

(IB)

and pharmaceutically acceptable salts, tautomers, isotopologues,

stereoisomers and prodrugs thereof, wherein R^3, and R^4 are as defined herein.

[0010] A compound of formula **(I)** or formula **(IB)** or a pharmaceutically acceptable salt, tautomer, isotopologue, stereoisomer or prodrug thereof (each being referred to herein as an "Diaminopyrimidine Compound") is useful for treating or preventing liver fibrotic disorders, or diabetes and/or metabolic syndrome leading to liver fibrotic disorders, as described herein. In another example, a Diaminopyrimidine Compound is useful for treating or preventing a condition treatable or preventable by inhibition of a JNK pathway, as described herein.

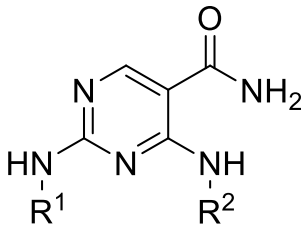
[0011] In one example, provided herein are Diaminopyrimidine Compounds as described in the instant disclosure, such as, for example, in Tables 1, 2 and 3.

[0012] In one example, provided herein are pharmaceutical compositions comprising an effective amount of a Diaminopyrimidine Compound as described herein, and a pharmaceutically acceptable carrier, excipient or vehicle. In some examples, the pharmaceutical composition is suitable for oral, parenteral, mucosal, transdermal or topical administration.

[0013] In one example, provided herein are methods for treating or preventing liver fibrotic disorders, such as non-alcoholic steatohepatitis, steatosis, cirrhosis, primary sclerosing cholangitis, primary biliary cirrhosis, hepatitis, hepatocellular carcinoma, and liver fibrosis coincident with chronic or repeated alcohol ingestion, with infection, with liver transplant, or with drug induced liver injury, comprising administering to a subject in need thereof an effective amount of a Diaminopyrimidine Compound as described herein; and a pharmaceutically acceptable carrier, excipient or vehicle. In another example, provided herein are methods for treating or preventing diabetes or metabolic syndrome leading to liver fibrotic disorders, such as non-alcoholic steatohepatitis, steatosis, hepatitis, or cirrhosis, comprising administering to a subject in need thereof an effective amount of a Diaminopyrimidine Compound. Also provided herein are methods for treating or

preventing a condition treatable or preventable by inhibition of a JNK pathway, comprising administering to a subject in need thereof an effective amount of a Diaminopyrimidine Compound as described herein; and a pharmaceutically acceptable carrier, excipient or vehicle.

[00013a] In one aspect, the present disclosure refers to the use of: (i) a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof,

wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted saturated or partially saturated alkylcycloalkyl, or substituted or unsubstituted alkylheterocyclyl, provided that R^1 is not 2-aminocyclohexyl;

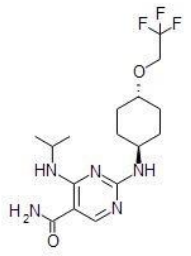
R^2 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted saturated C_{5-10} cycloalkyl, substituted or unsubstituted saturated or partially saturated alkylcycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

provided the compound is not
2-(2-aminoethylamino)-4-(methylamino)pyrimidine-5-carboxamide,
2-(2-aminopropylamino)-4-(cyclohexylamino)pyrimidine-5-carboxamide,
2-(2-amino-2-oxoethylamino)-4-(cyclohexylamino)pyrimidine-5-carboxamide,
2-(2-aminoethylamino)-4-(cyclohexylamino)pyrimidine-5-carboxamide,
4-(cyclopentylamino)-2-(methylamino)pyrimidine-5-carboxamide;

in the manufacture of a medicament for the treatment or prevention of interstitial pulmonary fibrosis; chronic allograft nephropathy; antibody mediated rejection; cystic fibrosis; mucous colitis; Huntington's disease; pancreatitis; nephritis; lupus erythematosus; Type II diabetes; obesity; left ventricular hypertrophy; ischemic damages of heart, lung, gut, kidney, liver, pancreas, spleen or brain; preservation of the organ for transplantation; graft versus host disease; endotoxin shock; burn from exposure to fire, chemicals or radiation;

eczema; skin graft; epilepsy; Alzheimer's disease; Parkinson's disease; or immunological response to bacterial or viral infection.

