DICHLOROPHENOL HSD17B13 INHIBITORS AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application Serial No. 63/113,555 filed November 13, 2020; U.S. Provisional Application Serial No. 63/113,557 filed November 13, 2020; U.S. Provisional Application Serial No. 63/170,855 filed April 5, 2021; and U.S. Provisional Application Serial No. 63/225,282 filed July 23, 2021 which are hereby incorporated by reference in their entirety.

BACKGROUND OF THE INVENTION

[0002] Nonalcoholic fatty liver diseases (NAFLDs) including NASH (nonalcoholic steatohepatitis) are considered to be hepatic manifestations of the metabolic syndrome and are characterized by the accumulation of triglycerides in the liver of patients without a history of excessive alcohol consumption. The majority of patients with NAFLD are obese or morbidly obese and have accompanying insulin resistance. The incidence of NAFLD/NASH has been rapidly increasing worldwide consistent with the increased prevalence of obesity, and it is currently the most common chronic liver disease.

[0003] NAFLD is classified into simple steatosis, in which only hepatic steatosis is observed, and NASH, in which intralobular inflammation and ballooning degeneration of hepatocytes is observed along with hepatic steatosis. The proportion of patients with NAFLD who have NASH is still not clear but might range from 20-40%. NASH is a progressive disease and may lead to liver cirrhosis and hepatocellular carcinoma. Twenty percent of NASH patients are reported to develop cirrhosis, and 30-40% of patients with NASH cirrhosis experience liver-related death. Recently, NASH has become the third most common indication for liver transplantation in the United States. Currently, the principal treatment for NAFLD/NASH is lifestyle modification by diet and exercise. However, pharmacological therapy is indispensable because obese patients with NAFLD often have difficulty maintaining improved lifestyles.

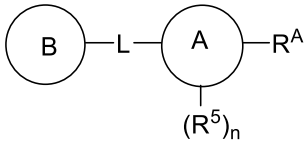
[0004] 17β-Hydroxysteroid dehydrogenases (HSD17Bs) comprise a large family of 15 members some of which involved in sex hormone metabolism. Some HSD17Bs enzymes also play key roles in cholesterol and fatty acid metabolism. A recent study showed that hydroxysteroid 17β-dehydrogenase 13 (HSD17B13), an enzyme with unknown biological function, is a novel liver-specific lipid droplet (LD)-associated protein in mouse and humans. HSD17B13 expression is markedly upregulated in patients and mice with non-alcoholic fatty liver disease (NAFLD). Hepatic overexpression of HSD17B13 promotes lipid accumulation in the liver. HSD17B13 could also have potential as a biomarker of chronic liver disease, such as alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD) (for example: steatosis, nonalcoholic steatohepatitis (NASH), NASH-fibrosis, or cirrhosis), steatohepatitis, and liver cancer.

SUMMARY

[0005] Provided herein are methods, compounds, and compositions useful for reducing expression or activity of HSD17B13 in a subject in need thereof. Also, provided herein are methods, compounds, and compositions comprising HSD17B13 specific inhibitors, which can be useful in reducing the morbidity

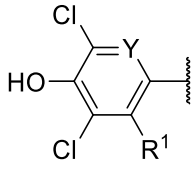
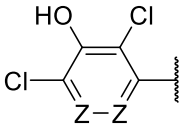
of HSD17B13-related diseases or conditions in a subject in need thereof. Such methods, compounds, and compositions can be useful, for example, to treat, prevent, delay or ameliorate liver disease, metabolic disease, or cardiovascular disease.

[0005a] In an aspect of the present disclosure, there is provided a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I),

wherein:

Ring B is  or ;

Y is N or CR^1;

each Z is independently N or CR^1;

each R^1 are independently hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl;

L is $-C(=O)NR^3-$;

R^3 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl;

each R^4 is independently hydrogen, deuterium, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl;

Ring A is a 3- to 12-membered ring optionally comprising 1-4 heteroatoms selected from the group consisting of O, S, N, P, and B;

each R^5 is independently hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, -SH, $-SR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl;

or two R^5 on the same atom are taken together to form an oxo;

n is 0-6;

R^A is:

(a) $-C(=O)NR^{10}R^{11}$; or

(b) C_4-C_{10}alkyl optionally substituted with one or more R^{Aa}; or

(c) $-(C(R^{12})_2)_p$cycloalkyl, $-(C(R^{12})_2)_p$heterocycloalkyl, $-(C(R^{12})_2)_p$aryl, or $-(C(R^{12})_2)_p$heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ab};

R^{10} and R^{11} are independently hydrogen, C_1-C_{10}alkyl, C_1-C_{10}haloalkyl, C_1-C_{10}deuteroalkyl, C_1-C_{10}hydroxyalkyl, C_1-C_{10}aminoalkyl, C_1-C_{10}heteroalkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl,

heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{10a};

each R^{10a} is independently deuterium, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NHS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-C(=O)C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{10b};

or two R^{10a} on the same atom are taken together to form an oxo;

each R^{10b} is independently deuterium, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NHS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-C(=O)C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{10b} on the same atom are taken together to form an oxo;

each R^{Aa} are independently deuterium, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NHS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-C(=O)C(=O)NR^cR^d$, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aaa};

or two R^{Aa} on the same atom are taken together to form an oxo;

each R^{Ab} are independently deuterium, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NHS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-C(=O)C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aaa};

or two R^{Ab} on the same atom are taken together to form an oxo;

each R^{Aaa} is independently deuterium, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NHS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-C(=O)C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl,

C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{12} is independently hydrogen, deuterium, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{12} on the same carbon are taken together to form a cycloalkyl or a heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -OH, -OCH_3, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl;

or two R^{12} on adjacent carbon are taken together to form a cycloalkyl optionally substituted with deuterium, halogen, -OH, -OCH_3, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl;

p is 1-4;

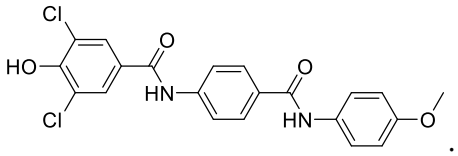
each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -$S(=O)CH_3$, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(=O)CH_3$, -C(=O)OH, -$C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -$S(=O)CH_3$, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(=O)CH_3$, -C(=O)OH, -$C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl; and

each R^c and R^d are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -$S(=O)CH_3$, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(=O)CH_3$, -C(=O)OH, -$C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -$S(=O)CH_3$, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(=O)CH_3$, -

C(=O)OH, -C(=O)OCH$_3$, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, C$_1$-C$_6$deuteroalkyl, C$_1$-C$_6$hydroxyalkyl, C$_1$-C$_6$aminoalkyl, or C$_1$-C$_6$heteroalkyl; provided that the compound is not



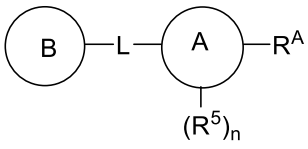
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[0005b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier.

[0005c] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a liver disease, a metabolic disease, or a cardiovascular disease in a subject in need thereof.

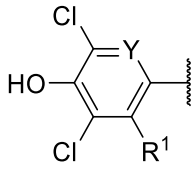
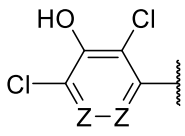
[0005d] In another aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition disclosed herein, for use in therapy.

[0006] Disclosed herein is a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I),

wherein:

Ring B is  or ;

Y is N or CR^1;

each Z is independently N or CR^1;

each R^1 are independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -NR^{c}R^d, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, or C$_1$-C$_6$deuteroalkyl;

L is -O-, -C(=O)NR^3-, -NR^{3}C(=O)-, -C(=O)C(R^4)$_2$-, or -C(R^4)$_2$C(=O)-;

R^3 is hydrogen, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, or C$_1$-C$_6$deuteroalkyl;

each R^4 is independently hydrogen, deuterium, halogen, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, or C$_1$-C$_6$deuteroalkyl;

Ring A is a 3- to 12-membered ring optionally comprising 1-4 heteroatoms selected from the group consisting of O, S, N, P, and B;

each R^5 is independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NR^{c}R^d, C$_1$-C$_6$alkyl, C$_1$-C$_6$haloalkyl, or C$_1$-C$_6$deuteroalkyl;

or two R^5 on the same atom are taken together to form an oxo;

n is 0-6;

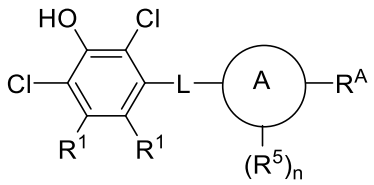
R^A is:

(a) $-C(=O)NR^{10}R^{11}$; or

(b) C_4-C_{10}alkyl optionally substituted with one or more R^{Aa}; or

(c) $-(C(R^{12})_2)_p$cycloalkyl, $-(C(R^{12})_2)_p$heterocycloalkyl, $-(C(R^{12})_2)_p$aryl, or $-(C(R^{12})_2)_p$heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ab};

R^{10} and R^{11} are independently hydrogen, C_1-C_{10}alkyl, C_1-C_{10}haloalkyl, C_1-C_{10}deuteroalkyl, C_1-C_{10}hydroxyalkyl, C_1-C_{10}aminoalkyl, C_1-C_{10}heteroalkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl,



Formula (Id).

[0011] Also disclosed herein is a pharmaceutical composition comprising a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier.

[0012] Also disclosed herein is a method of treating a disease in a subject in need thereof, the method comprising administering a pharmaceutically effective amount of a compound disclosed herein, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition disclosed herein. In some examples of a method of treating a disease, the disease is a liver disease, a metabolic disease, or a cardiovascular disease. In some examples of a method of treating a disease, the disease is NAFLD. In some examples of a method of treating a disease, the disease is NASH. In some examples of a method of treating a disease, the disease is drug induced liver injury (DILI). In some examples of a method of treating a disease, the disease is associated with HSD17B13. In some examples of a method of treating a disease, the diseases is alcoholic liver disease. In some examples of a method of treating a disease, the disease is cirrhosis. In some examples of a method of treating a disease, the disease is decompensated portal hypertension. In some examples of a method of treating a disease, the disease is cholestatic liver disease.

