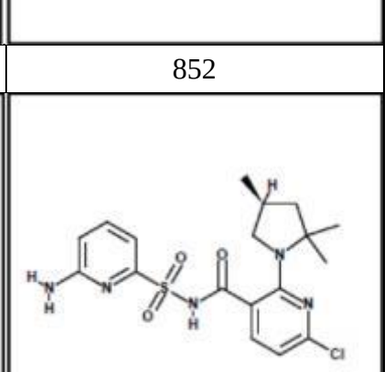
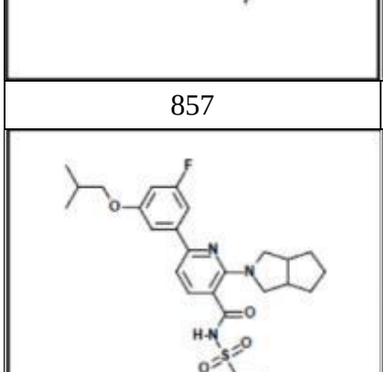
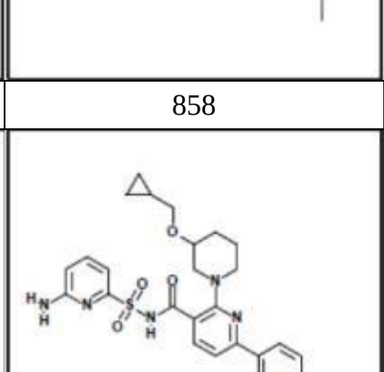
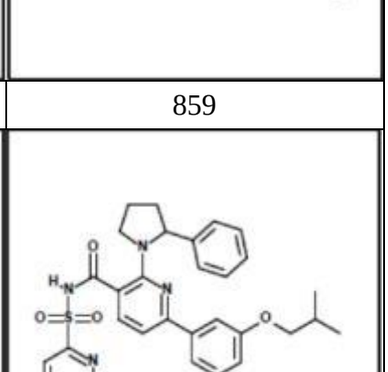
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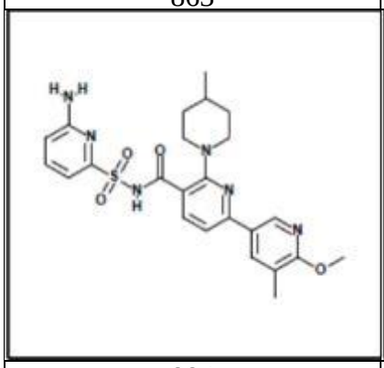
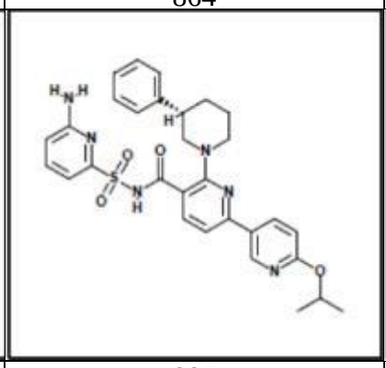
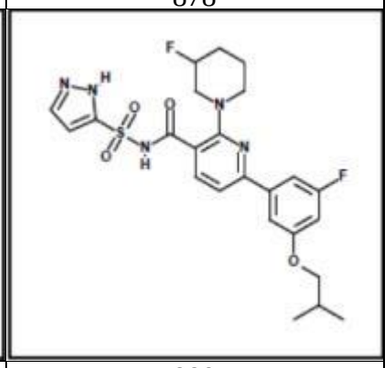
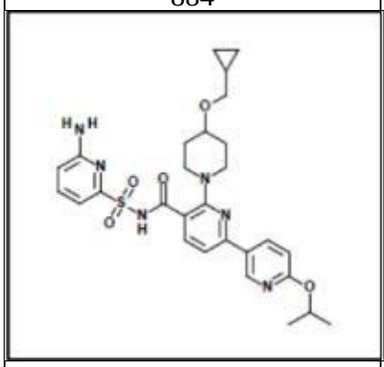
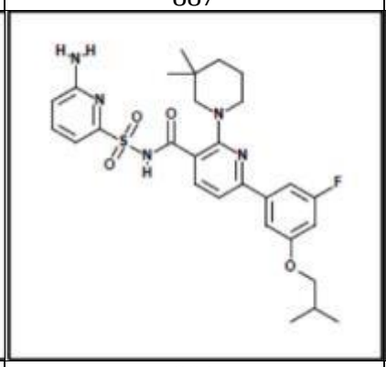
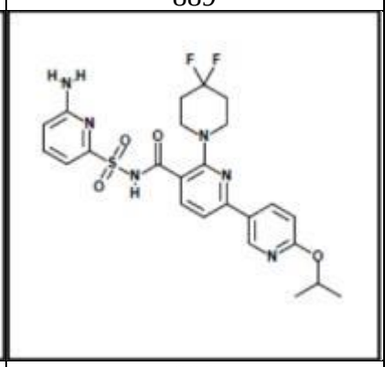
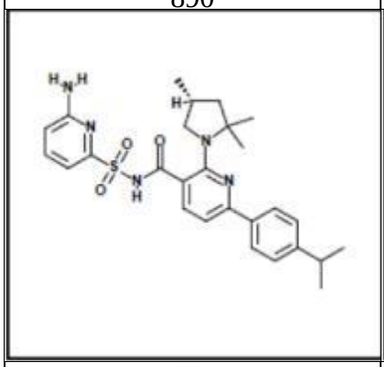
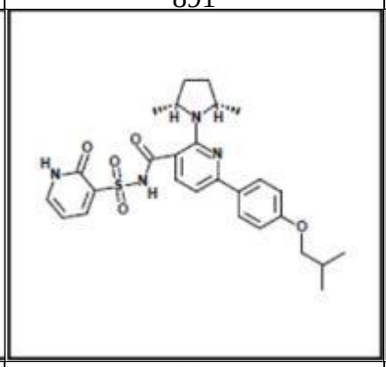
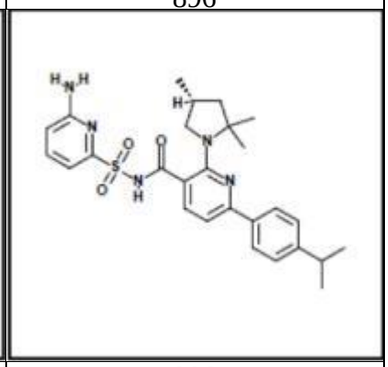
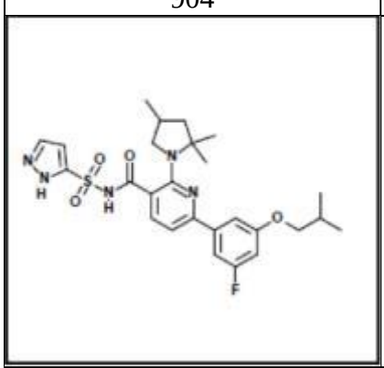
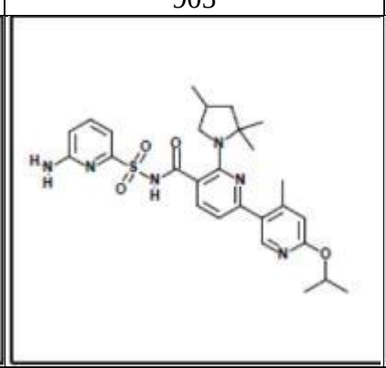
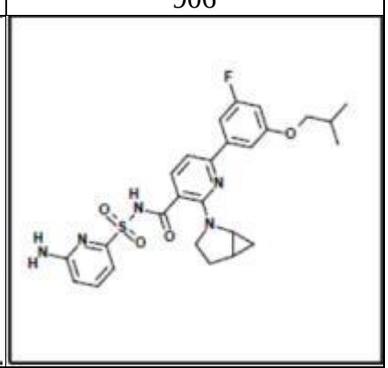
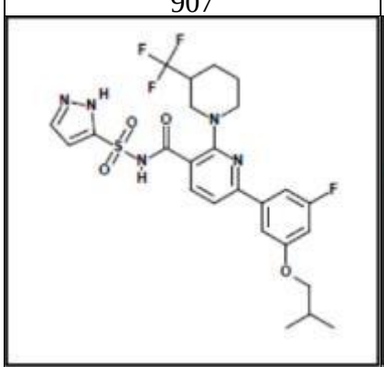
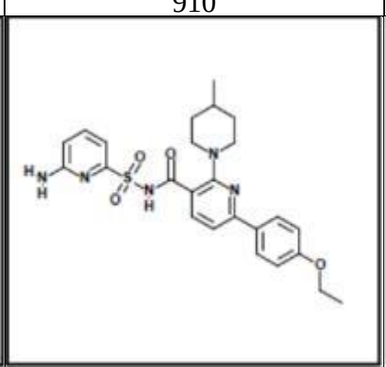
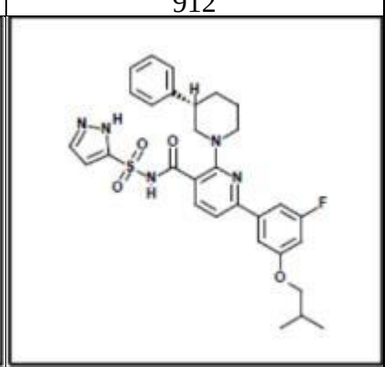
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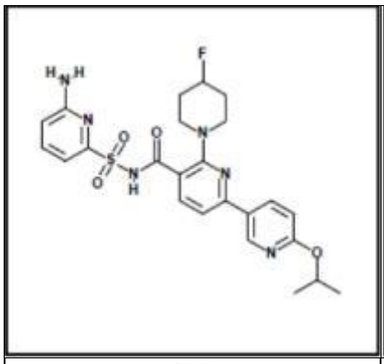
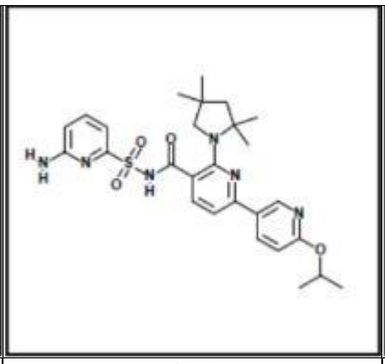
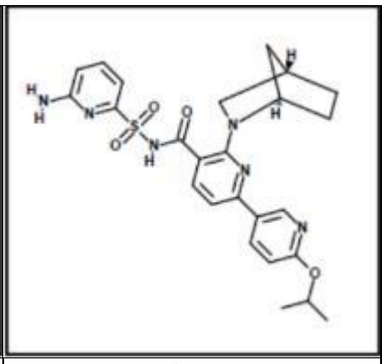
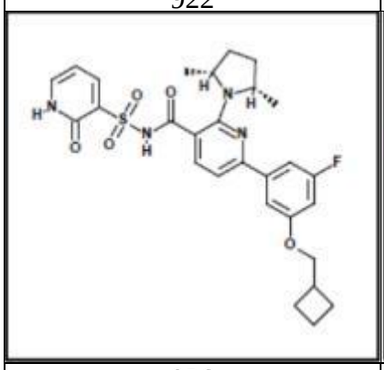
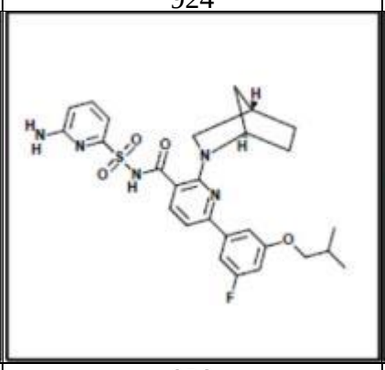
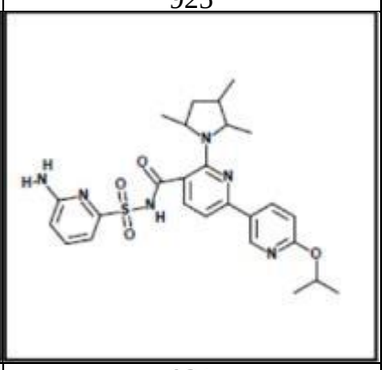
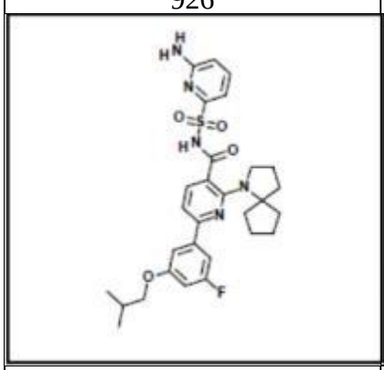
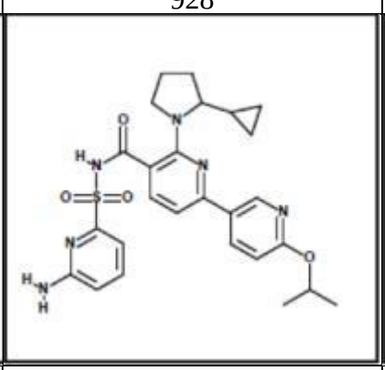
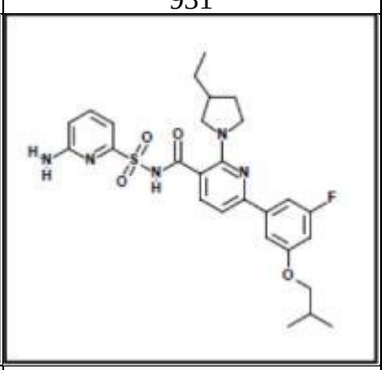
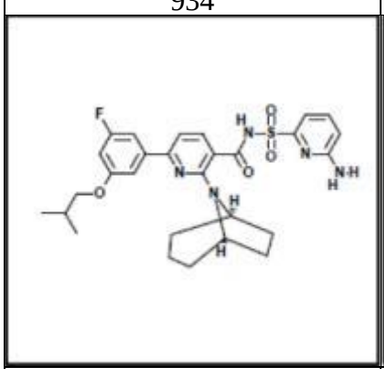
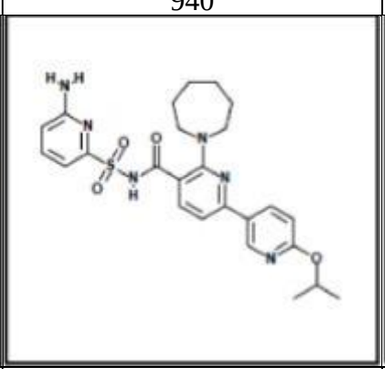
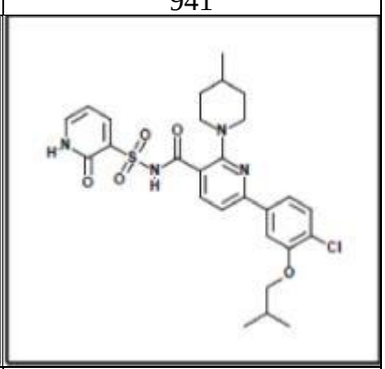
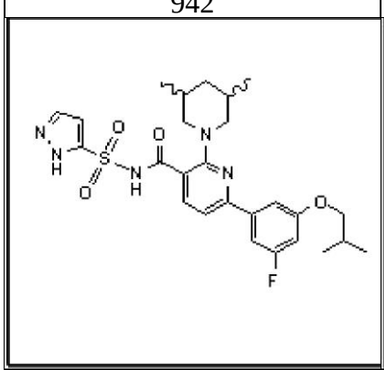
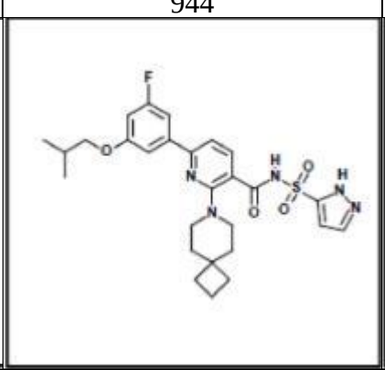
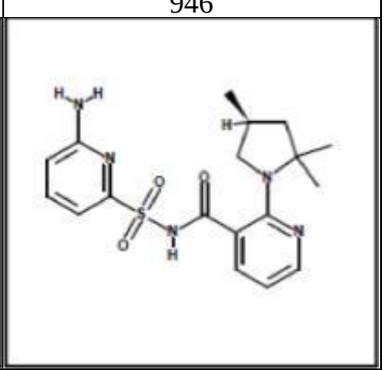
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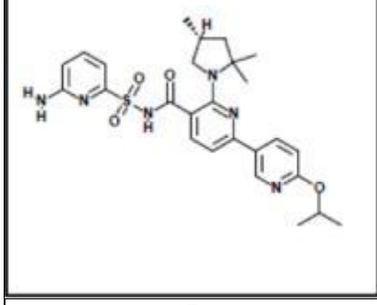
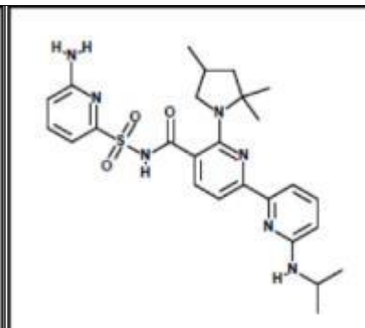
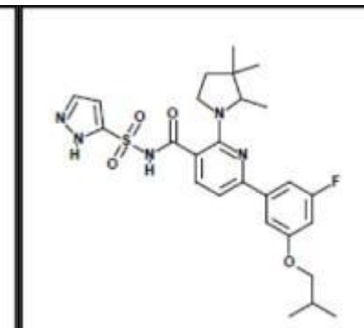
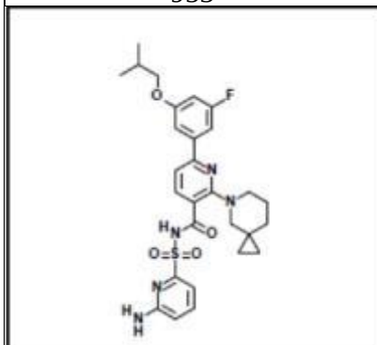
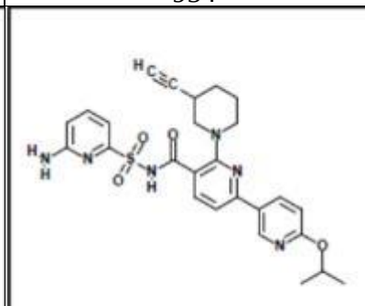
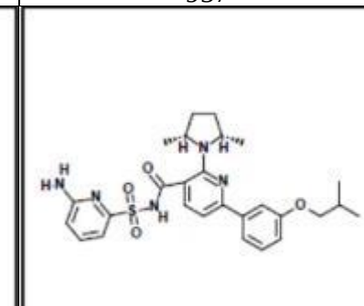
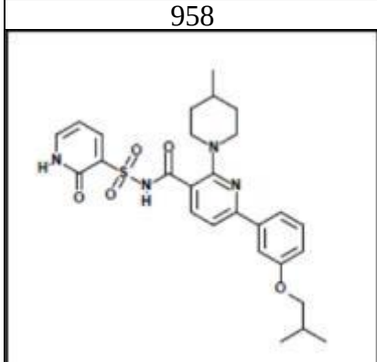
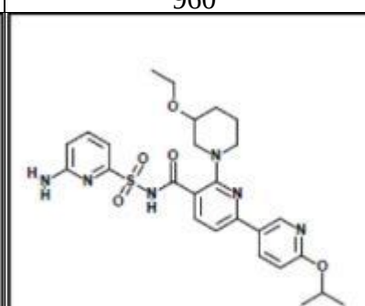
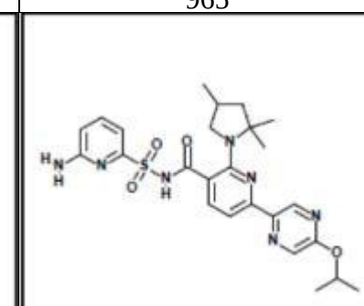
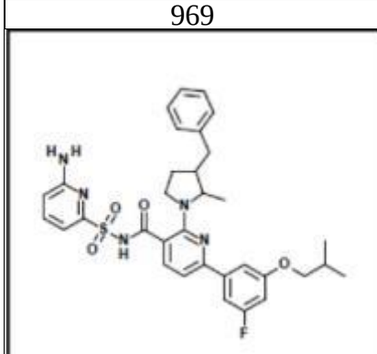
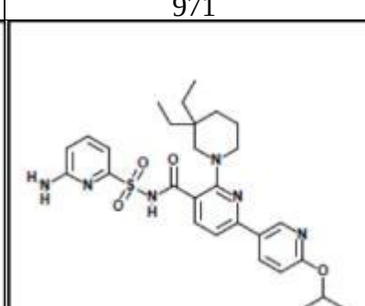
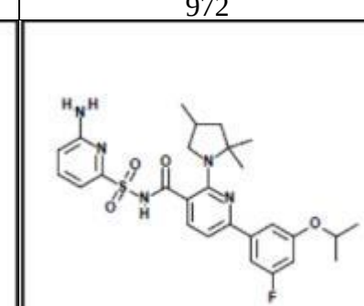
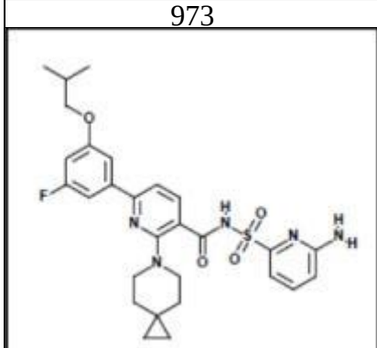
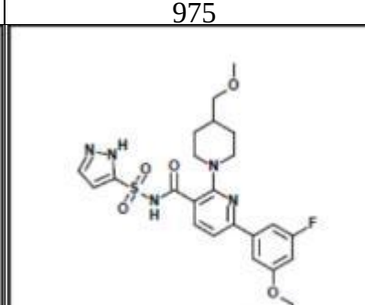
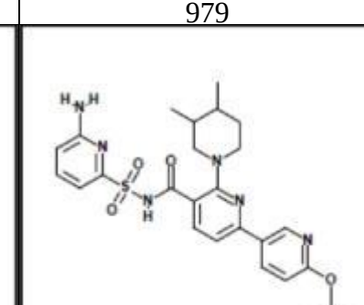
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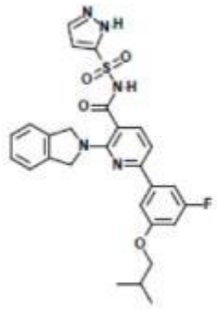
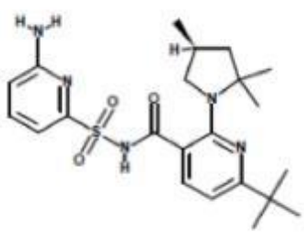
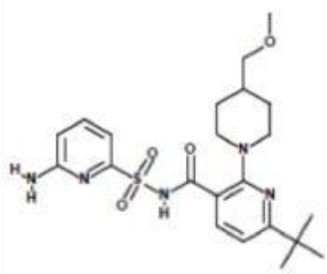
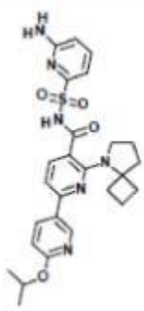
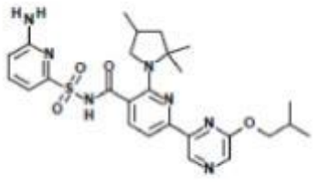
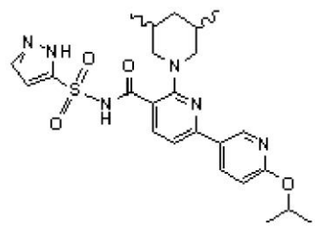
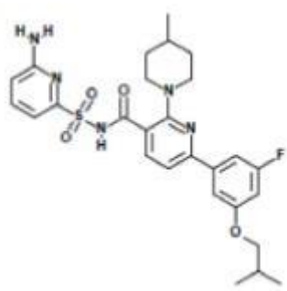
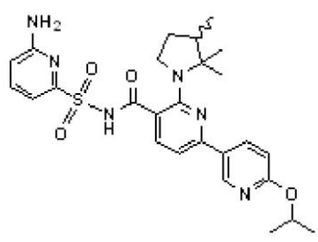
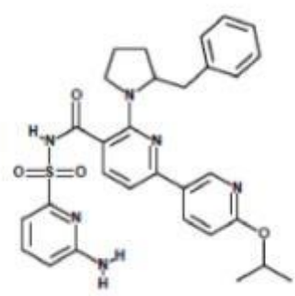
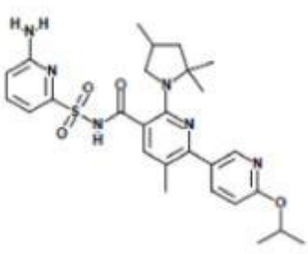
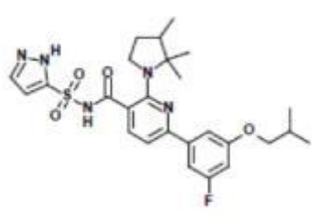
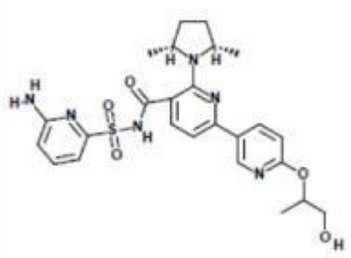
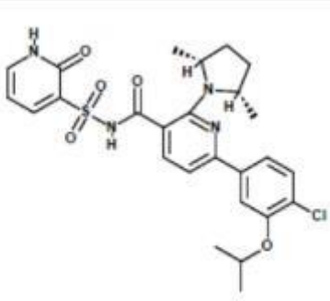
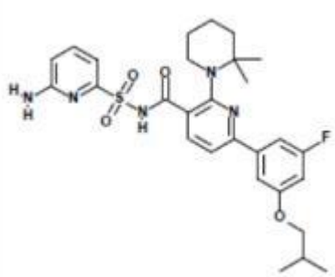
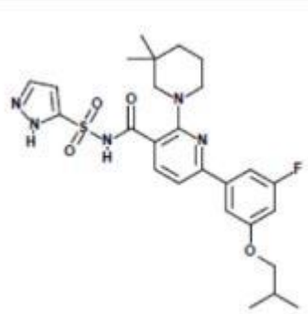
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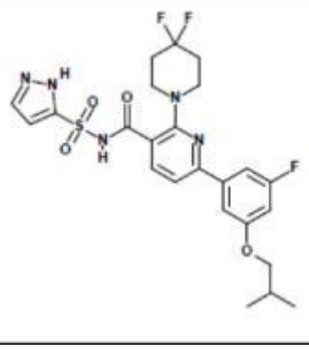
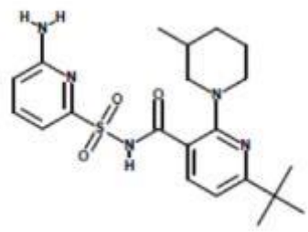
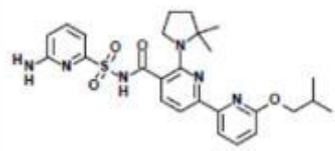
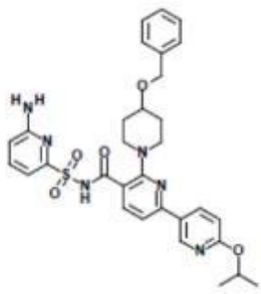
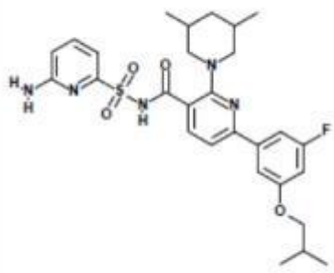
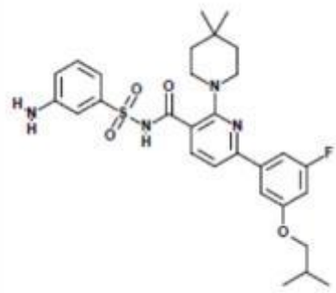
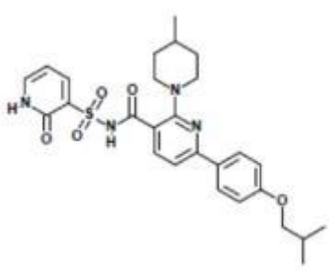
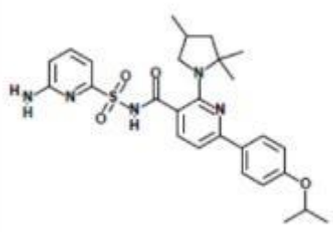
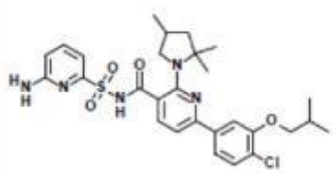
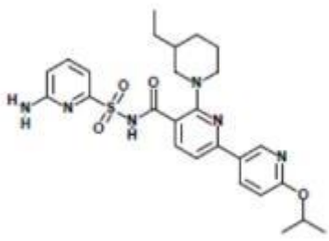
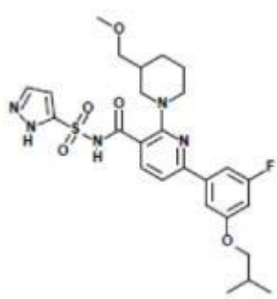
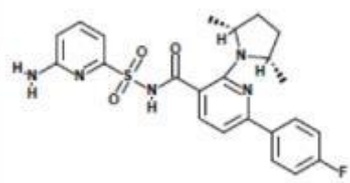
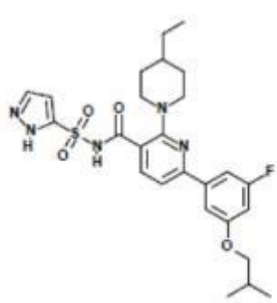
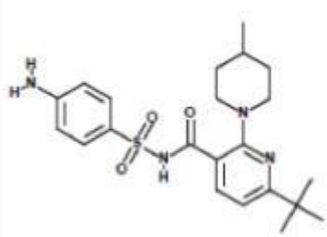
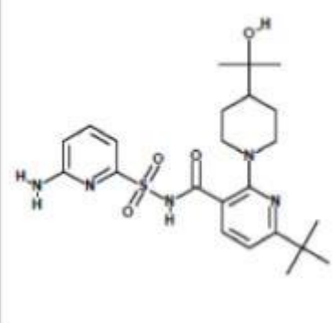
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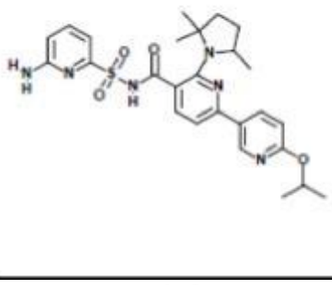
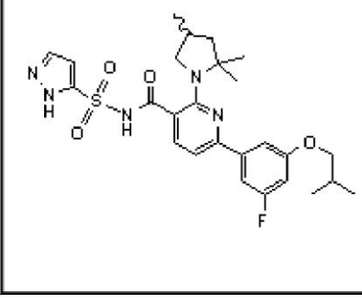
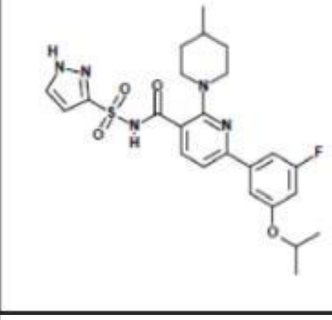
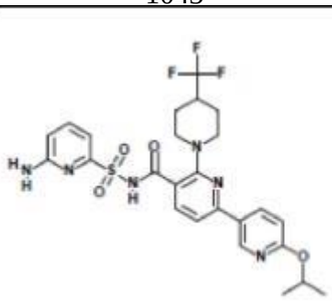
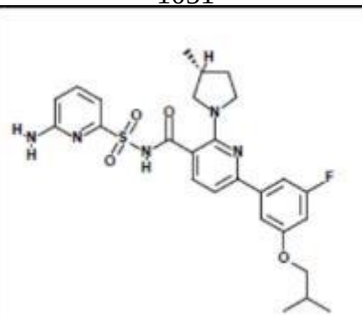
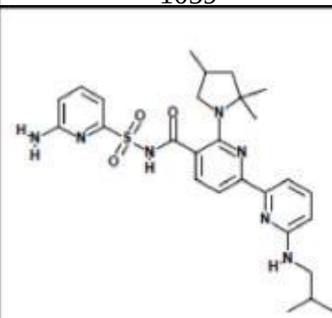
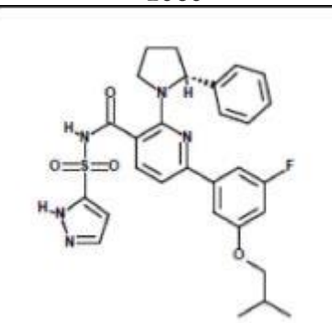
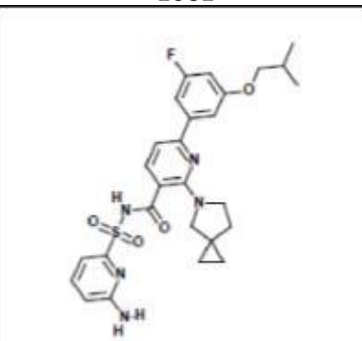
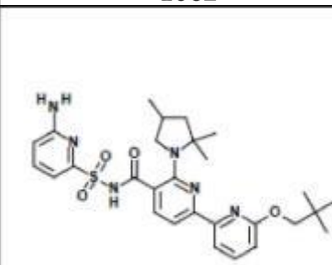
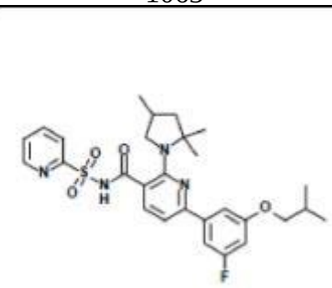
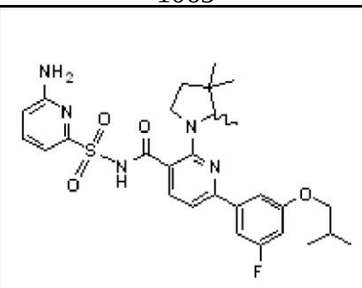
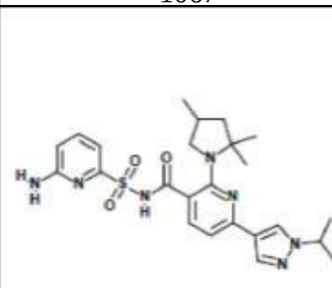
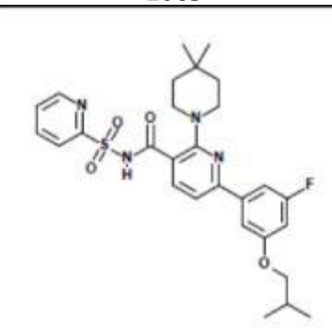
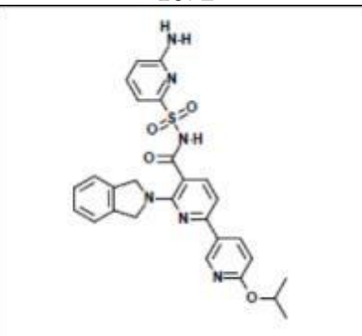
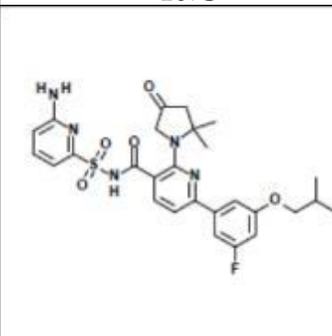
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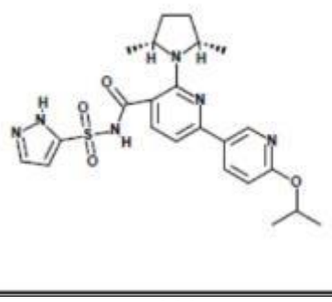
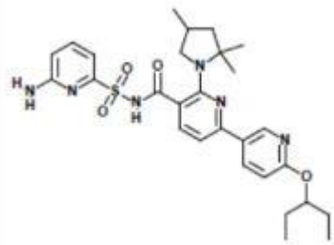
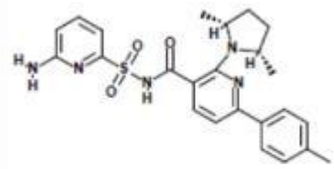
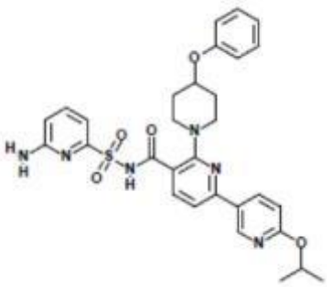
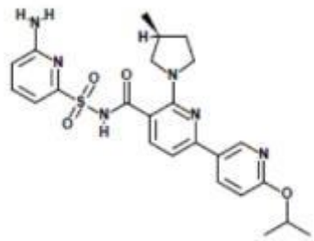
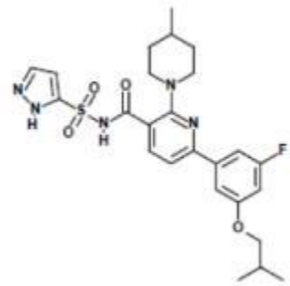
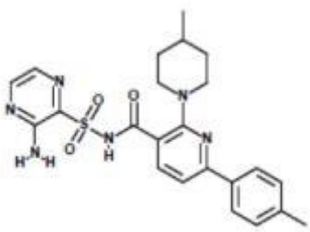
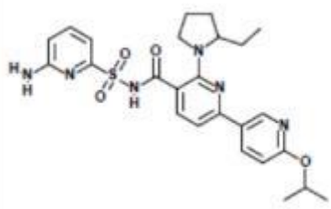
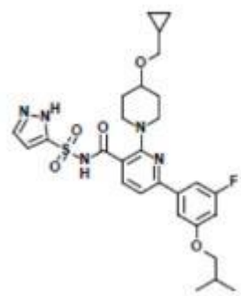
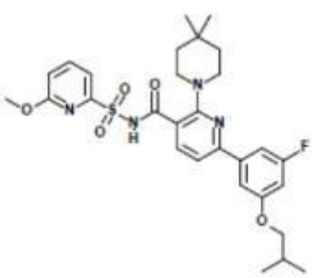
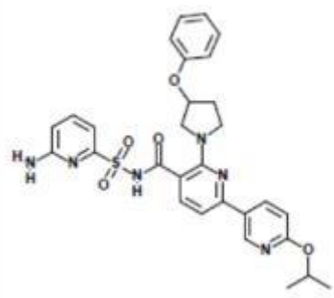
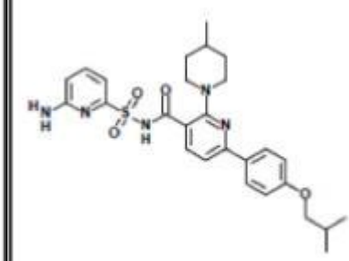
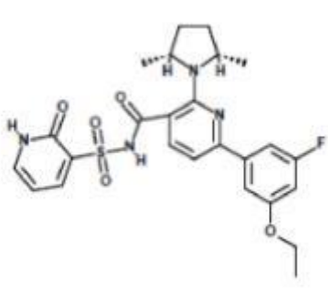
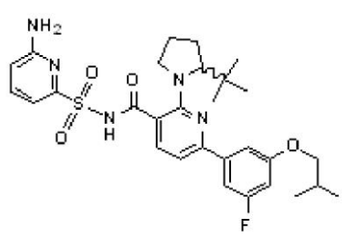
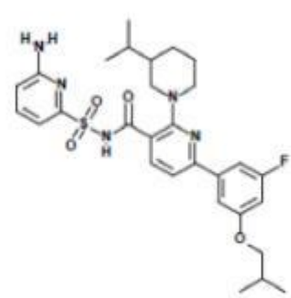
		
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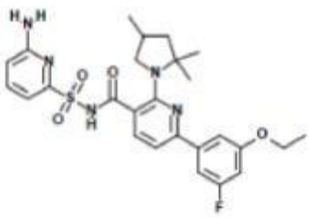
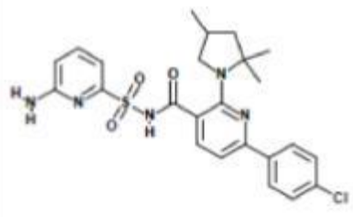
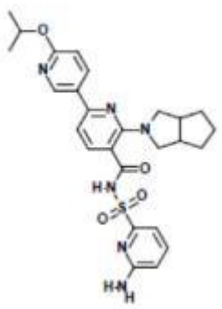
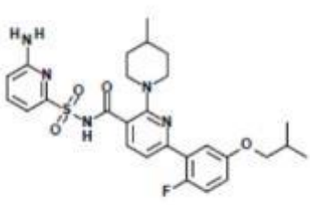
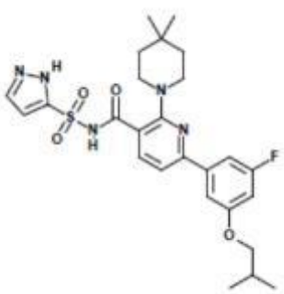
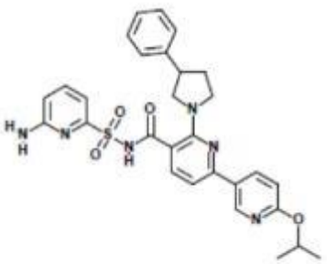
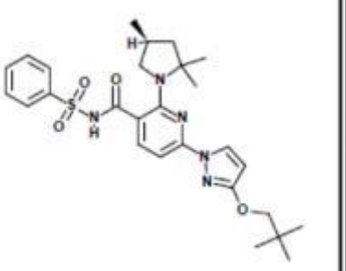
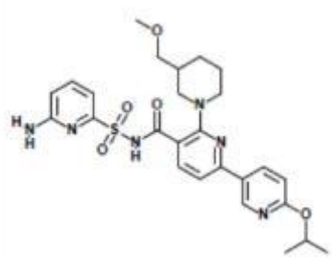
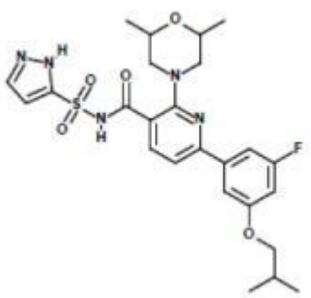
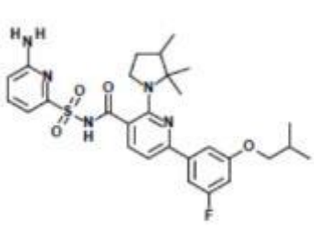
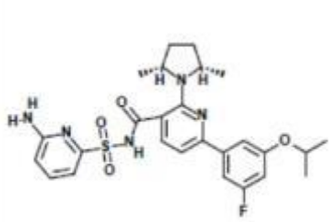
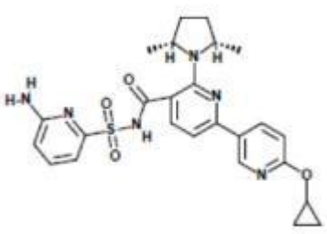
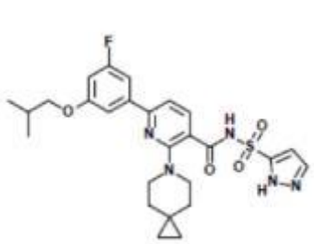
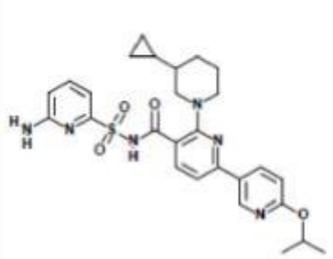
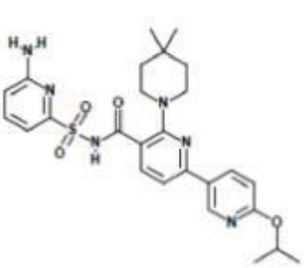
		
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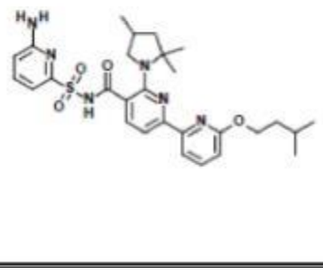
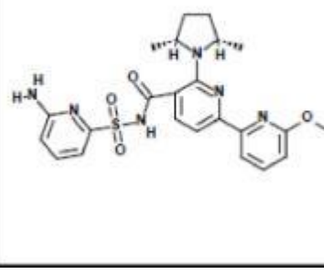
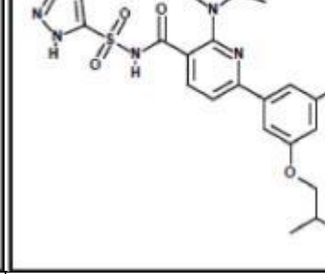
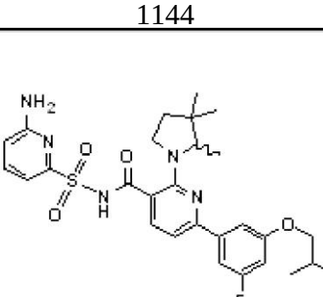
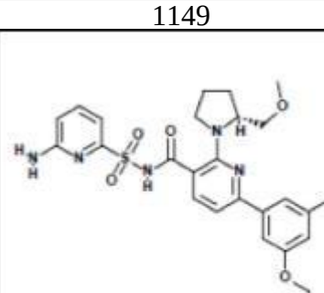
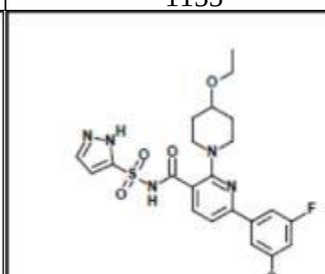
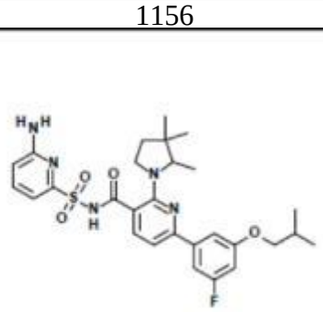
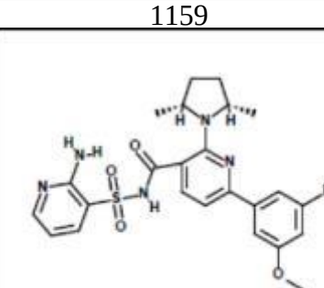
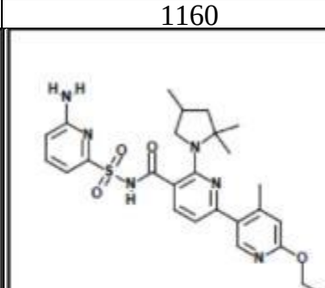
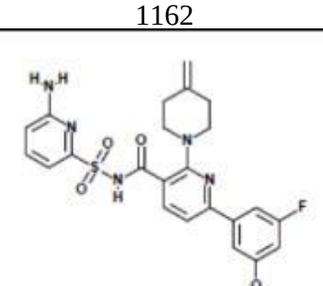
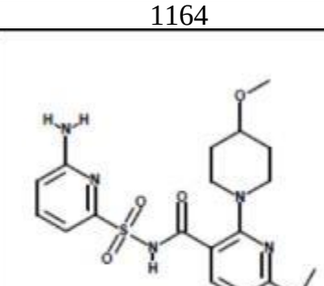
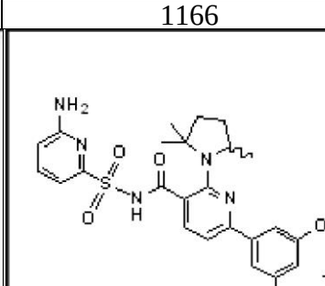
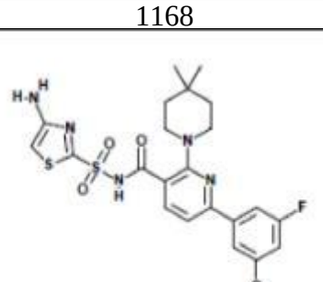
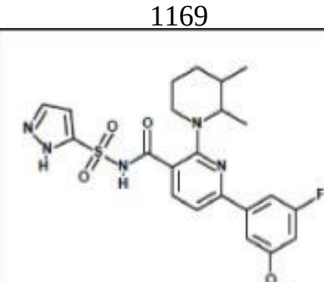
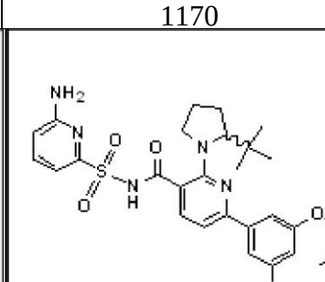
		
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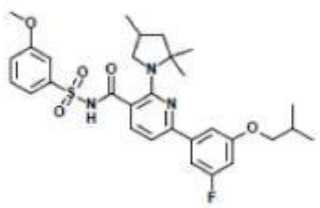
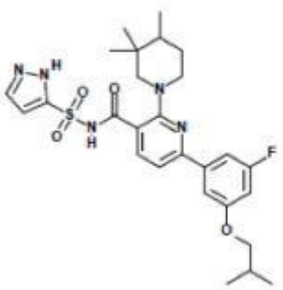
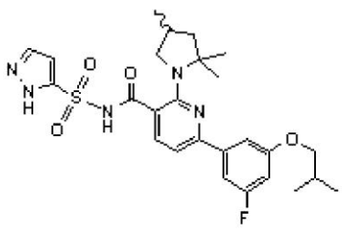
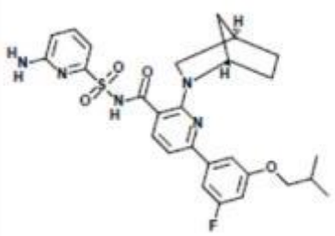
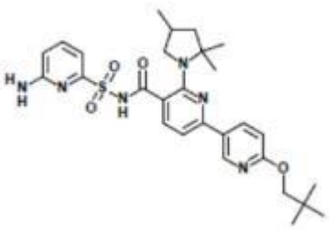
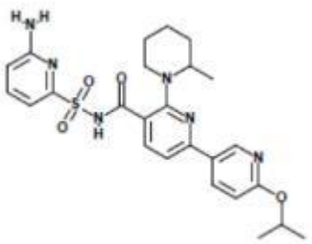
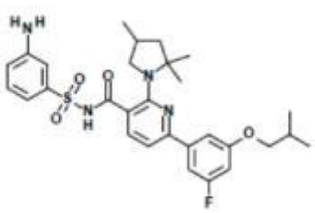
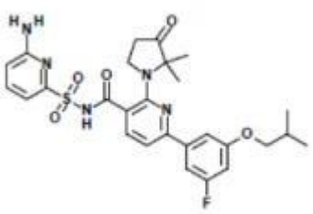
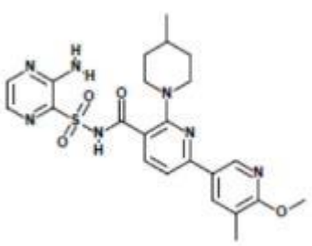
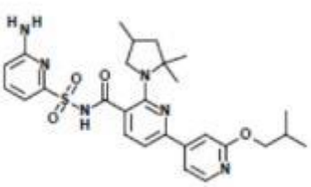
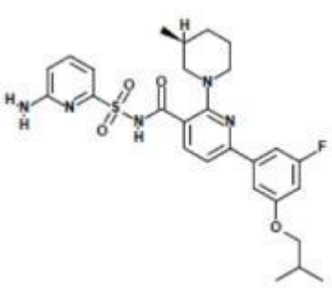
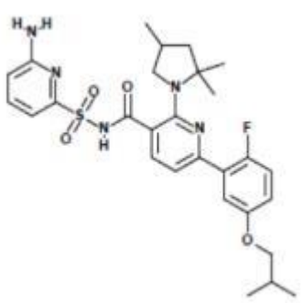
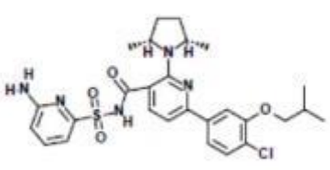
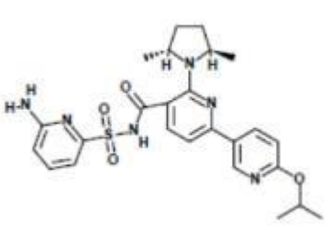
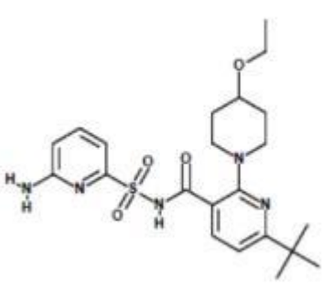
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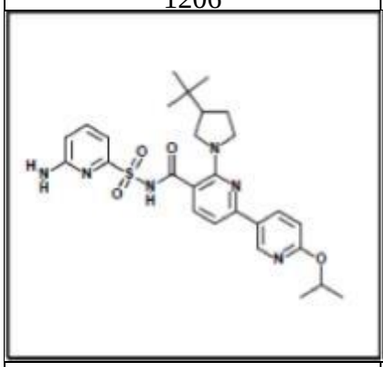
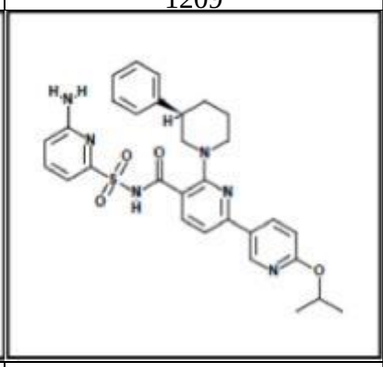
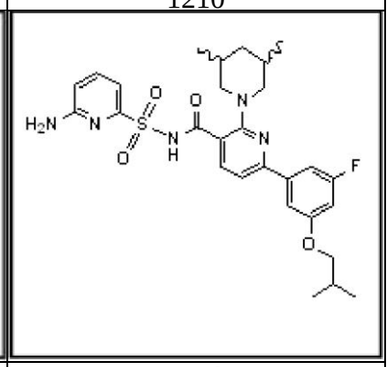
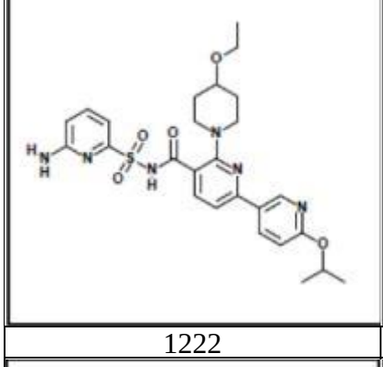
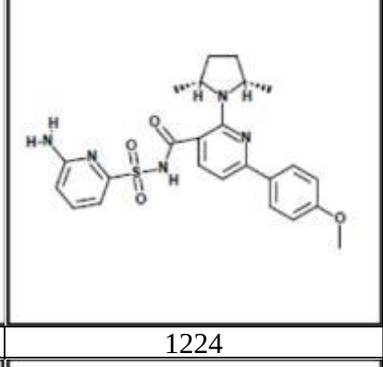
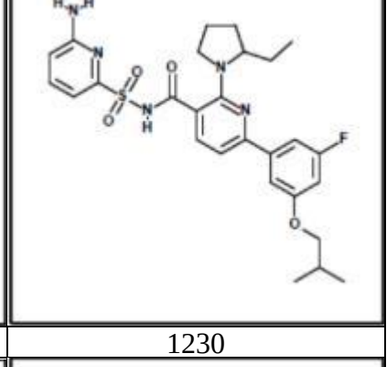
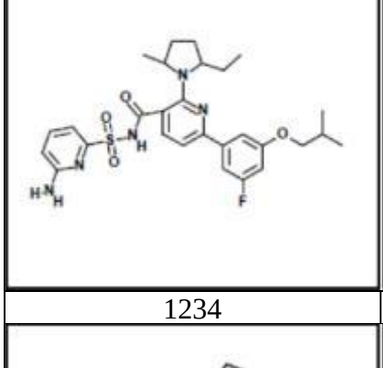
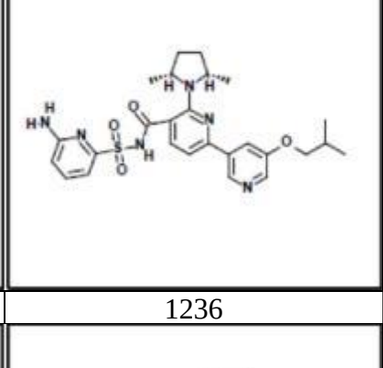
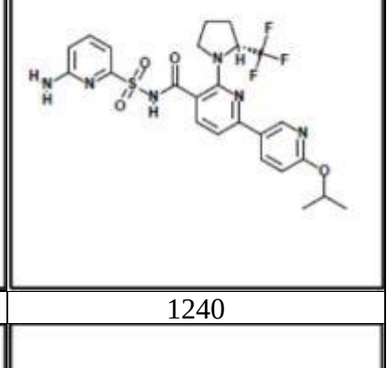
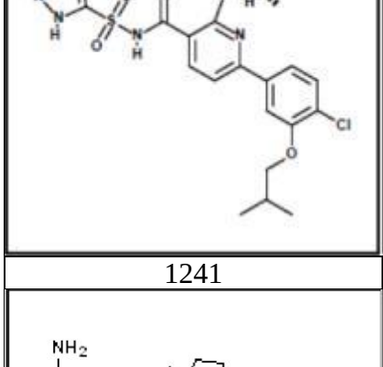
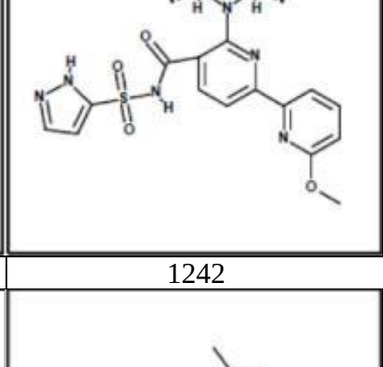
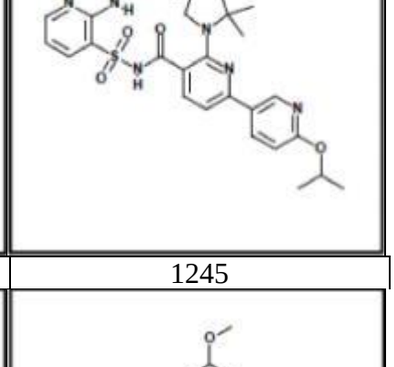
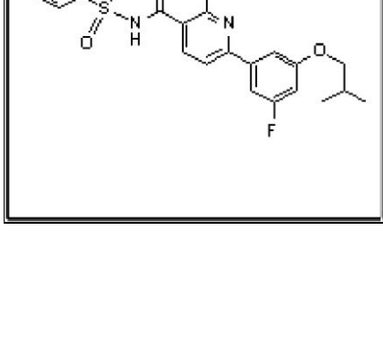
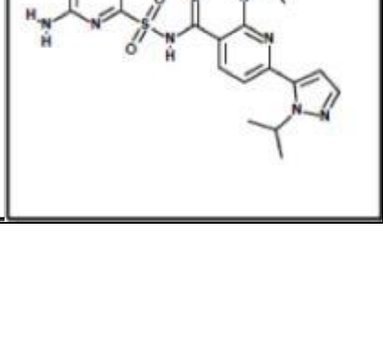
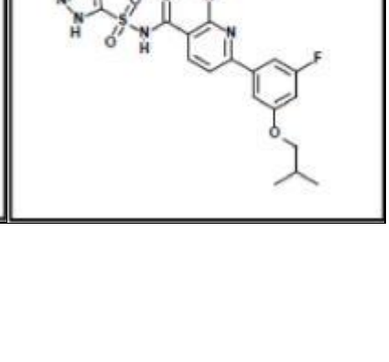
		