[0013b] In another aspect, the present disclosure refers to use of a compound in the manufacture of a medicament for the treatment or prevention of interstitial pulmonary fibrosis; chronic allograft nephropathy; antibody mediated rejection; cystic fibrosis; mucous colitis; Huntington's disease; pancreatitis; nephritis; lupus erythematosus; Type II diabetes; obesity; left ventricular hypertrophy; ischemic damages of heart, lung, gut, kidney, liver, pancreas, spleen or brain; preservation of the organ for transplantation; graft versus host disease; endotoxin shock; burn from exposure to fire, chemicals or radiation; eczema; skin graft; epilepsy; Alzheimer's disease; Parkinson's disease; or immunological response to bacterial or viral infection;
wherein the compound of formula (I) is that wherein the compound is .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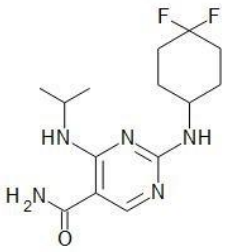
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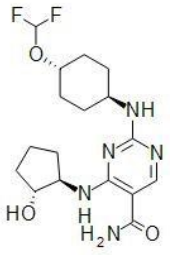
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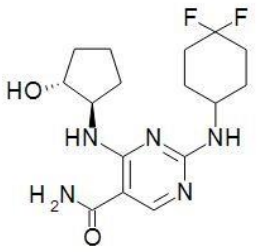
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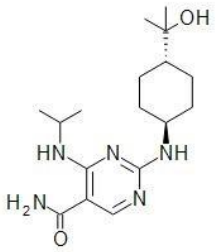
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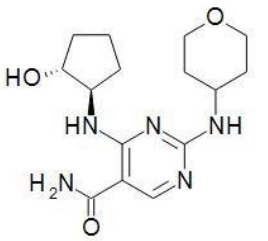
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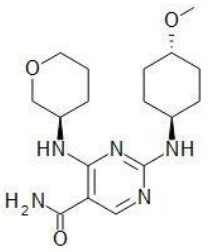
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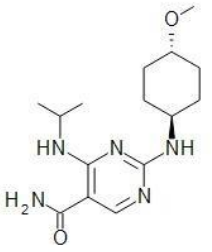
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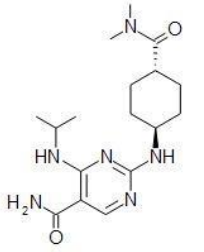
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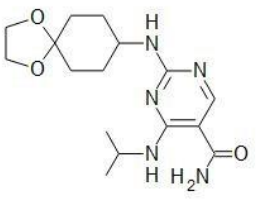
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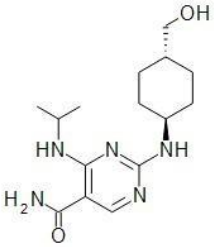
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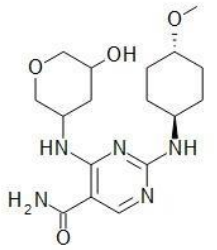
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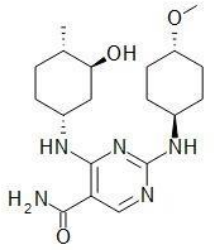
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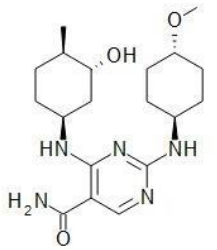
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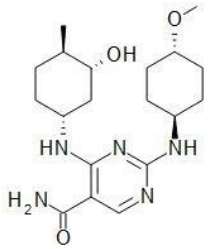
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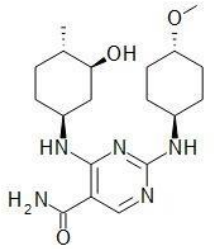
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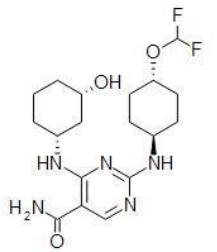
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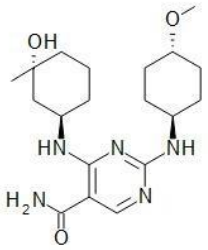
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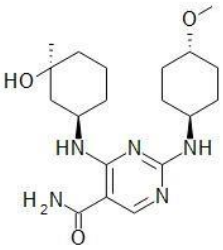
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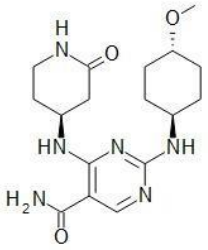
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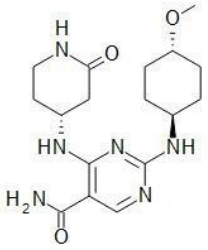
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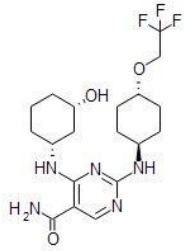
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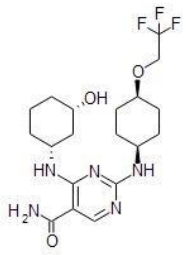
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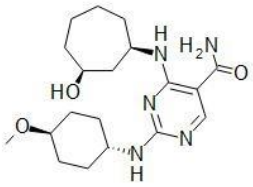
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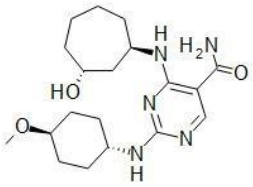
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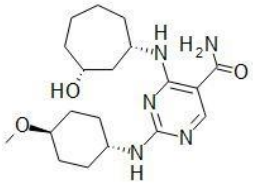
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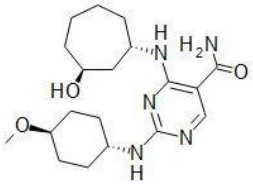
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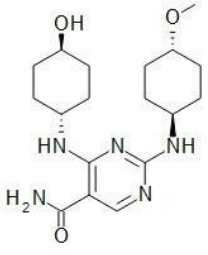
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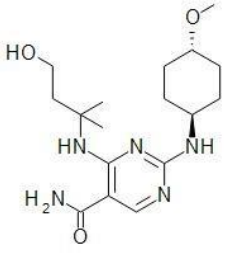
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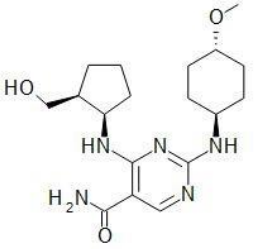
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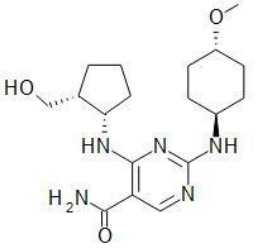
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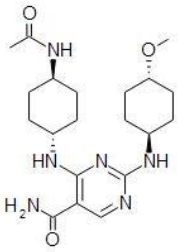
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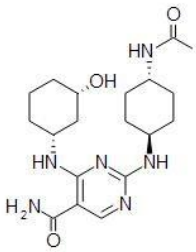
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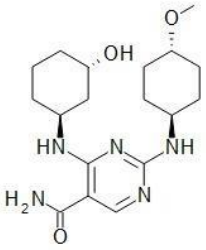
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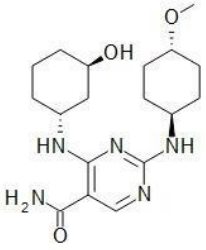
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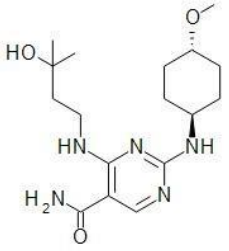
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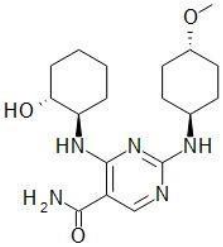
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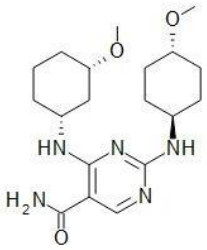
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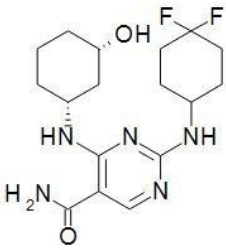
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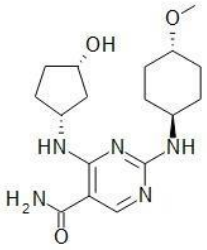
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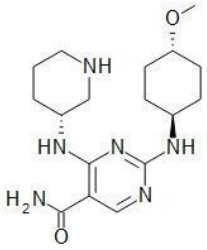
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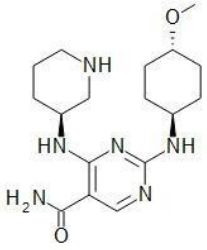
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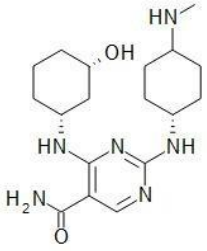
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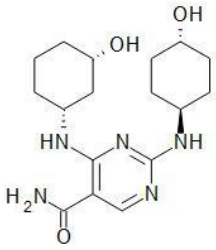
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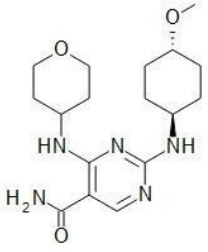
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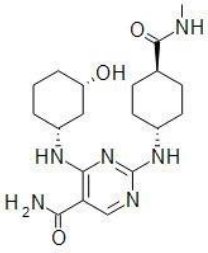
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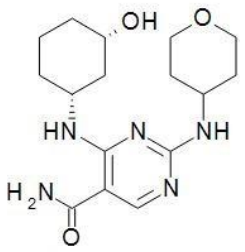
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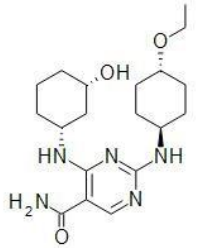
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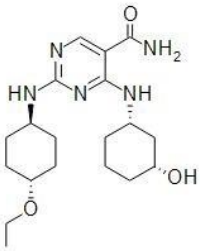
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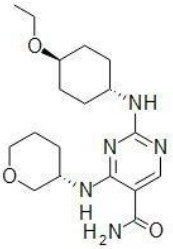
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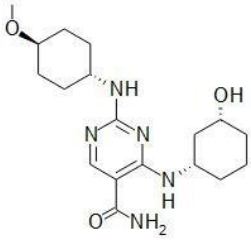
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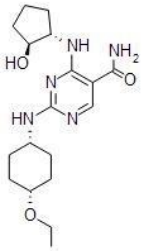
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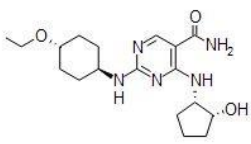
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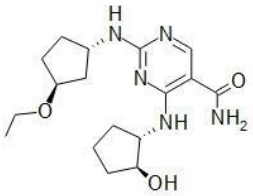
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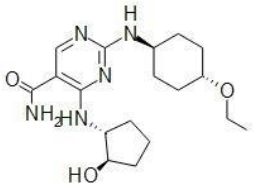
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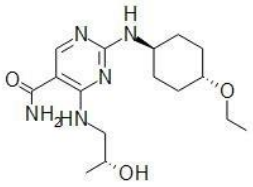
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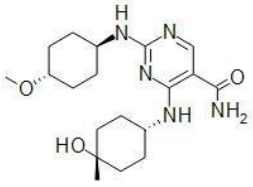
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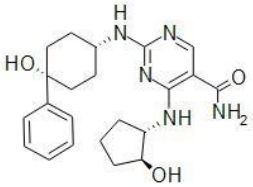
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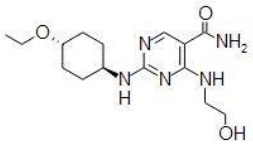
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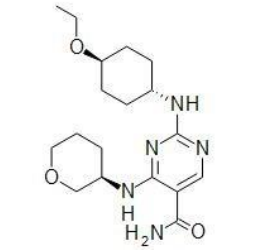
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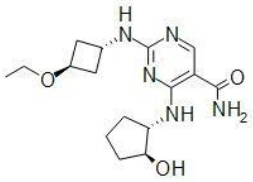
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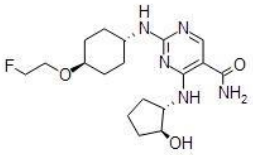
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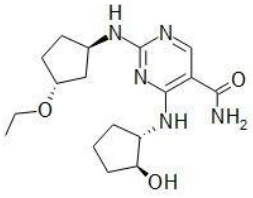
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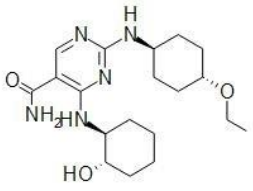
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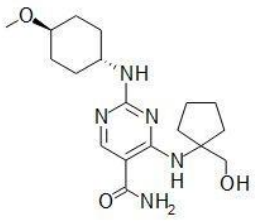
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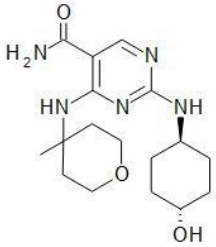
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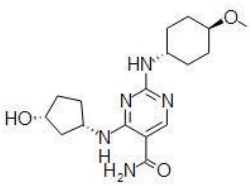
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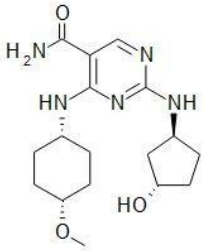
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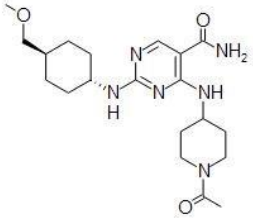
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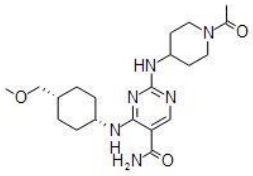
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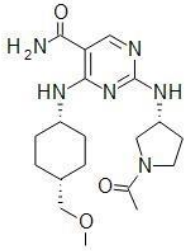
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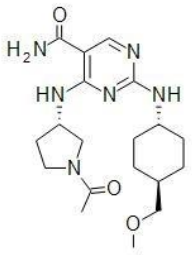
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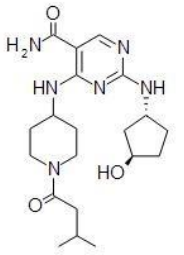
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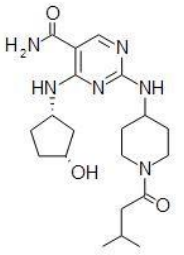
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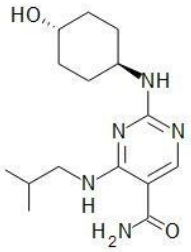
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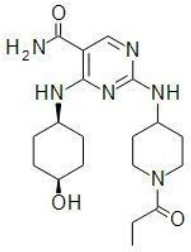
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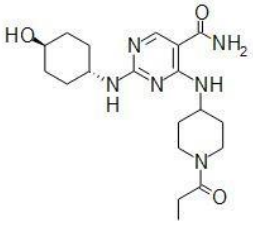
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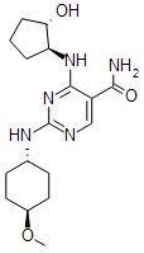
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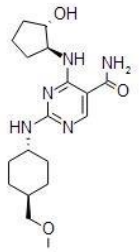
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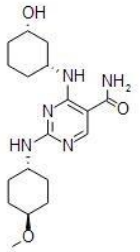
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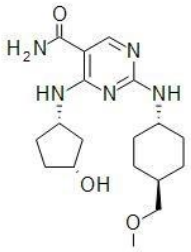
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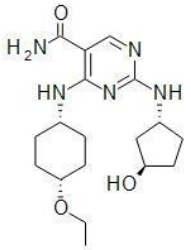
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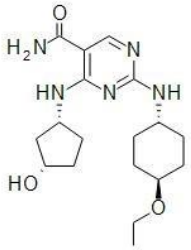
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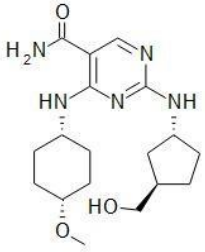
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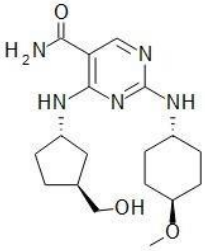
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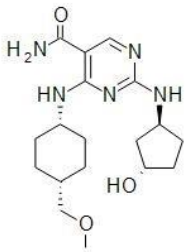
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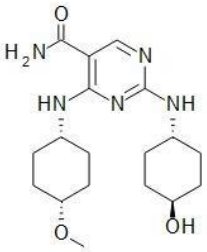
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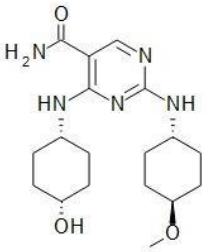
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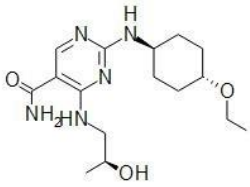
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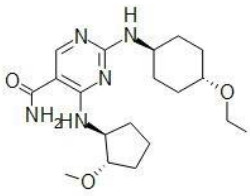
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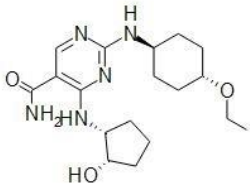
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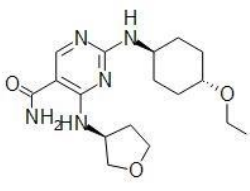
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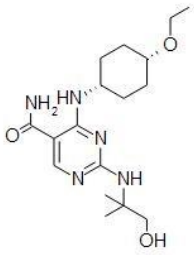
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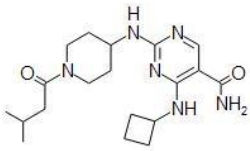
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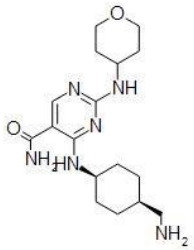
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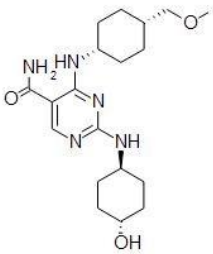
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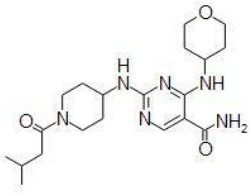
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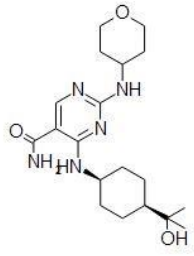
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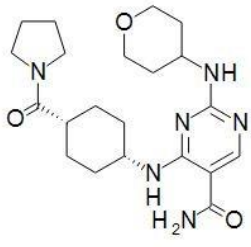
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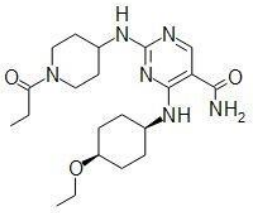
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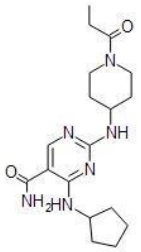
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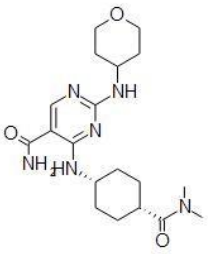
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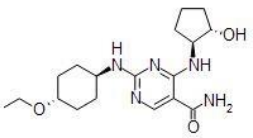
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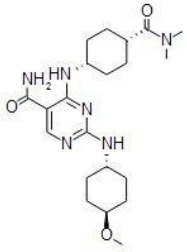
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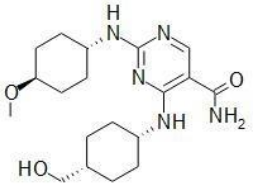
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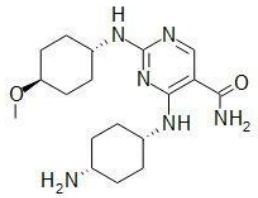
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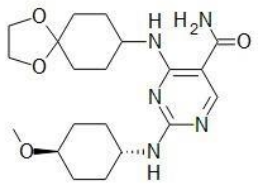
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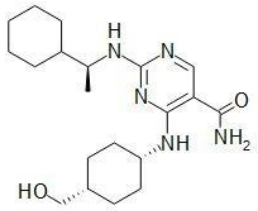
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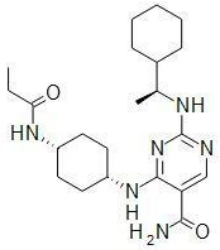
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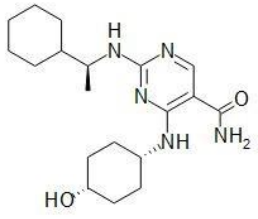
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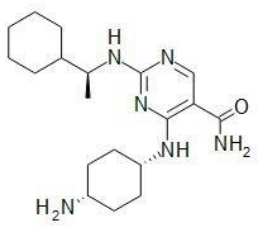
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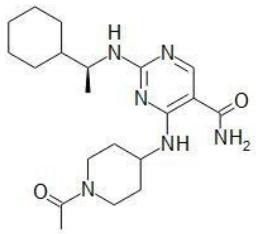
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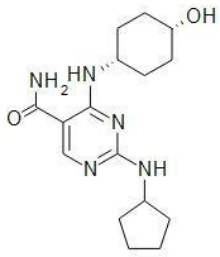
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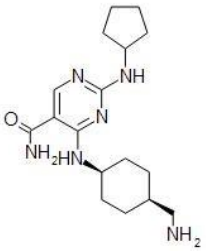
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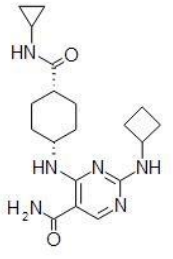
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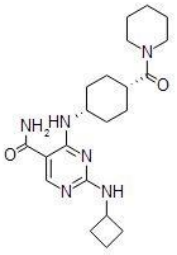
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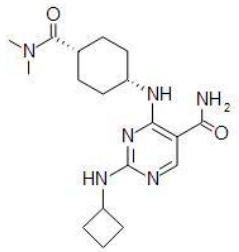
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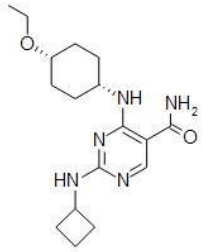
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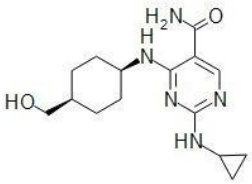
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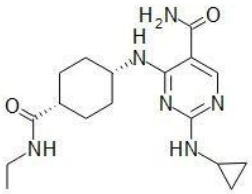
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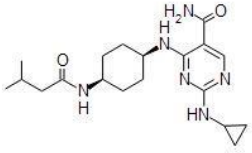
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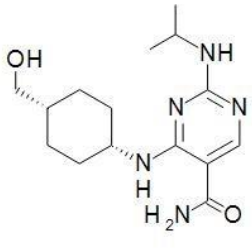
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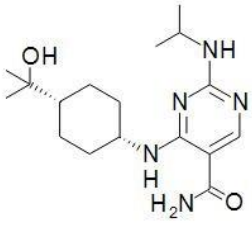
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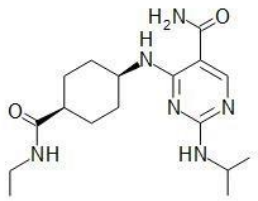
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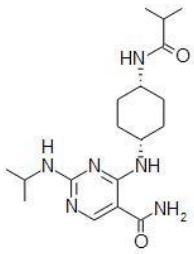
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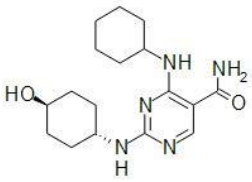
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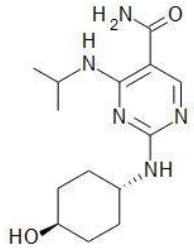
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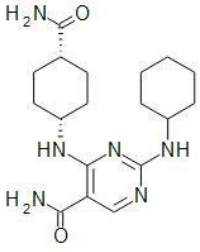
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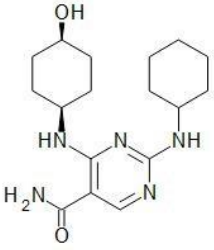
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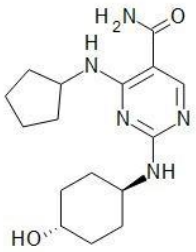
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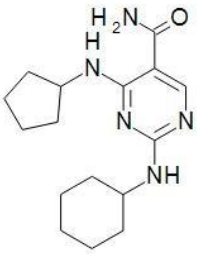
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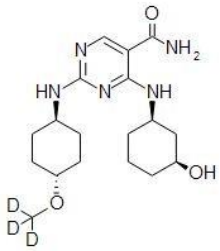
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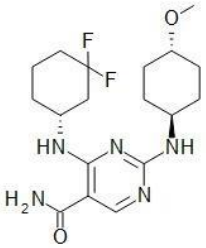
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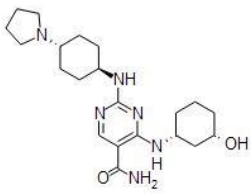
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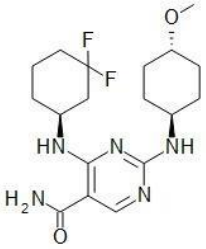
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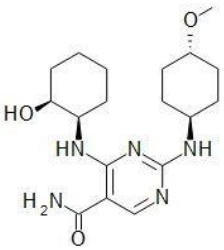
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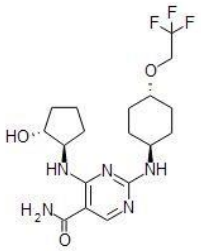
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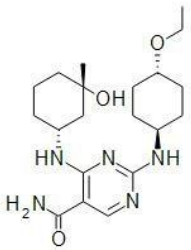
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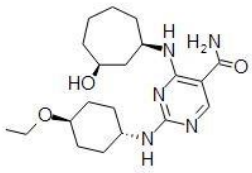
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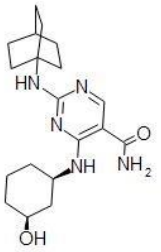
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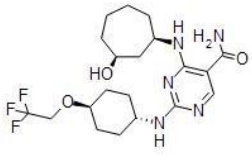
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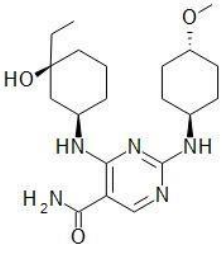
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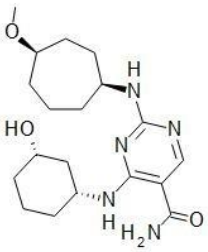
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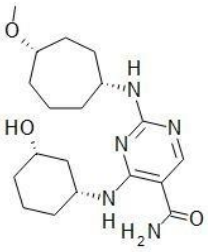
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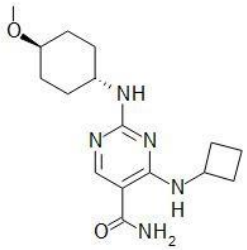
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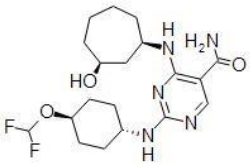
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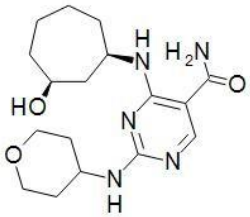
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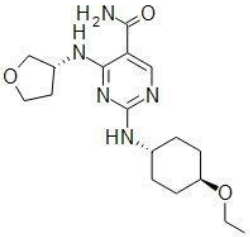
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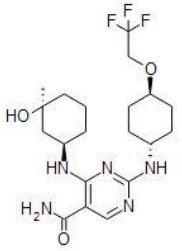
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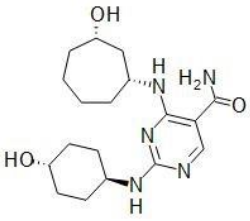
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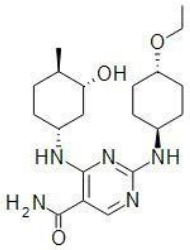
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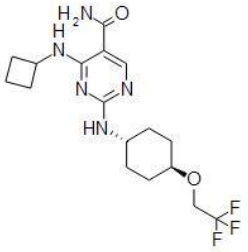
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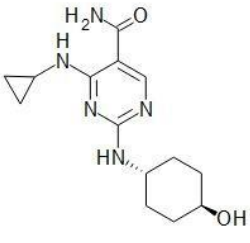
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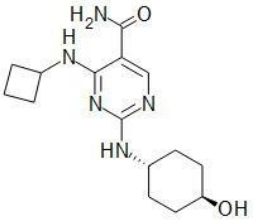
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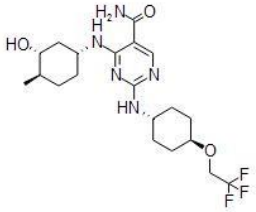
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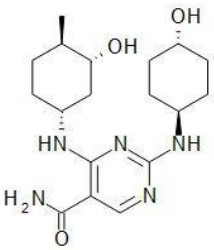
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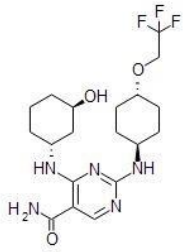
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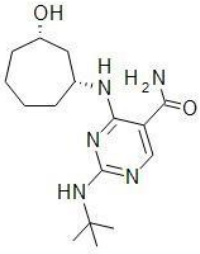
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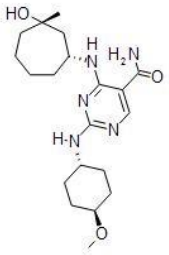
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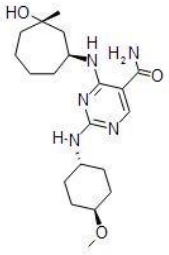
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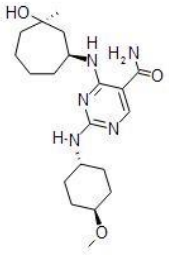
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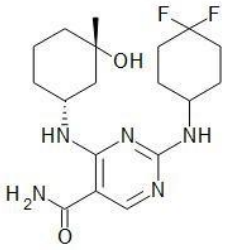
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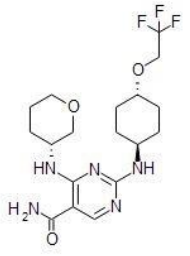
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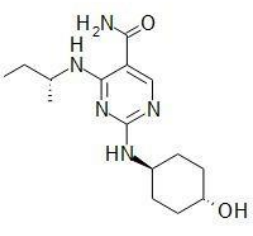
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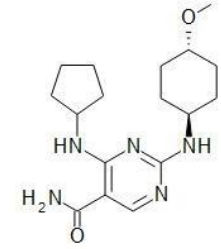
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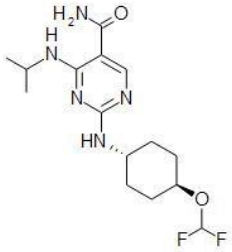
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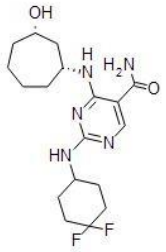
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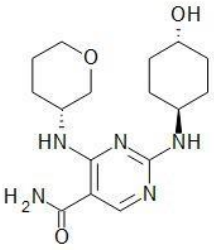
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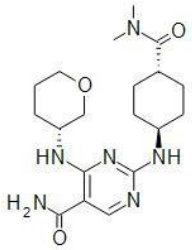
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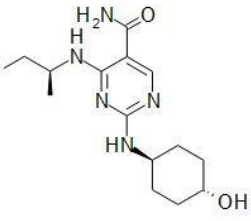
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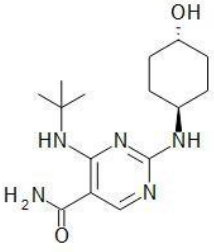
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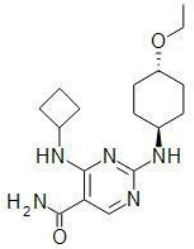
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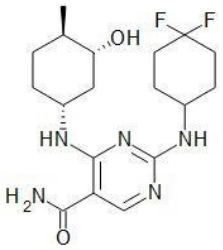
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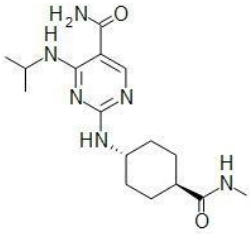
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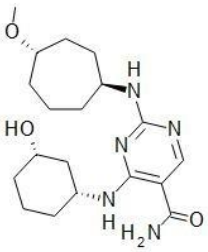
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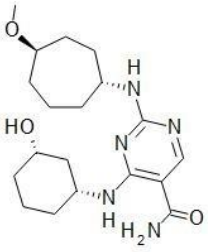
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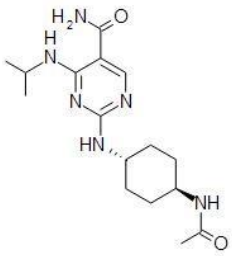
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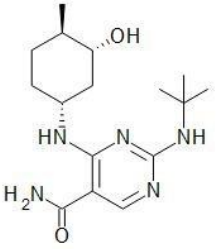
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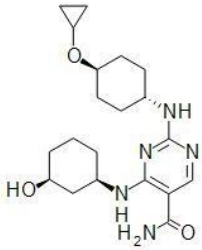
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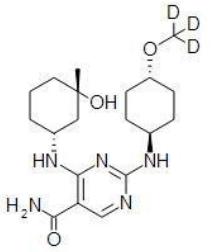
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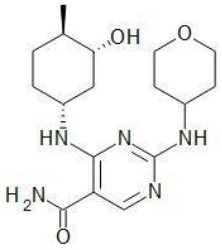
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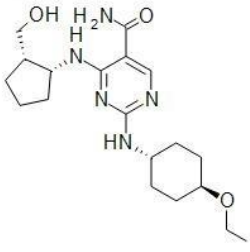
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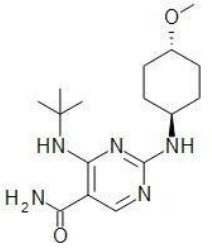
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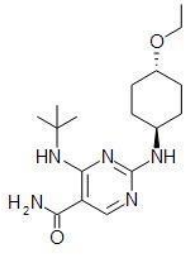
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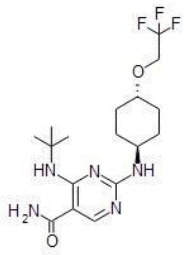
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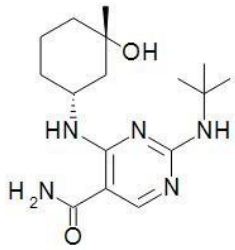
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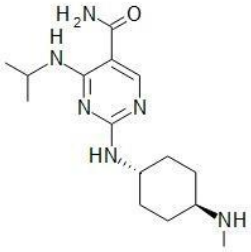
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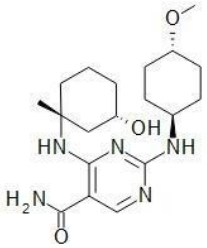
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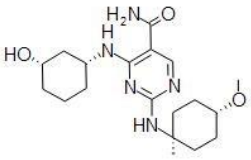
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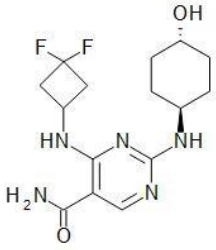
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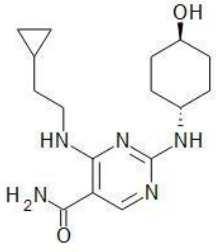
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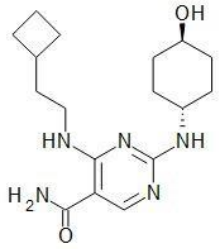
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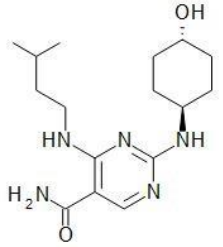
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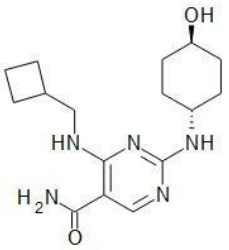
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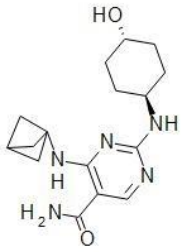
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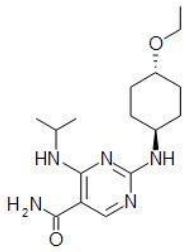
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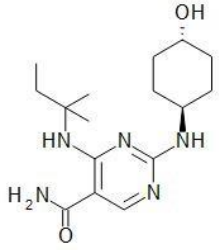
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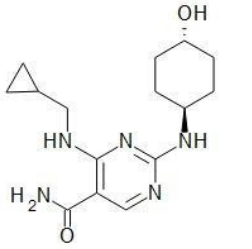
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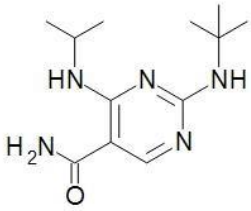
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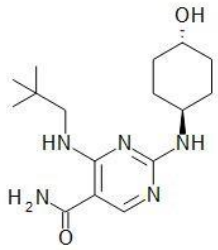
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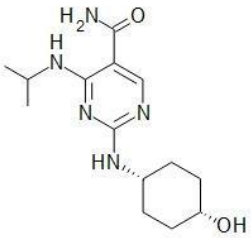
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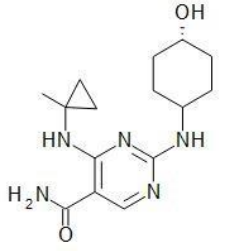
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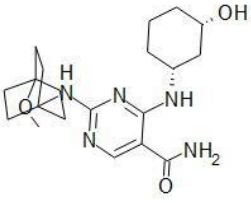
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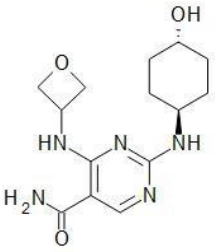
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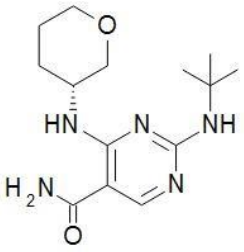
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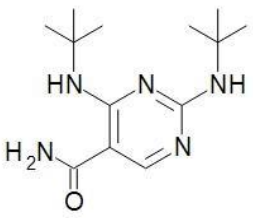
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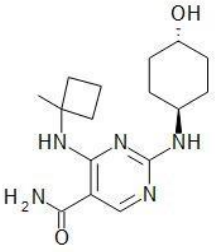
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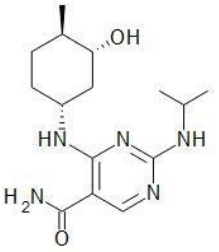
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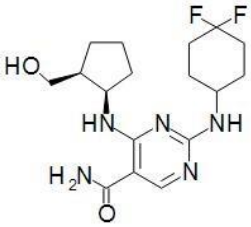
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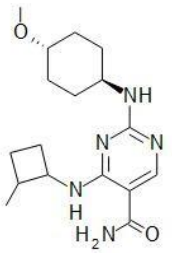
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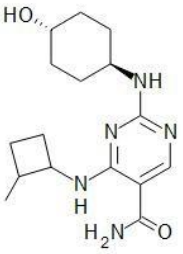