INCORPORATION BY REFERENCE

[0013] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

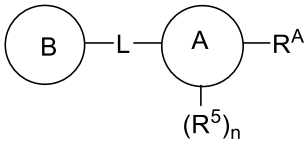
[0014] In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments. However, one skilled in the art will understand that the invention may be practiced without these details. In other instances, well-known structures have not been shown or described in detail to avoid unnecessarily obscuring descriptions of the embodiments. Unless the context requires otherwise, throughout the specification and claims which follow, the word “comprise” and variations thereof, such as, “comprises” and “comprising” are to be construed in an open, inclusive sense, that is, as “including, but not limited to.” Further, headings provided herein are for convenience only and do not interpret the scope or meaning of the claimed invention.

[0015] Reference throughout this specification to “some embodiments” or “an embodiment” means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearances of the phrases “in one embodiment” or “in an

CLAIMS

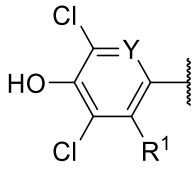
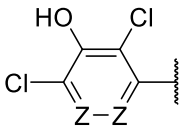
WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof:



Formula (I),

wherein:

Ring B is  or ;

Y is N or CR^1;

each Z is independently N or CR^1;

each R^1 are independently hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl;

L is $-C(=O)NR^3-$;

R^3 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl;

each R^4 is independently hydrogen, deuterium, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl;

Ring A is a 3- to 12-membered ring optionally comprising 1-4 heteroatoms selected from the group consisting of O, S, N, P, and B;

each R^5 is independently hydrogen, deuterium, halogen, -CN, -OH, $-OR^a$, -SH, $-SR^a$, $-NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl;

or two R^5 on the same atom are taken together to form an oxo;

n is 0-6;

R^A is:

(a) $-C(=O)NR^{10}R^{11}$; or

(b) C_4-C_{10}alkyl optionally substituted with one or more R^{Aa}; or

(c) $-(C(R^{12})_2)_p$cycloalkyl, $-(C(R^{12})_2)_p$heterocycloalkyl, $-(C(R^{12})_2)_p$aryl, or $-(C(R^{12})_2)_p$heteroaryl; wherein the cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Ab};

R^{10} and R^{11} are independently hydrogen, C_1-C_{10}alkyl, C_1-C_{10}haloalkyl, C_1-C_{10}deuteroalkyl, C_1-C_{10}hydroxyalkyl, C_1-C_{10}aminoalkyl, C_1-C_{10}heteroalkyl, C_2-C_{10}alkenyl, C_2-C_{10}alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{10a};

each R^{10a} is independently deuterium, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NHS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-C(=O)C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{10b};

or two R^{10a} on the same atom are taken together to form an oxo;

each R^{10b} is independently deuterium, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NHS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-C(=O)C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{10b} on the same atom are taken together to form an oxo;

each R^{Aa} are independently deuterium, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NHS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-C(=O)C(=O)NR^cR^d$, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aaa};

or two R^{Aa} on the same atom are taken together to form an oxo;

each R^{Ab} are independently deuterium, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NHS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-C(=O)C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is optionally and independently substituted with one or more R^{Aaa};

or two R^{Ab} on the same atom are taken together to form an oxo;

each R^{Aaa} is independently deuterium, halogen, -CN, $-NO_2$, -OH, $-OR^a$, $-OC(=O)R^a$, $-OC(=O)OR^b$, $-OC(=O)NR^cR^d$, -SH, $-SR^a$, $-S(=O)R^a$, $-S(=O)_2R^a$, $-S(=O)_2NR^cR^d$, $-NR^cR^d$, $-NR^bC(=O)NR^cR^d$, $-NR^bC(=O)R^a$, $-NR^bC(=O)OR^b$, $-NHS(=O)_2R^a$, $-C(=O)R^a$, $-C(=O)C(=O)R^a$, $-C(=O)OR^b$, $-C(=O)NR^cR^d$, $-C(=O)C(=O)NR^cR^d$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

each R^{12} is independently hydrogen, deuterium, halogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

or two R^{12} on the same carbon are taken together to form a cycloalkyl or a heterocycloalkyl; wherein the cycloalkyl and heterocycloalkyl is optionally substituted with deuterium, halogen, -OH, -OCH_3, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl;

or two R^{12} on adjacent carbon are taken together to form a cycloalkyl optionally substituted with deuterium, halogen, -OH, -OCH_3, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl;

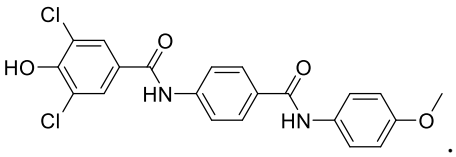
p is 1-4;

each R^a is independently C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -$S(=O)CH_3$, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(=O)CH_3$, -C(=O)OH, -$C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

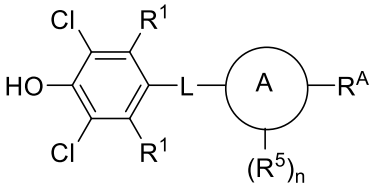
each R^b is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -$S(=O)CH_3$, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(=O)CH_3$, -C(=O)OH, -$C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl; and

each R^c and R^d are independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, C_1-C_6heteroalkyl, C_2-C_6alkenyl, C_2-C_6alkynyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, C_1-C_6alkyl(cycloalkyl), C_1-C_6alkyl(heterocycloalkyl), C_1-C_6alkyl(aryl), or C_1-C_6alkyl(heteroaryl); wherein each alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, aryl, and heteroaryl is independently optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -$S(=O)CH_3$, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(=O)CH_3$, -C(=O)OH, -$C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl;

or R^c and R^d are taken together with the atom to which they are attached to form a heterocycloalkyl optionally substituted with one or more oxo, deuterium, halogen, -CN, -OH, -OCH_3, -$S(=O)CH_3$, -$S(=O)_2CH_3$, -$S(=O)_2NH_2$, -$S(=O)_2NHCH_3$, -$S(=O)_2N(CH_3)_2$, -NH_2, -$NHCH_3$, -$N(CH_3)_2$, -$C(=O)CH_3$, -C(=O)OH, -$C(=O)OCH_3$, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6deuteroalkyl, C_1-C_6hydroxyalkyl, C_1-C_6aminoalkyl, or C_1-C_6heteroalkyl; provided that the compound is not



2. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein the compound of Formula (I) is of Formula (Ib):



Formula (Ib).

3. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

each R^1 is hydrogen.

4. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^3 is hydrogen.

5. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

Ring A is a 3- to 6-membered ring optionally comprising 1-4 heteroatoms selected from the group consisting of O, S, or N.

6. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

Ring A is a 8- to 12-membered bicyclic ring optionally comprising 1-4 heteroatoms selected from the group consisting of O, S, or N.

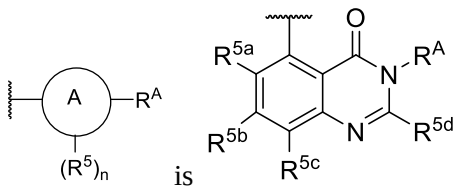
7. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

Ring A is a 5-membered heteroaryl.

8. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

Ring A is dihydroquinazoline, isoindoline, or 2,3-dihydrobenzooxazepine.

9. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:



is

wherein R^{5a}, R^{5b}, R^{5c}, and R^{5d} are independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl.

10. The compound of claim 9, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{5a} is deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl; and R^{5b}, R^{5c}, and R^{5d} are independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl.

11. The compound of claim 9, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

wherein R^{5b} is deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl; and R^{5a}, R^{5c}, and R^{5d} are independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl.

12. The compound of claim 9, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

wherein R^{5c} is deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl; and R^{5a}, R^{5b}, and R^{5d} are independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl.

13. The compound of claim 9, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

wherein R^{5d} is deuterium, halogen, -CN, -OH, -OR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl; and R^{5a}, R^{5b}, and R^{5c} are independently hydrogen, deuterium, halogen, -CN, -OH, -OR^a, -SH, -SR^a, -NR^cR^d, C_1-C_6alkyl, C_1-C_6haloalkyl, or C_1-C_6deuteroalkyl.

14. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^A is -C(=O)$NR^{10}R^{11}$.

15. The compound of claim 14, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{11} is hydrogen.

16. The compound of claim 14, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^{10} is C_1-C_{10}alkyl optionally substituted with one or more R^{10a} or C_1-C_6alkyl(aryl) wherein the aryl is optionally substituted with one or more R^{10a}.

17. The compound of claim 1, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^A is C_4-C_{10}alkyl optionally substituted with one or more R^{Aa}.

18. The compound of claim 17, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

R^A is -$(C(R^{12})_2)_p$aryl; wherein the aryl is optionally and independently substituted with one or more R^{Ab}.

19. The compound of claim 18, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

each R^{12} is hydrogen or two R^{12} on the same carbon are taken together to form a cycloalkyl.

20. The compound of claim 18, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

each R^{12} is hydrogen or two R^{12} on adjacent carbon are taken together to form a cycloalkyl.