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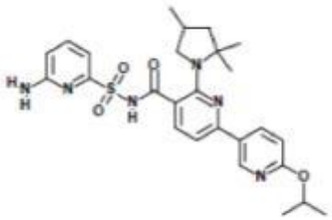
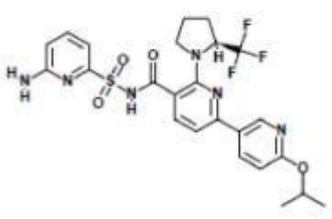
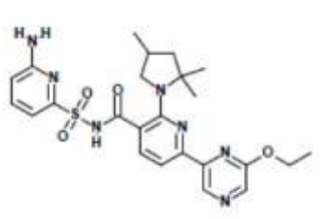
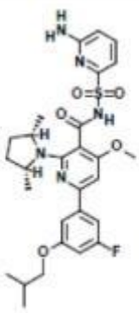
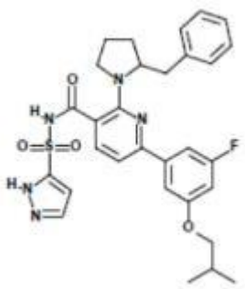
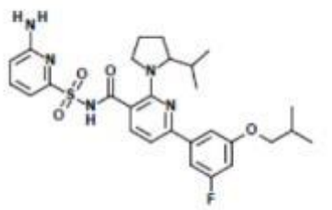
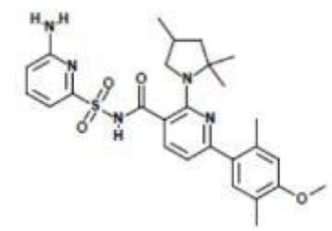
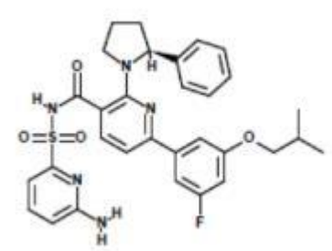
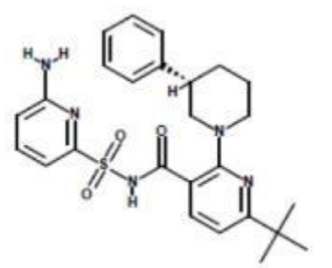
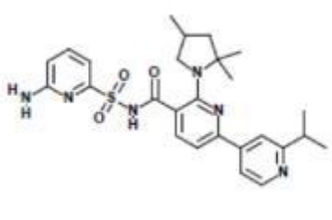
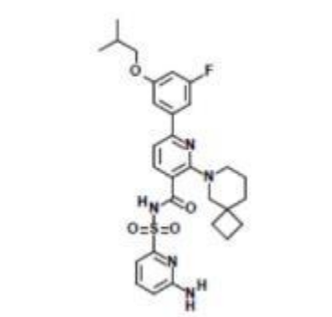
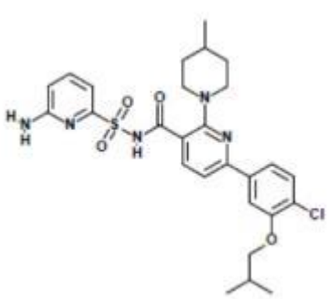
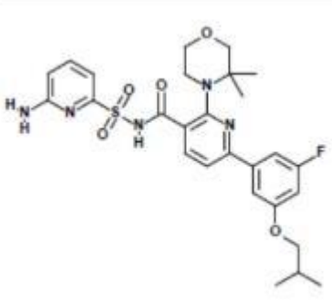
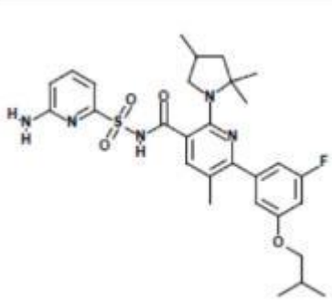
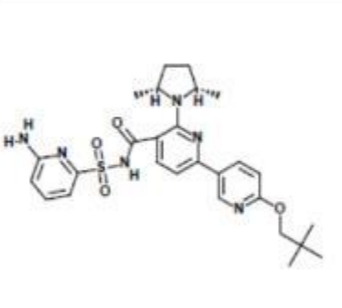
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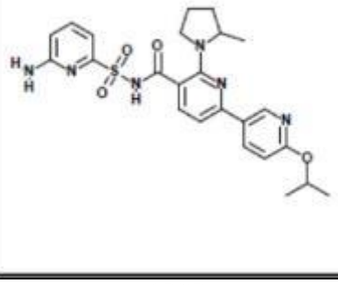
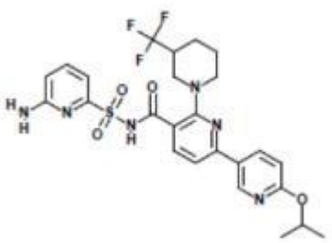
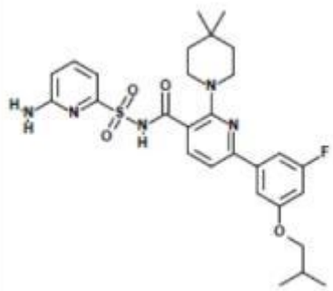
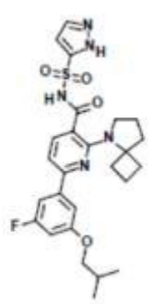
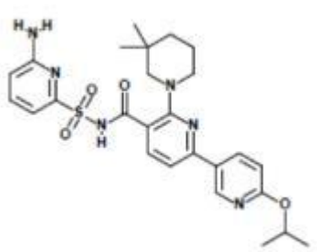
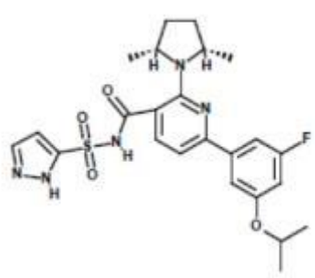
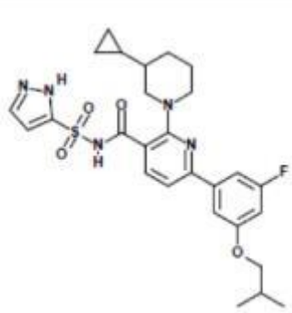
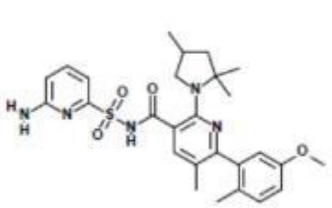
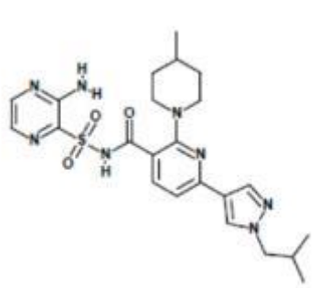
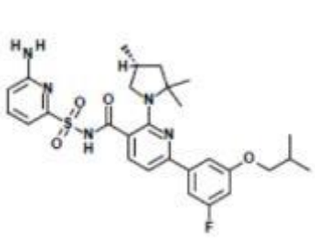
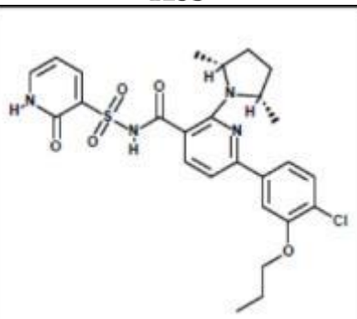
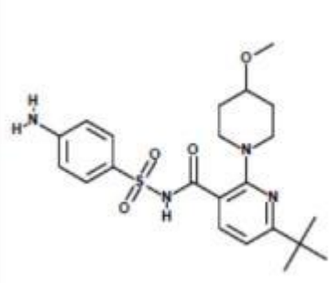
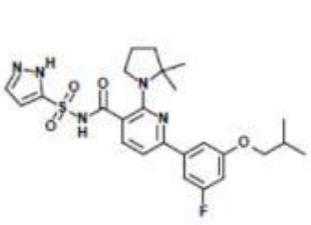
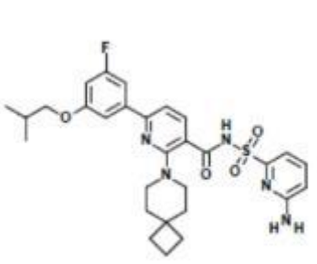
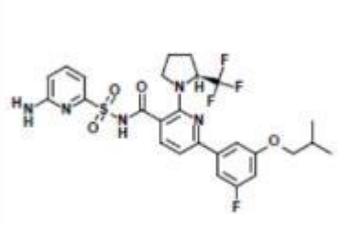
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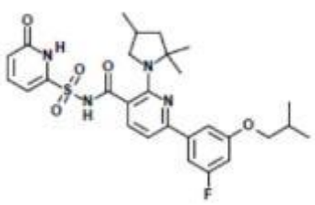
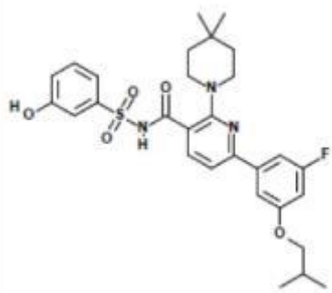
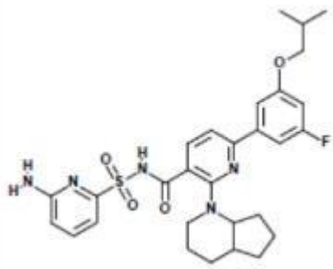
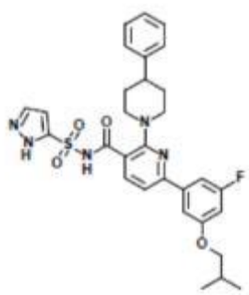
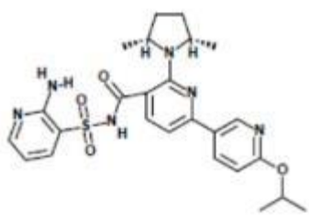
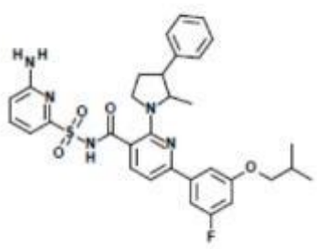
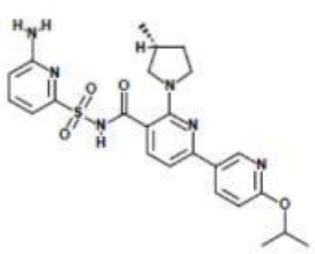
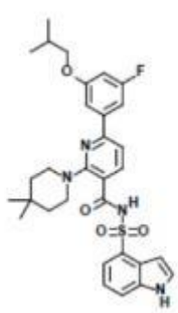
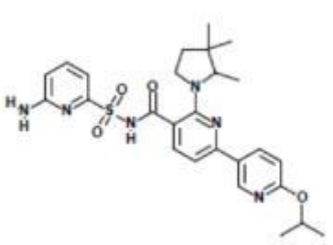
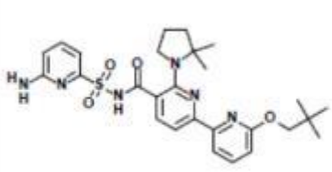
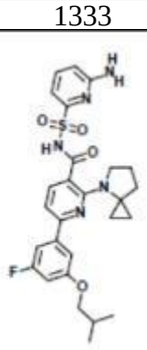
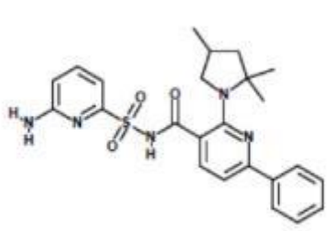
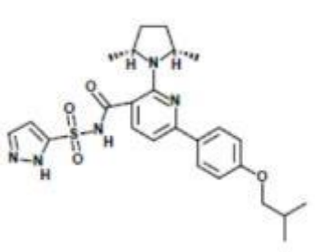
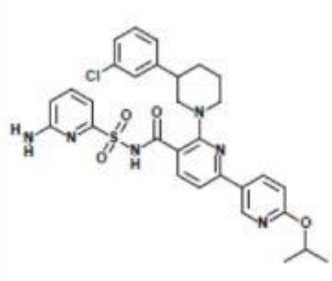
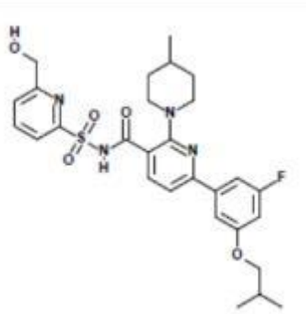
		