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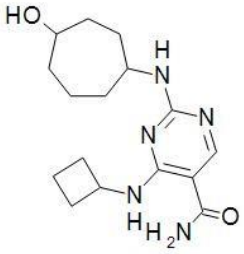
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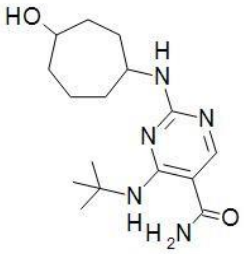
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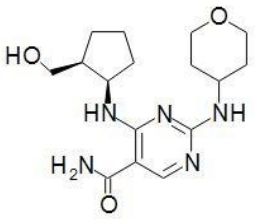
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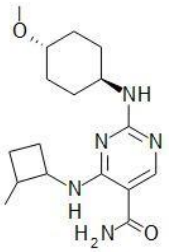
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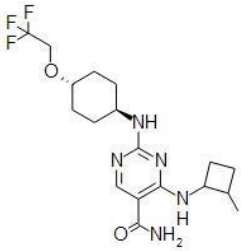
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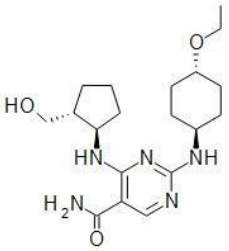
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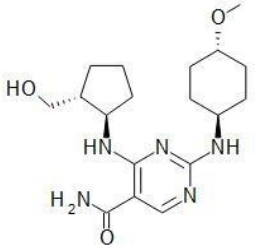
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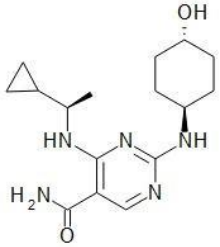
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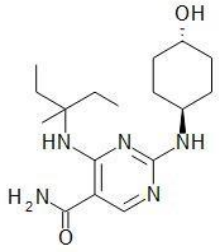
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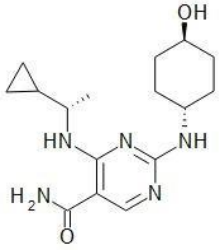
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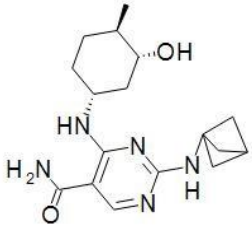
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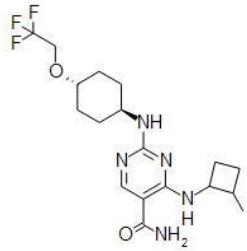
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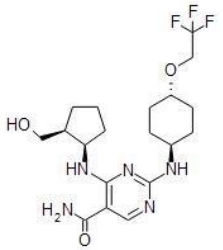
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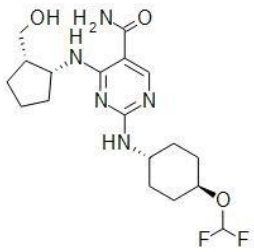
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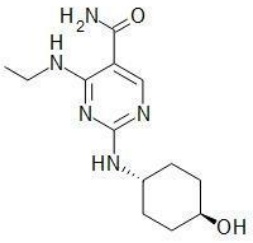
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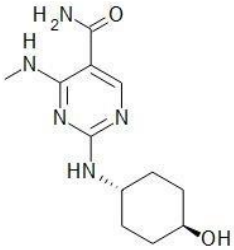
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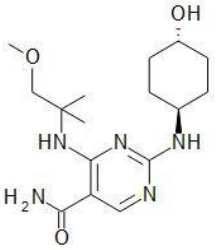
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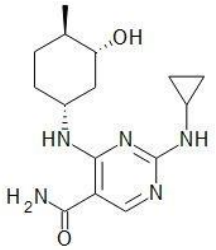
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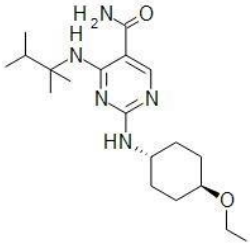
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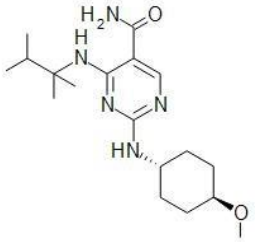
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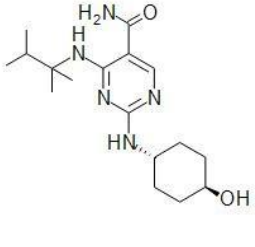
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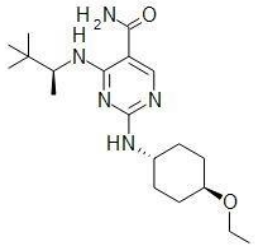
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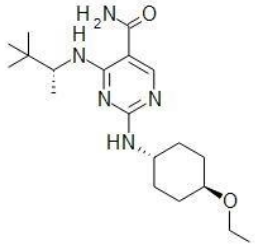
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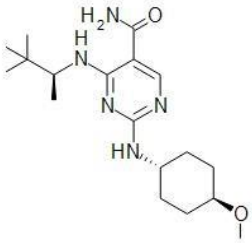
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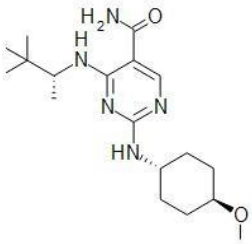
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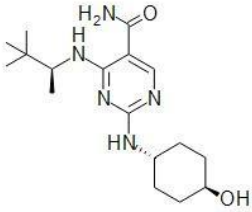
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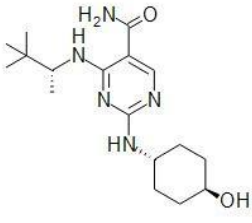
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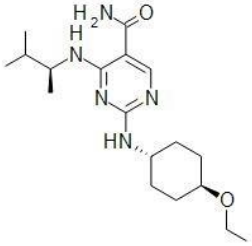
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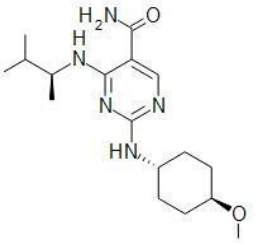
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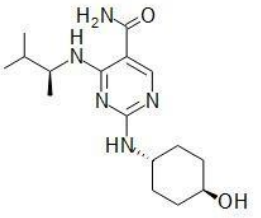
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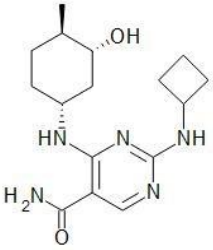
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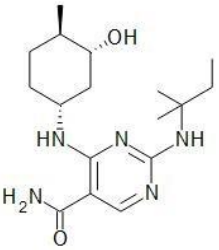
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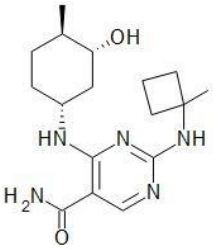
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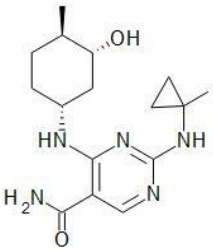
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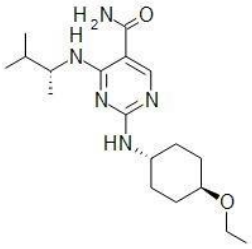
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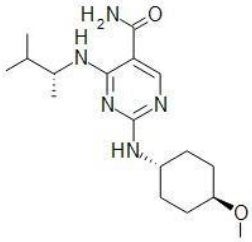
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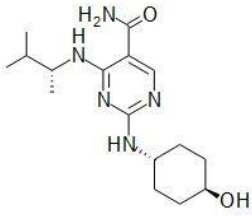
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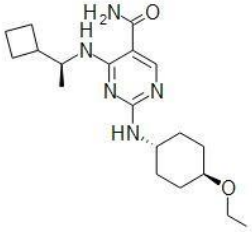
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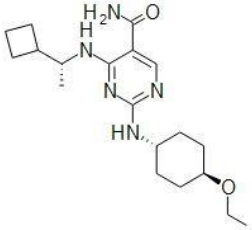
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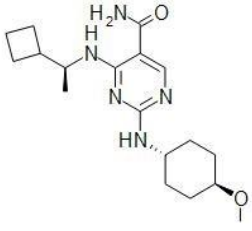
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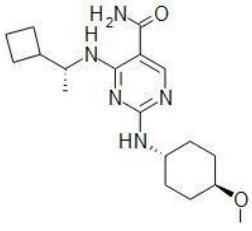
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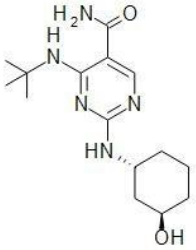
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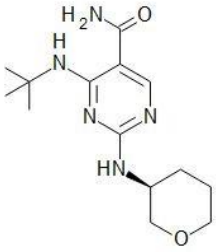
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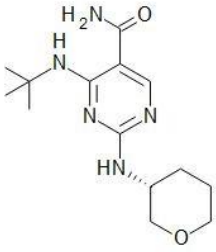
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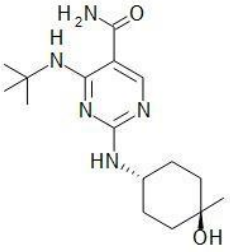
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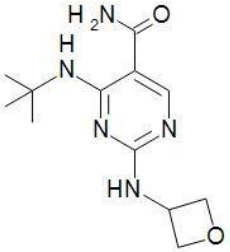
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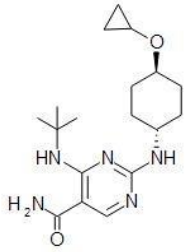
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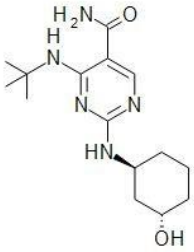
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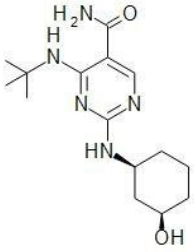
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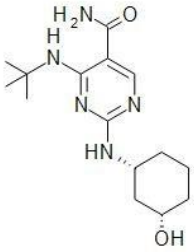
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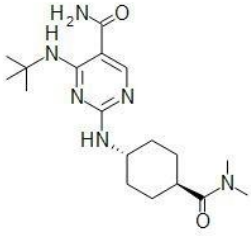
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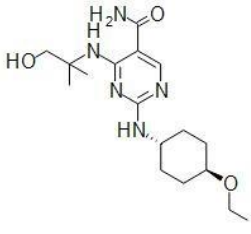
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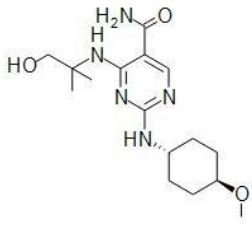
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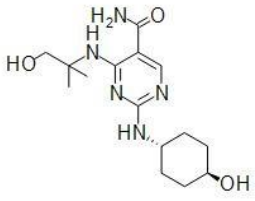
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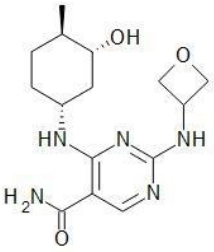
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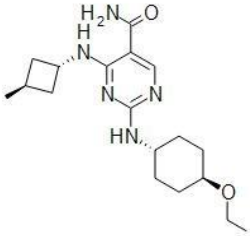
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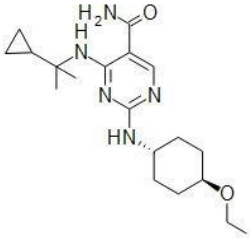
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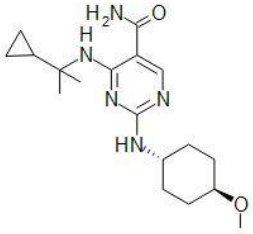
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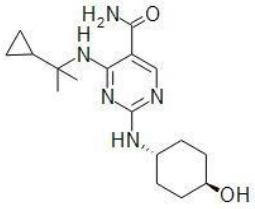
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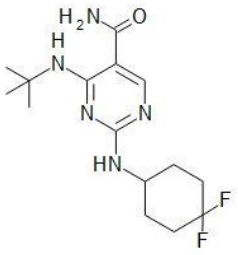
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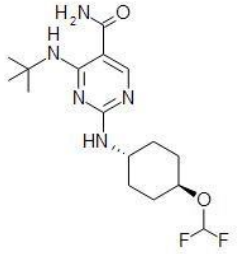
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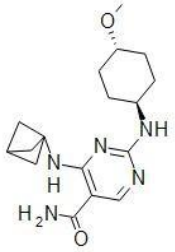
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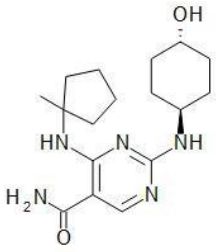
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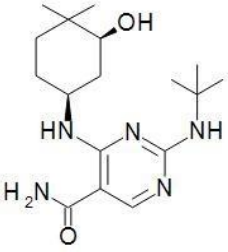
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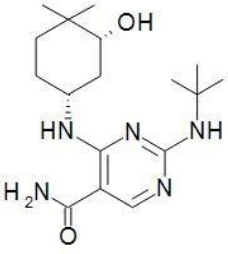
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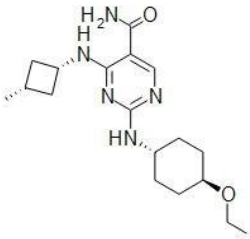
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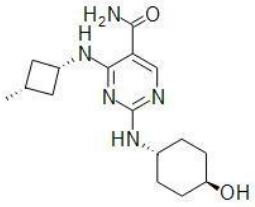
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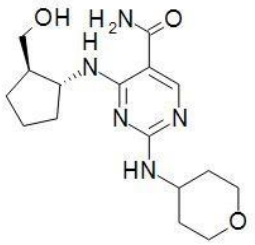
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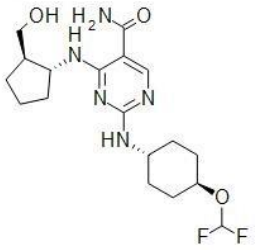
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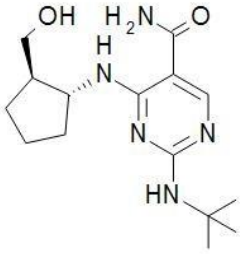
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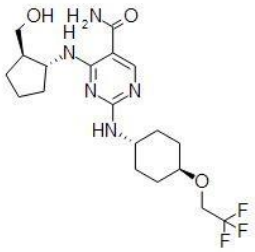
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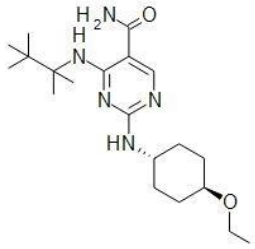
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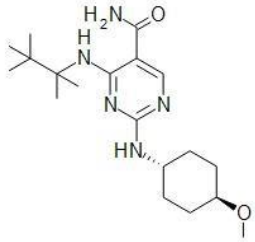
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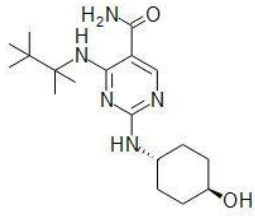
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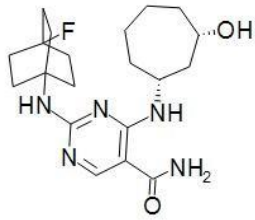
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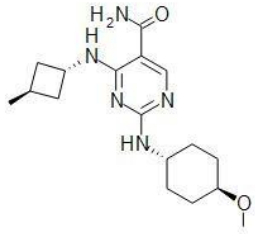
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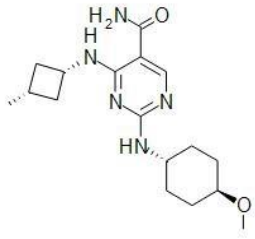
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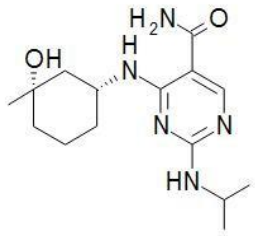
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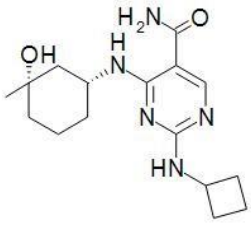
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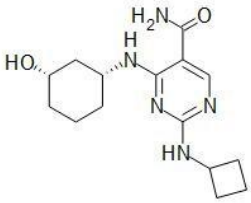
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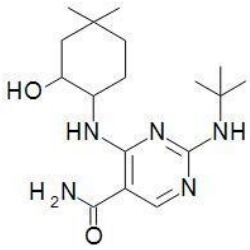
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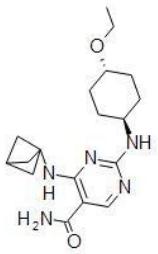
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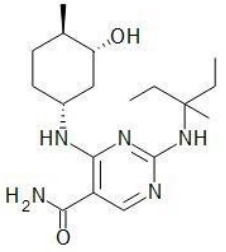
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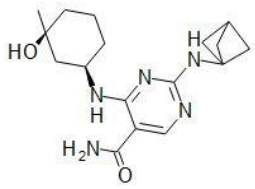
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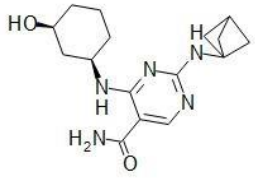
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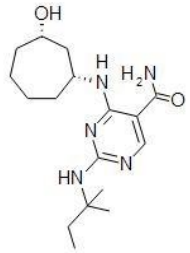
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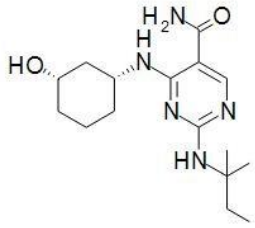
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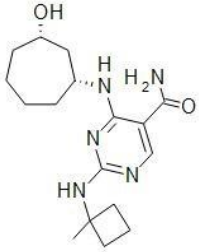
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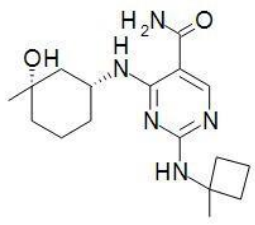
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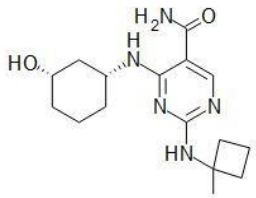
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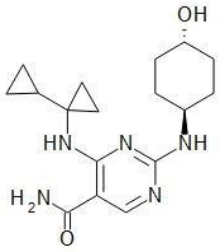
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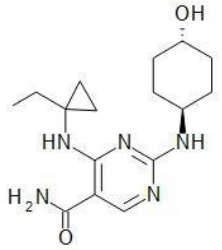
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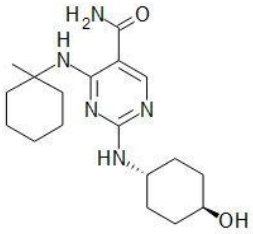
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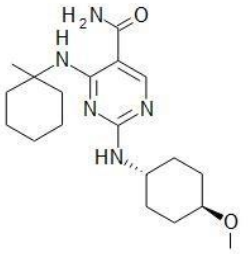
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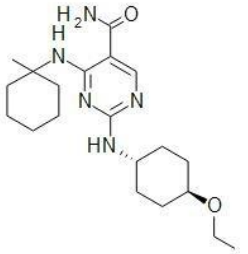
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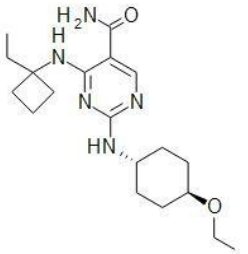
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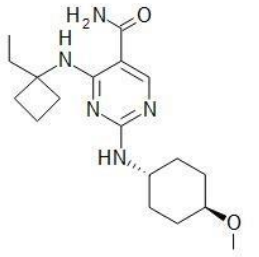
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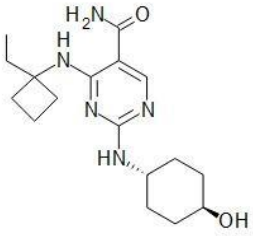
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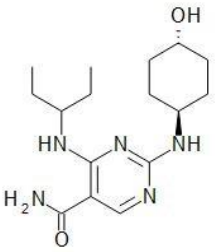
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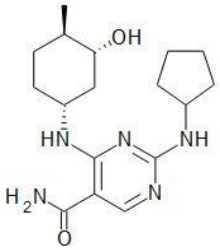
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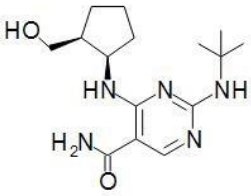
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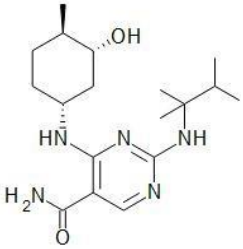
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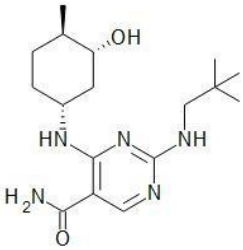
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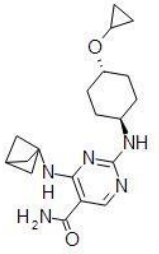
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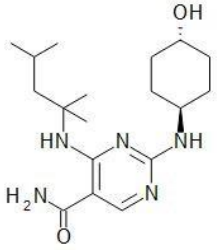
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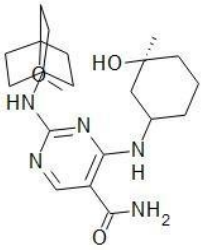
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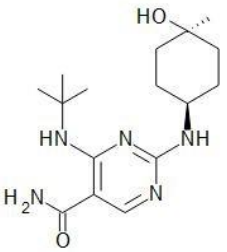
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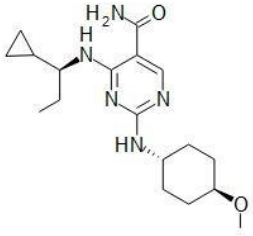
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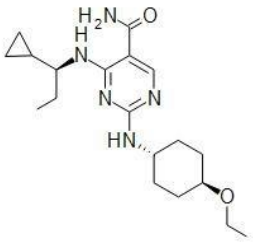
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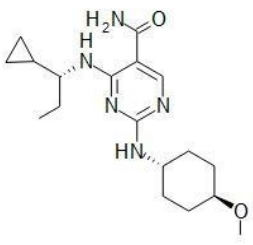
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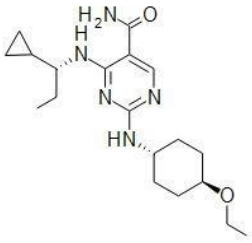
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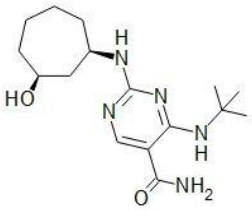
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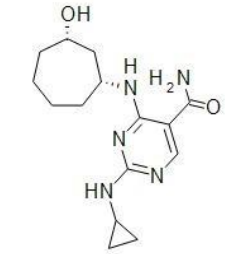
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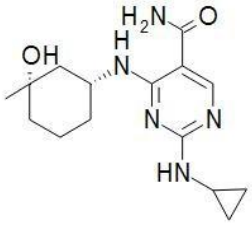
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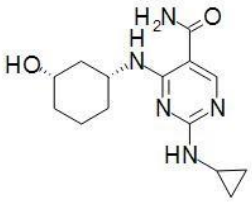
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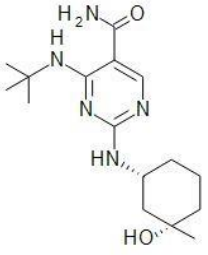
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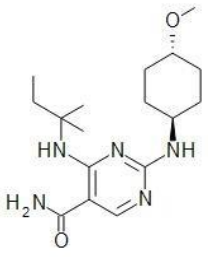
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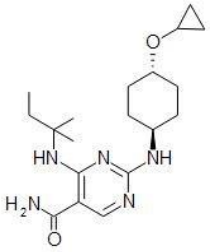
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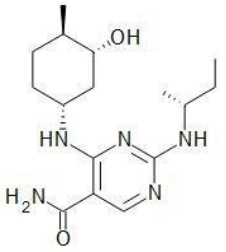
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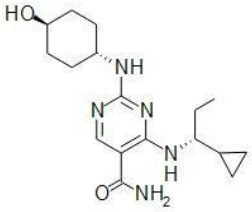
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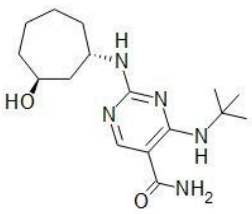
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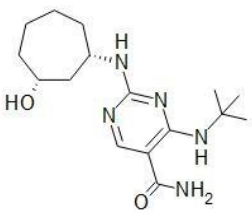
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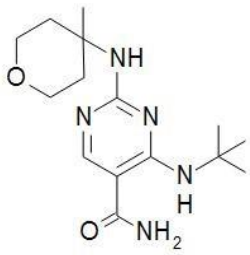
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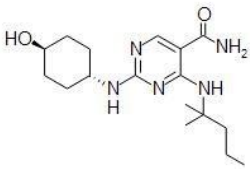
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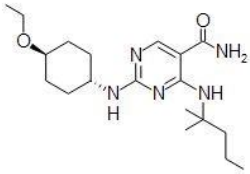
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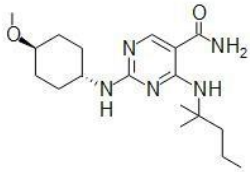
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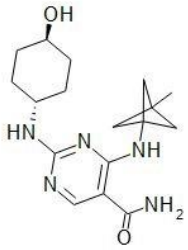
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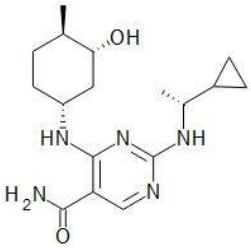
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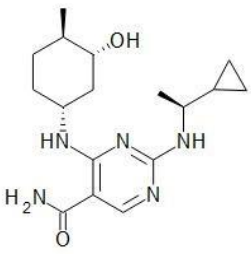
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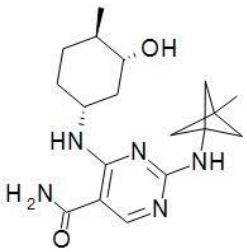
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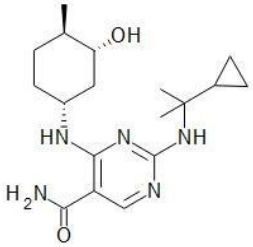
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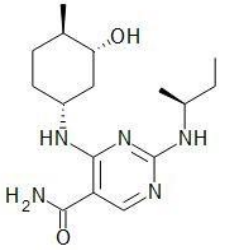
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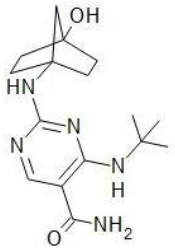
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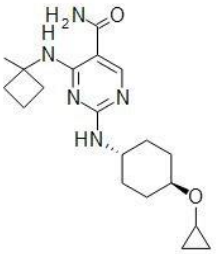
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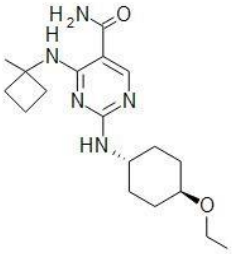
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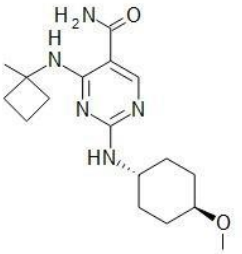
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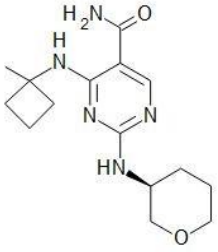
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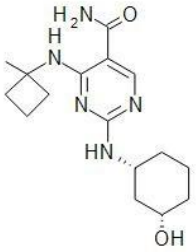
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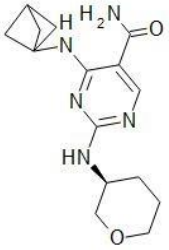
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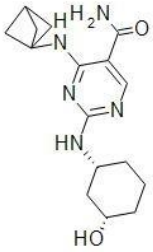
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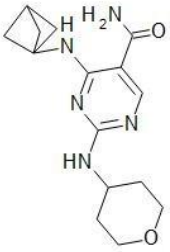
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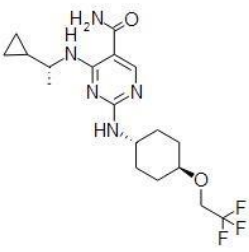
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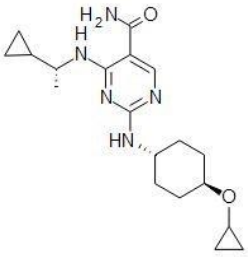
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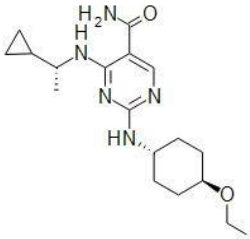
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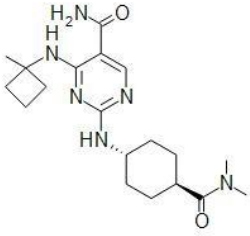
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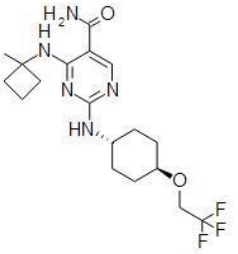
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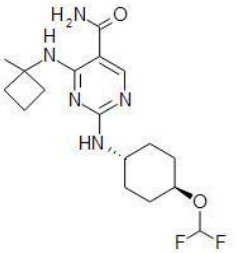
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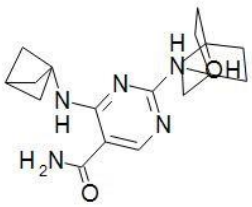
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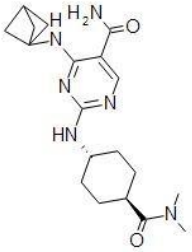
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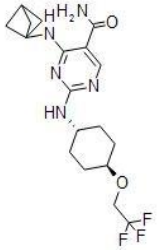
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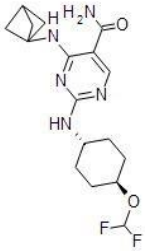
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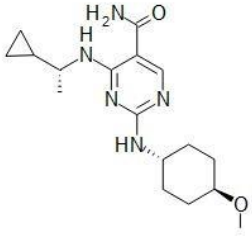
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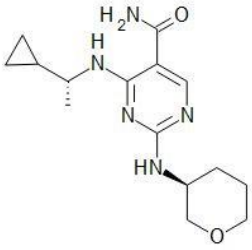
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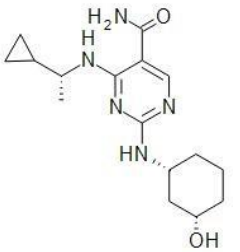
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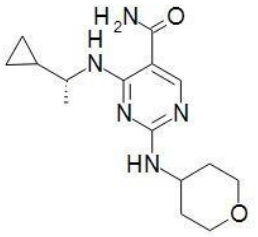
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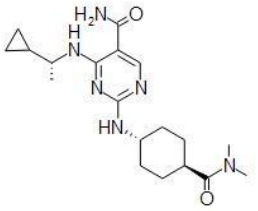
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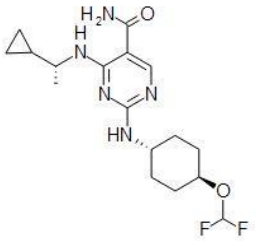
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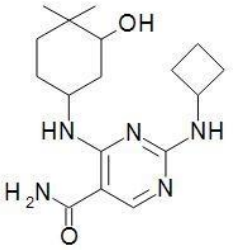
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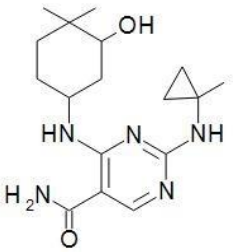
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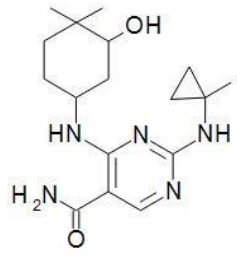
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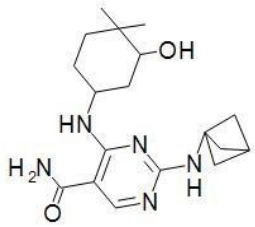
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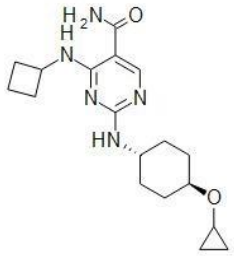
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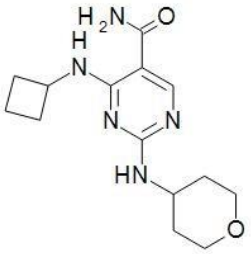
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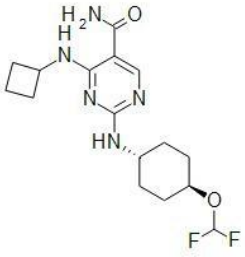
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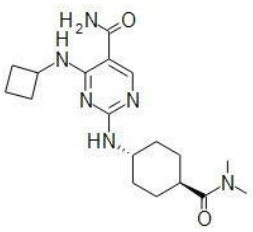
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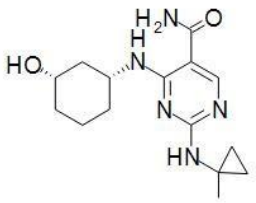
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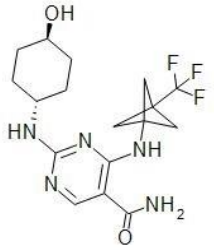
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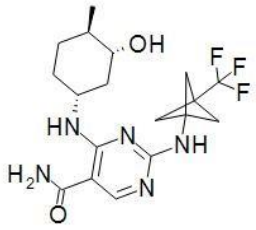
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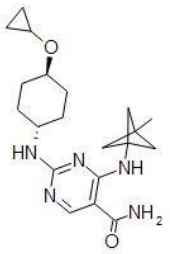
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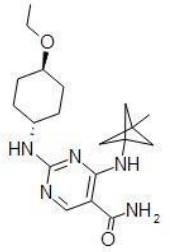
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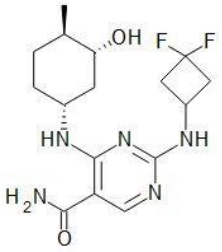
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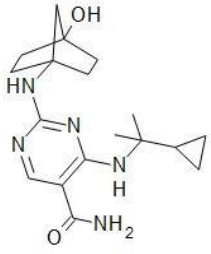
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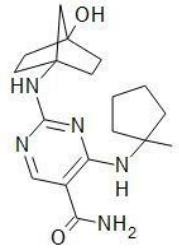
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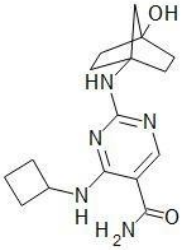
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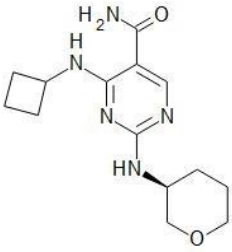
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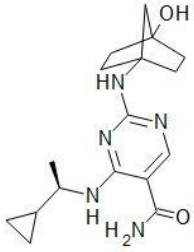
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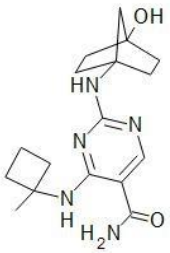
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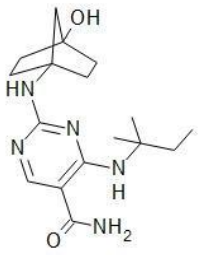
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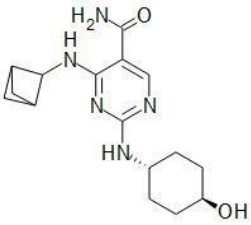
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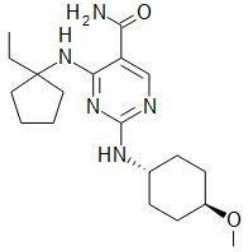
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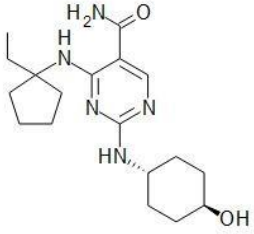
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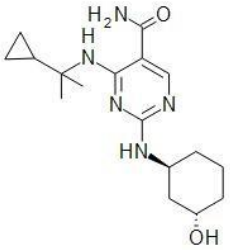
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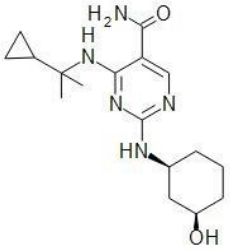
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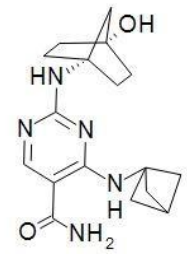
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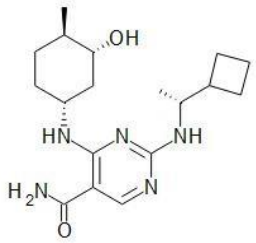
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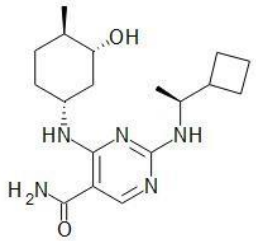
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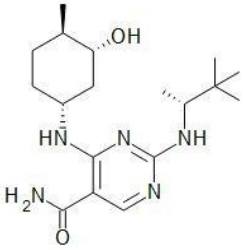
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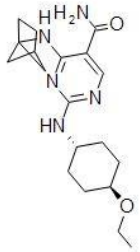
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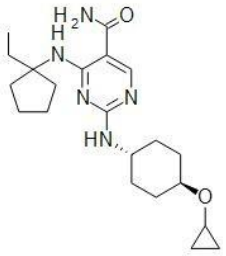
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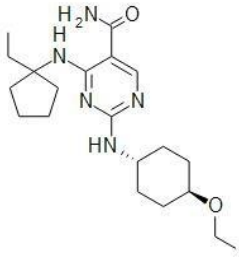
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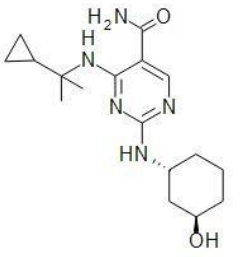
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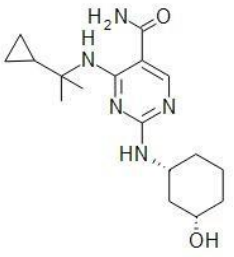
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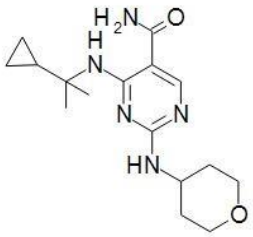
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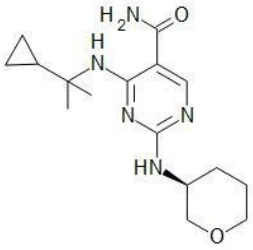
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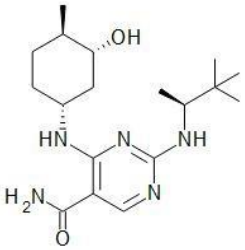
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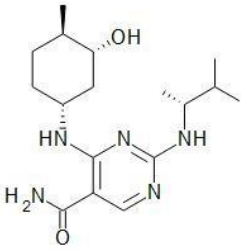
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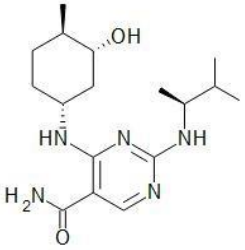
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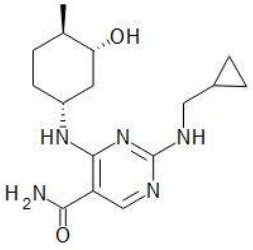
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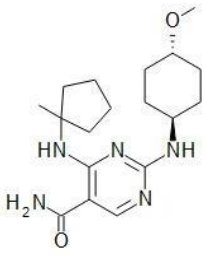
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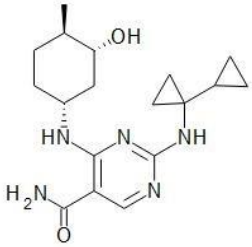
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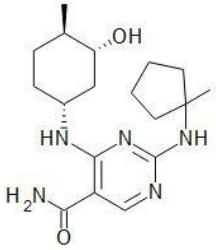
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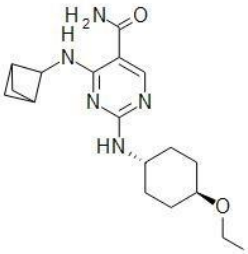
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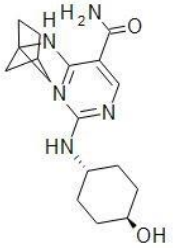
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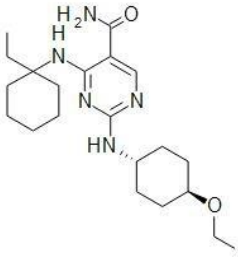
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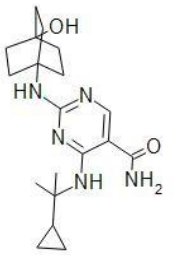
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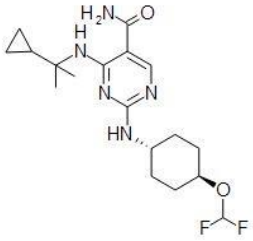
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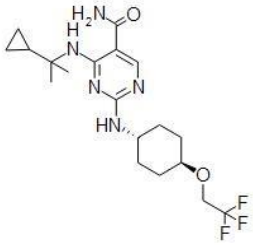
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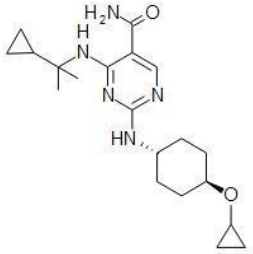
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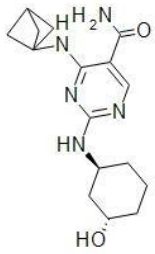
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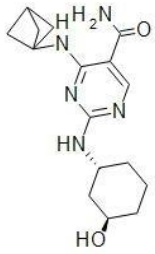
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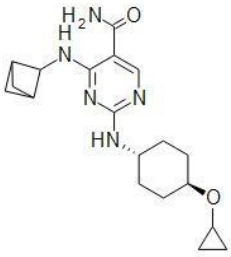
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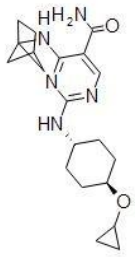
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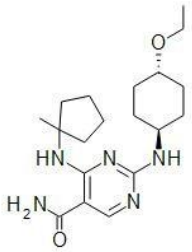
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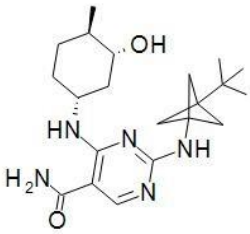
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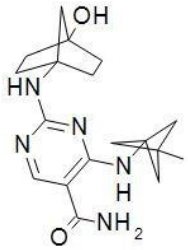
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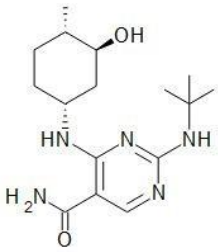
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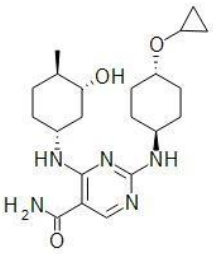
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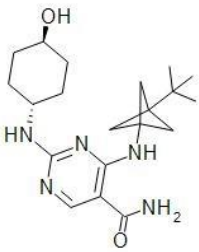
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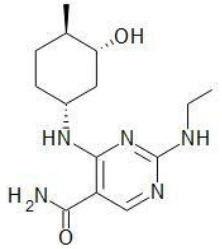