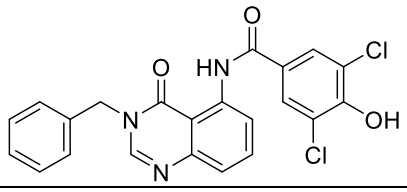
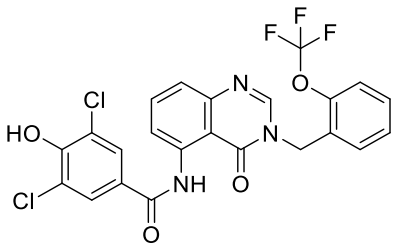
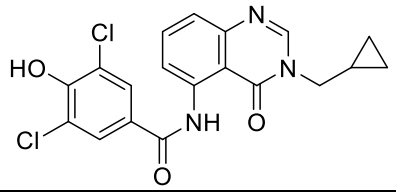
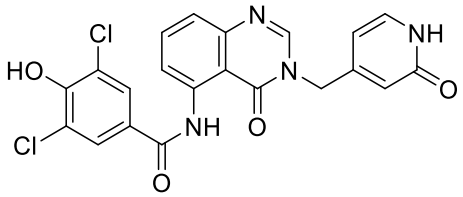
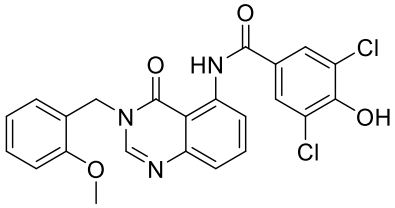
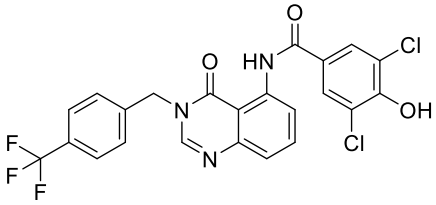
21. The compound of claim 18, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

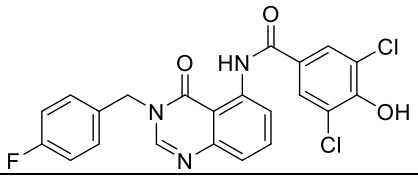
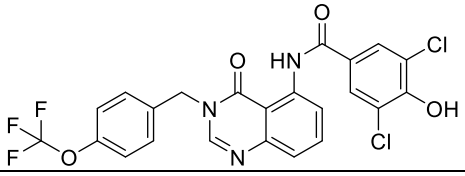
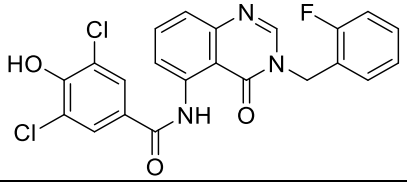
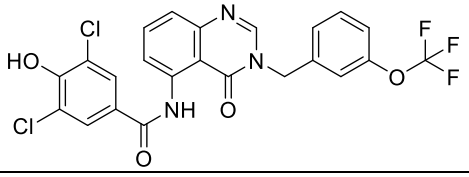
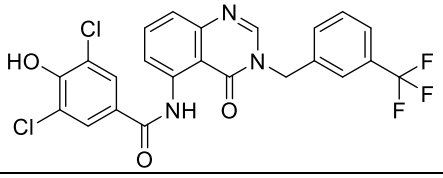
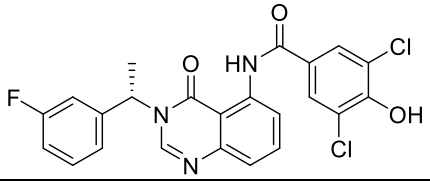
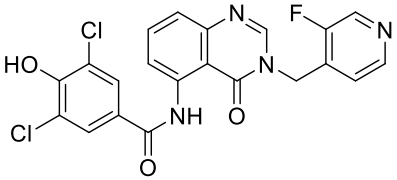
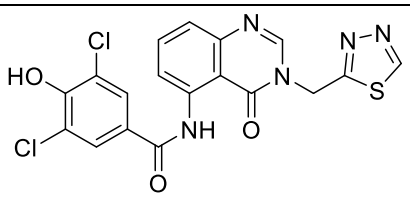
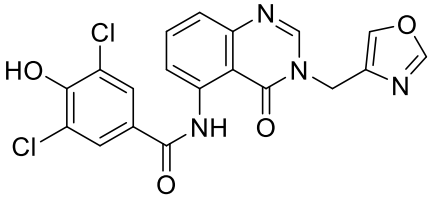
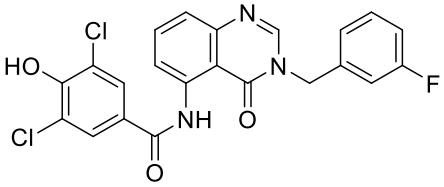
each R^{12} is hydrogen.

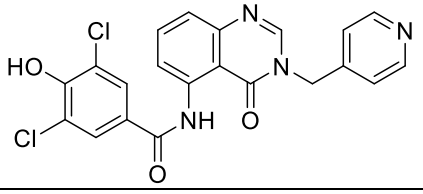
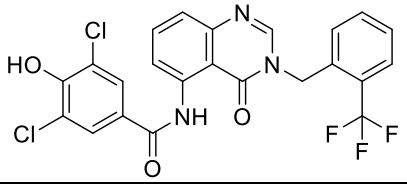
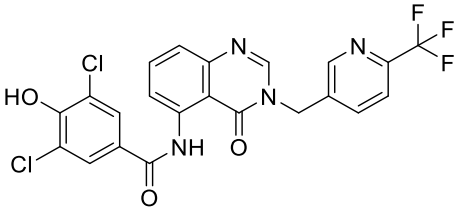
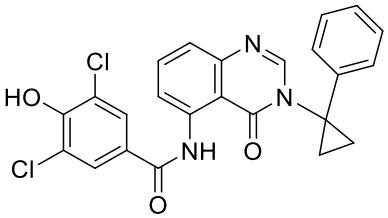
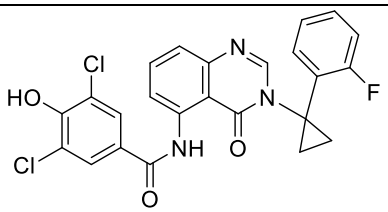
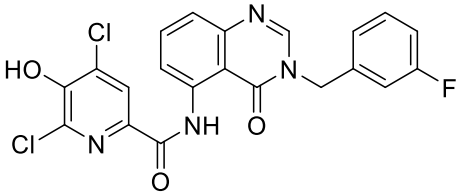
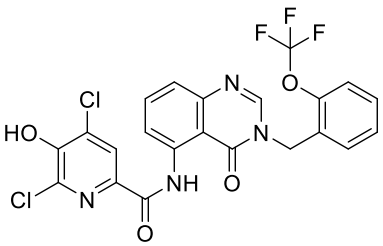
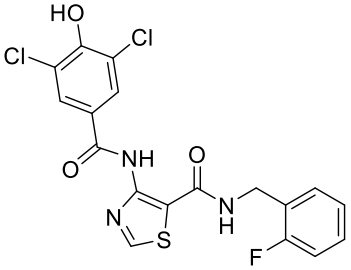
22. The compound of claim 18, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, wherein:

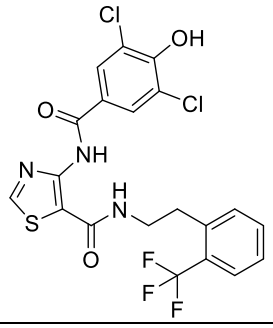
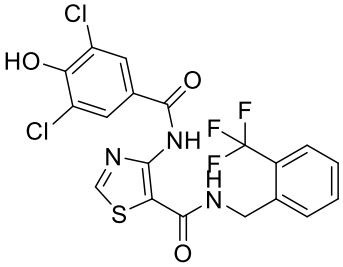
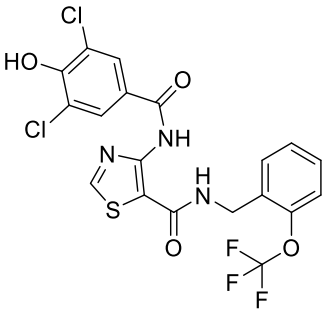
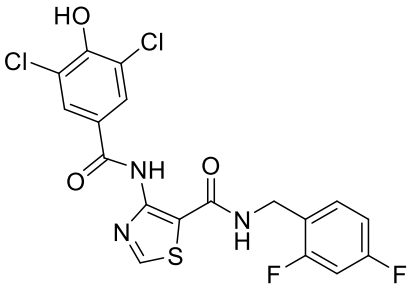
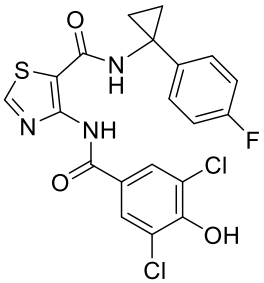
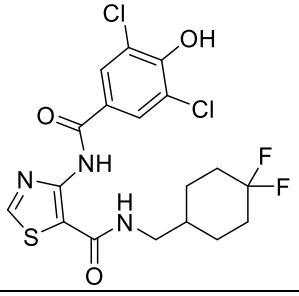
p is 1.