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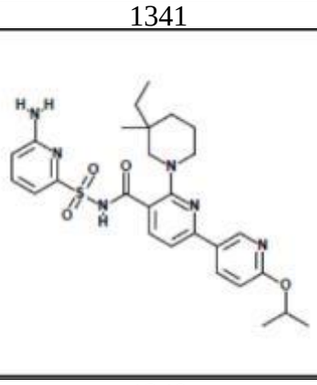
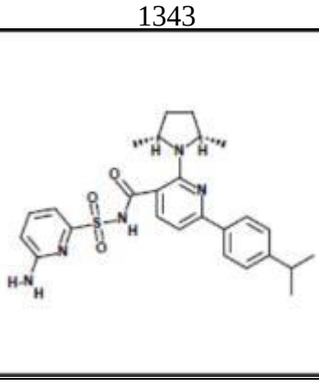
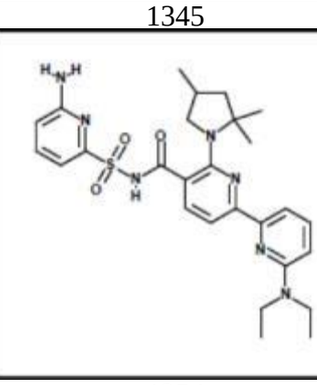
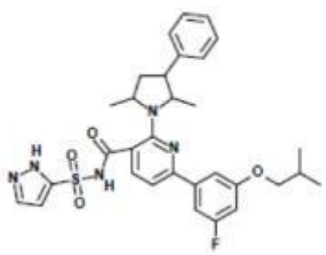
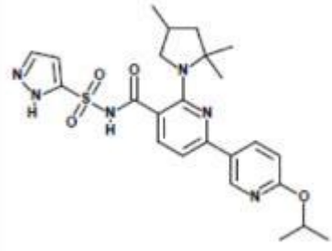
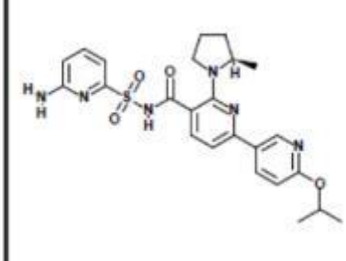
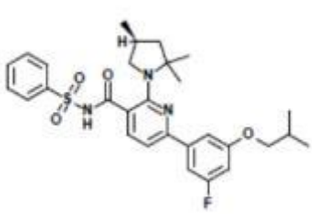
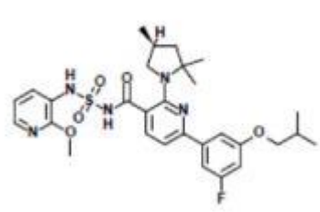
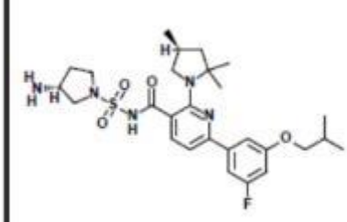
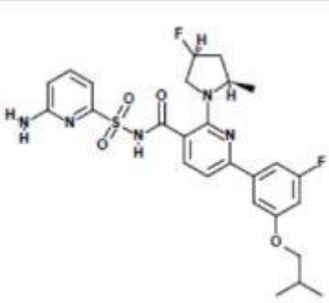
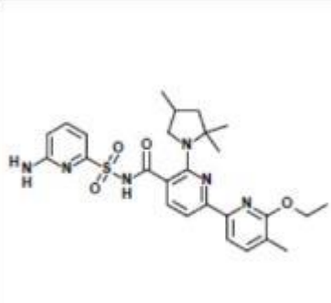
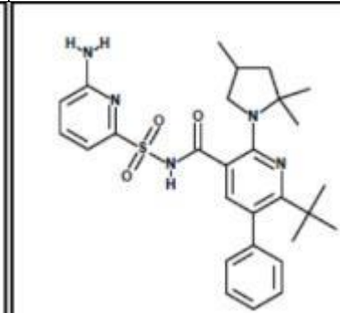
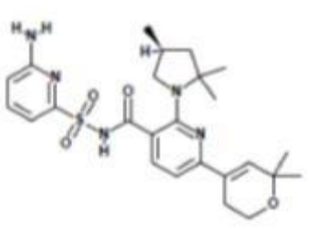
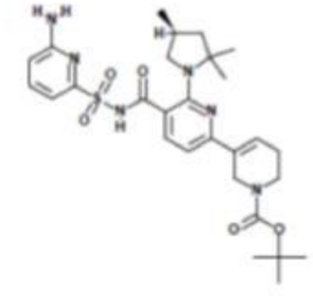
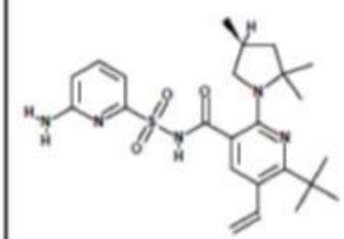
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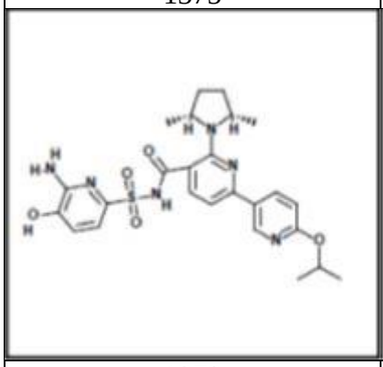
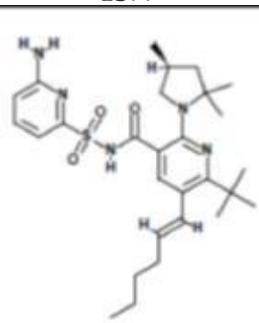
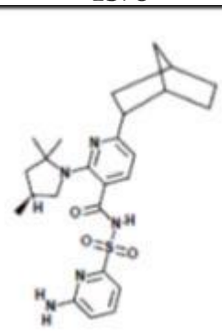
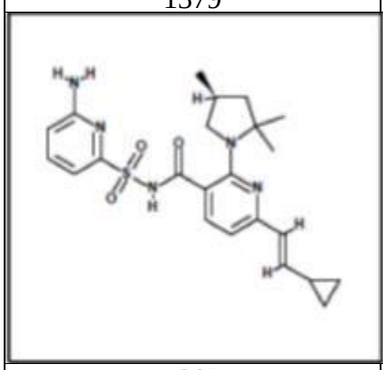
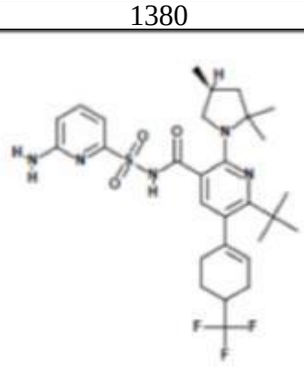
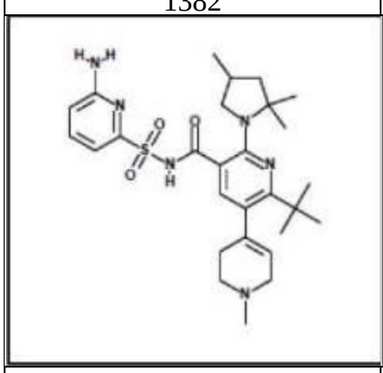
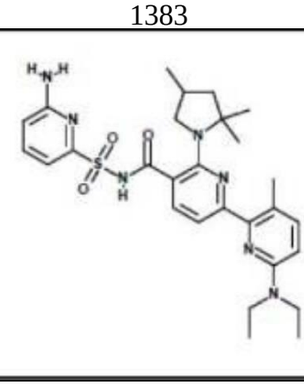
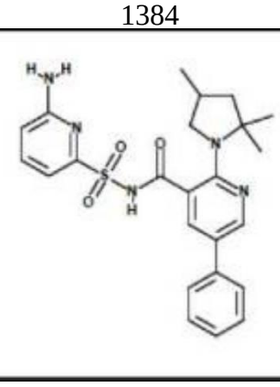
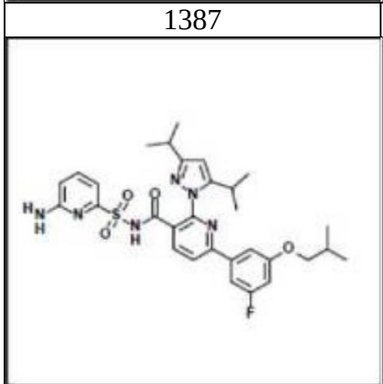
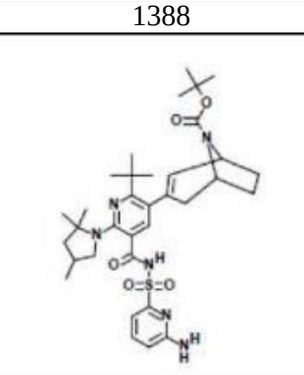
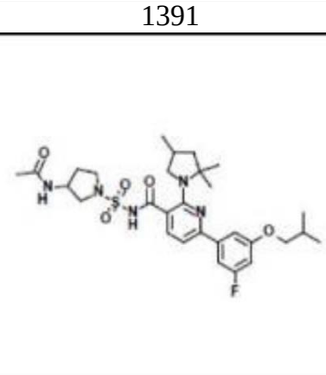
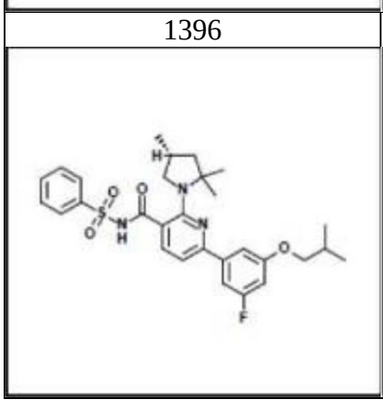
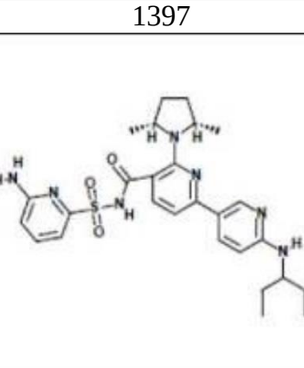
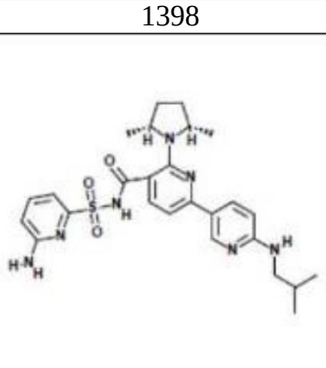
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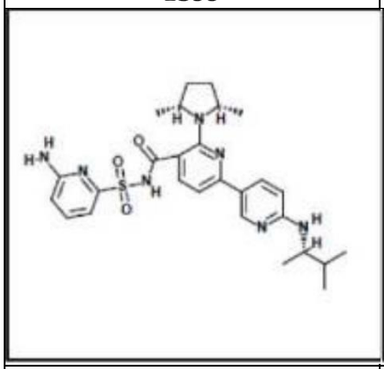
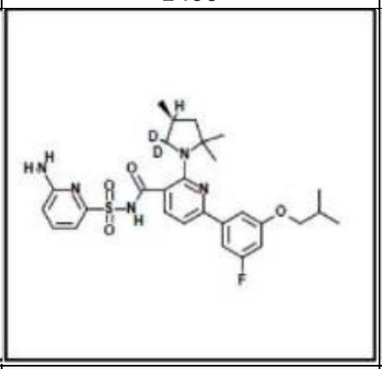
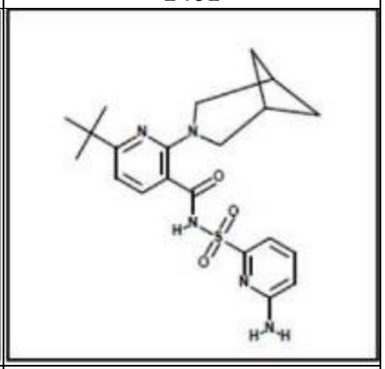
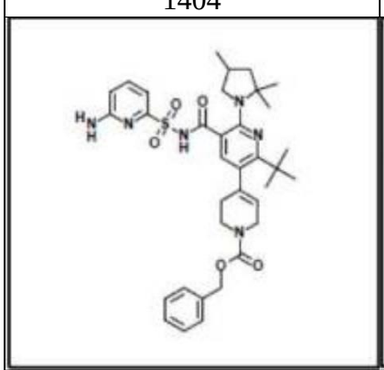
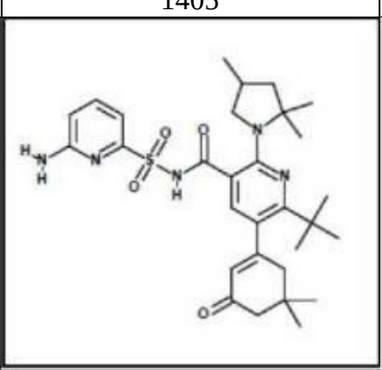
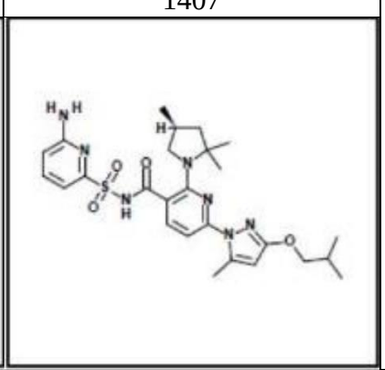
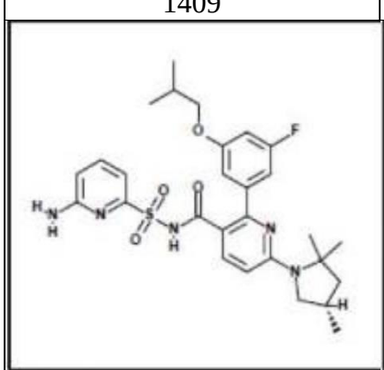
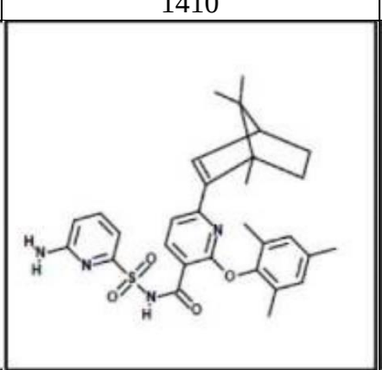
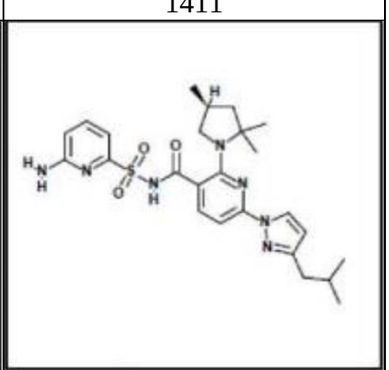
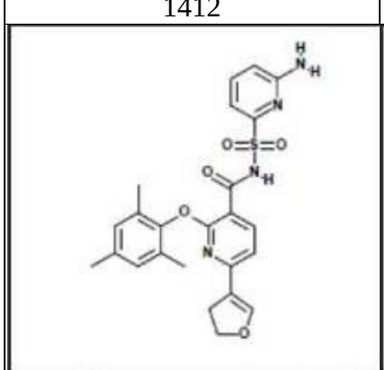
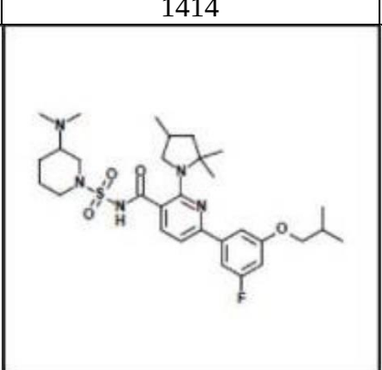
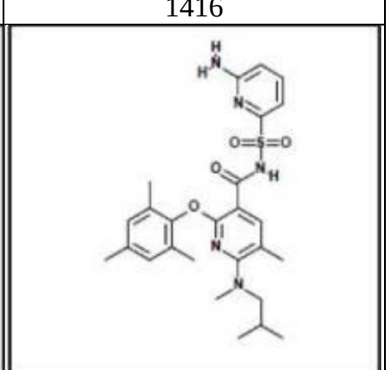
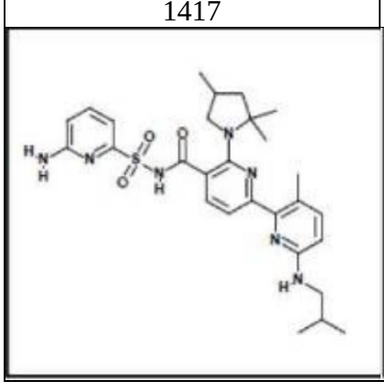
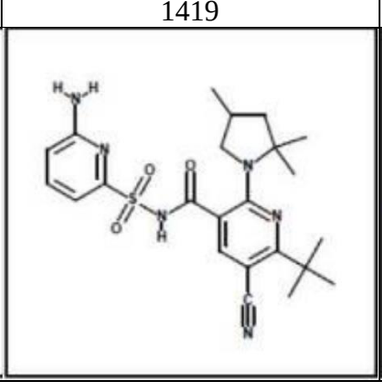
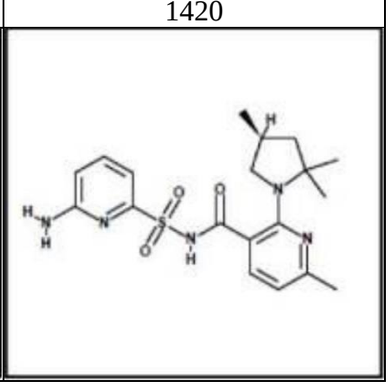
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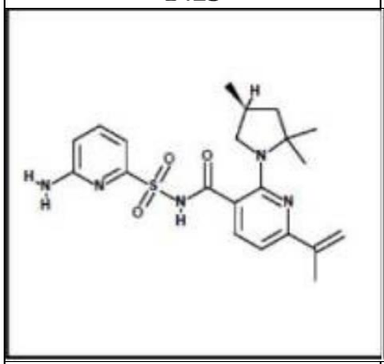
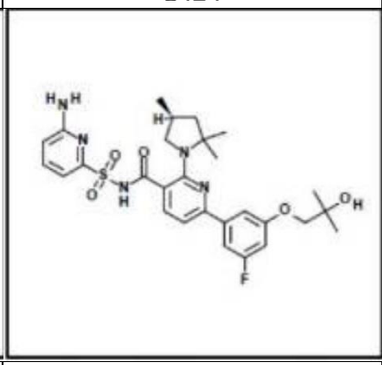
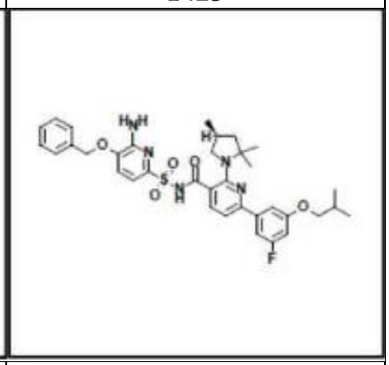
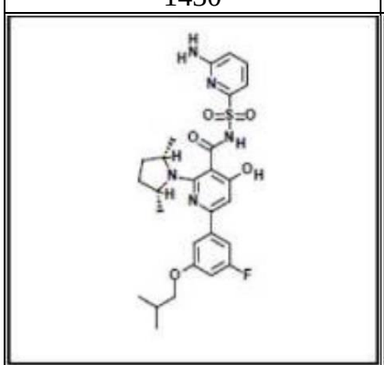
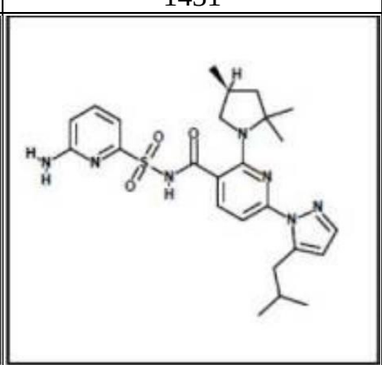
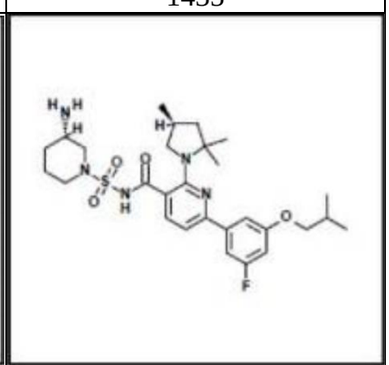
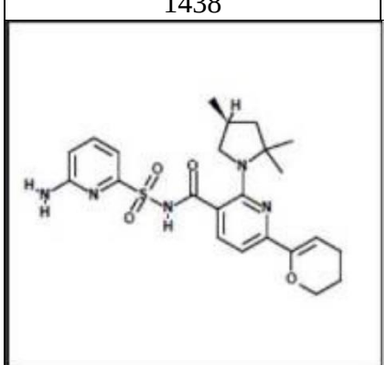
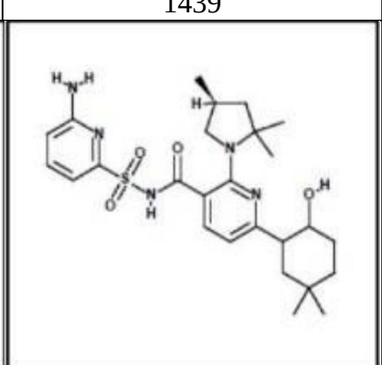
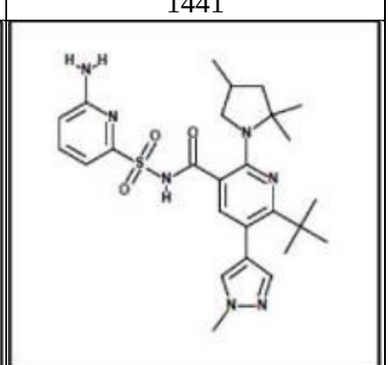
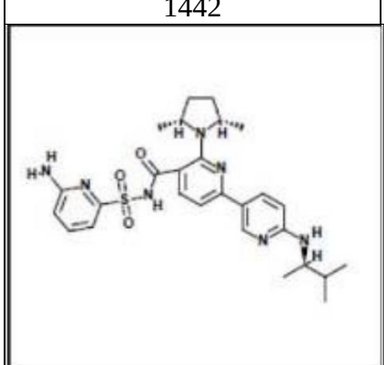
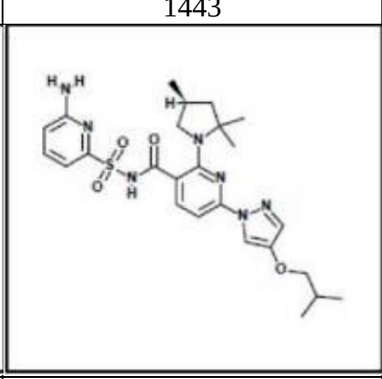
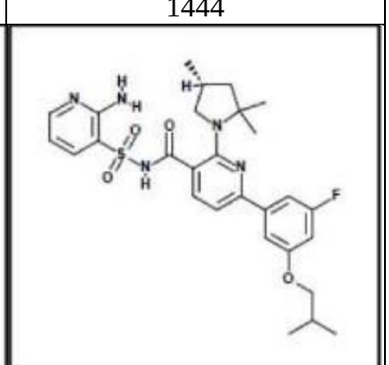
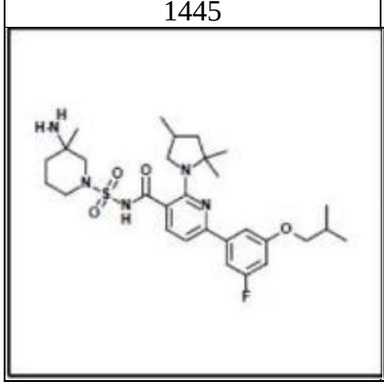
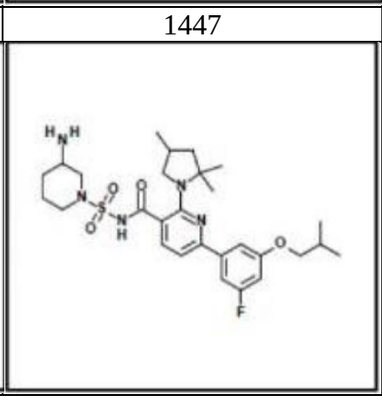
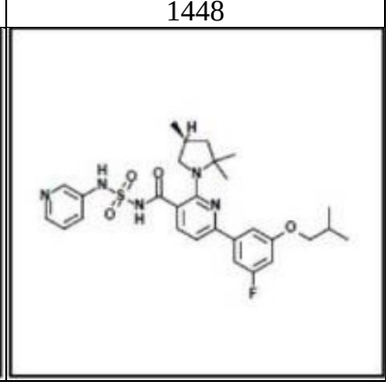
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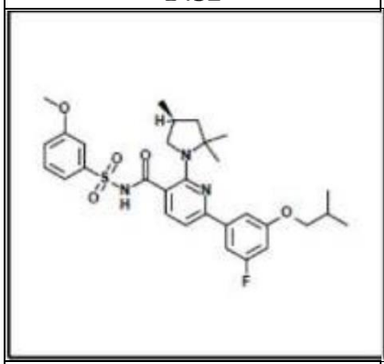
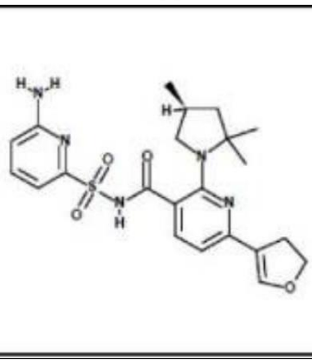
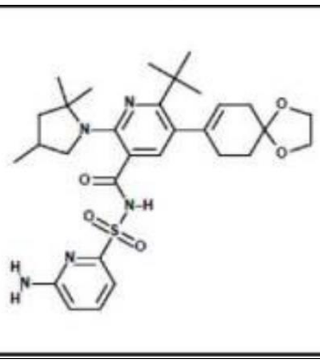
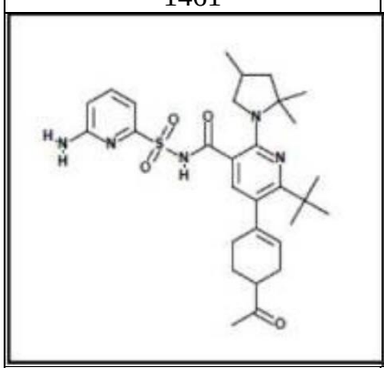
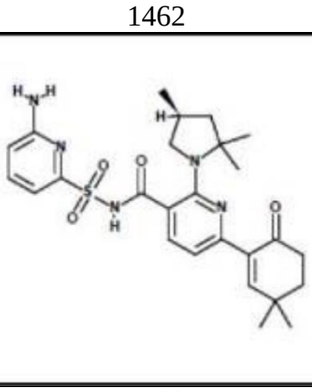
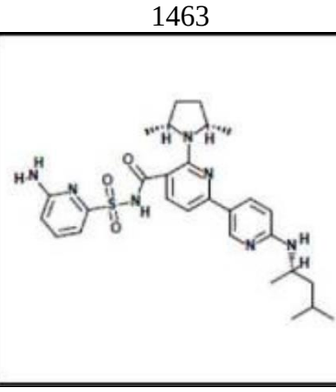
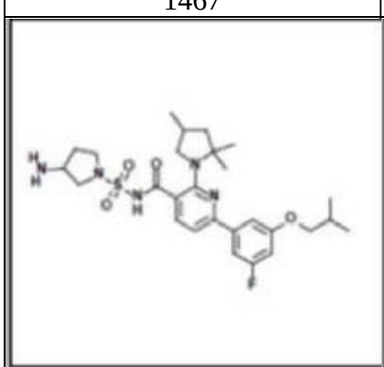
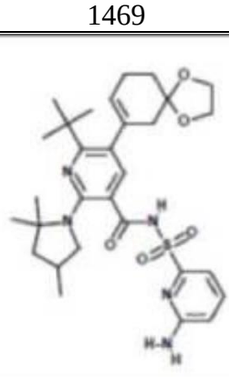
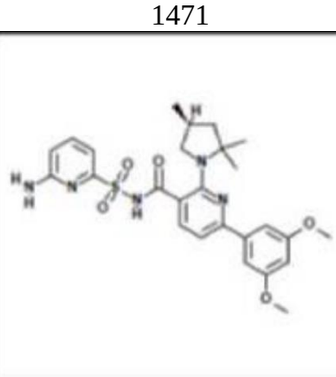
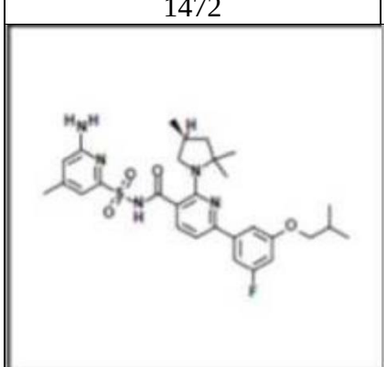
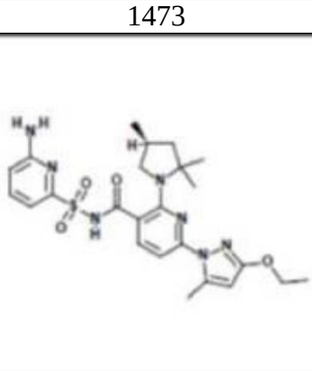
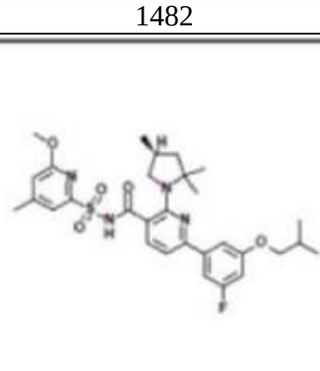
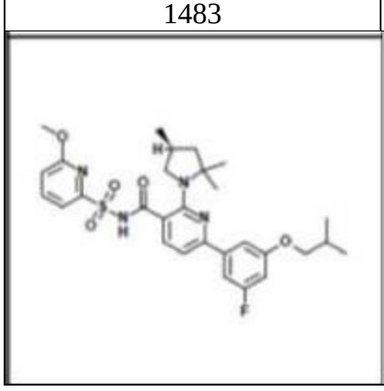
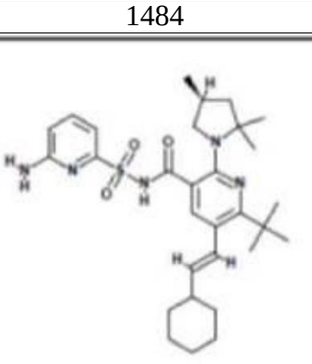
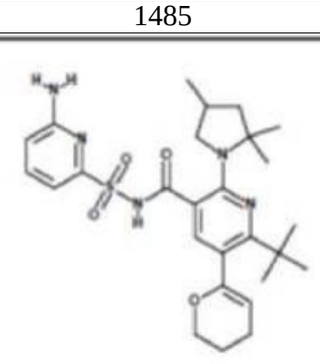
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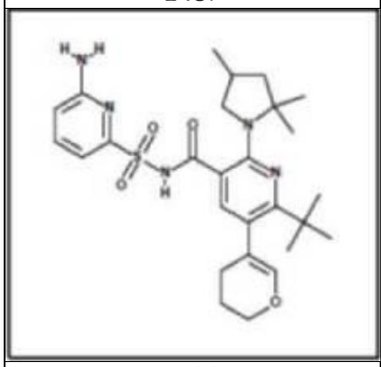
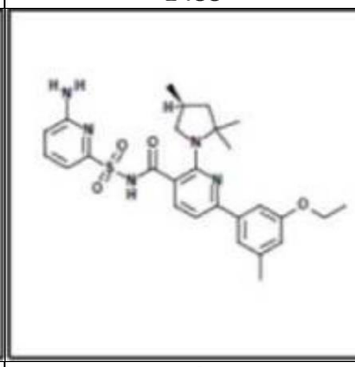
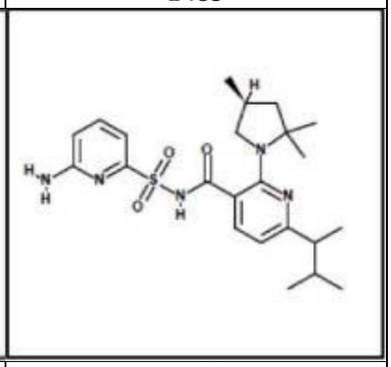
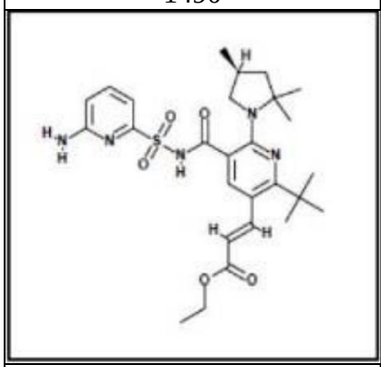
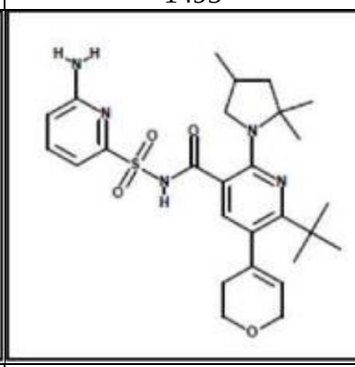
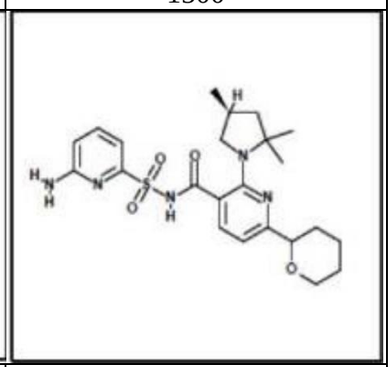
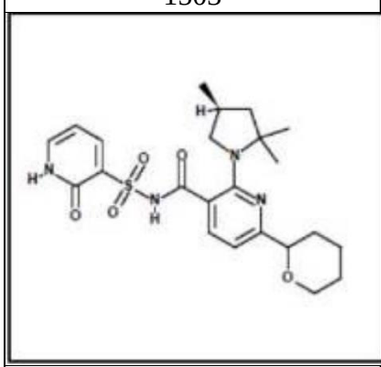
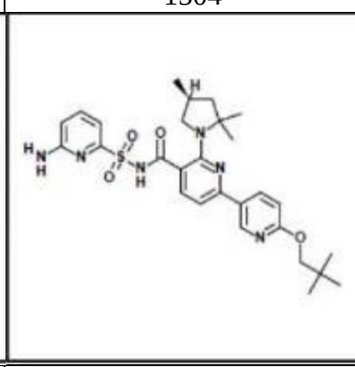
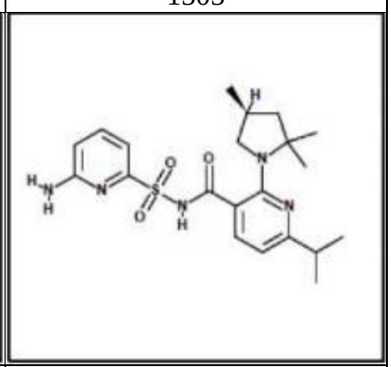
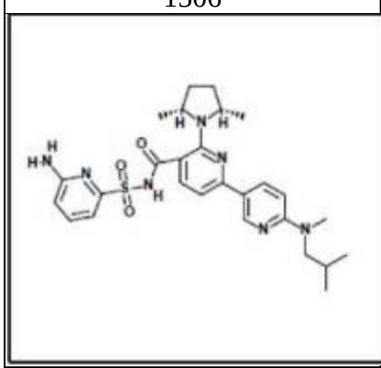
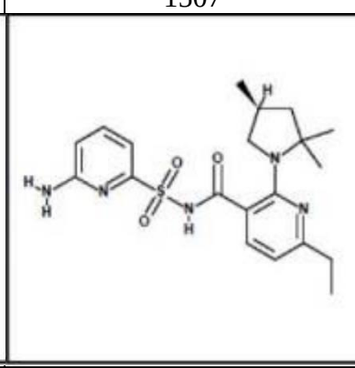
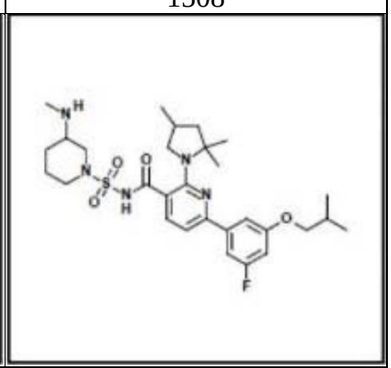
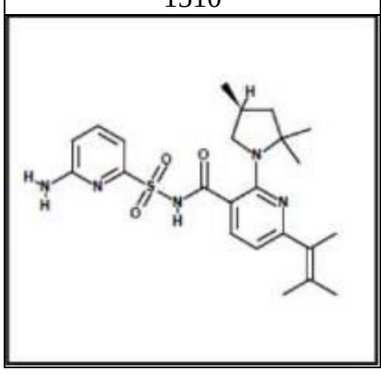
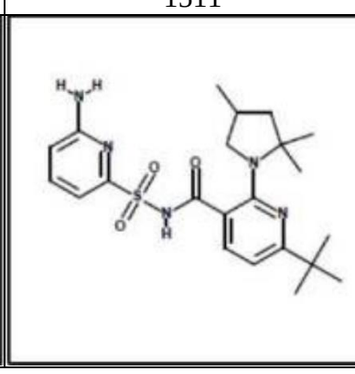
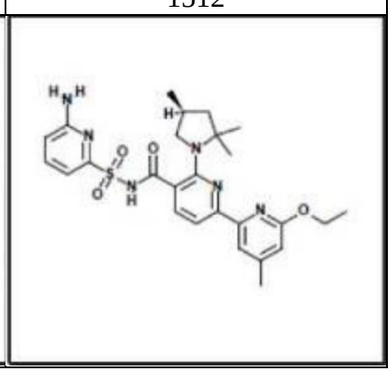
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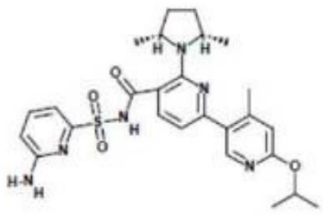
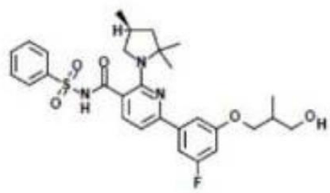
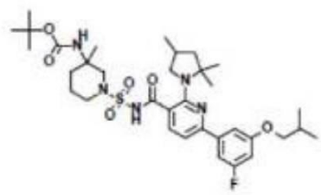
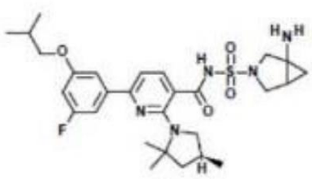
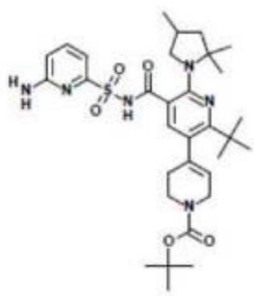
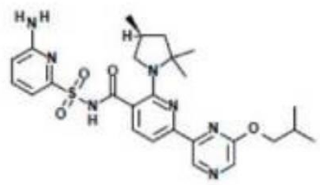
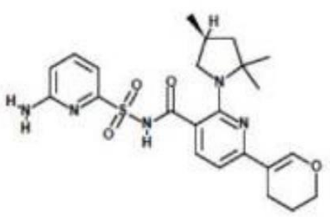
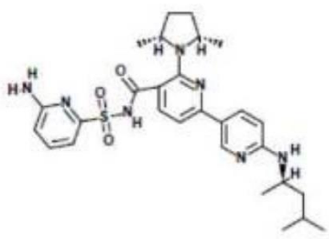
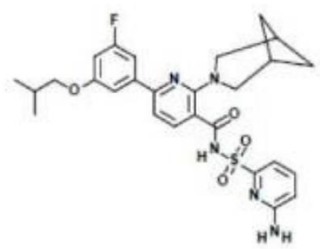
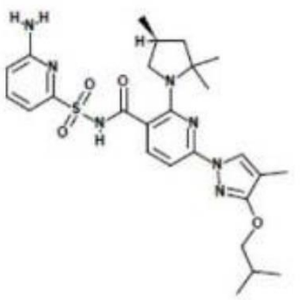
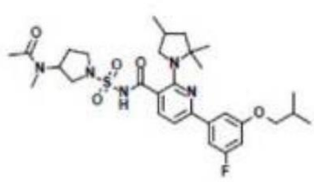
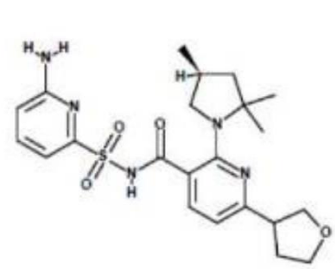
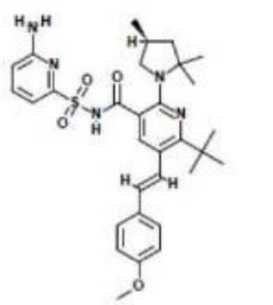
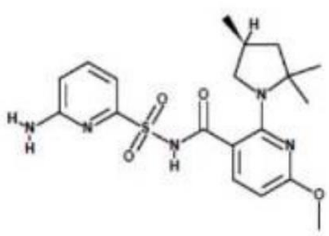
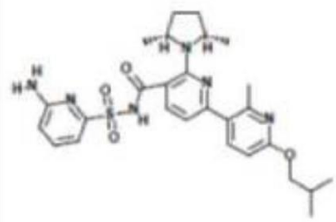
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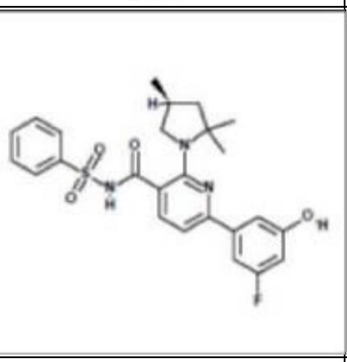
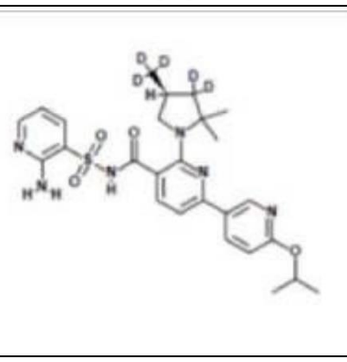
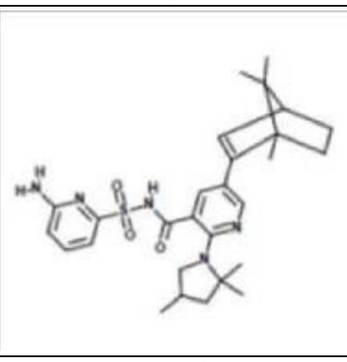
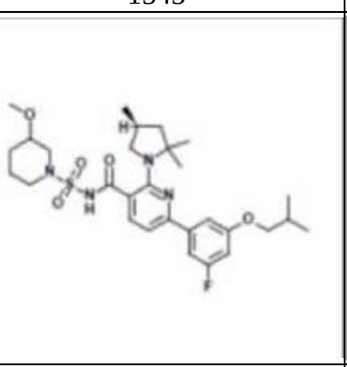
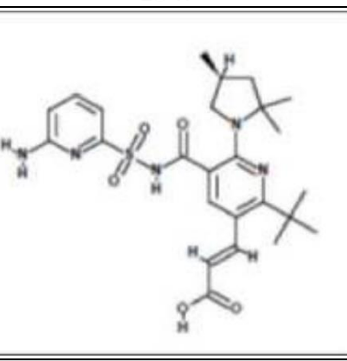
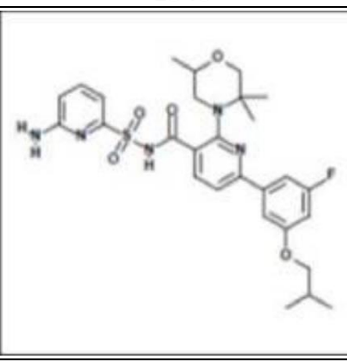
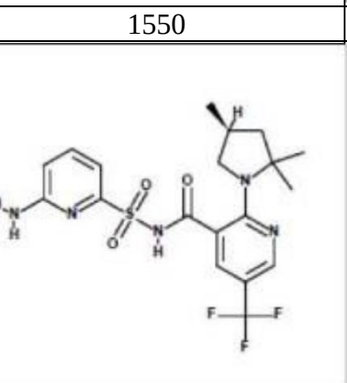
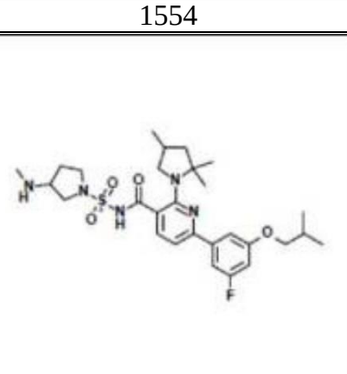
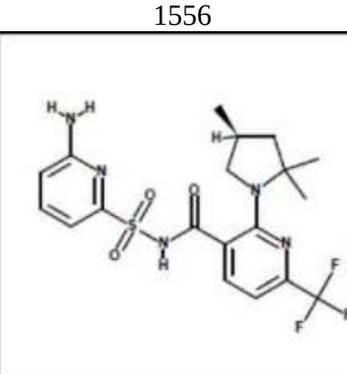
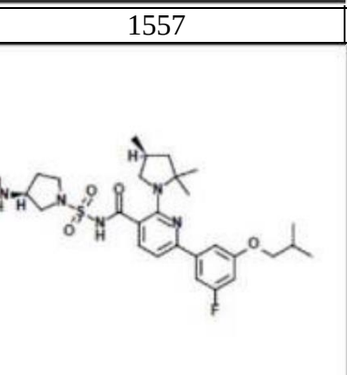
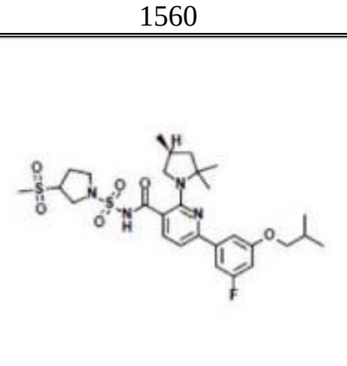
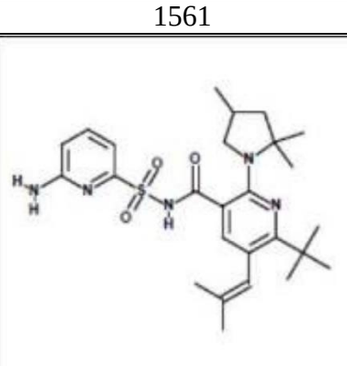
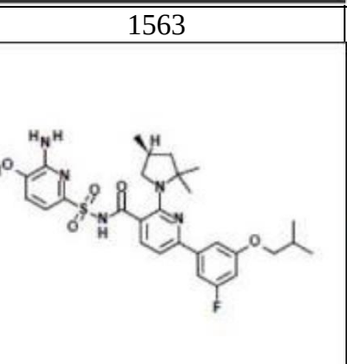
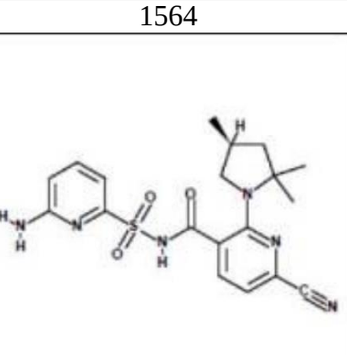
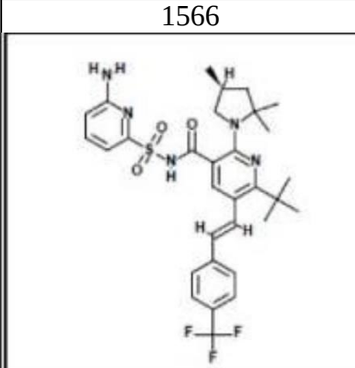
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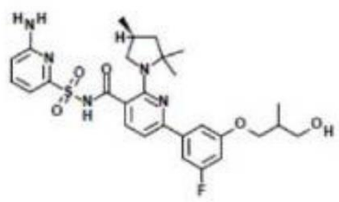
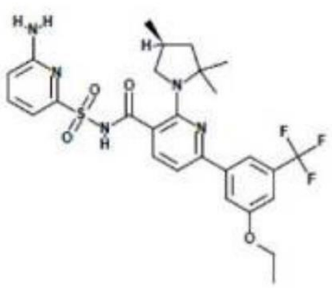
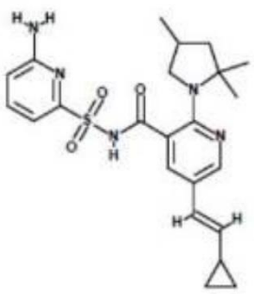
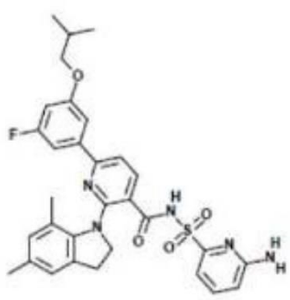
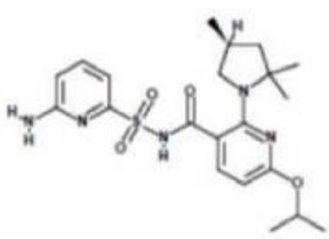
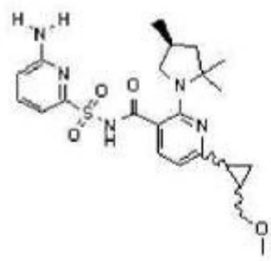
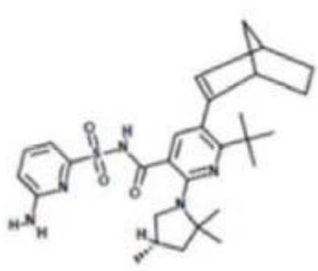
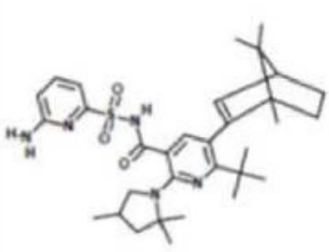
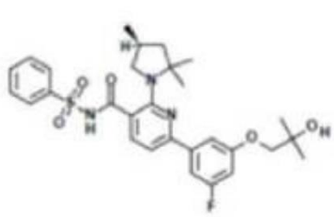
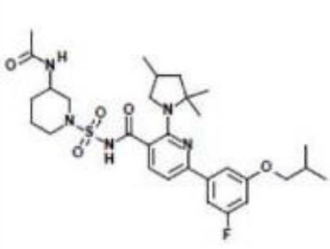
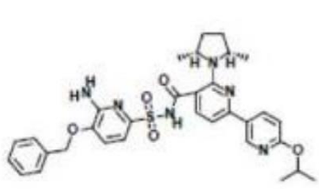
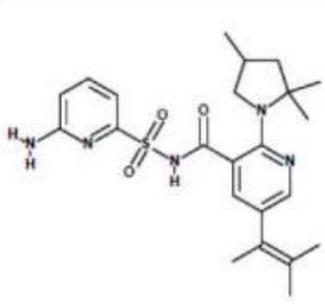
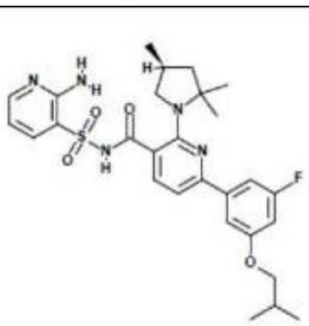
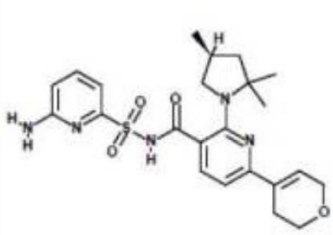
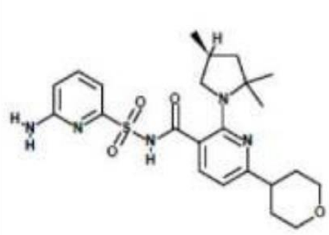
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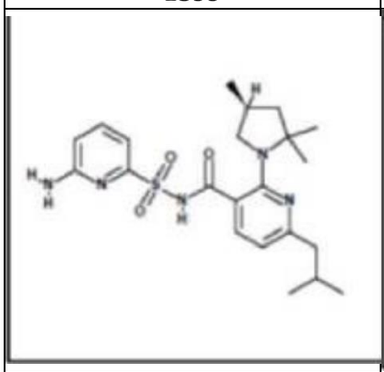
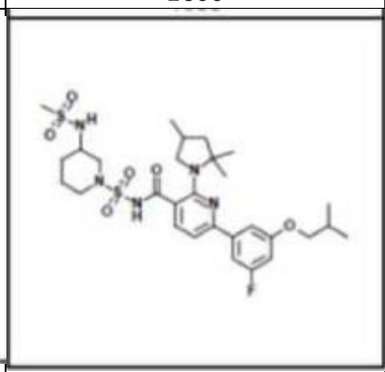
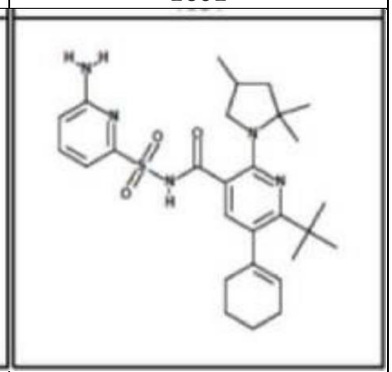
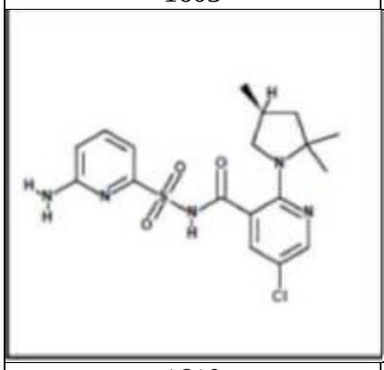
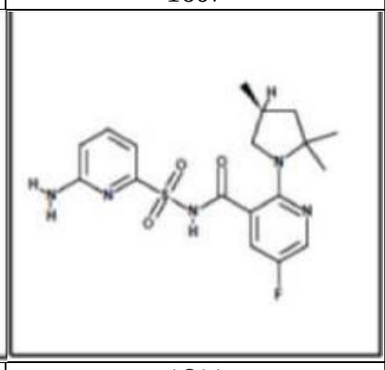
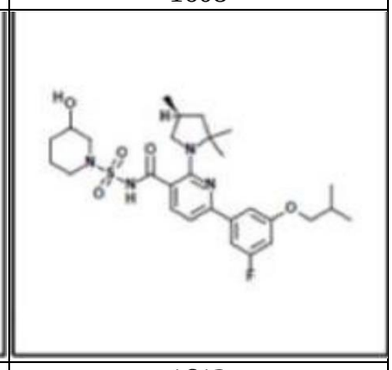
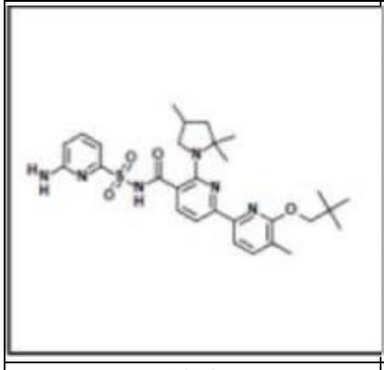
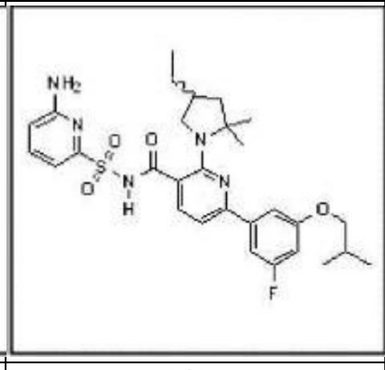
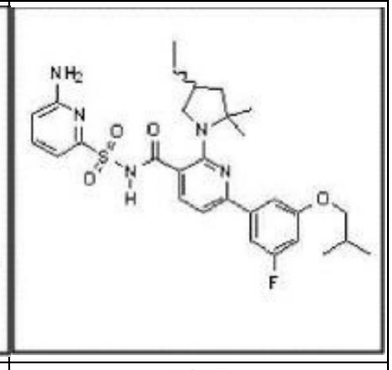
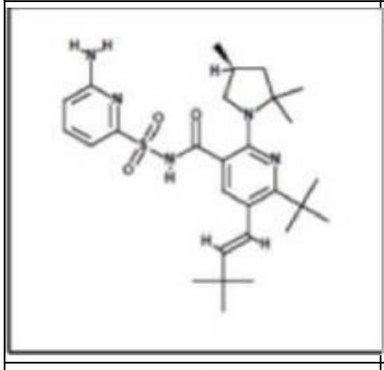
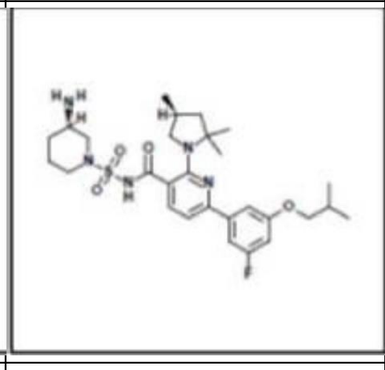
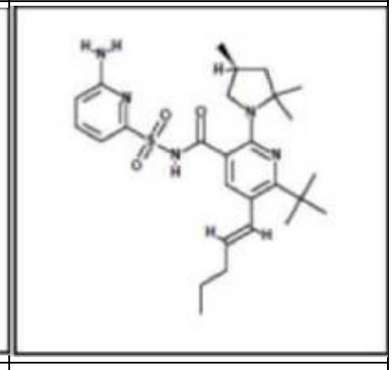
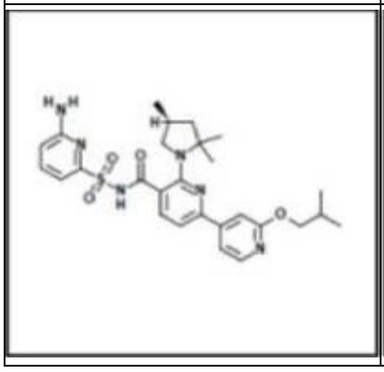
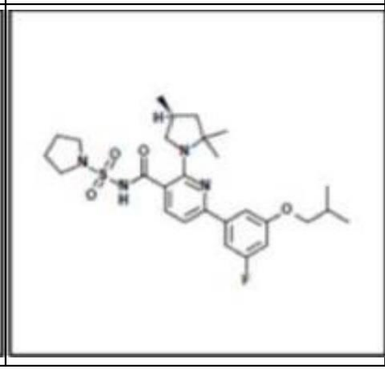
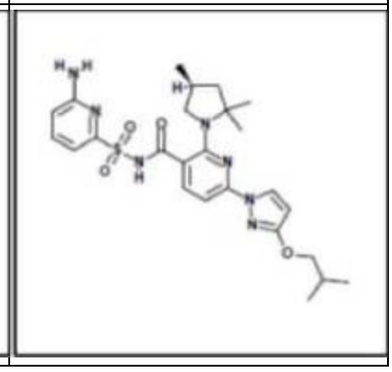
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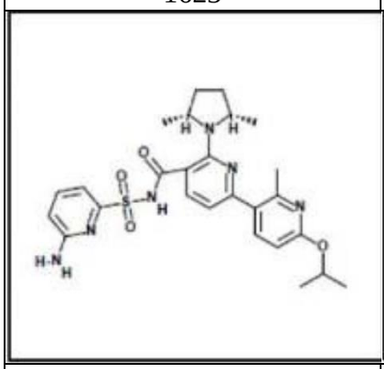
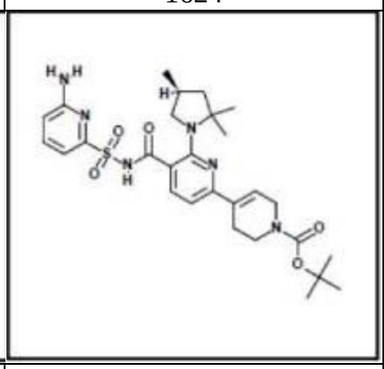
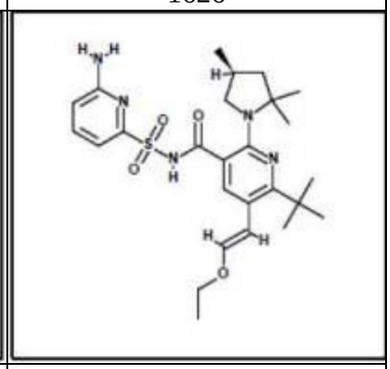
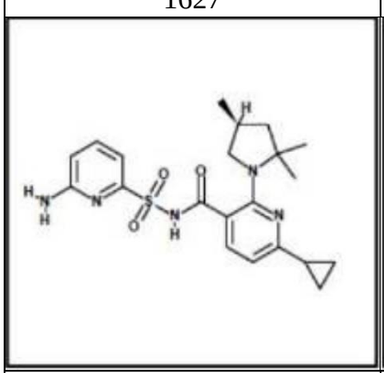
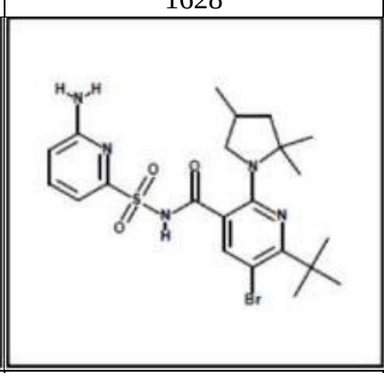
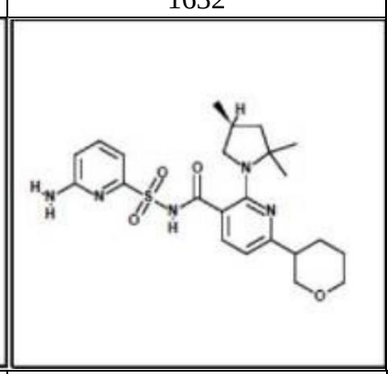
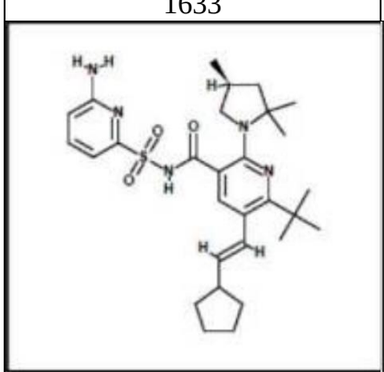
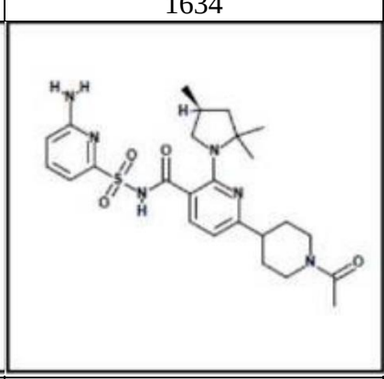
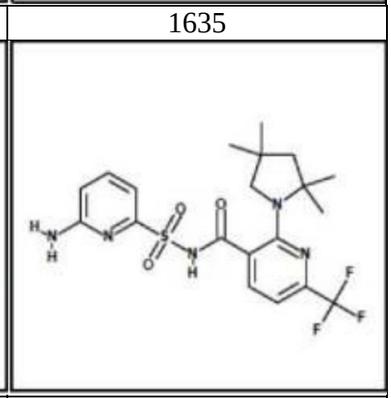
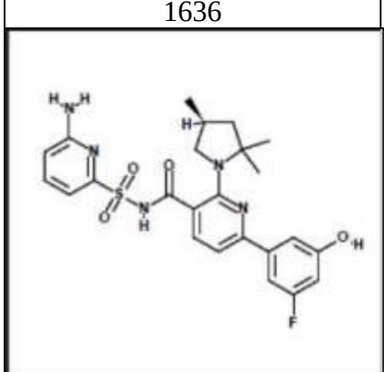
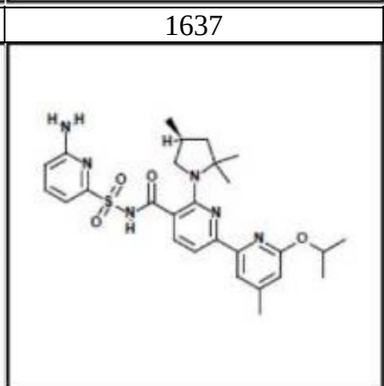
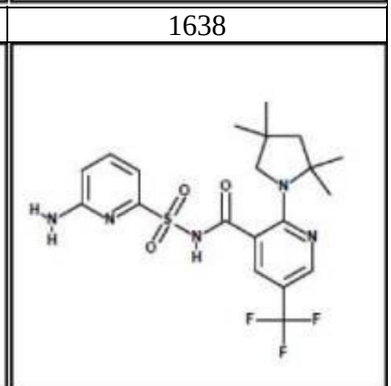
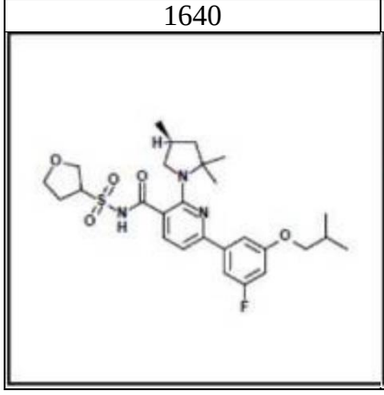
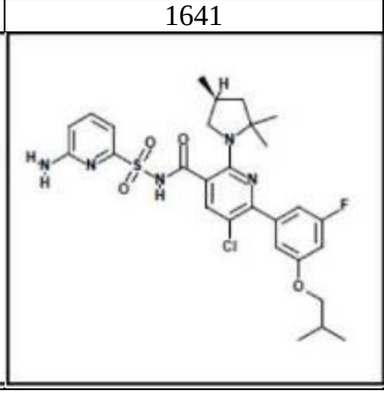
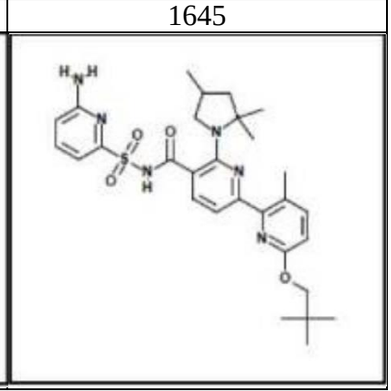
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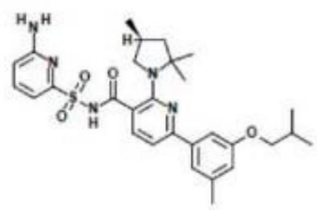
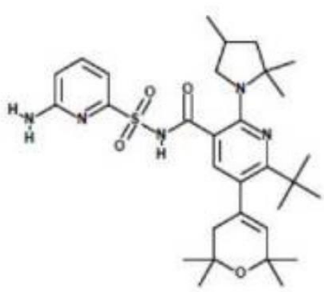
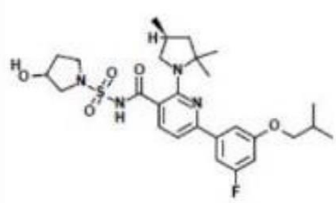
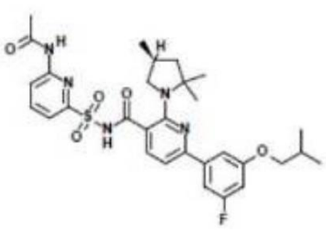
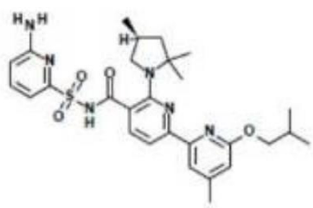
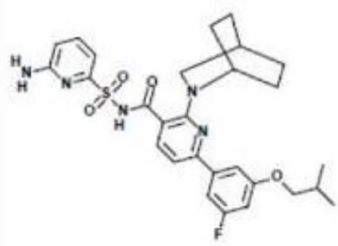
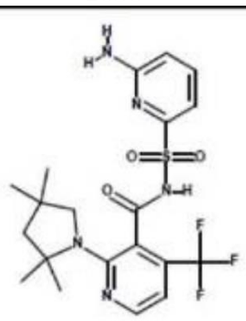
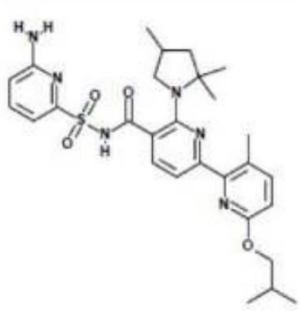
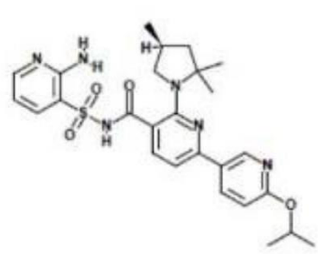
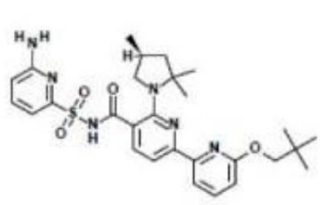
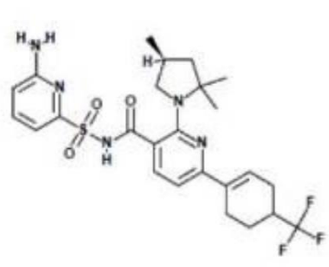
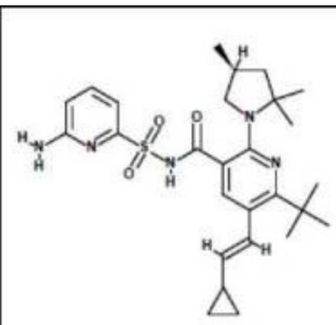
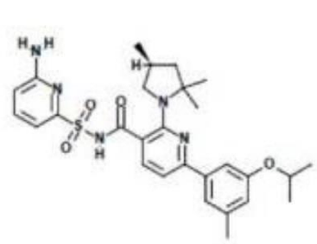
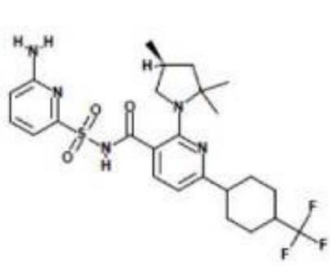
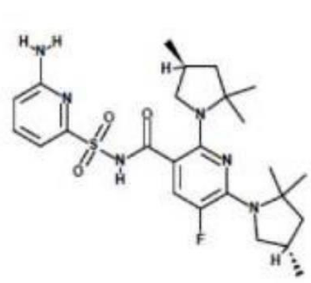
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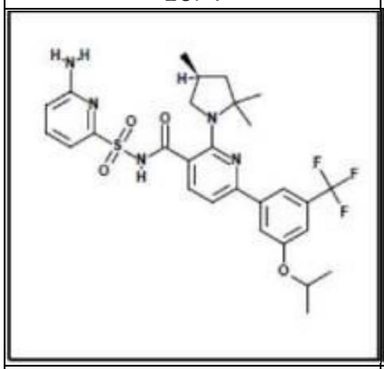
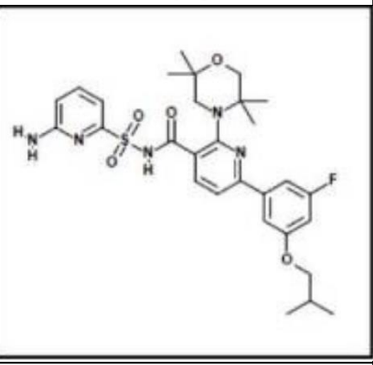
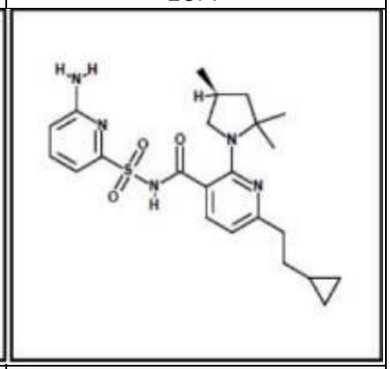
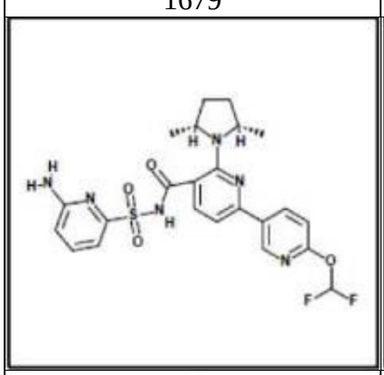
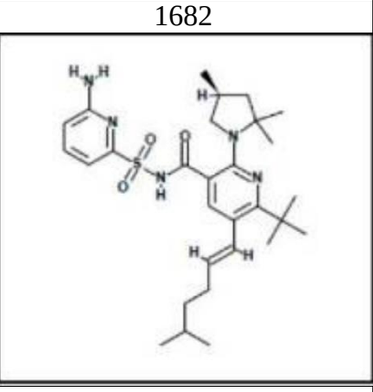
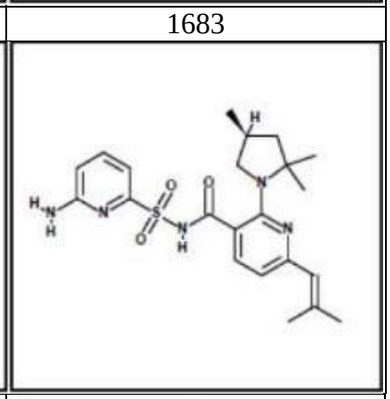
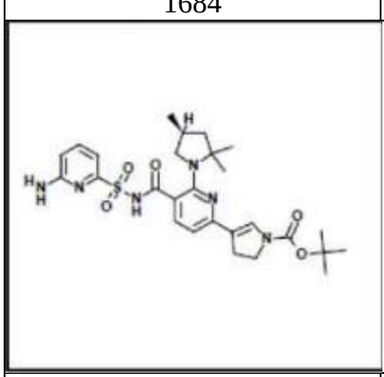
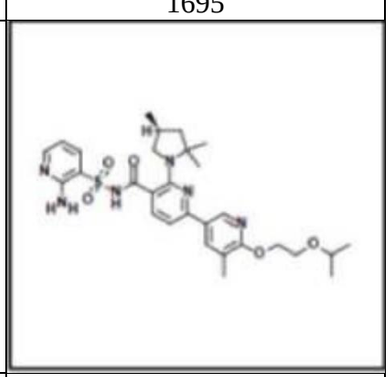
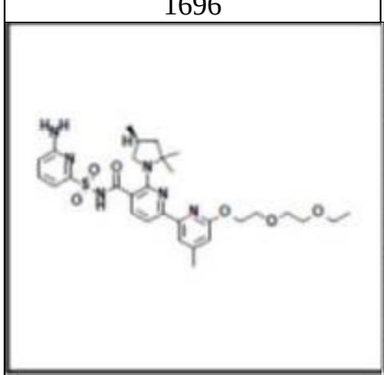
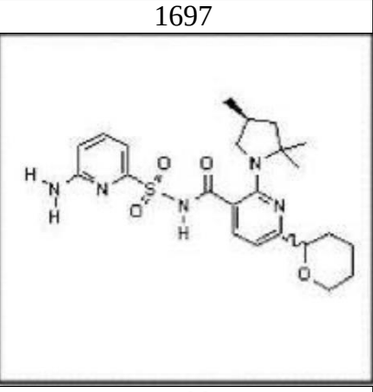
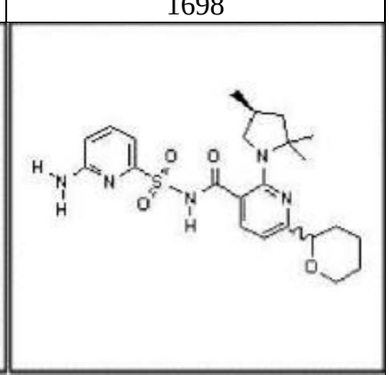
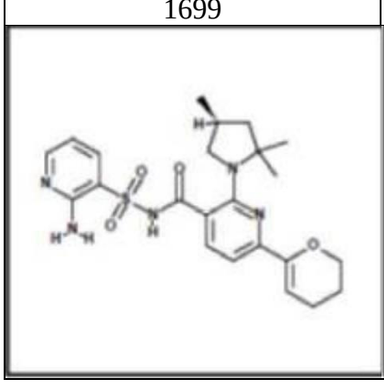
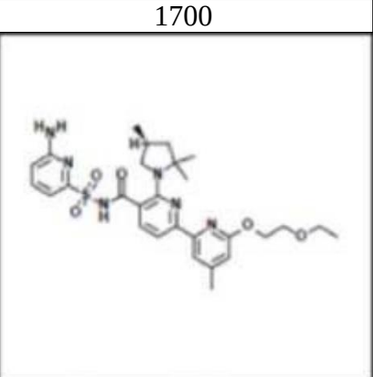
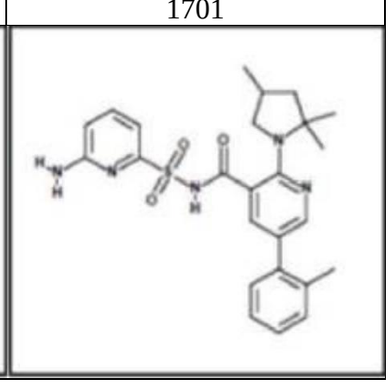
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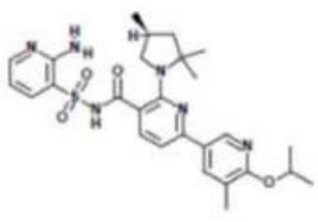
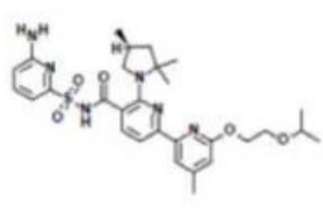
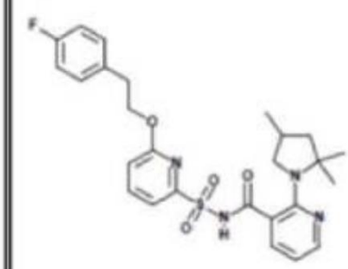
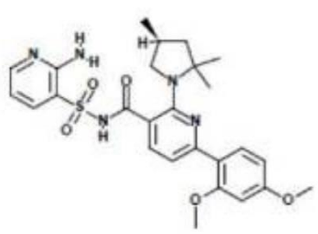
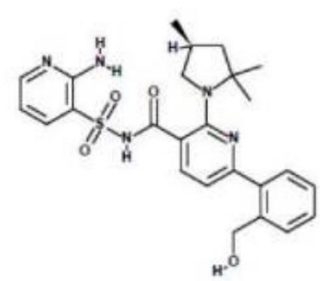
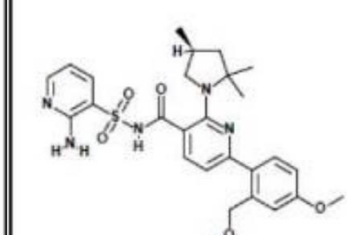
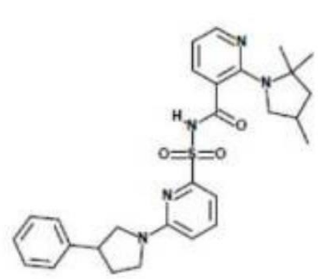
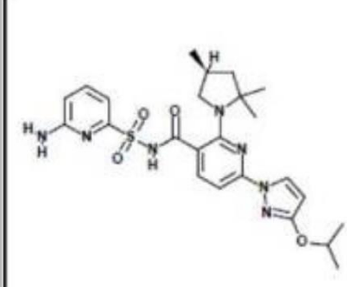
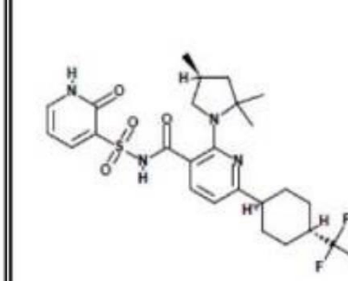
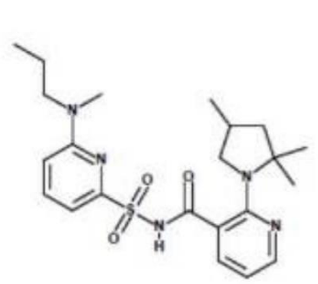
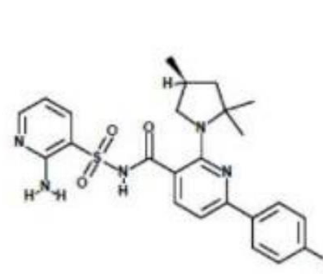
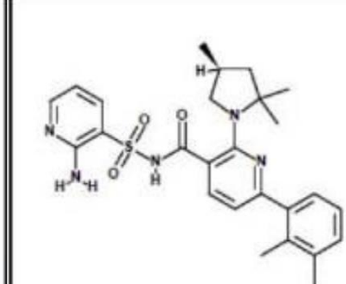
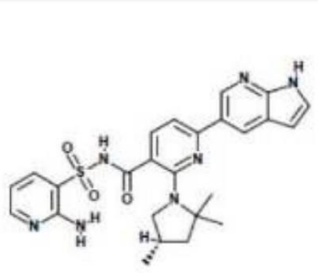
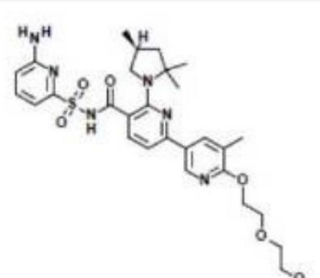
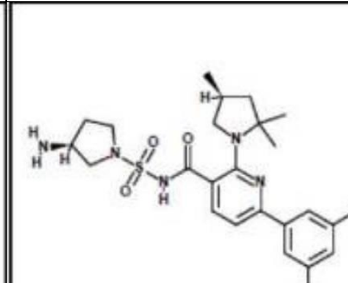
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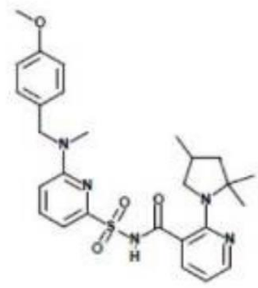
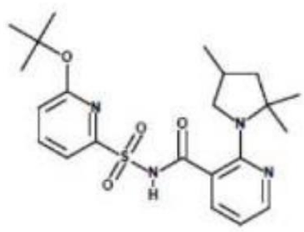
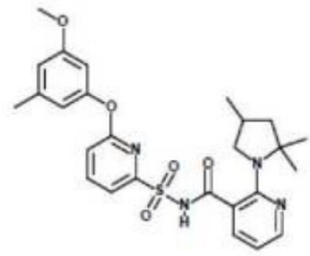
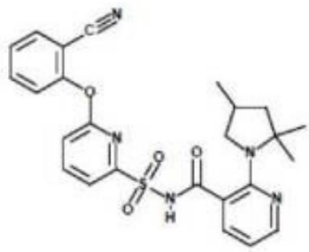
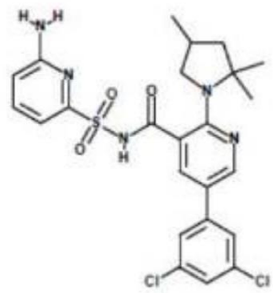
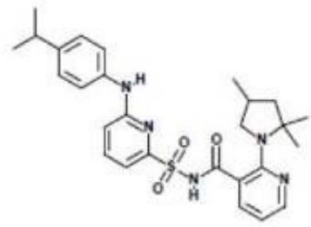
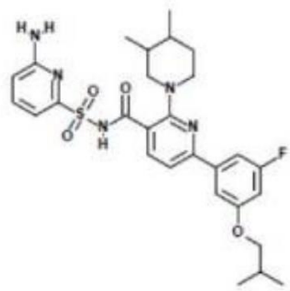
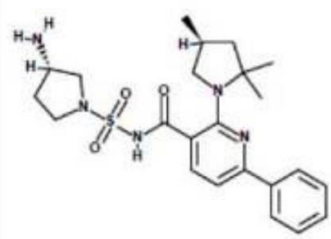
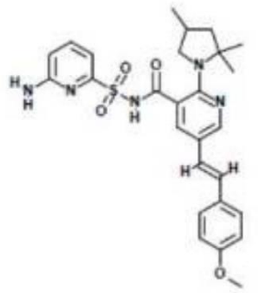
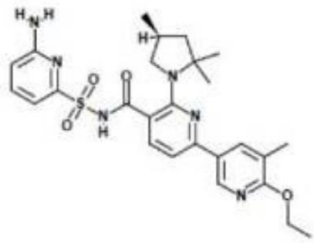
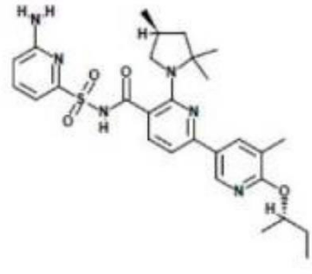
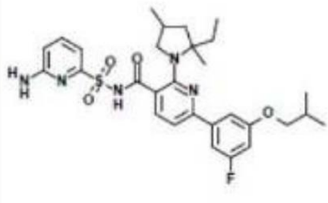
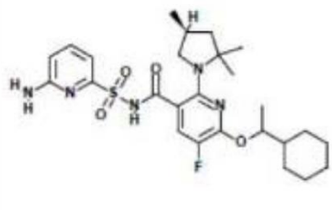
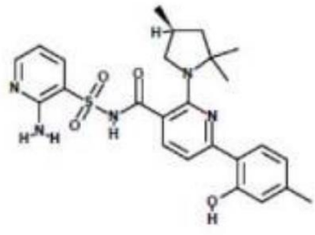
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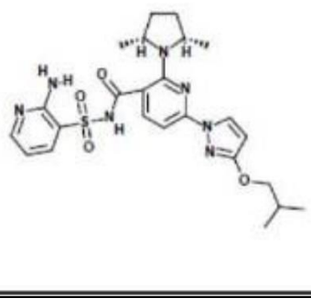
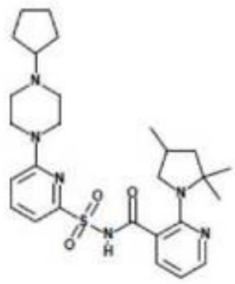
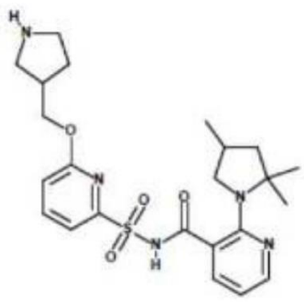
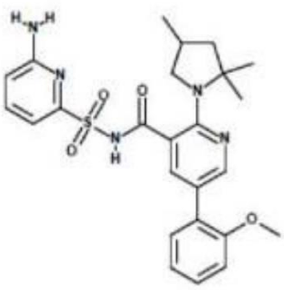
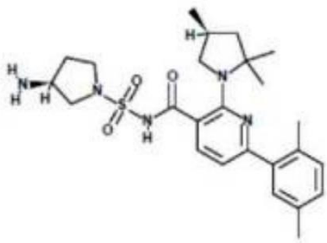
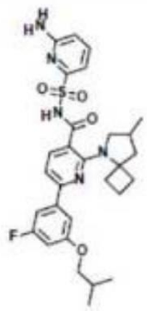
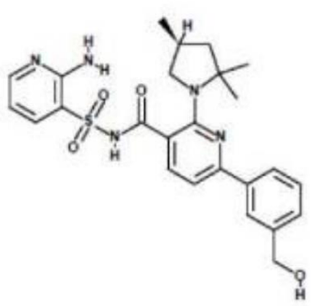
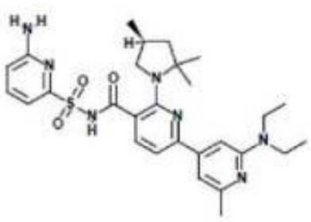
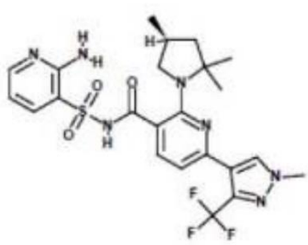
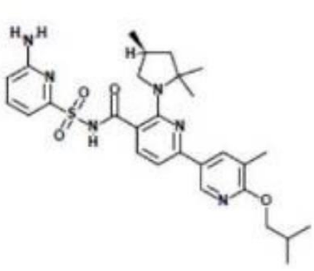
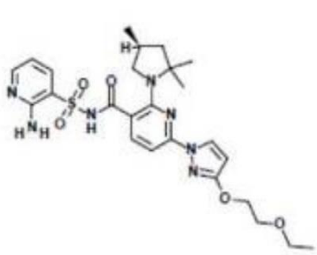
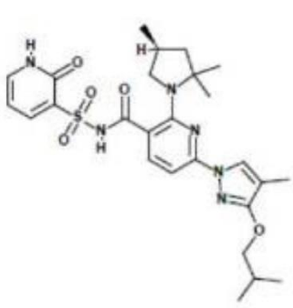
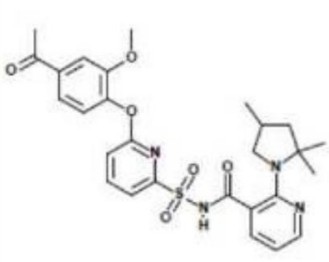
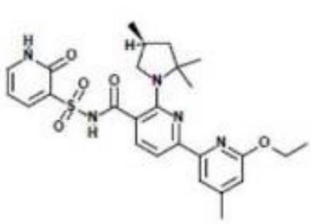
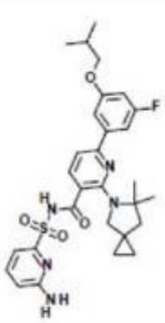
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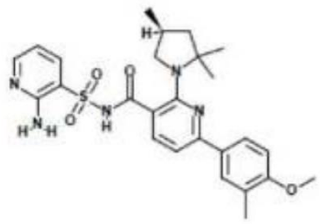
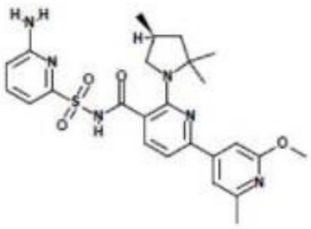
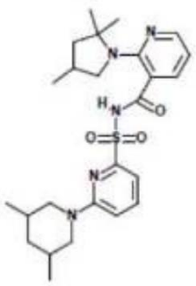
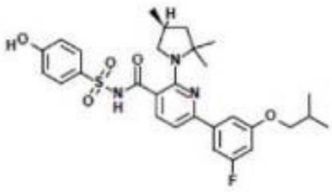
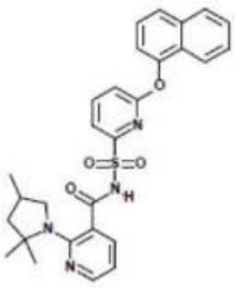
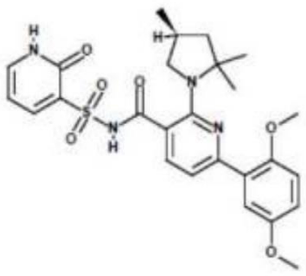
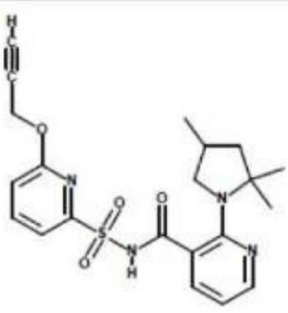
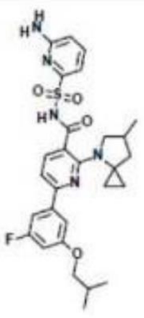
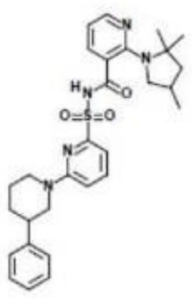
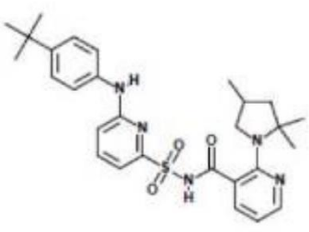
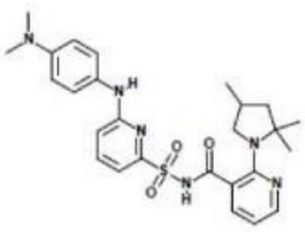
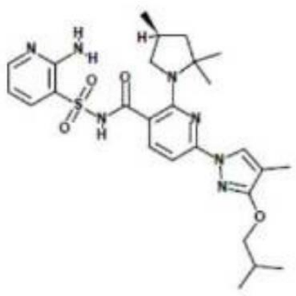
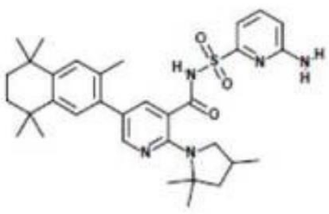
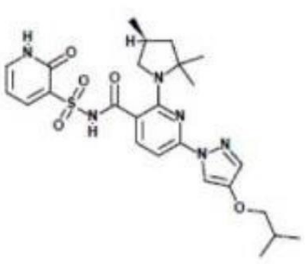
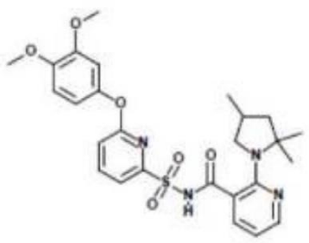
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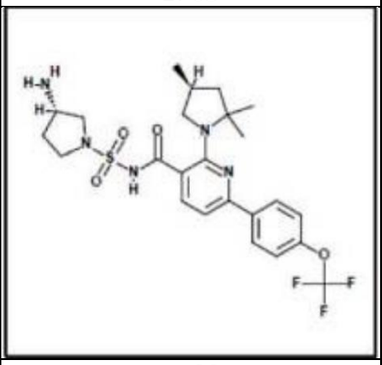
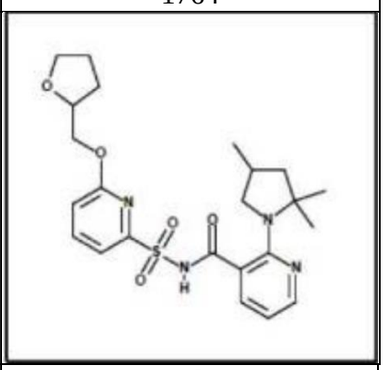
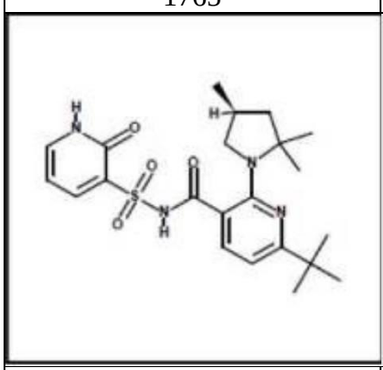
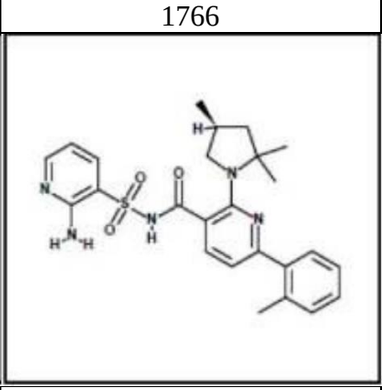
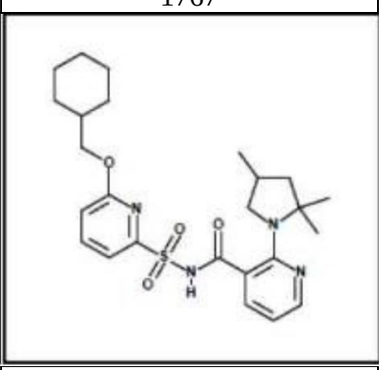
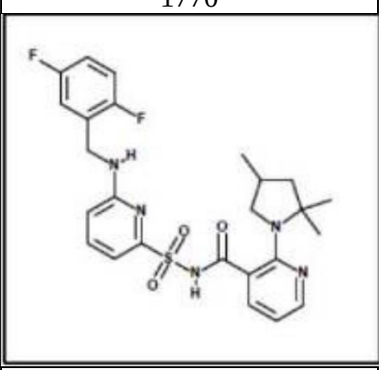
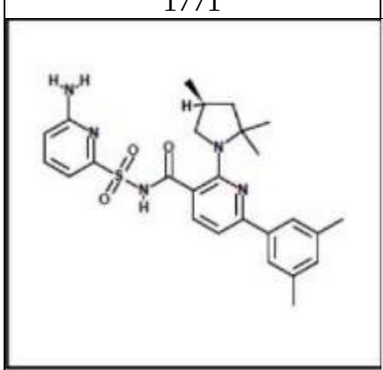
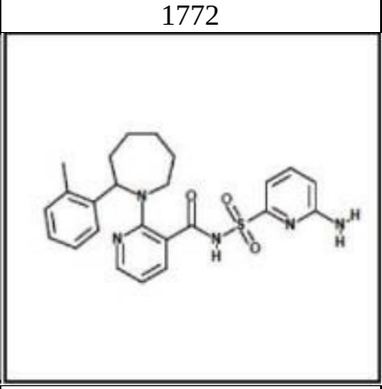
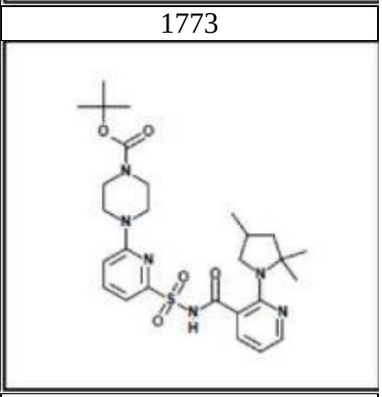
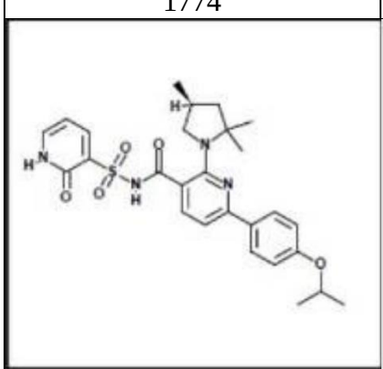
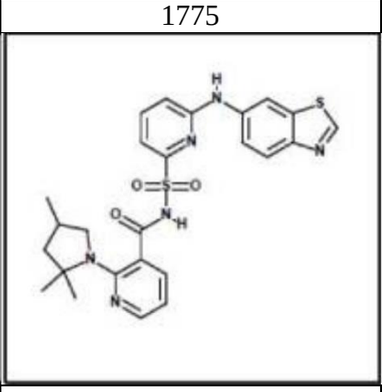
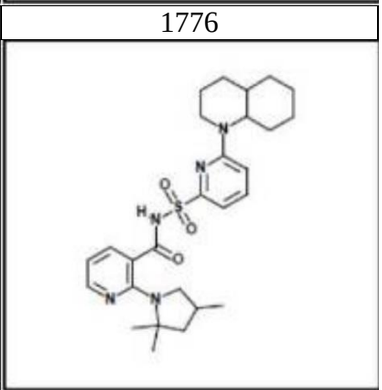
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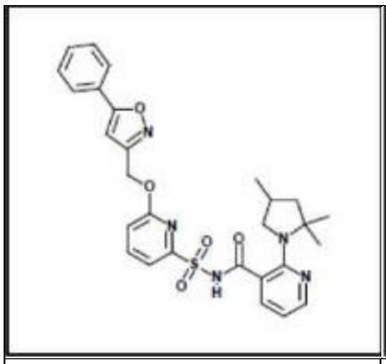
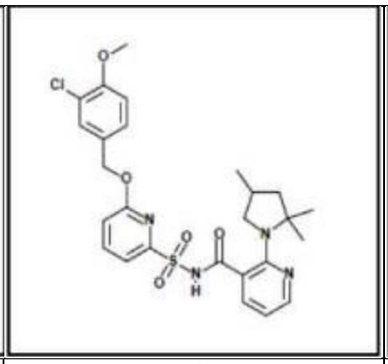
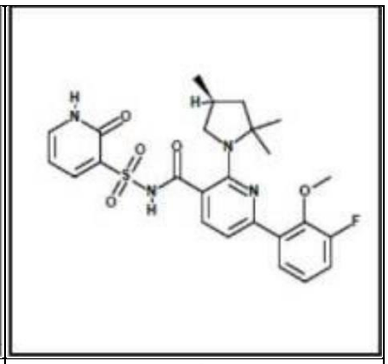
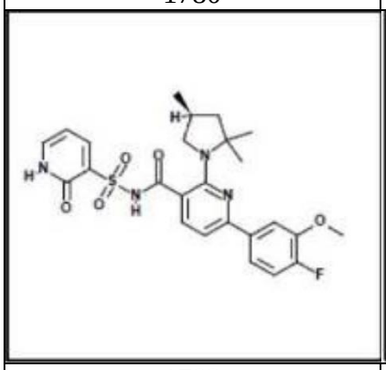
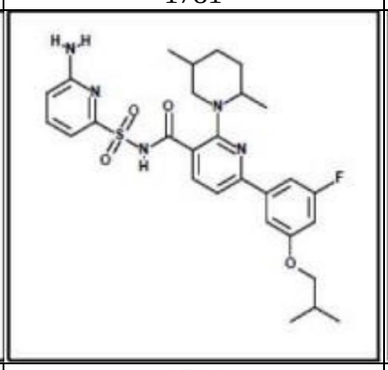
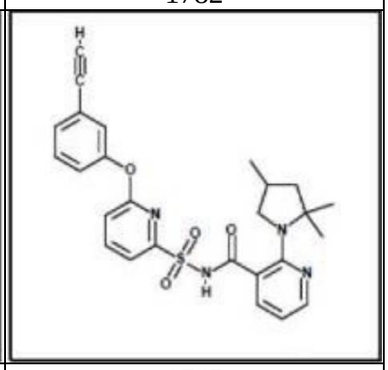
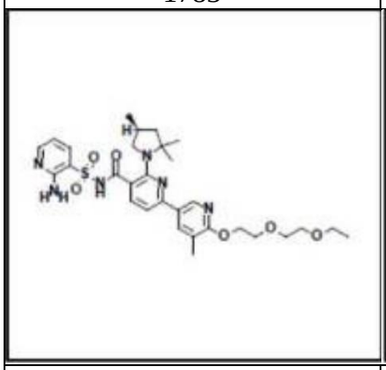
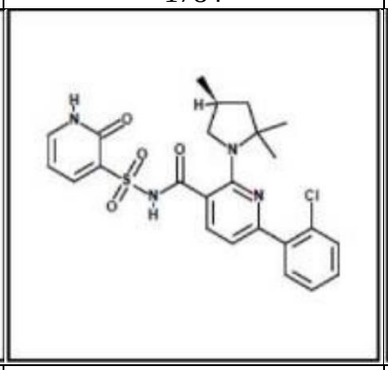
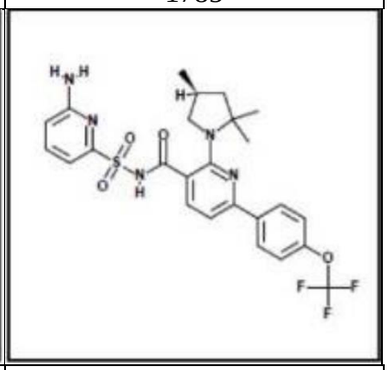
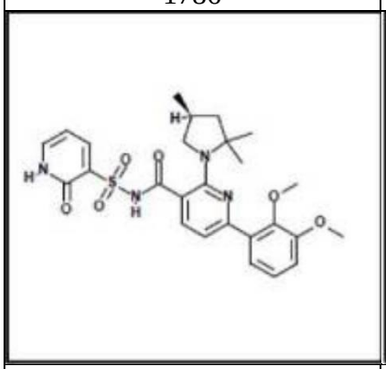
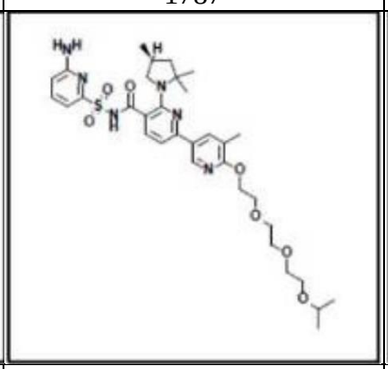
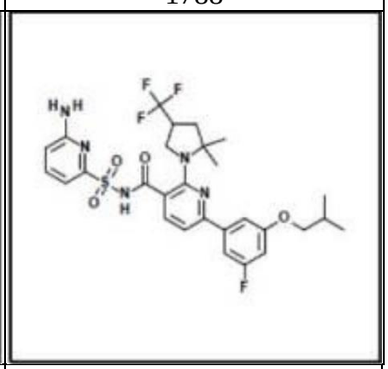
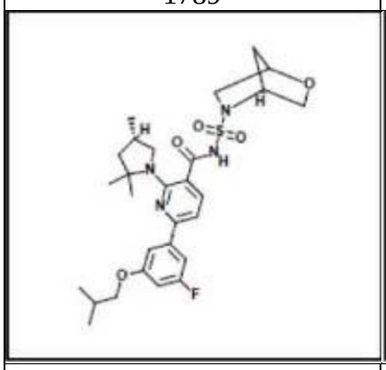
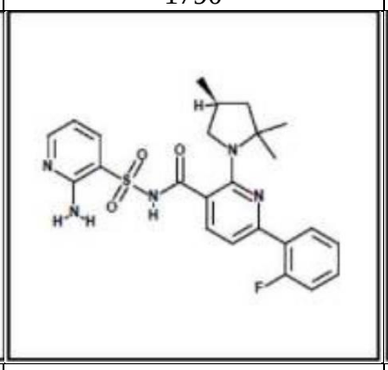
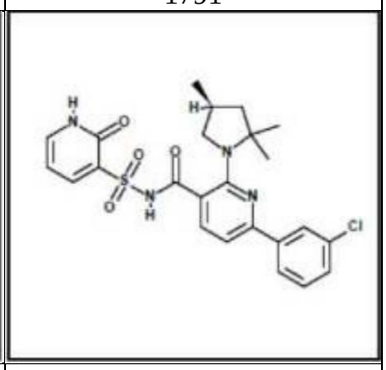
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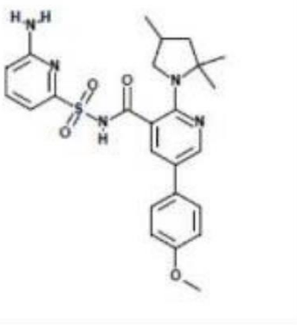
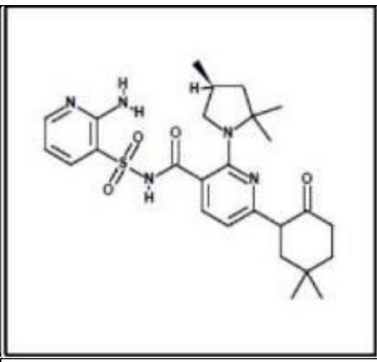
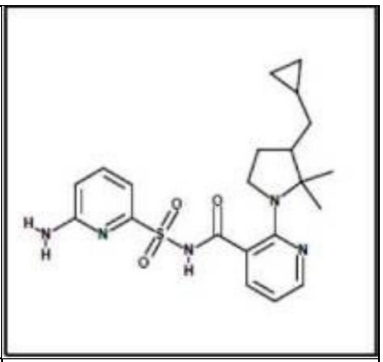
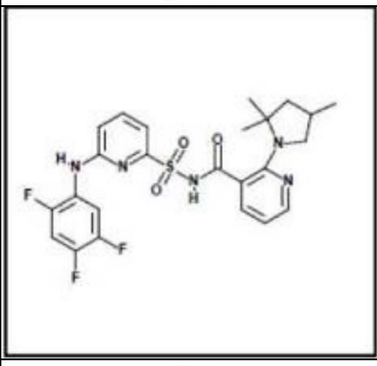
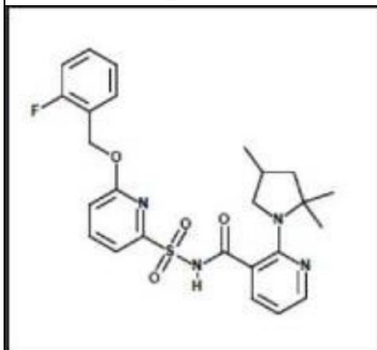
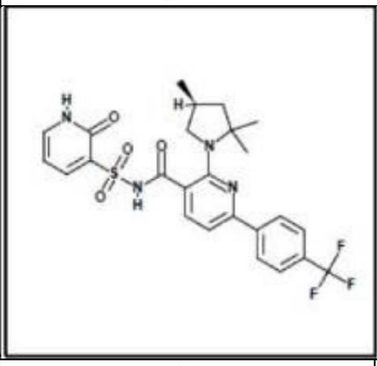
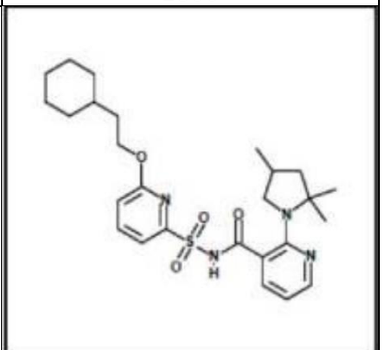
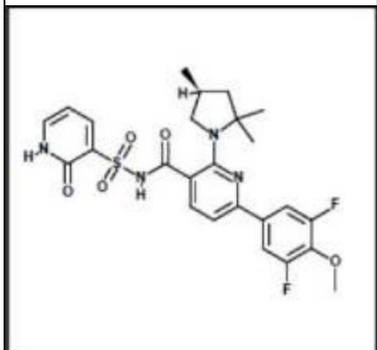
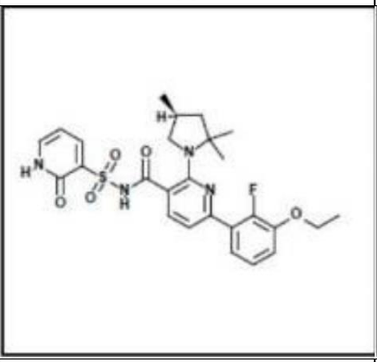
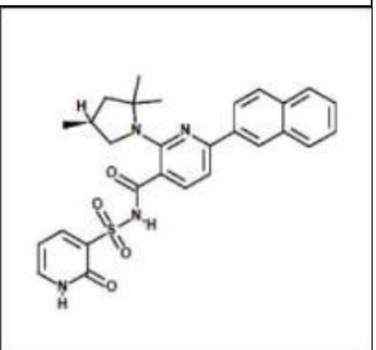
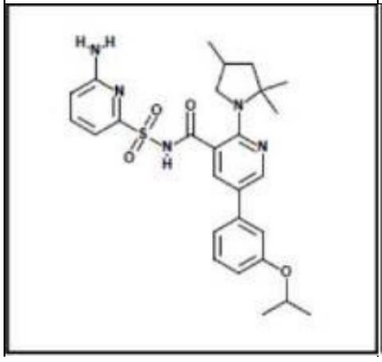
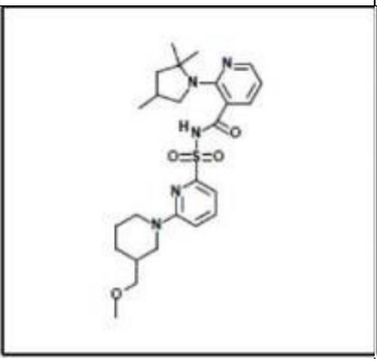
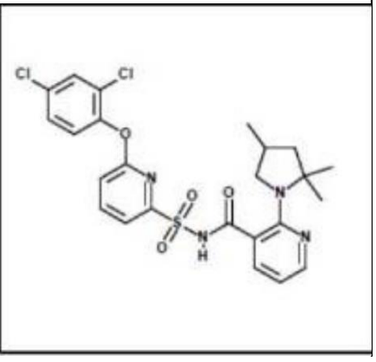
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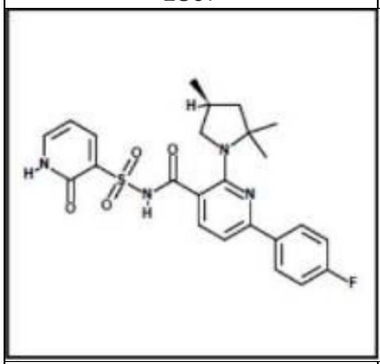
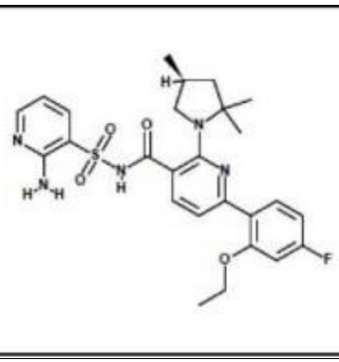
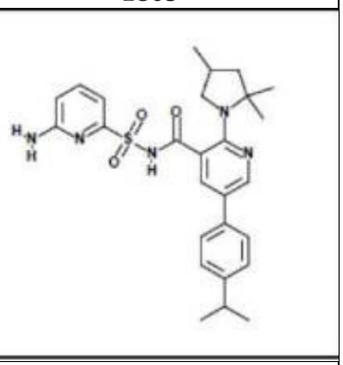
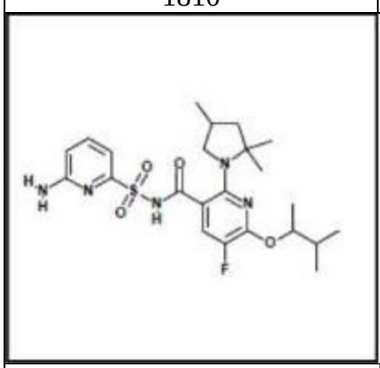
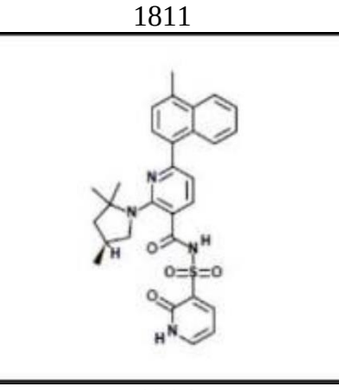
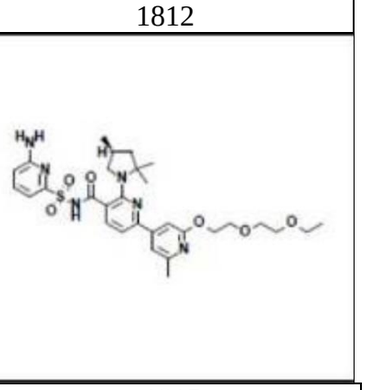
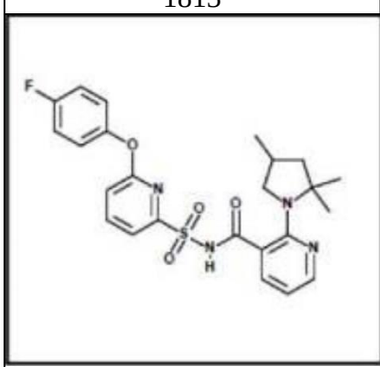
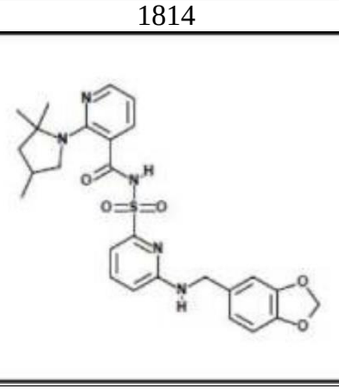
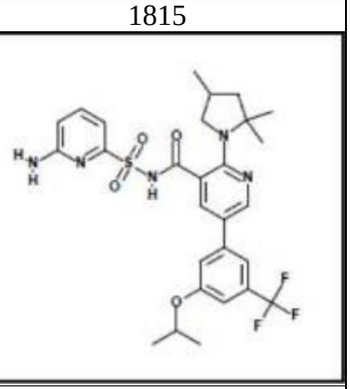
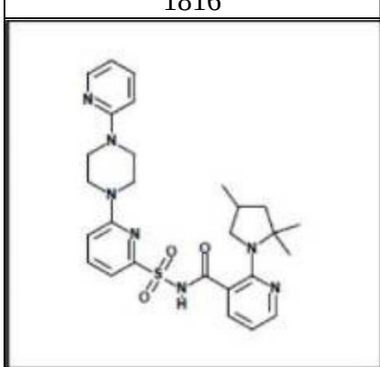
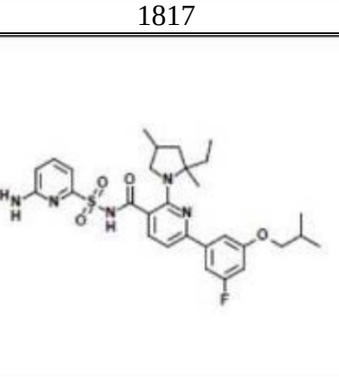
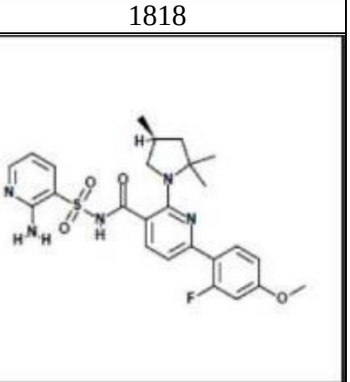
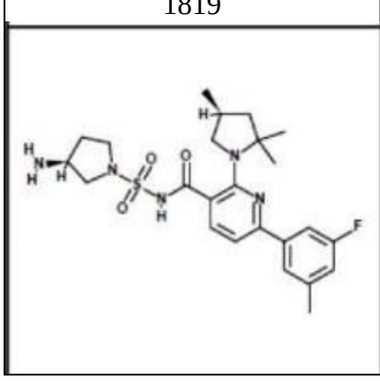
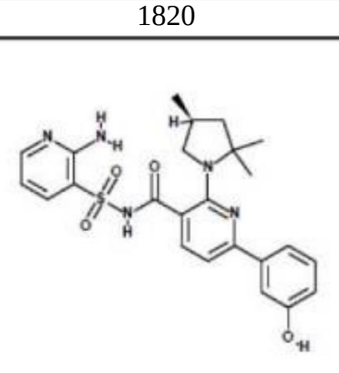
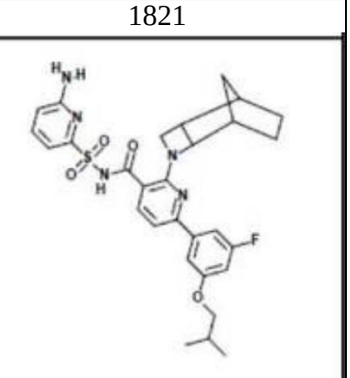
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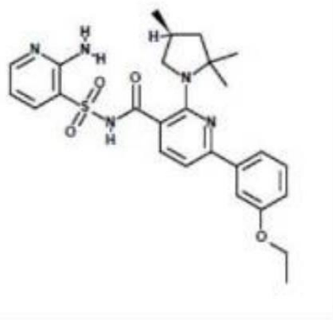
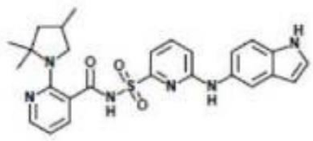
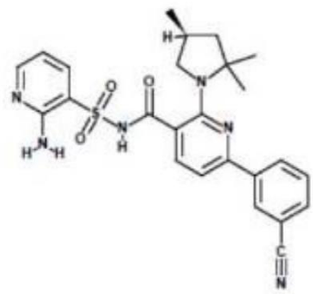
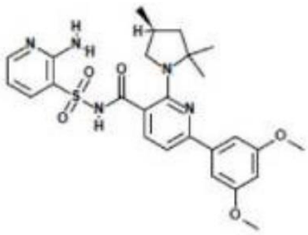
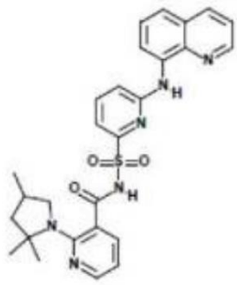
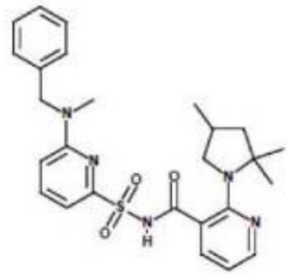
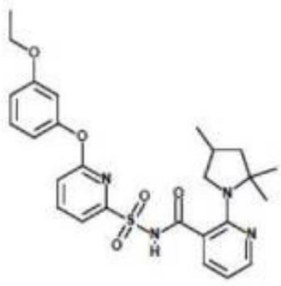
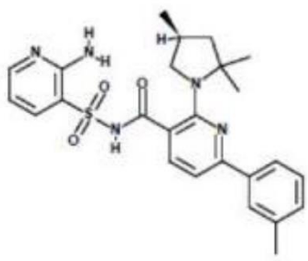
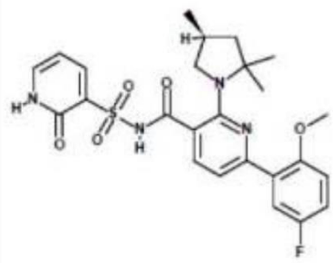
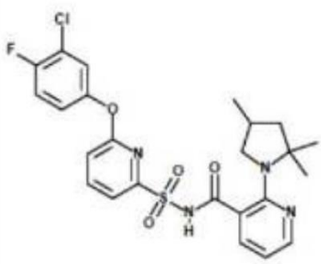
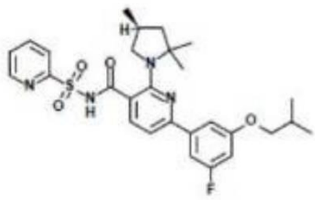
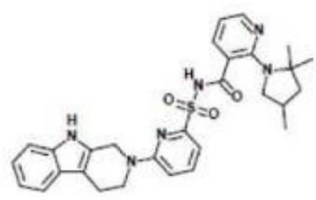
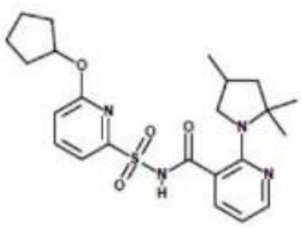
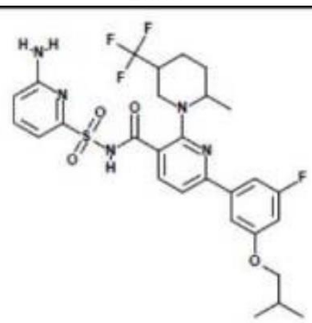
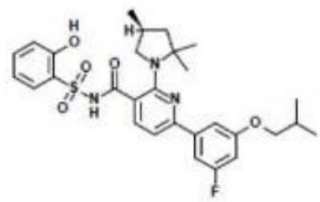
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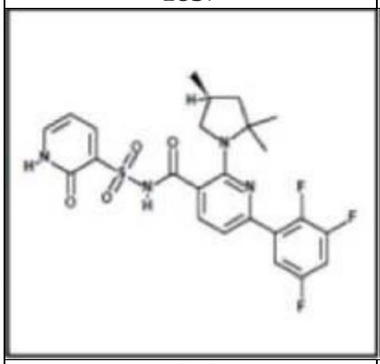
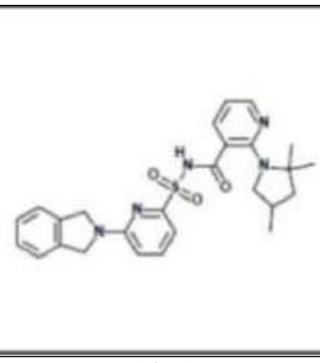
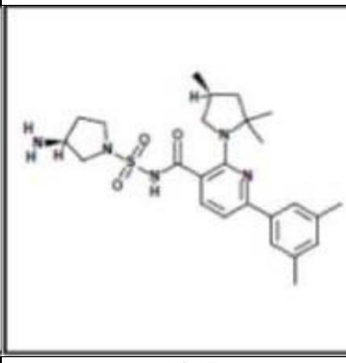
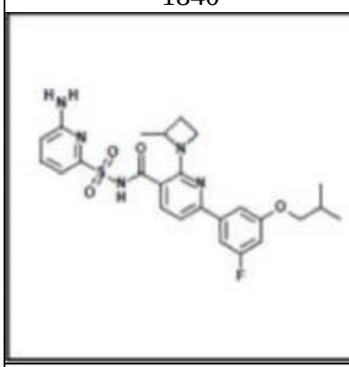
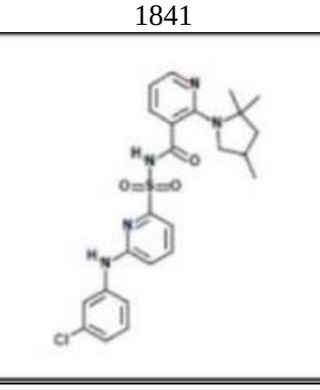
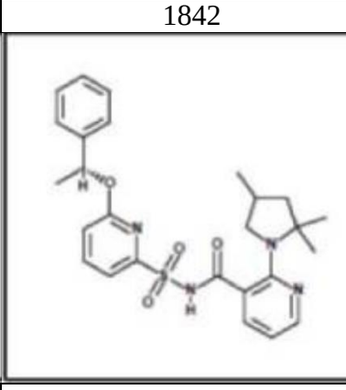
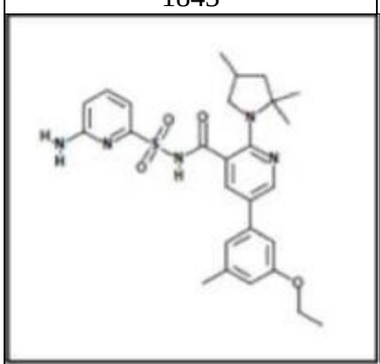
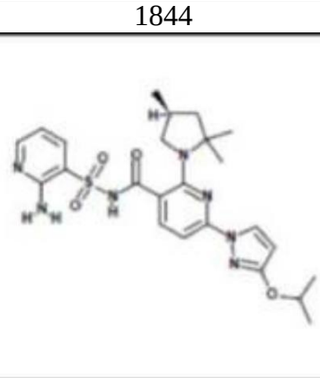
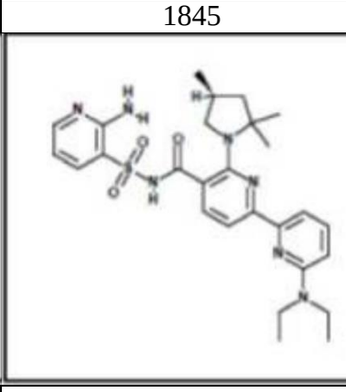
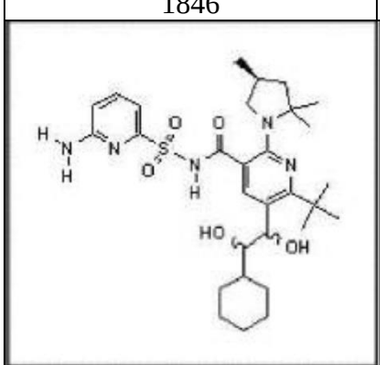
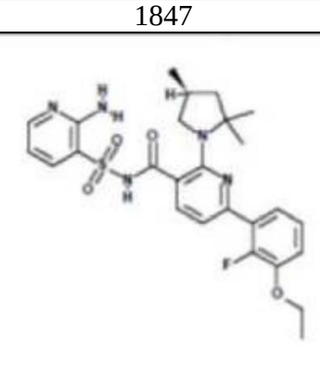
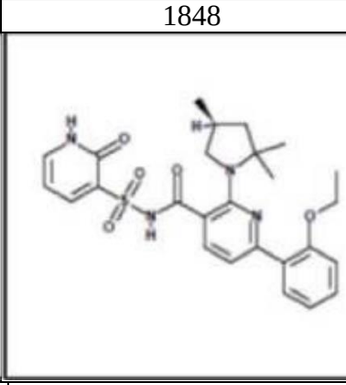
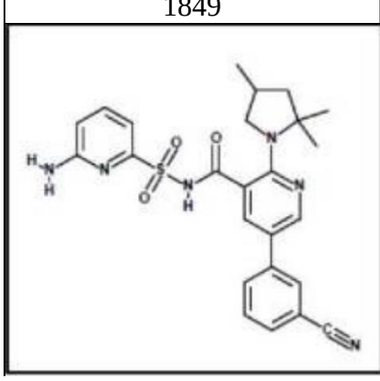
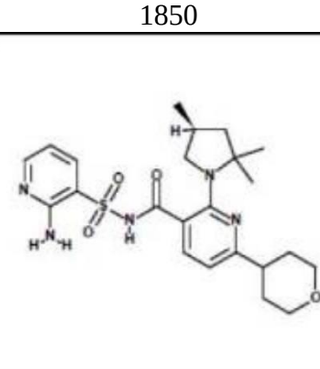
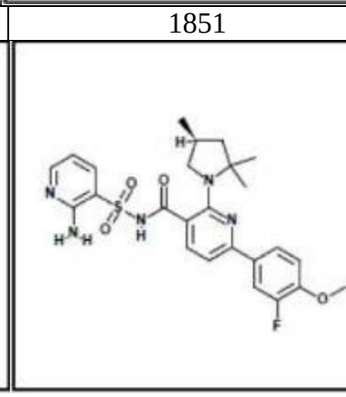
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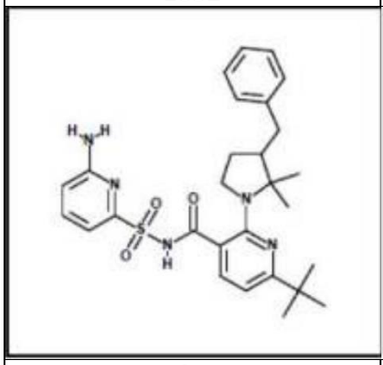
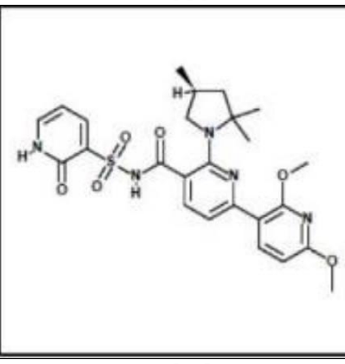
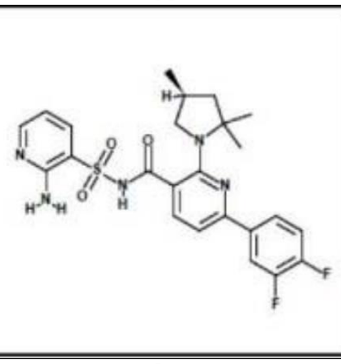
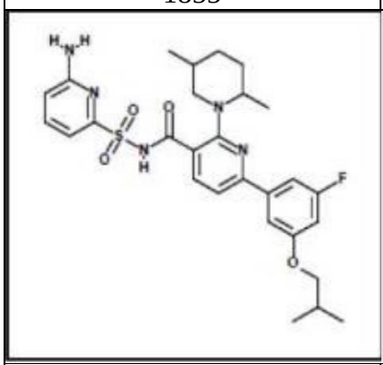
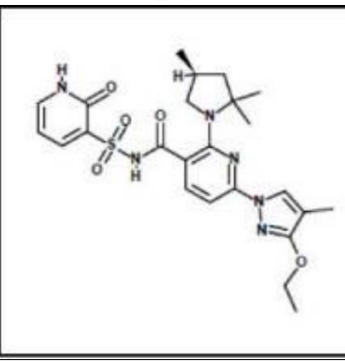
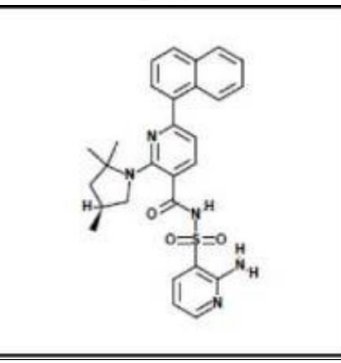
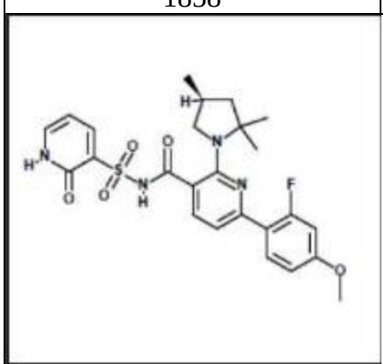
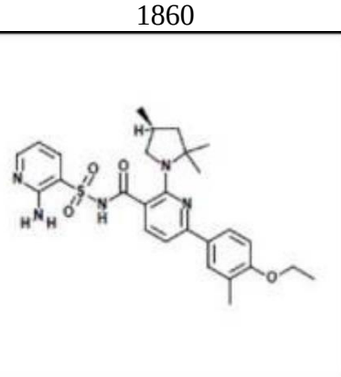
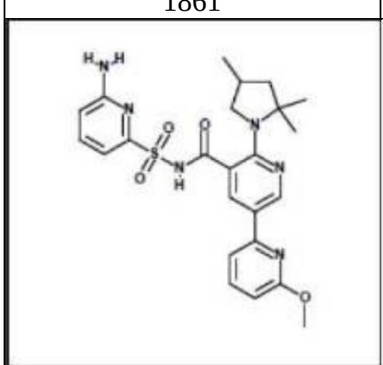
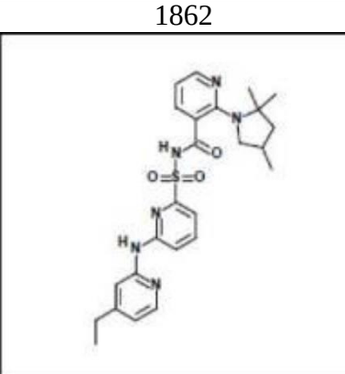
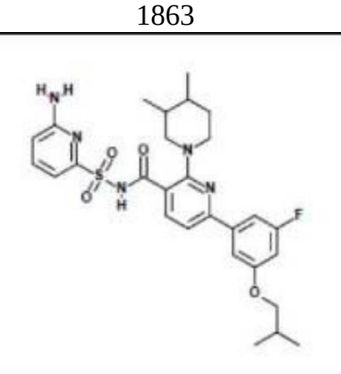
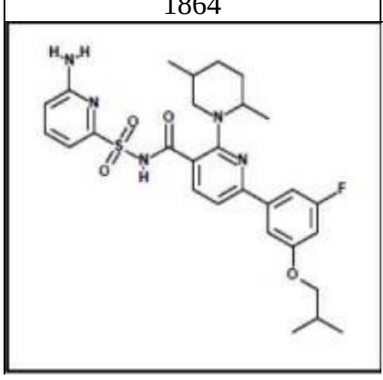
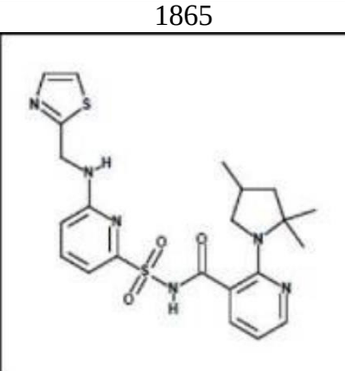
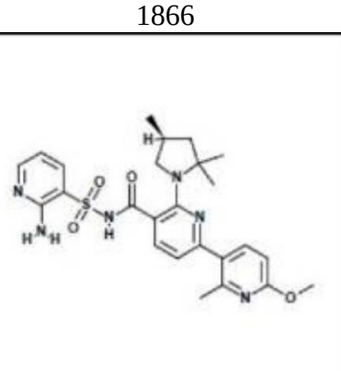
		