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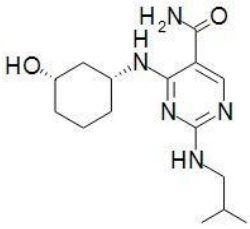

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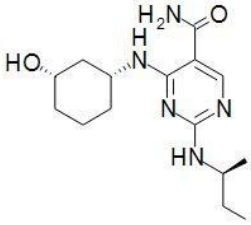

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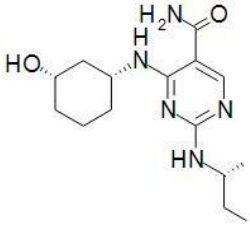

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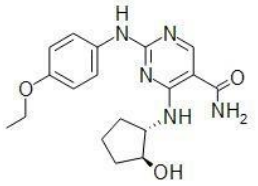
or a pharmaceutically acceptable salt, tautomer, stereoisomer, or enantiomer thereof.

[0013c] In yet another aspect, the present disclosure refers to the use of a compound in the manufacture of a medicament for the treatment or prevention of interstitial pulmonary fibrosis; chronic allograft nephropathy; antibody mediated rejection; cystic fibrosis; mucous colitis; Huntington's disease; pancreatitis; nephritis; lupus erythematosus; Type II diabetes; obesity; left ventricular hypertrophy; ischemic damages of heart, lung, gut, kidney, liver, pancreas, spleen or brain; preservation of the organ for transplantation; graft versus host disease; endotoxin shock; burn from exposure to fire, chemicals or radiation; eczema; skin

graft; epilepsy; Alzheimer's disease; Parkinson's disease; or immunological response to bacterial or viral infection; wherein the compound of formula (I) is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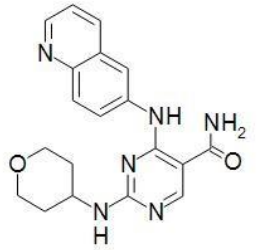
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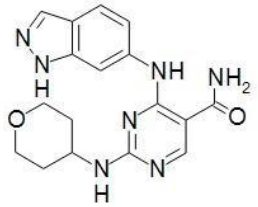
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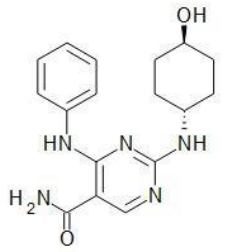
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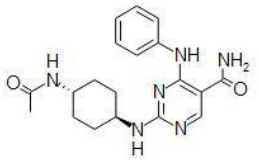
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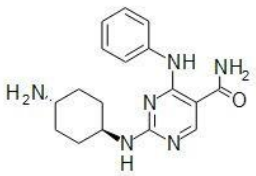
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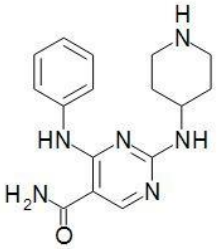
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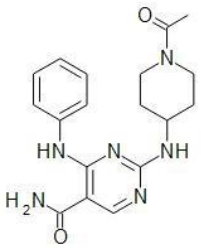
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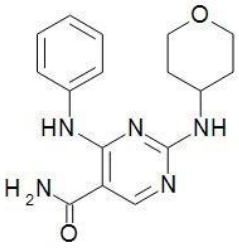
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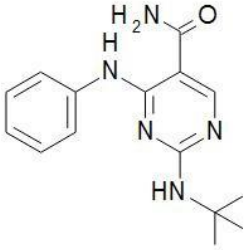
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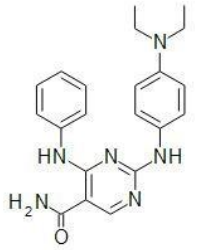
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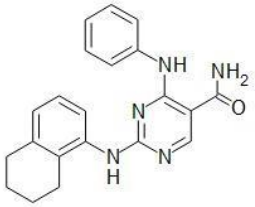
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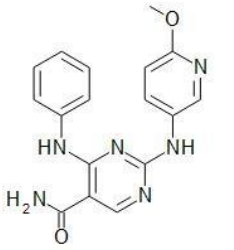
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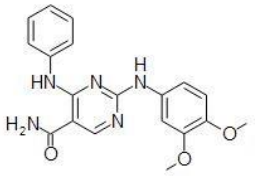
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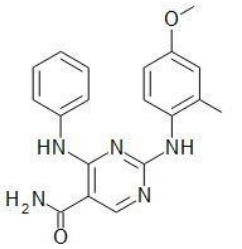
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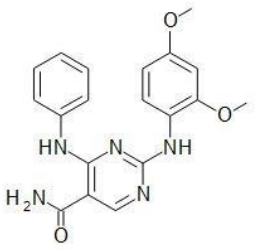
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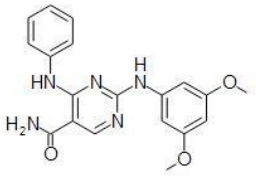
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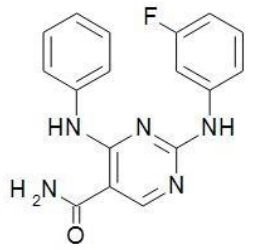
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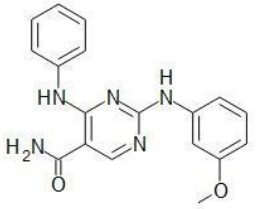
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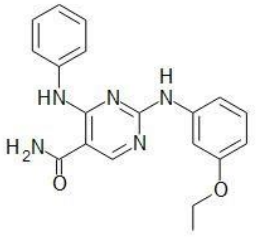
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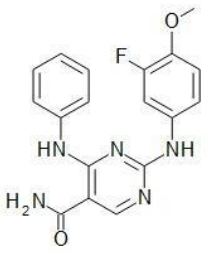
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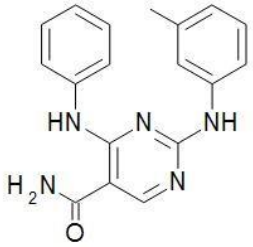
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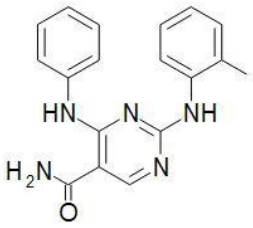
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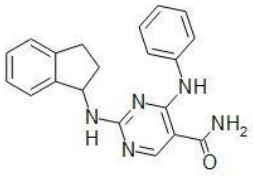
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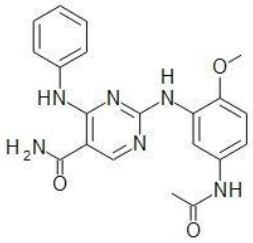
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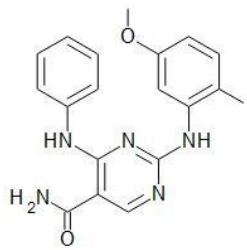
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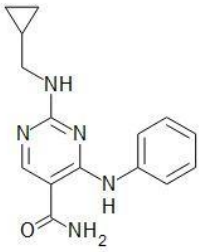
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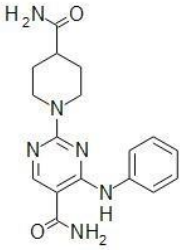
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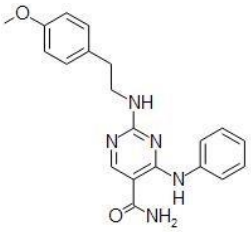
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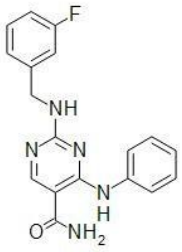
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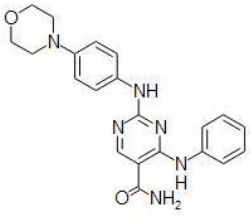
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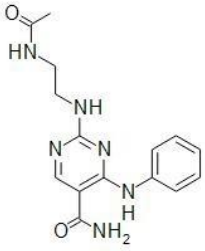
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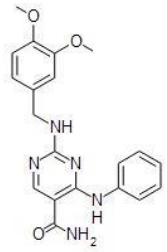
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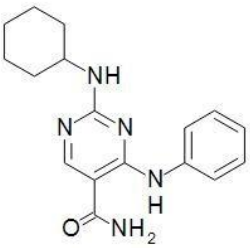
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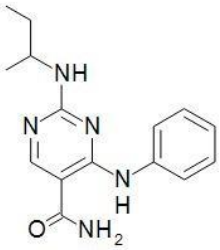
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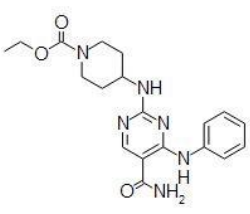
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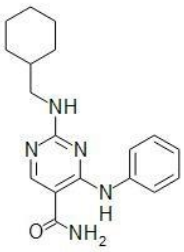
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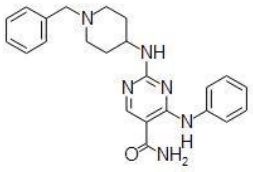
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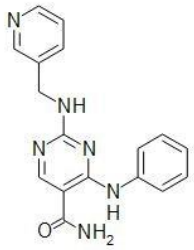
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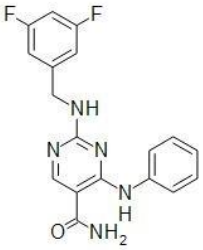
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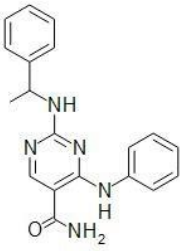
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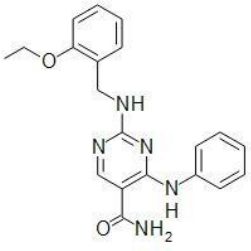
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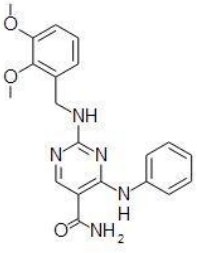
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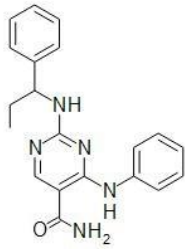
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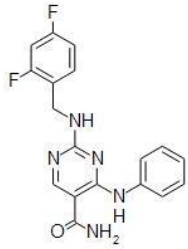
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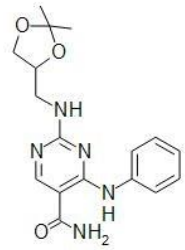
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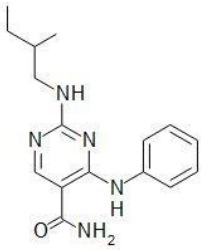
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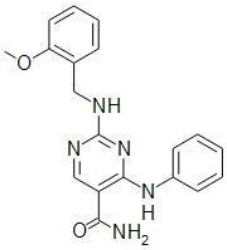
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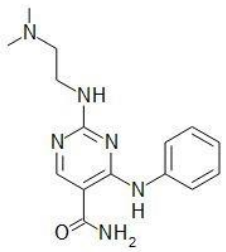
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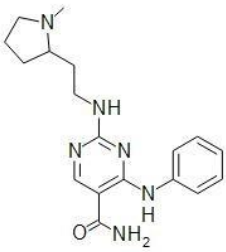
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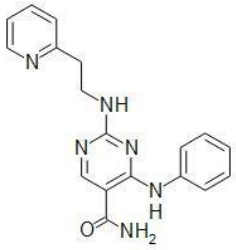
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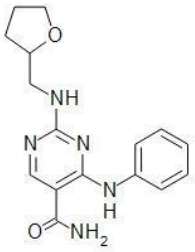
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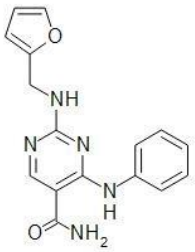
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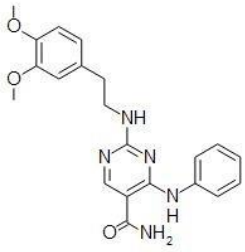
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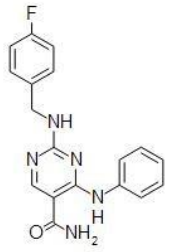
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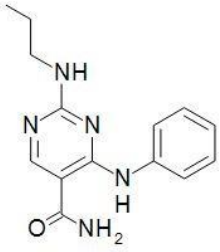
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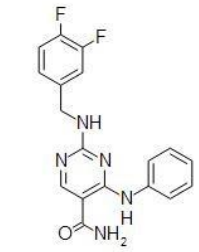
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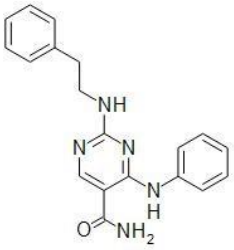
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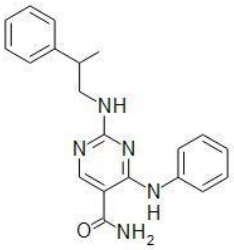
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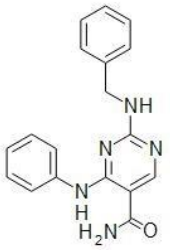
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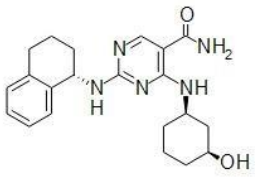
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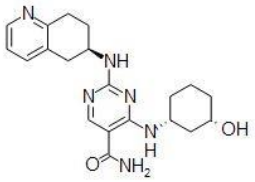
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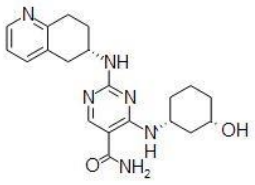
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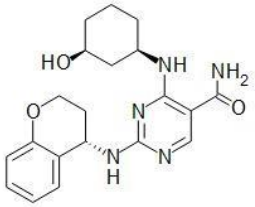
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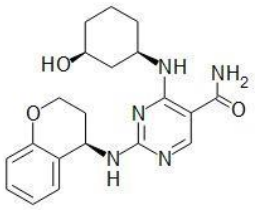
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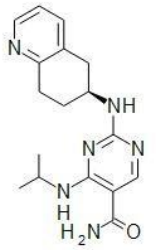
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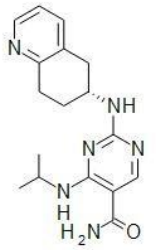
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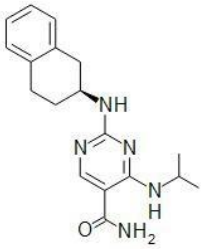
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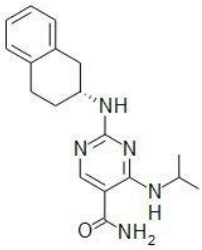
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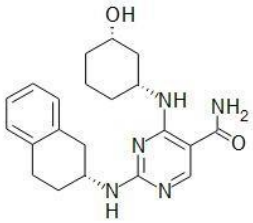
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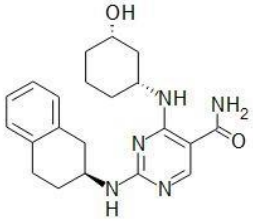
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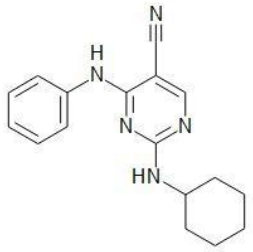
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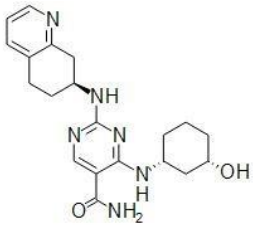
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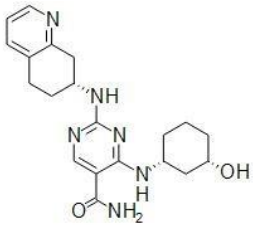
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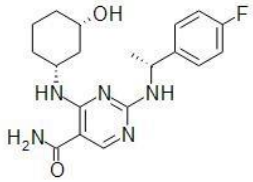
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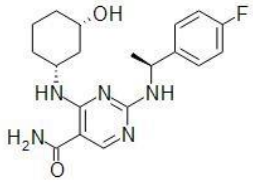
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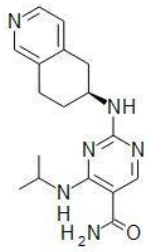
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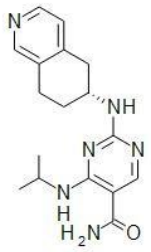
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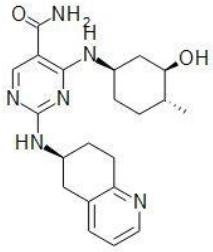
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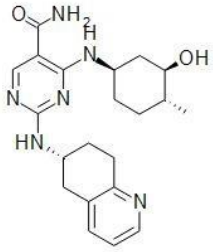
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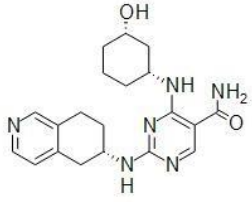
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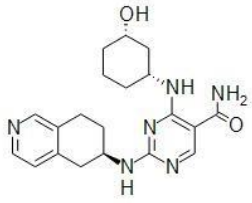
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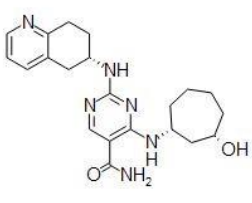
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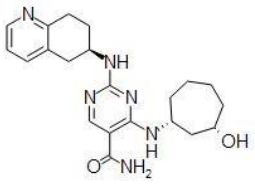

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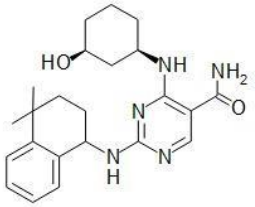

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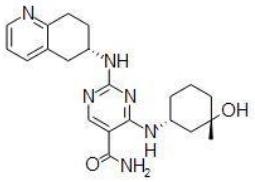

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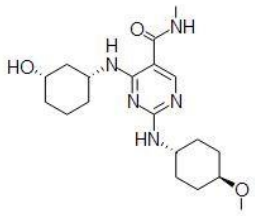

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or a pharmaceutically acceptable salt, tautomer, stereoisomer, or enantiomer thereof

[0014] In one example, provided herein are methods for inhibiting a kinase, for example JNK1, JNK2 or both, in a cell expressing said kinase, comprising contacting said cell with an effective amount of a Diaminopyrimidine Compound as described herein.

[0015] In another example provided herein are methods for preparing Diaminopyrimidine Compounds as described herein.

[0016] The present examples can be understood more fully by reference to the detailed description and examples, which are intended to exemplify non-limiting examples.

DETAILED DESCRIPTION

DEFINITIONS

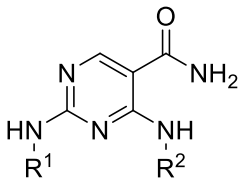
[0017] An "alkyl" group is a saturated, partially saturated, or unsaturated straight chain or branched non-cyclic hydrocarbon having from 1 to 10 carbon atoms, typically from 1 to 8 carbons or, in some embodiments, from 1 to 6, 1 to 4, or 2 to 6 or carbon atoms. Representative alkyl groups include -methyl, -ethyl, -n-propyl, -n-butyl, -n-pentyl and -n-hexyl; while saturated branched alkyls include -isopropyl, -sec-butyl, -isobutyl,

-*tert*-butyl, -isopentyl, -neopentyl, tert-pentyl, -2-methylpentyl, -3-methylpentyl, -4-methylpentyl, -2,3-dimethylbutyl and the like. Examples of unsaturated alkyl groups include, but are not limited to, vinyl, allyl, -CH=CH(CH_3), -CH=C(CH_3)$_2$, -C(CH_3)=CH_2, -C(CH_3)=CH(CH_3), -C(CH_2CH_3)=CH_2, -CCH, -CC(CH_3), -CC(CH_2CH_3), -CH_2CCH, -CH_2CC(CH_3) and -CH_2CC(CH_7CH_3), among others. An alkyl group can be substituted or unsubstituted. When the alkyl groups described herein are said to be "substituted," they may be substituted with any substituent or substituents as those found in the exemplary compounds and embodiments disclosed herein, as well as halogen (chloro, iodo, bromo, or fluoro); alkyl; hydroxyl; alkoxy; alkoxyalkyl; amino; alkylamino; carboxy; nitro; cyan; thiol; thioether; imine; imide; amidine; guanidine; enamine; aminocarbonyl; acylamino; phosphonato; phosphine; thiocarbonyl; sulfonyl; sulfone

What is claimed is:

1. A use of:

(i) a compound of formula (I):



(I)

or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof,

wherein:

R^1 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted cycloalkyl, substituted or unsubstituted non-aromatic heterocyclyl, substituted or unsubstituted saturated or partially saturated alkylcycloalkyl, or substituted or unsubstituted alkylheterocyclyl, provided that R^1 is not 2-aminocyclohexyl;

R^2 is substituted or unsubstituted C_{1-8} alkyl, substituted or unsubstituted saturated C_{5-10} cycloalkyl, substituted or unsubstituted saturated or partially saturated alkylcycloalkyl, or substituted or unsubstituted non-aromatic heterocyclyl;

provided the compound is not

2-(2-aminoethylamino)-4-(methylamino)pyrimidine-5-carboxamide,
2-(2-aminopropylamino)-4-(cyclohexylamino)pyrimidine-5-carboxamide,
2-(2-amino-2-oxoethylamino)-4-(cyclohexylamino)pyrimidine-5-carboxamide,
2-(2-aminoethylamino)-4-(cyclohexylamino)pyrimidine-5-carboxamide,
or 4-(cyclopentylamino)-2-(methylamino)pyrimidine-5-carboxamide;

in the manufacture of a medicament for the treatment or prevention of interstitial pulmonary fibrosis; chronic allograft nephropathy; antibody mediated rejection; cystic fibrosis; mucous colitis; Huntington's disease; pancreatitis; nephritis; lupus erythematosus; Type II diabetes; obesity; left ventricular hypertrophy; ischemic damages of heart, lung, gut, kidney, liver, pancreas, spleen or brain; preservation of the organ for transplantation; graft versus host disease; endotoxin shock; burn from exposure to fire, chemicals or radiation; eczema; skin graft; epilepsy; Alzheimer's disease; Parkinson's disease; or immunological response to bacterial or viral infection.