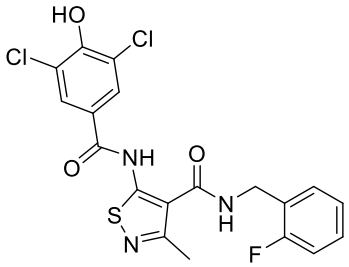
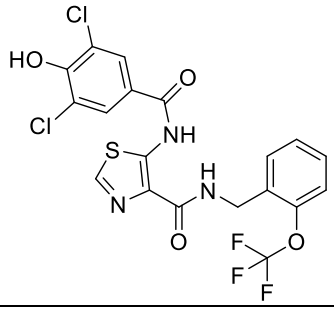
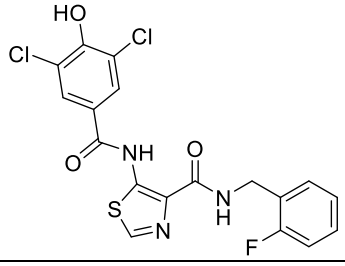
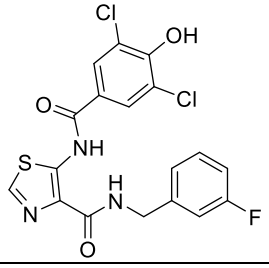
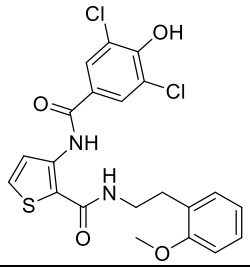
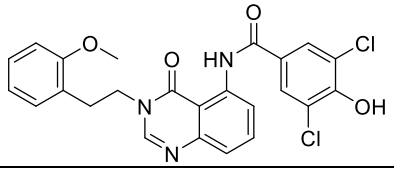
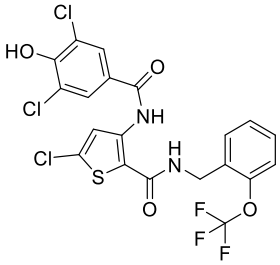
23. The compound of claim 1 selected from the group consisting of:

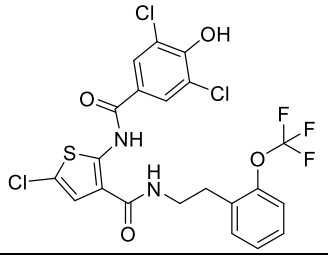
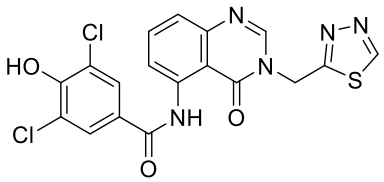
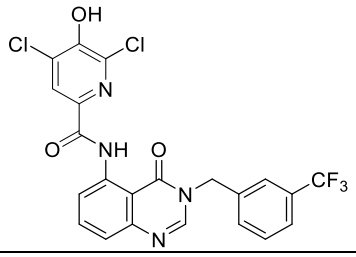
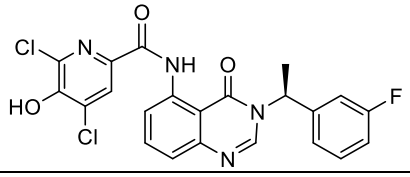
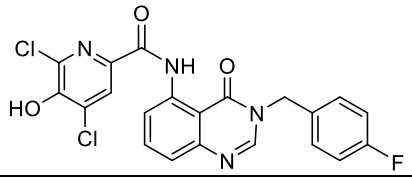
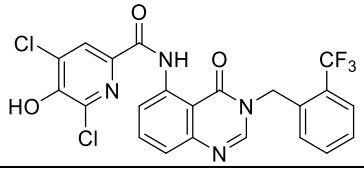
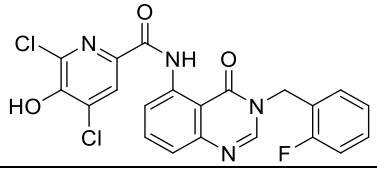
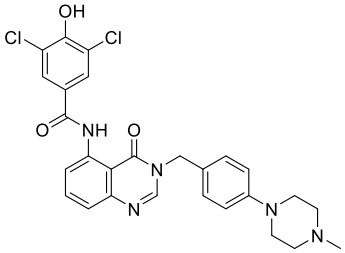
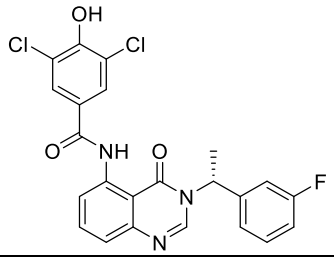
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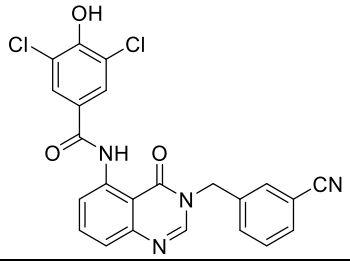
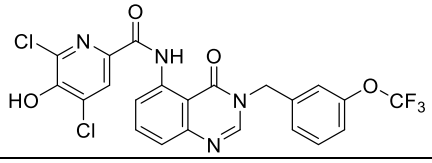
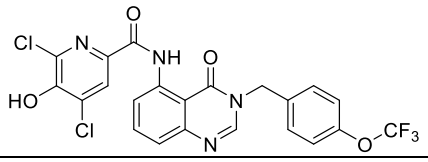
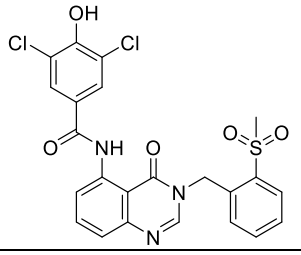
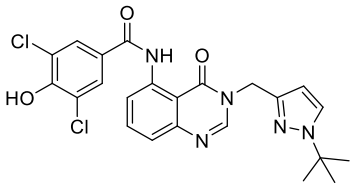
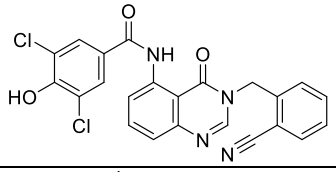
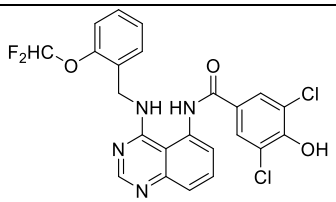
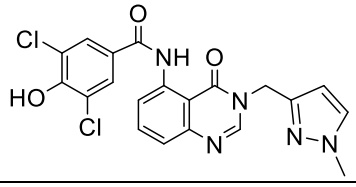
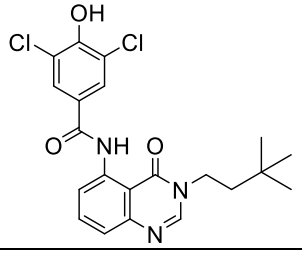
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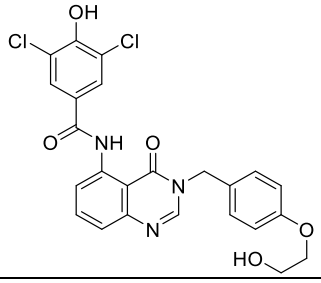
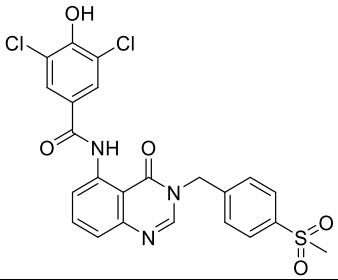
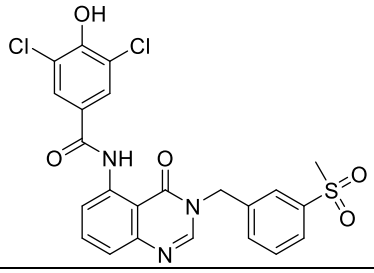
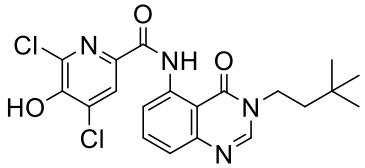
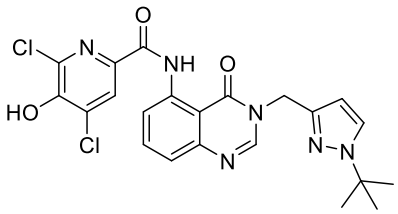
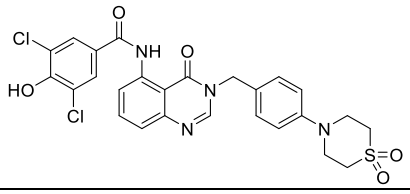
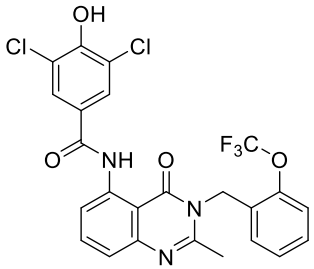
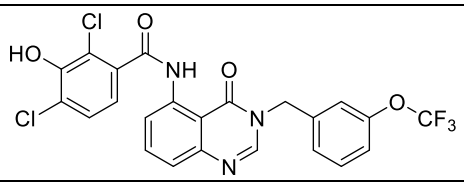
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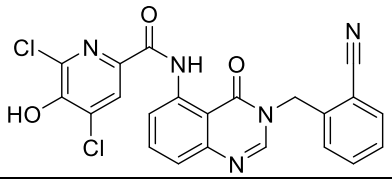
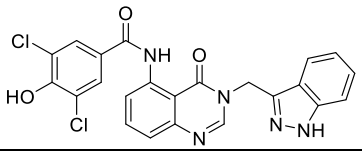
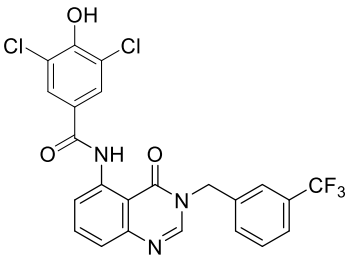
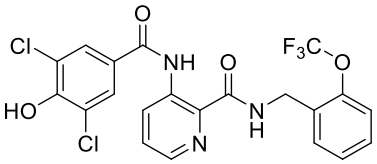
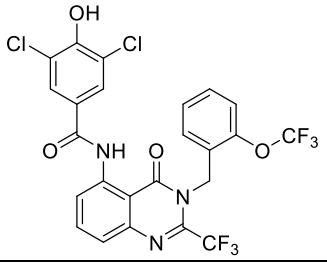
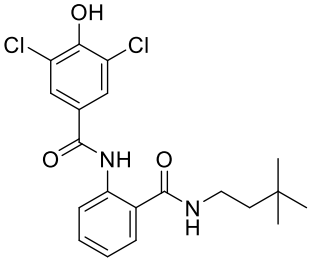
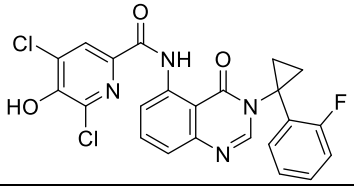
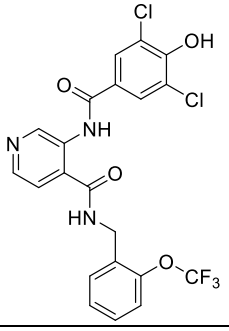
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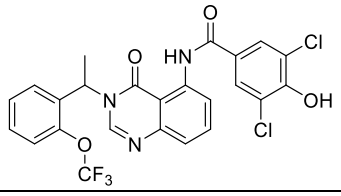
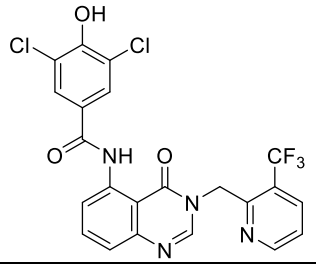
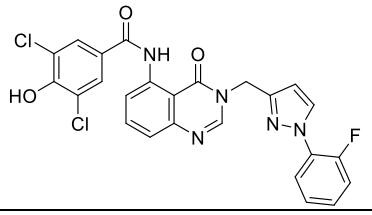
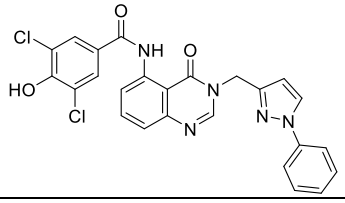
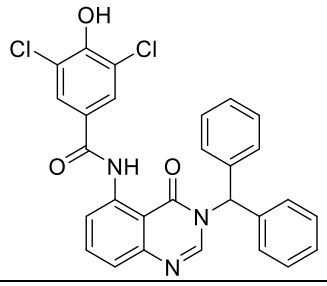
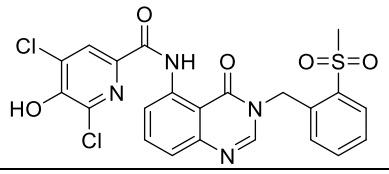
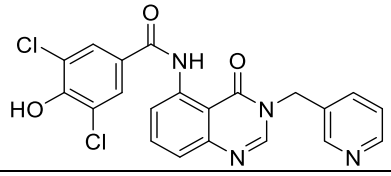
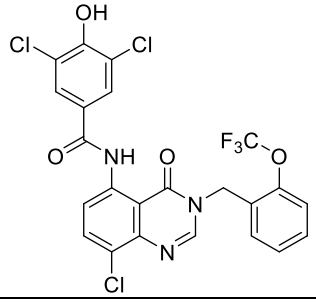
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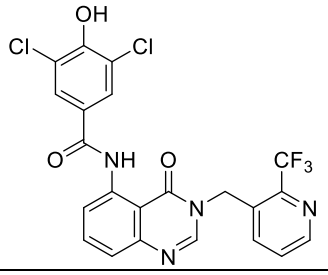
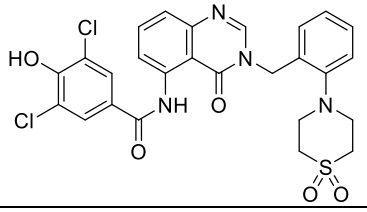
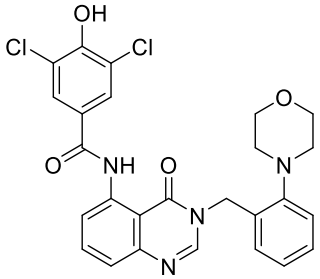
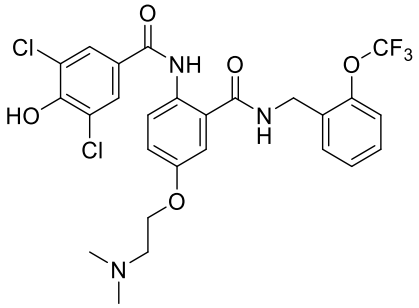