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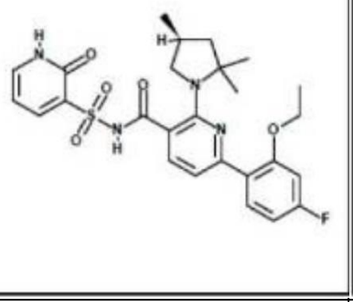
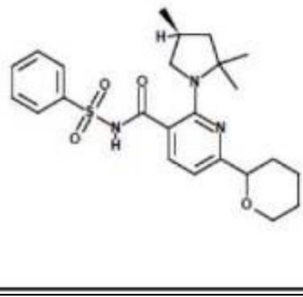
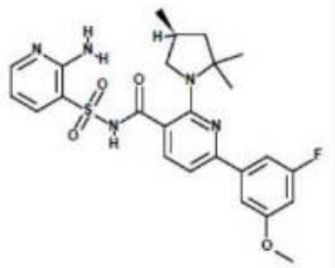
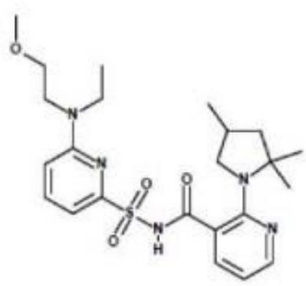
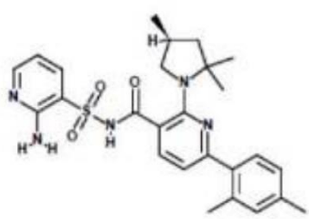
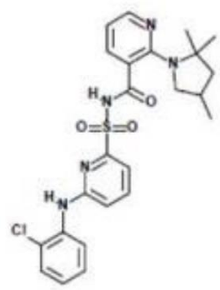
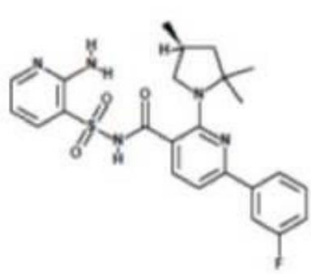
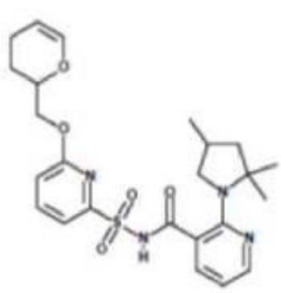
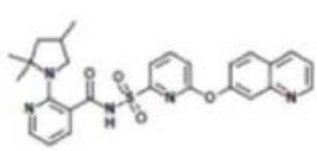
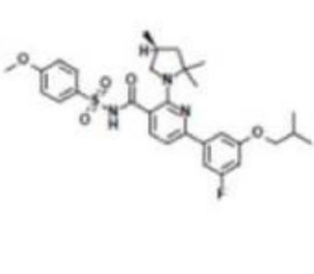
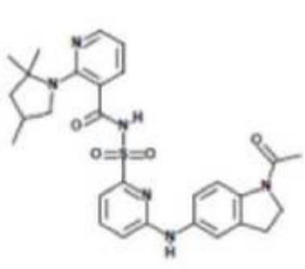
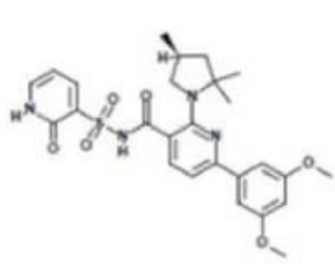
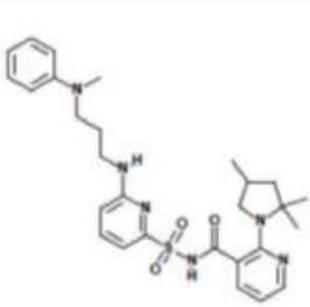
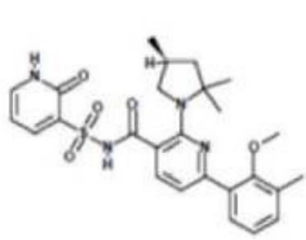
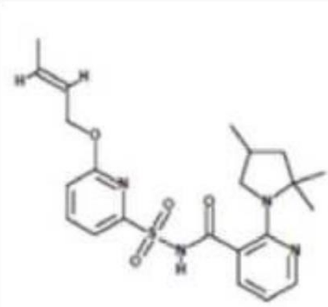
		
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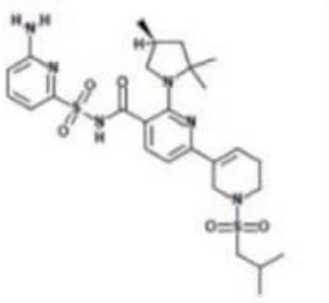
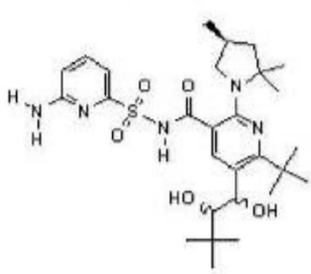
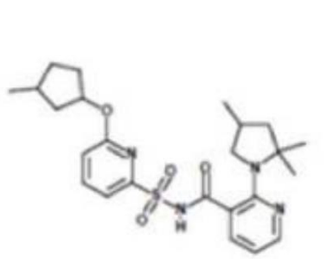
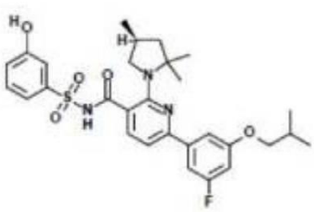
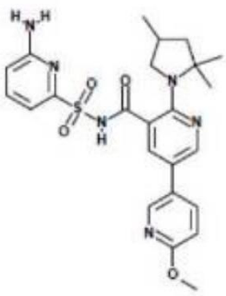
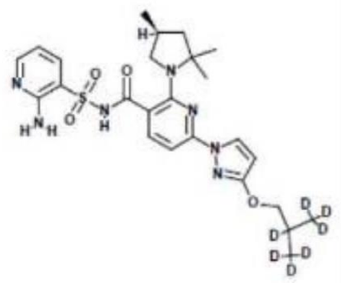
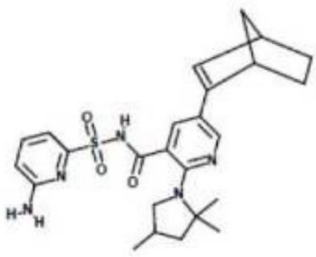
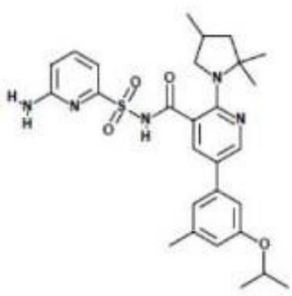
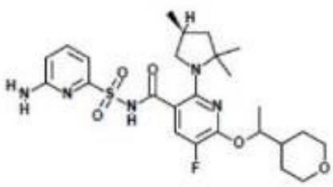
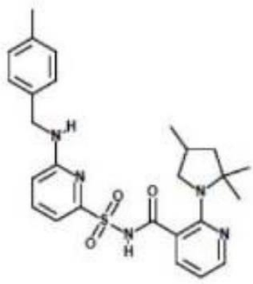
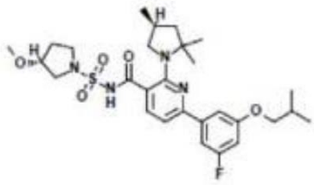
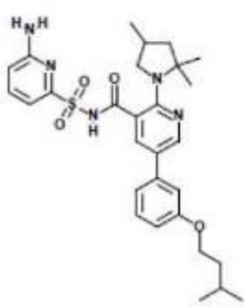
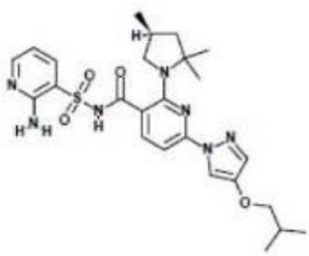
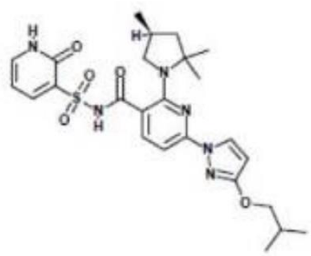
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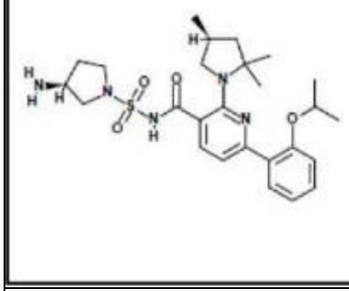
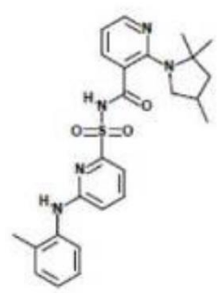
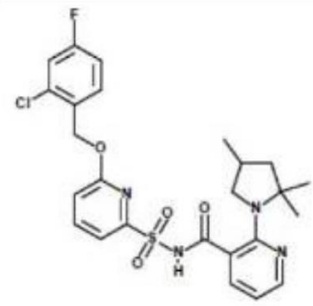
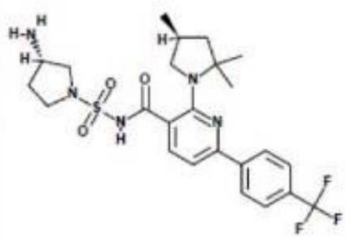
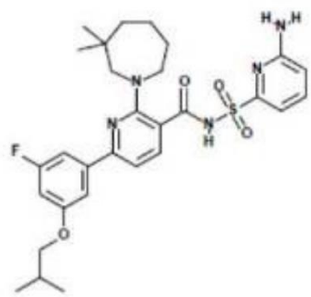
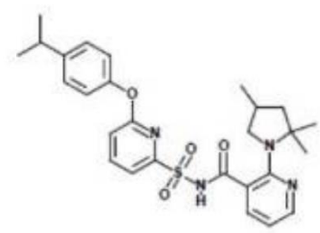
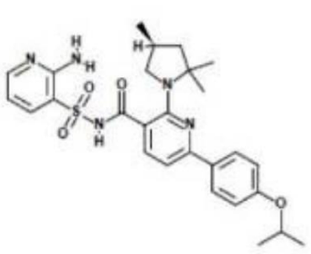
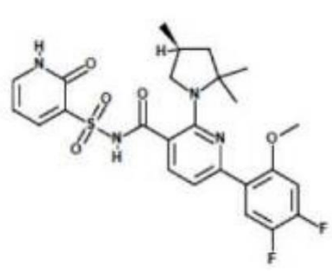
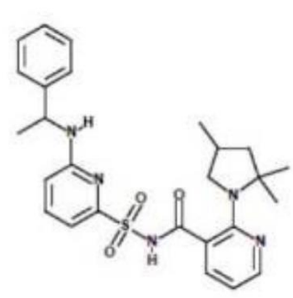
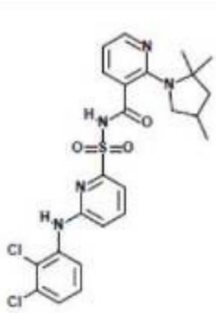
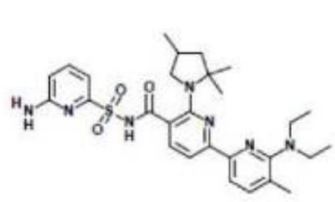
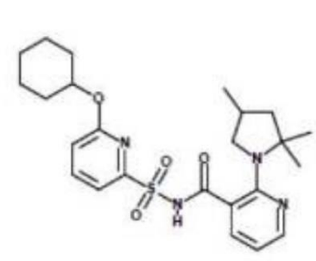
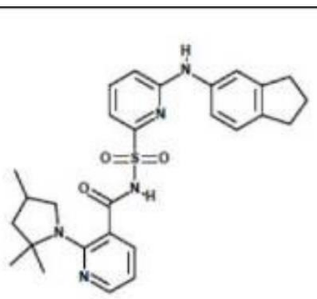
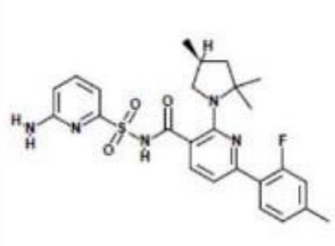
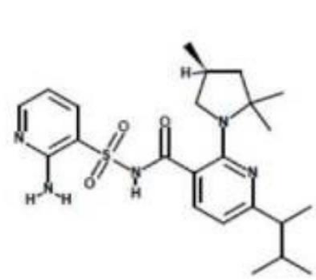
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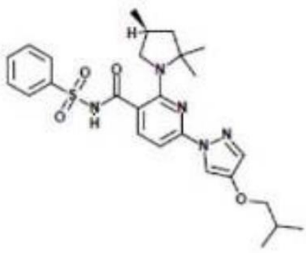
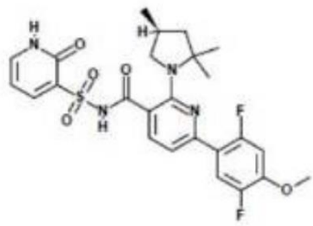
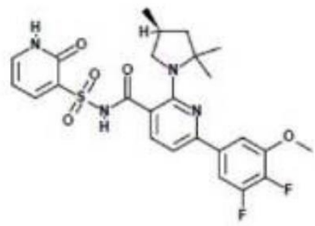
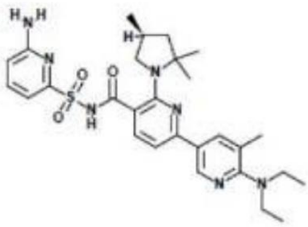
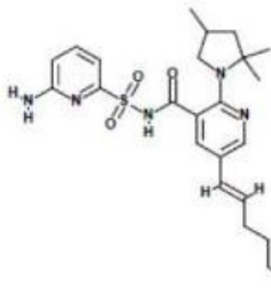
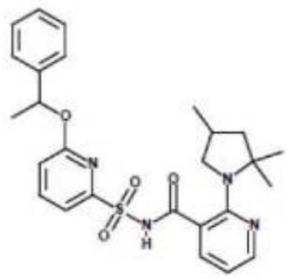
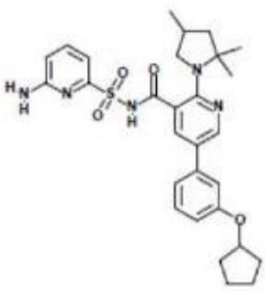
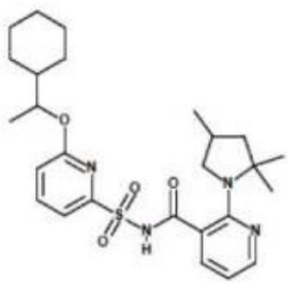
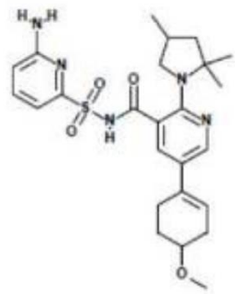
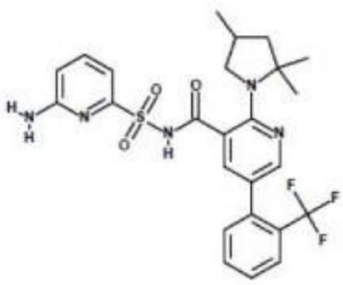
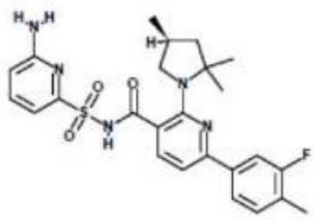
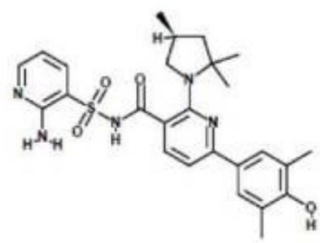
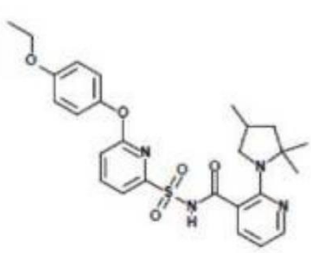
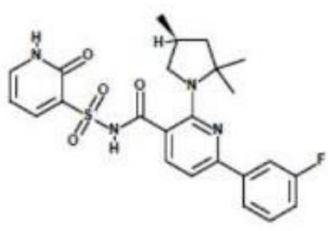
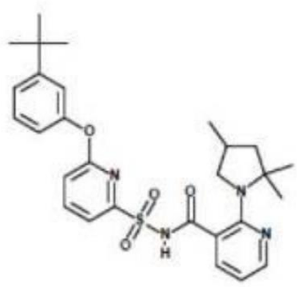
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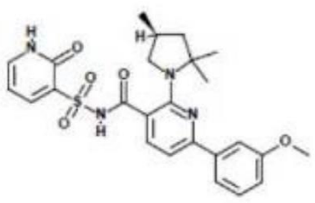
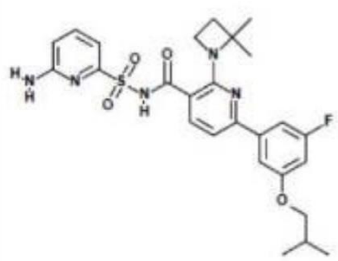
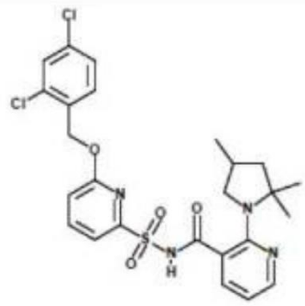
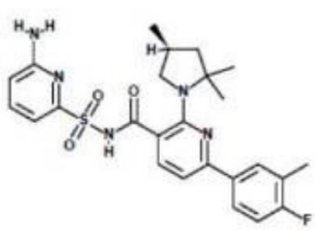
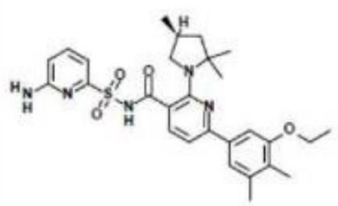
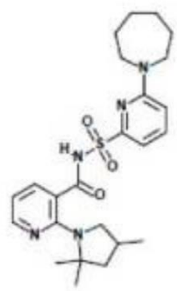
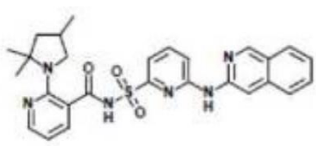
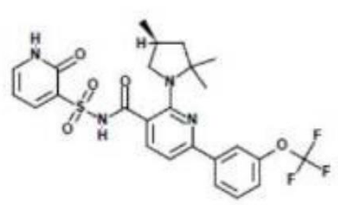
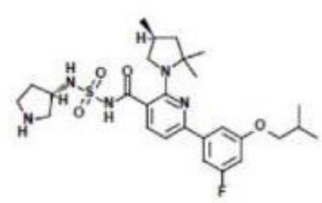
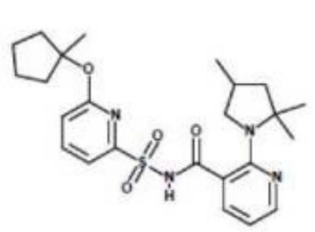
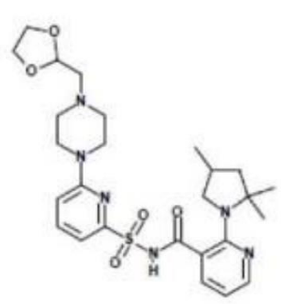
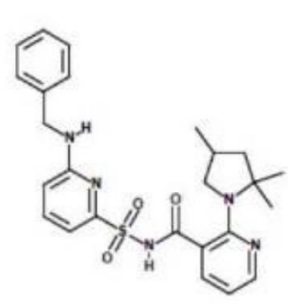
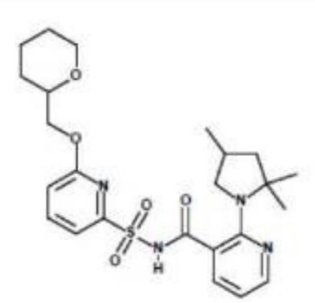
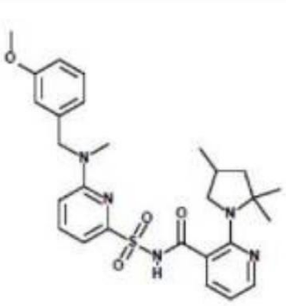
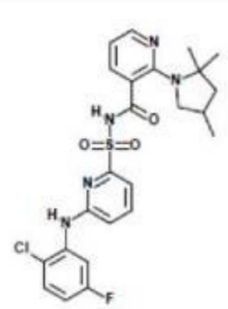
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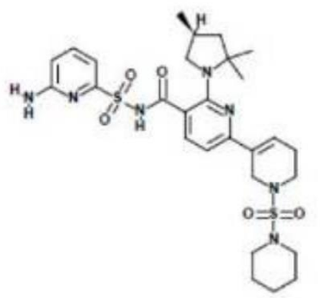
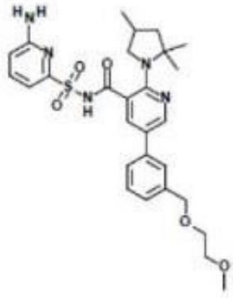
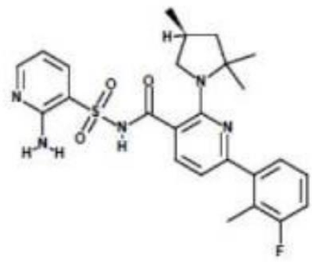
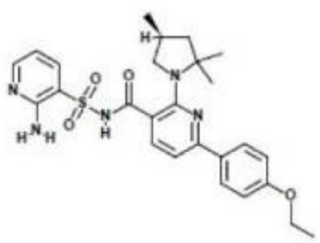
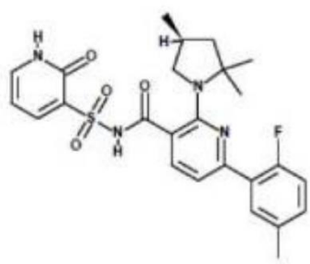
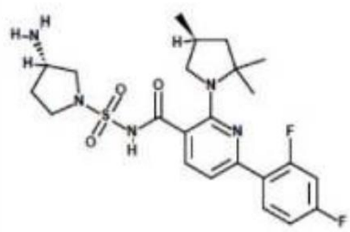
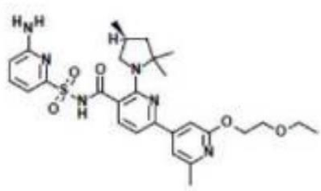
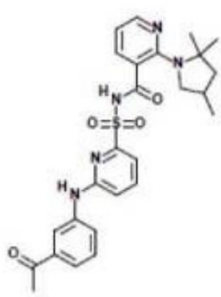
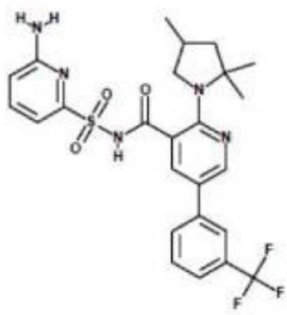
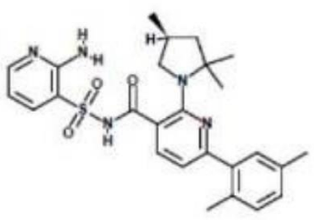
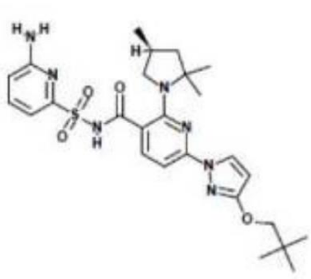
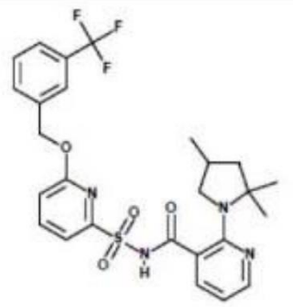
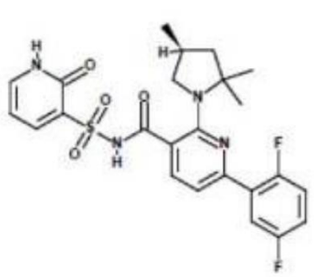
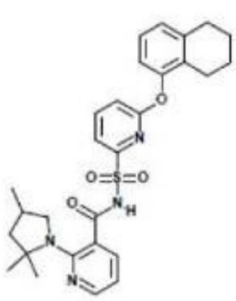
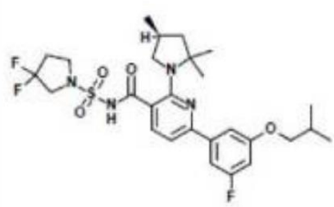
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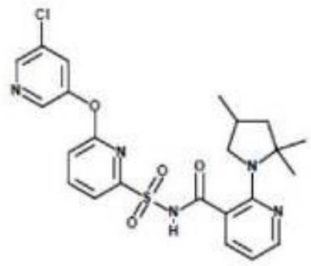
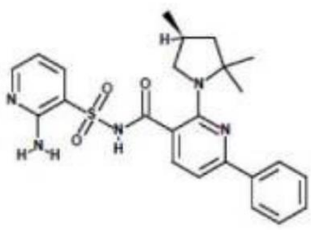
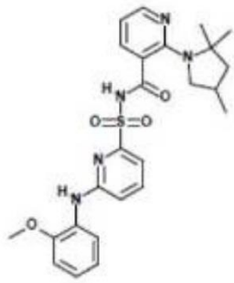
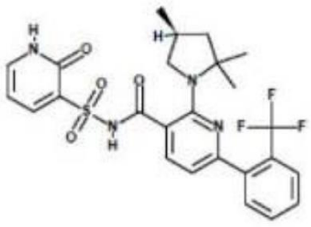
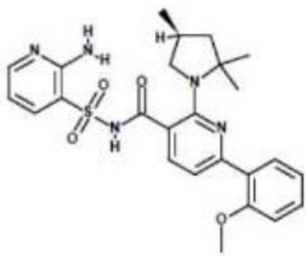
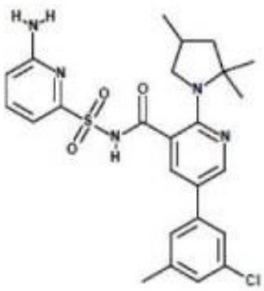
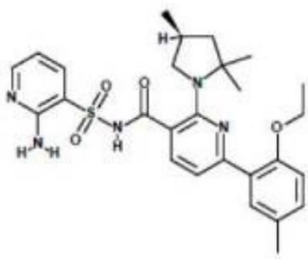
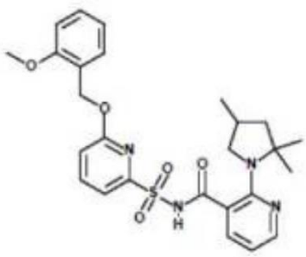
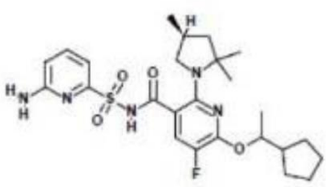
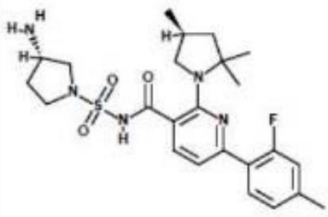
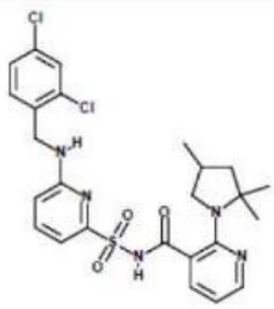
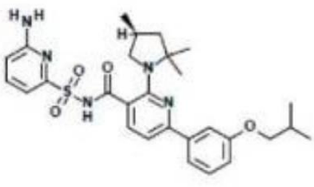
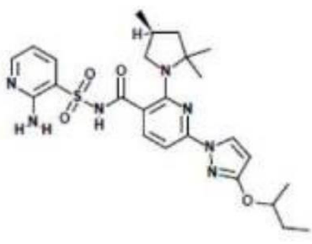
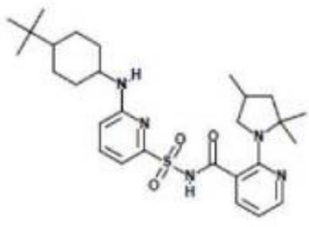
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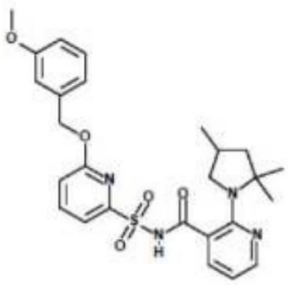
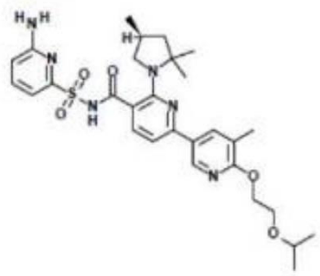
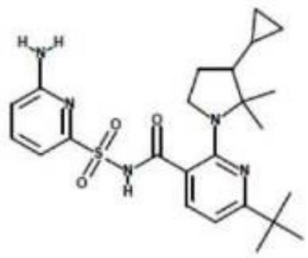
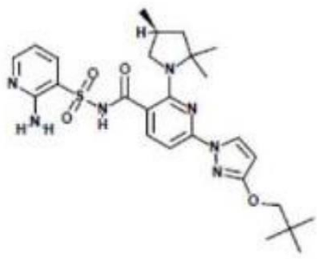
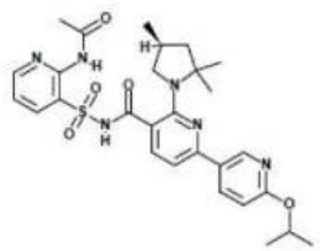
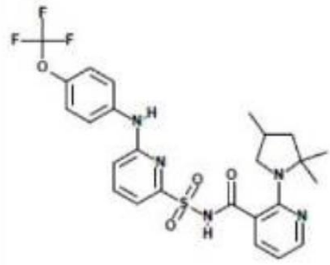
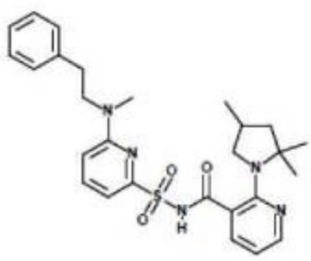
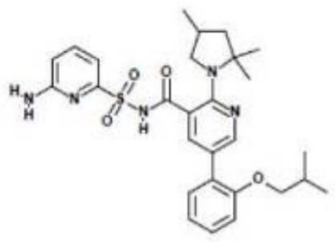
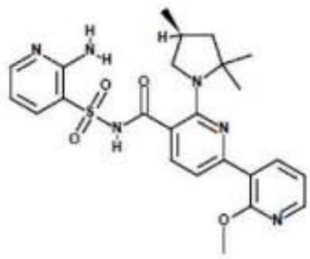
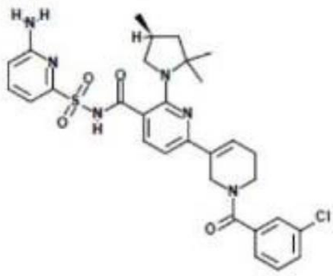
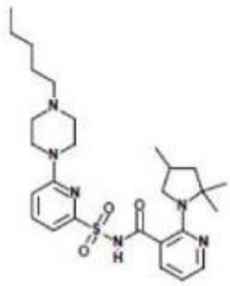
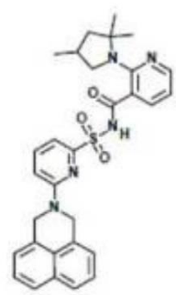
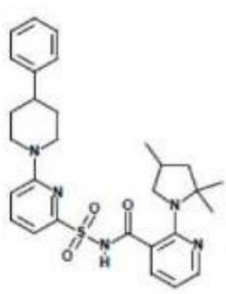
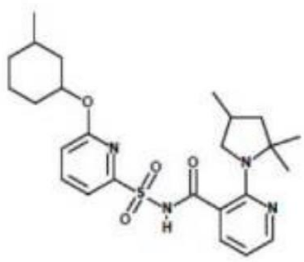
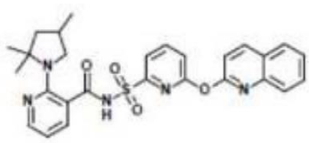
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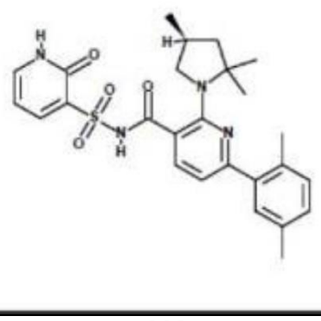
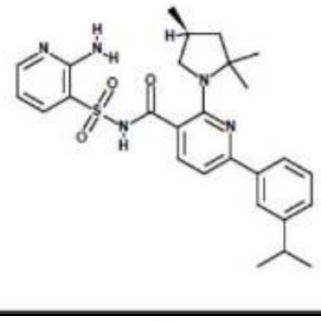
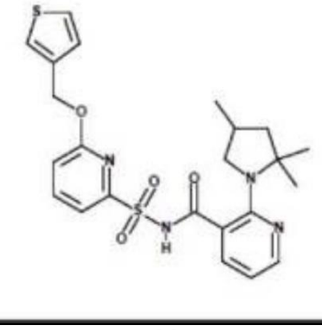
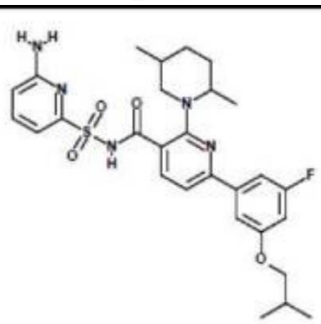
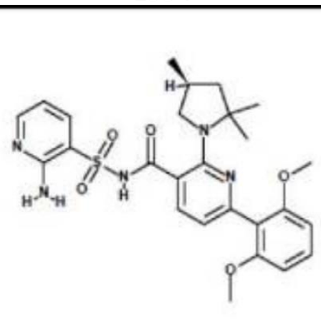
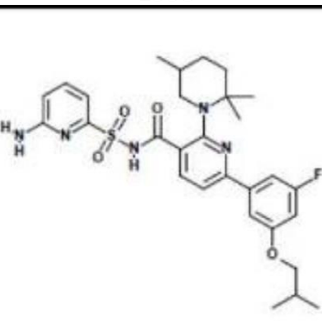
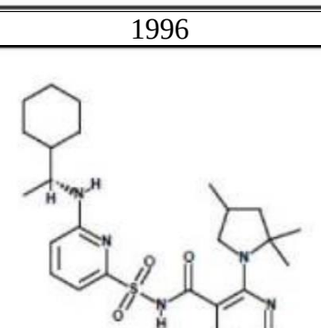
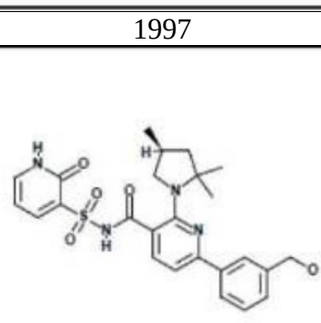
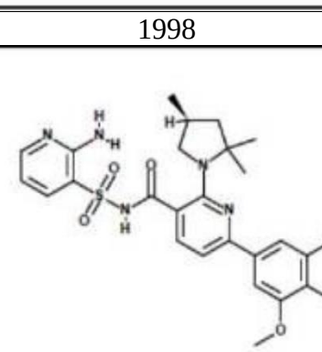
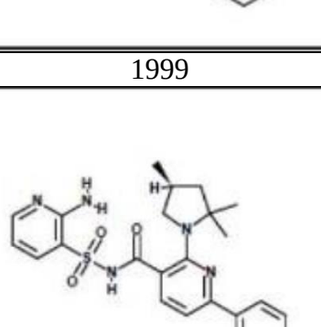
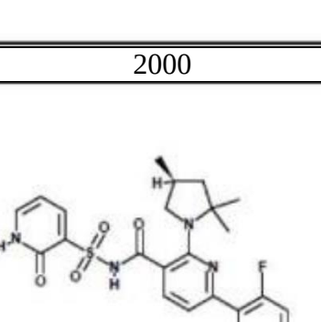
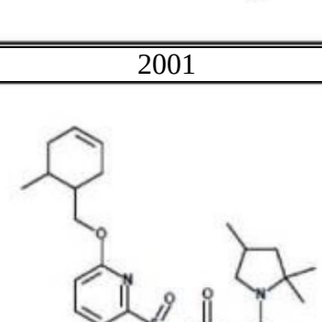
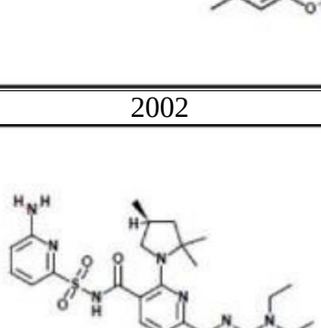
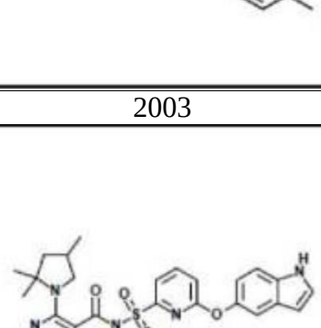
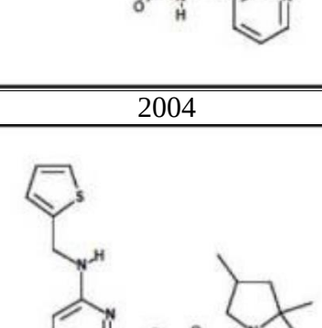
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1921	1922	1923
		