2. The use of claim 1, wherein the compound of formula (I) is that wherein R^1 is a branched C_{3-8} alkyl.

3. The use of claim 1, wherein the compound of formula (I) is that wherein R^1 is a substituted or unsubstituted cycloalkyl.

4. The use of claim 1, wherein the compound of formula (I) is that wherein R^1 is a substituted or unsubstituted non-aromatic heterocyclyl.

5. The use of claim 1, wherein the compound of formula (I) is that wherein R^1 is a substituted or unsubstituted saturated or partially saturated alkylcycloalkyl.

6. The use of claim 1, wherein the compound of formula (I) is that wherein R^1 is a substituted or unsubstituted alkylheterocyclyl.

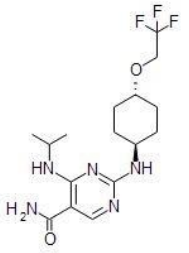
7. The use of claim 1, wherein the compound of formula (I) is that wherein R^2 is a substituted or unsubstituted C_{1-8} alkyl.

8. The use of claim 1, wherein the compound of formula (I) is that wherein R^2 is a substituted or unsubstituted C_{5-10} cycloalkyl.

9. The use of claim 1, wherein the compound of formula (I) is that wherein R^2 is a substituted or unsubstituted saturated or partially saturated alkylcycloalkyl.

10. The use of claim 1, wherein the compound of formula (I) is that wherein R^2 is a substituted or unsubstituted non-aromatic heterocyclyl.

11. Use of a compound in the manufacture of a medicament for the treatment or prevention of interstitial pulmonary fibrosis; chronic allograft nephropathy; antibody mediated rejection; cystic fibrosis; mucous colitis; Huntington's disease; pancreatitis; nephritis; lupus erythematosus; Type II diabetes; obesity; left ventricular hypertrophy; ischemic damages of heart, lung, gut, kidney, liver, pancreas, spleen or brain; preservation of the organ for transplantation; graft versus host disease; endotoxin shock; ~~psoriasis;~~ burn from exposure to fire, chemicals or radiation; eczema; skin graft; epilepsy; Alzheimer's disease; Parkinson's disease; or immunological response to bacterial or viral infection; wherein the compound of formula (I) is: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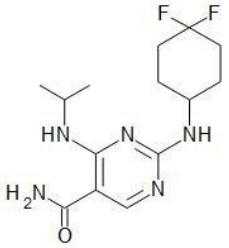
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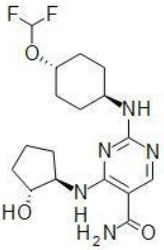
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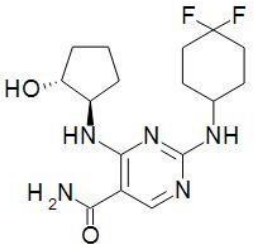
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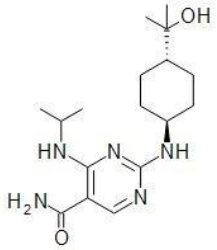
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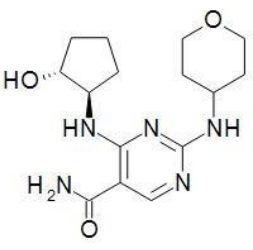
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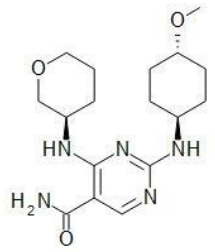
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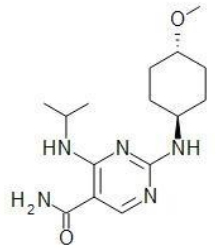
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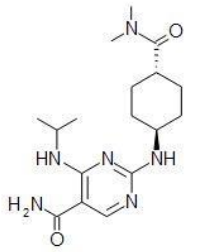
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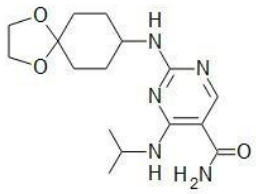
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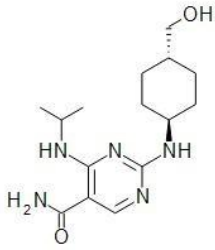
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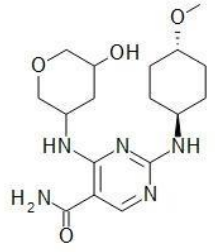
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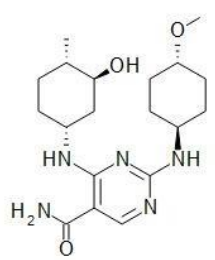
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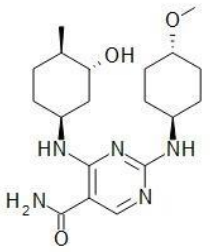
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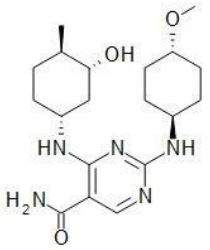
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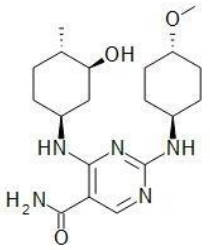
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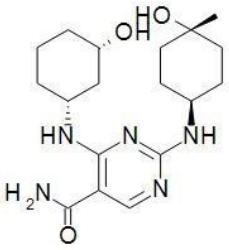
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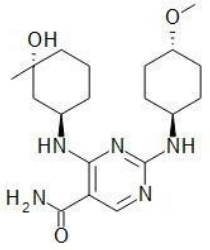
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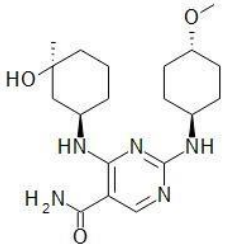
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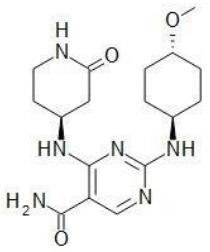
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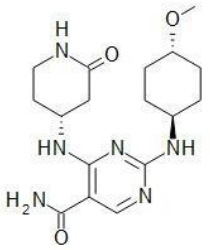
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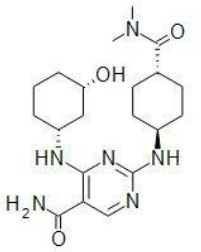
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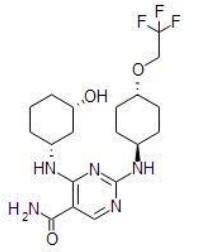
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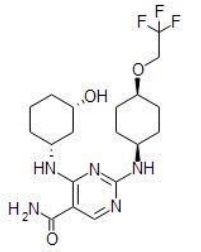
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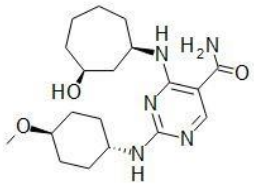
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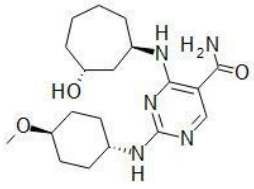
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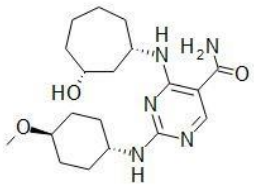
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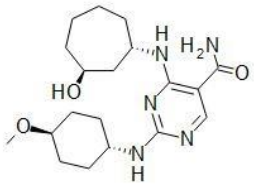
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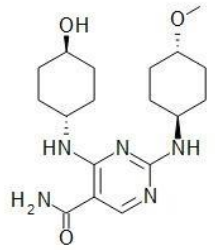
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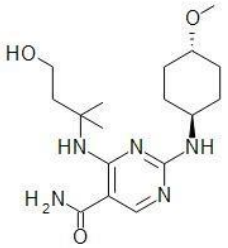
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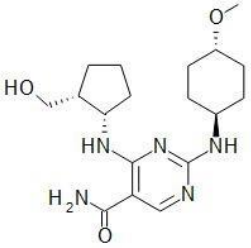
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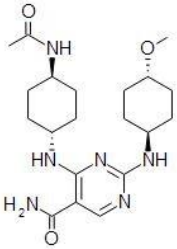
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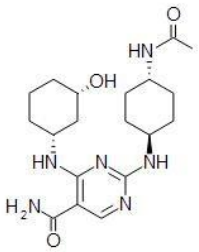
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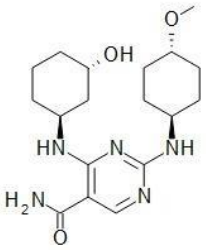
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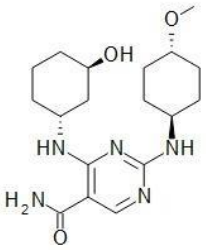
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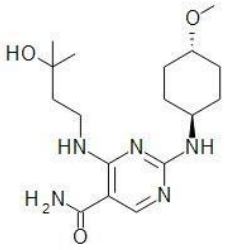
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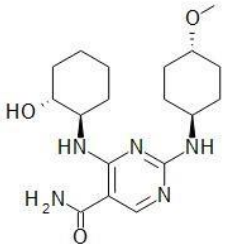
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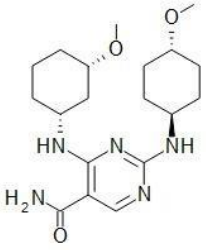
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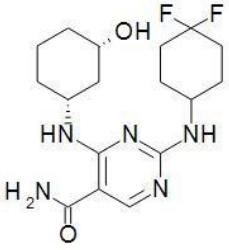
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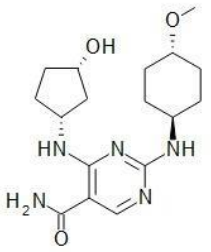
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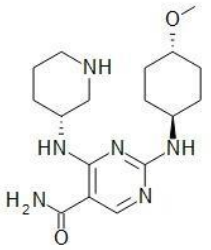
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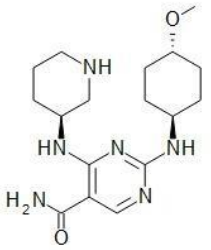
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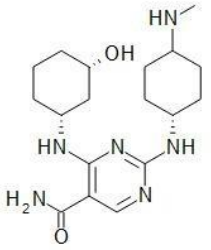
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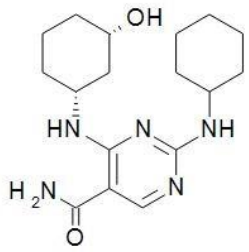
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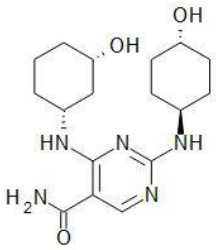
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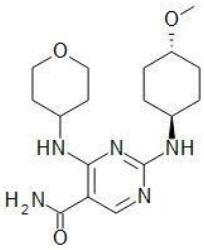
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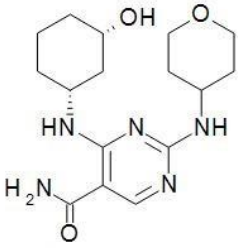
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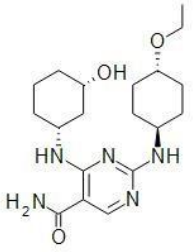
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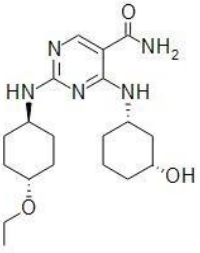
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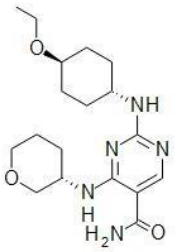
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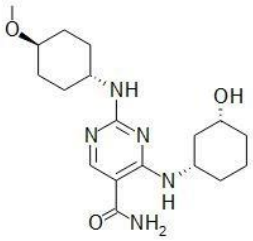
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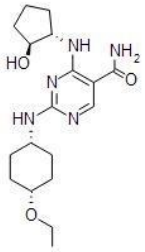
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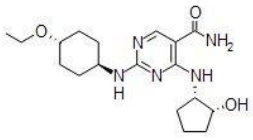
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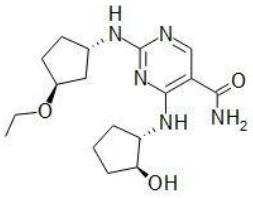
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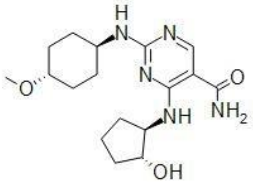
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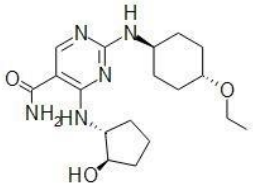
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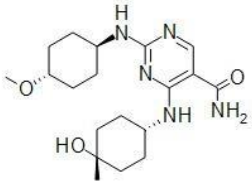

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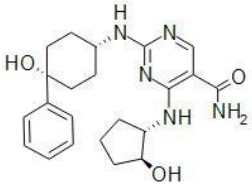

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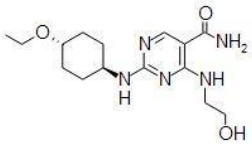

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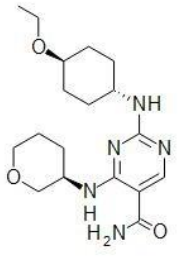

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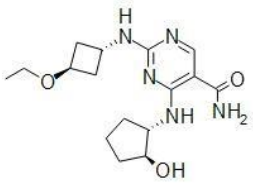

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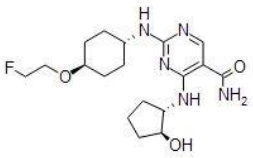

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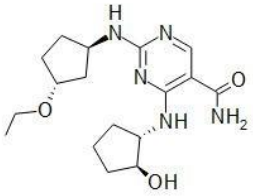

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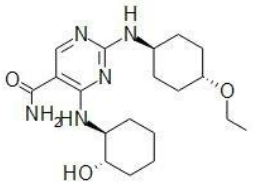

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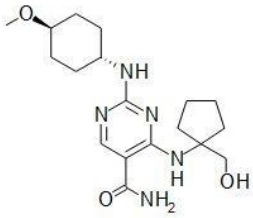

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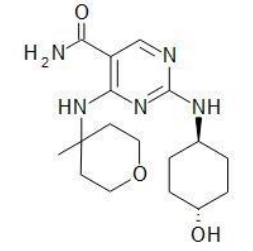

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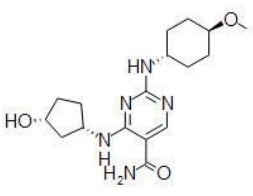

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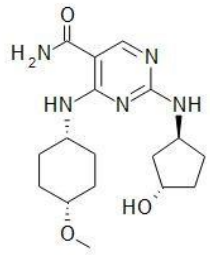
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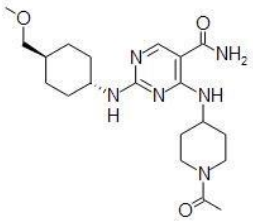
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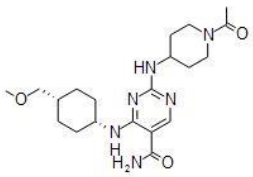
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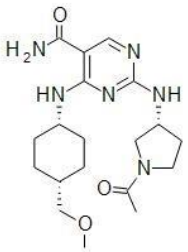
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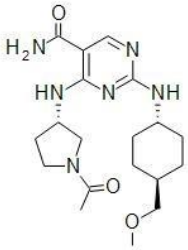
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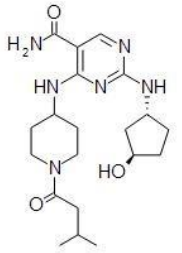
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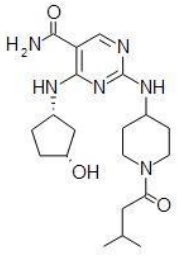
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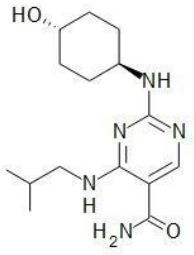
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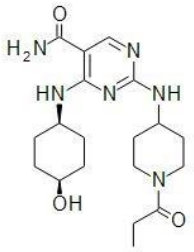
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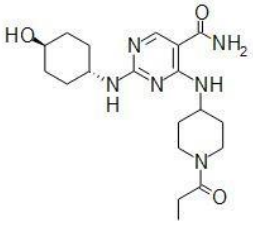
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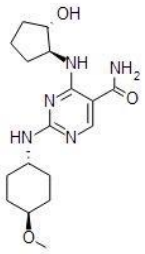
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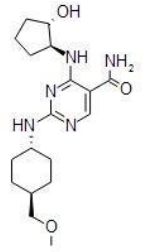
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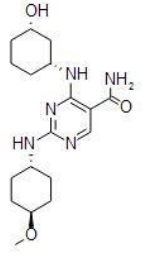
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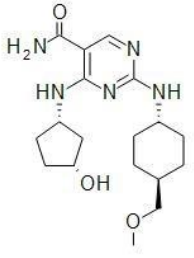
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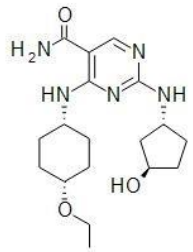
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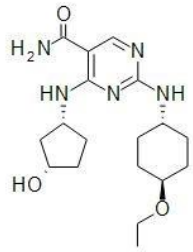
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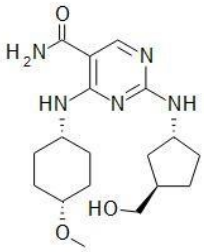
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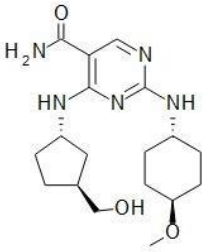
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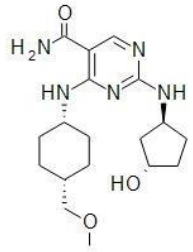
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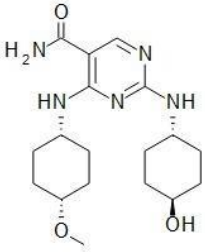
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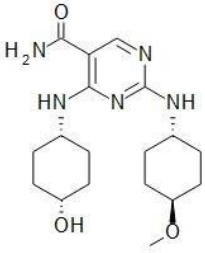
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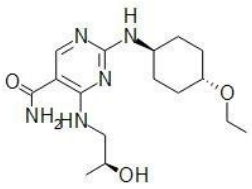
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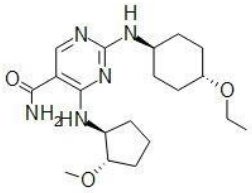
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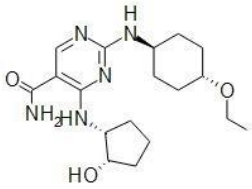
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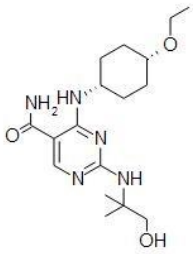
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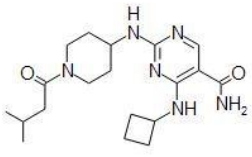
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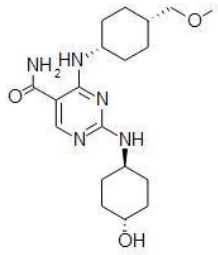
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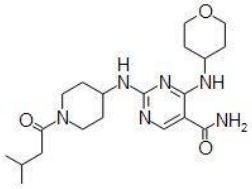
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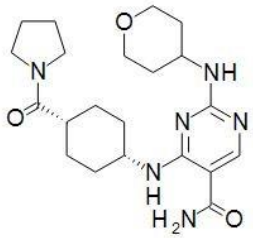
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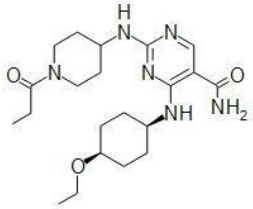
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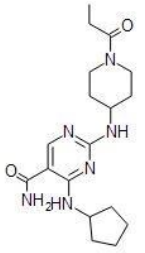
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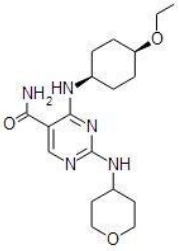
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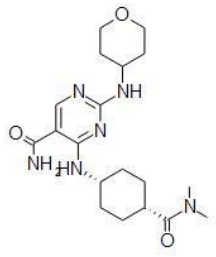
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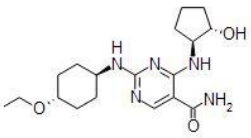
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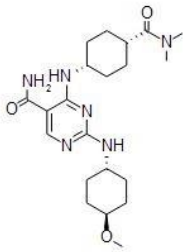
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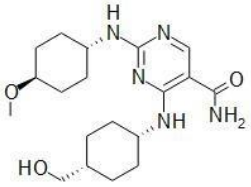
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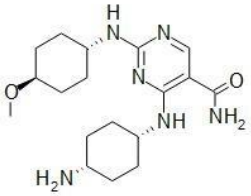
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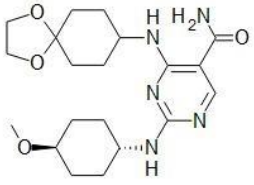
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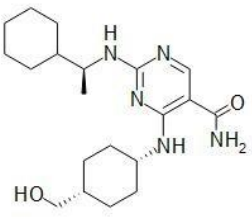
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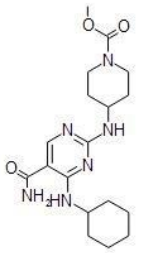
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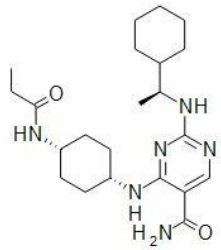
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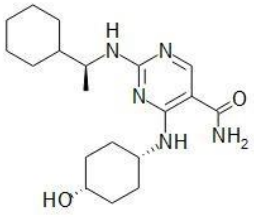
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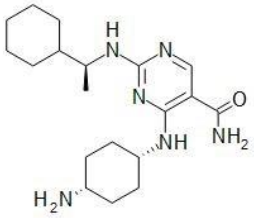
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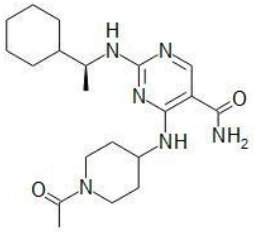
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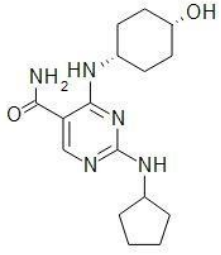
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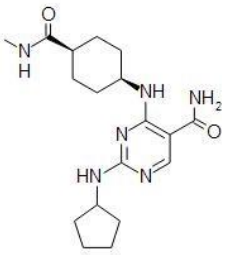
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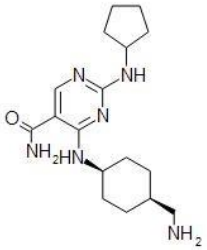
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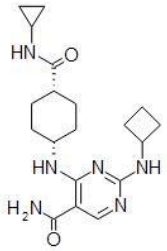
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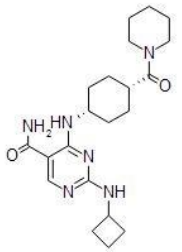
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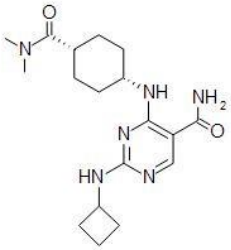
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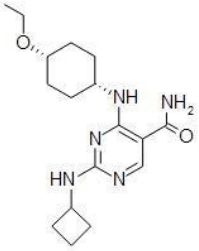
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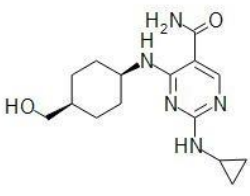
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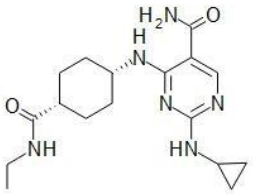
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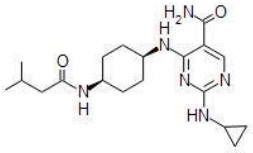
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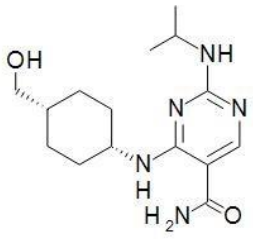
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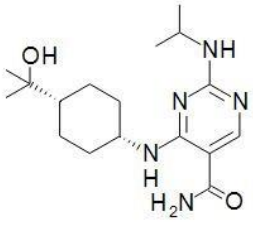
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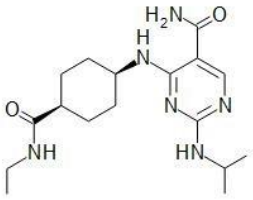
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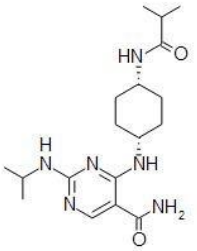
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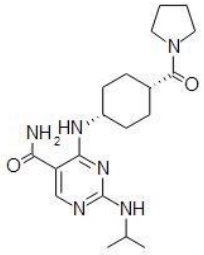
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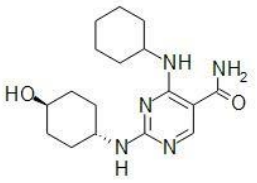
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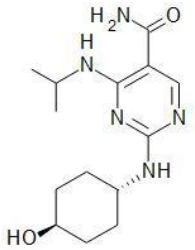
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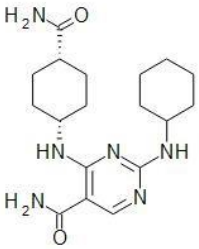
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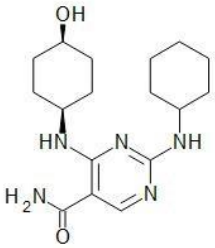
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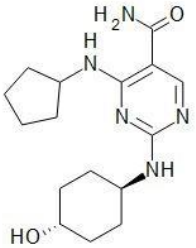
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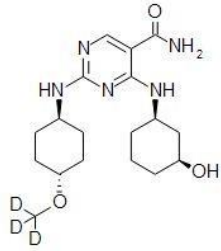
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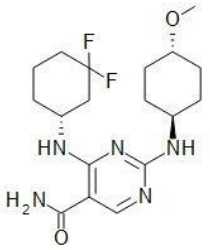
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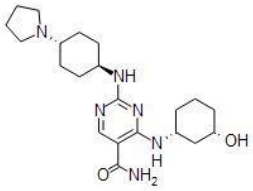
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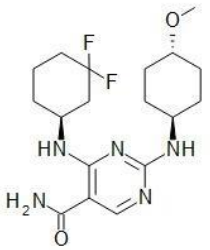
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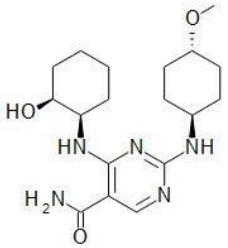
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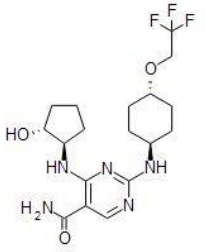
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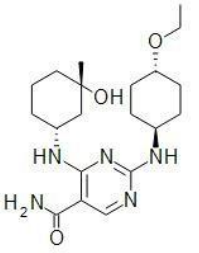
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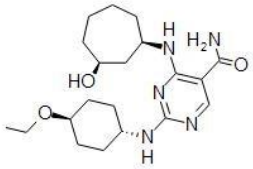
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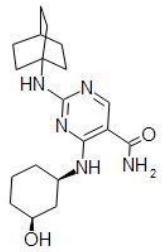
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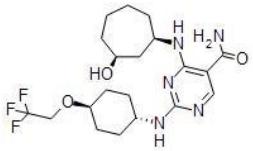
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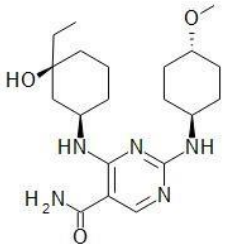
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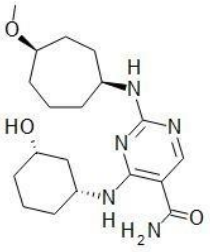
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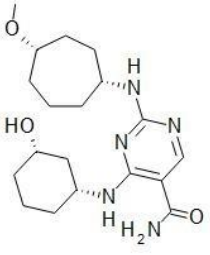
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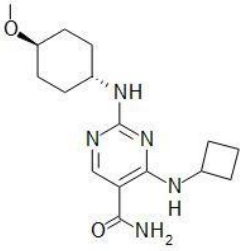
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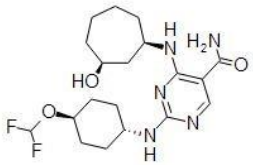