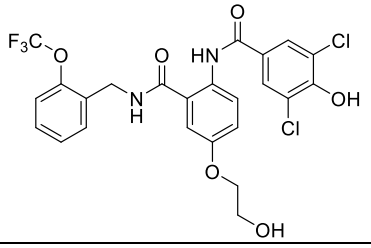
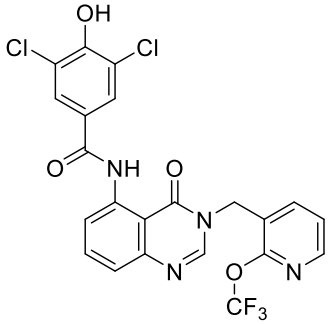
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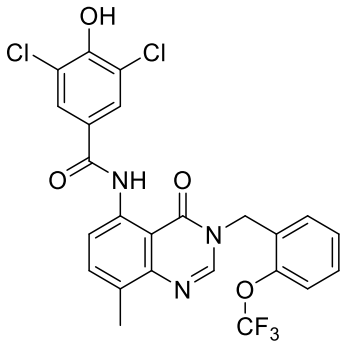
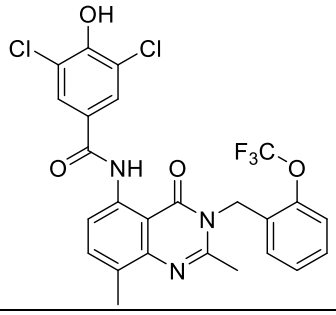
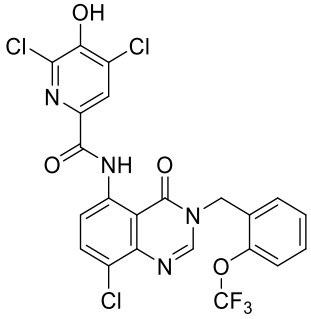
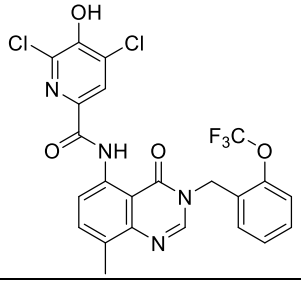
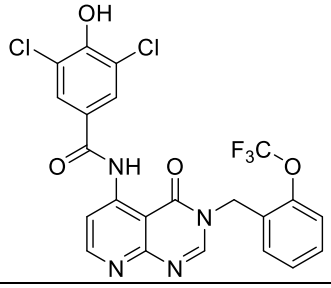
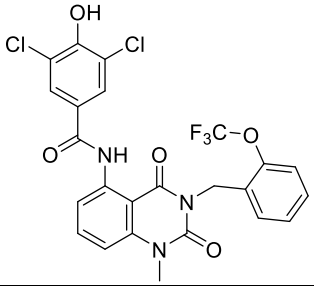
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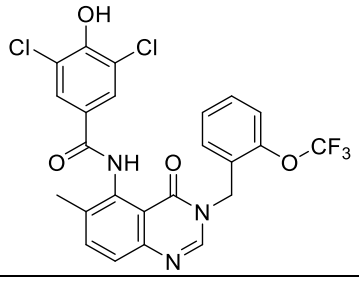
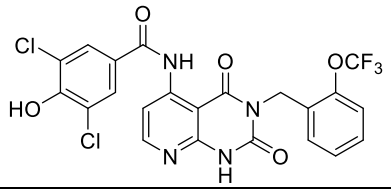
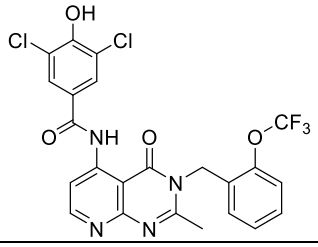
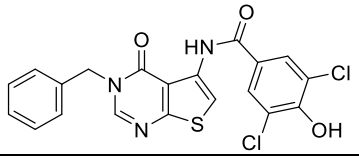
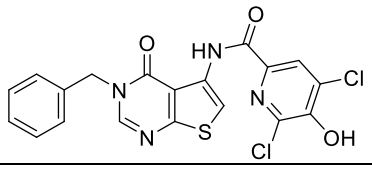
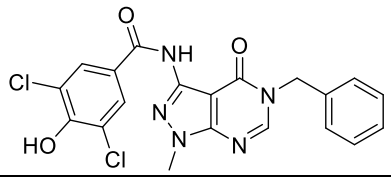
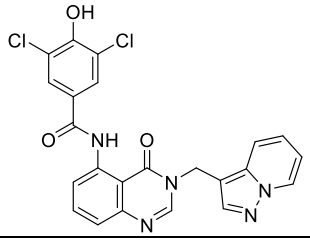
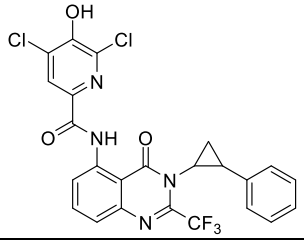
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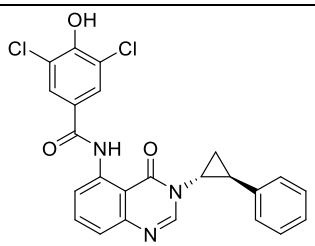
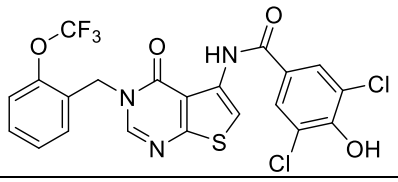
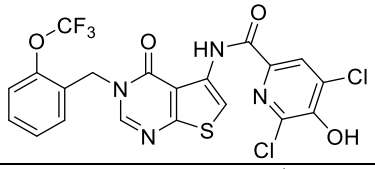
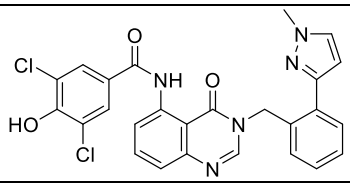
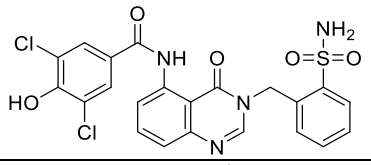
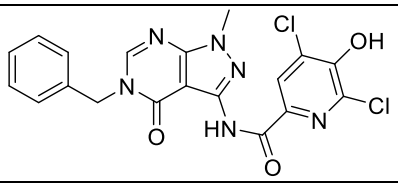
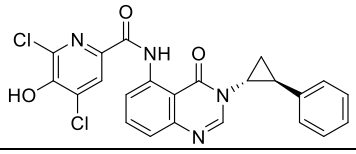
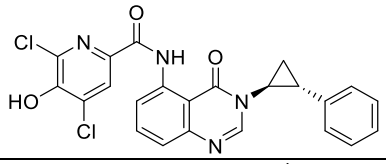
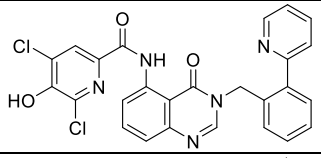
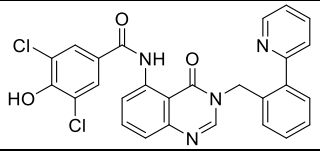
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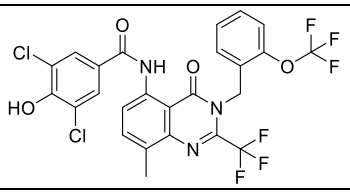
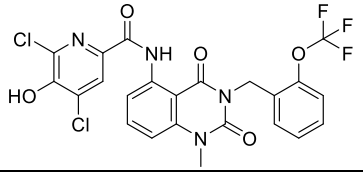
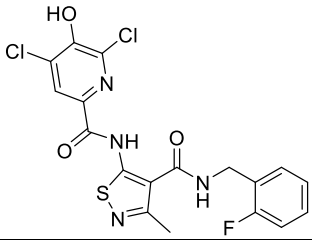
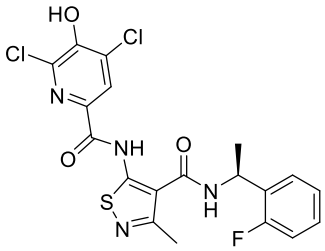
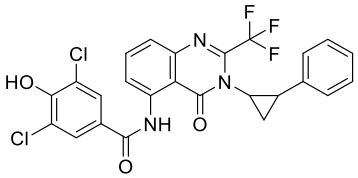
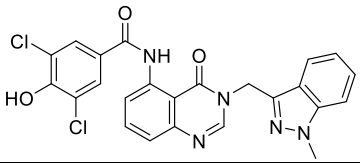
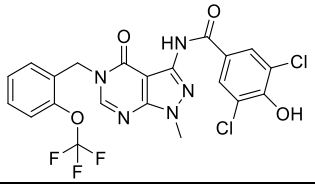
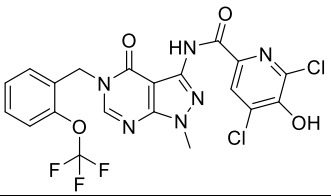
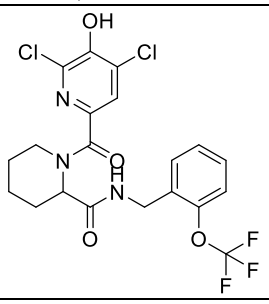
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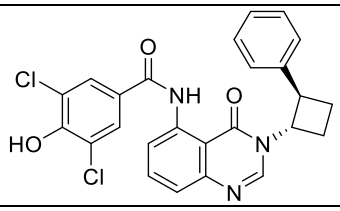
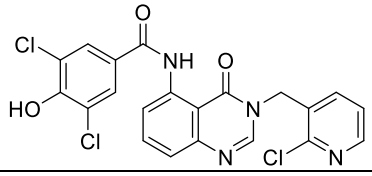
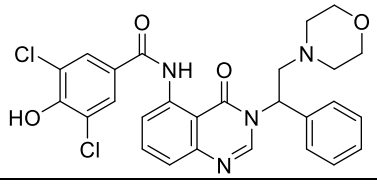
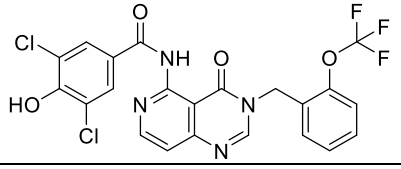
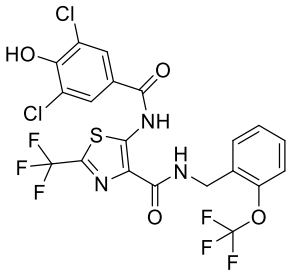
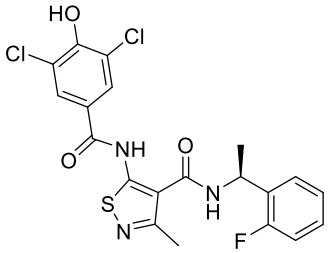
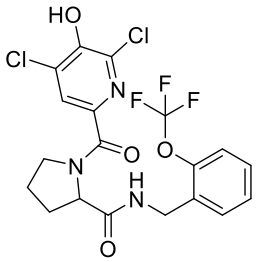
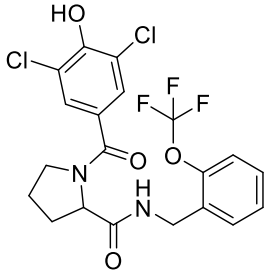
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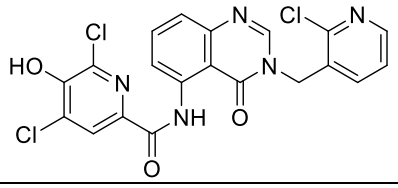