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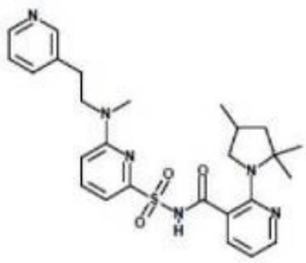
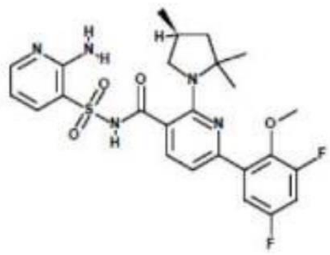
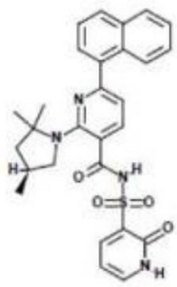
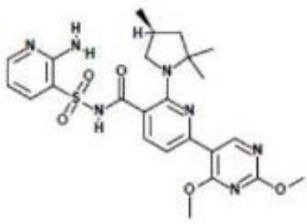
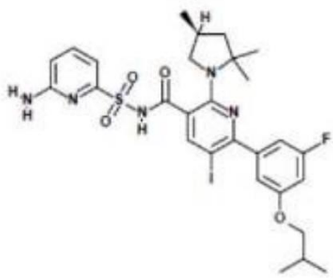
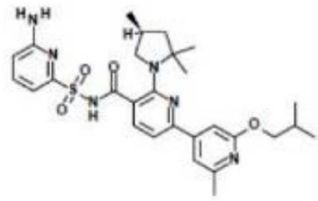
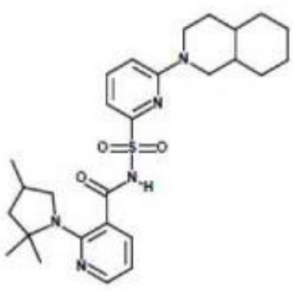
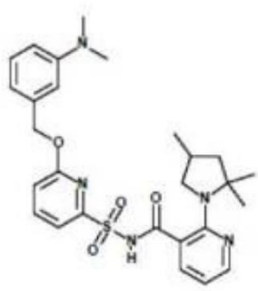
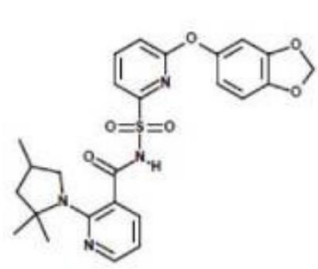
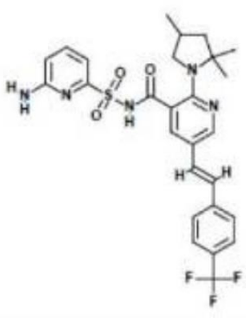
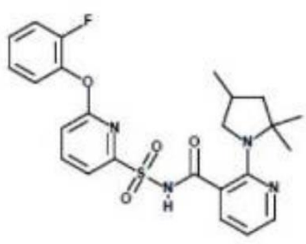
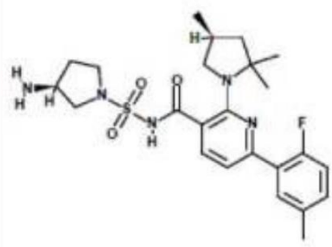
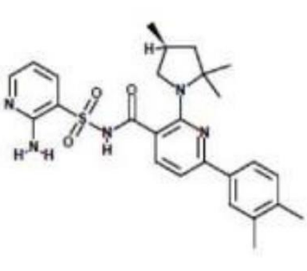
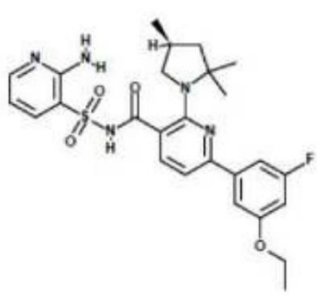
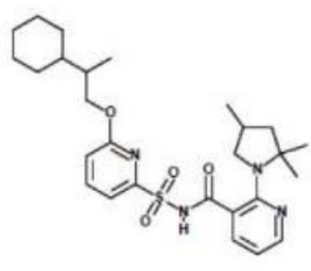
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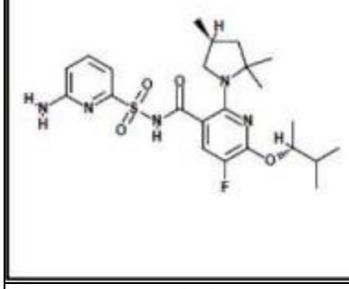
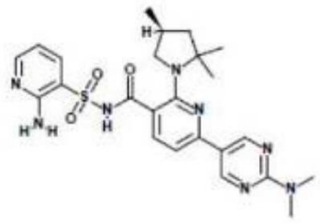
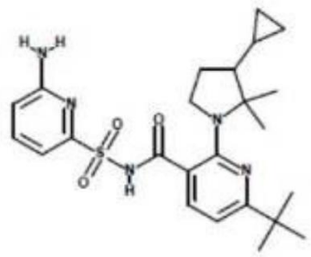
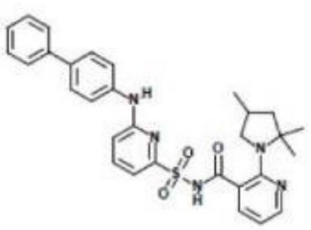
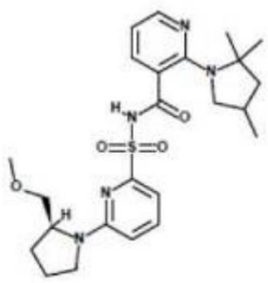
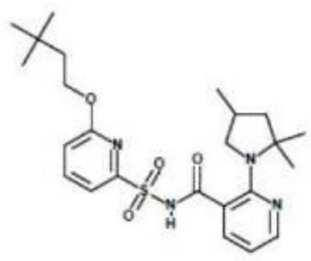
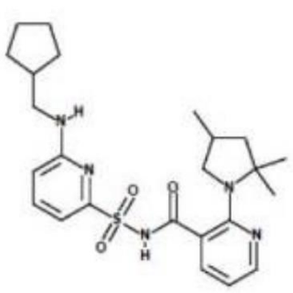
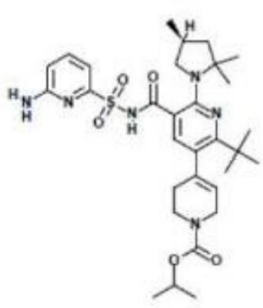
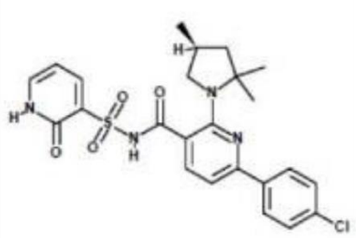
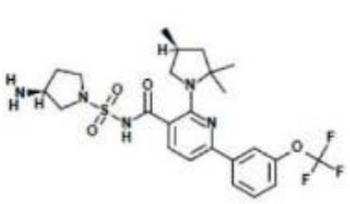
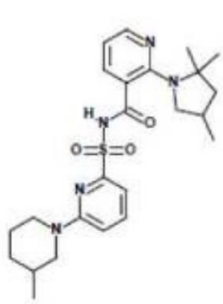
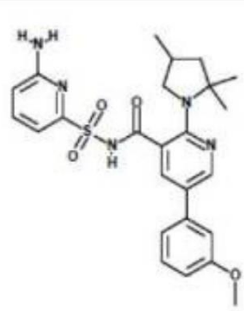
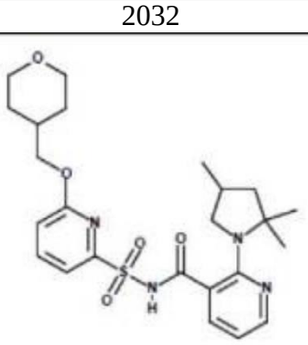
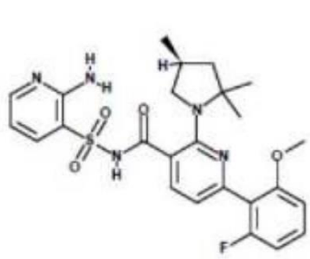
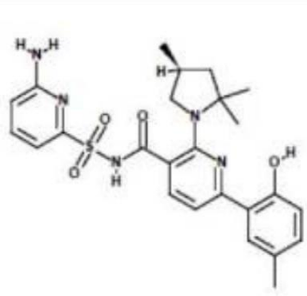
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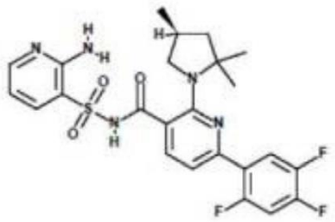
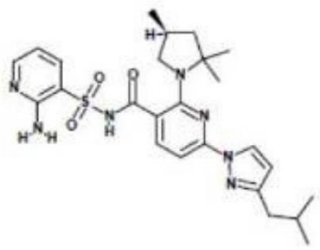
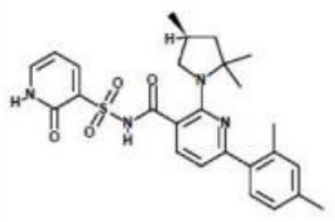
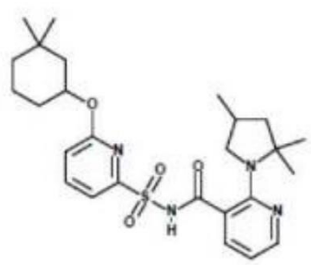
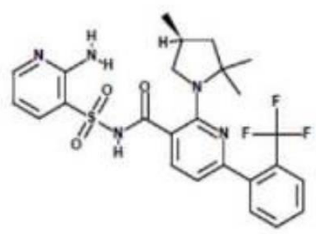
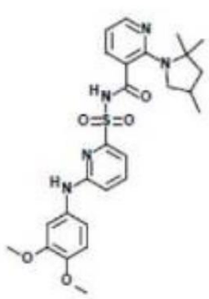
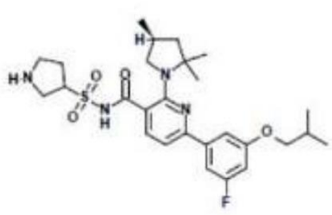
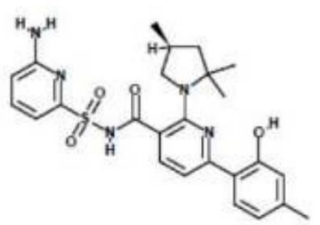
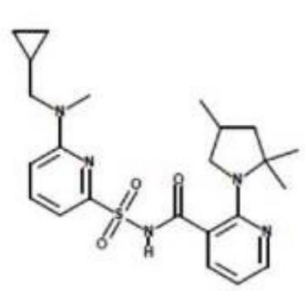
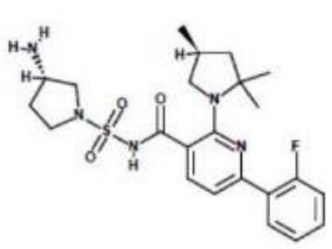
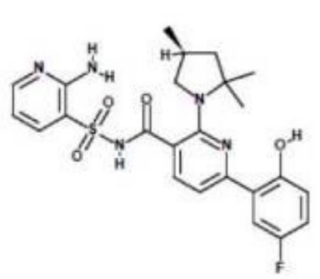
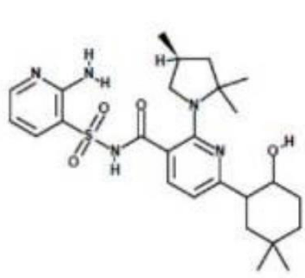
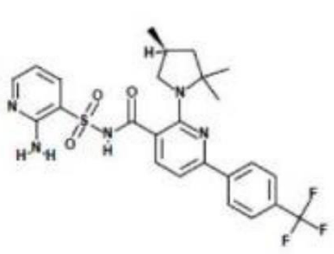
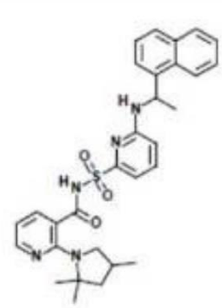
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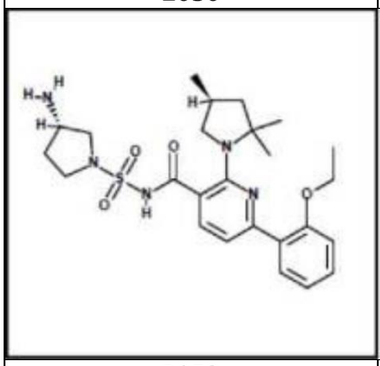
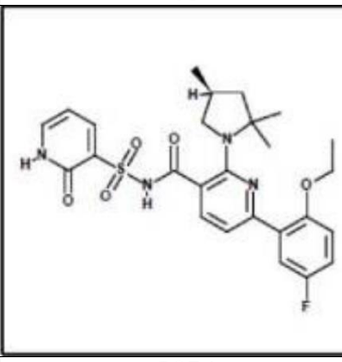
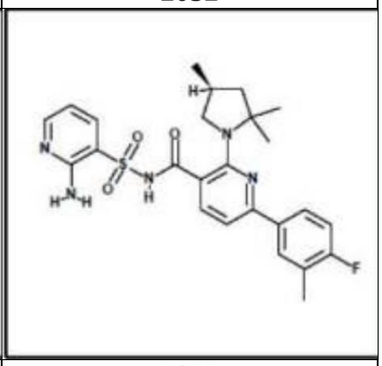
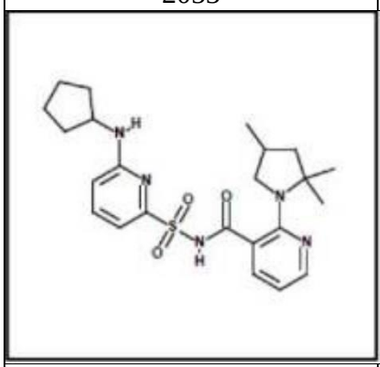
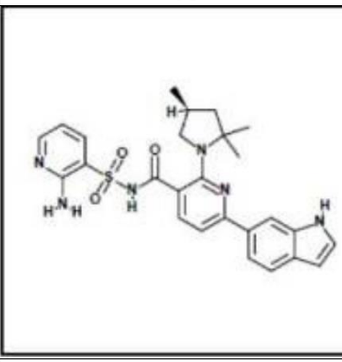
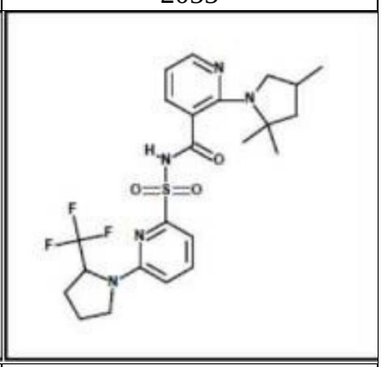
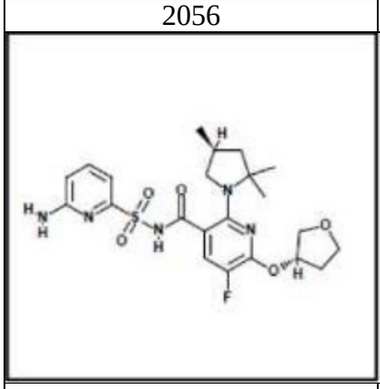
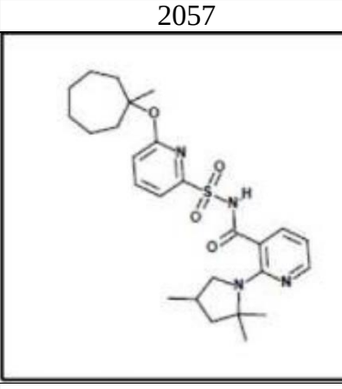
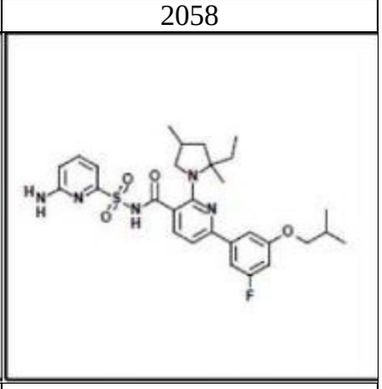
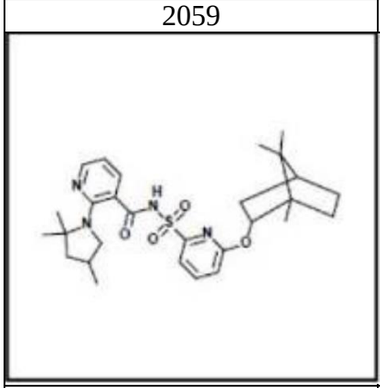
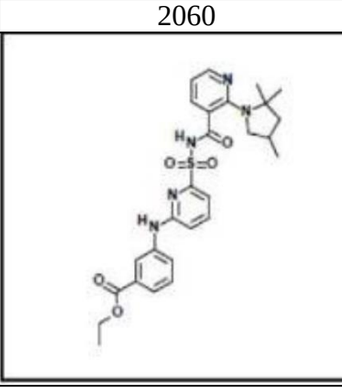
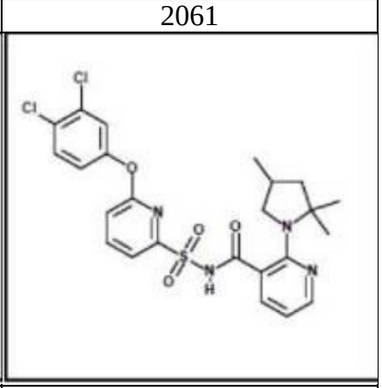
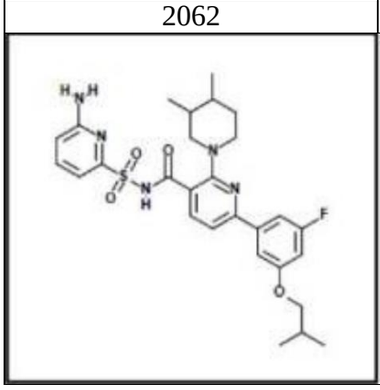
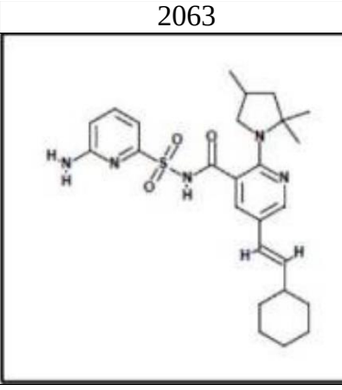
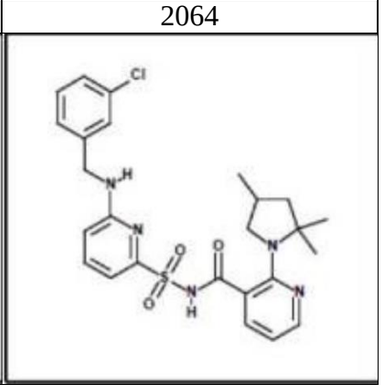
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1987	1988	1989
		

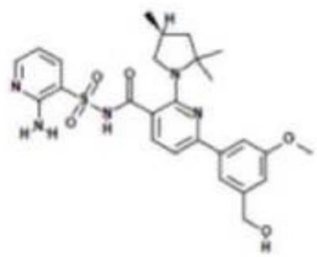
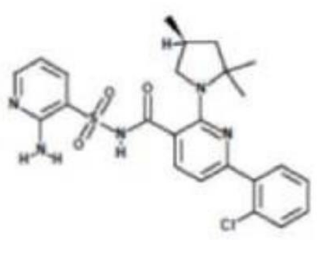
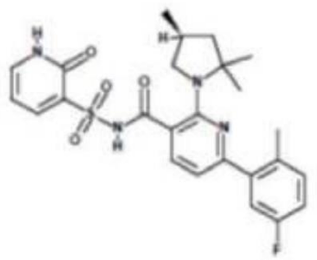
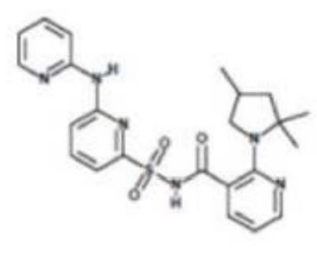
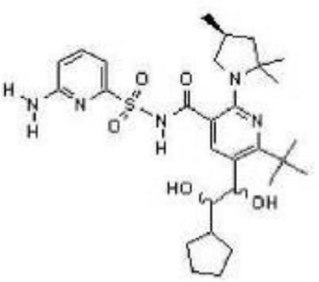
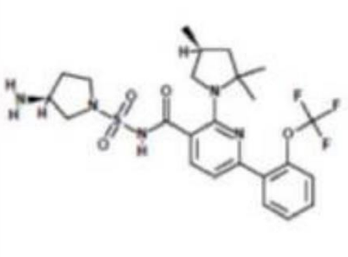
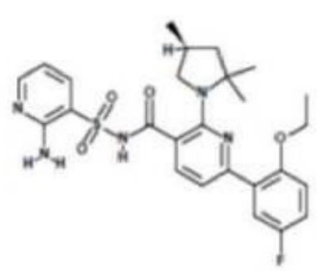
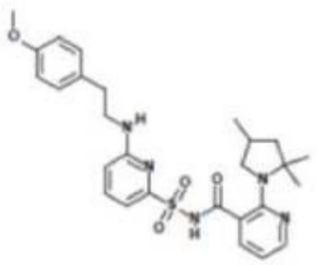
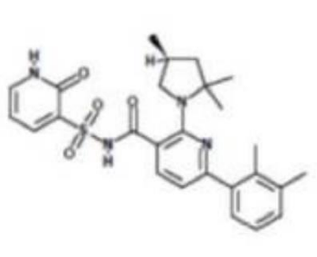
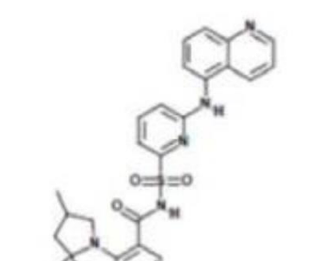
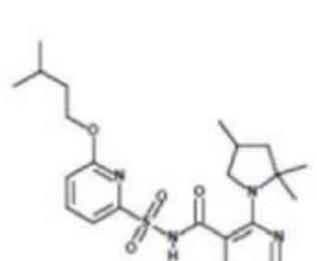
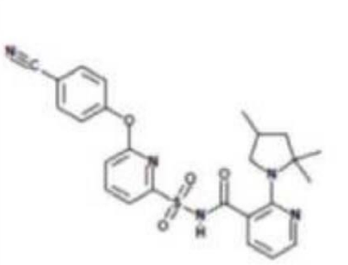
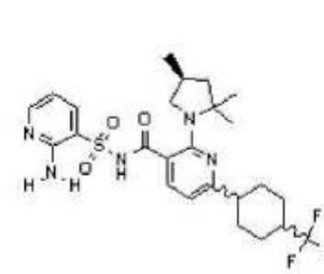
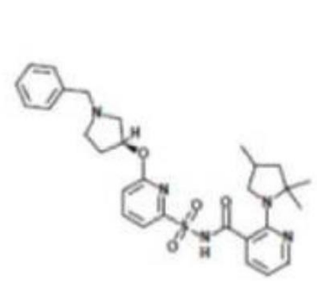
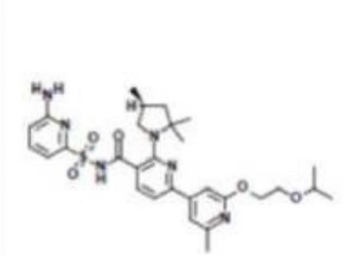
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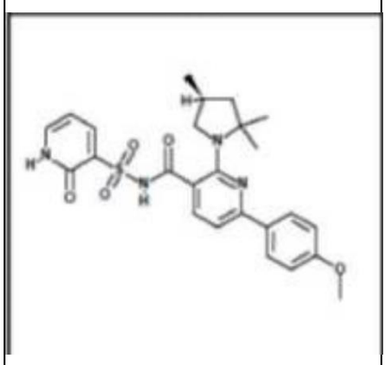
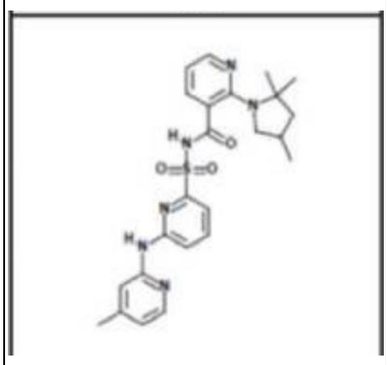
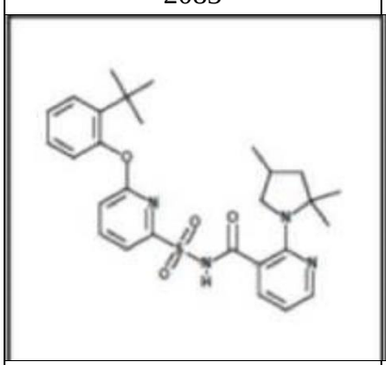
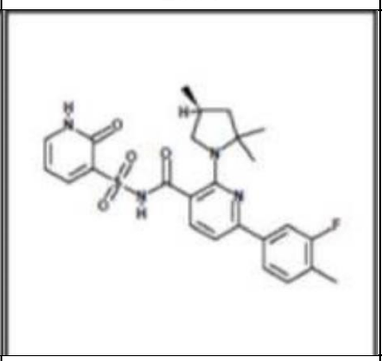
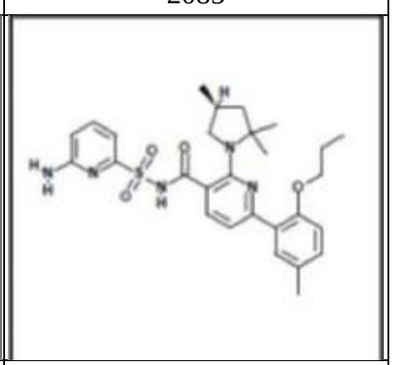
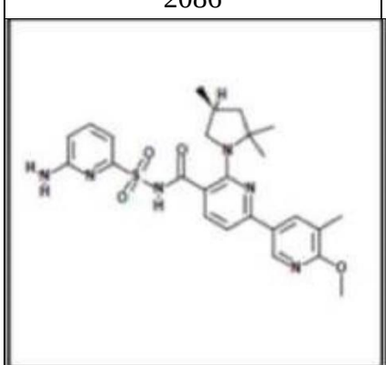
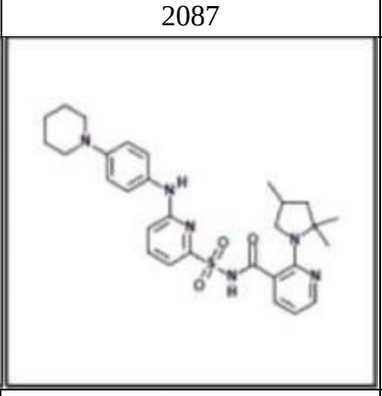
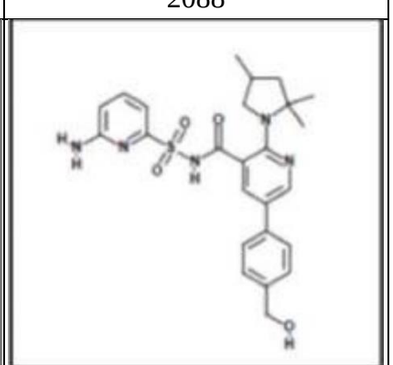
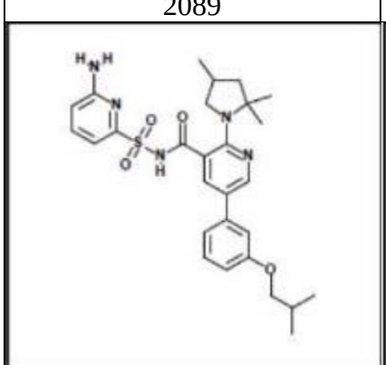
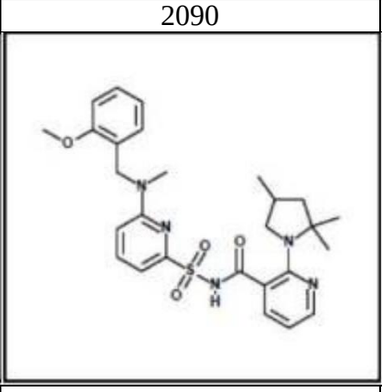
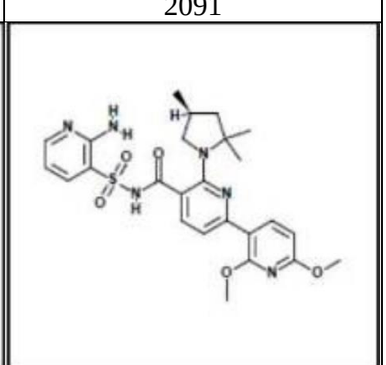
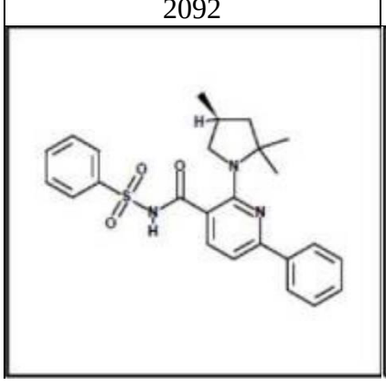
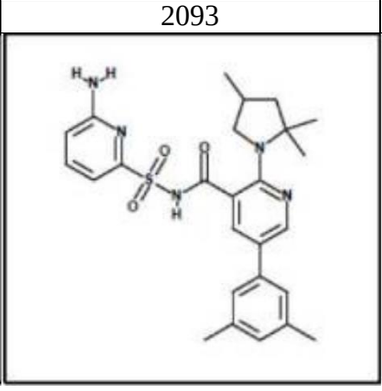
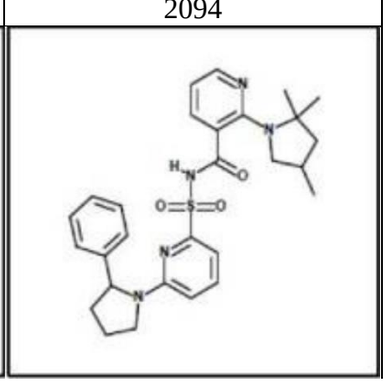
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2008	2009	2010
		