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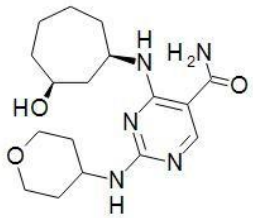

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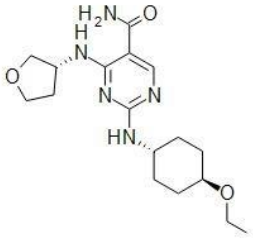

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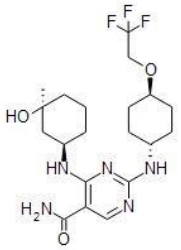

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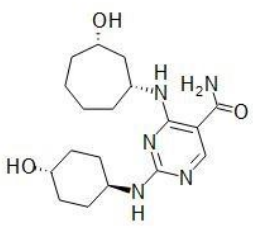

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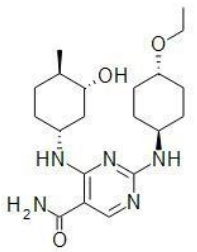
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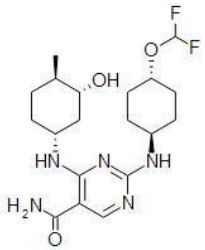
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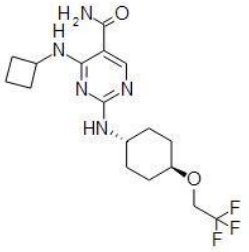
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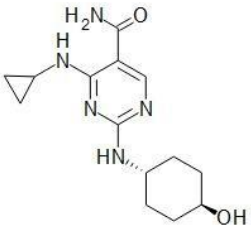
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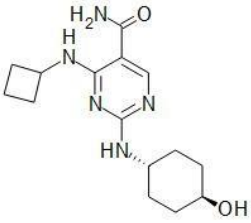
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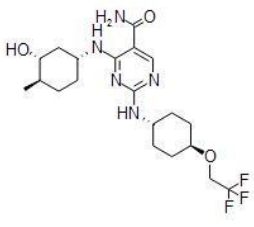
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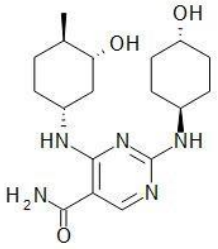
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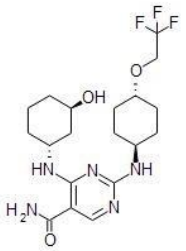
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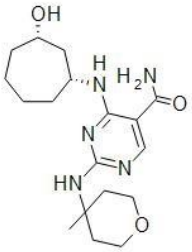
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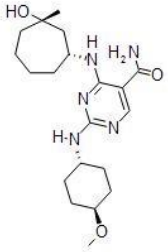
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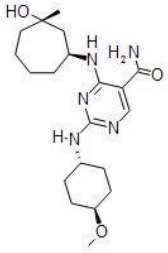
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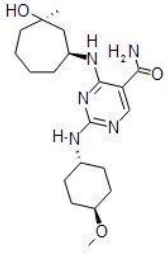
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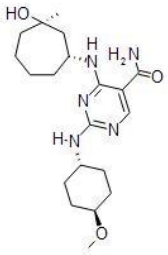
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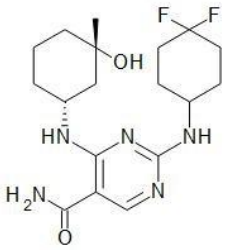
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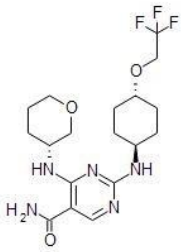
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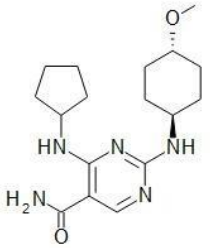
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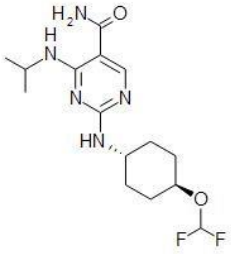
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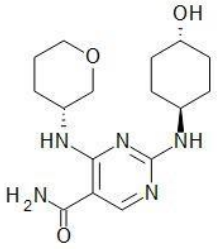
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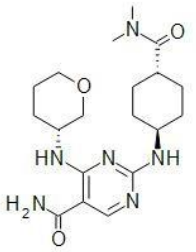
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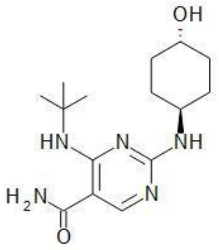
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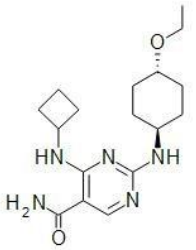
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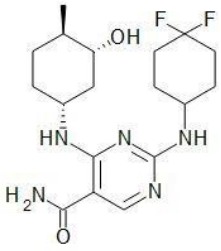
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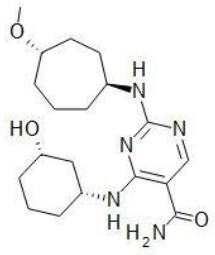
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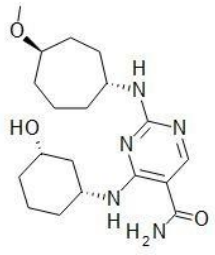
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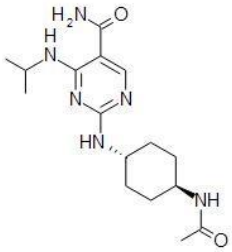
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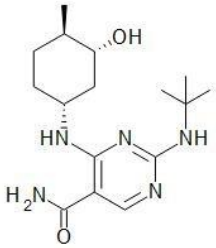
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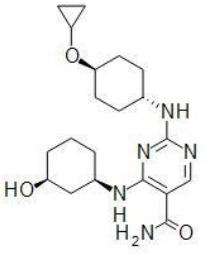
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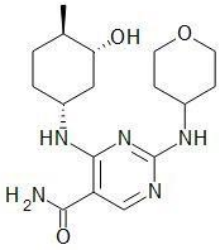
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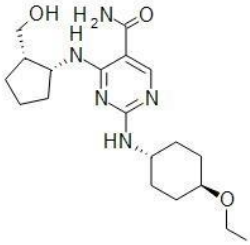
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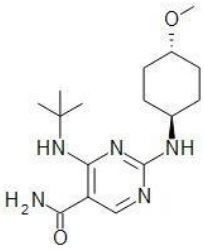
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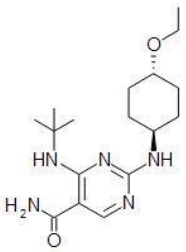
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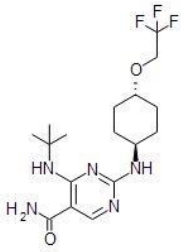
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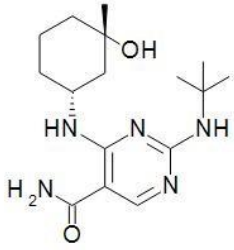
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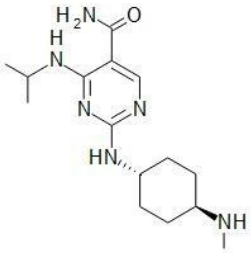
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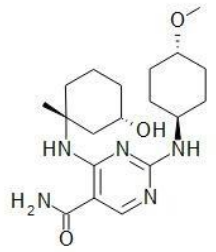
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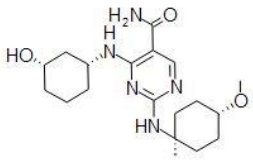
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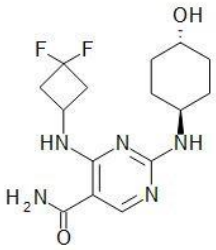
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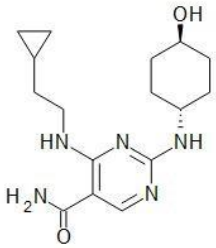
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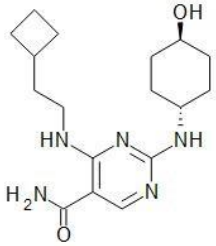
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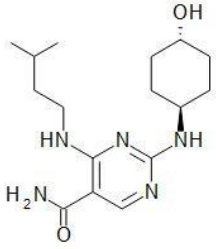
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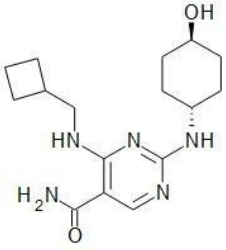
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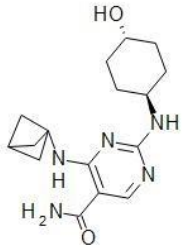
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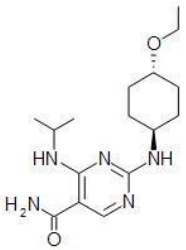
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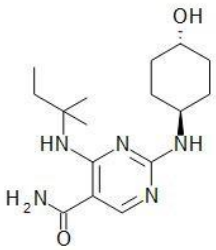
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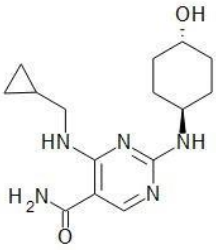
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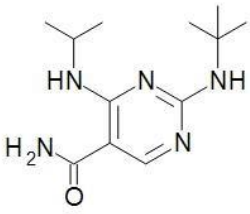
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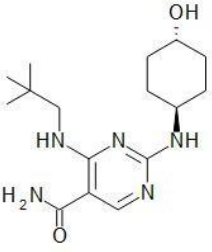
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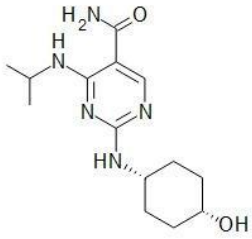
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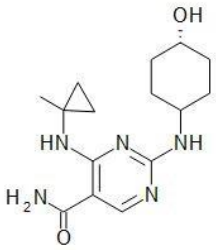
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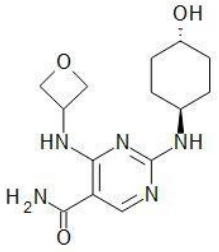
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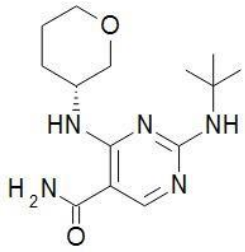
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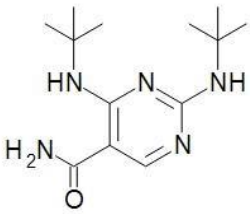
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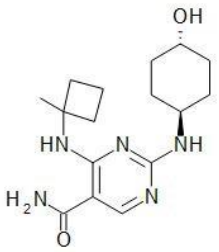
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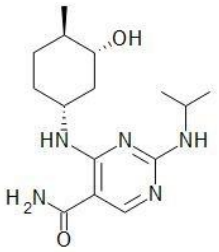
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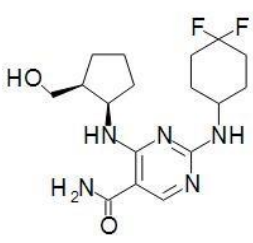
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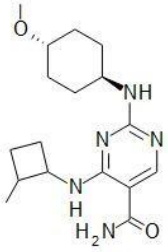
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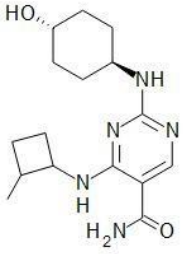
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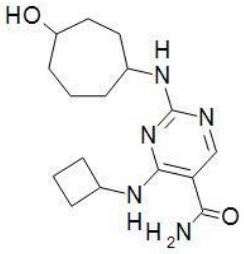
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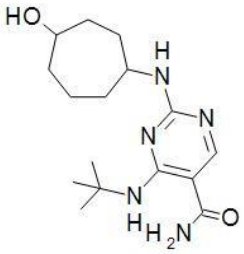
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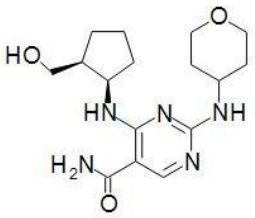
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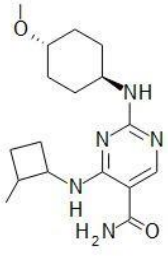
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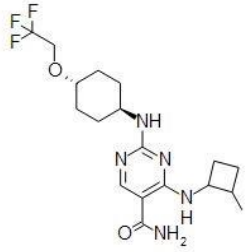
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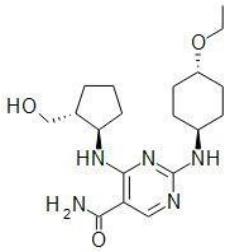
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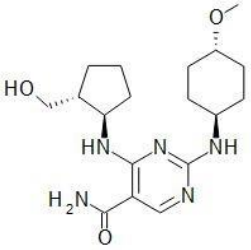
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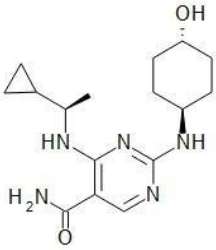
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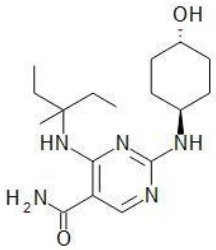
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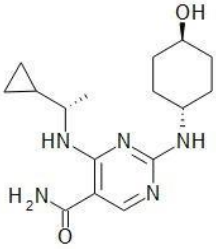
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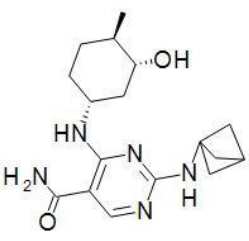
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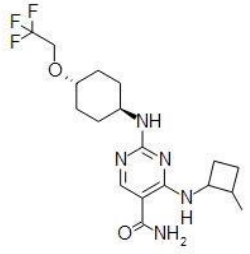
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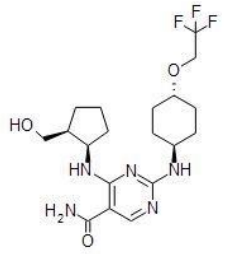
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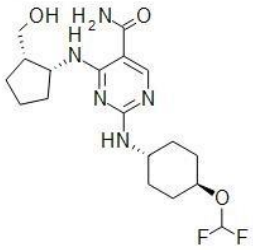
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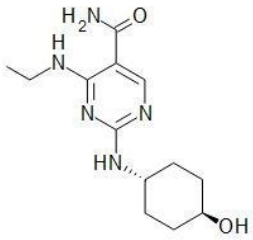
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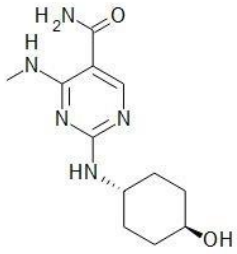
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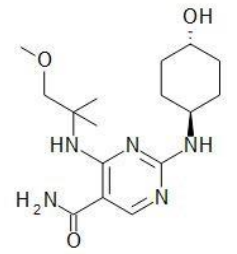
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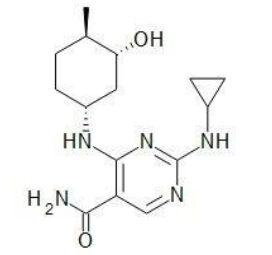
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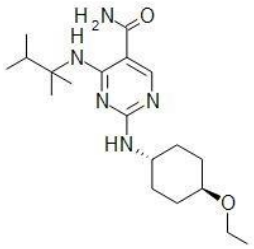
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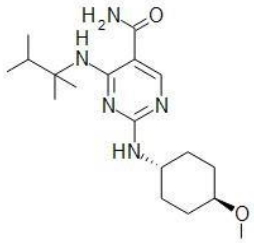
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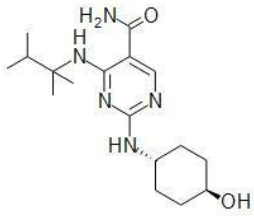
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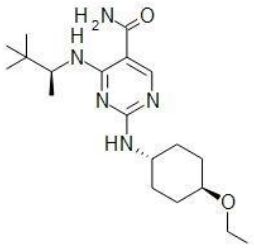
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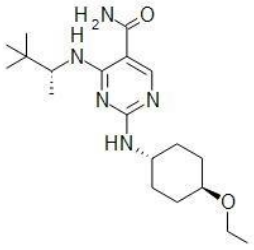
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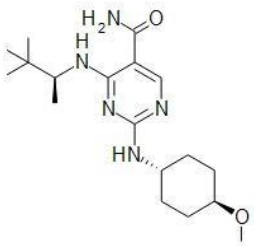
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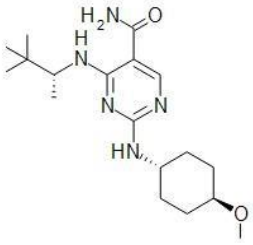
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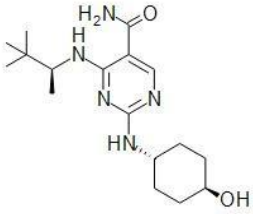
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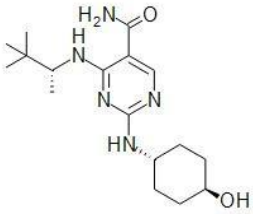
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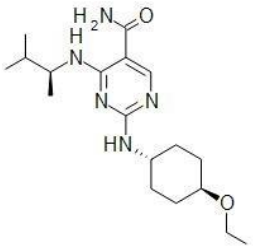
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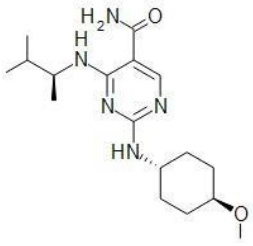
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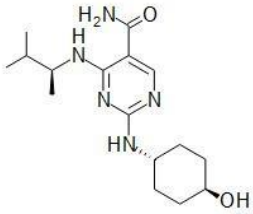
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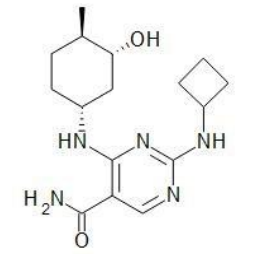
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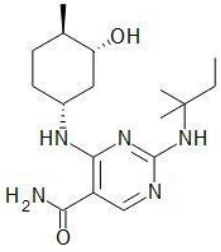
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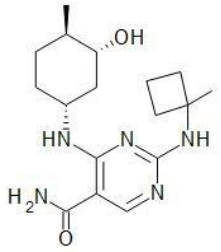
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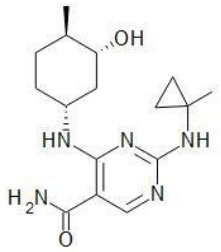
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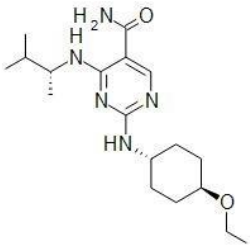
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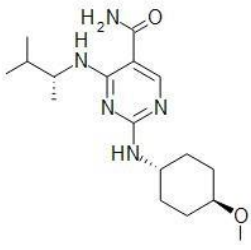
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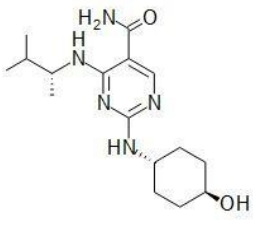
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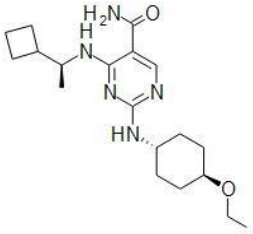
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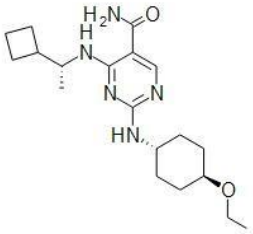
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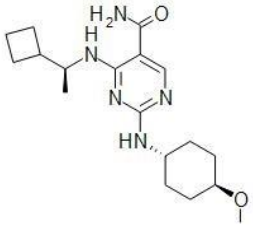
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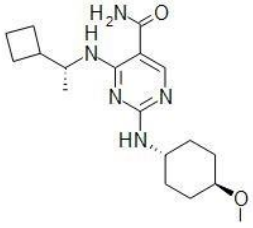
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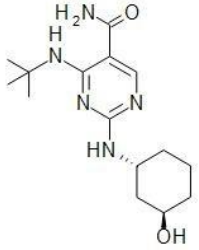
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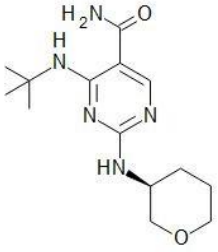
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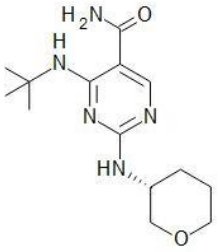
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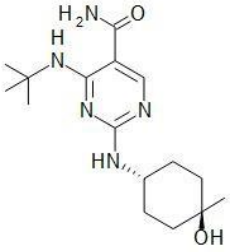
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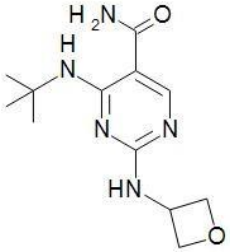
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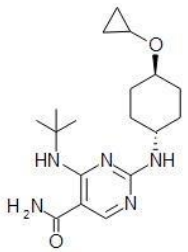
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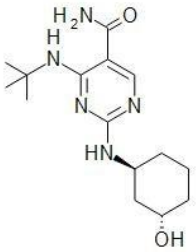
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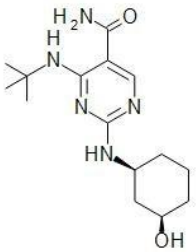
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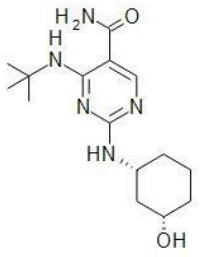
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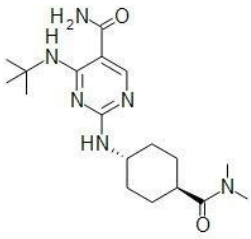
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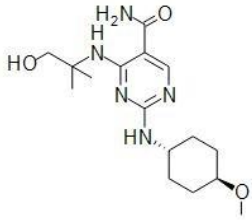
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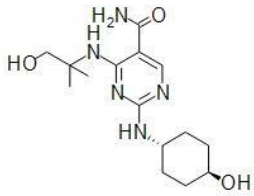
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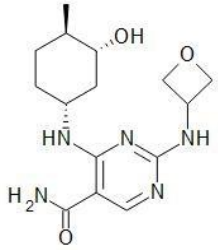
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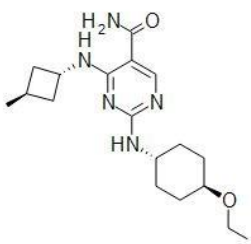
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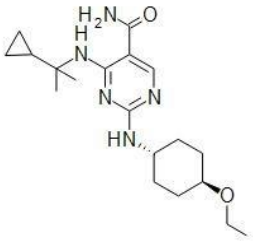
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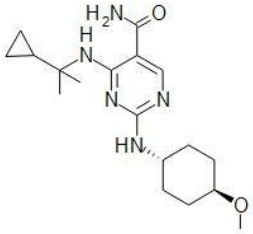
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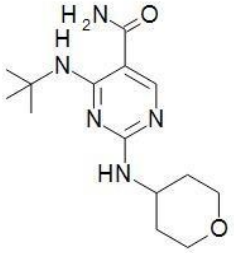
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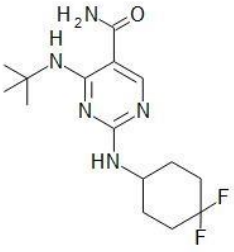
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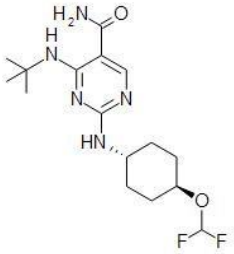
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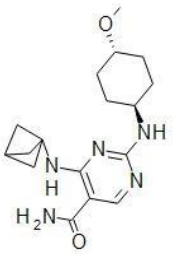
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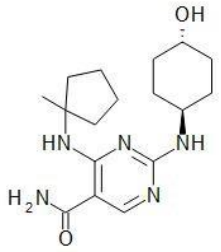
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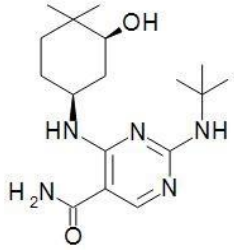
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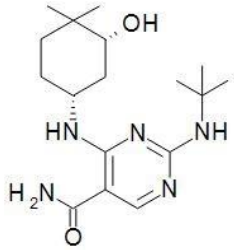
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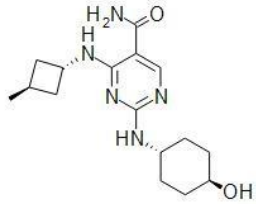
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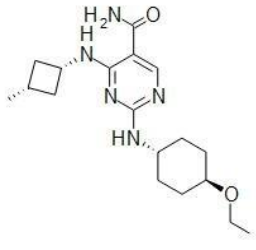
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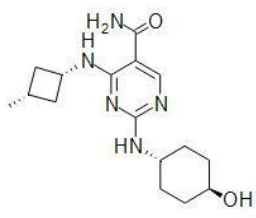
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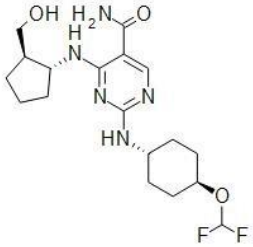
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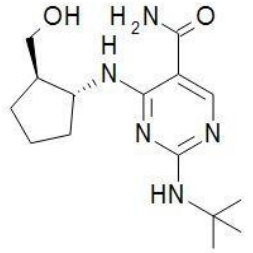
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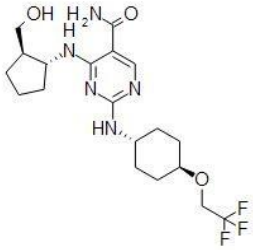
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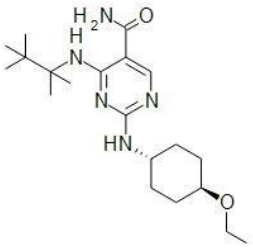
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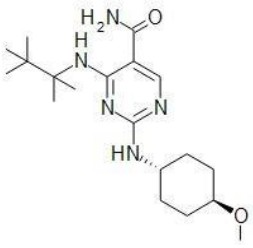
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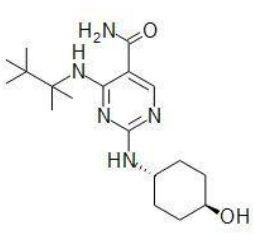
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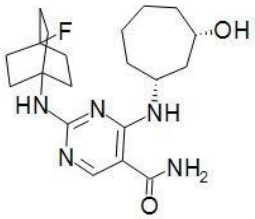
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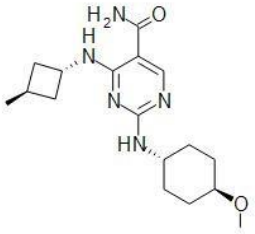
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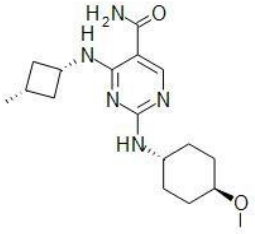
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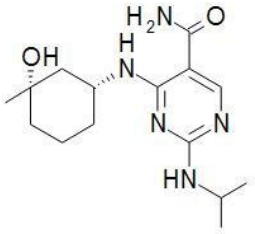
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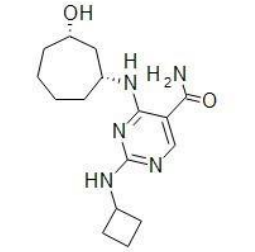
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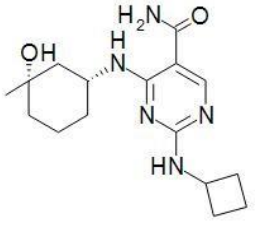
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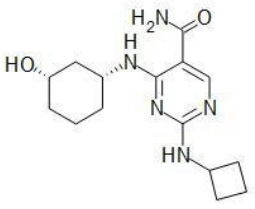
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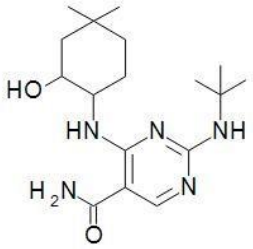