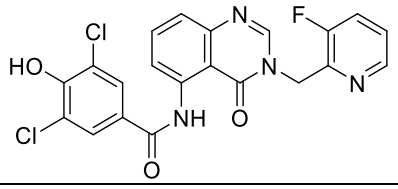
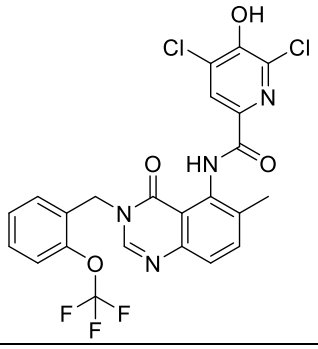
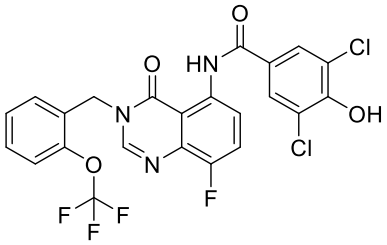
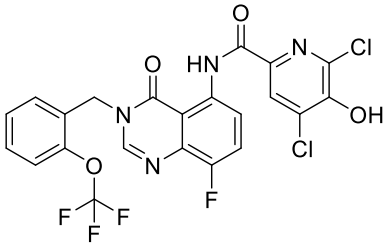
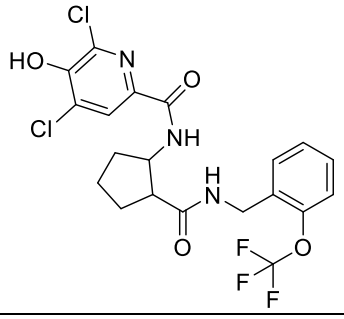
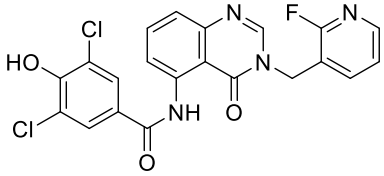
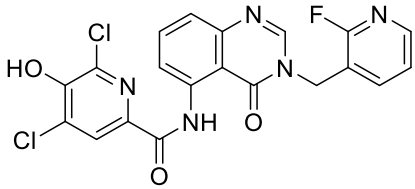
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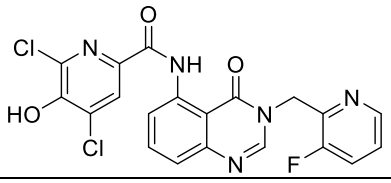
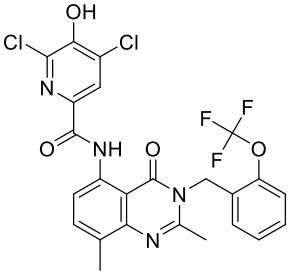
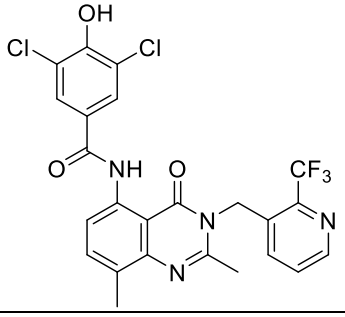
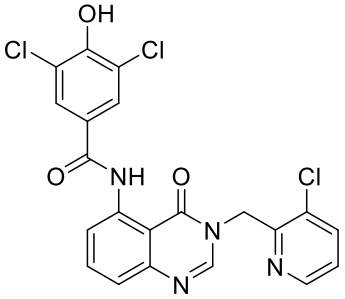
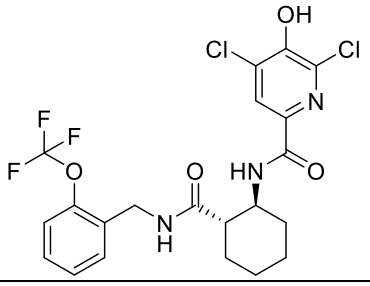
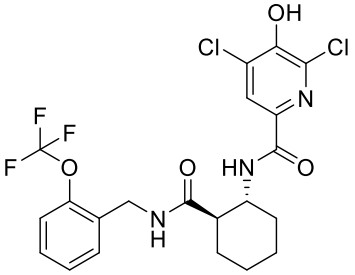
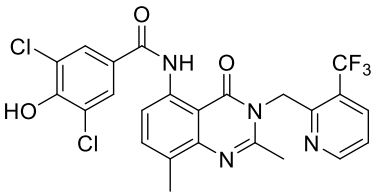
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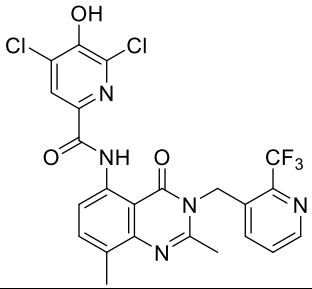
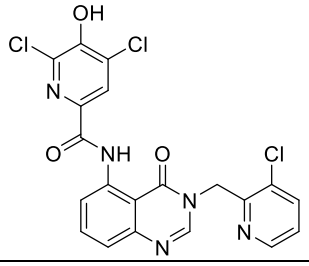
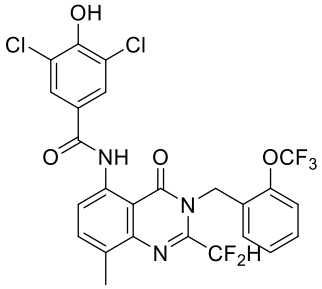
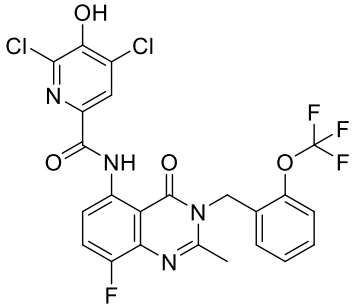
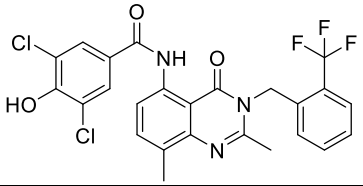
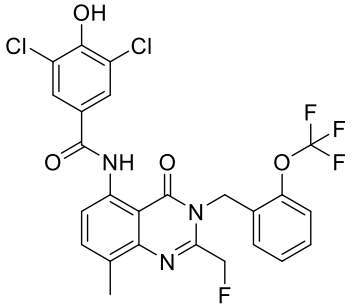
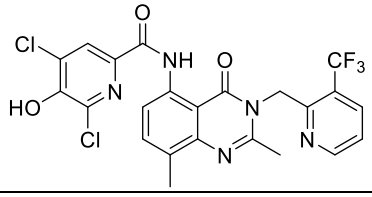
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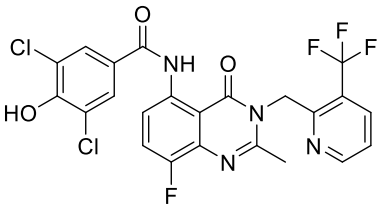
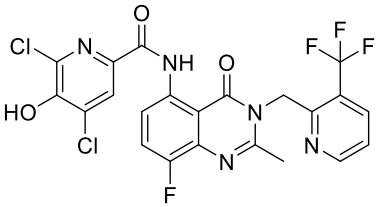
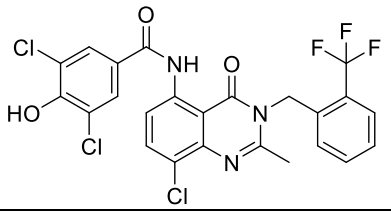
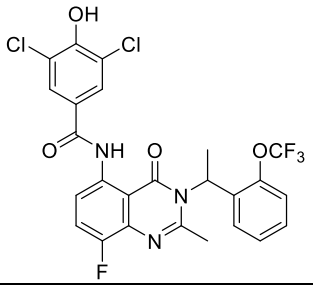
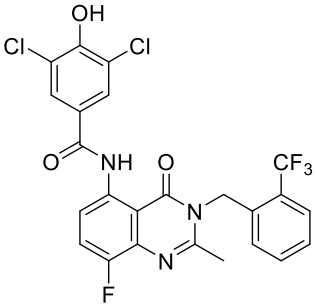
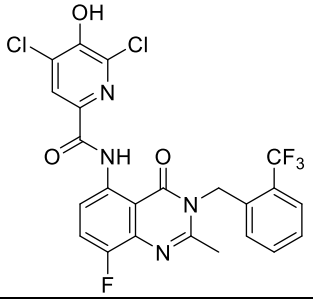
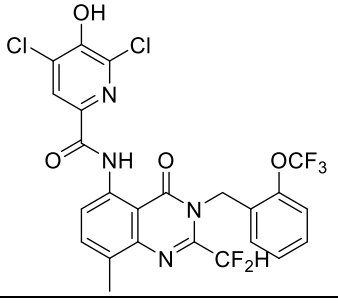
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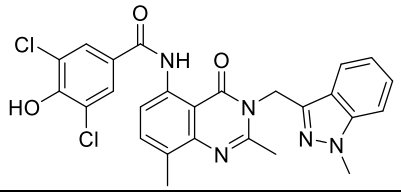
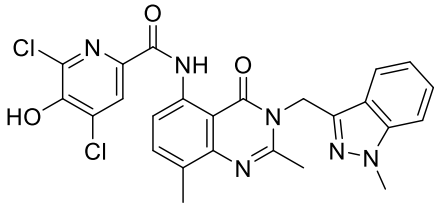
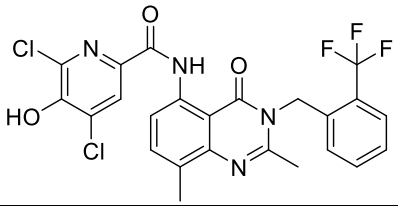
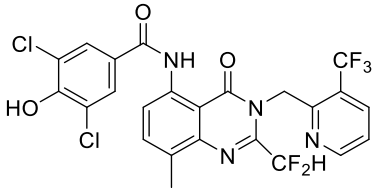
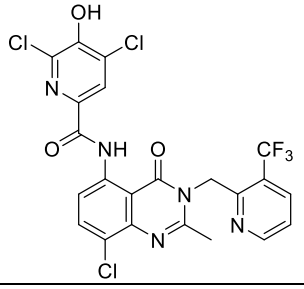
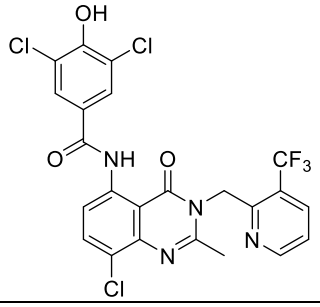
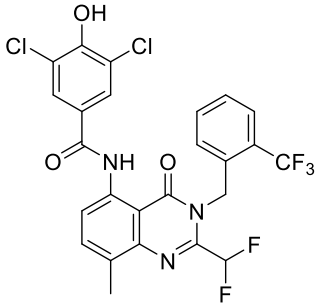
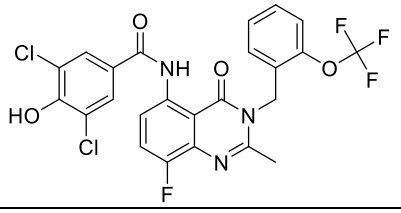
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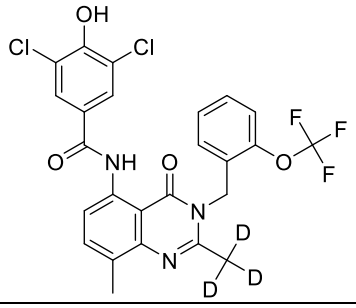
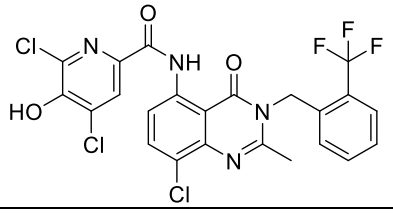
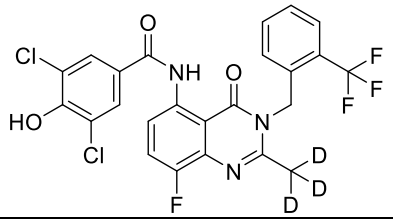
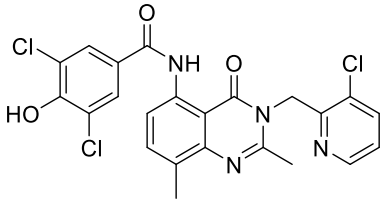
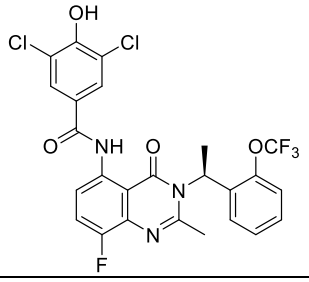
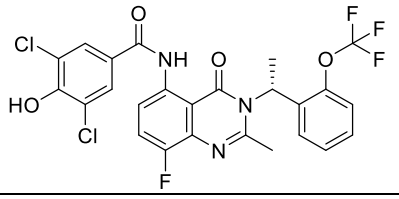
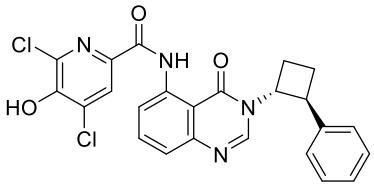
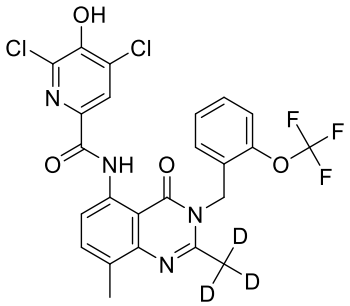
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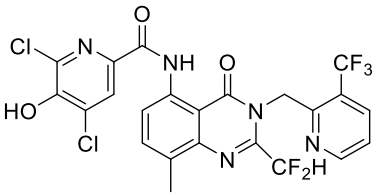