2011	2012	2013
		
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2017	2018	2019
		

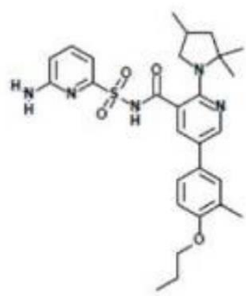
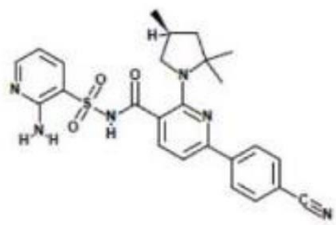
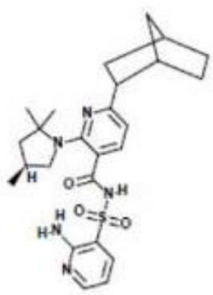
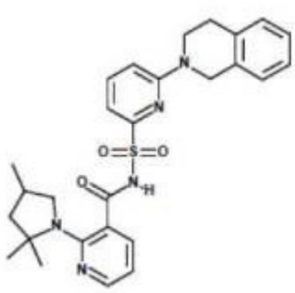
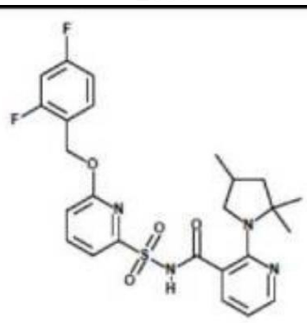
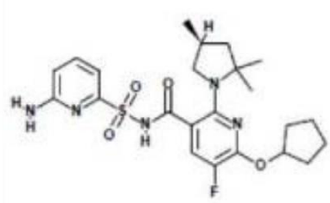
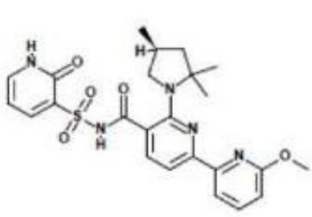
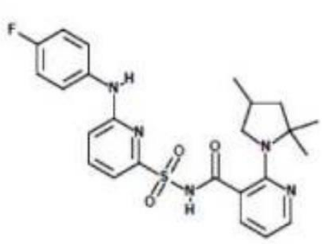
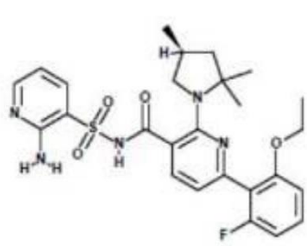
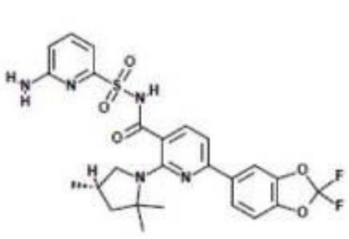
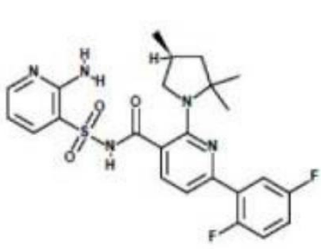
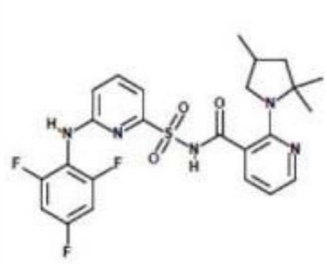
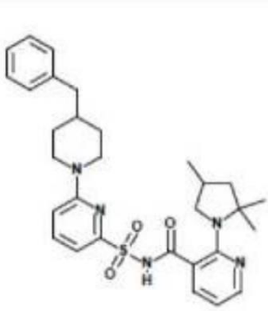
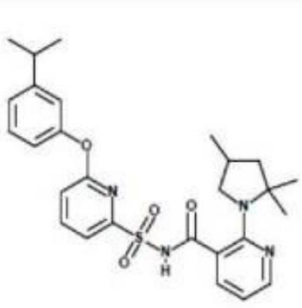
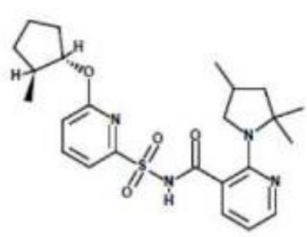
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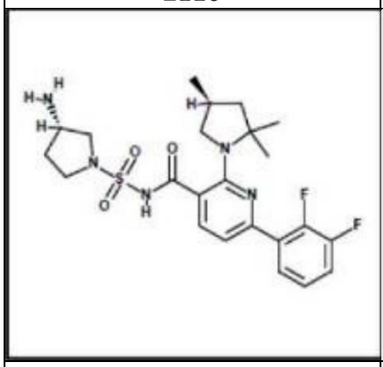
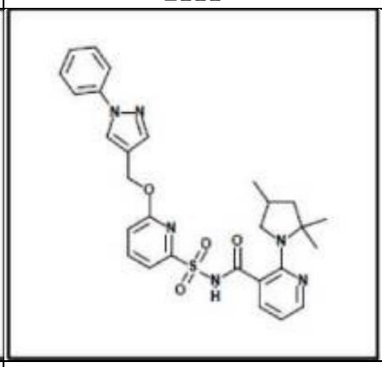
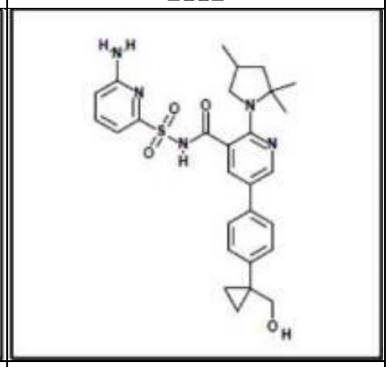
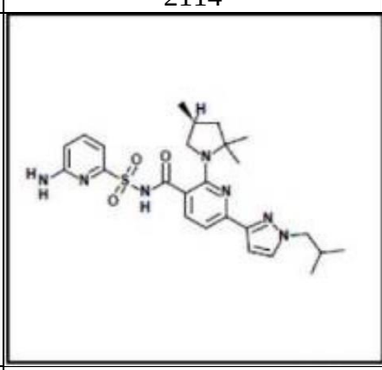
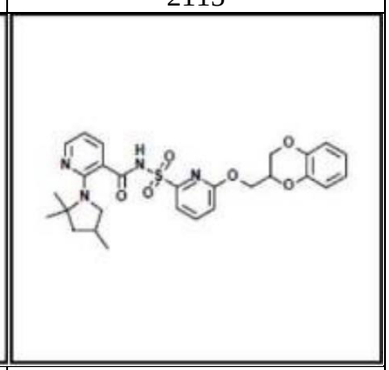
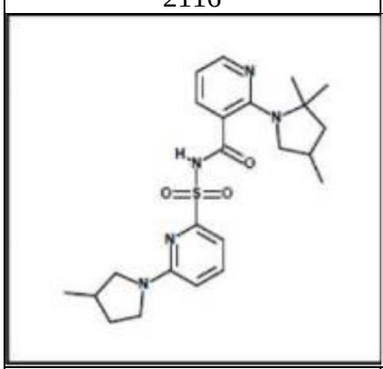
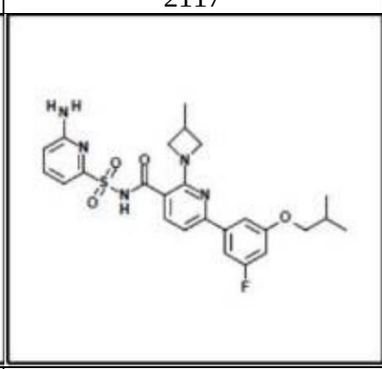
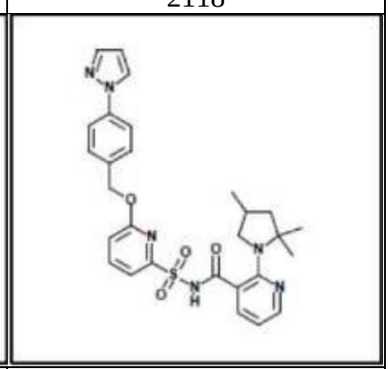
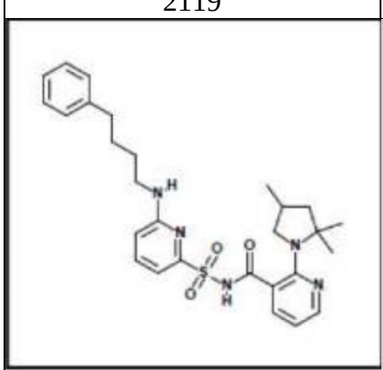
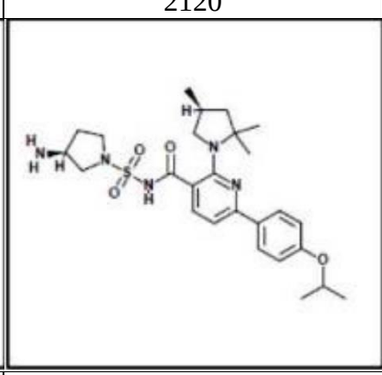
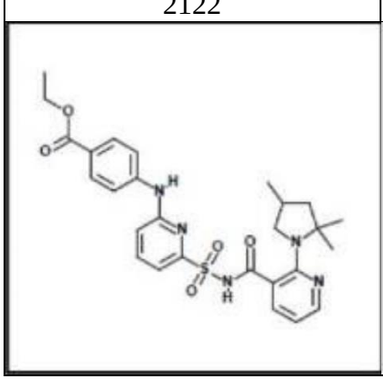
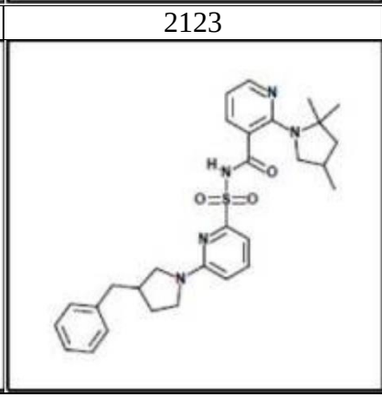
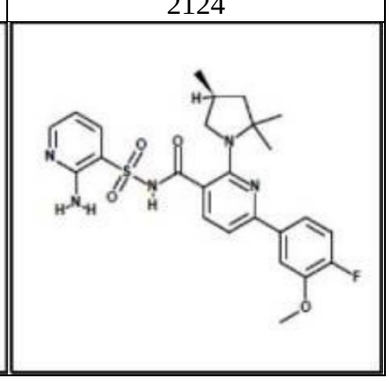
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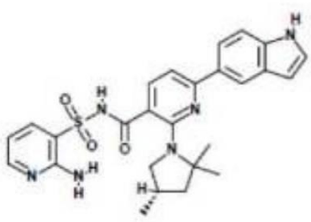
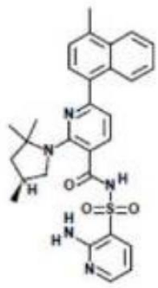
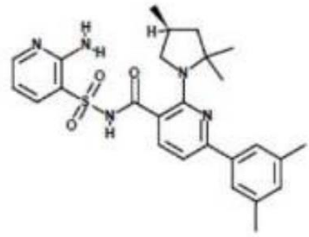
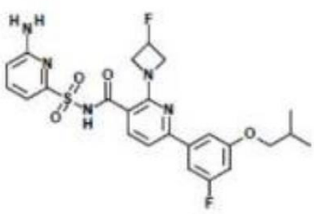
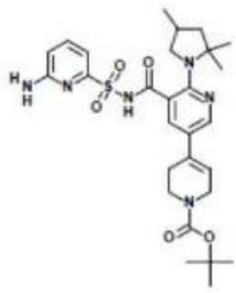
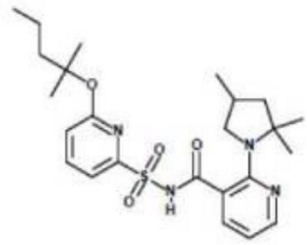
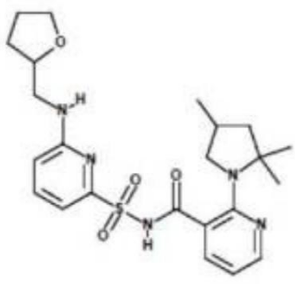
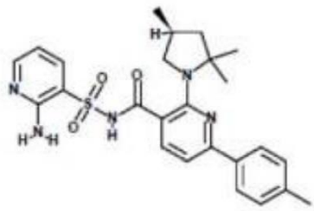
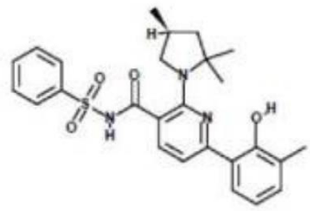
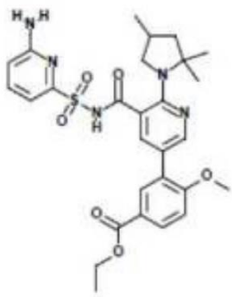
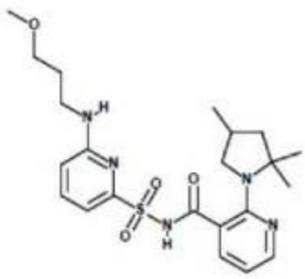
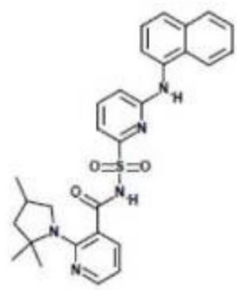
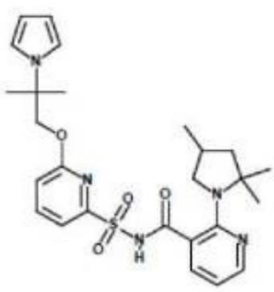
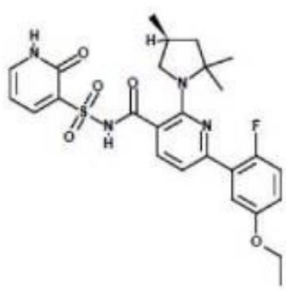
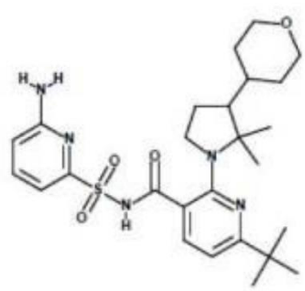
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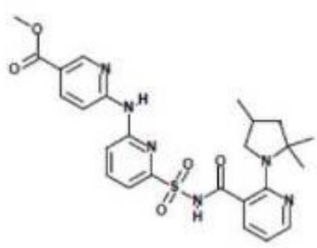
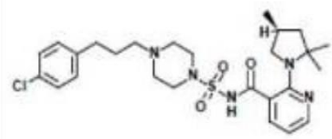
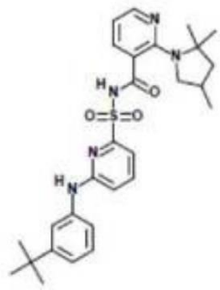
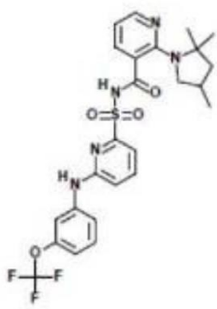
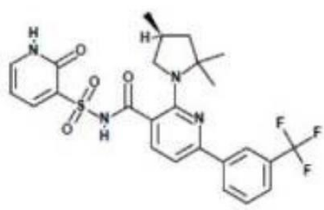
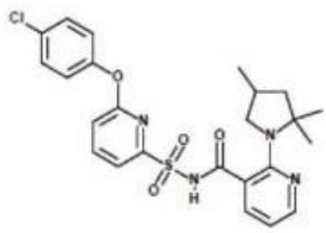
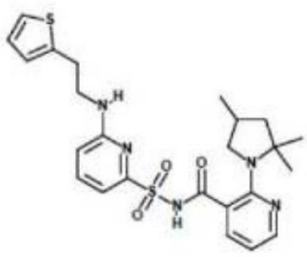
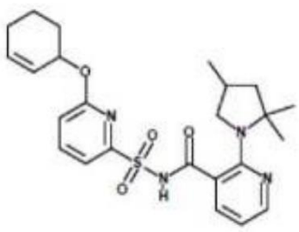
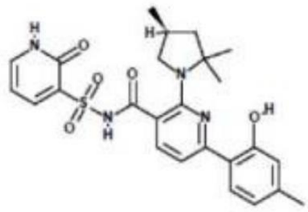
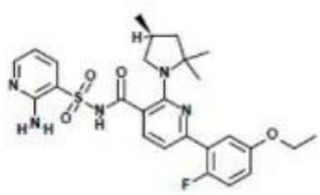
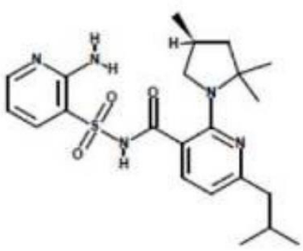
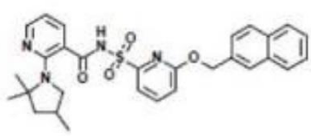
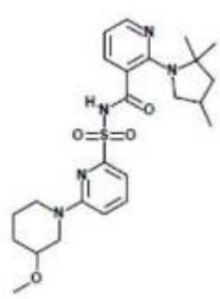
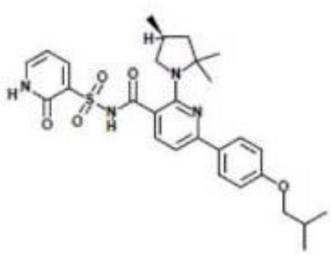
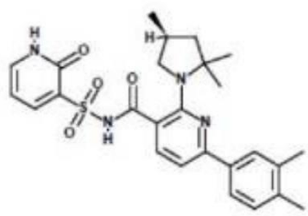
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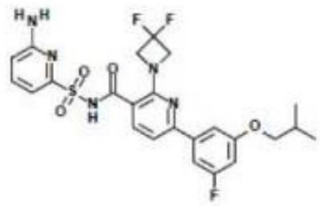
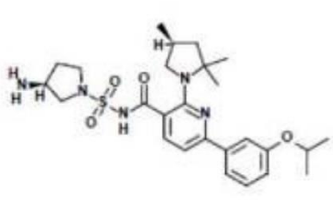
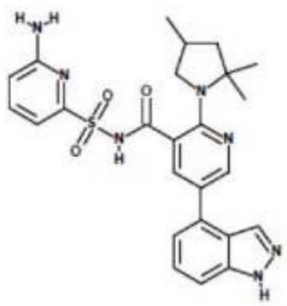
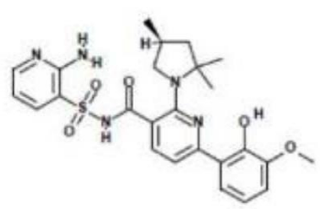
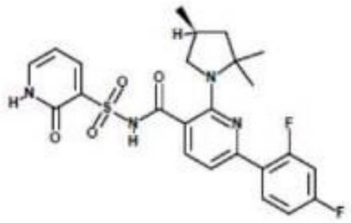
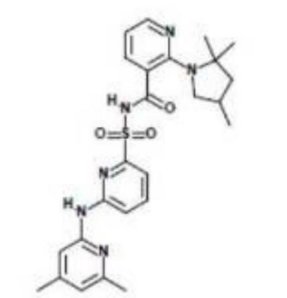
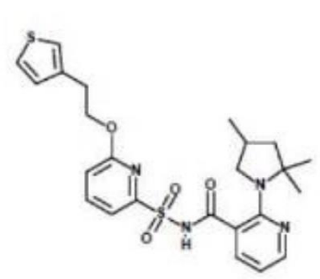
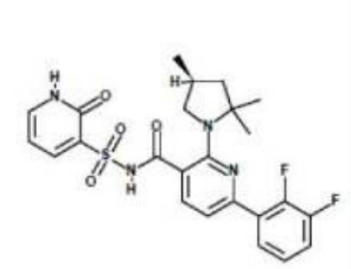
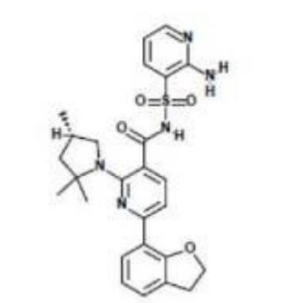
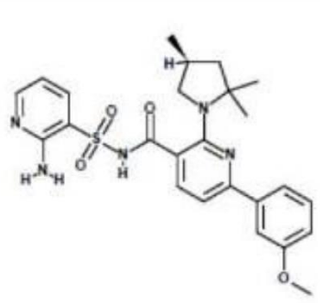
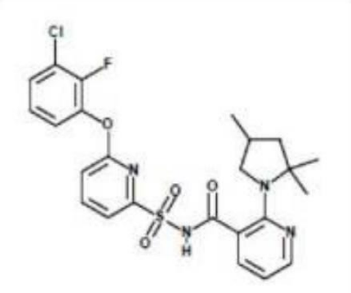
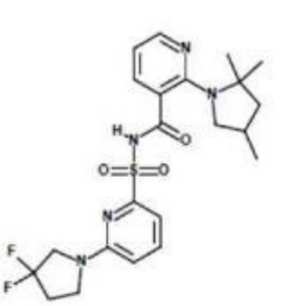
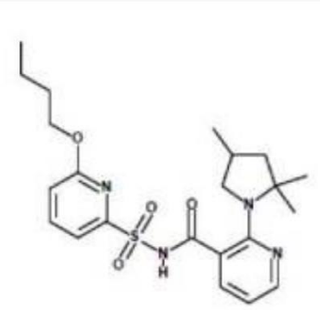
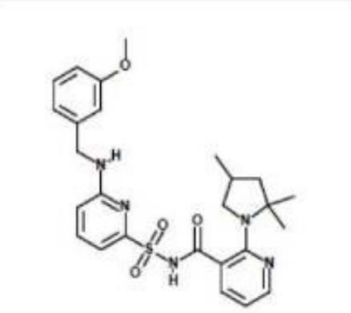
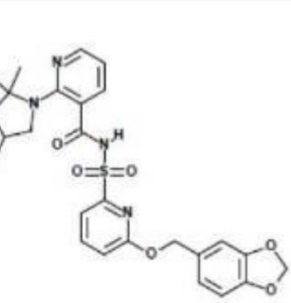
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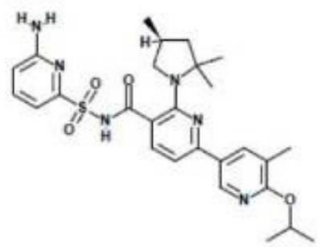
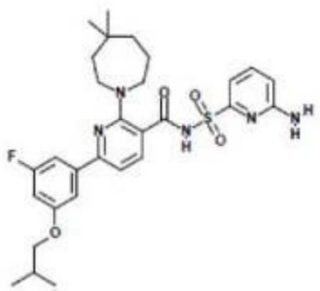
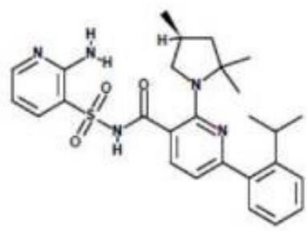
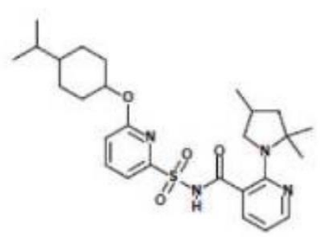
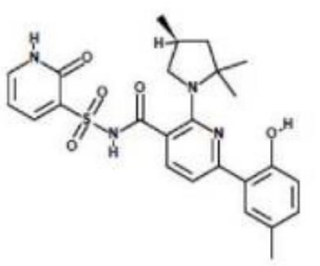
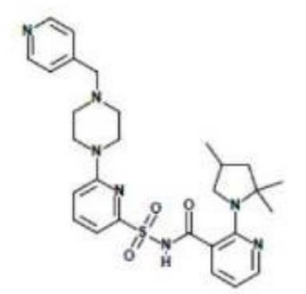
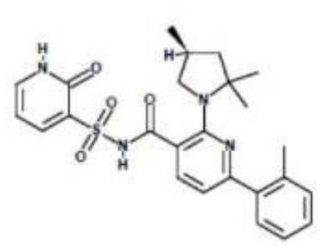
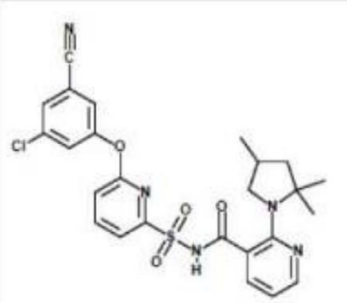
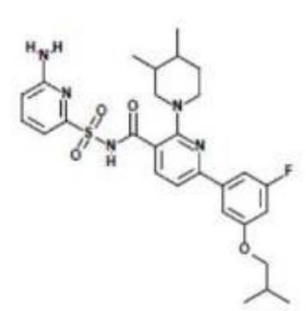
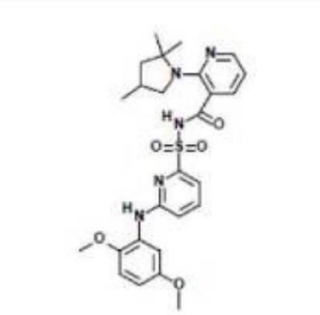
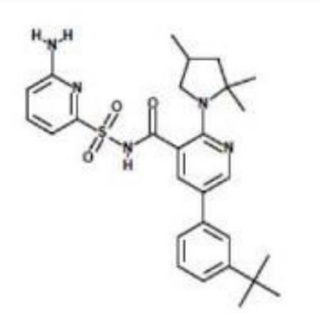
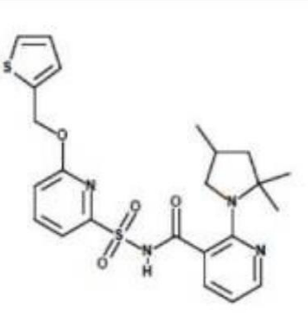
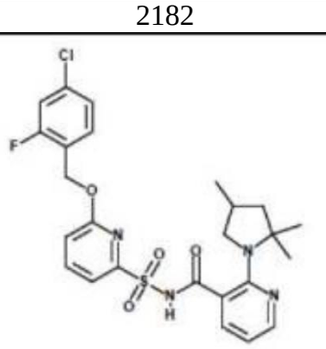
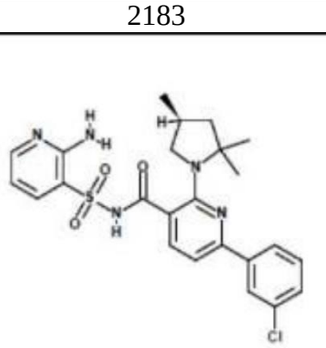
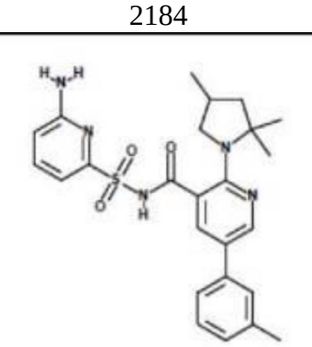
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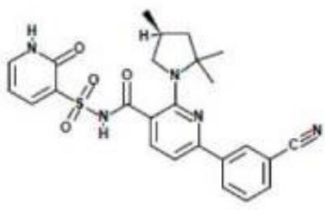
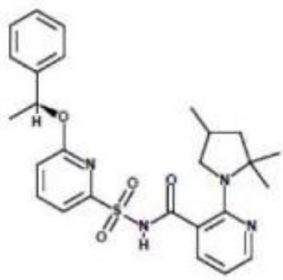
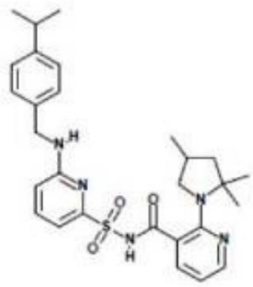
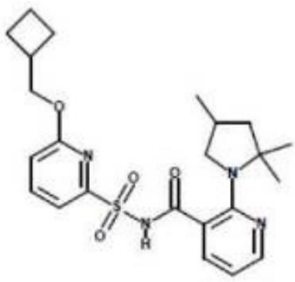
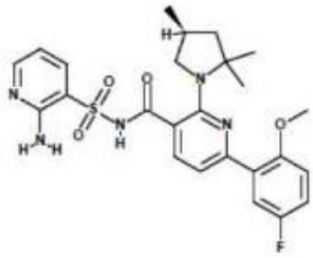
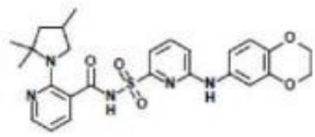
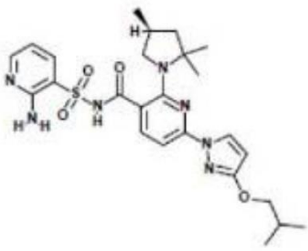
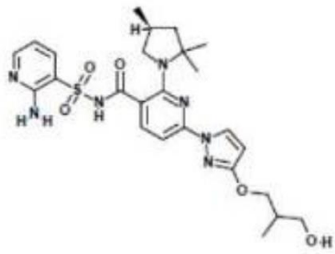
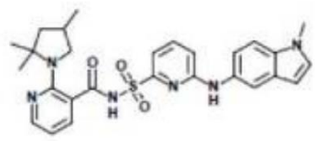
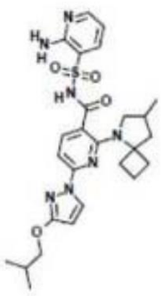
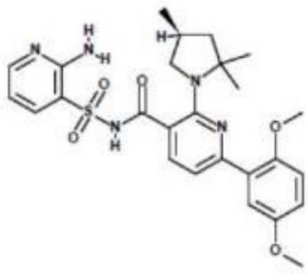
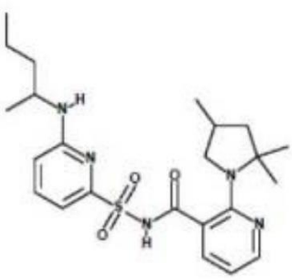
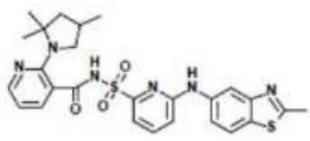
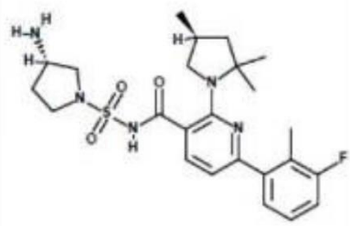
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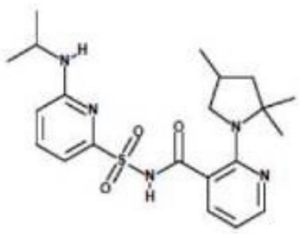
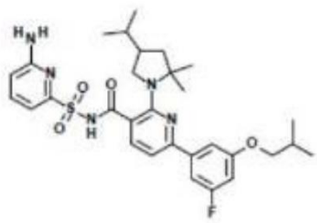
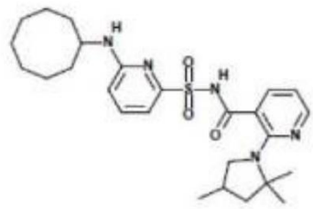
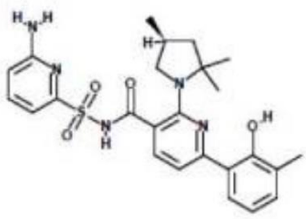
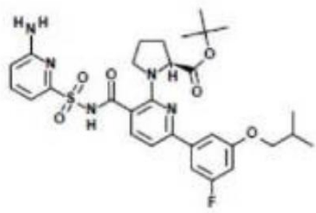
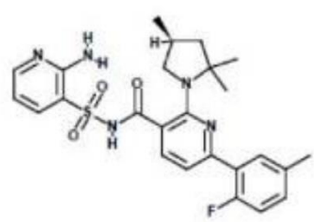
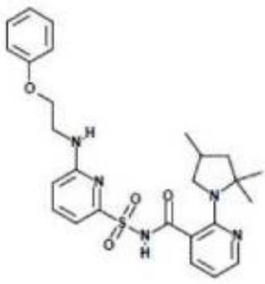
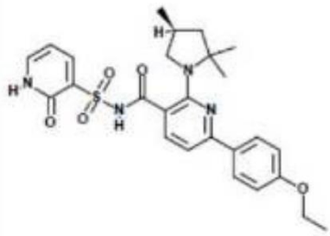
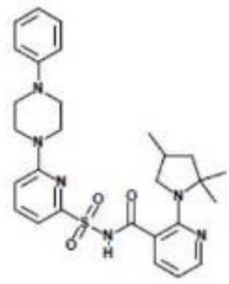
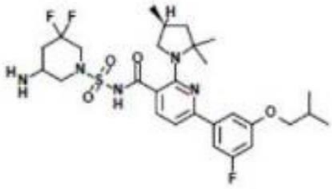
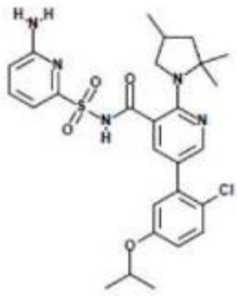
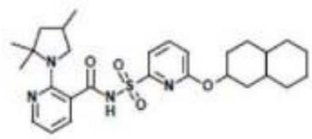
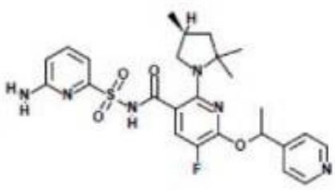
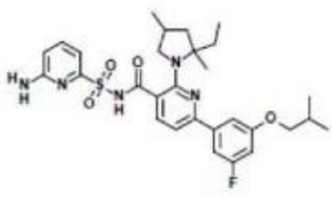
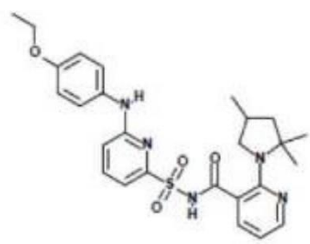
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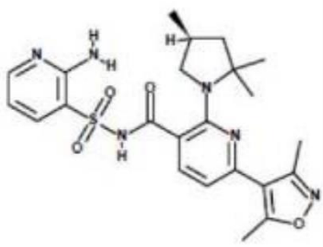
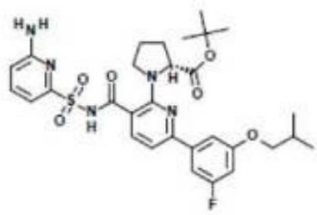
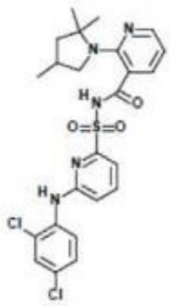
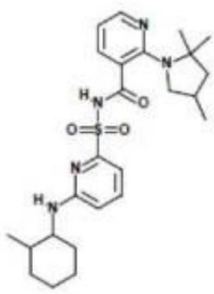
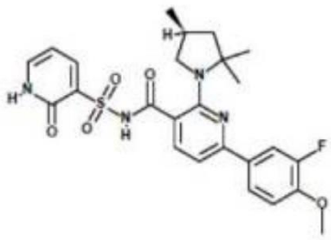
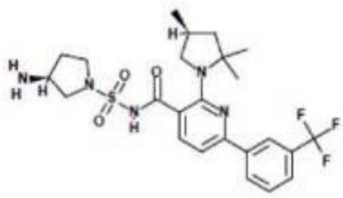
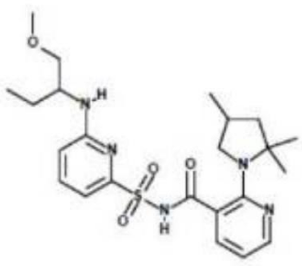
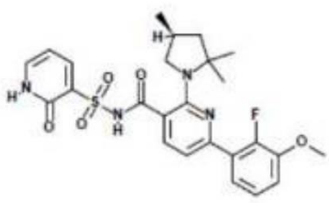
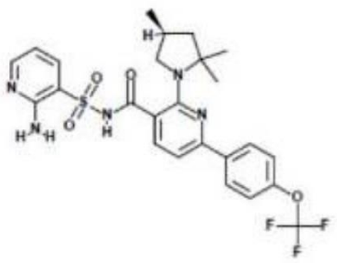
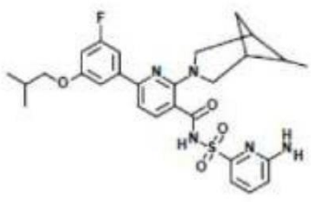
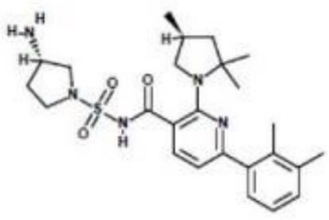
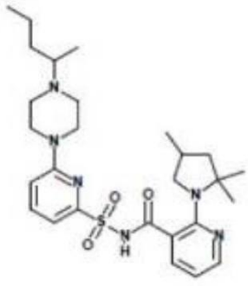
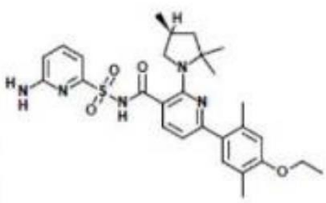
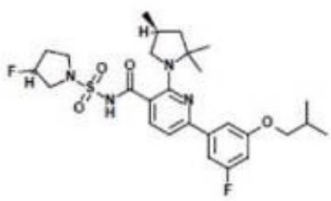
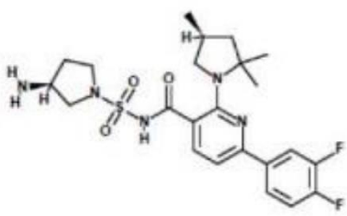
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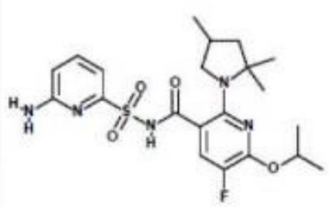
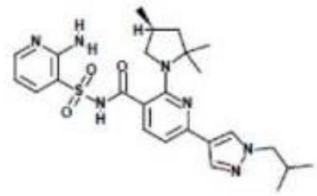
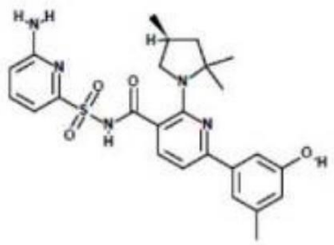
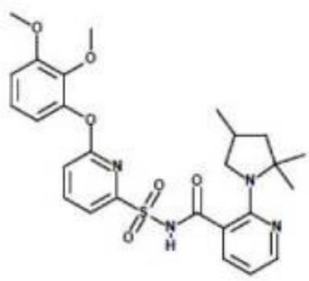
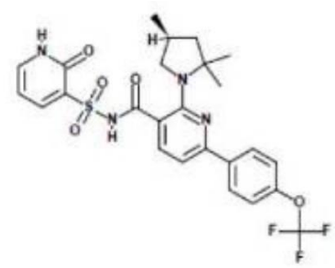
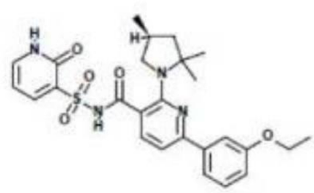
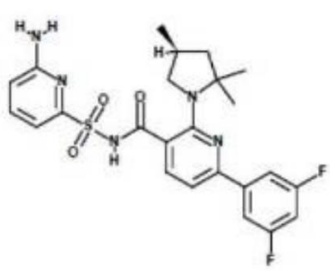
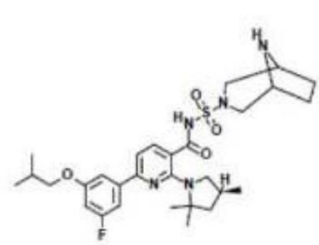
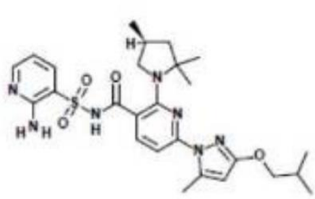
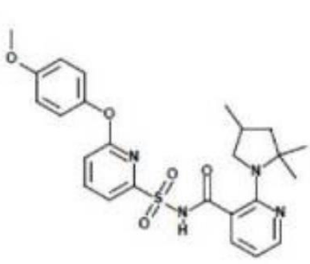
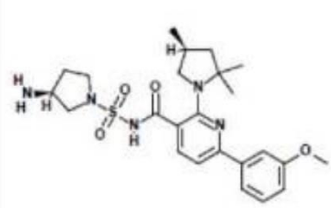
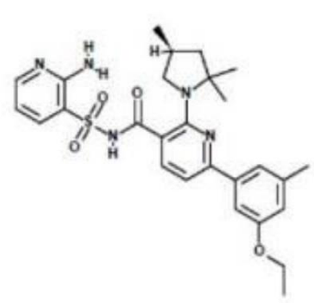
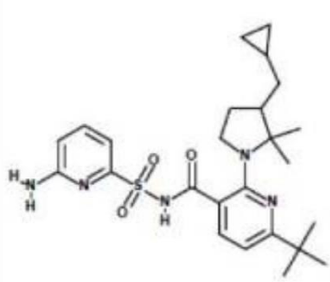
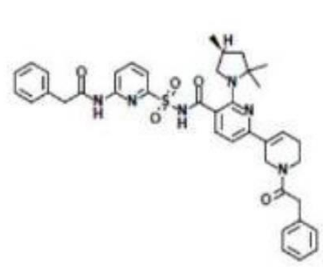
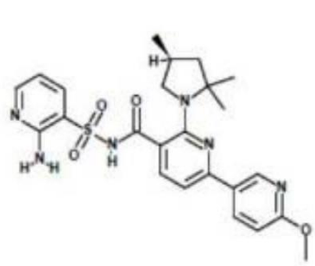
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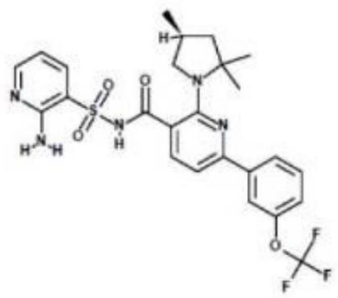
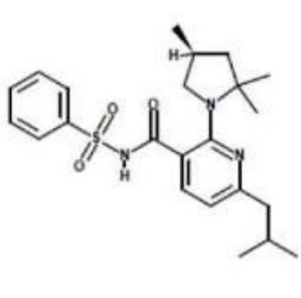
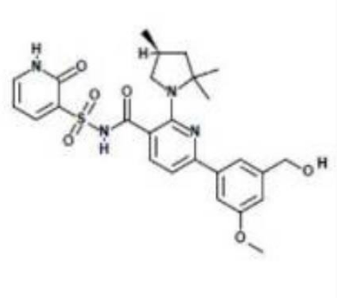
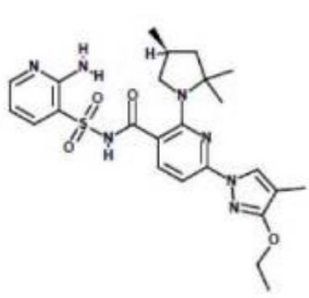
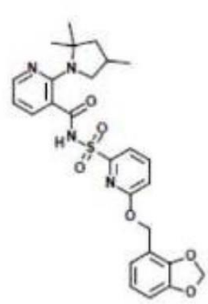
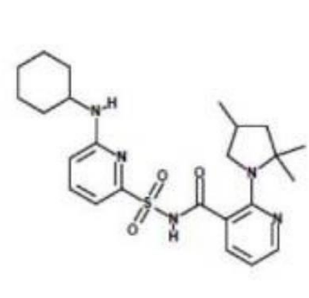
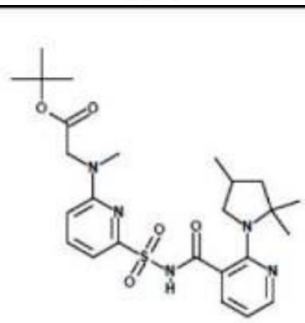
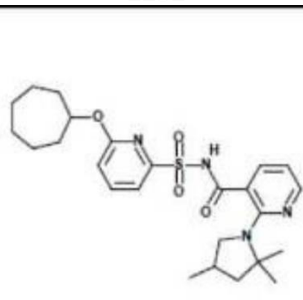
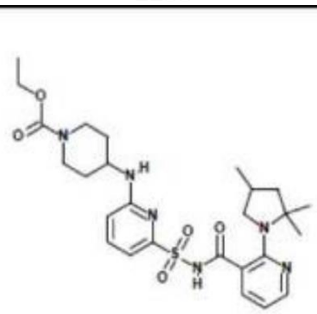
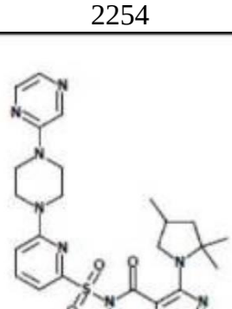
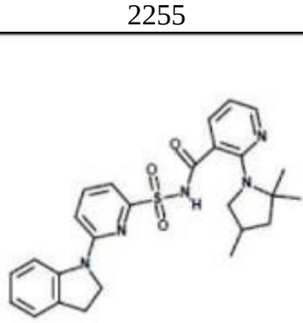
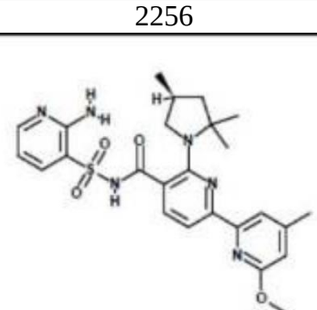
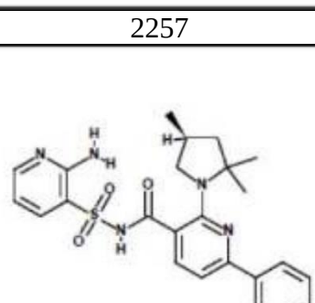
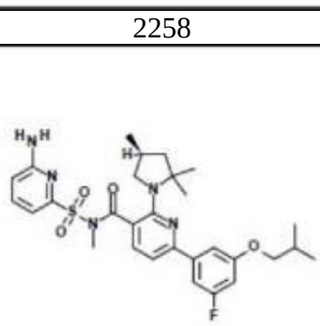
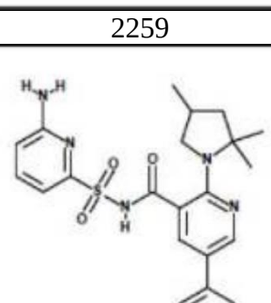
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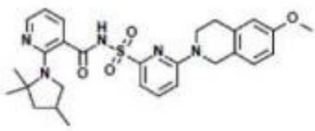
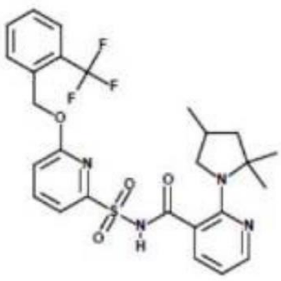
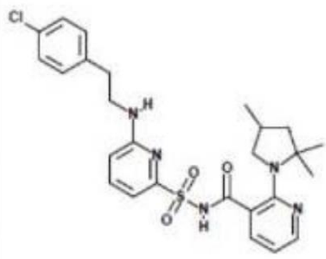
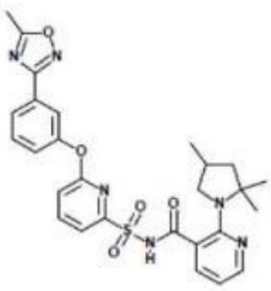
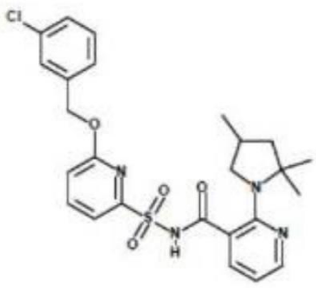
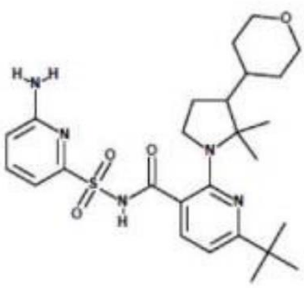
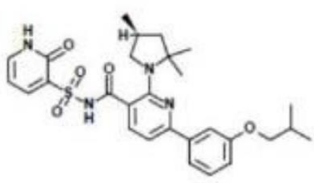
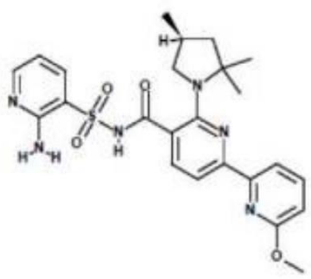
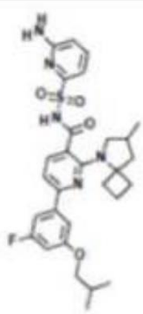
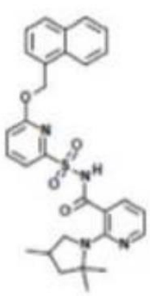
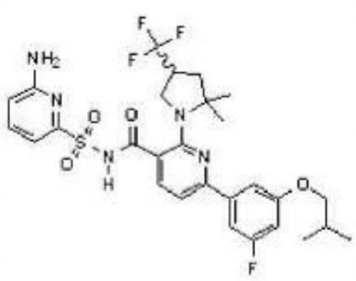
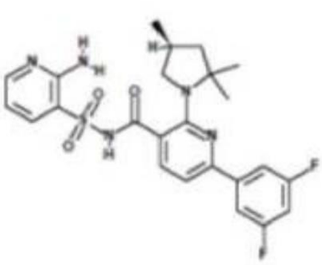
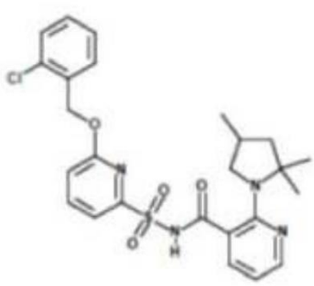
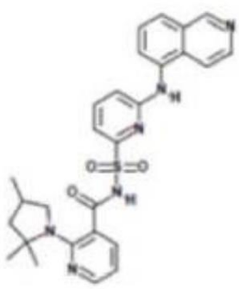
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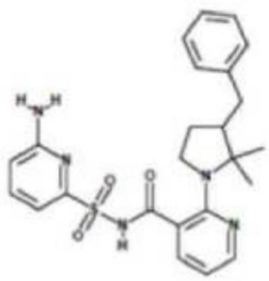
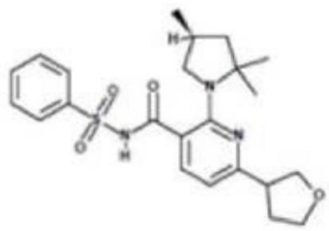
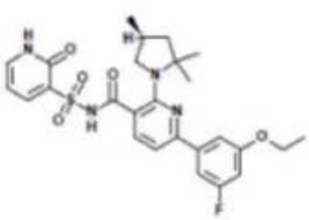
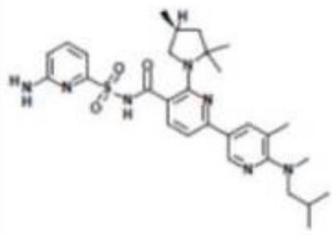
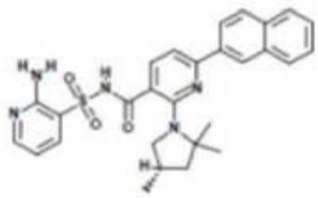
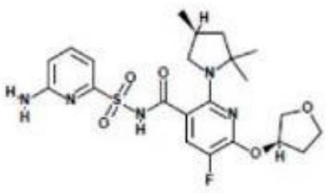
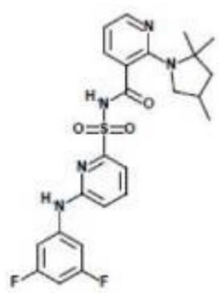
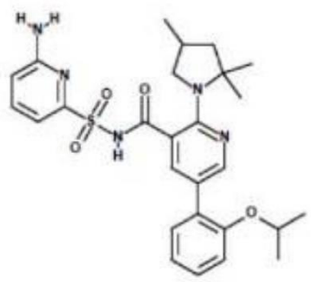
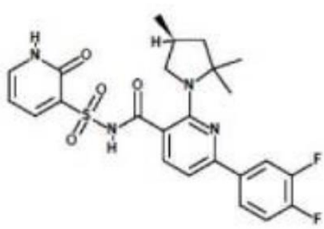
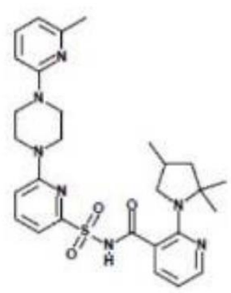
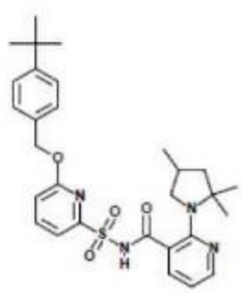
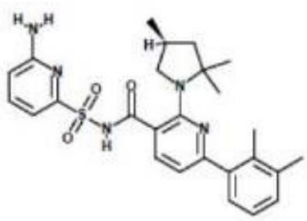
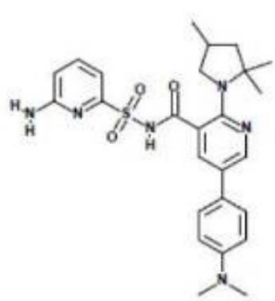
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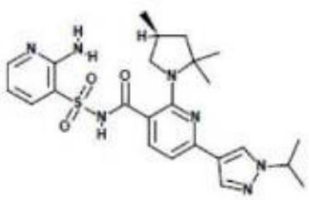
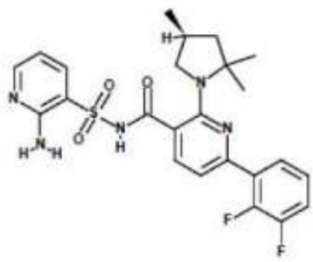
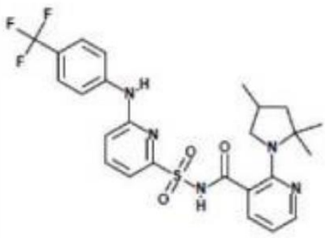
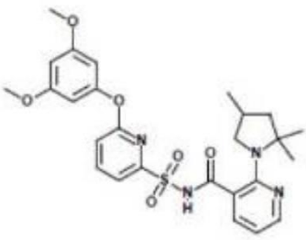
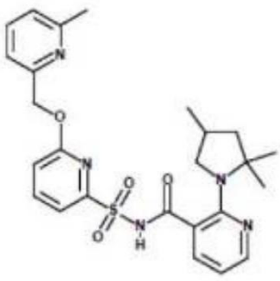
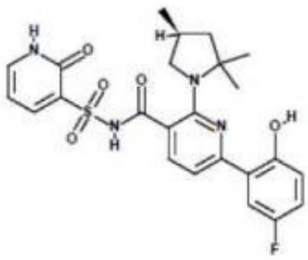
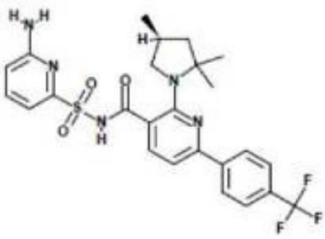
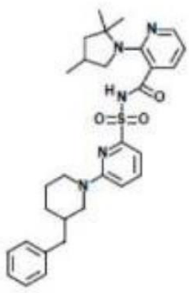
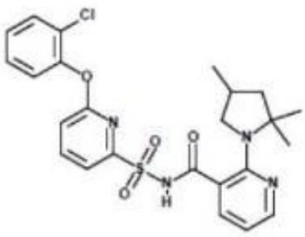
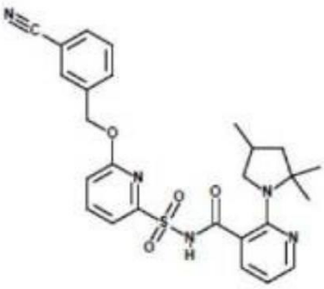
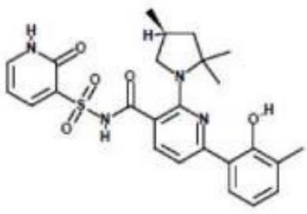
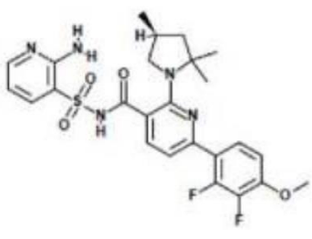
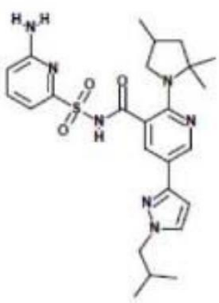
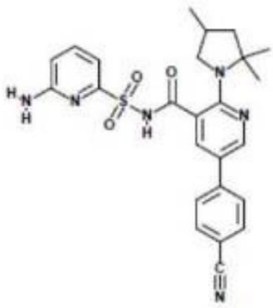
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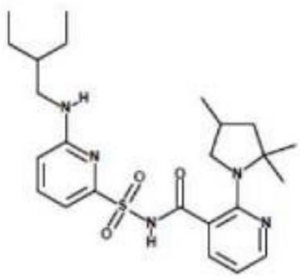
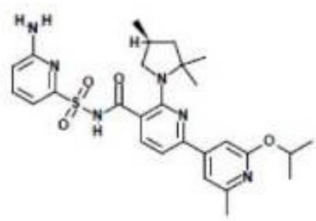
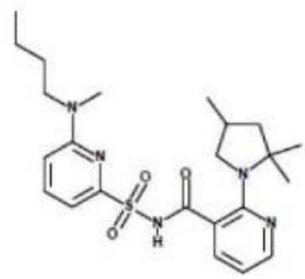
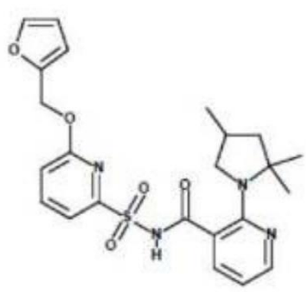
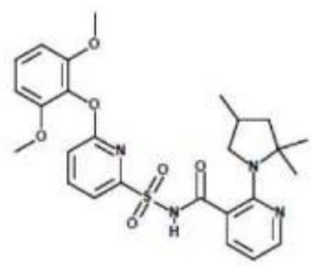
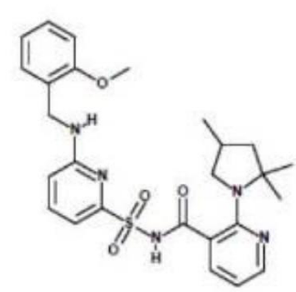
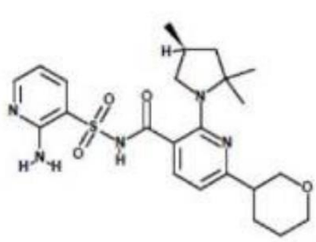
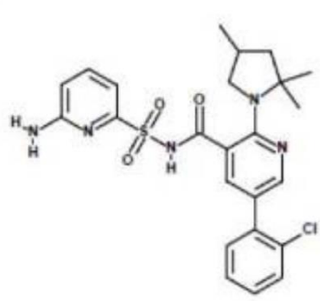
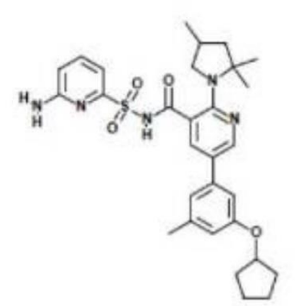
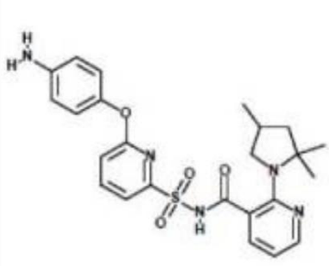
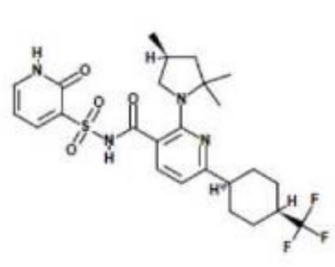
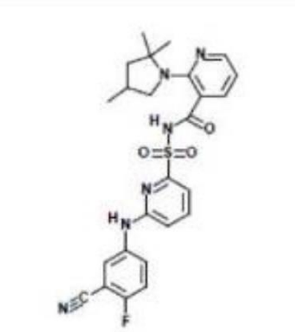
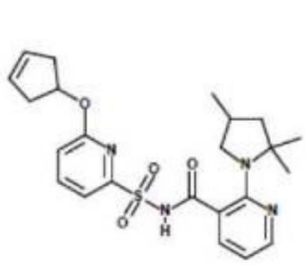
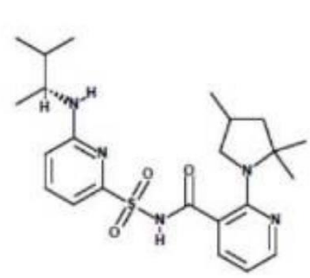
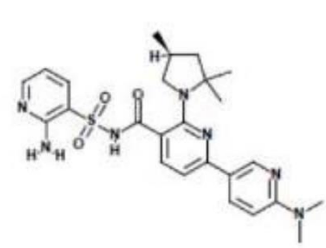
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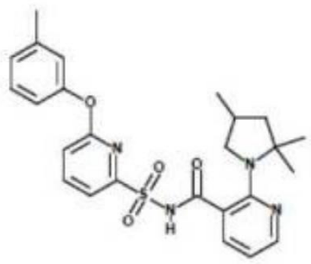
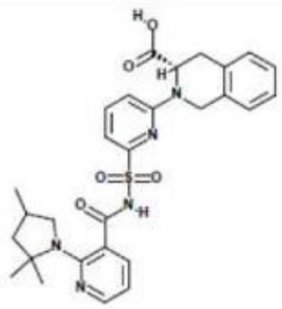
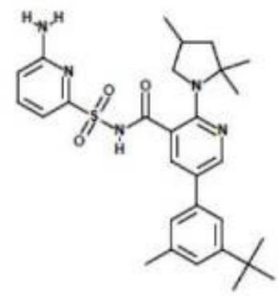
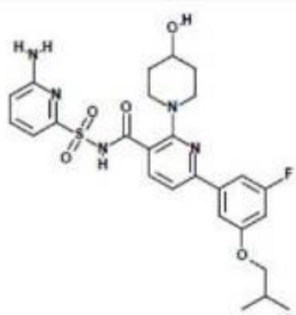
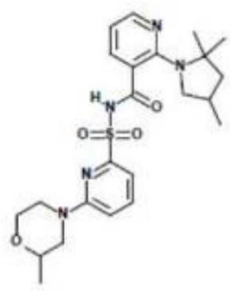
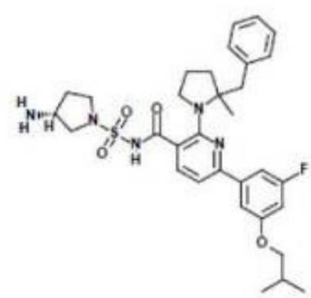
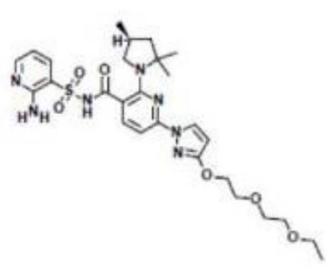
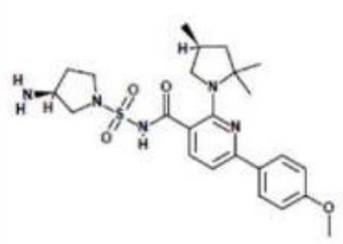
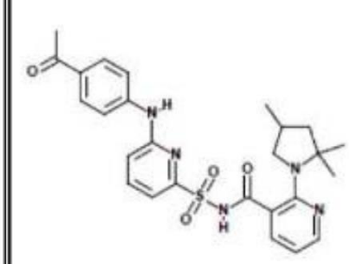
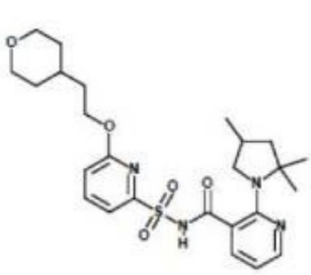
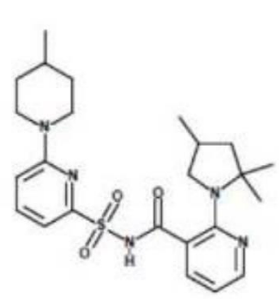
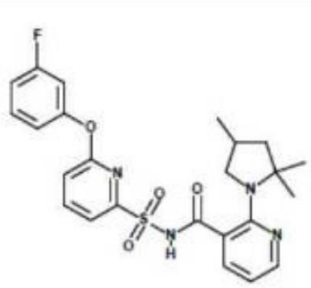
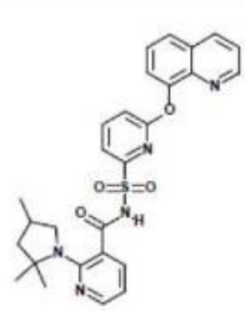
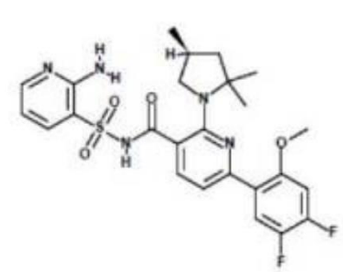
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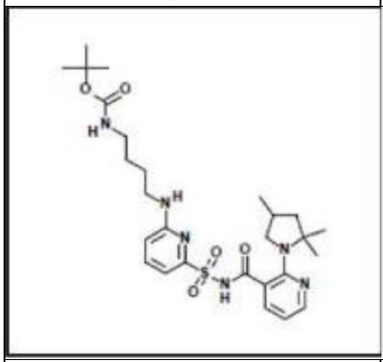
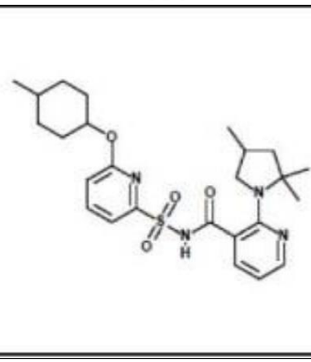
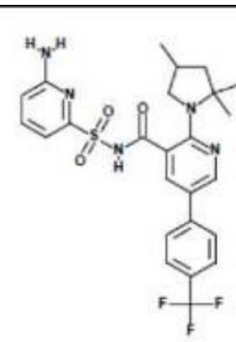
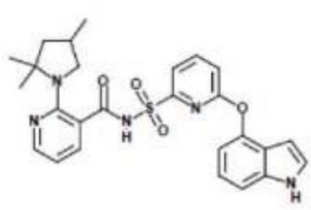
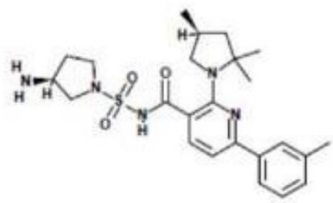
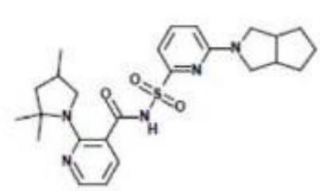
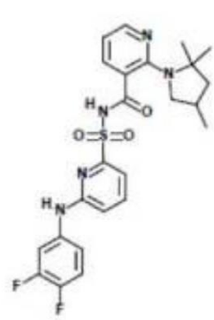
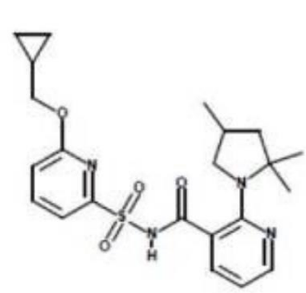
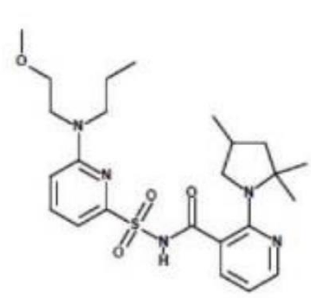
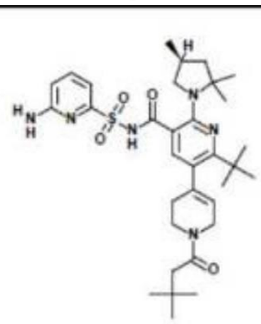
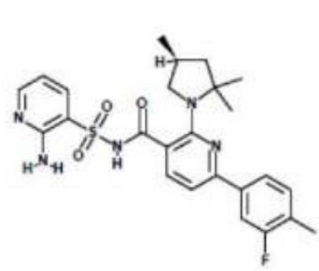
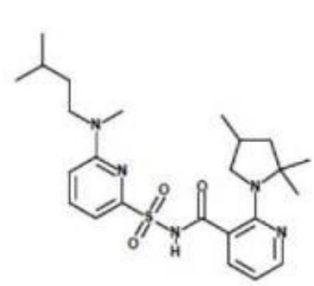
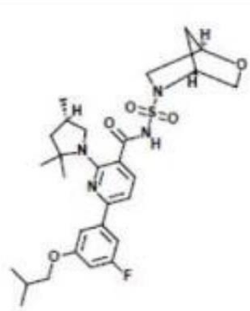
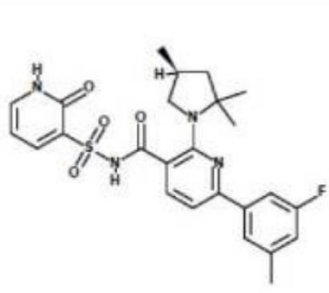
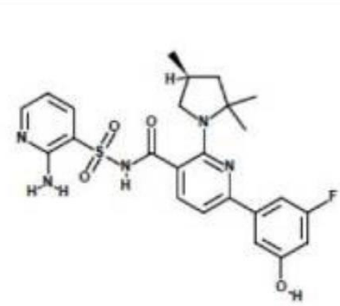
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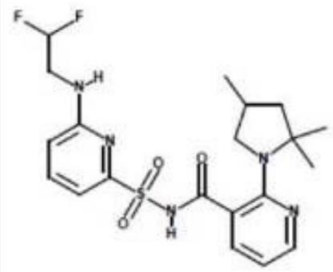
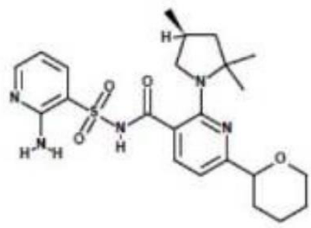
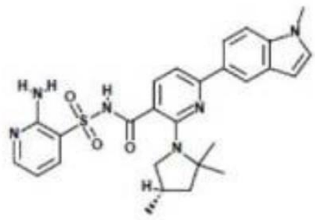
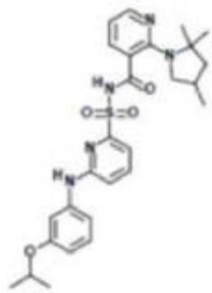
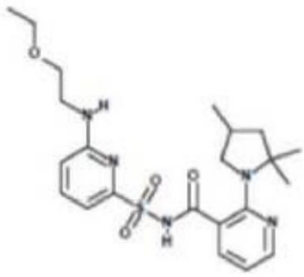
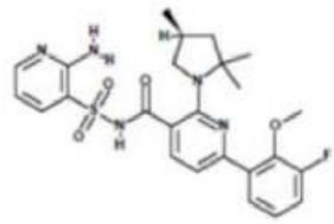
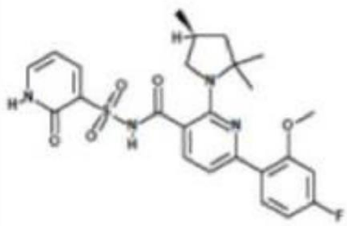
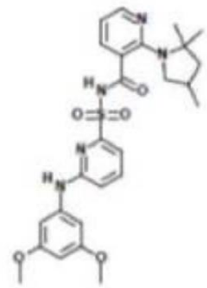
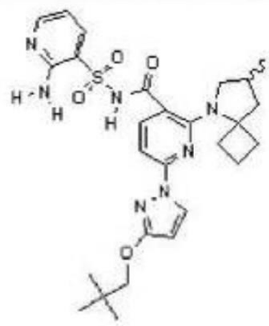
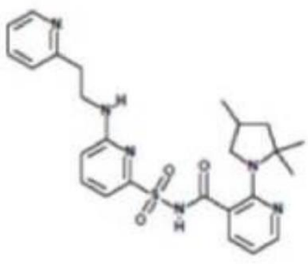
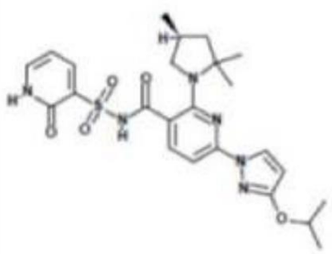
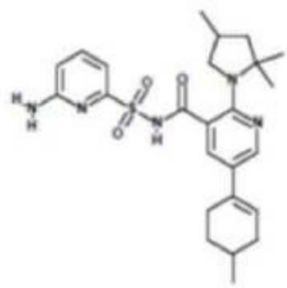
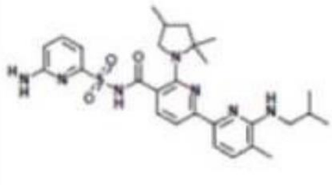
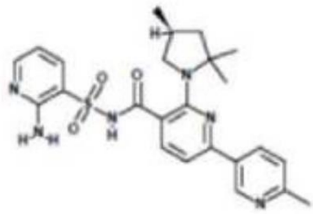
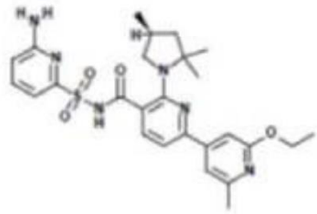
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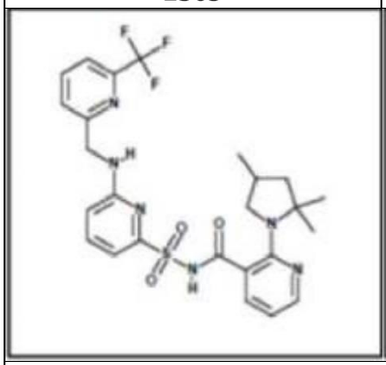
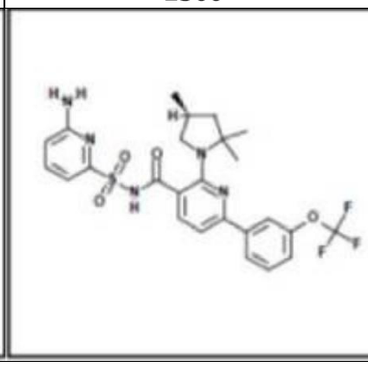
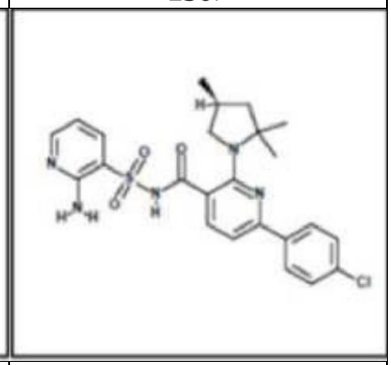
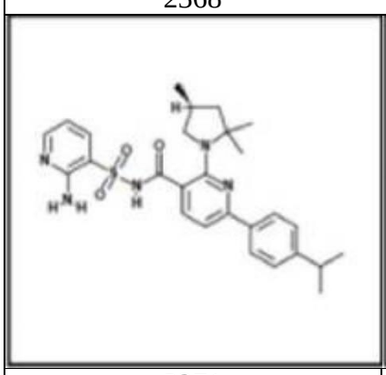
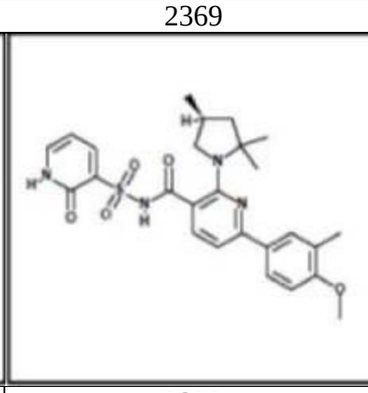
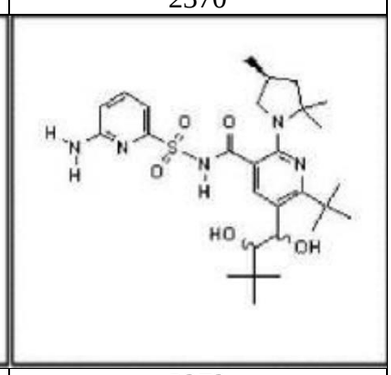
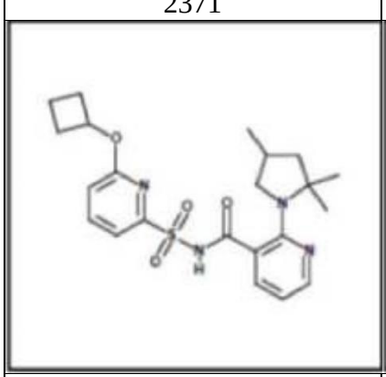
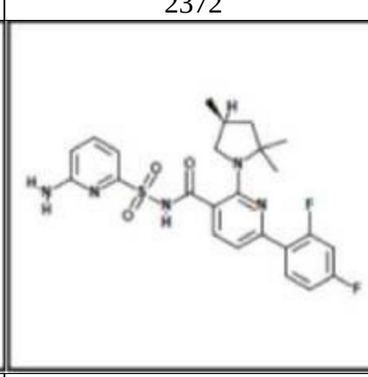
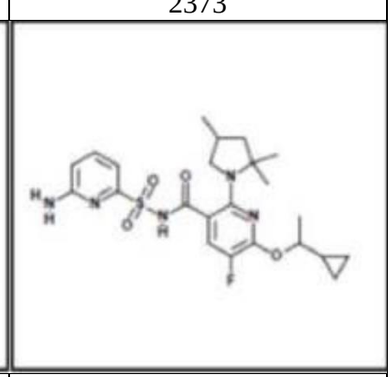
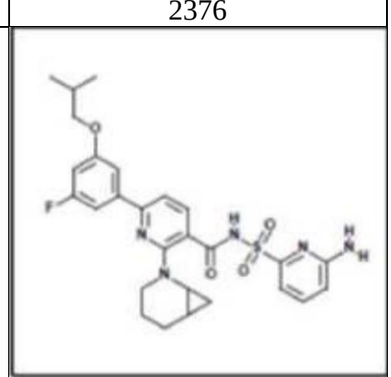
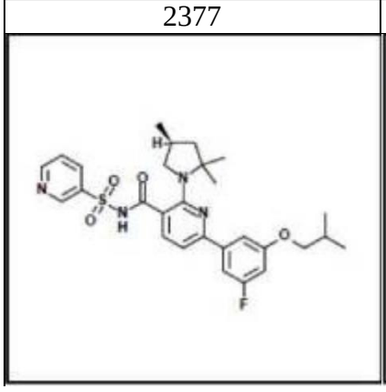
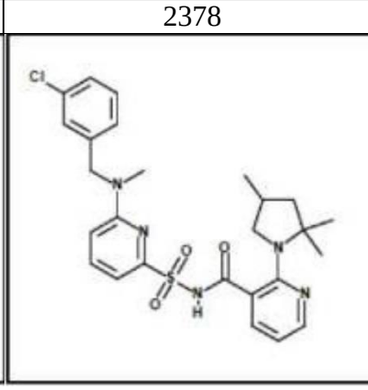
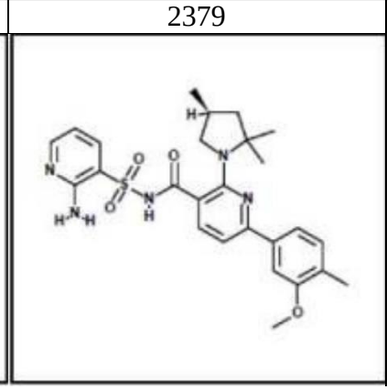
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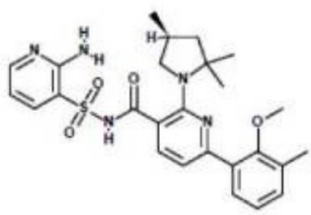
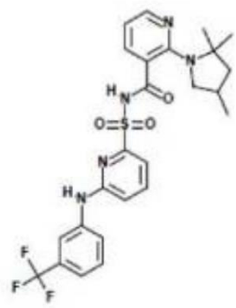
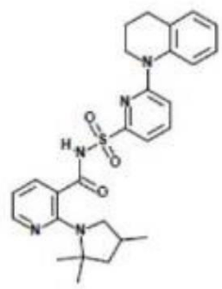
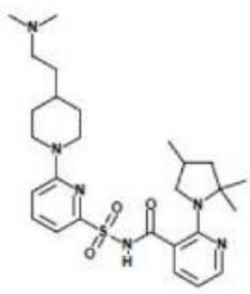
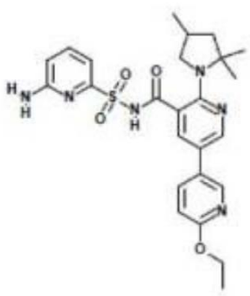
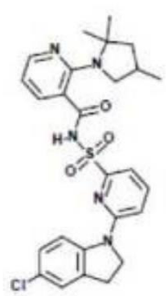
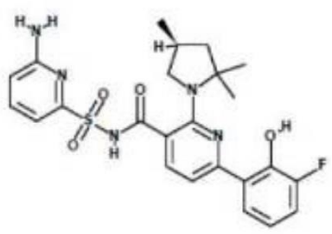
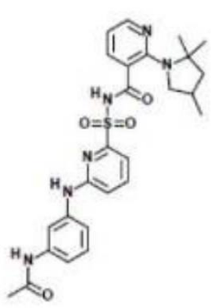
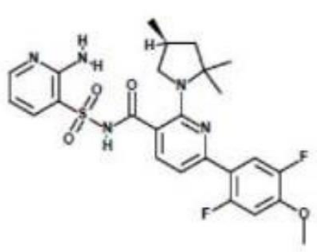
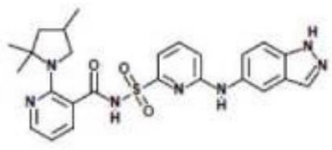
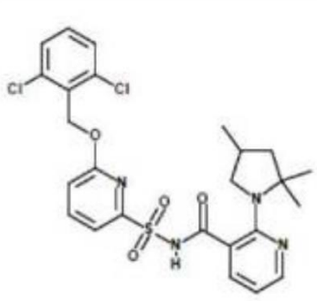
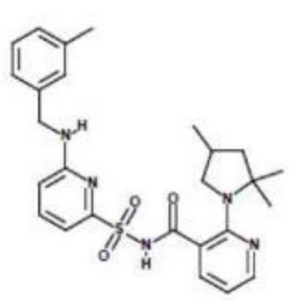
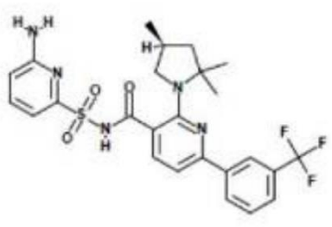
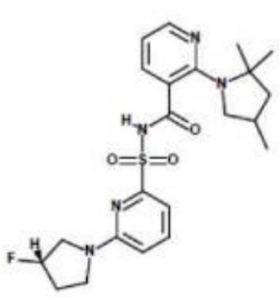
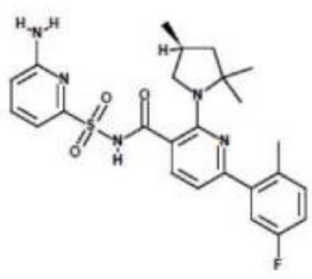
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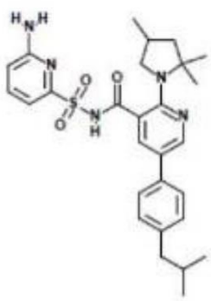
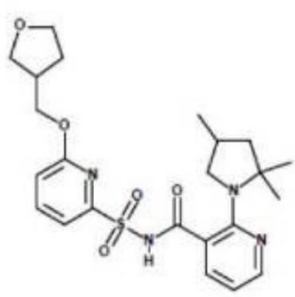
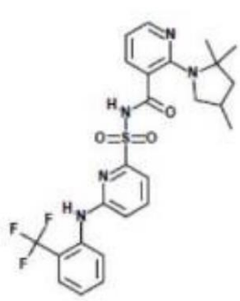
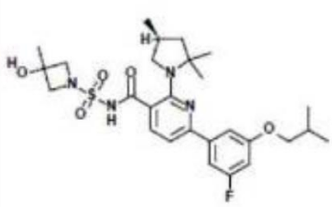
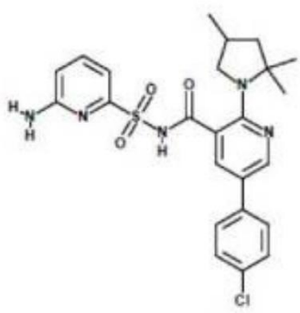
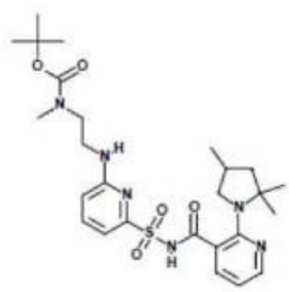
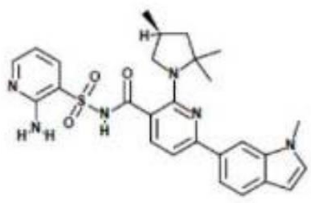
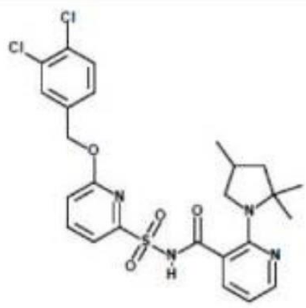
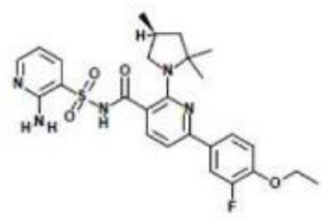
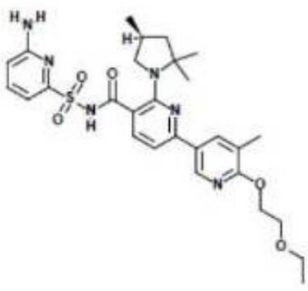
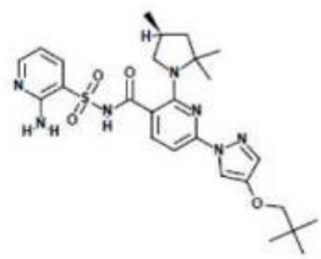
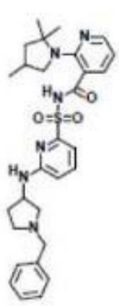
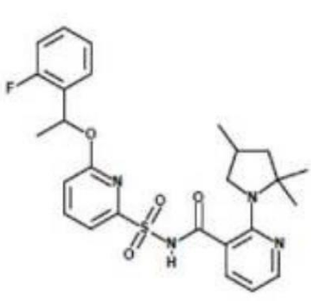
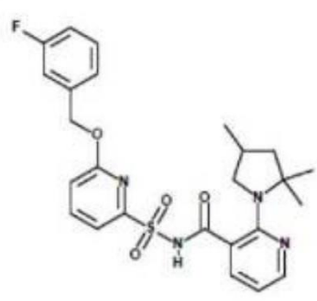
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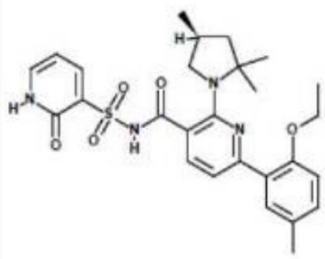
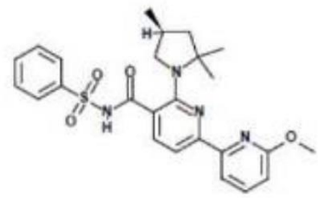
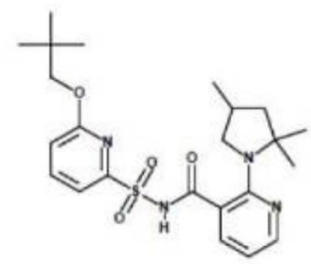
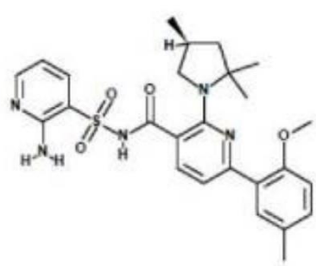
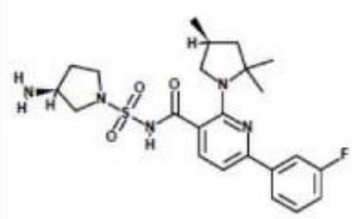
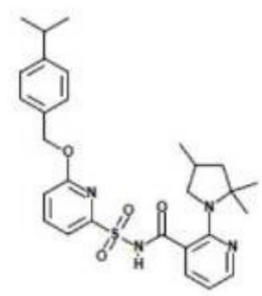
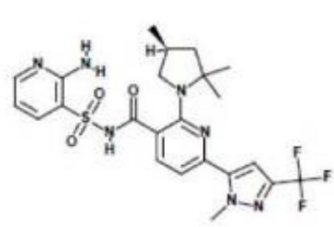
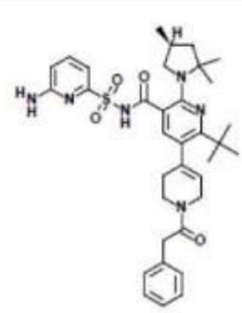