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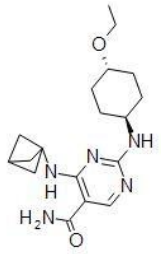
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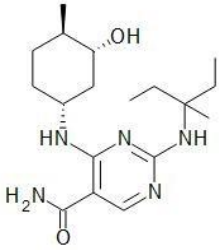
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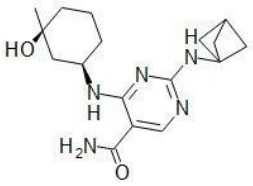
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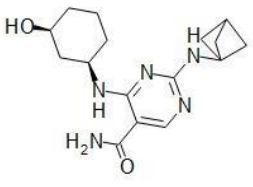
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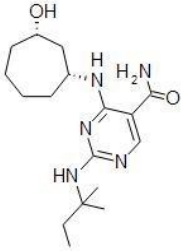
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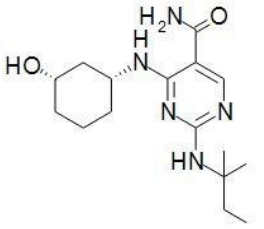
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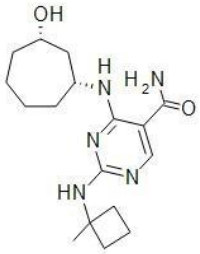
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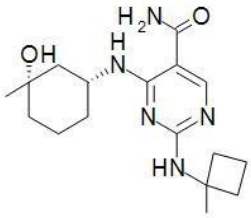
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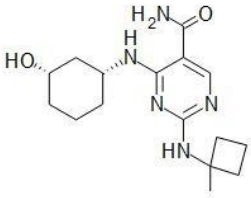
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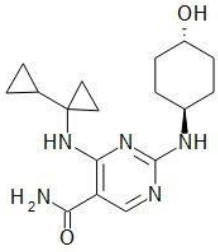
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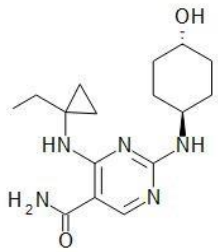
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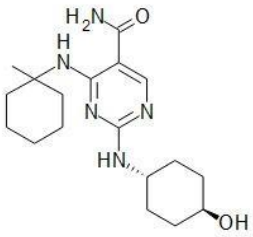
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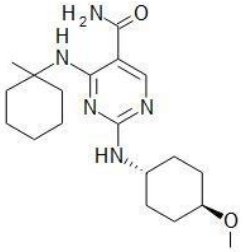
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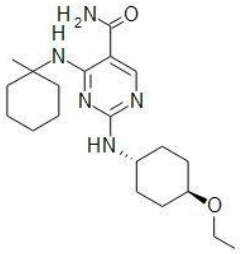
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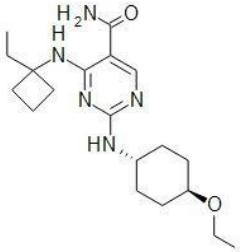
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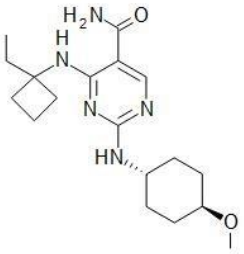
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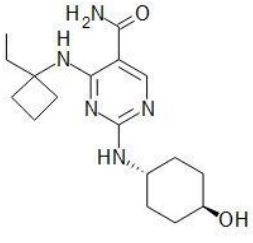
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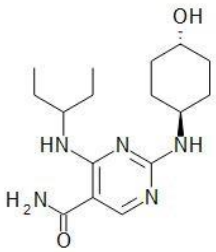
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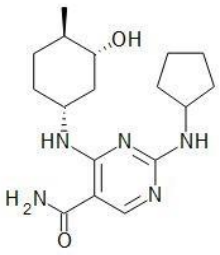
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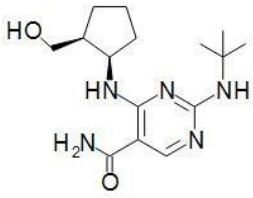
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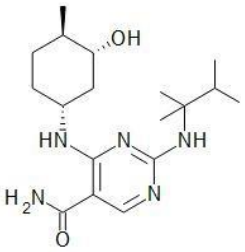
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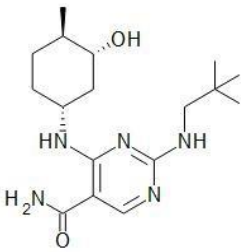
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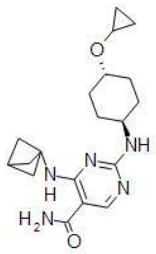
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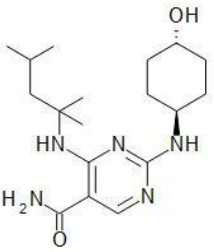
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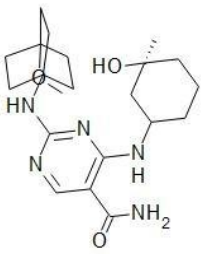
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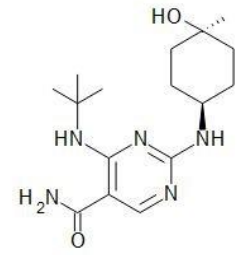
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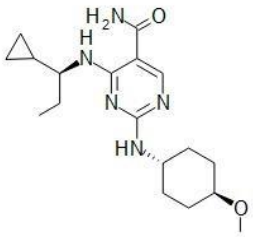
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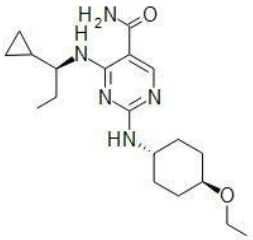
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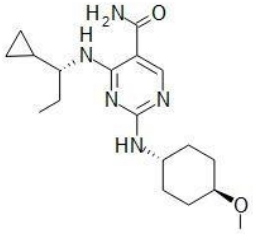
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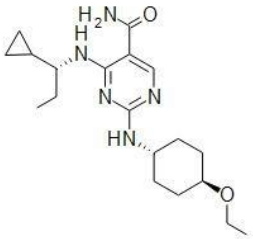
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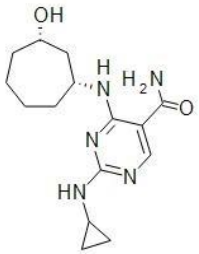
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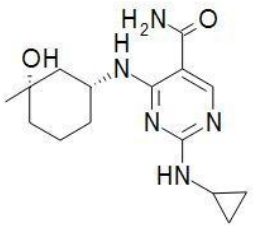
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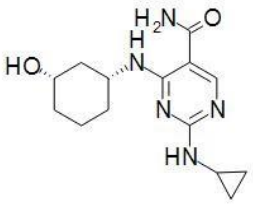
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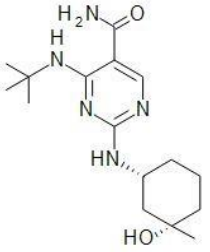
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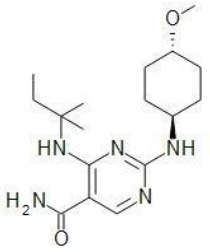
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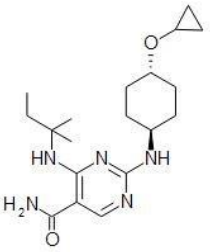
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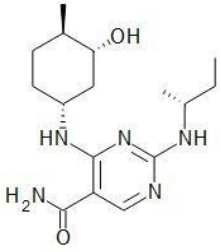
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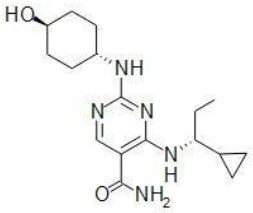
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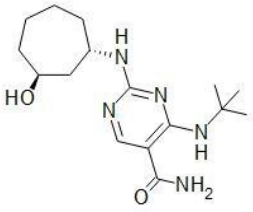
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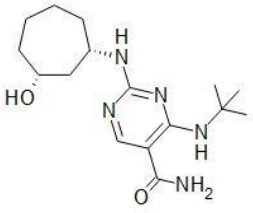
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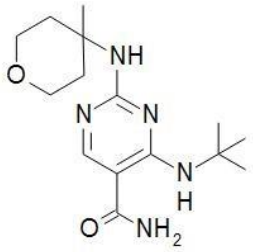
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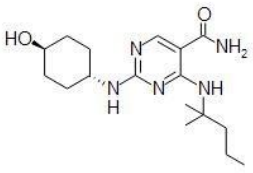
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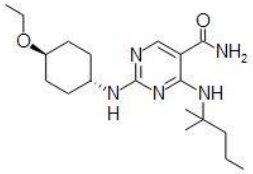
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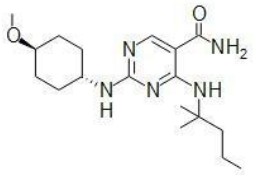
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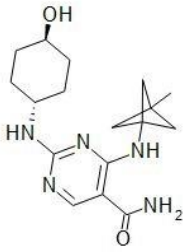
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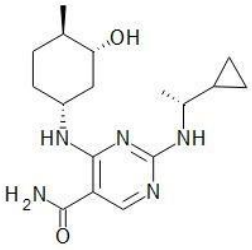
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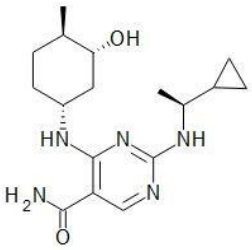
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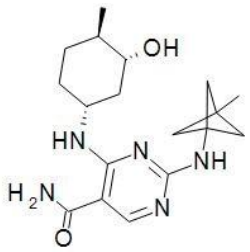
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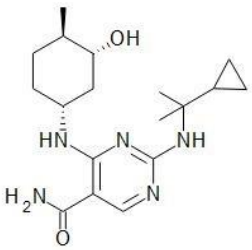
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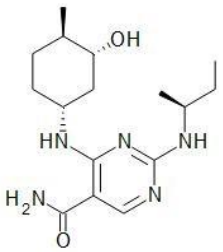
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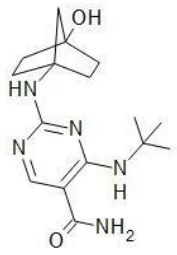
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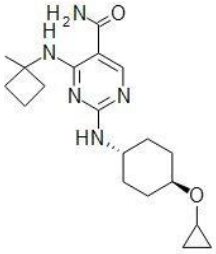
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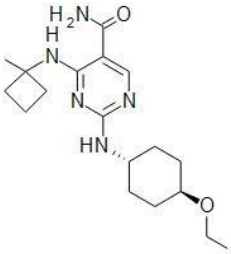
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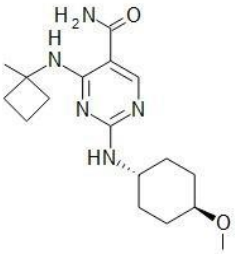
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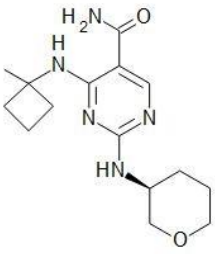
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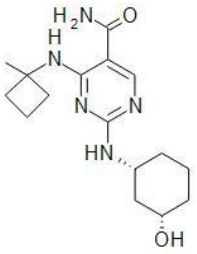
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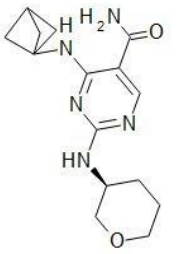
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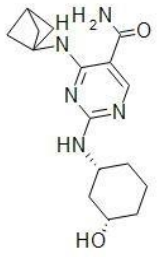
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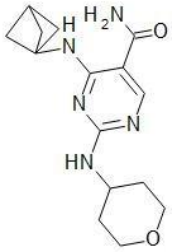
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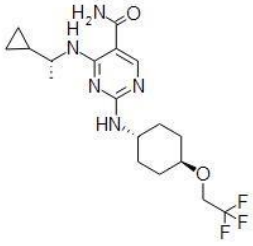
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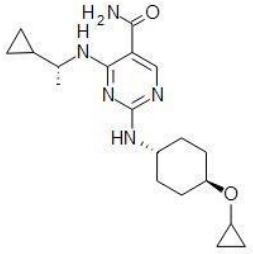
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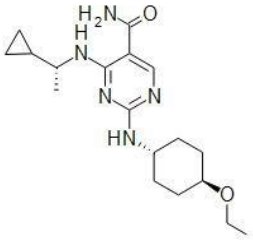
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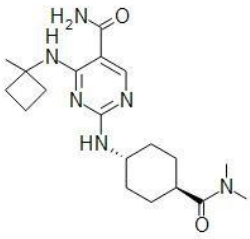
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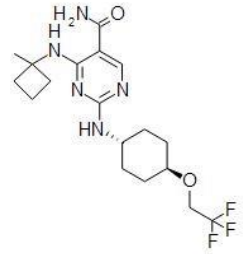
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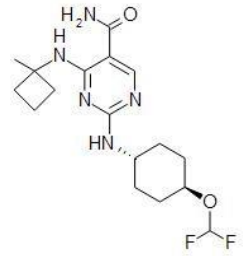
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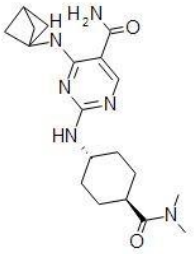
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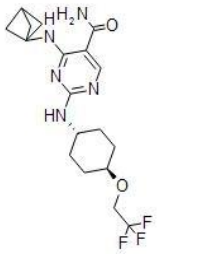
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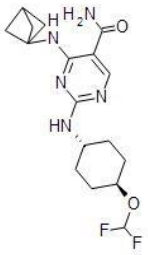
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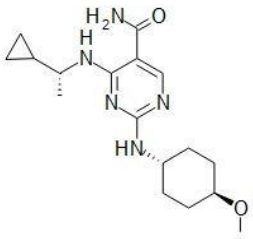
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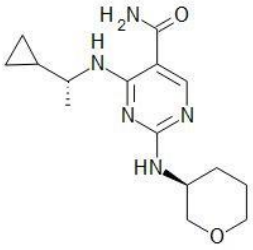
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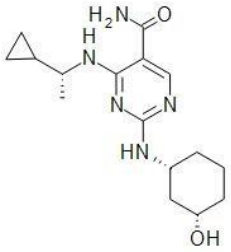
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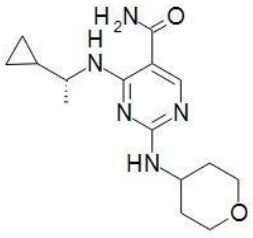
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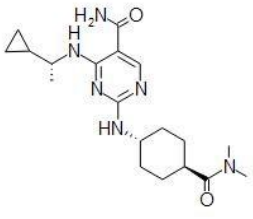
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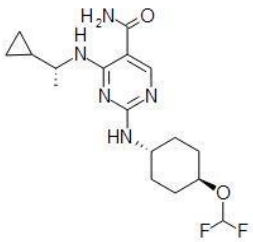
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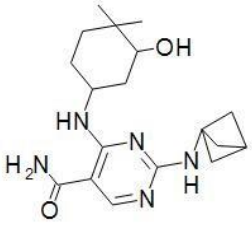
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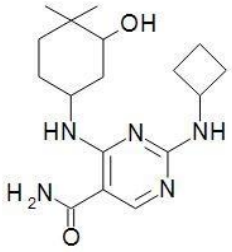
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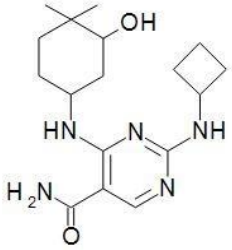
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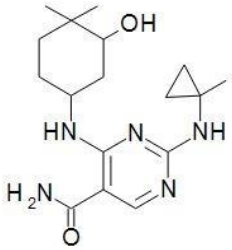
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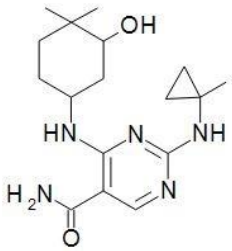
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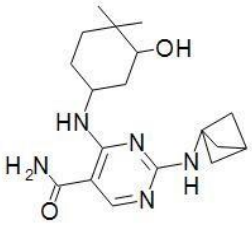
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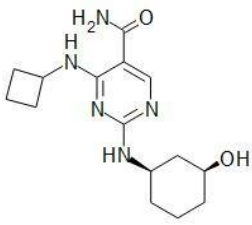
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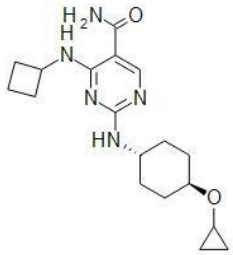
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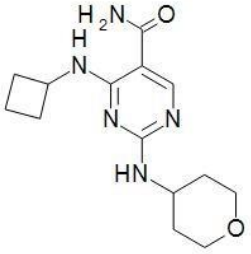
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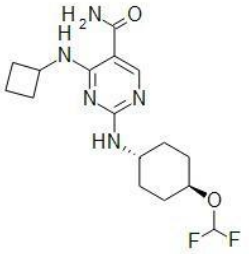
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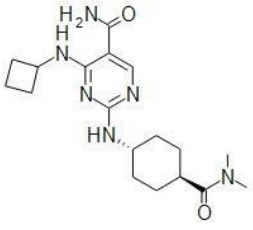
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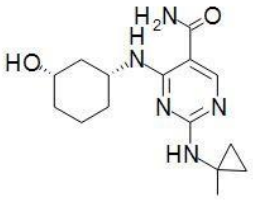
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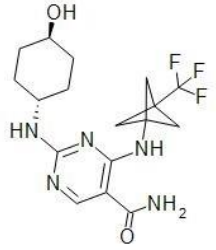
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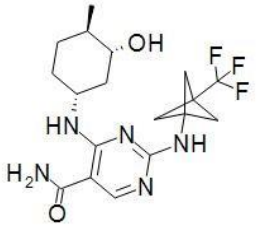
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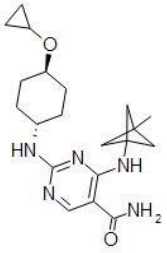
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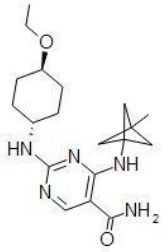
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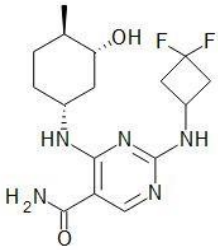
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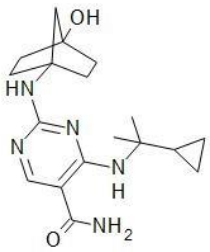
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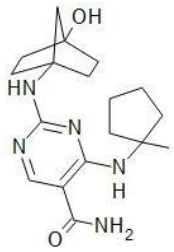
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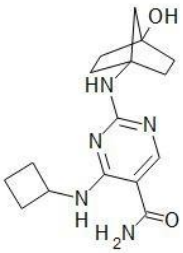
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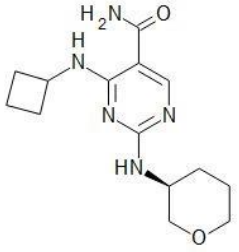
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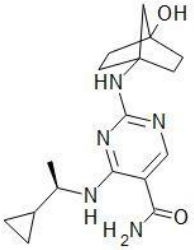
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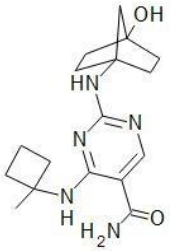
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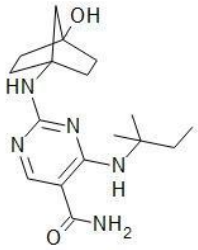
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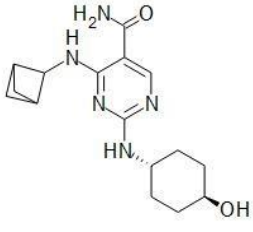
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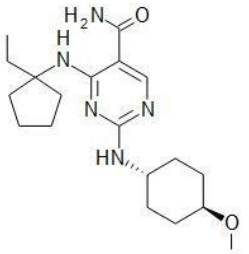
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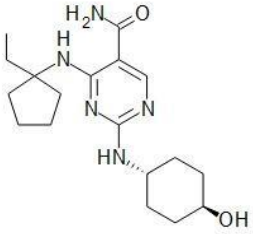
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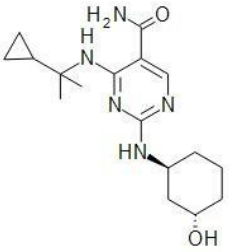
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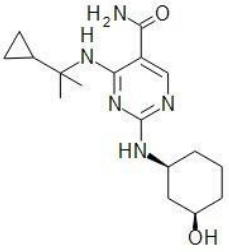
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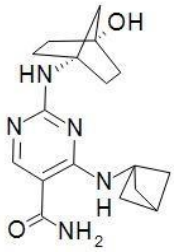
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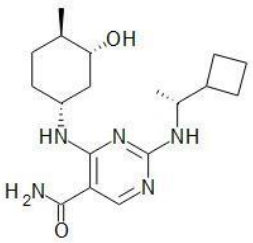
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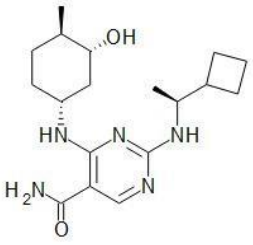
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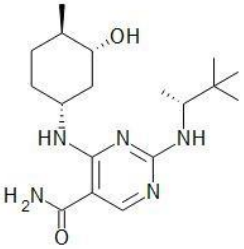
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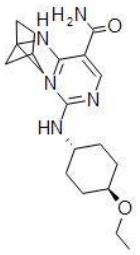
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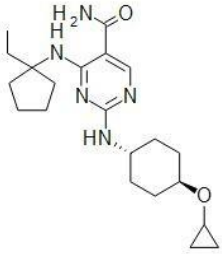
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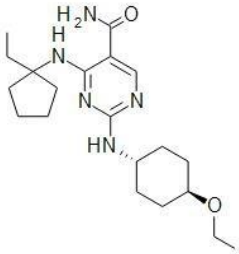
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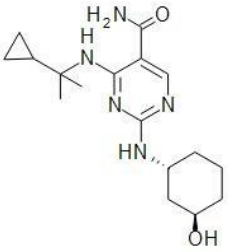
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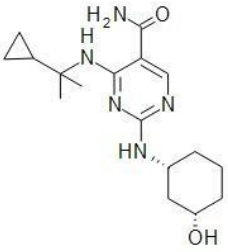
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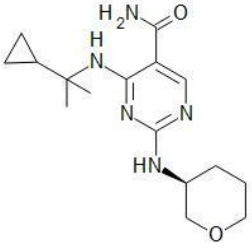
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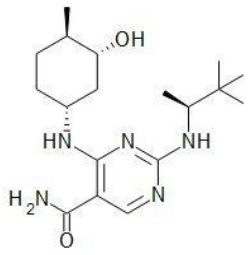
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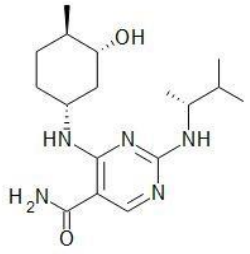
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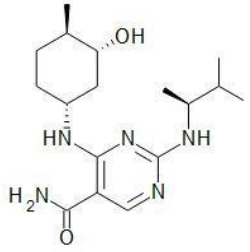
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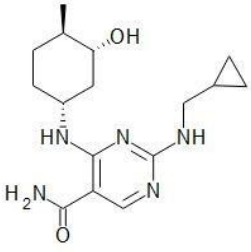
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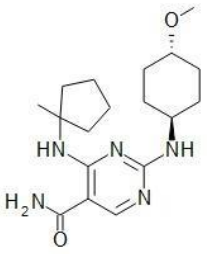
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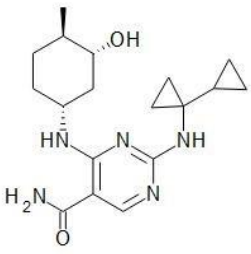
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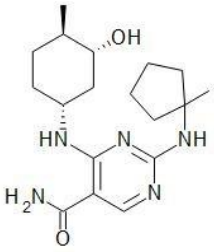
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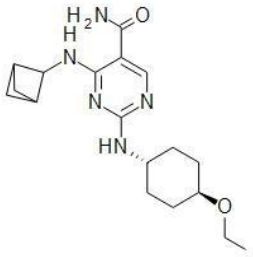
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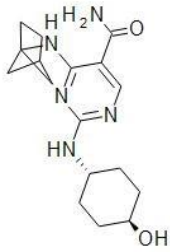
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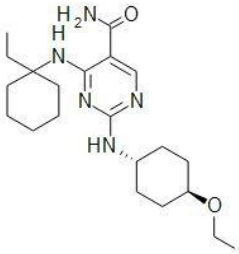
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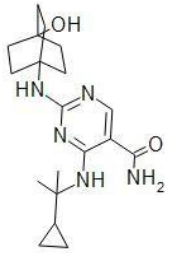
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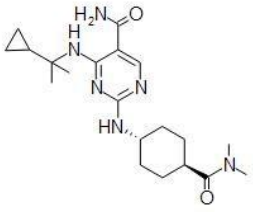
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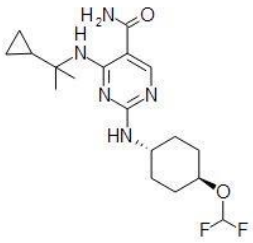
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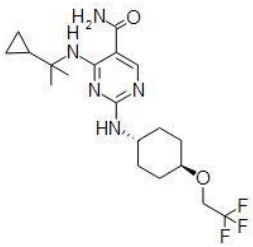
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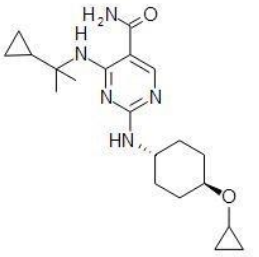
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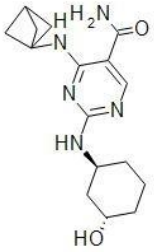
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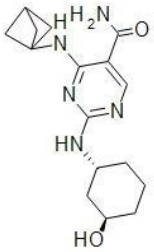
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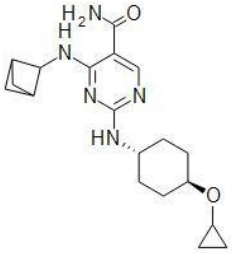
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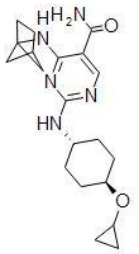
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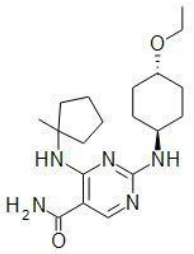
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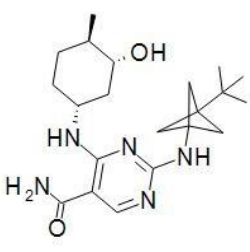
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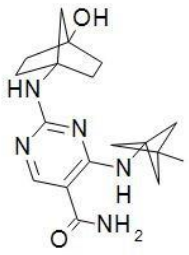
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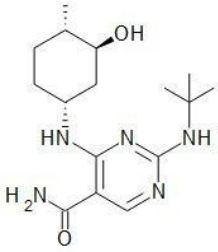
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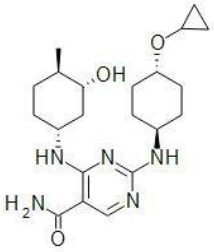
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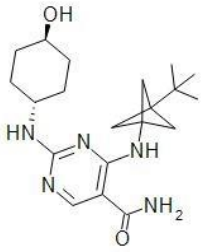
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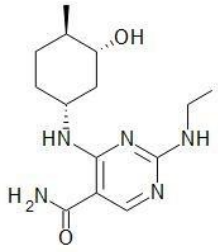
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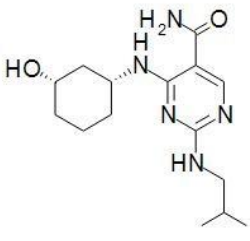
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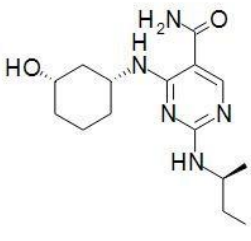
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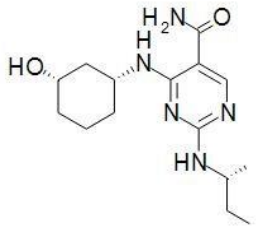