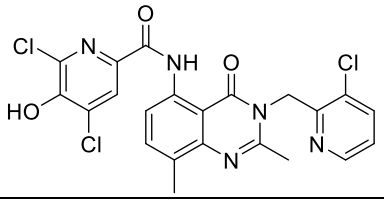
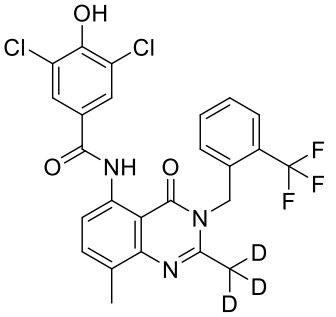
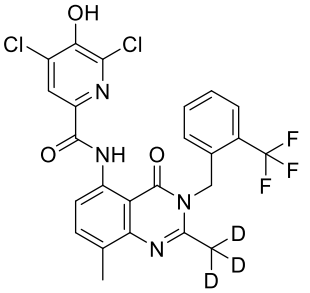
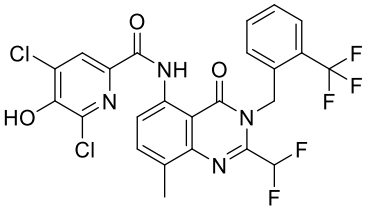
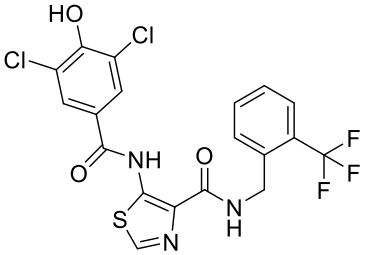
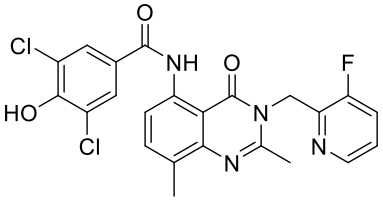
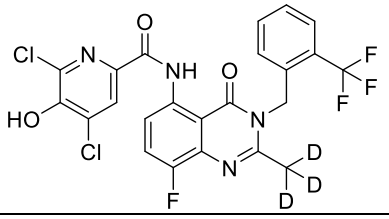
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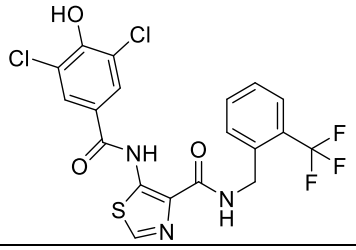
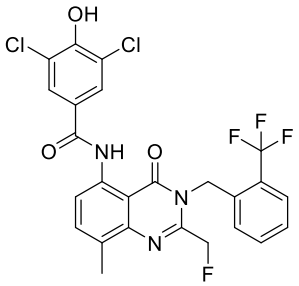
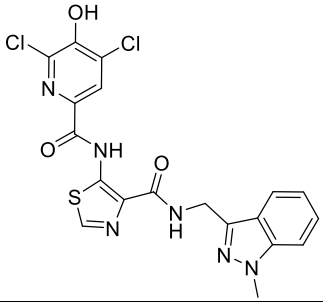
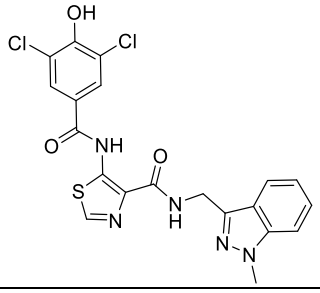
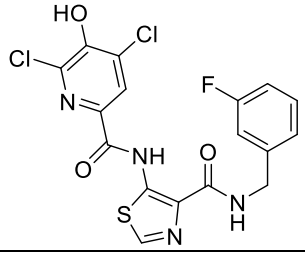
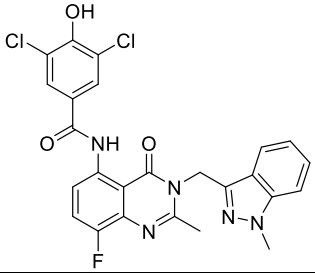
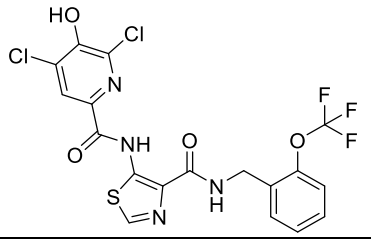
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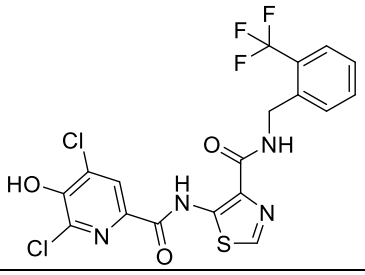
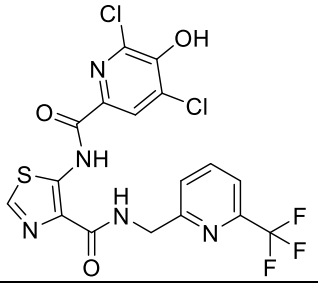
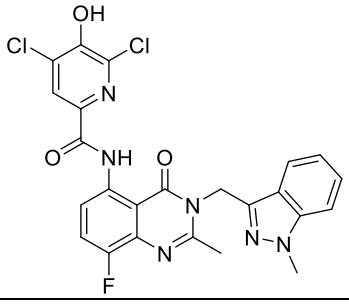
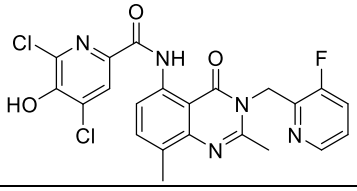
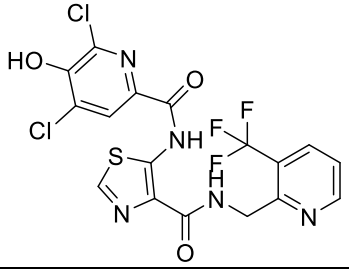
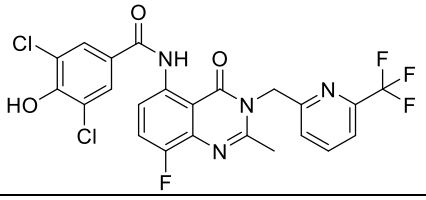
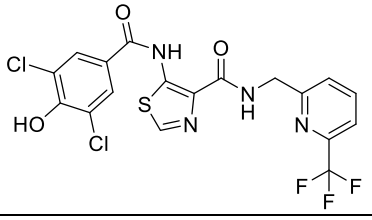
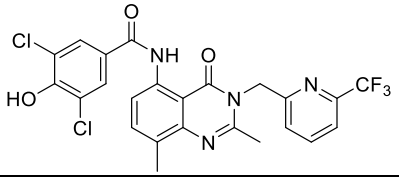
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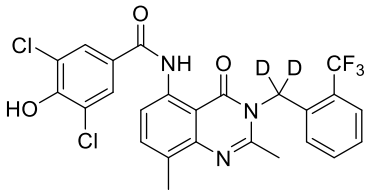
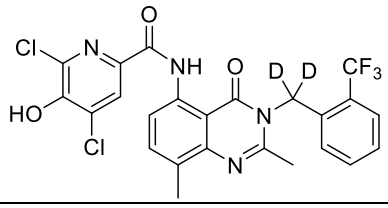
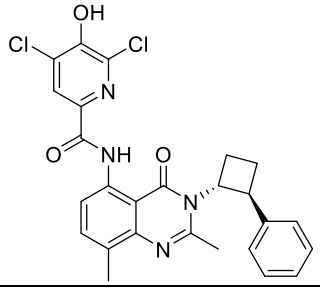
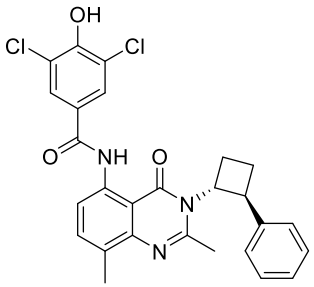
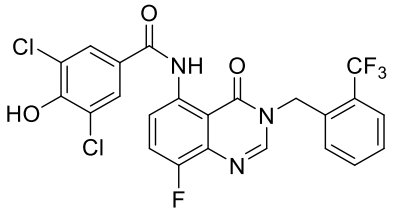
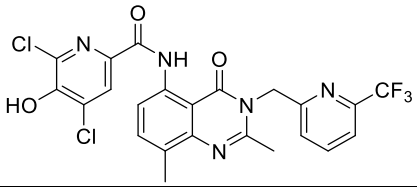
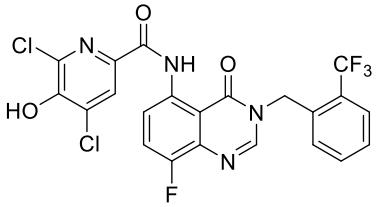
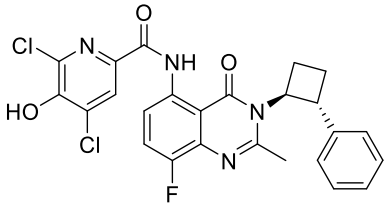
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or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof.

24. A pharmaceutical composition comprising a compound of any one of claims 1-23, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, and a pharmaceutically acceptable carrier.

25. Use of a compound of any one of claims 1-23, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition of claim 24, in the manufacture of a medicament for treating a liver disease, a metabolic disease, or a cardiovascular disease in a subject in need thereof.

26. A compound of any one of claims 1-23, or a pharmaceutically acceptable salt, solvate, or stereoisomer thereof, or a pharmaceutical composition of claim 24, for use in therapy.