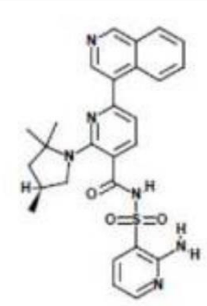
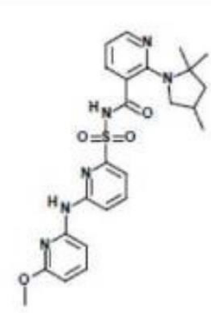
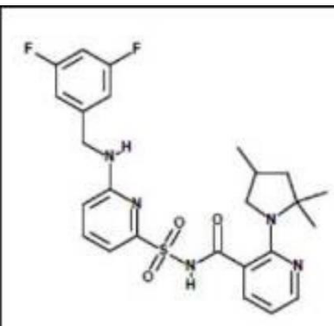
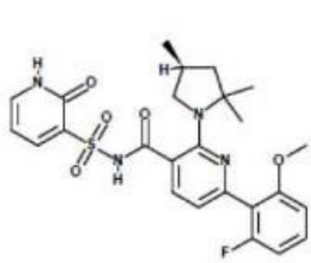
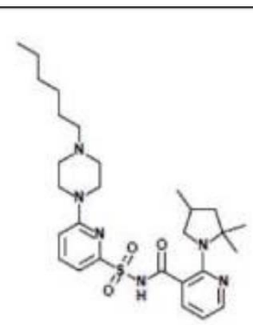
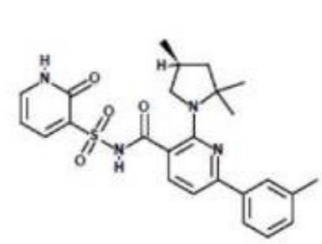
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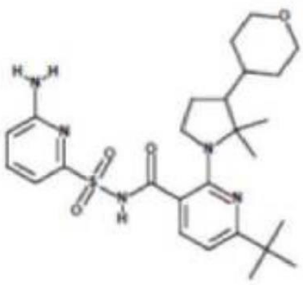
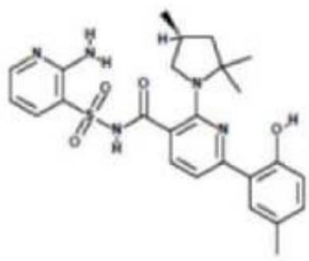
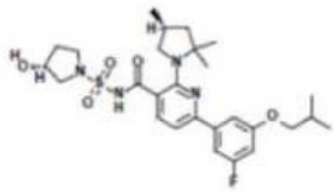
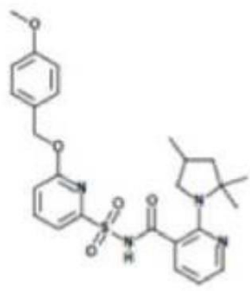
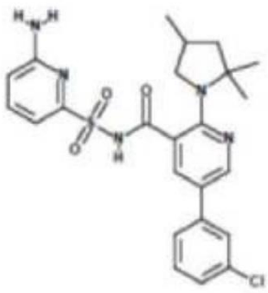
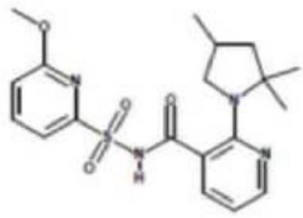
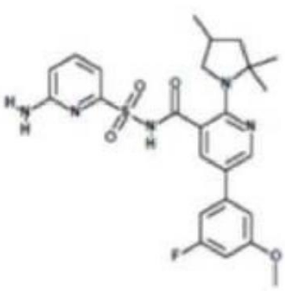
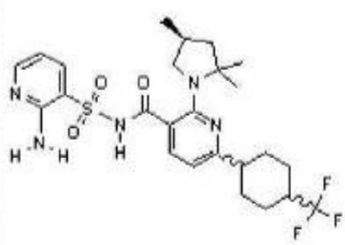
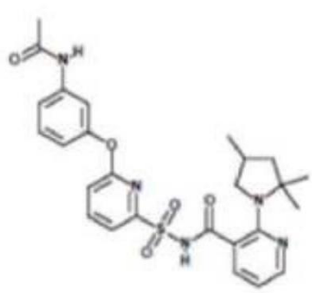
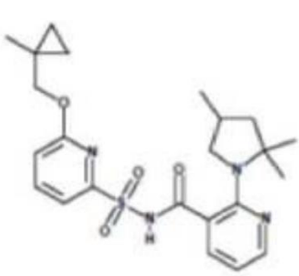
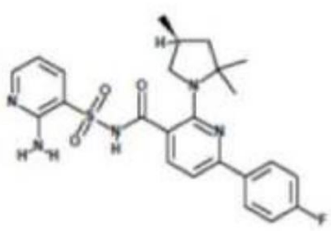
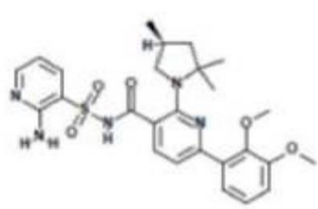
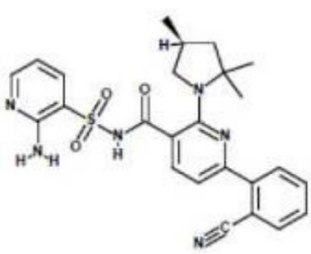
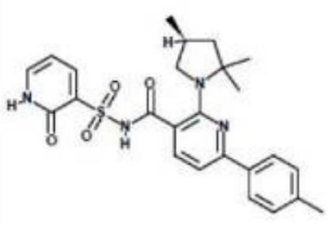
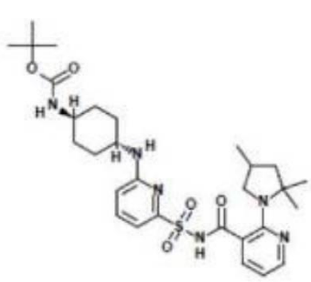
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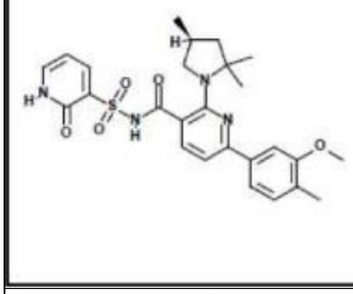
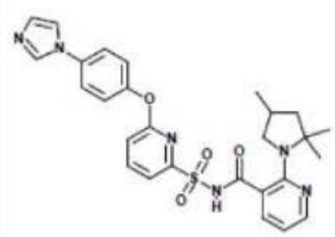
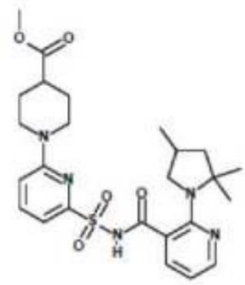
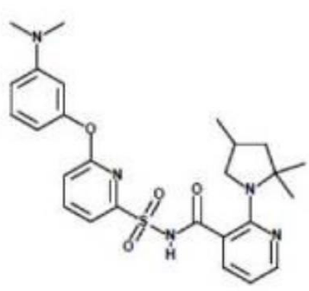
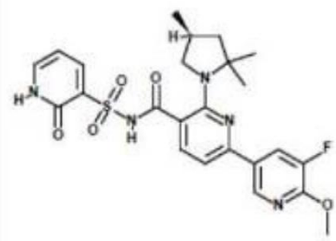
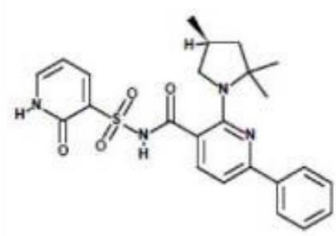
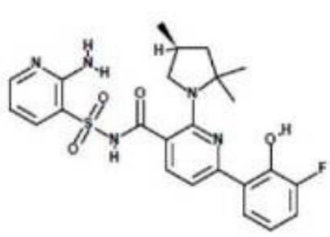
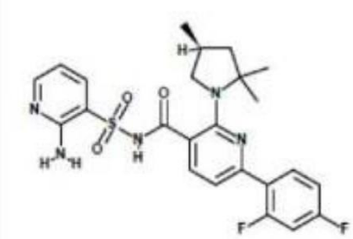
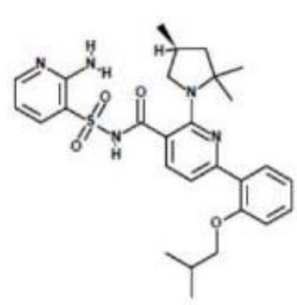
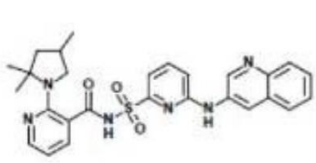
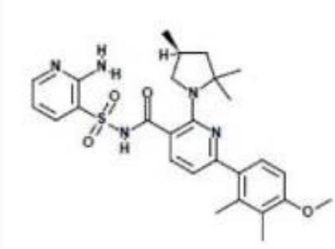
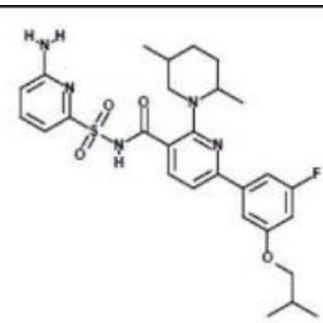
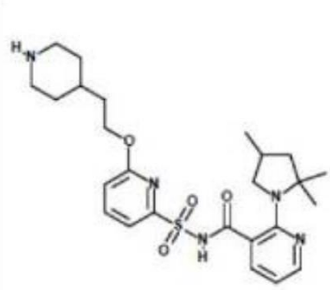
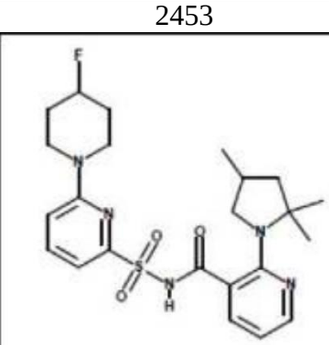
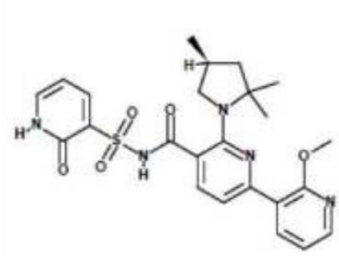
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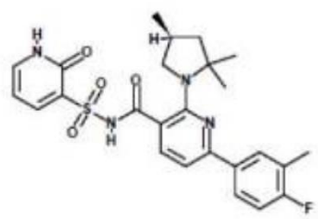
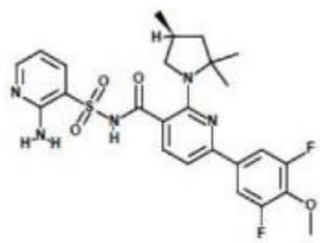
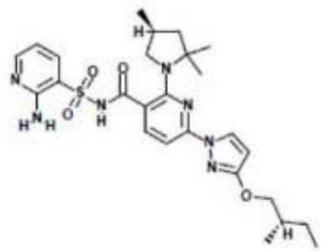
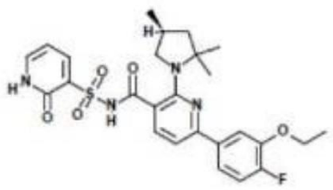
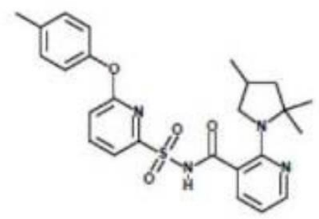
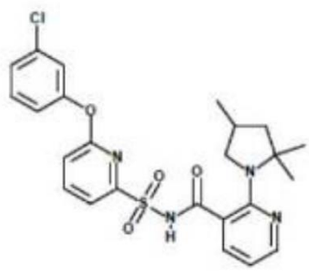
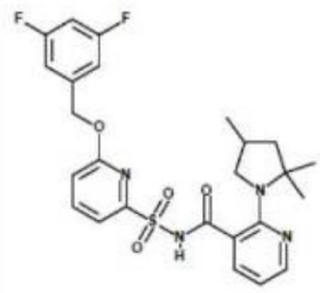
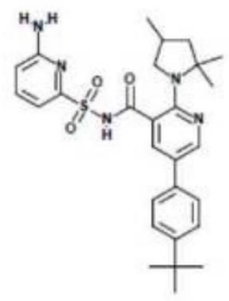
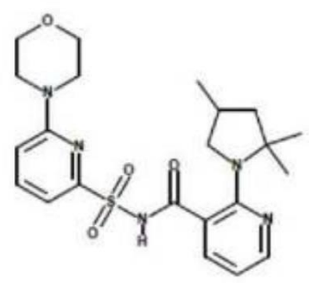
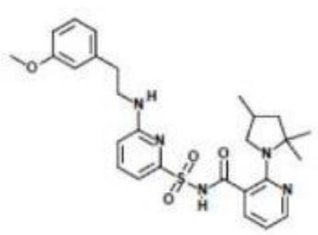
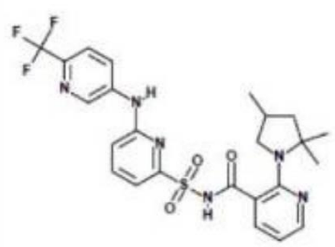
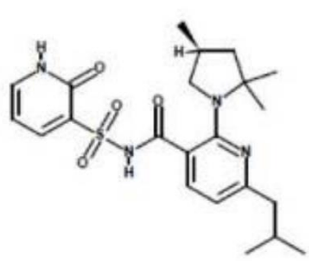
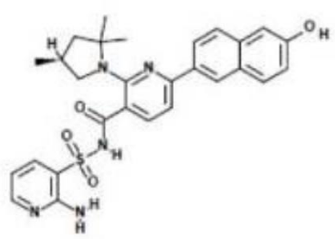
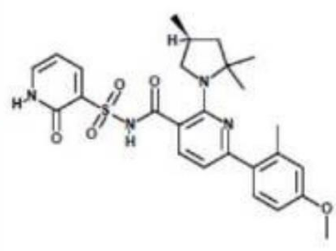
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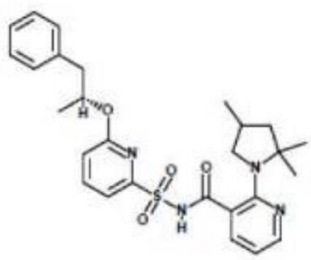
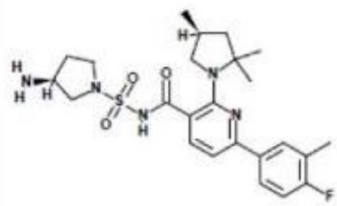
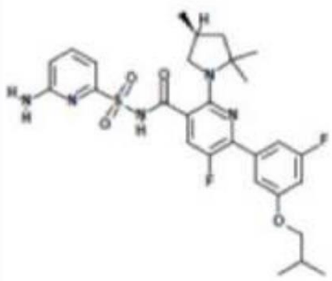
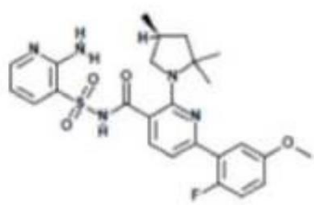
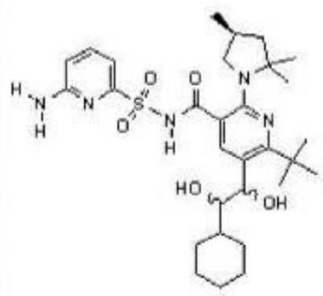
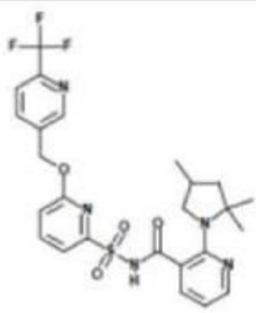
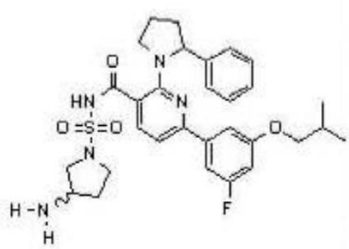
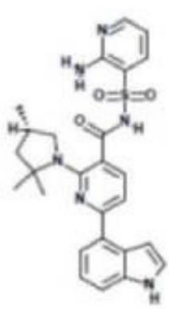
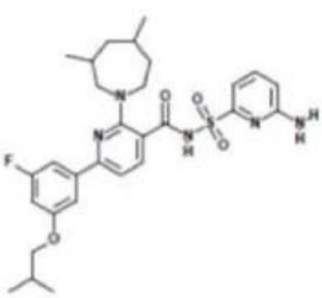
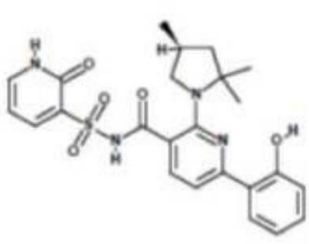
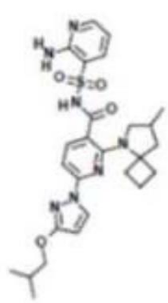
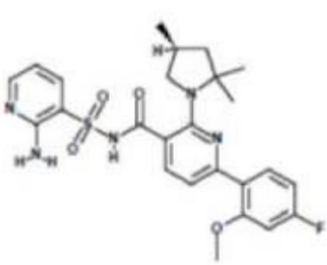
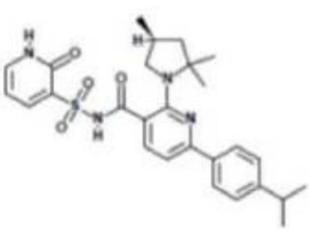
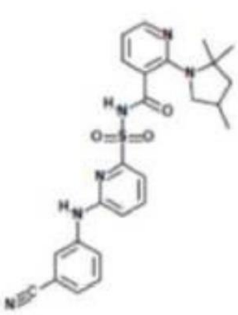
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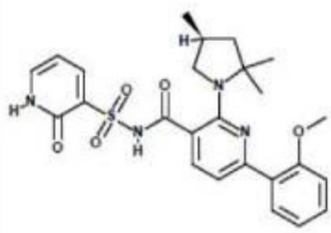
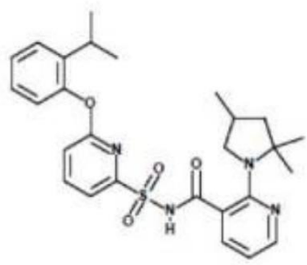
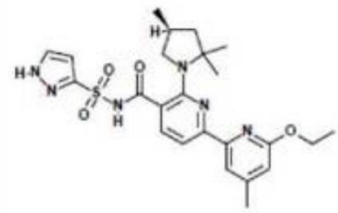
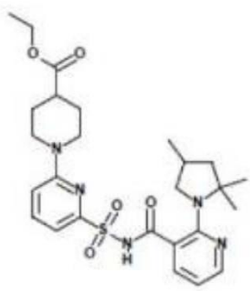
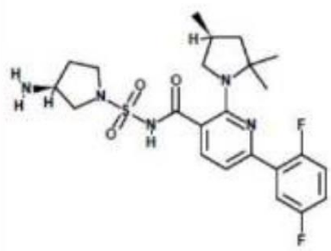
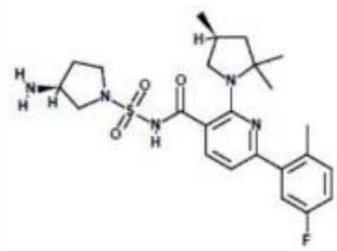
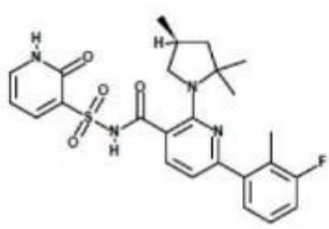
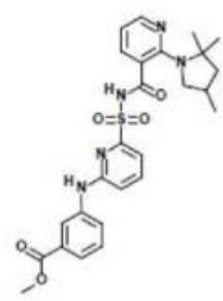
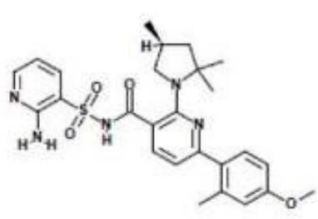
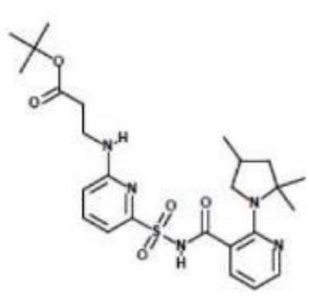
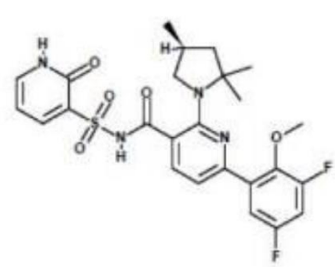
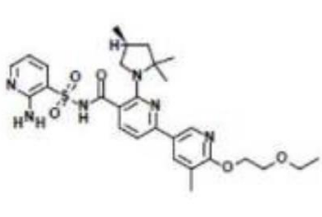
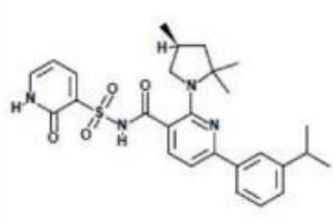
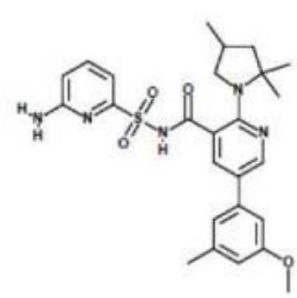
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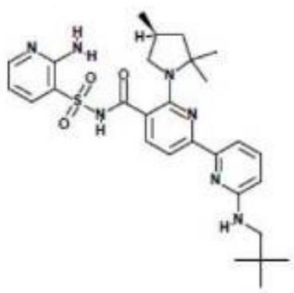
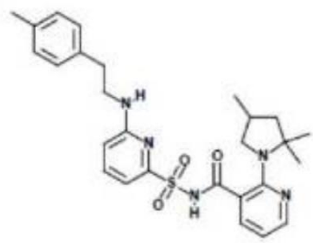
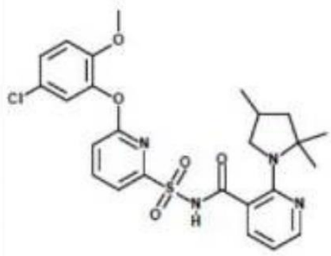
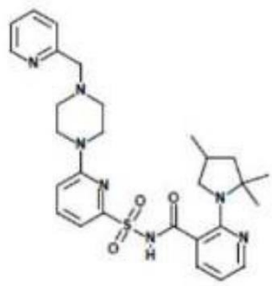
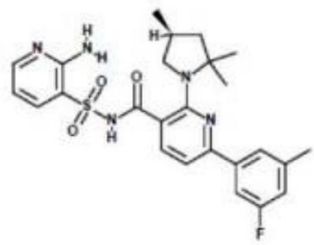
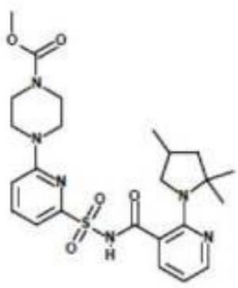
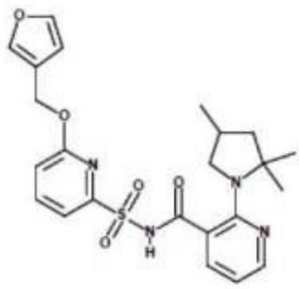
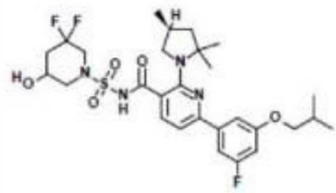
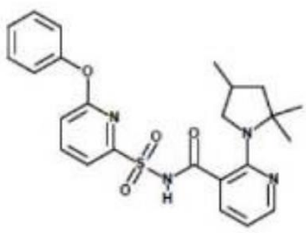
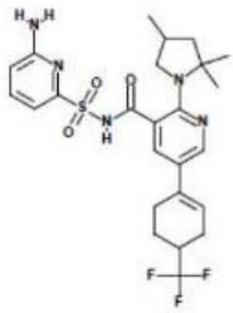
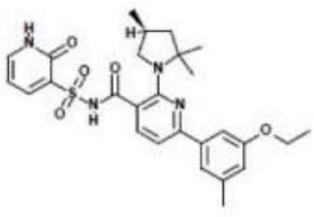
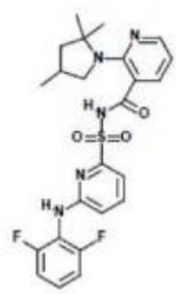
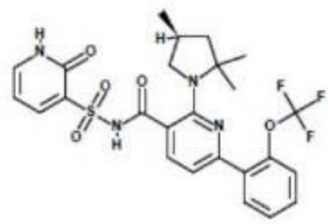
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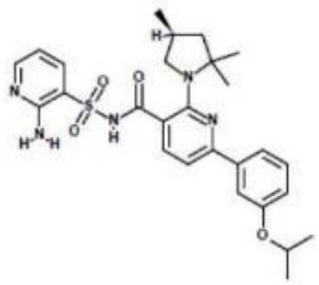
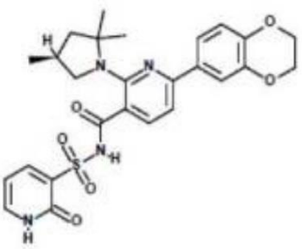
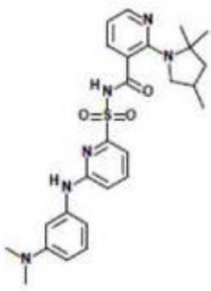
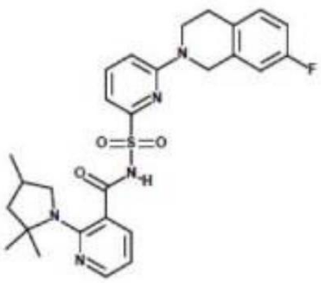
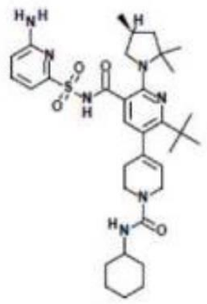
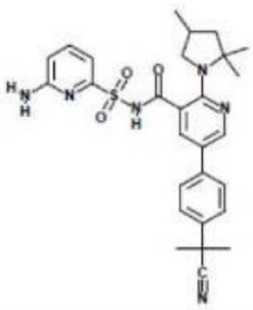
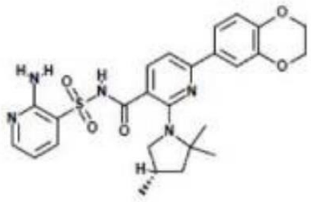
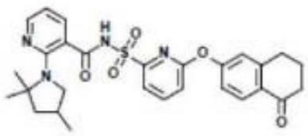
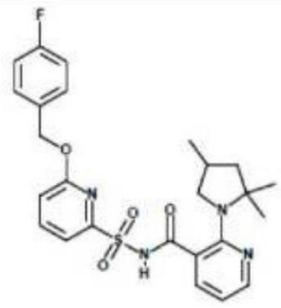
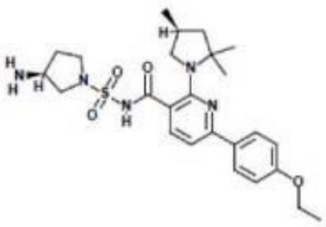
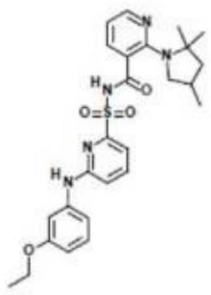
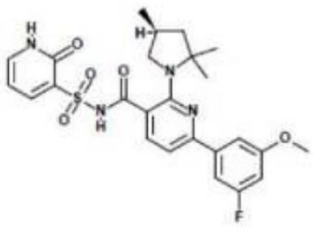
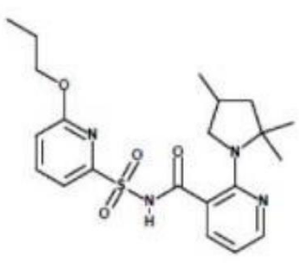
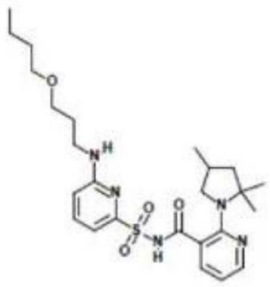
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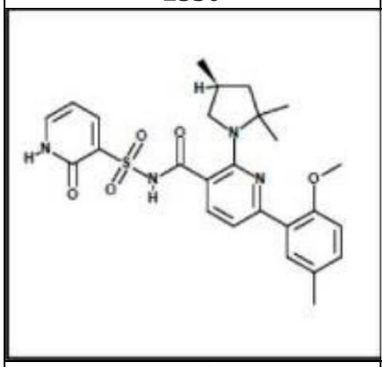
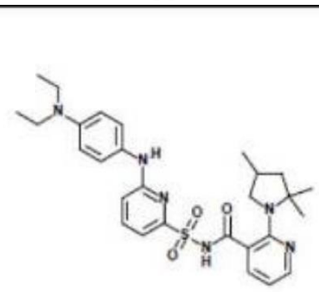
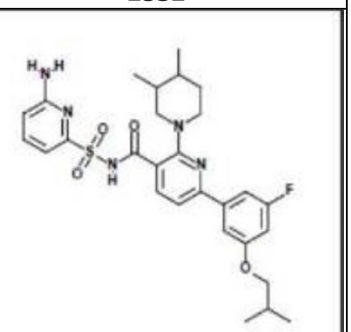
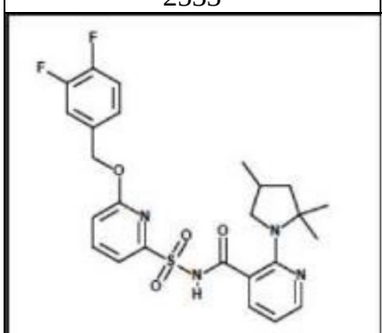
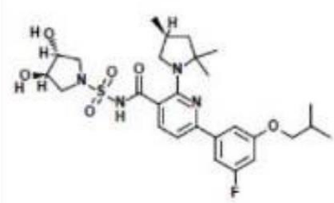
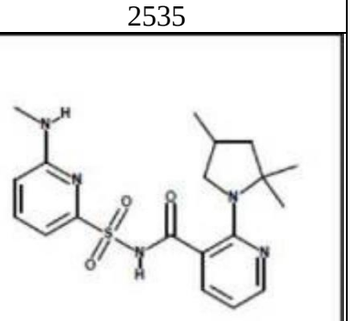
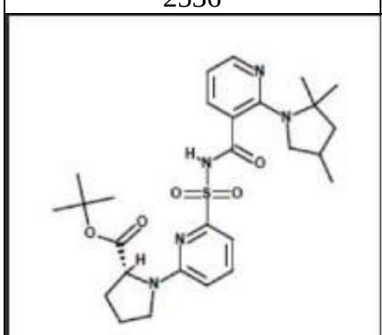
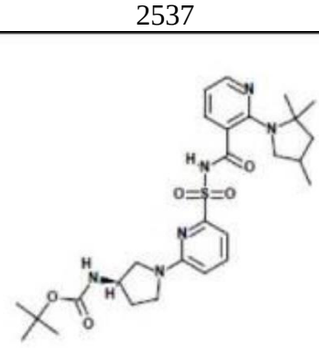
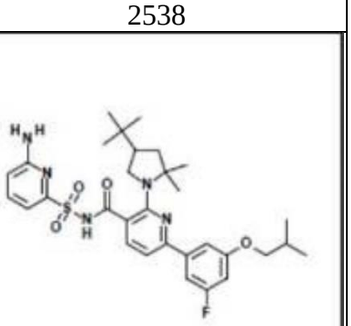
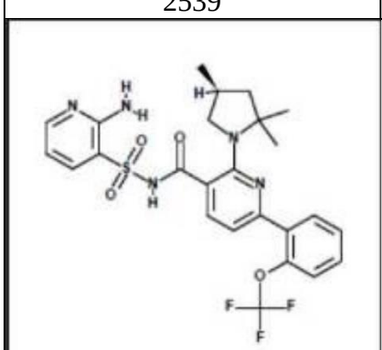
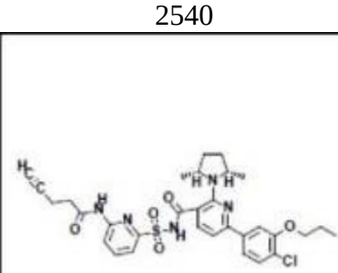
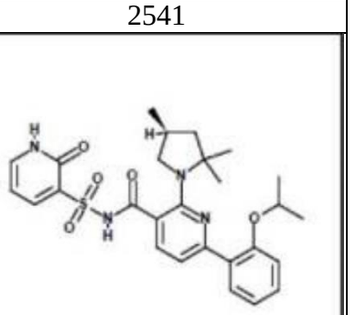
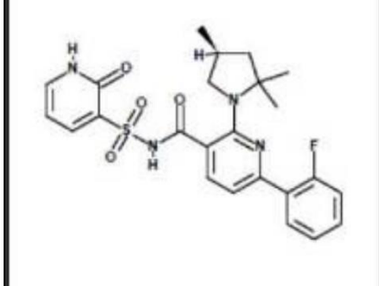
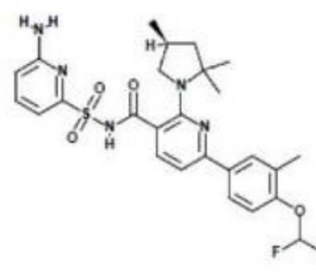
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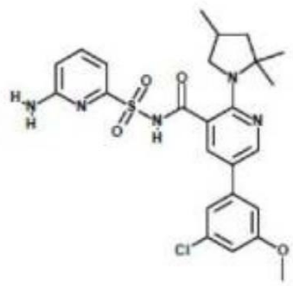
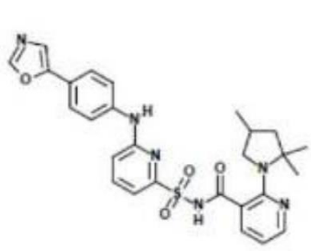
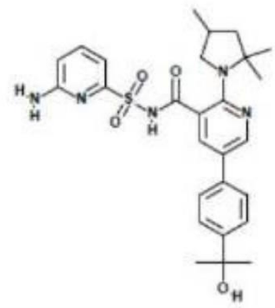
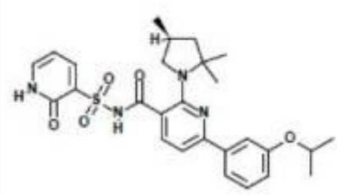
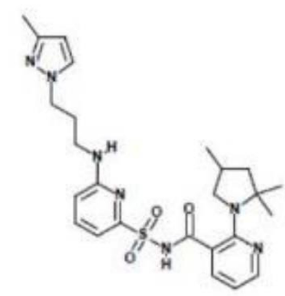
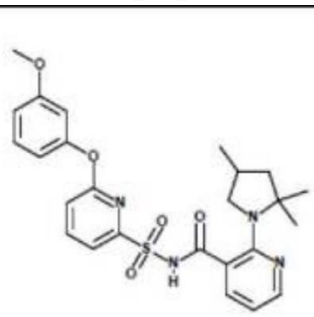
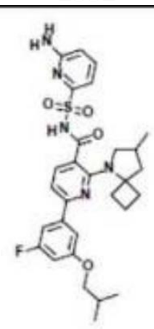
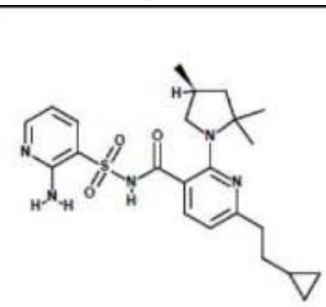
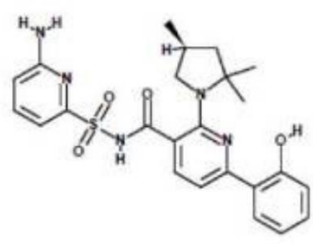
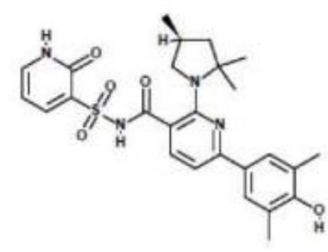
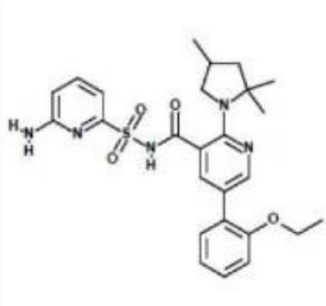
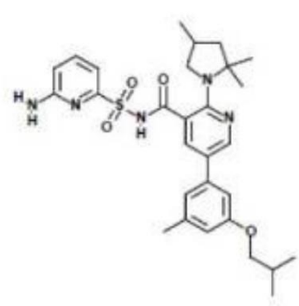
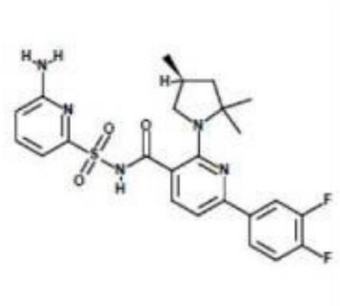
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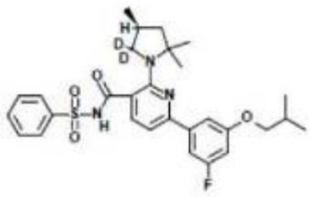
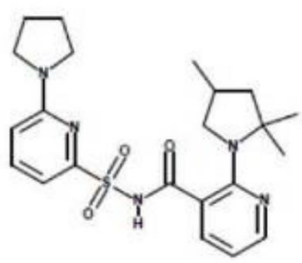
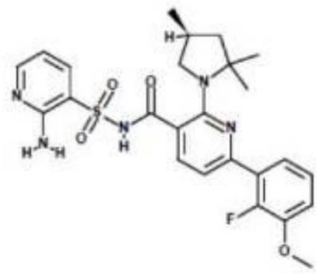
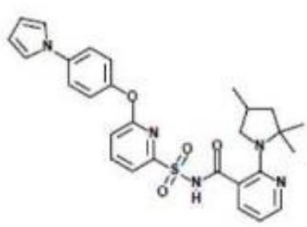
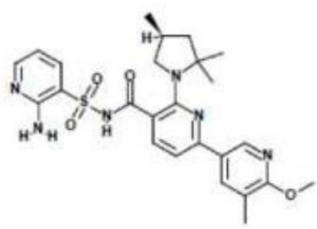
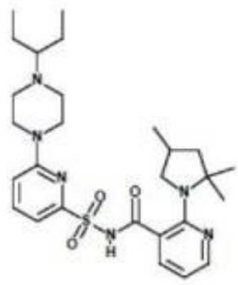
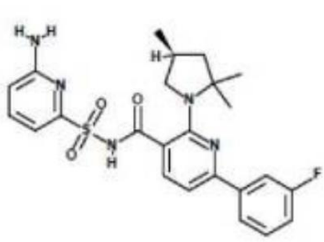
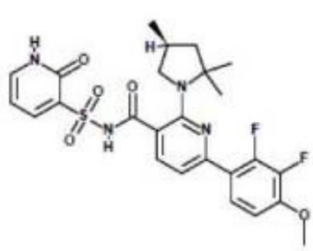
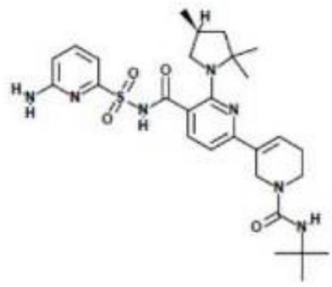
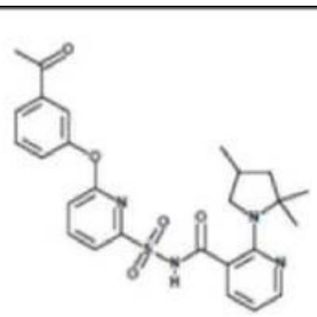
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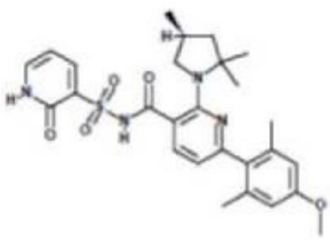
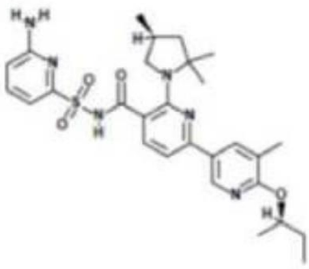
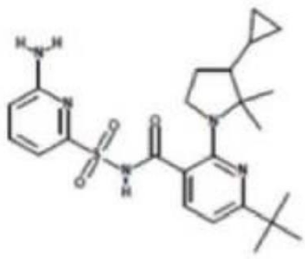
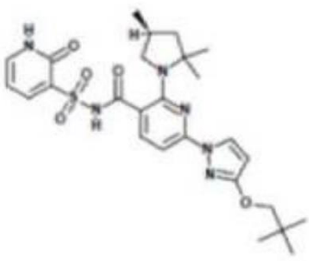
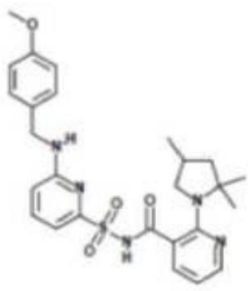
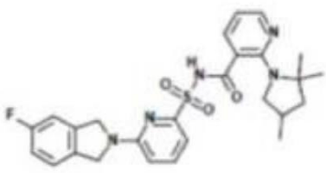
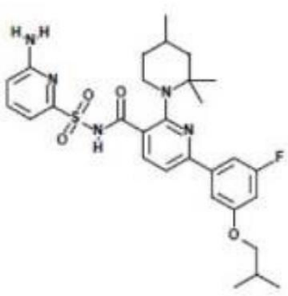
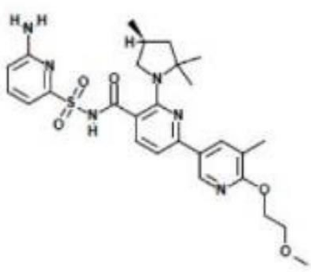
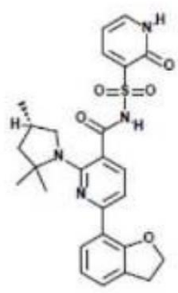
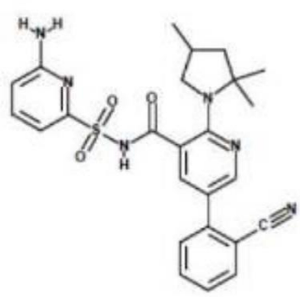
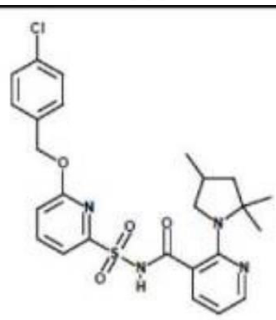
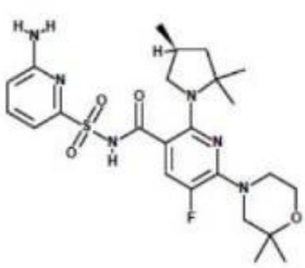
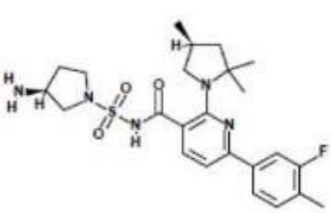
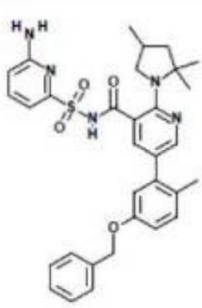
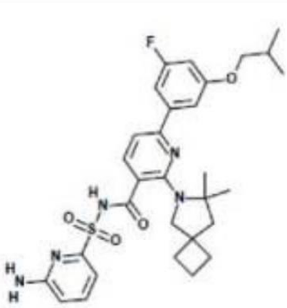
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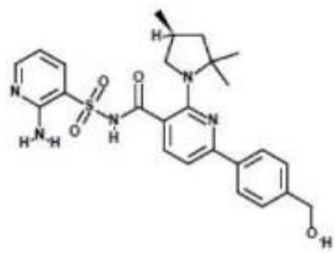
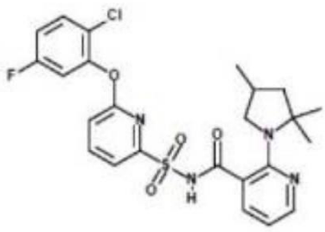
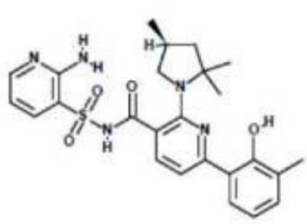
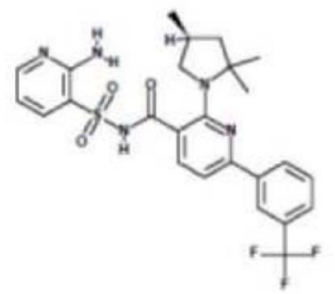
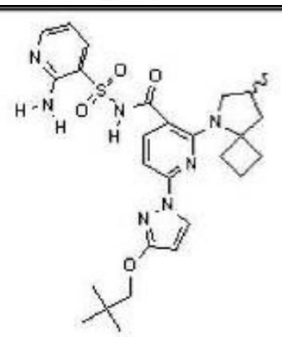
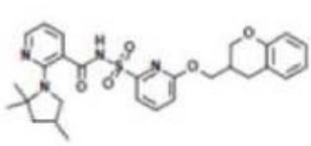
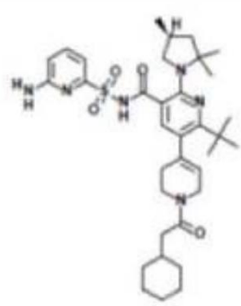
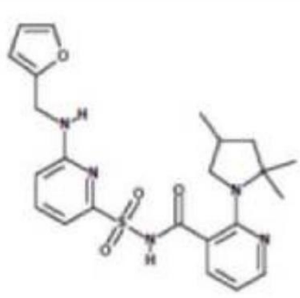
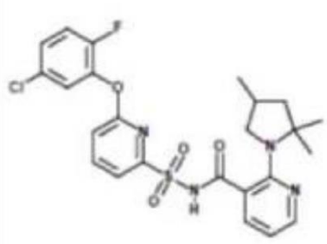
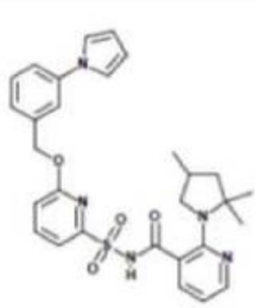
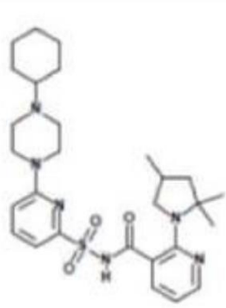
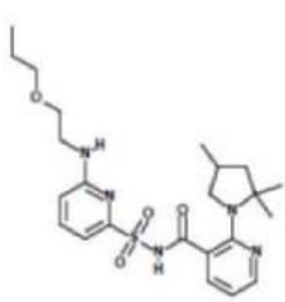
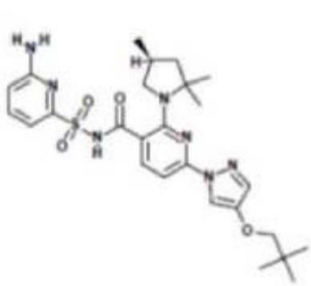
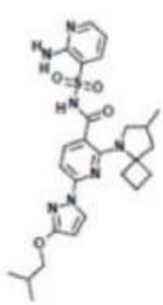
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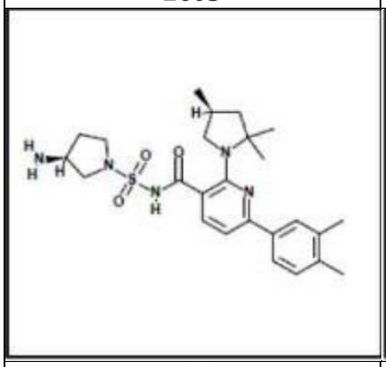
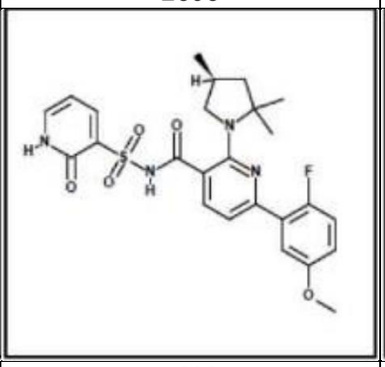
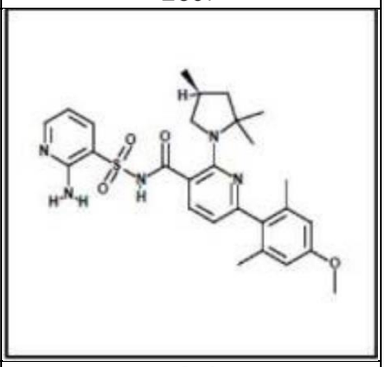
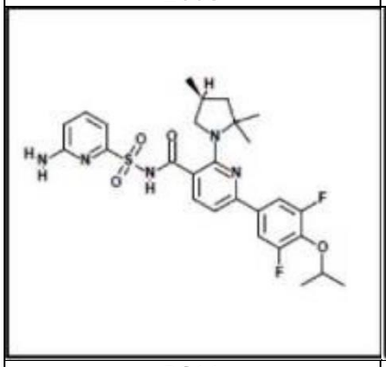
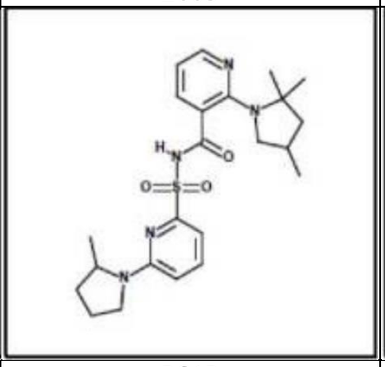
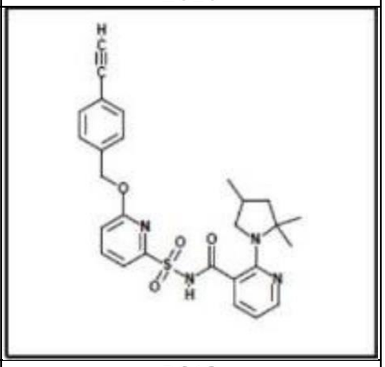
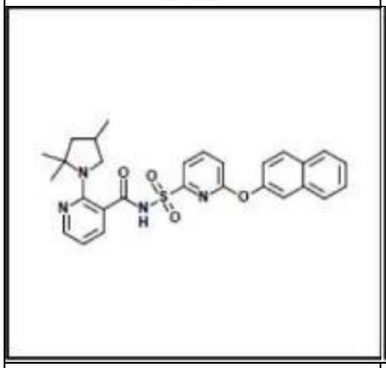
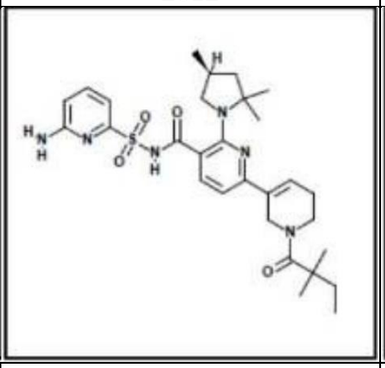
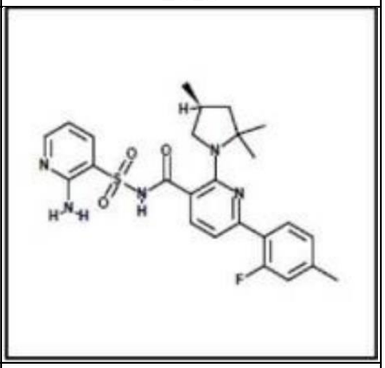
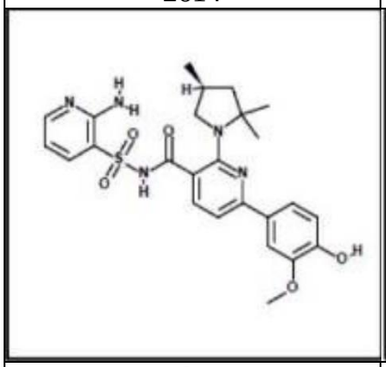
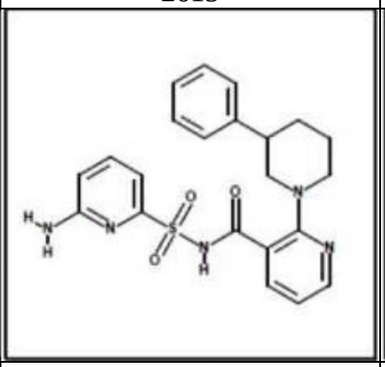
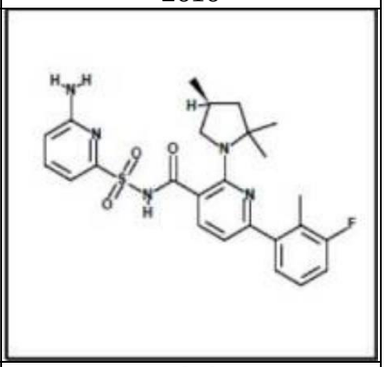
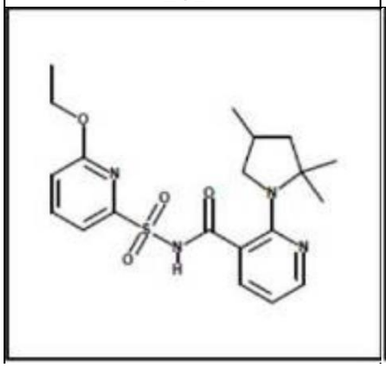
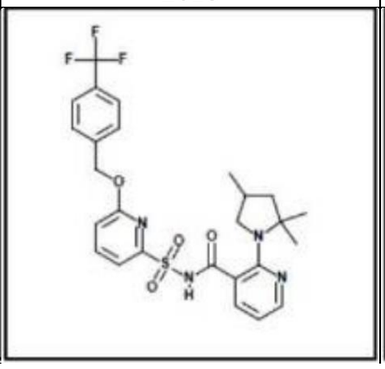
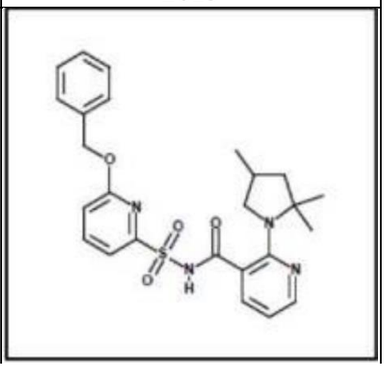
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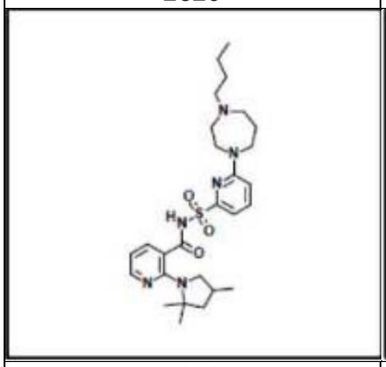
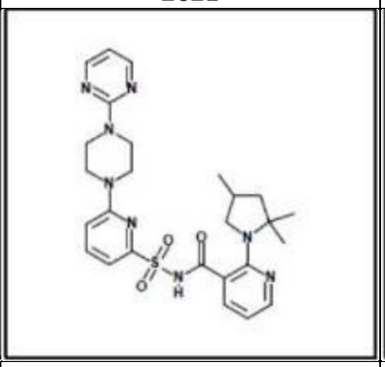
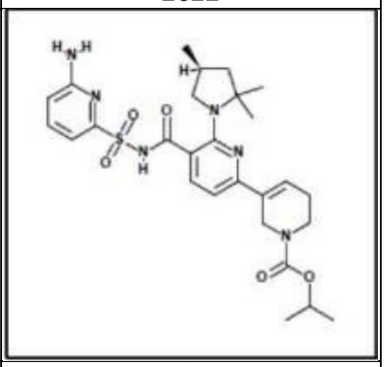
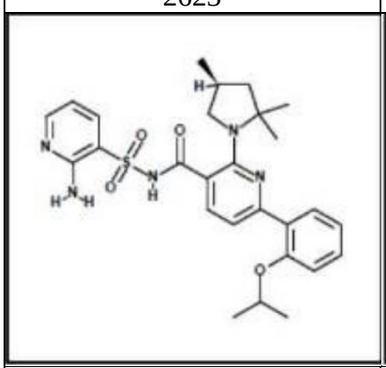
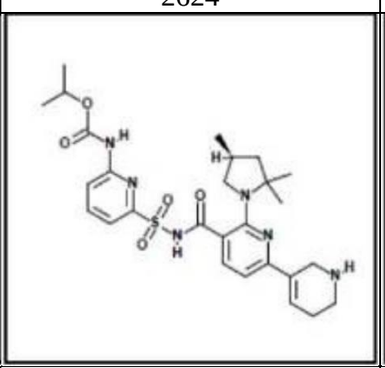
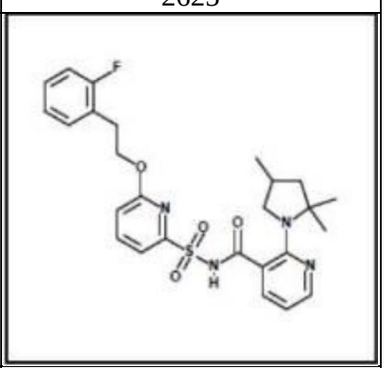
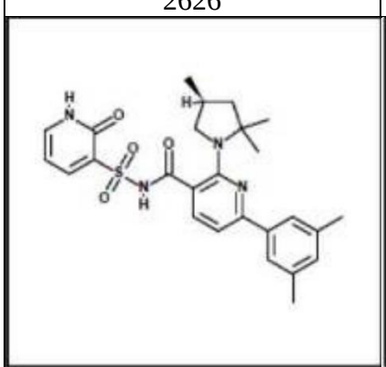
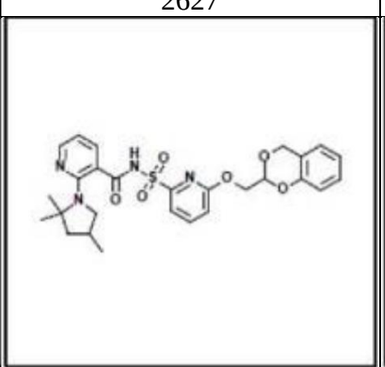
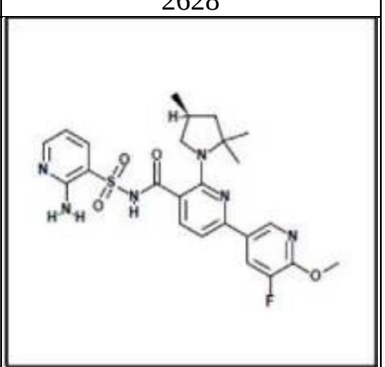
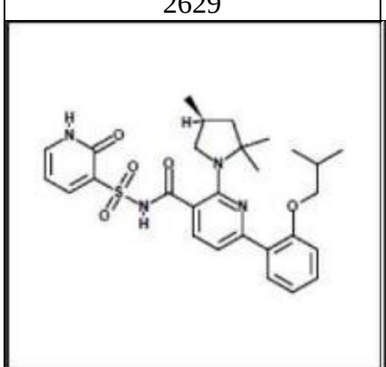
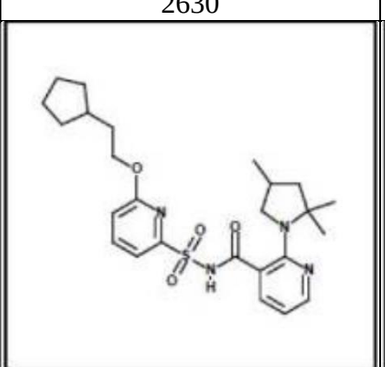
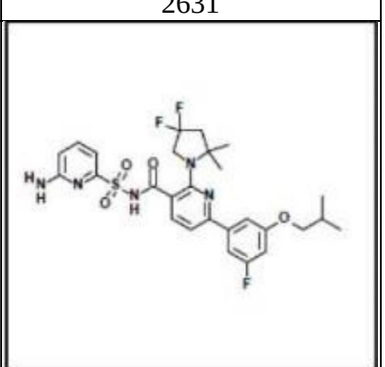
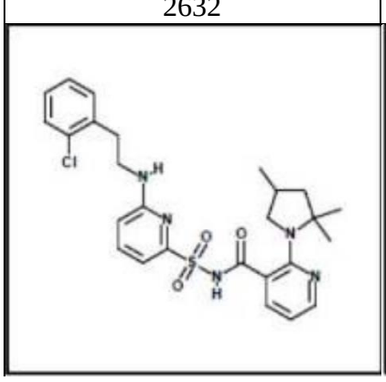
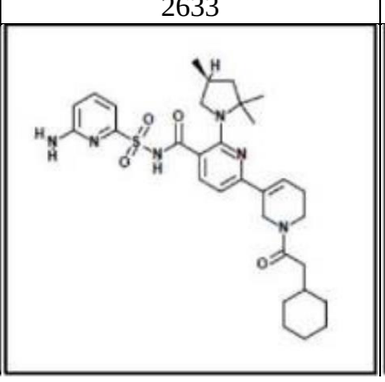
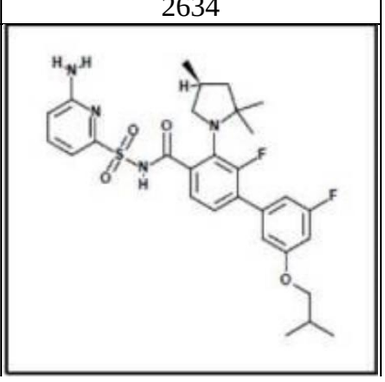
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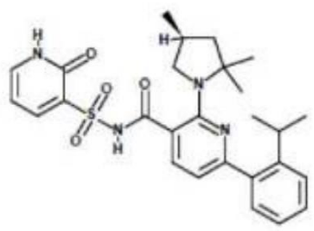
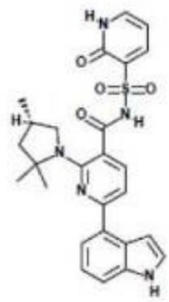
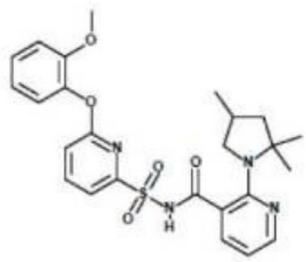
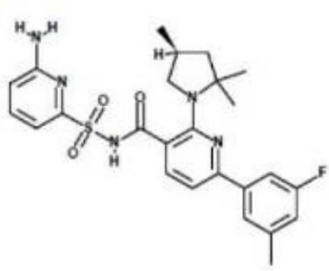
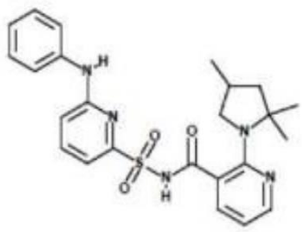
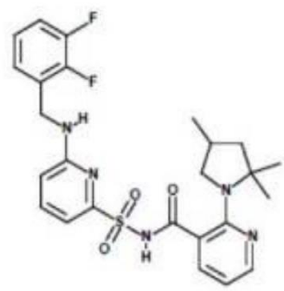
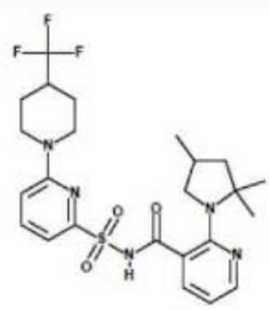
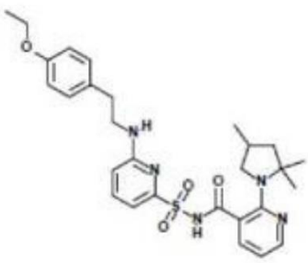
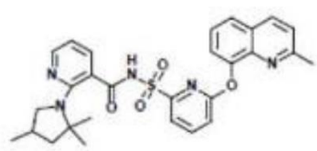
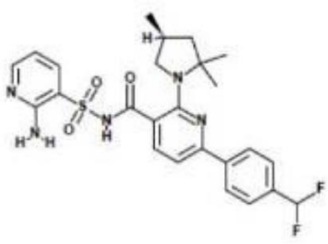
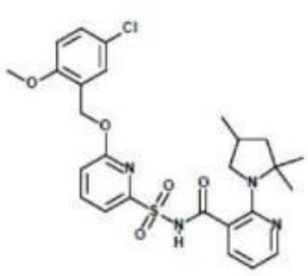
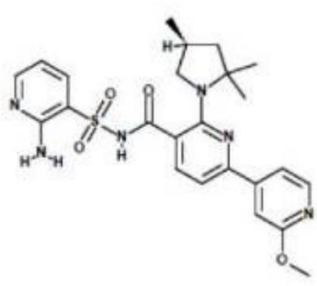
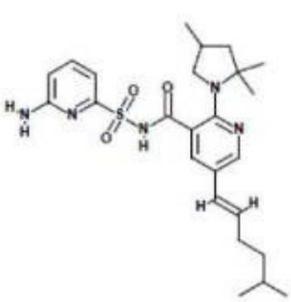
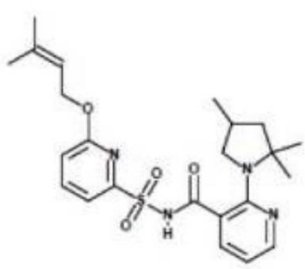
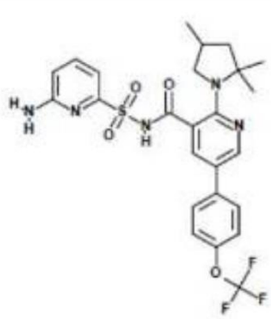
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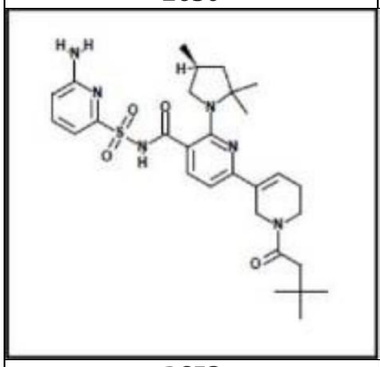
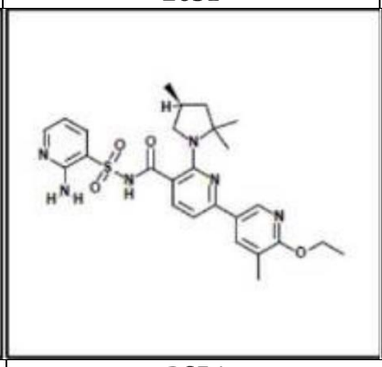
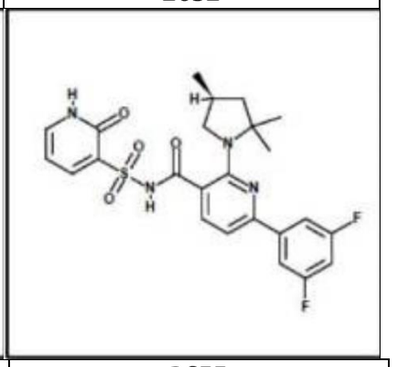
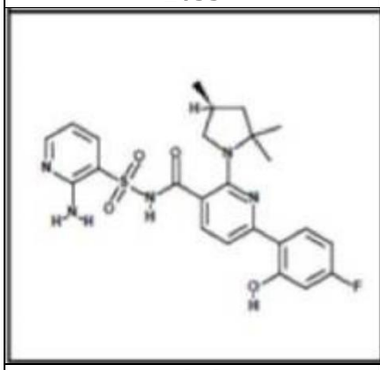
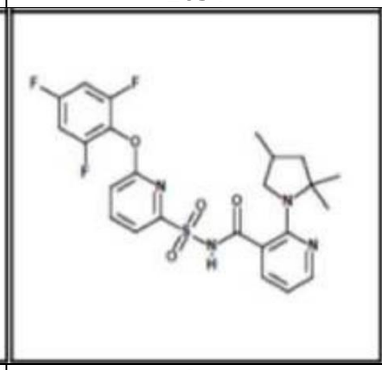
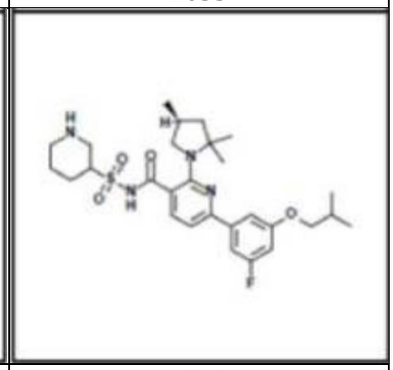
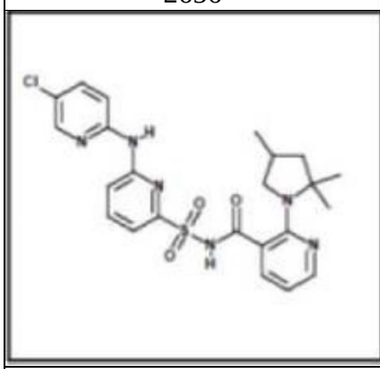
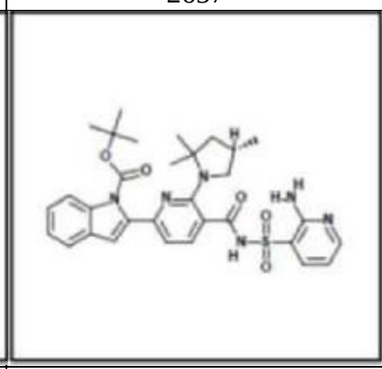
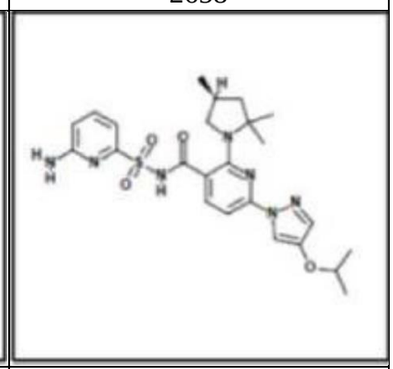
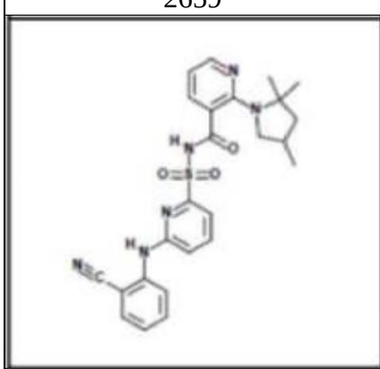
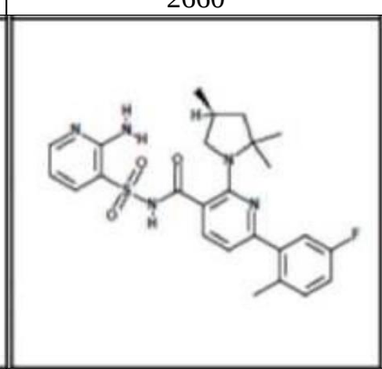
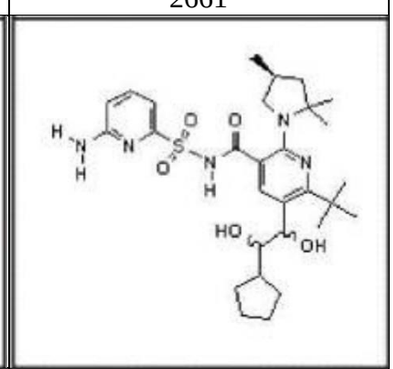
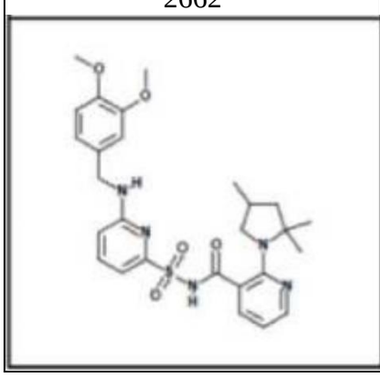
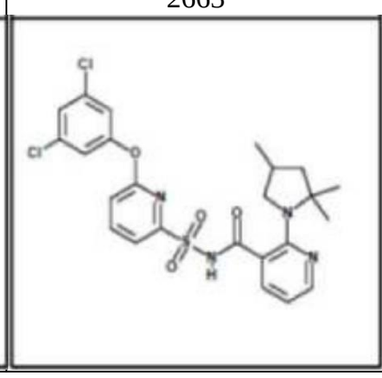
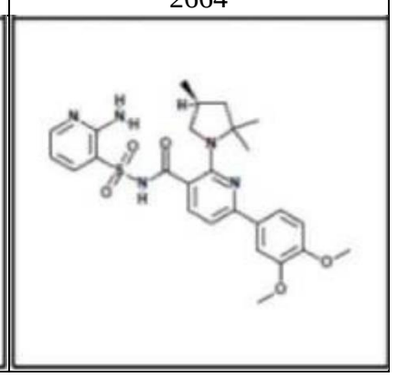
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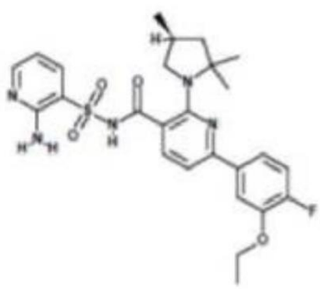
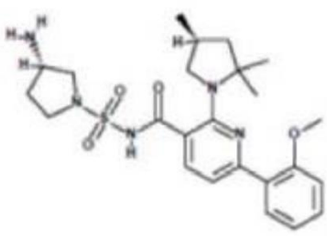
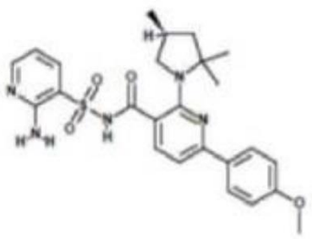
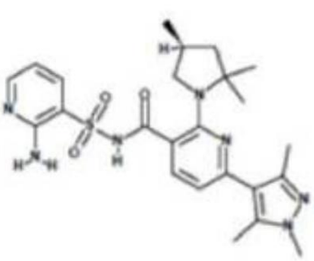
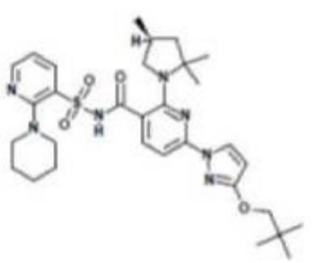
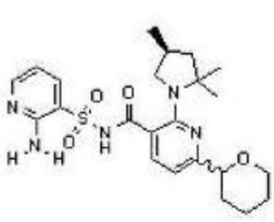
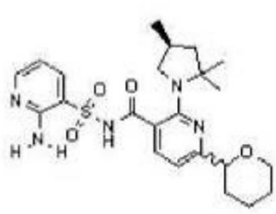
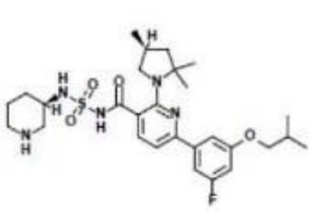
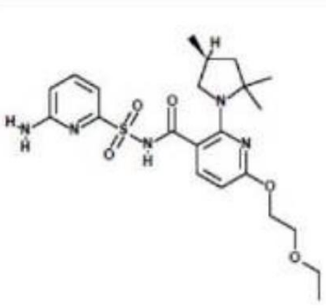
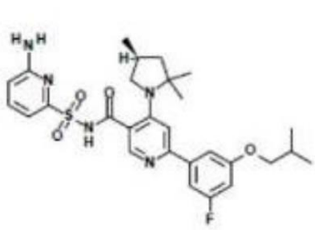
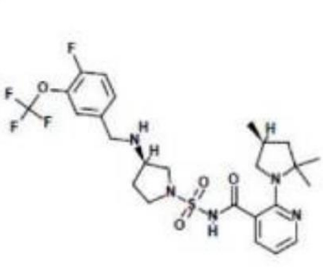
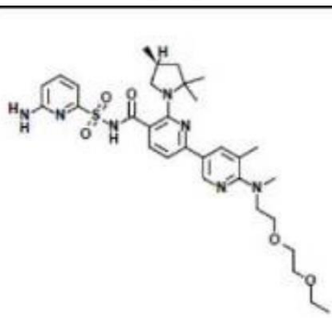
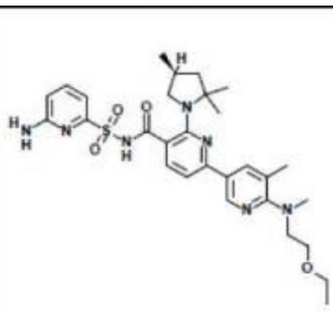
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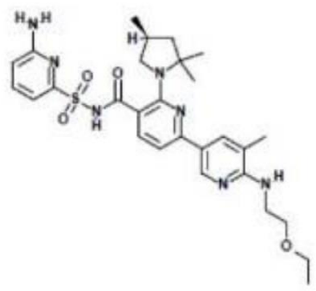
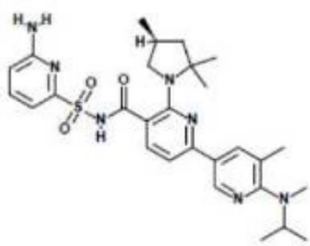
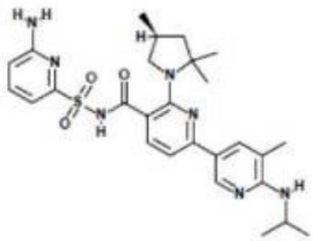
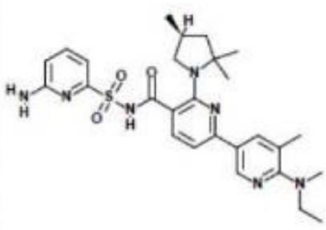
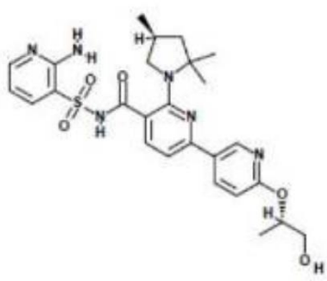
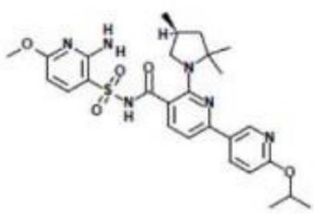
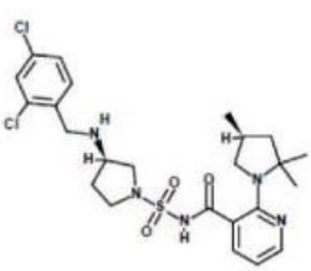
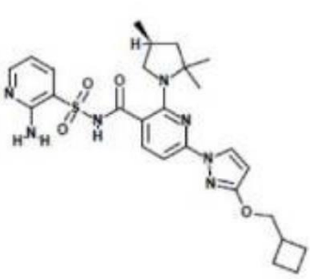
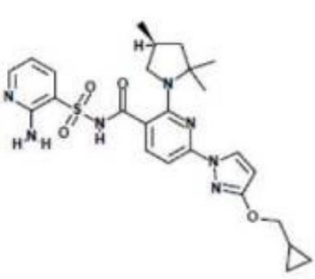
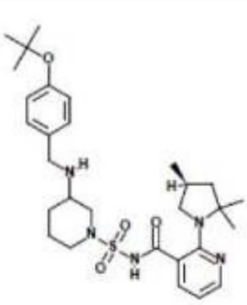
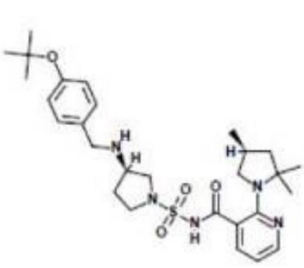
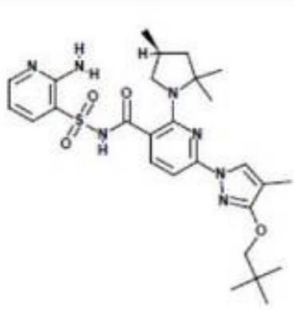
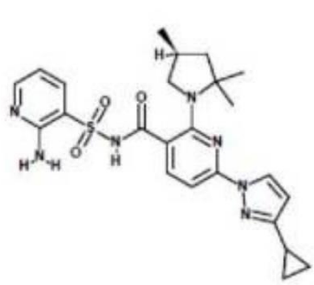
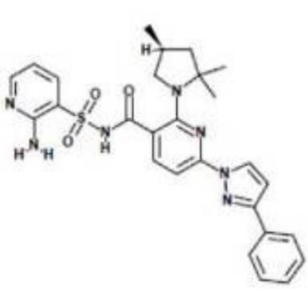
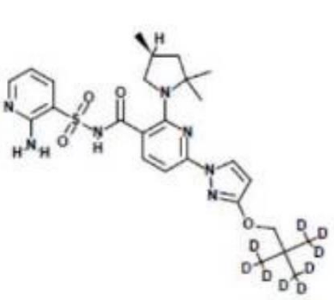
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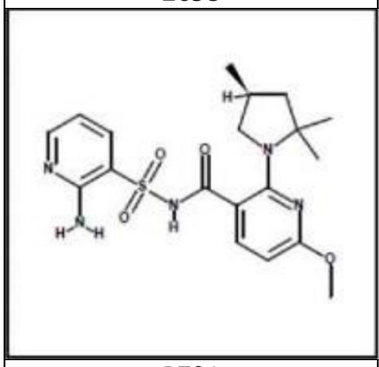
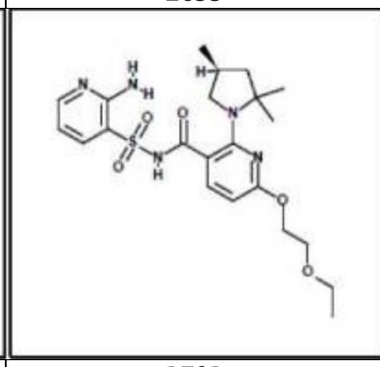
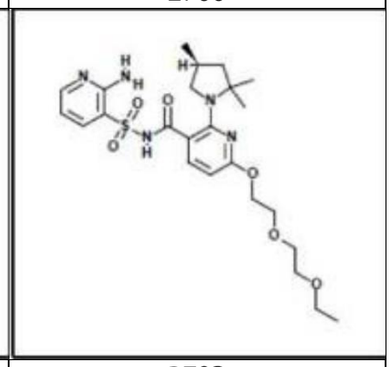
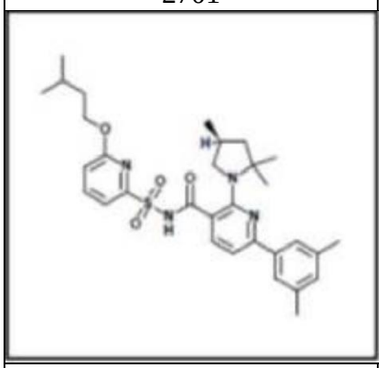
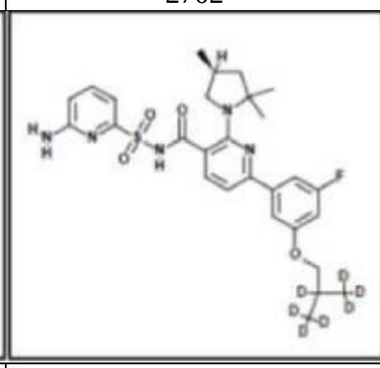
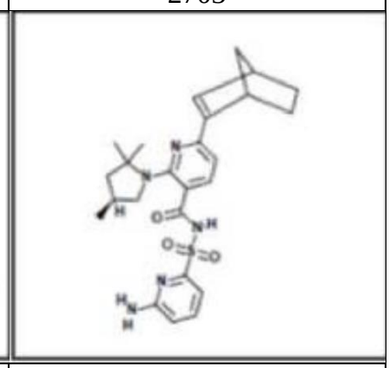
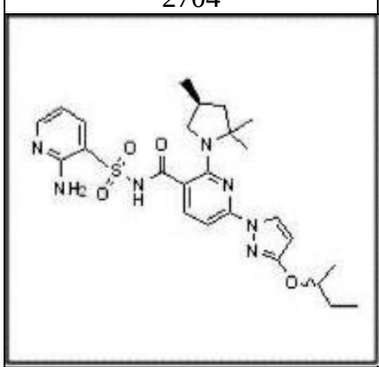
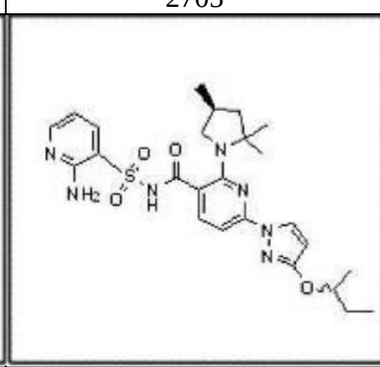
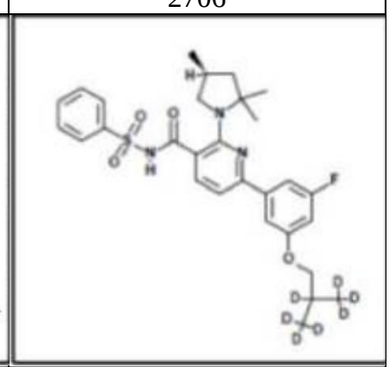
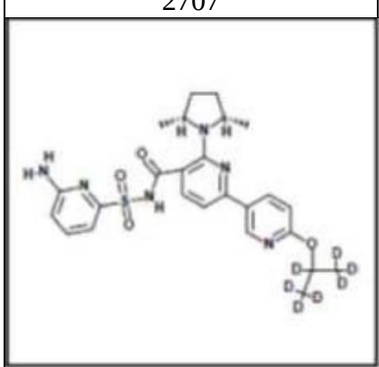
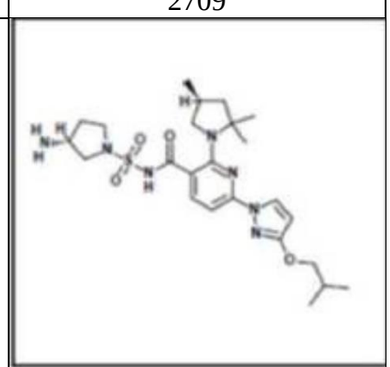
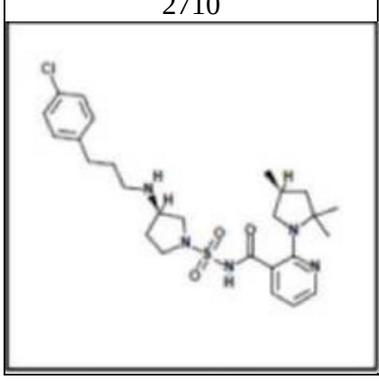
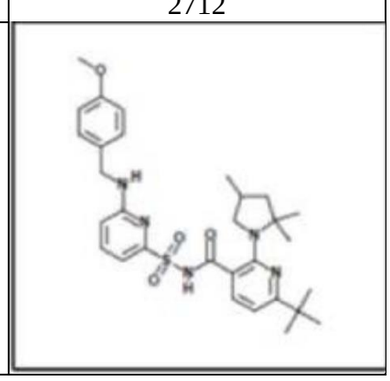
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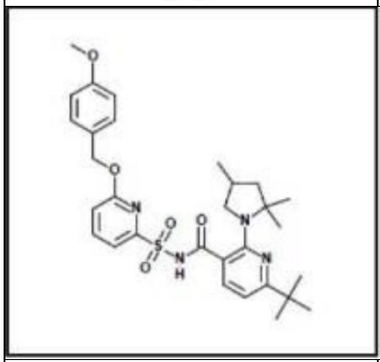
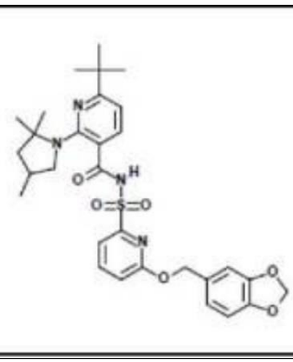
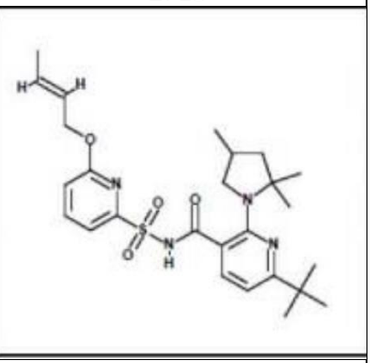
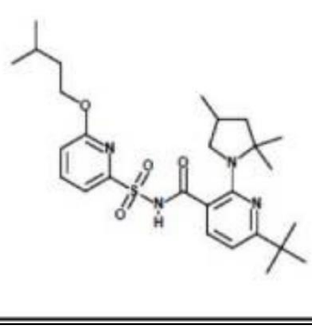
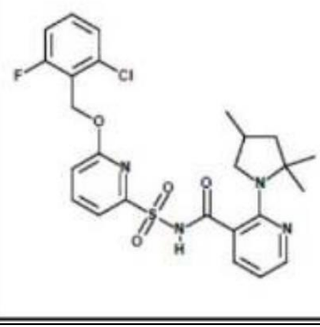
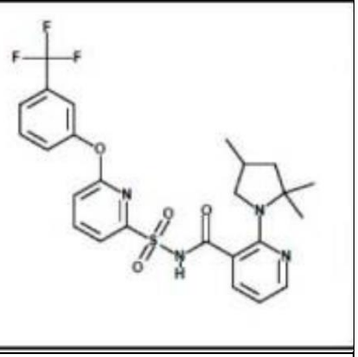
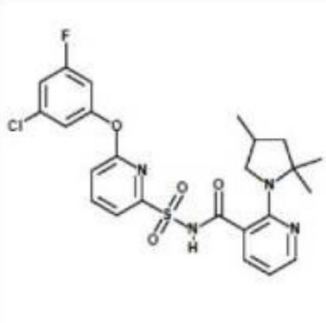
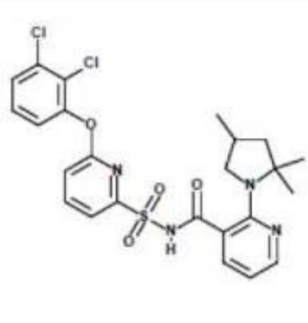
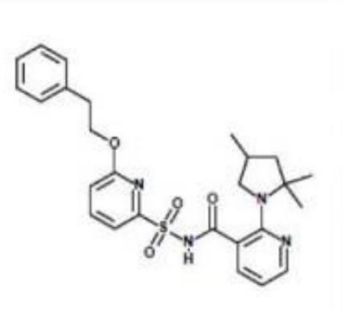
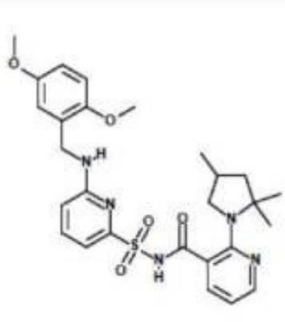
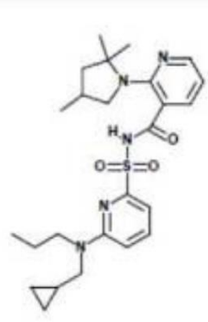
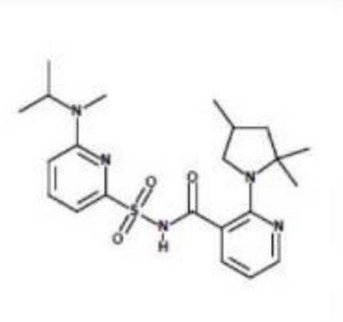
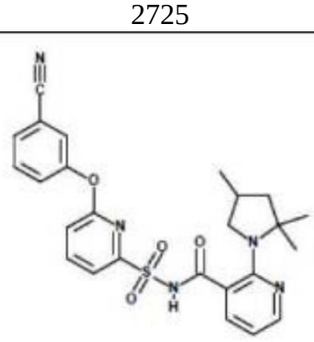
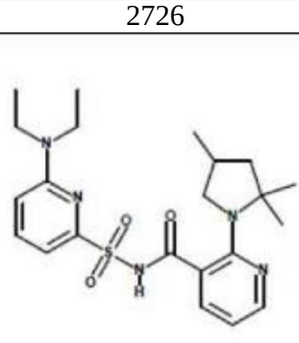
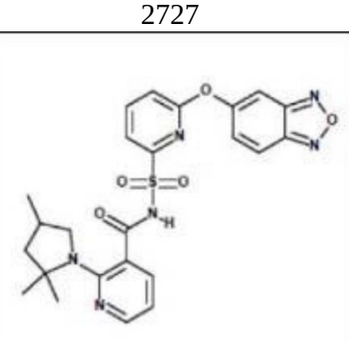
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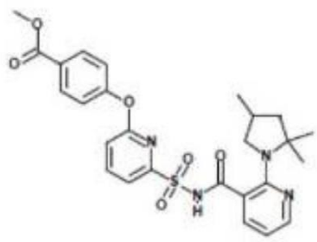
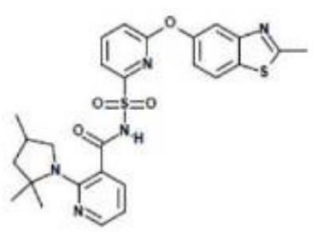
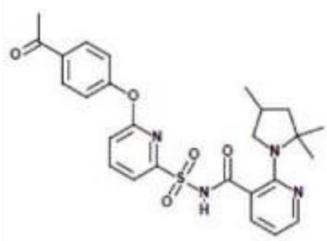
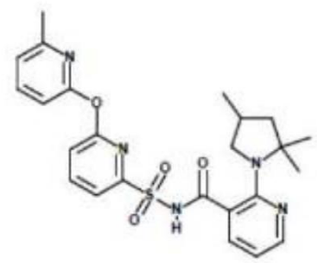
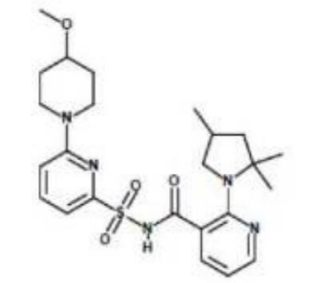
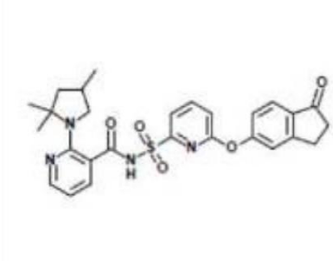
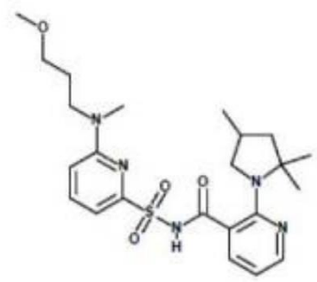
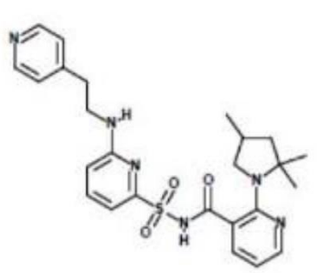
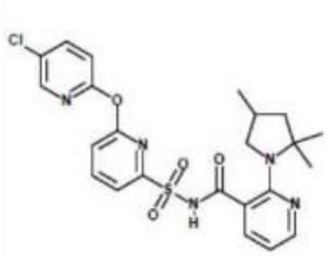
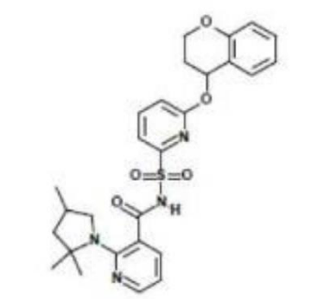
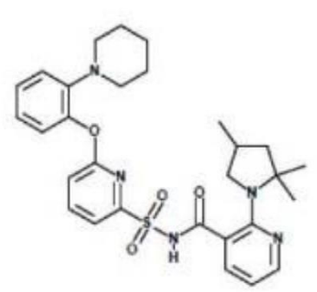
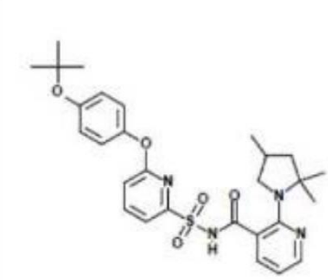
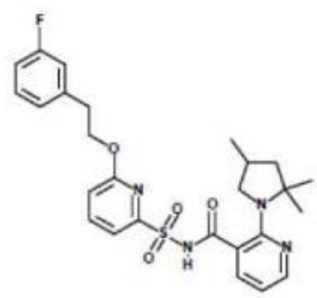
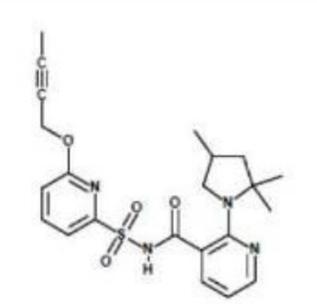
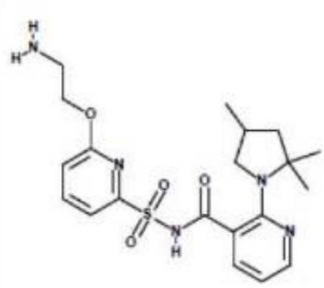
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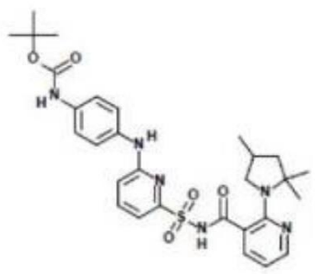
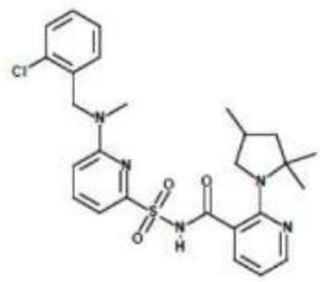
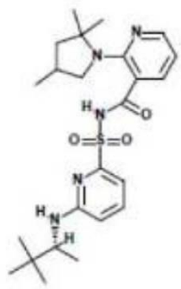
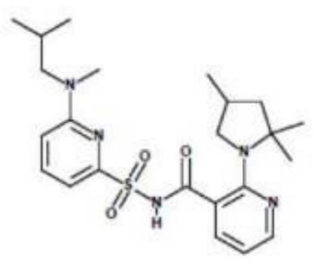
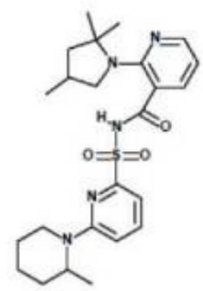
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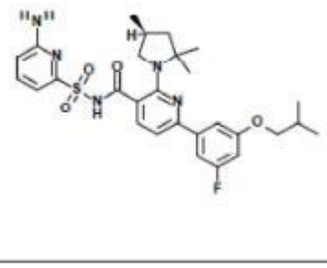
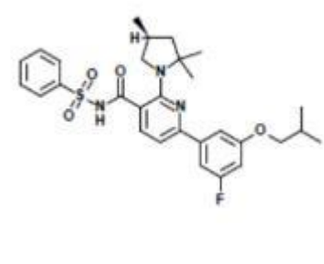
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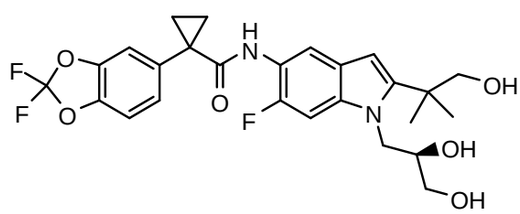
2743	2744	2745
		