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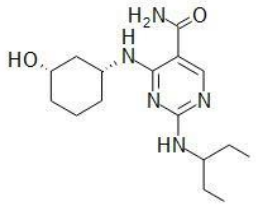

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or a pharmaceutically acceptable salt, tautomer, stereoisomer, or enantiomer thereof.

12. Use of a compound in the manufacture of a medicament for the treatment or prevention of interstitial pulmonary fibrosis; chronic allograft nephropathy; antibody mediated rejection; cystic fibrosis; mucous colitis; Huntington's disease; pancreatitis; nephritis; lupus erythematosus; Type II diabetes; obesity; left ventricular hypertrophy; ischemic damages of heart, lung, gut, kidney, liver, pancreas, spleen or brain; preservation of the organ for transplantation; graft versus host disease; endotoxin shock; burn from exposure to fire, chemicals or radiation; eczema; skin graft; epilepsy; Alzheimer's disease; Parkinson's disease; or immunological response to bacterial or viral infection; wherein the compound of formula (I) is:



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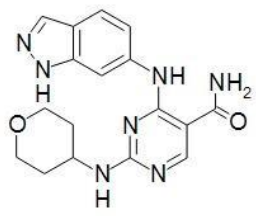

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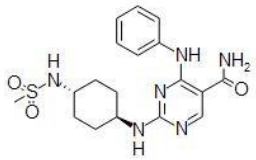
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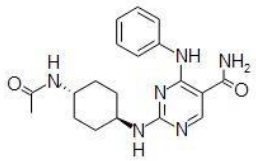
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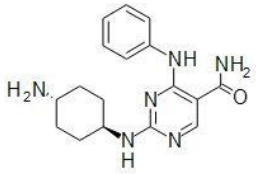
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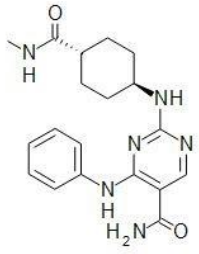
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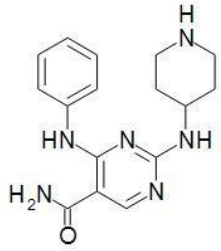
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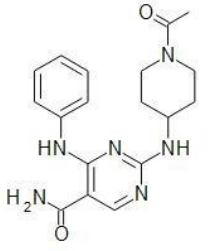
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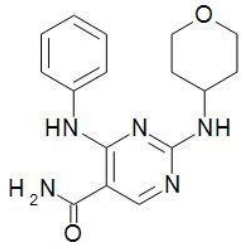
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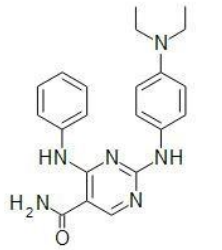
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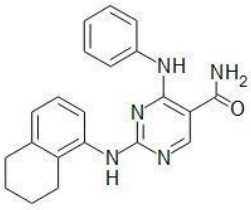
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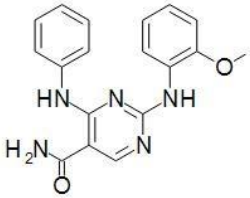
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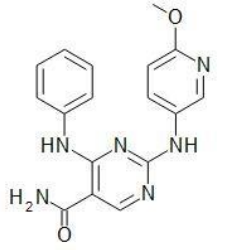
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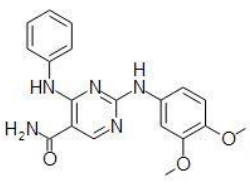
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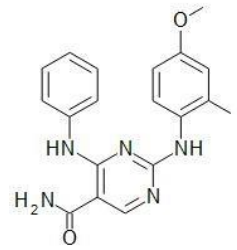
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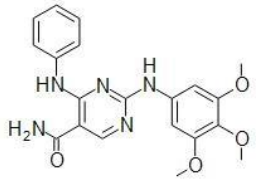
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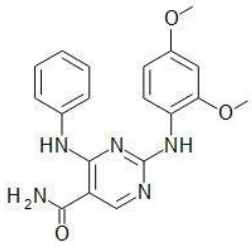
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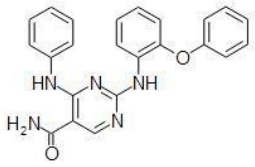
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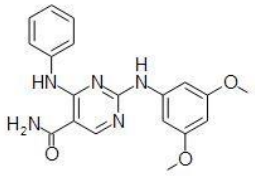
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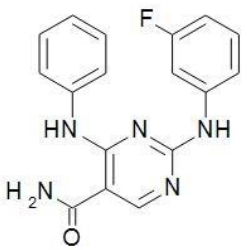
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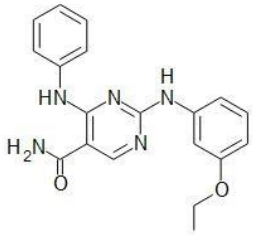
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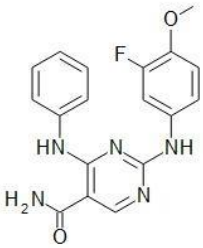
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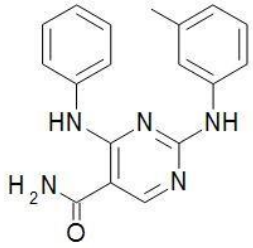
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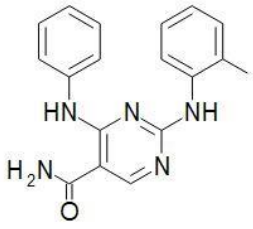
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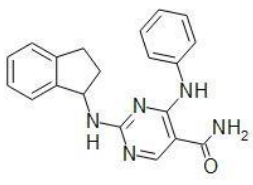
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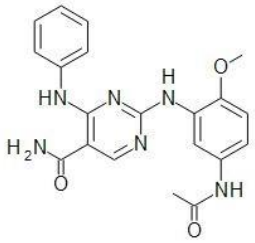
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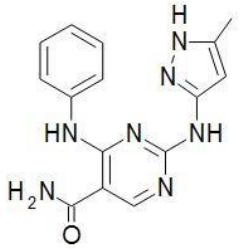
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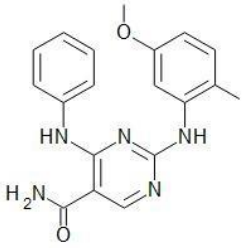
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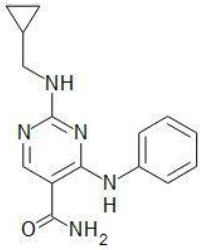
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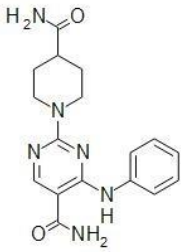
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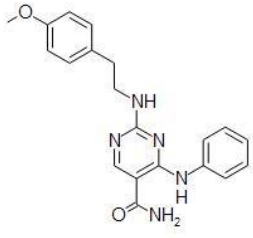
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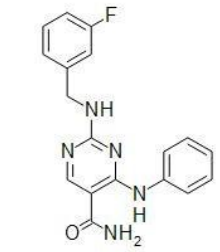
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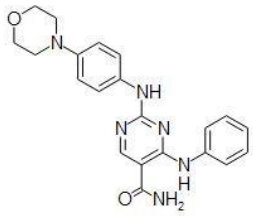
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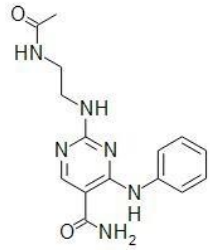
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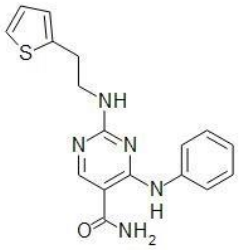
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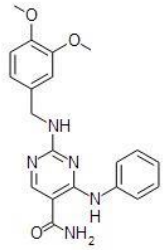
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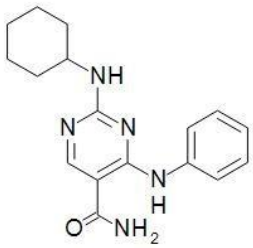
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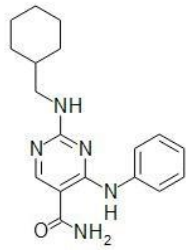
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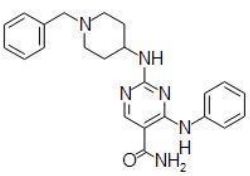
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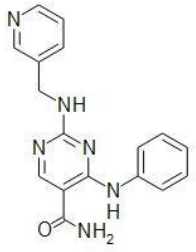
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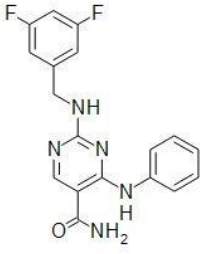
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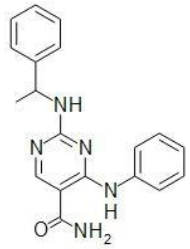
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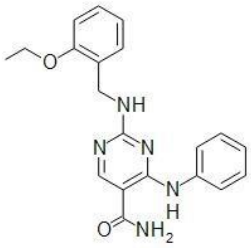
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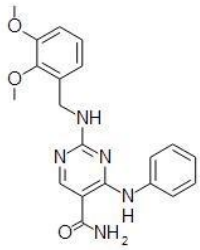
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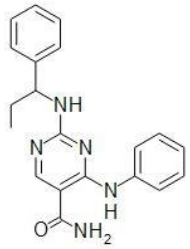
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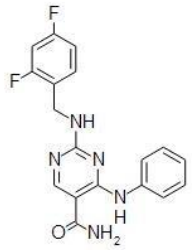
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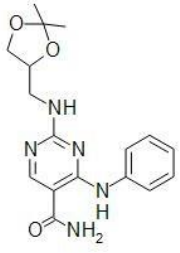
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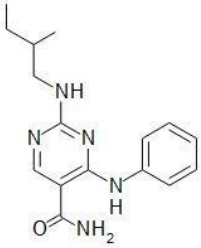
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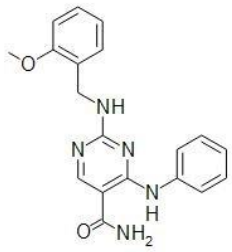
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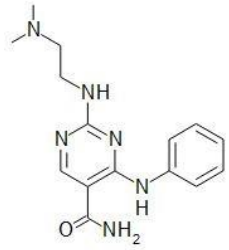
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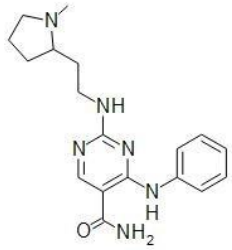
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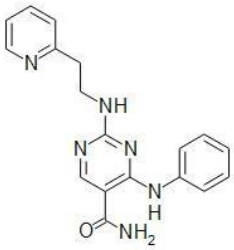
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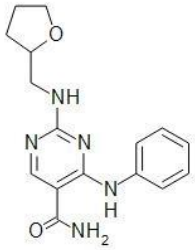
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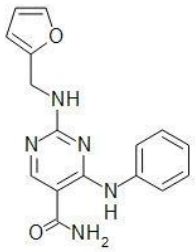
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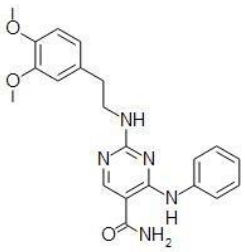
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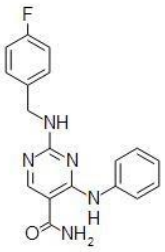
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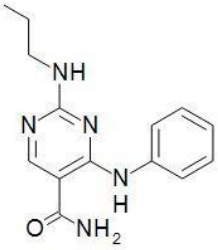
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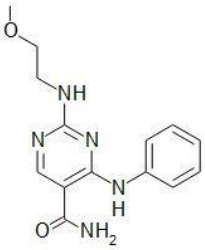
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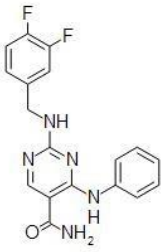
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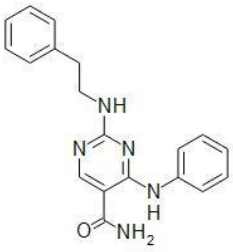
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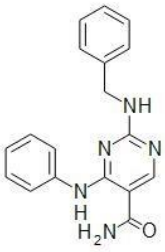
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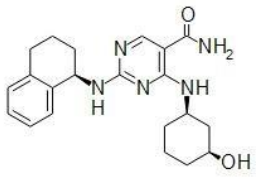
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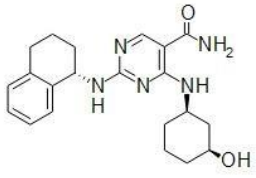
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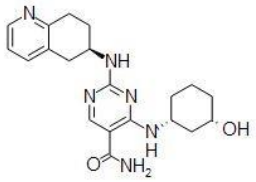
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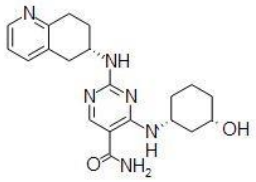
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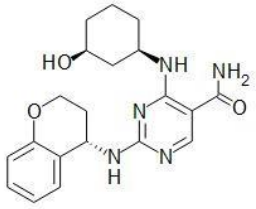
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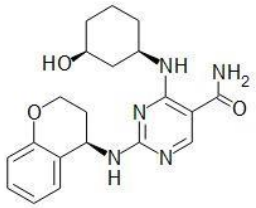
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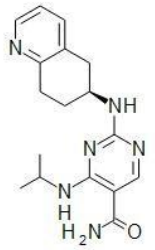
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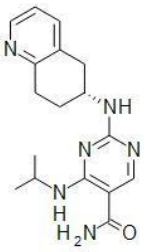
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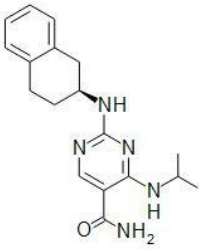
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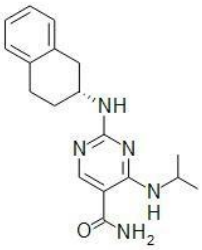
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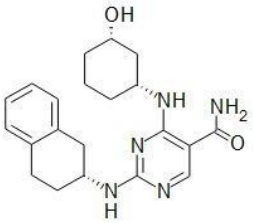
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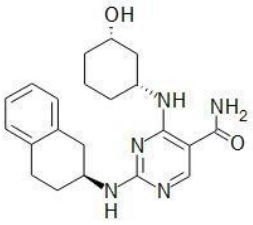
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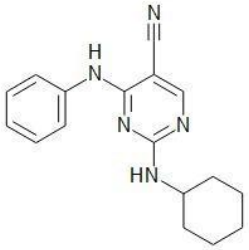
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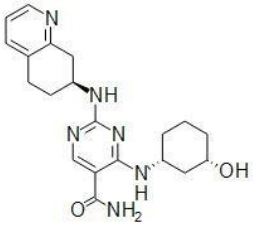
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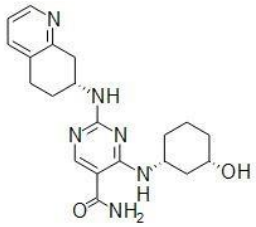
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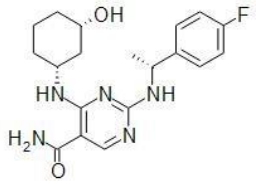
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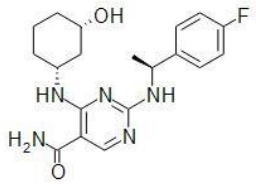
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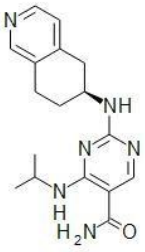
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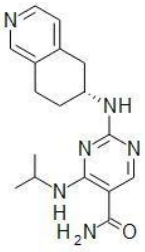
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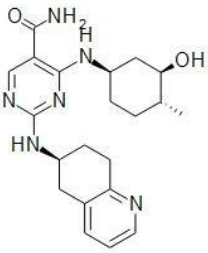
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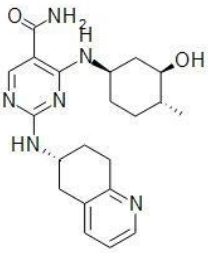
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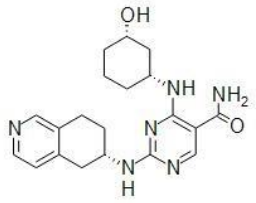
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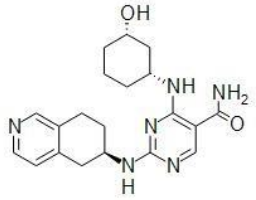
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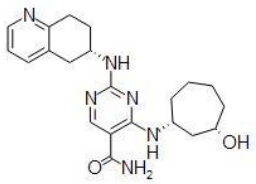
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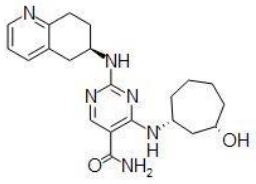
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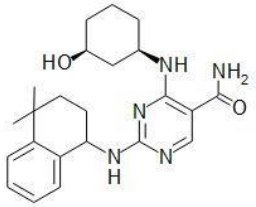
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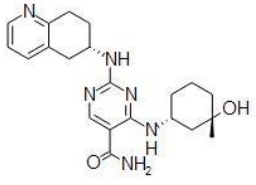
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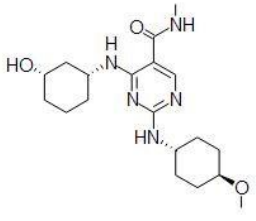
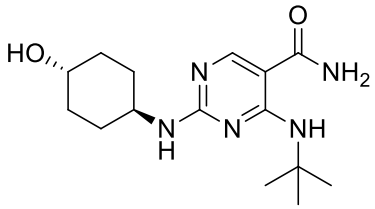

,
or a pharmaceutically acceptable salt, tautomer, stereoisomer, or enantiomer thereof.

13. The use of claim 1, wherein the compound is that wherein the compound at a concentration of 10 μM inhibits JNK1 by at least about 50%.

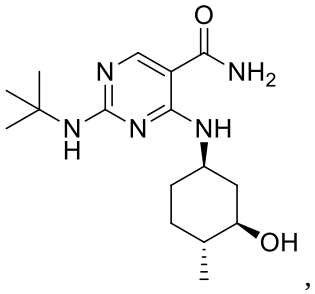
14. The use of claim 1, wherein the compound of formula (I) is:



,

or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

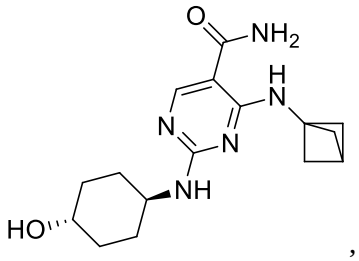
15. The use of claim 1, wherein the compound of formula (I) is:



,

or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

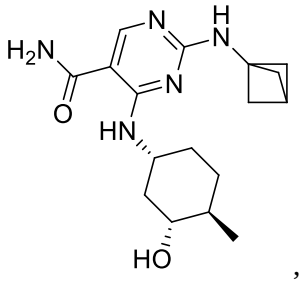
16. The use of claim 1, wherein the compound of formula (I) is:



,

or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

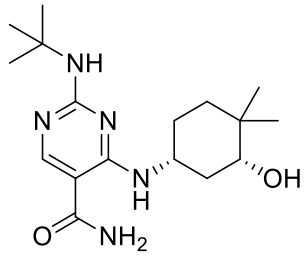
17. The use of claim 1, wherein the compound of formula (I) is:



,

or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

18. The use of claim 1, wherein the compound of formula (I) is:



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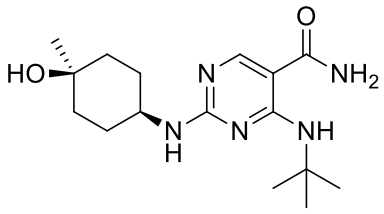
or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

19. The use of claim 1, wherein the compound of formula (I) is:



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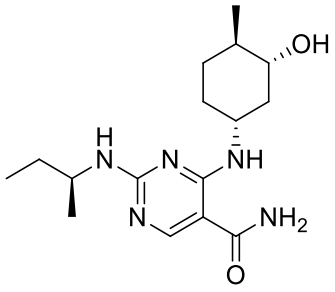
or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

20. The use of claim 1, wherein the compound of formula (I) is:



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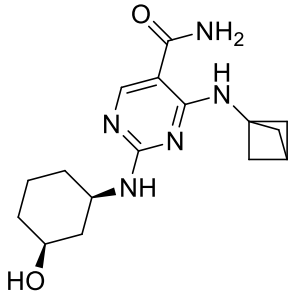
or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

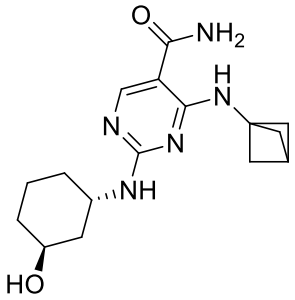
21. The use of claim 1, wherein the compound of formula (I) is:



,

or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

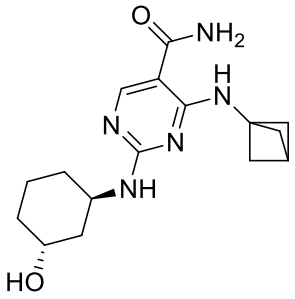
22. The use of claim 1, wherein the compound of formula (I) is:



,

or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

23. The use of claim 1, wherein the compound of formula (I) is:



,

or a pharmaceutically acceptable salt, tautomer, stereoisomer, enantiomer, or isotopologue thereof.

24. The use of claim 1, wherein interstitial pulmonary fibrosis is treated or prevented.