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25. El compuesto según la Reivindicación 24, o una sal farmacéuticamente aceptable del mismo, en donde el compuesto se selecciona entre:

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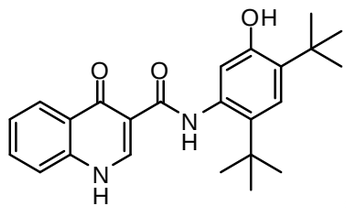
26. Una composición farmacéutica que comprende el compuesto de acuerdo con cualquiera de las Reivindicaciones 1-25 y un portador farmacéuticamente aceptable.

27. La composición farmacéutica de acuerdo con la Reivindicación 26, que además comprende



o una sal farmacéuticamente aceptable del mismo.

28. La composición farmacéutica de acuerdo con la Reivindicación 26 o Reivindicación 27, que además comprende:



,

o una sal farmacéuticamente aceptable del mismo.

****

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES
E. S. D.

Re: Expediente No. NC2017/0004538
Solicitud de Patente de Invención Titulada: "DERIVADOS CÍCLICOS DE SULFONILCARBOXAMIDA ACTIVOS COMO MODULADORES DEL REGULADOR DE LA CONDUCTANCIA TRANSMEMBRANA DE LA FIBROSIS QUÍSTICA"
Solicitante: VERTEX PHARMACEUTICALS INCORPORATED
Nuestra Ref.: P2017/000069

RESPUESTA AL OFICIO No. 13104, NOTIFICADO EL 06 DE NOVIEMBRE 2018 (PRIMER EXAMEN DE FONDO)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal de prórroga previsto en el artículo 45 de la Decisión 486, en los siguientes términos:

1. En primer lugar, con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un **Capítulo Reivindicatorio Modificado** que reemplaza en su totalidad al Capítulo Reivindicatorio presentado con la respuesta al requerimiento de forma, el 27 de octubre de 2017, en el cual se realizaron las siguientes modificaciones:

- se eliminaron las Reivindicaciones 1 a 3, 8 a 14, 21 a 23, 30 a 141, 144 a 148, 150, 151 y 153 a 185;
- se introdujeron las nuevas Reivindicaciones 1, 18 a 23 y 25, las cuales se dirigen a compuestos de Fórmulas Ib-iii, Ib-iv, Ib-v y Ib-vi y encuentran soporte en las páginas 100 a 181 del Capítulo Descriptivo;
- las nuevas Reivindicaciones 2 a 17, 24 y 26 a 28 corresponden a las antiguas Reivindicaciones 4 a 7, 15 a 20, 24 a 29, 142, 143, 149 y 152, respectivamente;
- la nueva Reivindicación 24 (antigua Reivindicación 142) ahora incluye las estructuras de los compuestos de la Tabla 1;
- se eliminaron sustituyentes específicos y compuestos que se encuentran por fuera del alcance de la nueva Reivindicación 1 de las restantes reivindicaciones.

Valga anotar que las modificaciones efectuadas en el Capítulo Reivindicatorio cumplen a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que éstas de ninguna manera implican una ampliación de la protección correspondiente a la divulgación contenida en la solicitud original. Por el contrario, éstas constituyen una drástica limitación de la materia inicialmente reclamada.

2. a- El Examinador eleva las siguientes objeciones en relación con la claridad y concisión del Capítulo Reivindicatorio:

- las Reivindicaciones 1 y 174 carecen de claridad porque contienen la expresión "*siempre que los restos que contienen anillo B y anillo C se sustituyan en posiciones adyacentes en el anillo A*", la cual indica una ubicación relativa que no se puede establecer con precisión. El Examinador sugiere incluir las estructuras específicas de los compuestos cíclicos y mencionar el grado de separación de los sustituyentes en el anillo A;
- la Reivindicación 142 hace referencia a la Tabla 1, lo cual no es permitido. El Examinador sugiere incluir en dicha reivindicación las estructuras químicas o los nombres IUPAC de los compuestos a los que se hace referencia;
- las Reivindicaciones 1, 15, 30, 42, 44, 56, 66, 68, 84, 96 y 112 carecen de concisión porque se refieren a sustituyentes generales tales como "*anillo arilo C_6–C_{10}; anillo cicloalquilo C_3–C_{10}; o un anillo heteroarilo o heterocíclico C_3–C_{14}, en donde cualquiera de 1 a 4 átomos de anillo son, de modo independiente, O, S, N o NR, alquilo C_1–C_6 o fluoroalquilo; alcoxi C_1–C_6 o fluoroalcoxi; alquenilo C_1–C_6; alquinilo C_1–C_6; (alquilen C_1–C_9)–R_4, fluoroalquilo; alquenilo C_1–C_6; alquinilo C_1–C_6; alcoxi C_1–C_6 o fluoroalcoxi; o arilo C_6–C_{10}; anillo heteroarilo o heterocíclico C_3–C_{10}*". El Examinador señala que dichas definiciones pueden llevar a una cantidad indeterminada de compuestos, lo cual no permite establecer el alcance de la materia que se desea proteger. El Examinador sugiere definir específicamente los anillos A, B y C, así como los sustituyentes accesorios de acuerdo con que se encuentran soportado en el Capítulo Descriptivo;
- la Reivindicación 175 repite materia reclamada en la Reivindicación 1, lo cual afecta su concisión.

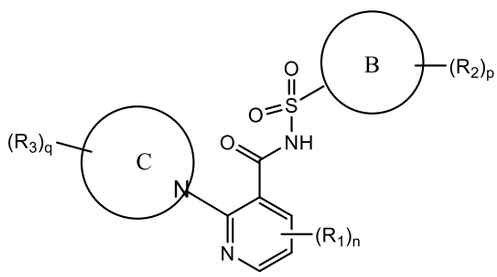
Adicionalmente, el Examinador señala que el Capítulo Descriptivo no divulga la invención de manera suficiente para que sea reproducida por una persona medianamente versada en la materia, ya que no hay evidencia de la obtención de composiciones o kits de partes que comprenden compuestos reclamados junto con otros agentes activos, o de los efectos que se obtienen mediante dichas composiciones o kits.

b- i) En primer lugar, llamo respetuosamente la atención del Examinador sobre las modificaciones realizadas en el Capítulo Reivindicatorio Modificado adjunto, tal y como lo mencioné en el numeral 1 del presente memorial, del cual se eliminaron las

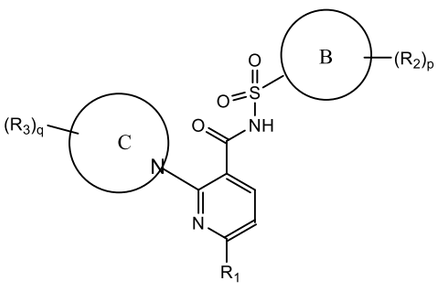
Reivindicaciones 1 a 3, 8 a 14, 21 a 23, 30 a 141, 144 a 148, 150, 151 y 153 a 185. En vista de estas modificaciones, considero completamente superadas las objeciones en relación con dichas reivindicaciones.

Adicionalmente, en relación con la nueva Reivindicación 24 (antigua Reivindicación 142), me permito señalar que se eliminó la referencia a la Tabla 1 y, en su lugar, se introdujeron las estructuras de los compuestos de dicha tabla correspondientes, los cuales se encuentran dentro del alcance de la nueva Reivindicación 1. Por lo tanto, también considero superada la objeción del Examinador en relación con la mención de elementos del Capítulo Descriptivo en las reivindicaciones.

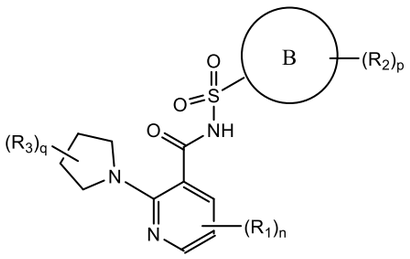
ii) Ahora bien, en relación con la objeción del Examinador sobre la supuesta falta de concisión del Capítulo Reivindicatorio debido a la amplitud de las definiciones de los sustituyentes, me permito en primer lugar señalar que la materia reclamada en el Capítulo Reivindicatorio Modificado adjunto se limitó drásticamente, de manera que ahora se reclaman compuestos de Fórmulas Ib-iii, Ib-iv, Ib-v y Ib-vi:



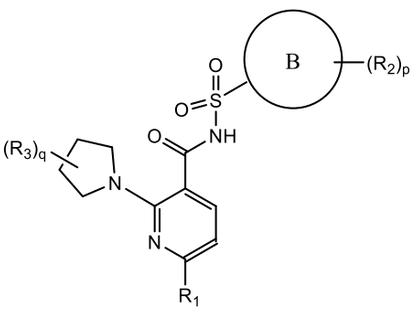
Ib-iii



Ib-iv



Ib-v



Ib-vi

Como se puede observar en las fórmulas anteriores, el anillo A (que se encontraba originalmente en la Fórmula I), se ha limitado en todos los compuestos a un anillo de piridina sustituido con R_1 y el anillo C en las fórmulas Ib-v y Ib-vi corresponde únicamente a un anillo de pirrolidina sustituido con R_3 (opciones que se encuentran dentro del alcance de la definición del Anillo C en las Fórmulas Ib-iii y Ib-iv).

No obstante las drásticas limitaciones introducidas en los compuestos reclamados, me permito señalar que las expresiones "*anillo arilo C_6-C_{10}", "anillo cicloalquilo C_3-C_{10}", "anillo heteroarilo o heterocíclico C_3-C_{14}", "en donde cualquiera de 1 a 4 átomos de anillo son independientemente O, S, N o NR", "alquilo o fluoroalquilo C_1-C_6", "alcoxi o*

fluoroalcoxi C_1-C_6”, *“alquenilo C_1–C_6”*, *“alquinilo C_1–C_6”*, *“(alquilen C_1–C_9)–R_4”*, *“fluoroalquilo”*, *“alquenilo C_1–C_6”*, *“alquinilo C_1-C_6”*, *“alcoxi o fluoroalcoxi C_1-C_6”*, y *“anillo heteroarilo o heterocíclico C_3-C_{10}*” objetadas por el Examinador por considerarlas poco concisas, son completamente claras para la persona medianamente versada en la materia en tanto están acompañadas por el número de átomos que comprenden tales grupos. Adicionalmente, los grupos y sustituyentes de la invención cuentan con una definición completa en las páginas 7 a 14 del Capítulo Descriptivo.

En este punto resulta relevante recordar que el Capítulo Descriptivo de una solicitud de patente está dirigido a personas medianamente versadas en la materia, esto es, personas en el área de la química, las cuales están en total capacidad de comprender que tales expresiones son alusivas a ciertas modalidades de la invención las cuales simplemente representan que una cadena carbonada esté formada por el número de átomos de carbono indicado en las reivindicaciones o que un anillo contiene átomos diferentes al carbono, como cualquier libro de química orgánica básica lo enseña.

En particular, las expresiones utilizadas para definir los sustituyentes son válidas en tanto encuentran soporte en el hecho que un inventor está en su derecho de reclamar protección para la totalidad de un concepto inventivo desarrollado, **sin importar la amplitud de éste**, siempre y cuando se conserve el principio de unidad de invención y no haya arte previo que afecte su patentabilidad. Así, una reivindicación puede ser tan amplia como se requiera para así poder enmarcar la totalidad del concepto inventivo desarrollado, y no solamente las modalidades preferidas o específicamente ejemplificadas en la solicitud. En este sentido, el uso de dichas expresiones únicamente pretende proteger diferentes modalidades del invento, las cuales encuentran soporte en el Capítulo Descriptivo y en los Ejemplos, y que evidentemente están dentro del concepto desarrollado legítimamente por los inventores.

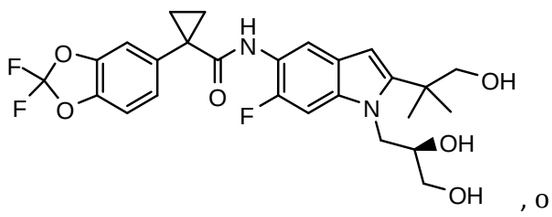
Así, en el presente caso, la materia reclamada en el Capítulo Reivindicatorio Modificado adjunto corresponde al concepto inventivo desarrollado por los inventores, y no debería existir obligación alguna de limitar los compuestos reivindicados, pues esta medida reduciría injustamente el concepto inventivo a que el inventor tiene derecho. Asimismo, la posibilidad de obtener la invención en diversas modalidades es una práctica aceptada a nivel mundial en el ámbito de las patentes, ya que una patente de invención no se limita a una única modalidad, sino que cubre un concepto inventivo global que abarca diferentes modalidades (diversas materializaciones de la invención) ligadas por un efecto técnico común que finalmente delimita el alcance de la invención.

Por lo tanto, no existe requerimiento alguno que determine que los ejemplos deban ilustrar todos y cada uno de los compuestos que se encuentran dentro del alcance de la invención, o que las reivindicaciones sólo pueden reclamar lo ilustrado en los ejemplos, ya que lo fundamental es que el Capítulo Descriptivo proporcione la información necesaria para que la persona medianamente versada en la materia pueda reproducir la invención, sin tener que

acudir a experimentación adicional excesiva. Además, vale la pena recordarle al Examinador que la función de los Ejemplos en el Capítulo Descriptivo es **estrictamente ilustrativa** y de ninguna manera puede considerarse como el único alcance reivindicable posible. De hecho, reclamar estrictamente aquello ejemplificado en el Capítulo Descriptivo limita injustamente el alcance de la protección a la cual el inventor tiene derecho, de tal forma que para que existiera una infracción, dichos elementos específicos ilustrados en los ejemplos deberían necesariamente estar presentes en el producto o proceso infractor, lo que fácilmente podría lograrse al tratarse de elementos que pueden ser cambiados o modificados. En el presente caso **el Capítulo Descriptivo divulga más de 2.700 ejemplos de compuestos**, 12 diferentes rutas de síntesis y datos de caracterización de los mismos (como se puede observar en la Tabla 2), proporcionando suficiente soporte para el alcance reclamado en el Capítulo Reivindicatorio Modificado.

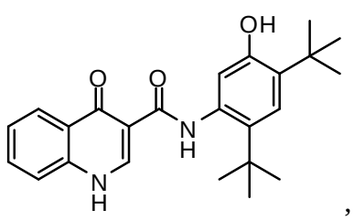
En vista de lo anterior y de la drástica limitación que ya se ha introducido en el Capítulo Reivindicatorio Modificado, considero que éste corresponde a una generalización razonable del concepto inventivo que se encuentra divulgado y soportado de manera clara y suficiente para que una persona medianamente versada en la materia pueda ejecutarla o reproducirla, incluyendo todas las definiciones de los sustituyentes reclamados, y sería capaz de hacerlo sin acudir a experimentación adicional excesiva, por lo que cumple los requisitos de claridad, concisión y soporte.

iii) Por otra parte, en relación con las nuevas Reivindicaciones 27 y 28 (antiguas Reivindicaciones 149 y 152) que reclaman composiciones que comprenden los compuestos de la invención junto con un agente terapéutico adicional específico, me permito señalar que el Capítulo Descriptivo proporciona soporte para dichas modalidades, donde el agente terapéutico adicional es el compuesto (*R*)-1-(2,2-difluorobenzo[d][1,3]dioxol-5-il)-N-(1-(2,3-dihidroxipropil)-6-fluoro-2-(1-hidroxi-2-metilpropan-2-il)-1H-indol-5-il)ciclopropancarboxamida (tezacaftor) o una de sus sales farmacéuticamente aceptables:



, o

N-(5-hidroxi-2,4-diter-butil-fenil)-4-oxo-1H-quinolin-3-carboxamida (ivacaftor) o una de sus sales farmacéuticamente aceptables:



,

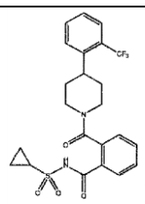
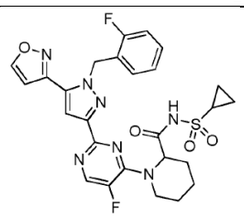
respectivamente en las páginas 486 y 510.

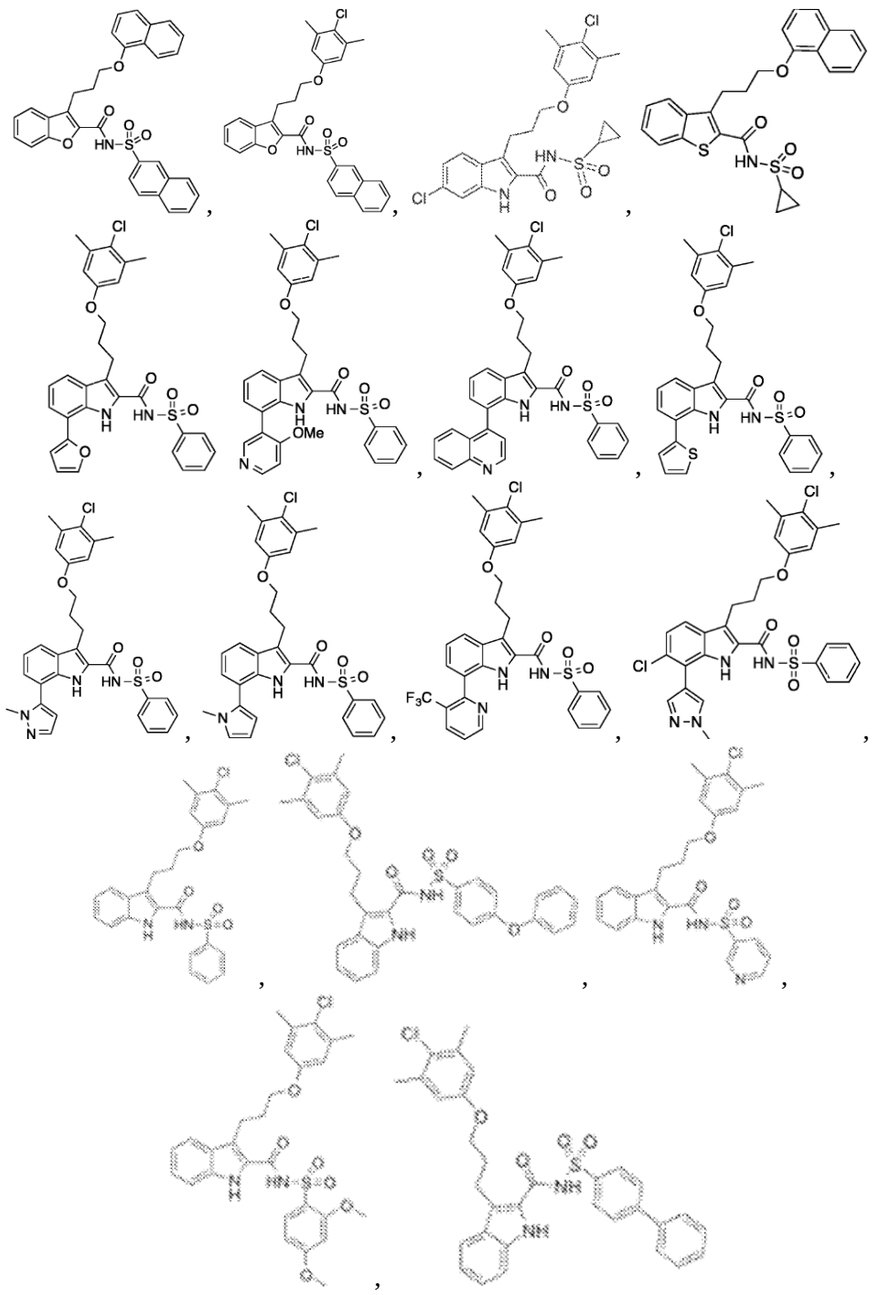
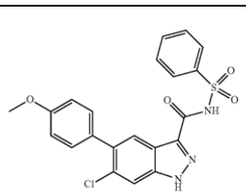
Más aún, en relación con los efectos que se obtienen de la combinación de los compuestos de la invención con estos dos agentes terapéuticos adicionales particulares, me permito presentar en el Anexo 1 de este escrito, información adicional relacionada con los estudios de Fase 1 y Fase 2 de tres diferentes regímenes de combinación de compuestos de la presente invención, con los agentes tezacaftor e ivacaftor, en donde se puede observar el efecto sinérgico de estos agentes terapéuticos en la función respiratoria de pacientes con fibrosis quística. Estos resultados se representan en un incremento en el porcentaje de predicción del volumen espirado máximo en el primer segundo de la espiración forzada (ppFEV1) de 9,7 y 12 para los compuestos VX-152 y VX-440 en estudios de fase 2 con pacientes con una mutación *F508del*, y de 7,3 y 9,5 en pacientes con dos copias del gen mutado, que estaban recibiendo tezacaftor e ivacaftor.

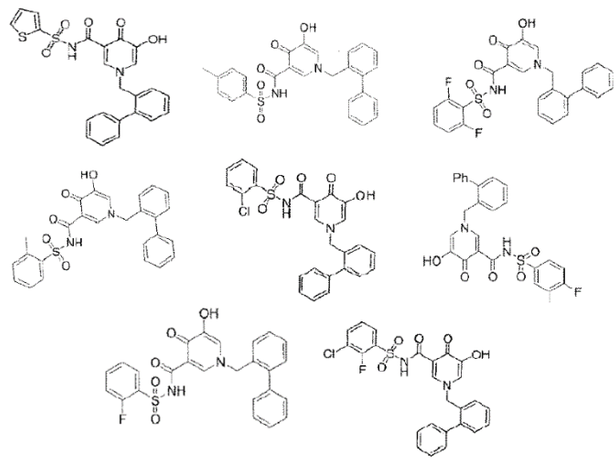
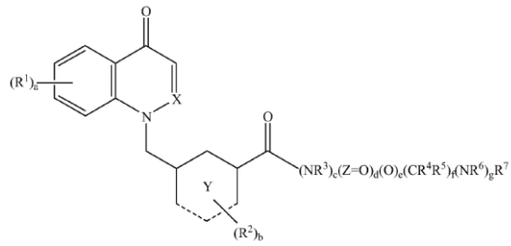
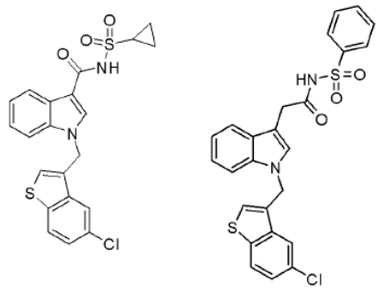
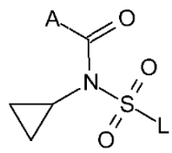
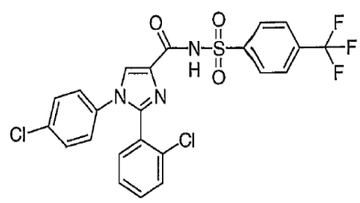
Por lo tanto, como se puede observar en el documento anexo, las composiciones que comprenden los compuestos de la invención en combinación con tezacaftor e ivacaftor, fueron obtenidas y ensayadas y se demostró en dichos ensayos que estas tienen un efecto sinérgico en pacientes con fibrosis quística.

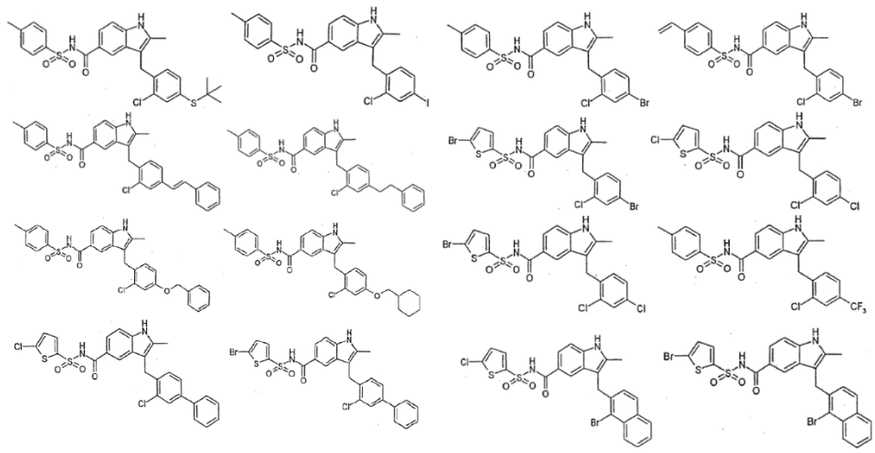
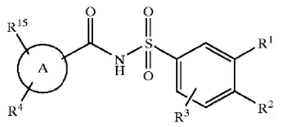
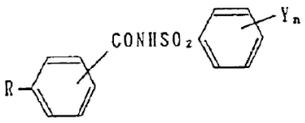
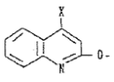
Así las cosas, considero que las objeciones elevadas por el Examinador con respecto a falta de claridad, concisión y sustento en el Capítulo Descriptivo, del Capítulo Reivindicatorio Modificado quedan superadas, por lo que éste cumple con lo establecido en el artículo 30 de la Decisión 486.

3. a- El Examinador señala que las patentes WO2014/152013 (D1), WO2014/144100 (D2), WO2014/047427 (D3), US2013/267493 (D4), WO2010/110231 (D5), WO2009/027730 (D6), WO2008/100867 (D7), WO2007/113327 (D8), WO2005/099705 (D9), US2005/171185 (D10), US2002/086887 (D11) y EP0194599 (D12) afectan la novedad de modalidades comprendidas en las reivindicaciones puesto que cada una de dichos documentos enseña compuestos específicos que se encuentran dentro del alcance de la fórmula *Markush* reclamada en la Reivindicación 1. En particular, el Examinador señala las siguientes divulgaciones que anticiparían los compuestos reclamados en la presente invención:

Documento citado	**Compuesto que afecta la novedad**
D1	 Página 63
D2	 Compuesto I-144

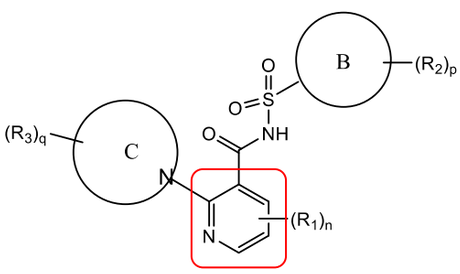
Documento citado	Compuesto que afecta la novedad
D3	 Compuestos 25, 27, 65, 67, 86, 90, 92, 95, 100, 101, 102, 121, 131 to 133, 138 y 139
D4	 Compuesto 118

Documento citado	Compuesto que afecta la novedad
D5	 Páginas 159 a 165
D6	 Z es SO; c y d son 1; e, f y g son 0 y Y es fenilo
D7	 Compuestos 196 y 199
D8	 Compuestos 100 a 103, 123, 135, 169, 261, 399, 400, 404 y 405
D9	 Compuesto 16

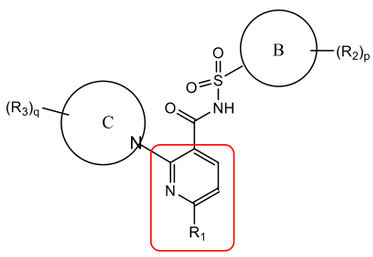
Documento citado	Compuesto que afecta la novedad
D10	 Compuestos 17 a 21, 23 a 26, 29, 31, 32, 34 a 37, 41, 43, 44, 46, 49 y 50
D11	 Compuestos de fórmula (I) donde A es fenilo
D12	 Compuestos de fórmula (I) donde R es 

El Examinador añade que las reivindicaciones dependientes no aportan características adicionales que le confieran novedad a los compuestos reclamados, por lo cual se considera que dichas reivindicaciones también carecen de novedad.

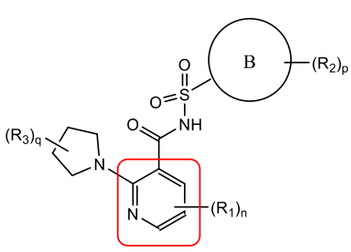
b- En respuesta a las objeciones del Examinador, me permito en primer lugar reiterar que el Capítulo Reivindicatorio Modificado fue limitado de tal manera que ahora reclama compuestos de Fórmula Ib-iii, Ib-iv, Ib-v y Ib-vi, todos los cuales tienen un anillo piridina en su estructura en la posición del Anillo A:



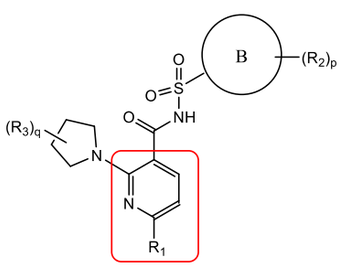
Ib-iii



Ib-iv



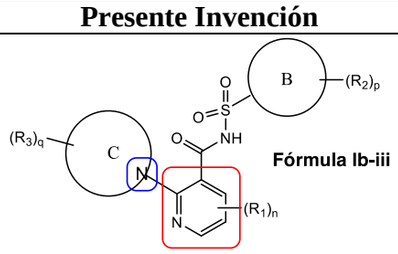
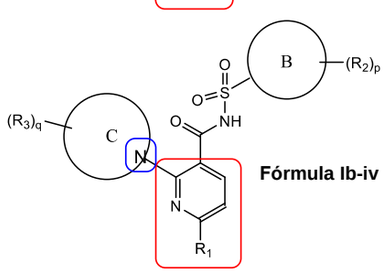
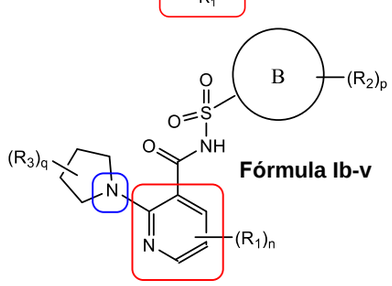
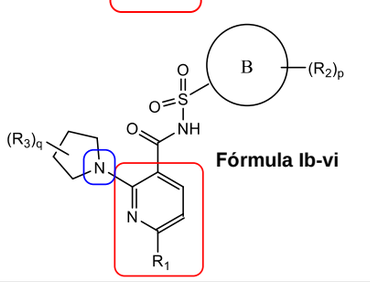
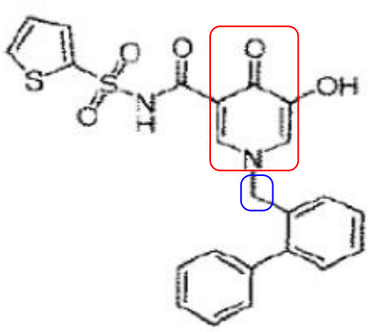
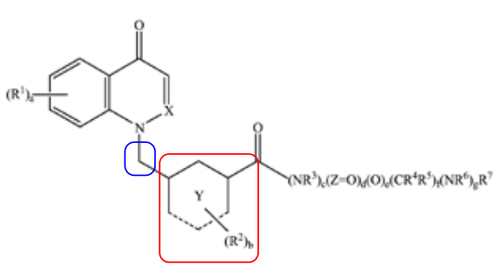
Ib-v



Ib-vi

Por el contrario, los compuestos divulgados en los documentos citados por el Examinador no presentan dicha característica estructural:

- Los compuestos citados por el Examinador de los documentos D1, D2, D4, D7 a D10 y D12 no contienen un anillo de piridina en su estructura;
- ninguno de los compuestos que cita el Examinador de D3 posee un anillo de piridina unido al grupo carbonílico, sino por el contrario, todos los compuestos de D3 poseen un heterociclo bicíclico en la misma posición;
- los compuestos de D11 cuando el anillo A es fenilo, no divulgan un grupo piridina unido al grupo carbonilo tal como se reclama en la presente invención.
- En cuanto a los compuestos de D5, estos se diferencian de los compuestos de la presente invención en que el heterociclo nitrogenado que corresponde a la piridina en los compuestos reclamados, está unido a través de un átomo de carbono con el anillo en la posición del anillo C de la presente invención, mientras que en los compuestos reclamados, la piridina (anillo A), está unida directamente al átomo de nitrógeno del heterociclo que corresponde al anillo C;
- De forma similar. los compuestos de D6, no incluyen un anillo de piridina (dado que el anillo Y es fenilo) unido directamente al átomo de nitrógeno de un heteroarilo o heterociclo nitrogenado, tal como ocurre con los compuestos de la presente invención.

Presente Invención	**Ejemplo de D5**
 **Fórmula Ib-iii**  **Fórmula Ib-iv**  **Fórmula Ib-v**  **Fórmula Ib-vi**	
Ejemplo de D6	
	

En este punto es importante resaltar que para fundamentar una afectación válida contra la novedad de una invención, el arte previo debe divulgar explícitamente todas y cada una de las características de la invención.[1] Es más, el Tribunal Andino de Justicia (TAJ) ha determinado que para establecer una objeción válida contra la novedad, la divulgación del arte previo debe ser lo suficientemente detallada para que una persona versada en la materia pueda usar dicha información para reproducir y explotar la invención.[2] En el presente caso, teniendo en cuenta las drásticas limitaciones introducidas en la materia reclamada, ninguno de los documentos citados por el Examinador divulga explícitamente todas y cada una de las características estructurales de los compuestos reclamados en el Capítulo Reivindicatorio Modificado adjunto, por lo cual éstos resultan novedosos sobre D1 a D12.

4. a- El Examinador considera que el título de la presente solicitud es general y no se relaciona con el objeto de la solicitud.

b- En respuesta a la objeción del Examinador, me permito a modificar el título de la presente solicitud como sigue:

"DERIVADOS CÍCLICOS DE SULFONILCARBOXAMIDA ACTIVOS COMO MODULADORES DEL REGULADOR DE LA CONDUCTANCIA TRANSMEMBRANA DE LA FIBROSIS QUÍSTICA (CFTR)"

5. Por lo tanto, considero que la presente solicitud cumple con los requisitos de patentabilidad establecidos por la Decisión 486 y por consiguiente solicito respetuosamente que el Despacho proceda con la concesión de la patente. Sin embargo, si el Despacho lo considera necesario, de presentarse nuevas objeciones, solicito amablemente proceda a realizar un segundo examen de fondo, para lo cual adjunto el comprobante de pago de la tasa de examen correspondiente.

Atentamente,

CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295

Anexos:

- Capítulo Reivindicatorio Modificado;
- Comprobante de pago correspondiente a la tasa de examen;
- Anexo 1: Resultados de ensayos Fase 1 y Fase 2.

[1] Comunidad Andina de Naciones, *op. cit.*, Sección 9.4
[2] Proceso 06-IP-89 (http://intranet.comunidadandina.org/Documentos/Procesos/209-IP-2005.doc); y Proceso 36-IP-2004 (http://www.notinet.com.co/serverfiles/servicios/archivos/30jul04/ca36-04.htm)